Arene oxidation with malonoyl peroxides

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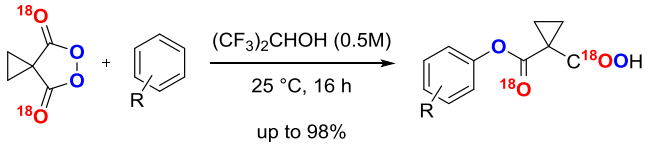
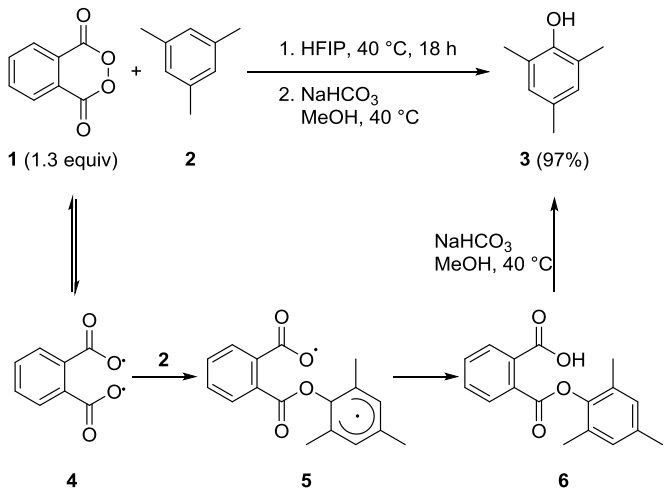
Supporting Information Placeholder



ABSTRACT: Malonoyl peroxide **7**, prepared in a single step from the commercially available diacid, is an effective reagent for the oxidation of aromatics. Reaction of an arene with peroxide **7** at room temperature leads to the corresponding protected phenol which can be unmasked by aminolysis. An ionic mechanism consistent with the experimental findings and supported by isotopic labeling, Hammett analysis, EPR investigations and reactivity profile studies is proposed.

The oxidation and functionalization of hydrocarbons is a central facet of the chemical industry for the production of high-tonnage commodities and the preparation of high-value pharmaceuticals, agrochemicals and fine chemicals. Therefore, methods for selective oxidation of C—H bonds are of great importance.[1] Phenols represent a key class of oxidized hydrocarbon.[2] While there are a small number of reports in which arenes are oxidized to the respective phenols using peroxides and strong acids as additives,[3] the oxidation of aromatic C—H bonds still presents a synthetic challenge specifically with respect to avoiding over oxidation.

Scheme 1. C—H oxidation using phthaloyl peroxide.[2]



A recent report from the laboratories of Houk and Siegel described a metal-free oxidation of aromatic carbon-hydrogen bonds which was proposed to proceed through an intriguing reverse-rebound mechanism (Scheme 1).[4] Reaction of mesitylene **2** with 1.3 equiv. of phthaloyl peroxide **1** in hexafluoroisopropanol (HFIP) followed by basic solvolysis gave the phenol **3** (97%).

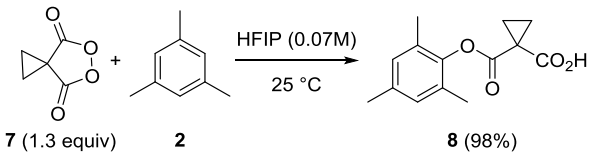
The method outlined in Scheme 1 represents a significant advance in arene oxidation. The proposed mechanistic pathway for the transformation suggested homolytic fission of the weak oxygen—oxygen bond leading to diradical **4**. Addition of this radical to the arene gives **5** which though H-atom abstraction provides the observed product **6**. Ester hydrolysis leads to the phenol **3** (97%, 2 steps). The procedure has wide functional group tolerance and arene over oxidation did not prove problematic. We believed two fundamental opportunities existed for development of this procedure: Firstly, phthaloyl peroxide **1** is known to be very shock sensitive and explodes violently when heated, representing a significant hazard.[5,6] Secondly, the proposed reverse-rebound mechanism leading to **6** was based upon theoretical studies. Provision of experimental evidence to support this pathway would be of great importance to the understanding and development of this procedure.

In recent years we have been interested in the chemistry of cyclic diacylperoxides and have shown that malonoyl peroxide **7**,[7] and related derivatives,[8] are effective for the *syn*-dihydroxylation of alkenes.[9] This reagent provides significant advantages over phthaloyl peroxide **1** within the *syn*-dihydroxylation reaction in terms of yield, selectivity, reaction rate, substrate scope and operating temperature.[10,11] Given our experience in understanding the mechanism of reactions involving the peroxide **7**,[12] together with the specific advantages provided in alkene dihydroxylation we elected to investigate the reactivity of **7** in the oxidation of arenes. Within this report we show that **7** reacts with arenes in the presence of a hydro-

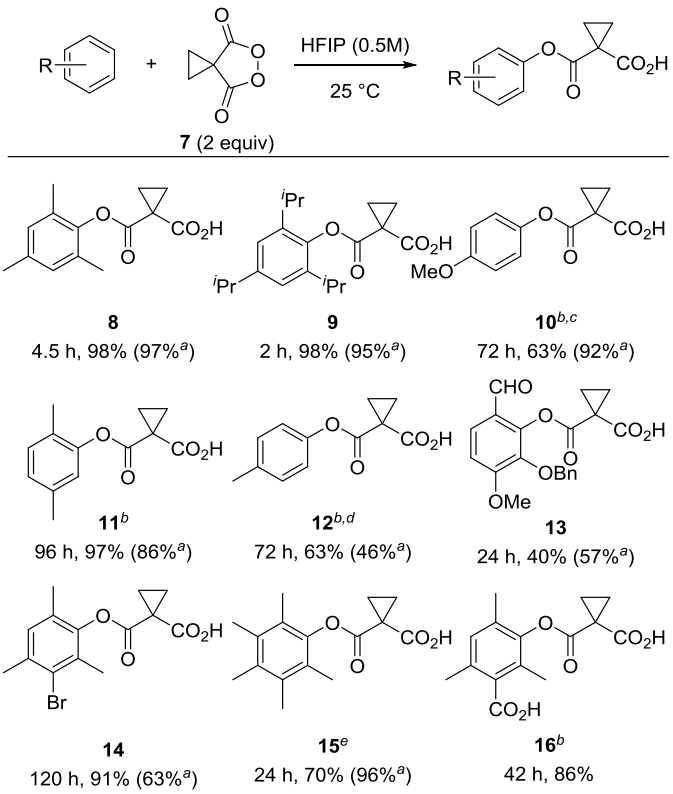
gen bond donor to give the corresponding functionalized aromatic and present data consistent with the arene and peroxide reacting through an ionic pathway.

As a starting point to our investigations we reacted mesitylene **2** with malonoyl peroxide **7** under the conditions reported by Houk and Siegel (0.07M; 40 °C).[2] Reaction of mesitylene **2** with 1.3 equivalents of peroxide **7** in hexafluoroisopropanol (HFIP) gave the adduct **8** (94%; 20 h). More conveniently, this reaction could be performed at room temperature (25 °C) rather than 40 °C without compromise in yield (**8**, 98%) (Scheme 2). Cleavage of the ester ($MeNH_2$, EtOH, 25 °C, 1 h) gave the corresponding phenol **3** (92% over 2 steps). Delighted by these excellent preliminary results and given the distinct advantages of malonoyl peroxide **7** over phthaloyl peroxide **1** outlined above we examined this transformation further.

Scheme 2. Malonoyl peroxide mediated oxidation of mesitylene.



Brief optimization of the reaction conditions showed that transformations could be performed at room temperature and considerably higher concentration (0.5M) than those reported previously (0.07M) (see Supporting Information).



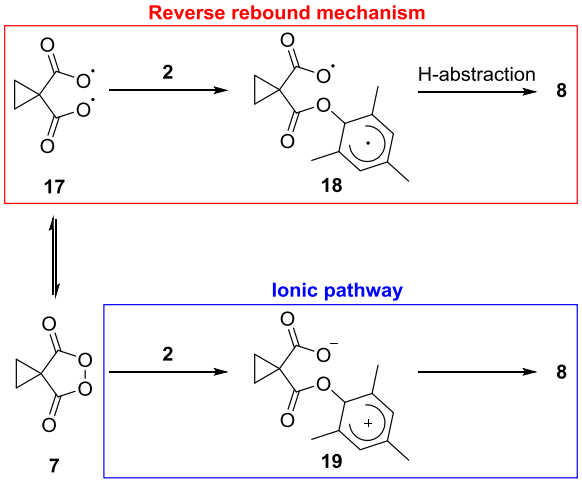
[a]Isolated yield of phenol using phthaloyl peroxide **1** reported in reference 2. [b]The reaction was perfomed at 50 °C. [c]1:1.6 mixture of *o*- and *p*-isomers obtained. [d]1:1 mixture of *o*- and *p*-isomers obtained. [e]1.1 equiv of malonoyl peroxide **7** used.

Figure 1. Arene oxidation with malonoyl peroxide 1.

Houk and Siegel showed their transformation to have broad functional group tolerance, describing the oxidation of over 50 substrates.[2] Direct comparison of the reaction using malonoyl peroxide **1** to those obtained for phthaloyl peroxide **2** on a selection of these substrates showed the transformation to proceed with similar yield and selectivity (Figure 1). Functional group tolerance mirrored that obtained with phthaloyl peroxide, which bodes well for further reaction development. We therefore believe that malonoyl peroxide **7** represents an effective alternative to the explosive phthaloyl peroxide **2** in the oxidation of arenes.

In order to understand the reaction further a series of experiments were undertaken to probe the mechanistic course of the process. The reverse-rebound mechanism proposed for the reaction of phthaloyl peroxide **1** was based upon theoretical calculations.[2] We sought to obtain experimental data using malonoyl peroxide **7** to underpin knowledge of this transformation. An analogous reverse-rebound mechanism with peroxide 7 would involve homolytic cleavage of the peroxide bond to give the diradical species **17** which on addition to the arene would give the intermediate **18**. Re-aromatization of **18** through H-atom abstraction would lead to the observed product **8**. In addition to this reverse-rebound mechanism we also considered an ionic pathway based on the established reactivity of **7** with alkenes.[10] Thus, nucleophilic attack of the electron rich arene **2** on the weak peroxide bond would lead to intermediate **19**, which upon re-aromatization would give **8**.

Scheme 3. Potential mechanistic course of reaction.

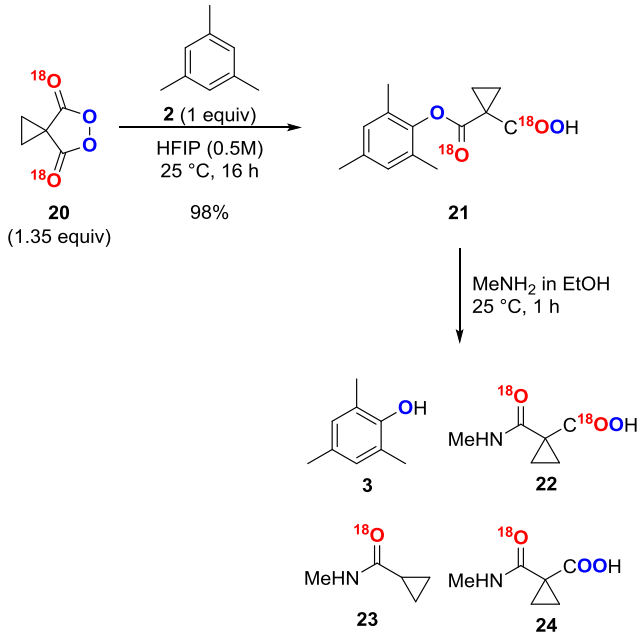


Based upon reactivity patterns an ionic process appeared plausible: the reaction required electron rich aromatics to proceed, with electron donating groups directing the addition of the peroxide to the *ortho*/*para* positons. Interestingly, aromatic substrates containing electron withdrawing groups proved unreactive within this transformation. For example, acetophenone, benzoic acid, methyl benzoate and benzonitrile all proved to be unreactive to peroxide **7** under the optimized reaction conditions (**7** (2 equiv), HFIP 0.5M, 25 °C). Conducting the reaction of mesitylene **2** and malonoyl peroxide **7** in HFIP (i) in the presence of light and air; (ii) exposed to light under an argon atmosphere; (iii) in the dark in an aerobic environment; (iv) in the dark under an inert atmosphere; all showed no significant differences in outcome with reactions giving the product **8** (90–92% yield) after 6 h. In addition, conducting the reaction at 4 °C, in the dark under an argon atmosphere gave the product (83% yield) after 24 h. Com-

bined these observations show the reaction to proceed under very mild conditions and did not rule out an ionic pathway.

Further investigations were carried out using ^{18}O isotopically labelled malonoyl peroxide **20** as a mechanistic probe, which was prepared from cyclopropane-1,1-dicarboxylic acid (see Supporting Information for full details). Treatment of mesitylene **2** with 1 equivalent of malonoyl peroxide **20** (25 °C, 16 h) gave the ester **21** with two labels incorporated in the structure (Scheme 4). Mass spectrometric analysis was consistent with incorporation of one label in the carboxylic acid terminus of the molecule, and a second label in the carbonyl oxygen atom of the ester. No labelled oxygen was observed in the newly formed carbon—oxygen bond. To corroborate this finding, a sample of **21** was treated with methylamine and the crude reaction mixture analyzed by GCMS. The observed products were 2,4,6-trimethylphenol **3**, amides **22** and **24** containing either one or two ^{18}O labels, and amide **23** resulting from decarboxylation. These findings show that no scrambling of the ^{18}O label from the peroxide **20** is observed during the course of reaction and are consistent with addition of an arene nucleophile to the weak O—O peroxide bond.

Scheme 4. Reaction of mesitylene with isotopically labelled peroxide **20**.



It was possible that reversible formation of the labelled diradical **25** could proceed without scrambling, if the rate of peroxide bond formation is quicker than bond rotation (Figure 2).[13] This would mean that **26** and **27** would not be present in solution. However, the observed selectivity in C—O bond formation would require addition of the diradical **25** to the aromatic ring to occur specifically through the labelled oxygen atom to achieve the results observed. It is not clear how this selectivity would occur within a reverse-rebound process.

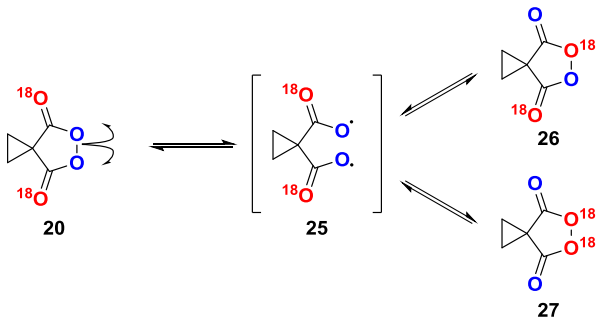


Figure 2. Potential scrambling of labels on formation of diradical.

The data assembled at this stage was consistent with an ionic interaction between the aromatic substrate and the peroxide **7**. To gain further evidence for the formation of a carbocation intermediate, a Hammett analysis was conducted on the arene oxidation. Mono substituted mesitylene derivatives were reacted with one equivalent of malonoyl peroxide **7** (Figure 3), monitoring peroxide consumption against an internal standard by ^{1}H NMR spectroscopy. Determination of the initial rates provided a linear Hammett plot based on literature σ_{meta} values.[14]

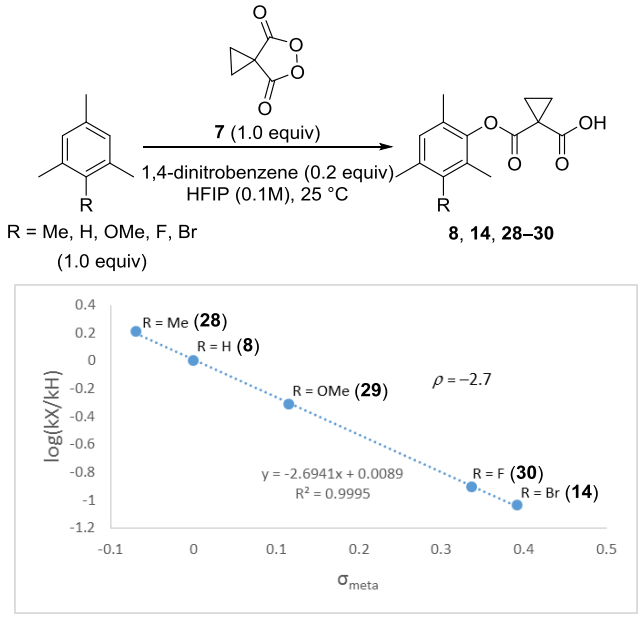


Figure 3. Hammett analysis of arene oxidation with peroxide **7**.

The Hammett plot (Figure 2) showed an excellent linear relationship for both electron withdrawing and donating substituents in the *meta*-position indicating that the same mechanism is in operation with each substrate examined. The gradient of the line, ρ, gave a moderate negative value of -2.7 indicating a considerable build-up of positive charge during the transition state of the reaction, consistent with an aryl carbocation intermediate (e.g. **19**). As expected, reactions of substrates with a *meta*-electron donating substituent (e.g. **28**) proceeded at a significantly faster rate than those containing a *meta*-electron-withdrawing group (e.g. **14** and **30**).

To probe further the possibility of the reaction proceeding through the diradical intermediate **17** we examined the homolytic bond cleavage of peroxide **7** through DFT calculations ((U)B3LYP/6-31+G(d)). Of importance was the use of trifluoroethanol as the solvent in a CPCM, providing a more accurate reflection of the reaction medium when compared to

the previous approaches to modelling this class of transformation.[2] A transition state **TS1** (29.7 kcalmol^{-1}) to form the diradical species **17** (24.8 kcalmol^{-1}) from peroxide **7** was found (Figure 4), a particularly high barrier for a reaction that proceeds readily at 4 °C.

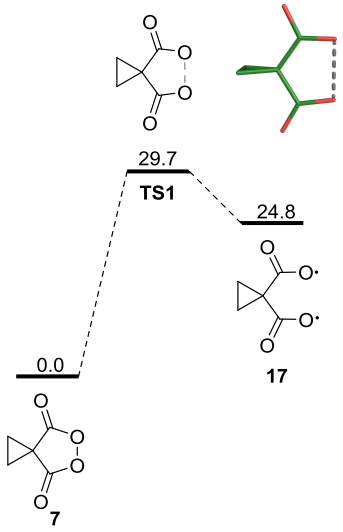


Figure 4. Peroxide homolytic cleavage (kcal mol^{-1}).

The potential of **17** being present within the reaction mixture was also examined using electron paramagnetic resonance (EPR) spectroscopy experiments using 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) **31**, a spin trap used in EPR spectroscopy for the detection of oxygen based radicals.[15] DMPO was inert to the peroxide **7** in HFIP, as shown by control experiments. Mixtures of mesitylene **2** and malonoyl peroxide **7** in both the presence and absence of DMPO were analyzed by EPR spectroscopy. In each of these experiments no radicals were detected providing further important evidence in support of an ionic pathway.

In summary, reaction of an arene with malonoyl peroxide **7** at room temperature in the presence of a hydrogen bond donor leads to the corresponding functionalized aromatic. Experimental findings supported by isotopic labeling, Hammett analysis, EPR studies and reactivity profile studies support an ionic reaction pathway. The importance of the phenol functional group in imparting unique structural, physical and electronic properties within molecules suggest this simple, effective and high yielding method for the oxidation of aromatics will provide a useful route for the late stage aromatic functionalization. Given the specific advantages of malonoyl peroxide **7** over phthaloyl peroxide **1**, it is expected that this methodology will be of great use in the introduction of the phenol functionality.

ASSOCIATED CONTENT

Supporting Information

Analytical data, experimental procedures and NMR spectra for all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

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Supporting Information

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Contents

Safety Warning!

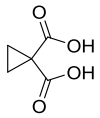
Peroxides are particularly dangerous. These procedures should be carried out by knowledgeable laboratory workers. DSC data for malonoyl peroxide **1** is given in Tomkinson et al., *J. Am. Chem. Soc.* **2010**, *132*, 14409 (page S89, Supporting Information) and shows an onset temperature of 114.5 °C.

General Experimental Details

Commercially available solvents and reagents were used without further purification or drying and all reactions performed under an air atmosphere unless otherwise stated. Flash chromatography was carried out using Merck Kieselgel 60 H silica. Analytical thin layer chromatography was carried out using aluminum-backed plates coated with Merck Kieselgel 60 GF254 that were visualized under UV light (at 254 nm) or stained using $KMnO_4$ or *p*-anisaldehyde. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III or a Bruker Avance spectrometer, operating at 400 MHz (^{1}H) and 101 MHz (^{13}C), respectively, or Bruker Avance DRX spectrometer, operating at 500 MHz (^{1}H) and 125 MHz (^{13}C). Chemical shifts were reported in parts per million (ppm) in the scale relative to $CHCl_3$, 7.26 ppm for ^{1}H NMR and 77.16 for ^{13}C NMR; DMSO-d_6, 2.50 ppm for ^{1}H NMR and 39.52 for ^{13}C NMR; acetone-d_6, 2.05 for ^{1}H NMR and 206.26 for ^{13}C NMR. Multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; hept, heptet; m, multiplet; br, broad. Coupling constants are measured in Hertz (Hz). Low-resolution mass spectra (LRMS) were recorded on an Agilent 6130 single quadrupole with APCI/ESI dual source, on a ThermoQuest Finnigan LCQ DUO electrospray, or on an Agilent 7890A GC system, equipped with a 30 m DB5MS column connected to a 5975C inert XL CI MSD with Triple-Axis Detector. High-resolution mass spectra (HRMS) were obtained courtesy of the EPSRC National Mass Spectrometry Facility at Swansea University, UK. Infrared spectra were recorded on a Shimadzu IRAffinity-1 equipped with ATR (Attenuated Total Reflectance) and were reported in cm^{-1}. Melting points were obtained on a Stuart SMP11 device. *In vacuo* refers to evaporation under reduced pressure using a rotary evaporator connected to a diaphragm pump, followed by the removal of trace volatiles using a high vacuum (oil) pump.

Experimental Procedures and Analytical Data

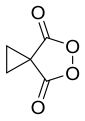
Malonoyl peroxide 7 synthesis



S1

To 500 mL 50% aq. NaOH, benzyltriethylammonium chloride (56.5 g, 248 mmol, 1.0 equiv) was added. The resulting suspension was vigorously stirred using a mechanical stirrer and a mixture of diethyl malonate (37.5 mL, 248 mmol, 1.0 equiv) and 1,2-dibromoethane (31.9 mL, 334 mmol, 1.35 equiv) was added. The reaction mixture was stirred for 2 h at room temperature and then the contents of the flask were transferred to a 2 L Erlenmeyer flask with water (3 × 50 mL). The resulting mixture was cooled down to 15 °C in an ice bath after which it was acidified with 500 mL HCl (37%, (12 M)) over 1.5 h, keeping the temperature below 25 °C. The aqueous layer was extracted with Et_2O (3 × 300 mL). All ether layers were combined and washed with 500 mL brine, and then dried ($MgSO_4$). The solvent was removed under vacuum and the resulting white-yellow solids were triturated with petroleum ether to afford the title compound **S1** as white solids (24.5 g, 192 mmol, 78%).[1]

m.p. 133 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (s, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.8, 27.3, 16.2; LRMS (APCI/ESI) *m/z* 129.1 $[M–H]^-$; IR (ATR)/cm^{-1} 2988, 2820, 1705.



7

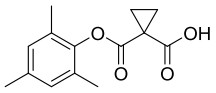
Dicarboxylic acid **S1** (4.0 g, 30.7 mmol, 1.0 equiv) was weighed into a 100 mL round bottom flask equipped with a stir bar and wrapped in parafilm. The flask was immersed into a water bath and methanesulfonic acid (31.0 mL, (1.0 M)) was added. Urea hydrogen peroxide (8.7 g, 93 mmol, 3.0 equiv) was added in three portions over one minute and the flask was loosely capped and allowed to stir over 18–20 h behind a blast shield. Afterward, the reaction was diluted with EtOAc (40 mL) and ice (40 mL) and stirred for 10 min. The layers were separated and the aqueous layer was extracted again with EtOAc (2 × 40 mL). The organic layers were combined and washed with a saturated solution of $NaHCO_3$ (3 × 40 mL), brine (40 mL) and dried ($MgSO_4$). The solvent was then removed to afford malonoyl peroxide **7** as white solids (3.0-3.2 g, 23-25 mmol, 76-81%).

m.p. 77–78 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 23.8, 19.9; IR (ATR)/cm^{-1}: 3121, 1829, 1788.

General procedure for the oxidation of arenes (General Procedure 1)

Malonoyl peroxide **7** (77 mg, 0.60 mmol) was weighed directly into the reaction vial. Then, 1,1,1,3,3,3-hexafluoroisopropanol (0.6 mL) was added, followed by the addition of the arene (0.30 mmol). The vial was sealed with a screw cap and placed in a heating block set to 25 °C unless noted otherwise and the reaction was allowed to stir for the specified time. Upon completion, the mixture was diluted with EtOAc (20 mL) and stirred with a saturated solution of $Na_2S_2O_5$ in water (20 mL) for 2 h. The layers were then separated and the aqueous solution was extracted with EtOAc (2 × 20 mL). The organic extracts were combined and washed with brine (20 mL) and dried ($MgSO_4$). The solution was concentrated and, if needed, the crude was chromatographed on silica gel (EtOAc) to afford the target compound.

Mesitylene ester 8



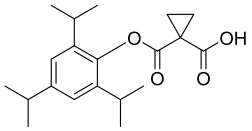
8

Ester **8** was prepared according to General Procedure 1 using mesitylene **2** (42 µL, 0.30 mmol). The title compound was isolated after work-up as a white solid (74 mg, 0.30 mmol, 98%).

Reaction time: 4.5 h.

m.p. 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (s, br, 1H), 6.89 (s, 2H), 2.28 (s, 3H), 2.11–2.04 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 170.5, 144.8, 136.5, 129.7, 129.3, 25.4, 22.5, 20.8, 16.2; LRMS (ESI) *m/z* 249.1 $[M+H]^+$; HRMS (FTMS-NSI) calculated for $C_{14}H_{17}O_4$ $[M+H]^+$ 249.1121, found 249.1124; IR (ATR)/cm^{-1} 3017, 2922, 1744, 1686.

1,3,5-Triisopropylbenzene ester 9



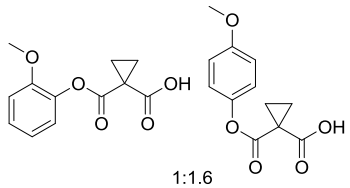
9

Ester **9** was prepared according to General Procedure 1 using 1,3,5-triisopropylbenzene **S2** (73 µL, 0.3 mmol). The title compound was isolated after work-up as a yellow solid (99 mg, 0.3 mmol, 98%).

Reaction time: 2 h.

m.p. 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (s, br, 1H), 7.01 (s, 2H), 2.90 (hept, *J* = 6.8 Hz, 1H), 2.69 (hept, *J* = 6.8 Hz, 2H), 2.07 (s, 4H), 1.25 (d, *J* = 6.8 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 6H), 1.18 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 170.5, 148.0, 142.4, 139.5, 122.3, 34.3, 27.9, 25.3, 24.2, 24.1, 22.9, 22.6; LRMS (ESI) *m/z* 333.2 $[M+H]^+$; HRMS (FTMS-NSI) calculated for $C_{20}H_{29}O_4$ $[M+H]^+$ 333.2060, found 333.2063; IR (ATR)/cm^{-1} 2961, 1746, 1688.

Anisole esters 10 and 10'



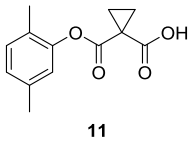
Esters **10** and **10'** were prepared according to General Procedure 1 using anisole **S3** (107 µL, 1.0 mmol). at 50 °C. A 1:1.6 mixture of the title compounds was obtained after work-up as a yellow oil (138 mg, 0.60 mmol, 63%).

Reaction time: 72 h.

Temperature: 50 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.17 (br, s, 2H), 7.28–7.22 (m, 1H), 7.05–6.88 (m, 7H), 3.83 (s, 3H), 3.80 (s, 3H), 2.14–2.07 (m, 2H), 2.04–1.97 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 174.3, 170.7, 170.6, 148.2, 147.3, 136.8, 131.6, 130.3, 129.7, 127.4, 127.1, 121.4, 120.8, 25.6, 22.7, 22.6, 21.0, 16.2; LRMS (ESI) *m/z* 219.1 $[M–H]^–$; IR (ATR)/$cm^{–1}$: 3119, 2839, 1757, 1694.

***p*-Xylene ester 11**



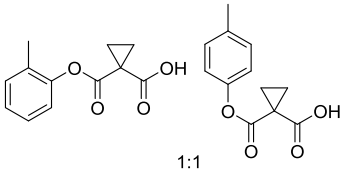
11

Ester **11** was prepared according to General Procedure 1 using *p*-xylene **S4** (37 µL, 0.30 mmol). The title compound was isolated after work-up as a colorless oil (68 mg, 0.29 mmol, 97%).

Reaction time: 96 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, br, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.80 (s, 1H), 2.33 (s, 3H), 2.11 (s, 3H), 2.05–2.00 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 170.6, 148.0, 137.5, 131.3, 127.9, 126.4, 121.8, 25.6, 22.5, 20.9, 15.7; LRMS (ESI) *m/z* 233.1 $[M–H]^–$; HRMS (FTMS-CI) calculated for $C_{13}H_{13}O_4$ $[M–H]^–$ 233.0819, found 233.0821; IR (ATR)/$cm^{–1}$ 2955, 2924, 1749, 1694.

Toluene esters 12 and 12'



1:1
12:**12'**

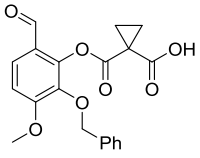
Esters **12** and **12'** were prepared according to General Procedure 1 using toluene **S5** (107 µL, 1.0 mmol), malonoyl peroxide **7** (256 mg, 2.0 mmol) in HFIP (2.0 mL). A 1:1 mixture of the title compounds was obtained after work-up as a colorless oil (138 mg, 0.63 mmol, 63%).

Reaction time: 72 h.

Temperature: 50 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.67 (s, br, 2H), 7.29–7.18 (m, 5H), 7.01–6.97 (m, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 2.36 (s, 3H), 2.17 (s, 3H), 2.07–1.98 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 174.3, 170.7, 170.6, 148.2, 147.3, 136.8, 131.6, 130.3, 129.7, 127.4, 127.1, 121.4, 120.8, 25.6, 22.7, 22.6, 21.0, 16.2; LRMS (ESI) *m/z* 219.1 $[M–H]^-$; IR (ATR)/cm^{-1} 3030, 2096, 1748, 1694.

3-Benzyloxy-4-methoxybenzaldehyde ester 13



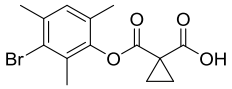
13

Ester **13** was prepared according to General Procedure 1 using 3-benzyloxy-4-methoxybenzaldehyde **S6** (73 mg, 0.30 mmol). After work-up, the crude reaction mixture was passed through a plug of silica gel using EtOAc as eluent. Evaporation of the solvent provided ester **13** as a colorless oil (43 mg, 0.12 mmol, 40%).

Reaction time: 24 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.83 (s, br, 1H), 9.80 (s, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.41–7.31 (m, 5H), 7.02 (d, *J* = 8.7 Hz, 1H), 5.04 (s, 2H), 4.02 (s, 3H), 2.02–1.77 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.1, 174.0, 170.1, 158.8, 142.8, 140.6, 136.7, 129.7, 128.8, 128.7, 128.4, 122.3, 110.1, 75.8, 56.6, 25.8, 23.0; LRMS (ESI) *m/z* 393.1 $[M+Na]^+$; HRMS (FTMS-NSI) calculated for $C_{20}H_{17}O_7$ $[M–H]^-$ 369.0980, found 369.0976; IR (ATR)/cm^{-1} 2925, 1759, 1690, 1597.

Bromomesitylene ester 14



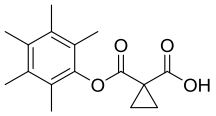
14

Ester **14** was prepared according to General Procedure 1 using 2-bromomesitylene **S7** (55 µL, 0.36 mmol). After work-up, the title compound **14** was isolated as a white solid (107 mg, 0.33 mmol, 91%).

Reaction time: 5 days.

m.p. 157–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.78 (s, br, 1H), 7.01 (s, 1H), 2.38 (s, 3H), 2.20 (s, 3H), 2.09–2.03 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 170.3, 144.9, 137.1, 130.3, 129.7, 128.4, 125.4, 25.5, 23.7, 22.5, 17.3, 16.2; LRMS (ESI) *m/z* 326.9 [M(^{79}Br) + H]$^{+}$, 329.0 [M(^{81}Br) + H]$^{+}$; HRMS (FTMS-NSI): calculated for $C_{14}H_{16}{}^{79}BrO_4$ 327.0226 [M+H]$^{+}$, and for $C_{14}H_{16}{}^{81}BrO_4$ 329.0206 [M+H]$^{+}$, found 327.0225 [M(^{79}Br)+H]$^{+}$, 329.0203 [M(^{81}Br)+H]$^{+}$; IR (ATR)/cm^{-1} 2900, 1743, 1684, 1130.

Pentamethylbenzene ester 15



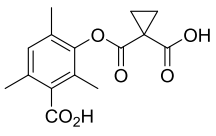
15

Ester **15** was prepared according to General Procedure 1 using pentamethylbenzene **S8** (100 mg, 0.67 mmol) and malonoyl peroxide **7** (95 mg, 0.74 mmol) in HFIP (1.34 mL). The title compound **15** was isolated as a dark yellow solid (128 mg, 0.46 mmol, 70%) after work-up.

Reaction time: 24 h.

m.p. 144–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.95 (s, br, 1H), 2.22 (s, 9H), 2.15–2.05 (m, 4H), 2.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 170.6, 144.8, 134.0, 133.8, 124.8, 25.4, 22.4, 16.7, 16.5, 13.4; HRMS (FTMS-NSI) calculated for $C_{16}H_{21}O_4$ [M+H]$^{+}$ 277.1434, found 277.1433; IR (ATR)/cm^{-1}: 3022, 2930, 1732, 1705, 1144.

2,4,6-Trimethyl benzoic acid ester 16



16

Ester **16** was prepared according to General Procedure 1 using 2,4,6-trimethylbenzoic acid **S9** (49 mg, 0.30 mmol). After the standard work-up procedure, the crude was re-dissolved in EtOAc

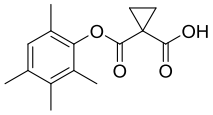
(20 mL), and extracted with a saturated solution of $NaHCO_3$ (aq., 3 × 20 mL). The resulting aqueous solution was slowly acidified with HCl (1.0 M) until cloudy (pH 1), extracted with EtOAc (3 × 20 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford a white oily solid which was triturated with petroleum ether to afford the title compound **16** as a white solid (75 mg, 0.26 mmol, 86%).

Reaction time: 42 h.

Temperature: 50 °C.

m.p. 179–180 °C (dec); ^{1}H NMR (400 MHz, acetone-d_6) δ 9.63 (s, br, 2H), 7.01 (s, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 1.72–1.61 (m, 4H); ^{13}C NMR (101 MHz, acetone-d_6) δ 170.4, 170.0, 169.4, 146.6, 134.8, 132.8, 132.0, 130.8, 127.7, 28.0, 19.3, 17.6, 16.2, 13.6; LRMS (ESI) *m/z* 290.9 $[M–H]^–$; HRMS (FTMS-NSI) calculated for $C_{15}H_{15}O_6$ $[M–H]^–$ 291.0874, found 291.0872; IR (ATR)/cm$^{–1}$ 2967, 1765, 1730, 1684.

Isodurene ester 28



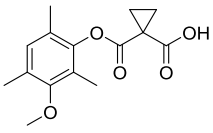
28

Ester **28** was prepared according to General Procedure 1 using isodurene **S10** (15 µL, 0.10 mmol). The title compound was isolated after work-up as a colorless oil (26 mg, 0.10 mmol, 98%).

Reaction time: 30 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 2.24 (s, 3H), 2.16 (s, 3H), 2.11–2.04 (m, 7H), 2.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 170.5, 145.0, 135.2, 134.6, 129.9, 127.8, 126.0, 25.3, 22.8, 20.5, 16.1, 15.8, 13.2; LRMS (ESI) *m/z* 261 $[M–H]^–$; HRMS (FTMS-NSI) calculated for $C_{15}H_{19}O_4$ $[M+H]^+$ 263.1278, found 263.1278; IR (ATR)/cm$^{–1}$ 2924, 2868, 1748, 1694.

2,4,6-Trimethylanisole ester 29



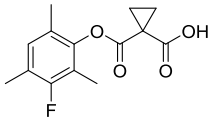
29

Ester **29** was prepared according to General Procedure 1 using 2,4,6-trimethylanisole **S11** (47 µL, 0.30 mmol). The crude product obtained after work-up was passed through an $–NH_2$ cartridge using CH_2Cl_2 (20 mL) to remove all impurities. Then the cartridge was flushed with a saturated solution of HCl in Et_2O (20 mL); the resulting ether solution was removed *in vacuo* to afford the title compound **29** as a colorless oil (81 mg, 0.29 mmol, 98%).

Reaction time: 6 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, br, 1H), 6.89 (s, 1H), 3.69 (s, 3H), 2.24 (s, 3H), 2.07–1.99 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 170.9, 155.6, 145.4, 130.2, 129.5, 124.9, 123.2, 60.2, 25.6, 22.2, 15.9, 15.8, 9.9; LRMS (ESI) *m/z* 279.1 $[M+H]^+$; HRMS (FTMS-APCI) calculated for $C_{15}H_{19}O_5$ $[M+H]^+$ 279.1227, found 279.1225; IR (ATR)/cm^{-1} 3015, 2932, 1747, 1697.

2-Fluoromesitylene ester 30



30

Ester **30** was prepared according to General Procedure 1 using 2-fluoromesitylene **S12** (43 µL, 0.30 mmol). After the standard work-up procedure, the crude was triturated with petroleum ether to afford the title compound **30** as a white solid (77 mg, 0.29 mmol, 96%).

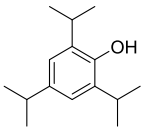
Reaction time: 8 h.

m.p. 105–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 6.89 (d, $^{4}J_{HF}$ = 8.2 Hz, 1H), 2.22 (s, 3H), 2.09-2.00 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ, 173.8, 170.4, 158.0 (d, $^{1}J_{CF}$ = 243.4 Hz), 145.0 (d, $^{3}J_{CF}$ = 6.7 Hz), 130.0 (d, $^{3}J_{CF}$ = 6.0 Hz), 124.5 (d, $^{4}J_{CF}$ = 4.0 Hz), 123.2 (d, $^{2}J_{CF}$ = 18.3 Hz), 117.4 (d, $^{2}J_{CF}$ = 20.6 Hz), 25.5, 22.6, 15.85, 14.5 (d, $^{3}J_{CF}$ = 3.1 Hz), 8.9 (d, $^{3}J_{CF}$ = 4.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 120.90 (s, 1F); LRMS (ESI) *m/z* 264.9 $[M–H]^–$; HRMS (FTMS-NSI) calculated for $C_{14}H_{14}O_4F_1$ $[M–H]^–$ 265.0882, found 265.0877; IR (ATR)/cm^{-1} 2988, 2887, 1753, 1694.

General procedure for the aminolysis of ester intermediates (General Procedure 2)

The crude product of the arene oxidation (1.0 equiv) was dissolved in the minimum amount of EtOH. To this solution, $MeNH_2$ in EtOH (33% $MeNH_2$ w/v, 20 equiv $MeNH_2$) was added and the mixture was stirred for 1 h at 25 °C. The solvent was then removed *in vacuo* and the resulting crude was chromatographed on silica gel using the specified solvent system for each substrate.

2,4,6-Triisopropylphenol S13

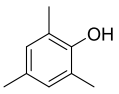


S13

2,4,6-Triisopropylphenol **S13** was prepared according to General Procedure 2 using ester **9** (67 mg, 0.20 mmol). The crude was chromatographed on silica gel (EtOAc:petroleum ether, 1:1) to afford 2,4,6-triisopropylphenol **S13** as a brown oil (41 mg, 0.19 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 2H), 4.63 (s, 1H), 3.16 (hept, *J* = 6.7 Hz, 2H), 2.86 (hept, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 12H), 1.25 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1, 140.9, 133.5, 121.5, 34.0, 27.5, 24.5, 22.9; LRMS (EI) *m/z* 220.11 [M+•]; HRMS (FTMS-APCI) calculated for $C_{15}H_{25}O_1$ $[M+H]^+$ 221.1900, found 221.1898; IR (ATR)/cm^{-1} 2959, 2928, 2868.

2,4,6-Trimethylphenol 3

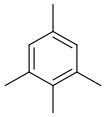


3

2,4,6-Trimethylphenol **3** was prepared according to General Procedure 2 using ester **8** (50 mg, 0.20 mmol). The crude was chromatographed on silica gel (EtOAc:petroleum ether, 1:1) to afford 2,4,6-trimethylphenol **3** as a beige solid (25 mg, 0.18 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 2H), 2.24–2.21 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 129.4, 129.3, 122.9, 20.5, 15.9; LRMS (EI) *m/z* 136.08 [M•]; IR (ATR)/cm^{-1} 3389, 2972, 2914.

Synthesis of isodurene S10



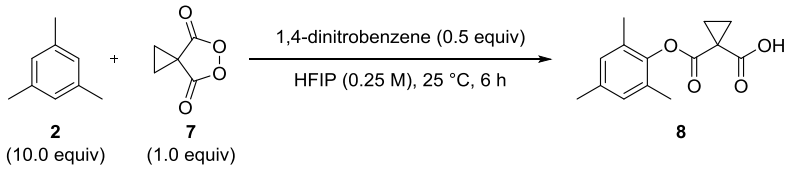
S10

To a pre-dried Schlenk flask equipped with a stirrer, under an argon atmosphere at –78 °C, 2.4 mL dry Et_2O were added *via* syringe. Then 2-bromomesitylene **S7** (1.22 mL, 8.0 mmol, 1.0 equiv) was added. A (1.52 M) solution of *t*-butyllityhium in pentane (10.5 mL, 16.0 mmol, 2.0 equiv) was slowly added to the flask over a period of 10–15 min at –78 °C. The mixture was allowed to warm up to room temperature over 1.5 h and was checked by ^{1}H NMR for consumption of 2-bromomesitylene **S7**. The white mixture was cooled down to –78 °C again and iodomethane (1.49 mL, 24.0 mmol, 3.0 equiv) was added to it dropwise over 20 min. The mixture was then stirred overnight, allowing it to warm up to room temperature. Then, CH_2Cl_2 (20 mL) and water (10 mL) were added to the mixture and the biphasic solution was stirred for 30 min at room temperature. The layers were separated and the aqueous was further extracted with CH_2Cl_2 (2 × 20 mL), after which the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resulting crude was distilled under reduced pressure (72 °C, 12 mbar) using a Vigreux column to afford the title compound **S10** as a colorless oil (541 mg, 4.0 mmol, 50%).

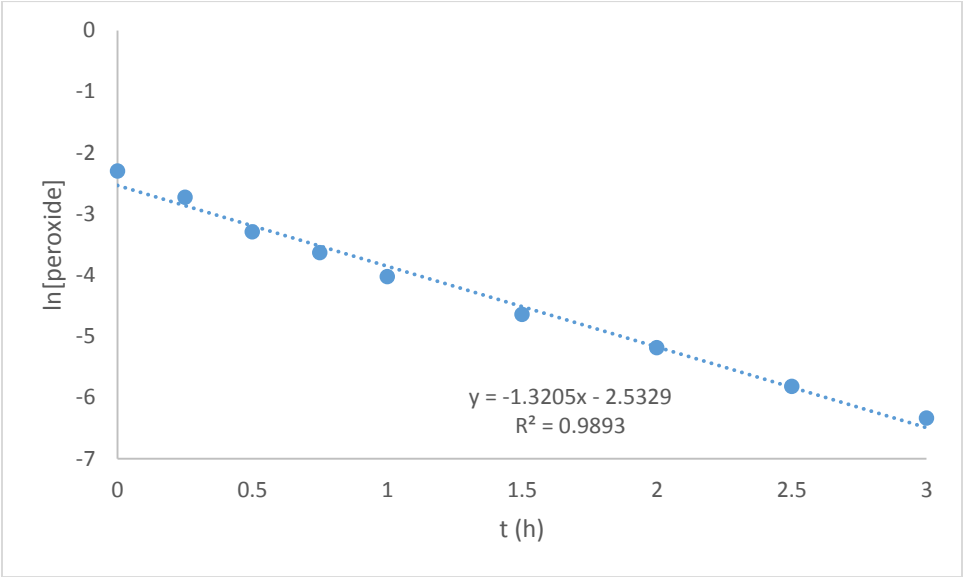
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 2H), 2.29–2.24 (m, 9H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 134.7, 132.0, 128.5, 20.9, 20.6, 15.1; LRMS (CI) *m/z* 135.1 $[M+H]^+$ HRMS (FTMS-APCI) calculated for $C_{10}H_{15}$ $[M+H]^+$ 135.1168, found 135.1168; IR (ATR)/cm^{-1} 2999, 2916, 1485.

Reaction kinetics

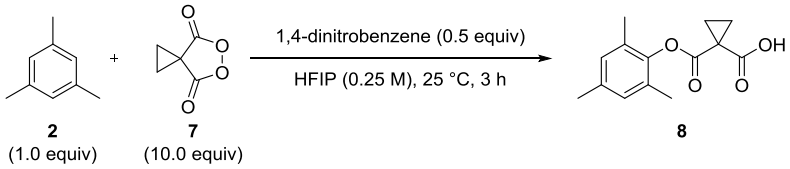
Reaction order in malonoyl peroxide 7



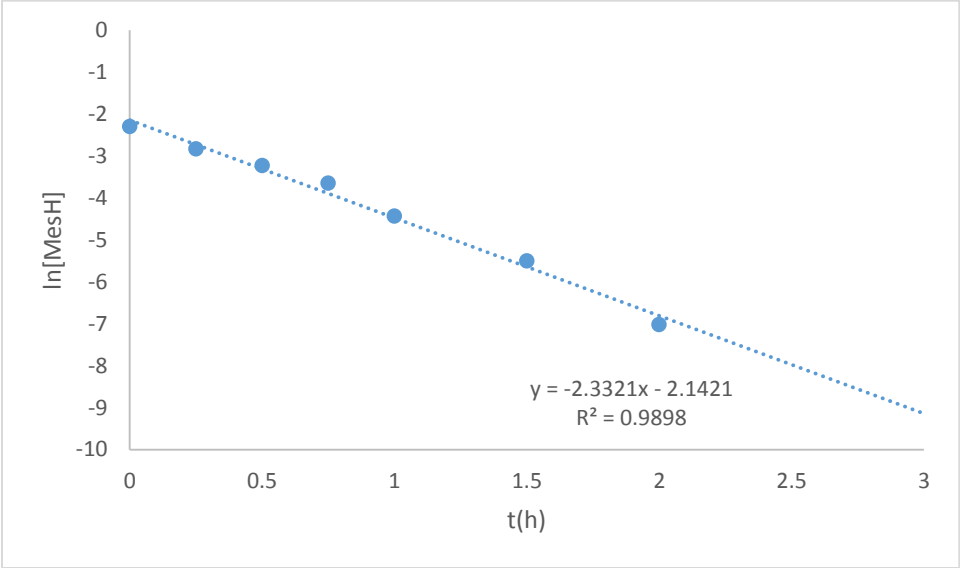
Malonoyl peroxide **7** (32 mg, 0.25 mmol, 1.0 equiv) was weighed into a 7 mL vial. Then, a standard solution of 1,4-dinitrobenzene in HFIP (0.02 M) (2.5 mL, 0.2 equiv 1,4-dinitrobenzene) was added and a 40 µL aliquot was diluted in 0.5 mL $CDCl_3$ to record the initial ratio (internal standard *vs* peroxide). Mesitylene **2** (348 µL, 2.5 mmol, 10.0 equiv) was added and the reaction was stirred at 25 °C. 40 µL aliquots were sampled at different times and were immediately diluted in $CDCl_3$ (0.5 mL); this stopped the reaction, providing identical ^{1}H NMR spectra after 3 h of standing. The results shown are an average of two runs.



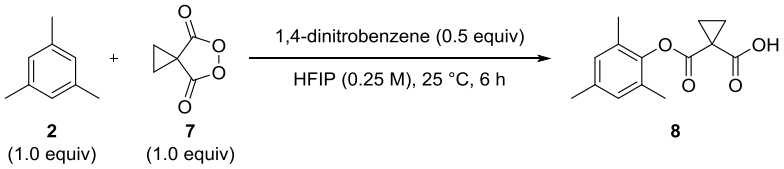
Reaction order in mesitylene 2



Malonoyl peroxide **7** (320 mg, 2.5 mmol, 10.0 equiv) was weighed into a 7 mL vial. Then, a standard solution of 1,4-dinitrobenzene in HFIP (0.02 M) (2.5 mL, 0.2 equiv 1,4-dinitrobenzene) was added. Mesitylene **2** (35 µL, 0.25 mmol, 1.0 equiv) was added and the reaction was stirred at 25 °C. 40 µL aliquots were sampled at different times and were immediately diluted in $CDCl_3$ (0.5 mL); this stopped the reaction, providing identical ^1H NMR spectra after 3 h of standing. The results shown are an average of two runs.



Overall reaction order



2 (1.0 equiv) **7** (1.0 equiv) **8**

Malonoyl peroxide **7** (32 mg, 0.25 mmol, 1.0 equiv) was weighed into a 7 mL vial. Then, a standard solution of 1,4-dinitrobenzene in HFIP (0.125 M) (1.0 mL, 0.5 equiv 1,4-dinitrobenzene) was added and a 40 µL aliquot was diluted in 0.5 mL $CDCl_3$ to record the initial ratio (internal standard *vs* peroxide). Mesitylene **2** (35 µL, 0.25 mmol, 1.0 equiv) was added and the reaction was stirred at 25 °C. 40 µL aliquots were sampled at different times and were immediately diluted in $CDCl_3$ (0.5 mL); this stopped the reaction, providing identical ^1H NMR spectra after 3 h of standing. The results are an average of two runs.

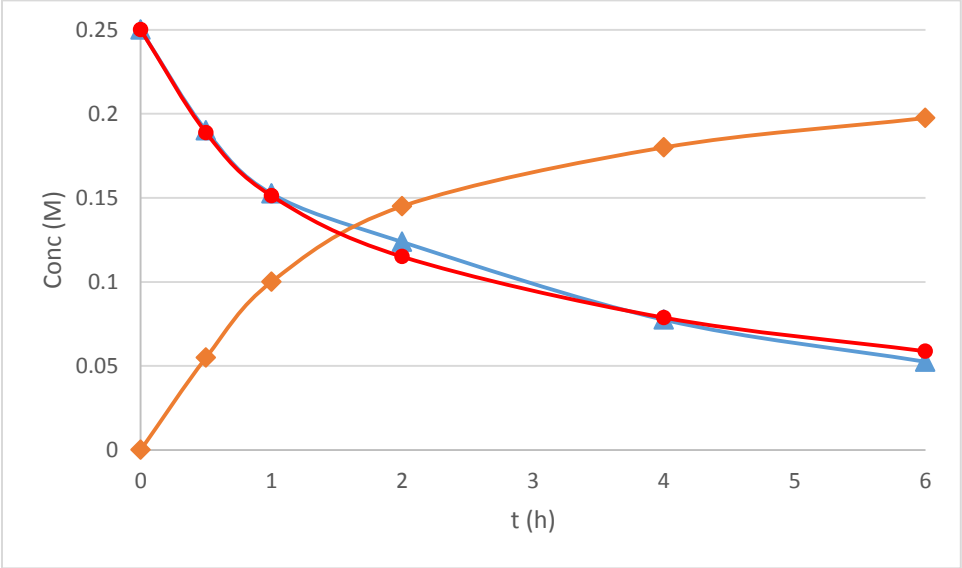
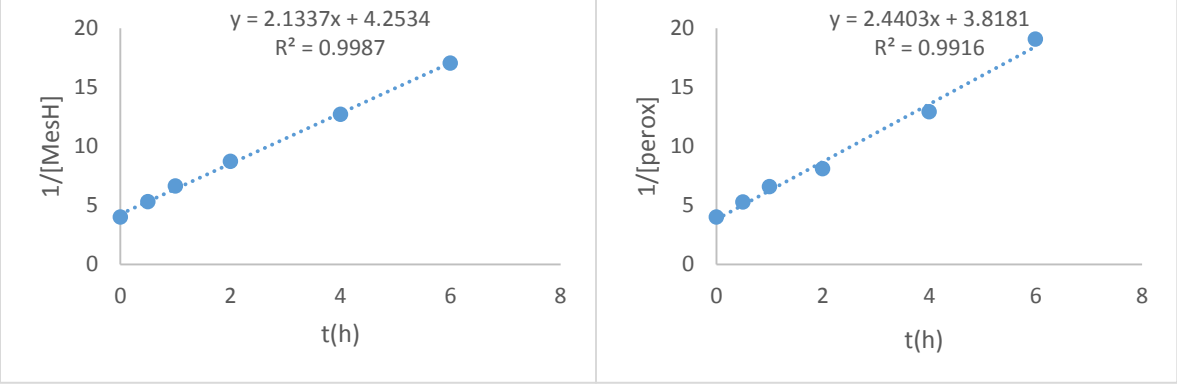
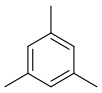


Figure 1: Reaction profile of the malonoyl peroxide **7** (▲, (0.25 M)) mediated oxidation of mesitylene **2** (●, (0.25 M)) leading to single product **8** (◆, (0.25 M)



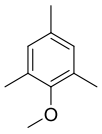
General procedure for the Hammett analysis (General Procedure 3)

To a 7 mL vial, malonoyl peroxide **7** (38 mg, 0.30 mmol, 1.0 equiv) was weighed. A standard solution of 1,4-dinitrobenzene in HFIP (0.01 M) (3.0 mL, 0.20 equiv 1,4-dinitrobenzene) was then added. A 100 µL aliquot was taken and diluted in $CDCl_3$ (0.5 mL) to record the initial ratio (internal standard *vs* peroxide). Afterward, the arene (0.30 mmol, 1.0 equiv) was added and the reaction was stirred at 25 °C. 100 µL aliquots were taken at the specified times and were immediately diluted in $CDCl_3$ (0.5 mL), providing identical ^1H NMR spectra after 3 h of standing. All reactions were performed in duplicate.



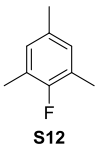
2

General Procedure 3 was applied to mesitylene **2** (42 µL, 0.30 mmol, 1.0 equiv). The consumption of peroxide was monitored against the internal standard at the following time intervals (min): 1, 3, 5, 7, 10, 15, 20, 25, 30.



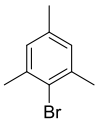
S11

General Procedure 3 was applied to 2,4,6-trimethylanisole **S11** (47 µL, 0.30 mmol, 1.0 equiv). The consumption of peroxide was monitored against the internal standard at the following time intervals (min): 1, 5, 10, 15, 30, 45, 60, 75, 90.



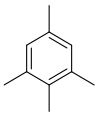
S12

General Procedure 3 was applied to 2-fluoromesitylene **S12** (43 µL, 0.30 mmol, 1.0 equiv). The consumption of peroxide was monitored against the internal standard at the following time intervals (min): 1, 5, 10, 15, 30, 45, 60, 75, 90.



S7

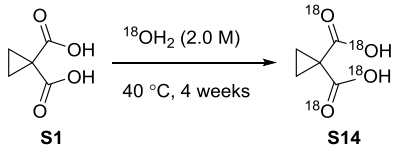
General Procedure 3 was applied to 2-bromomesitylene **S7** (45 µL, 0.30 mmol, 1.0 equiv). The consumption of peroxide was monitored against the internal standard at the following time intervals (h): 0.5, 1, 2, 3, 4.



S10

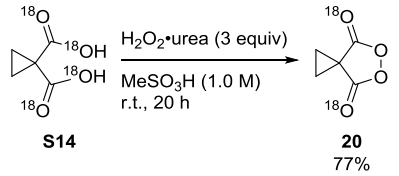
To a 7 mL vial, a standard solution of 1,4-dinitrobenzene in HFIP (0.01 M) (2.0 mL, 0.20 equiv 1,4-dinitrobenzene) was added. Isodurene **S10** (30 µL, 0.20 mmol, 1.0 equiv) was then added. A 100 µL aliquot was taken and diluted in $CDCl_3$ (0.5 mL) to record the initial ratio (internal standard *vs* isodurene). Malonoyl peroxide **7** (26 mg, 0.20 mmol, 1.0 equiv) was then added. 100 µL aliquots were retrieved at the specified time intervals and quenched in vials containing $CDCl_3$ (0.6 mL) and a saturated solution of $Na_2S_2O_5$ in water (0.8 mL). The organic layers were collected and filtered through a short plug of $MgSO_4$ directly into the NMR tube. The data was recorded at the following time intervals (min): 1, 2, 3, 4, 5, 7, 10.

^{18}O Labeling experiments



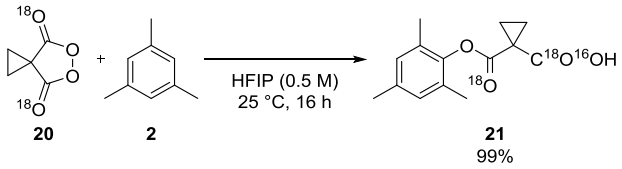
Cyclopropyl malonic acid **S1** (260 mg, 2.0 mmol, 1.0 equiv) was weighed in a 5 mL round bottom flask; the flask was sealed under argon and $^{18}OH_2$ (97% ^{18}O incorporation, 1.0 mL, 55 mmol, 26.5 equiv) was added. The mixture was stirred for 14 days at 40 °C and then the $^{18}OH_2$ was carefully removed under reduced pressure, ensuring that no air or moisture from the atmosphere contaminated the sample. The resulting solid compound was re-dissolved in $^{18}OH_2$ (97% ^{18}O incorporation, 1.0 mL, 55 mmol, 26.5 equiv) and stirred for another 14 days at 40 °C. Afterward, the $^{18}OH_2$ was removed under reduced pressure to afford the ^{18}O enriched cyclopropyl malonic acid **19** in quantitative yield (white solid). The desired compound **S14** was stored under Ar at –18 °C.

The spectroscopic data matched that of cyclopropyl malonic acid **S1**. LRMS (ESI) *m/z* 137.1 $[M–H]^-$, (85% abundance) and 134.9 $[M–H]^-$, (15% abundance).



^{18}O enriched cyclopropyl malonic acid **S14** (62 mg, 0.45 mmol, 1.0 equiv) was weighed in a 7 mL vial, then $MeSO_3H$ (0.45 mL, (1.0 M)) was added. H_2O_2•urea (127 mg, 1.4 mmol, 3.0 equiv) was then carefully added and the mixture was allowed to react for 20 h at room temperature. The mixture was then diluted in EtOAc (10 mL) and stirred with ice (10 mL) for 15 min until the ice melted. The layers were separated and the aqueous layer was further extracted with EtOAc (2 × 10 mL). The organic extracts were combined and washed with saturated $NaHCO_3$ (aq., 3 × 10 mL), brine (10 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford labeled malonoyl peroxide **20** as a white solid (46 mg, 0.35 mmol, 77%).

The spectroscopic data matches that of malonoyl peroxide **7**.

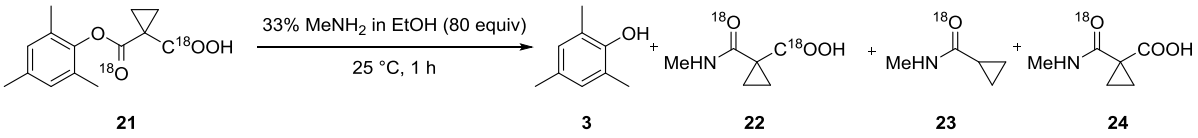


20 **2** **21** 99%

The ^{18}O labelled peroxide **20** (30 mg, 0.23 mmol, 1.35 equiv) was weighed into a 1.5 mL vial and then HFIP (0.23 mL, (0.5 M)) was added. Mesitylene **2** (23 µL, 0.17 mmol, 1.0 equiv) was added *via* syringe to the mixture. The reaction was stirred for 16 h and the mixture was diluted in EtOAc (10 mL) and stirred with saturated $Na_2S_2O_5$ (aq., 10 mL) for 2 h at room temperature. The layers were separated and the aqueous phase was further extracted with EtOAc (2 × 10 mL). The organic extracts were combined and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded doubly labelled ester **21** (45 mg, 0.17 mmol, 99%).

The ^{1}H and ^{13}C NMR spectra matched that of non-labeled ester **8**. LRMS (ESI) *m/z* 252.9, 250.9 $[M+H]^+$; fragmentation of these ions using LRMS and HRMS showed no ^{18}O attached to the aromatic ring.

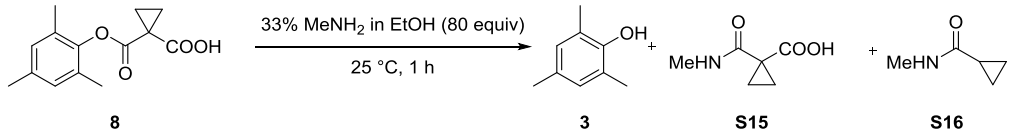
The ester bond was cleaved using $MeNH_2$ and the crude reaction mixture was analyzed using a GC Agilent 7890A GC system, equipped with a 30 m × 250 µm × 0.25 µm DB5MS column connected to a 5975C inert XL CI MSD with Triple-Axis Detector. GC program: 40 °C (4 min), then 20 °C/min to 320 °C (hold 10 min).



21 **3** **22** **23** **24**

^{18}O labeled ester **21** (10 mg, 0.040 mmol, 1.0 equiv) was weighed into a 1.5 mL vial and $MeNH_2$ in EtOH (33 wt%, 0.4 mL, 80.0 equiv) was added. The reaction was stirred for 1 h at 25 °C and then the solvent was removed under reduced pressure. The resulting crude mixture (10 mg) was analyzed by GCMS/CI, providing three signals:

1. Retention time (min): 7.918; *m/z* 102.0 $[M+H]^+$: decarboxylated amide **23** with one ^{18}O label.
2. Retention time (min): 9.348; *m/z* 137.1 $[M+H]^+$: 2,4,6-trimethylphenol **3**, no ^{18}O label.
3. Retention time (min): 10.671; *m/z* 147.9 $[M+H]^+$: amide **22** with two ^{18}O labels; *m/z* 145.9 $[M+H]^+$: amide **24** with one ^{18}O label.



8 **3** **S15** **S16**

Ester **8** (50 mg, 0.20 mmol, 1.0 equiv) was weighed into a 7 mL vial and $MeNH_2$ in EtOH (33 wt%, 2.0 mL, 80.0 equiv) was added. The reaction was stirred for 1 h at 25 °C and then the solvent was removed under reduced pressure. The resulting crude mixture (64 mg) was analyzed by GCMS/CI, providing three signals:

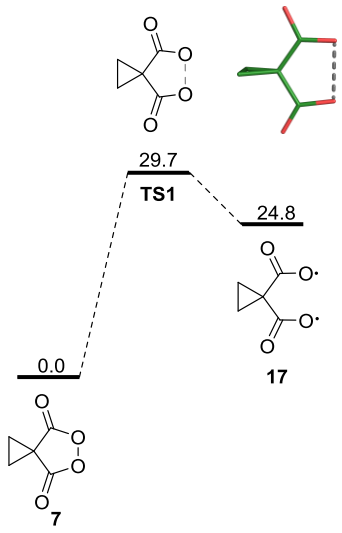
1. Retention time (min): 8.111; *m/z* 100.0 $[M+H]^+$; decarboxylated amide **S16**.
2. Retention time (min): 9.398; *m/z* 137.1 $[M+H]^+$; 2,4,6-trimethylphenol **3**.
3. Retention time (min): 10.834; *m/z* 143.9 $[M+H]^+$; amide **S15**.

The crude mixture for this reaction was chromatographed on silica gel (EtOAc:petroleum ether, 1:1) to afford 2,4,6-trimethylphenol **3** as a beige solid (15 mg, 0.11 mmol, 56%). *Note*: 2,4,6-trimethylphenol **3** is volatile (b.p. 220 °C (lit.)[2]).

DFT Calculations

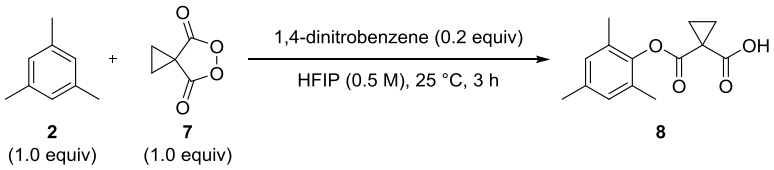
DFT calculations were performed using the Gaussian09 pack of programs.[3] Optimizations of ground states and transition states were performed at the (U)B3LYP/6-31G level of theory.[4] These optimized structures were then characterized using frequency calculations at the UB3LYP/6-31+G(d) level of theory and evaluated by a SCRF (self-consistent reaction field) with 2,2,2-trifluoroethanol CPCM solvation.[5] Frequency data was analyzed *via* a classical approach where fully converged local minima (peroxide **7** and diradical species **17**) contain no imaginary frequencies and transition states (**TS1**) have one imaginary frequency.

Below, a transition state using identical atom coordinates to our previous dihydroxylation study is shown.[6] Transition state **TS1** (29.7 kcal mol^{-1}) which forms diradical species **17** from peroxide **7** was found.

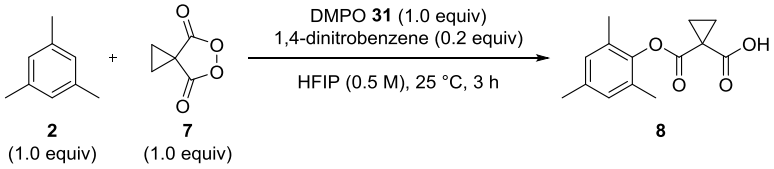


EPR experiments

Blank testing



Malonoyl peroxide **7** (26 mg, 0.20 mmol, 1.0 equiv) was weighed into a 1.5 mL vial equipped with a stir bar. A standard solution of 1,4-dinitrobenzene in HFIP (0.04 M) (0.4 mL, 0.20 equiv 1,4-dinitrobenzene) was then added and a 20 µL aliquot was diluted in $CDCl_3$ to record the initial ratio (^{1}H NMR) between the internal standard and malonoyl peroxide **7**. Mesitylene **2** (28 µL, 0.20 mmol, 1.0 equiv) was then added and the reaction was monitored by ^{1}H NMR over 3 h. The reaction showed 52% conversion after 1 h and 73% after 3 h with no byproducts/co-products.



Malonoyl peroxide **7** (26 mg, 0.20 mmol, 1.0 equiv) was weighed into a 1.5 mL vial equipped with a stir bar. A standard solution of 1,4-dinitrobenzene in HFIP (0.04 M) (0.4 mL, 0.20 equiv 1,4-dinitrobenzene) was then added and a 20 µL aliquot was diluted in $CDCl_3$ to record the initial ratio (^{1}H NMR) between the internal standard and malonoyl peroxide **7**. DMPO (23 mg, 0.20 mmol) and mesitylene **2** (28 µL, 0.20 mmol, 1.0 equiv) were then added and the reaction was monitored by ^{1}H NMR over 3 h. The reaction showed 48% conversion after 1 h and 68% after 3 h with no byproducts/co-products.

Purification of DMPO[7]

Commercially available (Fluorochem, 5 g, brown solid with a low melting point) 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO, 1.6 g) was weighed directly into a 10 mL round bottom flask which was equipped with a Vigreux column and a short-path condenser with three 10 mL round bottom flasks as fractions. The system was placed under vacuum (4.1 mbar). The oil bath was heated to 140 °C and the vapor temperature of DMPO was 88 °C at 4.1 mbar. 1.2 g of DMPO (colorless oil) were distilled in a 10 mL round bottom flask and stored under argon. The collected DMPO became a crystalline white solid after storing in the freezer (–24 °C).

Sample preparation for EPR studies

(0.5 M) Solutions of DMPO, malonoyl peroxide **7** and mesitylene **2** in 2,2,2-trifluoroethanol (TFE) were prepared under nitrogen. The EPR spectrometer was calibrated using a (0.05 M) solution of TEMPO in TFE.

Blank samples of the (0.5 M) solutions of DMPO and malonoyl peroxide **7** in TFE were first subjected to EPR spectroscopy.

0.1 mL of the (0.5 M) solution of malonoyl peroxide **7** in TFE was mixed with 0.2 mL of the (0.5 M) solution of DMPO in TFE and the resulting sample was monitored by EPR spectroscopy.

To 0.1 mL of the (0.5 M) solution of malonoyl peroxide **7** in TFE, mesitylene **2** (5.6 µL, 0.04 mmol) was added and the resulting mixture was analyzed by EPR spectroscopy. This mixture was then combined with 0.2 mL of the (0.5 M) solution of DMPO in TFE and the resulting mixture was analyzed by EPR spectroscopy.

The experiments were repeated using HFIP as a solvent and all of the experiments were performed in duplicate.

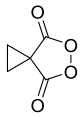
No radicals were observed by EPR spectroscopy in any of the experiments performed.

Cartesian coordinates

The number of imaginary frequencies relate to structures optimized at the (U)B3LYP/6-31+G(d) level of theory, using 2,2,2-trifluoroethanol (TFE) CPCM model.

All Gibbs Free Energies were calculated at 298.15 K.

Peroxide 7



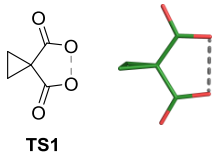
7

Gibbs Free Energy (in Hartrees), B3LYP/6-31+G(d) in TFE: –493.676511

Number of imaginary frequencies: 0

O	4.32923300	-1.05445300	0.93896000
C	3.35719900	-1.37479800	0.30400400
O	3.45848100	-1.51658800	-1.07120700
C	1.97127900	-1.67441000	0.69314600
C	1.25266500	-2.00472900	-0.54639600
O	2.14715000	-1.90930700	-1.60109500
C	1.28187900	-0.94046000	1.85535700
C	1.63731100	-2.36080300	2.02802000
O	0.11049500	-2.31772700	-0.76574700
H	1.89307000	-0.18403000	2.33666700
H	0.85407500	-3.10924200	1.96653400
H	2.50162600	-2.61600200	2.63236800
H	0.24549900	-0.67725800	1.67085100

Peroxide homolytic cleavage transition state (TS1)



TS1

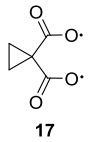
Gibbs Free Energy (in Hartrees), UB3LYP/6-31+G(d) in TFE: –493.629200

Number of imaginary frequencies: 1 (–228.63 cm^{-1})

C	-0.00201000	1.58114600	-0.74888200
C	0.00306800	1.58712400	0.73992400
H	-0.91029200	1.84513800	-1.27897600
H	0.92783100	1.79462000	-1.26346300

H	-0.90145400	1.85558800	1.27418400
H	0.93654100	1.80486900	1.24608800
C	-0.02134600	0.22753600	0.00109600
O	-1.18607200	-1.88430000	0.01210900
O	1.11709700	-1.87858500	0.00140300
C	-1.22517200	-0.61069400	0.00846500
C	1.28777700	-0.56408900	0.00004100
O	-2.39939000	-0.03033600	0.01090100
O	2.37347100	0.04569000	-0.00236200

Diradical species 17



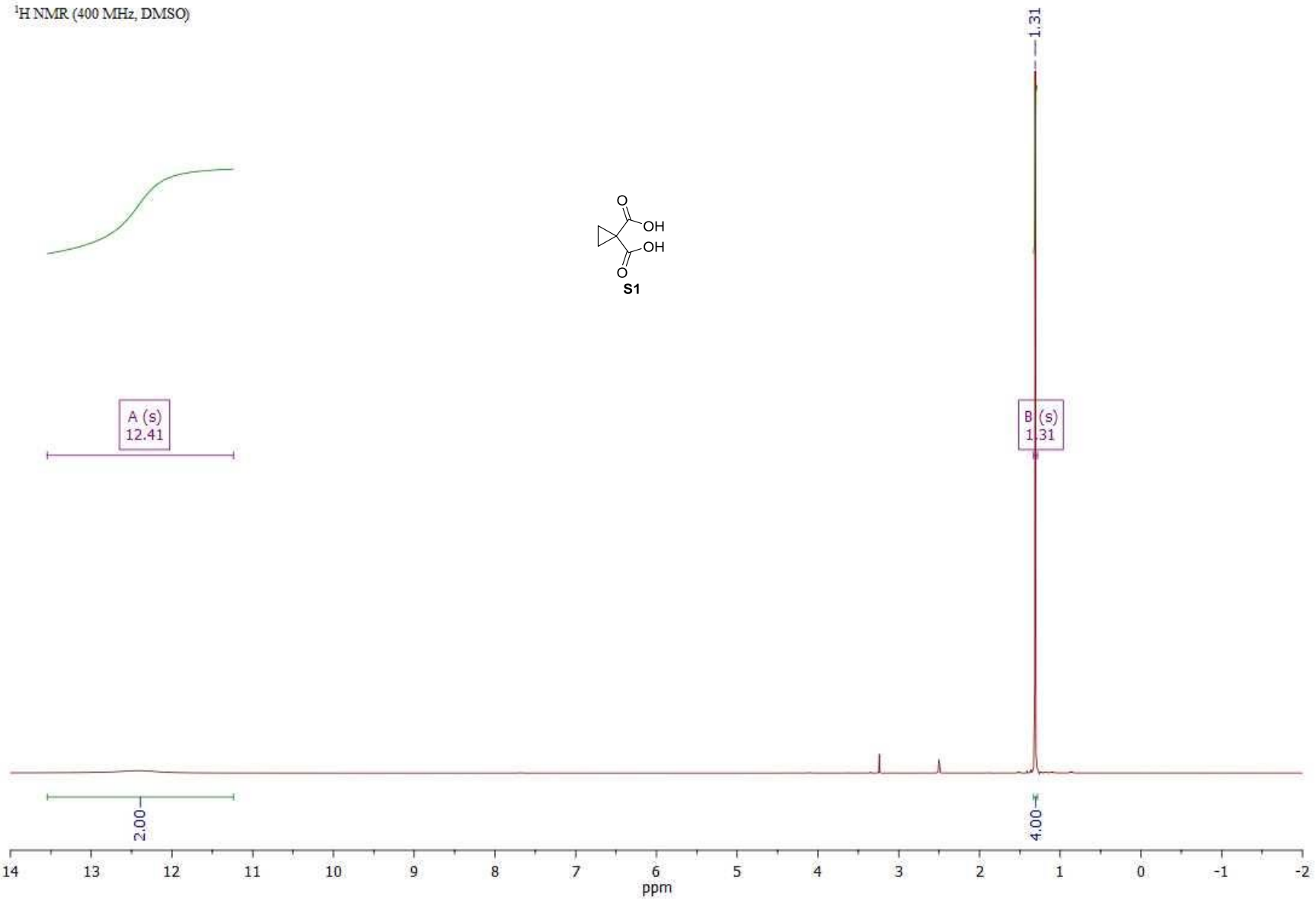
17

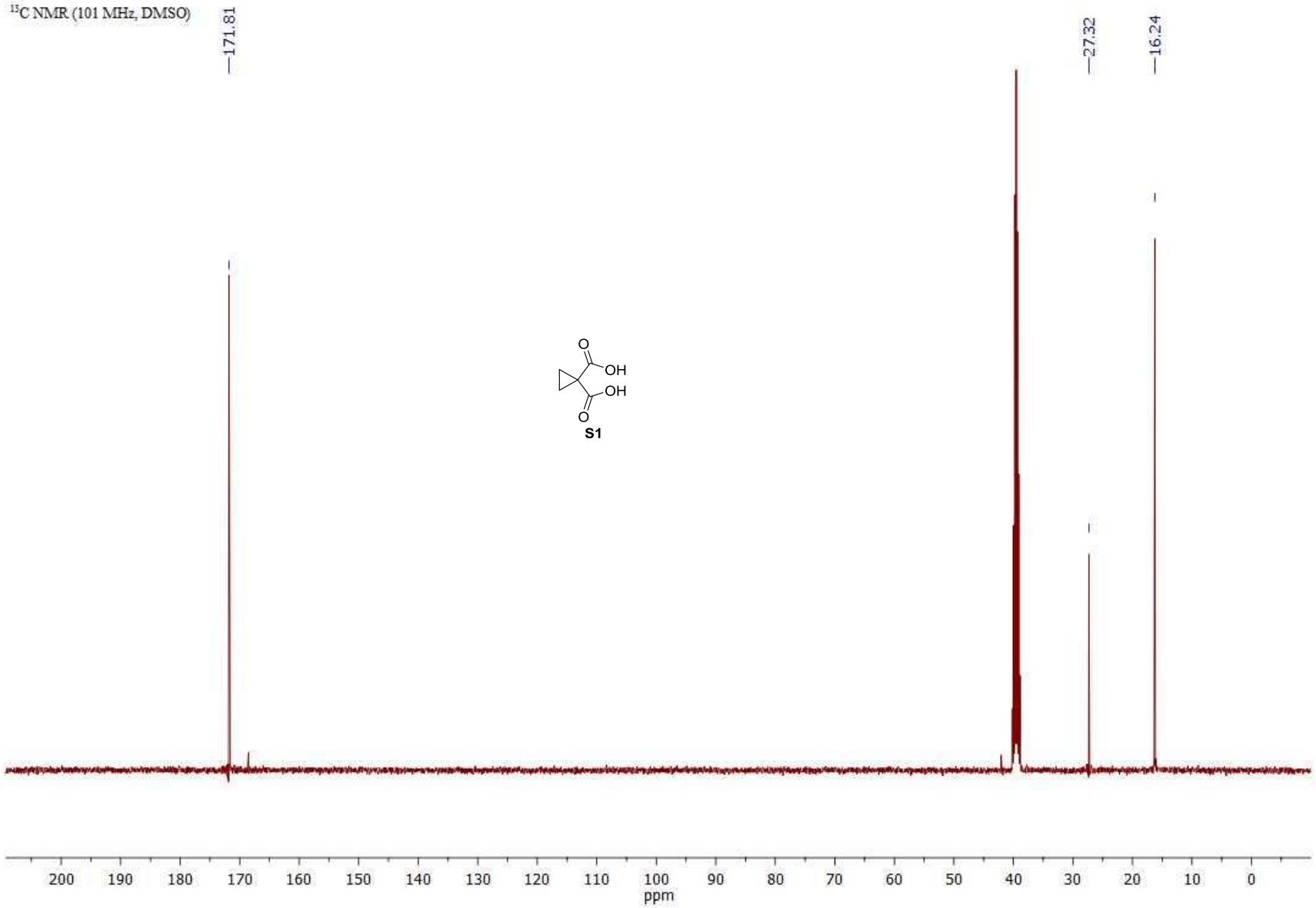
Gibbs Free Energy (in Hartrees), UB3LYP/6-31+G(d) in TFE: –493.637030

Number of imaginary frequencies: 0

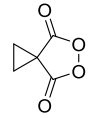
C	-4.13972000	0.11480700	1.05920300
C	-2.69503200	-0.09702000	0.87732900
H	-4.79591500	0.02556400	0.19981700
H	-4.58542600	-0.10199200	2.02421600
H	-2.31947800	-0.33856900	-0.11136500
H	-2.10877300	-0.46419600	1.71314700
C	-3.21099700	1.35656400	1.03796800
O	-3.02774600	3.43715400	-0.22507300
O	-2.78378900	3.25854900	2.50683200
C	-3.24154300	2.18866500	-0.18188500
C	-2.95229400	2.01418900	2.33488400
O	-3.48470000	1.73404800	-1.33742500
O	-2.87427400	1.39379900	3.43487500

^{1}H and ^{13}C NMR Spectra

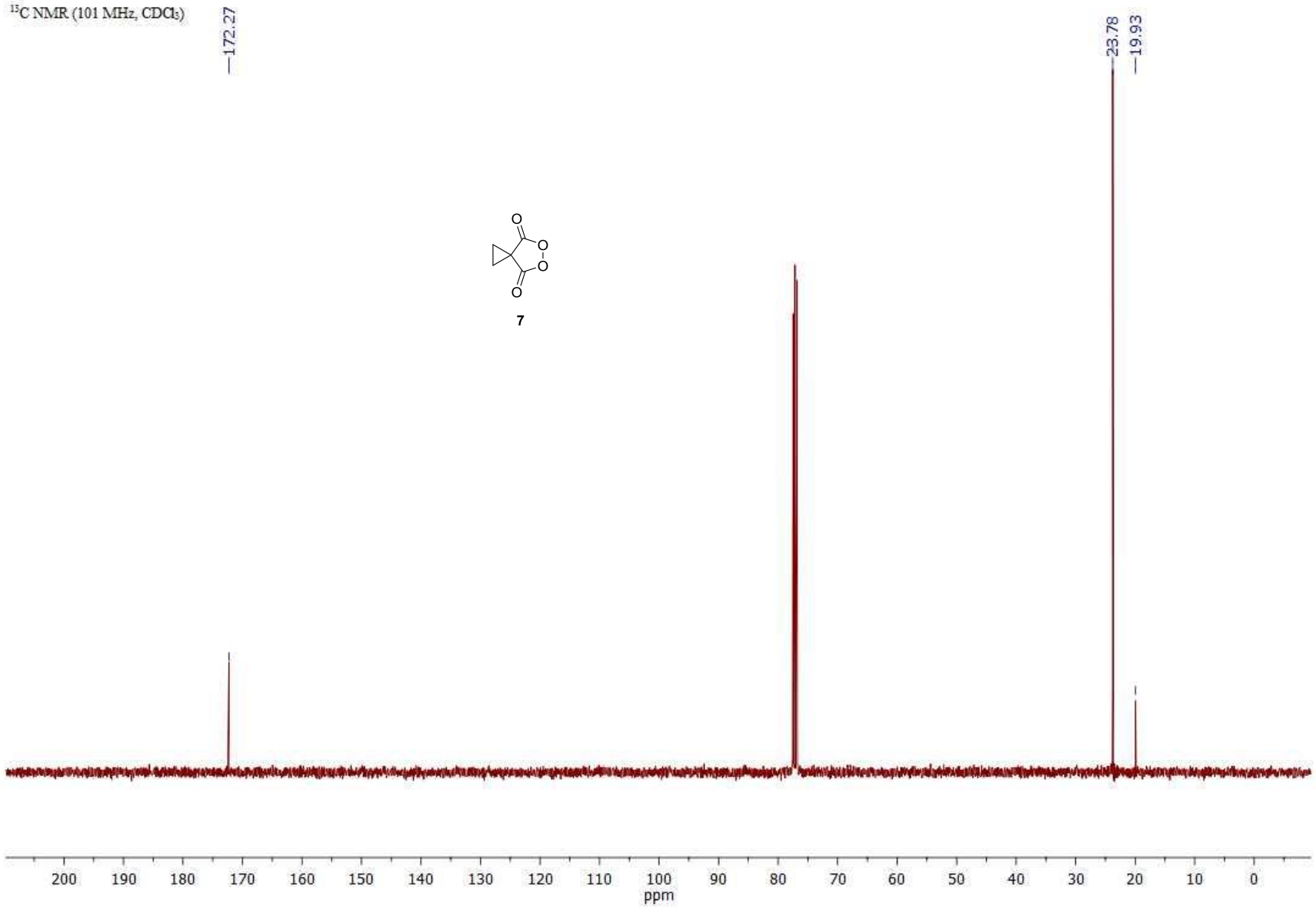

^{1}H NMR (400 MHz, DMSO)
1.31
OH
OH
O
O
S1
A (s)
12.41
B (s)
1.31
2.00
4.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

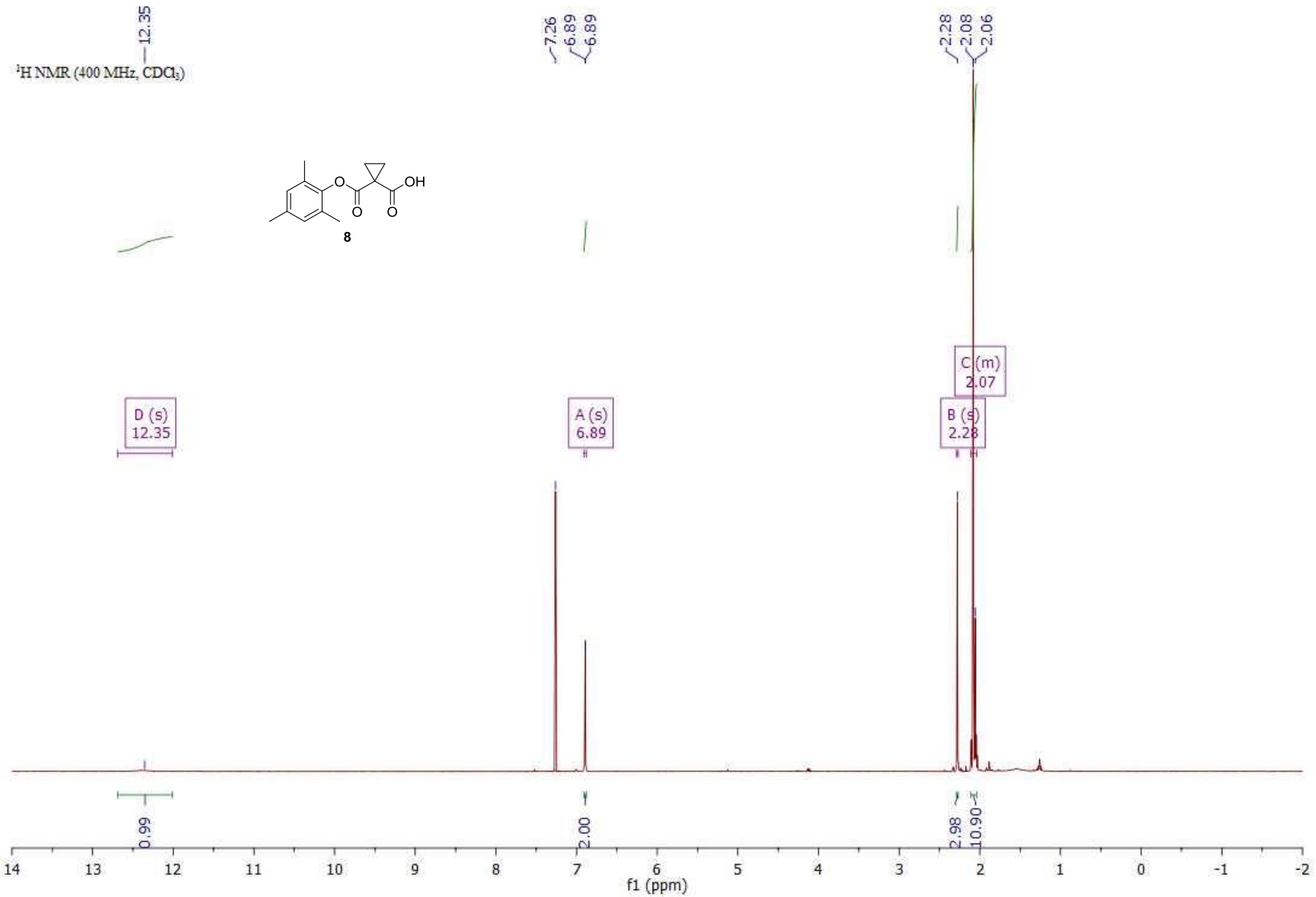

^{13}C NMR (101 MHz, DMSO)
171.81
27.32
16.24
OH
OH
S1
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

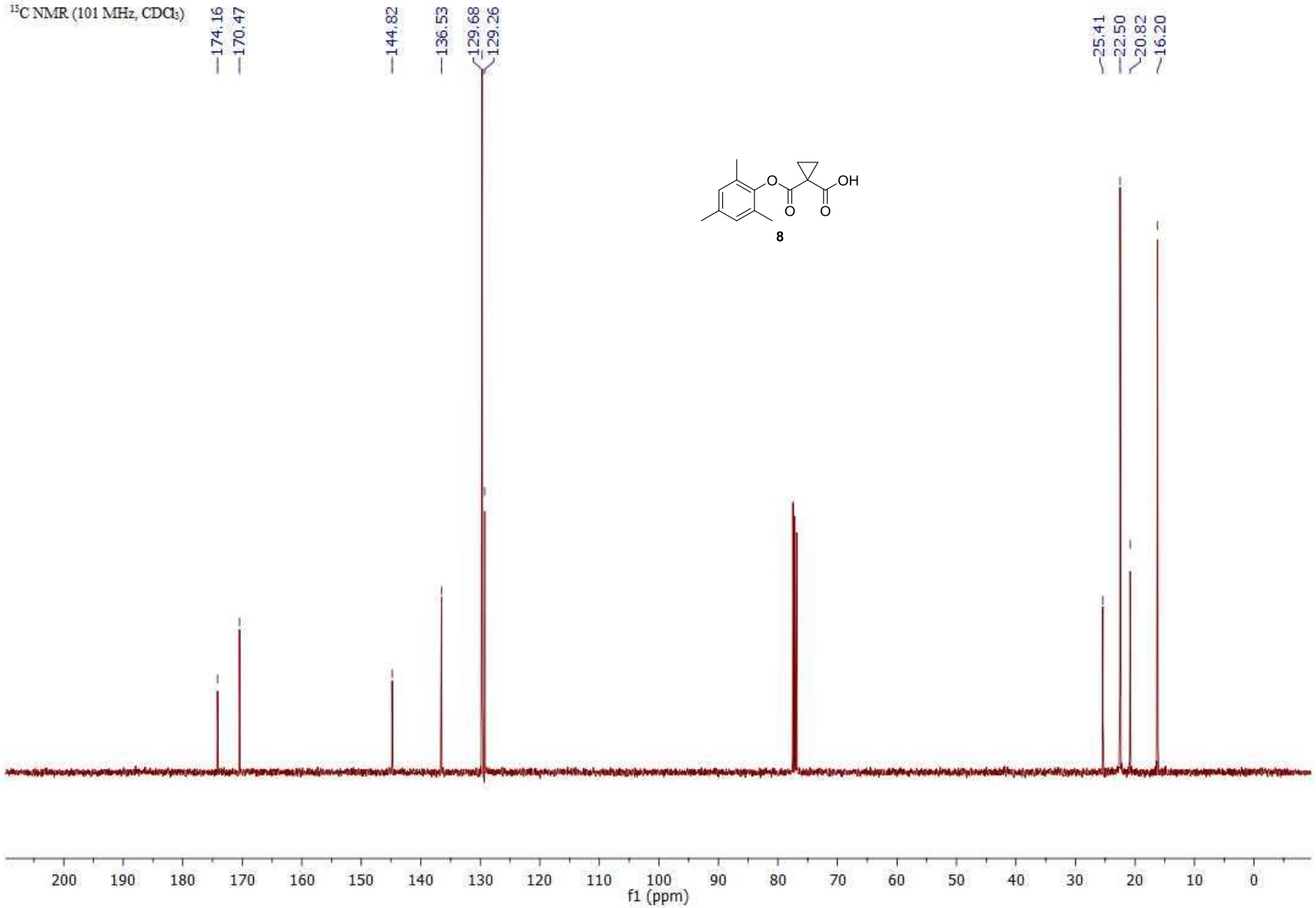
^{1}H NMR (400 MHz, $CDCl_3$)

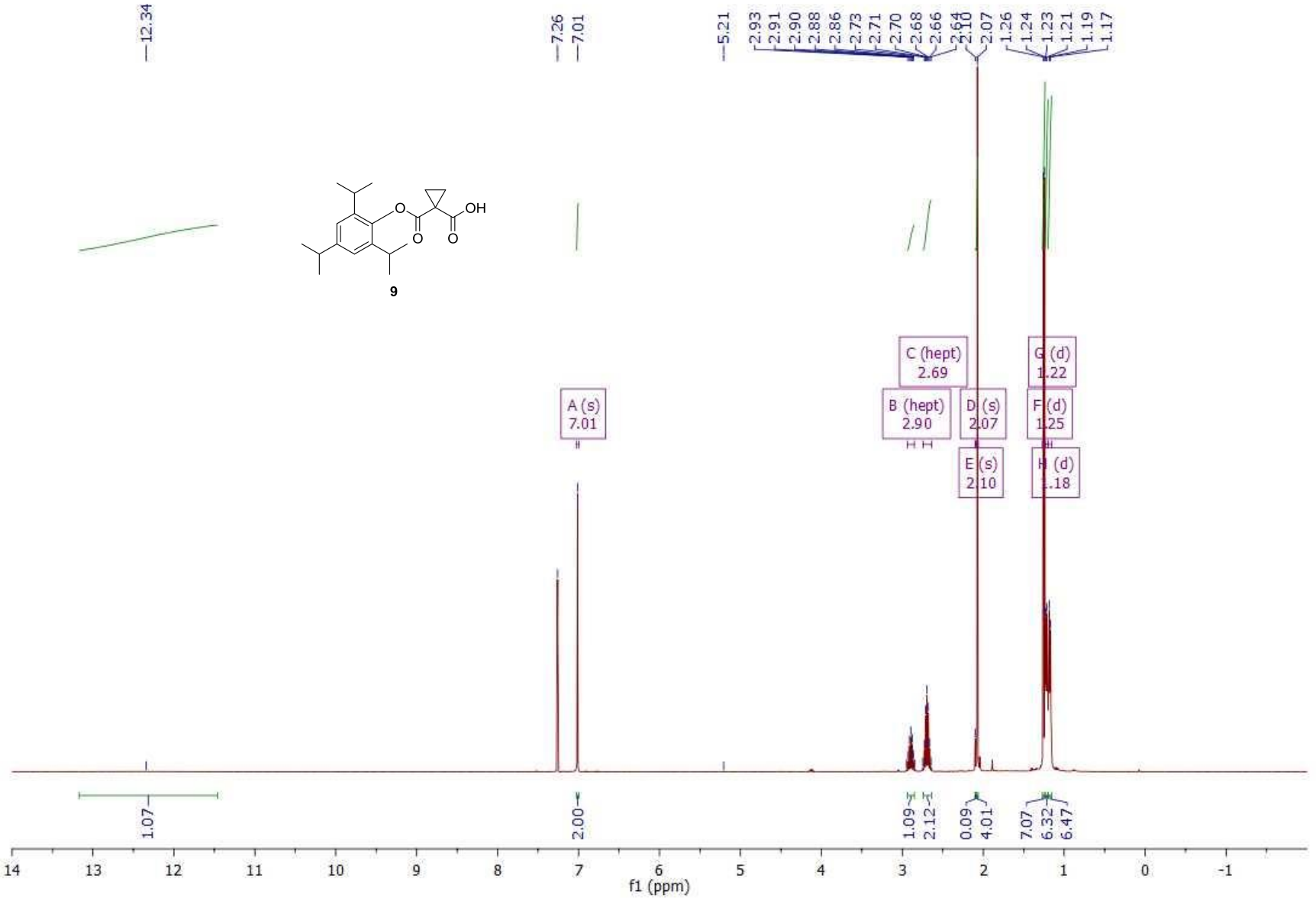


7

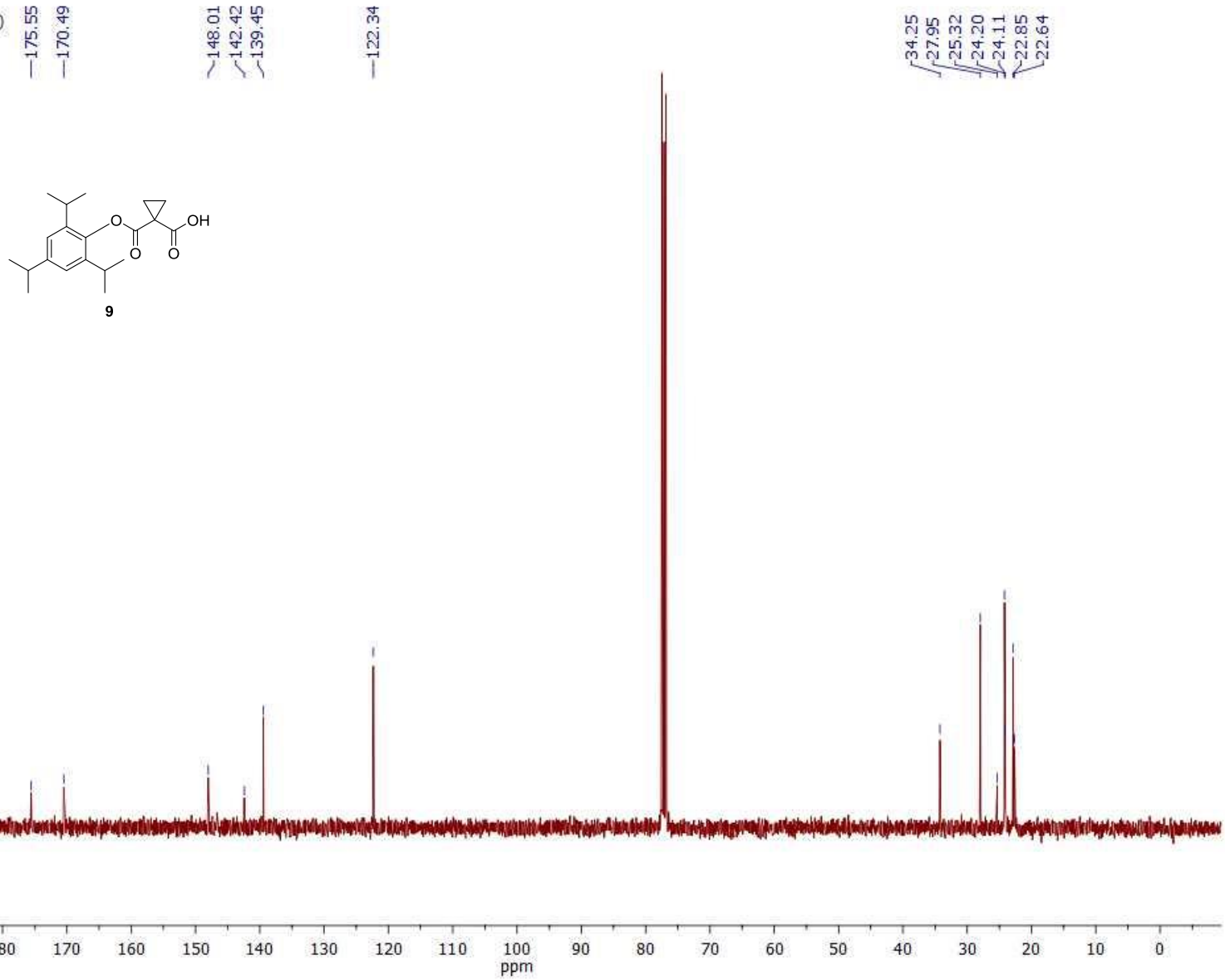

^{13}C NMR (101 MHz, CDCl$_3$)
172.27
23.78
19.93
7
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


12.35
^{1}H NMR (400 MHz, CDCl$_3$)
7.26
6.89
6.89
2.28
2.08
2.06
OH
O
O
O
8
D (s)
12.35
A (s)
6.89
C (m)
2.07
B (s)
2.28
0.99
2.00
2.98
10.90
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

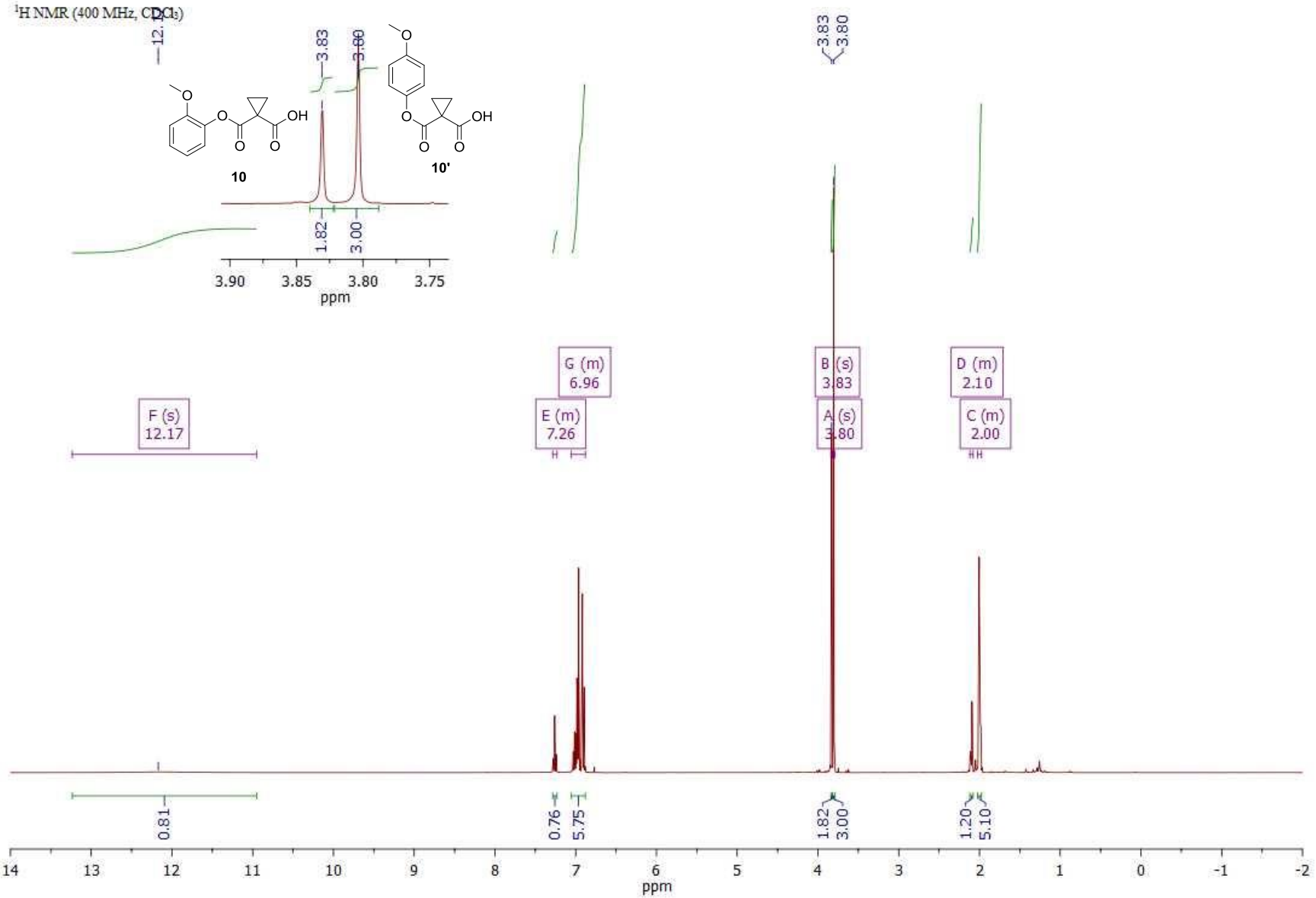

^{13}C NMR (101 MHz, CDCl$_3$)
174.16
170.47
144.82
136.53
129.68
129.26
25.41
22.50
20.82
16.20
O
O
O
OH
8
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

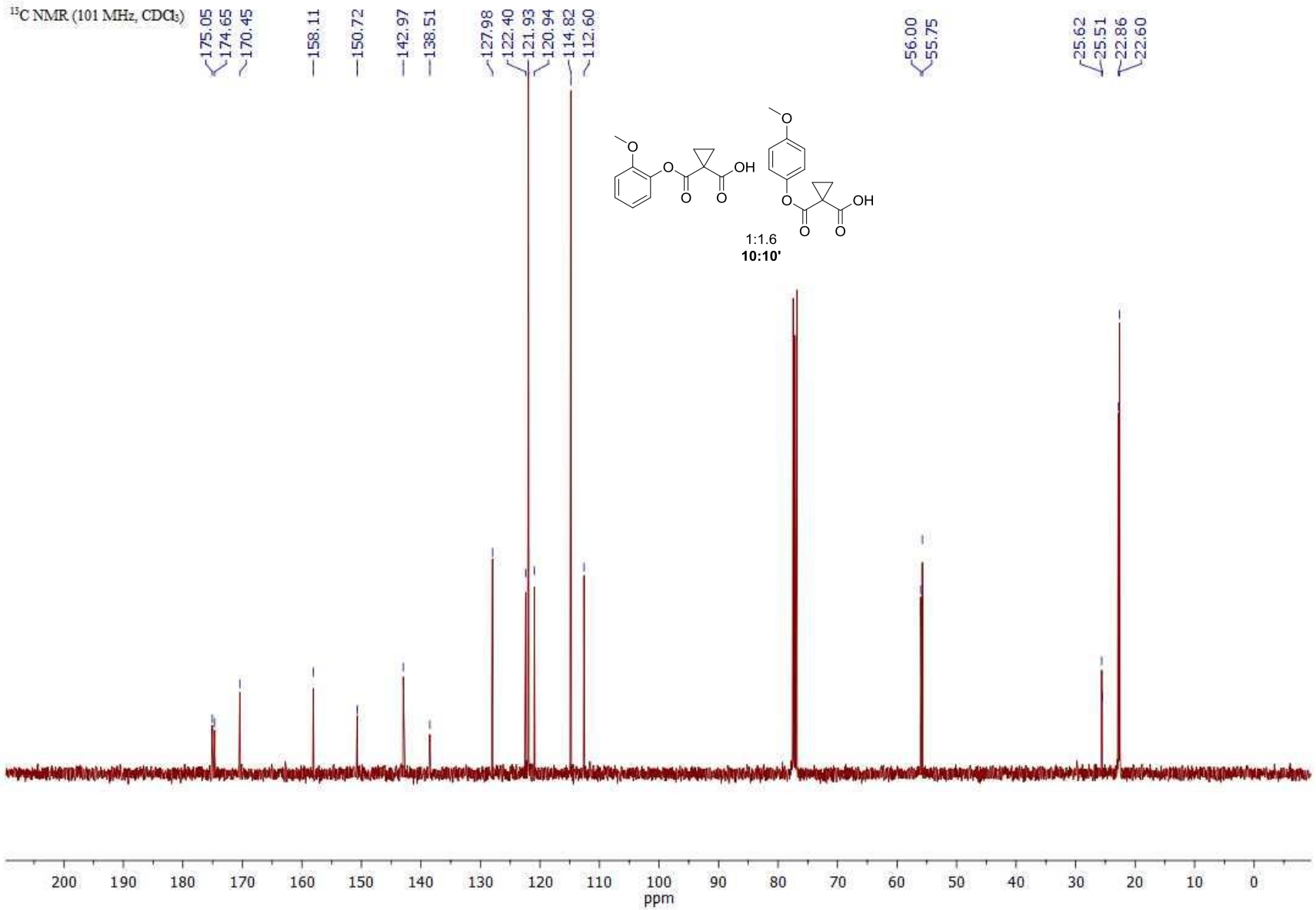

12.34
7.26
7.01
5.21
2.93
2.91
2.90
2.88
2.86
2.73
2.71
2.70
2.68
2.66
2.64
2.10
2.07
1.26
1.24
1.23
1.21
1.19
1.17
OH
O
O
O
9
A (s)
7.01
C (hept)
2.69
B (hept)
2.90
D (s)
2.07
E (s)
2.10
G (d)
1.22
F (d)
1.25
(d)
1.18
1.07
2.00
1.09
2.12
0.09
4.01
7.07
6.32
6.47
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

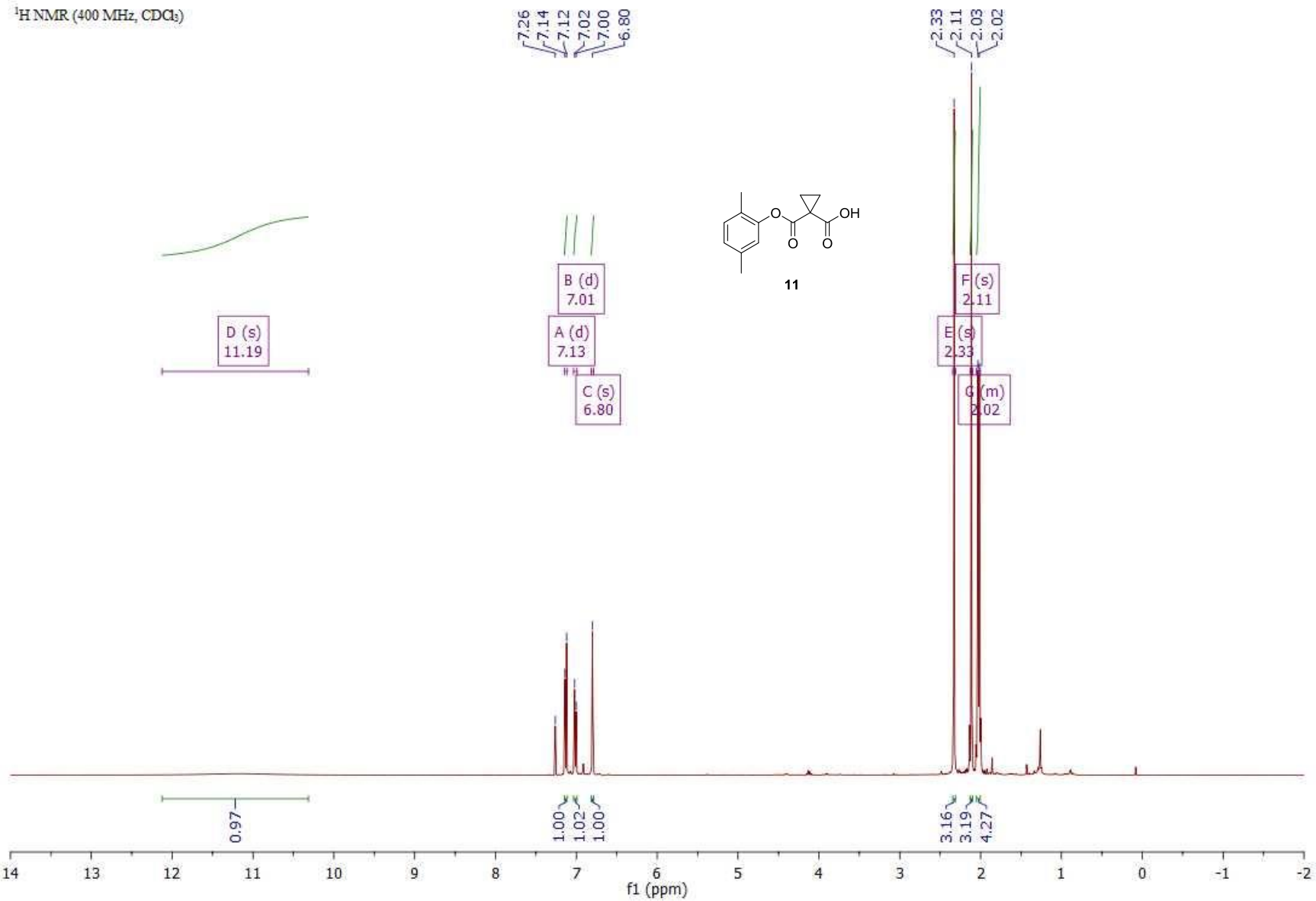
^{13}C NMR (101 MHz, $CDCl_3$)

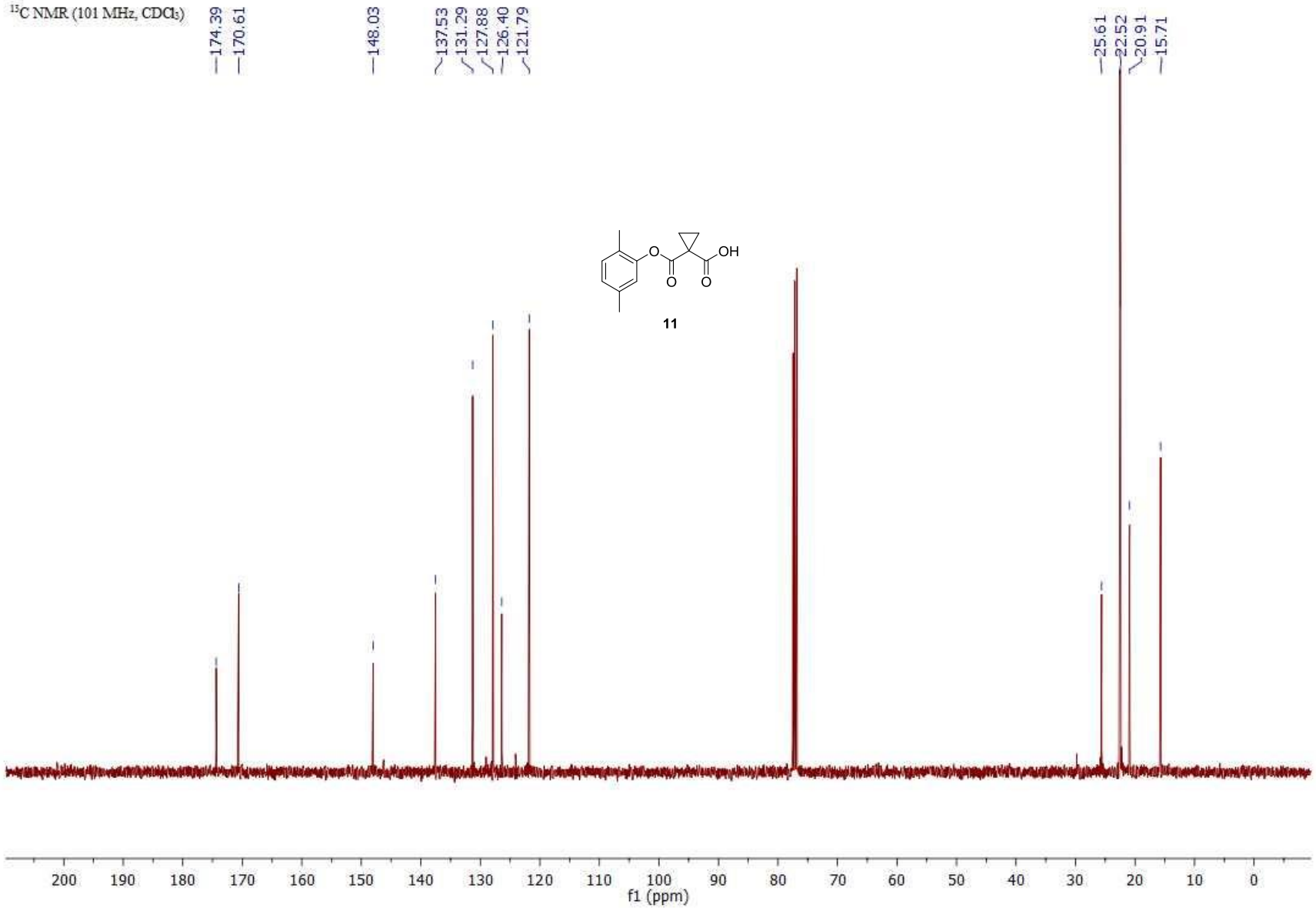


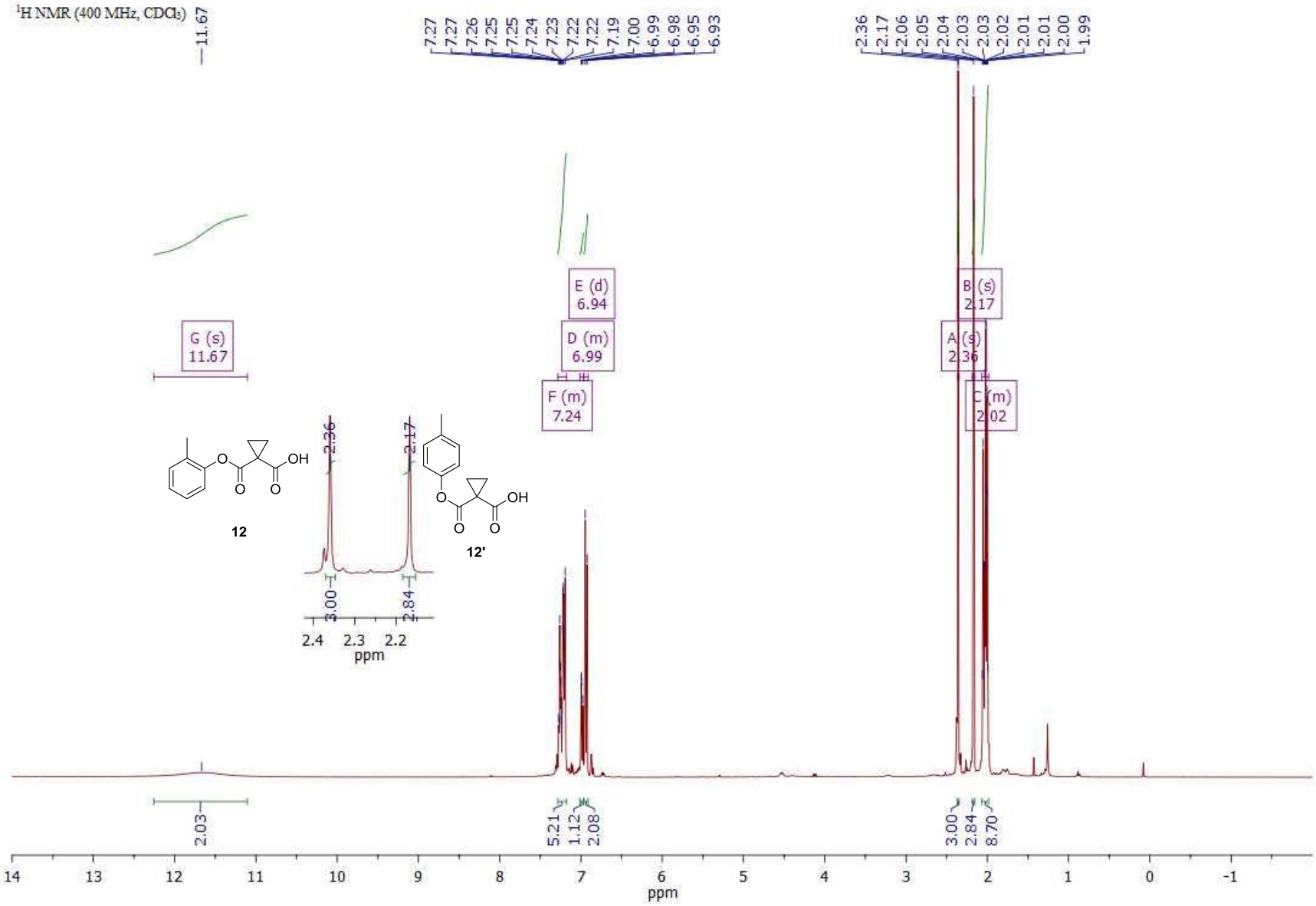
9

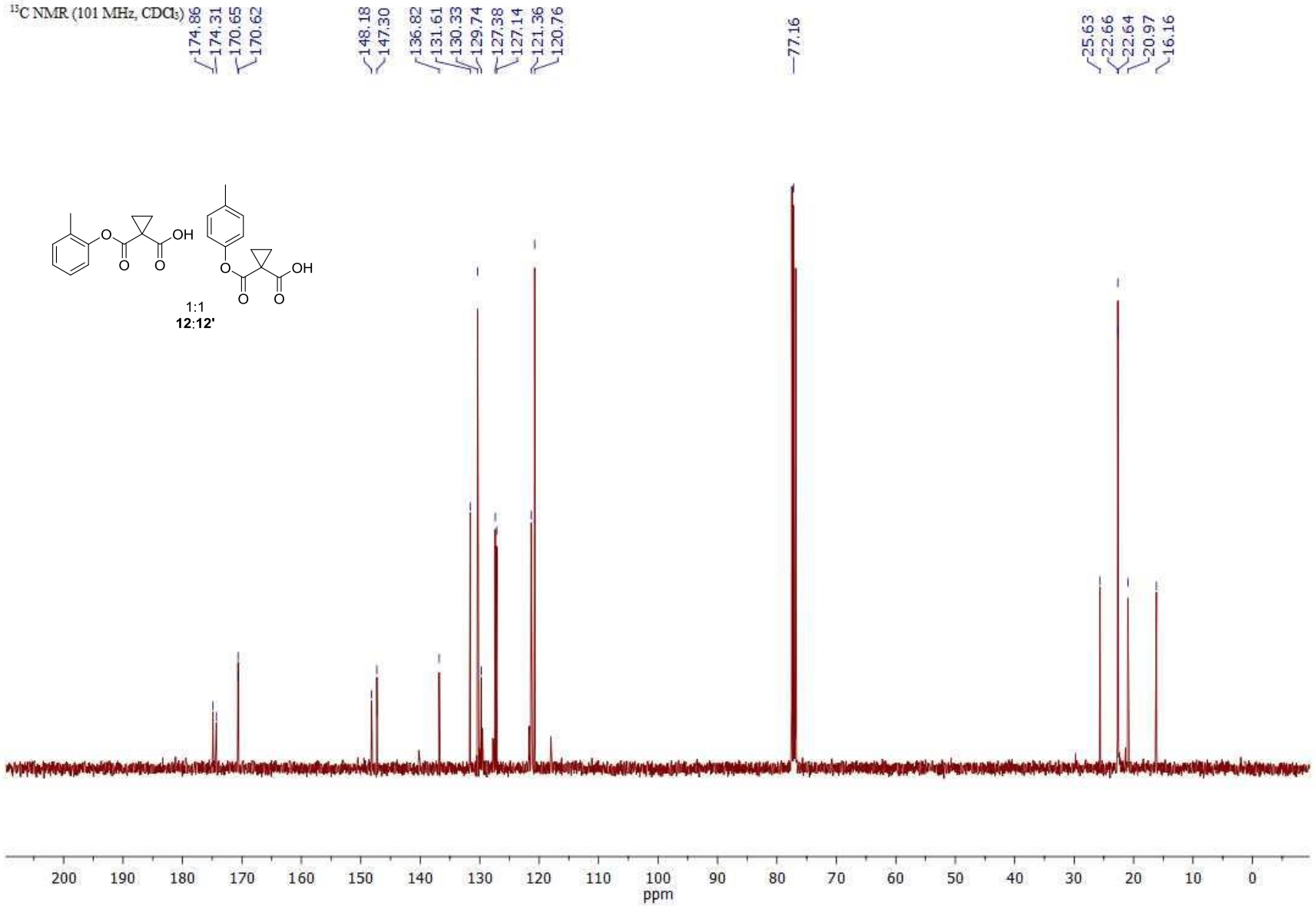

1H NMR (400 MHz, CDCl3)
12.17
3.83
3.80
10
10'
1.82
3.00
3.90
3.85
3.80
3.75
ppm
F (s)
12.17
G (m)
6.96
E (m)
7.26
B (s)
3.83
A (s)
3.80
D (m)
2.10
C (m)
2.00
0.81
0.76
5.75
1.82
3.00
1.20
5.10
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

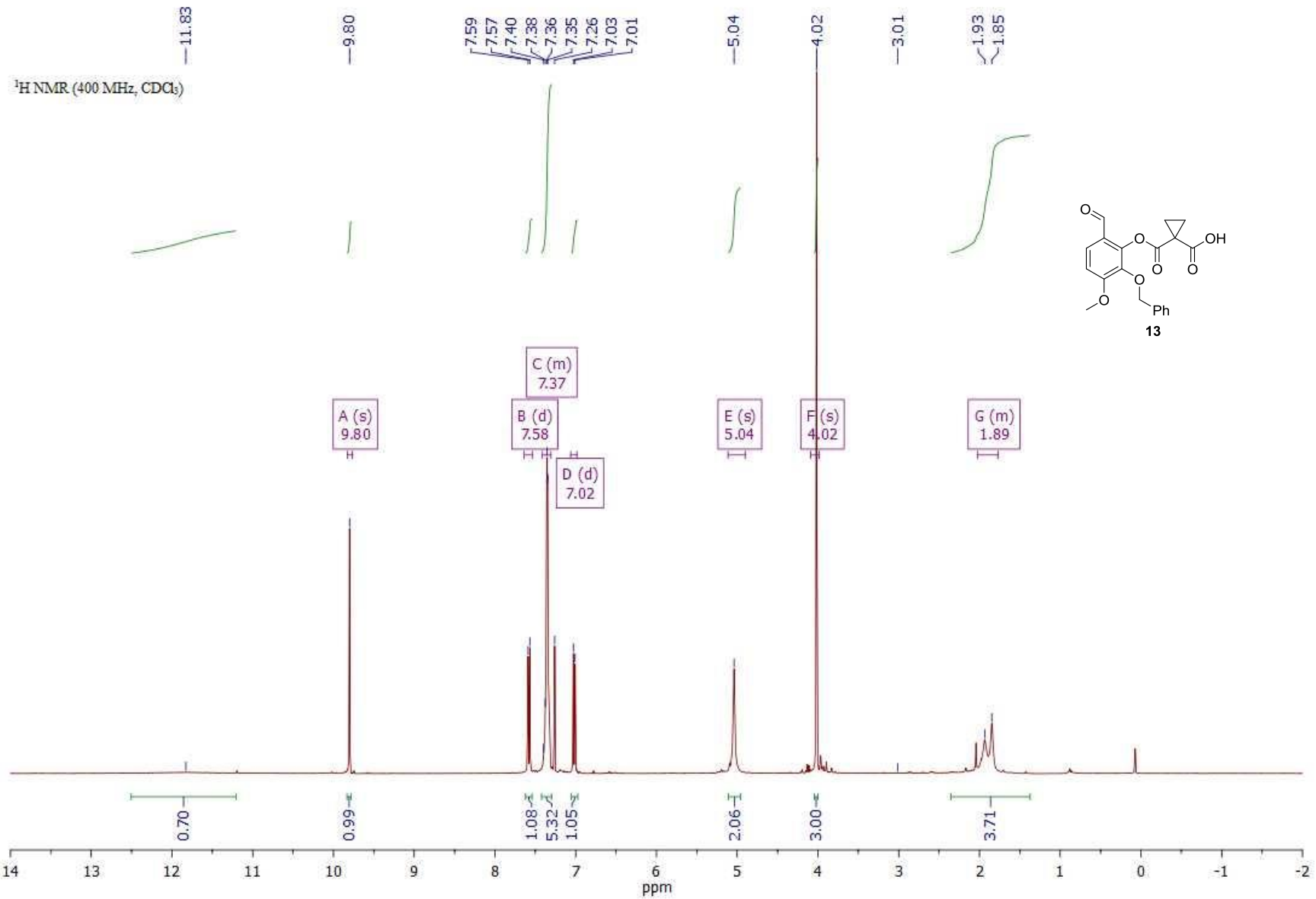

^{13}C NMR (101 MHz, CDCl$_3$)
175.05
174.65
170.45
158.11
150.72
142.97
138.51
127.98
122.40
121.93
120.94
114.82
112.60
56.00
55.75
25.62
25.51
22.86
22.60
OH
OH
1:1.6
10:10'
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

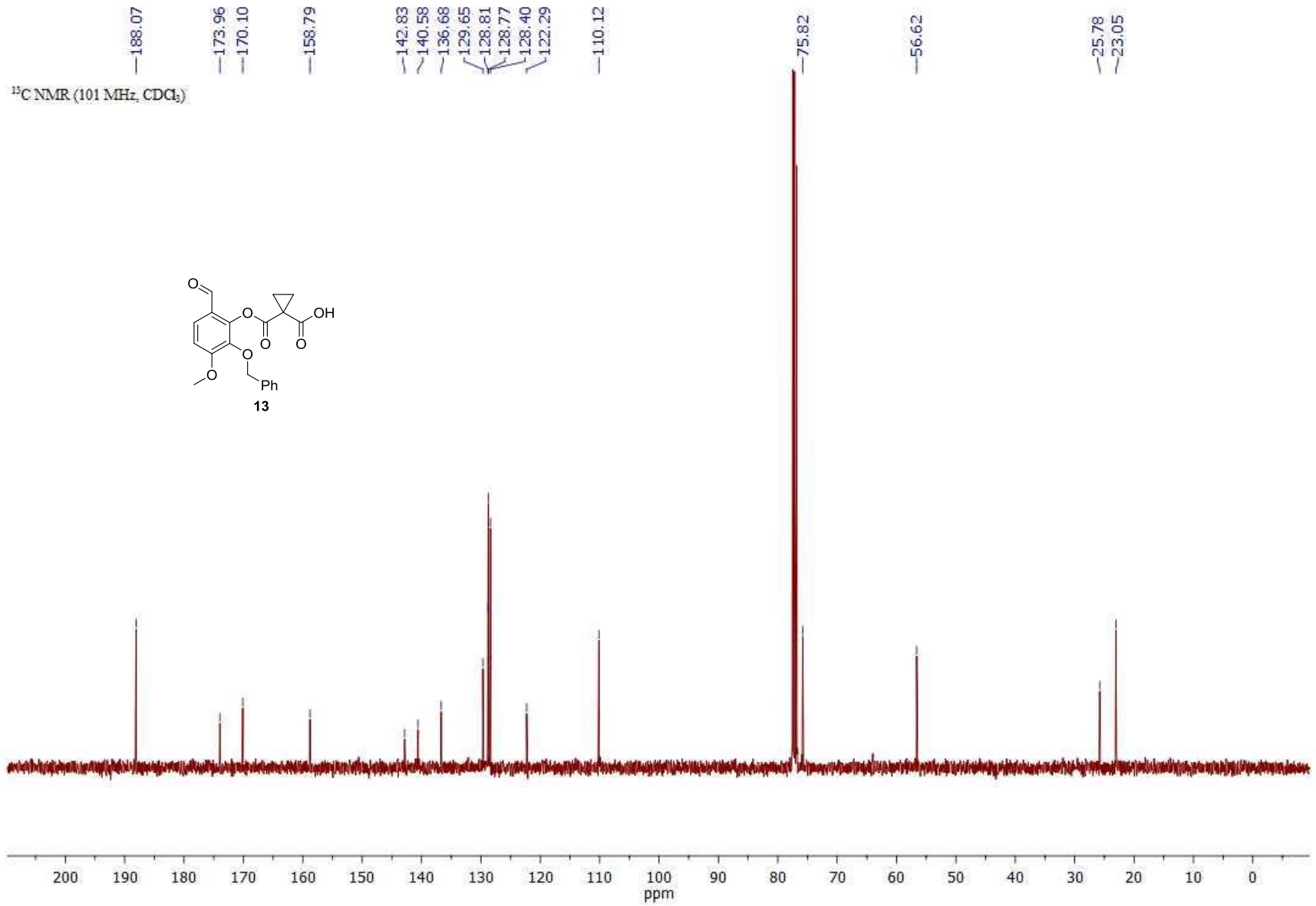

^{1}H NMR (400 MHz, CDCl$_3$)
7.26
7.14
7.12
7.02
7.00
6.80
2.33
2.11
2.03
2.02
OH
O
O
O
11
D (s)
11.19
B (d)
7.01
A (d)
7.13
C (s)
6.80
F (s)
2.11
E (s)
2.33
G (m)
2.02
0.97
1.00
1.02
1.00
3.16
3.19
4.27
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

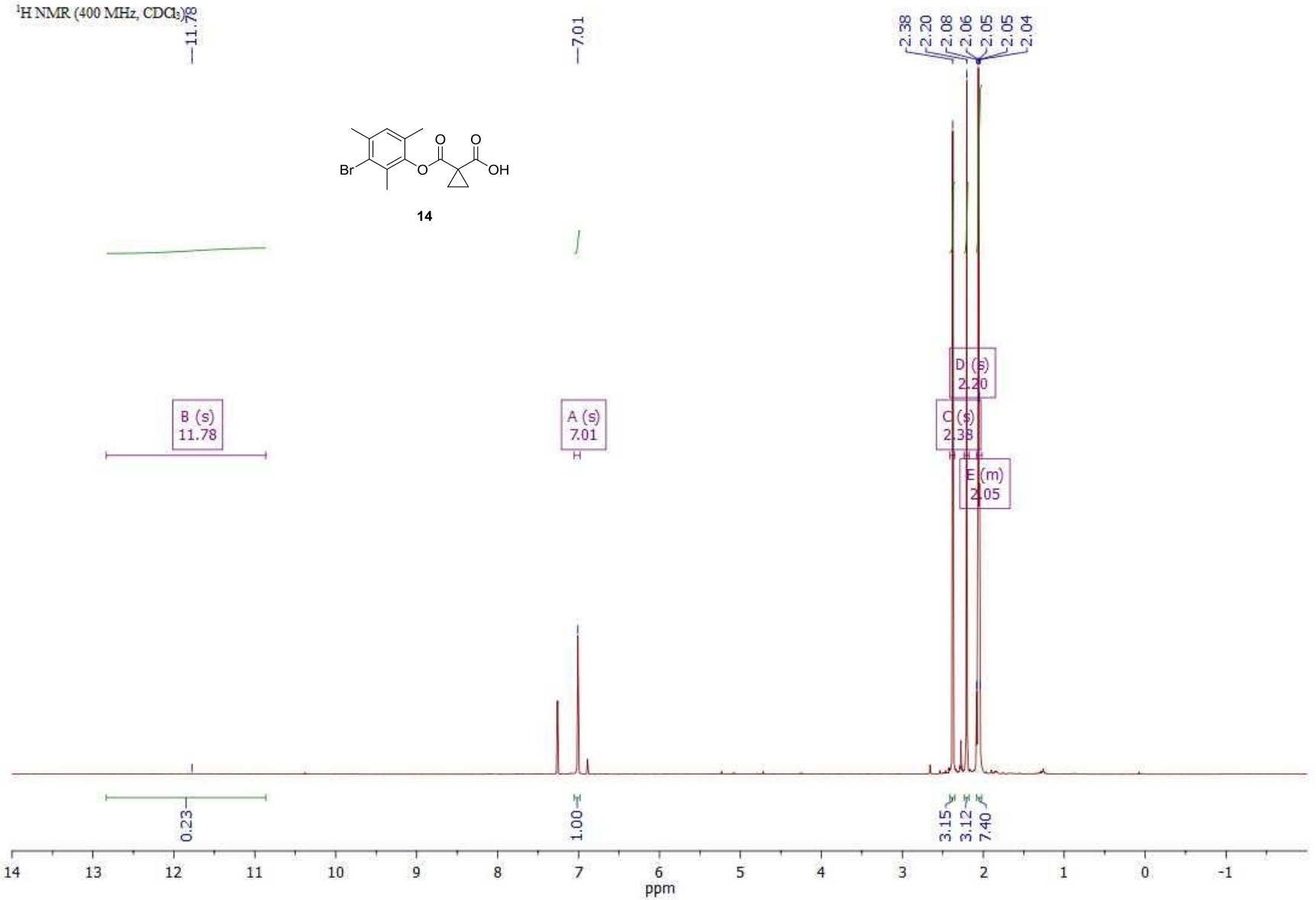

^{13}C NMR (101 MHz, CDCl$_3$)
174.39
170.61
148.03
137.53
131.29
127.88
126.40
121.79
25.61
22.52
20.91
15.71
O
O
O
OH
11
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{1}H NMR (400 MHz, CDCl$_3$)
11.67
7.27 7.27 7.26 7.25 7.25 7.24 7.23 7.22 7.22 7.19 7.00 6.99 6.98 6.95 6.93
2.36 2.17 2.06 2.05 2.04 2.03 2.03 2.02 2.01 2.01 2.00 1.99
G (s) 11.67
E (d) 6.94
D (m) 6.99
F (m) 7.24
B (s) 2.17
A (s) 2.36
C (m) 2.02
12
12'
2.36
2.17
3.00
2.84
2.4 2.3 2.2
ppm
2.03
5.21
1.12
2.08
3.00
2.84
8.70
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
ppm


^{13}C NMR (101 MHz, CDCl$_3$)
174.86
174.31
170.65
170.62
148.18
147.30
136.82
131.61
130.33
129.74
127.38
127.14
121.36
120.76
77.16
25.63
22.66
22.64
20.97
16.16
OH
OH
1:1
12:12'
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

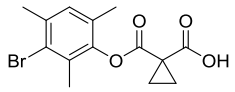

11.83
9.80
7.59
7.57
7.40
7.38
7.36
7.35
7.26
7.03
7.01
5.04
4.02
3.01
1.93
1.85
^{1}H NMR (400 MHz, CDCl$_3$)
A (s)
9.80
B (d)
7.58
C (m)
7.37
D (d)
7.02
E (s)
5.04
F (s)
4.02
G (m)
1.89
0.70
0.99
1.08
5.32
1.05
2.06
3.00
3.71
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm
O
O
OH
O
O
O
Ph
13


188.07
173.96
170.10
158.79
142.83
140.58
136.68
129.65
128.81
128.77
128.40
122.29
110.12
75.82
56.62
25.78
23.05
13C NMR (101 MHz, CDCl3)
O
O
O
OH
O
O
O
Ph
13
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


^{1}H NMR (400 MHz, CDCl$_3$)
11.78
7.01
2.38
2.20
2.08
2.06
2.05
2.05
2.04
Br
O
O
O
OH
14
B (s)
11.78
A (s)
7.01
D (s)
2.20
C (s)
2.38
E (m)
2.05
0.23
1.00
3.15
3.12
7.40
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

^{13}C NMR (101 MHz, $CDCl_3$)

173.78
170.31
144.94
137.06
130.27
128.36
125.42
25.54
23.70
22.54
17.34
16.21



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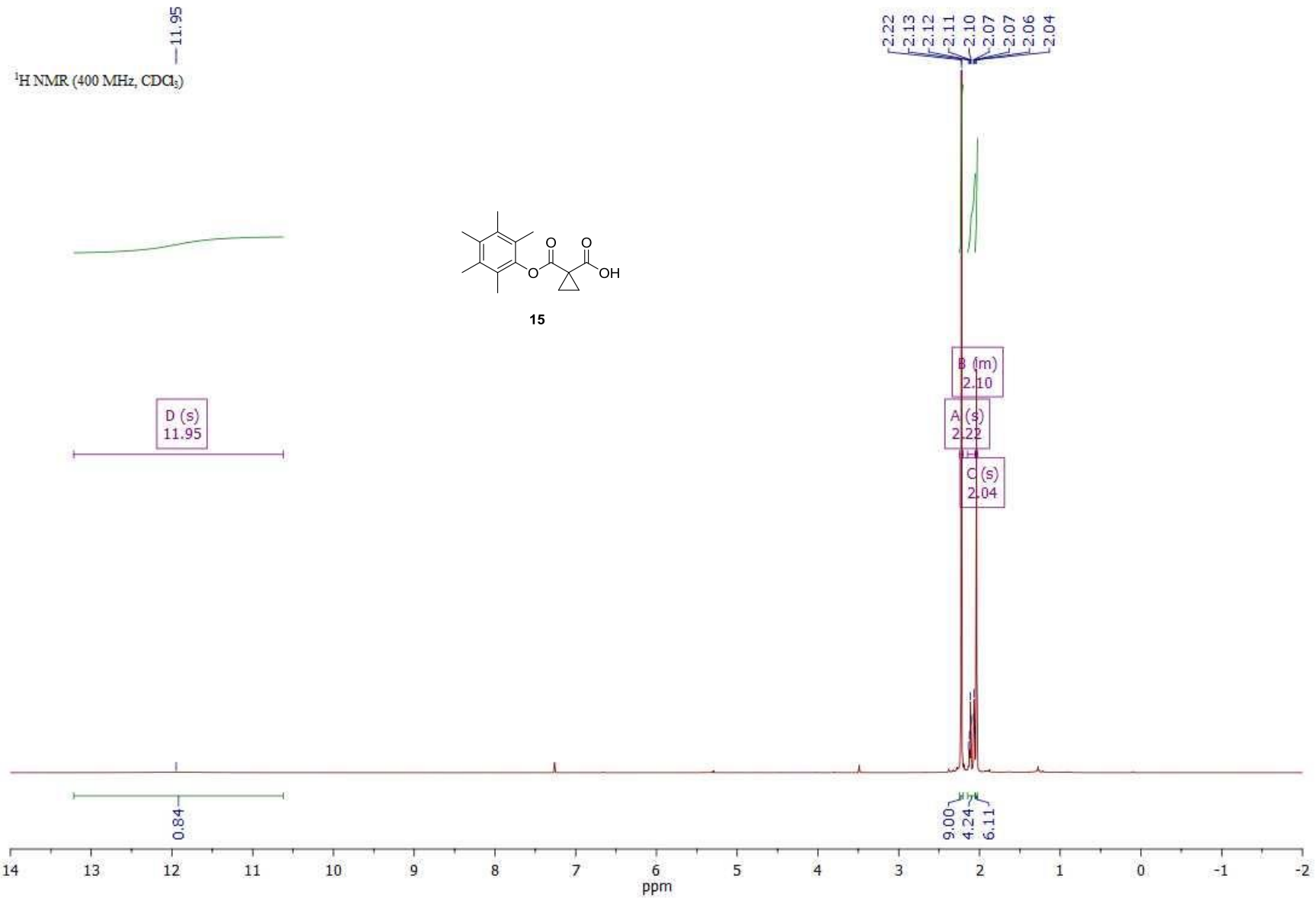
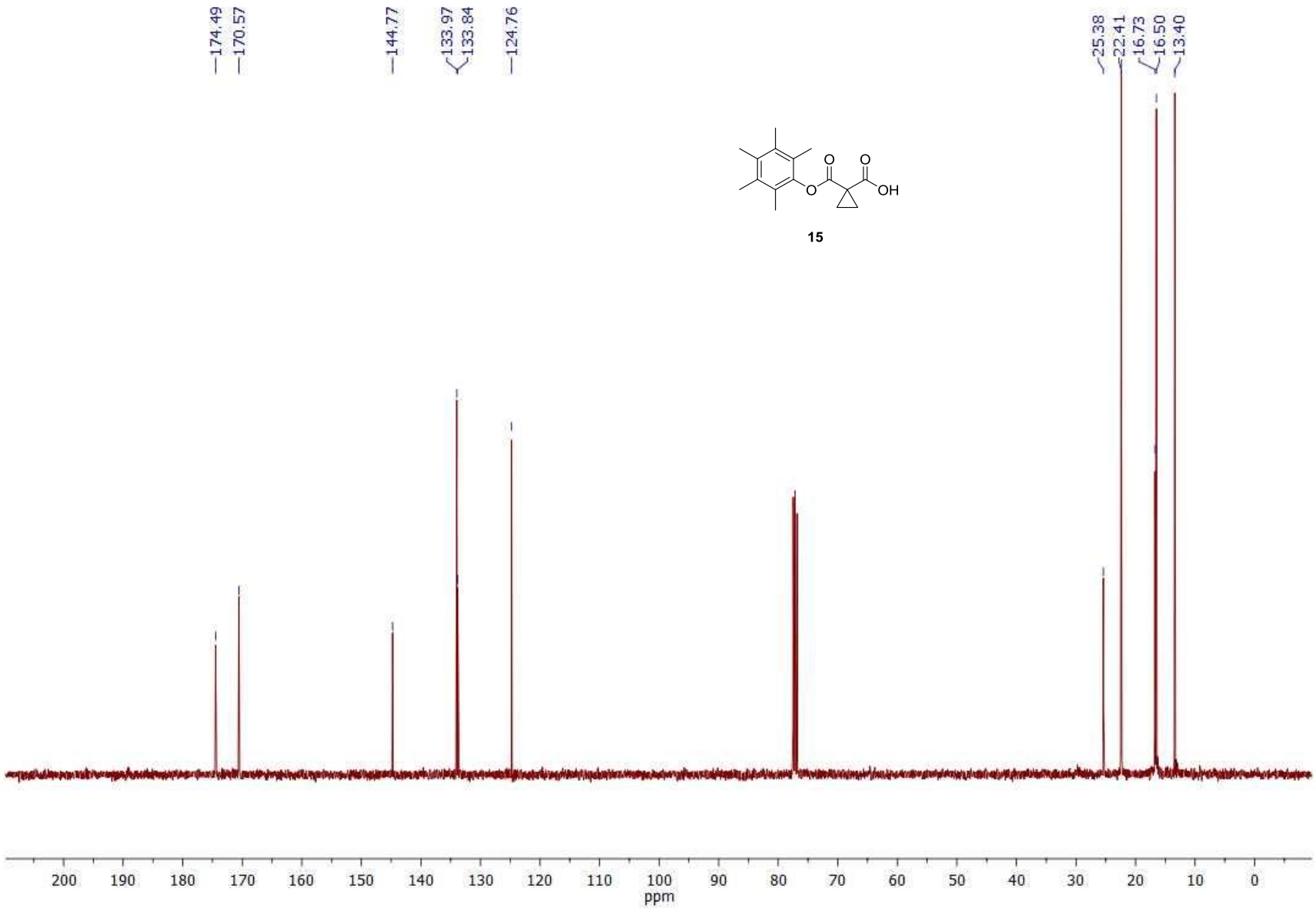
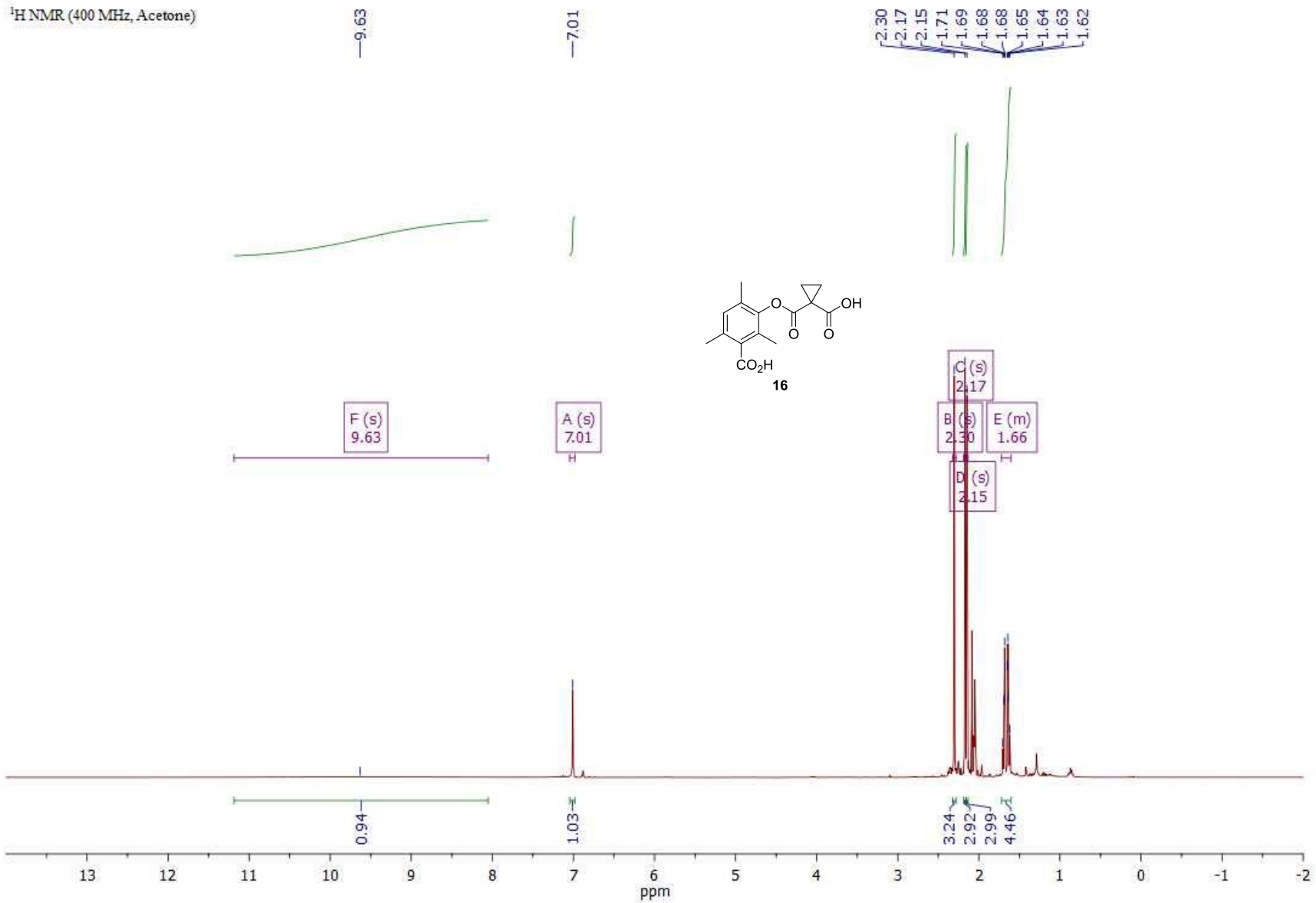
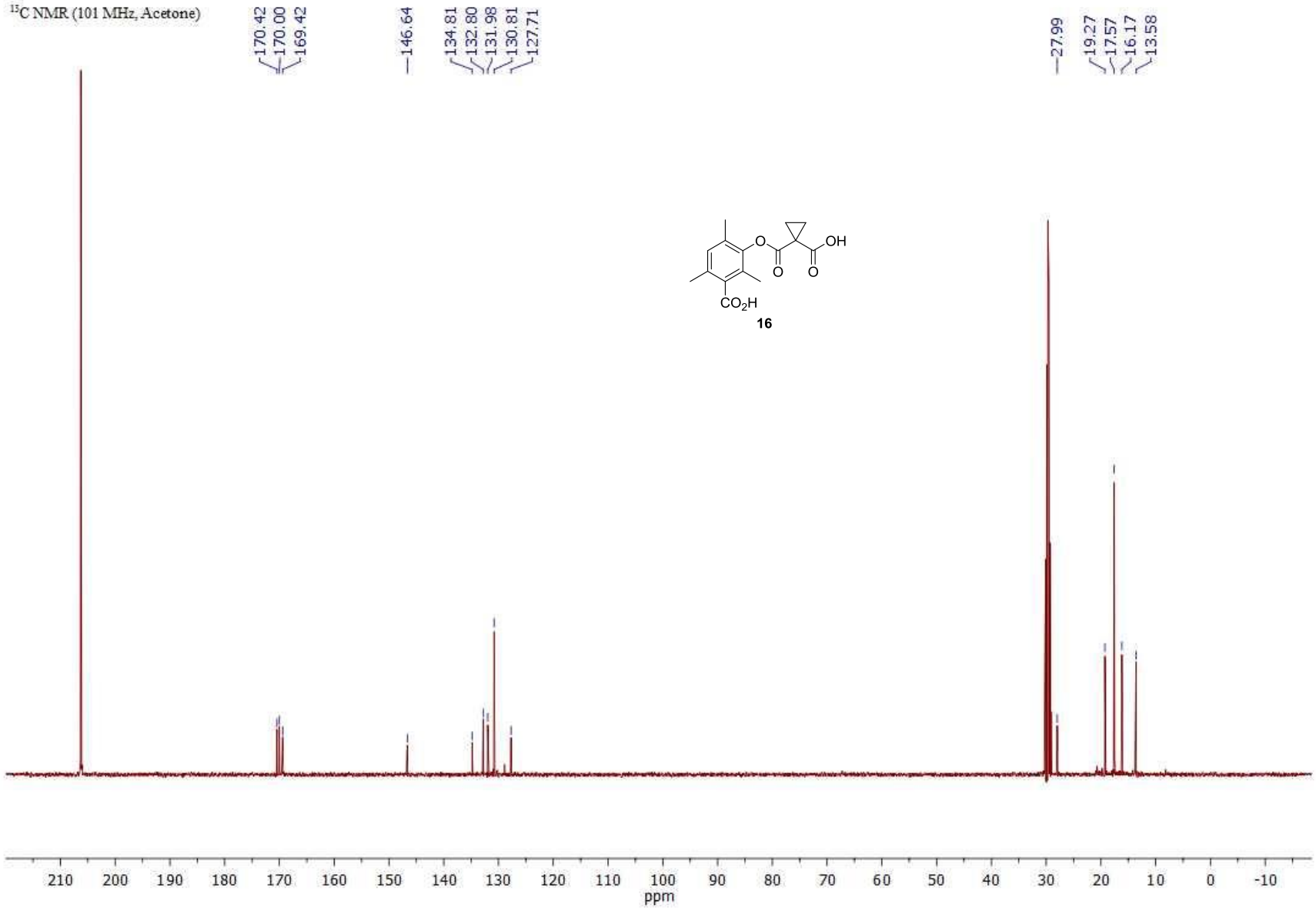
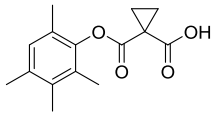

11.95
2.22
2.13
2.12
2.11
2.10
2.07
2.07
2.06
2.04
^{1}H NMR (400 MHz, CDCl$_3$)
O
O
O
OH
15
B (m)
2.10
A (s)
2.22
C (s)
2.04
D (s)
11.95
0.84
9.00
4.24
6.11
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm


174.49
170.57
144.77
133.97
133.84
124.76
25.38
22.41
16.73
16.50
13.40
O
O
O
OH
15
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


^{1}H NMR (400 MHz, Acetone)
9.63
7.01
2.30
2.17
2.15
1.71
1.69
1.68
1.68
1.65
1.64
1.63
1.62
OH
O
O
O
CO_2H
16
F (s)
9.63
A (s)
7.01
H
C (s)
2.17
B (s)
2.30
E (m)
1.66
H
D (s)
2.15
0.94
1.03
3.24
2.92
2.99
4.46
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm


^{13}C NMR (101 MHz, Acetone)
170.42
170.00
169.42
146.64
134.81
132.80
131.98
130.81
127.71
27.99
19.27
17.57
16.17
13.58
O
OH
O
O
CO_2H
16
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

^{1}H NMR (400 MHz, $CDCl_3$)



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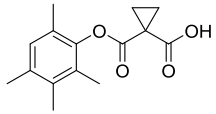
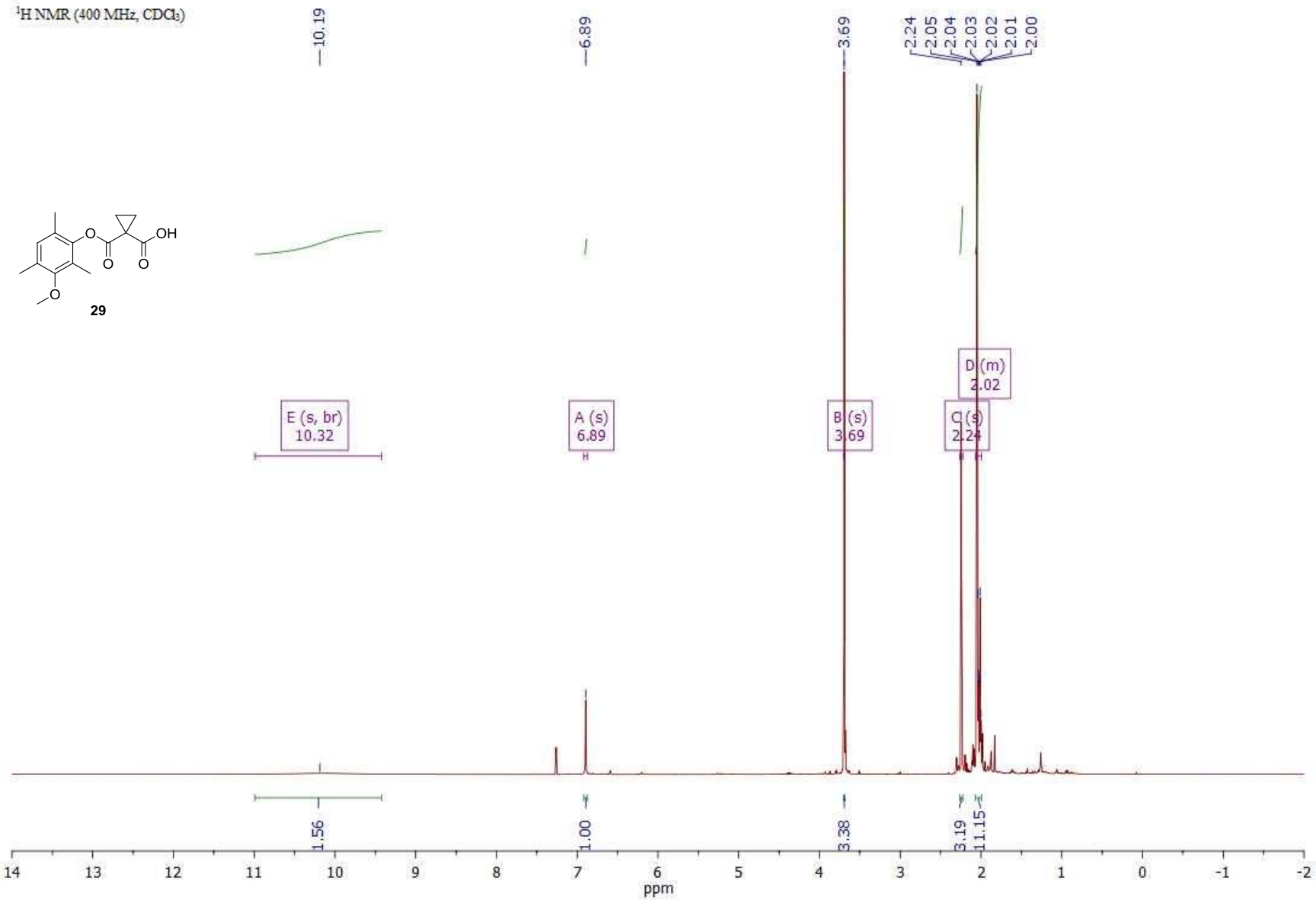
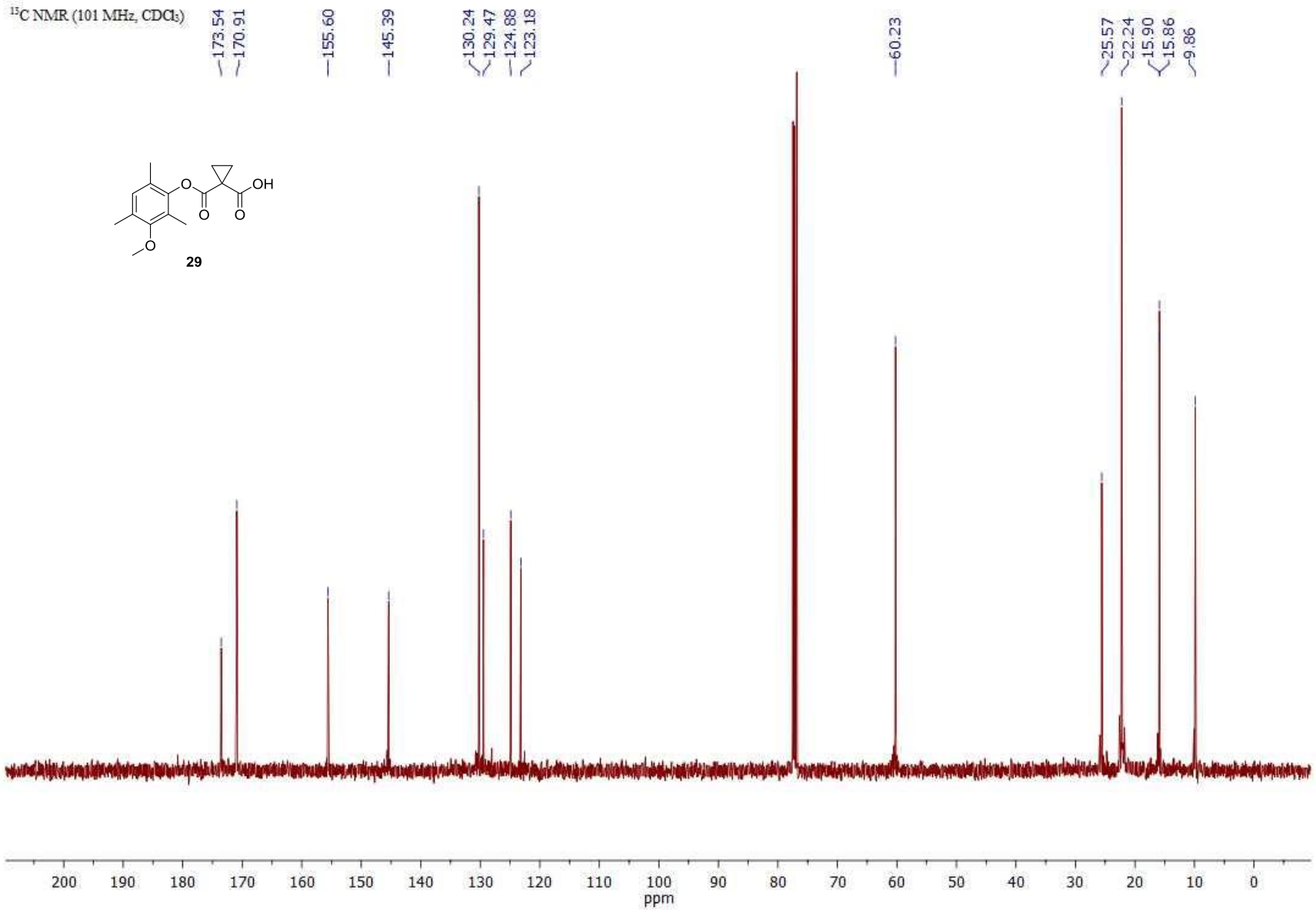
^{13}C NMR (101 MHz, $CDCl_3$)

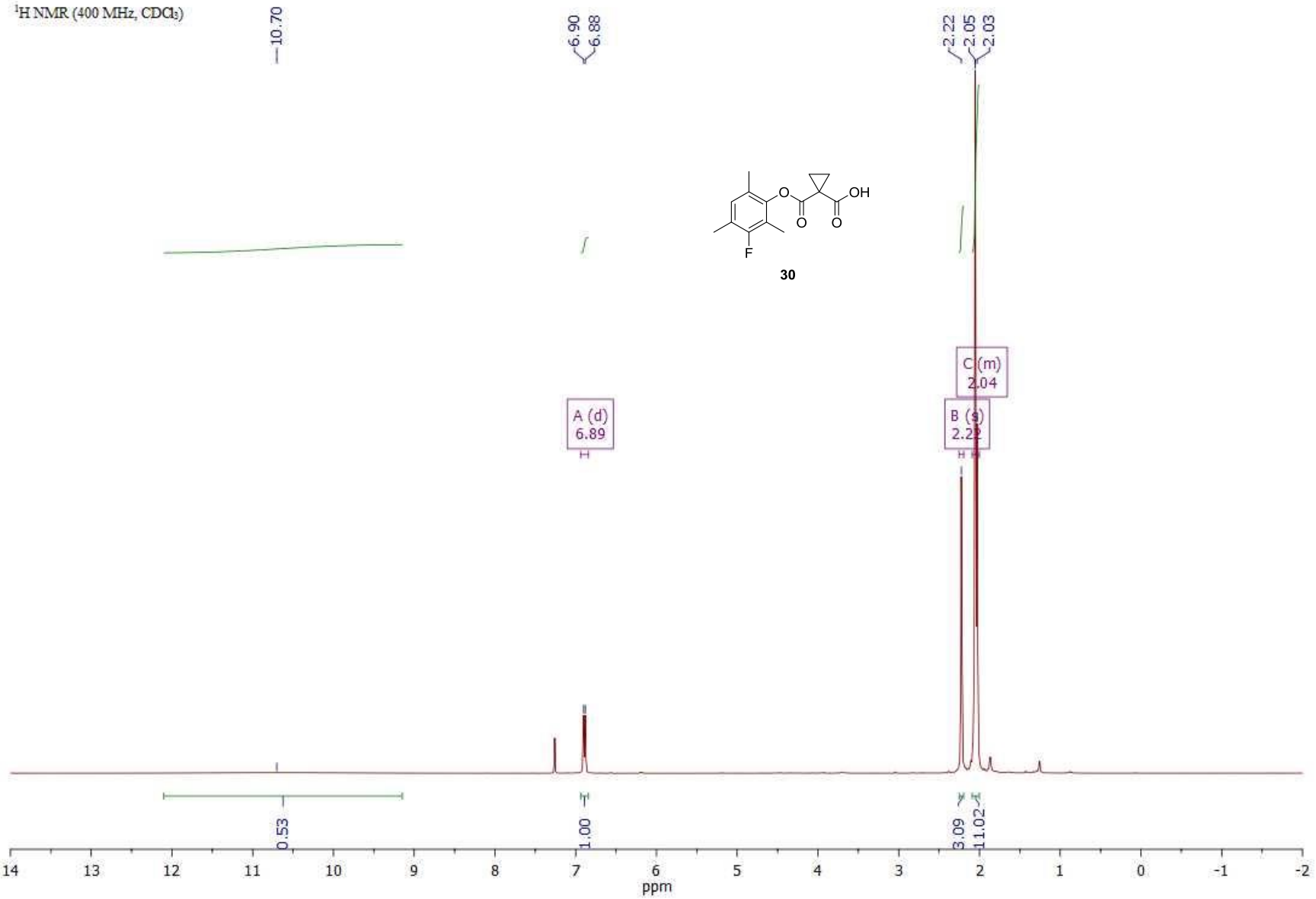
174.64
170.46
144.97
135.19
134.56
129.95
127.80
125.97
25.31
22.76
20.46
16.15
15.84
13.20



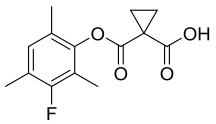
28


^{1}H NMR (400 MHz, CDCl$_3$)
10.19
6.89
3.69
2.24
2.05
2.04
2.03
2.02
2.01
2.00
OH
O
O
O
O
29
E (s, br)
10.32
A (s)
6.89
B (s)
3.69
C (s)
2.24
D (m)
2.02
1.56
1.00
3.38
3.19
11.15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm


^{13}C NMR (101 MHz, CDCl$_3$)
173.54
170.91
155.60
145.39
130.24
129.47
124.88
123.18
60.23
25.57
22.24
15.90
15.86
9.86
OH
O
O
O
O
29
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

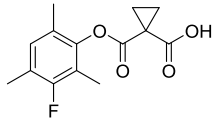

^{1}H NMR (400 MHz, CDCl$_3$)
10.70
6.90
6.88
2.22
2.05
2.03
O
O
O
OH
F
30
C (m)
2.04
A (d)
6.89
B (s)
2.22
0.53
1.00
3.09
1.02
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

^{13}C NMR (101 MHz, $CDCl_3$)



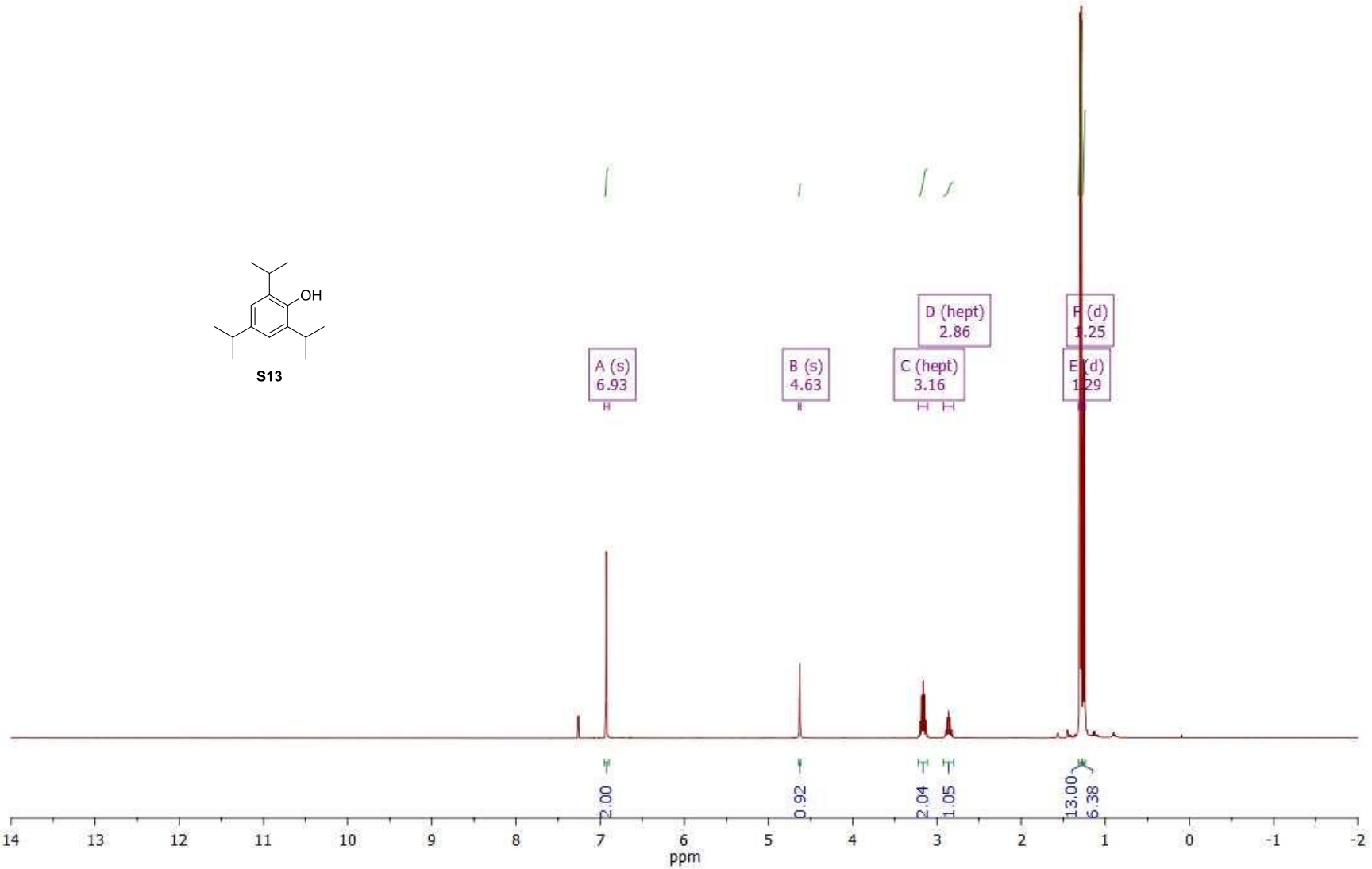
30

^{19}F NMR (376 MHz, $CDCl_3$)

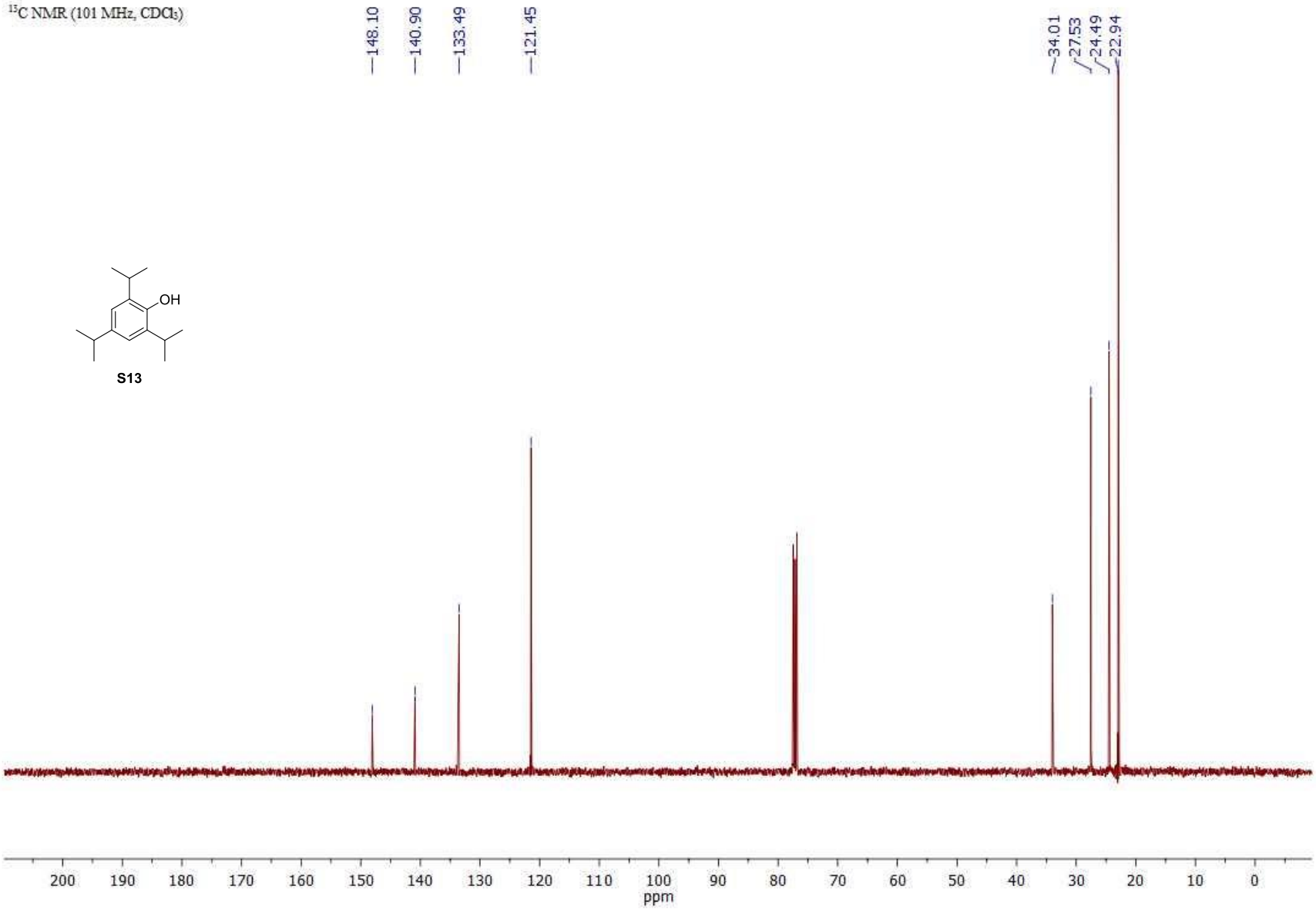


30

^{1}H NMR (400 MHz, $CDCl_3$)

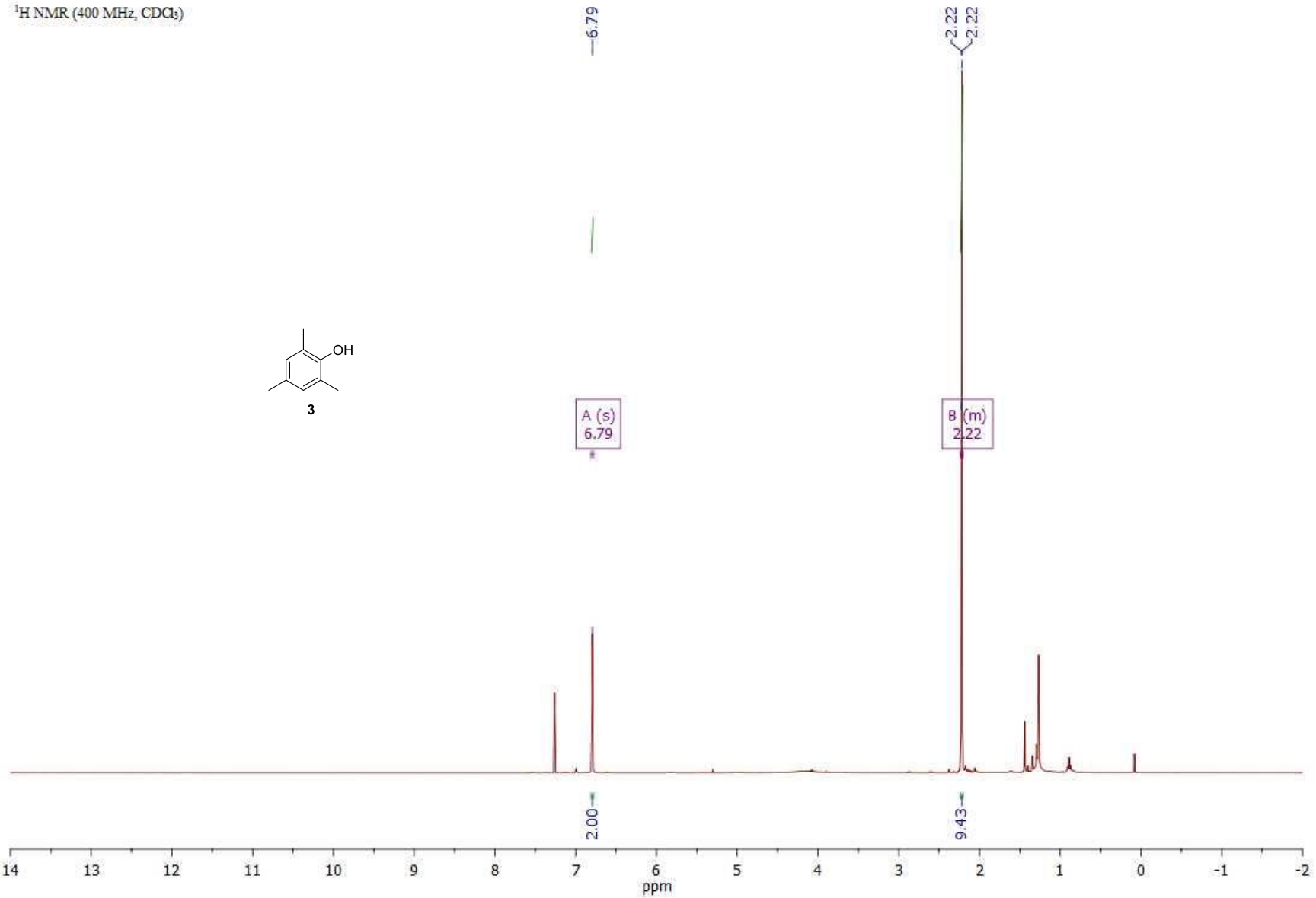


^{13}C NMR (101 MHz, $CDCl_3$)

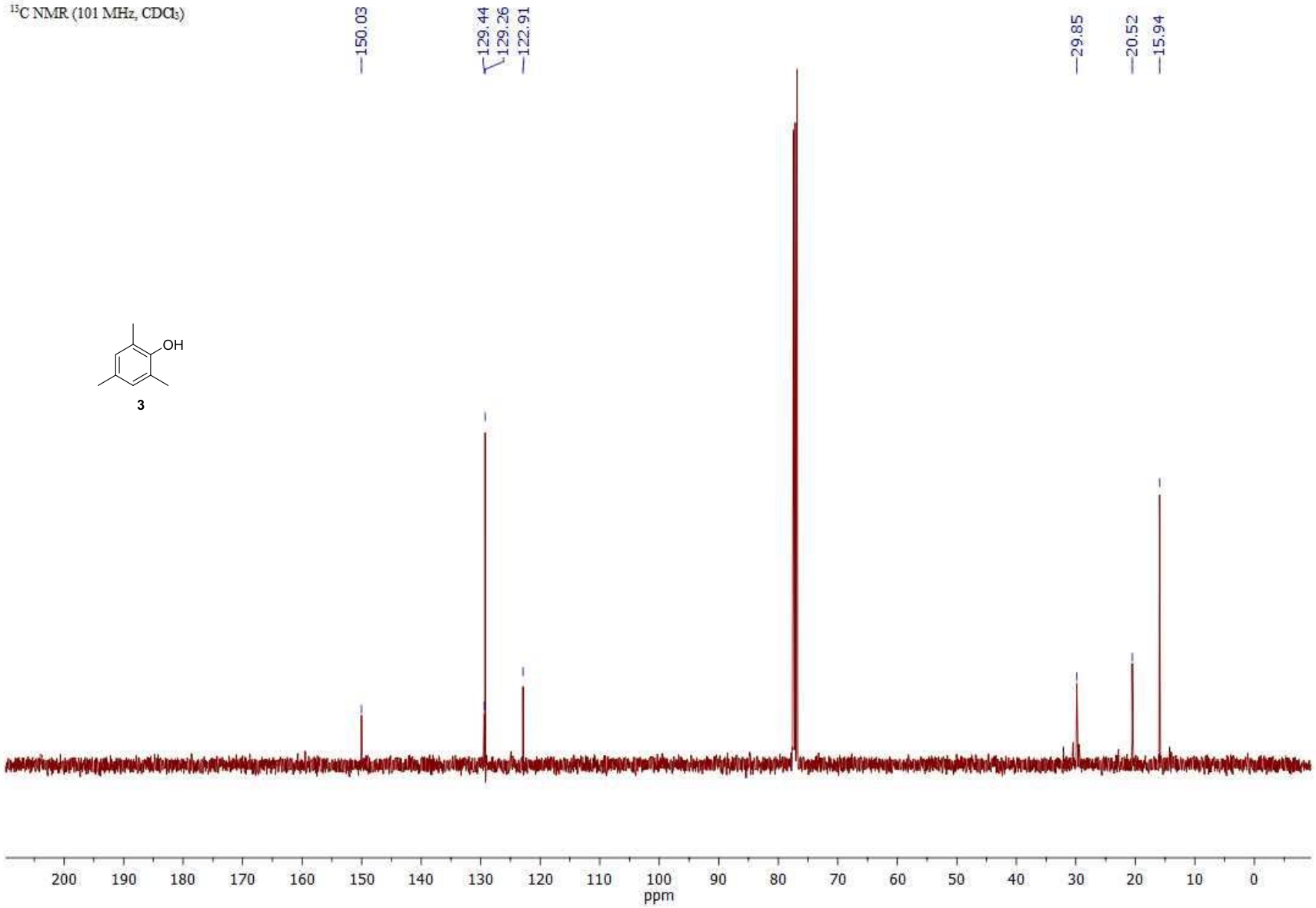


S13

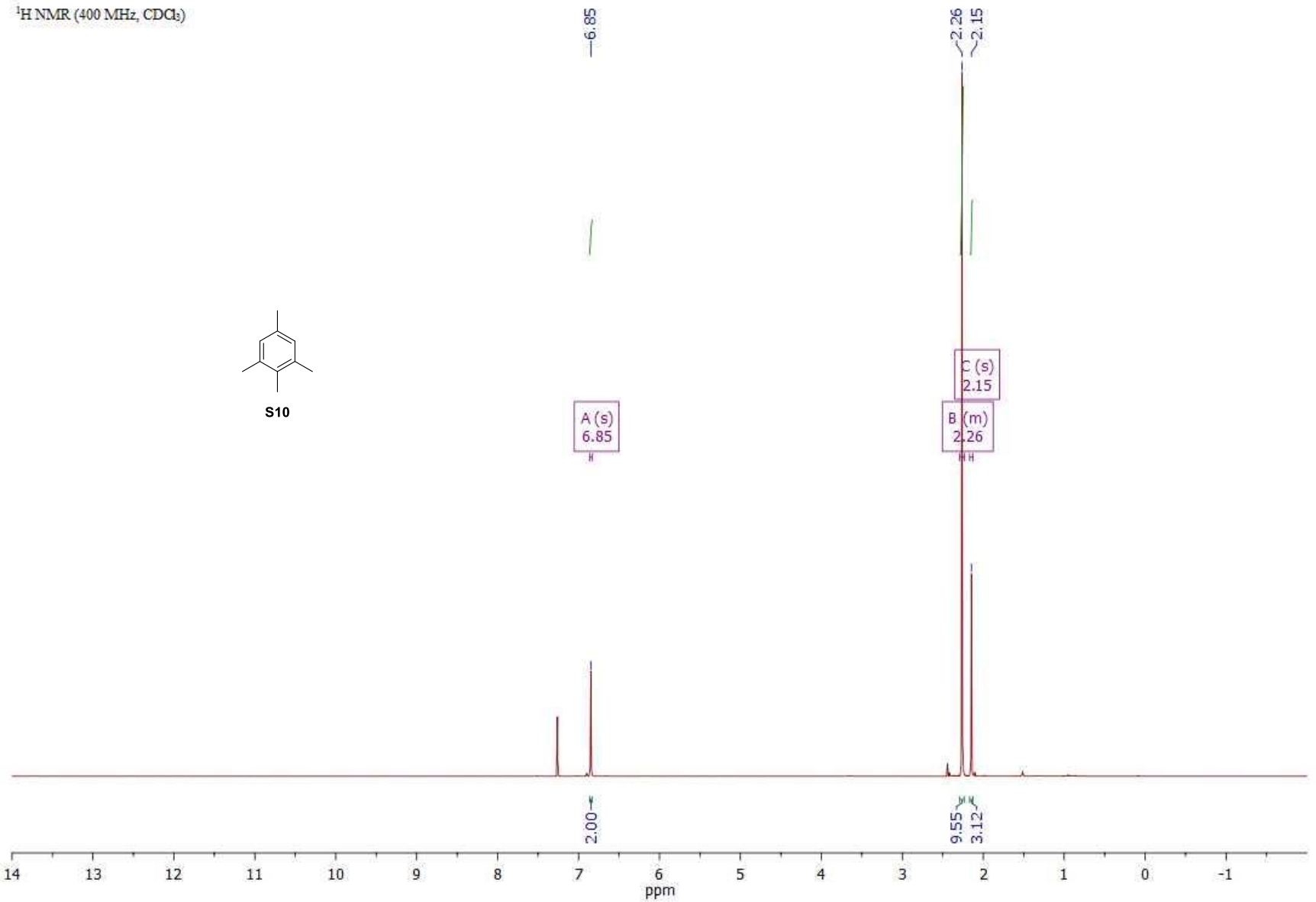
^{1}H NMR (400 MHz, $CDCl_3$)



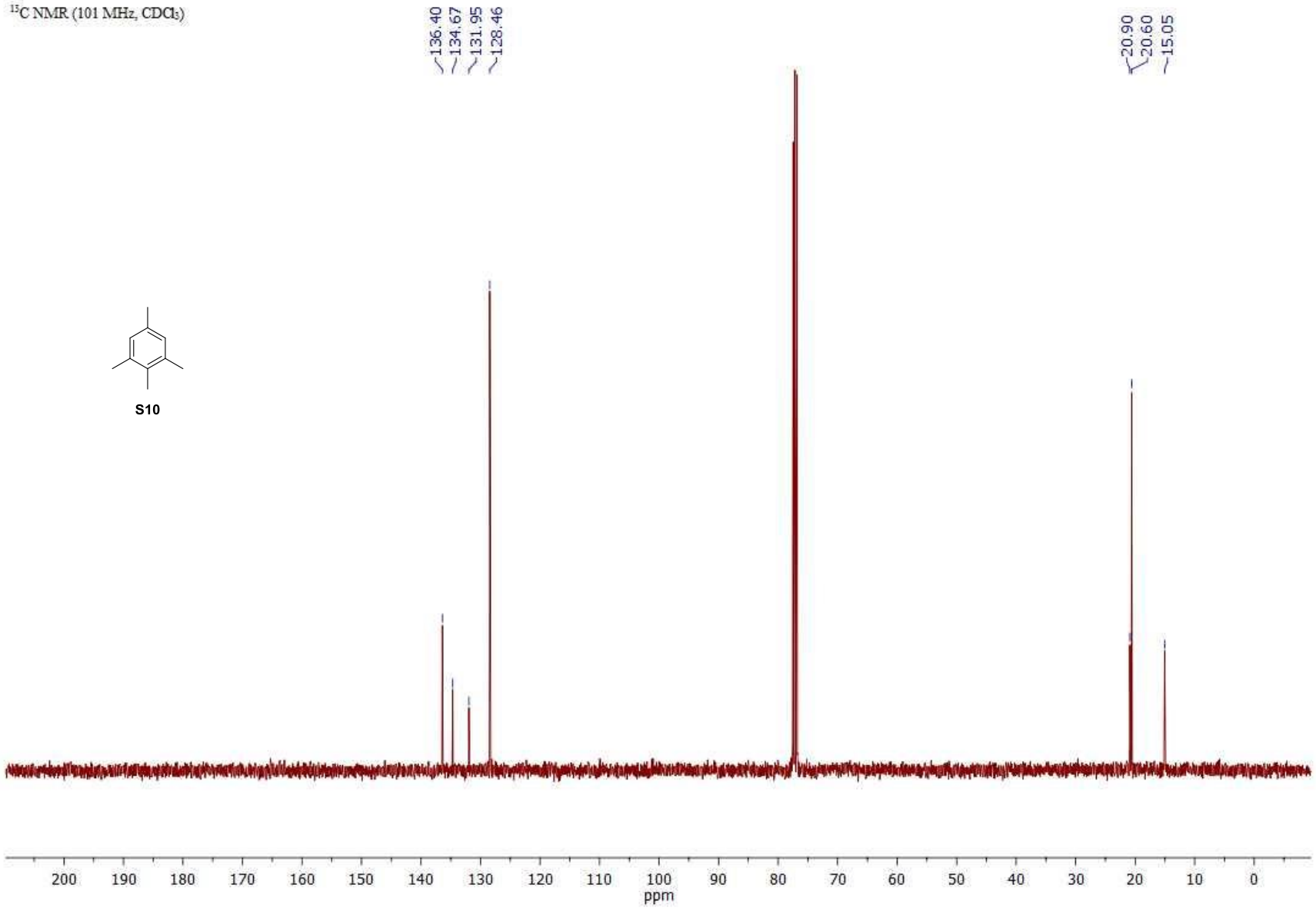
^{13}C NMR (101 MHz, $CDCl_3$)



3


^{1}H NMR (400 MHz, CDCl$_3$)
6.85
2.26
2.15
S10
A (s)
6.85
C (s)
2.15
B (m)
2.26
2.00
9.55
3.12
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

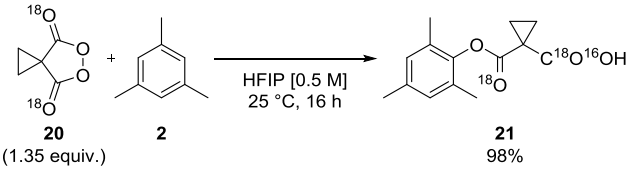
^{13}C NMR (101 MHz, $CDCl_3$)



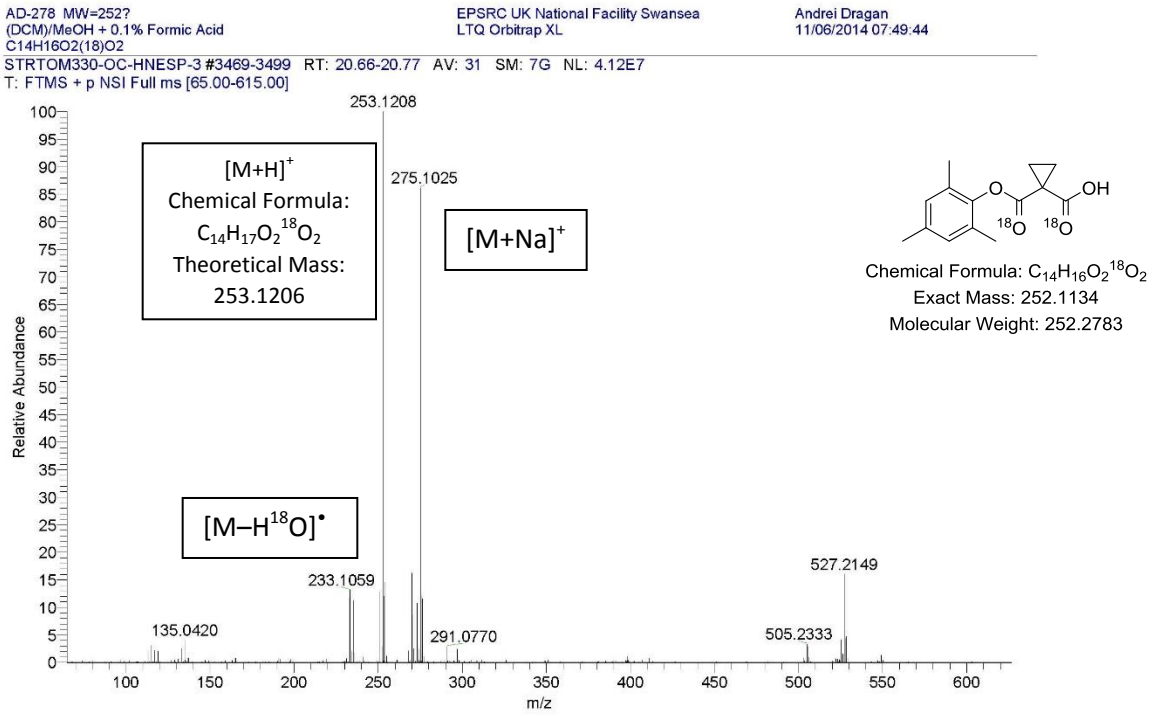
S10

Mass Spectrometry Data

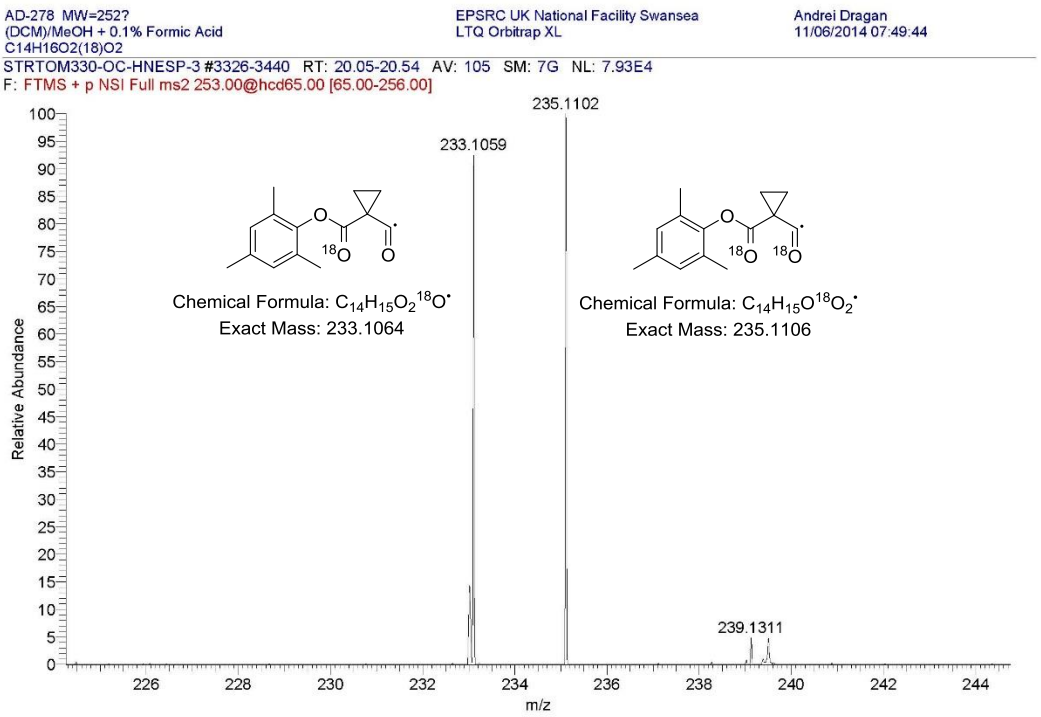
Reaction of mesitylene 2 with ^{18}O labeled peroxide 20



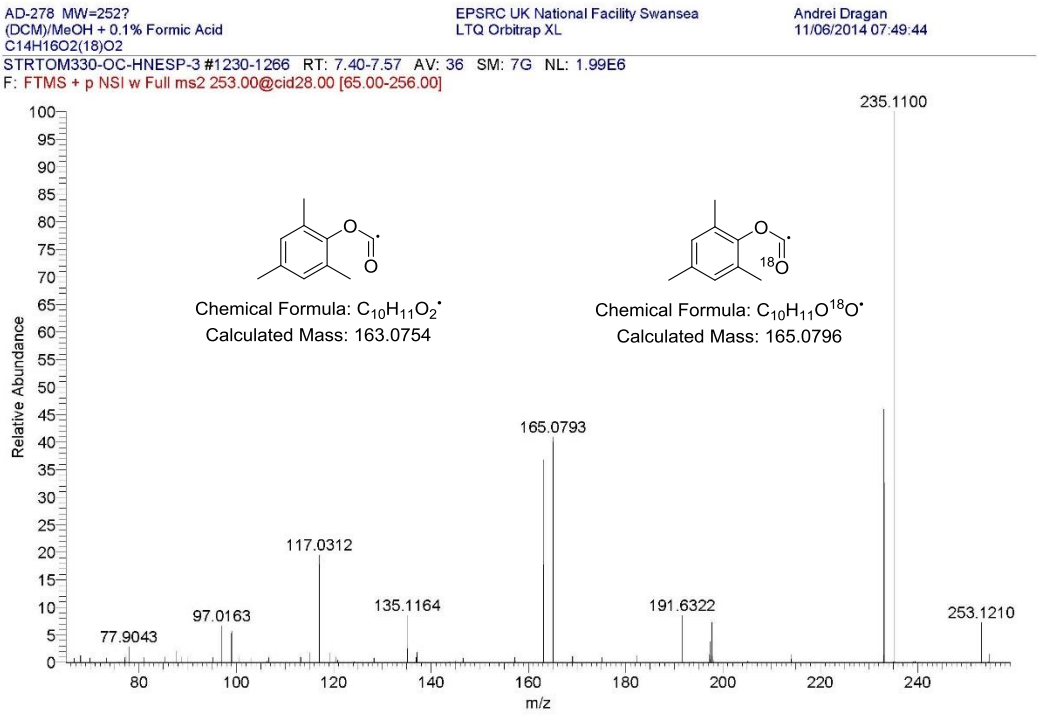
HRMS Analysis of 21 showing $[M+H]^+$ ion at 253.1208, showing incorporation of two ^{18}O labels

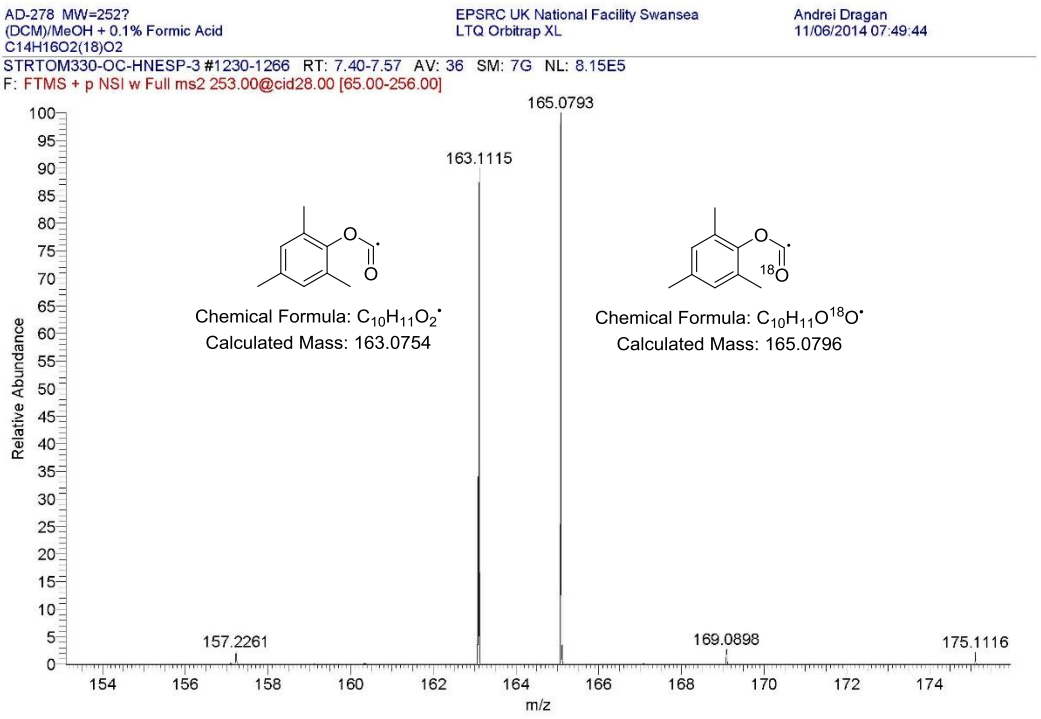


HRMS MS^2 analysis of $[M+H]^+$ ion at 253.1208, showing loss of H_2O and $H_2{}^{18}O$

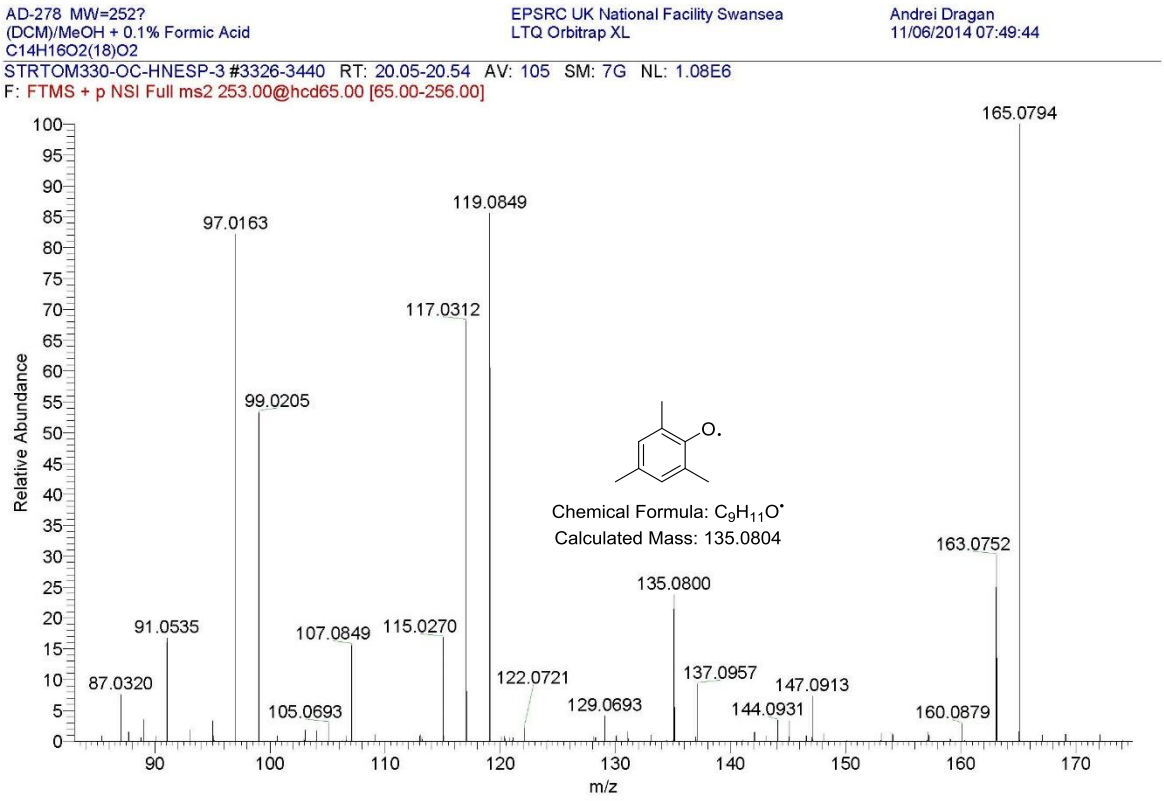


HRMS MS^2 analysis of $[M+H]^+$ ion at 253.1208, showing loss of $C_4H_5O_2^{\bullet}$ and $C_4H_5O^{18}O^{\bullet}$

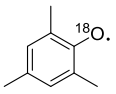




HRMS MS^2 analysis of [M+H]$^+$ ion at 253.1208, showing no labeled ^{18}O attached to arene

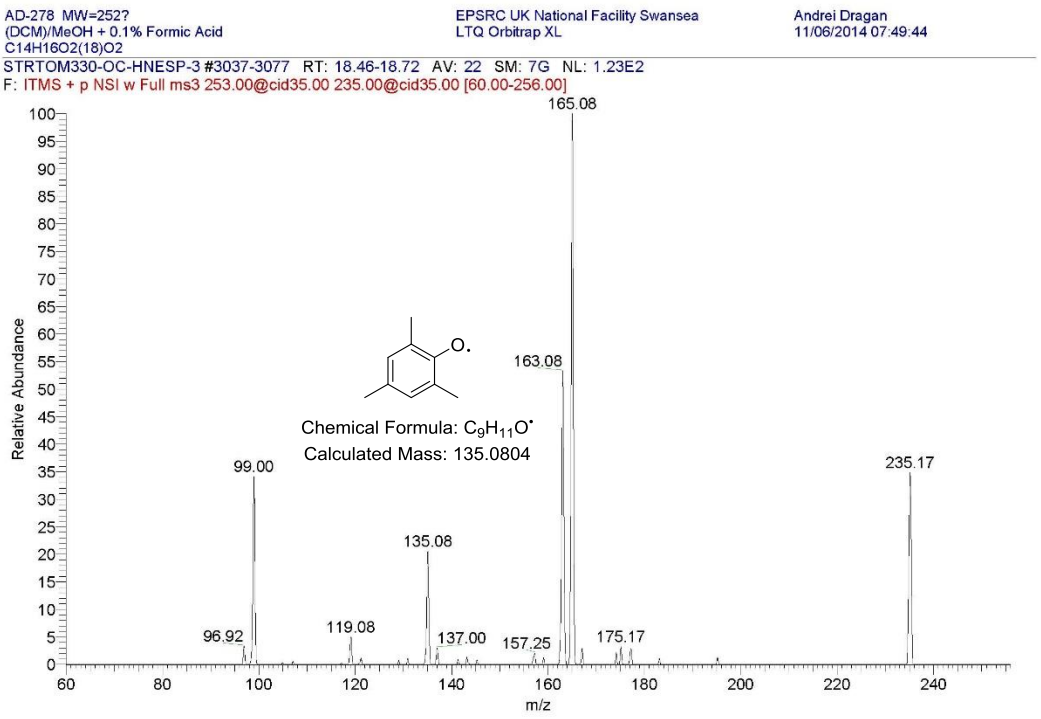


Note: The obtained value at 137.0957 did not fit the acceptable tolerance window for HRMS of ± 10.00 ppm. A theoretical isotope for the labeled species is shown below.



Chemical Formula: $C_9H_{11}{}^{18}O•$
Calculated Mass: 137.0852

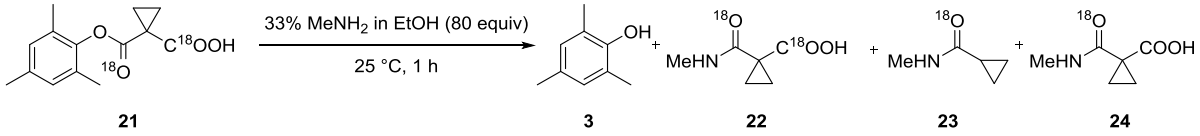
HRMS MS^3 analysis of $[M+H]^+$ ion at 253.1208 and ion at 235.17, showing no labeled ^{18}O attached to arene

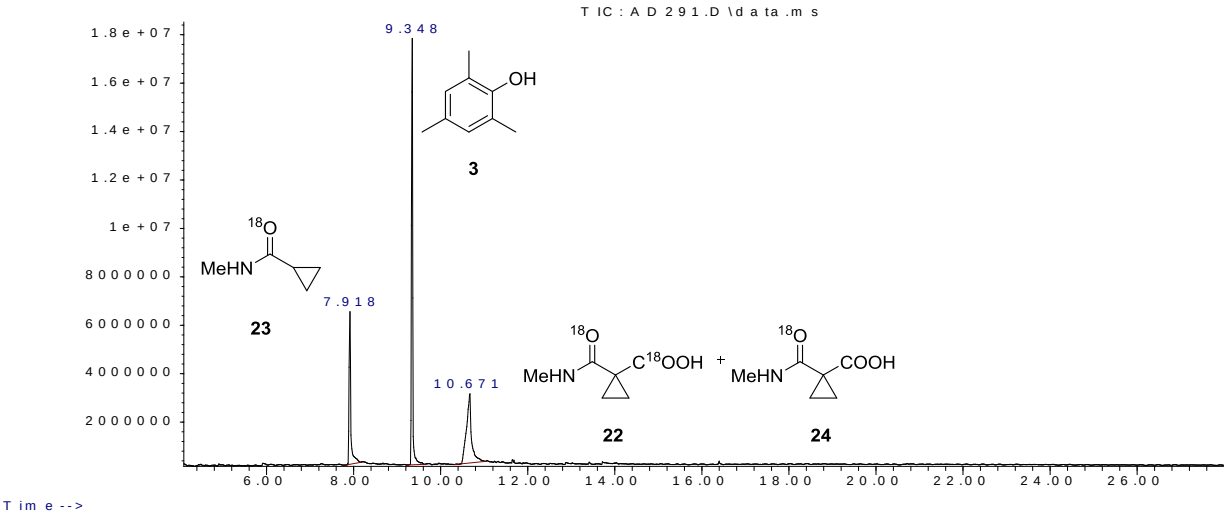


Note: Sensitivity was poor when using FTMS and a different method (ITMS) was used for MS^3 analysis, hence the accuracy of this method is based on only two decimal places.

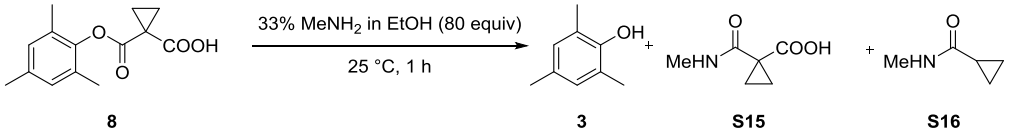
Cleavage of ester C—O bond using $MeNH_2$ followed by GC/LRMS (CI) analysis of crude

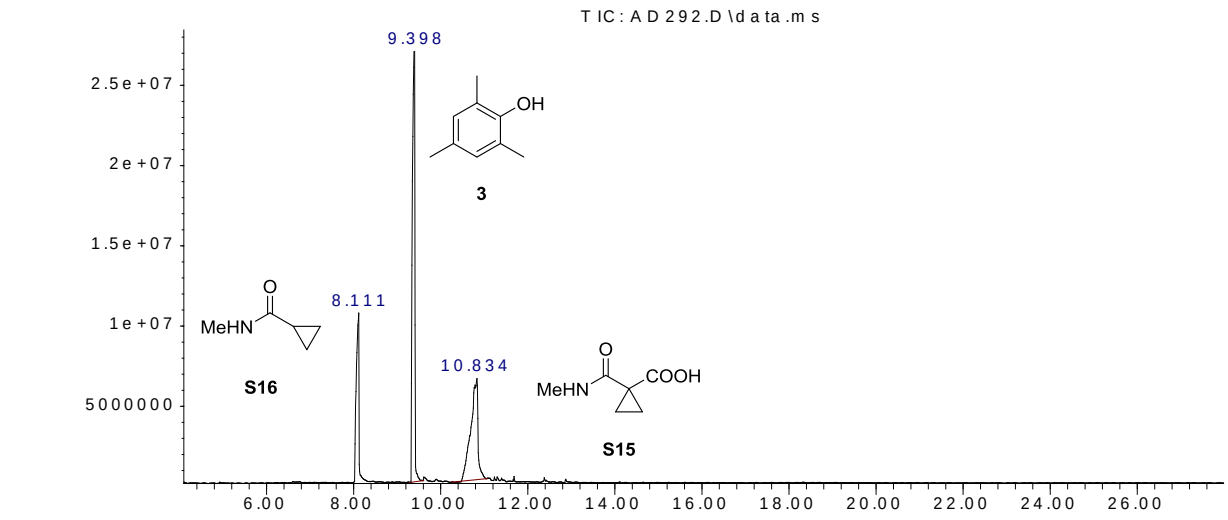
GC spectrum of crude reaction mixture after aminolysis of doubly ^{18}O labeled ester **21**



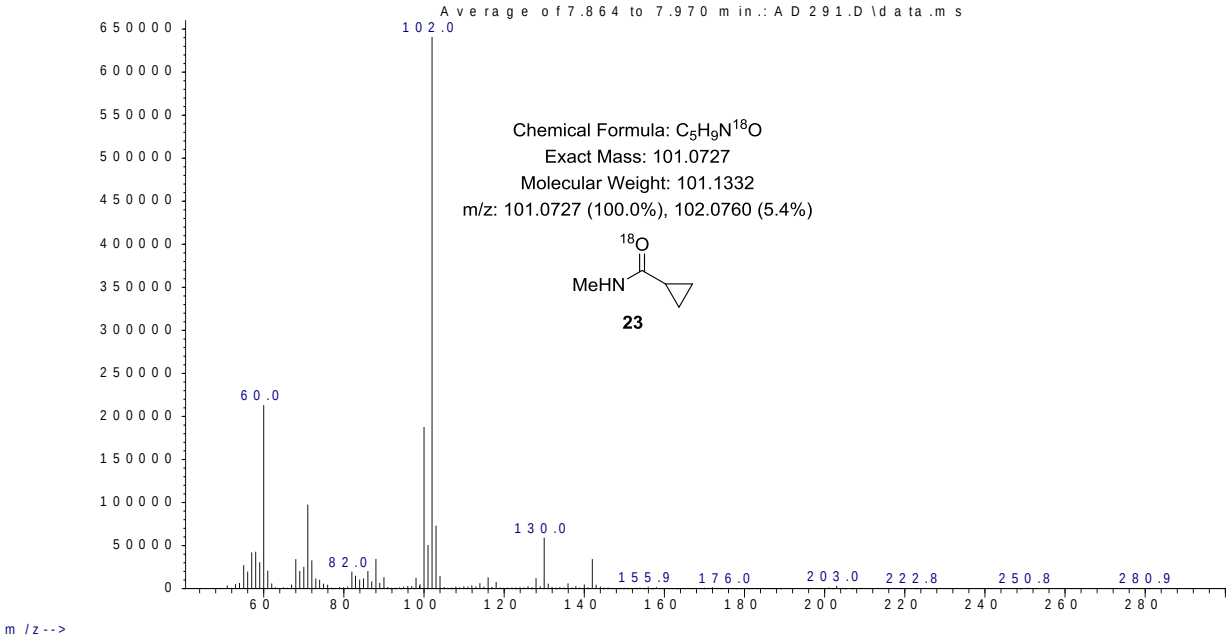


GC spectrum of crude reaction mixture after aminolysis of non-labeled ester **8**

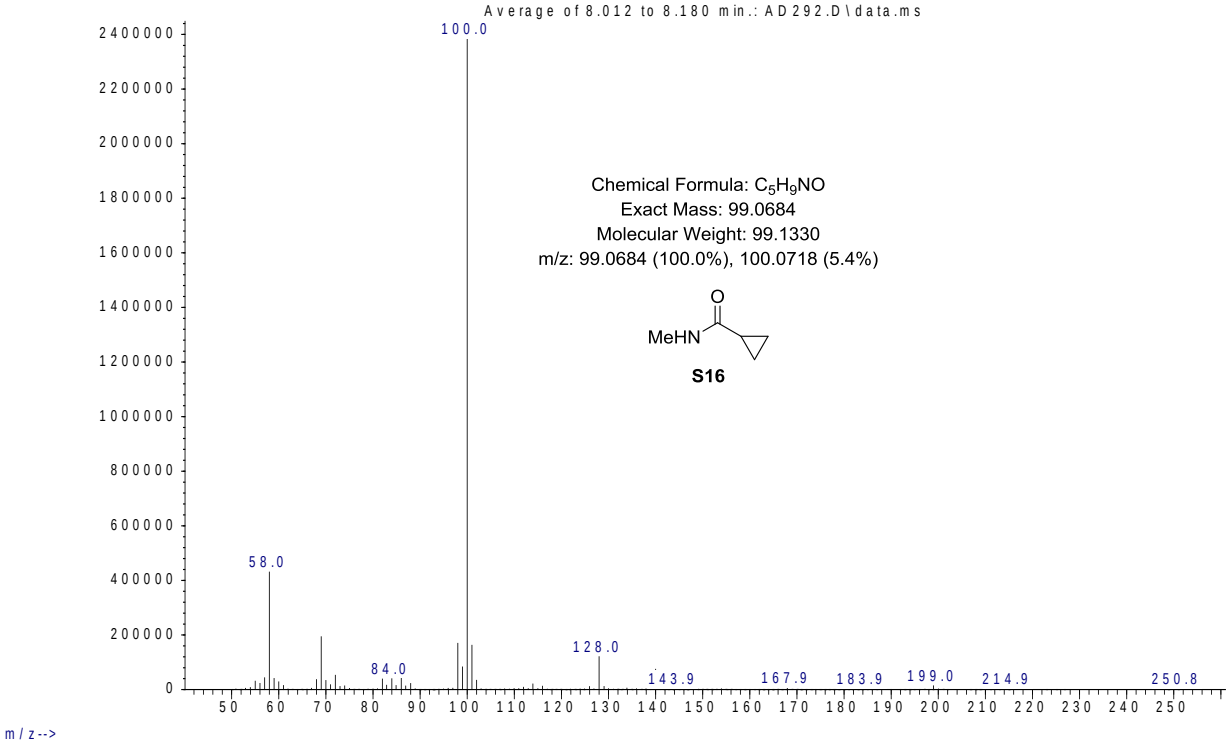




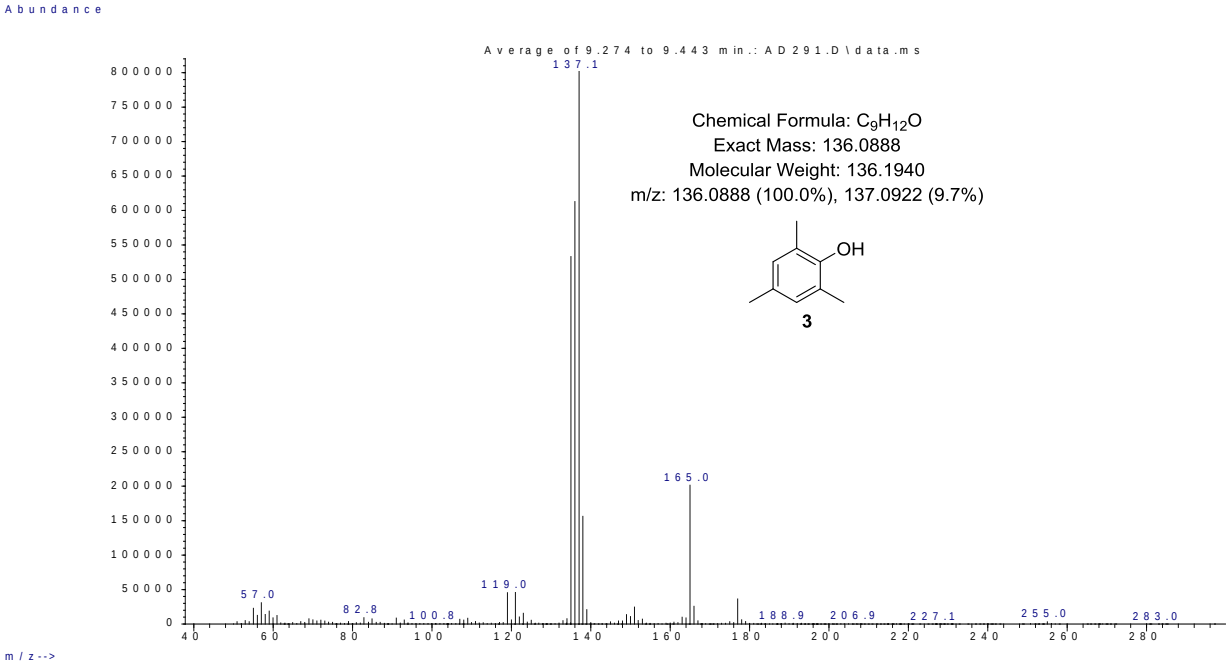
MS (CI) of GC peak at 7.918 min showing $[M+H]^+$ of ^{18}O labeled decarboxylated amide **23** upon cleavage of doubly ^{18}O labeled ester **21**



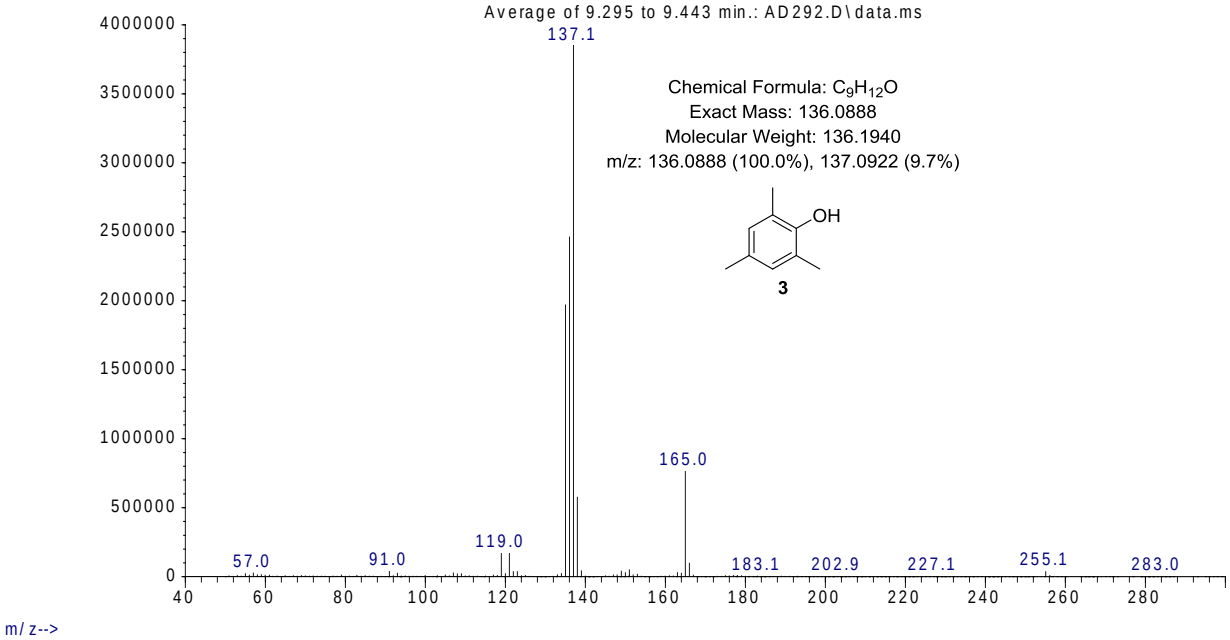
MS (CI) of GC peak at 8.111 min showing $[M+H]^+$ of decarboxylated amide **S16** upon cleavage of non-labeled ester **8**



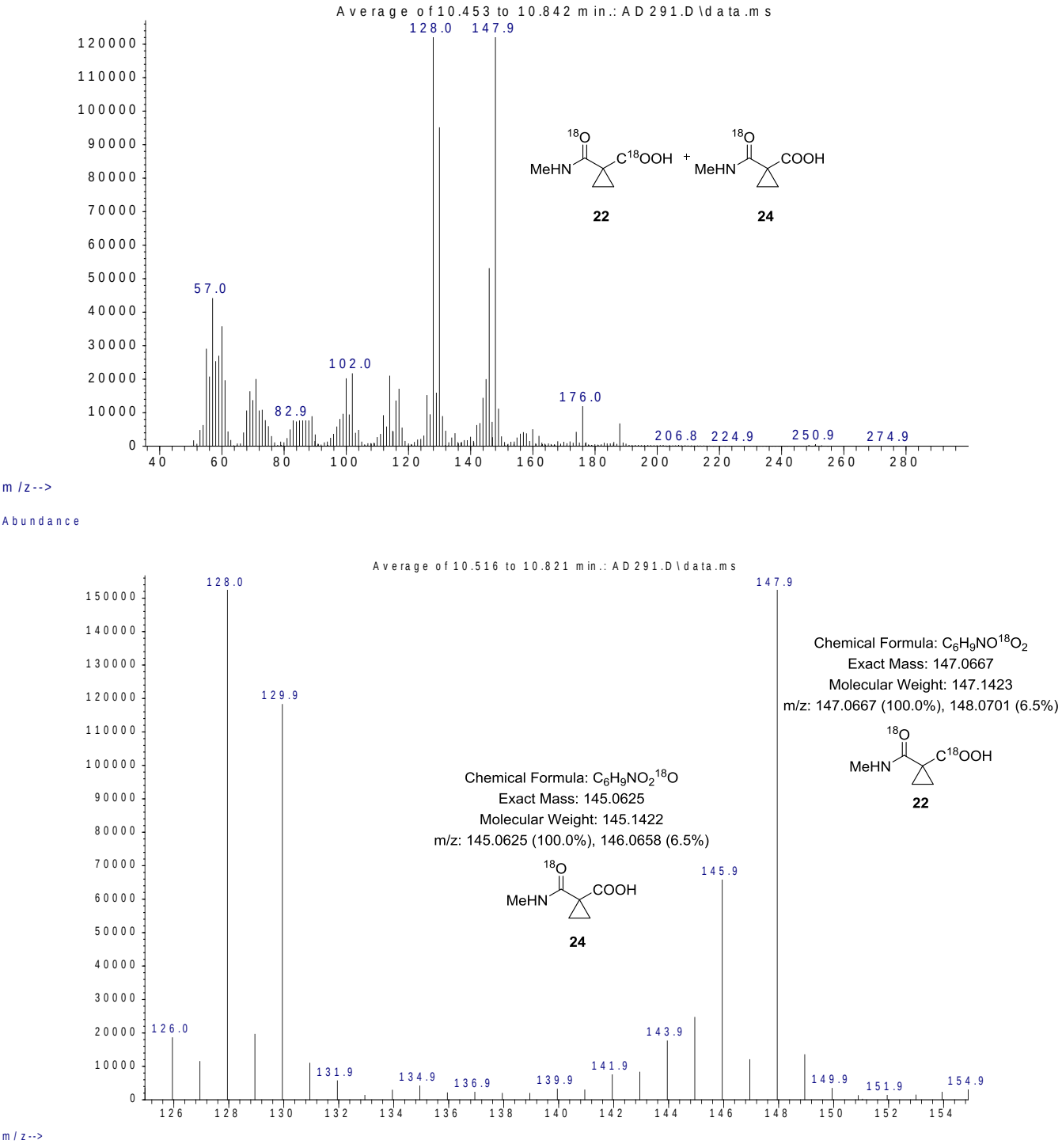
MS (CI) of GC peak at 9.348 min showing $[M+H]^+$ of phenol **3** upon cleavage of doubly ^{18}O labeled ester **21**



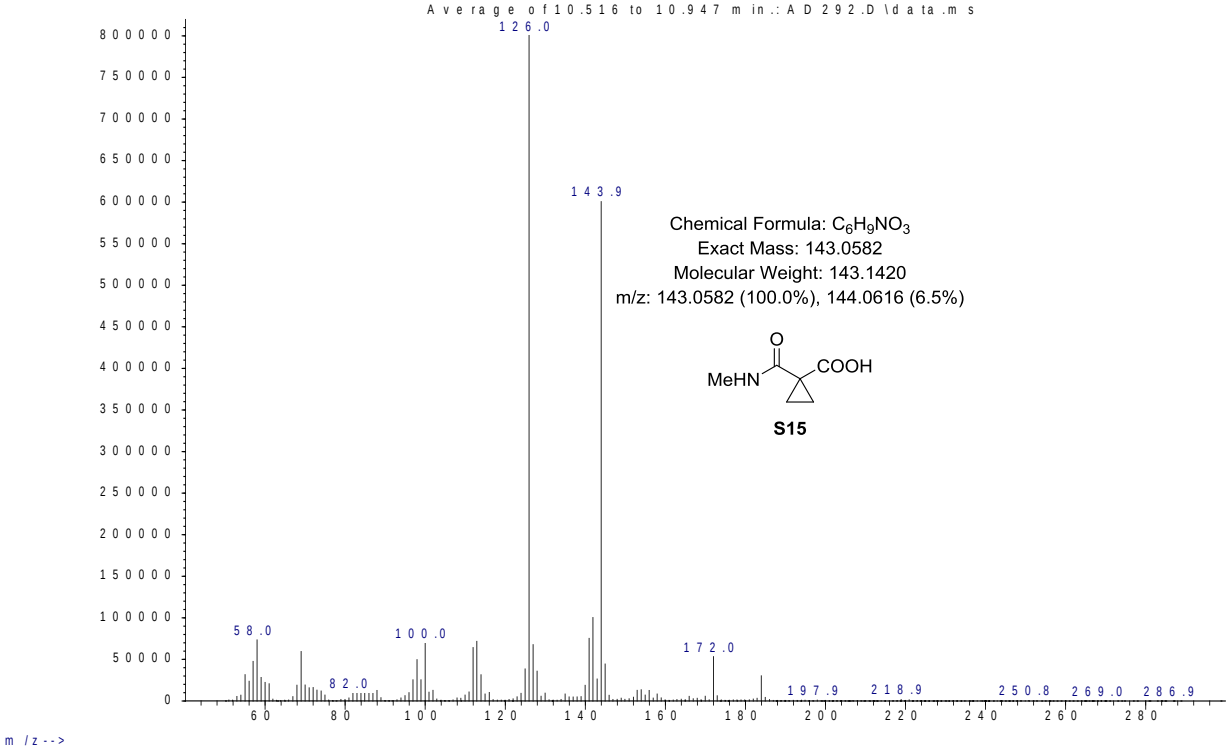
MS (CI) of GC peak at 9.398 min showing $[M+H]^+$ of phenol **3** upon cleavage of non-labeled ester **8**



MS (CI) of GC peak at 10.671 min showing $[M+H]^+$ of ^{18}O labeled amides **22** and **24** upon cleavage of doubly ^{18}O labeled ester **21**



MS (CI) of GC peak at 10.834 min showing $[M+H]^+$ of amide **S15** upon cleavage of non-labeled ester **8**



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