ELECTRONIC SUPPORTING INFORMATION

Sulfation made simple: A strategy for synthesising sulfated molecules

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CONTENTS

S1. General Methods:

All reactions involving moisture sensitive reagents were carried out in an oven-dried reaction vessel under nitrogen or argon. All anhydrous solvents were either directly obtained from an SPS or treated with 4 Å molecular sieves 24 h prior to use. Solvents used for work up procedures and column chromatography were of technical grade from Honeywell, VWR and Fischer Scientific. Unless stated otherwise, solvents were removed by rotary evaporation under a reduced pressure between 30-50 °C. All chemical reagents were used as received unless stated otherwise.

Reactions were monitored by TLC analysis on Merck silica gel 60 F_{254} using UV light and/or potassium permanganate.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance® III (400 MHz) spectrometer at 400 and 101 MHz, respectively. Chemical shift data for protons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane (TMS: δ 0.0) and referenced internally to the residual proton of the solvent. The deuterated solvents used for NMR analysis were: chloroform ($CDCl_3$: δ_H 7.26, δ_C 77.16), dimethyl sulfoxide ($(CD_3)_2SO$: δ_H 2.50, δ_C 39.52), methanol (CD_3OD: δ_H 3.31, δ_C 49.00) and deuterium oxide (D_2O: δ_H 4.79). Coupling constants are given in hertz (Hz). All individual assignments were made using 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, and ^{1}H-^{13}C HMBC) spectroscopy. The spectroscopic data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiple, br = broad and combinations thereof), coupling constant, integration and structural assignment.

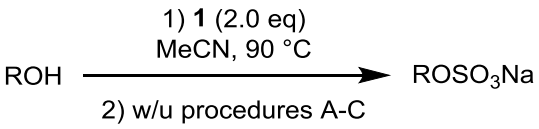
Mass spectra were recorded on a Waters Xevo G2-XS Tof or Synap G2-S mass spectrometer using Zspray, Electro-spray ionisation in positive (ESI+) and negative (ESI-) mode and chemical ionisation (CI).

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR and a Varian 660-IR FTIR spectrometer using Agilent Resolution Pro, with absorption maxima

(ν_{max}) reported in cm^{-1}. Optical rotations were measured using a Bellingham and Stanley ADP450 Series Peltier® polarimeter at 20 °C using the D line of sodium (589.3 nm) at the indicated concentration and solvent.

S2. General Procedures

General procedure 1. Synthetic procedure for the preparation of alkyl sulfates using tributyl sulfo ammonium betaine (Bu_3NSO_3, **1**).



A flame dried 25 mL Schlenk flask was charged with ROH (1.0 mmol) and **1** (2.0 eq. per OH group) under argon. Anhydrous MeCN was added (giving a concentration of 0.50-0.25 Mol dm^{-3} to the limiting reagent) and the reaction mixture heated at 90 °C, monitored by TLC. After the reaction was complete the flask was cooled to room temperature and the solvent removed under reduced pressure. The flask was charged with H_2O (20 mL) and the aqueous mixture extracted with EtOAc (4 × 30 mL). The organic extracts were pooled, dried ($MgSO_4$), filtered and the filtrate solvent was removed *in vacuo* to afford the desired sulfate ester as its tributylammonium salt.

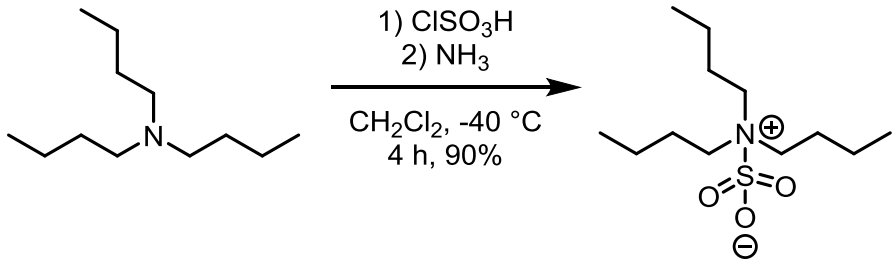
Work-up procedure A: The flask containing the tributylammonium salt was charged with EtOH (30 mL) and sodium 2-ethylhexanoate (5.0 eq. per sulfate group). The reaction mixture was stirred vigorously for 1 h at room temperature. The solid was collected by filtration, washed with EtOH (3 × 20 mL) and dried to a constant weight to afford the desired sulfate as its sodium salt.

Work-up procedure B: The flask containing the tributylammonium salt was charged with Et_2O (30 mL), EtOH (5 mL) and sodium 2-ethylhexanoate (5.0 eq. per sulfate group). The reaction mixture was stirred vigorously for 1h at room temperature. The solid was removed by filtration, washed with a small amount of cold EtOH and dried to a constant weight to afford the desired sulfate as its sodium salt.

Work-up procedure C: The flask containing the tributylammonium salt was charged with MeCN (20 mL) and sodium iodide (5.0 eq. per sulfate group). The reaction mixture was stirred vigorously for 1h at room temperature. The solid was removed by filtration, washed with MeCN (3 × 30 mL) and dried to a constant weight to afford the desired sulfate as its sodium salt.

S3. Compound characterisation

Preparation of tributyl sulfo ammonium betaine (**1**) [1]



A three necked round bottom flask was fitted with a temperature probe and a pressure equalising dropping funnel. The flask under an atmosphere of argon was charged with tributylamine (59.4 mL, 0.25 moles) and anhydrous CH_2Cl_2 (200 mL). The solution was stirred vigorously and cooled to -40 °C (MeCN/CO_2). A solution of chlorosulfonic acid (16.75 mL, 0.253 moles) in anhydrous CH_2Cl_2 (200 mL) was added dropwise over 2 h at a rate ensuring the internal temperature did not exceed -30 °C. After full addition of the chlorosulfonic acid solution, and stirring for a further 1 h, ammonia gas was gently bubbled through the reaction mixture until pH 7 was achieved. The white solid was removed by vacuum filtration, washed with CH_2Cl_2 (100 mL) and the filtrate was collected. The solvent was removed *in vacuo* and the crude product was treated with cold H_2O (500 mL). The precipitate was collected, washed with water (5 × 100 mL) and freeze dried. Recrystallisation from CH_2Cl_2/hexane affording **1** as a white solid (59.8 g, 0.23 mol, 90%).

M.P. 95-96 °C (from CH_2Cl_2/H_2O). Lit. 94 °C[1]

IR. ν_{max} cm^{-1} 2962w (C-H), 2875w (C-H), 1473m (C-H), 1293m (O-S), 1052m (O-S).

^{1}H NMR. δ_H (400 MHz, $CDCl_3$) 3.32 – 3.22 (m, 6H, N($C\underline{H}_2$)$_3$), 1.87 – 1.73 (m, 6H, $C\underline{H}_2$), 1.37 (dt, J = 7.4 Hz, 6H, $C\underline{H}_2$), 0.98 (t, J = 7.4 Hz, 9H, $C\underline{H}_3$).

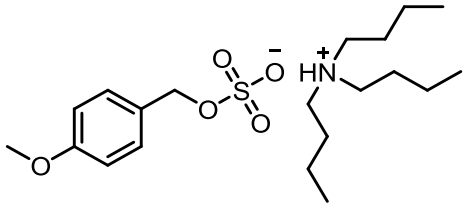
^{13}C NMR. δ_C (101 MHz, $CDCl_3$) 57.1 (N($\underline{C}H_2$)$_3$), 25.6 ($\underline{C}H_2$), 20.6 ($\underline{C}H_2$), 13.7 ($\underline{C}H_3$).

LRMS. *m*/*z* (ESI-) 264.1 ([M-H]$^-$, 100%), 208.1 ([M-C_4H_{10}]$^-$, 53).

HRMS. *m*/*z* (ESI-) $C_{12}H_{26}NO_3S$ [M-H]$^-$ calcd 264.1613, found: 264.1612.

Stability measurement of **1** showed that prolonged exposure to moisture in the air gave ~ 12% degradation of **1** after 15 d by ^{1}H NMR spectroscopy. Exclusion of moisture from the storage atmosphere (e.g N_2 or Ar atmosphere) in the vial containing **1** gave longer term stability (minimum 1 month per batch).

Tributylammonium 4-methoxybenzyl sulfate (**3c**)



Following **general procedure 1**: 4-methoxybenzyl alcohol (138 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the solvent removed *in vacuo*. The crude reaction product was purified (SiO_2; CH_2Cl_2/MeOH, 9:1, R_f = 0.6) to yield the title compound as a clear oil (350 mg, 87%).

IR. ν_{max} cm^{-1} 3467w br, 2960m, 2874w, 1613w, 1514s, 1465m, 1247s, 1196s

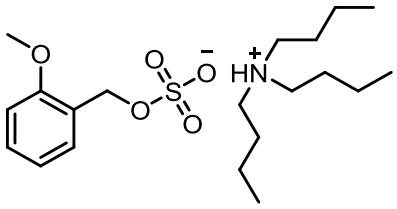
^{1}H NMR. δ_H (400 MHz, $CDCl_3$) 9.85 (br s, 1H, NH), 7.34 – 7.28 (m, 2H), 6.85 – 6.79 (m, 2H), 5.00 (s, 2H, ArCH_2), 3.77 (s, 3H, OCH_3), 3.03 – 2.90 (m, 6H, N(CH_2)$_3$), 1.73 – 1.58 (6H, m), 1.33 (h, *J* = 7.4 Hz, 6H), 0.91 (t, *J* = 7.4 Hz, 9H)

^{13}C NMR. δ_C (101 MHz, $CDCl_3$) 159.5, 130.1, 128.9, 113.7, 69.5, 55.3, 52.6, 25.3, 20.1, 13.6

LRMS. *m*/*z* (ESI+) 186.2 (100%, [M-OMe]$^{2+}$), 589.4 (20%, [M+HNBu$_3$]$^{+}$)

HRMS. *m*/*z* (ESI+) $C_{32}H_{65}N_2O_5S$ requires 589.4614, found 589.4619 [M+HNBu$_3$]$^{+}$

Tributylammonium 2-methoxybenzyl sulfate (**3f**)



Following **general procedure 1**: 2-methoxybenzyl alcohol (138 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (1.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the solvent removed *in vacuo*. The crude reaction product was purified (SiO_2; CH_2Cl_2/MeOH, 9:1, R_f = 0.6) to yield the title compound as a clear oil (350 mg, 87%).

IR. ν_{max} cm^{-1} 3442br, 2960w, 2874w, 1604w, 1590w, 1494m, 1463m, 1243s, 1196s

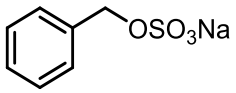
^{1}H NMR. δ_H (400 MHz, $CDCl_3$) 9.81 (br s, 1H, NH), 7.46 (d, *J* = 5.5 Hz, 1H), 7.25 – 7.20 (m, 1H), 6.90 (app. t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.15 (s, 2H, $ArCH_2$), 3.79 (s 3H, OCH_3), 3.03 – 2.91 (m, 6H, $N(CH_2)_3$), 1.67 (m, 6H), 1.33 (h, *J* = 6.8 Hz, 6H), 0.92 (t, *J* = 6.8 Hz, 9H).

^{13}C NMR. δ_C (101 MHz, $CDCl_3$) 157.1, 129.4, 128.9, 125.4, 120.4, 110.2, 64.8, 55.4, 52.6, 25.3, 20.1, 13.6.

LRMS. *m*/*z* (ESI+) 186.2 (100%, $[M\text{-}OMe]^{2+}$), 589.4 (60%, $[M+HNBu_3]^+$.

HRMS. *m*/*z* (ESI+) $C_{32}H_{65}N_2O_5S$ requires 589.4614, found 589.4617 $[M+HNBu_3]^+$.

Preparation of sodium benzyl sulfate (**4a**)[2]



Following **general procedure 1**: benzyl alcohol (108 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and purified by **work up procedure A** to yield the title sulfate as a bright white solid (200 mg, 95%).

M.P. 194-196 °C (lit. 194-196 °C)[2]

IR. ν_{max} cm^{-1} 3064 w, 3032 w, 1455 w, 1204 s.

^{1}H NMR. δ_H (400 MHz, CD_3OD) 7.46 – 7.27 (m, 5H, Ar), 5.03 (s, 2H, $ArC\underline{H}_2$).

^{13}C NMR. δ_C (101 MHz, CD_3OD) 136.4, 128.0, 127.7 (CH and q), 69.4.

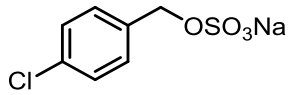
LRMS. *m*/*z* (ESI+) 233.0 ($[M+Na]^+$, 100%).

Data were consistent with the literature.

Control experiment with sequential PyH to Bu_4N cation exchange

Following **general procedure 1**: benzyl alcohol (108 mg, 1.0 mmol) and Py-SO_3 (2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2 h. The reaction was cooled to room temperature and Bu_4NI (2.0 eq.) was added ans stirred for 10 min. Solvents were removed *in vacuo* and the redsidue dissolved in EtOH (25 mL). Sodium-2-ethylhexanoated (5.0 eq.) was added and the mixture stirred for 1 h at room temperature. The precipitate was collected by filtration, washed with EtOH and dried under vacuum to afford **4a** as a white solid (99 mg, 47%_

Sodium 4-chlorobenzyl sulfate (**4b**)



Following **general procedure 1**: 4-chlorobenzyl alcohol (142 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and purified by **work up procedure A** to yield the title sulfate as a bright white solid (229 mg, 94%).

M.P. 202-204 °C

IR. ν_{max} cm^{-1} 2193 w, 1205 w.

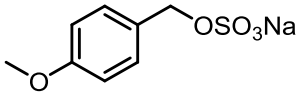
^{1}H NMR. δ_H (400 MHz, CD_3OD) 7.46 – 7.28 (m, 4H, Ar), 4.99 (s, 2H, $ArCH_2$).

^{13}C NMR. δ_C (101 MHz, CD_3OD) 136.8, 134.8, 130.6, 129.5, 69.8.

LRMS. *m*/*z* (ESI+) 266.9 ($[M+Na]^+$, 100%).

HRMS. *m*/*z* (ESI+) $C_7H_6ClNa_2O_4S$ requires 266.9470, found 266.9471 $[M+Na]^+$.

Sodium 4-methoxybenzyl sulfate (**4c**)



Tributylammonium 4-methoxybenzyl sulfate (**3c**) (161 mg, 0.4 mmol) was subjected to **work up procedure C** to yield the title compound as an lustrous white solid (93 mg, 86%).

M.P. 100 ˚C (decomposed to a pink solid)

IR. ν_{max} cm^{-1} 3014w, 2842w, 1612w, 1514m, 1250s

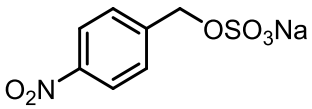
^{1}H NMR. δ_H (400 MHz, $(CD_3)_2SO$) 7.25 (d, *J* = 8.1 Hz, 2H, Ar), 6.89 (d, *J* = 8.1 Hz, 2H, Ar), 4.69 (s, 2H, ArC<u>H</u>$_2$), 3.74 (s, 3H, OC<u>H</u>$_3$).

^{13}C NMR. δ_C (101 MHz, $(CD_3)_2SO$) 158.7, 129.7, 129.4, 113.6, 67.3, 55.1.

LRMS. *m*/*z* (ESI+) 281.1 ($[M+Na+H_2O]^+$, 100%), 263.0 ($[M+Na]^+$, 10).

HRMS. *m*/*z* (ESI+) $C_8H_9O_5Na_2S$ requires 262.9965, found 262.9966 $[M+Na]^+$.

Sodium 4-nitrobenzyl sulfate (**4d**)



Following **general procedure 1**: 4-nitrobenzyl alcohol (153 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the contents purified by **work up procedure B**. Recrystalisation from hot MeOH afforded the title compound as light yellow crystals (216 mg, 85%).

M.P. 162-167 °C (dec.)

IR. ν_{max} cm^{-1} 2685w, 2593w, 1613w, 1536s, 1351s, 1239s

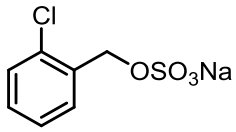
^{1}H NMR. δ_H (400 MHz, D_2O) 8.26–8.21 (m, 2H), 7.69–7.55 (m, 2H), 5.17 (s, 2H, ArC<u>H</u>$_2$).

^{13}C NMR. δ_C (101 MHz, D_2O) 147.4, 143.2, 128.4, 123.8, 69.1.

LRMS. *m*/*z* (ESI+) 277.9 ([M+Na]$^+$, 100%).

HRMS. *m*/*z* (ESI+) $C_7H_6NO_6Na_2S$ requires 277.9711, found 277.9712 [M+Na]$^+$.

Sodium 2-chlorobenzyl sulfate (**4e**)



Following **general procedure 1:** 2-chlorobenzyl alcohol (142 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and purified by **work up procedure A** to yield the title compound as a white solid (242 mg, 99%).

M.P. 219-221 °C

IR. ν_{max} cm^{-1} 3580w, 1478w, 1252s, 1203s

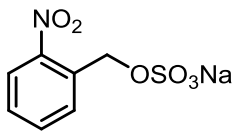
^{1}H NMR. δ_H (400 MHz, D_2O) 7.52–7.43 (m, 2H), 7.39–7.31 (m, 2H), 5.15 (s, 2H, ArC$\underline{H}_2$).

^{13}C NMR. δ_C (101 MHz, D_2O) 133.5, 132.5, 130.8, 130.4, 129.5, 127.3, 68.1.

LRMS. *m*/*z* (ESI+) 266.9 ([M^{35}Cl+Na]$^+$, 100%), 268.9 ([M^{37}Cl+Na]$^+$, 30%).

HRMS. *m*/*z* (ESI+) $C_7H_6O_4Na_2SCl$ requires 266.9471, found 266.9475 [M^{35}Cl+Na]$^+$.

Sodium 2-nitrobenzyl sulfate (**4g**)[3]



Following **general procedure 1**: 2-nitrobenzyl alcohol (153 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the contents purified by **work up procedure B**.

Recrystalisation from hot MeOH yielded the title sulfate as light yellow crystals (180 mg, 71 %).

M.P. 109-111 °C (dec.)

IR. ν_{max} cm^{-1} 1610w, 1526s, 1334s, 1225s

^{1}H NMR. δ_H (400 MHz, D_2O) 8.14–8.08 (m, 1H), 7.78–7.69 (m, 2H), 7.59–7.52 (m, 1H), 5.41 (s, 2H, ArC$\underline{H}_2$).

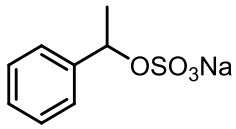
^{13}C NMR. δ_C (101 MHz, D_2O) 144.2, 134.4, 131.2, 129.5, 129.3, 125.0, 67.1.

LRMS. *m*/*z* (ESI+) 277.9 ([M+Na]$^+$, 100%).

HRMS. *m*/*z* (ESI+) $C_7H_6NO_6Na_2S$ requires 277.9711, found 277.9713 [M+Na]$^+$.

Data were in accordance with literature.

Sodium 1-phenylethyl sulfate (**4h**) [4]



Following **general procedure 1**: 1-phenyl ethanol (122 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and purified by **work up procedure B**. The final solid was suspended in EtOAc and filtered to yield the desired sulfate as its sodium salt (200 mg, 89%).

M.P. 165-167 °C

IR. ν_{max} cm^{-1} 1582w, 1388w, 1148s

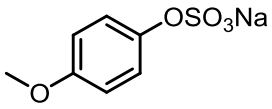
^{1}H NMR. δ_H (400 MHz, CD_3OD) 7.43–7.38 (m, 2H), 7.34–7.28 (m, 2H), 7.27–7.21 (m, 1H), 5.46 (q, *J* = 6.6 Hz, 1H, ArC$\underline{H}$), 1.60 (d, *J* = 6.6 Hz, 3H, C$\underline{H}_3$).

^{13}C NMR. δ_C (101 MHz,CD_3OD) 144.0, 129.2, 128.5, 127.0, 78.0, 23.7.

LRMS. *m*/*z* (ESI+) 695.2 ([3M+Na]$^+$, 100%), 225.0 ([M+H]$^+$, 40%).

HRMS. *m*/*z* (ESI+) $C_8H_{10}O_4NaS$ requires 225.0198, found 225.0199 [M+H]$^+$.

Sodium 4-methoxyphenyl sulfate (**4i**)



Following **general procedure 1**: 4-methoxy phenol (124 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 5 h. The flask was cooled and purified by **work up procedure B** to yield the desired sulfate as its sodium salt (176 mg, 78%).

M.P. 265 °C (dec.)

IR. ν_{max} cm^{-1} 2955w 2499w, 1504s; 1199s.

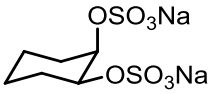
^{1}H NMR. δ_H (400 MHz, CD_3OD) 6.75–6.67 (m, 4H, Ar), 3.69 (s, 3H, $OC\underline{H}_3$).

^{13}C NMR. δ_C (101 MHz, CD_3OD) 154.4, 152.1, 116.7, 115.7, 56.1.

LRMS. *m*/*z* (ESI+) 331.2 ([3M+2MeCN+Na]$^+$, 100%), 516.3 ([2M+MeCN+Na+H]$^+$, 10%),

HRMS. *m*/*z* (ESI+) $C_8H_{10}O_4NaS$ requires 225.0198, found 225.0199, $C_9H_{10}NNa_2O_5S$ requires 290.0075, found 290.0076 [M+MeCN+Na].

Sodium (1*R*, 2*S*)-cyclohexane-1,2-diyl bis(sulfate) (**5**)[5]



Following **general procedure 1**: *cis*-cyclohexanediol (116 mg, 1.0 mmol) and **1** (1.06 g, 4.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 5.0 h. The flask was cooled and purified by **work up procedure A**. Recrystalisation from hot EtOH yielded the title sulfate as a bright white solid (290 mg, 91%).

M.P. 203-205 °C (dec.)

IR. ν_{max} cm^{-1} 2946w, 1456w, 1328w, 1258w, 1232w, 1200w.

^{1}H NMR. δ_H (400 MHz, D_2O) 4.57 – 4.52 (m, 2H)), 1.98-1.95 (m, 2H), 1.76 – 1.55 (m, 4H), 1.49 – 1.33 (m, 2H).

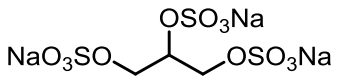
^{13}C NMR. δ_C (101 MHz, D_2O) 77.8, 27.7, 20.8.

LRMS. *m*/*z* (ESI+) 342.9 ([M+Na]$^+$, 100%), 306.85 (40%), 164.92 (32%).

HRMS. *m*/*z* (ESI+) $C_6H_{10}O_8Na_3S_2$ requires 342.9510, found 342.9514 [M+Na]$^+$.

Data were in accordance with literature.

Sodium propane-1,2,3-triyl tris(sulfate) (**6**)[6]



Following **general procedure 1**: Glycerol (92 mg, 1.0 mmol) and **1** (1.59 g, 6.0 mmol) were dissolved in dry MeCN (4.0 mL) and heated under reflux for 8 h. The flask was cooled and purified by **work up procedure A**. Recrytalisation from hot EtOH yielded the title sulfate as a bright white solid (365 mg, 92%).

M.P. 210 °C (dec.)

IR. ν_{max} cm^{-1} 1639 w, 1216 s.

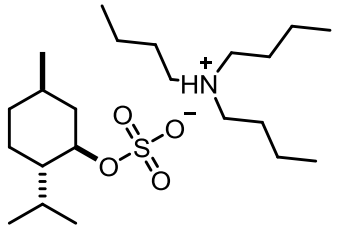
^{1}H NMR. δ_H (400 MHz, D_2O) 4.80 (p, *J* = 4.8 Hz, 1H, C<u>H</u>OSO$_3$Na), 4.27 (qd, *J* = 11.1, 4.8 Hz, 4H, C<u>H$_2$</u>OSO$_3$Na).

^{13}C NMR. δ_C (101 MHz, D_2O) 74.5, 66.2.

LRMS. *m*/*z* (ESI+) 420.8 (100%, [M+Na]$^+$), 306.85 (50%).

HRMS. *m*/*z* (ESI+) $C_3H_5O_{12}Na_4S_3$ requires 420.8534, found 420.8538 [M+Na]$^+$

Tributylammonium (±)-2-*iso*propyl-5-methylcyclohexyl sulfate (**7**)



Following **general procedure 1**: (±)-menthol (156 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 3 h. The flask was cooled and the solvent was removed under reduced pressure. The crude

contents were purified (SiO_2; CH_2Cl_2/MeOH, 9:1, R_f = 0.45) to yield the title compound as a white crystalline solid (330 mg, 78%).

M.P. 92 °C

IR. ν_{max} cm^{-1} 2957 m, 2870 m, 1458 m, 1248 s

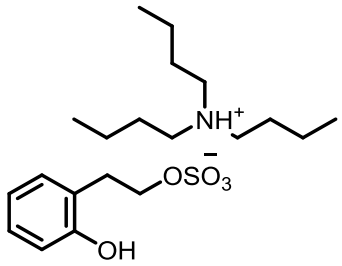
^{1}H NMR. δ_H (400 MHz, $CDCl_3$) 9.95 (br s, 1H, NH), 4.16 (td, *J* = 10.7, 4.4 Hz, 1H, CHOSO$_3$), 3.04 – 2.94 (m, 6H, N(CH_2)$_3$), 2.49 – 2.43 (m, 1H, CH^{i}Pr), 2.26 (sd, *J* = 7.0, 2.5 Hz, 1H, CH(CH_3)$_2$), 1.74 – 1.63 (m, 6H, N(CH_2)$_3$), 1.63 – 1.57 (m, 2H), 1.35 (h, *J* = 7.4 Hz, 6H), 1.24 (tdd, *J* = 10.7, 3.4, 1.7 Hz, 1H), 1.10 – 0.96 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 9H), 0.82 (dd, *J* = 6.8, 4.4 Hz, 6H), 0.77 (d, *J* = 6.8 Hz, 3H, CH_3).

^{13}C NMR. δ_C (101 MHz, $CDCl_3$) 78.9, 52.6, 48.1, 42.0, 34.4, 31.6, 25.4, 25.3, 23.2, 22.2, 21.2, 20.1, 16.0, 13.6.

LRMS. *m*/*z* (ESI+) 607.62 (100%, [M+NBu$_3$]$^+$).

HRMS. *m*/*z* (ESI+) $C_{34}H_{75}N_2O_4S$ requires 647.5448, found 647.5446 [M+NBu$_3$]$^+$.

Sodium 2-hydroxyphenylethanol sulfate (**8**)



Following **general procedure 1**: 2-hydroxyphenyl ethanol (138 mg, 1.0 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in dry MeCN (4.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography CH_2Cl_2/MeOH (19:1 to 9:1) to afford the title compound as a clear oil (300 mg, 74%)

IR. ν_{max} cm^{-1} 3259 br, 2962 w, 2874 w, 1596 w, 1456 m, 1245 s, 1200 s

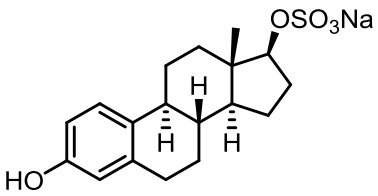
^{1}H NMR. (400 MHz, $CDCl_3$) 7.94 (br s, 2H), 7.08 – 6.97 (m, 2H), 6.89 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.72 (td, *J* = 8.0, 1.3 Hz, 1H), 4.26 (t, *J* = 6.7 Hz, 2H, CH_2), 2.98 (t, *J* = 6.7 Hz, 2H, CH_2), 2.96 – 2.88 (m, 6H, N(CH_2)$_3$), 1.69 – 1.55 (m, 6H), 1.29 (h, *J* = 7.4 Hz, 6H), 0.88 (t, *J* = 7.4 Hz, 9H, CH_3)

^{13}C NMR. (101 MHz, $CDCl_3$) δ_C 155.2, 130.3, 127.5, 124.0, 119.4, 115.8, 68.15, 52.4, 30.5, 25.1, 19.6, 13.2

LRMS. *m*/*z* (ESI+) 589.50 (100%, $[M+NHBu_3]^+$).

HRMS. *m*/*z* (ESI+) $C_{32}H_{65}N_2O_5S$ requires: 589.4614, Found: 589.4617 $[M+NHBu_3]^+$.

Sodium (17β)-estra-1,3,5(10)-triene-3-ol,17-sulfate (**9a**)



Following **general procedure 1**: β-Estradiol (272 mg, 1.0 mmol) and **1** (398 mg, 1.5 mmol) were dissolved in dry MeCN (4.0 mL) and heated under reflux for 3 h. The flask was cooled and the solvent was removed under reduced pressure. The contents were purified (SiO_2; CH_2Cl_2/MeOH, 9:1, R_f = 0.16) to yield an intermediate tributylammonium sulfate as a clear oil (321 mg, 0.6 mmol). The intermediate was purified by **work up procedure C** to yield the title compound as a bright white solid (225 mg, 60%).

M.P. 170 °C (dec. to a green solid);

IR. ν_{max} cm^{-1} 3432 br, 2925 w, 2869 w, 1612 w, 1499 w, 1210 s

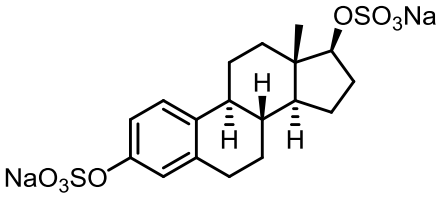
^{1}H NMR. δ_H (400 MHz, $(CD_3)_2SO$) 9.01 (s, 1H, O<u>H</u>), 7.04 (d, *J* = 8.5 Hz, 1H, C1<u>H</u>), 6.50 (dd, *J* = 8.5, 2.6 Hz, 1H, C2<u>H</u>), 6.42 (d, *J* = 2.6 Hz, 1H, C4<u>H</u>), 4.05 (t, *J* = 8.5 Hz, 1H), 2.69 (d, *J* = 6.8 Hz, 2H), 2.29–2.13 (m, 1H), 2.16–1.83 (m, 3H), 1.84–1.70 (m, 1H), 1.66-1.44 (m, 2H), 1.33-1.06 (m, 6H), 0.68 (s, 3H, C<u>H</u>$_3$).

^{13}C NMR. δ_C (101 MHz, $(CD_3)_2SO$) 154.9, 137.1, 130.4, 126.1, 114.9, 112.7, 84.1, 49.2, 43.5, 42.4, 38.5, 36.6, 29.2, 28.2, 26.9, 26.0, 22.7, 11.7.

LRMS. *m*/*z* (ESI-) 351.13 (100%, $[M-Na]^-$), 725.32 (100%, $[2M-Na]^-$), 703.31 (90%, $[2M-2Na+H]^-$)

HRMS *m*/*z* (ESI-) $C_{18}H_{23}O_5S$ requires 351.1268, found 351.1268 $[M-Na]^-$

Sodium (8*R*,9*S*,13*S*,14*S*,17*S*)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-*6H*-cyclopenta[*a*]phenanthrene-3,17-diyl bis(sulfate) (**9b**)



Adapted from **general procedure 1**: β-Estradiol (136 mg, 0.5 mmol) and **1** (663 mg, 2.5 mmol) were dissolved in dry MeCN (1.0 mL) and heated under reflux for 4 h. The flask was cooled and the solvent was removed under reduced pressure. The crude product was purified by **work up procedure C** to produce a white solid containing <4% **12a** as an impurity (calculated by ^{1}H-NMR). Recrystallization form MeOH/EtOAc afforded the title compound as a bright white solid (200 mg, 84%).

M.P. 137-140 °C (dec. to a red solid)

$[\alpha]_D^{25}$ 6.51 (1.0, H_2O)

IR. ν_{max} cm^{-1} 2926 w, 2868 w, 1609 w, 1499 w, 1214 s

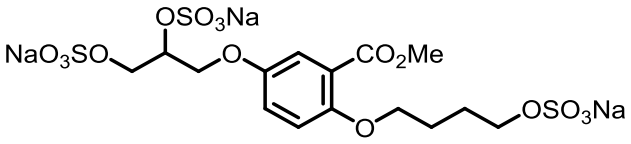
^{1}H NMR. δ_H (400 MHz, $(CD_3)_2SO$) δ 7.15 (d, *J* = 8.5 Hz, 1H), 6.93–6.75 (m, 2H), 4.05 (q, *J* = 10.9, 9.7 Hz, 1H, C17-H), 2.85–2.67 (m, 2H), 2.31–2.17 (m, 1H), 2.17–2.09 (m, 1H), 2.09–1.87 (m, 2H), 1.87–1.70 (m, 1H), 1.69–1.48 (m, 2H), 1.44–1.05 (m, 6H), 0.70 (s, 3H).

^{13}C NMR. δ_C (101 MHz, $(CD_3)_2SO$) 151.1, 136.1, 134.8, 125.5, 120.5, 118.0, 84.1, 49.2, 43.6, 42.4, 38.3, 36.6, 29.2, 28.2, 26.8, 25.9, 22.7, 11.7.

LRMS. *m*/*z* (ESI+) 499.05 (100%, $[M+Na]^+$), 379.01 (50%), 261.01 (50%).

HRMS. *m*/*z* (ESI+) $C_{18}H_{22}O_8Na_3S_2$ requires 499.0449, found 499.0450 $[M+Na]^+$.

Sodium 3-(3-(methoxycarbonyl)-4-(4-(sulfonatooxy)butoxy)phenoxy)propane-1,2-diyl bis(sulfate) (**10**)[7]



Following **general procedure 1**: **13** (314 mg, 1.0 mmol) and **1** (1.59 g, 6.0 mmol) were dissolved in dry MeCN (4.0 mL) and heated under reflux for 12 h. The flask was

cooled and purified by **work up procedure C** to yield the title compound as a white solid (470 mg, 76%).

M.P. 218 °C (dec.)

IR. ν_{max} cm^{-1} 3493, 2951, 1707

^{1}H NMR. δ_H (400 MHz, D_2O) 7.42 (d, *J* = 3.2 Hz, 1H, ArH), 7.25 (dd, *J* = 9.1, 3.2 Hz, 1H, ArH), 7.13 (d, *J* = 9.2 Hz, 1H, ArH), 4.88 (p, *J* = 4.8 Hz, 1H, CHOSO$_3$Na), 4.46 – 4.30 (m, 3H), 4.27 (dd, *J* = 11.0, 5.1 Hz, 1H), 4.12 (dt, *J* = 8.1, 5.6 Hz, 4H), 3.91 (s, 3H, CH_3), 1.94 – 1.81 (m, 4H, $(CH_2)_2$).

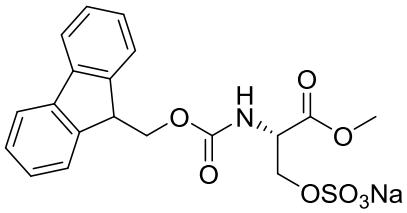
^{13}C NMR. δ_C (101 MHz, D_2O) δ_C 167.9, 152.1, 151.2, 121.1, 119.6, 116.9, 116.0, 74.5, 69.3, 68.6, 66.9, 65.9, 52.2, 24.8, 24.4.

LRMS. *m*/*z* (ESI+) 642.94 (100%, $[M+Na]^+$), 541.00 (80%, $[M-SO_3]^+$, 439.06 (50%, $[M-Na(SO_3)_2]^+$

HRMS. *m*/*z* (ESI+) $C_{15}H_{19}Na_3O_{16}S_3$ requires: 642.9426, Found: 642.9420 $[M+Na^+]$

Data in accordance with literature.

Sodium (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl sulfate (**11**)



Following **general procedure A**: Methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-serinate (170 mg, 0.5 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in 2 mL dry MeCN and heated under reflux for 6 h. The tributylammonium salt was purified by cation exchange procedure C to yield the title sulfate as a bright white solid (210 mg, 95%).

Low Temperature method

Methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-serinate (170 mg, 0.5 mmol) and **1** (530 mg, 2.0 mmol) were dissolved in 2 mL dry DMF and heated at 38 °C for 52 h.

The flask was charged with H_2O (20 mL) and the aqueous mixture extracted with EtOAc (4 × 30 mL). The organic extracts were pooled and dried over anhydrous $MgSO_4$. Filtration of the solid and removal of the solvent under reduced pressure yielded the desired sulfate as its tributylammonium salt. The tributylammonium salt was purified by cation exchange procedure C to yield the title sulfate as a bright white solid (200 mg, 90%).

M.P. 179-182 °C (decomposed at 189 °C)

$[\alpha]_D^{25}$ 4.20 (1.0, H_2O)

IR. ν_{max} cm^{-1} 3602w, 3389m, 3025w, 1740m, 1709s, 1621w, 1522s.

^{1}H NMR. δ_H (400 MHz, DMSO-d_6) 7.89 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.37 – 7.30 (m, 2H), 4.33 (td, J = 7.0, 4.3 Hz, 1H), 4.25 (br q, J = 4.3 Hz, 3H), 4.10 (dd, J = 11.0, 4.3 Hz, 1H), 3.97 (dd, J = 11.0, 6.6 Hz, 1H), 3.65 (s, 3H, C$\underline{H}_3$).

^{13}C NMR. δ_C (101 MHz, DMSO-d_6) 170.6, 155.9, 143.8, 140.7, 127.7, 127.2, 125.4, 120.2, 66.0, 64.8, 54.4, 52.1, 46.6

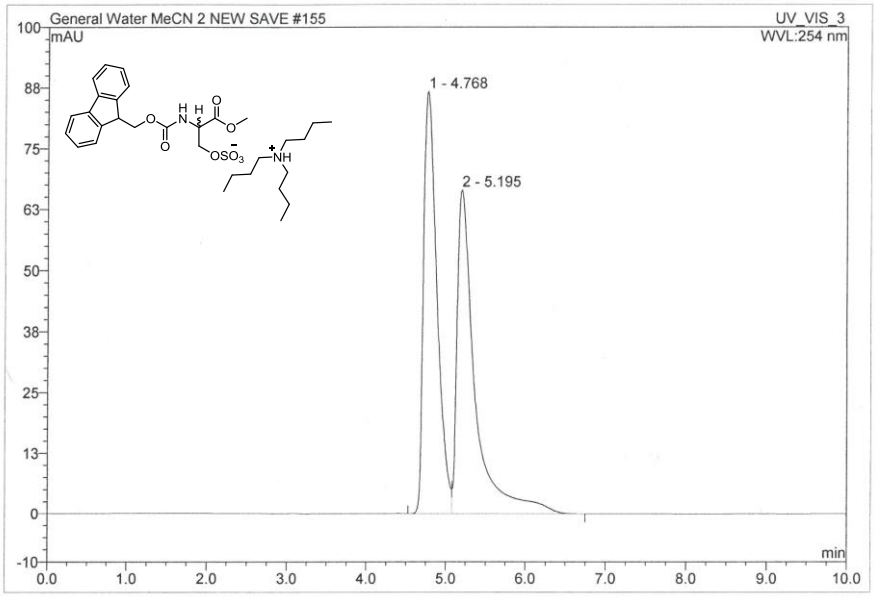
LRMS. m/z (ESI+) 466.06 (100%, $[M+2Na]^+$), 909.10 (50%, $[2M+3Na]^+$).

HRMS. m/z (ESI+) $C_{19}H_{18}NO_8Na_2S$ requires 466.0549, found 466.0555 $[M+2Na]^+$.

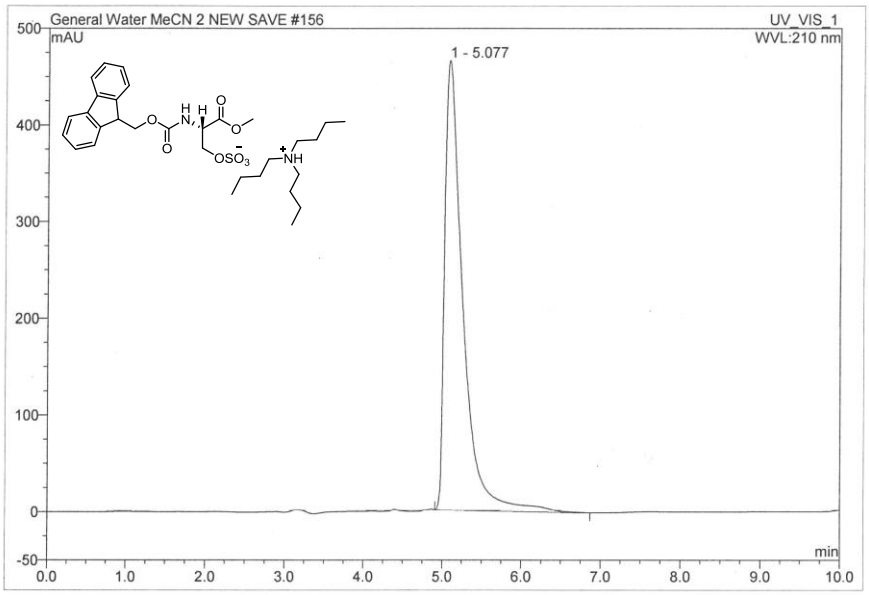
Chiral HPLC traces are provided for the intermediate Bu_4N salt of **11**.

Phenomenex® Cellulose 1 chiral HPLC column traces for the sulfation step on 11

Conditions used: MeCN/H_2O (2:3) 1 ml min^{-1}



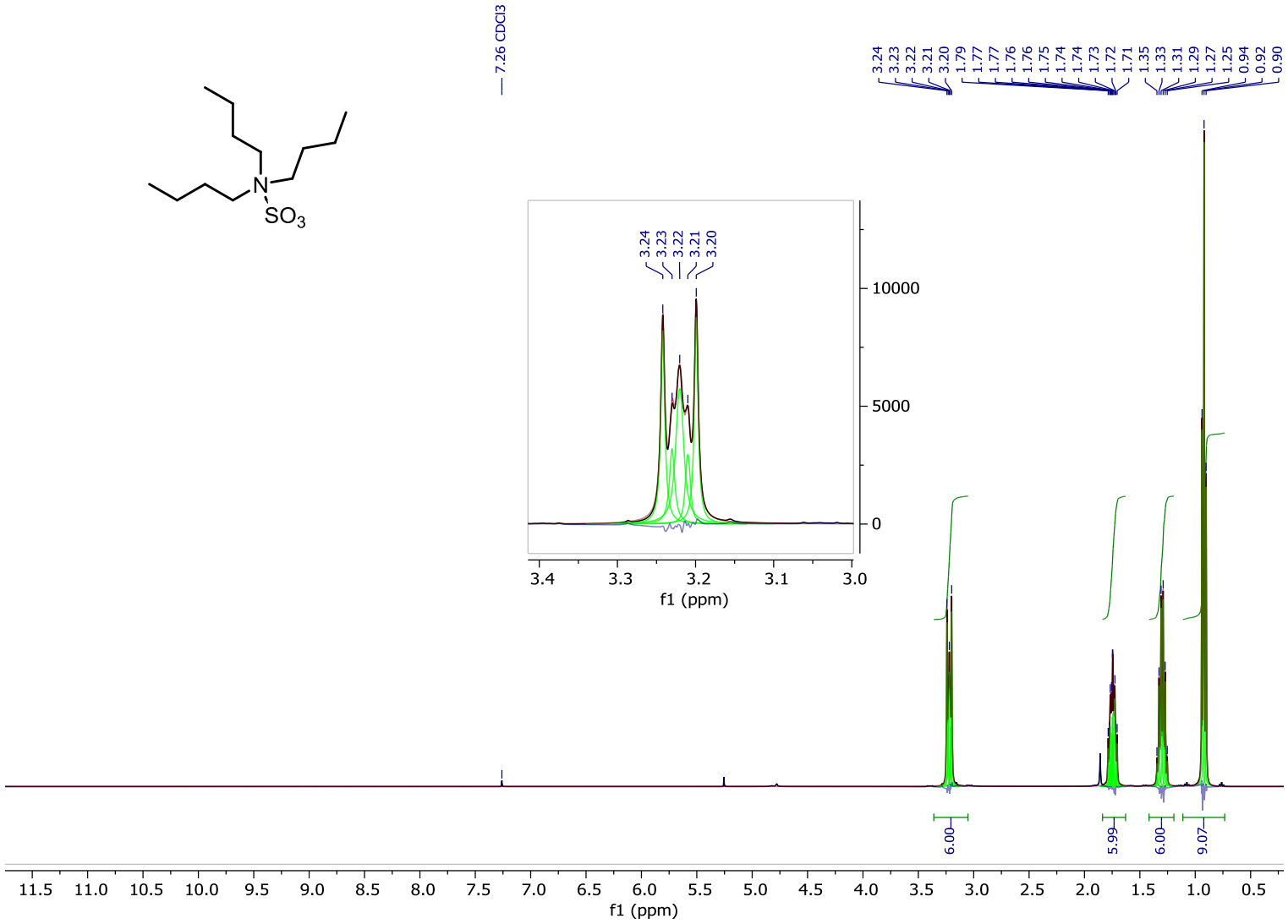
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.77	n.a.	86.819	17.037	49.41	n.a.	BM
2	5.19	n.a.	66.548	17.446	50.59	n.a.	MB
Total:			153.367	34.484	100.00	0.000	



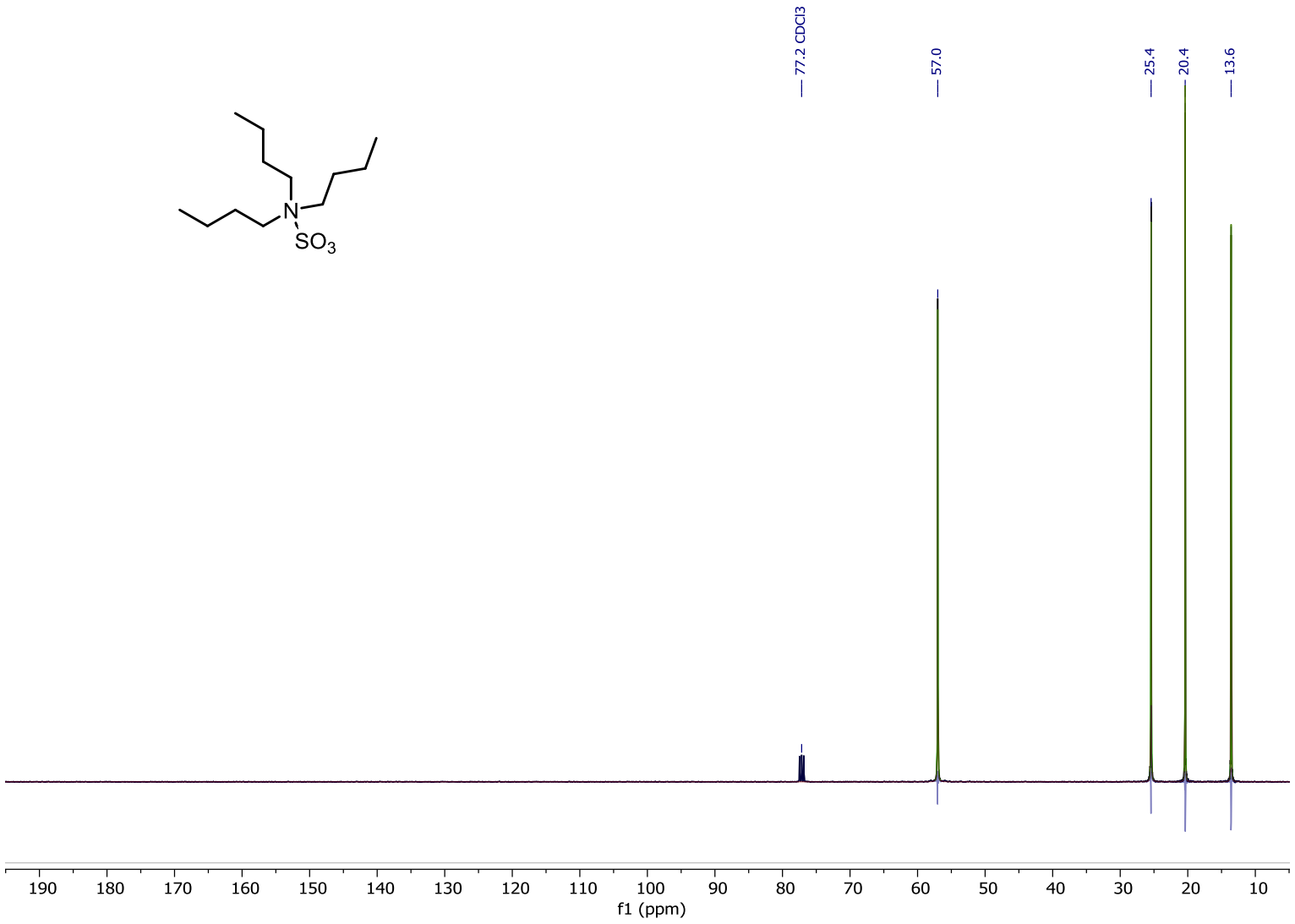
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.08	n.a.	464.930	123.916	100.00	n.a.	BMB
Total:			464.930	123.916	100.00	0.000	

S4. Copies of ^{1}H and ^{13}C NMR spectra

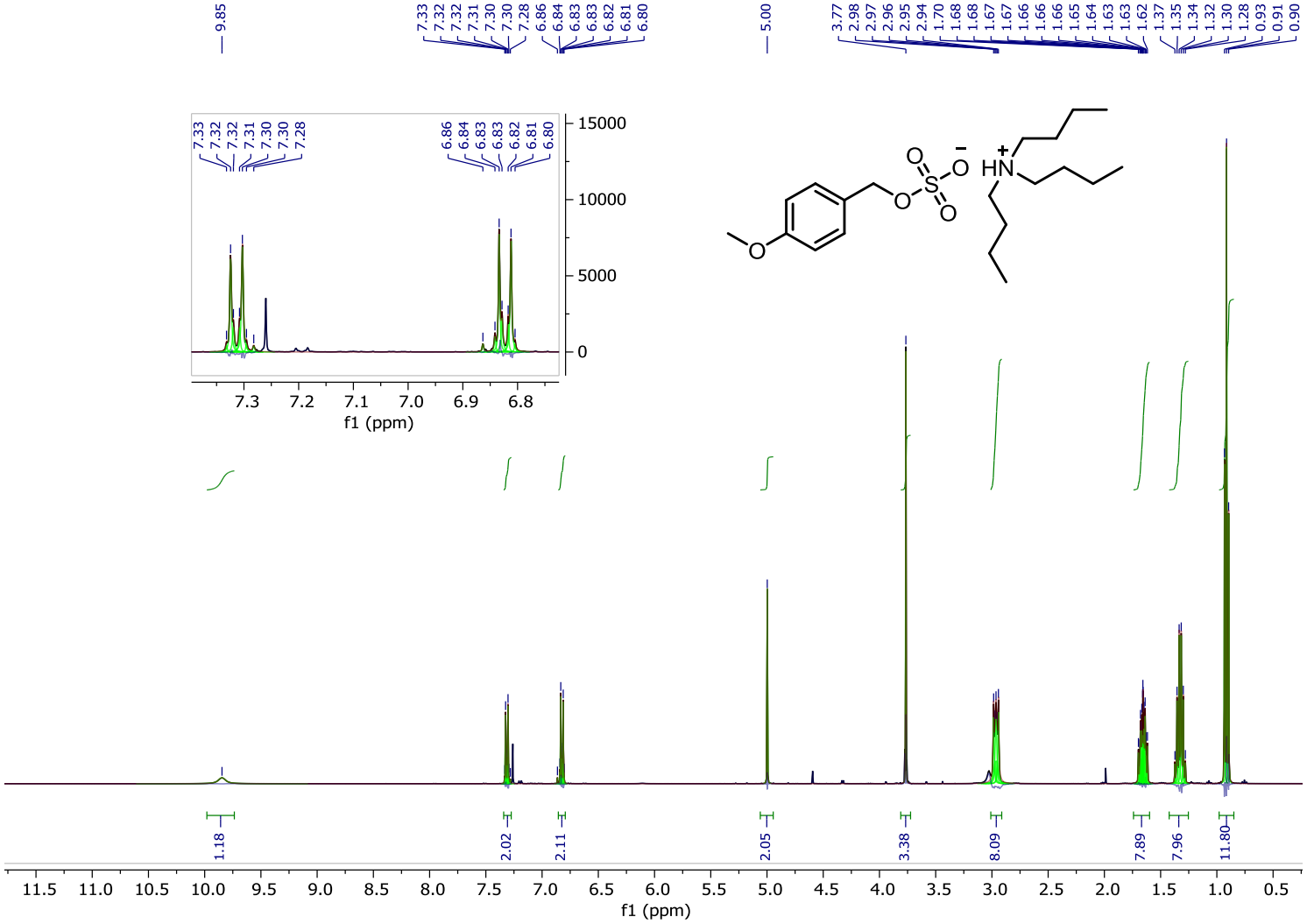
^{1}H NMR spectrum of **1** (400 MHz, $CDCl_3$)



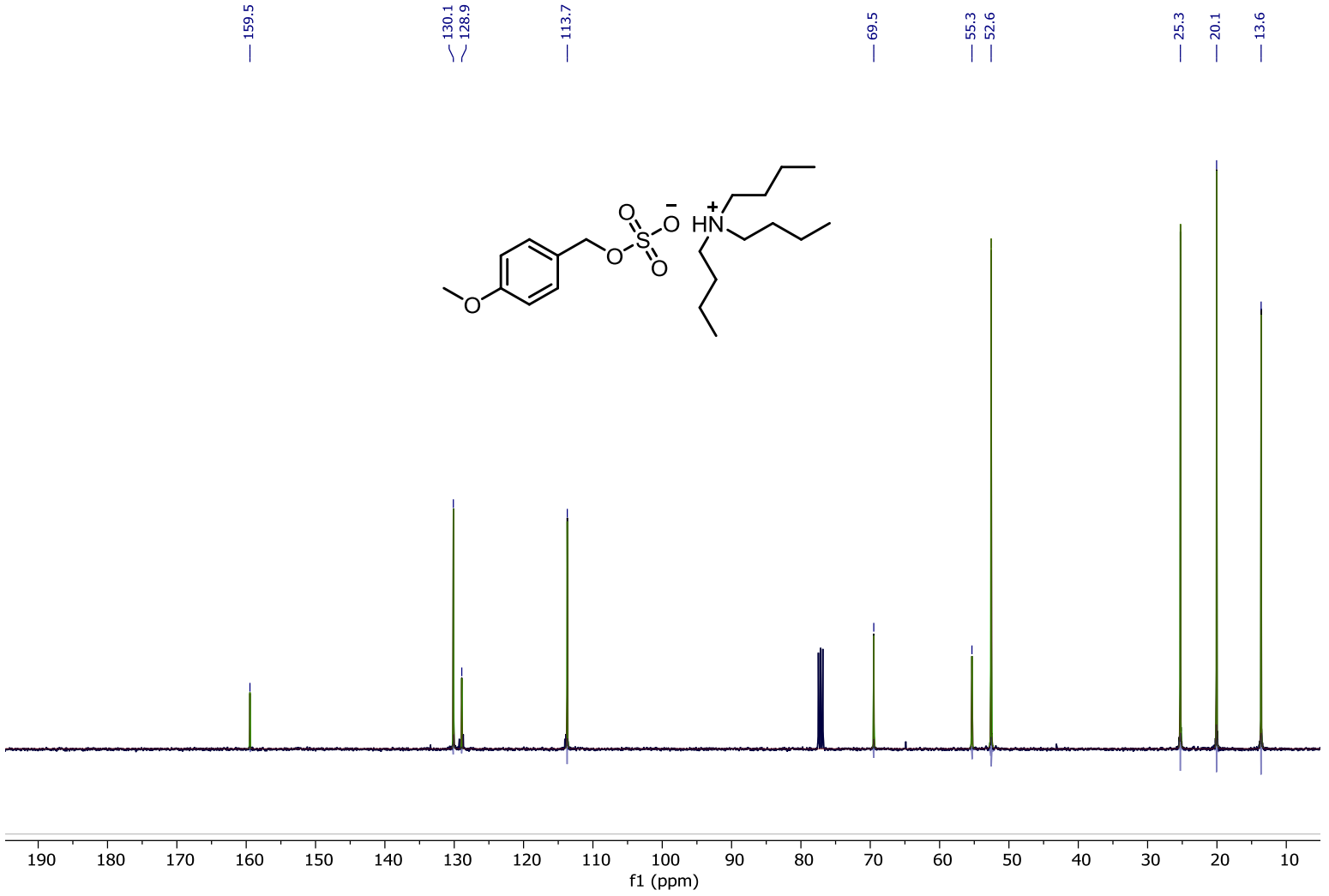
^{13}C NMR spectrum of **1** (101 MHz, $CDCl_3$)



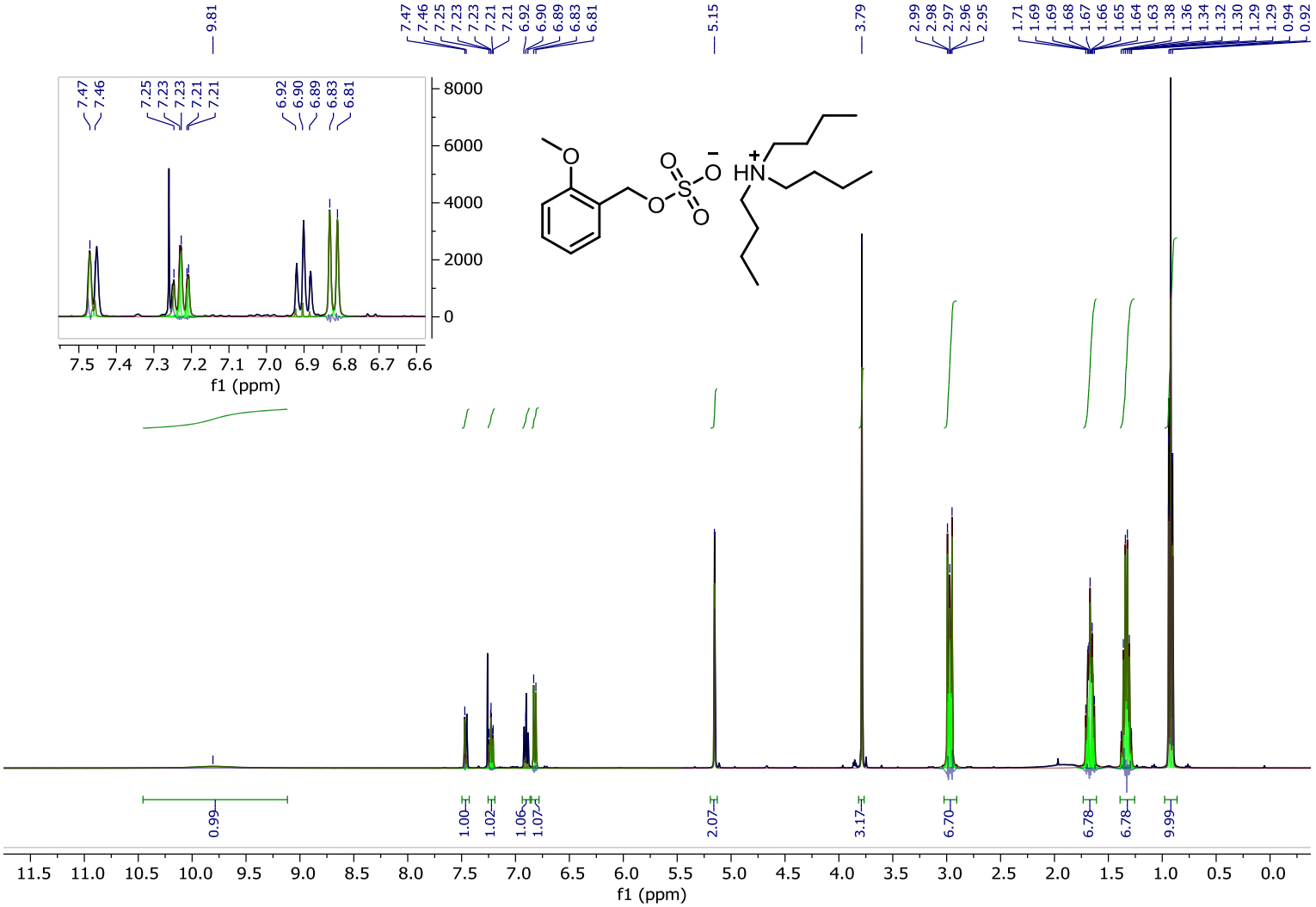
^{1}H NMR spectrum of **3c** (400 MHz, $CDCl_3$)



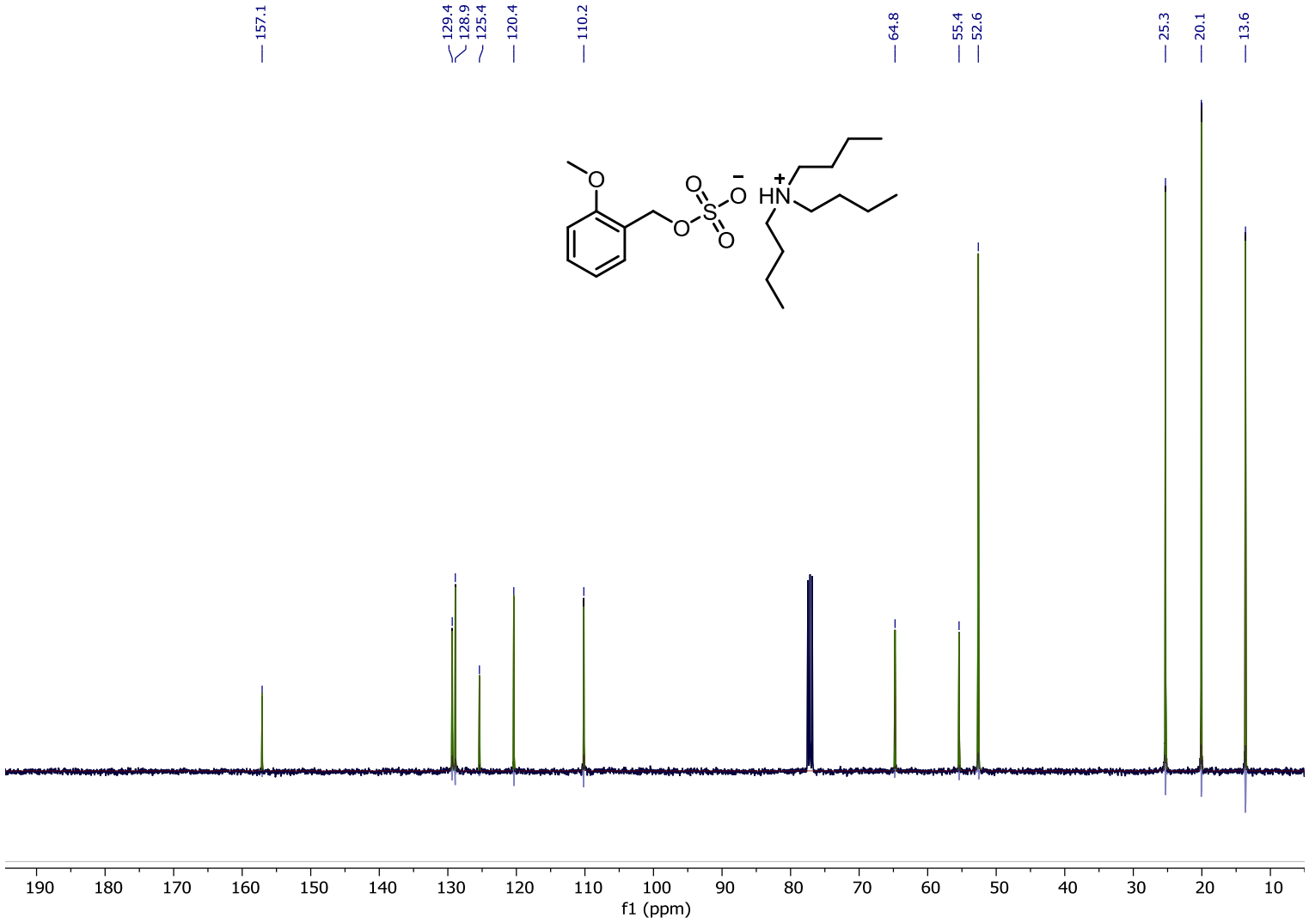
^{13}C NMR spectrum of **3c** (101 MHz, $CDCl_3$)



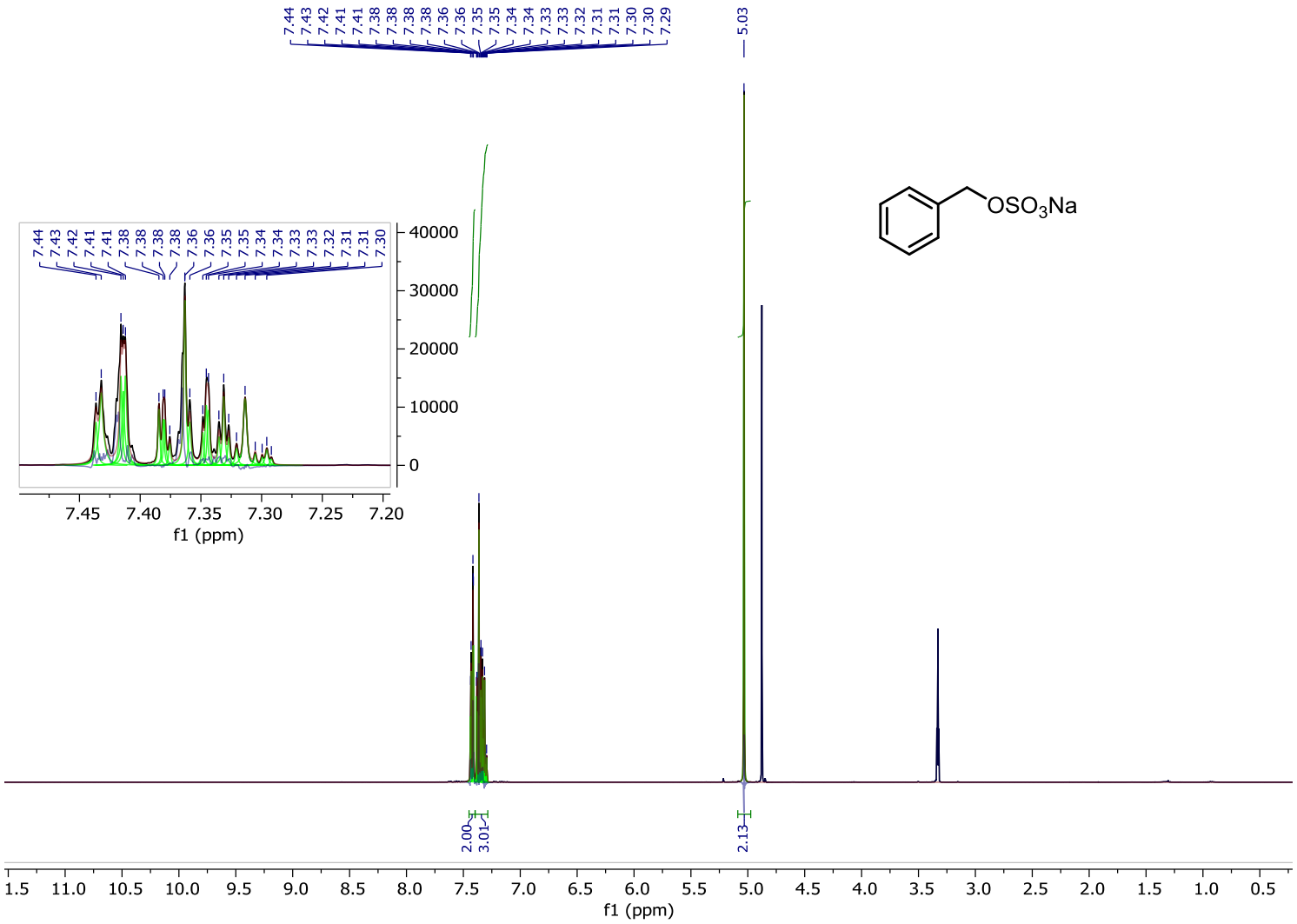
^{1}H NMR spectrum of **3f** (400 MHz, $CDCl_3$)



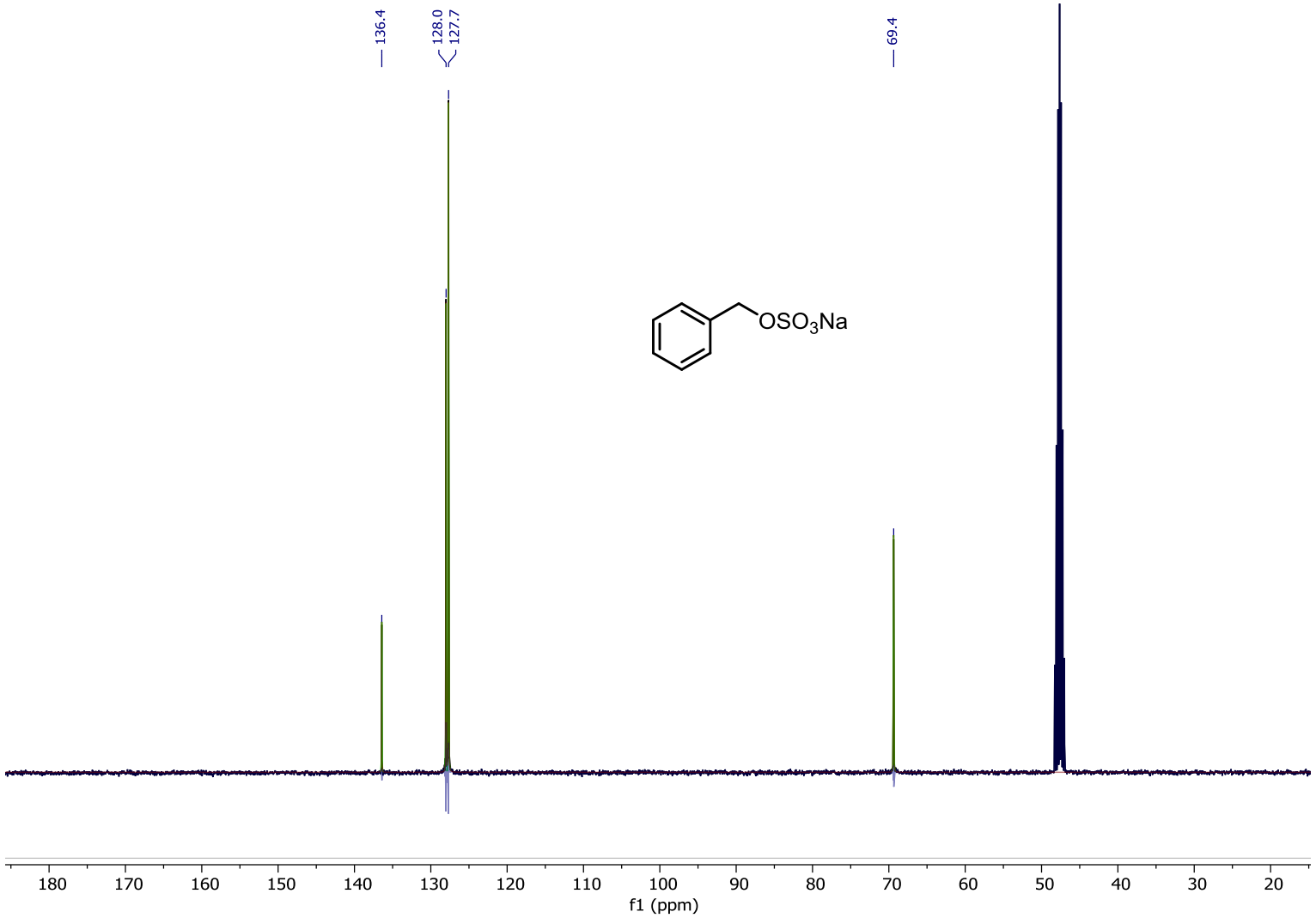
^{13}C NMR spectrum of **3f** (101 MHz, $CDCl_3$)



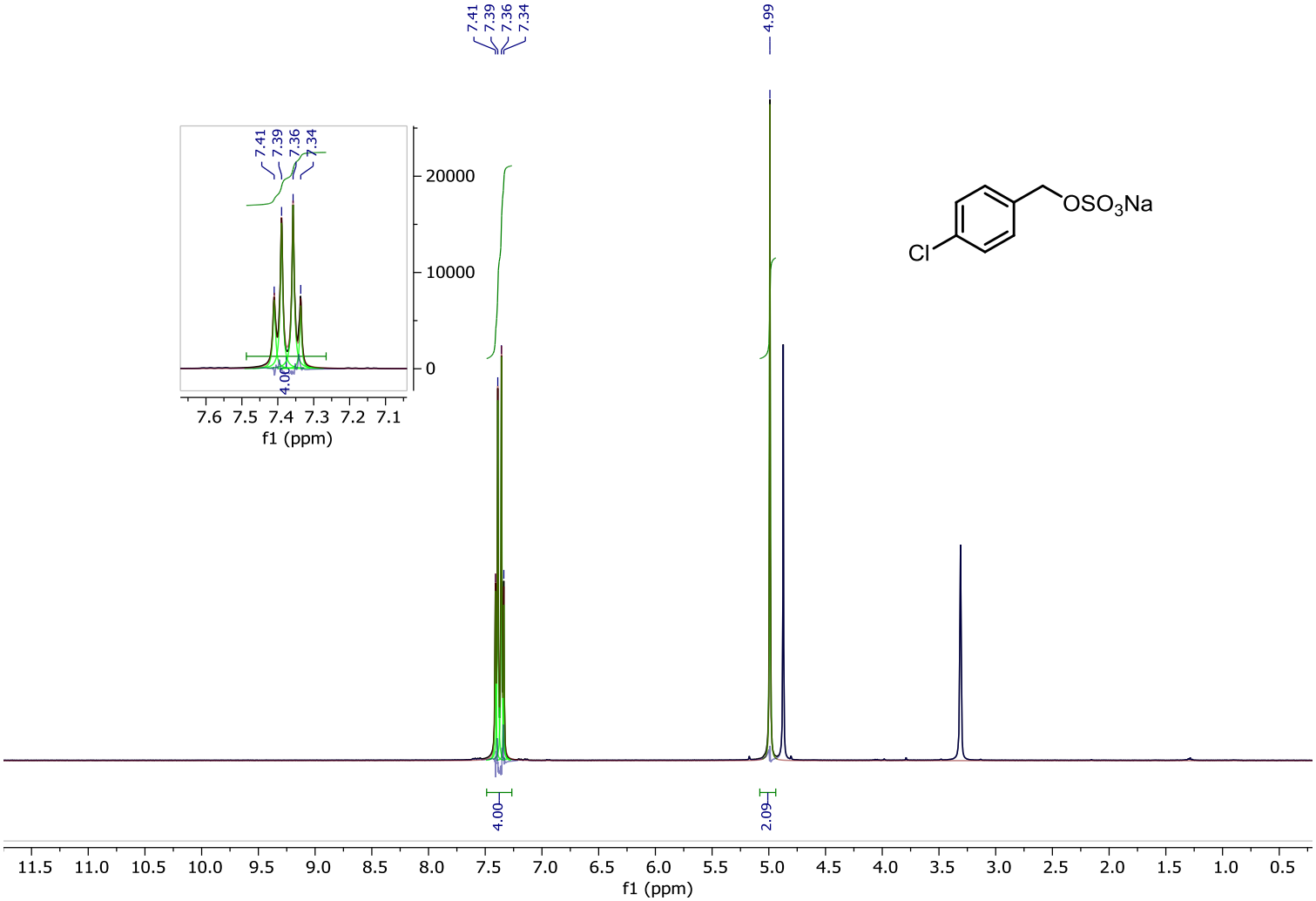
^{1}H NMR of spectrum **4a** (400 MHz, CD_3OD)



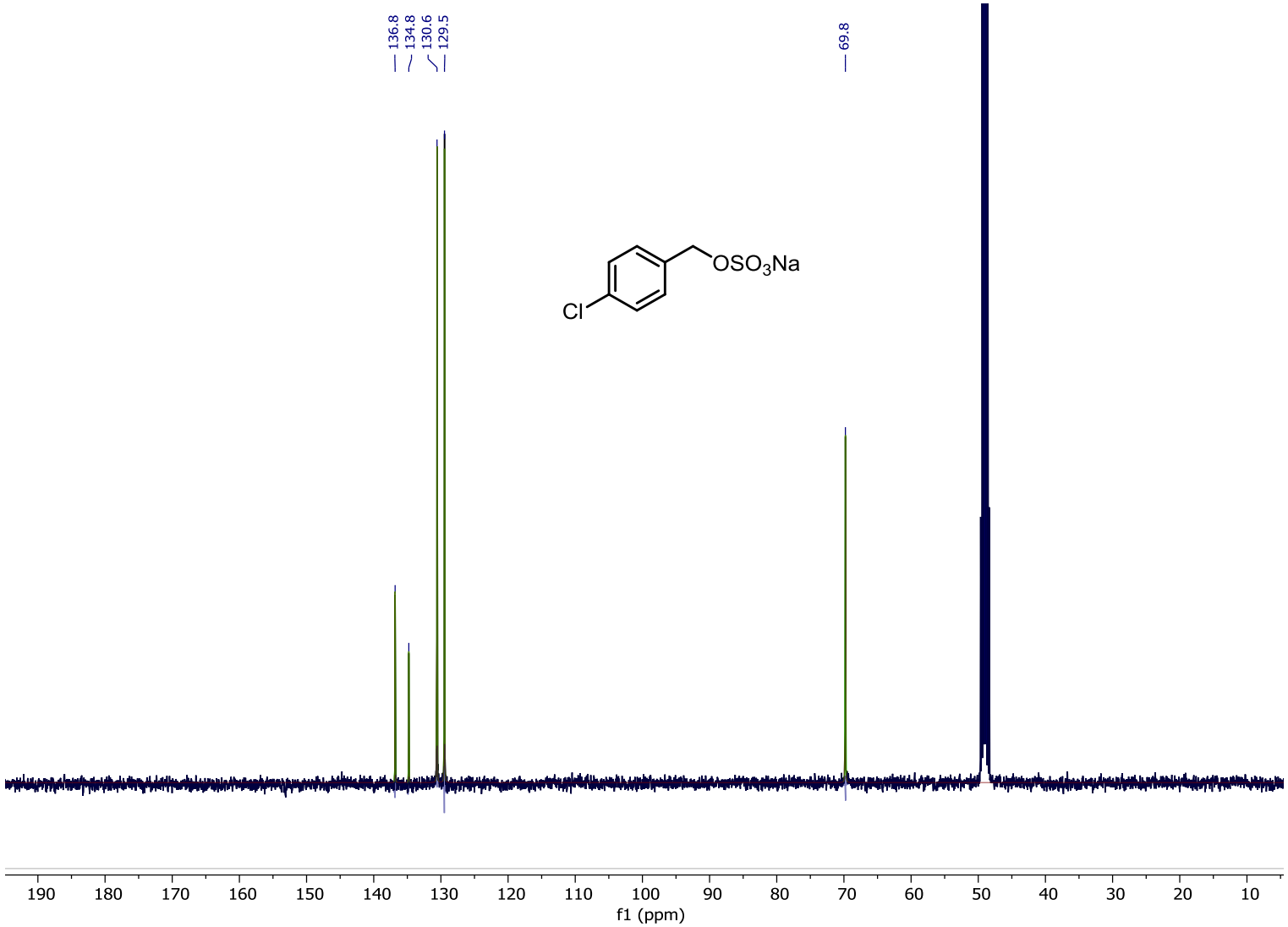
^{13}C NMR spectrum of **4a** (101 MHz, CD_3OD)



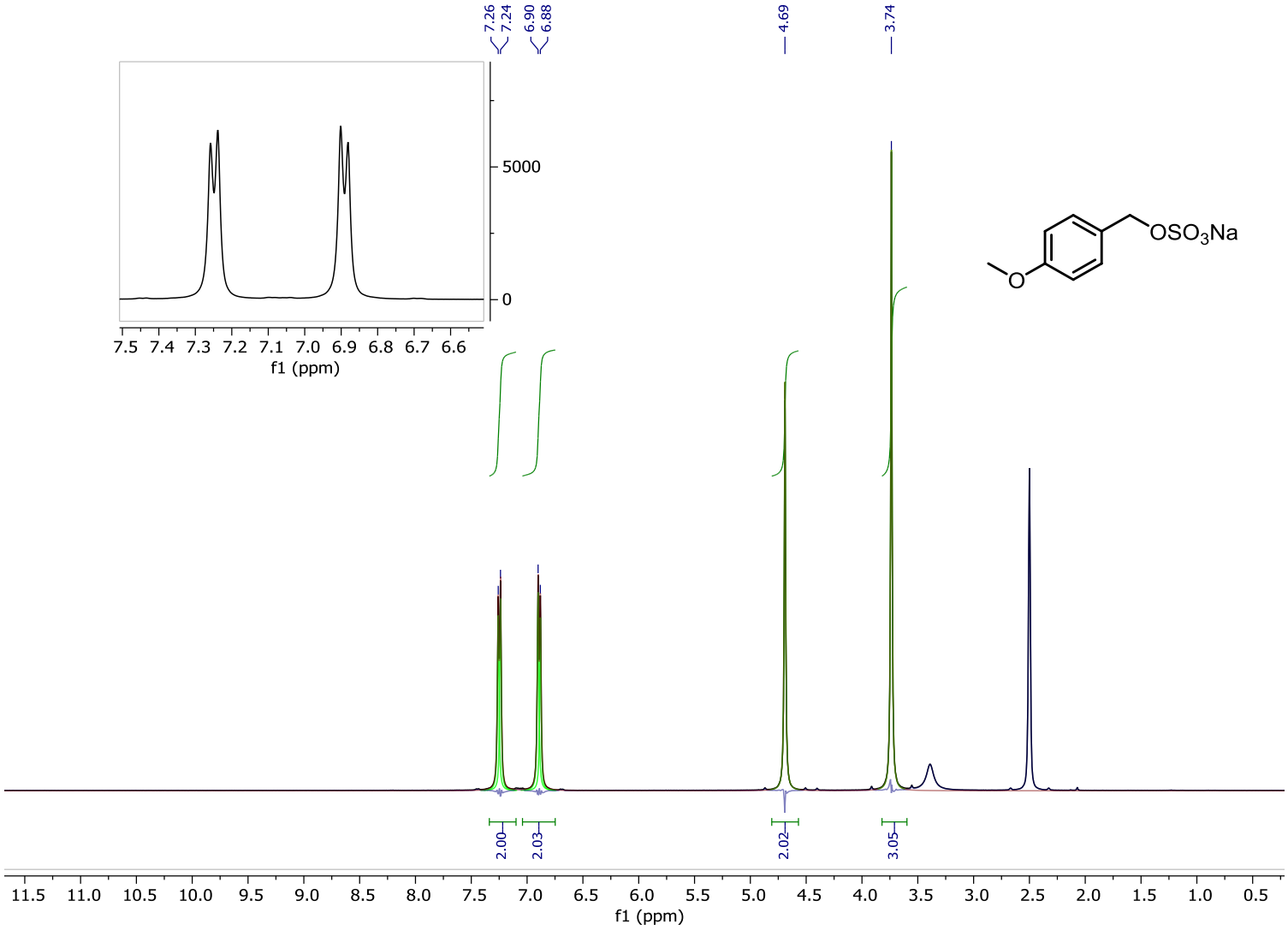
^{1}H NMR spectrum of **4b** (400 MHz, CD_3OD)



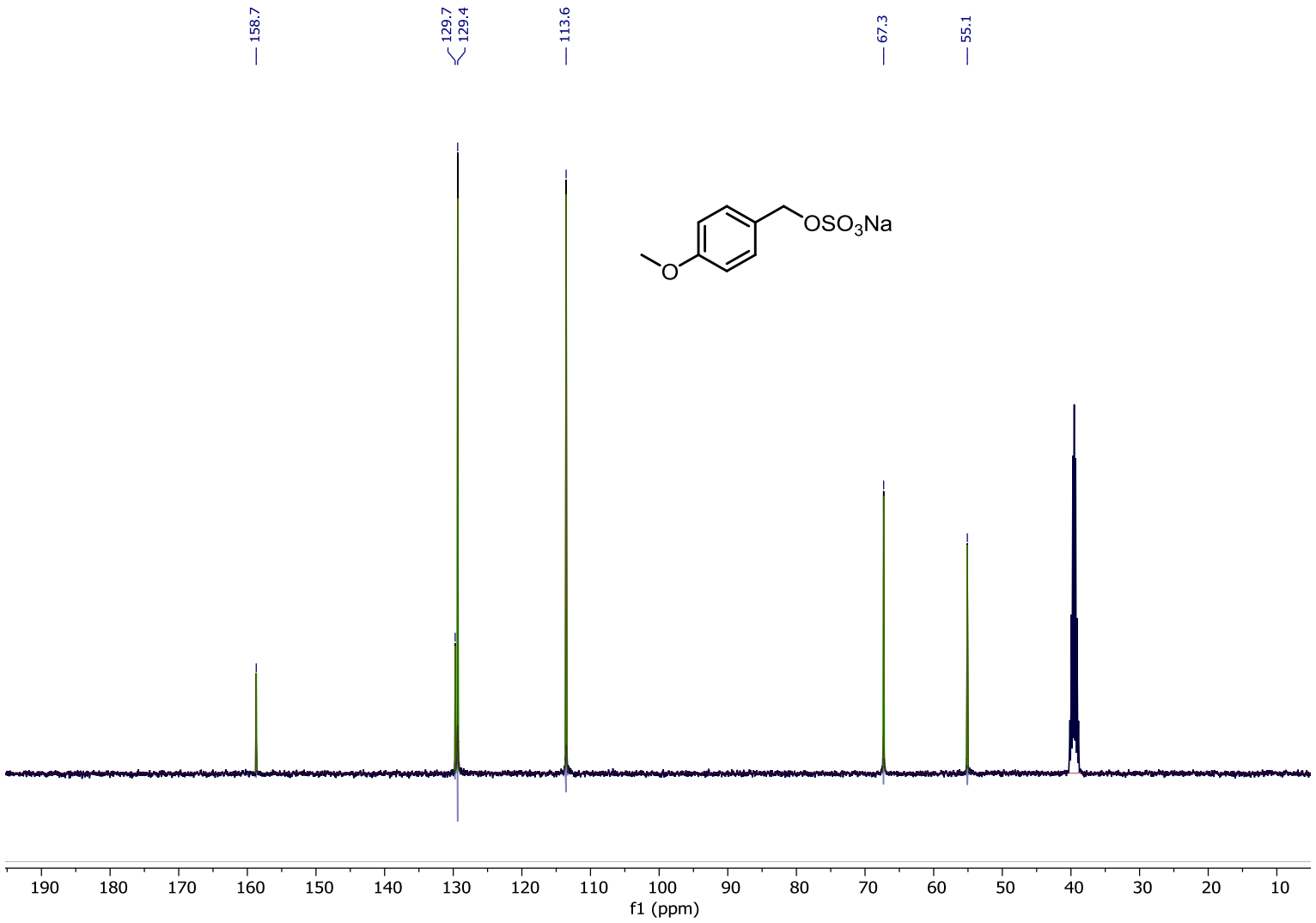
^{13}C NMR spectrum of **4b** (101 MHz, CD_3OD)



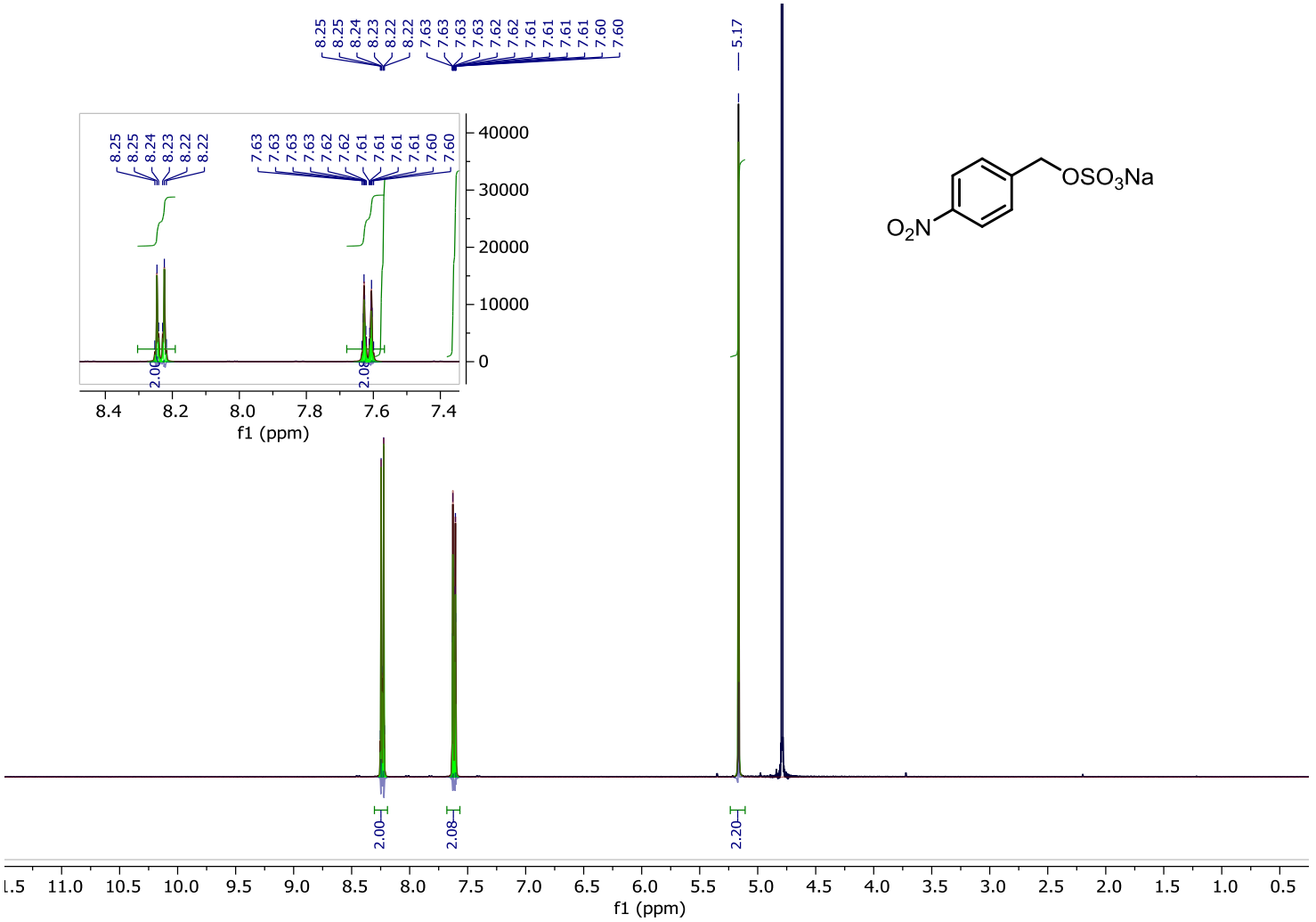
^{1}H NMR spectrum of **4c** (400 MHz, d_6-DMSO)



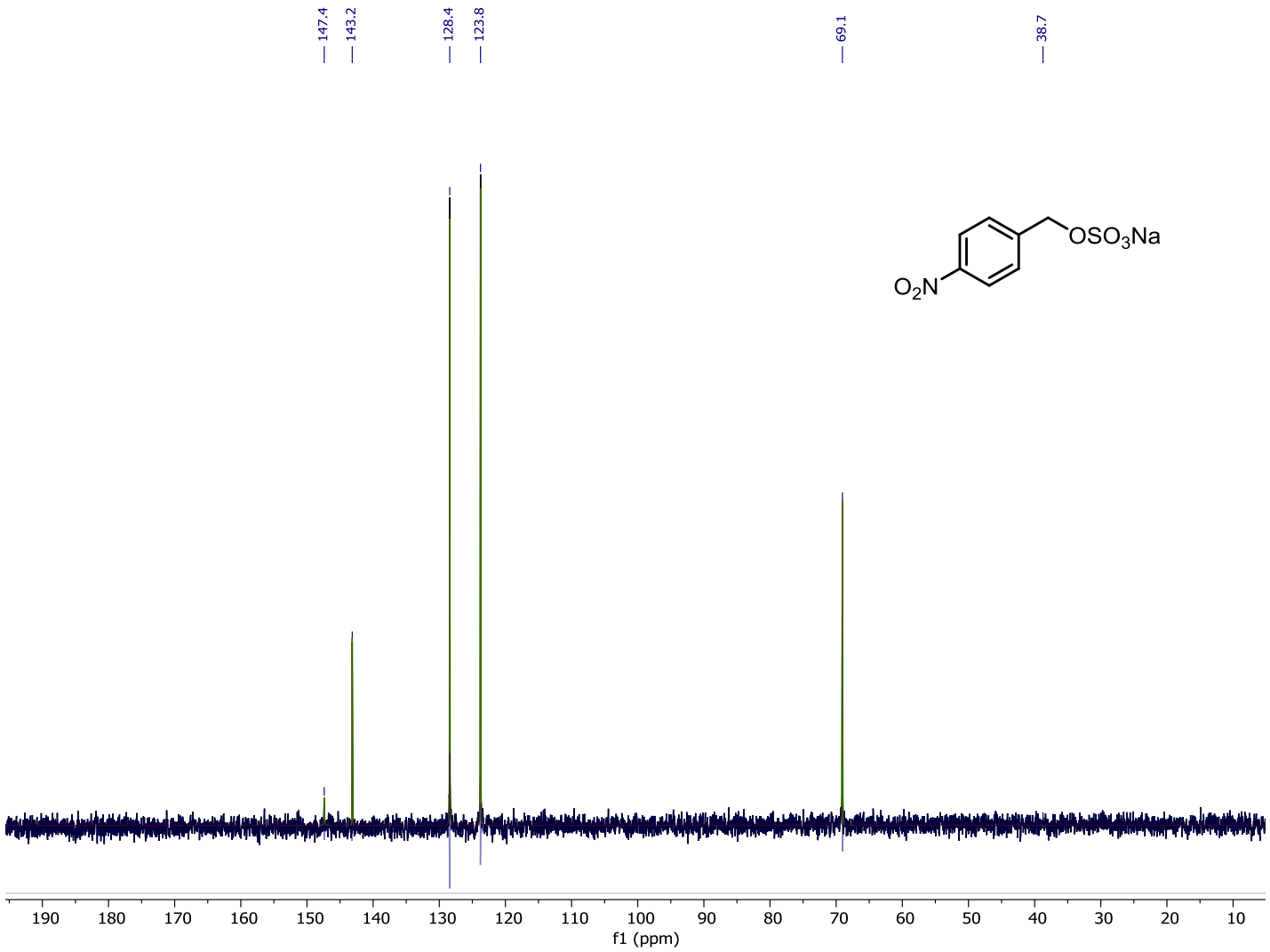
^{13}C NMR spectrum of **4c** (101 MHz, d$_6$-DMSO)



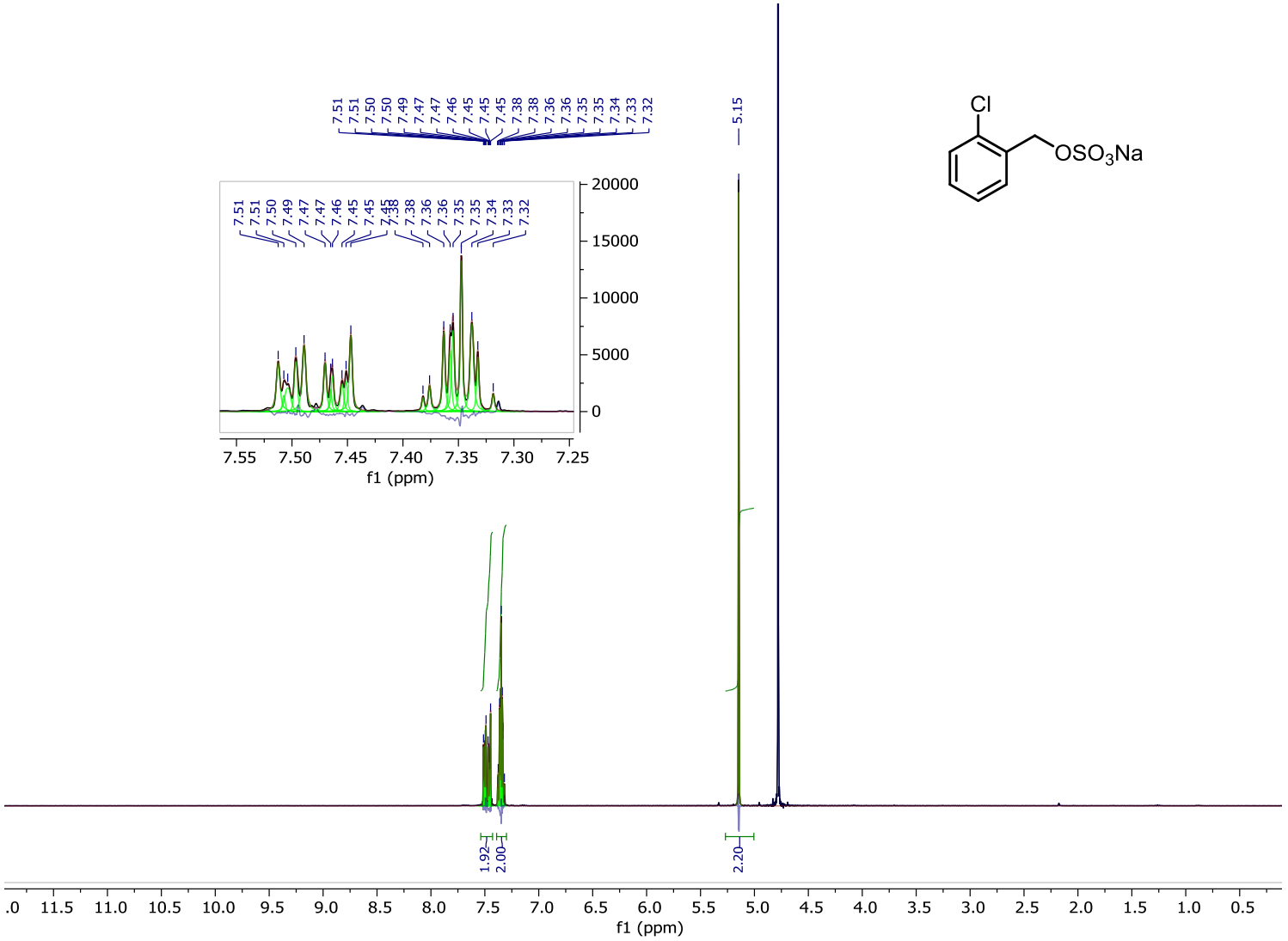
^{1}H NMR spectrum of **4d** (400 MHz, D_2O)



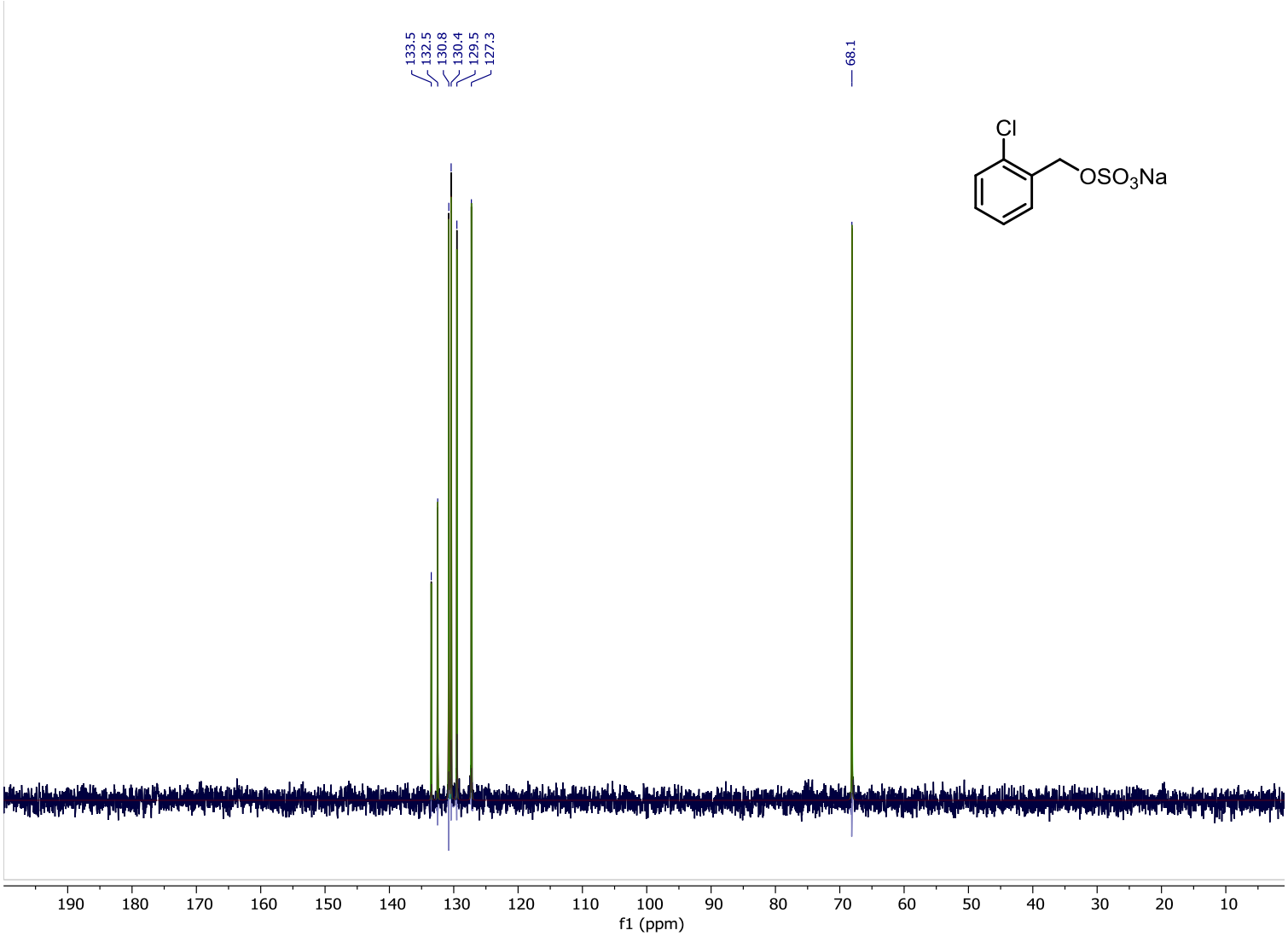
^{13}C NMR spectrum of **4d** (101 MHz, D_2O)



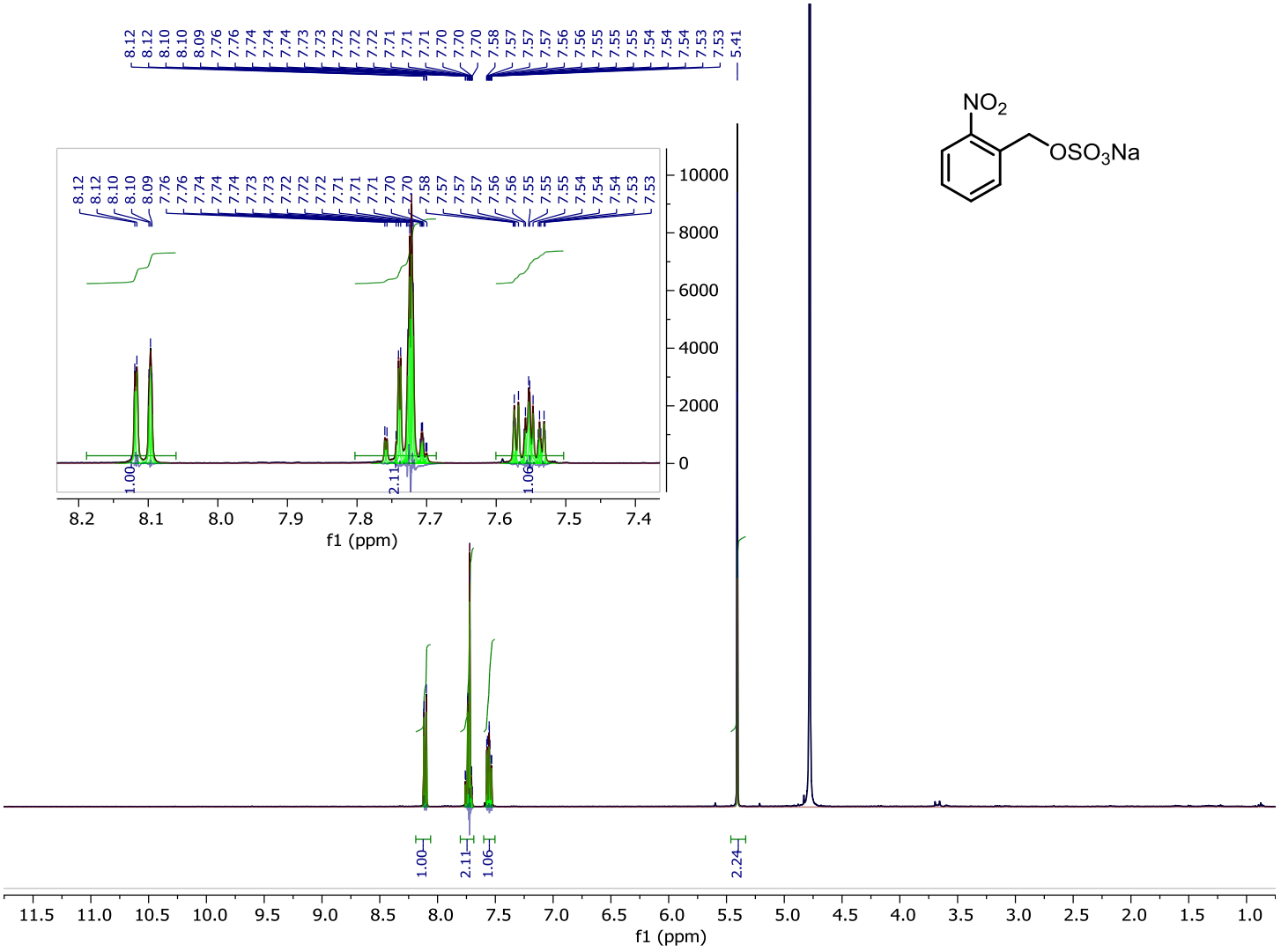
^{1}H NMR spectrum of **4e** (400 MHz, D_2O)



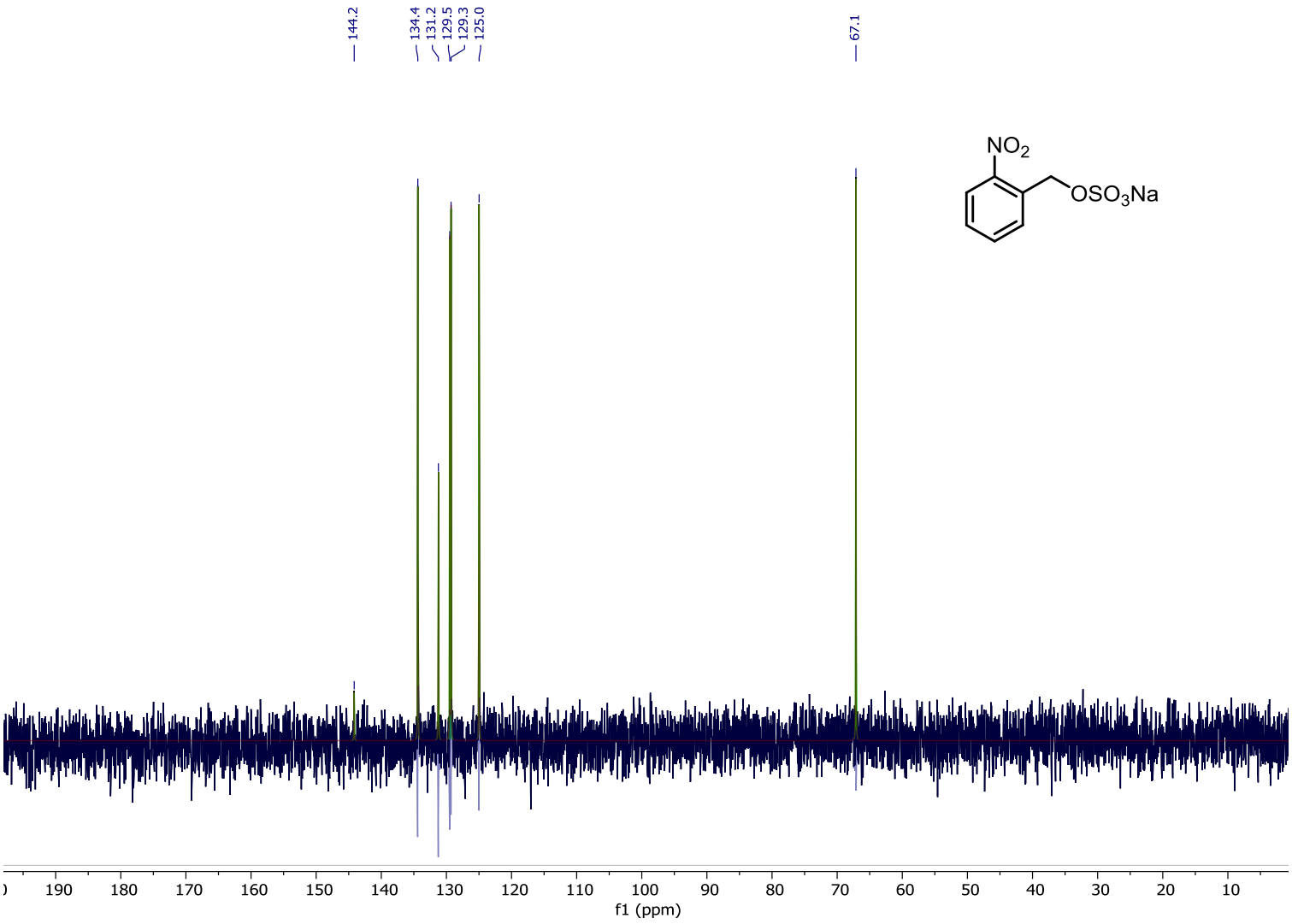
^{13}C NMR spectrum of **4e** (101 MHz, D_2O)



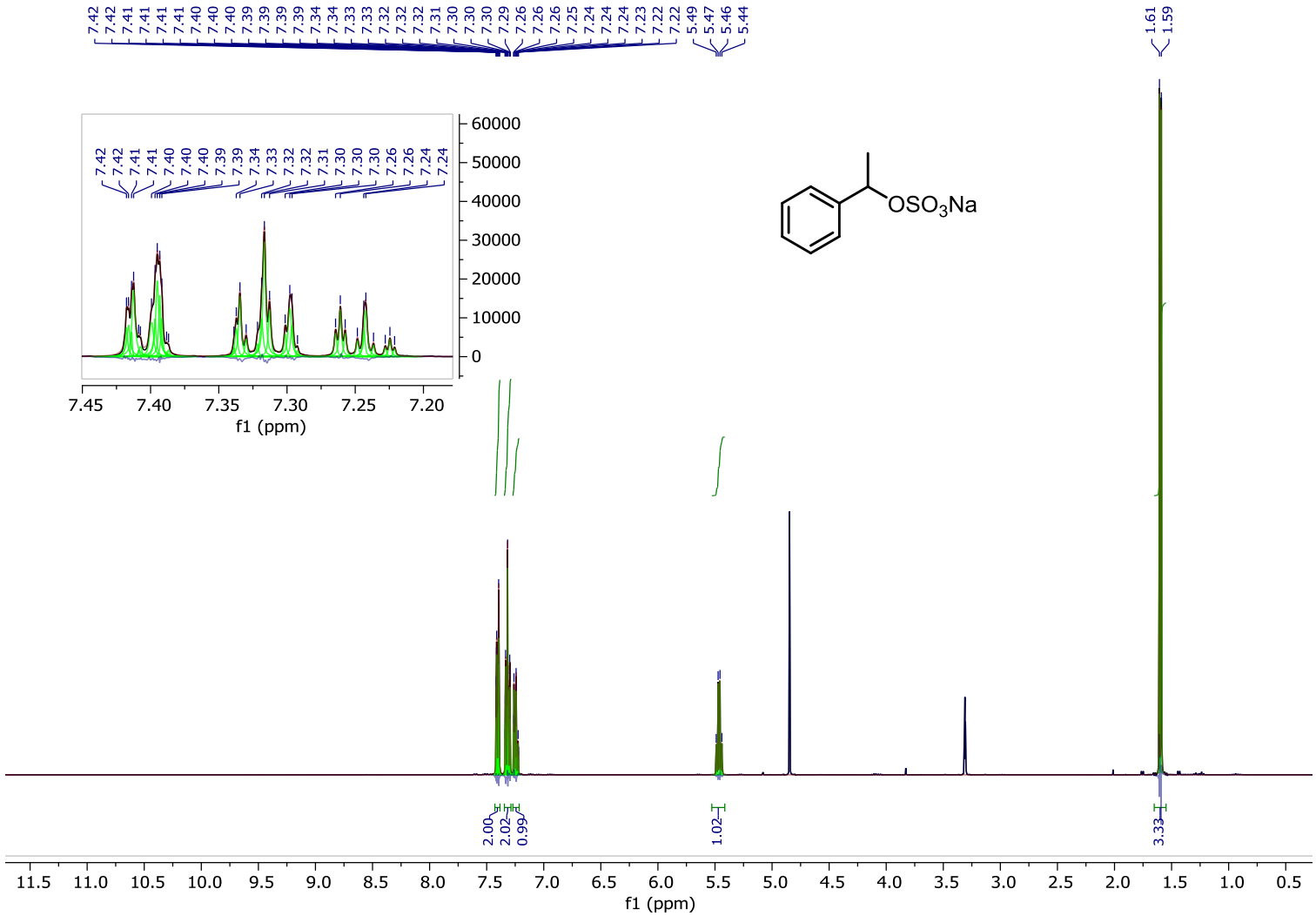
^{1}H NMR spectrum of **4g** (400 MHz, D_2O)



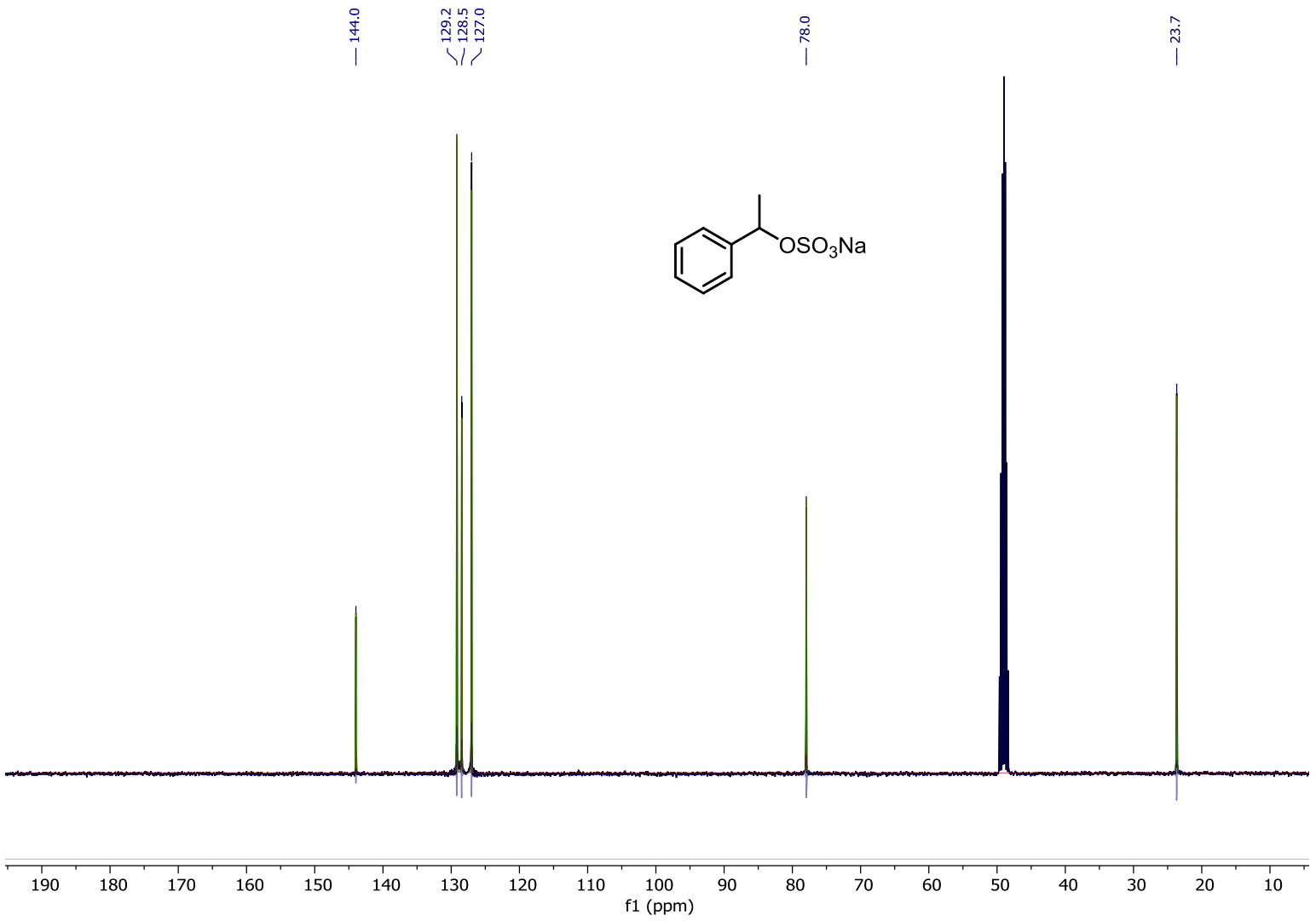
^{13}C NMR spectrum of **4g** (101 MHz, D_2O)



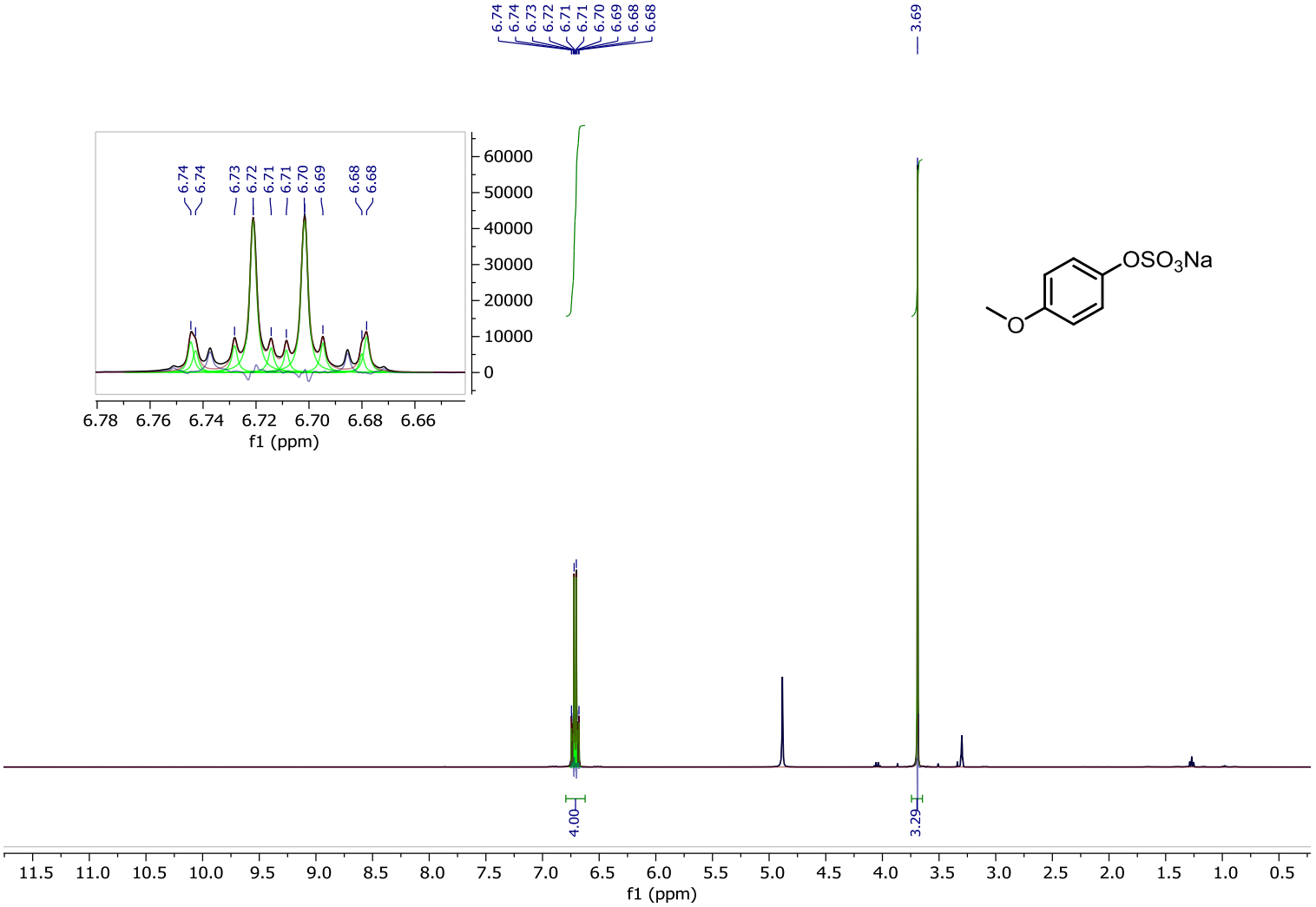
^{1}H NMR spectrum of **4h** (400 MHz, CD_3OD)



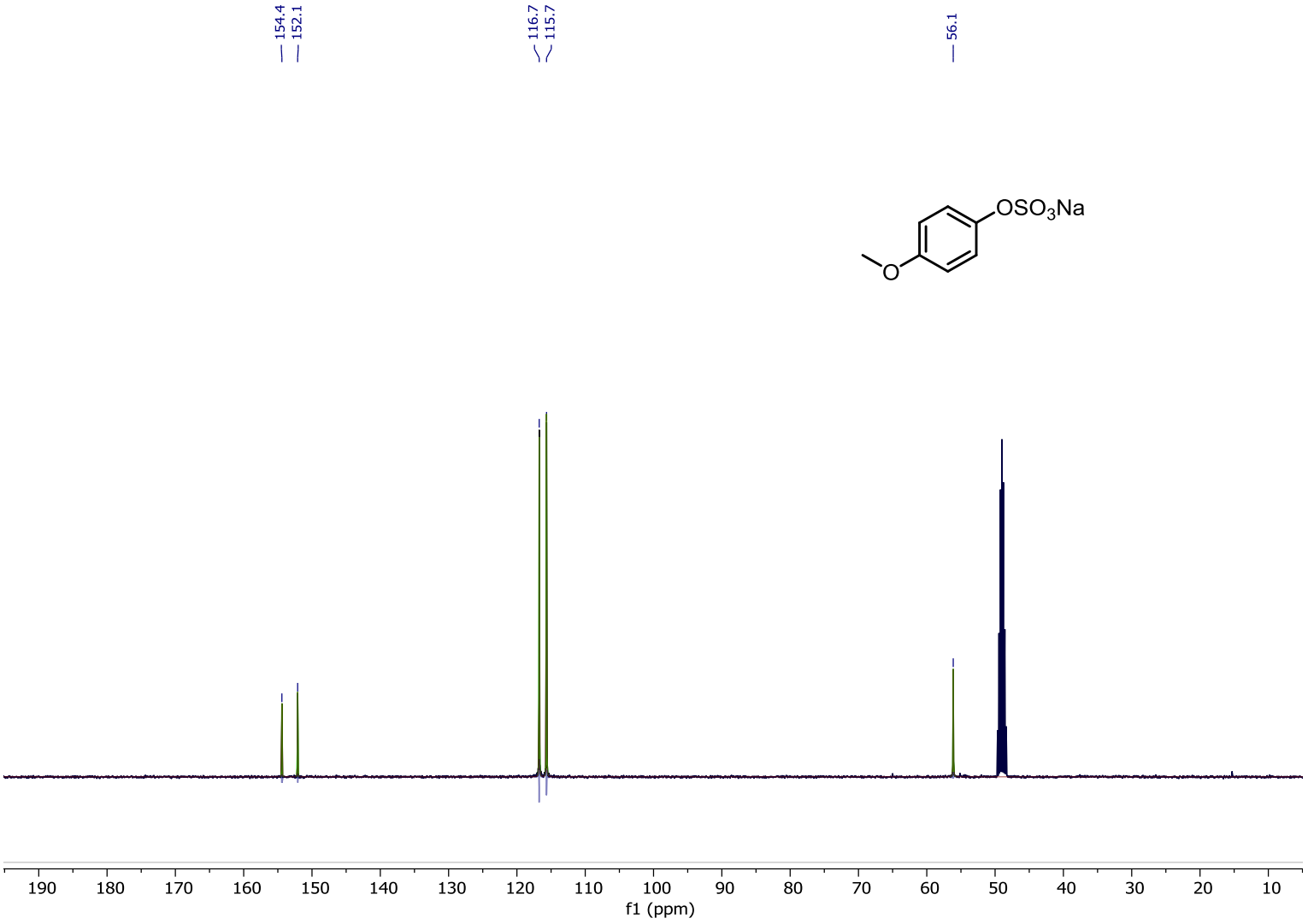
^{13}C NMR spectrum of **4h** (101 MHz, CD_3OD)



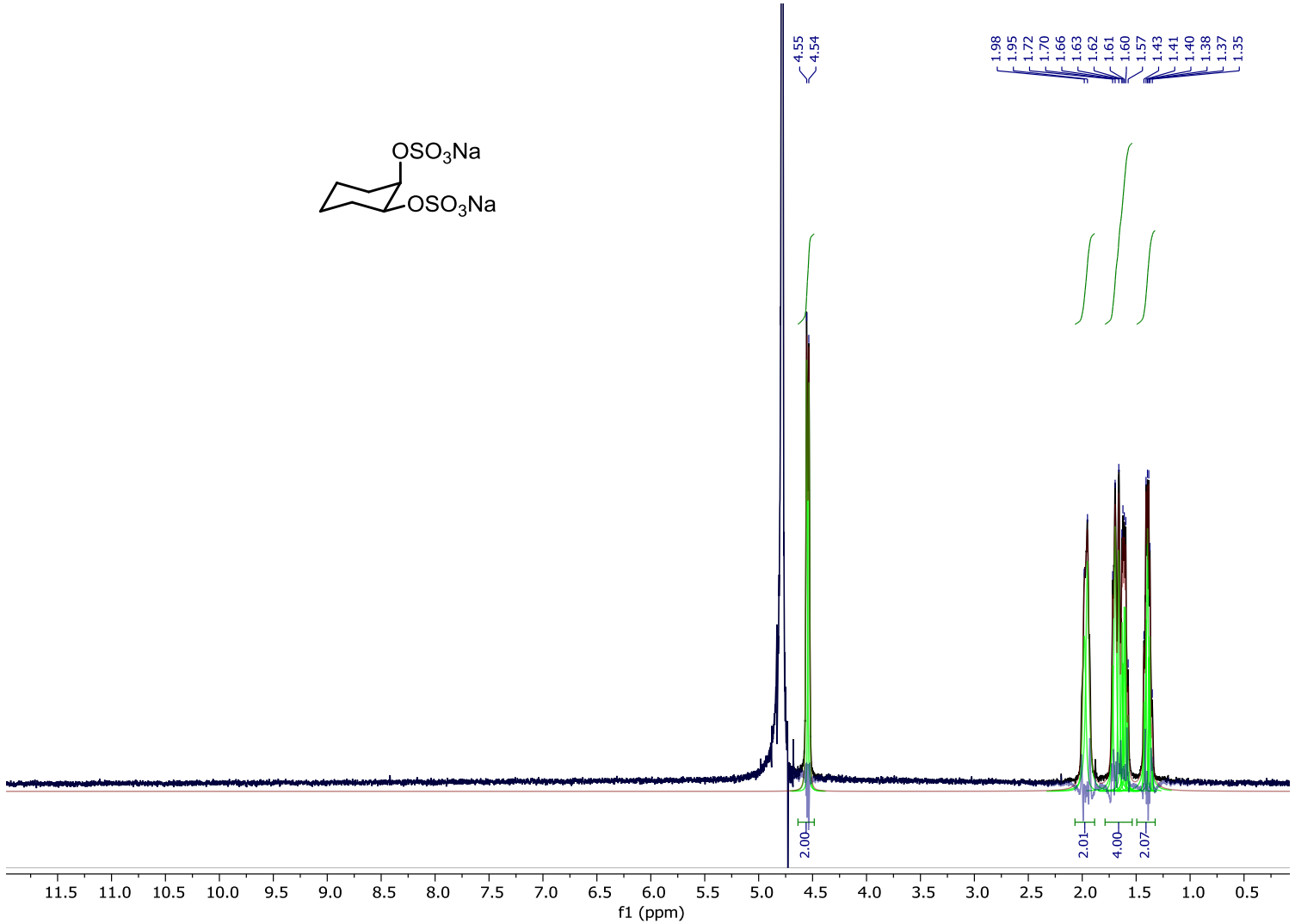
^{1}H NMR spectrum of **4i** (400 MHz, CD_3OD)



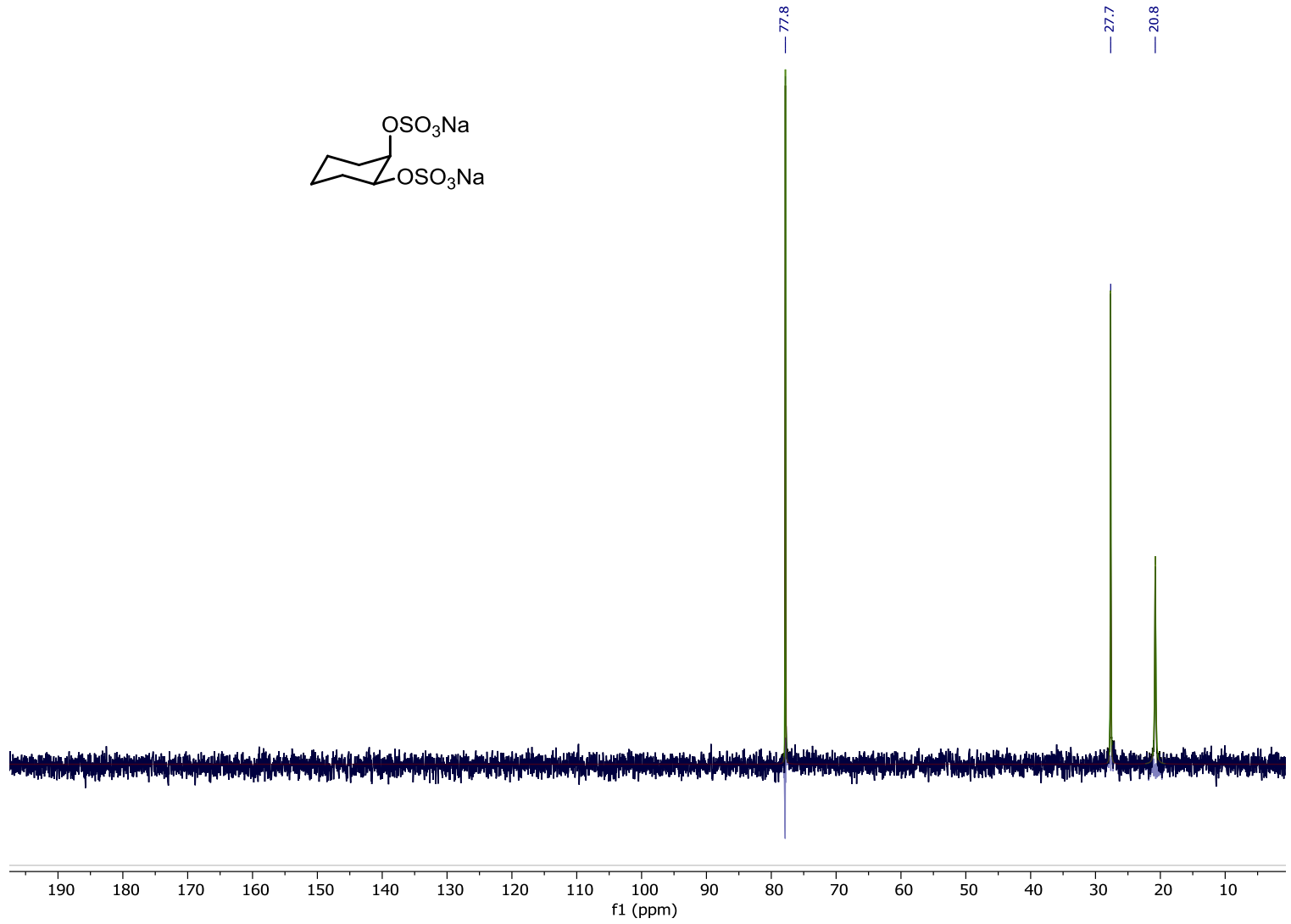
^{13}C NMR spectrum of **4i** (101 MHz, CD_3OD)



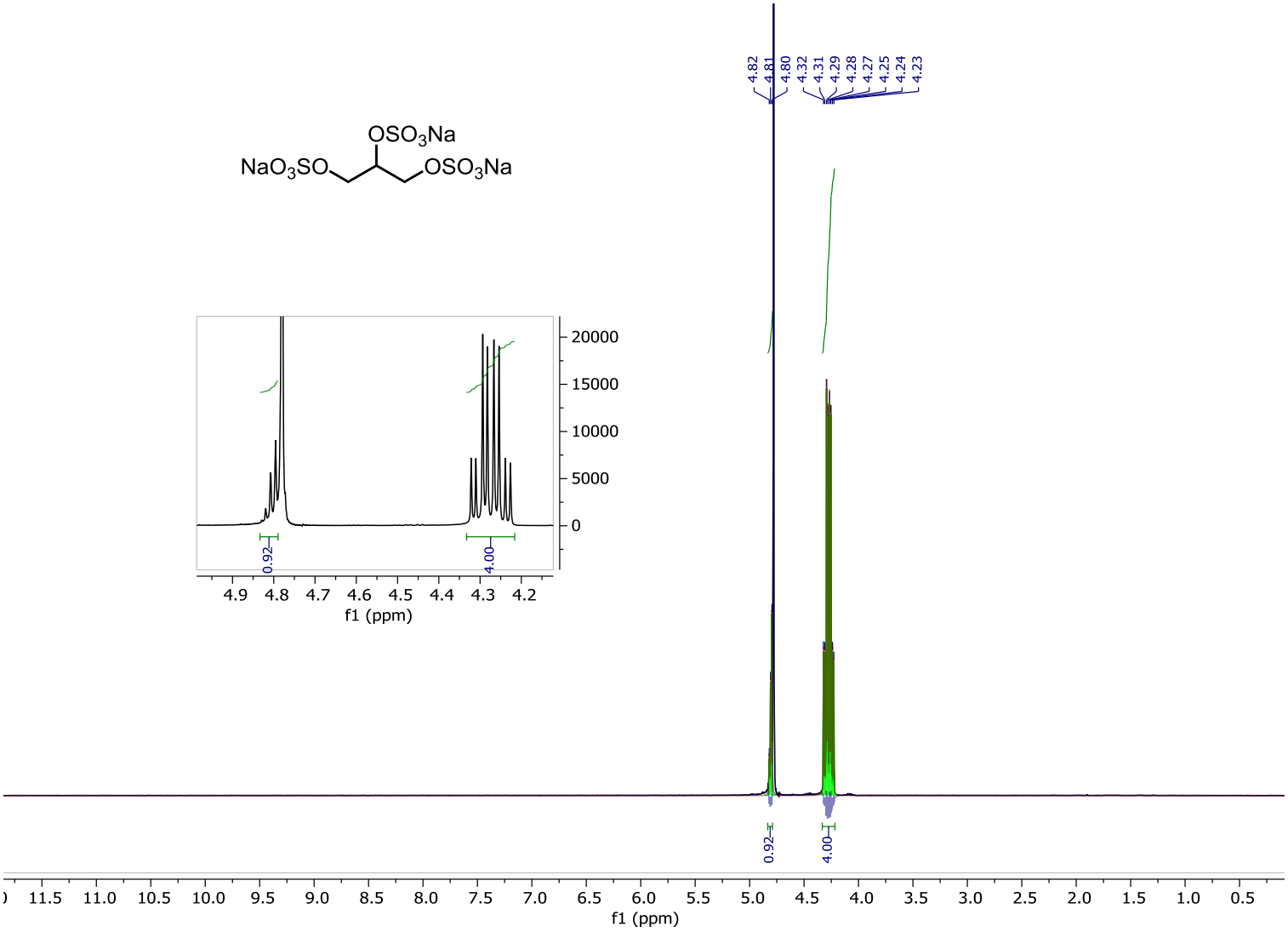
^{1}H NMR spectrum of **5** (400 MHz, D_2O)



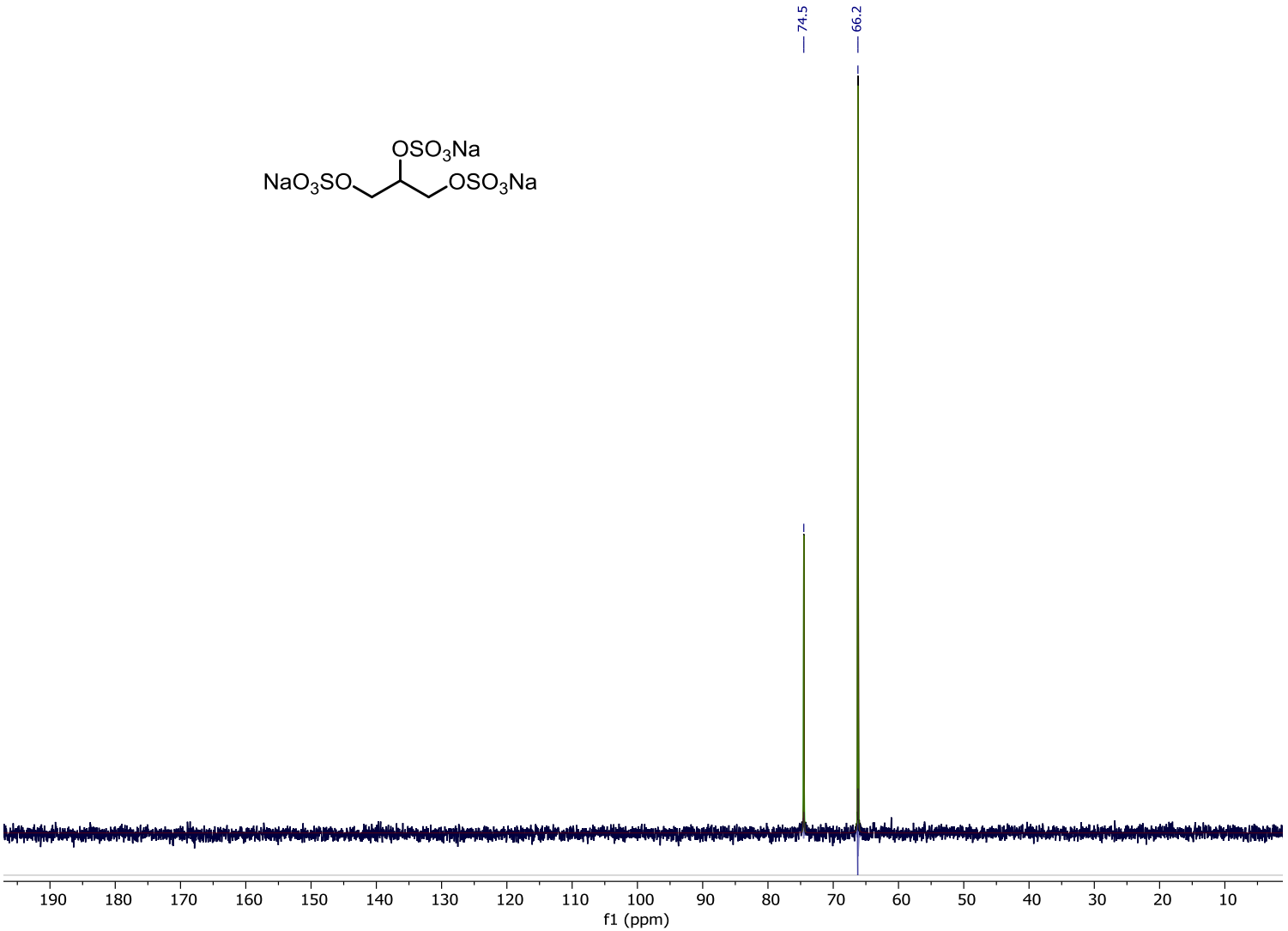
^{13}C NMR spectrum of **5** (101 MHz, D_2O)



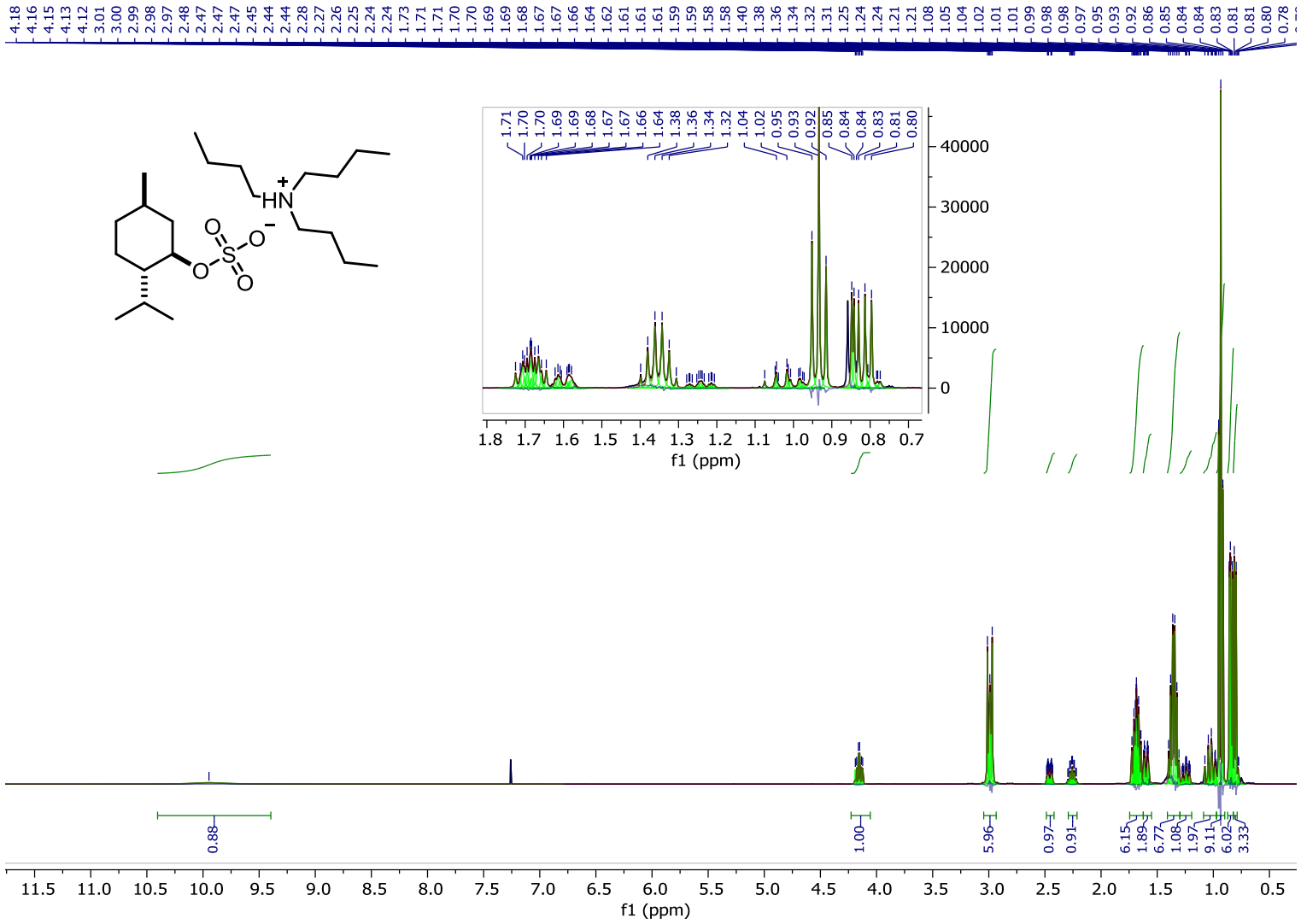
^{1}H NMR spectrum of 6 (400 MHz, D_2O)



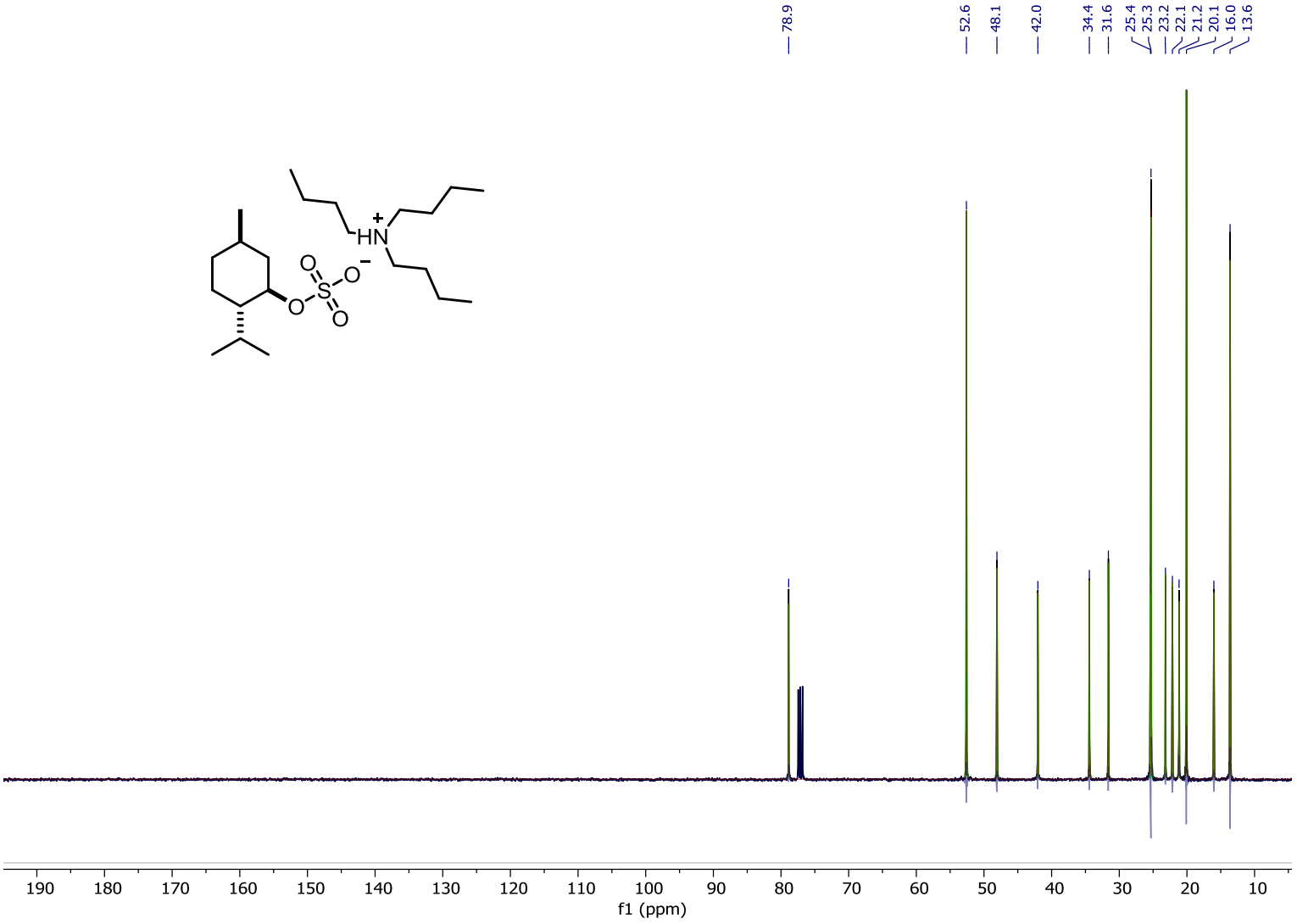
^{13}C NMR spectrum of **6** (101 MHz, D_2O)



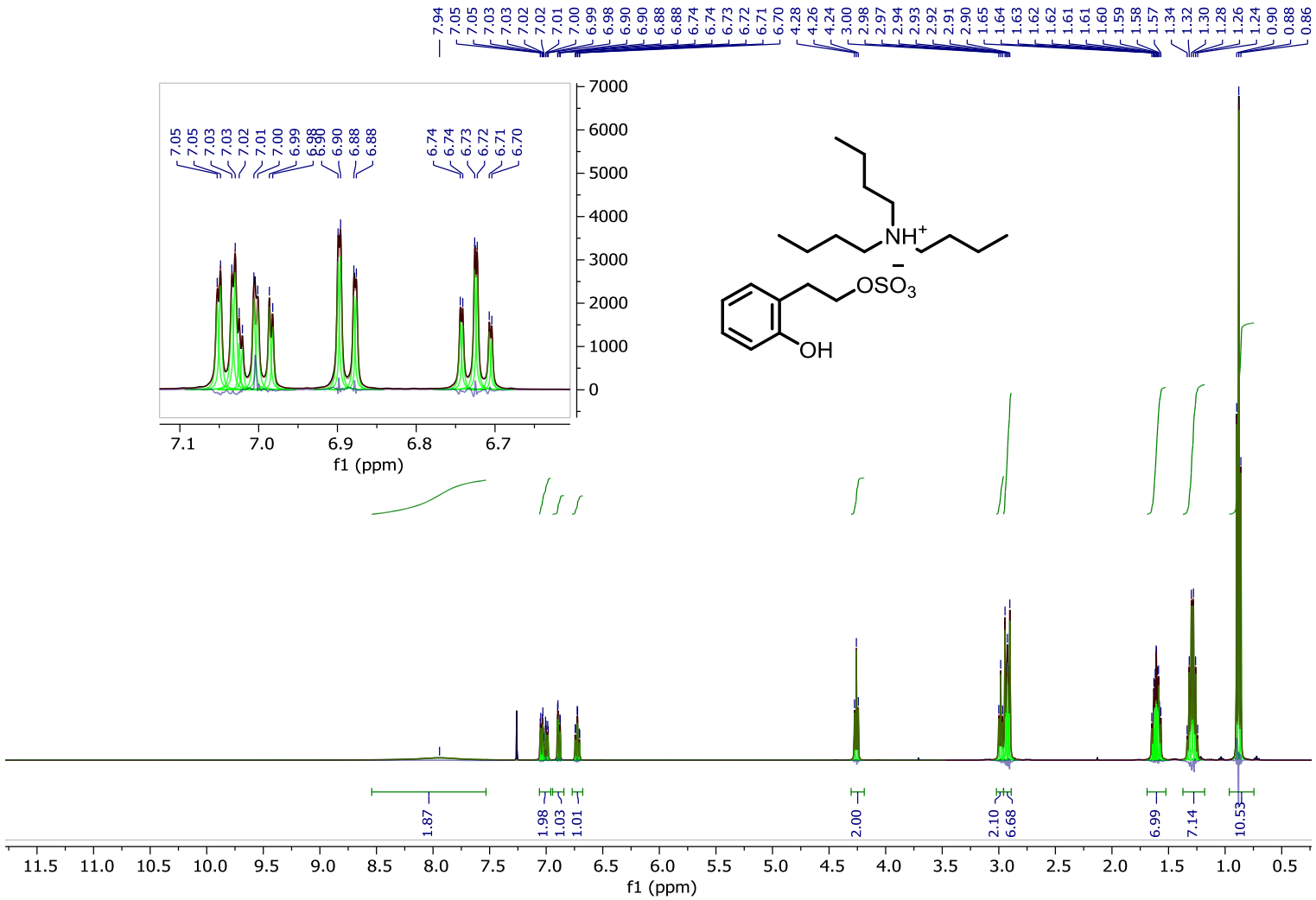
^{1}H NMR spectrum of **7** (400 MHz, $CDCl_3$)



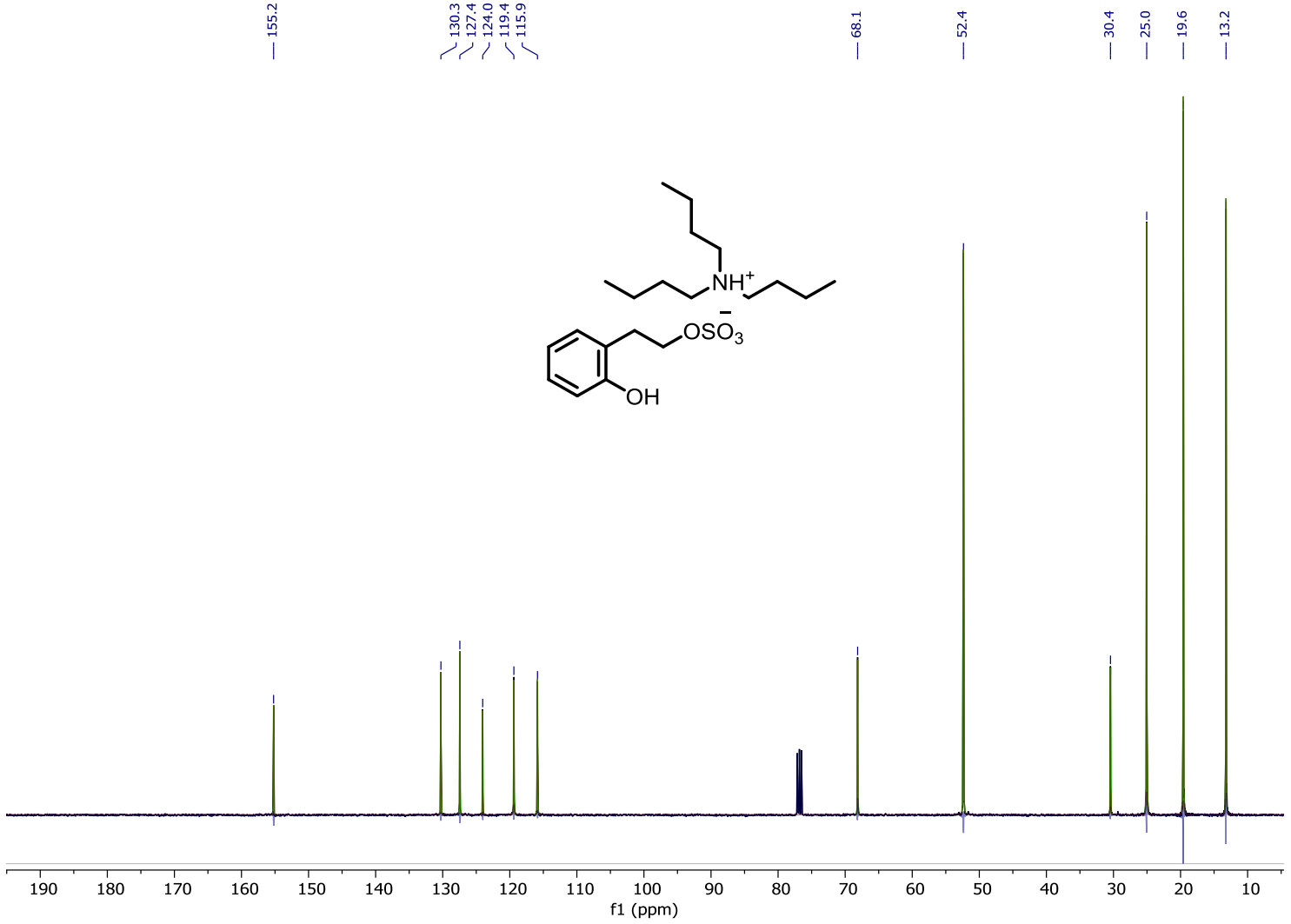
^{13}C NMR spectrum of **7** (101 MHz, $CDCl_3$)



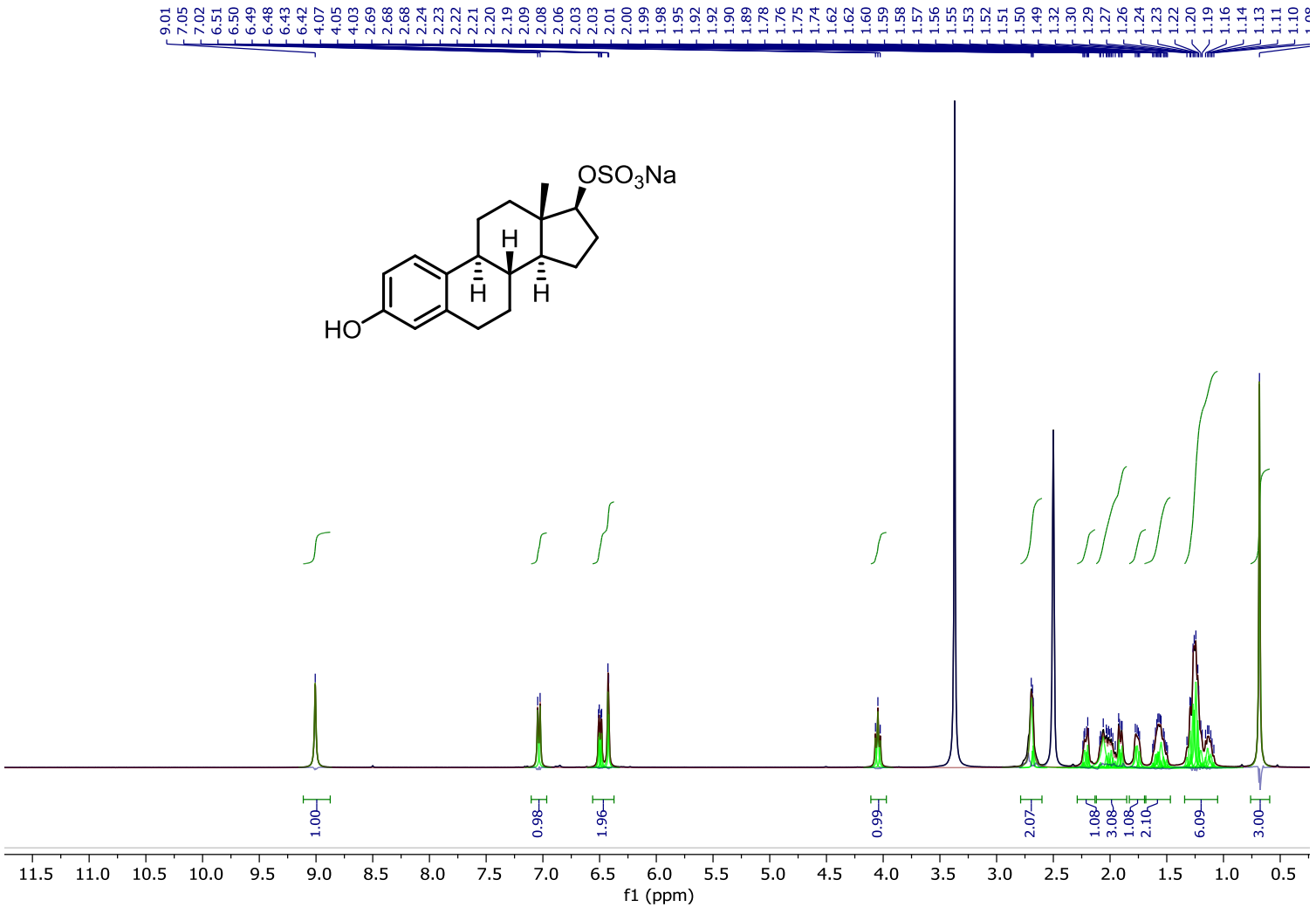
^{1}H NMR spectrum of **8** (400 MHz, $CDCl_3$)



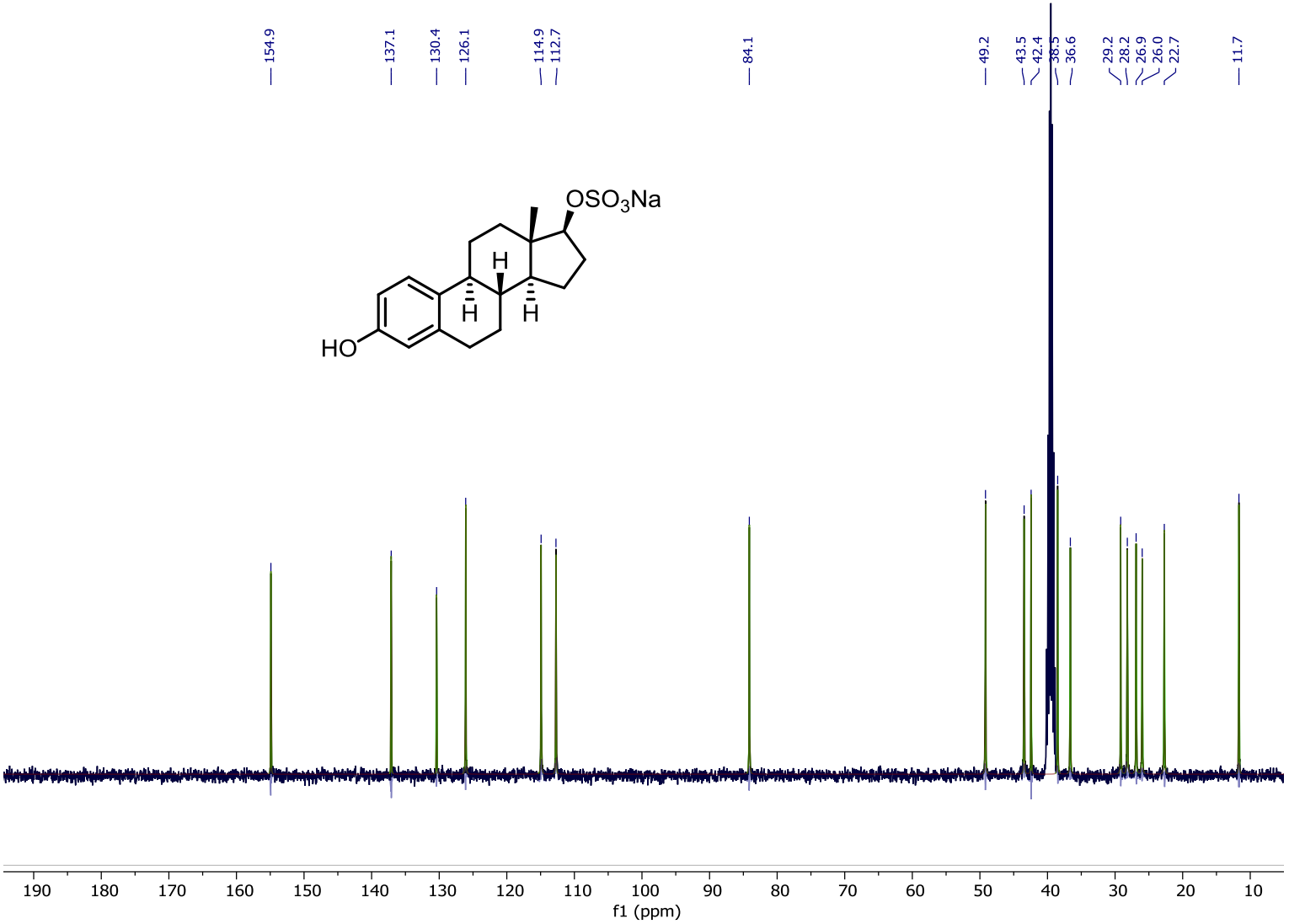
^{13}C NMR spectrum of **8** (400 MHz, $CDCl_3$)



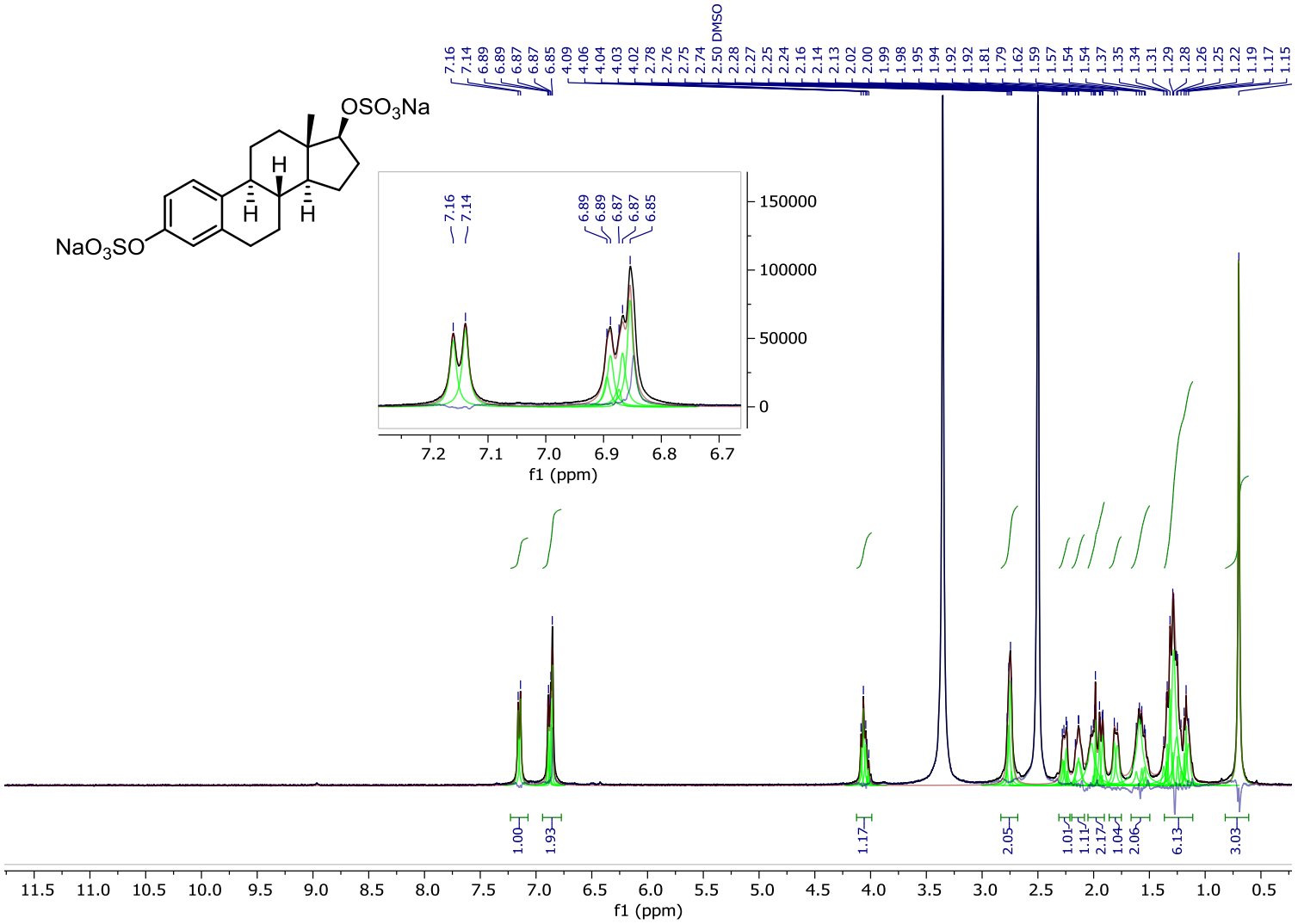
^{1}H NMR spectrum of **9a** (400 MHz, d_6-DMSO)



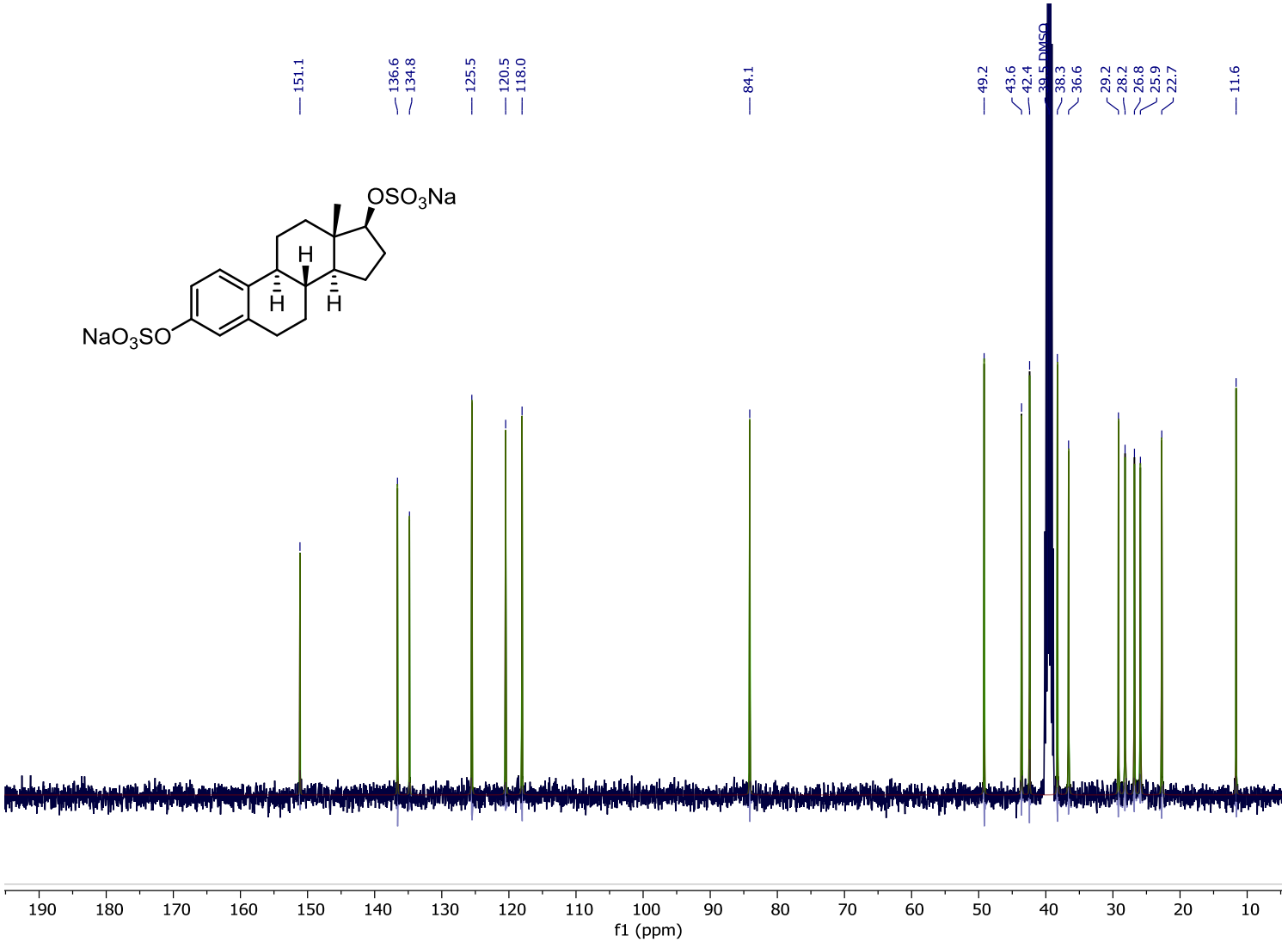
^{13}C NMR spectrum of **19a** (101 MHz, d$_6$-DMSO)



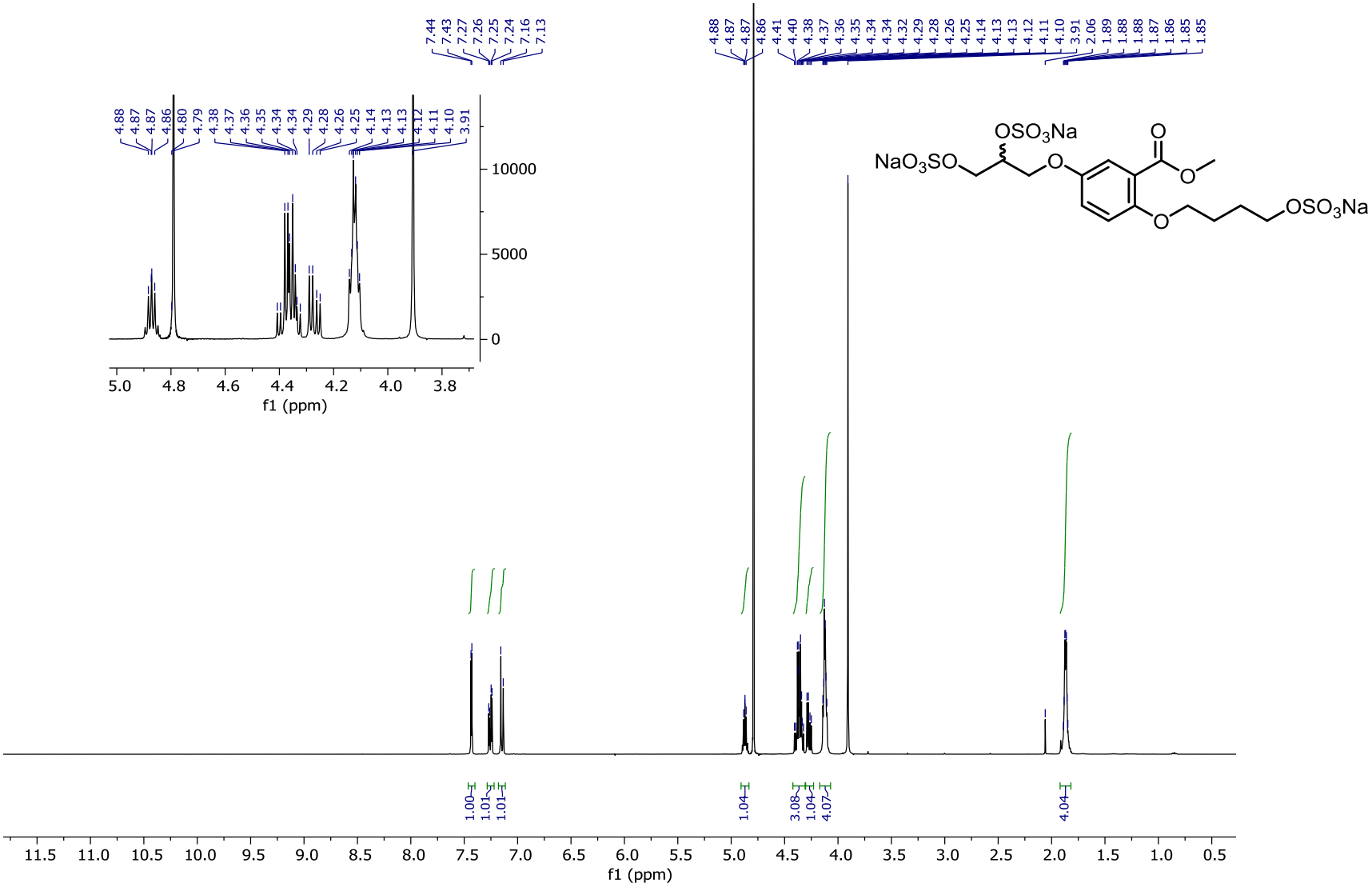
^{1}H NMR spectrum of **9b** (400 MHz, DMSO-d_6)



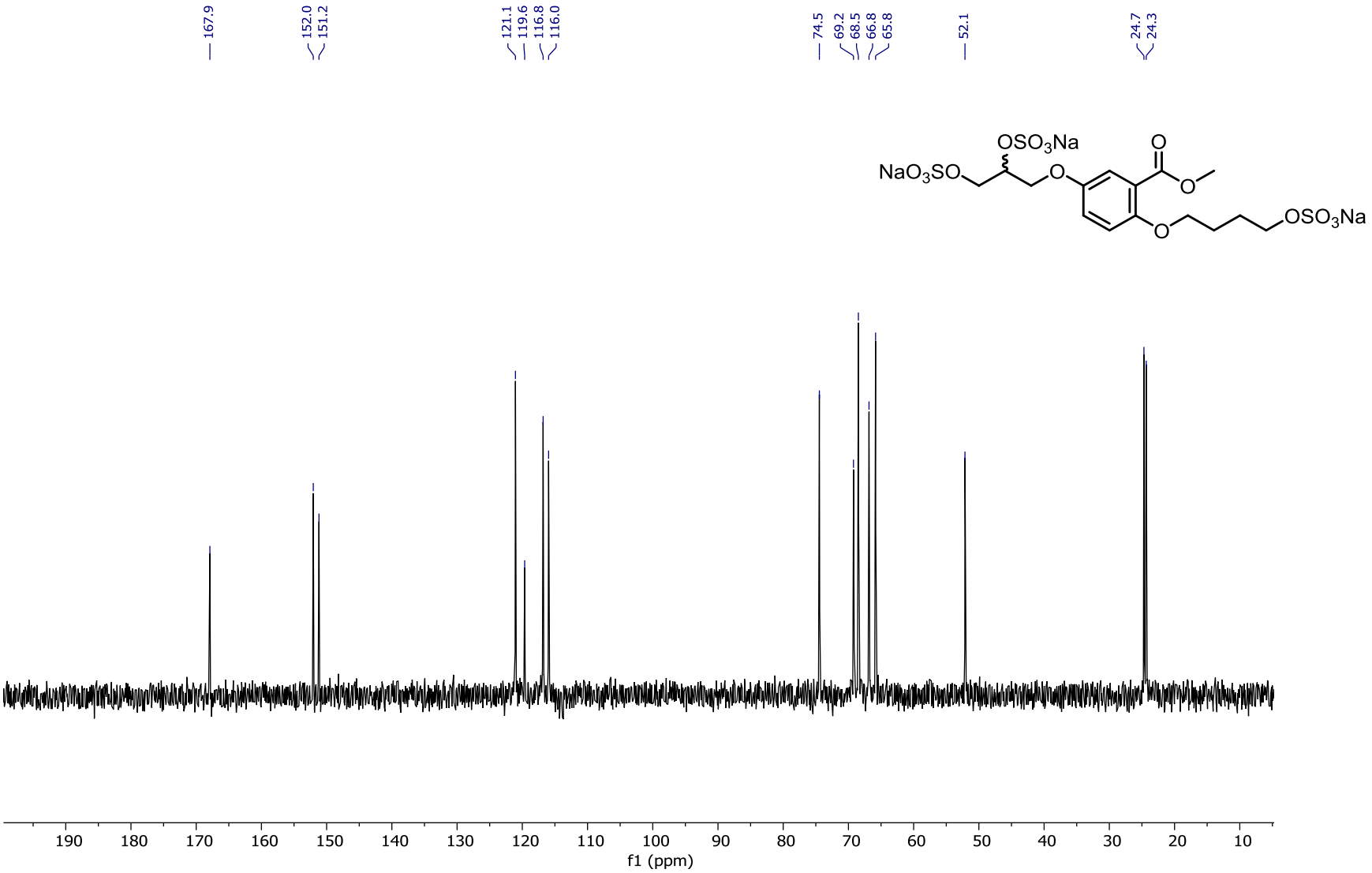
^{13}C NMR spectrum of **9b** (100 MHz, DMSO-d_6)



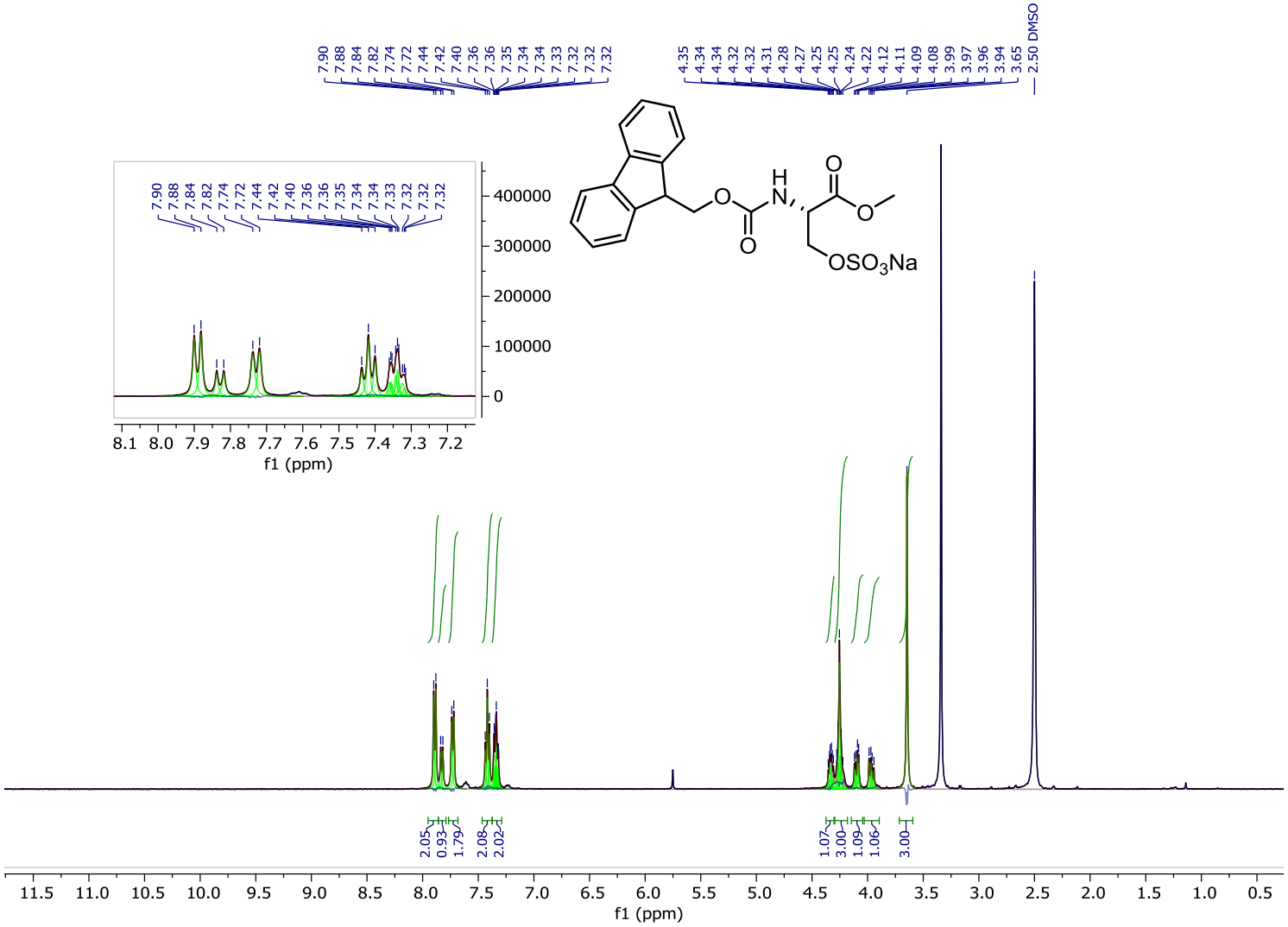
^{1}H NMR spectrum of **10** (400 MHz, D_2O)



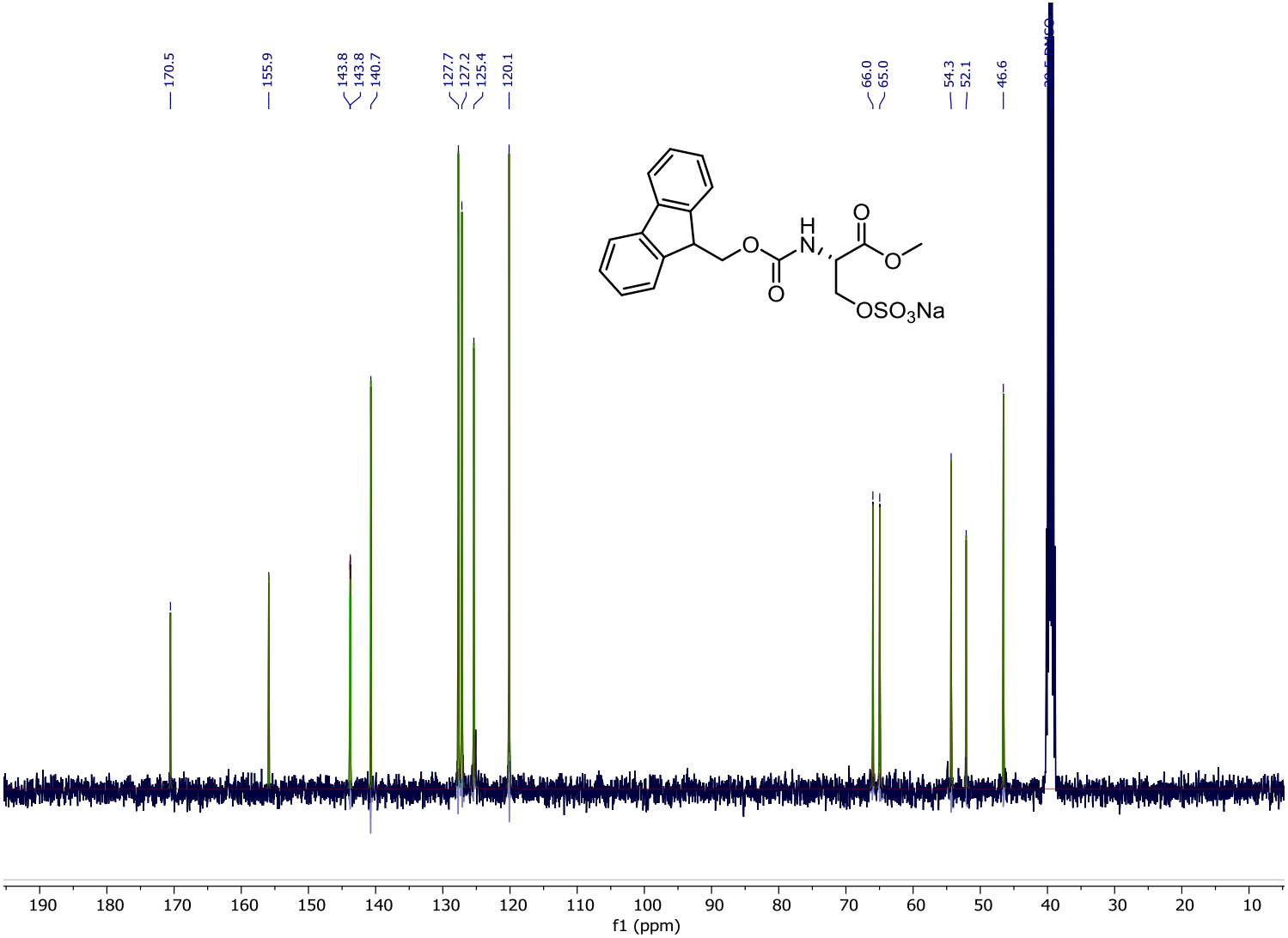
^{13}C NMR spectrum of **10** (101 MHz, D_2O)



^{1}H NMR spectrum of **11** (400 MHz, DMSO-d_6)



^{13}C NMR spectrum of **11** (100 MHz, DMSO-d_6)



S5. Crystallographic data for **1**

Crystal Data for $C_{12}H_{27}NO_3S$ (M =265.40 g/mol): trigonal, space group R3c (no. 161), a = 14.3352(2) Å, c = 12.2455(2) Å, V = 2179.28(8) Å^3, Z = 6, T = 100.01(10) K, μ(CuKα) = 1.969 mm^{-1}, *Dcalc* = 1.213 g/cm^3, 8776 reflections measured (16.14° ≤ 2Θ ≤ 147.692°), 977 unique (R_{int} = 0.0273, R_{sigma} = 0.0115) which were used in all calculations. The final R_1 was 0.0209 (I > 2σ(I)) and wR_2 was 0.0570 (all data).

The dataset was measured on an Agilent SuperNova diffractometer using an Atlas detector. The data collection was driven and processed and an absorption correction was applied using CrysAlisPro.[8] The structure was solved using ShelXT[9] and was refined by a full-matrix least-squares procedure on F^2 in ShelXL.[10] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom. Figures and reports were produced using OLEX2.[11]

The structure occupies a chiral space group and the absolute structure has been determined from the diffraction data, with the Flack parameter being -0.007 (8). The molecule lies on a 3-fold rotation axis running through N(1) and S(1) such that the butyl groups are all symmetrically equivalent.

The CIF for the crystal structures of **1** has been deposited with the CCDC and has been given the deposition number: CCDC 1894165.

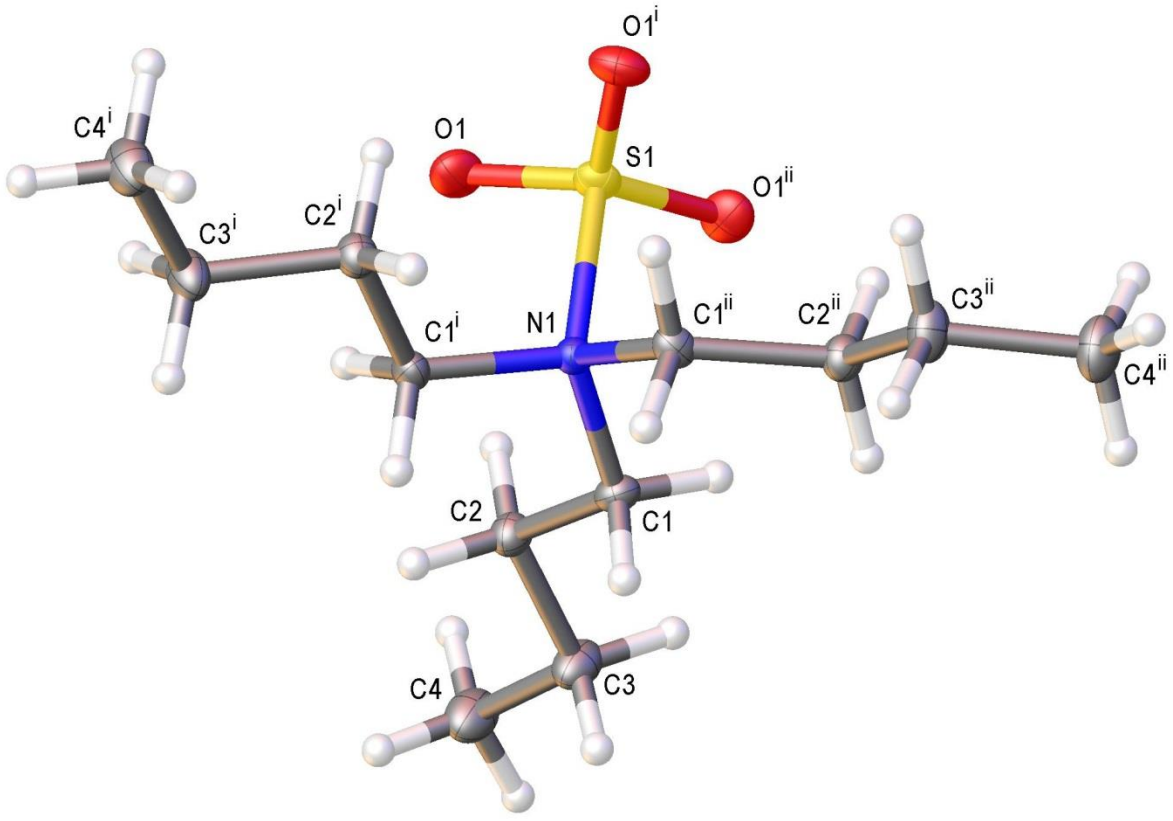


Figure S1: Crystal structure of compound **1** with ellipsoids drawn at the 50 % probability level. The molecule lies on a 3-fold rotation axis running through N(1) and S(1) such that the butyl groups are all symmetrically equivalent. Symmetry codes used the generate equivalent atoms: $1, y-x, 1-x, z, $2, 1-y, 1+x-y, z

S6. References

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