

Total synthesis of (±)-paracaseolide A and initial attempts on a Lewis acid mediated dimerization of its putative biosynthetic precursor

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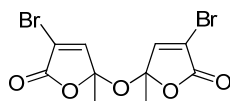
Supporting Information

Materials and Methods

All reagents were used as purchased from commercial suppliers. Solvents were purified by conventional methods prior to use. Reactions were monitored by thin layer chromatography using Machery-Nagel pre-coated TLC-sheets ALUGRAM® Xtra SIL G/UV254 and visualized with potassium permanganate [potassium permanganate (2.4 g), K₂CO₃ (16 g), 5% NaOH (4.0 mL), H₂O (240 mL)], ceric ammonium molybdate [phosphomolybdic acid (25 g), Ce(SO₄)₂·2 H₂O (10 g), H₂SO₄ conc. (60 mL), H₂O (940 mL)]. Chromatographic purification was performed as flash chromatography on Fluka silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically purified and spectroscopically pure compounds. NMR spectra were recorded on a Bruker AV-400 (operating at 400 MHz for ¹H and 100 MHz for ¹³C acquisitions), a Bruker AV-2400 (operating at 400 MHz for ¹H and 100 MHz for ¹³C acquisitions), or a Bruker DRX-500 (operating at 500 MHz for ¹H and 125 MHz for ¹³C acquisitions). Chemical shifts δ are reported in ppm with the solvent resonance as the internal standard: chloroform-d₁: 7.26 (¹H-NMR), 77.00 (¹³C-NMR). Coupling constants *J* are given in Hertz (Hz). Multiplicities are classified as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet and combinations thereof, or m = multiplet or br = broad signal. Analytical gas chromatography was performed on a Varian CP-3800 with a flame ionization detector (FID) and a Varian autosampler (CP-8400) using a capillary column (WCOT Fused Silica 15 m x 0.25 mm, 0.25 μ m CP-SIL 5CB) and nitrogen as carrier gas. High resolution mass spectra were obtained on a FinniganThermoQuest MAT 95XL. IR spectra were obtained on a Bruker ALPHA FT-IR Platinum ATR. Absorbance frequencies $\tilde{\nu}$ are reported in reciprocal centimeters (cm⁻¹). All new compounds reported here were racemic and their spectroscopic data is given below.

Procedures

Dibromo-dimer 7

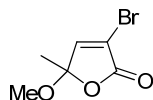


To an oven-dried 50 mL flask, containing a solution of 1.20 g (7.69 mmol, 1.00 eq.) 2-methyl-5-oxo-2,5-dihydrofuran-2-yl acetate (**6**) in 30 mL absolute dichloromethane, 866 μ L (16.9 mmol, 2.20 eq.) bromine was added dropwise and the resulting solution was heated to reflux for 3 hours. The reaction was allowed to cool to ambient temperature and quenched by addition of 10 mL sat. $\text{Na}_2\text{S}_2\text{O}_3$ -solution and 10 mL H_2O . After extraction with dichloromethane (3x 15 mL) the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/diethyl ether, 6/1 $\rightarrow$ 5/1) to afford 1.10 g (2.99 mmol, 78%) of the title compound.

^1H -NMR (300 MHz, CDCl_3) δ : 7.66 (s, 1H), 2.20 (s, 3H); ^1H -NMR (400 MHz, DMSO-d^6) δ : 7.87 (s, 1H), 1.57 (s, 3H); ^{13}C -NMR (100 MHz, DMSO-d^6) δ : 166.1, 154.1, 113.3, 106.9, 24.48; GC/MS (EI): DB-50_L, t_r = 7.72 min; m/z = 175, 177 $[\text{M-C}_5\text{H}_4\text{BrO}_3]^+$, compound **7** is too labile to facilitate detection of $[\text{M}]^+$ or $[\text{M}+\text{H}]^+$ employing different ionisation modes (EI, ESI, APCI); IR (ATR): 3098, 1783, 1602, 1439, 1380, 1278, 1250, 1139, 1101, 1067, 961, 870, 771, 751, 969, 576, 547, 397 cm^{-1} .

C₁₀H₈Br₂O₅ (367.98).

Bromobutenolide 8

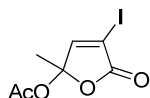


An oven-dried 10 mL flask, containing a solution of 87.4 mg (0.328 mmol, 1.00 eq.) 5,5'-oxybis(3-bromo-5-methylfuran-2(5H)-one) (**7**) and 9.0 mg (0.048 mmol, 0.20 eq.) *p*TSA· H_2O in 3.0 mL absolute methanol was heated to reflux for 1 hour. The reaction was allowed to cool to ambient temperature and quenched by addition of 3.0 mL sat. NaHCO_3 -solution. After extraction with diethyl ether (3x 5 mL) the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 20/1 $\rightarrow$ 15/1) to afford 37.0 mg (0.179 mmol, 38%) of the title compound.

^1H -NMR (500 MHz, CDCl_3) δ : 7.23 (s, 1H), 3.27 (s, 3H), 1.68 (s, 3H); ^{13}C -NMR (125 MHz, CDCl_3) δ : 165.5, 150.9, 116.2, 108.6, 51.58, 23.76; MS (EI): m/z = 206, 208 $[\text{M}]^+$; 191, 193 $[\text{M-Me}]^+$; 175, 177 $[\text{M-OMe}]^+$; IR (ATR): 3076, 2951, 1764, 1614, 1455, 1381, 1269, 1216, 1178, 1127, 1111, 1053, 983, 942, 889, 838, 761, 711, 603, 578, 432, 404 cm^{-1} ; m.p.: 79.1°C.

C₆H₇BrO₃ (207.02).

Iodobutenolide 9

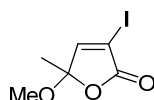


To an oven-dried 250 mL flask, containing a solution of 3.10 g (19.9 mmol, 1.00 eq.) 2-methyl-5-oxo-2,5-dihydrofuran-2-yl acetate (**6**) in 75 mL solvent mixture (chloroform/pyridine 1/1), a solution of 20.2 g (79.4 mmol, 4.00 eq.) iodine in 75 mL solvent mixture (chloroform/pyridine 1/1) was added and the resulting solution was heated to 45°C for 24 hours. The reaction was allowed to cool to ambient temperature and quenched by addition of 250 mL sat. Na₂S₂O₃-solution. After extraction with diethyl ether (3x 120 mL) the combined organic phases were dried over Na₂SO₄ and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 5/1 → 2/1) to afford 5.20 g (18.5 mmol, 93%) of the title compound.

¹H-NMR (300 MHz, CDCl₃) δ: 7.88 (s, 1H), 2.06 (s, 3H), 1.79 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ: 168.5, 166.4, 158.0, 108.0, 88.58, 22.88, 21.33; GC/MS (EI): DB-50_L, t_r = 8.62 min; m/z = 282 [M]⁺; HR-MS (ESI) m/z calculated for C₅H₄IO₂ [M-OAc]⁺ 222.9250, found 222.9249; IR (ATR): 3104, 2999, 2940, 1762 cm⁻¹.

C₇H₇IO₄ (282.03).

Iodobutenolide 10

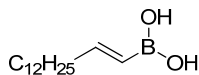


To an oven-dried 10 mL flask, containing a solution of 209 mg (0.737 mmol, 1.00 eq.) 4-iodo-2-methyl-5-oxo-2,5-dihydrofuran-2-yl acetate (**9**) in 4.0 mL absolute methanol, 10.5 μL (0.147 mmol, 0.20 eq.) acetyl chloride was added and the resulting solution was heated to reflux for 3.5 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 8/1 → 7/1) to afford 142 mg (0.558 mmol, 76%) of the title compound.

¹H-NMR (300 MHz, CDCl₃) δ: 7.45 (s, 1H), 3.25 (s, 3H), 1.64 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ: 166.9, 159.6, 110.7, 89.07, 51.58, 23.55; GC/MS (EI): DB-50_L, t_r = 7.82 min; m/z = 294 [M]⁺; MS (ESI): m/z = 223 [M-OMe]⁺.

C₆H₇IO₃ (254.02).

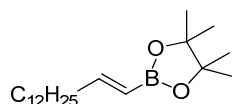
Vinylboronic acid 12¹



¹H-NMR (400 MHz, DMSO-d₆) δ: 7.42 (s, 2H), 6.42 (dt, *J* = 17.8, 6.4 Hz, 1H), 5.29 (d, *J* = 17.8 Hz, 1H), 2.05 (dd, *J* = 13.2, 6.5 Hz, 2H), 1.38 – 1.23 (m, 20H), 0.85 (t, *J* = 6.7 Hz, 3H); ¹³C-NMR (125 MHz, DMSO-d₆) δ: 150.0, 35.01, 31.30, 29.06 (2C), 29.02(2C), 28.92, 28.72, 28.62, 28.09, 22.10, 13.95, C-1 not detected; MS (ESI): m/z = 263 [M+Na]⁺; HR-MS (-ESI) m/z calculated for C₁₄H₂₈BO₂ [M-H]⁻ 239.2182, found 239.2187; IR (ATR): 3330, 2956, 2916, 2849, 1634, 1468, 1424, 1349, 1257, 1234, 1147, 1030, 988, 932, 789, 719, 642, 620, 584, 522 cm⁻¹; m.p.: 80.3°C.

C₁₄H₂₉BO₂ (240.19).

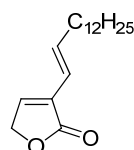
Alkenylboronate 17²



¹H-NMR (300 MHz, CDCl₃) δ: 6.63 (dt, *J* = 18.0, 6.4 Hz, 1H), 5.42 (dt, *J* = 17.9, 1.5 Hz, 1H), 2.20 – 2.07 (m, 2H), 1.46 – 1.35 (m, 2H), 1.34 – 1.14 (m, 30H), 0.87 (t, *J* = 6.7 Hz, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ: 154.9, 82.95, 35.84, 31.91, 29.67, 29.66, 29.63, 29.58, 29.50, 29.35, 29.24, 28.21, 24.76, 22.68, 14.12, C-1 not detected; GC/MS (EI): DB-50_L, *t_r* = 10.90 min; *m/z* = 322 [M]⁺.

C₂₀H₃₉BO₂ (322.33).

3-Alkenylbutenolide 13

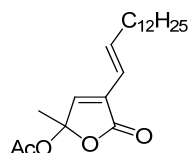


Under argon-atmosphere a 25 mL flask, containing a solution of 67.9 mg (0.416 mmol, 1.00 eq.) 3-bromofuran-2(5H)-one (**11**), 100 mg (0.416 mmol, 1.00 eq.) (*E*)-tetradec-1-en-1-ylboronic acid (**12**), 407 mg (1.25 mmol, 3.00 eq.) Cs₂CO₃ and 13.6 mg (0.021 mmol, 5 mol%) dichloro[1,1'-bis(di-*tert*-butylphosphino) ferrocene] palladium(II) [Pd(dtbpf)Cl₂, (Pd-118)] in 11,0 mL absolute degassed solvent mixture (THF/H₂O 10/1) was heated to 80°C for 1 hour. The reaction was allowed to cool to ambient temperature and quenched by addition of 10 mL H₂O. After extraction with diethyl ether (3x 10 mL) the combined organic phases were dried over Na₂SO₄ and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/diethyl ether, 5/1 → 2/1) to afford 79.7 mg (0.286 mmol, 69%) of the title compound.

¹H-NMR (400 MHz, CDCl₃) δ: 7.13 (s, 1H), 6.85 – 6.74 (m, 1H), 6.12 (d, *J* = 15.9 Hz, 1H), 4.80 (s, 2H), 2.16 (q, *J* = 7.1 Hz, 2H), 1.48 – 1.38 (m, 2H), 1.26 (d, *J* = 8.0 Hz, 18H), 0.87 (t, *J* = 6.8 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ: 172.6, 141.9, 138.7, 129.7, 118.2, 69.63, 33.38, 31.90, 29.66, 29.64, 29.63, 29.56, 29.46, 29.34, 29.22, 28.75, 22.67, 14.10; GC/MS (EI): DB-50_L, *t_r* = 11.77 min; *m/z* = 278 [M]⁺; HR-MS (ESI) *m/z* calculated for C₁₈H₃₁O₂ [M+H]⁺ 279.2319, found 279.2324.

C₁₈H₃₀O₂ (278.43).

3-Alkenylbutenolide 14



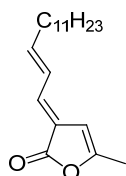
Under argon-atmosphere a flame-dried 25 mL flask, containing a solution of 100 mg (0.355 mmol, 1.00 eq.) 4-iodo-2-methyl-5-oxo-2,5-dihydrofuran-2-yl acetate (**9**), 102 mg (0.425 mmol, 1.20 eq.) (*E*)-tetradec-1-en-1-ylboronic acid (**12**), 162 mg (1.06 mmol, 3.00 eq.) CsF and 11.6 mg (0.018 mmol, 5 mol%) dichloro[1,1'-bis(di-*tert*-butylphosphino) ferrocene] palladium(II) [Pd(dtbpf)Cl₂, (Pd-118)] in 7,0 mL absolute degassed THF was heated to 60°C for 1 hour. The reaction was allowed to cool to ambient temperature and quenched by addition of 10 mL H₂O. After extraction with diethyl ether (3x 10 mL) the combined organic phases were dried over Na₂SO₄

and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/diethyl ether, 15/1 $\rightarrow$ 10/1) to afford 96.9 mg (0.276 mmol, 78%) of the title compound and 19.6 mg (0.067 mmol, 19%) of elimination product (*E*)-5-methyl-3-((*E*)-tetradec-2-en-1-ylidene)furan-2(3H)-one (**16**).

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.22 (s, 1H), 6.85 (dt, J = 15.8, 7.1 Hz, 1H), 6.07 (dd, J = 15.9, 0.6 Hz, 1H), 2.22 – 2.11 (m, 2H), 2.06 (s, 3H), 1.82 (s, 3H), 1.49 – 1.36 (m, 2H), 1.26 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 168.9, 168.7, 141.7, 141.5, 131.0, 117.6, 105.4, 33.54, 31.91, 29.66, 29.64, 29.63, 29.55, 29.45, 29.34, 29.22, 28.59, 23.06, 22.68, 21.53, 14.12; MS (EI): m/z = 350 $[\text{M}]^+$; HR-MS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{31}\text{O}_2$ $[\text{M-OAc}]^+$ 291.2319, found 291.2325; calculated for $\text{C}_{21}\text{H}_{34}\text{NaO}_4$ $[\text{M+Na}]^+$ 373.2349, found 373.2353; calculated for $\text{C}_{21}\text{H}_{34}\text{KO}_4$ $[\text{M+K}]^+$ 389.2089, found 389.2093; IR (ATR): 2960, 2914, 2849, 1775, 1742 cm^{-1} .

C₂₁H₃₄O₄ (350.49).

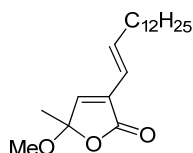
Triene 16



$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 6.87 (d, J = 10.0 Hz, 1H), 6.39 – 6.18 (m, 2H), 5.96 – 5.90 (m, 1H), 2.22 (dd, J = 13.6, 6.9 Hz, 2H), 2.13 (s, 3H), 1.49 – 1.39 (m, 2H), 1.34 – 1.22 (m, 16H), 0.87 (t, J = 6.7 Hz, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 169.7, 155.3, 147.2, 134.1, 126.5, 124.7, 101.2, 33.51, 31.90, 29.61, 29.60, 29.53, 29.41, 29.33, 29.21, 28.68, 22.67, 14.62, 14.11; HR-MS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{31}\text{O}_2$ $[\text{M+H}]^+$ 291.2319, found 291.2324; IR (ATR): 3113, 2916, 2848, 1762, 1638 cm^{-1} .

C₁₉H₃₀O₂ (290.44).

3-Alkenylbutenolide 15



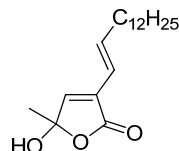
Under argon-atmosphere a flame-dried 25 mL flask, containing a solution of 140 mg (0.551 mmol, 1.00 eq.) 3-iodo-5-methoxy-5-methylfuran-2(5H)-one (**10**), 159 mg (0.661 mmol, 1.20 eq.) (*E*)-tetradec-1-en-1-ylboronic acid (**12**), 251 mg (1.65 mmol, 3.00 eq.) CsF and 18.0 mg (0.028 mmol, 5 mol%) dichloro[1,1'-bis(di-tert-butylphosphino) ferrocene] palladium(II) $[\text{Pd}(\text{dtbpf})\text{Cl}_2$, (Pd-118)] in 10,8 mL absolute degassed THF was heated to 60°C for 1.5 hours. The reaction was allowed to cool to ambient temperature and quenched by addition of 10 mL H_2O . After extraction with diethyl ether (3x 10 mL) the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/diethyl ether, 20/1 $\rightarrow$ 5/1) to afford 160 mg (0.495 mmol, 90%) of the title compound.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 6.86 (dt, J = 15.7, 7.0 Hz, 1H), 6.71 (s, 1H), 6.09 (dd, J = 15.9, 0.6 Hz, 1H), 3.21 (s, 3H), 2.16 (dt, J = 8.0, 4.1 Hz, 2H), 1.63 (s, 3H), 1.48 – 1.39 (m, 2H), 1.25 (s, 18H), 0.87 (t, J = 6.7 Hz, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 169.4, 142.9, 141.0, 132.4, 117.8, 106.8, 51.14, 33.51, 31.90, 29.65, 29.64, 29.62,

29.55, 29.44, 29.34, 29.24, 28.62, 24.03, 22.67, 14.11; GC/MS (EI): DB-50_L, t_r = 11.75 min; m/z = 322 $[M]^+$; HR-MS (ESI) m/z calculated for $C_{20}H_{35}O_3$ $[M+H]^+$ 323.2581, found 323.2589.

C₂₀H₃₄O₃ (322.48).

3-Alkenylbutenolide **4**

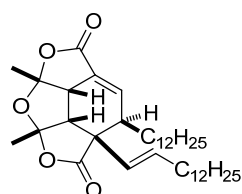


A 10 mL flask, containing a solution of 27.0 mg (0.077 mmol, 1.00 eq.) (*E*)-2-methyl-5-oxo-4-(tetradec-1-en-1-yl)-2,5-dihydrofuran-2-yl acetate (**14**) and 7.10 mg (0.169 mmol, 2.20 eq.) LiOH·H₂O in 1.0 mL solvent mixture (THF/H₂O 3/1) was stirred at ambient temperature for 4 hours. The reaction was quenched by addition of 10 mL 1N-HCl-solution. After extraction with diethyl ether (3x 5 mL) the combined organic phases were dried over Na₂SO₄ and the solvent was removed *in vacuo* to afford 23.7 mg (0.077 mmol, quant.) of the title compound.

¹H-NMR (300 MHz, CDCl₃) δ : 6.88 – 6.71 (m, 2H), 6.04 (d, J = 15.8 Hz, 1H), 3.60 (br s, 1H), 2.15 (q, J = 6.9 Hz, 2H), 1.69 (s, 3H), 1.47 – 1.37 (m, 2H), 1.25 (br s, 18H), 0.87 (t, J = 6.7 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃) δ : 169.8, 143.8, 141.1, 130.8, 117.7, 103.8, 33.50, 31.90, 29.66, 29.64, 29.63, 29.56, 29.45, 29.34, 29.22, 28.63, 24.81, 22.67, 14.11; HR-MS (ESI) m/z calculated for $C_{19}H_{33}O_3$ $[M+H]^+$ 309.2424, found 309.2416; calculated for $C_{19}H_{32}NaO_3$ $[M+Na]^+$ 331.2244, found 331.2239; IR (ATR): 2960, 2914, 2849, 1756, 1659 cm⁻¹.

C₁₉H₃₂O₃ (308.46).

Paracaseolide A (**1**)^{3a,b}



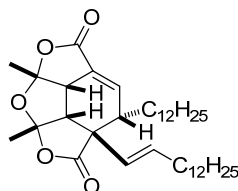
A sealed 10 mL flask, containing 309 mg (1.00 mmol, 1.00 eq.) (*E*)-5-hydroxy-5-methyl-3-(tetradec-1-en-1-yl)furan-2(5H)-one (**4**) was heated to 110 °C for 14 hours, whereupon the reaction was allowed to cool to ambient temperature. ¹H-NMR of the crude product showed a mixture of Paracaseolide A (**1**), its *C*7-Epimer (*C*7-*epi* **1**), α,γ -disubstituted butenolide **19** and starting material **4** in a ratio of 3.7 / 1 / 1.2 / 1.4. The reaction was resumed for further 20 hours, after which complete conversion was achieved. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 5/1 $\rightarrow$ 2/1) to afford 167 mg (0.279 mmol, 56%) Paracaseolide A (**1**), 37.7 mg (0.063 mmol, 13%) of its *C*7-Epimer (*C*7-*epi* **1**) and 34.2 mg (0.111 mmol, 11%) α,γ -disubstituted butenolide **19**.

¹H-NMR (300 MHz, CDCl₃) δ : 7.24 (dd, J = 7.8, 3.0 Hz, 1H), 5.83 (dt, J = 15.7, 6.9 Hz, 1H), 5.48 (d, J = 15.8 Hz, 1H), 3.37 (dd, J = 9.5, 3.1 Hz, 1H), 3.30 (d, J = 9.6 Hz, 1H), 3.03 (ddd, J = 11.2, 7.6, 3.7 Hz, 1H), 2.11 (q, J = 6.7 Hz, 2H), 1.75 (s, 3H), 1.71 – 1.65 (m, 1H), 1.61 (s, 3H), 1.42 – 1.34 (m, 2H), 1.33 – 1.14 (m, 39H), 0.87 (t, J = 6.7 Hz, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ : 175.1, 166.2, 144.7, 135.1, 129.3, 126.2, 115.4, 113.8, 58.31, 50.17, 46.63, 45.03, 32.67, 31.89, 29.66, 29.63, 29.60, 29.52, 29.39, 29.33, 29.09, 28.99, 28.18, 27.93, 26.52,

25.65, 22.67, 14.10; HR-MS (ESI) m/z calculated for $C_{38}H_{63}O_5$ $[M+H]^+$ 599.4670, found 599.4667; calculated for $C_{38}H_{62}NaO_5$ $[M+Na]^+$ 621.4489, found 621.4484.

$C_{38}H_{62}O_5$ (598.90).

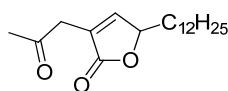
C-7 epi 1^{3b}



1H -NMR (300 MHz, $CDCl_3$) δ : 6.98 (dd, $J = 4.0, 3.4$ Hz, 1H), 5.68 (dt, $J = 15.7, 6.8$ Hz, 1H), 5.43 (d, $J = 15.8$ Hz, 1H), 3.28 (ddd, $J = 9.9, 3.1, 2.0$ Hz, 1H), 3.20 (d, $J = 9.9$ Hz, 1H), 2.21 – 2.05 (m, 3H), 1.74 (s, 3H), 1.59 (s, 3H), 1.43 – 1.20 (s, 42H), 0.88 (t, $J = 6.7$ Hz, 6H); ^{13}C -NMR (75 MHz, $CDCl_3$) δ : 173.2, 165.8, 144.3, 135.2, 130.2, 127.2, 114.7, 113.7, 59.88, 55.26, 47.37, 45.85, 32.62, 31.91, 29.67, 29.64, 29.62, 29.58, 29.42, 29.38, 29.35, 29.15, 29.00, 28.56, 27.49, 26.64, 25.59, 22.68, 14.12; HR-MS (ESI) m/z calculated for $C_{38}H_{63}O_5$ $[M+H]^+$ 599.4670, found 599.4670; calculated for $C_{38}H_{62}NaO_5$ $[M+Na]^+$ 621.4489, found 621.4486.

$C_{38}H_{62}O_5$ (598.90).

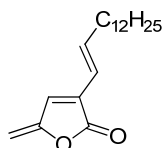
Rearranged butenolide 19^{3a,b}



1H -NMR (300 MHz, $CDCl_3$) δ : 7.37 (d, $J = 1.4$ Hz, 1H), 5.03 – 4.92 (m, 1H), 3.44 (s, 2H), 2.25 (s, 3H), 1.79 – 1.59 (m, 2H), 1.50 – 1.37 (m, 2H), 1.35 – 1.18 (m, 18H), 0.87 (t, $J = 6.8$ Hz, 3H); ^{13}C -NMR (75 MHz, $CDCl_3$) δ : 203.1, 173.4, 152.2, 126.5, 81.98, 38.79, 33.29, 31.86, 30.21, 29.57 (2C), 29.54, 29.44, 29.33, 29.29, 29.26, 24.94, 22.63, 14.08; GC/MS (EI): DB-50_L, $t_r = 11.95$ min; $m/z = 308$ $[M]^+$; MS (ESI): $m/z = 309$ $[M+H]^+$, 331 $[M+Na]^+$, 347 $[M+K]^+$; HR-MS (ESI) m/z calculated for $C_{19}H_{33}O_3$ $[M+H]^+$ 309.2424, found 309.2429.

$C_{19}H_{32}O_3$ (308.46).

Triene 20

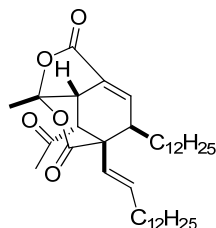


Under argon-atmosphere a flame-dried 10 mL flask, containing a solution of 31.3 mg (0.101 mmol, 1.00 eq.) (*E*)-5-hydroxy-5-methyl-3-(tetradec-1-en-1-yl)furan-2(5H)-one (**4**) and 11.4 mg (0.051 mmol, 0.50 eq.) $ZnBr_2$ in 2,0 mL absolute dichloromethane was heated to reflux for 1 hour. The reaction was allowed to cool to ambient temperature and quenched by addition of 2 mL H_2O . After extraction with dichloromethane (3x 5 mL) the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether $\rightarrow$ petroleum ether/ethyl acetate 7/1) to afford 3.90 mg (0.013 mmol, 13%) of the title compound and 6.00 mg (0.010 mmol, 20%) of C7-epi **1**.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 6.99 (s, 1H), 6.88 (dt, $J = 15.8, 7.1$ Hz, 1H), 6.17 (d, $J = 15.9$ Hz, 1H), 5.12 (d, $J = 2.4$ Hz, 1H), 4.80 (d, $J = 2.5$ Hz, 1H), 2.19 (td, $J = 7.9, 1.2$ Hz, 2H), 1.48 – 1.39 (m, 2H), 1.35 – 1.17 (m, 18H), 0.87 (t, $J = 6.7$ Hz, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 168.8, 153.9, 141.6, 132.5, 130.6, 118.4, 96.20, 33.69, 31.91, 29.66, 29.63 (2C), 29.55, 29.44, 29.35, 29.22, 28.65, 22.68, 14.12; HR-MS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{30}\text{O}_2$ $[\text{M}+\text{H}]^+$ 291.2319, found 291.2317.

$\text{C}_{19}\text{H}_{30}\text{O}_2$ (290.44).

Isomer 18

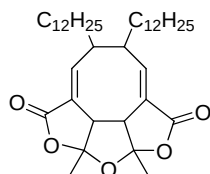


Under argon-atmosphere a flame-dried 10 mL flask, containing a solution of 100 mg (0.324 mmol, 1.00 eq.) (*E*)-5-hydroxy-5-methyl-3-(tetradec-1-en-1-yl)furan-2(5H)-one (**4**), 146 mg (0.648 mmol, 2.00 eq.) ZnBr_2 and 4Å-MS in 2,0 mL absolute dichloromethane was heated to reflux for 20 hours. The reaction was allowed to cool to ambient temperature and filtered through a short pad of celite. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (petroleum ether $\rightarrow$ petroleum ether/diethyl ether 2/1) to afford 7.80 mg (0.013 mmol, 8%) of the title compound, 3.90 mg (0.013 mmol, 4%) of elimination product (*E*)-5-methylene-3-(tetradec-1-en-1-yl)furan-2(5H)-one (**20**) and 10.2 mg (0.017 mmol, 11%) of cyclooctadiene **21**.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.09 – 7.03 (m, 1H), 5.80 (dt, $J = 15.6, 6.3$ Hz, 1H), 5.70 (d, $J = 15.7$ Hz, 1H), 3.35 (d, $J = 4.9$ Hz, 1H), 3.16 (dd, $J = 3.3, 2.0$ Hz, 1H), 2.25 (s, 3H), 2.22 – 2.16 (m, 1H), 2.16 – 2.08 (m, 2H), 1.78 (s, 3H), 1.55 – 1.48 (m, 2H), 1.48 – 1.35 (m, 3H), 1.35 – 1.19 (m, 37H), 0.88 (t, $J = 6.7$ Hz, 6H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 207.9, 173.5, 165.4, 146.1, 132.9, 129.2, 128.5, 108.3, 62.24, 59.07, 50.95, 41.24, 34.91, 32.44, 31.90, 31.17, 29.66, 29.63, 29.58, 29.51, 29.44, 29.38, 29.34, 29.15, 28.96, 28.38, 24.62, 22.68, 14.12; HR-MS (ESI) m/z calculated for $\text{C}_{38}\text{H}_{63}\text{O}_5$ $[\text{M}+\text{H}]^+$ 599.4670, found 599.4669; calculated for $\text{C}_{38}\text{H}_{62}\text{NaO}_5$ $[\text{M}+\text{Na}]^+$ 621.4489, found 621.4488; calculated for $\text{C}_{38}\text{H}_{62}\text{KO}_5$ $[\text{M}+\text{K}]^+$ 637.4229, found 637.4228.

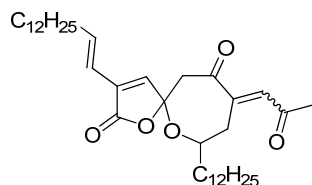
$\text{C}_{38}\text{H}_{62}\text{O}_5$ (598.90).

Cyclooctadiene 21



$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 6.90 (d, $J = 7.2$ Hz, 2H), 3.35 (s, 2H), 2.69 – 2.44 (m, 2H), 1.64 (s, 6H), 1.51 – 1.37 (m, 2H), 1.34 – 1.20 (m, 40H), 1.13 – 1.01 (m, 2H), 0.87 (t, $J = 6.7$ Hz, 6H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 165.5 (2C), 149.3 (2C), 133.5 (2C), 113.5 (2C), 59.35 (2C), 45.90 (2C), 31.90 (2C), 31.53 (2C), 29.63 (4C), 29.59 (4C), 29.54 (2C), 29.49 (2C), 29.34 (2C), 28.48 (2C), 24.38 (2C), 22.68 (2C), 14.12 (2C); HR-MS (ESI) m/z calculated for $\text{C}_{38}\text{H}_{63}\text{O}_5$ $[\text{M}+\text{H}]^+$ 599.4670, found 599.4676. **$\text{C}_{38}\text{H}_{62}\text{O}_5$** (598.90).

Ketal 22

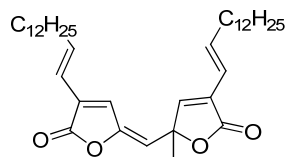


Under argon-atmosphere a flame-dried 10 mL flask, containing a solution of 100 mg (0.324 mmol, 1.00 eq.) (*E*)-5-hydroxy-5-methyl-3-(tetradec-1-en-1-yl)furan-2(5H)-one (**4**) and 95.8 mg (0.324 mmol, 1.00 eq.) FeBr₃ in 4.0 mL absolute 1,2-dichloroethane was stirred at 0°C for 15 hours. The reaction was quenched by addition of 4 mL H₂O. After extraction with diethyl ether (3x 5 mL) the combined organic phases were dried over Na₂SO₄ and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetat 8/1 → 6/1) to afford 7.10 mg (0.012 mmol, 7%) of the title compound, 12.2 mg (0.020 mmol, 13%) of *C*7-*epi* **1** and 8.20 mg (0.014 mmol, 9%) of compound **23**.

¹H-NMR (300 MHz, CDCl₃) δ: 8.08 (s, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.05 – 6.88 (m, 1H), 6.25 (d, *J* = 16.0 Hz, 1H), 3.79 – 3.63 (m, 1H), 3.58 – 3.23 (m, 2H), 2.23 (s, 3H), 2.08 – 1.94 (m, 1H), 1.73 – 1.61 (m, 1H), 1.45 (d, *J* = 6.7 Hz, 2H), 1.25 (m, 42H), 0.87 (t, *J* = 6.6 Hz, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ: 204.1, 195.7, 167.8, 157.8, 151.5, 143.7, 140.6, 132.0, 130.7, 119.1, 118.8, 42.71, 39.37, 33.88, 31.95, 31.91 (2C), 30.15, 29.70, 29.63 (6C), 29.57, 29.55, 29.50, 29.43, 29.35 (2C), 29.23, 28.59, 26.23, 22.68 (2C), 14.12 (2C); HR-MS (ESI) *m/z* calculated for C₃₈H₆₃O₅ [M+H]⁺ 599.4670, found 599.4672.

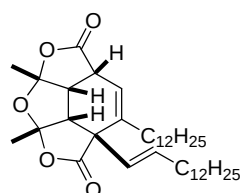
C₃₈H₆₂O₅ (598.90).

Compound 23



¹H-NMR (300 MHz, CDCl₃) δ: 7.39 (s, 1H), 6.92 (s, 1H), 6.90 – 6.73 (m, 2H), 6.15 (d, *J* = 15.9 Hz, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 5.37 (s, 1H), 2.25 – 2.11 (m, 4H), 1.72 (s, 3H), 1.49 – 1.39 (m, 4H), 1.36 – 1.18 (m, 36H), 0.88 (t, *J* = 6.7 Hz, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ: 170.9, 167.8, 147.7, 147.6, 142.0, 139.6, 133.1, 129.5, 128.1, 118.1, 118.1, 111.7, 83.76, 33.70, 33.46, 31.91, 29.65, 29.63, 29.56, 29.55, 29.47, 29.43, 29.34, 29.24, 29.21, 28.72, 28.62, 25.53, 22.68, 14.12; HR-MS (ESI) *m/z* calculated for C₃₈H₆₁O₄ [M+H]⁺ 581.4564, found 581.4558; **C₃₈H₆₀O₄** (580.88).

Isomer 24



To an oven-dried 10 mL flask, containing a solution of 60.0 mg (0.100 mmol, 1.00 eq.) *C*7-*epi* **1** in 1.0 mL absolute THF, 44.8 μL (0.300 mmol, 3.00 eq.) DBU was added and the resulting solution was heated to reflux

for 20 hours. The reaction was stopped despite incomplete conversion. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 3/1 → 2/1) to afford 10.9 mg (0.018 mmol, 18%) of the title compound.

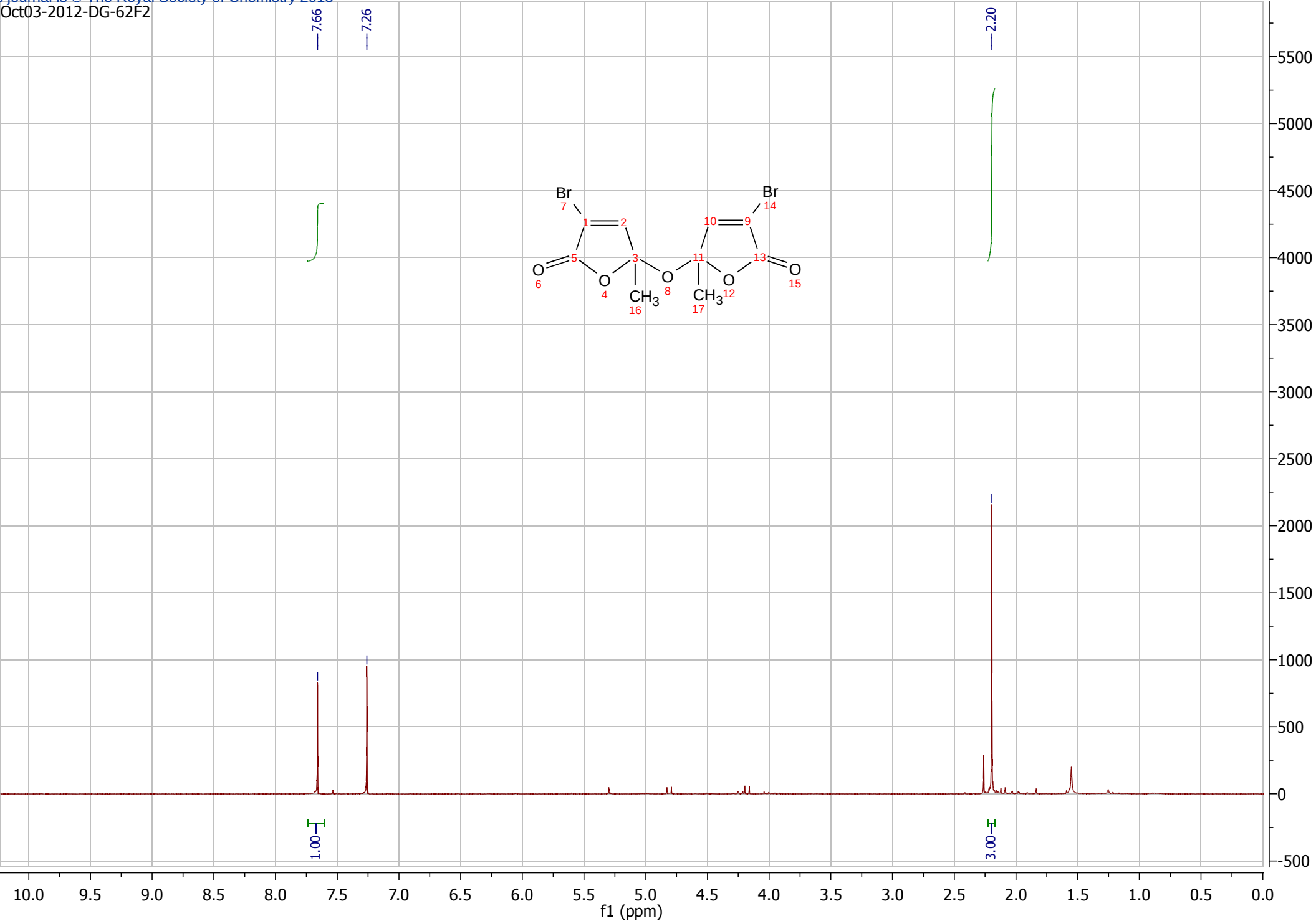
^1H -NMR (300 MHz, CDCl_3) δ : 5.89 (d, $J = 7.8$ Hz, 1H), 5.71 (dt, $J = 15.7, 6.8$ Hz, 1H), 5.37 (d, $J = 15.8$ Hz, 1H), 3.75 – 3.66 (m, 1H), 3.04 (dd, $J = 12.2, 9.9$ Hz, 1H), 2.84 (d, $J = 12.3$ Hz, 1H), 2.38 – 2.24 (m, 1H), 2.19 – 2.05 (m, 2H), 1.72 (s, 3H), 1.67 (s, 3H), 1.50 – 1.18 (m, 41H), 0.88 (t, $J = 6.7$ Hz, 6H); ^{13}C -NMR (75 MHz, CDCl_3) δ : 171.7, 171.6, 140.9, 134.6, 128.6, 116.6, 115.8, 115.5, 54.89, 54.22, 45.49, 40.17, 33.58, 32.43, 31.92, 29.67, 29.64, 29.63, 29.61, 29.46, 29.42, 29.36, 29.36, 29.25, 28.95, 27.85, 25.21, 24.70, 22.69, 14.12; HR-MS (ESI) m/z calculated for $\text{C}_{38}\text{H}_{63}\text{O}_5$ $[\text{M}+\text{H}]^+$ 599.4670, found 599.4673; calculated for $\text{C}_{38}\text{H}_{62}\text{KO}_5$ $[\text{M}+\text{K}]^+$ 637.4229, found 637.4233.

$\text{C}_{38}\text{H}_{62}\text{O}_5$ (598.90).

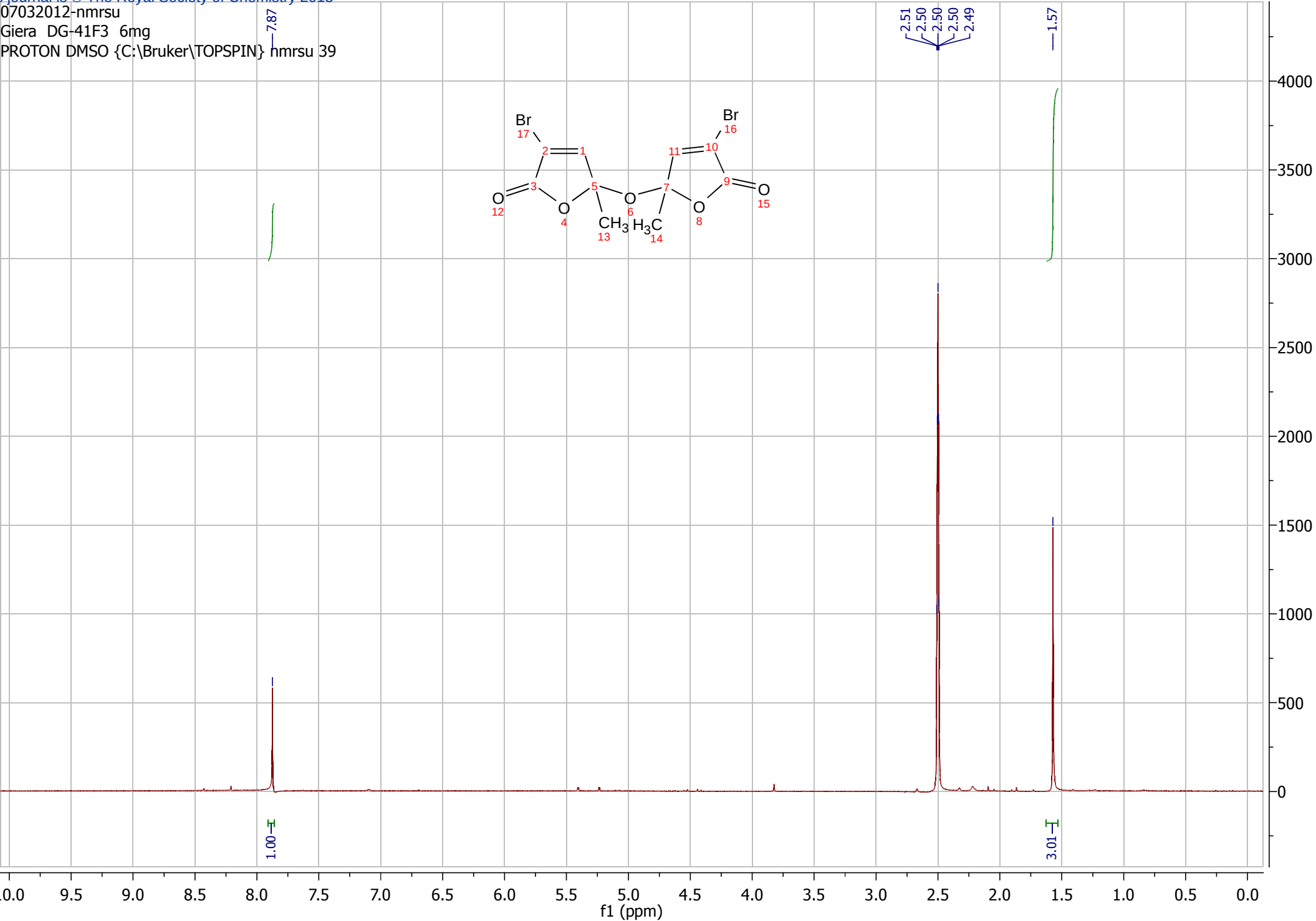
References

- [1] (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370. (b) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249.
- [2] Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127.
- [3] (a) Noutsias, D.; Vassilikogiannakis, G. *Org. Lett.* **2012**, *14*, 3565. (b) Vasamsetty, L.; Khan, F. A.; Mehta, G. *Tetrahedron Lett.* **2013**, *54*, 3522.

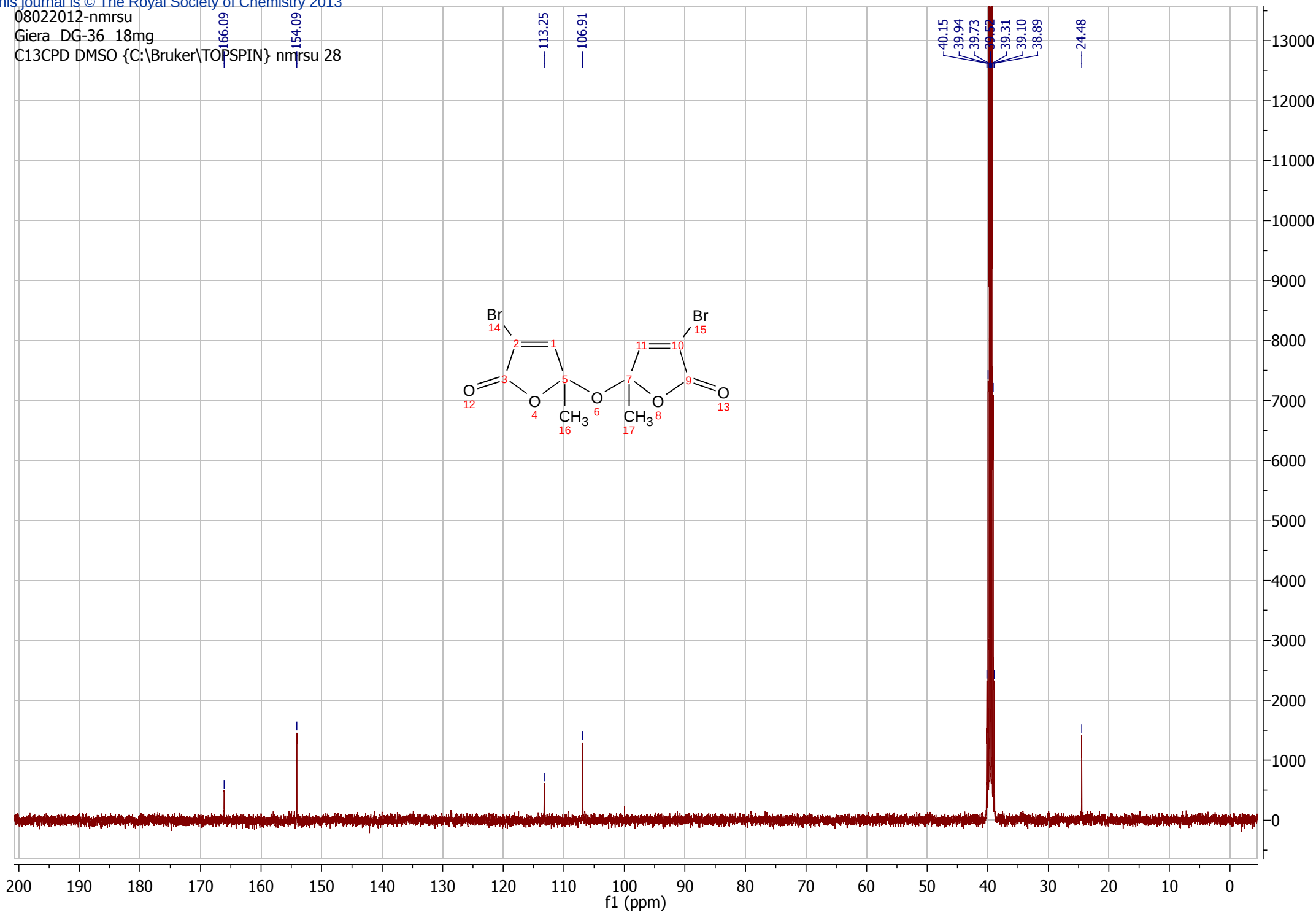
Spectra



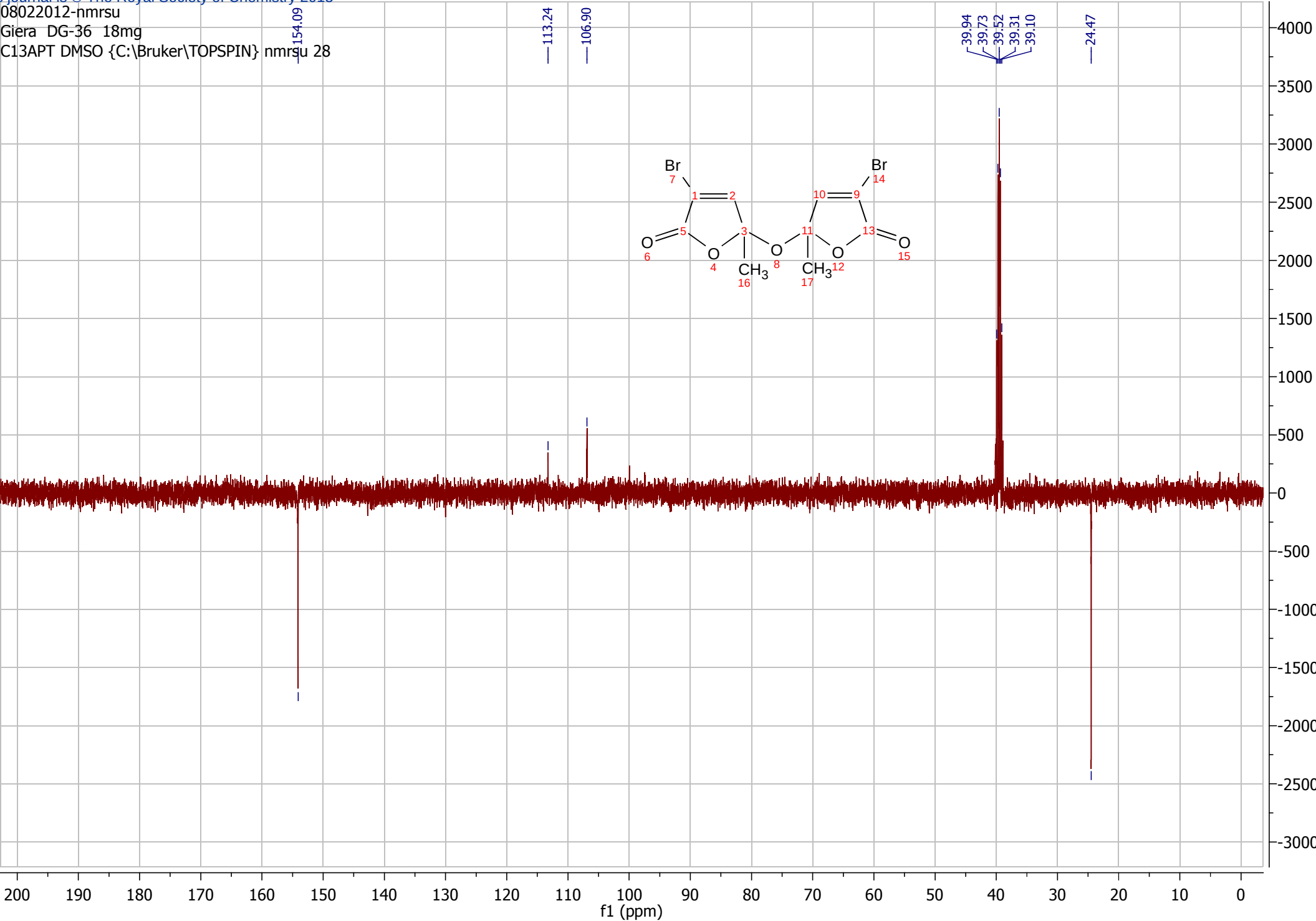
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PROTON DMSO {C:\Bruker\TOPSPIN} nmrsu 39



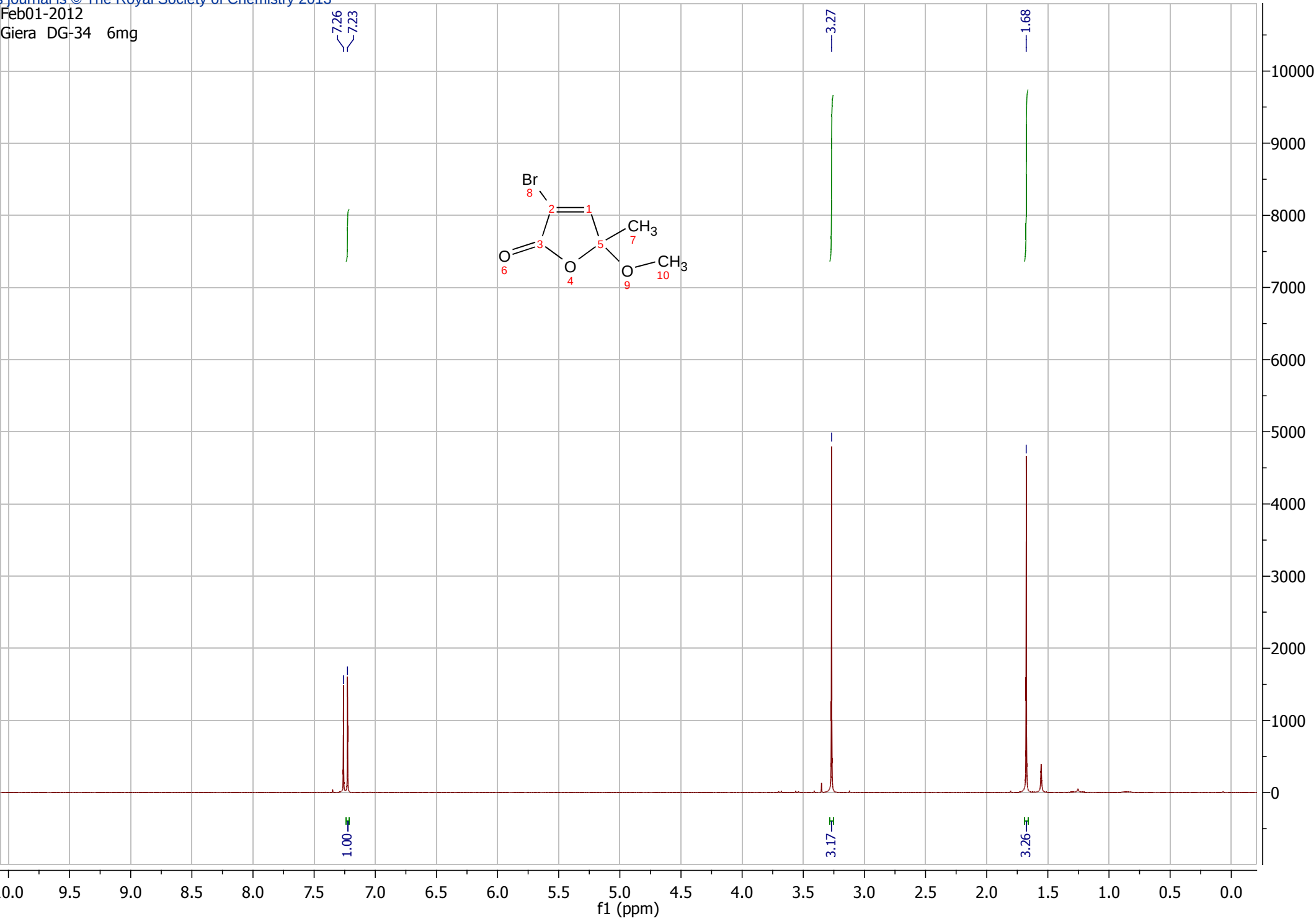
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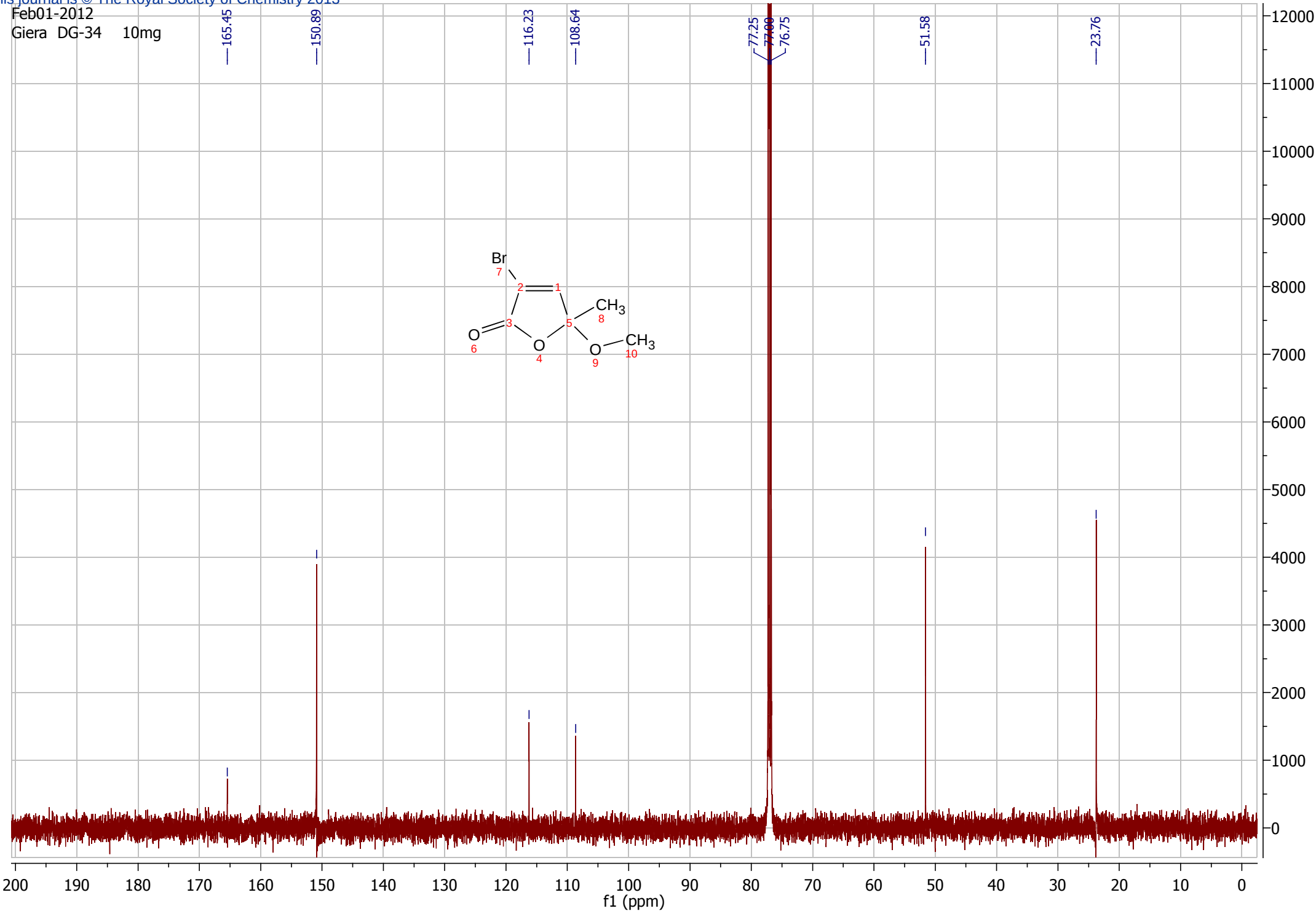
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154.09
28



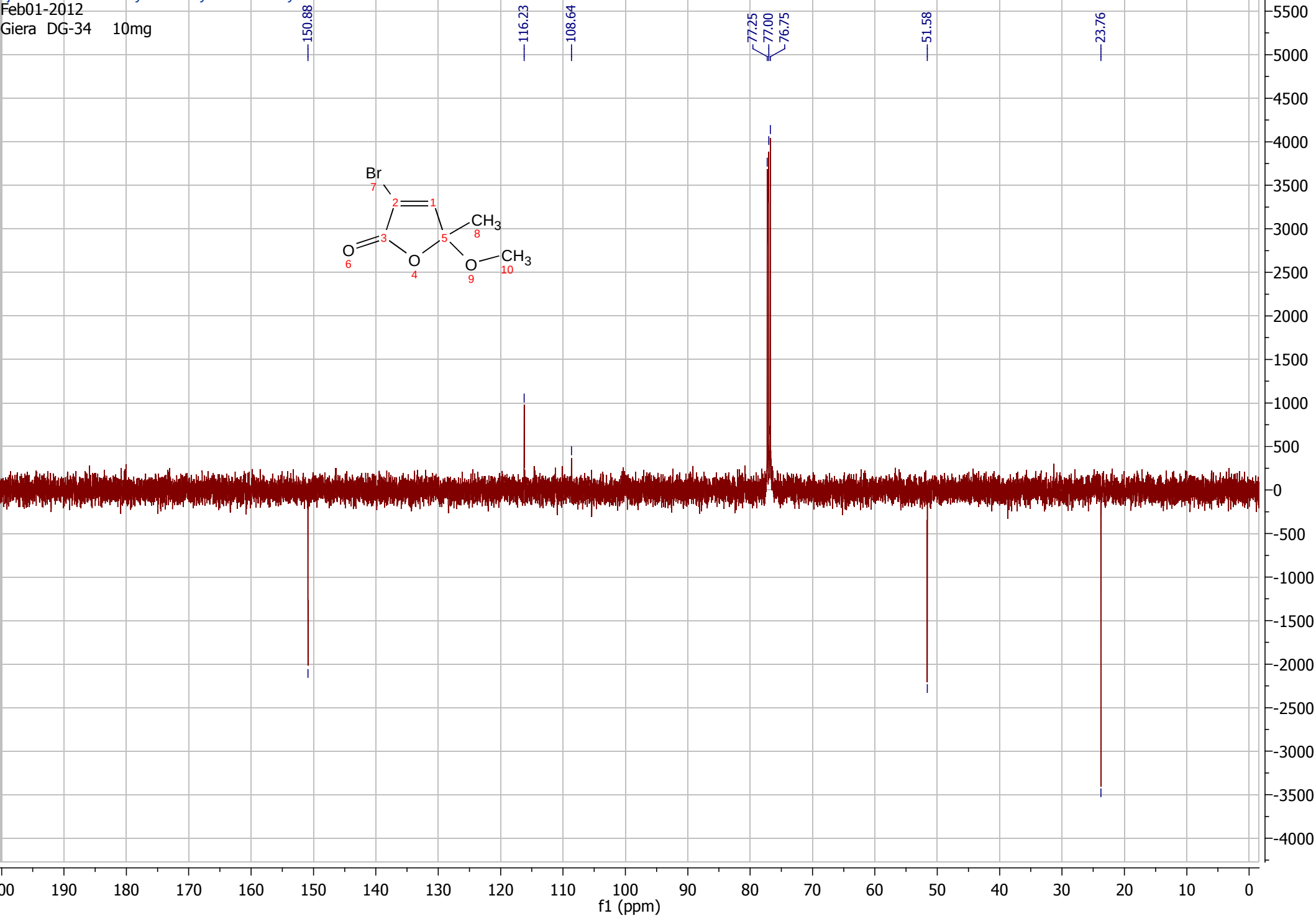
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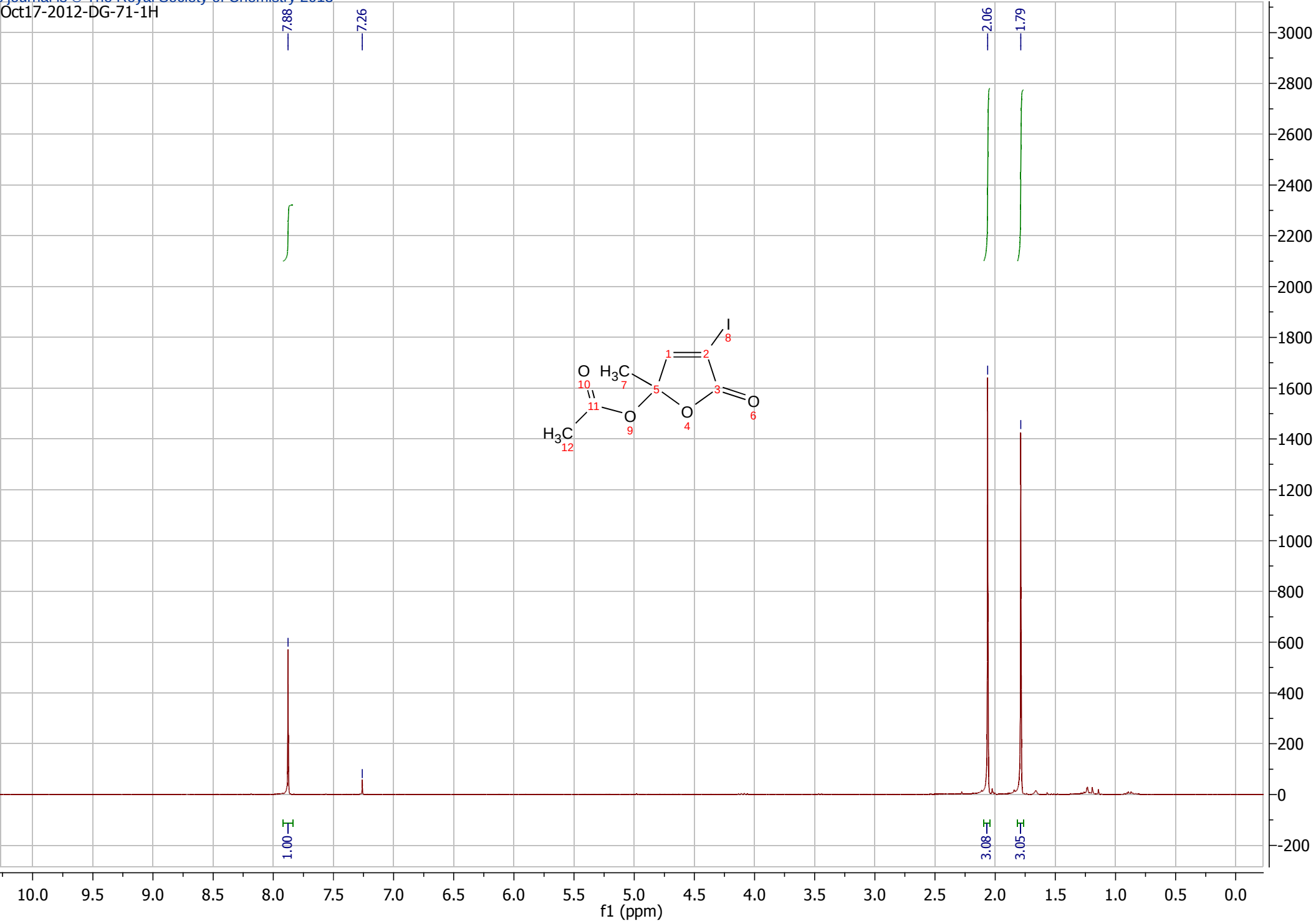


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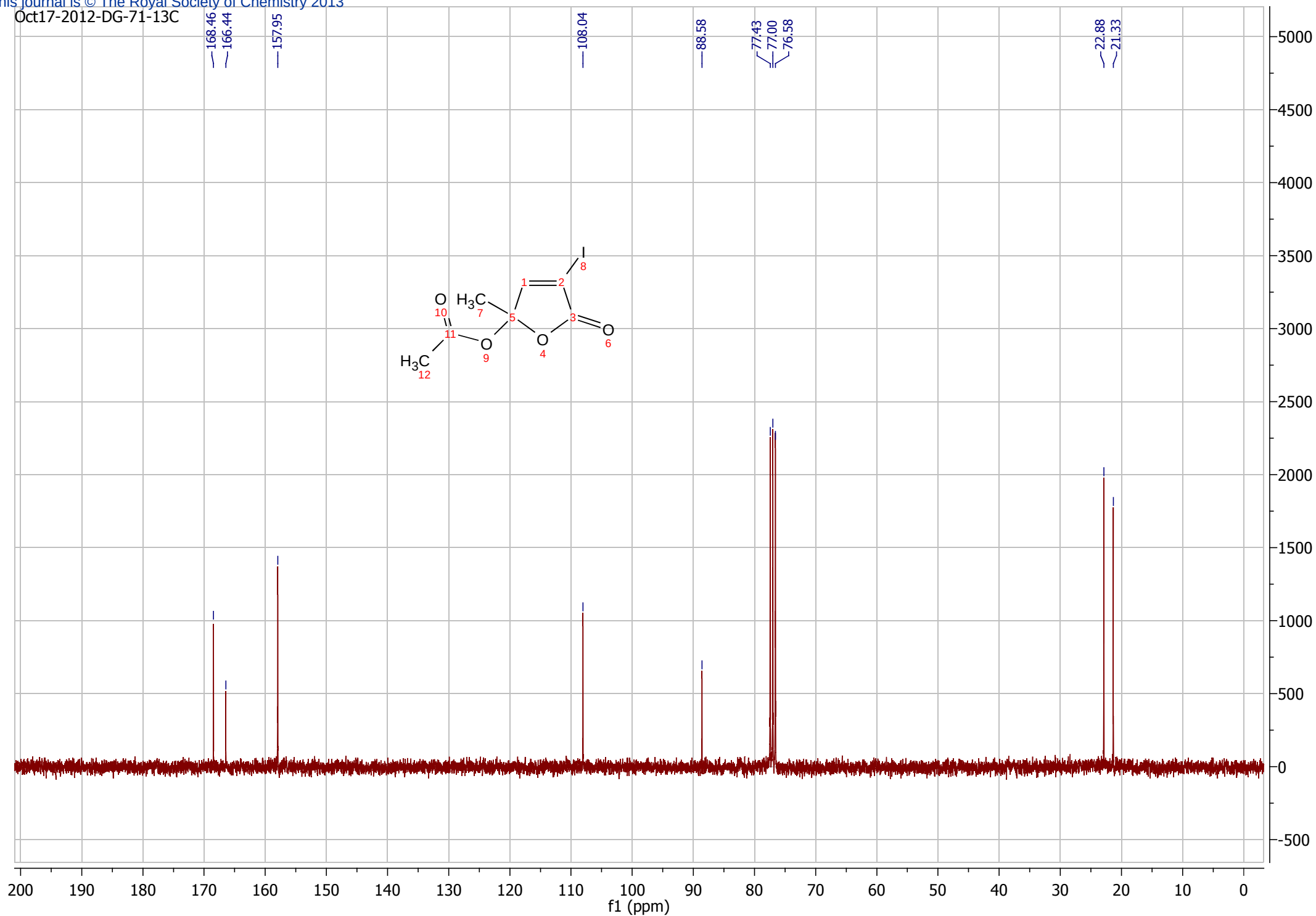


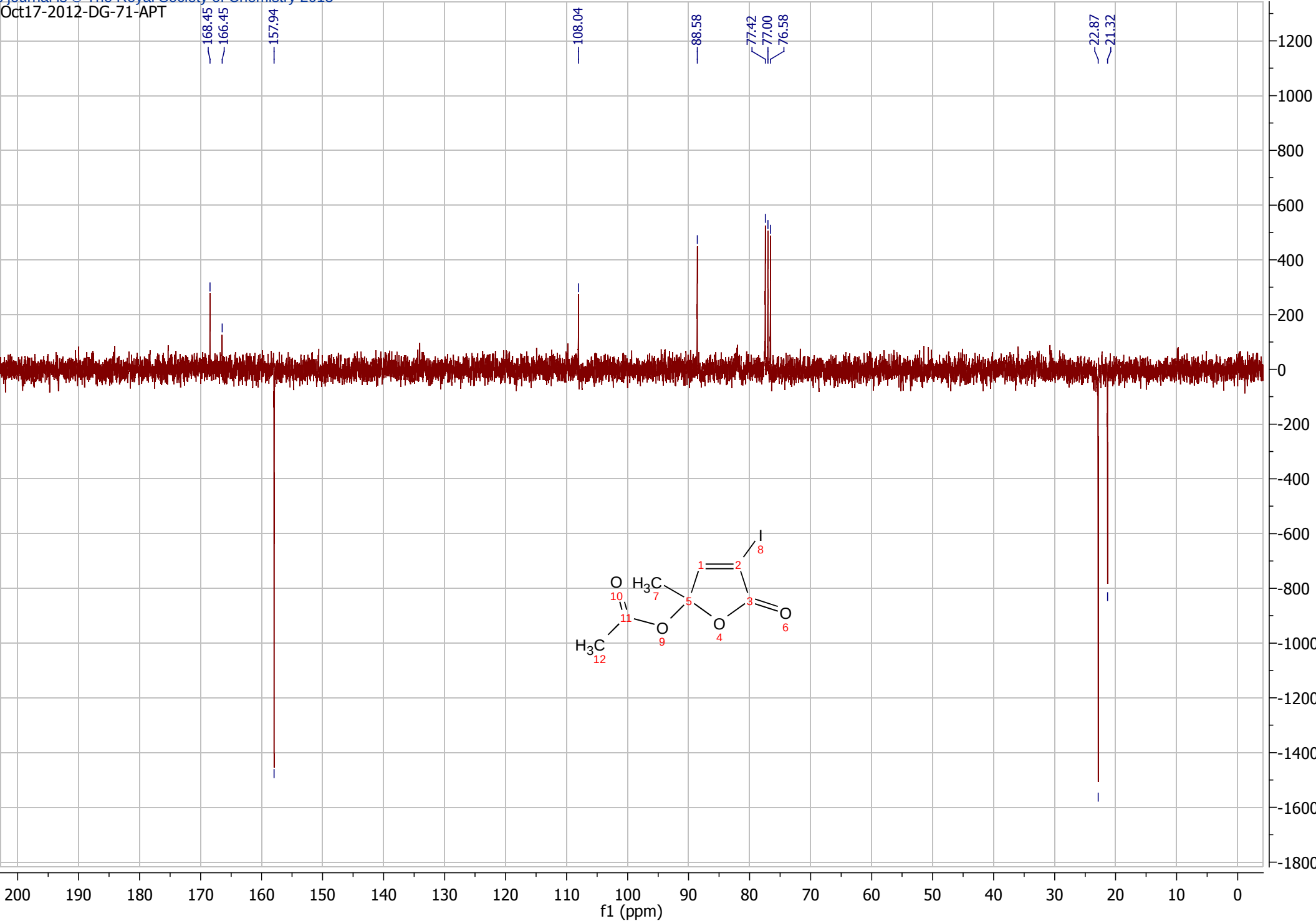
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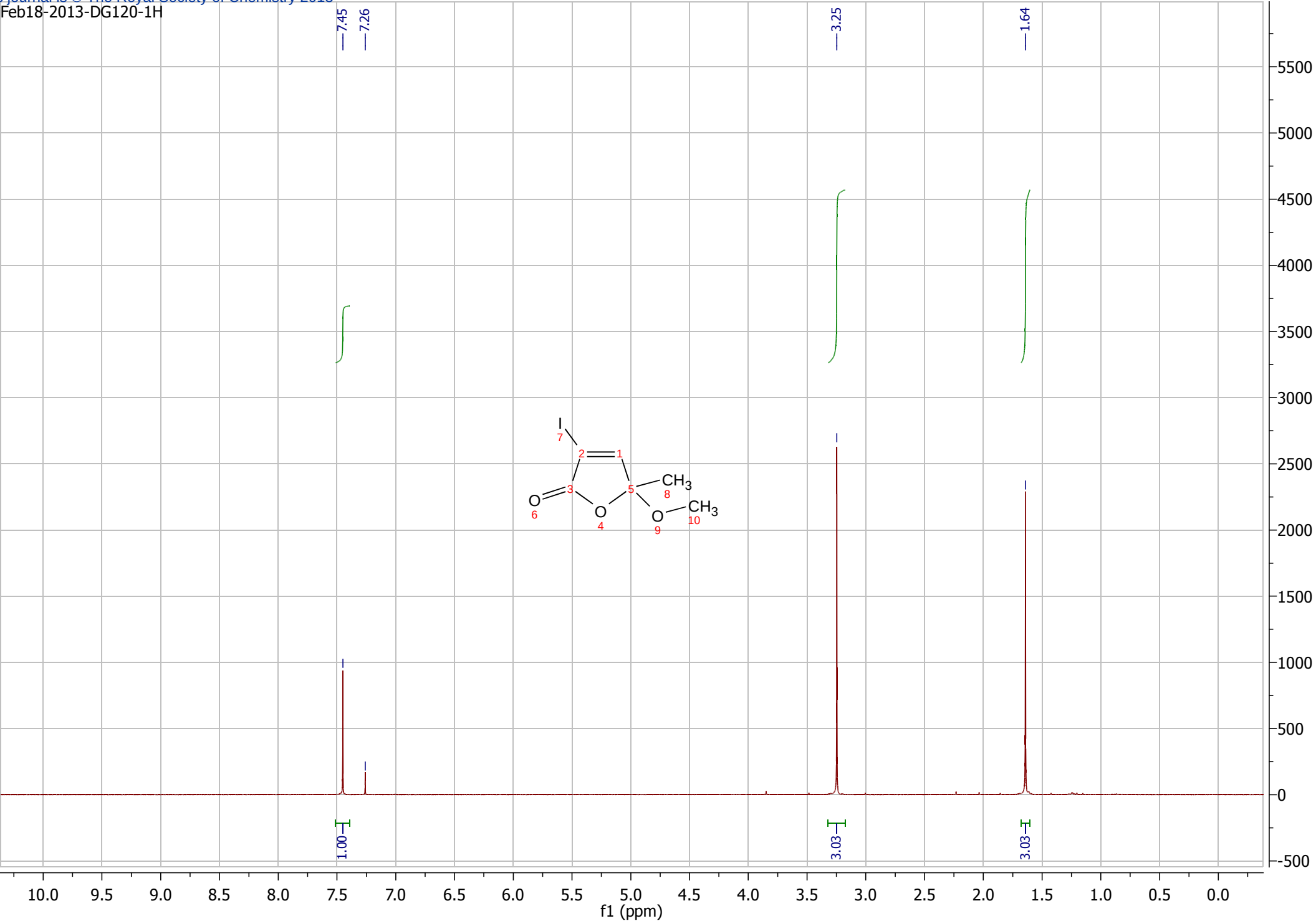


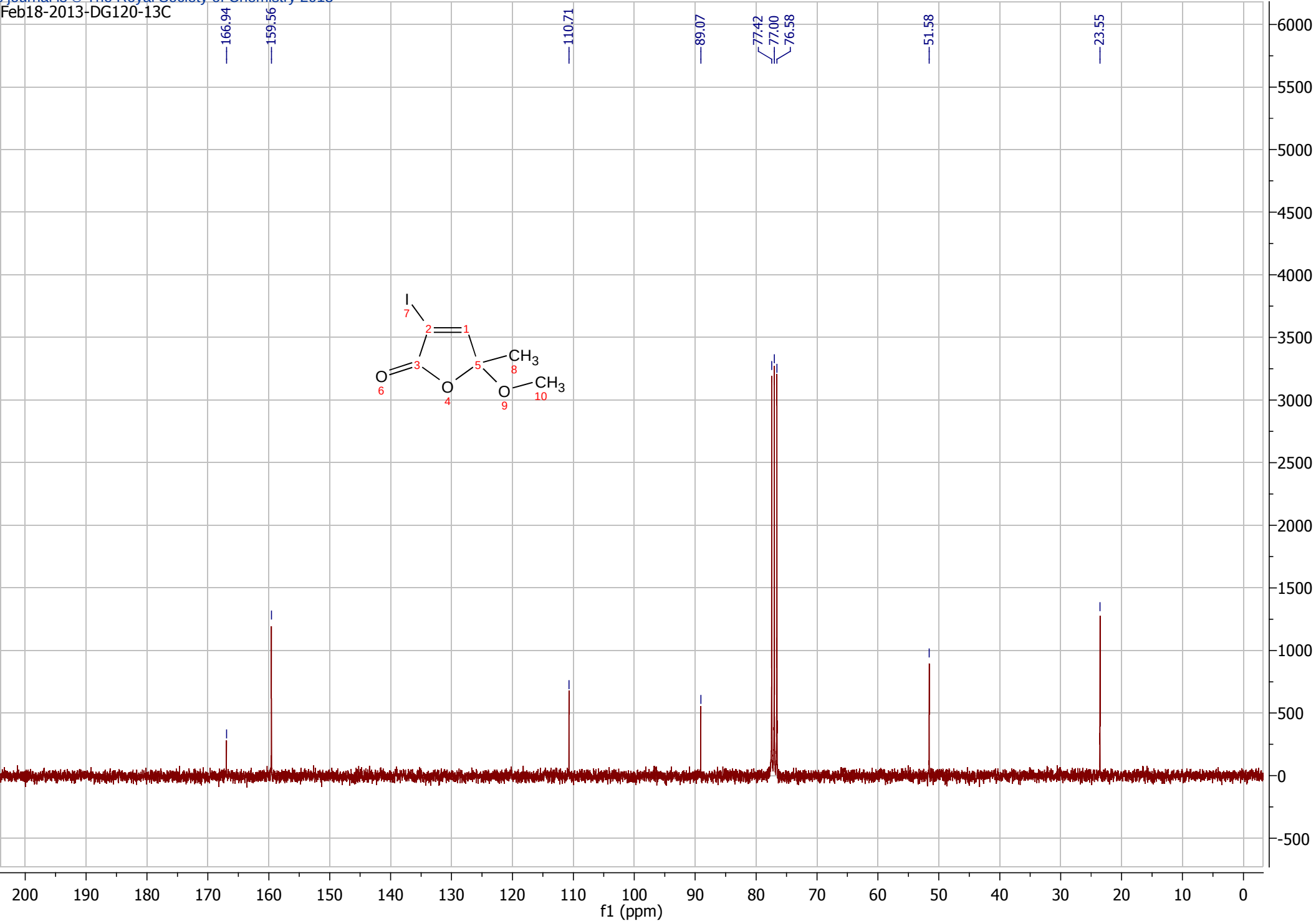


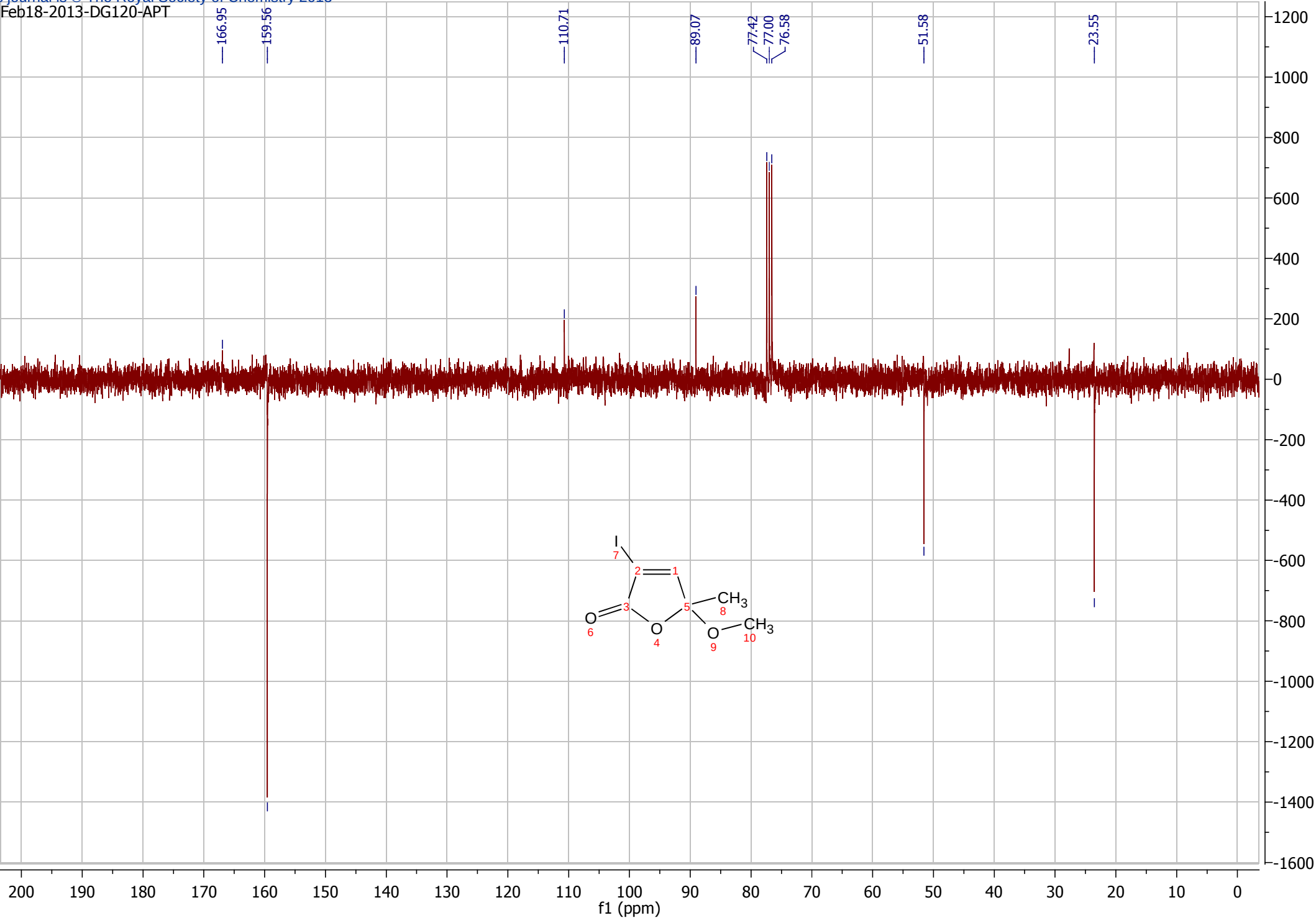
Oct17-2012-DG-71-13C





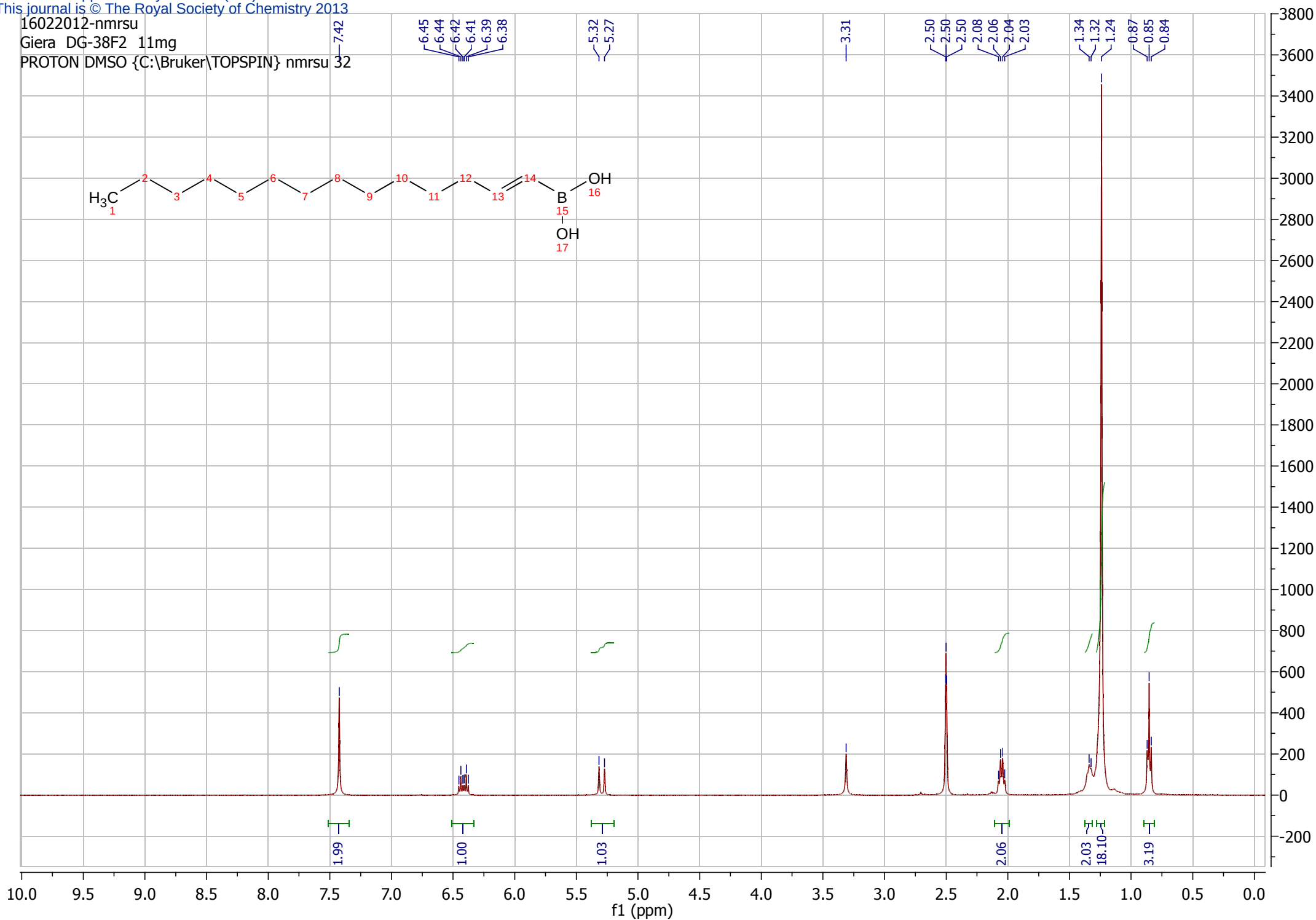




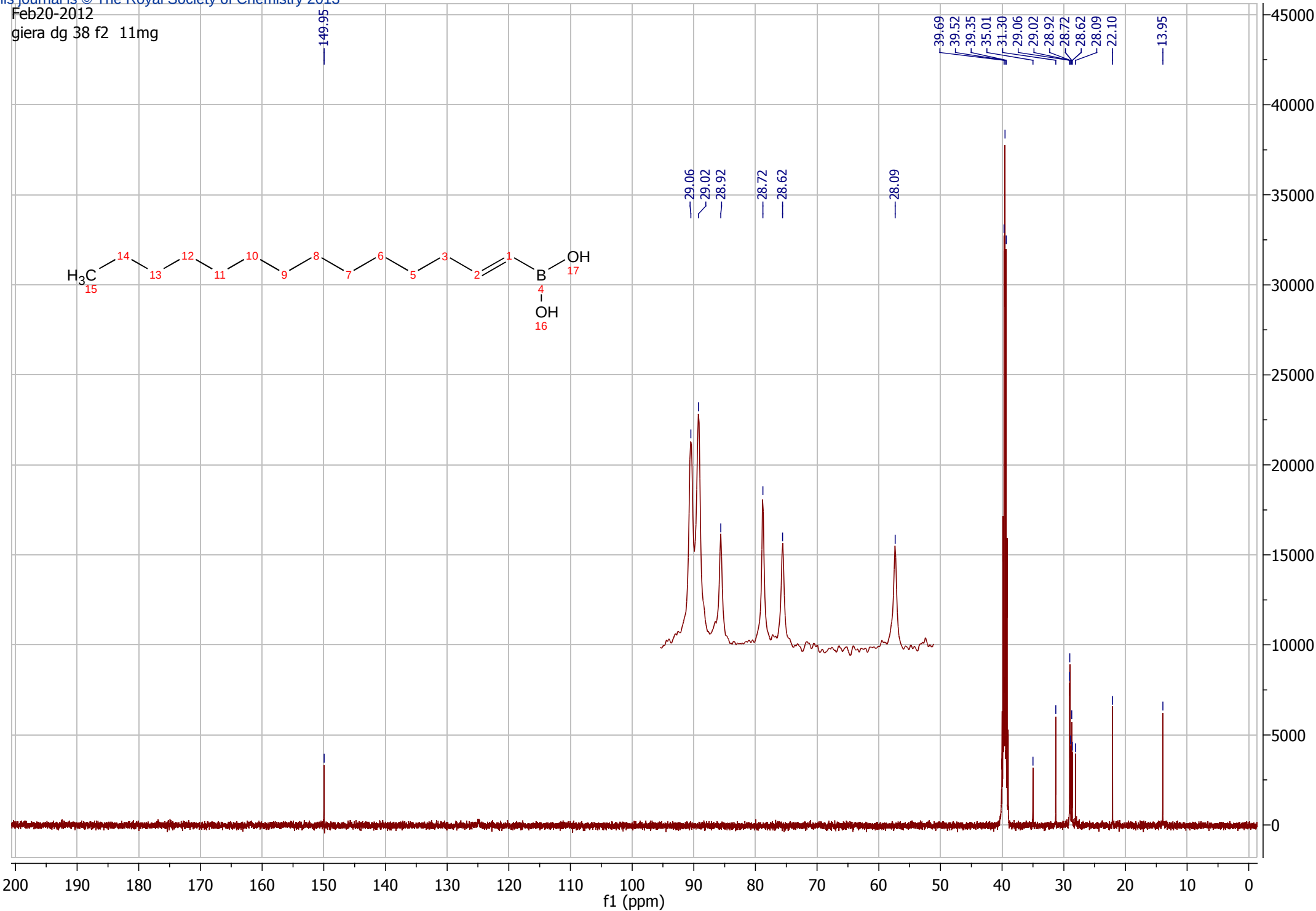


Giera	DG-38F2	11mg
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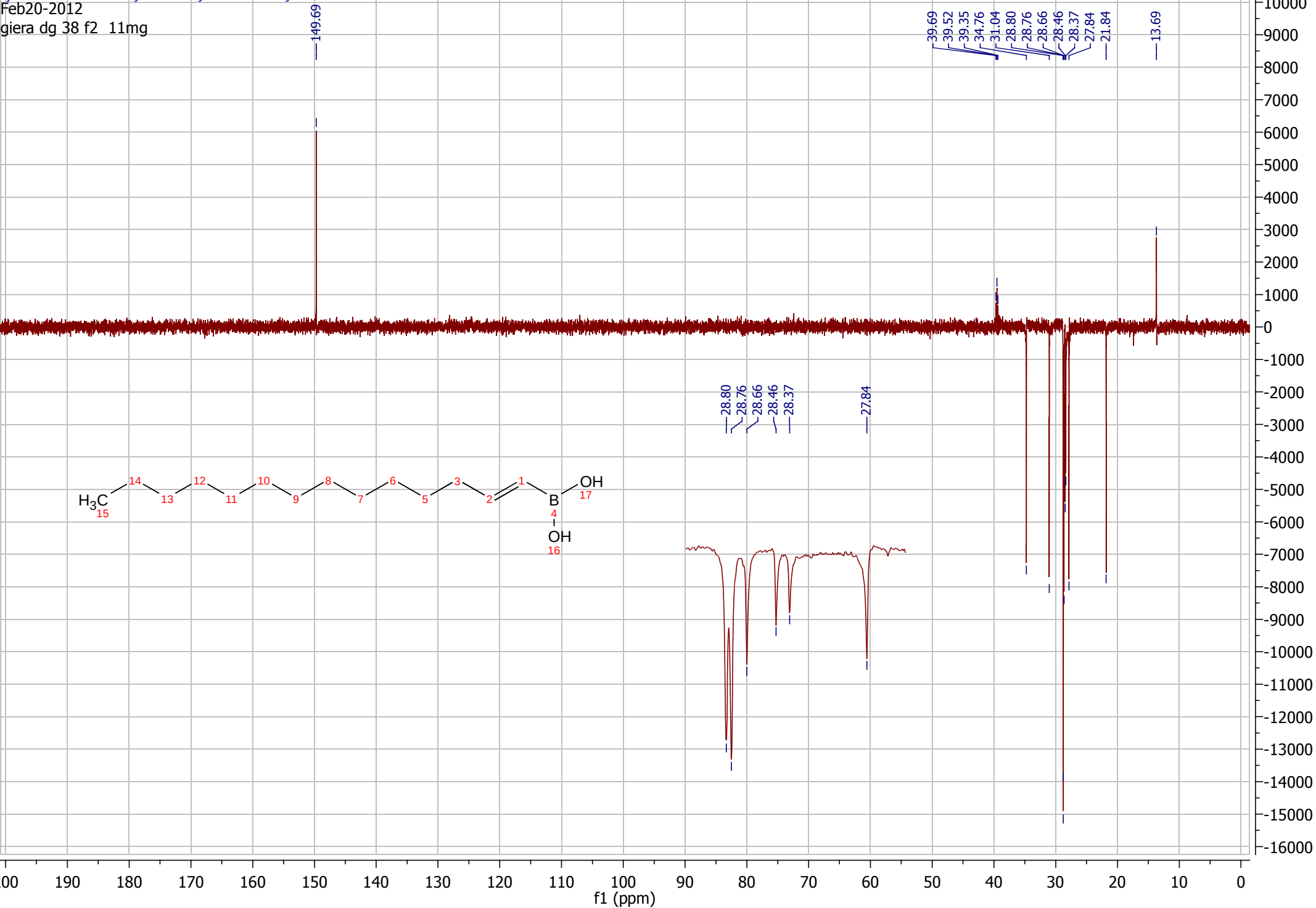
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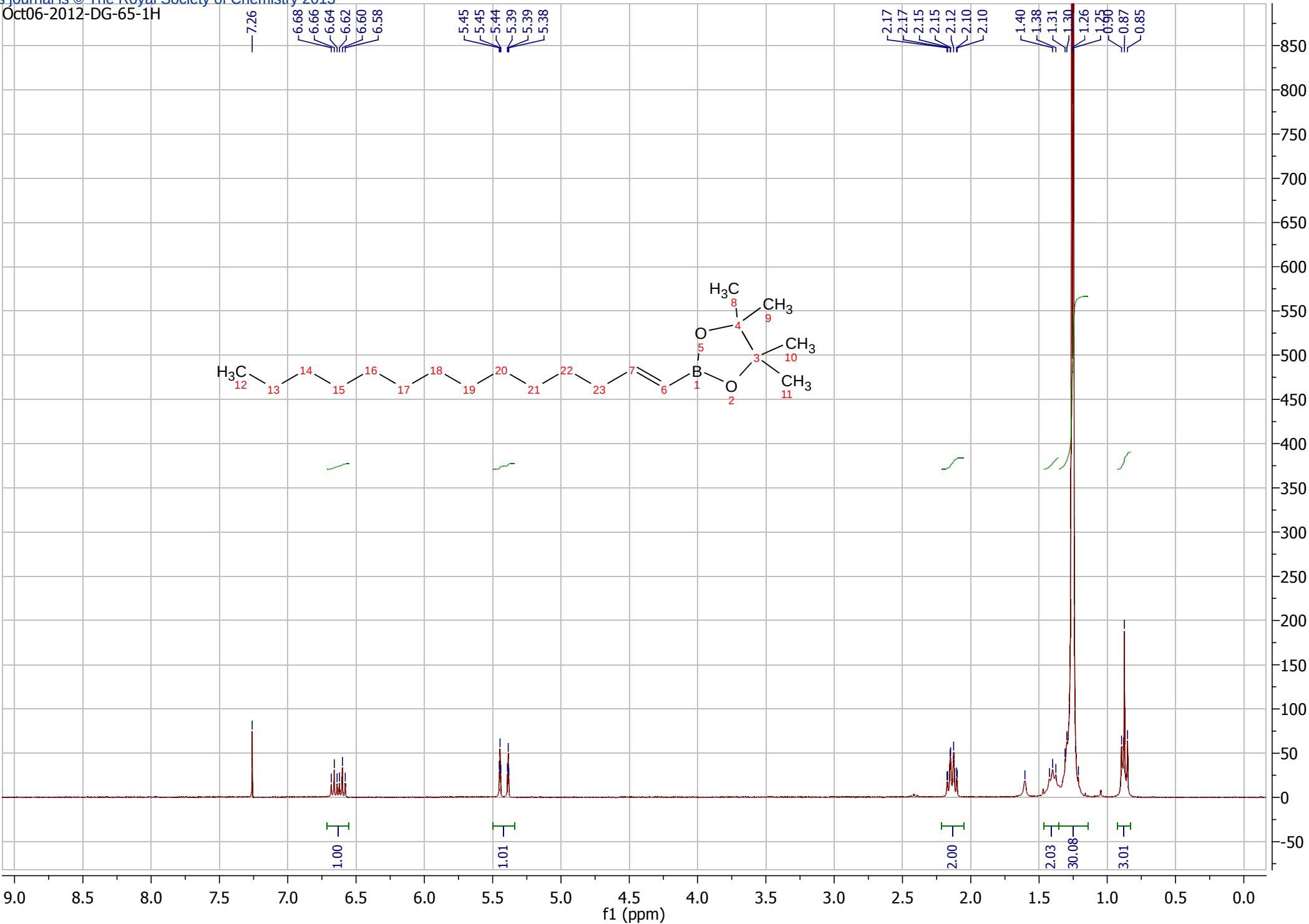


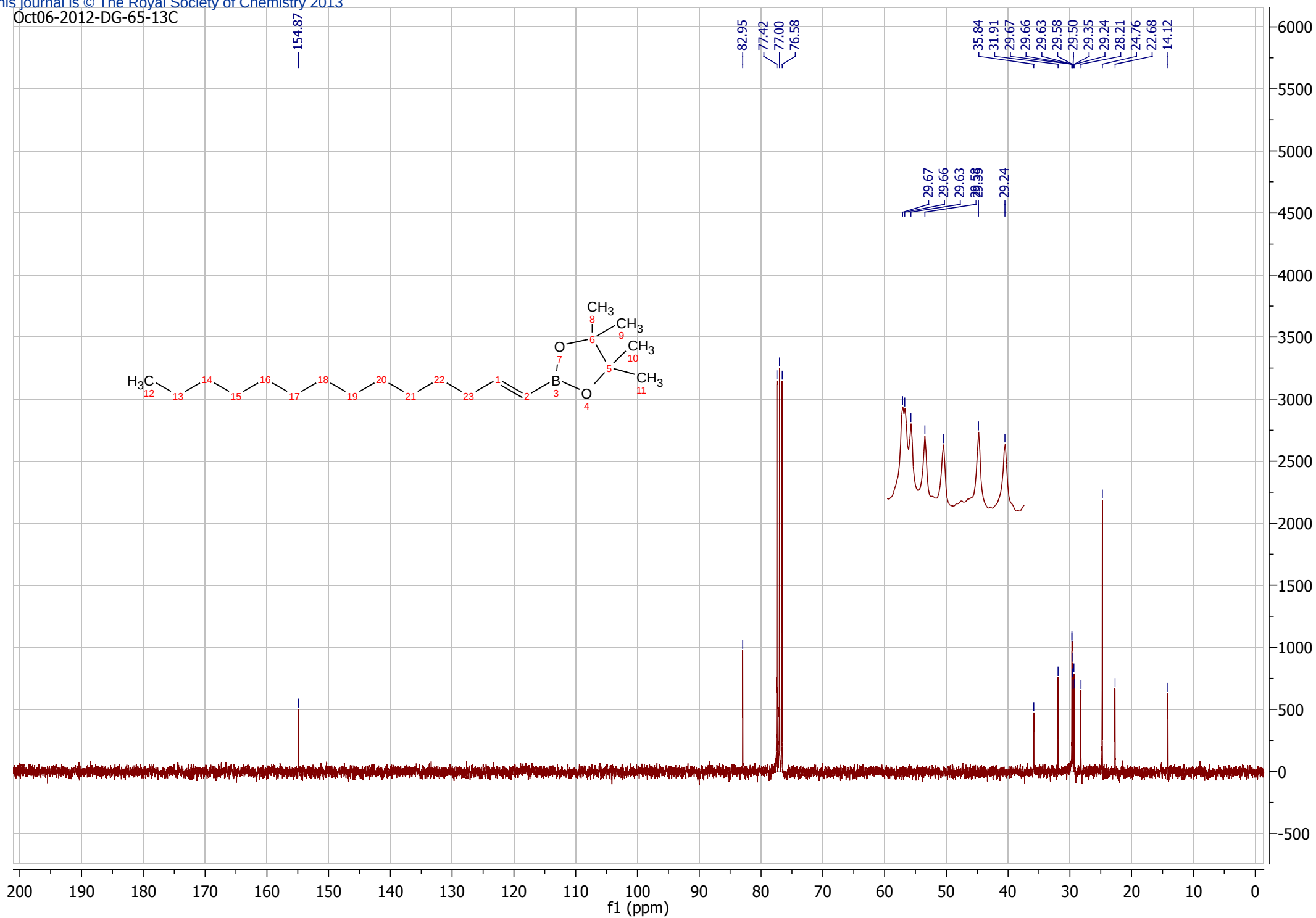
Feb20-2012
giera dg 38 f2 11mg

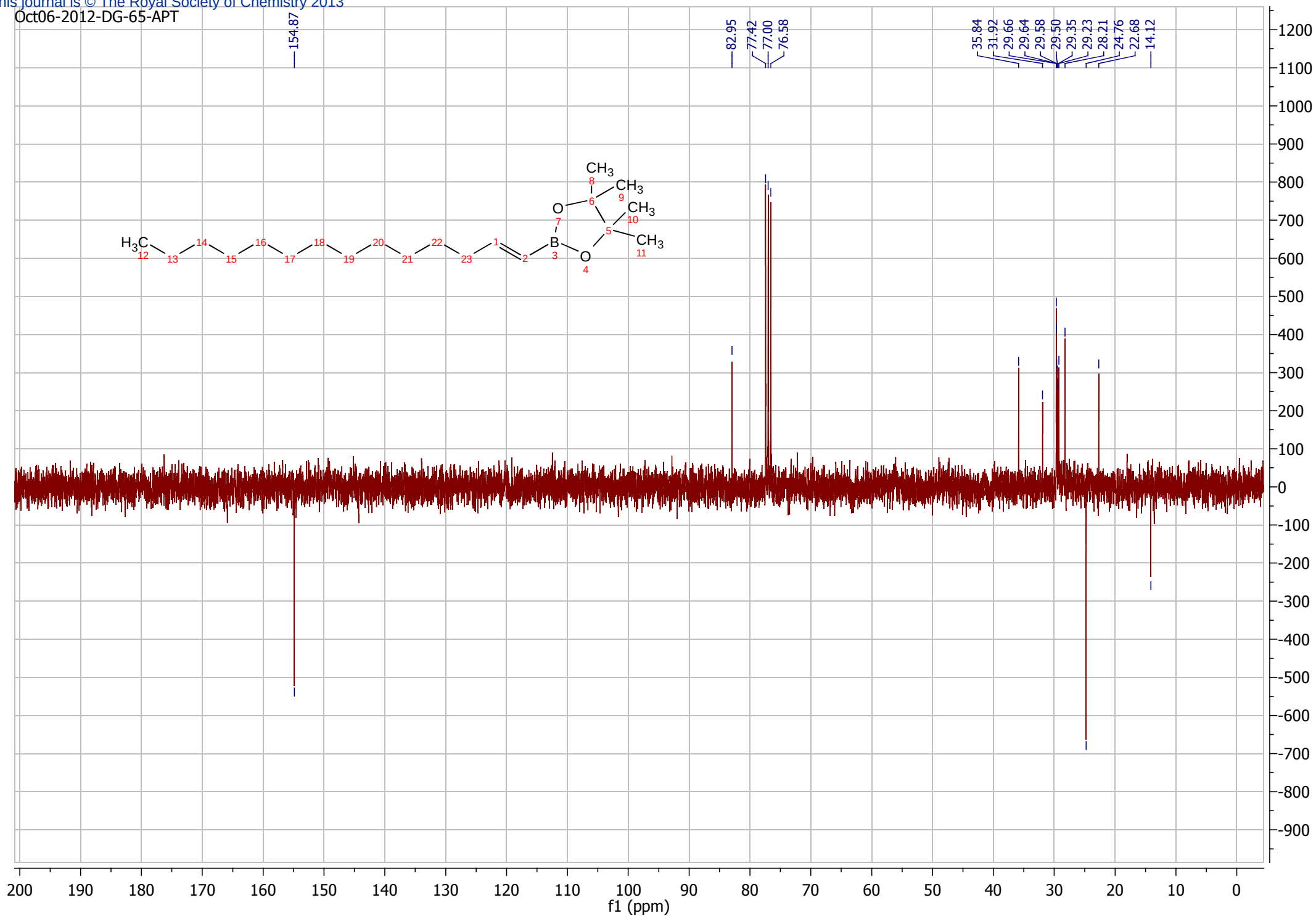
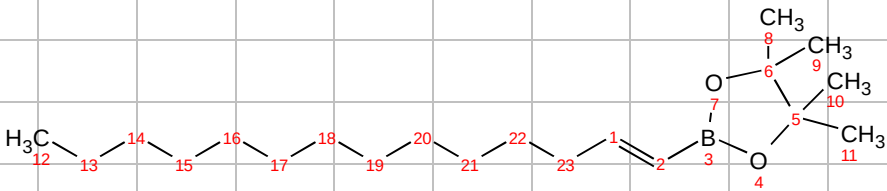


Feb20-2012
giera dg 38 f2 11mg

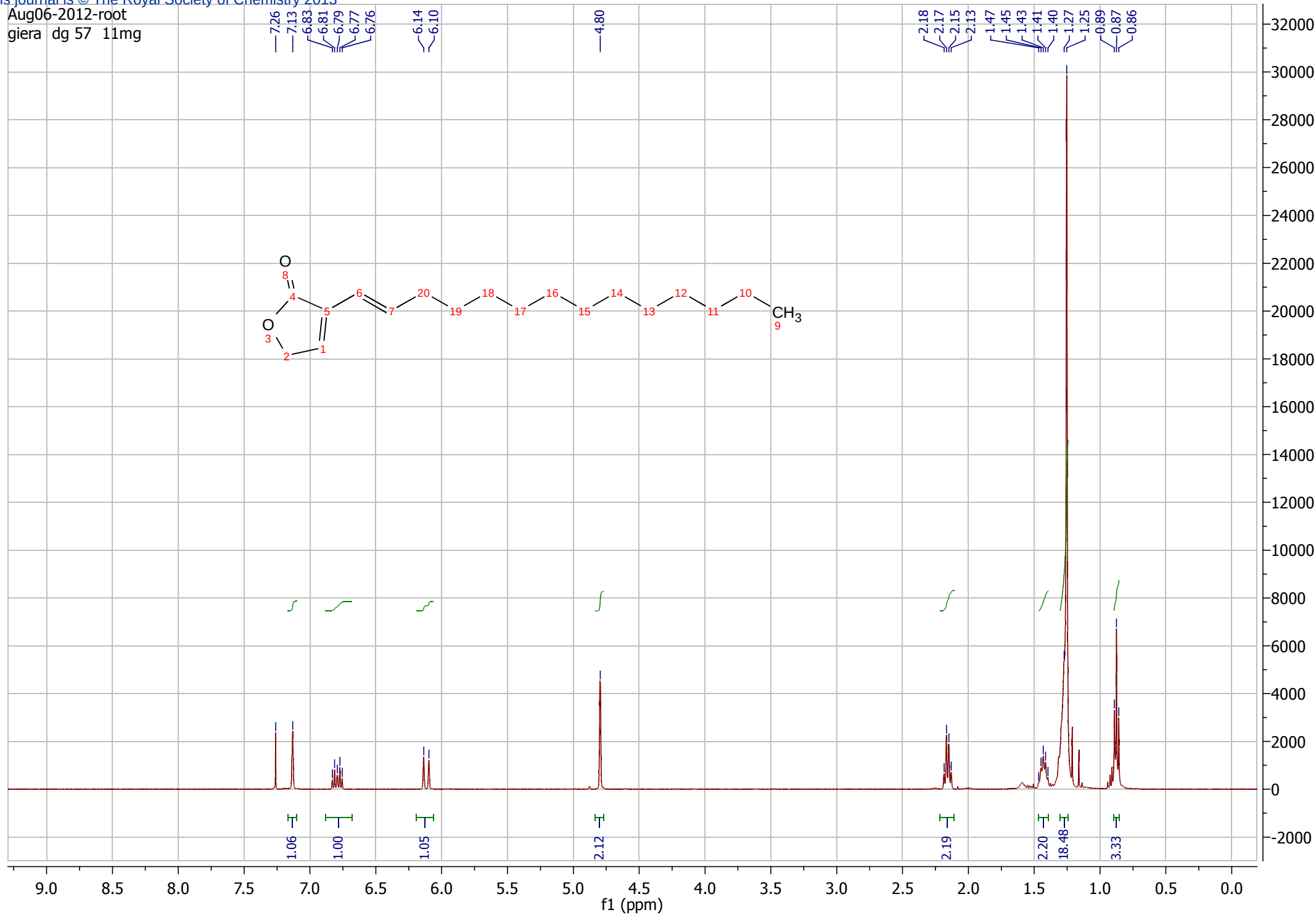




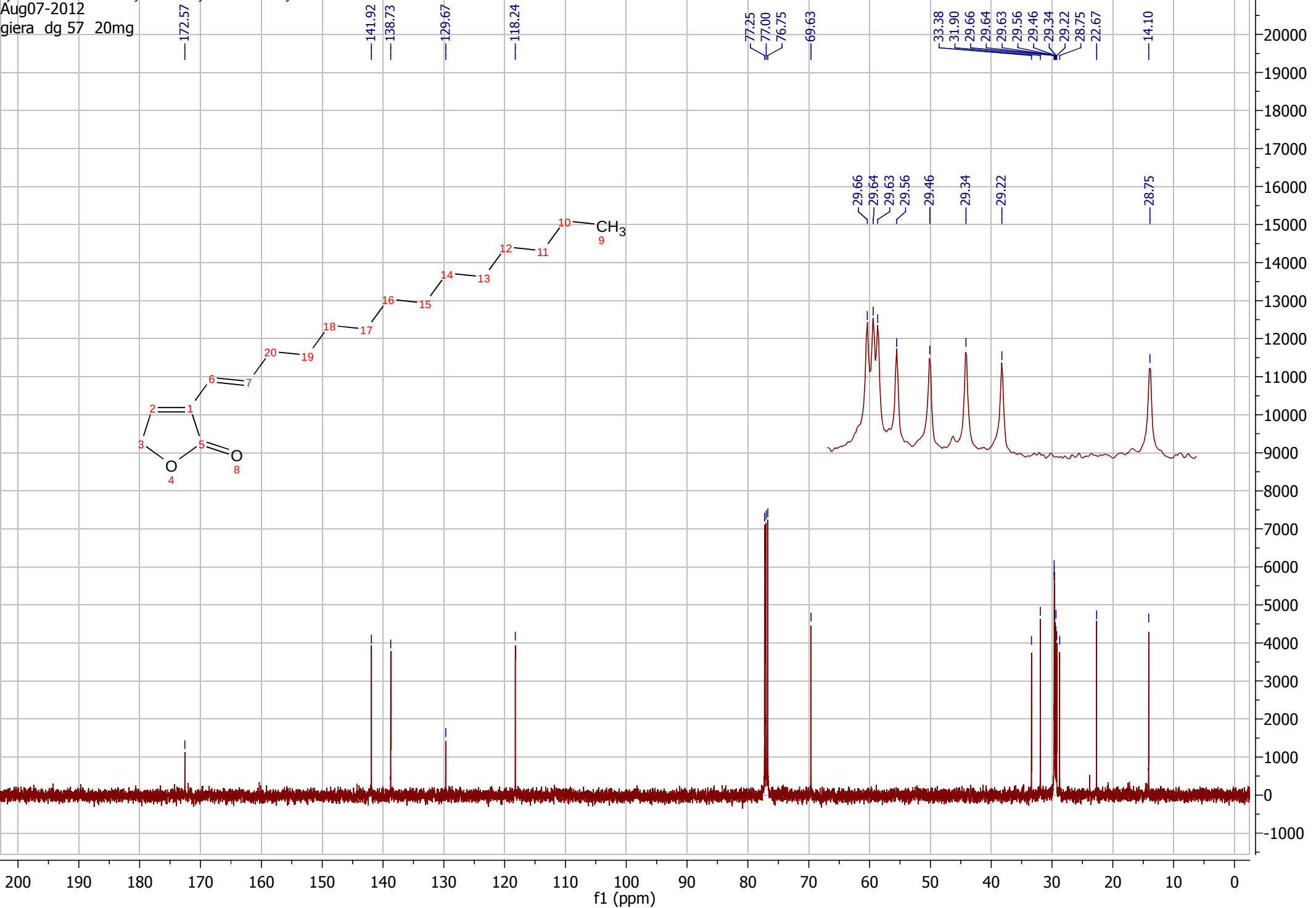




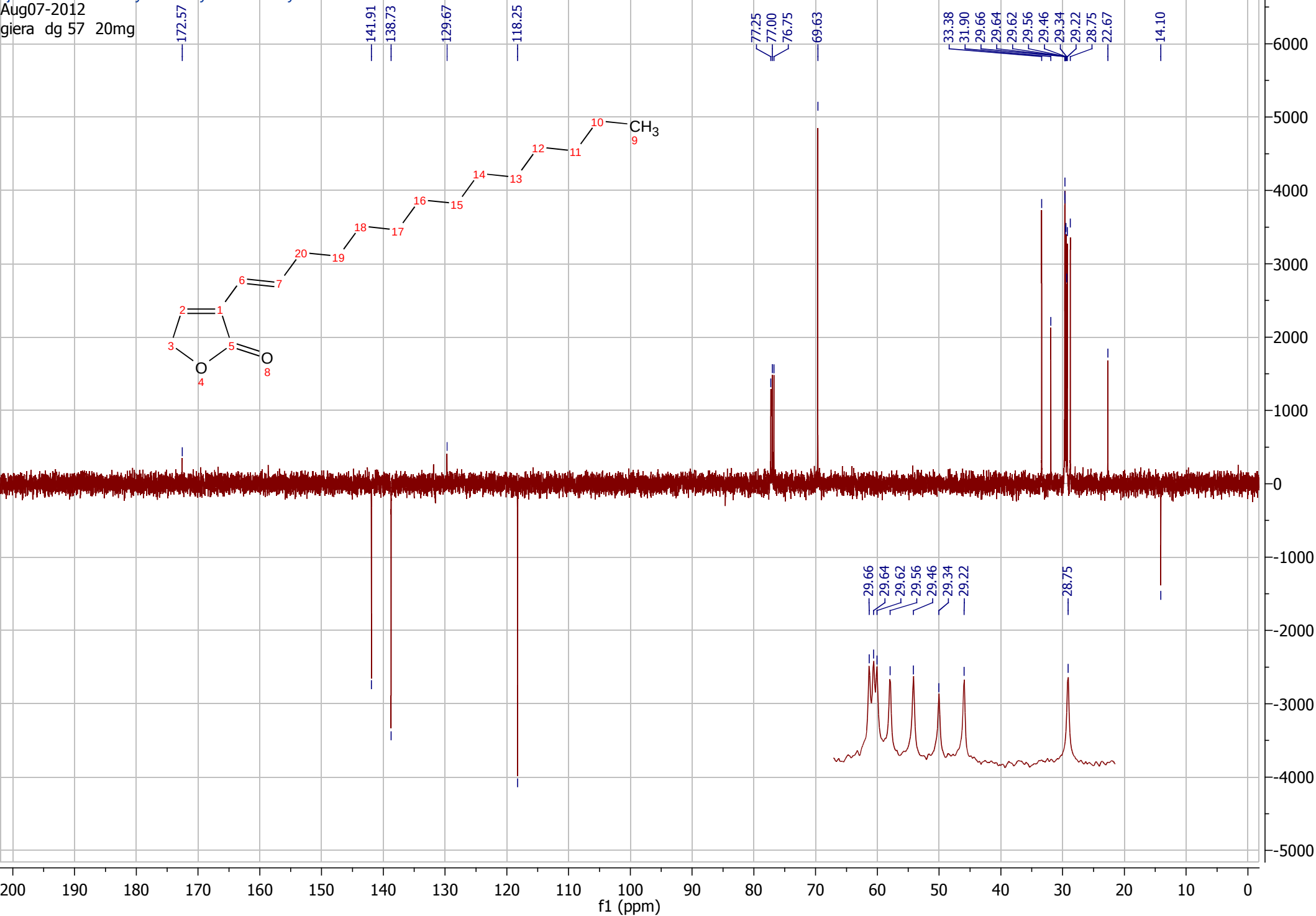
Aug06-2012-root
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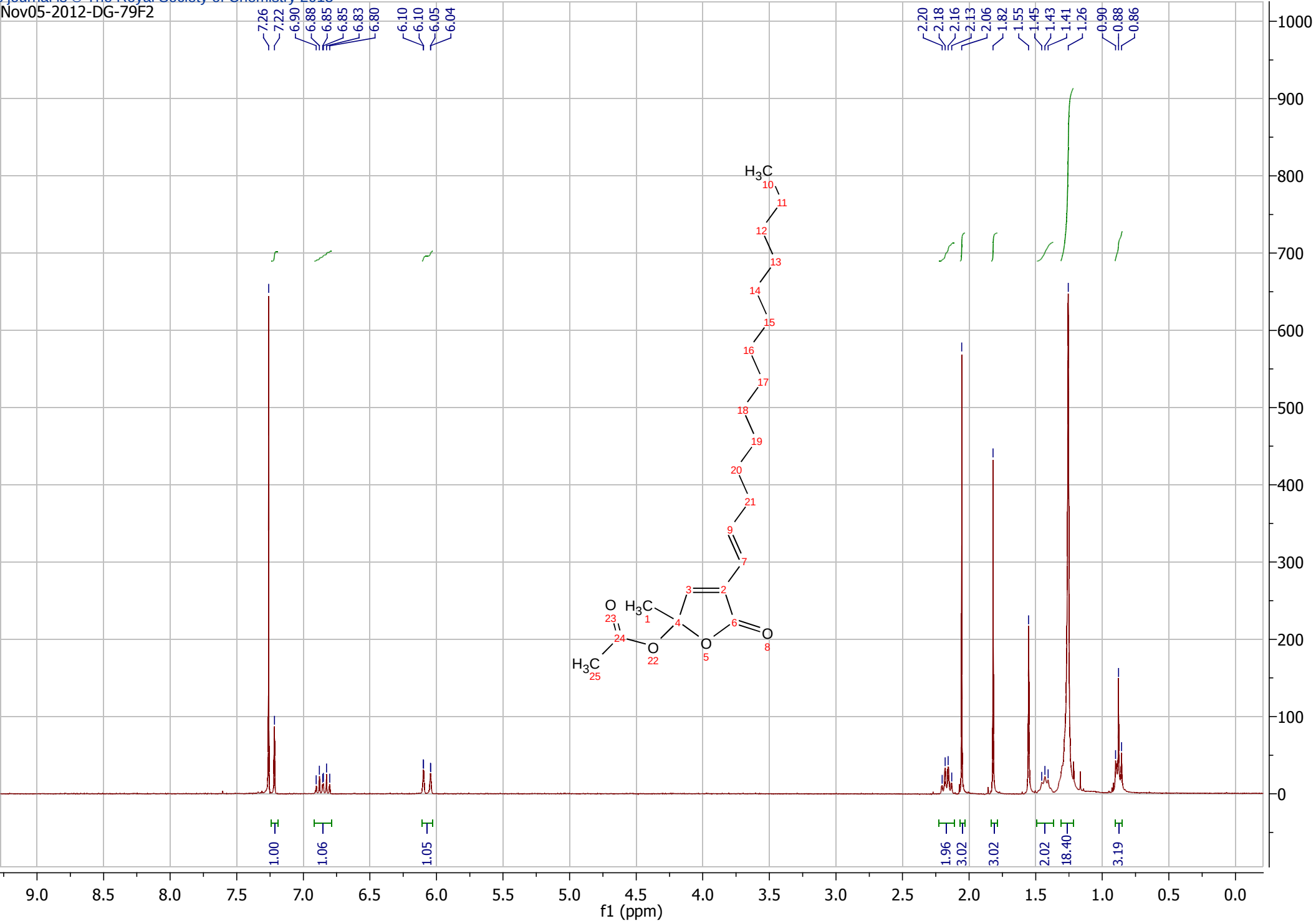
Aug07-2012
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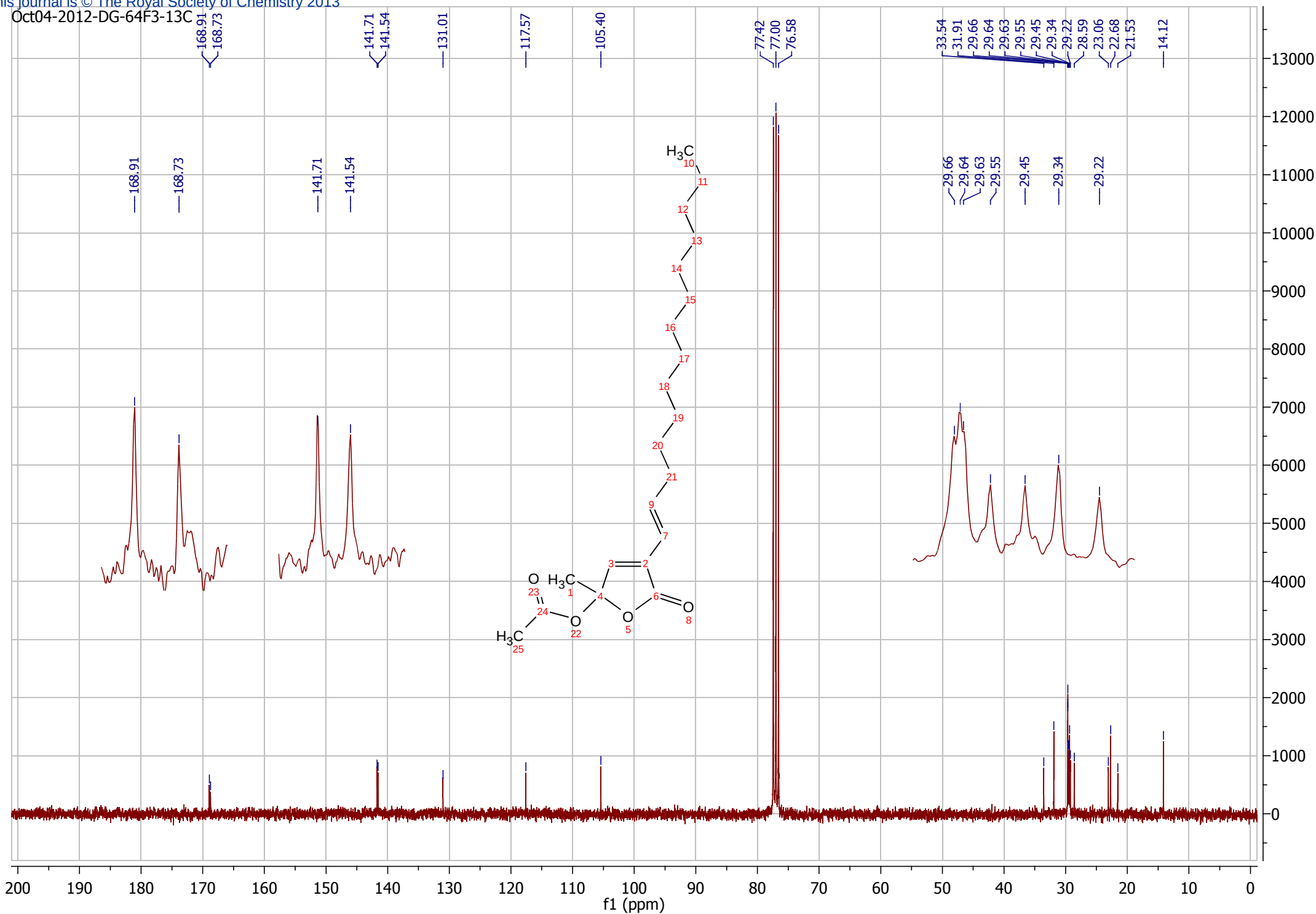
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giera dg 57 20mg



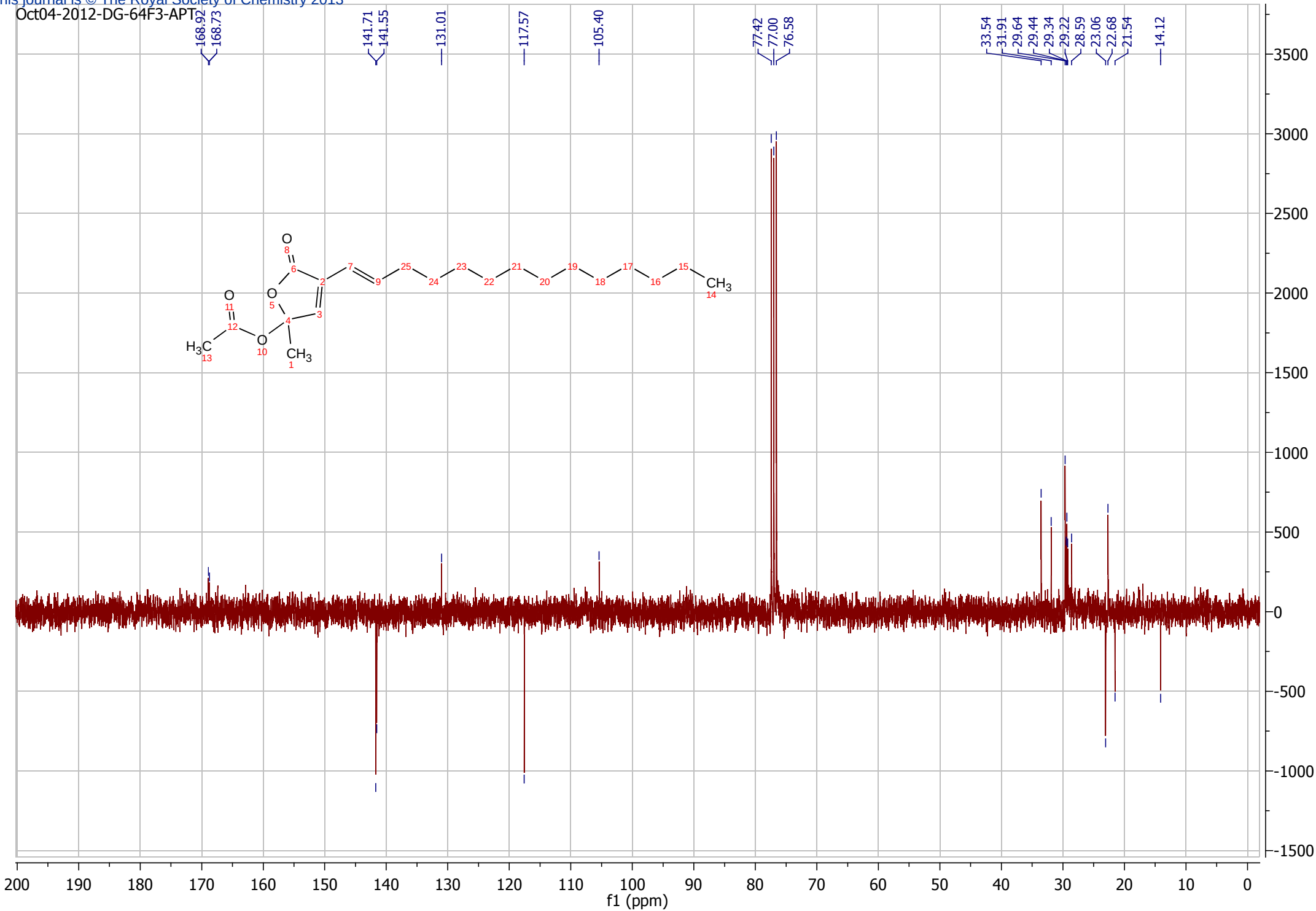
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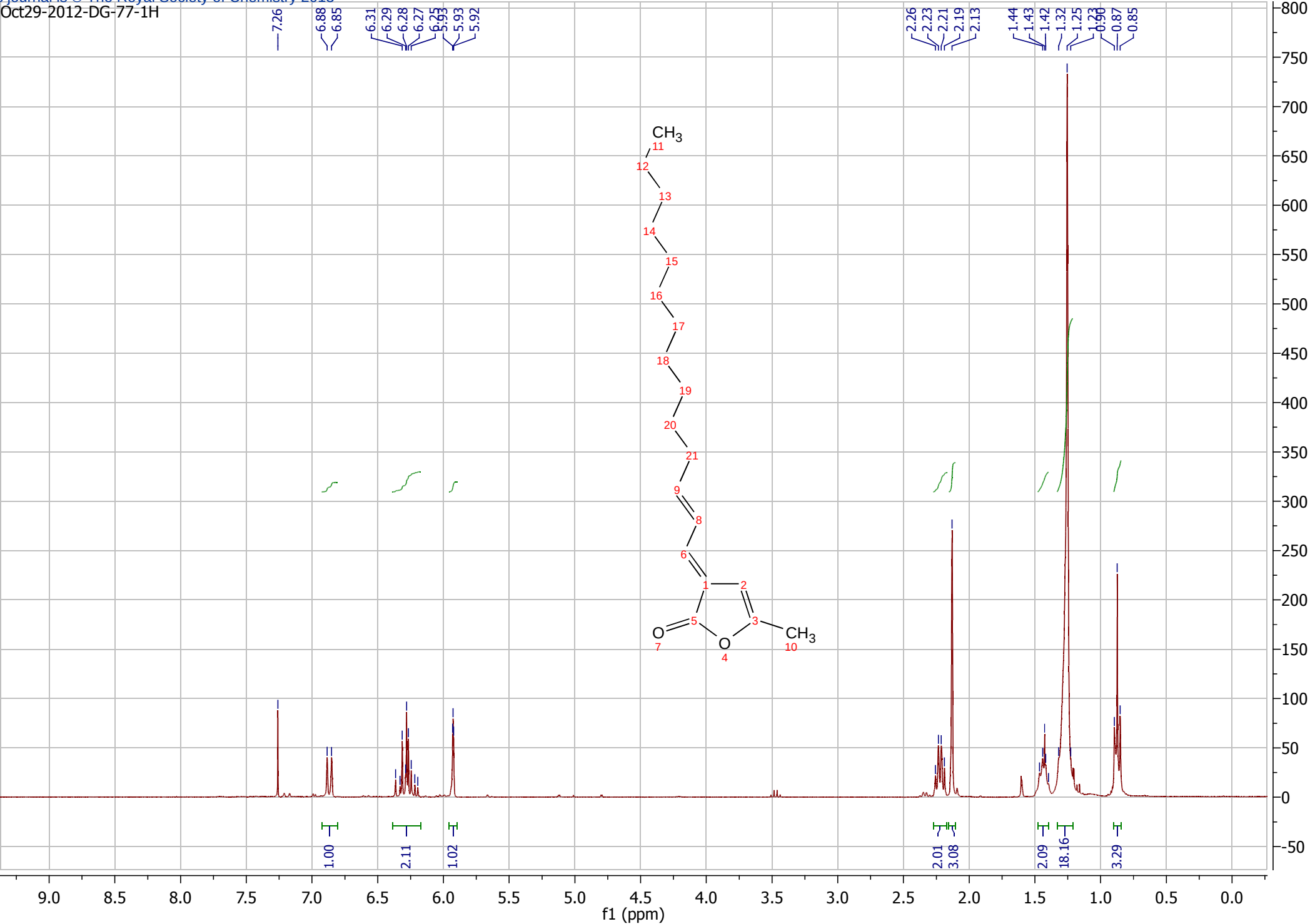


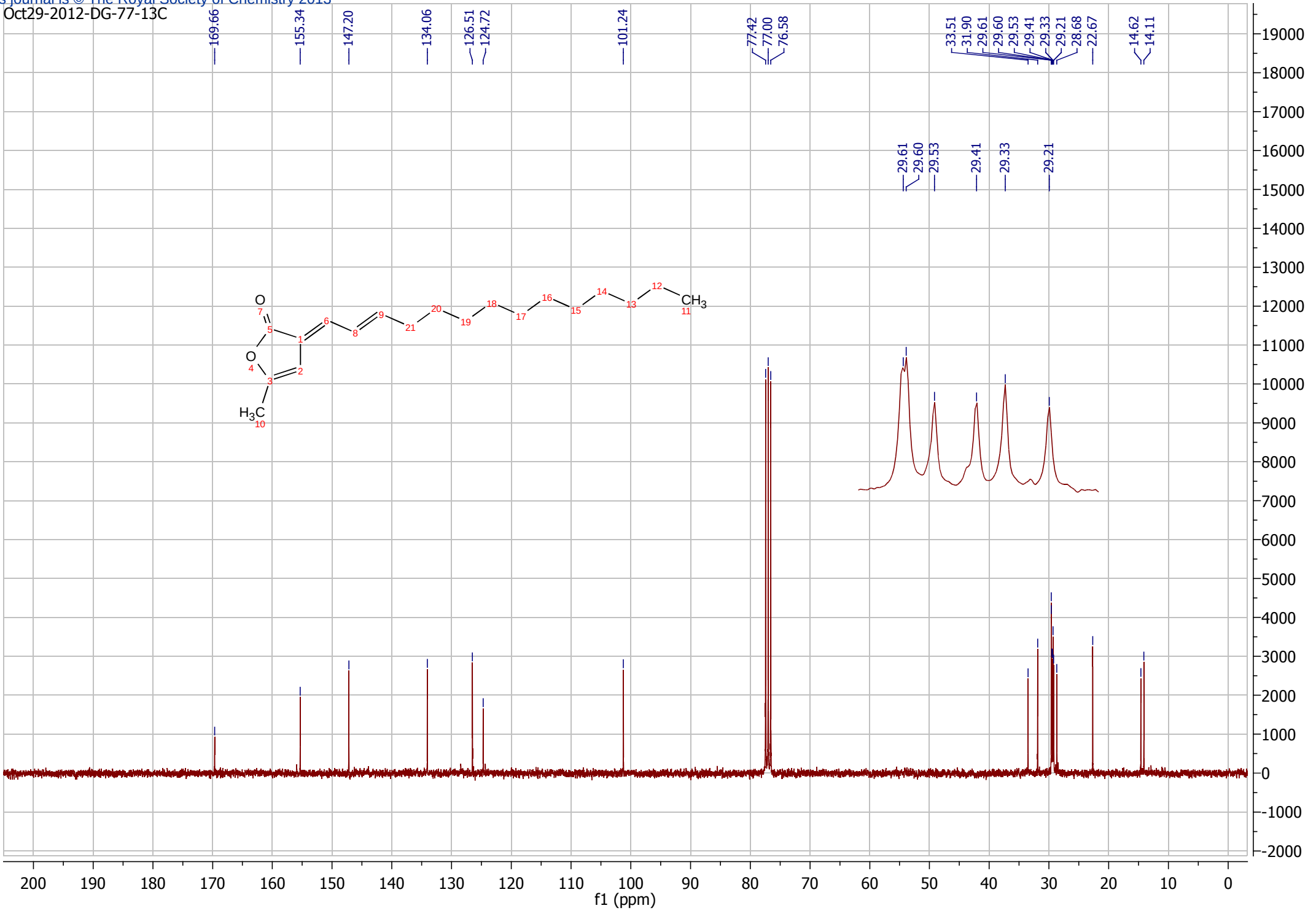
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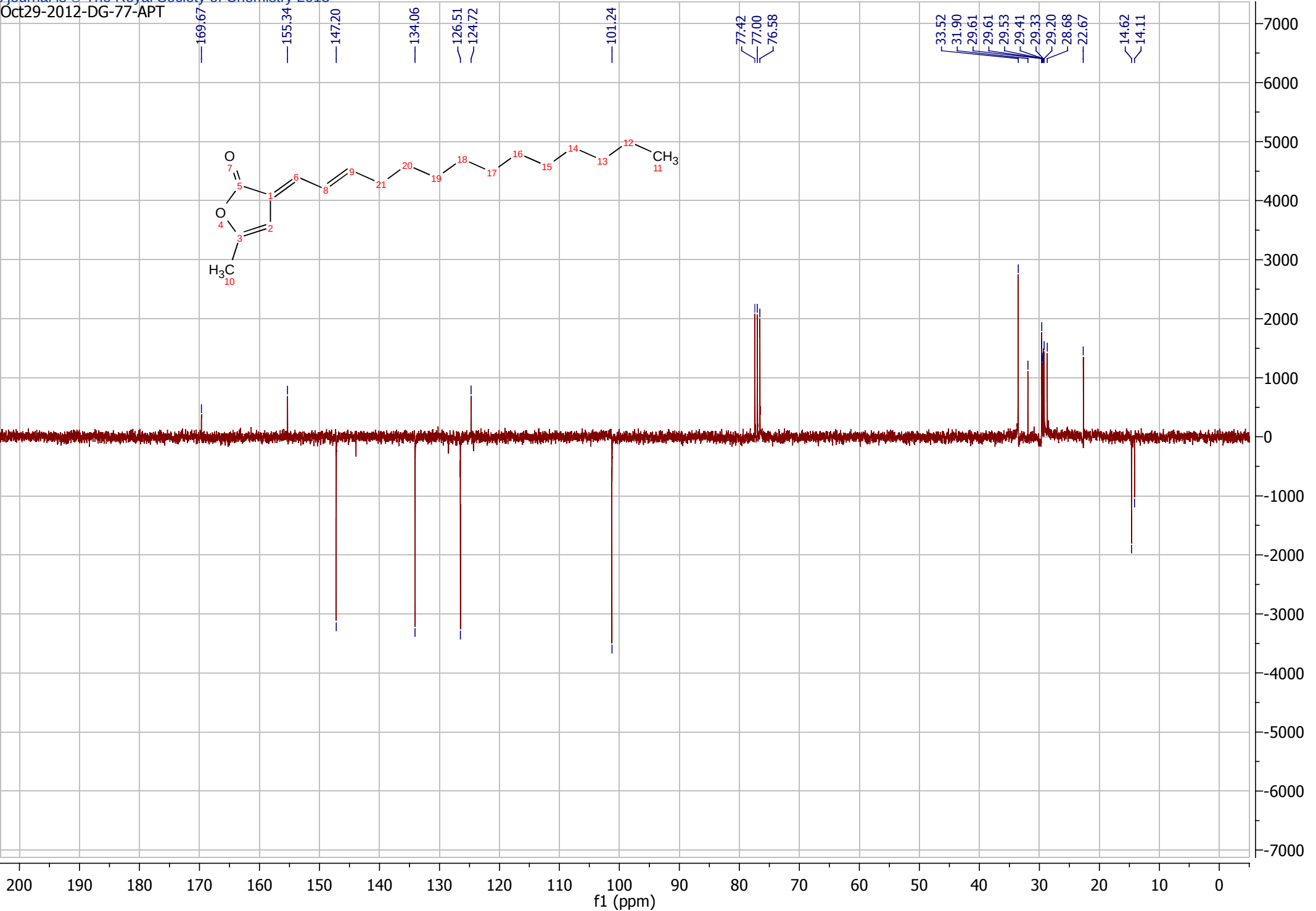
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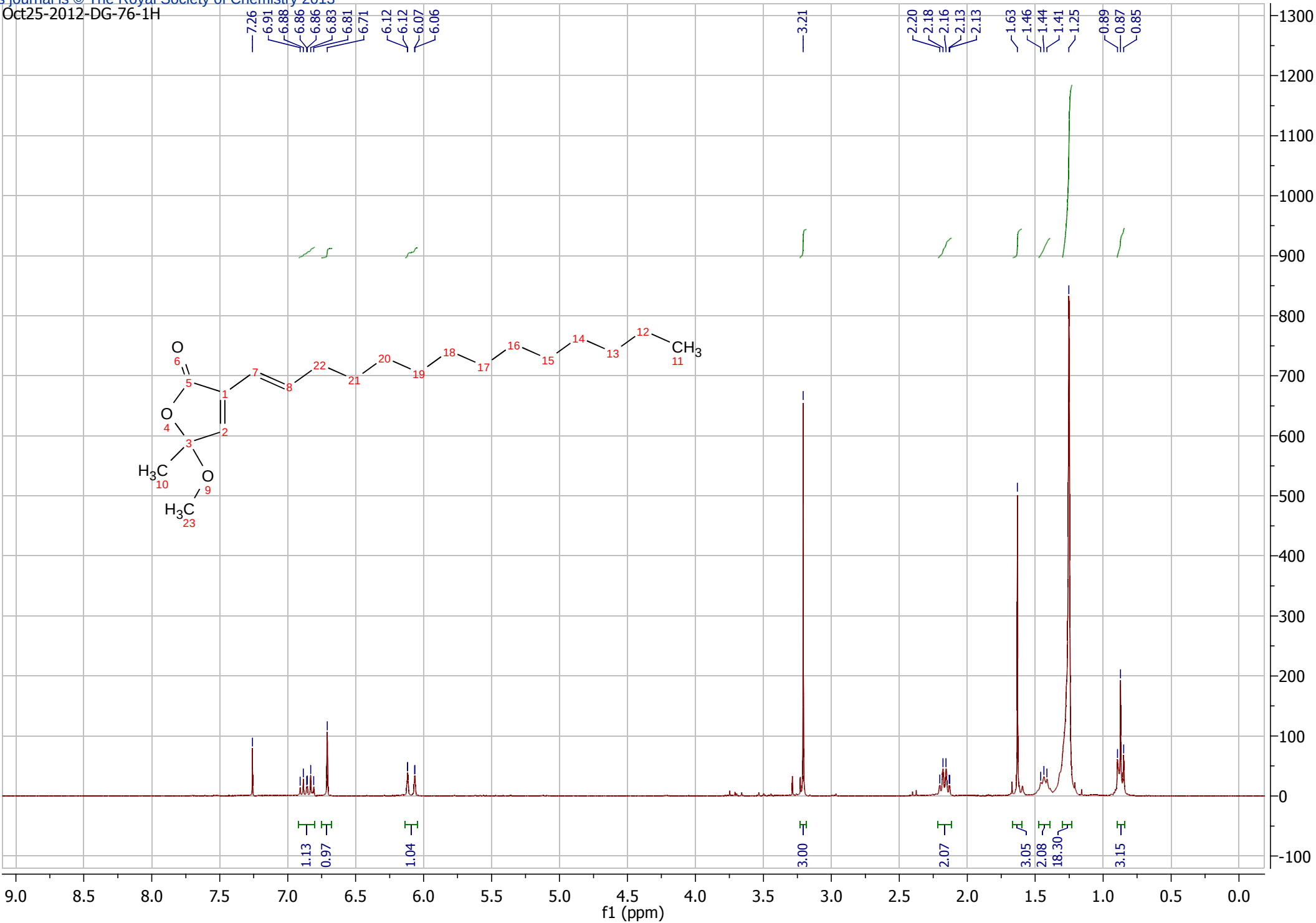


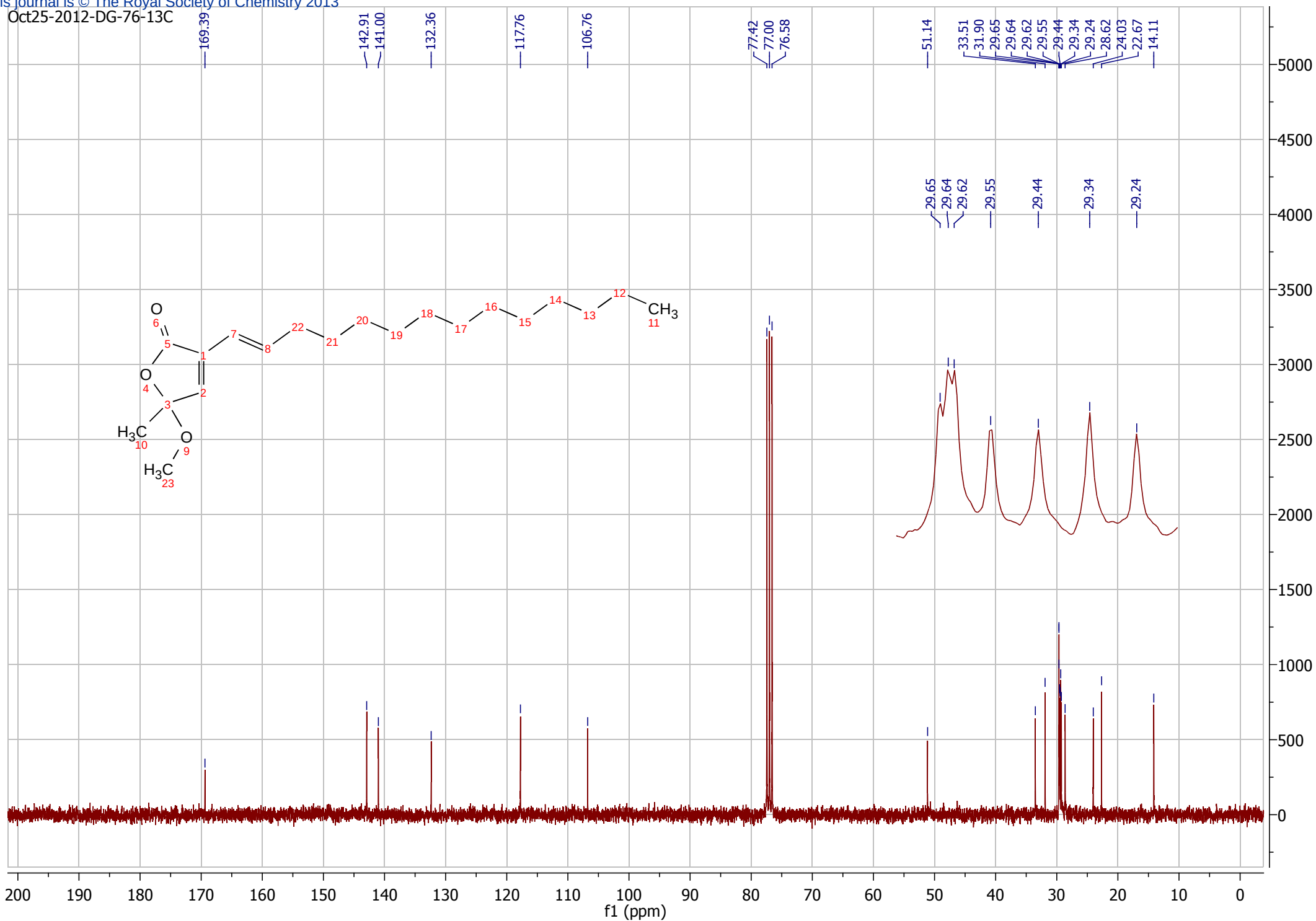
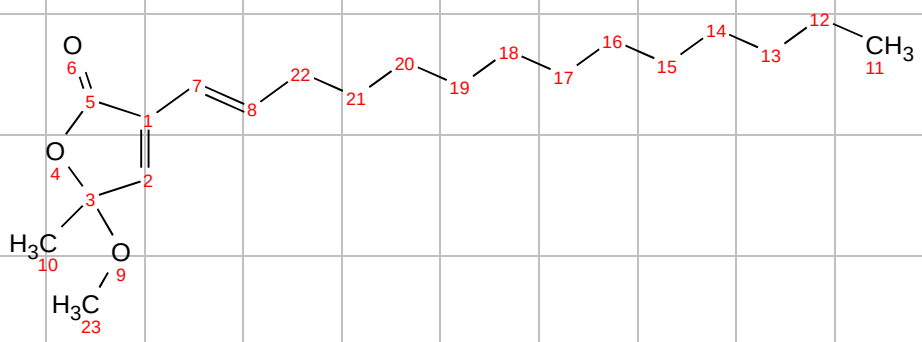


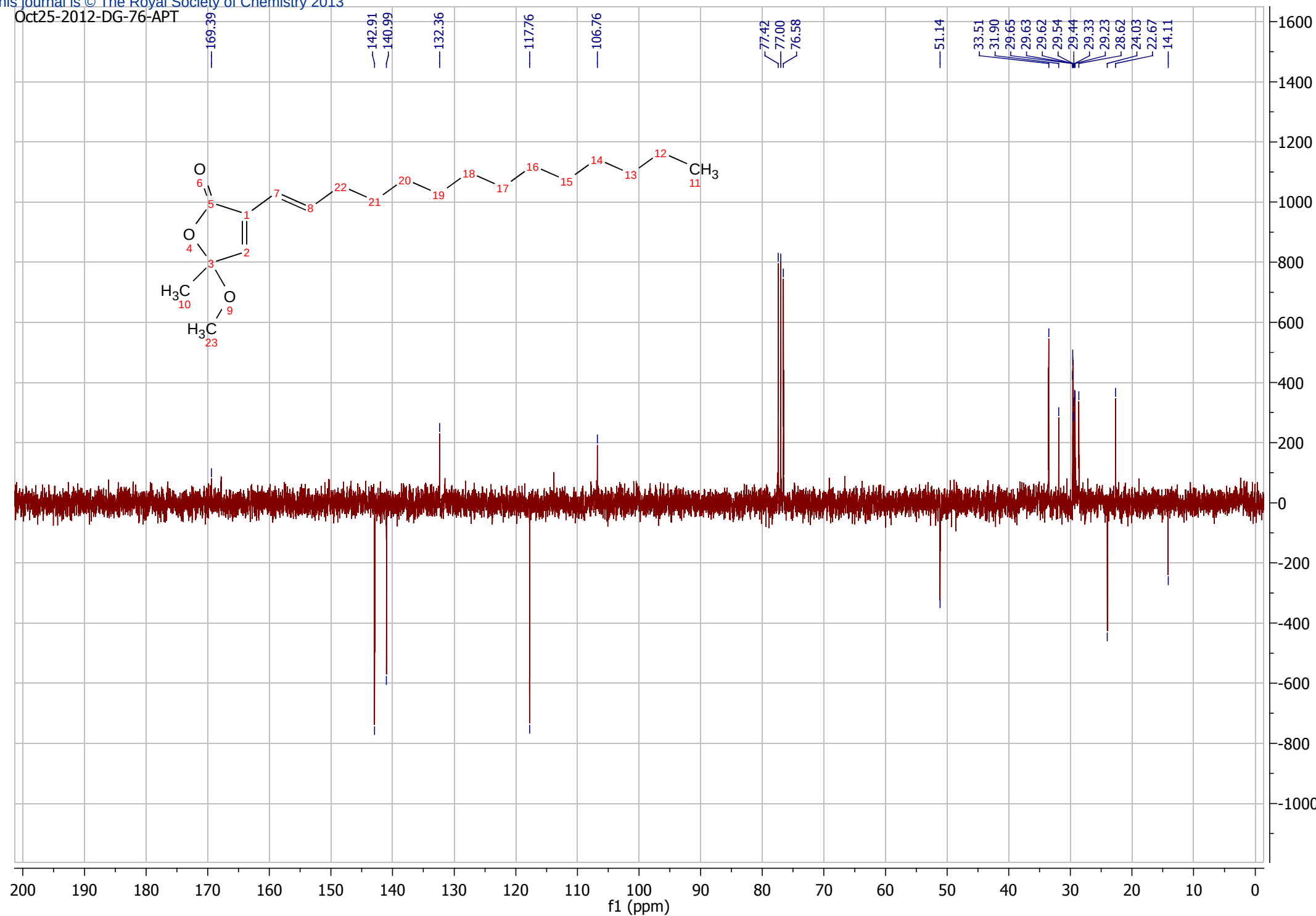
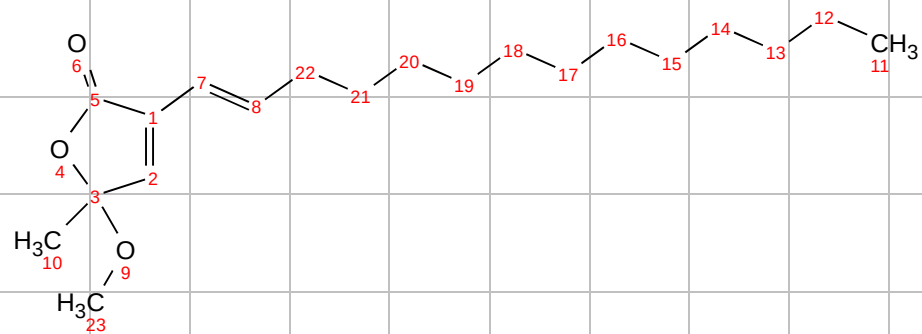


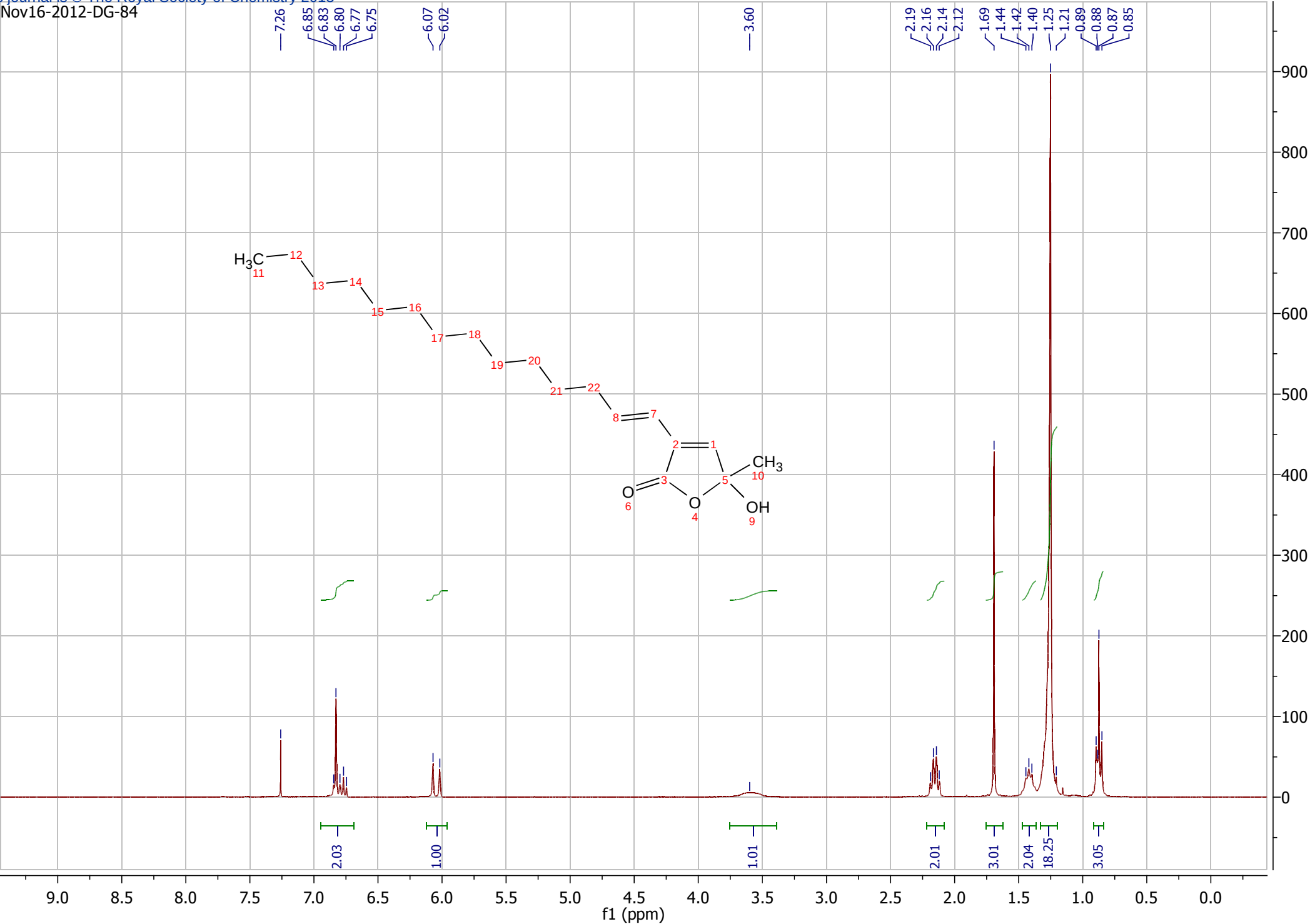
Oct29-2012-DG-77-APT



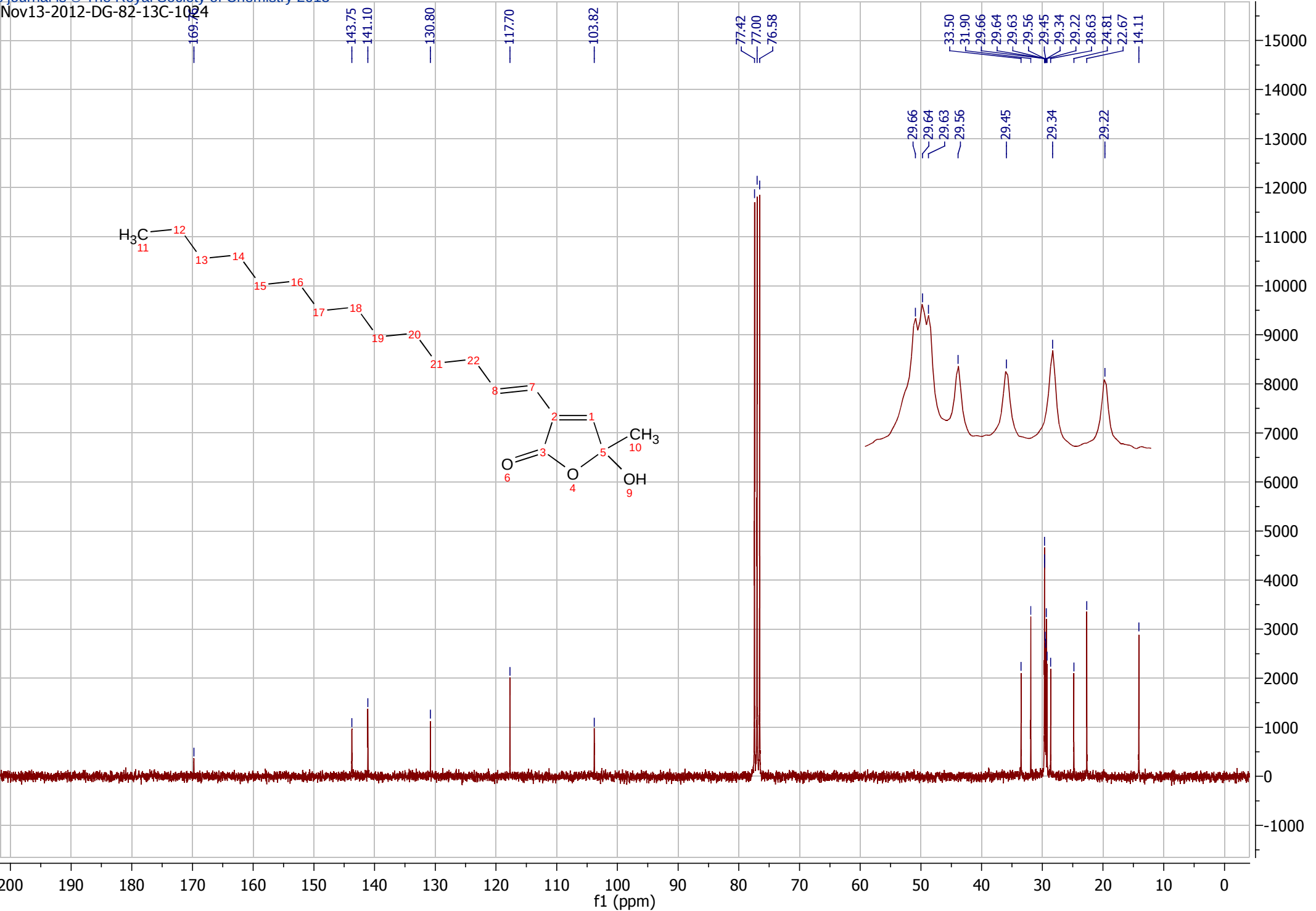




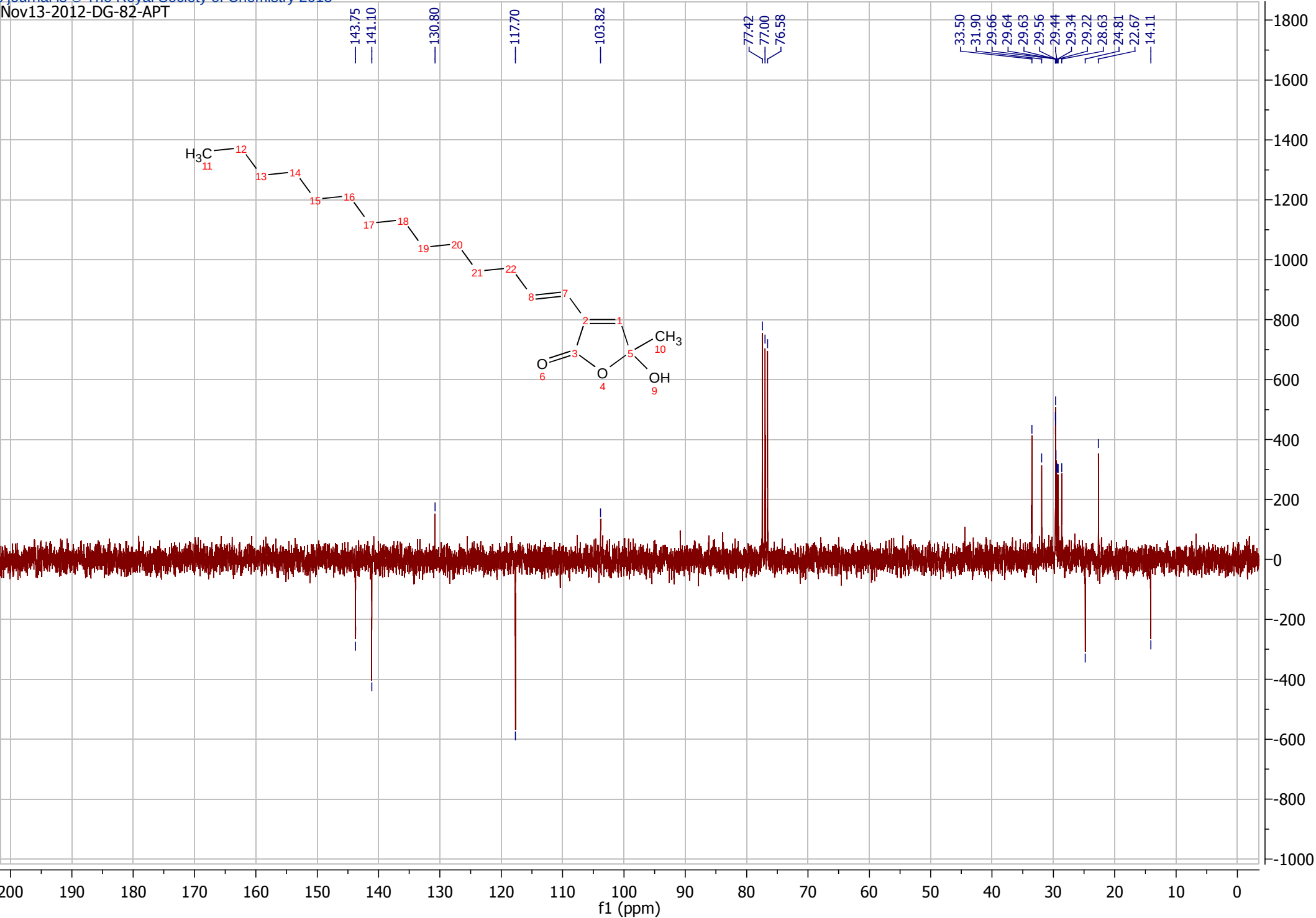


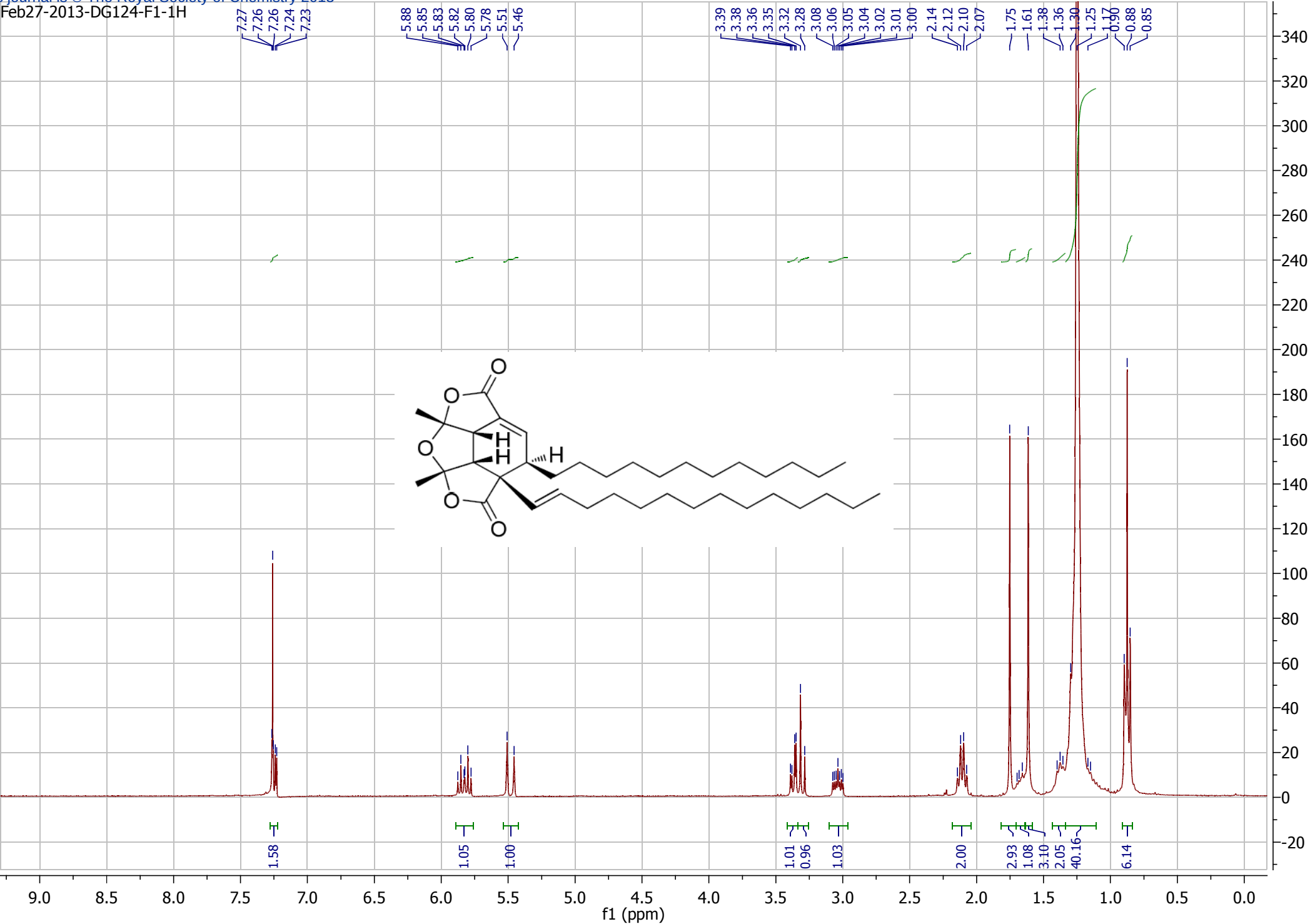


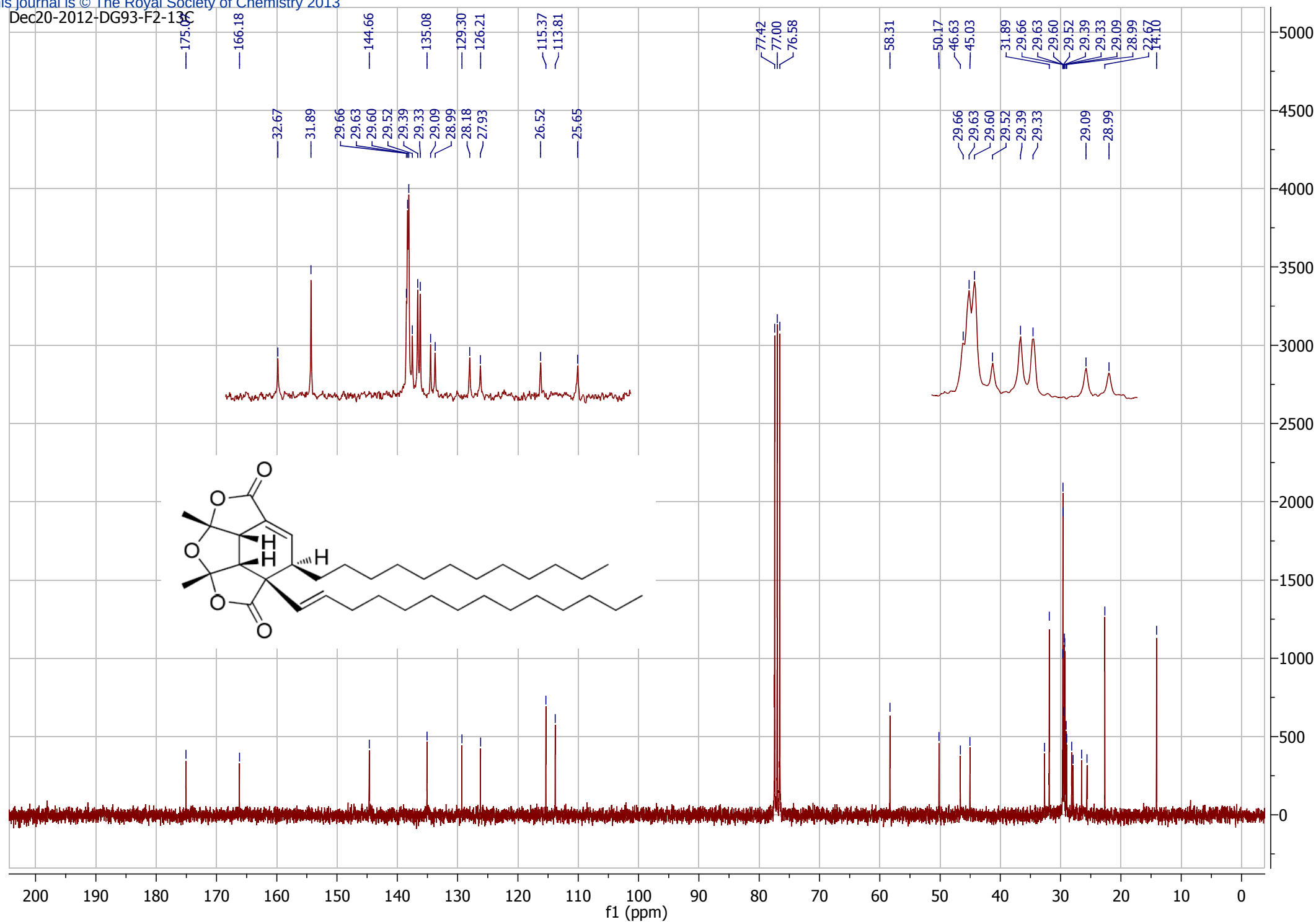
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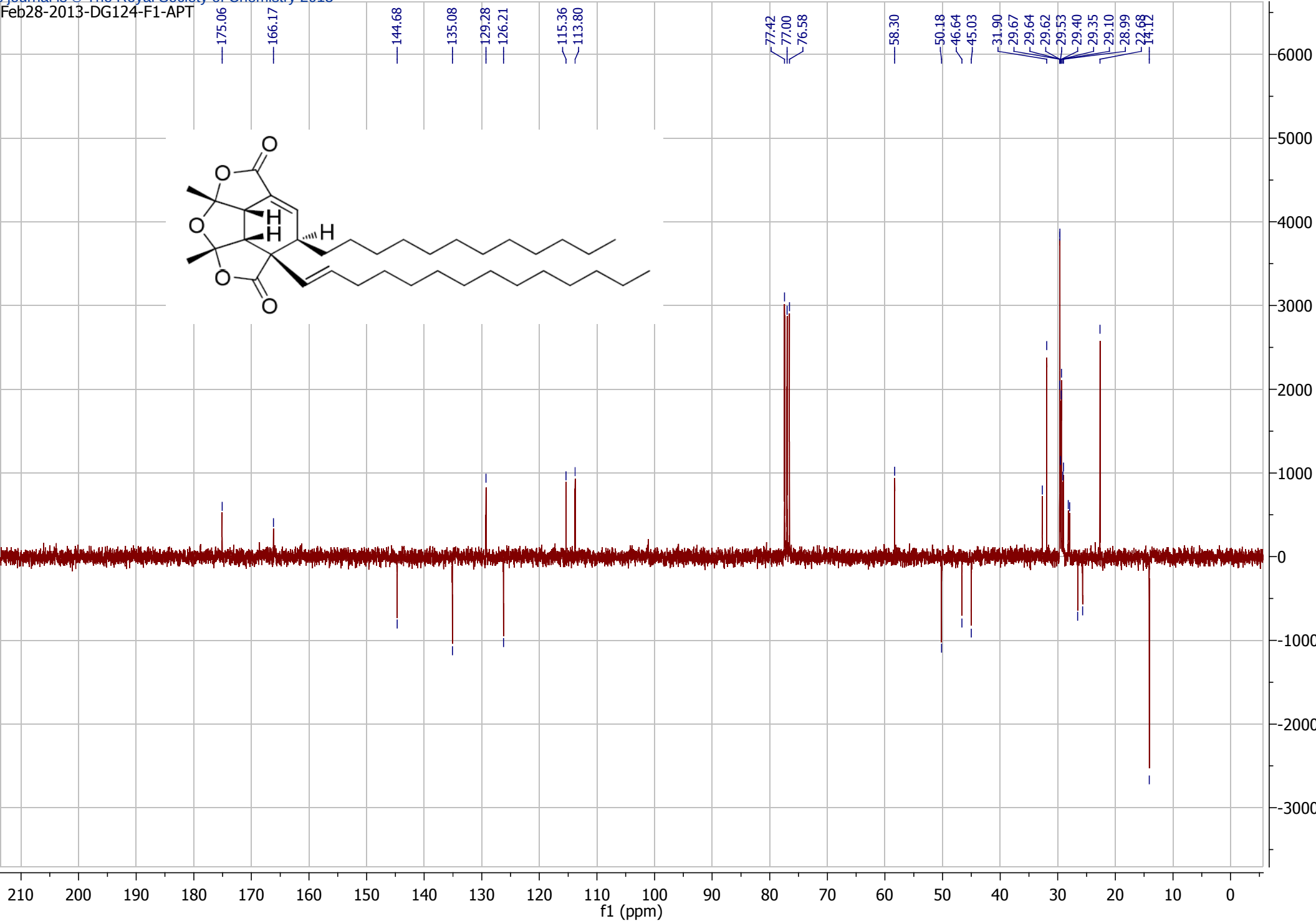
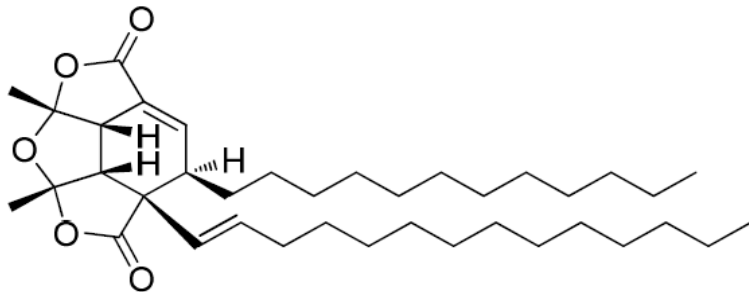


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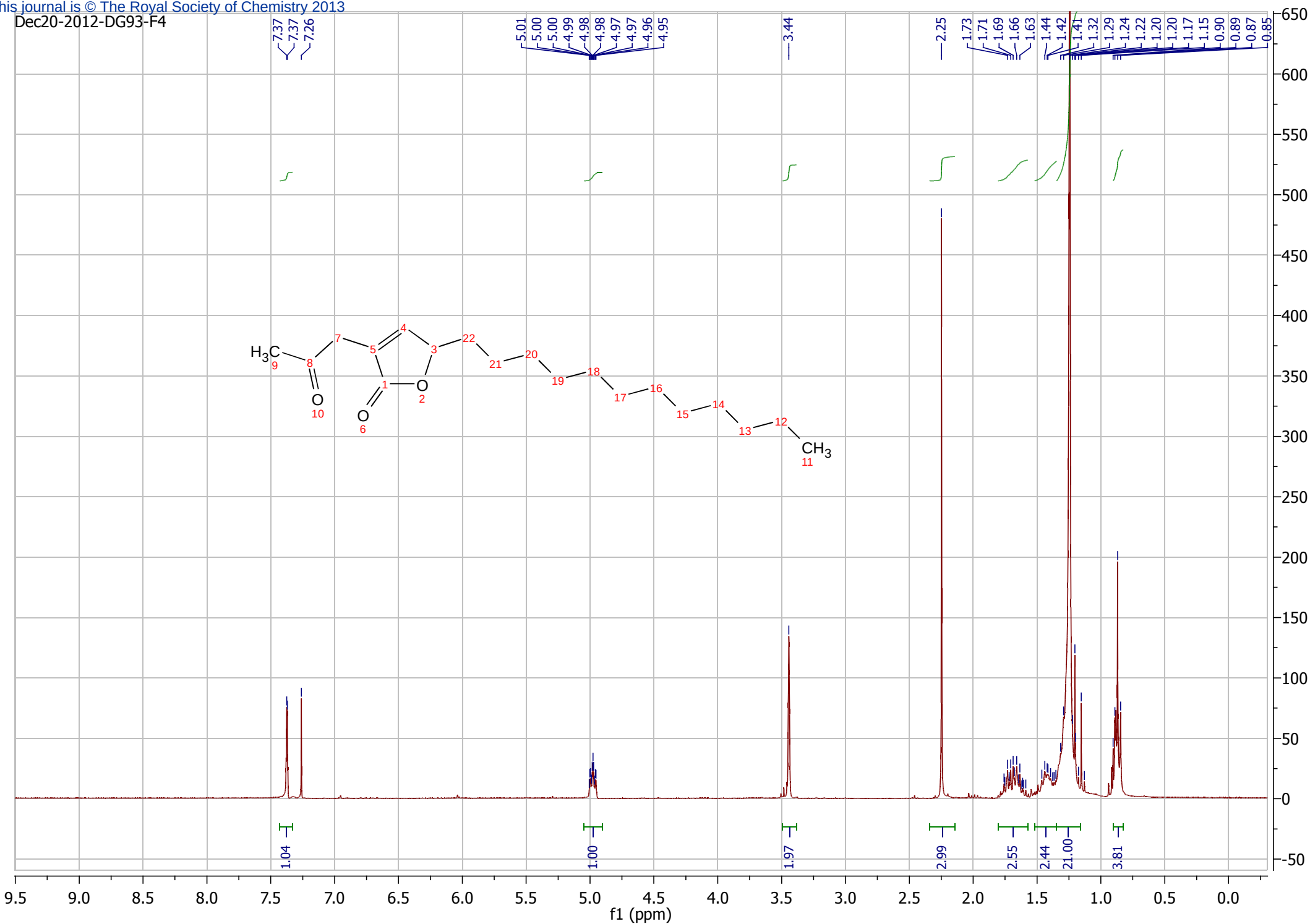




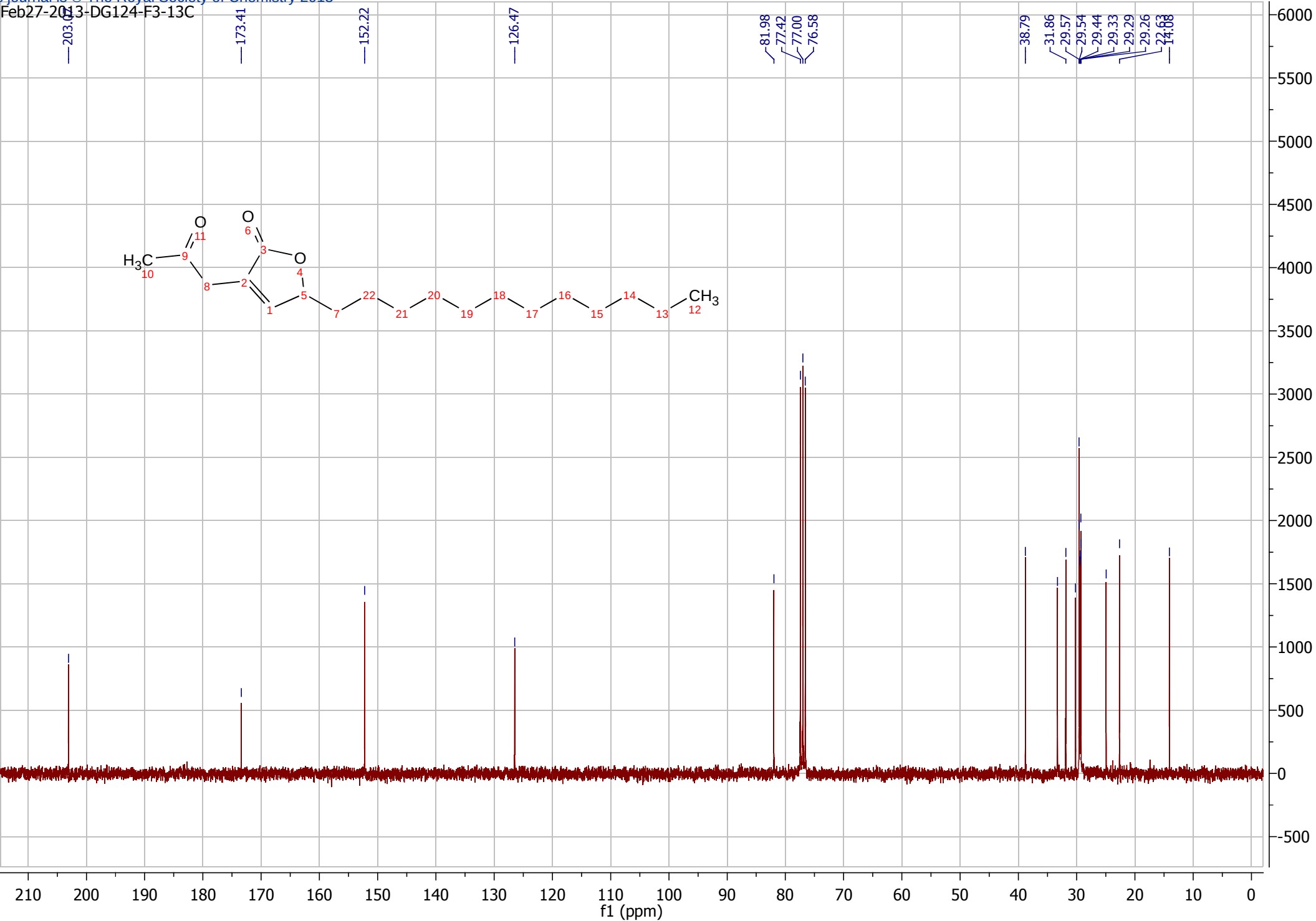




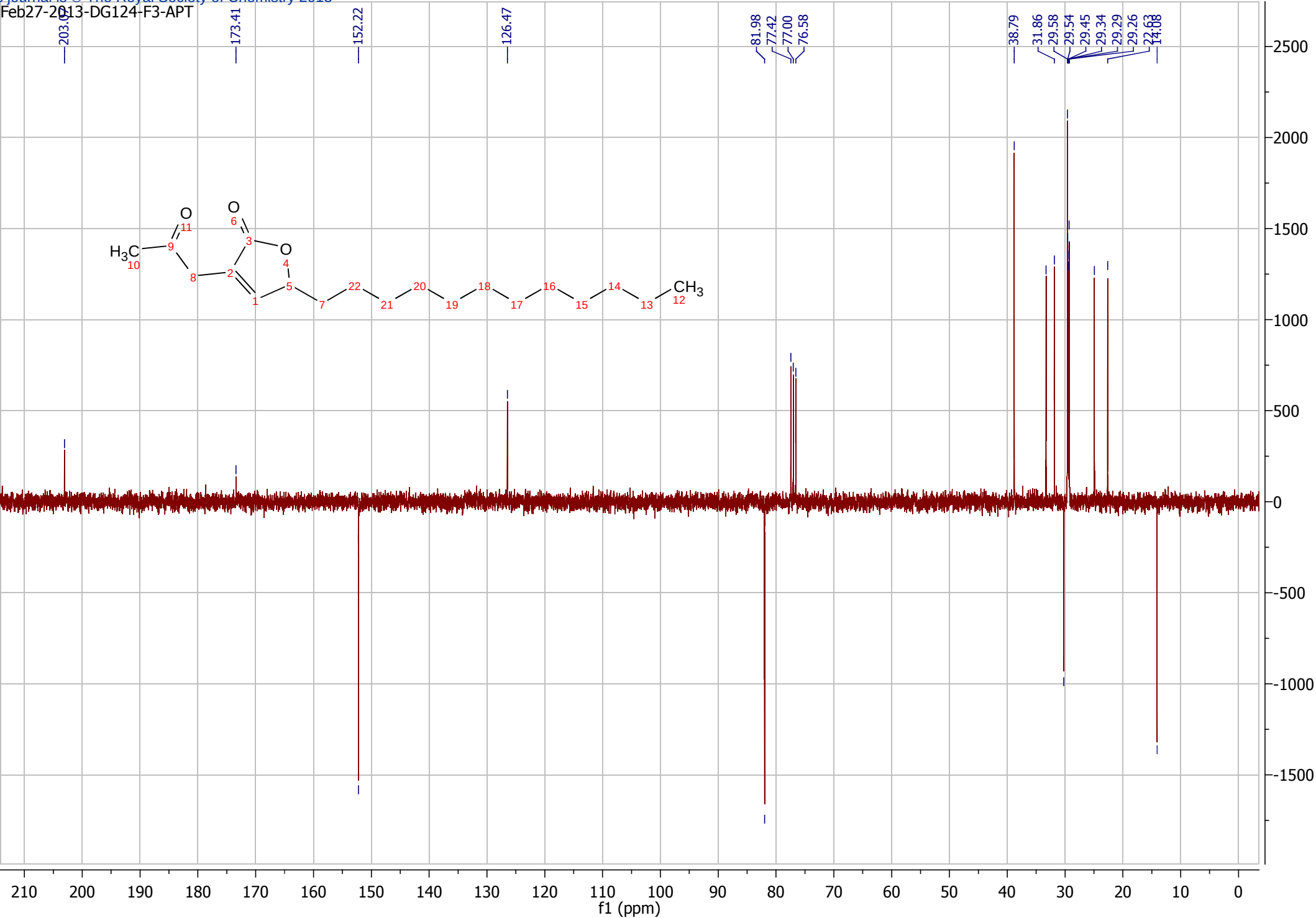
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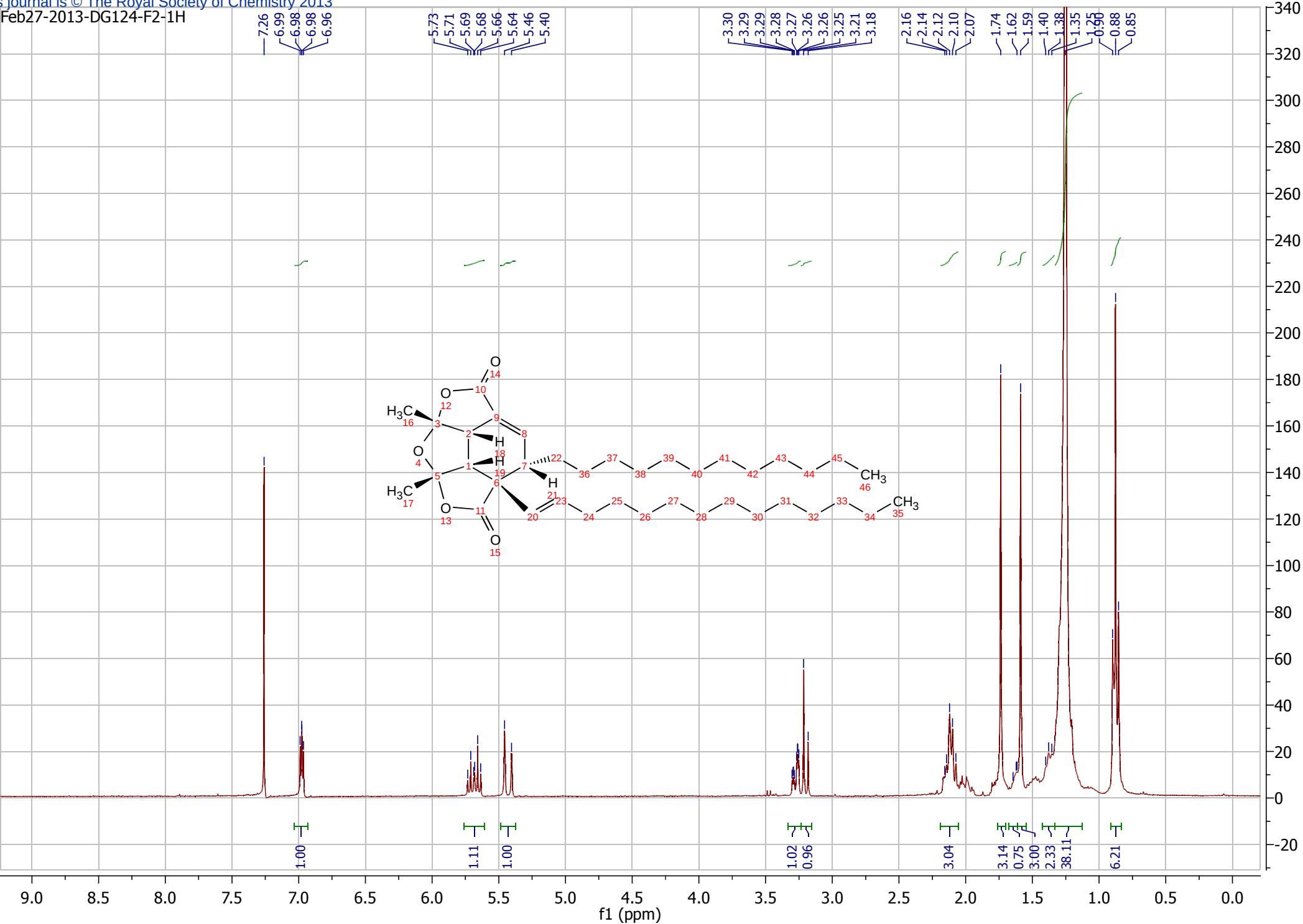


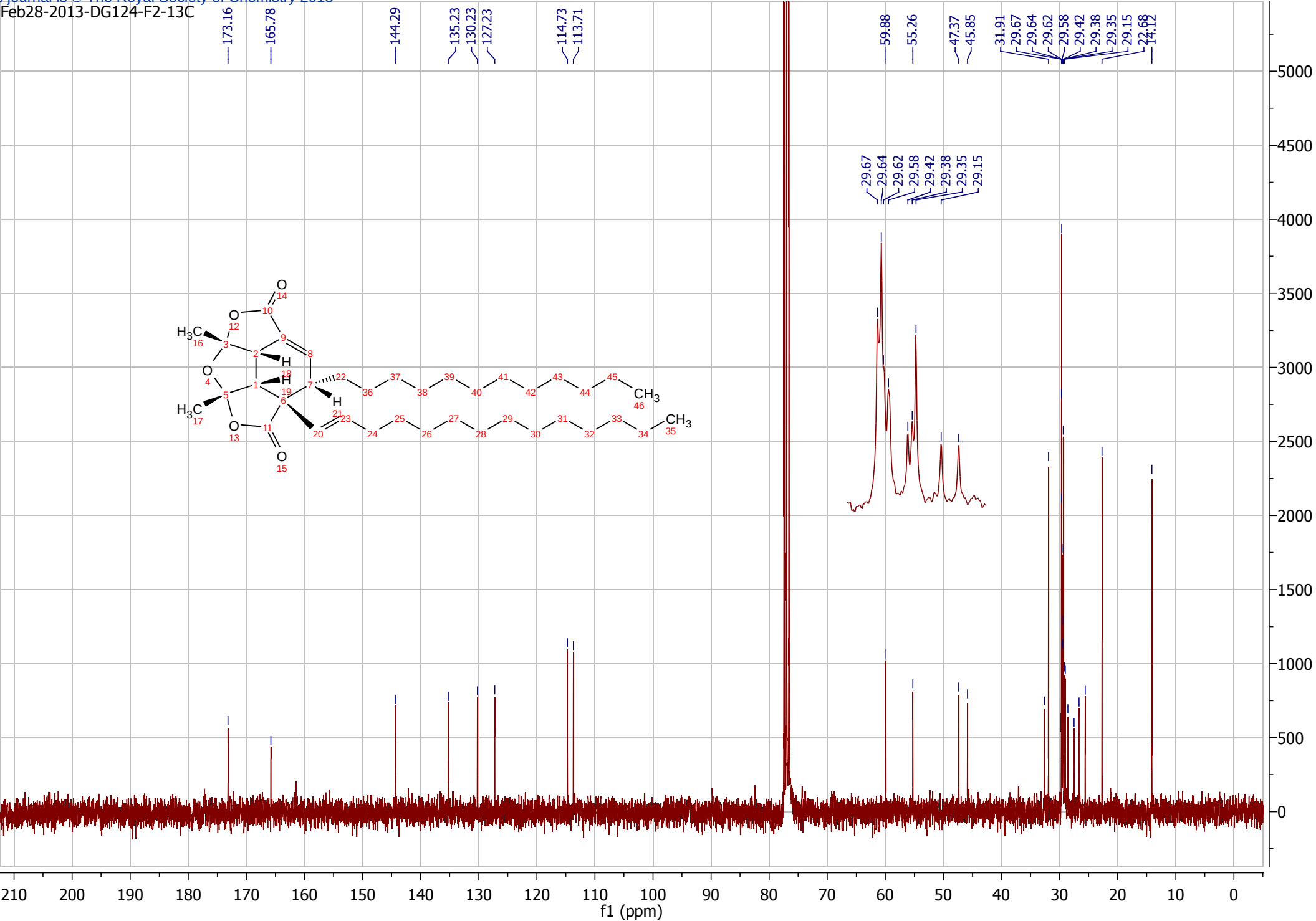
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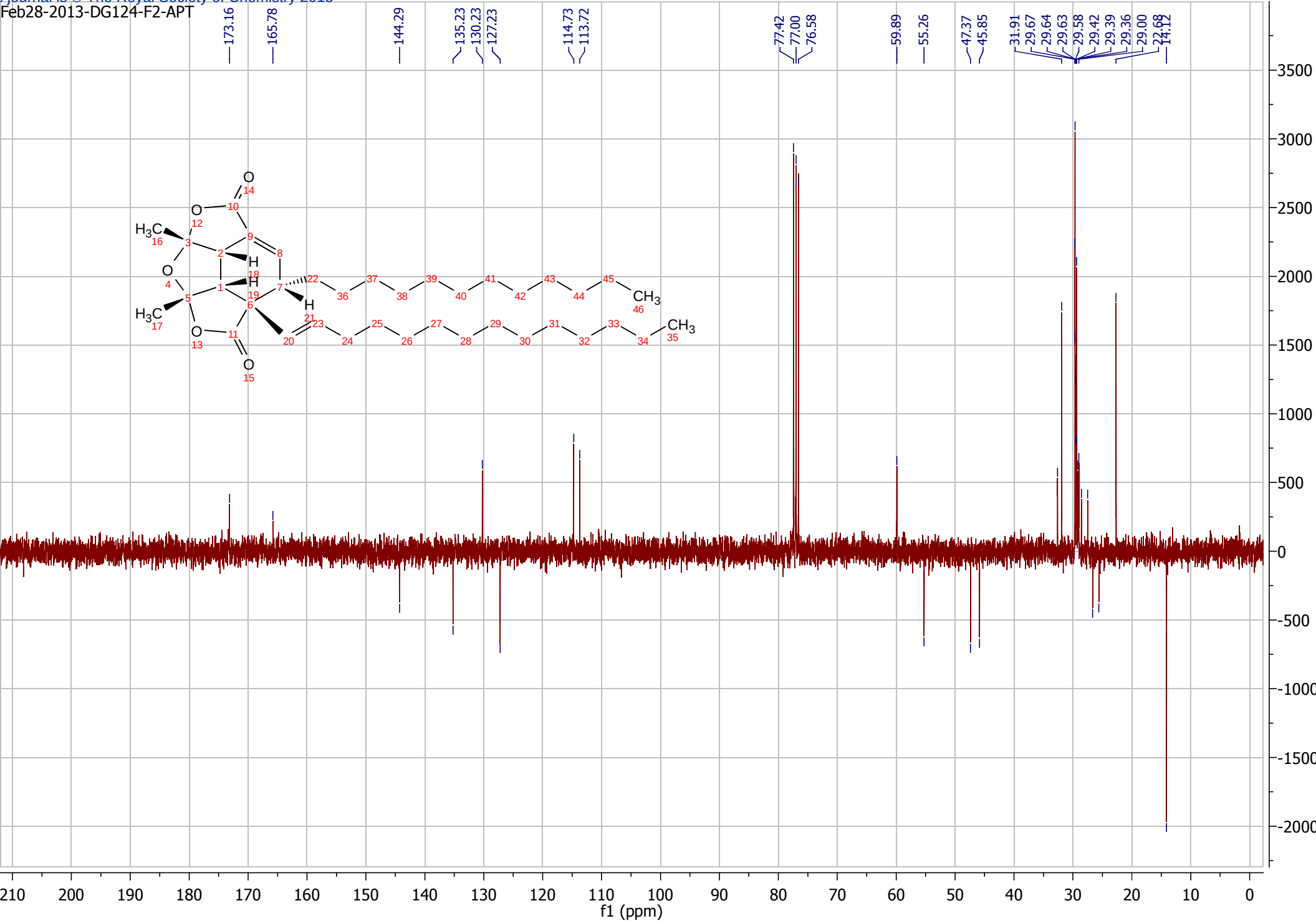
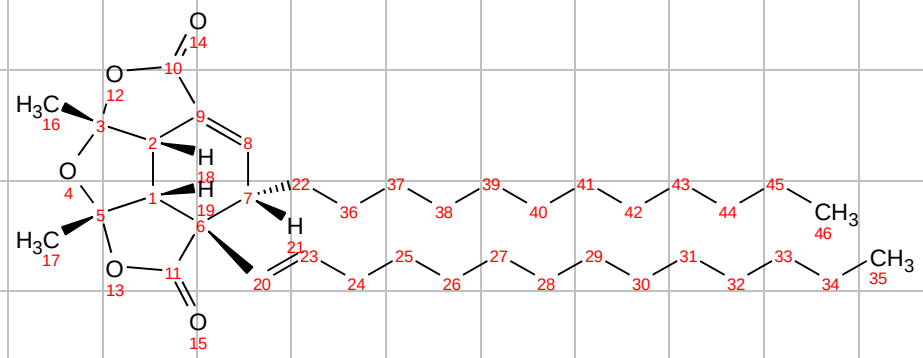


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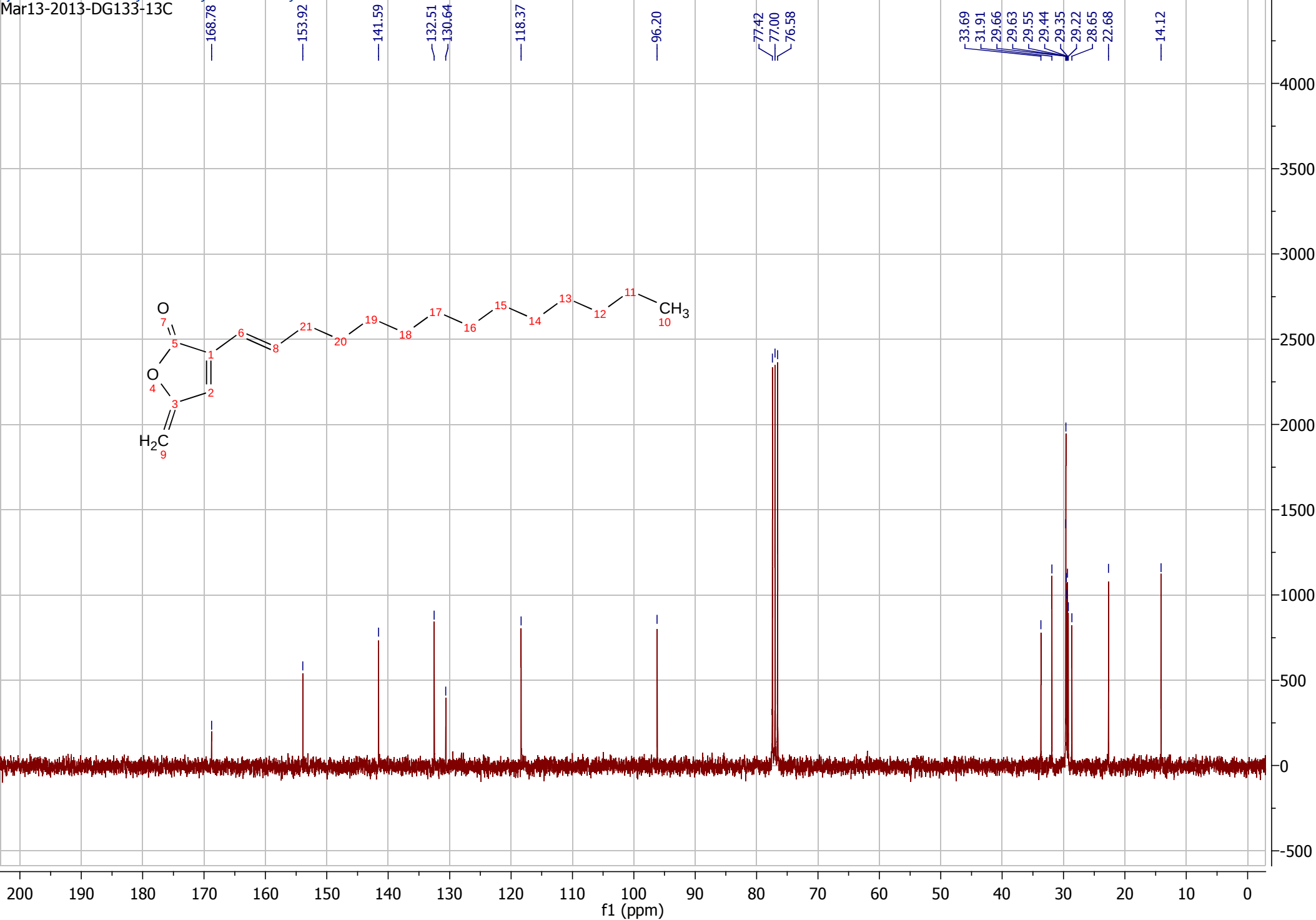


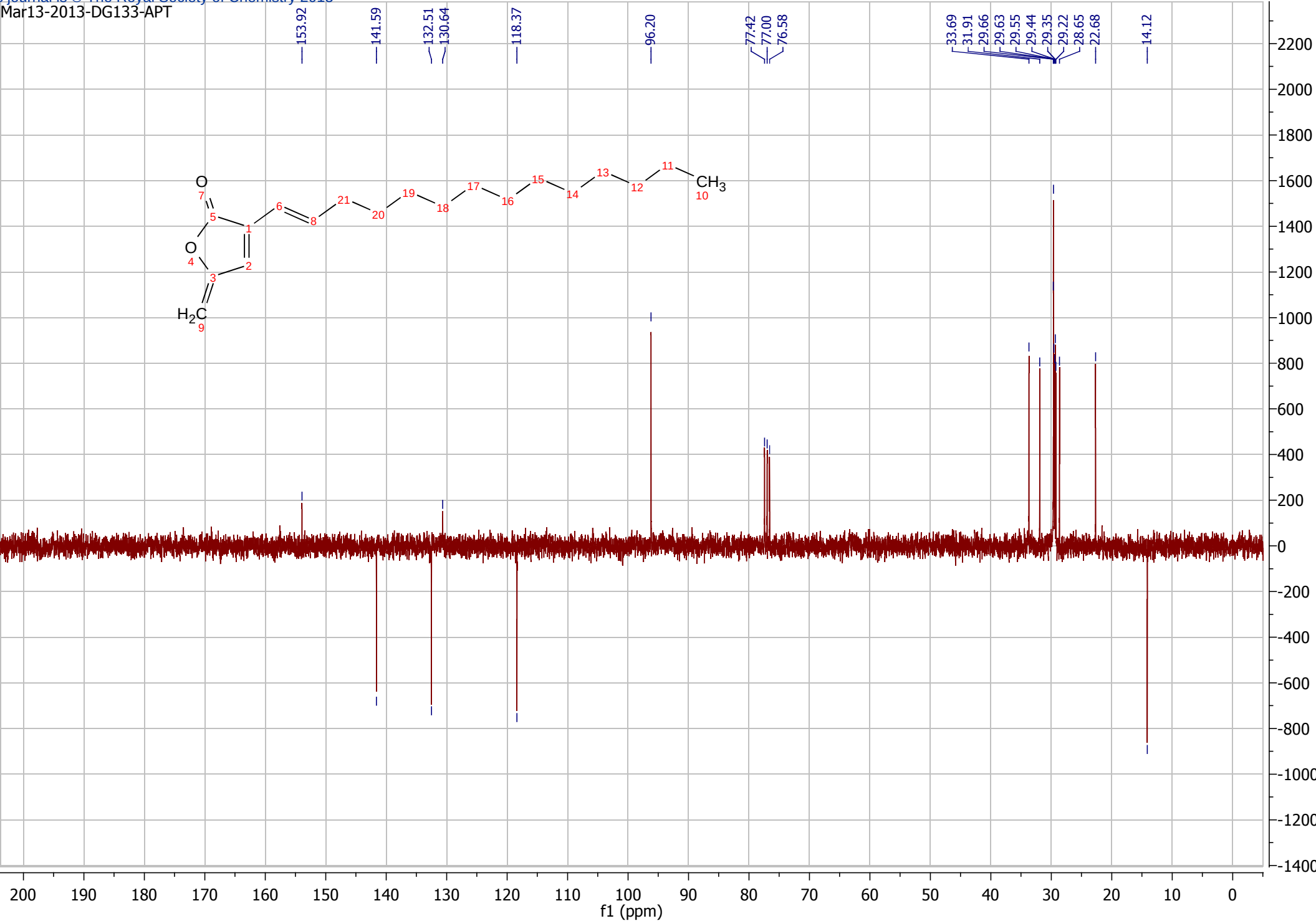


Mar13-2013-DG133-1H

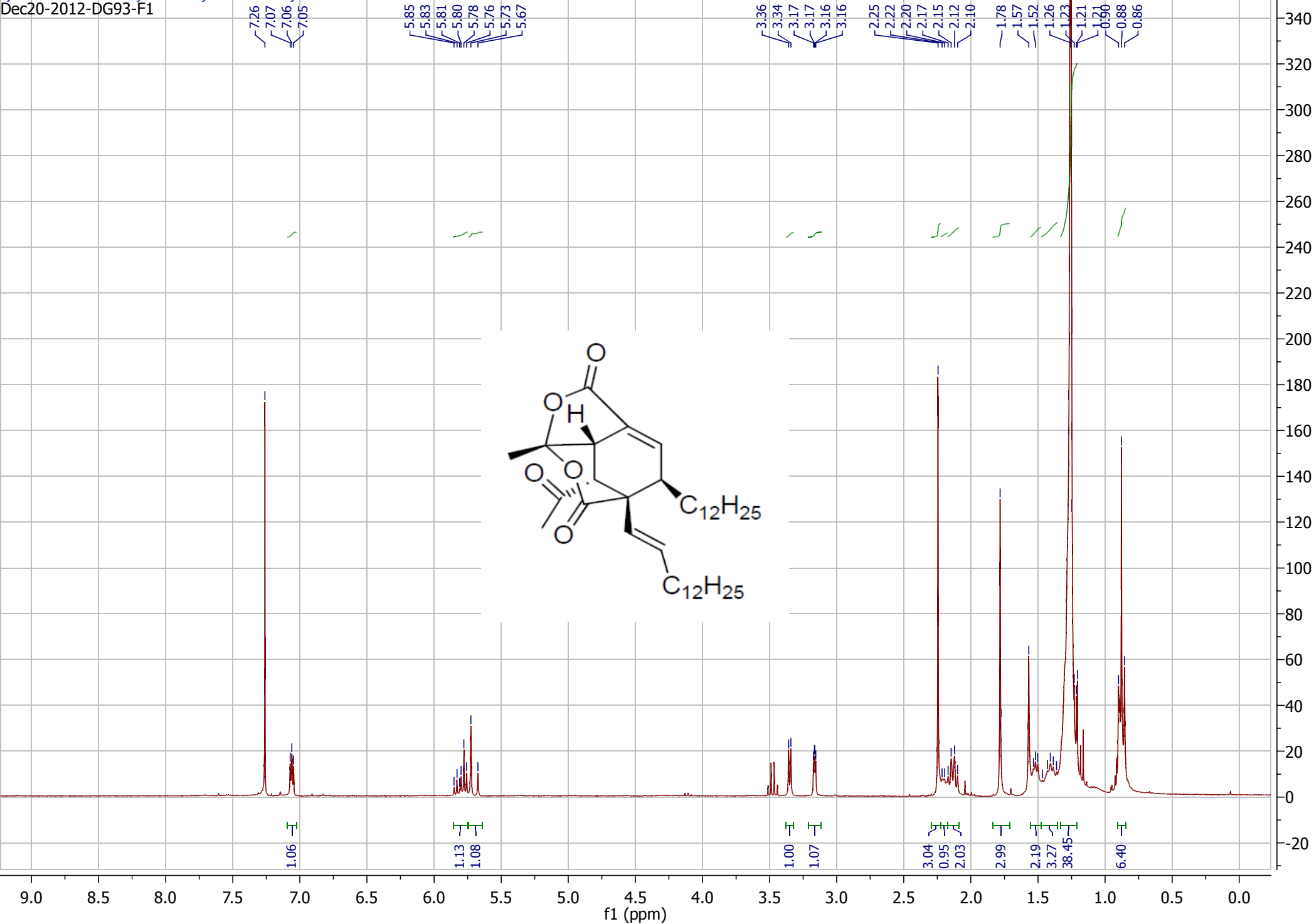


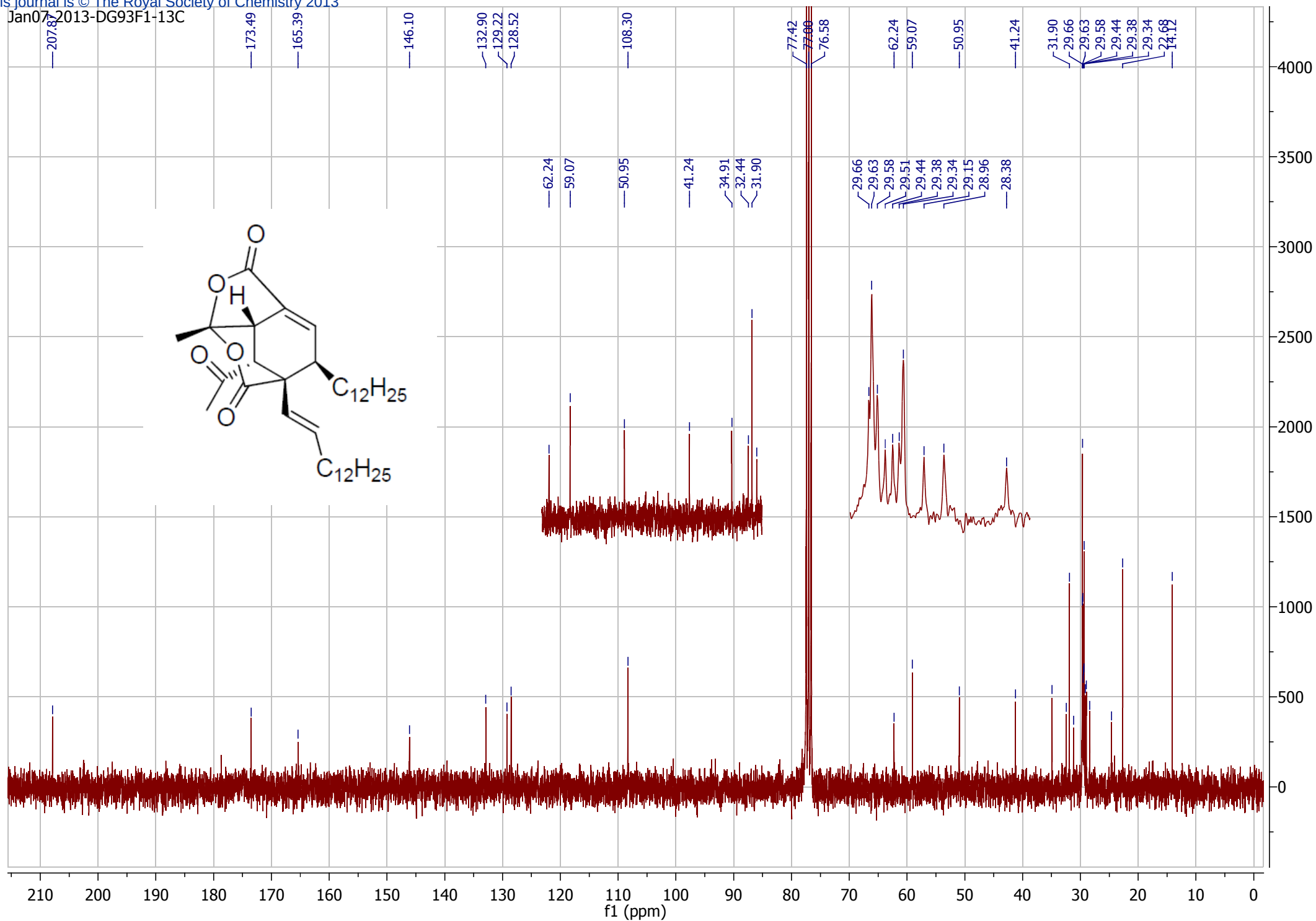
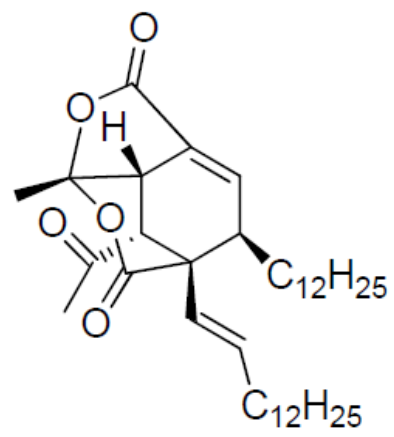
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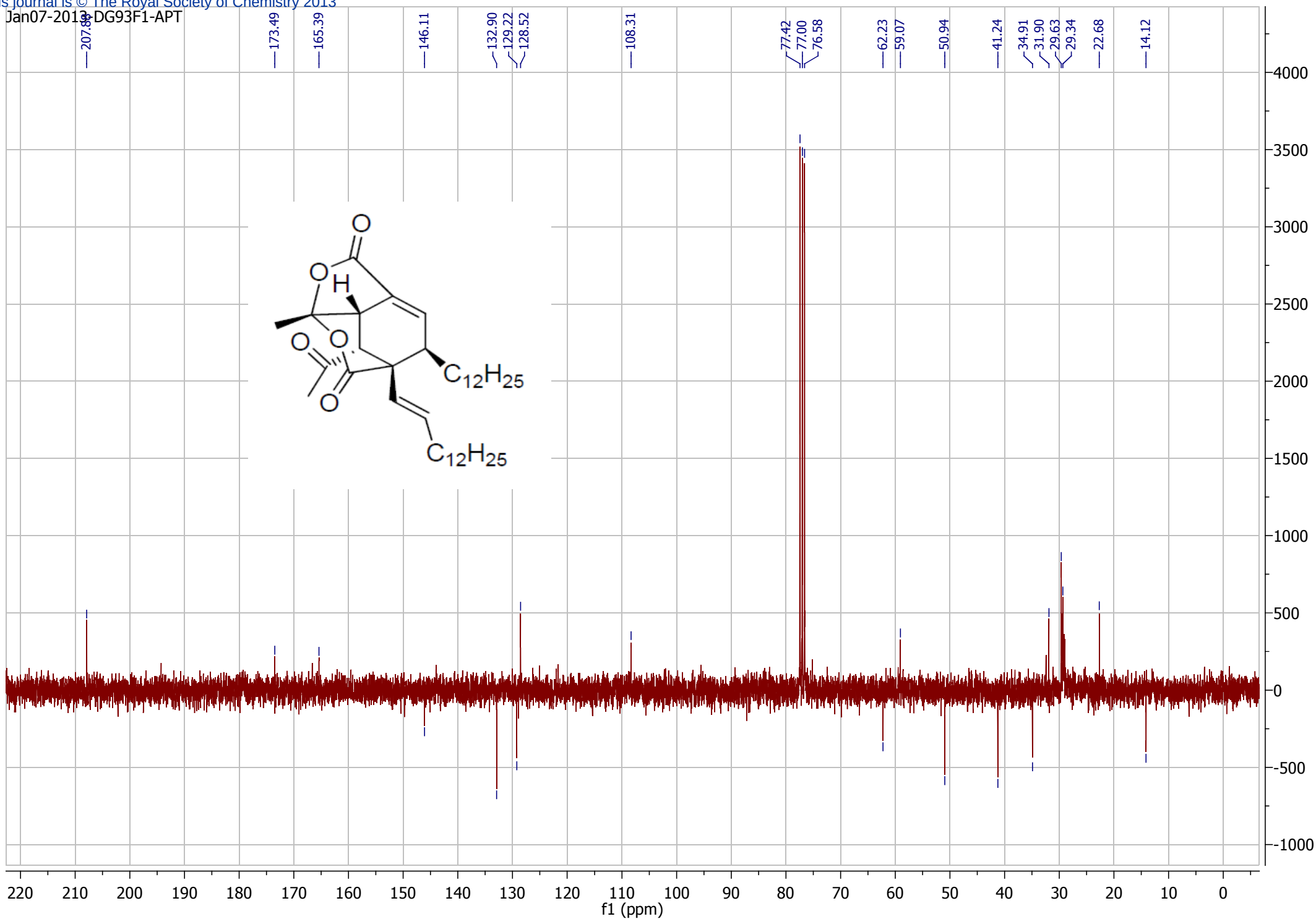


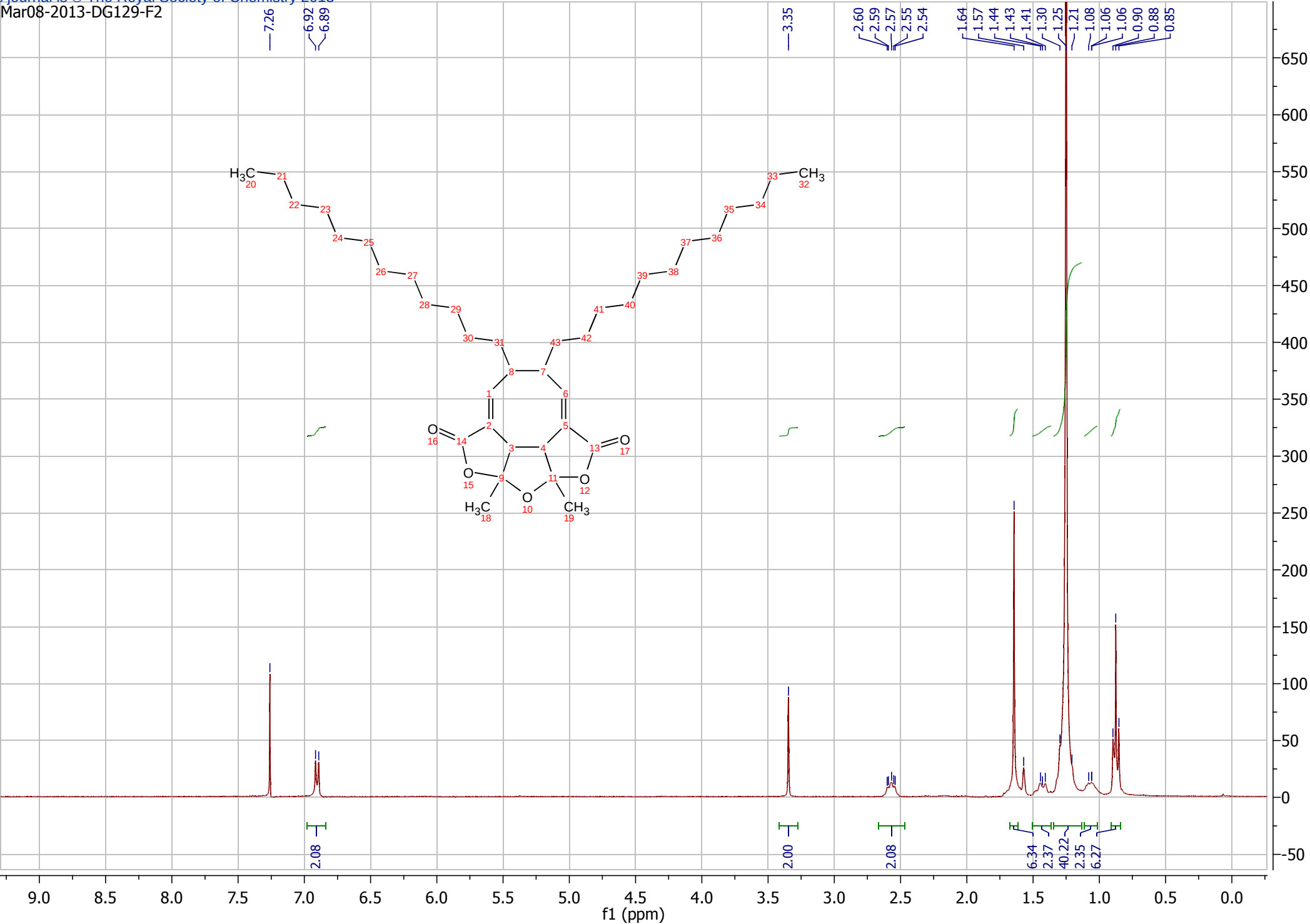


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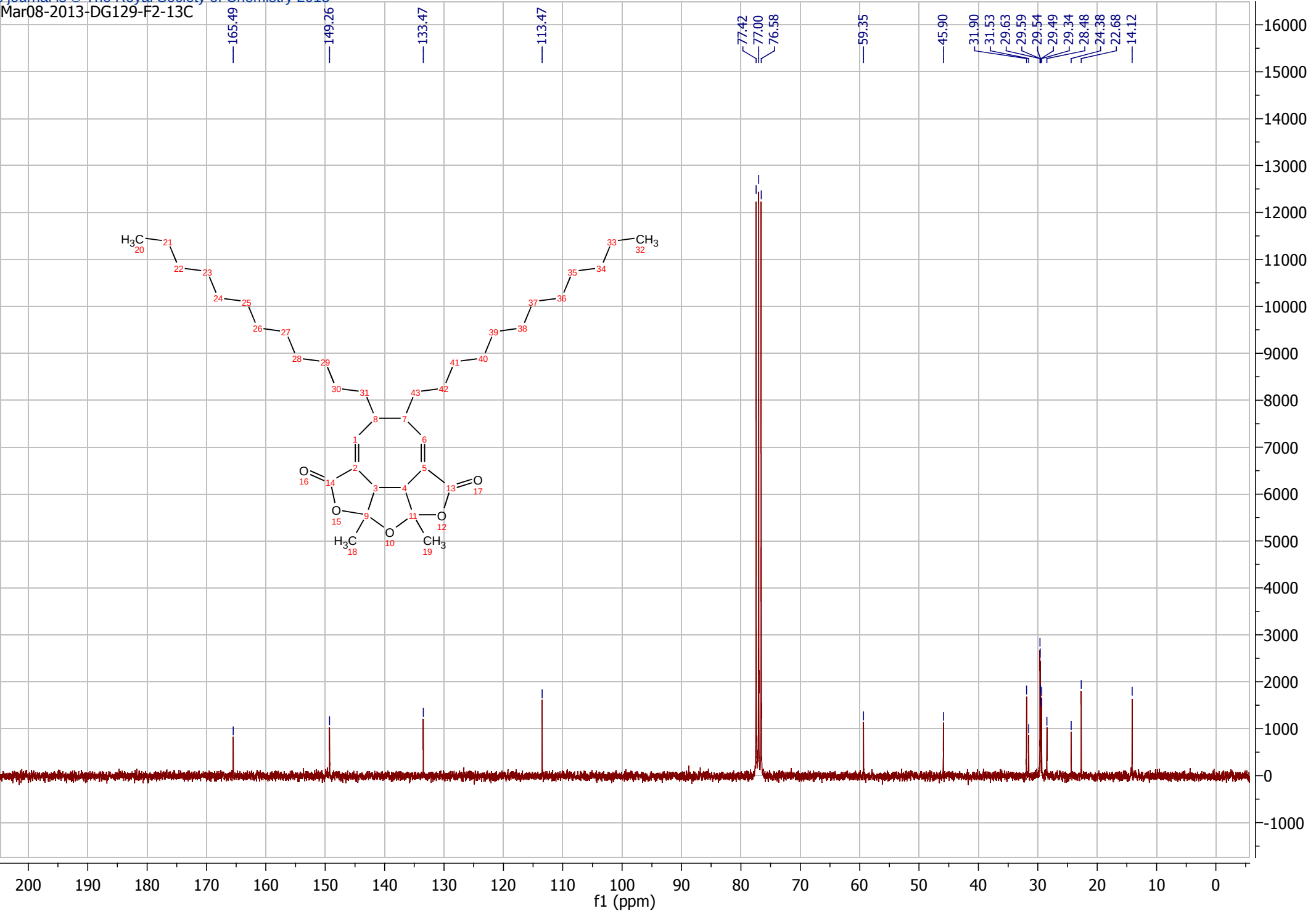




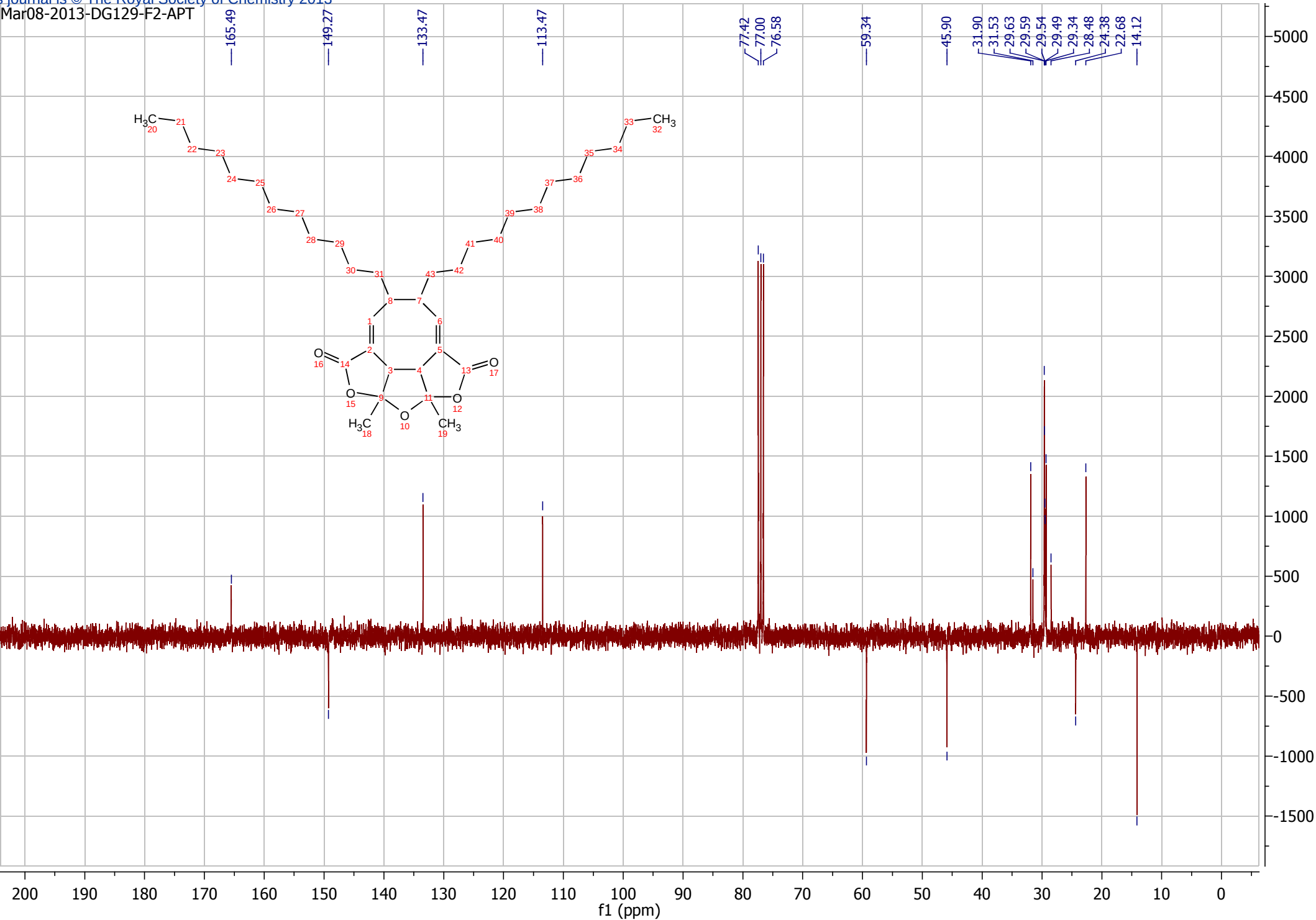


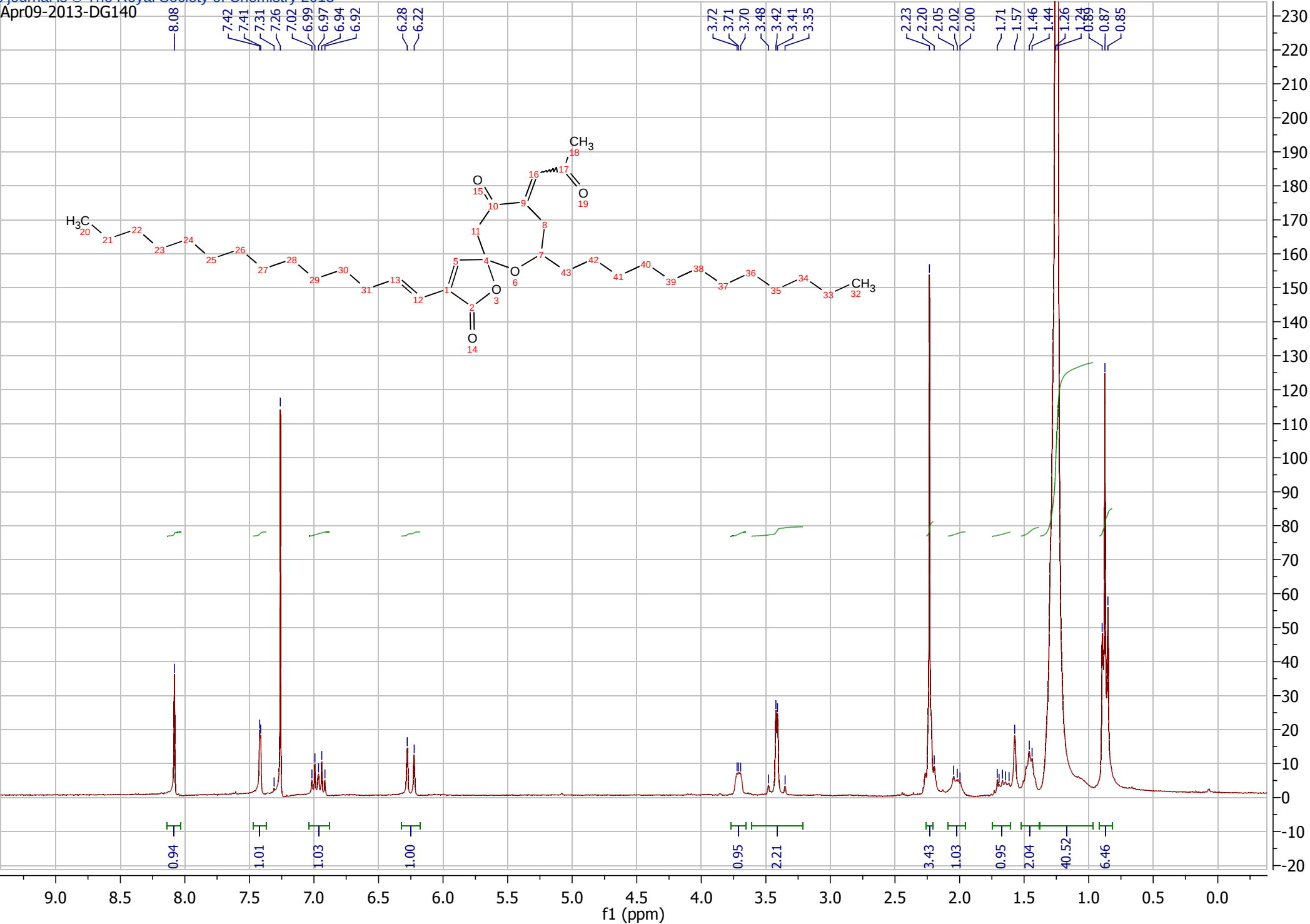


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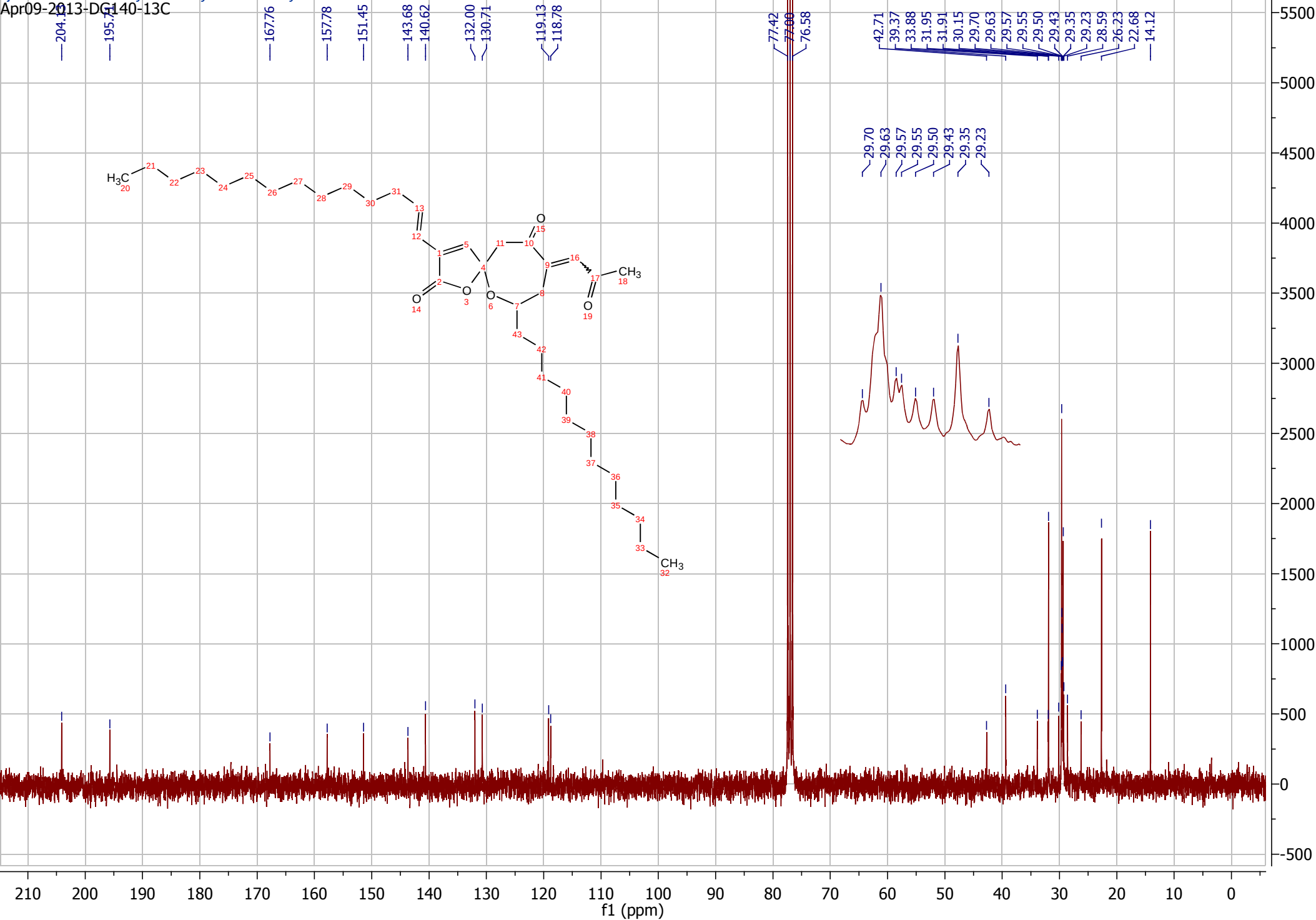


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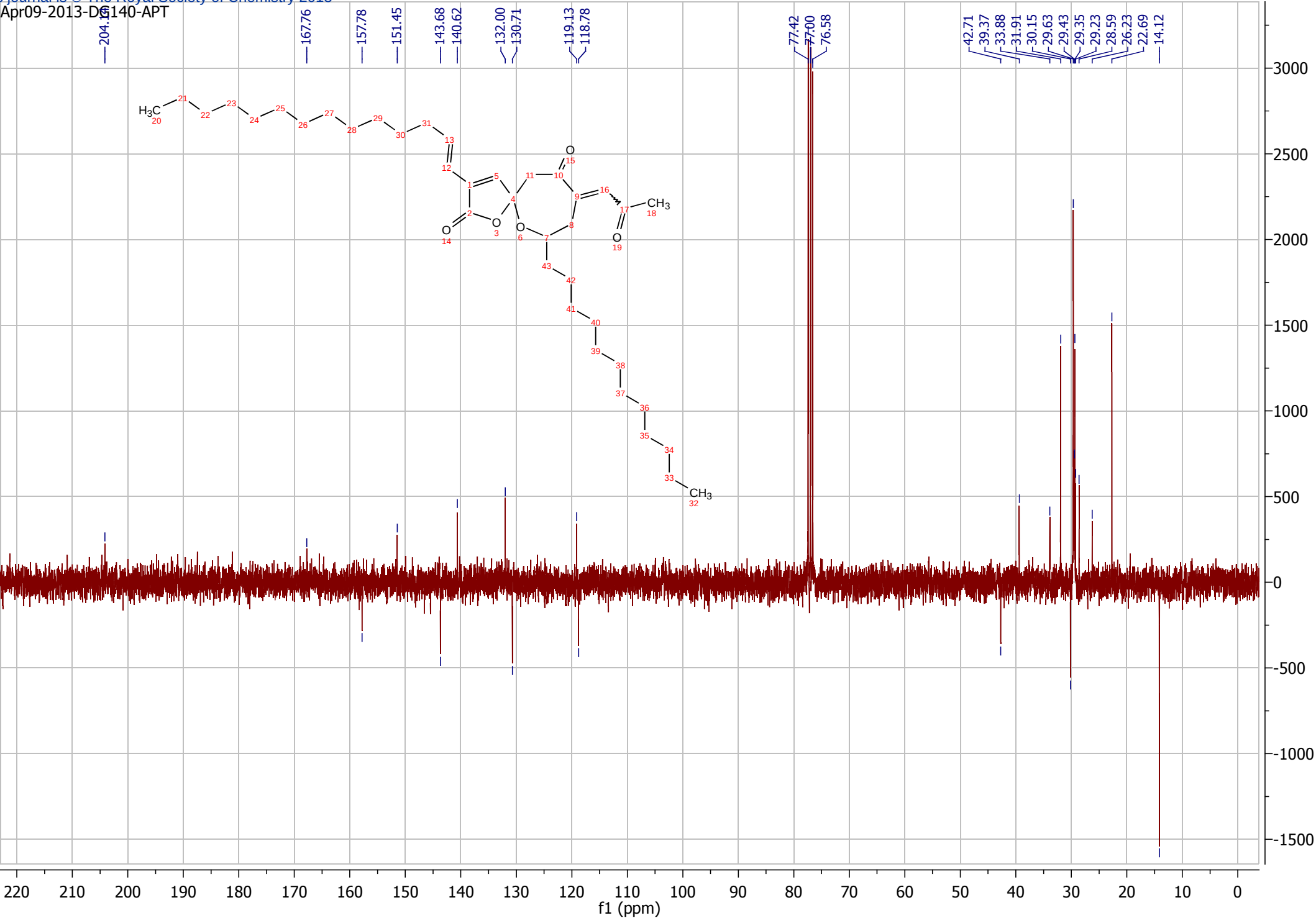




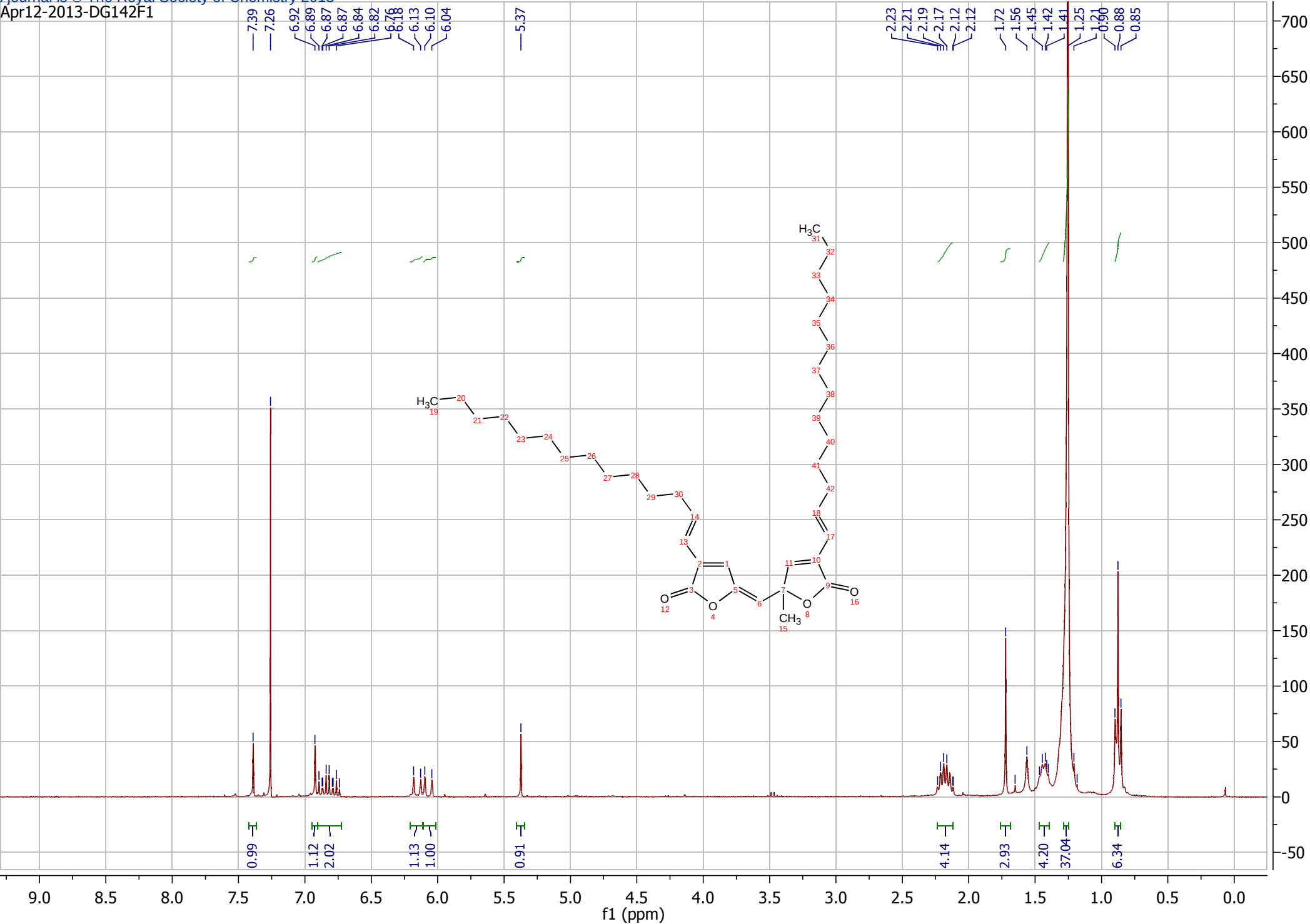
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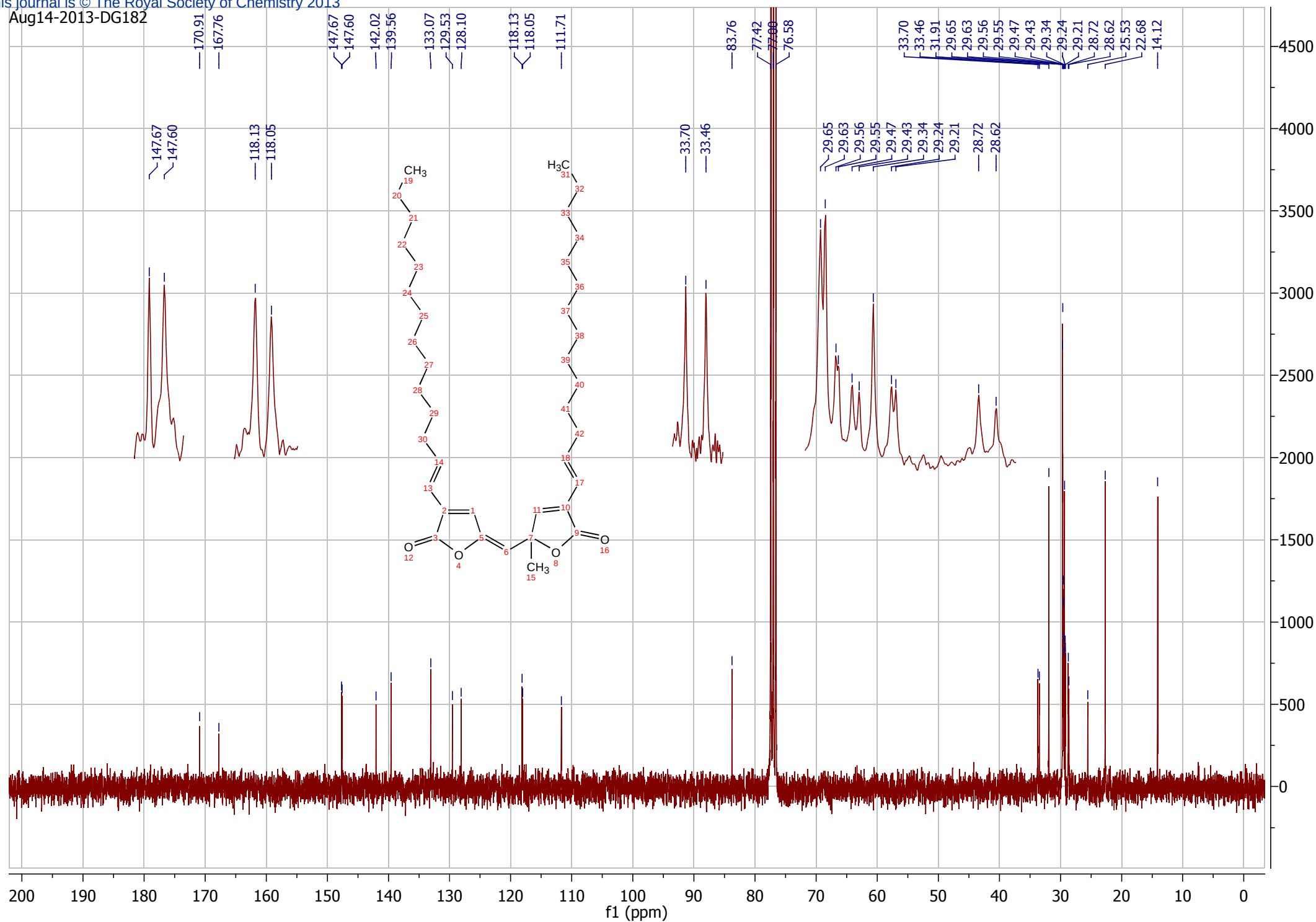
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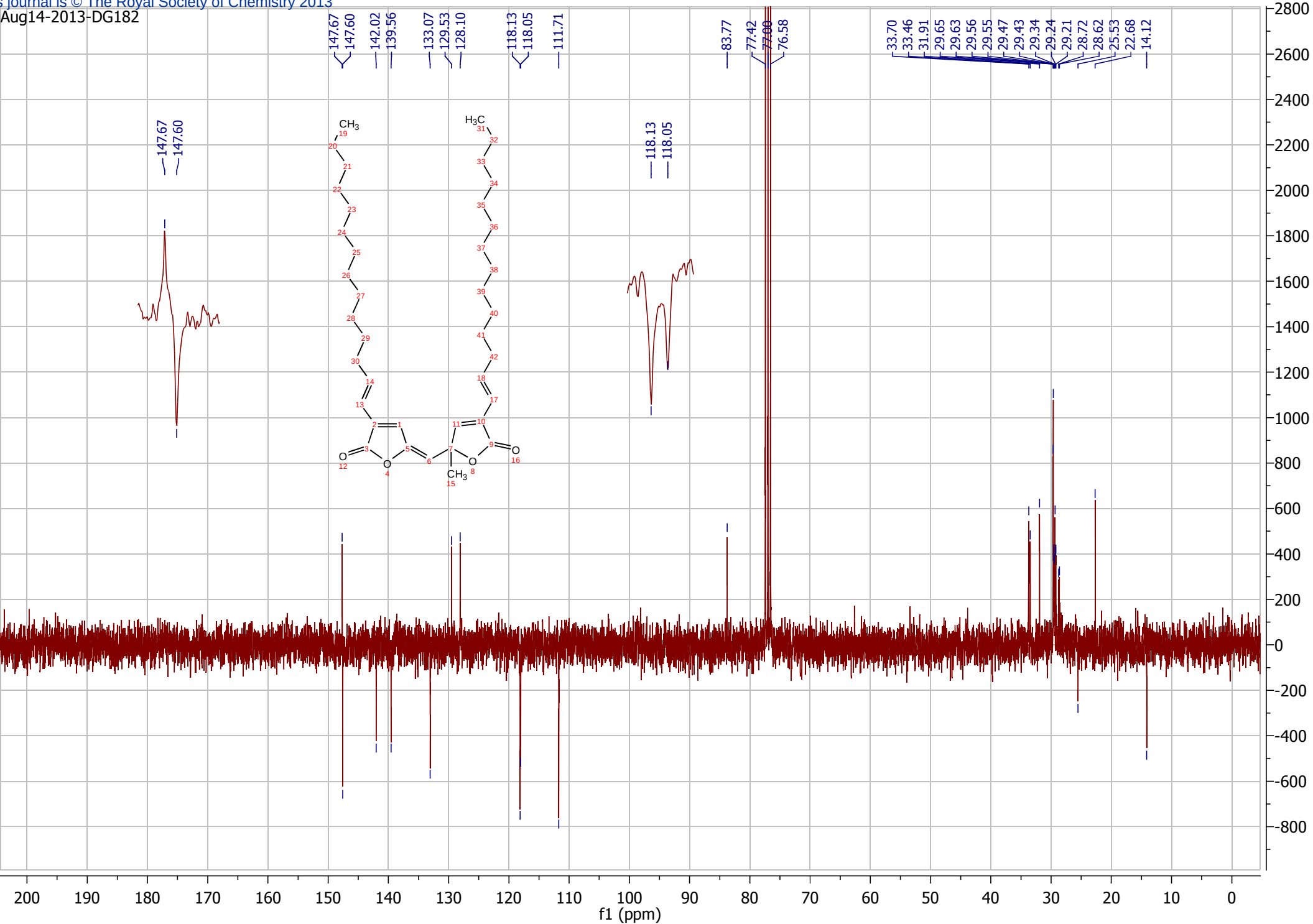
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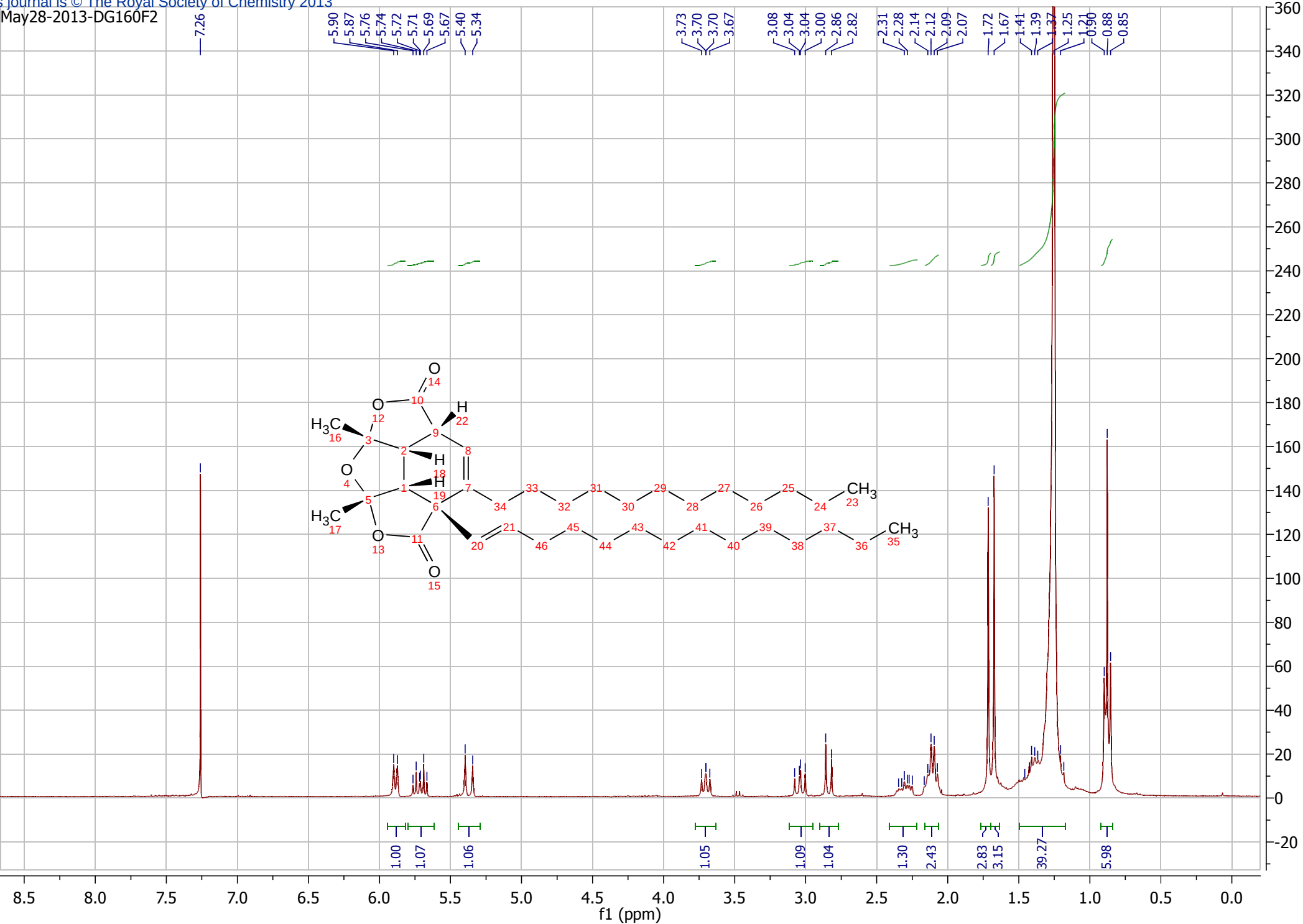
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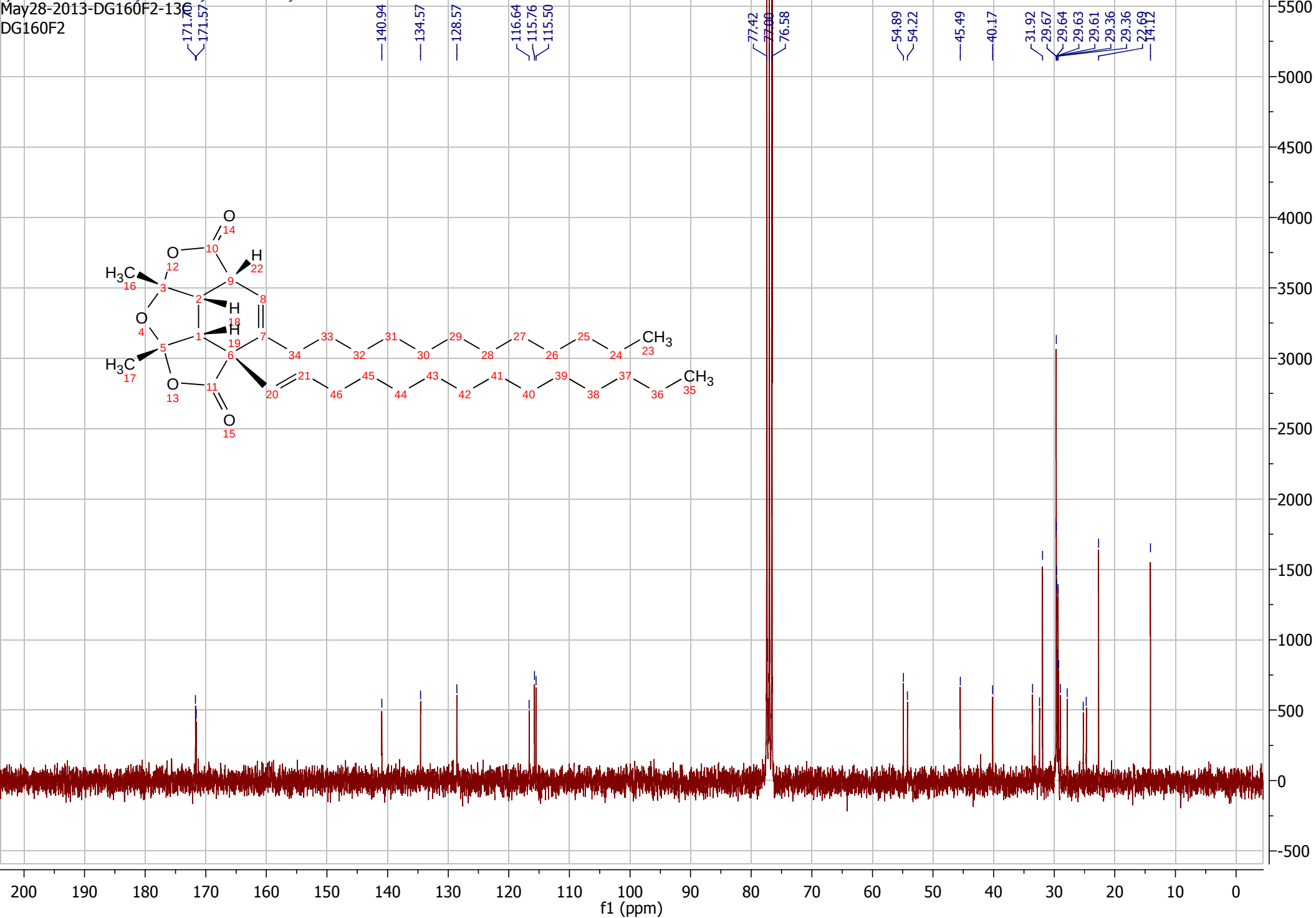
Aug14-2013-DG182



May28-2013-DG160F2



May28-2013-DG160F2-13C
DG160F2



May28-2013-DG160F2-APT
DG160F2

