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Synthesis and Evaluation of Cationic Norbornanes as Peptidomimetic Antibacterial Agents

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Experimental

General experimental

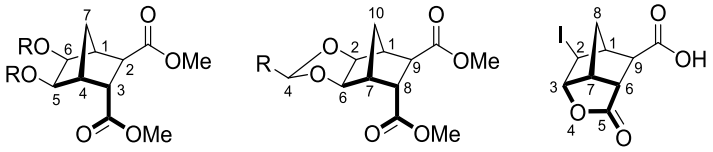
Chemicals purchased from commercial sources were used without further purification. Dry $CHCl_3$ and DMF were obtained using the Pure Solv solvent drying system (Innovative Technology, Inc., Amesbury, MA, USA). Solvents were degassed and passed through two drying chambers of alumina and stored and collected under a positive pressure of nitrogen gas.

All microwave reactions were conducted using a CEM Discover S-Class Explorer 48 Microwave Reactor, operating on a frequency of 50/60 Hz and continuous irradiation power from 0–300 W. All reactions were performed in sealed reaction vessels.

All melting points were obtained using Stuart Scientific SMP3 melting point apparatus and are uncorrected. All ^{1}H and ^{13}C NMR spectra were collected on either a JEOL JNM-GX 270 MHz FT-NMR spectrometer, a JEOL JNM-ECP 400 MHz FT-NMR spectrometer, or a BRUKER ADVANCE III 500 MHz FT-NMR spectrometer where indicated. All NMR experiments were performed at 25 °C unless otherwise stated. All 2D NMR experiments were performed on a BRUKER ADVANCE 500 MHz FT-NMR spectrometer. Samples were dissolved in $CDCl_3$, DMSO-d_6 or CD_3OD where specified with the residual solvent peak used as the internal reference – $CDCl_3$; 7.26 (^{1}H) and 77.0 (^{13}C), DMSO-d_6; 2.50 (^{1}H) and 39.52 (^{13}C), CD_3OD; 3.31 (^{1}H) and 49.0 (^{13}C).[1] Proton spectra are reported as chemical shift (ppm) δ (integral, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet and m = multiplet), coupling constant (Hz), assignment). Carbon spectra are reported as chemical shift δ (ppm).

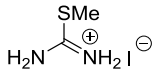
High resolution mass spectral data was collected on an Agilent Technologies 6520 QTOF mass spectrometer (LC-1200 series) under the following conditions: gas temperature (300 °C), nitrogen drying gas (10.0 L min^{-1}), capillary voltage (3500 V), fragmentor (140 V), and nebuliser (45 psi) in a 80% MeCN in H_2O solvent system. Analyte solutions were prepared in HPLC grade methanol (conc. ~ 1 mg mL^{-1}).

All norbornane-based compounds are named using the von-Baeyer system of nomenclature.[2] All other parts of the structure are named following the IUPAC guidelines. Numbering of norbornane protons follows the general structures shown below. Protons on the bridge carbon are labelled either *syn* (*s*) or *anti* (*a*) in regards to the priority functional group.



2-Methylisothiouronium iodide (S3)[3]

[CAS Reg. No. 14257-47-7]



A mixture of thiourea (10.0 g, 0.13 mol), iodomethane (8.2 mL, 0.13 mol) and MeOH (100 mL) was heated at 65 °C for 90 min. The MeOH was removed *in vacuo* and the resulting yellow solid was transferred to a sintered glass funnel and washed with Et_2O (5 × 50 mL) to afford compound the title compound (28.2 g, 99%) as an amorphous white powder.

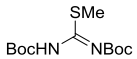
m.p: 115.3–117.6 °C (lit. 117 °C).[4]

^{1}H NMR (270 MHz, DMSO-d_6) δ 2.56 (3H, s, CH_3), 8.89 (4H, br s, NH_2).

^{13}C NMR (67.5 MHz, DMSO-d_6) δ 13.3, 171.1.

***N,N′*-Bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea (S4)**[3]

[CAS Reg. No. 107819-90-9]



To a stirring solution of 2-methylisothiouronium iodide **S3** (9.82 g, 45.0 mmol) in sat. $NaHCO_3$ (50 mL) and CH_2Cl_2 (105 mL) was added Boc_2O (19.67 g, 90.1 mmol) using CH_2Cl_2 (3 × 25 mL). After 48 h the reaction mixture was transferred to a separatory funnel and the organic phase was isolated and the aqueous phase was extracted using CH_2Cl_2 (2 × 50 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude solid was stirred (EtOH/H_2O, 1:9, 100 mL) for 1 h before the mixture was cooled to 0 °C and solid was collected by vacuum filtration, washing with H_2O (EtOH/H_2O, 1:9, 50 mL) gives the title compound (12.26 g, 94%) as a white powder.

m.p: 122.3–123.8 °C (lit. 127 °C).[5]

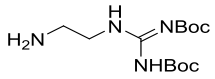
^{1}H NMR (270 MHz, $CDCl_3$) δ 1.51 (9H, br s, *t*-Bu), 1.53 (9H, br s, *t*-Bu), 2.40 (3H, s, CH_3), 11.61 (1H, br s, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 28.2, 81.1, 83.4, 150.9, 160.9, 171.6.

HRMS (ESI, *m/z*) for $C_{12}H_{22}N_2O_4S$ $[M + Na]^+$ calc. 313.1193; found 313.1186.

2-[2,3-Bis(*tert*-butoxycarbonyl)guanidino]ethylamine (11)[6]

[CAS Reg. No. 203258-44-0]



A solution of Boc-protected methylisothiourea **S4** (20.4 g, 70.3 mmol) in CH_2Cl_2 (110 mL) was added in one portion to a stirred solution of 1,2-ethylenediamine (11.7 mL, 176 mmol) in CH_2Cl_2 (150 mL). The reaction was stirred at 21 °C for 90 min. The reaction mixture was then transferred to a separatory funnel and washed with H_2O (2 × 80 mL), brine (80 mL), then dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* at ambient temperature to afford the title compound (20.7 g, 97%) as a white powder.

m.p: 96.2–100.1 °C.

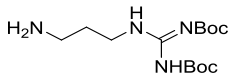
^{1}H NMR (270 MHz, $CDCl_3$) δ 1.50 (9H, br s, *t*-Bu), 1.51 (9H, br s, *t*-Bu), 2.90 (2H, t, *J* = 6.2 Hz, CH_2), 3.49 (2H, app. q, *J* = 5.5 Hz, CH_2), 8.67 (1H, br s, NH), 11.51 (1H, br s, NH).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 28.2, 28.4, 41.1, 43.5, 79.4, 83.2, 153.3, 156.5, 163.7.

HRMS (ESI, *m/z*) for $C_{13}H_{26}N_4O_4$ $[M + H]^+$ calc. 303.2027; found 303.2032.

2-[2,3-Bis(*tert*-butoxycarbonyl)guanidino]propylamine (17)[6]

[CAS Reg. No. 214151-16-3]

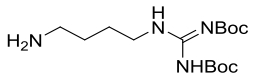


Performed as for the synthesis of amine **11**, using Boc-protected methylisothiourea **S4** (565 mg, 2.0 mmol) in CH_2Cl_2 (4.5 mL) and 1,3-diaminopropane (406 µL, 4.9 mmol) in CH_2Cl_2 (2.7 mL). The reaction was stirred at 21 °C for 40 min and the product was isolated as a colourless oil (476 mg, 70%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 1.49 (9H, br s, *t*-Bu), 1.50 (9H, br s, *t*-Bu), 1.73 (2H, quin, *J* = 6.7 Hz, CH_2), 2.79 (2H, t, *J* = 6.7 Hz, CH_2), 3.51 (2H, app. q, *J* = 6.7 Hz, CH_2), 8.43 (1H, br s, NH), 11.47 (1H, br s, NH).

2-[2,3-Bis(*tert*-butoxycarbonyl)guanidino]butylamine (16)[6]

[CAS Reg. No. 128009-23-4]



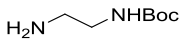
Synthesis of compound **16** was achieved as per **11**, using Boc-protected methylisothiourea **S4** (564 mg, 1.9 mmol) in CH_2Cl_2 (4.5 mL) and 1,4-diaminobutane (488 µL, 4.9 mmol) in CH_2Cl_2 (2.7 mL). The reaction was allowed to stir at 21 °C for 75 min and the product was isolated as a colourless oil (438 mg, 61%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44–1.67 (22H, m, 2 × *t*-Bu, 2 × CH_2), 2.12 (2H, br s, NH_2), 2.78 (2H, t, *J* = 6.9 Hz, CH_2), 3.42 (2H, app. q, *J* = 6.9 Hz, CH_2), 8.37 (1H, br s, NH), 11.50 (1H, br s, NH).

HRMS (ESI, *m/z*) calculated for $C_{15}H_{30}N_4O_4$ $[M+ H]^+$ 331.2340; found 331.2352.

2-(*tert*-Butoxycarbonylamino)ethylamine (6)[7]

[CAS Reg. No. 57260-73-8]



A solution of Boc_2O (8.35 g, 38.3 mmol) in THF (75 mL) was added dropwise, over approximately 30 min, to a stirred solution of 1,2-ethylenediamine (8.4 mL, 125 mmol) in THF (25 mL). The reaction was stirred for approximately 4 h after which time the solution was filtered and the solvent then removed *in vacuo* to afford the desired product (5.65 g, 92%) as a viscous oil.

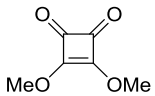
^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (2H, br s, NH_2), 1.43 (9H, br s, *t*-Bu), 2.78 (2H, t, *J* = 6.0 Hz, C*H*$_2$NH), 3.15 (2H, q, *J* = 6.0 Hz, C*H*$_2$$NH_2$), 4.83 (1H, br s, NH).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 28.4, 40.7, 41.8, 43.4, 156.3.

HRMS (ESI, *m/z*) for $C_7H_{16}N_2O_2$ $[M + H]^+$ calc. 161.1285; found 161.1290.

3,4-Dimethoxy-3-cyclobutene-1,2-dione (S5) [8]

[CAS Reg. No. 5222-73-1]



To a stirring solution of squaric acid (1.00 g, 8.78 mmol) in MeOH (18 mL) was added trimethyl orthoformate (1.9 mL, 17.6 mmol) and the reaction was heated at 65 °C for 24 h. The reaction mix was concentrated under reduced pressure before being diluted with $CHCl_3$ (20 mL). The organic phase was washed with sat. $NaHCO_3$ (2 × 10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was purified by a silica plug (10% EtOAc in CH_2Cl_2) to afford the title compound (896 mg, 72%) as a white solid.

R_f = 0.33 (10% EtOAc in CH_2Cl_2).

m.p: 52.5–54.9 °C (lit. 55.0 °C).[8]

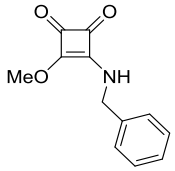
^{1}H NMR (270 MHz, $CDCl_3$) δ 4.37 (6H, s, 2 × CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 67.5, 184.6, 189.3.

HRMS (ESI, *m/z*) for $C_6H_6O_4$ $[M + H]^+$ calc. 143.0339; found 143.0340.

3-Benzylamine-4-methoxycyclobut-3-ene-1,2-dione (S2) [9]

[CAS Reg. No. 636601-12-2]



To a stirring solution of squaric ester **S5** (257 mg, 1.81 mmol) in MeOH (6.5 mL) was added benzylamine (200 μL, 1.83 mmol), and the reaction was stirred for 1 h at ambient temperature. The crude product was concentrated under vacuum before being purified by column chromatography (20% MeCN in CH_2Cl_2) to give the title compound (192 mg, 49%) as a white solid.

R_f = 0.5 (20% MeCN in CH_2Cl_2).

m.p: 122.9–123.7 °C (lit. 122–124 °C).[9]

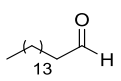
^{1}H NMR (400 MHz, DMSO-d_6, 40 °C) δ 4.29 (3H, s, OMe), 4.46 (1H, br s, CH_2), 4.68 (1H, br s, CH_2), 7.29–7.39 (5H, m, ArH), 9.06–9.27 (1H, m, NH).

^{13}C NMR (67.5 MHz, DMSO-d_6) δ 47.1, 60.1, 127.3, 127.4, 128.6, 138.2, 172.0, 177.5, 182.4, 189.4.

HRMS (ESI, *m/z*) for $C_{12}H_{11}NO_3$ $[M + H]^+$ calc. 218.0812; found 218.0818.

Hexadecanal (S6)[10]

[CAS Reg. No. 629-80-1]



To the stirring solution of DMSO (710 μL, 10.0 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added oxalyl chloride (440 μL, 5.0 mmol) under an inert atmosphere. After 20 min 1-hexadecanol (484 mg, 2.0 mmol) in CH_2Cl_2 (6 mL) was added and the reaction was stirred for 5.5 h at −41 °C. The reaction was quenched with Et_3N

(3 mL, 21.5 mmol) and slowly warmed to ambient temperature over 30 min. The reaction mix was washed with sat. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with 2M HCl (2 × 20 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow solid (389 mg, 81%).

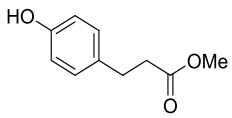
m.p: 36.4–38.0 °C (lit. 33.0–35.0 °C).[11]

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.4 Hz, CH_3), 1.25–1.30 (24H, m, 12 × CH_2), 1.62 (2H, t, *J* = 7.4 Hz, CH_2), 2.41 (2H, dt, *J* = 7.3, 1.9 Hz, CH_2), 9.76 (1H, t, *J* = 1.9 Hz, CHO).

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.2, 22.8, 29.3, 29.5, 29.6, 29.7, 29.8 (5 × C), 32.1, 44.1, 203.1.

Methyl-3-(4-hydroxyphenyl)propionate (S7) 170[12]

[CAS Reg. No. 5597-50-2]



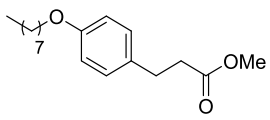
To the stirring solution of 3-(4-hydroxyphenyl)-propanoic acid (5.02 g, 30.23 mmol) in MeOH (50 mL), conc. H_2SO_4 (50 μL) was added and the reaction was heated at 65 °C for 16 h. The reaction mix was concentrated and the resulting yellow oil was dissolved in EtOAc (25 mL), washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound (4.78 g, 88%) as a viscous yellow oil that required no further purification.

^{1}H NMR (270 MHz, $CDCl_3$) δ 2.58–2.64 (2H, m, CH_2), 2.88 (2H, t, *J* = 7.4 Hz, CH_2), 3.67 (3H, s, Me), 5.85 (1H, br s, OH), 6.73–6.78 (2H, m, ArH), 7.01–7.07 (2H, m, ArH).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 30.2, 36.2, 51.9, 115.5 (2 × C), 129.5 (2 × C), 132.4, 154.3, 174.2.

HRMS (ESI, *m/z*) for $C_{10}H_{12}O_3$ $[M + H]^+$ calc. 181.0859; found 181.0857.

Methyl 3-[4-(octyloxy)phenyl]propanoate (S8)



A mixture of alcohol **S7** (1.01 g, 5.63 mmol), K_2CO_3 (2.33 g, 8.45 mmol), 1-iodooctane (2.6 mL, 14.4 mmol) and DMF (8.7 mL), was stirred for 4 d at ambient temperature protected from light. The reaction was diluted with EtOAc (30 mL), and the organic phase was washed with H_2O (3 × 25 mL), brine (25 mL), dried ($MgSO_4$),

filtered, and concentrated *in vacuo* to give a yellow liquid which was purified by column chromatography (pet. spirits–5% EtOAc in pet. spirits) which gave the title compound (1.26 g, 77%) as a colourless liquid.

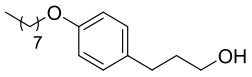
R_f = 0.44 (10% EtOAc in pet. spirits).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.7 Hz, CH_3), 1.28–1.48 (10H, m, 5 × CH_2), 1.76 (2H, quin, *J* = 6.6 Hz, CH_2), 2.60 (2H, dd, *J* = 8.2, 7.5 Hz, CH_2), 2.89 (2H, t, *J* = 7.6 Hz, CH_2), 3.67 (3H, s, OMe), 3.92 (2H, t, *J* = 6.6 Hz, OCH_2), 6.82 (2H, d, *J* = 8.6 Hz, ArH), 7.10 (2H, d, *J* = 8.6 Hz, ArH).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.2, 22.8, 26.2, 29.4 (2 × C), 29.5, 30.3, 32.0, 36.2, 51.7, 68.1, 114.6 (2 × C), 129.3 (2 × C), 132.5, 157.8, 173.6.

HRMS (ESI, *m/z*) for $C_{18}H_{28}O_3$ $[M + H]^+$ calc. 293.2111; found 293.2117.

3-[4-(Octyloxy)phenyl]propan-1-ol (S9)



Under an inert atmosphere, ester **S8** (1.08 g, 3.68 mmol) was stirred in PhMe (18 mL), at 0 °C before Red-Al (2.8 mL, 9.2 mmol) was slowly added. The reaction was warmed to ambient temperature over 30 min and then stirred for a further 16 h. The reaction mix was quenched with H_2O (15 mL) and was left to stir for 2 h. The crude product was extracted with EtOAc (2 × 20 mL), and the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was achieved by column chromatography (20% EtOAc in pet. spirits) to give the title compound (869 mg, 89%) as a white waxy solid.

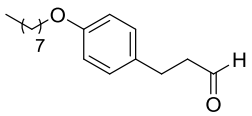
R_f = 0.25 (20% EtOAc in pet. spirits).

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.6 Hz, CH_3), 1.29–1.47 (10H, m, 5 × CH_2), 1.51 (1H, s, OH), 1.72–1.91 (4H, m, 2 × CH_2), 2.65 (2H, t, *J* = 7.3 Hz, $ArCH_2$), 3.66 (2H, t, *J* = 6.4 Hz, OCH_2), 3.93 (2H, t, *J* = 6.6 Hz, OCH_2), 6.80–6.85 (2H, m, ArH), 7.07–7.13 (2H, m, ArH).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.2, 22.8, 26.2, 29.4, 29.5 (2 × C), 31.3, 31.9, 34.6, 62.4, 68.2, 114.6 (2 × C), 129.4 (2 × C), 133.7, 157.4.

HRMS (ESI, *m/z*) for $C_{17}H_{28}O_2$ $[M + H]^+$ calc. 265.2162; found 265.2170.

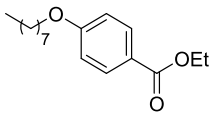
3-[4-(Octyloxy)phenyl]propanal (S10)



To the stirring solution of DMSO (1.1 mL, 15.3 mmol) in dry CH_2Cl_2 (60 mL) at −78 °C was added oxalyl chloride (660 μL, 7.7 mmol) under an inert atmosphere. After 20 min alcohol **S9** (809 mg, 3.06 mmol) in CH_2Cl_2 (16 mL) was added and the reaction was stirred for 5.5 h at −41 °C. The reaction mixture was quenched with Et_3N (5 mL) and warmed slowly to ambient temperature over 60 min. The reaction mix was washed with sat. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was washed with 2M HCl (30 mL), sat. $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound (668 mg, 83%) as a yellow oil that was used directly in ensuing reactions due to compound instability.

Ethyl 4-(octyloxy)benzoate (S11)[13]

[CAS Reg. No. 72885-31-5]



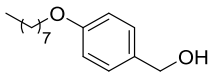
A stirring solution of ethyl 4-hydroxybenzoate (3.01 g, 18.11 mmol) and K_2CO_3 (7.56 g, 54.70 mmol) in DMF (28 mL) was protected from light and treated with 1-iodooctane (4.3 mL, 24.53 mmol) for 16 h. The solution was then diluted with EtOAc (25 mL), washed H_2O (3 × 50 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (pet. spirits–5% EtOAc in pet. spirits) provided the title compound (4.58 g, 91%) as a clear oil.

R_f = 0.40 (5% EtOAc in pet. spirits).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.7 Hz, CH_3), 1.29–1.48 (13H, m, 5 × CH_2CH_3), 1.80 (2H, app. quin, *J* = 6.7 Hz, C*H*$_2$CH$_2$O), 4.00 (2H, t, *J* = 6.6 Hz, CH_2O), 4.34 (2H, q, *J* = 7.1 Hz, C(O)OCH$_2$), 6.90 (2H, d, *J* = 8.9 Hz, ArH), 7.98 (2H, d, *J* = 9.0 Hz, ArH).

4-(Octyloxy)benzyl alcohol (S12)[14]

[CAS Reg. No. 67698-68-4]



To a stirring solution of **S11** (4.43 g, 15.91 mmol) in PhMe (32 mL) under N_2 at 0 °C was added a solution of Red-Al® (12.2 mL, 40.64 mmol 65 wt.% in PhMe) slowly and the resulting solution stirred for 30 min before being allowed to warm to ambient temperature and stirred for a further 16 h. The solution was quenched with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine

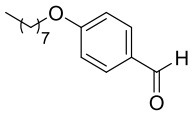
(25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in pet. spirits) to afford the title compound (3.08 g, 82%) as a transparent yellow oil.

R_f = 0.39 (20% EtOAc in pet. spirits).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.6 Hz, CH_3), 1.26–1.46 (10H, m, 5 × CH_2), 1.66 (1H, br s, OH), 1.75 (2H, app. quin, *J* = 6.9 Hz, C*H*$_2$CH$_2$O), 3.92 (2H, t, *J* = 6.6 Hz, CH_2O), 4.58 (2H, s, C*H*$_2$OH), 6.86 (2H, d, *J* = 8.6 Hz, ArH), 7.25 (2H, d, *J* = 8.8 Hz, ArH).

4-(Octyloxy)benzaldehyde (R13)[15]

[CAS Reg. No. 24083-13-4]

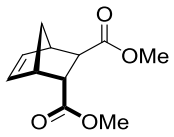


A solution of **S12** (3.00 g, 12.69 mmol) and manganese dioxide (21.44 g, 246.62 mmol) in $CHCl_3$ (36 mL) was stirred for 72 h at ambient temperature. The resulting slurry was filtered over celite and the filtrate concentrated *in vacuo* to afford the title compound (2.63 g, 88%) as a transparent yellow oil which was used without further purification.

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.8 Hz, CH_3), 1.29–1.46 (10H, m, 5 × CH_2), 1.81 (2H, app. quin, *J* = 8.2 Hz, C*H*$_2$CH$_2$O), 4.04 (2H, t, *J* = 6.6 Hz, CH_2O), 6.99 (2H, d, *J* = 8.8 Hz, ArH), 7.83 (2H, d, *J* = 8.8 Hz, ArH), 9.88 (1H, s, CHO).

Dimethyl bicyclo[2.2.1]hept-5-ene-3-*endo*-2-*exo*-dicarboxylate (S14)

[CAS Reg. No. 3014-58-2]



Method A[16]

To the stirring solution of dimethyl fumarate (65.3 g, 0.453 mol) in THF (200 mL), was added freshly cracked cyclopentadiene (40 mL, 0.476 mol), and the reaction was stirred at ambient temperature for 16 h. The solvent was removed under reduced pressure to give the title compound (95.2 g, 99%) as a clear liquid.

Method B[17]

A 35 mL MW vial was charged with dicyclopentadiene (2.0 mL, 15.0 mmol), dimethyl fumarate (2.88 g, 20.0 mmol) and hydroquinone (100 mg, 0.90 mmol), and heated using microwave irradiation to 150 °C for 2 h. The resulting orange oil was purified by flash column chromatography (10% EtOAc in pet. spirits) to give a clear oil (4.14 g, 98%).

R_f = 0.32 (10% EtOAc in pet. spirits).

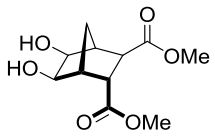
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (1H, dd, *J* = 8.8, 1.7 Hz, H7*s*), 1.61 (1H, d, *J* = 8.8 Hz, H7*a*), 2.68 (1H, dd, *J* = 3.1, 1.2 Hz, H2), 3.12 (1H, br s, H4), 3.25 (1H, br s, H1), 3.37 (1H, app. t, *J* = 5.6 Hz, H3), 3.64 (3H, s, Me), 3.71 (3H, s, Me), 6.06 (1H, dd, *J* = 5.6, 2.8 Hz, H6), 6.27 (1H, dd, *J* = 5.6, 3.1 Hz, H5).

^{13}C NMR (100 MHz, $CDCl_3$) δ 45.5, 46.9, 47.2, 47.5, 47.7, 51.7, 51.9, 135.3, 137.7, 174.0, 175.2.

HRMS (ESI, *m/z*) for $C_{11}H_{14}O_4$ $[M + Na]^+$ calc. 233.0784; found 233.0785.

Dimethyl 5,6-*exo*-dihydroxybicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (3)

[CAS Reg. No. 1228039-59-5]



Method A[18]

The dimethyl ester **S14** (3.05 g, 14.5 mmol) and NMO·H_2O (1.87 g, 16.0 mmol) were dissolved in a solution of H_2O/acetone (1:4, 36 mL) to which OsO_4 (4% in H_2O, 730 µL, 0.40 mol%) was added. The reaction was stirred for 3 d and then quenched with sat. $NaHSO_3$ (30 mL). The suspension was extracted with EtOAc (4 × 25 mL), and the combined organic phase was washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title compound (3.34 g, 94%) as a white solid.

Method B[19]

To a stirring solution of dimethyl ester **S14** (270 mg, 1.28 mmol), *t*-BuOH (4.7 mL) and H_2O (1.2 mL) at 0 °C, a solution of $KMnO_4$ (405 mg, 2.56 mmol), K_2CO_3 (212 mg, 1.54 mmol) in H_2O (6.0 mL) was added dropwise. The reaction was stirred for a further 25 min before consumption of starting material was observed by TLC analysis. The reaction mix was quenched with sat. $NaHSO_3$ (25 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound (181 mg, 58%) as a white solid.

m.p: 89.9–92.3 °C (lit. 81–84 °C).[18]

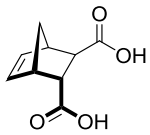
^{1}H NMR (270 MHz, $CDCl_3$) δ 1.33 (1H, d, *J* = 11.0 Hz, H7*s*), 1.78 (1H, dd, *J* = 11.0, 1.2 Hz, H7*a*), 2.40 (1H, br s, H1), 2.46 (1H, dd, *J* = 1.2, 4.5 Hz, H4), 2.63 (1H, d, *J* = 4.9 Hz, H2), 3.11 (1H, app. t, *J* = 5.1 Hz, H3), 3.62 (3H, s, Me), 3.64 (3H, s, Me), 3.71–3.77 (1H, m, H6), 3.85 (1H, br s, H5).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 31.8, 44.8, 46.2, 46.4, 48.2, 52.3, 52.5, 70.2, 73.3, 173.2, 174.2.

HRMS (ESI, *m/z*) for $C_{11}H_{16}O_6$ $[M + Na]^+$ calc. 267.0839; found 267.0836.

Bicyclo[2.2.1]hepta-5-ene-3-*endo*,2-*exo*-dicarboxylic acid (S1)[20]

[CAS Reg. No. 1200-88-0]



To the stirring solution of norbornene diester **S14** (1.24 g, 5.88 mmol) in THF (24.5 mL) was added 2M NaOH (12.3 mL, 24.5 mmol) and the reaction was stirred for 16 h at ambient temperature. The THF was removed under reduced pressure before the remaining aqueous solution was acidified to pH = 1 (2M HCl). The title compound (941 mg, 88%) was collected by vacuum filtration as a fine white powder.

m.p: 54.9–191.0 °C (slow decomposition) (lit. 186–187 °C).[21]

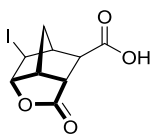
^{1}H NMR (270 MHz, DMSO-d_6) δ 1.33 (1H, dd, *J* = 8.5, 1.4 Hz, H7*s*), 1.49 (1H, d, *J* = 8.6 Hz, H7*a*), 2.42 (1H, dd, *J* = 4.0, 1.5 Hz, H2), 3.02–3.03 (1H, m, H4), 3.15–3.18 (2H, m, H3, H1), 6.05 (1H, dd, *J* = 5.5, 2.3 Hz, H6), 6.28 (1H, dd, *J* = 5.6, 3.1 Hz, H5), 12.28 (2H, br s, COOH).

^{13}C NMR (100 MHz, DMSO-d_6) δ 45.0, 46.8, 47.0, 47.1, 47.5, 135.0, 137.5, 174.2, 175.3.

HRMS (ESI, *m/z*) for $C_9H_{10}O_4$ $[M + Na]^+$ calc. 205.0468; found 205.0471.

2-*exo*-Ioda-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-*exo*-carboxylic acid (S15)[22]

[CAS Reg. No. 125226-89-3]



A solution of diacid **S1** (2.34 g, 12.84 mmol), $NaHCO_3$ (5.39 g, 64.2 mmol) and H_2O (40 mL) at ambient temperature was stirred for approximately 45 min, after which an aqueous solution of I_2/KI [0.2 M/0.6 M] was added until the solution maintained a dark brown colour. The mixture was left to stir for 20 min before addition of $Na_2S_2O_5$ resulting in the decolourisation of the solution. The reaction mix was then acidified to pH = 1 (6M H_2SO_4), resulting in a colour change to light yellow. The product was then extracted with CH_2Cl_2 (4 × 30 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give the desired iodolactone (3.76 g, 95%) as a white powder.

m.p: 129.0–132.6 °C (lit. 126.0–127.0 °C).[23]

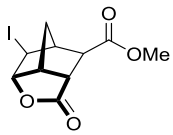
^{1}H NMR (270 MHz, $CDCl_3$) δ 1.98 (1H, ddd, *J* = 11.9, 2.3, 1.7 Hz, H7*s*), 2.38 (1H, dd, *J* = 12.1, 1.2 Hz, H7*a*), 2.91 (1H, s, H2), 3.10 (2H, m, H1, H3), 3.22–3.27 (1H, m, H4), 3.91 (1H, d, *J* = 2.6 Hz, H6), 5.16 (1H, d, *J* = 5.0 Hz, H5), 10.65 (1H, br s, COOH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 35.3, 41.0, 46.3, 50.1, 50.5, 88.7, 174.9, 177.4.

HRMS (ESI, *m/z*) for $C_9H_9IO_4$ $[M + Na]^+$ calc. 330.9438; found 330.9434.

Methyl-2-*exo*-ioda-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-*exo*-carboxylate (S16)[22]

[CAS Reg. No. 42392-48-3]



To a stirring solution of carboxylic acid **S15** (7.63 g, 24.8 mmol) in MeOH (34 mL), was added conc. H_2SO_4 (300 μL, 5.63 mmol) and the reaction was heated to 65 °C for 16 h. The reaction mix was concentrated and the resulting yellow sludge was dissolved in CH_2Cl_2 (40 mL), washed with H_2O (20 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting yellow viscous oil (7.15 g, 90%) required no further purification.

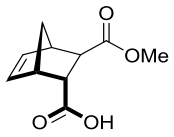
^{1}H NMR (270 MHz, $CDCl_3$) δ 1.93–1.99 (1H, m, H7*s*), 2.32 (1H, dd, *J* = 12.0, 1.4 Hz, H7*a*), 2.84 (1H, br s, H2), 3.02 (1H, br s, H3), 3.08–3.10 (1H, m, H1), 3.19–3.24 (1H, m, H4), 3.73 (3H, s, OMe), 3.88 (1H, d, *J* = 2.6 Hz, H6), 5.13 (1H, d, *J* = 5.0 Hz, H5).

^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 35.2, 41.1, 46.3, 50.3, 50.6, 53.0, 88.6, 170.7, 177.3.

HRMS (ESI, *m/z*) for $C_{10}H_{11}IO_4$ $[M + H]^+$ calc. 322.9775; found 322.9773.

***exo*-2-Methoxycarbonylbicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylic acid (19)**[22]

[CAS Reg. No. 36897-94-6]



Zinc (4.49 g, 68.7 mmol) was activated in 1M HCl (53 mL) until the solid turned from a dark black to a silvery grey (*c.a* 10 min). The HCl was decanted and the zinc was washed and decanted successively with H_2O (3 × 10 mL) and EtOH (3 × 10 mL). To the activated zinc a solution of iodolactone **S16** (7.14 g, 68.7 mmol) in EtOH (67 mL) was added, followed by AcOH (67 mL), and the reaction was heated to 79 °C for 3 h. The zinc was removed by filtration and the solvent was removed *in vacuo.* The crude product was diluted with $CHCl_3$ (100 mL) and washed with H_2O (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound (4.03 g, 93%) as a white solid.

m.p: 96.4–98.2 °C.

^{1}H NMR (270 MHz, $CDCl_3$) δ 1.48 (1H, dd, *J* = 8.9, 1.6 Hz, H7*s*), 1.62 (1H, d, *J* = 8.9 Hz, H7*a*), 2.65 (1H, dd, *J* = 4.5, 1.5 Hz, H2), 3.13 (1H, br s, H4), 3.29 (1H, br s, H1), 3.42 (1H, app. t, *J* = 3.9 Hz, H3), 3.72 (3H, s, OMe), 6.13 (1H, dd, *J* = 5.6, 2.8 Hz, H6), 6.29 (1H, dd, *J* = 5.6, 3.2 Hz, H5).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 45.7, 47.1, 47.6, 47.7, 48.1, 52.4, 135.3, 137.9, 175.0, 179.5.

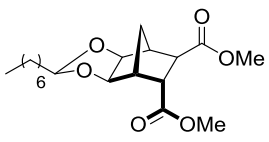
HRMS (ESI, *m/z*) for $C_{10}H_{12}O_4$ $[M - H]^-$ calc. 195.0663; found 195.0667.

General procedure A: acetal formation

To a stirring suspension of the appropriate diol, $TsOH·H_2O$ (0.05 equiv), $MgSO_4$ (1.0 equiv) and PhMe, was treated with the required aldehyde (1.5 equiv) at 110 °C for 3 h. Solid $MgSO_4$ was removed by filtration and the filtrate was diluted with EtOAc (30 mL), washed with H_2O (2 × 15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated i*n vacuo* to give the crude material which was purified by column chromatography (as specified below) to afford the title compound.

Dimethyl 4-heptyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxylate (4a)

[CAS Reg. No. 1233074-95-7]



Compound **4a** was prepared from diol **3** (3.40 g, 14.34 mmol) and octanal (3.36 mL, 21.5 mmol) according to general procedure A and was purified by column chromatography (10% EtOAc in pet. spirits) to give the title compound (4.66 g, 92%) as a colourless viscous oil.

Crystals suitable for x-ray analysis were obtained from slow evaporation of a 10% EtoAc in pet. spirits solution (see Figure S8).

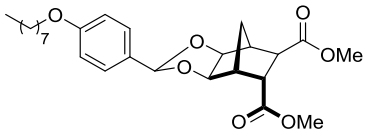
R_f = 0.26 (10% EtOAc in pet. spirits).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, *J* = 6.6 Hz, CH_3), 1.19–1.36 (11H, m, 5 × CH_2, H10*s*), 1.56–1.59 (2H, m, CHC*H*$_2$), 1.73 (1H, d, *J* = 10.8 Hz, H10*a*), 2.60 (2H, br s, H1, H7), 2.67 (1H, d, *J* = 4.5 Hz, H9), 3.18 (1H, app. t, *J* = 4.8 Hz, H8), 3.66 (6H, s, 2 × OMe), 3.85 (1H, d, *J* = 5.6 Hz, H6), 3.98 (1H, d, *J* = 5.6 Hz, H2), 4.61 (1H, t, *J* = 4.9 Hz, H4).

^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.3, 23.9, 28.9, 29.2, 31.3, 31.5, 32.5, 43.0, 43.4, 44.8, 45.0, 51.9, 52.1, 78.7, 81.2, 104.2, 173.0, 174.2.

HRMS (ESI, *m/z*) for $C_{19}H_{30}O_6$ $[M + Na]^+$ calc. 377.1935; found 377.1924.

Dimethyl 4-[4′-(octyloxy)phenyl]-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxylate (S17)



Compound **S17** was prepared from diol **3** (1.15 g, 4.71 mmol) and **S13** (1.59 g, 6.79 mmol) according to general procedure A and was purified by column chromatography (10% EtOAc in pet. spirits) to give the title compound (1.25 g, 57%) as a white powder.

R_f = 0.17 (10% EtOAc in pet. spirits).

m.p: 53.2–57.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.2 Hz, CH_3), 1.28-1.46 (11H, m, 5 × CH_2,H10*s*), 1.76 (2H, app. quin, *J* = 6.0 Hz, C*H*$_2$CH$_2$O), 2.01 (1H, dd, *J* = 10.9, 1.4 Hz, H10*a*), 2.71 (1H, dd, *J* = 5.5, 1.3 Hz, H7), 2.77 (1H, s, H1), 2.83 (1H, d, *J* = 4.5 Hz, H9), 3.28 (1H, app. t, *J* = 5.1 Hz, H8), 3.72 (3H, s, Me), 3.73 (3H, s, Me), 3.94 (2H, t, *J* = 6.6 Hz, CH_2), 4.08 (1H, d, *J* = 5.7 Hz, H6), 4.12 (1H, d, *J* = 5.7 Hz, H2), 5.53 (1H, s, H4), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 7.39 (2H, d, *J* = 8.7 Hz, ArH)

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.8, 26.1, 29.3, 29.4, 29.5, 31.9, 32.0, 43.5, 43.9, 45.3, 45.5, 52.3, 52.5, 68.2, 79.2, 81.7, 103.4, 114.6, 127.7, 128.2, 160.4, 172.9, 174.1.

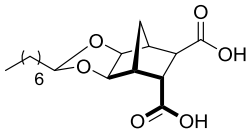
HRMS (ESI, *m/z*) for $C_{26}H_{37}O_7$ $[M + H]^+$ calc. 461.25338; found 461.25355.

General procedure B: hydrolysis of methyl esters

A biphasic solution of methyl ester in 2 M NaOH/THF (1:4) was stirred at ambient temperature for 16 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 8 mL) and the isolated aqueous phase was acidified to pH = 1 using 2 M HCl and extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound.

4-Heptyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxylic acid (5a)

[CAS Reg. No. 1233074-96-8]



The title compound (**5a**) was prepared from diester **4a** (1.00 g, 2.82 mmol) according to general procedure B and isolated white waxy solid (795 mg, 86%).

m.p: 141.1–143.2 °C (lit. 153.0–154.0 °C).[18]

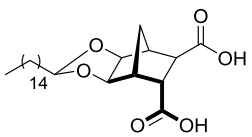
^{1}H NMR (270 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 6.4 Hz, CH_3), 1.19–1.33 (11H, m, 5 × CH_2, H10*s*), 1.50–1.61 (3H, m, CHCH_2, H10*a*), 2.40 (1H, d, J = 5.5 Hz, H1), 2.45 (1H, br s, H7), 2.54 (1H, br s, H9), 3.0 (1H, dd, J = 4.8, 0.6 Hz, H8), 3.88 (1H, d, J = 5.6 Hz, H6), 3.97 (2H, d, J = 5.6 Hz, H2), 4.62 (1H, t, J = 4.7 Hz, H4).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 22.1, 23.7, 28.6, 28.9, 31.2 (2 × C), 32.3, 42.6, 43.3, 44.4, 45.0, 78.2, 80.7, 103.2, 173.3, 174.6.

HRMS (ESI, *m/z*) for $C_{17}H_{26}O_6$ [M + Na]$^+$ calc. 349.1622; found 349.1627.

4-Hexadecyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxylic acid (5c)

[CAS Reg. No. 1233075-00-7]



The title compound (**5c**) was prepared from diester **4c** (258 mg, 0.56 mmol) according to general procedure B and isolated as an off-white solid (198 mg, 80%).

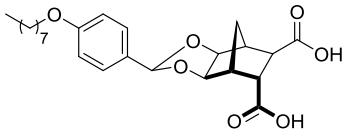
m.p: 126.7–133.8 °C (lit. 125.0–127.0 °C).[18]

^{1}H NMR (270 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 6.2 Hz, CH_3), 1.18–1.23 (27H, m, 13 × CH_2, H10*s*), 1.49–1.62 (3H, m, CHCH_2, H10*a*), 2.40 (1H, d, J = 5.0 Hz, H1), 2.45 (1H, br s, H7), 2.53 (1H, br s, H9), 3.00 (1H, app. t, J = 4.9 Hz, H8), 3.89 (1H, d, J = 5.4 Hz, H6), 3.96 (1H, d, J = 5.8 Hz, H2), 4.62 (1H, t, J = 4.7 Hz, H4).

^{13}C NMR (100 MHz DMSO-d_6) δ 13.9, 22.1, 23.6, 28.7, 28.9 (2 × C), 29.0 (7 × C), 31.2, 31.3, 32.3, 43.6, 43.3, 44.4, 45.0, 78.2, 80.7, 103.2, 173.3, 174.6.

HRMS (ESI, *m/z*) for $C_{25}H_{42}O_6$ $[M + Na]^+$ calc. 461.2874; found 461.2882.

4-[4′-(Octyloxy)phenyl]-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxylic acid (S18)



The title compound (**S18**) was prepared from diester **S17** (489.6 mg, 1.06 mmol) according to general procedure B and isolated as a white solid (382 mg, 83%).

m.p: 173.5–178.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 7.0 Hz, CH_3), 1.28-1.46 (11H, m, 5 × CH_2,H10*s*), 1.69 (2H, app. quin, J = 7.7 Hz, CH_2CH_2O), 2.01 (1H, d, J = 10.3 Hz, H10*a*), 2.46 (1H, d, J = 5.3 Hz, H7), 2.57 (1H, br s, H1), 2.65 (1H, d, J = 4.5 Hz, H9), 3.06 (1H, app. t, J = 5.1 Hz, H8), 3.97 (2H, t, J = 6.4 Hz, CH_2), 4.04 (1H, d, J = 5.6 Hz, H6), 4.13 (1H, d, J = 5.7 Hz, H2), 5.49 (1H, s, H4), 6.92 (2H, d, J = 8.6 Hz, ArH), 7.36 (2H, d, J = 8.6 Hz, ArH).

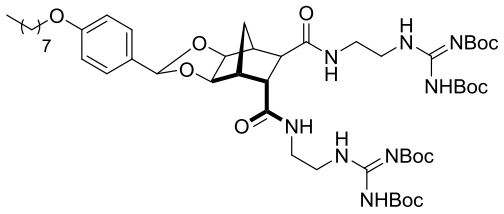
^{13}C NMR (125 MHz, DMSO-d_6) δ 14.0, 22.1, 25.5, 28.6, 28.66, 28.73, 31.23, 42.7, 43.4, 49.5, 45.1, 67.5, 78.5, 80.9, 102.3, 114.1, 127.9, 128.3, 159.6, 173.3, 174.5.

HRMS (ESI, *m/z*) for $C_{24}H_{33}O_7$ $[M + H]^+$ calc. 433.22208; found 433.21908.

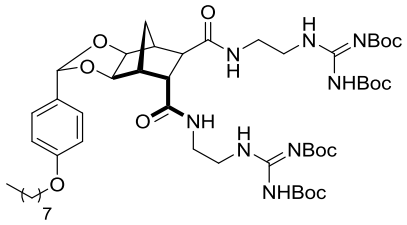
General procedure C: amide formation

A microwave vial was charged with the appropriate carboxylic acid, EDCI (3.0 equiv), HOBt (0.1 equiv) and anhydrous $CHCl_3$ and was stirred at ambient temperature for 30 min. The appropriate alkylamine (3.0 equiv) was then added and the reaction was heated at 50 °C for 30 min using microwave irradiation. The resulting homogenous clear solution was diluted with $CHCl_3$ (20 mL), washed with H_2O (2 × 10 mL), brine (8 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude material that was purified by column chromatography (as specified below) to give the title compound.

8-*endo*-9-*exo*-Di[2′-(2″,3″-bis-*tert*-butoxycarbonylguanidino)ethylcarbamoyl]-4-*exo*-[4′-(Octyloxy)phenyl]-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane (S19a)



8-*endo*-9-*exo*-Di[2′-(2″,3″-bis-*tert*-butoxycarbonylguanidino)ethylcarbamoyl]-4-*endo*-[4′-(Octyloxy)phenyl]-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane (S19b)



Compounds **S19a** and **S19b** were prepared from diacid **S18** (181 mg, 0.418 mmol) and amine **11** (380 mg, 1.25 mmol) according to general procedure C and after purification by column chromatography (50–70% EtOAc in pet. spirits) were each isolated as white solids (**S19a**; 182 mg, 36% and **S19b**; 21 mg, 5%).

S19a

R_f = 0.22 (70% EtOAc in pet. spirits).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.3 Hz, CH_3), 1.25–1.32 (10H, m, 5 × CH_2), 1.47–1.48 (36H, m, 4 × *t*-Bu), 1.62 (1H, d, *J* = 10.7 Hz, H10*s*), 1.73–1.78 (2H, m, CH_2), 1.98 (1H, d, *J* = 10.4 Hz, H10*a*), 2.52 (1H, d, *J* = 5.5 Hz, H1), 2.67 (1H, br s, H7), 2.79 (1H, d, *J* = 4.0 Hz, H9), 3.01 (1H, app. t, *J* = 5.1 Hz, H8), 3.34–3.59 (8H, m, 4 × CH_2), 3.94 (2H, t, *J* = 6.6 Hz, CH_2), 4.12 (1H, d, *J* = 5.7 Hz, H2), 4.20 (1H, t, *J* = 5.8 Hz, H6), 5.48 (1H, s, H4), 6.84–6.88 (3H, m, ArH, NH), 7.37 (2H, d, *J* = 8.5 Hz, ArH), 8.04 (1H, t, *J* = 4.2 Hz, NH), 8.50 (1H, t, *J* = 5.6 Hz, NH), 8.63 (1H, t, *J* = 5.9 Hz, NH), 11.44 (1H, s, NH), 11.47 (1H, s, NH).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.8, 26.1, 28.2, 28.4, 29.3 (2 × C), 29.4, 31.9, 32.7, 40.0, 40.1, 40.2, 42.2, 43.3, 44.3, 44.8, 47.7, 68.2, 79.3, 79.6, 79.9, 81.9, 83.4, 83.7, 103.2, 114.4 (2 × C), 128.1, 128.2, 153.2 (2 × C), 157.1, 157.9, 160.2, 163.0, 163.5, 171.9, 174.1.

HRMS (ESI, *m/z*) for $C_{50}H_{80}N_8O_{13}$ $[M + H]^+$ calc. 1001.5918; found 1001.5955.

S19b

R_f = 0.41 (70% EtOAc in pet. spirits).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.1 Hz, CH_3), 1.25–1.45 (10H, m, 5 × CH_2), 1.49–1.52 (36H, m, *t*-Bu), 1.60–1.62 (1H, m, H10*s*), 1.73–1.79 (2H, m, CH_2), 1.89 (1H, d, *J* = 9.7 Hz, H10*a*), 2.43 (1H, d, *J* = 5.4 Hz, H1), 2.64 (1H, br s, H7), 2.77 (1H, d, *J* = 4.1 Hz, H9), 2.96 (1H, app. t, *J* = 4.7 Hz, H8), 3.29–3.58 (8H, m, 4 × CH_2), 3.92 (2H, t, *J* = 6.6 Hz, CH_2), 4.06 (1H, d, *J* = 5.5 Hz, H2), 4.12 (1H, t, *J* = 5.6 Hz, H6), 6.15 (1H, s, H4), 6.84–6.84 (2H, m, ArH), 6.99 (1H, t, *J* = 5.1 Hz, NH), 7.25–7.27 (2H, m, ArH), 8.09 (1H, t, *J* = 4.1 Hz, NH), 8.51 (1H, t, *J* = 5.7 Hz, NH), 8.64 (1H, t, *J* = 6.0 Hz, NH), 11.48 (1H, s, NH), 11.49 (1H, s, NH).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 22.8, 26.2, 28.2, 28.4, 29.4 (2 × C), 29.5, 32.0, 32.8, 40.1, 40.2, 40.3, 42.4, 43.5, 44.2, 45.0, 47.7, 68.2, 78.8, 79.7, 80.0, 81.6, 83.5, 83.8, 104.6, 114.4 (2 × C), 127.1 (2 × C), 132.2, 153.3 (2 × C), 157.2, 158.0, 159.4, 163.0, 163.5, 171.9, 174.1.

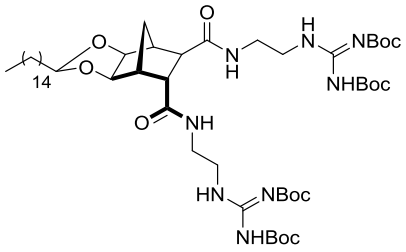
HRMS (ESI, *m/z*) for $C_{50}H_{80}N_8O_{13}$ $[M + H]^+$ calc. 1001.5918; found 1001.5955.

General procedure D: amidation of diacids.

A microwave vial was charged with the appropriate carboxylic acid, EDCI (1.5 equiv), HOBt (0.05 equiv) and dry DMF and was stirred at ambient temperature for 30 min. The appropriate alkylamine (1.5 equiv) was then added and the reaction was irradiated to 50 °C for 30 min. The resulting homogenous mixture was diluted with EtOAc (15 mL), washed with H_2O (3 × 8 mL), brine (8 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a solid that was purified by column chromatography (as specified below) which gave the title compound.

8-*endo*-9-*exo*-Di[2′-(2″,3″-bis-*tert*-butoxycarbonylguanidino)ethylcarbamoyl]-4-pentadecyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane (9c)

[CAS Reg. No. 1233075-01-8]



Compound **9c** was prepared from diacid **5c** (69 mg, 0.16 mmol) and amine **11** (140 mg, 0.47 mmol) according to general procedure D and after purification by column chromatography (20–70% EtOAc in pet. spirits) was isolated as a clear oil (117 mg, 74%).

R_f = 0.47 (70% EtOAc in pet. spirits).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.8 Hz, CH_3), 1.24–1.39 (27H, m, 13 × CH_2, H10*s*), 1.49–1.50 (36H, m, *t*-Bu), 1.58–1.62 (2H, m, CHC*H*$_2$), 1.78 (1H, d, *J* = 9.6 Hz, H10*a*), 2.44 (1H, d, *J* = 5.6 Hz, H1), 2.57 (1H, br s, H7), 2.70 (1H, d, *J* = 5.4 Hz, H9), 2.94 (1H, app. t, *J* = 5.3 Hz, H8), 3.34–3.44 (4H, m, 2 × CH_2), 3.52–3.58 (4H, m, 2 × CH_2), 3.95 (1H, d, *J* = 5.7 Hz, H2), 4.03 (1H, d, *J* = 5.6 Hz, H6), 4.61 (1H, t, *J* = 4.8 H7), 6.87 (1H, t, *J* = 5.2 Hz, NH), 8.00 (1H, t, *J* = 4.2 Hz, NH), 8.50 (1H, t, *J* = 5.7 Hz, NH), 8.63 (1H, t, *J* = 6.1 Hz, NH), 11.45 (1H, s, NH), 11.47 (1H, s, NH).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 22.8, 24.4, 28.2, 28.4, 29.5, 29.7 (3 × C), 29.8 (6 × C), 32.1, 32.5, 33.0, 40.0, 40.1, 40.2, 42.2, 43.0, 44.3, 44.4, 47.8, 79.0, 79.7, 79.9, 81.7, 83.4, 83.7, 104.1, 153.2 (2 × C), 157.1, 157.9, 163.0, 163.5, 172.1, 174.2.

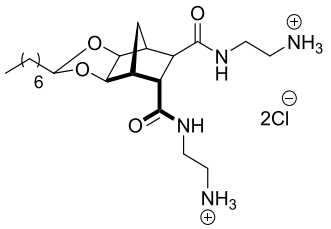
HRMS (ESI, *m/z*) for $C_{51}H_{90}N_8O_{12}$ $[M + H]^+$ calc. 1007.6751; found 1007.6771.

General procedure E: deprotection of Boc groups

To a stirring solution of Boc-protected amine/guanidine and MeOH was added dropwise AcCl (10.0 equiv), and the reaction was stirred for 24 h at ambient temperature (in instances when ^{1}H NMR spectroscopy indicated the presence of Boc-groups the crude material was retreated using the aforementioned conditions). The reaction mixture was concentrated under vacuum and co-evaporated with MeOH (2 × 0.5 mL), to afford the title compound.

4-Heptyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxamidoethylamine hydrogen chloride (8a)

[CAS Reg. No. 1233074-99-1]



Compound **8a** was synthesised from Boc-protected amine **7a** (650 mg, 1.06 mmol) according to general procedure E as a white solid (510 mg, 99%).

m.p: 243.0–243.4 °C.

^{1}H NMR (270 MHz, CD_3OD) δ 0.90 (3H, t, *J* = 6.5 Hz, CH_3), 1.29–1.48 (11H, m, 5 × CH_2, H10*s*), 1.56–1.64 (2H, m, CHC*H*$_2$), 1.75 (1H, d, *J* = 9.8 Hz, H10*a*), 2.51 (1H, br s, H9), 2.62–2.65 (2H, m, H1, H7), 3.03–3.10

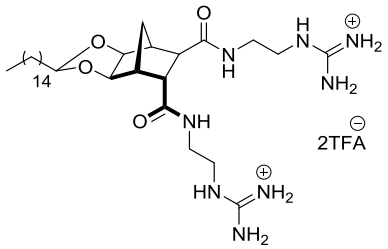
(4H, m, 2 × CH_2), 3.23 (1H, app. t, *J* = 4.9 Hz, H8), 3.35–3.63 (4H, m, 2 × CH_2), 4.00 (1H, d, *J* = 5.7 Hz, H6), 4.04 (1H, d, *J* = 5.5 Hz, H2), 4.66 (1H, t, *J* = 4.7 Hz, H4).

^{13}C NMR (67.5 MHz, CD_3OD) δ 14.4, 23.7, 25.2, 28.2, 30.3, 30.6, 32.7, 32.9, 33.9, 38.4, 38.5, 40.8, 44.9, 45.1, 47.1, 47.3, 80.0, 82.8, 105.1, 175.1, 177.0.

HRMS (ESI, *m/z*) for $C_{21}H_{38}N_4O_4$ $[M + 2H]^{2+}$ calc. 206.1519; found 206.1528.

4-Pentadecyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxamidoethylguanidine hydrogen 2,2,2-trifluoroacetate (1)

[CAS Reg. No. 1233075-03-0]

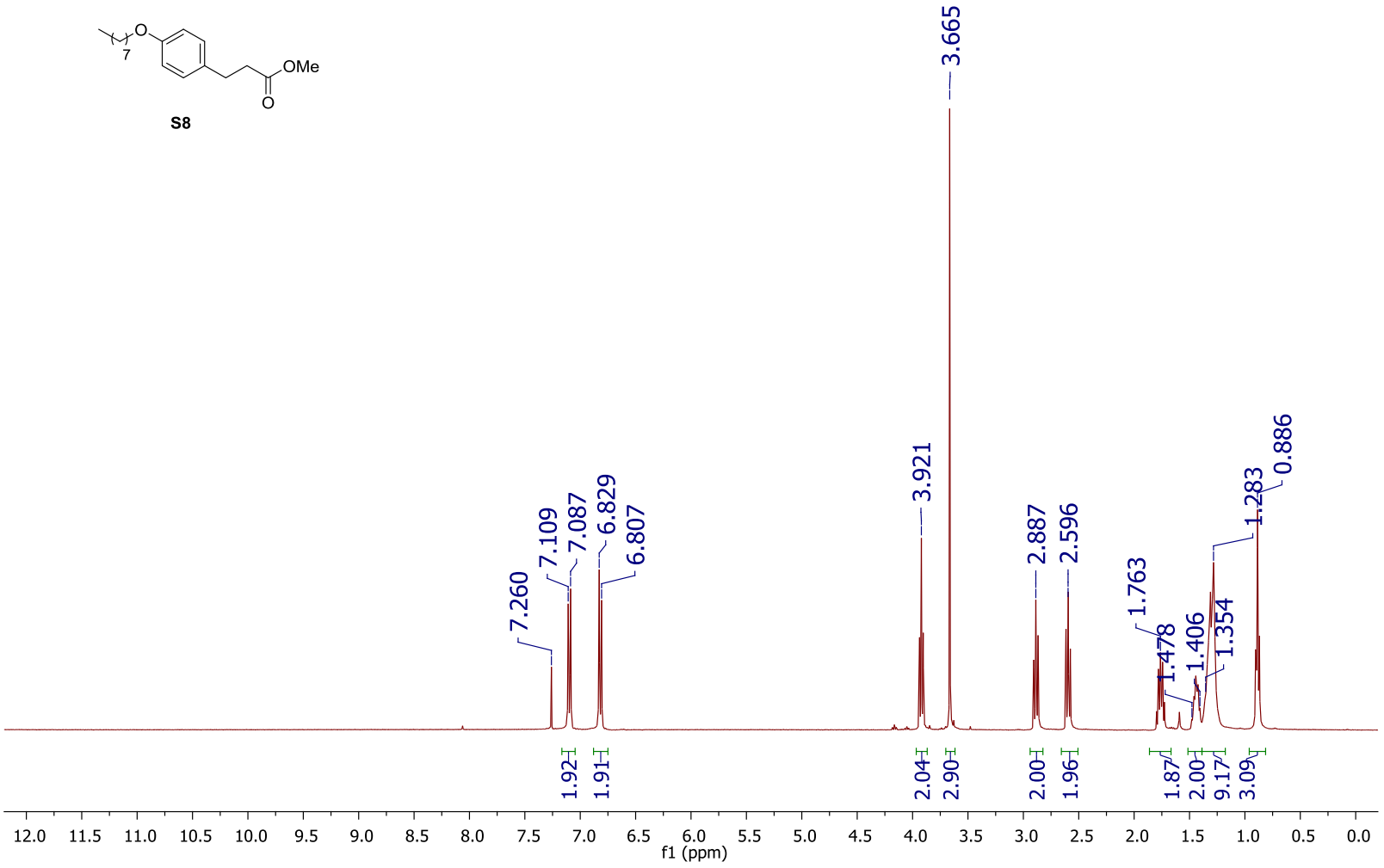


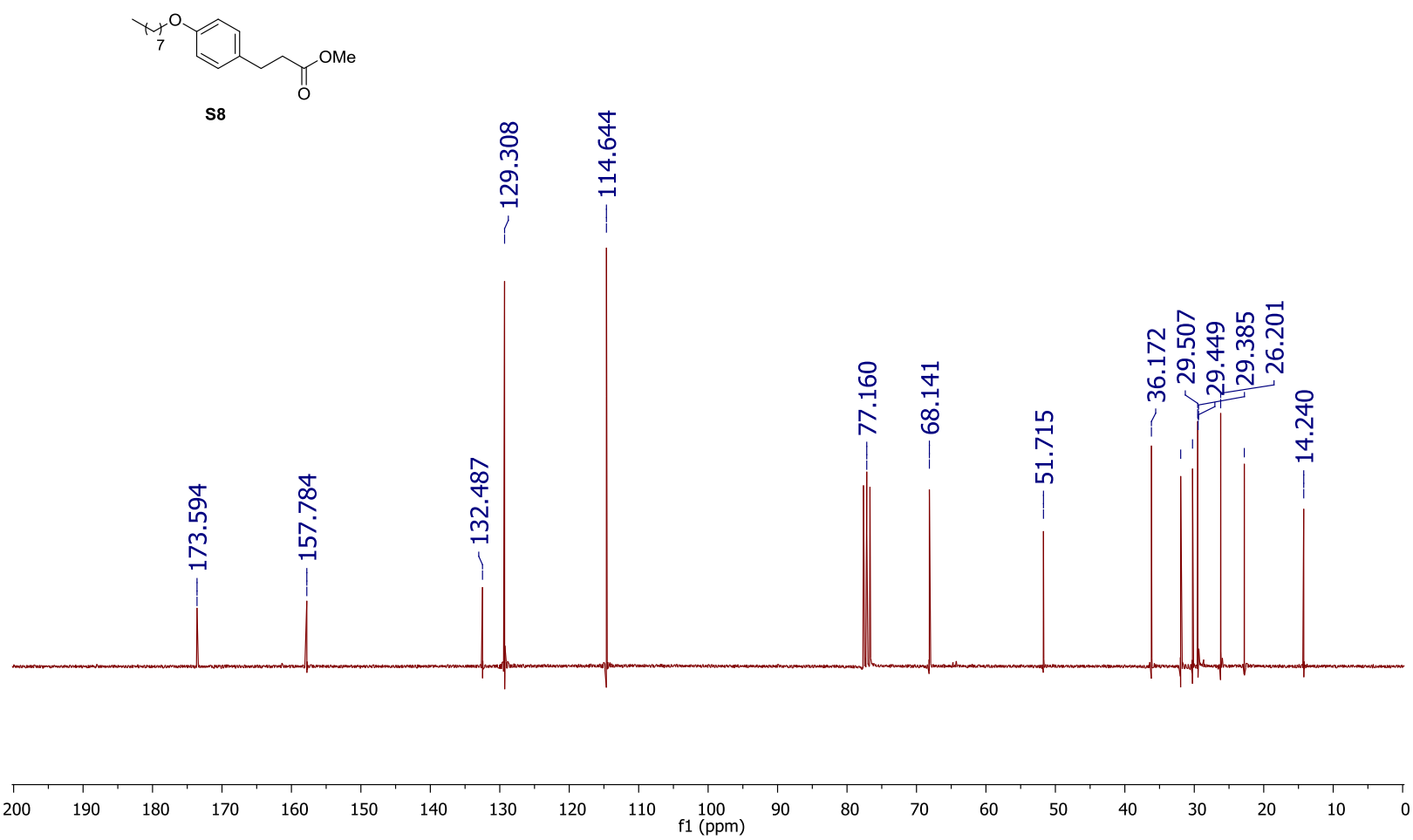
To the stirring solution of Boc-protected guanidine **9c** (58 mg, 0.058 mmol) in CH_2Cl_2 (1.2 mL) was added trifluoroacetic acid (420 μL, 5.5 mmol) and the reaction was stirred at ambient temperature for 48 h. The solvent was removed under reduced pressure and the sample was co-evaporated with $CHCl_3$ (2 × 1 mL) and concentrated *in vacuo* to give the title compound (29 mg, 60%) as a yellow resin.

^{1}H NMR (500 MHz, CD_3OD) δ 0.90 (3H, t, *J* = 6.8 Hz, CH_3), 1.29–1.41 (26H, m, 13 × CH_2) 1.47 (1H, d, *J* = 10.4 Hz, H10*s*), 1.54–1.61 (2H, m, CHC*H*$_2$), 1.74 (1H, d, *J* = 9.8 Hz, H10*a*), 2.44 (1H, br s, H1), 2.60–2.61 (2H, m, H9, H7), 3.21 (1H, t, *J* = 4.7 Hz, H8), 3.28–3.42 (8H, m, 4 × CH_2), 3.99 (1H, d, *J* = 5.6 Hz, H2), 4.04 (1H, d, *J* = 5.6 Hz, H6), 4.56 (1H, t, *J* = 4.7 Hz, H4).

^{13}C NMR (125 MHz, CD_3OD) δ 14.4, 23.7, 25.2, 28.2, 30.5, 30.7 (2 × C), 30.75 (4 × C), 30.77 (2 × C), 32.7, 33.1, 33.9, 39.6, 39.7, 41.9 (2 × C), 44.9, 45.1, 46.8, 47.7, 79.9, 82.9, 105.1, 158.9 (2 × C), 174.7, 176.6.

HRMS (ESI, *m/z*) for $C_{35}H_{48}N_6O_4S_2$ $[M + H]^+$ calc. 681.3251; found 681.3251.


O
7
OMe
O
S8
7.260
7.109
7.087
6.829
6.807
3.921
3.665
2.887
2.596
1.763
1.478
1.406
1.354
1.283
0.886
1.92
1.91
2.04
2.90
2.00
1.96
1.87
2.00
9.17
3.09
12.0 11.5 11.0 10.5 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)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77.160
68.141
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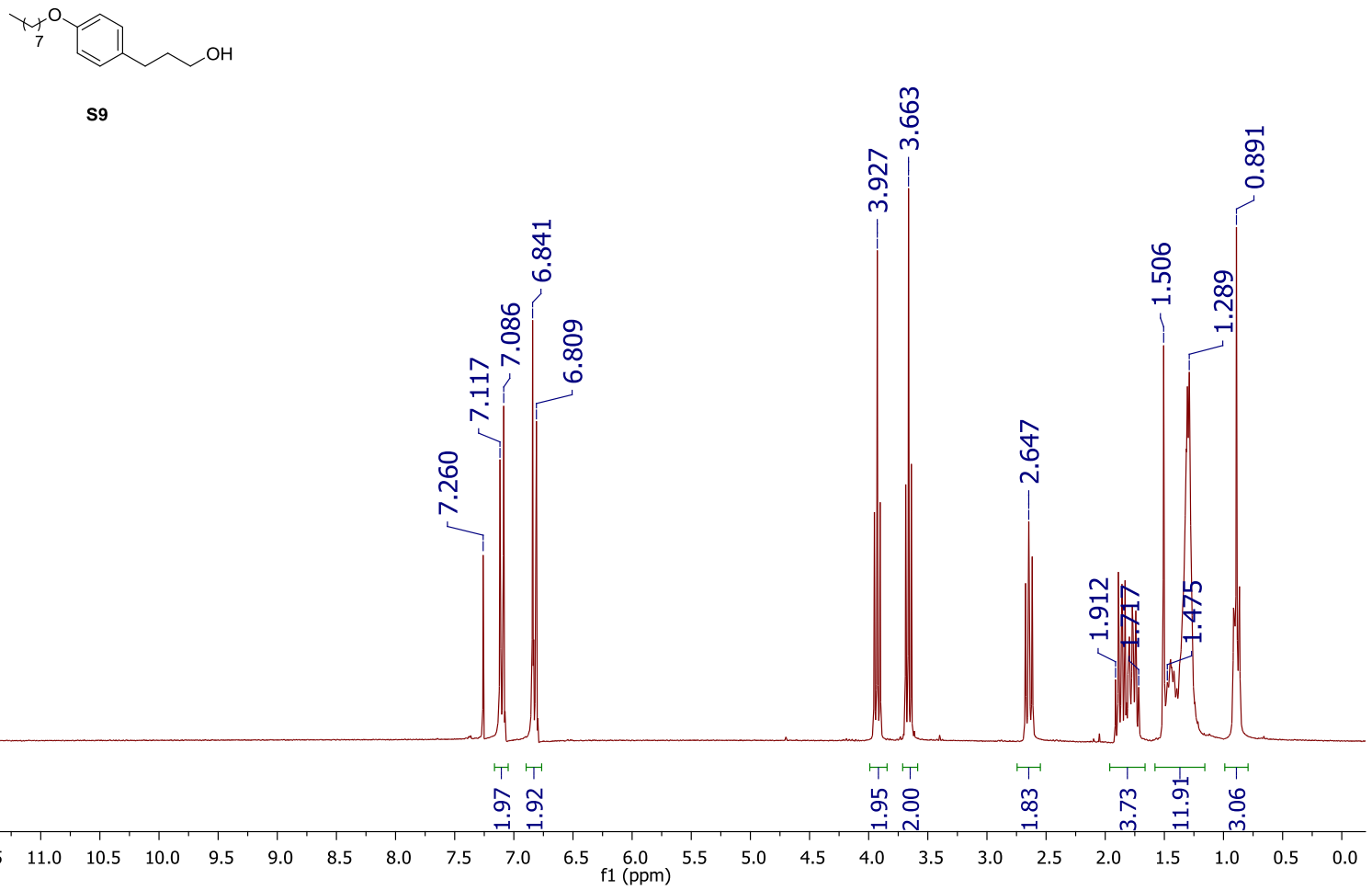
29.449
29.385
26.201
14.240
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.086
6.841
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3.663
2.647
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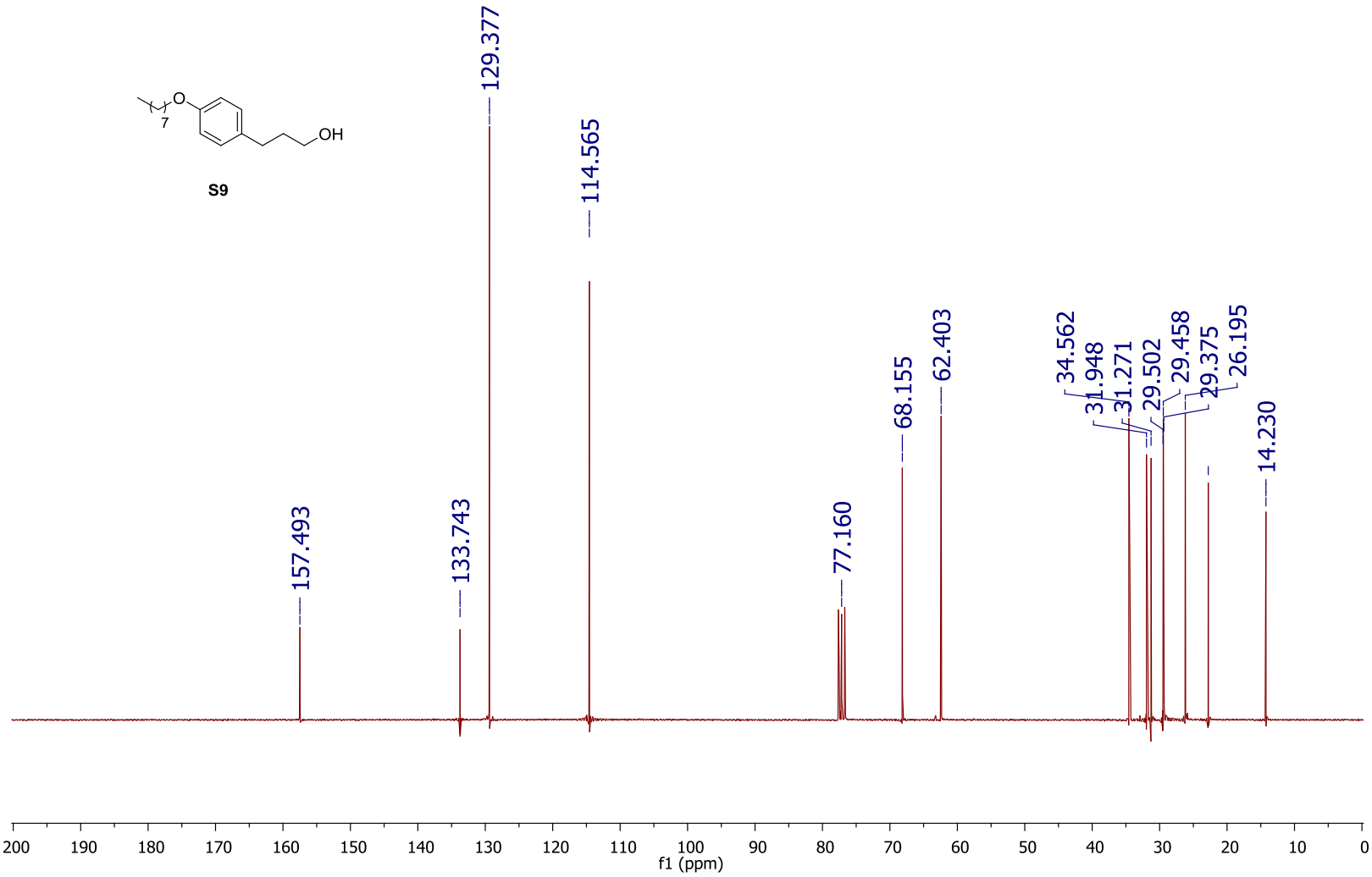
1.717
1.475
1.506
1.289
0.891
1.97
1.92
1.95
2.00
1.83
3.73
11.91
3.06
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


S9
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114.565
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31.271
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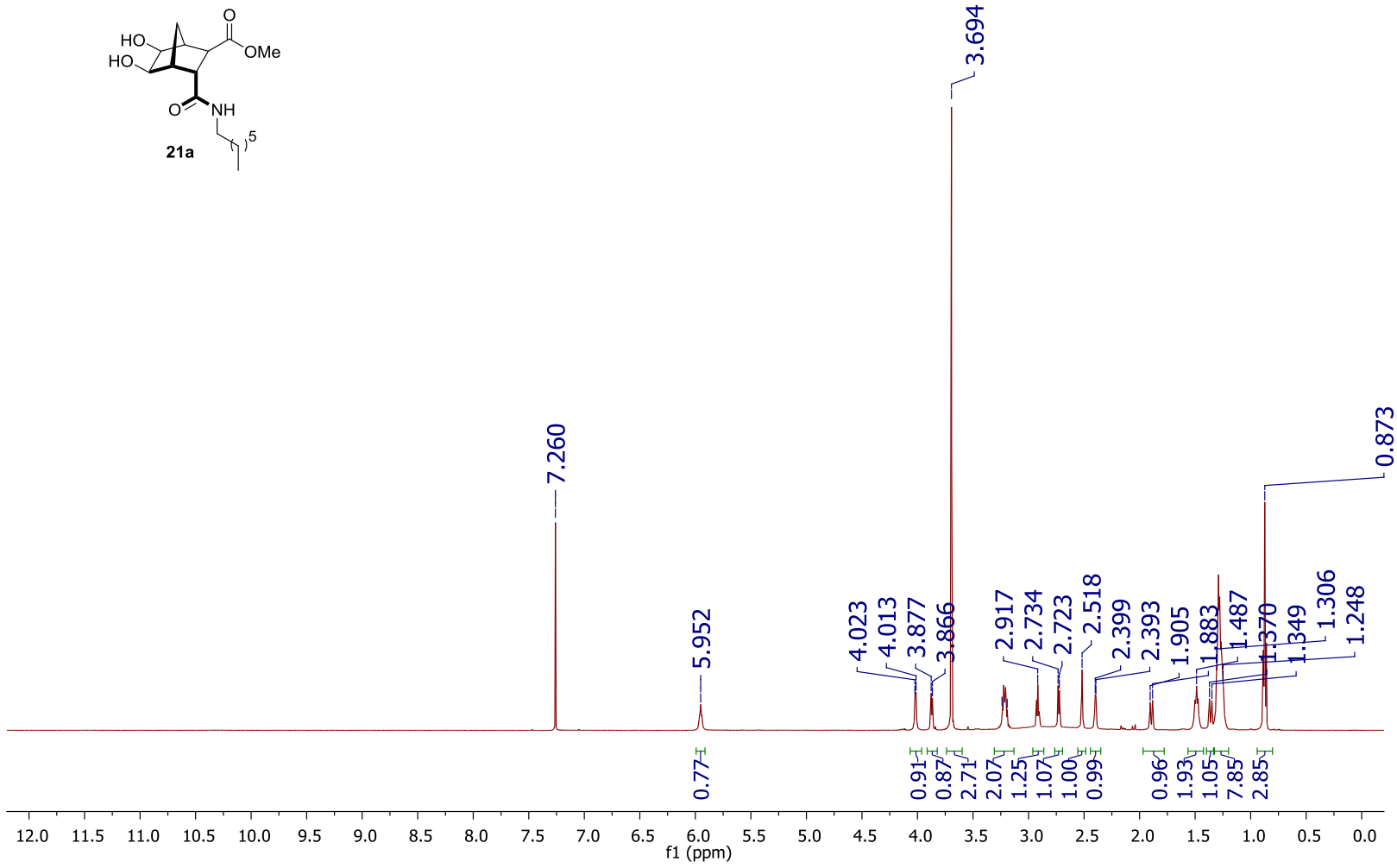
14.230
f1 (ppm)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O
NH
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4.023
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3.866
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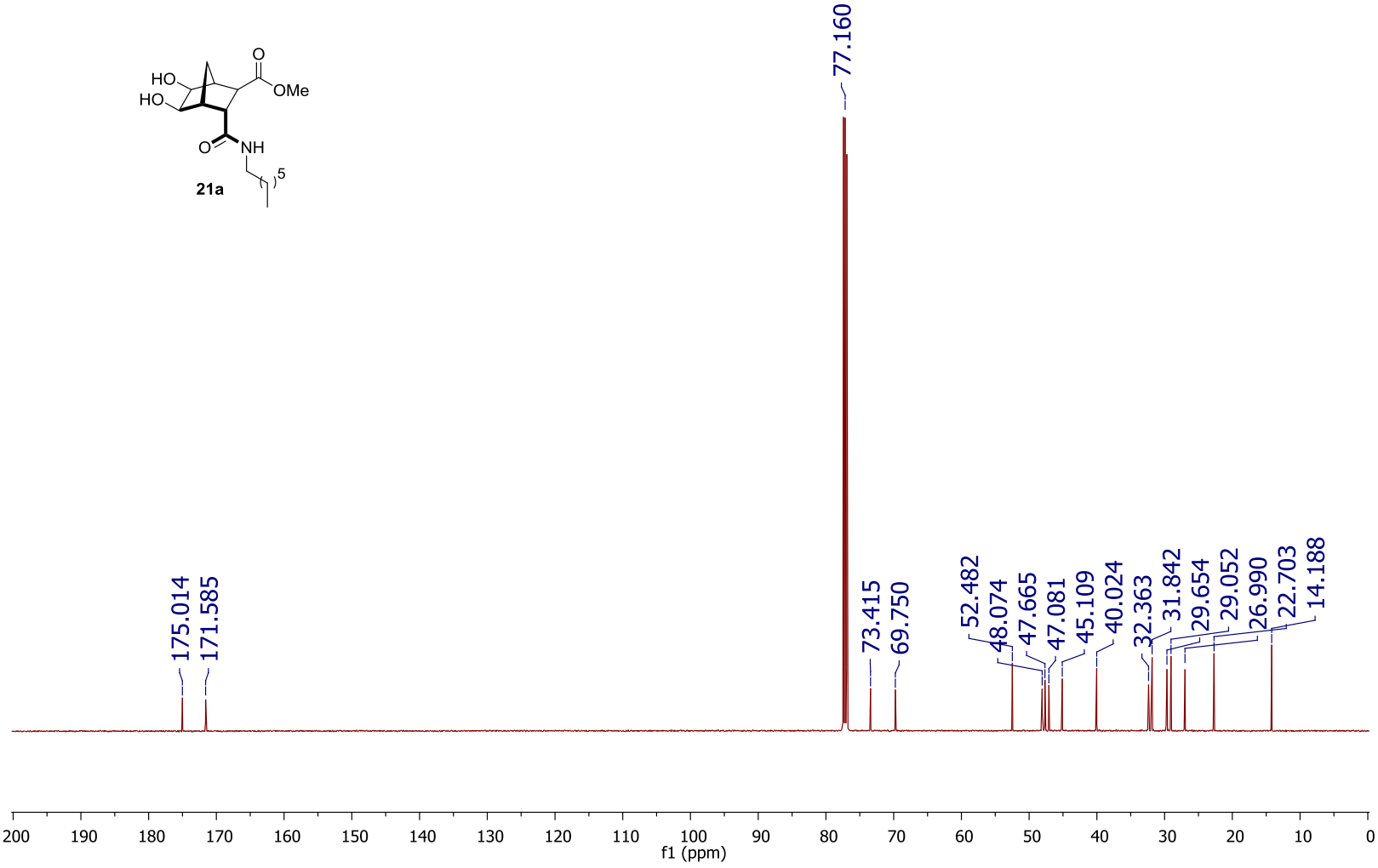
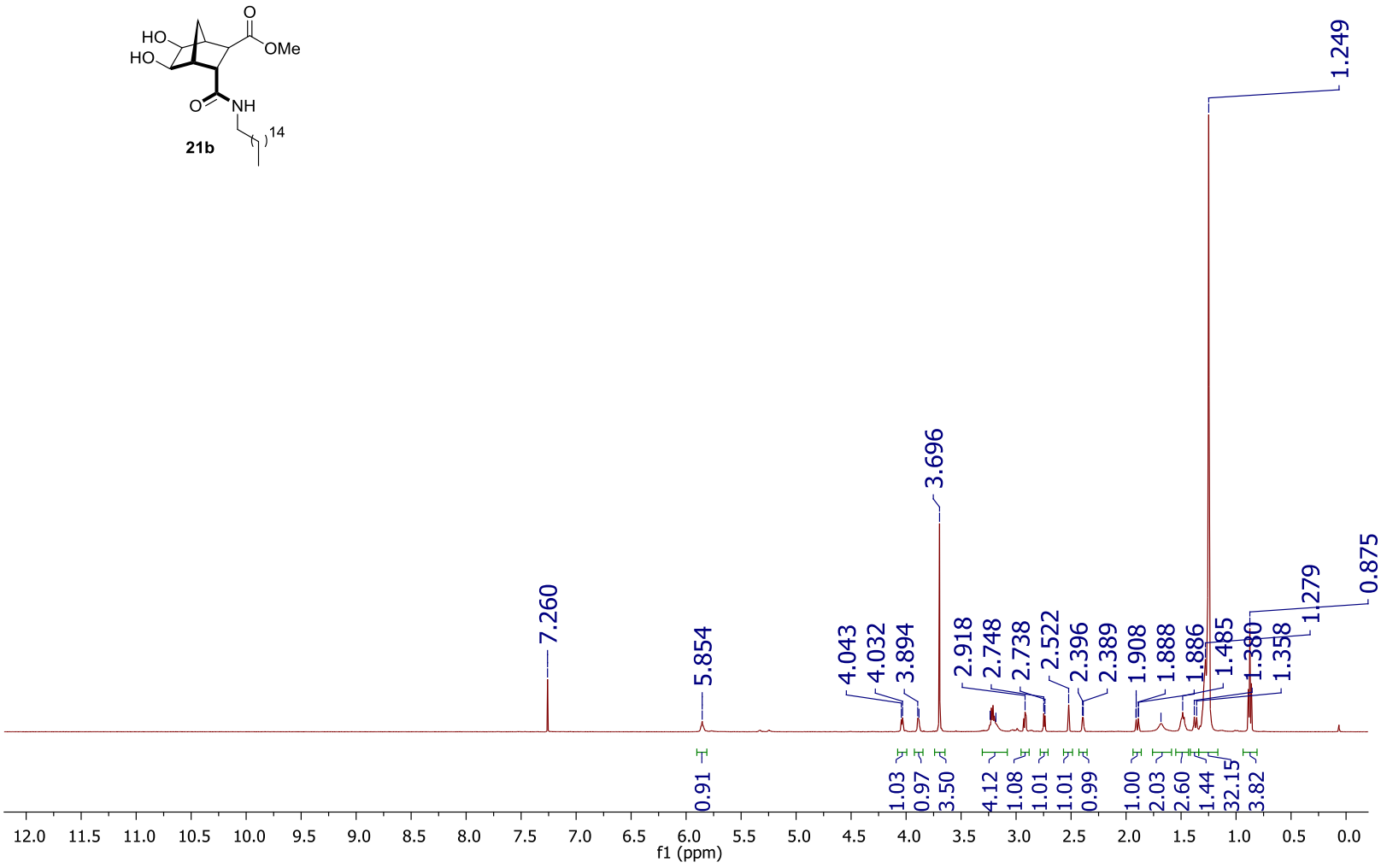
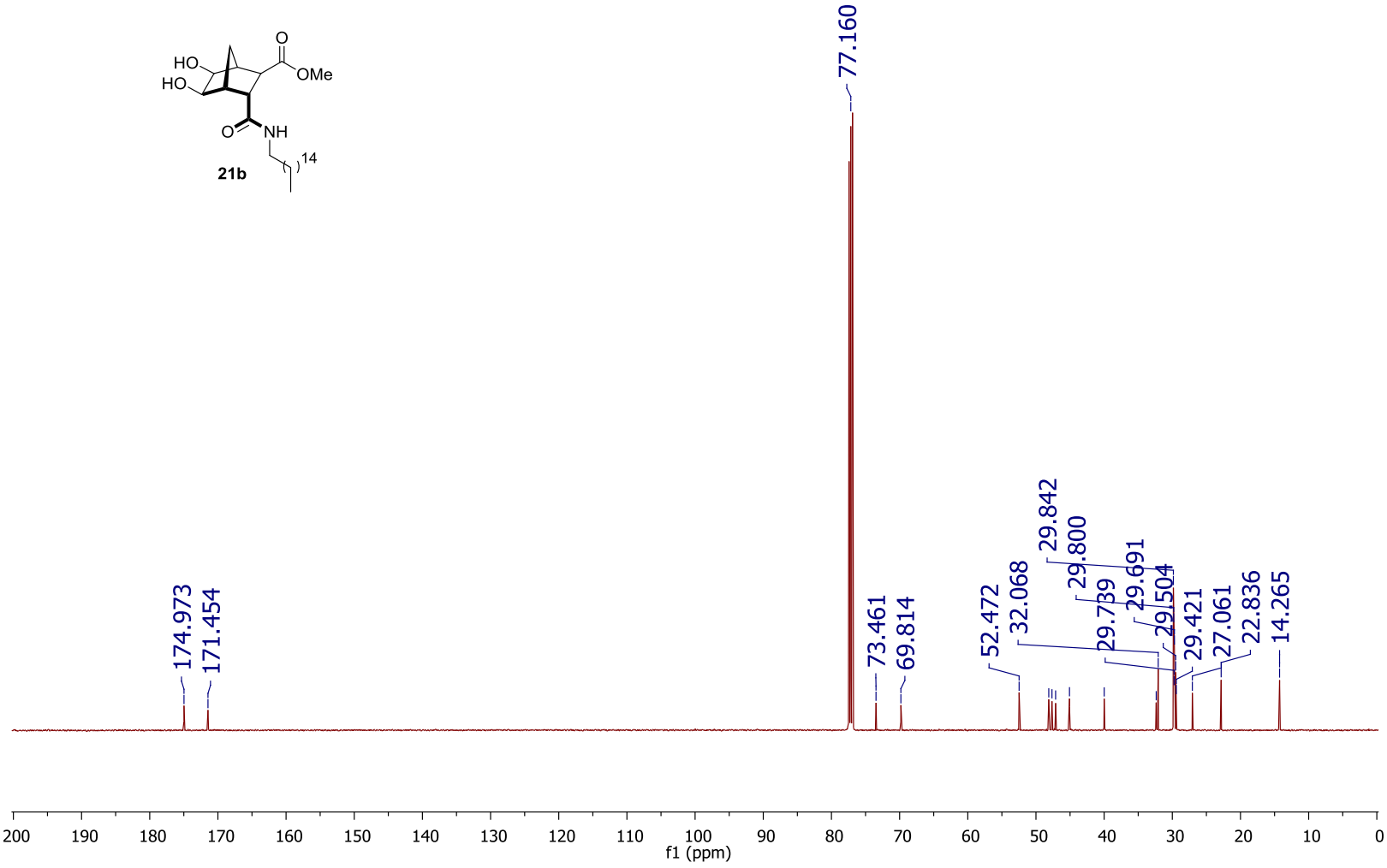
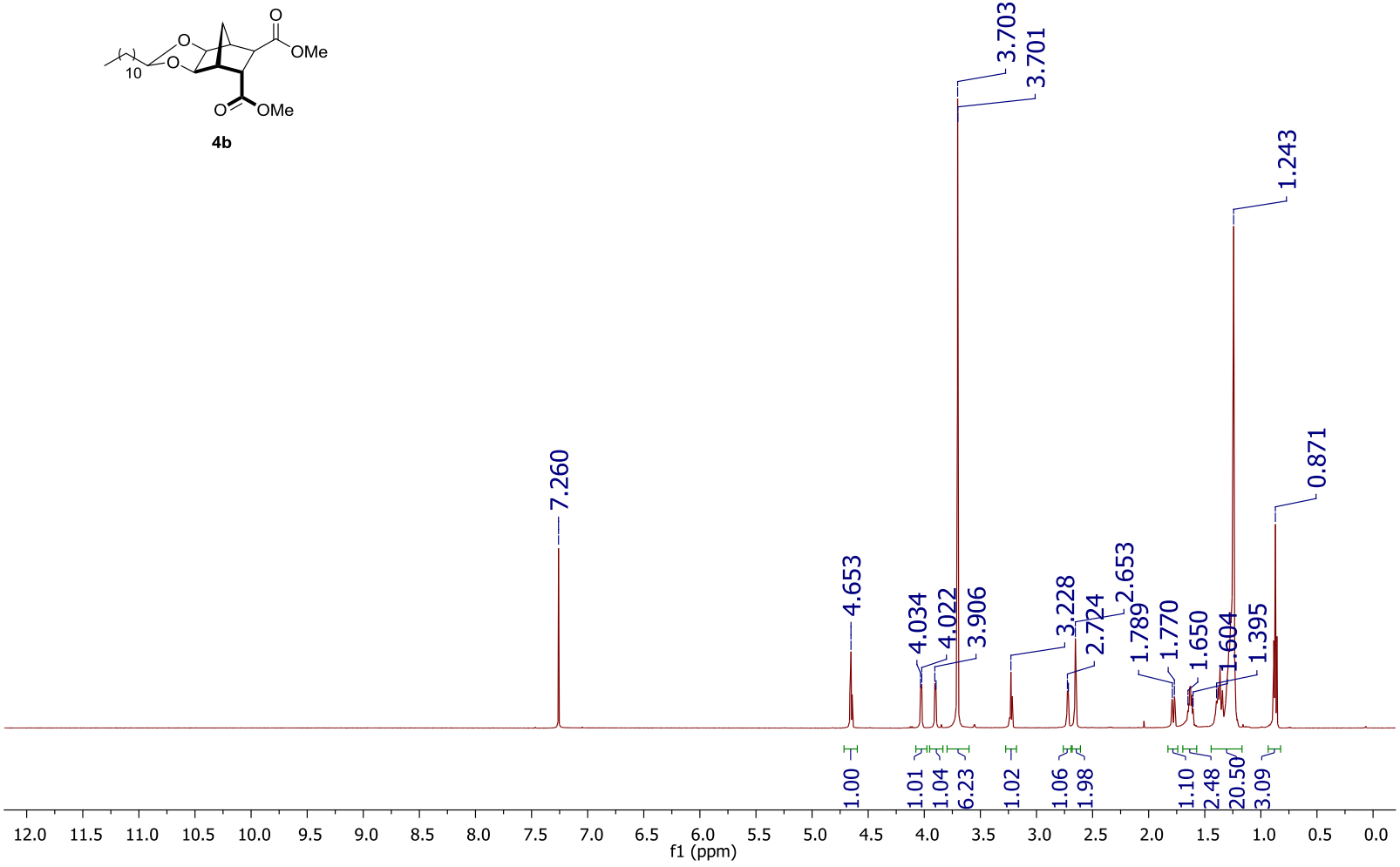
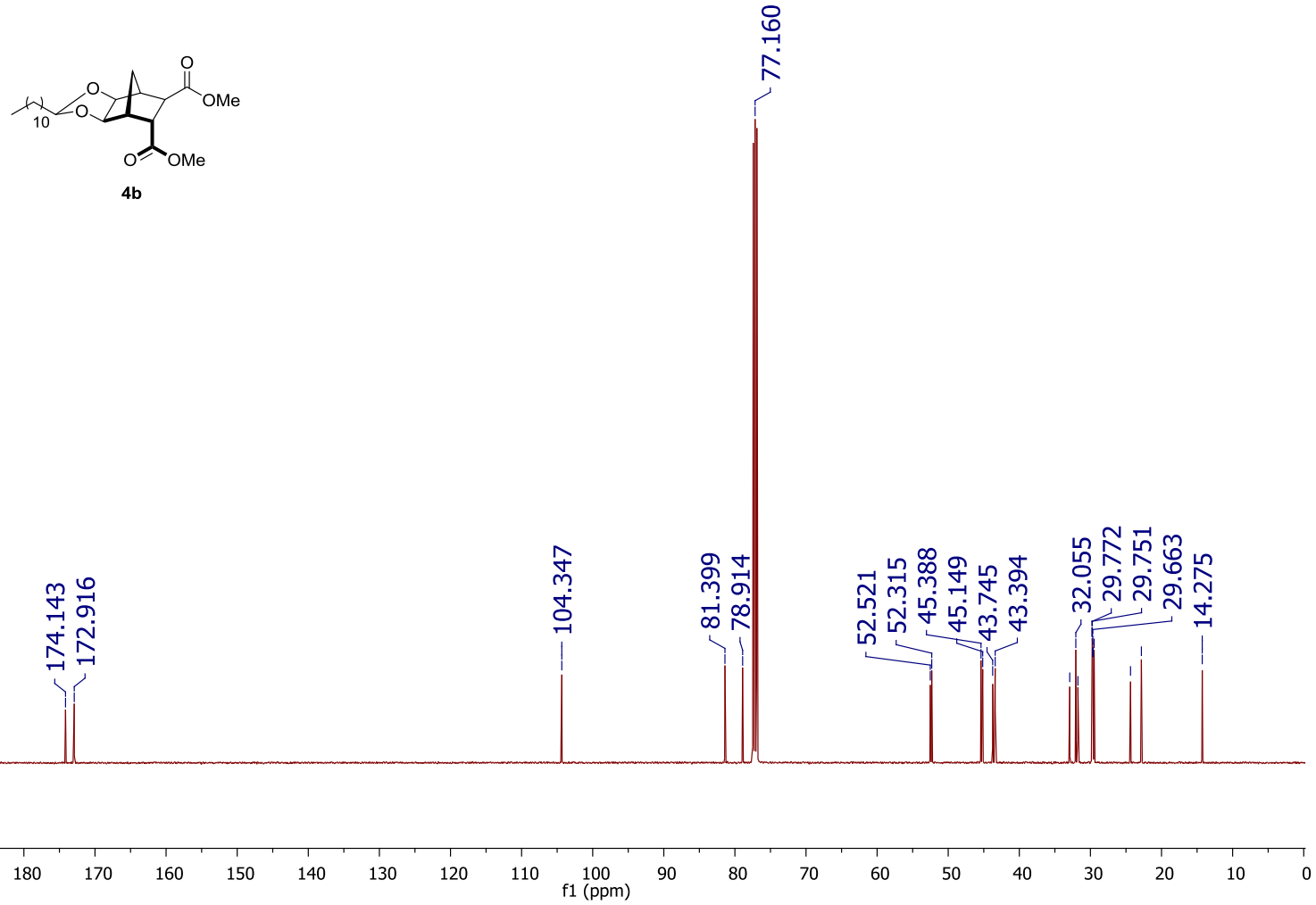
2.723
2.518
2.399
2.393
1.905
1.883
1.487
1.370
1.349
1.306
1.248
0.873
0.77
0.91
0.87
2.71
2.07
1.25
1.07
1.00
0.99
0.96
1.93
1.05
7.85
2.85
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

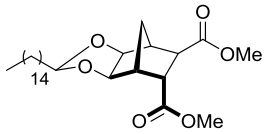

HO
HO
O
OMe
O
NH
5
21a
77.160
175.014
171.585
73.415
69.750
52.482
48.074
47.665
47.081
45.109
40.024
32.363
31.842
29.654
29.052
26.990
22.703
14.188
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


HO
HO
O
OMe
O
NH
14
21b
7.260
5.854
4.043
4.032
3.894
3.696
2.918
2.748
2.738
2.522
2.396
2.389
1.908
1.888
1.886
1.485
1.380
1.358
1.279
1.249
0.875
0.91
1.03
0.97
3.50
4.12
1.08
1.01
1.01
0.99
1.00
2.03
2.60
1.44
32.15
3.82
12.0 11.5 11.0 10.5 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)


HO
HO
O
OMe
O
NH
14
21b
174.973
171.454
77.160
73.461
69.814
52.472
32.068
29.842
29.800
29.691
29.739
29.504
29.421
27.061
22.836
14.265
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

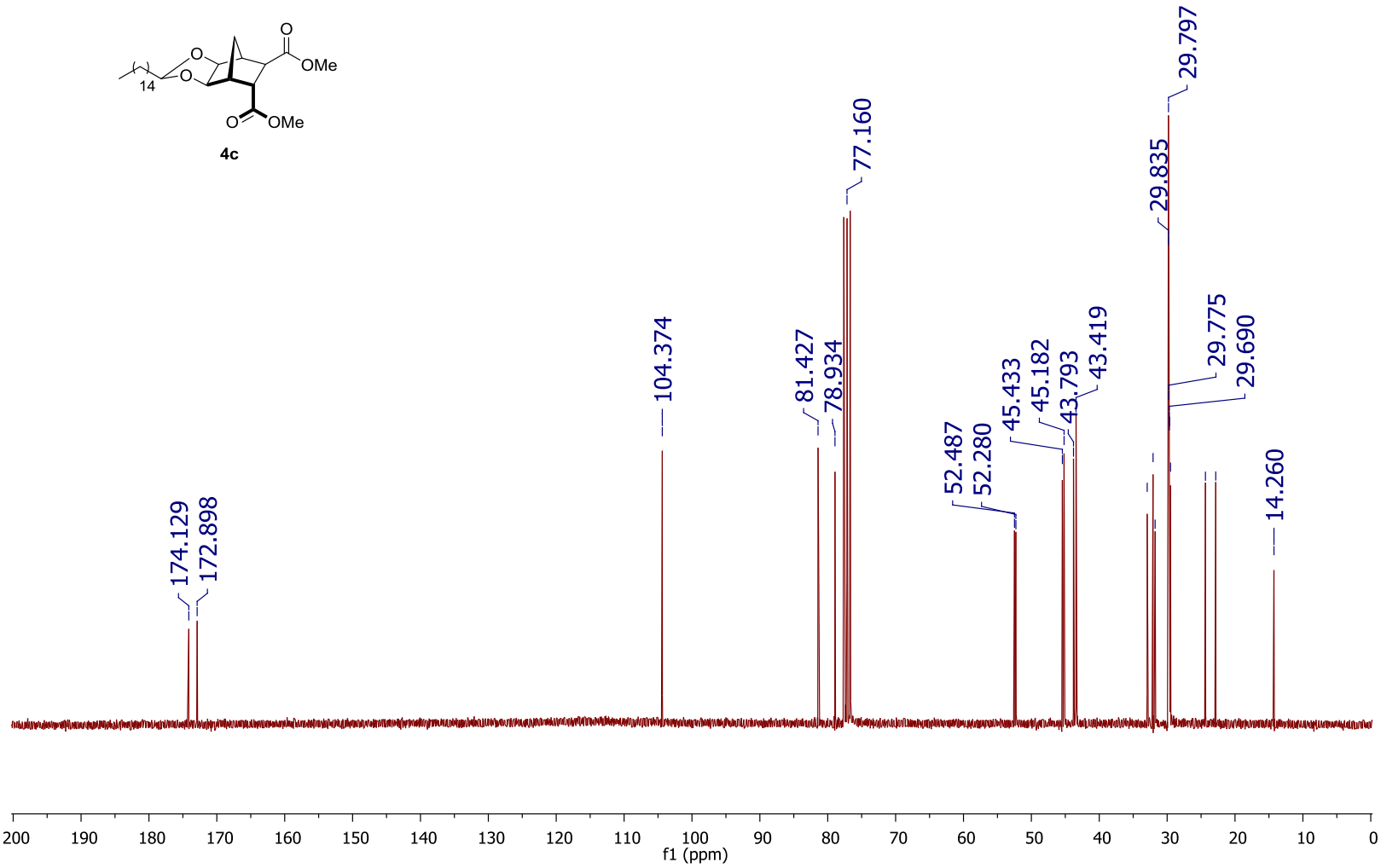

O
OMe
O
10
O
O
OMe
4b
7.260
4.653
4.034
4.022
3.906
3.703
3.701
3.228
2.724
2.653
1.789
1.770
1.650
1.604
1.395
1.243
0.871
1.00
1.01
1.04
6.23
1.02
1.06
1.98
1.10
2.48
20.50
3.09
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

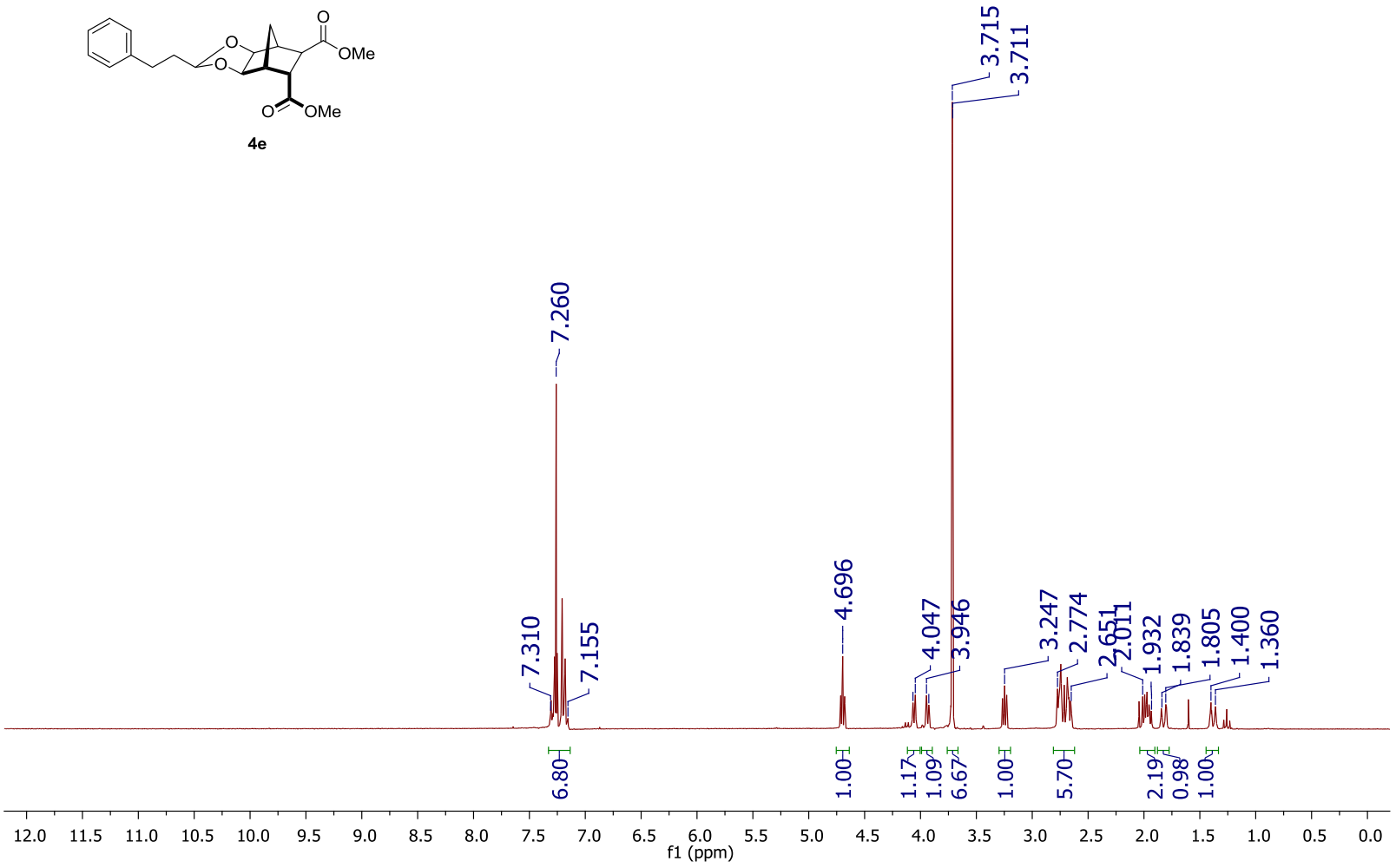

O
OMe
O
O
10
O
OMe
4b
77.160
174.143
172.916
104.347
81.399
78.914
52.521
52.315
45.388
45.149
43.745
43.394
32.055
29.772
29.751
29.663
14.275
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

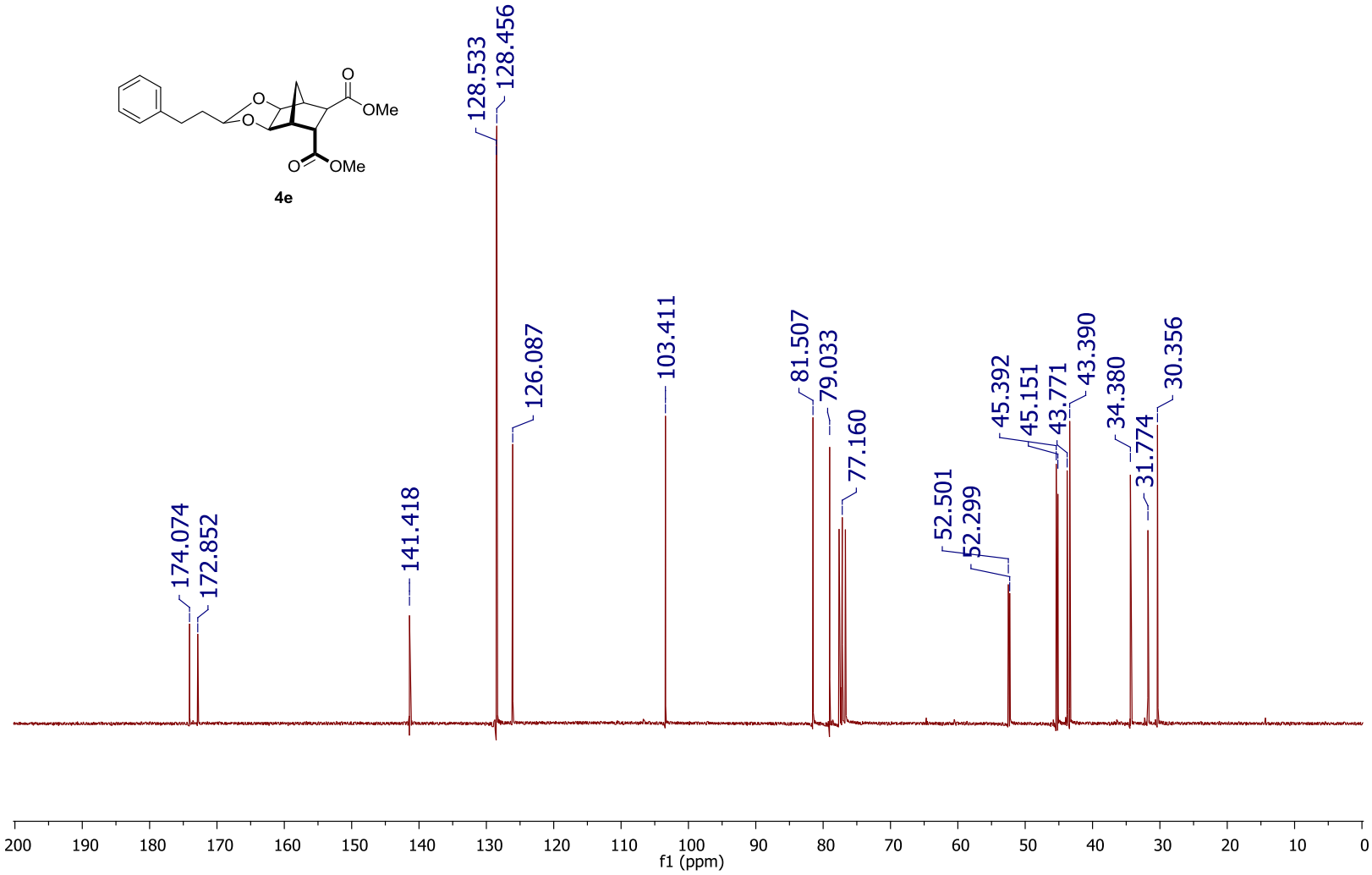

O
OMe
14
O
O
OMe

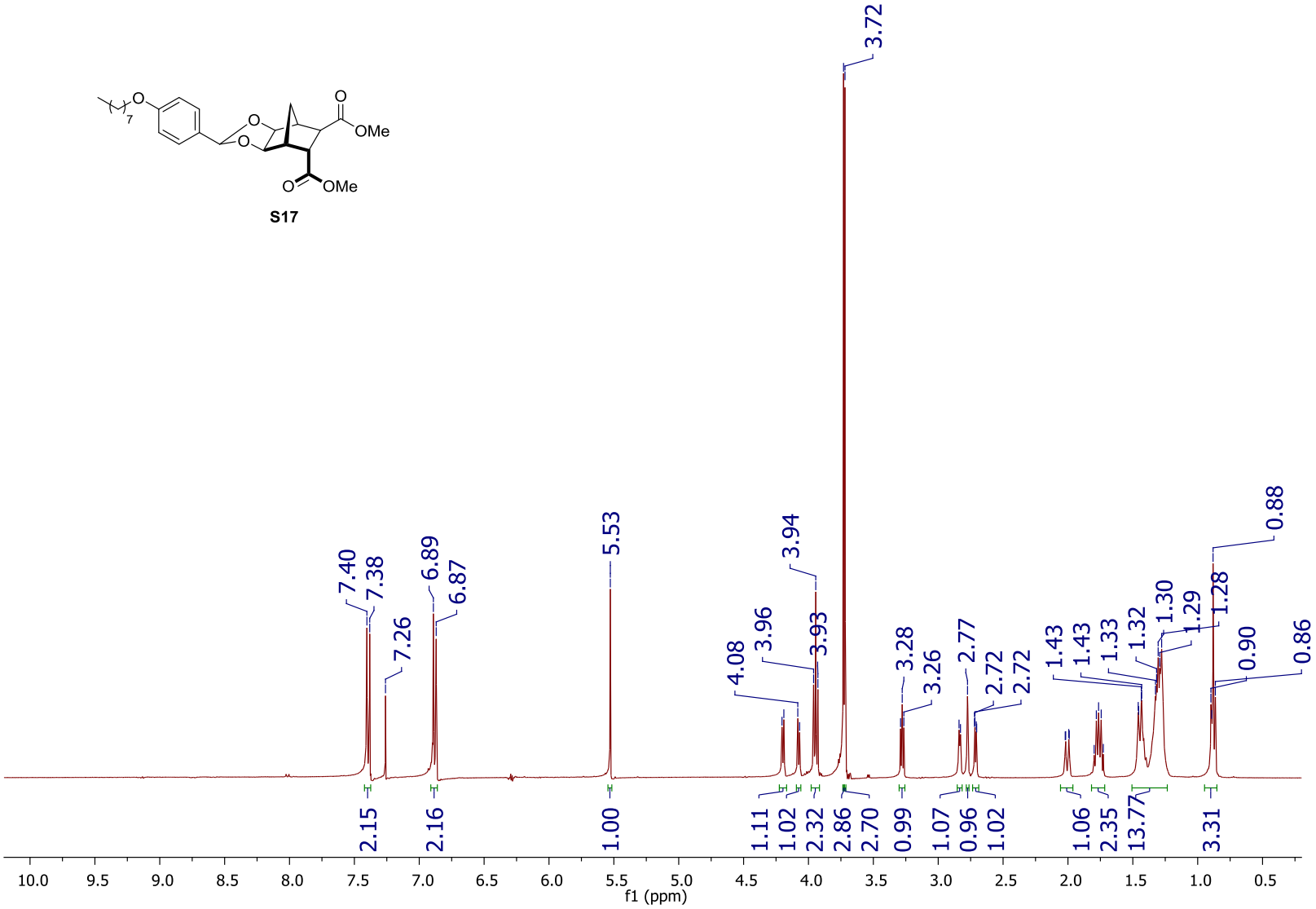
4c

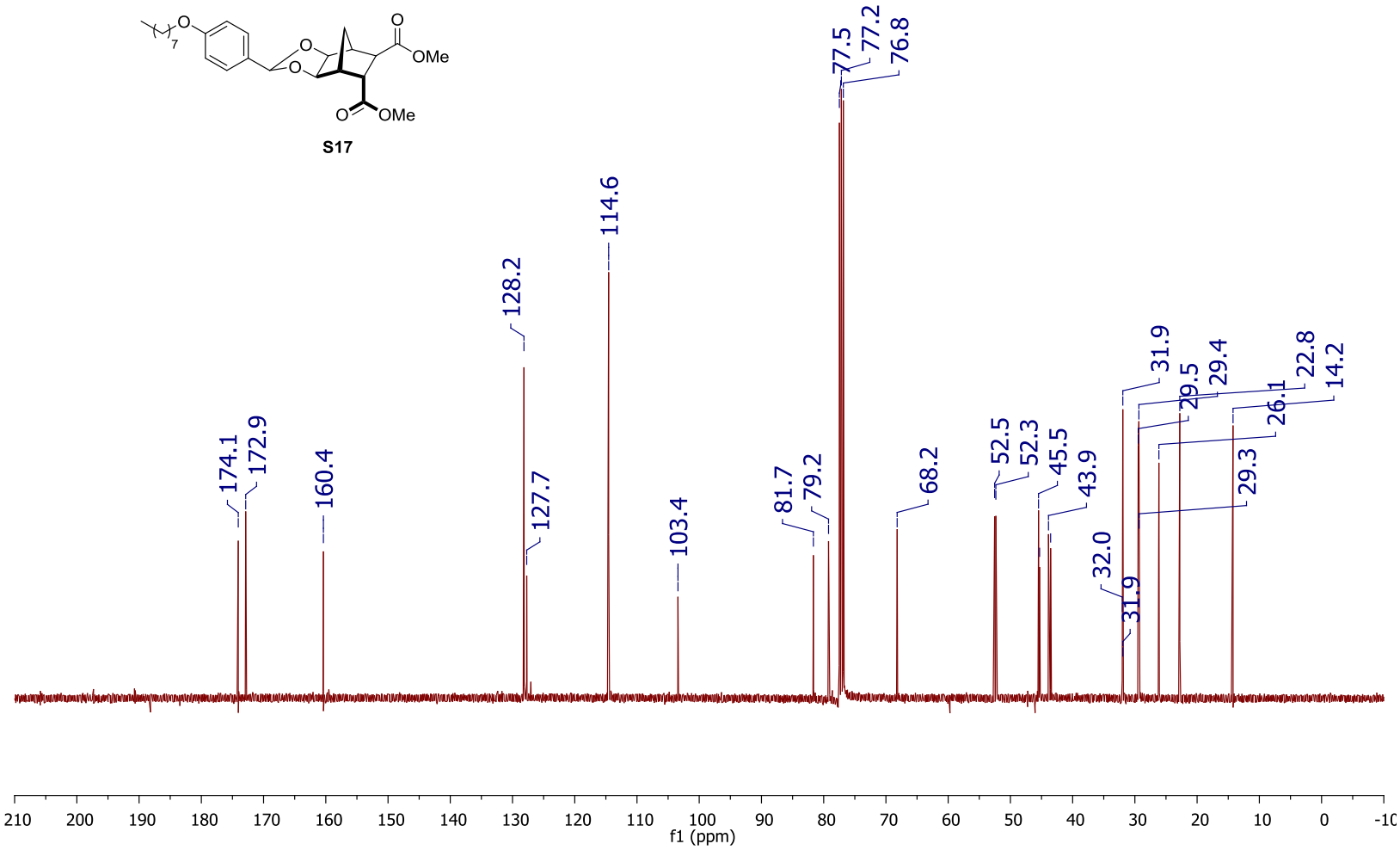
7.260
4.654
4.038
4.018
3.912
3.703
3.228
2.727
2.655
2.646
1.800
1.765
1.663
1.592
1.406
1.245
0.875
1.00
1.08
1.06
7.96
1.02
1.07
2.09
0.61
2.40
27.30
3.04
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

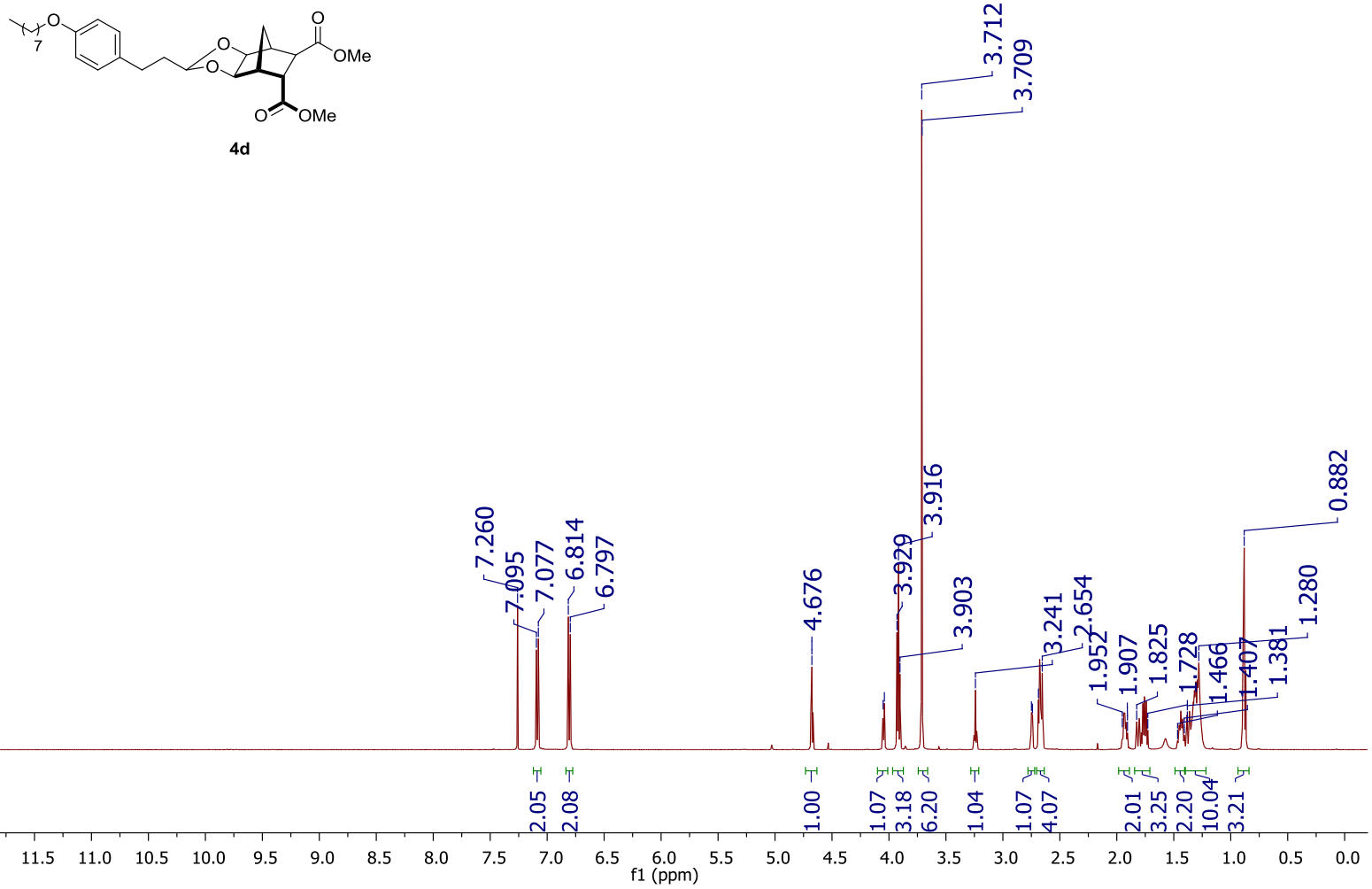

O
OMe
14
O
O
O
OMe
4c
174.129
172.898
104.374
81.427
78.934
77.160
52.487
52.280
45.433
45.182
43.793
43.419
29.797
29.835
29.775
29.690
14.260
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

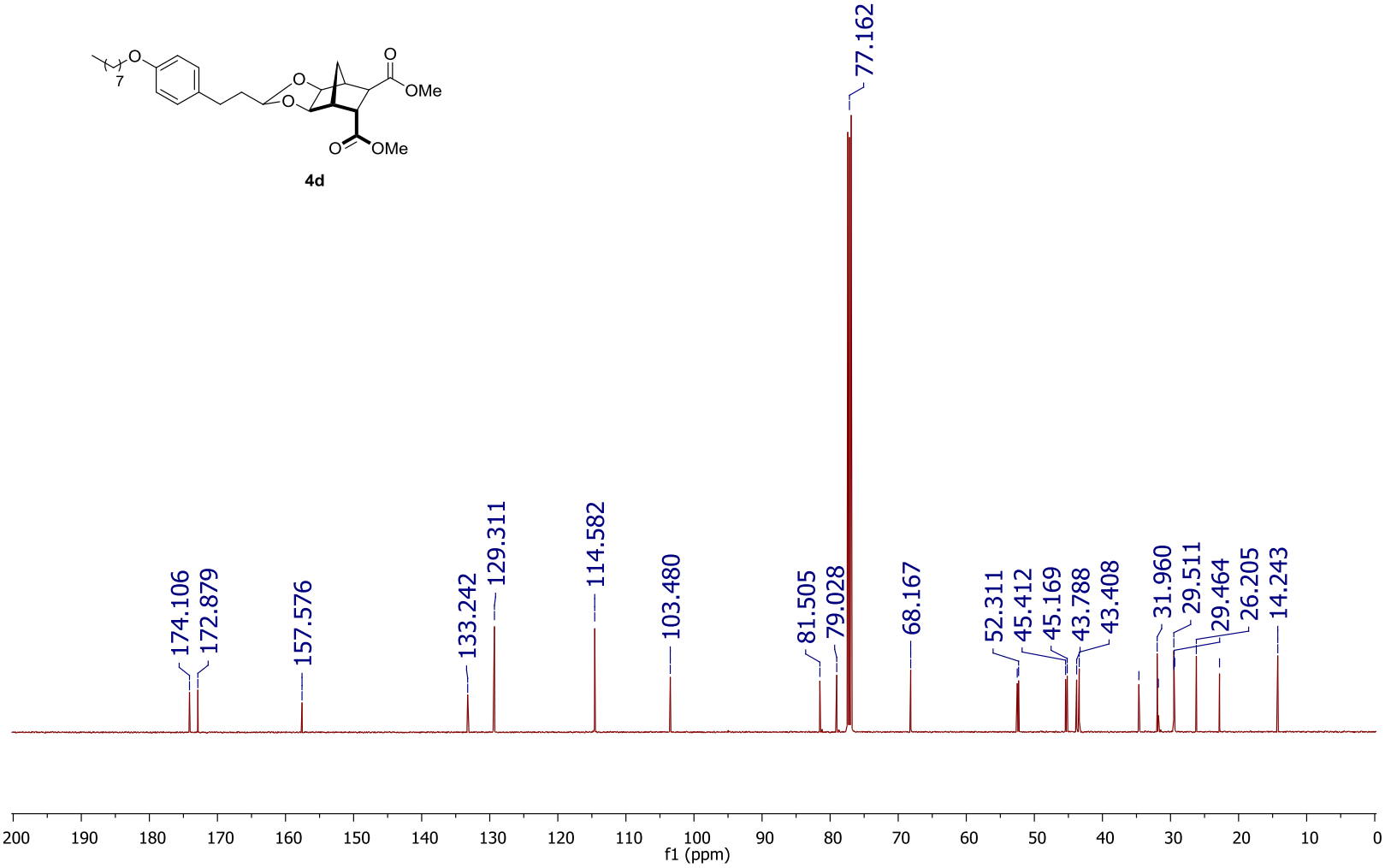

O
OMe
O
O
O
OMe
4e
7.310
7.260
7.155
4.696
4.047
3.946
3.715
3.711
3.247
2.774
2.651
2.011
1.932
1.839
1.805
1.400
1.360
6.80
1.00
1.17
1.09
6.67
1.00
5.70
2.19
0.98
1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

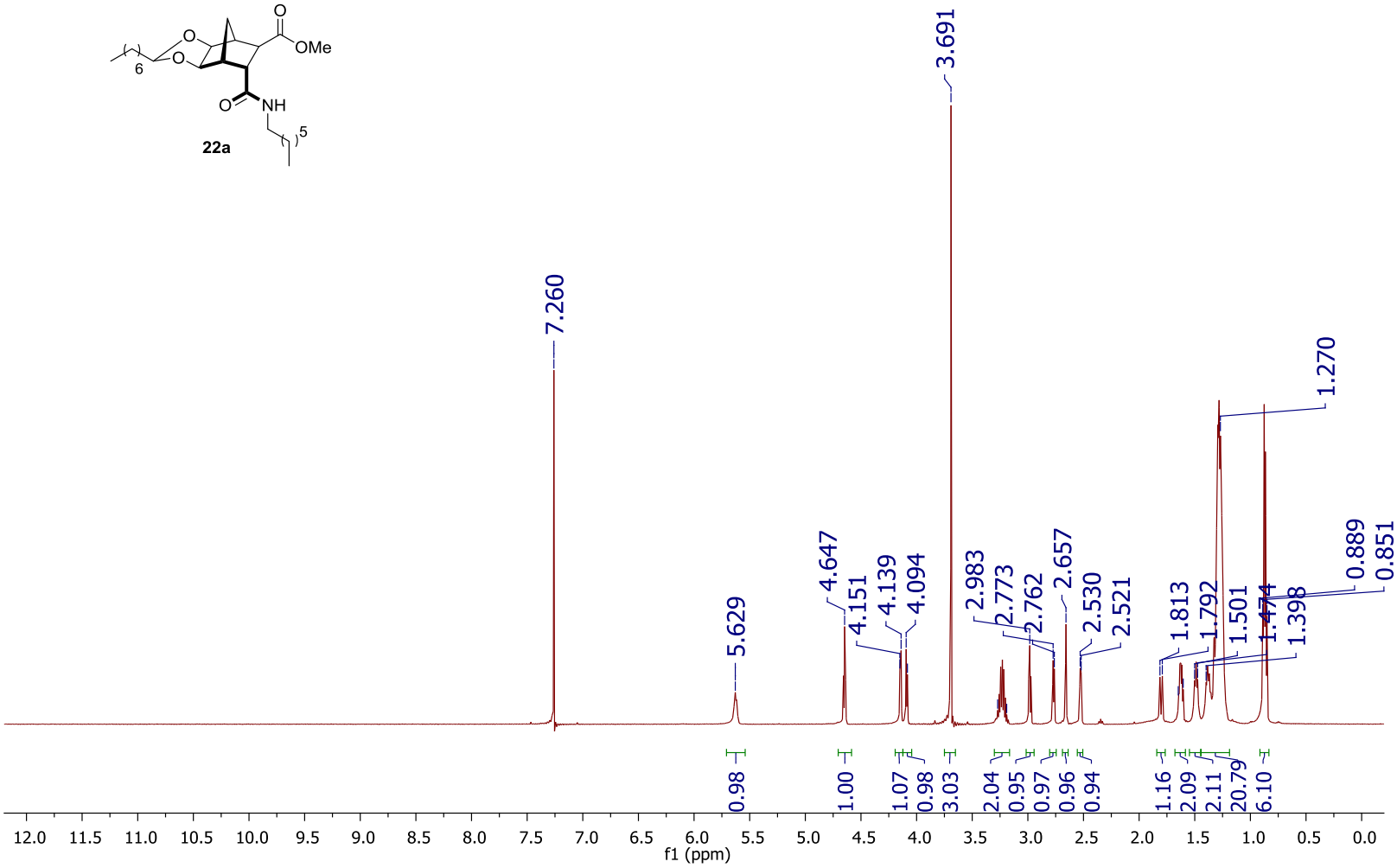

4e
128.533
128.456
126.087
103.411
81.507
79.033
77.160
52.501
52.299
45.392
45.151
43.771
43.390
34.380
31.774
30.356
174.074
172.852
141.418
f1 (ppm)

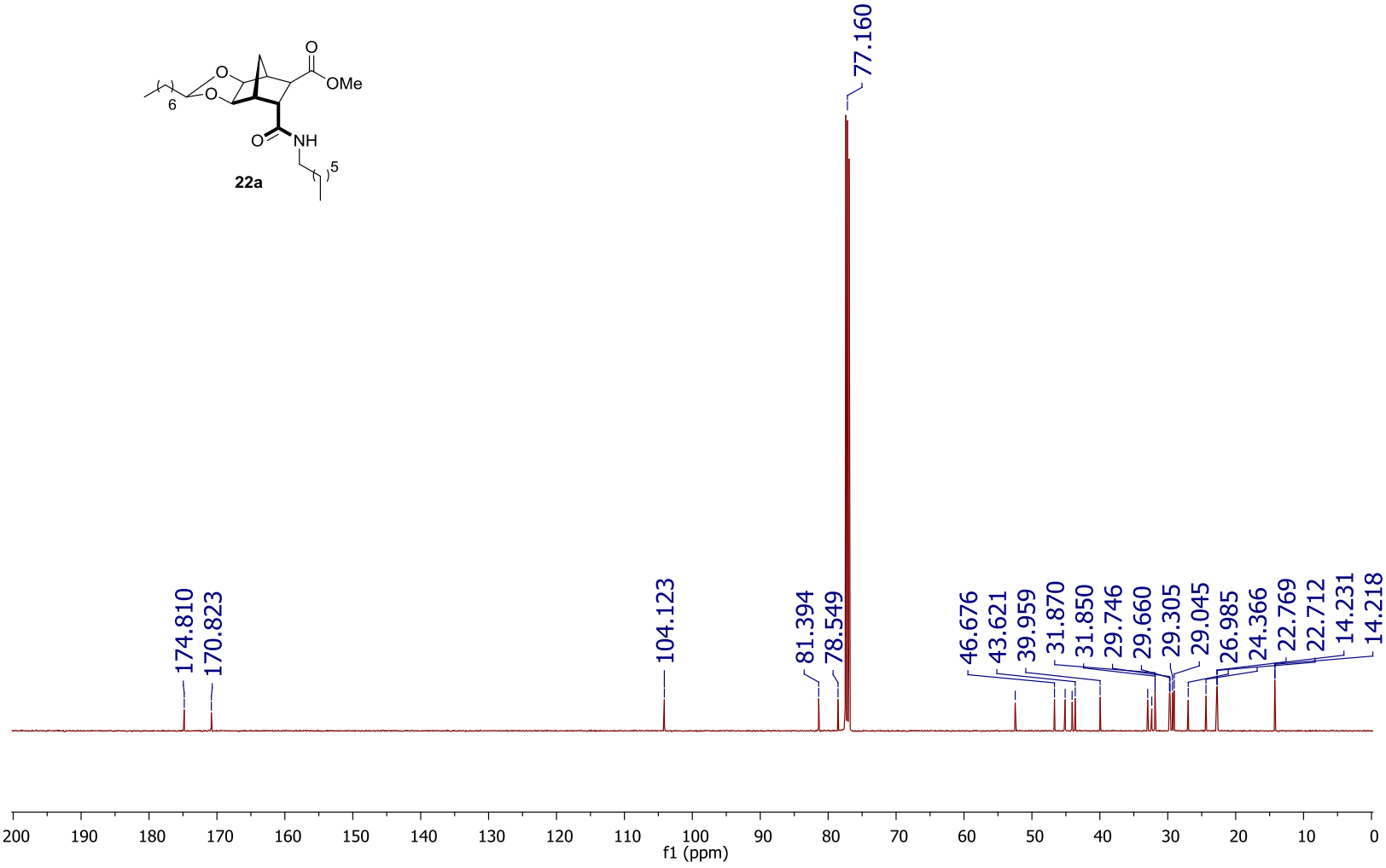

O
7
O
O
O
OMe
O
OMe
S17
3.72
7.40
7.38
7.26
6.89
6.87
5.53
4.08
3.96
3.94
3.93
3.28
3.26
2.77
2.72
2.72
1.43
1.43
1.33
1.32
1.30
1.29
1.28
0.90
0.88
0.86
2.15
2.16
1.00
1.11
1.02
2.32
2.86
2.70
0.99
1.07
0.96
1.02
1.06
2.35
13.77
3.31
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

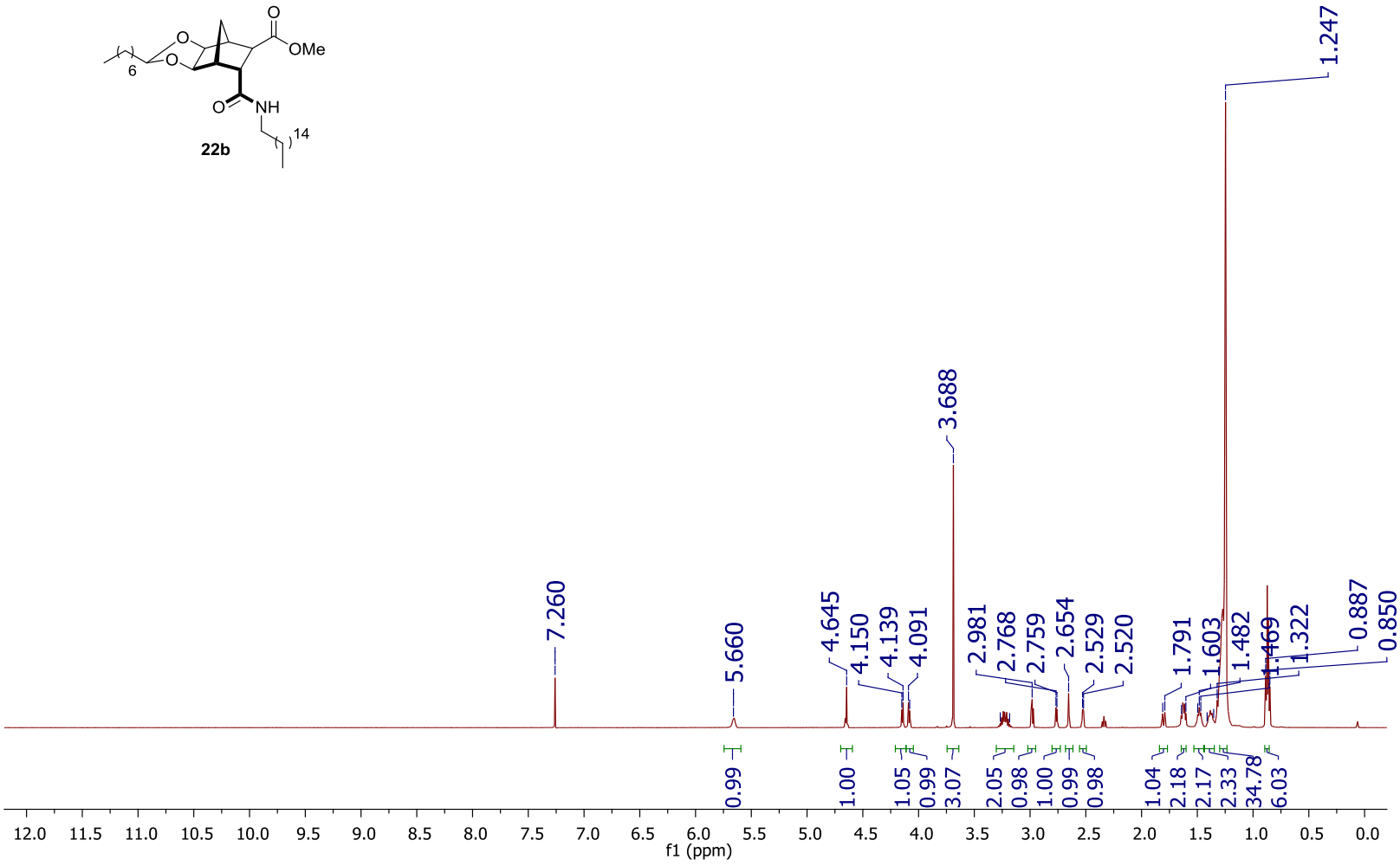

S17
174.1
172.9
160.4
128.2
127.7
114.6
103.4
81.7
79.2
77.5
77.2
76.8
68.2
52.5
52.3
45.5
43.9
32.0
31.9
31.9
29.5
29.4
29.3
26.1
22.8
14.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

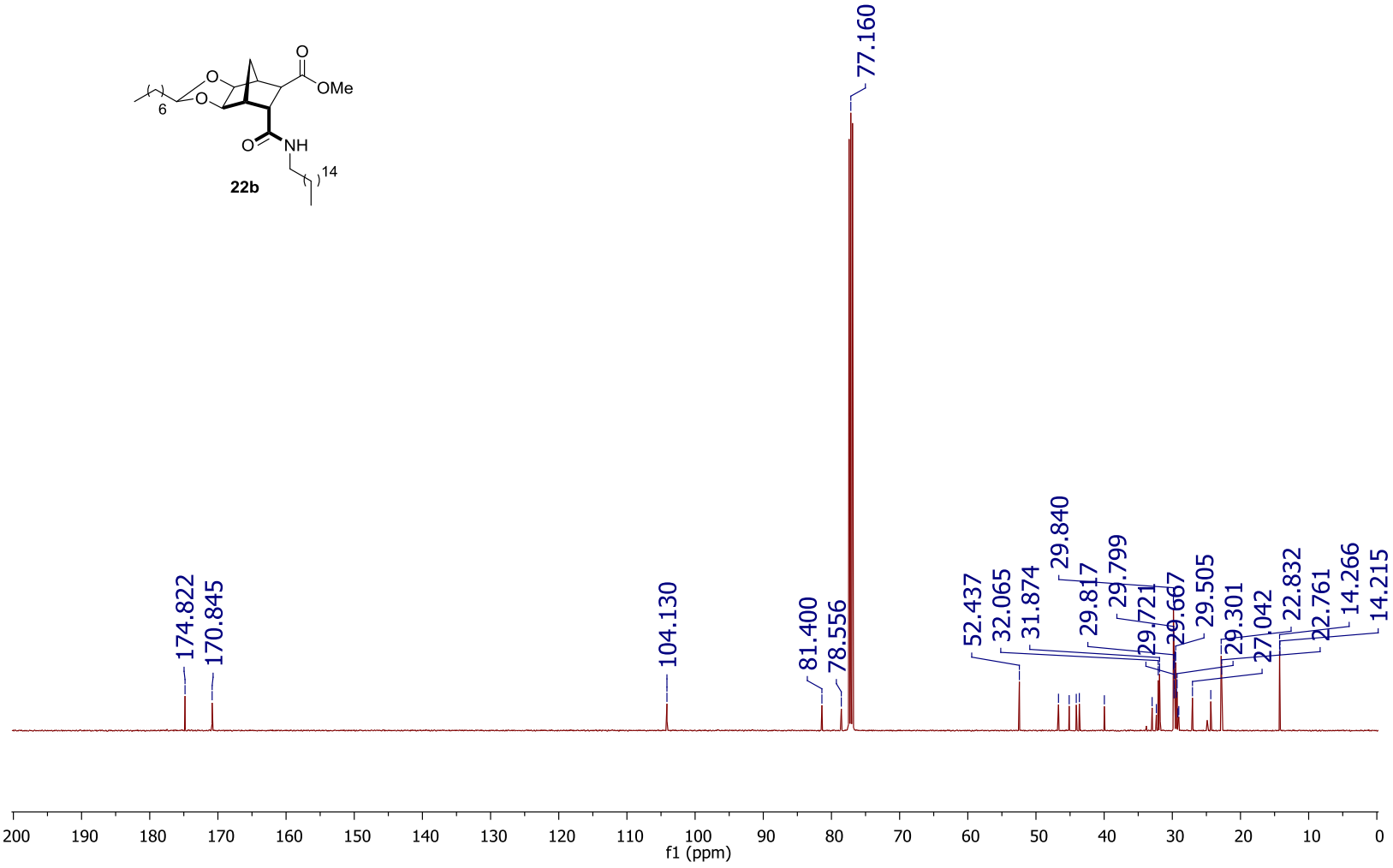

O
7
O
O
O
OMe
O
OMe
4d
7.260
7.095
7.077
6.814
6.797
4.676
3.929
3.916
3.903
3.712
3.709
3.241
2.654
1.952
1.907
1.825
1.728
1.466
1.407
1.381
1.280
0.882
2.05
2.08
1.00
1.07
3.18
6.20
1.04
1.07
4.07
2.01
3.25
2.20
10.04
3.21
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

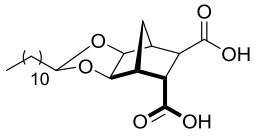

4d
77.162
174.106
172.879
157.576
133.242
129.311
114.582
103.480
81.505
79.028
68.167
52.311
45.412
45.169
43.788
43.408
31.960
29.511
29.464
26.205
14.243
f1 (ppm)


22a
7.260
5.629
4.647
4.151
4.139
4.094
3.691
2.983
2.773
2.762
2.657
2.530
2.521
1.813
1.792
1.501
1.474
1.398
1.270
0.889
0.851
0.98
1.00
1.07
0.98
3.03
2.04
0.95
0.97
0.96
0.94
1.16
2.09
2.11
20.79
6.10
f1 (ppm)


O
OMe
O
O
6
O
NH
5
22a
77.160
174.810
170.823
104.123
81.394
78.549
46.676
43.621
39.959
31.870
31.850
29.746
29.660
29.305
29.045
26.985
24.366
22.769
22.712
14.231
14.218
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

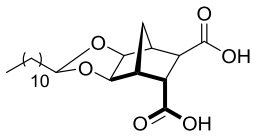

O
OMe
O
O
6
O
NH
14
22b
7.260
5.660
4.645
4.150
4.139
4.091
3.688
2.981
2.768
2.759
2.654
2.529
2.520
1.791
1.603
1.482
1.469
1.322
1.247
0.887
0.850
0.99
1.00
1.05
0.99
3.07
2.05
0.98
1.00
0.99
0.98
1.04
2.18
2.17
2.33
34.78
6.03
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
OMe
O
O
6
O
NH
14
22b
174.822
170.845
104.130
81.400
78.556
77.160
52.437
32.065
31.874
29.840
29.817
29.799
29.721
29.667
29.505
29.301
27.042
22.832
22.761
14.266
14.215
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
OH
O
10
O
O
OH

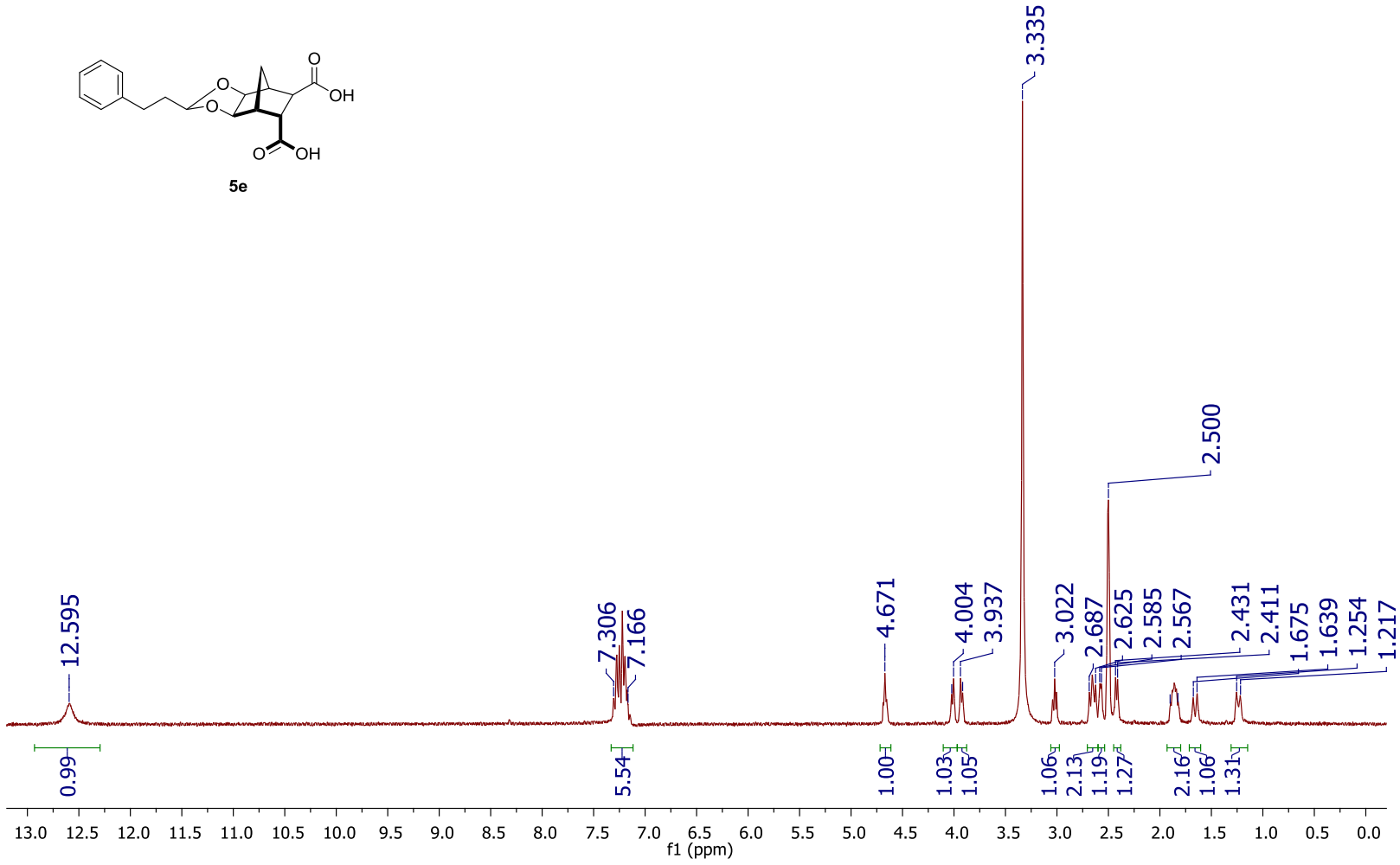
5b

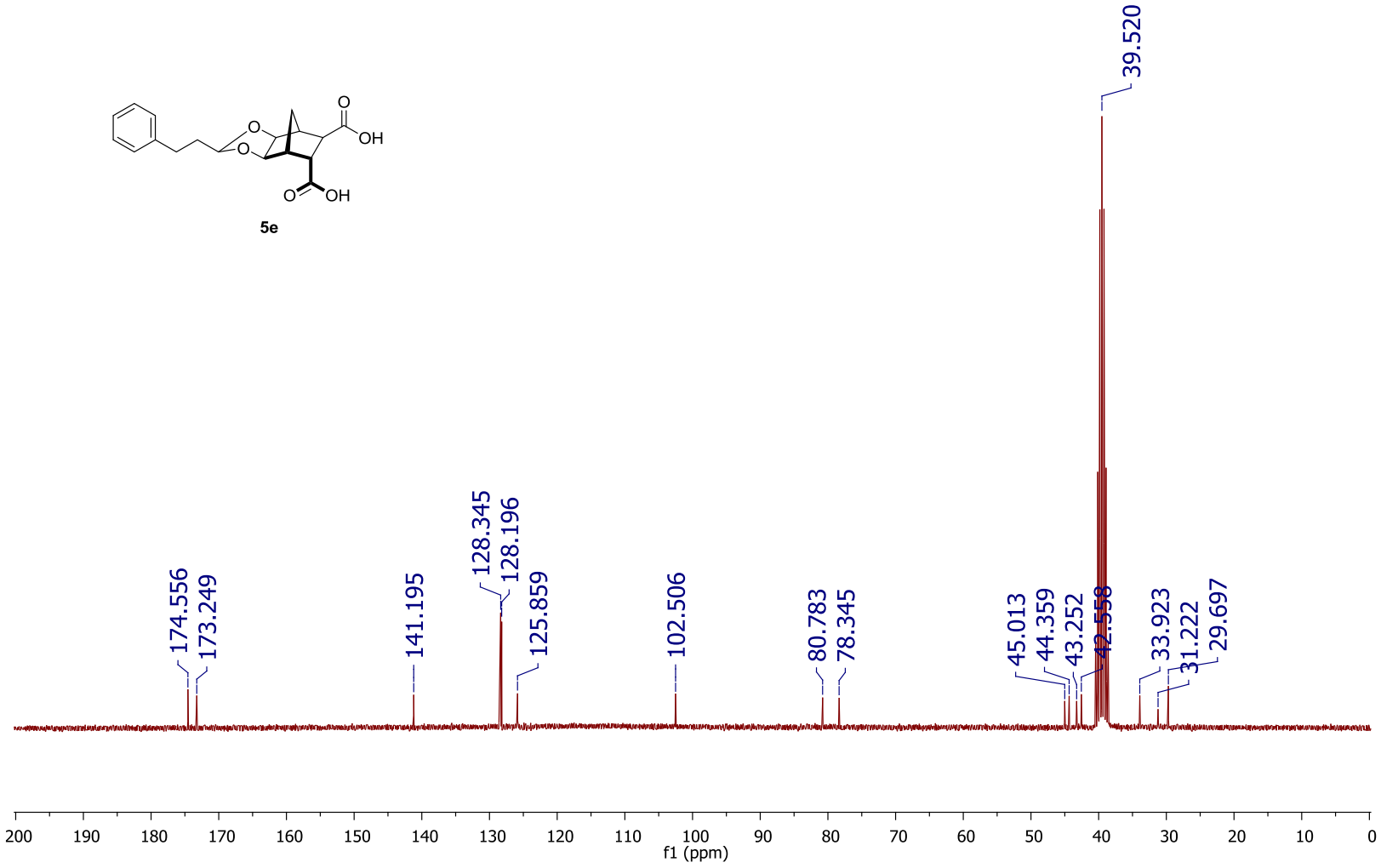
4.911
4.674
4.022
3.986
3.310
3.171
2.582
2.563
1.760
1.737
1.627
1.586
1.417
1.292
0.901
1.00
1.86
0.95
0.91
0.91
0.91
0.93
1.90
18.81
2.89
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

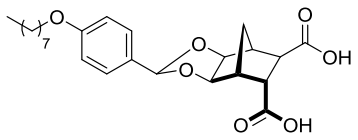

O
OH
10
O
O
O
OH

5b

176.861
175.498
105.220
82.671
80.184
46.616
46.410
44.949
44.441
33.089
30.756
30.656
23.757
14.456
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

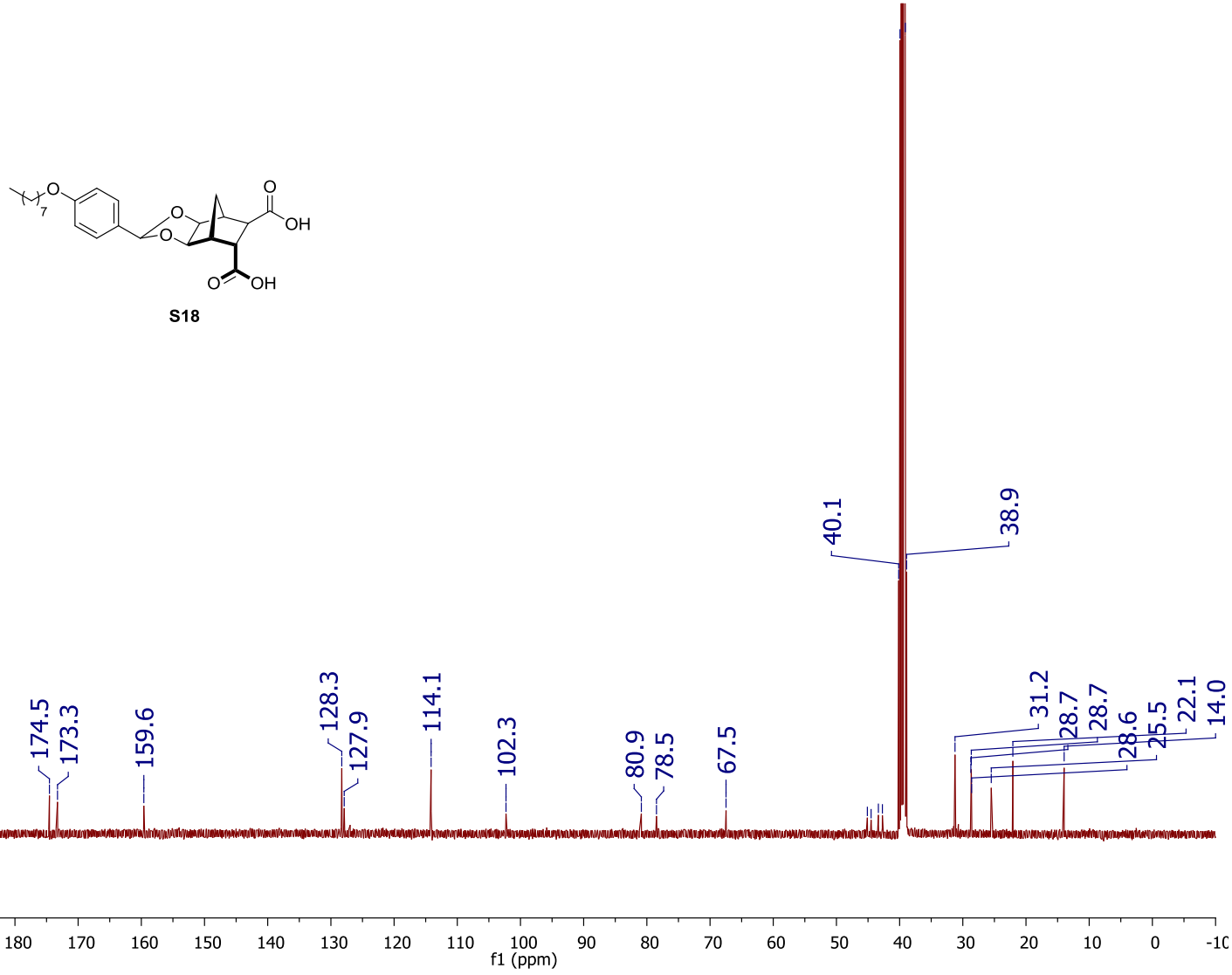

O
OH
O
O
O
OH
5e
12.595
7.306
7.166
4.671
4.004
3.937
3.335
3.022
2.687
2.625
2.585
2.567
2.500
2.431
2.411
1.675
1.639
1.254
1.217
0.99
5.54
1.00
1.03
1.05
1.06
2.13
1.19
1.27
2.16
1.06
1.31
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

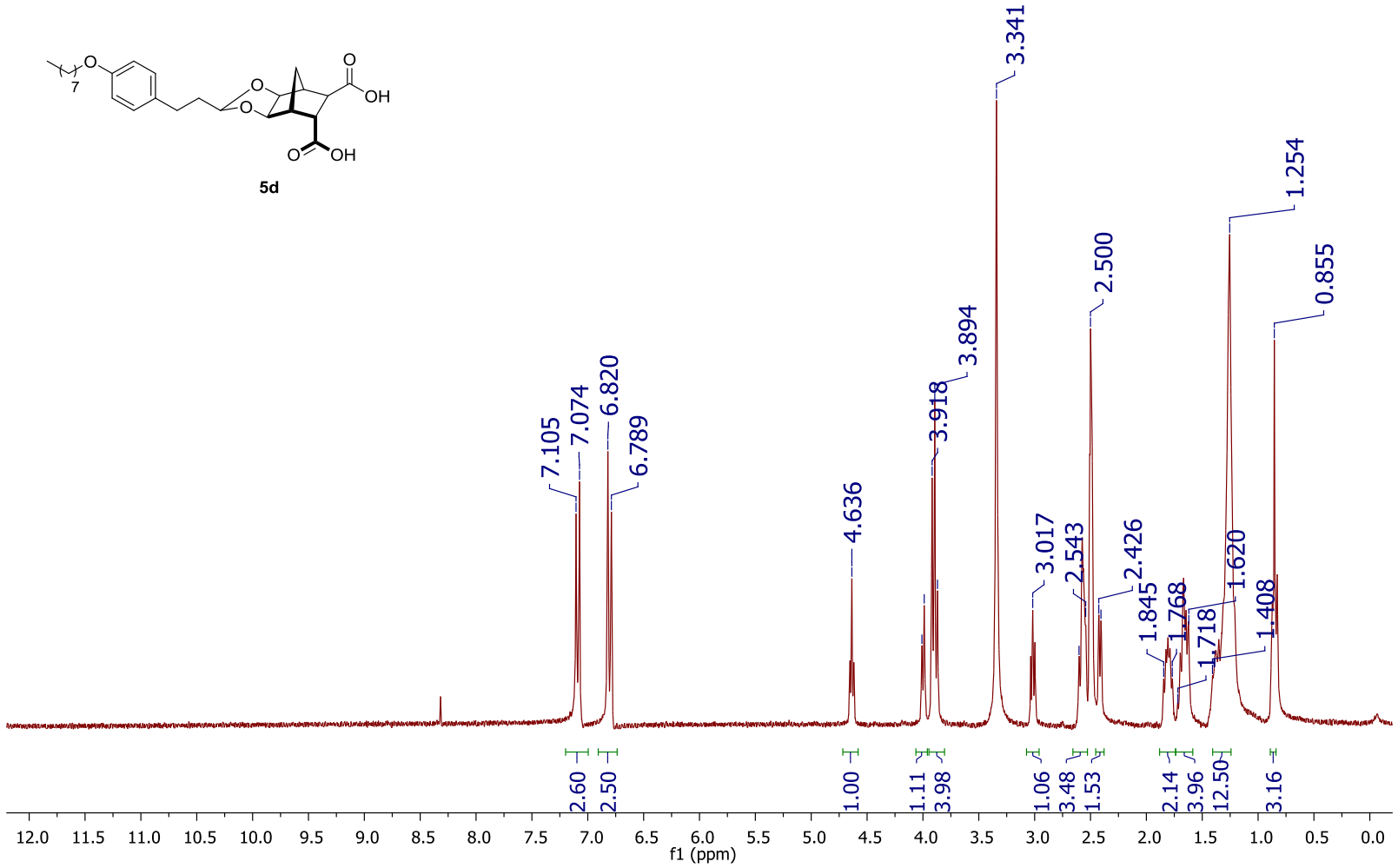

O
OH
O
O
O
OH
5e
39.520
174.556
173.249
141.195
128.345
128.196
125.859
102.506
80.783
78.345
45.013
44.359
43.252
42.558
33.923
31.222
29.697
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

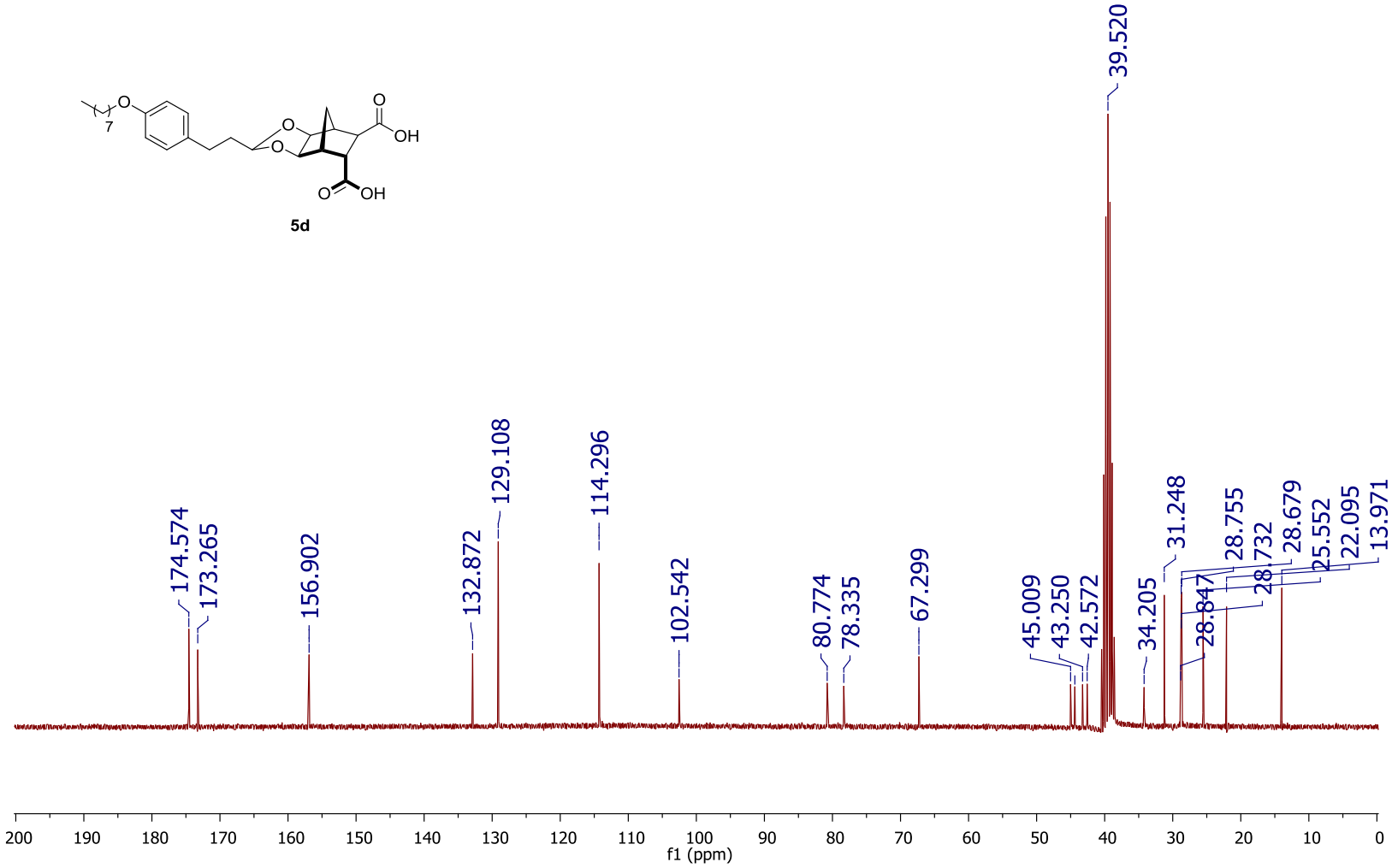

O
7
O
O
O
OH
O
OH

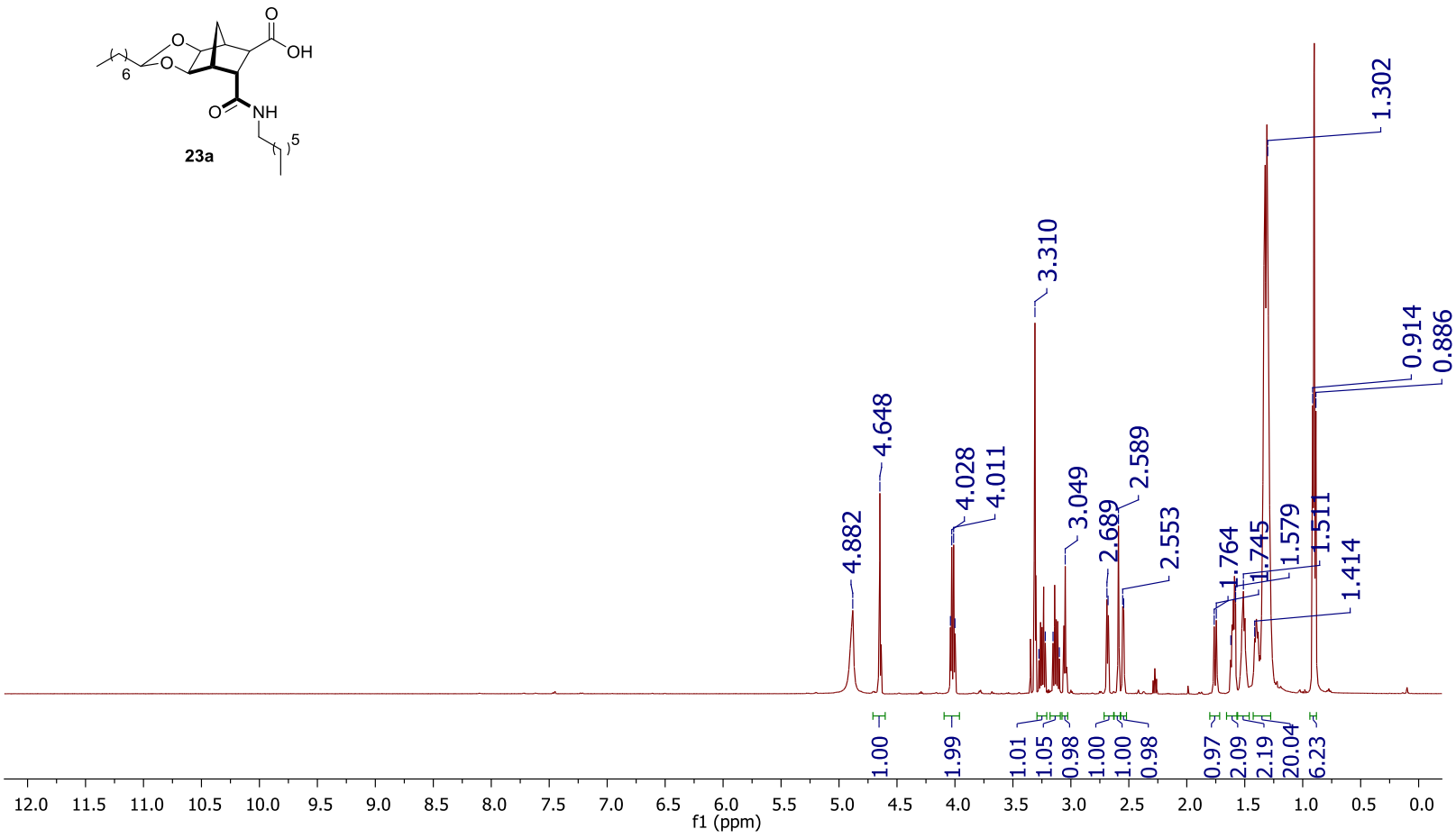
S18

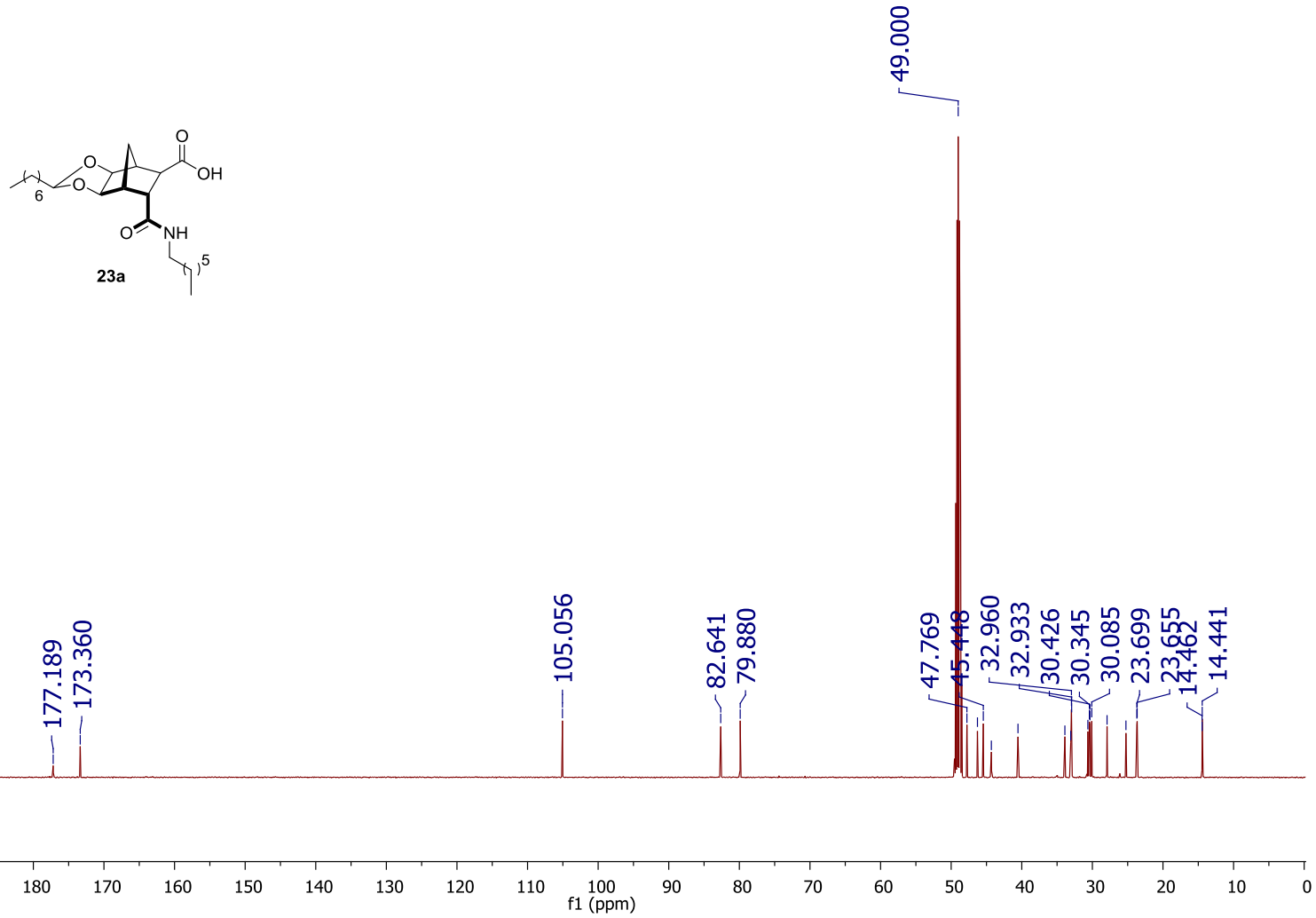
7.37
7.34
6.93
6.91
5.49
4.12
4.05
3.97
3.95
3.94
3.38
2.57
2.50
2.50
2.50
1.69
1.67
1.32
1.29
1.28
1.25
1.23
0.87
0.86
0.84
2.20
2.36
1.00
1.11
1.10
2.62
1.03
1.10
1.21
1.29
1.01
2.50
16.34
3.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

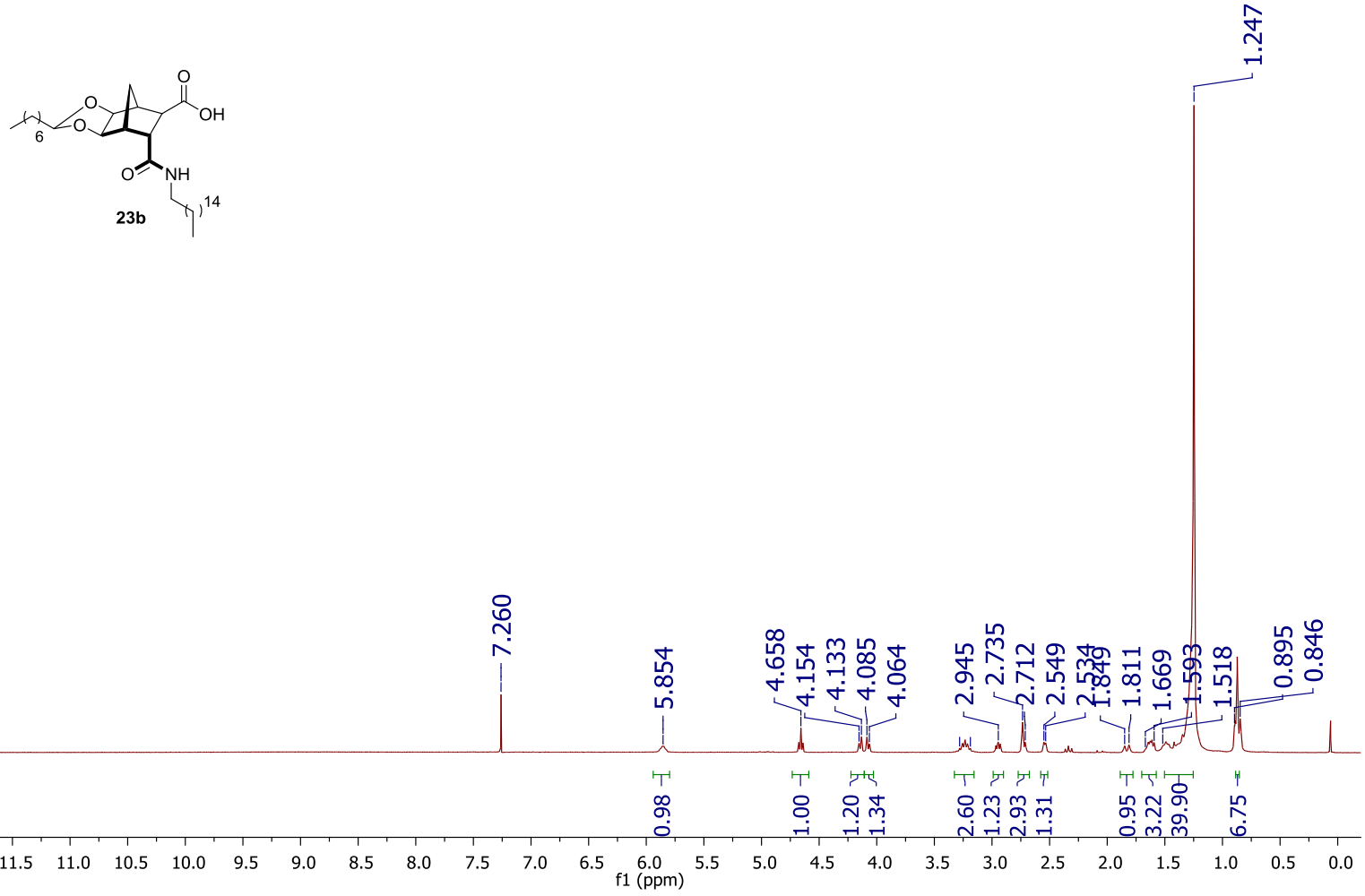

O
7
O
O
O
OH
O
OH
S18
174.5
173.3
159.6
128.3
127.9
114.1
102.3
80.9
78.5
67.5
40.1
38.9
31.2
28.7
28.7
28.6
25.5
22.1
14.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

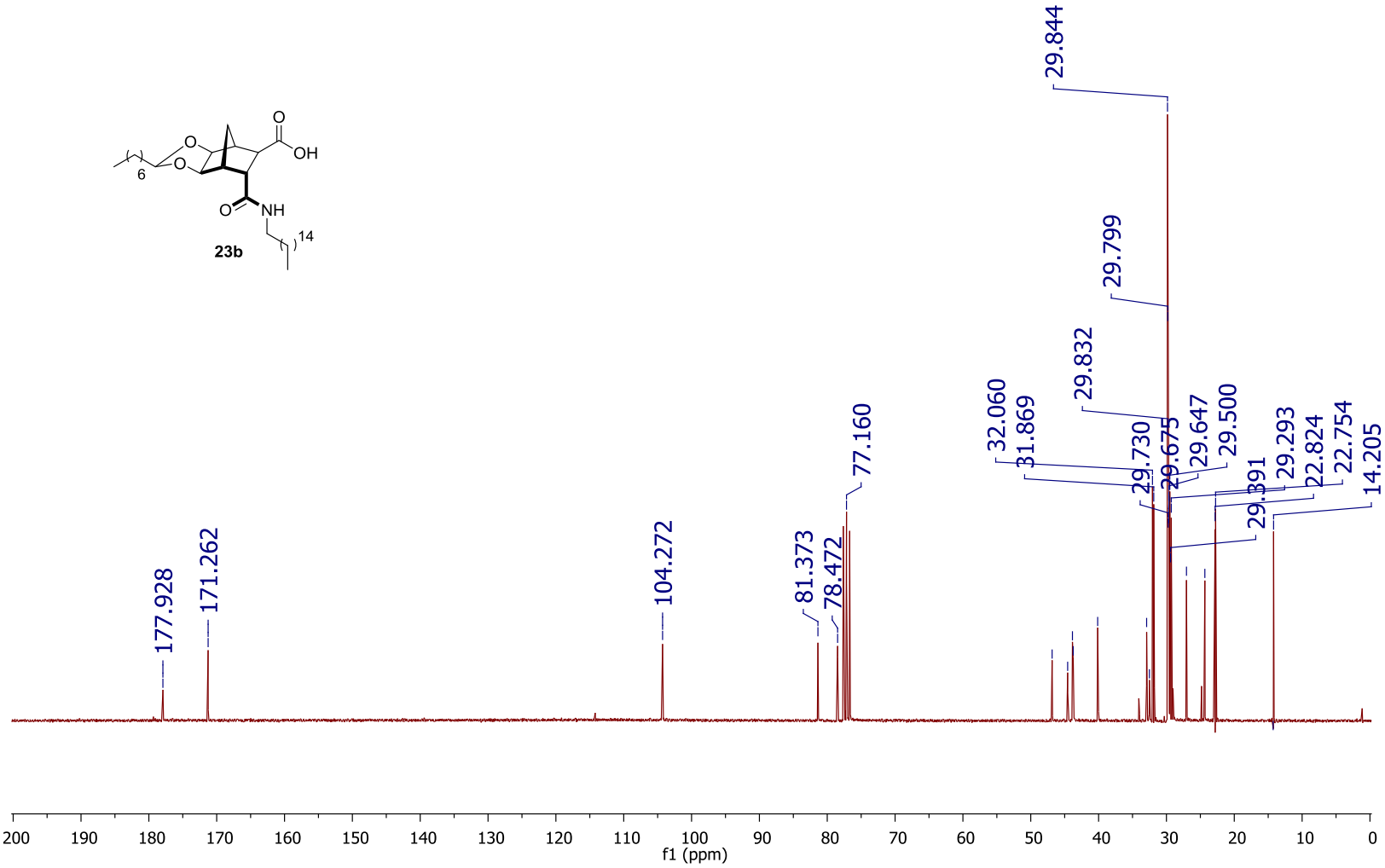

5d
7.105
7.074
6.820
6.789
4.636
3.918
3.894
3.341
3.017
2.543
2.500
2.426
1.845
1.768
1.718
1.620
1.408
1.254
0.855
2.60
2.50
1.00
1.11
3.98
1.06
3.48
1.53
2.14
3.96
12.50
3.16
f1 (ppm)

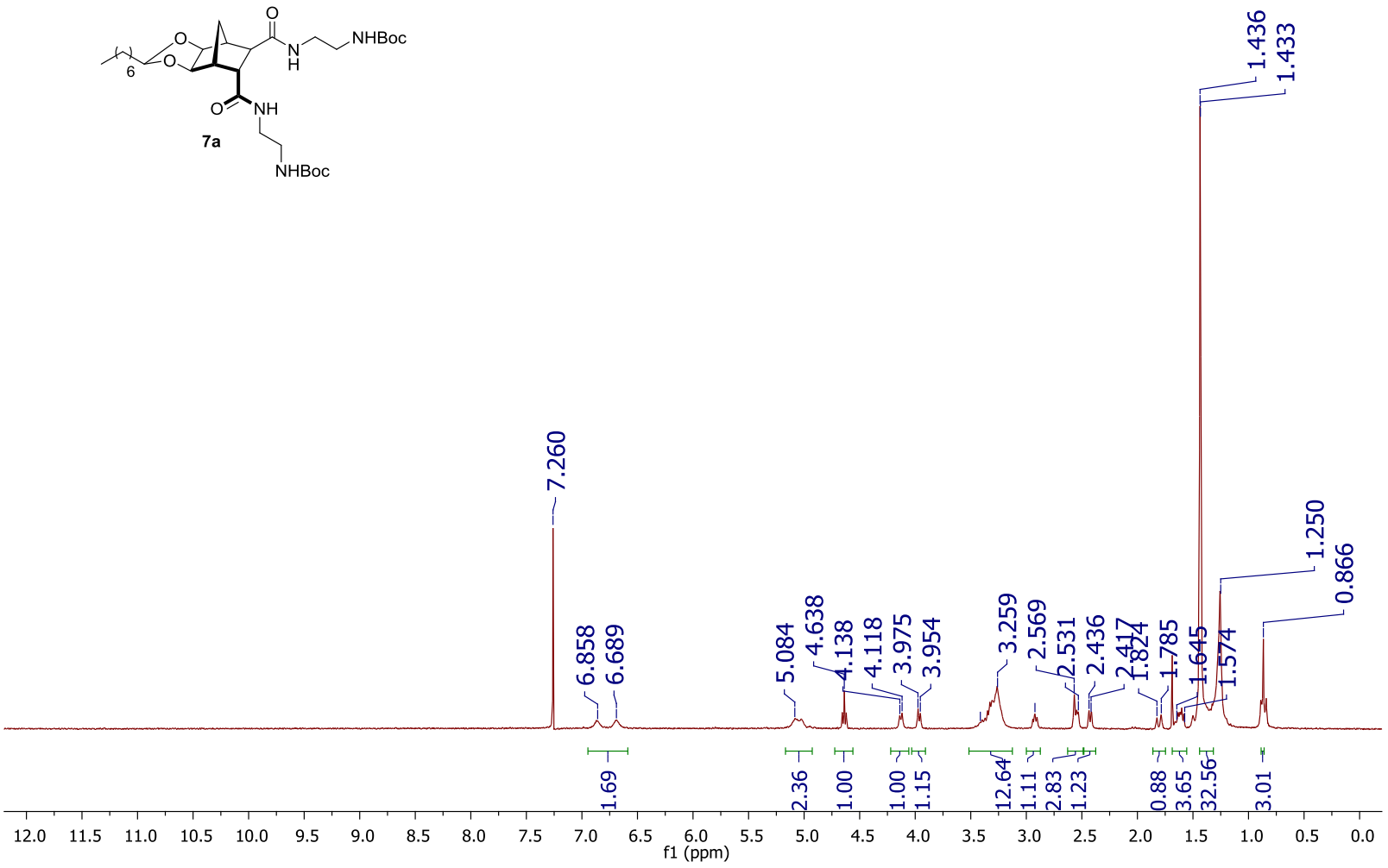

O
7
O
O
O
OH
O
OH
5d
174.574
173.265
156.902
132.872
129.108
114.296
102.542
80.774
78.335
67.299
45.009
43.250
42.572
39.520
34.205
31.248
28.847
28.755
28.732
28.679
25.552
22.095
13.971
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

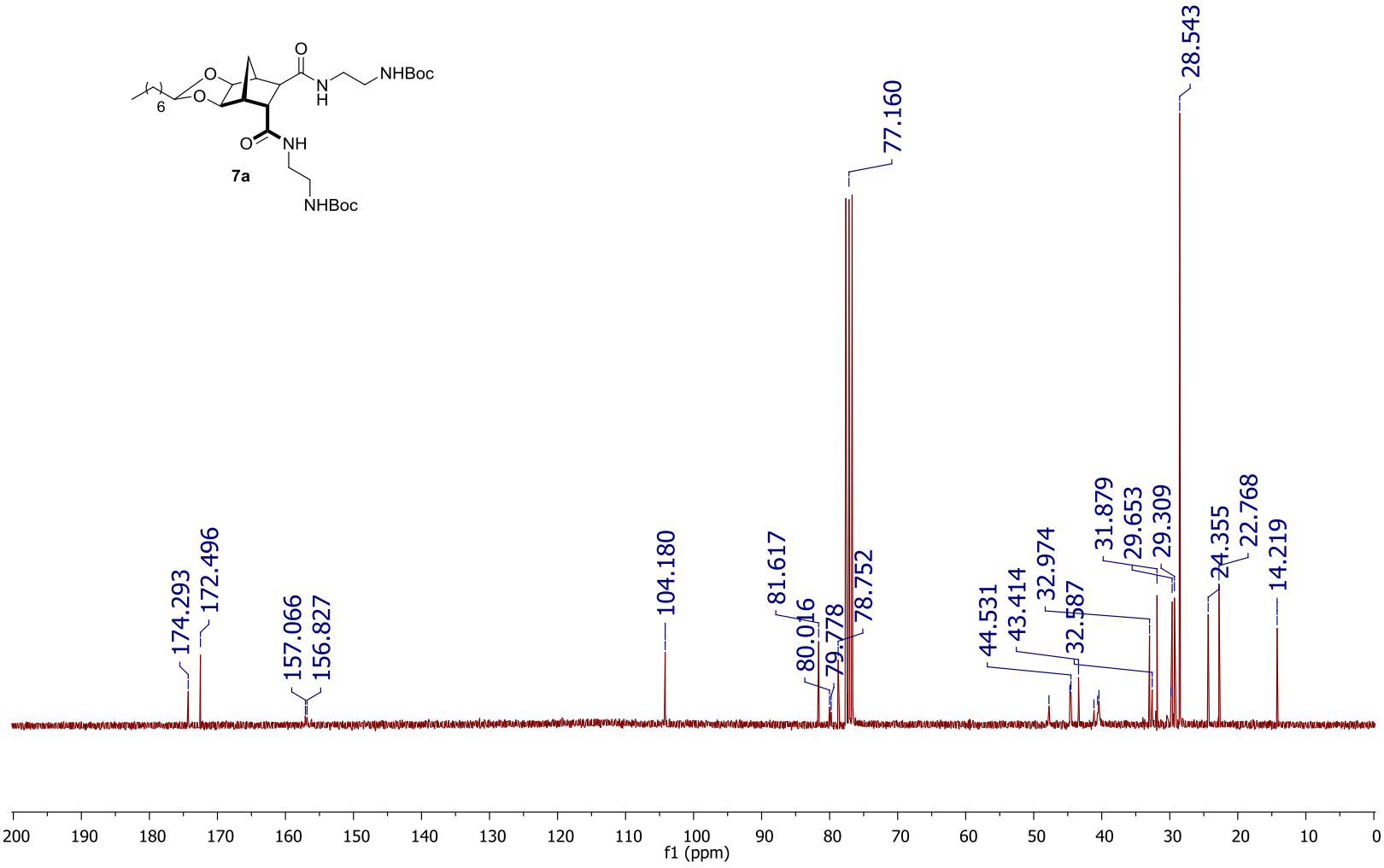

O
OH
O
O
6
O
NH
5
23a
4.882
4.648
4.028
4.011
3.310
3.049
2.689
2.589
2.553
1.764
1.745
1.579
1.511
1.414
1.302
0.914
0.886
1.00
1.99
1.01
1.05
0.98
1.00
1.00
0.98
0.97
2.09
2.19
20.04
6.23
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

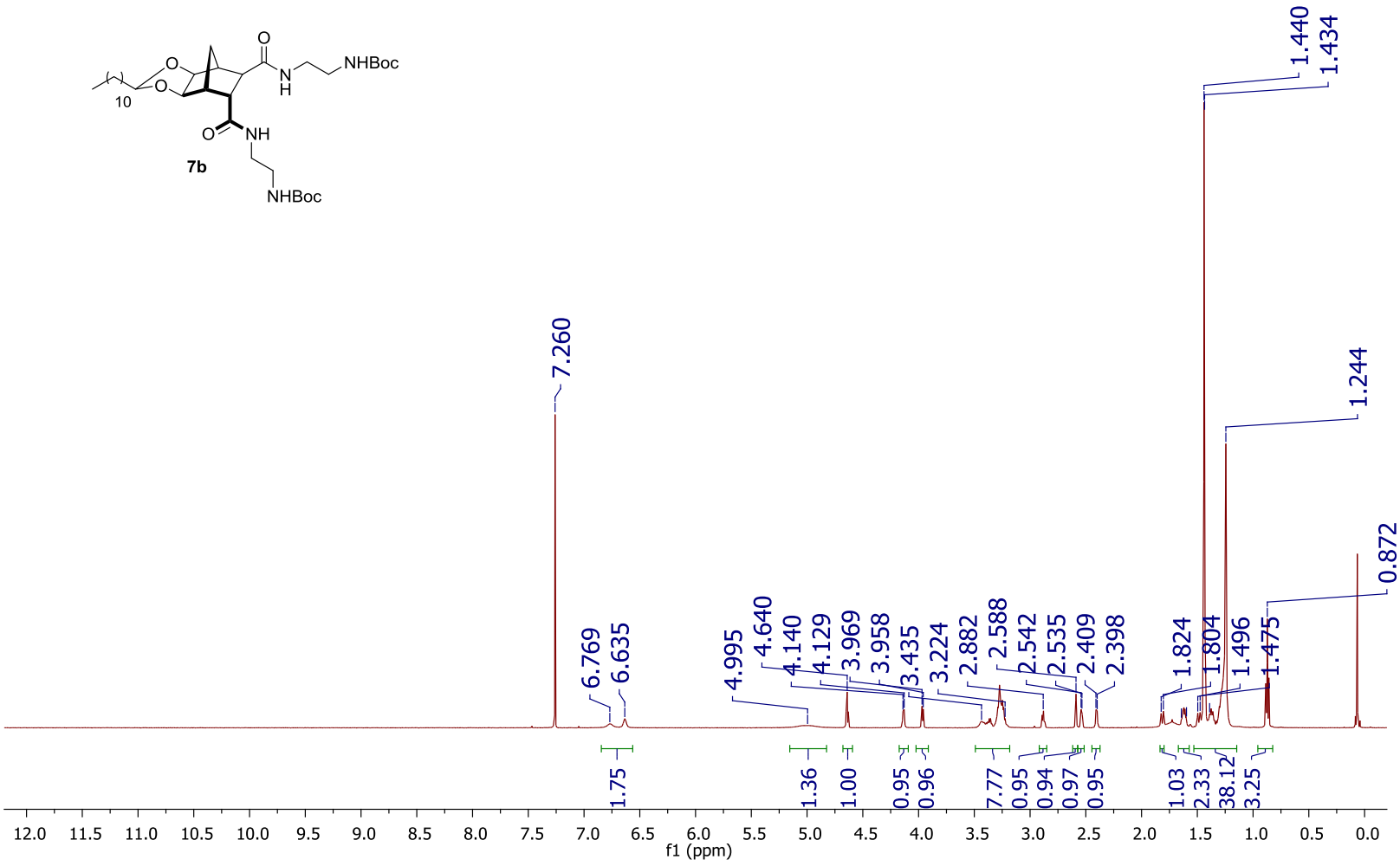

O
OH
O
O
6
O
NH
5
23a
49.000
177.189
173.360
105.056
82.641
79.880
47.769
45.448
32.960
32.933
30.426
30.345
30.085
23.699
23.655
14.462
14.441
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

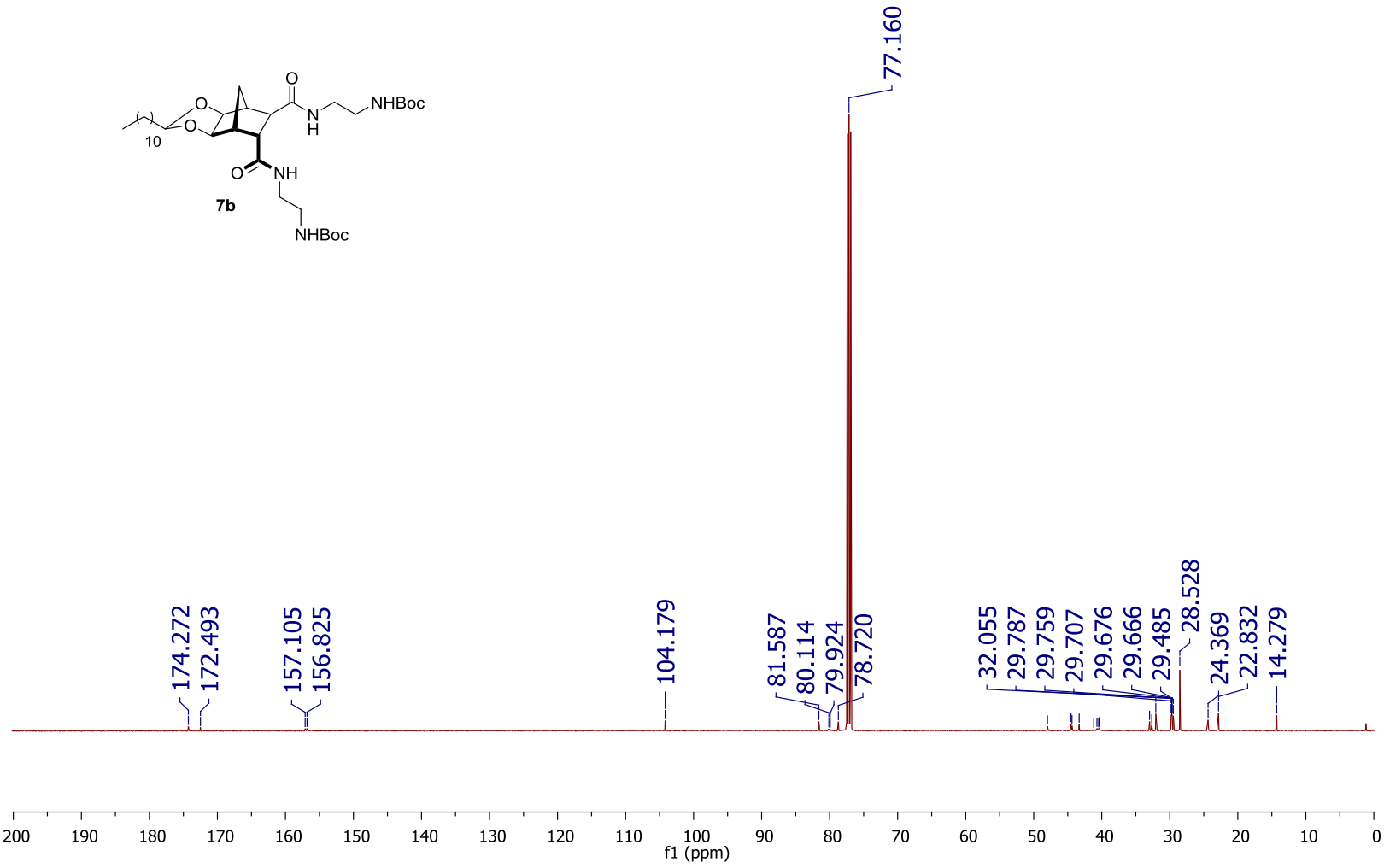

O
OH
O
O
6
O
NH
14
23b
7.260
5.854
4.658
4.154
4.133
4.085
4.064
2.945
2.735
2.712
2.549
2.534
1.849
1.811
1.669
1.593
1.518
1.247
0.895
0.846
0.98
1.00
1.20
1.34
2.60
1.23
2.93
1.31
0.95
3.22
39.90
6.75
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

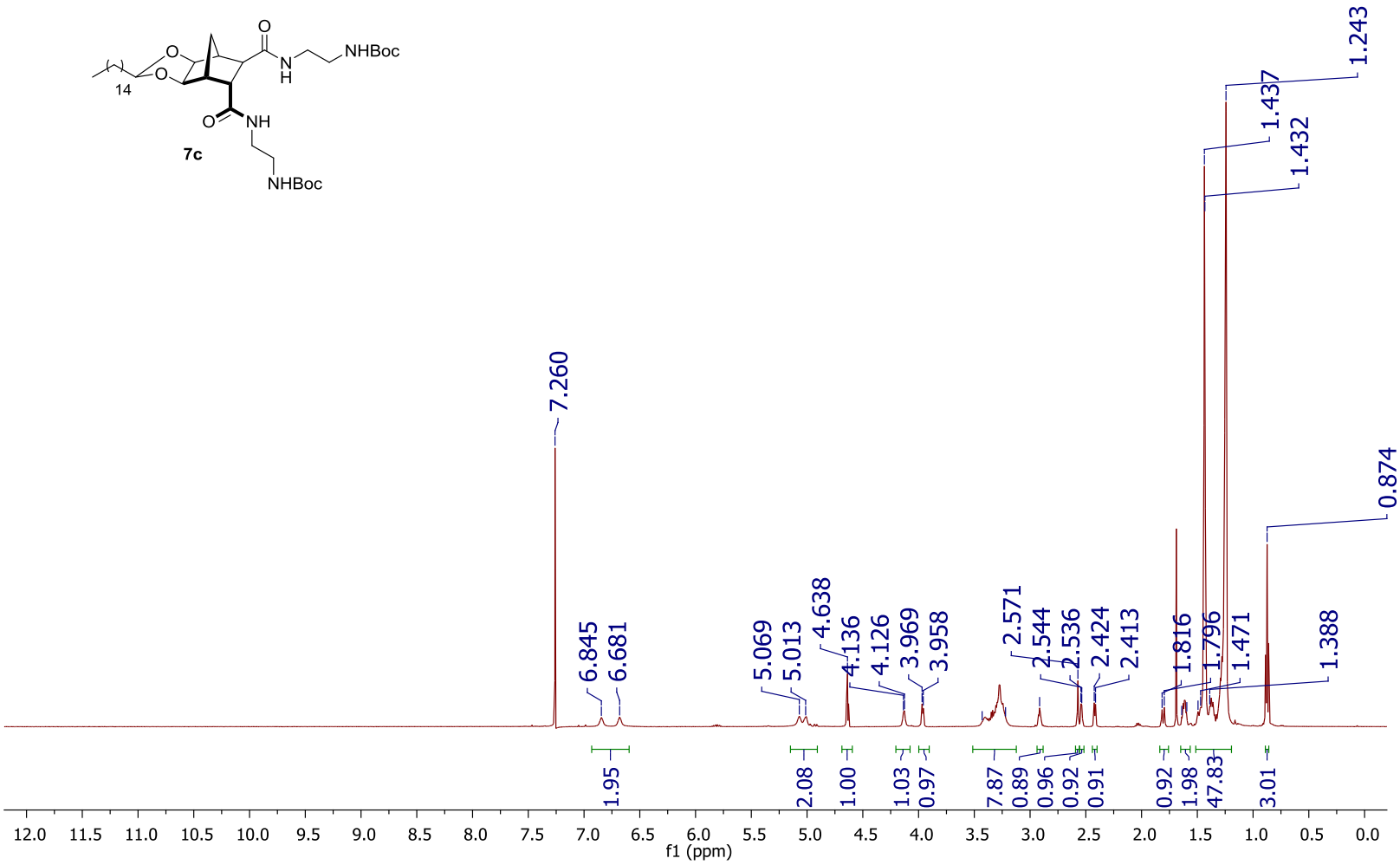

23b
177.928
171.262
104.272
81.373
78.472
77.160
32.060
31.869
29.844
29.799
29.832
29.730
29.675
29.647
29.500
29.391
29.293
22.824
22.754
14.205
f1 (ppm)

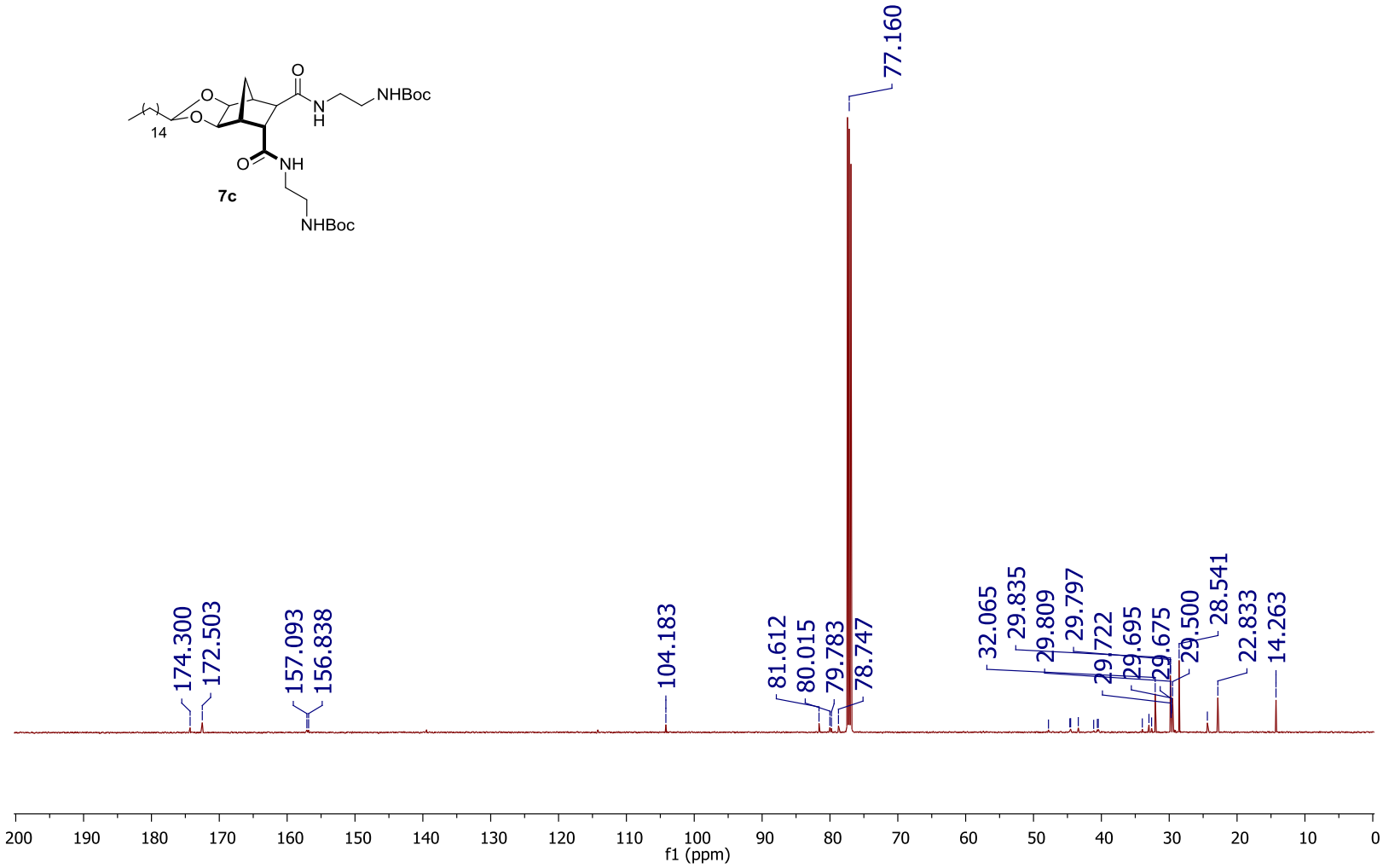

7a
NHBoc
NHBoc
7.260
6.858
6.689
5.084
4.638
4.138
4.118
3.975
3.954
3.259
2.569
2.531
2.436
2.417
1.824
1.785
1.645
1.574
1.436
1.433
1.250
0.866
1.69
2.36
1.00
1.00
1.15
12.64
1.11
2.83
1.23
0.88
3.65
32.56
3.01
f1 (ppm)

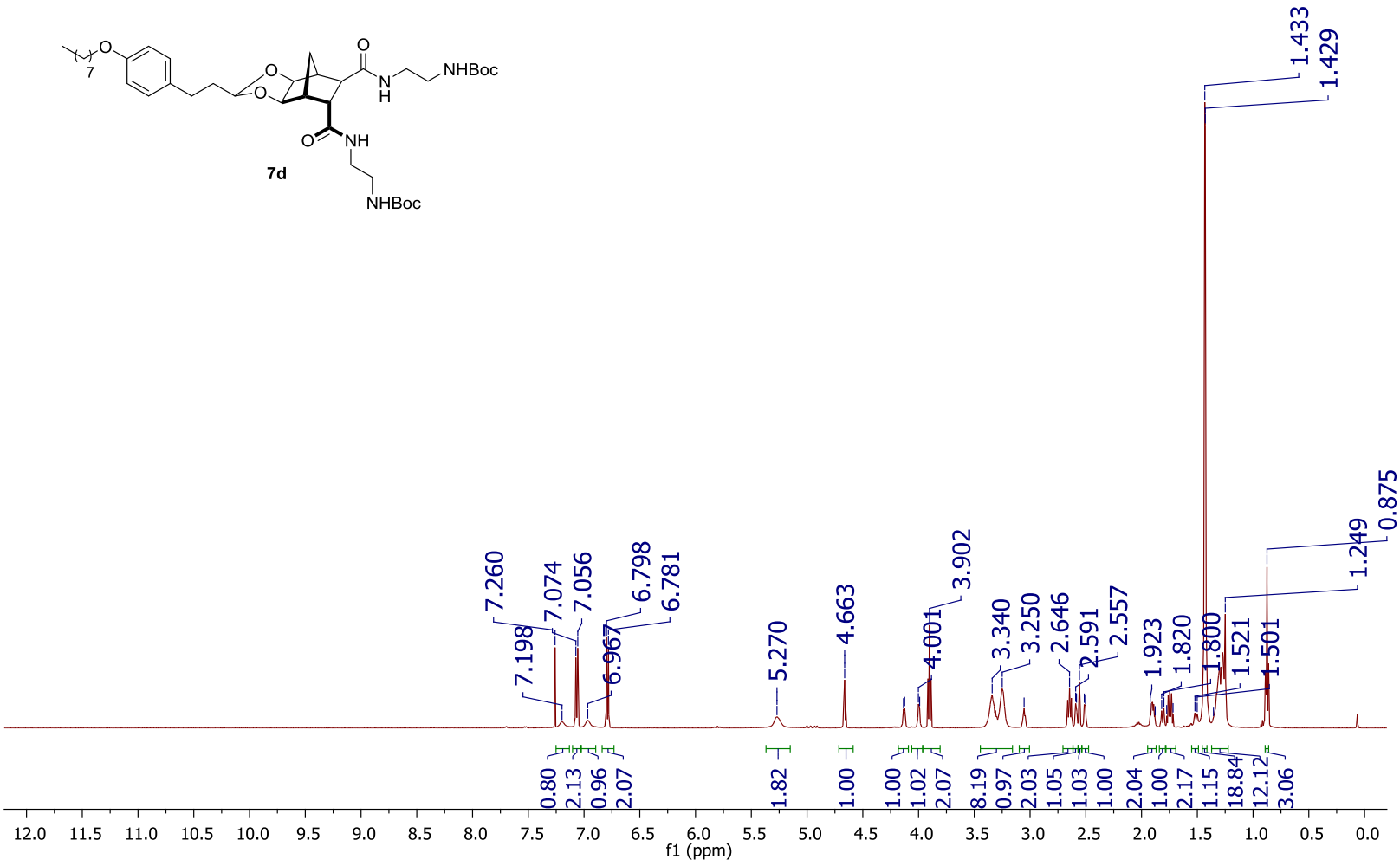

7a
NHBoc
NHBoc
174.293
172.496
157.066
156.827
104.180
81.617
80.016
79.778
78.752
77.160
44.531
43.414
32.974
32.587
31.879
29.653
29.309
28.543
24.355
22.768
14.219
f1 (ppm)

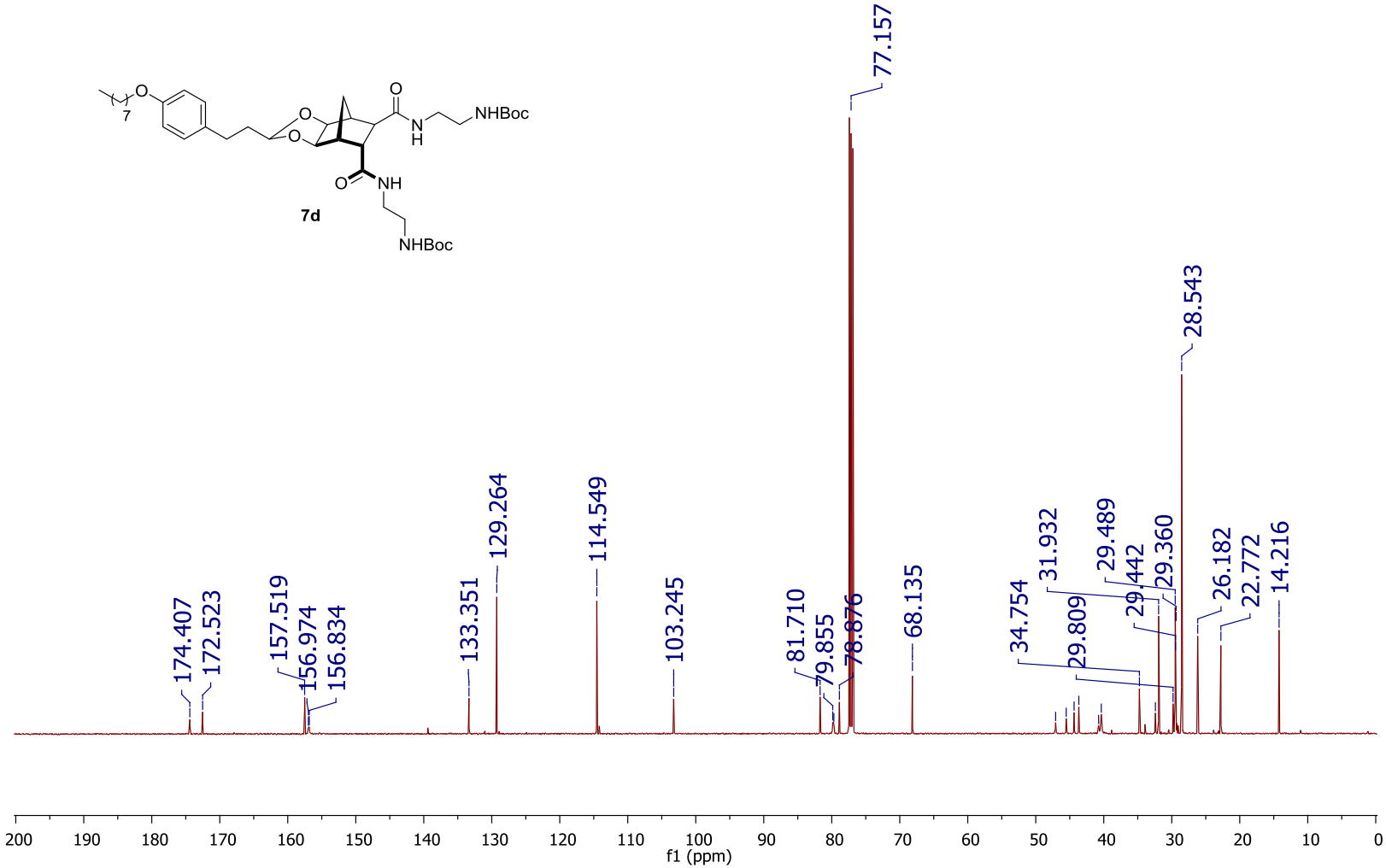

7b
NHBoc
NHBoc
10
7.260
6.769
6.635
4.995
4.640
4.140
4.129
3.969
3.958
3.435
3.224
2.882
2.588
2.542
2.535
2.409
2.398
1.824
1.804
1.496
1.475
1.440
1.434
1.244
0.872
1.75
1.36
1.00
0.95
0.96
7.77
0.95
0.94
0.97
0.95
1.03
2.33
38.12
3.25
f1 (ppm)


O
O
O
N
H
NHBoc
10
O
NH
NHBoc
7b
77.160
174.272
172.493
157.105
156.825
104.179
81.587
80.114
79.924
78.720
32.055
29.787
29.759
29.707
29.676
29.666
29.485
28.528
24.369
22.832
14.279
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

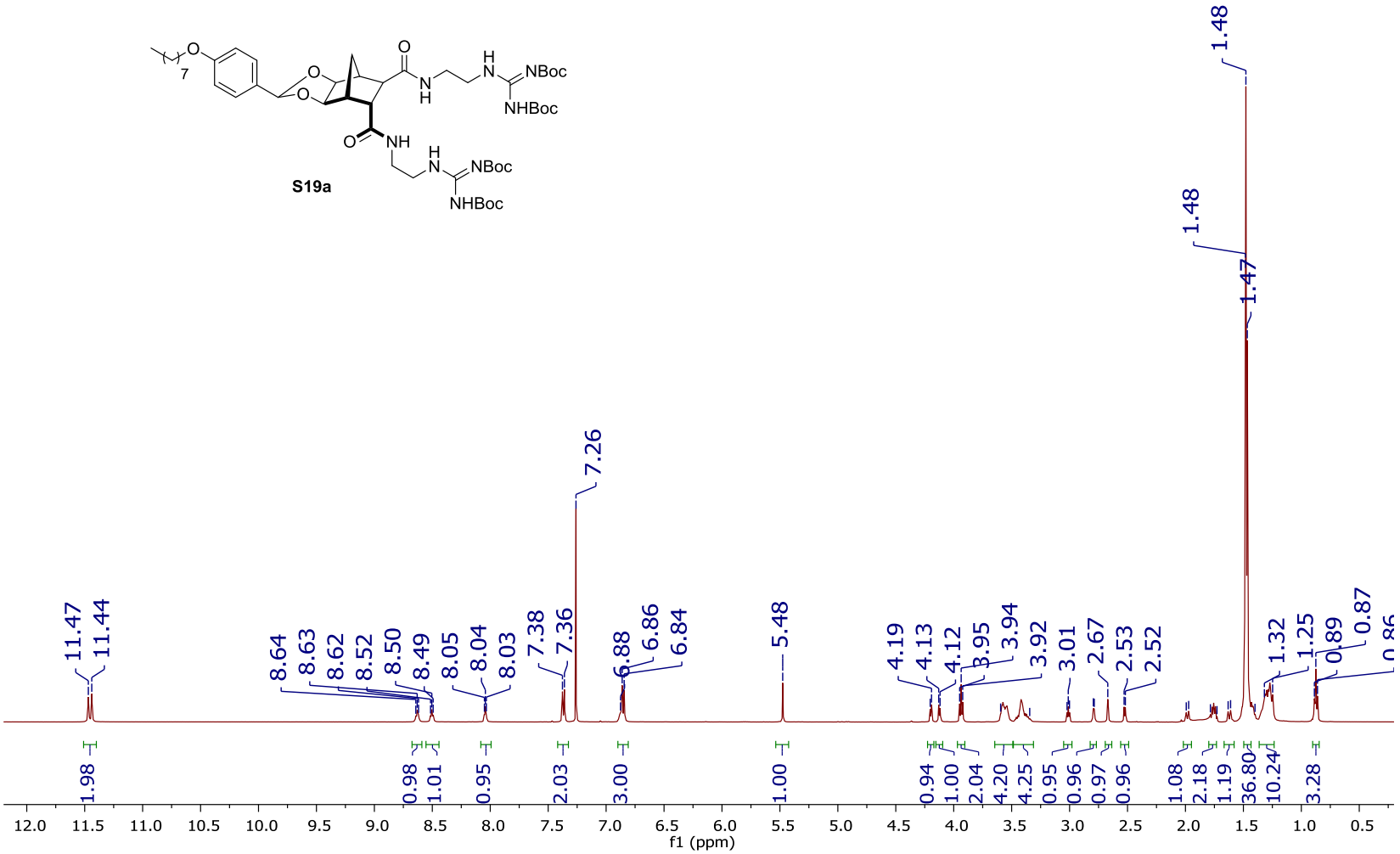

7c
NHBoc
NHBoc
7.260
6.845
6.681
5.069
5.013
4.638
4.136
4.126
3.969
3.958
2.571
2.544
2.536
2.424
2.413
1.816
1.796
1.471
1.437
1.432
1.243
0.874
1.388
1.95
2.08
1.00
1.03
0.97
7.87
0.89
0.96
0.92
0.91
0.92
1.98
47.83
3.01
f1 (ppm)


7c
14
O
O
O
N
H
NHBoc
O
NH
NHBoc
77.160
174.300
172.503
157.093
156.838
104.183
81.612
80.015
79.783
78.747
32.065
29.835
29.809
29.797
29.722
29.695
29.675
29.500
28.541
22.833
14.263
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

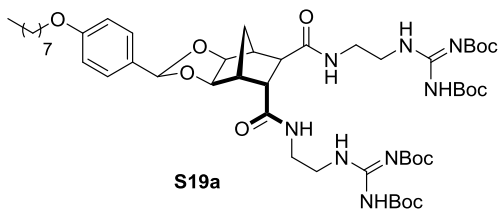

7d
NHBoc
NHBoc
7.260
7.198
7.074
7.056
6.967
6.798
6.781
5.270
4.663
4.001
3.902
3.340
3.250
2.646
2.591
2.557
1.923
1.820
1.800
1.521
1.501
1.433
1.429
1.249
0.875
0.80
2.13
0.96
2.07
1.82
1.00
1.00
1.02
2.07
8.19
0.97
2.03
1.05
1.03
1.00
2.04
1.00
2.17
1.15
18.84
12.12
3.06
f1 (ppm)


7d
NHBoc
NHBoc
NH
NH
O
O
O
O
O
7
174.407
172.523
157.519
156.974
156.834
133.351
129.264
114.549
103.245
81.710
79.855
78.876
77.157
68.135
34.754
31.932
29.809
29.489
29.442
29.360
28.543
26.182
22.772
14.216
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

SMH07-059C
SMH07-059C - 1H
PROTON CDCl3 {C:\Data_500\Shane} nmr 3

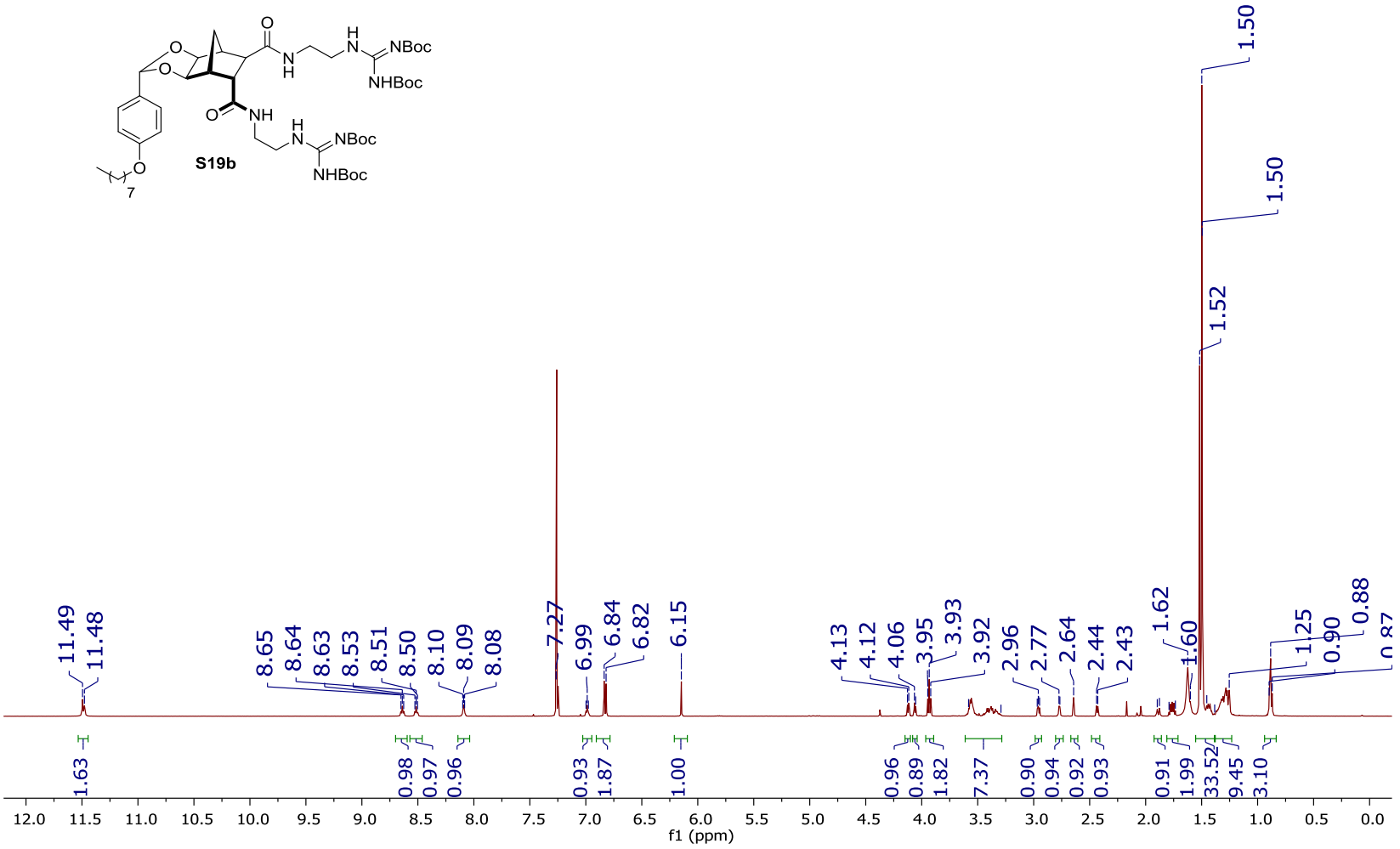


SMH07-059C
SMH07-059C - 13C
C13CPD CDCl3 {C:\Data_500\Shane} nmr 3

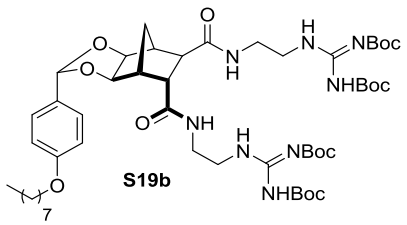


S19a

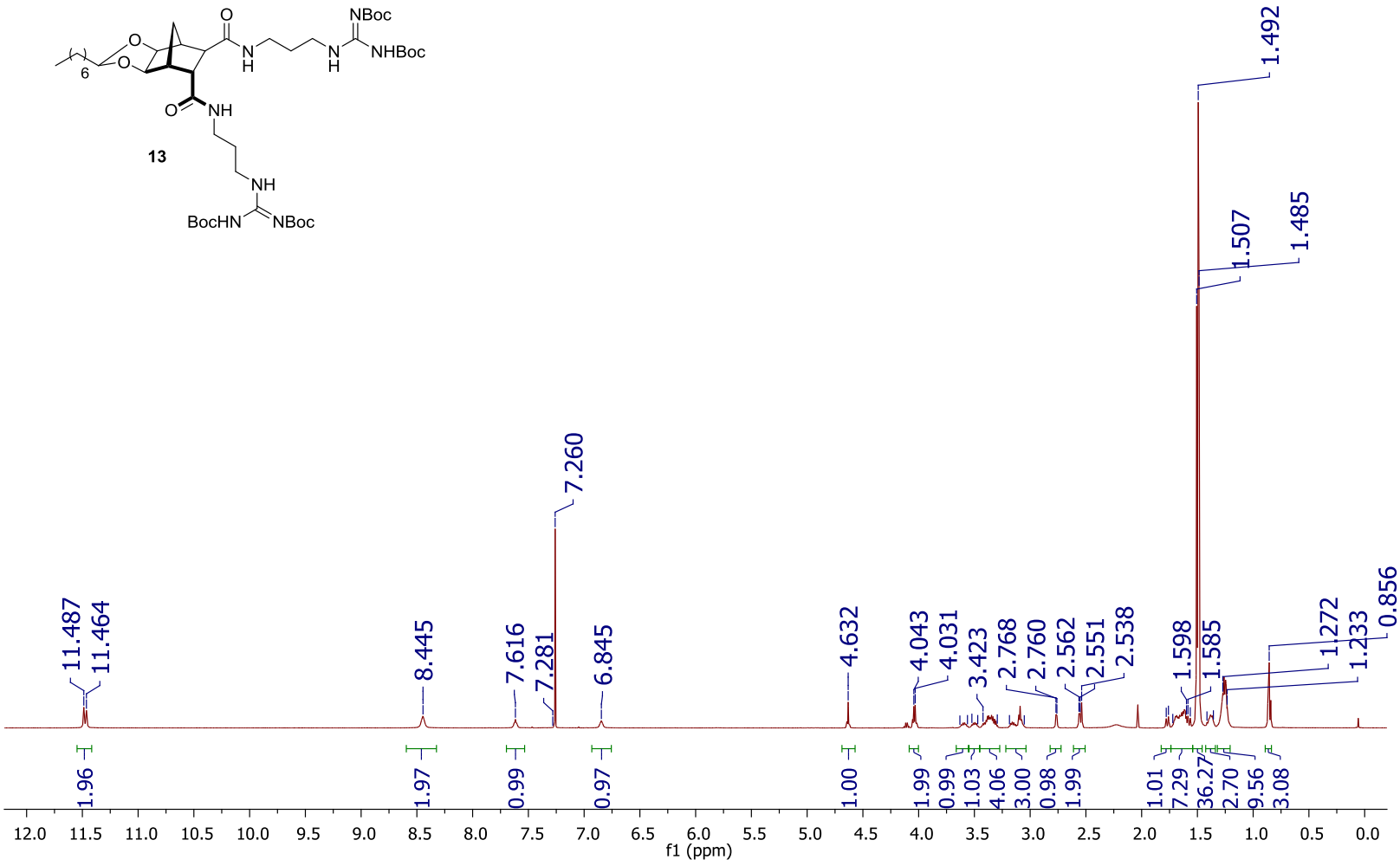
Endo phenyl (minor isomer)
SMH07-59B 1H

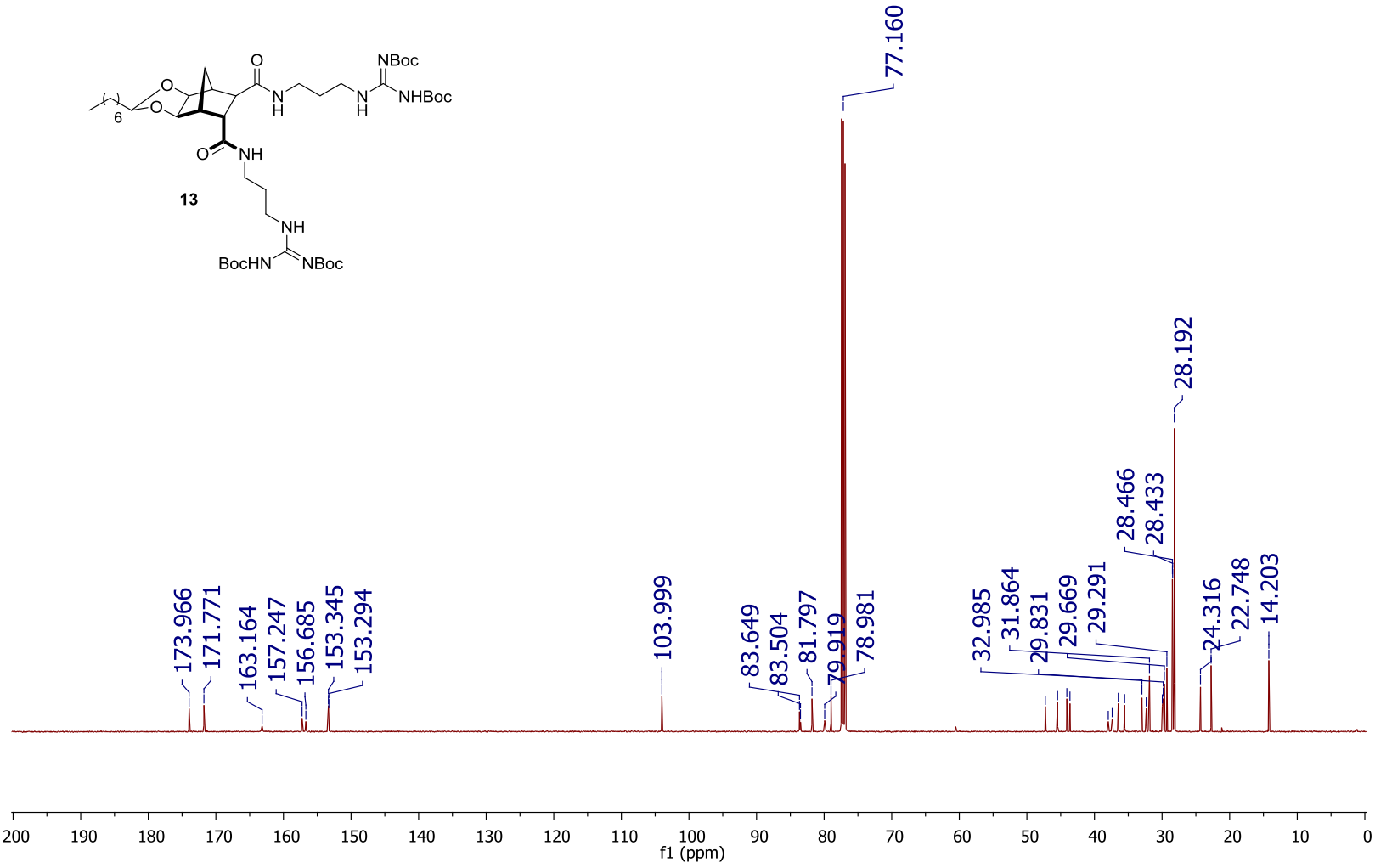


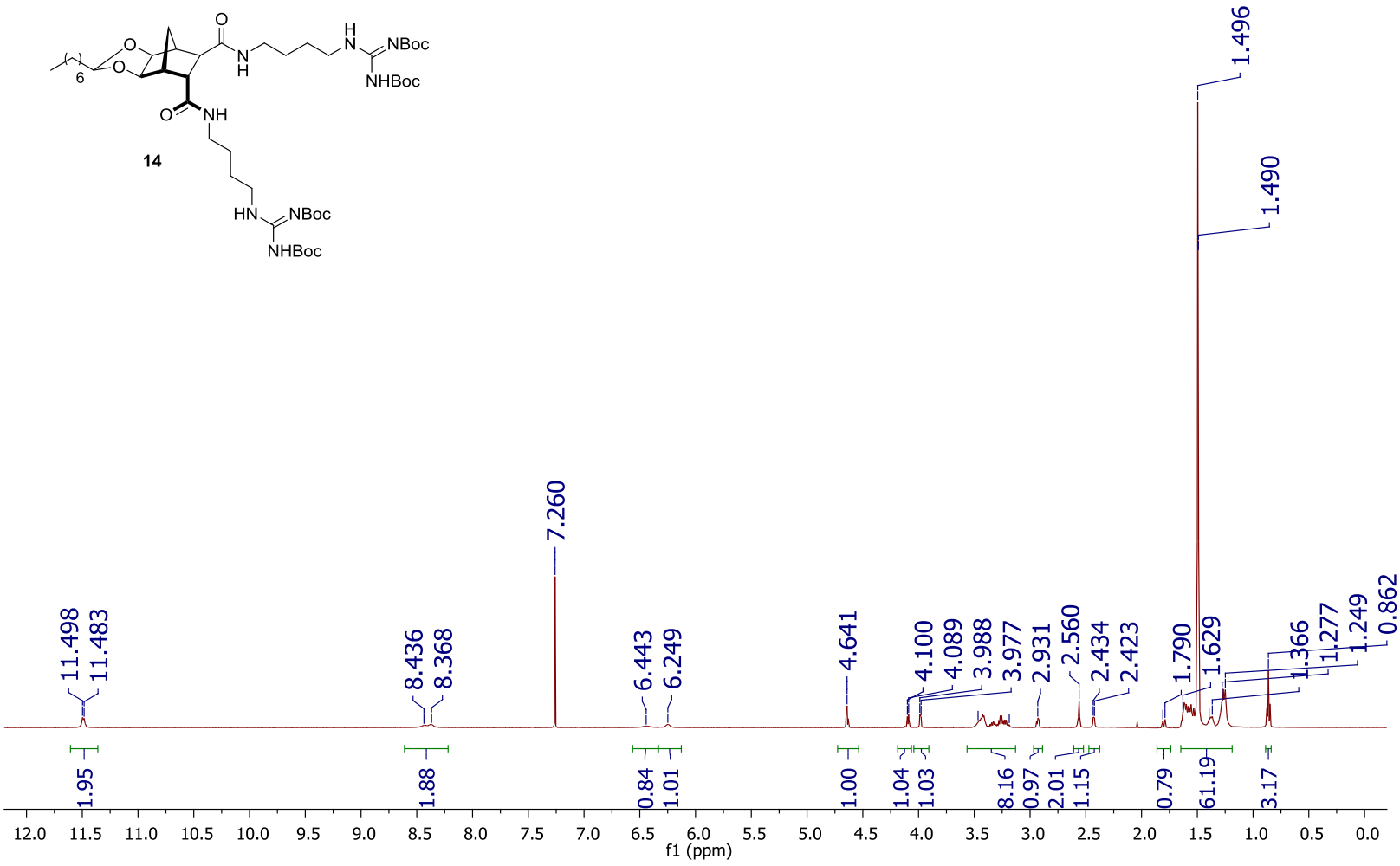
SMH07-059B
SMH07-059B - 13C
C13CPD CDCl3 {C:\Data_500\Shane} nmr 2

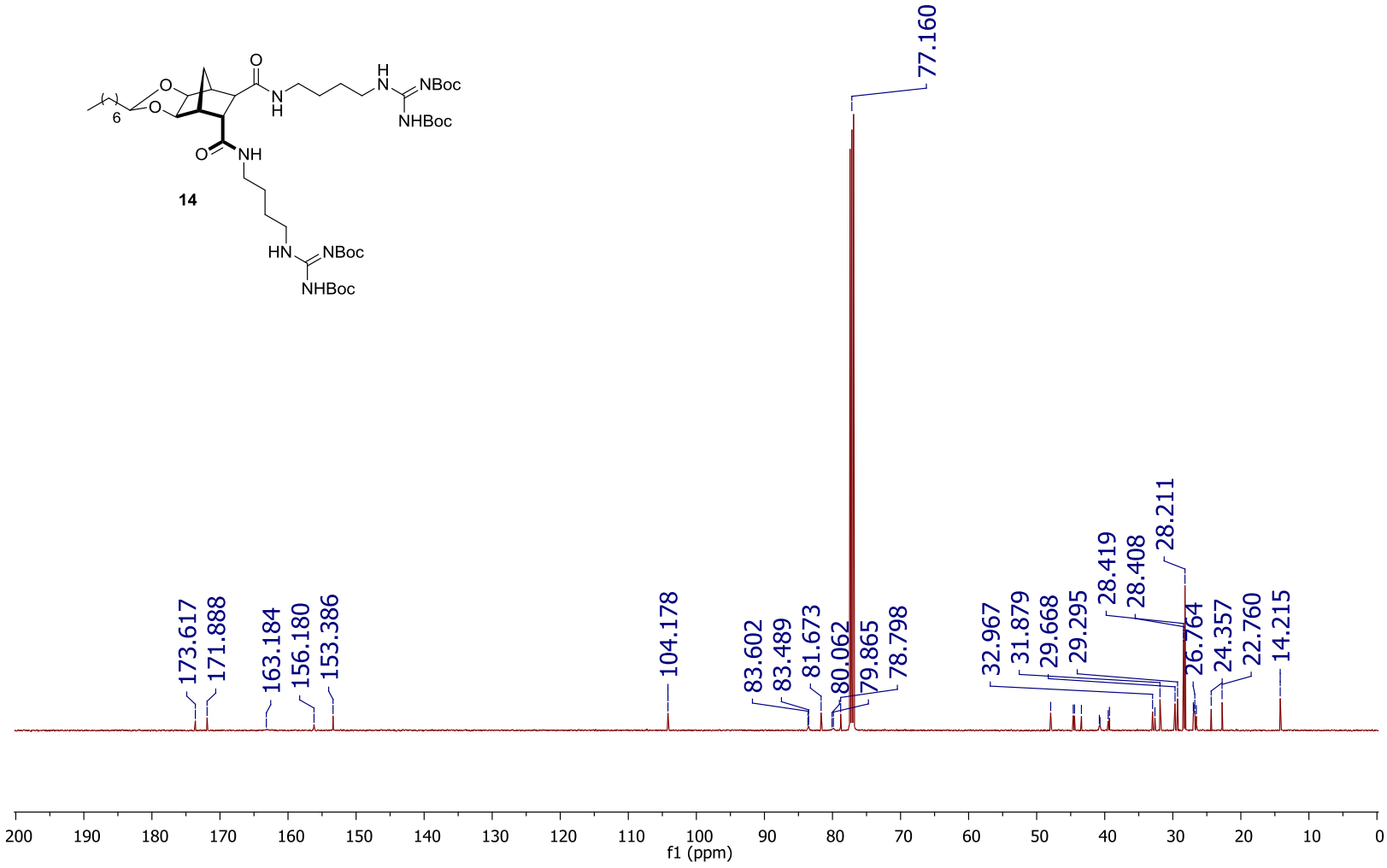


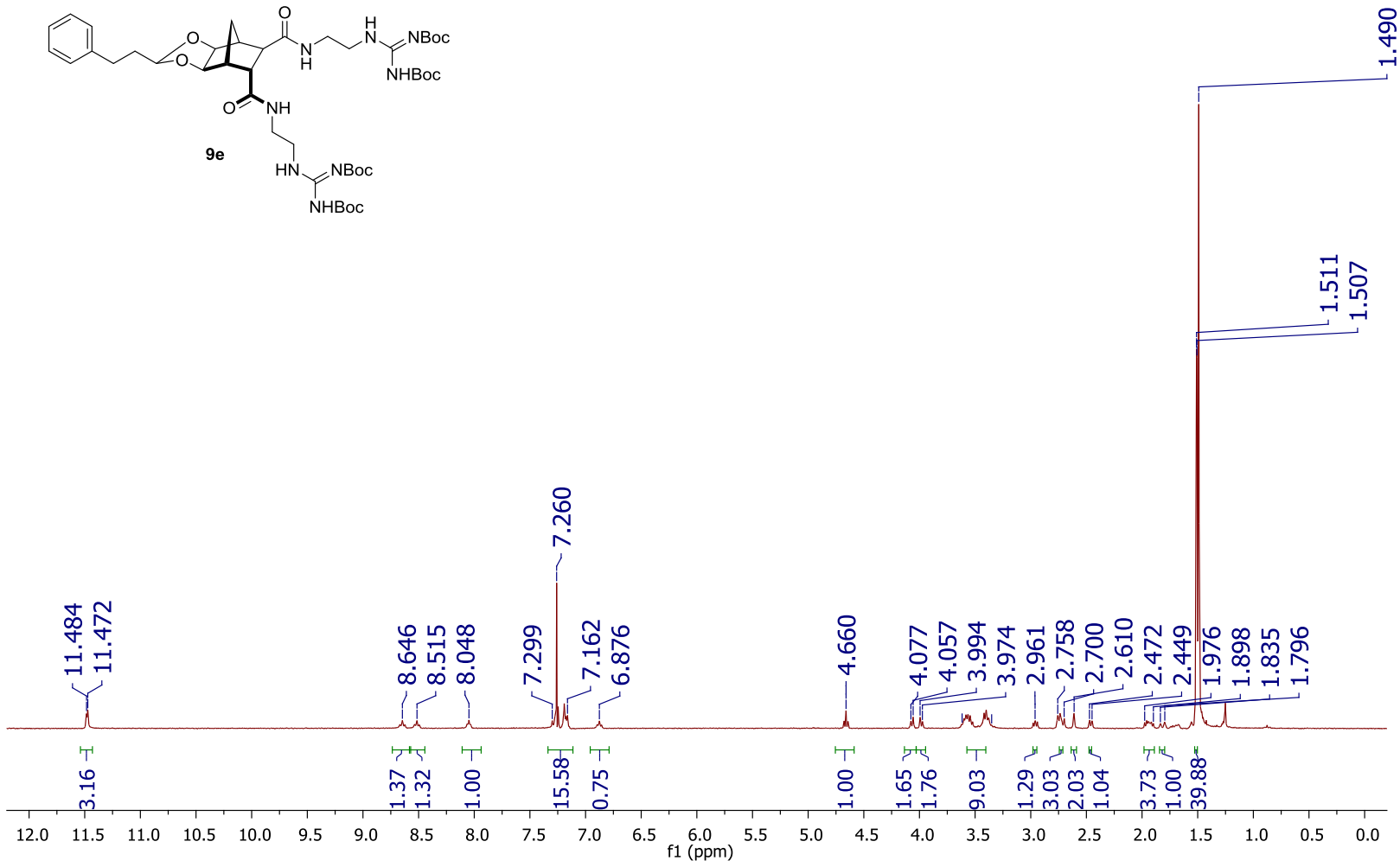
S19b

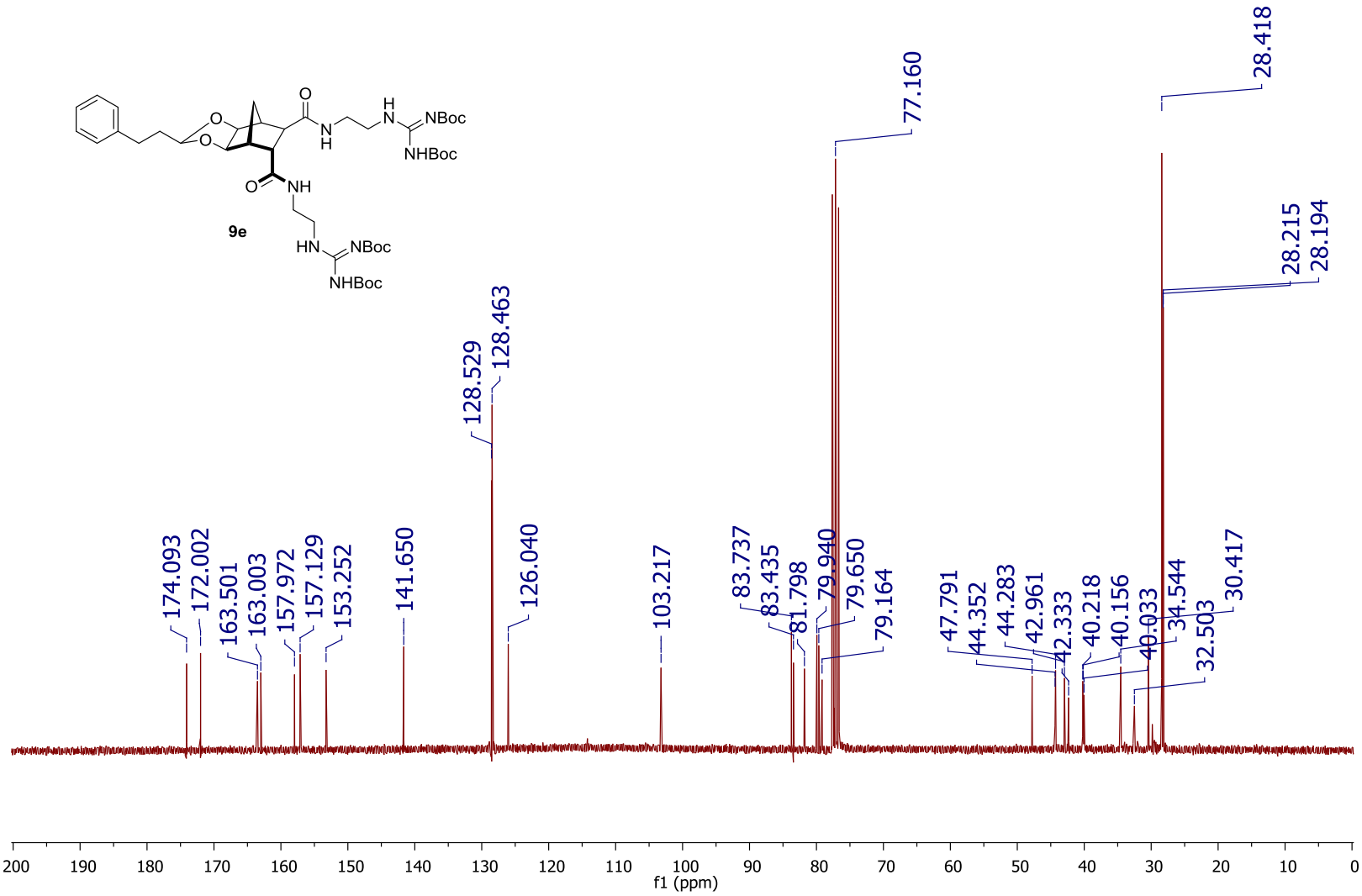

13
NBoc
NHBoc
BocHN
NBoc
11.487
11.464
8.445
7.616
7.281
7.260
6.845
4.632
4.043
4.031
3.423
2.768
2.760
2.562
2.551
2.538
1.598
1.585
1.492
1.507
1.485
1.272
1.233
0.856
1.96
1.97
0.99
0.97
1.00
1.99
0.99
1.03
4.06
3.00
0.98
1.99
1.01
7.29
36.27
2.70
9.56
3.08
f1 (ppm)

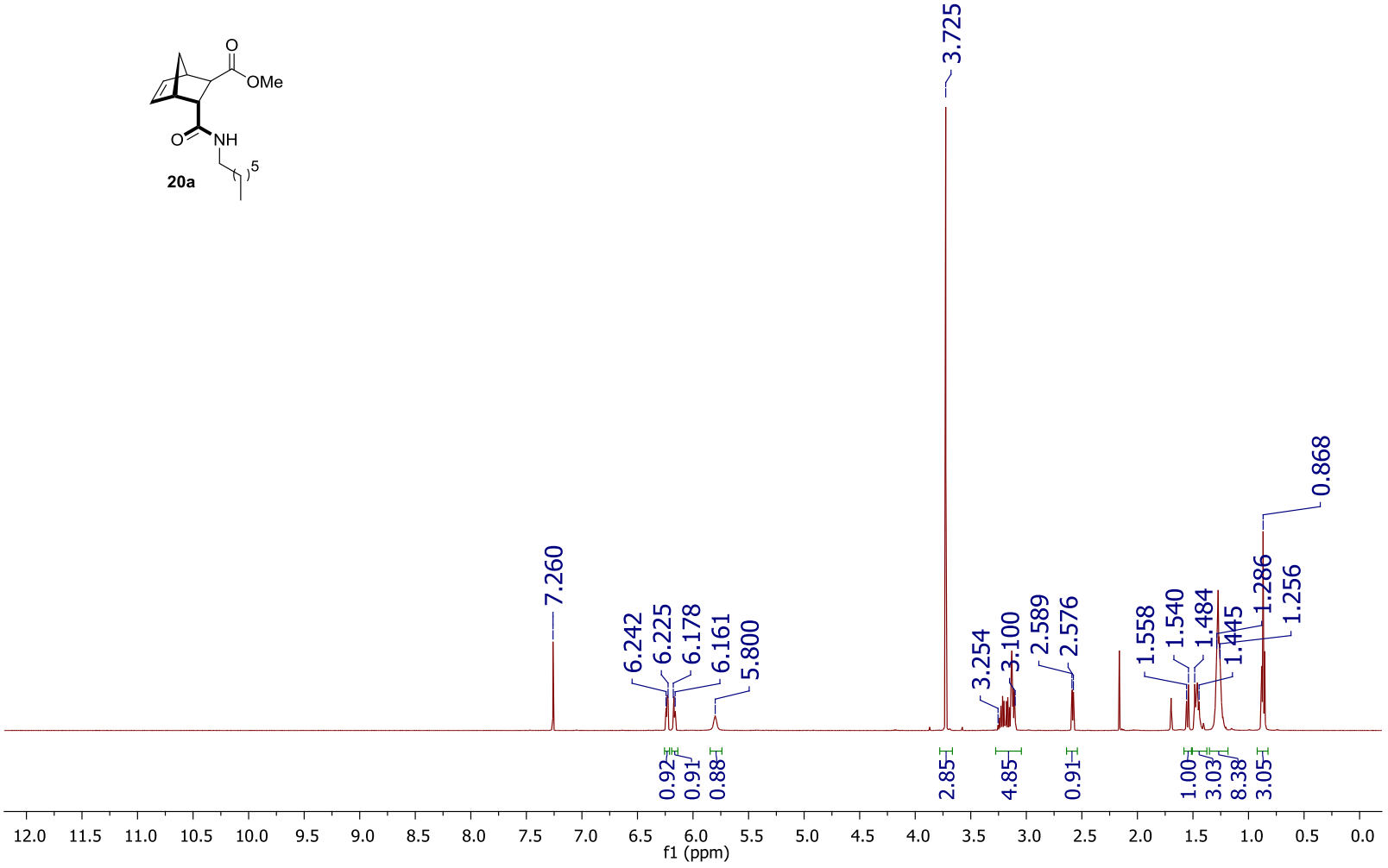

13
77.160
28.192
28.466
28.433
173.966
171.771
163.164
157.247
156.685
153.345
153.294
103.999
83.649
83.504
81.797
79.919
78.981
32.985
31.864
29.831
29.669
29.291
24.316
22.748
14.203
f1 (ppm)

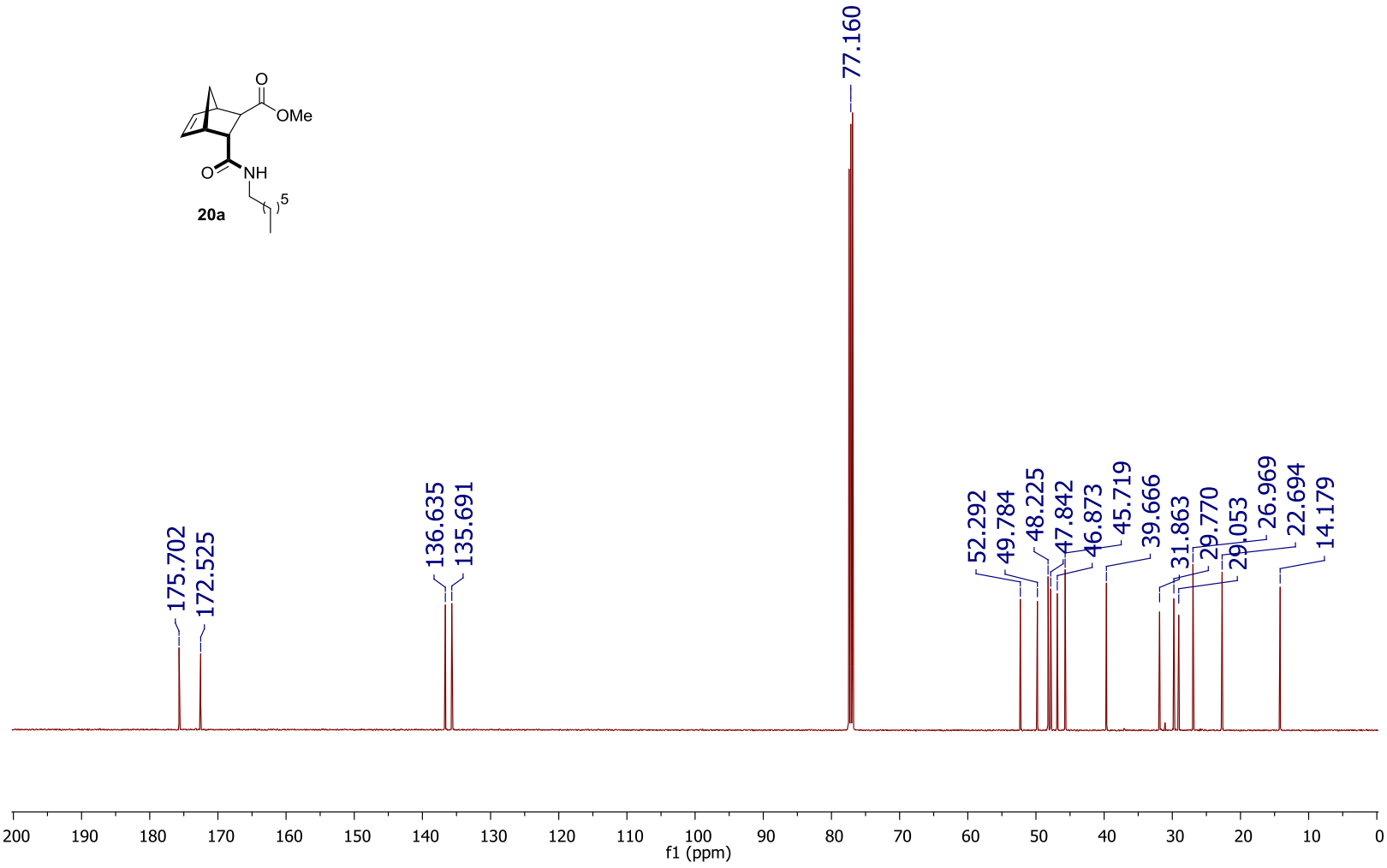

14
11.498
11.483
8.436
8.368
7.260
6.443
6.249
4.641
4.100
4.089
3.988
3.977
2.931
2.560
2.434
2.423
1.790
1.629
1.496
1.490
1.366
1.277
1.249
0.862
1.95
1.88
0.84
1.01
1.00
1.04
1.03
8.16
0.97
2.01
1.15
0.79
61.19
3.17
f1 (ppm)

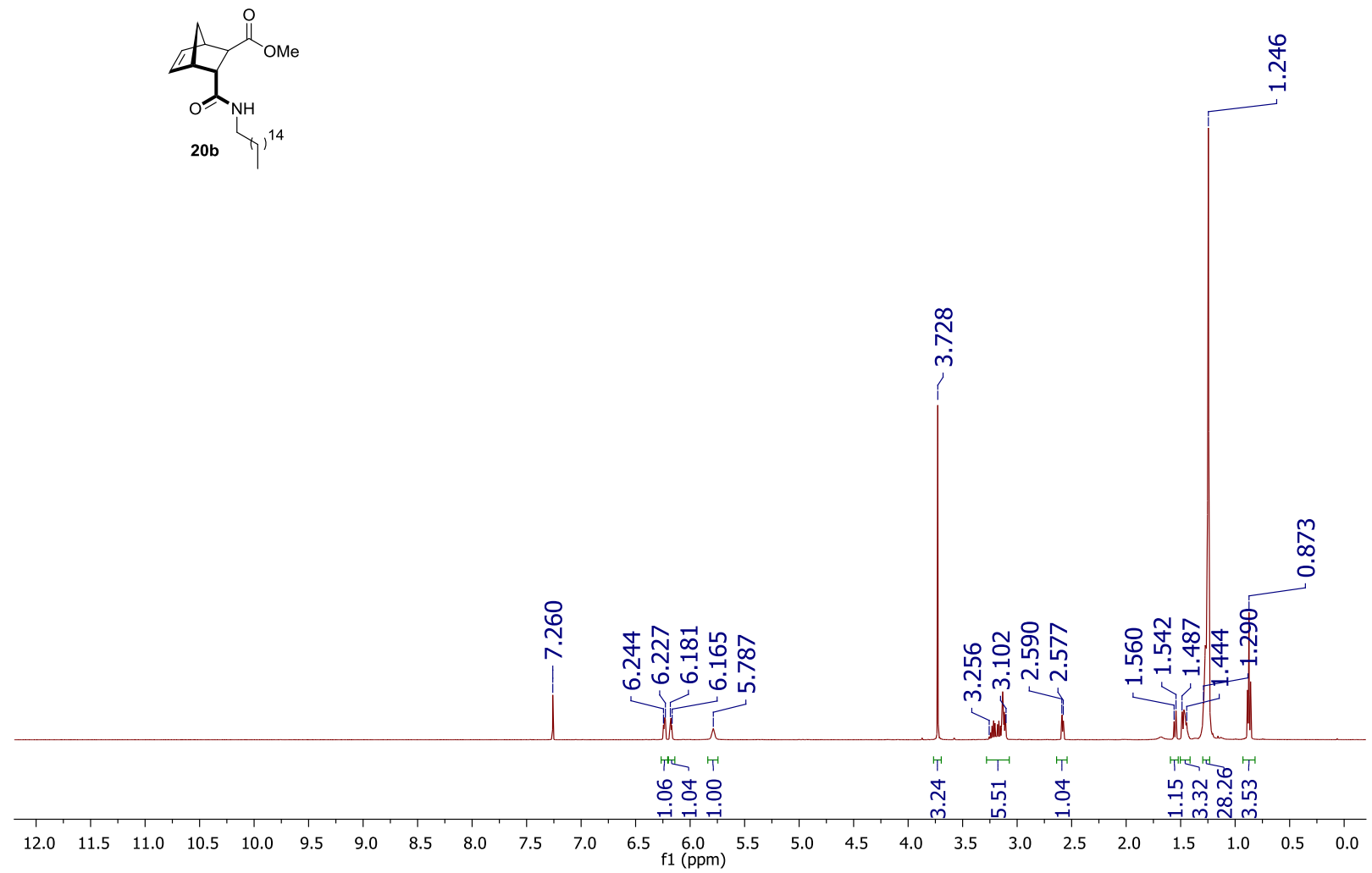

14
77.160
173.617
171.888
163.184
156.180
153.386
104.178
83.602
83.489
81.673
80.062
79.865
78.798
32.967
31.879
29.668
29.295
28.419
28.408
28.211
26.764
24.357
22.760
14.215
f1 (ppm)

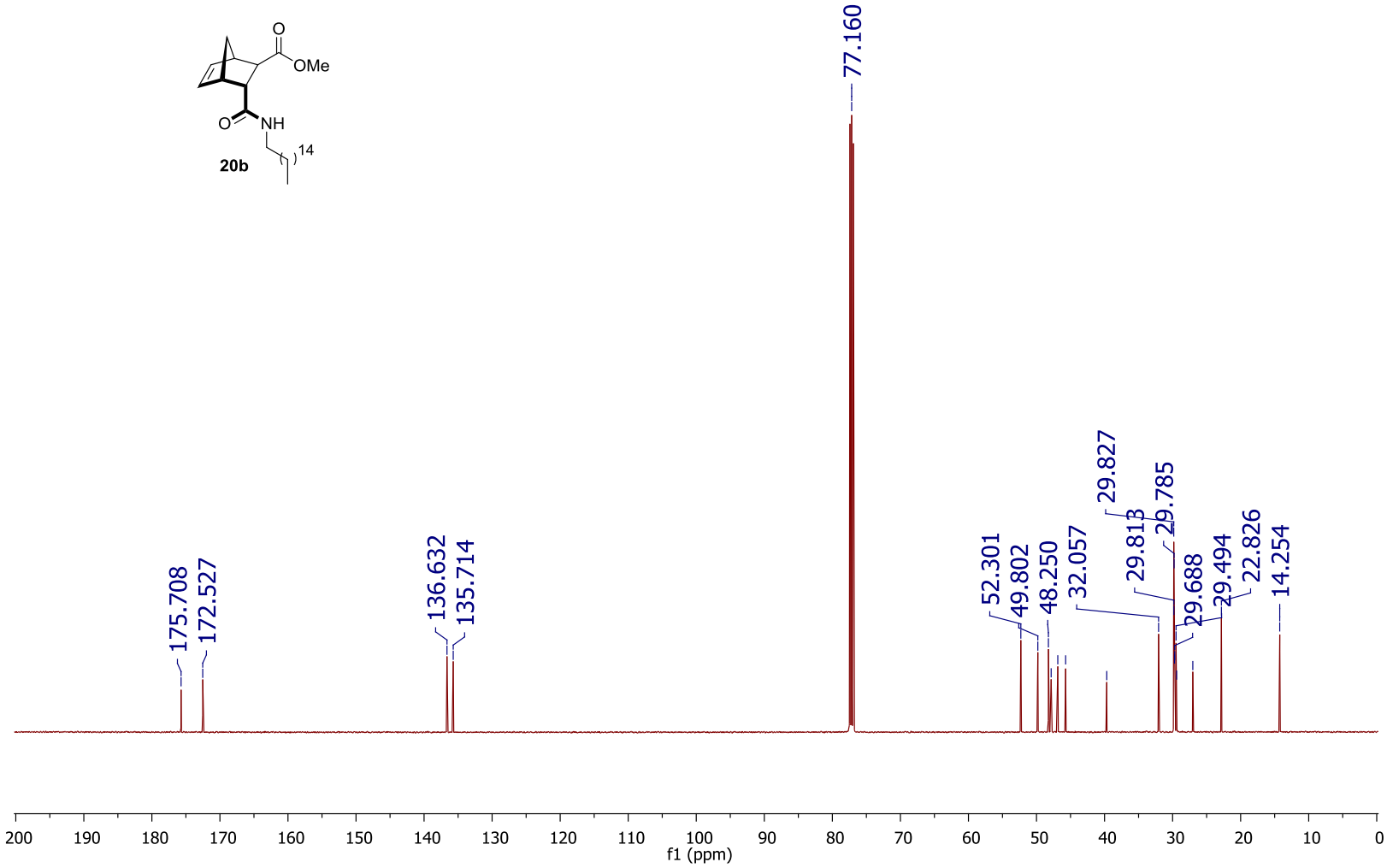

9e
11.484
11.472
8.646
8.515
8.048
7.299
7.260
7.162
6.876
4.660
4.077
4.057
3.994
3.974
2.961
2.758
2.700
2.610
2.472
2.449
1.976
1.898
1.835
1.796
1.511
1.507
1.490
3.16
1.37
1.32
1.00
15.58
0.75
1.00
1.65
1.76
9.03
1.29
3.03
2.03
1.04
3.73
1.00
39.88
f1 (ppm)

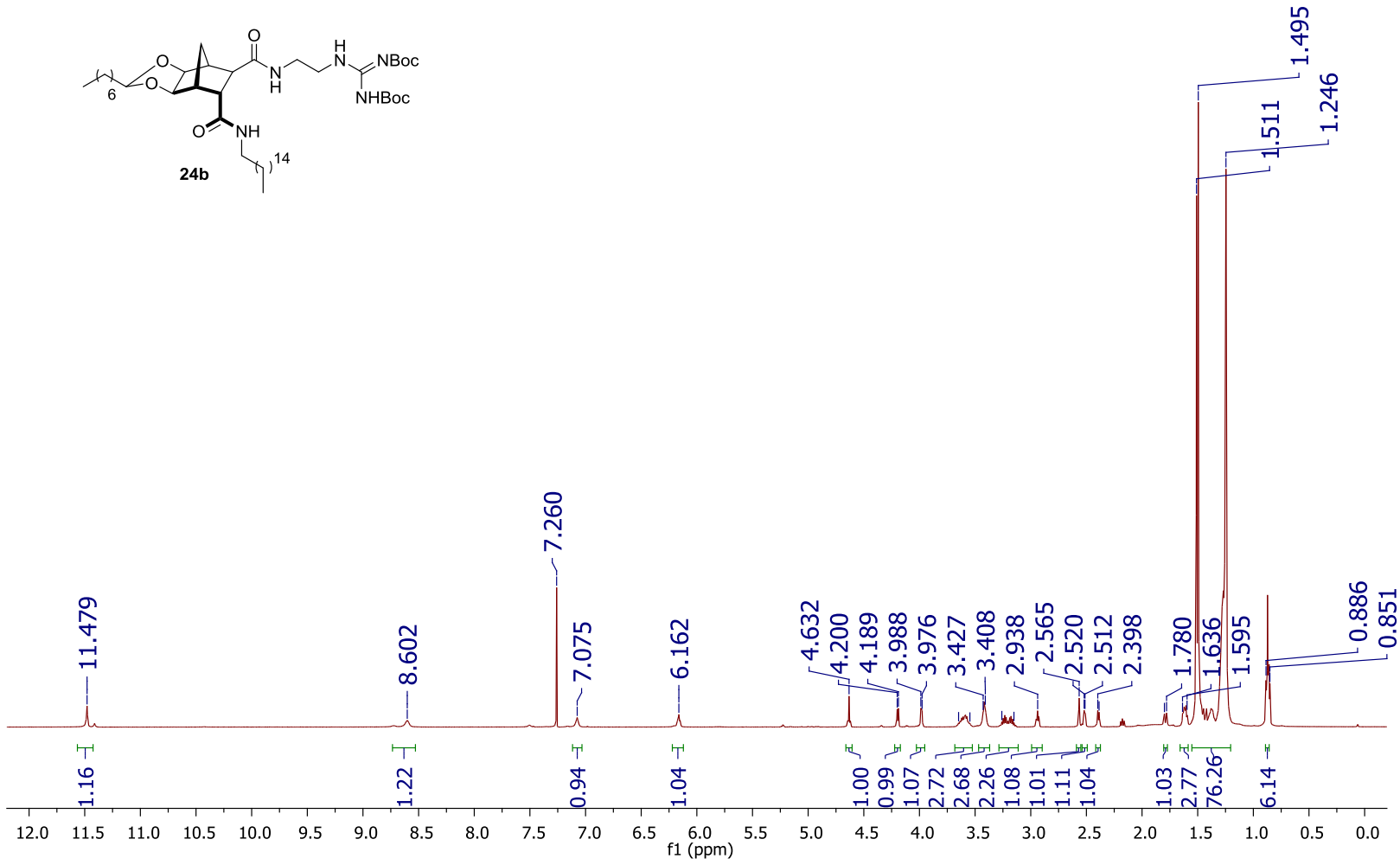

9e
NBoc
NHBoc
NH
HN
O
174.093
172.002
163.501
163.003
157.972
157.129
153.252
141.650
128.529
128.463
126.040
103.217
83.737
83.435
81.798
79.940
79.650
79.164
77.160
47.791
44.352
44.283
42.961
42.333
40.218
40.156
40.033
34.544
32.503
30.417
28.418
28.215
28.194
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

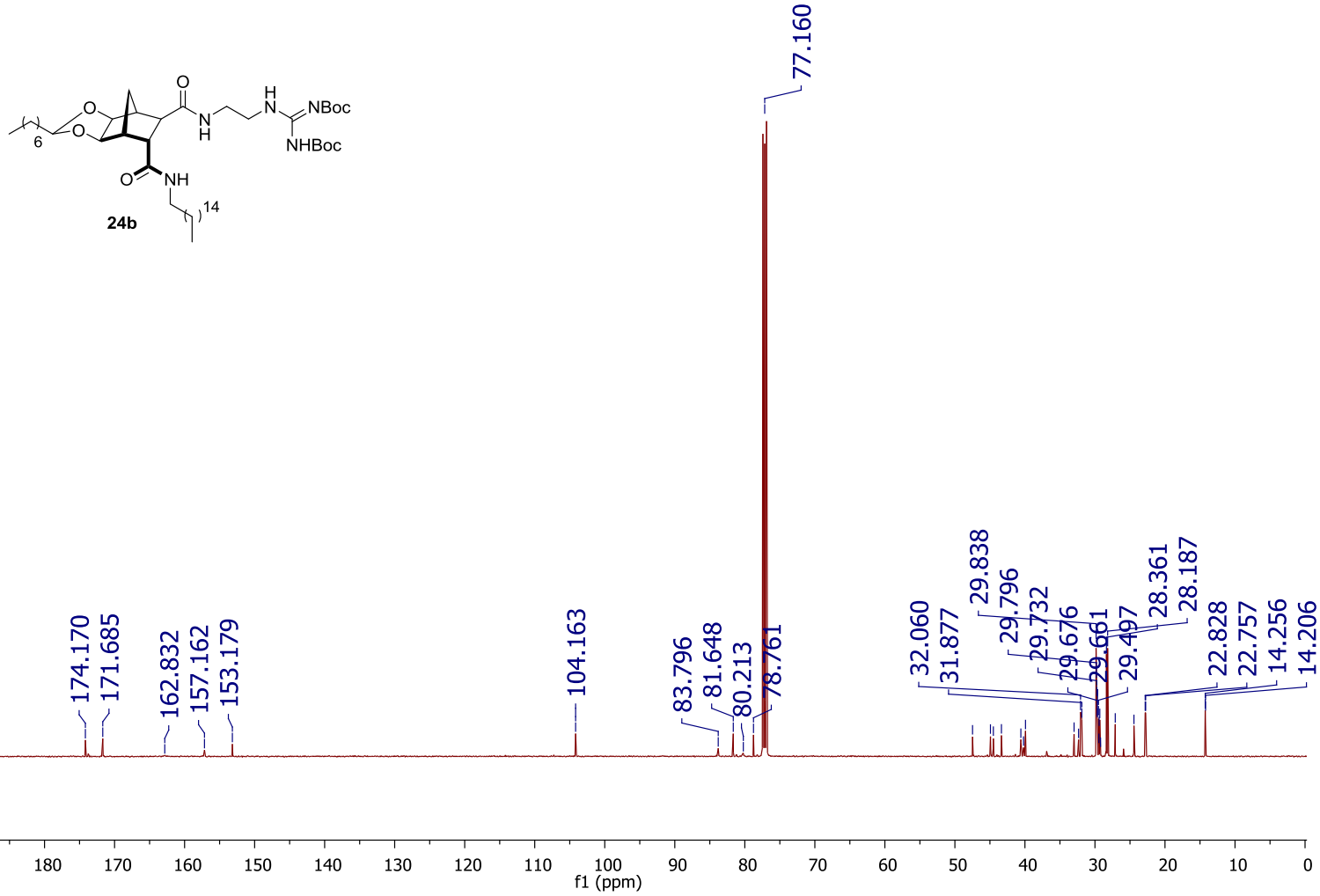

O
OMe
O
NH
5
20a
7.260
6.242
6.225
6.178
6.161
5.800
3.725
3.254
3.100
2.589
2.576
1.558
1.540
1.484
1.445
1.286
1.256
0.868
0.92
0.91
0.88
2.85
4.85
0.91
1.00
3.03
8.38
3.05
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

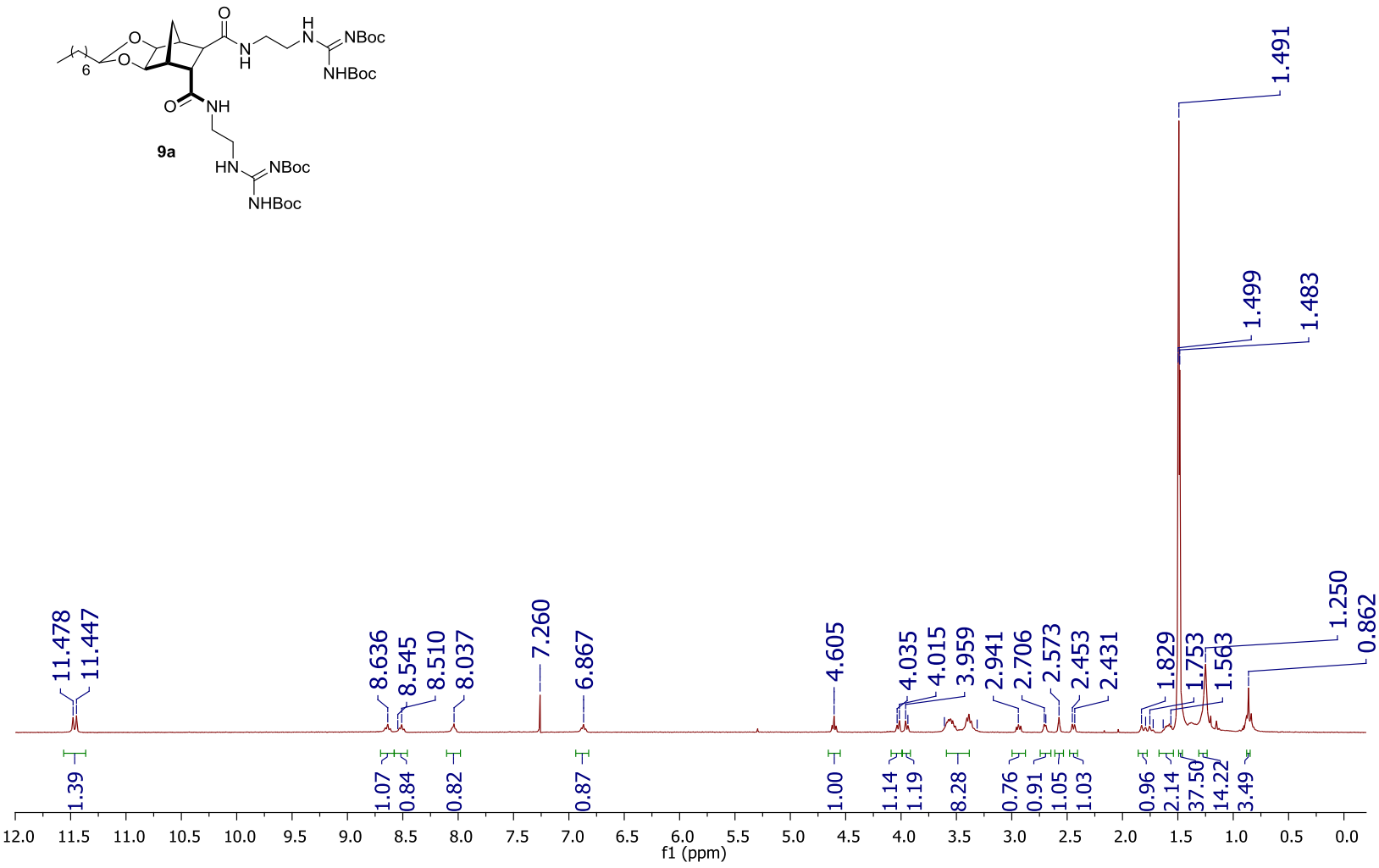

O
OMe
O
NH
5
20a
77.160
175.702
172.525
136.635
135.691
52.292
49.784
48.225
47.842
46.873
45.719
39.666
31.863
29.770
29.053
26.969
22.694
14.179
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

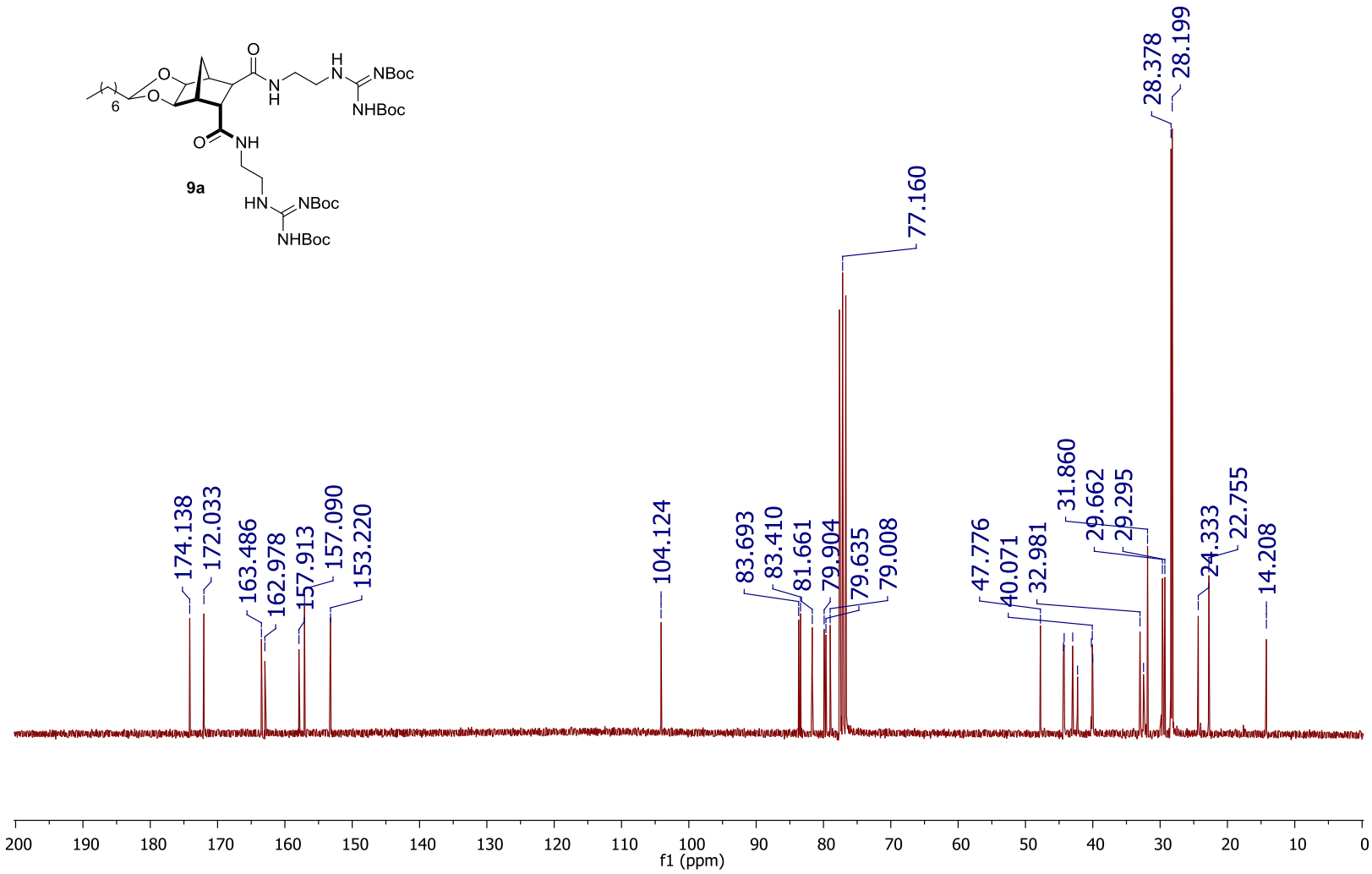

O
OMe
O
NH
14
20b
7.260
6.244
6.227
6.181
6.165
5.787
3.728
3.256
3.102
2.590
2.577
1.560
1.542
1.487
1.444
1.290
1.246
0.873
1.06
1.04
1.00
3.24
5.51
1.04
1.15
3.32
28.26
3.53
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

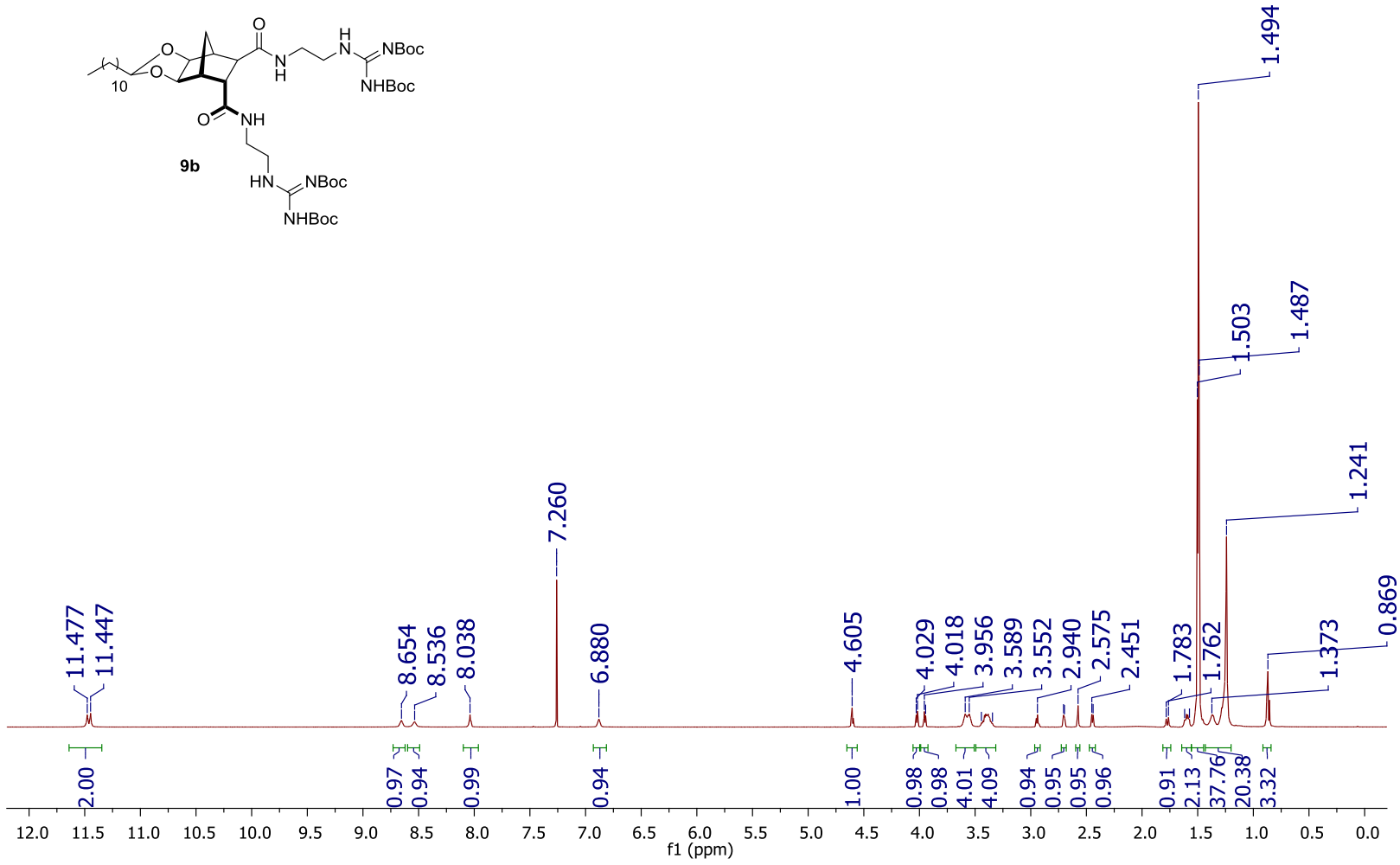

O
OMe
O
NH
14
20b
77.160
175.708
172.527
136.632
135.714
52.301
49.802
48.250
32.057
29.827
29.813
29.785
29.688
29.494
22.826
14.254
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

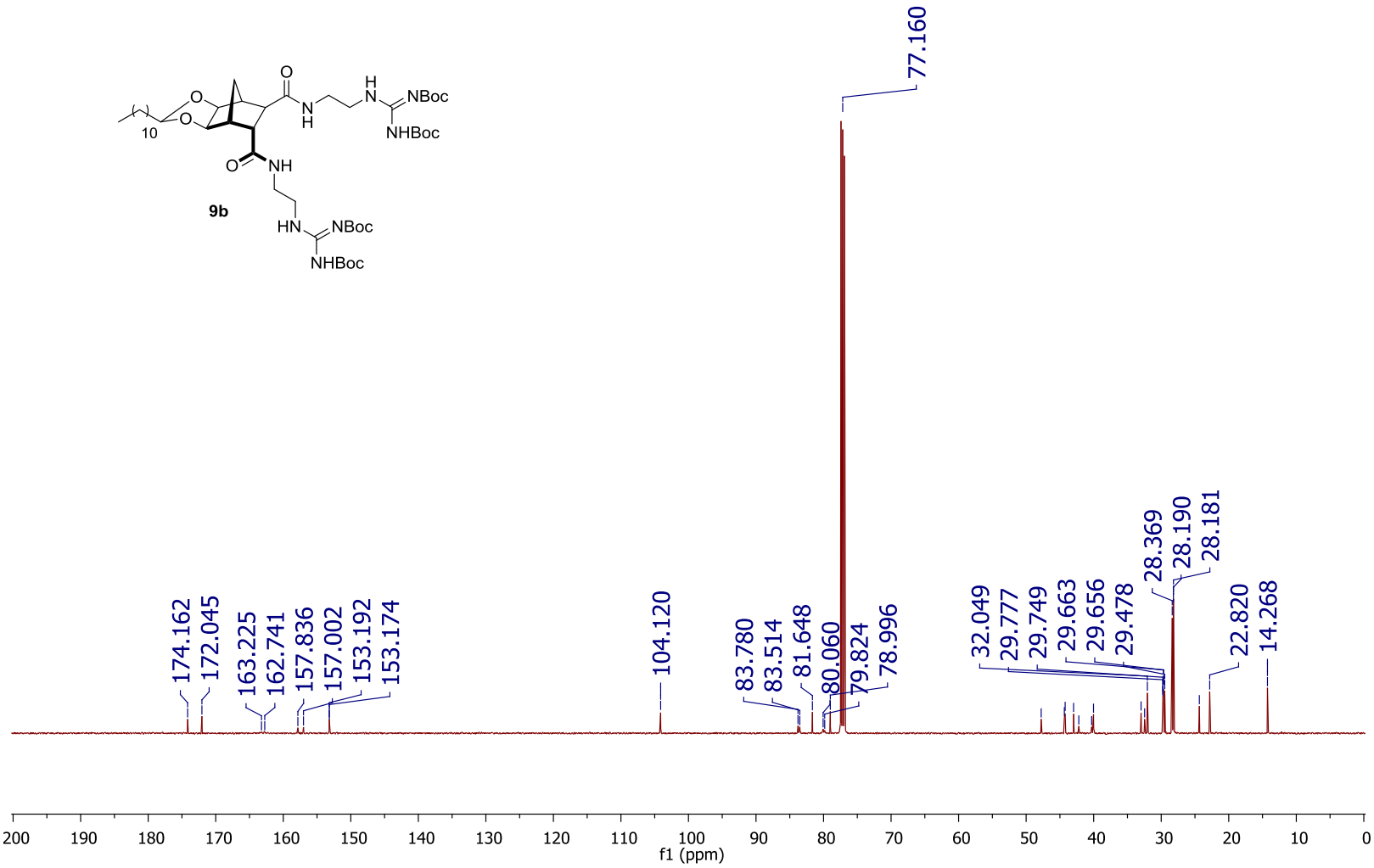

24b
11.479
8.602
7.260
7.075
6.162
4.632
4.200
4.189
3.988
3.976
3.427
3.408
2.938
2.565
2.520
2.512
2.398
1.780
1.636
1.595
1.511
1.495
1.246
0.886
0.851
1.16
1.22
0.94
1.04
1.00
0.99
1.07
2.72
2.68
2.26
1.08
1.01
1.11
1.04
1.03
2.77
76.26
6.14
f1 (ppm)

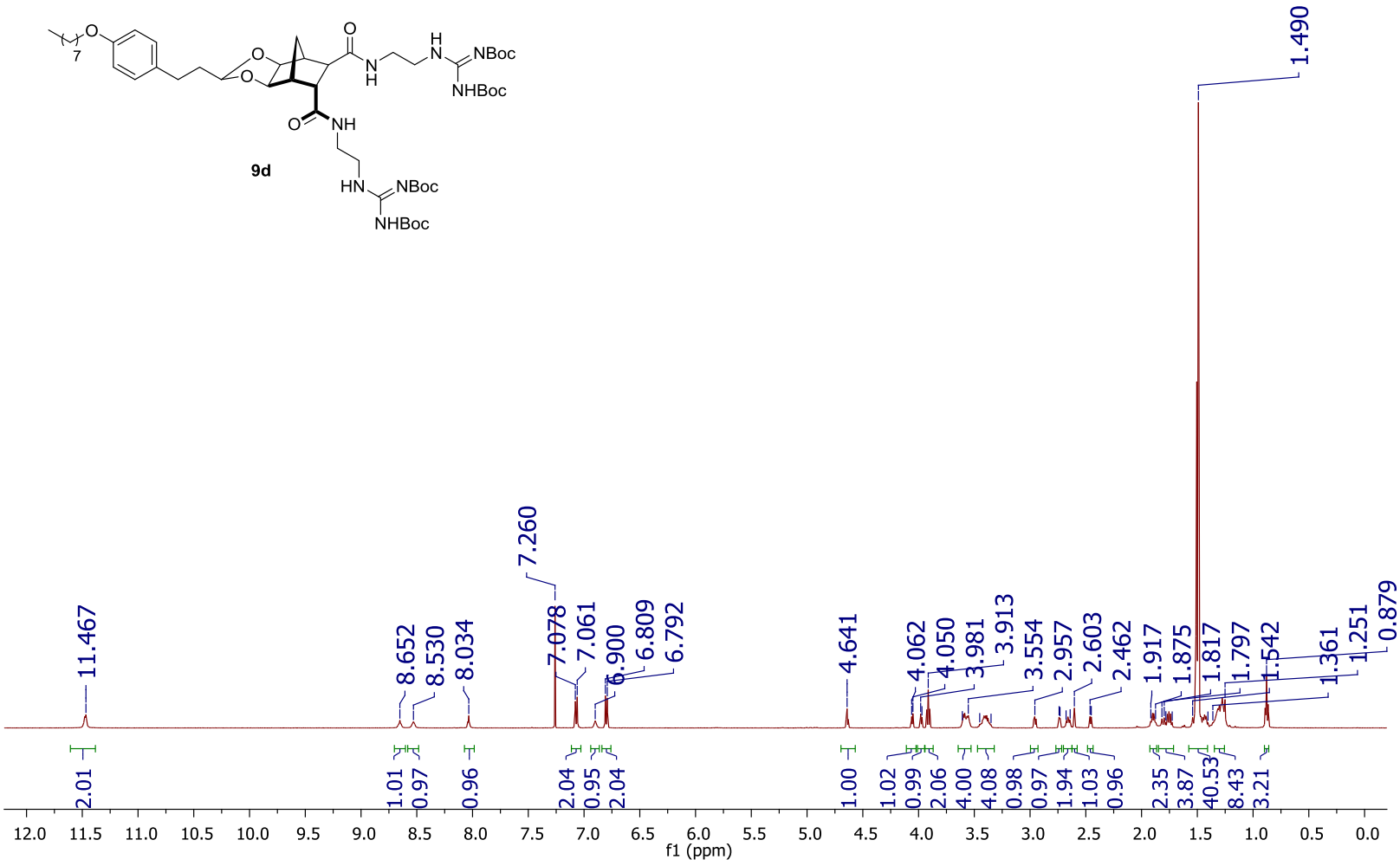

24b
77.160
174.170
171.685
162.832
157.162
153.179
104.163
83.796
81.648
80.213
78.761
32.060
31.877
29.838
29.796
29.732
29.676
29.661
29.497
28.361
28.187
22.828
22.757
14.256
14.206
f1 (ppm)

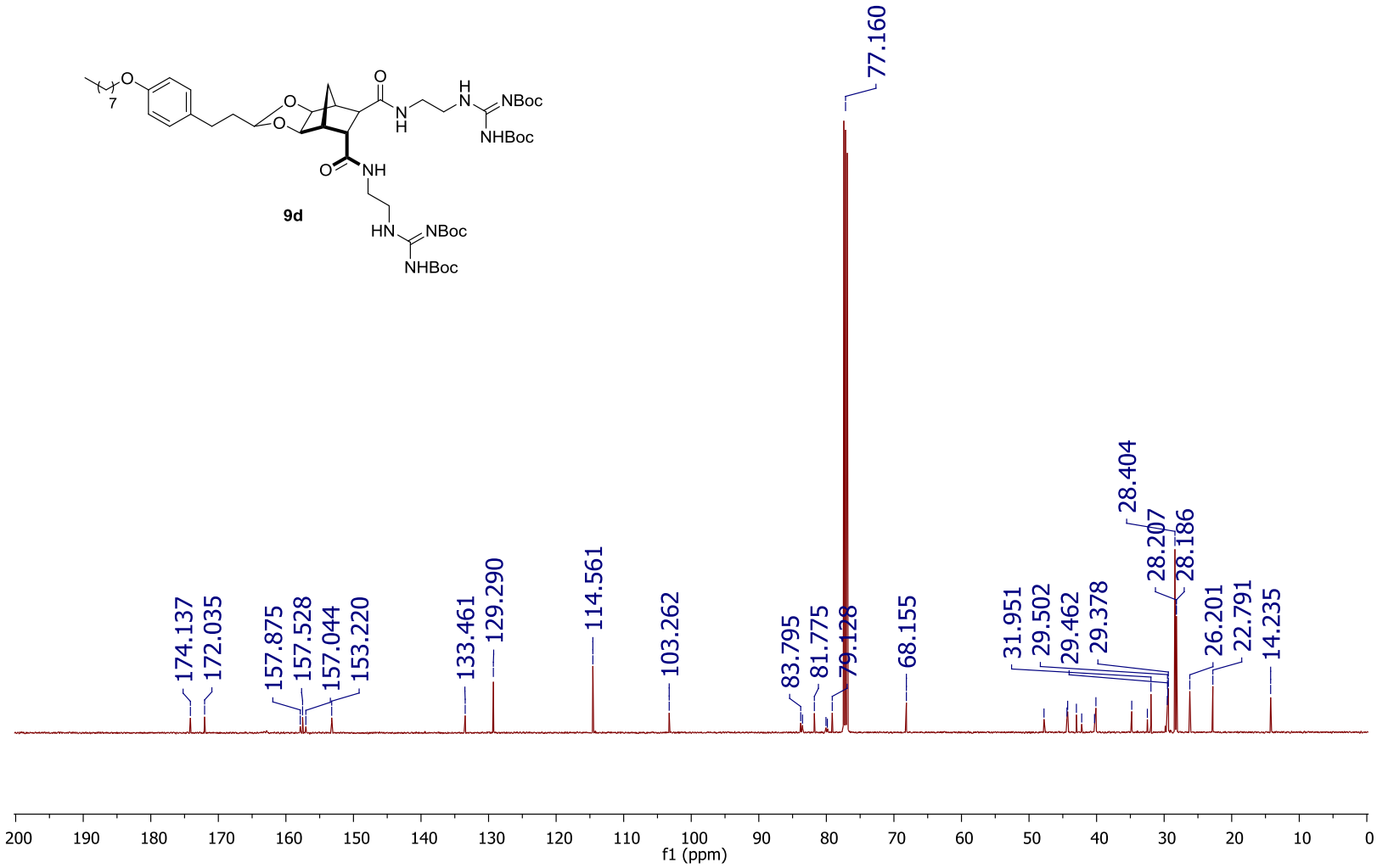

9a
11.478
11.447
8.636
8.545
8.510
8.037
7.260
6.867
4.605
4.035
4.015
3.959
2.941
2.706
2.573
2.453
2.431
1.829
1.753
1.563
1.491
1.499
1.483
1.250
0.862
1.39
1.07
0.84
0.82
0.87
1.00
1.14
1.19
8.28
0.76
0.91
1.05
1.03
0.96
2.14
37.50
14.22
3.49
f1 (ppm)

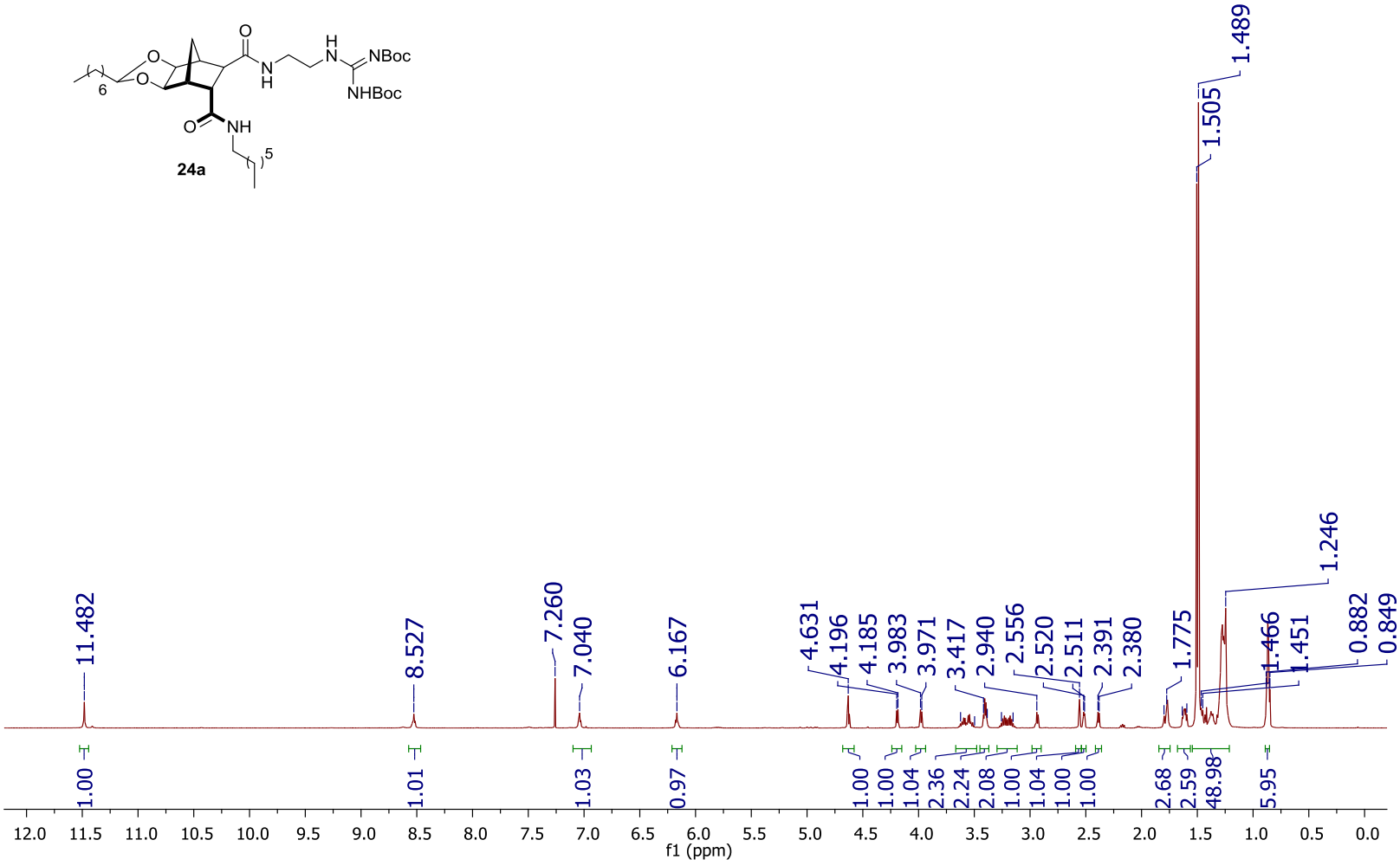

9a
174.138
172.033
163.486
162.978
157.913
157.090
153.220
104.124
83.693
83.410
81.661
79.904
79.635
79.008
77.160
47.776
40.071
32.981
31.860
29.662
29.295
28.378
28.199
24.333
22.755
14.208
f1 (ppm)

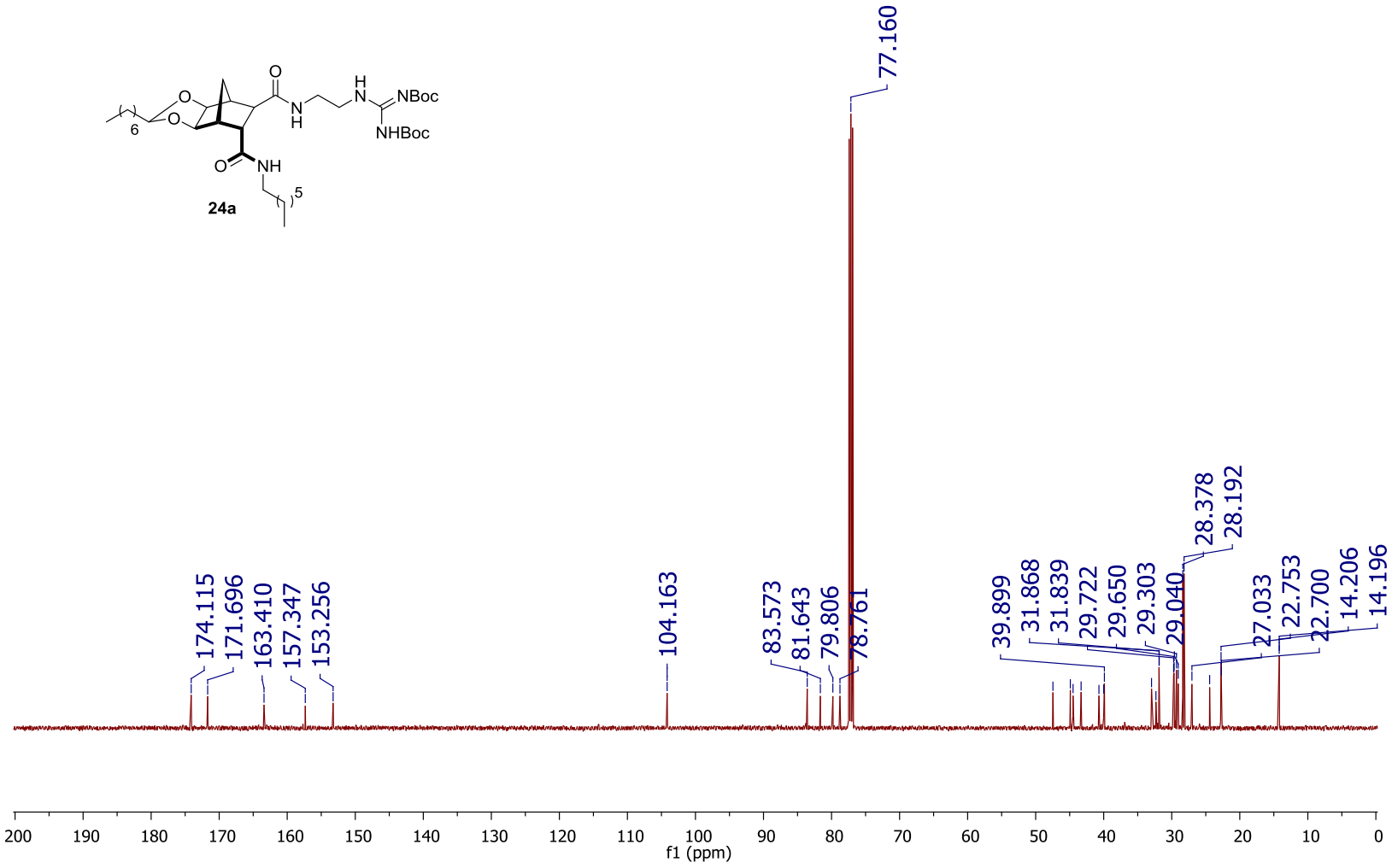

9b
11.477
11.447
8.654
8.536
8.038
7.260
6.880
4.605
4.029
4.018
3.956
3.589
3.552
2.940
2.575
2.451
1.783
1.762
1.494
1.503
1.487
1.241
1.373
0.869
2.00
0.97
0.94
0.99
0.94
1.00
0.98
0.98
4.01
4.09
0.94
0.95
0.95
0.96
0.91
2.13
37.76
20.38
3.32
f1 (ppm)

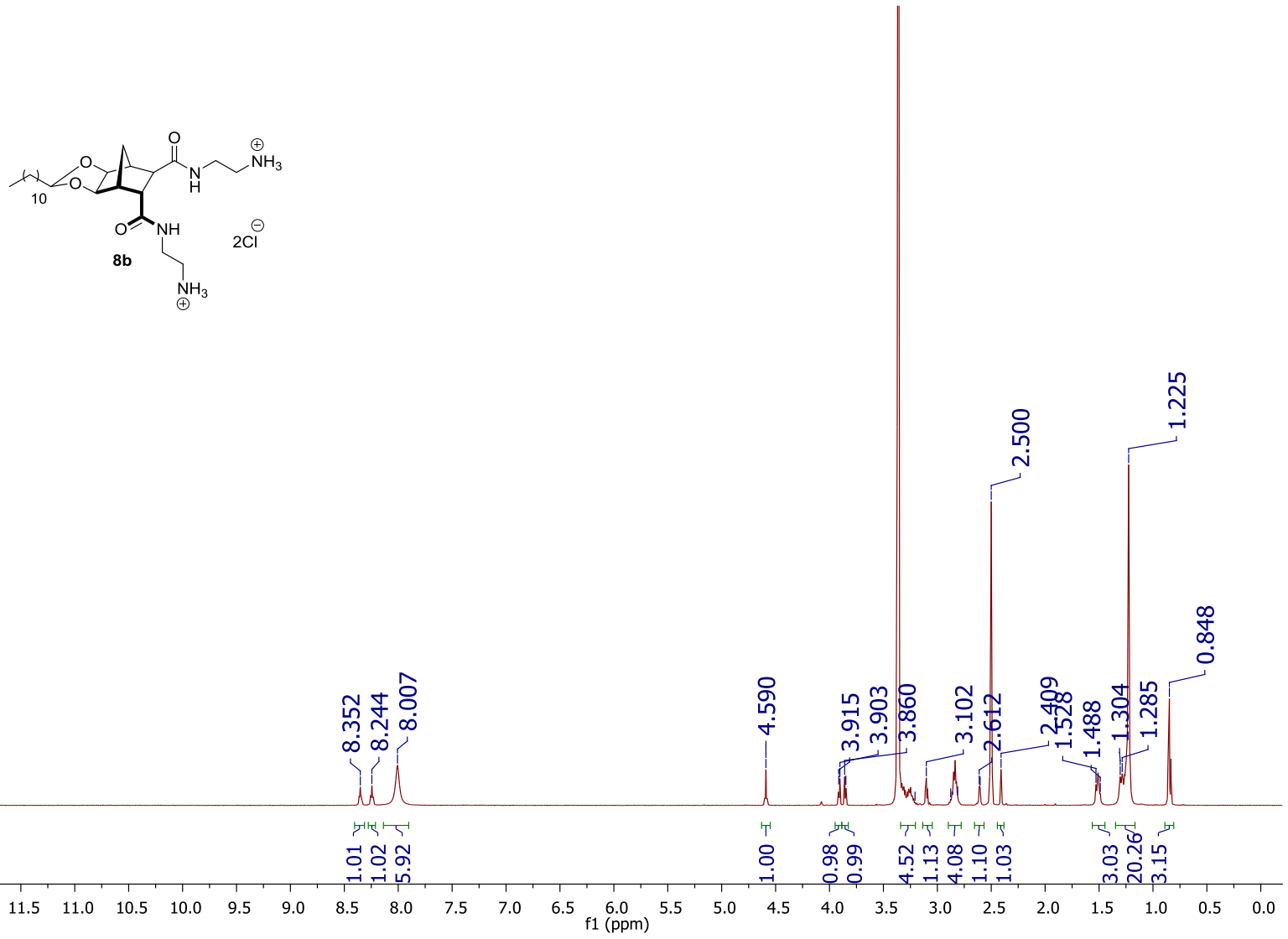

9b
10
NBoc
NHBoc
NBoc
NHBoc
77.160
174.162
172.045
163.225
162.741
157.836
157.002
153.192
153.174
104.120
83.780
83.514
81.648
80.060
79.824
78.996
32.049
29.777
29.749
29.663
29.656
29.478
28.369
28.190
28.181
22.820
14.268
f1 (ppm)

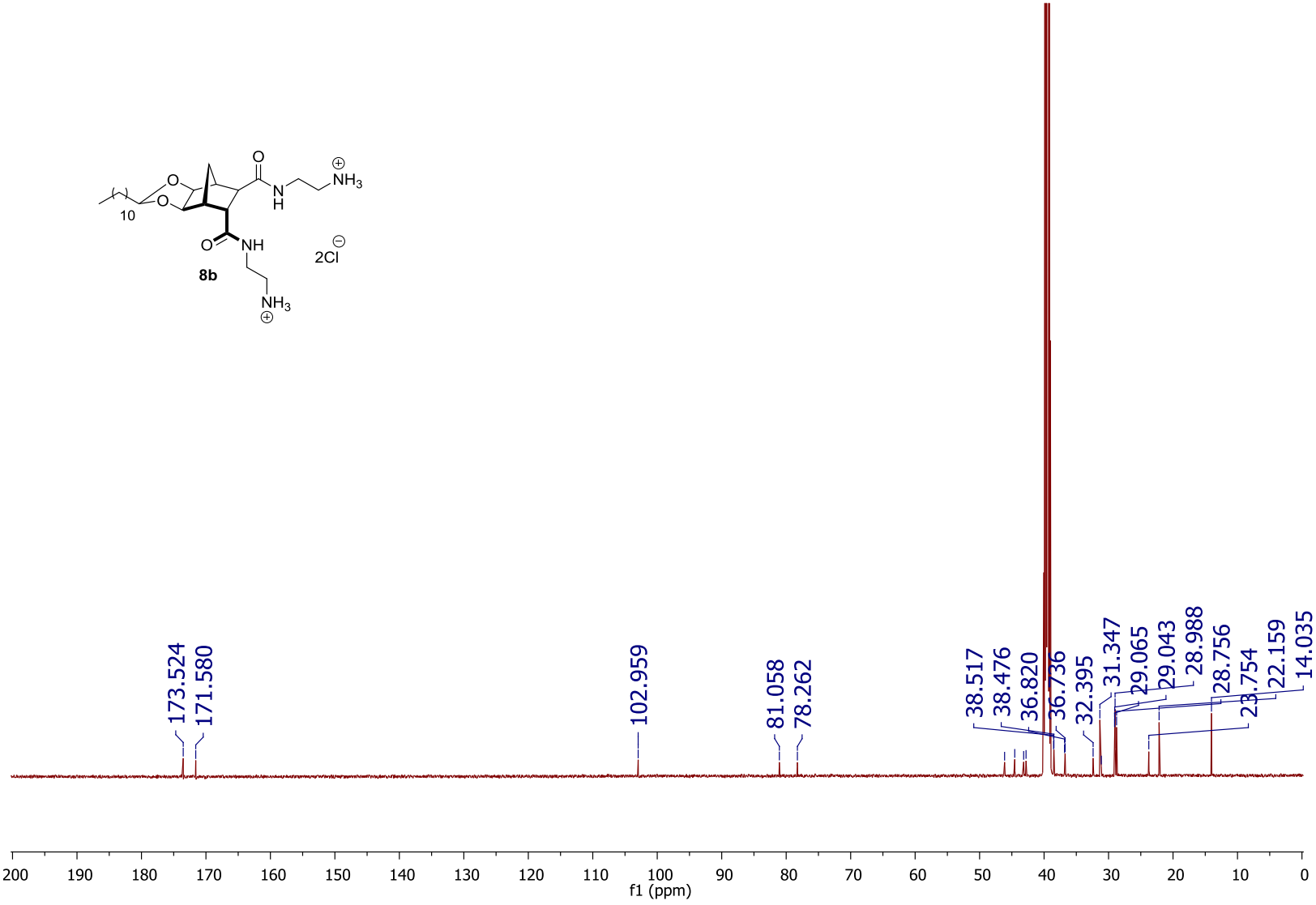

9d
11.467
8.652
8.530
8.034
7.260
7.078
7.061
6.900
6.809
6.792
4.641
4.062
4.050
3.981
3.913
3.554
2.957
2.603
2.462
1.917
1.875
1.817
1.797
1.542
1.490
1.361
1.251
0.879
f1 (ppm)

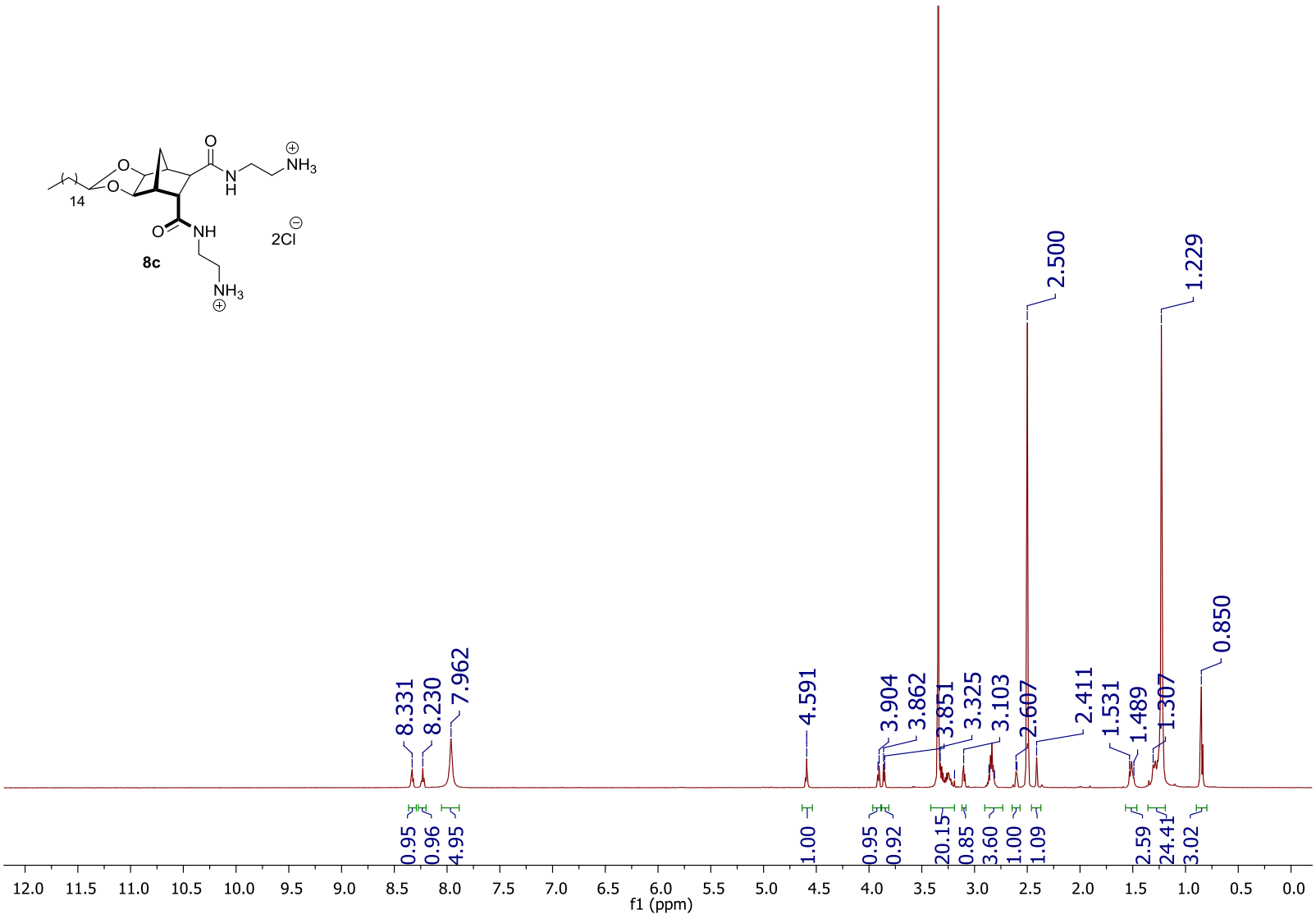

9d
77.160
174.137
172.035
157.875
157.528
157.044
153.220
133.461
129.290
114.561
103.262
83.795
81.775
79.128
68.155
31.951
29.502
29.462
29.378
28.404
28.207
28.186
26.201
22.791
14.235
f1 (ppm)

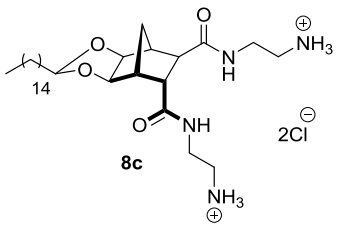

24a
11.482
8.527
7.260
7.040
6.167
4.631
4.196
4.185
3.983
3.971
3.417
2.940
2.556
2.520
2.511
2.391
2.380
1.775
1.505
1.489
1.466
1.451
1.246
0.882
0.849
f1 (ppm)


24a
77.160
174.115
171.696
163.410
157.347
153.256
104.163
83.573
81.643
79.806
78.761
39.899
31.868
31.839
29.722
29.650
29.303
29.040
28.378
28.192
27.033
22.753
22.700
14.206
14.196
f1 (ppm)


8b
2Cl
8.352
8.244
8.007
4.590
3.915
3.903
3.860
3.102
2.612
2.500
2.409
1.528
1.488
1.304
1.285
1.225
0.848
f1 (ppm)

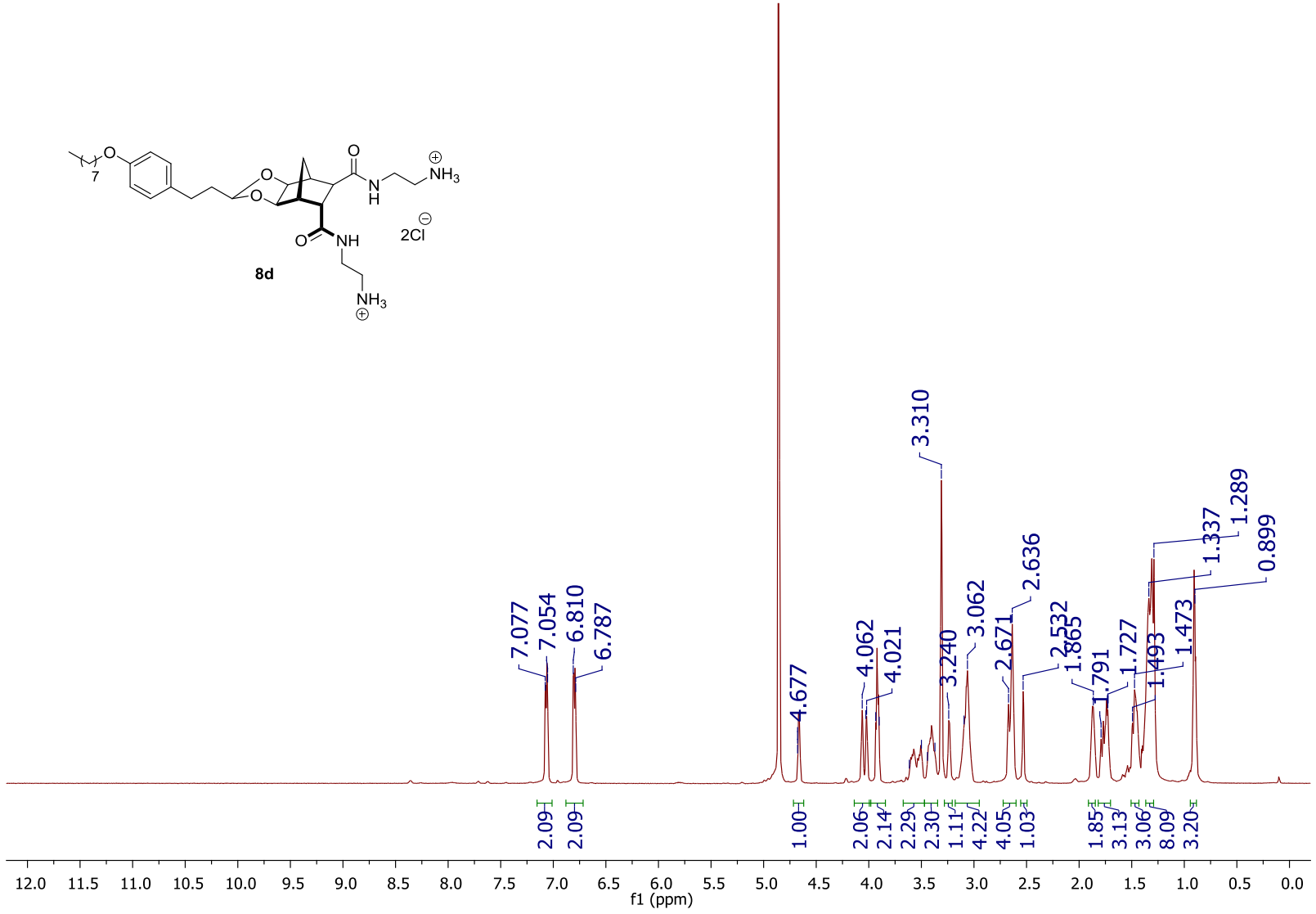

10
O
O
O
N
H
NH3
O
NH
2Cl
8b
NH3
173.524
171.580
102.959
81.058
78.262
38.517
38.476
36.820
36.736
32.395
31.347
29.065
29.043
28.988
28.756
23.754
22.159
14.035
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

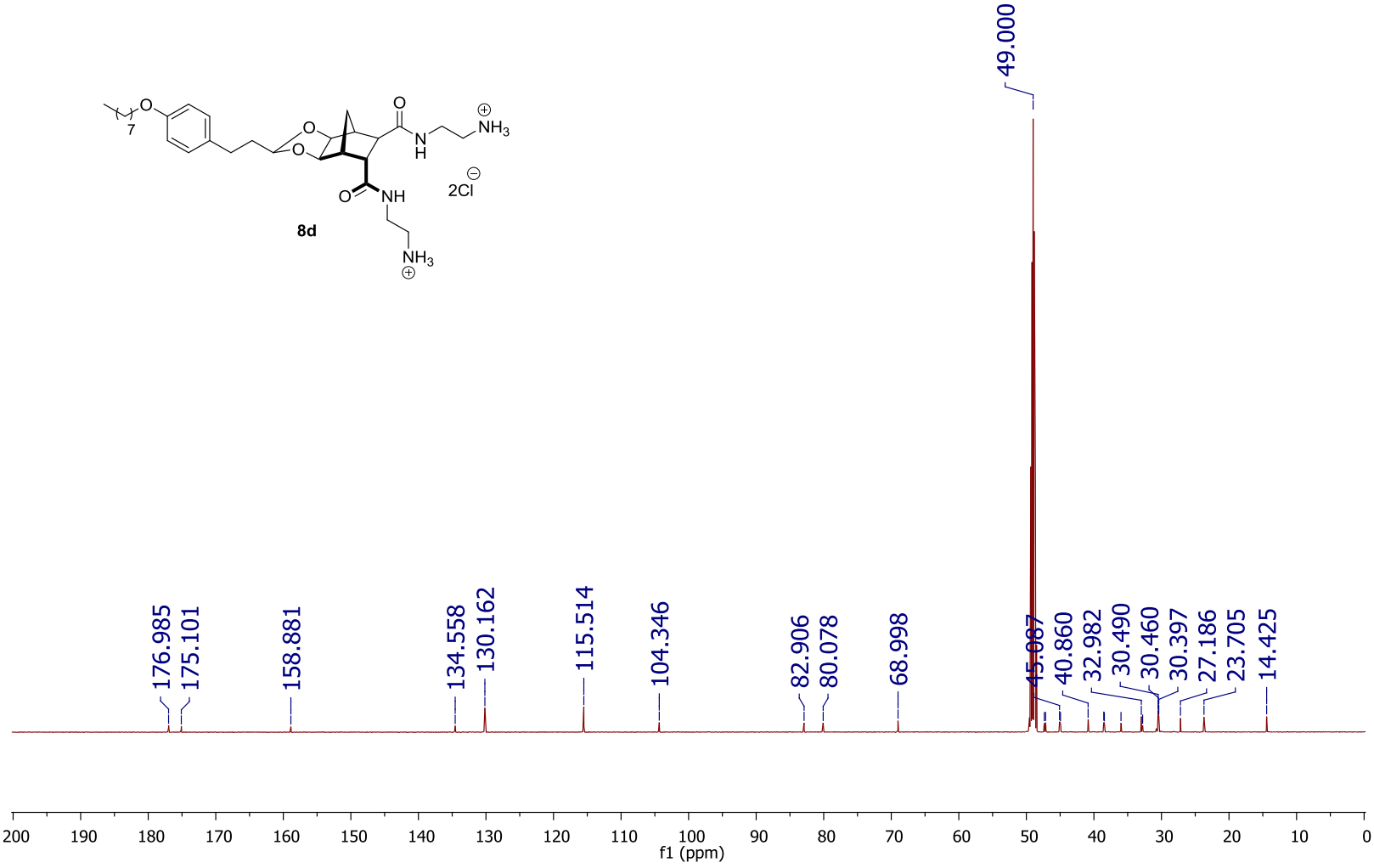

14
O
O
O
N
H
NH3
O
NH
2Cl
8c
NH3
8.331
8.230
7.962
4.591
3.904
3.862
3.851
3.325
3.103
2.607
2.500
2.411
1.531
1.489
1.307
1.229
0.850
0.95
0.96
4.95
1.00
0.95
0.92
20.15
0.85
3.60
1.00
1.09
2.59
24.41
3.02
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

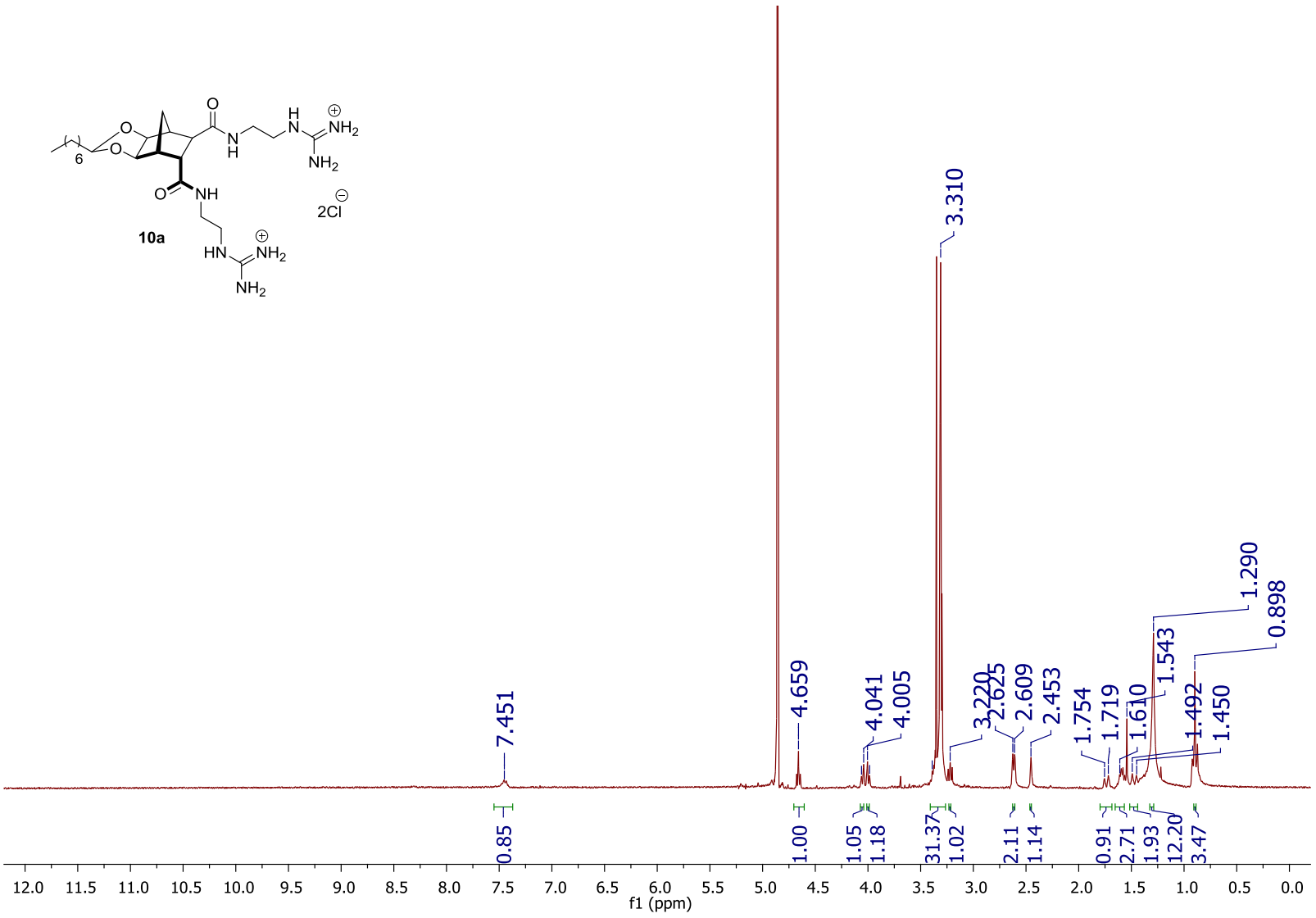

O
O
O
14
N
H
NH3
O
NH
2Cl
NH3

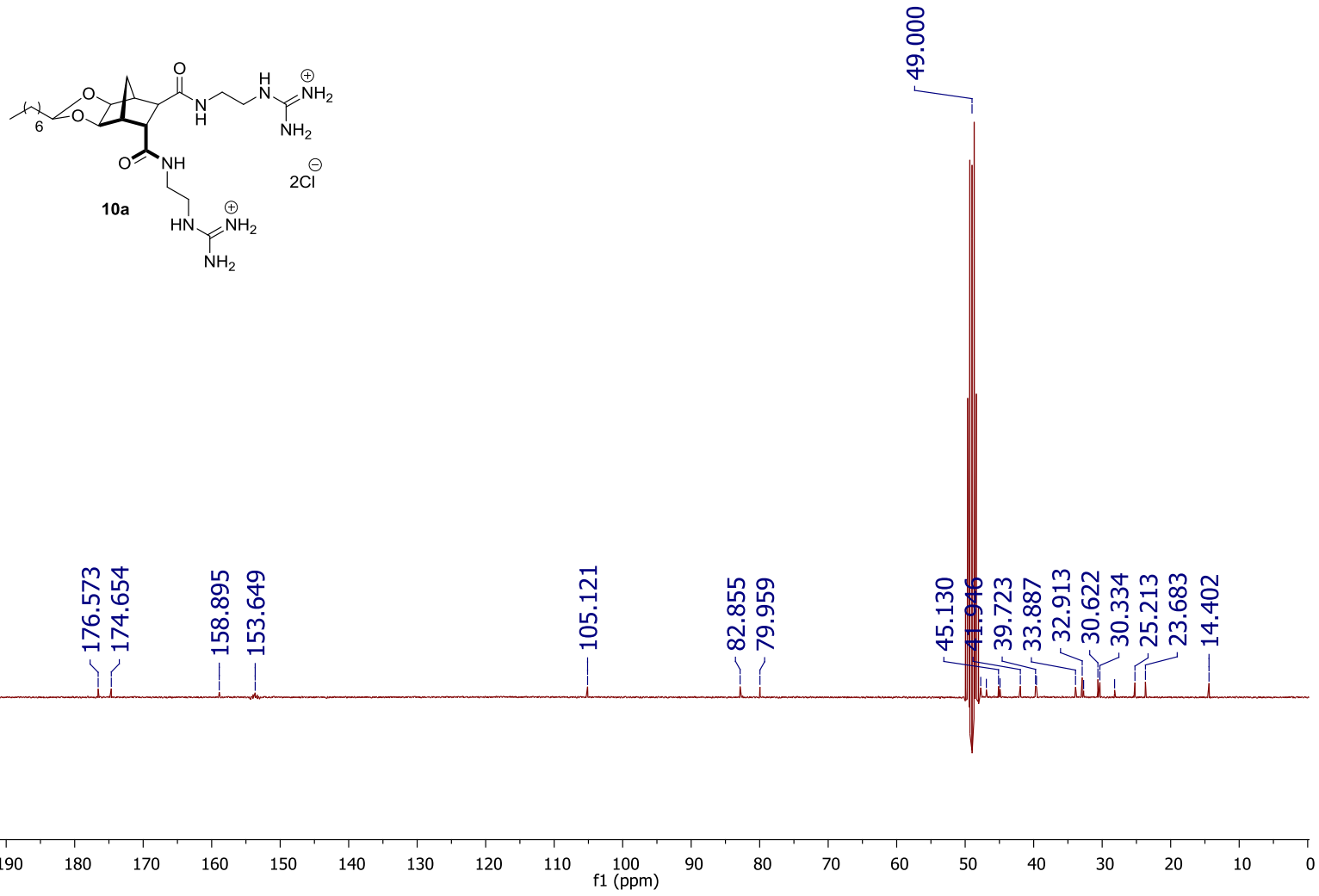
8c

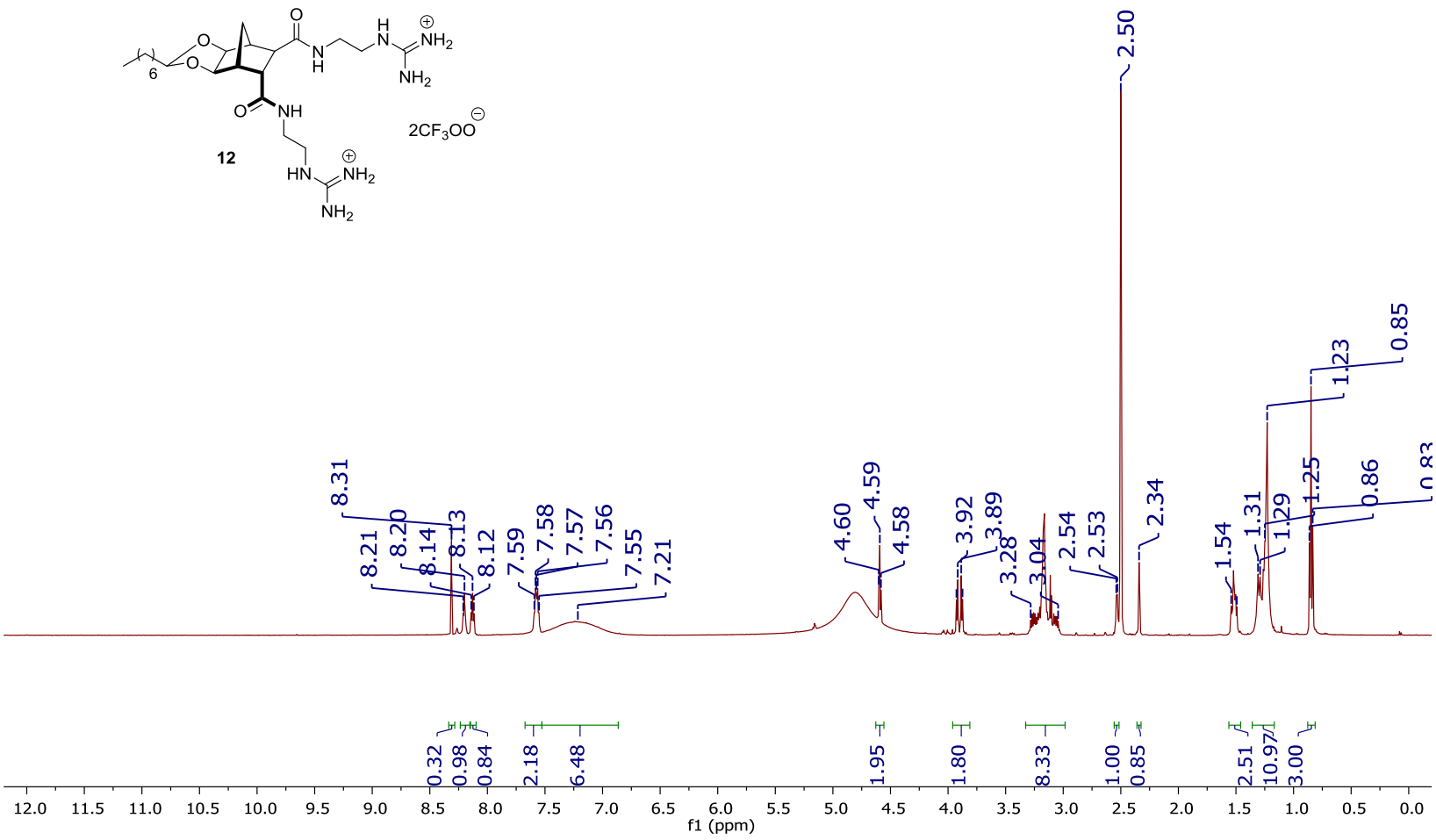
39.520
173.486
171.537
102.938
81.044
78.250
38.493
38.447
36.801
36.720
32.399
31.336
29.068
29.045
28.991
28.747
23.762
22.144
14.018
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

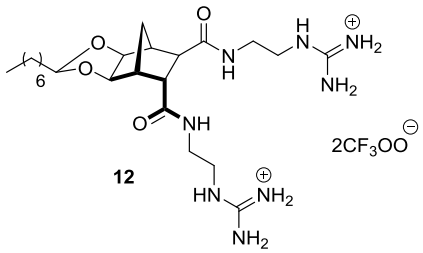

8d
2Cl
7.077
7.054
6.810
6.787
4.677
4.062
4.021
3.310
3.240
3.062
2.671
2.636
2.532
1.865
1.791
1.727
1.493
1.473
1.337
1.289
0.899
2.09
2.09
1.00
2.06
2.14
2.29
2.30
1.11
4.22
4.05
1.03
1.85
3.13
3.06
8.09
3.20
f1 (ppm)


8d
2Cl
176.985
175.101
158.881
134.558
130.162
115.514
104.346
82.906
80.078
68.998
49.000
45.087
40.860
32.982
30.490
30.460
30.397
27.186
23.705
14.425
f1 (ppm)


10a
2Cl
7.451
4.659
4.041
4.005
3.310
3.220
2.625
2.609
2.453
1.754
1.719
1.610
1.543
1.492
1.450
1.290
0.898
0.85
1.00
1.05
1.18
31.37
1.02
2.11
1.14
0.91
2.71
1.93
12.20
3.47
f1 (ppm)

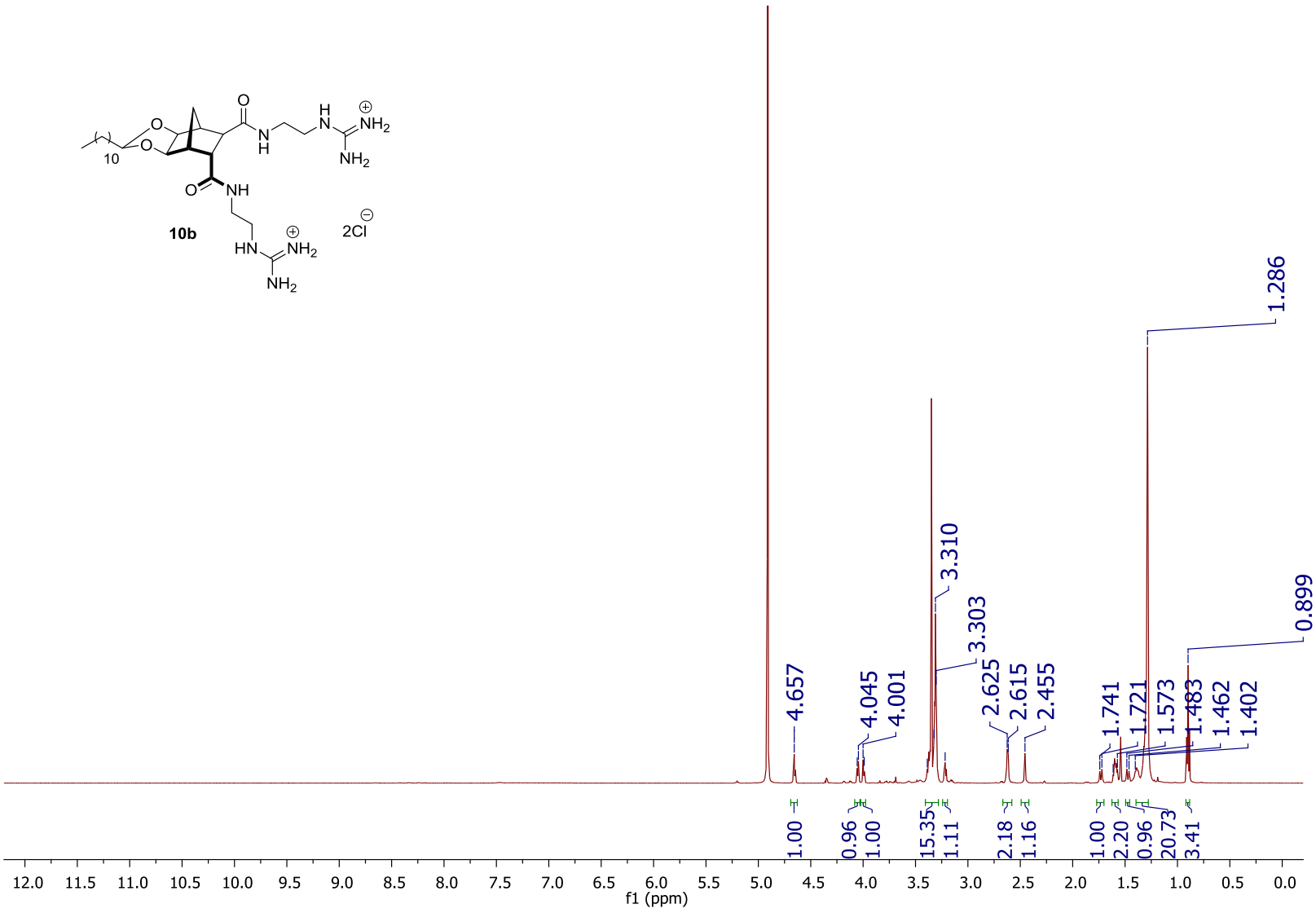

10a
2Cl
49.000
176.573
174.654
158.895
153.649
105.121
82.855
79.959
45.130
41.946
39.723
33.887
32.913
30.622
30.334
25.213
23.683
14.402
f1 (ppm)

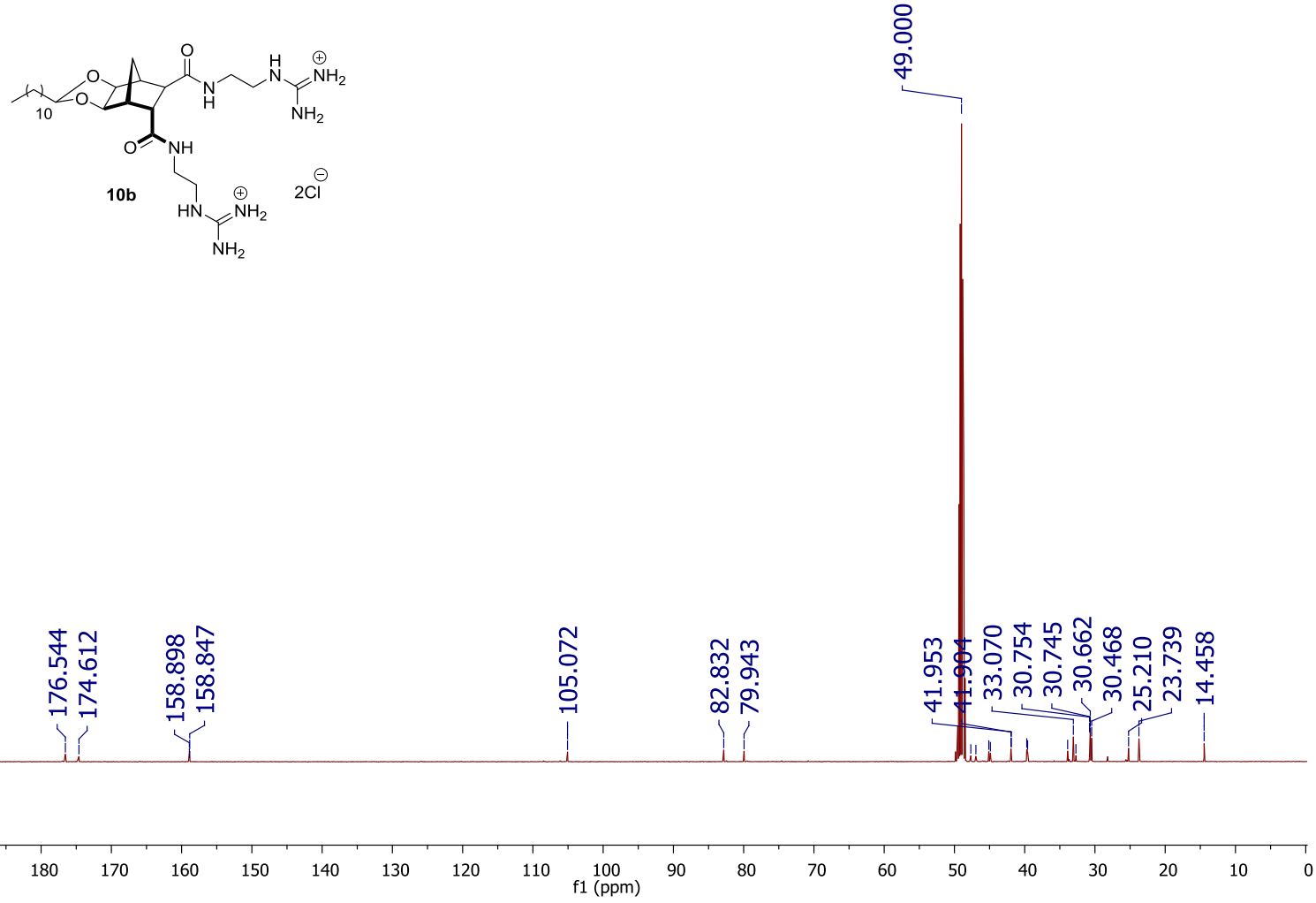

12
2CF3OO
8.31
8.21
8.20
8.14
8.13
8.12
7.59
7.58
7.57
7.56
7.55
7.21
4.60
4.59
4.58
3.92
3.89
3.28
3.04
2.54
2.53
2.50
2.34
1.54
1.31
1.29
1.25
1.23
0.86
0.85
0.32
0.98
0.84
2.18
6.48
1.95
1.80
8.33
1.00
0.85
2.51
10.97
3.00
f1 (ppm)

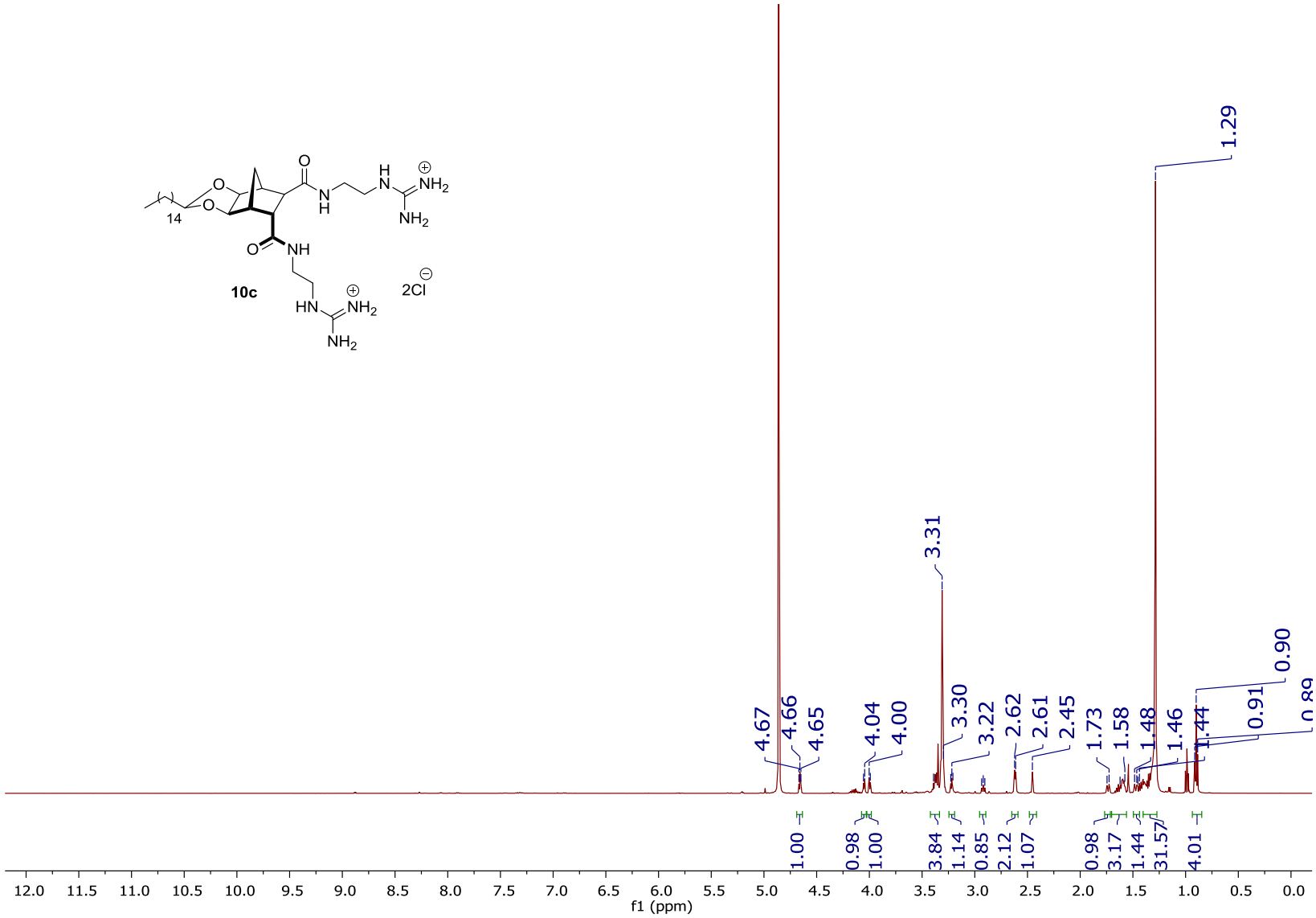

6
O
O
O
N
H
H
N
NH2
NH2
O
NH
2CF3OO
HN
NH2
NH2

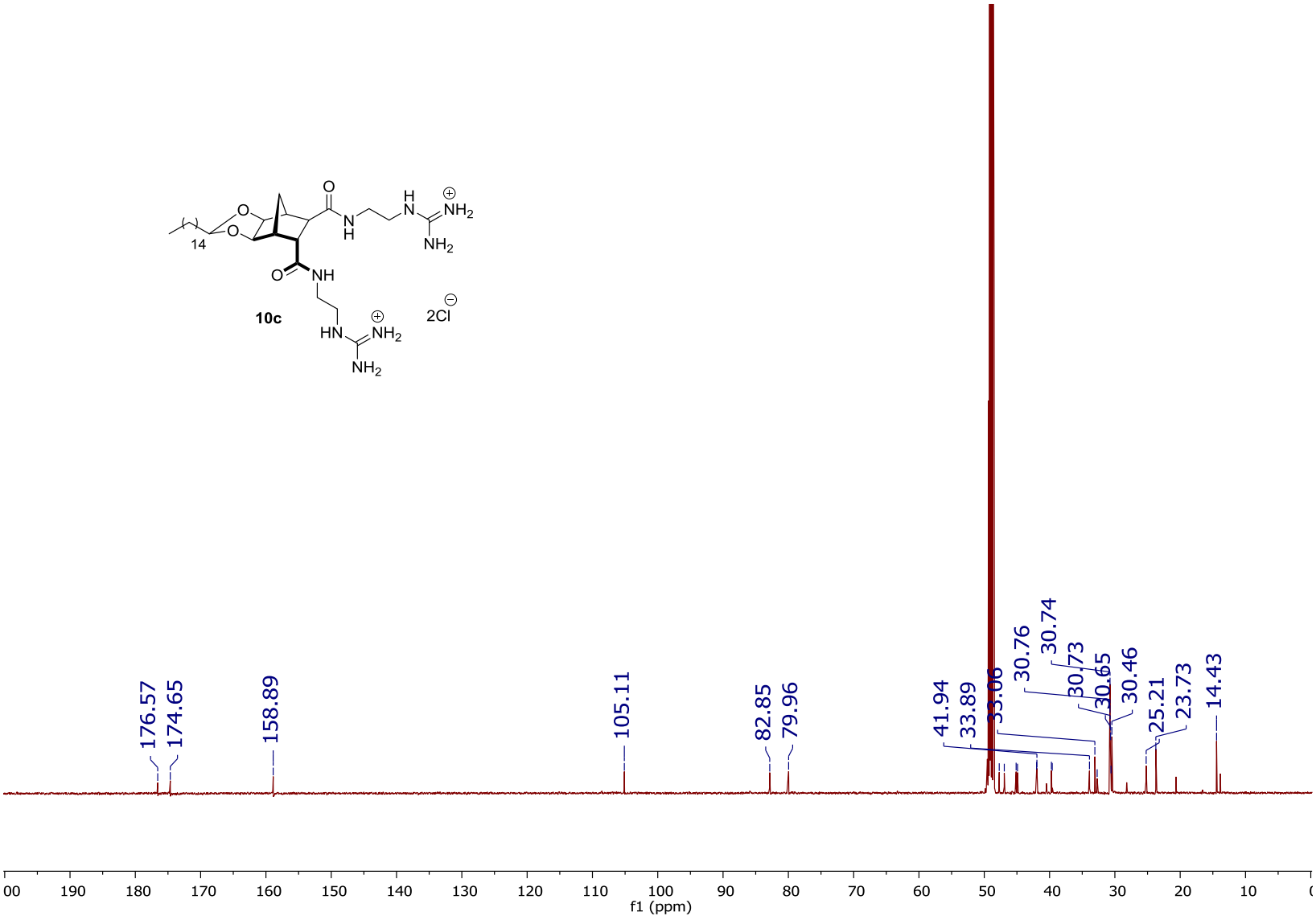
12

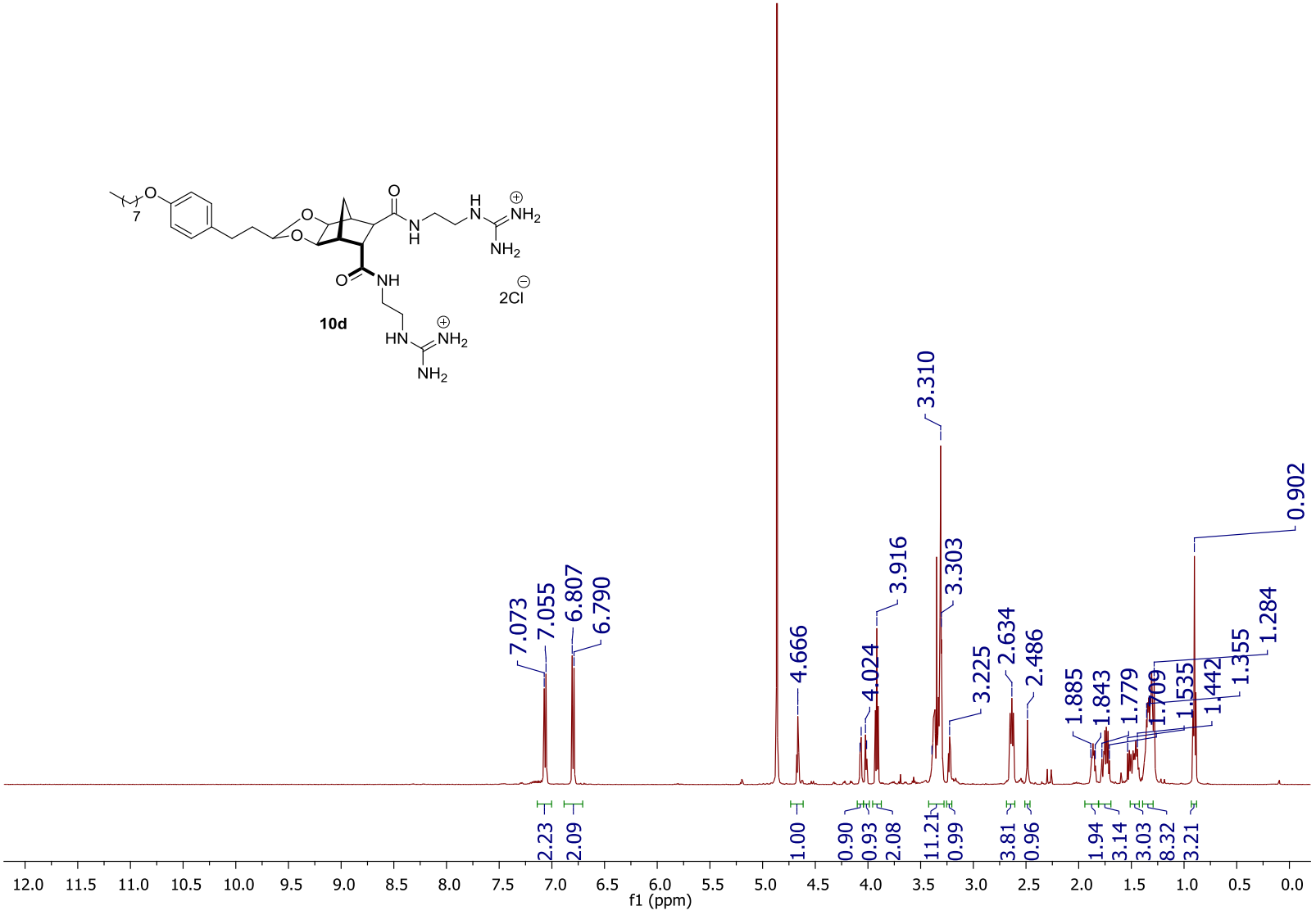
173.06
171.25
156.62
102.61
80.71
78.84
77.83
45.95
43.97
42.87
42.36
40.08
40.00
37.80
37.71
32.01
30.83
28.56
28.26
23.37
21.70
13.59
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

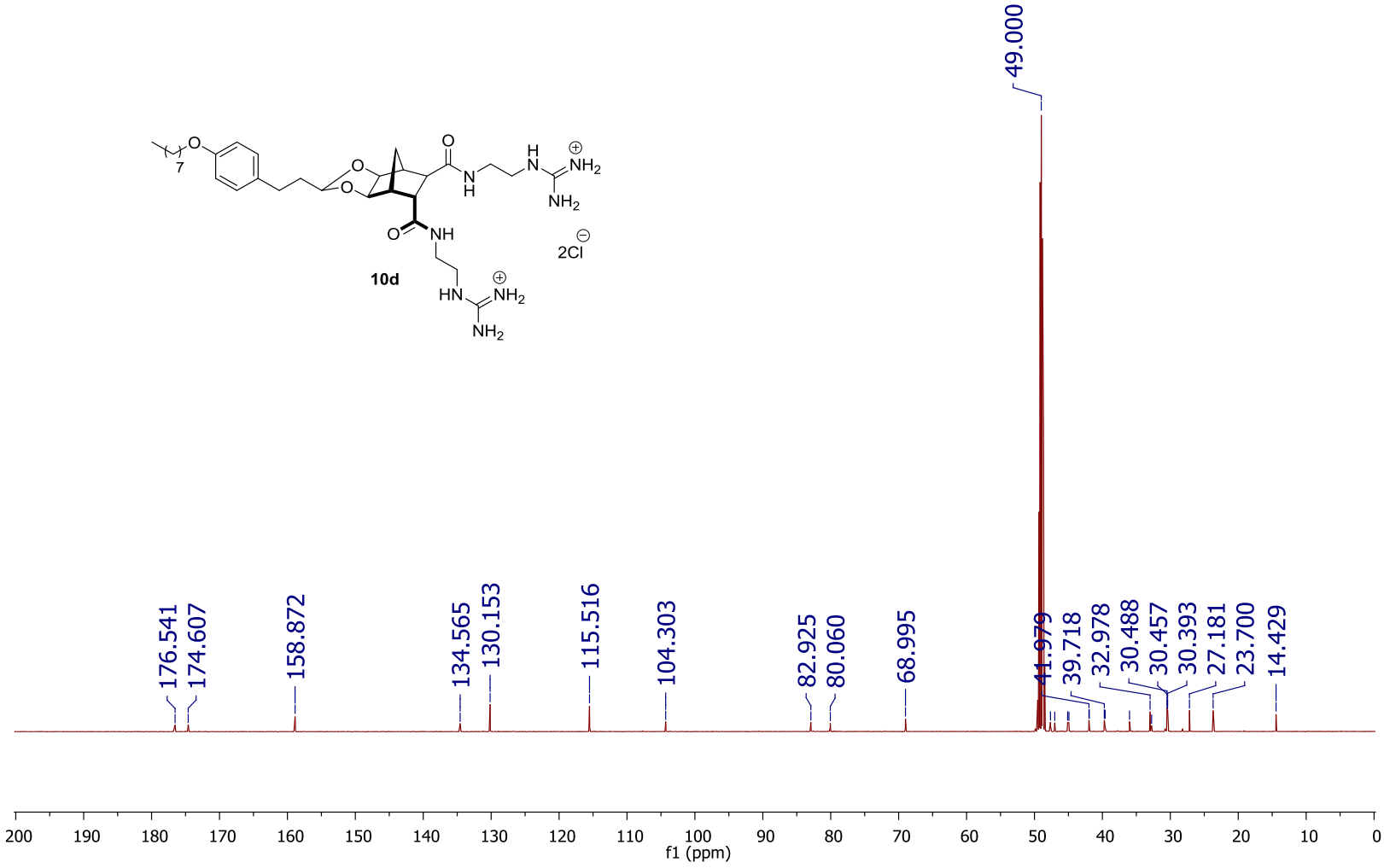

10
10b
2Cl
1.286
0.899
4.657
4.045
4.001
3.310
3.303
2.625
2.615
2.455
1.741
1.721
1.573
1.483
1.462
1.402
1.00
0.96
1.00
15.35
1.11
2.18
1.16
1.00
2.20
0.96
20.73
3.41
f1 (ppm)


10b
2Cl
49.000
176.544
174.612
158.898
158.847
105.072
82.832
79.943
41.953
41.904
33.070
30.754
30.745
30.662
30.468
25.210
23.739
14.458
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


10c
2Cl
1.29
0.90
0.91
3.31
4.67
4.66
4.65
4.04
4.00
3.30
3.22
2.62
2.61
2.45
1.73
1.58
1.48
1.46
1.44
1.00
0.98
1.00
3.84
1.14
0.85
2.12
1.07
0.98
3.17
1.44
31.57
4.01
f1 (ppm)


10c
2Cl
176.57
174.65
158.89
105.11
82.85
79.96
41.94
33.89
33.06
30.76
30.74
30.73
30.65
30.46
25.21
23.73
14.43
f1 (ppm)


10d
2Cl
7.073
7.055
6.807
6.790
4.666
4.024
3.916
3.310
3.303
3.225
2.634
2.486
1.885
1.843
1.779
1.709
1.535
1.442
1.355
1.284
0.902
2.23
2.09
1.00
0.90
0.93
2.08
11.21
0.99
3.81
0.96
1.94
3.14
3.03
8.32
3.21
f1 (ppm)


10d
2Cl
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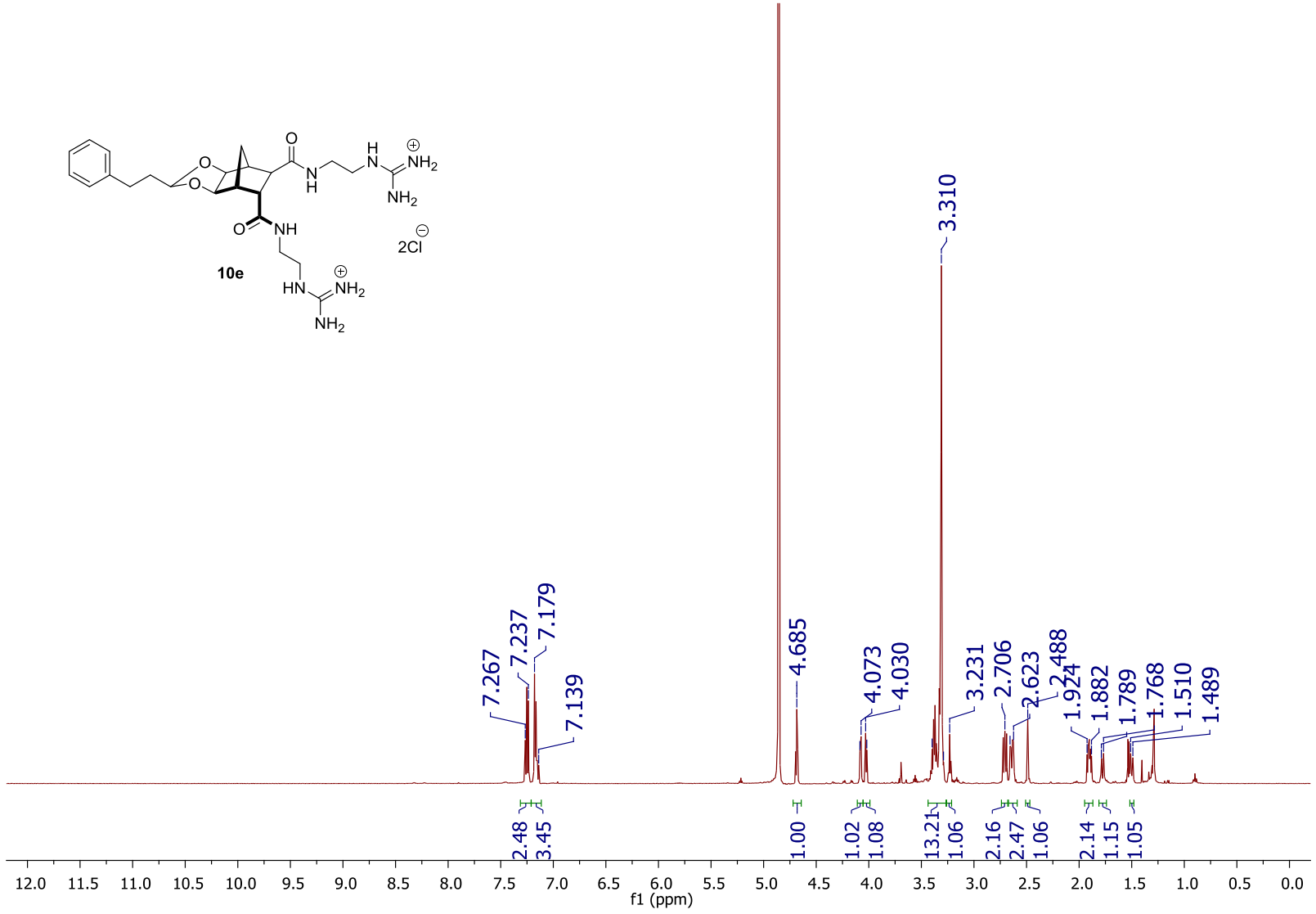
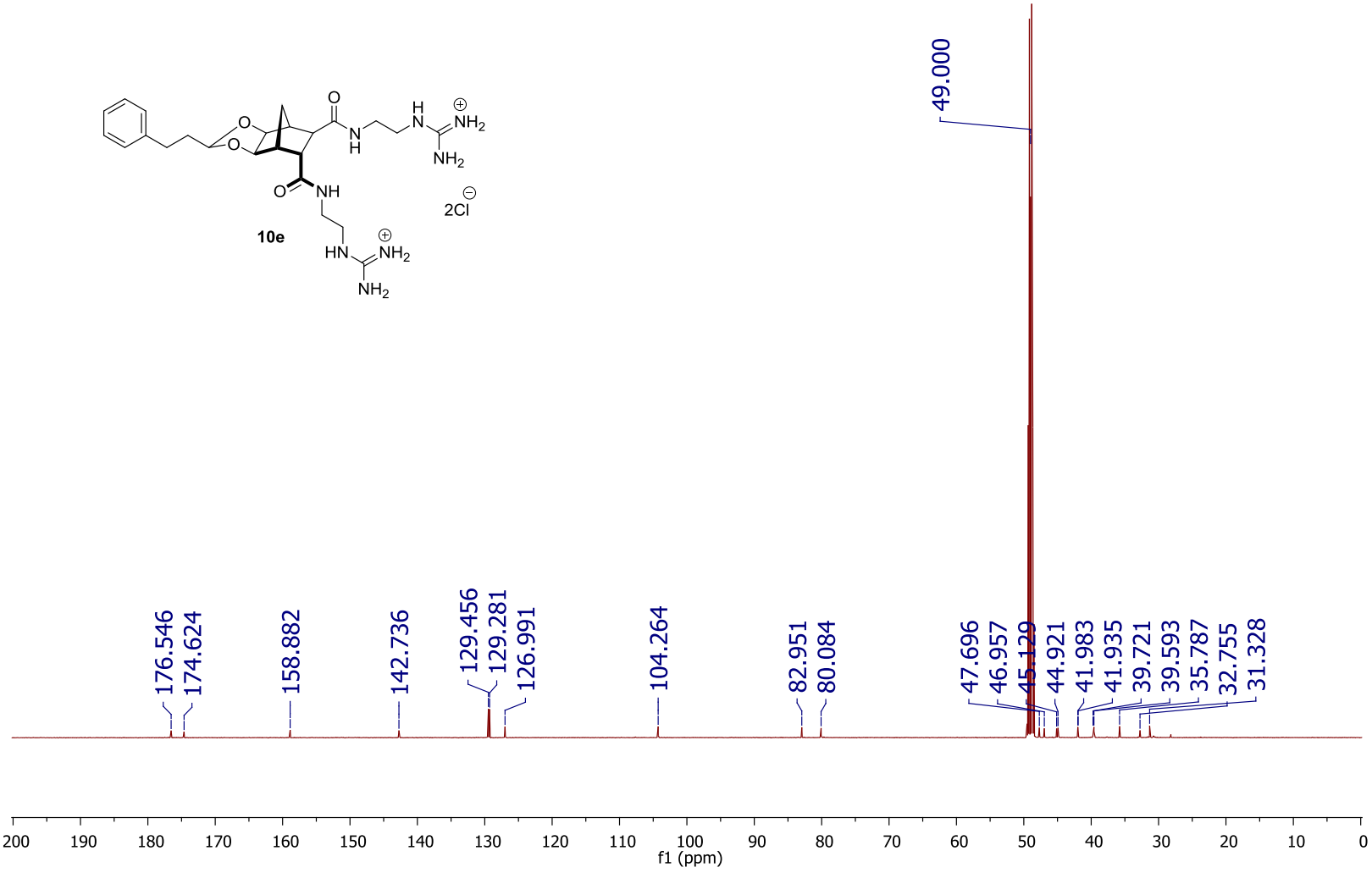
174.607
158.872
134.565
130.153
115.516
104.303
82.925
80.060
68.995
41.979
39.718
32.978
30.488
30.457
30.393
27.181
23.700
14.429
f1 (ppm)


10e
2Cl
7.267
7.237
7.179
7.139
4.685
4.073
4.030
3.310
3.231
2.706
2.623
2.488
1.924
1.882
1.789
1.768
1.510
1.489
2.48
3.45
1.00
1.02
1.08
13.21
1.06
2.16
2.47
1.06
2.14
1.15
1.05
f1 (ppm)


10e
2Cl
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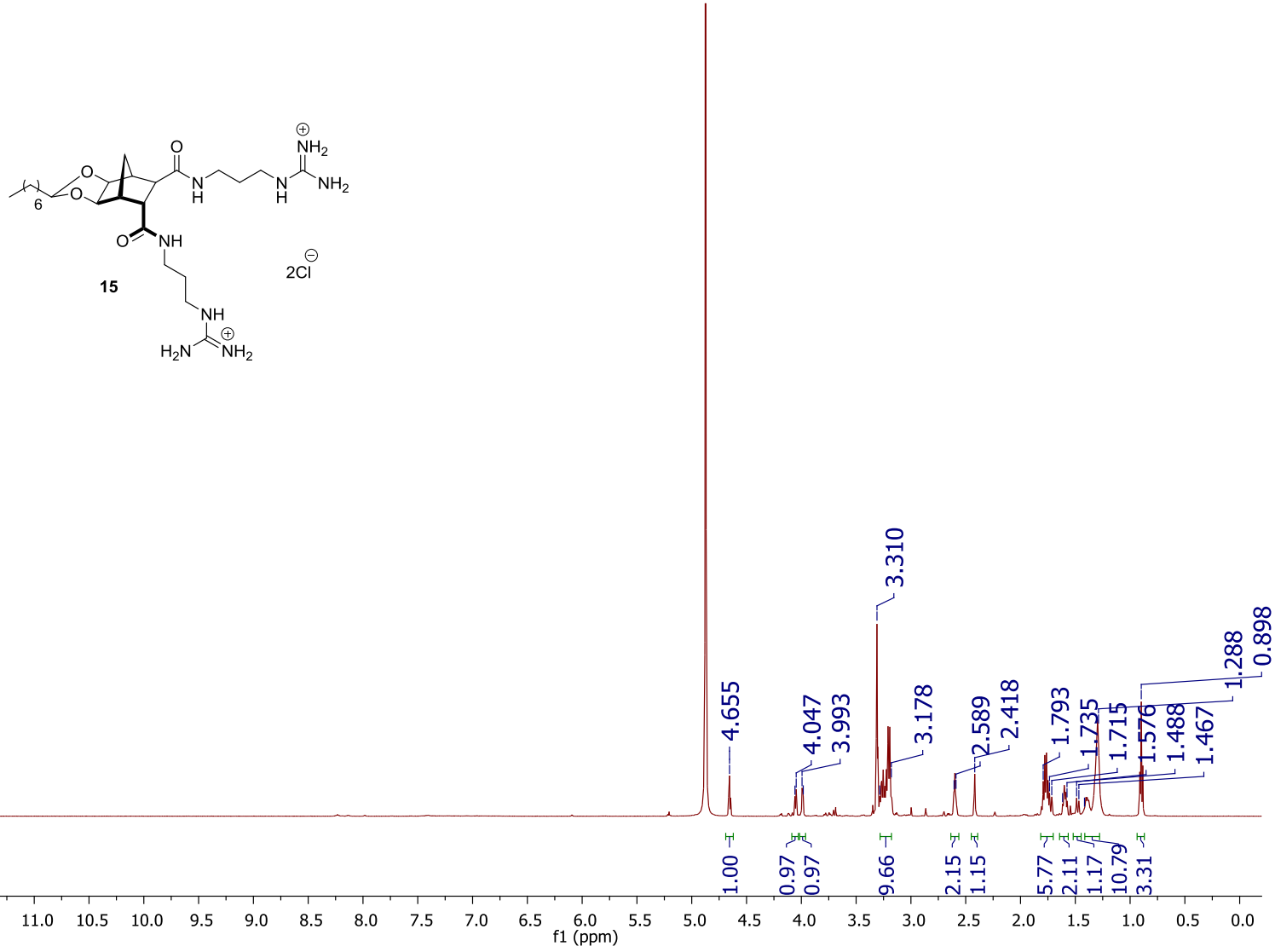
174.624
158.882
142.736
129.456
129.281
126.991
104.264
82.951
80.084
47.696
46.957
45.129
44.921
41.983
41.935
39.721
39.593
35.787
32.755
31.328
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


15
2Cl
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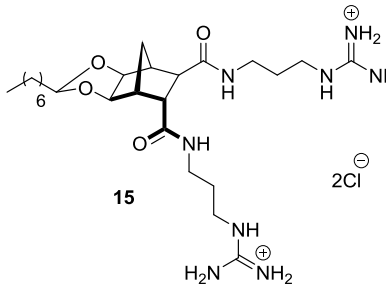
3.993
3.310
3.178
2.589
2.418
1.793
1.735
1.715
1.576
1.488
1.467
1.288
0.898
1.00
0.97
0.97
9.66
2.15
1.15
5.77
2.11
1.17
10.79
3.31
f1 (ppm)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NH2
O
N
H
N
H
NH2
6
O
NH
2Cl
15
NH
H2N
NH2

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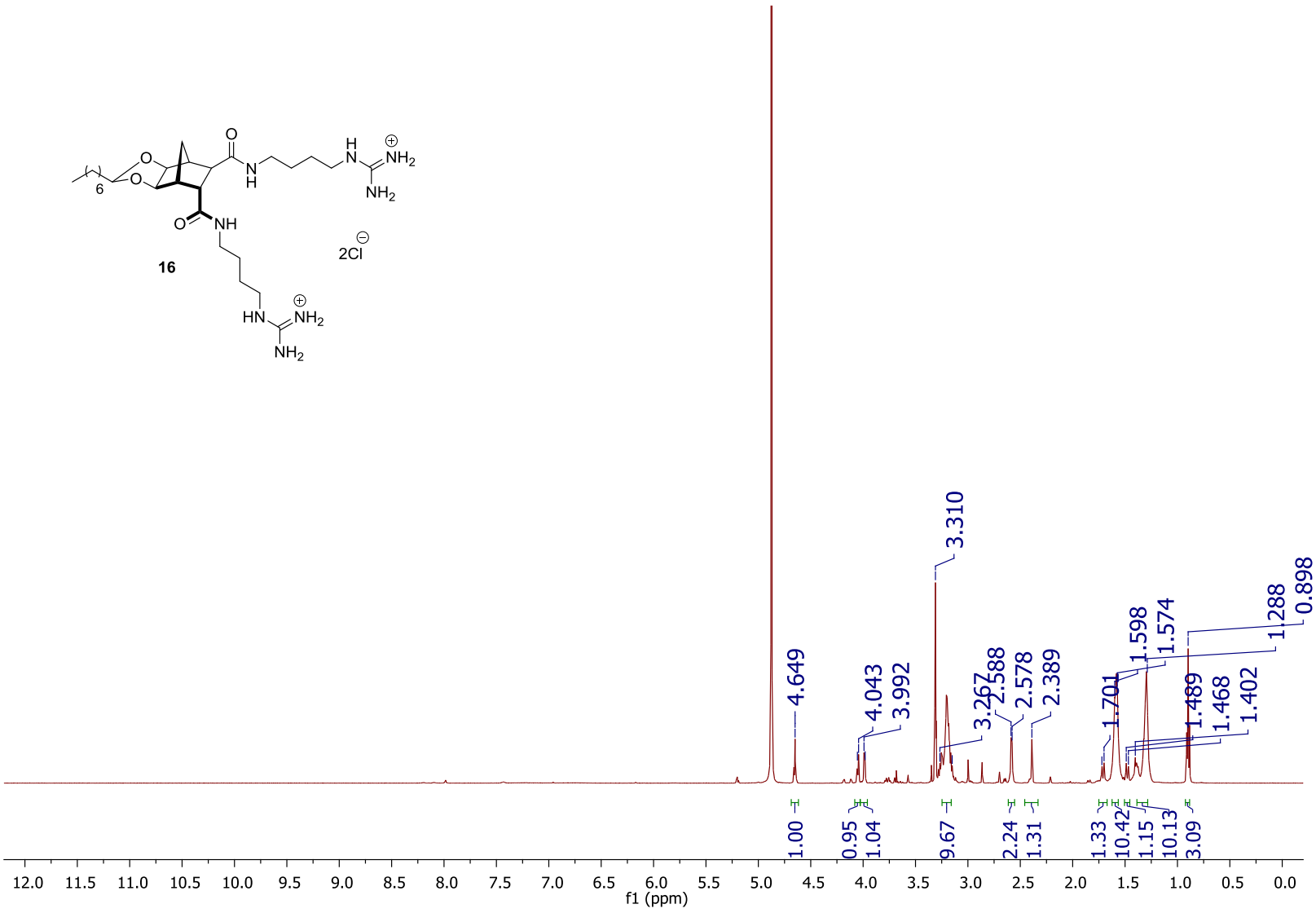
174.116
158.662
105.099
82.906
79.972
39.994
37.706
32.909
30.615
30.325
29.929
29.903
25.204
23.680
14.407
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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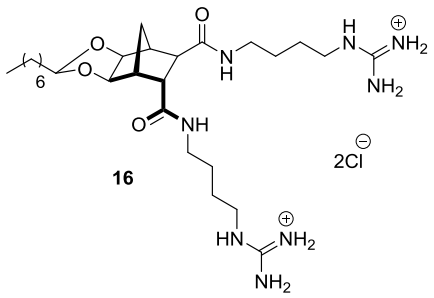
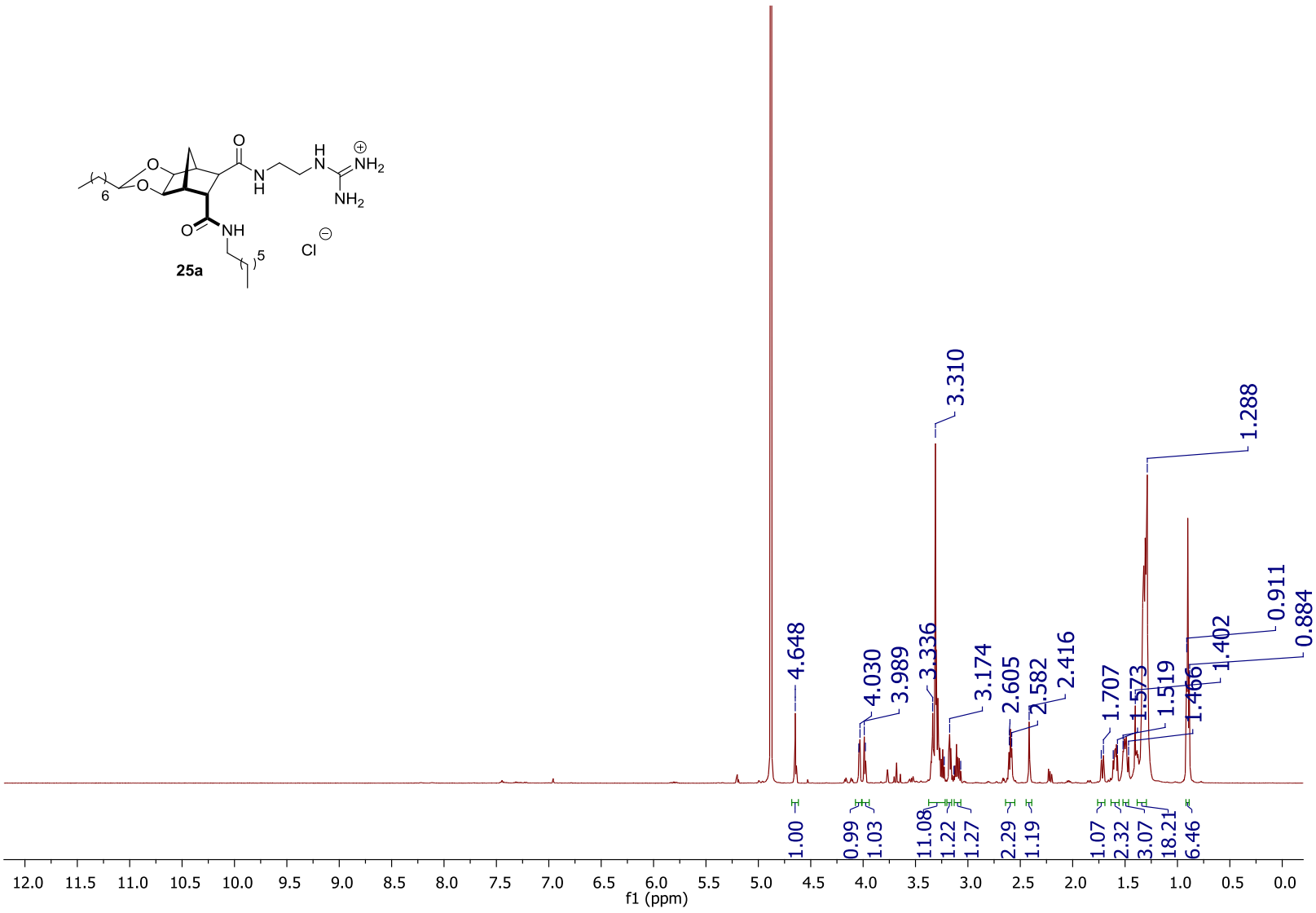
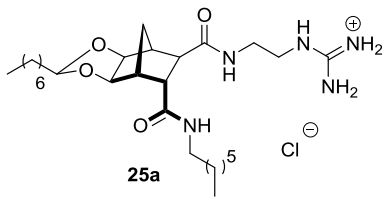
4.043
3.992
3.310
3.267
2.588
2.578
2.389
1.701
1.598
1.574
1.489
1.468
1.402
1.288
0.898
1.00
0.95
1.04
9.67
2.24
1.31
1.33
10.42
1.15
10.13
3.09
f1 (ppm)


O
O
O
6
N
H
H
N
NH2
NH2
O
NH
HN
NH2
NH2
2Cl

16

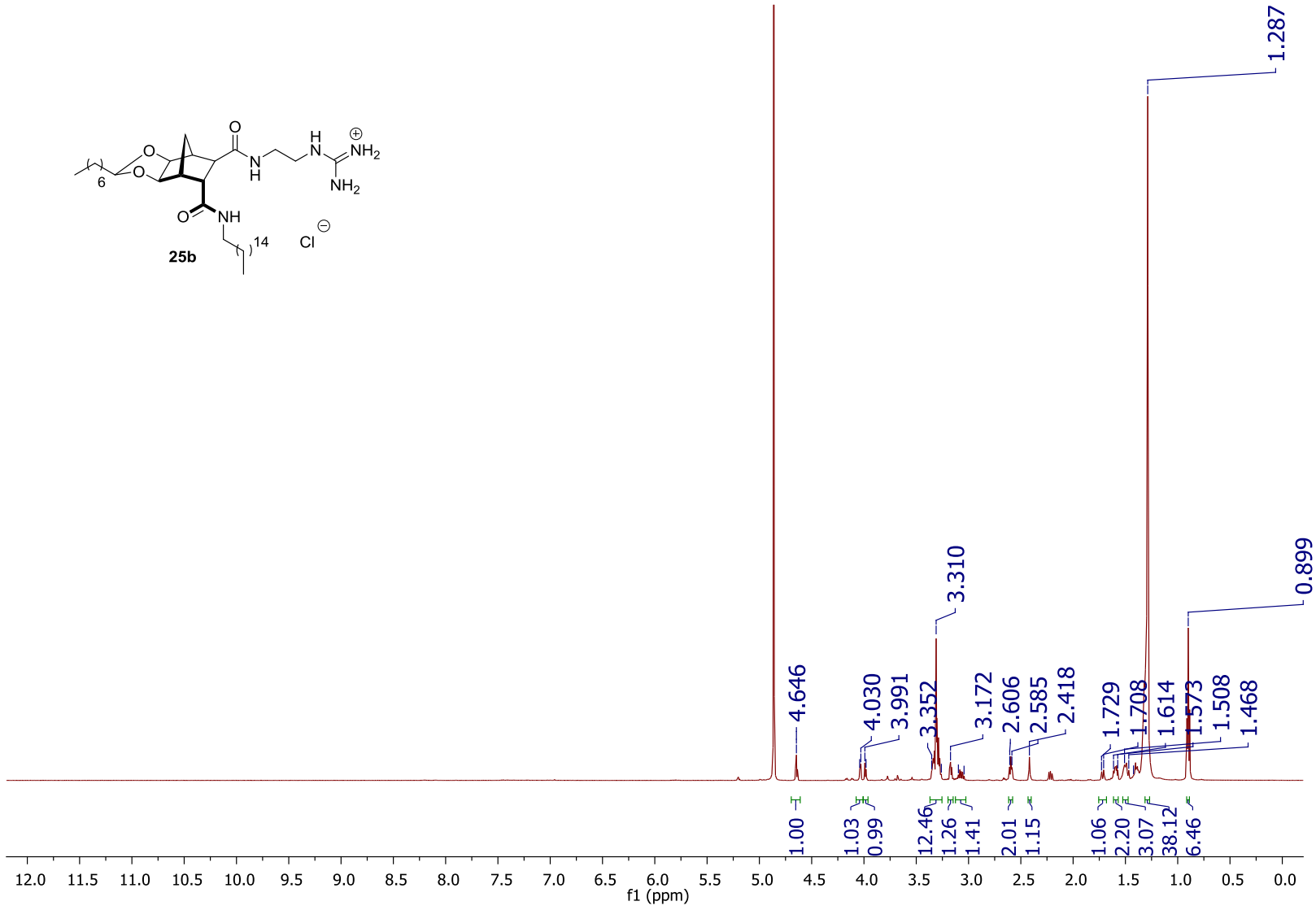
175.917
173.870
158.588
105.064
82.910
79.983
42.090
39.886
32.909
30.625
30.323
27.689
27.230
25.201
23.678
14.411
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

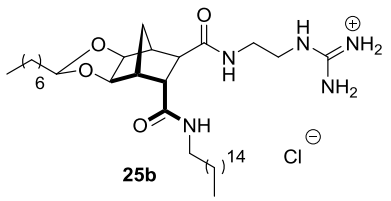

25a
4.648
4.030
3.989
3.336
3.310
3.174
2.605
2.582
2.416
1.707
1.573
1.519
1.466
1.402
1.288
0.911
0.884
1.00
0.99
1.03
11.08
1.22
1.27
2.29
1.19
1.07
2.32
3.07
18.21
6.46
f1 (ppm)


O
H
N
⊕
NH2
O
N
H
NH2
6
O
O
O
NH
5
Cl
⊖

25a

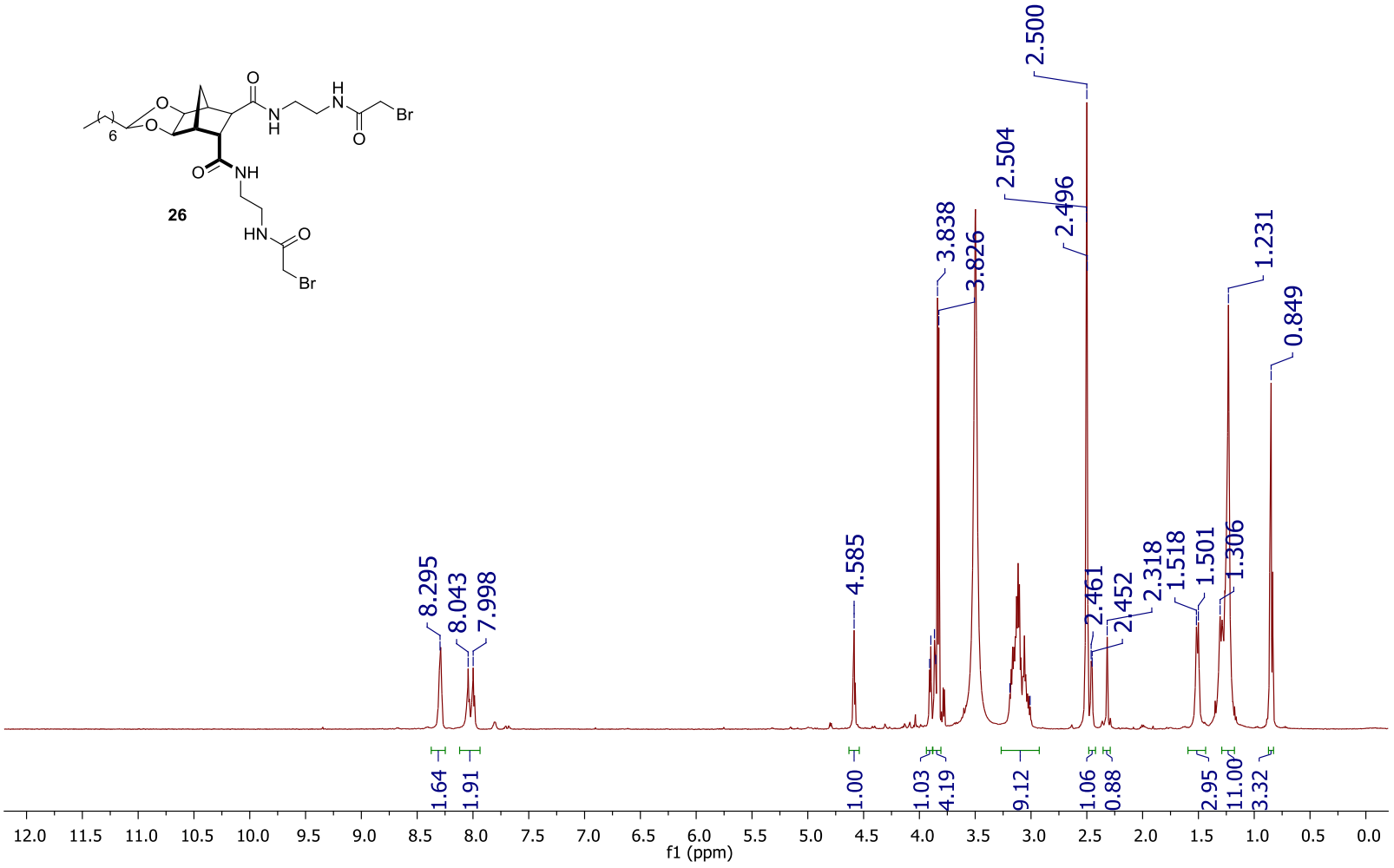
176.762
173.525
158.877
105.071
82.868
80.007
32.946
32.910
30.611
30.425
30.331
30.078
27.949
23.682
23.646
14.440
14.412
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

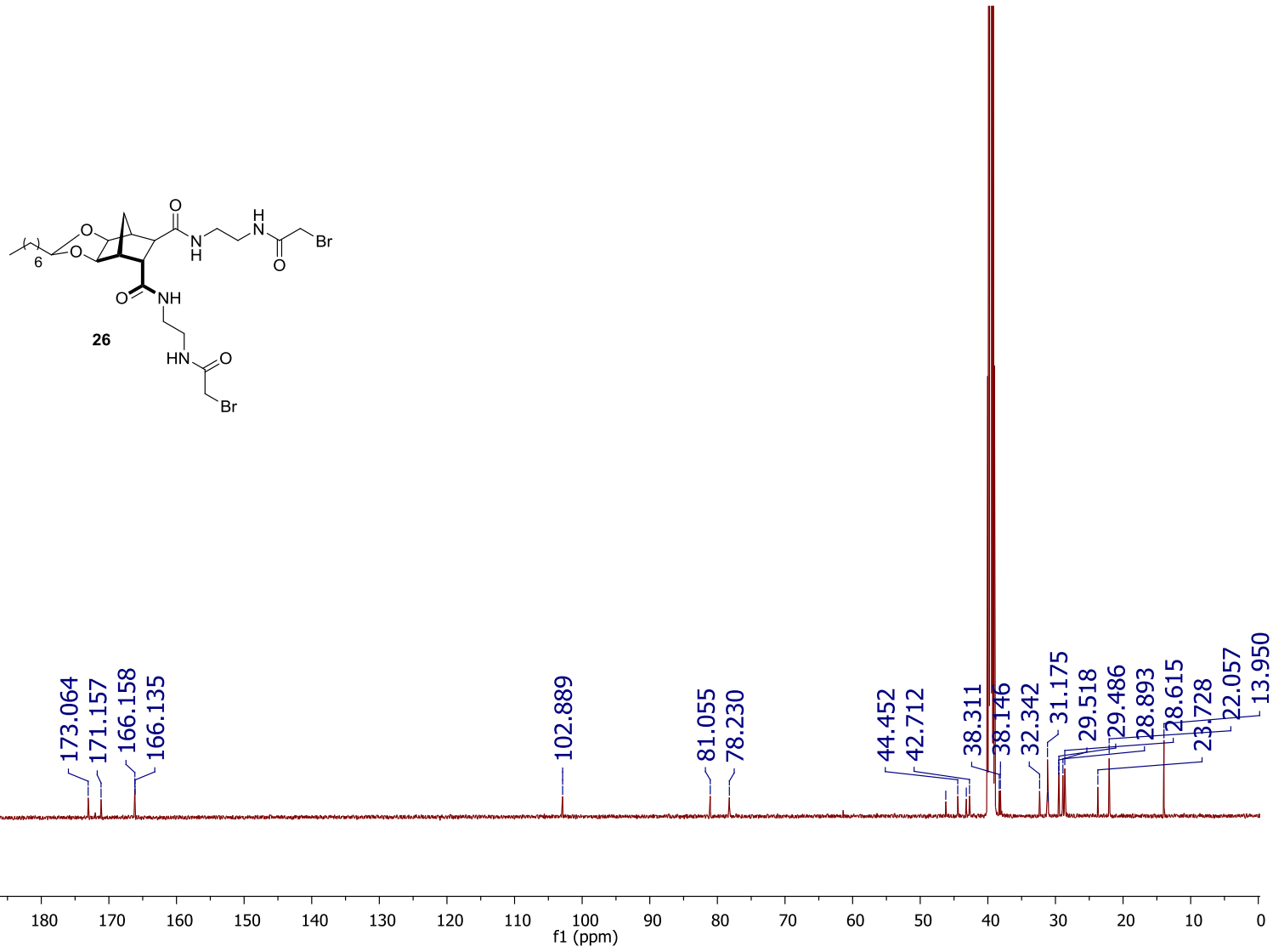

25b
1.287
0.899
3.310
4.646
4.030
3.991
3.352
3.172
2.606
2.585
2.418
1.729
1.708
1.614
1.573
1.508
1.468
1.00
1.03
0.99
12.46
1.26
1.41
2.01
1.15
1.06
2.20
3.07
38.12
6.46
f1 (ppm)

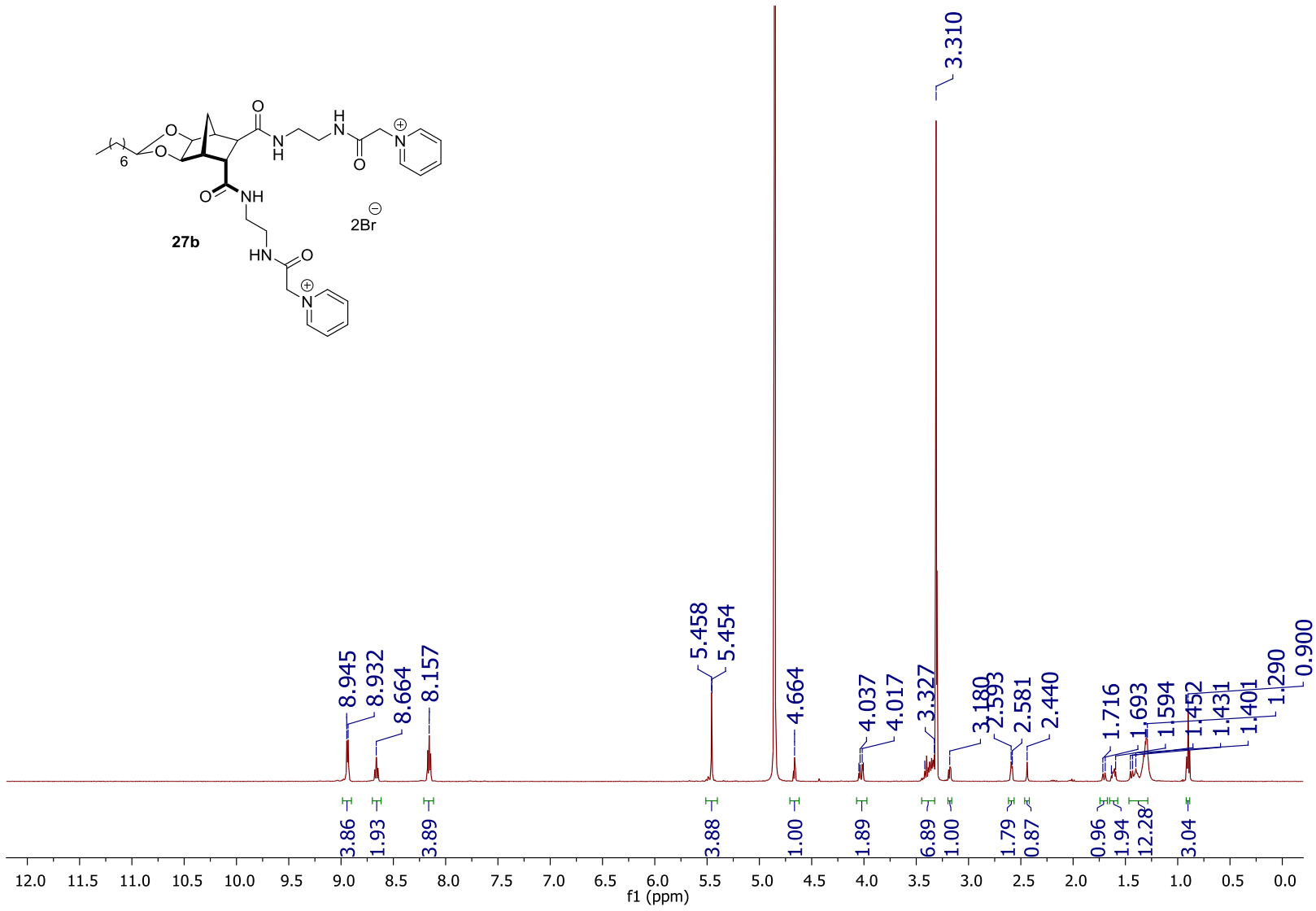

O
O
O
6
H
N
NH2
NH2
O
NH
14
Cl

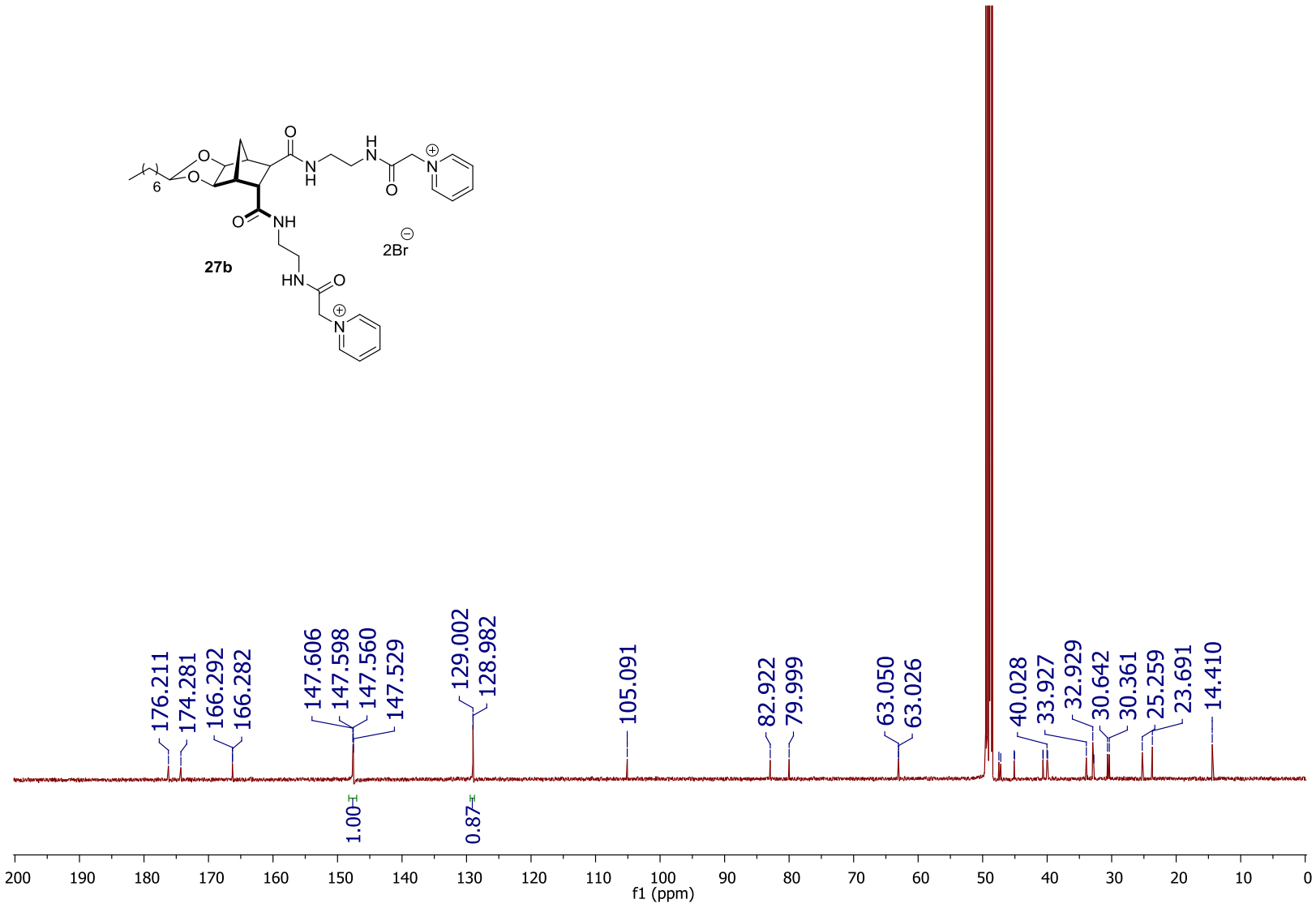
25b

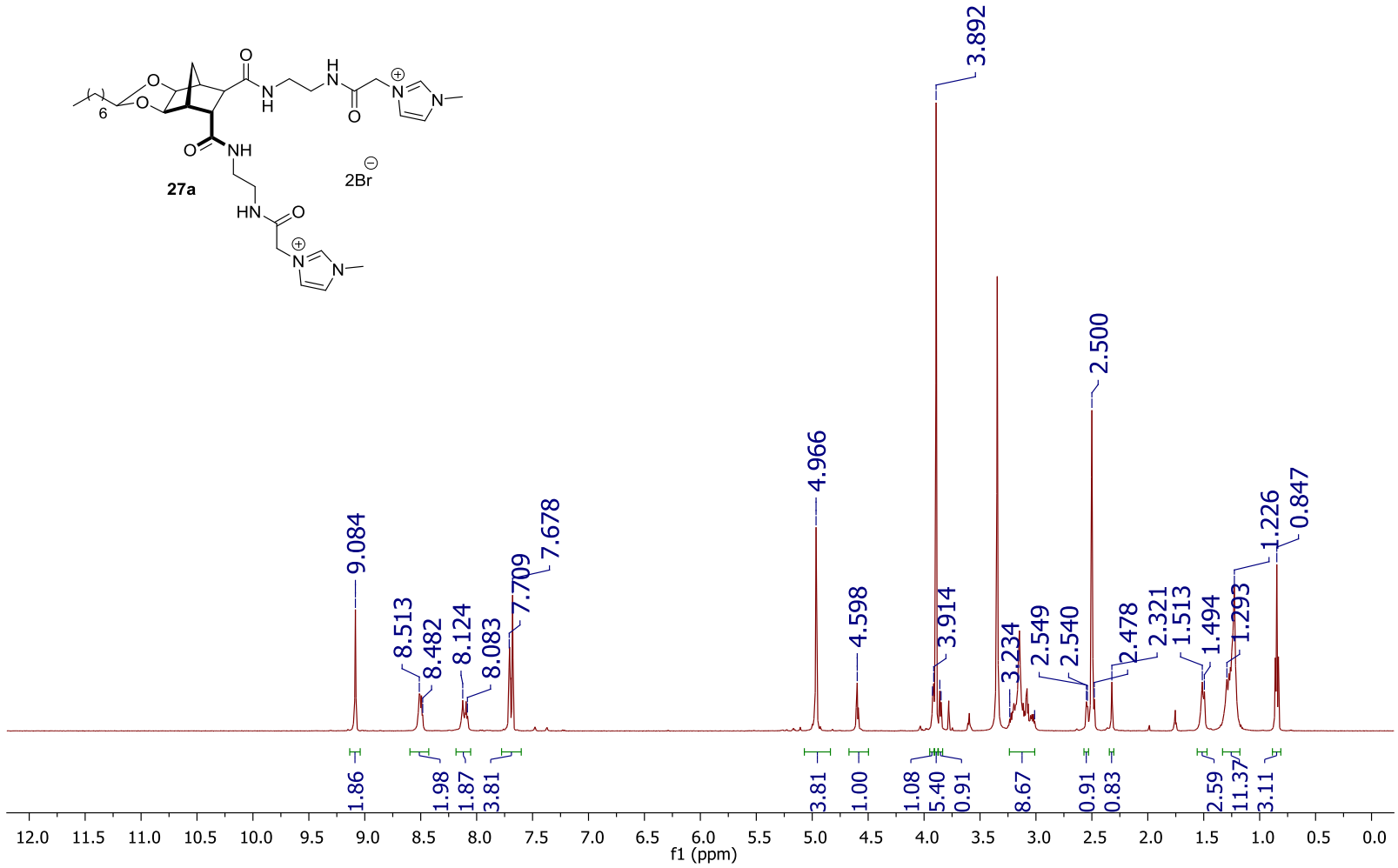
176.768
173.524
158.883
105.082
82.873
80.021
33.073
30.807
30.765
30.694
30.476
30.392
30.351
23.734
23.692
14.445
14.425
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


26
8.295
8.043
7.998
4.585
3.838
3.826
2.504
2.500
2.496
2.461
2.452
2.318
1.518
1.501
1.306
1.231
0.849
1.64
1.91
1.00
1.03
4.19
9.12
1.06
0.88
2.95
11.00
3.32
f1 (ppm)


26
173.064
171.157
166.158
166.135
102.889
81.055
78.230
44.452
42.712
38.311
38.146
32.342
31.175
29.518
29.486
28.893
28.615
23.728
22.057
13.950
f1 (ppm)


27b
2Br
3.310
8.945
8.932
8.664
8.157
5.458
5.454
4.664
4.037
4.017
3.327
3.180
2.593
2.581
2.440
1.716
1.693
1.594
1.452
1.431
1.401
1.290
0.900
3.86
1.93
3.89
3.88
1.00
1.89
6.89
1.00
1.79
0.87
0.96
1.94
12.28
3.04
f1 (ppm)


27b
2Br
176.211
174.281
166.292
166.282
147.606
147.598
147.560
147.529
129.002
128.982
105.091
82.922
79.999
63.050
63.026
40.028
33.927
32.929
30.642
30.361
25.259
23.691
14.410
1.00
0.87
f1 (ppm)


27a
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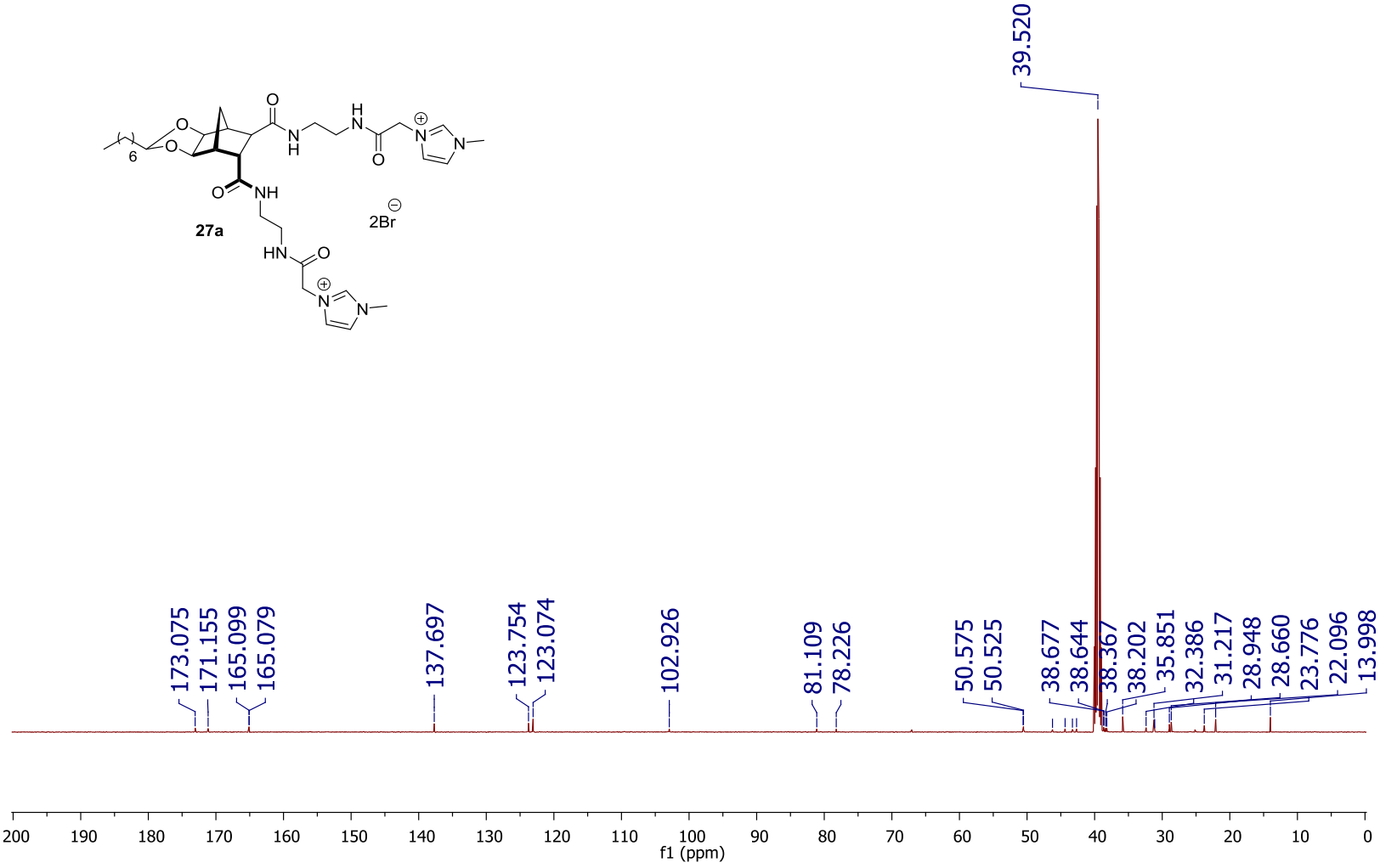
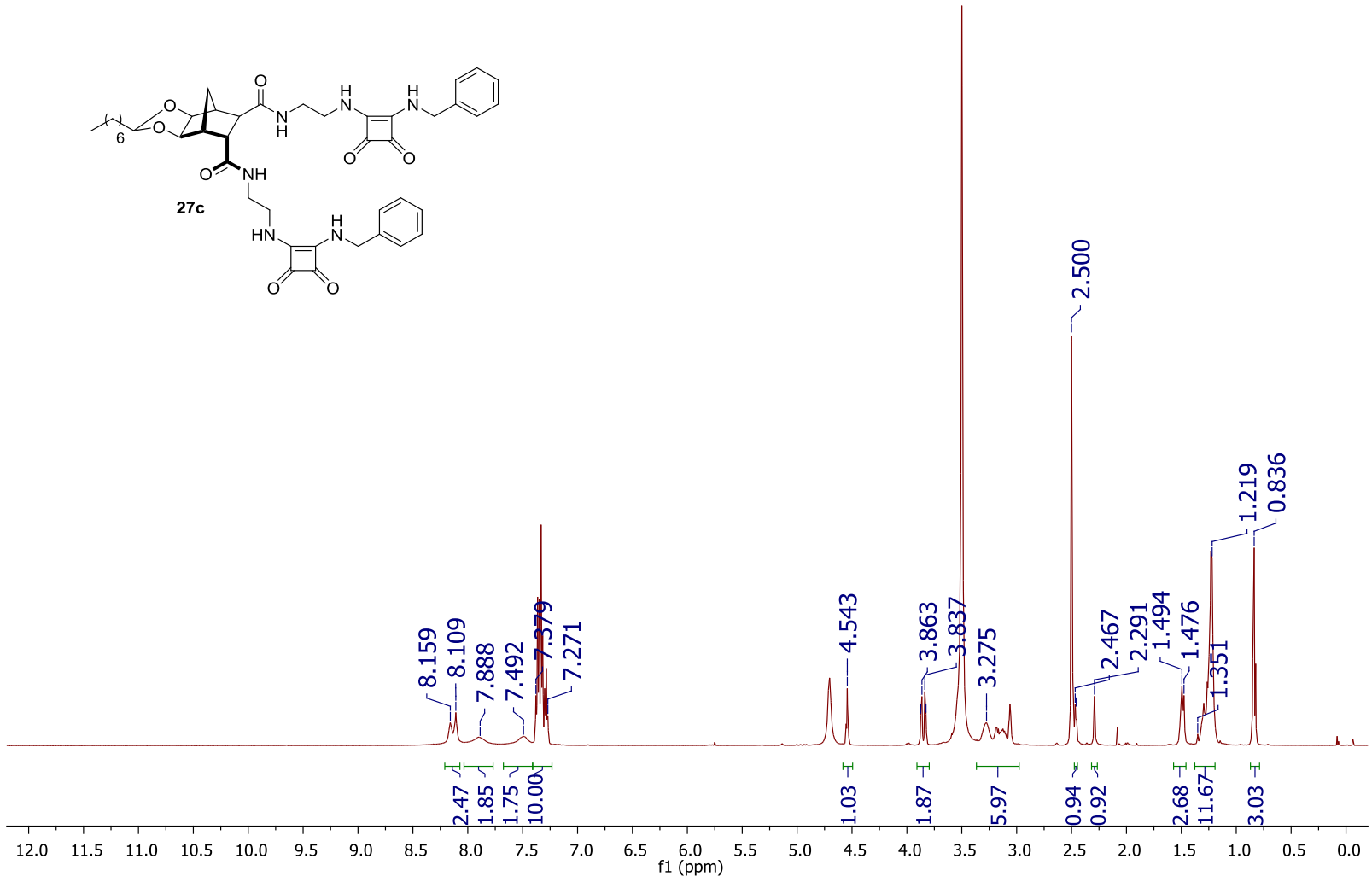
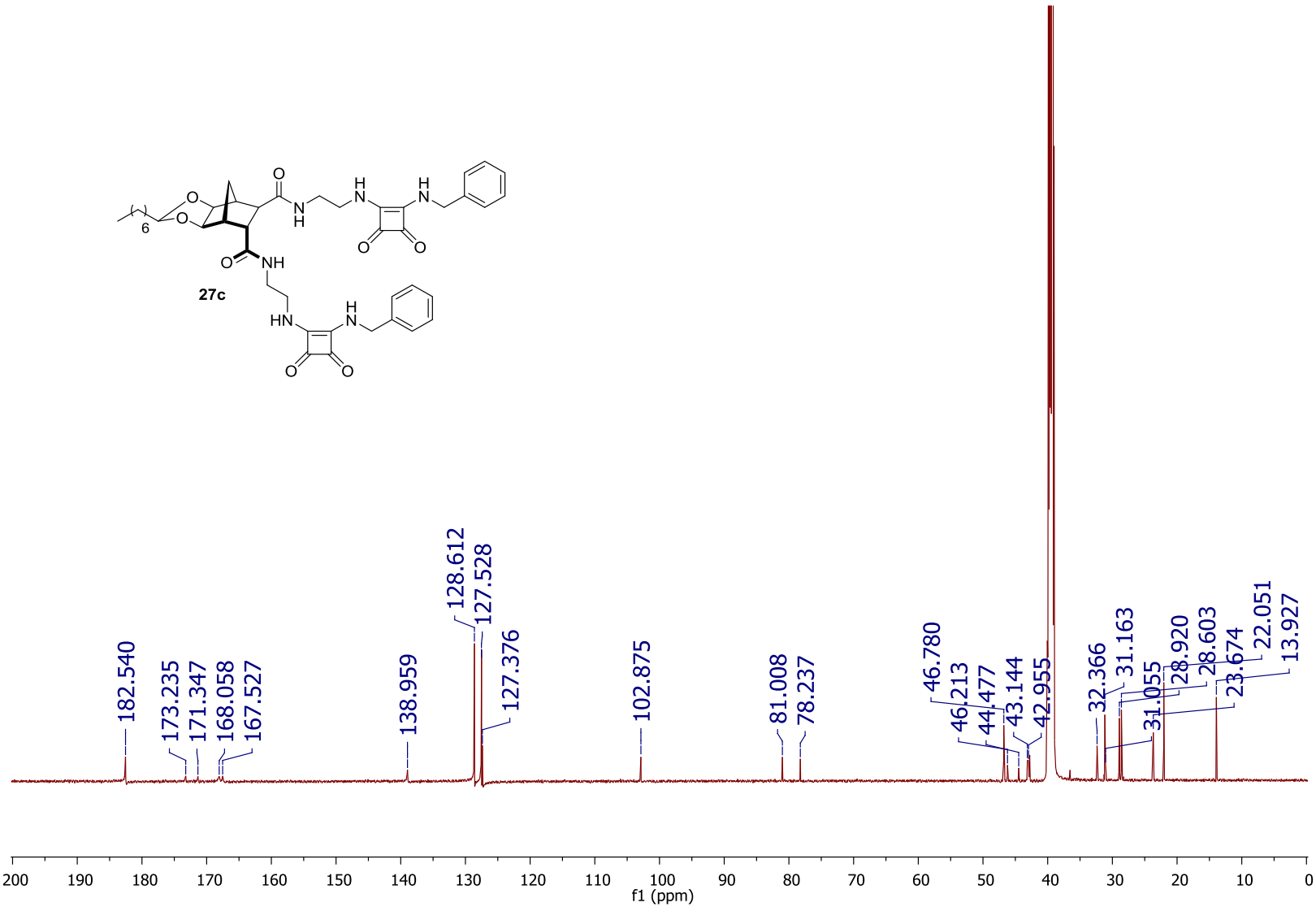
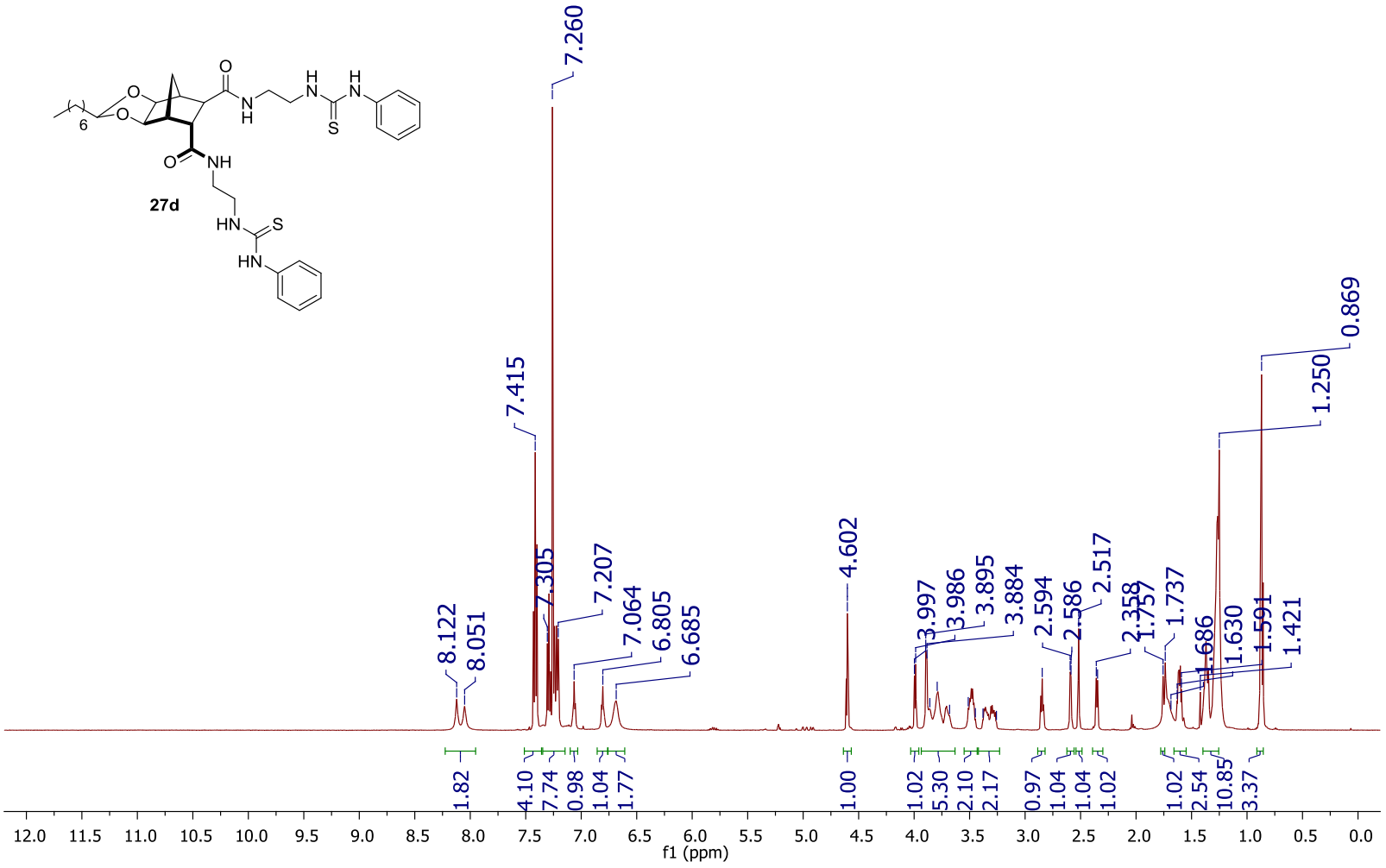
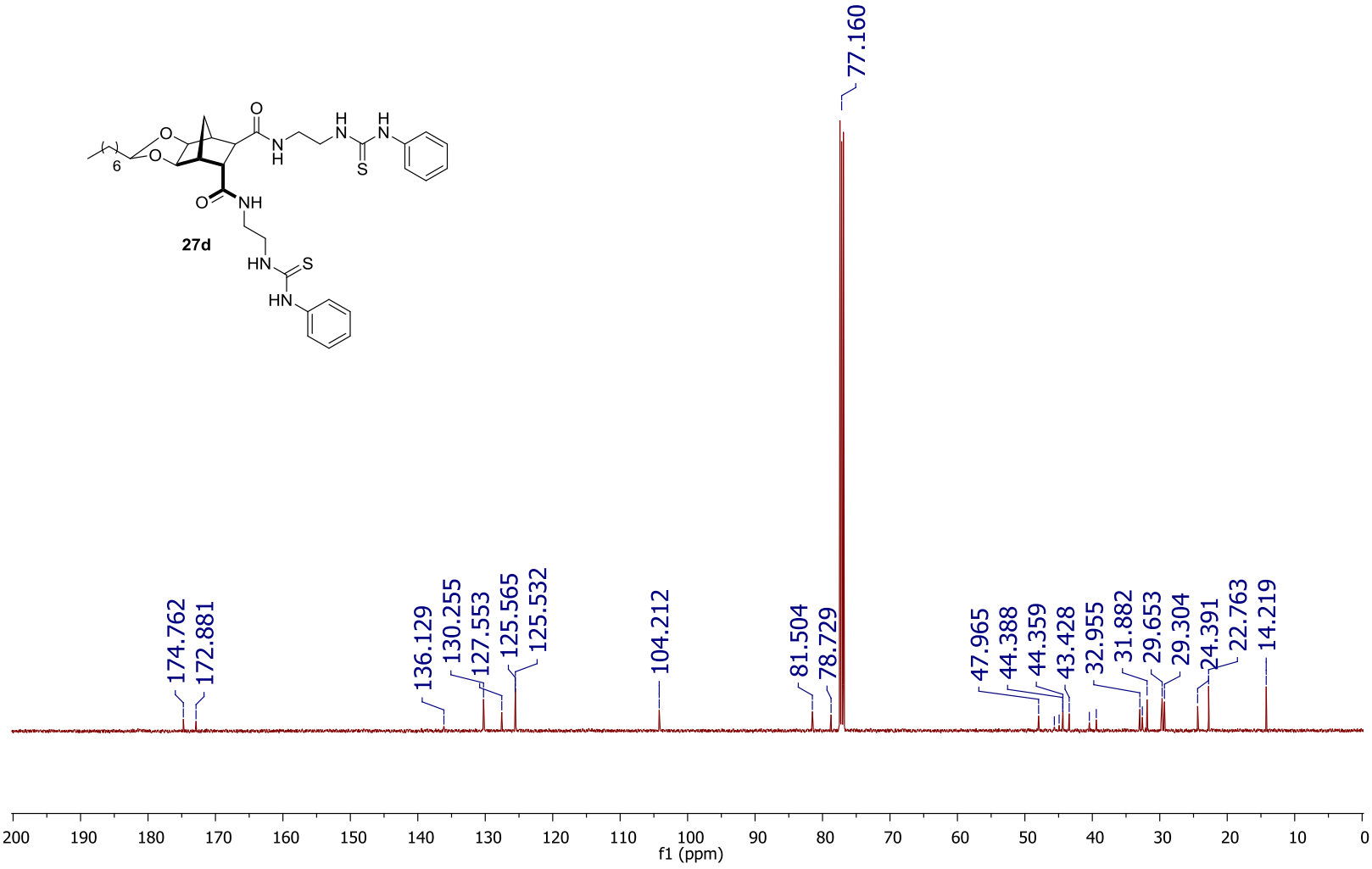
9.084
8.513
8.482
8.124
8.083
7.709
7.678
4.966
4.598
3.914
3.892
3.234
2.549
2.540
2.500
2.478
2.321
1.513
1.494
1.293
1.226
0.847
1.86
1.98
1.87
3.81
3.81
1.00
1.08
5.40
0.91
8.67
0.91
0.83
2.59
11.37
3.11
f1 (ppm)


27a
2Br
39.520
173.075
171.155
165.099
165.079
137.697
123.754
123.074
102.926
81.109
78.226
50.575
50.525
38.677
38.644
38.367
38.202
35.851
32.386
31.217
28.948
28.660
23.776
22.096
13.998
f1 (ppm)


27c
8.159
8.109
7.888
7.492
7.379
7.271
4.543
3.863
3.837
3.275
2.500
2.467
2.291
1.494
1.476
1.351
1.219
0.836
2.47
1.85
1.75
10.00
1.03
1.87
5.97
0.94
0.92
2.68
11.67
3.03
f1 (ppm)


27c
182.540
173.235
171.347
168.058
167.527
138.959
128.612
127.528
127.376
102.875
81.008
78.237
46.780
46.213
44.477
43.144
42.955
32.366
31.163
31.055
28.920
28.603
23.674
22.051
13.927
f1 (ppm)


27d
7.260
7.415
7.305
7.207
7.064
6.805
6.685
8.122
8.051
4.602
3.997
3.986
3.895
3.884
2.594
2.586
2.517
2.358
1.757
1.737
1.686
1.630
1.591
1.421
1.250
0.869
1.82
4.10
7.74
0.98
1.04
1.77
1.00
1.02
5.30
2.10
2.17
0.97
1.04
1.04
1.02
1.02
2.54
10.85
3.37
f1 (ppm)


27d
174.762
172.881
136.129
130.255
127.553
125.565
125.532
104.212
81.504
78.729
77.160
47.965
44.388
44.359
43.428
32.955
31.882
29.653
29.304
24.391
22.763
14.219
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Single Pulse Experiment

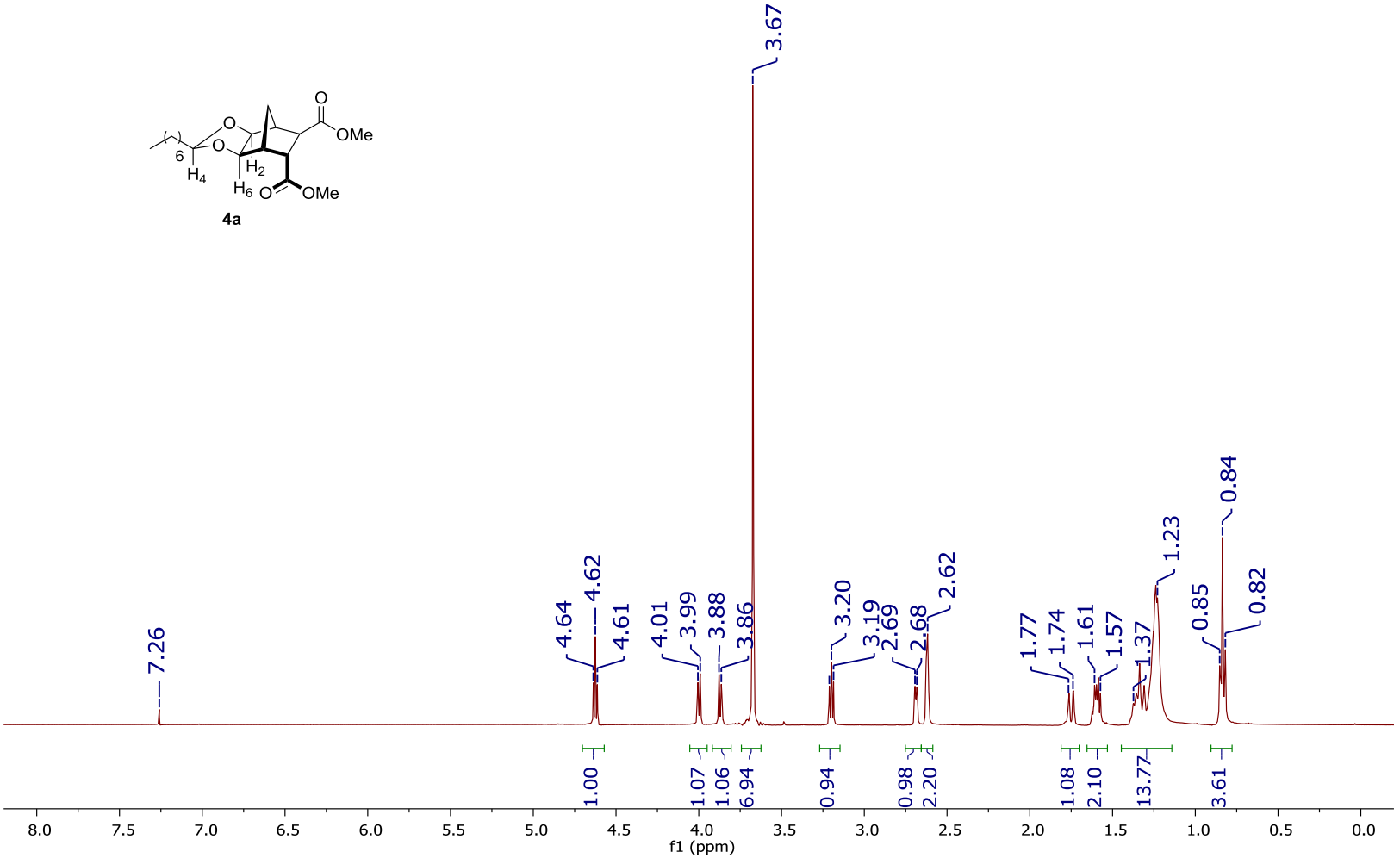


Figure S1: ^{1}H NMR spectra of acetal **4a**

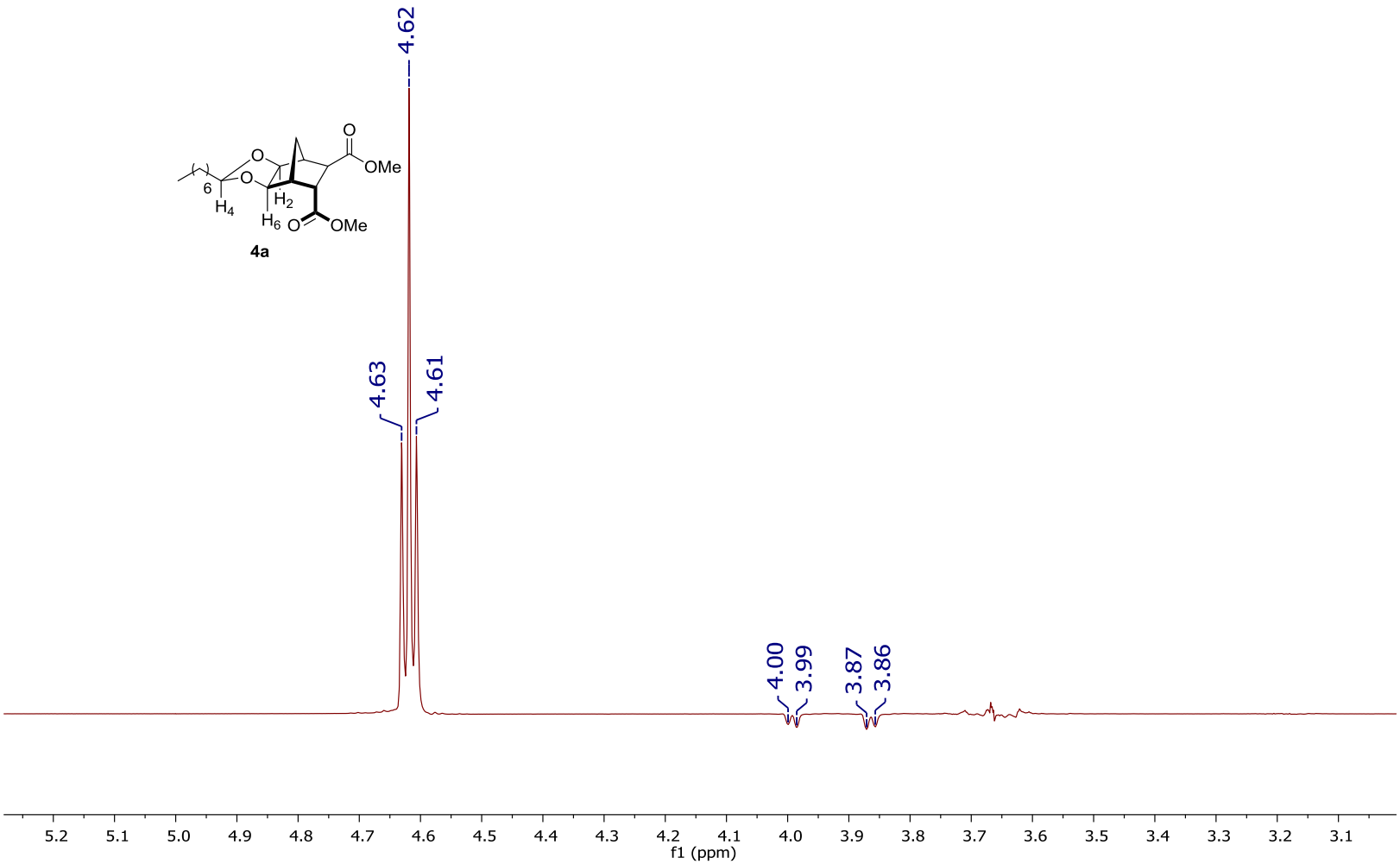


Figure S2: 1D Difference NOE spectra of acetal **4a** where proton H4 (δ = 4.62 ppm) has been irradiated.

SMH07-059C
SMH07-059C - 1H
PROTON CDCl3 {C:\Data_500\Shane} nmr 3

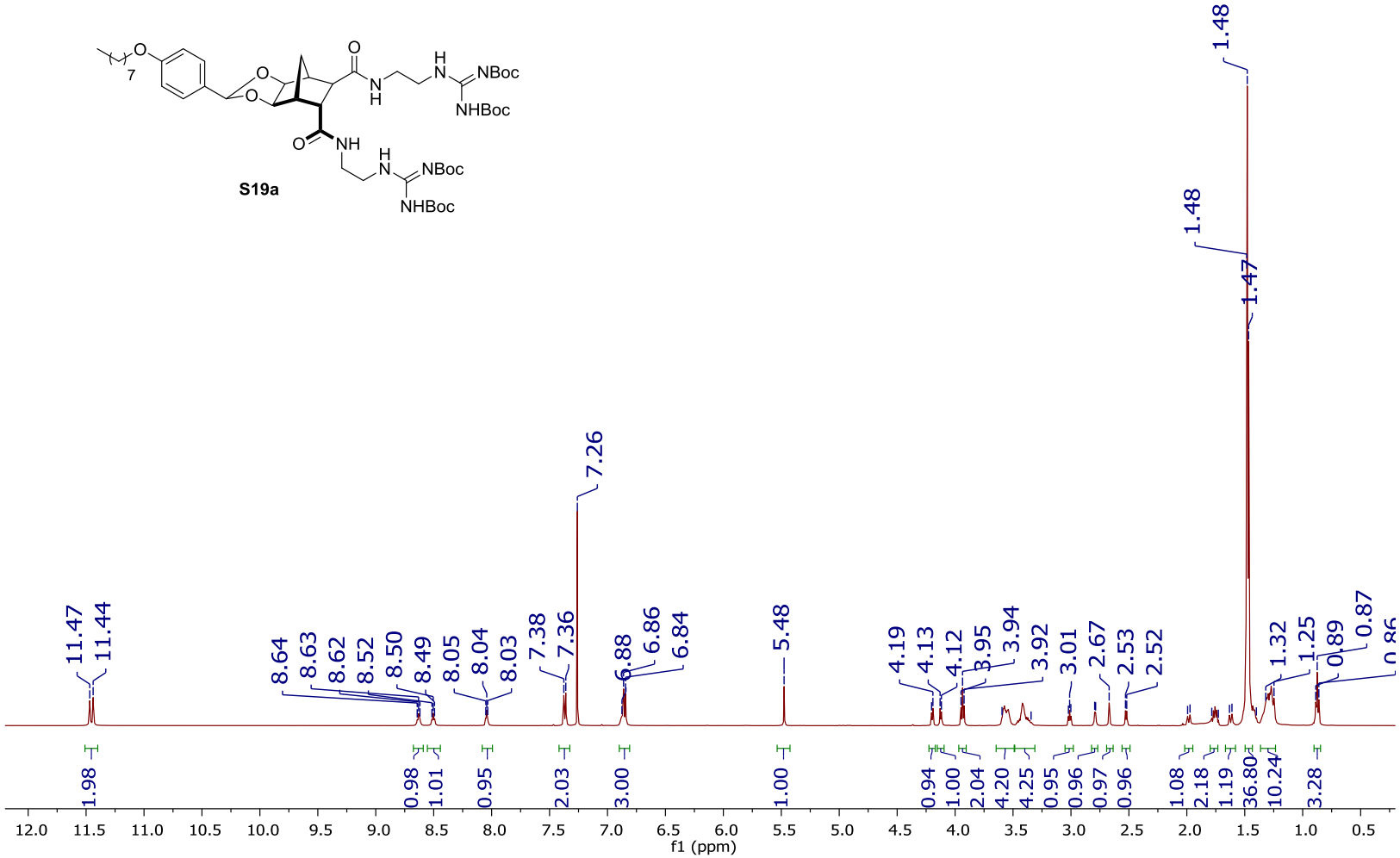


Figure S3: ^{1}H NMR spectra of **S19a**

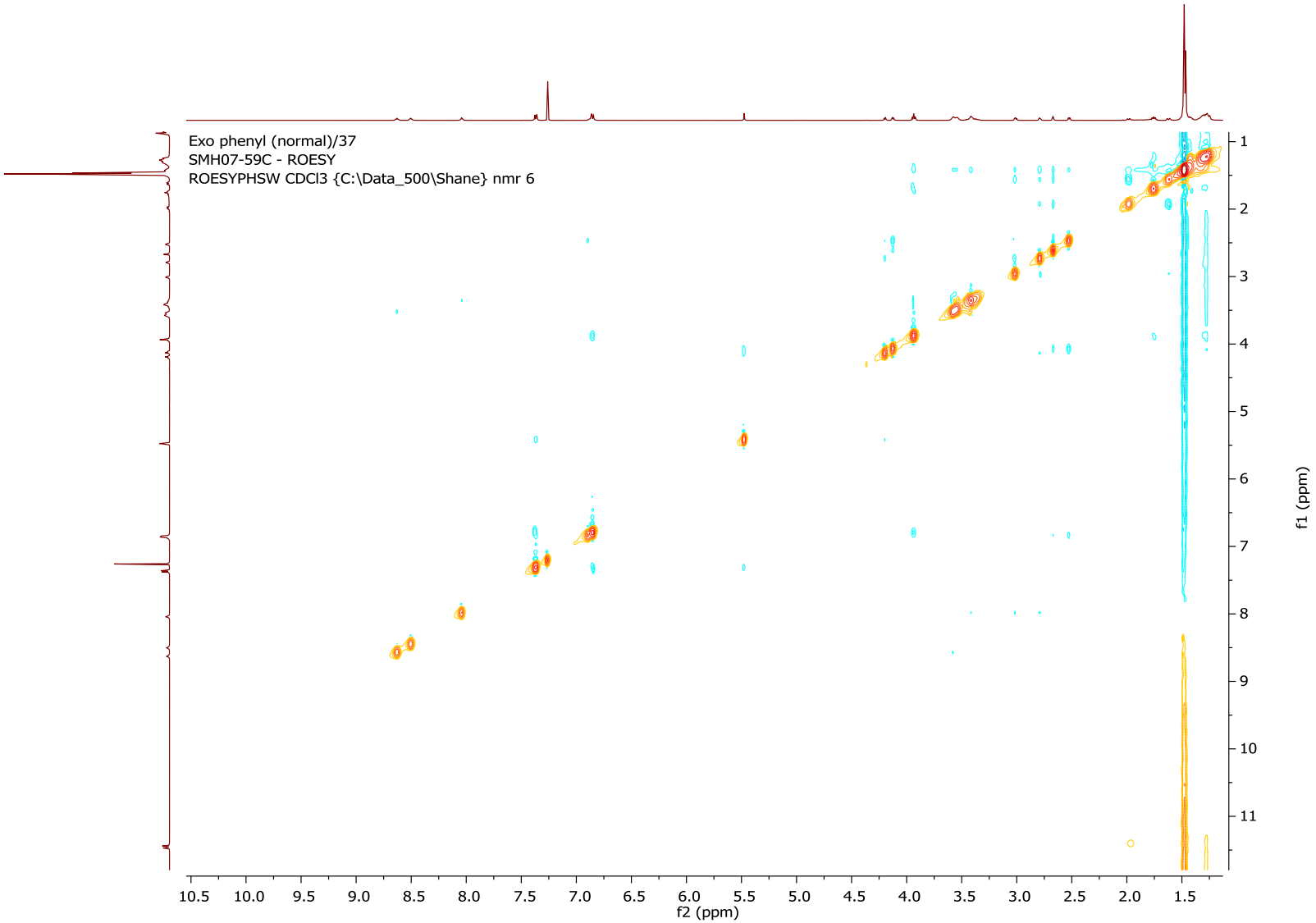


Figure S4: ROESY spectra of **S19a** (1.5–10.5 ppm)

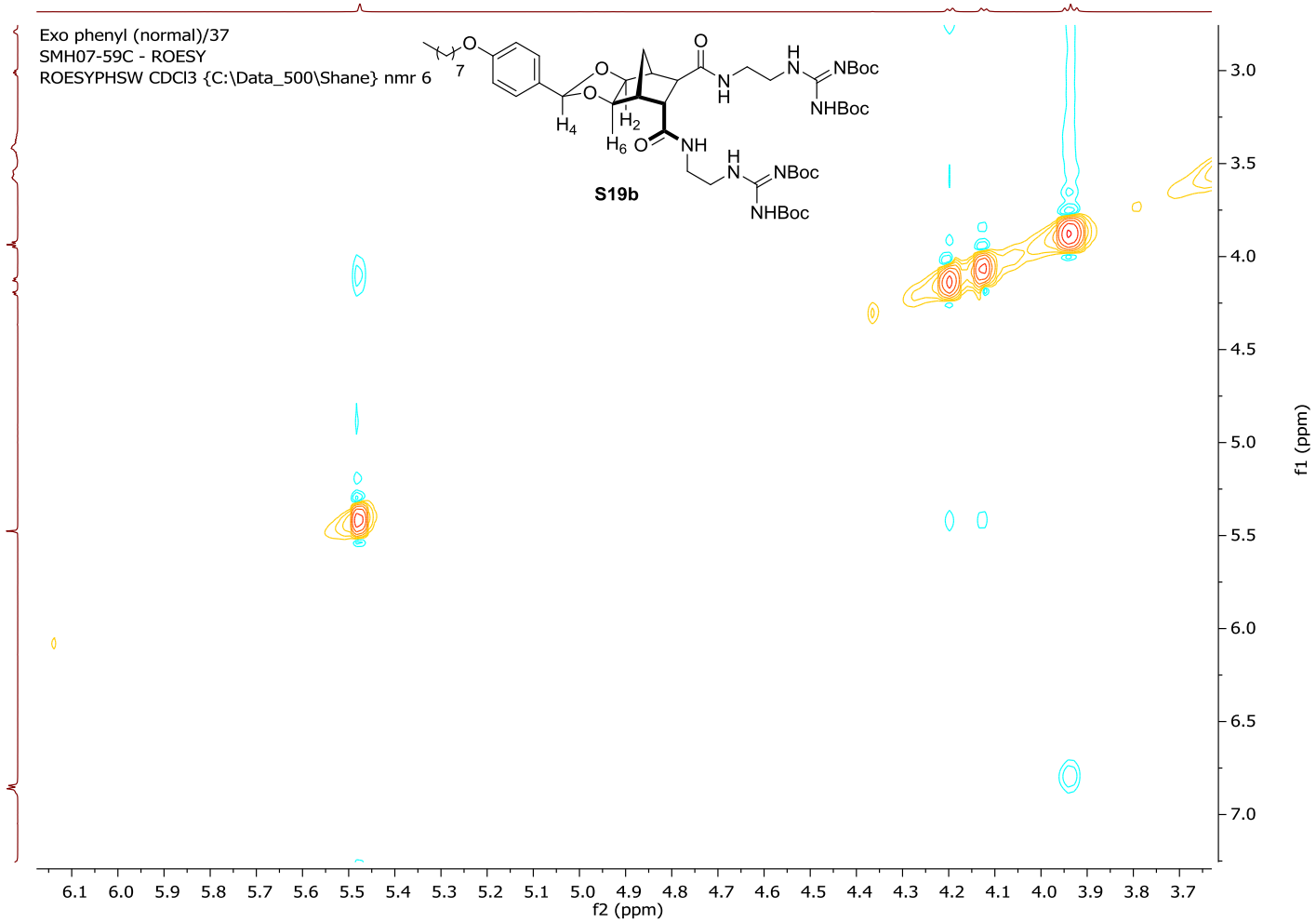


Figure S5: ROESY spectra of **S19b** (3.7–6.1 ppm)

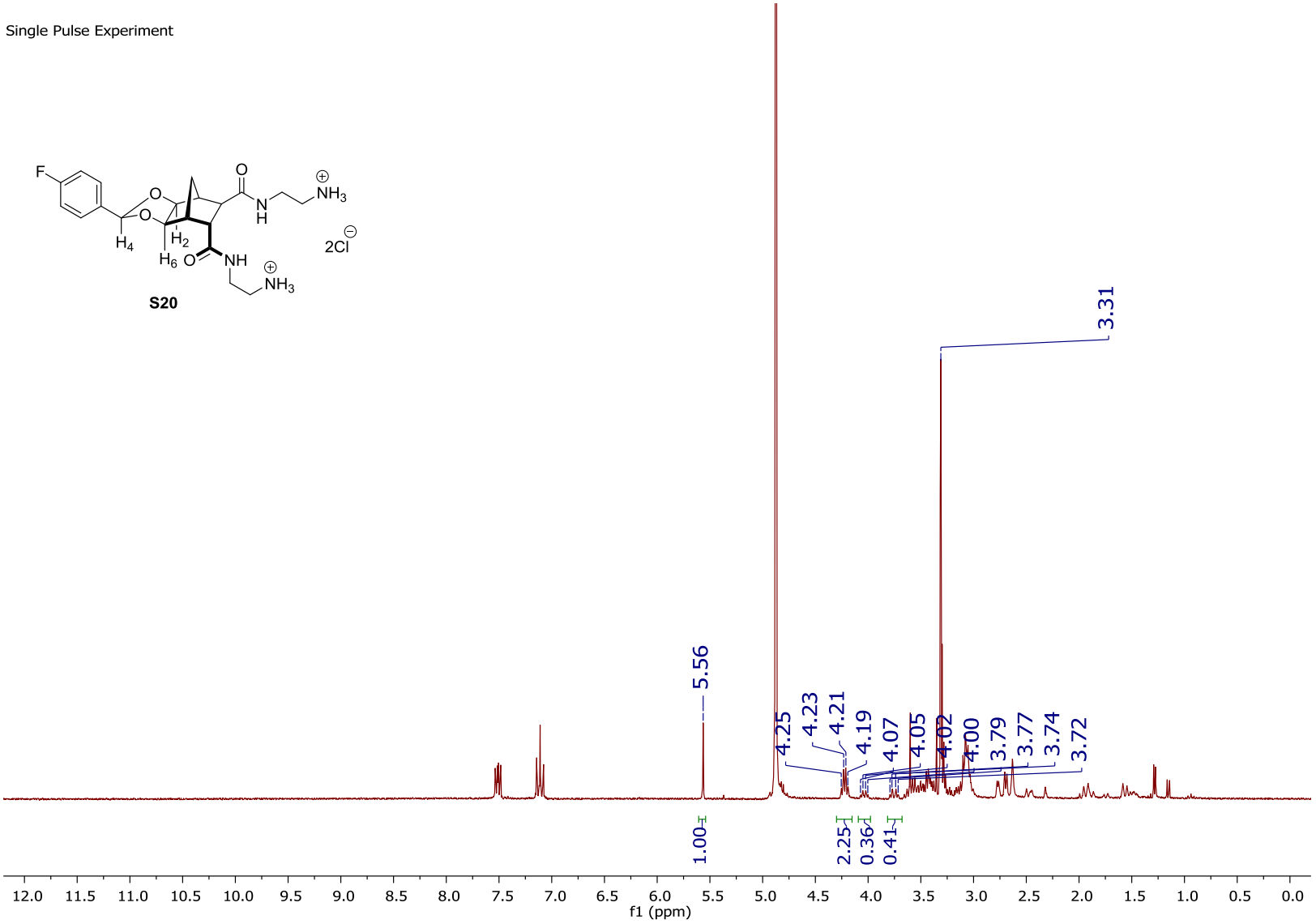
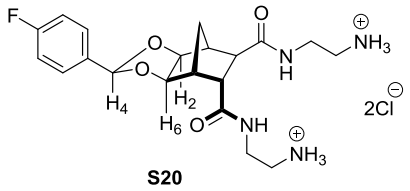


Figure S6: ^{1}H NMR spectra of **S20** (0–12.0 ppm) in CD_3OD, highlighting the relative integrations of the H4 proton to the H2 and H6 protons of the desired product and unwanted side products

Single Pulse Experiment



S20

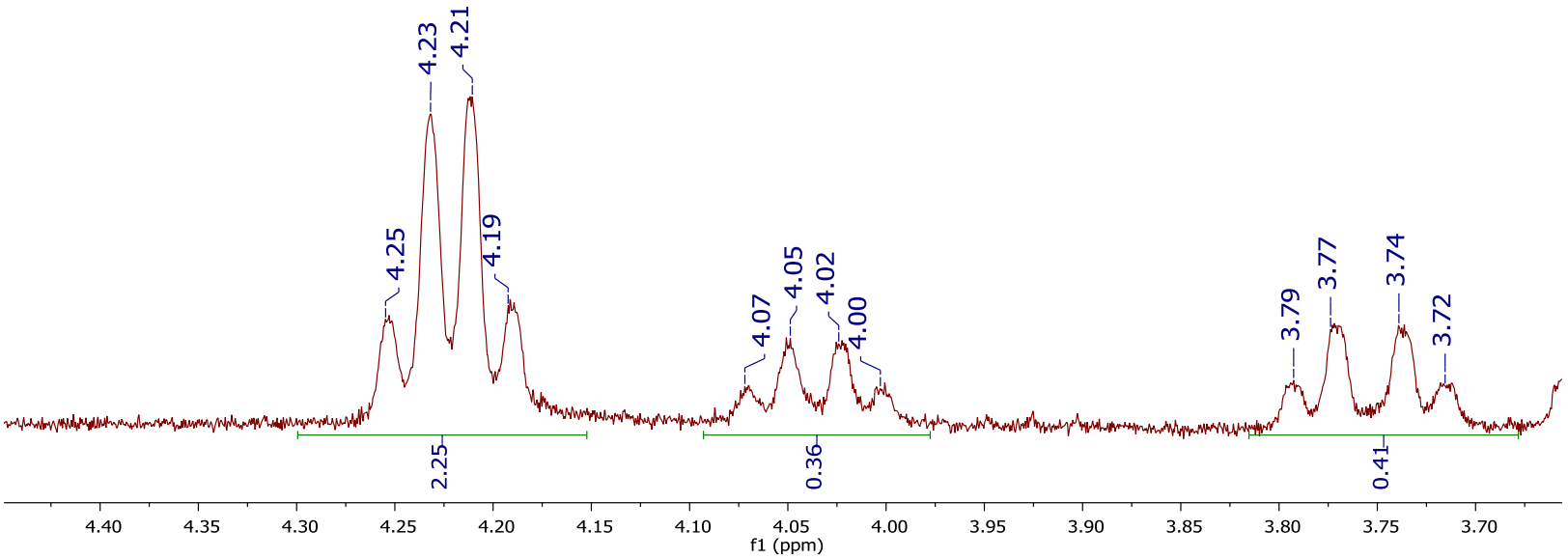


Figure S7: ^{1}H NMR spectra of **S20** (3.7–4.4 ppm) in CD_3OD highlighting the H2 and H6 protons of the desired product and unwanted side products

Intensity data were collected with an Oxford Diffraction SuperNova CCD diffractometer using Mo-K radiation, the temperature during data collection was maintained at 130.0(1) using an Oxford Cryosystems cooling device. The structure was solved by direct methods and difference Fourier synthesis.[24] Thermal ellipsoid plots were generated using the program ORTEP-3[25] integrated within the WINGX suite of programs.[26]

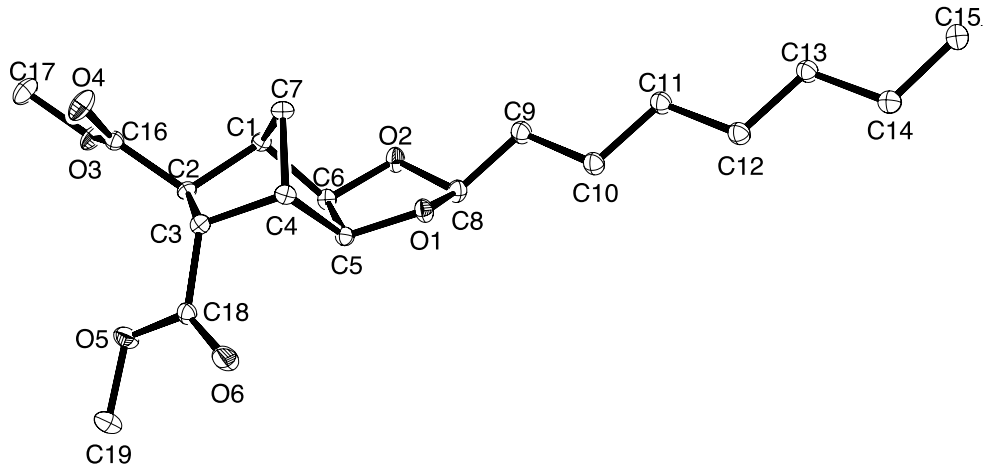


Figure S8. Thermal ellipsoid plot of **4a** Ellipsoids are at the 30% probability level

Crystal data for **4a**. $C_{19}H_{30}O_6$, M = 354.43, T = 130.0 K, λ = 0.7107, 554.22, space group P -1, a = 5.6122(2), b = 9.9184(5), c = 17.5824(10) Å, α = 102.312(5), β = 94.807(4)° γ = 102.041(4)°, V 926.69(8) Å^3, Z = 2, D_c = 1.270 Mg M^{-3} μ(Mo-Kα) 0.093 mm^{-1}, F(000) = 384, crystal size 0.59 x 0.54 x 0.23 mm^3, 7072 reflections measured, 4297 independent reflections [R(int) = 0.0188], the final R was 0.0448 [$I > 2\sigma(I)$ 3512 data] and wR(F^2) was 0.1112 (all data).

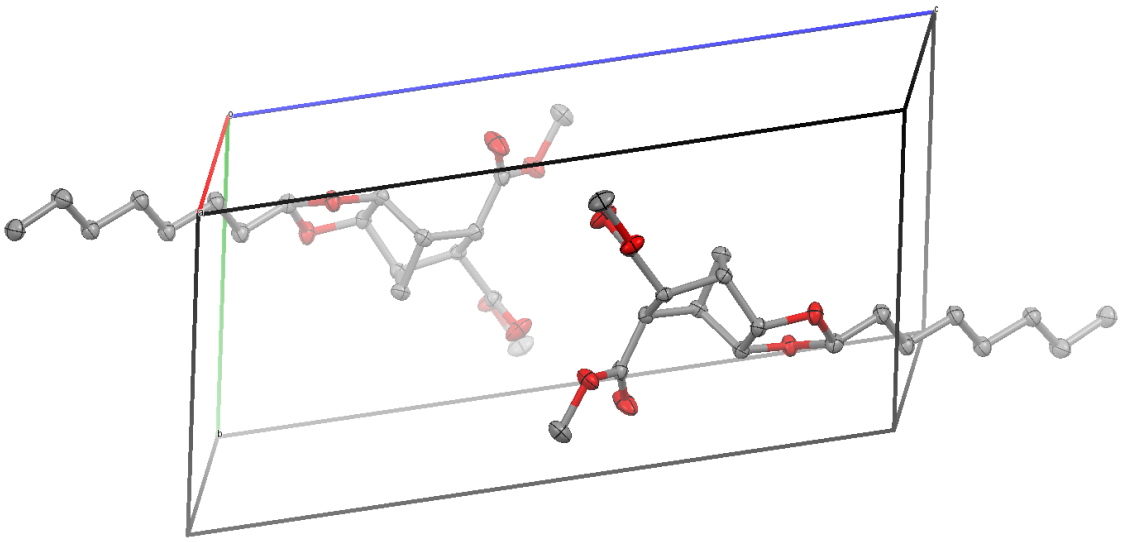


Figure S9. Unit cell structure of **4a** highlighting the amphiphilic packing.

Table S1: Bacterial strains used for Minimum Inhibitory Concentration (MIC) and disk diffusion (DD) assay

Organism	Strain	Strain description	Assay
Escherichia coli	ATCC 25922	FDA strain Seattle 1946	MIC
Klebsiella pneumoniae	ATCC 13883	Control strain	DD
Klebsiella pneumoniae	ATCC 700603	MDR (Multi-drug resistant)	MIC
Acinetobacter baumannii	ATCC 19606	Type strain	MIC/DD
Pseudomonas aeruginosa	ATCC 27853	Type strain	MIC/DD
Staphylococcus aureus	ATCC 43300	MRSA (methicillin resistant *S. aureus*)	MIC/DD
Enterococcus faecium	ATCC 700221	VRE (vancomycin resistant Enterococcus)	DD
Staphylococcus aureus	Clinical isolate from UQCCR collection	mMRSA (multi-resistant methicillin resistant *S. aureus)*	MIC
Staphylococcus aureus	NARSA-NRS 17	GISA (glycopeptide-intermediate *S. aureus*)	MIC
Staphylococcus aureus	NARSA-NRS 1	VISA (vancomycin-intermediate *S. aureus*)	MIC
Streptococcus pneumoniae	ATCC 700677	MDR (Multi-drug resistant)	MIC
Enterococcus faecalis	Clinical isolate from UQCCR collection	VanA (vancomycin resistant)	MIC

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