Electronic Supplementary Information

A Laboratory-Scale Continuous Flow Chlorine Generator for Organic Synthesis

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Contents:

General remarks. ^{1}H-NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 mm) at 25 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.0 mL min^{-1}. The following gradient was applied: linear increase from solution 30% B to 100% B in 8 min, hold at 100% solution B for 2 min. GC/MS (FOCUS-GC/DSQ II MS, ThermoFisher) monitoring was based on electron impact ionization (70 eV) using a HP/5MS column (30 m×0.250 mm×0.025 μm). After 1 min at 50 °C the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium and the flow rate 1.0 mL min^{-1} in constant-flow mode. GC-FID analysis was performed on a standard GC instrument with a flame ionization detector, using an HP5 column (30 m, 0.250 mm, 0.025 mm). After 1 min at 50 °C the temperature was increased in 25 °C min–1 steps up to 300 °C and kept at 300 °C for 4 min. The detector gas for the flame ionization was H2 and compressed air (5.0 quality). Flash chromatography purifications were carried out on an automated flash chromatography system using cartridges packed with KP-SIL, 60 Å (32-63 μm particle size). All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. 1.5 M NaOCl solutions were prepared by diluting commercial NaOCl 12%Cl (purchased from Carl Roth GmbH) with distilled water. All prepared NaOCl solutions were titrated using the standard KI/$Na_2S_2O_4$ procedure to determine their exact concentration prior use.

Experimental procedure for the generation, extraction, and separation of clorine and its quantification by titration (cf. Table 1).

The flow setup (Figure S1) consisted of three separate feeds (Feed A, Feed B, and Feed C). The reagents were introduced in the flow reactor using peristaltic pumps from Vapourtec (E-series). Feed A consisted of a 1.5 M solution of sodium hypochlorite in water. Feed B consisted of 6 M HCl in water. Feed C consisted of the corresponding organic solvent. Solutions A and B were mixed using a PEEK cross-assembly (0.5 mm i.d.) before entering a PFA tubing (0.8 mm i.d., 100 μL) where the chlorine was rapidly generated (gas evolution could be visually observed). The combined streams A and B were mixed with C using a second PEEK cross-assembly (0.5 mm i.d.) before entering a residence time unit (PFA tubing, 0.8 mm i.d., 800 μL). The biphasic mixture then entered a liquid-liquid membrane separator (Zaiput, 1.0 μm pore-size membrane). The aqueous phase was collected in a flask containing a saturated $Na_2S_2O_4$ solution. When the system was stable the organic phase was collected, under

stirring, in a flask containing 1 g KI and 1 mL H_2SO_4 (conc) in 50 mL water. The water solution turned brown rapidly due to the formation of I_2. After 10 min (corresponding to a theoretical amount of 1.5 mmol of Cl_2) the resulting solution was titrated with a standard 0.2 M $Na_2S_2O_4$ solution using standard procedures.

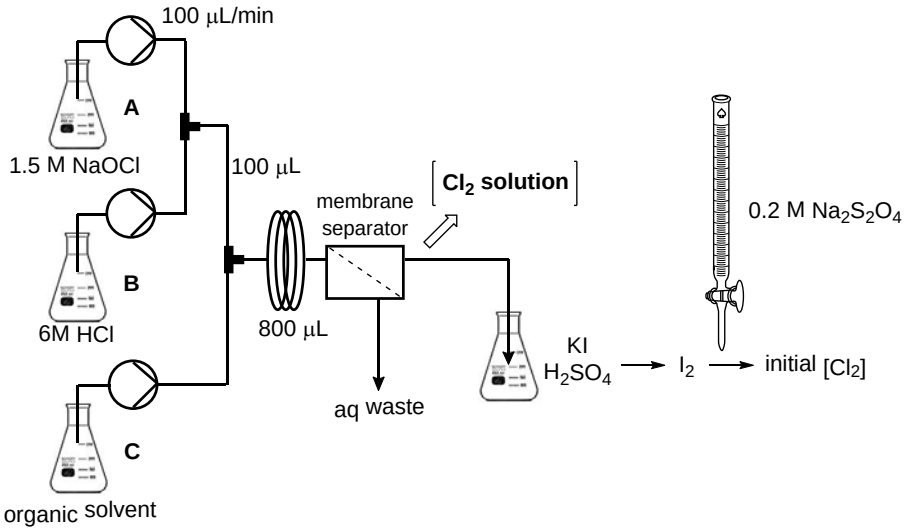
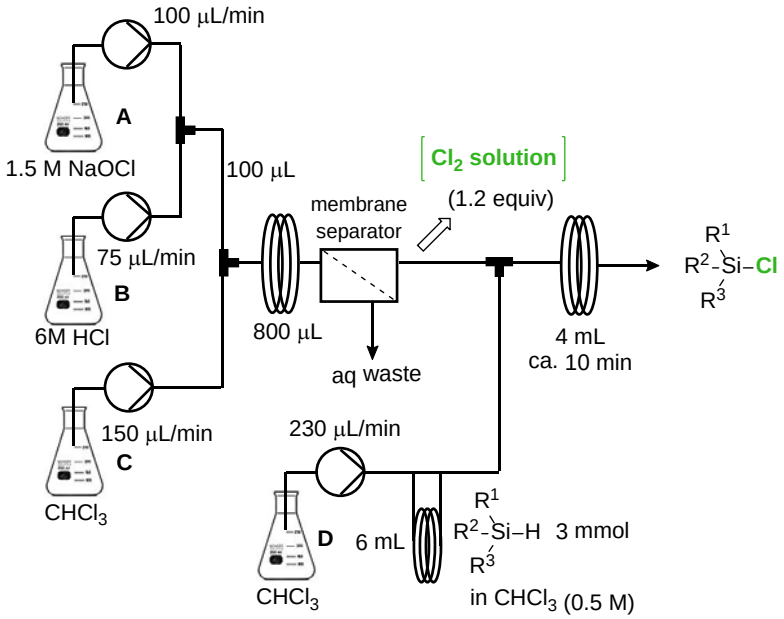


Figure S1. Continuous flow setup for the generation, extraction, and separation of clorine and determination of the process yield by titration using the KI/$Na_2S_2O_4$ system.

Continuous flow setup and general procedure for the preparation of chlorosilanes under continuous flow conditions



The same setup as for the generation, extraction, and separation of Cl_2 described above was used. The organic phase output of the liquid-liquid membrane separator was connected to Feed D using a Y-

mixer (0.5 i.d.), which consisted of 6 mL a 0.5 M solution of the corresponding silane in $CHCl_3$. Feed D was introduced using a sample loop when the system was stable. After a residence time of 10 min at rt, the reaction mixture was collected in a round-bottomed flask and immediately evaporated under reduced pressure, yielding the pure chlorosilanes.

Triisopropylsilylchloride (2a) (561 mg, 99,8%); ^{1}H NMR (300 MHz, CDCl3 δ 1.25 (m, 3H), 1.12 (d, *J* = 6.6 Hz, 18H); ^{13}C NMR (75 MHz, CDCl3) δ 17.7, 13.7.

Triphenylsilylchloride (2c) (880 mg, 96%); ^{1}H NMR (300 MHz, CDCl3) δ 7.69 (d, *J* = 6.4 Hz, 6H), 7.49 (dd, *J* = 14.3, 7.2 Hz, 9H); ^{13}C NMR (75 MHz, CDCl3) δ 135.2, 132.9, 130.8, 128.1.

Preliminary batch experiments for the selective oxidation of secondary alcohols using the chlorine-pyridine complex

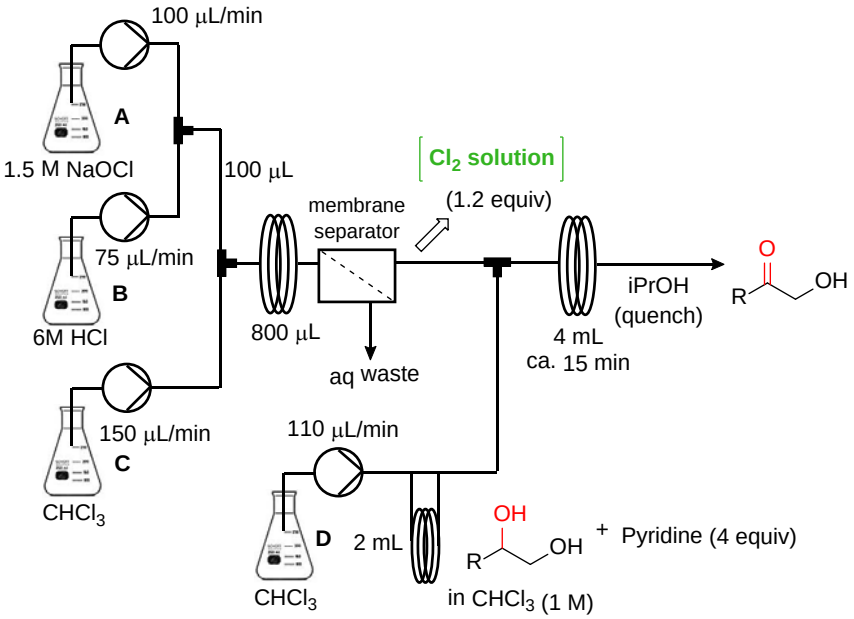
For the preliminary batch experiments the continuous flow setup for the generation/extraction/separation of chlorine as described above was used. The organic phase output from the liquid-liquid membrane separator was collected under stirring in a 10 mL vial containing 1,2-hexanediol (0.5 mmol) and pyridine in chloroform at room temperature.

Table S1. Preliminary batch experiments for the selective oxidation of secondary alcohols using the Cl_2-Py complex.[a]

Entry	Pyridine (equiv)	Substrate conc. (M)	Cl_2 (equiv)	Time (min)	Conv (%)[b]	Select (%)[b]
1	1	0.5	1.20	10	-	-
2	2	0.5	1.20	20	70	60
3	3	0.5	1.05	40	85	95
4	3	0.5	1.20	20	94	95
5	3	0.5	1.30	25	91	87
6	4	0.5	1.20	20	96	95
7	4	1	1.20	15	99	99

[a] Conditions: 10 mL vial with 0.5 mmol substrate and pyridine in $CHCl_3$, rt. [b] Determined by GC-FID.

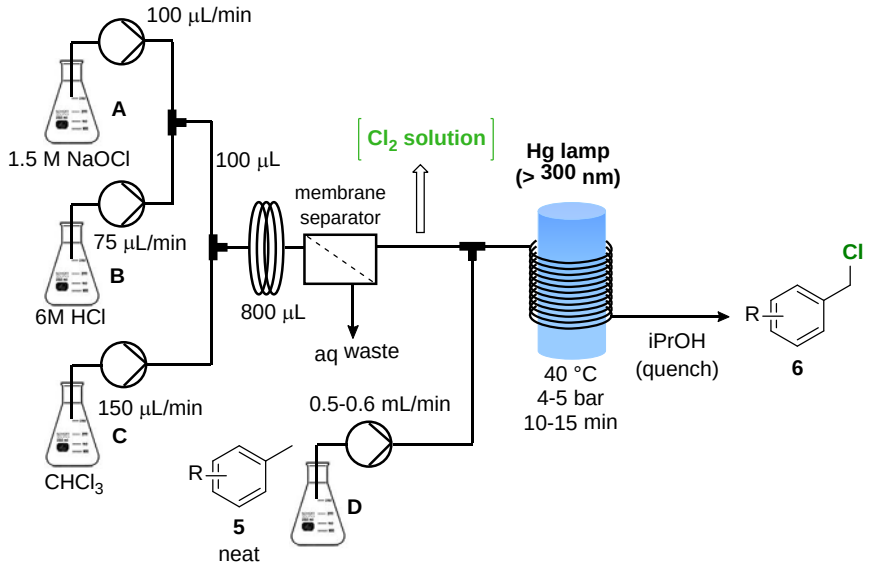
General procedure for the selective oxidation of secondary alcohols using the Cl_2-Py complex under continuous flow conditions



The same setup as for the generation, extraction, and separation of Cl_2 described above was used. The organic phase output of the liquid-liquid membrane separator was connected to Feed D using a Y-mixer (0.5 i.d.), which consisted of 2 mL of a 1.0 M solution of the diol in $CHCl_3$. Feed D was introduced using a sample loop when the system was stable. After a residence time of ca. 15 min at rt, the reaction mixture was collected in a round-bottomed flask containing an excess of iPrOH (quench). Then, the solvent was evaporated and the residue purified by column chromatography.

1-Hydroxyhexane-2-one (4a). (368 mg, 53%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (s, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.74 – 1.53 (m, 2H), 1.35 (m, *J* = 14.4, 7.3 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 68.0, 38.2, 25.8, 22.3, 13.7; MS (EI) m/z: 116 (8%), 85 (75%), 57 (100%).
2-Ethyl-1-hydroxyhexane-3-one (4b). (376 mg, 44%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 – 3.62 (m, 2H), 2.64 (ddd, *J* = 13.8, 7.1, 4.1 Hz, 1H), 2.48 (t, *J* = 7.3 Hz, 2H), 1.74 – 1.46 (m, 4H), 0.93 (td, *J* = 7.4, 2.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.2 (s), 62.4 (s), 54.9 (s), 44.8 (s), 21.3 (s), 16.8 (s), 13.7 (s), 11.8 (s); MS (EI) m/z: 144 (5%), 126 (2%), 101 (15%), 89 (100%), 71 (74%), 55 (88%).
2-Hydroxy-1-phenylethanone (4c). (400 mg, 48%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.87 (m, 2H), 7.72 – 7.59 (m, 1H), 7.59 – 7.47 (m, 2H), 4.90 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4 (s), 134.3 (s), 133. (s), 129,0 (s), 127.7 (s), 65.5 (s); MS (EI) m/z: 136 (4%), 105 (100%), 77 (58%).

General procedure for the continuous flow photochlorination of toluene derivatives

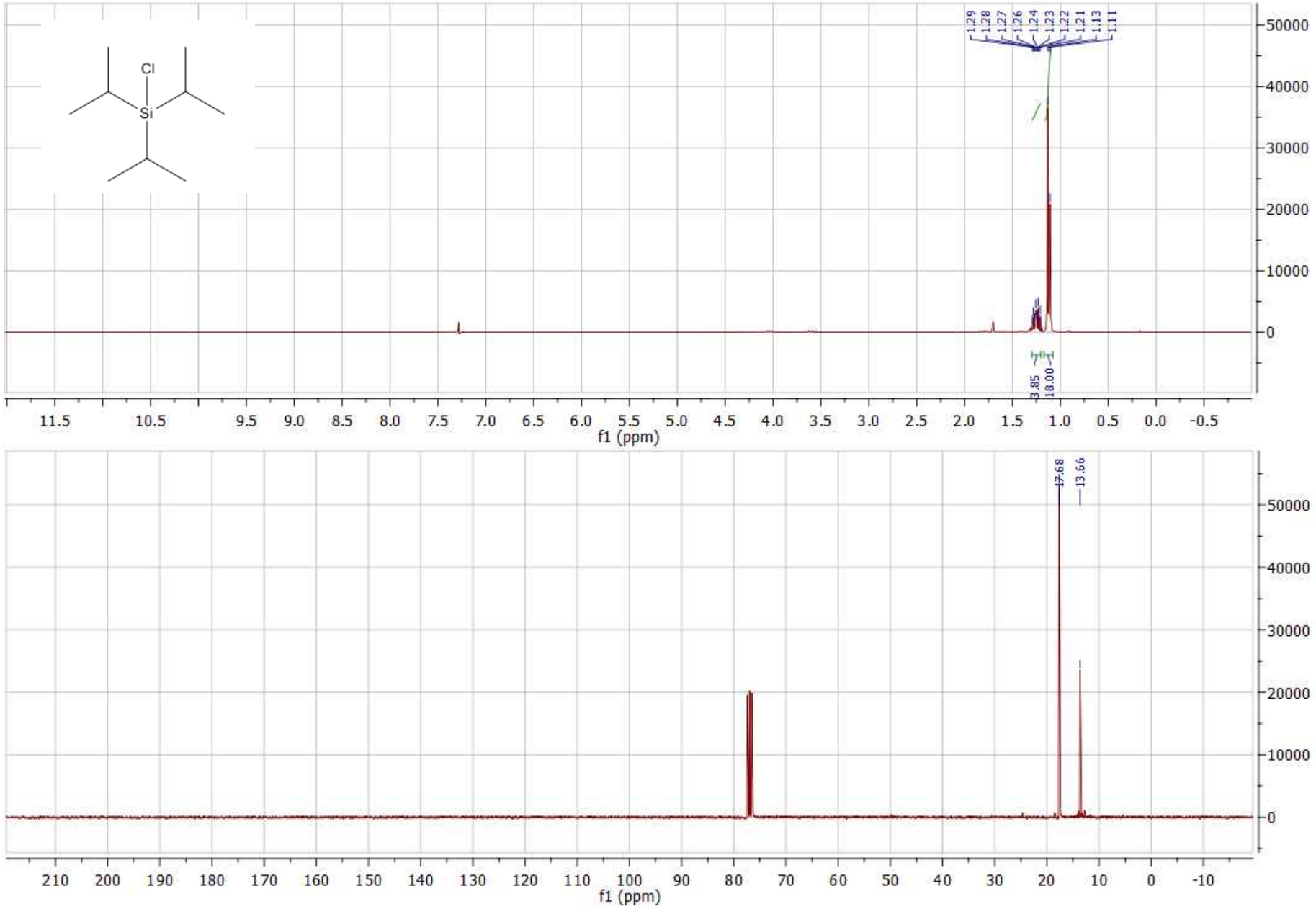


The same setup as for the generation, extraction, and separation of Cl_2 described above was used. The organic phase output of the liquid-liquid membrane separator was connected to Feed D using a Y-mixer (0.5 i.d.), which contained a stream of the neat toluene derivative. The reaction mixture entered the photoreactor (Vapourtec UV-150, Hg lamp at 50% power -75W-, 300 nm cutoff filter) for which temperature had been set at 40 °C. To avoid a possible expansion of the $CHCl_3$ at elevated temperatures, a backpressure regulator adjusted to 4-5 bar was placed at the reactor output. After a residence time of ca. 20 min, the reaction mixture was collected in a round-bottomed flask containing an excess of iPrOH (quench). The crude reaction mixture was analyzed by GC-MS and GC-FID using anisole as internal standard (added after quench).

Table S2. Optimization of the continuous flow photochlorination of toluene derivatives.

Entry	Substrate	Temp (°C)	Irrad. wavelength (nm)	Flow rate (µL/min)[a]	Time (min)	GC Yield (%)[b]	Selectivity (%)[b]
1	Toluene	40	No light	574	15	< 1	99
2	Toluene	40	365 nm	574	15	96	99
3	Toluene	40	> 300	574	15	99	99
4	Toluene	40	> 300	287	25	91	99
5	Toluene	60	> 300	574	15	94	99
6	3-Nitrotoluene	40	> 300	640	15	87	99
7	4-Methylanisol	40	> 300	681	15	99	81
8	o-Xylene	40	> 300	652	15	99	99

[a] The flow rates for the toluene derivatives were modified to keep the ratio toluene/Cl_2 constant to a value of ca. 50 and have comparable values for the selectivity (as the residence time variation was very small). [b] Determined by GC-FID.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1.28
1.27
1.26
1.24
1.23
1.22
1.21
1.13
1.11
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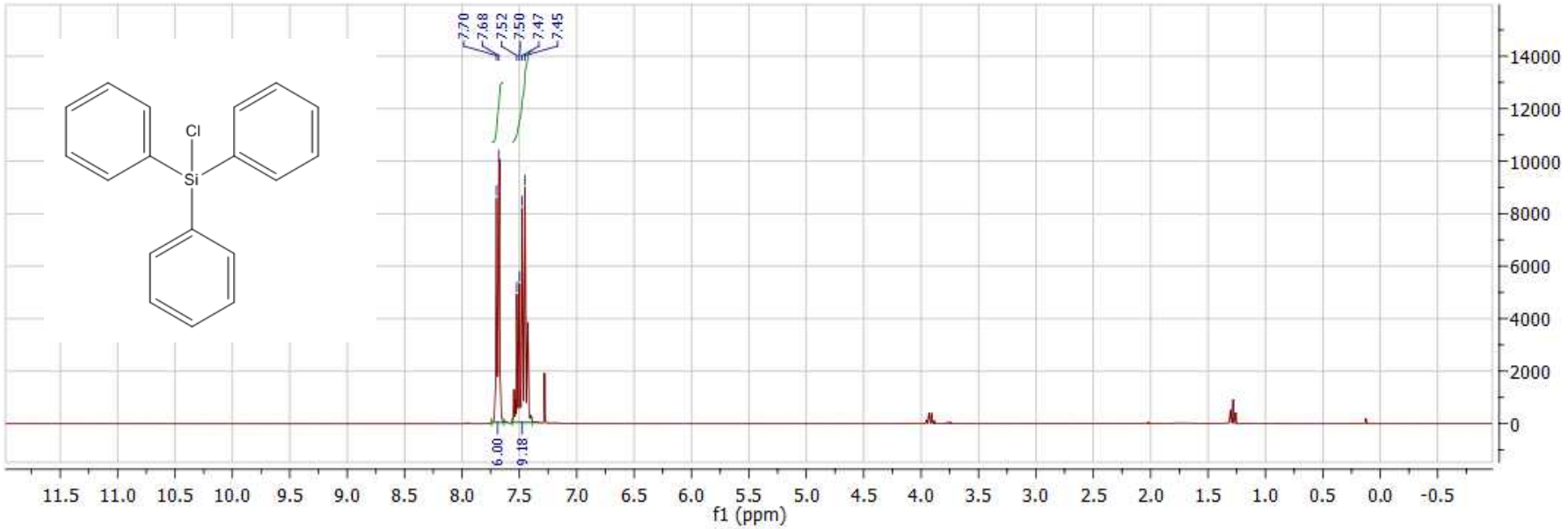
18.00
f1 (ppm)
17.68
13.66
f1 (ppm)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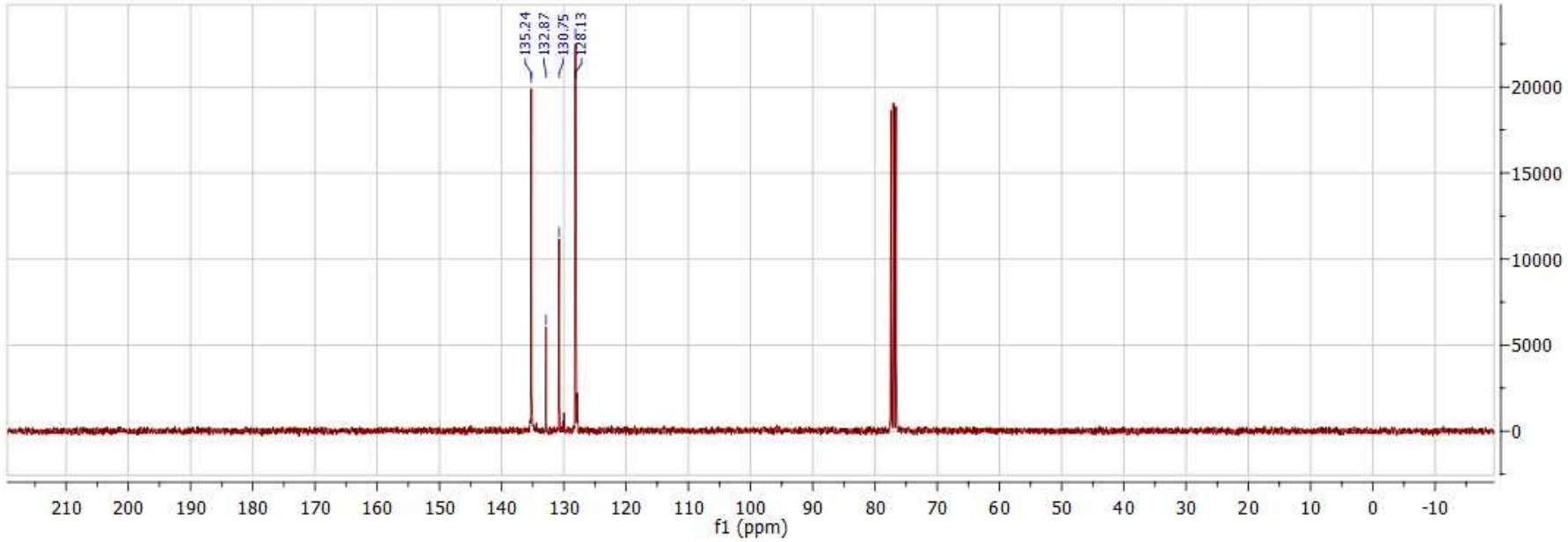
7.47
7.45
Cl
Si
6.00
9.18
f1 (ppm)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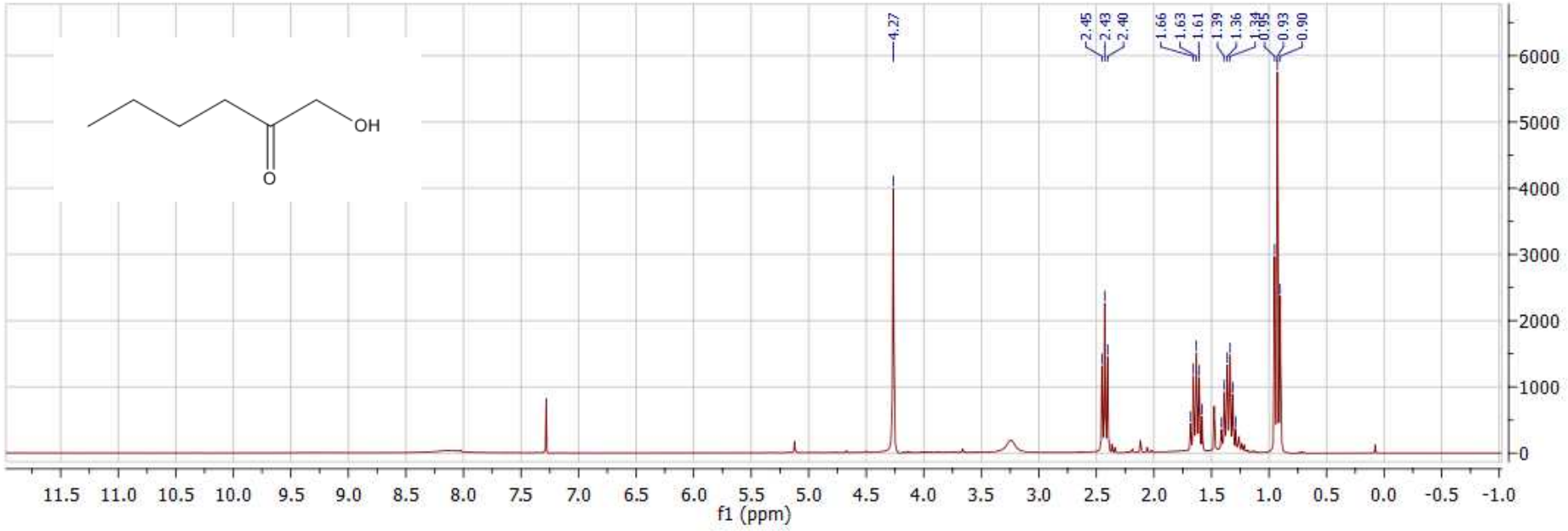
128.13
f1 (ppm)


OH
O
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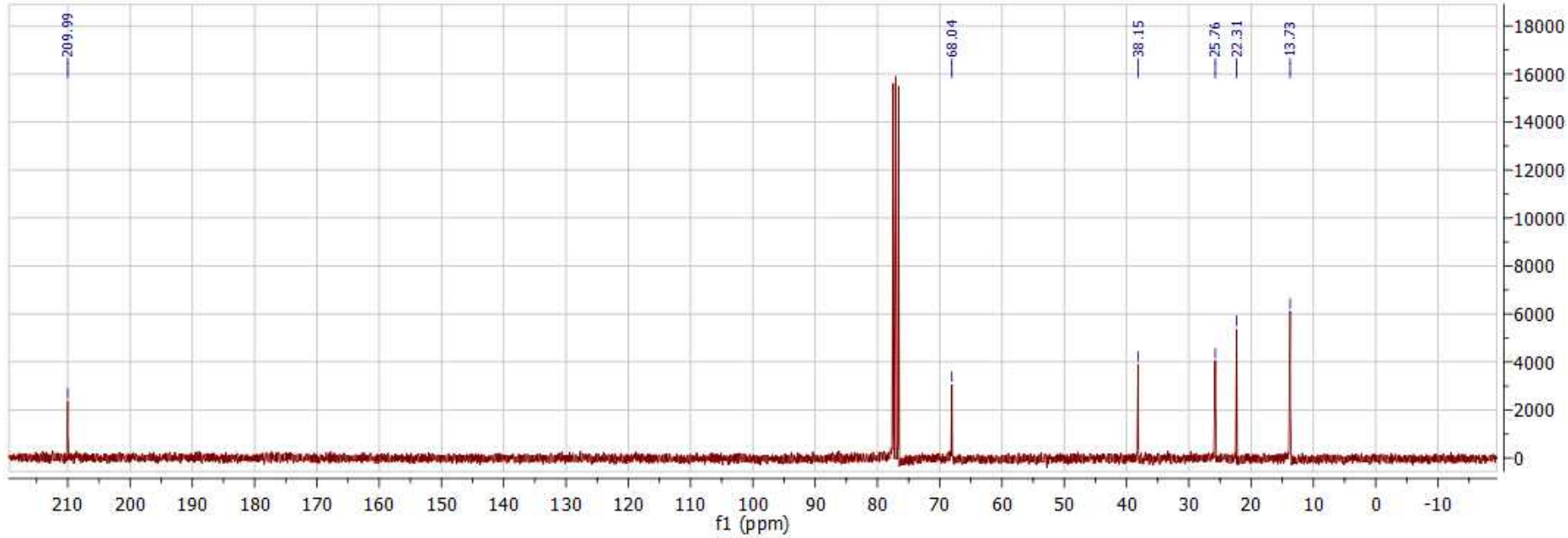
2.43
2.40
1.66
1.63
1.61
1.39
1.36
0.93
0.90
f1 (ppm)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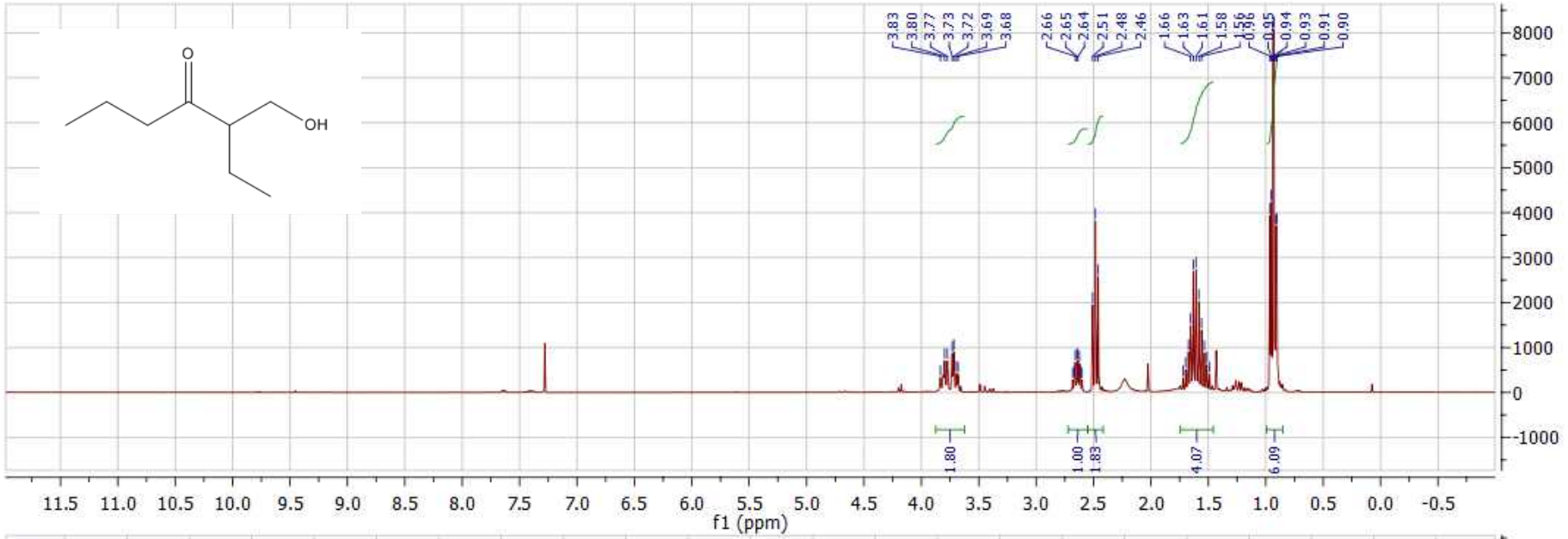
22.31
13.73
f1 (ppm)


O
OH
3.83
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3.72
3.69
3.68
2.66
2.65
2.64
2.51
2.48
2.46
1.66
1.63
1.61
1.58
1.56
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0.90
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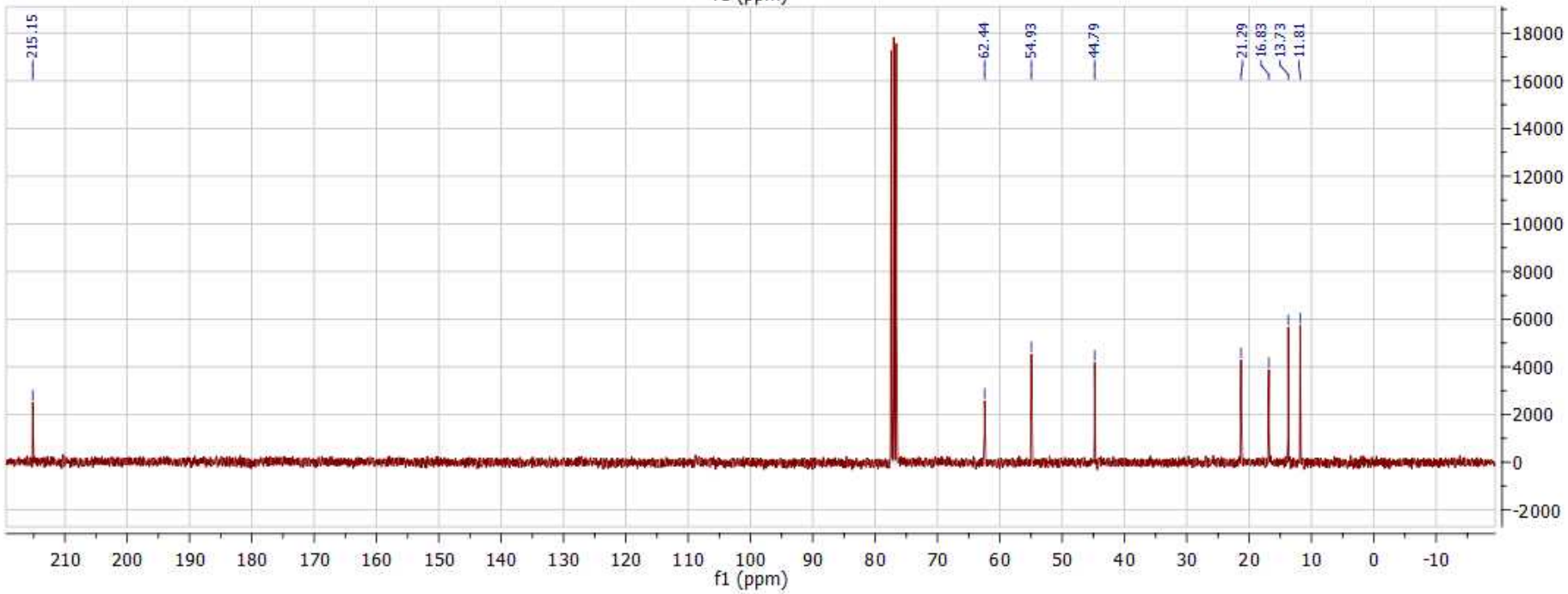
4.07
6.09
f1 (ppm)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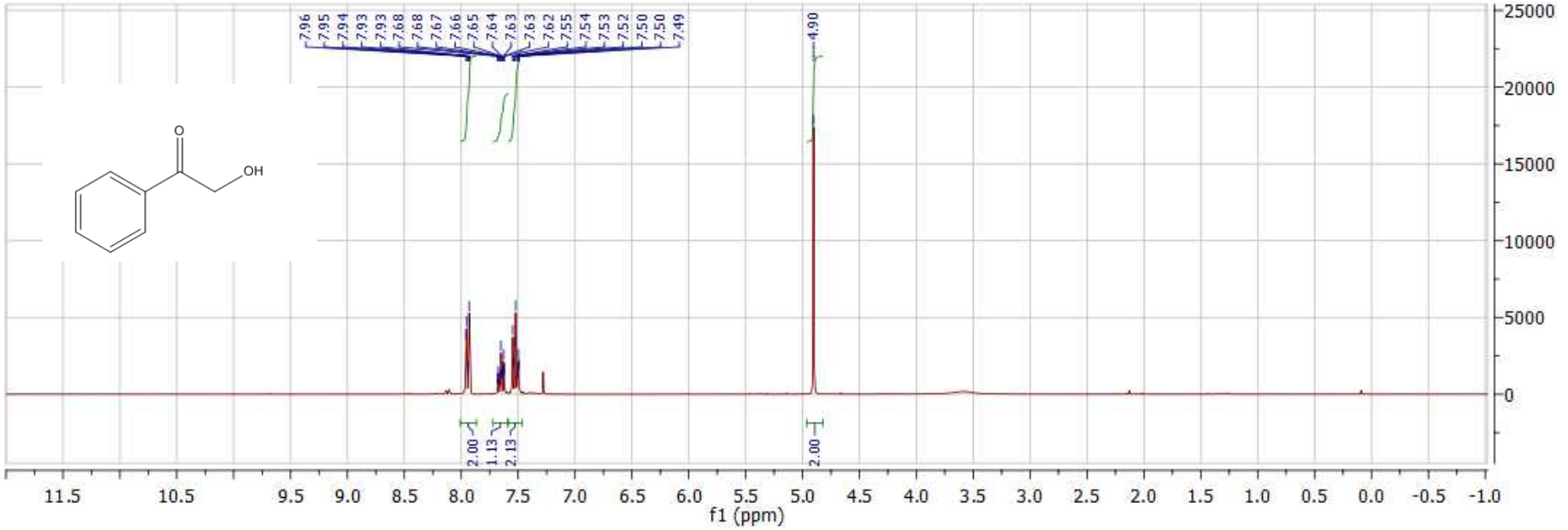
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7.50
7.50
7.49
4.90
O
OH
2.00
1.13
2.13
2.00
25000
20000
15000
10000
5000
0
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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2.5
2.0
1.5
1.0
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0.0
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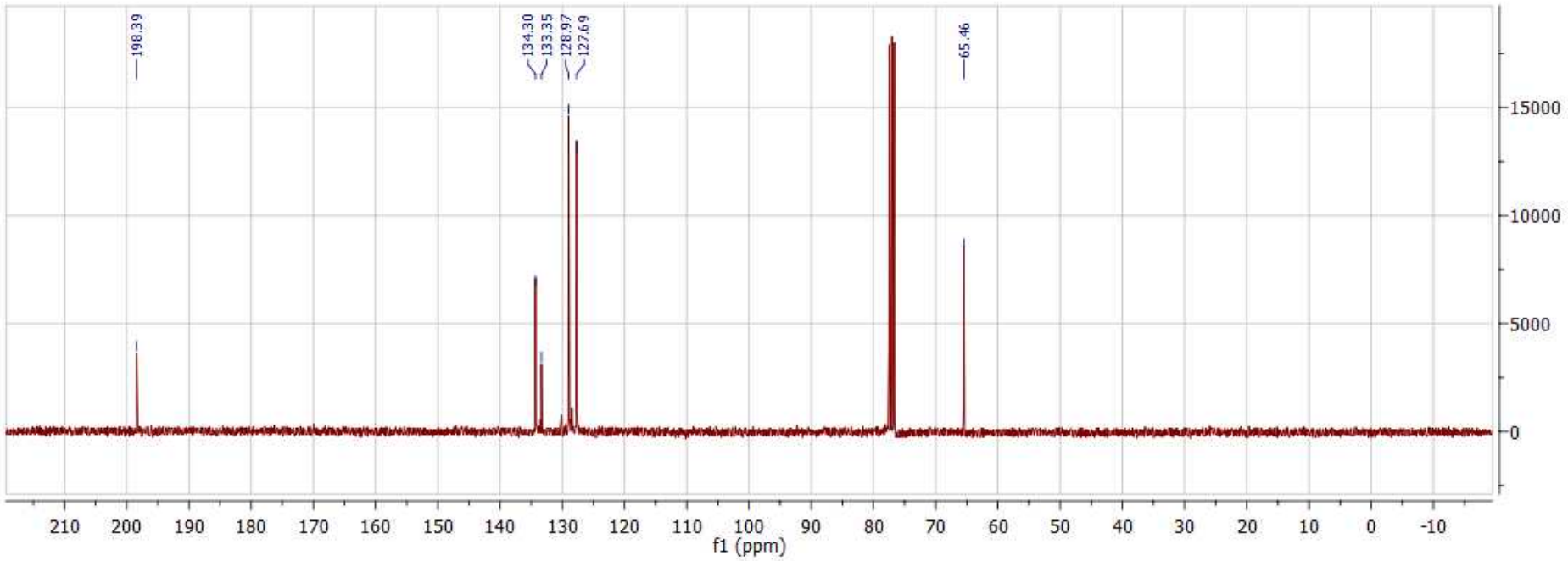
-1.0
f1 (ppm)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180
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150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)