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SUPPORTING INFORMATION

Cooperative Iodine and Photoredox Catalysis for Direct Oxidative Lactonization of Carboxylic Acids

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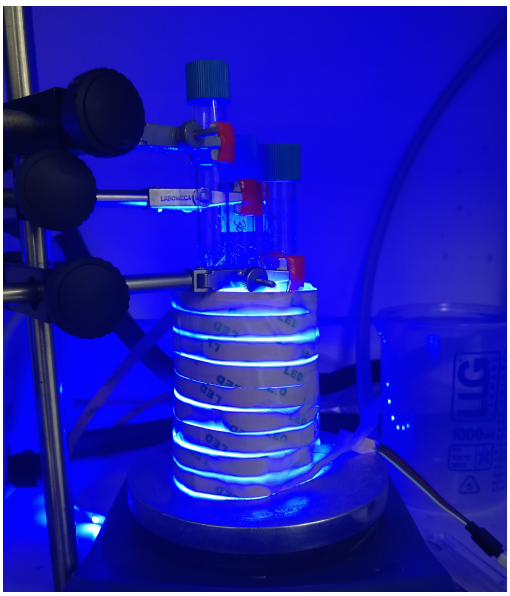
1. General information

Solvents and reagents used in this project were purchased from Aldrich, Acros and TCI. Column chromatographies were performed with silica gel (Merck, type 60, 0.063-0.2 mm). NMR spectra were recorded on a Bruker Avance 400 or 500 MHz spectrometer. The chemical shifts are given in ppm normalized to the shift of chloroform as residue in the deuterated chloroform (^{1}H NMR: δ = 7.26 and ^{13}C NMR: 77.0 ppm), while the multiplicities are stated as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet). HRMS measurements were performed on a Kratos MS 50 instrument. IR spectra were recorded a Bruker Alpha instrument in the solid state. Raman spectroscopic measurements were performed on a Renishaw inVia Raman microscope equipped with a thermoelectrically cooled CCD camera and a fiber-optic-cable for the excitation (532 nm beam) and collection of the Raman spectra, where the laser beam was focused on a point in the reaction mixture in the glass cuvette and an approx. laser power of 100mW was used. The iodine (TCI, I0604) and the 2,4,6-Triphenylpyrilium tetrafluoroborate (Aldrich, 272345-5G) used in the dual photoredox-catalyzed C-H amination process were used without any further purification.

2. Experimental set-up

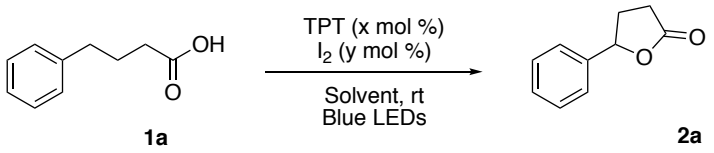
As experimental set-up, a stirring plate and a common flexible 5050 RGB LED strip were used. The LED light strip was coiled up in 9 turns with an inner diameter of 7.5 cm allowing 62 individual LEDs to face the vial placed in the center of the photoreactor. If not indicated differently, blue light irradiation (peak wavelength of 456 nm ± 12 nm) was applied in the reactions matching the maximum absorption wavelength of the photoredox catalyst.

Figure S-1: Experimental set-up



3. Screening of the cooperative catalysis for the direct oxidative cyclization

Table S-2: Optimization of the cooperative catalysis



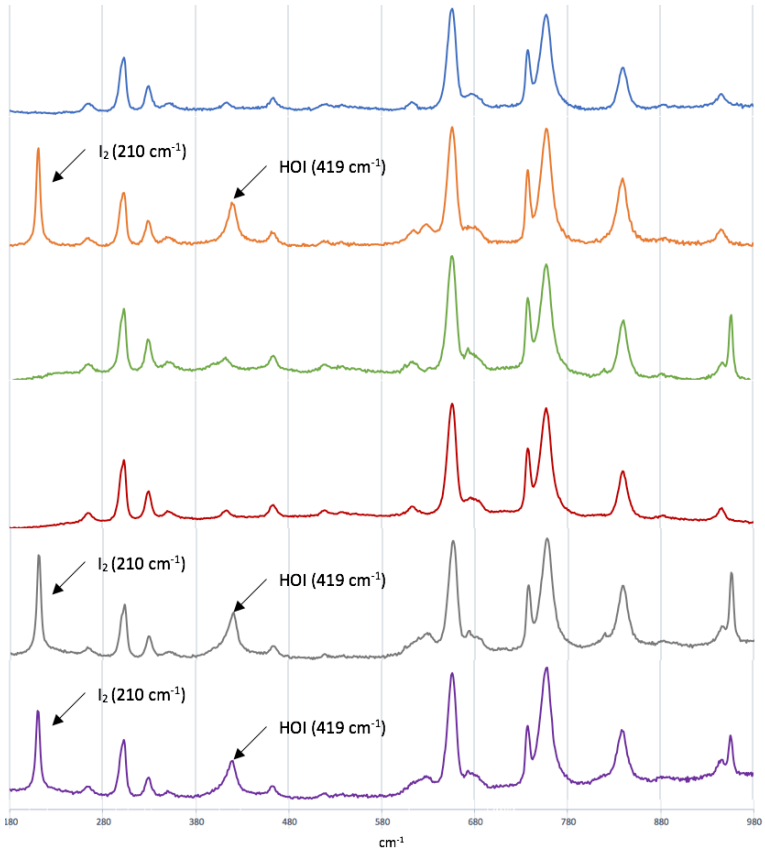
1a **2a**

Entry[a]	x	y	Solvent	Time (h)	Conversion (%)
1	-	5	DCE/HFIP	18h	nr[b]
2	-	10	DCE/HFIP	18h	nr[b]
3	2	-	DCE/HFIP	18h	21
4	1	5	DCE/HFIP	18h	70
5	1.5	5	DCE/HFIP	18h	71
6	2	5	DCE/HFIP	18h	95 [94][c]
7	2.5	5	DCE/HFIP	18h	64
8	2	7.5	DCE/HFIP	18h	53
9	2	10	DCE/HFIP	18h	22
10	2	5	DCE/HFIP	24h	77
11	2	5	DCE/HFIP	48h	Decomposition
12	2	5	DCE	18h	56
13	2	5	DCM	18h	35
14	2	5	HFIP	18h	44
15	2	5	Chloroben/HFIP	18h	52
16	2	5	Toluene/HFIP	18h	nr[b]
17	2	5	ACN/HFIP	18h	25
18	2	5	THF/HFIP	18h	Decomposition
19	2	5	DCE dried	18h	30
20	2	5	DCE/HFIP dried	18h	60
21	2	5	DCE/HFIP	18h	nr[b,d]
22	2	5	DCE/HFIP	18h	[80][c,e]

[a] Reaction conditions: all reactions were carried out with 0.3 mmol of **1a**, stirred in 3 mL of solvent under blue irradiation. [b] nr: no reaction. [c] The number between brackets refers to isolated yield after purification by column chromatography. [d] Reaction performed in the absence of light.[e] Reaction performed with 1mmol of **1a**.

4. RAMAN Spectroscopic investigations

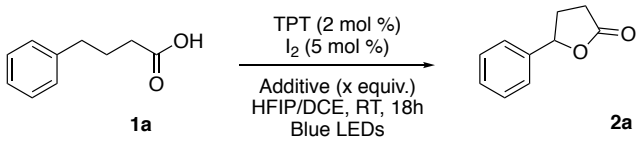
Figure S-3: RAMAN spectra



To clarify our hypothesis that the hypoiodite could be generated in the media, we performed RAMAN spectroscopic investigation of our reaction system. Previously, Ishihara and ourselves carried out these experiments to identify hypoiodite as the active species in related iodine catalyses.[1,2] A Renishaw inVia Raman microscope was used for the investigation, which was equipped with a thermoelectrically cooled CCD camera and a fiber-optic-cable for the excitation. Samples (glass cuvette containing the solution to measure) were irradiated with a laser beam with a wavelength of 532 nm. For all measurements, the energy of the laser was approximately 100 mW.
The first experiment was to get the spectrum of the solvent mixture HFIP/DCE (1:1). The spectrum is depicted in Figure S-3 on top (blue) and shows different bands assigned to the solvent in the system.
Then, an iodine solution (3.8 mg, 0.015 mmol) was added to 1 mL of the solvent mixture. The spectrum was recorded and depicted in Figure S-3 (orange). 2 new bands are now visible, the first one at 210 cm^{-1} assigned to molecular iodine I_2 and the other one at the hypoiodite IO^- at 419 cm^{-1}. Regarding the spectrum of the solution of TPT (2.4 mg, 0.006 mmol) in 1 mL of the solvent mixture depicted Figure S-3 in green, we observed one new band visible at 957 cm^{-1}. The spectrum of the solution of the substrate **1a** (49.3 mg, 0.3 mmol) in 1 ml of the solvent mixture is comparable with the one of the solvent mixture without any new bands.
At this point, the reaction was investigated. To this end, the substrate **1a** (49.3 mg, 0.3 mmol), TPT (2.4 mg, 0.006 mmol) and molecular iodine (3.8 mg, 0.015 mmol) were added to a vial containing 1 mL of the solvent mixture, stirred in the dark in order to dissolve everything and the RAMAN spectrum was measured 1h after. The spectrum is shown Figure S-3 (grey) and we noticed the presence of both molecular iodine at 210 cm^{-1} and the hypoiodite at 419 cm^{-1}. The last experiment is the measurement of a solution of **1a** (49.3 mg, 0.3 mmol), TPT (2.4 mg, 0.006 mmol) and molecular iodine (3.8 mg, 0.015 mmol) irradiated under blue light during 3 hours. The spectrum (Figure S-3, purple) is showing us that hypoiodite at 419 cm^{-1} and molecular iodine at 210 cm^{-1} are still present in the reaction medium. It confirms the equilibrium between molecular iodine, hydrogen iodide and hypoiodite.

5. Quenching experiments

Scheme S-4: Quenching experiments by radical quenchers

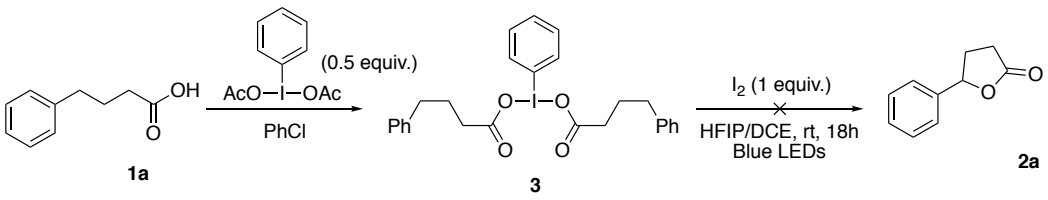


Additive = BHT (1 equiv.): nr
= TEMPO (2 equiv.): nr

To determine if our reaction is involving radical species, we carried out two different quenching experiments (Scheme S-4). To this end, BHT (66 mg, 0.3 mmol, 1 equiv.) or TEMPO (93.7 mg, 0.6 mmol, 2 equiv.) were separately added to a solution of the substrate **1a** (49.3 mg, 0.3 mmol, 1 equiv.), molecular iodine (3.8 mg, 0.015 mmol, 5 mol %) and TPT (2.4 mg, 0.006 mmol, 2 mol %) in the solvent mixture HFIP/DCE 1:1 (3 mL). The solutions were irradiated 18h at rt under blue light. NMR yields were measured using 1,3,5-trimethoxybenzene as a standard. Both reactions were quenched by either BHT or TEMPO. As a conclusion, we assumed that the process is working under a radical pathway.

6. Investigation of the reactivity of the [bis(4-phenylbutanoxy)iodo]benzene 3

Scheme S-5: Formation and reactivity of the [bis(4-phenylbutanoxy)iodo]benzene 3



*Synthesis of the [bis(4-phenylbutanoxy)iodo]benzene **3***: A solution of the substrate **1a** (328 mg, 2 mmol, 1 equiv.) and (diacetoxyiodo)benzene (322 mg, 1 mmol, 0.5 equiv.) in chlorobenzene was stirred 10 minutes. Then, the solvent was removed under vacuum. We repeated three times this procedure to finally got **3** as an oil in 98 % yield (520 mg, 0.98 mmol).

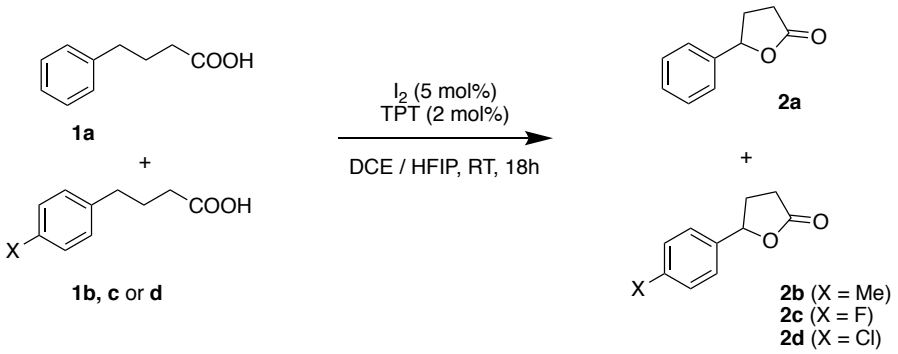
*Reactivity of the [bis(4-phenylbutanoxy)iodo]benzene **3***: A solution of **3** (53 mg, 0.1 mmol, 1equiv.) and molecular iodine (25.4 mg, 0.1 mmol, 1 equiv.) in a solvent mixture HFIP/DCE (15 mL) was stirring 18h at rt under blue LEDs irradiation. The solvent was then removed and a crude NMR was taken. As expected, no trace of product was observed indicating that the O-I bond is formed but decomposes under irradiation to regenerate the starting material and traces of alkane due to the decarboxylation.

[bis(4-phenylbutanoxy)iodo]benzene 3:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.60 – 7.56 (m, 1H), 7.48 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 2H), 7.28 – 7.23 (m, 4H), 7.19 – 7.15 (m, 2H), 7.13 – 7.10 (m, 4H), 2.58 (t, *J* = 7.6 Hz, 4H), 2.28 (t, *J* = 7.4 Hz, 4H), 1.91 – 1.84 (m, 4H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.6, 141.7, 135.1, 131.8, 131.0, 128.6, 128.4, 126.0, 122.0, 35.3, 33.5, 27.4.
HRMS: 3 is not stable under usual ionization conditions.
IR v(cm^{-1}): 3025, 2928, 1646, 1496, 1443, 1225, 994, 735, 698.
The spectrum of **3** is depicted on page 39.

7. Hammett correlation studies

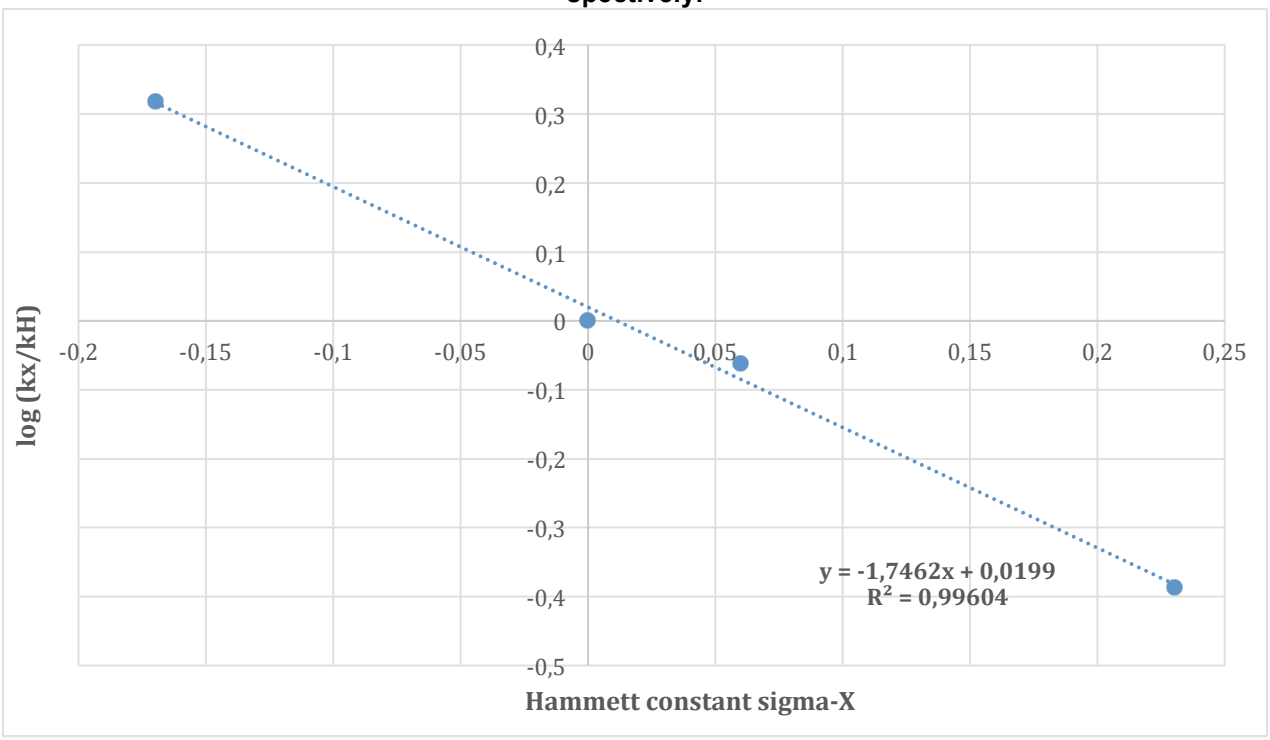
Scheme S-6: Hammett correlation



The requisite carboxylic acid **1a** and **1b**, **c** or **d** (0.3 mmol, 1.0 equiv.), iodine (3.8 mg, 0,015 mmol, 5 mol%) and 2,4,6-tetraphenylpyrylium tetrafluoroborate (2.4 mg, 0,003 mmol, 2 mol%) were added to a reaction tube. 1.5 mL of DCE and 1.5 mL of 1,1,1,3,3,3-hexafluoroisopropanol were added and the resulting mixture was stirred to form a homogeneous solution. Then, the reaction was irradiated with blue LEDs for 18h at room temperature. After 18h of irradiation, Chloroform was added and the mixture washed three times with a mixture of saturated solution of $Na_2S_2O_3$ and $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel using a mixture of hexane and ethyl acetate to give the pure product. For each independent run, the ratio of the two products (**2a** vs **2b**, **c** or **d** respectively) was calculated with a 5% error from the resulting ^{1}H NMR spectra.

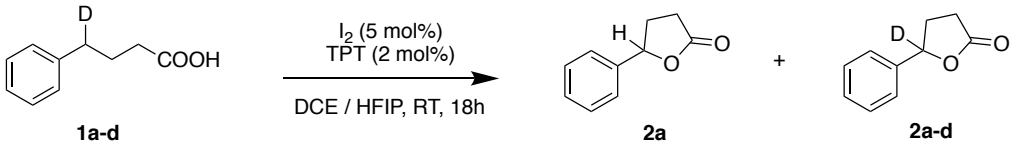
Entry	X	Log(k_X/k_H)	Hammett constant $\sigma_{p\text{-}X}$
1	Cl	-0,387	0.23
2	F	-0,061103	0.06
3	H	0	0
4	Me	0,31803	-0.17

Figure S-7: Hammett correlation studies. Kinetic competition experiments between 1a and 1b, c or d respectively.



8. Kinetic isotope effect

Scheme S-8: Determination of the KIE



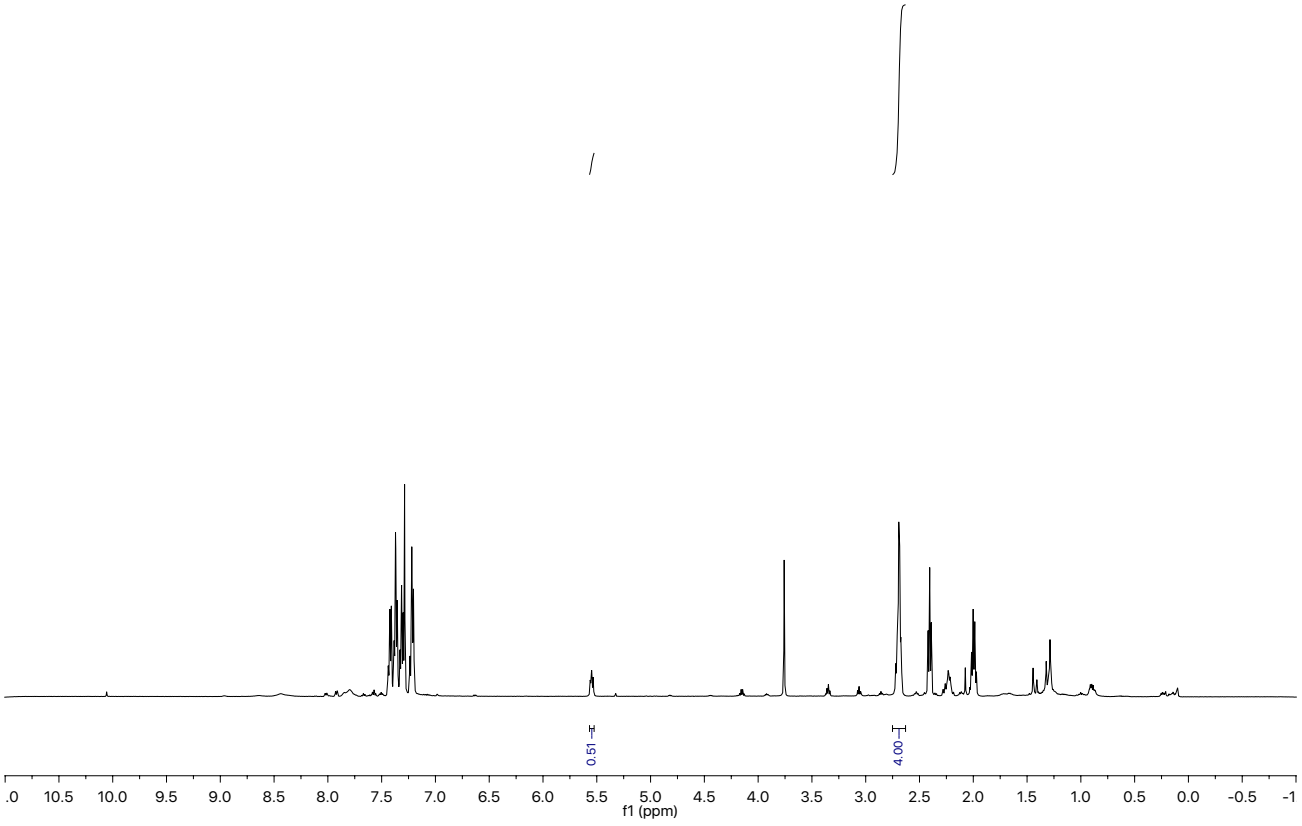
1a-d **2a** **2a-d**

$K_H / K_D = 1.0$

The kinetic isotope effect was determined by an intramolecular isotope-labelling experiment. For this investigation, the mono-deuterated substrate **1a-d** was synthesised (GP-2') and subjected to the optimised reaction conditions.

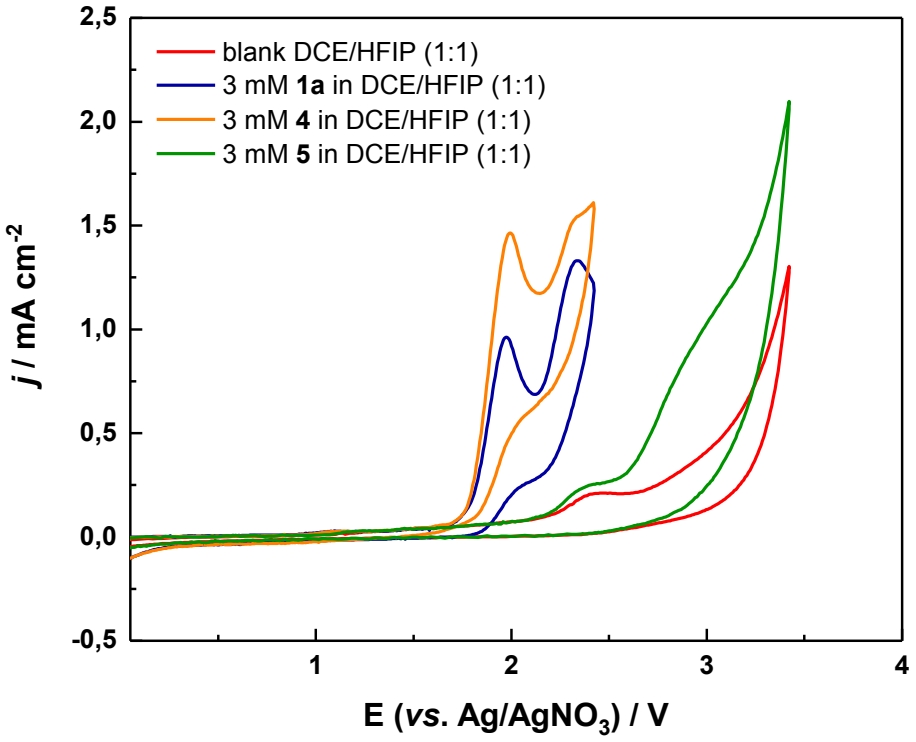
The carboxylic acid **1a-d** (16.5 mg, 0.1 mmol, 1.0 equiv.), iodine (1.3 mg, 0,005 mmol, 5 mol%) and 2,4,6-tetraphenylpyrylium tetrafluoroborate (0.8 mg, 0,001 mmol, 2 mol%) were added to a reaction tube. 0.5 mL of DCE and 0.5 mL of 1,1,1,3,3,3-hexafluoroisopropanol were added and the resulting mixture was stirred to form a homogeneous solution. Then, the reaction was irradiated with blue LEDs for 18h at room temperature. After 18h of irradiation, Chloroform was added and the mixture washed three times with a mixture of saturated solution of $Na_2S_2O_3$ and $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude was taken up in $CDCl_3$ and the resulting mixture was transferred to a NMR tube for analysis. The ^{1}H-NMR spectrum (Figure S-6) revealed a KIE value of 1.0 indicating that we are quickly losing the benzylic proton to form the benzylic radical.

Figure S-9: Crude ^{1}H-NMR spectrum to determine the KIE.

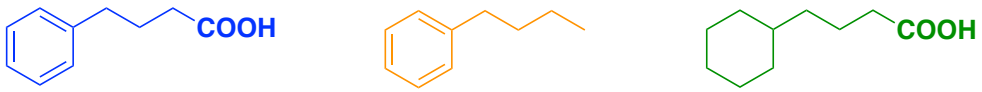


9. Cyclic voltammetry

Figure S-10: Cyclic voltammograms



Cyclic voltammograms of the blank (red line), 3 mM 4-phenylbutyric acid (**1a**, blue line), 3 mM 4-phenylbutane (**4**, orange line) and 3 mM 4-cyclohexylbutyric acid (**5**, green line); working electrode: glassy carbon; supporting electrolyte: Bu_4NBF_4; reference electrode: $Ag/AgNO_3$; scan rate: 50 mV/s.



1a **4** **5**

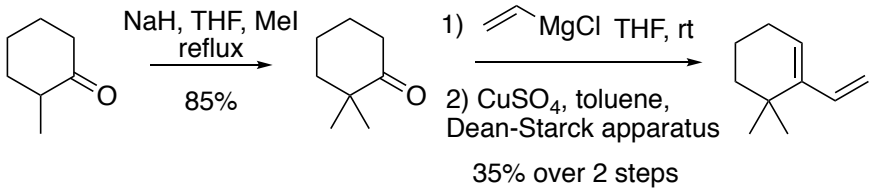
Cyclic voltammetry was carried out in a three-electrode cell using a Parstat 2273 potentiostat (Princeton Applied Research). As working electrode, a glassy carbon disk (diameter: 3 mm) and as counter electrode a platinum wire were used. The working electrode was polished using alumina (0.05 μm) prior to each experiment. As reference served a $Ag/AgNO_3$ electrode (silver wire in 0.1 M Bu_4NClO_4/CH_3CN; 0.01 M $AgNO_3$).[3] The reference electrode was separated from the cell with a Vycor frit. 1,1,1,3,3,3-Hexafluoroisopropanole (99%, Fluorochem) and 1,2-dichloroethane (99+%, Alfa Aesar) were used as received. As supporting electrolyte served Bu_4NBF_4 (99%, Aldrich). The electrolyte was purged with Argon (5 min) prior to each experiment.

As a conclusion, it can be assumed that TPT is oxidizing the phenyl ring instead of the carboxylic acid throughout the initial step of our proposed mechanism.

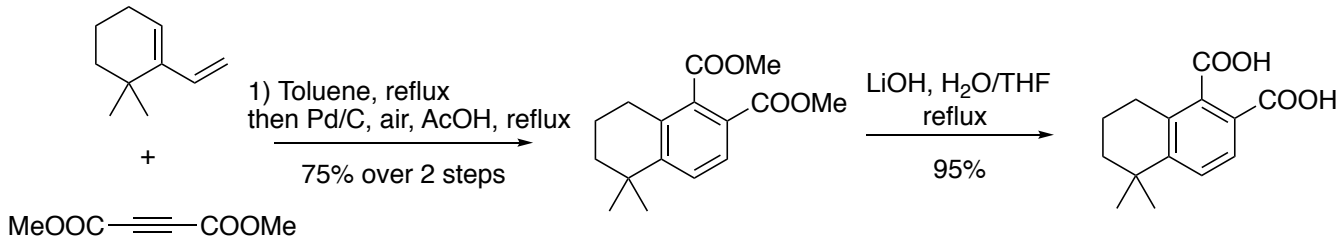
10. Attempts to afford the Miltiorin D

Following the procedures reported in literature,[4,5,6] we synthesized the substrate 5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylic acid (*CAS 92252-43-2*) in order to assess it in our optimized conditions. Unfortunately, only starting material was recovered. Even high catalyst loadings (5 mol% of TPT and 15 mol% of iodine) did not provide the desire lactonization.

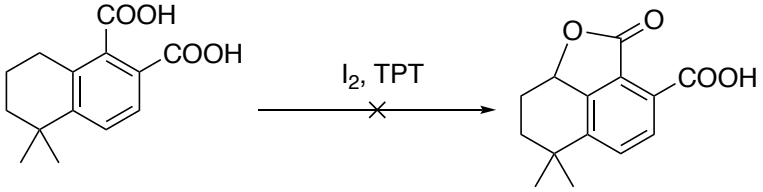
Following the procedures reported in literature[4] we achieved the 6,6-dimethyl-1-vinylcyclohex-1-ene.



Following the procedures reported in literature,[5.6] we synthesized the target substrate 5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylic acid (*CAS 92252-43-2*).



Attempts to access the desire lactone were not successful due to the fact that the arene moiety is too electron-deficient to be oxidised by TPT*.



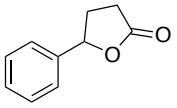
5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylic acid (CAS 92252-43-2) was isolated as a red solid in an overall yield of 21%.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 2.89 (t, *J* = 6.4 Hz, 2H), 1.90 – 1.81 (m, 2H), 1.72 – 1.64 (m, 2H), 1.32 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.9, 171.2, 153.0, 135.3, 133.3, 128.2, 128.1, 123.6, 38.3, 34.9, 31.7, 27.4, 19.0.

11. Procedures and Characterization Data

11.1 General Procedure for the lactonization (GP-1)

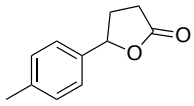
The requisite carboxylic acid **1** (0.3 mmol, 1.0 equiv.), iodine (3.8 mg, 0,015 mmol, 5 mol%) and 2,4,6-tetraphenylpyrylium tetrafluoroborate (2.4 mg, 0,003 mmol, 2 mol%) were added to a reaction tube. 1.5 mL of DCE and 1.5 mL of 1,1,1,3,3,3-hexafluoroisopropanol were added and the resulting mixture was stirred to form a homogeneous solution. Then, the reaction was irradiated with blue LEDs for 18h at room temperature. After 18h of irradiation, DCM was added and the mixture washed three times with a saturated solution of $Na_2S_2O_3$ and $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel using a mixture of hexane and ethyl acetate to give the pure product.

5-phenyldihydrofuran-2(3H)-one 2a



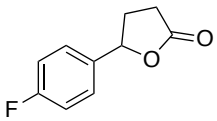
Following the general procedure GP-1, **2a** was isolated as a pale yellow oil in 94% yield (45.8 mg, 0.28 mmol).
For the 1mmol-Scale experiment, **2a** was obtained in 80% yield (130.9 mg, 0.8 mmol).
The NMR spectra match those previously described in literature.[7,8]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.32 (m, 5H), 5.52 (dd, *J* = 7.99, 6.14 Hz, 1H), 2.71 – 2.62 (m, 3H), 2.26 – 2.14 (m, 1H),
^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.0, 139.5, 128.9, 128.6, 125.4, 81.3, 31.1, 29.1.

5-(p-tolyl)dihydrofuran-2(3H)-one 2b



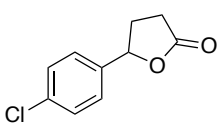
Following the general procedure GP-1, **2b** was isolated as a white solid in 65% yield (34.3 mg, 0.2 mmol). The NMR spectra match those previously described in literature.[7,9]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 – 7.19 (m, 4H), 5.48 (dd, *J* = 8.07, 6.21 Hz, 1H), 2.67 – 2.59 (m, 3H), 2.36 (s, 3H), 2.23 – 2.15 (m, 1H),
^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.1, 138.5, 136.5, 129.5, 125.5, 81.5, 31.1, 29.2, 21.3.

5-(4-fluorophenyl)dihydrofuran-2(3H)-one 2c



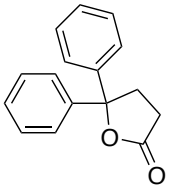
Following the general procedure GP-1, **2c** was isolated as a white solid in 86% yield (46 mg, 0.26 mmol). The NMR spectra match those previously described in literature.[7,8]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.28 (m, 2H), 7.10 – 7.04 (m, 2H), 5.48 (dd, *J* = 8.37, 5.83 Hz, 1H), 2.69 – 2.60 (m, 3H), 2.22 – 2.10 (m, 1H),
^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.7, 162.8 (d, $J_{C–F}$ = 247.2 Hz), 135.2 (d, $J_{C–F}$ = 3.23 Hz), 127.3 (d, $J_{C–F}$ = 8.26 Hz), 115.8 (d, $J_{C–F}$ = 21.7 Hz), 80.8, 31.1, 29.1.
^{19}F NMR (376 MHz, $CDCl_3$): δ = -113.5.

5-(4-chlorophenyl)dihydrofuran-2(3H)-one 2d



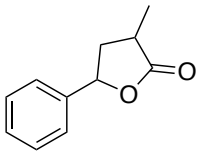
Following the general procedure GP-1, **2d** was isolated as a pale yellow oil in 51% yield (30 mg, 0.15 mmol). The NMR spectra match those previously described in literature.[7,10]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.33 (m, 2H), 7.28 – 7.24 (m, 2H), 5.47 (dd, *J* = 8.21, 6.13 Hz, 1H), 2.7 – 2.59 (m, 3H), 2.20 – 2.08 (m, 1H),
^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.6, 138.0, 134.4, 129.1, 126.8, 80.5, 31.1, 29.0.

5,5-diphenyldihydrofuran-2(3*H*)-one 2e



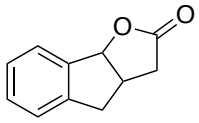
Following the general procedure GP-1, **2e** was isolated as a white solid in 21% yield (15 mg, 0.06 mmol). The NMR spectra match those previously described in literature. HRMS, IR spectrum and the melting point are also described in literature.[8]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.40 (m, 4H), 7.37 – 7.32 (m, 4H), 7.30 – 7.26 (m, 2H), 2.91 (t, *J* = 7.7 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.2, 143.2, 128.7, 128.0, 125.5, 89.9, 35.8, 29.2.

3-methyl-5-phenyldihydrofuran-2(3H)-one 2f



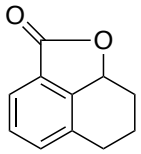
Following the general procedure GP-1, **2f** was isolated as a pale yellow oil in 74% yield (39.1 mg, 0.22 mmol). The NMR spectra match those previously described in literature. HRMS and IR spectrum are also described in literature.[7,11]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.30 (m, 5H), 5.57 (dd, *J* = 7.8, 4.6 Hz, 0.4H), 5.36 (m, 0,6H), 2.86 – 2.78 (m, 1.4H), 2.78 – 2.71 (m, 0.4H), 2.47 – 2.42 (m, 0.4H), 2.39 – 2.33 (m, 0.4H), 1.90 – 1.81 (m, 0.6H), 1.34 (s, 1.5H), 1.33 (s, 1.5H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.0, 179.3, 139.9, 139.3, 128.9, 128.8, 128.6, 128.3, 125.6, 125.1, 79.3, 78.4, 40.1, 38.5, 36.5, 33.7, 15.5, 15.1.

3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one 2g



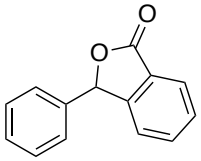
Following the general procedure GP-1, **2g** was isolated as a pale yellow oil in 71% yield (37 mg, 0.21 mmol). The NMR spectra match those previously described in literature.[12]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.5 Hz, 1H), 7.37 – 7.26 (m, 3H), 5.89 (d, *J* = 7.0 Hz, 1H), 3.41 – 3.29 (m, 2H), 2.94 – 2.86 (m, 2H), 2.42 – 2.36 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.0, 142.6, 138.9, 130.1, 127.7, 126.5, 125.5, 87.8, 38.0, 37.5, 35.8.

6,7,8,8a-tetrahydro-2H-naphtho[1,8-bc]furan-2-one 2h



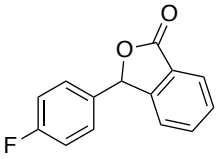
Following the general procedure GP-1, **2h** was isolated as a pale yellow oil in 21% yield (11 mg, 0.06 mmol).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 – 7.66 (m, 1H), 7.44 (td, *J* = 7.5, 0.7 Hz, 1H), 7.38 (dq, *J* = 7.5, 1.0 Hz, 1H), 5.23 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.04 (dddd, *J* = 17.8, 8.2, 2.3, 1.2 Hz, 1H), 2.78 – 2.71 (m, 1H), 2.52 (ddt, *J* = 11.6, 5.3, 3.8 Hz, 1H), 2.22 – 2.17 (m, 1H), 1.99 – 1.94 (m, 1H), 1.41 (dtd, *J* = 13.1, 11.7, 4.3 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.8, 149.6, 134.2, 132.4, 130.0, 124.6, 122.9, 78.3, 27.6, 24.9, 19.8.
HRMS: calc. for $C_{11}H_{11}O_2^+$: 175.0747; found: 175.0754.
IR ν(cm^{-1}): 2920, 1754, 1482, 1448, 1355, 1254, 1088, 982, 733.

3-phenylisobenzofuran-1(3H)-one 2i



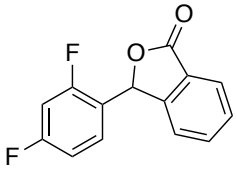
Following the general procedure GP-1, **2i** was isolated as a white solid in 74% yield (46.2 mg, 0.22 mmol). The NMR spectra match those previously described in literature. HRMS, IR spectrum and the melting point are also described in literature.[13,14]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.7 Hz, 1H), 7.65 (td, *J* = 7.5, 1.2 Hz, 1H), 7.55 (tt, *J* = 7.5, 0.9 Hz, 1H), 7.39 – 7.36 (m, 3H), 7.33 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.29 – 7.27 (m, 2H), 6.40 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 149.8, 136.6, 134.4, 129.5, 129.4, 129.1, 127.1, 125.8, 125.7, 123.0, 82.8.

3-(4-fluorophenyl)isobenzofuran-1(3H)-one 2j



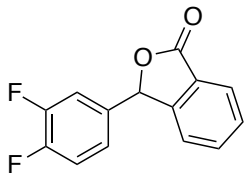
Following the general procedure GP-1, **2j** was isolated as a white solid in 73% yield (50 mg, 0.22 mmol). The NMR spectra match those previously described in literature. The melting point is also described in literature.[15,16]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.6 Hz, 1H), 7.68 (td, *J* = 7.5, 1.2 Hz, 1H), 7.58 (tt, *J* = 7.5, 0.8 Hz, 1H), 7.33 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.10 – 7.06 (m, 2H), 6.40 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4, 164.6 (d, J_{C-F} = 248.9 Hz), 149.5, 134.5, 132.4 (d, J_{C-F} = 3.2 Hz), 129.7, 129.2 (d, J_{C-F} = 8.4 Hz), 125.9, 125.8, 123.0, 116.1 (d, J_{C-F} = 21.9 Hz), 82.1.
^{19}F NMR (376 MHz, $CDCl_3$): δ = -111.9.

3-(2,4-difluorophenyl)isobenzofuran-1(3*H*)-one 2k



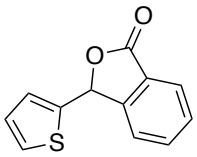
Following the general procedure GP-1, **2k** was isolated as a white solid in 31% yield (25 mg, 0.10 mmol).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.7 Hz, 1H), 7.68 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.57 (tt, *J* = 7.5, 0.8 Hz, 1H), 7.40 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.10 (td, *J* = 8.4, 6.2 Hz 1H), 6.92 – 6.82 (m, 2H), 6.68 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 163.4 (dd, J_{C-F} = 251.4, 12.1 Hz), 160.9 (dd, J_{C-F} = 251.1, 12.2 Hz), 148.9 134.7, 129.8, 129.2 (dd, J_{C-F} = 10.0, 4.9 Hz), 125.9, 125.6, 122.8 (d, J_{C-F} = 2.1 Hz), 120.3 (dd, J_{C-F} = 13.3, 3.8 Hz), 112.1 (dd, J_{C-F} = 21.6, 3.7 Hz), 104.6 (t, J_{C-F} = 25.3 Hz), 76.3 (d, J_{C-F} = 3.6 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ = -108.0 (d, J_{F-F} = 8.3 Hz), -114.2 (d, J_{F-F} = 8.3 Hz).
HRMS: calc. for $C_{14}H_8F_2O_2$: 247.0565; found: 247.0569.
IR ν(cm^{-1}): 1754, 1600, 1508, 1288, 1207, 1143, 1101, 973, 738.
T_M: 88 – 90 ºC.

3-(3,4-difluorophenyl)isobenzofuran-1(3*H*)-one 2l



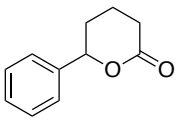
Following the general procedure GP-1, **2l** was isolated as a white solid in 72% yield (53 mg, 0.21 mmol).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.6 Hz, 1H), 7.68 (td, *J* = 7.5, 1.2 Hz, 1H), 7.59 (tt, *J* = 7.5, 0.8 Hz, 1H), 7.34 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.09 – 7.06 (m, 2H), 6.35 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 151.8 (dd, $J_{C–F}$ = 250.8, 11.9 Hz), 149.8 (dd, $J_{C–F}$ = 247.6, 10.7 Hz), 149.0 134.7, 133.6 (dd, $J_{C–F}$ = 5.4, 4.2 Hz), 129.9, 126.0, 125.6, 123.5 (dd, $J_{C–F}$ = 6.6, 3.7 Hz), 122.9, 118.1 (d, $J_{C–F}$ = 17.6 Hz), 116.3 (d, $J_{C–F}$ = 18 Hz), 81.4 (d, $J_{C–F}$ = 1.5 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ = -135.8 (d, $J_{F–F}$ = 21.1 Hz), -136.2 (d, $J_{F–F}$ = 21.0 Hz).
HRMS: calc. for $C_{14}H_8F_2O_2$: 247.0565; found: 247.0573.
IR ν(cm^{-1}): 1759, 1516, 1465, 1285, 1105, 1060, 1017, 942, 732.
T_M: 80 – 83 ºC.

3-(thiophen-2-yl)isobenzofuran-1(3*H*)-one 2m



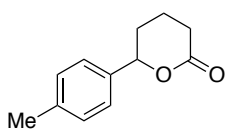
Following the general procedure GP-1, **2m** was isolated as a pale yellow oil in 60% yield (39 mg, 0.18 mmol).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.71 (td, *J* = 7.5, 1.1 Hz, 1H), 7.60 (tt, *J* = 7.5, 0.8 Hz, 1H), 7.48 – 7.46 (m, 1H), 7.37 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.15 (ddd, *J* = 3.6, 1.2, 0.7 Hz, 1H), 7.02 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.67 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ =169.9, 148.8, 139.0, 134.5, 129.9, 128.0, 127.7, 127.2, 126.1, 125.8, 123.3, 78.0.
HRMS: calc. for $C_{12}H_9O_2S$: 217.0320; found: 217.0318.
IR ν(cm^{-1}): 1746, 1465, 1285, 1212, 1066, 938, 694.

6-phenyltetrahydro-2*H*-pyran-2-one 2n



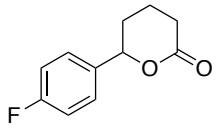
Following the general procedure GP-1, **2n** was isolated as a pale yellow oil in 57% yield. The NMR spectra match those previously described in literature.[17]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 – 7.29 (m, 5H), 5.36 (dd, *J* = 10.4, 3.4 Hz, 1H), 2.71 (dtd, *J* = 17.8, 6.3, 1.1 Hz, 1H), 2.58 (dt, *J* = 17.8, 7.8 Hz, 1H), 2.22 – 2.12 (m, 1H), 2.04 – 1.94 (m, 2H), 1.93 – 1.80 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.4, 139.9, 128.7, 128.4, 125.8, 81.8, 30.6, 29.6, 18.7.

6-(*p*-tolyl)tetrahydro-2*H*-pyran-2-one 2o



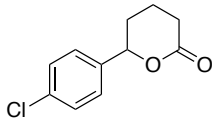
Following the general procedure GP-1, **2o** was isolated as a white solid in 35% yield. The NMR spectra match those previously described in literature.[18]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.16 (m, 4H), 5.33 (dd, *J* = 10.4, 3.3 Hz, 1H), 2.70 (dt, *J* = 17.6, 6.3 Hz, 1H), 2.57 (dt, *J* = 17.8, 7.8 Hz, 1H), 2.35 (s, 3H), 2.20 – 2.10 (m, 1H), 2.03 – 1.93 (m, 2H), 1.93 – 1.80 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5, 138.1, 136.8, 129.3, 125.7, 81.6, 30.5, 29.5, 21.1, 18.6.

6-(4-fluorophenyl)tetrahydro-2*H*-pyran-2-one 2p



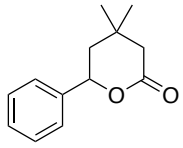
Following the general procedure GP-1, **2p** was isolated as a white solid in 54% yield. The NMR spectra match those previously described in literature.[19]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.29 (m, 2H), 7.10 – 7.02 (m, 2H), 5.32 (dd, *J* = 10.7, 3.3 Hz, 1H), 2.71 (dtd, *J* = 17.8, 6.3, 1.1 Hz, 1H), 2.57 (dt, *J* = 17.8, 7.9 Hz, 1H), 2.20 – 2.11 (m, 1H), 2.04 – 1.95 (m, 2H), 1.90 – 1.77 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 162.7 (d, $J_{C–F}$ = 246.9 Hz), 135.7 (d, $J_{C–F}$ = 3.2 Hz), 127.7 (d, $J_{C–F}$ = 8.4 Hz), 115.7 (d, $J_{C–F}$ = 21.5 Hz), 81.2, 30.7, 29.6, 18.8.
^{19}F NMR (376 MHz, $CDCl_3$): δ = -113.8.

6-(4-chlorophenyl)tetrahydro-2*H*-pyran-2-one 2q



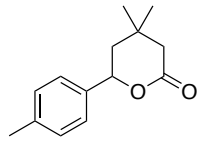
Following the general procedure GP-1, **2q** was isolated as a white solid in 50% yield. The NMR spectra match those previously described in literature.[18]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.33 (m, 2H), 7.30 – 7.26 (m, 2H), 5.32 (dd, *J* = 10.7, 3.3 Hz, 1H), 2.71 (dtd, *J* = 17.8, 6.3, 1.1 Hz, 1H), 2.57 (dt, *J* = 17.8, 7.9 Hz, 1H), 2.20 – 2.11 (m, 1H), 2.03 – 1.93 (m, 2H), 1.89 – 1.75 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 138.4, 134.2, 128.9, 127.2, 81.0, 30.7, 29.6, 18.7.

4,4-dimethyl-6-phenyltetrahydro-2*H*-pyran-2-one 2r



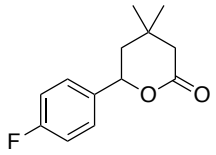
Following the general procedure GP-1, **2r** was isolated as a pale yellow oil in 59% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.29 (m, 5H), 5.38 (dd, *J* = 12.1, 3.6 Hz, 1H), 2.51 (dd, *J* = 16.6, 1.8 Hz, 1H), 2.35 (d, *J* = 16.7 Hz, 1H), 1.92 (ddd, *J* = 14.3, 3.6, 1.7 Hz, 1H), 1.76 (dd, *J* = 14.3, 12.1 Hz, 1H), 1.22 (s, 3H), 1.11 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.7, 139.8, 128.7, 128.4, 125.9, 79.1, 45.2, 44.1, 31.2, 30.3, 27.6.
HRMS: calc. for $C_{13}H_{17}O_2$: 205.1234; found: 205.1236.
IR ν(cm^{-1}): 2956, 1734, 1234, 1153, 1026, 753, 698.

4,4-dimethyl-6-(*p*-tolyl)tetrahydro-2*H*-pyran-2-one 2s



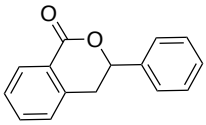
Following the general procedure GP-1, **2s** was isolated as a colorless oil in 43% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.29 (m, 5H), 5.38 (dd, *J* = 12.1, 3.6 Hz, 1H), 2.51 (dd, *J* = 16.6, 1.8 Hz, 1H), 2.35 (d, *J* = 16.7 Hz, 1H), 1.92 (ddd, *J* = 14.3, 3.6, 1.7 Hz, 1H), 1.76 (dd, *J* = 14.3, 12.1 Hz, 1H), 1.22 (s, 3H), 1.11 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.8, 138.2, 136.9, 129.4, 125.9, 79.1, 45.2, 44.1, 31.2, 30.3, 27.6, 21.3.
HRMS: calc. for $C_{14}H_{19}O_2$: 219.1391; found: 219.1390.
IR ν(cm^{-1}): 2955, 1735, 1370, 1269, 1234, 1154, 1076, 1030, 796.

6-(4-fluorophenyl)-4,4-dimethyltetrahydro-2*H*-pyran-2-one 2t



Following the general procedure GP-1, **2t** was isolated as a white solid in 67% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.29 (m, 2H), 7.09 – 7.02 (m, 2H), 5.35 (dd, *J* = 12.2, 3.5 Hz, 1H), 2.50 (dd, *J* = 16.6, 1.7 Hz, 1H), 2.34 (d, *J* = 16.7 Hz, 1H), 1.90 (ddd, *J* = 14.3, 3.6, 1.7 Hz, 1H), 1.73 (dd, *J* = 14.2, 12.2 Hz, 1H), 1.21 (s, 3H), 1.11 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5, 162.7 (d, *J* = 246.9 Hz), 135.6 (d, *J* = 3.1 Hz), 127.8 (d, *J* = 8.2 Hz), 115.6 (d, *J* = 21.6 Hz), 78.4, 45.2, 44.0, 31.2, 30.3, 27.6.
^{19}F NMR (376 MHz, $CDCl_3$): δ = -113.4.
HRMS: calc. for $C_{13}H_{16}FO_2$: 223.1140; found: 223.1142.
IR ν(cm^{-1}): 2958, 1724, 1604, 1513, 1371, 1237, 1151, 1075, 1026, 1012, 803.
T_M: 45.6 - 48.6 ºC.

3-phenylisochroman-1-one 2u



Following the general procedure GP-1, **2u** was isolated as a yellow oil in 96% yield. The NMR spectra match those previously described in literature.[20]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.51 – 7.33 (m, 7H), 7.29 (d, *J* = 7.6 Hz, 1H), 5.55 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.34 (dd, *J* = 16.5, 12.0 Hz, 1H), 3.13 (dd, *J* = 16.5, 3.2 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.4, 139.1, 138.7, 134.0, 130.5, 128.8, 128.8, 128.0, 127.5, 126.2, 125.2, 80.1, 35.7.

11.2 General Procedure for the Substrate synthesis (GP-2)

Step 1: Friedel-Craft Reaction
In a flame-dried Schlenk flask were added substituted benzene (10 mL), which was used as solvent, and anhydrous aluminum chloride (4 g, 30 mmol, 3 equiv.). The mixture was stirred using a magnetic stirrer at room temperature for 30 min. To this mixture, succinic anhydride (1.0 g, 10 mmol, 1 equiv.) was added in portions with continuous stirring. Vigorous reaction started with the evolution of HCl gas. Stirring was continued for overnight at 80°C. HCl (1M) was added to the mixture to hydrolyze. The reaction was extracted with EtOAc. The combined organic layers were washed with a solution of 10 % NaOH. To the combined aqueous layers were added a 6 N HCl solution to adjust pH = 1-2. The aqueous phase was then extracted again with EtOAc and dried over Na_2SO_4 before to be concentrated. The crude compound was used in the next step without any purifications.

Step 2: Reduction of the ketone
Hydrazine hydrate (20.4 mmol, 4 equiv.) and KOH pellets (20.4 mmol, 4 equiv.) were added to a solution of the crude from the step 1 (5.1 mL, 1 equiv.) in ethylene glycol (10 mL), and the reaction mixture was heated to 180 °C for 10 h. The reaction mixture was cooled to room temperature and diluted with water. The aqueous layer was washed with diethyl ether, acidified with a solution of 6N HCl and then extracted twice with diethyl ether. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate and 1 % of acetic acid as eluent.

11.3 General Procedure for the substrate Synthesis (GP-2')

Step 1': Friedel-Craft Reaction
In a flame-dried Schlenk flask were added substituted benzene (10 mL), which was used as solvent, and anhydrous aluminum chloride (4 g, 30 mmol, 3 equiv.). The mixture was stirred using a magnetic stirrer at room temperature for 30 min. To this mixture, phthalic anhydride (1.48 g, 10 mmol, 1 equiv.) was added in portions with continuous stirring. Vigorous reaction started with the evolution of HCl gas. Stirring was continued for overnight at 80°C. HCl (1M) was added to the mixture to hydrolyze. The reaction was extracted with EtOAc. The combined organic layers were washed with a solution of 10 % NaOH. To the combined aqueous layers were added a 6 N HCl solution to adjust pH = 1-2. The aqueous phase was then extracted again with EtOAc and dried over Na_2SO_4 before to be concentrated. The crude compound was used in the next step without any purifications.

Step 2': Reduction of the ketone (Part 1)
Trifluoroacetic acid (4.1 mL) was added dropwise to a solution of the crude of the previous step (4.1 mmol, 1.0 equiv) and triethylsilane (12.3 mmol, 3.0 equiv) in chloroform (4.1 mL) at 0 ºC. The solution was then heated at reflux for 18 h. After cooling to room temperature, the reaction was diluted with diethyl ether and washed twice with brine, dried with sodium sulfate, and concentrated. The intermediates were used without any purifications.

Step 3': reduction of the ketone (Part 2)
A flame dried Schlenk tube equipped with a stirrer bar was charged with the crude from the previous step, Pd/C (20 w%) and ethyl acetate (5 mL/mmol) were added and the reaction was stirred under atmospheric pressure of hydrogen gas overnight. The mixture was filtered through Celite and concentrated to yield the crude ester which was purified by column chromatography using hexane/ethyl acetate and 1 % of acetic acid as eluent.

11.4 Procedure to synthesise 4,4-diphenylbutanoic acid 1e

In a flame-dried Schlenk flask was added benzene (10 mL), which was used as solvent, and anhydrous aluminum chloride (245 mg, 1.8 mmol, 1.5 equiv.). The mixture was stirred using a magnetic stirrer at room temperature for 30 min. To this mixture, 5-phenyldihydrofuran-2(3H)-one (Synthetized by GP-1, 200 mg, 1.23 mmol, 1 equiv.) was added in portions with continuous stirring for overnight at 80°C. HCl (1M) was added to the mixture to hydrolyze. The reaction was extracted with EtOAc. The combined organic layers were washed with a solution of 10 % NaOH. To the combined aqueous layers were added a 6 N HCl solution to adjust pH = 1-2. The aqueous phase was then extracted again with EtOAc and dried over Na_2SO_4 before to be concentrated. The crude acid was purified by column chromatography using hexane/ethyl acetate and 1 % of acetic acid as eluent to finally got **1e** (106 mg, 0.44 mmol, 36% yield).

11.5 Procedure to synthesise 2-methyl-4-phenylbutanoic acid 1f

A Schlenk tube equipped with a stirrer bar was charged with the 4-phenylbutanoic acid (1.64 g, 10 mmol, 1 equiv.) and THF (20 mL). The vessel was then cooled down to 0ºC. LDA (2M solution, 12.5 mL, 25 mmol, 2.5 equiv.) was added dropwise and the mixture was stirring 30 min at 0ºC. At this point, MeI (1.37 mL, 22 mmol, 2.2 equiv.) was added dropwise and the reaction was allowed to reach room temperature overnight. A saturated aqueous solution of NH_4Cl was added and the reaction was extracted with diethyl ether. The combined organic layers were washed with a solution of 10 % NaOH. To the combined aqueous layers were added a 6 N HCl solution to adjust pH = 1-2. The aqueous phase was then extracted again with diethyl ether and dried over Na_2SO_4 before to be concentrated. The crude acid was purified by column chromatography using hexane/ethyl acetate and 1 % of acetic acid as eluent to finally got **1f** (1.41 g, 8 mmol, 80% yield).

11.6 Procedure to synthesise 2-(2,3-dihydro-1H-inden-2-yl)acetic acid 1g

Step 1
A Schlenk tube equipped with a stirrer bar was charged with the trimethylphosphonoacetate (1.62 mL, 10 mmol, 1.0 equiv) and THF (5 mL/mmol) and the vessel was cooled to 0º C. *n*-BuLi (5 mL of a 2 M solution, 10 mmol, 1.0 equiv) was added dropwise and the reaction was stirred for one hour upon which time the 2-indanone (1.32 g, 10 mmol, 1.0 equiv) was added and the reaction was stirred for 18 hours at room temperature. A saturated aqueous solution of NH_4Cl was added and the resulting mixture extracted with diethyl ether (3 times). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude was not purified in this step.

Step 2
A flame dried Schlenk tube equipped with a stirrer bar was charged with the crude from the previous step, Pd/C (20 w%) and ethanol (5 mL/mmol) were added and the reaction was stirred under atmospheric pressure of hydrogen gas overnight. The mixture was filtered through Celite and concentrated to yield the crude ester which was not purified in this step.

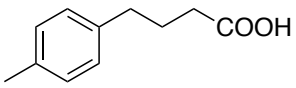
Step 3
The crude ester was stirred with $LiOH.H_2O$ (840 mg, 20 mmol, 2 equiv.) in a mixture of THF/H_2O (1/1) overnight. The reaction was washed with diethyl ether. The aqueous layer was acidified with a 6 N HCl solution to adjust pH = 1-2. The aqueous phase was then extracted again with diethyl ether and dried over Na_2SO_4 before to be concentrated. The crude acid was purified by column chromatography using Hexane/Ethyl acetate and 1 % of acetic acid as eluent to finally got **1g** (1.07 g, 6.1 mmol, 61% yield).

11.7 Procedure to synthesise 2-phenethylbenzoic acid 1u

Step 1
A schlenk tube equipped with a stirrer bar was charged with the (Phenylmethyl)triphenylphosphonium bromide (2.8 g, 6.5 mmol, 1.3 equiv.) and THF (15 mL) and the vessel was cooled to 0ºC. *n*-BuLi (5.2 mL of a 2.5 M solution, 13 mmol, 2.6 equiv.) was added dropwise and the reaction was stirred for one hour to form the ylide. Then, 2-carboxybenzaldehyde (750 mg, 5 mmol, 1 equiv.) was added portion wise and the mixture was stirred for 18h at room temperature. A aqueous solution of 1 M HCl was added and the resulting mixture extracted with diethyl ether (3 times). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude acid was purified by column chromatography using Hexane/Ethyl acetate and 1 % of acetic acid as eluent.

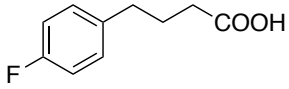
Step 2
A flame dried Schlenk tube equipped with a stirrer bar was charged with the purified compound from the previous step, Pd/C (20 w%) and ethanol (5 mL/mmol) were added and the reaction was stirred under atmospheric pressure of hydrogen gas overnight. The mixture was filtered through Celite to yield **1u** (905 mg, 4 mmol, 80% yield).

4-(*p*-tolyl)butanoic acid 1b



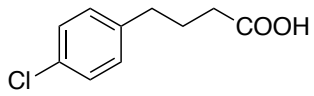
Following the general procedure GP-2, **1b** was isolated as a white solid in 66% yield. The NMR spectra match those previously described in literature. HRMS and the melting point are also described in literature.[21,22]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 – 7.08 (m, 4H), 2.70 – 2.64 (m, 2H), 2.43 – 2.32 (m, 5H), 2.04 – 1.92 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.2, 137.9, 135.3, 129.0, 128.2, 34.4, 33.2, 26.2, 20.9.

4-(4-fluorophenyl)butanoic acid 1c



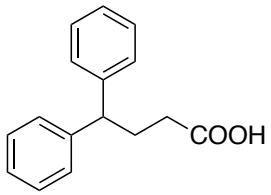
Following the general procedure GP-2, **1c** was isolated as a white solid in 64% yield. The melting point is described in literature.[23]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 – 7.14 (m, 2H), 6.97 – 7.02 (m, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.03 – 1.90 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.9, 161.4 (d, $J_{C–F}$ = 243.7 Hz), 136.8 (d, $J_{C–F}$ = 3.2 Hz), 129.8 (d, $J_{C–F}$ = 7.8 Hz), 115.17 (d, $J_{C–F}$ = 21.1 Hz), 34.16, 33.2, 26.3 (d, $J_{C–F}$ = 1.2 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ = -117.5.

4-(4-chlorophenyl)butanoic acid 1d



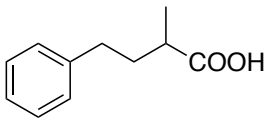
Following the general procedure GP-2, **1d** was isolated as a white solid in 54% yield. The NMR spectra match those previously described in literature. HRMS and the melting point are also described in literature.[24]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.21 (m, 2H), 7.17 – 7.12 (m, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.03 – 1.92 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.0, 139.6, 131.8, 129.8, 128.5, 34.3, 33.2, 26.1.

4,4-diphenylbutanoic acid 1e



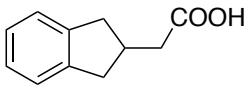
Following the procedure above-mentioned, **1e** was isolated as a white solid in 36% yield. The NMR spectra match those previously described in literature. HRMS, IR spectrum and the melting point are also described in literature.[25]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.29 (m, 8H), 7.29 – 7.21 (m, 2H), 4.02 (t, *J* = 7.6 Hz, 1H), 2.52 – 2.43 (m, 2H), 2.43 – 2.35 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.6, 143.9, 128.6, 127.8, 126.4, 50.3, 32.3, 30.3.

2-methyl-4-phenylbutanoic acid 1f



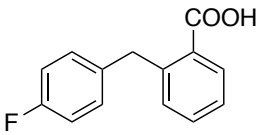
Following the procedure above-described, **1f** was isolated as a yellow oil in 80% yield. The NMR spectra match those previously described in literature. IR spectrum is also described in literature.[26]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 2.73 – 2.68 (m, 2H), 2.59 – 2.49 (m, 1H), 2.14 – 2.03 (m, 1H), 1.83 – 1.72 (m, 1H), 1.27 (dd, *J* = 7.0, 0.7 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.0, 148.9, 138.1, 128.1, 125.3, 34.4, 33.4, 31.4, 26.2.

2-(2,3-dihydro-1*H*-inden-2-yl)acetic acid 1g



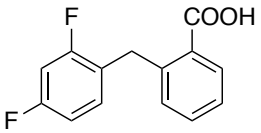
Following the procedure above-mentioned, **1g** was isolated as a white solid in 85% yield. The NMR spectra match those previously described in literature. The melting point is also described in literature.[27]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 – 7.13 (m, 4H), 3.25 – 3.15 (m, 2H), 3.00 – 2.85 (m, 1H), 2.75 – 2.65 (m, 2H), 2.62 – 2.55 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.7, 142.5, 126.4, 124.5, 39.8, 38.9, 35.9.

2-(4-fluorobenzyl)benzoic acid 1j



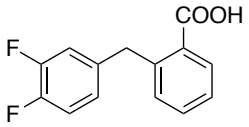
Following the general procedure GP-2', **1j** was isolated as a white solid in 58% yield. The melting point is described.[16]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 – 8.08 (m, 1H), 7.52 (td, *J* = 7.5, 1.3 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.14 (ddd, *J* = 8.2, 5.5, 1.8 Hz, 2H), 6.97 (td, *J* = 8.6, 1.5 Hz, 2H), 4.44 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8, 161.3 (d, J_{C-F} = 243.9 Hz), 143.3, 136.4 (d, J_{C-F} = 3.2 Hz), 133.1, 131.8, 131.7, 130.4 (d, J_{C-F} = 7.8 Hz), 128.3, 126.5, 115.1 (d, J_{C-F} = 21.2 Hz), 38.9.
^{19}F NMR (376 MHz, $CDCl_3$): δ = -117.5.

2-(2,4-difluorobenzyl)benzoic acid 1k



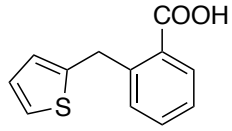
Following the general procedure GP-2', **1k** was isolated as a white solid in 48% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.50 (td, *J* = 7.6, 1.5 Hz, 1H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.00 (td, *J* = 8.5, 6.5 Hz, 1H), 6.84 – 6.74 (m, 2H), 4.44 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 161.5 (dd, J_{C-F} = 249.0, 12.3 Hz), 161.0 (dd, J_{C-F} = 248.5, 12.1 Hz), 142.1, 133.4, 132.0, 131.5 (dd, *J* = 10.7, 6.2 Hz), 131.5, 128.5, 126.8, 123.7 (dd, J_{C-F} = 15.9, 3.8 Hz), 111.1 (dd, J_{C-F} = 20.9, 3.8 Hz), 103.7 (t, J_{C-F} = 25.7 Hz), 32.4 (d, J_{C-F} = 2.7 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ = -113.17 (d, J_{F-F} = 7.0 Hz), -113.32 (d, J_{F-F} = 6.7 Hz).
HRMS: calc. for $C_{14}H_9F_2O_2$: 247.0577; found: 247.0576.
IR ν(cm^{-1}): 2961, 1678, 1620, 1574, 1505, 1413, 1266, 1137, 1096, 731.
T_M: 106 – 110 ºC.

2-(3,4-difluorobenzyl)benzoic acid 1l



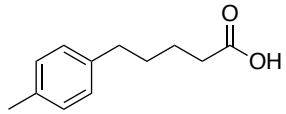
Following the general procedure GP-2', **1l** was isolated as a white solid in 52% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.53 (td, *J* = 7.5, 1.5 Hz, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.23 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.04 (dt, *J* = 10.3, 8.3 Hz, 1H), 6.95 (ddd, *J* = 11.5, 7.6, 2.2 Hz, 1H), 6.92 – 6.85 (m, 1H), 4.40 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 150.2 (dd, $J_{C–F}$ = 247.5, 12.6 Hz), 149.6 (dd, $J_{C–F}$ = 245.9, 12.6 Hz), 142.6 (d, $J_{C–F}$ = 0.8 Hz), 137.9 (dd, $J_{C–F}$ = 5.4, 3.9 Hz), 133.4, 132.1, 131.9, 128.3, 127.0, 124.8 (dd, $J_{C–F}$ = 6.0, 3.5 Hz), 117,8 (d, $J_{C–F}$ = 17.1 Hz), 117.0 (dd, $J_{C–F}$ = 17.0, 0.8 Hz), 39.0 (d, $J_{C–F}$ = 1.3 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ = -138.41 (d, $J_{F–F}$ = 21.2 Hz), -142.11 (d, $J_{F–F}$ = 21.4 Hz).
HRMS: calc. for $C_{14}H_9F_2O_2$: 247.0575; found: 247.0576.
IR ν(cm^{-1}): 2927, 1676, 1521, 1434, 1409, 1270, 1208, 1118, 732.
T_M: 127 – 128 ºC.

2-(thiophen-2-ylmethyl)benzoic acid 1m



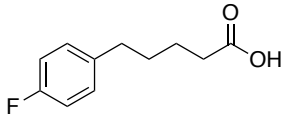
Following the general procedure GP-2', **1m** was isolated as yellow oil in 24% yield. The NMR spectra match those previously described in literature. HRMS, IR spectrum and the melting point are also described in literature.[28]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.52 (td, *J* = 7.5, 1.5 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.14 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.92 (dd, *J* = 5.2, 3.4 Hz, 1H), 6.82 (dq, *J* = 3.4, 1.1 Hz, 1H), 4.66 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ =173.0, 143.5, 143.1, 133.3, 131.9, 131.3, 127.9, 126.8, 126.7, 125.4, 123.9, 34.1.

5-(*p*-tolyl)pentanoic acid 1o



Following the general procedure GP-2, **1o** was isolated as a pale yellow solid in 56% yield. The NMR spectra match those previously described in literature.[29]
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 – 7.05 (m, 4H), 2.64 – 2.57 (m, 2H), 2.41 – 2.35 (m, 2H), 2.32 (s, 3H), 1.72 – 1.62 (m, 4H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.2, 139.1, 135.4, 129.2, 128.4, 35.2, 34.1, 31.0, 24.4, 21.1.

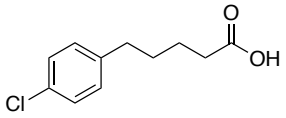
5-(4-fluorophenyl)pentanoic acid 1p



Following the general procedure GP-2, **1p** was isolated as a pale yellow solid in 54% yield. The NMR spectra match those previously described in literature.[30]
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.14 – 7.07 (m, 2H), 6.98 – 6.93 (m, 1H), 6.86 – 6.83 (m, 1H), 2.63 – 2.56 (m, 2H), 2.40 – 2.35 (m, 2H), 1.71 – 1.61 (m, 4H).

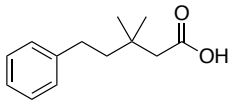
^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.2, 161.4 (d, *J* = 243.4 Hz), 137.7 (d, *J* = 3.2 Hz), 129.8 (d, *J* = 7.7 Hz), 115.2 (d, *J* = 21.1 Hz), 34.8, 34.0, 31.0, 24.3.
^{19}F NMR (376 MHz, $CDCl_3$): δ = -117.9.

5-(4-chlorophenyl)pentanoic acid 1q



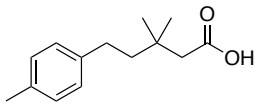
Following the general procedure GP-2, **1q** was isolated as a pale yellow solid in 54% yield. The NMR spectra match those previously described in literature.[31]
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 – 7.22 (m, 2H), 7.12 – 7.07 (m, 2H), 2.64 – 2.57 (m, 2H), 2.40 – 2.34 (m, 2H), 1.71 – 1.59 (m, 4H).
^{13}C NMR (101 MHz, $CDCl_3$): 180.0, 140.5, 131.7, 129.8, 128.6, 35.0, 33.9, 30.8, 24.3.

3,3-dimethyl-5-phenylpentanoic acid 1r



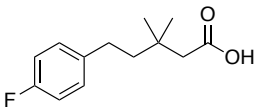
Following the general procedure GP-2', **1r** was isolated as a colorless oil in 65% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 2.68 – 2.58 (m, 2H), 2.34 (s, 2H), 1.73 – 1.64 (m, 2H), 1.14 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.0, 142.9, 128.5, 128.5, 125.8, 45.9, 44.5, 33.5, 30.9, 27.4.
HRMS: calc. for $C_{11}H_{11}NaO_2$: 227.1040; found: 227.1041.
IR v(cm^{-1}): 3026, 2959, 1700, 1454, 1408, 1248, 795, 697.

3,3-dimethyl-5-(*p*-tolyl)pentanoic acid 1s



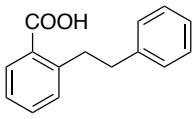
Following the general procedure GP-2', **1s** was isolated as a white solid in 45% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 – 7.08 (m, 4H), 2.63 – 2.54 (m, 2H), 2.33 (s, 3H), 1.70 – 1.60 (m, 2H), 1.12 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.8, 139.8, 135.3, 129.2, 128.4, 45.9, 44.7, 33.5, 30.4, 27.4, 21.1.
HRMS: calc. for $C_{14}H_{18}NaO_2$: 241.1199; found: 241.1199.
IR v(cm^{-1}): 2963, 1693, 1319, 1280, 1249, 808.
T_M: 65.0 – 67.0 ºC.

5-(4-fluorophenyl)-3,3-dimethylpentanoic acid 1t



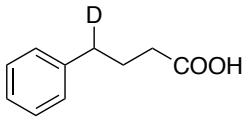
Following the general procedure GP-2', **1t** was isolated as a white solid in 52% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 – 7.10 (m, 2H), 6.98 – 6.92 (m, 2H), 2.62 – 2.55 (m, 2H), 2.32 (s, 2H), 1.66 – 1.59 (m, 2H), 1.11 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.4, 161.3 (d, $J_{C–F}$ = 243.1 Hz), 138.5 (d, $J_{C–F}$ = 3.2 Hz), 129.8 (d, $J_{C–F}$ = 7.7 Hz), 115.2 (d, $J_{C–F}$ = 21.1 Hz), 45.7, 44.5, 33.5, 30.1, 27.5.
^{19}F NMR (376 MHz, $CDCl_3$): δ = -117.7.
HRMS: calc. for $C_{13}H_{15}FNaO_2$: 245.0948; found: 245.0947.
IR v(cm^{-1}): 2964, 2932, 1694, 1509, 1320, 1287, 1214, 822.
T_M: 76.2 – 78.2 ºC.

2-phenethylbenzoic acid 1u



Following the procedure above-mentioned, **1u** was isolated as a white solid in 80% yield. The NMR spectra match those previously described in literature.[32]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dq, *J* = 7.9, 1.5 Hz, 1H), 7.50 (tt, *J* = 7.5, 1.6 Hz, 1H), 7.38 – 7.18 (m, 8H), 3.41 – 3.35 (m, 2H), 3.04 – 2.92 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5, 145.0, 142.1, 133.2, 132.0, 131.7, 128.7, 128.5, 128.2, 126.4, 126.1, 38.3, 37.3.

4-phenylbutanoic-4-d acid 1a-d



Following the general procedure GP-2', **1a-d** was isolated as a as a white solid in 72% yield. This compound was previously described in literature.[33]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 2.71 – 2.64 (m, 1H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.03 – 1.94 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.9, 141.2 (d, $J_{H\text{-}D}$ = 4.3 Hz), 128.5 (d, $J_{H\text{-}D}$ = 6.8 Hz), 126.1, 35.0, 34.6 (t, $J_{H\text{-}D}$ = 19.6 Hz), 33.3 (d, $J_{H\text{-}D}$ = 3.3 Hz), 26.2 (d, $J_{H\text{-}D}$ = 9.8 Hz).

12. References

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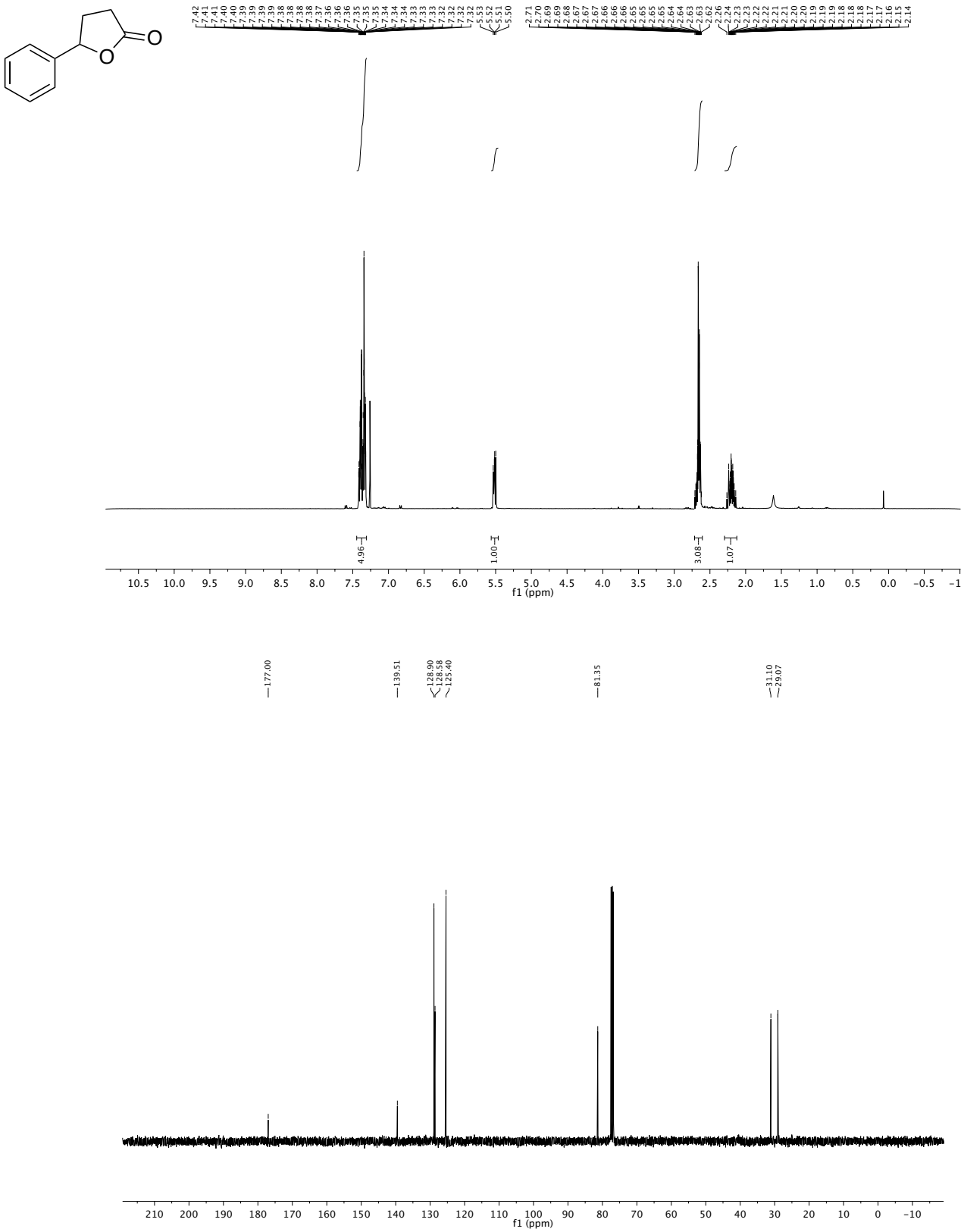
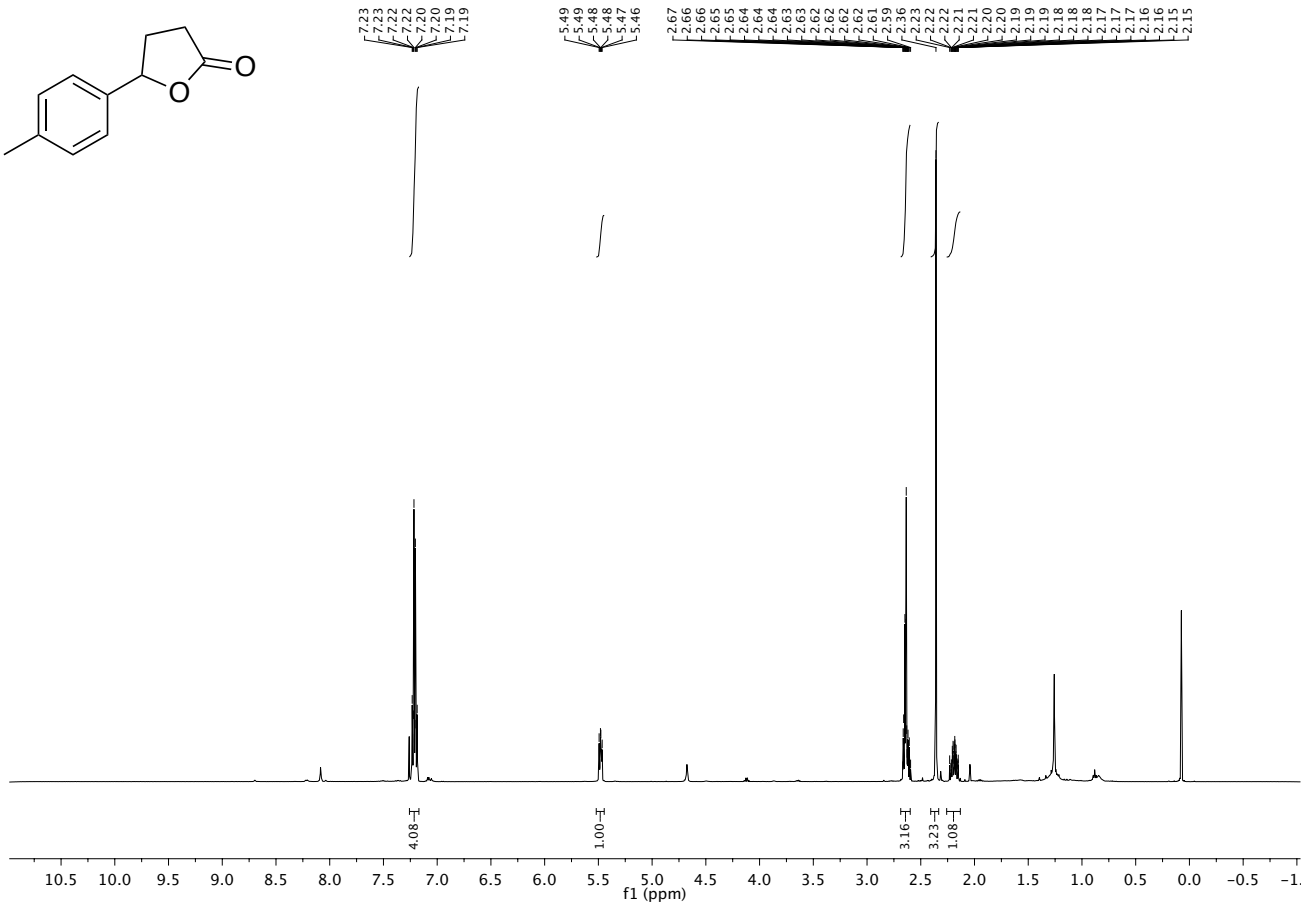
13. NMR Spectra

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7.22
7.20
7.20
7.19
7.19
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5.49
5.48
5.48
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5.46
2.67
2.66
2.66
2.65
2.65
2.64
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2.62
2.62
2.62
2.61
2.59
2.36
2.23
2.22
2.22
2.21
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2.20
2.20
2.19
2.19
2.19
2.18
2.18
2.18
2.17
2.17
2.17
2.16
2.16
2.15
2.15
O
O
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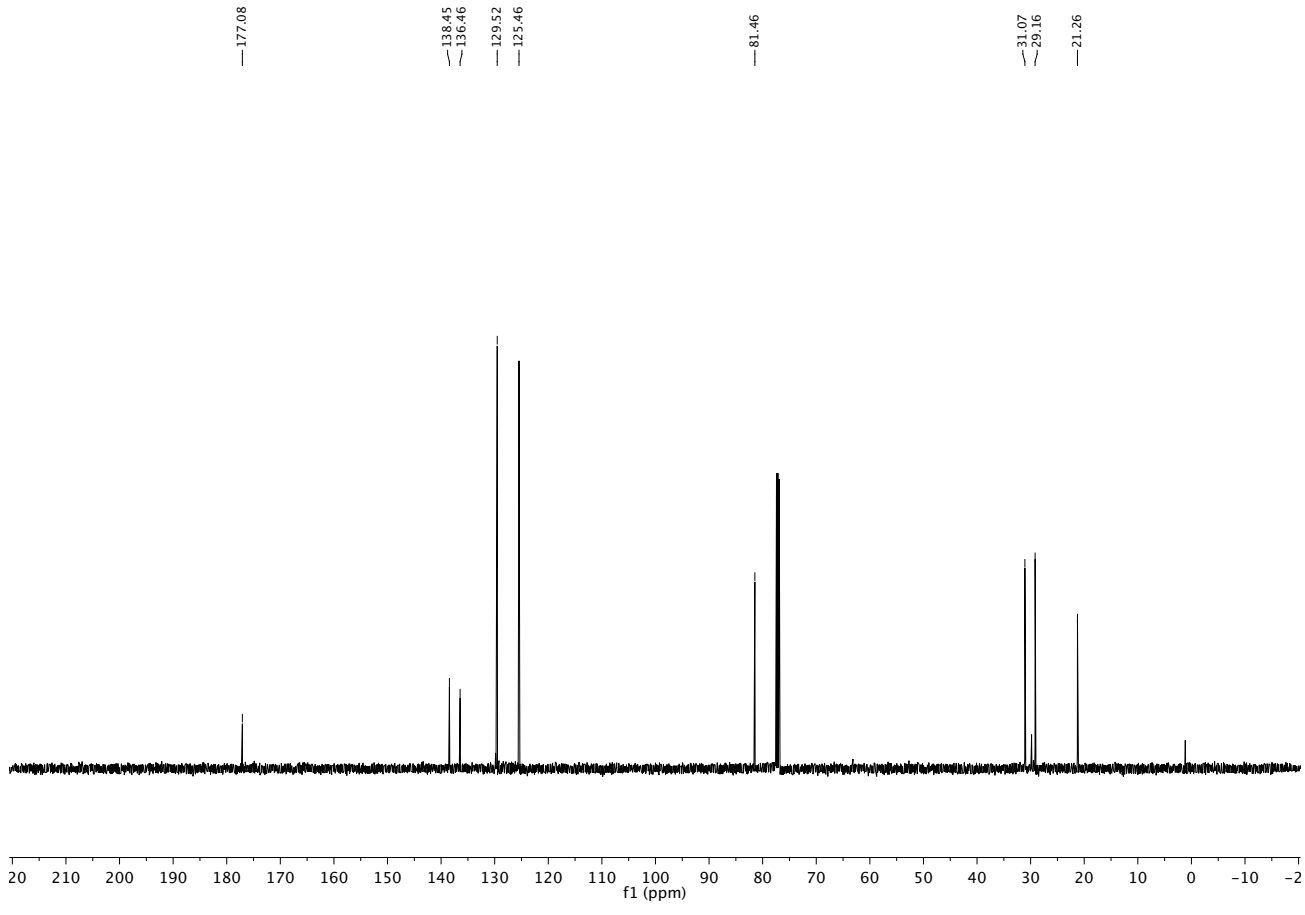
1.00
3.16
3.23
1.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)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29.16
21.26
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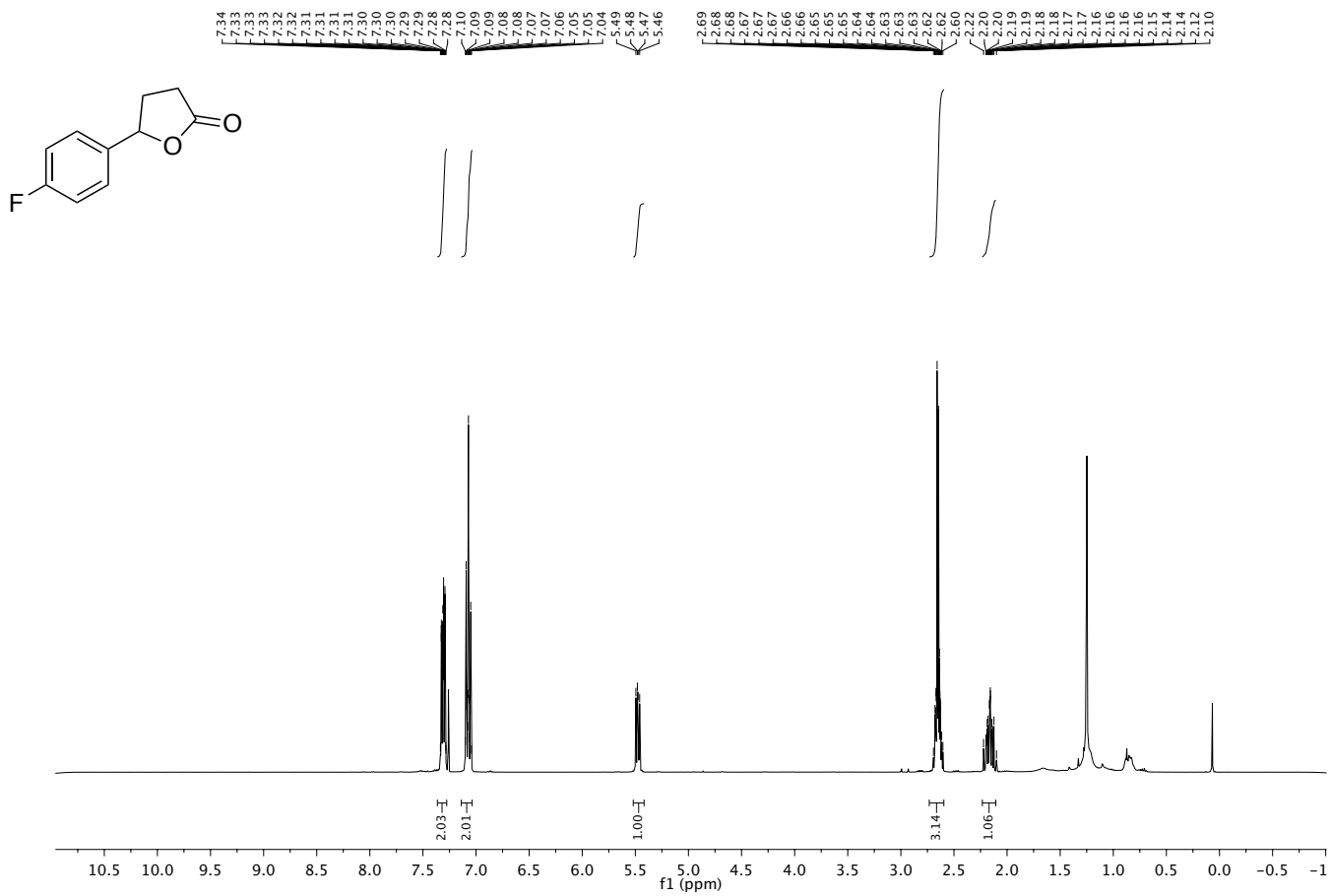
f1 (ppm)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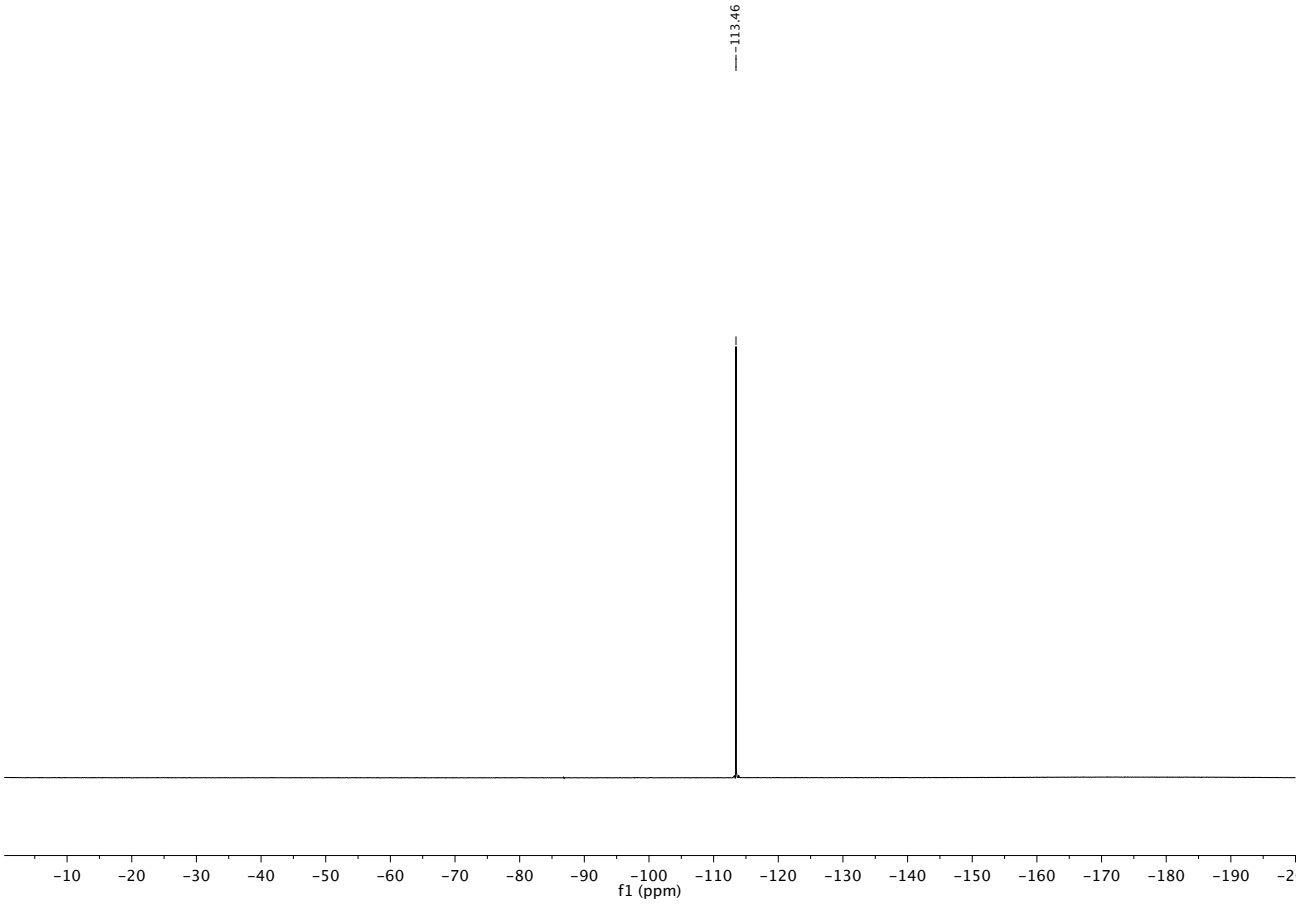
f1 (ppm)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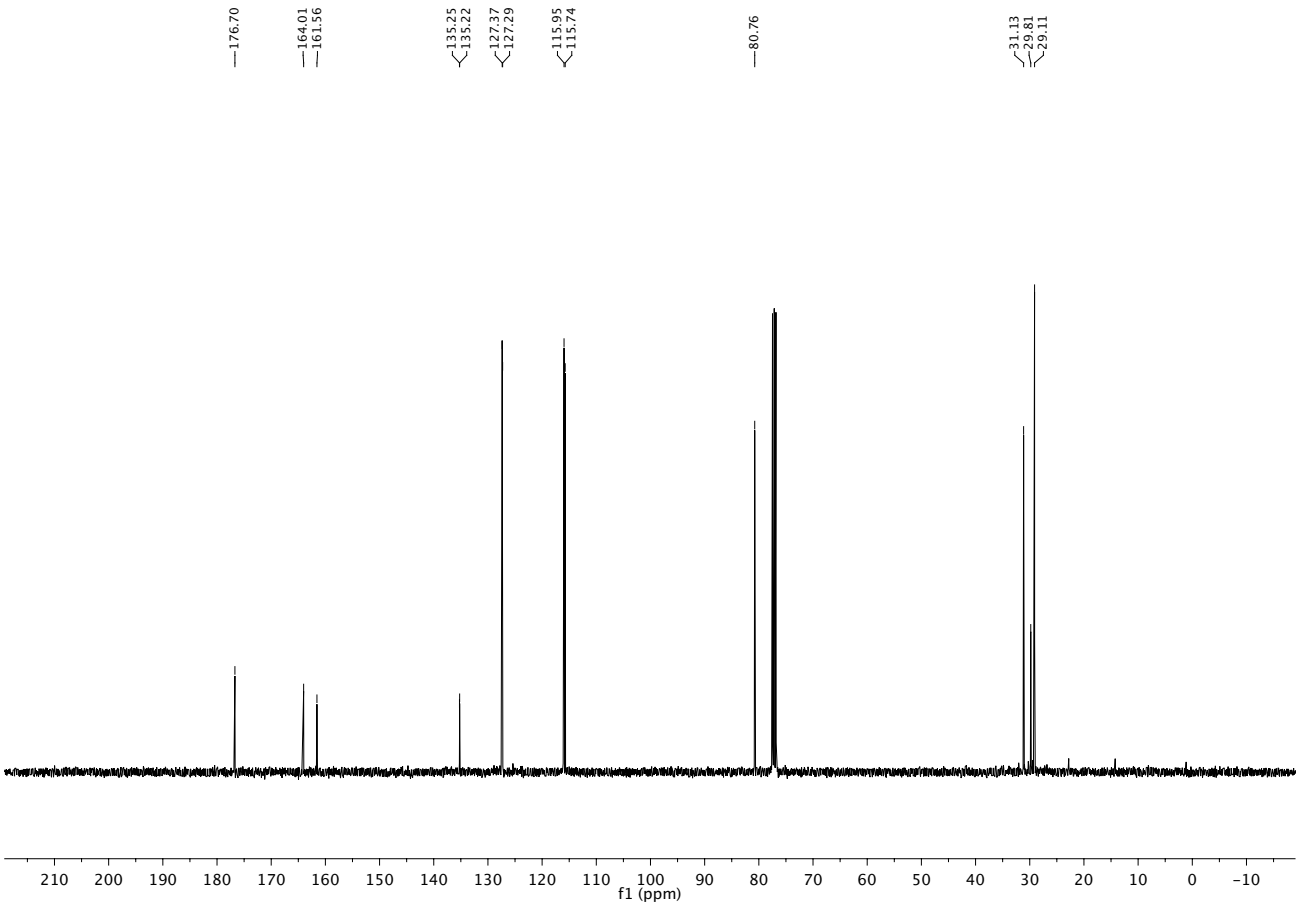
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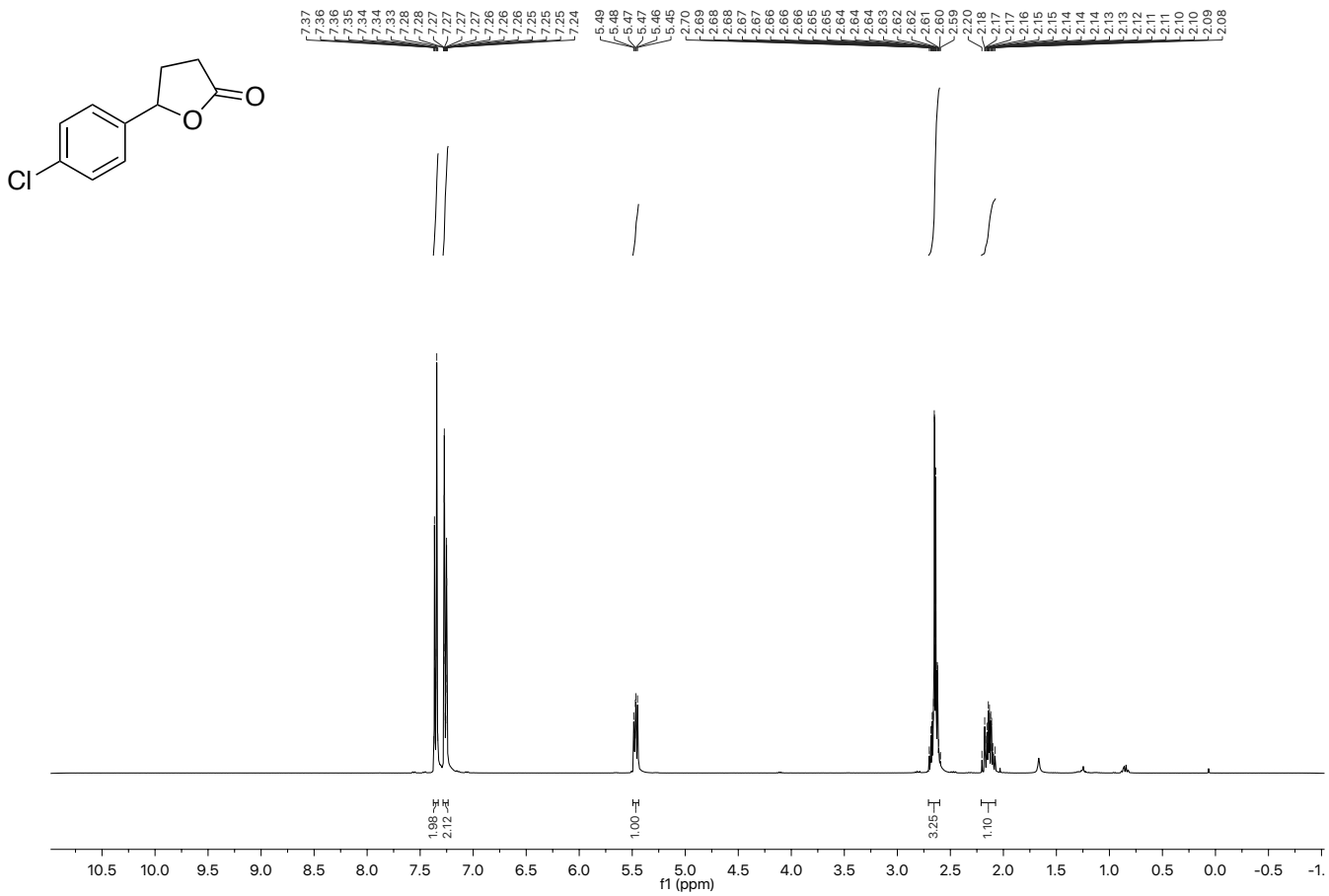
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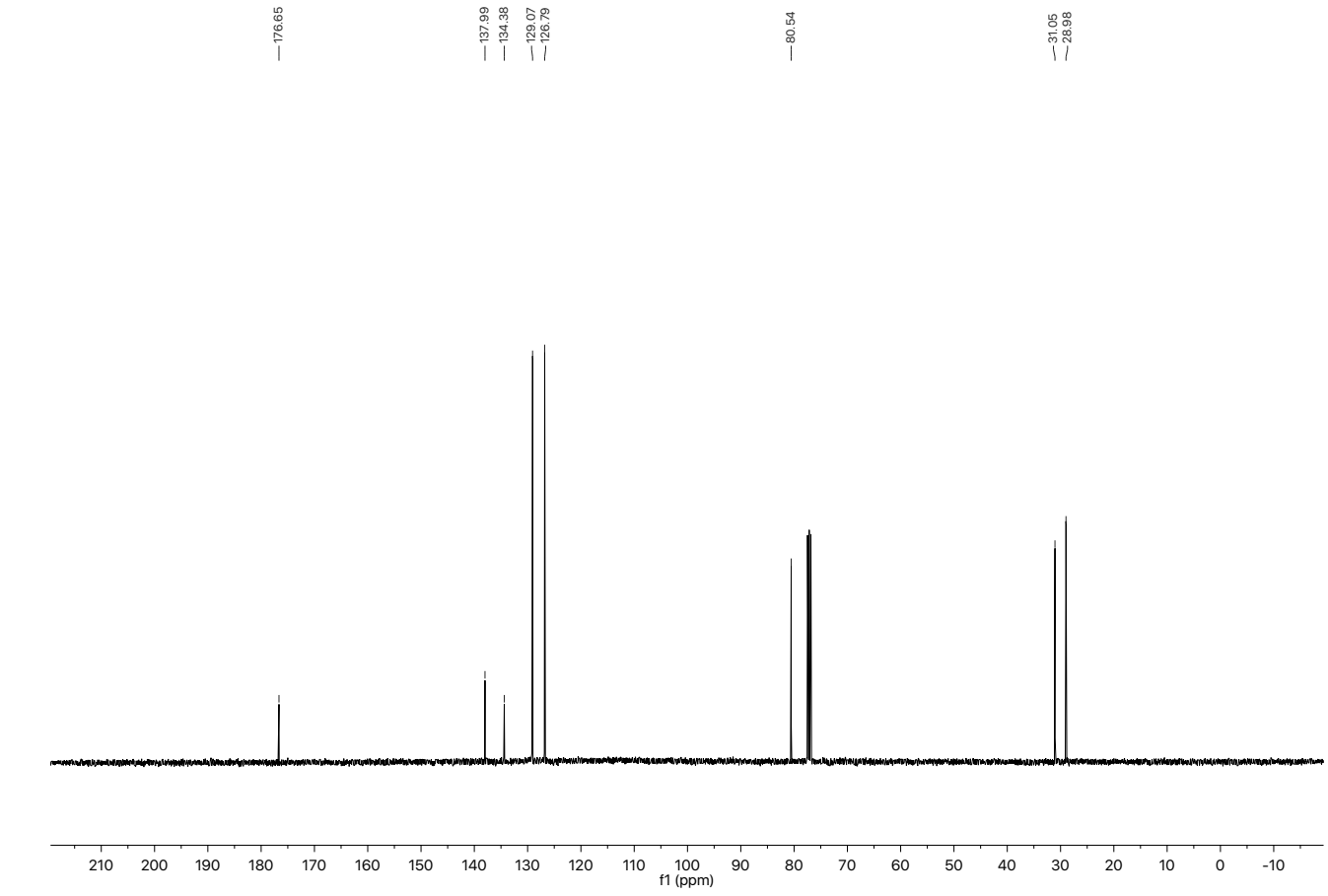
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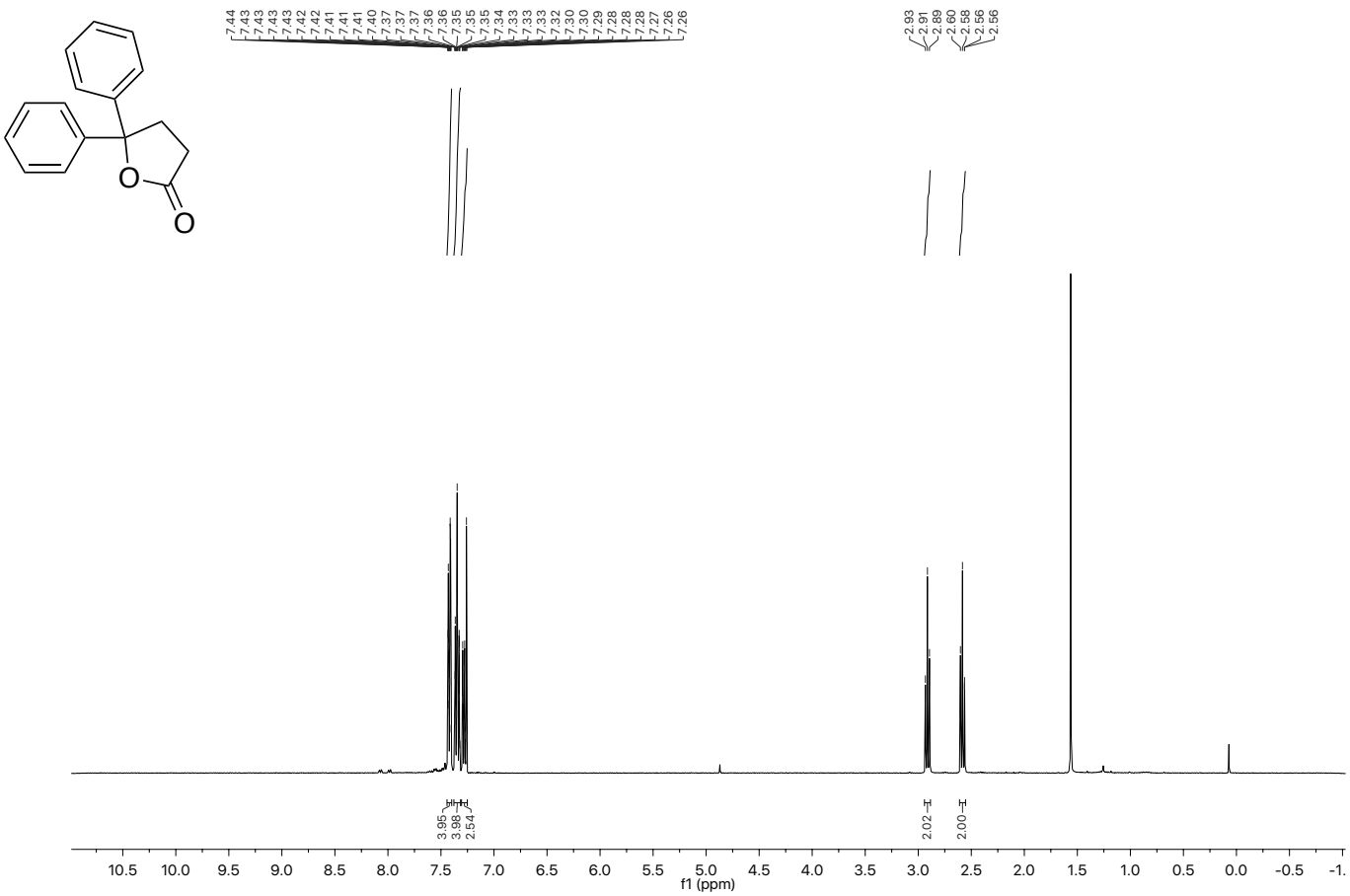
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2.93 2.91 2.89 2.60 2.58 2.56 2.56
O
O
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10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
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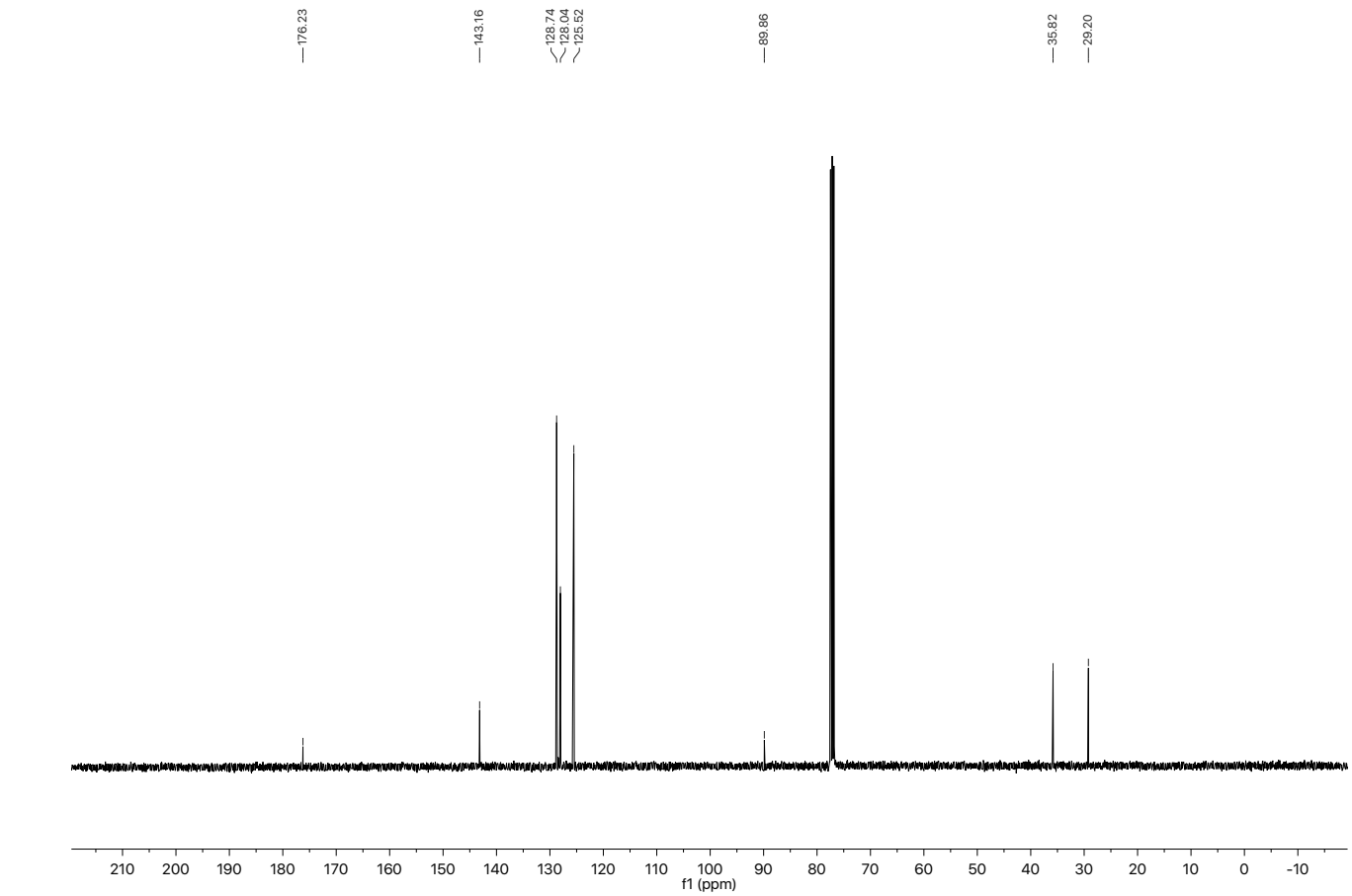
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29.20
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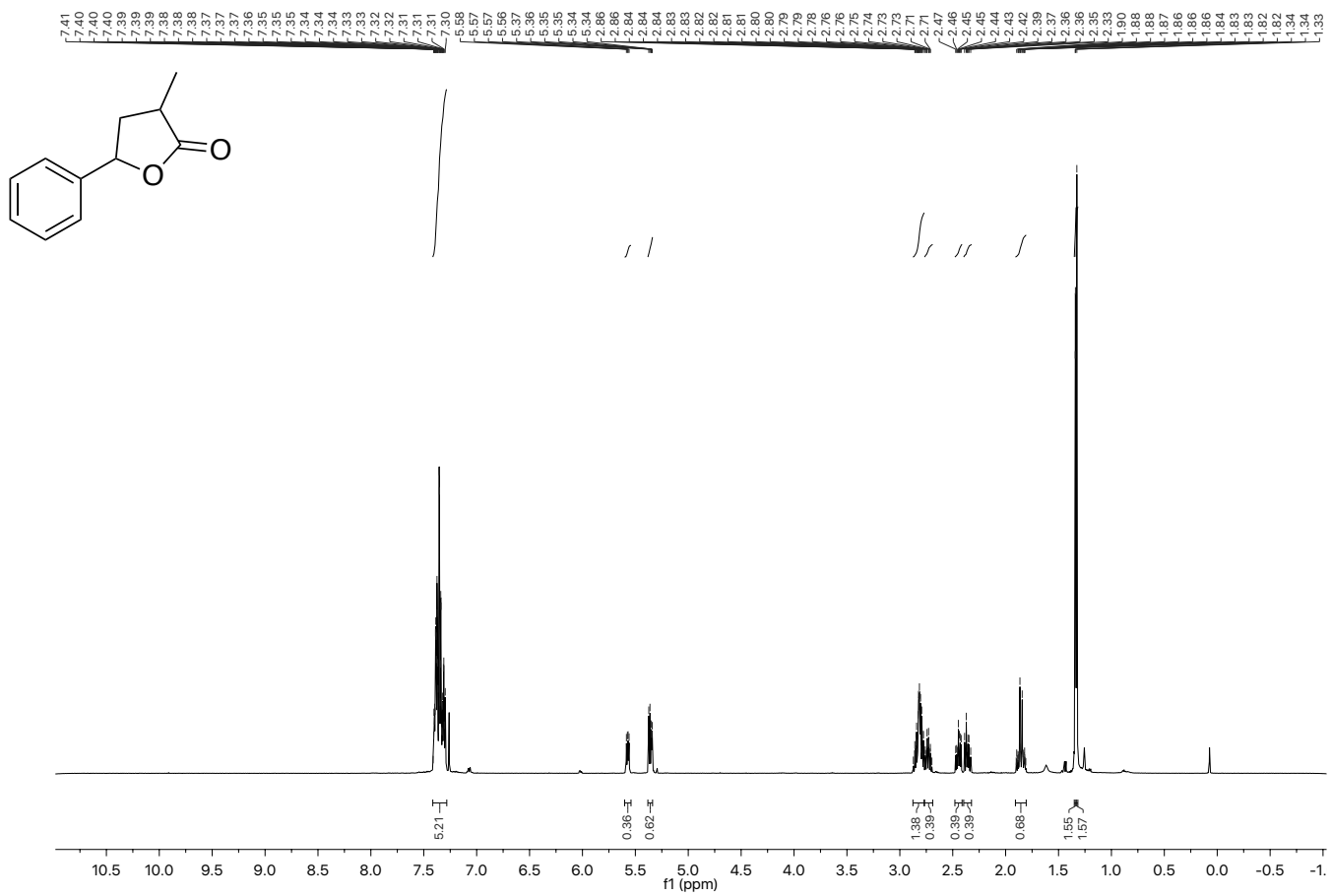
f1 (ppm)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5.58 5.57 5.57 5.56 5.37 5.36 5.35 5.35 5.34 5.34 2.86 2.86 2.84 2.84 2.84 2.83 2.83 2.82 2.82 2.81 2.81 2.80 2.80 2.79 2.79 2.78 2.76 2.76 2.75 2.74 2.73 2.71 2.71 2.47 2.46 2.45 2.45 2.44 2.43 2.42 2.39 2.37 2.36 2.36 2.35 2.33 1.90 1.88 1.88 1.87 1.86 1.86 1.86 1.84 1.83 1.82 1.82 1.34 1.34 1.33
O
O
5.21
0.36
0.62
1.38
0.39
0.39
0.39
0.68
1.55
1.57
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
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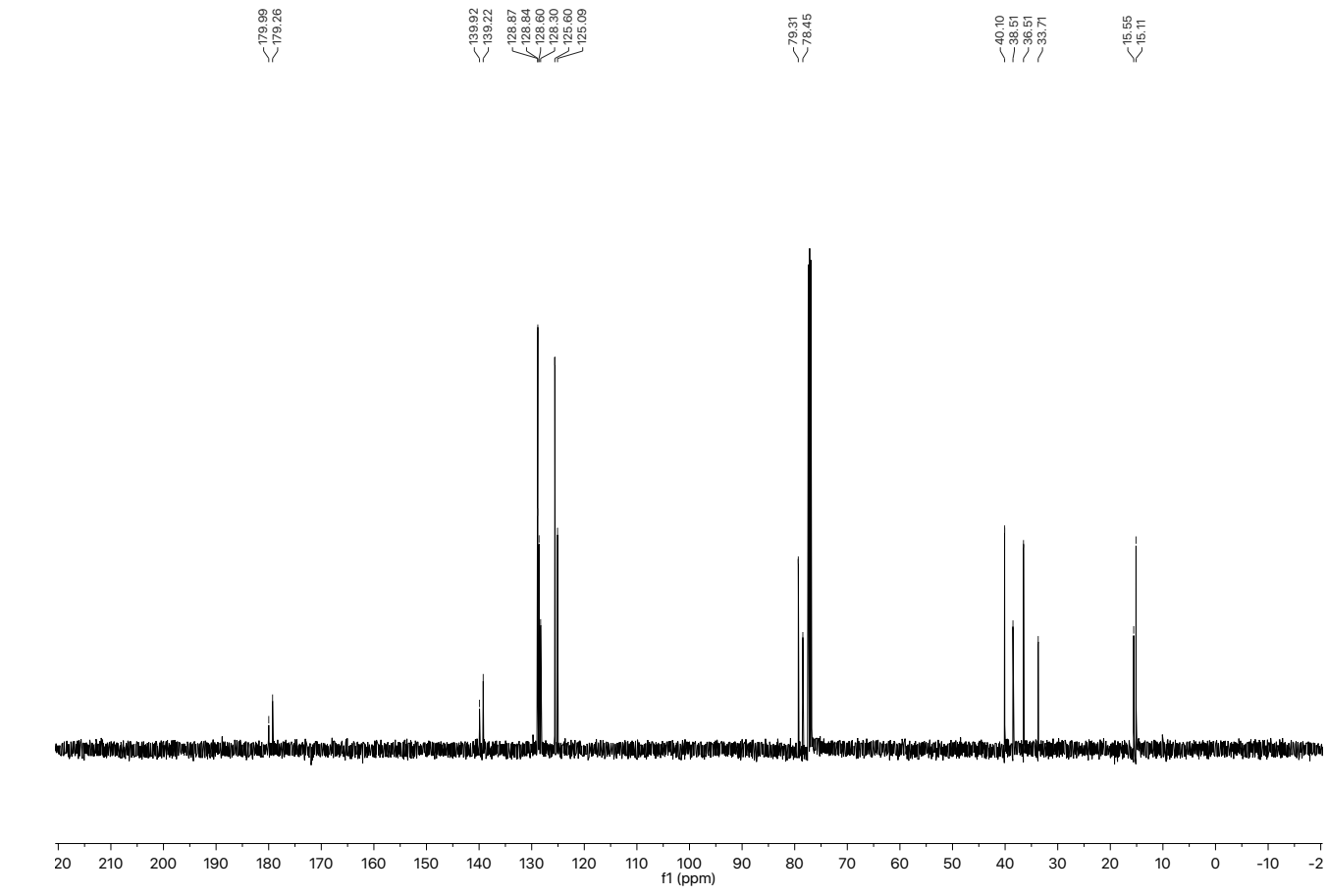
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125.09
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40.10
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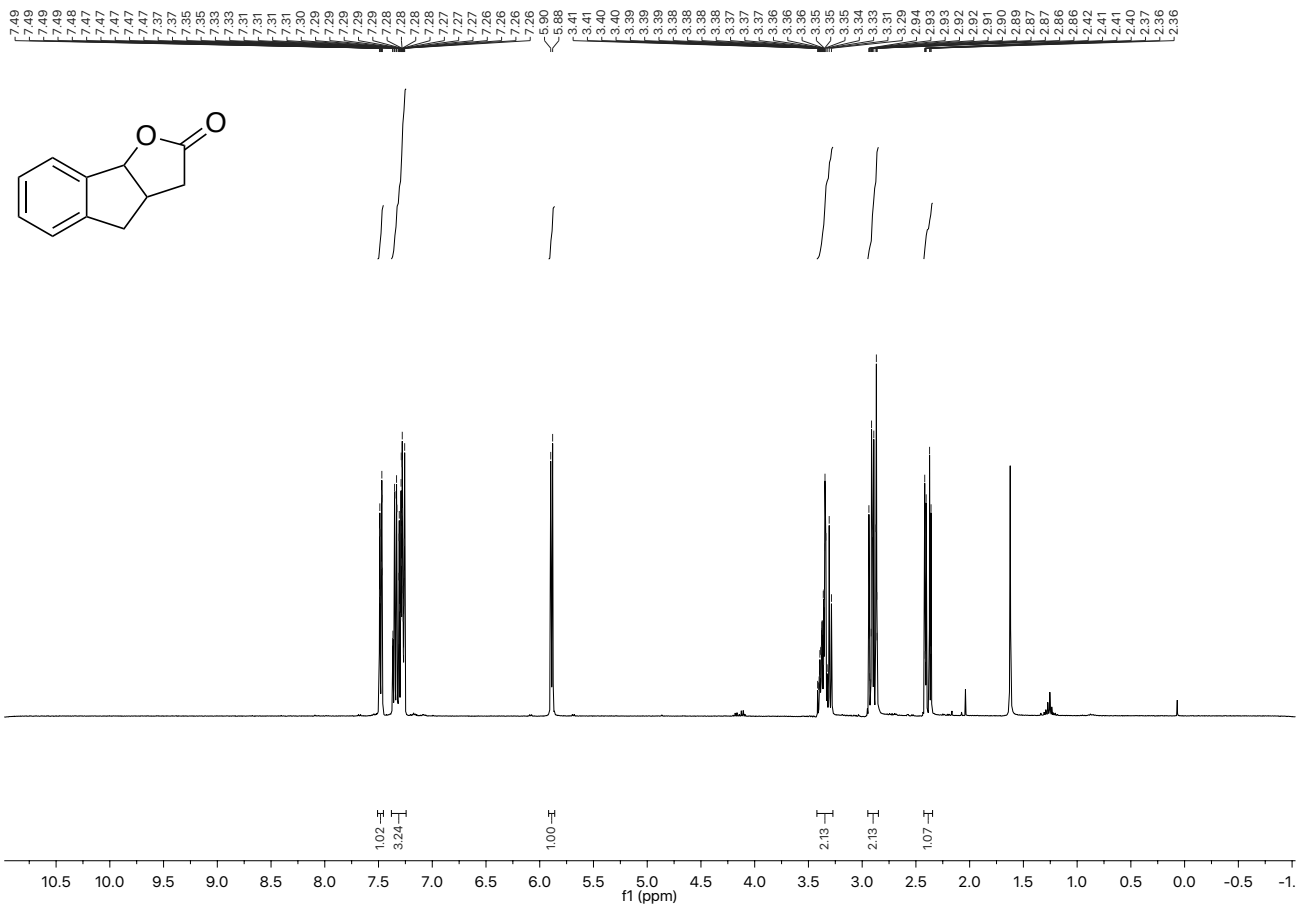
f1 (ppm)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O
O
1.02
3.24
1.00
2.13
2.13
1.07
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
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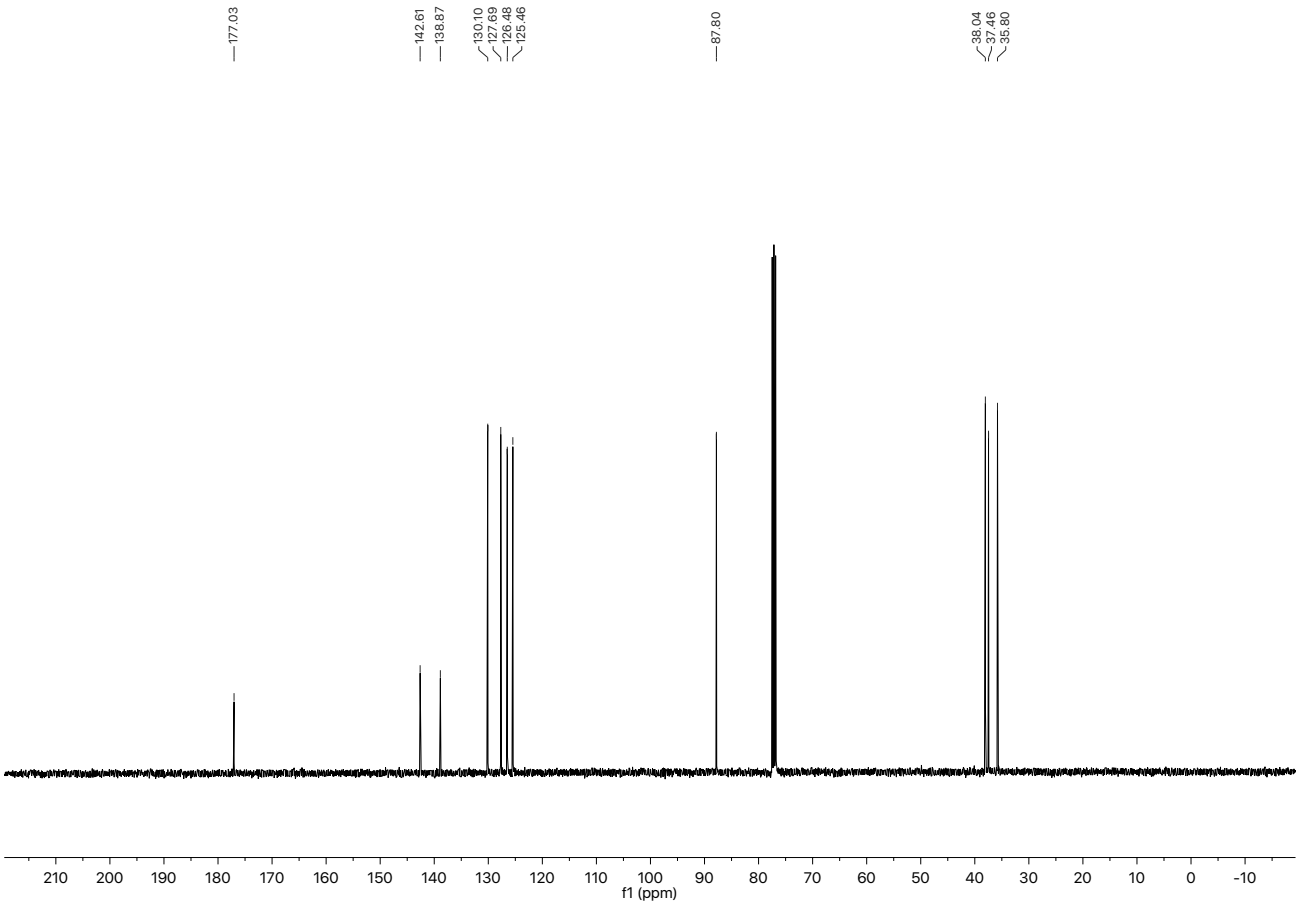
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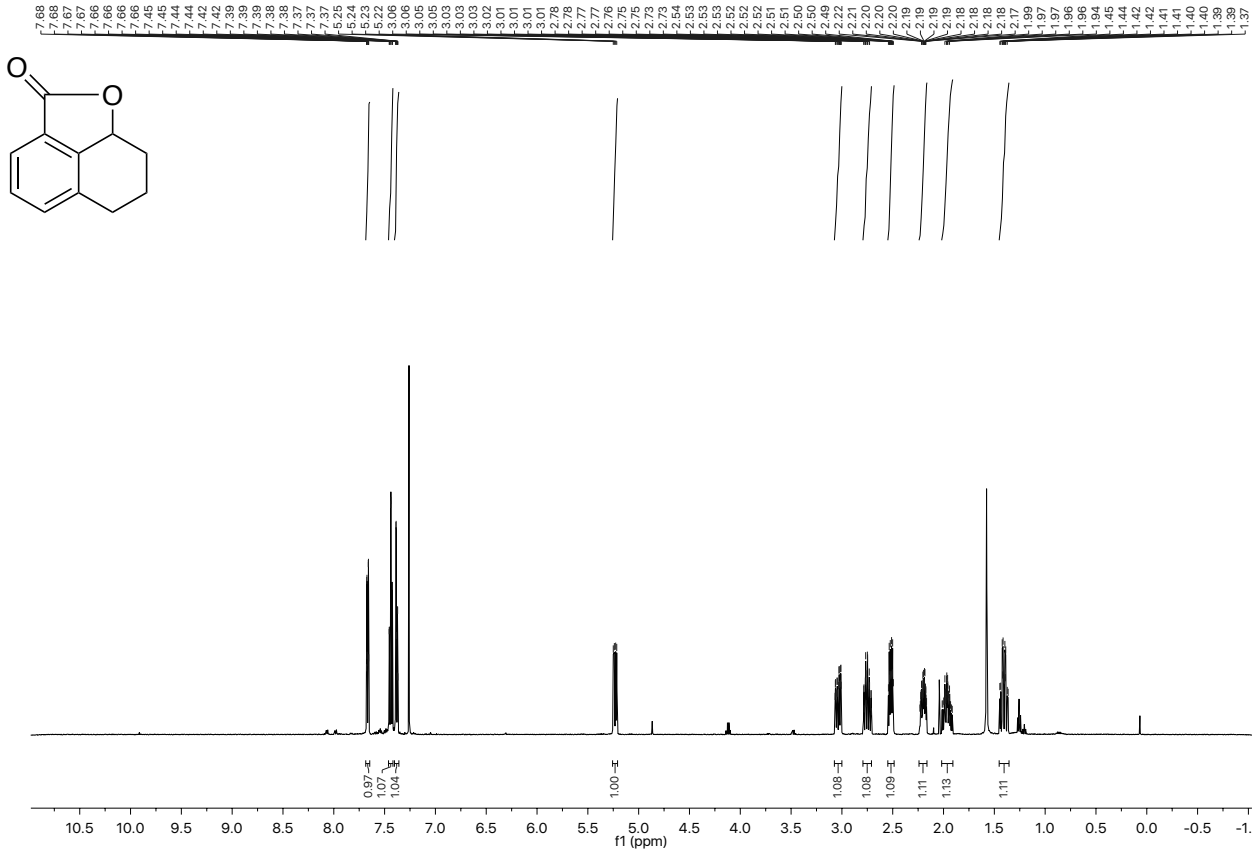
f1 (ppm)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1.09
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1.13
1.11
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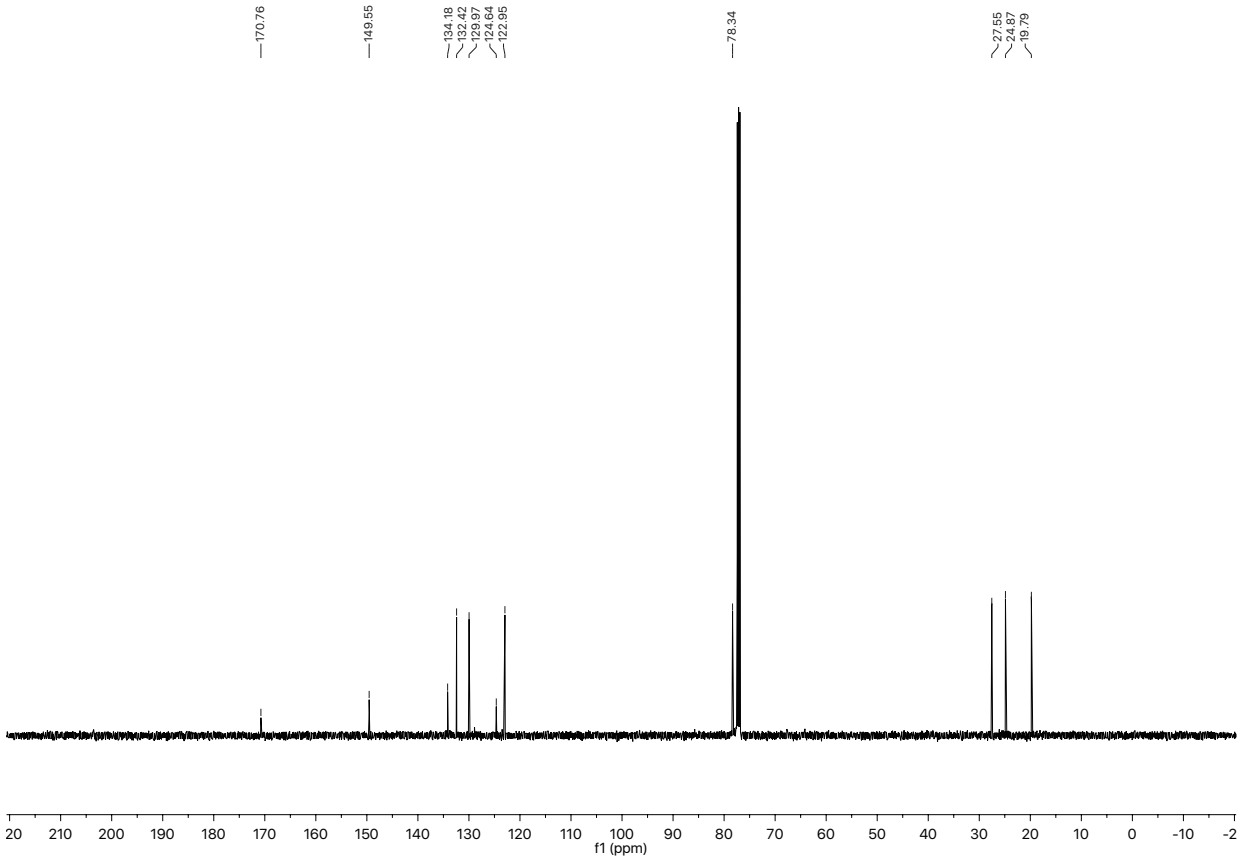
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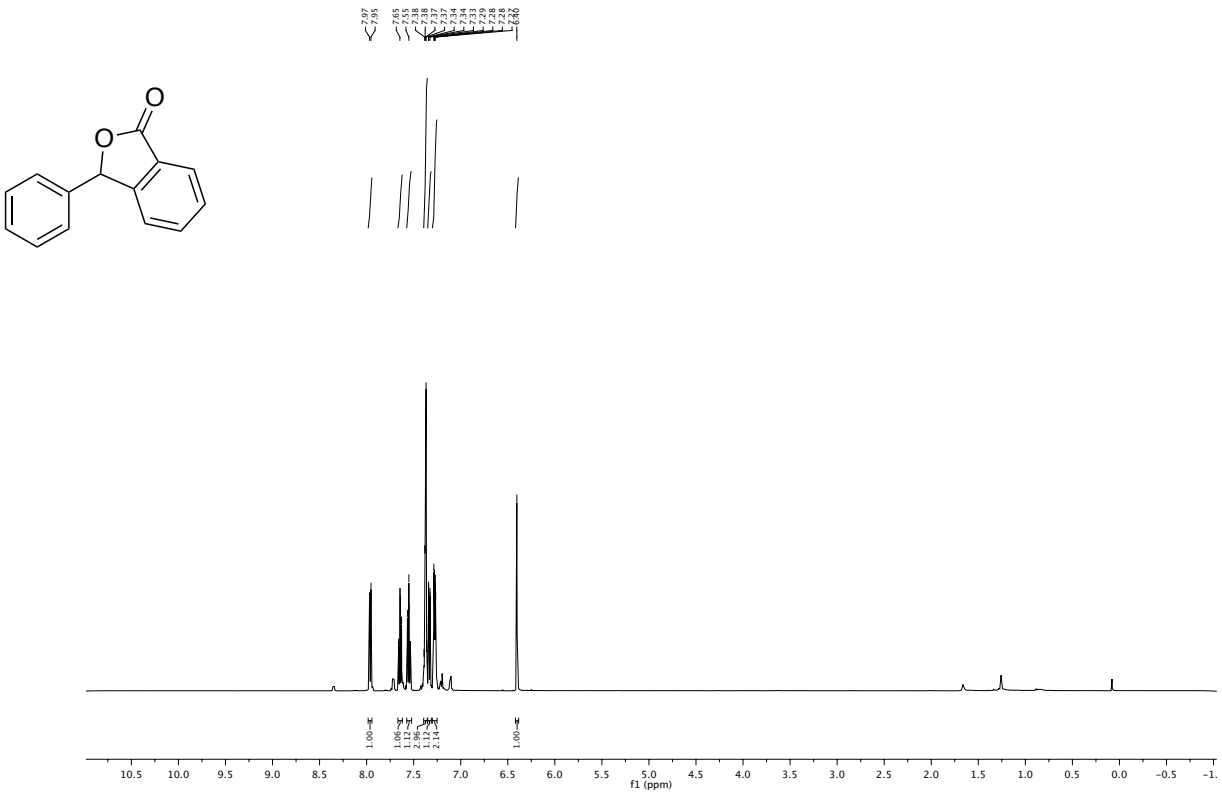
f1 (ppm)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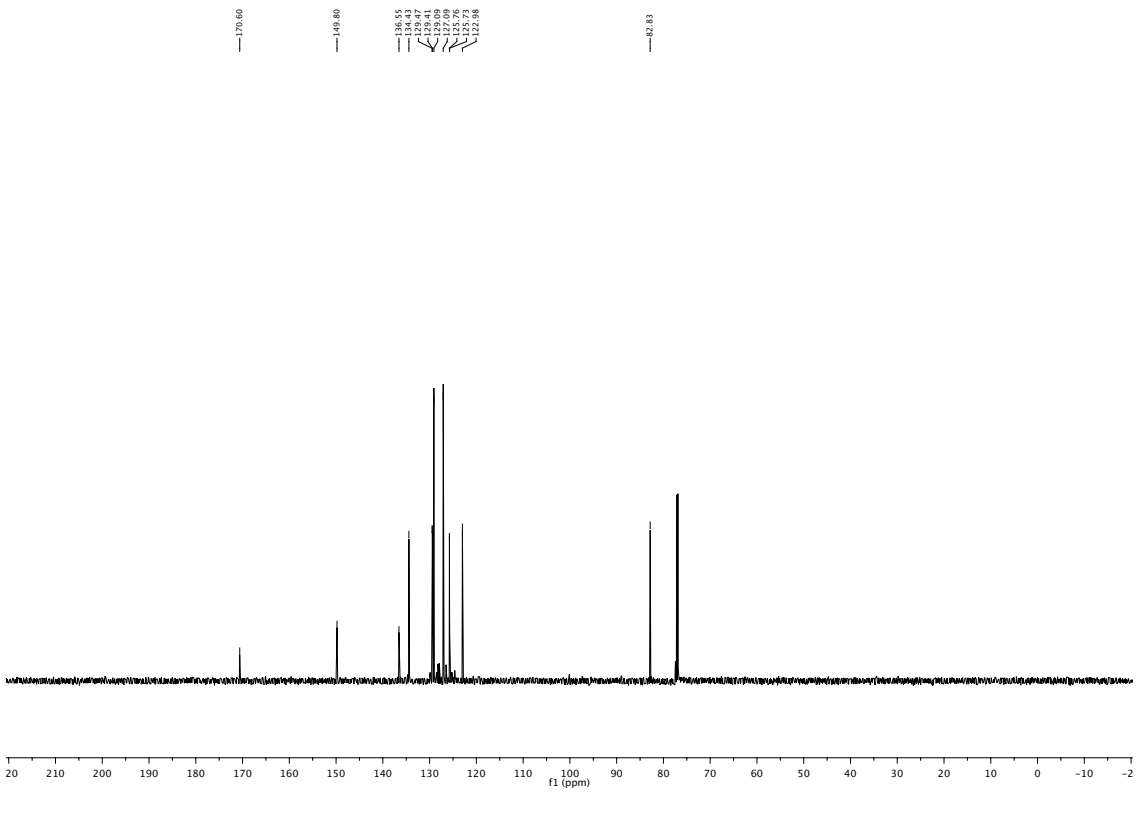
1.02
2.96
1.12
2.14
1.00
f1 (ppm)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127.09
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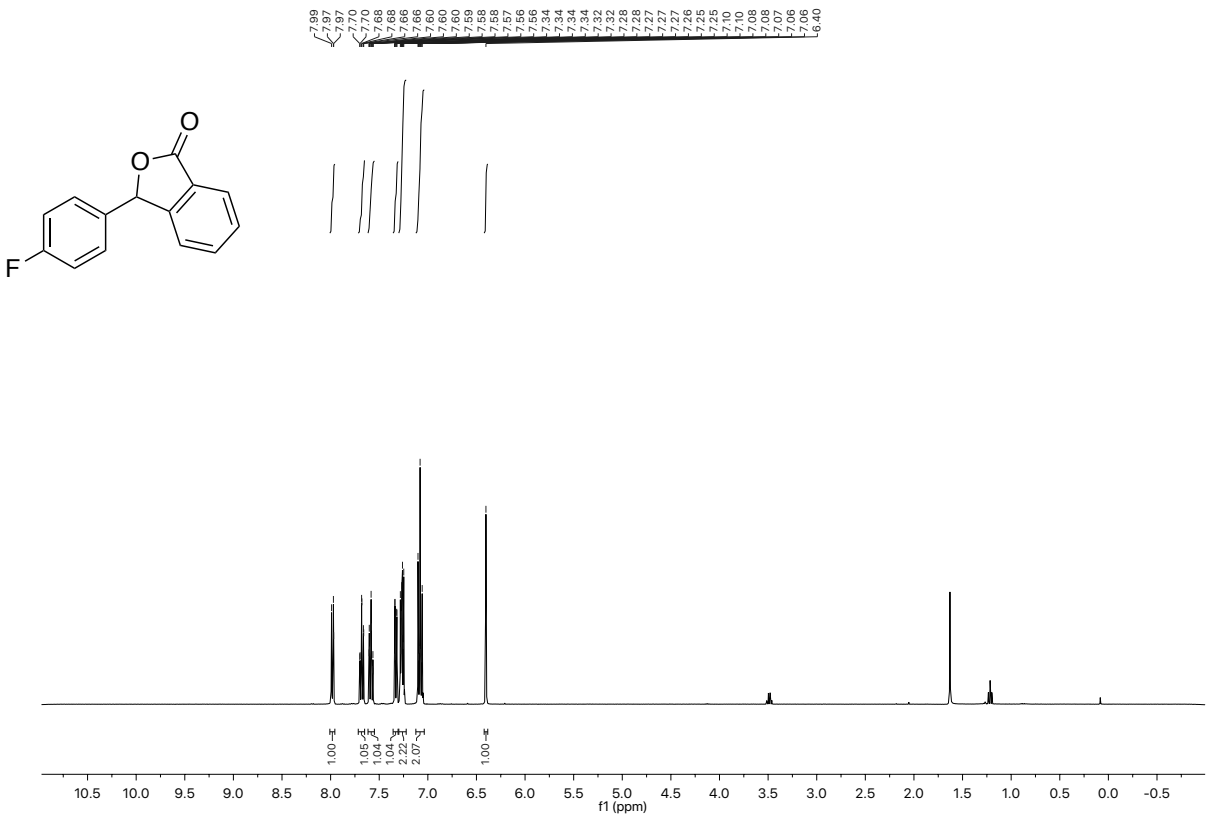
125.73
122.98
82.83
f1 (ppm)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7.28
7.27
7.27
7.27
7.26
7.25
7.25
7.10
7.08
7.08
7.07
7.06
7.06
6.40
O
O
F
1.00
1.05
1.04
1.04
2.22
2.07
1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
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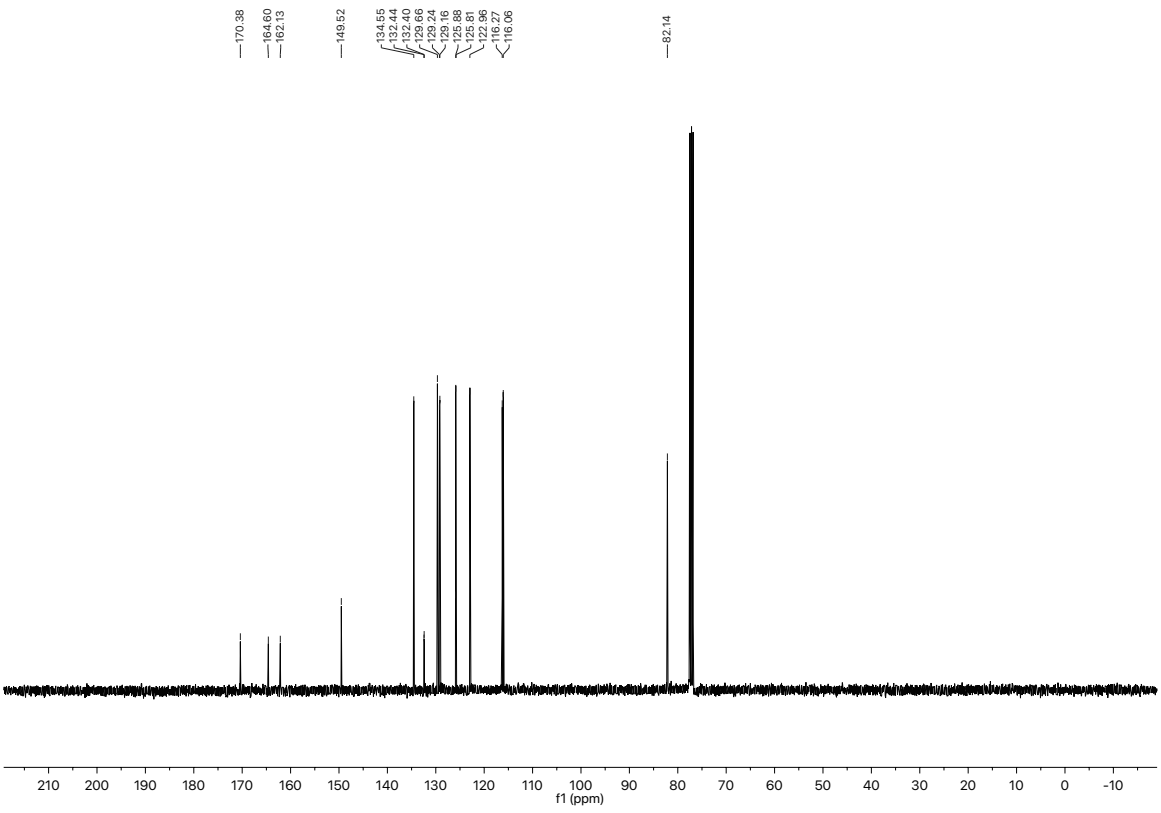
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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129.66
129.24
129.16
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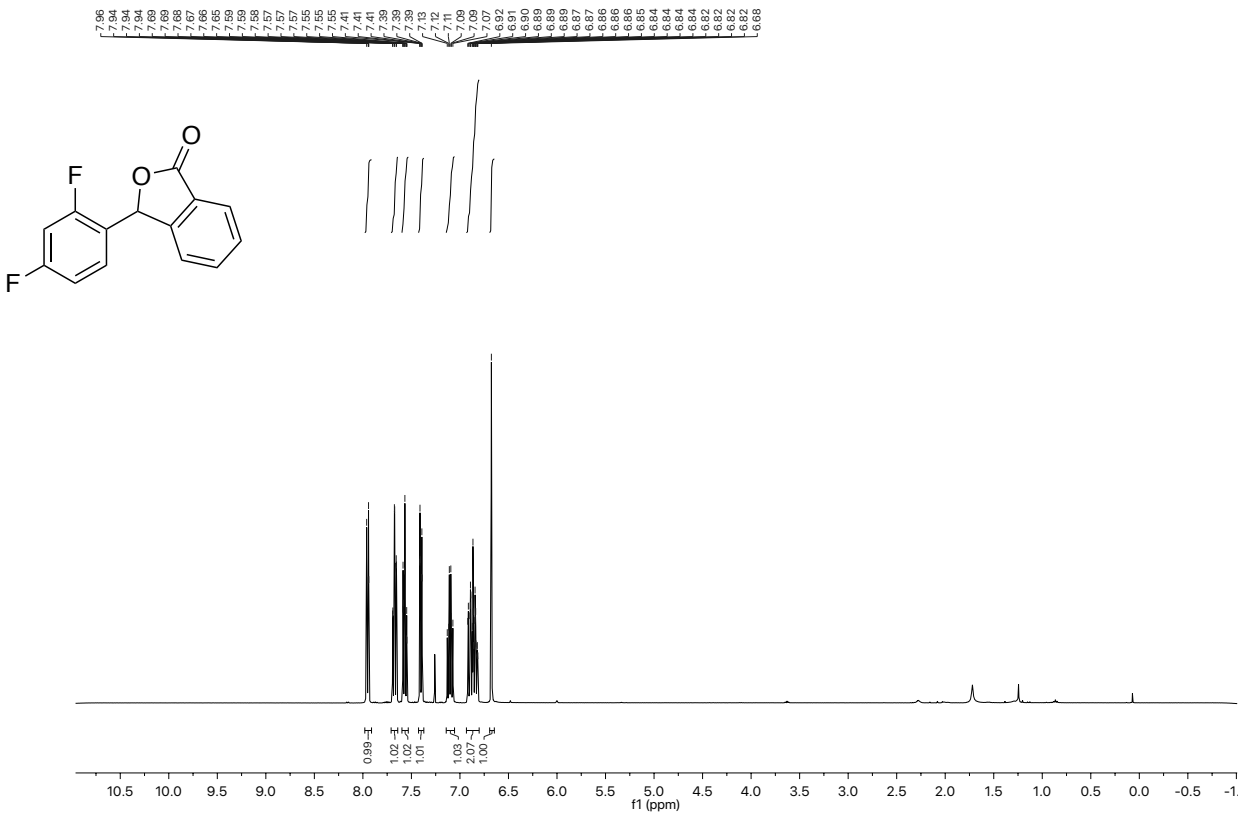
125.81
122.96
116.27
116.06
82.14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.55
7.55
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7.41
7.39
7.39
7.39
7.13
7.12
7.11
7.09
7.09
7.07
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6.91
6.90
6.89
6.89
6.89
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6.86
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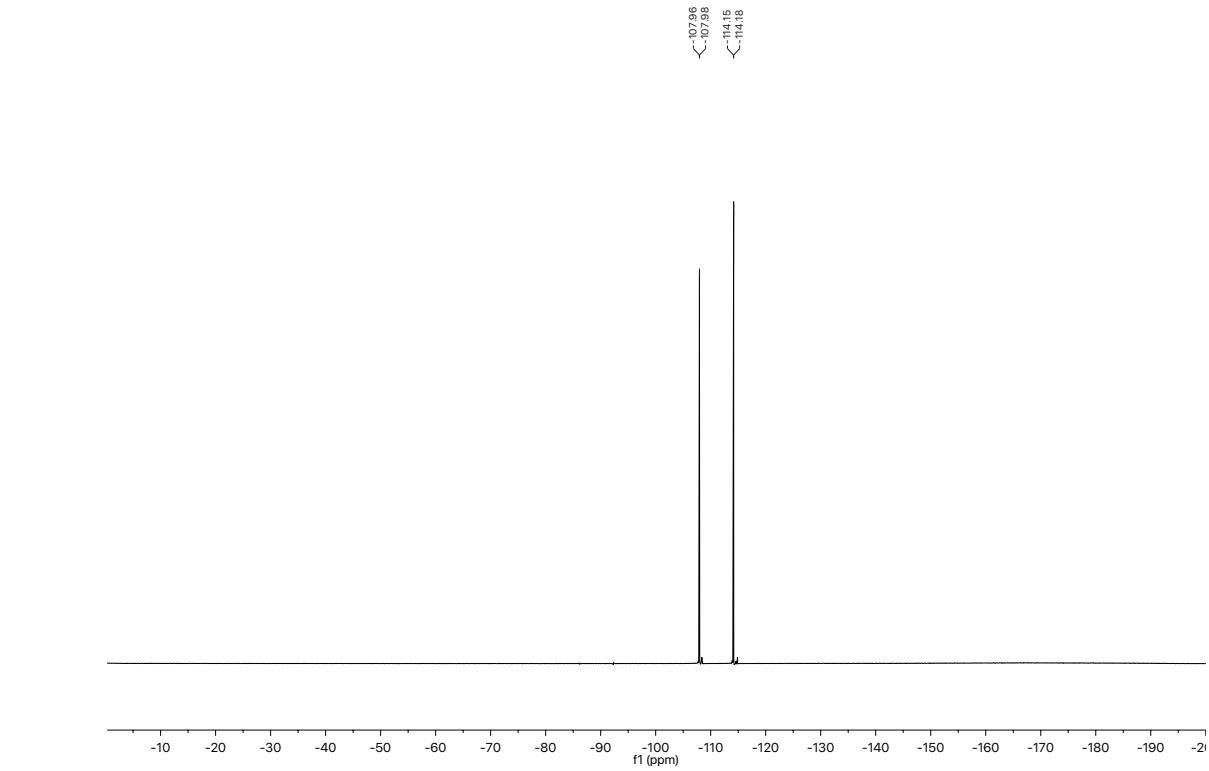
6.86
6.85
6.84
6.84
6.84
6.84
6.82
6.82
6.82
6.82
6.68
O
O
F
F
0.99
1.02
1.02
1.01
1.03
2.07
1.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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-107.98
-114.15
-114.18
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-20
-30
-40
-50
-60
-70
-80
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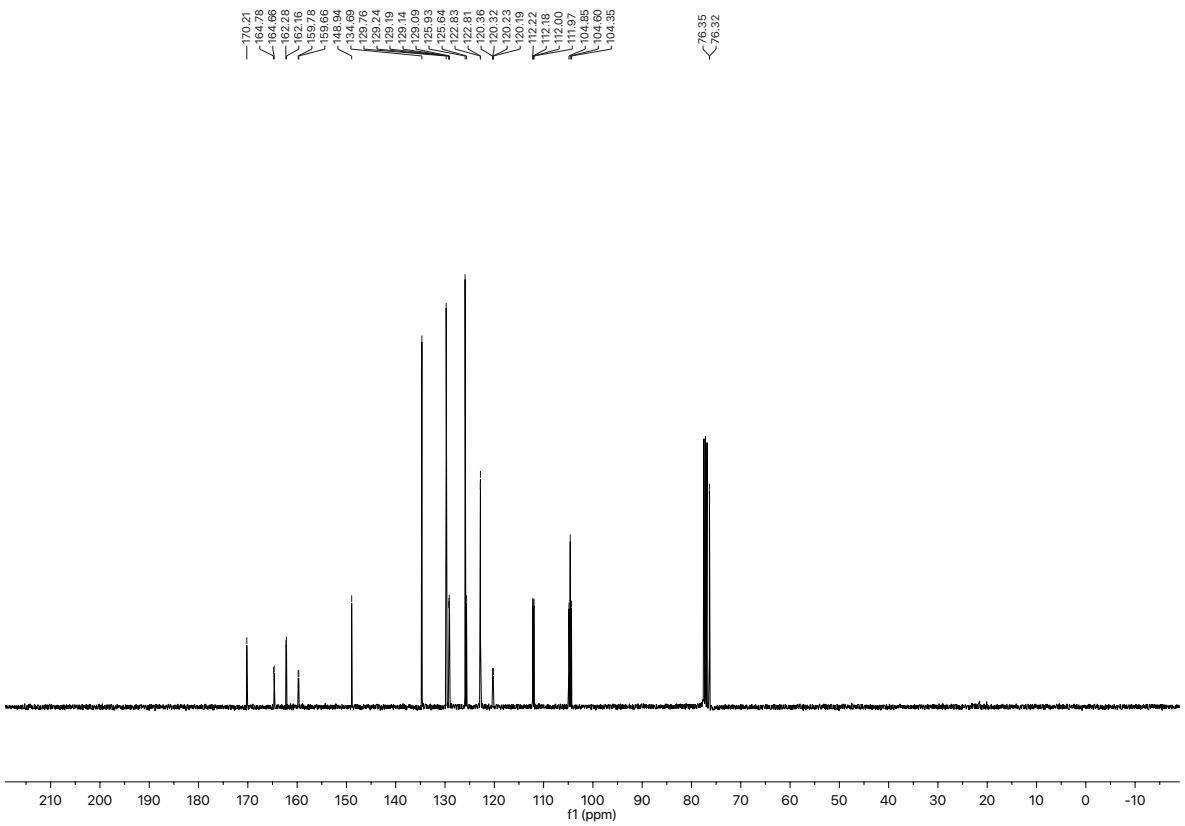
-150
-160
-170
-180
-190
f1 (ppm)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129.09
125.93
125.64
122.83
122.81
120.36
120.32
120.23
120.19
117.22
112.18
112.00
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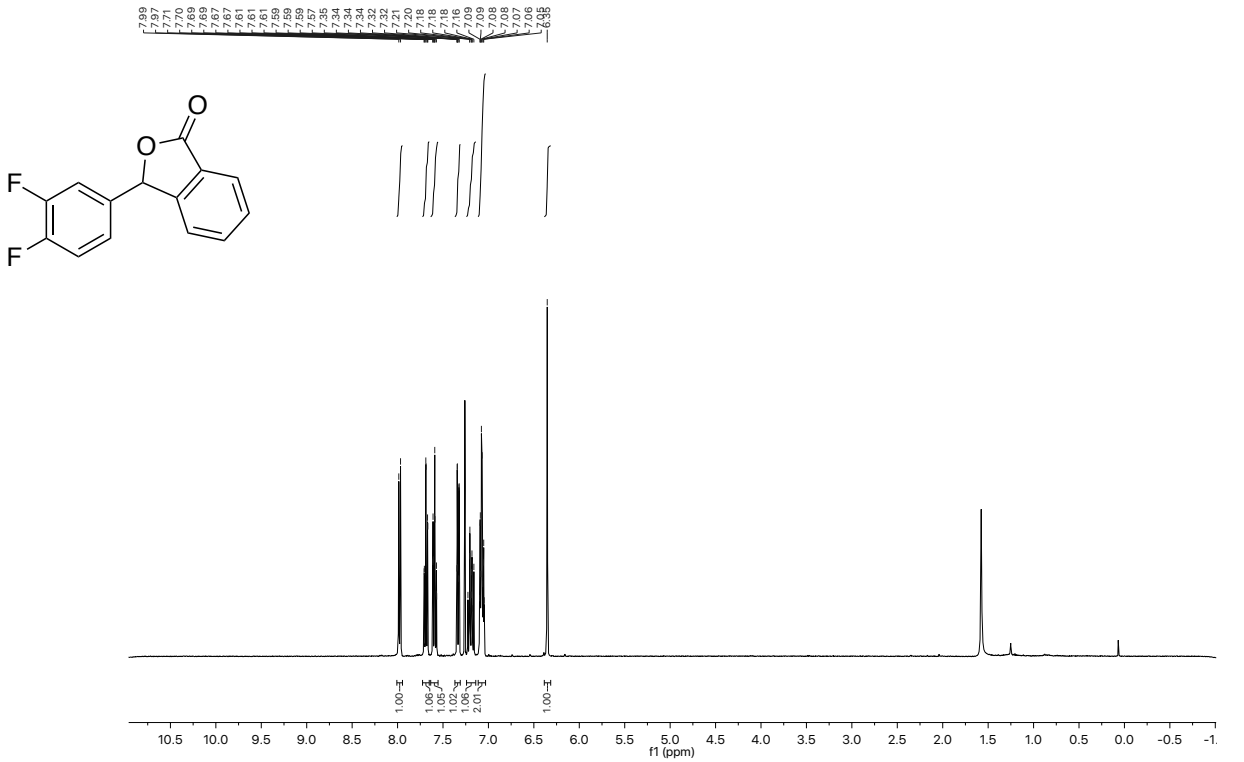
104.35
76.35
76.32
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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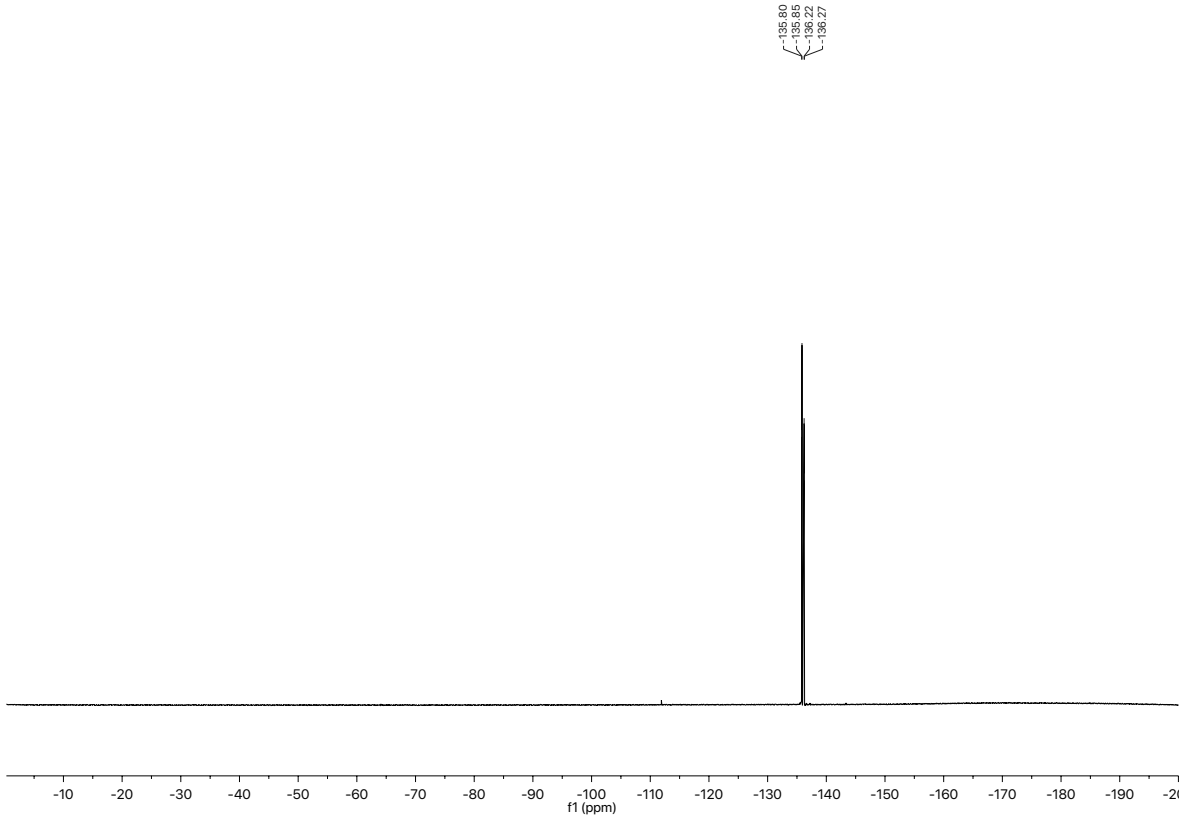
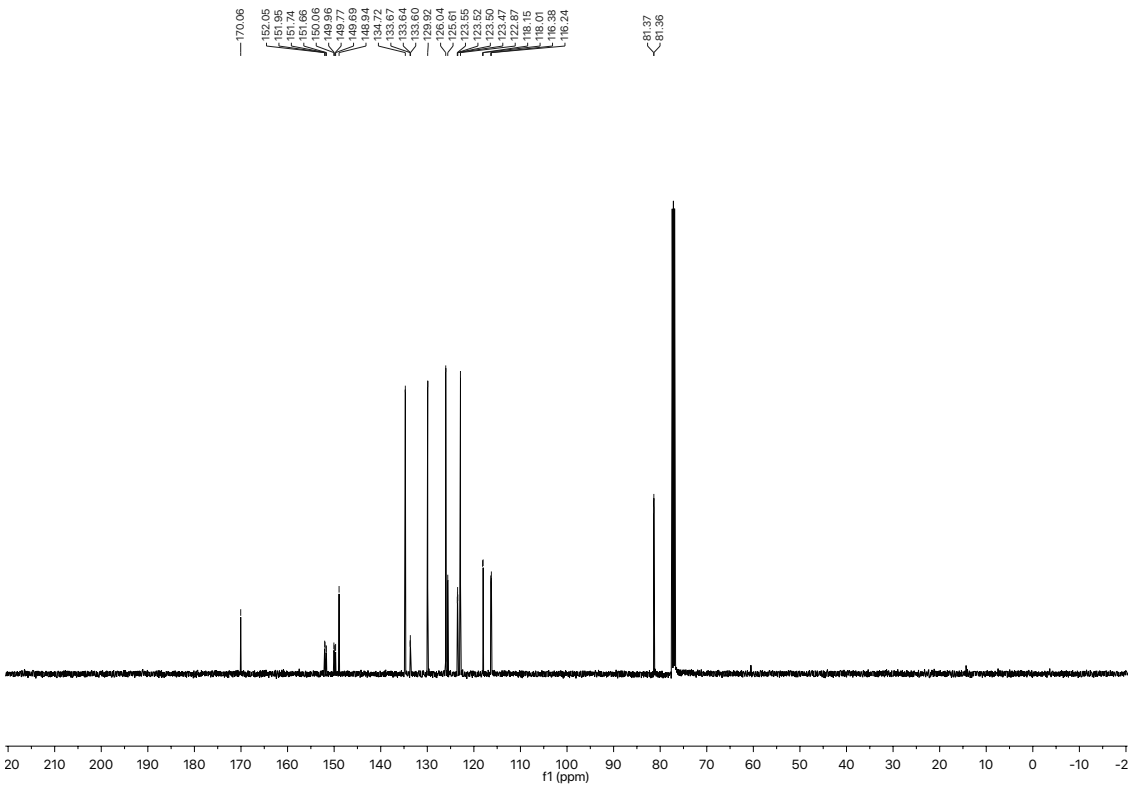
7.67
7.61
7.59
7.57
7.35
7.34
7.32
7.21
7.20
7.18
7.16
7.09
7.08
7.07
6.95
O
O
F
F
1.00
1.06
1.05
1.02
1.06
2.01
1.00
f1 (ppm)


135.80
135.85
136.22
136.27
f1 (ppm)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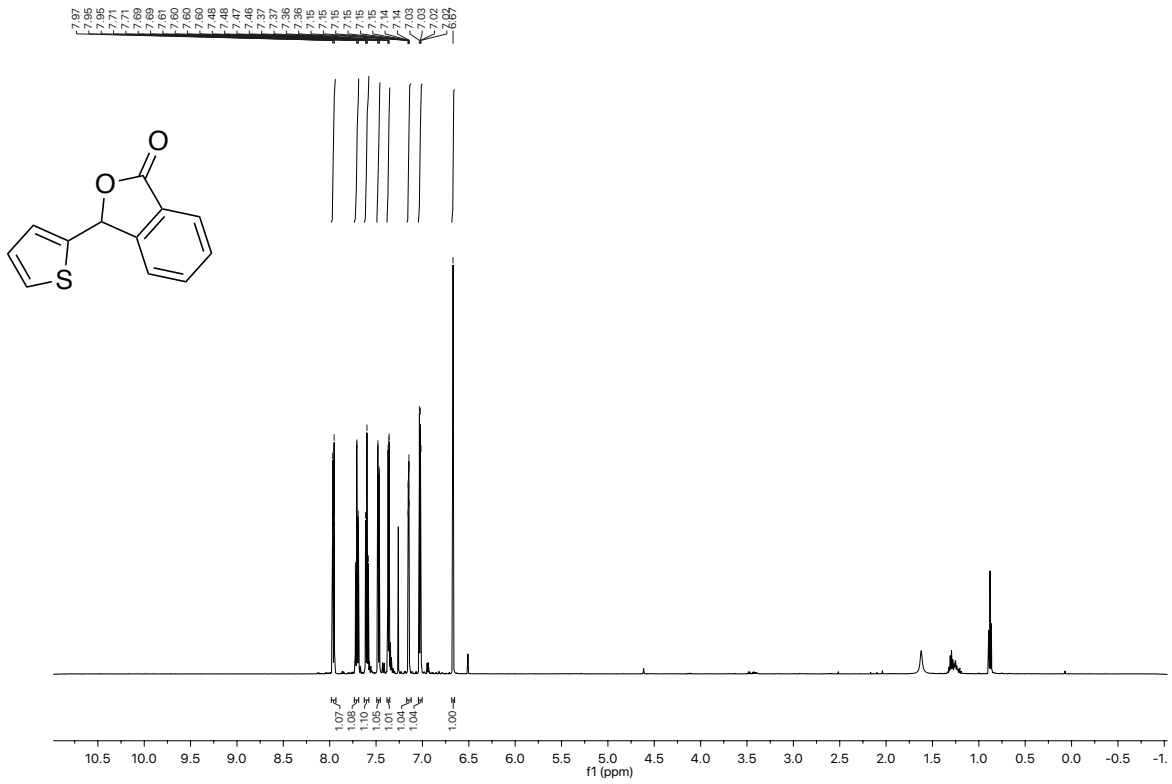
152.05
151.95
151.74
151.66
150.06
149.96
149.77
149.69
148.94
134.72
133.67
133.64
133.60
129.92
126.04
125.61
123.55
123.52
123.50
123.47
122.87
118.15
118.01
116.38
116.24
81.37
81.36
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2
f1 (ppm)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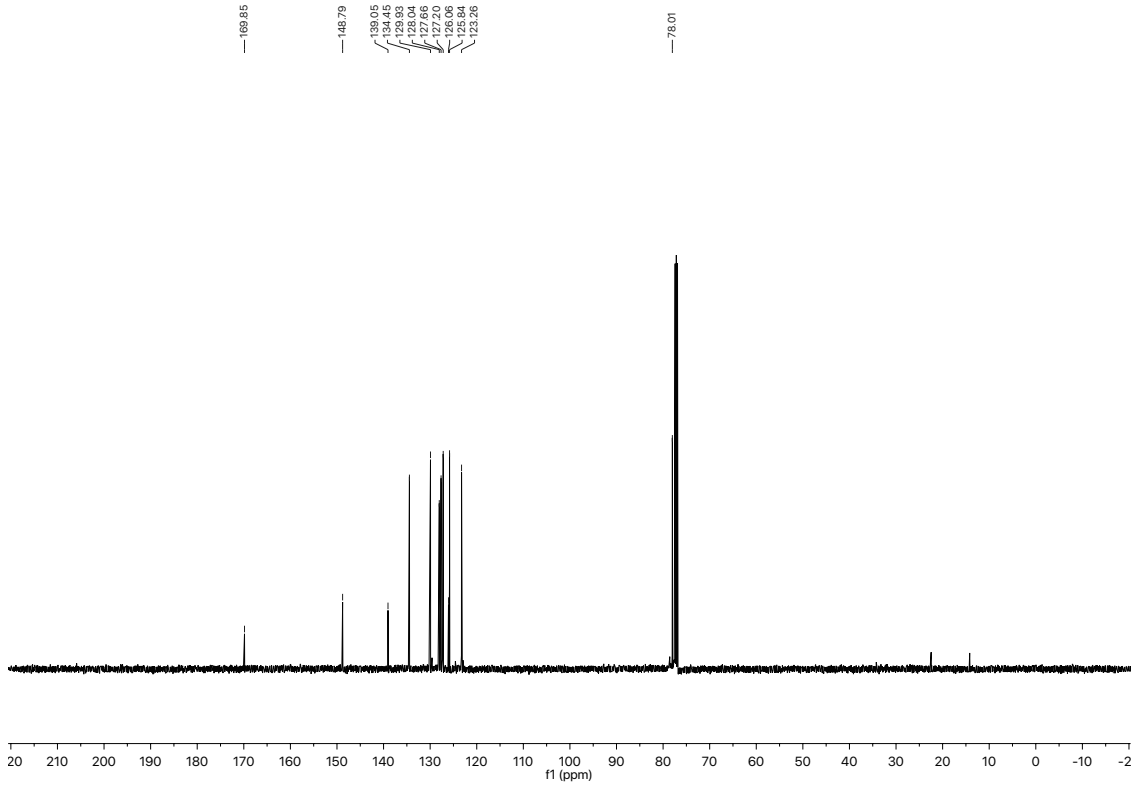
7.47
7.46
7.37
7.36
7.15
7.14
7.03
7.02
6.67
O
O
S
1.07
1.08
1.10
1.05
1.01
1.04
1.04
1.00
f1 (ppm)


169.85
148.79
139.05
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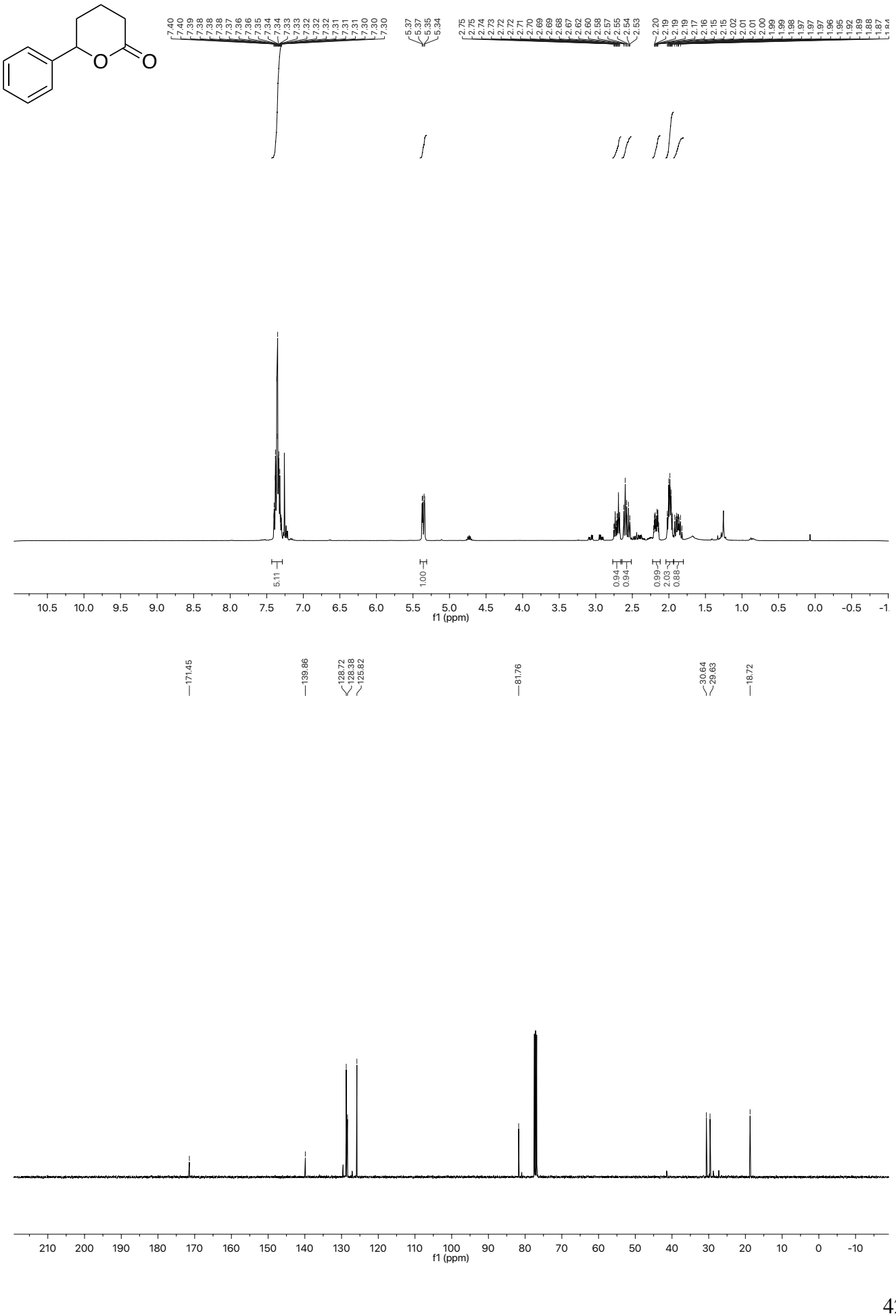
129.04
127.65
127.20
126.06
125.84
123.26
78.01
f1 (ppm)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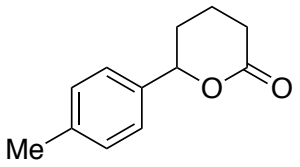
5.37 5.37 5.35 5.34
2.75 2.75 2.74 2.73 2.72 2.72 2.71 2.70 2.69 2.69 2.68 2.67 2.62 2.60 2.58 2.57 2.55 2.54 2.53
2.20 2.19 2.19 2.19 2.17 2.16 2.15 2.15 2.02 2.01 2.01 2.00 1.99 1.99 1.98 1.97 1.97 1.97 1.96 1.95 1.92 1.89 1.88 1.87
O
O
5.11
1.00
0.94
0.94
0.99
2.03
0.88
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
171.45
139.86
128.72
128.38
125.82
81.76
30.64
29.63
18.72
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
O
O

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5.32
5.31
2.73
2.71
2.71
2.70
2.70
2.68
2.68
2.67
2.66
2.61
2.59
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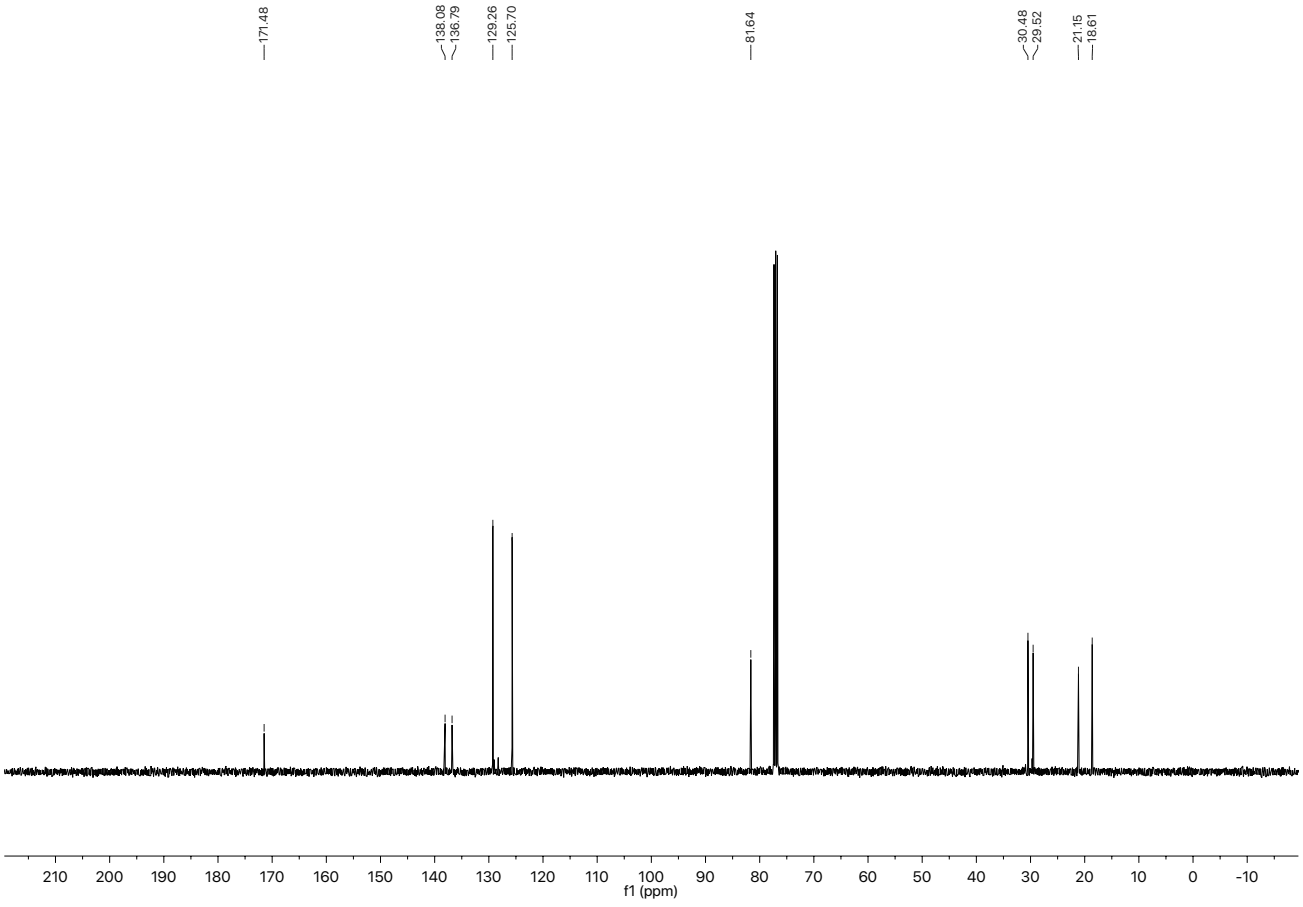
1.94
1.91
1.90
1.89
1.88
1.88
1.87
1.86
1.85
1.85
4.28
1.00
0.99
1.04
2.90
1.07
1.87
0.78
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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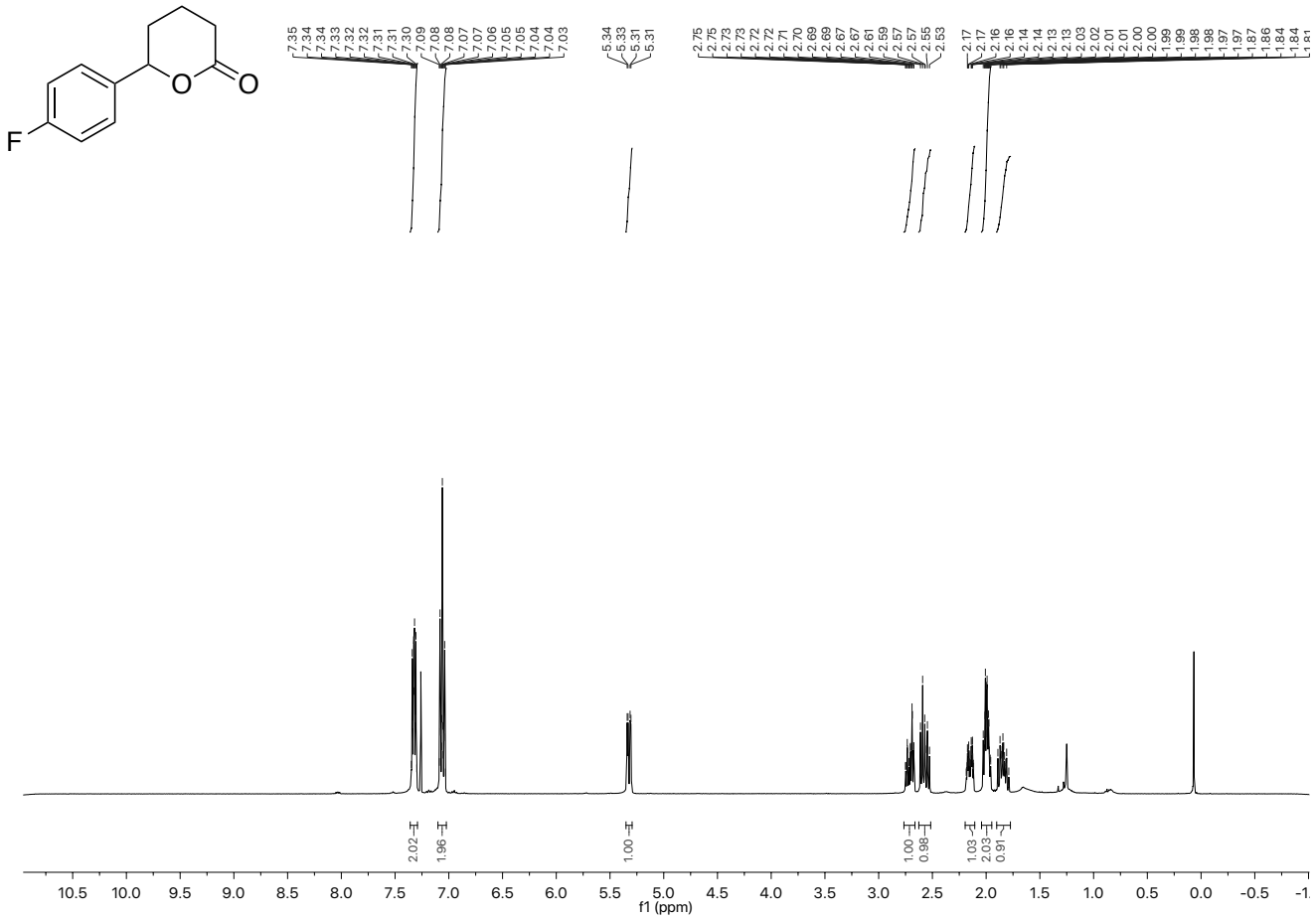
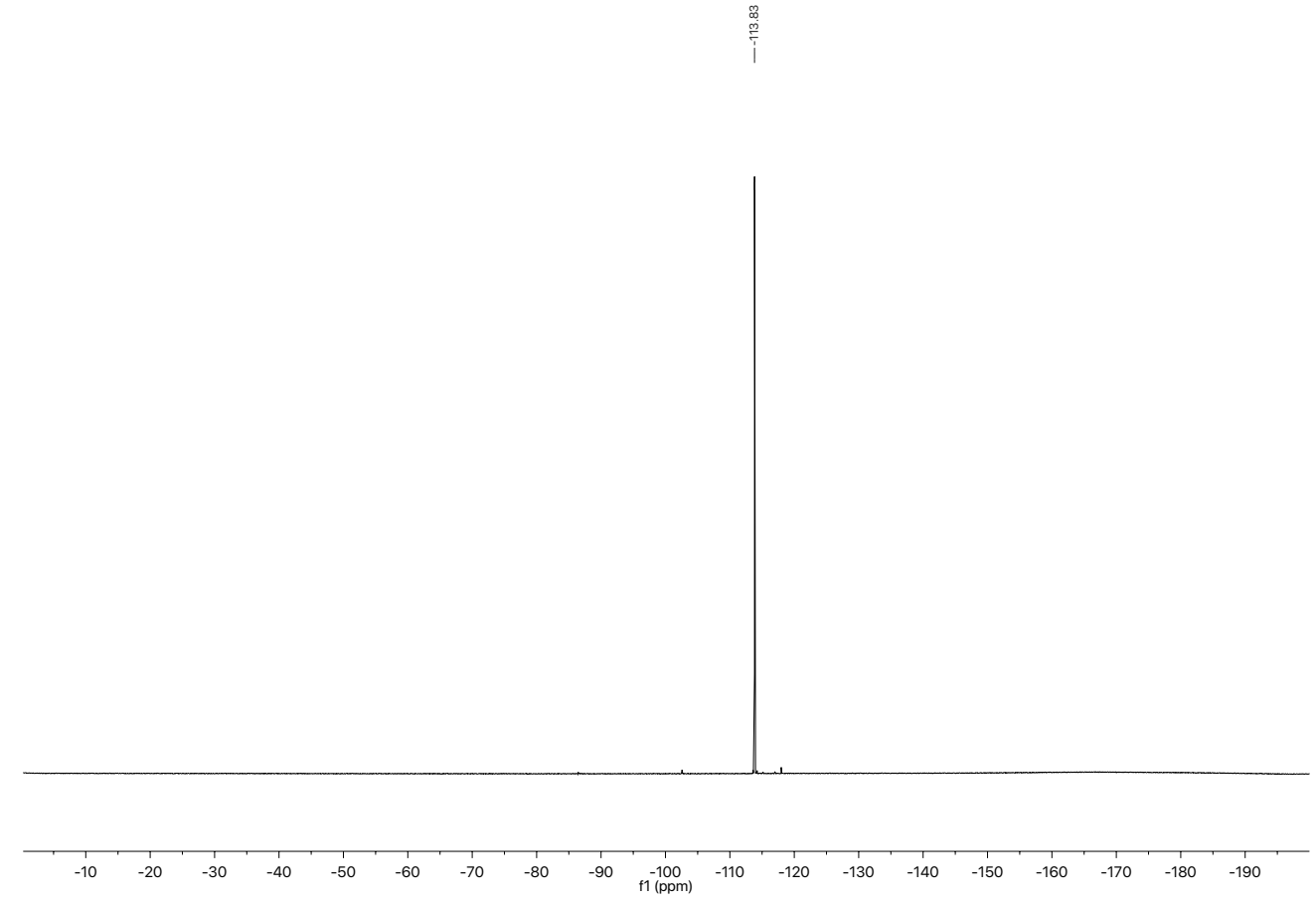
29.52
21.15
18.61
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


F
O
O
7.35 7.34 7.34 7.33 7.32 7.32 7.31 7.31 7.30 7.09 7.08 7.08 7.07 7.07 7.06 7.05 7.05 7.04 7.04 7.03
5.34 5.33 5.31 5.31
2.75 2.75 2.73 2.73 2.72 2.72 2.71 2.70 2.69 2.69 2.67 2.67 2.61 2.59 2.57 2.57 2.55 2.53
2.17 2.17 2.16 2.16 2.14 2.13 2.13 2.03 2.02 2.01 2.01 2.00 2.00 1.99 1.99 1.98 1.98 1.97 1.97 1.87 1.86 1.84 1.84
2.02
1.96
1.00
1.00
0.98
1.03
2.03
0.91
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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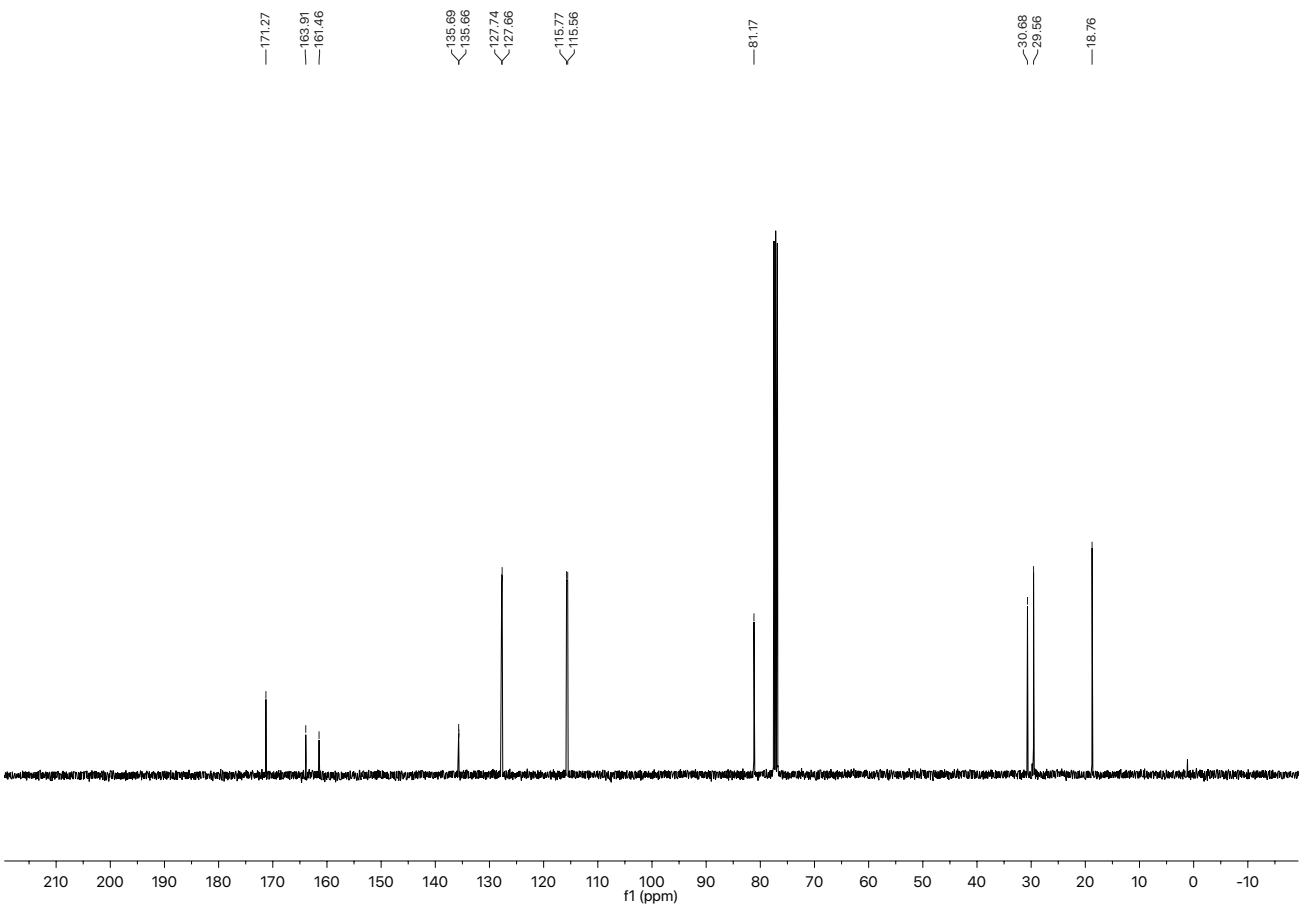
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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135.69
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127.74
127.66
115.77
115.56
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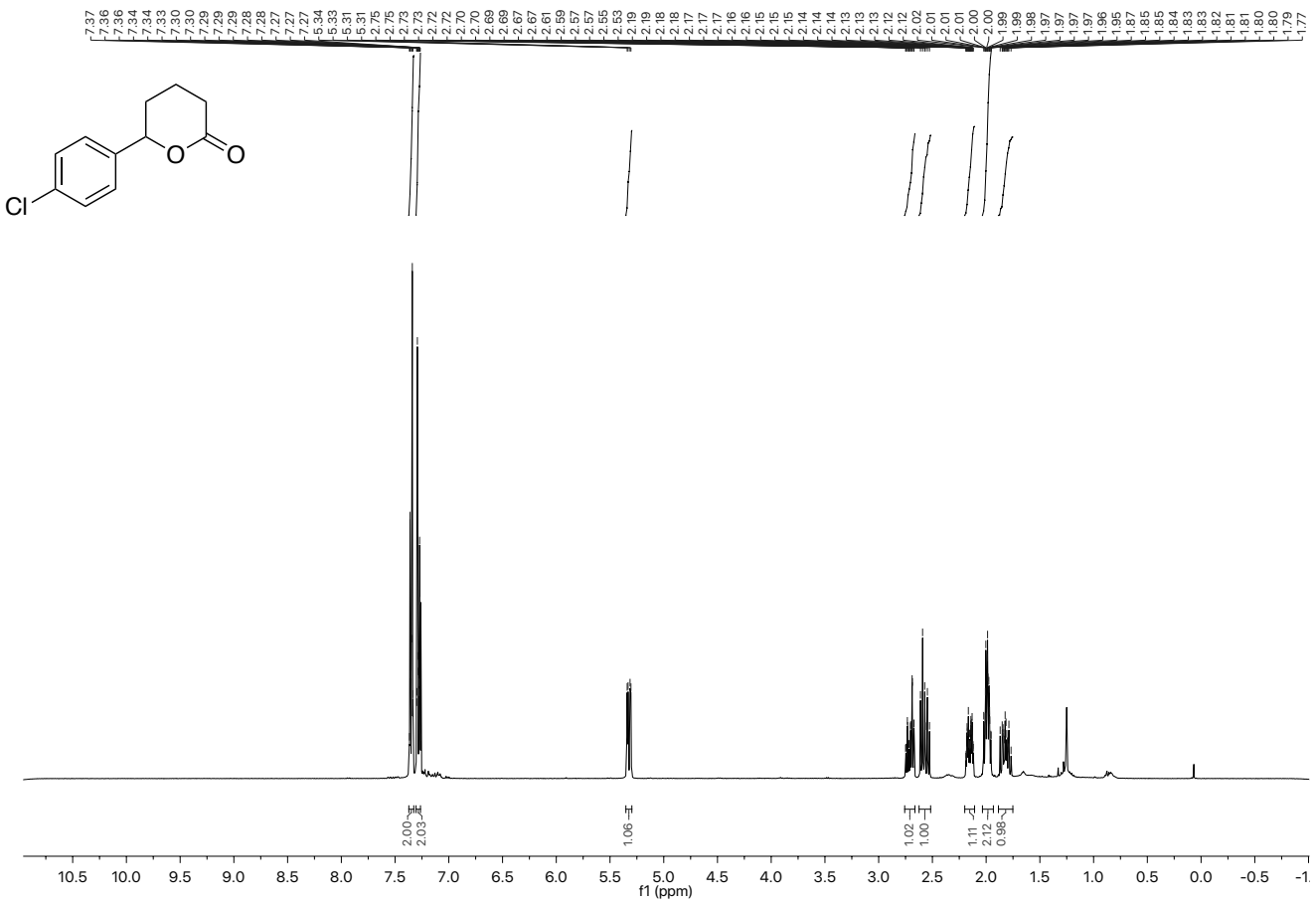
30.68
29.56
18.76
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Cl
O
O
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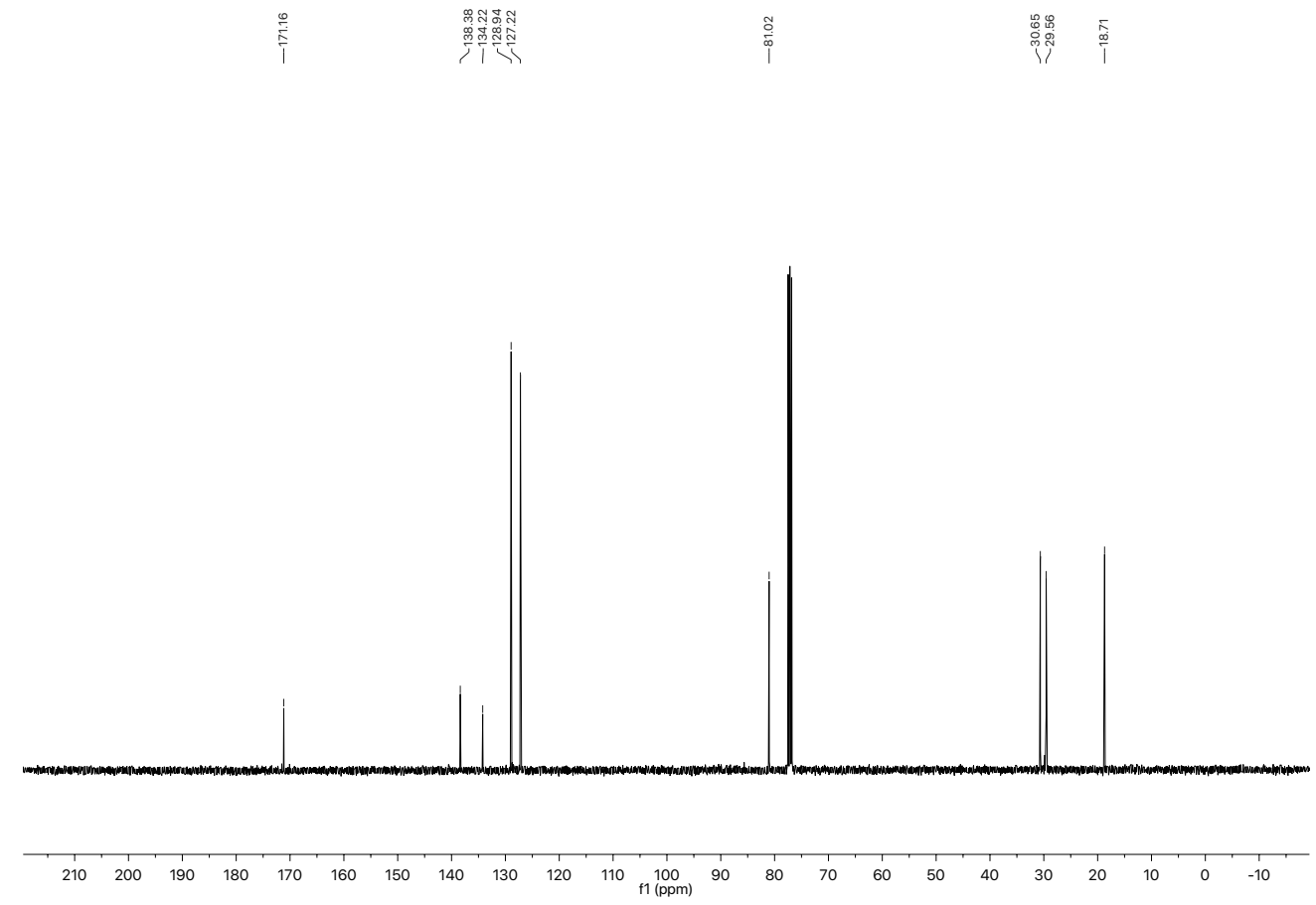
2.03
1.06
1.02
1.00
1.11
2.12
0.98
f1 (ppm)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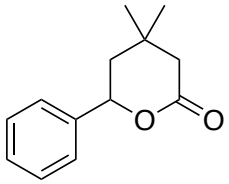

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1.00
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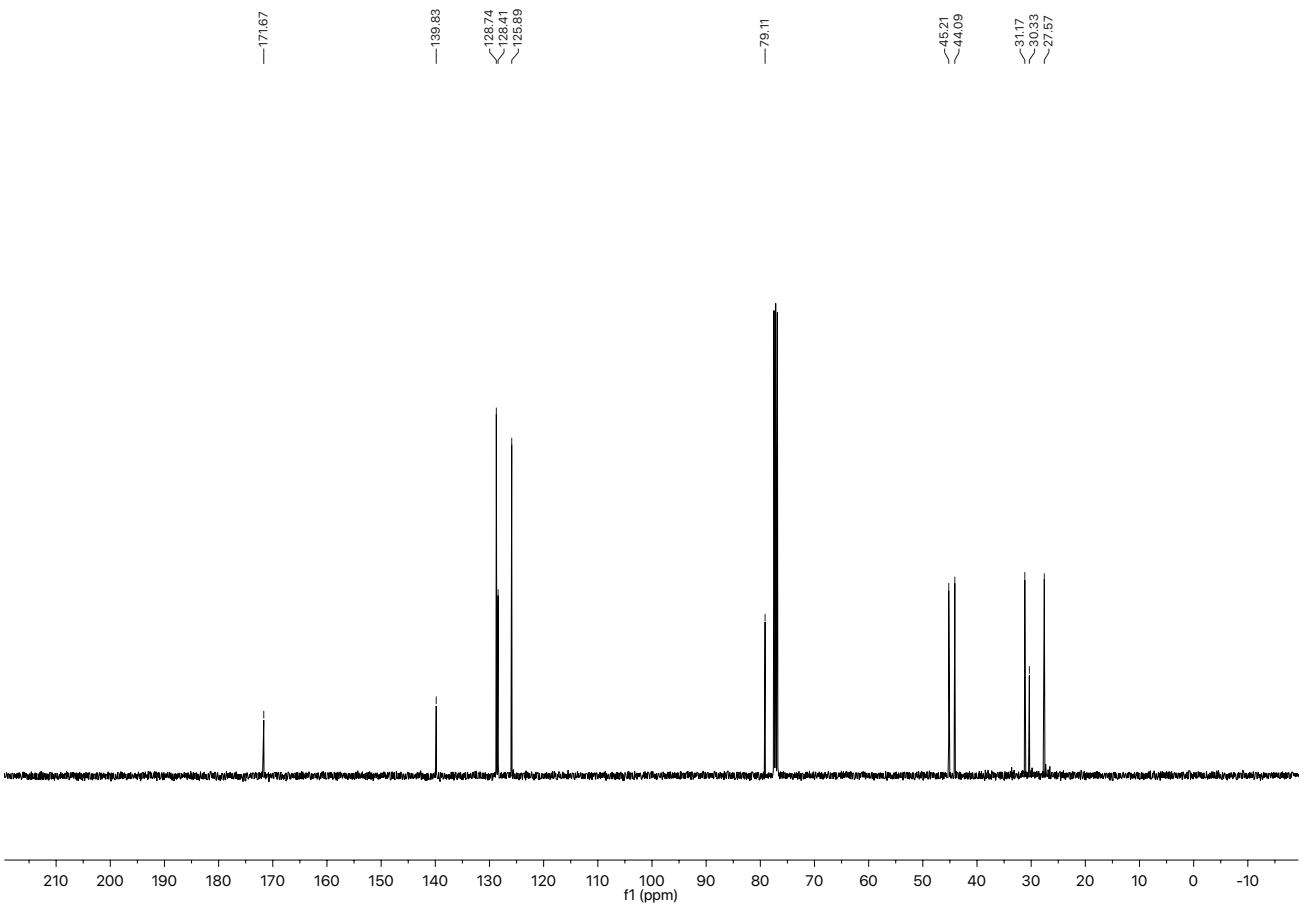
3.15
f1 (ppm)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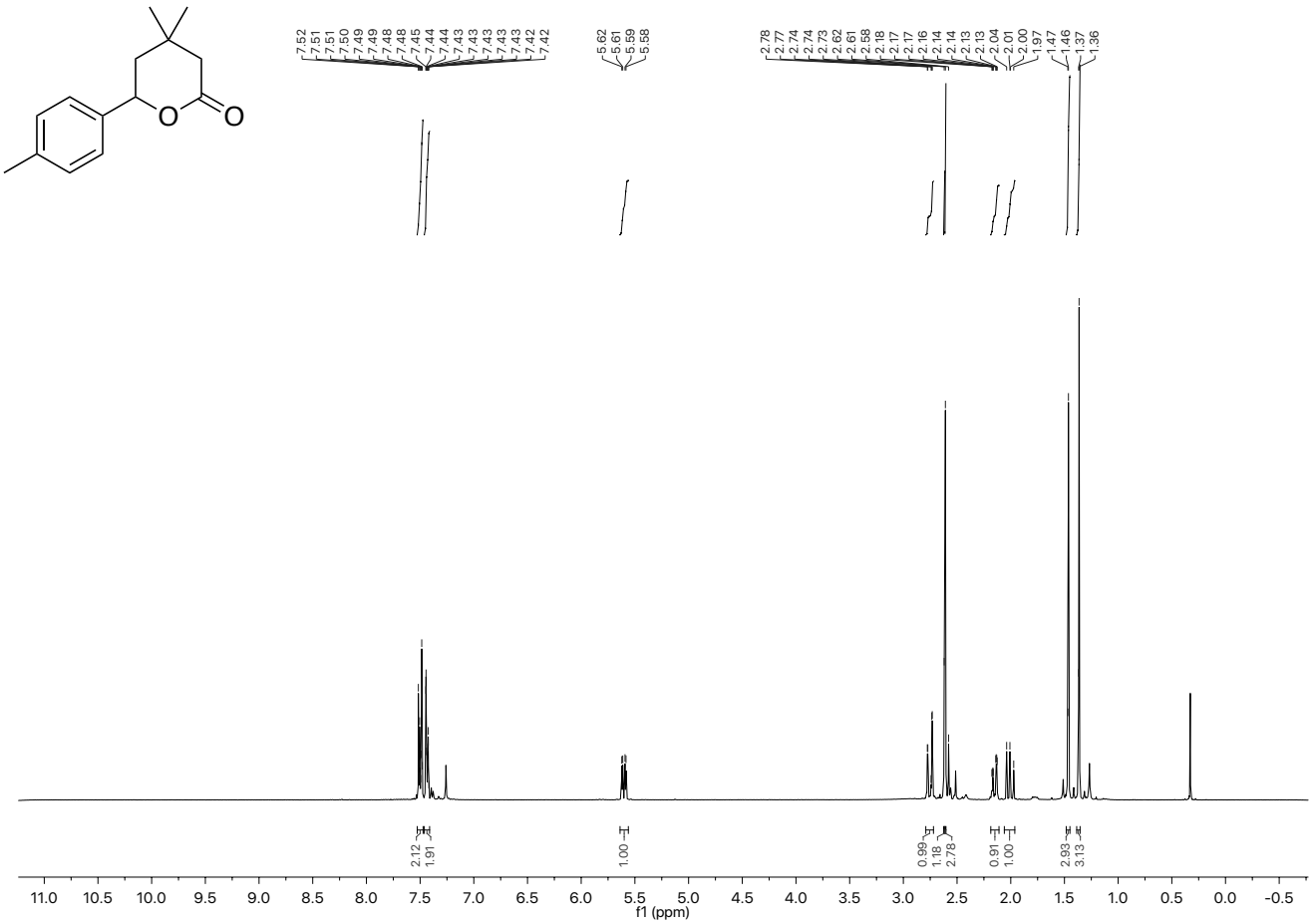
44.09
31.17
30.33
27.57
f1 (ppm)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2.04
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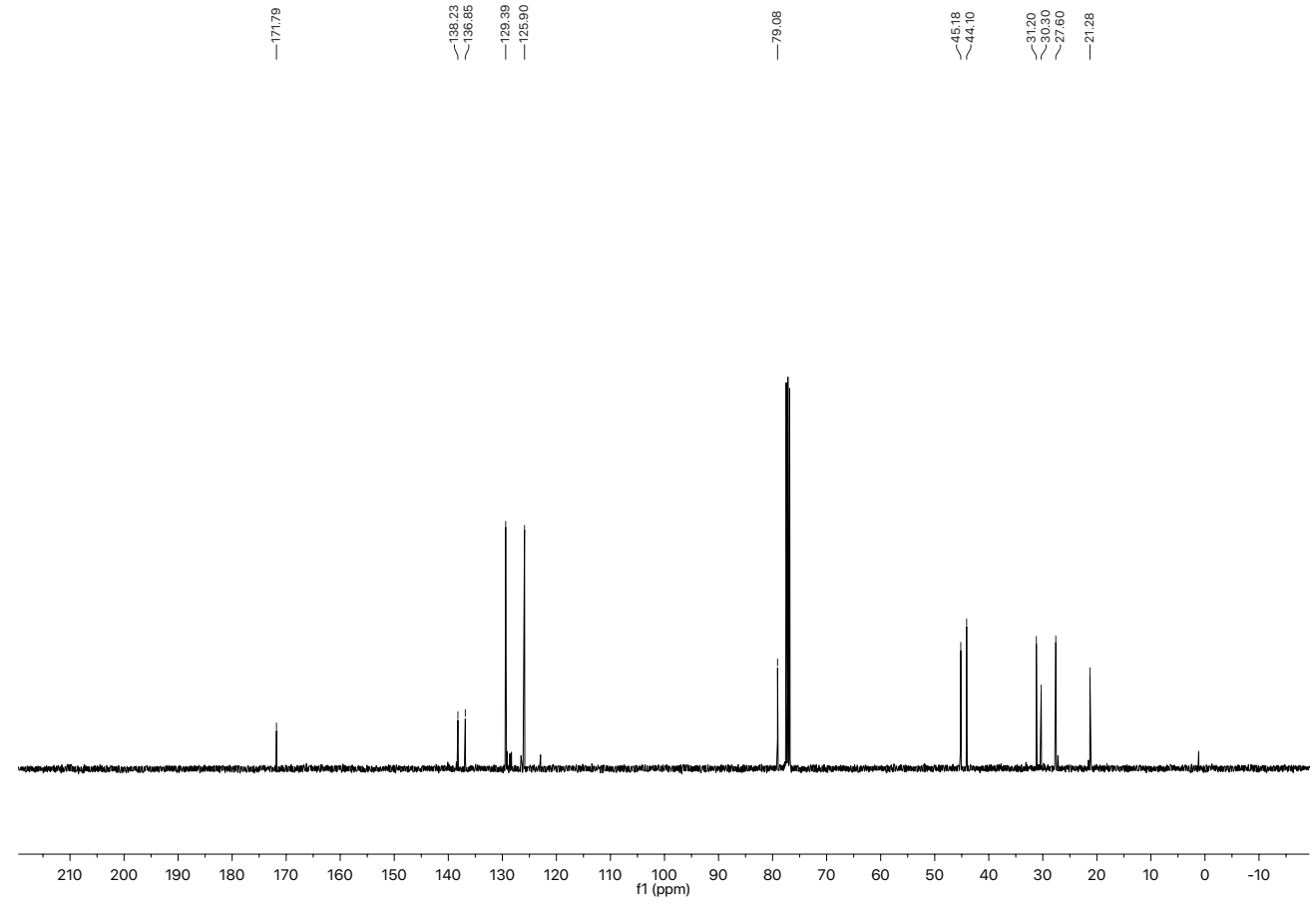
1.46
1.37
1.36
O
O
2.12
1.91
1.00
0.99
1.18
2.78
0.91
1.00
2.93
3.13
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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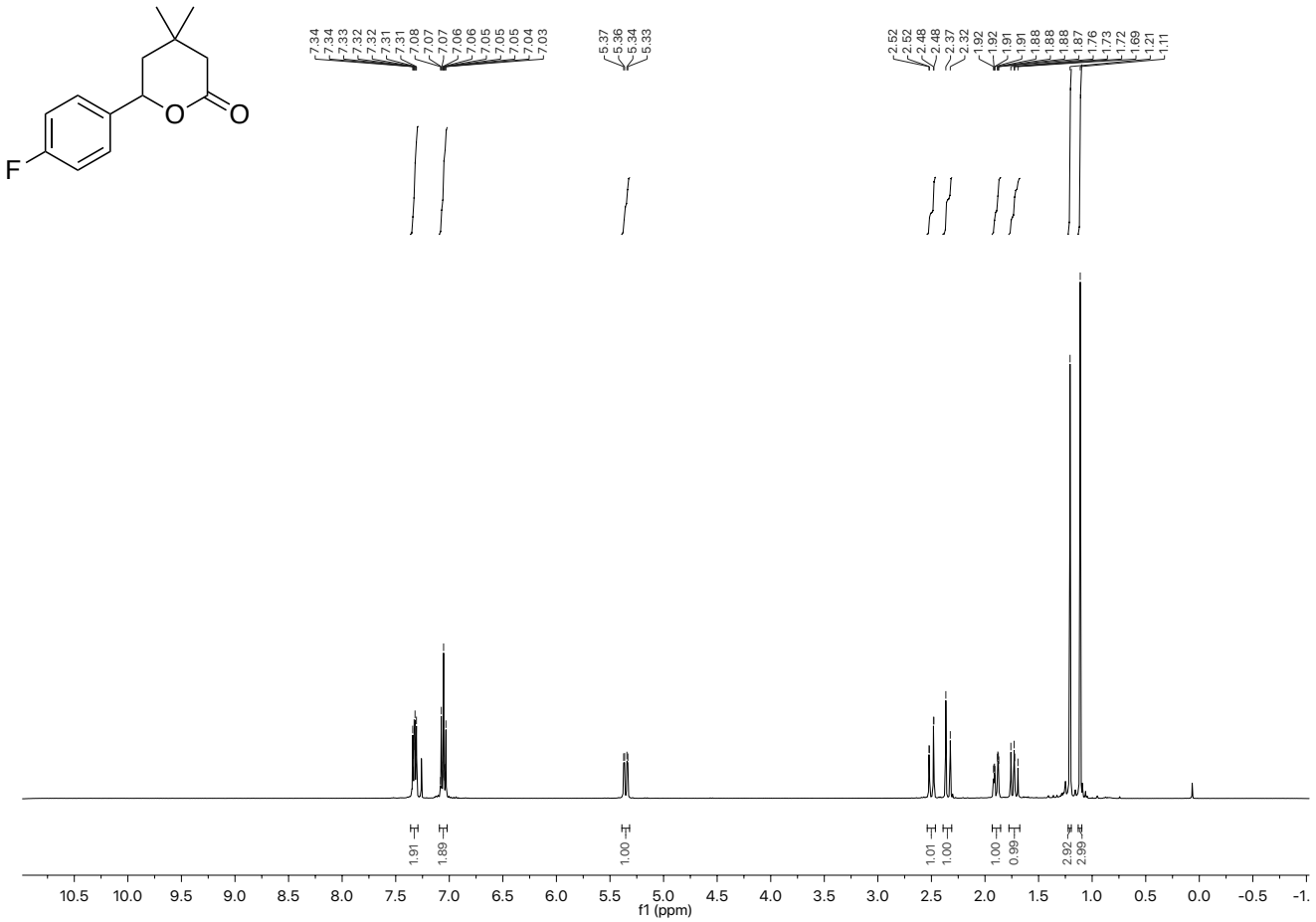
31.20
30.30
27.60
21.28
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


F
O
O
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7.34
7.33
7.32
7.32
7.31
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7.08
7.07
7.07
7.06
7.06
7.05
7.05
7.05
7.04
7.03
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5.36
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1.11
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1.89
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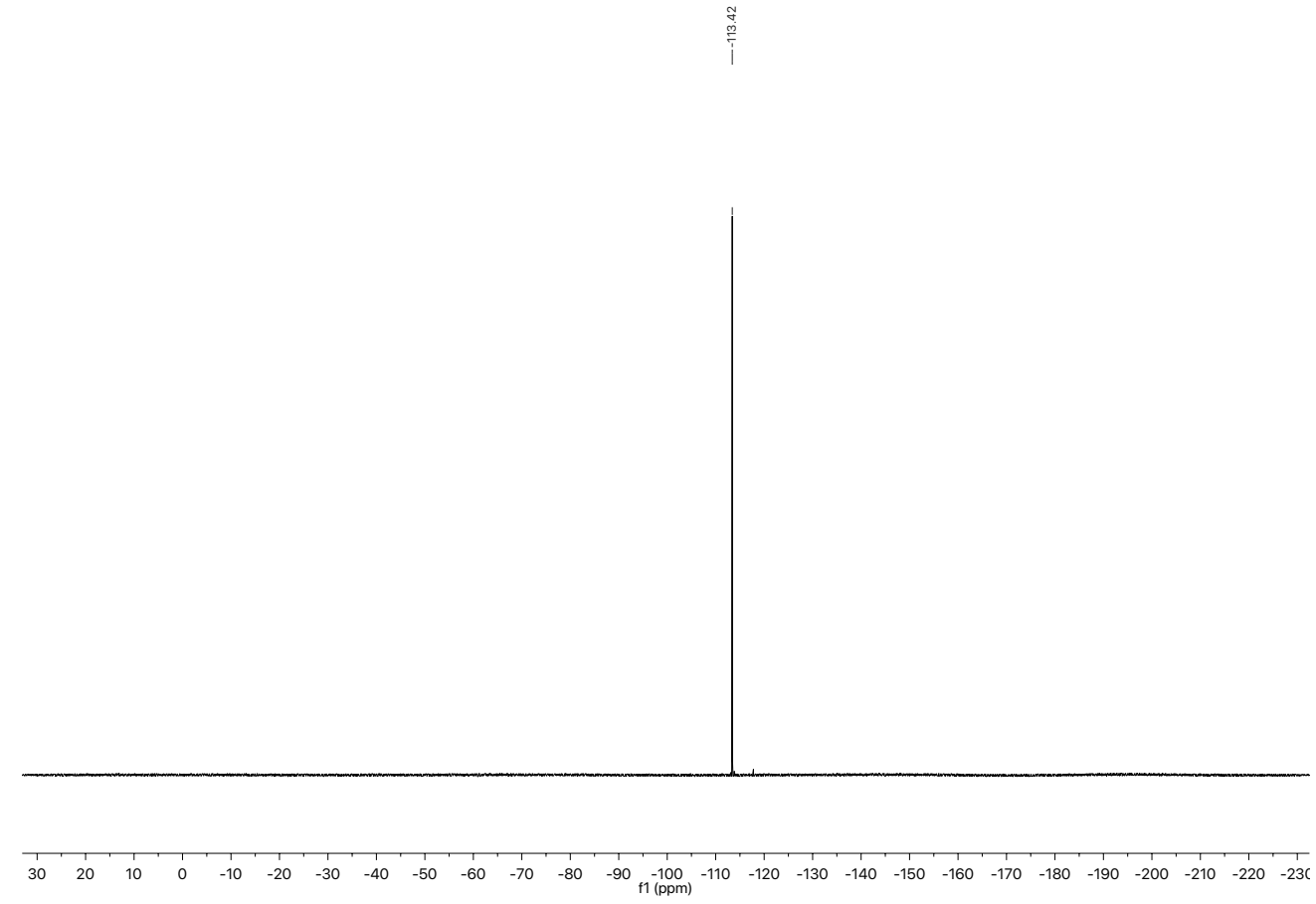
1.01
1.00
1.00
0.99
2.92
2.99
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)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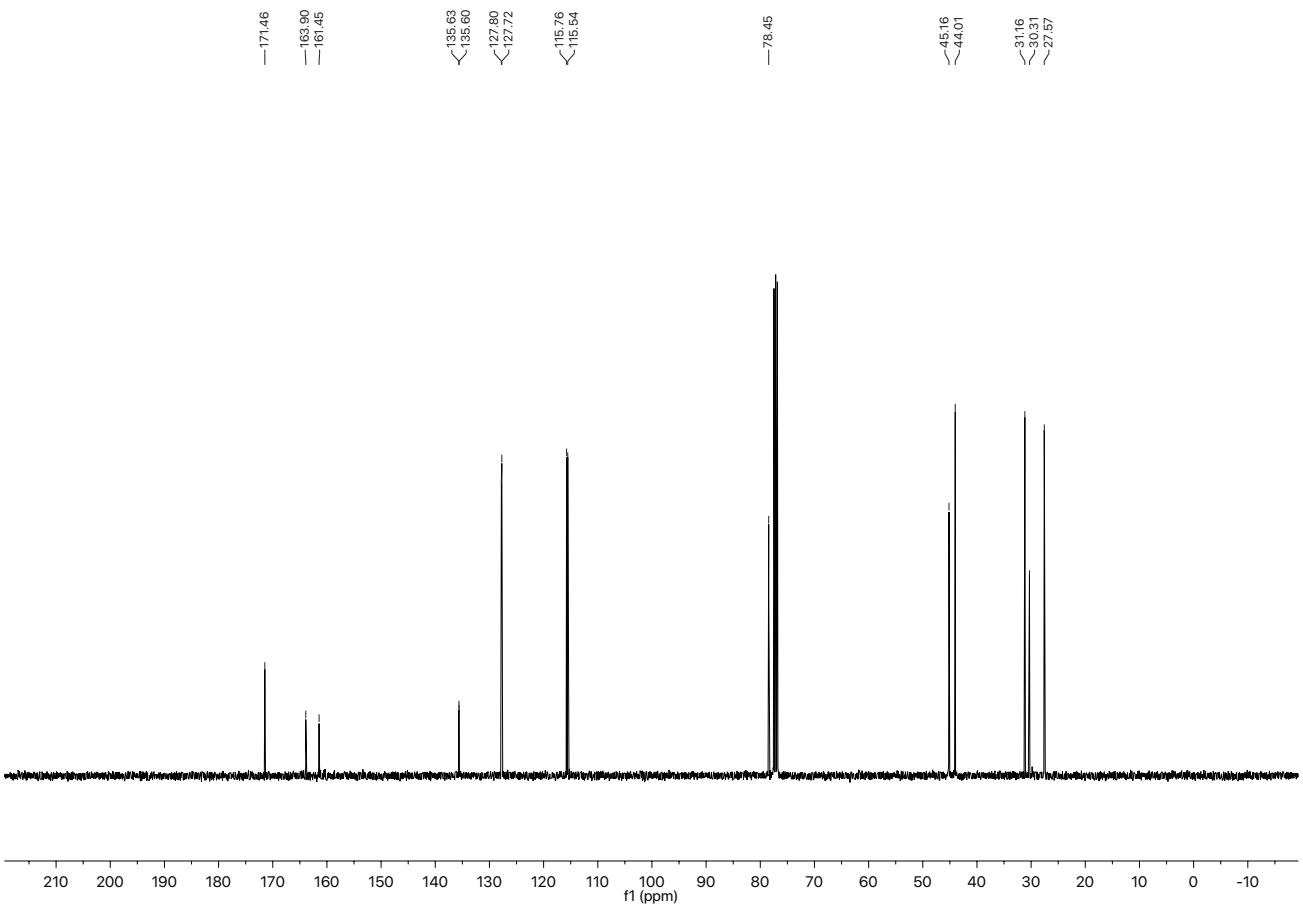
f1 (ppm)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127.72
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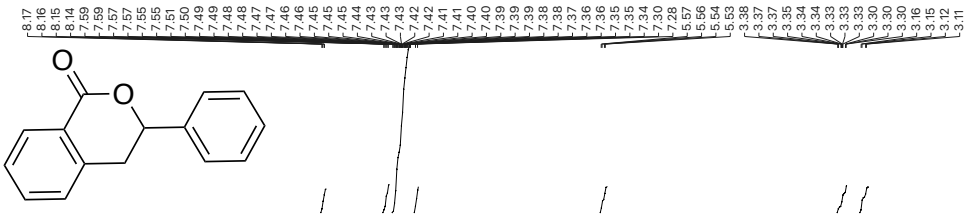
115.54
78.45
45.16
44.01
31.16
30.31
27.57
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.49
7.48
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7.46
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7.43
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7.42
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7.37
7.36
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7.35
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7.34
7.30
7.28
5.57
5.56
5.54
5.53
3.38
3.37
3.37
3.35
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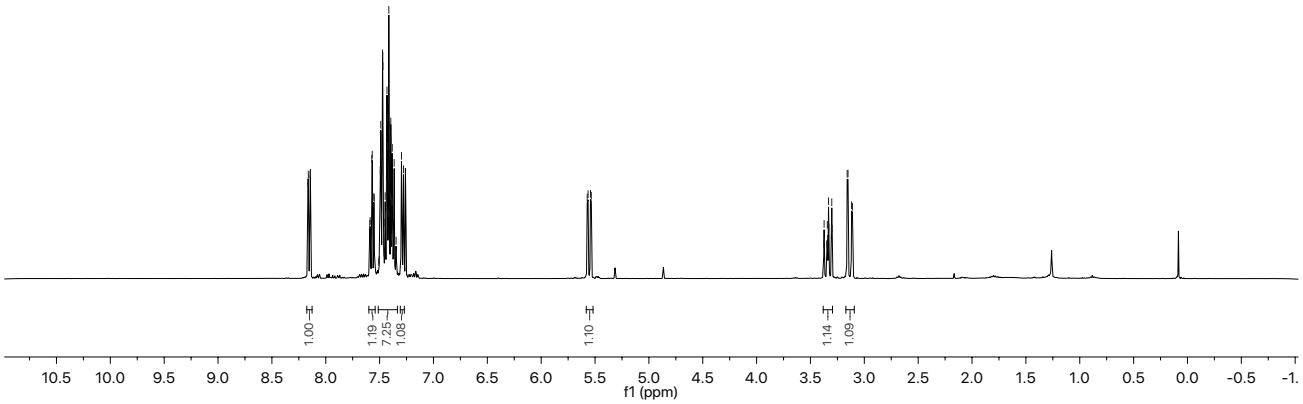
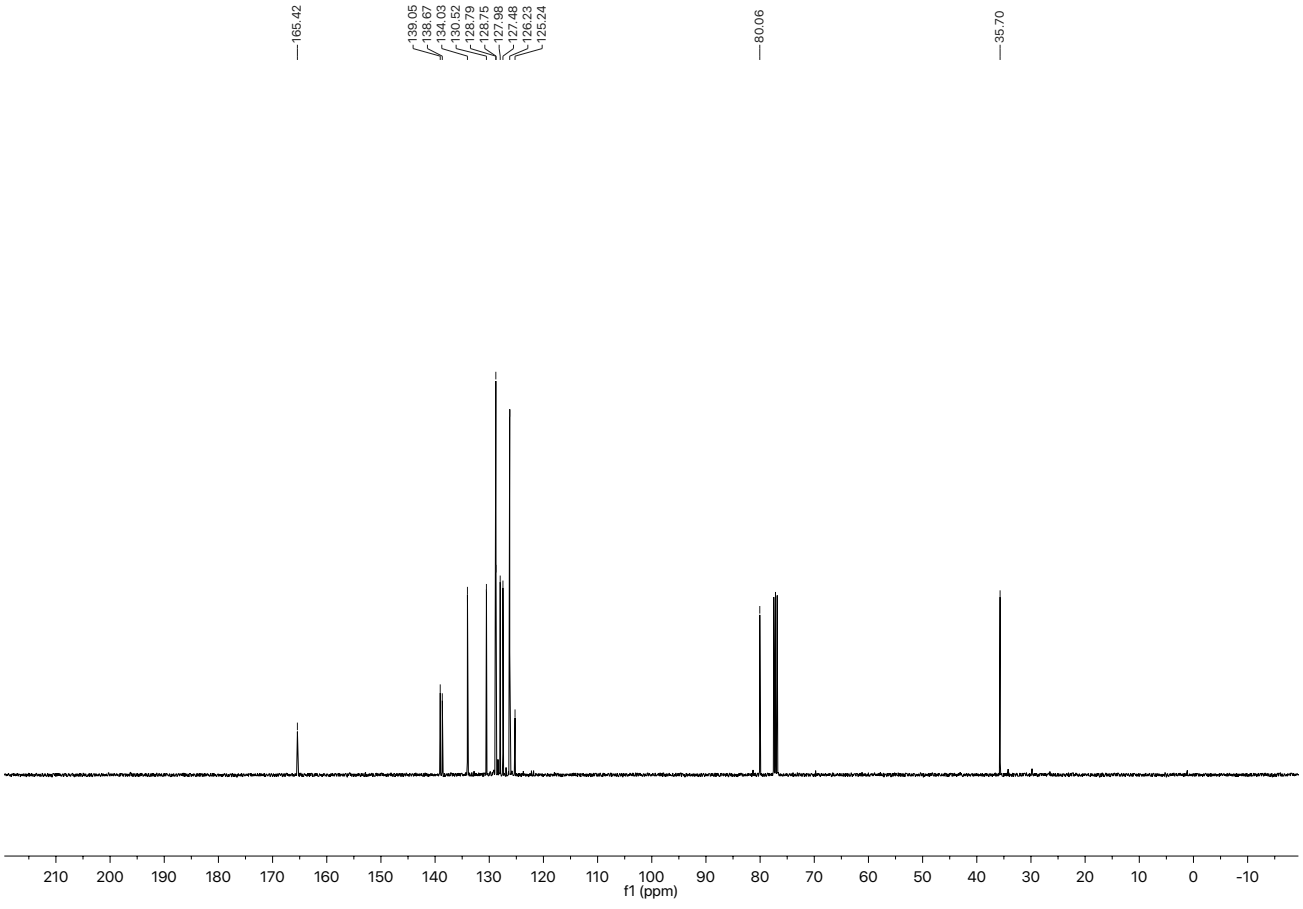
3.15
3.12
3.11
O
O


1.00
1.19
7.25
1.08
1.10
1.14
1.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)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138.67
134.03
130.52
128.79
128.75
127.98
127.48
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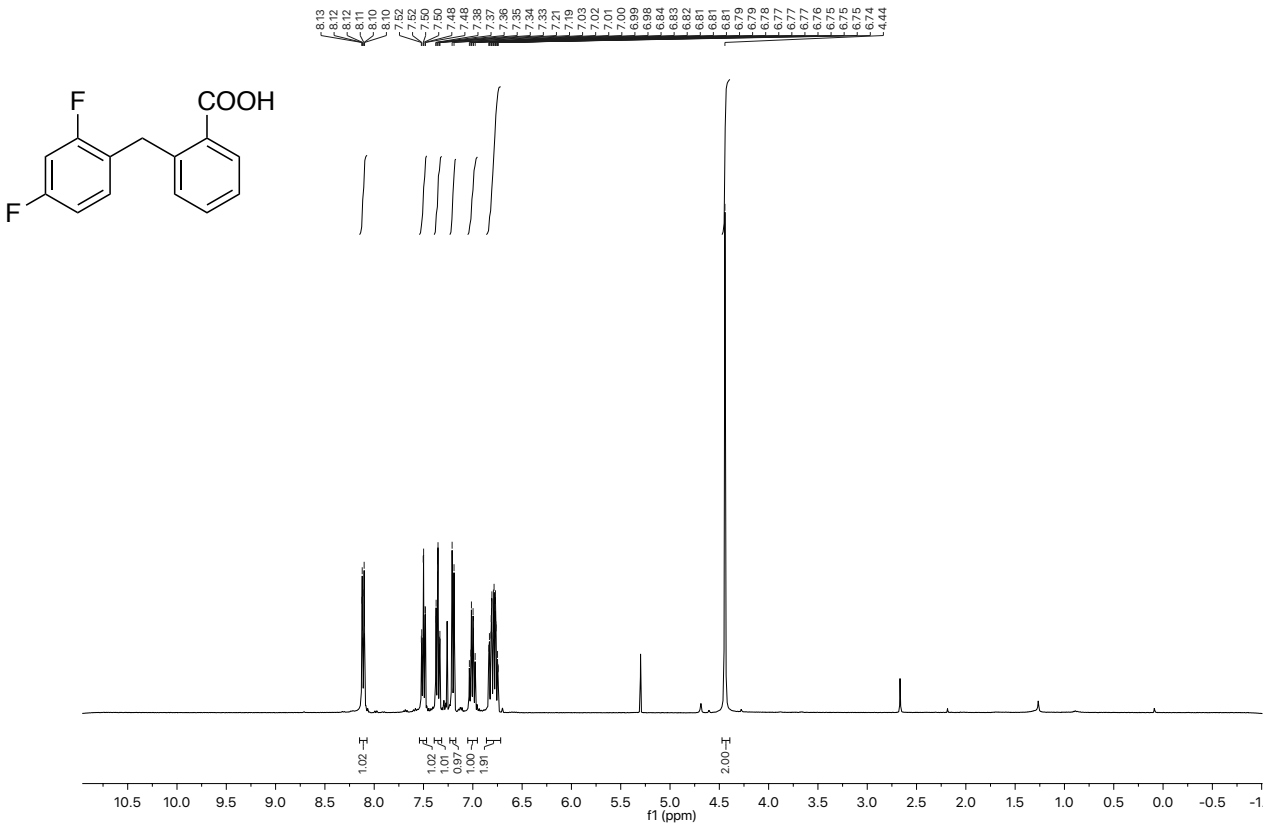
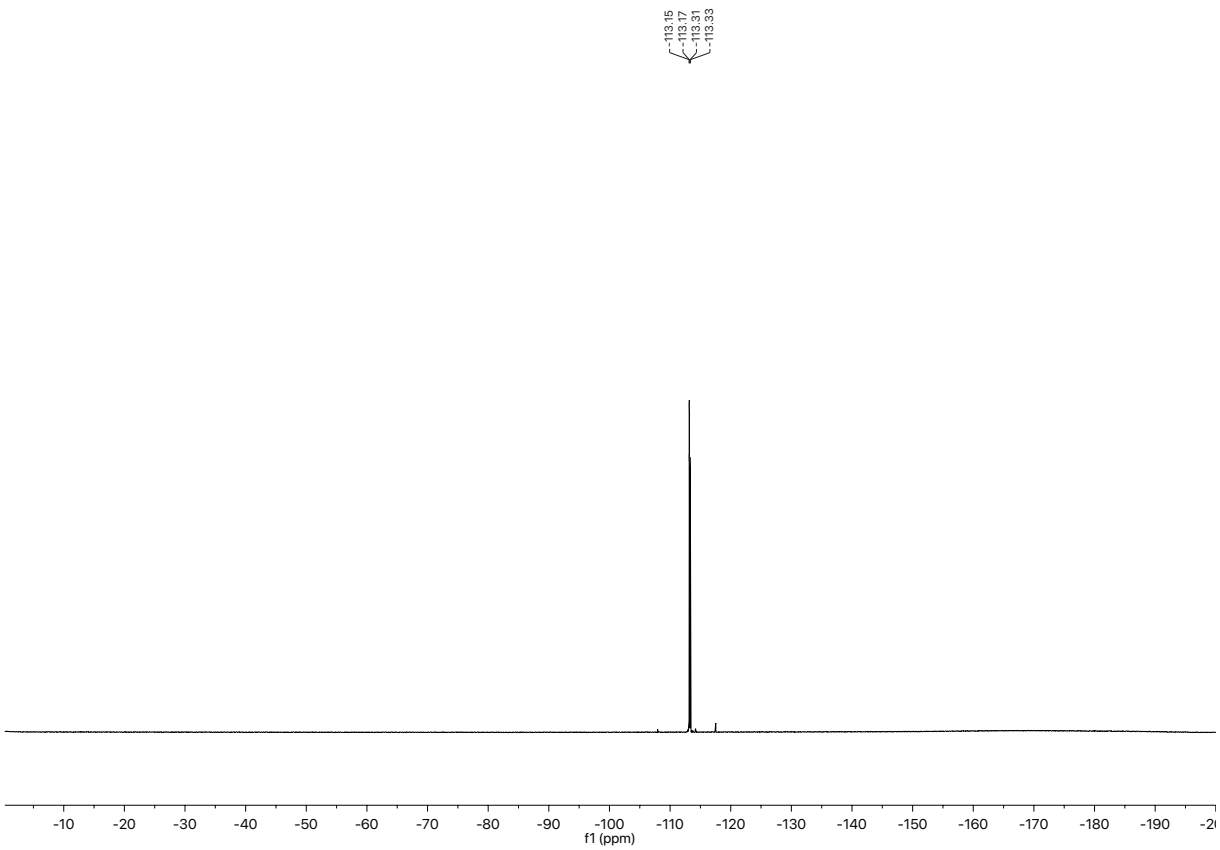
125.24
80.06
35.70
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


F
COOH
F
8.13
8.12
8.12
8.11
8.10
7.52
7.50
7.50
7.48
7.48
7.38
7.37
7.36
7.35
7.34
7.33
7.21
7.19
7.03
7.02
7.01
7.00
6.99
6.98
6.84
6.83
6.82
6.81
6.81
6.81
6.79
6.79
6.78
6.77
6.77
6.76
6.75
6.75
6.74
4.44
1.02
1.02
1.01
0.97
1.00
1.91
2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)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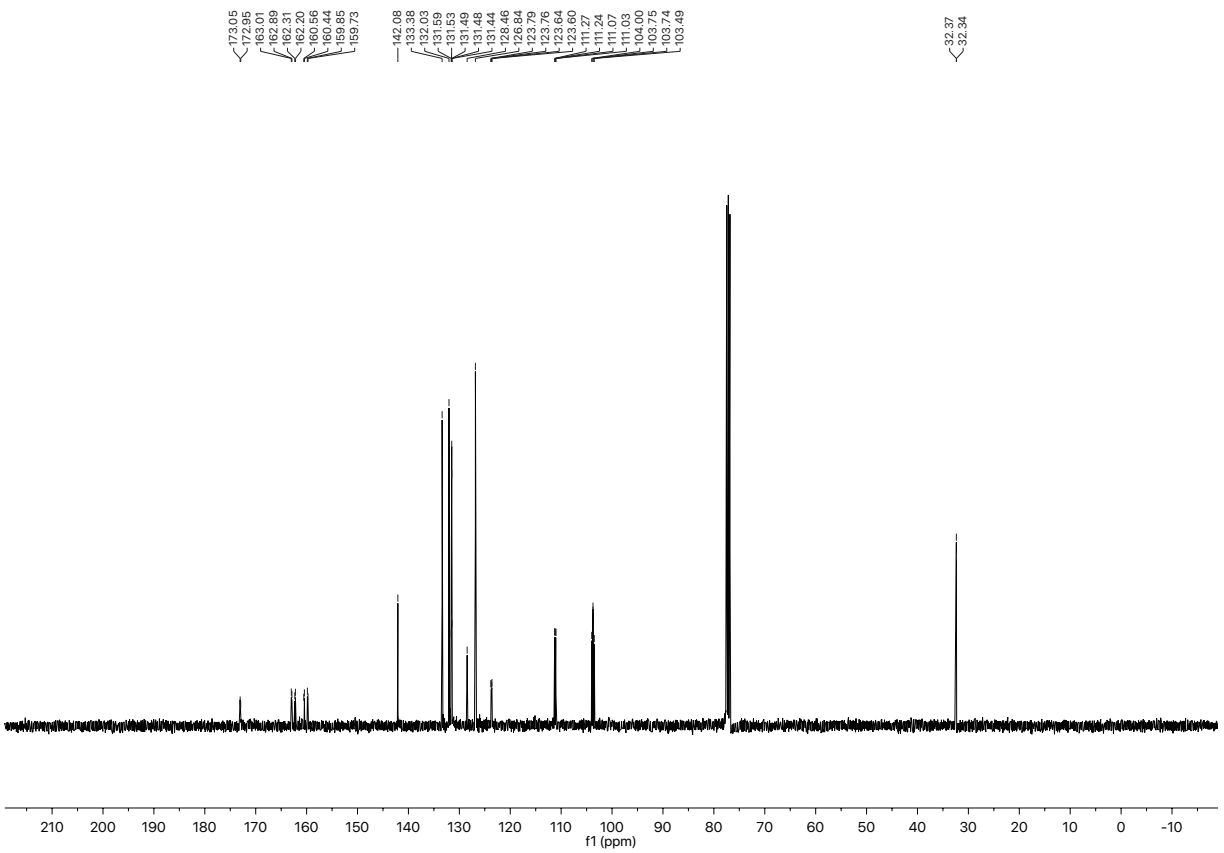
-113.17
-113.31
-113.33
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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172.95
163.01
162.89
162.31
162.20
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160.44
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159.73
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133.38
132.03
131.59
131.53
131.49
131.48
131.44
128.46
126.84
123.79
123.76
123.64
123.60
111.27
111.24
111.07
111.03
104.00
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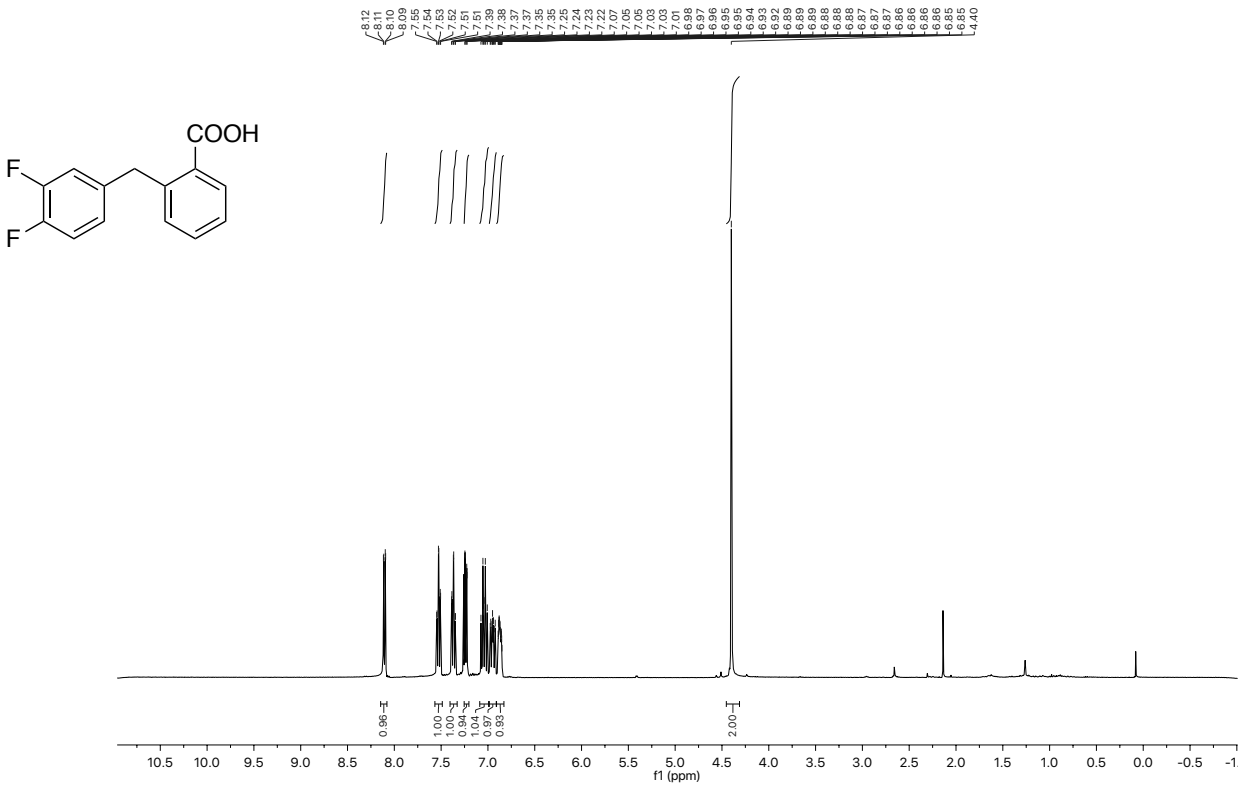
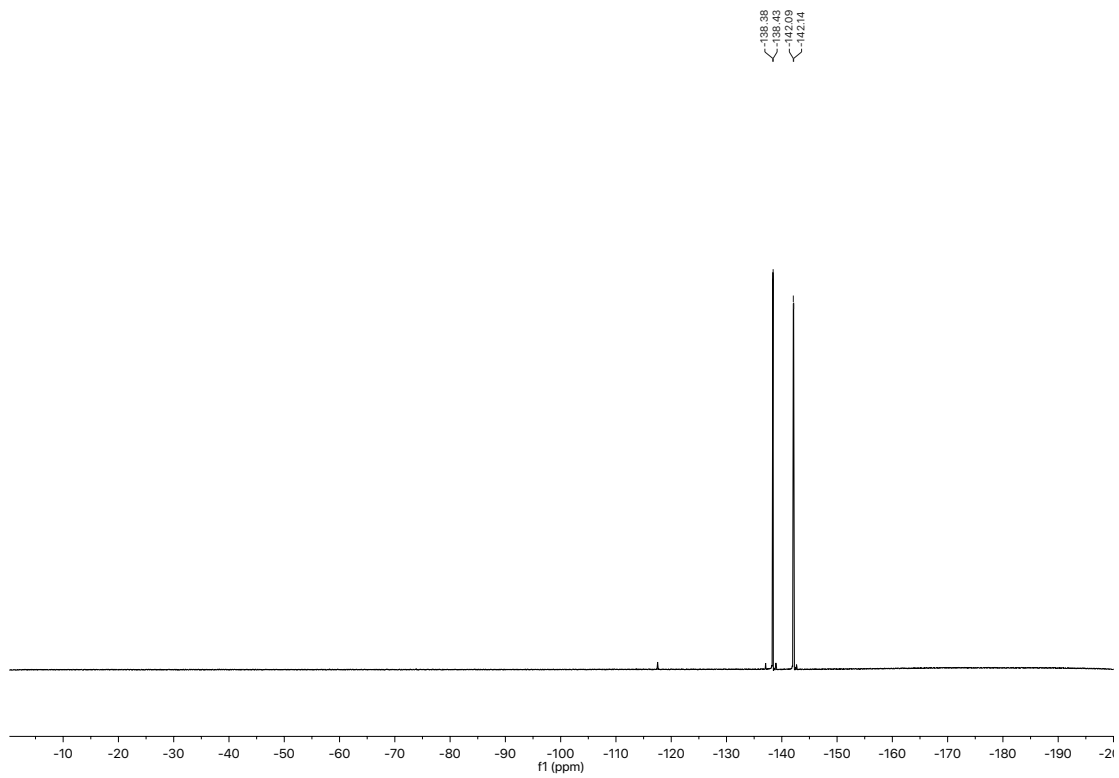
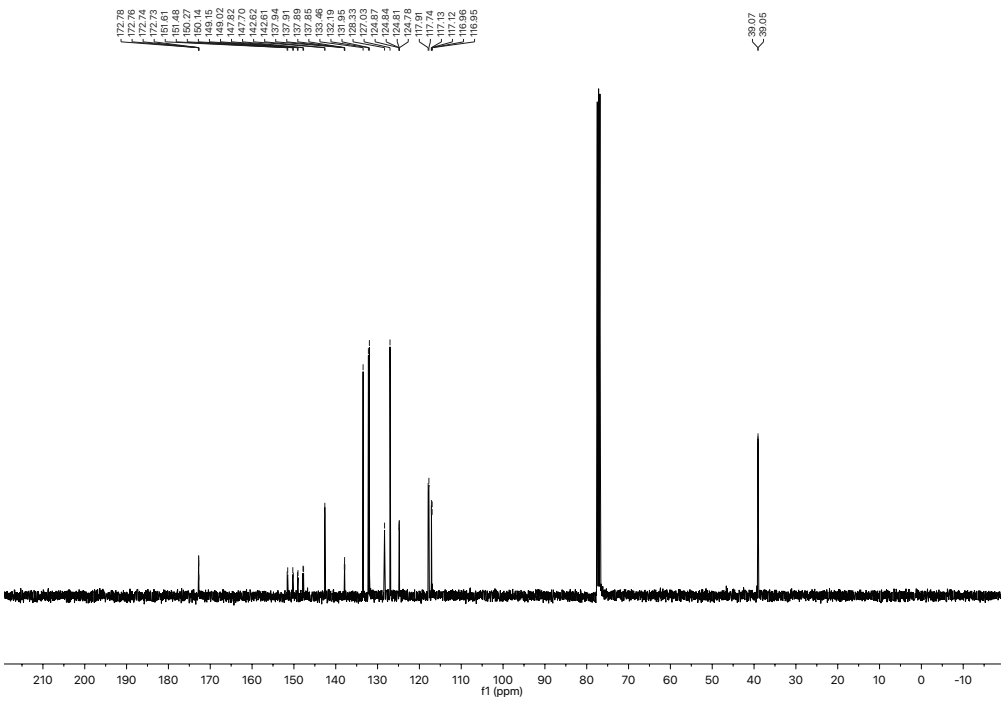
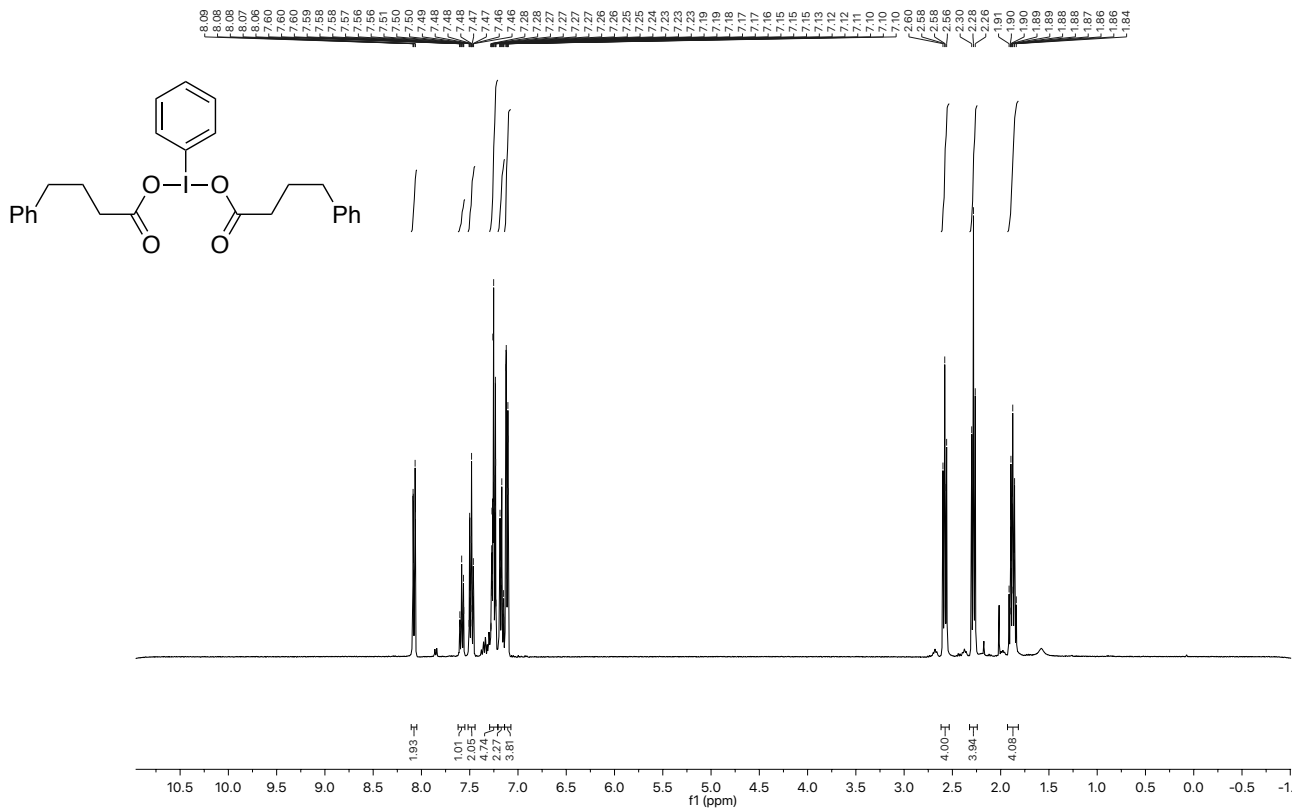
103.49
32.37
32.34
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


COOH
F
F
f1 (ppm)


f1 (ppm)


172.78
172.76
172.74
172.73
151.61
151.48
150.27
150.14
149.15
149.02
147.82
147.70
142.62
142.61
137.94
137.91
137.89
137.85
133.46
133.19
131.95
128.33
127.03
124.87
124.84
124.81
124.78
117.91
117.74
117.13
117.12
116.96
116.95
39.07
39.05
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Ph
O
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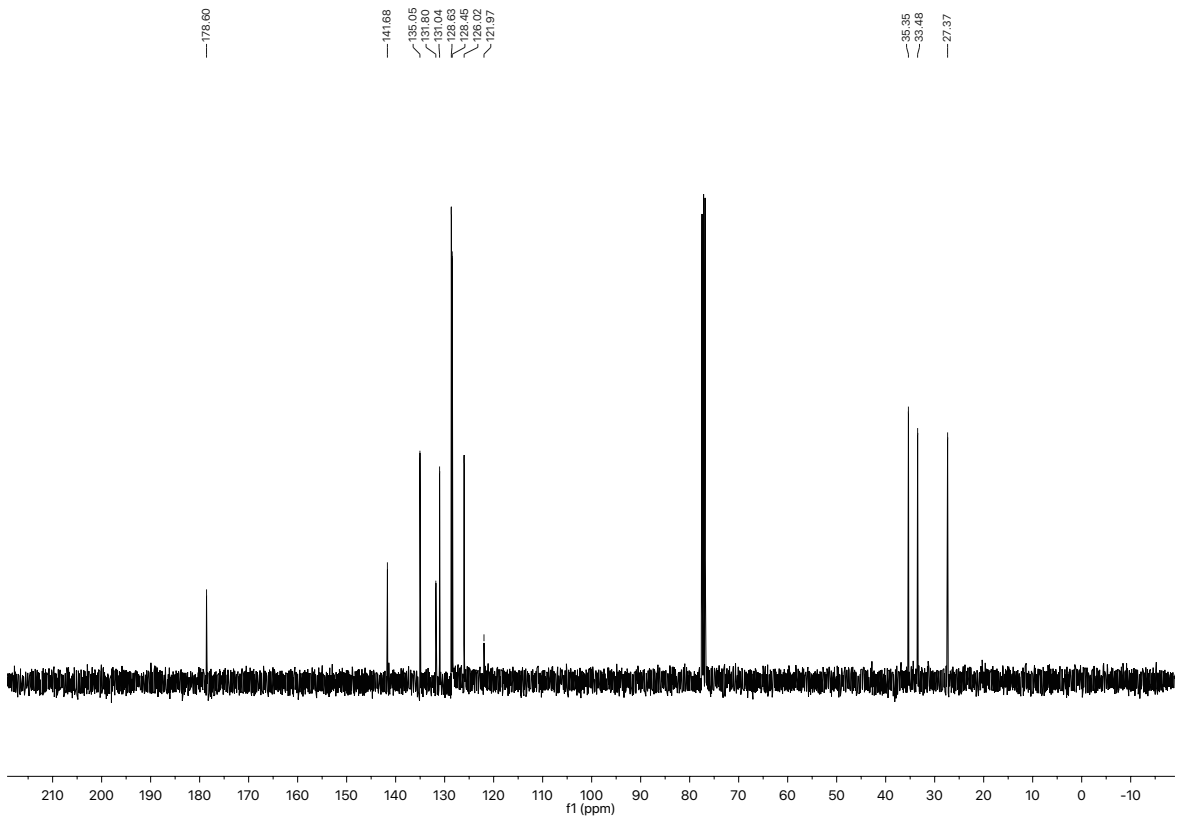
Ph
f1 (ppm)


f1 (ppm)