Supplementary information

Towards Ideality: The Synthesis of (+)-Kalkitoxin and (+)-Hydroxyphthioceranic Acid by Assembly-Line Synthesis

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General Information

All air- and water-sensitive reactions were carried out in oven-dried glassware under a N_2 atmosphere using standard Schlenk techniques. Analytical TLC was performed on aluminium backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F254. Compounds were visualized by exposure to UV-light or stained using Phosphomolybdic acid (PMA) or $KMnO_4$ followed by heating. Flash column chromatography was performed using Merck Silica Gel 60 (40-63 μm). All mixed solvent eluents are reported as v/v solutions.

^{1}H- and ^{13}C- Nuclear Magnetic Resonance (NMR) spectra were acquired at various field strengths as indicated using JEOL ECS 300, JEOL ECS 400, Varian 400 and Varian VNMRS500 spectrometers. ^{1}H spectra were referenced internally to the residual protio solvent resonance ($CHCl_3$ = 7.27 ppm, C_6D_6 = 7.13 ppm). ^{13}C spectra were referenced internally to the residual protio solvent resonance ($CHCl_3$ = 77.0 ppm; C_6D_6 = 128.06 ppm). ^{11}B spectra were referenced externally to $BF_3{\cdot}OEt_2$. ^{1}H and ^{13}C NMR coupling constants are reported in Hertz (Hz). Coupling constants are reported as follows: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, qiun = quintet, sx = sextet, sept = spetet, m = multiplet, dd = doublet of doublet, etc. Assignment of signals in ^{1}H- and ^{13}C-spectra was performed using ^{1}H-^{1}H COSY, DEPT, HMQC and HMBC experiments where appropriate. ^{13}C signals adjacent to boron are generally not observed due to quadrupolar relaxation. Impurity at 29.7 ppm in ^{13}C spectra is due to trace amounts of Apiezon high vacuum grease.

High resolution mass spectra were recorded using Electronic Ionization (EI), Electron Spray Ionization (ESI) or Chemical Ionization (CI). For CI, methane or NH_4OAc/MeOH was used. GC-MS was perfomed on an Agilent 6890 apparatus. All IR data was obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer 241MC polarimeter. Melting points were determined with a Boetius hot stage apparatus and were not corrected.

Chiral HPLC was performed using Daicel Chiralpak IA, IB or AS-H columns (4.6 × 250 mm × 5 μm) fitted with the respective guard (4 × 10 mm) and monitored by DAD (Diode Array Detector) on a Agilent 1100 system equipped with HP Chemstation software using. Chiral SFC was performed using Diacel Chiralpak Whelk-01 columns (4.6 × 250 mm × 5 μm) on a Waters TharSFC system and monitored by DAD (Diode Array Detector).

Materials and reagents

All reagents were used as received unless otherwise stated. Anhydrous Et_2O, PhMe and CH_2Cl_2 were dried using a purification column composed of activated alumina.[1] Anhydrous Et_2O was stored over 3 Å mol sieves. Methyl *tert*-butyl ether (TBME) used in reactions were obtained by distilling over calcium hydride and were stored over 3 Å mol sieves. Where stated solvents were degassed using the freeze-pump-thaw method.[2] TMEDA, triethylamine and *N*,*N*-diisopropylethylamine (Hunig's base) were distilled over CaH_2 and stored in a Young's tube under N_2. (−)-Sparteine was obtained from the commercially available sulfate pentahydrate salt (ABCR chemicals) and isolated according to literature procedure.[3] (+)-Sparteine was obtained as the free base (BOC sciences), distilled over CaH_2 and stored in a Young's tube under N_2. The sparteine free base readily absorbs atmospheric carbon dioxide (CO_2) and should be stored in a Young's tube under argon/N_2 at −20 °C. Organolithiums were periodically titrated using *N*-benzylbenzamide.[4] Solutions of *n*BuLi where precipitate had formed were discarded as these were found to not be effective in Sn-Li exchange reactions.

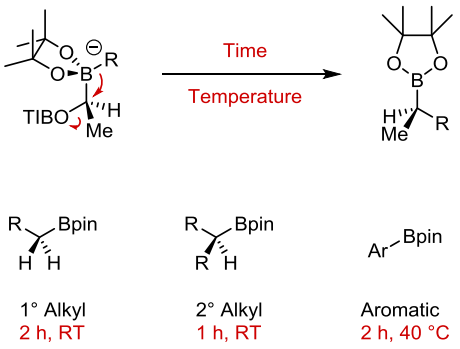
General procedures

General procedure 1 (GP1)

A solution of stannane **S25** (1.30 eq) in a Schlenk reaction vessel was dissolved in anhydrous Et_2O (0.2 M) under an atmosphere of nitrogen. The reaction mixture was cooled to –78 °C (white precipitate of stannane **S25** in Et_2O at –78 °C). *n*BuLi (1.5–1.6 M in hexanes, 1.30 eq) was added dropwise to the reaction mixture at –78 °C. The reaction mixture was stirred for 1 h at –78 °C (when the tin–lithium exchange is complete the reaction mixture will be a translucent pale yellow solution with no stannane precipitate remaining). Boronic ester (0.5 M in anhydrous Et_2O, 1.0 eq) was then added dropwise to the reaction mixture at –78 °C. The reaction mixture was stirred at –78 °C for 30 min (the pale yellow solution loses its colour on the addition of the boronic ester). The reaction mixture was removed from the cooling bath and stirred at the desired temperature for the desired time (see below for time and temperature guide for 1,2-migration; as the 1,2-metallate rearrangement occurs a white precipitate of TIBOLi forms). The reaction mixture was filtered through silica (~10 mm depth of wetted (Et_2O) silica, using a filter frit connected directly to an oven dried receiving vessel) to give a colourless to pale yellow translucent solution. The silica was washed with Et_2O (reagent grade, 5 mL), the filter frit was removed and solvent was removed (*in situ*) under reduced pressure to give the crude boronic ester. The crude boronic ester could then be re-dissolved in anhydrous Et_2O and used in further homologations or purified by flash column chromatography.

1,2-Migration Time Guide

1,2-Migration times for boron ate complexes derived from lithiated benzoate **1** in Et_2O have been determined by ^{11}B NMR. 2° alkyl boronic esters migrate faster than 1° alkyl boronic esters. Aromatic boronic esters require heating to promote 1,2-migration.



General procedure 2 (GP2)

A solution of boronic ester (1.0 eq.) and chloroiodomethane (3.0 eq.) was dissolved in anhydrous Et_2O (0.2 M) under an atmosphere of nitrogen. The reaction mixture was cooled to –95 °C (MeOH /$N_{2(l)}$). *n*BuLi (1.5–1.6 M in hexanes, 2.95 eq) was added dropwise to the reaction mixture at –95 °C. The reaction mixture was stirred for 10 min at –95 °C. The reaction mixture was removed from the cooling bath and stirred at room temperature for 1 h. The reaction mixture was filtered through silica (~10 mm depth of wetted (Et_2O) silica, using a filter frit connected directly to an

oven dried receiving vessel) to give a colourless to pale yellow translucent solution. The silica was washed with Et_2O (reagent grade, 5 mL), the filter frit was removed and solvent was removed (*in situ*) under reduced pressure to give the crude boronic ester. The crude boronic ester could then be re-dissolved in anhydrous Et_2O (to make a 0.5 M solution) and used in further homologations or purified by flash column chromatography.

General Procedure 3 (GP3)

A solution of boronic ester (1.0 eq.) and bromochloromethane (3.0 eq.) was dissolved in anhydrous Et_2O (0.25 M) under an atmosphere of nitrogen. The reaction mixture was cooled to –78 °C (acetone/dry ice). *n*BuLi (1.5–1.6 M in hexanes, 2.5 eq.) was added dropwise to the reaction mixture at –78 °C. The reaction mixture was stirred for 20 min at –78 °C. The reaction mixture was removed from the cooling bath and stirred at room temperature for 1 h. The reaction mixture was filtered through silica (~10 mm depth of wetted (Et_2O) silica, using a filter frit connected directly to an oven dried receiving vessel) to give a colourless to pale yellow translucent solution. The silica was washed with Et_2O (reagent grade, 5 mL), the filter frit was removed and solvent was removed (*in situ*) under reduced pressure to give the crude boronic ester. The crude boronic ester could then be re-dissolved in anhydrous Et_2O and used in further homologations or purified by flash column chromatography.

General procedure 4 (GP4)

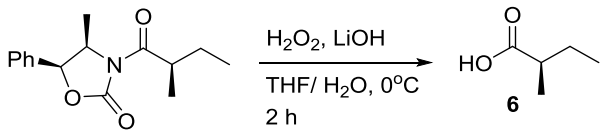
A premixed solution of NaOH (2 M)/H_2O_2 (30% aq.) (2:1, 3 mL) was added dropwise to a solution of boronic ester (20–100 mg scale) in THF (2 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred at this temperature for 1-4 h (reaction was monitored by TLC). The reaction mixture was diluted with H_2O (2 mL) and Et_2O (2 mL). The phases were separated and the aqueous phase washed with Et_2O (3 × 2 mL). The combined organic phases were washed with H_2O (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

Total Synthesis of (+)-Kalkitoxin 3

Methoxyamine

DIPEA (18.9 mL, 108 mmol, 1.2 eq) was added to a solution of methoxyamine hydrochloride (7.52 g, 90 mmol, 1.0 eq) in glycerol (40 mL) in a 100 mL round bottom flask. The reaction mixture was heated at 50 °C for 2 h. Oven dried distillation apparatus (with Vigreux column) and receiving vessel was then attached to the reaction vessel. Methoxyamine (bp: 48–50 °C) was distilled from the reaction mixture (oil bath: 110 °C; distillation temperature: 40 °C) to give pure methoxyamine (2.64 g, 35%) as a colourless liquid. Methoxyamine was stored at 4 °C under an atmosphere of nitrogen.

(*R*)-2-methylbutanoic acid 6[5]



A stirred solution of (4*R*,5*S*)-4-methyl-3-((*R*)-2-methylbutanoyl)-5-phenyloxazolidin-2-one (1.9 g, 7.4 mmol, 1.0 eq) in THF/H_2O (v/v 2:1; 33 mL) was cooled to 0 °C. H_2O_2 (30%$_{aq}$, 5.5 mL, 37 mmol) was added, followed by a solution of LiOH (0.28 g, 12 mmol) in H_2O (10 mL). The reaction mixture was stirred at 0 °C for 2 h before the addition of a solution of Na_2SO_3 (4.0 g) in H_2O (16 mL). The reaction mixture was stirred for 30 min at 0 °C and then buffered to pH 9–10 with $NaHCO_3$ (sat. aq.). THF was removed under reduced pressure and the chiral auxiliary was recovered by extraction with CH_2Cl_2 (3 × 25 mL). The aqueous phase was acidified to pH 1 with H_2SO_4 (2 M) and extracted with Et_2O (3 × 25 mL) to give (*R*)-2-methylbutyric acid **6** (680 mg; 90%) as a colourless oil.

Spectral data were in accordance with the published values.[6]

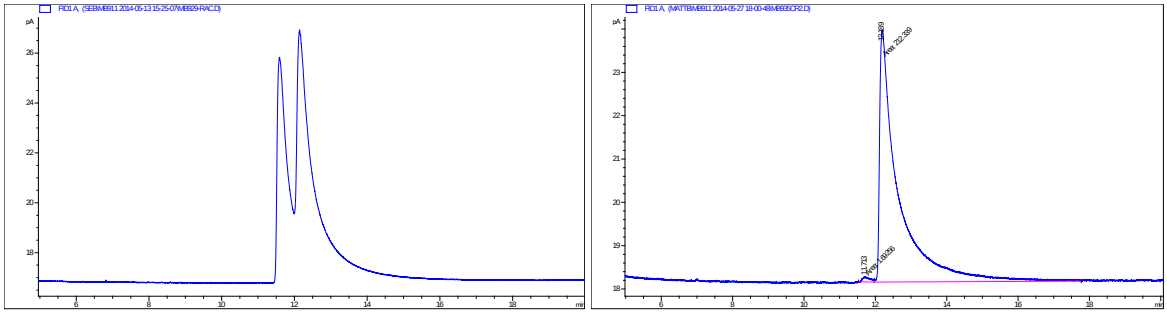
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{21}}$: –17.3 (*c* 1.04, CH_2Cl_2)

Lit[6] $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –16.0 (*c* 1.00, CH_2Cl_2)

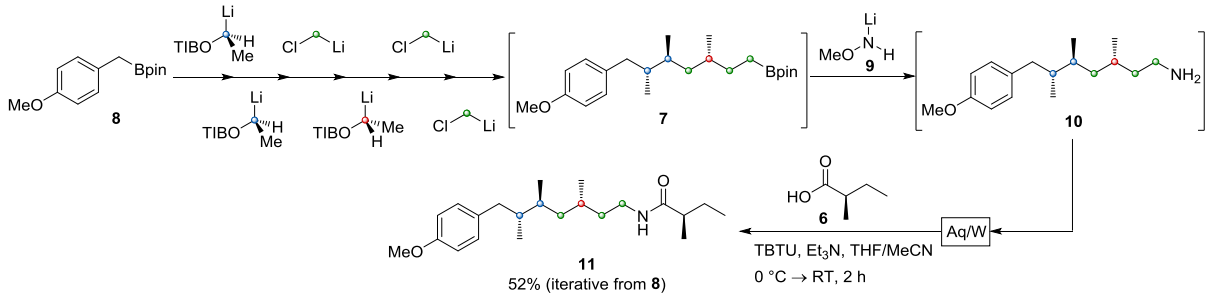
^{1}H NMR (400 Hz, $CDCl_3$): 9.47 (1H, br. s, OH), 2.41 (1H, sex, *J* = 6.9 Hz, CH), 1.71 (1H, dquin, *J* = 13.7, 7.4 Hz, C*H*H), 1.51 (1H, dqd, *J* = 13.7, 7.4, 6.5 Hz, C*H*H), 1.19 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.96 (1H, t, *J* = 7.4 Hz, CH_2CH_3)

^{13}C NMR (100 Hz, $CDCl_3$): 183.1 (C5), 40.8 (C3), 26.5 (C2), 16.4 (C4), 11.5 (C1)

Chiral GC: Beta DM chiraldex column (15 m), constant pressure 20 psi, 1.6 mL/min, 90 °C isothermal, 30 min, t_R = 11.7 min (*S*-minor), 12.2 min (*R*-major), e.r. = 0.8:99.2



Iterative homologation, amination and peptide coupling towards amide 11



2-(4-Methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **8** (794 mg, 3.20 mmol, 1.00 eq) was subjected to six iterative homologations, Morken amination and then peptide coupling. After each homologation reaction, the reaction mixture was filtered through a plug of silica and solvent was removed under reduced pressure to give the crude boronic ester for the subsequent reaction.

1st homologation (GP1): Stannane **(*S*)-S25** (1.83 g, 4.16 mmol, 1.30 eq, 99.9 : 0.1 e.r.) and *n*BuLi (1.54 M in hexanes, 2.70 mL, 4.16 mmol, 1.30 eq) in anhydrous Et_2O (30 mL)

2nd homologation (GP1): Stannane **(*S*)-S25** (1.83 g, 4.16 mmol, 1.30 eq, 99.9 : 0.1 e.r.) and *n*BuLi (1.54 M in hexanes, 2.70 mL, 4.16 mmol, 1.30 eq) in anhydrous Et_2O (21 mL)

3rd homologation (GP2): Chloroiodomethane (0.70 mL, 9.60 mmol, 3.00 eq) and *n*BuLi (1.54 M in hexanes, 6.13 mL, 9.44 mmol, 2.95 eq) in anhydrous Et_2O (16 mL)

4th homologation (GP1): Stannane **(*R*)-S25** (1.83 g, 4.16 mmol, 1.30 eq, 99.9 : 0.1 e.r.) and *n*BuLi (1.54 M in hexanes, 2.70 mL, 4.16 mmol, 1.30 eq) in anhydrous Et_2O (21 mL)

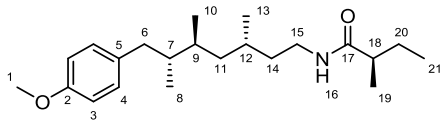
5th homologation (GP2): Chloroiodomethane (0.70 mL, 9.60 mmol, 3.00 eq) and *n*BuLi (1.54 M in hexanes, 6.13 mL, 9.44 mmol, 2.95 eq) in anhydrous Et_2O (16 mL)

6th homologation (GP2): Chloroiodomethane (0.70 mL, 9.60 mmol, 3.00 eq) and *n*BuLi (1.54 M in hexanes, 6.13 mL, 9.44 mmol, 2.95 eq) in anhydrous Et_2O (16 mL)

Morken amination: *t*BuLi (1.9 M in pentane, 8.42 mL, 16.0 mmol, 5.0 eq) was added dropwise to a solution of methoxyamine (0.83 mL, 16.0 mmol, 5.0 eq) in anhydrous THF (40 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min before the dropwise addition of a solution of crude boronic ester **7** (3.20 mmol (assumed), 1.0 eq) in anhydrous THF (7 mL). The reaction

mixture was stirred at –78 °C for 1 h. The cooling bath was removed and the reaction mixture warmed to 60 °C and stirred at this temperature for 12 h. The reaction mixture was cooled to room temperature and diluted with H_2O (30 mL) and EtOAc (20 mL). The phases were separated and the aqueous phase extracted with EtOAc (4 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give crude amine **10** which was used in further transformations without purification.

Peptide coupling: Et_3N (1.33 mL, 9.60 mmol, 3.0 eq) was added to a solution of TBTU (1.23 g, 3.84 mmol, 1.2 eq) and (*R*)-(–)-2-Methylbutyric acid **6** (392 mg, 3.84 mmol, 1.2 eq) in anhydrous MeCN (16 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min before the addition of a solution of crude amine **10** (3.20 mmol (assumed), 1.0 eq) in anhydrous THF (10 mL). The reaction mixture was warmed to room temperature and stirred at this temperature for 2 h. The reaction mixture was diluted with water (20 mL) and hexane (5 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were dried (MgSO4), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane : EtOAc 90 : 10 → 60 : 40) to give amide **11** (579 mg, 52%(from boronic ester **8**)) as a light brown oil.



$[\alpha]_D^{21}$: –30.4 (*c* 1.1, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): 7.09–7.01 (2H, m, H4), 6.85–6.78 (2H, m, H3), 5.45 (1H, br. s, H16), 3.79 (3H, s, H10), 3.39–3.15 (2H, m, H15), 2.61 (1H, dd, *J* = 13.5, 5.4 Hz, H6), 2.22 (1H, dd, *J* = 13.5, 9.3 Hz, H6'), 2.08 (2H, apt. sex, *J* = 7.1 Hz, H18), 1.71–1.60 (2H, m, H7 and 1 × H20), 1.59–1.32 (5H, m, H9, H12, H14 and 1 × H20), 1.20–1.11 (2H, m, H11), 1.13 (3H, d, *J* = 7.1 Hz, H19), 0.90 (3H, t, *J* = 7.1 Hz, H21), 0.87 (3H, d, *J* = 6.7 Hz, H13), 0.85 (3H, d, *J* = 7.0 Hz, H10), 0.77 (3H, d, *J* = 6.8 Hz, H8)

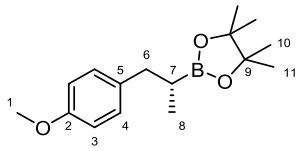
^{13}C NMR (100 MHz, $CDCl_3$): 176.4 (C17), 157.5 (C2), 134.0 (C5), 129.9 (C4), 113.5 (C3), 55.2 (C1), 43.3 (C18), 40.7 (C7), 39.7 (C11), 38.8 (C6), 38.1 (C14), 37.5 (C15), 33.8 (C9), 28.2 (C12), 27.3 (C20), 19.1 (C13), 17.5 (C19), 16.7 (C10), 15.6 (C8), 11.9 (C21)

HRMS (ESI^+): calculated for $C_{22}H_{37}NO_2Na$ [M+Na^+]: 370.2717; found 370.2724

IR (ν_{max}/cm^{-1}, neat): 817, 1037, 1244, 1511, 1642, 2874, 2927, 2960, 3295

Stepwise synthesis of boronic ester 7

(*R*)-2-(1-(4-Methoxyphenyl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S26)



According to **GP1**. Stannane **(*S*)-S25** (571 mg, 1.30 mmol, 1.30 eq, 99.9 : 0.1 e.r.) and *n*BuLi (1.55 M in hexanes, 0.84 mL, 1.30 mmol, 1.30 eq) in anhydrous Et_2O (6.0 mL), followed by addition of boronic ester **8** (248 mg, 1.00 mmol, 1.00 eq) in anhydrous Et_2O (1.5 mL) gave after flash column chromatography (penatane:Et_2O 97:3 → 95:5) boronic ester **S26** (243 mg, 88%) as a colourless oil.

Spectral data were in accordance with the published values.[7]

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$: –5.24 (*c* 0.57, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): 7.15–7.08 (2H, m, H4), 6.84 – 6.77 (2H, m, H3), 3.79 (3H, s, H1), 2.75 (1H, dd, *J* = 13.7, 7.5 Hz, H6), 2.49 (1H, dd, *J* = 13.7, 8.3 Hz, H6'), 1.33 (1H, m, H7), 1.20 (6H, s, H10 or H11), 1.19 (6H, s, H10 or H11), 0.96 (3H, d, *J* = 7.3 Hz, H8)

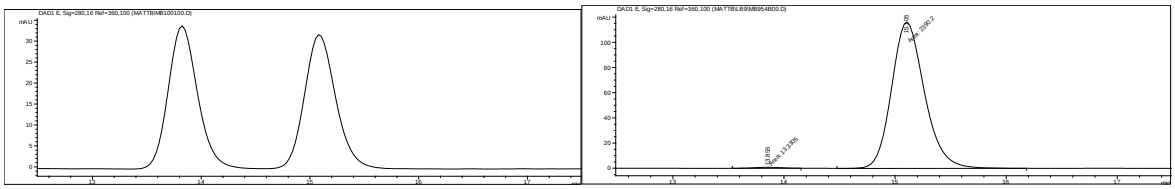
^{13}C NMR (101 MHz, $CDCl_3$): 157.6 (C2), 134.4 (C5), 129.7 (C4), 113.4 (C3), 82.9 (C9), 55.2 (C1), 38.0 (C6), 24.7 (C10 or C11), 24.7 (C10 or C11), 15.1 (C8)

Boronic ester **S26** (17.2 mg, 62.3 µmol) was oxidised according to **GP4** and after flash column chromatography (pentane:Et_2O 70:30 → 50:50) to give the corresponding alcohol (8.8 mg, 85%) as a colourless oil for chiral HPLC analysis and confirmation of absolute stereochemistry.

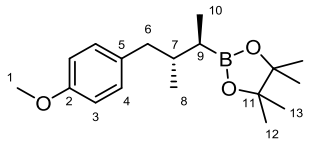
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$: –27.3 (*c* 0.29, $CHCl_3$)

Lit[8] $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{21}}$: +27.0 (*c* 4.4, $CHCl_3$, (*S*), 99%ee)

Chiral HPLC: Diacel Chiralpak IA column, 5% *i*PrOH in hexane, 0.7 mL/min, 20 °C, t_R = 13.86 min (*S*-minor), 15.11 min (*R*-major), e.r. = 99.5 : 0.5



2-((2*R*,3*R*)-4-(4-Methoxyphenyl)-3-methylbutan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*S*27)



According to **GP1**. Stannane **(*S*)-S25** (465 mg, 1.06 mmol, 1.30 eq, 99.9 : 0.1 e.r.) and *n*BuLi (1.55 M in hexanes, 0.69 mL, 1.06 mmol, 1.30 eq) in anhydrous Et_2O (5.0 mL), followed by addition of boronic ester **S26** (226 mg, 0.82 mmol, 1.00 eq) in anhydrous Et_2O (1.0 mL) gave after flash column chromatography (pentane:Et_2O 97:3 → 94:6) boronic ester **S27** (242 mg, 97%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{21}}$: –8.73 (*c* 0.57 $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): 7.13–7.06 (2H, m, 2H, H3), 6.86–6.78 (2H, m, H4), 3.79 (3H, s, H1), 2.75 (1H, dd, *J* = 13.4, 5.2 Hz, 1H, H6), 2.26 (1H, dd, *J* = 13.4, 9.3 Hz, H6'), 1.84–1.72 (1H, m, H7), 1.27 (12H, s, H12 and H13), 1.11–0.89 (1H, m, H9), 1.01 (3H, d, *J* = 6.2 Hz, H7), 0.83 (3H, d, *J* = 6.8 Hz, H8)

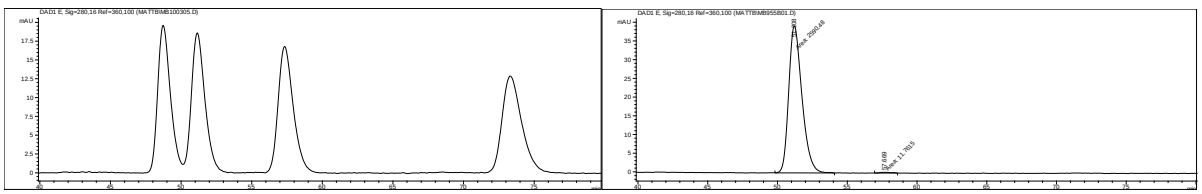
^{13}C NMR (100 MHz, $CDCl_3$): 157.5 (C2), 134.2 (C5), 130.1(C4), 113.4 (C3), 82.8 (C11), 55.2 (C1), 41.2 (C6), 38.3 (C7), 25.1(C12 or C13), 25.0 (C12 or C13), 18.3 (C10), 13.3 (C8)

HRMS (EI$^+$): calculated for $C_{18}H_{29}BO_3$ [M$^+$]: 304.2210; found 304.2204

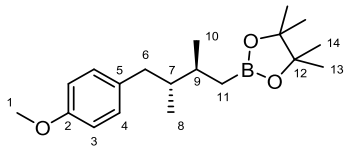
IR (ν_{max}/cm^{-1}, neat): 2976, 2956, 1611, 1511, 1312, 1245, 1143

Boronic ester **S27** (10.0 mg, 32.9 µmol) was oxidised according to **GP4** and after flash column chromatography (pentane:Et_2O 80:20 → 60:40) to give the corresponding alcohol (6.3 mg, 99%) as a colourless oil for chiral HPLC analysis.

Chiral HPLC: Diacel Chiralpak IA column (25cm), 2% *i*PrOH in hexane, 0.5 mL/min, 0 °C, t_R = 48.73 (minor stereoisomer), 51.15 (major stereoisomer), 57.33 (minor stereoisomer), 73.31 (minor stereoisomer), stereoisomer ratio = 99.5 (major) : 0.5 (all minor)



2-((2*S*,3*R*)-4-(4-Methoxyphenyl)-2,3-dimethylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*S*28)



According to **GP2**. Chloroiodomethane (0.17 mL, 2.27 mmol, 3.00 eq) and *n*BuLi (1.55 M in hexanes, 1.42 mL, 2.20 mmol, 2.90 eq) in anhydrous Et_2O (1.9 mL) gave after flash column chromatography (pentane:Et_2O 95:5) boronic ester **S28** (224 mg, 93%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{21}}$: +2.83 (*c* 0.71 $CHCl_3$)

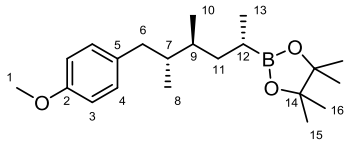
^{1}H NMR (400 MHz, $CDCl_3$): 7.11–7.03 (2H, m, H3), 6.86–6.78 (2H, m, H4), 3.79 (3H, s, H1), 2.71 (1H, dd, *J* = 13.3, 4.3 Hz, H6), 2.14 (1H, dd, *J* = 13.3, 10.1 Hz, 1H, H5), 1.86–1.74 (1H, m, H9), 1.66–1.52 (1H, m, 1H, H7), 1.27 (12H, s, H13 and H14), 0.95 (3H, d, *J* = 6.8 Hz, H10), 0.97–0.88 (1H, m, H11), 0.75 (3H, d, *J* = 6.8 Hz, H8), 0.69 (1H, dd, *J* = 15.1, 10.0 Hz, H11')

^{13}C NMR (101 MHz, $CDCl_3$): 157.5 (C2), 134.4 (C5), 130.0 (C4), 113.5 (C3), 82.9 (C12), 55.2 (C1), 41.9 (C7), 38.9 (C6), 33.9 (C9), 24.9 (C13 or C14), 24.8 (C13 or C14), 19.3 (C10), 15.4 (C8)

HRMS (EI^+): calculated for $C_{19}H_{31}BO_3$ [M^+]: 318.2366; found 318.2359

IR (ν_{max}/cm^{-1}, neat): 2929, 1511, 1365, 1313, 1245, 1143

2-((2*S*,4*S*,5*R*)-6-(4-Methoxyphenyl)-4,5-dimethylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*S*29)



According to **GP1**. Stannane **(*R*)-S25** (398 mg, 0.91 mmol, 1.30 eq, 99.9 : 0.1 e.r.) and *n*BuLi (1.60 M in hexanes, 0.57 mL, 0.91 mmol, 1.30 eq) in anhydrous Et_2O (4.0 mL), followed by addition of boronic ester **S28** (222 mg, 0.70 mmol, 1.00 eq) in anhydrous Et_2O (1.0 mL) gave after flash column chromatography (pentane:Et_2O 97:3 → 95:5) boronic ester **S29** (218 mg, 91%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{21}}$: –6.52 (*c* 0.92, $CHCl_3$)

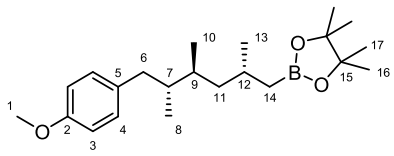
^{1}H NMR (400 MHz, $CDCl_3$): 7.10–7.04 (2H, m, H4), 6.86–6.78 (2H, m, H3), 3.79 (3H, s, H1), 2.66 (1H, dd, *J* = 13.4, 4.7 Hz, H6), 2.18 (1H, dd, *J* = 13.4, 9.9 Hz, H6'), 1.75–1.63 (1H, m, H7), 1.62–1.50 (1H, m, H9), 1.35 (2H, apt. t, *J* = 7.5 Hz, H11), 1.25 (12H, s, H15 and H16), 1.14–1.02 (1H, m, H12), 0.95 (3H, d, *J* = 7.2 Hz, H13), 0.86 (3H, d, *J* = 6.8 Hz, H10), 0.77 (3H, d, *J* = 6.8 Hz, H8)

^{13}C NMR (101 MHz, $CDCl_3$): 157.5 (C2), 134.4 (C5), 129.9 (C4), 113.5 (C3), 82.8 (C14), 55.2 (C1), 40.0 (C7), 38.2 (C6), 35.8 (C11), 35.5 (C9), 24.73 (C15 or C16), 24.71 (C15 or C16), 16.2 (C10), 16.1 (C8), 15.3 (C13)

HRMS (EI^+): calculated for $C_{21}H_{35}BO_3$ [M^+]: 346.2679; found 346.2676

IR (ν_{max}/cm^{-1}, neat): 2956, 2926, 1512, 1245, 1143, 1038

2-((2*R*,4*S*,5*R*)-6-(4-Methoxyphenyl)-2,4,5-trimethylhexyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S30)



According to **GP2**. Chloroiodomethane (0.14 mL, 1.87 mmol, 3.00 eq) and *n*BuLi (1.60 M in hexanes, 1.13 mL, 1.81 mmol, 2.90 eq) in anhydrous Et_2O (1.6 mL) gave after flash column chromatography (pentane:Et_2O 96:4 → 94:6) boronic ester **S30** (197 mg, 88%) as a colourless oil.

$[\alpha]_D^{21}$: –25.5 (c 0.71, $CHCl_3$)

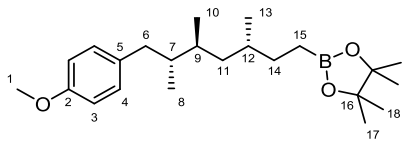
^{1}H NMR (400 MHz, $CDCl_3$): 7.10–7.04 (2H, m, H4), 6.85–6.78 (2H, m, H3), 3.79 (3H, s, H1), 2.62 (1H, dd, *J* = 13.4, 5.1 Hz, H6), 2.21 (1H, dd, *J* = 13.4, 9.5 Hz, H6'), 1.83–1.72 (1H, m, H12), 1.70–1.59 (1H, m, H7), 1.58–1.48 (1H, m, H9), 1.26 (12H, s, H16 and H17), 1.24–1.09 (2H, m, H11), 0.88 (3H, d, *J* = 6.5 Hz, H13), 0.87 (3H, d, *J* = 6.7 Hz, H10), 0.81 (1H, dd, *J* = 15.1, 6.7 Hz, H14), 0.78 – 0.71 (1H, m, H14') 0.76 (3H, d, *J* = 6.9 Hz, H8)

^{13}C NMR (101 MHz, $CDCl_3$): 157.5 (C2), 134.3 (C5), 129.9 (C4), 113.5 (C3), 82.8 (C15), 55.2 (C1), 42.5 (C11), 40.7 (C7), 38.8 (C6), 34.2 (C9), 27.0 (C12), 24.9 (C16 or C17), 24.8 (C16 or C17), 21.8 (C13), 16.7 (C10), 15.6 (C8)

HRMS (EI^+): calculated for $C_{22}H_{37}BO_3$ [M^+]: 360.2836; found 360.2837

IR (ν_{max}/cm^{-1}, neat): 2956, 2924, 1511, 1369, 1245, 1143, 846

2-((3*R*,5*S*,6*R*)-7-(4-Methoxyphenyl)-3,5,6-trimethylheptyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7)



According to **GP2**. Chloroiodomethane (0.12 mL, 1.60 mmol, 3.00 eq) and *n*BuLi (1.60 M in hexanes, 0.97 mL, 1.55 mmol, 2.90 eq) in anhydrous Et_2O (1.8 mL) gave after flash column chromatography (pentane:Et_2O 96:4 → 94:6) boronic ester **7** (182 mg, 91%) as a colourless oil.

$[\alpha]_D^{20}$: –2.0 (*c* 1.0, $CHCl_3$)

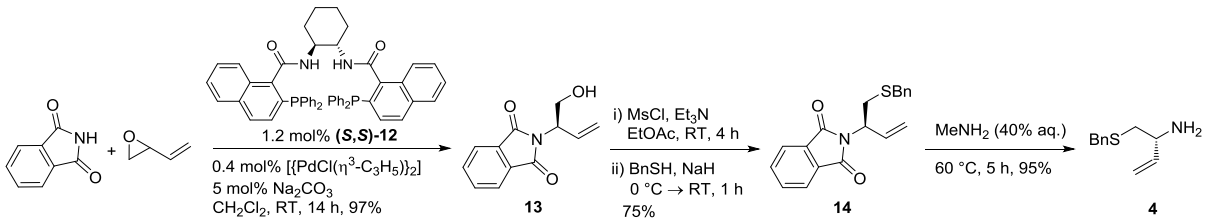
^{1}H NMR (400 MHz, $CDCl_3$): 7.09–7.03 (2H, m, H4), 6.84–6.79 (2H, m, H3), 3.80 (3H, s, H1), 2.62 (1H, dd, *J* = 13.5, 5.1 Hz, H6), 2.21 (1H, dd, *J* = 13.5, 9.5 Hz, H6'), 1.70–1.60 (1H, m, H7), 1.59–1.49 (1H, m, H9), 1.46–1.35 (1H, m, H12), 1.34–1.24 (2H, m, H14), 1.26 (12H, s, H17 and H18), 1.19 (1H, ddd, *J* = 13.3, 10.1, 3.3 Hz, H11), 1.10 (1H, ddd, *J* = 13.3, 9.4, 3.8 Hz, H11'), 0.90–0.74 (2H, m, H15), 0.84 (3H, d, *J* = 6.8 Hz, H10), 0.82 (3H, d, *J* = 6.3 Hz, H13), 0.76 (3H, d, *J* = 6.9 Hz, H8)

^{13}C NMR (101 MHz, $CDCl_3$): 157.5 (C2), 134.3 (C5), 129.9 (C4), 113.5 (C3), 82.9 (C16), 55.2 (C1), 40.8 (C7), 39.5 (C11), 38.8 (C6), 34.0 (C9), 32.4 (C12), 32.3 (C14), 24.83 (C17 or C18), 24.82 (C17 or C18), 18.9 (C13), 16.7 (C10), 15.6 (C8)

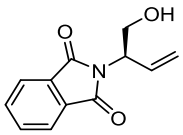
HRMS (ESI^+): calculated for $C_{23}H_{39}BNaO_3$ [M+Na$^+$]: 397.2884; found 397.2883

IR (ν_{max}/cm^{-1}, neat): 846, 967, 1038, 1144, 1245, 1370, 1463, 1511, 1612, 2873, 2925, 2957

Synthesis of the amino thioether 4



(*R*)-2-(1-Hydroxybut-3-en-2-yl)isoindoline-1,3-dione (13)



A reaction vessel containing $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (13 mg, 0.036 mmol, 0.4 mol%), (*S,S*)-DACH-naphthyl Trost ligand **(*S,S*)-12** (85 mg, 0.11 mmol, 1.2 mol%), Na_2CO_3 (48 mg, 0.45 mmol, 5 mol%) and phthalimide (1.3 g, 9.0 mmol, 1.0 eq) is evacuated and refilled with nitrogen (× 3). Anhydrous CH_2Cl_2 (72 mL) is added to the reaction mixture and the resulting solution is stirred at room temperature for 10 min. Butadiene monoepoxide (0.73 mL, 9.0 mmol, 1.0 eq) was added and the reaction mixture was stirred at room temperature for 12 h. The pale yellow reaction mixture was concentrated under reduced pressure and the crude material was purified by column chromatography (pentane:Et_2O 70:30 → 30:70) to give allylic amide **13** (1.9 g, 97%) as a colourless solid.

Spectral data were in accordance with the published values.[9]

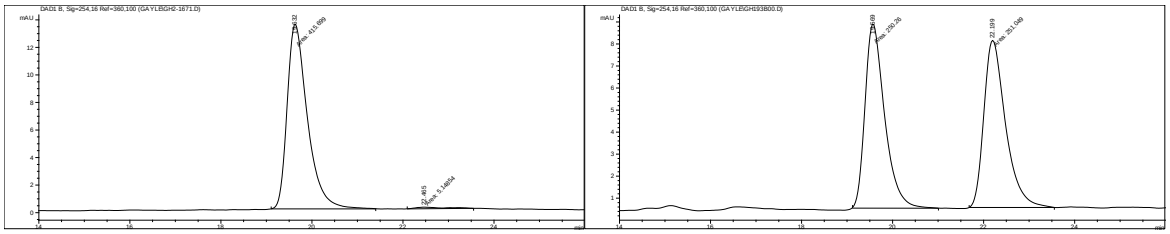
$[\alpha]_D^{25}$: +72.0 (*c* 1.02, CH_3Cl)

Lit[9] $[\alpha]_D^{25}$: –74.2 (*c* 1.02, CH_2Cl_2, (*S*), 96% ee)

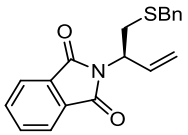
^{1}H NMR (400 Hz, $CDCl_3$): 7.87–7.81 (2H, m, H_{Ar}), 7.76–7.69 (2H, m, H_{Ar}), 6.20–6.09 (1H, ABX, CH), 5.31–5.22 (2H, m, 2×CH), 4.93 (1H, dddt, *J* = 8.0, 7.0, 4.5, 1.3 Hz, NCH), 4.14 (1H, ddd, *J* = 11.7, 8.7, 8.0 Hz, OC*H*H), 3.95 (1H, ddd, *J*=11.7, 4.5, 4.1 Hz, OCH*H*), 2.78 (1H, dd, *J* = 8.7, 4.1 Hz, OH)

^{13}C NMR (101 Hz, $CDCl_3$): 168.5 (C=O), 134.2 (CH), 131.9(CH), 131.7 (C_{Ar}-C), 123.4 (C_{Ar}-H), 18.8 (CH_2), 62.9 (OCH_2), 55.9 (NCH)

Chiral HPLC: Diacel Chiralpak IB column (25 cm), 10% *i*PrOH in hexane, 0.7 mL/min, 20 °C, t_R = 19.63 min (*R*-major), 22.45 min (*S*-minor), e.r. = 99:1



(*R*)-2-(1-(Benzylthio)but-3-en-2-yl)isoindoline-1,3-dione (14)



Methanesulfonyl chloride (0.28 mL, 3.7 mmol, 1.3 eq) was added dropwise to a solution of allylic amide **13** (660 mg, 3.0 mmol, 1.0 eq) and Et_3N (0.55 mL, 4.0 mmol) in anhydrous EtOAc (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred at this temperature for 4 h. The reaction mixture was diluted with EtOAc (30 mL). The organic phase was washed with H_2O (2 × 10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give crude (*R*)-2-(1,3- dioxoisoindolin-2-yl)but-3-en-1-yl methanesulfonate **(S31)**.

In a separate flask, benzyl mercaptan (0.71 mL, 6.0 mmol, 2.0 eq) was added dropwise to a solution of NaH (0.22 g; 5.5 mmol) in anhydrous DMF (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min before the addition of sulfonate **S31** as a solution in anhydrous DMF (7 mL). After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with toluene (40 mL) and washed with H_2O (2 × 25 mL) and washed with brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (pentane:Et_2O 100:0 → 90:10) to give (*R*)-2- (1-benzylthio)but-3-en-2-yl)isoindoline-1,3-dione (**14**, 740 mg, 75%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{23}}$: –80.9 (*c* 0.56, CH_2Cl_2)

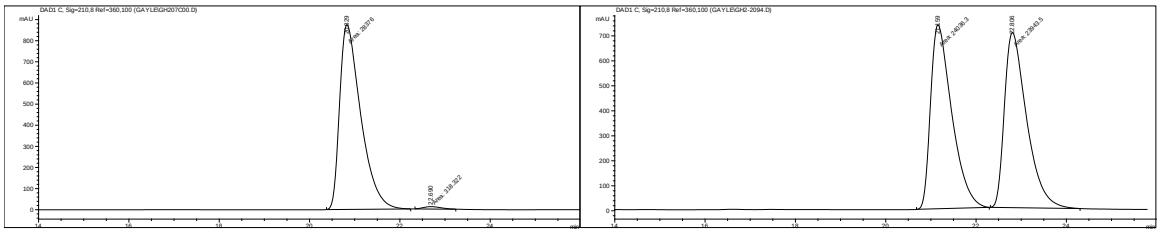
^{1}H NMR (400 Hz, $CDCl_3$): 7.88–7.83 (2H, m, H_{Ar}), 7.76–7.69 (2H, m, H_{Ar}), 7.36–7.20 (5H, m, H_{Ar}), 6.21 (1H, ddd, *J* = 17.2, 10.2, 7.5 Hz, CH), 5.29–2.19 (2H, m, CH_2), 4.90 (1H, m, NCH), 3.76 (1H, d, *J* = 13.4 Hz, PhCH*H*S), 3.72 (1H, d, *J* = 13.4 Hz, PhC*H*HS), 3.18 (1H, dd, *J* = 13.9, 10.5 Hz, SC*H*H), 2.81 (1H, dd, *J* = 13.9, 5.5 Hz, SCH*H*)

^{13}C NMR (101 Hz, $CDCl_3$): 167.9 (C=O), 137.6 (C_{Ar}-C), 134.2 (CH), 134.0 (C_{Ar}-H), 131.8 (C_{Ar}-C), 128.9 (C_{Ar}-H), 128.5 (C_{Ar}-H), 127.1 (C_{Ar}-H), 123.3(C_{Ar}-H), 118.4 (CH_2), 52.3 (NCH), 35.5 (Ph*C*H_2S), 32.8 (SCH_2)

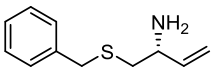
HRMS: (ESI) calcd. for $C_{19}H_{17}NaNO_2S$ ($M+Na^+$): 346.0872; Found 346.0869

IR (ν_{max}/cm^{-1}, neat): 1703, 1381, 1352, 1332, 1081, 713, 697, 529

Chiral HPLC: Diacel Chiralpak IB column (25 cm), 1% *i*PrOH in hexane, 0.7 mL/min, 20 °C, t_R = 20.83 min (*R*-major), 22.71 min (*S*-minor), e.r. = 99:1

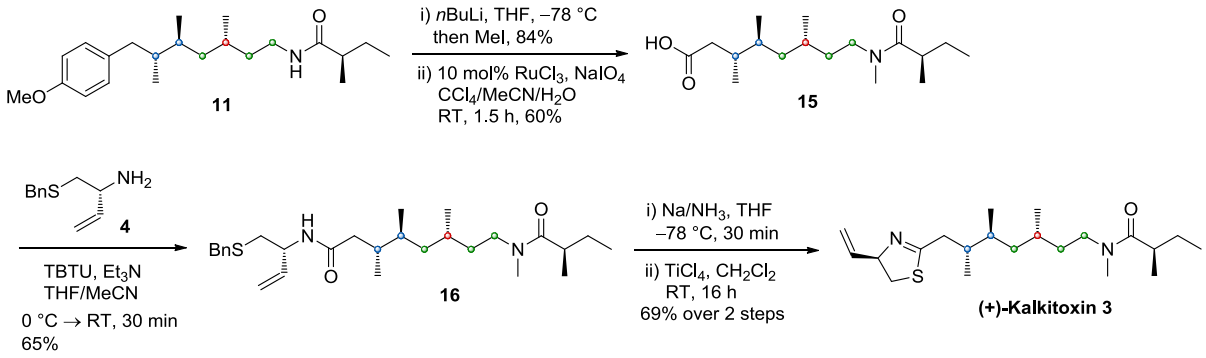


(*R*)-1-(Benzylthio)but-3-en-2-amine (4)

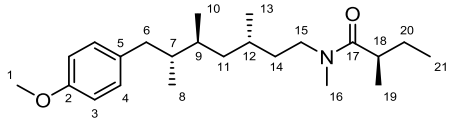


(*R*)-2-(1-Benzylthio)but-3-en-2-yl)isoindoline-1,3-dione **(14)** (160 mg, 0.5 mmol, 1.0 eq) was suspended in CH_3NH_2 (40% aq., 5 mL) and warmed to 60 °C and stirred at this temperature for 5 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to remove excess methylamine. The crude mixture was extracted with EtOAc (2 × 15 mL) and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford amino thioether **4** (92 mg, 95%) as a pale yellow oil. This material was used without further purification.

Completion of the Synthesis of (+)-Kalkitoxin 3



(*R*)-*N*-((3*S*,5*S*,6*R*)-7-(4-Methoxyphenyl)-3,5,6-trimethylheptyl)-*N*,2-dimethylbutanamide (S32)



*n*BuLi (1.6 M in hexane, 0.74 mL, 1.19 mmol, 1.8 eq) was added dropwise to a solution of amide **11** (230 mg, 0.66 mmol, 1.0 eq) in anhydrous THF (6.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 10 min before the dropwise addition of MeI (0.25 mL, 2.64 mmol, 4.0 eq). The reaction mixture was stirred at –78 °C for 10 min before being warmed to room temperature and stirred at this temperature for 1 h. The reaction mixture was diluted with $NaHCO_3$ (sat. aq., 10 mL). The phases were separated and the aqueous layer extracted with EtOAc (5 × 20 mL). The combined organic phases were washed with brine (2 × 20 mL), dried (Na_2SO_4) and filtered. The solvents were removed under reduced pressure to give the crude product which was purified by flash column chromatography (pet ether:EtOAc 70:30) to give amide **S32** (200 mg, 84%) as colourless oil.

Amide rotamers are observed in the ^{1}H and ^{13}C NMR spectra of amide **S32**.

$[\alpha]_D^{20}$: –39.3 (*c* 1.2, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): 7.09–7.02 (2H, m, H4), 6.86–6.78 (2H, m, H3), 3.79 (1.4H, s, H1), 3.70 (1.6H, s, H1), 3.42 (1H, t, *J* = 7.7 Hz, H15), 3.39–3.24 (1H, m, H15'), 3.02 (1.6H, s, H16), 2.94 (1.4H, s, H16), 2.67–2.53 (2H, m, H6 and H18), 2.29–2.18 (1H, m, H6'), 1.78–1.60 (2H, m, H7 and H20), 1.60–1.33 (5H, m, H9, H12, 2×H14 and H20'), 1.28–1.15 (2H, m, H11), 1.12 (1.4H, d, *J* = 6.7 Hz, H19), 1.10 (1.6H, d, *J* = 6.7 Hz, H19), 0.92–0.86 (7.4H, m, H10, H13 and H21), 0.85 (1.6H, d, *J* = 6.8 Hz, CH_3), 0.79 (1.4H, d, *J* = 7.0 Hz, H8), 0.77 (1.6H, d, *J* = 6.8 Hz, H8)

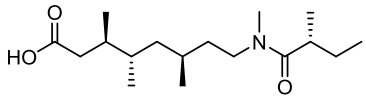
^{13}C NMR (126 MHz, $CDCl_3$): 176.4 (C17), 176.1 (C17), 157.6 (C2), 157.5 (C2), 134.1 (C5), 133.9 (C5), 129.88 (C4), 129.85 (C4), 113.54 (C3), 113.48 (C3), 55.2 (C1), 48.1 (C15), 46.2 (C15), 40.7 (CH), 40.6 (CH), 39.9 (C11), 39.8 (C11), 38.9 (C6), 38.8 (C6), 37.38 (C14), 37.37 (C18), 37.2 (C18),

35.5 (C14), 35.2 (C16), 33.84 (CH), 33.82 (CH), 33.7 (C16), 28.33 (CH), 28.27 (CH), 27.4 (C20), 27.1 (C20), 19.2 (CH_3), 19.1 (CH_3), 17.7 (C19), 17.1 (C19), 16.6 (CH_3), 15.7 (C8), 15.6 (C8), 12.2 (CH_3), 12.00 (CH_3)

HRMS (ESI^+): calculated for $C_{23}H_{39}NO_2Na$ [M+Na^+]: 384.2873; found 384.2877

IR (ν_{max}/cm^{-1}, neat): 817, 1036, 1245, 1511, 1640, 2873, 2925, 2959

(3*R*,4*S*,6*S*)-8-((*R*)-*N*,2-Dimethylbutanamido)-3,4,6-trimethyloctanoic acid (15)



A solution of amide **S32** (190 mg, 0.52 mmol, 1.0 eq), $NaIO_4$ (1.67 g, 7.9 mmol, 15.2 eq) and $RuCl_3$ (10 mg, 0.05 mmol, 0.1 eq) in CCl_4 (2.5 mL), MeCN (2.5 mL) and H_20 (5.0 mL) was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with H_2O (20 mL) and CH_2Cl_2 (40 mL), the phases separated and the aqueous phase extracted with CH_2Cl_2 (2 × 40 mL). The combined organic phases were filtered through a plug of silica, the plug of silica was washed with EtOAc (40 mL) and the combined organic filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (pet ether:EtOAc 50:50) to give amide **15** (93 mg, 60%) as colourless oil.

Spectral data were in accordance with the published values.[10]

Amide rotamers are observed in the ^1H and ^{13}C NMR spectra of amide **15**.

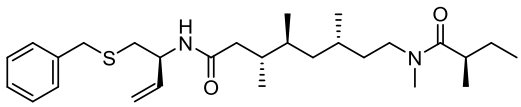
$[\alpha]_D^{20}$: –38.9 (*c* 0.36, $CHCl_3$)

Lit[10] $[\alpha]_D^{20}$: –35.0 (*c* 0.40, $CHCl_3$)

^1H NMR (400 MHz, $CDCl_3$): 8.80 (1H, br. s, CO_2H), 3.47–3.14 (2H, m, NCH_2), 2.99 (1.5 H, s, NCH_3 rotamer), 2.90 (1.5 H, s, NCH_3 rotamer), 2.65–2.46 (1H, m, C(O)CH), 2.32 (1H, dd, *J* = 14.6, 4.2 Hz, C*H*HCO_2H), 2.05 (1H, m, CH*H*CO_2H), 1.93 (1H, br. m, CH), 1.66 (1H, m, CH*H*CH_3), 1.58–1.26 (5H, m, 2×CH and CH_2 and C*H*HCH_3), 1.15–0.98 (5H, m, CH_2 and CH_3), 0.94–0.70 (12H, m, 4 × CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): 178.6 (C=O), 178.4 (C=O), 176.9 (N-C=O), 176.5 (N-C=O), 48.1 (NCH_2), 46.2 (NCH_2) 40.3 (CH_2), 40.2 (CH_2), 38.03 (CH_2), 37.95 (CH_2), 37.3 (CH), 37.2 (CH'), 37.0 (CH_2), 35.3 (NCH_3), 35.2 (CH_2), 35.1 (CH), 34.9 (CH), 34.2 (CH), 34.1 (CH), 33.8 (NCH_3), 28.08 (CH), 28.07 (CH), 27.2 (CH_2), 26.9 (CH_2), 18.9 (CH_3), 17.5 (CH_3), 16.9 (CH_3), 16.5 (CH_3), 16.4 (CH_3), 15.94 (CH_3), 15.88 (CH_3), 12.0 (CH_3), 11.9 (CH_3)

(3*R*,4*S*,6*S*)-*N*-((*S*)-1-(Benzylthio)but-3-en-2-yl)-8-((*R*)-*N*,2-dimethylbutanamido)-3,4,6-trimethyloctanamide (16)



TBTU (67 mg, 0.21 mmol, 1.0 eq) was added to a solution of amide **15** (62 mg, 0.21 mmol, 1.0 eq), Et_3N (87 μL, 0.62 mmol, 3.0 eq) in MeCN (4.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min before the addition of amino thioether **4** (44 mg, 0.023 mmol, 1.1 eq) in THF (2.0 mL). The reaction mixture was warmed to room temperature and stirred at this temperature for 30 min. The solvents were removed under reduced pressure to give the crude product which was purified by flash column chromatography (pet ether:EtOAc 70:30) to give amide **16** (64 mg, 65%) as colourless oil.

Spectral data were in accordance with the published values.[10]

Amide rotamers are observed in the ^{1}H and ^{13}C NMR spectra of amide **16**.

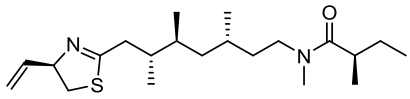
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: –12.5 (*c* 0.4, $CHCl_3$)

Lit[10] $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: –15.0 (*c* 1.16, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): 7.35–7.29 (4H, m, H_{Ar}), 7.28–7.21 (1H, m, H_{Ar}), 5.80 (1H, *J* = 17.2, 10.4, 5.3 Hz, CH), 5.78–5.59 (1H, br. m, NH), 5.23–5.12 (2H, m, CH_2), 4.77–4.68 (1H, m, NCH), 3.76 (1H, d, *J* = 13.4 Hz, PhC*H*H), 3.72 (1H, d, *J* = 13.4 Hz, PhCH*H*), 3.47–3.21 (2H, m, NCH_2), 3.01 (1.7H, s, NCH_3 rotamer), 2.93 (1.3 H, s, NCH_3 rotamer), 2.70–2.51 (3H, m, SCH_2 and C(O)CH), 2.23 (1H, dd, *J* = 13.8, 4.5 Hz, C(O)C*H*H), 2.06–1.91 (1H, m, CH), 1.88–1.79 (1H, m, C(O)C*H*H), 1.75–1.62 (1H, m, C*H*HCH$_3$), 1.61–1.30 (5H, m, 2×CH and CH_2 and CH*H*CH$_3$), 1.18–1.01 (5H, m, CH_2 and CH_3), 0.96–0.76 (12H, m, 4×CH_3)

^{13}C NMR (125 MHz, $CDCl_3$): 176.5 (C=O), 176.2 (C=O), 172.4 (C=O), 172.2 (C=O), 138.1 (C_{Ar}-C), 138.0 (C_{Ar}-C), 136.9 (CH), 136.9 (CH), 128.9 (C_{Ar}-H), 128.9 (C_{Ar}-H), 128.6 (C_{Ar}-H), 128.6 (C_{Ar}-H), 127.1 (C_{Ar}-H), 127.1 (C_{Ar}-H), 115.8 (CH_2), 49.8 (NCH), 48.1 (NCH_2), 46.1 (NCH_2), 40.8 (C(O)*C*H$_2$), 40.6 (C(O)*C*H$_2$), 40.6 (CH_2), 40.2 (CH_2), 37.4 (C(O)CH), 37.2 (C(O)CH), 37.2 (CH_2), 36.6 (PhCH_2), 36.6 (PhCH_2), 36.1 (SCH_2), 36.1 (SCH_2), 35.7 (CH), 35.4 (CH), 35.3 (CH_2), 35.3 (NCH_3), 34.4 (CH), 34.3 (CH), 33.7 (NCH_3), 28.2 (CH), 28.2 (CH), 27.4 (*C*H$_2$CH$_3$), 27.0 (*C*H$_2$CH$_3$), 19.2 (CH_3), 19.2 (CH_3), 17.8 (CH_3), 17.1 (CH_3), 16.5 (CH_3), 16.3 (CH_3), 16.2 (CH_3), 16.1 (CH_3)

(+)-Kalkitoxin 3



Under a positive pressure of N_2 ammonia was condensed into a vented Schlenk reaction flask at −78 °C to a volume of ~3 mL. Sodium (55 mg, 2.39 mmol, 28.0 eq) was added portion-wise (~5 mg) to the reaction vessel (colourless → blue). The sodium–ammonia mixture was stirred at −78 °C for 10 min. A solution of amide **16** (43 mg, 90.7 μmol, 26 eq) in anhydrous THF (1.5 mL) was added dropwise to the sodium–ammonia mixture and the reaction was stirred at −78 °C for 30 min. $NH_4Cl_{(s)}$ (~500 mg) was added portionwise (~50 mg) to the reaction mixture to quench the reaction (blue → colourless/white). The reaction mixture was warmed to room temperature and excess ammonia was removed under a positive pressure of nitrogen. The resulting residue was suspended in CH_2Cl_2 (3 × 10 mL), filtered and solvent removed under reduced pressure to give the crude thiol **S33** (approx. 40 mg) which was used in the subsequent reaction without purification. ^{1}H NMR analysis indicated complete conversion of amide **16** to thiol **S33**.

Freshly distilled $TiCl_4$ (30 μL, 0.27 mmol, 3.0 eq) was added dropwise to a solution of thiol **S33** (~90.7 μmol) in anhydrous CH_2Cl_2 (2.0 mL). The reaction mixture was stirred at room temperature for 16 h before being diluted with $NaHCO_3$ (sat. aq., 5 mL). The phases were separated and the aqueous phase extracted CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (pentane:EtOAc 50:50) to give (+)-kalkitoxin **3** (23 mg, 69%) as a colourless oil.

Spectral data were in accordance with the published values of synthetic kalkitoxin.[10] Additional *J* couplings are resolved in the ^{1}H NMR spectra and additional signals are resolved in the ^{13}C NMR relative to that of the isolated material.[11] These are due to the use of high resolution NMR experiments resolving signals of the amide rotamers.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +8.3 (*c* 0.36, $CHCl_3$)

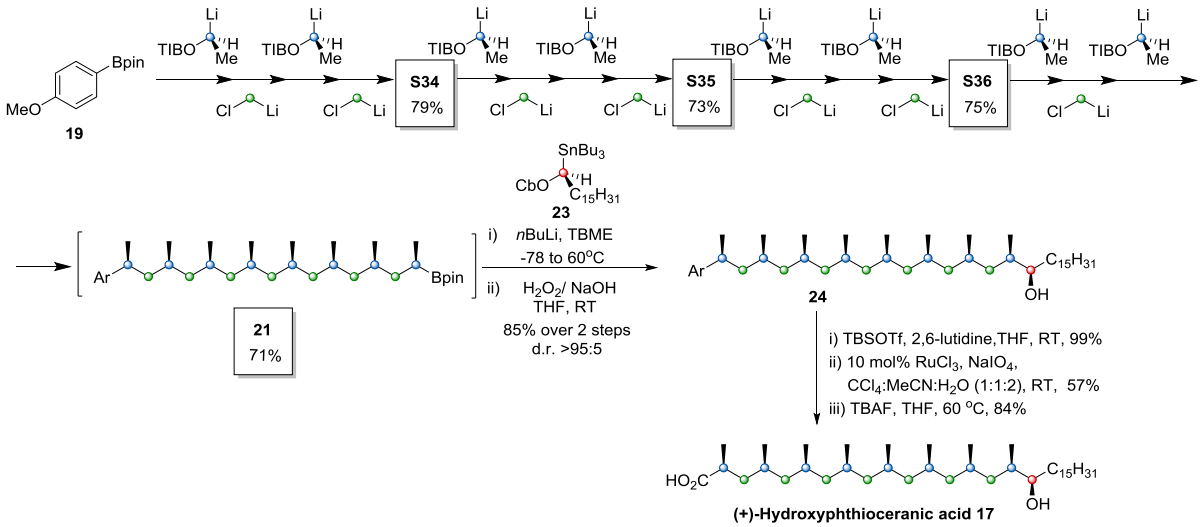
Lit $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +16.0 (*c* 0.07, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): 5.83 (1H, ddd, J = 16.9, 10.5, 6.1 Hz, CH), 5.22 (1H, dt, J = 1.5, 16.9 Hz, CH_2), 5.03–4.96 (1H, m, CH_2), 4.80–4.69 (1H, m, HCN), 3.40–3.27 (1.3H, m, CH_2), 2.98–2.87 (1.7H, m, CH_2), 2.79 (1.3H, s, NCH_3 rotamer), 2.73–2.67 (1H, m, CH_2), 2.54–2.45 (1H, m, CH_2), 2.42 (2.1H, s, NCH_3 rotamer and CH), 2.36–2.23 (1.6H, m, CH_2 and CH), 2.08–1.99 (1H, m, CH), 1.88–1.79 (1.3H, m, CH_2), 1.57–1.20 (4.7H, m, CH_2 and CH), 1.16 (1.3H, d, J = 6.5 Hz, CH_3 rotamer), 1.07 (1.7H, d, J = 7.10 Hz, CH_3 rotamer), 1.10–0.96 (2H, m, CH_2), 0.96–0.81 (~9H, m, CH_3), 0.77–0.66 (~3H, m, CH_3)

^{13}C NMR (125 MHz, C_6D_6): 175.4 (C=O), 175.1 (C=O), 170.1 (C=N), 169.9 (C=N), 138.3 (CH), 138.2 (CH), 115.34 (CH_2), 115.27 (CH_2), 79.2 (HCN), 47.8 (CH_2), 46.0 (CH_2), 40.3 (CH_2), 40.2 (CH_2), 38.81 (CH_2), 38.79 (CH_2), 38.6 (CH_2), 38.4 (CH_2), 37.58 (CH), 37.56 (CH), 37.5 (CH), 37.4 (CH_2), 37.3 (CH), 35.9 (CH_2), 34.6 (NCH_3), 34.5 (CH), 34.3 (CH), 33.5 (NCH_3), 28.4 (CH), 28.0 (CH_2), 27.6 (CH_2), 19.4 (CH_3), 19.2 (CH_3), 18.3 (CH_3), 17.6 (CH_3), 16.5 (CH_3), 16.41 (CH_3), 16.36 (CH_3), 12.5 (CH_3), 12.3 (CH_3)

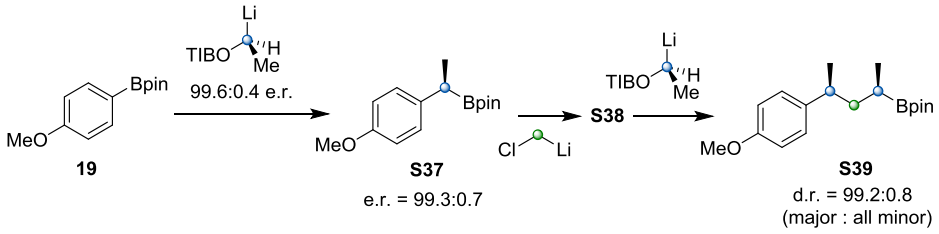
Total Synthesis of (+)-Hydrophthioceranic Acid 17

Overview:

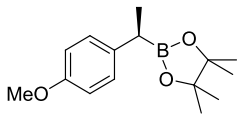


Determination of stereoselectivities

Boronic esters **S37** and **S38** were independently synthesized to confirm stereoselectivities for the first and third homologations towards the synthesis of (+)-hydrophthioceranic acid **17**.



(*R*)-2-(1-(4-Methoxyphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S37)



According to **GP1**. Stannane **(*R*)-S25** (571 mg, 1.3 mmol, 1.30 eq, 99.6:0.4 e.r.) and *n*BuLi (1.50 M in hexanes, 0.87 mL, 1.3 mmol, 1.30 eq) in anhydrous Et_2O (5 mL), followed by addition of boronic ester **19** (234 mg, 1.0 mmol) in anhydrous Et_2O (5 mL) gave after flash column chromatography (pentane:Et_2O, 98:2) boronic ester **S37** (215 mg, 82%) as a colourless oil.

Spectral data were in accordance with the published values.[12]

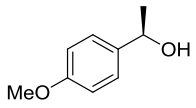
$[\alpha]_D^{22}$: –120.3 (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (2H, d, *J* = 8.5 Hz, H_{Ar}), 6.82 (2H, d, *J* = 8.7 Hz, H_{Ar}), 3.78 (3H, s, OCH_3), 2.37 (1H, q, *J* = 7.5 Hz, CH), 1.30 (3H, d, *J* = 7.5 Hz, CH_3), 1.21 (12H, d, *J* = 5.0 Hz, CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.2 (C_{Ar}-C), 137.0 (C_{Ar}-C), 129.0 (C_{Ar}-H), 113.7 (C_{Ar}-H), 83.2 (C-O), 55.2 (OCH_3), 24.62 (CH_3 of Bpin), 24.58 (CH_3 of Bpin), 17.4 (CH_3)

IR (ν_{max}/cm^{-1}, neat): 2976, 1508, 1318, 1242, 1141, 1038, 845, 827

(*R*)-1-(4-Methoxyphenyl)ethanol (S40)



Boronic ester **S37** (32 mg, 0.12 mmol) was oxidised according to **GP4** and after flash column chromatography (hexane:Et_2O:EtOAc, 70:20:10) to give the corresponding alcohol **S40** (14 mg, 95%) as a colourless oil for chiral HPLC analysis and confirmation of absolute stereochemistry.

Spectral data were in accordance with the published values.[13]

$[\alpha]_D^{22}$: +47.9 (*c* 0.6, $CHCl_3$)

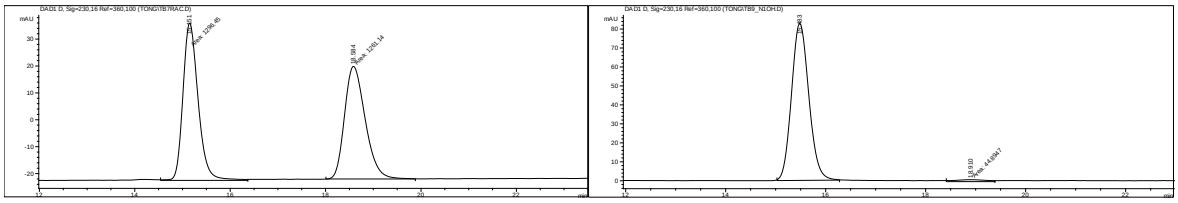
Lit[14] $[\alpha]_D^{23}$: +53.2 (*c* 1.3, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (2H, d, *J* = 8.4 Hz, H_{Ar}), 6.88 (2H, d, *J* = 8.7 Hz, H_{Ar}), 4.86 (1H, q, *J* = 6.4 Hz, CH), 3.81 (3H, s, OCH_3), 1.79 (1H, br s, OH), 1.48 (3H, d, *J* = 6.4 Hz, CH_3)

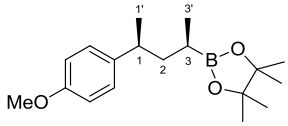
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0 (C_{Ar}-C), 138.0 (C_{Ar}-C), 126.6 (C_{Ar}-H), 113.8 (C_{Ar}-H), 70.0 (CH), 55.3 (OCH_3), 25.0 (CH_3)

IR (ν_{max}/cm^{-1}, neat): 3362, 2969, 1510, 1240, 1174, 1033, 829

Chiral HPLC: Diacel Chiralpak AS-H (25 cm), 5% *i*PrOH/hexane, 0.8 ml/min, t_R 15.48 min (major), 18.91 min (minor), e.r. = 99.3:0.7



2-((2*R*,4*S*)-4-(4-Methoxyphenyl)pentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S39)



1st homologation (GP2): A solution of boronic ester **S37** (102 mg, 0.38 mmol) and chloroiodomethane (0.12 mL, 1.56 mmol, 4.00 eq) in anhydrous Et_2O (4.0 mL) was added *n*BuLi

(1.50 M in hexanes, 1.04 mL, 1.56 mmol, 3.90 eq). The crude product was purified by flash column chromatography (pentane:Et_2O, 98:2) to give boronic ester **S38** (94 mg, 88%) as a colourless oil.

2nd homologation (GP1): Stannane **(*R*)-S25** (97 mg, 0.22 mmol, 1.30 eq, 99.6 : 0.4 e.r.) and *n*BuLi (1.50 M in hexanes, 0.15 mL, 0.22 mmol, 1.30 eq) in anhydrous Et_2O (1.0 mL), followed by addition of boronic ester **S38** (47 mg, 0.17 mmol, 1.00 eq) in anhydrous Et_2O (1.0 mL) gave after flash column chromatography (pentane:Et_2O, 97:3→95:5) boronic ester **S39** (45 mg, 87%) as a colourless oil.

$[\alpha]_D^{22}$: +10.6 (*c* 1.5, $CHCl_3$)

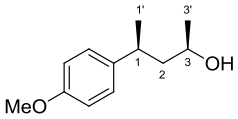
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (2H, d, *J* = 8.6 Hz, H_{Ar}), 6.83 (2H, d, *J* = 8.6 Hz, H_{Ar}), 3.79 (3H, s, OCH_3), 2.86–2.61 (1H, m, 1-CH), 1.88–1.65 (1H, m, 2-C*H*H), 1.54–1.38 (1H, m, 2-CH*H*), 1.22 (12H, s, CH_3), 1.20 (3H, s, 1'-CH_3), 0.95 (4H, s, 3'-CH_3, 3-CH)

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7 (C_{Ar}-C), 139.9 (C_{Ar}-C), 128 (C_{Ar}-H), 113.7 (C_{Ar}-H), 82.8 (C-O), 55.3 (OCH_3), 41.8 (2-CH_2), 37.5 (1-CH), 24.83 (CH_3 of Bpin), 24.79 (CH_3 of Bpin), 22.7 (1'-CH_3), 15.3 (3'-CH_3)

HRMS (ESI$^+$): calculated for $C_{18}H_{29}BNaO_3$ [M+Na$^+$]: 327.2105; found 327.2102

IR (ν_{max}/cm^{-1}, neat): 2955, 1511, 1370, 1313, 1244, 1143, 1036, 827

(2*R*,4*S*)-4-(4-Methoxyphenyl)pentan-2-ol (S41)



Boronic ester **S39** (44 mg, 0.14 mmol) was oxidised according to **GP4** and after flash column chromatography (hexane:Et_2O:EtOAc, 70:20:10) to give the corresponding alcohol **S41** (27 mg, 99%) as a colourless oil for chiral HPLC analysis.

$[\alpha]_D^{22}$: +9.8 (*c* 1.0, $CHCl_3$)

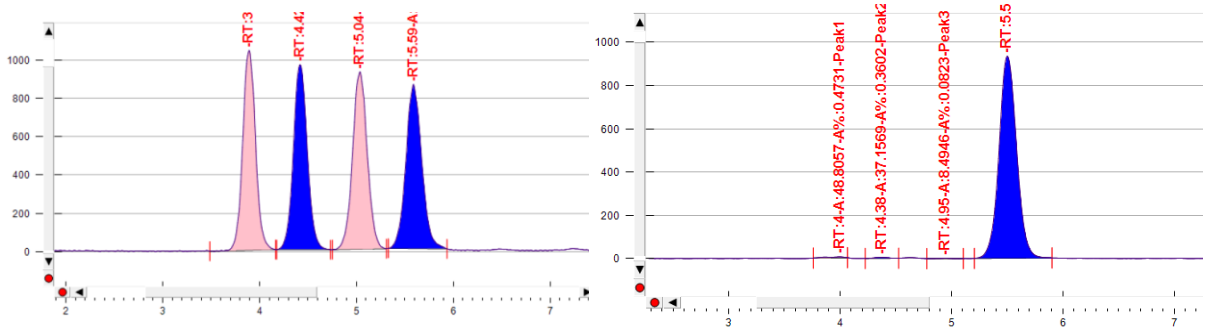
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (2H, d, *J* = 8.8 Hz, H_{Ar}), 6.85 (2H, d, *J* = 8.8 Hz, H_{Ar}), 3.81–3.71 (1H, m, 3-CH), 3.79 (3H, s, OCH_3), 2.88–2.75 (1H, m, 1-CH), 1.79 (1H, dt, *J* = 13.7, 7.8 Hz, 2-C*H*H), 1.62 (1H, ddd, *J* = 13.7, 7.2, 5.3 Hz, 2-CH*H*), 1.27 (1H, br s, OH), 1.24 (3H, d, *J* = 6.9 Hz, 1'-CH_3), 1.18 (3H, d, *J* = 6.2 Hz, 3'-CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C_{Ar}-C), 139.3 (C_{Ar}-C), 127.8 (C_{Ar}-H), 114.0 (C_{Ar}-H), 66.6 (3-CH), 55.3 (OCH_3), 48.1 (2-CH_2), 36.3 (1-CH), 23.8 (3'-CH_3), 22.7 (1'-CH_3)

HRMS (ESI$^+$): calculated for $C_{12}H_{18}BNaO_2$ [M+Na$^+$]: 217.1199; found 217.1197

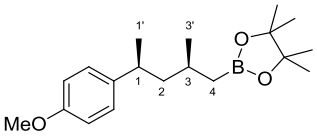
IR (ν_{max}/cm^{-1}, neat): 3324, 2961, 1511, 1242, 1177, 1034, 826, 807

Chiral SFC: Whelk-01, 5% *i*PrOH:hexane (1:1, v:v), 4 ml/min, 125 bar, 40 °C, t_R = 4.00 min (minor), 4.38 min (minor), 4.95 (minor) and 5.50 (major), stereoisomer ratio = 99.2 (major) : 0.8 (all minor).



Iterative homologations towards (+)-10-Hydrophthioceranic Acid 17

2-((2*S*,4*S*)-4-(4-Methoxyphenyl)-2-methylpentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S34)



4-methoxyphenyl boronic ester **19** (94 mg, 0.40 mmol, 1.00 eq) was subjected to four iterative homologations. After each homologation reaction, the reaction mixture was filtered through a plug of silica and solvent was removed under reduced pressure to give the crude boronic ester for the subsequent reaction.

1st homologation (GP1): Stannane **(*S*)-S25** (237 mg, 0.54 mmol, 1.35 eq, 99.6:0.4 e.r.) and *n*BuLi (1.60 M in hexanes, 0.33 mL, 0.52 mmol, 1.30 eq) in anhydrous Et_2O (1.0 mL)
2nd homologation (GP3): Bromochloromethane (8.0 μL, 1.20 mmol, 3.00 eq) and *n*BuLi (1.60 M in hexanes, 0.63 mL, 1.00 mmol, 2.50 eq) in anhydrous Et_2O (1.6 mL)
3rd homologation (GP1): Stannane **(*S*)-S25** (237 mg, 0.54 mmol, 1.35 eq, 99.6:0.4 e.r.) and *n*BuLi (1.60 M in hexanes, 0.33 mL, 0.52 mmol, 1.30 eq) in anhydrous Et_2O (1.0 mL)
4th homologation (GP3): Bromochloromethane (8.0 μL, 1.20 mmol, 3.00 eq) and *n*BuLi (1.60 M in hexanes, 0.63 mL, 1.00 mmol, 2.50 eq) in anhydrous Et_2O (1.6 mL)
After the 4th homologation, the crude product was purified by flash column chromatography (hexane:Et_2O 98:2 → 95:5) to give boronic ester **S34** (101 mg, 79%) as a colourless oil.

$[\alpha]_D^{22}$: +8.7 (*c* 1.0, $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (2H, d, *J* = 8.6 Hz, H_{Ar}), 6.83 (2H, d, *J* = 8.6 Hz, H_{Ar}), 3.79 (3H, s, OCH_3), 2.84–2.67 (1H, m, 1-CH), 1.65–1.49 (2H, m, 3-CH, 2-C*H*H), 1.40–1.32 (1H, m, 2-CH*H*), 1.24

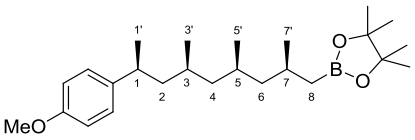
(12H, s, CH_3 of Bpin), 1.19 (3H, d, *J* = 6.9 Hz, 1'-CH_3), 0.92 (3H, d, *J* = 6.4 Hz, 3'-CH_3), 0.81 (1H, dd, *J* = 15.3, 6.0 Hz, 4-C*H*H), 0.65 (1H, dd, *J* = 15.2, 7.4 Hz, 4-CH*H*)

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7 (C_{Ar}-C), 139.9 (C_{Ar}-C), 128.0 (C_{Ar}-H), 113.7 (C_{Ar}-H), 82.9 (C-O), 55.3 (OCH_3), 48.4 (2-CH_2), 36.7 (1-CH), 27.1 (3-CH), 24.97 (CH_3 of Bpin), 24.89 (CH_3 of Bpin), 23.5 (1'-CH_3), 22.3 (3'-CH_3)

HRMS (ESI^+): calculated for $C_{19}H_{31}BNaO_3$ [M+Na^+]: 341.2262; found 341.2273

IR (ν_{max}/cm^{-1}, neat): 2955, 1511, 1370, 1313, 1244, 1143, 1036, 827

2-((2*S*,4*S*,6*S*,8*S*)-8-(4-Methoxyphenyl)-2,4,6-trimethylnonyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S35)



Boronic ester **S34** (104 mg, 0.33 mmol, 1.00 eq) was subjected to four iterative homologations. After each homologation reaction, the reaction mixture was filtered through a plug of silica and solvent was removed under reduced pressure to give the crude boronic ester for the subsequent reaction.

5th homologation (GP1): Stannane **(*S*)-S25** (198 mg, 0.45 mmol, 1.35 eq, 99.6:0.4 e.r.) and *n*BuLi (1.60 M in hexanes, 0.27 mL, 0.43 mmol, 1.30 eq) in anhydrous Et_2O (1.0 mL)

6th homologation (GP3): Bromochloromethane (7.0 μL, 0.99 mmol, 3.00 eq) and *n*BuLi (1.60 M in hexanes, 0.52 mL, 0.83 mmol, 2.50 eq) in anhydrous Et_2O (1.3 mL)

7th homologation (GP1): Stannane **(*S*)-S25** (198 mg, 0.45 mmol, 1.35 eq, 99.6:0.4 e.r.) and *n*BuLi (1.60 M in hexanes, 0.27 mL, 0.43 mmol, 1.30 eq) in anhydrous Et_2O (1.0 mL)

8th homologation (GP3): Bromochloromethane (7.0 μL, 0.99 mmol, 3.00 eq) and *n*BuLi (1.60 M in hexanes, 0.52 mL, 0.83 mmol, 2.50 eq) in anhydrous Et_2O (1.3 mL)

After the 8th homologation, the crude product was purified by flash column chromatography (hexane:Et_2O 98:2 - 95:5) to give boronic ester **S35** (96 mg, 73%) as a colourless oil.

$[\alpha]_D^{22}$: +6.3 (*c* 1.1, $CHCl_3$)

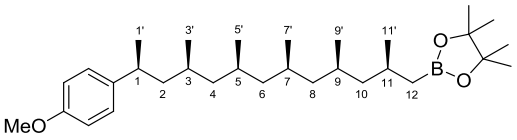
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (2H, d, *J* = 8.7 Hz, H_{Ar}), 6.81 (2H, d, *J* = 8.6 Hz, H_{Ar}), 3.77 (3H, s, OCH_3), 2.80–2.68 (1H, m, 1-CH), 1.79–1.71 (1H, m, 7-CH), 1.66–1.59 (1H, m, 2-C*H*H), 1.54–1.43 (1H, m, 5-CH), 1.31–1.20 (13H, m, 3-CH, 4×CH_3 of Bpin), 1.18–1.12 (5H, m, 2-CH*H*, 4-C*H*H, 1'-CH_3), 1.11–1.04 (1H, m, 6-C*H*H), 0.94–0.85 (4H, m, 6-CH*H*, 7'-CH_3), 0.85–0.75 (5H, m, 4-CH*H*, 8-C*H*H, 3'-CH_3), 0.64 (3H, d, *J* = 6.5 Hz, 5'-CH_3), 0.55 (1H, dd, *J* = 15.3, 8.5 Hz, 8-CH*H*)

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7 (C_{Ar}-C), 139.8 (C_{Ar}-C), 127.9 (C_{Ar}-H), 113.7 (C_{Ar}-H), 82.9 (C-O), 55.3 (OCH_3), 48.0 (6-CH_2), 45.9 (4-CH_2), 45.3 (2-CH_2), 36.6 (1-CH), 27.54 (3-CH), 27.45 (5-CH), 26.8 (7-CH), 25.0 (CH_3 of Bpin), 24.9 (CH_3 of Bpin), 24.0 (1'-CH_3), 23.2 (7'-CH_3), 20.7 (3'-CH_3), 20.3 (5'-CH_3)

HRMS (ESI$^+$): calculated for $C_{25}H_{43}BNaO_3$ [M+Na$^+$]: 425.3202; found 425.3205

IR (ν_{max}/cm^{-1}, neat): 2954, 2915, 1512, 1370, 1312, 1246, 1143, 828

2-((2*S*,4*S*,6*S*,8*S*,10*S*,12*S*)-12-(4-Methoxyphenyl)-2,4,6,8,10-pentamethyltridecyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S36)



Boronic ester **S35** (179 mg, 0.45 mmol, 1.00 eq) was subjected to four iterative homologations. After each homologation reaction, the reaction mixture was filtered through a plug of silica and solvent was removed under reduced pressure to give the crude boronic ester for the subsequent reaction.

9th homologation (GP1): Stannane **(*S*)-S25** (264 mg, 0.60 mmol, 1.35 eq, 99.6:0.4 e.r.) and *n*BuLi (1.60 M in hexanes, 0.36 mL, 0.58 mmol, 1.30 eq) in anhydrous Et_2O (1.0 mL)

10th homologation (GP3): Bromochloromethane (9.0 μL, 1.34 mmol, 3.00 eq) and *n*BuLi (1.60 M in hexanes, 0.70 mL, 1.10 mmol, 2.50 eq) in anhydrous Et_2O (1.8 mL)

11th homologation (GP1): Stannane **(*S*)-S25** (264 mg, 0.60 mmol, 1.35 eq, 99.6:0.4 e.r.) and *n*BuLi (1.60 M in hexanes, 0.36 mL, 0.58 mmol, 1.30 eq) in anhydrous Et_2O (1.0 mL)

12th homologation (GP3): Bromochloromethane (9.0 μL, 1.34 mmol, 3.00 eq) and *n*BuLi (1.60 M in hexanes, 0.70 mL, 1.10 mmol, 2.50 eq) in anhydrous Et_2O (1.8 mL)

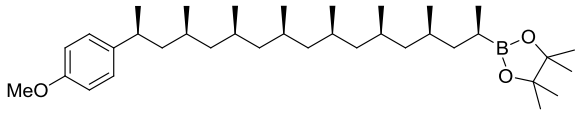
After the 12th homologation, the crude product was purified by flash column chromatography (hexane:Et_2O 98:2) to give boronic ester **S36** (161 mg, 75%) as a colourless oil.

$[\alpha]_D^{22}$: +9.0 (*c* 1.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (2H, d, *J* = 8.7 Hz, H_{Ar}), 6.84 (2H, d, *J* = 8.7 Hz, H_{Ar}), 3.80 (3H, s, OCH_3), 2.83–2.71 (1H, m, 1-CH), 1.85–1.75 (1H, m, 11-CH), 1.66 (1H, ddd, *J* = 13.8, 10.4, 3.7 Hz, 2-C*H*H), 1.57–1.49 (3H, m, 3×CH), 1.31–1.23 (13H, m, CH, 4×CH_3 of Bpin), 1.22–1.05 (8H, m, 2-CH*H*, 4/6/8/10-C*H*H, 1'-CH_3), 1.01–0.91 (4H, m, 10-CH*H*, 11'-CH_3), 0.90–0.87 (1H, m, 12-C*H*H), 0.86–0.72 (12H, m, 4/6/8-CH*H*, 3×CH_3), 0.66 (3H, d, *J* = 6.5 Hz, CH_3), 0.58 (1H, dd, *J* = 15.3, 8.6 Hz, 12-CH*H*)

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.6 (C_{Ar}-C), 139.6 (C_{Ar}-C), 127.8 (C_{Ar}-H), 113.6 (C_{Ar}-H), 82.8 (C-O), 55.2 (OCH_3), 47.4 (10-CH_2), 45.7 (CH_2), 45.6 (CH_2), 45.4 (CH_2), 45.1 (2-CH_2), 36.6 (1-CH), 27.6 (CH), 27.6 (CH), 27.23 (CH), 27.20 (CH), 26.8 (11-CH), 24.9 (CH_3 of Bpin), 24.8 (CH_3 of Bpin), 24.0 (1'-CH_3), 23.4 (11'-CH_3), 21.0 (CH_3), 20.82 (CH_3), 20.80 (CH_3), 20.69 (CH_3)
HRMS (ESI$^+$): calculated for $C_{31}H_{55}BNaO_3$ [M+Na$^+$]: 509.4142; found 509.4131
IR (ν_{max}/cm^{-1}, neat): 2953, 2914, 1512, 1371, 1312, 1246, 1144, 827

2-((2*R*,4*S*,6*S*,8*S*,10*S*,12*S*,14*S*,16*S*)-16-(4-Methoxyphenyl)-4,6,8,10,12,14-hexamethylheptadecan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (21)



Boronic ester **S36** (161 mg, 0.33 mmol, 1.00 eq) was subjected to three iterative homologations. After each homologation reaction, the reaction mixture was filtered through a plug of silica and solvent was removed under reduced pressure to give the crude boronic ester for the subsequent reaction.

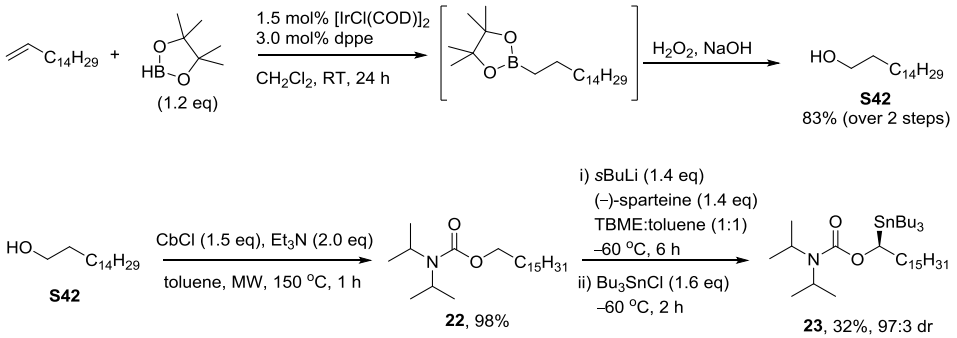
13th homologation (GP1): Stannane **(*S*)-S25** (196 mg, 0.45 mmol, 1.35 eq, 99.6:0.4 e.r.) and *n*BuLi (1.60 M in hexanes, 0.27 mL, 0.43 mmol, 1.30 eq) in anhydrous Et_2O (1.0 mL)
14th homologation (GP3): Bromochloromethane (7.0 μL, 0.99 mmol, 3.00 eq) and *n*BuLi (1.60 M in hexanes, 0.56 mL, 0.83 mmol, 2.50 eq) in anhydrous Et_2O (1.3 mL)
15th homologation (GP1): Stannane **(*S*)-S25** (196 mg, 0.45 mmol, 1.35 eq, 99.6:0.4 e.r.) and *n*BuLi (1.60 M in hexanes, 0.27 mL, 0.43 mmol, 1.30 eq) in anhydrous Et_2O (1.0 mL)
After the 15th homologation, the crude product was purified by flash column chromatography (hexane:Et_2O 98:2) to give boronic ester **21** (130 mg, 71%) as a colourless oil.

$[\alpha]_D^{22}$: +7.9 (*c* 0.8, $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (2H, d, *J* = 8.5 Hz, H_{Ar}), 6.82 (2H, d, *J* = 8.5 Hz, H_{Ar}), 3.77 (3H, s, OCH_3), 2.81–2.69 (1H, m, CH), 1.70–1.41 (7H, m, 5×CH, 2×C*H*H), 1.30–1.21 (13H, m, CH, 4×CH_3), 1.20–1.06 (10H, m, CH, CH*H*, 5×C*H*H), 1.01–0.89 (4H, m, CH*H*, CH_3), 0.88–0.72 (20H, m, 5×CH*H*, 5×CH_3), 0.66 (3H, d, *J* = 6.5 Hz, CH_3)
^{13}C NMR (126 MHz, $CDCl_3$): δ 157.6 (C_{Ar}-C), 139.6 (C_{Ar}-C), 127.8 (C_{Ar}-H), 113.7 (C_{Ar}-H), 82.7 (C-O), 55.2 (OCH_3), 45.56 (CH_2), 45.55 (CH_2), 45.53 (CH_2), 45.51 (CH_2), 45.3 (CH_2), 45.1 (CH_2), 40.8 (CH_2), 36.6 (CH), 29.6 (CH), 27.6 (CH), 27.43 (CH), 27.42 (CH), 27.4 (CH), 27.3 (CH), 24.8 (CH_3 of Bpin), 24.7 (CH_3 of Bpin), 24.0 (CH_3), 21.22 (CH_3), 21.21 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 16.5 (CH_3)

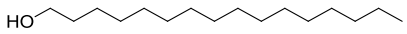
HRMS (ESI$^+$): calculated for $C_{36}H_{65}BNaO_3$ [M+Na$^+$]: 579.4925; found 579.4923

IR (ν_{max}/cm^{-1}, neat): 2952, 2913, 1512, 1458, 1371, 1245, 1143, 1040, 827

Preparation of Stannane 23



Hexadecan-1-ol (S42)[15]



To a Schlenk tube was added $[Ir(COD)Cl]_2$ (101 mg, 0.15 mmol, 1.5 mol%) and dppe (120 mg, 0.3 mmol, 3 mol%) under nitrogen atmosphere. Anhydrous CH_2Cl_2 (30 mL), pinacolborane (1.74 mL, 12.0 mmol, 1.2 eq), and 1-hexadecene (2.9 mL, 10.0 mmol, 1.0 eq) were added. The reaction mixture was stirred at room temperature for 24 h before diluted with methanol (10 mL) and water (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. The crude boronic ester was oxidised according to **GP4** and after flash column chromatography (hexane:Et_2O 80:20 → 70:30) to give alcohol **S42** (2.0 g, 83%) as a white solid.

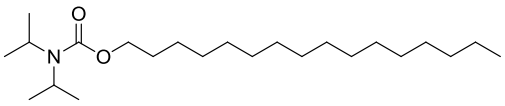
m.p.: 40-42 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75–3.55 (2H, m, CH_2), 1.65–1.50 (2H, m, CH_2), 1.43 (1H, br. s, OH), 1.38–1.10 (26H, m, 13×CH_2), 0.88 (3H, t, J = 6.8 Hz, CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 63.1 (CH_2), 32.9 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.73 (CH_2), 29.69 (CH_2), 29.68 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3)

IR (ν_{max}/cm^{-1}, neat): 3317, 2917, 2848, 1463, 1062, 719

Hexadecyl diisopropylcarbamate (22)[16]



To a solution of alcohol **S42** (1.46 g, 6.0 mmol, 1.0 eq) in anhydrous toluene (9 mL) was added diisopropyl carbamoyl chloride (1.47 g, 9.0 mmol, 1.5 eq) and triethylamine (1.7 mL, 12.0 mmol, 2.0 eq). The reaction mixture was heated at 150 °C in a microwave reactor for 2 h. The mixture was cooled to room temperature and diluted with Et_2O (20 mL). The organic phase was washed with HCl (10% aq., 2 × 10 mL) and brine (15 mL), dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane:EtOAc 90:10) to give carbamate **22** (2.17 g, 98 %) as a colourless oil.

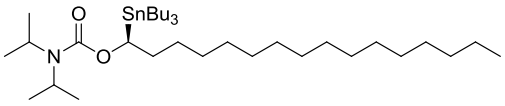
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (2H, app. t, *J* = 6.7 Hz, CH_2) 4.01&3.87 (2H, 2×br. s, CH), 1.71–1.61 (2H, m, CH_2), 1.41–1.26 (26H, m, 13×CH_2), 1.20 (12H, d, *J* = 6.8 Hz, 4×CH_3), 0.88 (3H, t, *J* = 6.8 Hz, CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.1 (C=O), 64.8 (CH_2), 45.7 (CH), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.64 (CH_2), 29.61 (CH_2), 29.43 (CH_2), 29.35 (CH_2), 29.1 (CH_2), 26.3 (CH_2), 22.8 (CH_2), 21.1 (CH_3), 14.2 (CH_3)

HRMS (ESI^+): calculated for $C_{23}H_{47}NNaO_2$ [$M+Na^+$]: 392.3499; found 392.3500

IR (ν_{max}/cm^{-1}, neat): 2922, 2853, 1694, 1435, 1308, 1287, 1133, 1066, 771

(*S*)-1-(Tributylstannyl)hexadecyl diisopropylcarbamate (23)



*s*BuLi (1.35 M in hexanes, 0.31 mL, 0.42 mmol, 1.4 eq) was added dropwise to a solution of (–)-sparteine (0.1 mL, 0.42 mmol, 1.4 eq) and carbamate **22** (111 mg, 0.3 mmol, 1.0 eq) in TBME:toluene (1:1, 4 mL) at –60 °C. The reaction mixture was stirred at –60 °C for 6 h before the dropwise addition of tributyltin chloride (0.13 mL, 0.48 mmol, 1.6 eq). The reaction mixture was stirred at –60 °C for further 2 h before being warmed to room temperature and then stirred at room temperature for 1 h. The reaction mixture was diluted with H_3PO_4 (5% aq., 10 mL) and stirred for a further 20 min. The phases were separated and the aqueous phase extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with water (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column

chromatography (hexane:Et_2O, 98:2 → 95:5) to give stannane **23** (62 mg, 32%, 86% brsm) as a colourless oil.

$[\alpha]_D^{22}$: +15.5 (*c* 1.2, $CHCl_3$)

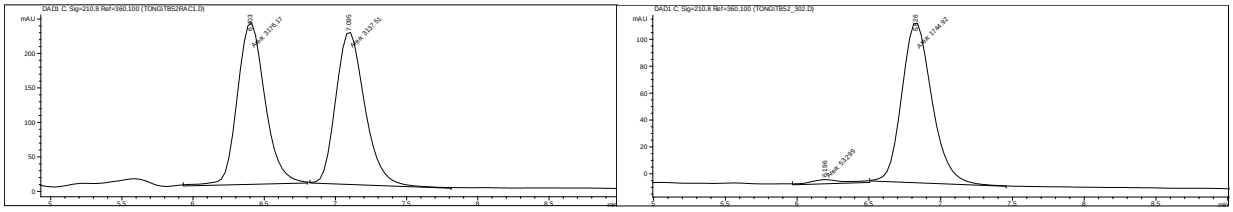
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78–4.49 (1H, m, CH), 4.07&3.70 (2H, 2×br. s, CH), 2.01–1.66 (2H, m, CH_2), 1.57–1.40 (6H, m, CH_2), 1.39–1.21 (32H, m, CH_2), 1.18 (12H, d, *J* = 6.7 Hz, CH_3 of 2×*i*Pr), 0.98–0.74 (18H, m, 3×CH_2-Sn, 4×CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.4 (C=O), 71.7 (CH-Sn), 46.2 (CH of *i*Pr), 45.1 (CH of *i*Pr), 34.7 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 21.5 (CH_3 of *i*Pr), 20.8 (CH_3 of *i*Pr), 14.2 (CH_3), 13.8 (CH_3 of *n*Bu), 9.9 (CH_2 of *n*Bu)

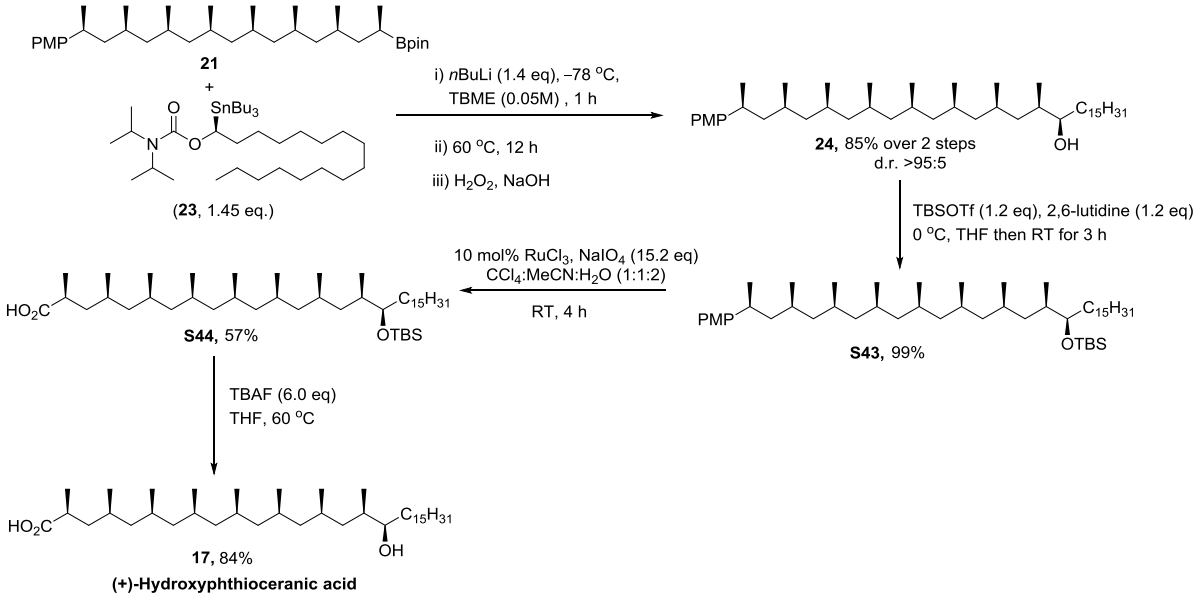
HRMS (ESI^+): calculated for $C_{35}H_{73}NNaO_2Sn$ [$M+Na^+$]: 682.4563; found 682.4569

IR (ν_{max}/cm^{-1}, neat): 2955, 2922, 2852, 1671, 1435, 1294, 1047, 773

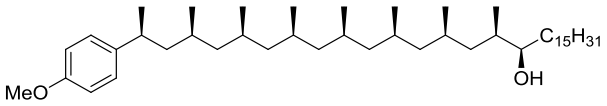
Chiral HPLC: Diacel Chiralpak IA clumn (25 cm), 100% hexane, 0.7 ml/min, t_R 6.20 min (*R*-minor), 6.83 min (*S*-major), e.r. = 97:3



Completion of the Synthesis of (+)-Hydroxyphthioceranic Acid 17



(16*R*,17*R*,19*R*,21*R*,23*R*,25*S*,27*S*,29*S*,31*S*)-31-(4-Methoxyphenyl)-17,19,21,23,25,27,29-heptamethyldotriacontan-16-ol (24)



*n*BuLi (1.6 M in hexanes, 9.0 μL, 0.13 mmol, 1.4 eq) was added dropwise to a solution of stannane **23** (90 mg, 0.14 mmol, 1.45 eq) in anhydrous TBME (1.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h before the dropwise additon of a solution of boronic ester **21** (53 mg, 0.10 mmol, 1.0 eq) in anhydrous TBME (1.0 mL). The reaction mixture was stirred at –78 °C for 1 h before being warmed to 60 °C and stirred at this temperature for 12 h. The reaction mixture was cooled to room temperature and diluted with water (5 mL) and Et_2O (5 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude boronic ester was oxidised according to **GP4** and after flash column chromatography (hexane:Et_2O 95:5) to give the corresponding alcohol **24** (54 mg, 85%, d.r. = >95:5 by NMR) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$: +21.1 (*c* 1.0, $CHCl_3$)

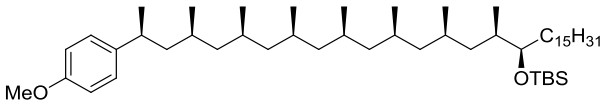
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (2H, d, *J* = 8.5 Hz, H_{Ar}), 6.84 (2H, d, *J* = 8.5 Hz, H_{Ar}), 3.80 (3H, s, OCH_3), 3.59–3.44 (1H, m, CH), 2.88–2.58 (1H, m, CH), 1.72–1.51 (7H, m, 7×CH), 1.50–1.37 (5H, m, 2×C*H*H, CH_2, OH), 1.35–1.31 (3H, m, CH*H*, CH_2), 1.30–1.24 (22H, m, 11×CH_2),), 1.23–1.10 (9H, m, 6×C*H*H, CH_3), 0.98–0.92 (1H, m, CH*H*), 0.91–0.73 (27H, m, 6×CH*H*, 7×CH_3), 0.68 (d, *J* = 6.5 Hz, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.6 (C_{Ar}-C), 139.6 (C_{Ar}-C), 127.8 (C_{Ar}-H), 113.7 (C_{Ar}-H), 74.3 (CH-OH), 55.2 (OCH_3), 45.5 (CH_2), 45.4 (CH_2), 45.36 (CH_2), 45.34 (CH_2), 45.32 (CH_2), 45.1 (CH_2), 41.2 (CH_2), 36.6 (CH), 35.1 (CH), 34.9 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.70 (CH_2), 29.69 (CH_2), 29.67 (CH_2), 29.66 (CH_2), 29.65 (CH_2), 29.64 (CH_2), 29.4 (CH_2), 27.60 (CH), 27.58 (CH), 27.56 (CH), 27.5 (CH), 27.3 (CH), 26.4 (CH_2), 24.1 (CH_3), 22.7 (CH_2), 21.39 (CH_3), 21.38 (CH_3), 21.25 (CH_3), 21.23 (CH_3), 20.9 (CH_3), 20.7 (CH_3), 14.1 (CH_3), 14.0 (CH_3)

HRMS (ESI$^+$): calculated for $C_{46}H_{86}NaO_2$ [M+Na$^+$]: 693.6520; found 693.6509

IR (ν_{max}/cm^{-1}, neat): 3357, 2953, 2921, 2852, 1512, 1458, 1376, 1247, 827

***tert*-Butyl(((16*R*,17*R*,19*R*,21*R*,23*R*,25*S*,27*S*,29*S*,31*S*)-31-(4-methoxyphenyl)-17,19,21,23,25,27,29-heptamethyldotriacontan-16-yl)oxy)dimethylsilane (S43)**



TBSOTf (2.0 µL, 0.09 mmol, 1.2 eq) was added dropwise to a stirred solution of alcohol **24** (52 mg, 0.08 mmol, 1.0 eq) and 2,6-lutidine (1.1 μL, 0.09 mmol, 1.2 eq) in anhydrous THF (2.0 mL) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with NH_4Cl (sat. aq., 5 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material purified by flash column chromatography (hexane:Et_2O 99:1 → 98:2) to give TBS ether **S43** (60 mg, 99%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$: +24.2 (*c* 1.2, $CHCl_3$)

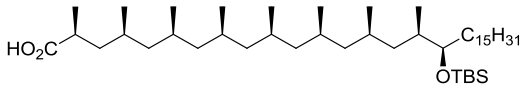
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (2H, d, *J* = 8.5 Hz, H_{Ar}), 6.85 (2H, d, *J* = 8.5 Hz, H_{Ar}), 3.81 (3H, s, OCH_3), 3.52–3.49 (1H, m, CH), 2.82–2.75 (1H, m, CH), 1.74–1.51 (7H, m, 7×CH), 1.46–1.37 (4H, m, 2×C*H*H, CH_2), 1.34–1.31 (3H, m, CH*H*, CH_2), 1.30–1.24 (22H, m, 11×CH_2),), 1.23–1.12 (9H, m, 6×C*H*H, CH_3), 0.98–0.75 (37H, m, 7×CH*H*, 10×CH_3), 0.68 (3H, d, *J* = 6.5 Hz, CH_3), 0.05 (6H, s, 2×CH_3)

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.6 (C_{Ar}-C), 139.6 (C_{Ar}-C), 127.8 (C_{Ar}-H), 113.7 (C_{Ar}-H), 75.8 (CH), 55.2 (OCH_3), 45.52 (CH_2), 45.49 (CH_2), 45.33 (CH_2), 45.32 (CH_2), 45.2 (CH_2), 45.0 (CH_2), 41.0 (CH_2), 36.6 (CH), 34.8 (CH), 33.9 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.71 (CH_2), 29.68 (CH_2), 29.67 (CH_2), 29.65 (CH_2), 29.4 (CH_2), 28.0 (CH), 27.8 (CH), 27.7 (CH), 27.6 (CH), 27.5 (CH), 27.3 (CH), 26.0 (CH_3 of *t*Bu-Si), 25.99 (CH_2), 24.1 (CH_3), 22.7 (CH_2), 21.6 (CH_3), 21.5 (CH_3), 21.34 (CH_3), 21.32 (CH_3), 20.9 (CH_3), 20.7 (CH_3), 18.2 (C-Si), 15.1 (CH_3), 14.1 (CH_3), –4.1 (CH_3-Si), –4.3 (CH_3-Si)

HRMS (ESI$^+$): calculated for $C_{52}H_{100}NaO_2Si$ [M+Na$^+$]: 807.7385; found 807.7370

IR (ν_{max}/cm^{-1}, neat): 2953, 2923, 2853, 1512, 1460, 1376, 1248, 1042, 828, 772

(2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*,17*R*)-17-((tert-Butyldimethylsilyl)oxy)-2,4,6,8,10,12,14,16-octamethyldotriacontanoic acid (S44)[17-18]



A solution of TBS ether **S43** (75 mg, 0.10 mmol, 1.0 eq), $NaIO_4$ (309 mg, 1.44 mmol, 15.2 eq) and $RuCl_3$ (2 mg, 0.01 mmol, 0.1 eq) in CCl_4 (1.0 mL), MeCN (1.0 mL) and H_20 (2.0 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with H_2O (5.0 mL) and EtOAc (15 mL), the phases were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with water (10 mL), brine (10 ml), dried over $MgSO_4$ and solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane:EtOAc 95:5 → 90:10) to give carboxylic acid **S44** (40 mg, 57%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$: +21.5 (*c* 1.3, $CHCl_3$)

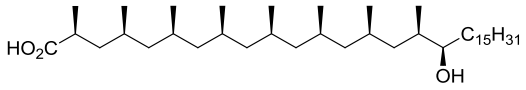
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51–3.48 (1H, m, C*H*-OTBS), 2.65–2.55 (1H, m, C*H*-CO_2H), 1.80 (1H, ddd, *J* = 13.8, 9.9, 4.3 Hz, C*H*H), 1.70–1.49 (7H, m, 7×CH), 1.43–1.35 (4H, m, 2×C*H*H, CH_2), 1.33–1.29 (3H, m, CH*H*, CH_2), 1.28–1.25 (22H, m, 11×CH_2), 1.24–1.17 (8H, m, 5×C*H*H, CH_3), 1.04 (1H, ddd, *J* = 13.7, 9.2, 4.8 Hz, CH*H*), 0.93–0.77 (39H, m, 6×CH*H*, 11×CH_3), 0.04 (6H, s, 2×CH_3)

^{13}C NMR (126 MHz, $CDCl_3$): δ 182.8 (C=O), 75.8 (CH), 45.5 (CH_2), 45.34 (CH_2), 45.27 (CH_2), 45.2 (CH_2), 45.0 (CH_2), 41.0 (CH_2), 40.7 (CH_2), 37.2 (CH), 34.8 (CH), 33.9 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.70 (CH_2), 29.69 (CH_2), 29.67 (CH_2), 29.66 (CH_2), 29.64 (CH_2), 29.4 (CH_2), 28.2 (CH), 28.0 (CH), 27.8 (CH), 27.7 (CH), 27.5 (CH), 27.3 (CH), 26.0 (3×CH_3 of *t*Bu-Si), 25.98 (CH_2), 22.7 (CH_2), 21.8 (CH_3), 21.5 (CH_3), 21.3 (2×CH_3), 20.9 (CH_3), 20.6 (CH_3), 18.18 (CH_3), 18.15 (C-Si), 15.1 (CH_3), 14.1 (CH_3), –4.1 (CH_3), –4.3 (CH_3)

HRMS (ESI$^-$): calculated for $C_{46}H_{93}O_3Si$ [M–H$^+$]: 721.6899; found 721.6892

IR (ν_{max}/cm^{-1}, neat): 2953, 2923, 2853, 1707, 1462, 1377, 1250, 1064, 834, 772

(+)-Hydroxyphthioceranic acid 17



TBAF (1.0 M solution in THF, 0.30 mL, 0.27 mmol, 6.0 eq) was added to a solution of carboxylic acid **S44** (33 mg, 0.05 mmol, 1.0 eq) in anhydrous THF (1.0 mL) at room temperature. The reaction mixture was warmed to 60 °C and stirred at this temperature until starting material was consumed (monitored by TLC). The reaction mixture was cooled to room temperature and diluted with water (5.0 mL). The reaction mixture was extracted with Et_2O (3×15 mL). The combined organic phases were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2:Et_2O 100:0 → 95:5) to give (+)-hydroxyphthioceranic acid **17** (23 mg, 84%) as a pale yellow oil.

Spectral data were in accordance with the published values.[19]

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$: +20.8 (*c* 0.9, $CHCl_3$)

Lit.[19] $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{23}}$: +18.8 (*c* 0.9, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.61–3.46 (1H, m, C*H*-OH), 2.68–2.51 (1H, m, C*H*-CO_2H), 1.78 (1H, ddd, *J* = 13.8, 10.1, 4.2 Hz, C*H*H), 1.67–1.51 (7H, m, 7×CH), 1.51–1.37 (5H, m, OH, 2×C*H*H, CH_2), 1.35–1.26 (25H, m, CH*H*, 12×CH_2), 1.25–1.16 (8H, m, 5×C*H*H, CH_3), 1.04 (1H, ddd, *J* = 13.8, 9.5, 4.5 Hz, CH*H*), 0.94–0.78 (30H, m, 6×CH*H*, 8×CH_3)

^{13}C NMR (126 MHz, $CDCl_3$): δ 181.9 (C=O), 74.3 (CH-OH), 45.5 (2×CH_2), 45.43 (CH_2), 45.38 (2×CH_2), 40.98 (CH_2), 40.97 (CH_2), 37.2 (CH), 35.0 (CH), 34.9 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.69 (CH_2), 29.68 (CH_2), 29.67 (CH_2), 29.65 (CH_2), 29.64 (CH_2), 29.63 (CH_2), 29.4 (CH_2), 28.3 (CH), 27.8 (CH), 27.7 (CH), 27.6 (CH), 27.5 (2×CH), 26.3 (CH_2), 22.7 (CH_2), 21.54 (CH_3), 21.49 (CH_3), 21.23 (CH_3), 21.22 (CH_3), 21.0 (CH_3), 20.5 (CH_3), 18.3 (CH_3), 14.1 (CH_3), 14.0 (CH_3)

HRMS (ESI$^-$): calculated for $C_{40}H_{79}O_3$ [M–H$^+$]: 607.6035; found 607.6034

IR (ν_{max}/cm^{-1}, neat): 3412, 2953, 2921, 2852, 1707, 1460, 1377, 1227, 973, 803

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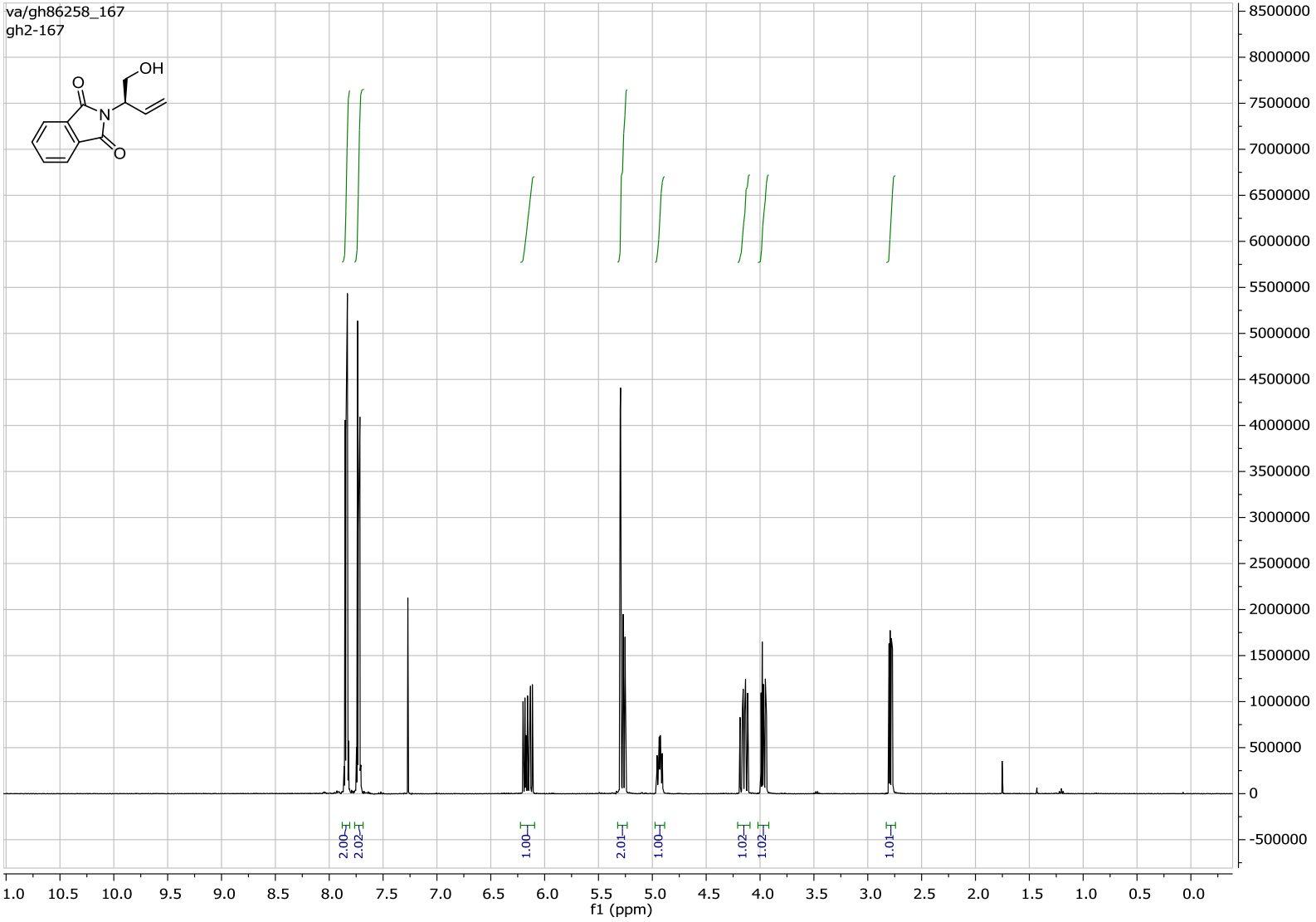
NMR Spectra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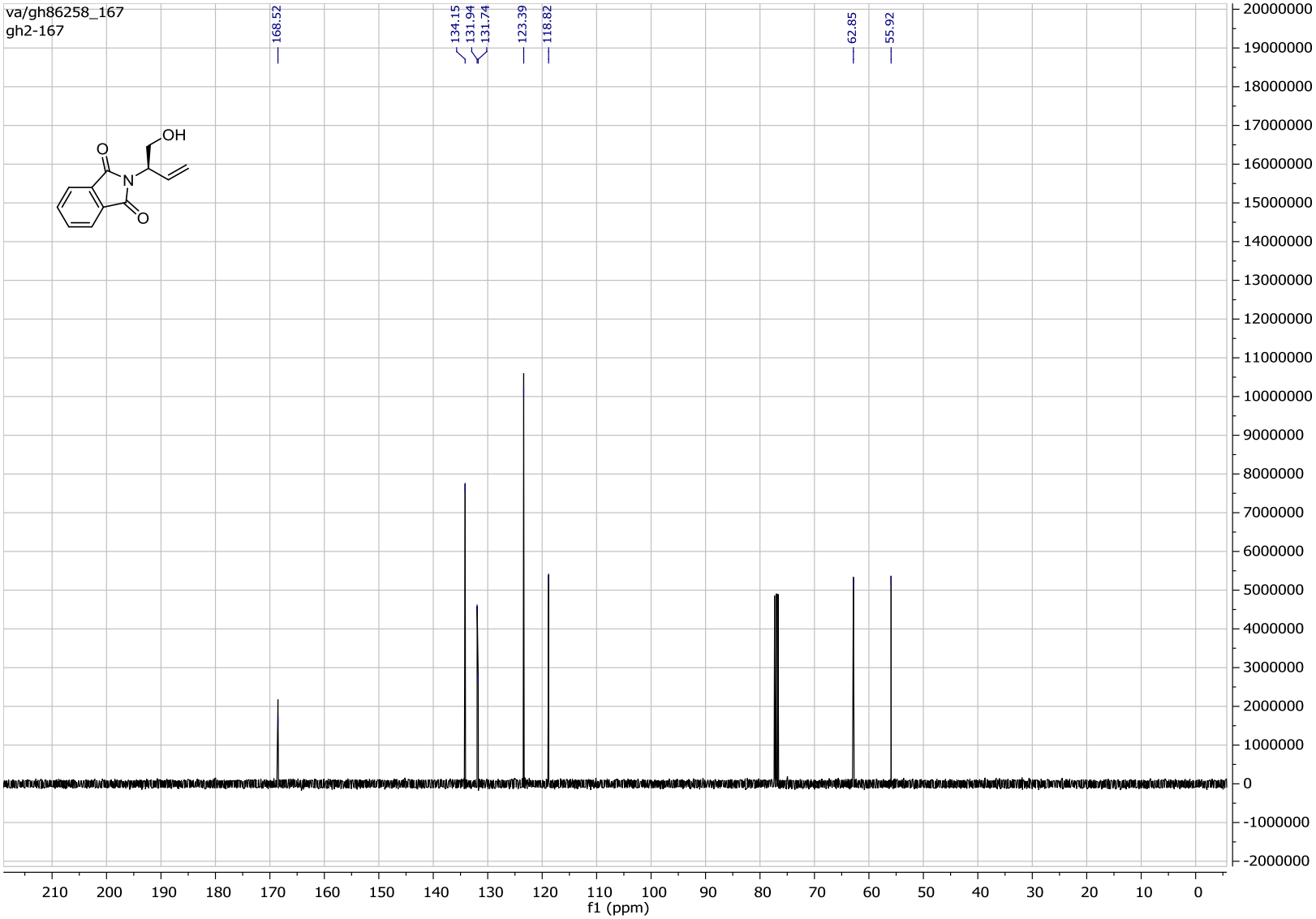
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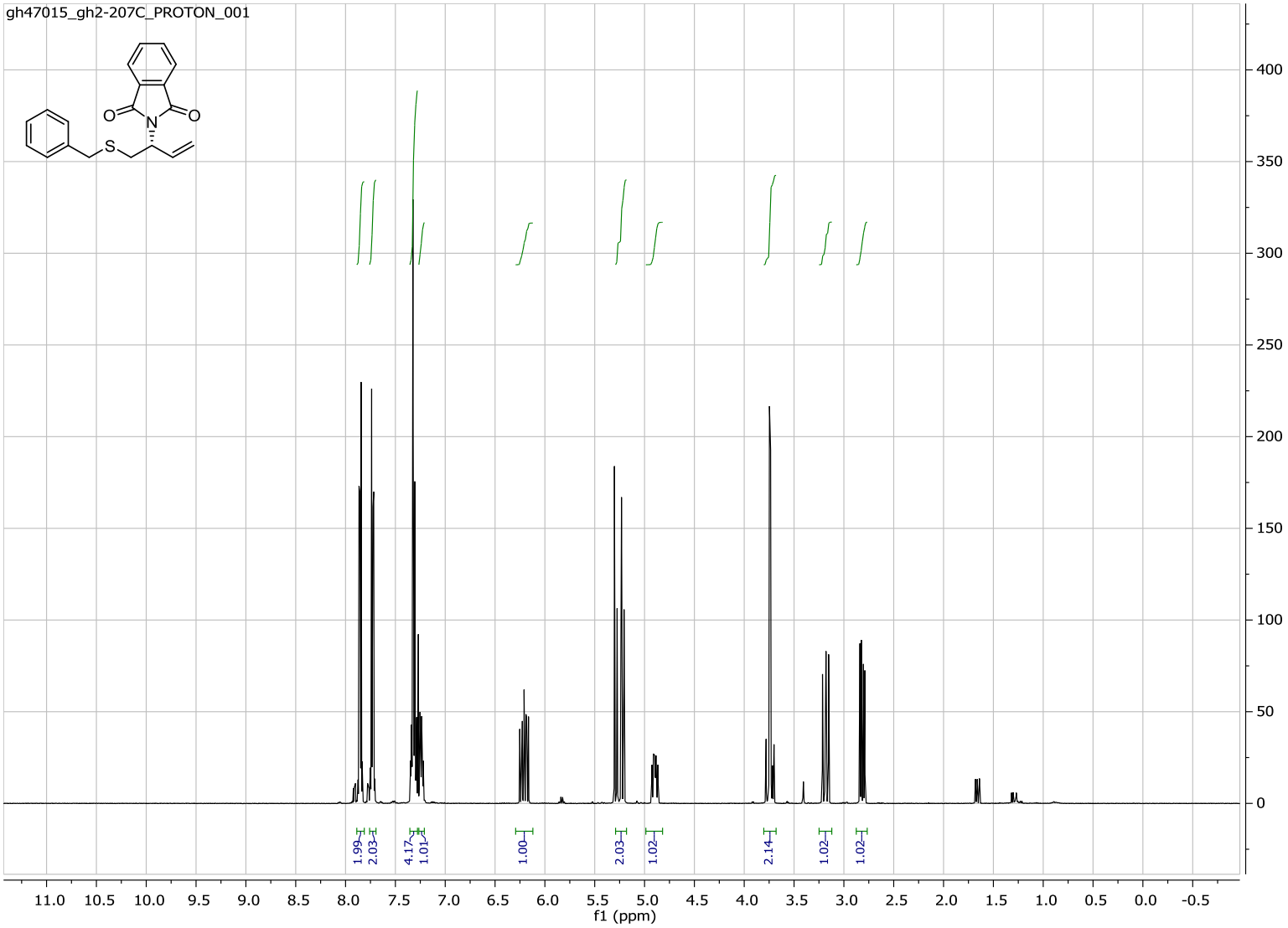
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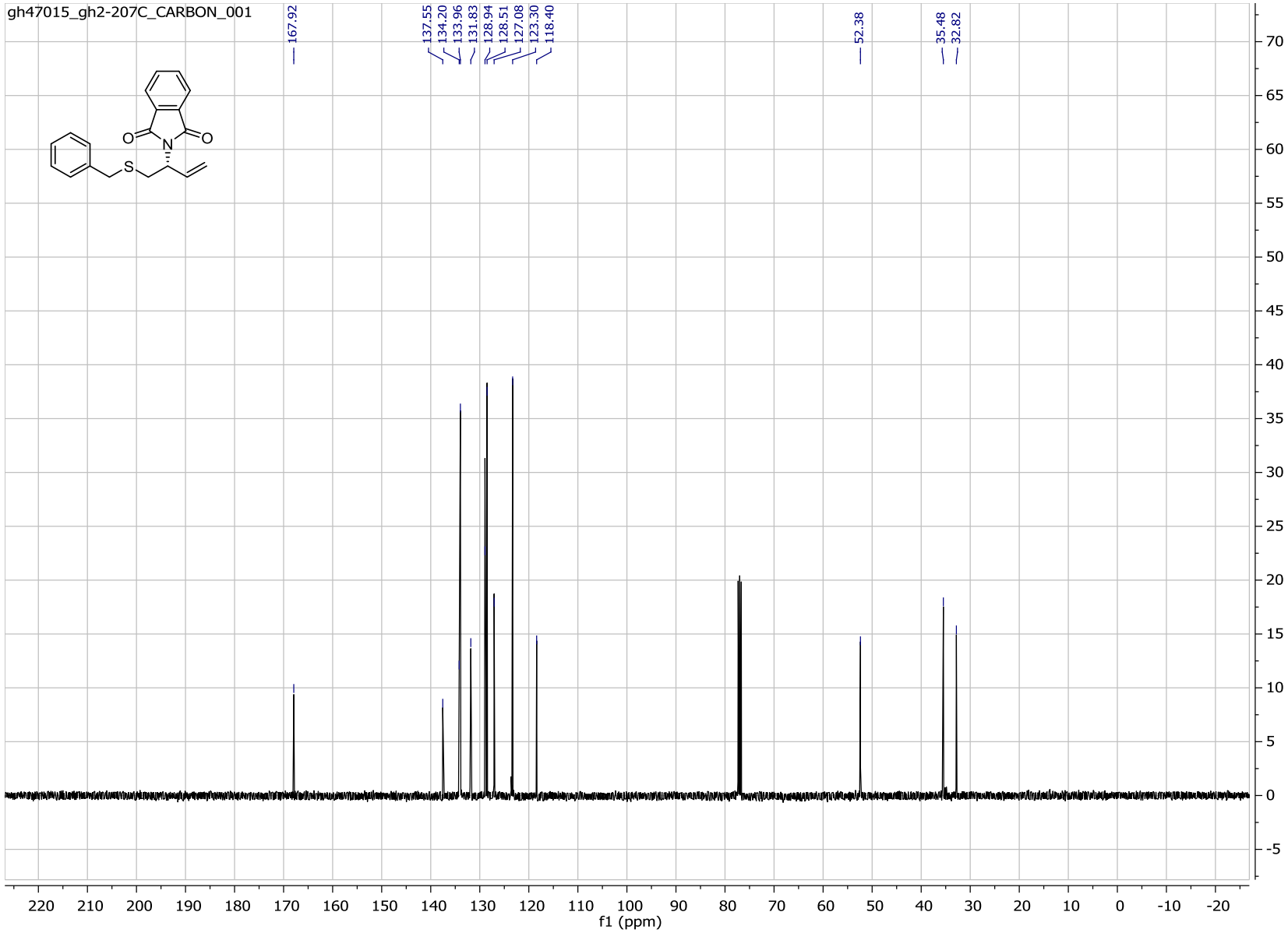
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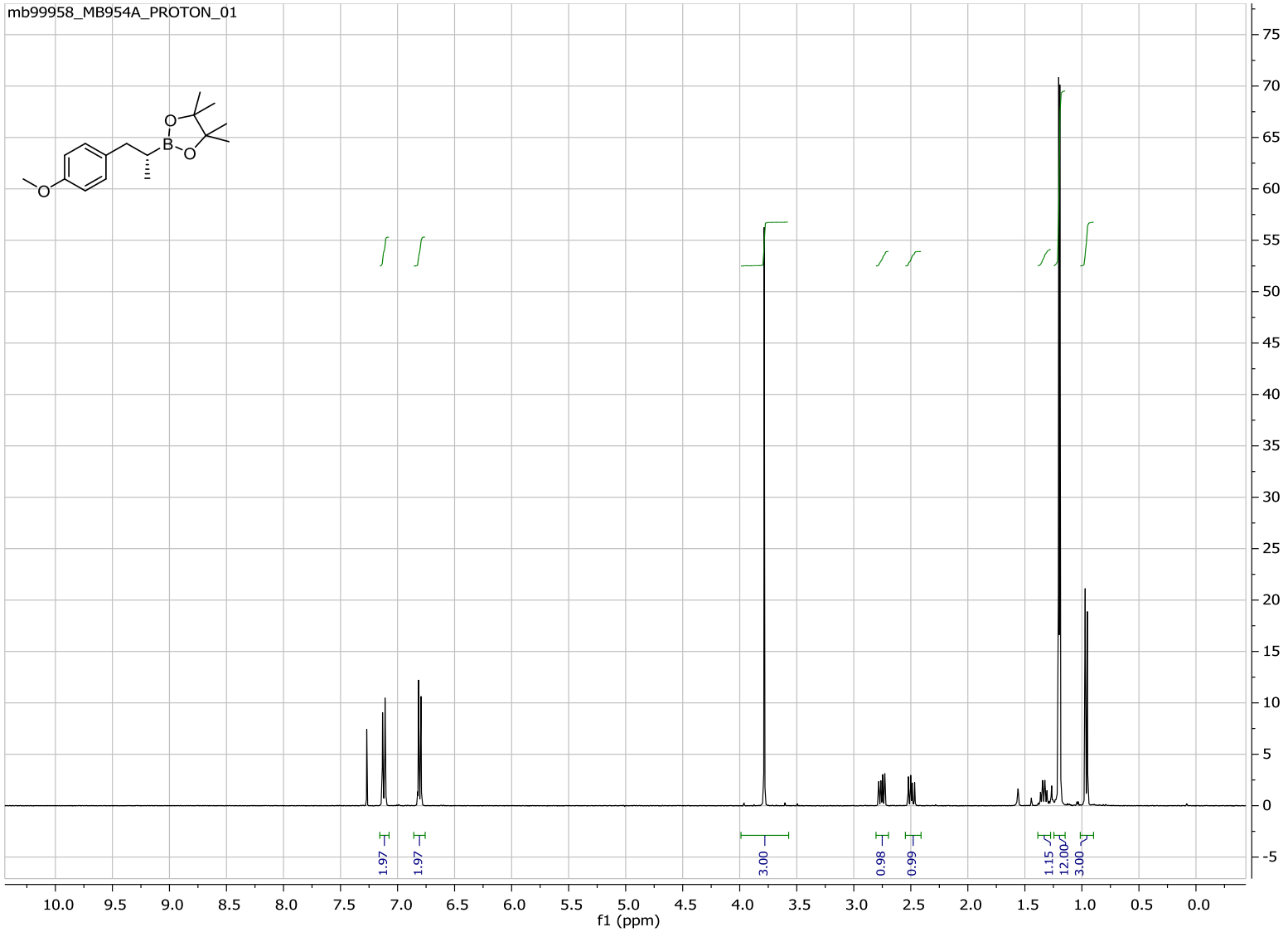
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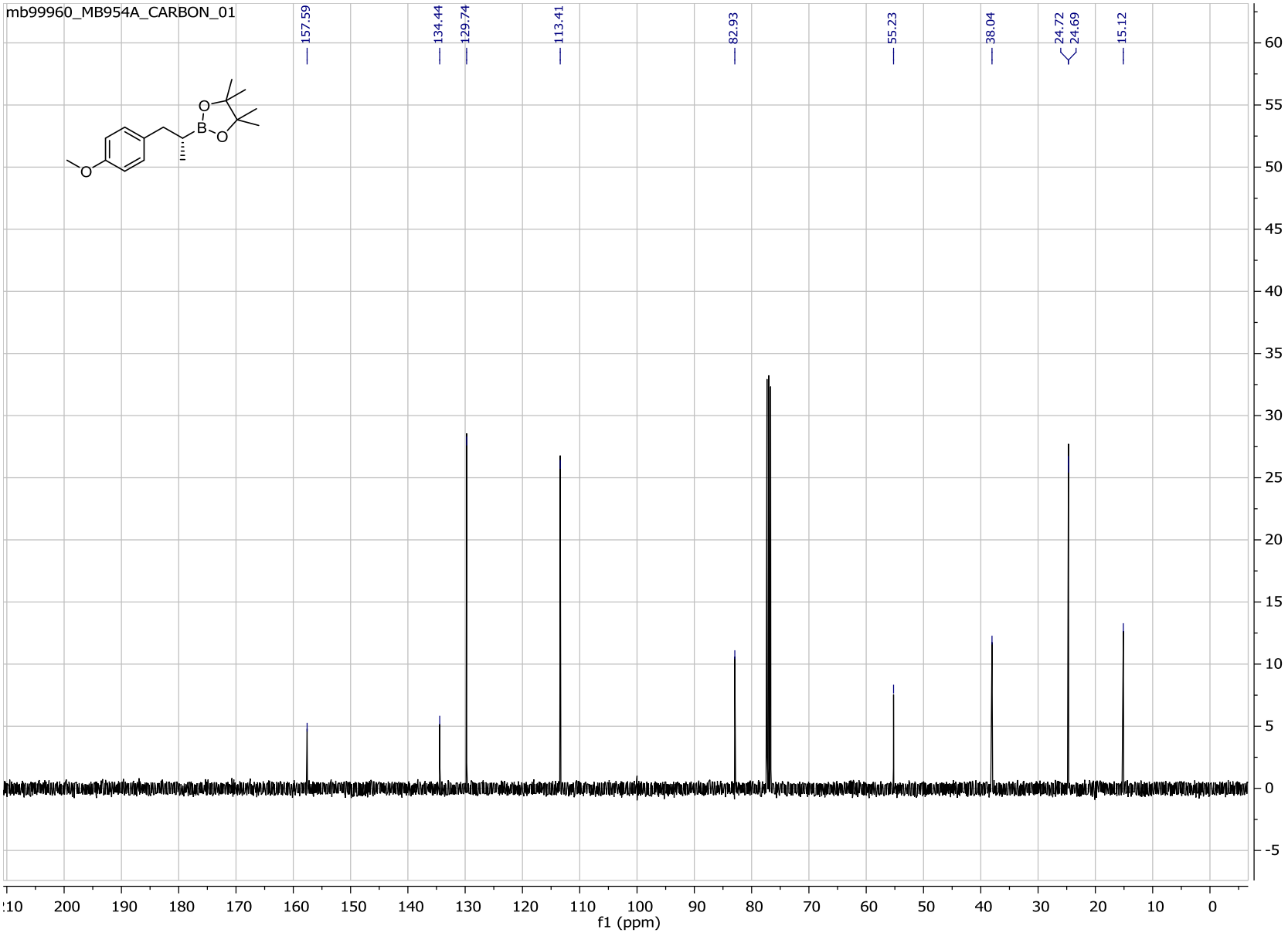
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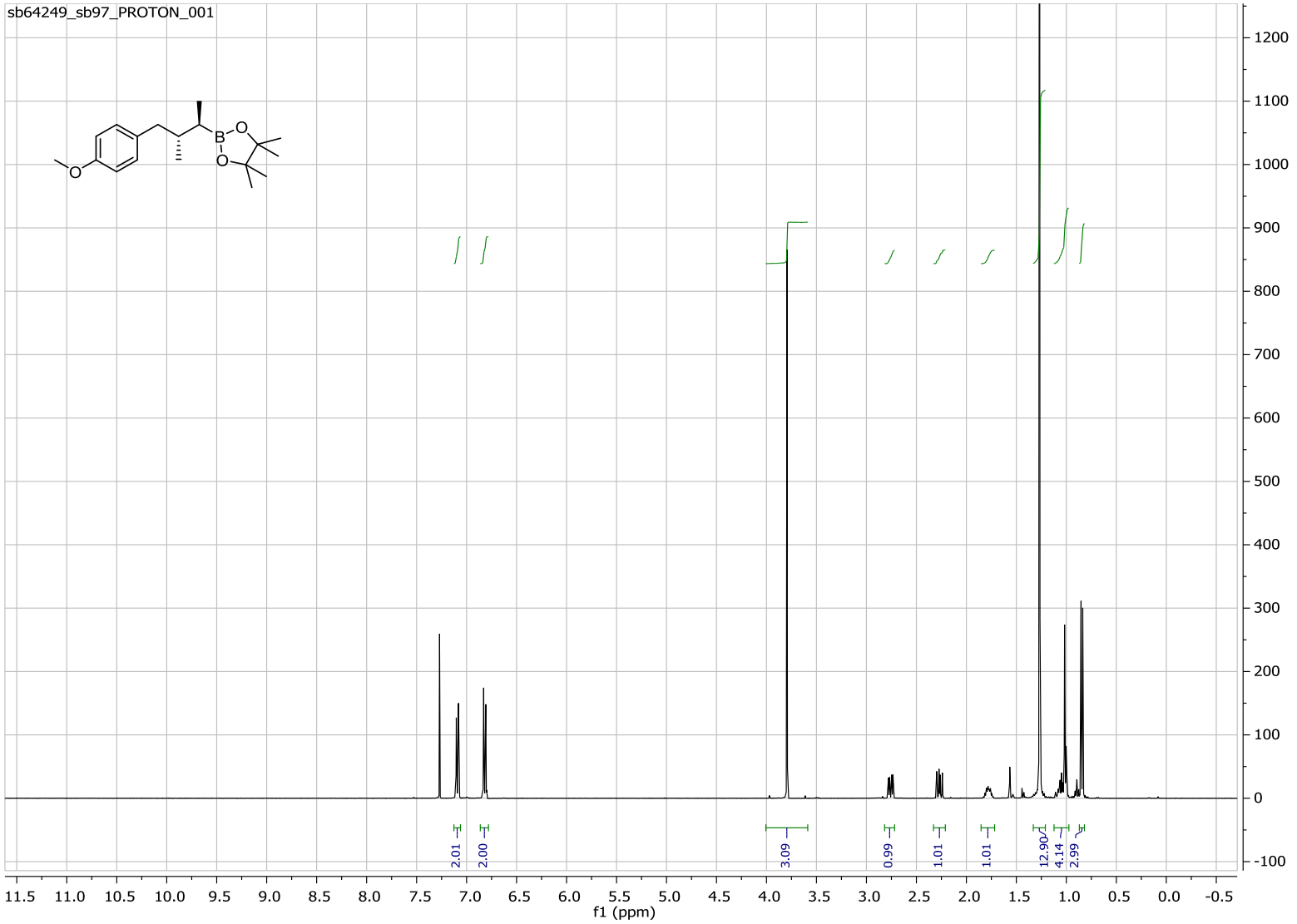
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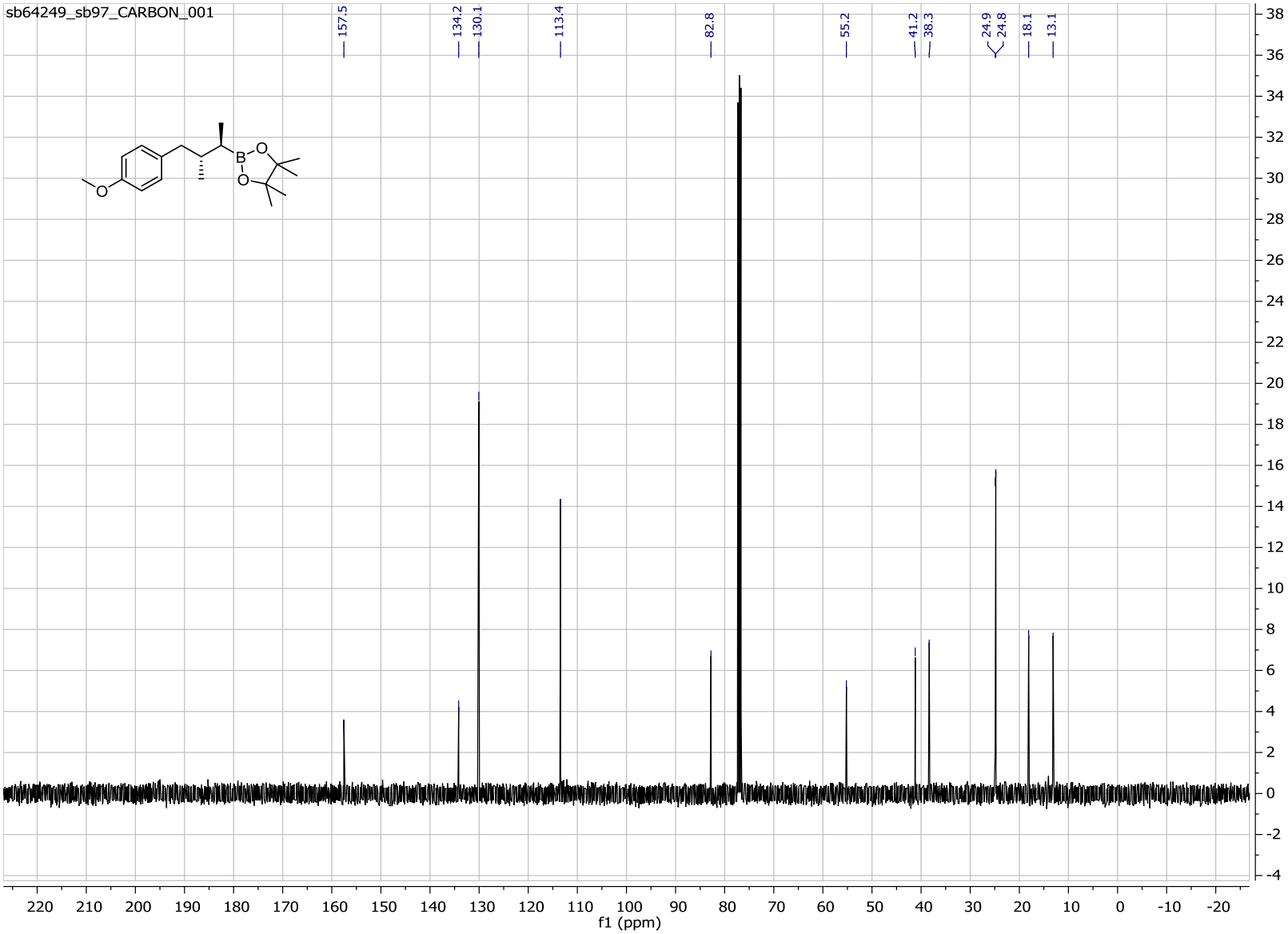
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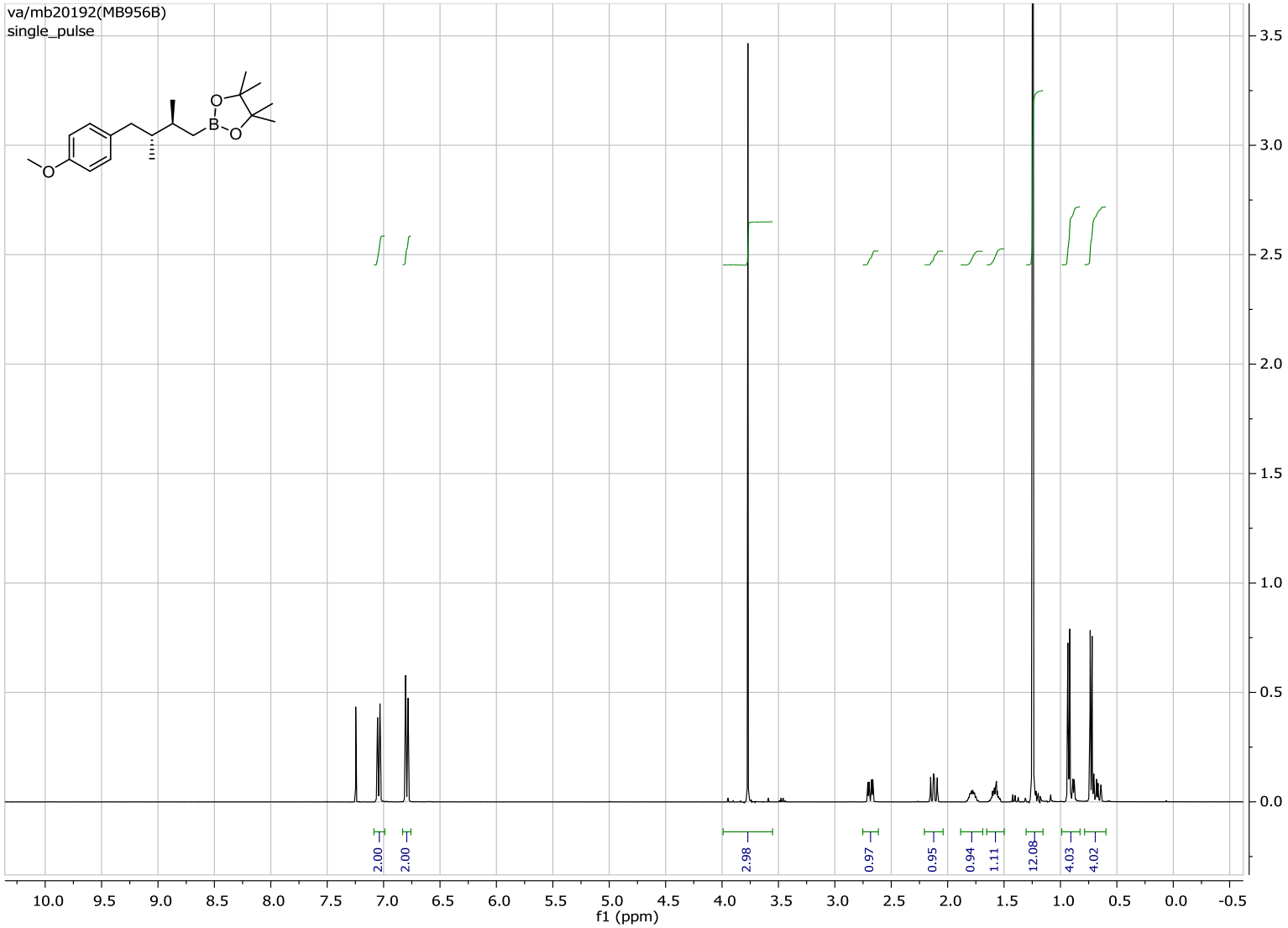
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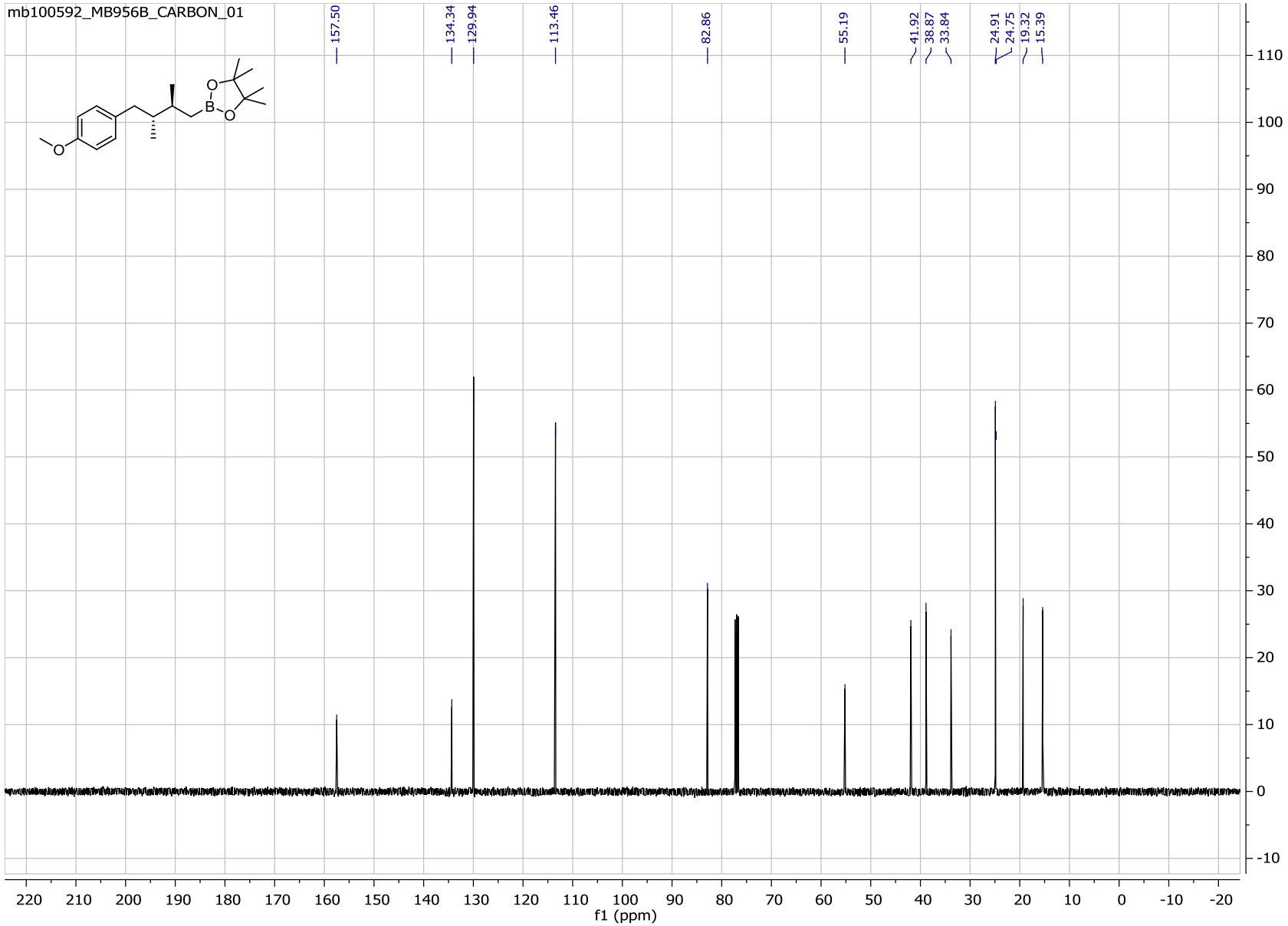
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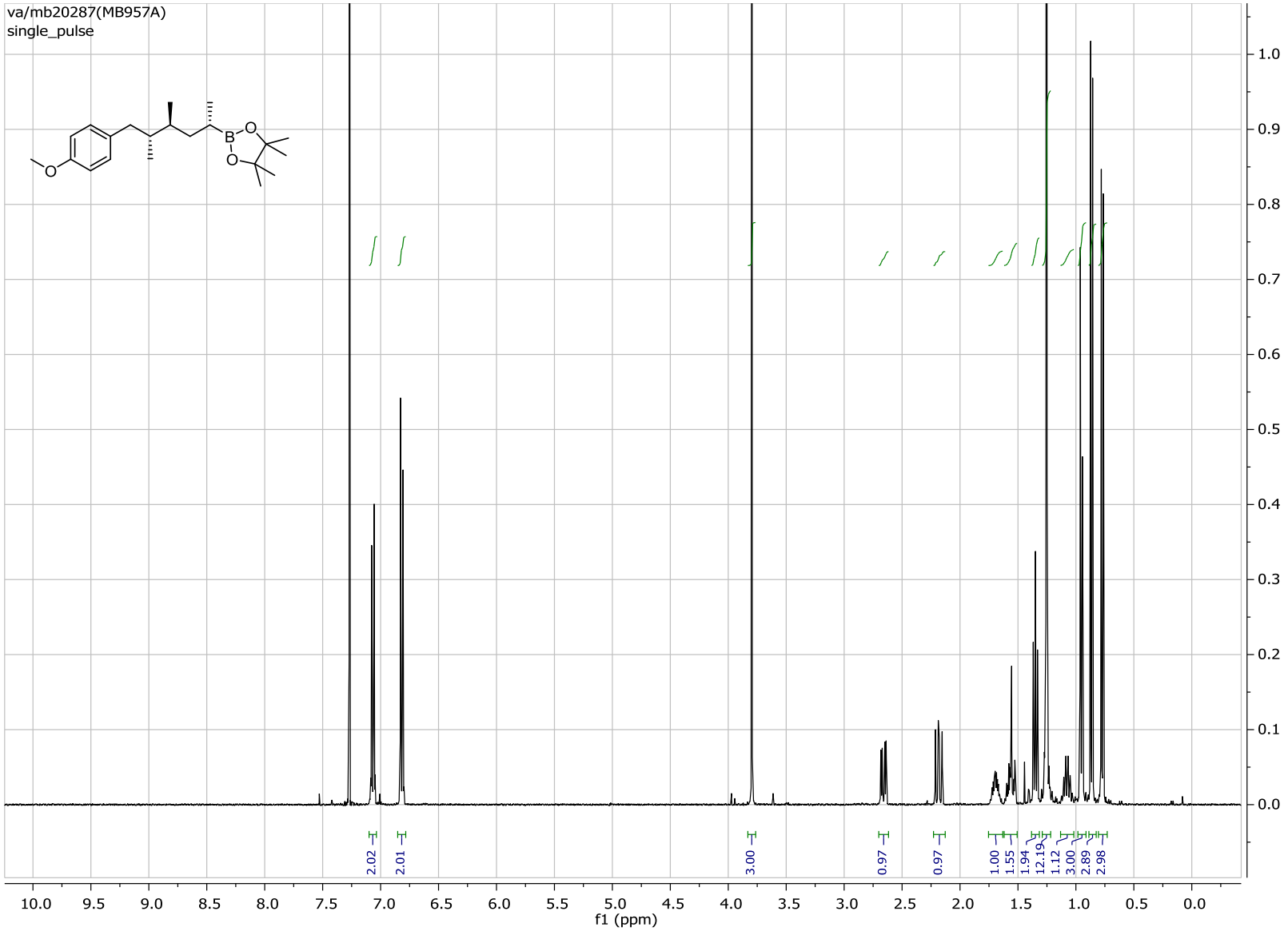
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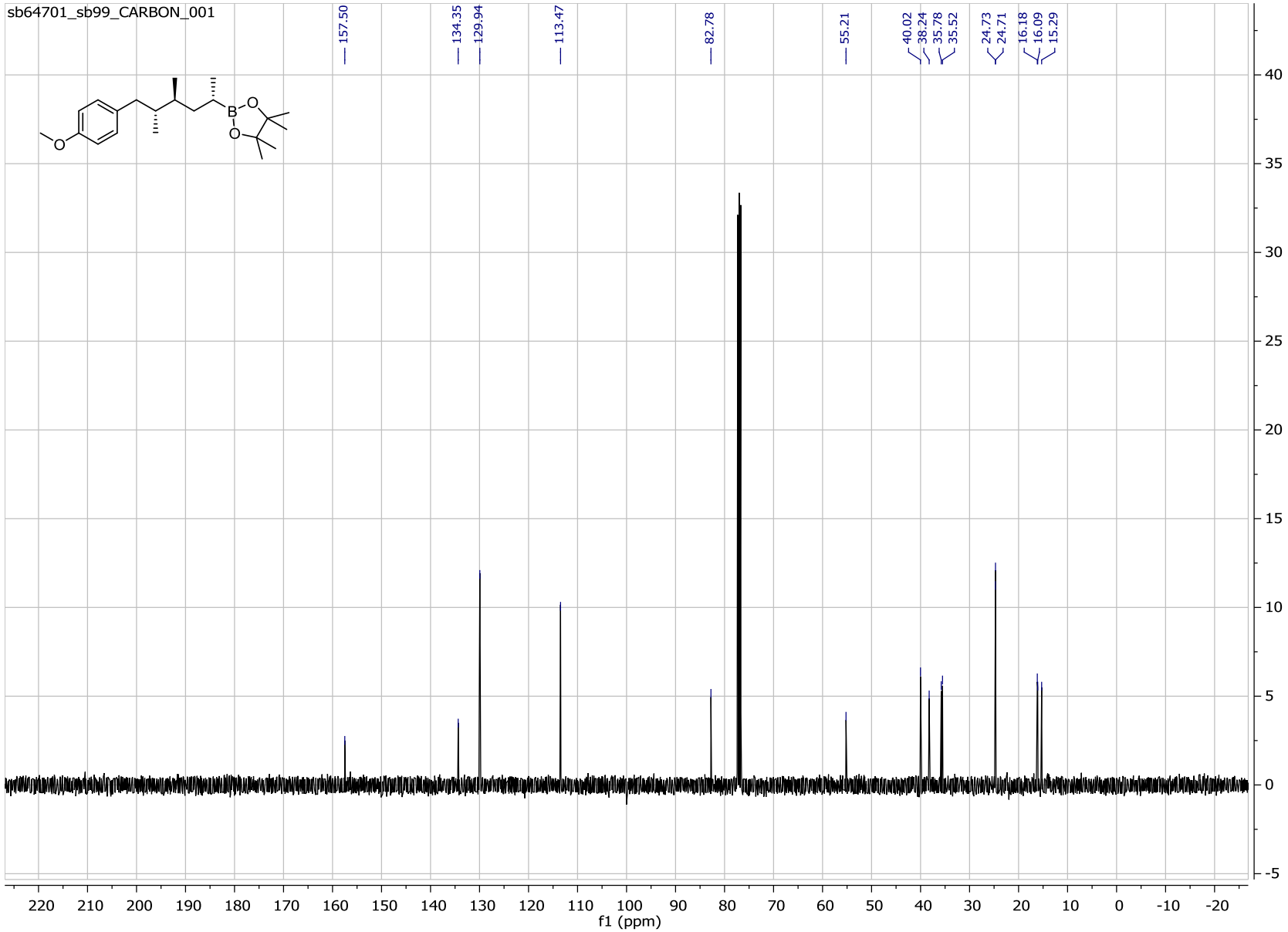
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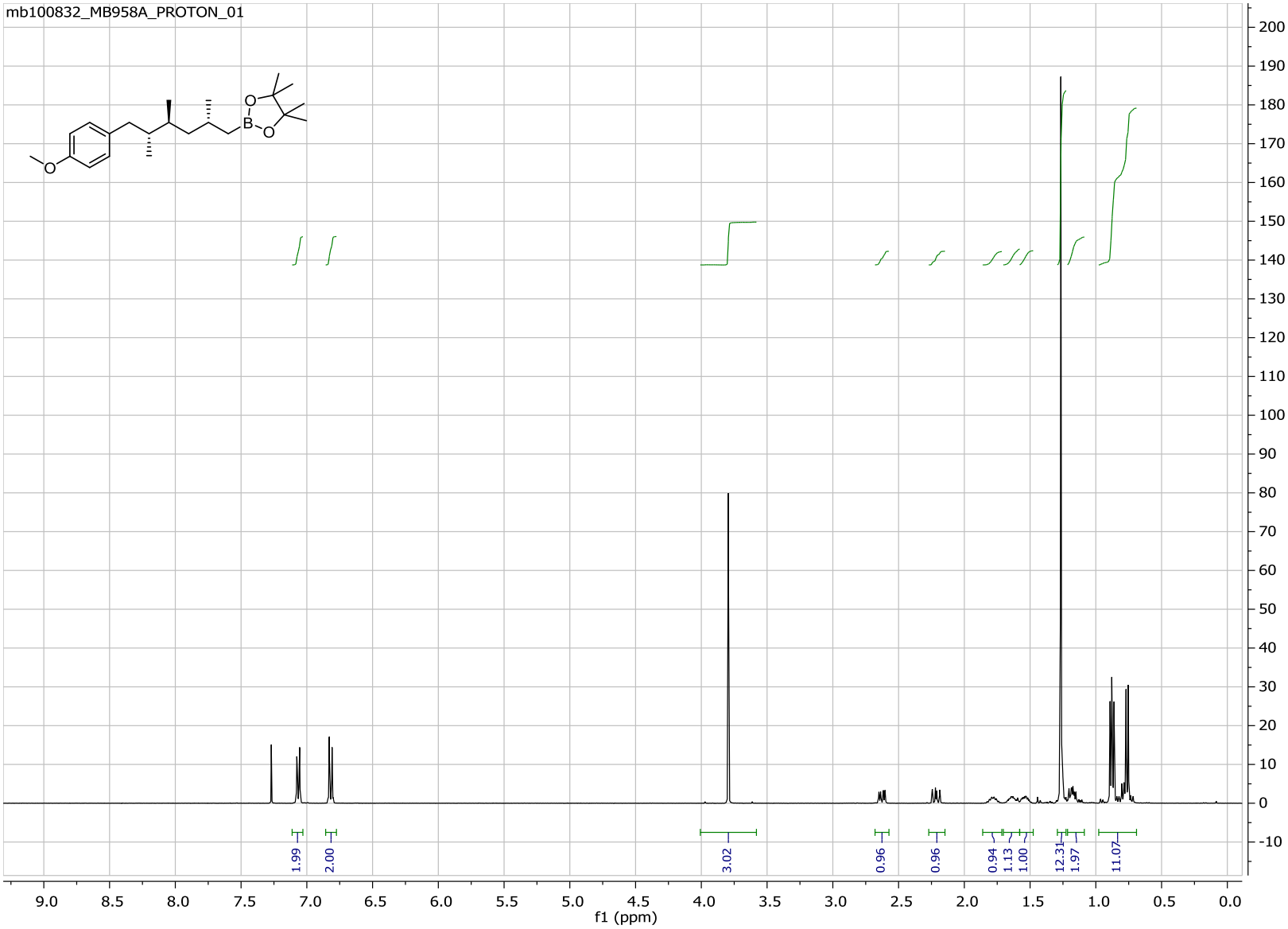
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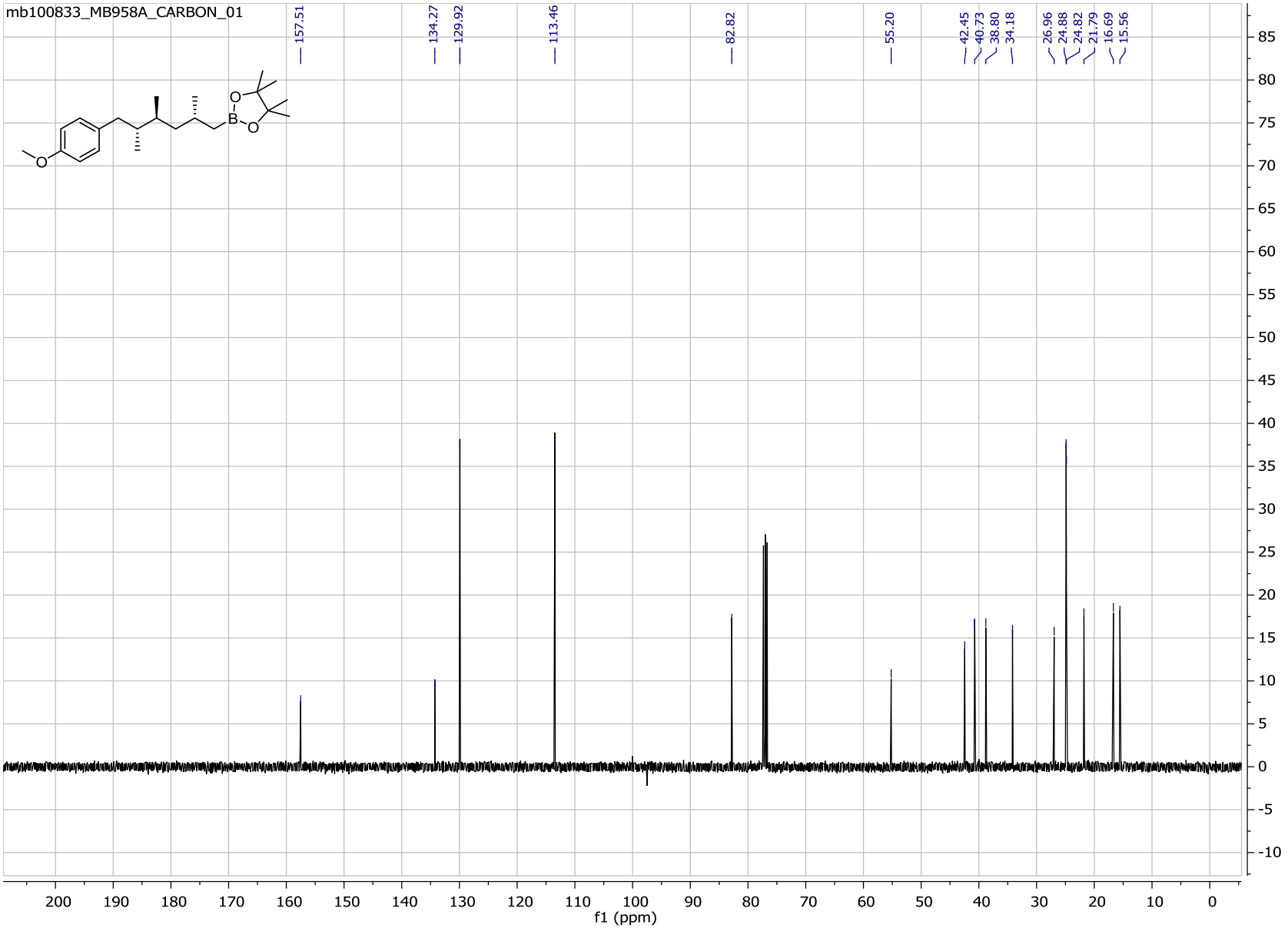
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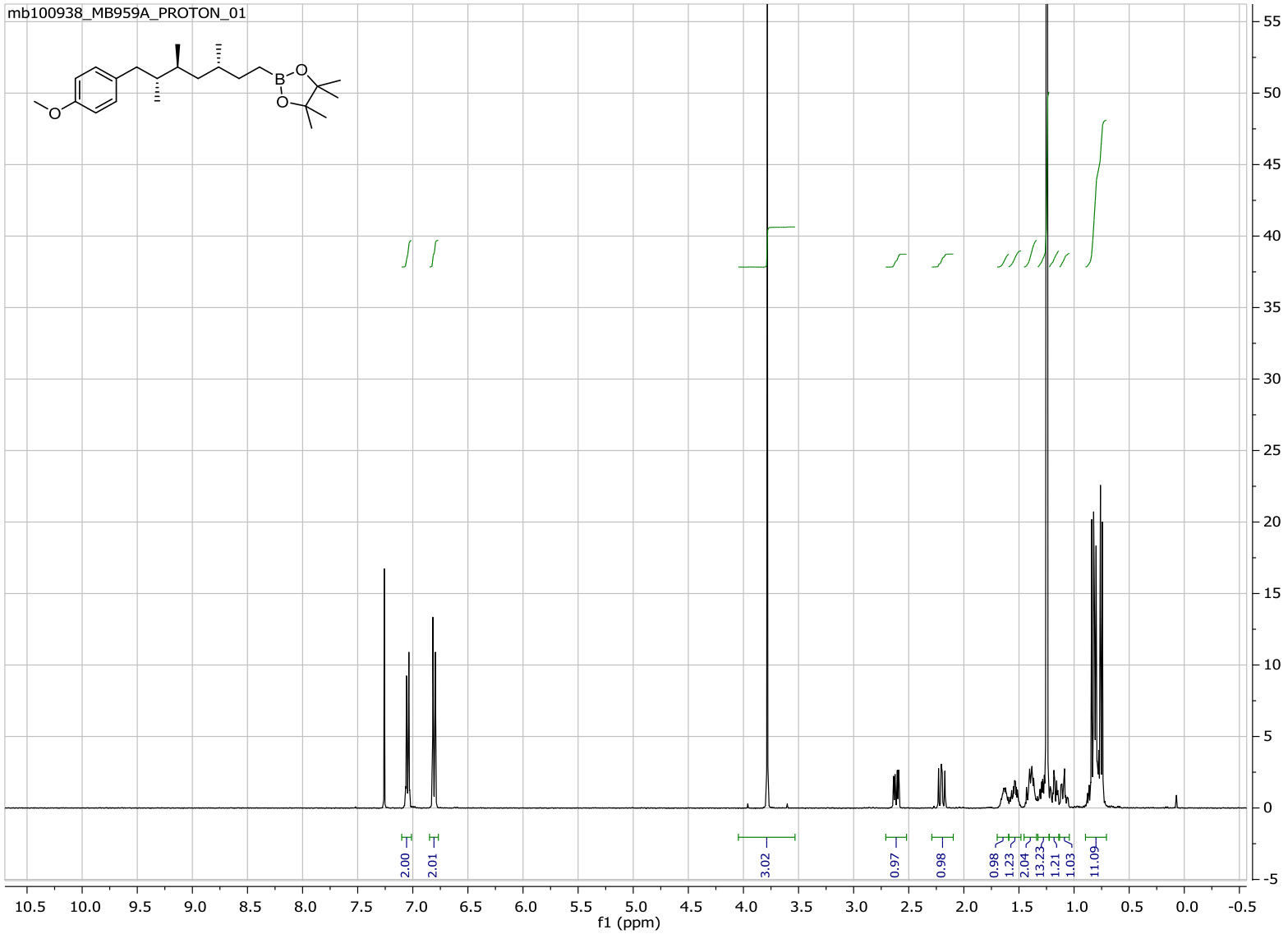
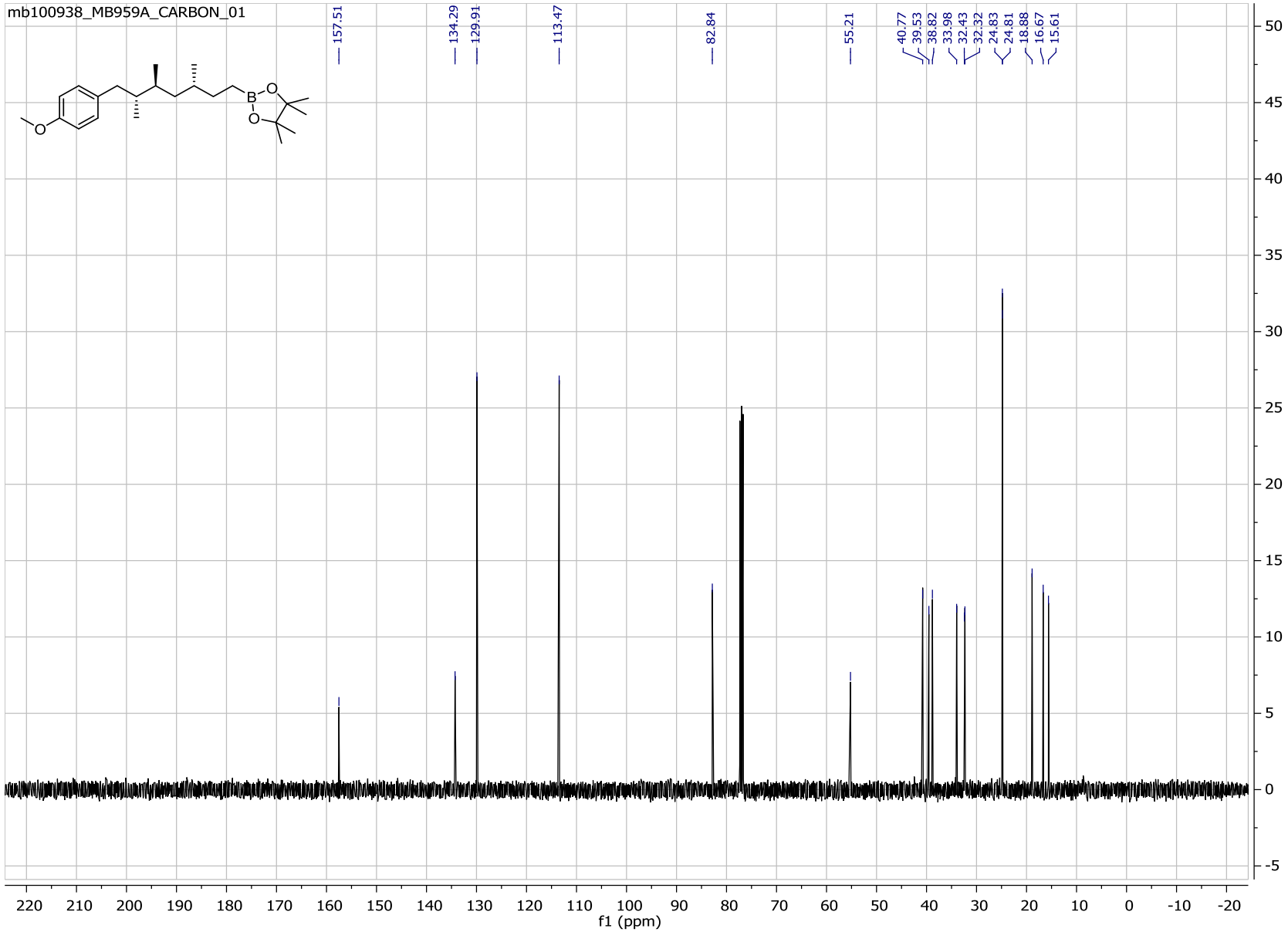
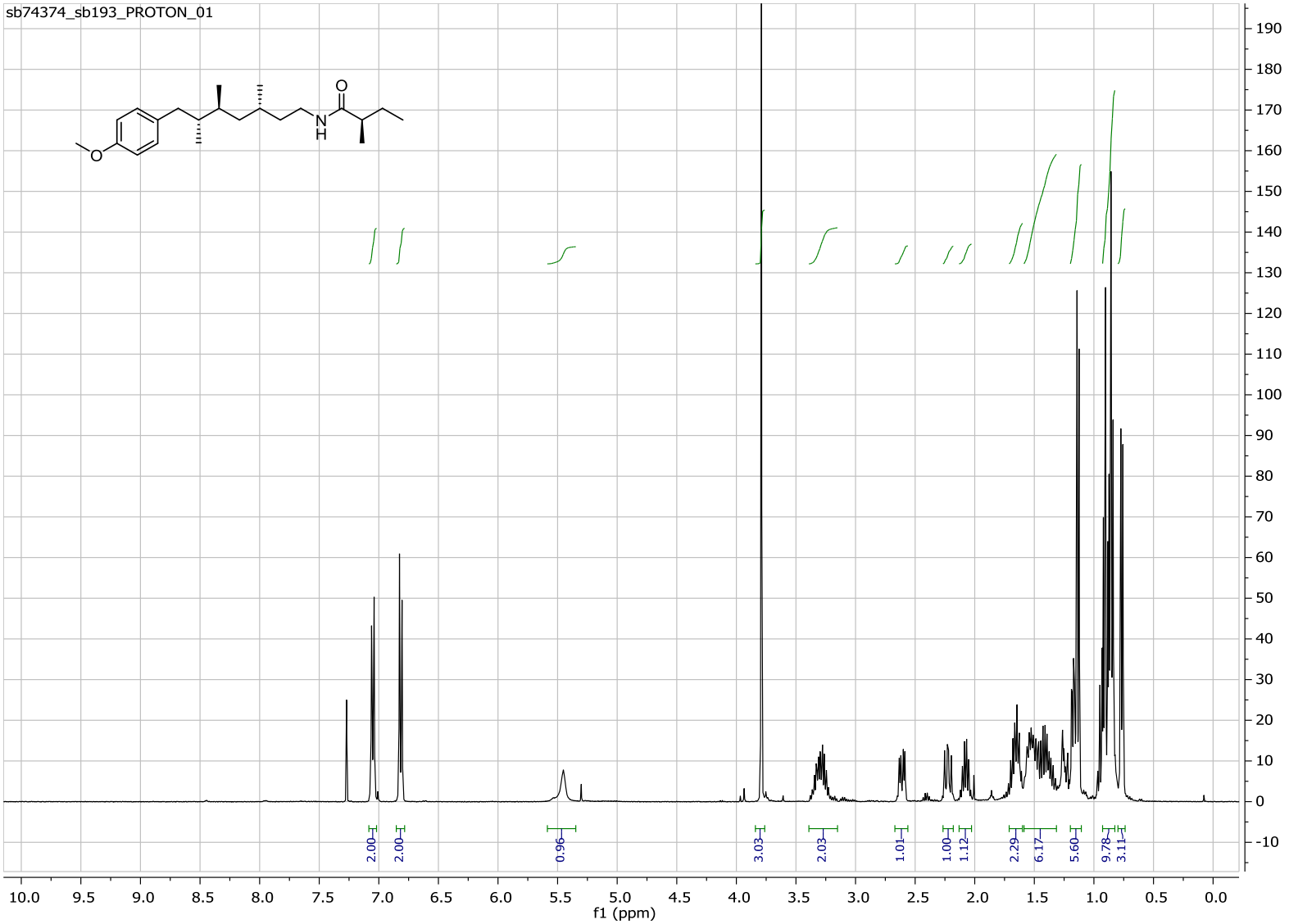
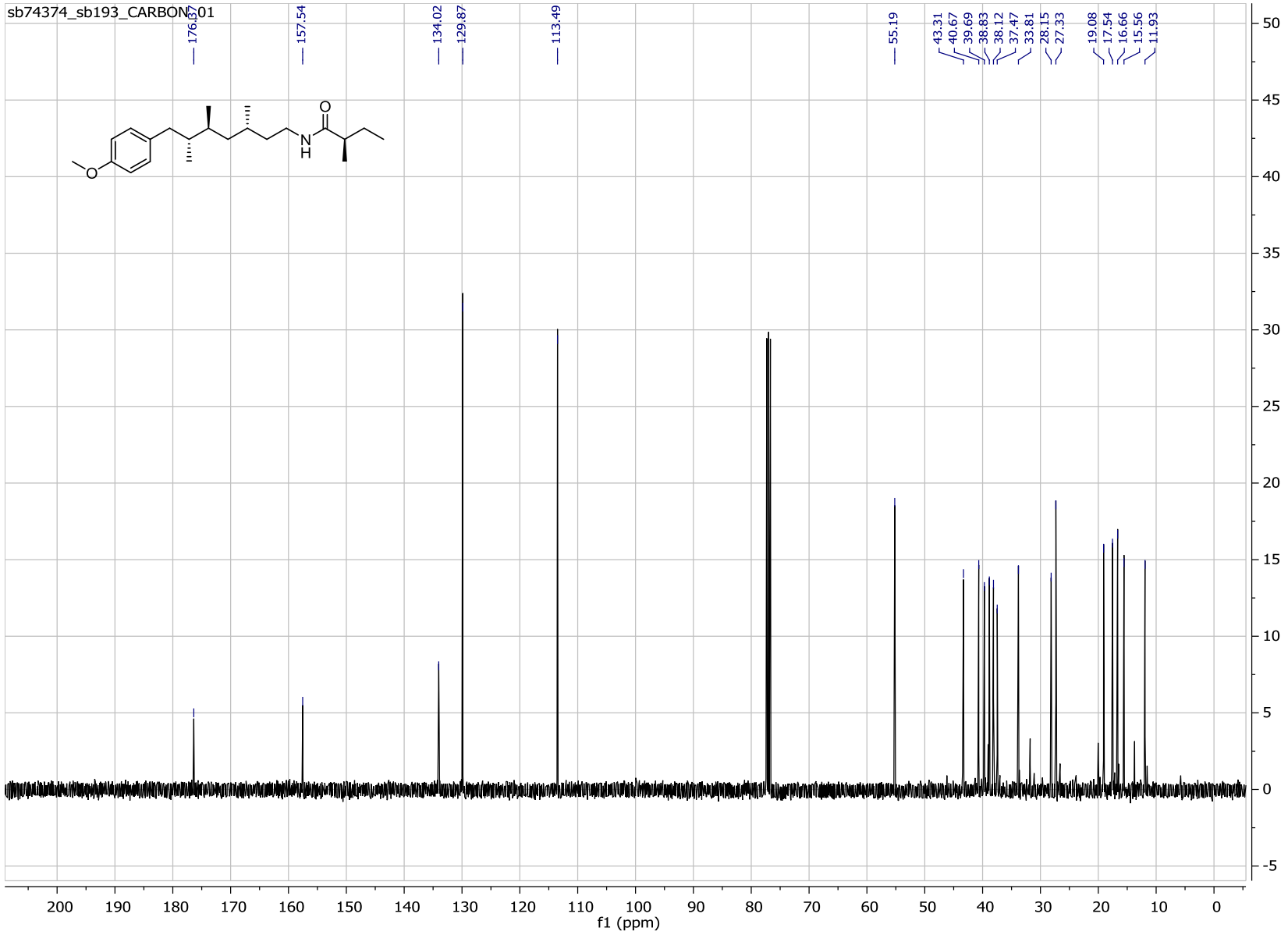
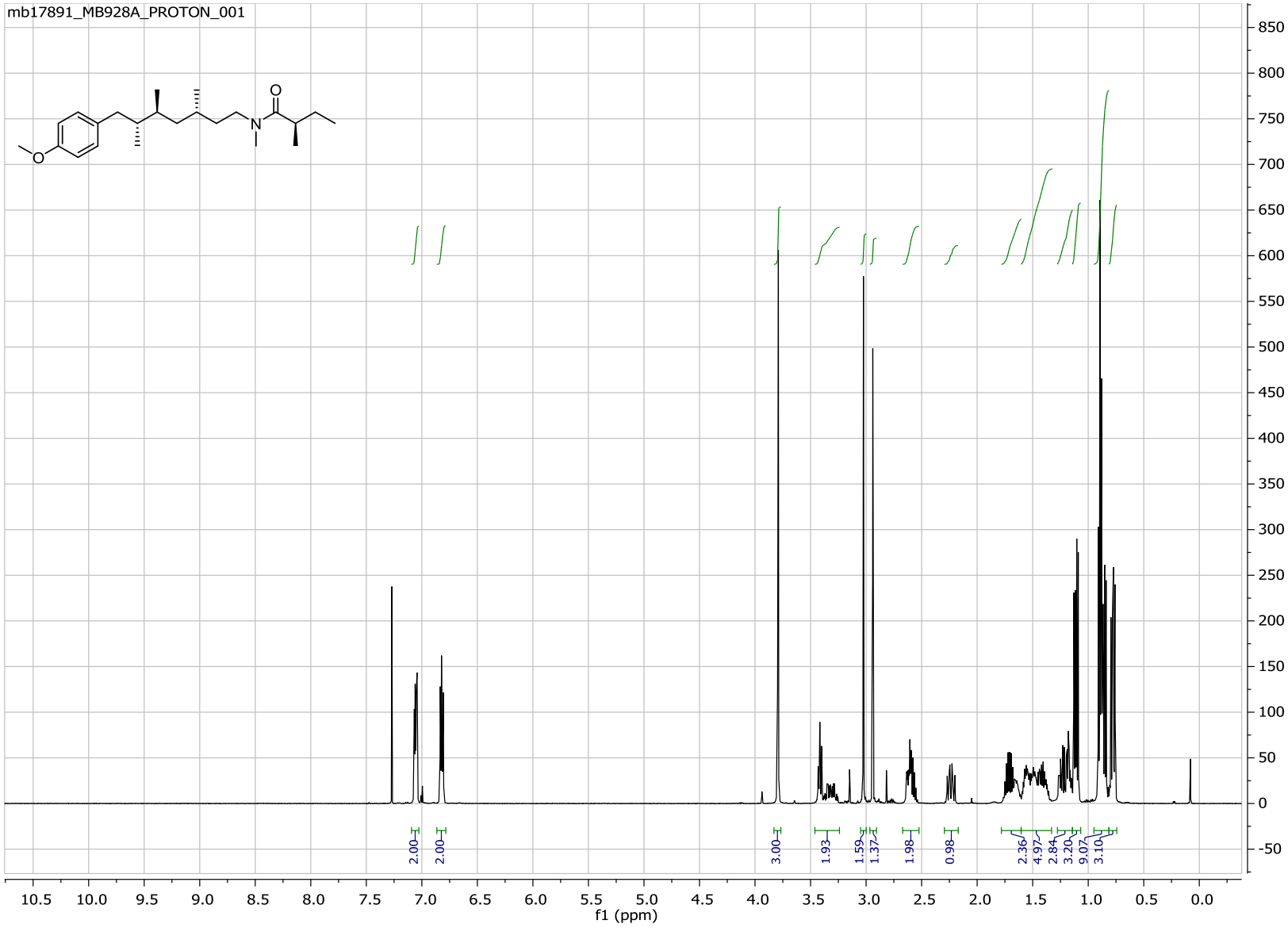
42.45
40.73
38.80
34.18
26.96
24.88
24.82
21.79
16.69
15.56
O
B
O
O
f1 (ppm)

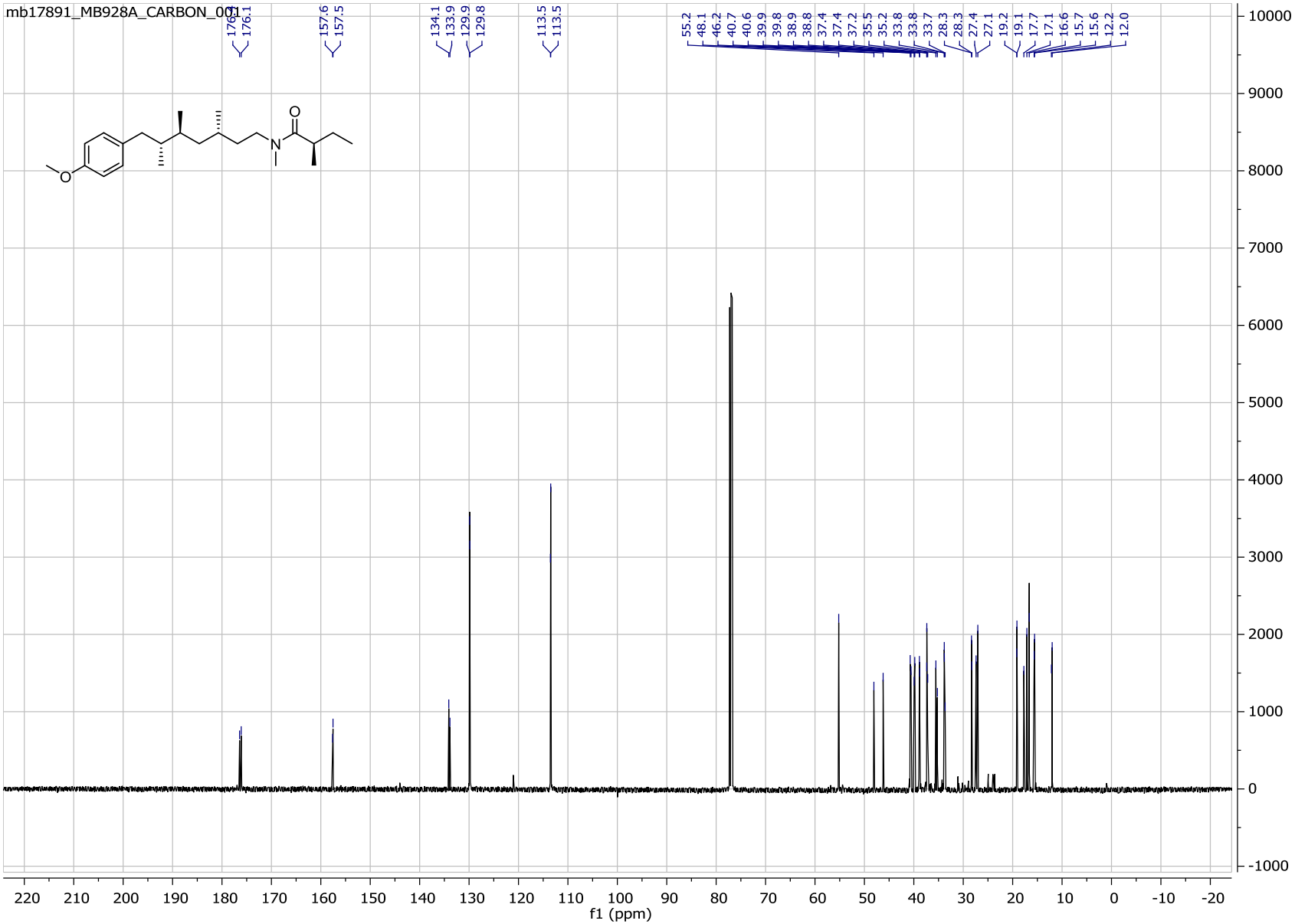

mb100938_MB959A_PROTON_01
O
B
O
O
2.00
2.01
3.02
0.97
0.98
0.98
1.23
2.04
13.23
1.21
1.03
11.09
f1 (ppm)

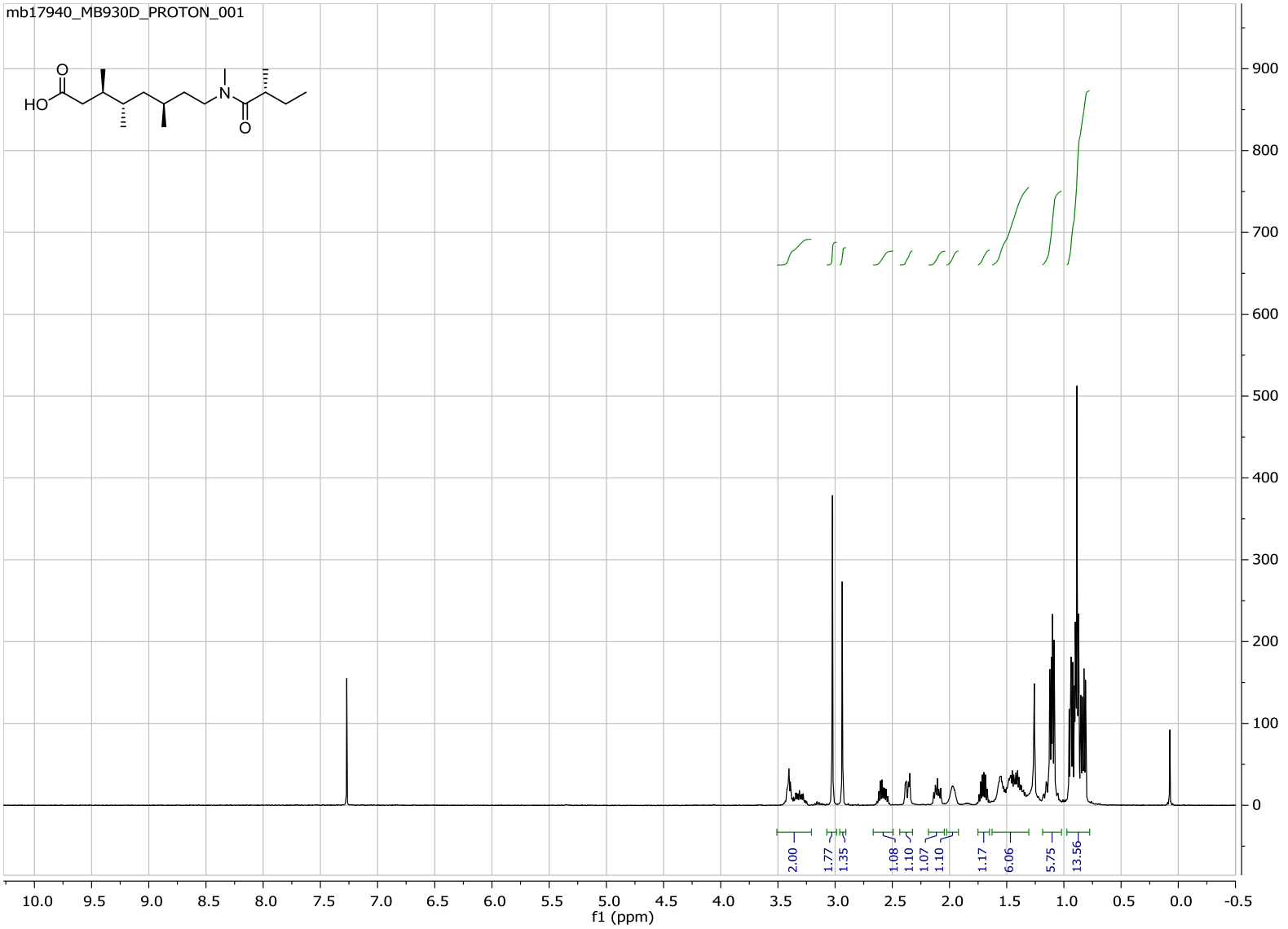

mb100938_MB959A_CARBON_01
157.51
134.29
129.91
113.47
82.84
55.21
40.77
39.53
38.82
33.98
32.43
32.32
24.83
24.81
18.88
16.67
15.61
f1 (ppm)

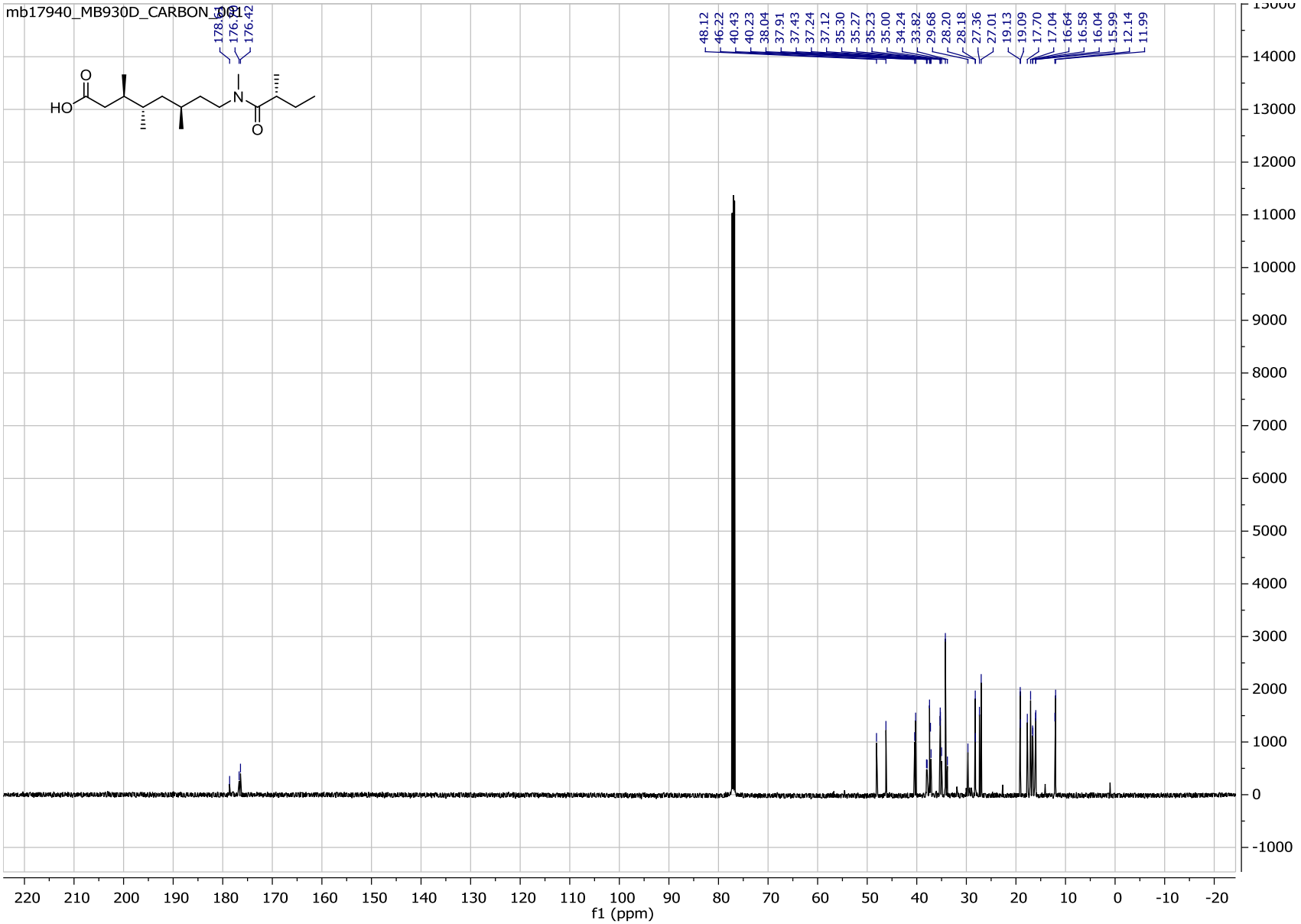

sb74374_sb193_PROTON_01
O
N
H
O
2.00
2.00
0.96
3.03
2.03
1.01
1.00
1.12
2.29
6.17
5.60
9.78
3.11
f1 (ppm)

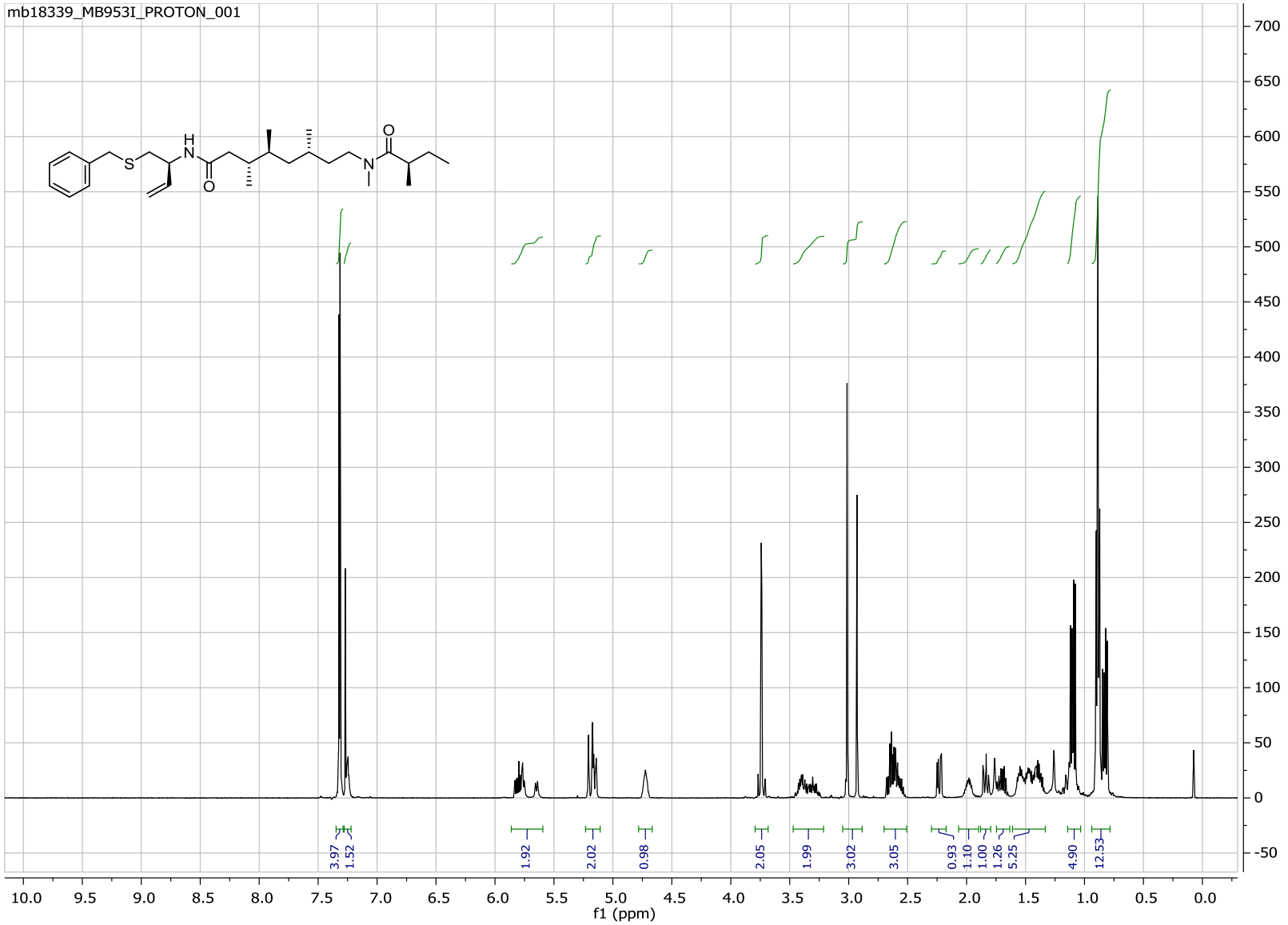

sb74374_sb193_CARBON_01
176.57
157.54
134.02
129.87
113.49
55.19
43.31
40.67
39.69
38.83
38.12
37.47
33.81
28.15
27.33
19.08
17.54
16.66
15.56
11.93
O
N
H
O
50
45
40
35
30
25
20
15
10
5
0
-5
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


mb17891_MB928A_PROTON_001
O
N
O
2.00
2.00
3.00
1.93
1.59
1.37
1.98
0.98
2.36
4.97
2.84
3.20
9.07
3.10
f1 (ppm)

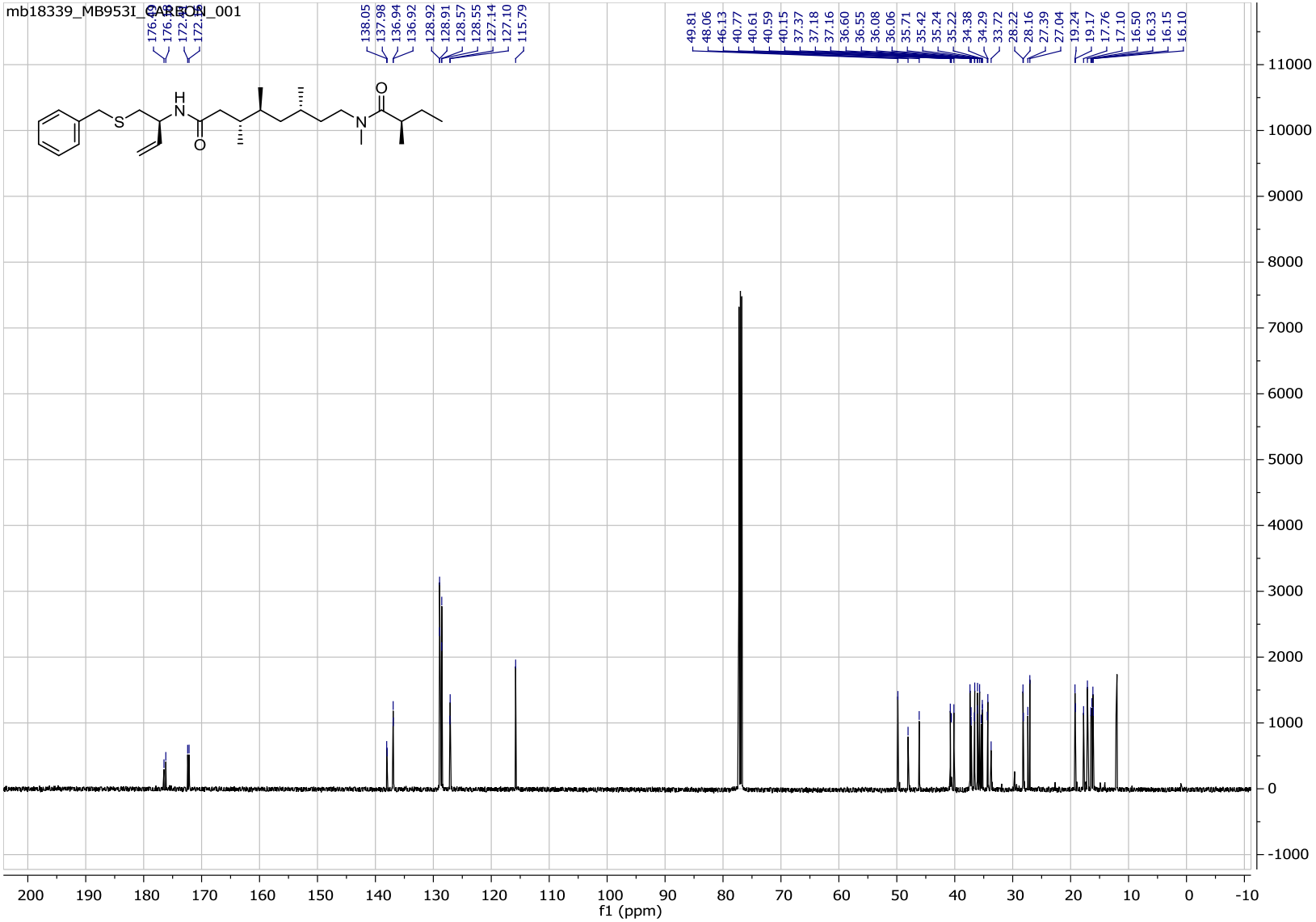

mb17891_MB928A_CARBON_001
176.2
176.1
157.6
157.5
134.1
133.9
129.9
129.8
113.5
113.5
55.2
48.1
46.2
40.7
40.6
39.9
39.8
38.9
38.8
37.4
37.4
37.2
35.5
35.2
33.8
33.7
28.3
28.3
27.4
27.1
19.2
19.1
17.7
17.1
16.6
15.7
15.6
12.2
12.0
O
N
O
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

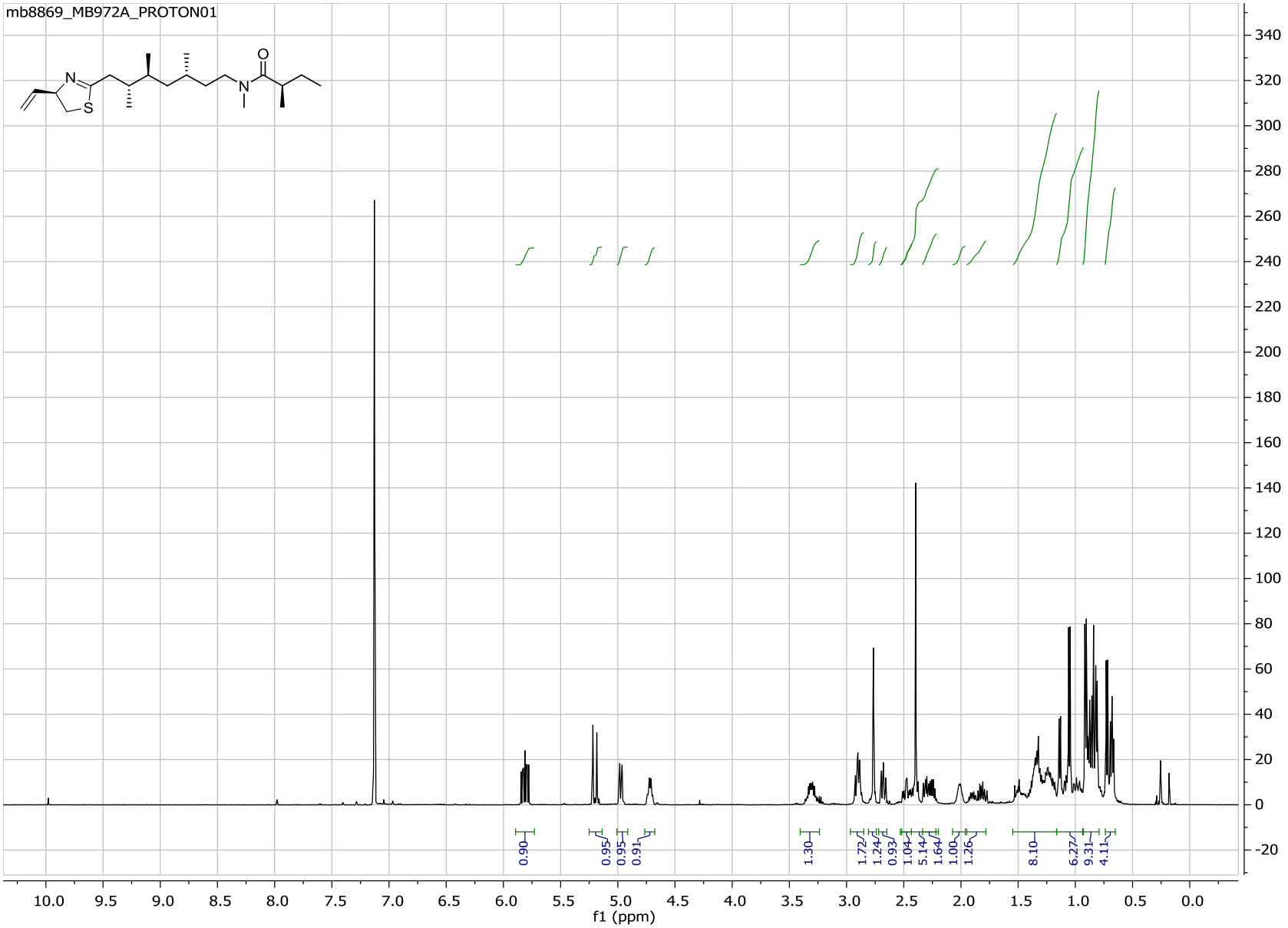

mb17940_MB930D_PROTON_001
HO
O
N
O
900
800
700
600
500
400
300
200
100
0
2.00
1.77
1.35
1.08
1.10
1.07
1.10
1.17
6.06
5.75
13.56
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

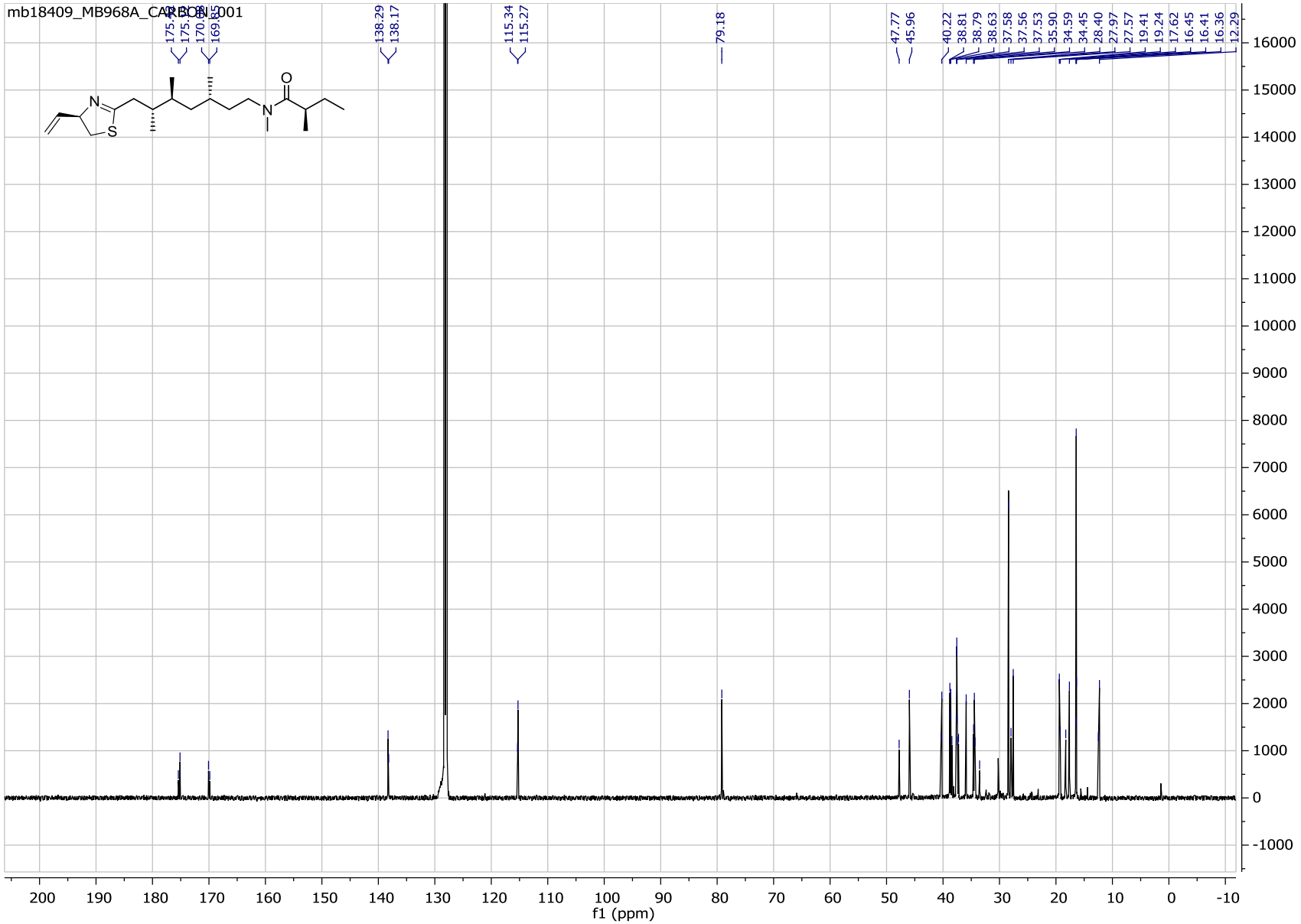

mb17940_MB930D_CARBON_001
178.55
176.01
176.42
48.12
46.22
40.43
40.23
38.04
37.91
37.43
37.24
37.12
35.30
35.27
35.23
35.00
34.24
33.82
29.68
28.20
28.18
27.36
27.01
19.13
19.09
17.70
17.04
16.64
16.58
16.04
15.99
12.14
11.99
HO
O
N
O
f1 (ppm)

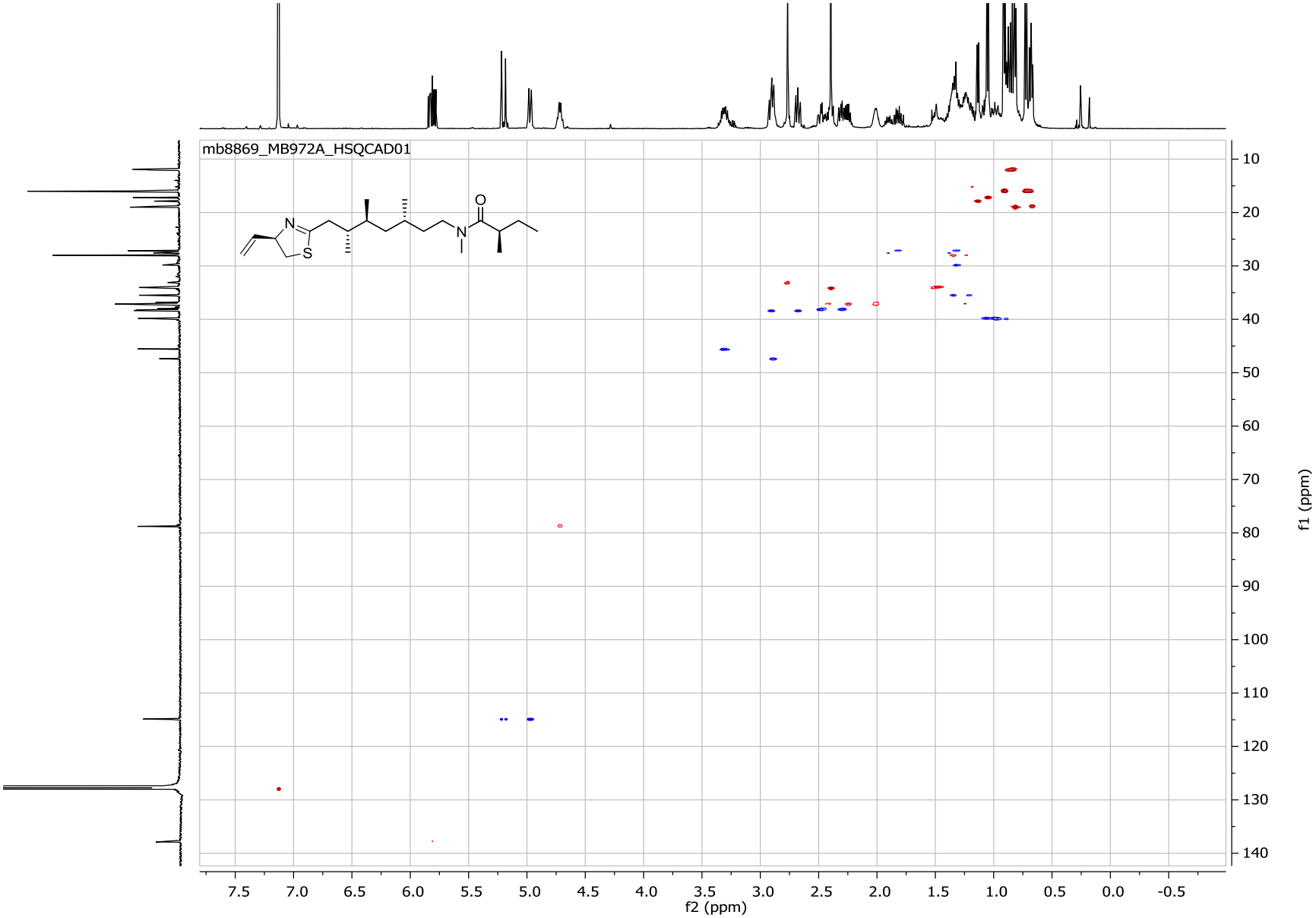

mb18339_MB953I_PROTON_001
f1 (ppm)
3.97
1.52
1.92
2.02
0.98
2.05
1.99
3.02
3.05
0.93
1.10
1.00
1.26
5.25
4.90
12.53

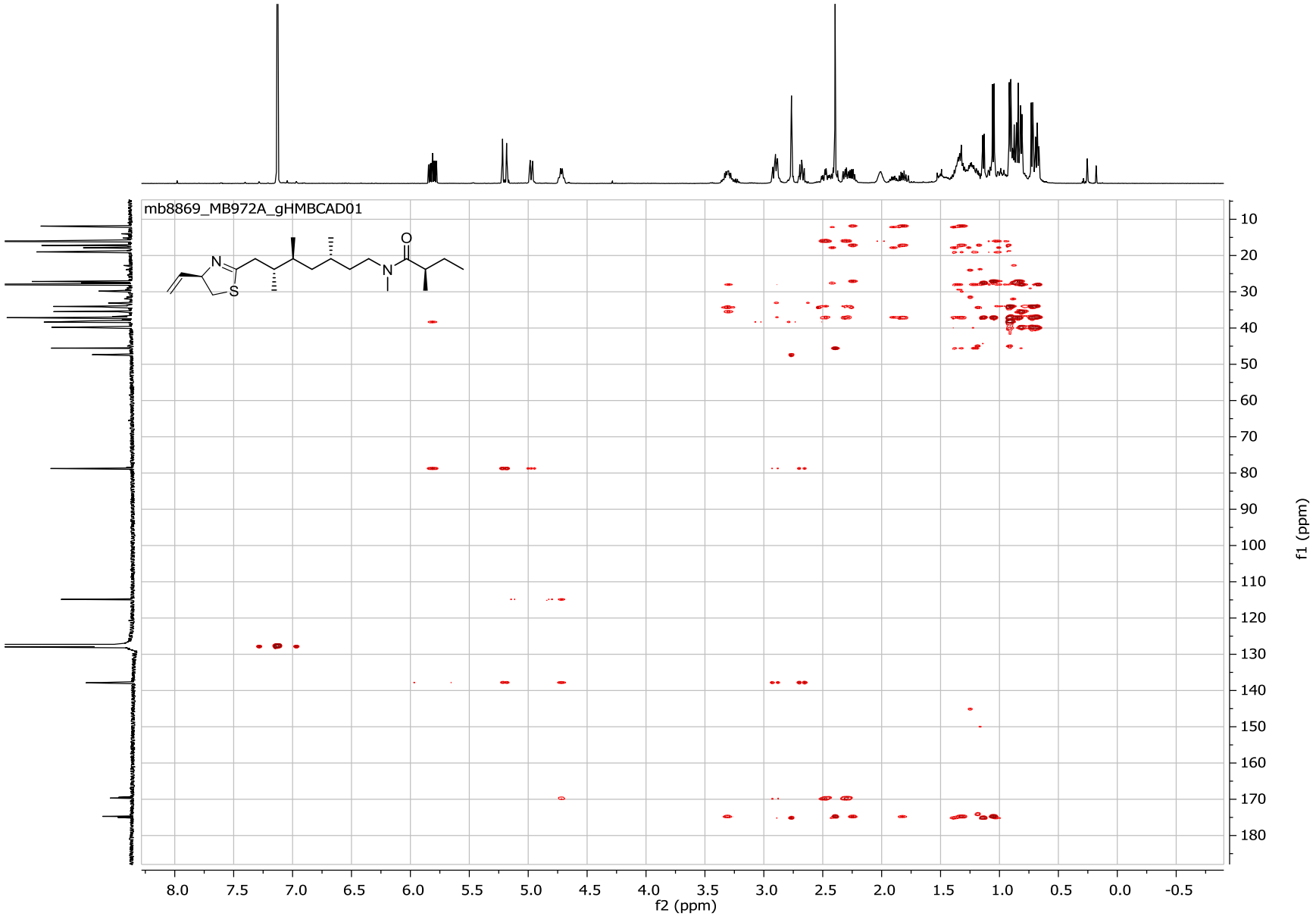
(+)-Kalkitoxin

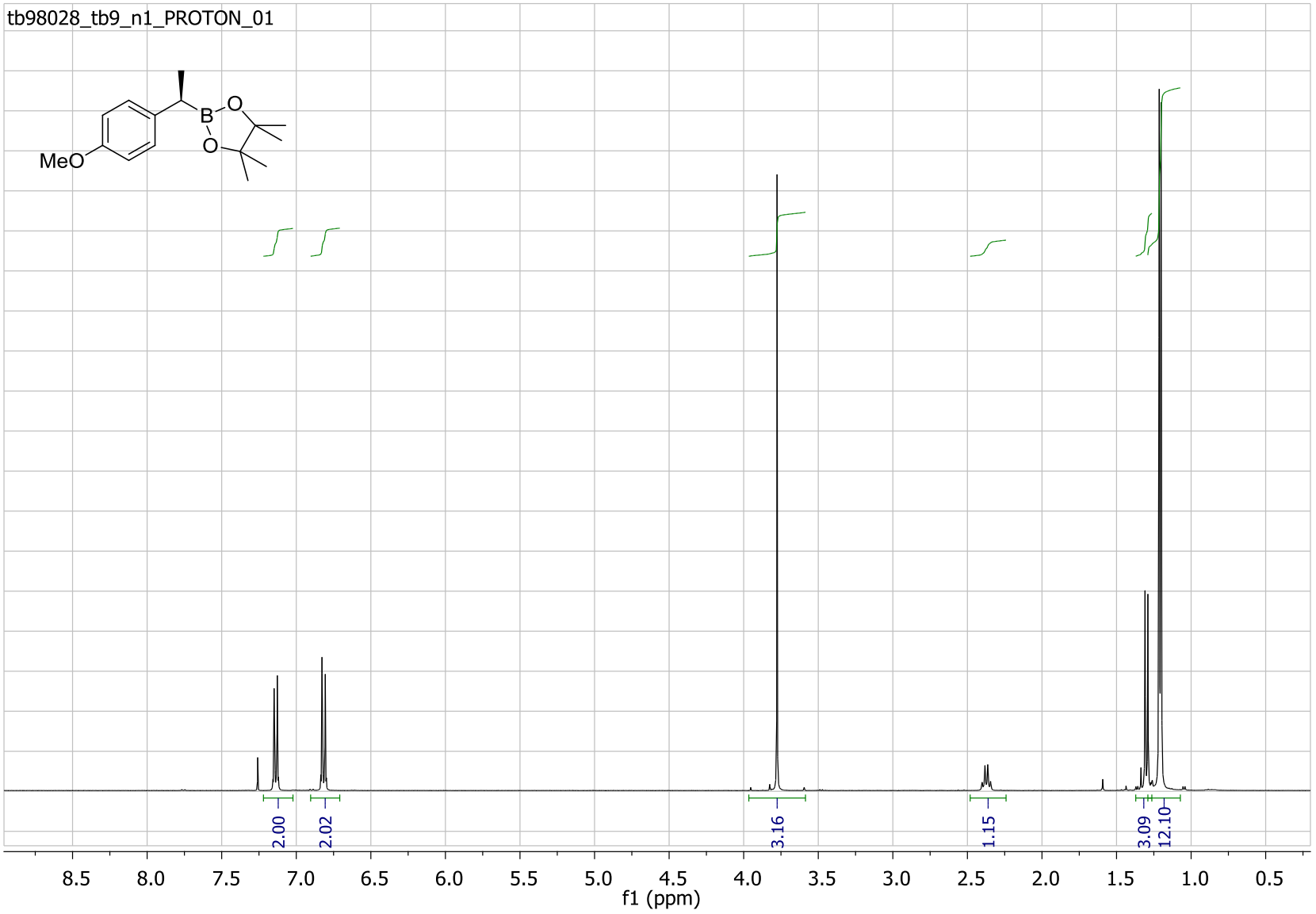

mb18339_MB953I_CARBON_001
176.
176.
172.
172.
138.05
137.98
136.94
136.92
128.92
128.91
128.57
128.55
127.14
127.10
115.79
49.81
48.06
46.13
40.77
40.61
40.59
40.15
37.37
37.18
37.16
36.60
36.55
36.08
36.06
35.71
35.42
35.24
35.22
34.38
34.29
33.72
28.22
28.16
27.39
27.04
19.24
19.17
17.76
17.10
16.50
16.33
16.15
16.10
S
H
N
O
O
N
O
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

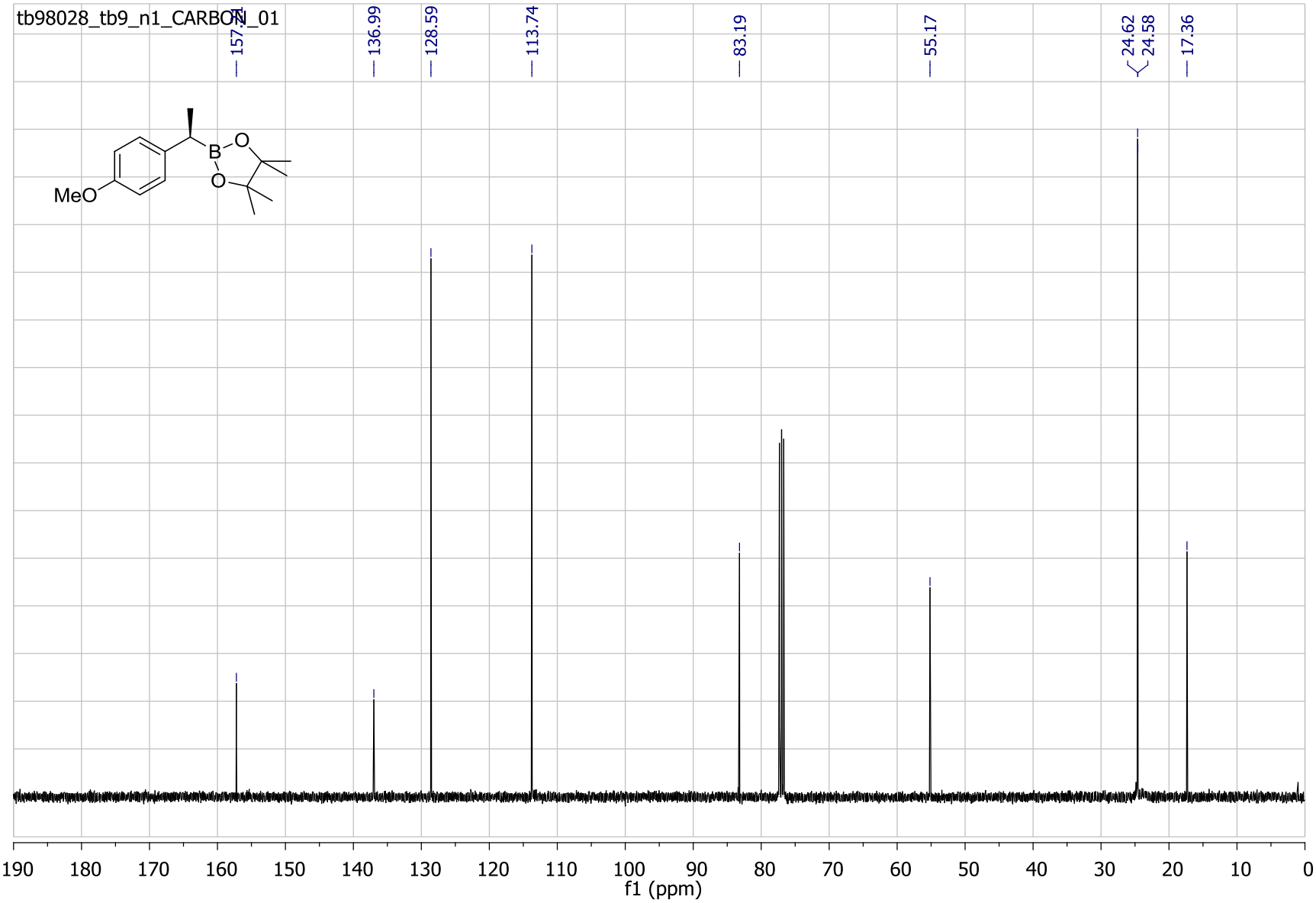

mb8869_MB972A_PROTON01
N
S
N
O
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
0.90
0.95
0.95
0.91
1.30
1.72
1.24
0.93
1.04
5.14
1.64
1.00
1.26
8.10
6.27
9.31
4.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

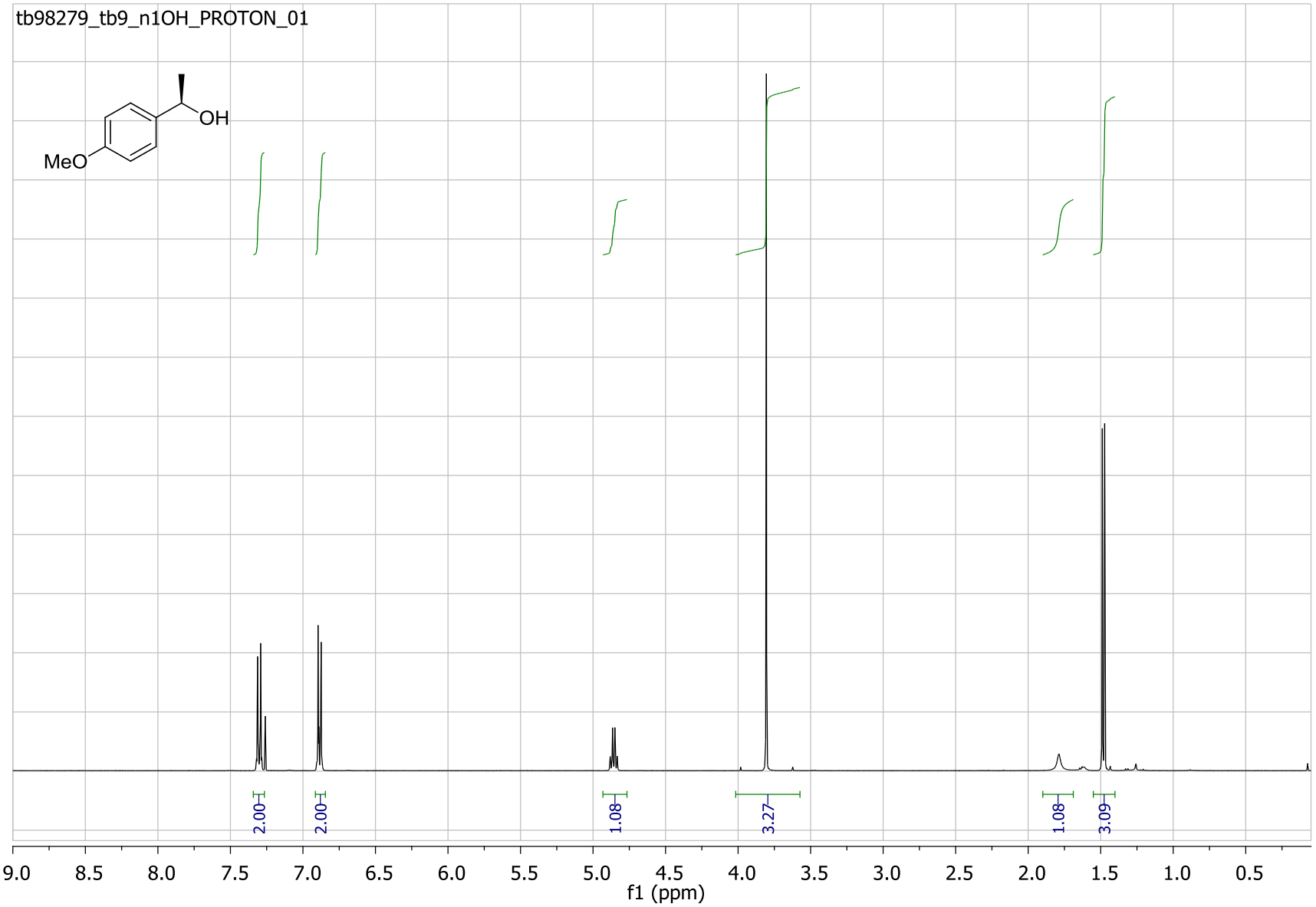

mb18409_MB968A_CARBON_001
175.43
175.18
170.85
169.85
138.29
138.17
115.34
115.27
79.18
47.77
45.96
40.22
38.81
38.79
38.63
37.58
37.56
37.53
35.90
34.59
34.45
28.40
27.97
27.57
19.41
19.24
17.62
16.45
16.41
16.36
12.29
N
S
O
N
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

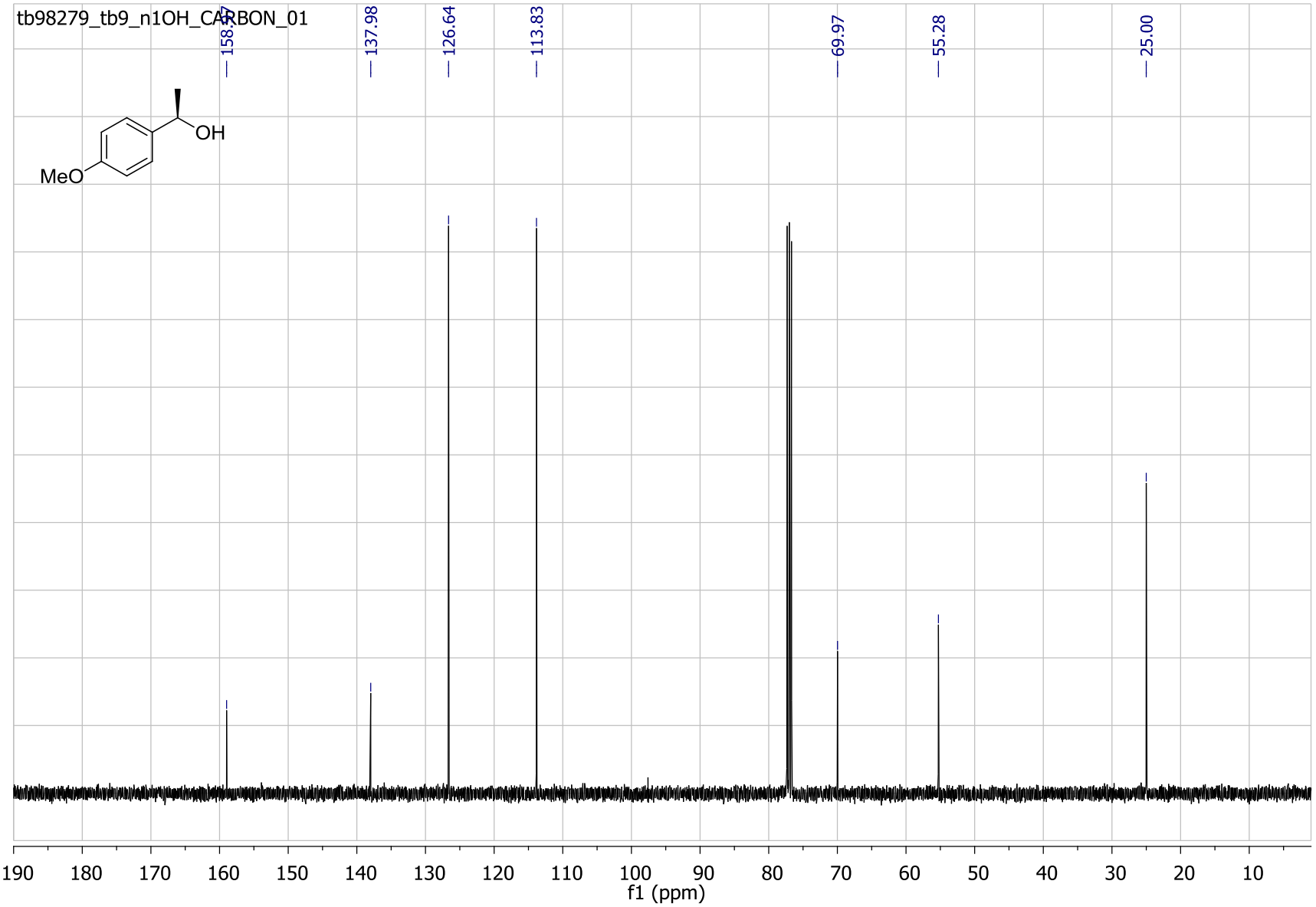

mb8869_MB972A_HSQCAD01
N
S
N
O
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)

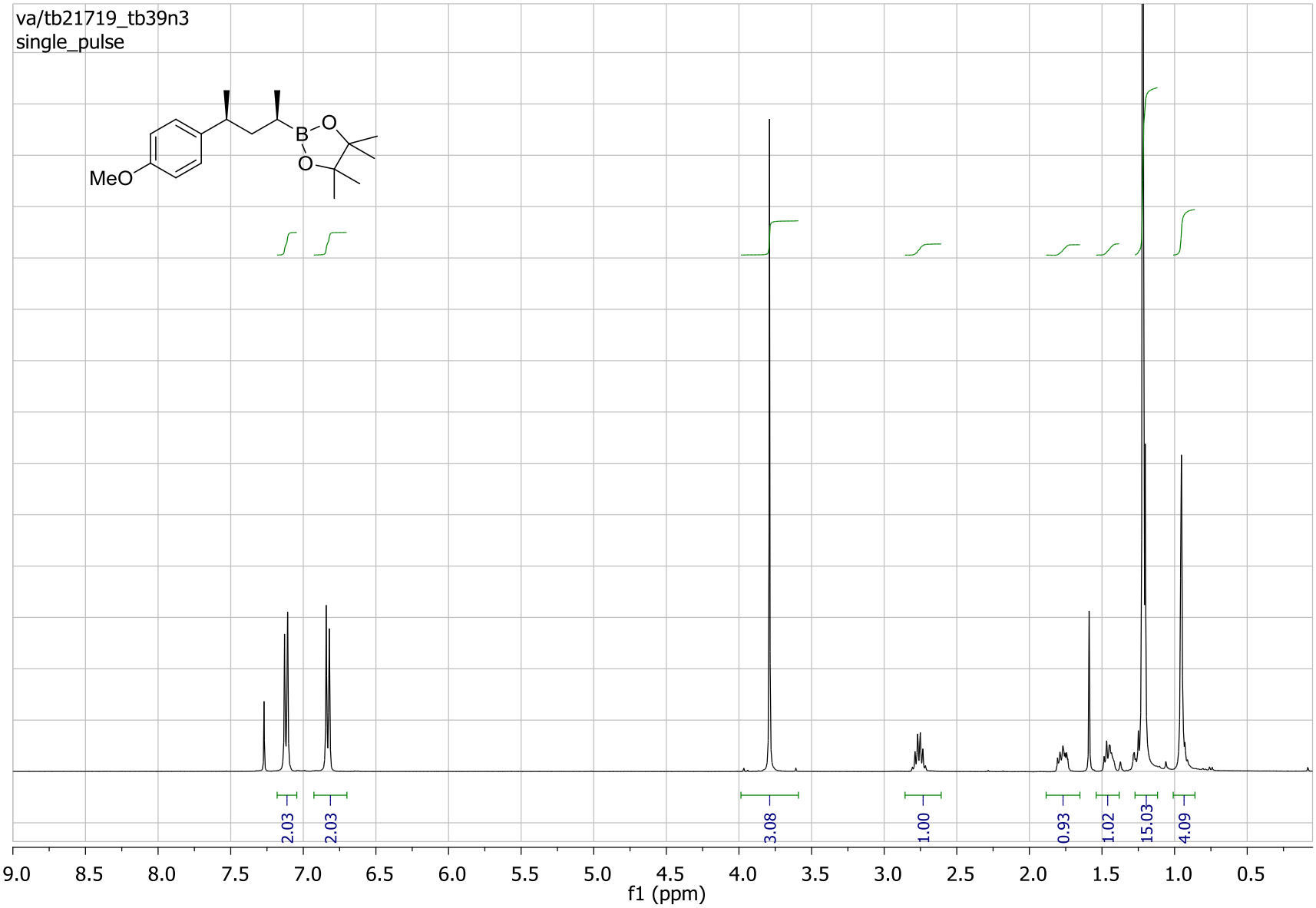

mb8869_MB972A_gHMBCAD01
N
S
N
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

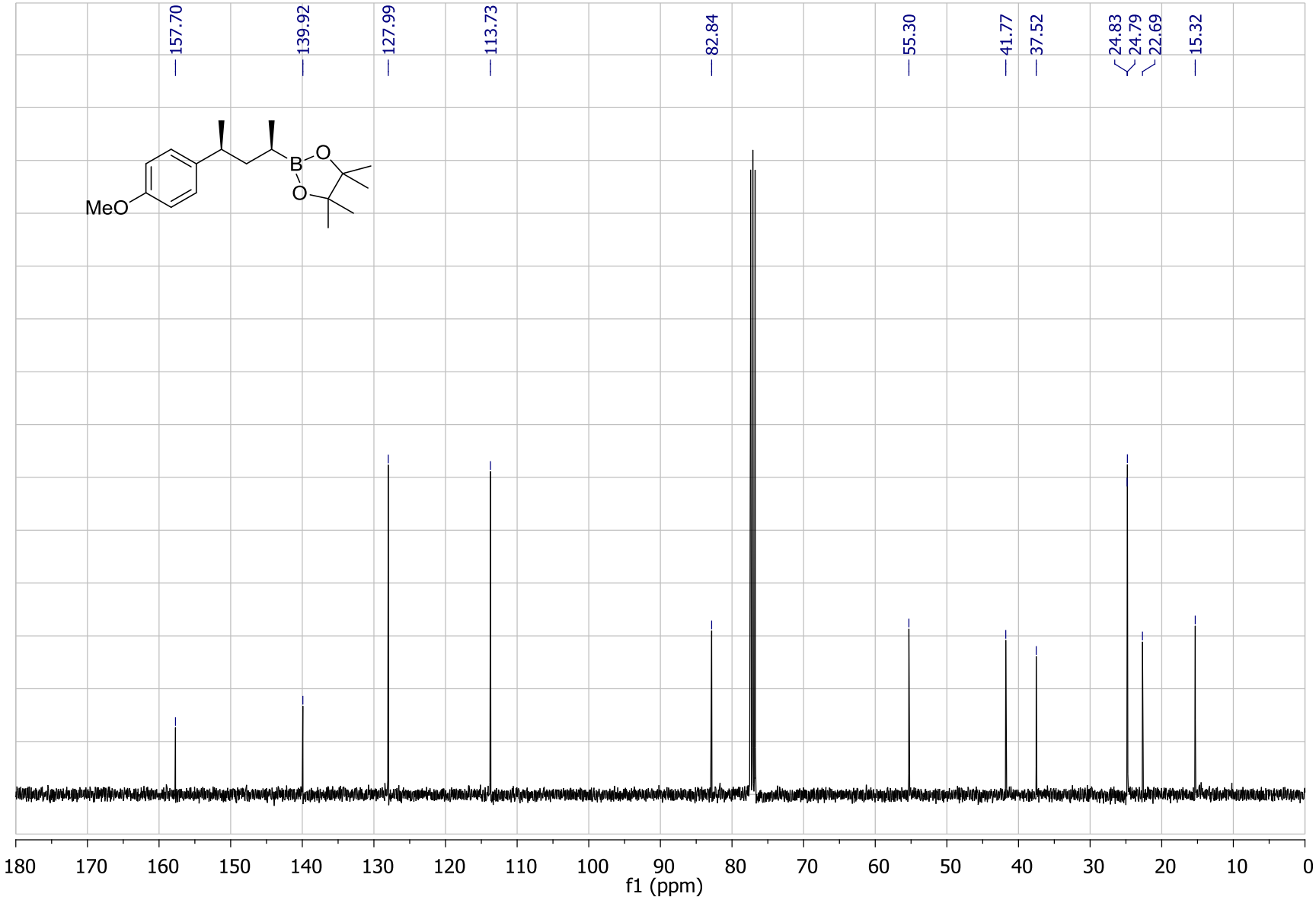

tb98028_tb9_n1_PROTON_01
MeO
B
O
O
2.00
2.02
3.16
1.15
3.09
12.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

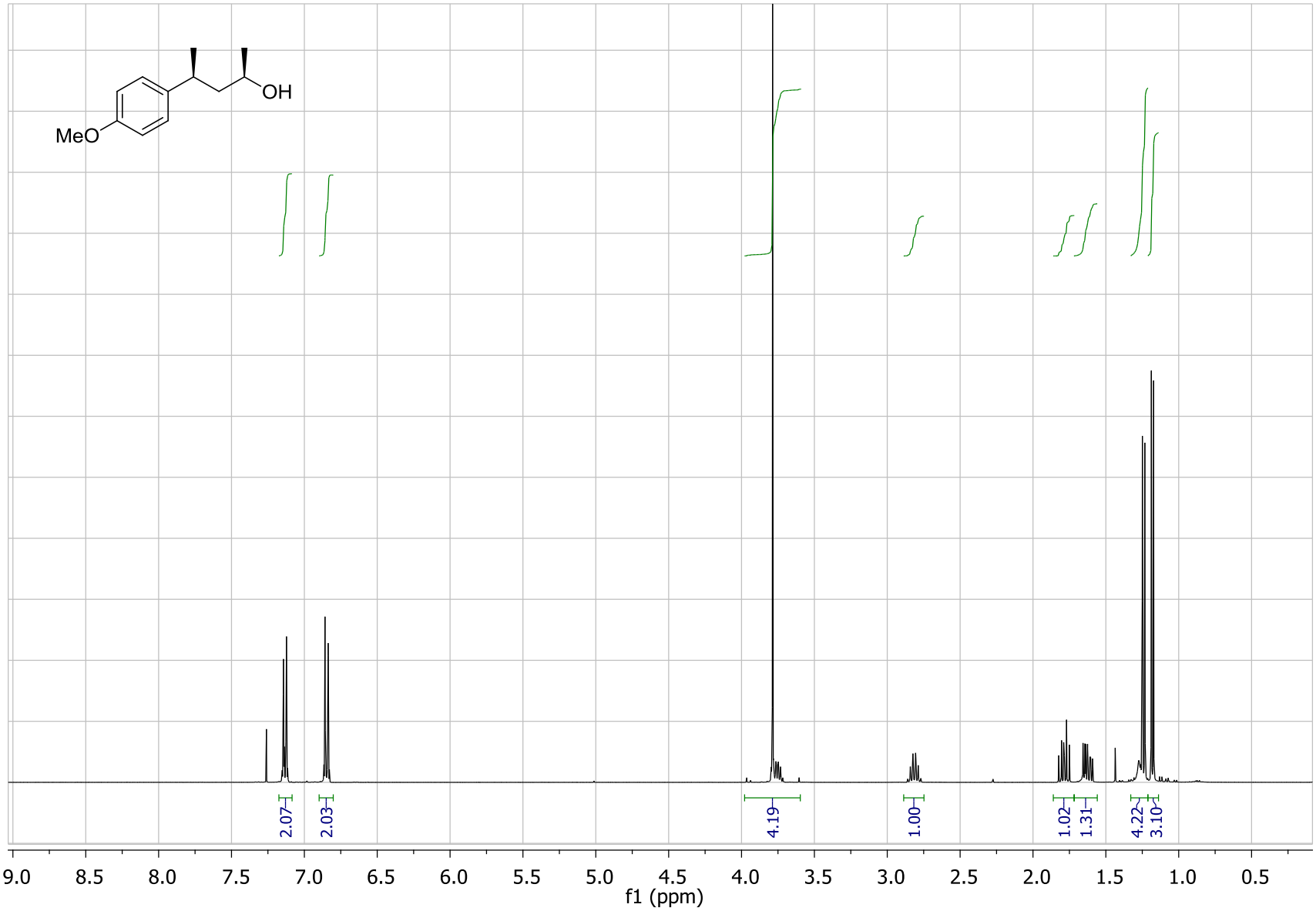

tb98028_tb9_n1_CARBON_01
157.71
136.99
128.59
113.74
83.19
55.17
24.62
24.58
17.36
MeO
B
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

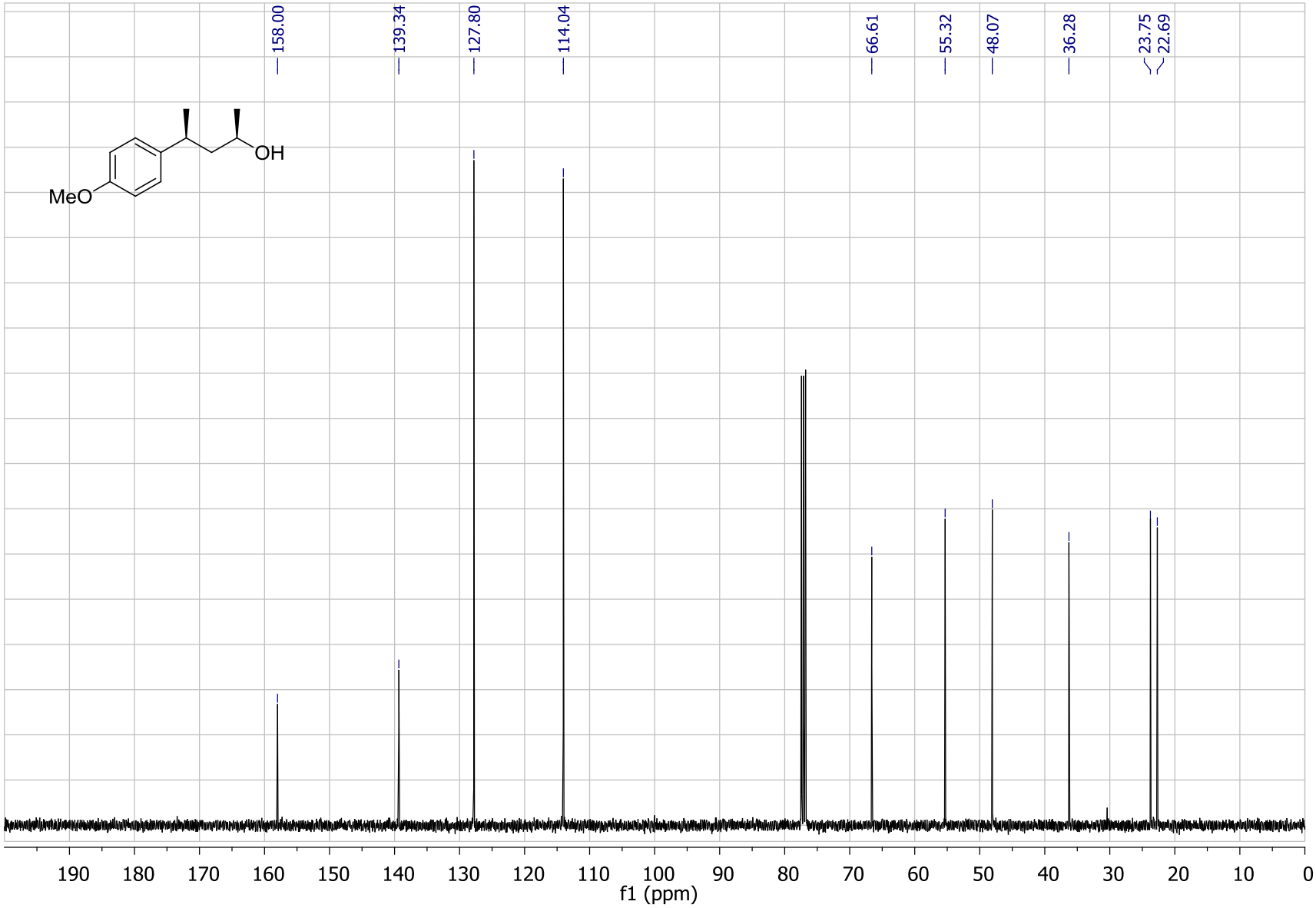

tb98279_tb9_n1OH_PROTON_01
OH
MeO
2.00
2.00
1.08
3.27
1.08
3.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

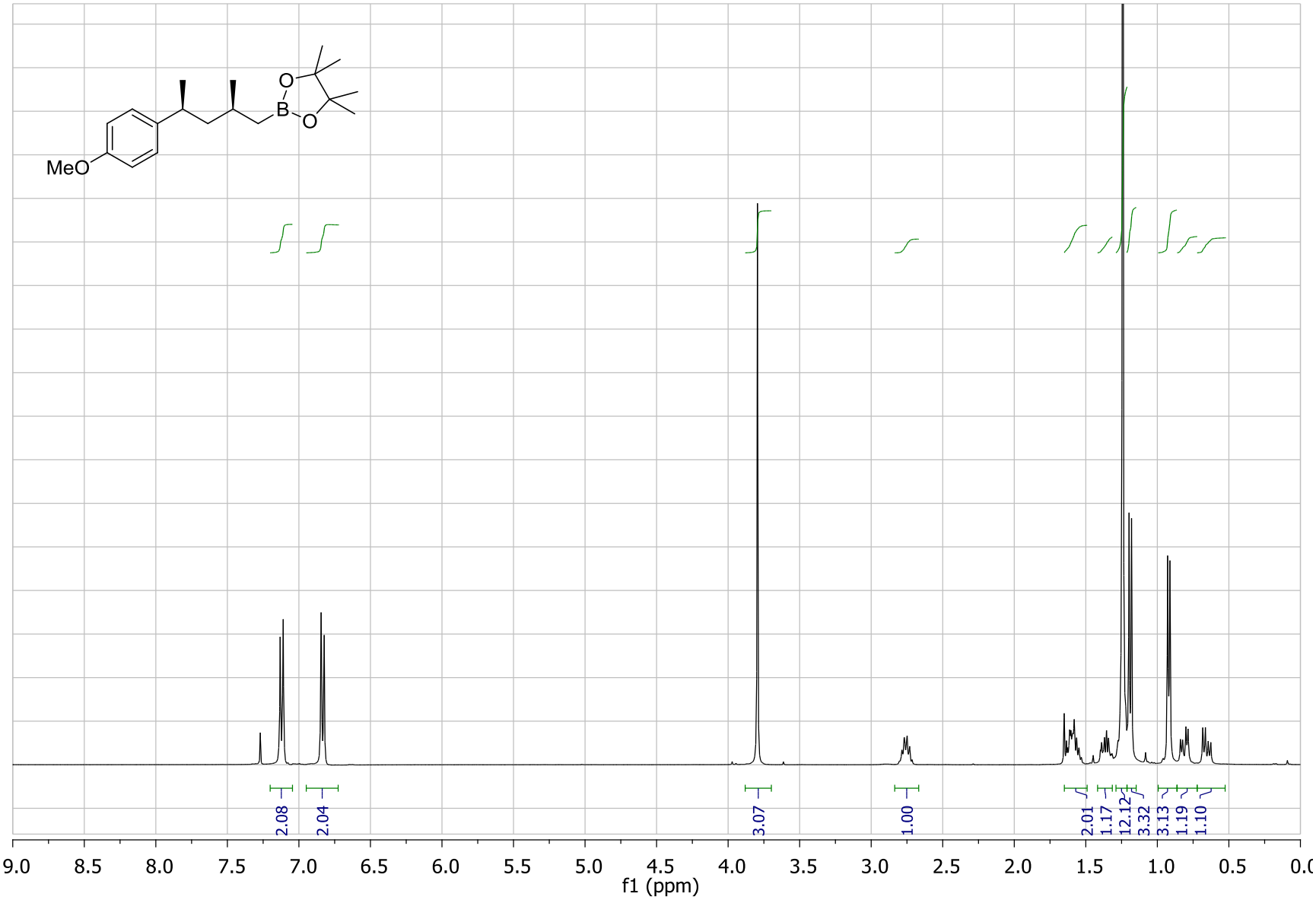

tb98279_tb9_n1OH_CARBON_01
158.47
137.98
126.64
113.83
69.97
55.28
25.00
OH
MeO
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

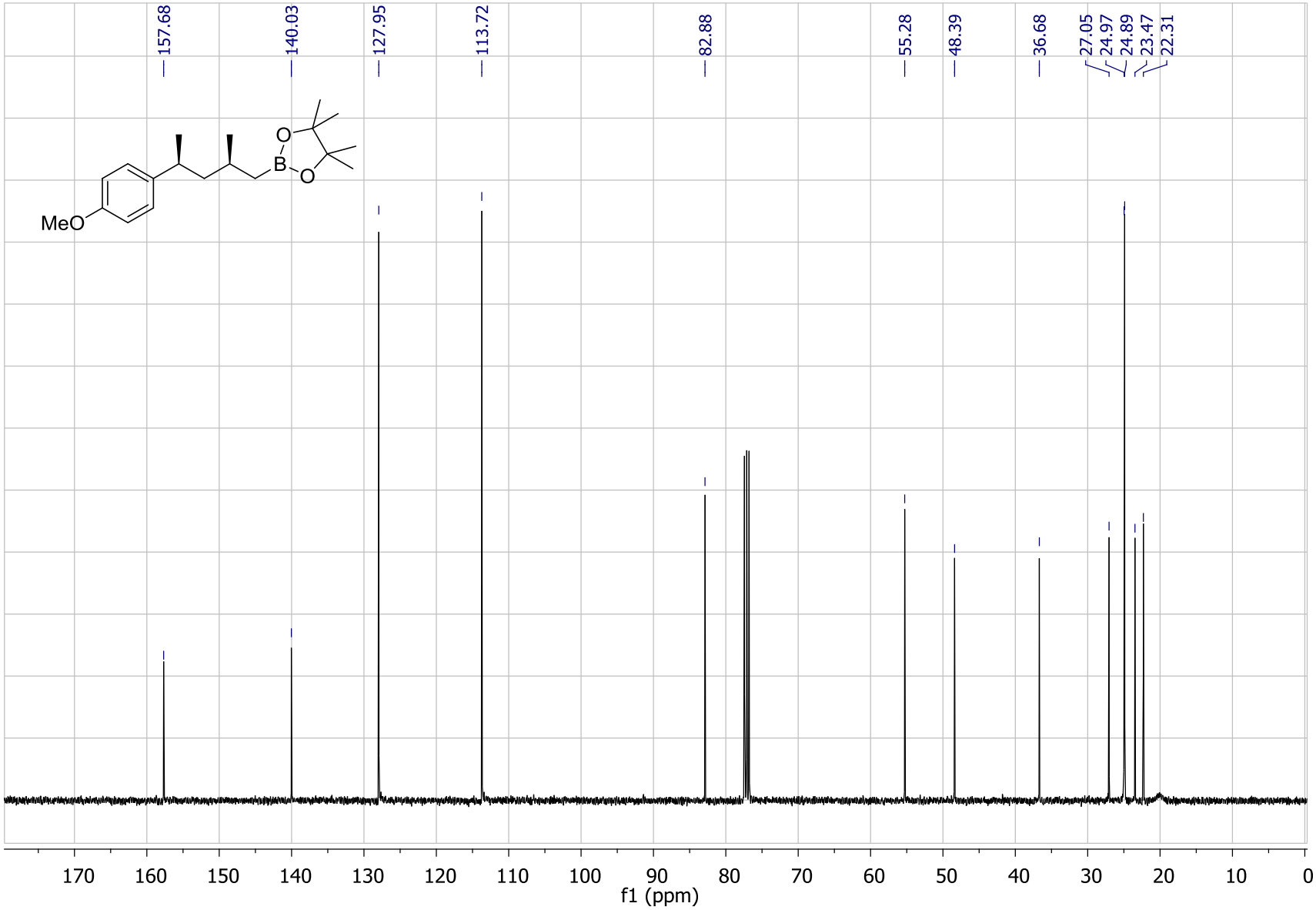

va/tb21719_tb39n3
single_pulse
MeO
B
O
O
2.03
2.03
3.08
1.00
0.93
1.02
15.03
4.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

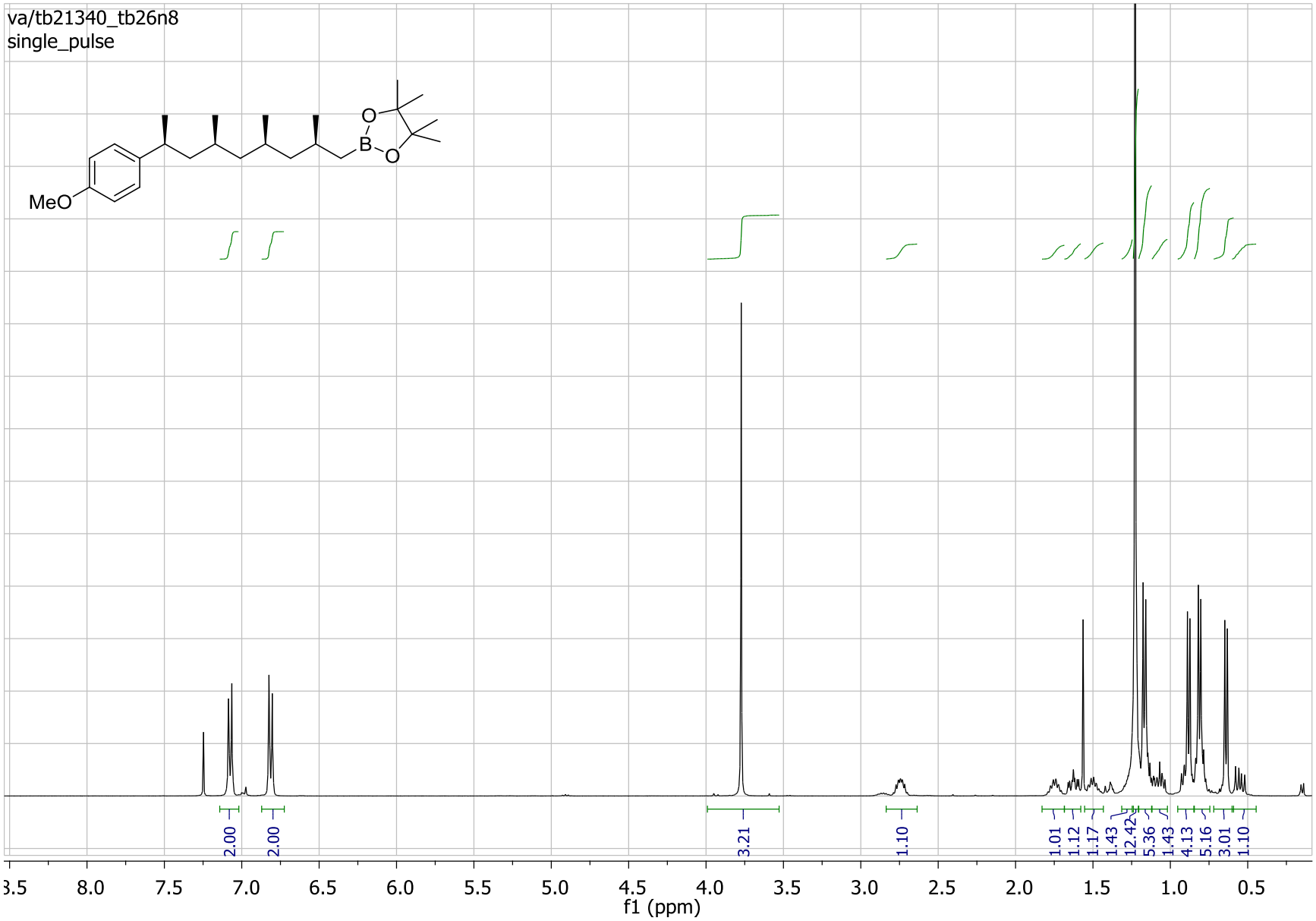

157.70
139.92
127.99
113.73
82.84
55.30
41.77
37.52
24.83
24.79
22.69
15.32
MeO
B
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

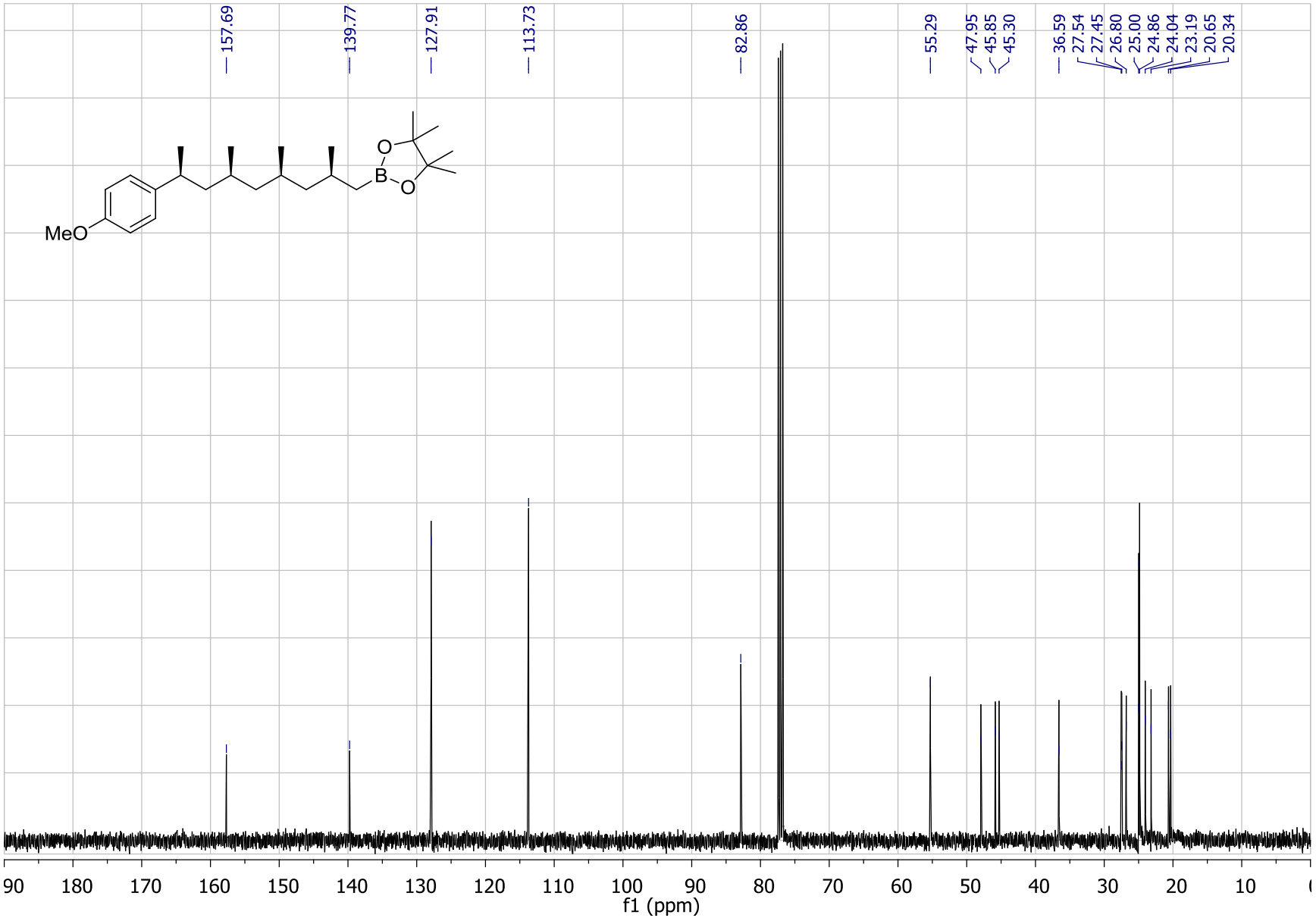

MeO
OH
2.07
2.03
4.19
1.00
1.02
1.31
4.22
3.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

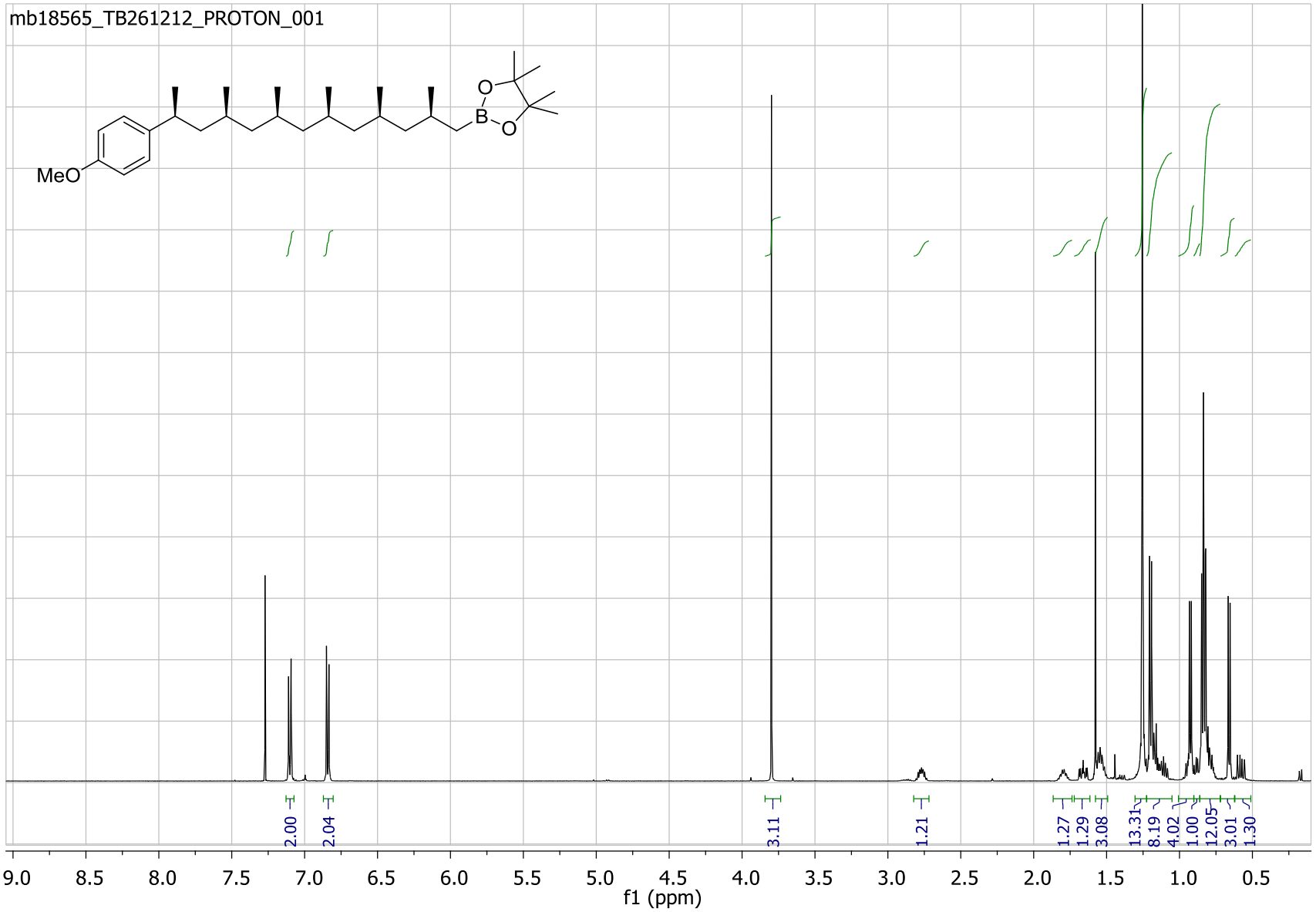

158.00
139.34
127.80
114.04
66.61
55.32
48.07
36.28
23.75
22.69
OH
MeO
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

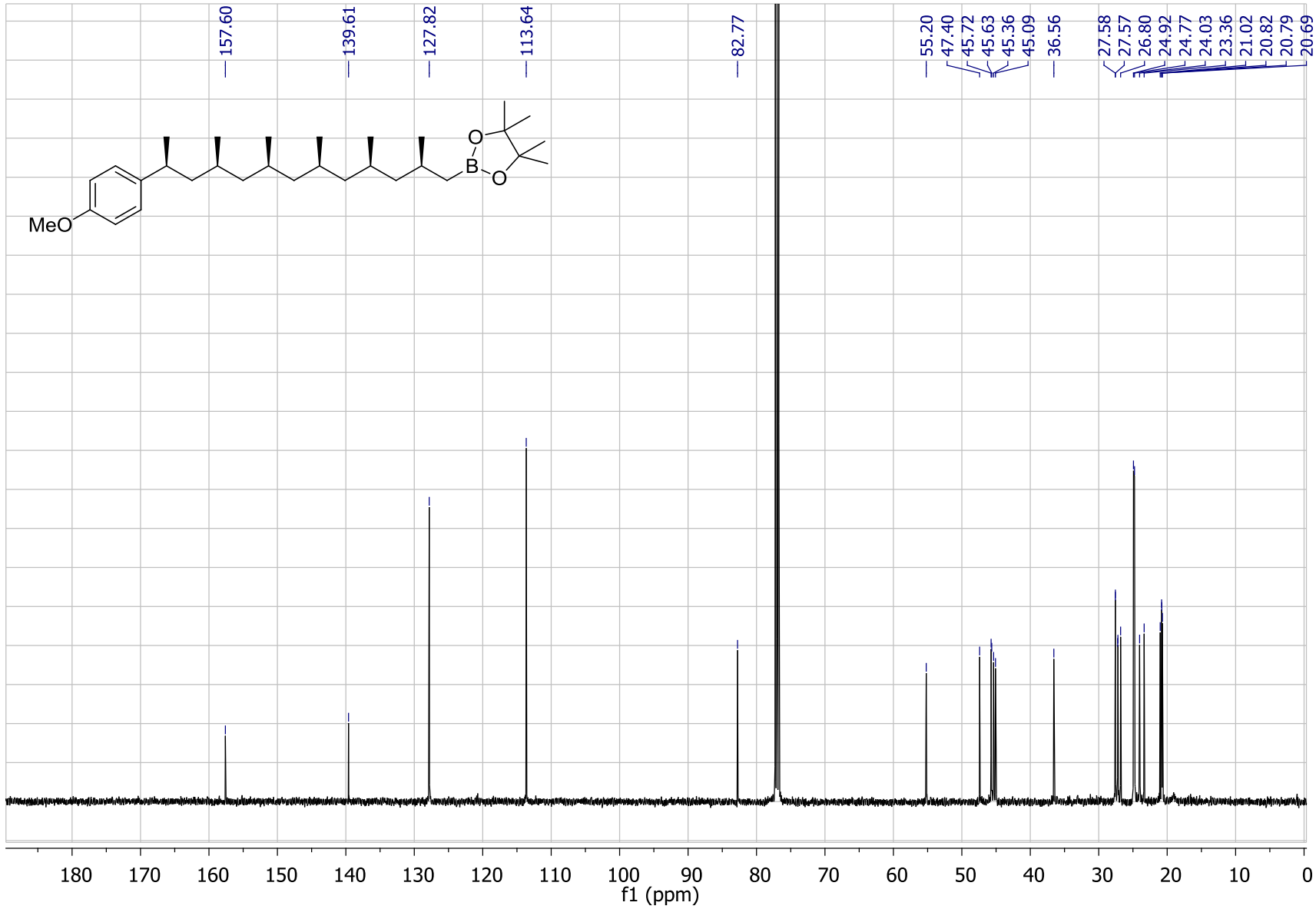

MeO
O
B
O
2.08
2.04
3.07
1.00
2.01
1.17
12.12
3.32
3.13
1.19
1.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

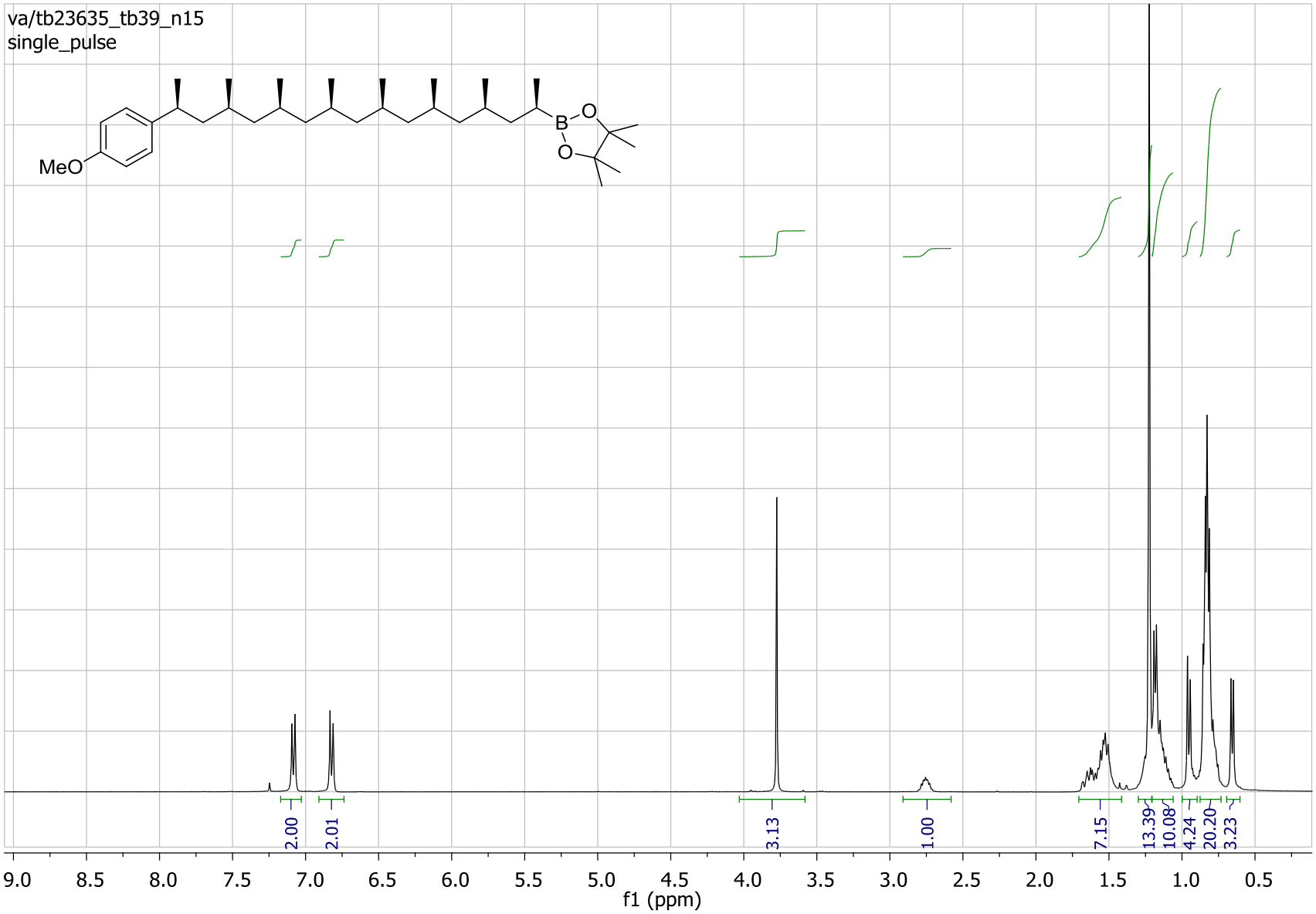

157.68
140.03
127.95
113.72
82.88
55.28
48.39
36.68
27.05
24.97
24.89
23.47
22.31
MeO
O
B
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

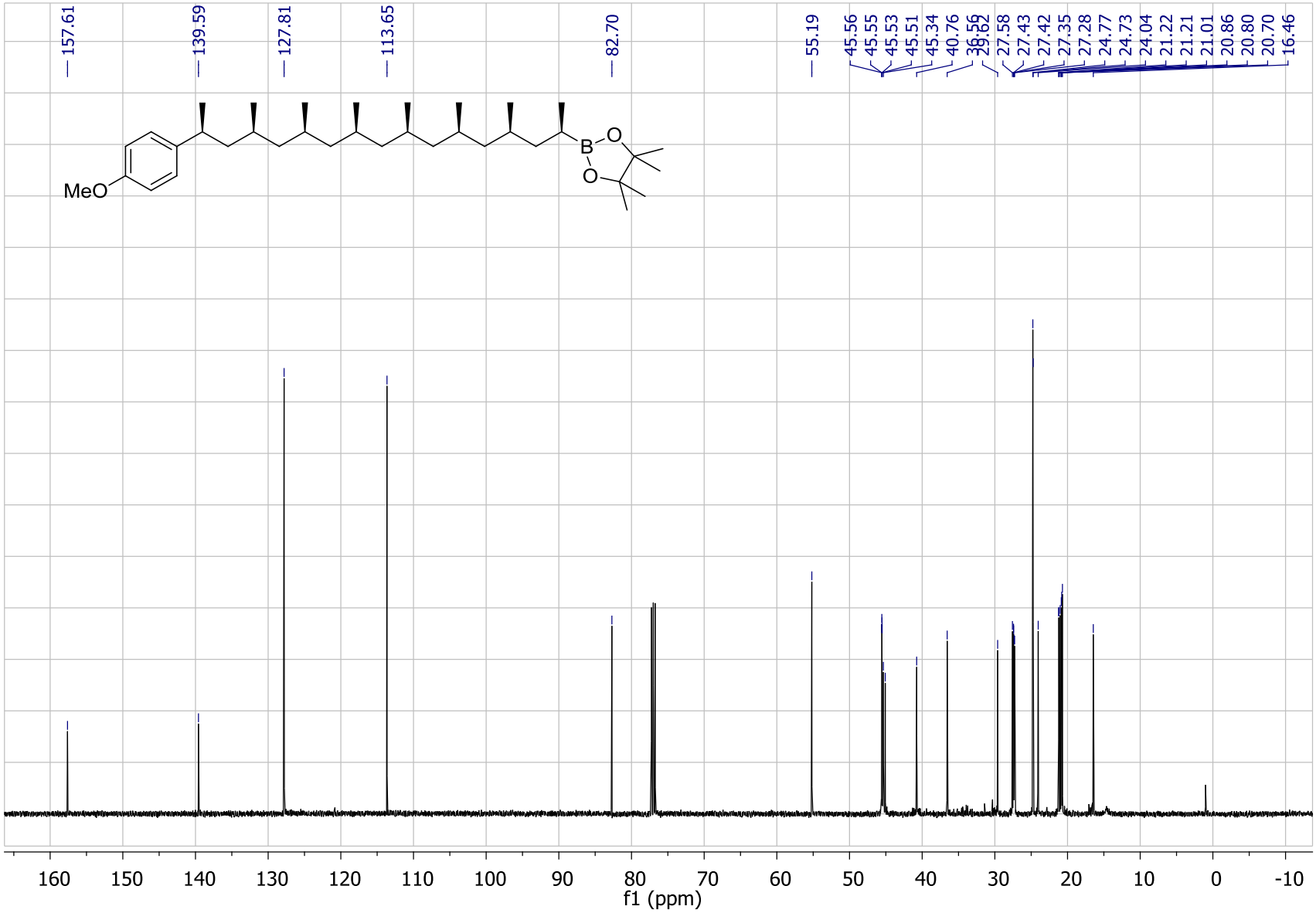

va/tb21340_tb26n8
single_pulse
MeO
O
B
O
2.00
2.00
3.21
1.10
1.01
1.12
1.17
1.43
12.42
5.36
1.43
4.13
5.16
3.01
1.10
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

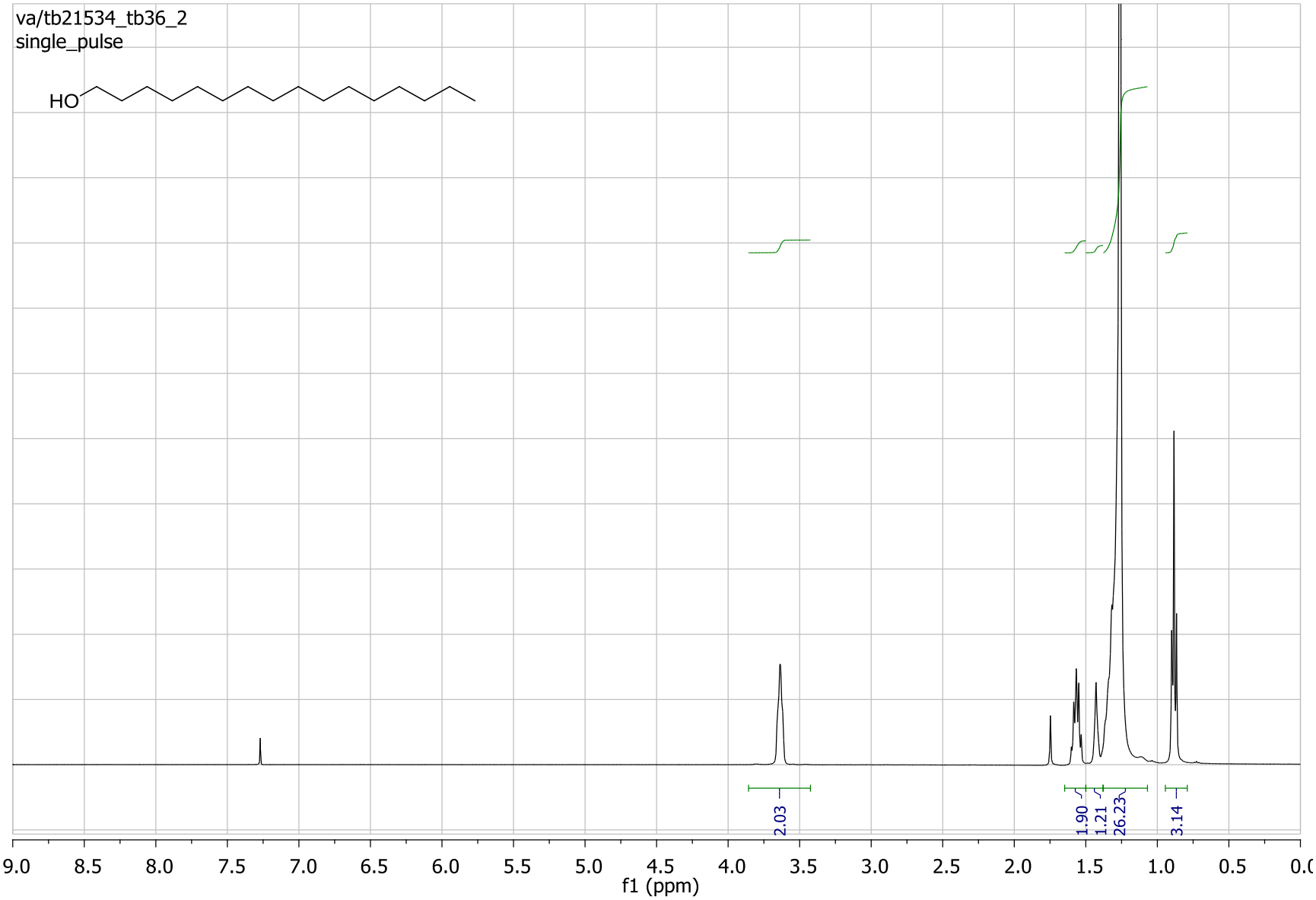

157.69
139.77
127.91
113.73
82.86
55.29
47.95
45.85
45.30
36.59
27.54
27.45
26.80
25.00
24.86
24.04
23.19
20.65
20.34
MeO
O
B
O
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

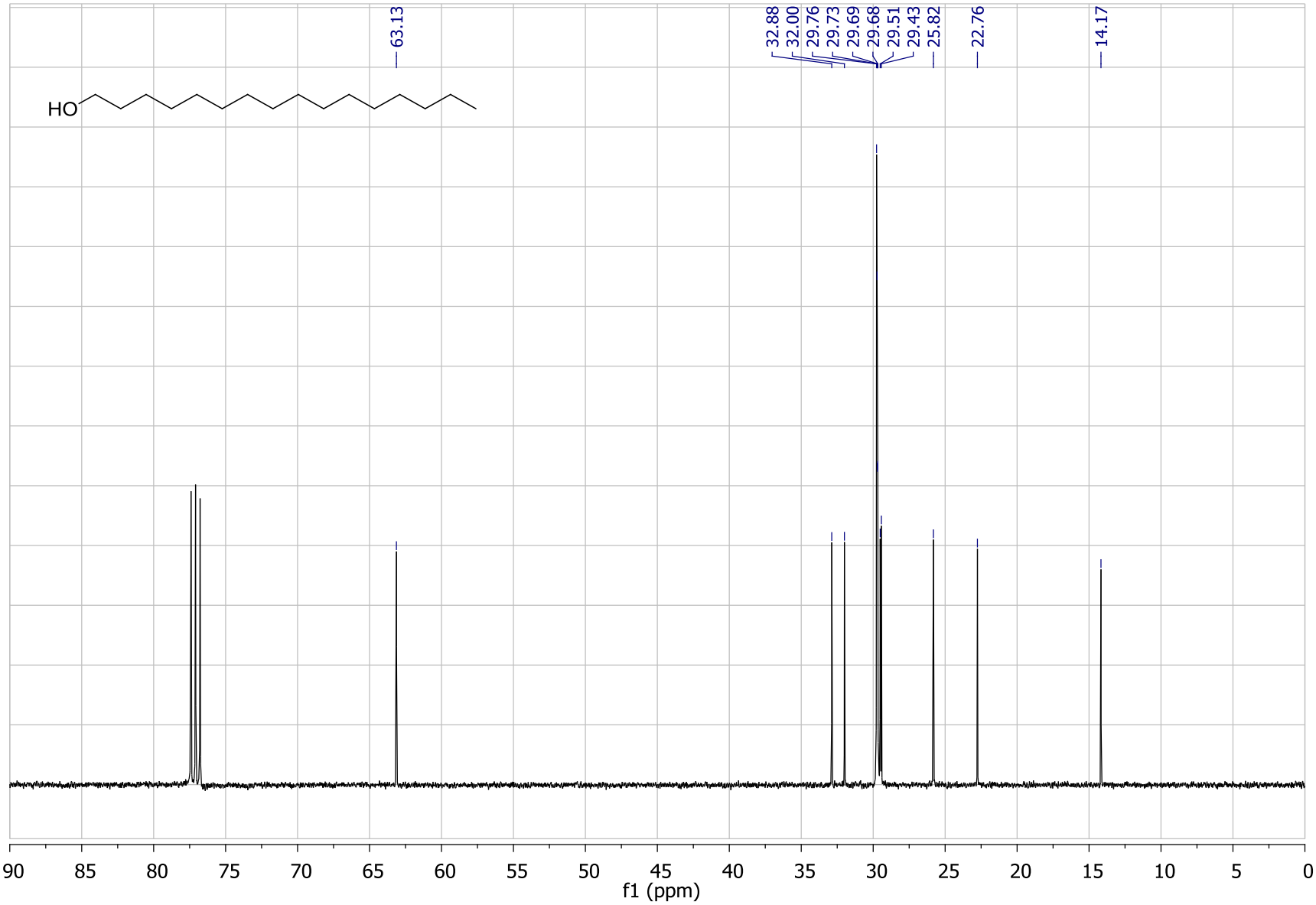

mb18565_TB261212_PROTON_001
MeO
O
B
O
2.00
2.04
3.11
1.21
1.27
1.29
3.08
13.31
8.19
4.02
1.00
12.05
3.01
1.30
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

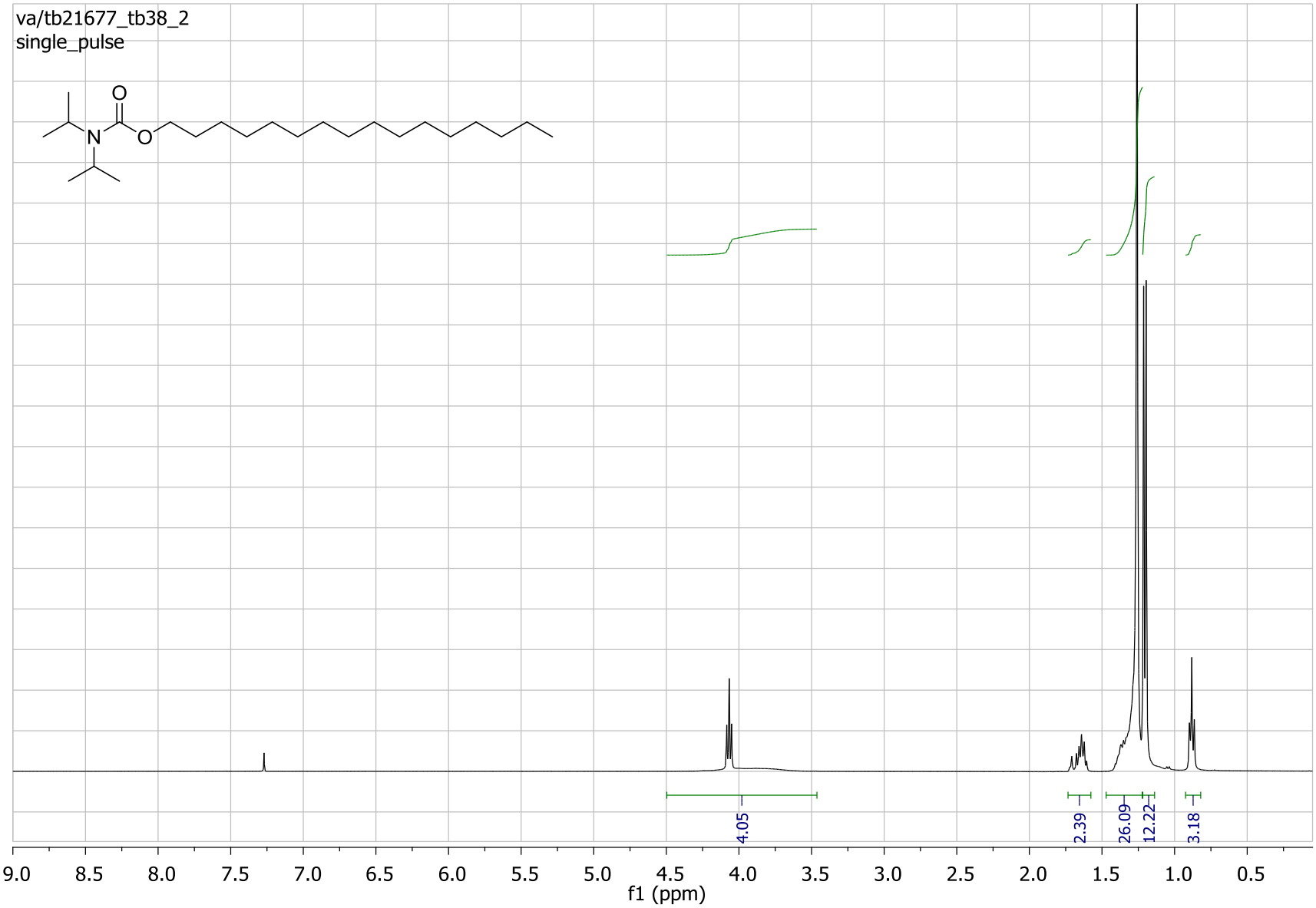

157.60
139.61
127.82
113.64
82.77
55.20
47.40
45.72
45.63
45.36
45.09
36.56
27.58
27.57
26.80
24.92
24.77
24.03
23.36
21.02
20.82
20.79
20.69
MeO
O
B
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

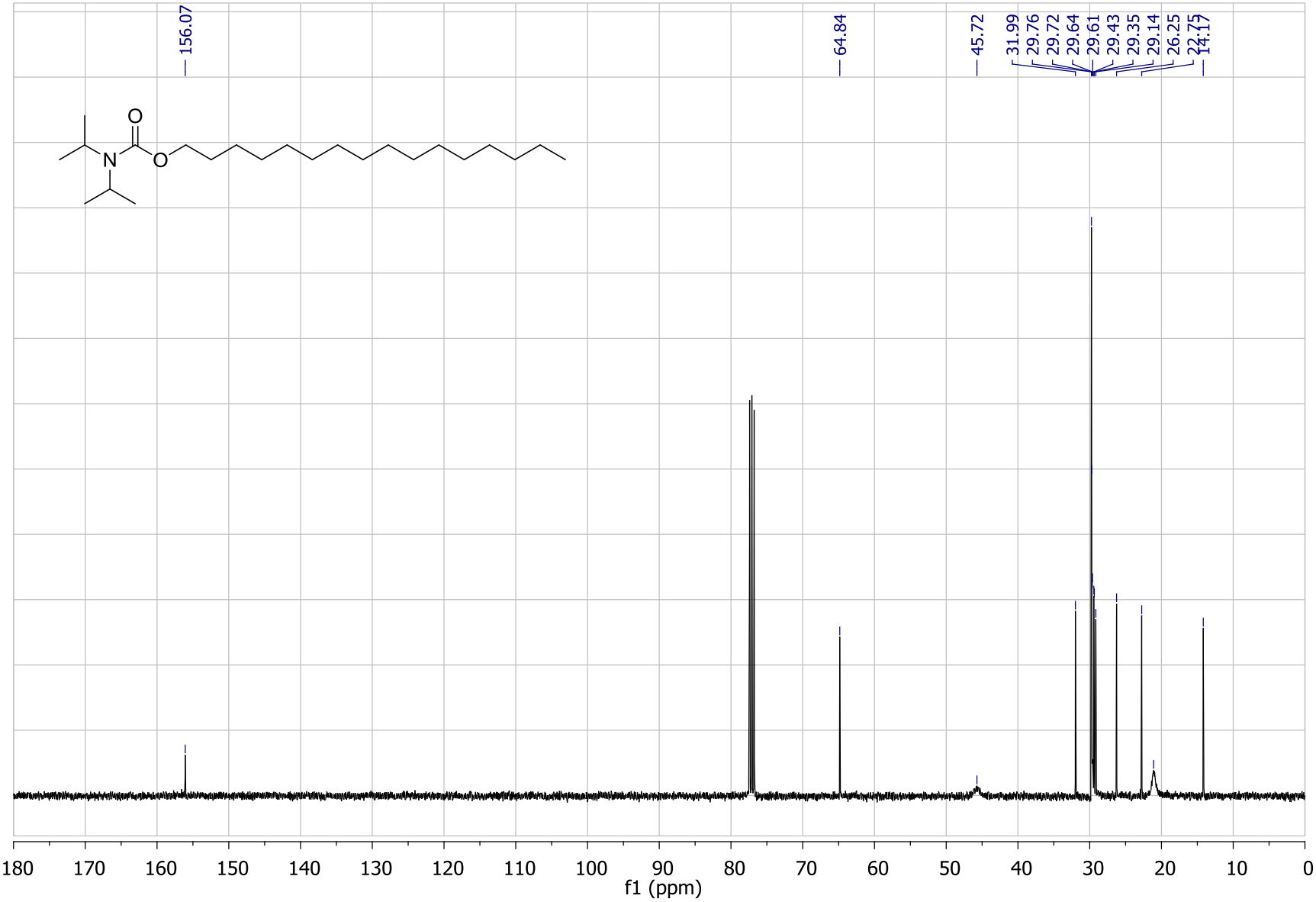

va/tb23635_tb39_n15
single_pulse
MeO
B
O
O
2.00
2.01
3.13
1.00
7.15
13.39
10.08
4.24
20.20
3.23
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

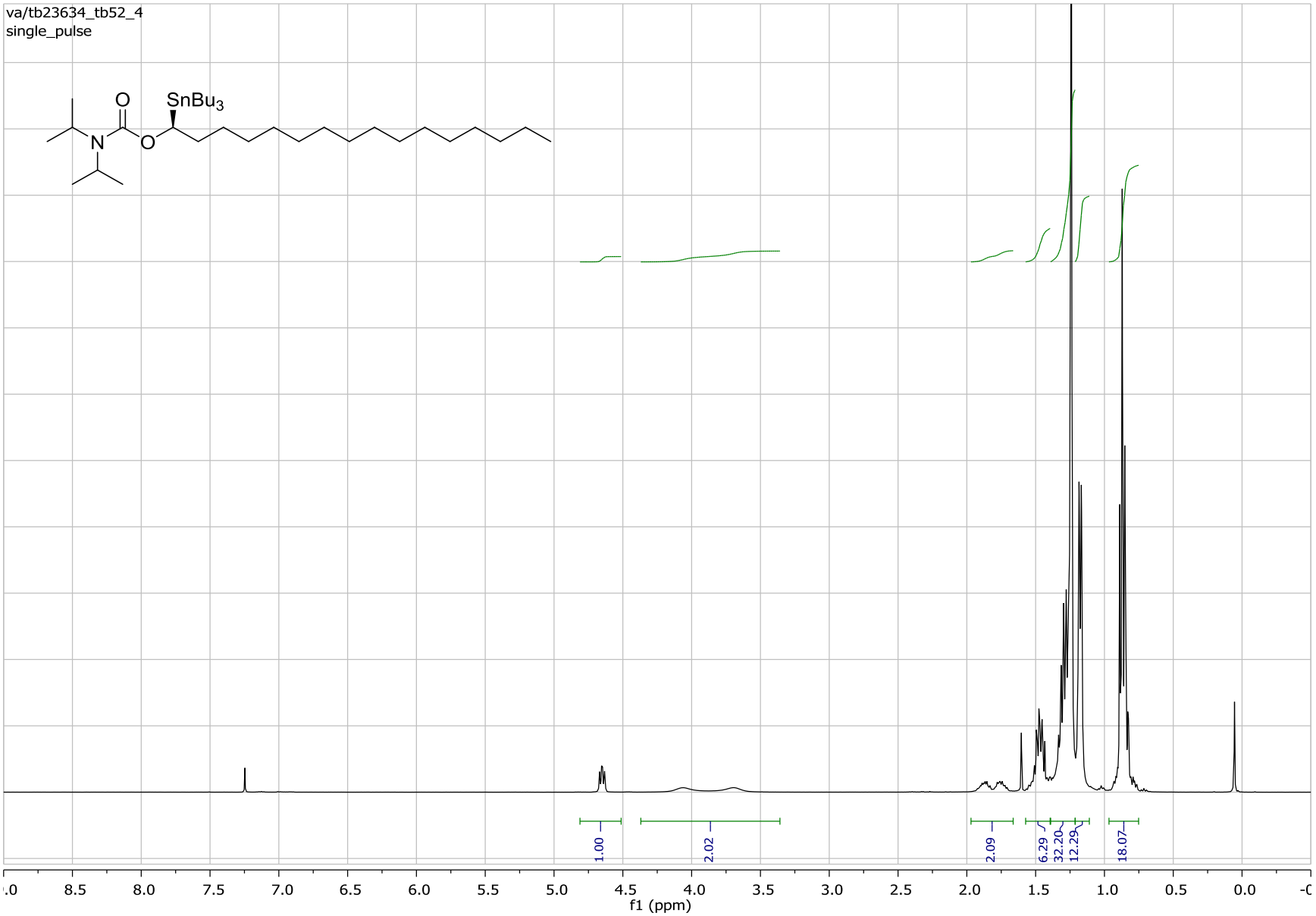

157.61
139.59
127.81
113.65
82.70
55.19
45.56
45.55
45.53
45.51
45.34
40.76
36.56
29.62
27.58
27.43
27.42
27.35
27.28
24.77
24.73
24.04
21.22
21.21
21.01
20.86
20.80
20.70
16.46
MeO
B
O
O
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

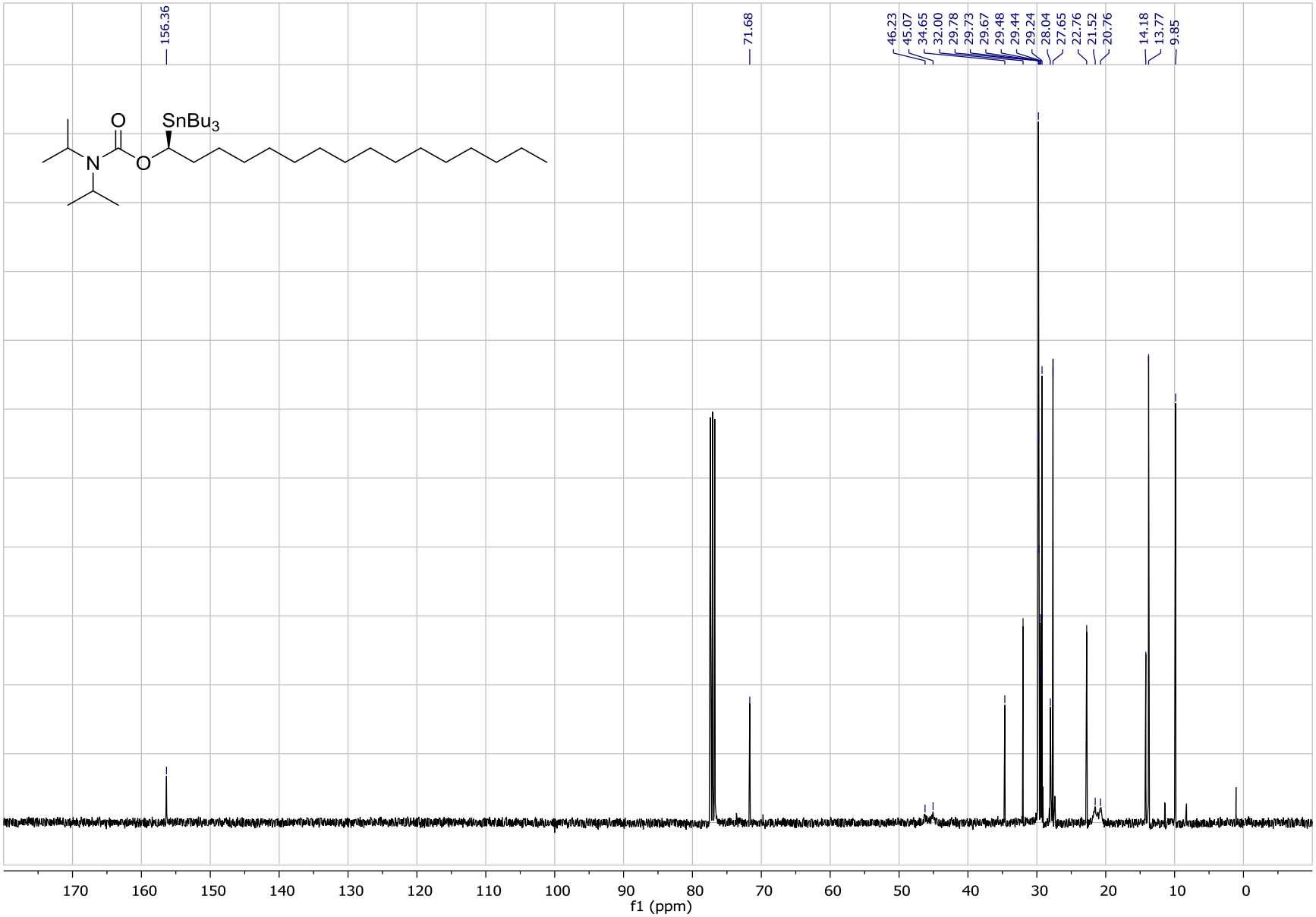

va/tb21534_tb36_2
single_pulse
HO
2.03
1.90
1.21
26.23
3.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

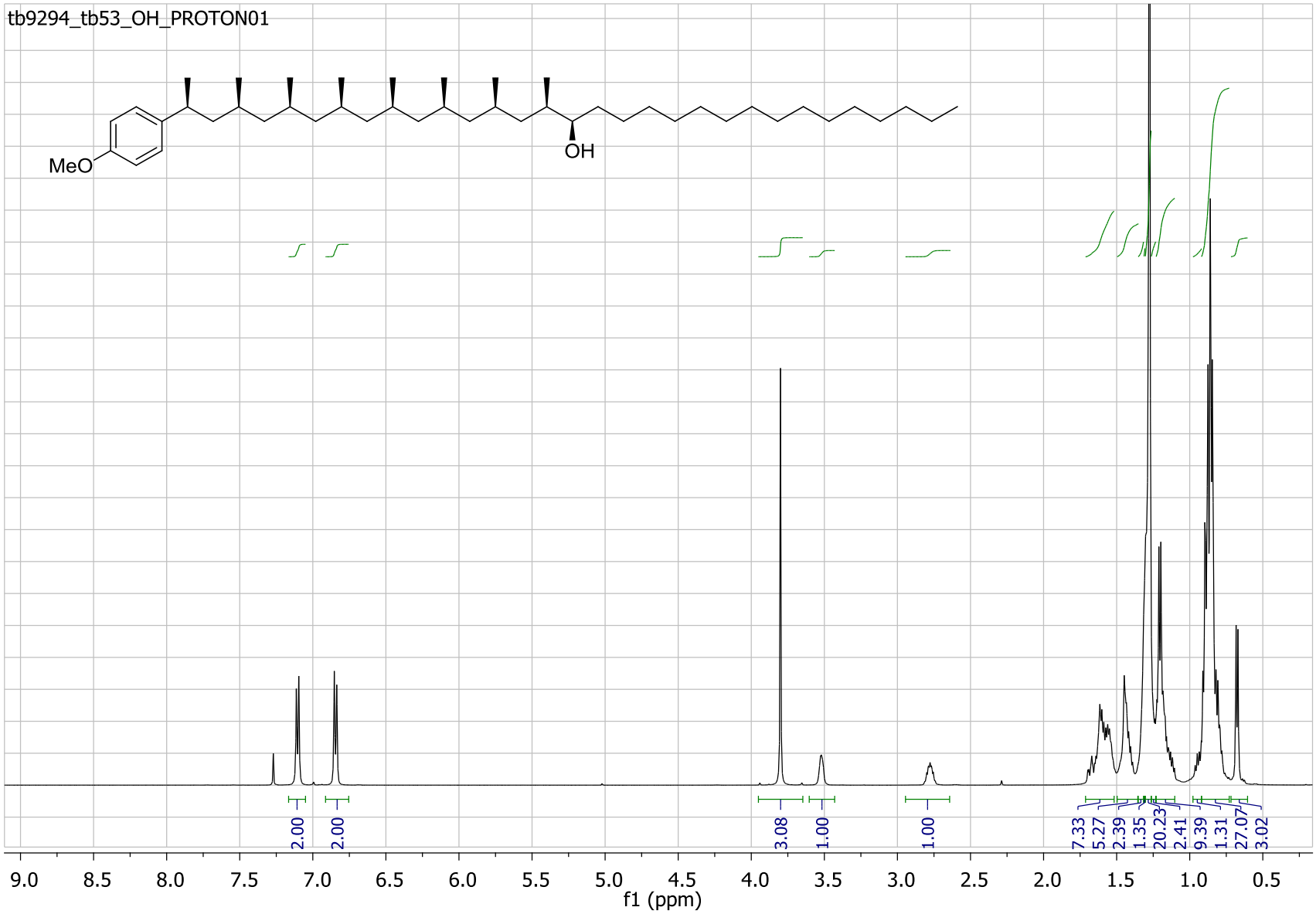

63.13
32.88
32.00
29.76
29.73
29.69
29.68
29.51
29.43
25.82
22.76
14.17
HO
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)

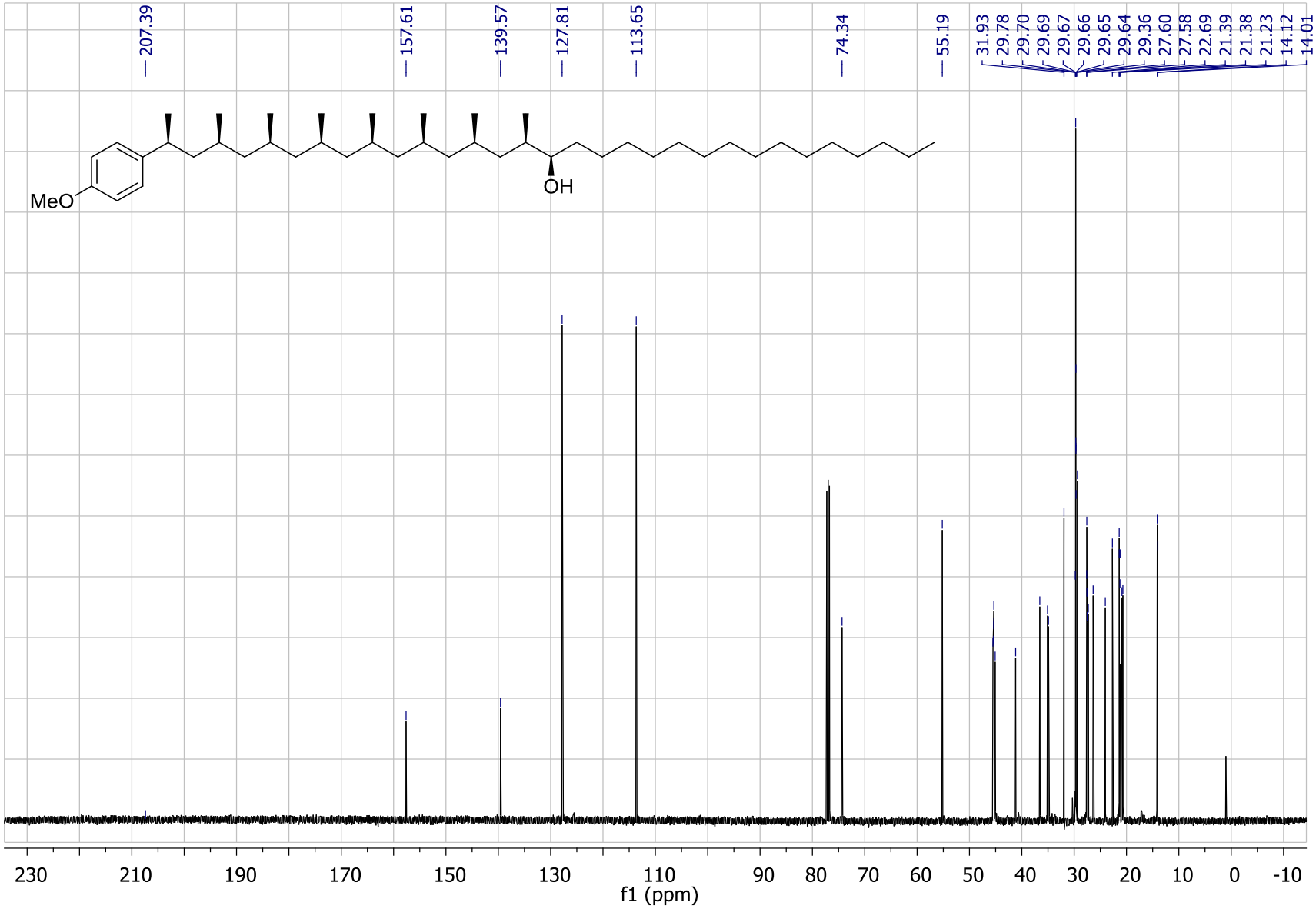

va/tb21677_tb38_2
single_pulse
O
N
O
4.05
2.39
26.09
12.22
3.18
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

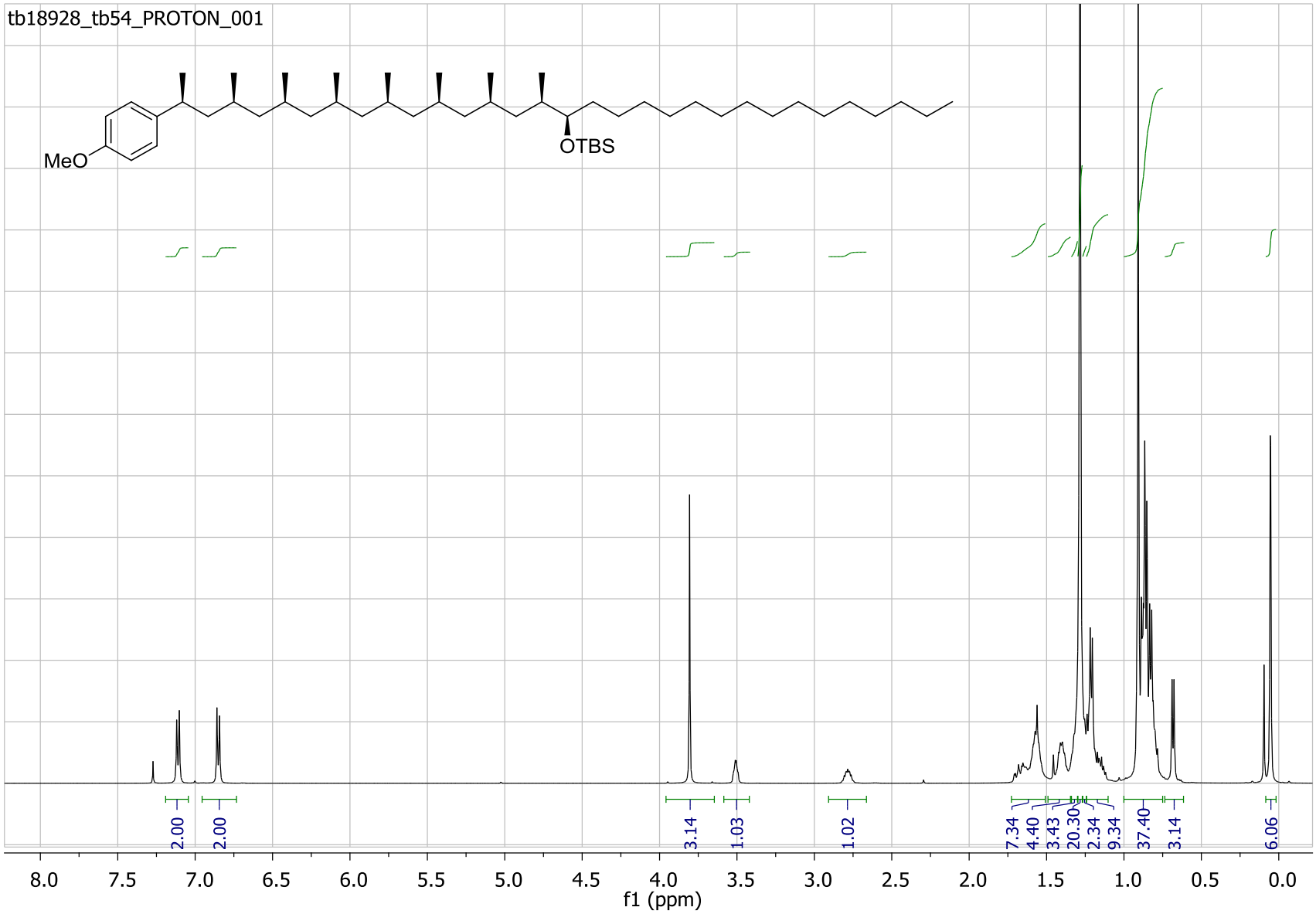

156.07
64.84
45.72
31.99
29.76
29.72
29.64
29.61
29.43
29.35
29.14
26.25
22.75
14.17
O
N
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

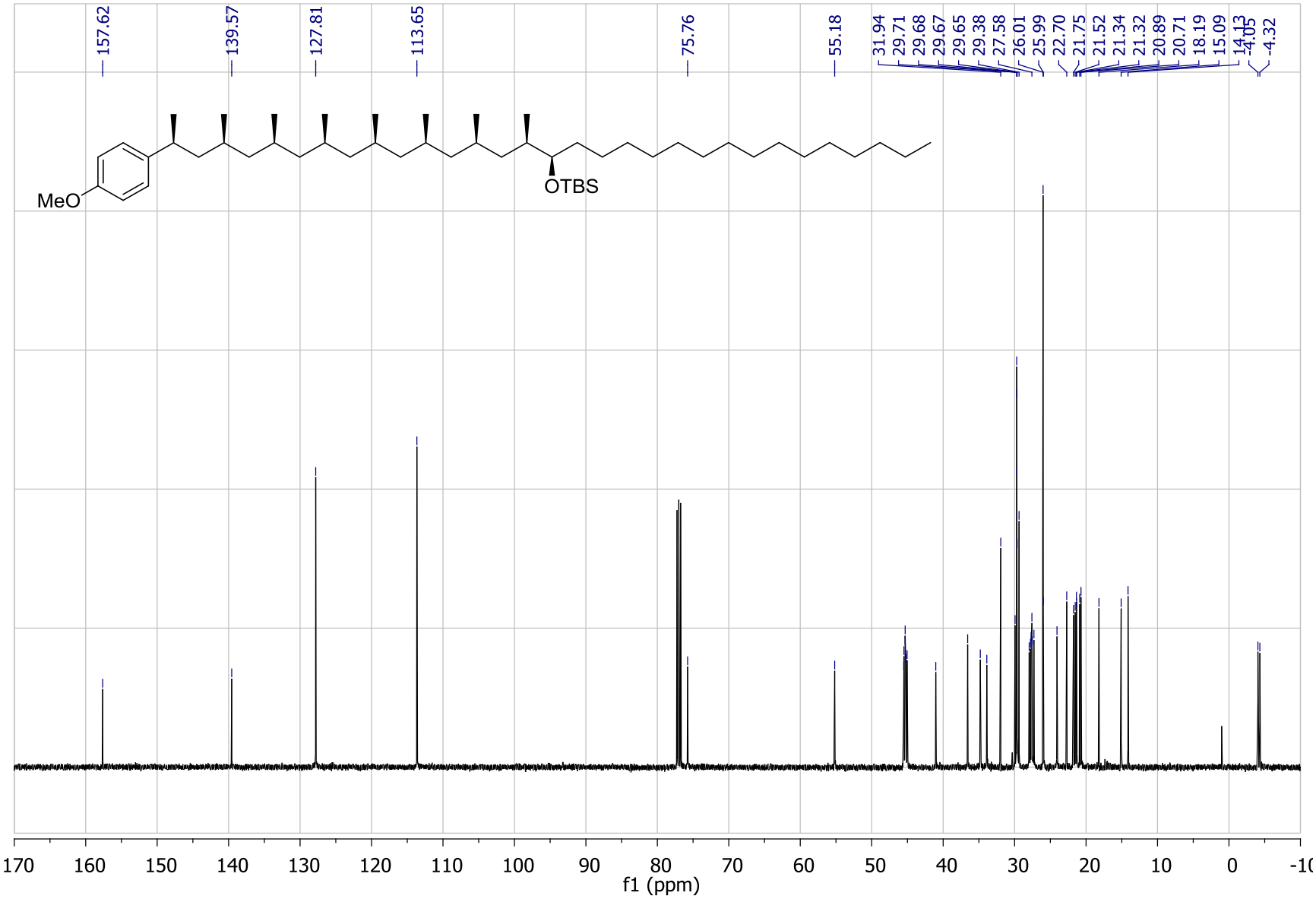

va/tb23634_tb52_4
single_pulse
O
SnBu3
N
O
1.00
2.02
2.09
6.29
32.20
12.29
18.07
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

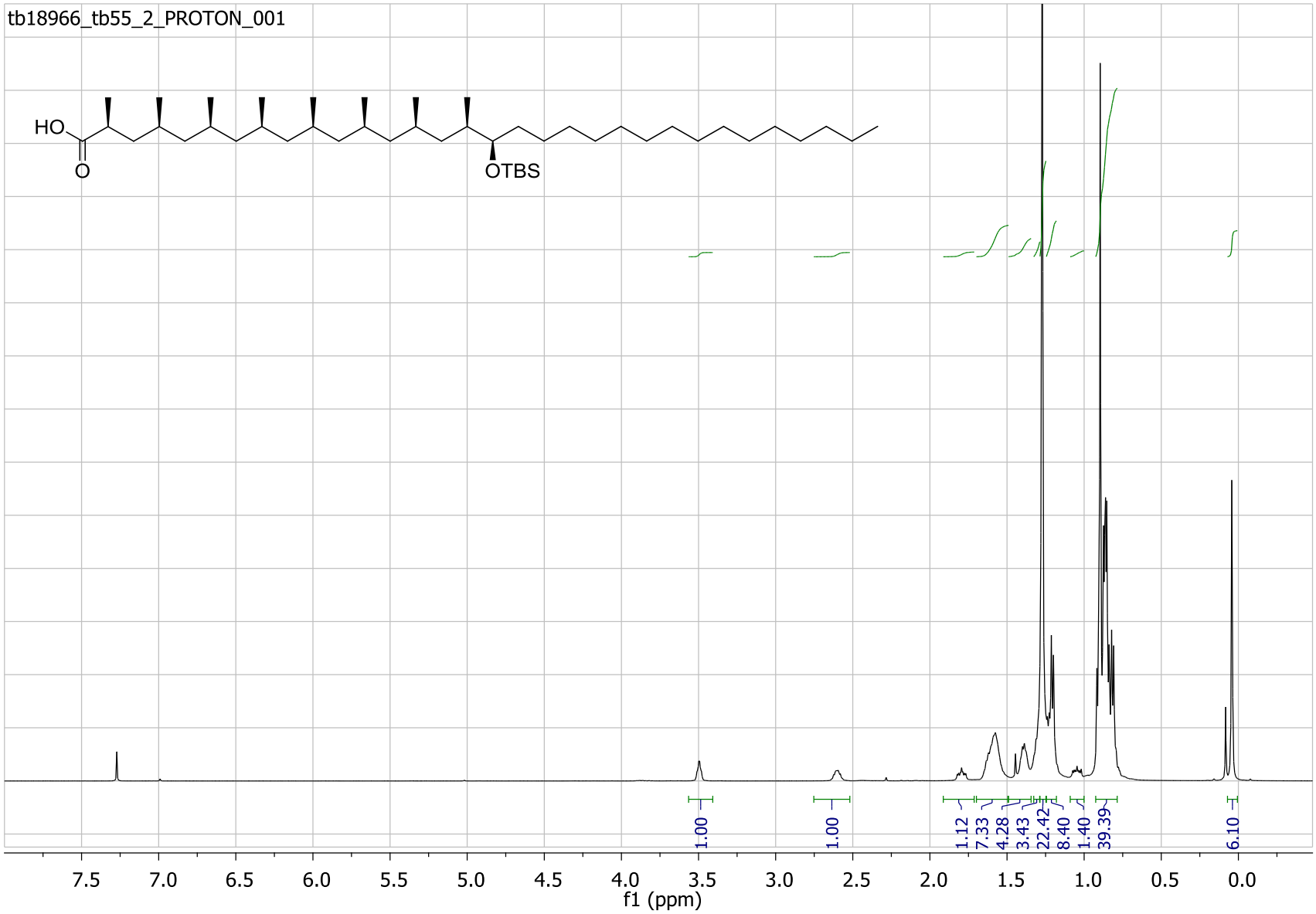

156.36
71.68
46.23
45.07
34.65
32.00
29.78
29.73
29.67
29.48
29.44
29.24
28.04
27.65
22.76
21.52
20.76
14.18
13.77
9.85
O
SnBu3
N
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

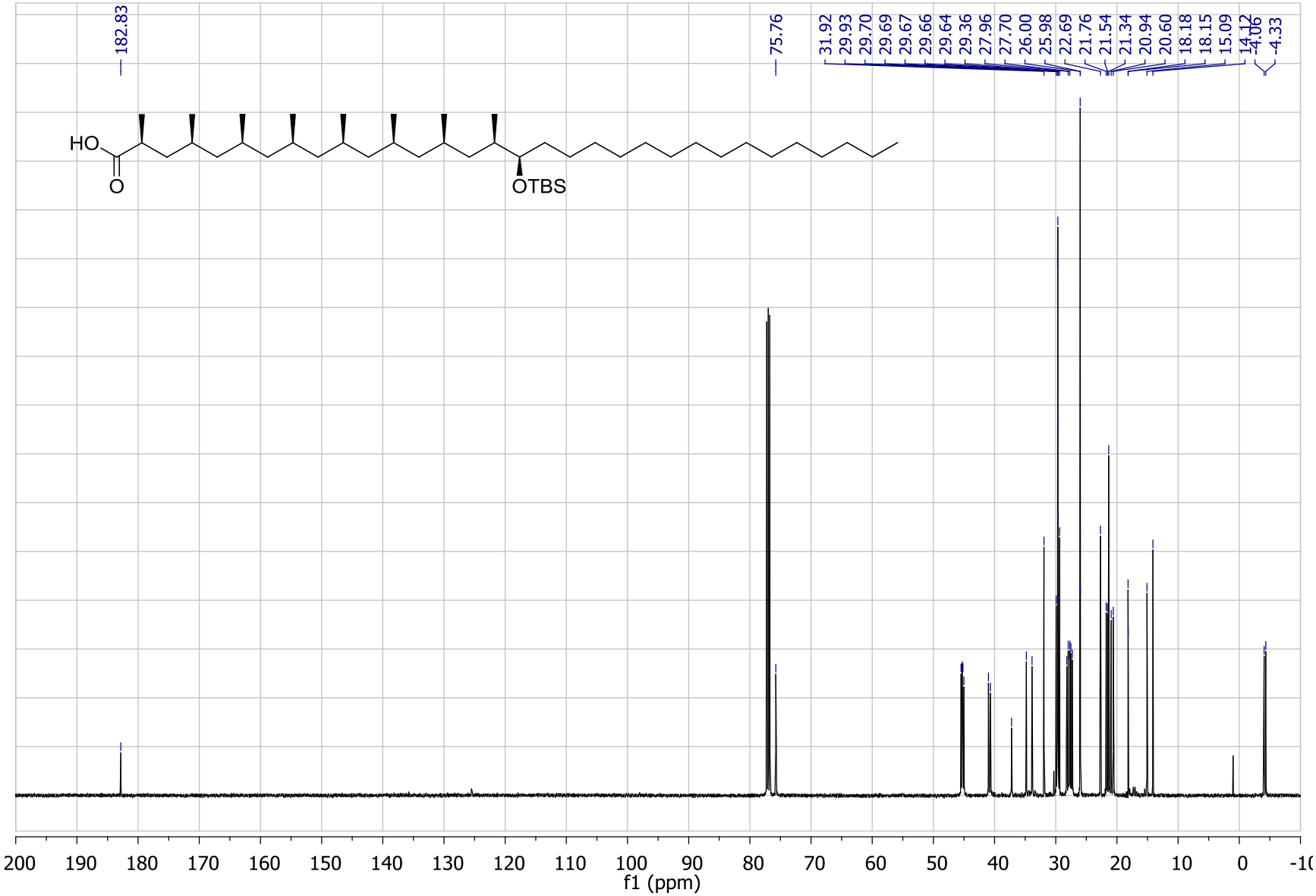

tb9294_tb53_OH_PROTON01
MeO
OH
2.00
2.00
3.08
1.00
1.00
7.33
5.27
2.39
1.35
20.23
2.41
9.39
1.31
27.07
3.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

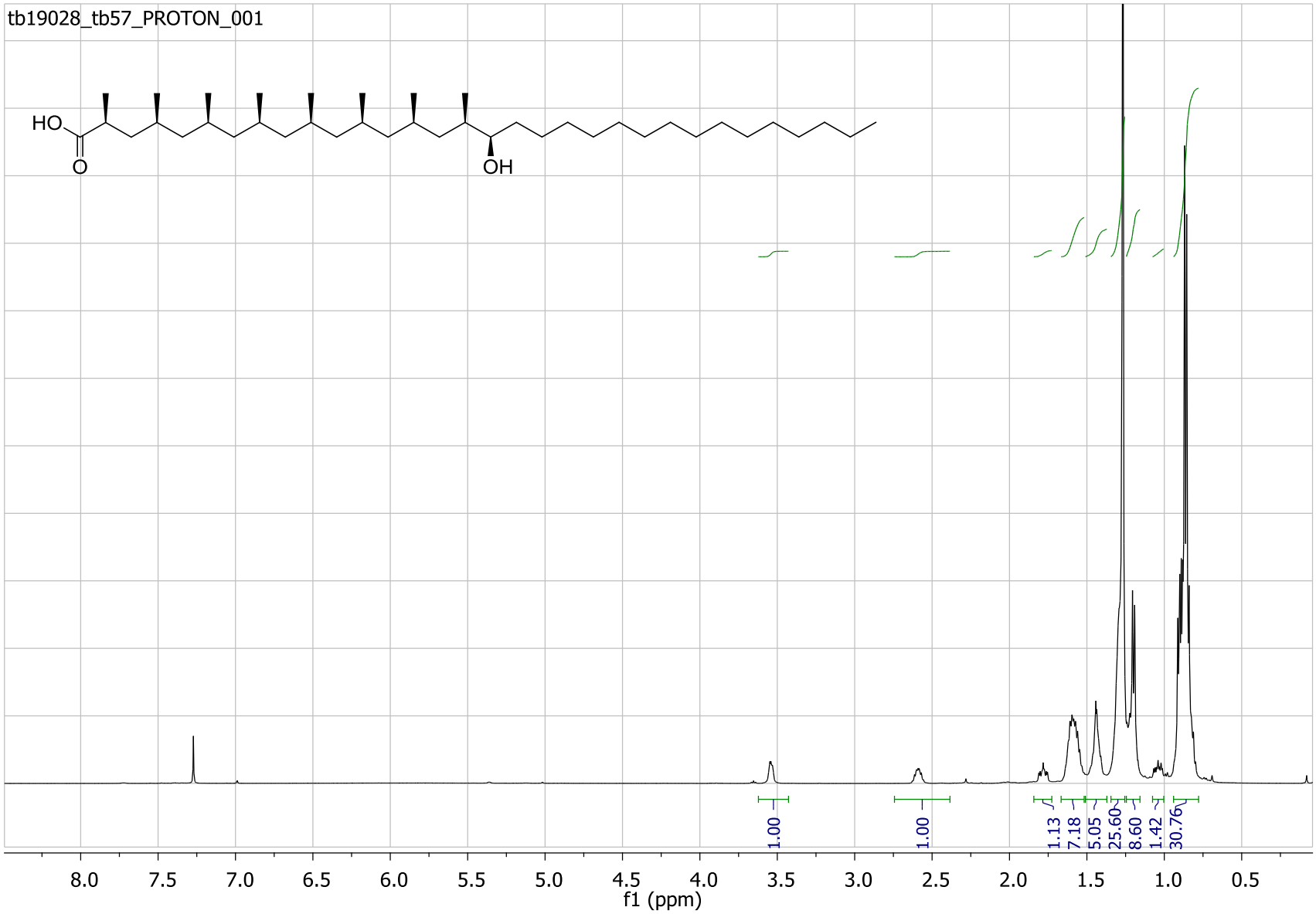

207.39
157.61
139.57
127.81
113.65
74.34
55.19
31.93
29.78
29.70
29.69
29.67
29.66
29.65
29.64
29.36
27.60
27.58
22.69
21.39
21.38
21.23
14.12
14.01
MeO
OH
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

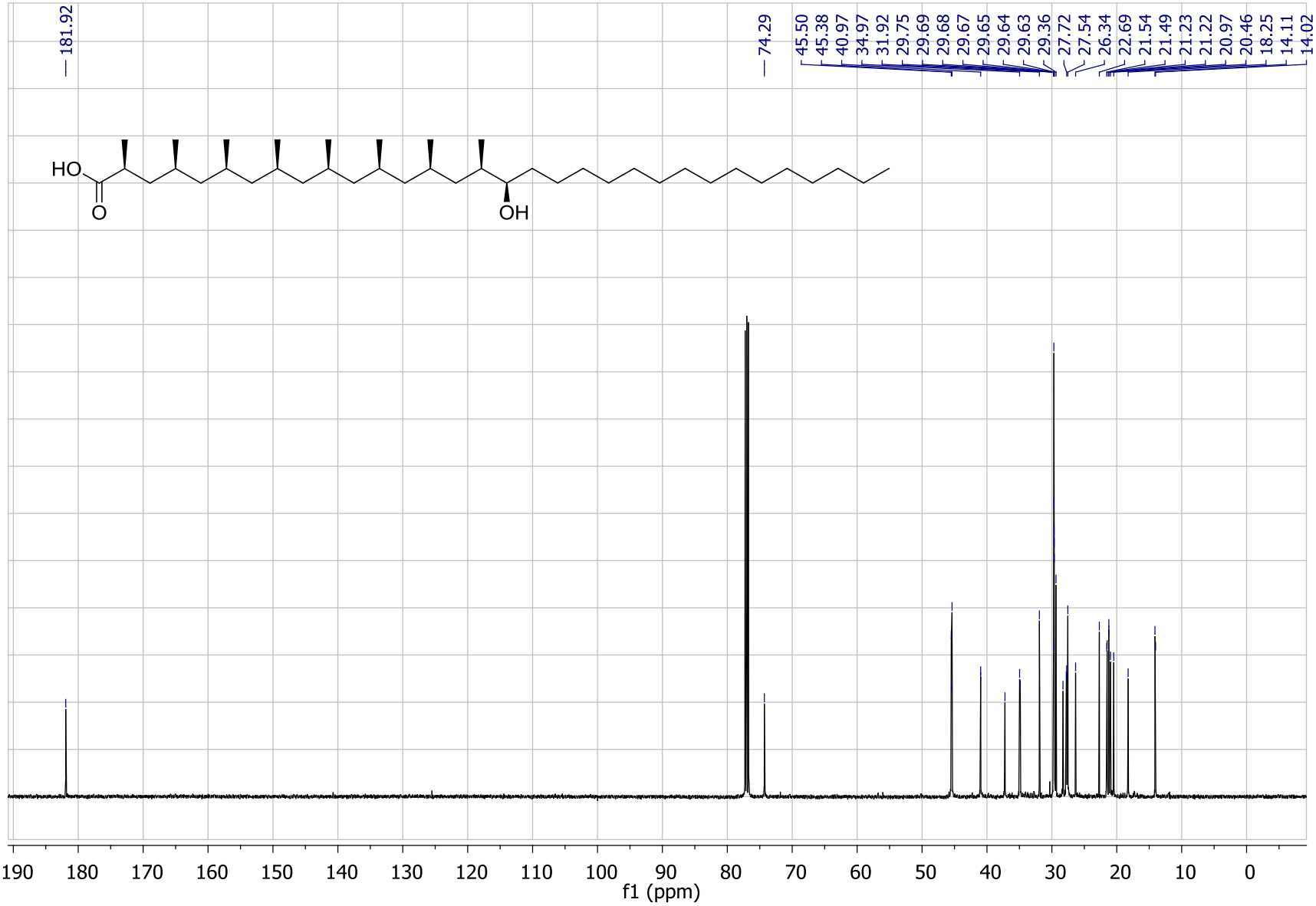

tb18928_tb54_PROTON_001
MeO
OTBS
2.00
2.00
3.14
1.03
1.02
7.34
4.40
3.43
20.30
2.34
9.34
37.40
3.14
6.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


157.62
139.57
127.81
113.65
75.76
55.18
31.94
29.71
29.68
29.67
29.65
29.38
27.58
26.01
25.99
22.70
21.75
21.52
21.34
21.32
20.89
20.71
18.19
15.09
14.13
14.05
-4.32
MeO
OTBS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


tb18966_tb55_2_PROTON_001
HO
O
OTBS
1.00
1.00
1.12
7.33
4.28
3.43
22.42
8.40
1.40
39.39
6.10
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)


182.83
75.76
31.92
29.93
29.70
29.69
29.67
29.66
29.64
29.36
27.96
27.70
26.00
25.98
22.69
21.76
21.54
21.34
20.94
20.60
18.18
18.15
15.09
14.12
14.06
-4.33
HO
O
OTBS
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


tb19028_tb57_PROTON_001
HO
O
OH
1.00
1.00
1.13
7.18
5.05
25.60
8.60
1.42
30.76
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)


181.92
74.29
45.50
45.38
40.97
34.97
31.92
29.75
29.69
29.68
29.67
29.65
29.64
29.63
29.36
27.72
27.54
26.34
22.69
21.54
21.49
21.23
21.22
20.97
20.46
18.25
14.11
14.02
HO
O
OH
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)