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Graphical Abstract

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Straightforward synthesis of functionalized (*E*)-3-acylacrylic acids

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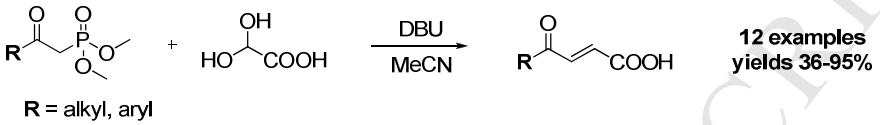

R = alkyl, aryl

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Straightforward synthesis of functionalized (*E*)-3-acylacrylic acids

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ABSTRACT

An experimentally simple, mild and straightforward synthetic route towards diversely functionalized (*E*)-3-acylacrylic acids is described, with Horner-Wadsworth-Emmons (HWE) reaction as the key step. The substrate scope and limitations of the HWE reaction were investigated with a range of β-ketophosphonates. Glyoxylic acid monohydrate was demonstrated to be fully compatible with the HWE reaction conditions, thus avoiding a troublesome hydrolysis of the corresponding 3-acylacrylates in the last step and providing a valuable synthetic shortcut.

1. Introduction

The (*E*)-3-acylacrylic moiety can be found in numerous natural products of diverse structural complexity and biological properties (Fig. 1).[1]

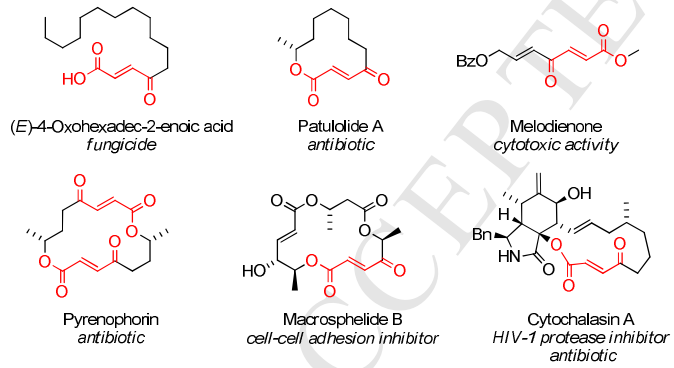
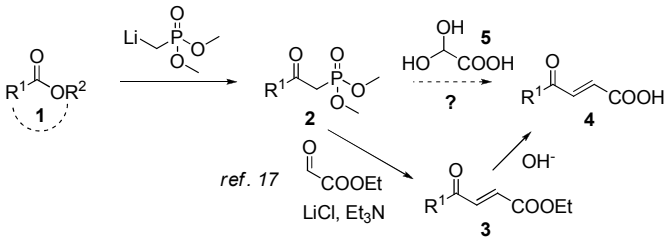


Fig. 1. Examples of natural compounds bearing 3-acylacrylic subunit.

Moreover, due to its dense functionality, compounds bearing the (*E*)-3-acylacrylic subunit exhibit interesting combinations of miscellaneous reactivities. These provide a multitude of synthetic options for further structural modifications, e.g. Michael and Michael-type additions,[2,3] Friedel-Crafts, Rauhut-Currier and Diels-Alder reactions,[4-6] decarboxylative couplings[7] or multicomponent reactions.[8] 3-Acylacrylic acids and esters have proven to be valuable synthetic precursors in syntheses of various heterocyclic derivatives[9] and compounds with therapeutic potential in general.[10] A broad applicability of 3-acylacrylic building blocks came hand in hand with the development of several complementary synthetic routes to access them. The classical methods are represented by either Friedel-Crafts acylation or condensation reactions of ketones with glyoxylic acid, targeting predominantly 3-aroylacrylic derivatives.[11] More advanced synthetic approaches towards 3-acylacrylates comprise e.g. multistep construction strategies,[12] isomerization reactions,[13] acylations with *trans*-vinylogous ester anion equivalent,[14] allylic oxidations,[15] oxidative opening of 2-substituted furans[16] and Horner-Wadsworth-Emmons (HWE) reaction of glyoxylic esters.[17] Due to our long-term interest in studies of crystallization-induced asymmetric transformations (CIAT) involving 3-acylacrylic acids as substrates,[3c,18] we looked for a general, straightforward and simple access to this class of compounds. A synthetic route relying on HWE reaction as a key step appeared to be attractive, since it starts from easily available esters of carboxylic acids **1** and allows for a very broad structural variability of the acyl chain (Scheme 1).



Scheme 1. Considered synthetic strategies towards 3-acylacrylic acids **4**

On the other hand, the necessity of a base-promoted hydrolysis in the final step could be regarded as a serious drawback since consideration of protection strategies might be

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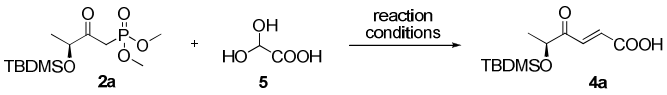
inevitable.[12c] Despite the highly reactive nature of 3-acylacrylates **3**, alkaline hydrolysis was reported to be applicable to simple and unfunctionalized 3-acylacrylate esters, providing the corresponding acids **4** in average yields.[15a,19] However, the hydrolysis protocols might turn incompatible with more sensitive substrates and, importantly, constitute an extra step towards the target compounds. Therefore we were intrigued by the possibility of performing HWE reactions directly with monohydrate of glyoxylic acid **5**, which would entail a simple, yet valuable synthetic shortcut (Scheme 1).

2. Results and discussion

As a model substrate for our initial investigations, we chose a readily available β-ketophosphonate **2a** (Table 1).[20]

Table 1. Reactivities of β-ketophosphonate **2a** and glyoxylic acid monohydrate **5** under different reaction conditions[a]



Entry	Reaction conditions	Conversion (%)[b]	Yield (%)[b]
1	2.6 equiv Et_3N, 1.0 equiv LiCl	36	32
2	2.6 equiv DBU, 1.0 equiv LiCl	65	61
3	2.6 equiv DBU	73	72
4	2.6 equiv DBU[c]	91	88

[a] General reaction conditions: 1.5 equiv **5** (0.3 M solution in MeCN), 0 °C, 30 min. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

[b] Determined by ^{1}H NMR analysis with internal standard

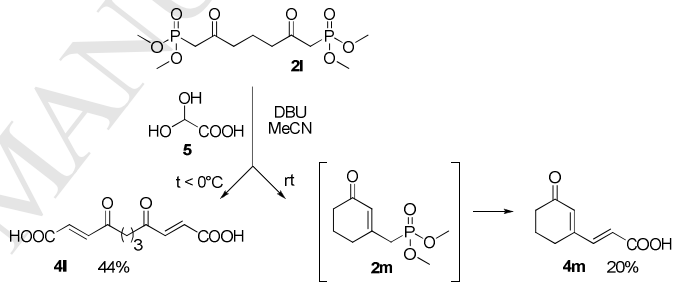
[c] A solution of **5** in MeCN was stored over 4Å molecular sieves for 24 h

Our brief screening of reaction conditions started with a protocol that had been successfully applied to esters of glyoxylic acid (entry 1).[17] We were pleased to find that despite using a free acid reagent **5**, the target 3-acylacrylic acid **4a** was formed in a yield of 32% within 30 minutes. Masamune and Roush have reported a significant acceleration of HWE reactions in the presence of DBU, presumably due to its increased basicity.[21] Indeed, application of DBU to our reaction system significantly improved reactivity of **2a** (entry 2). Although lithium cation is expected to increase the acidity of phosphonates *via* 1,3-dioxocomplexation,[21] we envisioned that under protic reaction conditions it might not be applicable (entry 3). With respect to the sensitive nature of 3-acylacrylates towards e.g. retro aldol and condensation reactions, we reduced water content in the reaction media by pre-drying a solution of **5** in MeCN over 4Å molecular sieves for a period of 24 hours. Apart from that, *in situ* generation of free glyoxylic acid was supposed to result in a more readily reacting system. Indeed, this procedure resulted in a faster conversion and a very good yield of acid **4a** (entry 4).

With the optimized conditions defined, applicability to a broader scope of phosphonate substrates was explored. For the purpose of our studies, a variety of diversely functionalized β-ketophosphonates **2b-m** was prepared (Table 2), utilizing a combination of slightly modified published protocols based on dimethyl methylphosphonate (DMMP).[22] In general, the target phosphonates were easily accessible and obtained in good yields. In agreement with the data published for related perfluoroalkylated β-ketophosphonates,[23] β-ketophosphonate **2k** (entry 11) was obtained as a mixture of oxo and enol tautomers in a ratio of 77:23, respectively, as determined by means of ^{1}H-NMR.

Next, reactivity of β-ketophosphonates **2b-m** in HWE reaction with a predried solution of glyoxylic acid monohydrate **5** was explored (Table 3). We were pleased to find that with the exception of **2k**, the investigated phosphonates were smoothly converted to the corresponding (*E*)-3-acylacrylic acids in modest to excellent yields of 36-95%. Importantly, due to mild reaction conditions, side chains decorated with a variety of functional groups were very well tolerated.

The observed unreactivity of phosphonate **2k** in the reaction system can be plausibly attributed to a strongly electron withdrawing nature of the perfluoropropyl substituent. The existence of **2k** as a mixture of oxo/enol tautomers is indicative of a relatively high stability and thus lowered nucleophilicity of the corresponding enolate, generated *in situ* upon deprotonation with DBU. As the most problematic turned out to be the sequence **1d→2d→4d**, providing rather unsatisfactory yields of 37% and 36%, respectively. Presumably due to increased reactivity of the methylene bridge, being additionally activated by the adjacent phenyl group, these compounds were more prone to side reactions. As anticipated, depending on the reaction conditions, diphosphonate **2l** can cyclize spontaneously to form phosphonate **2m** and thus serve as a precursor both for the acids **4l** and **4m** (Scheme 2).



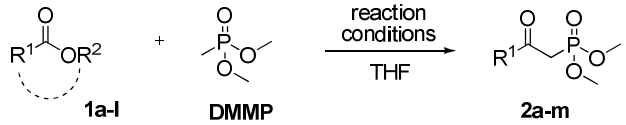
Scheme 2. HWE reaction of diphosphonate **2l** and glyoxylic acid monohydrate **5** under different temperature conditions

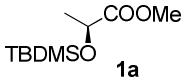
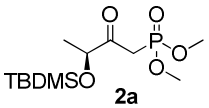
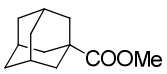
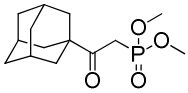
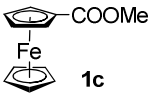
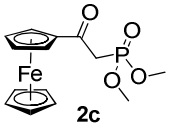
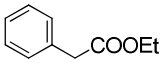
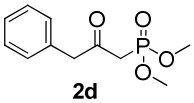
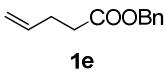
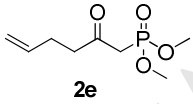
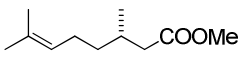
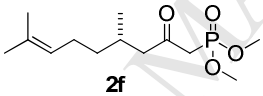
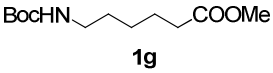
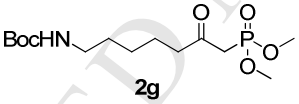
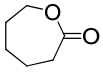
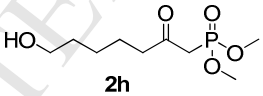
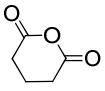
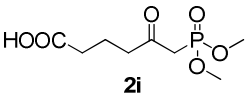
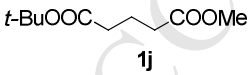
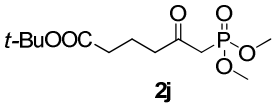
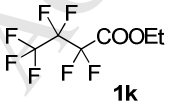
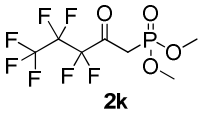
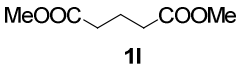
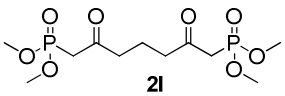
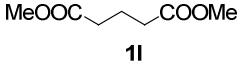
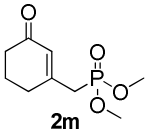
However, a careful control of the reaction temperature enables to obtain the diacid **4l** in an acceptable yield of 44% (Table 3, entry 12).

3. Conclusion

In summary, we have described a simple and straightforward synthetic route leading to diversely functionalized (*E*)-3-acylacrylic acids as synthetically versatile building blocks. The scope and limitation of the HWE reaction were studied with a range of substrates. We have demonstrated that glyoxylic acid monohydrate is fully compatible with the HWE reaction conditions, thus sparing a troublesome hydrolysis of the corresponding 3-acylacrylates in the last step. We are currently exploring applicability of this synthetic method to the preparation of ω-substituted fytoceramide derivatives.

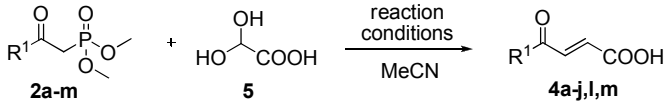
Table 2. Synthesis of β-ketophosphonates **2a-m**

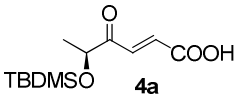
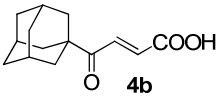
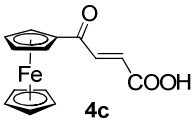
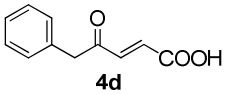
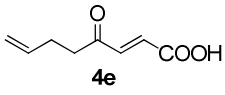
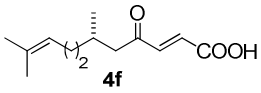
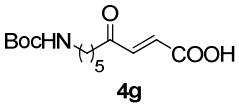
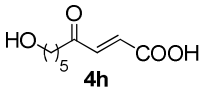
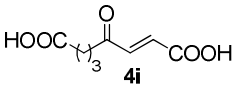
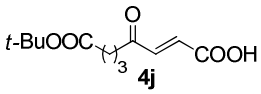
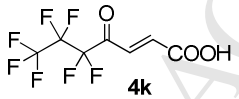
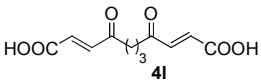
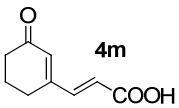


Entry	Ester **1**	Phosphonate **2**	Reaction conditions	Yield (%)[a]
1	 **1a**	 **2a**	2.5 equiv DMMP, 2.2 equiv *n*-BuLi -80 °C, 2 h	83
2	 **1b**	 **2b**	1.3 equiv DMMP, 2.3 equiv LDA -80 – 0 °C, 3 h	97
3	 **1c**	 **2c**	2.3 equiv DMMP, 3.5 equiv LDA 0 °C, 10 min	96
4	 **1d**	 **2d**	3.0 equiv DMMP, 3.0 equiv *n*-BuLi -80 °C, 1.5 h	37
5	 **1e**	 **2e**	2.3 equiv DMMP, 3.1 equiv LDA 0 °C, 1 h	86
6	 **1f**	 **2f**	3.0 equiv DMMP, 2.8 equiv *n*-BuLi -80 °C, 1.5 h	89
7	 **1g**	 **2g**	3.0 equiv DMMP, 2.9 equiv *n*-BuLi -80 °C, 1 h	88
8	 **1h**	 **2h**	2.0 equiv DMMP, 3.1 equiv LDA 0 °C, 5 h	88[b]
9	 **1i**	 **2i**	2.5 equiv DMMP, 2.5 equiv *n*-BuLi -80 – 0 °C, 30 min	57[c]
10	 **1j**	 **2j**	2.5 equiv DMMP, 2.5 equiv *n*-BuLi -80 °C, 2 h	72
11	 **1k**	 **2k**	0.8 equiv DMMP, 1.0 equiv LDA -80 – 0 °C, 1.5 h	70[d]
12	 **1l**	 **2l**	4.4 equiv DMMP, 4.4 equiv *n*-BuLi, -80 °C, 30 min	54
13	 **1l**	 **2m**	4 equiv DMMP, 4 equiv *n*-BuLi -80 °C – rt, overnight	89

[a] Yield of isolated product. [b] The product contains 8 mol% of **1h**. [c] The product contains 16 mol% of glutaric acid. [d] Yield based on DMMP; a mixture of oxo and enol tautomers 77:23, respectively.

Table 3. HWE reaction of β-ketophosphonates **2a-m** and glyoxylic acid monohydrate **5**[a]



Entry	Acid **4**	Reaction conditions	Yield (%)
1	 **4a**	1.5 equiv **5**, 2.6 equiv DBU, 0 °C, 1.5 h	81
2	 **4b**	2 equiv **5**, 4 equiv DBU, rt, 2.5 h	85
3	 **4c**	2 equiv **5**, 4 equiv DBU, rt, 20 min	95
4	 **4d**	1.8 equiv **5**, 4 equiv DBU, rt, 2 h	36
5	 **4e**	2 equiv **5**, 4 equiv DBU, 0 °C - rt, 1 h	55
6	 **4f**	2 equiv **5**, 4 equiv DBU, -20 °C, 1 h	93
7	 **4g**	2 equiv **5**, 2.5 equiv DBU, rt, 3h	55
8	 **4h**	2 equiv **5**, 4 equiv DBU, 0 °C - rt, 15 min	57
9	 **4i**	2 equiv **5**, 5 equiv DBU, 0 °C - rt, 1.5 h	62
10	 **4j**	2 equiv **5**, 4 equiv DBU, -20 °C, 3.5 h	65
11	 **4k**	2 equiv **5**, 4 equiv DBU, rt, no reaction; 50 °C - decomposition	0
12	 **4l**	3 equiv **5**, 6 equiv DBU, -40 °C, 1.5 h	44
13	 **4m**	2 equiv **5**, 4 equiv DBU, rt, 2 h	40

[a] A solution of **5** in MeCN was stored over 4Å molecular sieves for 24 h

4. Experimental section

4.1. General information

Melting points were measured on BÜCHI Melting Point B-540 and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded either on a Varian VXR-300 (300 and 75 MHz, respectively) or a Varian INOVA 600 spetrometer (600 and 151 MHz, respectively), with TMS as an internal standard. Chemical shifts are reported in parts per million (ppm). Optical rotations were measured on a JASCO P-1020 or a POLAR L-mP (IBZ Messtechnik) polarimeter (concentration *c* is given as g/100 mL). Orbitrap Velos PRO, Thermo Scientific, was used for HRMS measurements. Column chromatography was carried out on SiO_2 (silica gel Normasil 60 μm, 40-63, VWR Chemicals).

*4.2. (S)-Dimethyl 3-(tert-butyldimethylsilyloxy)-2-oxobutylphosphonate (**2a**)*

A flask was charged with dry THF (9 ml) and dimethyl methylphosphonate (1.05 ml, 2.5 equiv, 9.85 mmol) under an argon atmosphere. The solution was stirred and cooled to -80 °C, and *n*-BuLi (2.5M in hexanes, 3.5 ml, 8.75 mmol, 2.2 equiv) was added dropwise. The resulting mixture was stirred for 40 min at -80 °C and successively a solution of ester **1a** (860 mg, 3.94 mmol) in dry THF (3 ml) was added. The mixture was stirred at -80 °C for 2 h and poured into saturated aqueous NH_4Cl (15 ml), the aqueous layer was extracted with ethyl acetate (3 x 25 ml), and the combined organics were dried over Na_2SO_4, filtered and concentrated to yield a colurless oil. The crude product contained residual DMMP, which was removed by Kugelrohr distillation (65 °C, 3 h, 6.10^{-1} Torr) to give 1.02 g (83%) of phosphonate **2a** as a colourless oil; $[\alpha]_D^{25}$ = +14.8 (c 2.19, EtOH), lit.[20b]: +11.7 (c 1.42, EtOH, 20 °C); **^{1}H NMR** ($CDCl_3$): δ = 0.10 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.32 (d, J = 6.9 Hz, 3H), 3.31 (m, 2H), 3.79 (d, J_{HP} = 11.1 Hz, 3H), 3.80 (d, J_{HP} = 11.1 Hz, 3H), 4.24 (q, J = 6.9 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ = -4.9, -4.5, 18.1, 20.3, 25.8, 34.8 (d, J_{CP} = 134.2 Hz), 52.9 (d, J_{CP} = 6.3 Hz), 53.0 (d, J_{CP} = 6.3 Hz), 74.9 (d, J_{CP} = 3.0 Hz), 205.3 (d, J_{CP} = 6.8 Hz); HRMS calcd for $C_{12}H_{27}O_5PSi$ $(M+H)^+$: 311.1443; found: 311.1375.

*4.3. Dimethyl 2-(1-adamantyl)-2-oxoethylphosphonate (**2b**)*[24]

Ester **1b** (1.80 g, 9.26 mmol) was charged into a three-necked flask, the flask was closed and evacuated and refilled with argon thrice before dry THF (10 ml) and dimethyl methylphosphonate (1.29 ml, 1.3 equiv, 12.0 mmol) were added. The solution was stirred and cooled to -80 °C, and a freshly generated solution of LDA (1.64M in THF, 13 ml, 21.3 mmol, 2.3 equiv) was added dropwise. The resulting mixture was stirred for 15 min at -80 °C, giving a yellow homogeneous solution which was successively placed in an ice bath and stirred for additional 3 h. The mixture was quenched with 1M H_2SO_4 (21.3 ml, 2.3 equiv) added dropwise, the aqueous layer was extracted with ethyl acetate (4 x 50 ml), the combined organics were washed with a half-diluted brine (70 ml), the brine solution was once reextracted with ethyl acetate (30 ml), the organics were dried over Na_2SO_4, filtered and concentrated. The crude product was dried under high vacuum to give 2.57 g (97%) of phosphonate **2b** as pale yellow crystals; mp 44–46 °C; **^{1}H NMR** ($CDCl_3$): δ = 1.67-1.69 (bs, 3H), 1.74-1.76 (bs, 3H), 1.82 (m, 6H), 2.07 (bs, 3H), 3.15 (d, J_{HP} = 21.6 Hz, 2H), 3.79 (d, J_{HP} = 10.8 Hz, 6H); **^{13}C NMR** ($CDCl_3$): δ = 27.7, 34.4 (d, J_{CP} = 135.7 Hz), 36.3, 37.8, 47.5 (d, J_{CP} = 3.6 Hz), 52.9 (d, J_{CP} = 6.5 Hz), 207.0 (d, J_{CP} = 7.1 Hz); HRMS calcd for $C_{14}H_{23}O_4P$ $(M+H)^+$: 287.1407; found: 287.1408.

*4.4. Dimethyl 2-ferrocenyl-2-oxoethylphosphonate (**2c**)*

Ester **1c** (0.59 g, 2.43 mmol) was charged into a three-necked flask, the flask was closed and evacuated and refilled with argon thrice before dry THF (4 ml) and dimethyl methylphosphonate (0.60 ml, 2.3 equiv, 5.6 mmol) were added. The solution was stirred and cooled to 0 °C (ice bath), and a freshly generated solution of LDA (1.42M in THF, 6 ml, 8.5 mmol, 3.5 equiv) was added dropwise. The resulting mixture was stirred for 10 min at 0 °C, quenched with 1M H_2SO_4 (8.0 ml, 3.3 equiv) added dropwise, the aqueous layer was extracted with ethyl acetate (3 x 25 ml), the combined organics were washed with brine (15 ml), dried over Na_2SO_4, filtered and concentrated to give an oily residue. The crude product contained residual DMMP, which was removed by Kugelrohr distillation (50 °C, 2 h, 6.10^{-1} Torr) to give 0.79 g (96%) of phosphonate **2c** as an orange-purple oil; **^{1}H NMR** ($CDCl_3$): δ = 3.40 (d, J_{HP} = 21.9 Hz, 2H), 3.81 (d, J_{HP} = 11.4 Hz, 6H), 4.25 (s, 5H), 4.58 (s, 2H), 4.83 (s, 2H); **^{13}C NMR** ($CDCl_3$): δ = 38.6 (d, J_{CP} = 132.7 Hz), 53.1 (d, J_{CP} = 6.5 Hz), 70.1, 70.2, 73.2, 78.8 (d, J_{CP} = 3.8 Hz), 195.2 (d, J_{CP} = 6.3 Hz); HRMS calcd for $C_{14}H_{17}FeO_4P$ $(M+H)^+$: 337.0287; found: 337.0279.

*4.5. Dimethyl 2-oxo-3-phenylpropylphosphonate (**2d**)*

Compound **2d** was prepared by the same procedure as that for **2a**, under the reaction conditions specified in Table 2 (entry 4), as a pale yellow oil (37%); **^{1}H NMR** ($CDCl_3$): δ = 3.11 (d, J_{HP} = 22.5 Hz, 2H), 3.78 (d, J_{HP} = 11.1 Hz, 6H), 3.89 (s, 2H), 7.23-7.20 (m, 2H), 7.36-7.30 (m, 3H); **^{13}C NMR** ($CDCl_3$): δ = 40.2 (d, J_{CP} = 127.7 Hz), 50.8 (d, J_{CP} = 1.4 Hz), 53.1 (d, J_{CP} = 6.4 Hz), 127.3, 128.8, 129.6, 133.3, 199.5 (d, J_{CP} = 6.1 Hz); HRMS calcd for $C_{11}H_{15}O_4P$ $(M+H)^+$: 243.0786; found: 243.0804.

*4.6. Dimethyl 2-oxohex-5-enylphosphonate (**2e**)*[25]

Compound **2e** was prepared by the same procedure as that for **2c**, under the reaction conditions specified in Table 2 (entry 5; extraction with CH_2Cl_2), as a colourless oil (86%); **^{1}H NMR** ($CDCl_3$): δ = 2.30-2.40 (m, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 3.10 (d, J_{HP} = 22.8 Hz, 2H), 3.79 (d, J_{HP} = 11.1 Hz, 6H), 4.97-5.09 (m, 2H), 5.80 (m, 1H); **^{13}C NMR** ($CDCl_3$): δ = 27.4, 41.4 (d, J_{CP} = 127.5 Hz), 43.2 (d, J_{CP} = 1.3 Hz), 53.1 (d, J_{CP} = 6.5 Hz), 115.6, 136.3, 201.1 (d, J_{CP} = 6.2 Hz).

*4.7. (S)-Dimethyl 4,8-dimethyl-2-oxonon-7-enylphosphonate (**2f**)*

Compound **2f** was prepared by the same procedure as that for **2a**, under the reaction conditions specified in Table 2 (entry 6); purified by flash chromatography on silica gel (EA/hexanes = 1/1); colourless oil (89%); $[\alpha]_D^{24}$ = -5.6 (*c* 2.25, $CHCl_3$), lit.[26] for (*R*)-enantiomer: +5.05 (c 1.00, $CHCl_3$, 24 °C); **^{1}H NMR** ($CDCl_3$): δ = 0.91 (d, *J* = 6.6 Hz, 3H), 1.23-1.38 (m, 2H), 1.60 (s, 3H), 1.68 (s, 3H), 1.95-2.01 (m, 3H), 2.43 (dd, *J* = 7.8, 16.8 Hz, 1H), 2.60 (dd, *J* = 5.4, 17.1 Hz, 1H), 3.07 (m, 2H), 3.79 (d, J_{HP} = 11.1 Hz, 6H), 5.10 (t, *J* = 7.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ = 17.6, 19.5, 25.3, 25.6, 28.5, 36.6, 41.5 (d, J_{CP} = 128 Hz), 51.4 (d, J_{CP} = 1.5 Hz), 52.9 (d, J_{CP} = 6.5 Hz), 124.2, 131.5, 194.7, 201.6 (d, J_{CP} = 6.2 Hz).

*4.8. tert-Butyl 7-(dimethoxyphosphoryl)-6-oxoheptylcarbamate (**2g**)*[27]

Compound **2g** was prepared by the same procedure as that for **2a**, under the reaction conditions specified in Table 2 (entry 7), as a pale yellow oil (88%); **^{1}H NMR** ($CDCl_3$): δ = 1.25-1.36 (m, 2H), 1.43 (s, 9H), 1.44-1.50 (m, 2H), 1.54-1.64 (m, 2H), 2.61 (t, *J* = 7.2 Hz, 2H), 3.07 (d, J_{HP} = 22.5 Hz, 2H), 3.09 (t, *J* = 7.2 Hz, 2H), 3.79 (d, J_{HP} = 11.1 Hz, 6H), 4.54 (bs, 1H); **^{13}C-NMR** ($CDCl_3$): δ = 22.8, 25.9, 28.3, 29.7, 40.2, 41.2 (d, J_{CP} = 127.4 Hz), 43.8, 52.9 (d, J_{CP} = 6.4 Hz), 78.9, 155.9, 201.6 (d, J_{CP} = 6.0 Hz).

*4.9. Dimethyl 7-hydroxy-2-oxoheptylphosphonate (**2h**)*[28]

Compound **2h** was prepared by the same procedure as that for **2c**, under the reaction conditions specified in Table 2 (entry 8; extraction with CH_2Cl_2), as a yellow oil (88%); the product contains 8 mol% of **1h**; **^{1}H NMR** ($CDCl_3$): δ = 1.33-1.44 (m, 2H), 1.53-1.68 (m, 4H), 1.75 (s, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 3.08 (d, J_{HP} = 22.8 Hz, 2H), 3.63 (t, *J* = 6.3 Hz, 2H), 3.79 (d, J_{HP} = 11.1 Hz, 6H); **^{13}C NMR** ($CDCl_3$): δ = 23.1, 25.1, 32.3, 41.3 (d, J_{CP} = 127.7 Hz), 44.1 (d, J_{CP} = 1.5 Hz), 53.1 (d, J_{CP} = 6.5 Hz), 62.4, 202.1 (d, J_{CP} = 6.2 Hz).

*4.10. 6-(Dimethoxyphosphoryl)-5-oxohexanoic acid (**2i**)*[22a]

Compound **2i** was prepared by the same procedure as that for **2b**, under the reaction conditions specified in Table 2 (entry 9); residual DMMP was removed by Kugelrohr distillation (70 °C, 5 h, 6.10^{-1} Torr); pale yellow oil (57%); the product contains 16 mol% of glutaric acid; **^{1}H NMR** ($CDCl_3$): δ = 1.91 (m , 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 3.15 (d, J_{HP} = 22.8 Hz, 2H), 3.80 (d, J_{HP} = 11.4 Hz, 6H), 11.29 (s, 1H); **^{13}C NMR** ($CDCl_3$): δ = 18.3, 32.6, 41.2 (d, J_{CP} = 128.2 Hz), 42.8 (d, J_{CP} = 1.6 Hz), 53.2 (d, J_{CP} = 6.5 Hz), 177.5, 201.0 (d, J_{CP} = 6.2 Hz).

*4.11. tert-Butyl 6-(dimethoxyphosphoryl)-5-oxohexanoate (**2j**)*[22a]

Compound **2j** was prepared by the same procedure as that for **2a**, under the reaction conditions specified in Table 2 (entry 10); additionally purified by flash chromatography on silica gel (EA); colourless oil (72%); **^{1}H NMR** ($CDCl_3$): δ = 1.44 (s, 9H), 1.86 (m, 2H), 2.25 (t, *J* = 7.2 Hz, 2H), 2.68 (t, *J* = 7.2 Hz), 3.08 (d, J_{HP} = 22.5 Hz, 2H), 3.79 (d, J_{HP} = 11.1 Hz, 6H); **^{13}C NMR** ($CDCl_3$): δ = 18.7, 28.0, 34.1, 41.2 (d, J_{CP} = 127.7 Hz), 42.9 (d, J_{CP} = 1.3 Hz), 53.0 (d, J_{CP} = 6.4 Hz), 80.2, 172.3, 201.0 (d, J_{CP} = 6.2 Hz).

*4.12. Dimethyl 3,3,4,4,5,5,5-heptafluoro-2-oxopentylphosphonate (**2k**)*

A flask was charged with a freshly generated solution of LDA (0.23M in THF, 5 ml, 1.15 mmol, 1.2 equiv) under an argon atmosphere. The solution was stirred and cooled to -80 °C, and dimethyl methylphosphonate (100 µl, 0.94 mmol) dissolved in dry THF (3 ml) was added. The resulting mixture was stirred for 1 h at -80 °C and successively a solution of ester **1k** (200 µl, 1.15 mmol) in dry THF (2.5 ml) was added. The mixture was stirred for 1 h at -80 °C, afterwards allowed to warm to 0 °C, stirred for additional 30 min and then concentrated (20 °C, 10 mBar). The residue was treated with 10% aq HCl (1 ml) and stirred for 30 min, the mixture was quenched with water (1 ml), the aqueous layer was extracted with CH_2Cl_2 (3 x 10 ml), the organics were dried over Na_2SO_4, filtered and concentrated to give 0.21 g (70%) of phosphonate **2k** as a yellow oil containing a mixture of oxo and enol tautomers in a ratio of 77:23, respectively; **^{1}H NMR** ($CDCl_3$) *oxo tautomer*: δ = 3.47 (d, J_{HP} = 22.2 Hz, 2H), 3.86 (d, J_{HP} = 11.4 Hz, 6H); *enol tautomer*: δ = 3.78 (d, J_{HP} = 11.7 Hz, 6H), 5.04 (d, J_{HP} = 8.1 Hz, 1H); HRMS calcd for $C_7H_8F_7O_4P$ $(M+H)^+$: 321.0126; found: 321.0105.

*4.13. Tetramethyl 2,6-dioxoheptane-1,7-diyldiphosphonate (**2l**)*[22c]

Compound **2l** was prepared by the same procedure as that for **2a**, under the reaction conditions specified in Table 2 (entry 12; quench with 1M H_2SO_4, extraction with CH_2Cl_2), as a colourless oil (54%); **^{1}H NMR** ($CDCl_3$): δ = 1.87 (quintet, *J* = 6.9 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 4H), 3.09 (d, J_{HP} = 22.5 Hz, 4H), 3.79 (d, J_{HP} = 11.4 Hz, 12H); **^{13}C NMR** ($CDCl_3$): δ = 17.1, 41.3 (d, J_{CP} = 127.7 Hz), 42.6 (d, J_{CP} = 1.5 Hz), 53.1 (d, J_{CP} = 6.5 Hz), 201.3 (d,

J_{CP} = 6.2 Hz); HRMS calcd for $C_{11}H_{22}O_8P_2$ $(M+H)^+$: 345.0868; found: 345.0812.

*4.14. Dimethyl (3-oxocyclohex-1-enyl)methylphosphonate (**2m**)[22c]*

Compound **2m** was prepared by the same procedure as that for **2a**, under the reaction conditions specified in Table 2 (entry 13; extraction with CH_2Cl_2); purified by flash chromatography on silicagel (EA) and afterwards by Kugelrohr distillation (80 °C, 3 h, 6.10^{-1} Torr); pale yellow oil (89%); **^{1}H NMR** ($CDCl_3$): δ = 2.03 (m, 2H), 2.39 (m, 2H), 2.48 (m, 2H), 2.78 (dd, *J* = 0.6 Hz, J_{HP} = 23.4 Hz, 2H), 3.77 (d, J_{HP} = 10.8 Hz, 6H), 5.98 (d, *J* = 4.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ = 22.6, 30.4 (d, J_{CP} = 2.7 Hz), 35.2 (d, J_{CP} = 134.7 Hz), 36.9, 53.1 (d, J_{CP} = 6.7 Hz), 129.5 (d, J_{CP} = 10.9 Hz), 155.7 (d, J_{CP} = 10.8 Hz), 199.1 (d, J_{CP} = 3.2 Hz); HRMS calcd for $C_9H_{15}O_4P$ $(M+H)^+$: 219.0786; found: 219.0824.

*4.15. (S,E)-5-(tert-Butyldimethylsilyloxy)-4-oxohex-2-enoic acid (**4a**)*

A flask was charged with β-ketophosphonate **2a** (0.32 g, 1.03 mmol) and 0.33M solution of **5** in MeCN (4.7 ml, 1.55 mmol, 1.5 equiv), stored for 24 h over 4Å molecular sieves, was added under an argon atmosphere. The mixture was stirred and cooled to 0 °C (ice bath), DBU (0.40 ml, 2.68 mmol, 2.6 equiv) was added dropwise over a period of 30 min. The solution was stirred for an additional 1 h at the same temperature. The mixture was quenched with 1M H_2SO_4 (2.3 ml, 2.2 equiv), the aqueous layer was extracted with ethyl acetate (3 x 30 ml), the combined organics were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (EA/hexanes = 3/7 + 0.5% AcOH) to give 0.22 g (81%) of acid **4a** as a yellow oil; $[\alpha]_D^{25}$ = -17.2 (*c* 2.5, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$): δ = 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.34 (d, *J* = 6.9 Hz, 3H), 4.34 (q, *J* = 6.9 Hz, 1H), 6.80 (d, *J* = 15.6 Hz, 1H), 7.64 (d, *J* = 15.6 Hz, 1H); **^{13}C NMR:** ($CDCl_3$): δ = -4.9, -4.6, 18.2, 20.7, 25.8, 74.6, 131.0, 136.9, 170.5, 201.3; HRMS calcd for $C_{12}H_{22}O_4Si$ $(M+H)^+$: 259.1365; found: 259.1403.

*4.16. (E)-4-(1-Adamantyl)-4-oxobut-2-enoic acid (**4b**)[29]*

Compound **4b** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 2); 0.75M solution of **5** in MeCN was used; the product precipitated upon quenching with 1M H_2SO_4; yellow powder (85%); mp 193–195 °C; **^{1}H NMR** ($CDCl_3$): δ =1.69-1.84 (m, 12H), 2.09 (bs, 3H), 6.75 (d, *J* = 15.6 Hz, 1H), 7.62 (d, *J* = 15.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ = 27.6, 36.3, 37.3, 46.0, 130.1, 137.2, 170.8, 203.1; HRMS calcd for $C_{14}H_{18}O_3$ $(M+H)^+$: 235.1334; found: 235.1350.

*4.17. (E)-4-Ferrocenyl-4-oxobut-2-enoic acid (**4c**)*

Compound **4c** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 3); 1.0M solution of **5** in MeCN was used; purple crystals (95%); mp 174–174 °C; **^{1}H NMR** (acetone-d_6): δ = 4.26 (s, 5H), 4.73 (m, 2H), 4.96 (m, 2H), 6.76 (d, *J* = 15.3 Hz, 1H), 7.52 (d, *J* = 15.3 Hz, 1H); **^{13}C NMR** (acetone-d_6): δ = 70.7, 71.0, 74.4, 80.9, 129.5, 138.6, 167.0, 191.8; HRMS calcd for $C_{14}H_{12}FeO_3$ $(M+H)^+$: 285.0214; found: 285.0227.

*4.18. (E)-4-Oxo-5-phenylpent-2-enoic acid (**4d**)[12a]*

Compound **4d** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 4); 0.5M solution of **5** in MeCN was used; purified by flash chromatography on silicagel (EA/hexanes = 1/1 + 0.5% AcOH); pale yellow powder (36%); mp 105–107 °C; **^{1}H NMR** ($CDCl_3$): δ = 3.93 (s, 2H), 6.72 (d, *J* = 15.6 Hz, 1H), 7.15-7.35 (m, 6H); **^{13}C NMR** ($CDCl_3$): δ = 48.9, 127.5, 129.0, 129.5, 130.4, 132.6, 140.2, 170.4, 196.3.

*4.19. (E)-4-Oxoocta-2,7-dienoic acid (**4e**)[12a]*

Compound **4e** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 5); purified by flash chromatography on silica gel (EA + 0.5% AcOH); white powder (55%); mp 100–101 °C; **^{1}H NMR** (DMSO-d_6): δ = 2.23-2.30 (m, 2H), 2.83 (t, *J* = 7.2 Hz, 2H), 4.94-5.06 (m, 2H), 5.74-5.87 (m, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.90 (d, *J* = 15.9 Hz, 1H), 13.12 (s, 1H); **^{13}C NMR** (DMSO-d_6): δ = 27.1, 39.3, 115.3, 131.5, 137.2, 139.2, 166.6, 199.6.

*4.20. (S,E)-6,10-Dimethyl-4-oxoundeca-2,9-dienoic acid (**4f**)*

Compound **4f** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 6); purified by flash chromatography on silica gel (EA + 0.5% AcOH); white powder (93%); mp 70–71 °C; $[\alpha]_D^{23}$ = -3.8 (*c* 2.26, $CHCl_3$); **^{1}H NMR** (DMSO-d_6): δ = 0.84 (d, *J* = 6.9 Hz, 3H), 1.10-1.34 (m, 2H), 1.56 (s, 3H), 1.63 (s, 3H), 1.87-1.98 (m, 3H), 2.51 (dd, *J* = 8.1, 16.2 Hz, 1H), 2.70 (dd, *J* = 5.7, 16.2 Hz, 1H), 5.06 (m, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.88 (d, *J* = 16.2 Hz, 1H), 13.11 (bs, 1H); **^{13}C NMR** (DMSO-d_6): δ = 17.5, 19.5, 24.9, 25.5, 28.4, 36.3, 47.6, 124.4, 130.7, 131.5, 139.4, 166.6, 200.2; HRMS calcd for $C_{13}H_{20}O_3$ $(M+H)^+$: 225.1485; found: 225.1484.

*4.21. (E)-9-(tert-Butoxycarbonylamino)-4-oxonon-2-enoic acid (**4g**)*

Compound **4g** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 7); 0.4M solution of **5** in MeCN was used; crystallized from toluene/*n*-octane; white powder (55%); mp 81–82 °C; **^{1}H NMR** ($CDCl_3$): δ = 1.32-1.39 (m, 2H), 1.45 (s, 9H), 1.45-1.55 (m, 2H), 1.61-1.71 (m, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 3.11 (bs, 2H), 4.59 (bs, 1H), 6.10 (bs, 1H), 6.67 (d, *J* = 16.2 Hz, 1H), 7.09 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR** (DMSO-d_6): δ = 22.9, 25.8, 28.3, 29.3, 39.7, 40.3, 77.3, 131.4, 139.3, 155.6, 166.6, 200.3; HRMS calcd for $C_{14}H_{23}NO_5$ $(M+H)^+$: 286.1649; found: 286.1649.

*4.22. (E)-9-Hydroxy-4-oxonon-2-enoic acid (**4h**)*

Compound **4h** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 8); 1.0M solution of **5** in MeCN was used; purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 92/8 + 0.5% AcOH); white powder (57%); mp 88 °C; **^{1}H NMR** (DMSO-d_6): δ = 1.22-1.31 (m, 2H), 1.36-1.43 (m, 2H), 1.45-1.55 (m, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 3.36 (t, *J* = 6.6 Hz, 2H), 6.62 (d, *J* = 16.2 Hz, 1H), 6.89 (d, *J* = 16.2 Hz, 1H), 13.1 (s, 1H); **^{13}C NMR** (DMSO-d_6): δ = 23.1, 25.1, 32.3, 40.4, 60.6, 131.4, 139.3, 166.7, 200.4; HRMS calcd for $C_9H_{14}O_4$ $(M+H)^+$: 187.0965; found: 187.0965.

*4.23. (E)-4-Oxooct-2-enedioic acid (**4i**)*

Compound **4i** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 9); 1.0M solution of **5** in MeCN was used; purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 9/1 + 0.5% AcOH); white powder (62%); mp 157–159 °C; **^{1}H-NMR** (DMSO-d_6): δ = 1.69 (m, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 6.61 (d, *J* = 16.2 Hz, 1H), 6.86 (d, *J* = 16.2 Hz, 1H); **^{13}C-NMR** (DMSO-d_6): 18.7, 32.7, 39.5, 131.8, 139.0, 166.7, 174.1, 200.0; HRMS calcd for $C_8H_{10}O_5$ $(M-H)^-$: 185.0455; found: 185.0452.

*4.24. (E)-8-tert-Butoxy-4,8-dioxooct-2-enoic acid (**4j**)*

Compound **4j** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 10); crystallized from toluene/hexanes; colourless crystals (65%); mp 78–80 °C; **^{1}H NMR** ($CDCl_3$): δ = 1.45 (s, 9H), 1.93 (m, 2H), 2.29 (t, *J* = 7.2 Hz, 2H), 2.73 (t, *J* = 6.9 Hz, 2H), 6.69 (d, *J* = 15.9 Hz, 1H), 7.13 (d, *J* = 15.9 Hz, 1H), 10.67 (bs, 1H); **^{13}C NMR** ($CDCl_3$): δ = 18.9, 28.1, 34.3, 40.5, 80.7, 129.9, 140.8, 170.2, 172.6, 198.8; HRMS calcd for $C_{12}H_{18}O_5$ $(M+H)^+$: 243.1227; found: 243.1226.

*4.25. (2E,9E)-4,8-Dioxoundeca-2,9-dienedioic acid (**4l**)*

Compound **4l** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 12); DBU was added over 30 min; the product precipitated upon quenching with 1M H_2SO_4 and cooling; white powder (44%); mp 210 °C; **^{1}H NMR** (DMSO-d_6): δ =1.74 (quint, *J* = 7.2 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 4H), 6.61 (d, *J* = 16.2 Hz, 2H), 6.87 (d, *J* = 16.2 Hz, 2H), 12.98 (bs, 2H); **^{13}C NMR** (DMSO-d_6): δ = 17.3, 39.4, 131.4, 139.2, 166.6, 200.0; HRMS calcd for $C_{11}H_{12}O_6$ $(M+H)^+$: 241.0712; found: 241.0752.

*4.26. (E)-3-(3-Oxocyclohex-1-enyl)acrylic acid (**4m**)*

Compound **4m** was prepared by the same procedure as that for **4a**, under the reaction conditions specified in Table 3 (entry 13); purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 98/2 + 0.5% AcOH); white powder (40%); mp 214 °C; **^{1}H NMR** (DMSO-d_6): δ = 1.95 (m, 2H), 2.35 (m, 2H), 2.50 (m, 2H), 6.22 (s, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 7.33 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR** (DMSO-d_6): δ = 21.7, 24.1, 37.3, 125.3, 131.7, 143.9, 154.6, 166.9, 199.3; HRMS calcd for $C_9H_{10}O_3$ $(M+H)^+$: 167.0708; found: 167.0694.

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Supplementary data

Supplementary data related to this article can be found at …

Supporting Information

Straightforward synthesis of functionalized (*E*)-3-acylacrylic acids

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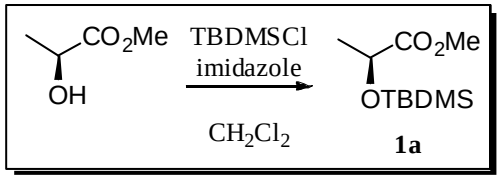
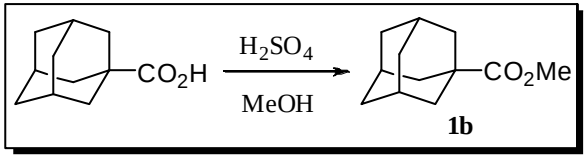
(*S*)-Methyl 2-(*tert*-butyldimethylsilyloxy)propanoate (1a)[1]



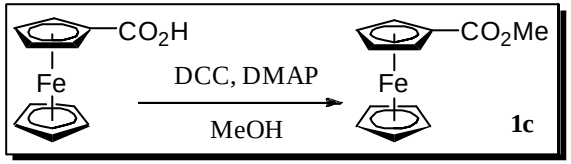
Imidazole (3.39 mmol, 0.23 g) was added to the solution of (-)-methyl-L-lactate (2.16 mmol, 0.20 mL) in anhydrous CH_2Cl_2 (6.5 mL) at 0°C. After 10 min of stirring at 0°C, *tert*-butyldimethylsilyl chloride (2.59 mmol, 0.40 g) was added and reaction mixture was stirred at room temperature for 6 h. Then cold water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to afford (*S*)-methyl 2-(*tert*-butyldimethylsilyloxy)propanoate **1a** (0.46 g, 97%) as clear oil; $[\alpha]_D^{23}$ = -27 (*c* 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$): δ = 0.07 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.40 (d, *J* = 6.8 Hz, 3H), 3.72 (s, 3H), 4.33 (q, *J* = 6.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ = -5.3, -5.0, 18.3, 21.3, 25.7, 51.8, 68.4, 174.5.

Adamantane-1-carboxylic acid methyl ester (1b)[2]



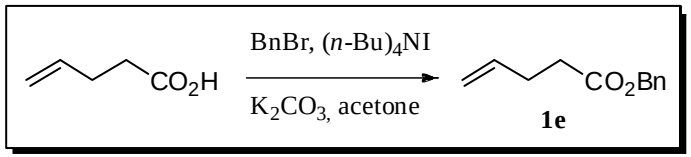
Conc. H_2SO_4 (5 mL) was added to the solution of adamantane-1-carboxylic acid (20 mmol, 3.60 g) in MeOH (100 mL). The reaction mixture was refluxed under argon atmosphere. After being refluxed for 3.5 h, a mixture was allowed to warm to room temperature, cold water (100 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give adamantane-1-carboxylic acid methyl ester **1b** (3.74g, 96%) as white crystals; mp 37-38 °C; **^{1}H NMR** ($CDCl_3$): δ = 1.71 (bs, 6H), 1.88 (m, 6H), 2.01 (bs, 3H), 3.65 (s, 3H).

Ferrocenecarboxylic acid methyl ester (1c)



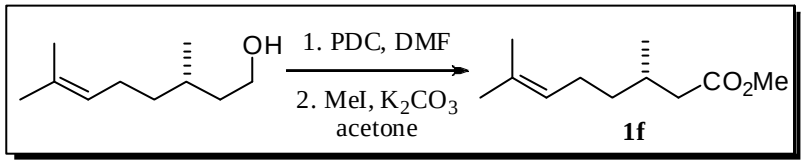
N,*N*'-Dicyclohexylcarbodiimide (4.40 mmol, 0.91 g) and 4-dimethylaminopyridine (4.40 mmol, 0.54 g) were added to the solution of ferrocenecarboxylic acid (4.40 mmol, 1.01 g) in dry MeOH (15 mL). The reaction mixture was flushed with argon and stirred at room temperature for 3h. The reaction mixture was concentrated and the residue was purified by flash chromatography on silicagel (ethyl acetate/hexanes = 1/9) to give ferrocenecarboxylic acid methyl ester **1c** (0.93 g, 86%) as orange crystals; mp 71°C; **^{1}H NMR** ($CDCl_3$): δ = 3.80 (s, 3H), 4.22 (s, 5H), 4.41 (m, 2H), 4.82 (m, 2H); **^{13}C NMR** ($CDCl_3$): δ = 51.7, 69.8, 70.2, 71.2, 71.4, 172.3; **HRMS** calcd for $C_{11}H_{10}FeO_2$ $(M+H)^+$: 245.0259; found: 245.0257.

Benzyl pent-4-enoate (1e)[3]



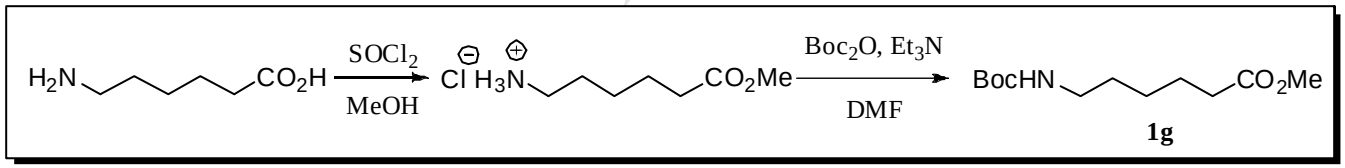
4-Pentenoic acid (8.72 mmol, 1.00 mL), benzyl bromide (10.46 mmol, 1.26 mL), anhydrous K_2CO_3 (43.6 mmol, 6.0 g) and tetrabutylammonium iodide (0.59 mmol, 0.22 g) were stirred in anhydrous acetone (100 mL) at room temperature overnight. The resulting suspension was filtered and the filtrate was concentrated. The residue was dissolved in ethyl acetate (50 mL), washed with 1M solution of HCl (25 mL), saturated $NaHCO_3$ (25 mL) and brine (25 mL). The combined organic phases were dried over Na_2SO_4, concentrated and purified by flash chromatography on silicagel (ethyl acetate/hexanes = 1/30) to give benzyl pent-4-enoate **1e** (1.55 g, 93%) as a colourless oil; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 2.38-2.42 (m, 2H), 2.45-2.48 (m, 2H), 4.99-5.07 (m, 2H), 5.12 (s, 2H), 5.79-5.85 (m, 1H), 7.32-7.38 (m, 5H).

(*S*)-Methyl 3,7-dimethyloct-6-enoate (1f)[4]



Pyridinium dichromate (15.52 mmol, 5.96 g) was dissolved in dry DMF (20 mL), a solution of (*S*)-citronellol (4.44 mmol, 0.69 g) in dry DMF (4 mL) was added and the resulting mixture was stirred at room temperature for 22 h. The mixture was poured into water (50 mL) and the aqueous phase was extracted with Et_2O (4 x 50 mL). The combined organic phases were washed with 1M H_2SO_4 (40 mL), brine (40 mL), dried over Na_2SO_4 and concentrated. The residue was dissolved in anhydrous acetone (30 mL) and K_2CO_3 (17.74 mmol, 2.45 g) and MeI (44.35 mmol, 2.76 mmol) were added to the solution. The reaction mixture was refluxed for 3.5 h and then diluted with ethyl acetate (75 mL). The obtained mixture was washed with brine (2 x 25 mL), the organic phase was dried over Na_2SO_4, concentrated and purified by flash chromatography on silicagel (hexanes/ Et_2O = 19/1) to afford (*S*)-methyl 3,7-dimethyloct-6-enoate **1f** (0.56 g, 69%) as a colourless oil; **$[\alpha]_D^{24}$** = -7.6 (*c* 2.5, $CHCl_3$); **^{1}H NMR** (600 Mhz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3H), 1.19-1.25 (m, 1H), 1.32-1.38 (m, 1H), 1.60 (s, 3H), 1.68 (s, 3H), 1.98 (m, 3H), 2.12 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.32 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.67 (s, 3H), 5.09 (m, 1H); **^{13}C NMR** (150 Mhz, $CDCl_3$): δ = 17.6, 19.6, 25.4, 25.7, 30.0, 36.7, 41.6, 51.3, 124.2, 131.5, 173.7.

Methyl 6-(*tert*-butoxycarbonylamino)hexanoate (1g)[5]

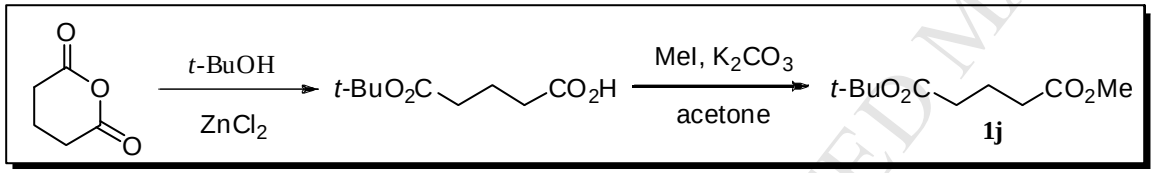


Thionyl chloride (114 mmol, 8.30 mL) was slowly added to dry MeOH (90 mL) at -15 °C and the resulting solution was

stirrted for 10 min at -10 °C. 6-Aminohexanoic acid (22.9 mmol, 3.00 g) was added and the mixture was stirred for 19 h at room temperature. The solution was concentrated, the residue was redissolved in MeOH (20 mL), cooled to -20°C and Et_2O (80 mL) was adde. Filtration afforded methyl ester hydrochloride (3.91g, 94%) as white crystals; mp 118-120 °C; **^{1}H-NMR** (CD_3OD): δ = 1.37-1.47 (m, 2H), 1.61-1.74 (m, 4H), 2.37 (t, *J* = 7.3 Hz, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 3.66 (s, 3H), 4.96 (bs, 1H); **^{13}C-NMR** (CD_3OD): δ = 25.4, 26.9, 28.2, 34.4, 40.6, 52.1, 175.6.

6-Aminohexanoic acid methyl ester hydrochloride (20.2 mmol, 3.66 g), Boc_2O (22.2 mmol, 4.84 g) and Et_3N (40.2 mmol, 5.6 mL) were stirred in dry DMF (40 mL) at room temperature for 0.5 h. Afterwards the mixture was quenched with water (50 mL), the aqueous phase was extracted with CH_2Cl_2 (2 x 70 mL), the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, concentrated and dried under a high vacuum (6.10^{-1} Torr, 60 °C, 4 h). The residue was purification by flash chromatography on silicagel (CH_2Cl_2) to afford methyl 6-(*tert*-butoxycarbonylamino)hexanoate **1g** (4.80 g, 97%) as a yellow-red oil; **^{1}H NMR** ($CDCl_3$): δ =1.23-1.55 (m, 15H), 1.65 (q, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.11 (t, *J* = 6 Hz, 2H), 3.67 (s, 3H), 4.65 (bs, 1H); **^{13}C NMR** (DMSO-d_6): δ = 24.2, 25.8, 28.2, 29.2, 33.2, 39.6, 51.1, 77.3, 155.6, 173.3.

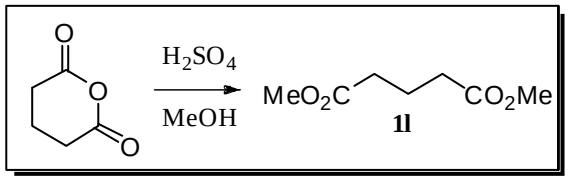
***tert*-Butyl methyl glutarate (1j)**[6]



$ZnCl_2$ (4.77 mmol, 0.65 g) and glutaric anhydride (30.93 mmol, 3.53 g) were added to dried and freshly distilled *tert*-butyl alcohol (186 mmol, 17.8 mL) under an argon atmosphere. The reaction mixture was stirred at 60°C overnight and then poured into saturated aqueous solution of $NaHCO_3$ (60 mL) and washed with CH_2Cl_2 (2x40 mL). The aqueous phase was acidified with conc. H_2SO_4 (pH = 1) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4 and concentrated give 5-*tert*-butoxy-5-oxopentanoic acid (2.67 g, 46%) as a colourless oil; **^{1}H NMR** ($CDCl_3$): δ = 1.45 (s, 3H), 1.92 (m, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H).

5-*tert*-Butoxy-5-oxopentanoic acid (0.95 mmol, 0.18 g) was dissolved in dry acetone (3 mL) and K_2CO_3 (3.79 mmol, 0.52 g) and MeI (9.47 mmol, 0.59 mL) were added. The reaction mixture was refluxed for 17 h, then was allowed to cool down and was quenched with ethyl acetate (20 mL). The mixture was washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated to give *tert*-butyl methyl glutarate **1j** (0.17 g, 91%) as a slightly yellow oil; **^{1}H NMR** ($CDCl_3$): δ = 1.44 (s, 9H), 1.91 (m, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.68 (s, 3H); **^{13}C NMR** ($CDCl_3$): δ = 20.3, 28.1, 33.1, 34.5, 51.5, 80.3, 172.2, 173.5.

Dimethyl glutarate (1l)[7]



Glutaric anhydride (29.4 mmol, 3.35 g) was dissolved in anhydrous MeOH (100 mL) and conc. H_2SO_4 (5.9 mmol, 0.31 mL) was added. After being stirred at room temperature for 18 h, the mixture was concentrated to a half volume and quenched with water (40 mL) afterwards. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give dimethyl glutarate **1l** (4.53 g, 96%) as a colourless clear oil; **^{1}H NMR** ($CDCl_3$): δ = 1.96 (quint, *J* = 7.2 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 4H).

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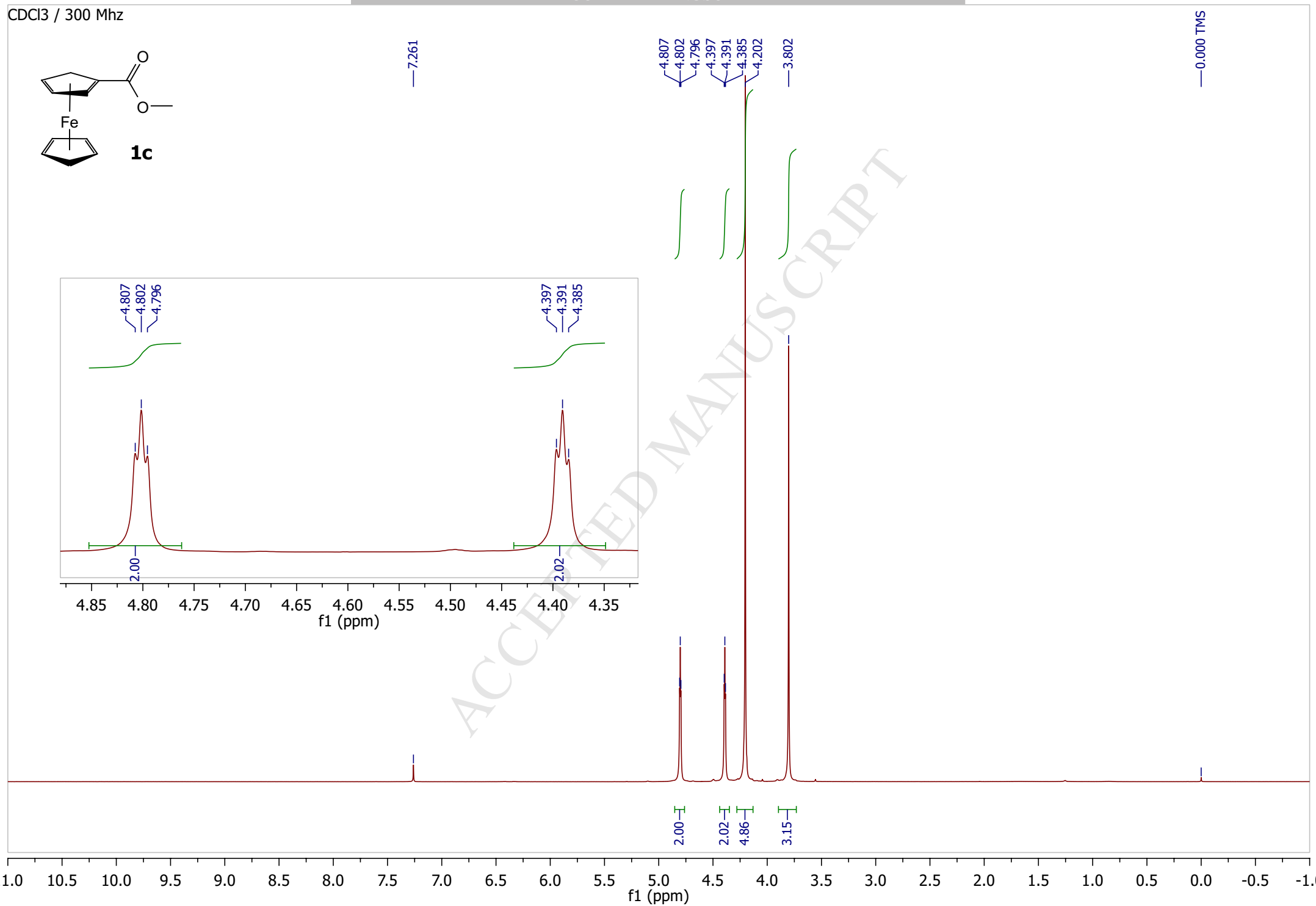
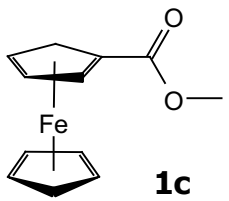


CDCl3 / 75 Mhz



1c

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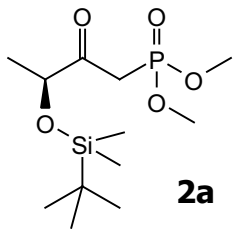

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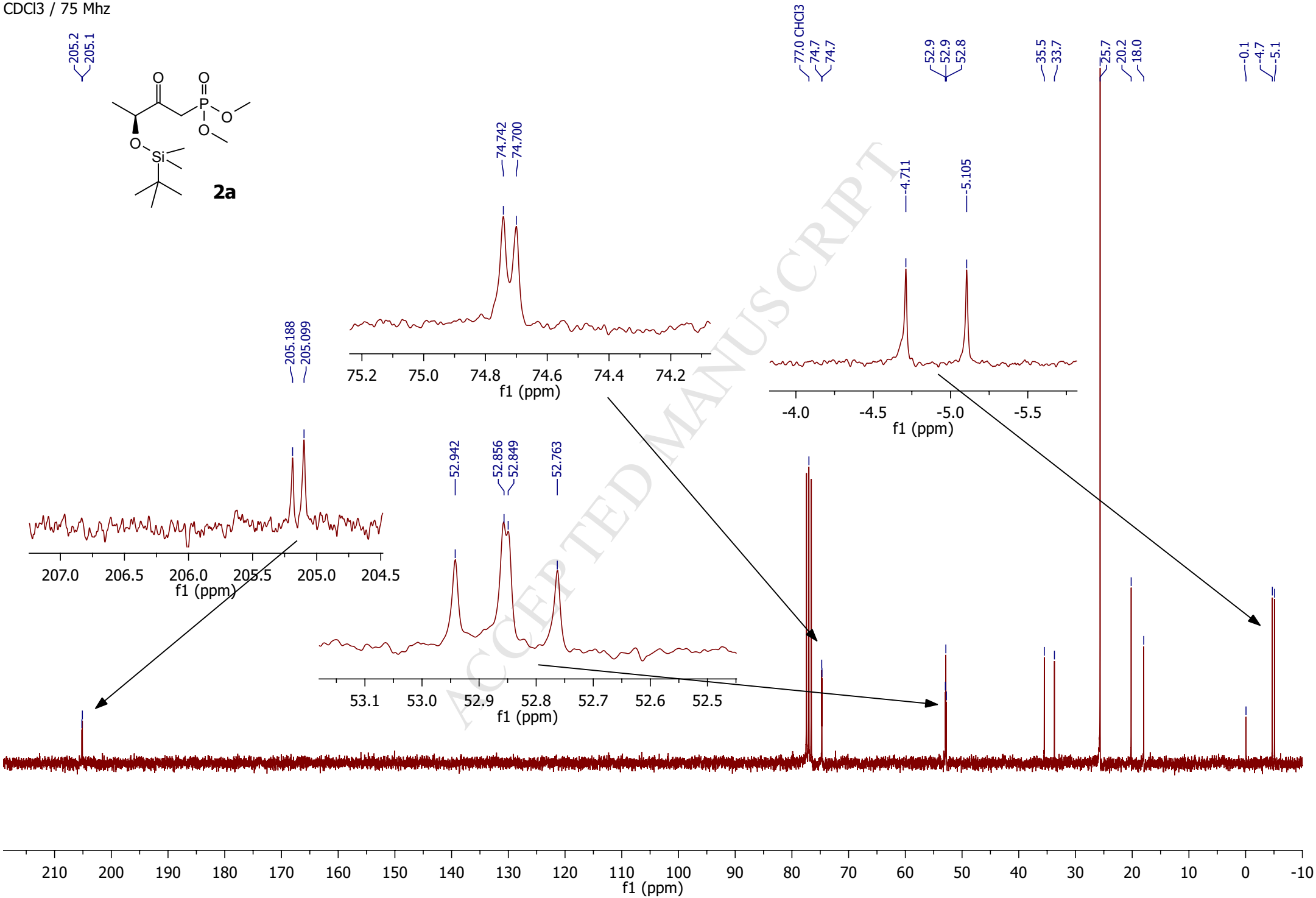

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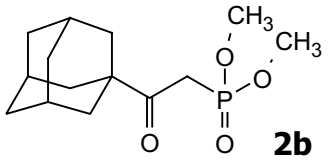

2b

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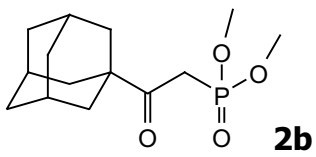

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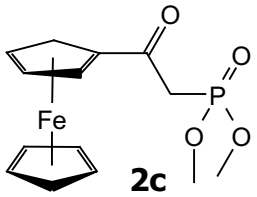

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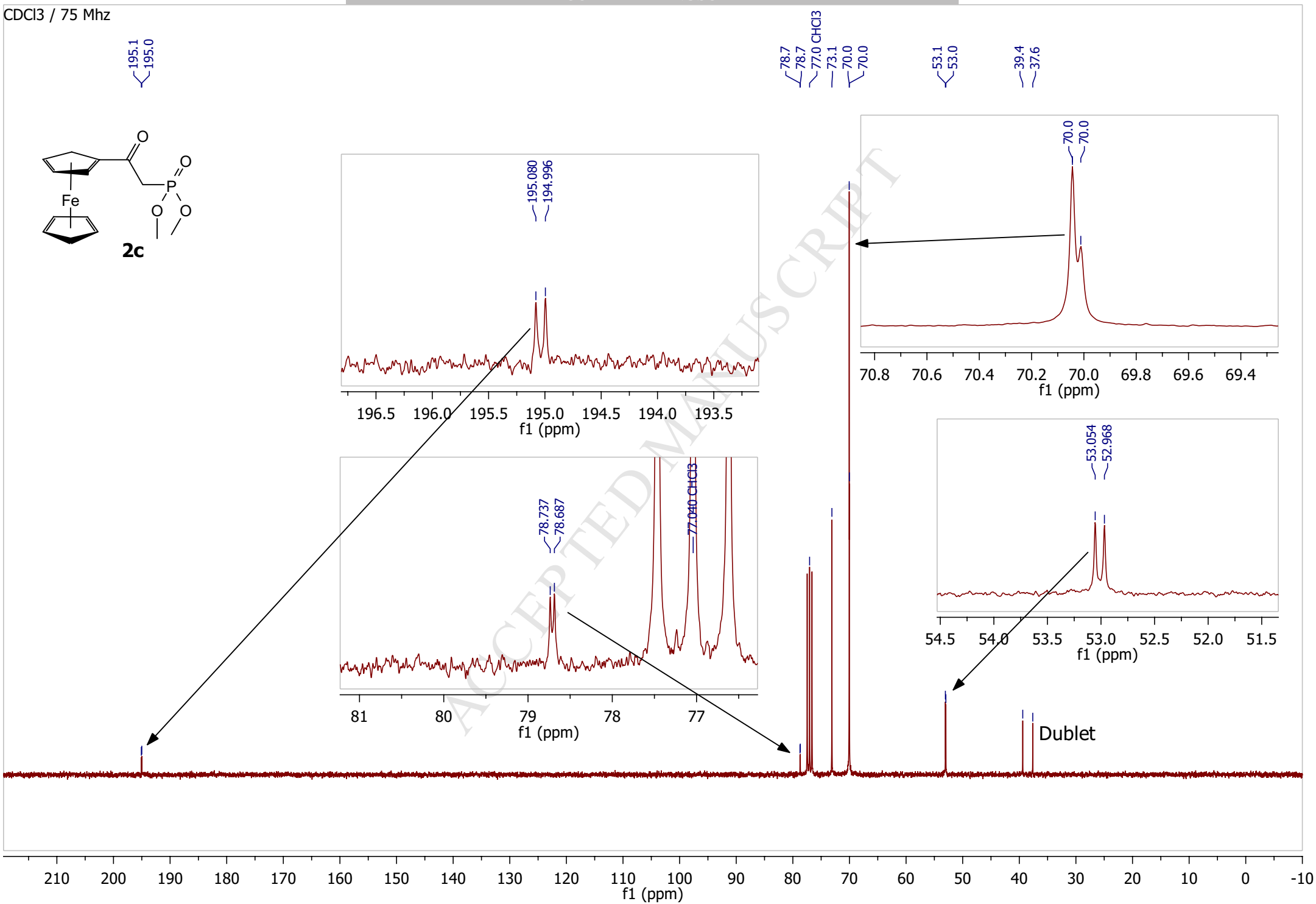

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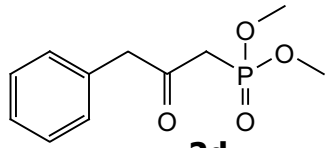

2d

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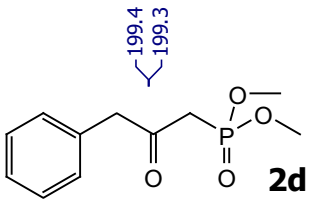

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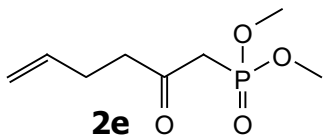

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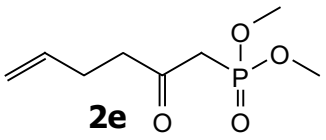

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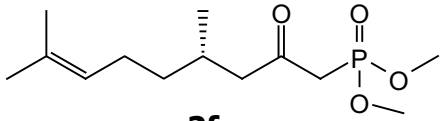

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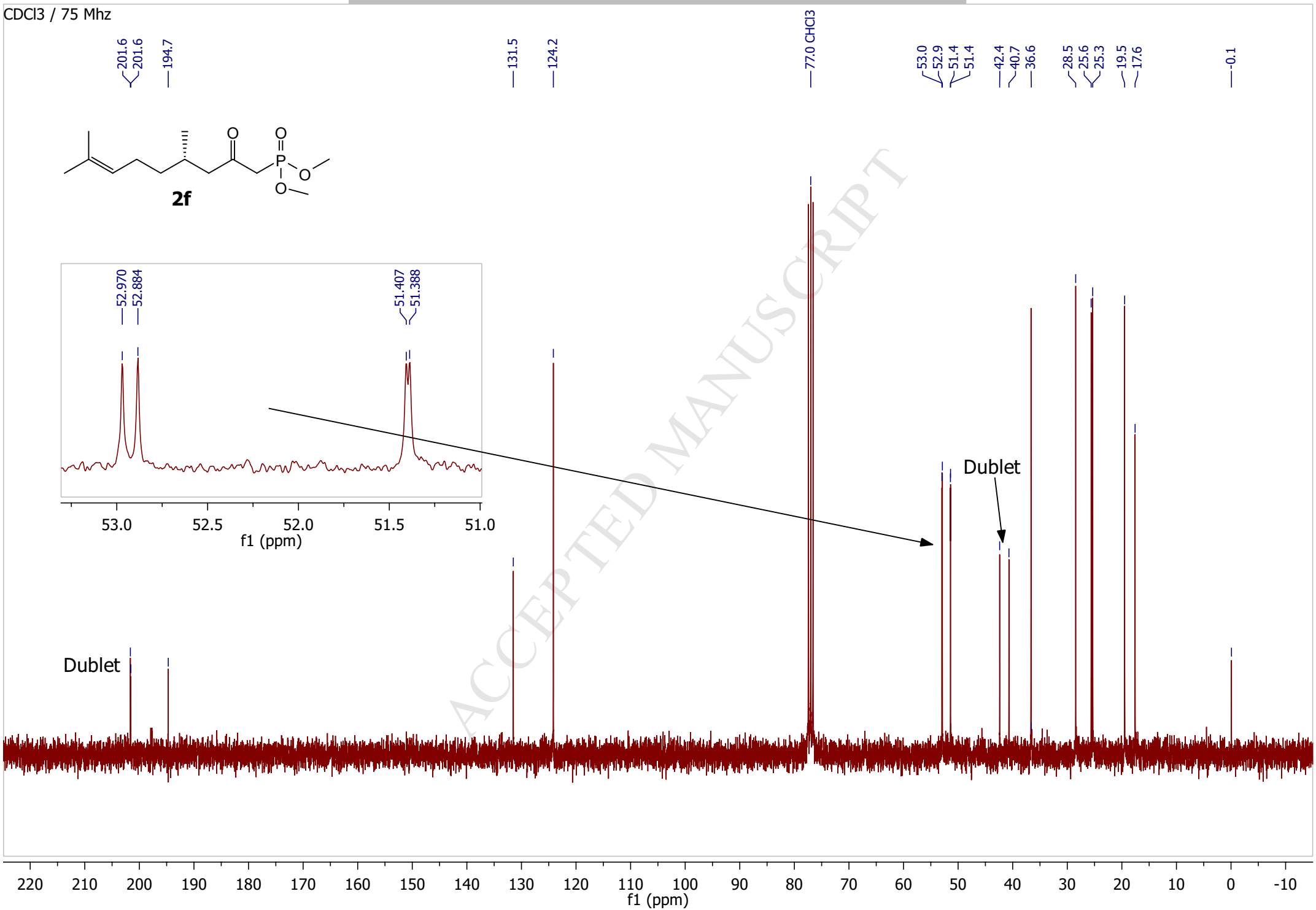

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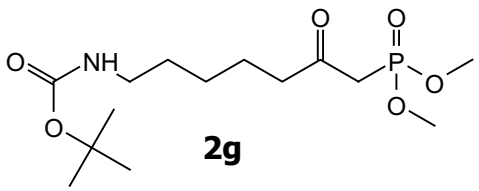
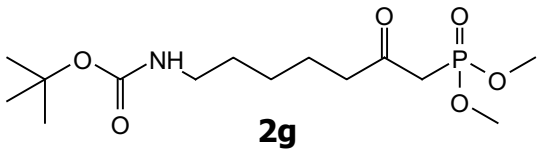


2g

CDCl3 / 75 Mhz



2g

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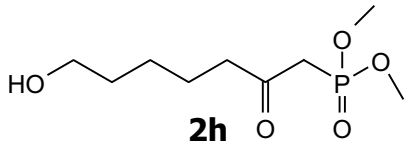

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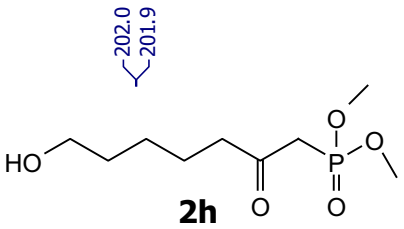

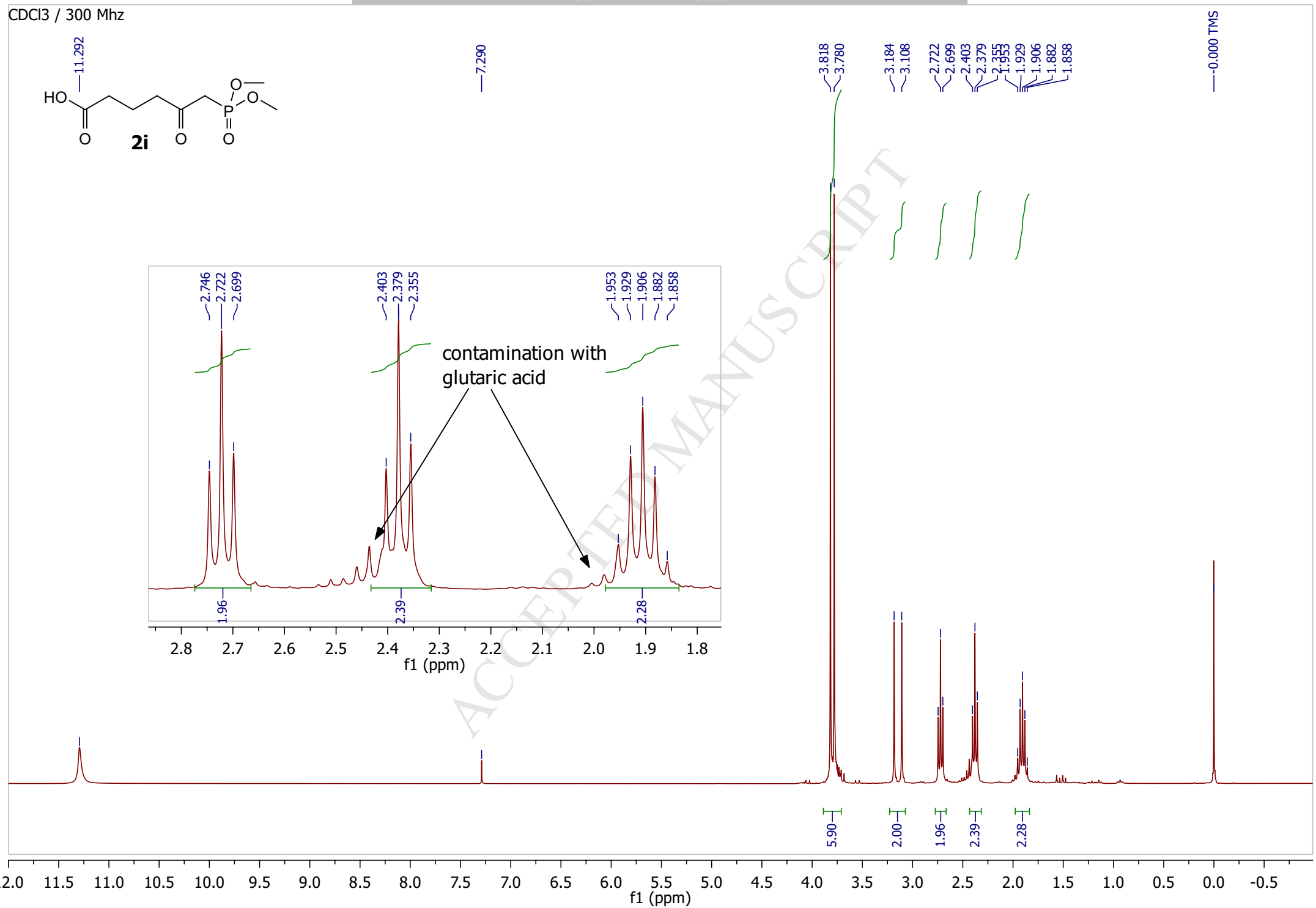

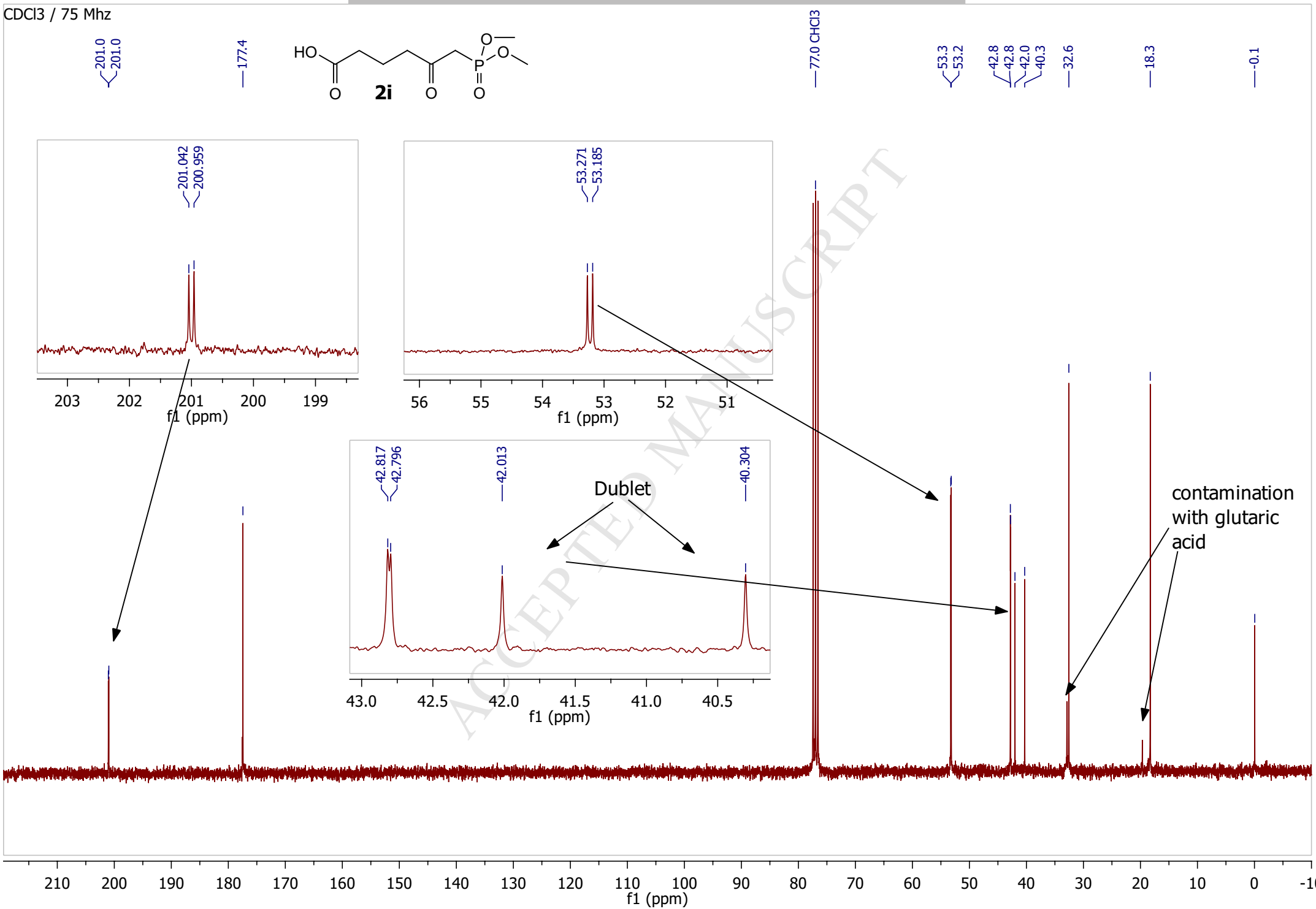

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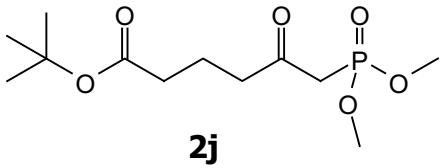

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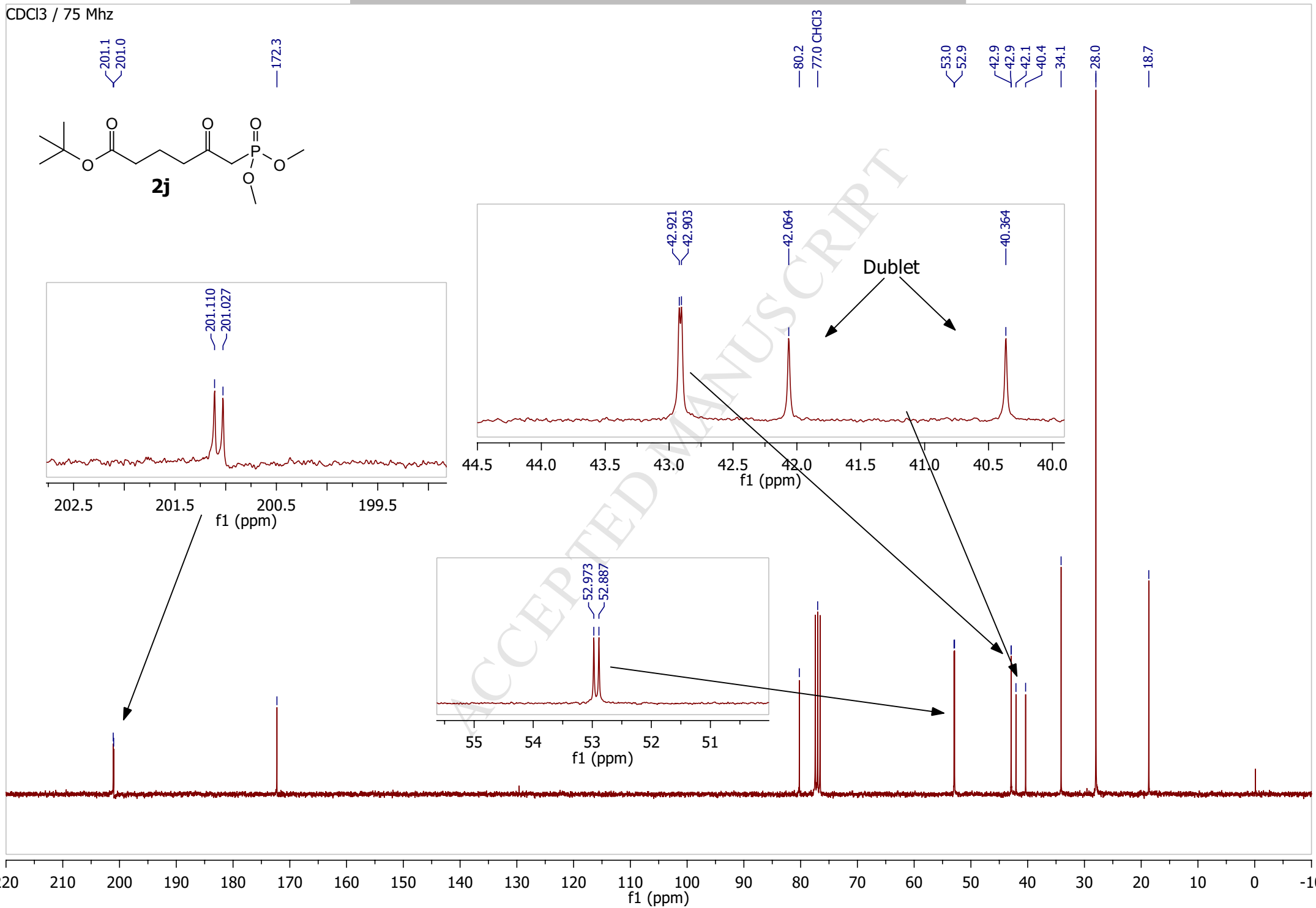

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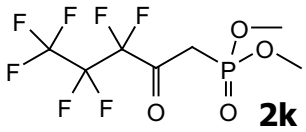

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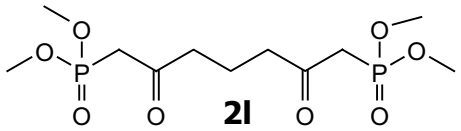

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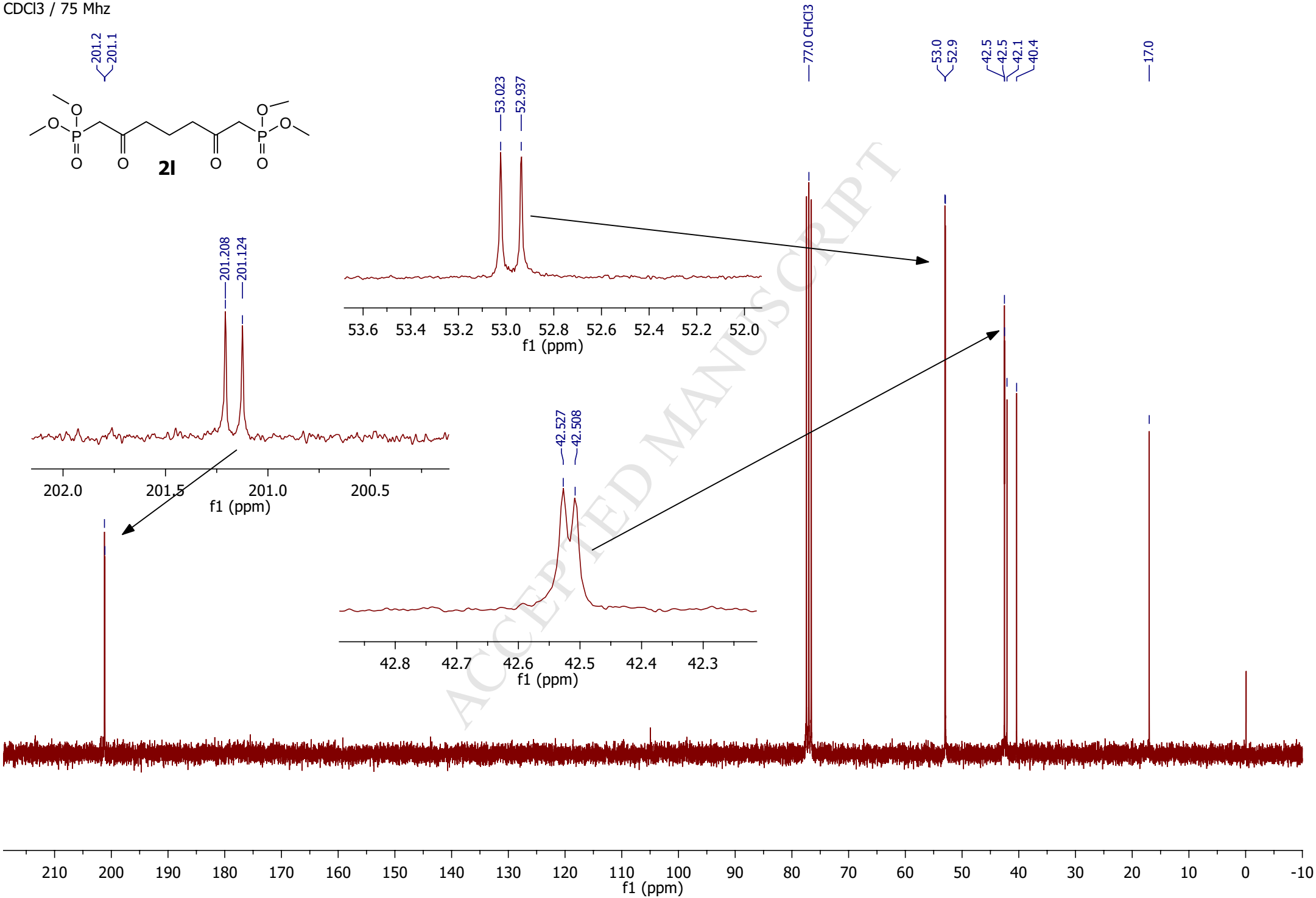

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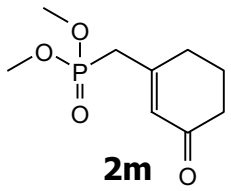

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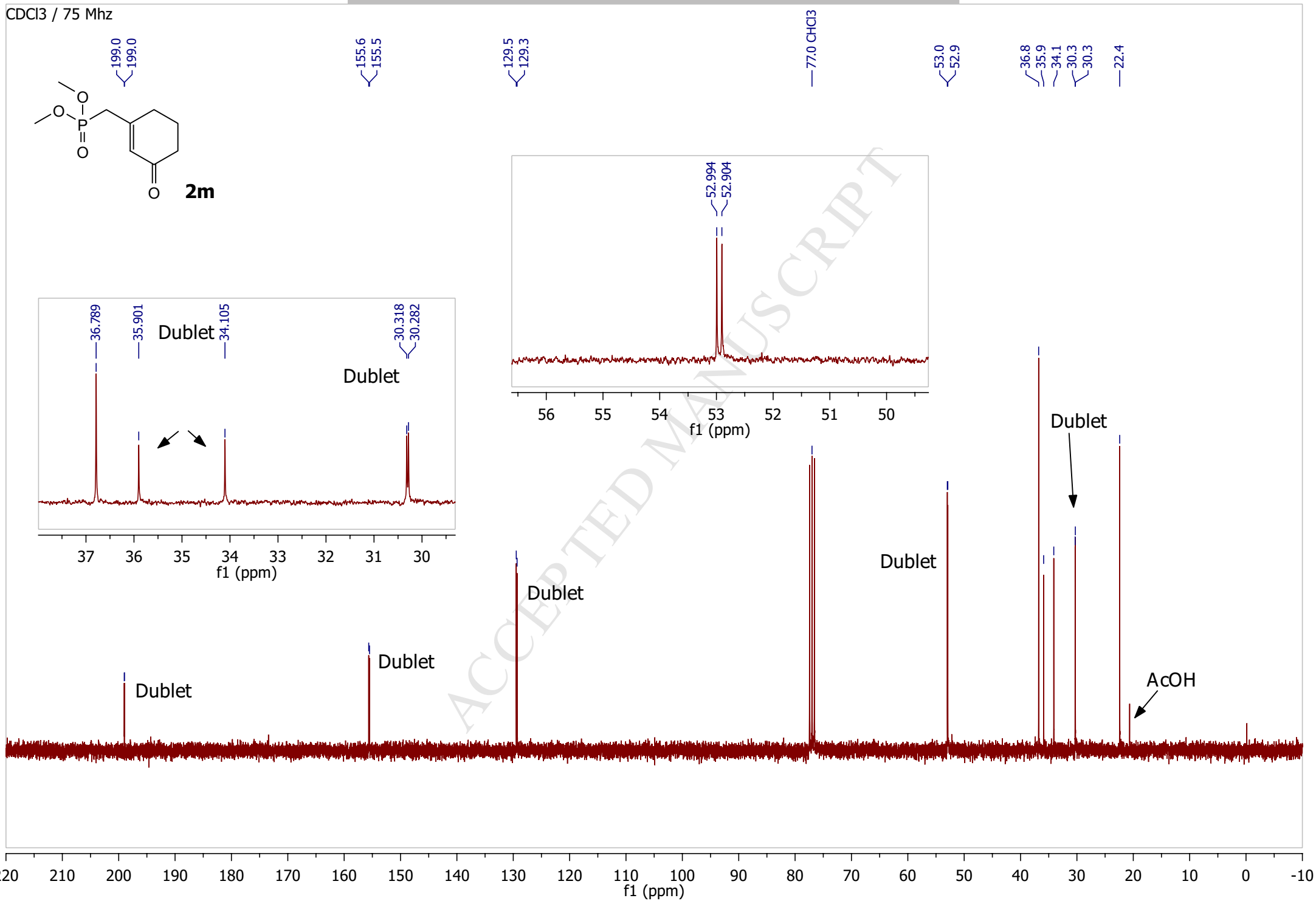

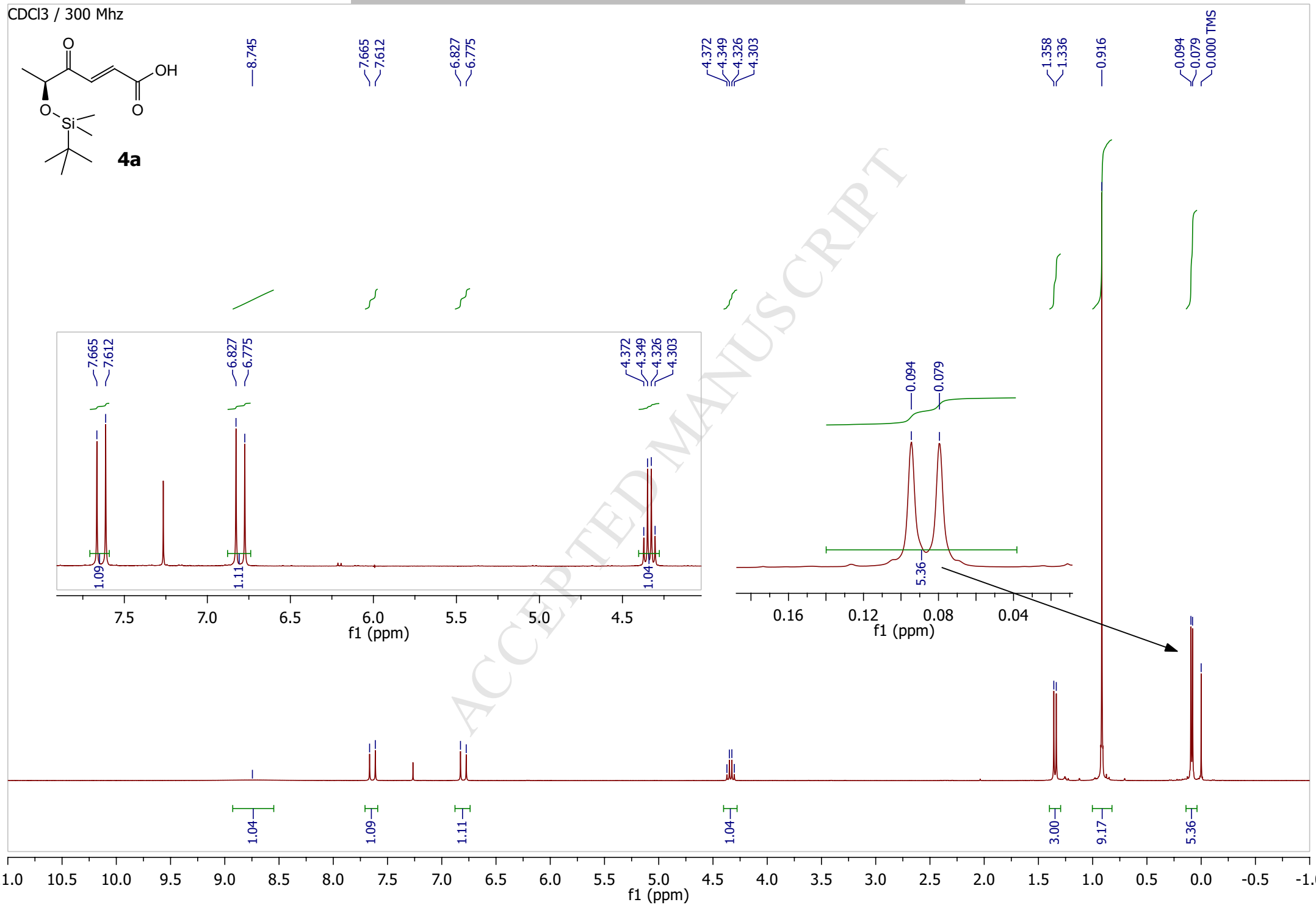

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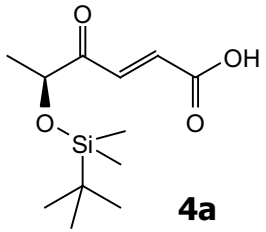

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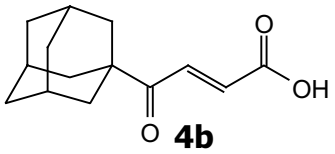

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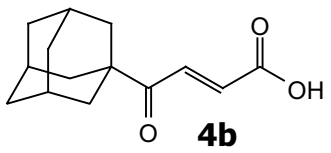

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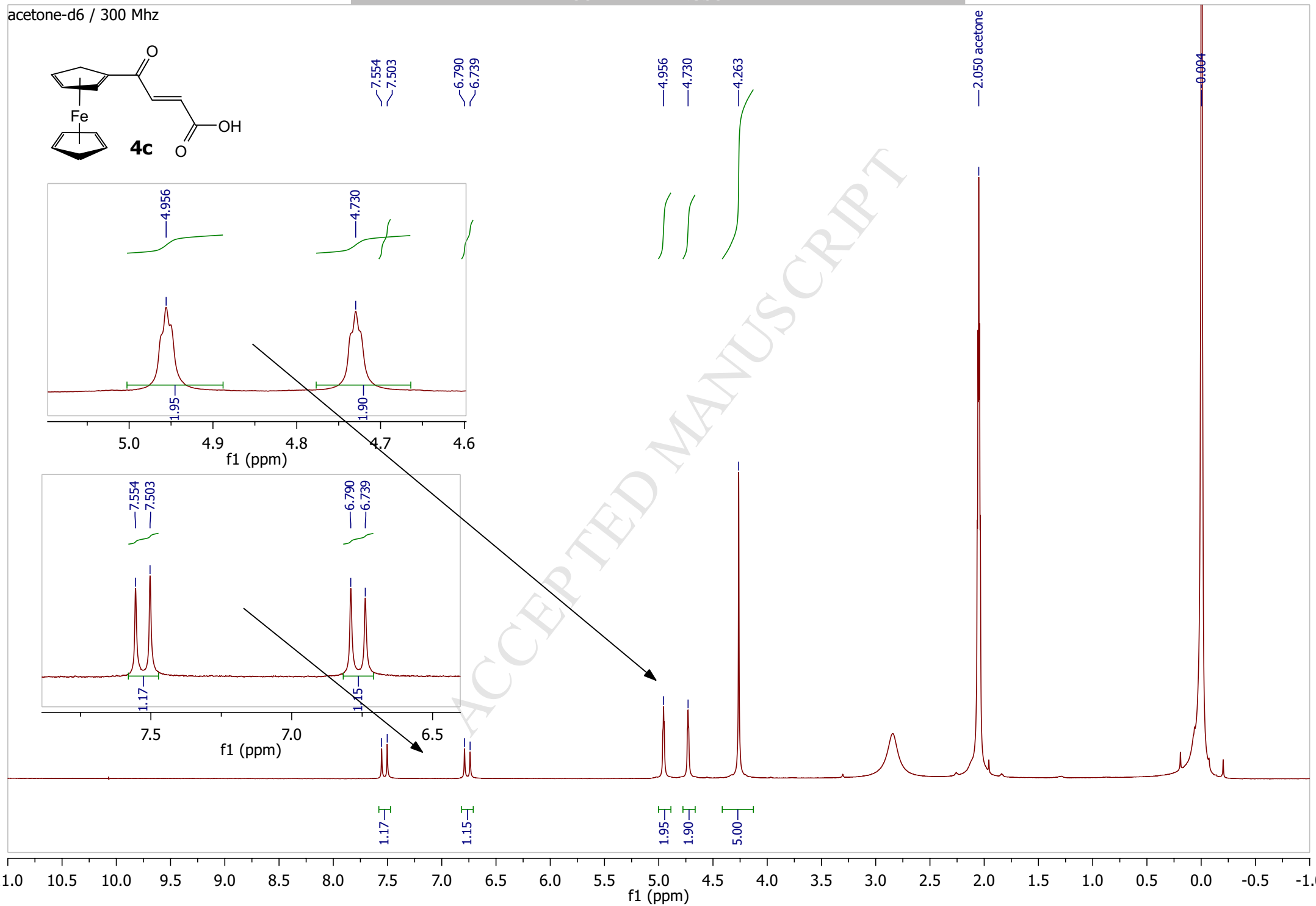

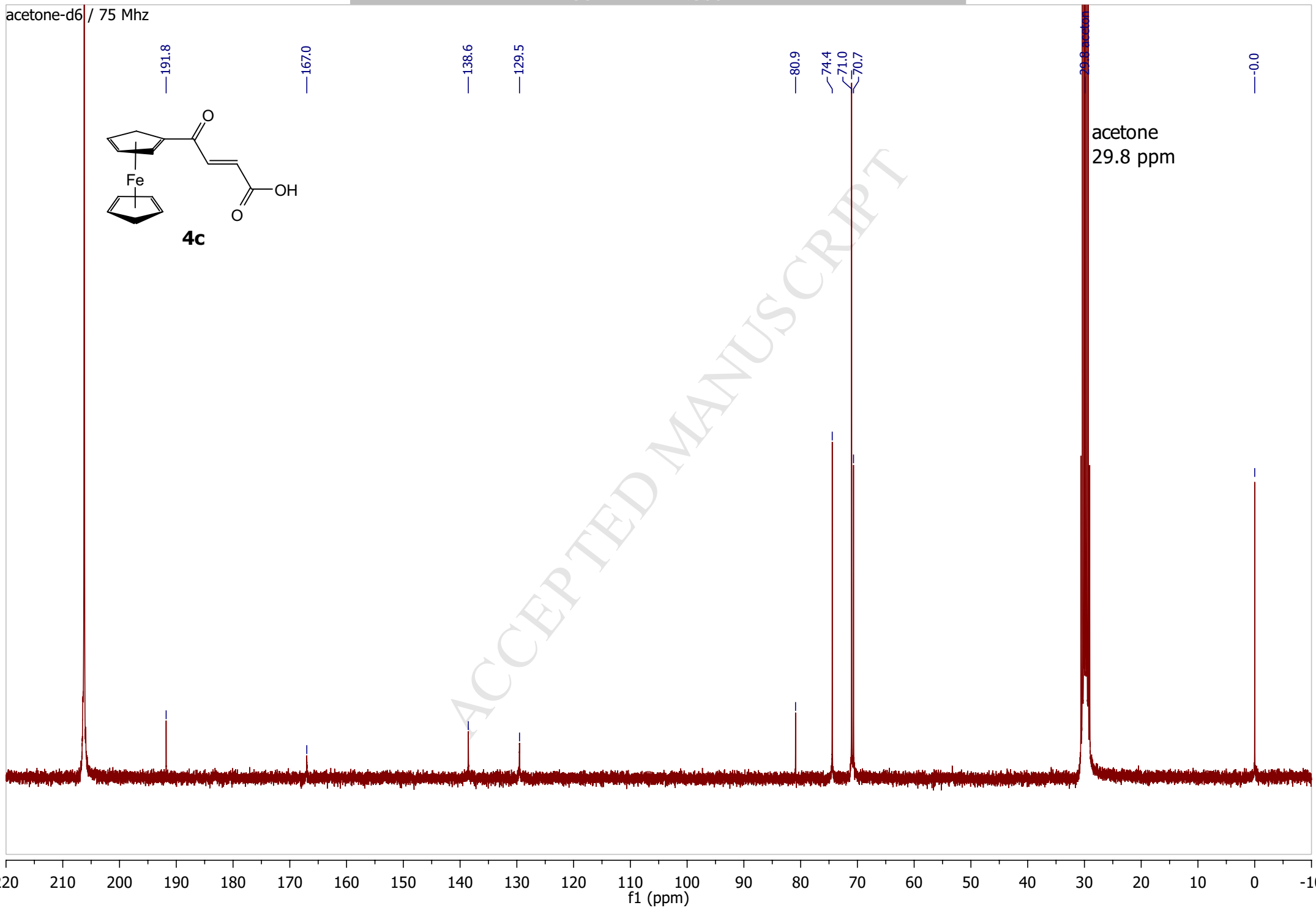

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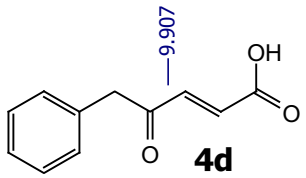

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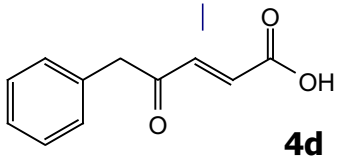

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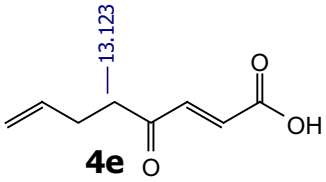

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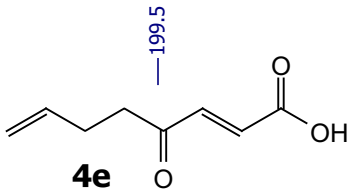

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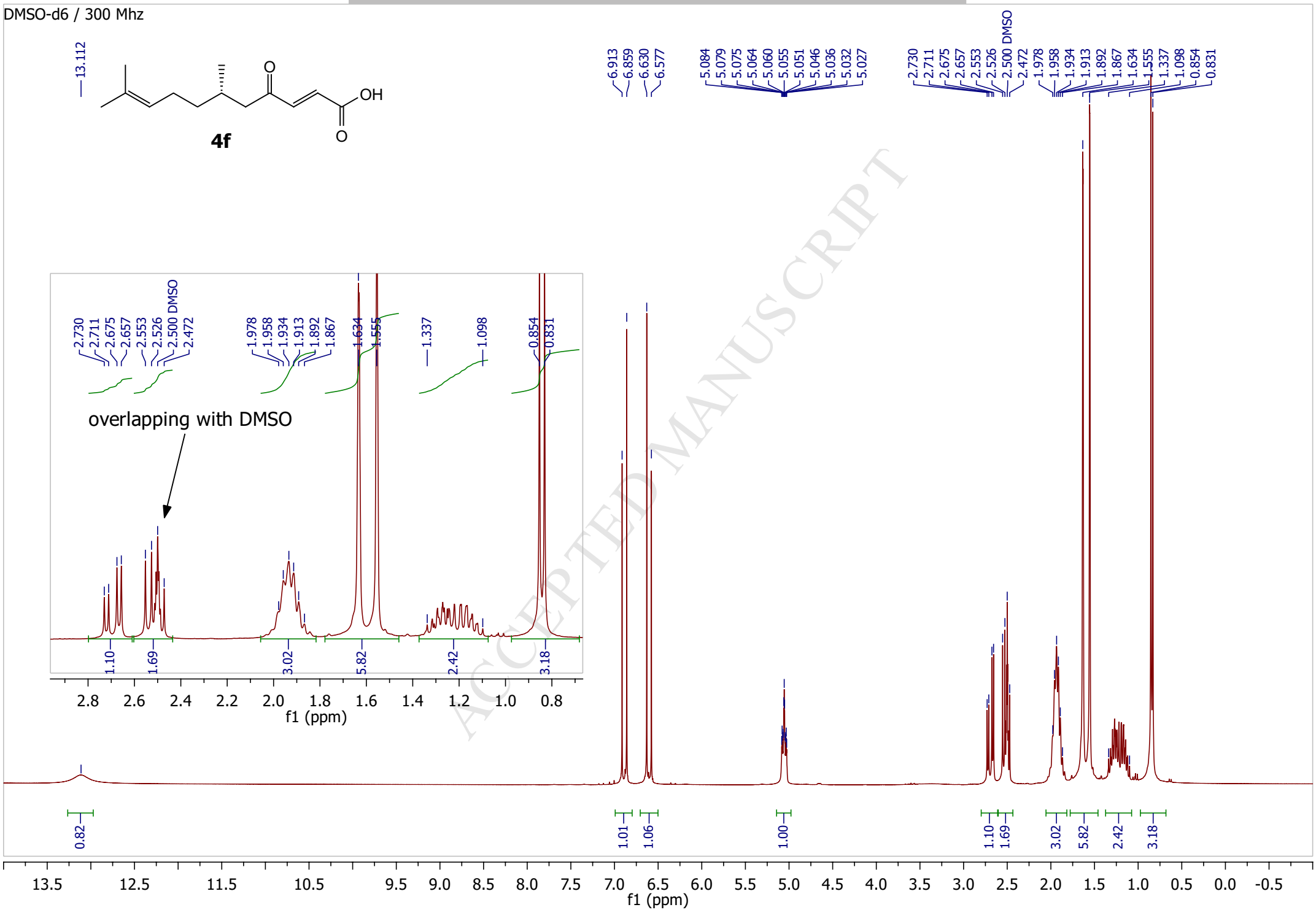

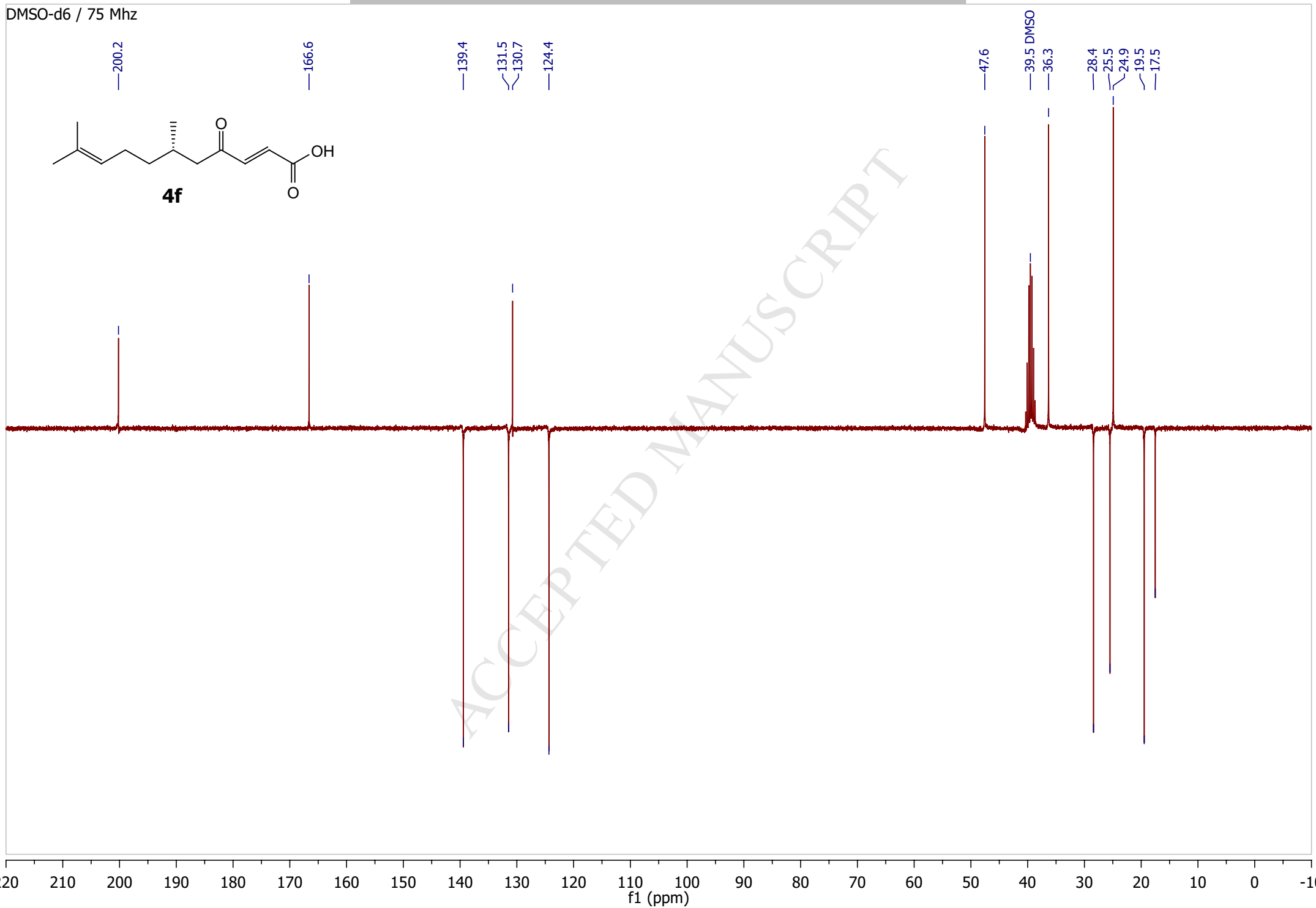

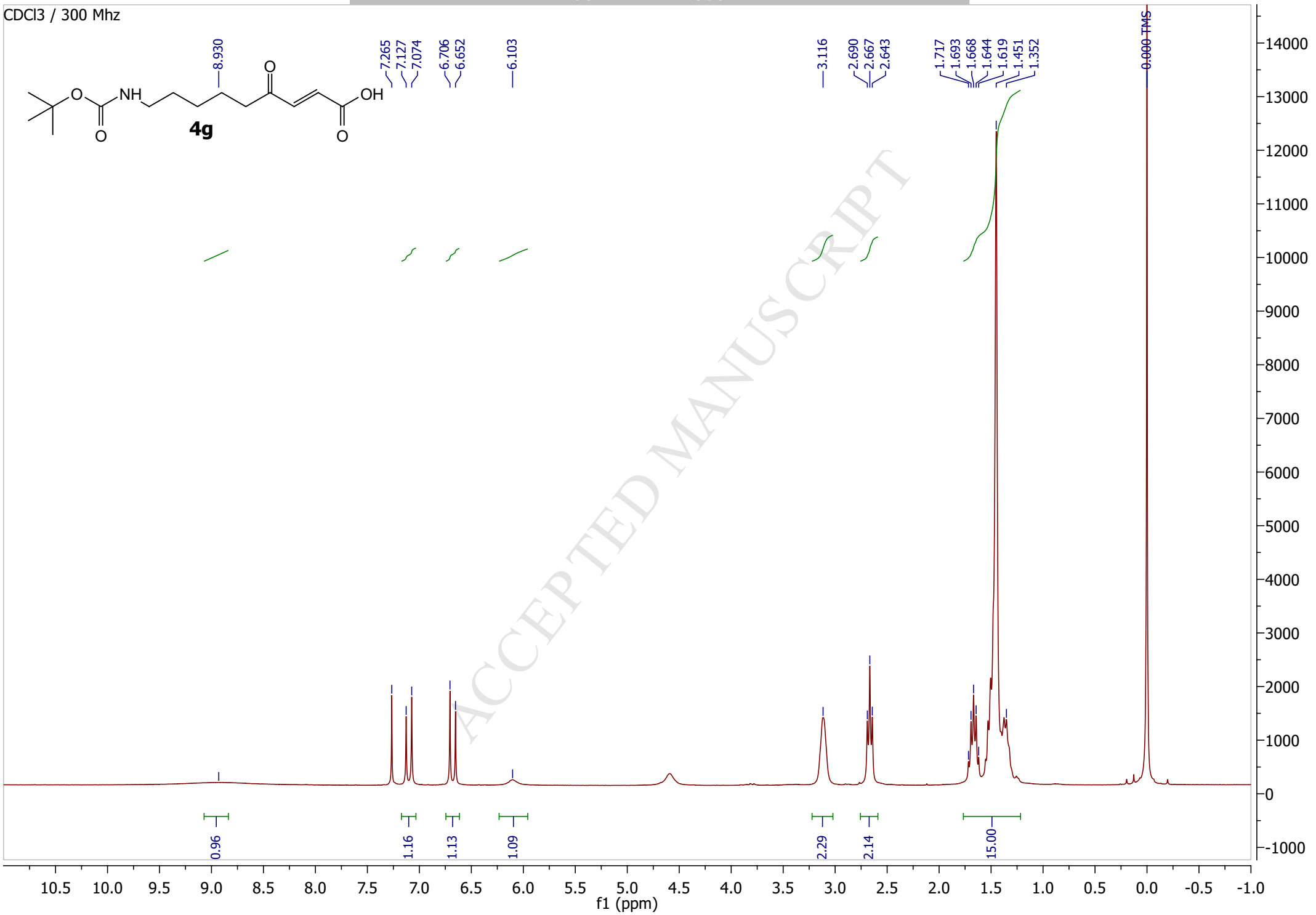

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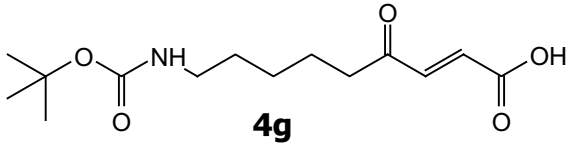

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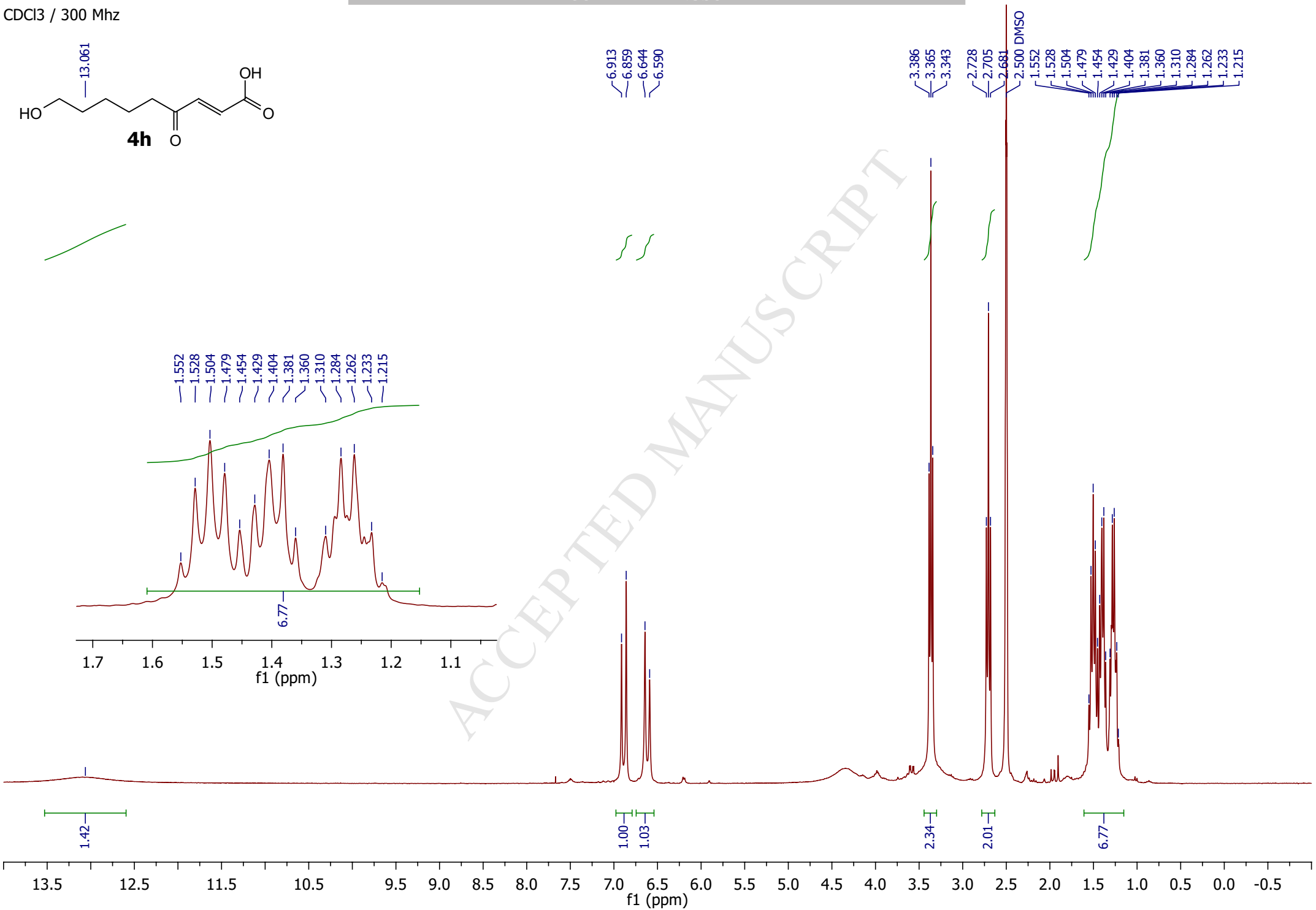

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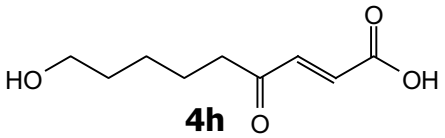

4h

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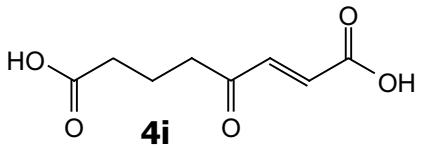

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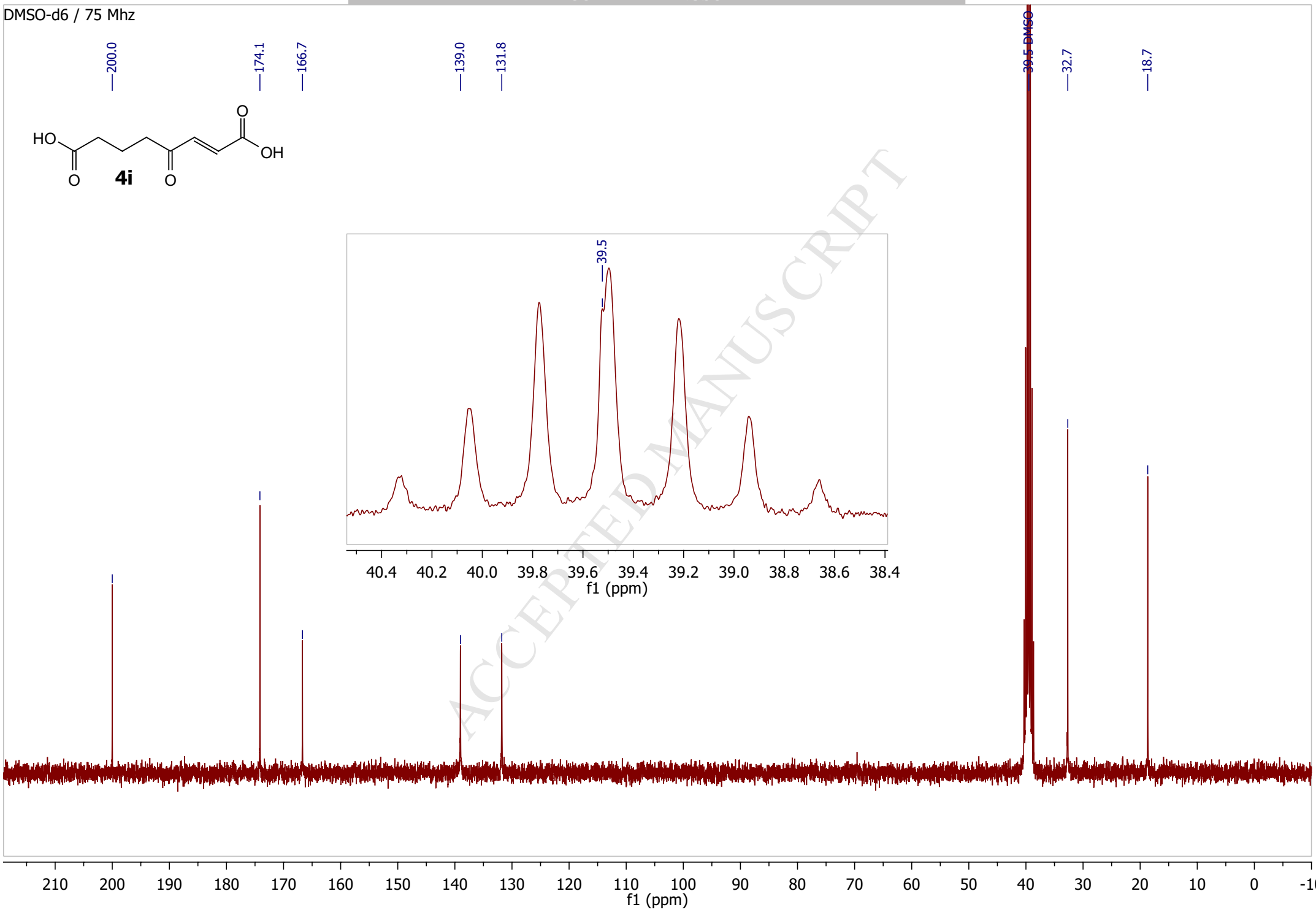

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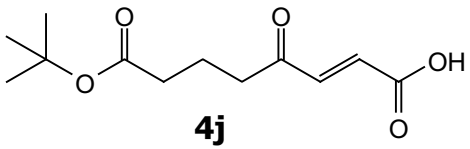
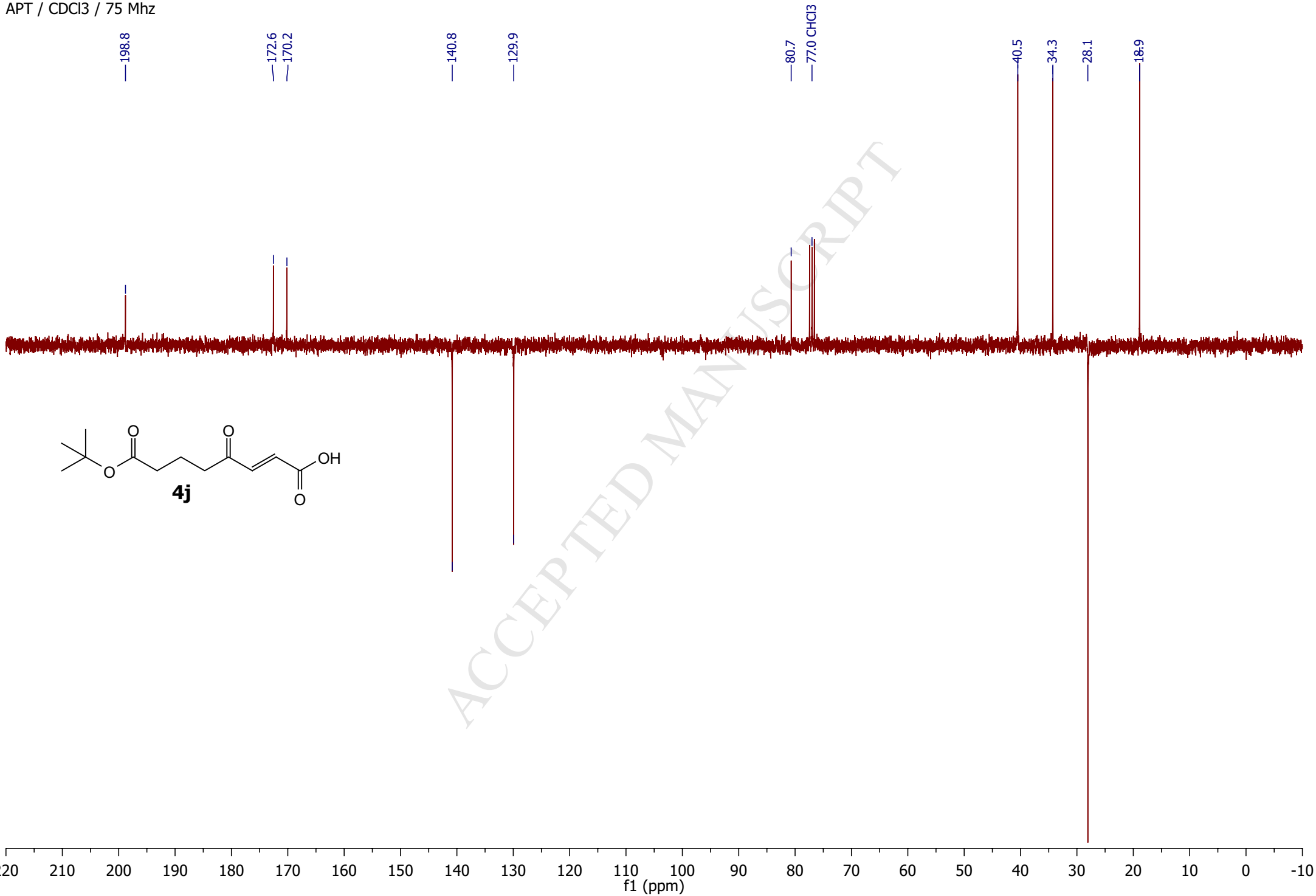


4j

APT / CDCl3 / 75 Mhz



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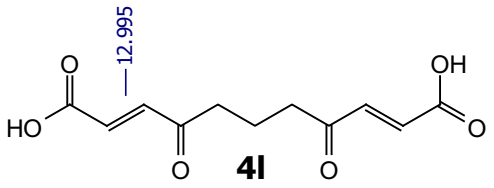

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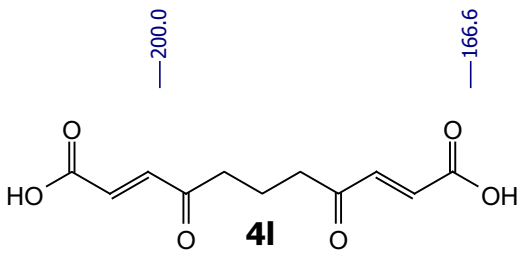

4l