Supporting Information

Synthesis of α-chloro-β-ketoesters via ytterbium(III) triflate-mediated decarboxylative Claisen-type condensation

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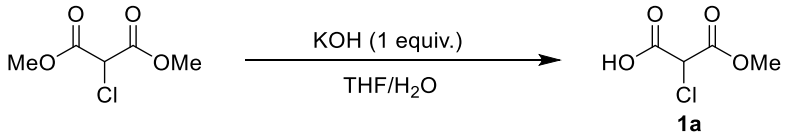
1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on a JEOL JNM-ECZ600R (600 MHz for ^{1}H, 151 MHz for $^{13}C\{^{1}H\}$ and 564 MHz for ^{19}F), and chemical shifts were referenced to internal tetramethylsilane (TMS, δ = 0.0 ppm) for ^{1}H and the central peak of $CDCl_3$ (δ = 77.0 ppm) or tetrahydrofuran-d_8 (δ = 25.3 ppm) for $^{13}C\{^{1}H\}$. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), m (multiplet). High-resolution MALDI-TOFMS measurements were performed on a JMS-S3000 Spiral-TOF mass spectrometer. The data were collected in a spiral positive mode with polyethylene glycol 200 or 400 as an internal mass calibrant, and sodium iodide as a cationization agent. Elemental analyses were performed on a Thermo Fisher Scientific Flash 2000 elemental analyzer. Flash column chromatography was performed using the Yamazen universal columns premium on silica gel (60 Å, particle size 0.025–0.040 mm).

2. Synthetic procedures and spectral data

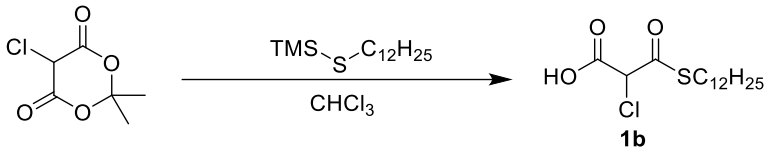
Preparation of Cl-MAHO 1a.



Prepared according to literature procedure with slight modifications.[1] To a cooled (0 °C) stirred solution of dimethyl chloromalonate (4.6 mL, 36.0 mmol) in THF/H_2O (1:10) was slowly added a 0.25 M aqueous potassium hydroxide (145 mL, 1 equiv.). After being stirred at 0 °C for 4 h, a 1 M aqueous Na_2CO_3 was added until the pH = 9. The aqueous layer was washed with diethyl ether, acidified with conc. HCl at 0 °C, and extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the Cl-MAHO **1a** (4.77 g, 87% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.25 (br s, 1H), 4.95 (s, 1H), 3.89 (s, 3H). The NMR spectra are consistent with the literature data.[1]

Preparation of *S*-dodecyl-Cl-MAHT (1b).

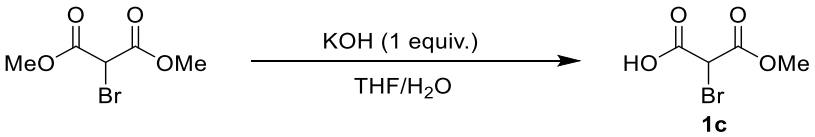


Prepared according to literature procedure with slight modifications.[2] To a mixture of chloro Meldrum's acid (2.43 g, 13.6 mmol, 1 equiv.) in chloroform was added (dodecylthio)trimethylsilane (4.47 g, 16.3 mmol, 1.2 equiv.) at room temperature. The reaction mixture was refluxed for 12 h. After cooling to room temperature, conc. HCl (2.3 mL, 27.2 mmol, 2 equiv.) in diethyl ether (45 mL) was added. After being further stirred for 2 h, the reaction mixture was concentrated with nitrogen flow, redissolved in DCM, dried over anhydrous Na_2SO4, filtered, and concentrated under

reduced pressure. The residue was purified by flash column chromatography to afford **1b** (2.72 g, 62% yield) as a white solid, mp 39–40 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90 (br s, 1H), 4.90 (s, 1H), 2.913 (t, *J* = 7.6 Hz, 2H), 1.56 (tt, *J* = 7.6, 7.6 Hz, 2H), 1.33–1.19 (m, 18H), 0.81 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.2, 168.9, 60.8, 31.9, 30.3, 29.6, 29.5, 29.4, 29.3, 29.0, 28.8, 28.7, 22.7, 14.1; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{15}H_{27}O_3ClNaS$ $[M+Na]^+$ *m/z* 345.1262, found 345.1257.

Preparation of Br-MAHO 1c.



Prepared according to literature procedure with slight modifications.[1] To a cooled (0 °C) stirred solution of dimethyl bromomalonate (2.6 mL, 20.0 mmol, 1 equiv.) in THF/H_2O (1:10) was slowly added a 0.25 M aqueous potassium hydroxide (80 mL, 1 equiv.). After being stirred at 0 °C for 4 h, a 1 M aqueous Na_2CO_3 was added until the pH = 9. The aqueous layer was washed with diethyl ether, acidified with conc. HCl at 0 °C, and extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the Br-MAHO **1c** (3.60 g, 91% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.69 (brs, 1H), 4.91 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 164.9, 54.3, 40.9; Anal. calcd for $C_4H_5O_4Br$: C 24.39, H 2.56; found: C 24.40, H 2.44.

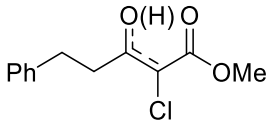
General procedure A for the decarboxylative condensation of acyl chlorides with 1a.

A solution of **1a** (2 equiv.), $Yb(OTf)_3$ (2 equiv.), and DIPEA (2 equiv.) in DME (0.15 M) was stirred at room temperature for 10 min. Then, another DIPEA (1 equiv.) and acyl chloride (1 equiv.) were added sequentially at 0 °C. After being stirred at room temperature for 2 h, the mixture was quenched with 10 wt% aqueous citric acid, and extracted with chloroform. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford target α-chloro-β-ketoester.

General procedure B for the decarboxylative condensation of acyl chlorides with 1a.

To a cooled (0 °C) solution of carboxylic acid (1 equiv.) and DMF (0.1 equiv.) in anhydrous DCM (0.1 M) was added oxalyl chloride (3 equiv.). After being stirred at room temperature for 3 h, the mixture was concentrated under reduced pressure to afford the crude acyl chloride **2**, which was used in next step without further purification.

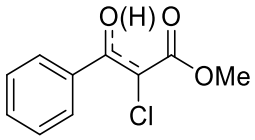
A solution of **1a** (2 equiv.), $Yb(OTf)_3$ (2 equiv.), and DIPEA (2 equiv.) in DME (0.15 M) was stirred at room temperature for 10 min. Then, another DIPEA (1 equiv.) and crude acyl chloride **2** (1 equiv.) were added sequentially at 0 °C. After being stirred at room temperature for 2 h, the mixture was quenched with 10 wt% aqueous citric acid, and extracted with chloroform. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford target α-chloro-β-ketoester.



Methyl 2-chloro-3-oxo-5-phenylpentanoate (3a).

3a was synthesized following the General procedure A. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 5:95). The reaction of 3-phenylpropanoyl chloride (148 μL, 1.00 mmol) afforded **3a** (207 mg, 86% yield, keto/enol ratio = 87:13) as a colorless oil.

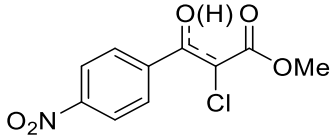
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.35 (s, 1H × 0.13), 7.31–7.18 (m, 5H), 4.78 (s, 1H × 0.87), 3.85 (s, 3H × 0.13), 3.77 (s, 3H × 0.87), 3.09–3.00 (m, 2H × 0.13), 3.04 (t, J = 7.2 Hz, 2H × 0.87), 2.95 (t, J = 7.2 Hz, 2H × 0.87), 2.83 (dd, J = 10.2, 7.2 Hz, 2H × 0.13); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 198.0, 165.4, 140.0, 128.6, 128.3, 126.4, 60.8, 53.7, 40.6, 29.5; (enol) δ 174.5, 169.8, 140.3, 128.5, 128.3, 126.3, 96.7, 52.8, 34.8, 31.7; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{12}H_{13}O_3ClNa$ $[M+Na]^+$ *m/z* 263.0445, found 263.0454.



Methyl 2-chloro-3-oxo-3-phenylpropanoate (3b).

3b was synthesized following the General procedure A. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of benzoyl chloride (11.5 μL, 0.100 mmol) afforded **3b** (20.1 mg, 95% yield, keto/enol ratio = 95:5) as a colorless oil.

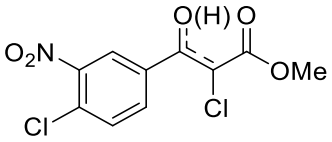
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.78 (s, 1H × 0.05), 8.00 (d, J = 7.4 Hz, 2H × 0.95), 7.77–7.76 (m, 2H × 0.05), 7.64 (t, J = 7.4 Hz, 1H × 0.95), 7.52 (t, J = 7.4 Hz, 2H × 0.95), 7.47–7.42 (m, 3H × 0.05), 5.65 (s, 1H × 0.95), 3.93 (s, 3H × 0.05), 3.84 (s, 3H × 0.95); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 188.1, 165.7, 134.4, 133.2, 129.3, 128.9, 57.6, 53.8; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{10}H_9O_3ClNa$ $[M+Na]^+$ *m/z* 235.0132, found 235.0132.



Methyl 2-chloro-3-(4-nitrophenyl)-3-oxopropanoate (3c).

3c was synthesized following the General procedure B. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of 4-nitrobenzoic acid (16.7 mg, 0.100 mmol) afforded **3c** (22.3 mg, 87% yield, keto/enol ratio = 86:14) as a white solid, mp 110–112 °C.

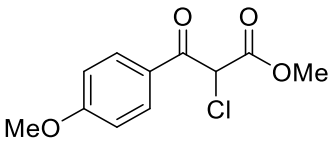
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.76 (s, 1H × 0.14), 8.36 (d, J = 9.0 Hz, 2H × 0.86), 8.30 (d, J = 9.0 Hz, 2H × 0.14), 8.18 (d, J = 9.0 Hz, 2H × 0.86), 7.95 (d, J = 9.0 Hz, 2H × 0.14), 5.61 (s, 1H × 0.86), 3.96 (s, 3H × 0.14), 3.87 (s, 3H × 0.86); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 186.9, 165.1, 150.8, 137.6, 130.4, 124.0, 57.9, 54.1; (enol) δ 170.2, 166.6, 148.7, 139.1, 130.1, 123.2, 98.1, 53.5; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{10}H_8NO_5ClNa$ $[M+Na]^+$ *m/z* 279.9983, found 279.9986.



Methyl 2-chloro-3-(4-chloro-3-nitrophenyl)-3-oxopropanoate (3d).

3d was synthesized following the General procedure B. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of 4-chloro-3-nitrobenzoic acid (20.1 mg, 0.100 mmol) afforded **3d** (26.5 mg, 91% yield, keto/enol ratio = 88:12) as a white solid, mp 44–45 °C.

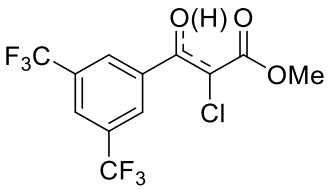
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.72 (s, 1H × 0.12), 8.43 (d, *J* = 2.5 Hz, 1H × 0.88), 8.28 (d, *J* = 2.5 Hz, 1H × 0.12), 8.07 (dd, *J* = 8.3, 2.5 Hz, 1H × 0.88), 7.91 (dd, *J* = 8.3, 2.5 Hz, 1H × 0.12), 7.66 (d, *J* = 8.3 Hz, 1H × 0.88), 7.57 (d, *J* = 8.3 Hz, 1H × 0.12), 5.49 (s, 1H × 0.88), 3.88 (s, 3H × 0.12), 3.80 (s, 3H × 0.88); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 185.5, 164.9, 148.2, 133.2, 133.0, 132.7, 132.4, 126.3, 57.6, 54.2; (enol) δ 170.2, 164.9, 134.0, 133.4, 132.9, 131.6, 129.3, 127.1, 98.1, 53.5; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{10}H_7NO_5Cl_2Na$ $[M+Na]^+$ *m/z* 313.9594, found 313.9575.



Methyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropanoate (3e).

3e was synthesized following the General procedure A. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of 4-methoxybenzoyl chloride (17.1 mg, 0.100 mmol) afforded **3e** (19.3 mg, 80% yield) as a colorless oil.

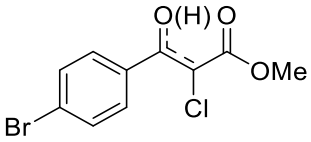
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 5.61 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.6, 166.0, 164.5, 131.8, 126.0, 114.2, 57.6, 55.6, 53.7; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{11}H_{11}O_4ClNa$ $[M+Na]^+$ *m/z* 265.0238, found 265.0239.



Methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2-chloro-3-oxopropanoate (3f).

3f was synthesized following the General procedure B. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of 3,5-bis(trifluoromethyl)benzoic acid (25.8 mg, 0.100 mmol) afforded **3f** (31.3 mg, 90% yield, keto/enol ratio = 89:11) as a colorless oil.

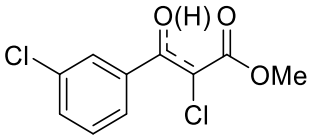
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.81 (s, 1H × 0.11), 8.44 (s, 2H × 0.89), 8.25 (s, 2H × 0.11), 8.14 (s, 1H × 0.89), 7.97 (s, 1H × 0.11), 5.61 (s, 1H × 0.89), 3.97 (s, 3H × 0.11), 3.89 (s, 3H × 0.89); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 185.9, 164.9, 134.7, (133.1, 132.9, 132.7, 132.4) (q, *J* = 34.7 Hz), 129.3, 127.5, (125.3, 123.5, 121.7, 119.9) (q, *J* = 273 Hz), 57.5, 54.2; ^{19}F NMR (564 MHz, $CDCl_3$) (keto) δ −62.95. (enol) δ −62.87; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{12}H_7O_3F_6ClNa$ $[M+Na]^+$ *m/z* 370.9880, found 370.9866.



Methyl 3-(4-bromophenyl)-2-chloro-3-oxopropanoate (3g).

3g was synthesized following the General procedure A. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of 4-bromobenzoyl chloride (22.0 mg, 0.100 mmol) afforded **3g** (27.0 mg, 93% yield, keto/enol ratio = 98:2) as a white solid, mp 37–38 °C.

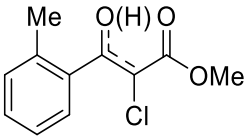
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.77 (s, 1H × 0.02), 7.87 (d, J = 8.8 Hz, 2H × 0.98), 7.87 (overlapped, 2H × 0.02), 7.66 (d, J = 8.8 Hz, 2H × 0.98), 7.58 (d, J = 8.1 Hz, 2H × 0.02), 5.58 (s, 1H × 0.98), 3.93 (s, 3H × 0.02), 3.84 (s, 3H × 0.98); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 187.2, 165.5, 132.3, 131.9, 130.7, 129.9, 57.7, 53.9; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{10}H_8O_3ClBrNa$ $[M+Na]^+$ *m/z* 312.9238, found 312.9252.



Methyl 2-chloro-3-(3-chlorophenyl)-3-oxopropanoate (3h).

3h was synthesized following the General procedure B. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of 3-chlorobenzoic acid (15.6 mg, 0.100 mmol) afforded **3h** (21.2 mg, 86% yield, keto/enol ratio = 96:4) as a colorless oil.

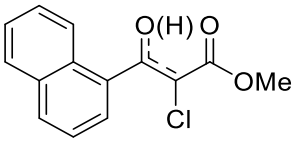
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.75 (s, 1H × 0.04), 7.98 (dd, J = 2.2, 1.5 Hz, 1H × 0.96), 7.88–7.87 (m, 1H × 0.96), 7.75–7.75 (m, 1H × 0.04), 7.67–7.66 (m, 1H × 0.04), 7.62 (dd, J = 8.1, 2.2 Hz, 1H × 0.96), 7.47 (t, J = 8.1 Hz, 1H × 0.96), 7.45–7.43 (m, 1H × 0.04), 7.38 (t, J = 8.1 Hz, 1H × 0.04), 5.59 (s, 1H × 0.96), 3.94 (s, 3H × 0.04), 3.85 (s, 3H × 0.96); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 187.1, 165.4, 135.4, 134.7, 134.4, 130.2, 129.3, 127.3, 57.5, 54.0; HRMS (MALDI-TOF, matrix: DIT) calcd for $C_{10}H_8O_3Cl_2Na$ $[M+Na]^+$ *m/z* 268.9743, found 268.9736.



Methyl 2-chloro-3-oxo-3-(o-tolyl)propanoate (3i).

3i was synthesized following the General procedure A. $MgCl_2$ was used instead of $Yb(OTf)_3$. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of 2-methylbenzoyl chloride (13.0 μL, 0.100 mmol) afforded **3i** (11.6 mg, 51% yield, keto/enol ratio = 83:17) as a colorless oil.

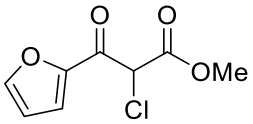
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.45 (s, 1H × 0.17), 7.69 (d, J = 8.3 Hz, 1H × 0.83), 7.46 (t, J = 8.3 Hz, 1H × 0.83), 7.36–7.24 (m, 2H × 0.83 + 4H × 0.17), 5.61 (s, 1H × 0.83), 3.94 (s, 3H × 0.17), 3.82 (s, 3H × 0.83), 2.53 (s, 3H × 0.83), 2.36 (s, 3H × 0.17); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 190.8, 165.8, 140.4, 133.7, 132.8, 132.4, 128.9, 125.8, 59.3, 53.7, 21.3; (enol) δ 171.6, 170.0, 135.8, 133.3, 130.3, 129.9, 128.0, 125.6, 98.1, 53.0, 19.1; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{11}H_{11}O_3ClNa$ $[M+Na]^+$ *m/z* 249.0289, found 249.0286.



Methyl 2-chloro-3-(naphthalen-1-yl)-3-oxopropanoate (3j).

3j was synthesized following the General procedure A. $MgCl_2$ was used instead of $Yb(OTf)_3$. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of 1-naphthoyl chloride (15.1 μL, 0.100 mmol) afforded **3j** (15.2 mg, 58% yield, keto/enol ratio = 75:25) as a colorless oil.

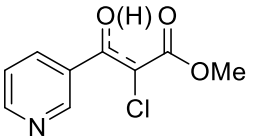
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.71 (s, 1H × 0.25), 8.61 (d, J = 8.3 Hz, 1H × 0.75), 8.07 (d, J = 8.3 Hz, 1H × 0.75), 7.98–7.88 (m, 2H × 0.75 + 3H × 0.25), 7.66–7.51 (m, 3H × 0.75 + 4H × 0.25), 5.79 (s, 1H × 0.75), 3.97 (s, 3H × 0.25), 3.80 (s, 3H × 0.75); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 190.8, 165.7, 134.4, 131.6, 130.7, 130.5, 128.8, 128.8, 128.6, 127.0, 125.5, 124.1, 59.7, 53.8; (enol) δ 170.5, 170.1, 134.0, 133.4, 131.0, 129.6, 128.4, 127.0, 126.7, 126.3, 125.0, 124.8, 99.1, 53.1; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{14}H_{11}O_3ClNa$ $[M+Na]^+$ *m/z* 285.0289, found 285.0281.



Methyl 2-chloro-3-(furan-2-yl)-3-oxopropanoate (3k).

3k was synthesized following the General procedure A. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of furan-2-carbonyl chloride (9.8 μL, 0.100 mmol) afforded **3k** (19.0 mg, 94% yield) as a colorless oil.

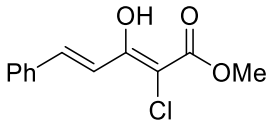
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J = 1.5 Hz, 1H), 7.43 (d, J = 3.7 Hz, 1H), 6.64 (dd, J = 3.7, 1.5 Hz, 1H), 5.51 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.6, 165.3, 149.5, 147.9, 120.5, 113.2, 57.5, 53.9; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_8H_7O_4ClNa$ $[M+Na]^+$ *m/z* 224.9925, found 224.9930.



Methyl 2-chloro-3-oxo-3-(pyridin-3-yl)propanoate (3l).

3l was synthesized following the General procedure A. The reaction was quenched with saturated aqueous NH_4Cl instead of citric acid. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:1). The reaction of nicotinoyl chloride hydrochloride (53.4 mg, 0.300 mmol) afforded **3l** (52.0 mg, 80% yield, keto/enol ratio = 92:8) as a yellow oil.

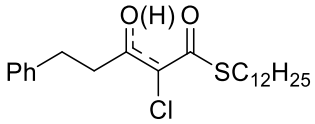
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.65 (s, 1H × 0.08), 9.13 (d, J = 2.0 Hz, 1H × 0.92), 8.93 (d, J = 2.0 Hz, 1H × 0.08), 8.76 (dd, J = 4.7, 1.6 Hz, 1H × 0.92), 8.59 (dd, J = 5.1, 1.6 Hz, 1H × 0.08), 8.22 (dt, J = 8.2, 2.0 Hz, 1H × 0.92), 8.01 (dt, J = 8.2, 2.0 Hz, 1H × 0.08), 7.41 (ddd, J = 8.2, 4.7, 1.6 Hz, 1H × 0.92), 7.32 (ddd, J = 8.2, 5.1, 1.6 Hz, 1H × 0.08), 5.60 (s, 1H × 0.92), 3.86 (s, 3H × 0.08), 3.77 (s, 3H × 0.92); ^{13}C NMR (150 MHz, $CDCl_3$) (keto) δ 187.3, 165.1, 154.3, 150.3, 136.5, 128.7, 123.7, 57.5, 53.9; (enol) δ 170.1, 166.3, 151.0, 149.4, 136.3, 129.3, 122.7, 97.6, 53.2; HRMS (MALDI-TOF, matrix: CHCA) calcd for $C_9H_9NO_3Cl$ $[M+H]^+$ *m/z* 214.0266, found 214.0273.



Methyl (2*E*,4*E*)-2-chloro-3-hydroxy-5-phenylpenta-2,4-dienoate (3m).

3m was synthesized following the General procedure A. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 5:95). The reaction of *trans*-cinnamoyl chloride (16.7 mg, 0.100 mmol) afforded **3m** (19.3 mg, 81% yield) as a pale yellow solid, mp 68–69 °C.

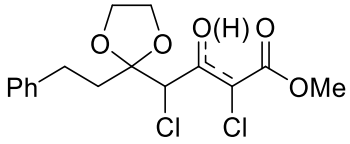
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.27 (d, *J* = 1.5 Hz, 1H), 7.58–7.56 (m, 2H), 7.54 (d, *J* = 16.1 Hz, 1H), 7.43–7.35 (m, 3H), 7.22 (dd, *J* = 16.1, 1.5 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 165.5, 139.6, 135.2, 129.9, 128.9, 128.0, 117.9, 97.5, 52.9; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{12}H_{11}O_3ClNa$ $[M+Na]^+$ *m/z* 261.0289, found 261.0294.



***S*-dodecyl (*E*)-2-chloro-3-hydroxy-5-phenylpent-2-enethioate (3n).**

3n was synthesized following the General procedure A. Cl-MAHT (**1b**) was used instead of Cl-MAHO (**1a**). Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:99). The reaction of 3-phenylpropanoyl chloride (14.8 μL, 0.100 mmol) afforded **3n** (35.6 mg, 87% yield, keto/enol ratio = 31:69) as a pink oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 13.16 (s, 1H × 0.69), 7.24–7.10 (m, 5H), 4.78 (s, 1H × 0.31), 3.06–2.99 (m, 1H × 0.31), 2.89–2.83 (m, 2H + 1H × 0.31), 2.84 (t, *J* = 7.4 Hz, 2H), 2.72–2.69 (m, 2H × 0.69), 1.59–1.48 (m, 2H), 1.35–1.19 (m, 18H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.6, 195.3, 192.1, 172.0, 140.3, 140.1, 128.5, 128.3, 128.3, 126.4, 126.3, 106.8, 67.6, 40.7, 35.2, 31.9, 31.6, 30.2, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.1, 29.1, 29.0, 28.9, 28.8, 28.8, 22.7, 14.1; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{23}H_{35}O_2SClNa$ $[M+Na]^+$ *m/z* 433.1939, found 433.1934.



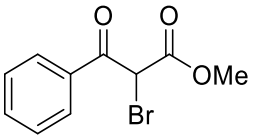
Methyl 2,4-dichloro-3-oxo-4-(2-phenethyl-1,3-dioxolan-2-yl)butanoate (3o).

3o was synthesized following the General procedure B. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of compound **2o** (111 mg, 0.410 mmol) afforded **3o** (116 mg, 78% yield, keto/enol ratio = 70:30) as a colorless oil.

[Note: the keto tautomer of **3o** consists of a mixture of diastereomers in a 54:46 ratio]

^{1}H NMR (600 MHz, $CDCl_3$) δ 12.49 (d, *J* = 1.4 Hz, 1H × 0.3), 7.29–7.26 (m, 2H), 7.21–7.17 (m, 3H), 5.43 (s, 1H × 0.7 × 0.54), 5.39 (s, 1H × 0.7 × 0.46), 5.23 (d, *J* = 1.4 Hz, 1H × 0.3), 4.90 (s, 1H × 0.7 × 0.46), 4.87 (s, 1H × 0.7 × 0.54), 4.23–4.02 (m, 4H), 3.88 (s, 3H × 0.3), 3.83 (s, 3H × 0.7 × 0.54), 3.83 (s, 3H × 0.7 × 0.46), 2.75–2.63 (m, 2H), 2.38–2.21 (m, 2H × 0.7), 2.08–2.02 (m, 2H × 0.3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.7, 191.3, 169.3, 166.7, 164.8, 164.5, 141.4, 140.9, 140.8, 128.4, 128.4, 128.3, 126.0, 126.0, 125.9, 110.7, 110.3, 99.5, 66.7, 66.7, 66.6, 66.5, 66.3, 66.1, 63.2,

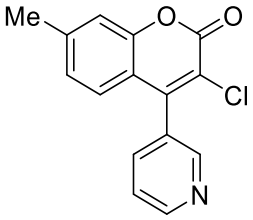
62.0, 60.2, 59.3, 58.0, 53.9, 53.8, 53.3, 36.6, 36.3, 35.9, 28.9, 28.7, 28.7; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{16}H_{18}O_5Cl_2Na$ $[M+Na]^+$ *m/z* 383.0424, found 383.0405.



Methyl 2-bromo-3-oxo-3-phenylpropanoate (3p).

3p was synthesized following the General procedure A. Br-MAHO **1c** was used instead of Cl-MAHO **1a**. Reaction time was 24h. Purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9). The reaction of benzoyl bromide (11.9 μL, 0.100 mmol) afforded **3p** (14.3 mg, 56% yield) as a white wax.

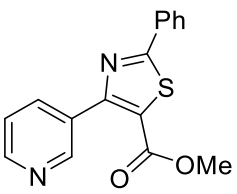
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.57 (t, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 8.1 Hz, 2H), 5.62 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.1, 165.7, 134.4, 133.2, 129.2, 128.9, 54.0, 45.8; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{10}H_9O_3BrNa$ $[M+Na]^+$ *m/z* 278.9627, found 278.9611.



3-Chloro-7-methyl-4-(pyridin-3-yl)-2*H*-chromen-2-one (4).

To a mixture of **3l** (21.3 mg, 0.100 mmol) and *m*-cresol (12.4 μL, 0.120 mmol, 1.2 equiv.) was added methanesulfonic acid (0.2 mL) at room temperature. After stirring for 24 h, the reaction mixture was carefully basified with a saturated aqueous $NaHCO_3$ at 0 °C, and extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: chloroform/methanol = 97:3) to afford **4** (21.4 mg, 79% yield) as a white solid, mp 167–175 °C.

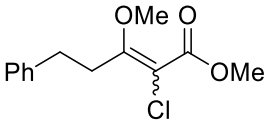
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.1 Hz, 1H), 8.55 (s, 1H), 7.65 (dt, *J* = 8.3, 2.1 Hz, 1H), 7.47 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.18 (s, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 152.1, 150.6, 149.0, 147.7, 143.8, 136.3, 129.4, 126.5, 126.2, 123.6, 120.4, 117.3, 117.2, 21.7; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{15}H_{11}NO_2Cl$ $[M+H]^+$ *m/z* 272.0473, found 272.0466.



Methyl 2-phenyl-4-(pyridin-3-yl)thiazole-5-carboxylate (5).

To a mixture of **3l** (21.3 mg, 0.100 mmol) in MeOH (1 mL) was added thiobenzamide (15.1 mg, 0.110 mmol, 1.1 equiv.) at room temperature. The reaction mixture was refluxed for 24 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the residue was redissolved in ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, water, and saturated brine sequentially, then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9 to 4:6) to afford **5** (22.5 mg, 76% yield) as a white solid, mp 117–118 °C.

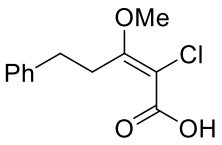
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.61 (s, 1H), 8.12 (dt, J = 8.3, 2.1 Hz, 1H), 7.98–7.96 (m, 2H), 7.46–7.40 (m, 3H), 7.34 (dd, J = 8.3, 4.8 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 161.7, 157.6, 150.7, 149.9, 137.3, 132.5, 131.5, 130.2, 129.2, 126.9, 123.0, 122.7, 52.6; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{16}H_{13}N_2O_2S$ $[M+H]^+$ *m/z* 297.0692, found 297.0694.



Methyl 2-chloro-3-methoxy-5-phenylpent-2-enoate (6).

To a cooled (0 °C) stirred solution of α-chloro-β-ketoester **3a** (503 mg, 2.09 mmol) in DCM/MeOH (4:1) (21 mL), was slowly added a 0.6 M solution of (trimethylsilyl)diazomethane in hexane (7.0 mL, 2 equiv.). After being stirred for 20 h at room temperature, the reaction mixture was concentrated with nitrogen flow and dried under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9) to afford the *E*- and *Z*-isomers of **6**: 403 mg (76% yield) of major isomer as a colorless oil, and 80.9 mg (15% yield) of minor isomer as a colorless oil. Although these isomers were separable, they were mixed for next step.

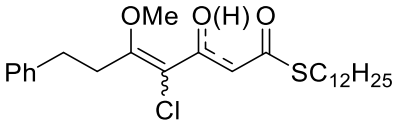
Major isomer of : TLC R_f 0.28 (ethyl acetate/hexane = 1:9); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32–7.21 (m, 5H), 3.83 (s, 3H), 3.78 (s, 3H), 3.18 (t, J = 8.4 Hz, 2H), 2.85 (t, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 164.6, 140.3, 128.6, 128.4, 126.5, 103.3, 55.8, 52.4, 34.0, 30.4. Minor isomer: TLC R_f 0.18 (ethyl acetate/hexane = 1:9); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H), 3.81 (s, 3H), 3.76 (s, 3H), 2.89–2.84 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 163.4, 140.2, 128.6, 128.3, 126.5, 107.2, 57.9, 52.5, 32.3, 32.0; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{13}H_{15}O_3ClNa$ $[M+Na]^+$ *m/z* 277.0602, found 277.0611.



(*Z*)-2-Chloro-3-methoxy-5-phenylpent-2-enoic acid (7).

To a cooled (0 °C) stirred solution of **6** (468 mg, 1.84 mmol) in H_2O/THF (1:3) (18 mL) was added a 2 M aqueous lithium hydroxide (1.84 mL, 2 equiv.). After being stirred at room temperature for 50 h, the reaction mixture was concentrated under reduced pressure. Then, chloroform was added to the residue, and a 10 wt% aqueous citric acid was carefully added until the pH = 4 while stirring. The resulting mixture was extracted with chloroform, and the extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization in chloroform to afford **7** (243mg, 55% yield) as white flakes, mp 162–163 °C dec.

^{1}H NMR (600 MHz, THF-d_8) δ 11.21 (brs, 1H), 7.29–7.15 (m, 5H), 3.84 (s, 3H), 3.20 (t, J = 8.3 Hz, 2H), 2.83 (t, J = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, THF-d_8) δ 168.5, 165.9, 141.9, 129.1, 126.9, 104.2, 55.9, 34.9, 31.1; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{12}H_{13}O_3ClNa$ $[M+Na]^+$ *m/z* 263.0445, found 263.0445.

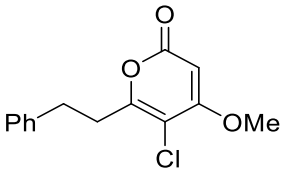


_S_-dodecyl 4-chloro-5-methoxy-3-oxo-7-phenylhept-4-enethioate (8)

To a solution of **7** (392 mg, 1.63 mmol) in THF (8 mL) was added 1,1'-carbonyldiimidazole (397 mg, 2.45 mmol, 1.5 equiv.), and the mixture was stirred for 30 min (mixture A). In another flask, DIPEA (417 μL, 2.45 mmol, 1.5 equiv.) was added to a solution of *S*-dodecyl-MAHT[3] (702 mg, 2.45 mmol, 1.5 equiv.) and $Mg(OTf)_2$ (790 mg, 2.45 mmol, 1.5 equiv.) in THF (8 mL), and the mixture was stirred for 10 min. Then, the resulting mixture was added to mixture A. The mixture was stirred at room temperature for 24 h, and a 10 wt% aqueous citric acid was carefully added until the pH = 4. The resulting mixture was extracted with ethyl acetate, and the combined extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9) to afford **8** (698 mg, 92% yield) as a brown oil.

[Note: Compound **8** exists in equilibrium between the *E*- and *Z*-isomers. The major isomer is present as a mixture of the keto and enol forms, and the minor isomer exists only in the keto form. The ratio of keto form of major isomer/enol form of major isomer/minor isomer = 76:11:13. Major isomer: TLC R_f 0.37 (ethyl acetate/hexane = 1:9). Minor isomer: TLC R_f 0.3 (ethyl acetate/hexane = 1:9).]

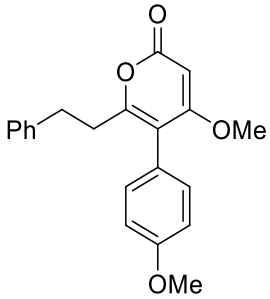
^{1}H NMR (600 MHz, $CDCl_3$) δ 13.73 (s, 1H × 0.11), 7.44–7.14 (m, 5H), 5.99 (s, 1H × 0.11), 4.04 (s, 2H × 0.76), 4.01 (s, 2H × 0.13), 3.83 (s, 3H × 0.11), 3.82 (s, 3H × 0.76), 3.71 (s, 3H × 0.13), 3.16–3.13 (m, 2H × 0.76), 3.10–3.06 (m, 2H × 0.13), 2.97–2.82 (m, 4H + 2H × 0.11), 1.67–1.53 (m, 2H), 1.40–1.26 (m, 18H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.0, 195.2, 192.7, 192.6, 189.0, 185.0, 168.8, 168.6, 167.3, 163.3, 140.2, 140.0, 139.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 126.5, 126.4, 126.3, 117.0, 110.5, 105.9, 99.8, 57.7, 55.9, 55.7, 55.4, 33.6, 33.5, 33.4, 31.8, 30.8, 30.7, 30.5, 29.5, 29.5, 29.4, 29.3, 29.2, 29.0, 28.7, 28.3, 22.6, 14.0; HRMS (MALDI-TOF, matrix: DHB) calcd for $C_{26}H_{39}O_3ClSNa$ $[M+Na]^+$ *m/z* 489.2201, found 489.2212.



5-Chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (10)

To a solution of **8** (698 mg, 1.50 mmol) in THF (15 mL) was added 1 M aqueous HCl (1.5 mL) at room temperature. After being stirred for 12 h, the mixture was extracted with chloroform. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was redissolved in DCM (15 mL), and 1,8-diazabicyclo[5.4.0]-7-undecene (298 μL, 2.00 mmol, 1.3 equiv.) was added. The mixture was stirred for 2 h, then DIPEA (765 μL, 4.50 mmol, 3 equiv.) and dimethyl sulfate (711 μL, 7.50 mmol, 5 equiv.) were added sequentially. After being further stirred for 24 h, the mixture was quenched with 1 M aqueous HCl and extracted with chloroform. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9) to afford **10** (293 mg, 74% yield) as a white solid, mp 112–113 °C.

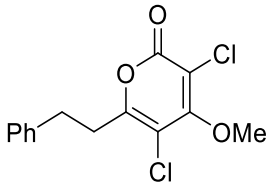
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31–7.21 (m, 5H), 5.50 (s, 1H), 3.88 (s, 3H), 2.99 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 162.5, 160.7, 139.6, 128.6, 128.3, 126.5, 108.1, 88.6, 56.9, 33.2, 32.3; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{14}H_{13}O_3ClNa$ $[M+Na]^+$ *m/z* 287.0445, found 287.0447.



4-Methoxy-5-(4-methoxyphenyl)-6-phenethyl-2*H*-pyran-2-one (11)

The following reaction was carried out under argon atmosphere. **10** (39.7 mg, 0.150 mmol), 4-methoxyphenylboronic acid (34.2 mg, 0.225 mmol, 1.5 equiv.), $Pd(OAc)_2$ (1.7 mg, 7.50 μmol, 5 mol%), 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (XPhos) (10.7 mg, 22.5 μmol, 15 mol%), and K_2CO_3 (45.6 mg, 0.33 mmol, 2.2 equiv.) were suspended in 1,4-dioxane/H_2O (9:1) (3 mL). After being stirred at room temperature for 30 min, the mixture was heated to 80 °C and stirred for 24 h. Then, the mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 3:7) to afford **11** (44.7 mg, 89% yield) as a white solid, mp 65–67 °C.

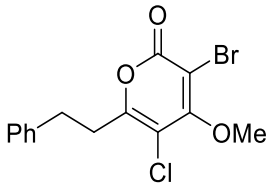
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17–7.10 (m, 3H), 6.94–6.93 (m, 2H), 6.79–6.76 (m, 2H), 6.72–6.70 (m, 2H), 5.44 (s, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 2.85 (t, *J* = 8.3 Hz, 2H), 2.54 (t, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 164.3, 161.4, 159.2, 140.0, 131.4, 128.4, 126.2, 123.2, 114.4, 113.7, 87.7, 56.2, 55.2, 33.3, 33.3; HRMS (MALDI-TOF, matrix: DHB) calcd for $C_{21}H_{20}O_4Na$ $[M+Na]^+$ *m/z* 359.1254, found 359.1265.



3,5-Dichloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (12a)

To a solution of **10** (26.4 mg, 0.100 mmol) and *N*-chlorosuccinimide (16.0 mg, 0.120 mmol, 1.2 equiv.) in acetonitrile (1 mL) was added trifluoroacetic acid (2.3 μL, 30.0 μmol, 0.3 equiv.) at room temperature. After being stirred for 24 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with chloroform. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9) to afford **12a** (28.6 mg, 96% yield) as a colorless oil.

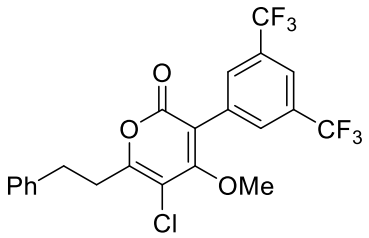
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24–7.12 (m, 5H), 4.10 (s, 3H), 2.92 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5, 159.6, 158.7, 139.3, 128.7, 128.3, 126.7, 110.6, 106.2, 61.6, 33.2, 32.4; HRMS (MALDI-TOF, matrix: DHB) calcd for $C_{14}H_{12}O_3Cl_2Na$ $[M+Na]^+$ *m/z* 321.0056, found 321.0062.



3-Bromo-5-chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (12b)

To a solution of **10** (132.3 mg, 0.500 mmol) and *N*-bromosuccinimide (106.8 mg, 0.600 mmol, 1.2 equiv.) in acetonitrile (5 mL) was added trifluoroacetic acid (11.5 μL, 0.150 mmol, 0.3 equiv.) at room temperature. After being stirred for 12 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with chloroform. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9) to afford **12b** (153.3 mg, 89% yield) as a light-yellow oil.

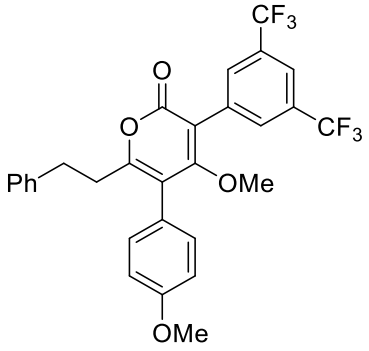
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24–7.12 (m, 5H), 4.00 (s, 3H), 2.92 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 159.8, 159.4, 139.3, 128.6, 128.3, 126.6, 110.7, 97.5, 61.4, 33.2, 32.4; HRMS (MALDI-TOF, matrix: ClCCA) calcd for $C_{14}H_{12}O_3ClBrNa$ $[M+Na]^+$ *m/z* 364.9551, found 364.9537.



3-(3,5-Bis(trifluoromethyl)phenyl)-5-chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (13)

The following reaction was carried out under argon atmosphere. **12b** (39.5 mg, 0.115 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (44.4 mg, 0.172 mmol, 1.5 equiv.), Pd(dppf)Cl_2·DCM (4.7 mg, 5.8 μmol, 5 mol%), and K_2CO_3 (35.0 mg, 0.253 mmol, 2.2 equiv) were suspended in 1,4-dioxane/H_2O (9:1) (5 mL). After being stirred at room temperature for 30 min, the mixture was heated to 70 °C and stirred for 18 h. Then, the mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9) to afford **13** (41.0 mg, 75% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.81 (s, 1H), 7.27–7.17 (m, 5H), 3.51 (s, 3H), 3.02–2.96 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 161.9, 161.4, 139.4, 133.4, (132.0, 131.7, 131.5, 131.3) (q, J = 33.2 Hz), 130.8, 128.7, 128.3, 126.7, (125.8, 124.0, 122.2, 120.4) (q, J = 273 Hz), 122.2, 110.8, 109.3, 62.0, 33.6, 32.4; ^{19}F NMR (564 MHz, $CDCl_3$) δ −62.71; HRMS (MALDI-TOF, matrix: DHB) calcd for $C_{22}H_{15}O_3F_6ClNa$ $[M+Na]^+$ *m/z* 499.0506, found 499.0515.



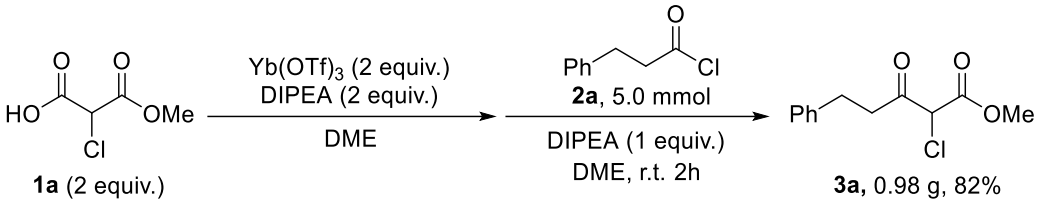
3-(3,5-Bis(trifluoromethyl)phenyl)-4-methoxy-5-(4-methoxyphenyl)-6-phenethyl-2*H*-pyran-2-one (14)

The following reaction was carried out under argon atmosphere. **13** (41.0 mg, 0.086 mmol), 4-methoxyphenylboronic acid (19.8 mg, 0.130 mmol, 1.5 equiv.), $Pd(OAc)_2$ (1.0 mg, 4.30 μmol, 5 mol%), 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (XPhos) (6.2 mg, 13.0 μmol, 15 mol%), and K_2CO_3 (26.2 mg, 0.19 mmol, 2.2 equiv.) were

suspended in 1,4-dioxane/H_2O (9:1) (2 mL). After being stirred at room temperature for 30 min, the mixture was heated to 80 °C and stirred for 36 h. Then, the mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 1:9) to afford **14** (40.4 mg, 85% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.76 (s, 1H), 7.20–7.12 (m, 3H), 6.96 (d, J = 7.6 Hz, 2H), 6.83 (s, 4H), 3.77 (s, 3H), 3.09 (s, 3H), 2.90 (t, J = 8.3 Hz, 2H), 2.64 (t, J = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.3, 163.4, 162.9, 159.6, 139.8, 134.2, (131.6, 131.4, 131.2, 131.0) (q, J = 33.2 Hz), 131.3, 130.9, 128.5, 128.4, 126.5, (126.0, 124.2, 122.4, 120.6) (q, J = 273 Hz), 123.4, 121.6, 116.6, 114.1, 108.5, 61.1, 55.3, 33.6, 33.4; ^{19}F NMR (564 MHz, $CDCl_3$) δ −62.65; HRMS (MALDI-TOF, matrix: DHB) calcd for $C_{29}H_{22}O_4F_6Na$ $[M+Na]^+$ *m/z* 571.1315, found 571.1296.

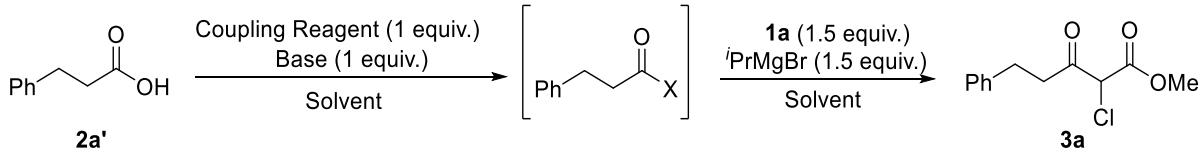
Gram-Scale synthesis of 3a.



A solution of **1a** (1.53 g, 10 mmol, 2 equiv.), $Yb(OTf)_3$ (6.20 g, 10 mmol, 2 equiv.), and DIPEA (1.70 mL, 10 mmol, 2 equiv.) in DME (35 mL) was stirred at room temperature for 15 min. Then, another DIPEA (0.85 mL, 5 mmol, 1 equiv.) and 3-phenylpropanoyl chloride (0.74 mL, 5 mmol, 1 equiv.) were added sequentially at 0 °C. After being stirred at room temperature for 2 h, the mixture was quenched with 10 wt% aqueous citric acid, and extracted with chloroform. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 5:95) to afford **3a** (0.98 g, 82% yield).

3. Optimization of the reaction conditions

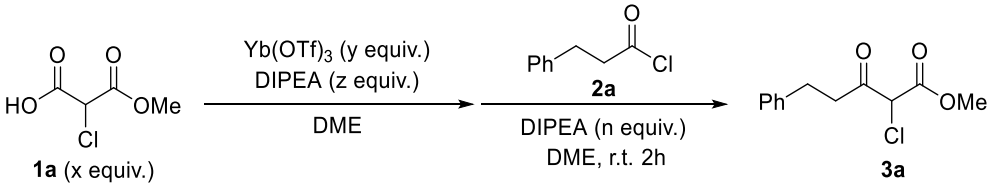
Table S1. Screening of coupling reagent.



Entry	Coupling Reagent	Base	Solvent	Yield [%][a]
1	COMU	DIPEA	DME	35
2	DIC	DIPEA	DME	4
3	EDCI	DIPEA	DME	10
4	DCC	DIPEA	DME	18
5	DIC	DMAP	DME	10
6	EDCI	DMAP	DME	12
7	DCC	DMAP	DME	19
8	DCC	DMAP	DCM	26
9	CDI	DIPEA	DME	14
10	CDT	DIPEA	DME	5
11	HATU	DIPEA	DMF	29
12	HBTU	DIPEA	DMF	13
13	BOP	DIPEA	DME	24
14	PyAOP	DIPEA	DME	29

[a] Yields were determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard.

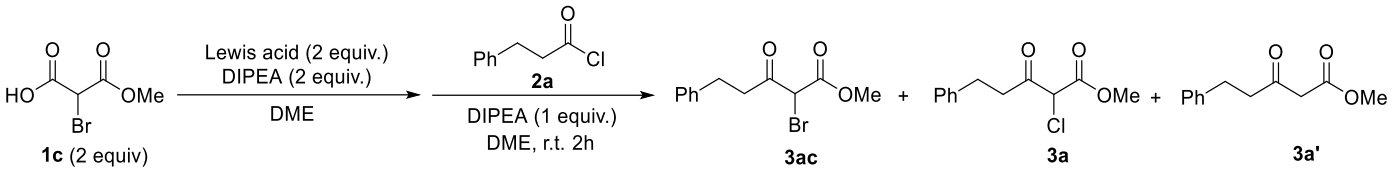
Table S2. Optimization of reaction conditions.



Entry	x	y	z	n	Yield [%][a]
1	1.5	1.5	1.5	1	81
2[b]	1.5	1.5	1.5	1	75
3	1.5	3	1.5	1	62
4	1.5	0.75	1.5	1	34
5	1.5	1.5	3	1	48
6	3	1.5	1.5	1	52
7	1.5	1.5	1.5	0.1	34
8	**2**	**2**	**2**	**1**	**89**
9	3	3	3	1	86

[a] Yields were determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. [b] The reaction time was 12 h.

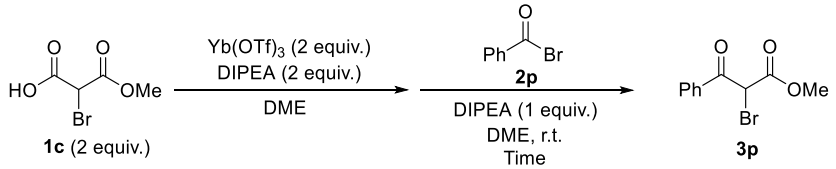
Table S3. Examination of synthesizing α-bromo-β-ketoester.



Entry	Lewis acid	Conversion [%]	Yield [%][a]		
			3ac	**3a**	**3a'**
1	$Yb(OTf)_3$	43	17	19	0
2	$MgBr_2$	58	23	16	0
3	$Mg(OTf)_2$	26	14	9	0
4	$MgCl_2$	54	0	49	0
5	^{i}PrMgBr	92	15	13	46

[a] Yields were determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard.

Table S4. Examination of synthesizing α-bromo-β-ketoester 3p.



Entry	Time	Yield [%][a]
1	2 h	35
2	4 h	38
3	24 h	56

[a] Yields were determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard.

4. X-ray crystallographic data

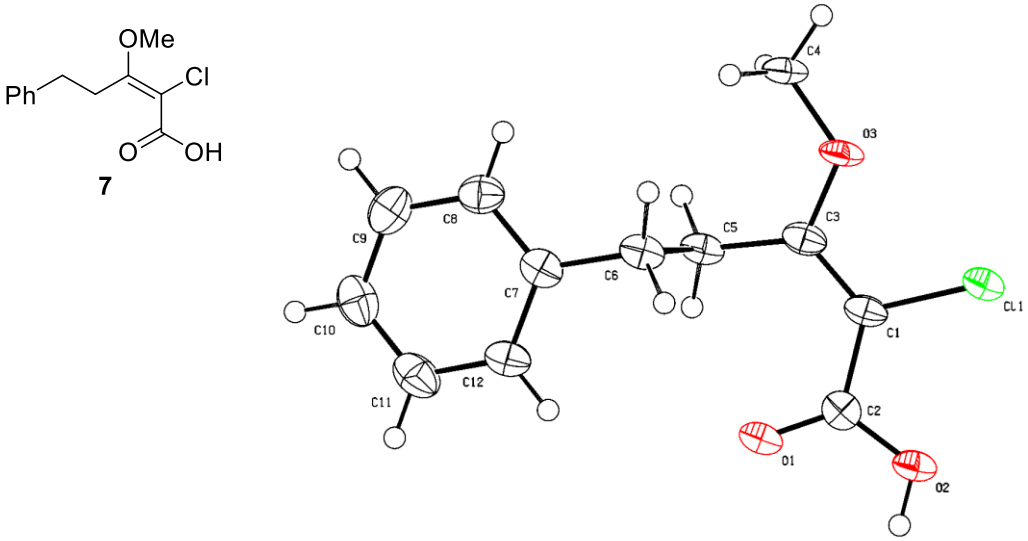


Figure S1. Thermal ellipsoid plot of the crystal structure of **7** at the 50% probability level

For X-ray diffraction of single crystal, data was collected on a Rigaku XtaLAB P200, λ (Cu-K$_\alpha$) = 1.54184 Å. The structure was solved by direct method (SHELXS-2013)[4] and refined on F^2 by full-matrix least-square techniques (SHELXL-2018).[5] Crystallographic data has been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 2502623 for **7**.

[Crystal data and structure refinement for 7][4]

Bond precision: C-C = 0.0064 Å Wavelength=1.54184

Cell: a=5.8919(4) b=8.2884(4) c=23.4295(14)

alpha=90 beta=97.035(6) gamma=90

Temperature: 93 K

	Calculated	Reported
Volume	1135.55(12)	1135.55(12)
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	$C_{12}H_{13}ClO_3$	$C_{12}H_{13}ClO_3$
Sum formula	$C_{12}H_{13}ClO_3$	$C_{12}H_{13}ClO_3$
Mr	240.67	240.67
Dx,g cm^{-3}	1.408	1.408
Z	4	4
Mu (mm^{-1})	2.902	2.902
F000	504.0	504.0
F000’	506.88	
h,k,lmax	7,10,29	7,10,29
Nref	2272	2272
Tmin,Tmax	0.482,0.944	0.666,1.000

Tmin’ 0.364

Correction method= # Reported T Limits: T_{min}=0.666 T_{max}=1.000

AbsCorr = MULTI-SCAN

Data completeness= 0.980 Theta(max)= 73.030

R(reflections)= 0.0765(1890) wR2(reflections)= 0.2192(2227)

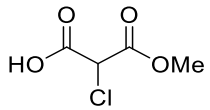
S = 1.145 Npar= 149

5. References

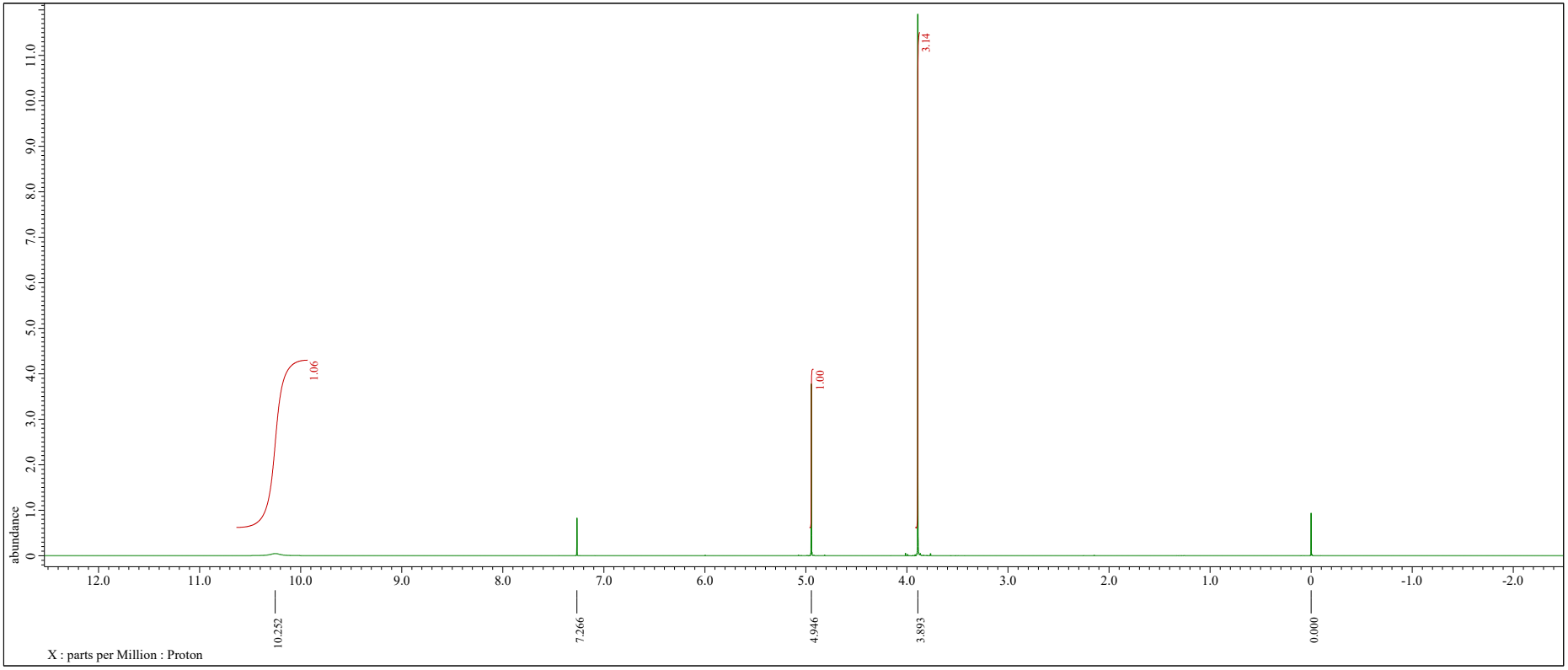
1 T. Xavier, S. Condon, C. Pichon, E. Le Gall and M. Presset, *Org. Lett.*, 2019, **21**, 6135.
2 R. Borrmann, D. Zetschok and H. Wennemers, *Org. Lett.*, 2022, **24**, 8683.
3 K. Akagawa and Kazuaki. Kudo, *Chem. Commun.*, 2017, **53**, 8645.
4 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112.
5 G. M. Sheldrick, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2015, **71**, 3.

6. Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra

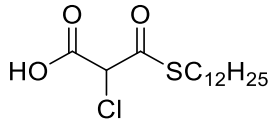
2-Chloro-3-methoxy-3-oxopropanoic acid (Cl-MAHO 1a)



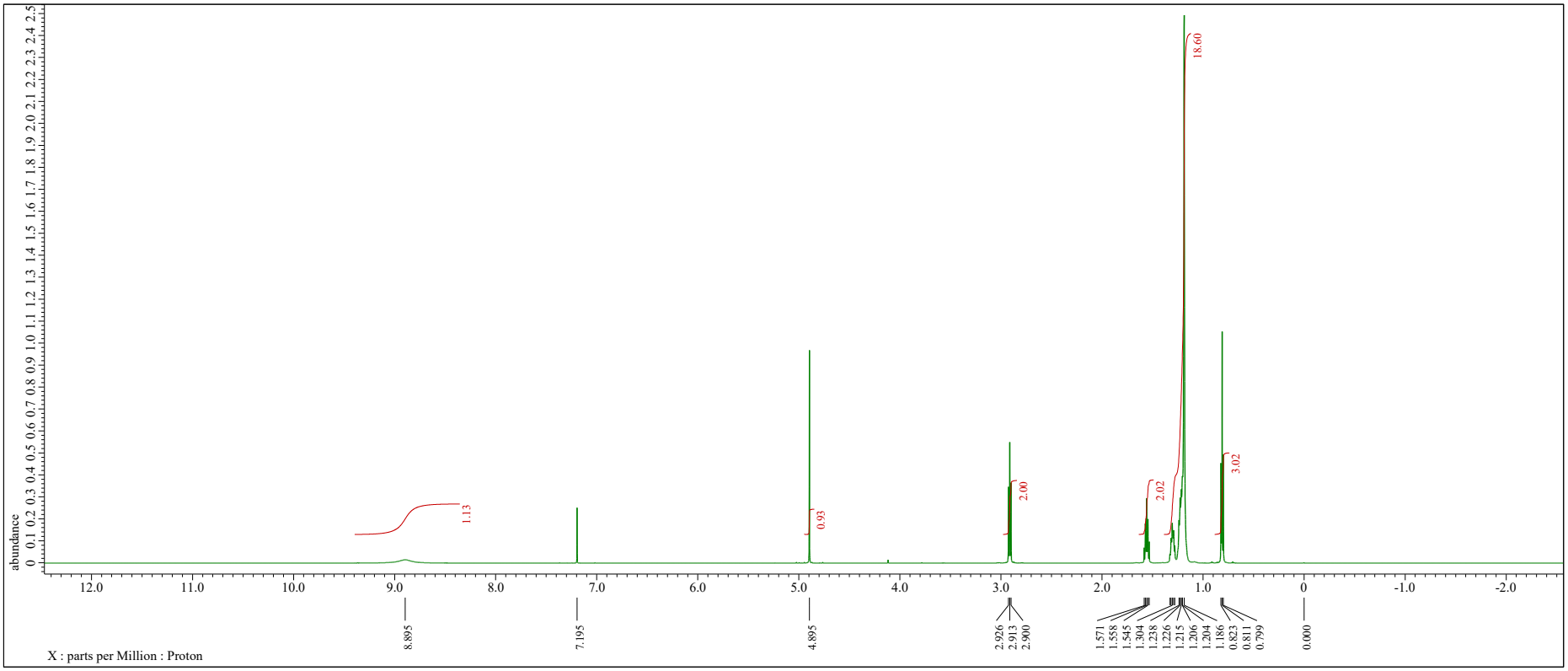
^{1}H NMR (600 MHz, $CDCl_3$)



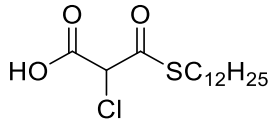
2-Chloro-3-(dodecylthio)-3-oxopropanoic acid (*S*-dodecyl-Cl-MAHT (1b))



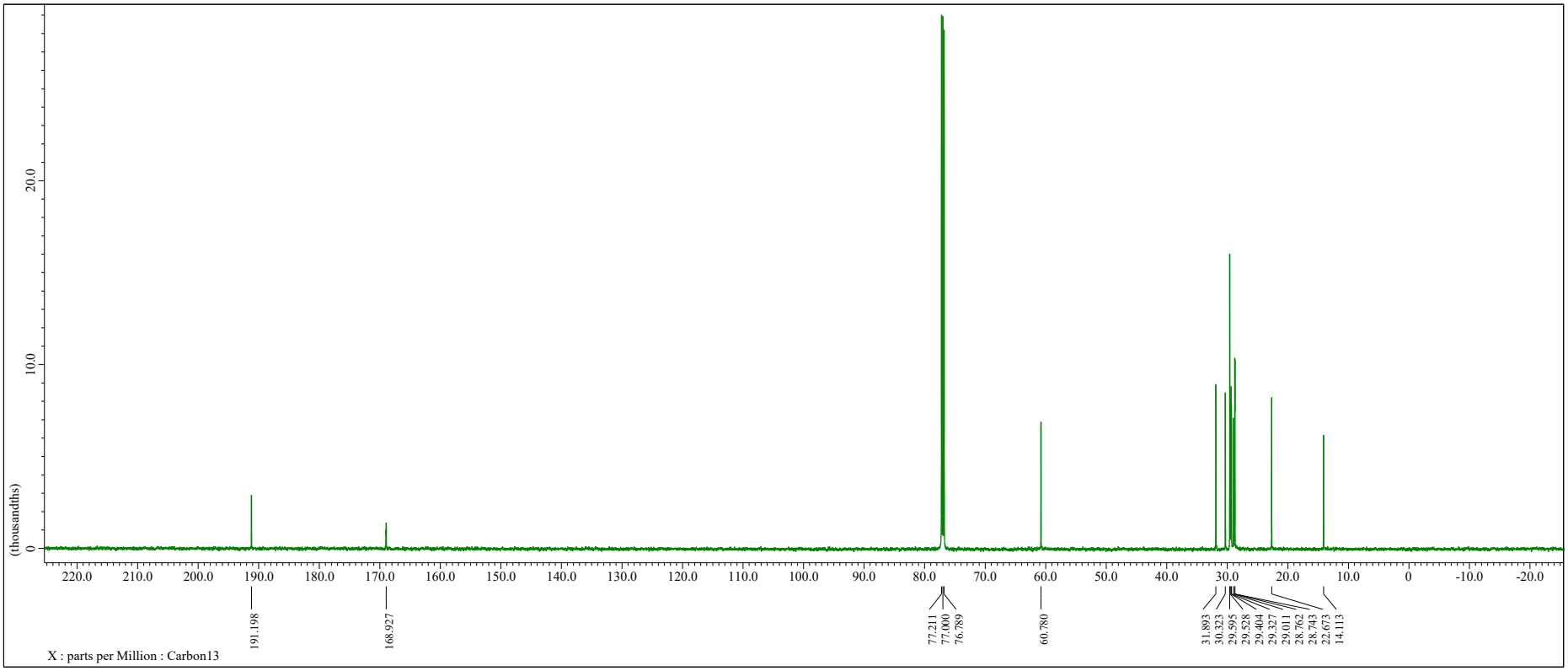
^{1}H NMR (600 MHz, $CDCl_3$)



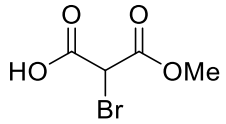
2-Chloro-3-(dodecylthio)-3-oxopropanoic acid (*S*-dodecyl-Cl-MAHT (1b))



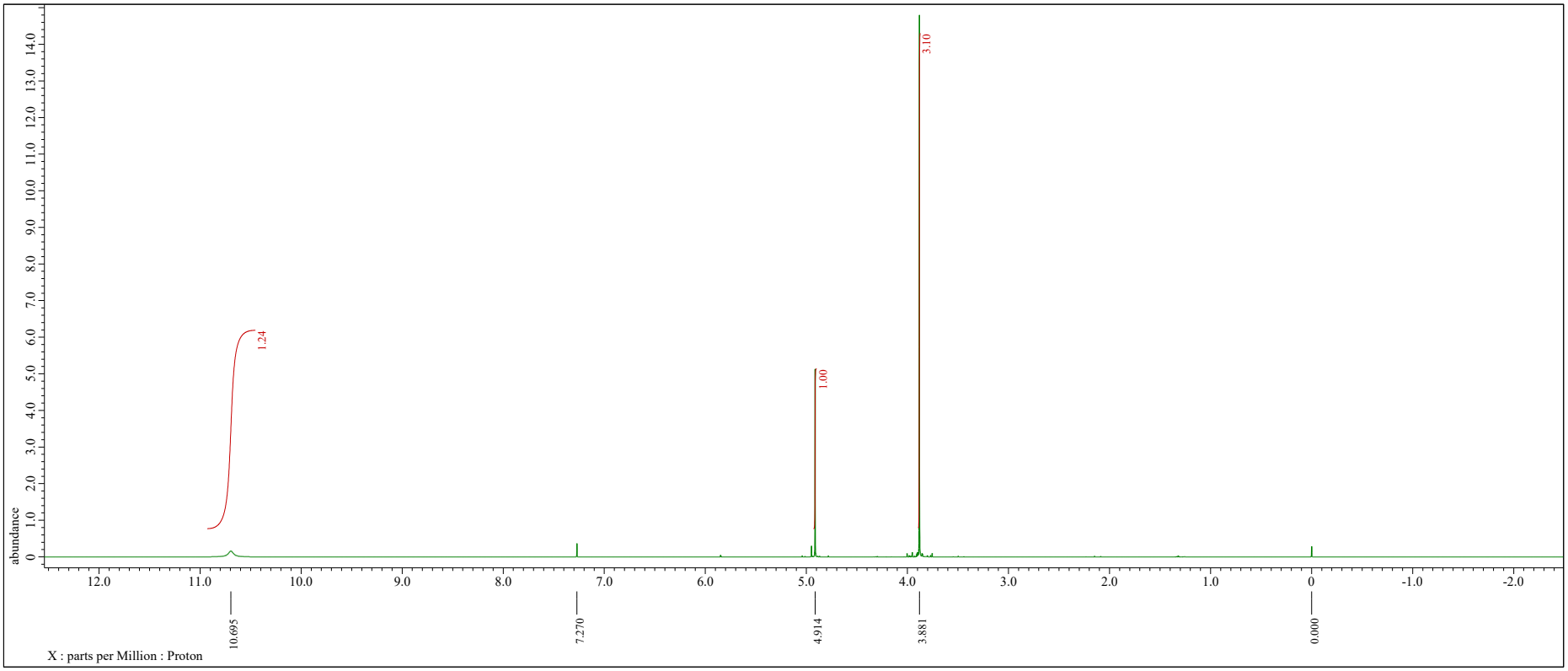
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



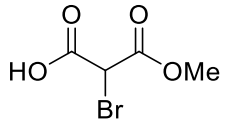
2-Bromo-3-methoxy-3-oxopropanoic acid (Br-MAHO 1c)



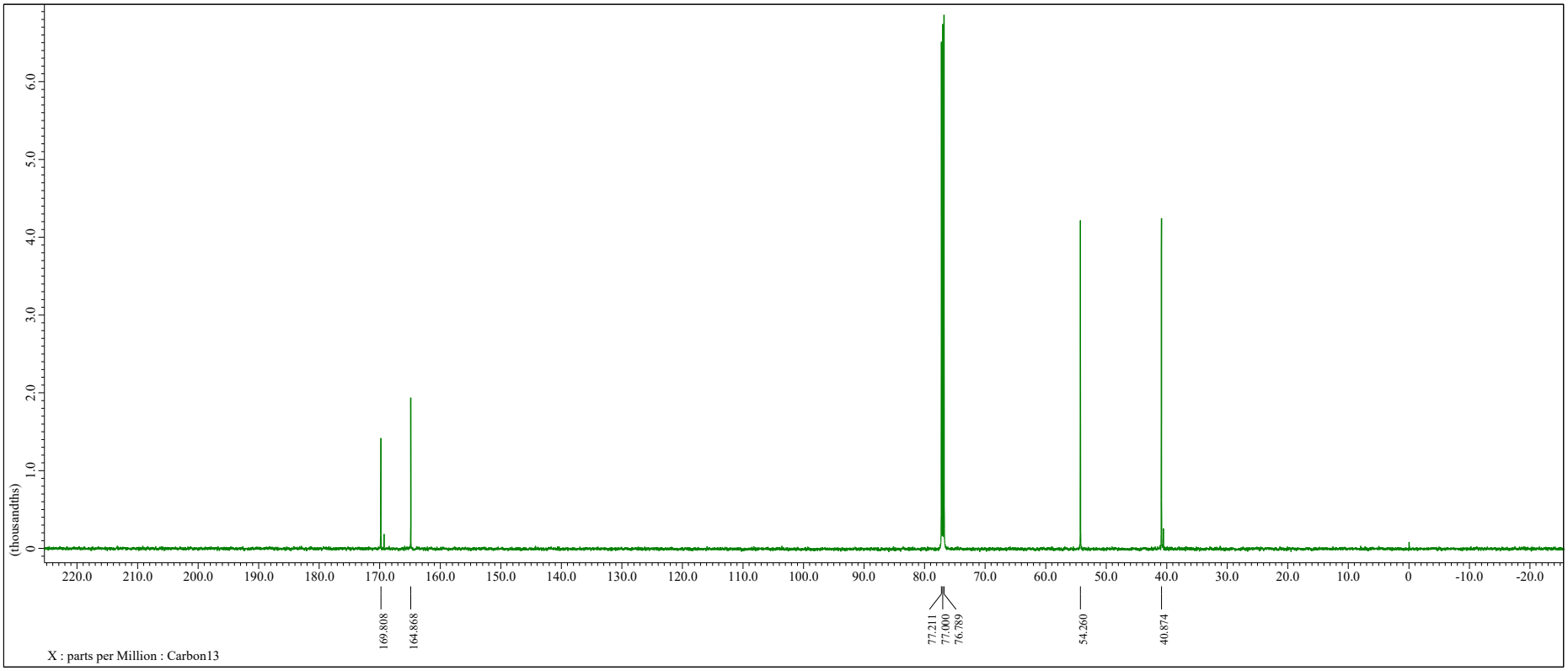
^{1}H NMR (600 MHz, $CDCl_3$)



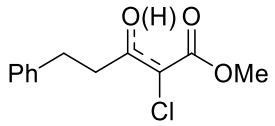
2-Bromo-3-methoxy-3-oxopropanoic acid (Br-MAHO 1c)



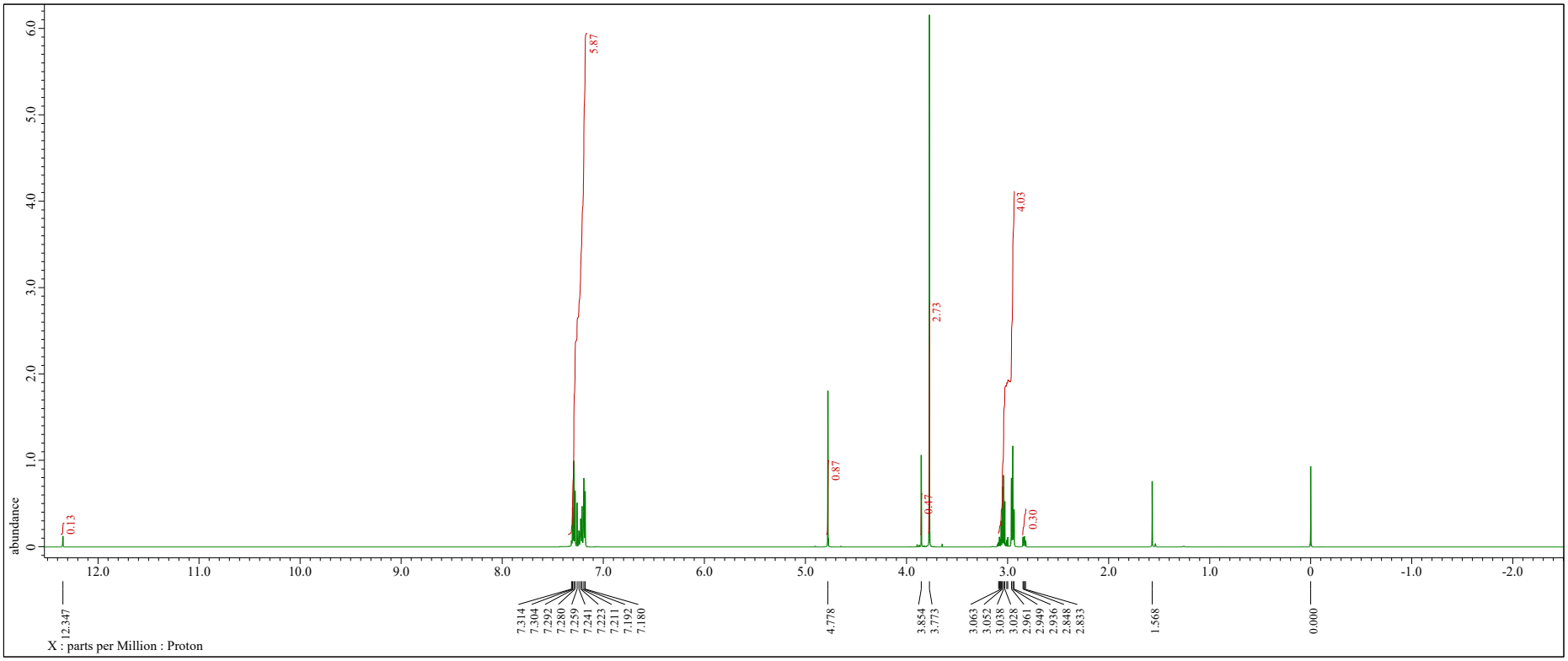
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



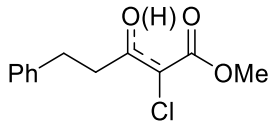
Methyl 2-chloro-3-oxo-5-phenylpentanoate (3a)



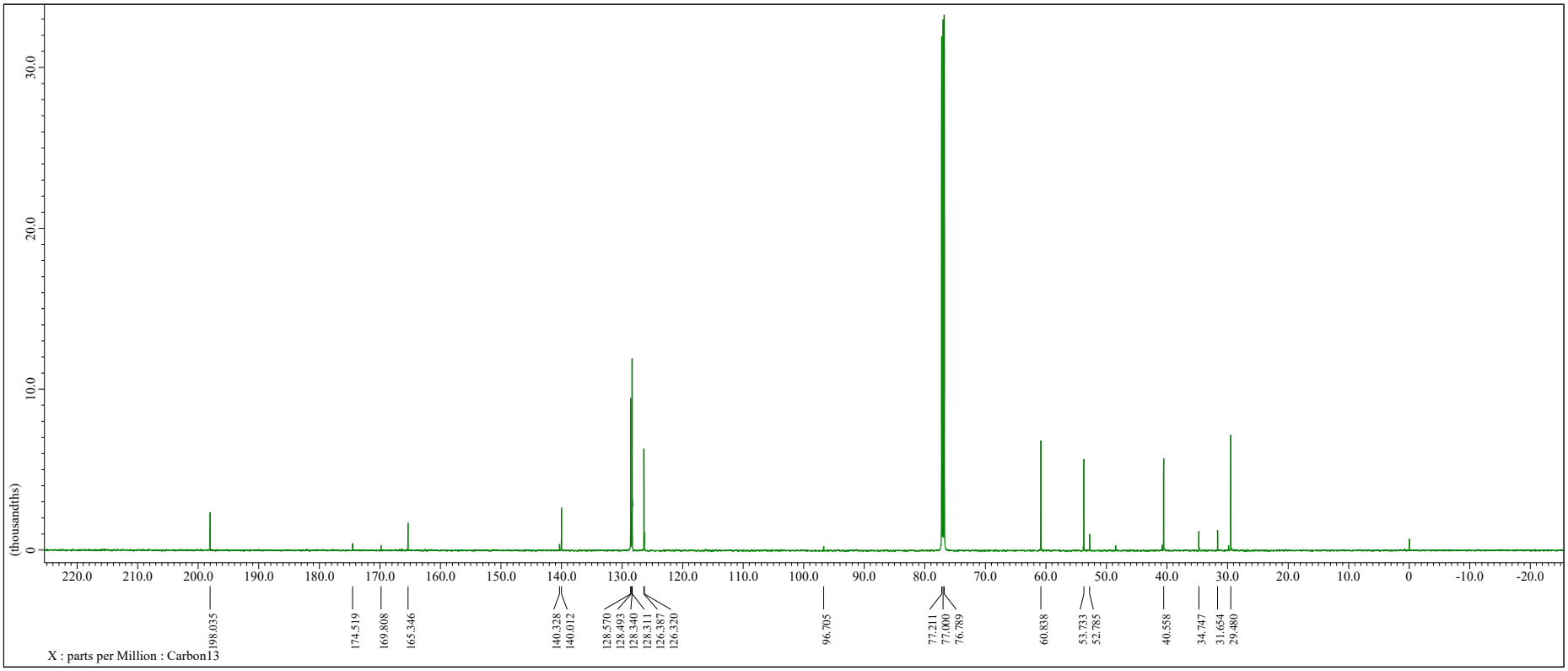
^{1}H NMR (600 MHz, $CDCl_3$)



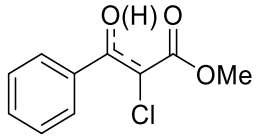
Methyl 2-chloro-3-oxo-5-phenylpentanoate (3a)



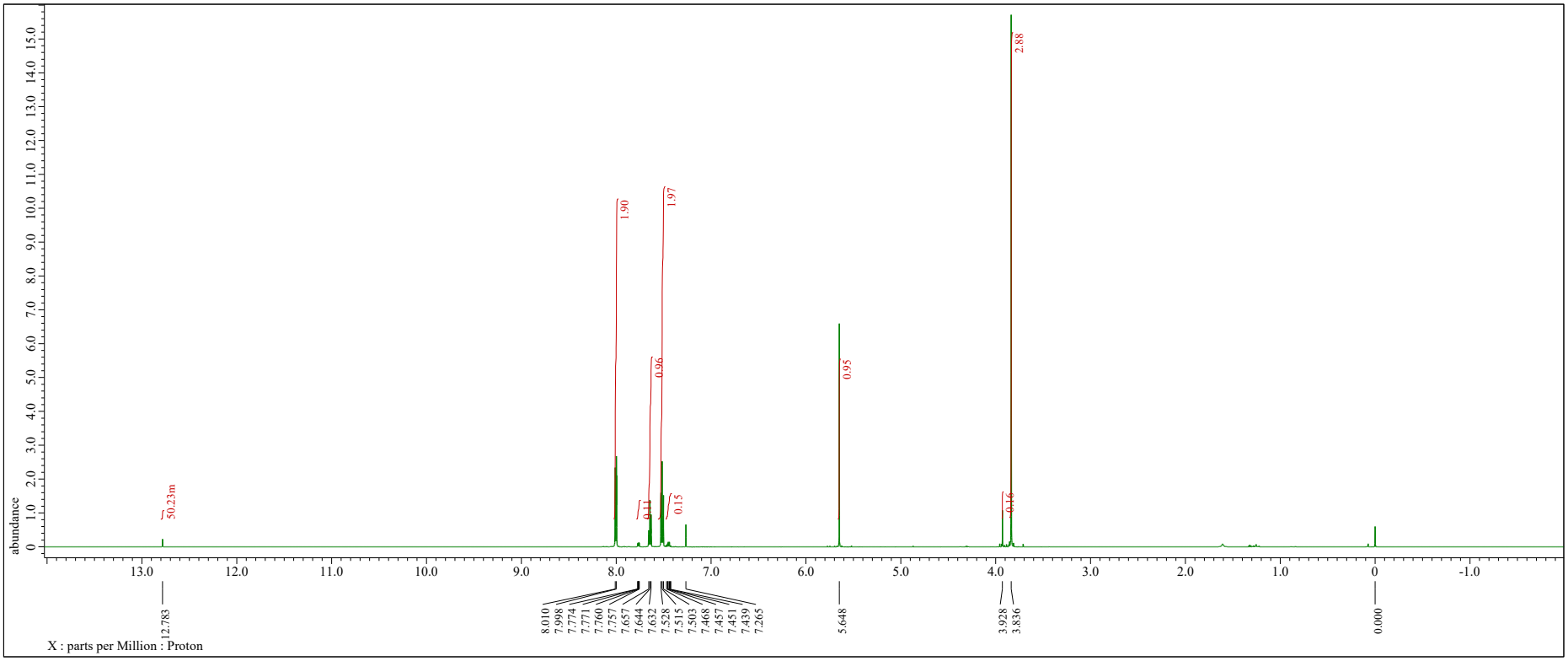
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



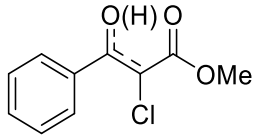
Methyl 2-chloro-3-oxo-3-phenylpropanoate (3b)



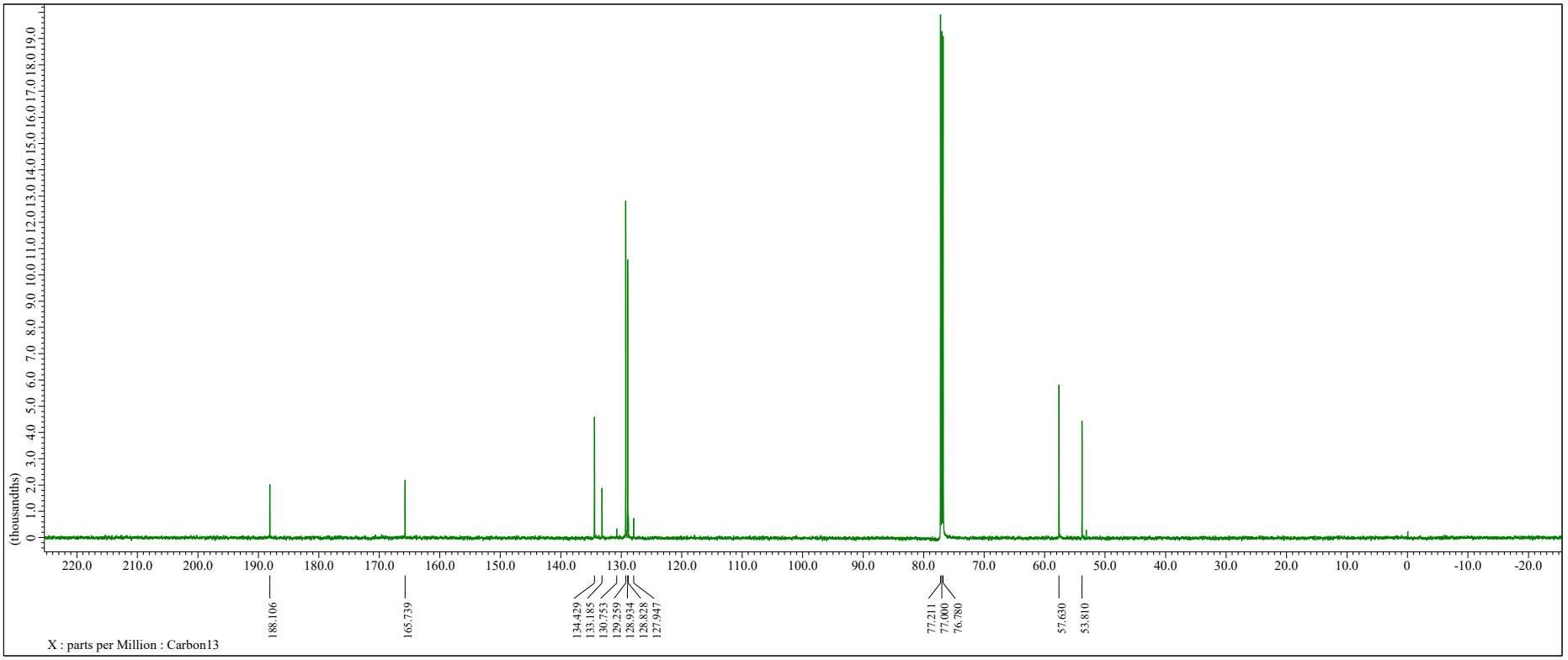
^{1}H NMR (600 MHz, $CDCl_3$)



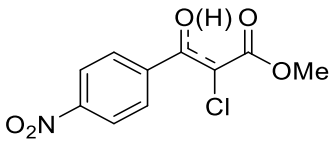
Methyl 2-chloro-3-oxo-3-phenylpropanoate (3b)



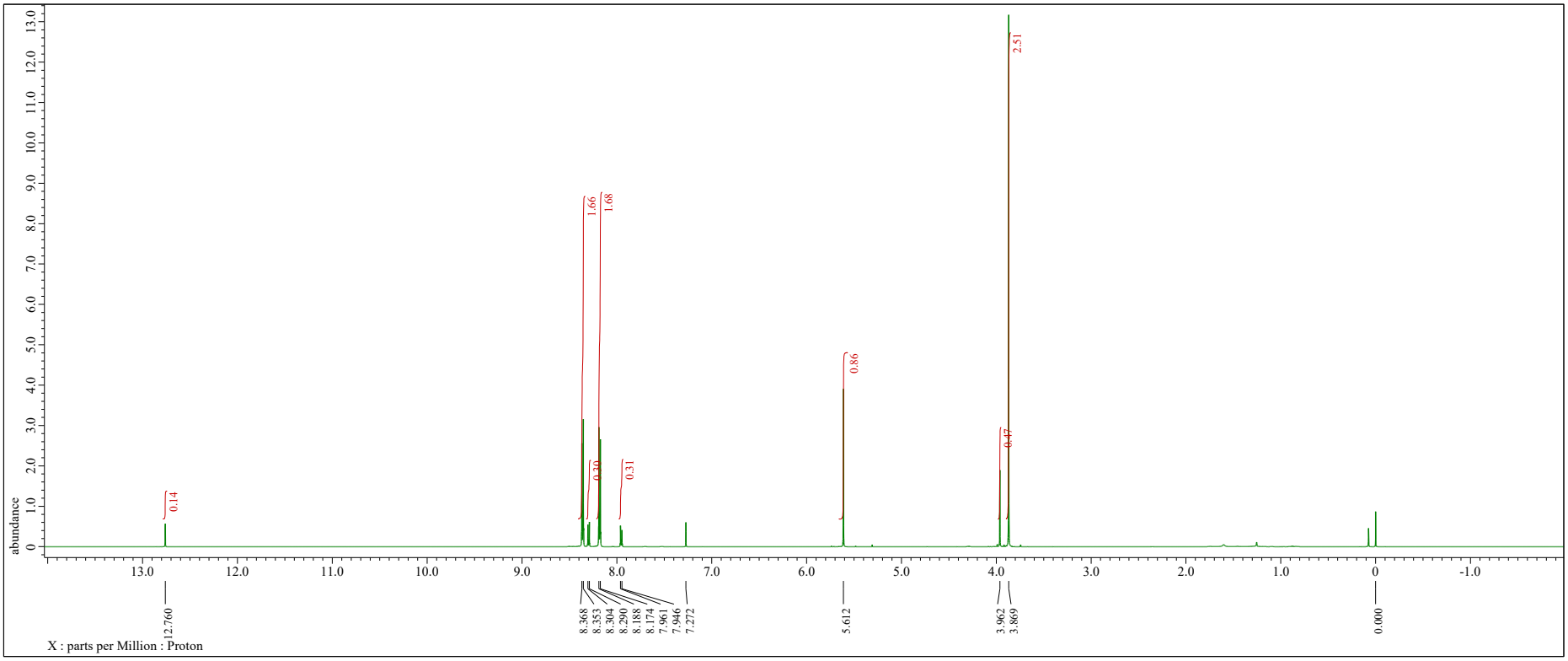
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



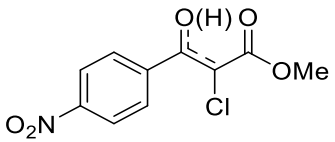
Methyl 2-chloro-3-(4-nitrophenyl)-3-oxopropanoate (3c)



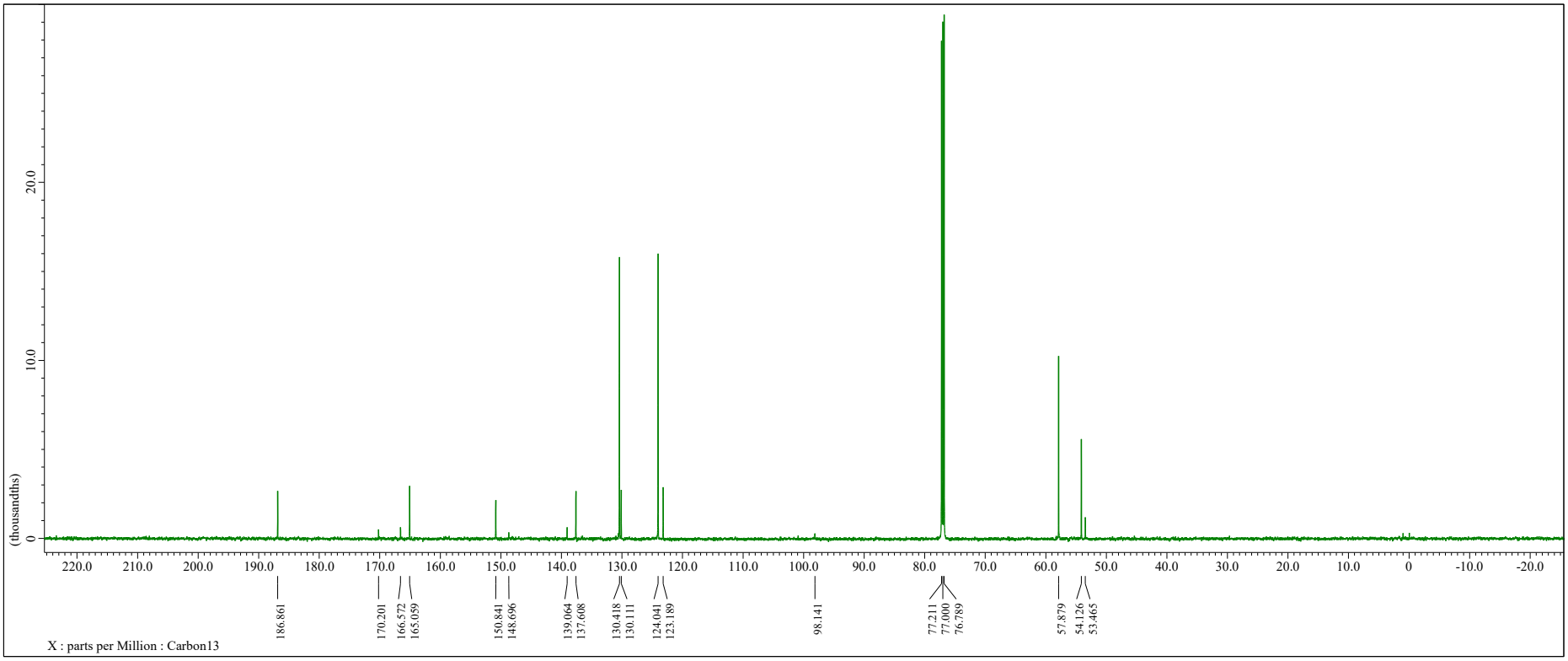
^{1}H NMR (600 MHz, $CDCl_3$)



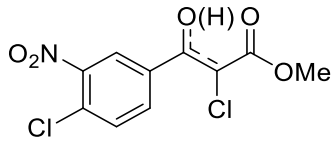
Methyl 2-chloro-3-(4-nitrophenyl)-3-oxopropanoate (3c)



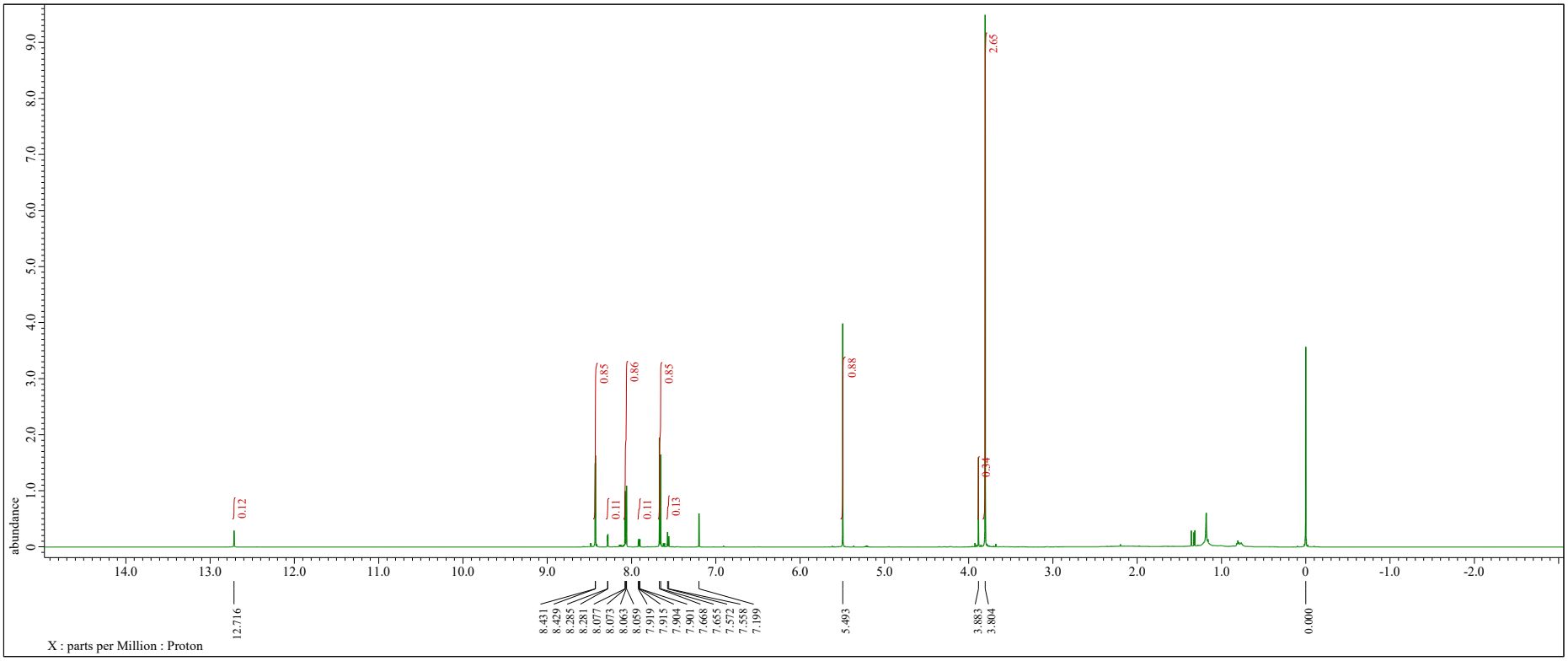
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



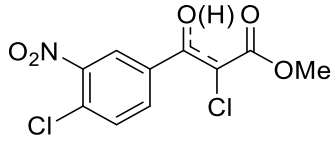
Methyl 2-chloro-3-(4-chloro-3-nitrophenyl)-3-oxopropanoate (3d)



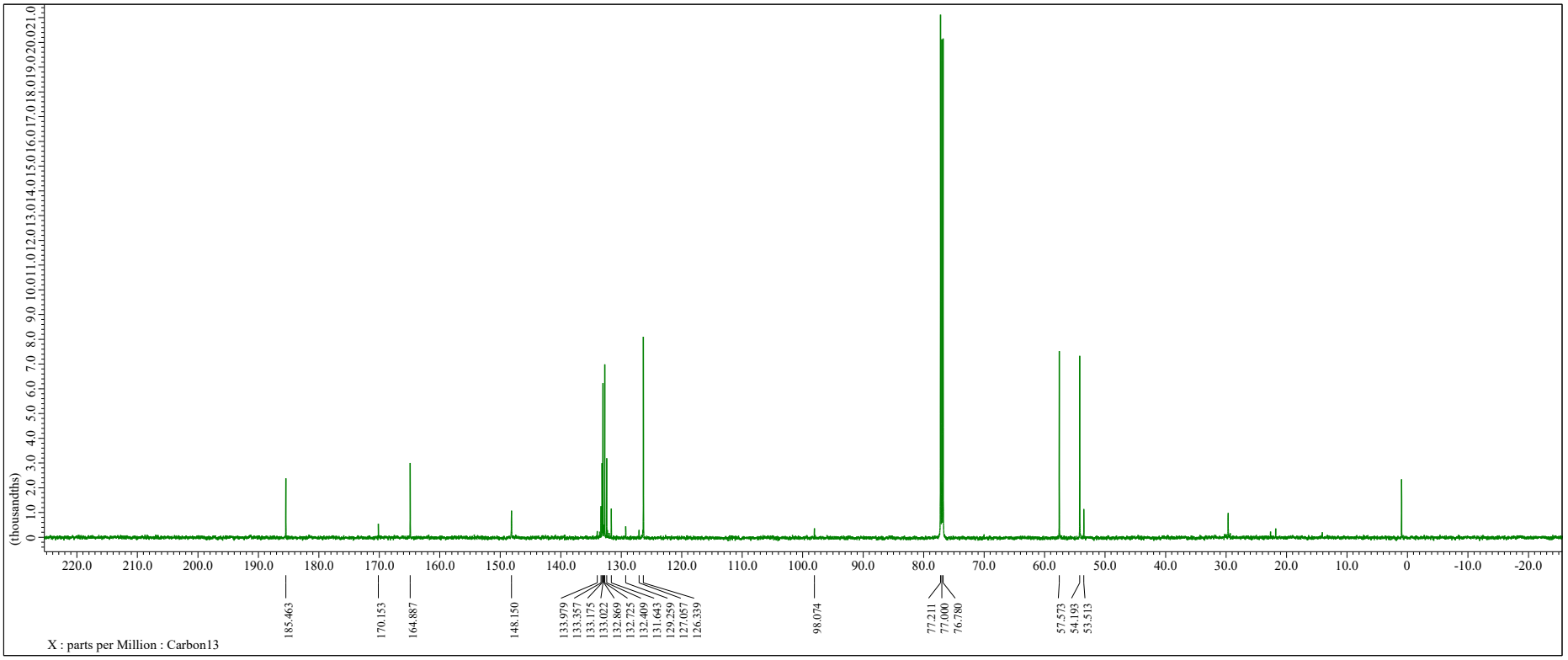
^{1}H NMR (600 MHz, $CDCl_3$)



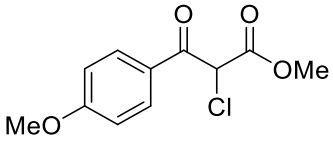
Methyl 2-chloro-3-(4-chloro-3-nitrophenyl)-3-oxopropanoate (3d)



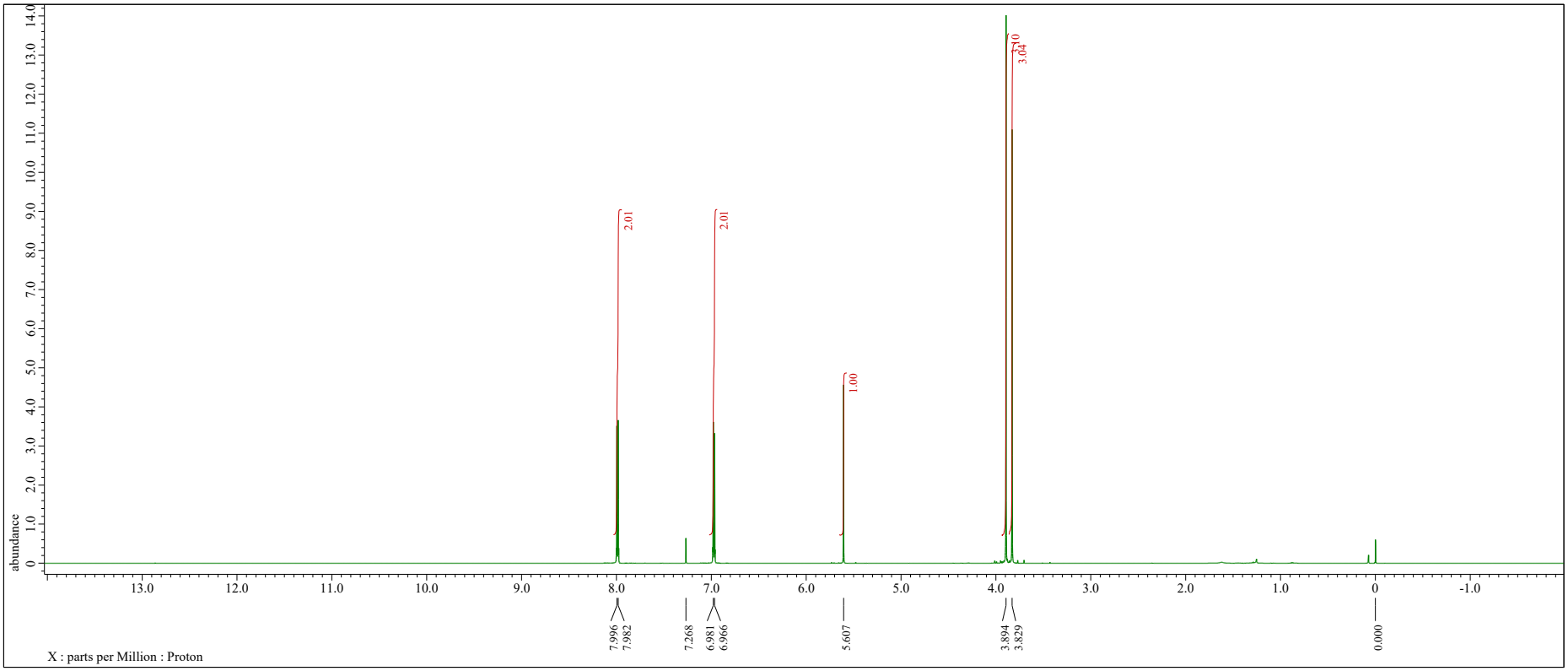
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



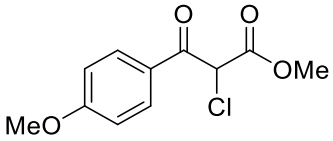
Methyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropanoate (3e)



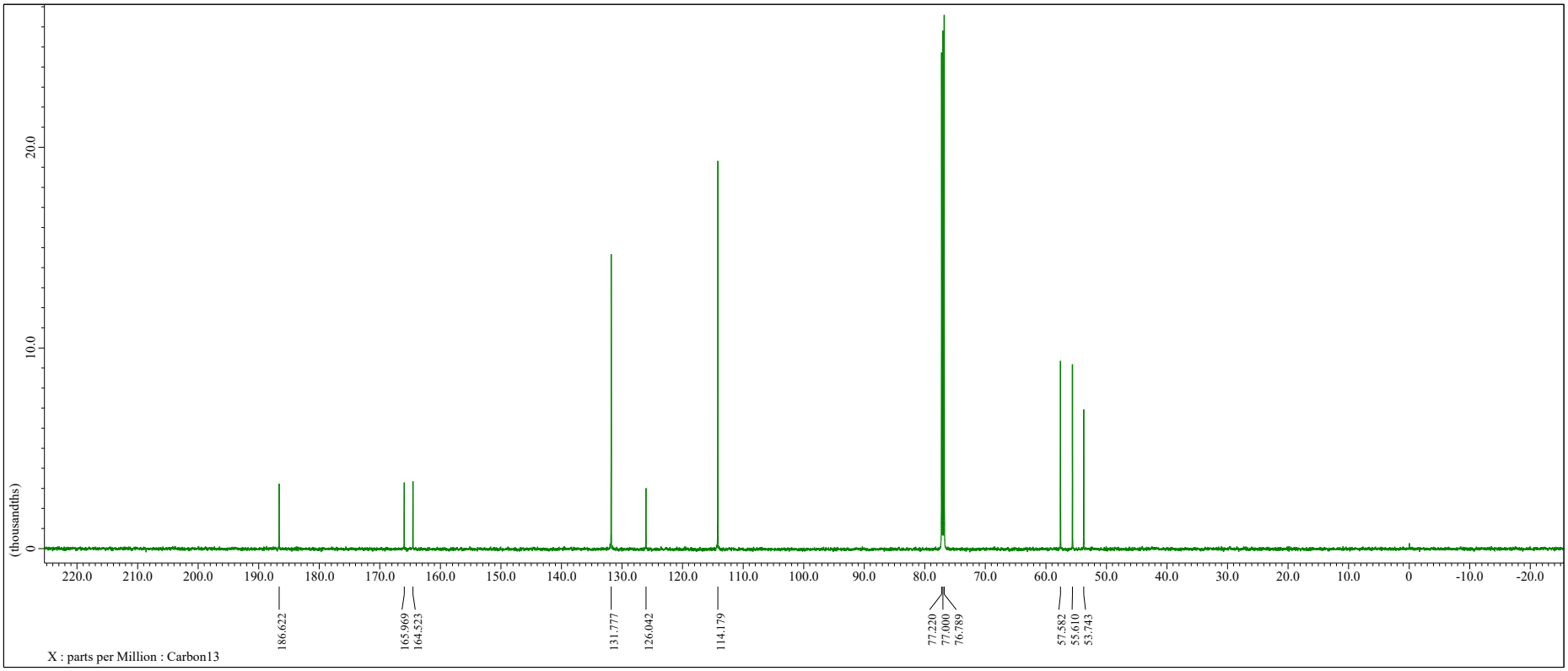
^{1}H NMR (600 MHz, $CDCl_3$)



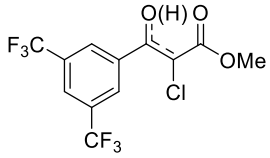
Methyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropanoate (3e)



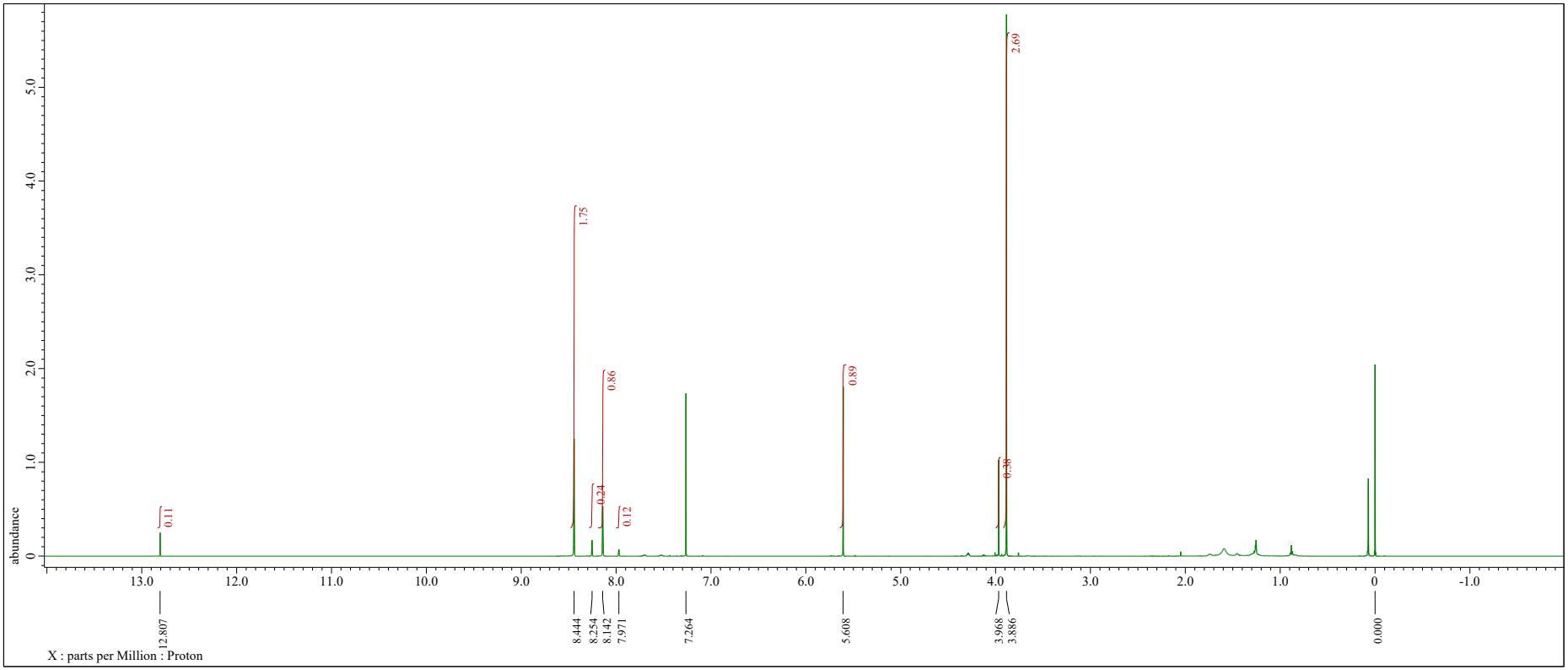
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



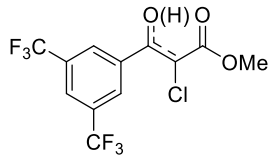
Methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2-chloro-3-oxopropanoate (3f)



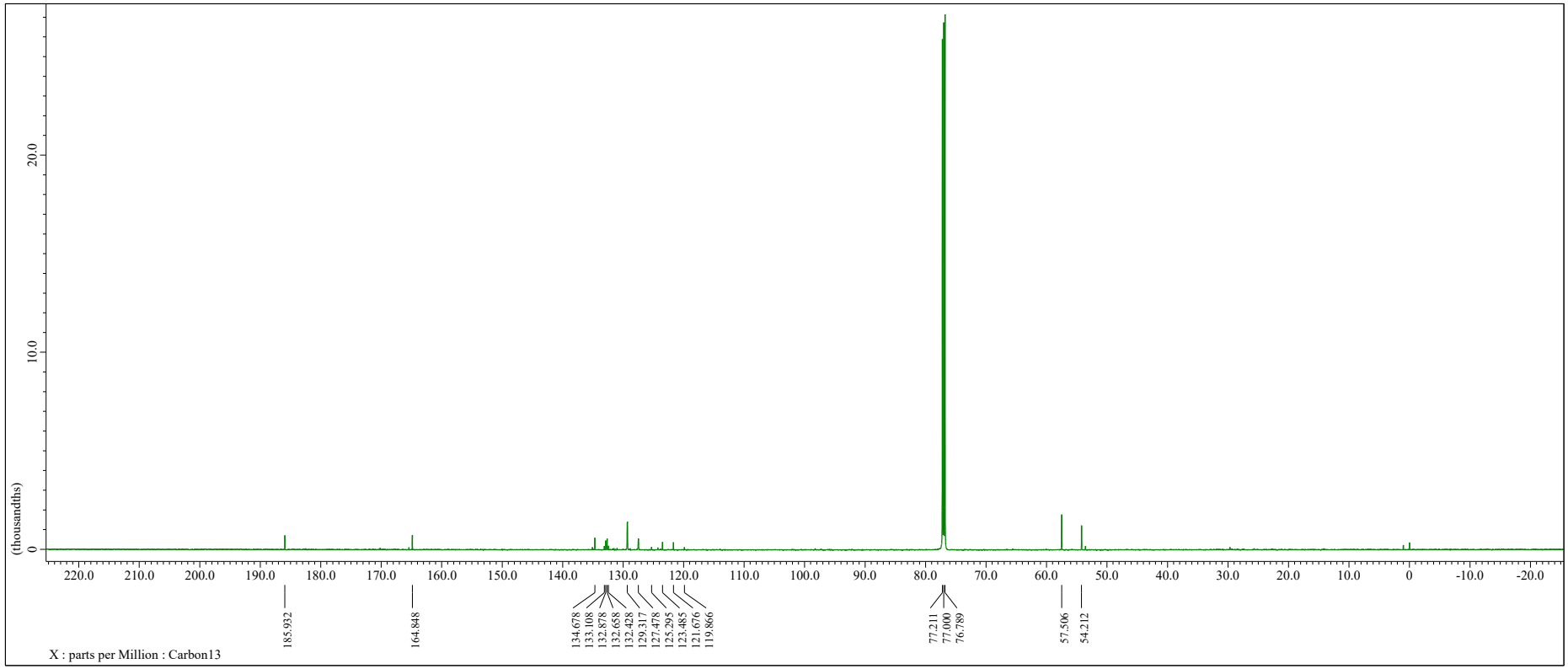
^{1}H NMR (600 MHz, $CDCl_3$)



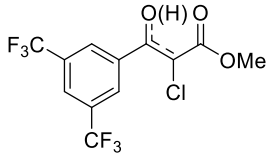
Methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2-chloro-3-oxopropanoate (3f)



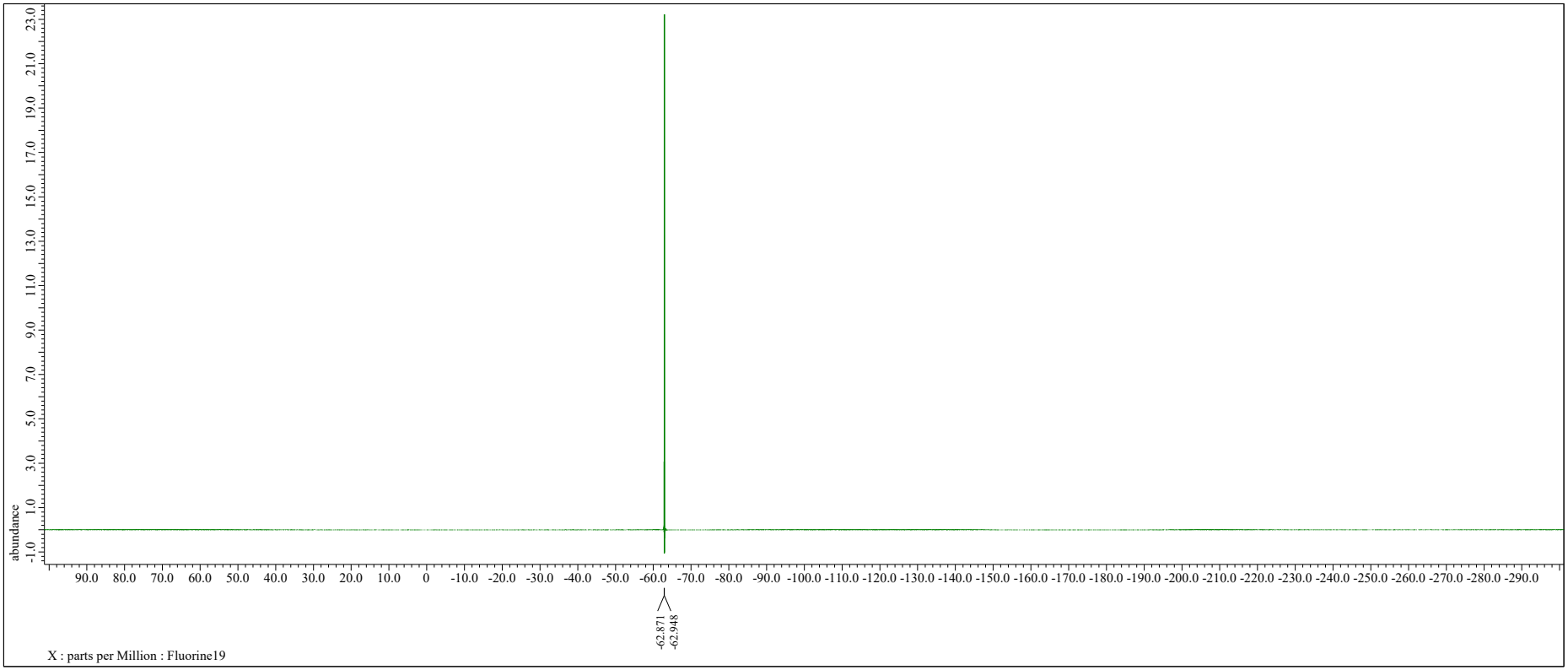
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



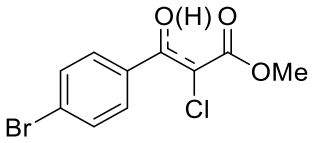
Methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2-chloro-3-oxopropanoate (3f)



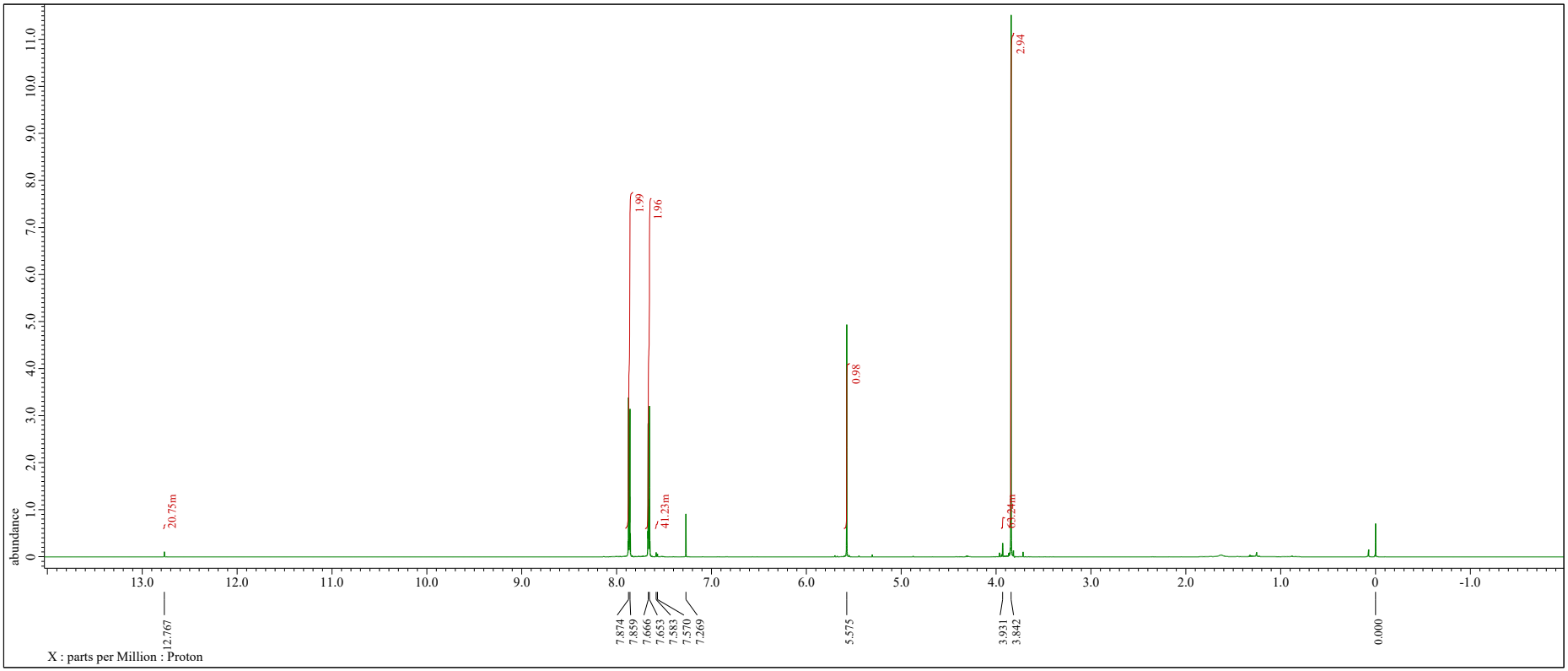
^{19}F NMR (564 MHz, $CDCl_3$)



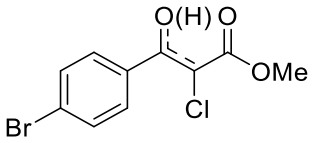
Methyl 3-(4-bromophenyl)-2-chloro-3-oxopropanoate (3g)



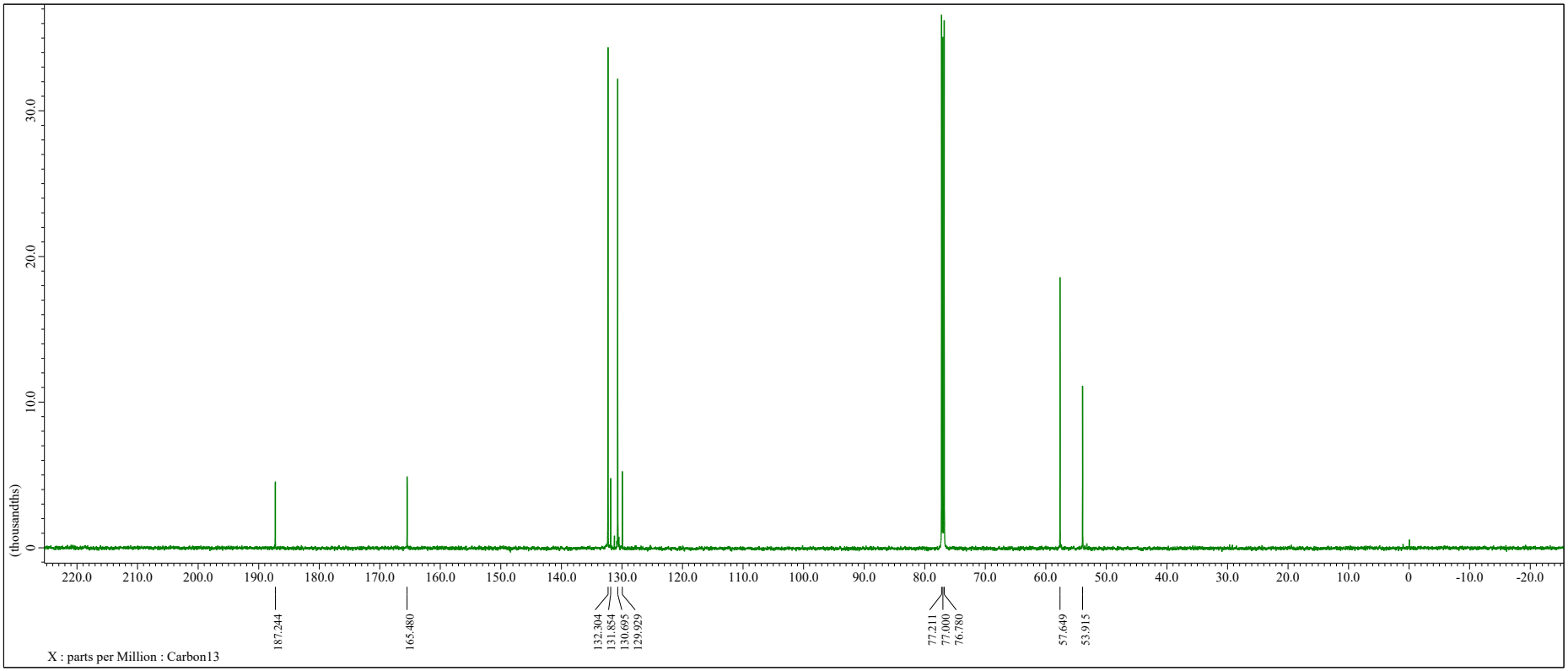
^{1}H NMR (600 MHz, $CDCl_3$)



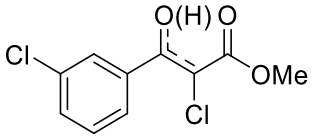
Methyl 3-(4-bromophenyl)-2-chloro-3-oxopropanoate (3g)



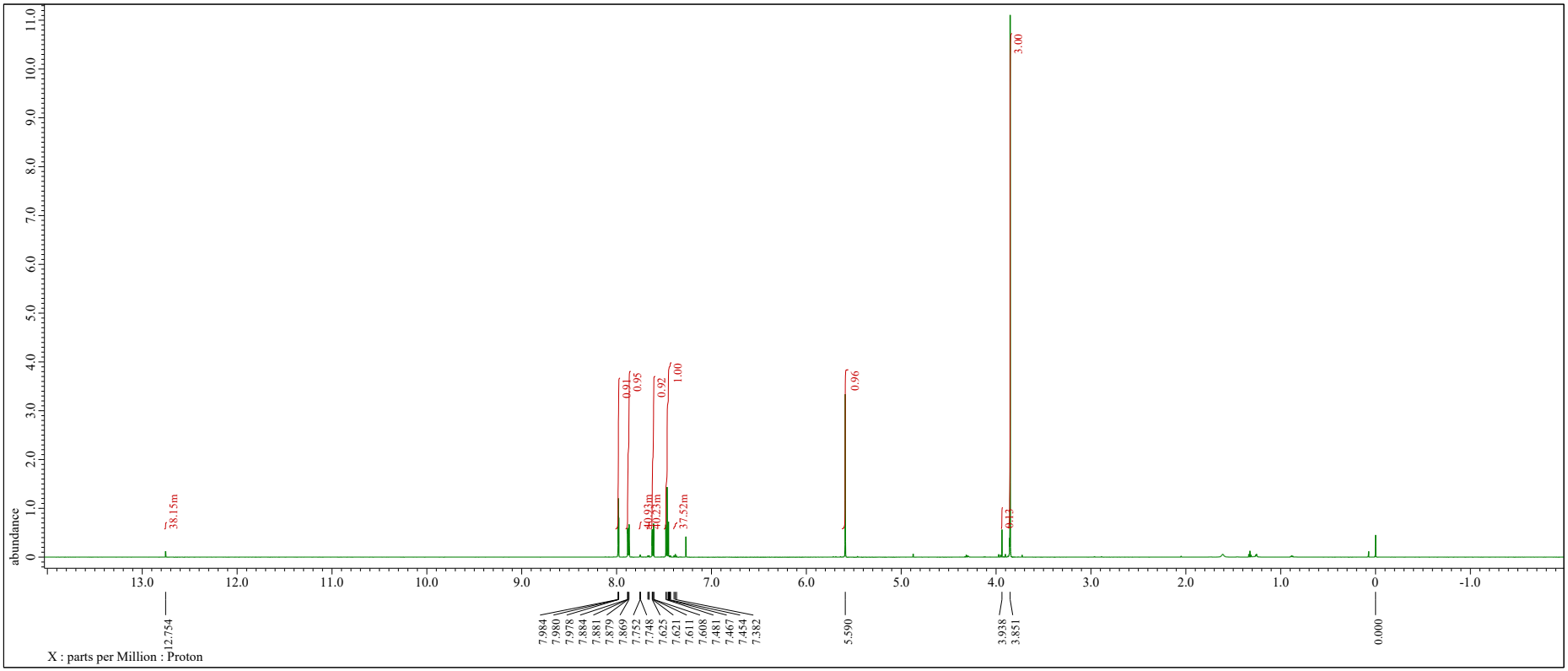
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



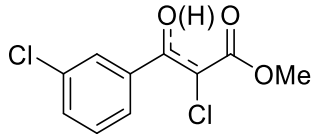
Methyl 2-chloro-3-(3-chlorophenyl)-3-oxopropanoate (3h)



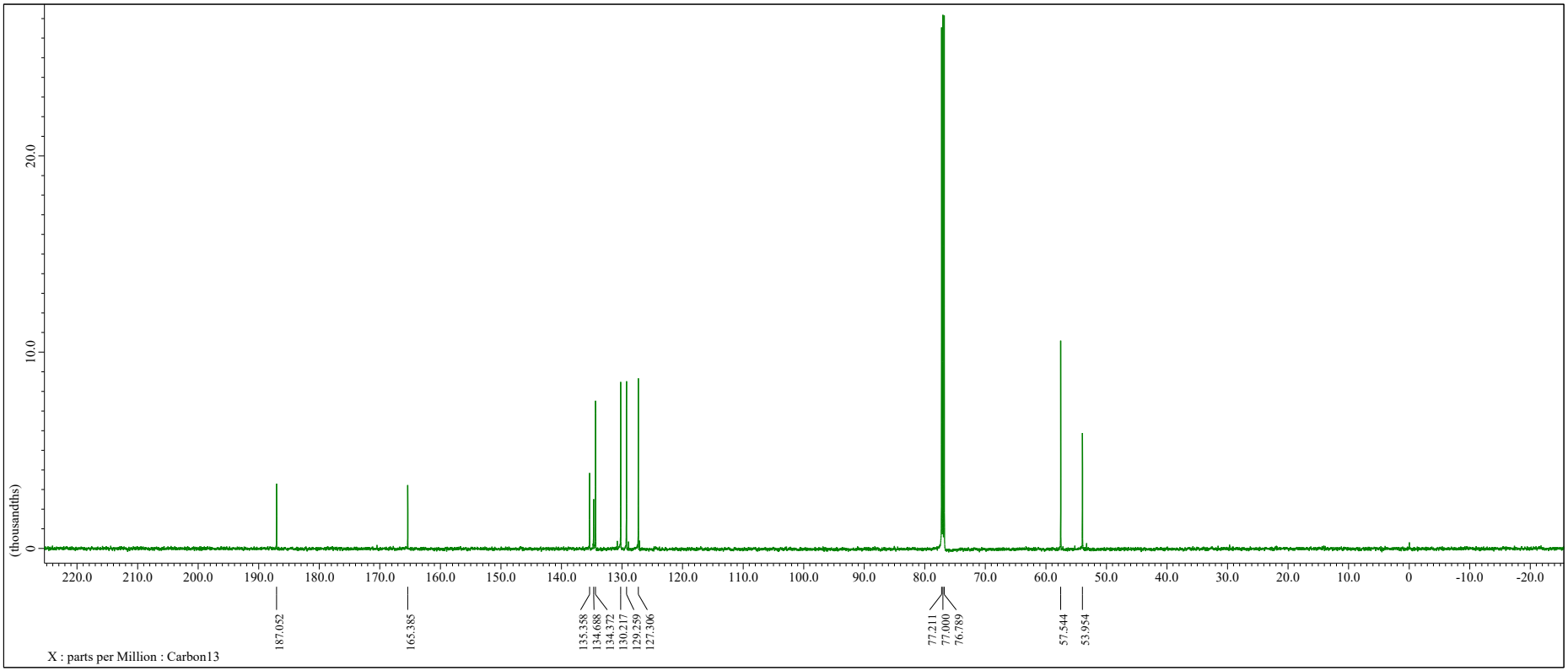
^{1}H NMR (600 MHz, $CDCl_3$)



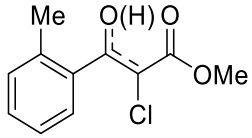
Methyl 2-chloro-3-(3-chlorophenyl)-3-oxopropanoate (3h)



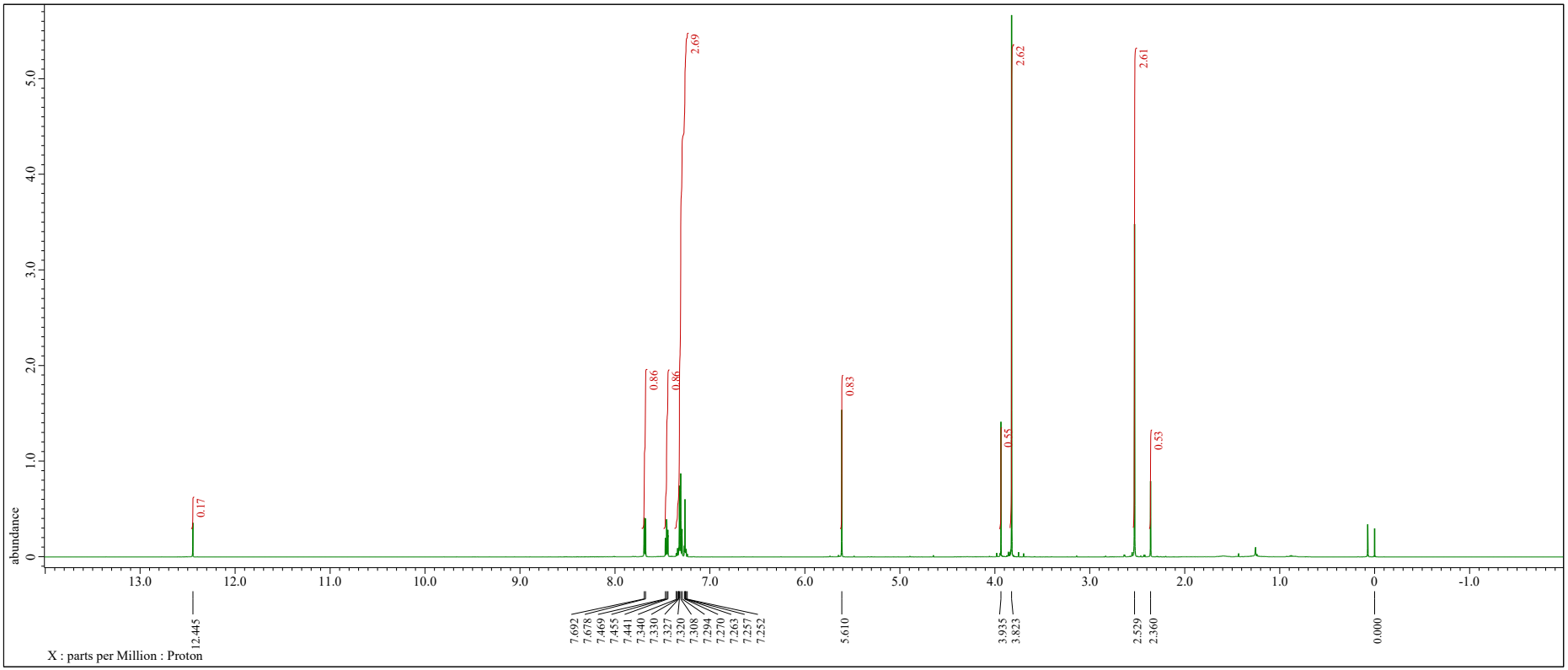
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



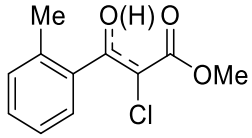
Methyl 2-chloro-3-oxo-3-(o-tolyl)propanoate (3i)



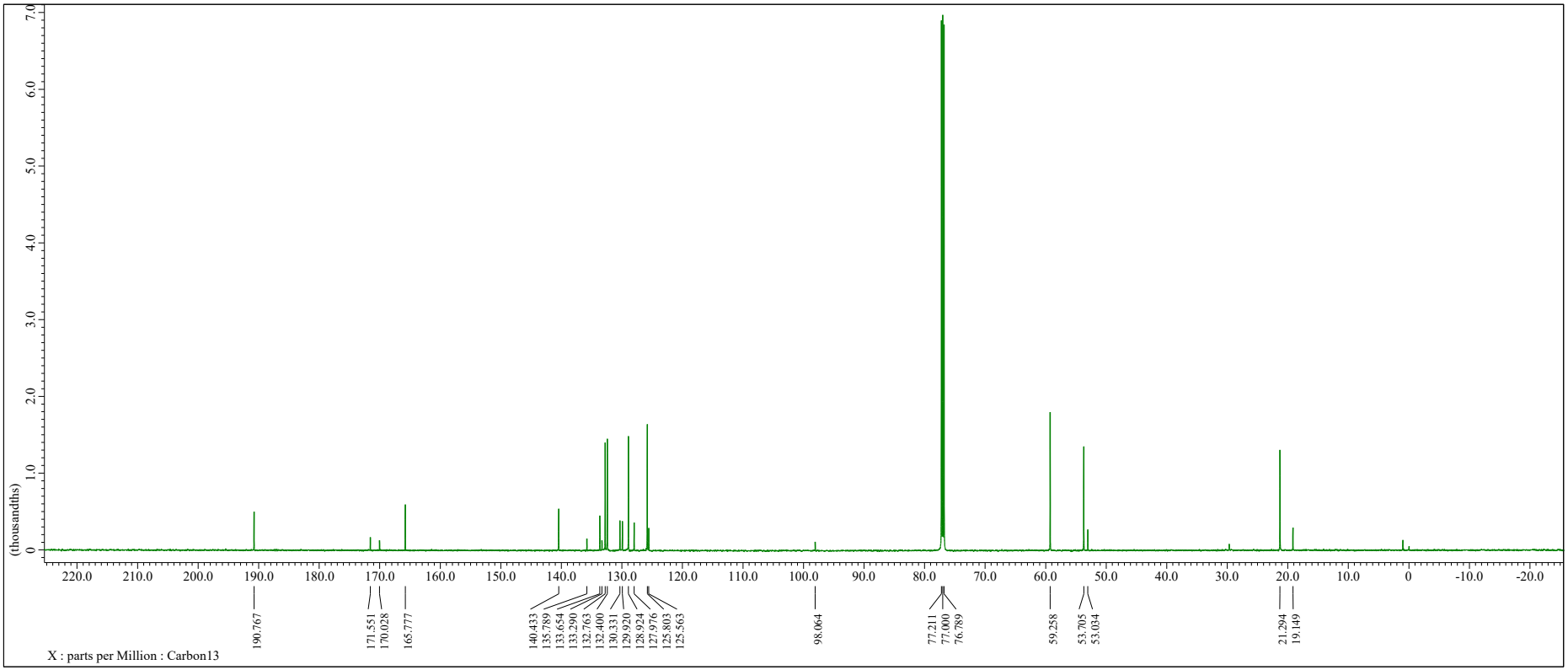
^{1}H NMR (600 MHz, $CDCl_3$)



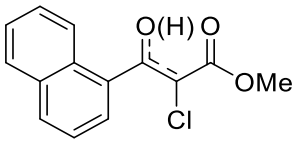
Methyl 2-chloro-3-oxo-3-(o-tolyl)propanoate (3i)



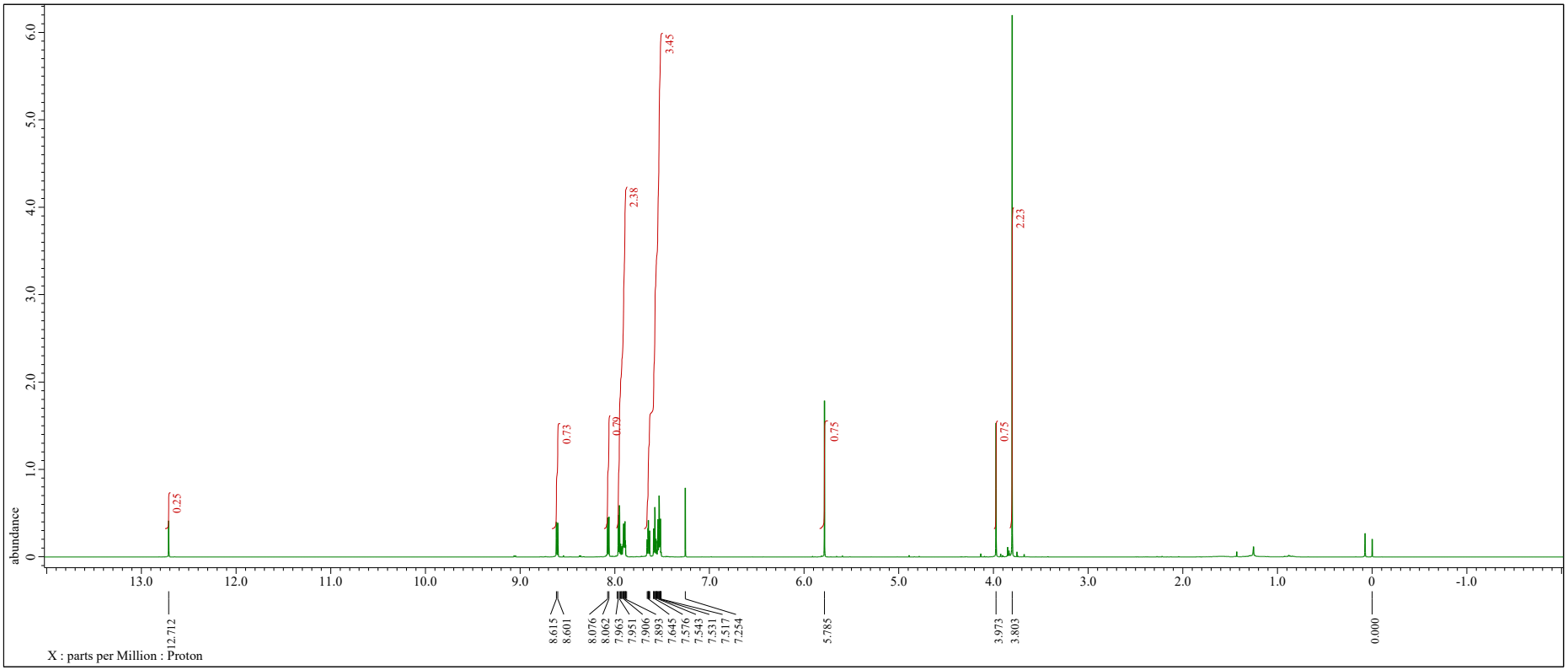
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



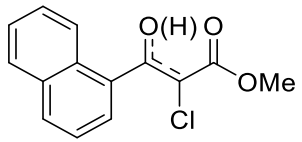
Methyl 2-chloro-3-(naphthalen-1-yl)-3-oxopropanoate (3j)



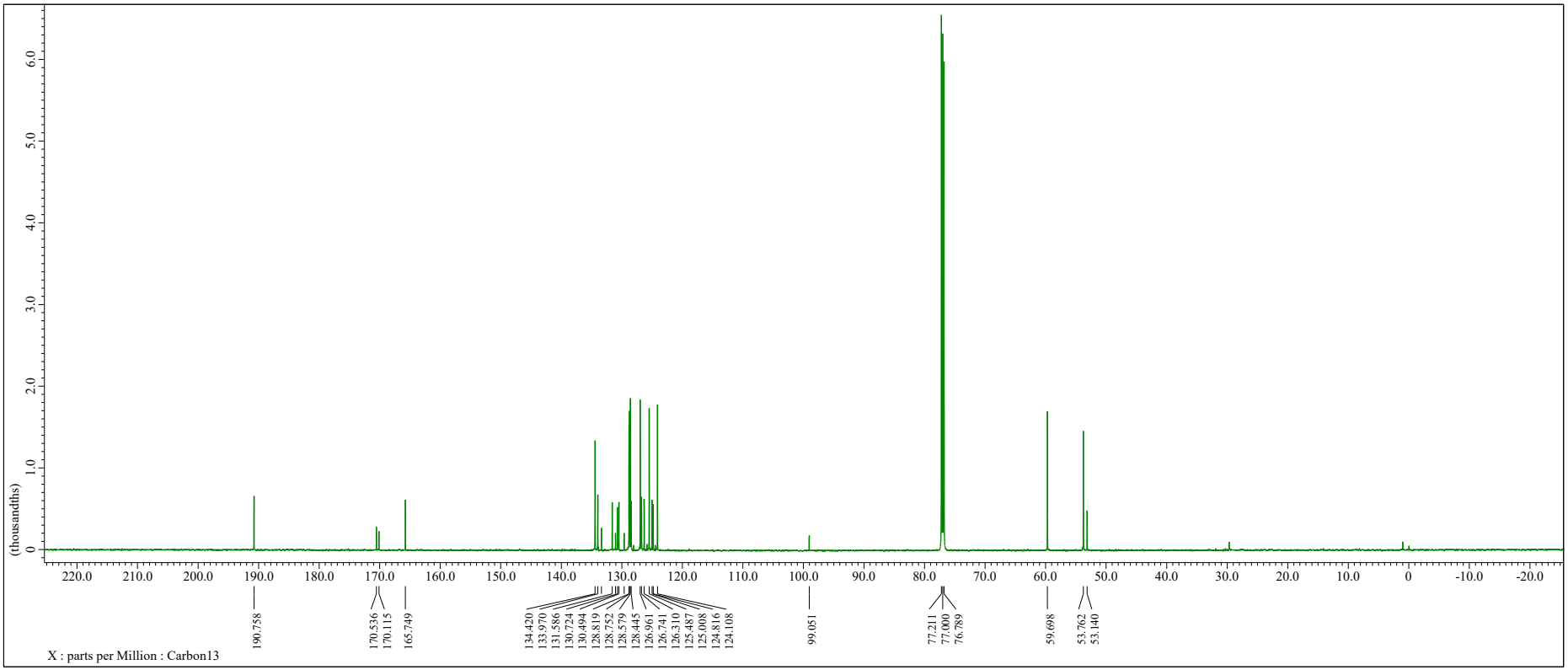
^{1}H NMR (600 MHz, $CDCl_3$)



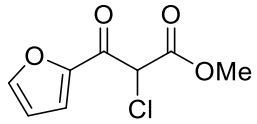
Methyl 2-chloro-3-(naphthalen-1-yl)-3-oxopropanoate (3j)



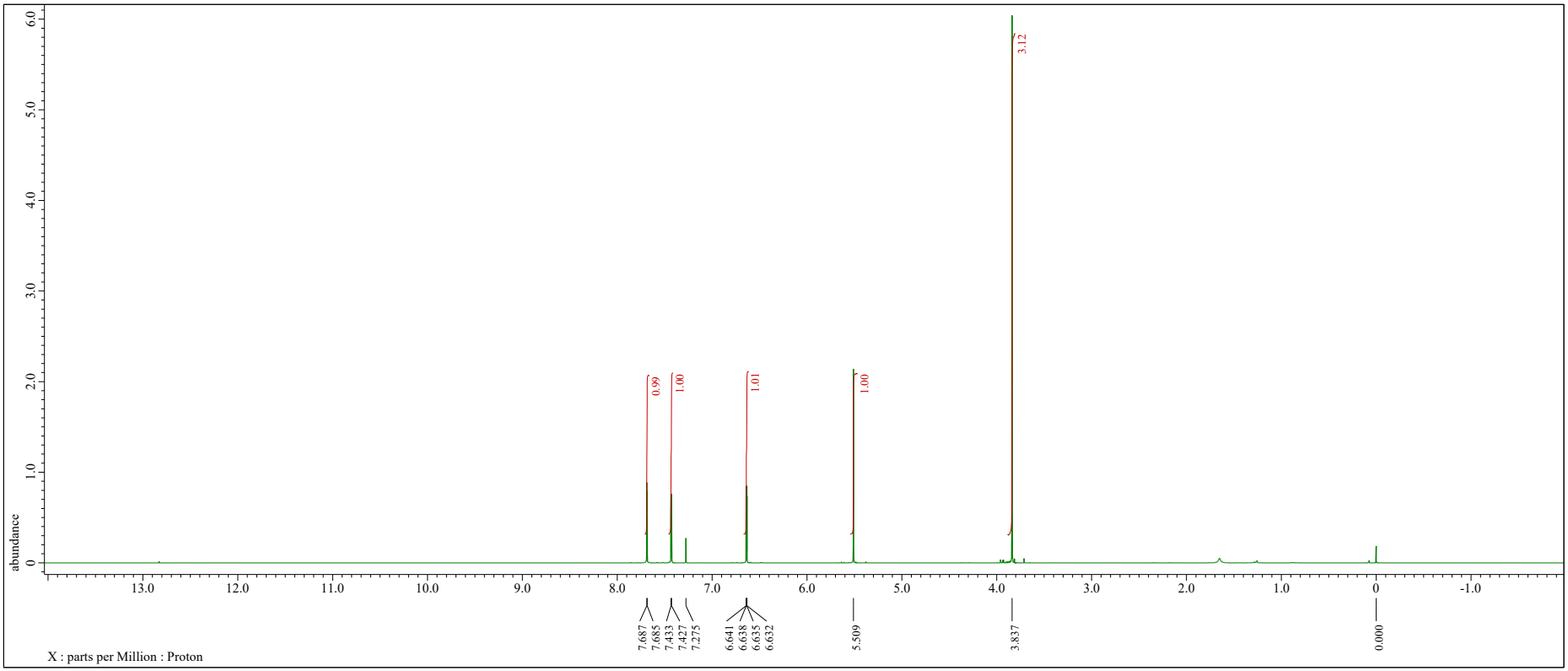
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



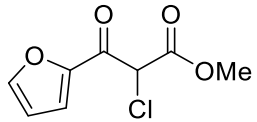
Methyl 2-chloro-3-(furan-2-yl)-3-oxopropanoate (3k)



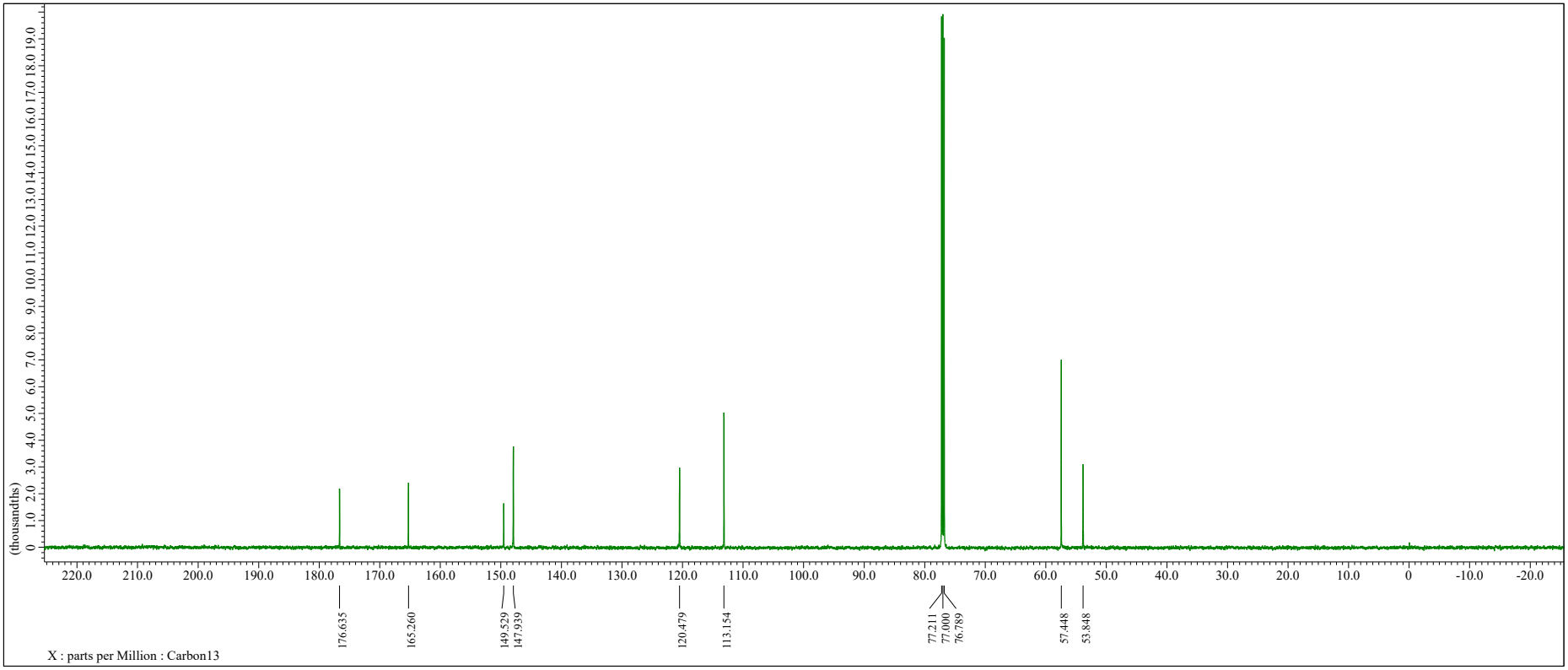
^{1}H NMR (600 MHz, $CDCl_3$)



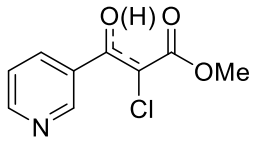
Methyl 2-chloro-3-(furan-2-yl)-3-oxopropanoate (3k)



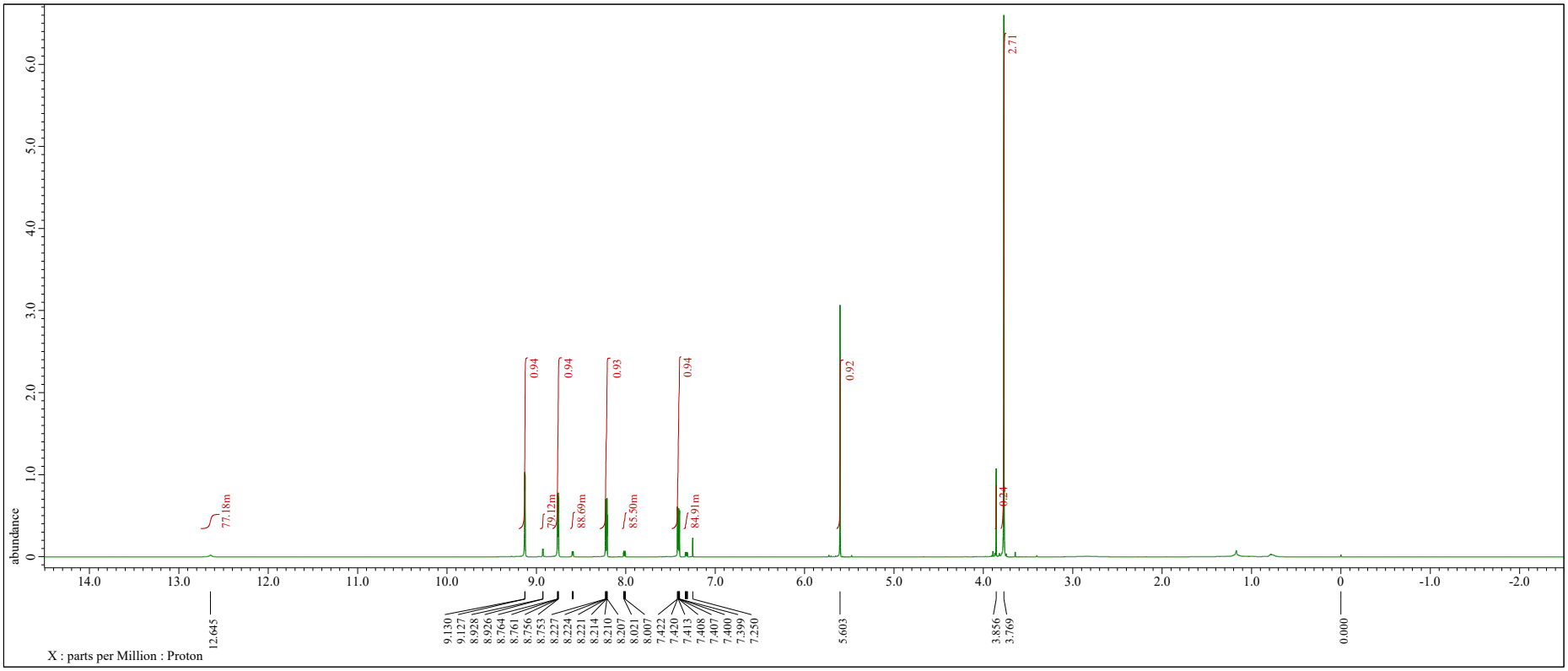
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



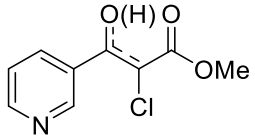
Methyl 2-chloro-3-oxo-3-(pyridin-3-yl)propanoate (3l)



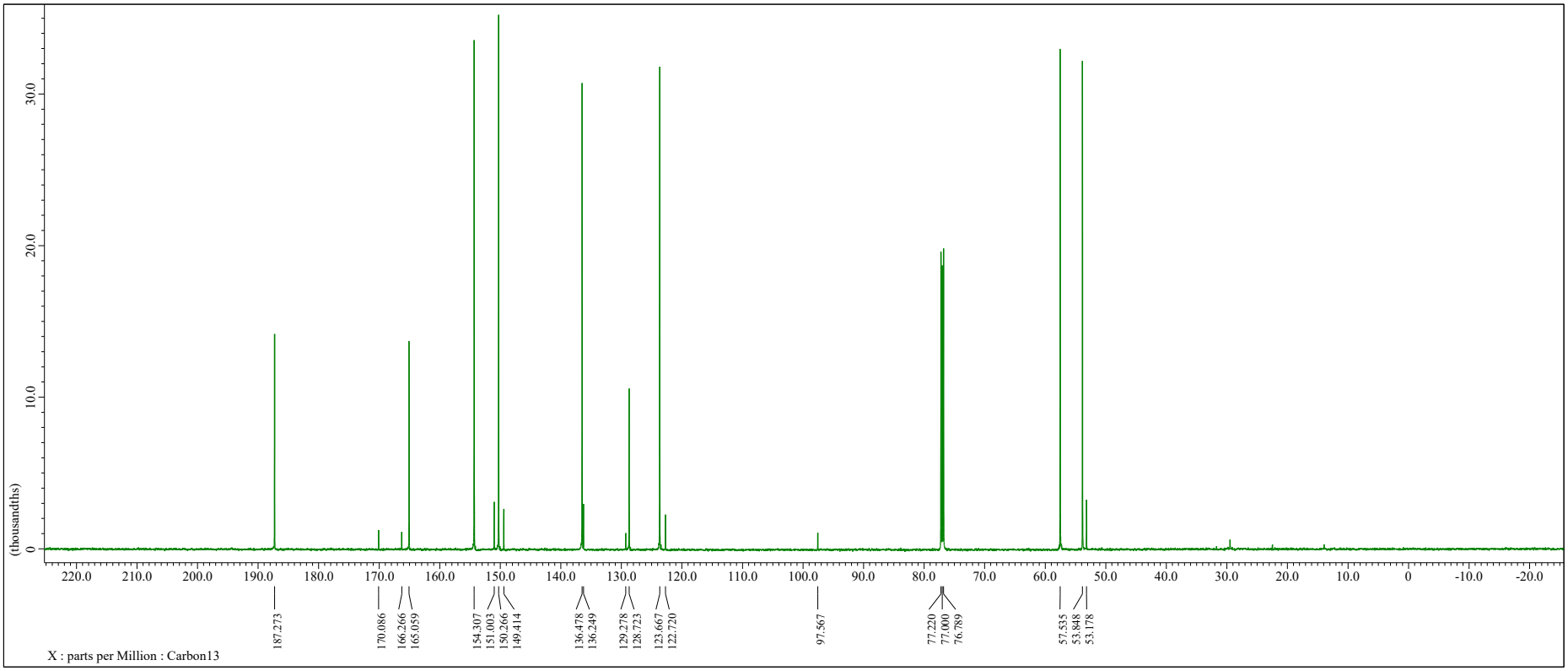
^{1}H NMR (600 MHz, $CDCl_3$)



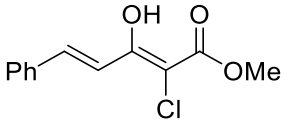
Methyl 2-chloro-3-oxo-3-(pyridin-3-yl)propanoate (3l)



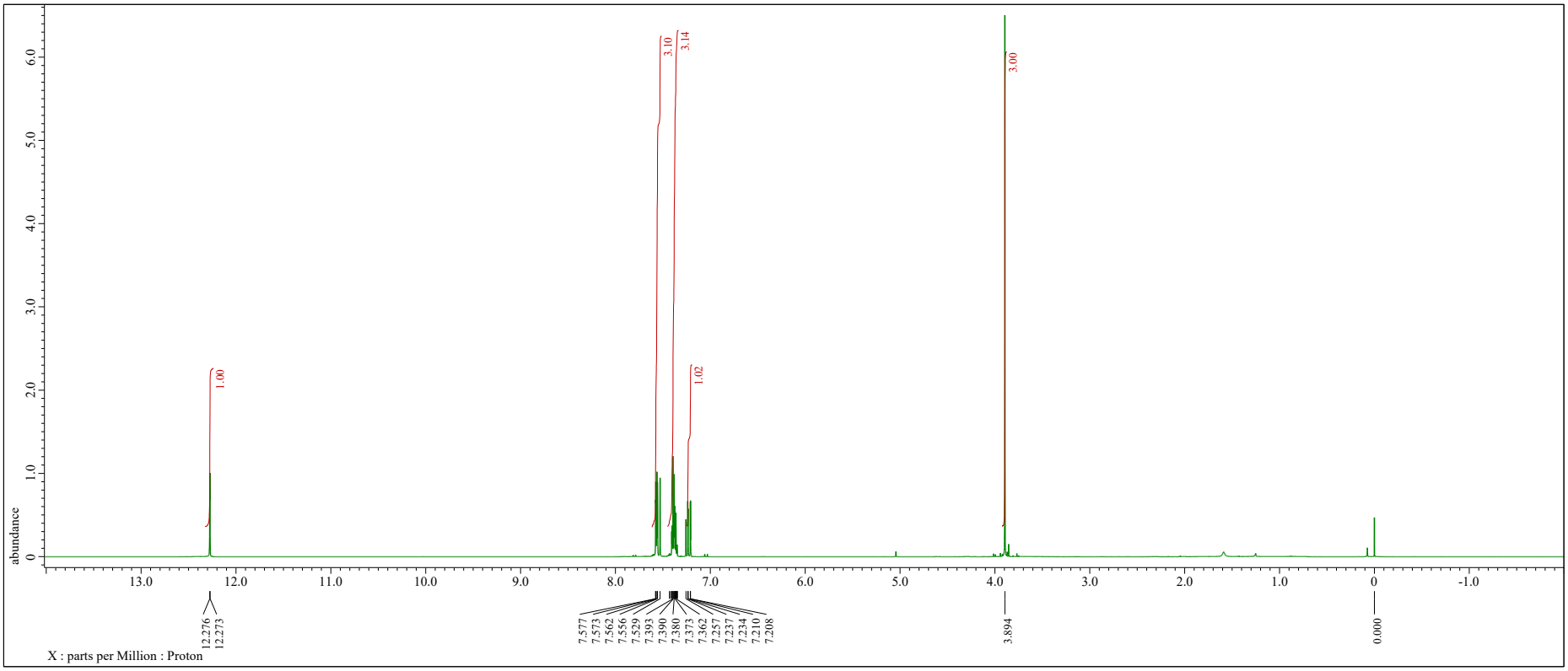
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



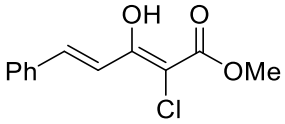
Methyl (2*E*,4*E*)-2-chloro-3-hydroxy-5-phenylpenta-2,4-dienoate (3m)



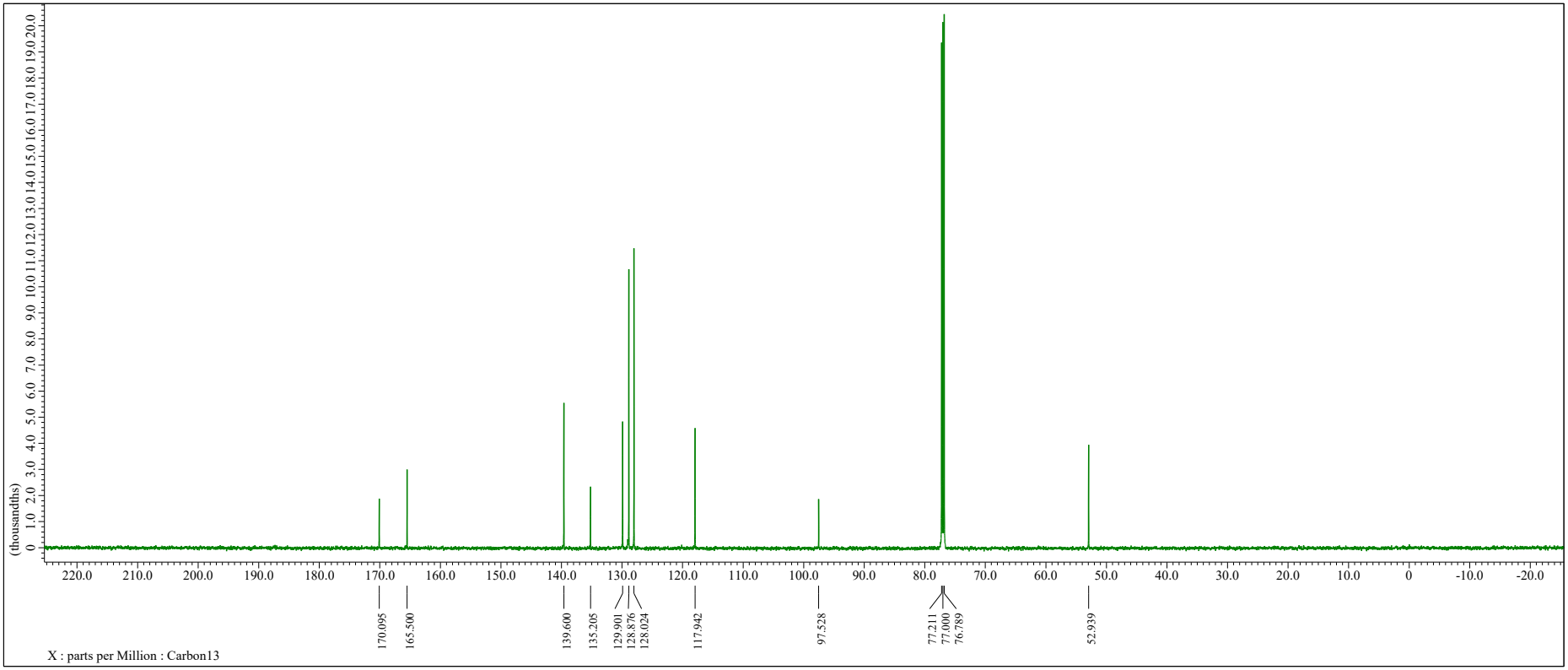
^{1}H NMR (600 MHz, $CDCl_3$)



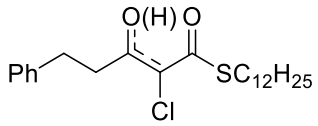
Methyl (2*E*,4*E*)-2-chloro-3-hydroxy-5-phenylpenta-2,4-dienoate (3m)



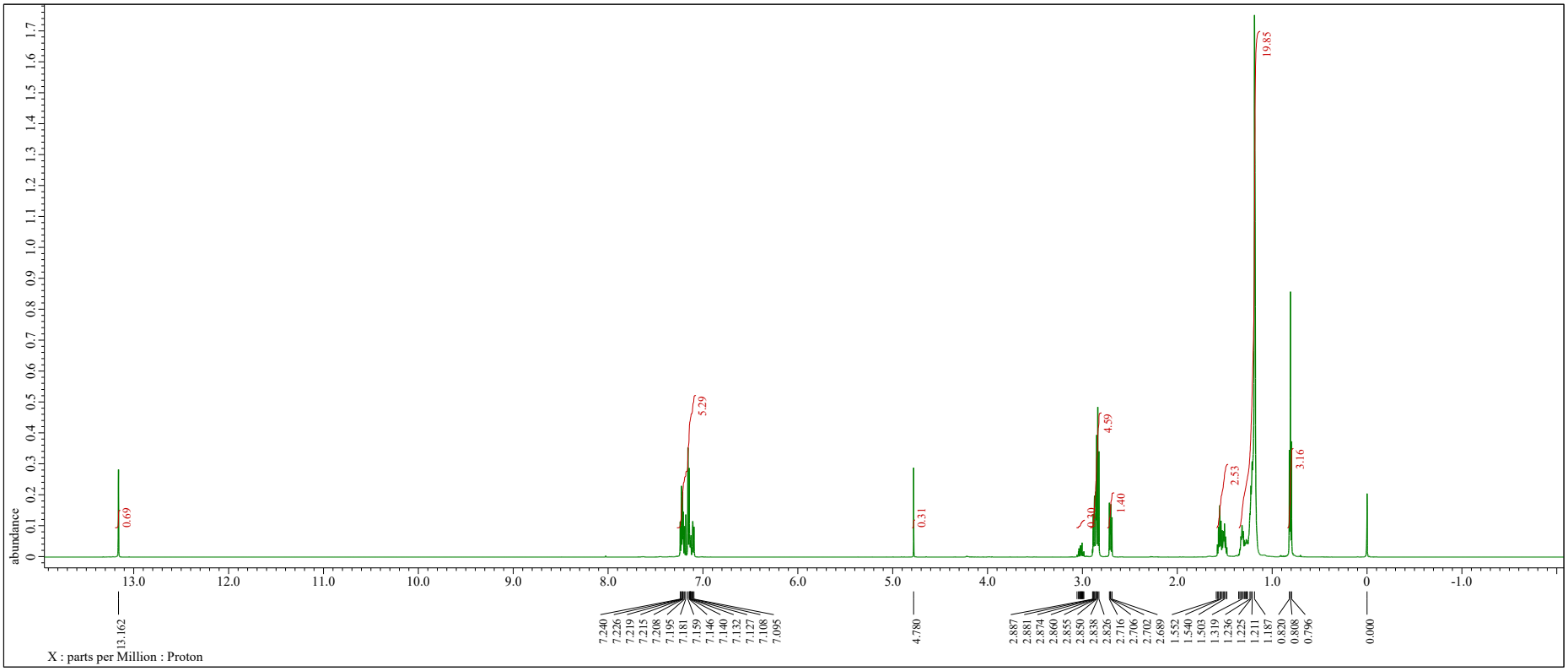
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



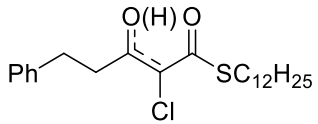
_S_-dodecyl (_E_)-2-chloro-3-hydroxy-5-phenylpent-2-enethioate (3n)



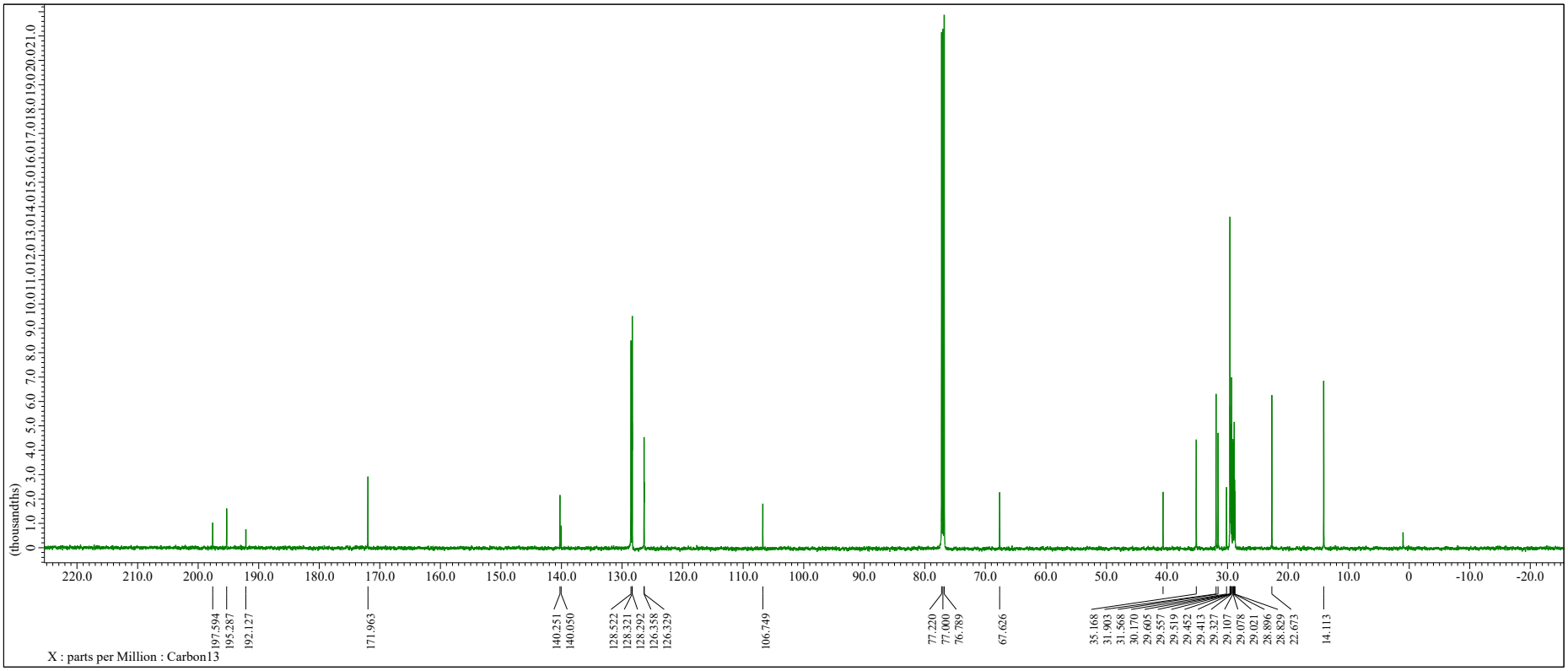
^{1}H NMR (600 MHz, $CDCl_3$)



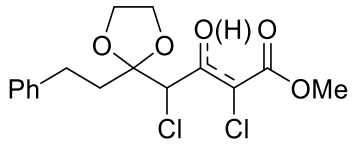
_S_-dodecyl (_E_)-2-chloro-3-hydroxy-5-phenylpent-2-enethioate (3n)



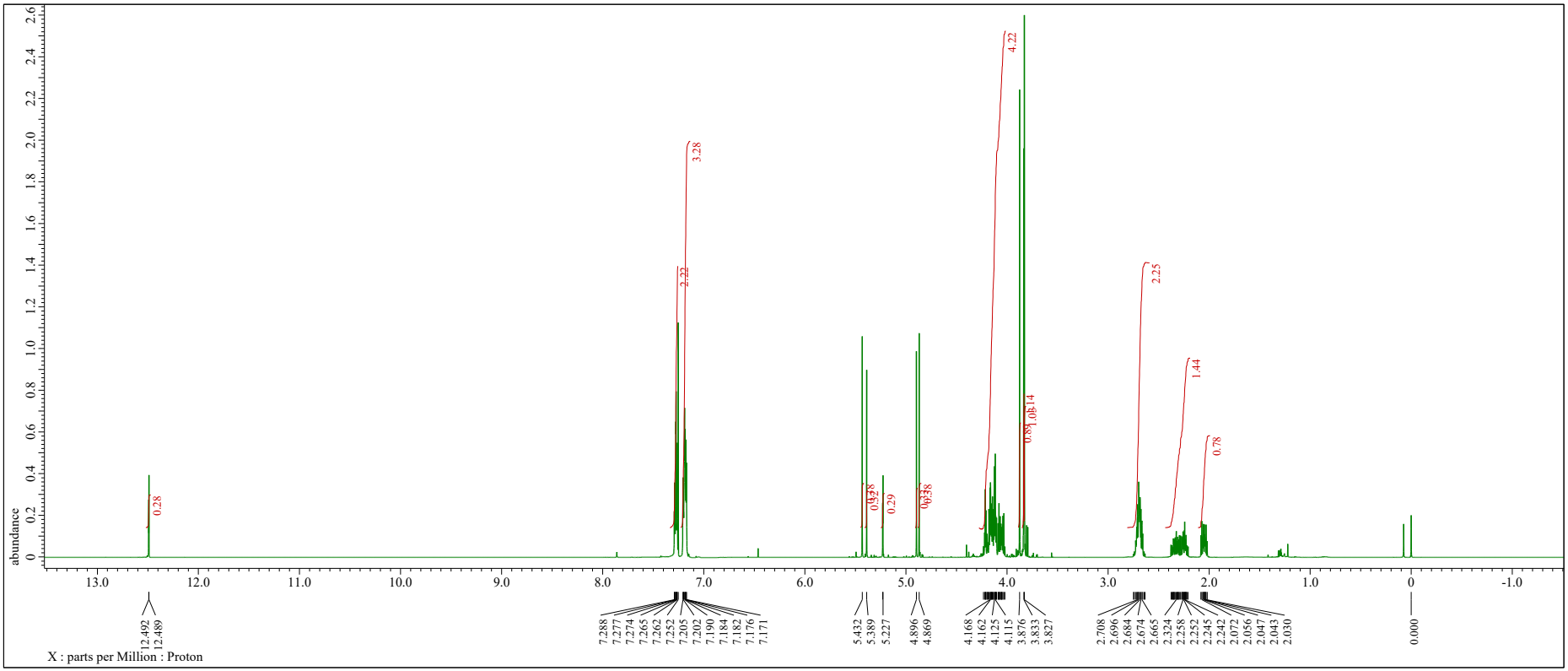
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



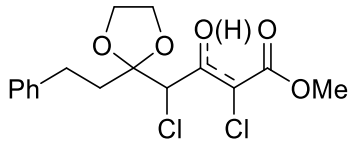
Methyl 2,4-dichloro-3-oxo-4-(2-phenethyl-1,3-dioxolan-2-yl)butanoate (3o)



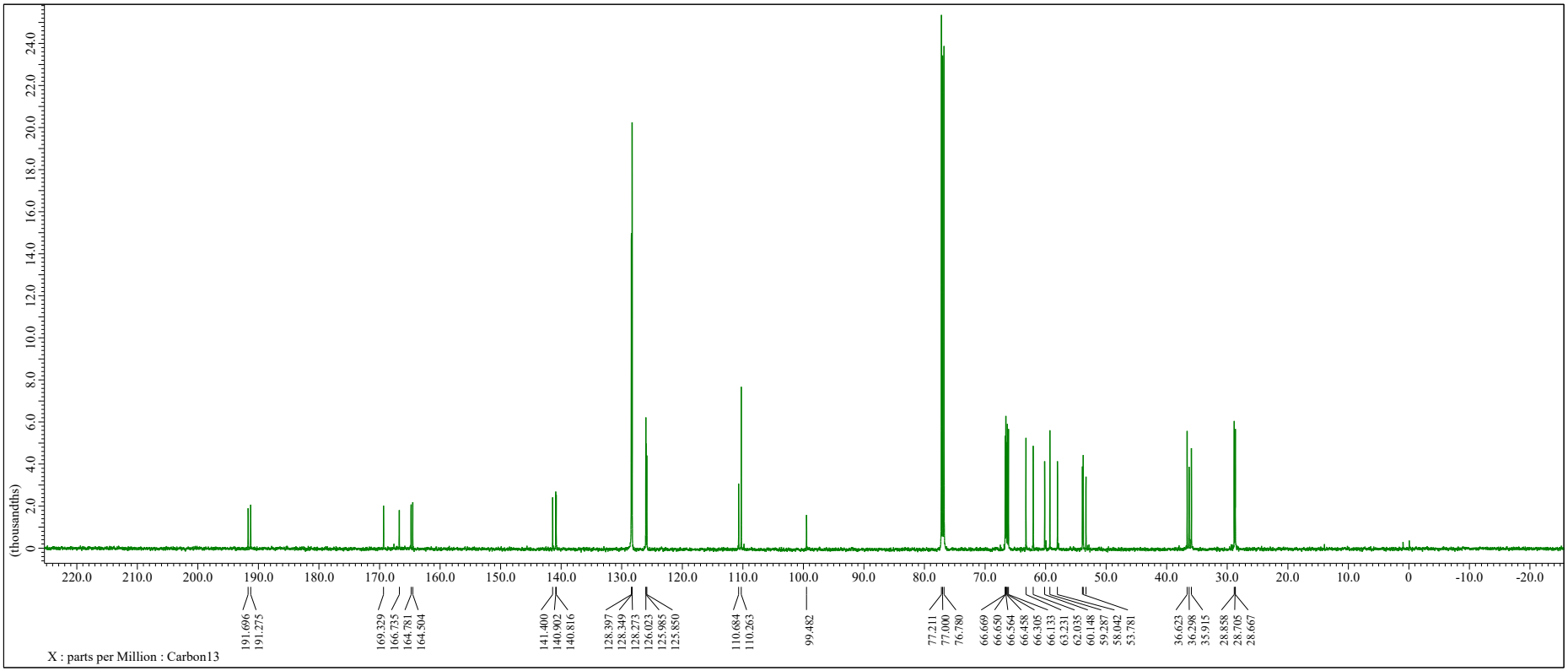
^{1}H NMR (600 MHz, $CDCl_3$)



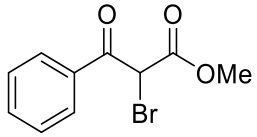
Methyl 2,4-dichloro-3-oxo-4-(2-phenethyl-1,3-dioxolan-2-yl)butanoate (3o)



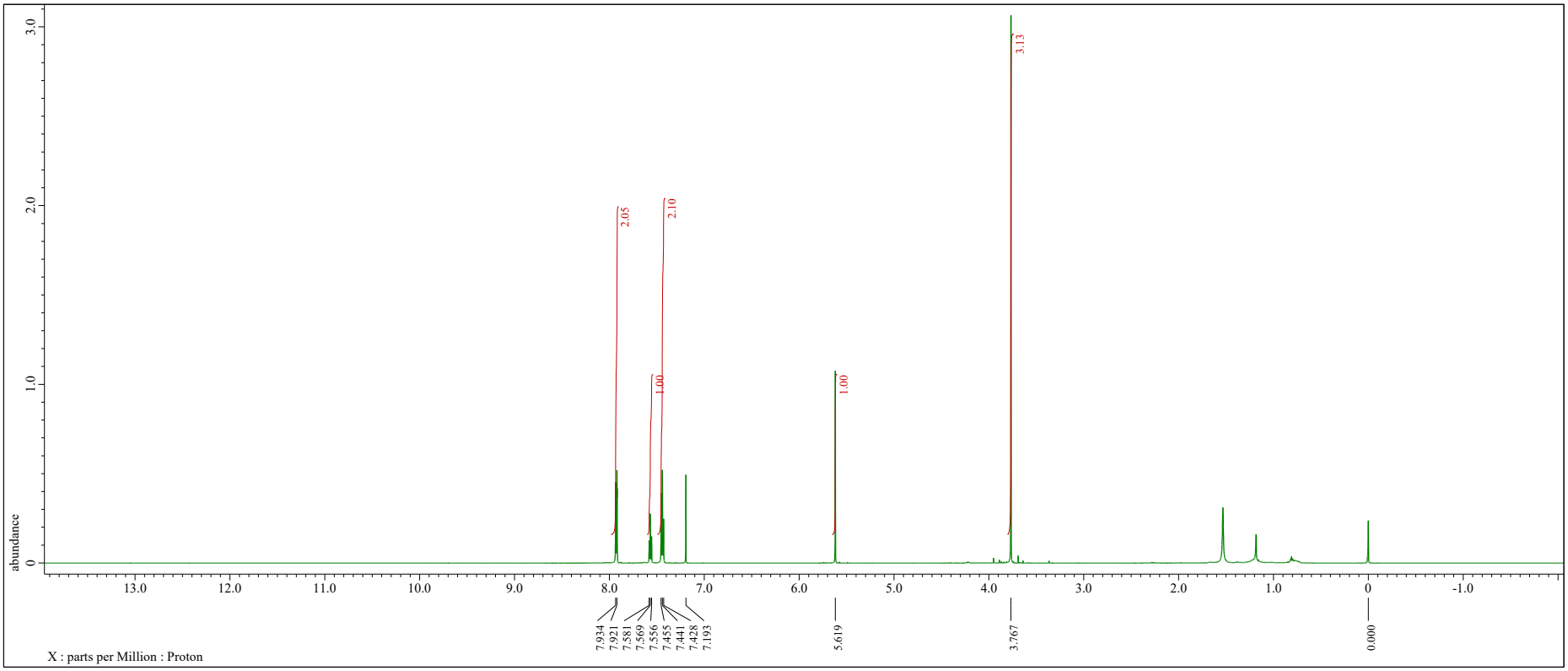
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



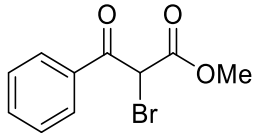
Methyl 2-bromo-3-oxo-3-phenylpropanoate (3p)



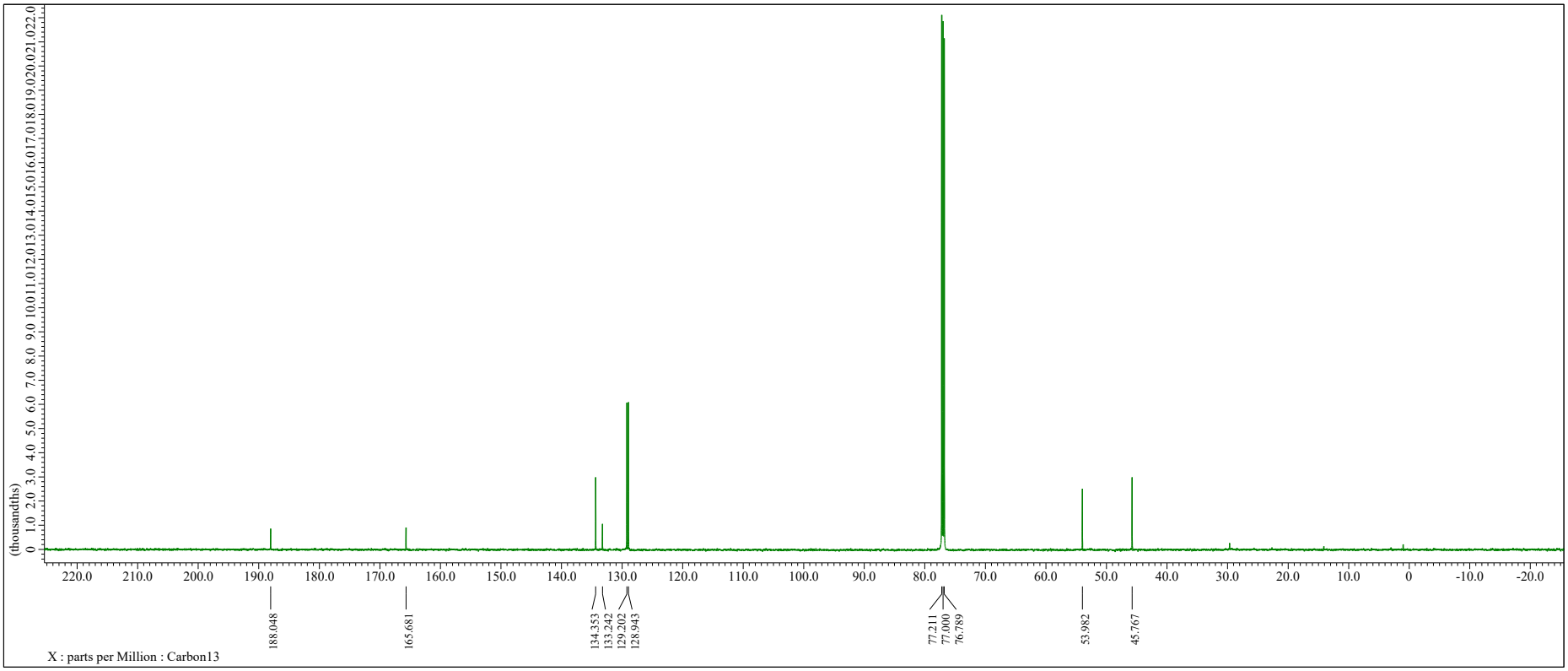
^{1}H NMR (600 MHz, $CDCl_3$)



Methyl 2-bromo-3-oxo-3-phenylpropanoate (3p)

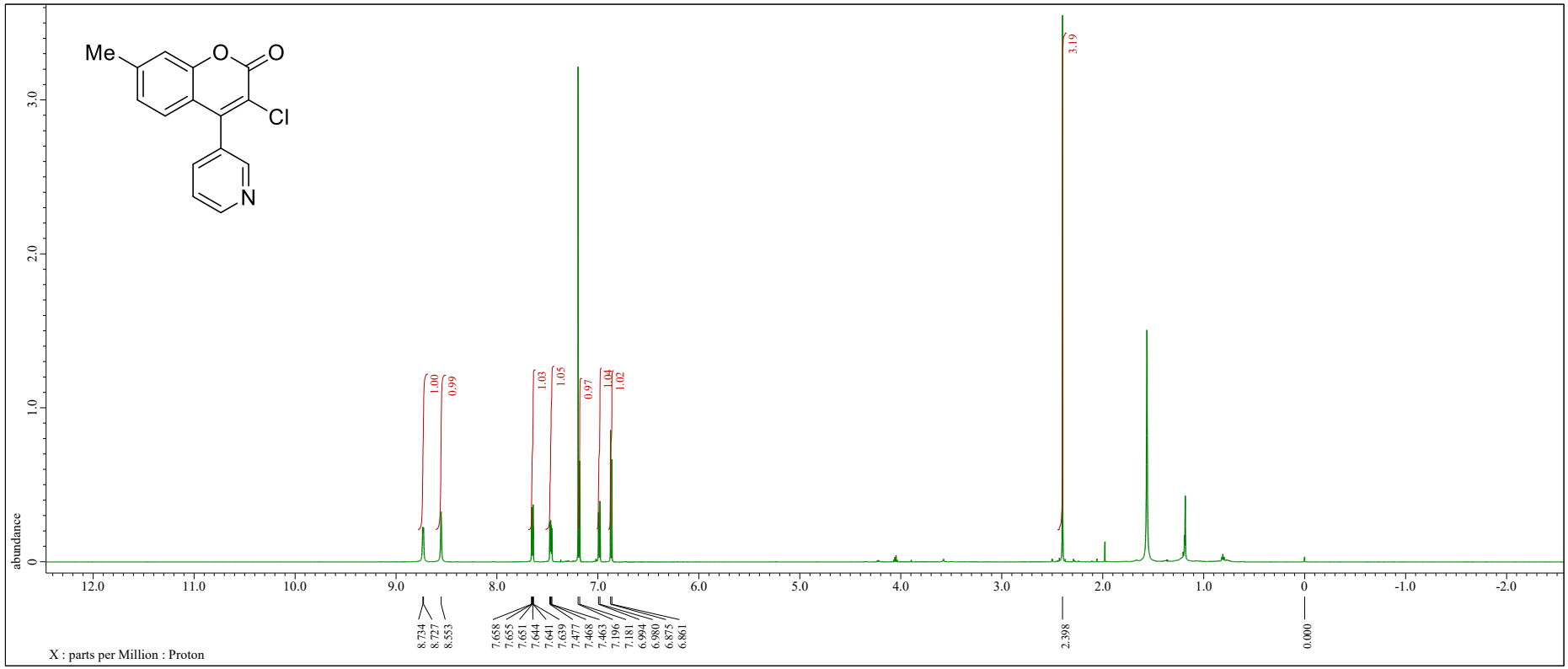


$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



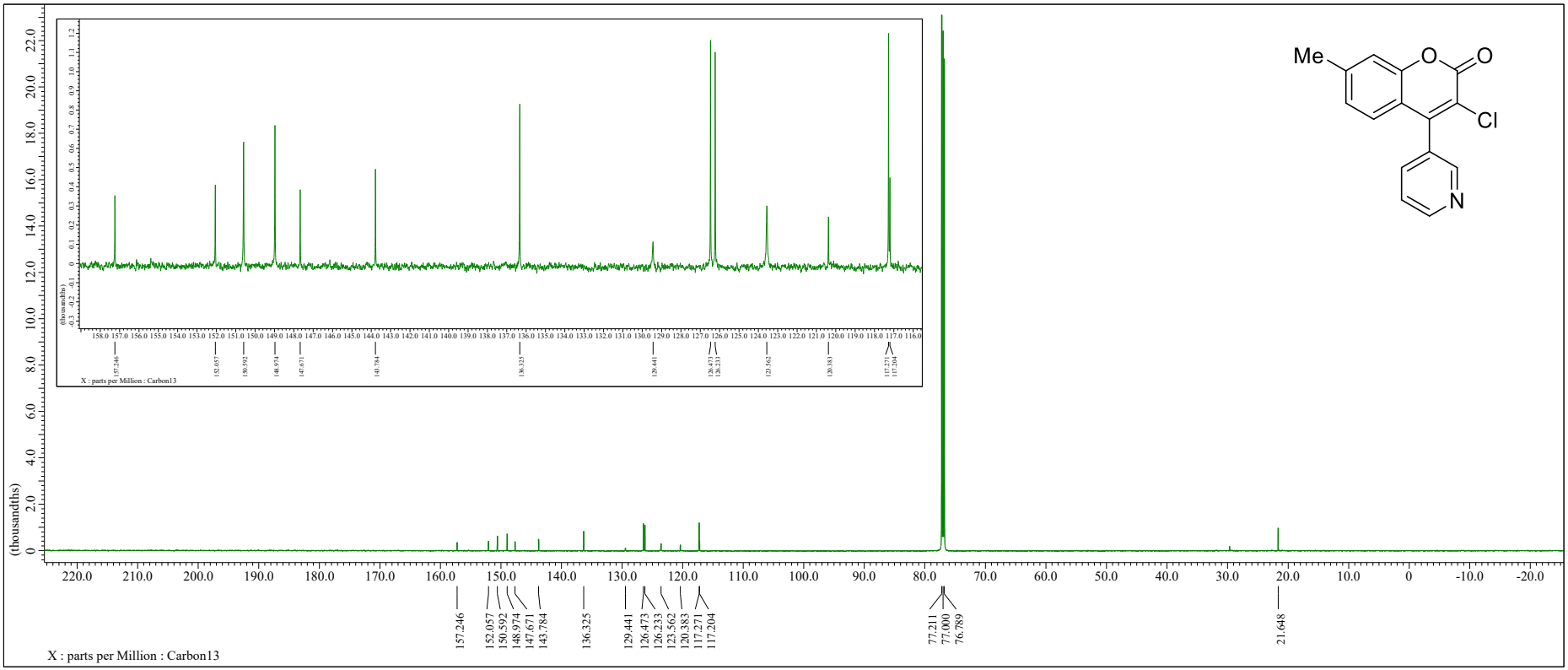
3-Chloro-7-methyl-4-(pyridin-3-yl)-2*H*-chromen-2-one (4)

^{1}H NMR (600 MHz, $CDCl_3$)



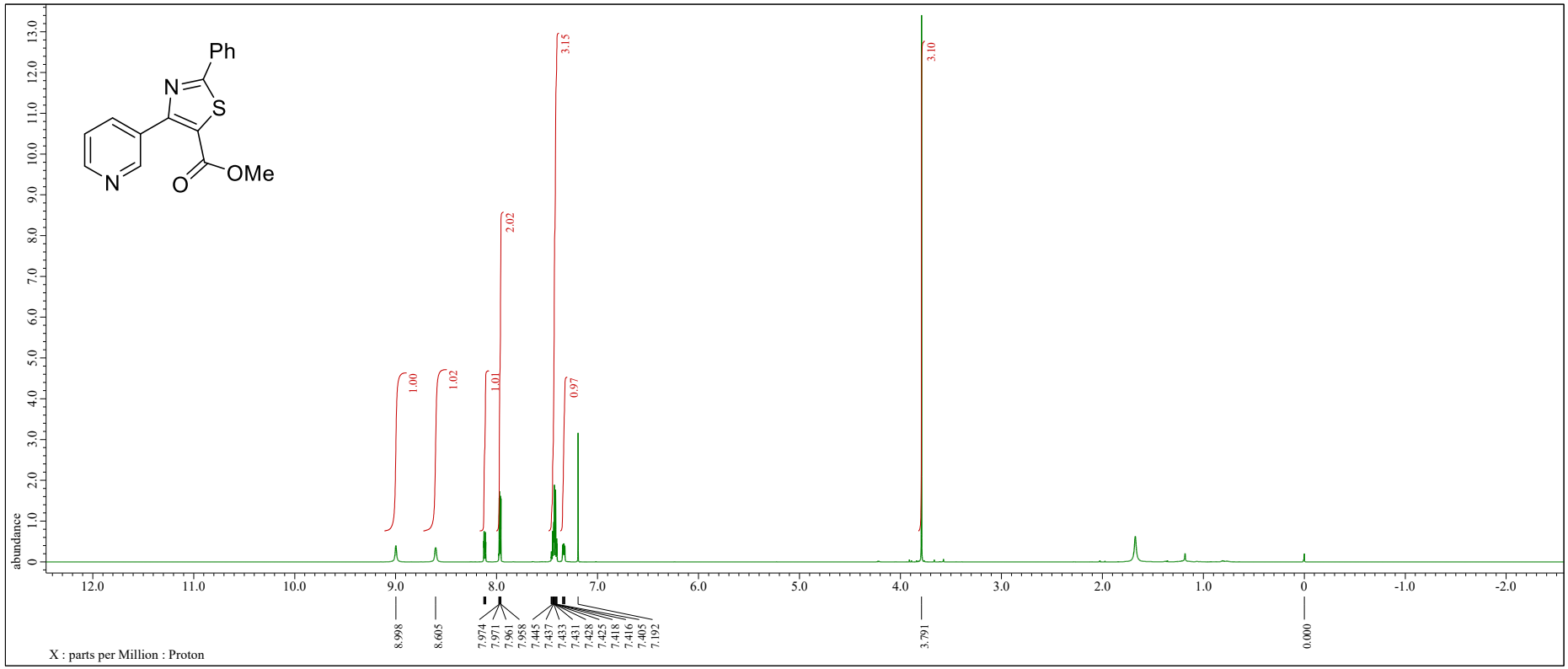
3-Chloro-7-methyl-4-(pyridin-3-yl)-2*H*-chromen-2-one (4)

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



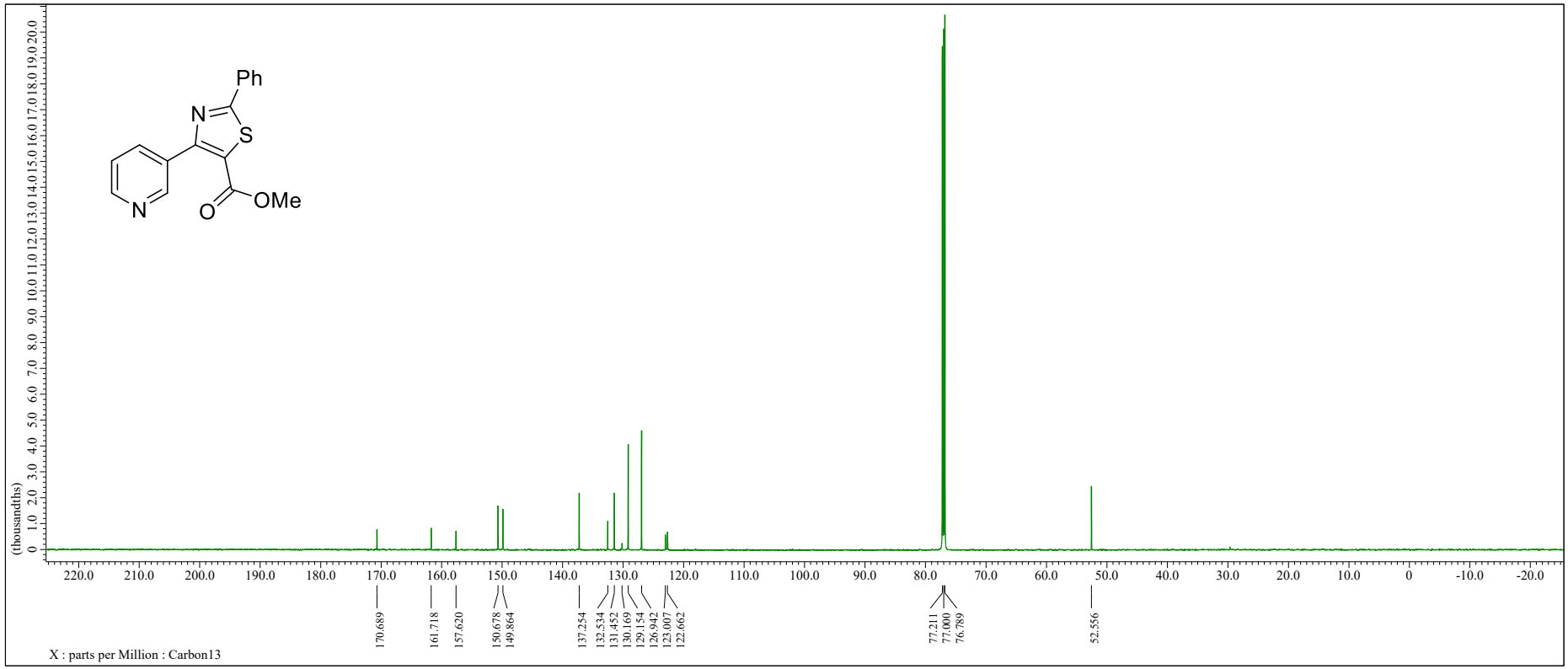
Methyl 2-phenyl-4-(pyridin-3-yl)thiazole-5-carboxylate (5)

^{1}H NMR (600 MHz, $CDCl_3$)

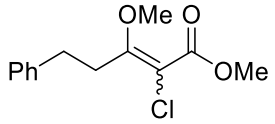


Methyl 2-phenyl-4-(pyridin-3-yl)thiazole-5-carboxylate (5)

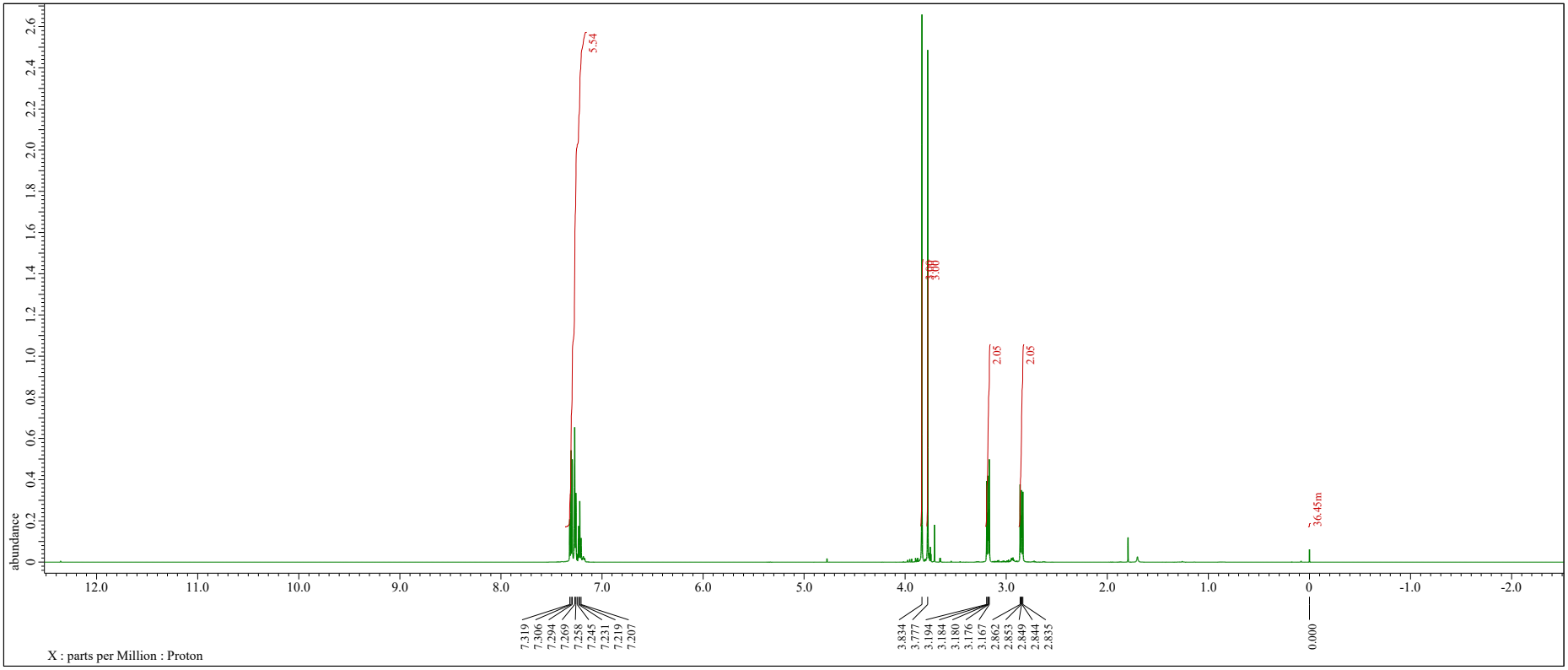
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



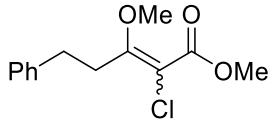
Methyl 2-chloro-3-methoxy-5-phenylpent-2-enoate (6) (Major isomer)



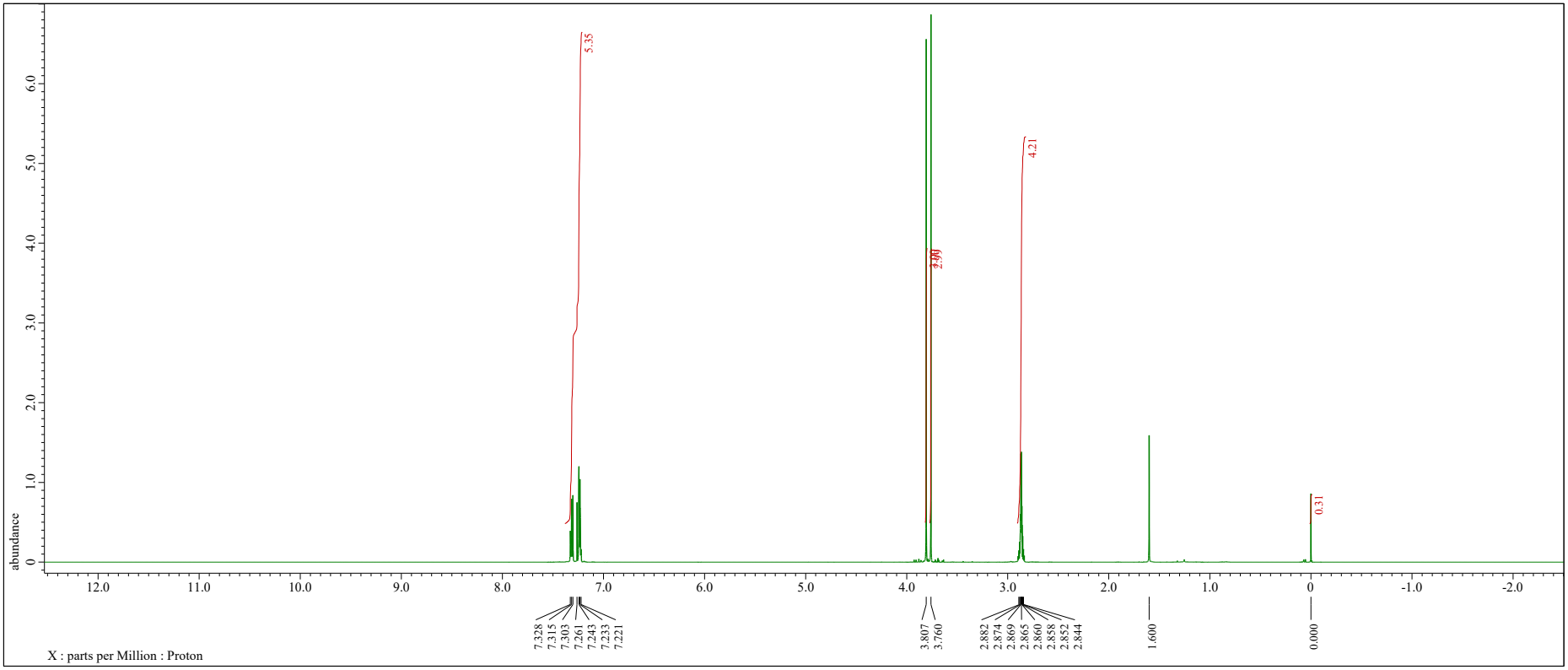
^{1}H NMR (600 MHz, $CDCl_3$)



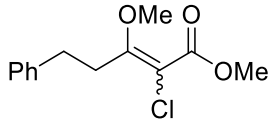
Methyl 2-chloro-3-methoxy-5-phenylpent-2-enoate (6) (Minor isomer)



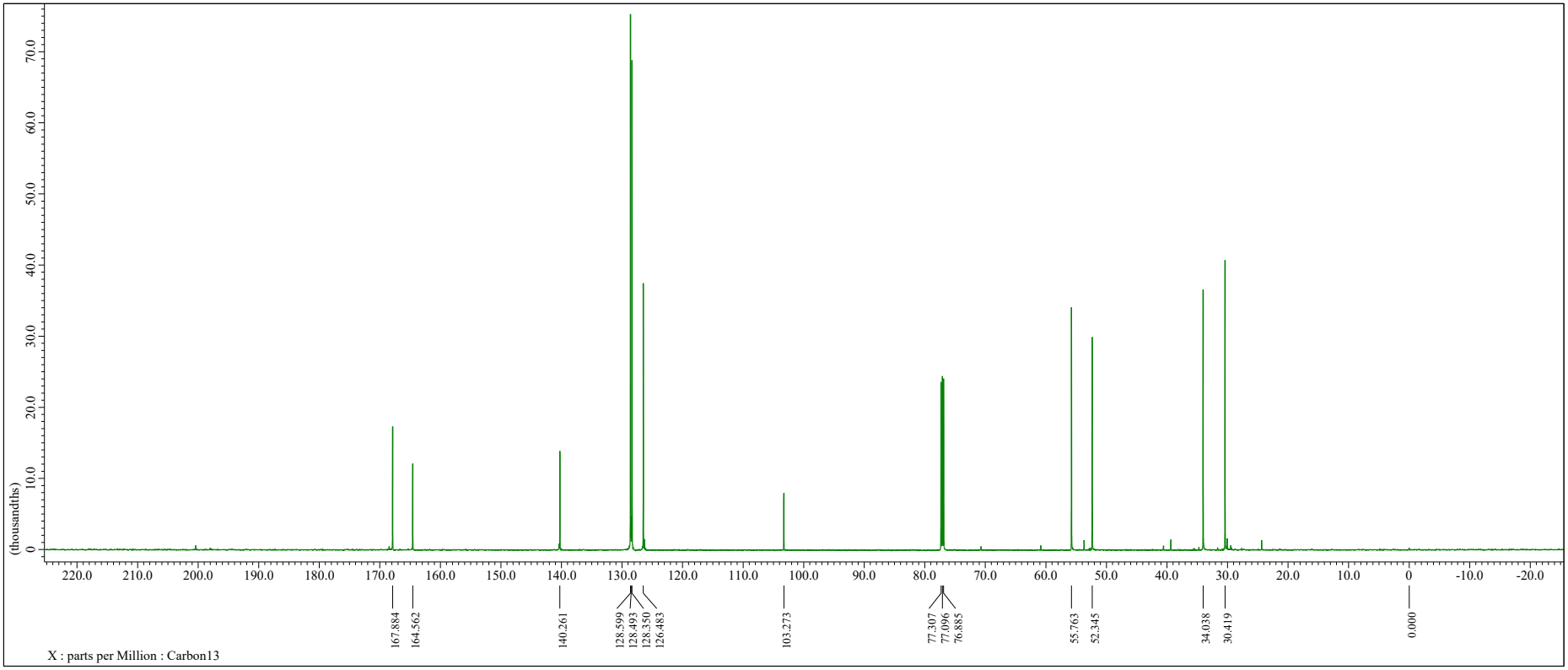
^{1}H NMR (600 MHz, $CDCl_3$)



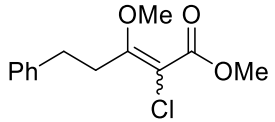
Methyl 2-chloro-3-methoxy-5-phenylpent-2-enoate (6) (Major isomer)



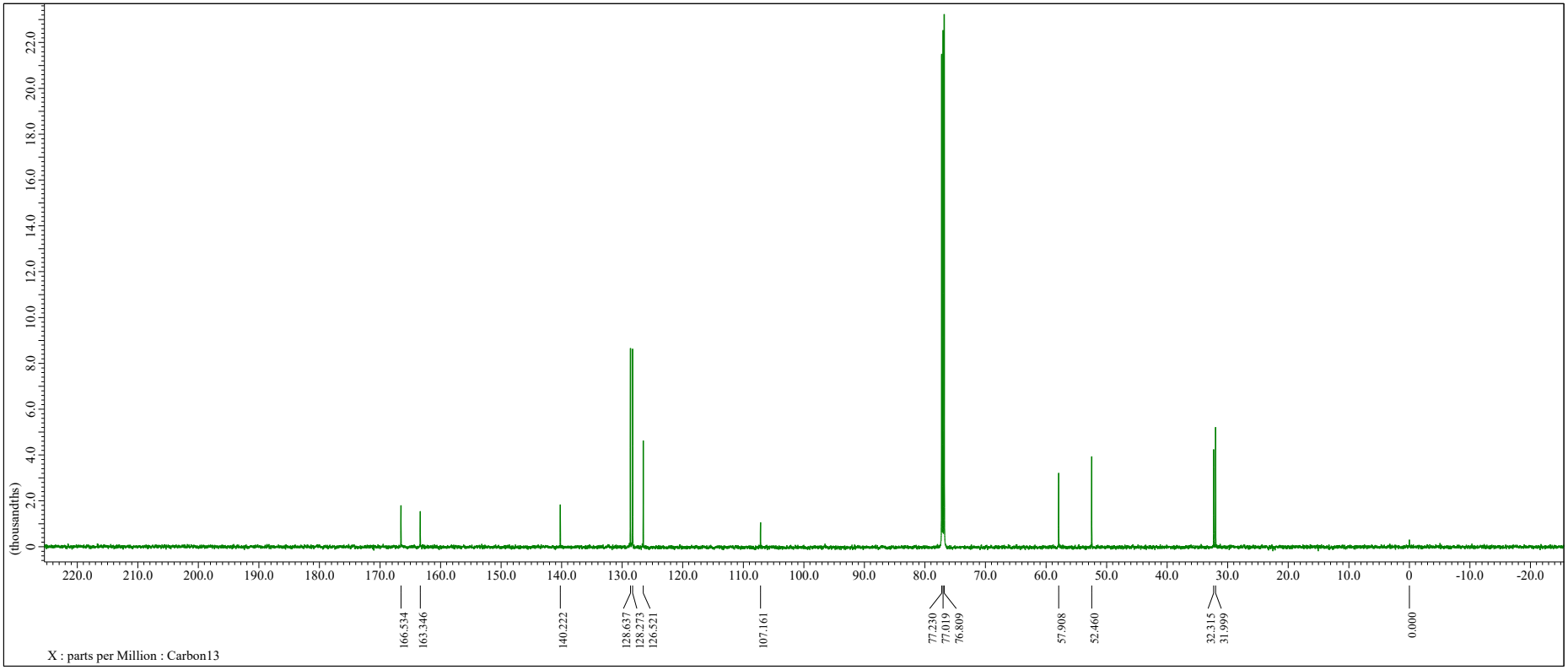
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



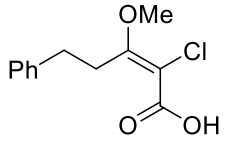
Methyl 2-chloro-3-methoxy-5-phenylpent-2-enoate (6) (Minor isomer)



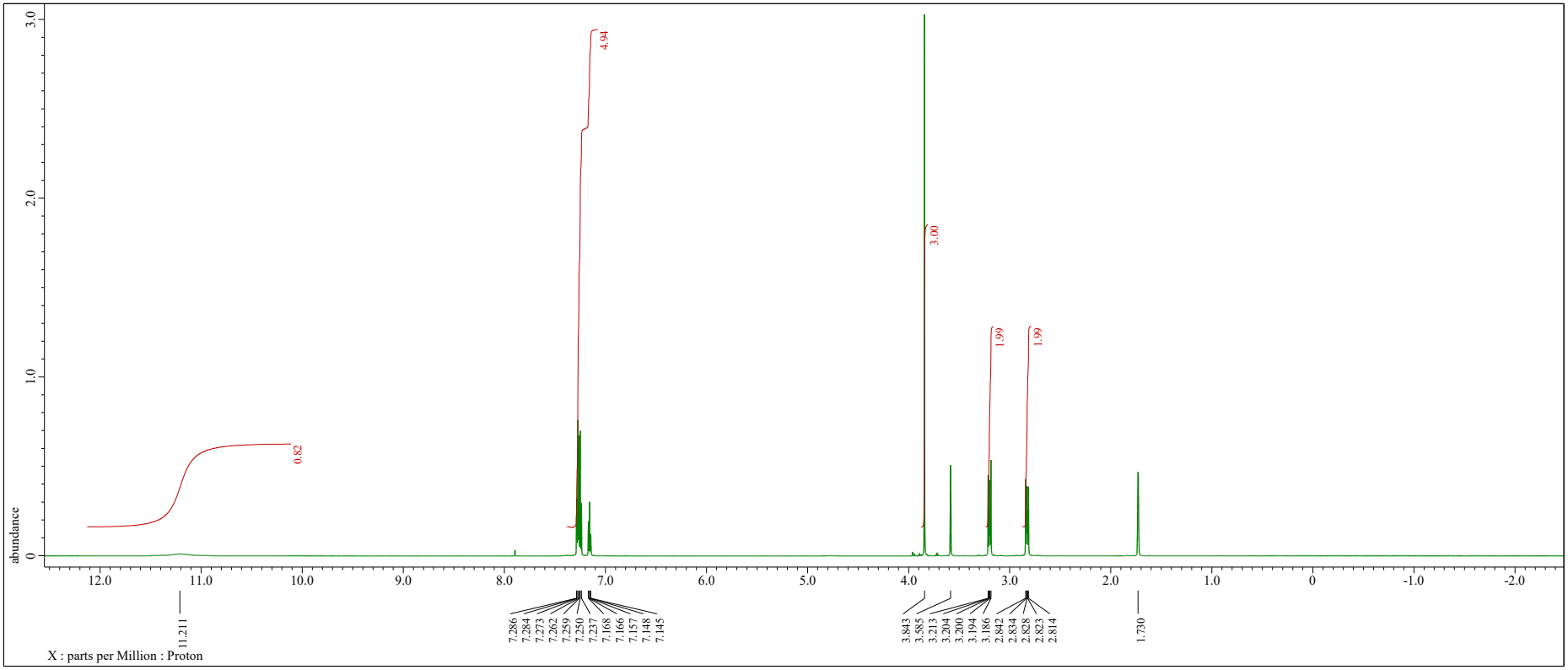
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



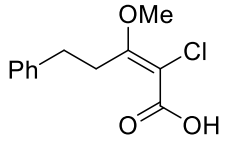
(*Z*)-2-Chloro-3-methoxy-5-phenylpent-2-enoic acid (7)



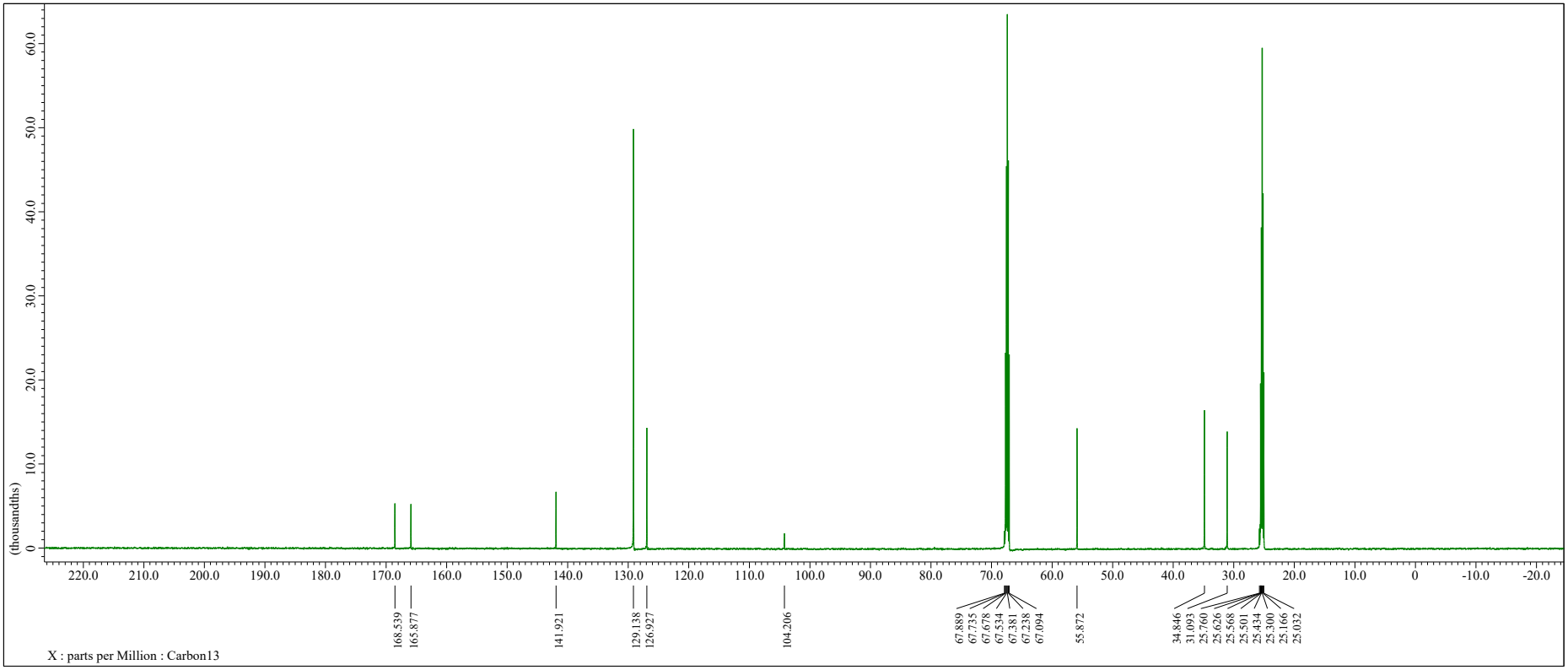
^{1}H NMR (600 MHz, THF-d$_8$)



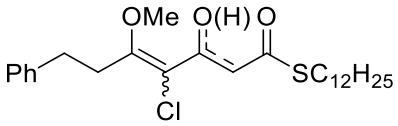
(*Z*)-2-Chloro-3-methoxy-5-phenylpent-2-enoic acid (7)



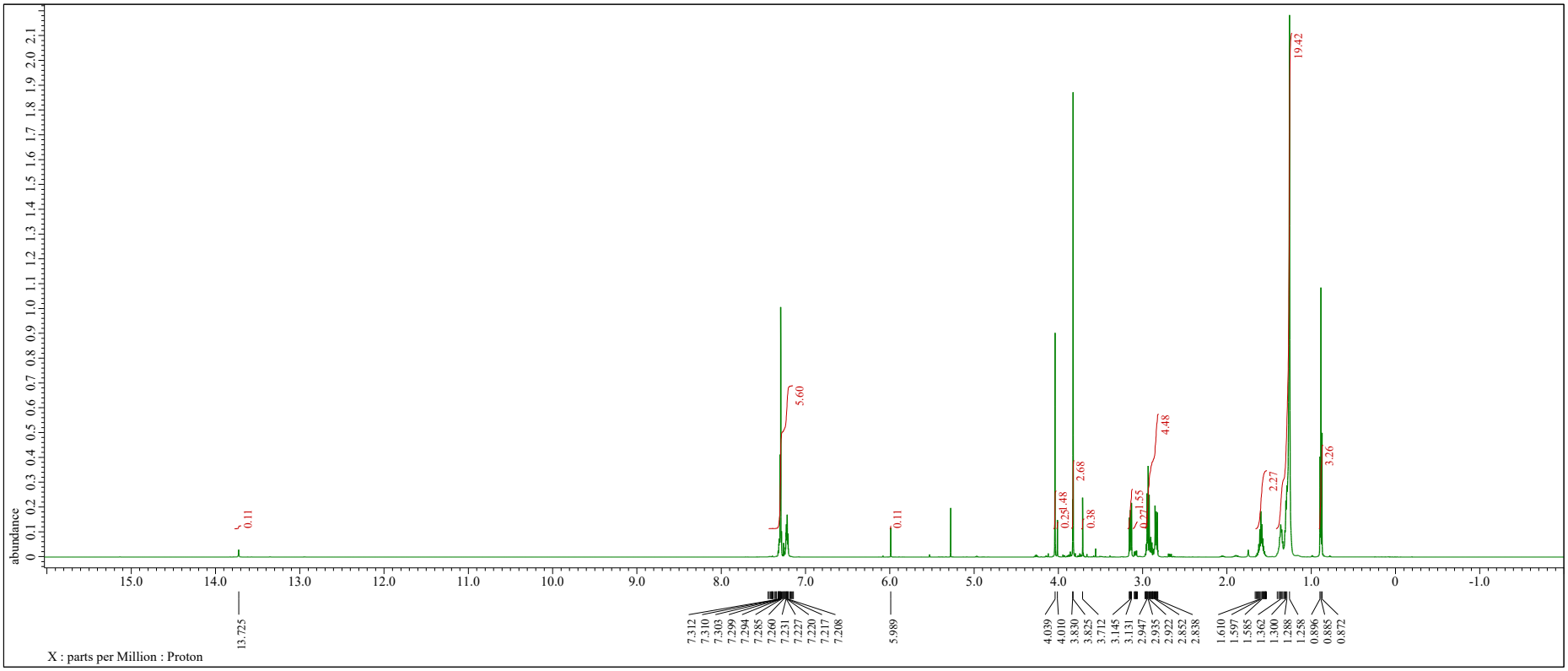
$^{13}C\{^{1}H\}$ NMR (150 MHz, THF-d_8)



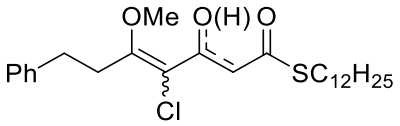
_S_-dodecyl 4-chloro-5-methoxy-3-oxo-7-phenylhept-4-enethioate (8)



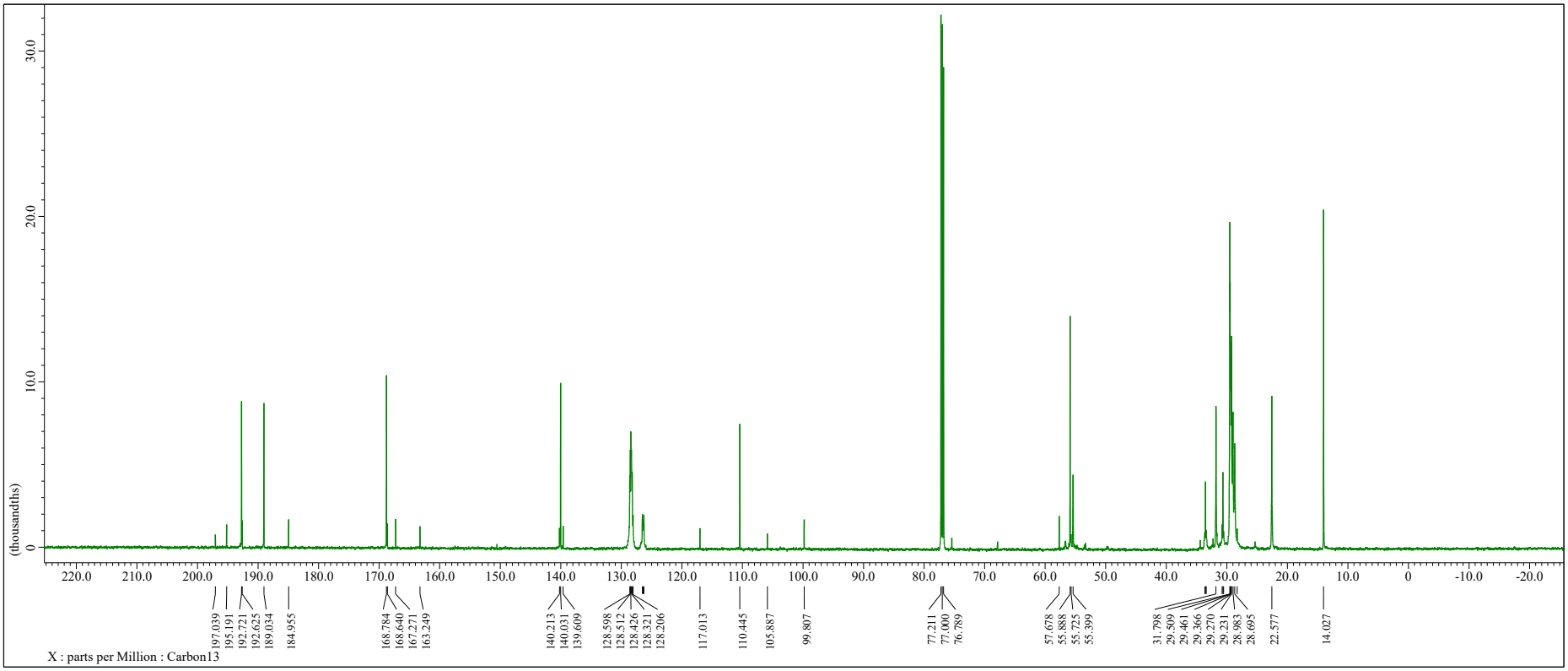
^{1}H NMR (600 MHz, $CDCl_3$)



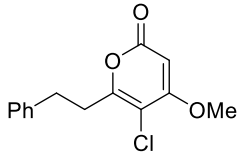
_S_-dodecyl 4-chloro-5-methoxy-3-oxo-7-phenylhept-4-enethioate (8)



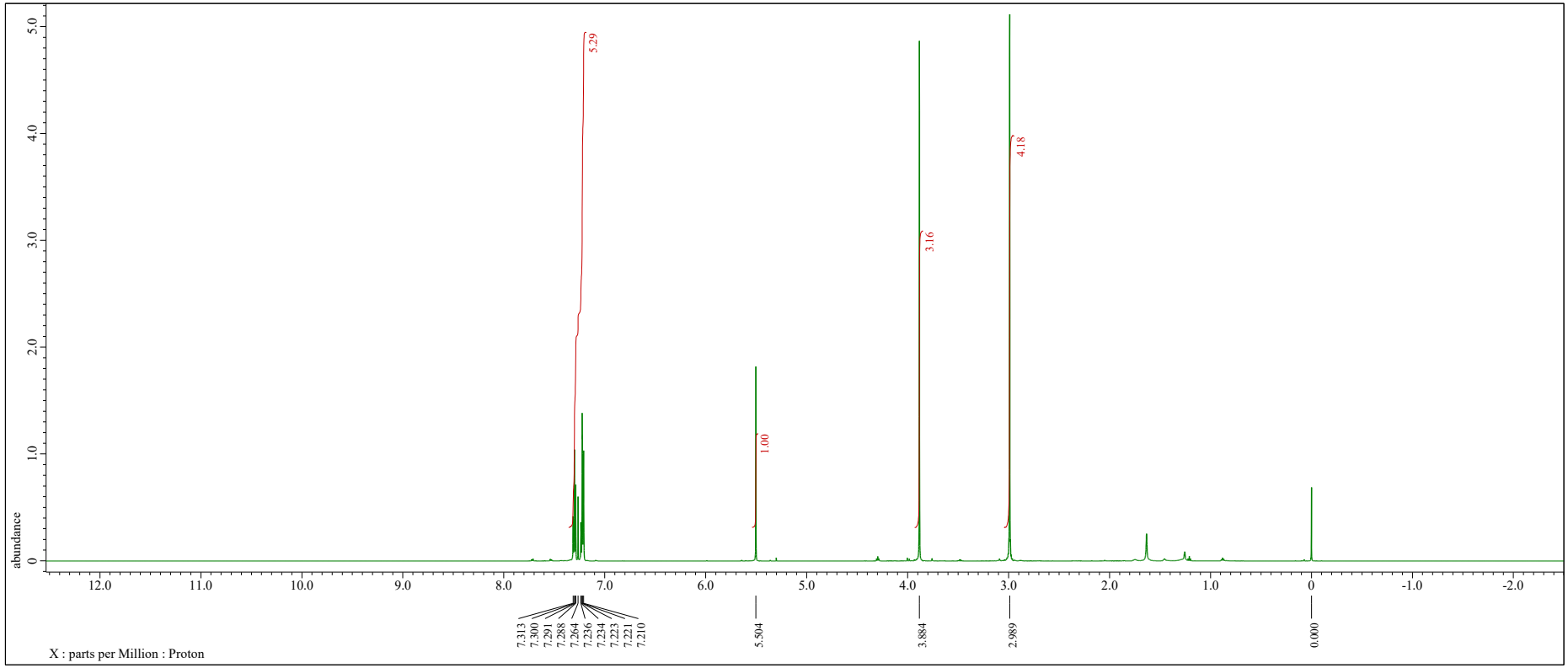
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



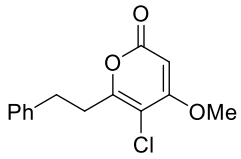
5-Chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (10)



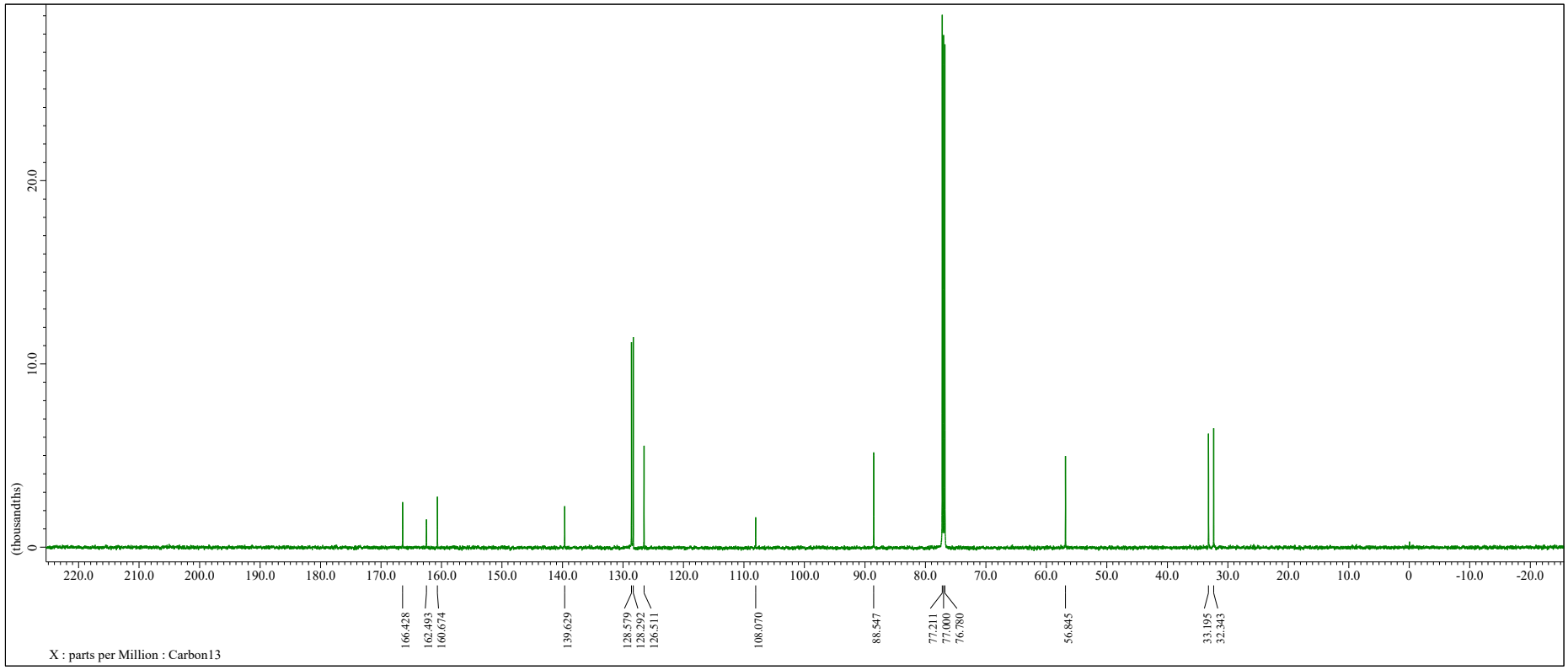
^{1}H NMR (600 MHz, $CDCl_3$)



5-Chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (10)

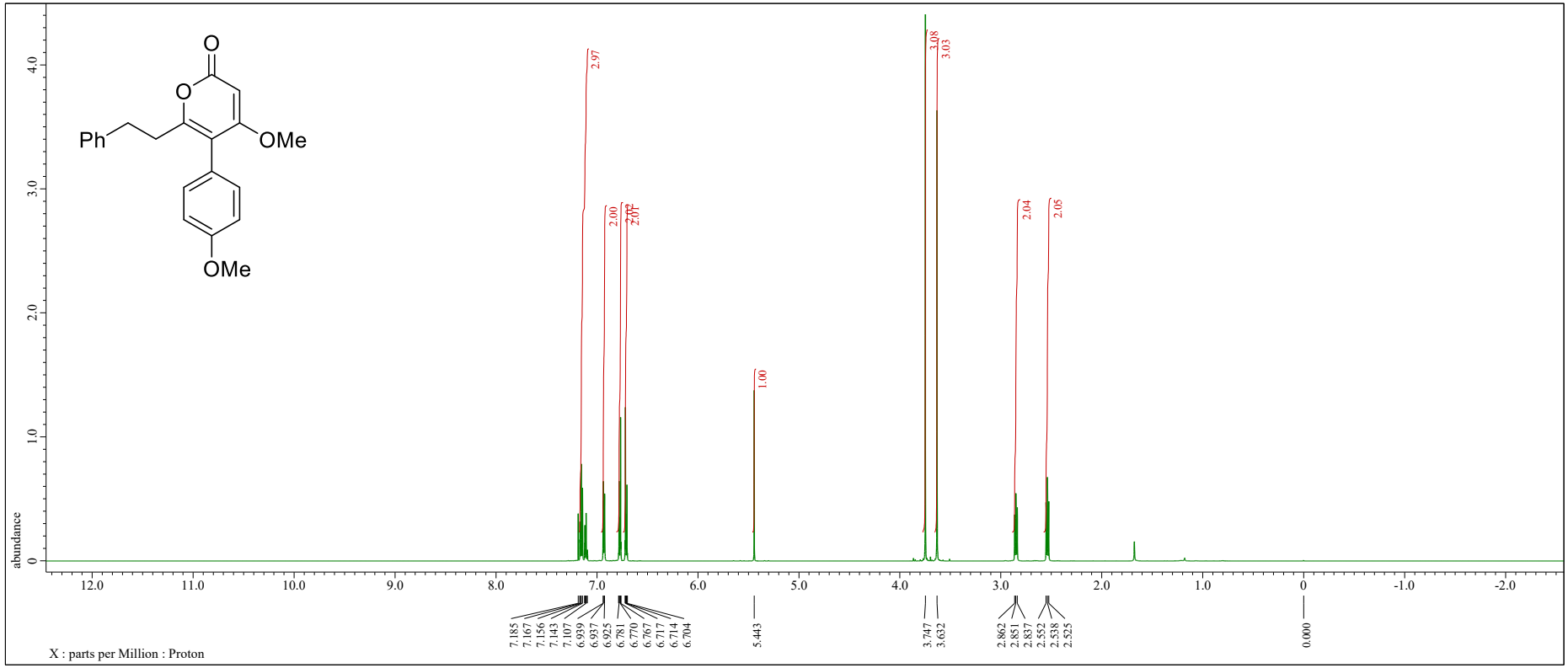


$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



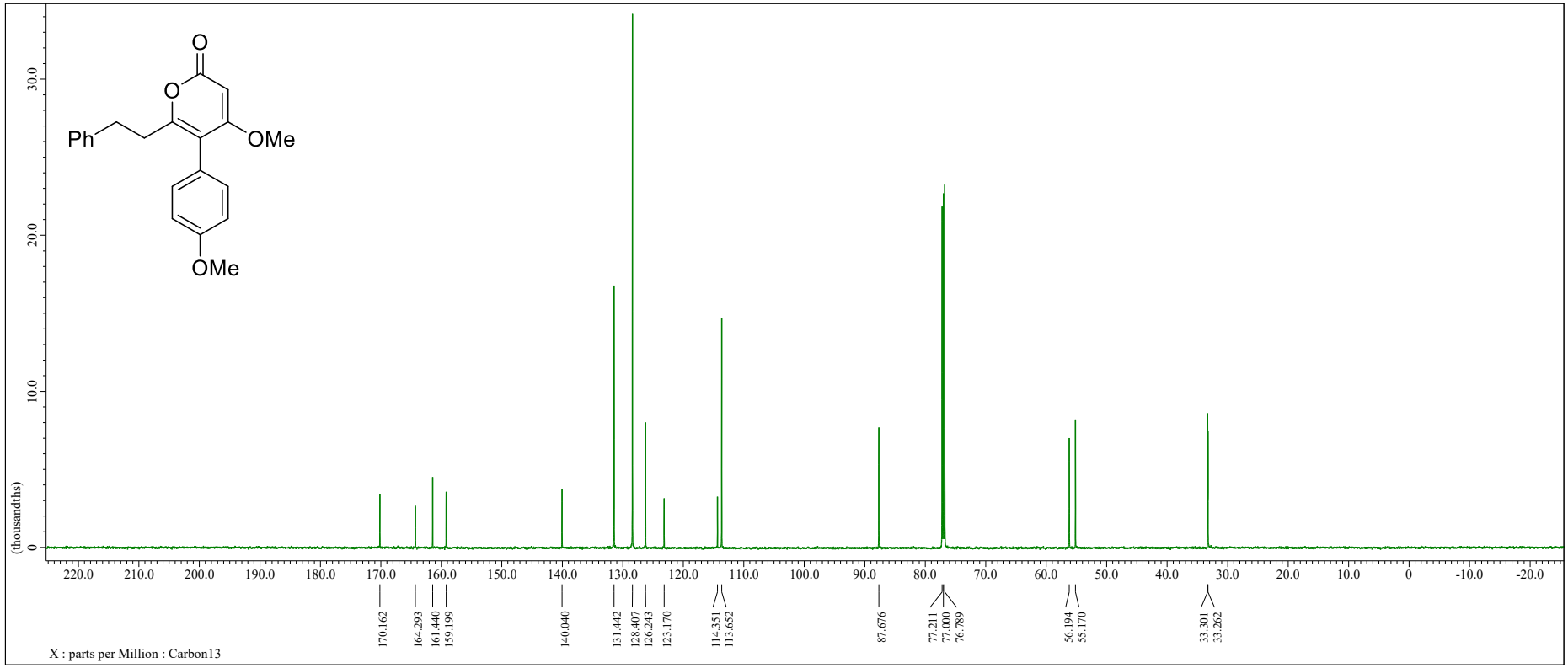
4-Methoxy-5-(4-methoxyphenyl)-6-phenethyl-2*H*-pyran-2-one (11)

^{1}H NMR (600 MHz, $CDCl_3$)

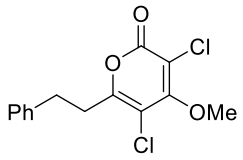


4-Methoxy-5-(4-methoxyphenyl)-6-phenethyl-2*H*-pyran-2-one (11)

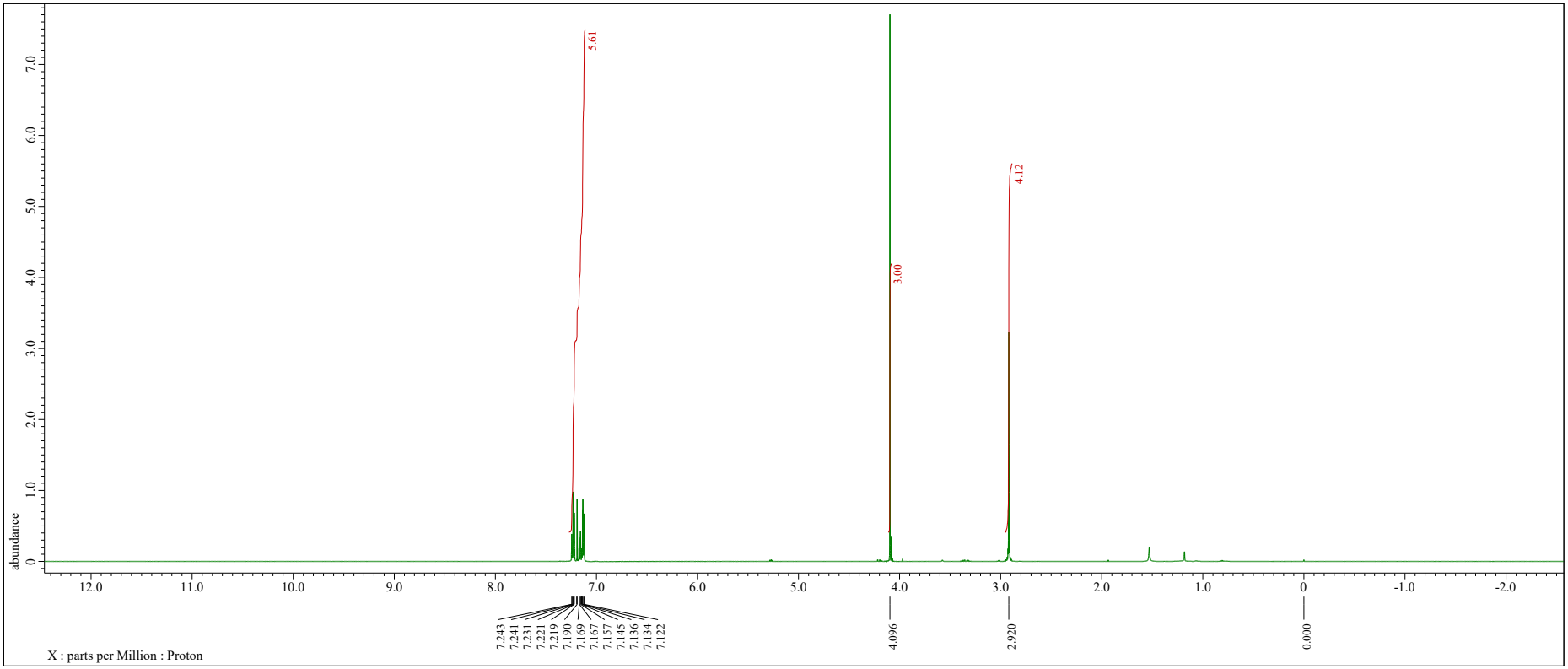
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



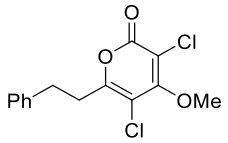
3,5-Dichloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (12a)



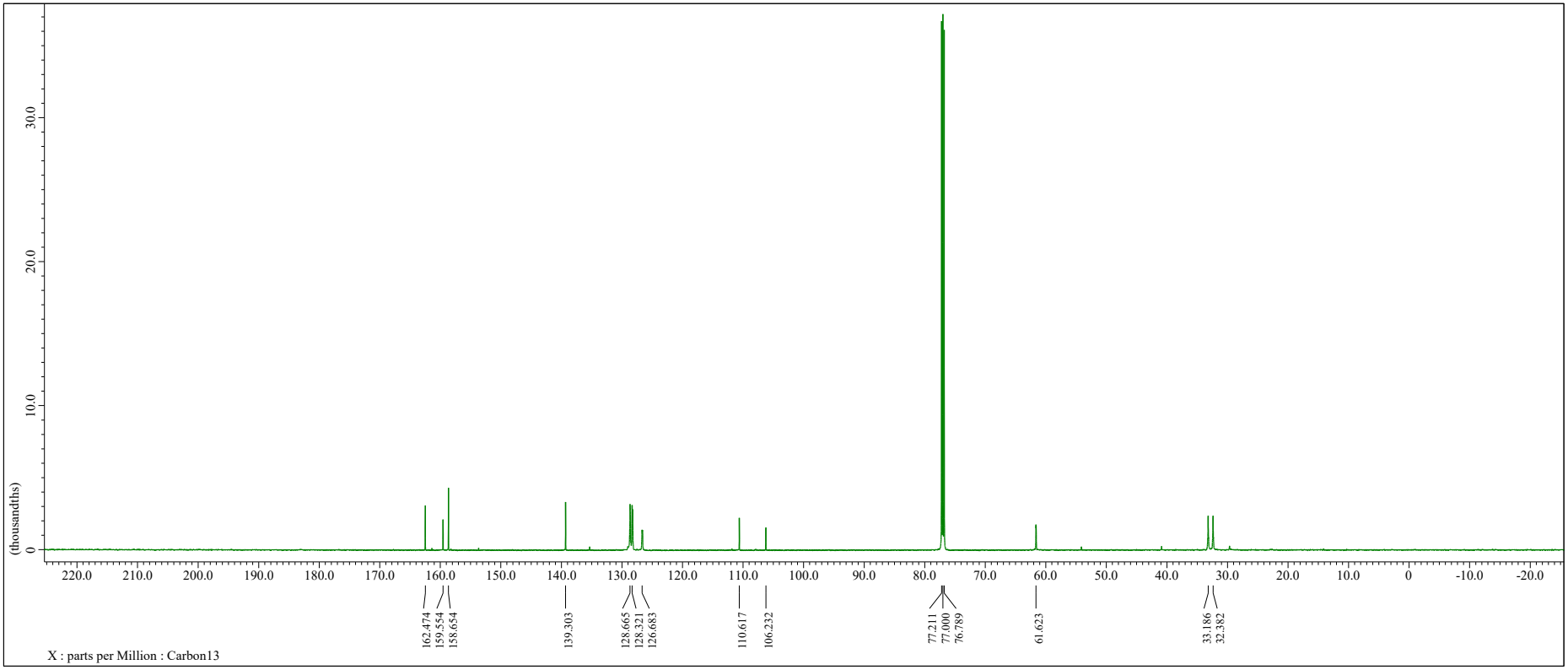
^{1}H NMR (600 MHz, $CDCl_3$)



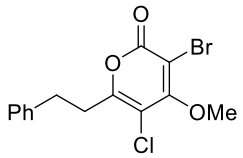
3,5-Dichloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (12a)



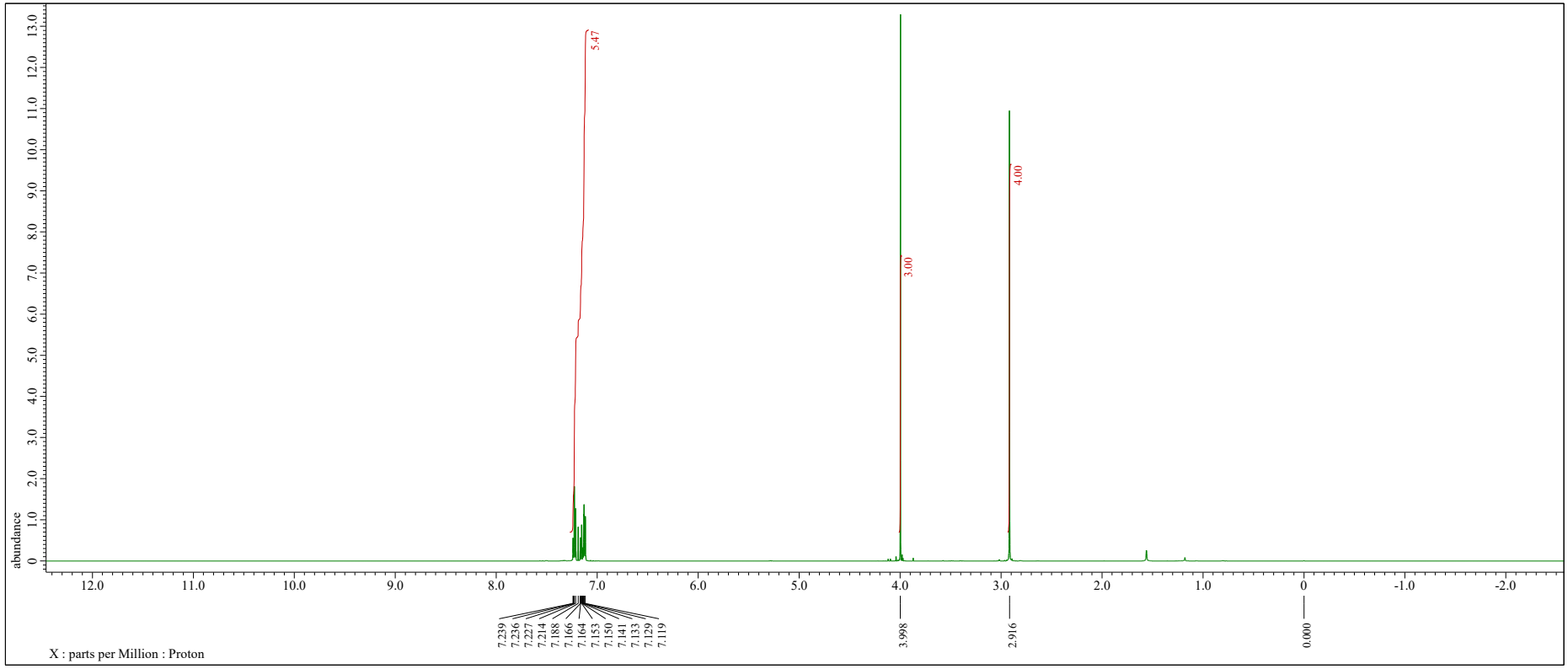
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



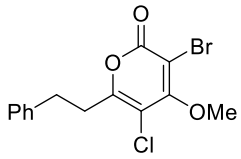
3-Bromo-5-chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (12b)



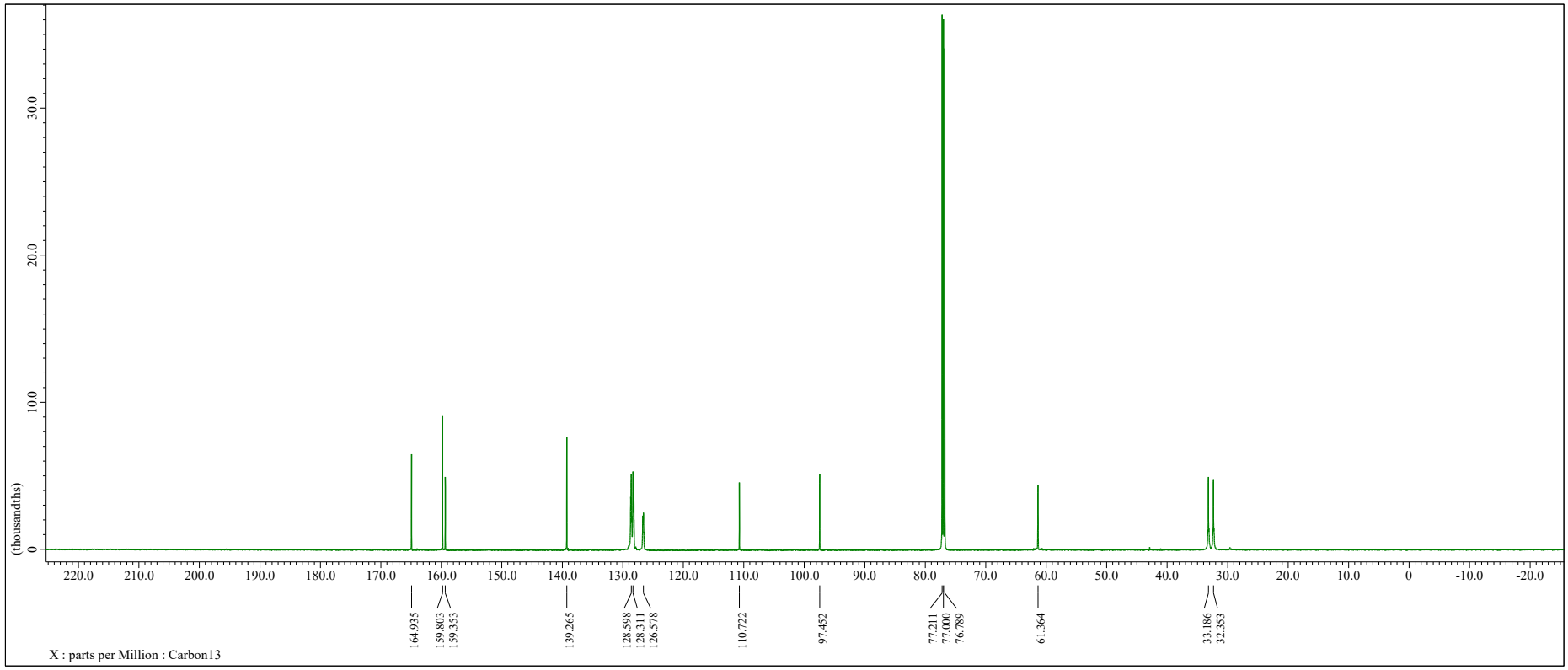
^{1}H NMR (600 MHz, $CDCl_3$)



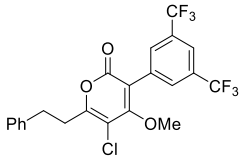
3-Bromo-5-chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (12b)



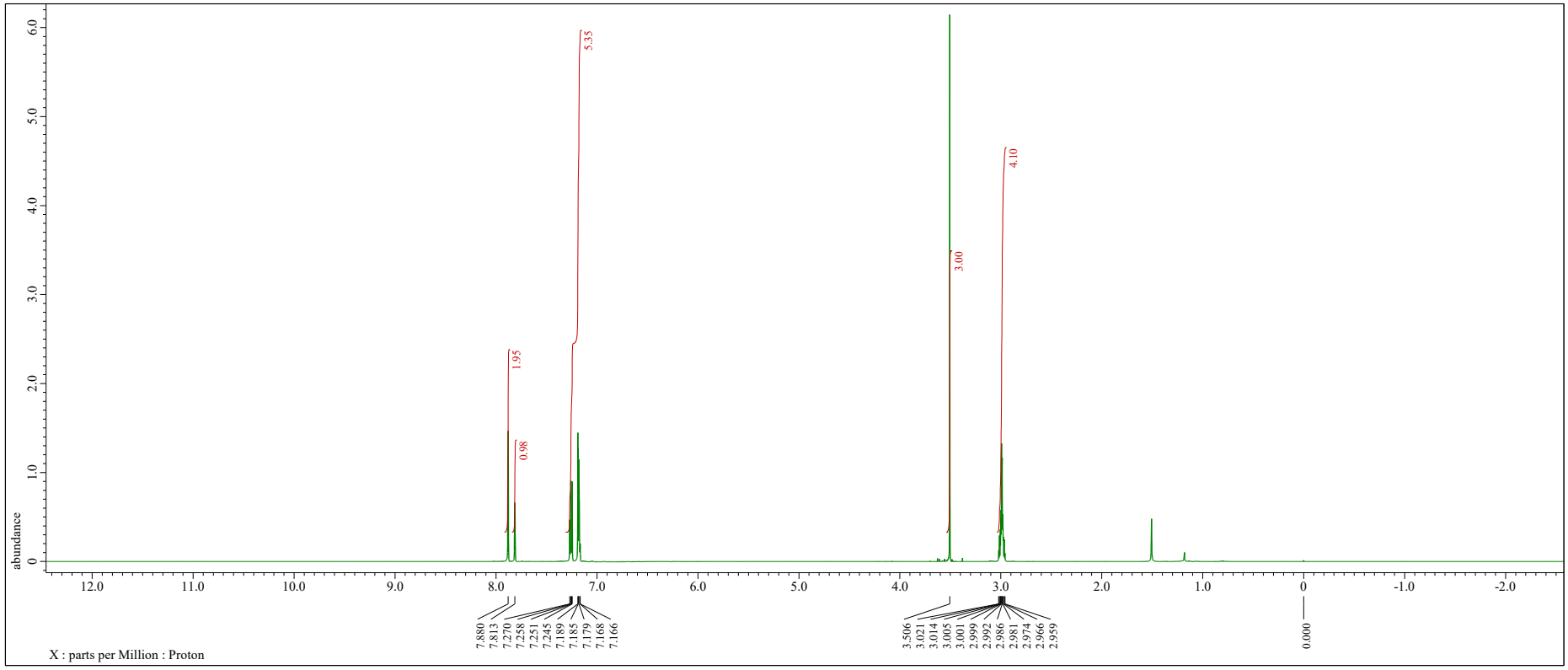
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



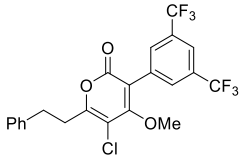
3-(3,5-Bis(trifluoromethyl)phenyl)-5-chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (13)



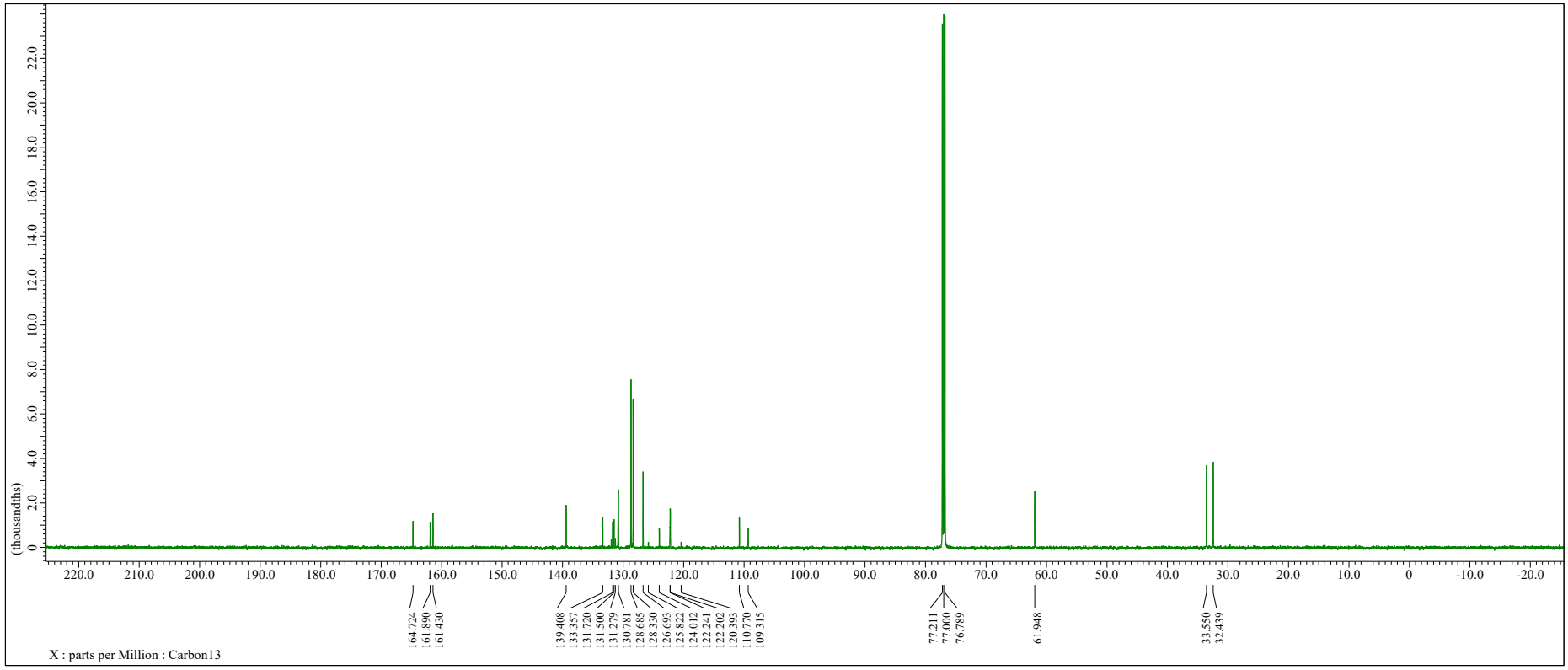
^{1}H NMR (600 MHz, $CDCl_3$)



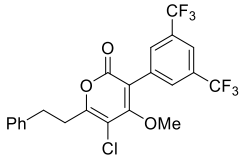
3-(3,5-Bis(trifluoromethyl)phenyl)-5-chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (13)



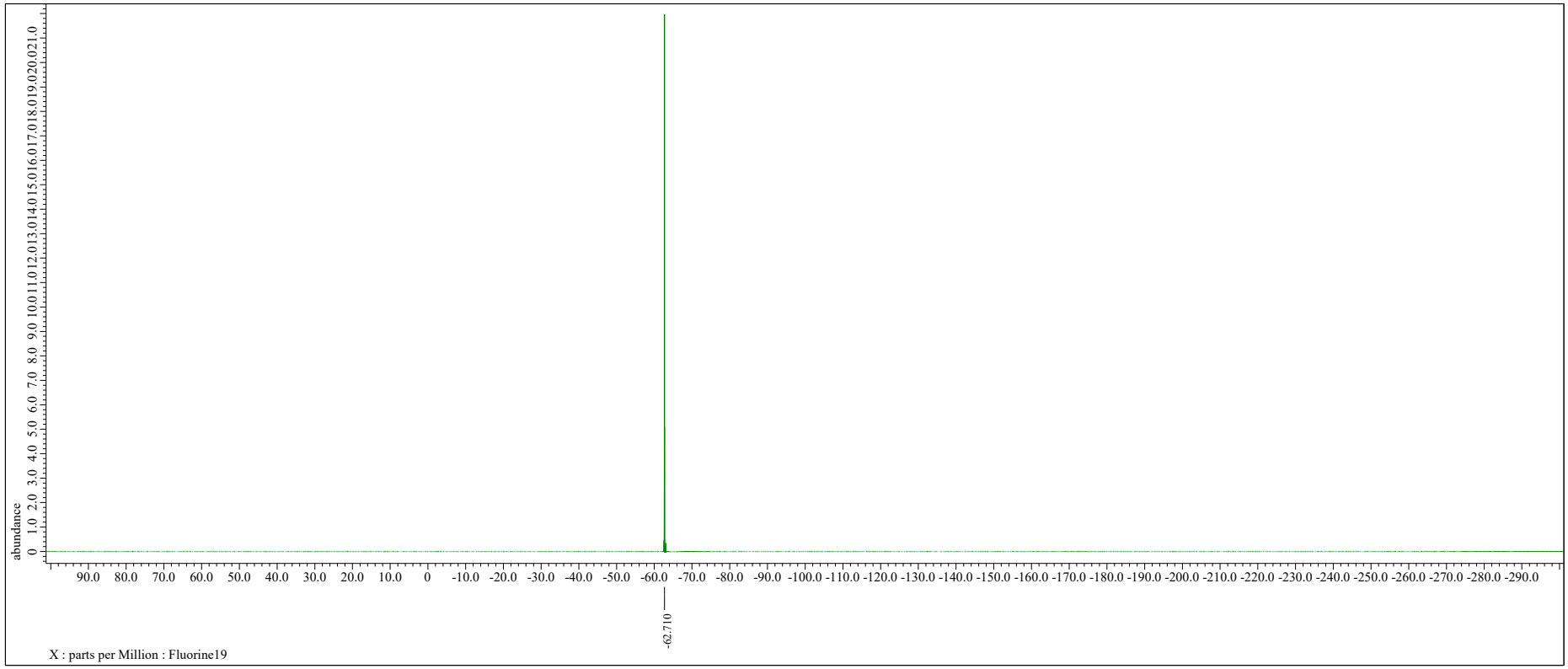
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



3-(3,5-Bis(trifluoromethyl)phenyl)-5-chloro-4-methoxy-6-phenethyl-2*H*-pyran-2-one (13)

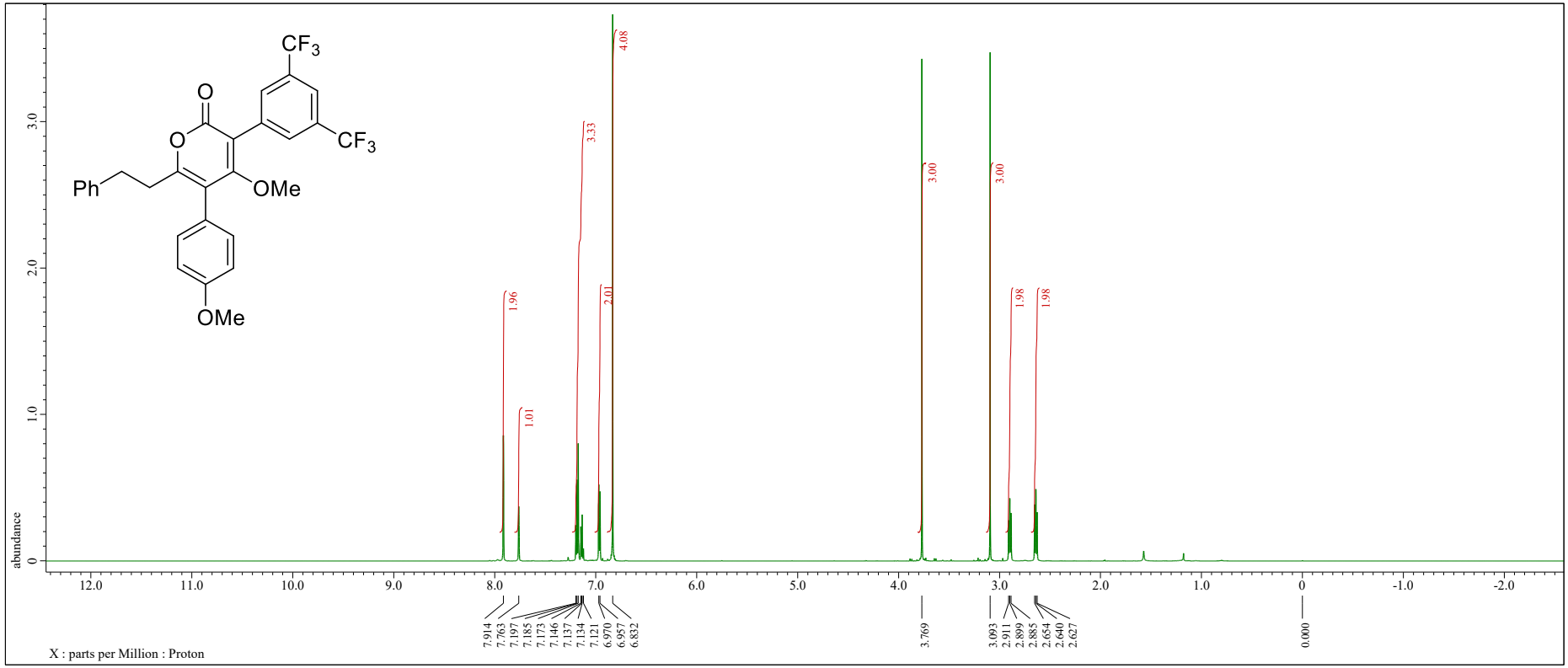


^{19}F NMR (564 MHz, $CDCl_3$)



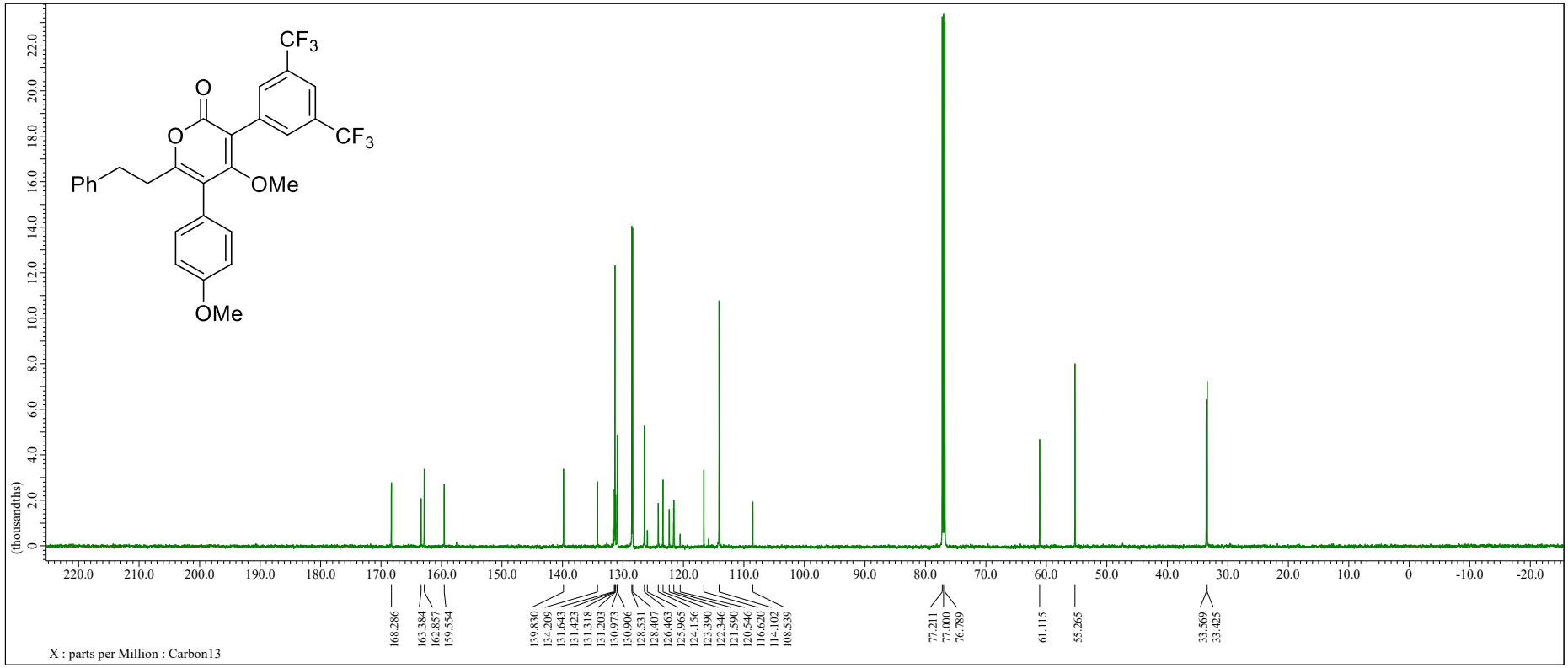
3-(3,5-Bis(trifluoromethyl)phenyl)-4-methoxy-5-(4-methoxyphenyl)-6-phenethyl-2*H*-pyran-2-one (14)

^{1}H NMR (600 MHz, $CDCl_3$)



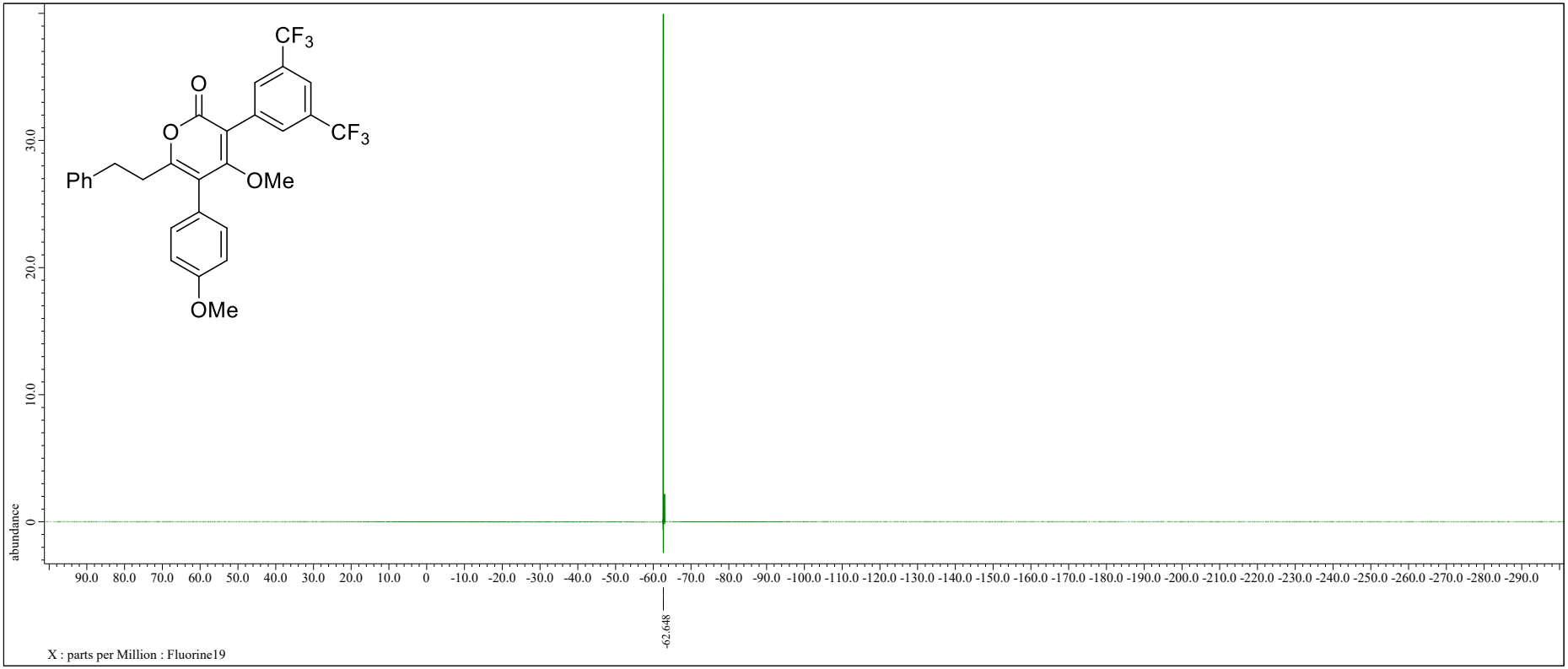
3-(3,5-Bis(trifluoromethyl)phenyl)-4-methoxy-5-(4-methoxyphenyl)-6-phenethyl-2*H*-pyran-2-one (14)

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$)



3-(3,5-Bis(trifluoromethyl)phenyl)-4-methoxy-5-(4-methoxyphenyl)-6-phenethyl-2*H*-pyran-2-one (14)

^{19}F NMR (564 MHz, $CDCl_3$)


CF3
O
O
CF3
Ph
OMe
OMe
30.0
20.0
10.0
0
abundance
90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0 -30.0 -40.0 -50.0 -60.0 -70.0 -80.0 -90.0 -100.0 -110.0 -120.0 -130.0 -140.0 -150.0 -160.0 -170.0 -180.0 -190.0 -200.0 -210.0 -220.0 -230.0 -240.0 -250.0 -260.0 -270.0 -280.0 -290.0
-62.648
X : parts per Million : Fluorine19