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Many significant bioactive compounds contain quaternary or fully substituted chiral centers. The stereoselective synthesis of these compounds is challenging, yet highly desired because quaternary chiral centers are an important framework in biologically active molecules. This research describes asymmetric methodologies that synthesize novel scaffolds that contain challenging chiral centers to access.

Utilizing a desymmetrization reaction of diesters and dinitriles catalyzed by commercially available Brønsted acids, the synthesis of lactones that contain fully substituted chiral centers is obtained. Previous work completed in the Petersen lab involved an intramolecular desymmetrization of hydroxy-diesters by a chiral phosphoric acid to generate a series of γ-lactones. The first project describes an application of the desymmetrization reaction developed to synthesize novel spirolactones and spirolactams with good yields and stereoselectivity. The next project is the development of desymmetrizations of diesters to access diverse scaffolds of lactones such a novel 1,4-morpholinones, 1,4-dioxanones, and 3,4-dihydrocoumarin with good to excellent yields and enantioselectivities. Lastly, a unique desymmetrization of dinitriles was examined to generate lactones with multiple stereocenters including a quaternary chiral center. This research entails efficient methodologies to access important lactones scaffolds that contain challenging chiral centers.

DESYMMETRIZATIONS OF DIESTERS AND DINITRILES TO SYNTHESIZE ENANTIOENRICHED LACTONES

by

Amber M. Kelley

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Doctor of Philosophy

Greensboro
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Approved by

_____
Committee Chair

To my father Andy Kelley, mother Rebecca Kelley, brothers Andrew, Marshall and William Kelley, grandma Barbara Kensik, grandpa Edwin Kelley, Osbin Perdomo, and angels Anna M. Kelley, Janet Kelley, and Donald Kensik

APPROVAL PAGE

This dissertation written by Amber M. Kelley has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

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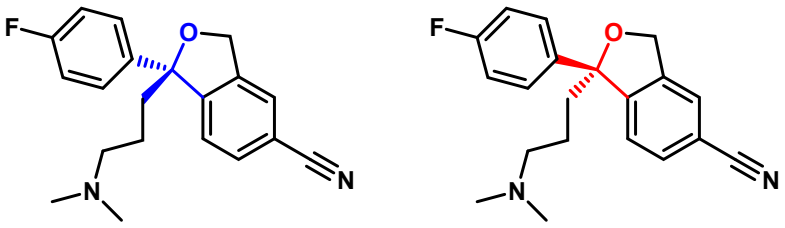
CHAPTER I

INTRODUCTION

1.1 Stereochemistry and its Significance

Many biologically active compounds contain one or more chiral centers in their molecular structure. Therefore, the optical purity of a compound can be directly correlated with its biological activity. The fixed spatial arrangement of a chiral molecule is an important factor involved in interactions with many proteins or enzymes. For example, Citalopram is a chiral compound used as a selective serotonin reuptake inhibiter for treatment of depression and anxiety (Figure 1). Studies have shown that the *S*-stereoisomer of Citalopram (**1**) is significantly more active than its opposite enantiomer *R*-Citalopram (**2**).[1] The differences in activity is a result of each enantiomer interacting with the serotonin reuptake receptor differently.[2] This makes it important to study compounds in their single enantiomeric form. Novel asymmetric reaction methodologies can help us obtain compounds as single enantiomers.



(S)-(+)-Citalopram (1) *(R)*-(-)-Citalopram (2)

Figure 1. Enantiomers of Citalopram

1.2 Asymmetric Methodologies: Quaternary Stereocenters

Stereoselective reactions remain a challenge in organic synthesis. One main challenge is the synthesis of stereocenters that contain enantioenriched quaternary substituted chiral centers. A central carbon that is chiral and has all four bonds directly connected with carbon atoms is a quaternary chiral carbon center. Quaternary chiral stereocenters are an important framework in many important bioactive compounds, so the development of these asymmetric reactions is highly desired.

1.2.1 Prochiral sp^2 C-C Bond Formation

A common strategy to yield optically pure quaternary chiral carbon centers is through formation of a carbon bond to a sp^2 hybridized prochiral carbon. Specific methods used in this strategy are formation of a carbon-carbon bond from a tetra- or tri-substituted alkene, a disubstituted metal carbenoid, or an enolate (Figure 2).[3, 4, 5, 6] This strategy is useful, but it is difficult to make a carbon bond to a fully substituted sp^2 carbon because of steric congestion. Another challenge is enantiotopic facial discrimination which results in limited substrate diversification.

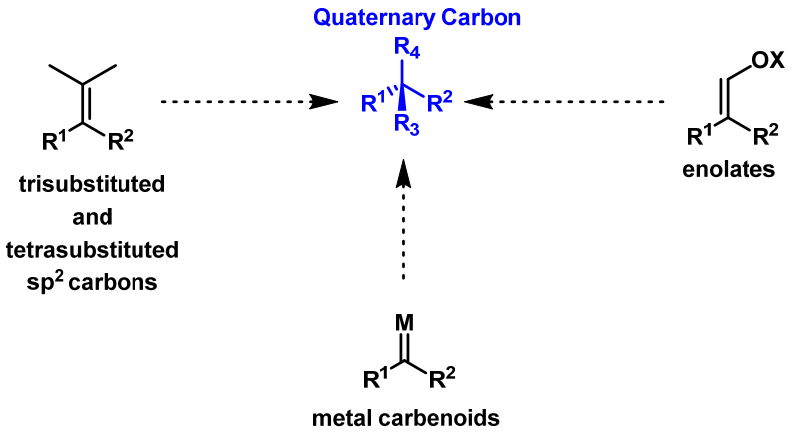


Figure 2. Prochiral sp^2 Carbon Bond Formations

1.2.2 Kinetic Resolutions

In a classical kinetic resolution strategy, an existing racemic quaternary center can be used in the starting material. The racemic starting material (+/- SM) reacts with a chiral catalyst to undergo a desired chemical transformation. When successful, each enantiomer in the racemate (+/- SM) possess different reaction rates because the starting material/chiral catalyst transition state energies are different. Ideally, both the recovered starting material and the product can have 100% enantiopurity, but they can only reach the 50% maximum yield if each enantiomer has a considerably different reaction rate. Classical kinetic resolutions are widely used to achieve enantiopurity.[7, 8, 9] The limitations however arise from the maximum yield of 50%, if 100% enantiopurity is obtained (Figure 3). If the reaction goes to completion the result is a racemic mixture of product, therefore the reaction must be stopped at a specific point.

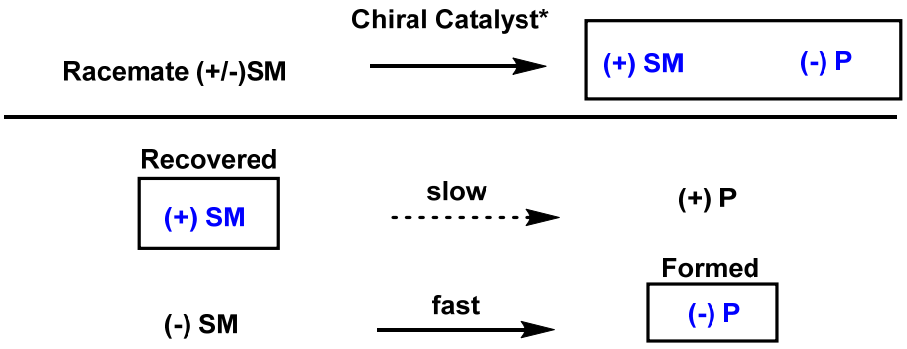


Figure 3. Kinetic Resolutions

The Petersen group reported an example of a classical kinetic resolution of hydroxy esters in the presence of chiral phosphoric acid catalysts to synthesize quaternary stereocenters,[10] by which DFT calculations support a dual activation model of the chiral phosphoric acid catalyst which plays an important role in the enantioselectivity (Figure 4).[11, 12]

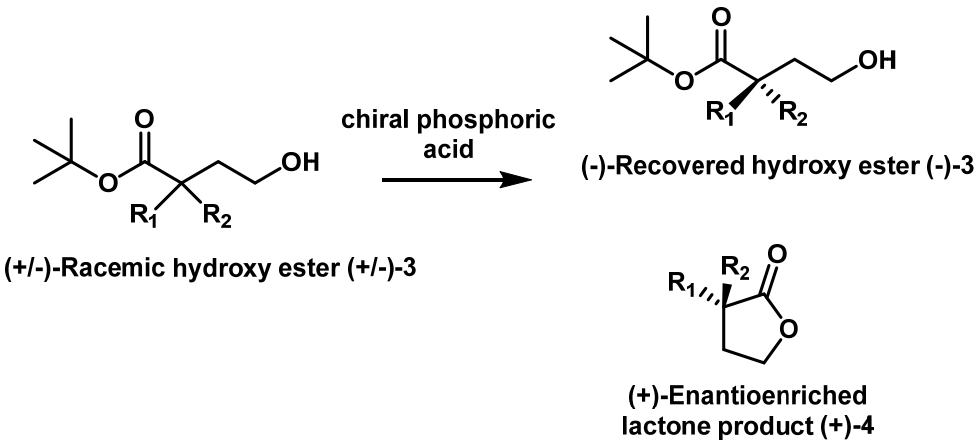


Figure 4. Kinetic Resolution of Hydroxy Esters

Another type of kinetic resolution is the dynamic kinetic resolution where a maximum yield of 100% and 100% ee can be achieved. This can be completed if each

enantiomer of the starting material will undergo a rapid racemization, and the reaction will ideally yield only one enantiomer (Figure 5).[13] However, it is challenging to obtain a system where the racemization is at a fast enough rate to achieve high enantioselectivity and reactivity.

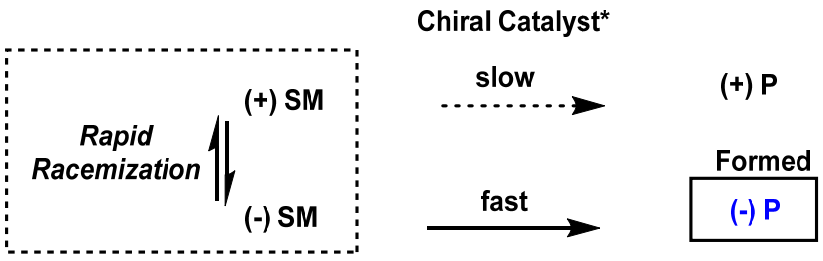


Figure 5. Dynamic Kinetic Resolutions

1.2.3 Desymmetrizations

In a kinetic resolution the starting material is racemic and is resolved. A desymmetrization sets a chiral quaternary stereocenter in a molecule where the quaternary carbon is established before the stereochemistry (Figure 6). Compounds that are prochiral or meso with two enantiotopic groups are used as starting material, and the symmetry is broken enantioselectively while reacting with a chiral catalyst. When transition state energies of the chiral catalyst and each enantiotopic group are significantly different, then the reaction will be highly enantioselective. Desymmetrizations of prochiral and meso compounds such as diols,[14] epoxides, aziridines,[15] and anhydrides[16] have been widely explored.

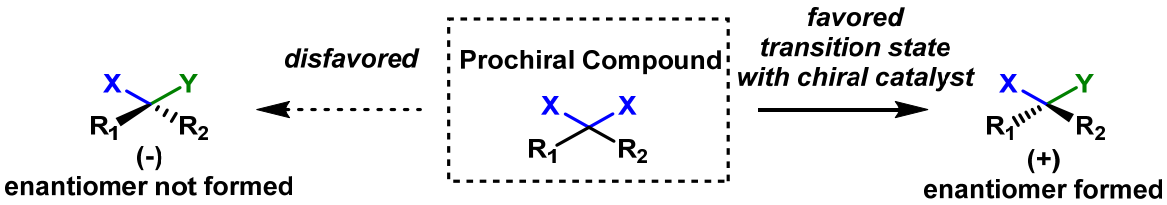


Figure 6. Desymmetrization Strategy

1.3 Desymmetrizations of Diesters and Dinitriles

1.3.1 Desymmetrizations of Diesters

Biocatalysis is a widely used method for enantioselective desymmetrizations of diesters. Specifically, much success in lipase enzyme-mediated diester desymmetrizations have been accomplished by enantioselective transformation of the prochiral diester to a chiral monoester. Work in the formation of tertiary carbon chiral centers has been readily explored using reactions with lipases and phenyl glutaric acid analogs (Figure 7). Palanomo and coworkers utilized *Rhizopus oryzae* lipase (ROL) to synthesize compound **6** in the absolute configuration of *R* with an enantiomeric excess of 92% and excellent yields.[17] Huang and coworkers synthesize a 4-fluorophenyl glutaric acid **8** in the *R* configuration with an enantioselectivity of 92% ee using Novozym 435 as a biocatalyst.[18]

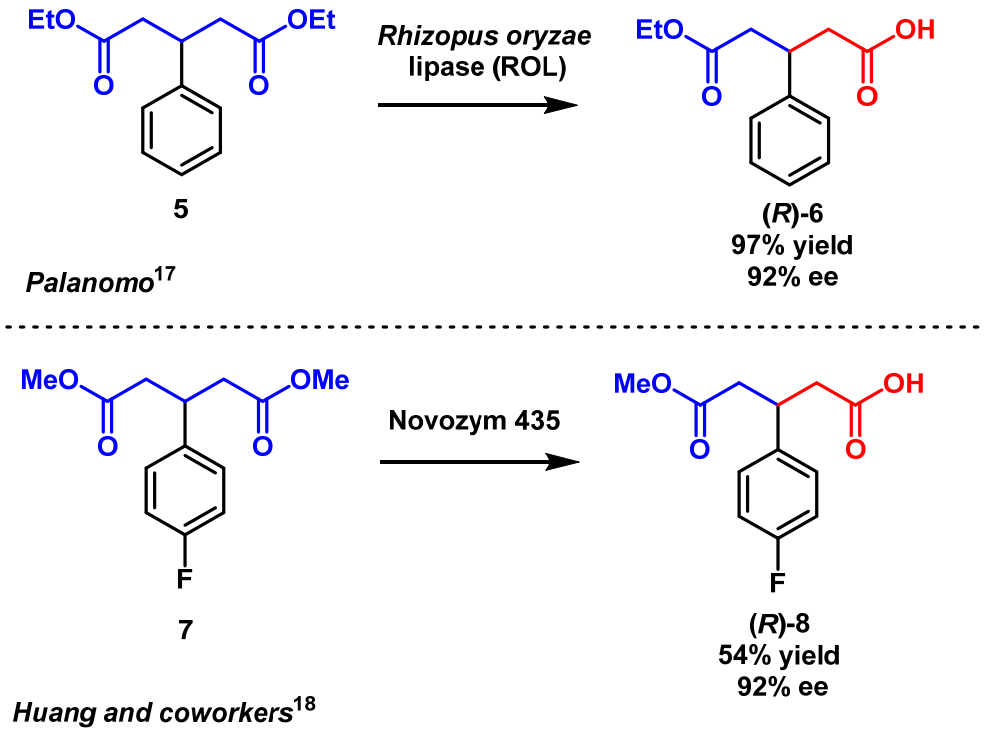


Figure 7. Enzymatic Desymmetrization to Synthesize Phenyl Glutaric Acid Analogs

Important building blocks with tertiary chiral centers with meso cyclohexene diesters such as **9** were used as starting materials in many enzyme mediated desymmetrization reactions. Novozym 435 was used by Goswami to achieve a scalable synthesis of the monoester **10** in a quantitative yield and 99% enantiomeric excess (Figure 8).[19]

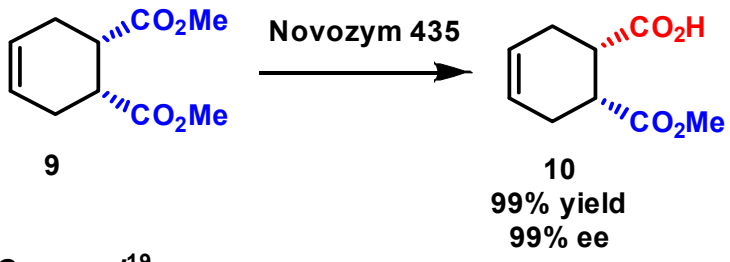


Figure 8. Enzymatic Desymmetrization of Meso Cyclohexene Diesters

The pig liver esterase enzyme (PLE) was discovered to be an excellent enzyme to enantioselectively hydrolyze several disubstituted malonate diesters to yield quaternary stereocenters. The production of methyl cysteine derivatives such as **13** was catalyzed by PLE by an enantioselective hydrolysis of malonate diester **11** to yield monoester **12** in good yield and excellent enantioselectivities by Masterson and co-workers and Kedrowski (Figure 9).[20, 21] A total synthesis of a antimicrobial drug (+)-Virantmycin by a PLE catalyzed desymmetrization of a malonate diester was to set the enantioenriched monoester as the chiral building block was also achieved by Back.[22]

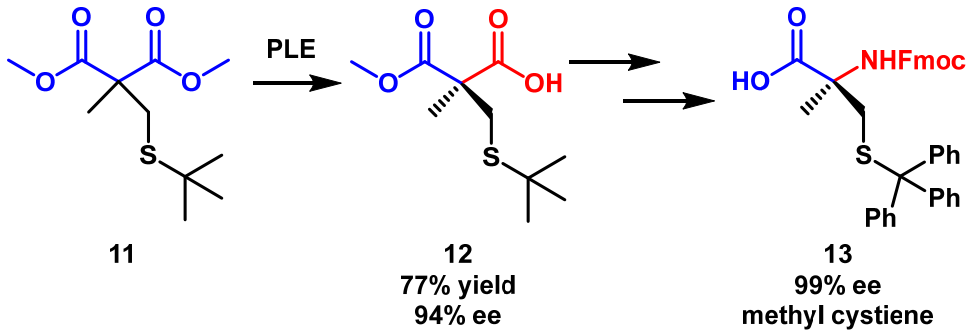


Figure 9. Desymmetrization by Pig Liver Esterase

Aside from enzymatic desymmetrizations of diesters, reports that use chiral phosphoric acids have also been described. Chiral phosphoric acids are mild reagents and are commercially and synthetically available in both configurations, so they can be used as an excellent alternative for enzymes. One of the few examples of a chiral phosphoric acid catalyzed desymmetrization of diesters is in a total synthesis of (-)-leuconoxine (**16**). Here, an intramolecular lactamization reaction of diester **14**, catalyzed by a phosphoric acid catalyst VAPOL (**17**), was used to synthesize a key chiral building block intermediate **15** in an enantiomeric excess of 75% in the synthesis of (-)-leuconoxine (**16**) (Figure 10).[23]

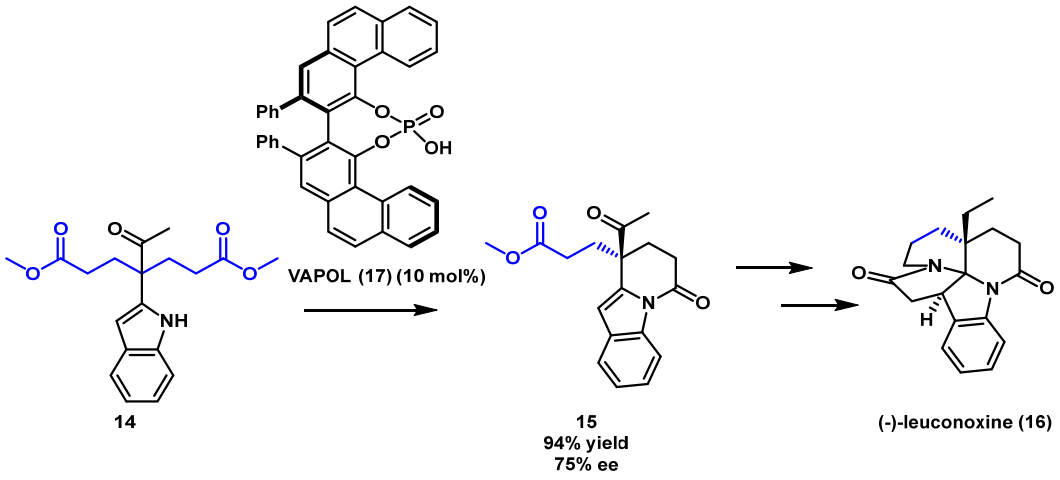


Figure 10. Chiral Phosphoric Acid Desymmetrization

The examples discussed above show substrate scopes that are quite small which limits the robustness of the reactions. An enantioselective ring opening of prochiral bislactones **18** was done by a chiral phosphoric acid catalyst **20** which included the production of several monoacids **19** with high enantioselectivities (Figure 11). The

enantioenriched product **19** was used as a chiral building block to achieve a total synthesis of (-)-Rhazinilam and (-)-Leucomidine B (Figure 11).[24]

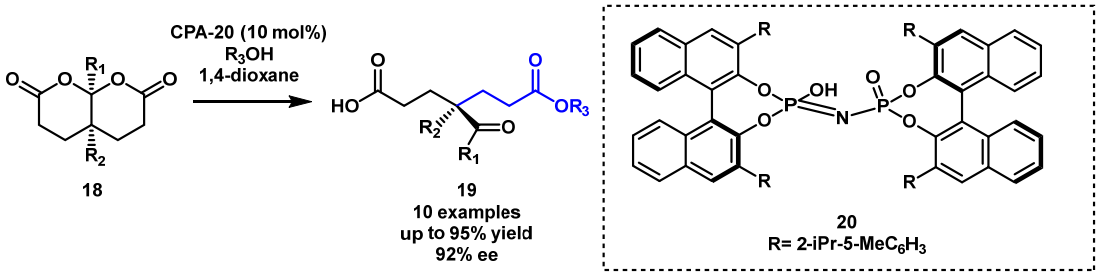


Figure 11. Ring Opening of Bislactones

Wilent and Petersen developed a desymmetrization of malonate diesters **22** using the chiral phosphoric acid catalyst TRIP (**21**), to synthesize several γ-lactones **23** in excellent enantioselectivities up to 98% ee and excellent yields (Figure 12).[25, 26] As proposed in the previously developed kinetic resolution of hydroxy esters by Petersen, a dual activation of the phosphoric acid catalyst promotes an enantioselective cyclization reaction to yield the enantioenriched lactones with quaternary chiral centers.[11,12]

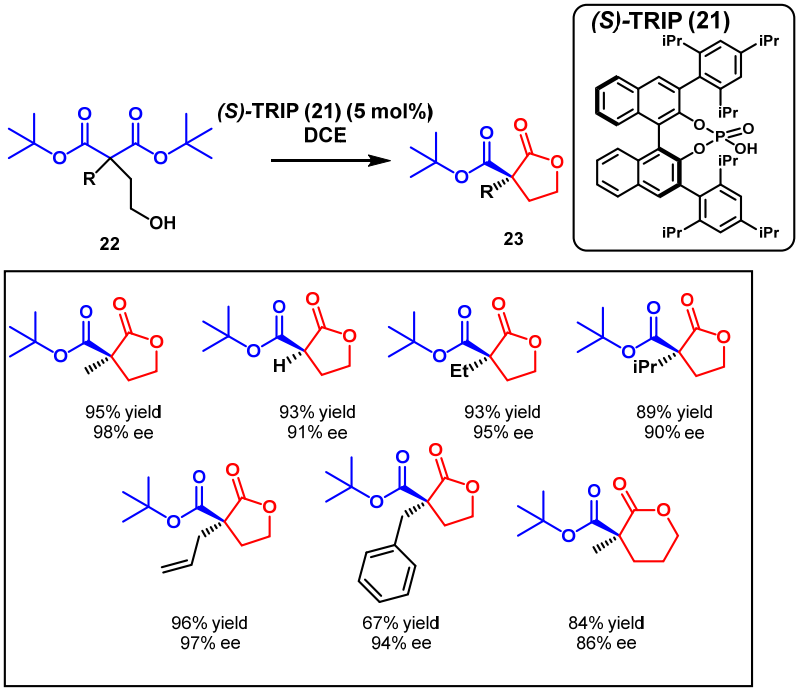


Figure 12. Desymmetrization of Diesters

1.3.2 Desymmetrizations of Dinitriles

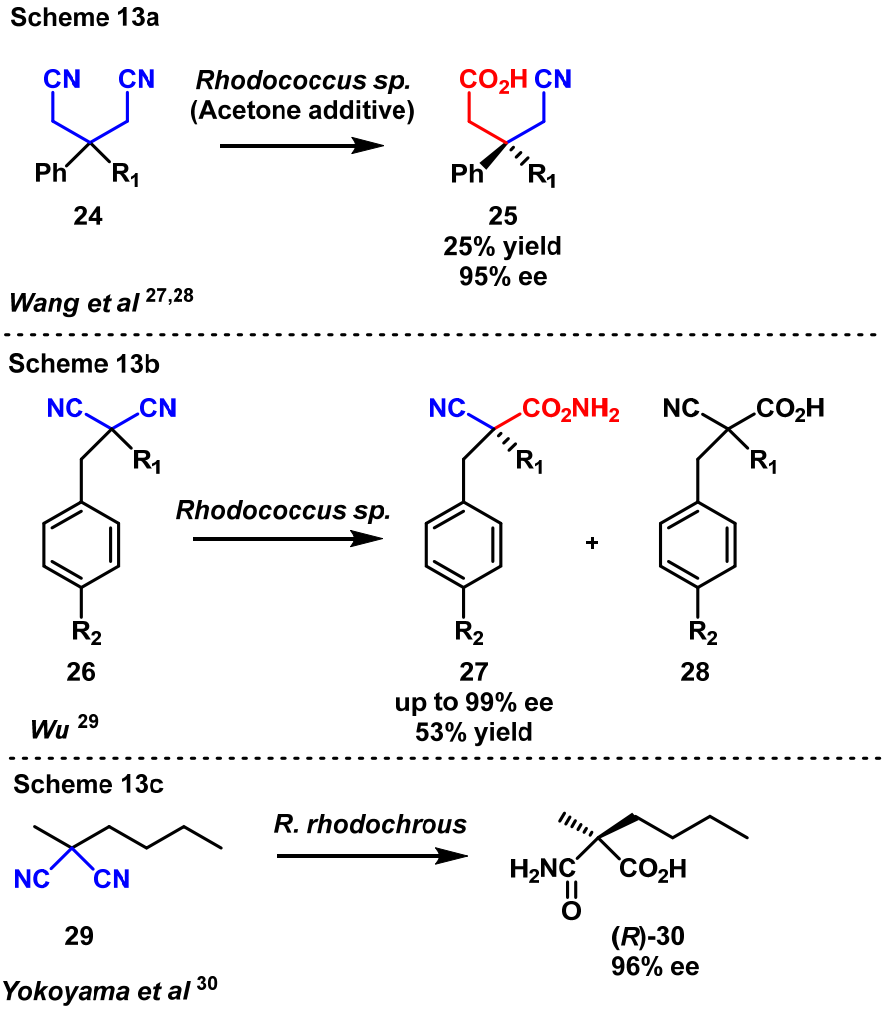


Figure 13. Biocatalytic Desymmetrizations of Dinitriles

As in the desymmetrization of diesters, enzymatic catalyzed desymmetrizations of dinitriles has also been investigated. The two general ways to transform nitriles using biocatalysts are by using hydrolase or hydratase enzymes. These enzymes transform nitriles into carboxylic acids or carboxamides. The desymmetrizations of dinitriles reported are all strictly biocatalytic transformations. Wang used one of the most common

nitrilase enzymes from *Rhodococcus erythropolis* AJ270 to do the desymmetrization of 3-arylgluronitriles **24** to yield cyanobutyric acids **25**, but the resulting products were made in low enantioselectivity (Scheme 13a, Figure 13). They were able to increase the enantioselectivities in the desymmetrization reaction to form cyanobutaric acid products **25** from 64% ee without acetone to 95% ee by using acetone as an additive (Scheme 13a, Figure 13).[27,28] Enzymatic desymmetrizations of malononitriles **26** were explored by Wu using *Rhodococcus* sp. CGMCC 0497. They yielded enantioenriched cyanoamides **27** with high enantioselectivities, although they did get a mixture of the cyanoamides **27** and cyanoacids **28** during the reaction (Scheme 13b, Figure 13).[29] When using *Rhodococcus rhodochrous* ATCC 21197 to a disubstituted malononitrile **29**, it enantioselectively yielded the amide carboxylic acid **30** in 96% ee (Scheme 13c, Figure 13).[30] Overall, the desymmetrization of dinitriles are limited to only biocatalytic reactions and these desymmetrizations have challenges in selectivity.

1.4 Conclusion

The synthesis of enantioenriched chiral building blocks that contain fully substituted and quaternary chiral centers are highly desired in chemical synthesis. The three-dimensional spacial arrangement can be specific to its biological activity. Current synthetic methodologies for preparation of fully substituted and quaternary chiral centers involves the addition to prochiral sp^2 carbons, kinetic resolutions, and desymmetrizations and they all face synthetic challenges. The biocatalytic enantioselective desymmetrizations of prochiral diesters and dinitriles have been studied, but little study has gone into alternative routes. Other possible synthetic routes such as desymmetrization

of diesters and dinitriles using mild Brønsted acids such as chiral phosphoric acid catalyst are a promising alternative route to various chemical transformation

CHAPTER II

ASYMMETRIC SYNTHESIS OF NOVEL SPIROCYCLES UTILIZING A PHOSPHORIC ACID CATALYZED DESYMMETRIZATION

This chapter is published as Kelley, A. M.; Minerali, E.; Wilent, J. E.; Chambers, N. J.; Stingley, K. J.; Wilson, G. T.; Petersen, K. S. *Tetrahedron Lett.* **2019**, *60*, 1262–1264.

2.1 Introduction

Spirocycles are a prevalent moiety of many natural products and significant biologically active compounds. Optically pure spirocycles that contain two fused rings with both lactones and lactams are rare because they are not easy to access synthetically. One of the most notable compounds that contains a spirocyclic moiety with a lactone is the oral contraceptive Drospirenone (**31**) also known as Yasmin (Figure 14).[31] Yasmin (**31**) and other spirocycles contain a tertiary spiro-carbon center which is well studied.[32]

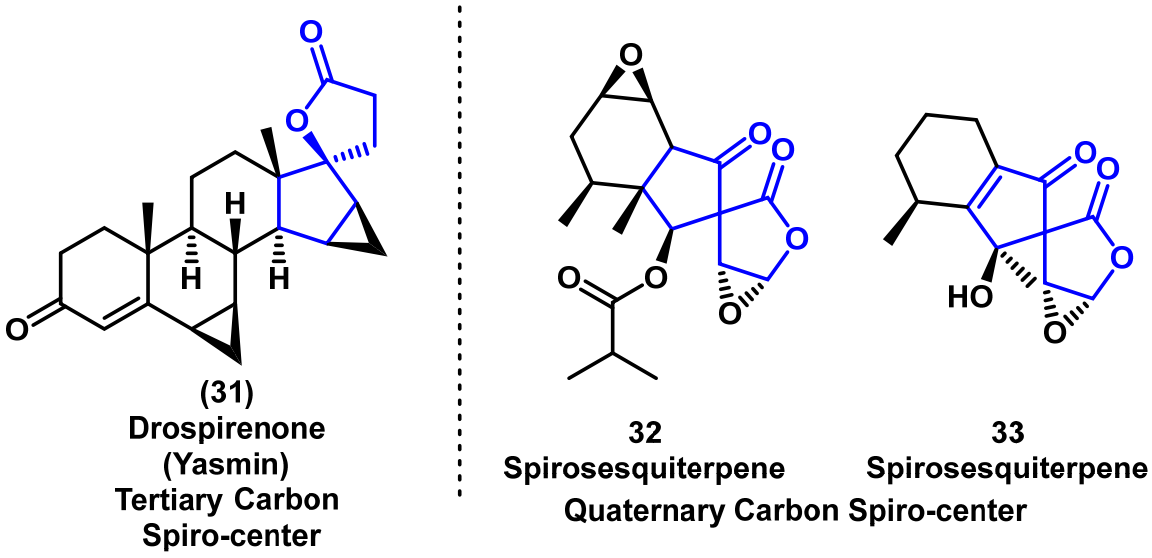


Figure 14. Representative Spirolactones

The synthesis of spiro-lactones and -lactams that contain enantioenriched quaternary spiro-carbon centers is challenging. Spirocycles that contain all carbon chiral centers are less common. Figure 14 shows spirosesquiterpenes **32** and **33**, some of the few examples of spirolactone natural products that contain quaternary spiro-stereocenters.[33, 34] Development of synthetic strategies of these novel spirocycles can expand the synthetic toolbox to access to these important scaffolds. Recently published in the Petersen lab is a straightforward synthetic route to novel spirocyclic scaffolds with chiral quaternary carbon spiro-centers.[35]

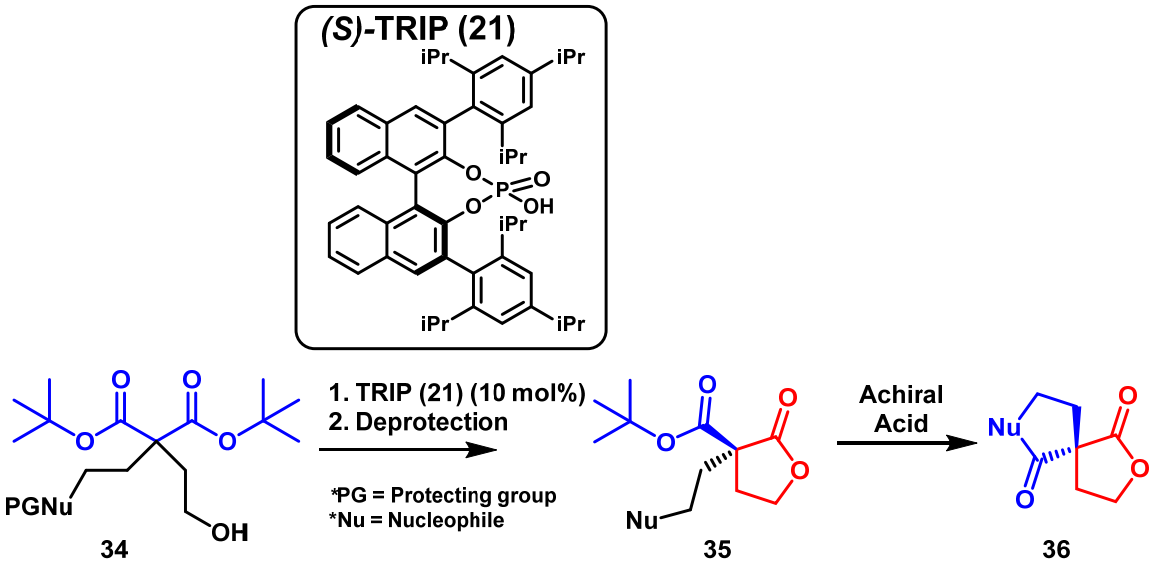


Figure 15. Synthetic Strategy to Obtain Spirocycles

Our strategy to access the spirocycle scaffold involves use of the desymmetrization reaction developed by Wilent and Petersen.[25, 26] The proposed mechanism is a dual activation of the chiral phosphoric acid catalyst TRIP (**21**, Figure 16).[11, 12] Diester **34** is reacted with the TRIP (**21**) to set the enantioenriched stereocenter by the enantioselective desymmetrization. After breaking the symmetry to form the lactone **35**, a second cyclization is achieved by a general achiral acid to yield the desired spirocycle **36** (Figure 15). This strategy allows for access to novel scaffolds using mild and viable reaction conditions.

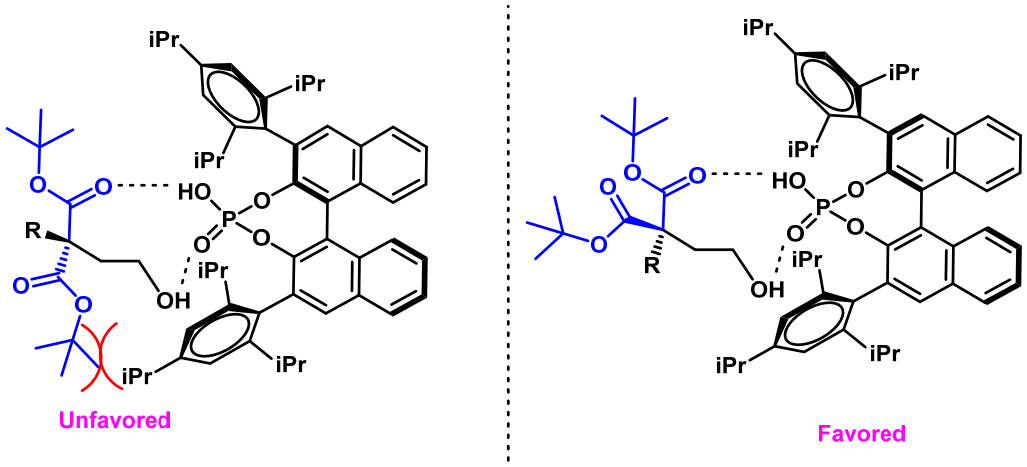


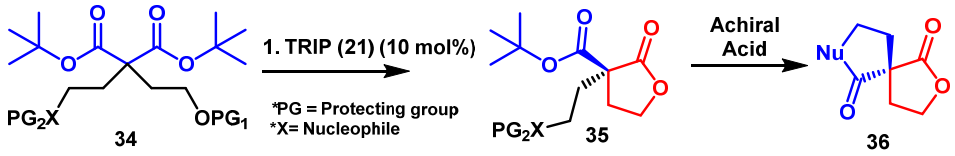
Figure 16. Dual Activation

2.2 Results and Discussion

Six novel spirolactones were derived from readily available dialkylated malonate diesters **34**. The preparation of spirocycle **36a** began by the deprotection of **34a** to yield the corresponding hydroxy-diester. This was reacted in the presence of catalyst **21** to yield lactone **35a** in excellent enantiopurity of 99% ee and 43% two step yield from **34a** (Table 1). During deprotection of the second nucleophile on lactone **35a**, the spirocycle **36a** was readily formed, although the resulting spirocycle was racemic. The synthesis of the second γ-δ-spirocycle **36b** was similar to the previous spirocycle **36a**, but gratifyingly did not result as a racemic spirocycle. The desymmetrization of dialkylated diester **34b** resulted with lactone **35b** in enantiomeric excess of 81%. The second cyclization resulted in a moderate drop of enantiomeric excess, with spirocycle **36b** obtained in a two-step yield of 78% and 63% ee. The synthesis of spirocycle **36c** was derived from the free alcohol of lactone **35b**. Alcohol **35b'** was modified by adding a nitrogen under Mitsunobu conditions to yield the precursor to the spirocycle **36c**. It was discovered using

trifluoroacidic acid, the *tert*-butyl ester was hydrolyzed to the carboxylic acid instead of formation of the desired spirocycle. To avoid this, lactonization of the carboxylic acid and internal amine was accomplished by CDI coupling to yield the enantioenriched spirocycle **36c** with enantiomeric excess of 70% ee. The lactone **35d** was synthesized from diester **34d** with a moderate enantioselectivity of 41% ee and 79% two step yield. The hydroxy-lactone of **35d** was treated with *p*-toluenesulfonic acid to yield the spirocycle **36d** with 24% ee. The γ-lactone-lactam spirocycle **36e**, was synthesized from diester **34e**. Deprotection of diester **34e**, followed by the enantioselective cyclization resulted in lactone **35e** with excellent yields and enantioselectivity (88% yield, 84% ee). The spirocycle **36e** was formed after a second cyclization using trifluoracetic acid in 85% yield and 60% ee. The product was recrystallized which brought the enantiomeric excess up to 85%. After the diester **34f** was deprotected, the corresponding hydroxy diester was treated with the TRIP (**21**) catalyst to yield lactone **35f** in 76% enantiomeric excess. The phenol synthesized from lactone **35f** was reacted with *p*-toluenesulfonic acid which resulted in a mild drop of enantiomeric excess to yield the spirocycle **36f** in 72% ee. The absolute configuration of the final spirocycles were determined by the crystallography data of spirocycle **36c** (Figure 17). All the spirocycles absolute configuration was based on the data of spirocycle **36c**. The results show that in the synthesize of every spirocycle, there is a moderate drop in enantioselectivity from the lactone to the final spirocycle. This is proposed to be a result of a competition between the nucleophilic attack at the carbonyls in the *tert*-butyl ester and the lactone which causes a scrambling of the stereocenter.

Table 1. Results of Spirocycles



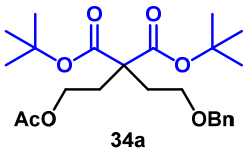
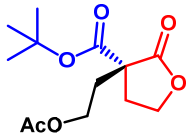
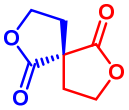
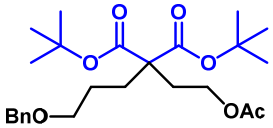
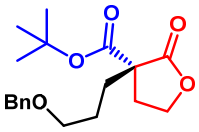
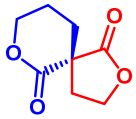
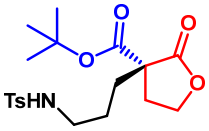
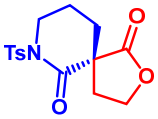
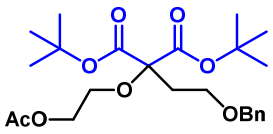
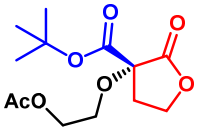
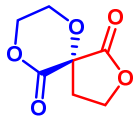
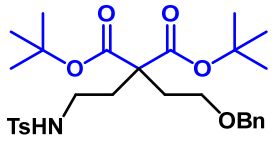
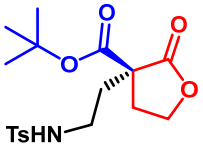
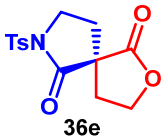
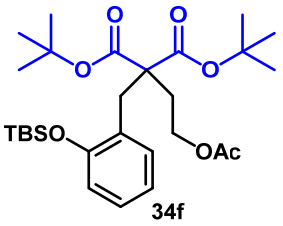
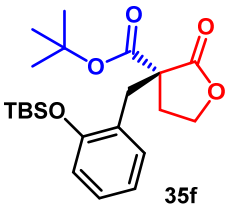
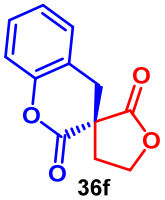
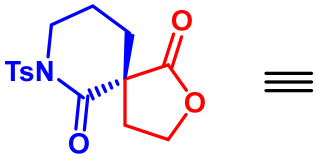
Diester	Lactone	Spirocycle
 34a	 35a 39% yield (from 34a) 99% ee	 36a 92% yield (from 35a) 0% ee
 34b	 35b 49% yield (from 34b) 81% ee	 36b 78% yield (from 35b) 63% ee
	 35c 56% yield (from 34b) 81% ee	 36c 41% yield (from 35c) 70% ee
 34d	 35d 79% yield (from 34d) 41% ee	 36d 60% yield (from 35d) 24% ee

Table 1. Results of Spirocycles (cont.)

Diester	Lactone	Spirocycle
 34e	 35e 88% yield (from 34e) 84% ee	 36e 85% yield 60% ee -> 85% after recrystallizaion
 34f	 35f 54% yield (from 34f) 76% ee	 36f 34% yield (from 35f) 72% ee

X-Ray Data



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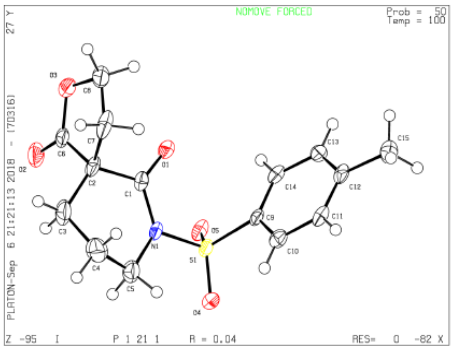


Figure 17. X-Ray Data

There are two pathways that could occur to result in the desired spirocycle during the second cyclization (Figure 18). Pathway 1 would result in a "retention" of stereochemistry from lactone **35b'**to spirocycle **(*R*)-36b**. In this pathway, the nucleophile would react with the carbonyl of the *tert*-butyl ester to produce the desired spirocycle. On the other hand, in Pathway 2 the second nucleophile could react with the carbonyl in the

lactone which would result in an "inversion" of stereochemistry, and finally the resulting alcohol would attack the carbonyl of the *tert*-butyl ester to yield the spirocycle **(*S*)-36b**. A masters student Tyler Wilson monitored the second cyclization of **35b'** via ^{1}H NMR experiment shown in Figure 19. This figure shows snapshots of the experiment where the signal at 3.6 ppm represent proton a (H^a), and the signal at 2.9 ppm represents proton b (H^b). This NMR experiment suggest that Pathway 1 is the favored pathway where there is a direct conversion of **35b'** to spirocycle **36b** and a retention of stereochemistry. To explain the moderate drop in enantioselectivity we postulated that there is an undetectable amount of intermediate **35b''**, that is going through Pathway 2, which is "inverting" the stereochemistry in trace amounts.

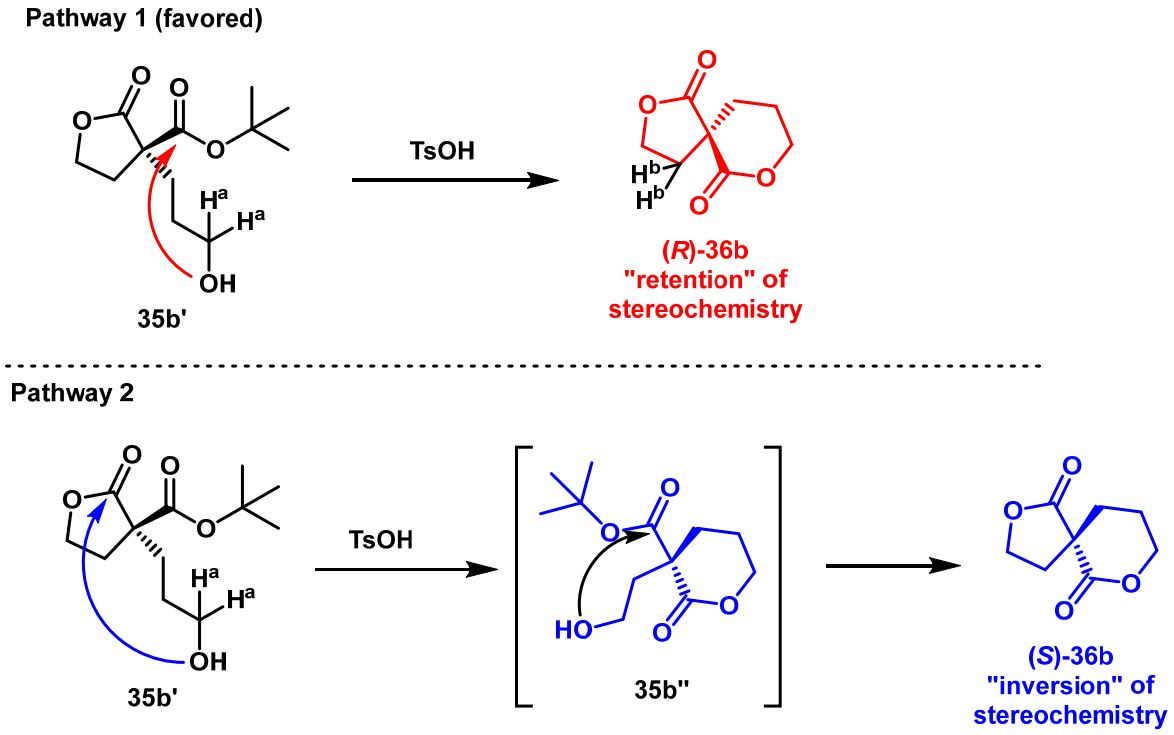


Figure 18. Mechanistic Considerations

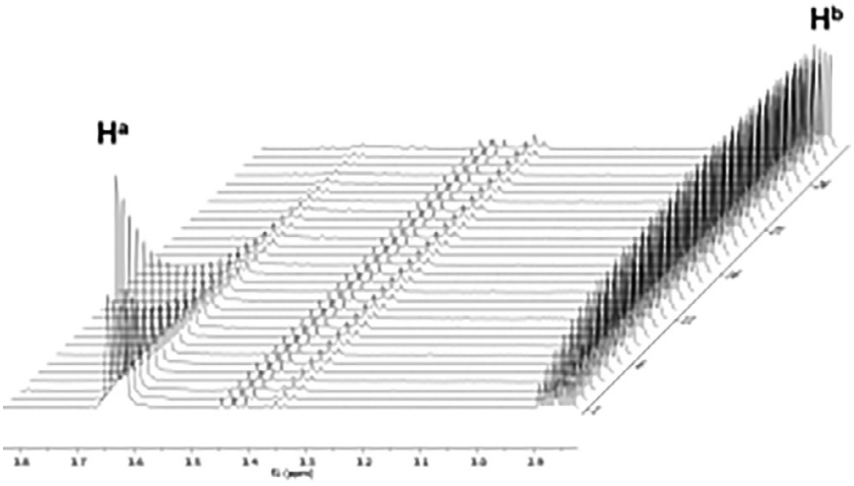


Figure 19. ^{1}H NMR Experiment

2.3 Conclusion

In conclusion, a facile synthesis of novel spirocyclic was achieved by using readily available prochiral diesters and Brønsted acids. The use of a chiral phosphoric acid catalyzed desymmetrization of diesters, allowed the enantioenriched quaternary chiral center to be set. Although during the final cyclization to form the spirocycles there was a moderate drop in enantioselectivity, this synthesis gives access to novel spirocyclic scaffolds that were previously not synthetically available.

CHAPTER III

ENANTIOSELECTIVE DESYMMETRIZATIONS OF DIESTERS TO SYNTHESIZE FULLY SUBSTITUTED CHIRAL CENTERS OF NOVEL 3,4-DIHDYROCOUMARINS AND RELATED COMPOUNDS

This chapter is published as Kelley, A. M.; Haywood, R. D.; White, J. C.; Petersen, K. S. *ChemistrySelect* **2020**, *5*, 3018–3022.

3.1 Introduction

Access to diverse scaffolds that closely resemble natural products is important in drug discovery and development. Some significant scaffolds are lactones that have a chiral center at the α-position of the carbonyl.[36, 37, 38] One example of a lactone that is known to have a diverse range of bioactivity is the coumarin moiety.[39, 40, 41, 42] Specifically, the 3,4-dihydrocoumarin moiety is an interesting scaffold, as well as other unique lactones such as 1,4-dioxanones and 1,4-morpholinones which contain an extra heteroatom in the ring such as an oxygen or nitrogen which are shown in Figure 20. An example of a 1,4-dioxanone with a chiral center at the α-position is compound **37** which is a potent shikimic acid pathway inhibiter.[43] Aside from 1,4-dioxanones, 1,4-morpholinones contains a nitrogen in the heterocycle. Schizine A **(38)** is a 1,4-morpholinone natural product that is isolated from *Schizophyllym commune* that has anticancer properties.[44] Examples of compounds that contain the 3,4-dihydrocoumarin core structure are the natural product Herbertenolide (**39**), and anticoagulant Ammodoremin (**40**, Figure 20).[45, 46] A facile, robust synthetic methodology that gives

access to these types of scaffolds with enantioenriched fully substituted chiral centers is highly valuable. This chapter describes a desymmetrization methodology yielding novel lactones that contain fully substituted chiral centers that was recently published by the Petersen laboratory at the University of North Carolina Greensboro.[47]

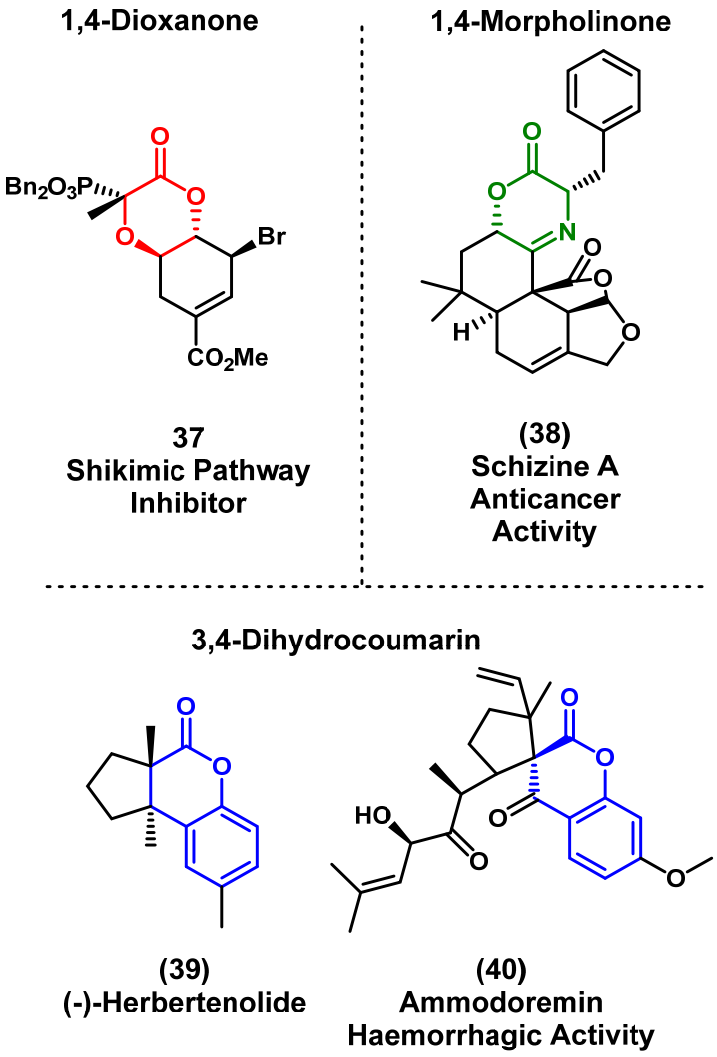


Figure 20. Representative Lactone Scaffolds

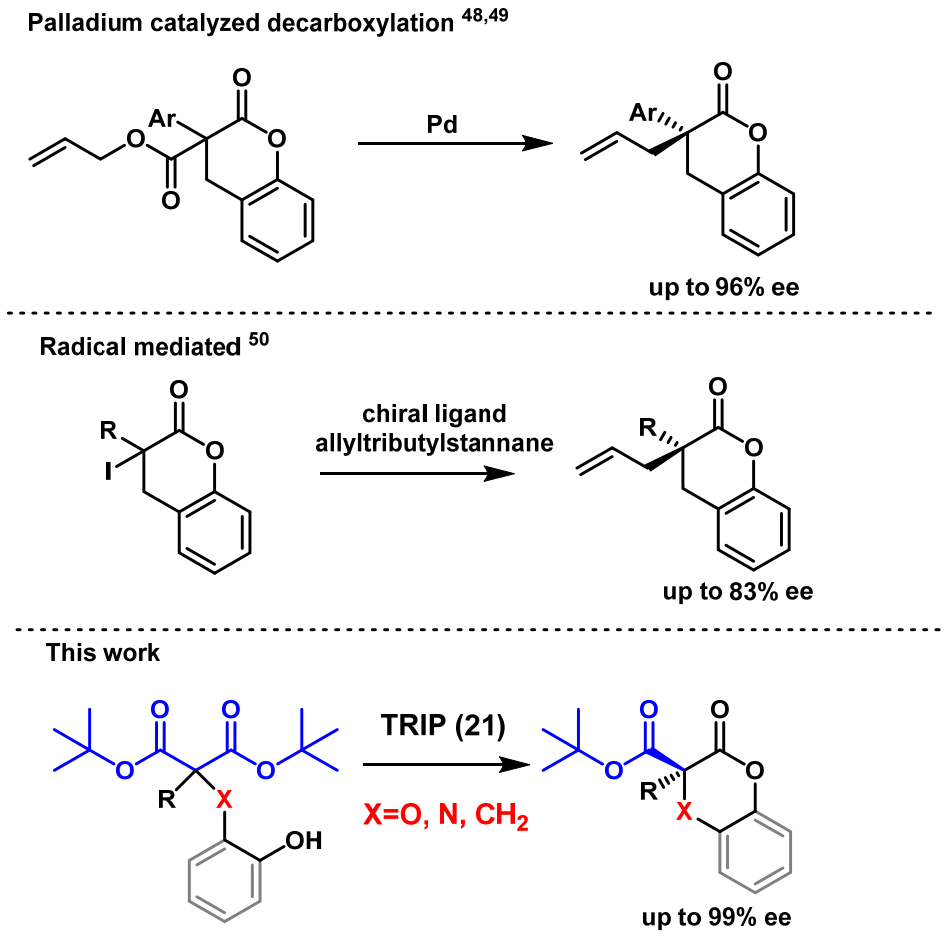


Figure 21. Synthetic Methodologies.

One of the major challenges in asymmetric methodology is synthetic access to diverse fully substituted chiral centers and scaffolds. Previous methodologies to synthesize the 3,4-dihyhdrocoumarin moiety with quaternary chiral stereocenters include palladium catalyzed decarboxylation, radical mediated processes, and use of organocatalysts (Figure 21).[48, 49, 50, 51] The organocatalytic reactions relies on tandem Michael additions/cyclization reactions.[51, 52] Unlike previous methods, this desymmetrization methodology provides access to a diverse array of scaffolds including

novel 3,4-dihydrocoumarin scaffolds. This methodology allowed for variability of the alkyl groups in the quaternary and fully substituted chiral centers which was a challenge in previous methods. The ability to achieve quaternary and fully substituted chiral center with carbon, oxygen, and nitrogen heteroatoms is also available using the described methodology.

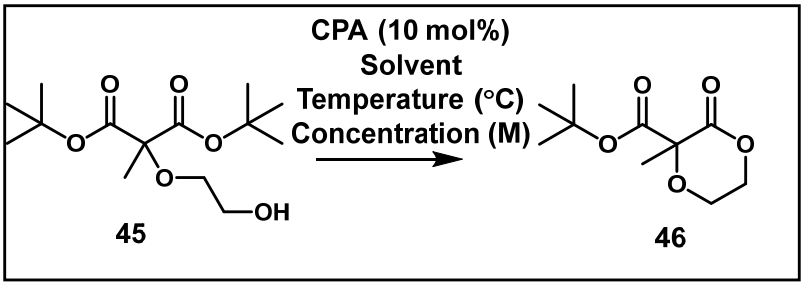
3.2 Results and Discussion

The investigation began by a catalyst screen of hydroxy-diester **45** and several chiral phosphoric acids (CPA) to synthesize lactone **46**. The reactions would only go to completion at high temperatures, so the catalyst screen was carried out at 100 ^{o}C in toluene. Treatment of diester **45** with chiral phosphoric acid catalyst **41** resulted in no reaction conversion (entry 1, Table 2). A screen of other chiral phosphoric acid catalyst showed TRIP (**21**) resulted in the preparation of lactone **46** in the highest overall enantioselectivity of 66% ee and yield of 66% (entry 2, Table 2). The reaction was further optimized using TRIP (**21**) catalyst by changing the concentration and temperature in toluene (entries 6-7, Table 2). By lowering the temperature and increasing the concentration to 0.5 M the enantioselectivities increased, but the yields greatly decreased. Solvents with high boiling points were examined which resulted in our optimized conditions of bromobenzene at 0.1 M and 100 ^{o}C which gave the highest yield of 89% and 80% ee (entry 9, Table 2).

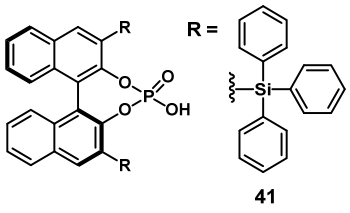
Optimized reaction conditions were used for the desymmetrization reaction of diesters to synthesize the 1,4-dioxanone synthesis (Table 3). The desymmetrization reaction of the α-substituted methyl diester **45** resulted in a lactonization with good

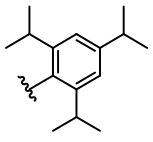
stereoselectivity and yields (**46**, 81% ee, 80% yield). Although once the α-substituted group was increased in size, the desymmetrization reaction resulted in lower reactivity and yields. The reaction of the diester **47** which contained an ethyl group resulted lactone **48** in a good yield, but moderate enantioselectivity (75% yield, 42% ee). Even larger α-substituted groups resulted in lactones **50** and **52** with lower yields and lower enantioselectivities. The reaction of malonate diester **53** resulted in 1,4-morpholinone **54** in moderate yield and enantioselectivity (48% yield, 40% ee).

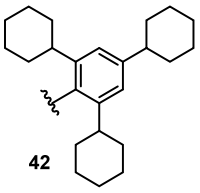
Table 2. Reaction Optimization

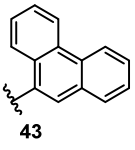


Entry	Catalyst	Solvent	Temp (°C)	Conc (M)	Yield %	ee %
1	41	Toluene	100	0.1	trace	--
2	21	Toluene	100	0.1	66	66
3	42	Toluene	100	0.1	33	55
4	43	Toluene	100	0.1	78	36
5	44	Toluene	100	0.1	38	0
6	21	Toluene	100	0.5	98	75
7	21	Toluene	80	0.5	39	88
8	21	CF_3Ph	100	0.1	75	70
9	21	BrPh	100	0.1	89	80









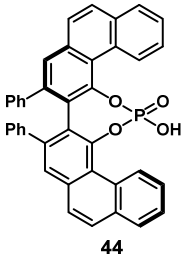
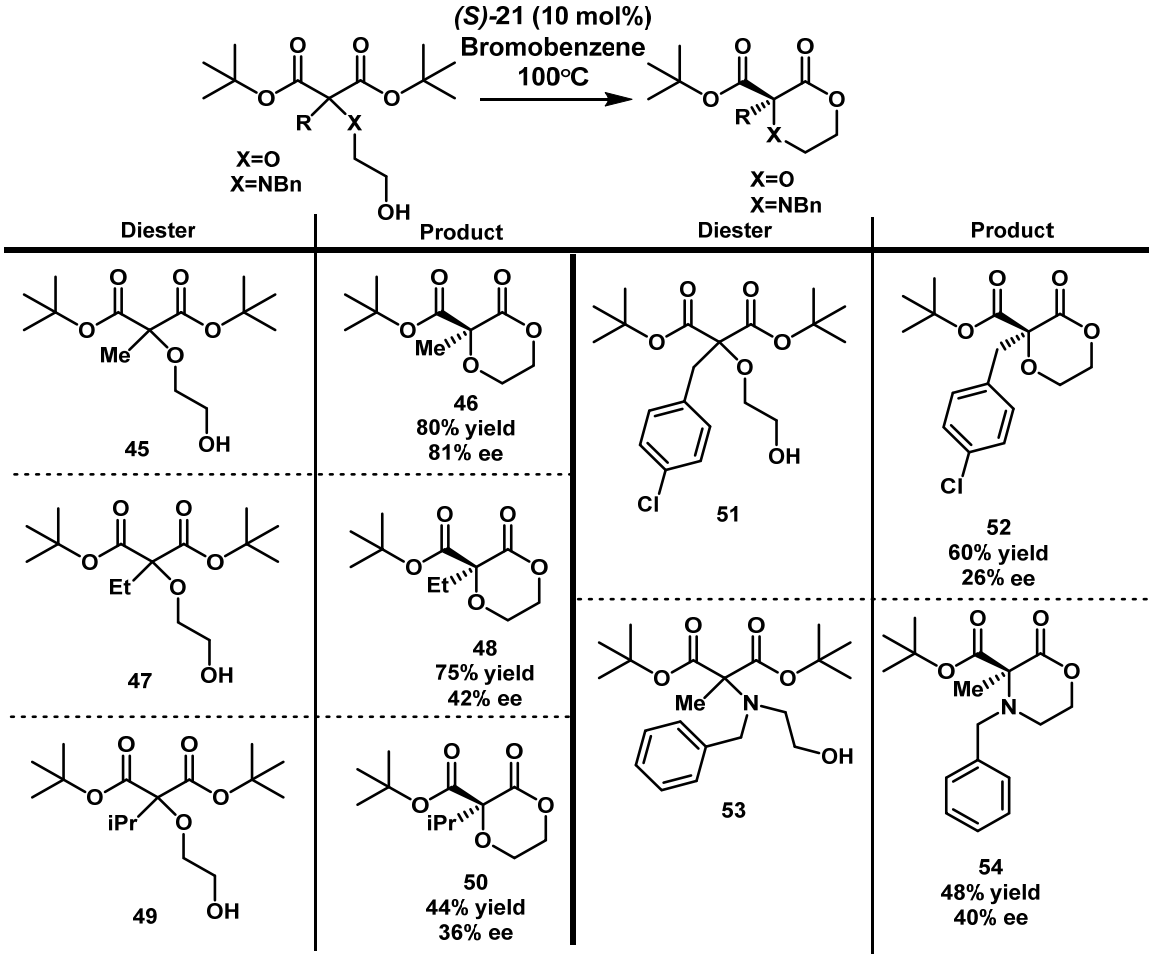


Table 3. Substrate Scope of 1,4-Dioxanones and 1,4-Morpholinones



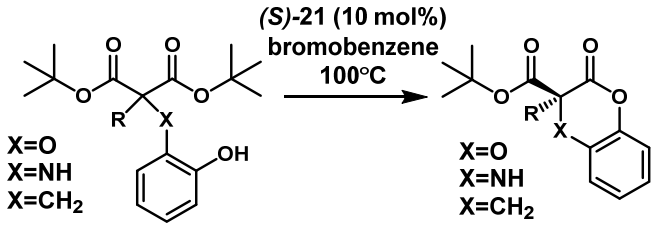
Next, the exploration of the synthesis of novel 3,4-dihydrocoumarin compounds with the optimized desymmetrization conditions was carried out. The main difference between the desymmetrizaiton of the previous diesters (Table 3) and this work is that the alkyl chains of the nucleophilic hydroxy group are functionalized. The first set of coumarins surveyed were 3,4-dihydrocoumarins that have a fully substituted chiral center containing an oxygen heteroatom. Diester **55**, which contains an α-substituted methyl group was subjected to optimized conditions and yielded the 3,4-dihydrocoumarin

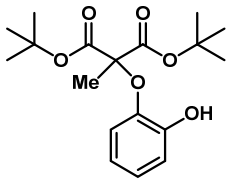
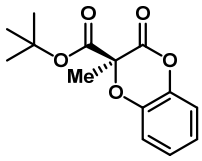
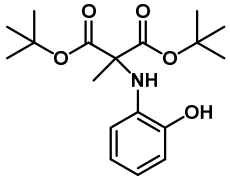
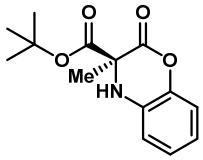
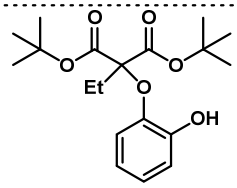
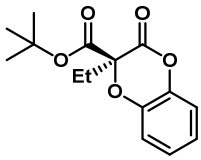
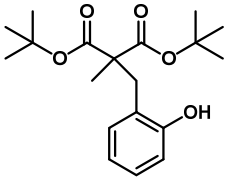
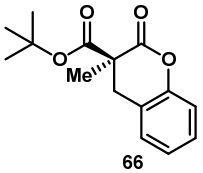
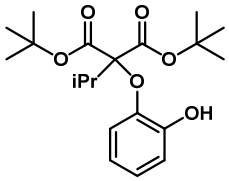
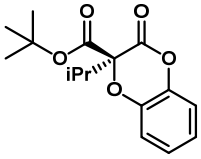
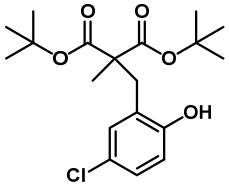
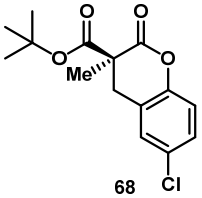
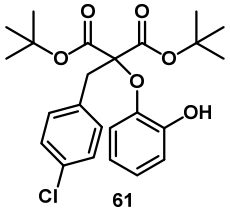
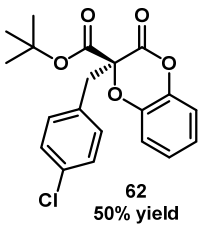
compound **56** in good yield and excellent enantiomeric excess (75% yield, 92% ee). Gratifyingly, upon increase of the steric size of the α-substituted groups, the enantioselectivities and reactivities did not decrease significantly (Table 4). Next, the synthesis of a 3,4-dihydrocoumarin that contain a fully substituted chiral center with a carbon-nitrogen bond was examined. The prochiral diester **63** underwent reaction with catalyst **21** and formed the 3,4-dihydrocoumarin **64** in good yields and enantioselectivity (50% yield, 87% ee). To our surprise, the desymmetrizaiton reaction worked well without a protecting group on the nitrogen. The synthesis of 3,4-dihydrocoumarins that contain an all carbon quaternary chiral center was very successful using the desymmetrizaiton methodology. Diester **65** was reacted with the optimized conditions and yielded 3,4-dihydrocoumarin **66** in excellent yields and enantioselectivity (96% yield, 99% ee). An example of a diester which contained a chloro-substituted phenol was examined. Diester **67** was reacted with 5 mol% of TRIP (**21**) catalyst and resulted in a 3,4-dihydrocoumarin **68** with a good enantiomeric excess of 82% ee, and 73% yield. The absolute configuration of 3,4-dihydrocoumarin **68** was determined by X-Ray crystallography, and all other lactone's absolute configuration was assigned based on its comparison (Figure 23).

Based on the observed outcome of stereochemistry we propose that π-stacking and sterics play a role in the transition state between the catalyst and the substrate. Computational studies a similar kinetic resolution, propose that there is a dual activation from the phosphoric acid catalyst on the substrate.[12] The Brønsted acidic proton from the chiral phosphoric acid activates the carbonyl on the diester while the Lewis basic oxygen

coordinates with the phenol. Pathway 1 is a favored transition state because of π-stacking and steric hindrance which results in a lower energy versus Pathway 2. Noncovalent interactions such as π-stacking between substrates and BINOL derived phosphoric acid catalysts have been previously supported by DFT calculations.[53,54] In pathway 2 we propose that the sterics of the *tert*-butyl ester and aryl groups of the chiral catalyst are disfavored (Figure 22).

Table 4. Substrate Scope of 3,4-Dihydrocoumarins



Diester	Product	Diester	Product
 55	 56 75% yield 92% ee	 63	 64 50% yield 87% ee
 57	 58 69% yield 86% ee	 65	 66 96% yield 99% ee
 59	 60 79% yield 56% ee	 67	 68 73% yield 82% ee[a]
 61	 62 50% yield 69% ee		

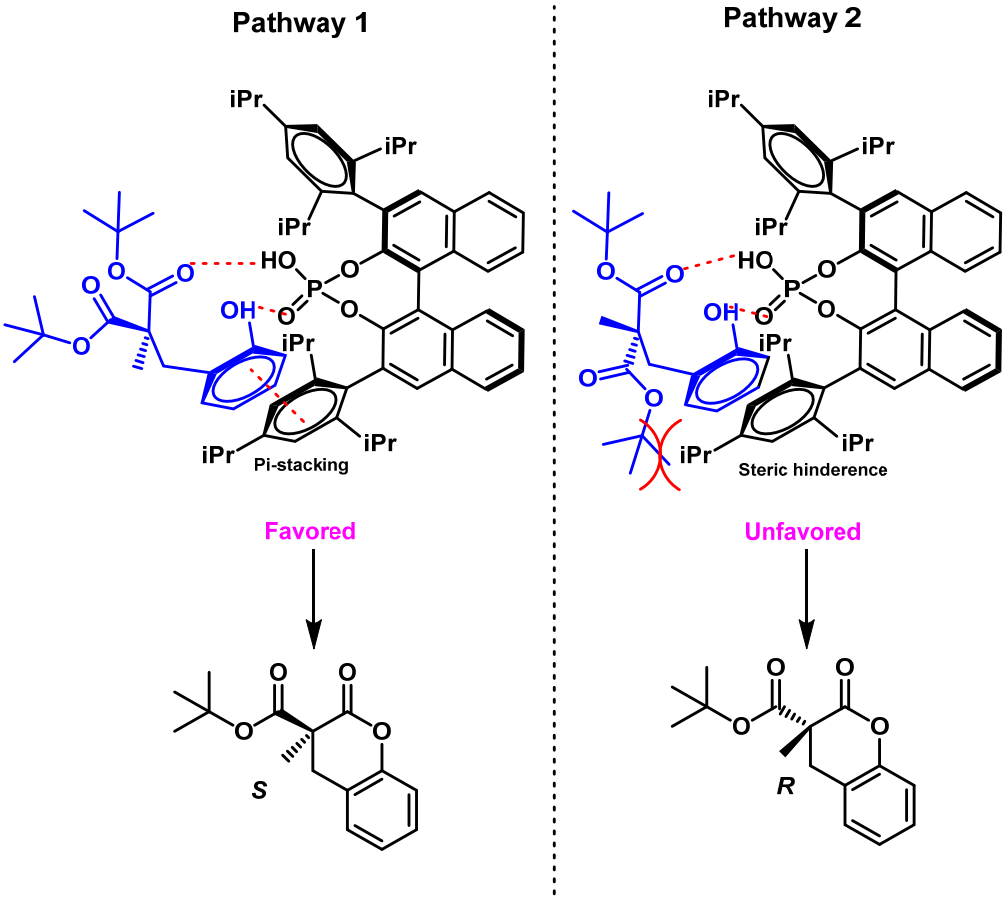


Figure 22. Rational of Stereochemistry

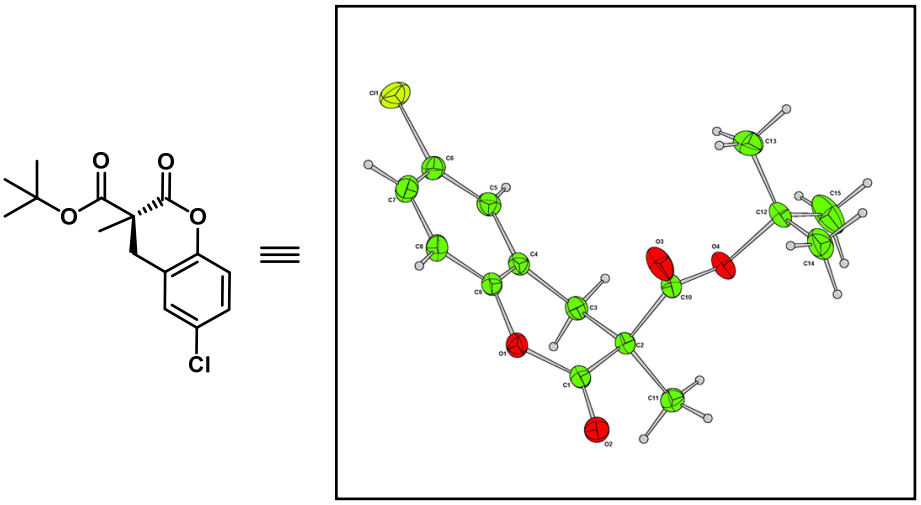


Figure 23. X-Ray Data

3.3 Conclusion

In summary, this desymmetrizaiton methodology provided facile access to novel enantioenriched 1,4-dioxanones, 1,4-morpholinones and 3,4-dihydrocuomarins. Utilizing the commercially available chiral catalyst (**21**), a desymmetrizaiton of diesters yielded a diverse scope of the lactone scaffold which contained fully substituted chiral centers. Although the 1,4-dioxanones and 1,4-morpholinones were prepared in moderate to good enantioselectivity, they were found to be limited by the size of the α-substituted alkyl group. On the other hand, the 3,4-dihydrocoumarin compounds were prepared in good to excelled enantioselectivity. We propose that the π-stacking and the sterics of the starting material and the chiral catalyst plays a role in the stereoselectivity.

CHAPTER IV

DESYMMETRIZATIONS OF DINITRILES TO SYNTHESIZE ASYMMETRIC LACTONES

4.1 Introduction

Novel methodologies to access chiral building blocks such as lactones are important to the synthetic chemistry community. An unexplored approach to access asymmetric scaffolds is utilizing nitriles as a source of an electrophilic carbon. One of the most notable reactions using an electrophilic nitrile is known as the Pinner reaction. Traditionally, the Pinner reaction proceeds via the formation of an imidate salt (Pinner salt) using an alcohol, nitrile, and gaseous HCl (Scheme 24a, Figure 42).[55] The addition of acid and water to a Pinner salt initiates a further hydrolysis to produce an ester. Since gaseous HCl is a difficult reagent to use, select other acid alternatives have been examined. One of these methods, the use of cyclopentyl methyl ether (CMPE) as solvent in 4N HCl which allowed facile filtration of the Pinner salt was developed by Watanabe and Coworkers (Scheme 24b, Figure 24).[56] A limitation of the Pinner reaction is its low substrate diversification and functionalization. This is partly due to protocols which require the reaction to be done under neat, highly acidic conditions of which one example is Ptaff and coworkers whom developed a Lewis acid activated Pinner reaction (Scheme 24c, Figure 24).[57] Alternatively, Aplander and coworkers developed a Pinner/hydrolysis reaction that was formed to use lactones which used an acidic resin, although the products lacked acid sensitive functional groups (Scheme 24d, Figure 24).[58] A close

examination of the use of Brønsted acids to activate nitriles in reactions such as the Pinner is needed. Mild Brønsted acids offer many potential advantages, including the potential to yield products that are enantioenriched and/or contain acid sensitive groups. We propose the use of mild Brønsted acids to desymmetrize dinitriles by an intramolecular lactonization to produce lactones with a nitrile handle that could be used in further modifications. This methodology will explore both diastereoselective and enantioselective variations, and this approach can provide an alternative Pinner/hydrolysis reaction to synthesize lactones in a stereoselective manner.

Previous work in the Petersen lab has centered around desymmetrizations of diesters utilizing the electrophilic carbon in the carbonyl to set stereocenters. This work uses the synthetic approach of the diester's desymmetrizaiton, but instead uses a dinitrile desymmetrization. Here, an intramolecular cyclization of the nitrile activated by a Brønsted acid yields a lactone with multiple stereocenters stereoselectivity.

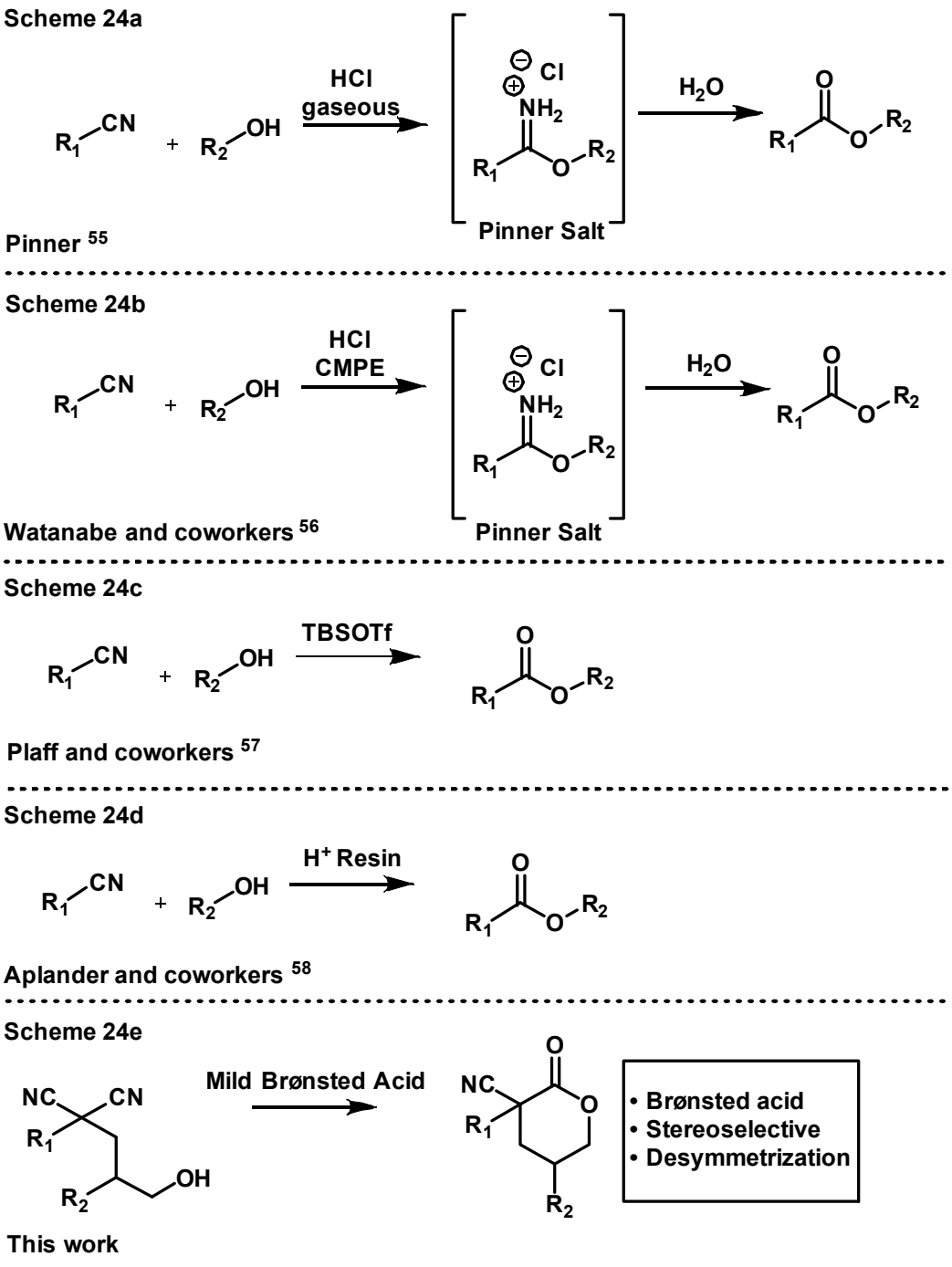


Figure 24. Pinner/Hydrolysis Reactions

4.2 Results and Discussion

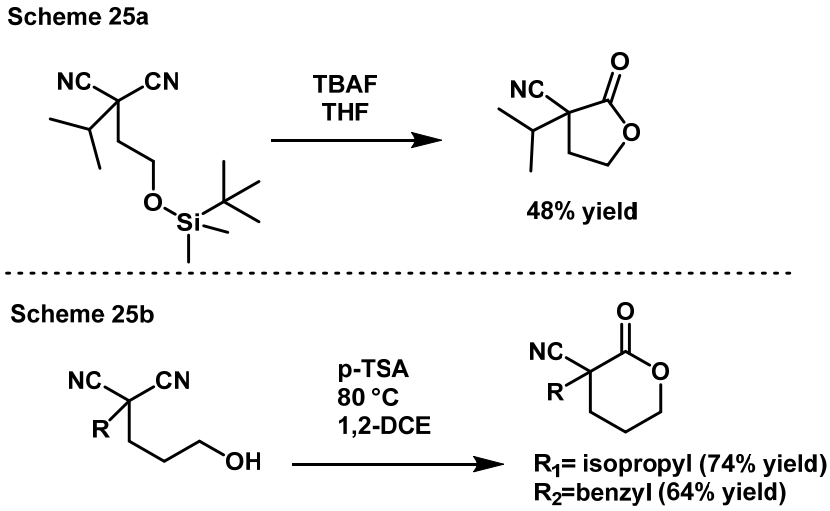


Figure 25. General Pinner/Hydrolysis Reaction

The investigation began to determine if the intramolecular cyclization of the internal alcohol and nitrile would yield a lactone. In scheme 25a an undergraduate student Emiri Michishita synthesized a gamma lactone by using TBAF to deprotect the alcohol. Instead of obtaining the alcohol, the lactone was produced in 48% yield (Figure 25). Masters student Tylisha Baber Ph.D, showed that delta lactones could be produced in good yields by reacting hydroxy dinitriles with a Brønsted acid in good yields (Scheme 25b, Figure 25). To explore the diastereoselective cyclization of a dinitrile, the reaction was optimized with dinitrile **(+/-)-69** using a series of Brønsted acids. Various sulfonic acids and trifluoroacetic acid were screened (entry 1-4, Table 5). The acid that resulted in the best overall yield and diastereoselectivity was methyl sulfonic acid (entry 4, Table 5). Interestingly, trifluoracetic acid resulted in the opposite major diastereomer than all the sulfonic acids. Based on these results, further reaction optimization was carried out using

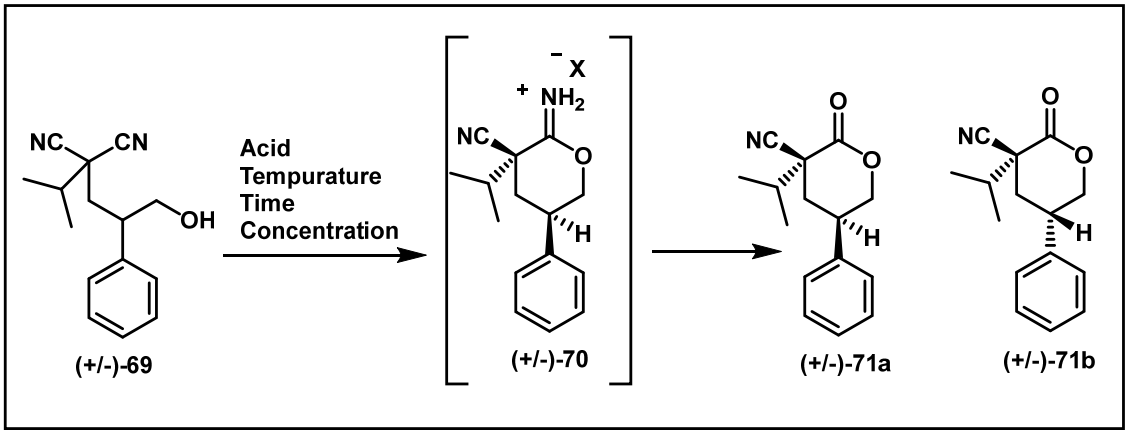
methyl sulfonic acid. A decrease in diastereoselectivity was observed as the reaction time increased which suggests an equilibrium between (+/-)-**69** and (+/-)-**70** is established. By increasing the temperature to 50 ^{o}C and decreasing the reaction concentration to 0.025 M the reaction yield was 35% and diastereomeric ratio was 5:1 after one hour (entry 9, Table 5). The temperature was increased further to 80 ^{o}C, and the reaction was completed after 1 hour, with good yield (75%) and diastereoselectivity (7:1 dr, entry 10, Table 5). It was determined that all the starting material was consumed upon reaction completion, and a carboxamide byproduct was being produced. The reaction time was decreased to 30 min but did not improve the yield and the dr was the same (entry 11, Table 5). Addition of molecular sieves did not result in improved results (entry 12, Table 5). Alternatively, a small amount of water was added the reaction, but this resulted in trace formation of product (entry 13, Table 5). Decreasing the concentration to 0.001M lowered the reaction yield and diastereoselectivity (entry 14, Table 5). Increasing the temperature to 100^{o} C in toluene resulted in a good yield but lower diastereoselectivity (entry 15, Table 5). The optimized reaction conditions were chosen to be 80 ^{o}C in DCE at 0.025 M for one hour (entry 10, Table 5).

Dialkylated dinitriles were prepared and reacted under optimized conditions to yield lactones with methyl sulfonic acid. The dinitriles that contained a phenyl group on the alkyl-hydroxy chain, once reacted under the optimized conditions resulted in the formation of lactones in good yields and excellent diastereoselectivities. When reacted under the optimized conditions dinitrile **69** produced lactone **71** in good diastereoselectivity and yield (75% yield, 7:1 dr). Dinitrile **72** was prepared and when

reacted under the optimized conditions resulted in the lactone **73** in good yield and diastereoselectivity (73% yield, 6:1 dr). Dinitrile **74** which contained a methyl substituent at the α-position resulted in formation of lactone **75** in an excellent yield of 84% and diastereomeric ratio of 7:1. When the substrates that contained a methyl group on the alkyl hydroxy chain were used, lactone yields were excellent, but the diastereoselectivity dropped a small amount. Dinitrile **76** which contained an α-substituted isopropyl group once reacted, afforded lactone **77** with an excellent yield of 98% and a diastereomeric ratio of 4:1. The dinitrile **78** with the benzyl α-substituted group was reacted to yield lactone **79** in excellent yield and good diastereoselectivity (92% yield, 6:1 dr). The dinitrile **80** was prepared with a *para*-chlorobenzyl α-substituted group to yield lactone **81** in a 5:1 diastereomeric ratio and 70% yield.

Our next goal was to synthesize an enantiopure lactone. Dinitriles were synthesized from commercially available enantioenriched monobromide **82**. Protection of the alcohol on compound **82** with a *tert*-butyl dimethyl silyl group yielded compound **83**. Alkylation of monosubstituted dinitrile **84** with compound **83** yielded a disubstituted dinitrile, which after deprotection yielded hydroxy-dinitrile **86**. Compound **86** was treated with methyl sulfonic acid and lactone **88** was produced in good diastereoselectivity (5:1 dr), excellent yield (98%), and enantiopurity (99% ee). Lactone **89** was prepared in the same way as lactone **88.** The dinitrile **85** was alkylated to yield a disubstituted malononitrile and then the tert-butyl methyl silyl group was removed to yield hydroxy dinitrile **87**. The reaction of **87** and the acid resulted in lower diastereoselectivity, but still good yield and enantiopurity.

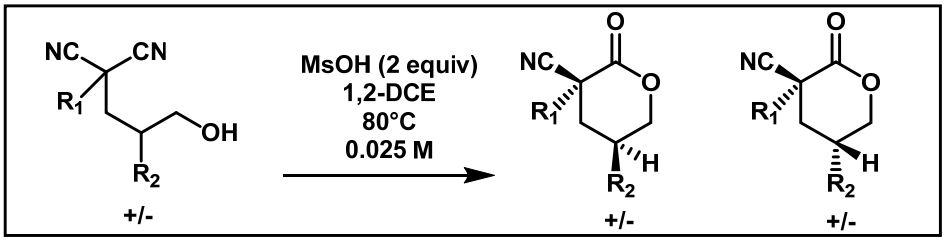
Table 5. Optimization of Pinner/Hydrolysis Reaction

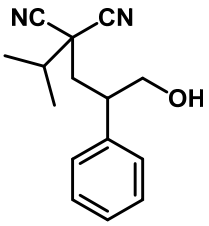
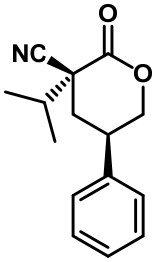
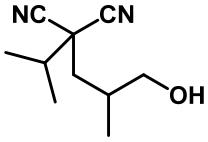
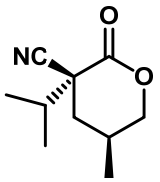
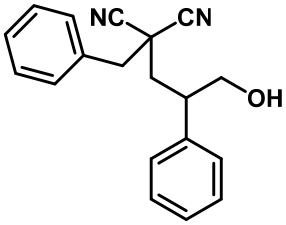
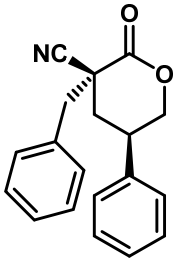
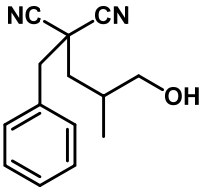
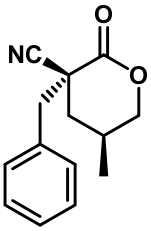
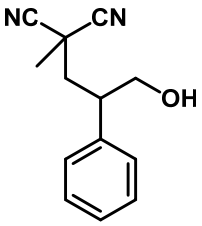
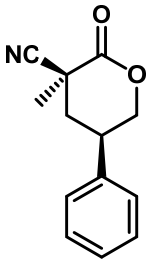
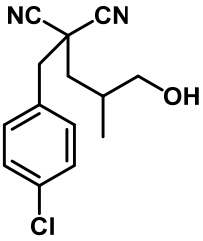
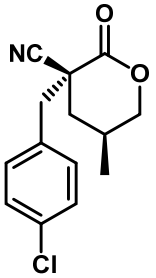


Entry	Acid	Tempurature (°C)	Solvent	Conc. M	Time	Yield %	D.R (Ratio)
1	TFA	RT	DCE	0.1 M	3 days	82%	1:4
2	CSA	RT	DCE	0.1 M	3 days	32%	3:1
3	TsOH	RT	DCE	0.1 M	3 days	45%	5:1
4	MsOH	RT	DCE	0.1 M	3 days	51%	5:1
5[a]	MsOH	RT	DCE	0.1 M	2 hr	20%	9:1
6[a]	MsOH	RT	DCE	0.1 M	4 hr	32%	7.5:1
7[a]	MsOH	RT	DCE	0.1 M	18hr	57%	7:1
8[a]	MsOH	RT	DCE	0.1 M	42hr	61%	6:1
9[c]	MsOH	50	DCE	0.025 M	1 hr	35%	5:1
10[c]	MsOH	80	DCE	0.025 M	1 hr	75%	7:1
11[c]	MsOH	80	DCE	0.025 M	30 min	60%	7:1
12[b,c]	MsOH	80	DCE	0.025 M	1 hr	58%	6:1
13[c]	MsOH	80	DCE/Water (20:1)	0.025 M	1 hr	Traces	--
14[c]	MsOH	80	DCE	0.001 M	1 hr	54 %	4:1
15[c]	MsOH	100	Toluene	0.025 M	1 hr	73 %	4:1

[a] yields and dr measured by GC
[b] molecular sieves
[c] 2 equivalence of acid
(isolated yields and dr measured by ^{1}H NMR)

Table 6. Substrate Scope



Dinitrile	Lactone	Dinitrile	Lactone
 (+/-)-69	 (+/-)-71 75% yield 7:1 DR	 (+/-)-76	 (+/-)-77 98 % yield 4:1 DR
 (+/-)-72	 (+/-)-73 73% yield 6:1 DR	 (+/-)-78	 (+/-)-79 92 % yield 6:1 DR
 (+/-)-74	 (+/-)-75 84% yield 7:1 DR	 (+/-)-80	 (+/-)-81 70 % yield 5:1 DR

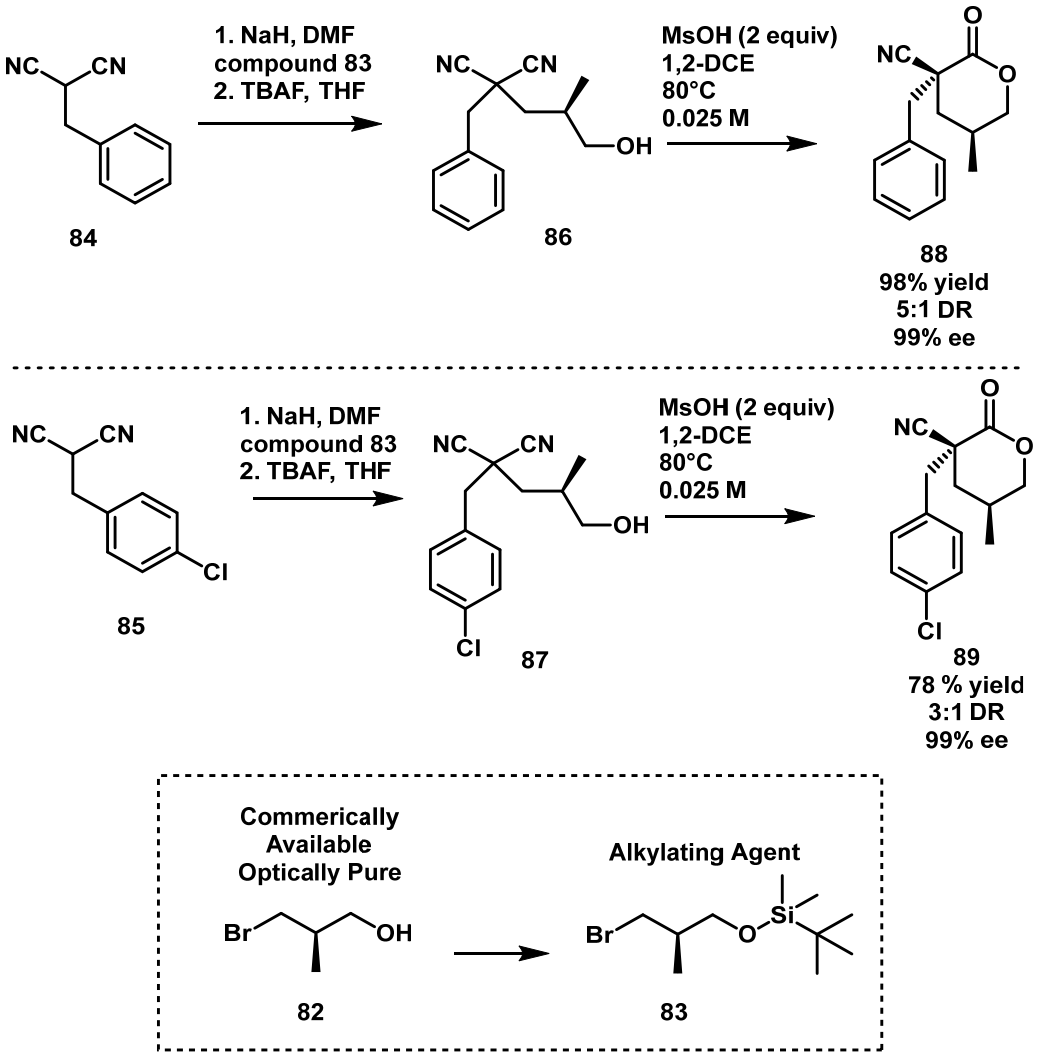
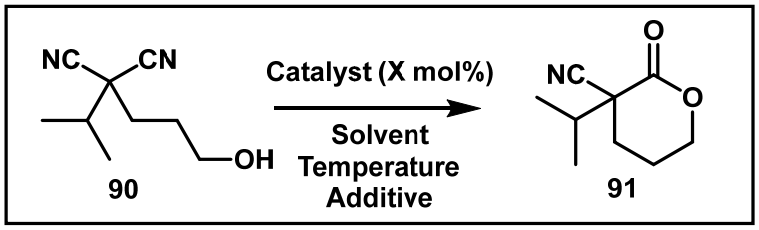
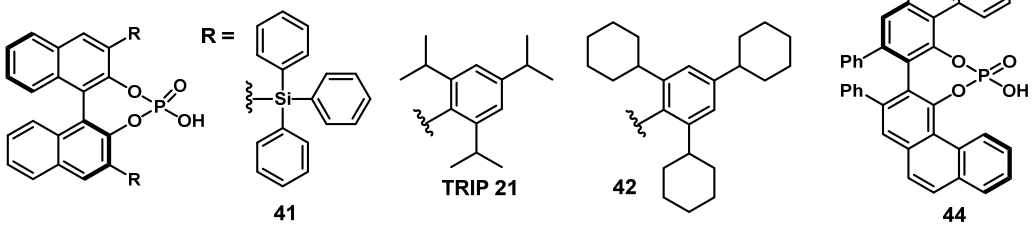


Figure 26. Synthesis of Enantiopure Lactones

Table 7. Optimization Enantioselective Pinner Reaction



Entry	Catalyst	mol %	Solvent	Temp	Additive	Yield	ee
1	41	20	DCE	Rt	--	11%	Rac
2	42	20	DCE	Rt	--	11%	Rac
3	44	20	DCE	Rt	--	--	--
4	21	20	DCE	Rt	--	30%	26%
5	21	10	DCE	5	--	14%	Rac
6	21	10	DCE	65	--	23%	20%
7	21	10	Toluene	100	--	52%	Rac
8	21	10	DCE	Rt	H_2O	--	--
9	21	10	DCE	Rt	4Å MS	--	--



The Pinner/hydrolysis has not yet been reported enantioselectively, therefore a chiral phosphoric acid catalyzed desymmetrization strategy was examined. By the preparation of prochiral dinitrile **90** and catalyst screen with chiral phosphoric acid catalysts, TRIP (**21**) was found to produce lactone **91** in modest enantiomeric excess (26% ee, entry 4, Table 7). Although the results are modest, this is the first reported

enantioselective acid catalyzed activation of a nitrile. Future work includes optimizing these reaction conditions.

4.3 Conclusion

In summary, a novel desymmetrization of dinitriles was developed utilizing mild Brønsted acid. An examination of several sulfonic acids and triflouroacidic acid showed that a Pinner/hydrolysis reaction could be achieved to produce lactones in good yields and stereoselectivities. By using methyl sulfonic acid several lactones were synthesized in high yields and diastereoselectivies.

CHAPTER V

EXPERIMENTAL

5.1 General Information

Unless noted, all solvents and reagents were obtained from commercial sources and used without further purification; anhydrous solvents were dried following standard procedures. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on 400 and 500 MHz spectrometer using $CDCl_3$ or $((CD_3)_2CO)$ as a solvent at rt. The NMR chemical shifts (δ) are reported in ppm. Abbreviations for ^{1}H NMR: s = singlet, d = doublet, m = multiplet, b = broad, t = triplet, q = quartet. The reactions were monitored by TLC using silica G F254 precoated plates. Flash chromatography was performed using flash grade silica gel (particle size: 40-63 μm, 230 × 400 mesh). Enantiomeric excess was determined by HPLC analysis. High Resolution Mass Spectra were acquired at UNCG Triad Mass Spectrometry Laboratory. The specific rotations were acquired on an analytical polarimeter.

5.2 Synthesis of Compound **36a**

5.2.1 Synthesis of Dialkylated Intermediate **34a**

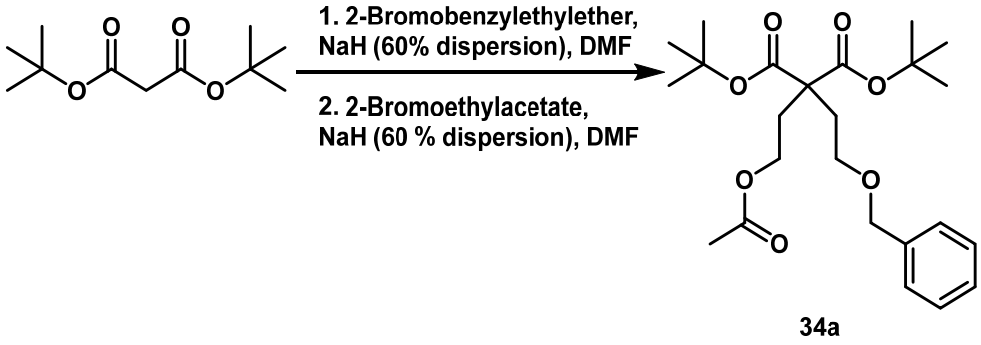


Figure 27**.** Dialkylated Intermediate **34a**

To a mixture of NaH (60% dispersion, 250 mg, 6.7 mmol) in DMF (30 mL), di-*tert*-butyl malonate (1.0 mL, 4.5 mmol) was added followed by 2-bromobenzylethylether (711 μL, 4.5 mmol). The reaction mixture was stirred overnight at rt, then quenched with water (10 mL) and diluted with ethyl acetate (30 mL). The layers were separated, and the organic layer was washed with water (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude material was purified using silica gel column chromatography (10% ethyl acetate/hexanes) to afford the mono alkylated intermediate as a colorless oil (650 mg, 43% yield) which was taken to the next step.

To a mixture of NaH (60% dispersion, 56 mg, 1.4 mmol) in DMF (7 mL), mono alkylated intermediate (250 mg, 0.7 mmol) and 2-bromoethylacetate (121 μL, 1.1 mmol) was added. The mixture was stirred overnight at rt, quenched with water (10 mL), and diluted with ethyl acetate (30 mL). The layers were separated, the organic layer was washed with water (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting

crude material was purified using silica gel column chromatography (10% ethyl acetate/hexanes) to afford **34a** as a colorless oil (220 mg, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.43 (s, 2H), 4.06 (t, J = 7.2 Hz, 2H), 3.43 (t, J = 6.9 Hz, 2H), 2.17 (m, 4H), 1.97 (s, 3H), 1.40 (s, 18H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.1, 138.2, 128.4, 127.8, 127.6, 81.6, 73.1, 66.0, 60.9, 55.5, 32.0, 30.9, 27.9, 21.0 ppm; IR (neat) 2977, 1722, 1367, 1226, 1145 cm^{-1}; HRMS (ESI): for $C_{24}H_{36}O_7$ $[M+Na]^+$: calcd. 459.2353; found 459.2352.

5.2.2 Synthesis of Lactone **35a**

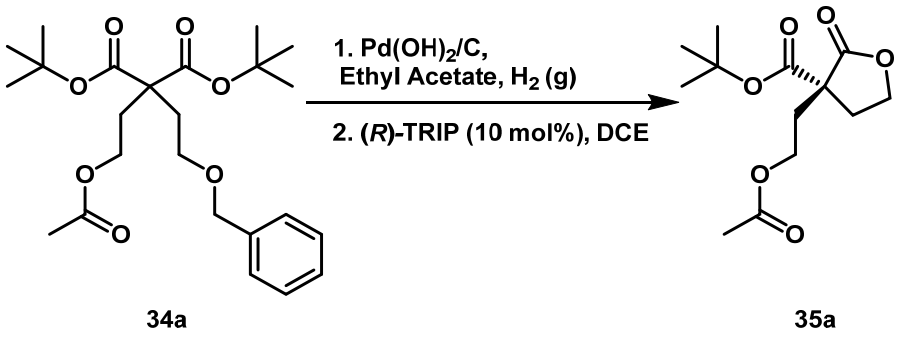


Figure 28. Lactone **35a**

To a mixture of compound **34a** (220 mg, 0.57 mmol) in ethyl acetate (6 mL) was added $Pd(OH)_2/C$ (22 mg). The flask was purged with hydrogen gas and stirred overnight. The reaction was filtered over a plug of Celite® and concentrated *in vacuo* to afford the alcohol intermediate as a colorless oil (158 mg, 91% yield) which was taken to the next step.

To a mixture of alcohol intermediate (89 mg, 0.25 mmol) in 1,2-dichoroethane (2.5 mL), (*R*)-TRIP (19 mg, 0.025 mmol) was added. The reaction mixture was stirred at

room temperature for 10 days then diluted with dichloromethane (5 mL) and water (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude material was purified by silica gel column chromatography (30% ethyl acetate/hexanes) to afford **35a** as a colorless oil (31 mg, 43% yield, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (m, 2H), 4.26 (m, 1H), 4.13 (m, 1H), 2.67 (m, 1H), 2.39 (m, 1H), 2.31 (m, 1H), 2.10 (m, 1H), 2.02 (s, 3H), 1.49 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 170.8, 168.0, 83.6, 66.4, 60.6, 53.1, 32.5, 31.9, 27.9, 20.9 ppm; HRMS (ESI): for $C_{13}H_{20}O_6$ $[M+Na]^+$: calcd. 295.1152; found 295.1144.

5.2.3 Synthesis of Spirocycle **36a**

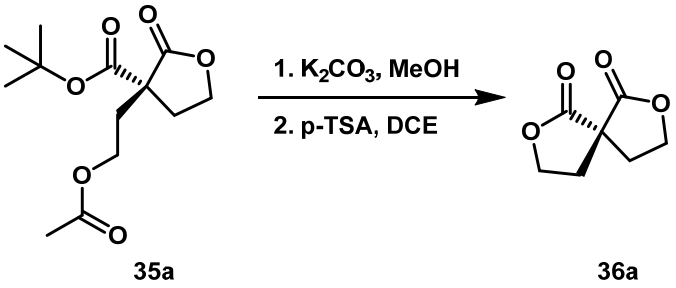


Figure 29. Spirocycle **36a**

To a mixture of lactone **35a** (30 mg, 0.1 mmol) in methanol (1 mL), K_2CO_3 (45 mg, 0.3 mmol) was added. The reaction was stirred for 2 hours after which the reaction was diluted with ethyl acetate (5 mL), and 1.0 M HCl was added until pH was neutral. The organic layer was separated and filtered through a $MgSO_4$ plug to yield the hydroxy lactone intermediate which was used in the next step.

To a solution of the hydroxy lactone intermediate (29 mg, 0.12 mmol) in dichloromethane (2 mL) was added *p*-toluenesulfonic acid (12 mg, 0.6 mmol), and the solution was stirred at room temperature for 48 hours. The reaction was extracted with ethyl acetate (2 x 10 mL) and water (1 x 10 mL). The organic phase was dried over $MgSO_4$ and concentrated to afford spirocycle **36a** as a white solid (18 mg, 92% yield, 0% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (m, 2H), 2.78 (m, 2H), 2.36 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 66.8, 50.0, 32.6 ppm; IR (neat) 2917, 2850, 1773, 1741, 1376, 1173, 1145 cm^{-1}; HRMS (ESI): for $C_7H_8O_4$ $[M+H]^+$: cacld. 157.0995; found 157.0498; MP = 98.7-100.3 °C.

5.3 Synthesis of Compound **36b**

5.3.1 Synthesis of Dialkylated Intermediate **34b**

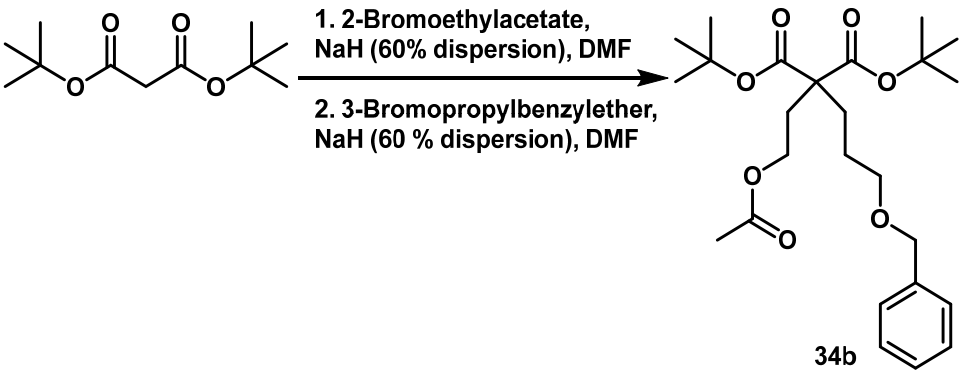


Figure 30. Dialkylated Intermediate **34b**

To a mixture of NaH (60% dispersion, 250 mg, 6.7 mmol) in DMF (30 mL), di-*tert* butyl malonate (1 mL, 4.5 mmol) was added followed by 2-bromoethylacetate (492 µL, 4.5 mmol). The mixture was stirred overnight at room temperature, then quenched

with water (10 mL) and diluted with ethyl acetate (30 mL). The layers were separated, the organic layer was washed with water (10 mL), dried over $MgSO_4$, and concentrated *in vacuo.* The resulting crude material was purified using column chromatography (10% ethyl acetate/hexanes) to afford the mono-alkylated intermediate as a colorless oil (804 mg, 69% yield) which was used in the next step.

The mono-alkylated intermediate (600 mg, 1.9 mmol) was added to a 25 mL round bottom flask containing NaH (60% dispersion, 150 mg, 3.9 mmol) in DMF (20 mL), followed by 3-bromopropylbenzylether (700 µL, 3.9 mmol). The mixture was stirred overnight at room temperature then quenched with water (10 mL) and diluted with ethyl acetate (30 mL). The layers were separated, the organic layer was washed with water (10 mL), dried over $MgSO_4$, and concentrated *in vacuo.* The resulting crude material was purified using silica gel column chromatography (10% ethyl acetate/hexanes) to afford **34b** as a colorless oil (421 mg, 49% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.48 (s, 2H), 4.06 (t, J = 7.2 Hz, 2H), 3.45 (t, J = 6.6 Hz, 2H), 2.16 (t, J = 7.2 Hz, 2H), 1.99 (s, 3H), 1.88 (m, 2H), 1.49 (m, 2H), 1.44 (s, 18H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 170.4, 138.6, 128.4, 127.7, 127.6, 81.6, 72.9, 70.3, 60.8, 56.6, 30.6, 29.1, 27.9, 24.5, 21.0 ppm; IR (neat) 2975, 1720, 1367, 1235, 1147 cm^{-1}; HRMS (ESI): for $C_{25}H_{38}O_7$ $[M+Na]^+$: calcd. 473.2516; found 473.2499.

5.3.2 Synthesis of Lactone **35b**

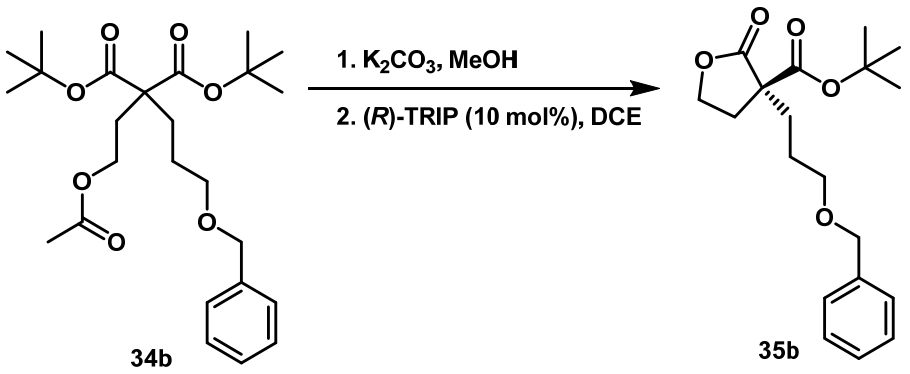


Figure 31. Lactone **35b**

To a mixture of compound **34b** (421 mg, 0.9 mmol) in methanol (9 mL), was added K_2CO_3 (387 mg, 2.8 mmol). The mixture was stirred at room temperature for one hour, then added to 1 M HCl (2 mL) and diluted with dichloromethane (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified using silica gel column chromatography (40% ethyl acetate/hexanes) to afford the intermediate alcohol as a colorless oil (221 mg, 60% yield) which was taken to the next step.

To a mixture of alcohol intermediate (72 mg, 0.17 mmol) in 1,2-dichloroethane (1.7 mL) followed by (*R*)-TRIP (13 mg, 0.017 mmol) was added. The reaction was stirred at room tempurature for 10 days, then diluted with dichloromethane (10 mL), and water (5 mL) was added. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude material was purified by silica gel column

chromatography (30% ethyl acetate/hexanes) to afford compound **35b** as a colorless oil (30 mg, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.48 (s, 2H), 4.30 (m, 2H), 3.49 (m, 2H), 2.66 (m, 1H), 2.22 (m, 1H), 2.11 (m, 1H), 1.82 (m, 1H), 1.74 (m, 1H), 1.56 (m, 1H), 1.45 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 168.6, 138.4, 128.5, 127.8, 83.1, 73.0, 69.9, 66.2, 54.6, 31.9, 30.8, 27.9, 25.2 ppm; IR (neat) 2976, 2342, 1770, 1721, 1368 cm^{-1}; HRMS (ESI): for $C_{19}H_{26}O_5$ $[M+Na]^+$: calcd. 357.1678; found 357.1661.

5.3.3 Synthesis of Spirocycle **36b**

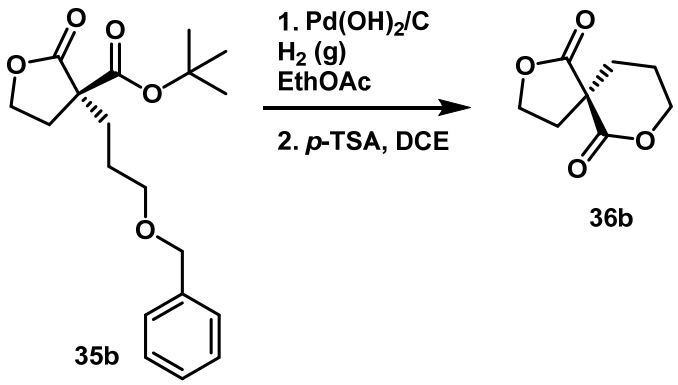


Figure 32. Spirocycle **36b**

To a mixture of lactone **35b** (32 mg, 0.09 mmol) in ethyl acetate (0.5 mL), $Pd(OH)_2/C$ (3.2 mg) was added. The flask was purged with hydrogen gas and stirred overnight. The reaction was filtered over a plug of Celite® and concentrated *in vacuo* to afford the intermediate hydroxy lactone **35b'** as a colorless oil (21 mg, 99% yield, 81% ee) which was used directly in the next step.

To a solution of the hydroxy lactone intermediate **35b'** (50.1 mg, 21 mmol) in 1,2-dichloroethane (2 mL) was added *p*-toluenesulfonic acid (39 mg, 0.21 mmol), and the solution was stirred at room temperature for 24 hours. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic phase was dried over $MgSO_4$ and concentrated to afford spirocycle **36b** as a white solid (27 mg, 78% yield, 63% ee). ^1H NMR (500 MHz, $CDCl_3$) δ 4.56 (m, 2H), 4.39 (m, 1H), 4.37 (m, 1H), 2.86 (m, 1H), 2.41 (m, 1H), 2.19 (m, 2H), 1.90 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 168.6, 70.9, 66.7, 50.3, 36.4, 30.3, 20.4 ppm; IR (neat) 2341, 1760, 1708, 1167, 1022 cm^{-1}; HRMS (ESI): for $C_8H_{10}O_4$ $[M+H]^+$: calcd. 171.0651; found 171.0654; MP = 46.2-48.0° C ; $[\alpha]_D^{23}$ = -2.5° (c = 0.5, $CHCl_3$).

5.4 Synthesis of Compound **36c**

5.4.1. Synthesis of Lactone **35c**

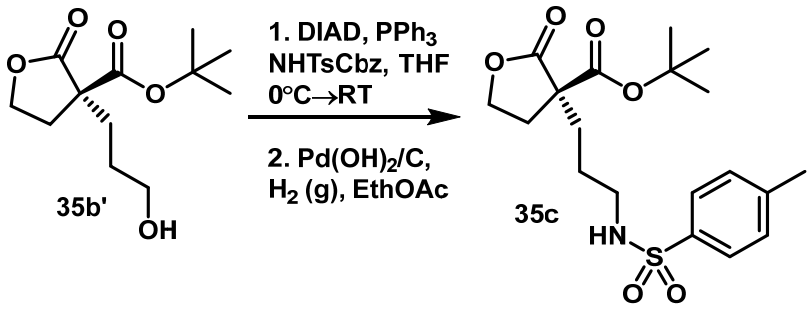


Figure 33. Lactone **35c**

To a mixture of triphenylphosphine (26 mg, 0.1 mmol), diisopropylazodicarboxylate (19 µL, 0.1 mmol), and THF (2 mL) was added at 0° C, followed by compound **35b'** (21 mg, 0.08 mmol) and *N*-tosyl benzamide (30 mg, 0.1

mmol). The reaction was stirred for 36 hours, and the solvent was evaporated *in vacuo*. The crude material was purified by silica gel column chromatography (30% ethyl acetate/hexanes) to afford a mixture of the desired intermediate which was used directly in the next step.

To crude material (50 mg), $Pd(OH)_2/C$ (5 mg), and ethyl acetate (1 mL) was added. The flask was purged with hydrogen gas, and the reaction was stirred overnight. The mixture was filtered through Celite©, concentrated, and the crude material was purified by silica gel column chromatography (30% ethyl acetate/hexanes) to afford **35c** as a colorless oil. (21 mg, overall 56% yield, 81% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.53 (bt, 1H), 4.30 (m, 2H), 2.94 (m, 2H), 2.59 (m, 1H), 2.42 (s, 3H), 2.14 (m, 1H), 1.94, (m, 1H), 1.73 (m, 1H), 1.66 (m, 1H), 1.49 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 168.6, 143.6, 136.8, 129.9, 127.1, 83.5, 66.2, 54.3, 43.1, 32.3, 30.8, 27.9, 25.1, 21.6 ppm; IR (neat) 3326, 2982, 2340, 1770, 1725, 1327 cm^{-1}; HRMS (ESI): for $C_{19}H_{27}O_6NS$ $[M+H]^+$: calcd. 398.1637; found 398.1634.

5.4.2 Synthesis of Spirocycle **36c**

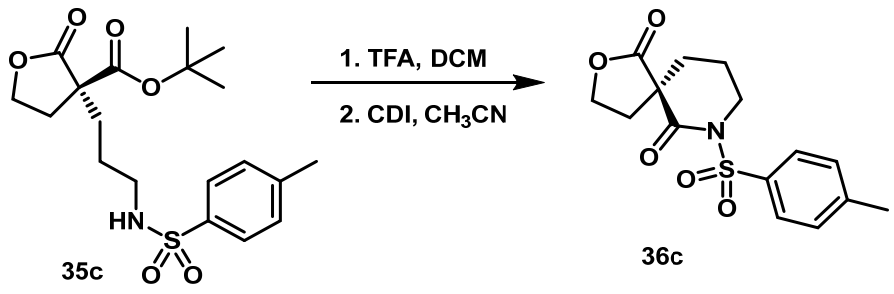


Figure 34. Spirocycle **36c**

A mixture of compound **35c** (40 mg, 0.10 mmol), dichloromethane (1 mL), and 0.5 mL of TFA was prepared. The reaction was stirred for 1 hour, and the solvent was removed to yield a colorless oil as the carboxylic acid which was used without further purification in the next step.

Mixture of CDI (28 mg, 0.17 mmol), acetonitrile (2 mL), and the carboxylic acid intermediate was prepared. The reaction was stirred for 12 hours, after which it was concentrated *in vacuo*. The reaction was purified by silica gel column chromatography (30% ethyl acetate/hexanes) to afford compound **36c** as a white solid. (13 mg, 41% two step yield, 70% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 4.43 (m, 1H), 4.31 (m, 1H), 4.07 (m, 1H), 3.93 (m ,1H), 2.81 (m, 1H), 2.42 (s, 3H), 2.30 (m, 2H), 2.11 (m, 1H), 1.89 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 168.5, 145.3, 135.2, 129.6, 128.6, 66.5, 52.6, 47.1, 35.7, 31.1, 21.8, 20.3 ppm; IR (Neat) cm^{-1} 2926, 2357, 1767, 1681, 1352, 1167 cm^{-1} ; HRMS (ESI): for $C_{15}H_{17}NO_5S$ $[M+H]^+$: calcd. 324.0905; found 324.0891; MP = 103.0-105.3^{o} C; $[\alpha]_D^{23}$ = 8.75^{o} (c= 0.6, $CHCl_3$).

5.5. Synthesis of Compound **36d**

5.5.1 Synthesis of Disubstituted Intermediate **34d**

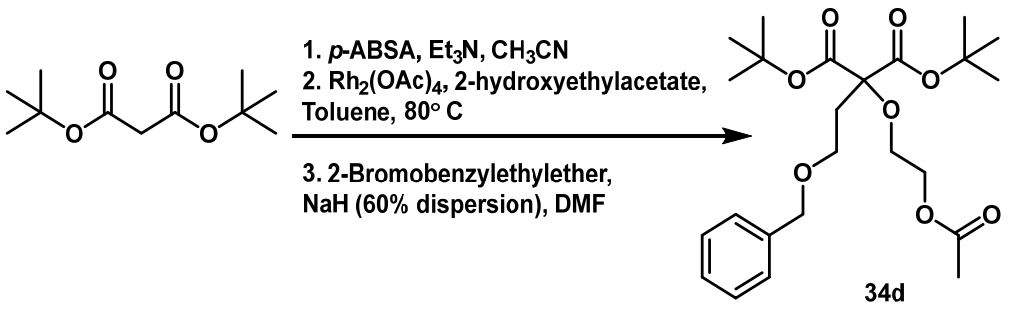


Figure 35. Disubstituted Intermediate **34d**

To a solution of *p*-acetoamidobenzylsulfonyl azide (1.08 g, 4.5 mmol) in acetonitrile (25 mL), triethylamine (0.62 mL, 4.5 mmol), and di-*tert*-butyl malonate (1 mL, 4.5 mmol) were added. The reaction was stirred at rt for 48 hours, after which time the mixture was concentrated *in vacuo* to near dryness. Hexanes (25 mL) was added to the crude material and the precipitate was filtered. The filtrate was concentrated *in vacuo* and used directly in the following procedure. To a 100 mL round bottom flask containing the above crude material (1.87 mg, 7.7 mmol), was added $Rh_2(OAc)_4$ (35 mg, 0.08 mmol), toluene (50 mL), and 2-hydroxyethylacetate (1.24 g, 11.5 mmol). The reaction was stirred at 70° C overnight, after which time the mixture was filtered over Celite© and purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford the intermediate as a colorless oil (936 mg, 33% yield) which was used directly in the next step.

To a mixture of NaH (60% dispersion, 45 mg, 1.2 mmol) and DMF (6 mL), was added the above intermediate (200 mg, 0.6 mmol) and 2-bromobenzylethylether (195 μL, 1.2 mmol). The mixture was stirred overnight at room temperature, then quenched with water (10 mL) and diluted with ethyl acetate. The layers were separated, the organic layer was washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified using silica gel column chromatography (30% ethyl acetate/hexanes) to afford **34d** as a colorless oil (205 mg, 41% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.47 (s, 2H), 4.22 (t, *J* = 1.0 Hz, 2H), 3.77 (t, *J* = 1.0 Hz, 2H), 3.53 (t, *J* = 6.9 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.02 (s, 3H), 1.45 (s, 18H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 167.4, 138.4, 128.4, 127.8, 127.6, 82.9, 82.6, 73.0, 64.8, 63.7, 33.7, 27.9, 21.0 ppm; IR (neat) 2977, 1732, 1368, 1242, 1130, 1101 cm^{-1}; HRMS ESI: for $C_{24}H_{36}O_8$ $[M+Na]^+$: calcd. 475.2308; found 475.230.

5.5.2 Synthesis of Lactone **35d**

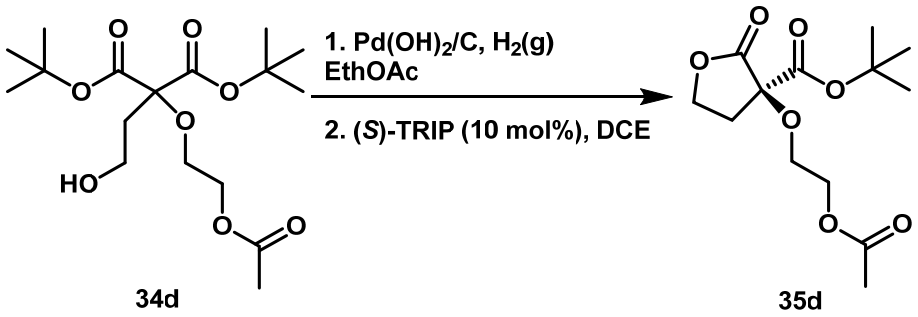


Figure 36. Lactone **35d**

To a flame dried round bottom flask, was added **34d** (118 mg, 0.26 mmol) in anhydrous ethyl acetate (3 mL) followed by $Pd(OH)_2/C$ (12 mg). The flask was purged

with hydrogen gas and stirred at room tempurature overnight. The reaction was filtered over a plug of Celite© and concentrated *in vacuo.* The resulting crude material was purified through silica gel column chromatography (40% ethyl acetate/hexanes) to afford the intermediate alcohol as a colorless oil (90 mg, 99% yield) which was used directly in the next step.

To a 10 mL round bottom flask the above alcohol (63 mg, 0.17 mmol) was added in 1,2-dichloroethane (1.7 mL) followed by (*S*)-TRIP (13 mg, 0.017 mmol). The mixture was stirred at room tempurature for 9 days after which time it was diluted with water (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified by silica gel column chromatography (30% ethyl acetate/hexane) to afford **35d** as a colorless oil (39 mg, 79% yield, 41% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (m, 2H), 4.23 (m, 2H), 4.04 (m, 2H), 2.66 (m, 1H), 2.48 (m, 1H), 2.07 (s, 3H), 1.50 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 171.1, 167.1, 84.3, 80.7, 65.8, 65.4, 63.6, 35.5, 28.0, 21.0 ppm; IR (neat) 2978, 2359, 1777, 1737, 1231, 1137 cm^{-1}; HRMS ESI: for ($C_{13}H_{20}O_7$) $[M+Na]^+$: calcd. 311.1101; found 311.1100.

5.5.3 Synthesis of Spirocycle **36d**

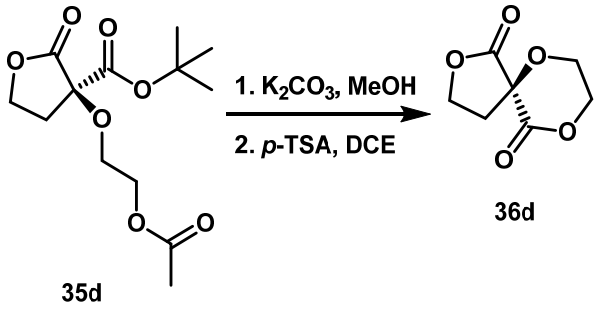


Figure 37. Spirocycle **36d**

To a 10 mL round bottom flask, was added lactone **35d** (39 mg, 0.13 mmol) in methanol (2 mL), followed by K_2CO_3 (57 mg, 0.39 mmol). The mixture was stirred at room tempurature for 30 min, then added to 1.0 M HCl (2 mL) and diluted with dichloromethane (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL), the combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield intermediate hydroxy lactone which was used without further purification (19 mg, 61% yield).

To a 10 mL round bottom flask was added intermediate hydroxy lactone (19 mg, 0.07 mmol) in 1,2-dichloroethane (1 mL) followed by *p*-toluene sulfonic acid (14 mg, 0.07 mmol). The mixture was stirred at room temperature for 48 hours, after which time the reaction was diluted with dichloromethane (5 mL) and washed with water (2 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The crude material was filtered through a plug of silica to afford **36d** as a white solid (12 mg, 99% yield, 24% ee). ^{1}H NMR (400 MHz, acetone-D_6) δ 4.66 (m, 1H), 4.57 (m, 1H), 4.46 (t, J = 6.6

Hz, 2H), 4.39 (m, 1H), 4.03 (m, 1H), 2.93 (m, 1H), 2.52 (m, 1H) ppm; ^{13}C NMR (100 MHz, acetone-D_6) δ 172.1, 165.9, 79.2, 69.3, 66.5, 60.7, 35.4 ppm; IR (neat) 2923, 1771, 1728 cm^{-1}; HRMS (ESI): for ($C_7H_8O_5$) $[M+H]^+$: calcd. 173.045; found 173.0443. MP = 75.2-78.0° C; $[a]_D^{23}$ = -1.7° (c = 0.6, MeOH).

5.6 Synthesis of Compound **36e**

5.6.1 Synthesis of Dialkylated Intermediate **34e**

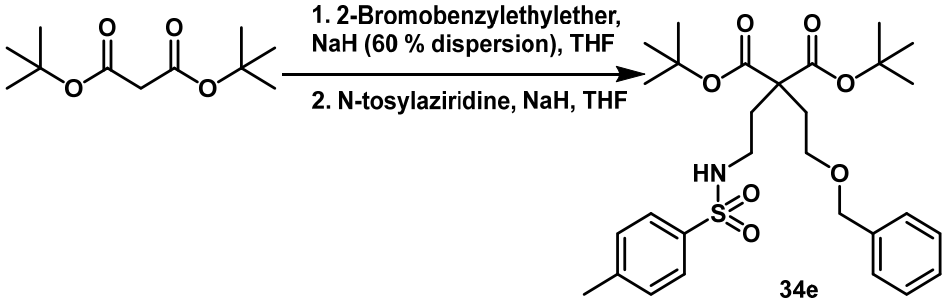


Figure 38. Dialkylated Intermediate **34e**

To a solution of NaH (60% dispersion, 0.13 g, 3.2 mmol) in THF (7.5 mL) was added di-*tert*-butyl malonate dropwise (0.68 g, 3.2 mmol), and the solution was stirred until gas evolution was complete. To the reaction mixture was added benzyl 2-bromoethyl ether (0.5 mL, 3.2 mmol), and the solution was stirred until reaction completion was determined by TLC analysis. The reaction was quenched with water (6 mL) and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford the monoalkylated intermediate as a colorless oil (0.75 g, 68% yield).

To a solution of NaH (60% dispersion, 0.28 g, 0.8 mmol) in THF (7 mL) was added the monoalkylated intermediate, and the solution was stirred until gas evolution was complete. To the reaction mixture was added *N*-tosyl aziridine (1 M in THF, 0.16 g, 0.08 mmol) at 0° C, and the solution was allowed to warm up to room tempurature overnight. The reaction was quench with water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (40% ethyl acetate/hexanes) to afford dialkylated intermediate **34e** as a colorless oil (210 mg, 48% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.28 (m, 7H), 4.80 (bs, 1H), 4.40 (s, 2H), 3.38 (t, *J* = 6.2 Hz, 2H), 2.89 (q, *J* = 6.9 Hz, 2H), 2.38 (s, 3H), 2.09 (t, *J* = 6.2 Hz, 2H), 2.01 (t, *J* = 7.3 Hz, 2H), 1.36 (s, 18H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 143.4, 138.0, 136.8, 129.7, 128.6, 128.0, 127.9, 127.2, 82.0, 73.3, 66.1, 56.5, 39.3, 32.4, 27.9, 21.6 ppm; IR (neat) 3291, 2976, 2933, 1721, 1367, 1154, 1093, 660, 550 cm^{-1} ; HRMS (ESI): for $C_{29}H_{41}NO_7S$ $[M+H]^+$: calcd. 548.2681; found 548.2671.

5.6.2 Synthesis of Lactone **35e**

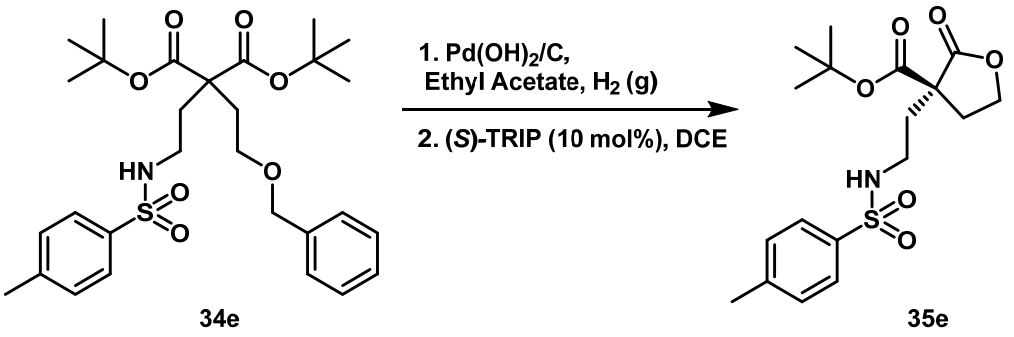


Figure 39. Lactone **35e**

To a solution of the dialkylated intermediate **34e** (58 mg, 0.11 mmol) in ethyl acetate (4 mL) was added $Pd(OH)_2/C$ (20 weight %, 7.7 mg, 0.06 mmol), and the solution was stirred under hydrogen pressure using a balloon filled with hydrogen gas at room tempurature until reaction completion was determined by TLC analysis. The reaction mixture was filtered through a plug of Celite©, and the filtrate was concentrated under vacuum, to afford intermediate alcohol as a colorless oil (47 mg, 96% yield). To a solution of *(S)*-TRIP (30 mg, 0.038 mmol) in 1,2 dichloroethane (2 mL) was added intermediate alcohol above (173 mg, 0.38 mmol) and the solution was stirred for 216 hr at room temperature. The reaction was extracted with ethyl acetate (2 x 10 mL) and water (10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to afford lactone **35e** (133 mg, 92% yield, 84% ee). ^{1}H NMR (500 MHz, Acetone-d6) δ 7.74 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 6.48 (bt, J = 6.1 Hz, 1H), 4.32 (m, 2H), 3.11 (m, 1H), 2.95 (m, 1H), 2.66 (m, 1H), 2.42 (s, 3H), 2.36 (m, 1H), 2.19 (m, 1H), 1.92 (m, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (126 MHz, Acetone-d6) δ 175.4, 170.9, 143.9, 138.7, 130.5, 127.8, 83.3, 67.1, 54.1, 40.2, 34.4, 32.8, 27.8, 21.4 ppm; HRMS (ESI): for $C_{18}H_{25}NO_6S$ $[M+H]^+$: calcd. 384.1480; found 384.1470.

5.6.3 Synthesis of Spirocycle **36e**

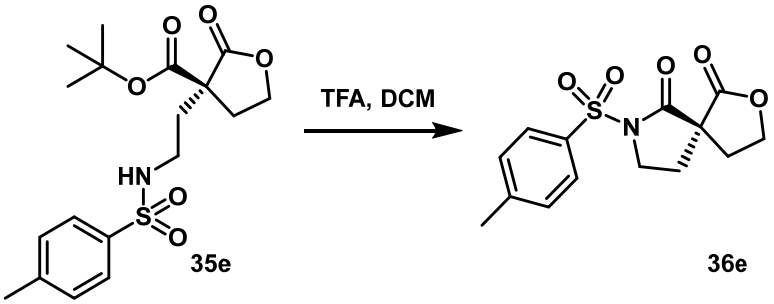


Figure 40**.** Spirocycle **36e**

To a solution of lactone intermediate **35e** (42.0 mg, 0.11 mmol) in dichloromethane (2 mL) was added excess trifluoroacetic acid (2 ml), and the solution was stirred overnight. The reaction was extracted with ethyl acetate (2 x 10 mL) and water (10 mL). The organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford **36e** as a white solid (29 mg, 85% yield, 60% ee). The compound was dissolved in ethyl acetate and warm hexanes, and let to cool to rt. The recrystallized material was filtered and rinsed with cold hexanes to result in 85% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* =8 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 4.48 (m, 1H), 4.32 (m, 1H), 4.07 (m, 2H), 2.73 (m, 1H), 2.52 (m , 1H), 2.43 (s, 3H), 2.16 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 170.1, 145.9, 134.2, 130.0, 128.2, 66.9, 53.1, 45.1, 32.1, 28.9, 21.9 ppm; IR (neat) 2923, 1765, 1716, 1358, 1348, 1167, 1105, 1024, 668, 585 cm^{-1}; HRMS (ESI): for $C_{14}H_{15}NO_6S$ $[M+Na]^+$: calcd. 310.0744; found 310.0745; MP = 134.2-136.6º C; $[a]_D^{23}$ = -35.2° (c = 0.25, $CHCl_3$).

5.7 Synthesis of Compound **36f**

5.7.1 Synthesis of Alkylating Agent

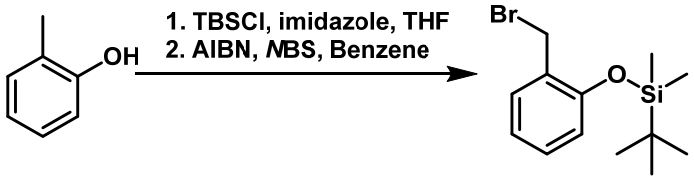


Figure 41. Alkylating Agent

DMF (10 mL) was added to a 50 mL flask followed by *o*-cresol (1.0 mL, 10 mmol). Imidazole (1.50 g, 22 mmol) was added, followed by TBSCl (1.66 g , 11 mmol). The reaction was stirred overnight and quenched with water after 21 hours. The mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified via flash column chromatography (10% ethyl acetate/hexanes) to obtain the TBS-protected *o*-cresol as a colorless oil which was used directly in the next step. To a 100 mL round bottom flask was added benzene (20 mL) followed by the TBS protected *o*-cresol (1.65 g, 7.4 mmol). Azobisisobutyronitrile (1.83 mg, 1.1 mmol) and *N*-bromosuccinimide (1.45 g, 8.2 mmol) were added, and the reaction was stirred for 4 hours under reflux at 90º C. The reaction mixture was cooled to room temperature and filtered through a fritted funnel with 1 inch of silica while being rinsed with hexanes. The corresponding bromide alkylating agent was obtained as a colorless oil without the need of further purification (1.99 g, 91% yield).

5.7.2 Synthesis of Dialkylated Intermediate **34f**

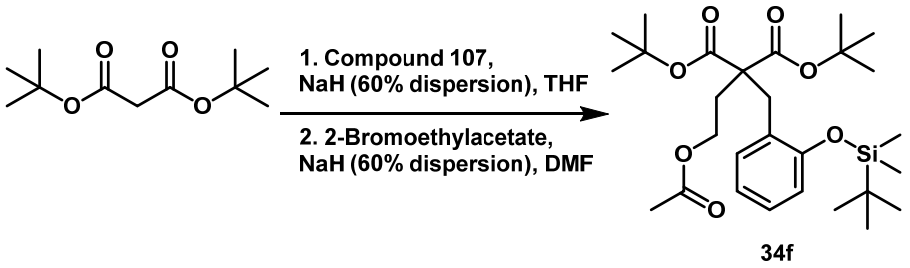


Figure 42. Dialkylated Intermediate **34f**

To a 50 mL round bottom flask containing NaH (60% dispersion, 94 mg, 2.3 mmol), was added di-*tert*-butyl malonate (0.35 mL, 1.6 mmol), THF (16 mL), and the previously synthesized alkylating agent (570 mg, 1.9 mmol). The mixture was stirred overnight at room tempurature, quenched with water (10 mL), and diluted with ethyl acetate (30 mL). The layers were separated, and the organic layer was washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified using silica gel column chromatography (10% ethyl acetate/hexanes) to afford the mono alkylated intermediate as a white solid (580 mg, 85% yield) which was taken directly to the next step. To a 50 mL round bottom flask containing NaH (60% dispersion, 93 mg, 2.3 mmol), was added the above intermediate (340 mg, 0.78 mmol), THF (8 mL), and 2-bromoethylacetate (0.26 mL, 2.3 mmol). The mixture was stirred overnight at room temperature, then quenched with water (10 mL), and diluted with ethyl acetate (30 mL). The layers were separated, the organic layer was washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting crude material was purified by silica gel column chromatography (10% ethyl

acetate/hexanes) to afford the dialkylated intermediate **34f** as a colorless oil (254 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (m, 1H), 7.06 (m, 1H), 6.82 (m, 1H), 6.77 (m, 1H), 4.11 (t, *J* = 8.0 Hz, 2H), 3.26 (s, 2H), 2.04 (t, *J* = 8.0 Hz, 2H), 1.95 (s, 3H), 1.44 (s, 18H), 1.00 (s, 9H), 0.21 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.4, 154.3, 131.1, 127.4, 119.0, 81.8, 61.4, 58.1, 32.1, 31.8, 27.9, 26.0, 21.1, 18.4, -4.0 ppm; HRMS (ESI): for $C_{28}H_{46}O_7Si$ $[M+H]^+$: calcd. 523.3091; found 523.3087.

5.7.3 Synthesis of Lactone **35f**

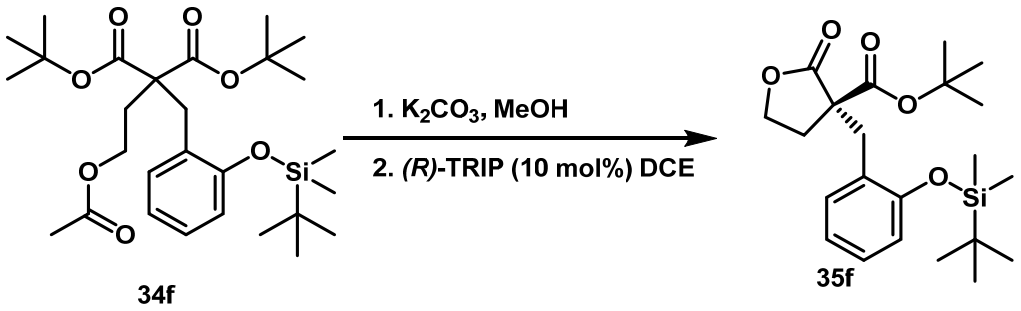


Figure 43. Lactone **35f**

To a 50 mL round bottom flask, was added compound **34f** (190 mg, 0.36 mmol) in methanol (7 mL), followed by K_2CO_3 (150 mg, 1.1 mmol). The mixture was stirred at room temperature for 30 min, water (10 mL) was added, and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The mixture was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to obtain the alcohol intermediate as a colorless oil which was used in the next step (117 mg, 67% yield). To a solution of (*R*)-TRIP (29.8 mg, 0.04 mol) in 1,2-dichloroethane (4 mL) was added the diester

intermediate (190 mg, 0.40 mmol). The mixture was stirred for 11 days at rt. Water (10 mL) was added to the reaction, and it was extracted with ethyl acetate (2 x 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford the lactone intermediate **35f** as a white solid (130 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 1H), 7.11 (m, 1H), 6.87 (m, 1H), 4.17 (q, *J* = 8.5 Hz, 1H), 3.83 (td, *J* = 8.5, 4.0 Hz, 1H), 3.51 (d, *J* = 12.0 Hz, 1H), 3.11 (d, *J* = 12.0 Hz, 1H), 2.46 (m, 1H), 2.24 (m, 1H), 1.48 (s, 9H), 0.99 (s, 9H), 0.22 (d, *J* = 19.7 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 169.1, 154.3, 131.8, 128.4, 126.6, 121.8, 118.6, 83.0, 66.4, 56.4, 31.8, 30.1, 27.9, 25.9, 18.3, -3.8, -4.3 ppm; HRMS (ESI): for $C_{26}H_{44}O_6Si$ $[M+H]^+$: calcd. 407.2253; found 407.2248; MP = 91.5-93.2° C.

5.7.4 Synthesis of Hydroxy-lactone **35f'**

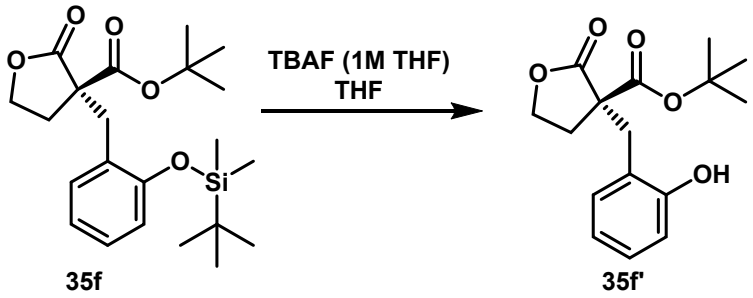


Figure 44. Hydroxy-lactone **35f'**

To a 10 mL round bottom flask was added compound **35f** (115 mg, 0.28 mmol) in THF (4 mL). *Tetra*-N-butylammonium fluoride (0.85 mL, 0.85 mmol) was added to the solution, and the reaction was left stirring at 0° C for 2 hours. The mixture was extracted with water (10 mL) and ethyl acetate (2 x 10 mL) and dried over $MgSO_4$, filtered and

concentrated. The crude material was purified by silica gel column chromatography (30% ethyl acetate/hexanes) to obtain hydroxy-lactone **35f'** as a yellow oil (80 mg, 97% yield, 75% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (m, 1H), 7.09 (bs, 1H), 7.06 (m, 1H), 6.89 (m, 1H), 6.85 (m, 1H), 4.31 (m, 1H), 4.22 (td, *J* = 8.0, 4.0 Hz, 1H), 3.30 (d, *J* = 14.7 Hz, 1H), 3.17 (d, *J* = 14.7 Hz, 1H), 2.58 (m, 1H), 2.47 (m, 1H), 1.45 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 169.5, 155.1, 121.9, 120.7, 117.8, 84.4, 56.6, 32.6, 31.3, 27.8 ppm; HRMS (ESI): for $C_{16}H_{20}O_5$ $[M+H]^+$: calcd. 293.1389; found 293.1380.

5.7.5 Synthesis of Spirocycle **36f**

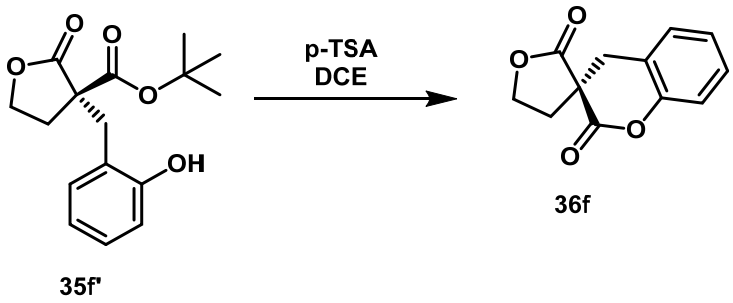


Figure 45. Spirocycle **36f**

To a 10 mL round bottom flask was added compound **35f'** (70 mg, 24 mmol) dissolved in dry 1,2-dichloroethane (2.5 mL) followed by *p*-toluenesulfonic acid (41 mg, 0.24 mmol). The reaction was stirred at room temperature for 36 hours. The mixture was extracted with water (10 mL) and ethyl acetate (2 x 10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by silica gel column chromatography (30% ethyl acetate/hexanes) to obtain **36f** as a white solid (18 mg, 35% yield, 72% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 1H), 7.23 (m, 1H), 7.16 (m, 1H), 7.10 (m, 1H),

4.45 (m, 2H), 3.62 (d, J = 16.2 Hz, 1H), 2.93 (d, J = 16.2 Hz, 1H), 2.62 (m, 1H), 2.23 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 165.7, 151.0, 128.6, 125.3, 119.6, 116.8, 65.7, 49.2, 33.8, 33.0 ppm; HRMS (ESI): for $C_{12}H_{10}O_4$ $[M+H]^+$: calcd. 219.0657; found 219.0651; MP = 140.1-141.8° C; $[a]_D$ = -9.09º c=0.22, $CHCl_3$).

5.8 Synthesis of Compound **46**

5.8.1 Synthesis of Monosubstituted Intermediate

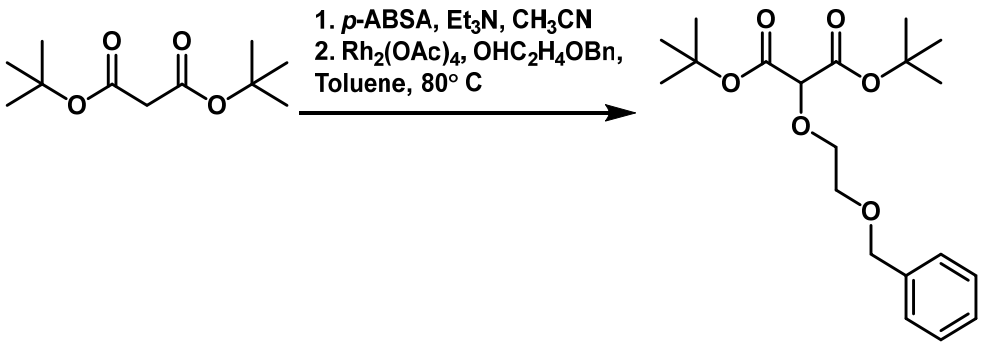


Figure 46. Monosubstituted Intermediate

A mixture of NaOH (5.2 g, 130 mmol) in ethylene glycol (30 mL, 536 mmol) was stirred at 55^0 C for one hour. benzyl bromide (9.02 mL, 76 mmol) was slowly added over a 30 min period, and the reaction was to stir for an additional one hour. The reaction was diluted with dichloromethane (50 mL), washed with water (3 x 20 mL), and washed with brine (3 x 20 mL). Organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Spectral data of alcohol matches previously published data (91% yield, 10.5 g).[1] A mixture of *para*-acetamidobenzylsulfonylazide (1.8 g, 4.9 mmol), di-*tert*-butyl malonate (1 mL, 4.5 mmol), triethylamine (684 µL, 4.9 mmol), and acetonitrile (30 mL) was stirred for 48 hours. The crude mixture was concentrated *in vacuo.* Hexanes

(50 mL) was added, the white solids were filtered off, and the filtrate was concentrated to afford a yellow oil diazomalonate compound (0.959 g). A mixture of $Rh_2(OAc)_4$ (17.0 mg, 0.039 mmol), toluene (30 mL), diazomalonate (0.959 g, 3.9 mmol), and alcohol (0.840 mL, 5.9 mmol) was added. The reaction was stirred overnight at 80^0 C, after which was filtered over Celite©, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford monosubstituted malonate diester as a colorless oil (287 mg, 20% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.56 (s, 2H), 4.40 (s, 1H), 3.80 (m, 2H), 3.69 (m, 2H), 1.47 (s, 18H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 138.3, 128.4, 127.8, 127.7, 82.7, 80.6, 73.4, 70.2, 69.5, 28.0 ppm; HRMS (ESI): for $C_{20}H_{30}O_6$ $[M+H]^+$: calcd. 367.2115; found 367.2102.

5.8.2 Synthesis of Disubstituted Intermediate

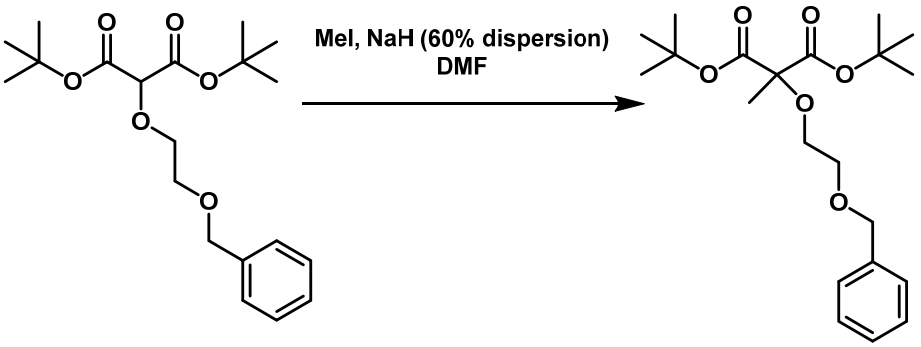


Figure 47. Disubstituted Intermediate

A mixture of NaH (60% dispersion, 65.0 mg, 1.7 mmol), DMF (8 mL), monosubstituted diester (314 mg, 0.85 mmol), and methyl iodide (106 µL, 1.7 mmol) was added at 0^0 C. Reaction was to let stir to room temperature overnight. The reaction

was quenched with H_2O (10 mL) and extracted with ethyl acetate (60 mL). The organic layer was washed with H_2O (3 x 20 mL) to remove DMF. Organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford the disubstituted malonate diester compound as a colorless oil (174 mg, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.58 (s, 2H), 3.74 (t, J = 5.5 Hz, 2H), 3.66 (t, J = 5.4 Hz, 2H), 1.55 (s, 3H), 1.47 (s, 18H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 168.6, 138.5, 128.4, 127.9, 127.6, 82.4, 82.2, 73.3, 69.3, 65.4, 28.0, 20.7 ppm; HRMS (ESI): for $C_{21}H_{32}O_6$ $[M+H]^+$: calcd. 381.2272; found 381.2267.

5.8.3 Synthesis of Alcohol **45**

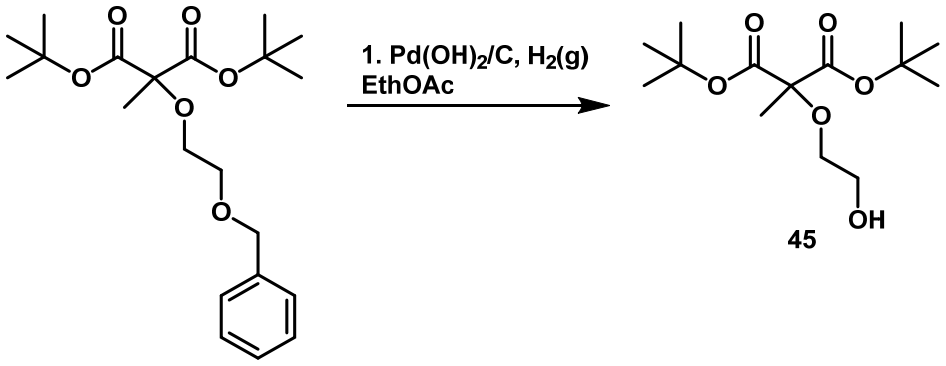


Figure 48. Alcohol **45**

$Pd(OH)_2/C$ (20 mg, 10 weight %) was added to a mixture of disubstituted diester (202 mg, 0.50 mmol) in ethyl acetate (5 mL). The flask was purged with H_2(g). After 12 hours under an atmosphere of H_2(g), the reaction was filtered through a plug of Celite© and concentrated *in vacuo*. The reaction was purified by silica gel column chromatography (40% ethyl acetate/hexanes) to afford compound **45** as a colorless oil

(111 mg, yield 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (m, 2H), 3.67 (m, 2H), 1.55 (s, 3H), 1.48 (s, 18H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 82.8, 82.1, 67.7, 62.0, 27.9, 20.7 ppm; HRMS (ESI): for $C_{14}H_{26}O_6$ $[M+H]^+$: cacld. 291.1807; found 291.1797.

5.8.4 Synthesis of Lactone **46**

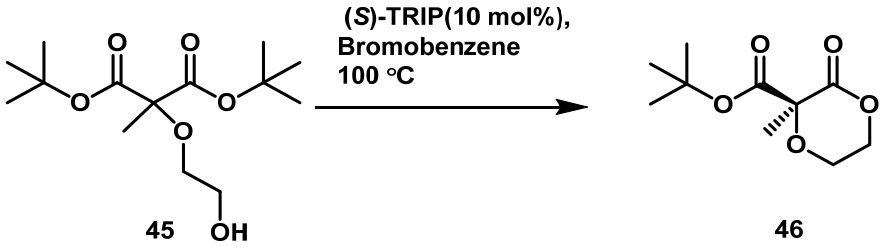


Figure 49. Lactone **46**

To a solution of alcohol **45** (57 mg, 0.19 mmol) in bromobenzene (2 mL), (*S)*-TRIP (10 mol%) was added. Stirred at 100^0 C for 5 days the reaction was concentrated *in vacuo* and purified by column chromatography (30% ethyl acetate/hexanes) to yield lactone **46** as a colorless oil . (34 mg, yield 80%, 81% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (m, 1H), 4.44 (m, 1H), 4.19 (m, 1H), 3.93 (m, 1H), 1.66 (s, 3H), 1.50 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 167.4, 83.8, 80.6, 68.4, 60.9, 27.9, 22.6 ppm; HRMS (ESI): for $C_{10}H_{16}O_5$ $[M+H]^+$: calcd. 217.1071; found 217.1070; $[a]_D^{20} = +5.87^o$ (c=1.6, $CHCl_3$).

5.9 Synthesis of Compound **48**

5.9.1 Synthesis of Disubstituted Intermediate

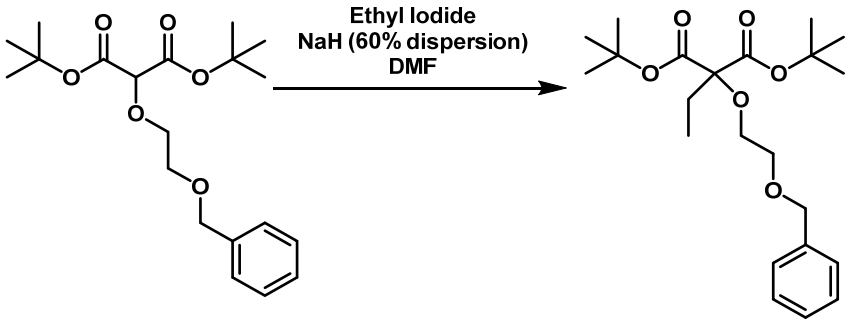


Figure 50. Disubstituted Intermediate

A mixture of NaH (60% dispersion, 64 mg, 1.6 mmol), DMF (8 mL), monosubstituted diester (300 mg, 0.82 mmol), and ethyl iodide (131 µL, 1.6 mmol) was added at 0^0 C. Reaction was to let stir to room temperature overnight. The reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (60 mL). The organic layer was washed with H_2O (3 x 20mL) to remove DMF. Organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford the disubstituted malonate diester as a colorless oil. (207 mg, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.59 (s, 2H), 3.69 (m, 4H), 1.99 (q, J = 7.4 Hz, 2H), 1.46 (s, 18H), 0.89 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 138.5, 128.4, 127.8, 127.6, 85.1, 82.2, 73.4, 69.4, 65.2, 28.0, 26.4, 7.4 ppm; HRMS (ESI): for $C_{22}H_{34}O_6$ $[M+H]^+$: calcd. 395.24282; found 395.24174.

5.9.2 Synthesis of Alcohol **47**

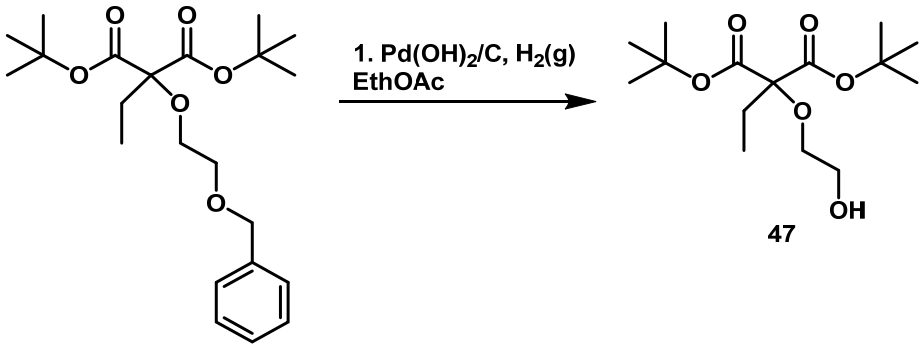


Figure 51. Alcohol **47**

$Pd(OH)_2/C$ (10 mg, 10 weight %) was added to a mixture of disubstituted diester (101 mg, 0.26 mmol) in ethyl acetate (5 mL). The flask was purged with $H_2(g)$. After 12 hours under an atmosphere of $H_2(g)$ the reaction was filtered through a plug of Celite© and concentrated *in vacuo*. The reaction was purified by silica gel column chromatography (40% ethyl acetate/hexanes) to afford compound **47** as a colorless oil. (56 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (m, 2H), 3.63 (m, 2H), 1.99 (q, J = 15, 7.5 Hz, 2H), 1.47 (s, 18H), 0.88 (t, J =7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 85.0, 82.7, 67.4, 62.0, 28.0, 27.0, 7.3 ppm; HRMS (ESI): for $C_{15}H_{28}O_6$ $[M+Na]^+$: calcd, 327.1784; found 327.1790.

5.9.3 Synthesis of Lactone **48**

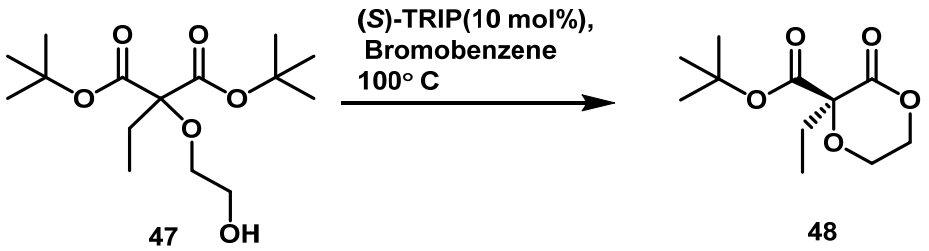


Figure 52. Lactone **48**

To a solution of alcohol **47** (92 mg, 0.3 mmol) in bromobenzene (3 mL), (*S)*-TRIP (10 mol%) was added. Stirred at 100^0 C for 5 days the reaction was concentrated *in vacuo* and purified by column chromatography (30% ethyl acetate/hexanes) to yield lactone **48** as a colorless oil (53 mg, yield 75%, 42% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (m, 1H), 4.40 (m, 1H), 4.26 (m, 1H), 3.93 (m, 1H) 2.10 (m, 2H), 1.49 (s, 9H), 0.98 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.6, 84.0, 83.6, 68.4, 61.0, 29.8, 27.9, 7.9 ppm; HRMS (ESI): for $C_{11}H_{18}O_5$ $[M+Na]^+$: calcd. 253.1052; found 253.1056; $[a]_D^{19}$ = +6.08° (c=2.5, $CHCl_3$).

5.10 Synthesis of Compound **50**

5.10.1 Synthesis of Disubstituted Intermediate

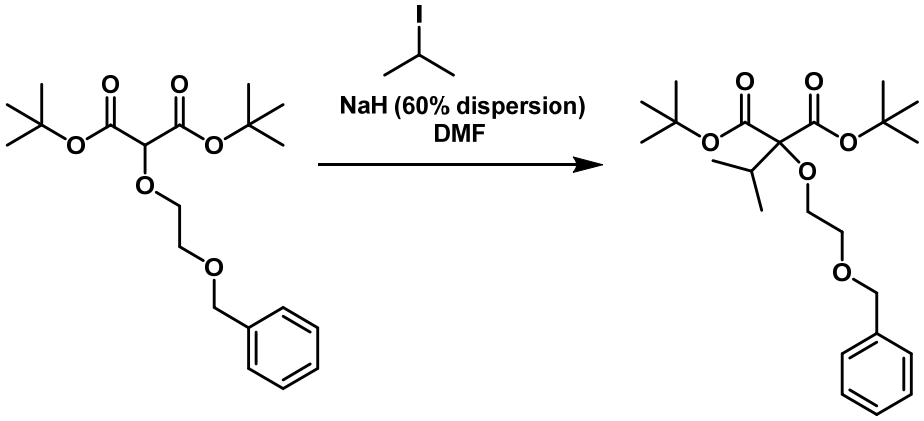


Figure 53. Disubstituted Intermediate

A mixture of NaH (60% dispersion, 65.0 mg, 1.6 mmol), DMF (8 mL), monosubstituted diester (306 mg, 0.83 mmol), and 2-iodopropane (165 µL, 1.6 mmol) was added at 0º C. Reaction was to let stir to room temperature overnight. The reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (60 mL). The organic layer was washed with H_2O (3 x 20mL) to remove DMF. Organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford the disubstituted malonate diester as a colorless oil (137 mg, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.60 (s, 2H), 3.86 (t, J = 5.4 Hz, 2H), 3.68 (t, J = 5.4 Hz, 2H), 2.37 (sep, 1H), 1.48 (s, 18H), 1.00 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 138.7, 128.4, 127.8. 127.5, 87.9, 82.2, 79.3, 69.8, 66.6, 34.5, 28.1, 17.5 ppm; HRMS (ESI) for $C_{23}H_{36}O_6$ $[M+H]^+$: calcd. 409.2585; found 409.2587.

5.10.2 Synthesis of Alcohol **49**

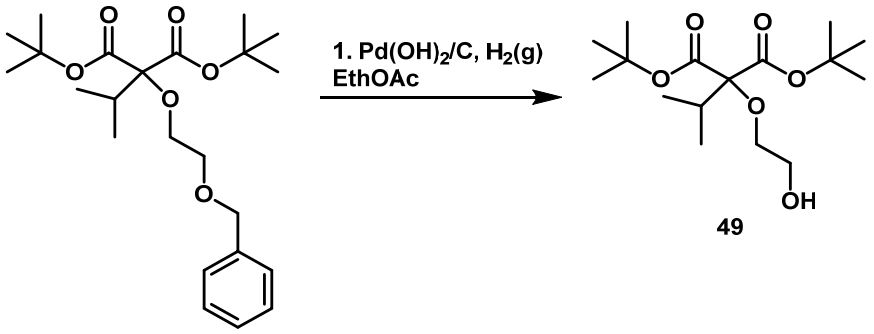


Figure 54. Alcohol **49**

$Pd(OH)_2/C$ (41 mg, 10 weight %) was added to a mixture of disubstituted diester (414 mg, 1.0 mmol) in ethyl acetate (5 mL). The flask was purged with $H_2(g)$. After 12 hours under an atmosphere of $H_2(g)$ the reaction was filtered through a plug of Celite© and concentrated *in vacuo*. The reaction was purified by silica gel column chromatography (40% ethyl acetate/hexanes) to afford compound **49** as a colorless oil (320 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (m, 2H), 3.72 (m, 2H) 2.35 (m, 1H) 1.49 (s, 18H) 0.98 (d, J = 6.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 87.7, 82.9, 69.1, 62.5, 35.1, 28.1, 17.4 ppm; HRMS (ESI): for $C_{16}H_{30}O_6$ $[M+Na]^+$: calcd. 341.1935; found 341.1940.

5.10.3 Synthesis of Lactone **50**

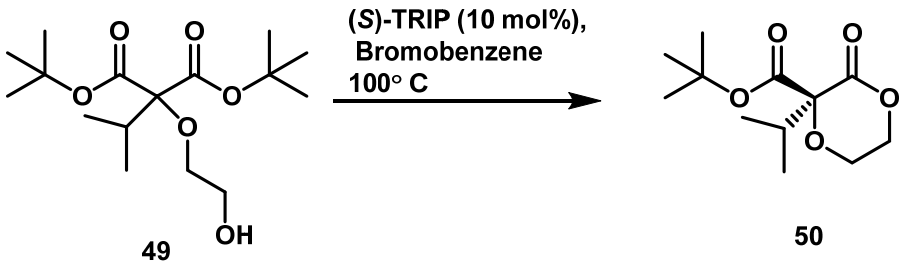


Figure 55. Lactone **50**

To a solution of alcohol **49** (97 mg, 0.3 mmol) in bromobenzene (3 mL), (*S)*-TRIP (10 mol%) was added. Stirred at 100^0 C for 5 days the reaction was concentrated *in vacuo* and purified by column chromatography (30% ethyl acetate/hexanes) to yield lactone **50** as a colorless oil (33 mg, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (m, 1H), 4.36 (m, 1H) 4.27 (m, 1H) 3.95 (m, 1H) 2.67 (m, 1H) 1.48 (s, 18H) 1.00 (d, J = 6.7 Hz, 3H) 0.57 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 165.9, 86.6, 83.5, 68.4, 61.2, 35.7, 27.9, 17.2, 16.2 ppm; HRMS (ESI): for $C_{12}H_{20}O_5$ $[M+Na]^+$: calcd. 267.1203; found 267.1204; $[a]_D^{19}$= -3.38° (c = 0.87, $CHCl_3$).

5.11 Synthesis of Compound **52**

5.11.1 Synthesis of Disubstituted Intermediate

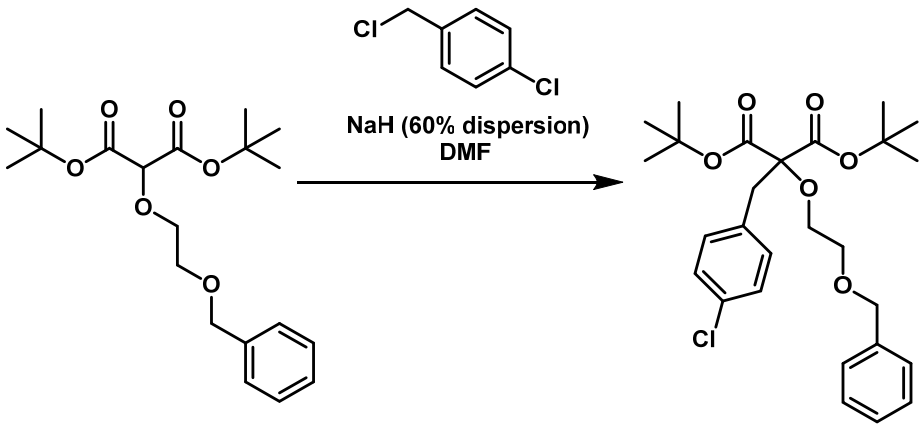


Figure 56. Disubstituted Intermediate

A mixture of NaH (60% dispersion, 55 mg, 1.4 mmol), DMF (7 mL), monosubstituted diester (252 mg, 0.69 mmol), and 4-chlorobenzyl chloride (87 mg, 1.4 mmol) was added at 0º C. Reaction was to let stir to room temperature overnight. The reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (60 mL). The organic layer was washed with H_2O (3 x 20mL) to remove DMF. Organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford the disubstituted malonate diester as a colorless oil (248 mg, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 7.23 (m, 2H), 7.14 (m, 2H), 4.57 (s, 2H), 3.86 (t, J = 5.1 Hz, 2H), 3.68 (t, J = 5.1 Hz, 2H), 3.21 (s, 2H), 1.40 (s, 18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 138.5, 134.1, 132.7, 132.0, 128.5, 128.0, 127.8, 127.7, 84.9, 82.8, 73.4,

69.6, 66.0, 39.5, 28.0 ppm; HRMS (ESI): for $C_{27}H_{35}O_6Cl$ $[M+Na]^+$: calcd. 513.2014; found 513.2031.

5.11.2 Synthesis of Alcohol **51**

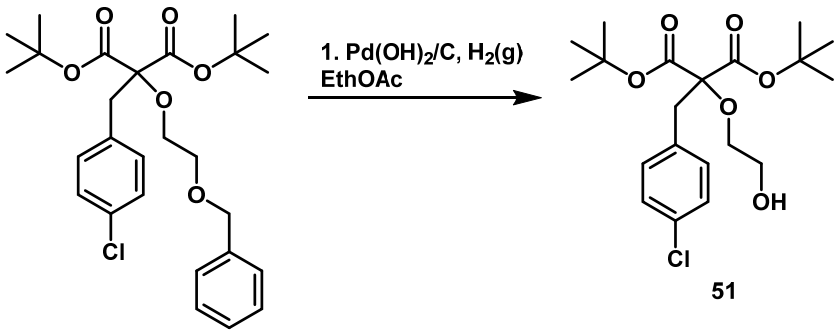


Figure 57. Alcohol **51**

$Pd(OH)_2/C$ (5 mg, 10 weight %) was added to a mixture of disubstituted diester (49 mg, 0.10 mmol) in ethyl acetate (1 mL). The flask was purged with $H_2(g)$. After 12 hours under an atmosphere of $H_2(g)$ the reaction was filtered through a plug of Celite© and concentrated *in vacuo*. The reaction was purified by silica gel column chromatography (40% ethyl acetate/hexanes) to afford compound **51** as a colorless oil (35 mg, 86% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 4H), 3.81 (m, 2H), 3.76 (m, 2H), 3.23 (s, 2H), 1.44 (s, 18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 131.8, 130.5, 128.2, 128.0, 84.7, 83.4, 68.4, 62.2, 40.2, 28.0 ppm; HRMS (ESI): for $C_{20}H_{29}ClO_6$ $[M+Na]^+$: cacld. 423.1550; found 423.1555.

5.11.3 Synthesis of Lactone **52**

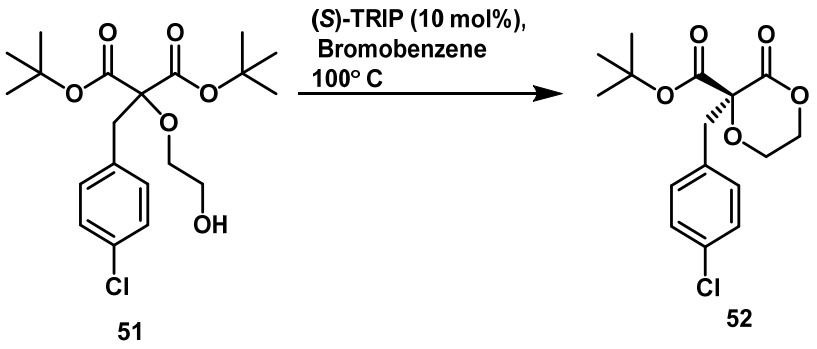


Figure 58. Lactone **52**

To a solution of alcohol **51** (59 mg, 0.14 mmol) in bromobenzene (1.4 mL), (*S)*-TRIP (10 mol%) was added. Stirred at 100º C for 5 days the reaction was concentrated *in vacuo* and purified by column chromatography (30% ethyl acetate/hexanes) to yield lactone **52** as a white solid (29 mg, 60% yield, 26% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 4H), 4.17 (m, 2H), 3.71 (m, 2H), 3.41 (d, J = 14.7 Hz, 1H), 3.17 (d, J = 14.1 Hz, 1H), 1.50 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 164. 5, 133.4, 133.0, 132.4, 128.5, 84.0, 83.8, 68.3, 61.2, 41.1, 27.9 ppm; HRMS (ESI): for $C_{16}H_{19}O_5Cl$ $[M+Na]^+$: calcd. 349.0813; found 349.0809; MP = 77.6-78.9º C; $[a]_D^{21}$ = -8.62º (c = 0.58, $CHCl_3$).

5.12 Synthesis of Compound **54**

5.12.1 Synthesis of Amine

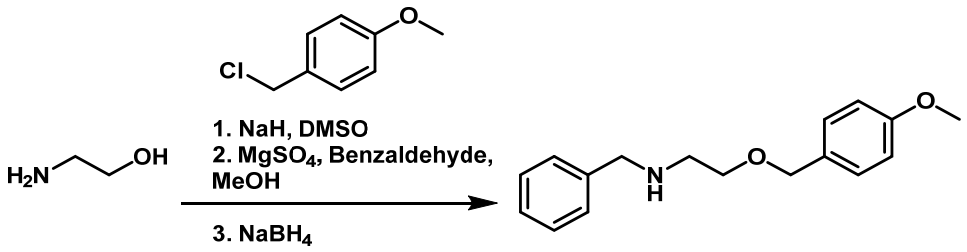


Figure 59. Amine

To a mixture of NaH (60% dispersion, 0.90 g, 24.0 mmol) and dimethyl sulfoxide (50 mL), ethanolamine (2.0 mL, 33.0 mmol) was slowly added to flask to form a slurry. Paramethoxybenzylchloride (2.2 mL, 16.5 mmol) was added via addition funnel over a 2-hour period. The reaction was stirred for an additional 2 hours. The reaction was quenched with water and extracted with dichloromethane (3 x 70 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude amine and was used directly in the next step. The above amine (2.8 g, 15.4 mmol) was added, followed by $MgSO_4$ (anhydrous, 3.7 g, 30.8 mmol), methanol (75 mL), and benzaldehyde (1.6 mL, 15.4 mmol). After reaction was stirred for 12 hours, the reaction was put in an ice bath and sodium borohydride (582 mg, 15.4 mmol) was added. The reaction was stirred for one hour and was quenched with water (20 mL) and extracted with dichloromethane (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* with no further purification to afford amine as a colorless oil (3.58 g, 85% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.18 (m, 7H), 6.86 (m, 2H), 4.44 (s,

2H), 3.79 (s, 2H), 3.58 (m, 2H), 2.82 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 140.3, 130.5, 129.5, 128.5, 128.3, 127.0, 113.9, 73.0, 69.5, 55.4, 54.0. 49.0 ppm; HRMS (ESI): for $C_{17}H_{21}NO_2$ $[M+H]^+$: calcd. 272.1645; found 272.1642.

5.12.2 Synthesis of Monosubstituted Intermediate

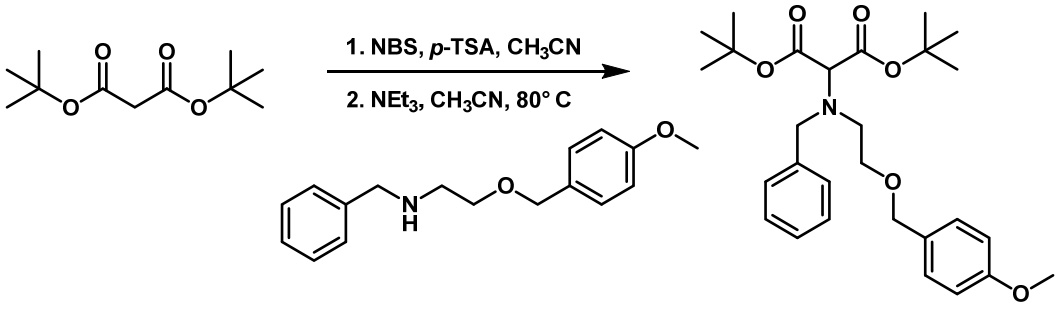


Figure 60. Monosubstituted Intermediate

To a mixture of *n*-bromosuccinimide (1.50 g, 8.5 mmol) in acetonitrile (40 mL), *para*-toluenesulfonic acid (72 mg, 0.42 mmol) and di-*tert*-butyl malonate (2.0 mL, 8.5 mmol) was added. After 48 hours the reaction mixture was quenched with saturated NH_4Cl (aq) (15 mL). The mixture was extracted with ethyl acetate (3 x 50 mL), and the organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude material was purified by silica gel column chromatography (5% ethyl acetate/hexanes) to bromo-di-*tert*-butyl malonate (788 mg, 31% yield).[2] To a mixture of acetonitrile (20 mL) and amine (1.2 g, 4.7 mmol), triethylamine (655 µL, 4.7 mmol) and bromo-di-*tert*-butyl malonate (701 mg, 2.3 mmol) was added. The reaction was heated in an oil bath at 80º C. After 48 hours the reaction was quenched with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layers were dried over $MgSO_4$, filtered, and

concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford monosubstituted diester as a colorless oil (413 mg, 35% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.30-7.23 (m, 3H), 7.21 (m, 2H), 6.83 (m, 2H), 4.38 (s, 2H), 4.09 (s, 1H), 3.95 (s, 2H), 3.78 (s, 3H), 3.52 (t, *J* = 6.2 Hz, 2H), 2.96 (t, *J* = 6.0 Hz, 2H), 1.45 (s, 18H) ppm; ^{13}C NMR (100 Hz, $CDCl_3$) δ 167.8, 159.1, 139.9, 130.7, 129.3, 128.7, 128.3, 127.0, 113.8, 81.9, 72.7, 70.0, 68,8, 56.9, 55.4, 51.5, 28.1 ppm; HRMS (ESI): for $C_{28}H_{39}NO_6$ $[M+H]^+$: calcd. 486.2856; found 486.2872.

5.12.3 Synthesis of Disubstituted Intermediate

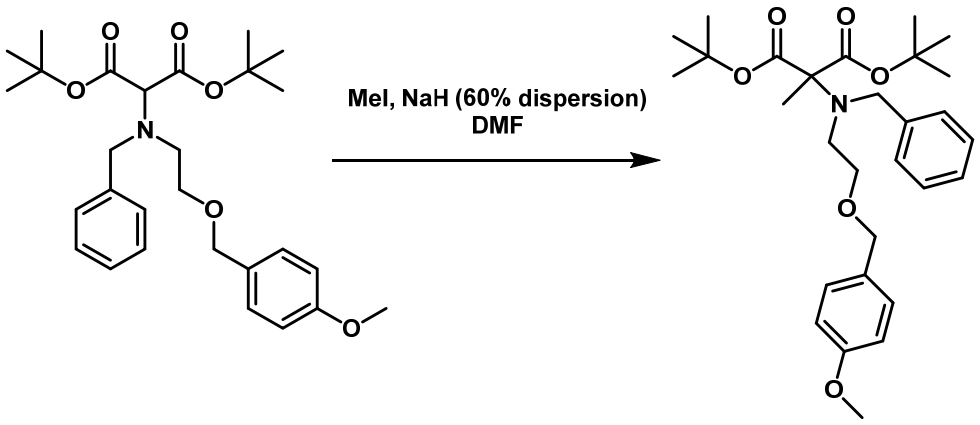


Figure 61. Disubstituted Intermediate

A mixture of NaH (60% dispersion, 65.0 mg, 1.7 mmol) in DMF (8 mL), monosubstituted diester (314 mg, 0.85 mmol) and MeI (106 µL, 1.7 mmol) was added at 0º C. Reaction was stirred and allowed to warm to room temperature overnight. The reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (60 mL). The organic layer was washed with H_2O (3 x 20mL) to remove DMF. The organic layer was

dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford the disubstituted malonate diester as a colorless oil (371 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.27 (m, 2H), 7.20 (m, 1H), 7.08 (m, 2H), 6.80 (m, 2H) 4.18 (s, 2H), 3.91 (s, 2H), 3.78 (s, 3H), 3.18 (t, J = 7.5 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 1.53 (s, 3H), 1.46 (s, 18H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 159.1, 141.1, 130.6, 129.3, 128.2, 128.1, 126.7, 113.7, 81.9, 74.0, 72.7, 69.8, 57.7, 55.4, 52.0, 28.1, 22.9 ppm; HRMS (ESI): for $C_{29}H_{41}NO_6$ $[M+H]^+$: calcd. 500.3012; found 500.3028.

5.12.4 Synthesis of Alcohol **53**

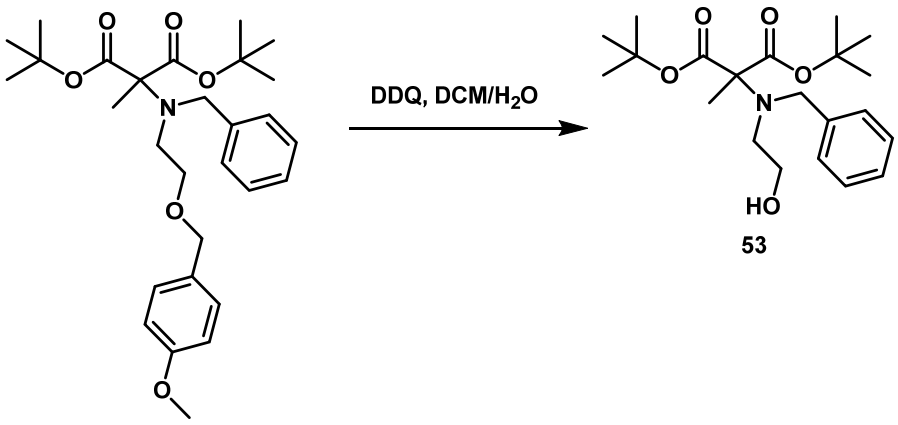


Figure 62. Alcohol **53**

A mixture of DDQ (252 mg, 1.1 mmol), dichloromethane (7 mL), water (799 µL), and disubstituted diester (371 mg, 0.74 mmol) was stirred for 2 hours. The reaction was added to dichloromethane (50 mL), and the organic layer was washed with sodium bicarbonate (20 mL), then brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by silica gel column

chromatography (20% ethyl acetate/hexanes) to afford alcohol **53** as a colorless oil (174 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.30 (m, 2H), 7.20 (m, 1H), 3.87 (s, 2H), 3.32 (q, *J* = 5.3 Hz, 2H), 3.13 (t, *J* = 5.4 Hz, 1H), 2.94 (t, *J* = 5.3 Hz, 2H). 1.47 (s, 21H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 141.8, 128.5, 127.5, 126.9, 82.5, 73.8, 60.6, 56.5, 56.4, 28.1, 22.8 ppm; HRMS (ESI): for $C_{21}H_{33}NO_5$ $[M+H]^+$: calcd. 380.2437; found 380.2426.

5.12.5 Synthesis of Lactone **54**

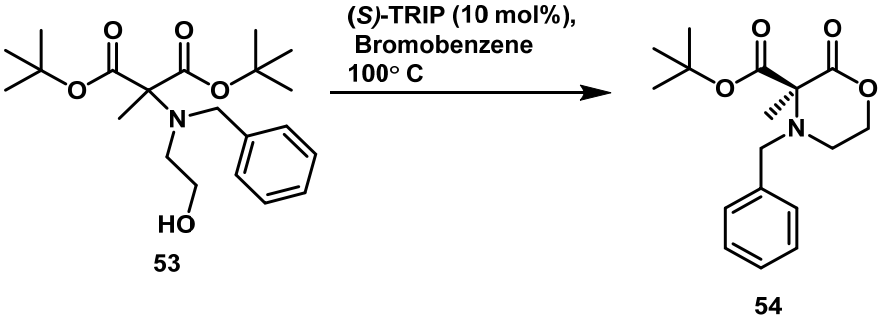


Figure 63. Lactone **54**

To a solution of alcohol **53** (170 mg, 0.44 mmol) in bromobenzene (4.4 mL), (*S*)-TRIP (33 mg, 10 mol%) was added. Stirred at 100º C for 3 days the reaction was concentrated i*n vacuo* and purified by column chromatography (30% ethyl acetate/hexanes) to yield lactone **54** as a colorless oil (58 mg, 43% yield, 40% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 4.32 (m, 2H), 3.88 (d, *J* = 15 Hz, 1H), 3.31 (d, *J* = 15 Hz, 1H), 3.09 (m, 1H), 2.65 (m, 1H), 1.70 (s, 3H), 1.53 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.0, 138.2, 128.2, 128.4, 127.6, 83.3, 70.2, 69.1,

54.2, 42.4, 28.2, 20.7 ppm; HRMS (ESI): for $C_{17}H_{23}NO_4$ $[M+H]^+$: calcd. 306.1700; found 306.1698; $[a]_D^{21} = -1.48^o$ (c=12.6, $CHCl_3$).

5.13 Synthesis of Compound 56

5.13.1 Synthesis of Phenol

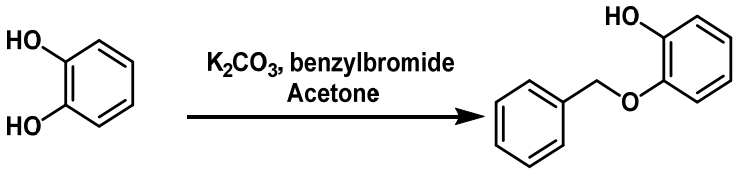


Figure 64. Phenol

To a mixture of K_2CO_3 (2.5 g, 18 mmol), acetone (50 mL) and catechol (2.0 g, 18 mmol), benzyl bromide (2.5 mL, 22 mmol) was added. The reaction was stirred at reflux for 3 hours after which the solids were filtered and rinsed with dichloromethane (100 mL) and the filtrate was collected and concentrated without further purification. Spectra matches previously published results to yield phenol (3.29 g, 84% yield).

5.13.2 Synthesis of Monosubstituted Intermediate

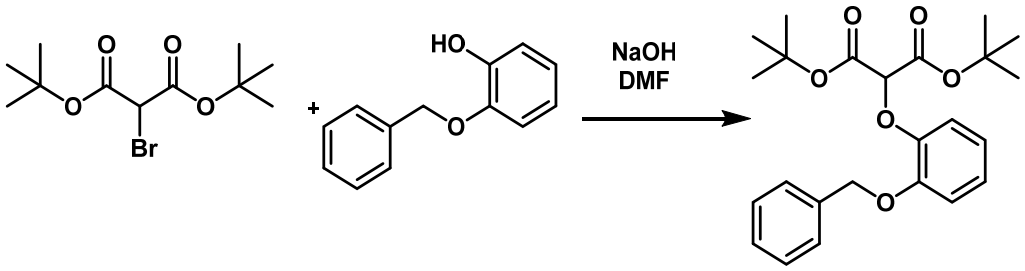


Figure 65. Monosubstituted Diester

To a solution of grinded NaOH (71 mg, 1.78 mmol) in DMF (15 mL), phenol (357 mg, 1.78 mmol), and bromomalonate (527 mg, 1.78 mmol) were added. After 12 hours, the reaction was added to water (10 mL), then extracted with ethyl acetate (3 x 30 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (10% ethyl acetate/petroleum ether) to afford monosubstituted diester as a colorless oil (383 mg, 52% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.37-7.28 (m, 3H), 7.05 (m, 1H), 6.98-6.84 (m, 3H), 5.14 (s, 2H), 5.06 (s, 1H), 1.45 (s, 18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 149.8, 147.3, 128.5, 127.8, 126.5, 124.0, 121.6, 119.7, 117.8, 115.6, 82.9, 79.7, 71.3, 28.0 ppm; HRMS (ESI): for $C_{24}H_{30}O_6$ $[M+Na]^+$: calcd. 437.1935; found 437.1928.

5.13.3 Synthesis of Disubstituted Intermediate

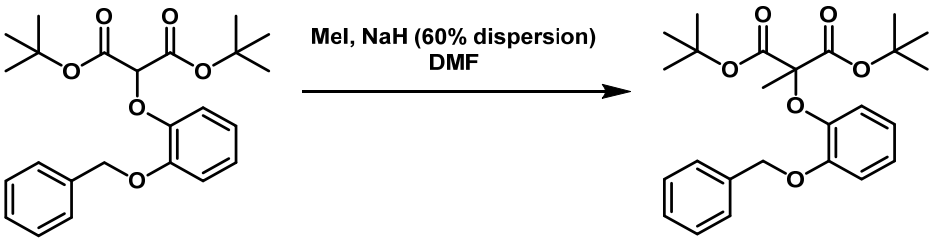


Figure 66. Disubstituted Intermediate

To a mixture of NaH (60% dispersion, 44 mg, 1.1 mmol) in THF (12 mL), malonate diester compound (414 mg, 0.94 mmol) and MeI (0.061 mL, 0.99 mmol) was added at 0º C. The reaction was stirred and warmed to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate

(100 mL). The organic layer was washed with H_2O (4 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5%→10% di-ethyl ether/petroleum ether) to afford di-substituted malonate diester compound as a colorless oil (482 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.36-7.26 (m, 3H), 7.14 (m, 1H), 6.99-6.81 (m, 3H), 5.10 (s, 2H), 1.58 (s, 3H), 1.45 (s, 18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 151.9, 145.1, 137.5, 128.5, 127.7, 127.4, 124.5, 123.0, 121.4, 115.6, 84.3, 82.4, 71.2, 27.9, 19.7 ppm; HRMS (ESI): for $C_{25}H_{32}O_6$ $[M+Na]^+$: calcd. 451.2097; found 451.2081.

5.13.4 Synthesis of Alcohol **55**

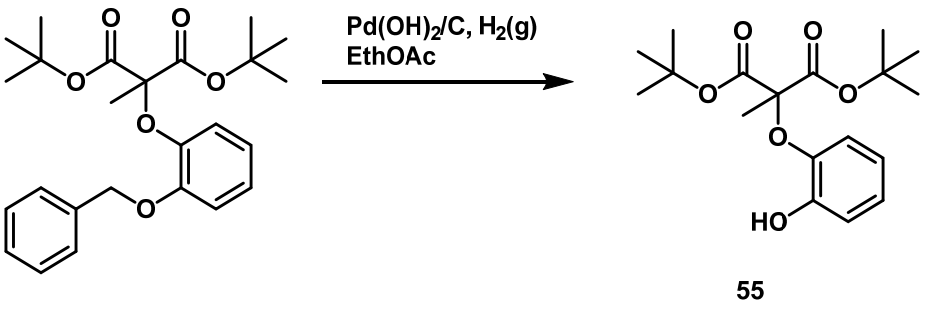


Figure 67. Alcohol **55**

$Pd(OH)_2/C$ (26 mg, 20 weight %) was added to a mixture of disubstituted diester (127 mg, 0.29 mmol) in ethyl acetate (3 mL) was added. The flask was purged with H_2(g). After 12 hours the reaction was filtered through a plug of Celite© and concentrated *in vacuo*. The reaction was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford phenol **55** (82 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 6.99 (m, 1H), 6.91 (m, 1H), 6.85 (m, 1H), 6.69 (m, 1H), 1.60, (s, 3H), 1.40

(s, 18H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.8, 151.1, 141.9, 126.1, 123.3, 119.3, 116.2, 85.0, 83.8, 27.7, 21.0 ppm; HRMS (ESI): for $C_{18}H_{26}O_6$ $[M+Na]^+$: calcd. 361.1622; found 361.1618.

5.13.5 Synthesis of Lactone **56**

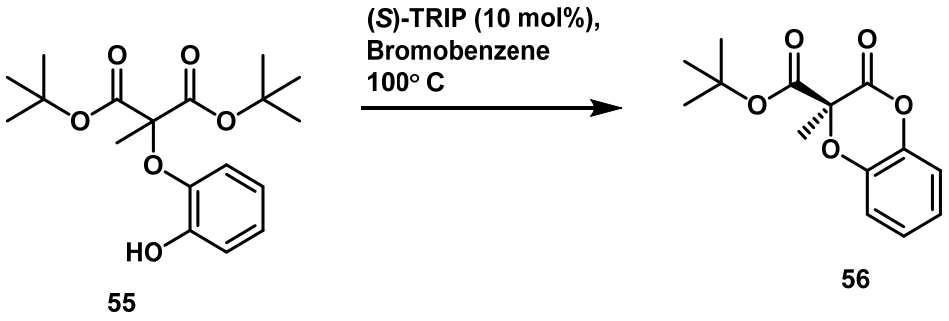


Figure 68. Lactone **56**

To a mixture of phenol **55** (82 mg, 0.24 mmol), and bromobenzene (2.4 mL), (*S)*-TRIP (10 mol%) was added. After stirring at 100º C for 3 days, the reaction was concentrated *in vacuo* and purified by column chromatography (10% ethyl acetate/hexanes) to yield lactone **56** as a yellow oil (47 mg, 75% yield, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.01 (m, 4H), 1.86 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.3, 142.1, 141.5, 125.4, 123.8, 118.0, 117.0, 84.7, 80.4, 27.6, 20.6 ppm; HRMS (ESI): for $C_{14}H_{16}O_5$ $[M+Na]^+$: calcd. 287.0878; found 287.0890; $[a]_D^{21}$ =-42.64º (c=0.53, $CHCl_3$).

5.14 Synthesis of Compound **58**

5.14.1 Synthesis of Disubstituted Intermediate

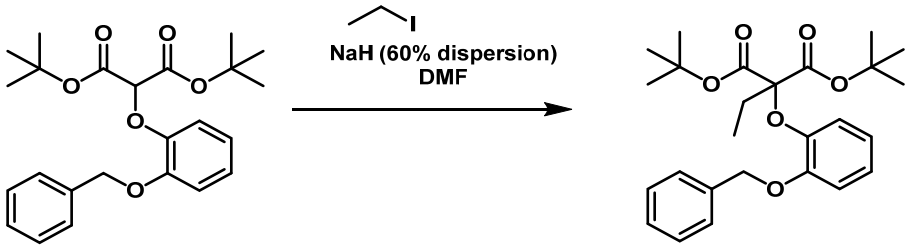


Figure 69. Disubstituted Intermediate

To a mixture of NaH (60% dispersion, 31 mg, 0.76 mmol) in THF (12 mL), malonate diester compound (266 mg, 0.64 mmol) and ethyl iodide (0.056 mL, 0.70 mmol) was added at 0º C. The reaction was stirred and warmed to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with H_2O (4 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5%→10% di-ethyl ether/petroleum ether) to afford di-substituted malonate diester as a colorless oil (211 mg, 74% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.34 (m, 3H), 7.06 (m, 1H), 6.90 (m, 2H), 6.81 (m, 1H) 5.12 (s, 2H), 2.22 (q, J = 7.5 Hz, 2H), 1.40 (s, 18H), 0.95 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 150.8, 146.0, 137.7, 128.4, 127.6, 127.4, 123.4, 121.4, 120.6, 115.8, 87.3, 82.4, 71.3, 27.8, 27.6, 7.7 ppm; HRMS (ESI): for $C_{26}H_{34}O_6$ $[M+Na]^+$: calcd. 465.2253; found 465.2237.

5.14.2 Synthesis of Alcohol **57**

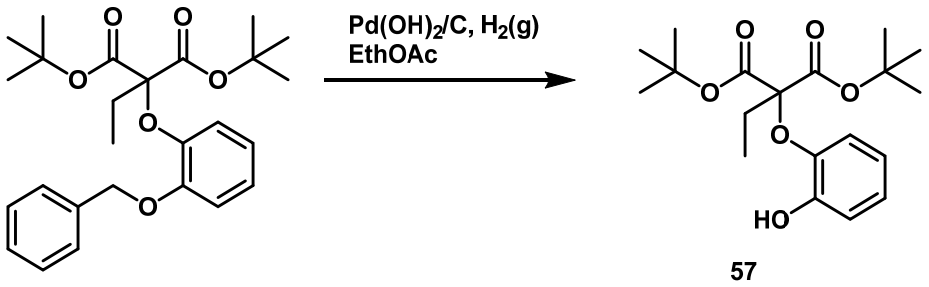


Figure 70. Alcohol **57**

$Pd(OH)_2/C$ (31 mg, 20 weight %) was added to a mixture of disubstituted diester (154 mg, 0.35 mmol) in ethyl acetate (3 mL) was added. The flask was purged with $H_2(g)$. After 12 hours the reaction was filtered through a plug of Celite© and concentrated *in vacuo*. The reaction was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford compound **57** as a colorless oil (117 mg, 95% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 6.97 (m, 1H), 6.90 (m, 1H), 6.83 (m, 1H), 6.66 (m, 1H), 2.21 (q, J = 7.4 Hz, 2H), 1.31 (s, 18H), 1.01 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 151.0, 143.1, 125.7, 122.2, 119.2, 115.8, 88.8, 83.6, 28.8, 27.6, 7.4 ppm; HRMS (ESI): for $C_{19}H_{28}O_6$ $[M+Na]^+$: calcd. 375.1784; found 375.1174.

5.14.3 Synthesis of Lactone **58**

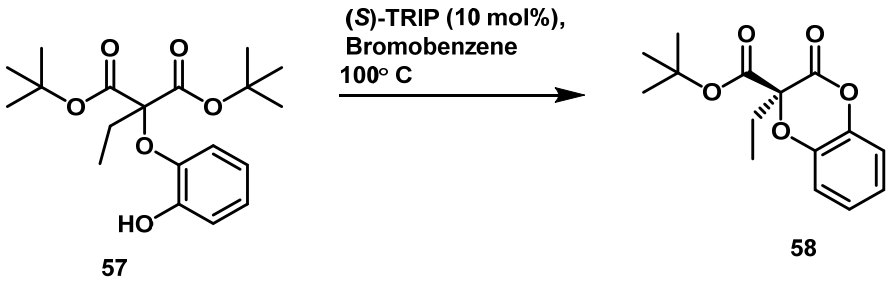


Figure 71. Lactone **58**

To a mixture of alcohol **57** (115 mg, 0.32 mmol), and bromobenzene (3.2 mL), (*S)*-TRIP (10 mol%) was added. After stirring at 100º C for 3 days, the reaction was concentrated *in vacuo* and purified by column chromatography (10% ethyl acetate/hexanes) to yield lactones **58** as a yellow oil (63 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-6.98 (m, 4H), 2.29 (m, 2H), 1.28 (s, 9H), 1.12 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 162.5, 142.3, 141.2, 125.4, 123.6, 118.0, 116.9, 84.6, 83.3, 27.8, 27.6, 7.7 ppm; HRMS (ESI): for $C_{15}H_{18}O_5$ $[M+H]^+$: calcd. 279.1227; found 279.1216; $[a]_D^{21}$ = , -20.20° (c=1.02, $CHCl_3$).

5.14.4 Synthesis of Diol **58'**

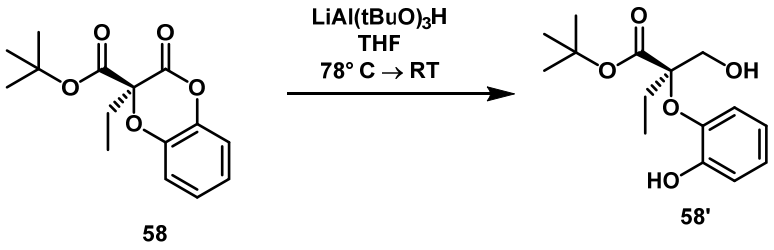


Figure 72. Diol **58'**

A mixture of lithium aluminum tri-*tert*-butoxy hydride (171 mg, 0.67 mmol) in THF (6 mL) was added and stirred in a dry ice/ acetone bath at -78° C for 5 minutes. Compound **58** (47 mg, 0.17 mmol) was added and reaction was to let warm to room temperature overnight. The reaction was quenched with saturated potassium sodium tartrate (10 mL), then extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography to afford compound **58'** as a colorless oil (6 mg, 13% yield, 86% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05-6.93 (m, 3H), 6.77-6.73 (m, 1H), 3.93 (m, 2H), 1.84 (q, *J* = 7.6 Hz, 2H), 1.52 (s, 9H), 0.87 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 151.1, 141.6, 125.8, 123.6, 119.5, 116.7, 87.9, 84.0, 65.9, 28.0, 26.6, 8.1 ppm.

5.15 Synthesis of Compound **60**

5.15.1 Synthesis of Disubstituted Intermediate

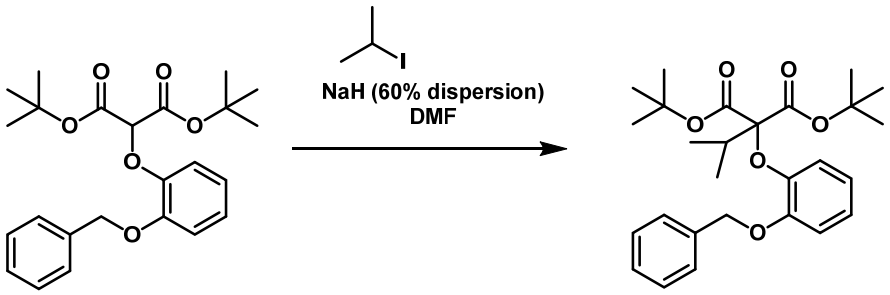
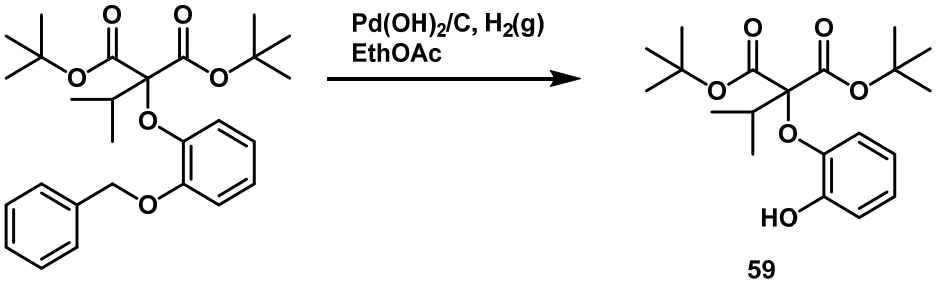


Figure 73. Disubstituted Intermediate

To a mixture of NaH (60% dispersion, 44 mg, 1.1 mmol) in THF (12 mL), malonate diester compound (389 mg, 0.93 mmol) and 2-iodopropane (0.098 mL, 0.99 mmol) was added at 0º C. The reaction was stirred and warmed to room temperature

overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with H_2O (4 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5%→10% di-ethyl ether/petroleum ether) to afford di-substituted malonate diester compound as a colorless oil (300 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.34 (m, 2H), 7.29 (m, 1H), 6.97-6.75 (m, 4H), 5.07 (s, 2H), 2.62 (m, 1H), 1.36 (s, 18H), 1.13 (d, J = 6.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 149.9, 147.4, 137.8, 128.4, 127.6, 127.4, 122.3, 121.1, 118.7, 115.9, 89.1, 82.1, 71.6, 36.7, 27.9, 17.6 ppm; HRMS (ESI): for $C_{27}H_{36}O_6$ $[M+H]^+$: calcd. 457.2585; found 457.2583.

5.15.2 Synthesis of Alcohol **59**



59

Figure 74. Alcohol **59**

$Pd(OH)_2/C$ (60 mg, 20 weight %) was added to a mixture of disubstituted diester (301 mg, 0.66 mmol) in ethyl acetate (6 mL) was added. The flask was purged with H_2(g). After 12 hours the reaction was filtered through a plug of Celite© and concentrated *in vacuo*. The reaction was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford phenol **59** as a white solid (230 mg, 95% yield.). ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.72 (s, 1H), 6.97 (m, 1H), 6.88 (m, 2H), 6.66 (m, 1H), 2.54 (m, 1H), 1.27 (s, 18H), 1.19 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 151.6, 143.9, 125.7, 122.5, 119.1, 116.0, 91.4, 83.6, 33.8, 27.5, 17.8 ppm; HRMS (ESI): for $C_{20}H_{30}O_6$ $[M+Na]^+$: calcd. 389.1935; found 389.1932; MP= 80.6-82.9º C.

5.15.3 Synthesis of Lactone **60**

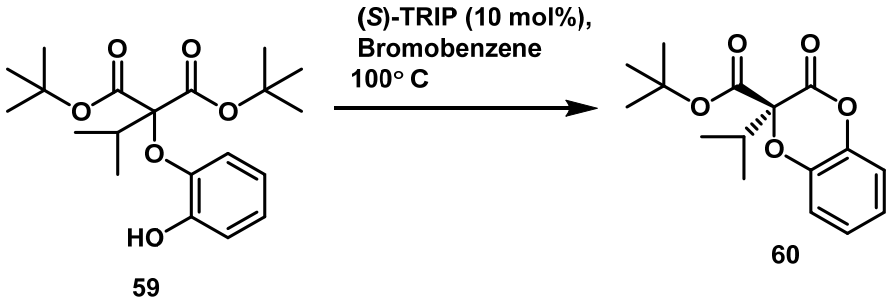


Figure 75. Lactone **60**

To a mixture of alcohol **59** (101 mg, 0.27 mmol), and bromobenzene (2.7 mL), (*S)*-TRIP (10 mol%) was added. After stirring at 100º C for 3 days, the reaction was concentrated *in vacuo* and purified by column chromatography (10% ethyl acetate/hexanes) to afford lactone **60** as a colorless oil (64 mg, 79% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17-6.97 (m, 4H), 2.81 (m, 1H), 1.29 (s, 9H) 1.16 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 161.9, 142.6, 140.8, 125.4, 123.3, 118.0, 116.8, 85.8, 84.5, 33.9, 27.7, 17.2, 16.3 ppm; HRMS (ESI): for $C_{16}H_{20}O_5$ $[M+Na]^+$: calcd. 315.1203; found 315.1191; $[a]_D^{26}$ = +3.85º (c= 0.52, $CHCl_3$).

5.15.4 Synthesis of Diol **60'**

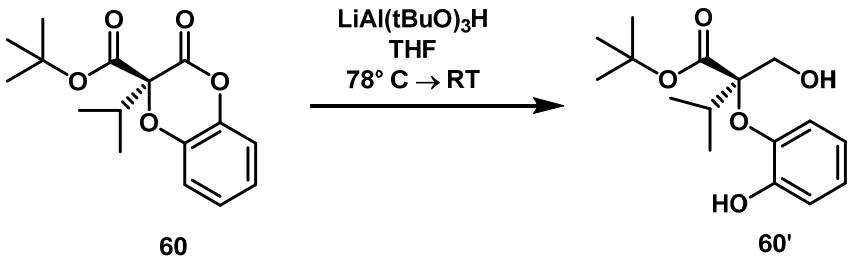


Figure 76. Diol **60'**

A mixture of lithium aluminum tri-tert-butoxy hydride (190 mg, 0.73 mmol) in THF (7 mL) was added and stirred in a dry ice/ acetone bath at -78° C for 5 minutes. Compound **60** (47 mg, 0.15 mmol) was added and reaction was to let warm to room temperature overnight. The reaction was quenched with saturated potassium sodium tartrate (10 mL), then extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography to afford compound **60'** as a colorless oil (8 mg, 18% yield, 56% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.01 (m, 2H), 6.95 (m, 1H), 6.75 (m, 1H), 4.18 (m, 1H), 3.83 (m, 1H), 2.26 (m, 1H), 1.50 (s, 9H), 1.08 (d, J = 6.5 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 151.2, 142.2, 126.0, 123.8, 119.4, 117.3, 90.8, 84.0, 64.4, 33.7, 28.0, 17.6, 17.0 ppm.

5.16 Synthesis of Compound **62**

5.16.1 Synthesis of Disubstituted Intermediate

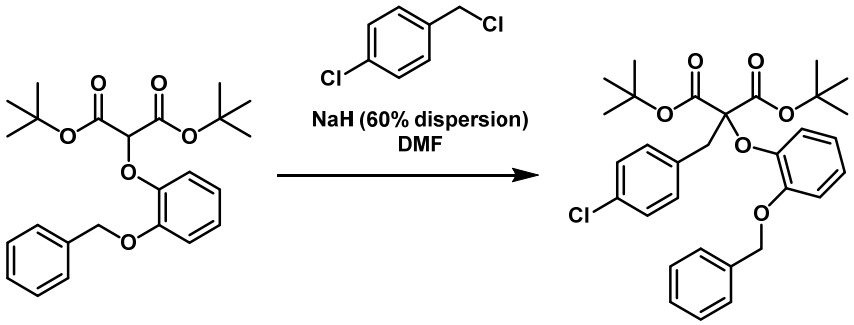


Figure 77. Disubstituted Intermediate

To a mixture of NaH (60% dispersion, 37 mg, 0.93 mmol) in THF (15 mL), malonate diester compound (323 mg, 0.78 mmol) and 4-chlorobenzyl chloride (136 mg, 0.85 mmol) was added at 0º C. The reaction was stirred and warmed to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with H_2O (4 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5%→10% di-ethyl ether/petroleum ether) to afford di-substituted malonate diester compound as a colorless oil (341 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.38-7.27 (m, 5H), 7.23, (m, 2H), 7.07, (m, 2H), 6.94 (m, 2H), 5.07, (s, 2H) 3.48 (s, 2H), 1.30 (s, 18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 150.9, 146.0, 137.3, 133.8, 132.8, 132.3, 128.7, 128.5, 127.9, 127.8, 123.6, 120.8, 120.7, 114.4, 87.2, 83.0, 71.0, 40.7, 27.7 ppm; HRMS (ESI): for $C_{31}H_{35}O_6Cl$ $[M+Na]^+$: calcd. 561.2014; found 561.2014.

5.16.2 Synthesis of Alcohol **61**

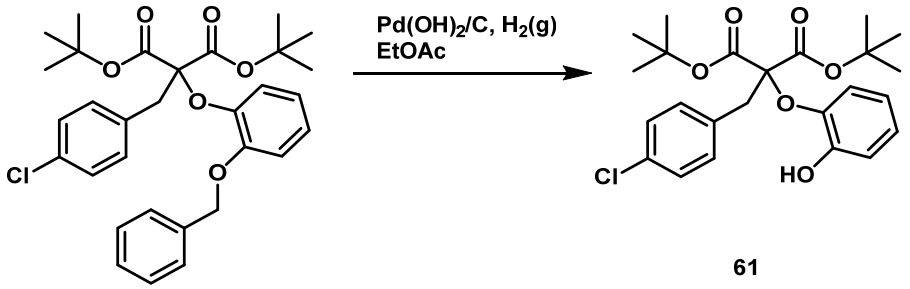


Figure 78. Alcohol **61**

$Pd(OH)_2/C$ (25 mg, 20 weight %) was added to a mixture of disubstituted diester (124 mg, 0.23 mmol) in ethyl acetate (3 mL) was added. The flask was purged with $H_2(g)$. After 12 hours the reaction was filtered through a plug of Celite© and concentrated *in vacuo*. The reaction was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford compound **61** as a white solid (63 mg, 61% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.26 (m, 4H), 6.99 (m, 1H), 6.89 (m, 2H), 6.69 (m, 1H), 3.49 (s, 2H), 1.25 (s, 18H) ppm; ^{13}C NMR (100 MHz) δ 166.9, 151.2, 143.2, 133.2, 133.1, 132.1, 128.3, 126.1, 122.2, 119.3, 116.0, 88.2, 84.3, 41.2, 27.5 ppm; HRMS (ESI): for $C_{24}H_{29}O_6Cl$ $[M+Na]^+$: calcd. 471.1545; found 471.1544; MP= 85.1-87.5º C.

5.16.3 Synthesis of Lactone **62**

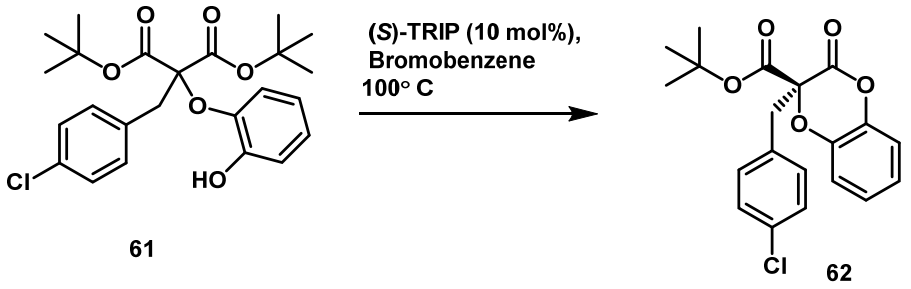


Figure 79. Lactone **62**

To a mixture of alcohol **61** (141 mg, 0.31 mmol), and bromobenzene (3.1 mL), (*S)*-TRIP (10 mol%) was added. After stirring at 100º C for 3 days, the reaction was concentrated *in vacuo* and purified by column chromatography (10% ethyl acetate/hexanes) to yield lactone **62** as a colorless oil (59 mg, 50% yield, 69% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.25 (m, 2H) 7.09 (m, 2H), 7.01 (m, 2H), 3.54 (m, 2H) 1.21 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 162.0, 141.9, 140.9, 133.6, 132.6, 132.0, 128.3, 125.5, 123.7, 118.0, 116.9, 85.1, 83.0, 39.0, 27.6 ppm; HRMS (ESI): for $C_{20}H_{19}O_5Cl$ $[M+Na]^+$: calcd. 397.0813; found 397.0801; $[a]_D^{21}$ = -43.36º (c= 1.19, $CHCl_3$).

5.17 Synthesis of Compound **64**

5.17.1 Synthesis of Disubstituted Intermediate

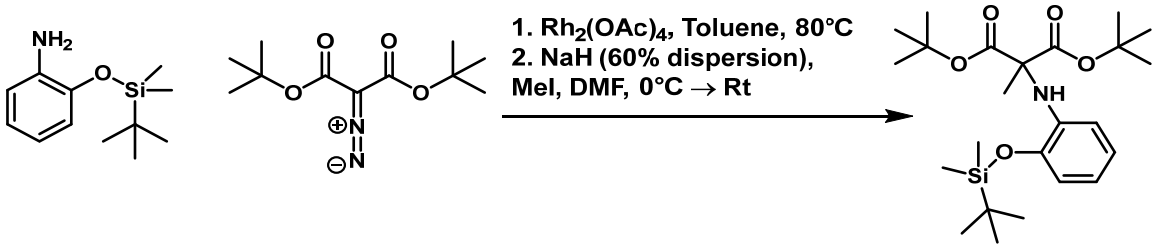
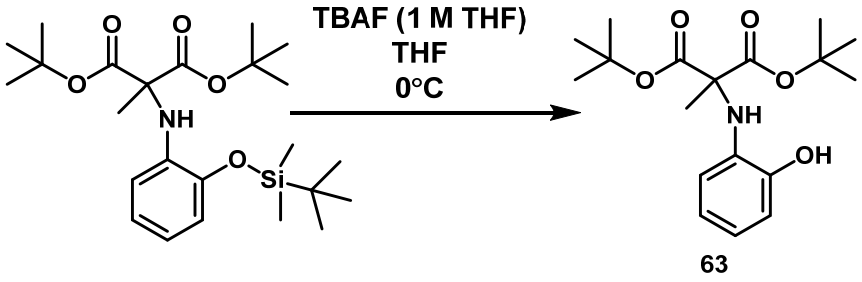


Figure 80. Disubstituted Intermediate

To a mixture of $Rh_2(OAc)_4$ (44 mg, 1.0 mmol), toluene (50 mL), and diazomalonate (579 mg, 2.3 mmol), amine (446 mg, 2.0 mmol) was added. The reaction was stirred overnight at 100º C, after which it was filtered over Celite® and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford monosubstituted diester as a colorless oil (430 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (m, 1H), 6.73 (m, 1H), 6.59 (m, 1H), 6.53 (m, 1H), 5.22 (d, J = 7.3 Hz, 1H), 4.51 (d, J = 7.4 Hz, 1H), 1.41 (s, 18H), 1.06 (s, 9H), 0.24 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 142.9, 137.9, 121.9, 117.9, 117.7, 111.3, 82.6, 62.1, 27.9, 25.9, 18.3, -4.2 ppm; HRMS (ESI): for $C_{23}H_{39}NO_5Si$ $[M+H]^+$: calcd. 438.2670; found 438.2666. To a mixture of NaH (60% dispersion, 36.0 mg, 0.90 mmol) in DMF (10 mL), monosubstituted diester (200 mg, 0.45 mmol), and MeI (56 µL, 0.9 mmol) was added at 0º C. The reaction was stirred and warmed to room temperature for 1 hour. The reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (60 mL). The organic layer was washed with H_2O (3 x 20 mL) to remove DMF. The

organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford the disubstituted malonate diester compound as a colorless oil (174 mg, 82% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 6.73 (m, 2H), 6.55 (m, 2H), 5.64 (s, 1H), 1.68 (s, 3H), 1.38 (s, 18H), 1.03, (s, 9H), 0.24 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 143.3, 136.9, 121.5, 117.9, 117.1, 112.4, 82.1, 65.4, 27.8, 25.9, 20.8, 18.3, -4.1 ppm; HRMS (ESI): for $C_{24}H_{41}NO_5Si$ $[M+H]^+$: calcd. 452.28322; found 452.28235.

5.17.2 Synthesis of Alcohol **63**



63

Figure 81. Alcohol **63**

To a mixture of di-substituted malonate diester (163 mg, 0.36 mmol), and THF (2 mL), was added tetrabutylammonium fluoride (1M THF, 1.08 mL, 1.08 mmol) at 0º C. The reaction was stirred at room temperature for 1 hour. The reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with H_2O (5 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford compound **63** as a yellow oil (70% yield, 85 mg). ^1H NMR (400 MHz, $CDCl_3$) δ

6.86 (m, 3H), 6.73 (m, 1H), 6.71 (s, 1H), 4.37 (s, 1H), 1.48 (s, 3H), 1.44 (s, 18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 150.6, 130.7, 124.0, 123.3, 120.3, 115.2, 82.8, 67.1, 27.8, 19.8 ppm; HRMS (ESI): for $C_{18}H_{27}NO_5$ $[M+H]^+$: calcd. 338.1962; found 338.1958.

5.17.3 Synthesis of Lactone **64**

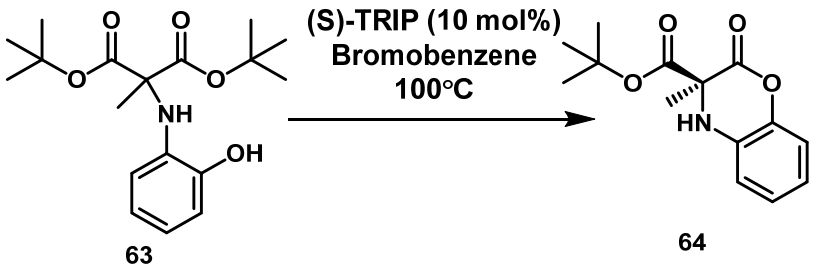


Figure 82. Lactone **64**

To a mixture of alcohol **63** (85 mg, 0.25 mmol) in bromobenzene (2.5 mL), (*S)*-TRIP (18 mg, 10 mol%) was added. After stirring at 100º C for 3 days, the reaction was concentrated *in vacuo* and purified by column chromatography (10% ethyl acetate/hexanes) to yield lactone **64** as a yellow solid (32 mg, 50% yield, 87% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (m, 2H), 6.87 (m, 1H), 6.81 (m, 1H), 4.46 (bs, 1H), 1.72 (s, 3H), 1.24 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 165.0, 141.5, 132.3, 125.0, 121.4, 116.7, 115.7, 84.3, 62.9, 27.6, 21.2 ppm; HRMS (ESI): for $C_{14}H_{17}NO_5$ $[M+Na]^+$: calcd. 286.1055; found 286.1059; MP= 119.0-123.9°C; $[a]_D^{21}$ =-53.33° (c= 0.18, $CHCl_3$).

5.18 Synthesis of Compound **66**

5.18.1 Synthesis of Disubstituted Intermediate

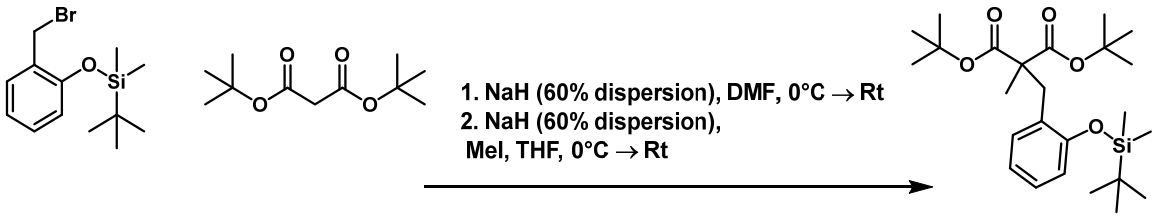


Figure 83. Disubstituted Intermediate

To a mixture of NaH (60% dispersion, 96 mg, 2.4 mmol) in THF (20 mL), di-tertbutyl malonate (347 mg, 1.6 mmol), and alkyl halide (578 mg, 1.9 mmol) was added at 0º C. The reaction was stirred and warmed to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with H_2O (4 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5%→10% di-ethyl ether/petroleum ether) to afford mono substituted malonate diester compound (77% yield, 523 mg). Spectra matches previously published data. To a mixture of NaH (60% dispersion, 44 mg, 1.1 mmol) in THF (12 mL), malonate diester compound (414 mg, 0.94 mmol) and methyl iodide (0.061 mL, 0.99 mmol) was added at 0º C. The reaction was stirred and warmed to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with H_2O (4 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5%→10% di-ethyl ether/petroleum ether) to afford di-substituted

malonate diester compound as a pale yellow oil (482 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (m 1H), 7.09–7.02 (m, 1H), 6.82 (m, 1H), 6.76 (m, 1H), 3.22 (s, 2H), 1.42 (s, 18H), 1.20 (s, 3H), 1.00 (s, 9H), 0.21 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.5, 131.4, 128.0, 127.7, 120.9, 118.7, 81.1, 56.3, 33.4, 28.0, 26.0, 19.2, 18.4, -4.0 ppm; HRMS (ESI): for $C_{25}H_{42}O_5Si$ $[M+Na]^+$: calcd. 473.2694; found 473.2691.

5.18.2 Synthesis of Alcohol **65**

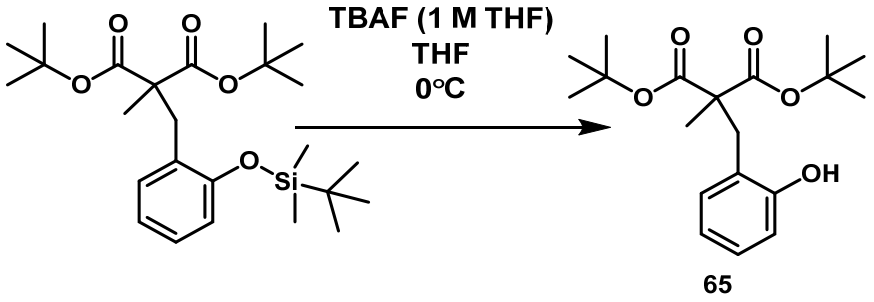


Figure 84. Alcohol **65**

To a mixture of di-substituted malonate diester (93mg, 0.20 mmol) in THF (4 mL), was added tetrabutylammonium fluoride (1.0 M THF, 4.2 mL, 0.42 mmol) at 0º C. The reaction was allowed to stir at room temperature for 2 hours. The reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with H_2O (5 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5%→10% ethyl acetate/hexanes) to afford phenol **65** as a pale yellow oil (259 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.13 (m, 1H), 6.98 (m, 1H), 6.89 (m, 1H), 6.78

(m, 1H), 3.04 (s, 2H) 1.35 (s, 21H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 155.5, 133.2, 128.6, 122.6, 119.7, 117.6, 82.5, 56.2, 36.1, 27.7, 21.4 ppm; HRMS (ESI): for $C_{19}H_{28}O_5$ $[M+Na]^+$: calcd. 359.1829; found 359.1827.

5.18.3 Synthesis of Lactone **66**

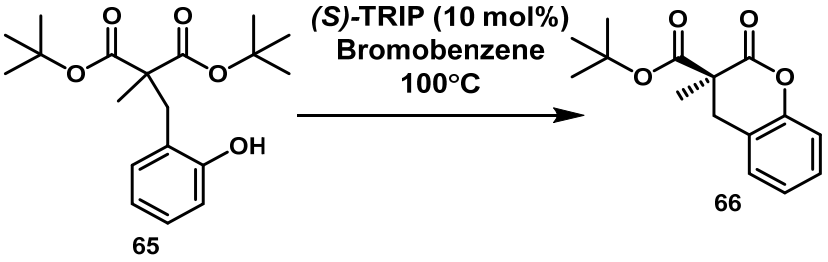


Figure 85. Lactone **66**

A mixture of alcohol **65** (70 mg, 0.20 mmol) in bromobenzene (2 mL), (*S)*-TRIP (15 mg, 10 mol%) was added. After stirring at 100º C for 3 days, the reaction was concentrated *in vacuo* and purified by column chromatography (10% ethyl acetate/hexanes) to yield lactone **66** as a white solid (50 mg, 96% yield, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 1H), 7.06 (m, 2H), 3.22 (d, J = 16.3 Hz, 1H), 2.95 (d, J = 16.0 Hz, 1H), 1.58 (s, 3H), 1.15 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 168.9, 151.9, 128.7, 128.3, 124.5, 121.8, 116.5, 83.3, 50.3, 35.9, 27.4, 20.7 ppm; HRMS (ESI): for $C_{15}H_{18}O_4$ $[M+Na]^+$: calcd. 285.1103; found 285.1102; MP= 61.0-63.5 ^{o}C; $[a]_D^{21}$ = - 47.50^{o} (c= 0.4, $CHCl_3$).

5.19 Synthesis of Compound **68**

5.19.1 Synthesis of Disubstituted Intermediate

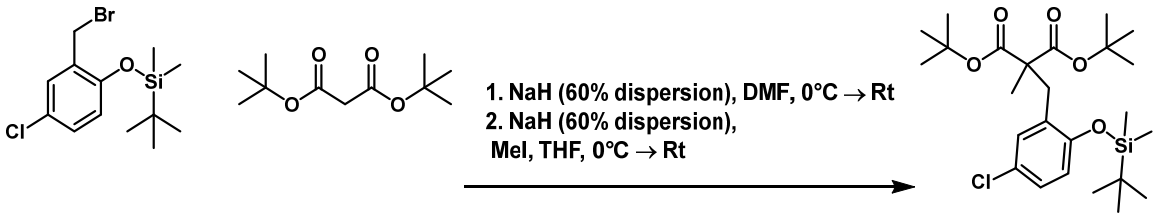


Figure 86. Disubstituted Intermediate

To a mixture of NaH (60% dispersion, 110 mg, 2.6 mmol) in THF (20 mL), di-*tert*-butyl malonate (0.4 mL, 1.7 mmol), and alkyl halide (720 mg, 2.1 mmol) was added at 0º C. Reaction was allowed to stir at room temperature overnight. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with H_2O (4 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford monosubstituted diester as a colorless oil (657 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 1H), 7.03 (m, 1H), 6.68 (m, 1H), 3.53 (t, J = 8.1 Hz, 1H), 3.02 (d, J = 8.0 Hz, 2H), 1.39 (s, 18H), 0.98 (s, 9H), 0.22 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 152.6, 131.1, 130.6, 127.5, 125.5, 119.3, 81.6, 53.2, 30.2, 27.9, 25.8, 18.3, -4.1 ppm; HRMS (ESI): for $C_{24}H_{39}ClO_5Si$ $[M+H]^+$: calcd. 471.2378; found 471.2328. To a mixture of NaH (60% dispersion, 80 mg, 1.9 mmol) in DMF (20 mL) was prepared and stirred in ice/water bath to cool. After 5 minutes monosubstituted diester (628 mg, 1.3 mmol) and methyl iodide (0.165 mL, 2.6 mmol) was added. After stirring for one hour the reaction was quenched with water and

extracted with ethyl acetate (100 mL). The organic layer was washed with H_2O (4 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford disubstituted diester as a colorless oil (316 mg, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 1H), 7.02 (m, 1H), 6.70 (m, 1H), 3.17 (s, 2H), 1.47 (s, 18H), 1.20 (s, 3H), 0.99 (s, 9H), 0.20 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 153.1, 131.2, 129.8, 127.4, 125.7, 119.8, 81.5, 56.4, 33.5, 28.0, 25.9, 19.4, 18.4, -4.1 ppm; HRMS (ESI): for $C_{25}H_{41}ClO_5Si$ $[M+H]^+$: calcd. 485.2484; found 485.2478.

5.19.2 Synthesis of Alcohol **67**

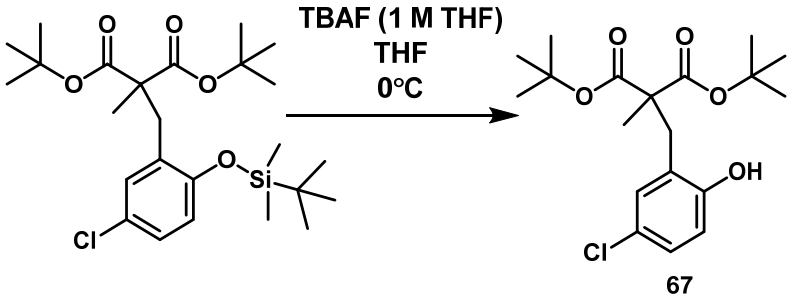


Figure 87. Alcohol **67**

To a mixture of disubstituted diester (133 mg, 0.27 mmol) in THF (3 mL), tetrabutylammonium fluoride (1.0 M THF, 0.82 mL, 0.82 mmol) was added at 0º C. The reaction was stirred at room temperature for 1 hour. The reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with H_2O (5 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes)

to afford compound **67** as a white solid (101 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.08 (m, 1H), 6.95 (m, 1H), 6.83 (m, 1H), 2.99 (s, 2H), 1.42 (s, 3H), 1.39 (s, 18H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 154.3, 132.5, 128.6, 124.6, 124.4, 119.2, 83.0, 56.4, 36.2, 27.8, 22.0 ppm; HRMS (ESI): for $C_{19}H_{27}O_5Cl$ $[M+Na]^+$: calcd. 393.14392; found 393.14359; MP= 96.7-99.3° C.

5.19.3 Synthesis of Lactone **68**

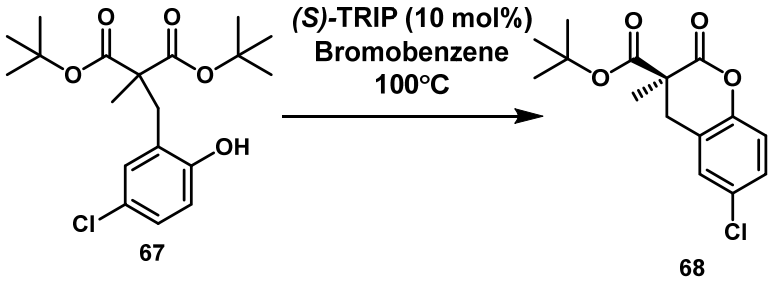


Figure 88. Lactone **68**

To a mixture of alcohol **67** (50 mg, 0.13 mmol) in bromobenzene (1.3 mL), (*S)*-TRIP (5 mg, 5 mol%) was added. After stirring at 100º C for 3 days, the reaction was concentrated *in vacuo* and purified by column chromatography (10% ethyl acetate/hexanes) to yield lactone **68** as a white solid (28 mg, 73% yield, 82% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 1H), 7.15 (m, 1H), 6.98 (m, 1H), 3.20 (d, J = 15.7 Hz, 1H), 2.92 (d, J = 15.8 Hz, 1H), 1.57 (s, 3H), 1.19 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.1, 150.4, 129.6, 128.7, 128.2, 123.5, 117.8, 83.7, 50.0, 35.5, 27.5, 20.7 ppm; HRMS (ESI): for $C_{15}H_{17}ClO_4$ $[M+Na]^+$: calcd. 319.0713; found 319.0719; MP= 102.5-104.3° C; $[a]_D^{21}$ = -13.00° (c=0.2, $CHCl_3$).

5.20 Synthesis of Compound **71**

5.20.1 Synthesis of Monoalkylated Dinitrile

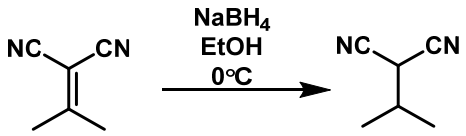


Figure 89. Monoalkylated Dinitrile

To a mixture of alkene (1.0 g, 9.4 mmol) in ethanol (40 mL), $NaBH_4$ (355 mg, 9.4 mmol) was slowly added at 0° C. After stirring for 10 min, the reaction was added to cold water (10 mL), followed by 5.0 M HCl (5 mL). The aqueous mixture was extracted with dichloromethane (60 mL), and the organic layer was dried with MgSO4, filtered, and concentrated to afford monosubstituted dinitrile as a colorless oil (823 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (d, J = 5.4 Hz, 1H), 2.36 (sept, 1H), 1.24 (d, J = 6.4 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.0, 31.3, 30.5, 19.6 ppm.

5.20.2 Synthesis of Alkylating Agent

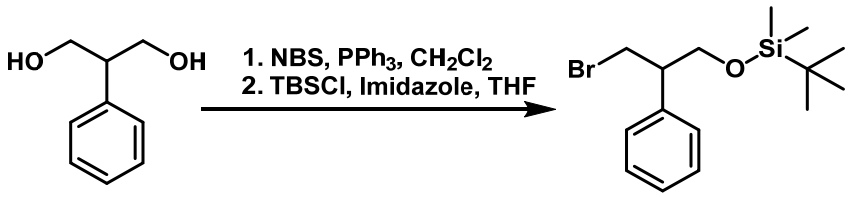


Figure 90. Alkylating Agent

To a mixture of diol (2 g, 13 mmol) in dichloromethane (100 mL), *N*-bromosuccinimide (2.3 g, 13 mmol) and triphenylphosphine (3.4 g, 13 mmol) was added at 0° C. The reaction stirred for 7 hours after which the reaction was concentrated. The

crude mixture was purified by silica gel column chromatography (30% ethyl acetate/hexanes) to obtain colorless oil as the mono-brominated alcohol (2.08 g, 73% yield). The alcohol was used directly in the next reaction. To a mixture of the brominated alcohol (2.08 g, 9.6 mmol) in THF (50 mL), TBSCl (2.5 g, 16.4 mmol) and imidazole was added (1.96 g, 28.8 mmol). The reaction stirred overnight and then was quenched with water (30 mL) and extracted with ethyl acetate (100 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (10% ethyl acetate/hexanes) to afford alkylating agent as a colorless oil (2.6 g, 82% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 3.95-3.77 (m, 3H), 3.62 (m, 1H), 3.12 (m, 1H), 0.87 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 128.5, 128.1, 127.3, 65.1, 50.2, 34.9, 25.9, 18.4, -5.4 ppm; HRMS (ESI/APCI): for $C_{15}H_{25}BrOSi$ $[M+H]^+$: calcd. 329.0931; found 329.0945.

5.20.3 Synthesis of Dialkylated Dinitrile

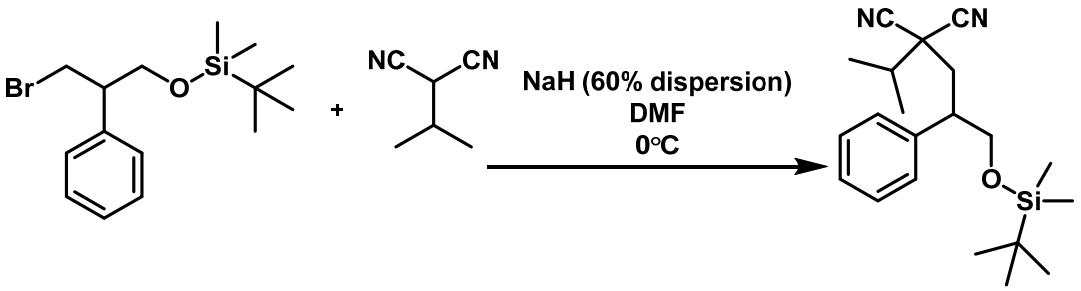


Figure 91. Disubstituted Intermediate

To a slurry of NaH (60% dispersion, 304 mg, 7.6 mmol) in DMF (30 mL), the malononitrile (823 mg, 7.6 mmol) was added slowly followed by alkylating agent (1.25

g, 3.8 mmol) at 0° C. The reaction allowed to warm overnight after which it was quenched with water (30 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford disubstituted dinitrile as a colorless liquid (826 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 5H), 3.79 (m, 1H), 3.67 (m, 1H), 3.13 (m, 1H), 2.57 (m, 1H), 2.24-2.08 (m, 2H), 1.18 (dd, J = 7.3 Hz, 6H), 0.88 (s, 9H), 0.02 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 128.9, 128.4, 128.0, 115.0, 114.5, 67.0, 46.3, 42.4, 36.9, 36.6, 25.9, 18.4, 18.3, 18.1, -5.3, -5.4 ppm. HRMS (ESI): for $C_{21}H_{32}N_2OSi$ $[M+H]^+$: calcd. 357.2357; found 357.2357.

5.20.4 Synthesis of Alcohol **69**

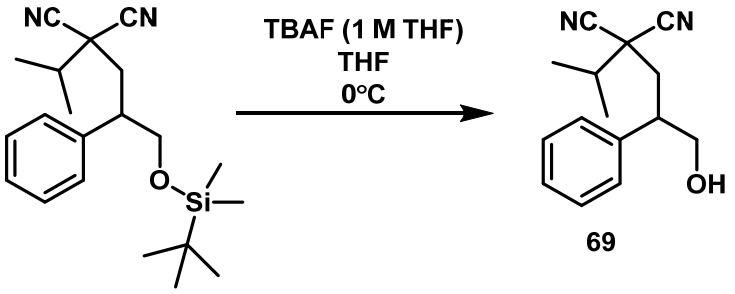


Figure 92. Alcohol **69**

To a mixture of disubstituted dinitrile (826 mg, 2.3 mmol) in THF (10 mL), TBAF (1.0 M THF, 6.9 mL, 6.9 mmol) was added at 0° C. The reaction was stirred at 0° C for 1 hour, and the reaction was quenched with water (20 mL) and extracted with ethyl acetate (60 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purified crude material through a silica gel column (15% ethyl acetate/hexanes) to afford

compound **69** as a colorless oil (458 mg, 82 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 3.88 (m, 1H), 3.79 (m, 1H), 3.20 (m, 1H), 2.44 (m, 1H), 2.13 (sept, 1H), 1.18 (t, *J* = 6.3 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 129.2, 128.4, 128.3, 115.2, 114.3, 66.5, 46.2, 42.4, 37.3, 36.9, 18.4, 18.2 ppm; HRMS (ESI): for $C_{15}H_{18}N_2O$ $[M+H]^+$: calcd. 243.1492; found 243.1491.

5.20.5 Synthesis of Lactone **71**

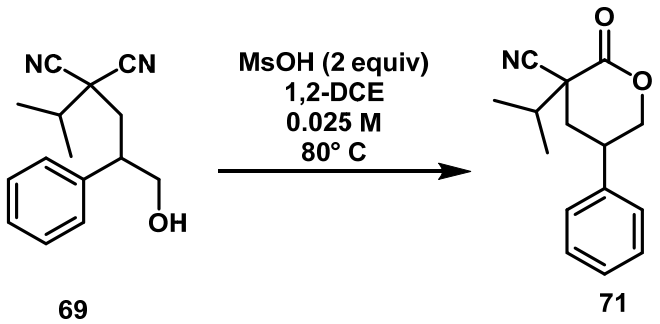


Figure 93. Lactone **71**

To a mixture of alcohol **69** (115 mg, 4.7 mmol) in 1,2-dichloroethane (18 mL), methyl sulfonic acid (91 mg, 9.4 mmol) was added. The reaction was stirred for one hour at 80^{o} C. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacou*. The crude material was purified thru a short plug of silica and rinsed with dichloromethane to afford lactone **71** as a colorless oil (86 mg, 75% yield, 7:1 d.r.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.31 (m, 3H), 7.24 (m, 2H), 4.59 (m, 1H), 4.29 (t, *J* = 11.4 Hz, 1H), 3.52 (m, 1H), 2.76 (m, 1H), 2.36 (m, 1H), 2.21 (t, *J* = 13.7, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$) δ 165.1, 137.4, 129.4, 128.4, 127.2, 119.5, 74.8, 49.2, 37.7, 35.2, 32.4, 17.6 ppm; HRMS (ESI): for $C_{15}H_{17}NO_2$ $[M+H]^+$: calcd. 202.08963; found 202.08864.

5.21 Synthesis of Compound **73**

5.21.1 Synthesis of Monoalkylated Dinitrile

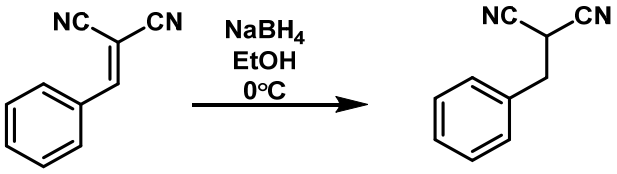


Figure 94. Monosubstituted Dinitrile

To a mixture of the above alkene (2.0 g, 12 mmol) in ethanol (120 mL), $NaBH_4$ (343 mg, 9.0 mmol) was slowly added at 0° C. After stirring for 10 min, the reaction was added to cold water (20 mL), followed by 5.0 M HCl (10 mL). The aqueous mixture was extracted with dichloromethane (150 mL), and the organic layer was dried with $MgSO_4$, filtered, and concentrated to afford monoalkylated dinitrile as a white solid (1.87 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 3H), 7.32 (m, 2H), 3.90 (t, J = 7.0 Hz, 1H), 3.28 (t, J = 7.0 Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.0, 129.4, 129.2, 129.0, 112.2, 36.9, 25.1 ppm.

5.21.2 Synthesis of Disubstituted Intermediate

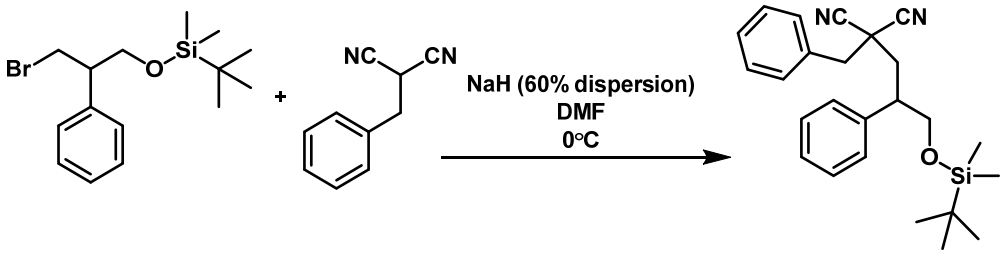


Figure 95. Disubstituted Intermediate

To a slurry of NaH (60% dispersion, 228 mg, 5.7 mmol) in DMF (15 mL), the malononitrile (899 mg, 5.7 mmol) was added slowly followed by alkylating agent (948 mg, 2.8 mmol) at 0° C. The reaction allowed to warm overnight after which it was quenched with water (30 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford dialkylated dinitrile as a colorless liquid. (380 mg, 33% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10H), 3.79 (m, 1H), 3.66 (m, 1H), 3.20-3.08 (m, 3H), 2.64 (m, 1H), 2.24 (m, 1H), 0.86 (s, 9H), -0.01 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 132.1, 130.4, 129.0, 128.8, 128.4, 128.0, 115.3, 114.8, 67.0, 46.3, 44.6, 39.1, 38.1, 25.9, 18.3, -5.4, -5.5 ppm; HRMS (ESI): for $C_{25}H_{32}N_2OSi$ $[M+H]^+$: calcd. 405.23567; found 405.23468.

5.21.3 Synthesis of Alcohol **72**

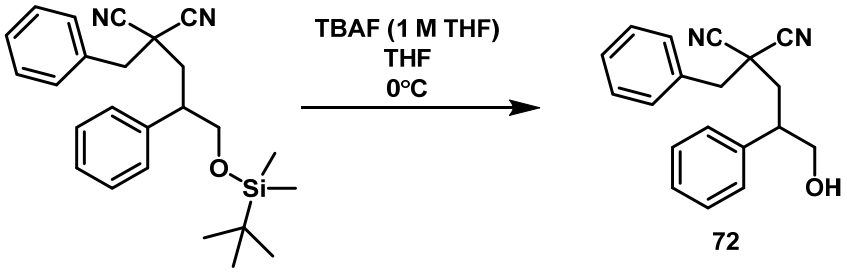


Figure 96. Alcohol **72**

To a mixture of dialkylated dinitrile (478 mg, 1.18 mmol) in THF (6 mL), TBAF (1.0 M THF, 3.5 mL, 3.5 mmol) was added at 0° C. The reaction was stirred at 0° C for 1 hour, and the reaction was quenched with water (20 mL) and extracted with ethyl acetate (60 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purified crude material through a silica gel column (15% ethyl acetate/hexanes) to afford compound **72** as a colorless oil (265 mg, 77% yield). ^{1}NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 10H), 3.88 (m, 1H), 3.79 (m, 1H), 3.24 (m, 1H), 3.12 (s, 2H), 2.56 (m, 1H), 2.29 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 131.9, 130.4, 129.3, 129.0, 128.9, 128.4, 128.3, 115.4, 114.5, 66.5, 60.5, 46.1, 44.6, 39.5, 38.3, 21.2, 14.3 ppm; HRMS (ESI): for $C_{19}H_{18}N_2O$ $[M+H]^+$: calcd. 291.14919; found 291.14868.

5.21.4 Synthesis of Lactone **73**

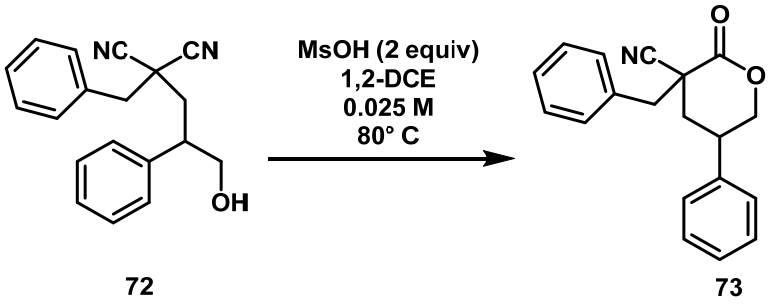


Figure 97**.** Lactone **73**

To a mixture of alcohol **72** (90 mg, 3.0 mmol) in 1,2-dichloroethane (12 mL), methyl sulfonic acid (60 mg, 6.0 mmol) was added. The reaction was stirred for one hour at 80^{o} C. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacou*. The crude material was purified thru a short plug of silica and rinsed with dichloromethane to afford lactone **73** as a white solid (66 mg, 73% yield, 6:1 d.r.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 8H), 7.13 (m, 2H), 4.57 (m, 1H), 4.14 (m, 1H), 3.51 (m, 2H), 3.34 (d, *J* = 14.4 Hz, 1H), 2.29 (m, 1H), 2.17 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 137.4, 133.3, 130.6, 129.3, 129.0, 128.3, 128.2, 127.2, 118.8, 75.1, 45.0, 42.5, 37.6, 36.3 ppm; HRMS (ESI): for $C_{19}H_{17}N_2O$ $[M+H]^+$: calcd. 292.13321; found 292.12395; MP= 152.5-155.6^{o} C.

5.22 Synthesis of Compound **75**

5.22.1 Synthesis of Monoalkylated Dinitrile

Figure 98. Monosubstituted Dinitrile

To a mixture of NaH (60% dispersion, 600 mg, 15 mmol) in THF (20 mL), malononitrile (1 g, 15 mmol) was carefully added at 0 °C, followed by alkyl halide (942 µL, 15 mmol). The reaction was allowed to warm to room temperature and stir overnight. The reaction was quenched with water (40 mL), and then extracted with ethyl acetate (2 x 100 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified through a silica gel column (20% ethyl acetate/hexanes) to afford the desired dinitrile as a white solid (407 mg, 35% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (q, *J* = 7.5 Hz, 1H), 1.78 (d, *J* = 6.6 Hz, 3H) ppm.

5.22.2 Synthesis of Disubstituted Intermediate

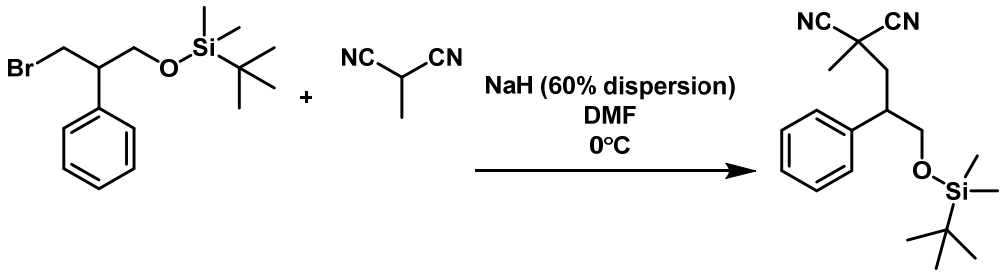


Figure 99. Disubstituted Intermediate

To a slurry of NaH (60% dispersion, 216 mg, 5.4 mmol) in DMF (20 mL), the malononitrile (587 mg, 7.3 mmol) was added slowly followed by alkylating agent (1.2 g, 3.6 mmol) at 0° C. The reaction allowed to warm overnight after which it was quenched with water (30 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford the dialkylated dinitrile as a colorless liquid (620 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 3.77 (m, 1H), 3.65 (m, 1 H), 3.10 (m, 1 H), 2.59 (m, 1H), 2.25 (m, 1H), 1.70 (s, 3H), 0.87 (s, 9H), 0.01 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 129.0, 128.4, 128.0, 116.2, 115.7, 67.0, 46.3, 40.7, 30.8, 26.2, 26.0, 18.3, -5.3, -5.4 ppm; HRMS (ESI): for $C_{19}H_{28}N_2OSi$ $[M+H]^+$: calcd. 329.20437; found 329.20392.

5.22.3 Synthesis of Alcohol **74**

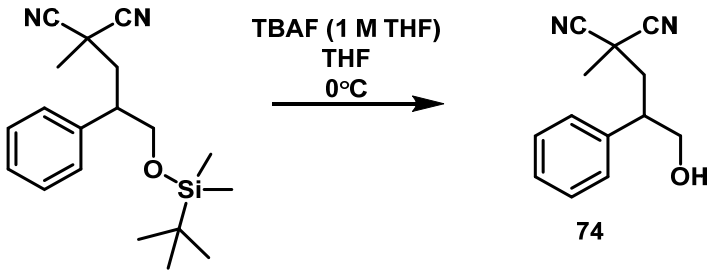
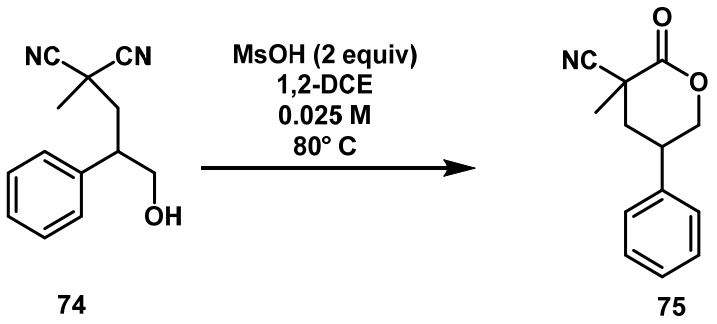


Figure 100. Alcohol **74**

To a mixture of dialkylated dinitrile (620 mg, 1.8 mmol) in THF (10 mL), TBAF (1.0 M THF, 5.6 mL, 5.6 mmol) was added at 0° C. The reaction was stirred at 0° C for 1 hour, and the reaction was quenched with water (20 mL) and extracted with ethyl acetate (60 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purified

crude material through a silica gel column (15% ethyl acetate/hexanes) to afford compound **91** as a colorless oil (140 mg, 36% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.27 (m, 5H), 3.86 (m, 1H), 3.77 (m, 1H), 3.19 (m, 1H), 2.52 (m, 1H), 2.28 (m, 1H), 1.73 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 129.3, 128.4, 128.3, 116.2, 115.5, 66.6, 46.2, 41.0, 30.8, 26.2 ppm; HRMS (ESI): for $C_{13}H_{14}N_2O$ $[M+H]^+$: calcd. 215.11789; found 215.11722.

5.22.4 Synthesis of Lactone **75**



74 **75**

Figure 101. Lactone **75**

To a mixture of alcohol **74** (114 mg, 0.53 mmol) in 1,2-dichloroethane (21 mL), methyl sulfonic acid (102 mg, 1.06 mmol) was added. The reaction was stirred for one hour at 80^{o} C. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified thru a short plug of silica and rinsed with dichloromethane to afford lactone **75** as a white solid (95 mg, 84% yield, 7:1 d.r). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.19 (m, 5H), 4.66 (m, 1H), 4.33 (m,

1H), 3.61 (m, 1H), 2.57 (m, 1H), 2.21 (m, 1H), 1.77 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 137.6, 129.4, 128.3, 127.2, 119.5, 75.4, 39.7, 39.5, 37.9, 24.2 ppm.

5.23 Synthesis of Compound **77**

5.23.1 Synthesis of Alkylating Agent

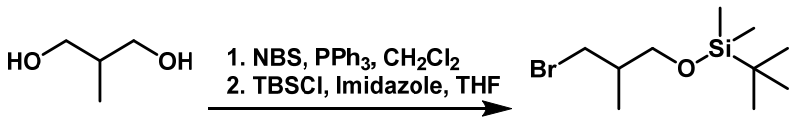


Figure 102. Alkylating Agent

To a mixture of diol (2 g, 22 mmol) in dichloromethane (200 mL), *N*-bromosuccinimide (3.8 g, 22 mmol) and triphenylphosphine (5.8 g, 22 mmol) was added at 0° C. The reaction stirred for 7 hours after which the reaction was concentrated. The crude mixture was purified by silica gel column chromatography (30% ethyl acetate/hexanes) to obtain colorless oil as the mono-brominated alcohol (2.5 g, 75% yield). The alcohol was used directly in the next reaction. To a mixture of the brominated alcohol (2.5 g, 16 mmol) in THF (50 mL), TBSCl (4.1 g, 27 mmol) and imidazole (3.3 g, 49 mmol) was added. The reaction stirred overnight and then was quenched with water (30 mL) and extracted with ethyl acetate (100 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (10% ethyl acetate/hexanes) to afford the alkylating agent as a colorless oil (3.3 g, 80% yield).

5.23.2 Synthesis of Disubstituted Intermediate

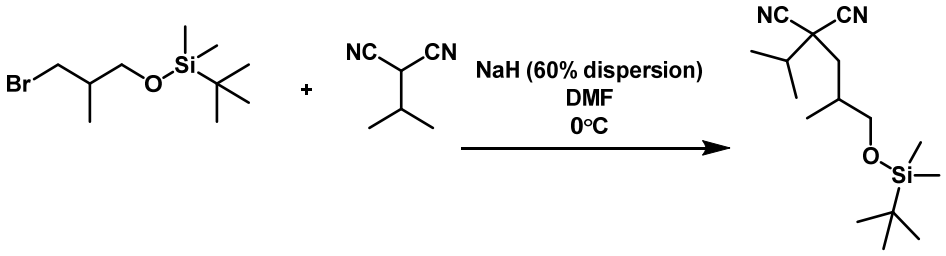


Figure 103. Disubstituted Intermediate

To a slurry of NaH (60% dispersion, 204 mg, 5.1 mmol) in DMF (40 mL), the malononitrile (737 mg, 6.8 mmol) was added slowly followed by alkylating agent (911 mg, 3.4 mmol) at 0° C. The reaction allowed to warm overnight after which it was quenched with water (30 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford dialkylated dinitrile as a colorless liquid (920 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (m, 1H), 3.40 (m, 1H), 2.17 (m, 2H), 2.05 (m, 1H), 1.62 (m, 1H), 1.24 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.7 Hz, 3H) 1.11 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.9, 115.3, 67.2, 42.1, 38.1, 36.9, 34.2, 25.9, 18.6, 18.4, 18.0, 17.1, -5.3, -5.4 ppm.

5.23.3 Synthesis of Alcohol **76**

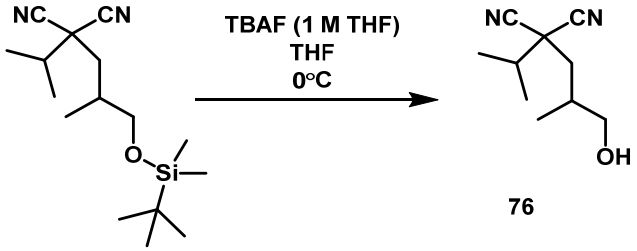


Figure 104. Alcohol **76**

To a mixture of dialkylated dinitrile (920 mg, 3.1 mmol) in THF (20 mL), TBAF (1.0 M THF, 9.3 mL, 9.3 mmol) was added at 0° C. The reaction was stirred at 0° C for 1 hour, and the reaction was quenched with water (20 mL) and extracted with ethyl acetate (60 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purified crude material through a silica gel column (15% ethyl acetate/hexanes) to afford compound **76** as a colorless oil (323 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (m, 1H), 3.50 (m, 1H), 2.21-2.05 (m, 3H), 1.74-1.57 (m, 2H), 1.26-120 (m, 6H), 1.15 (d, J = 7.0 Hz, 3H) ppm.

5.23.4 Synthesis of Lactone **77**

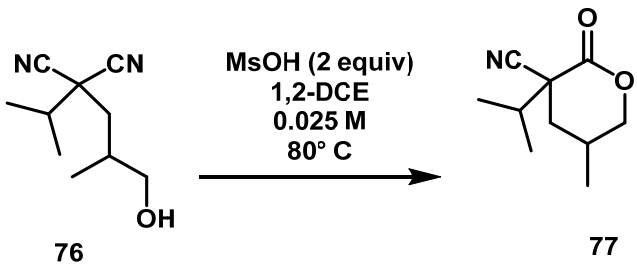


Figure 105. Lactone **77**

To a mixture of alcohol **76** (150 mg, 0.83 mmol) in 1,2-dichloroethane (33 mL), methyl sulfonic acid (159 mg, 1.6 mmol) was added. The reaction was stirred for one hour at 80° C. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacou*. The crude material was purified thru a short plug of silica and rinsed with dichloromethane to afford lactone **77** as a white solid (147 mg, 98% yield, 4:1 d.r.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (m, 1H), 3.87 (m, 1H), 2.66 (m, 1H), 2.39 (m, 1H), 2.11 (m, 1H), 1.62 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H) ppm.

5.24 Synthesis of Compound **79**

5.24.1 Synthesis of Disubstituted Intermediate

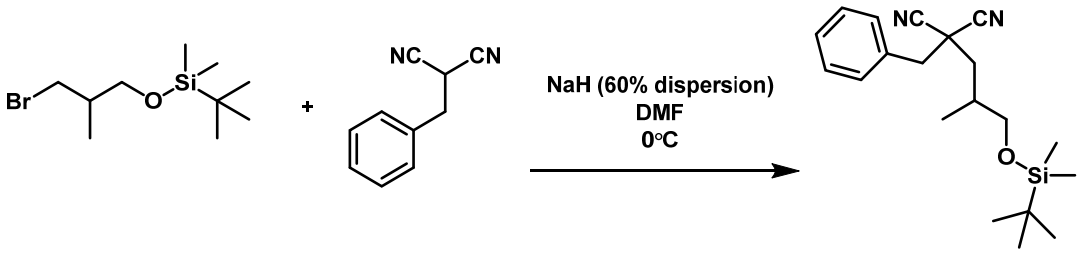


Figure 106. Disubstituted Intermediate

To a slurry of NaH (60% dispersion, 96 mg, 2.4 mmol) in DMF (16 mL), the malononitrile (500 mg, 3.2 mmol) was added slowly followed by alkylating agent (427 mg, 1.6 mmol) at 0° C. The reaction allowed to warm overnight after which it was quenched with water (30 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified

by silica gel column chromatography (10% ethyl acetate/hexanes) to afford dialkylated dinitrile as a colorless liquid (178 mg, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 5H), 3.59 (m, 1H), 3.39 (m, 1H), 3.20 (s, 2H), 2.25 (m, 1H), 2.07 (m, 1H), 1.69 (m, 1H), 1.11 (d, J = 7.2 Hz, 3H), 0.86 (s, 9H) 0.02 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1, 130.4, 129.0, 128.8, 116.2, 115.3, 67.1, 44.8, 40.4, 37.9, 34.1, 26.0, 18.3, 17.2, -5.3 ppm.

5.24.2 Synthesis of Alcohol **78**

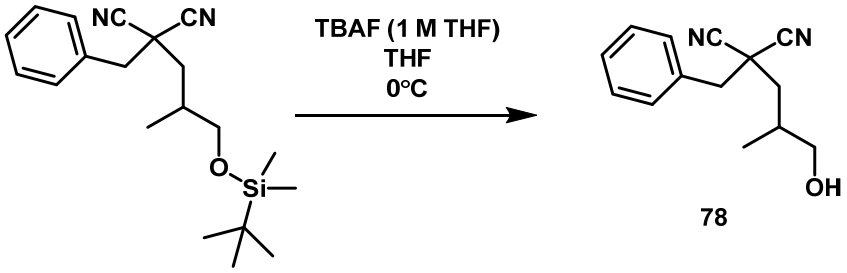


Figure 107. Alcohol **78**

To a mixture of dinitrile (178 mg, 0.5 mmol) in THF (4 mL), TBAF (1.0 M THF, 1.5 mL, 1.5 mmol) was added at 0° C. The reaction was stirred at 0° C for 1 hour, and the reaction was quenched with water (20 mL) and extracted with ethyl acetate (60 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purified crude material through a silica gel column (15% ethyl acetate/hexanes) to afford compound **78** as a colorless oil (74 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 5H), 3.68 (m, 1H), 3.48 (m, 1H), 3.21 (m, 2H), 2.28 (m, 1H), 2.11 (m, 1H), 1.83-1.70 (m, 2H), 1.14 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 130.4, 129.0, 128.9, 115.9, 115.6, 66.7, 44.8, 40.5, 38.1, 34.0, 17.2 ppm

5.24.3 Synthesis of Lactone **79**

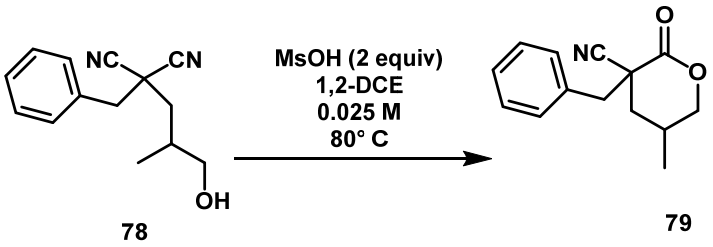


Figure 108. Lactone **79**

To a mixture of alcohol **78** (60 mg, 0.26 mmol) in 1,2-dichloroethane (10.4 mL), methyl sulfonic acid (50 mg, 0.52 mmol) was added. The reaction was stirred for one hour at 80^{o} C. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacou*. The crude material was purified thru a short plug of silica and rinsed with dichloromethane to afford lactone **79** as a white solid (55 mg, 92% yield, 6:1 d.r.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H), 4.40 (m, 1H), 3.75 (m, 1H), 3.44 (d, J = 14.0 Hz, 1H), 3.25 (d, J = 14.1 Hz, 1H), 2.38 (m, 1H), 2.02 (m, 1H), 1.59 (m, 1H), 0.94 (d, J = 7.0 Hz, 3H) ppm.

5.25 Synthesis of Compound **81**

5.25.1 Synthesis of Monoalkylated Dinitrile

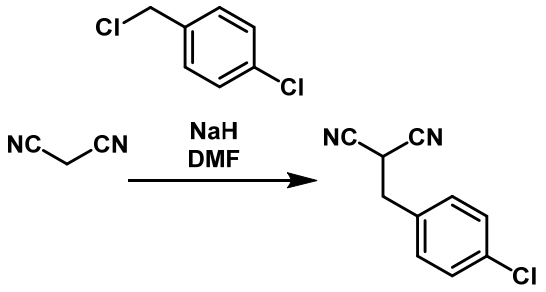


Figure 109. Monosubstituted Dinitrile

To a mixture of NaH (60% dispersion, 600 mg, 15 mmol) in THF (20 mL), malononitrile (1 g, 15 mmol) was carefully added at 0 °C, followed by 4-chlorobenzylchloride (2.4 g, 15 mmol). The reaction was allowed to warm to room temperature and stir overnight. The reaction was quenched with water (40 mL), and then extracted with ethyl acetate (2 x 100 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified through a silica gel column (20% ethyl acetate/hexanes) to afford the desired dinitrile product as a white solid (1.29 g, 45% yield).

5.25.2 Synthesis of Disubstituted Intermediate

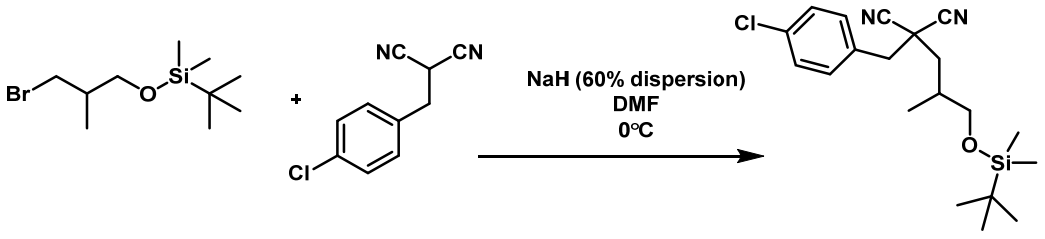


Figure 110. Disubstituted Intermediate

To a slurry of NaH (60% dispersion, 168 mg, 4.2 mmol) in DMF (20 mL), the malononitrile (816 mg, 4.2 mmol) was added slowly followed by alkylating agent (736 mg, 2.7 mmol) at 0° C. The reaction allowed to warm overnight after which it was quenched with water (30 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by silica gel column chromatography (10% ethyl acetate/hexanes) to afford dinitrile as a colorless liquid (465 mg, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.31 (m, 2H), 3.60 (m, 1H), 3.39 (m, 1H), 3.17 (s, 2H), 2.24 (m, 1H), 2.07 (m, 1H), 1.69 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H), 0.86 (s, 9H) 0.03 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 131.7, 130.5, 129.2, 115.9, 115.1, 67.0, 44.2, 40.4, 37.8, 34.1, 24.9, 18.3, 17.2, -5.4 ppm.

5.25.3 Synthesis of Alcohol **80**

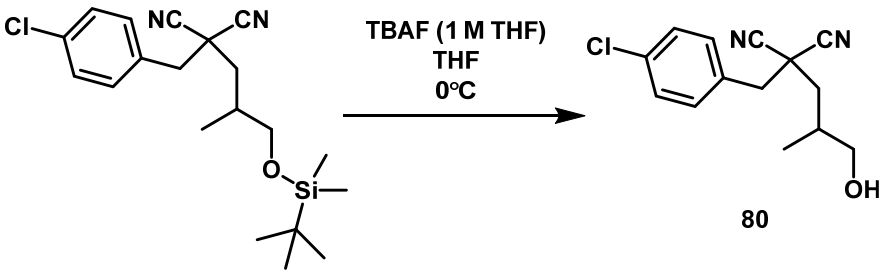
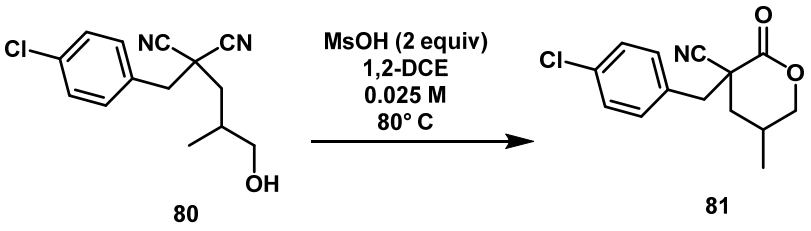


Figure 111. Alcohol **80**

To a mixture of disubstituted dinitrile (152 mg, 0.4 mmol) in THF (3 mL), TBAF (1.0 M THF, 1.2 mL, 1.2 mmol) was added at 0° C. The reaction was stirred at 0° C for 1 hour, and the reaction was quenched with water (20 mL) and extracted with ethyl acetate (60 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purified

crude material through a silica gel column (15% ethyl acetate/hexanes) to afford compound **80** as a colorless oil (53 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.31 (m, 2H), 3.71 (m, 1H), 3.50 (m, 1H), 3.19 (m, 2H), 2.29 (m, 1H), 2.12 (m, 1H), 1.79 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 131.7, 130.4, 129.3, 115.6, 115.3, 66.7, 44.1, 40.6, 38.1, 34.0, 17.2 ppm.

5.25.4 Synthesis of Lactone **81**



80 81

Figure 112. Lactone **81**

To a mixture of alcohol **80** (53 mg, 0.2 mmol) in 1,2-dichloroethane (8 mL), methyl sulfonic acid (38 mg, 0.4 mmol) was added. The reaction was stirred for one hour at 80^{o} C. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacou*. The crude material was purified thru a short plug of silica and rinsed with dichloromethane to afford lactone **81** as a white solid (37 mg, 70% yield, 5:1 d.r.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.22 (m, 2H), 4.44 (m, 1H), 3.79 (m, 1H), 3.41 (d, *J* = 14.0 Hz, 1H), 3.23 (d, *J* = 13.9 Hz, 1H), 2.42 (m, 1H), 2.02 (m, 1H), 1.55 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H) ppm.

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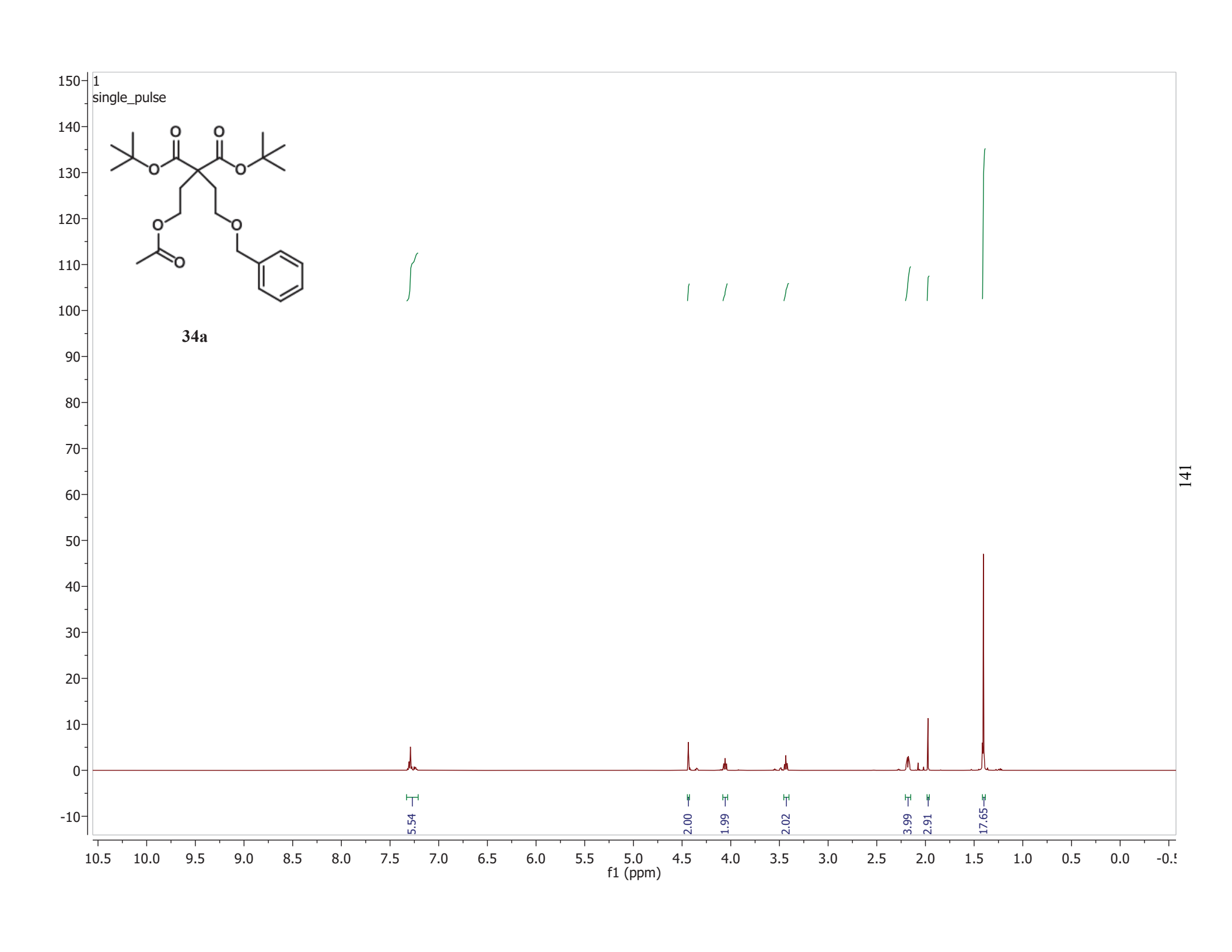
APPENDIX A

NMR SPECTRA

The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were plotted on 400 and 500 MHz spectrometer using $CDCl_3$ as a solvent at rt. The NMR chemical shifts (δ) are reported in ppm. Abbreviations for 1H NMR: s = singlet, d = doublet, m = multiplet, b = broad, t = triplet, q = quartet.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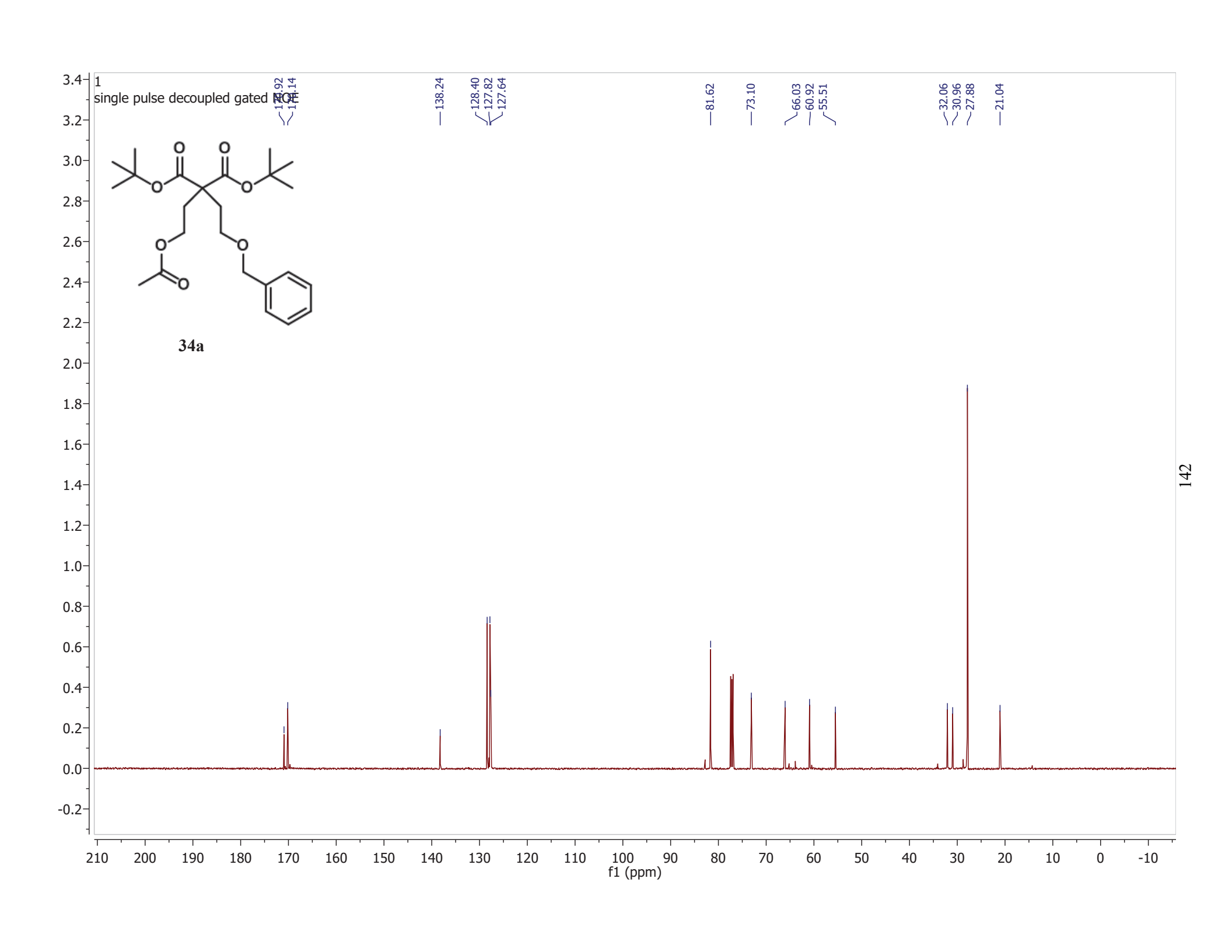
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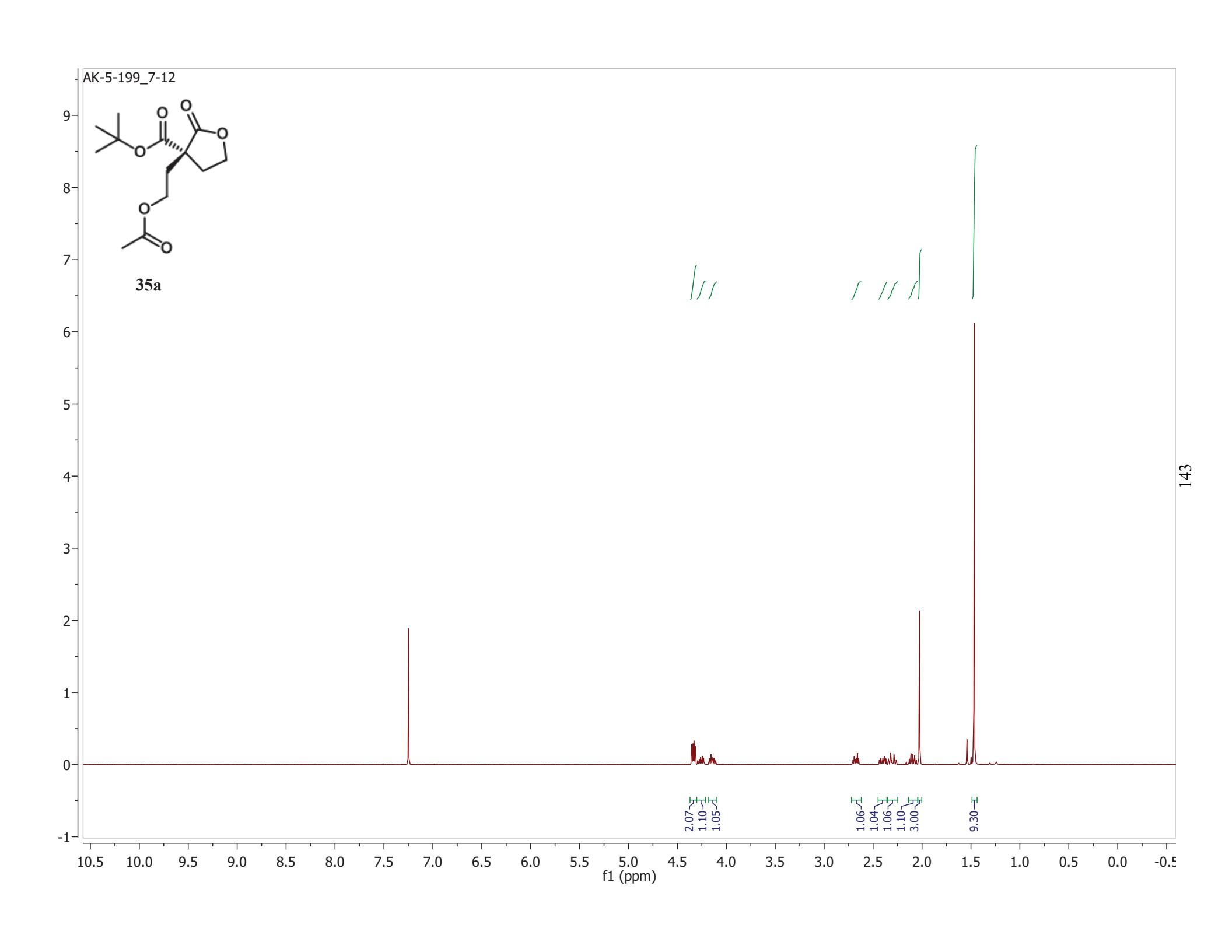
34a
142
f1 (ppm)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1.10
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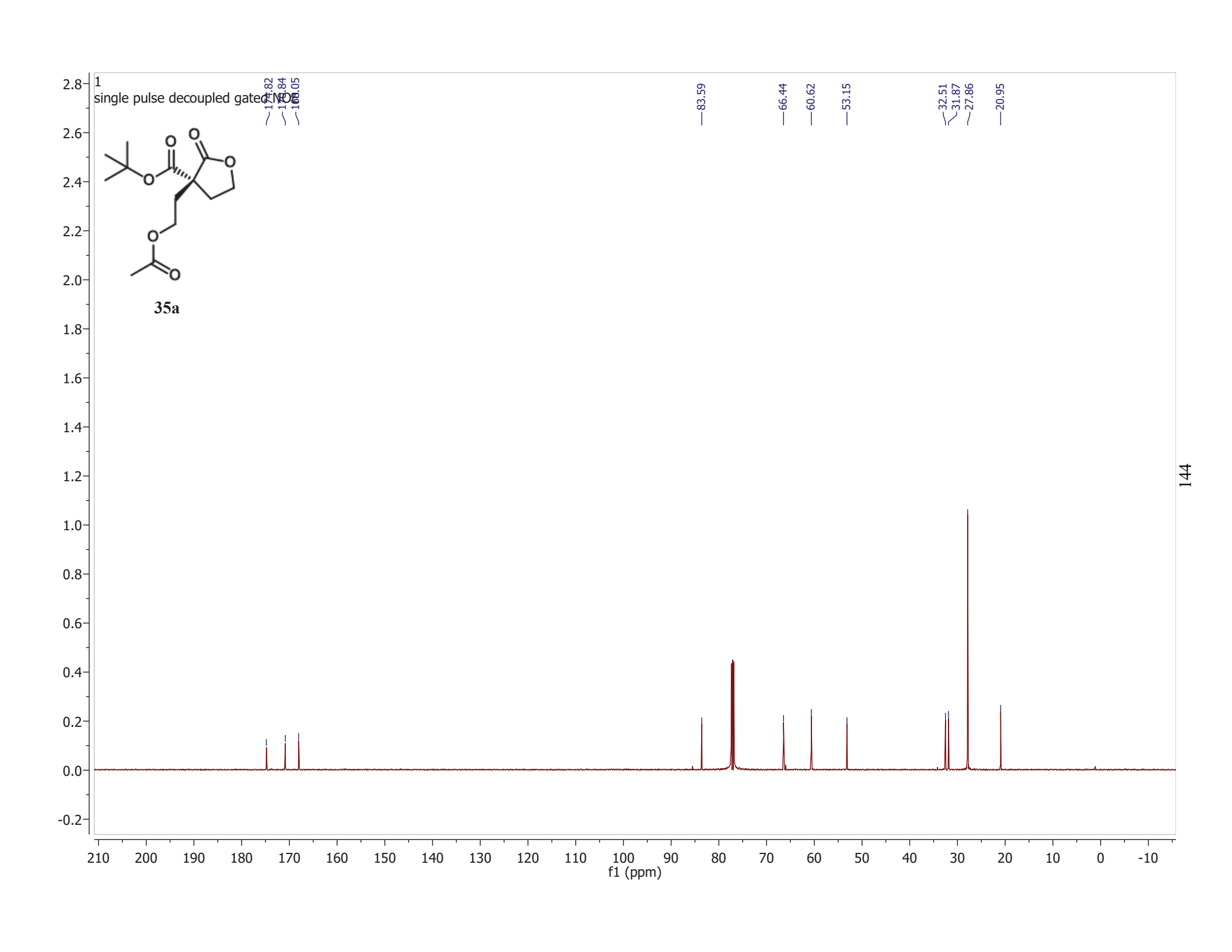
9.30
f1 (ppm)
143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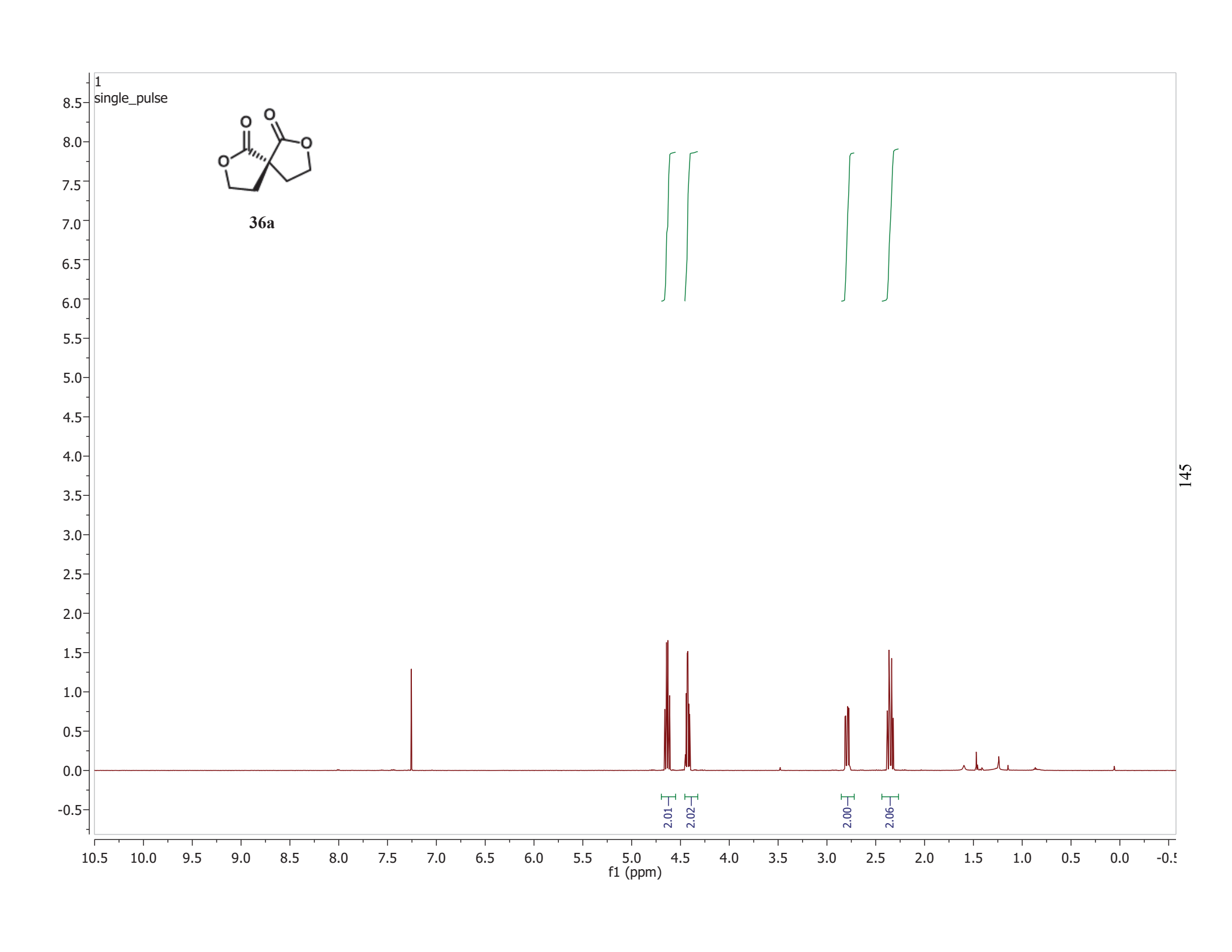
35a
144
f1 (ppm)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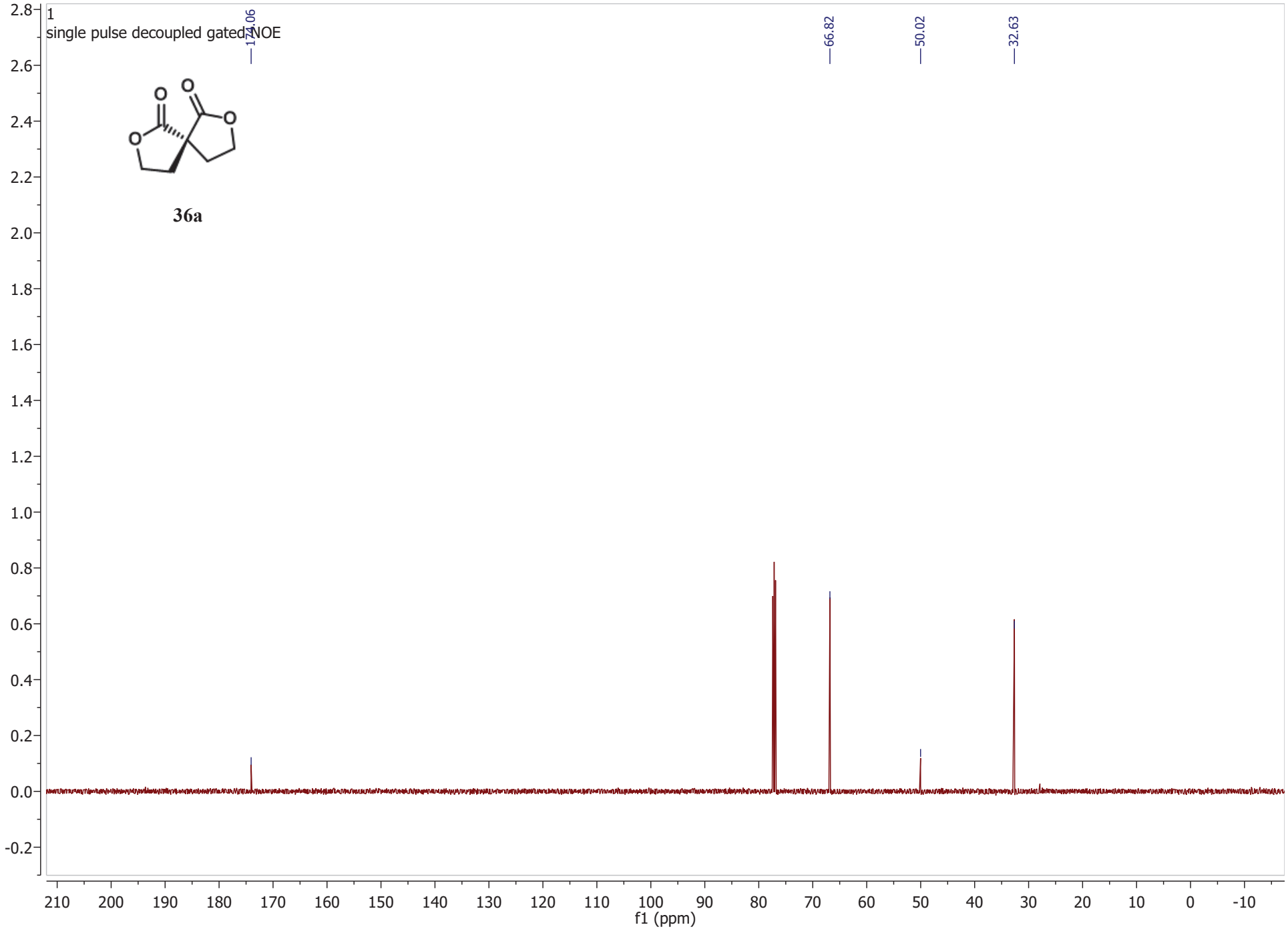
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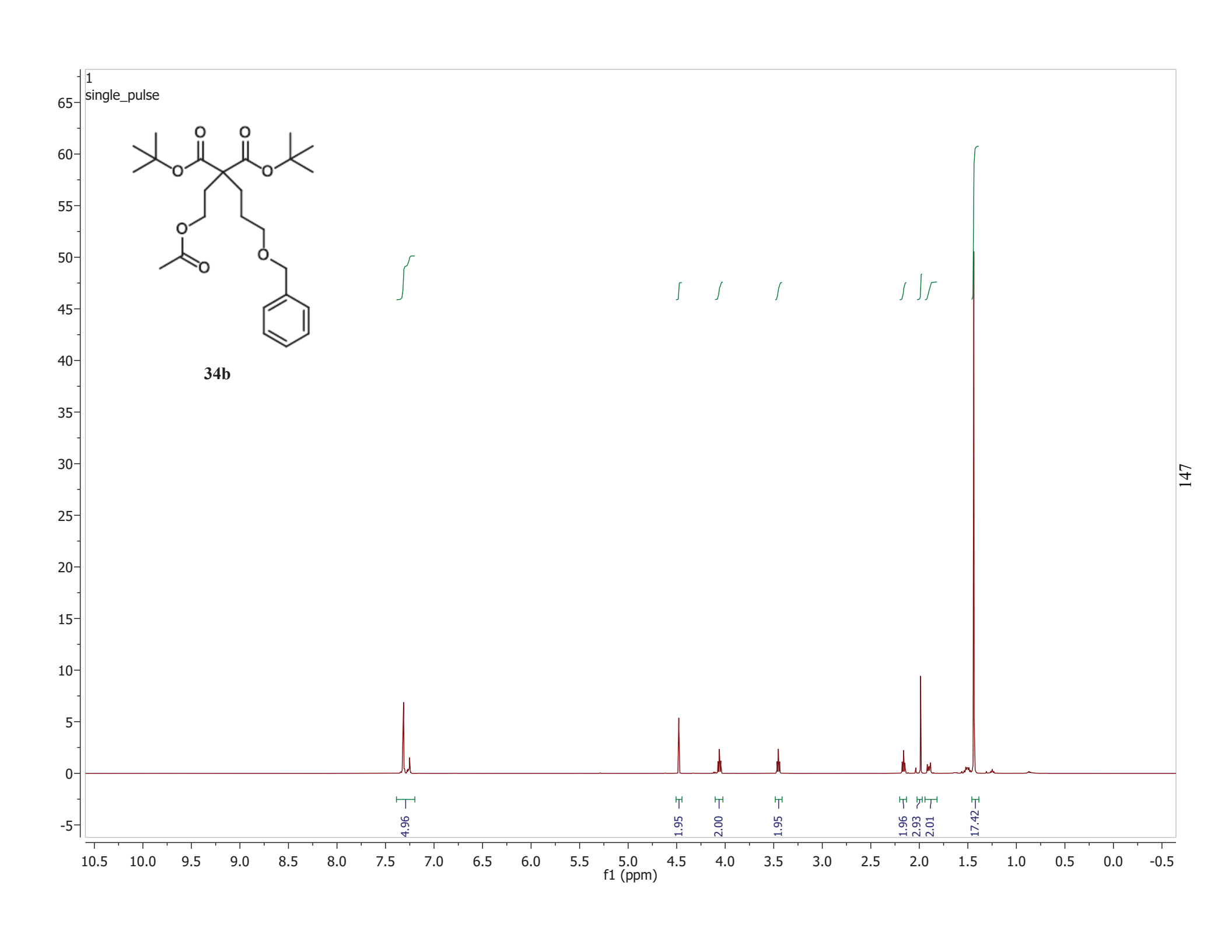
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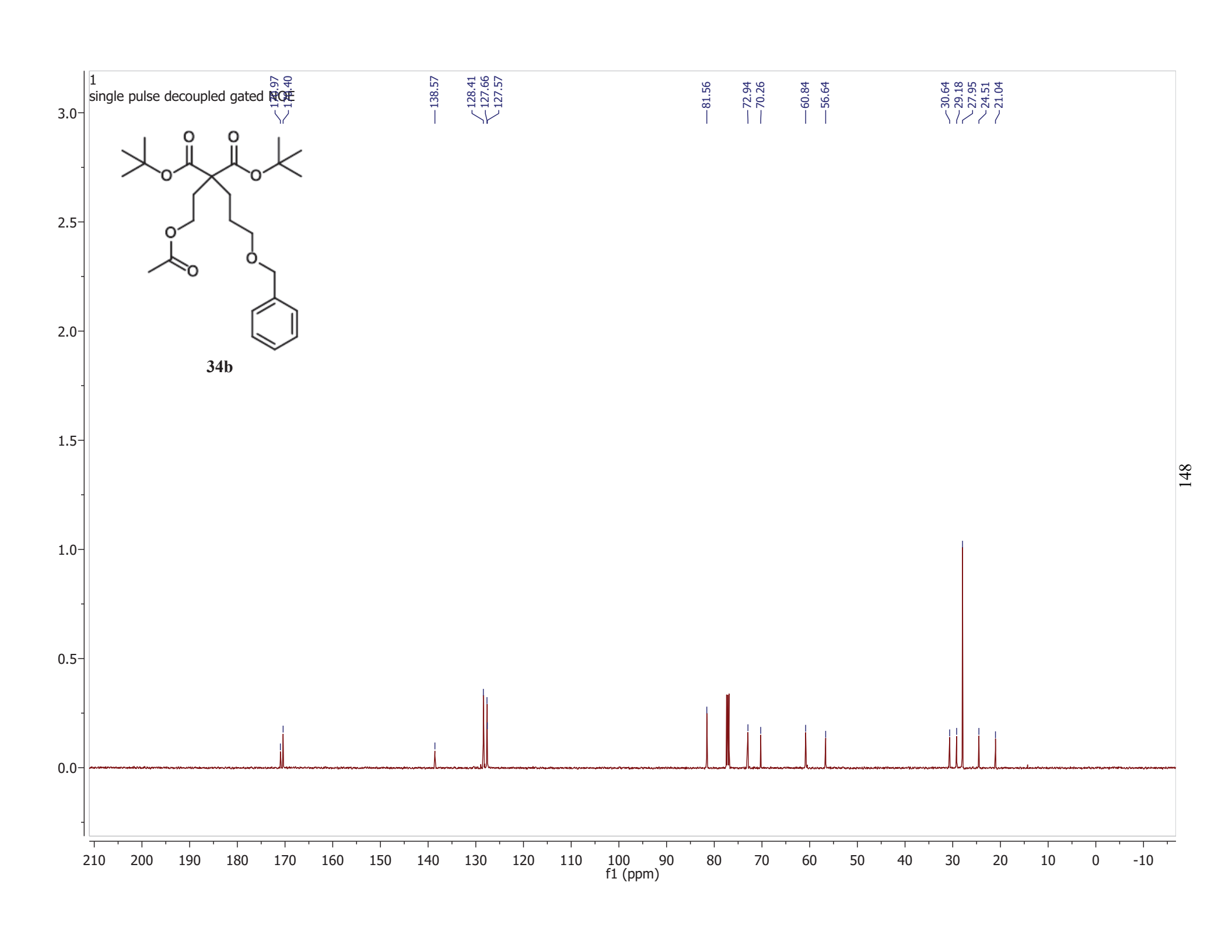
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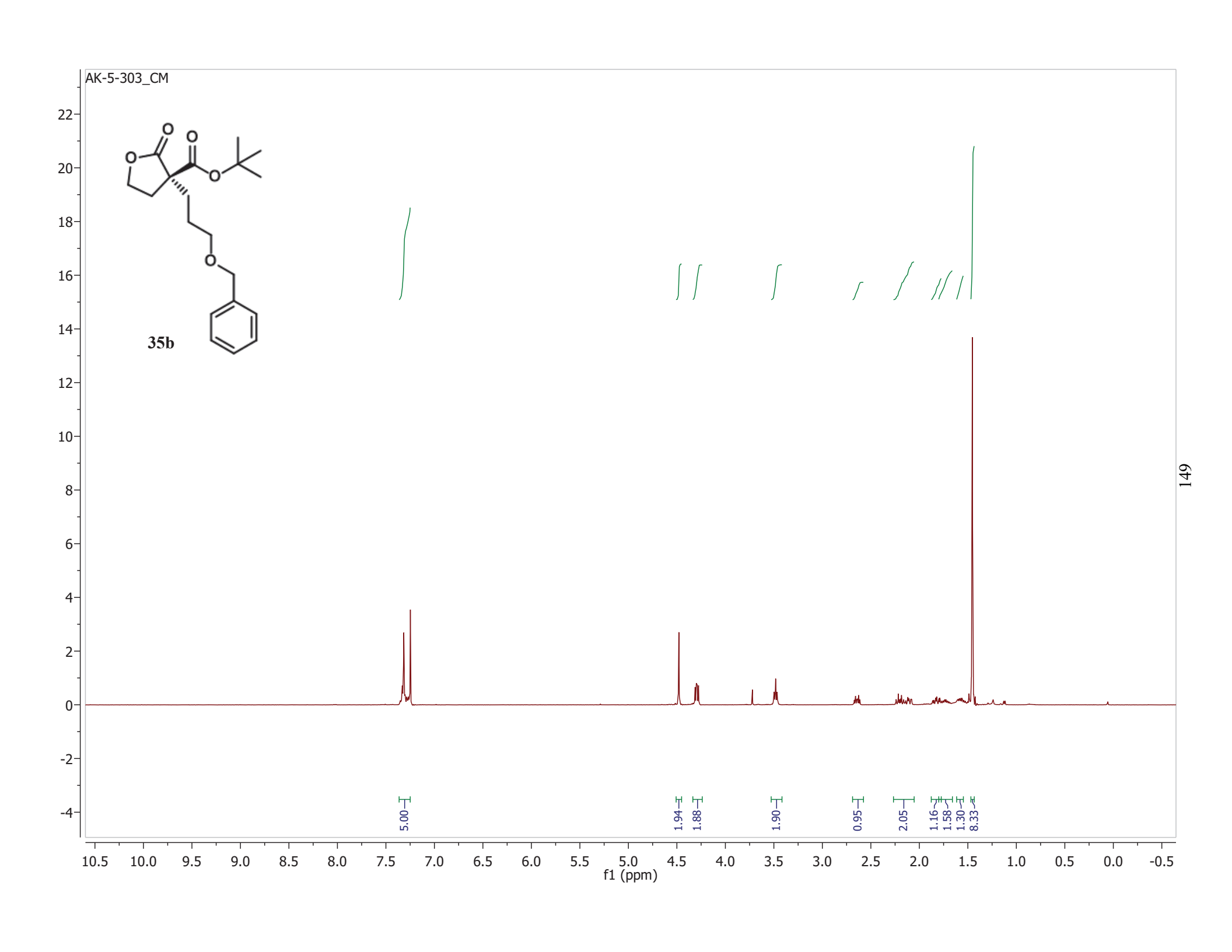
34b
148
f1 (ppm)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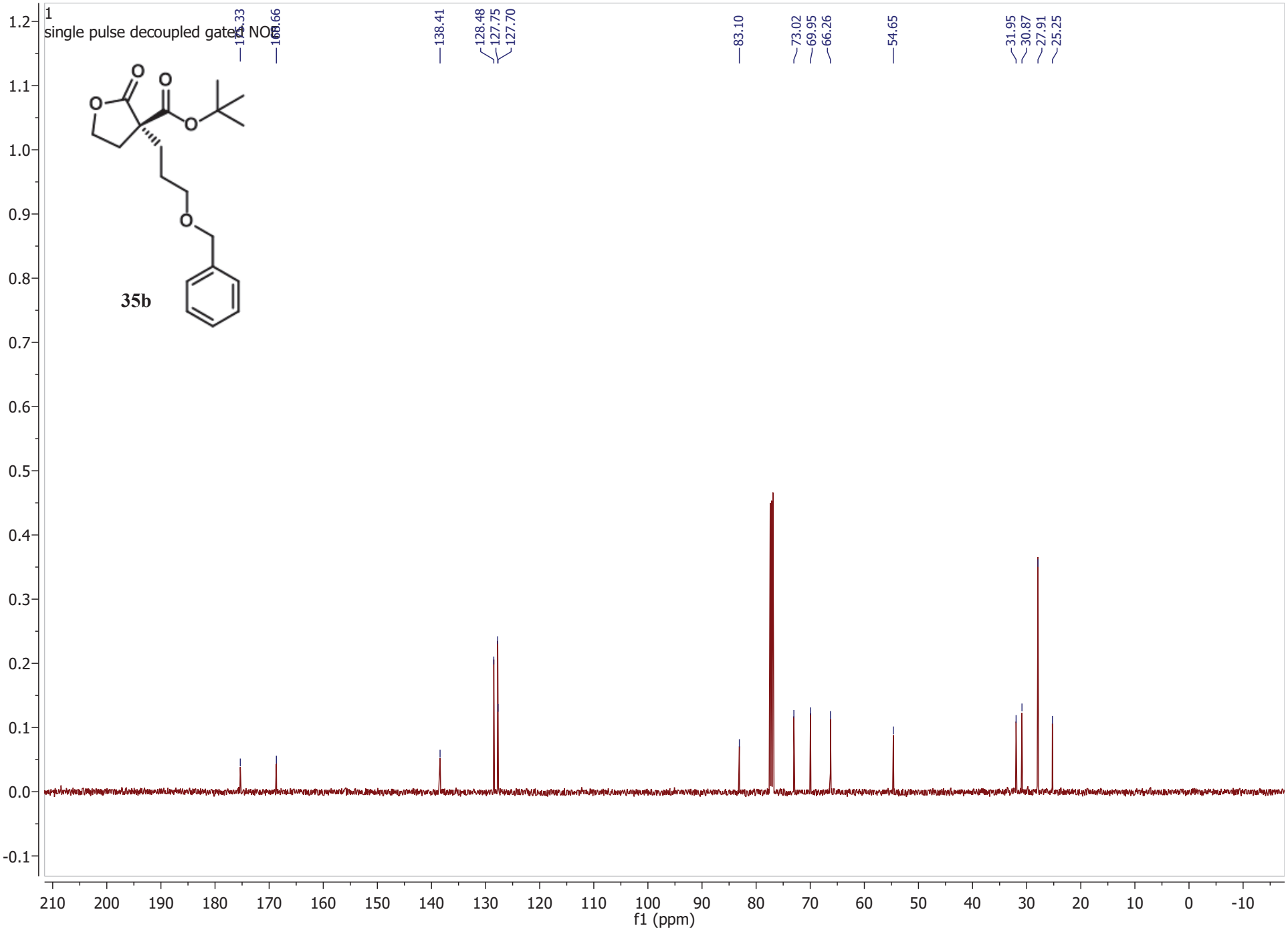
1.30
8.33
f1 (ppm)
149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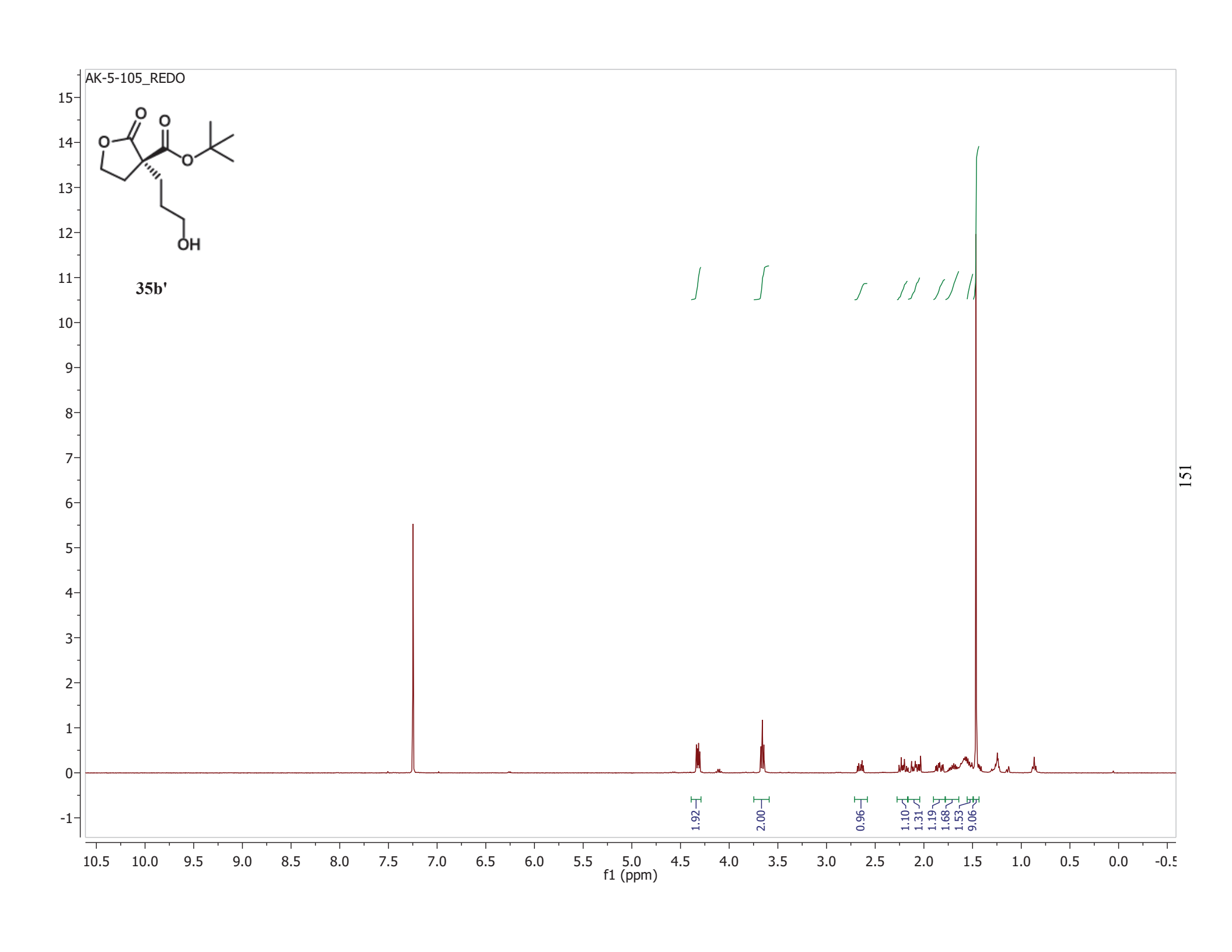
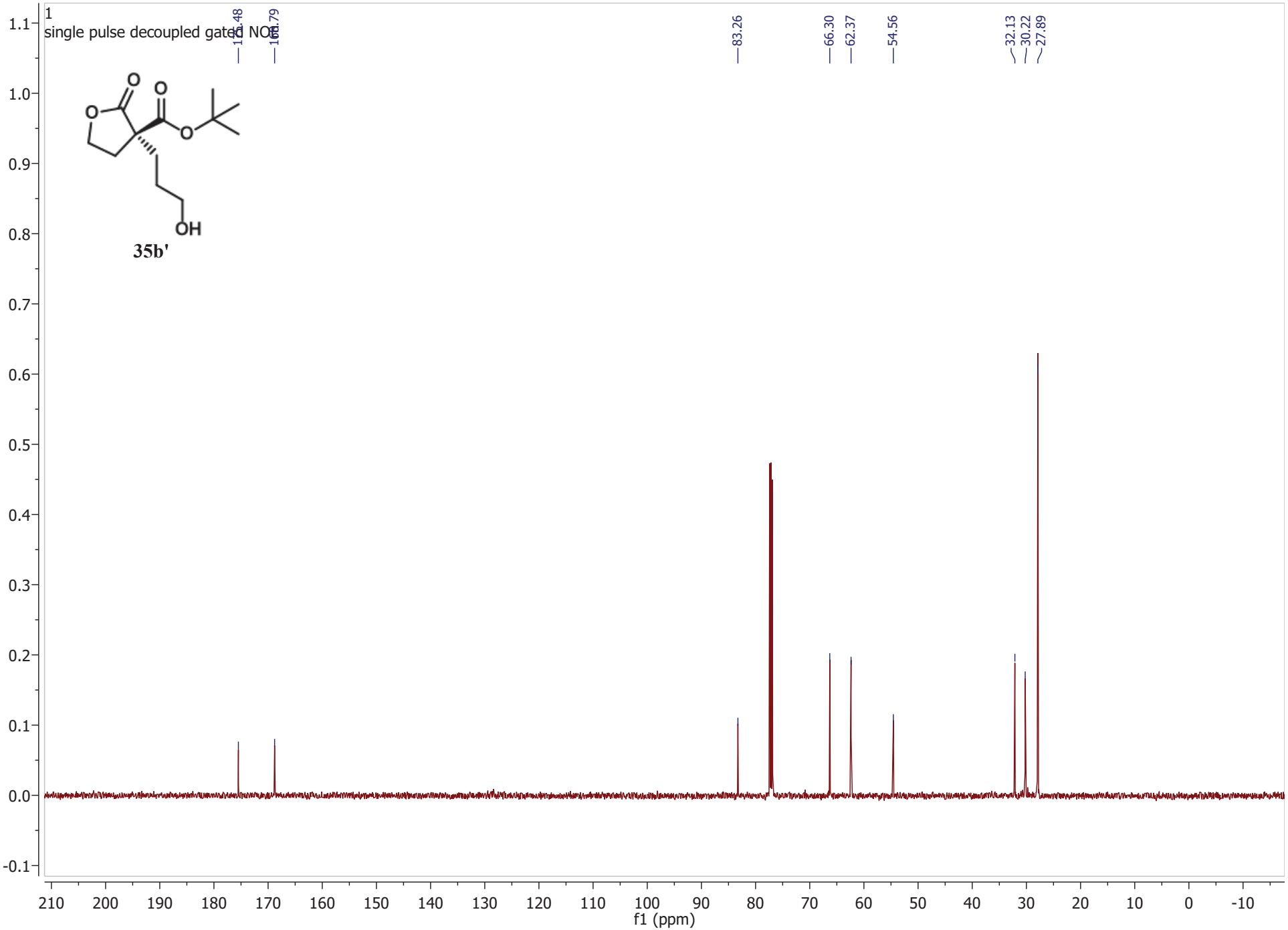
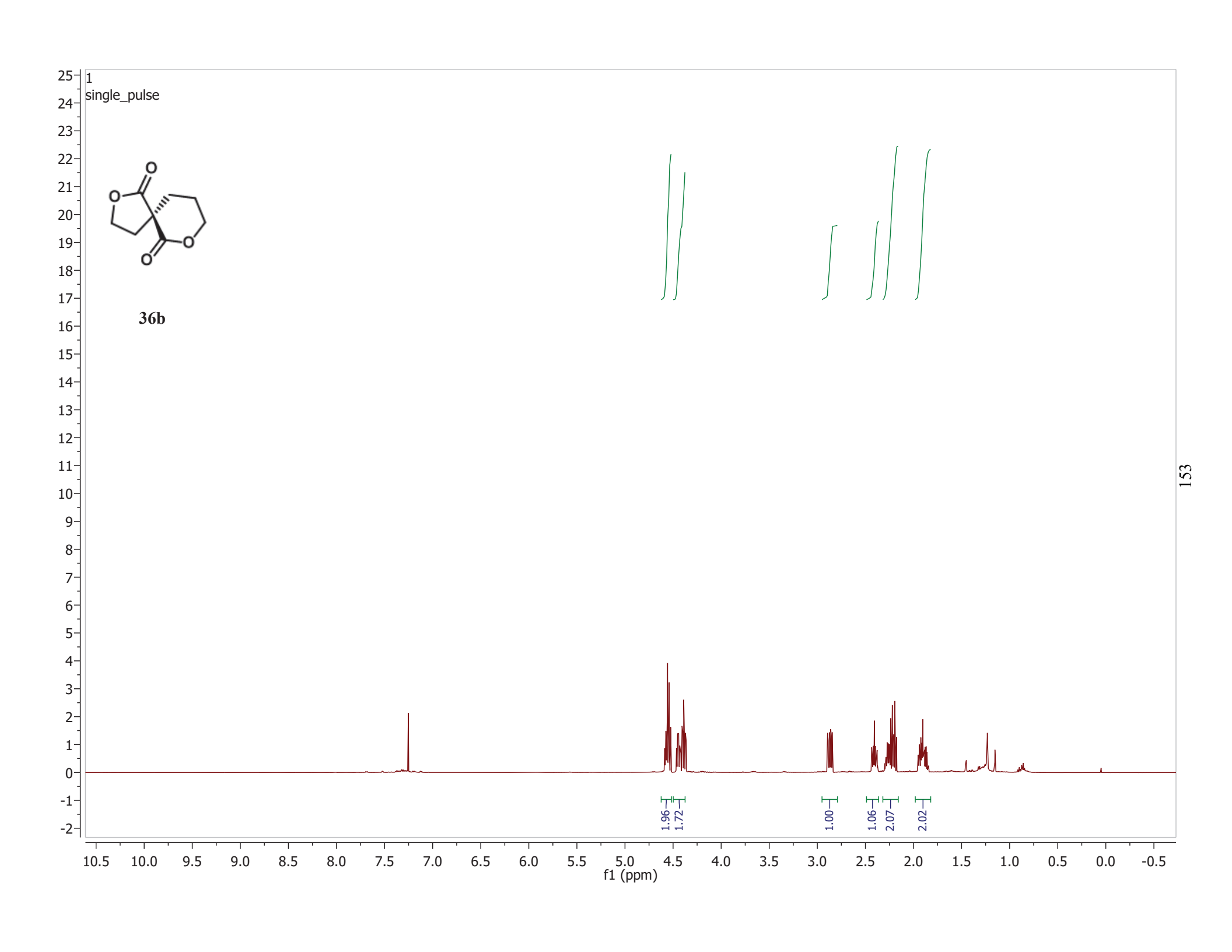
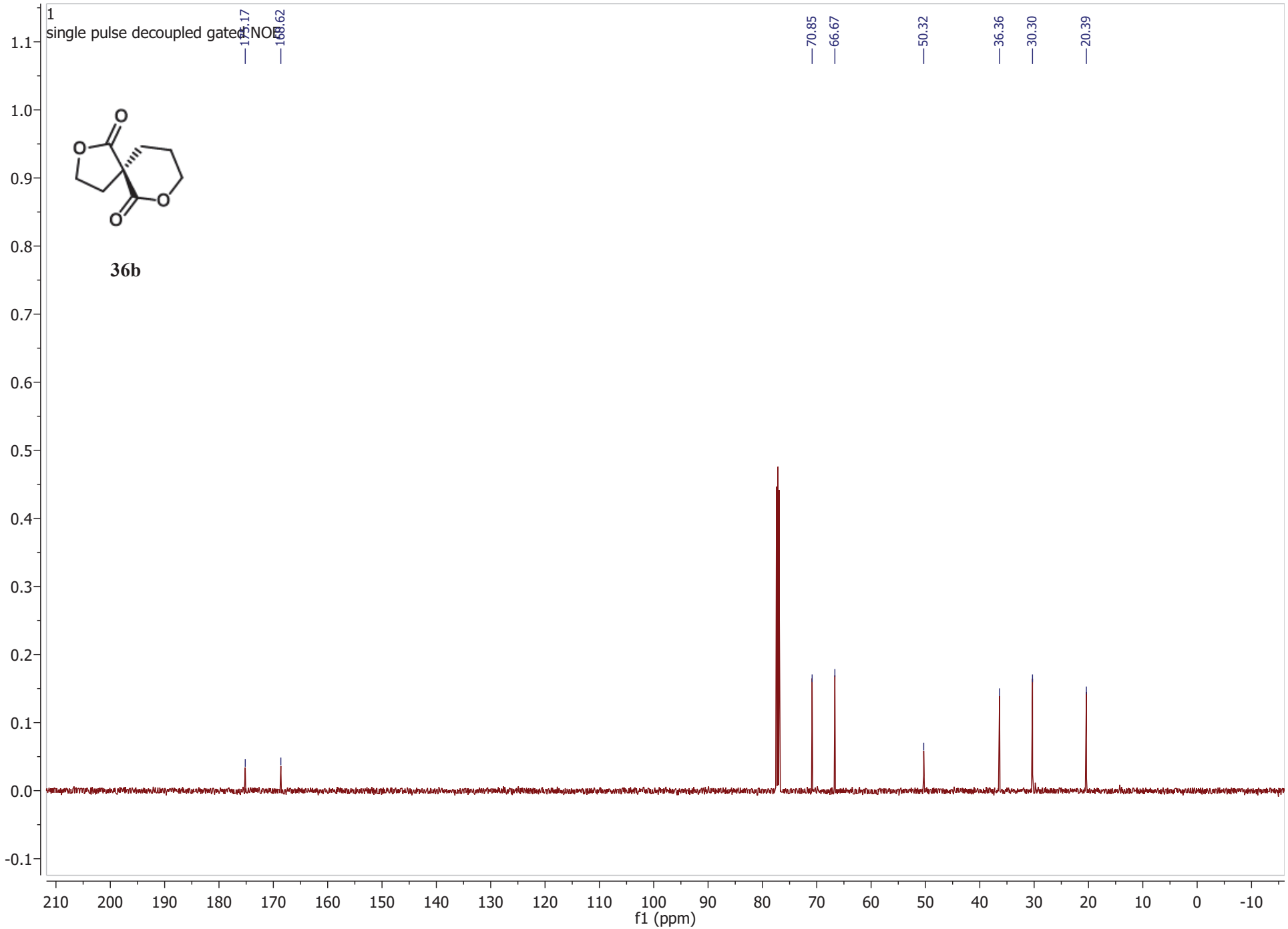
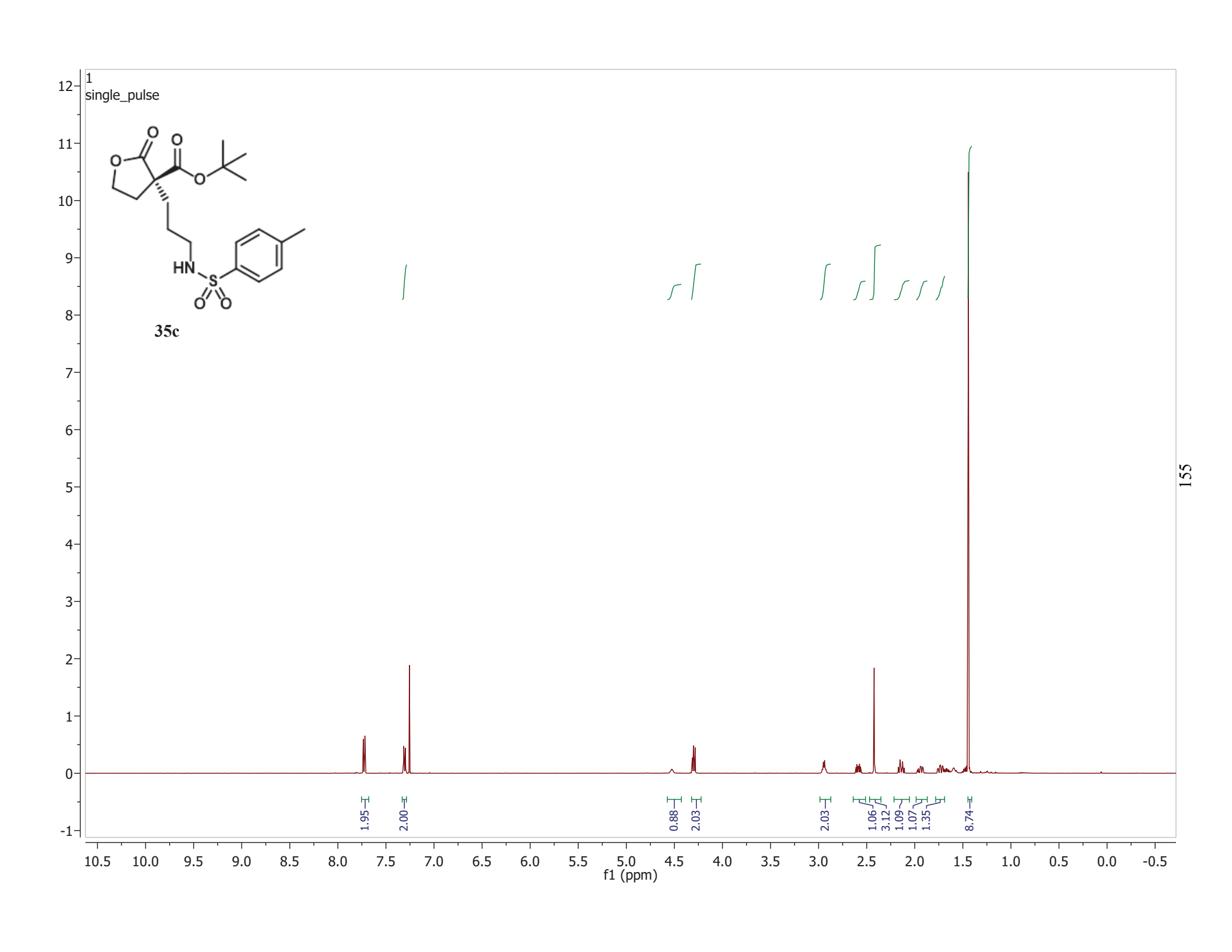
73.02
69.95
66.26
54.65
31.95
30.87
27.91
25.25
35b
150
f1 (ppm)

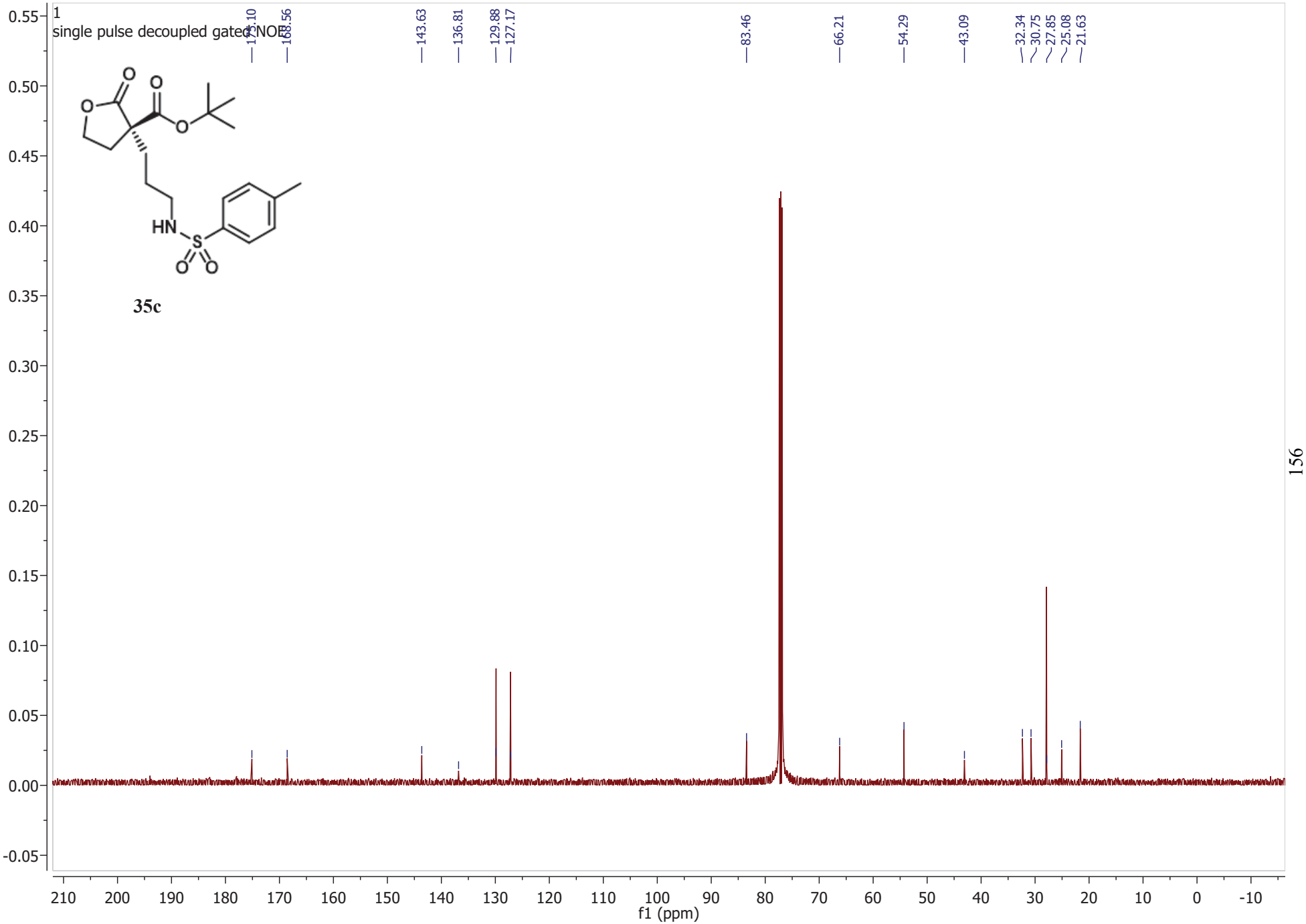

AK-5-105_REDO
35b'
1.92
2.00
0.96
1.10
1.31
1.19
1.68
1.53
9.06
f1 (ppm)
151

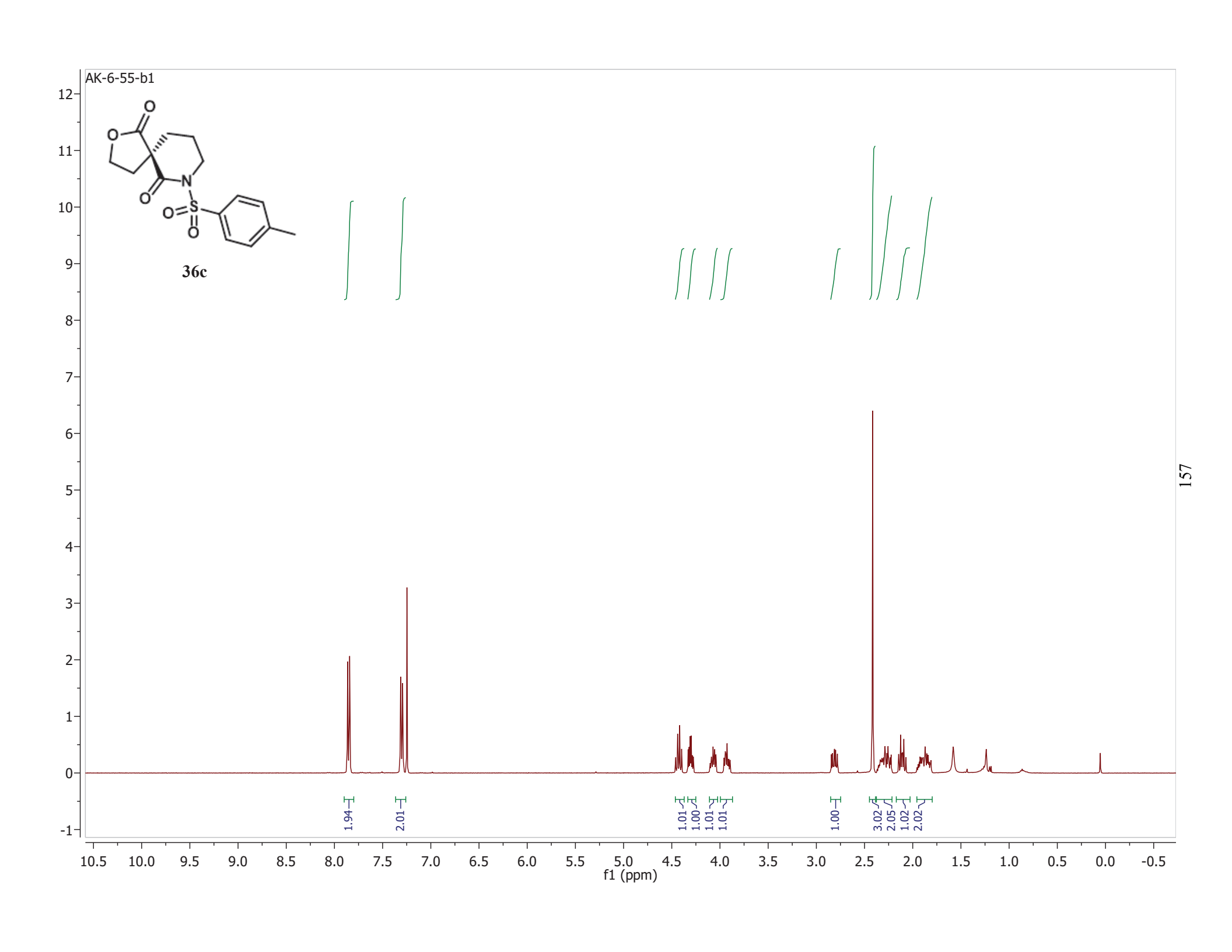

1
single pulse decoupled gated NOE
171.48
168.79
83.26
66.30
62.37
54.56
32.13
30.22
27.89
OH
35b'
152
f1 (ppm)

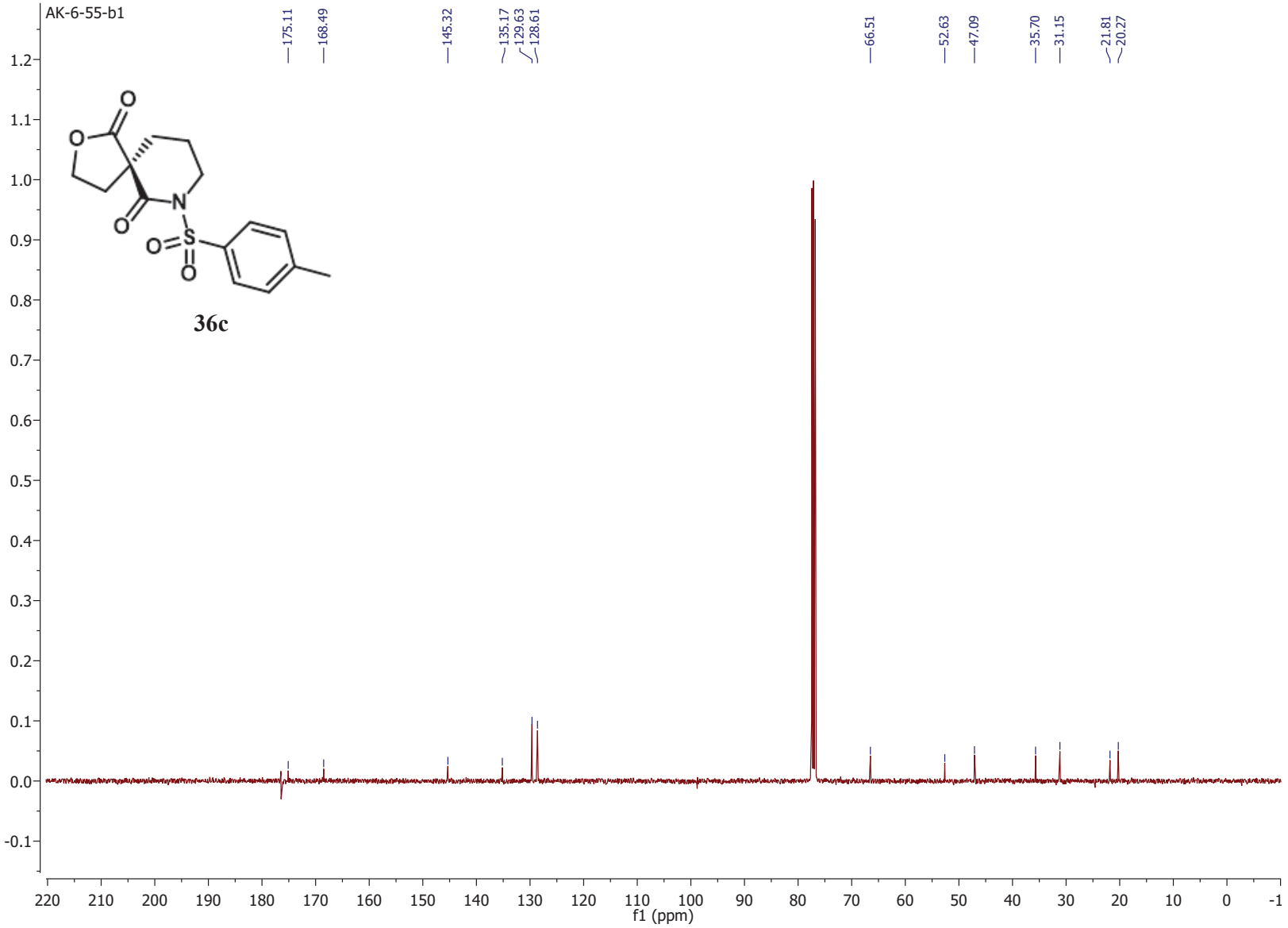

1
single_pulse
36b
1.96
1.72
1.00
1.06
2.07
2.02
f1 (ppm)
153

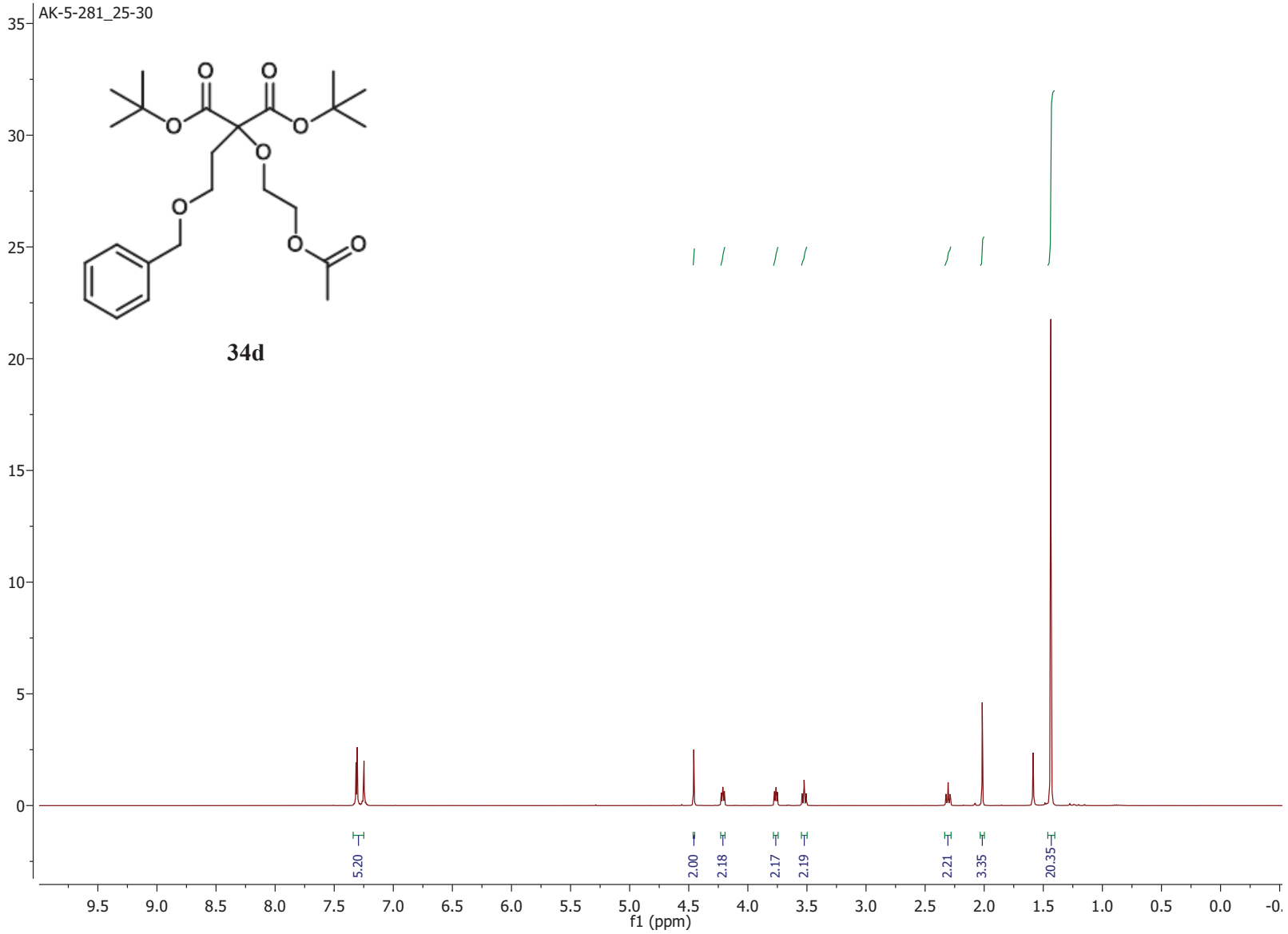

1
single pulse decoupled gated NOE
172.17
168.62
70.85
66.67
50.32
36.36
30.30
20.39
36b
f1 (ppm)
154

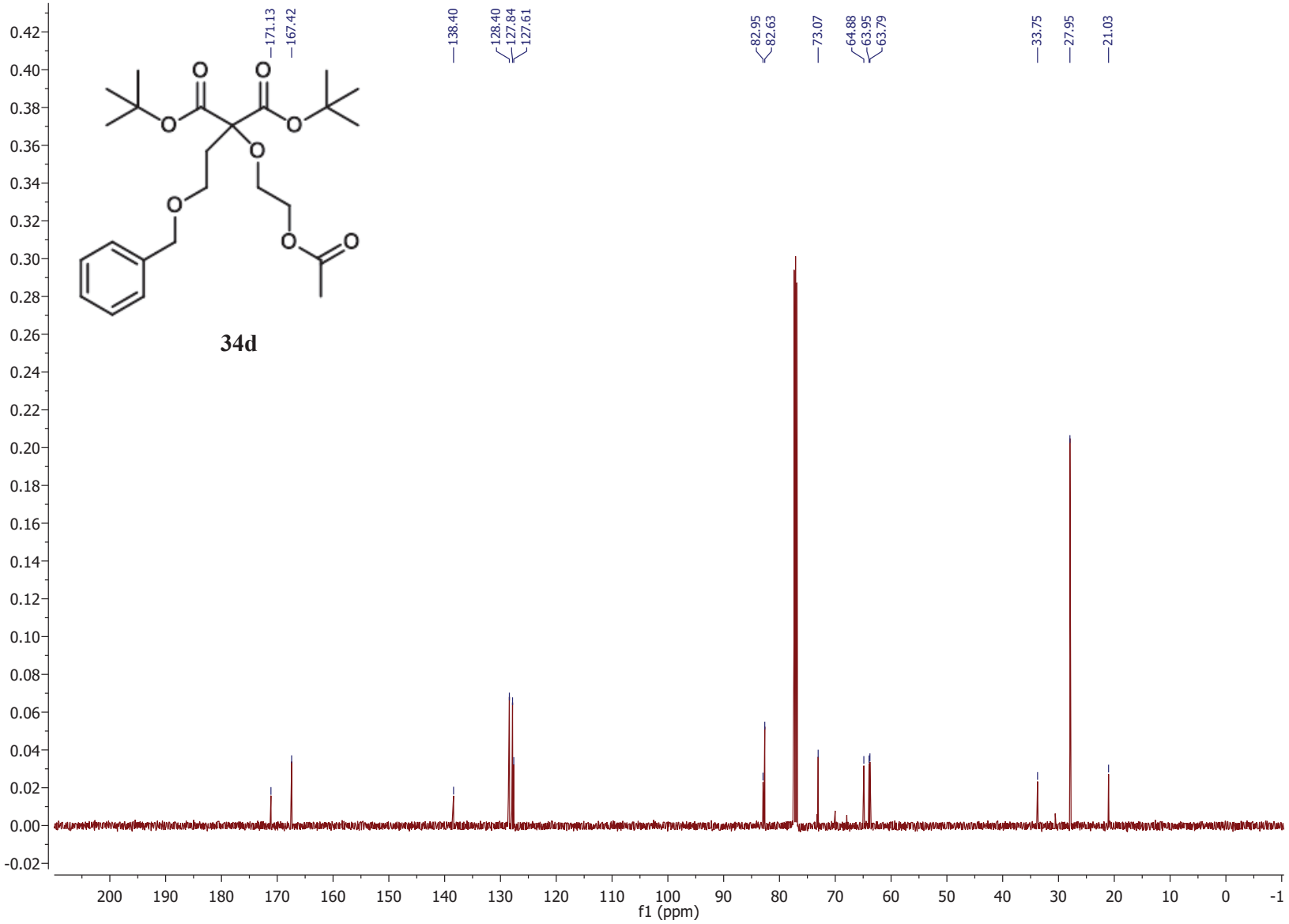

1
single_pulse
35c
1.95
2.00
0.88
2.03
2.03
1.06
3.12
1.09
1.07
1.35
8.74
f1 (ppm)
155


1
single pulse decoupled gated NOE
171.10
168.56
143.63
136.81
129.88
127.17
83.46
66.21
54.29
43.09
32.34
30.75
27.85
25.08
21.63
HN
S
O
O
35c
156
f1 (ppm)

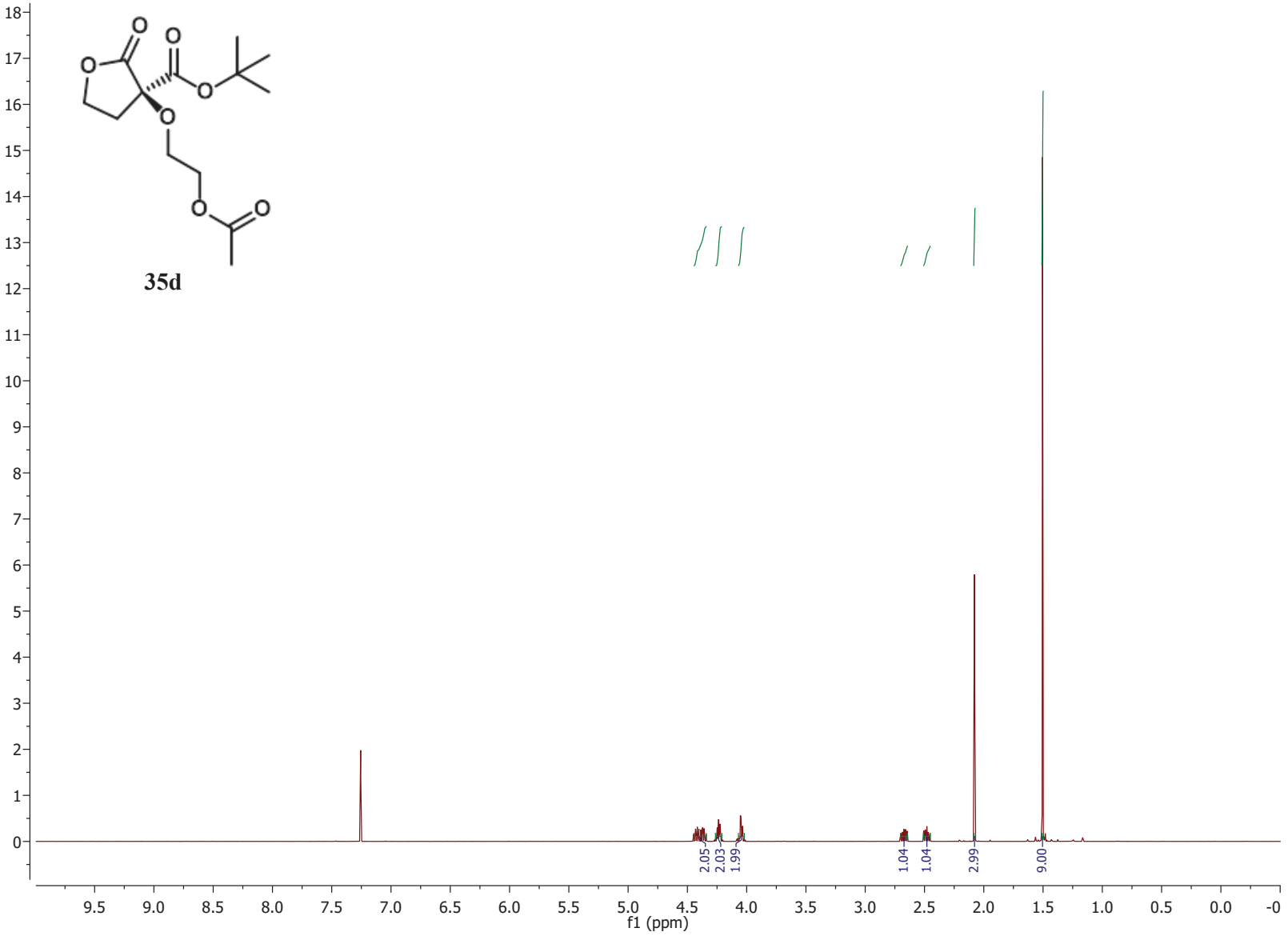

AK-6-55-b1
36c
1.94
2.01
1.01
1.00
1.01
1.01
1.00
3.02
2.05
1.02
2.02
f1 (ppm)
157

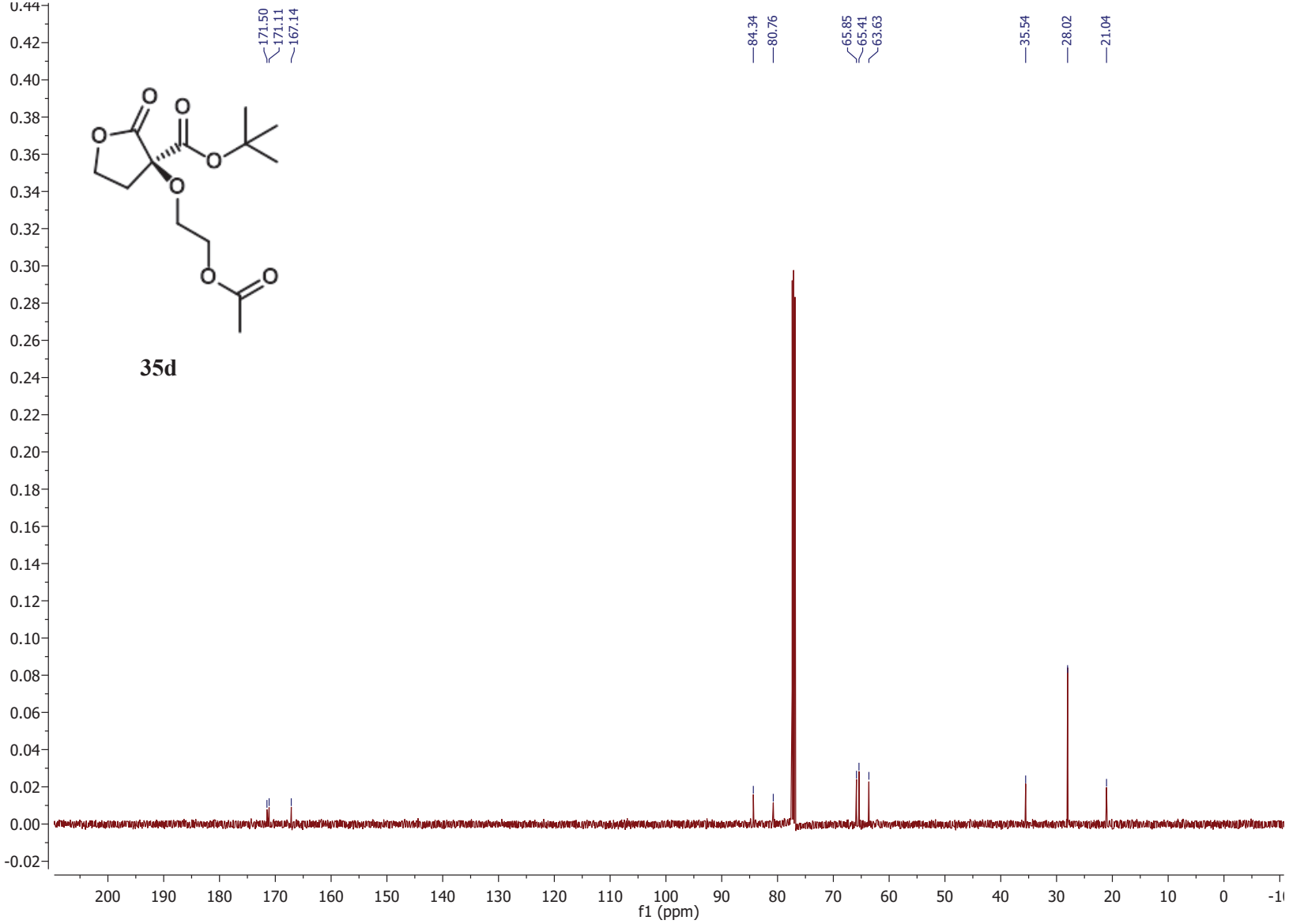

AK-6-55-b1
175.11
168.49
145.32
135.17
129.63
128.61
66.51
52.63
47.09
35.70
31.15
21.81
20.27
36c
f1 (ppm)

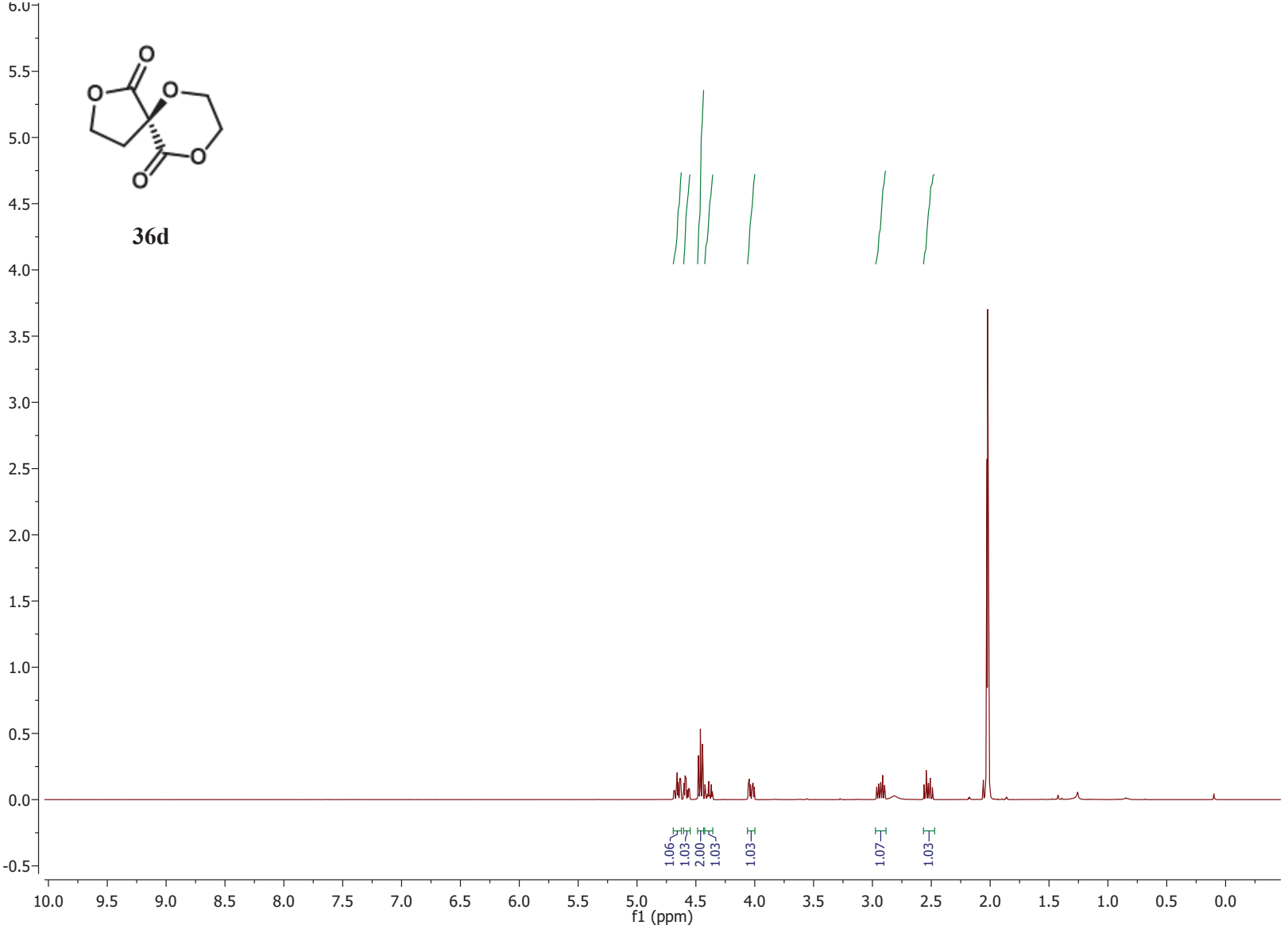

AK-5-281_25-30
34d
5.20
2.00
2.18
2.17
2.19
2.21
3.35
20.35
f1 (ppm)

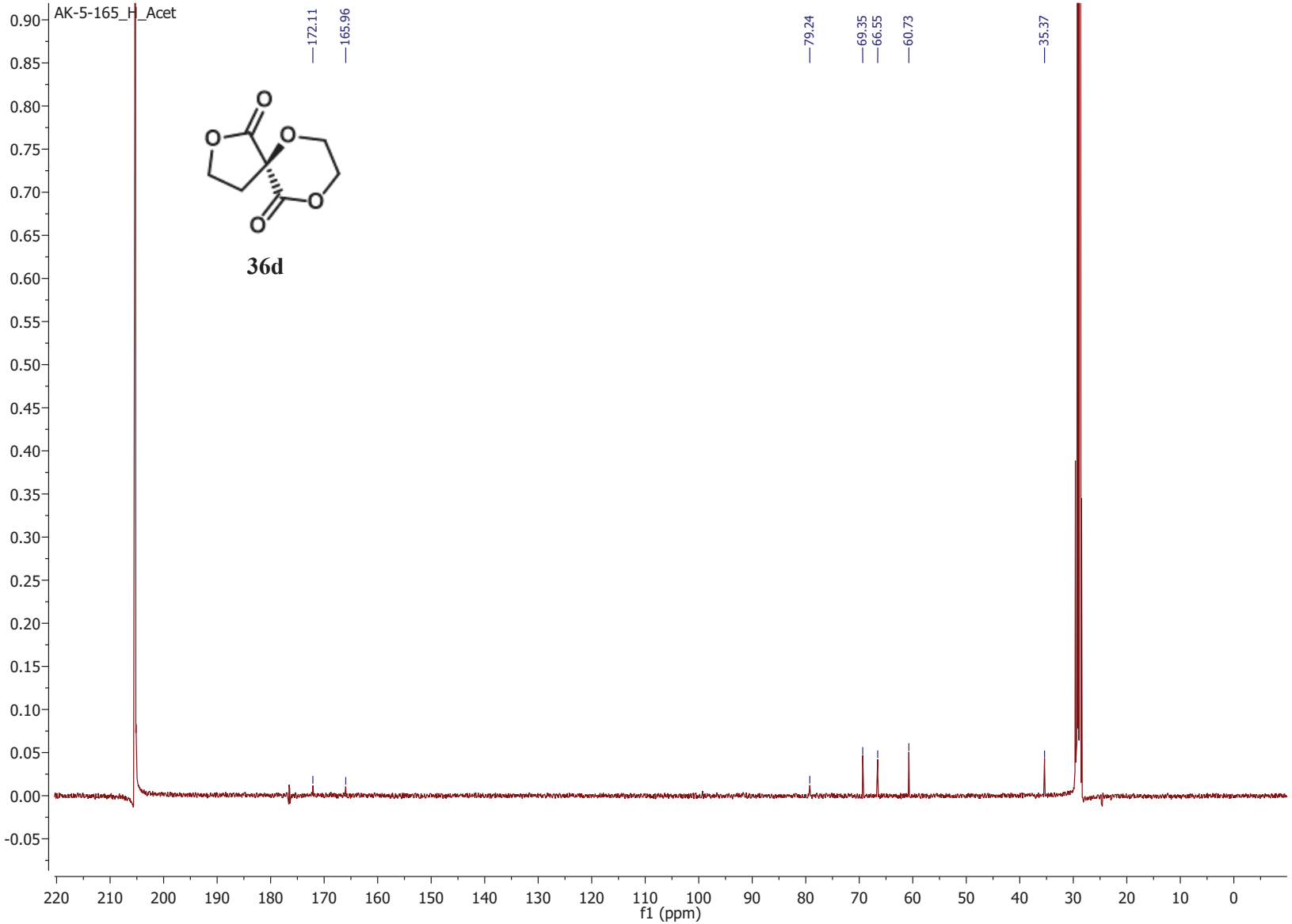

171.13
167.42
138.40
128.40
127.84
127.61
82.95
82.63
73.07
64.88
63.95
63.79
33.75
27.95
21.03
34d
f1 (ppm)

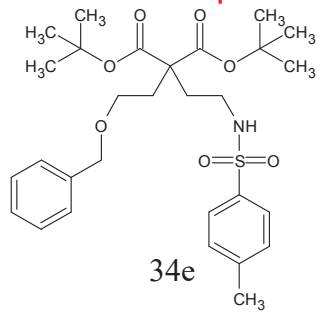
160


35d
2.05
2.03
1.99
1.04
1.04
2.99
9.00
f1 (ppm)

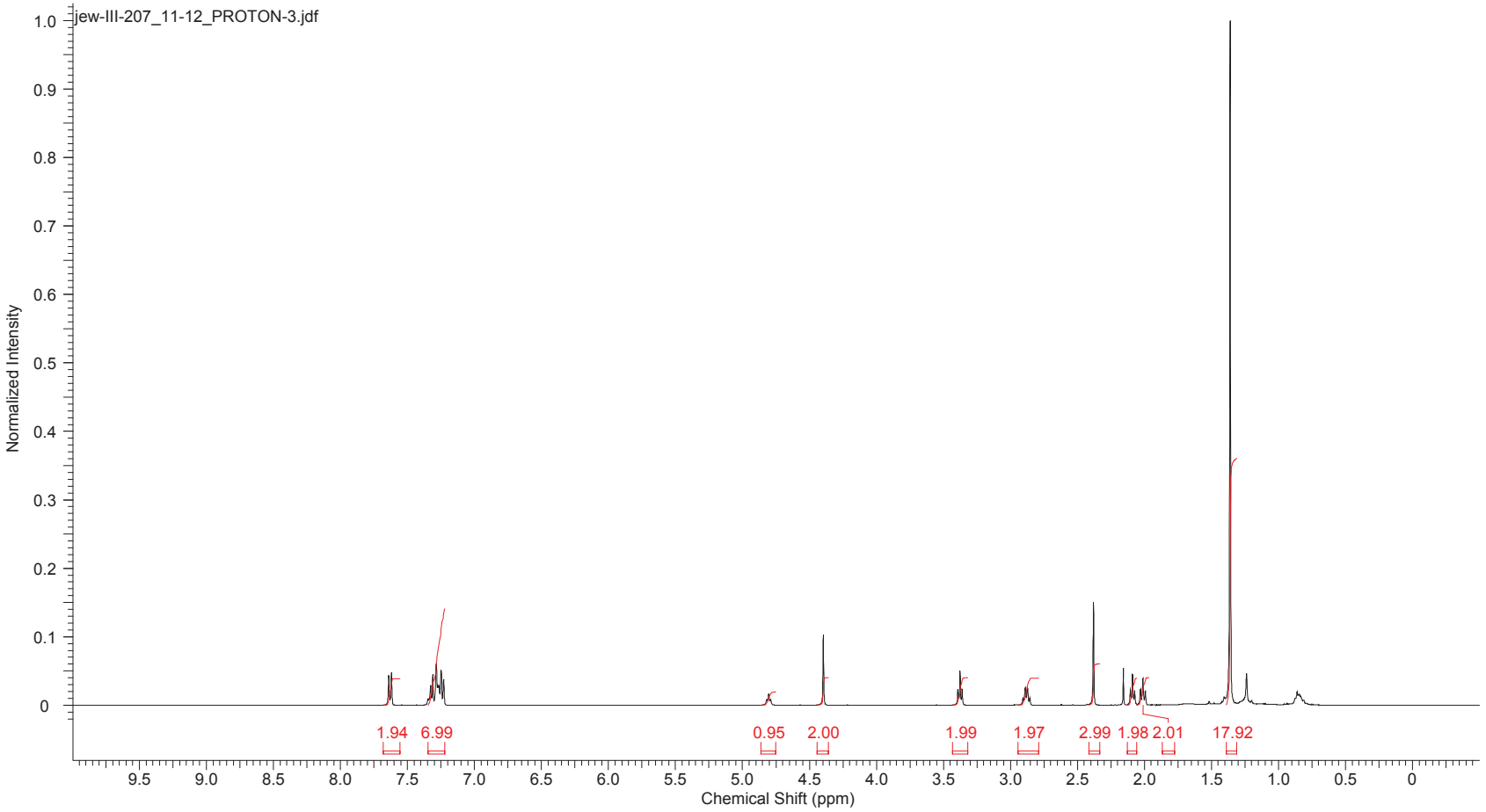

171.50
171.11
167.14
84.34
80.76
65.85
65.41
63.63
35.54
28.02
21.04
35d
f1 (ppm)

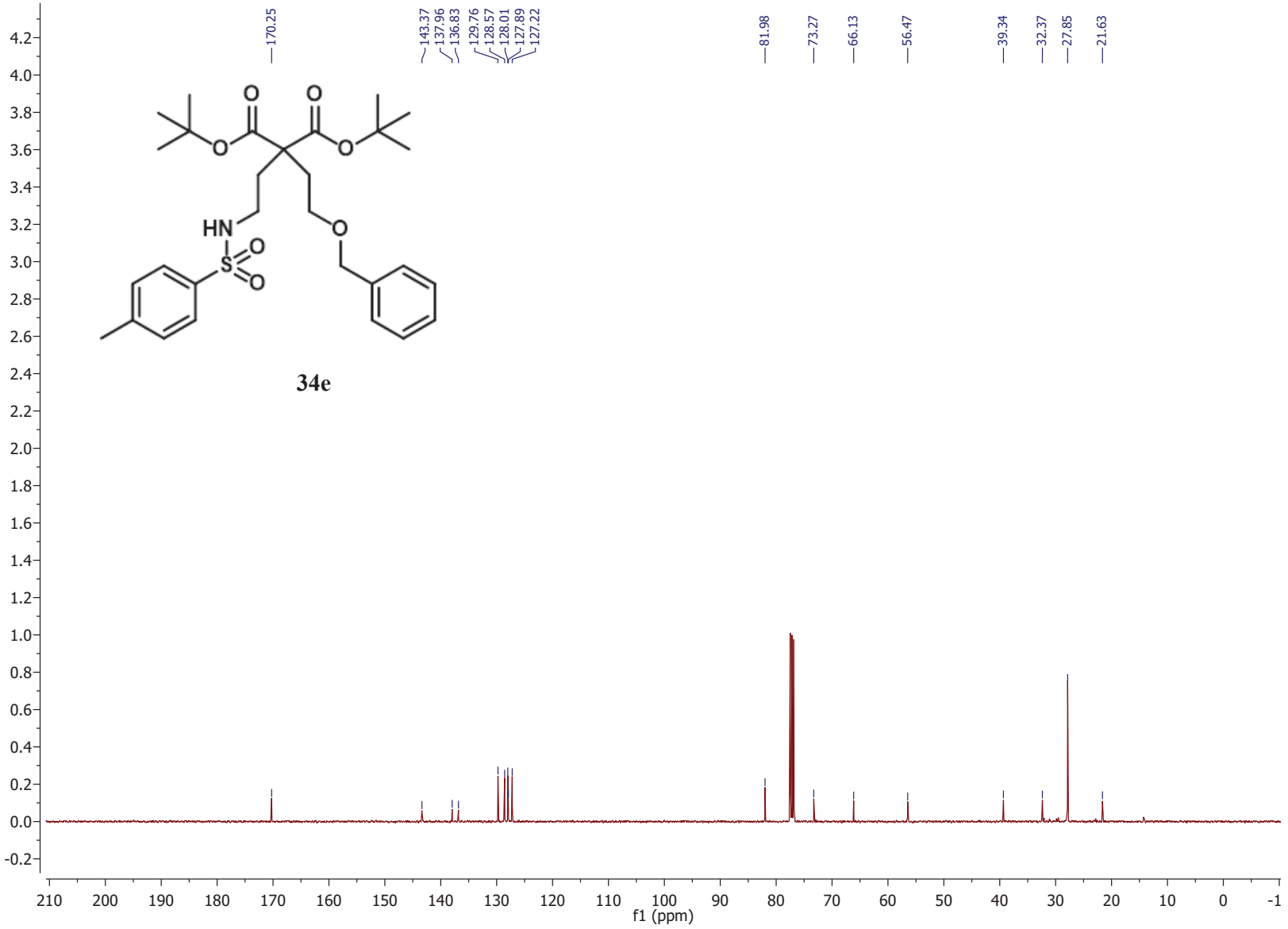

36d
f1 (ppm)
1.06
1.03
2.00
1.03
1.03
1.07
1.03


AK-5-165_H_Acet
172.11
165.96
79.24
69.35
66.55
60.73
35.37
36d
f1 (ppm)



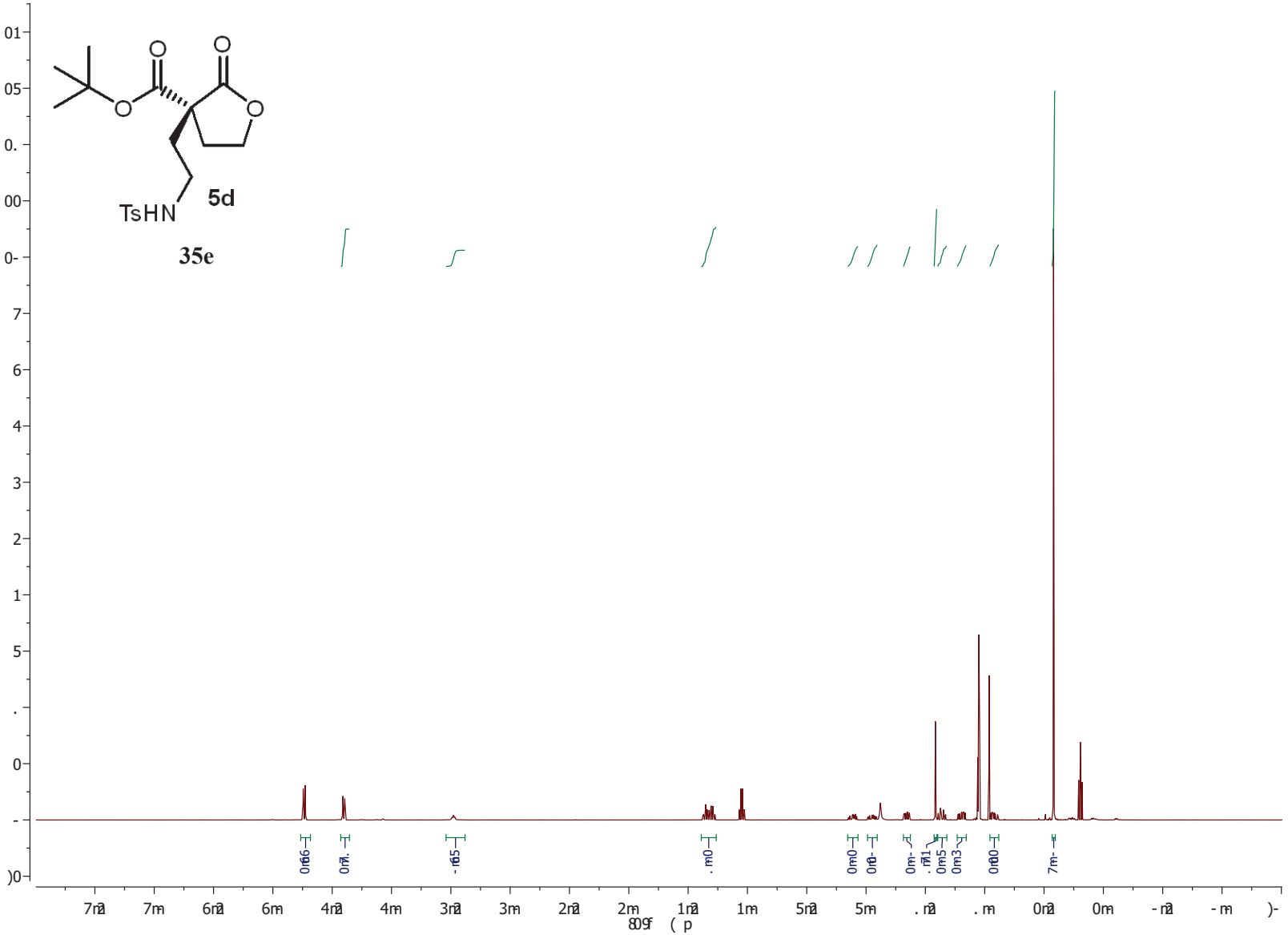
34e

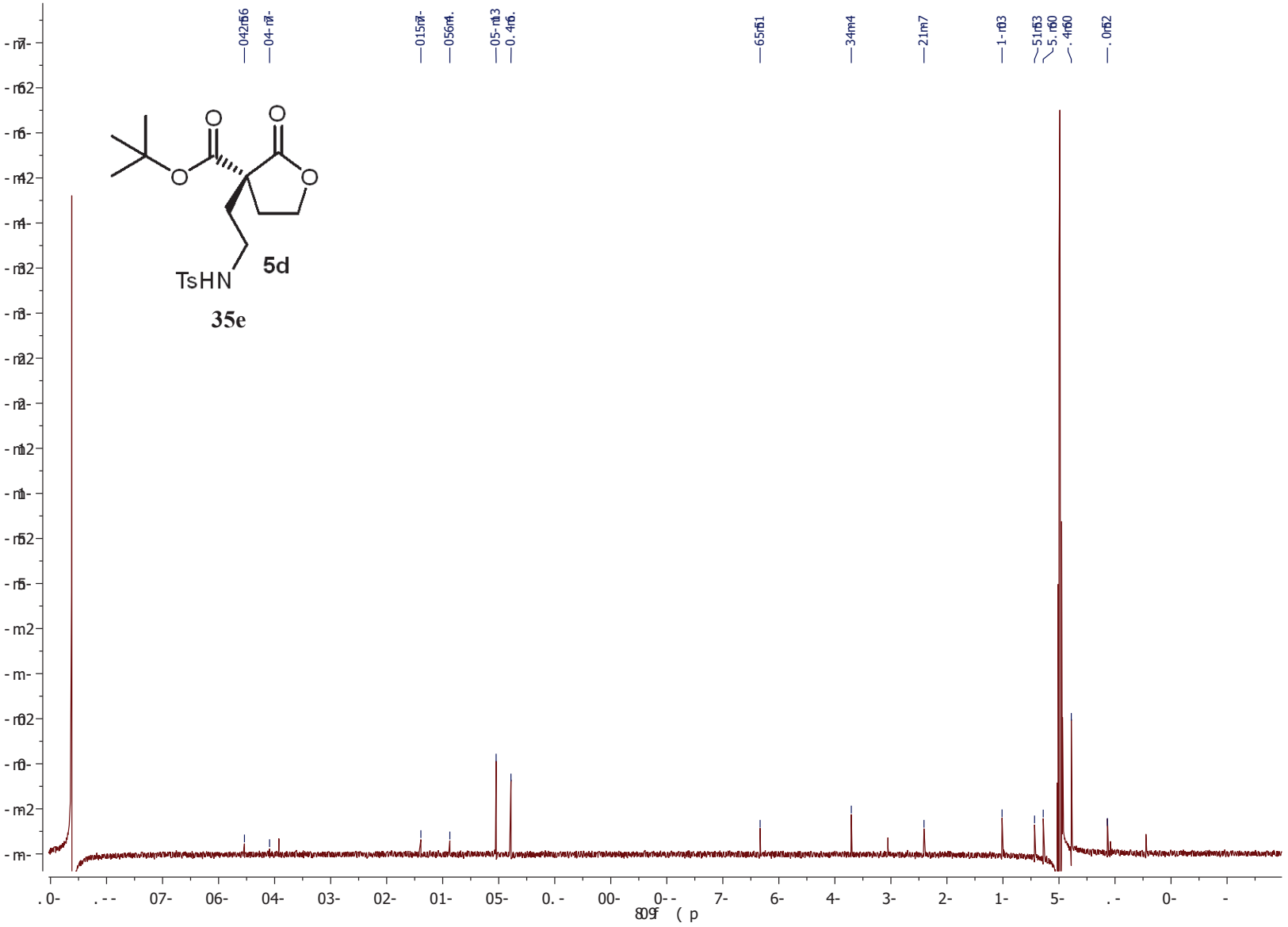


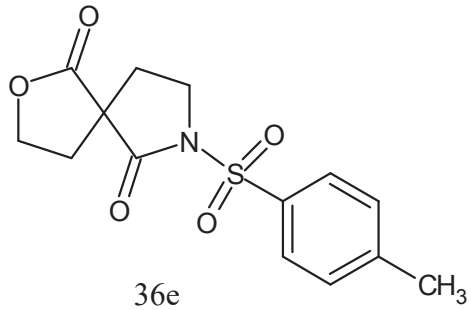

170.25
143.37
137.96
136.83
129.76
128.57
128.01
127.89
127.22
81.98
73.27
66.13
56.47
39.34
32.37
27.85
21.63
HN
S
O
f1 (ppm)

34e

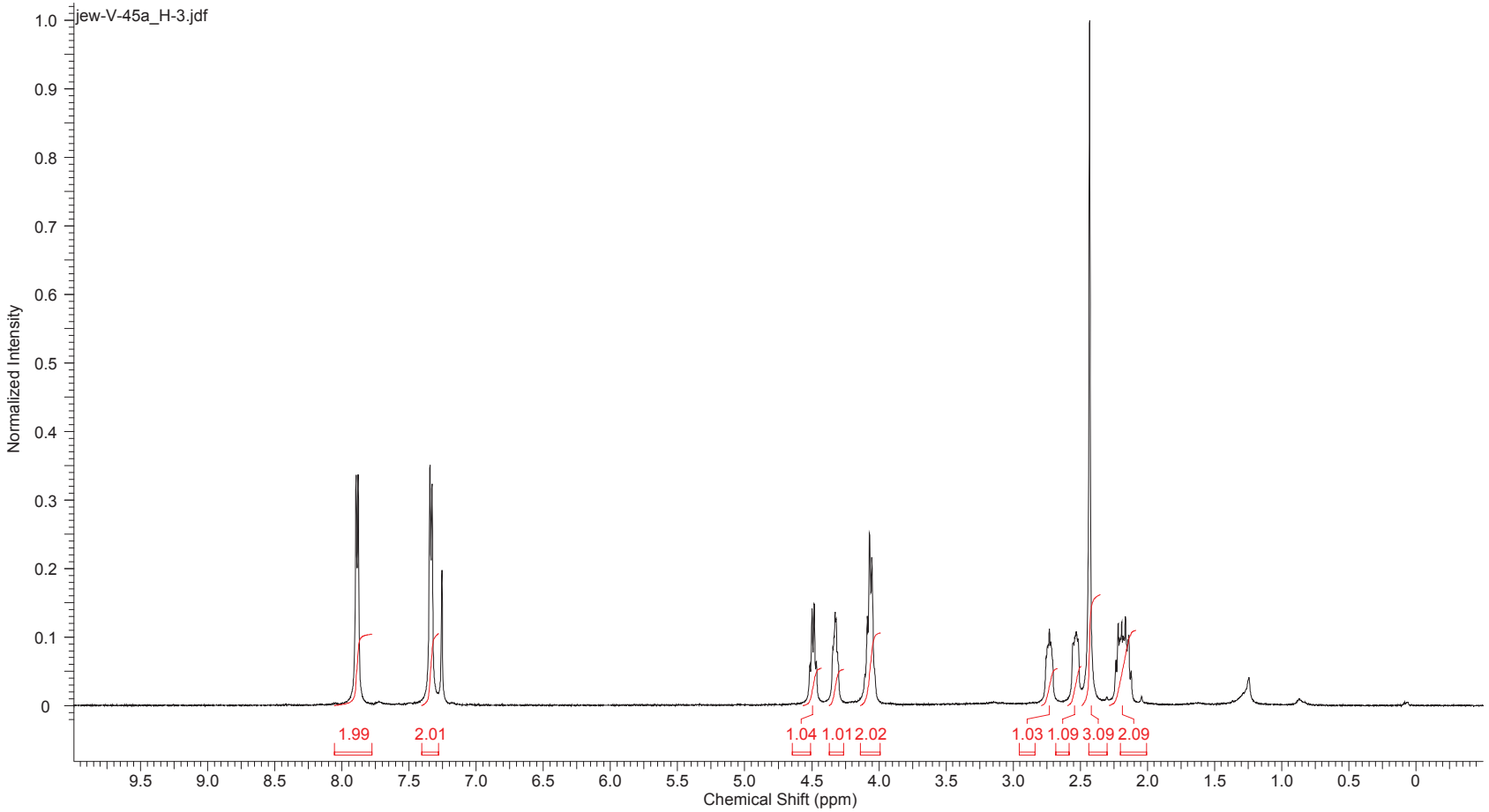
166


TsHN
5d
35e

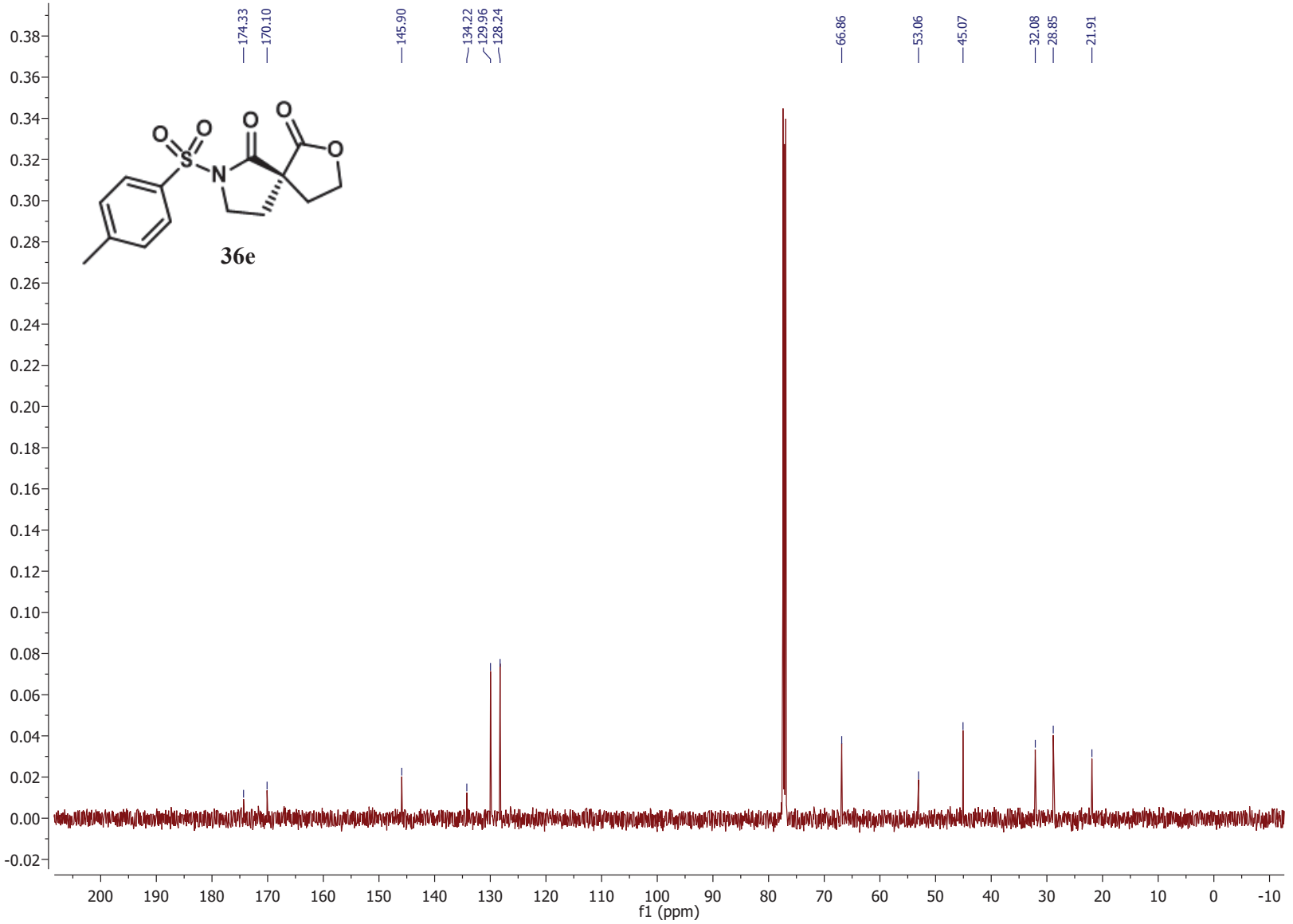

5d
TsHN
35e



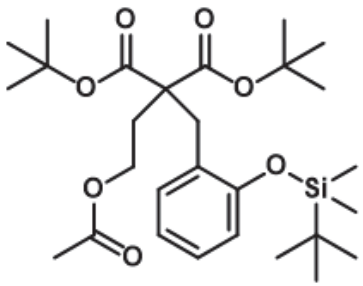
36e



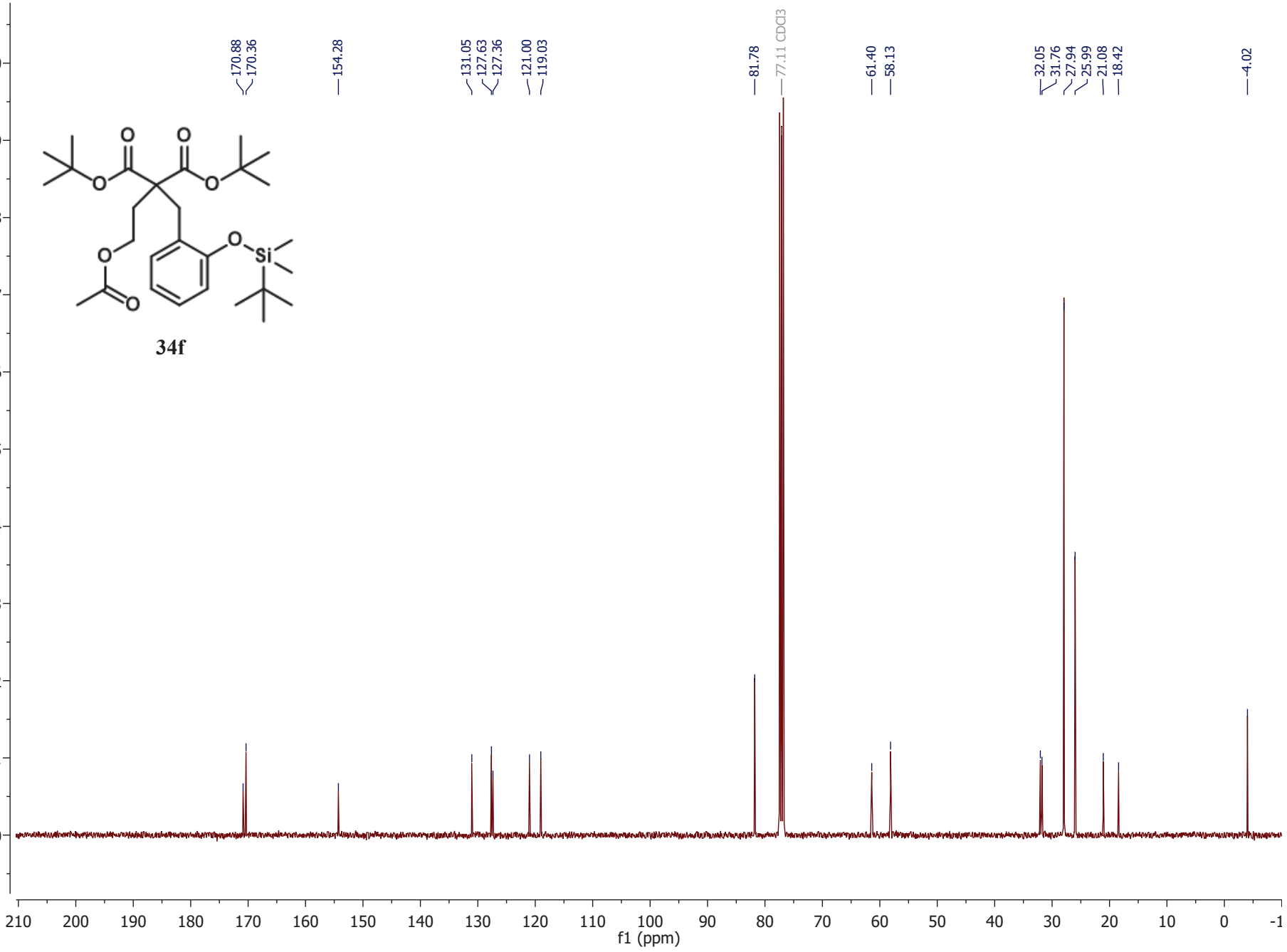
169

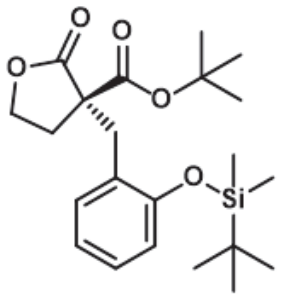

174.33
170.10
145.90
134.22
129.96
128.24
66.86
53.06
45.07
32.08
28.85
21.91
36e
f1 (ppm)

170

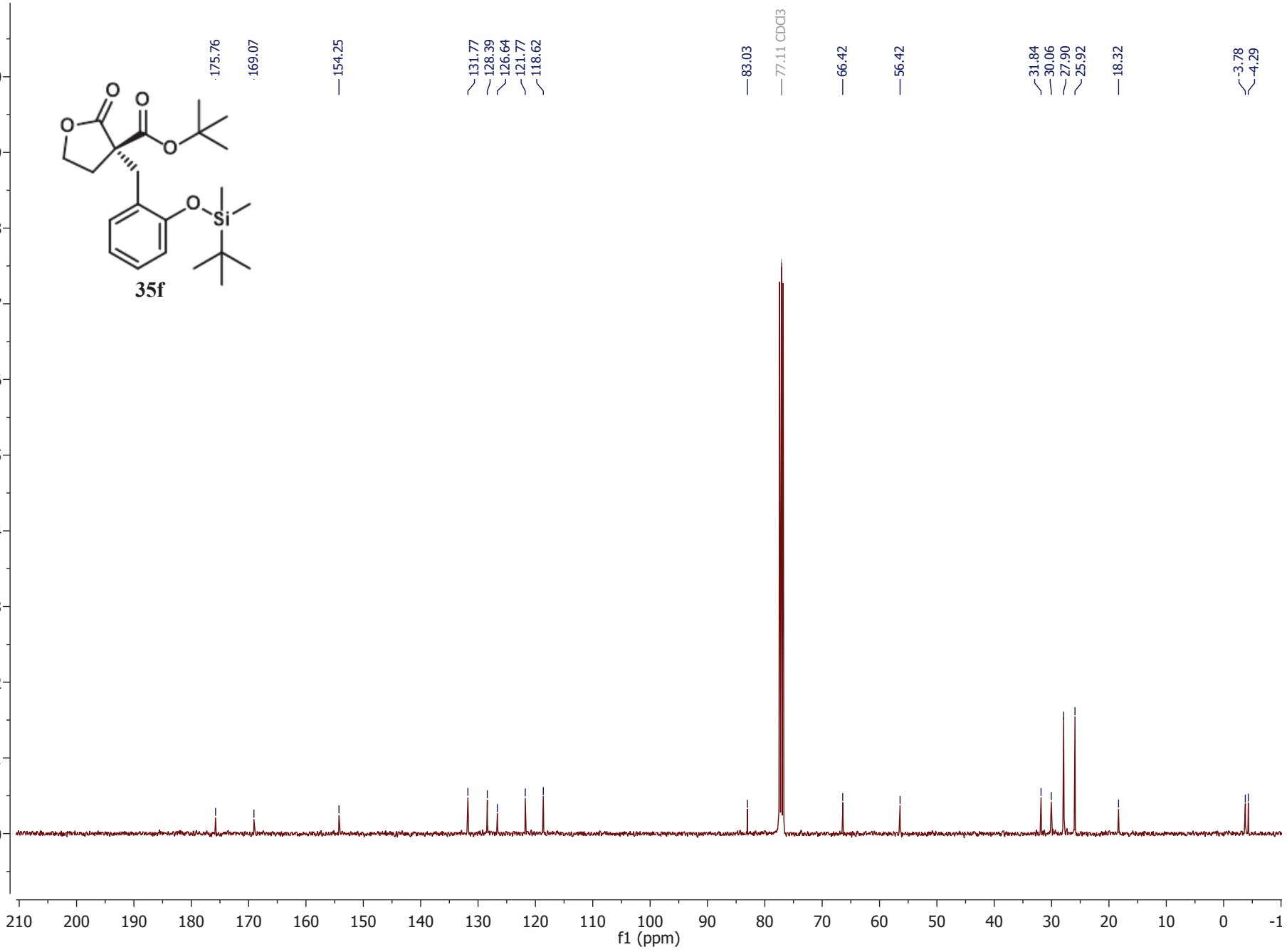


34f

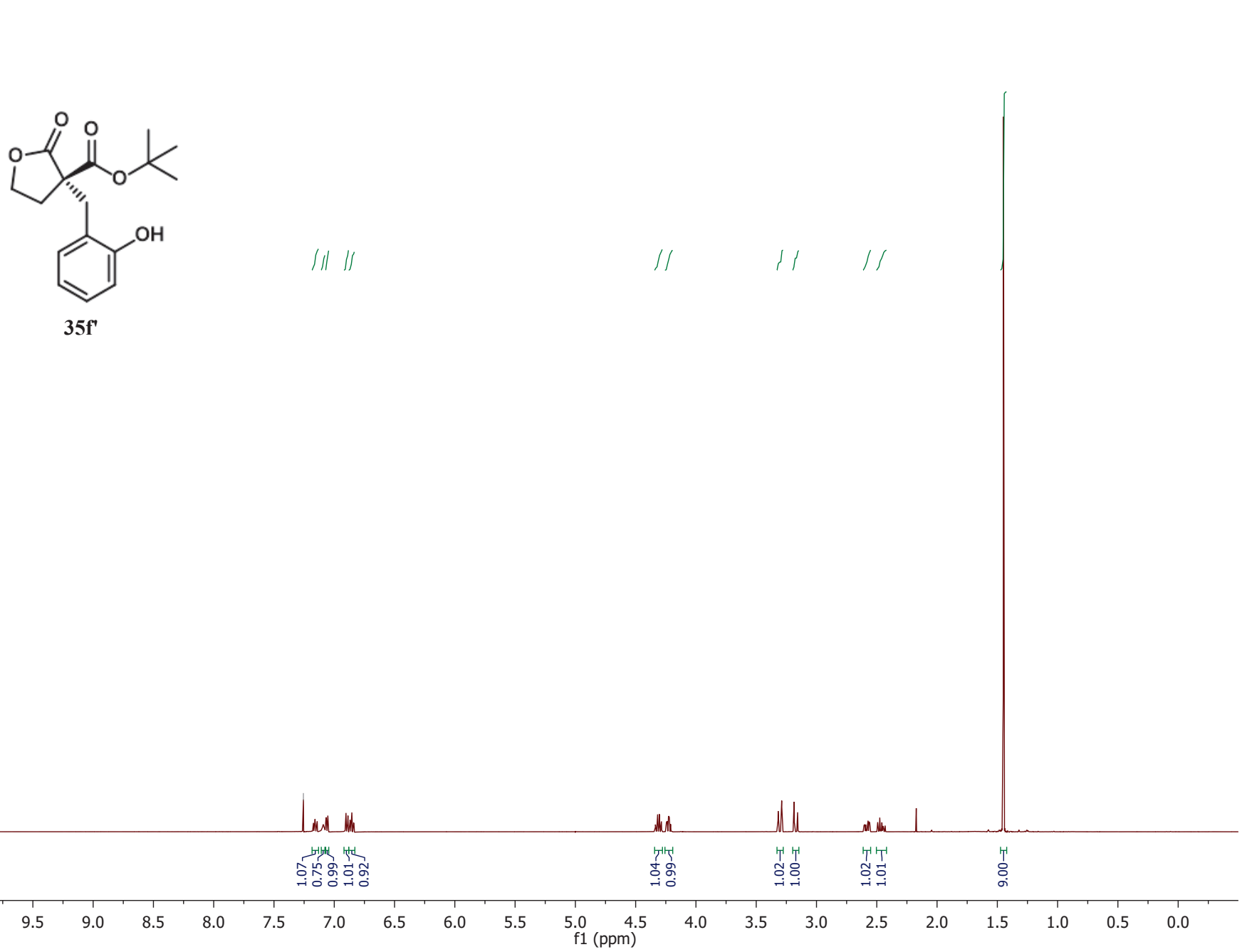

170.88
170.36
154.28
131.05
127.63
127.36
121.00
119.03
81.78
77.11 CDCl3
61.40
58.13
32.05
31.76
27.94
25.99
21.08
18.42
-4.02
34f
f1 (ppm)

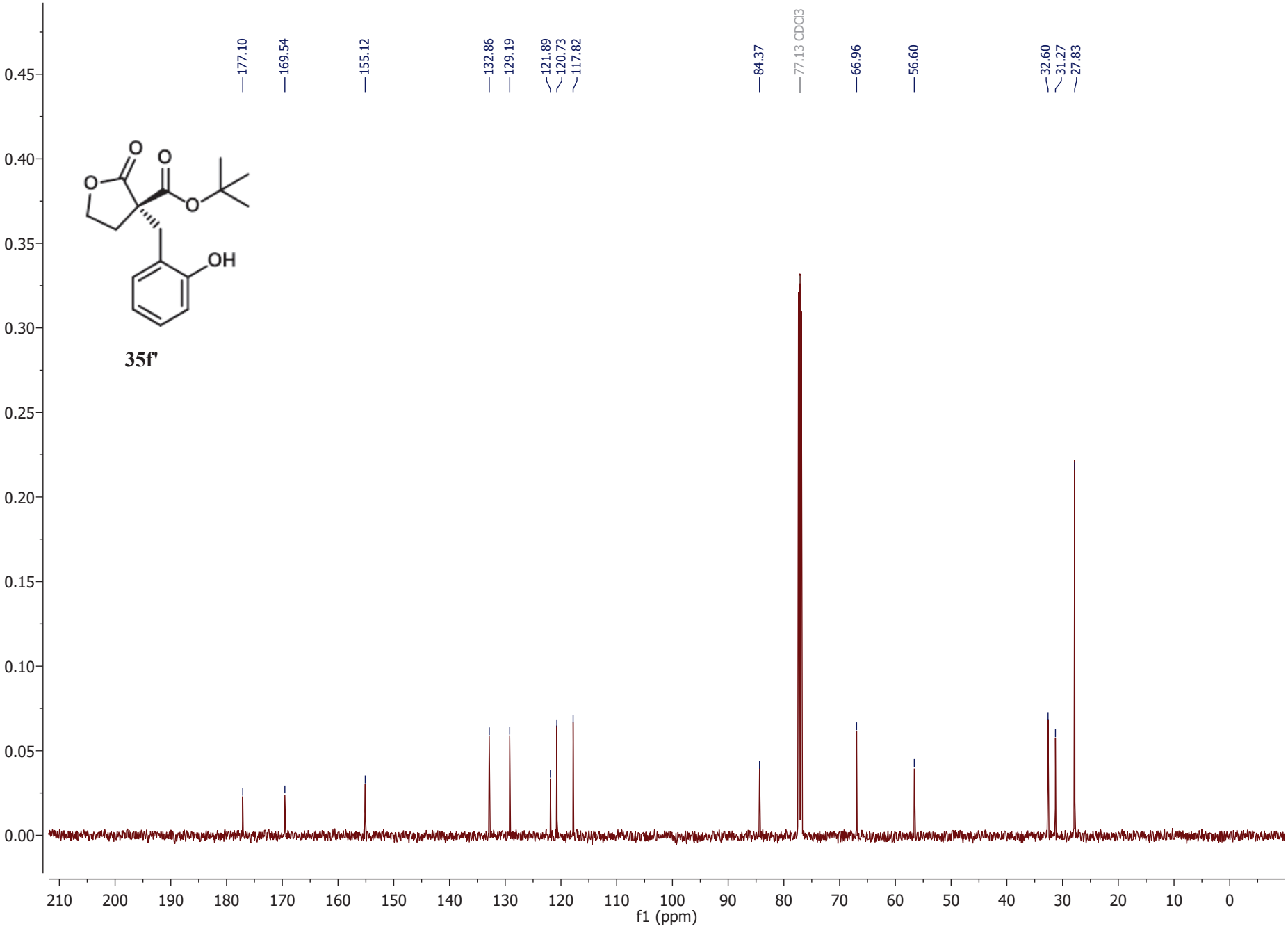


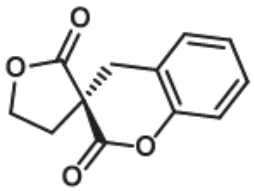
35f


175.76
169.07
154.25
131.77
128.39
126.64
121.77
118.62
83.03
77.11 CDCl3
66.42
56.42
31.84
30.06
27.90
25.92
18.32
-3.78
-4.29
35f
f1 (ppm)

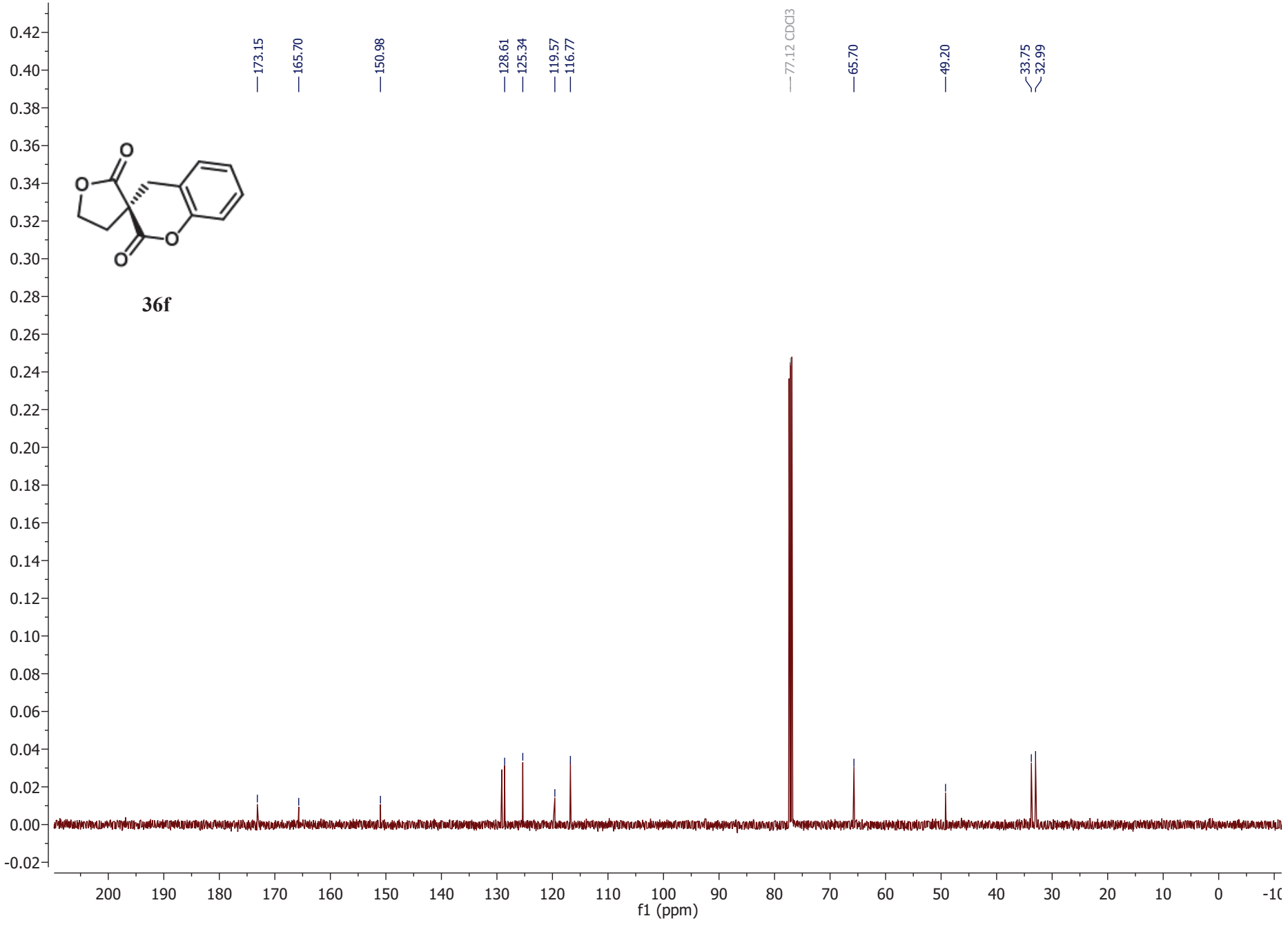
174

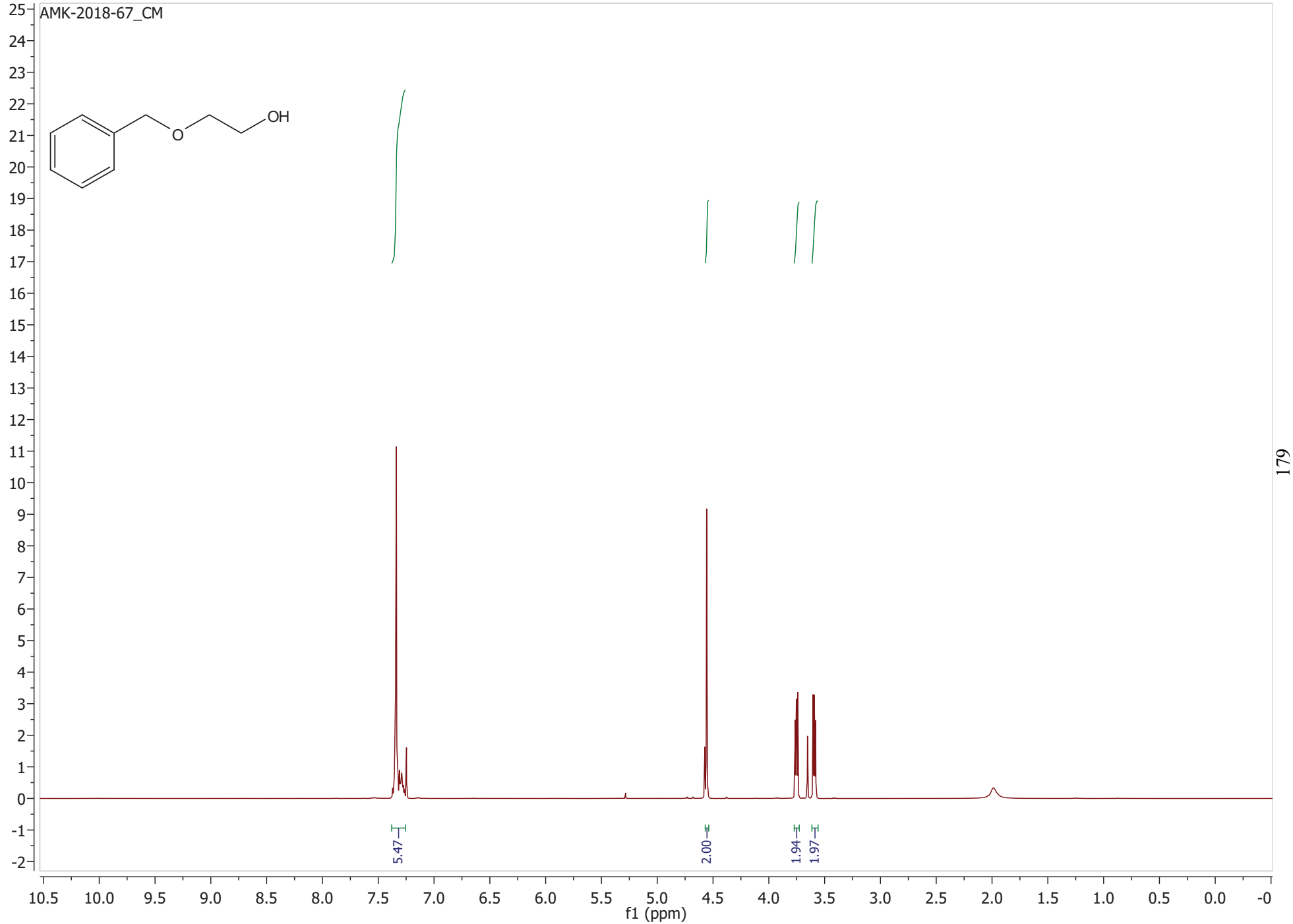

OH
35f'
1.07
0.75
0.99
1.01
0.92
1.04
0.99
1.02
1.00
1.02
1.01
9.00
f1 (ppm)

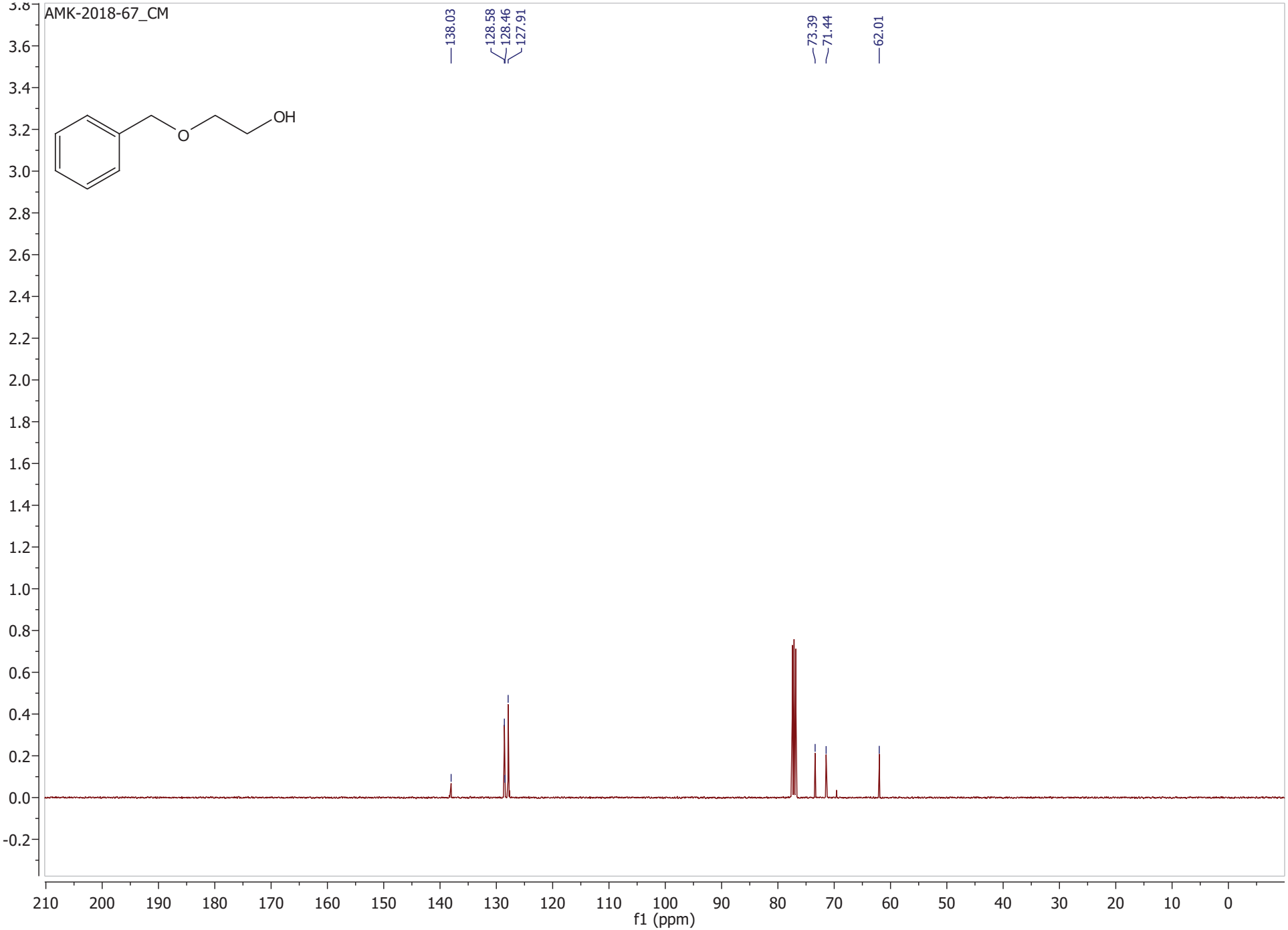

177.10
169.54
155.12
132.86
129.19
121.89
120.73
117.82
84.37
77.13 CDCl3
66.96
56.60
32.60
31.27
27.83
OH
35f'
f1 (ppm)

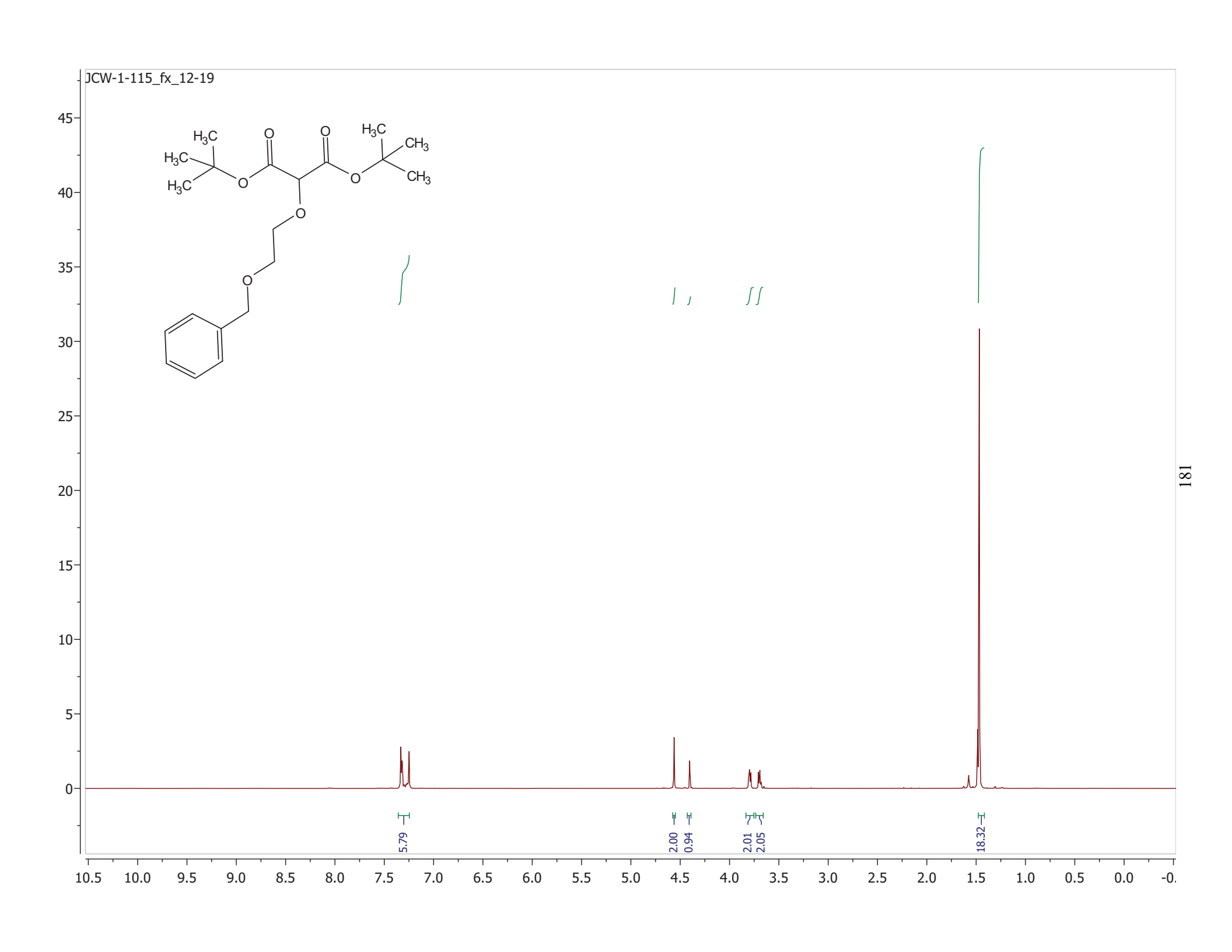


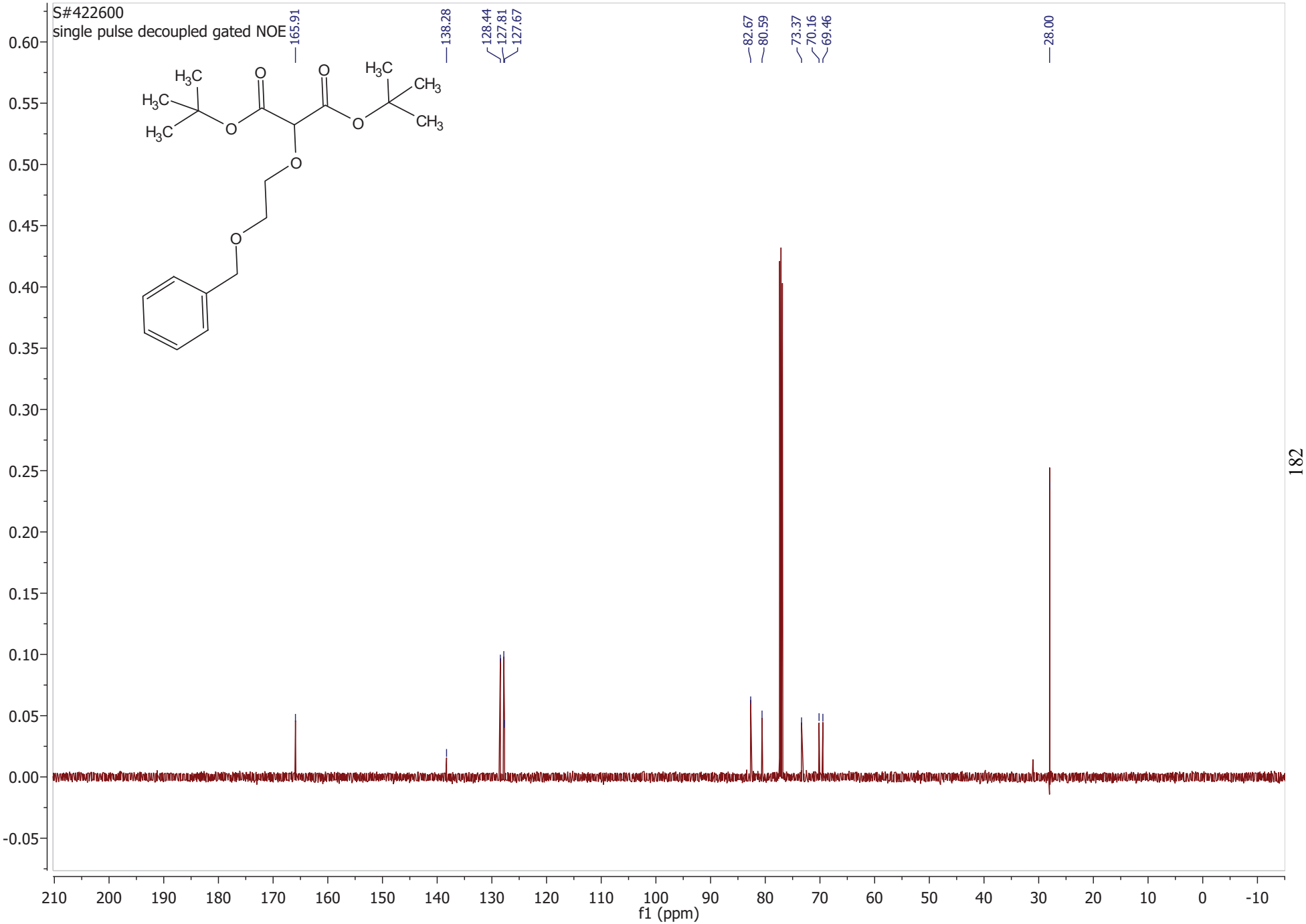
36f

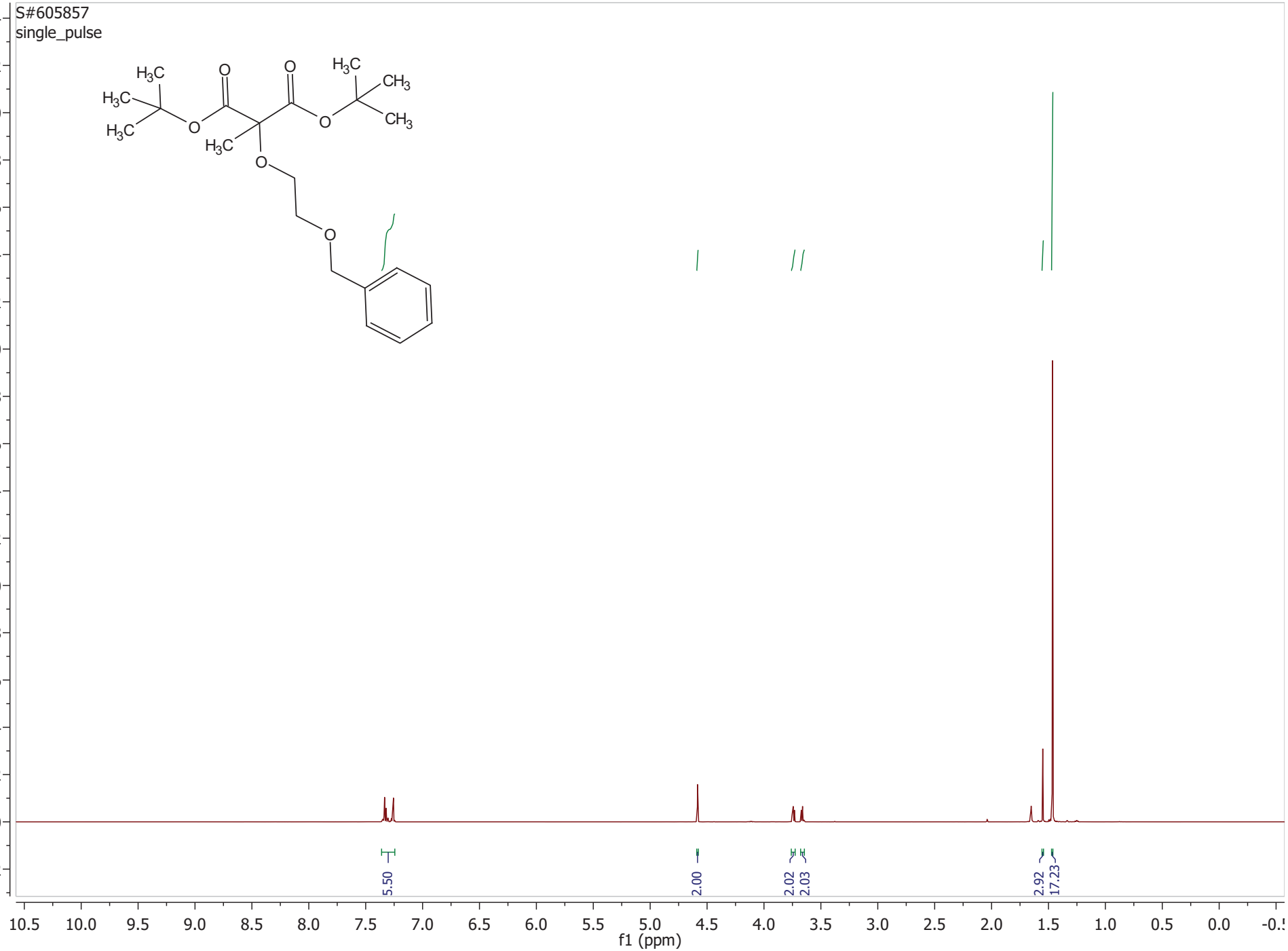

173.15
165.70
150.98
128.61
125.34
119.57
116.77
77.12 CDCl3
65.70
49.20
33.75
32.99
36f
f1 (ppm)

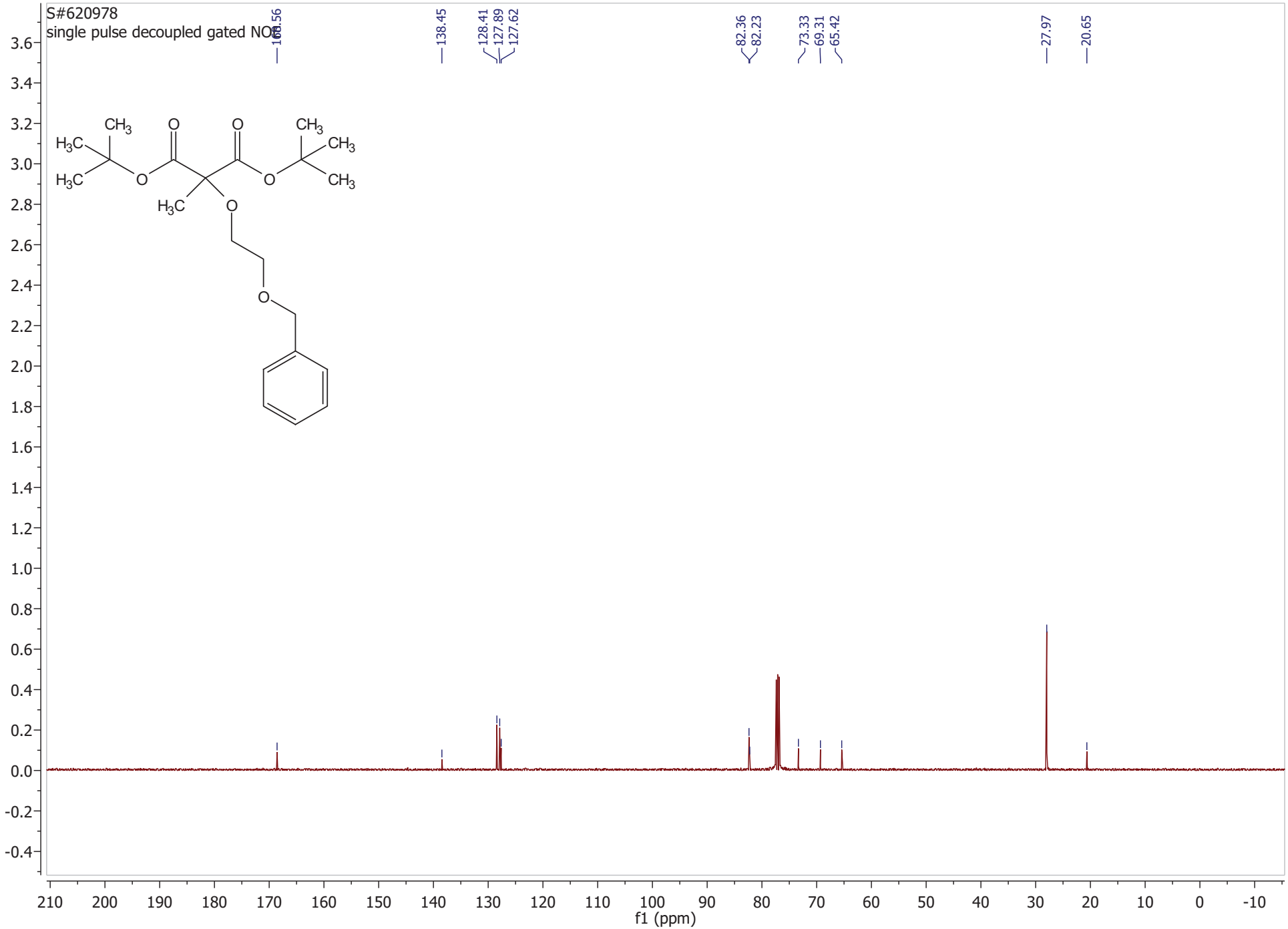

AMK-2018-67_CM
OH
O
5.47
2.00
1.94
1.97
f1 (ppm)

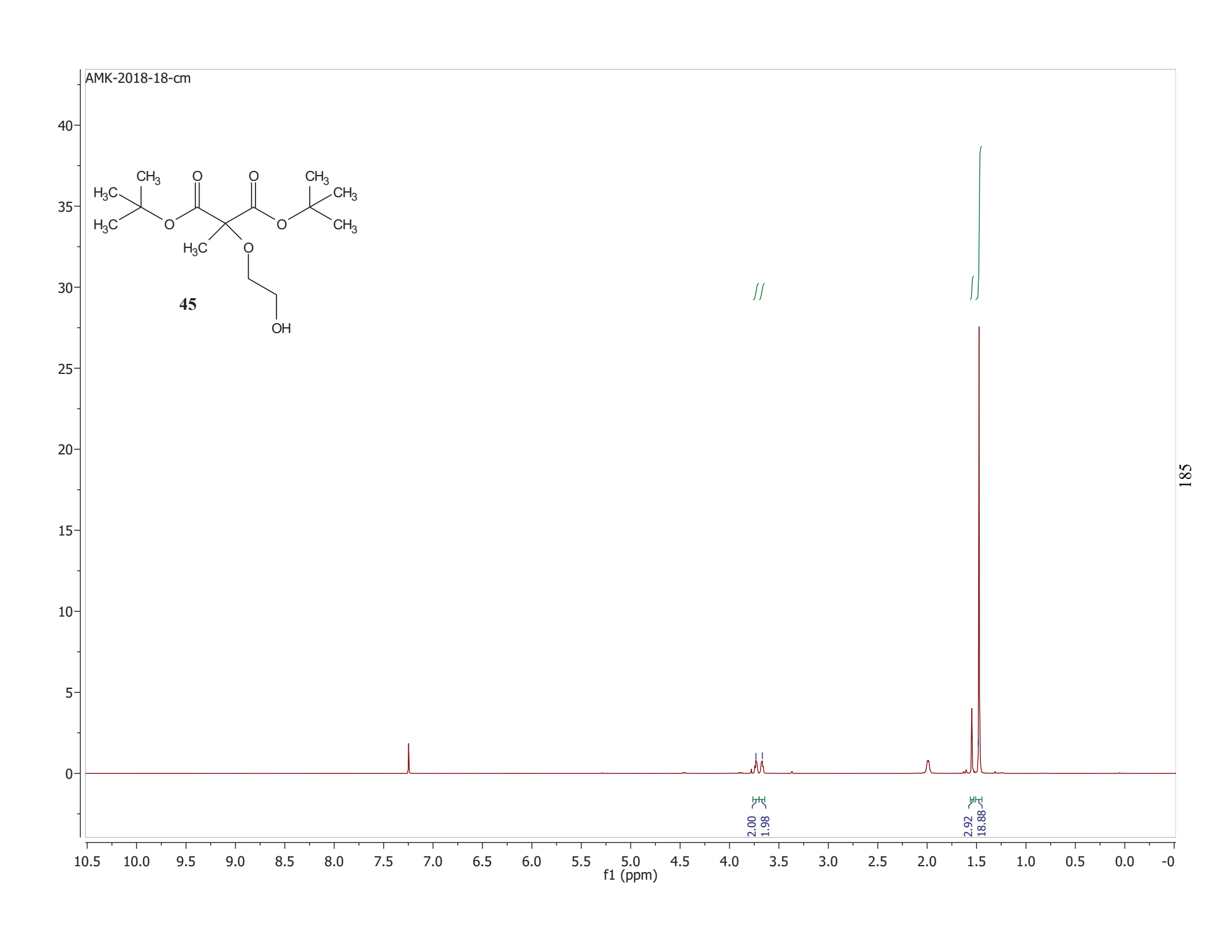

AMK-2018-67_CM
138.03
128.58
128.46
127.91
73.39
71.44
62.01
OH
O
f1 (ppm)
180

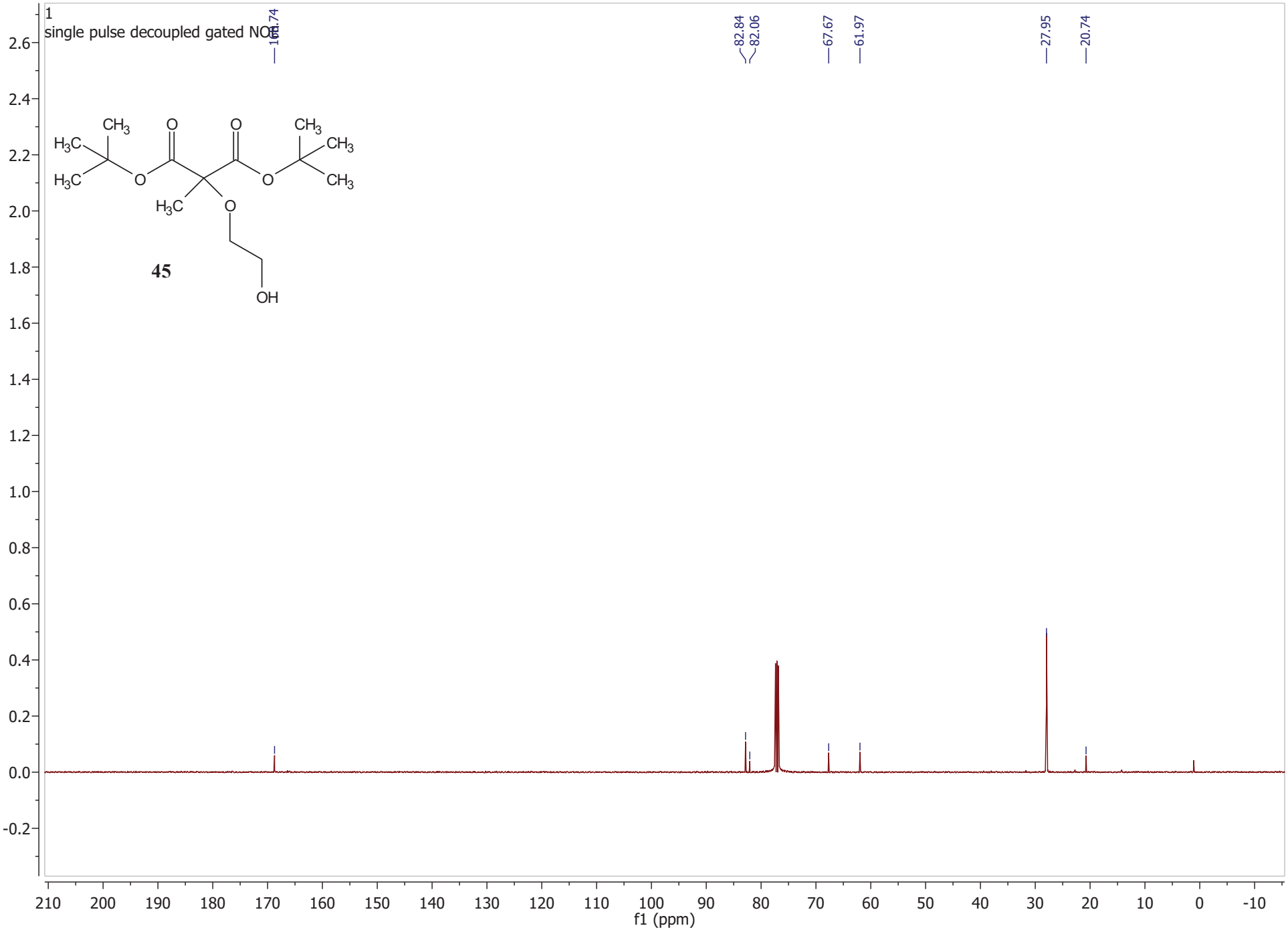

JCW-1-115_fx_12-19
181
5.79
2.00
0.94
2.01
2.05
18.32


S#422600
single pulse decoupled gated NOE
165.91
138.28
128.44
127.81
127.67
82.67
80.59
73.37
70.16
69.46
28.00
H3C
H3C
H3C
O
O
O
O
O
O
CH3
CH3
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
182

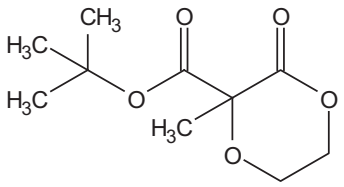

S#605857
single_pulse
H3C
H3C
H3C
O
O
O
O
H3C
CH3
CH3
H3C
O
O
5.50
2.00
2.02
2.03
2.92
17.23
f1 (ppm)
183


S#620978
single pulse decoupled gated NOE
168.56
138.45
128.41
127.89
127.62
82.36
82.23
73.33
69.31
65.42
27.97
20.65
CH3
H3C
H3C
O
O
O
CH3
CH3
CH3
H3C
O
O
184
f1 (ppm)


AMK-2018-18-cm
45
OH
2.00
1.98
2.92
18.88
f1 (ppm)
185


1
single pulse decoupled gated NOE
168.74
82.84
82.06
67.67
61.97
27.95
20.74
45
OH
f1 (ppm)

S#412938
single_pulse

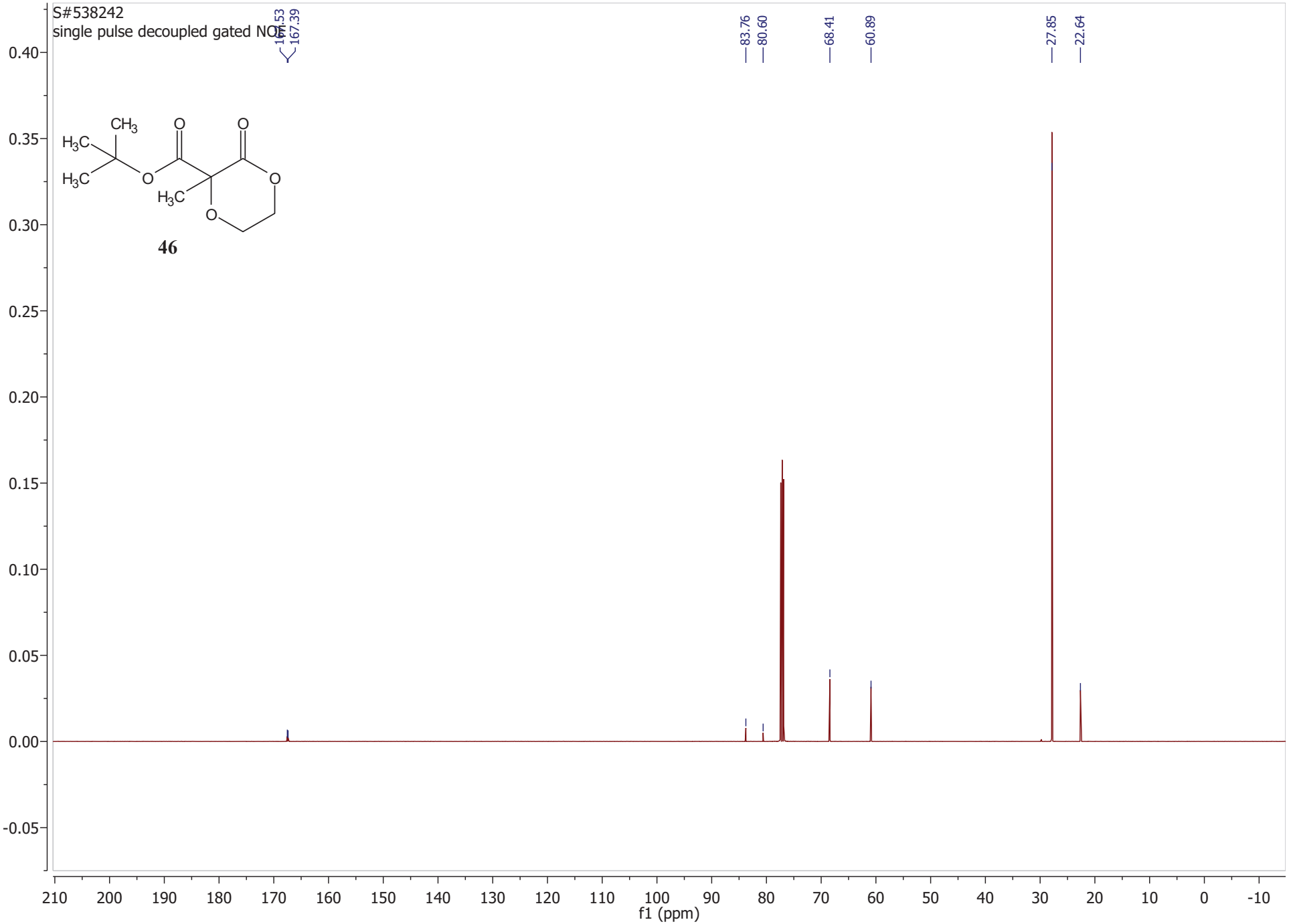


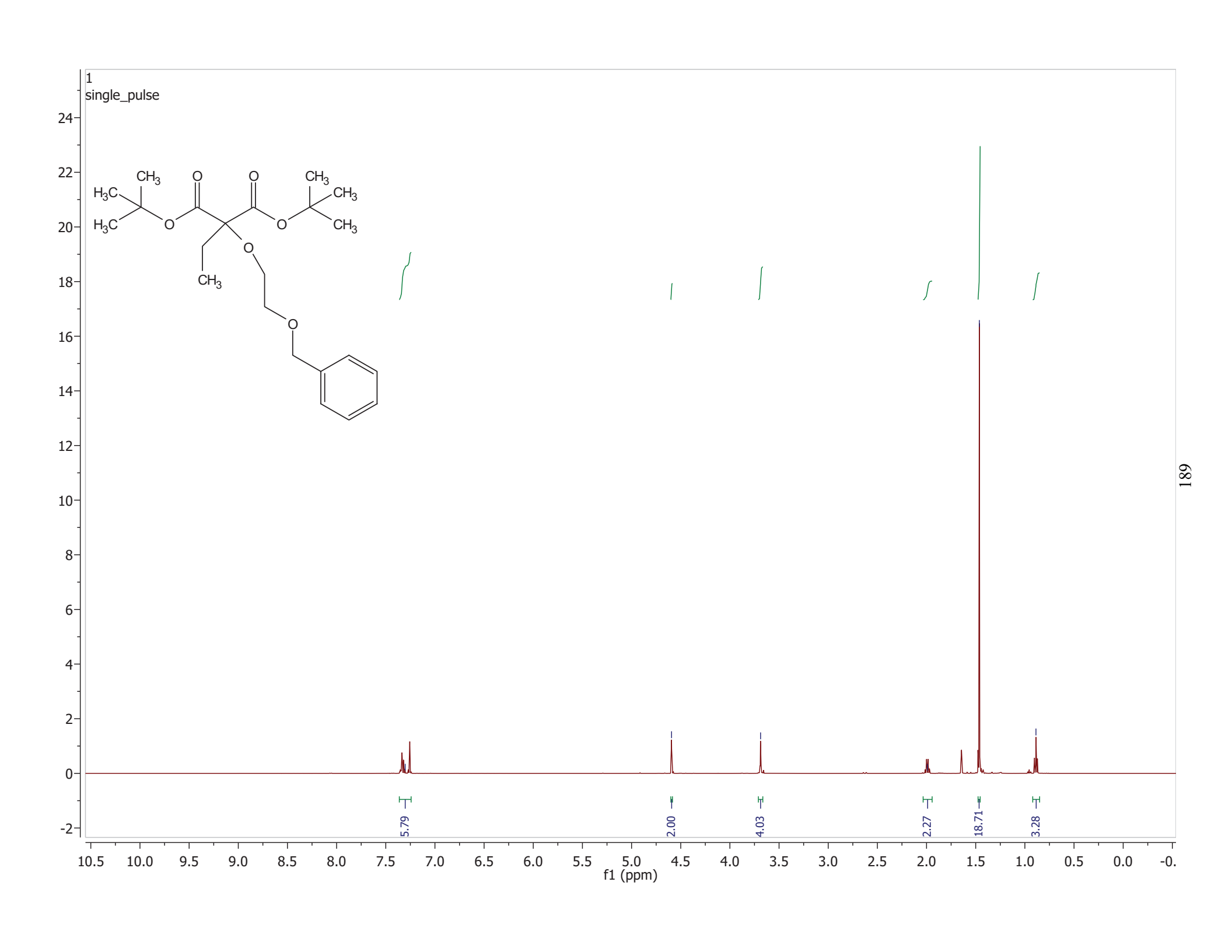
46

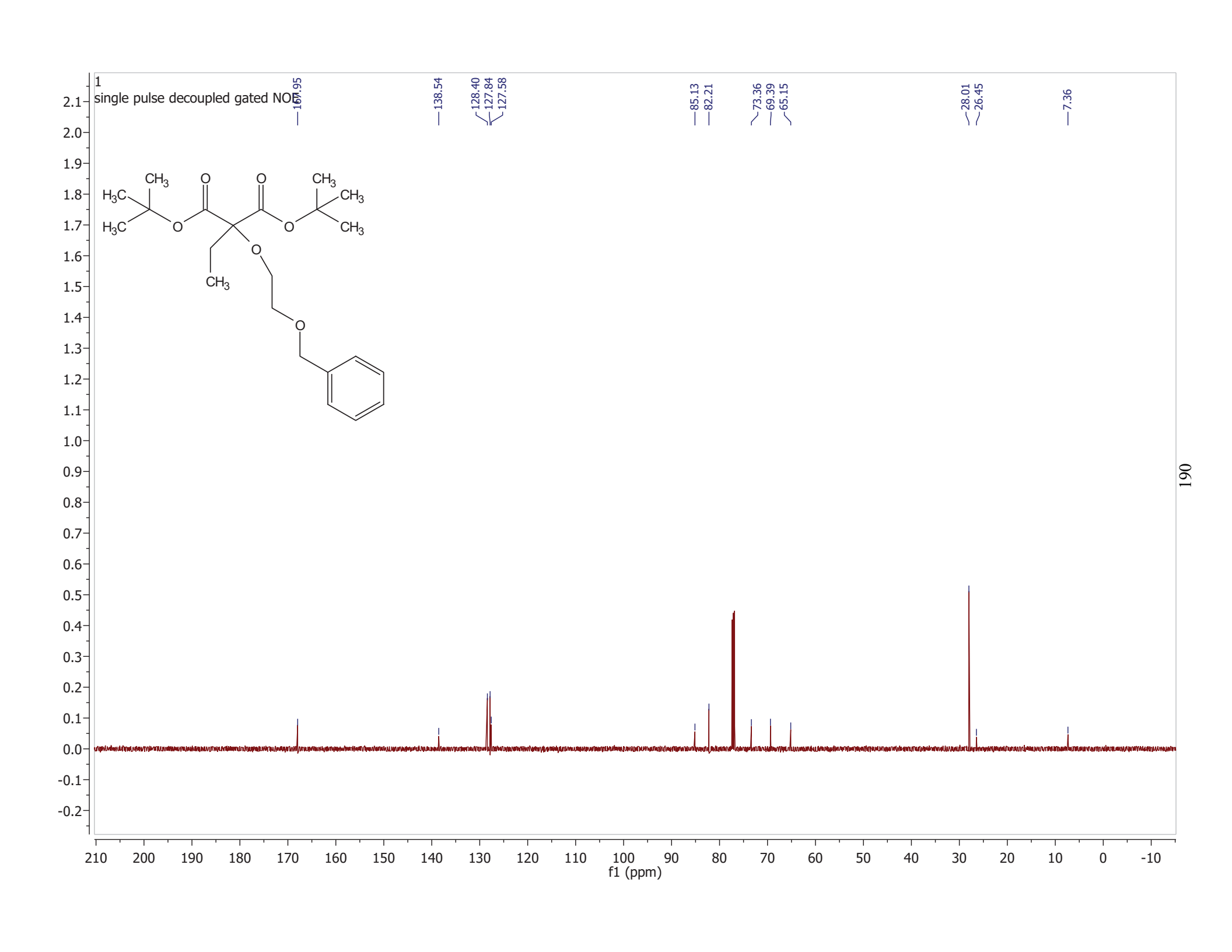
1.00
1.09
1.07
1.05
3.13
8.92

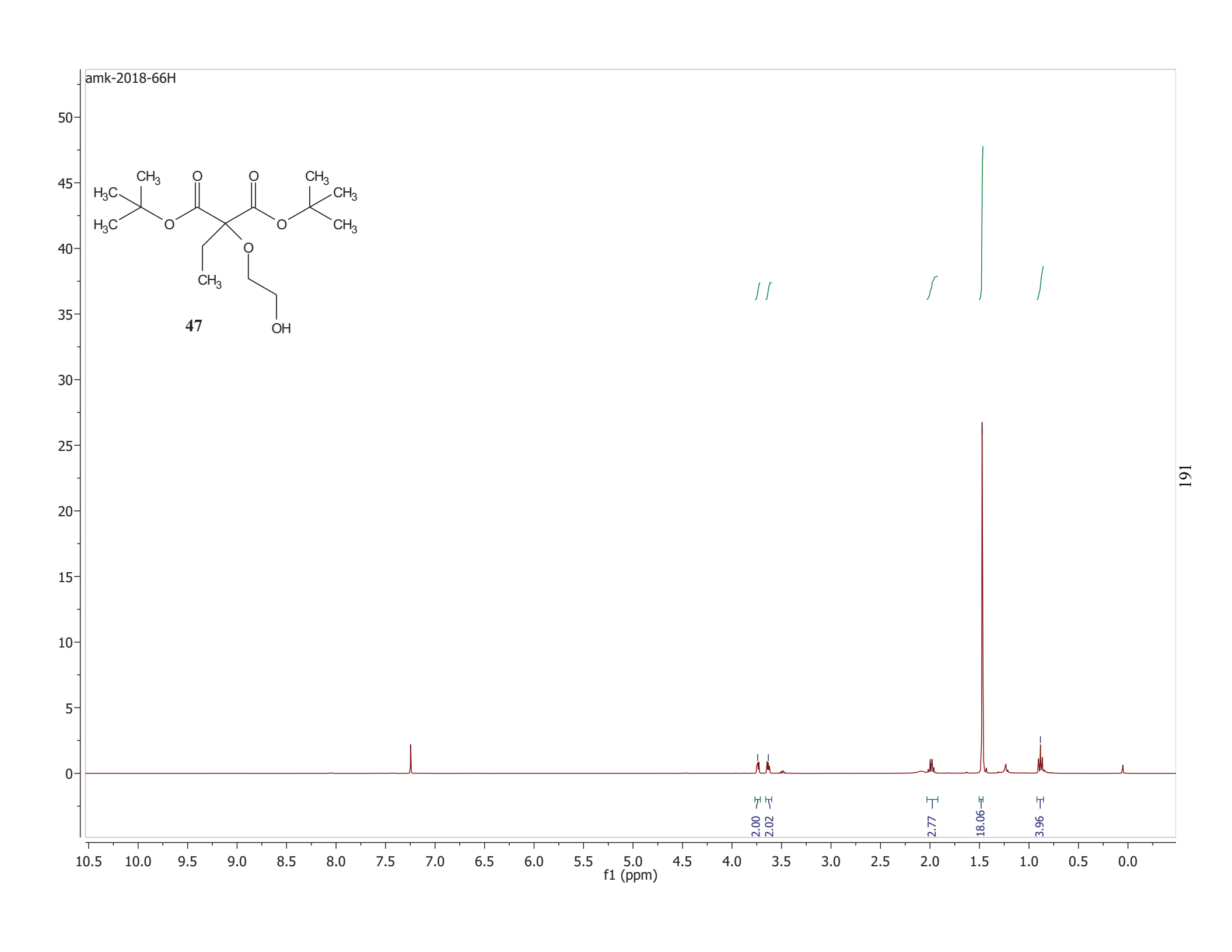
f1 (ppm)

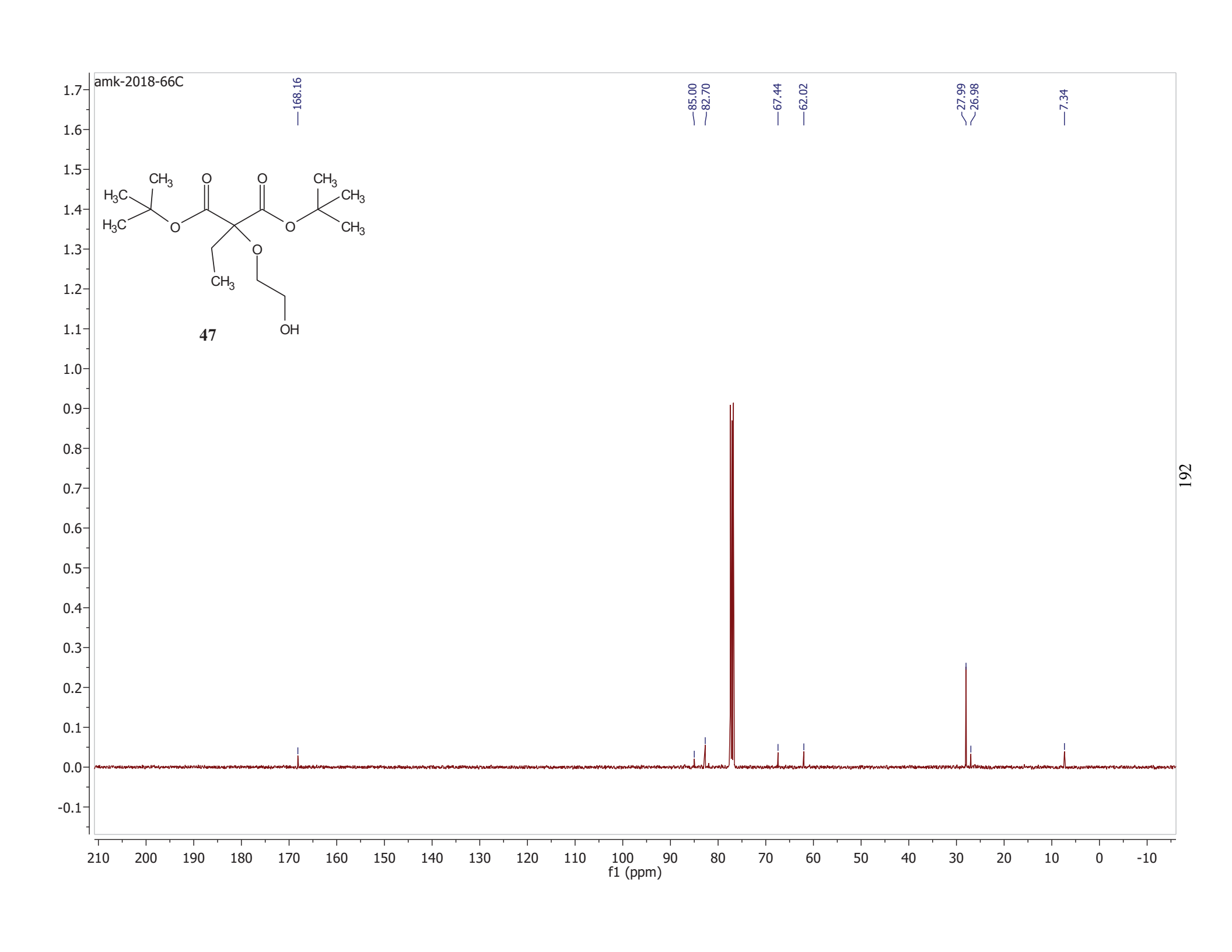
187

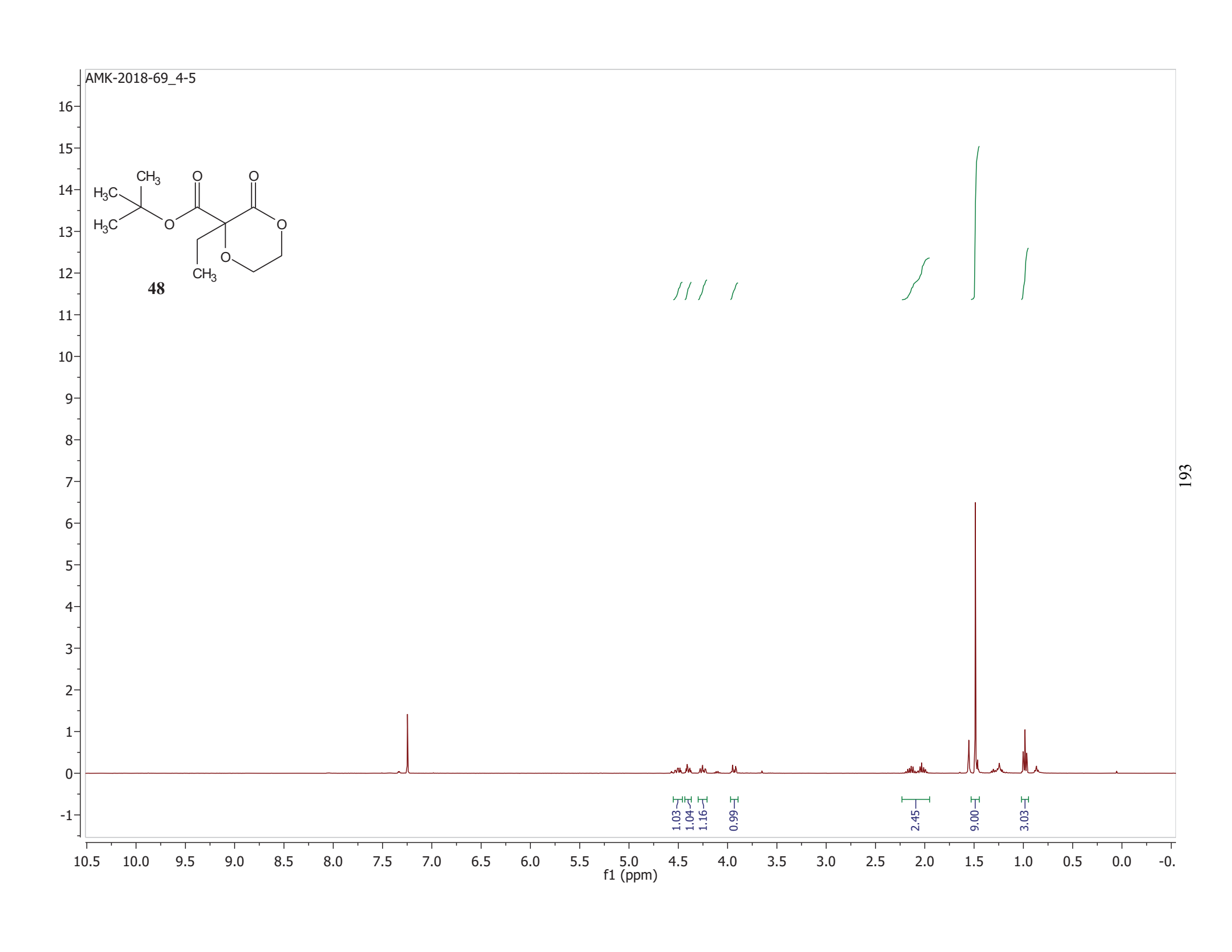

S#538242
single pulse decoupled gated NOE
167.53
167.39
83.76
80.60
68.41
60.89
27.85
22.64
CH3
H3C
H3C
H3C
O
O
O
O
O
46
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

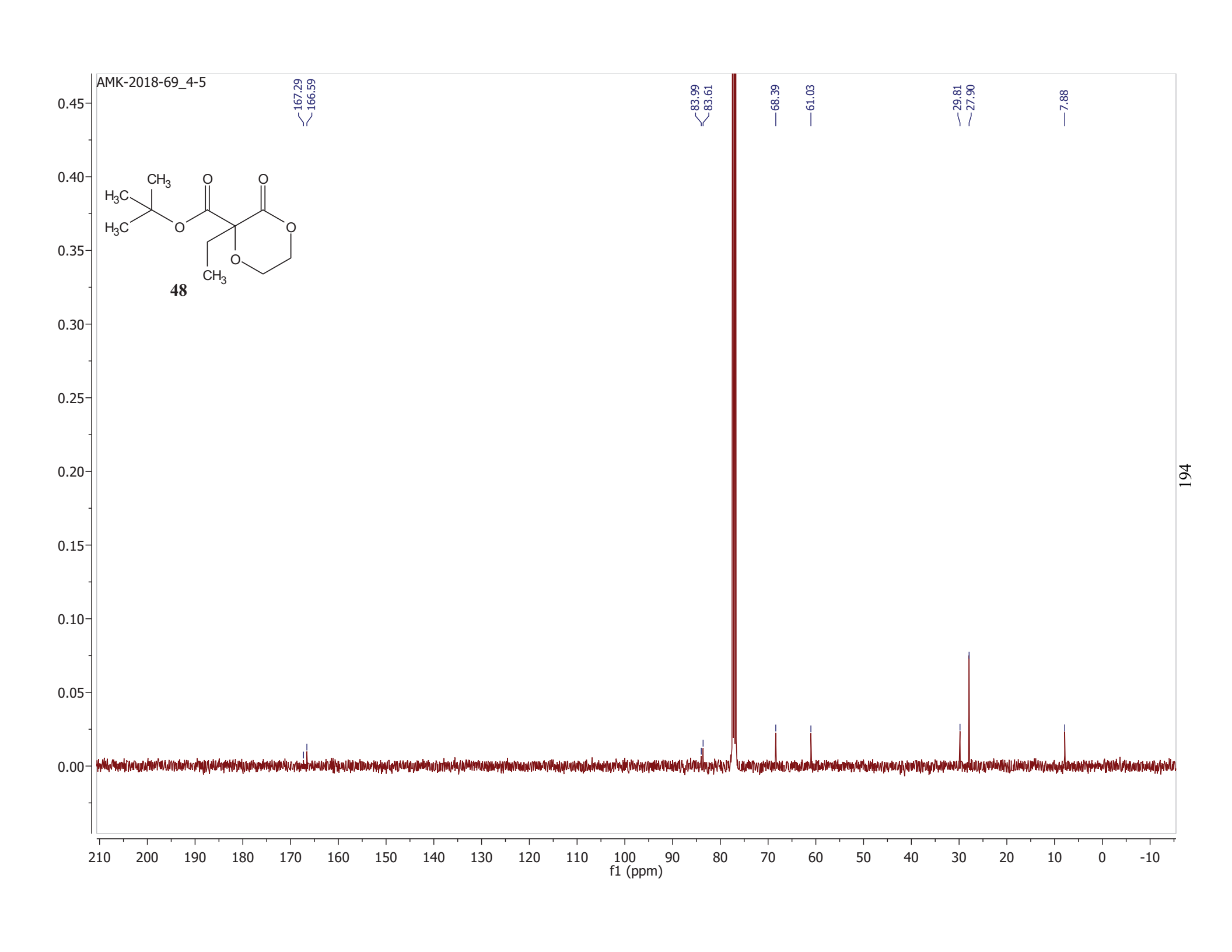

1
single_pulse
CH3
H3C
H3C
O
O
O
O
CH3
CH3
CH3
O
CH3
O
5.79
2.00
4.03
2.27
18.71
3.28
f1 (ppm)
189

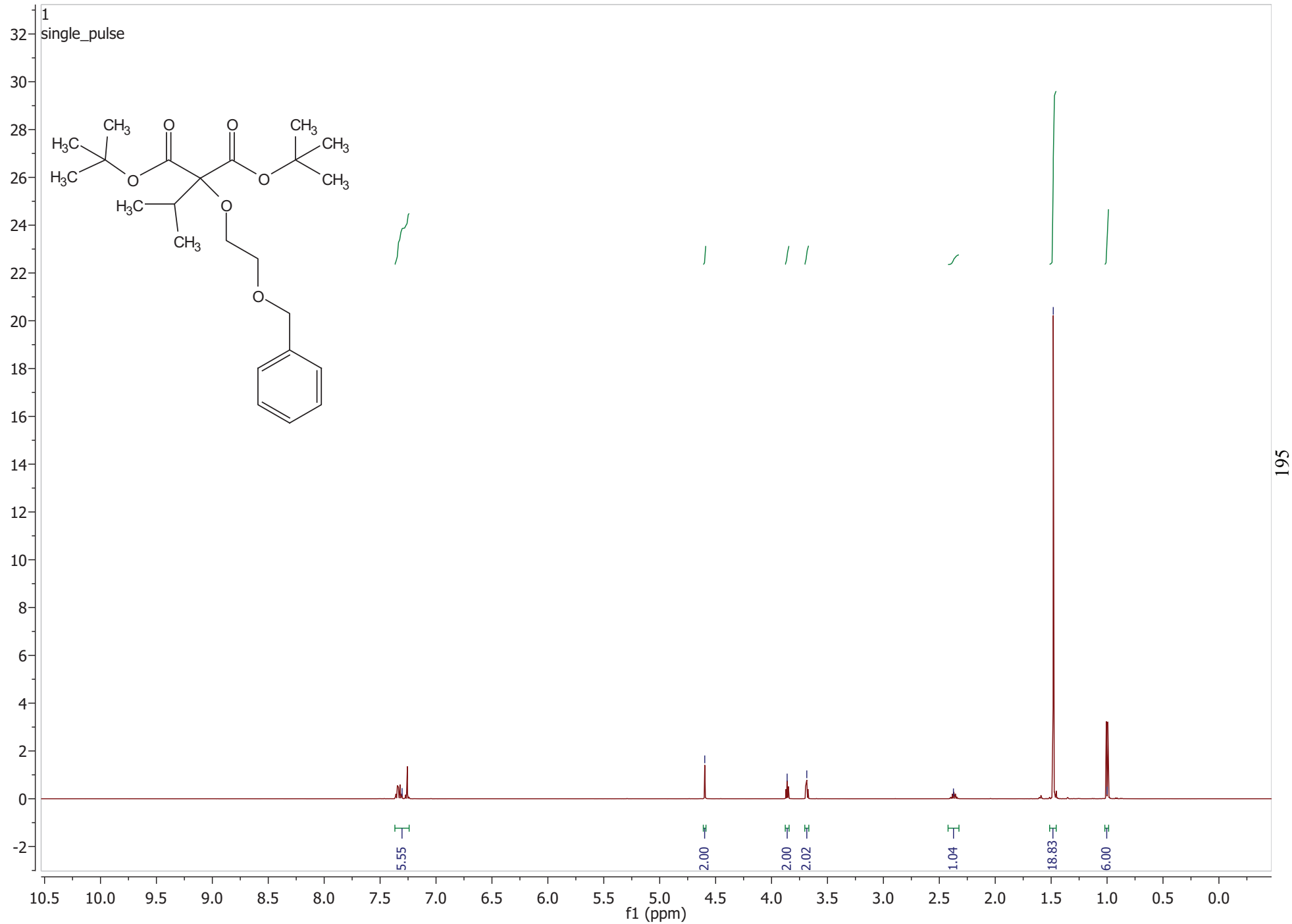

1
single pulse decoupled gated NOE
167.95
138.54
128.40
127.84
127.58
85.13
82.21
73.36
69.39
65.15
28.01
26.45
7.36
CH3
O
O
CH3
H3C
CH3
H3C
O
O
CH3
CH3
O
CH3
O
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
190

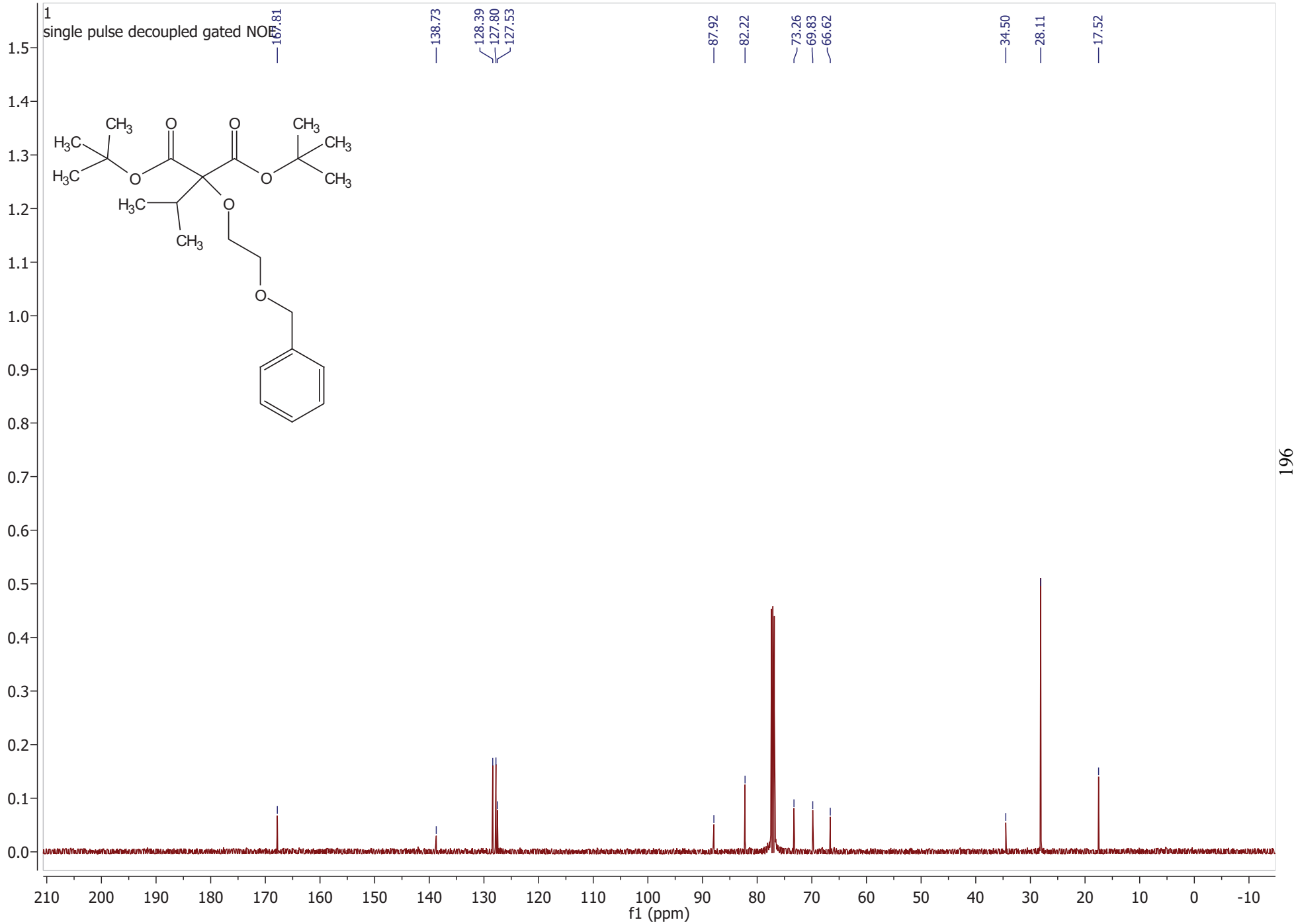

amk-2018-66H
47
OH
2.00
2.02
2.77
18.06
3.96
f1 (ppm)

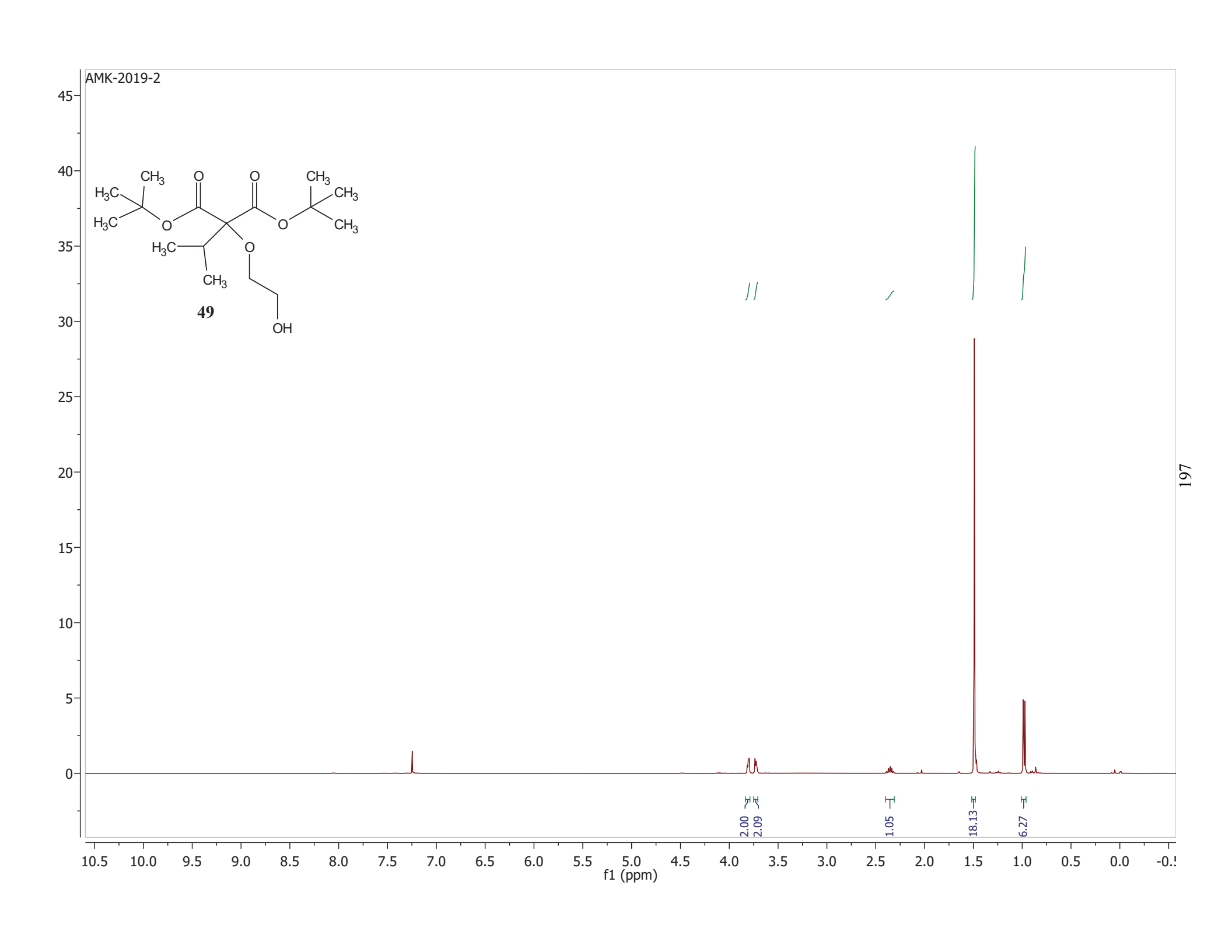

amk-2018-66C
168.16
85.00
82.70
67.44
62.02
27.99
26.98
7.34
47
192
f1 (ppm)

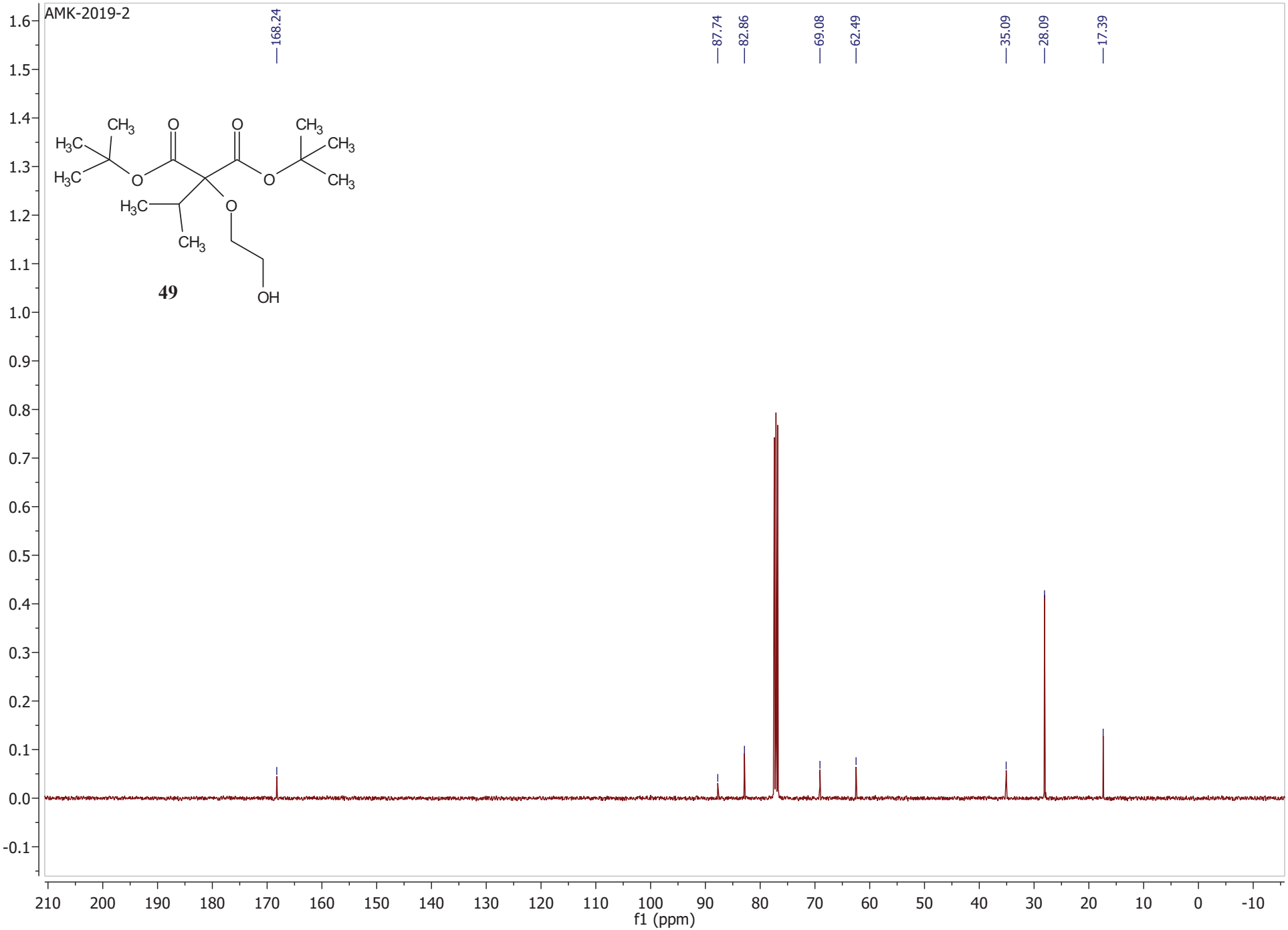

AMK-2018-69_4-5
48
f1 (ppm)
1.03
1.04
1.16
0.99
2.45
9.00
3.03

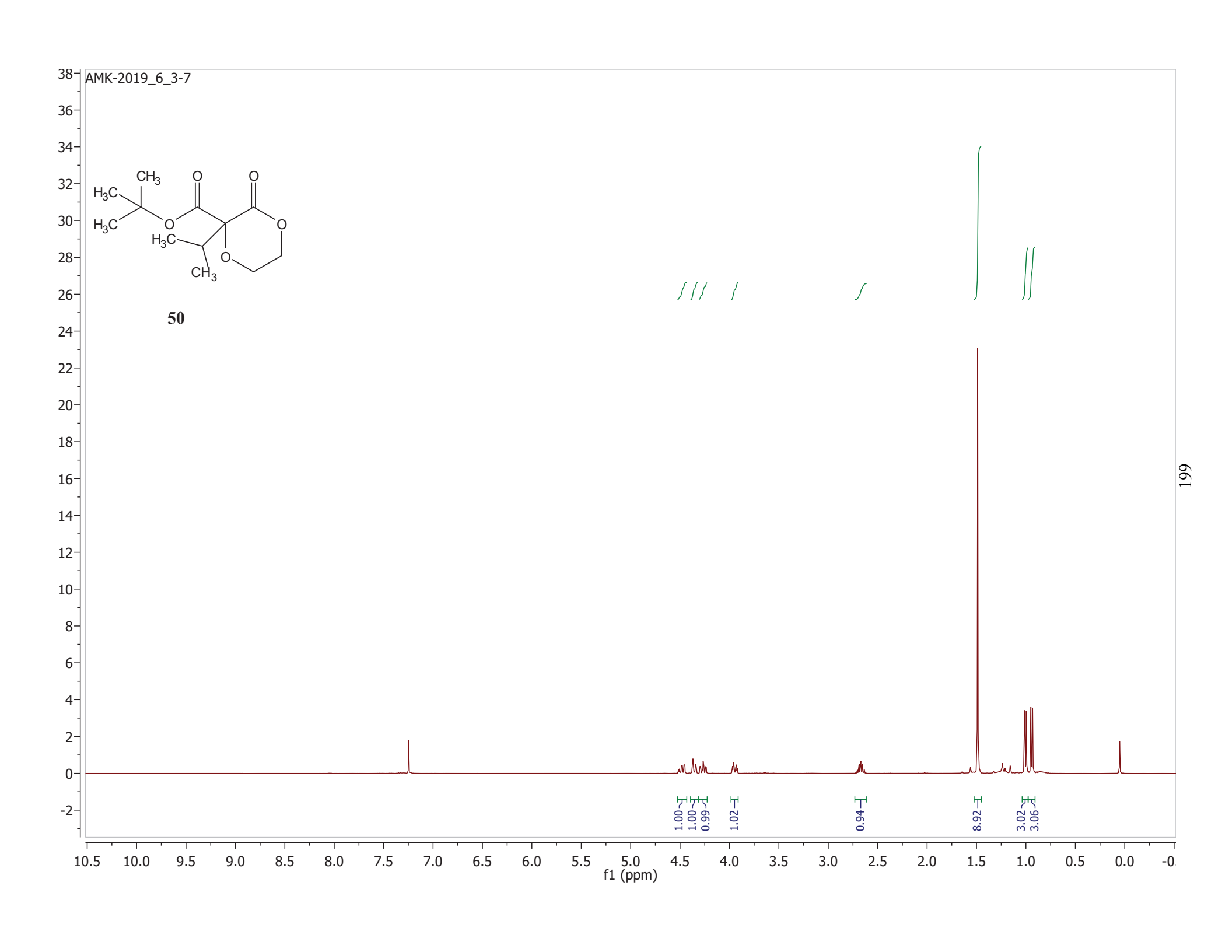

AMK-2018-69_4-5
167.29
166.59
83.99
83.61
68.39
61.03
29.81
27.90
7.88
CH3
H3C
H3C
O
O
O
O
O
CH3
48
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
194

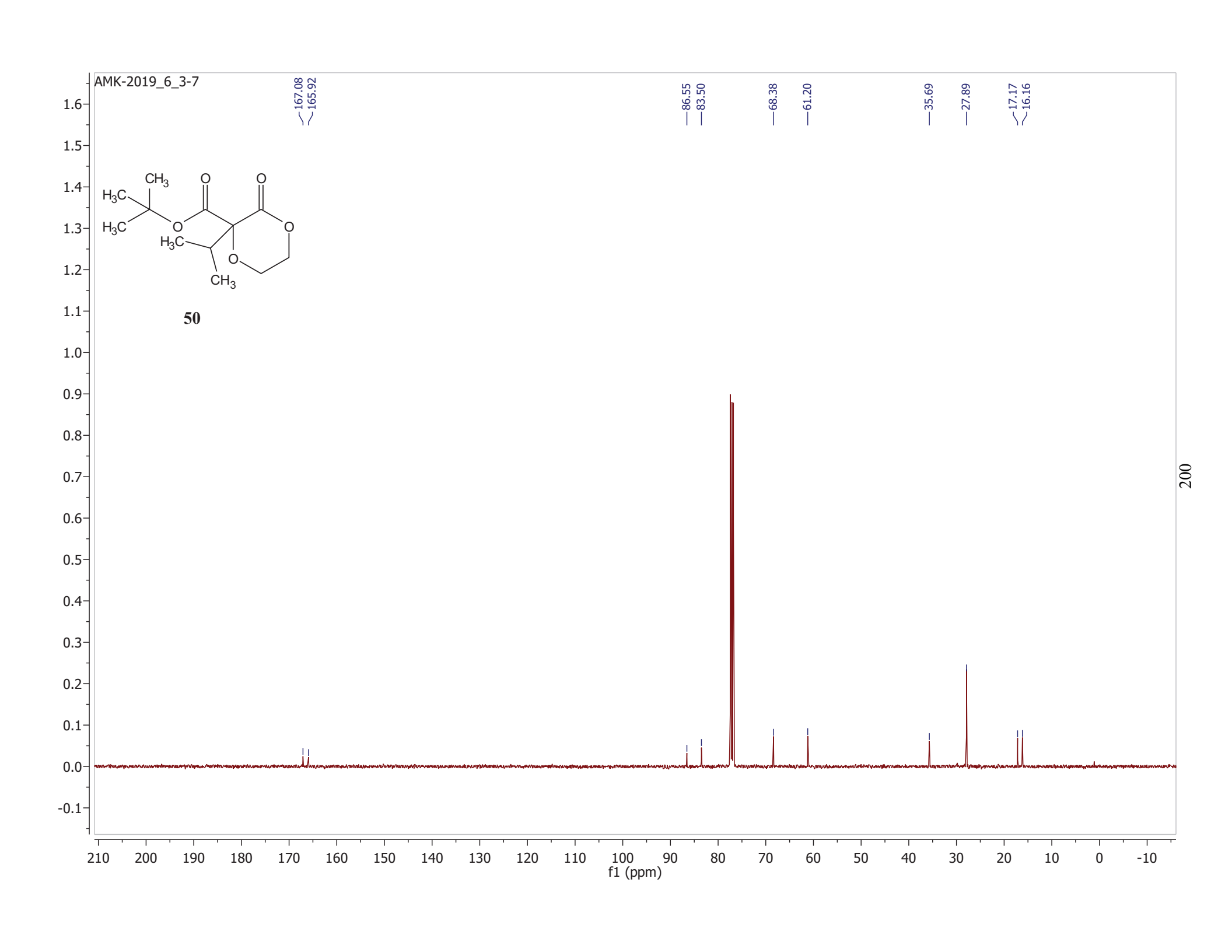

1
single_pulse
CH3
H3C
H3C
O
O
O
CH3
CH3
CH3
H3C
CH3
O
O
5.55
2.00
2.00
2.02
1.04
18.83
6.00
f1 (ppm)
195

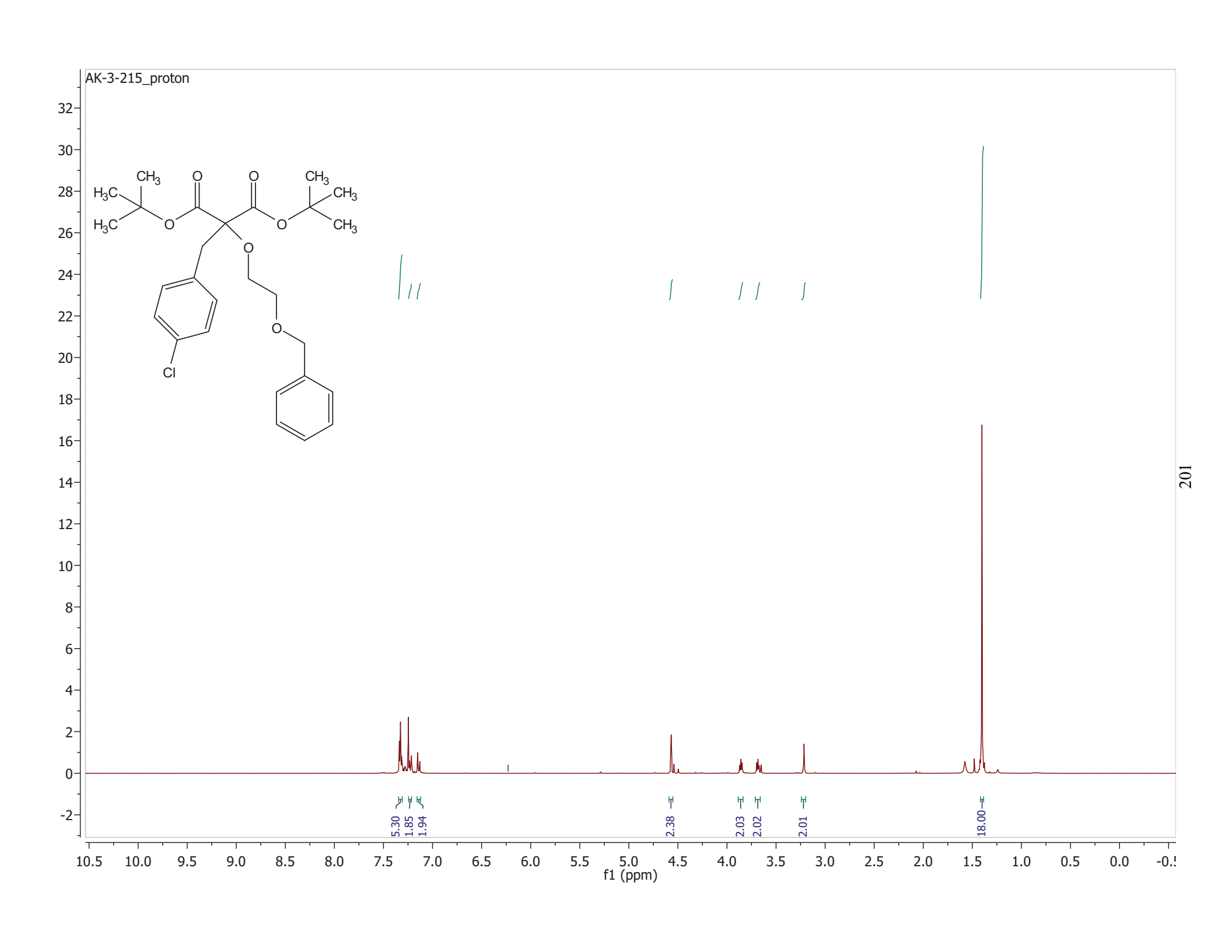

1
single pulse decoupled gated NOE
167.81
138.73
128.39
127.80
127.53
87.92
82.22
73.26
69.83
66.62
34.50
28.11
17.52
f1 (ppm)

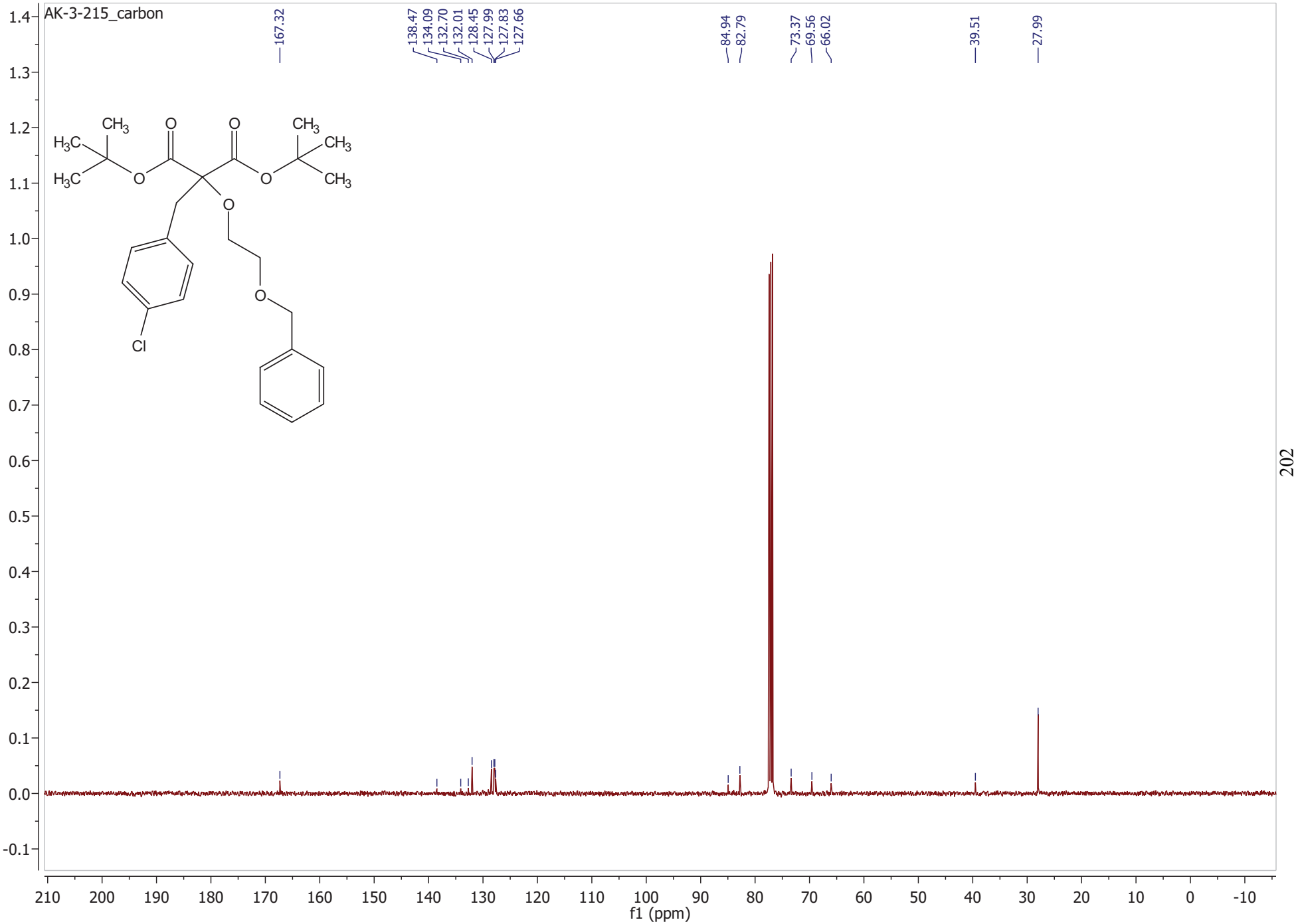

AMK-2019-2
CH3
H3C
H3C
O
O
O
CH3
CH3
CH3
H3C
O
CH3
OH
49
2.00
2.09
1.05
18.13
6.27
f1 (ppm)
197

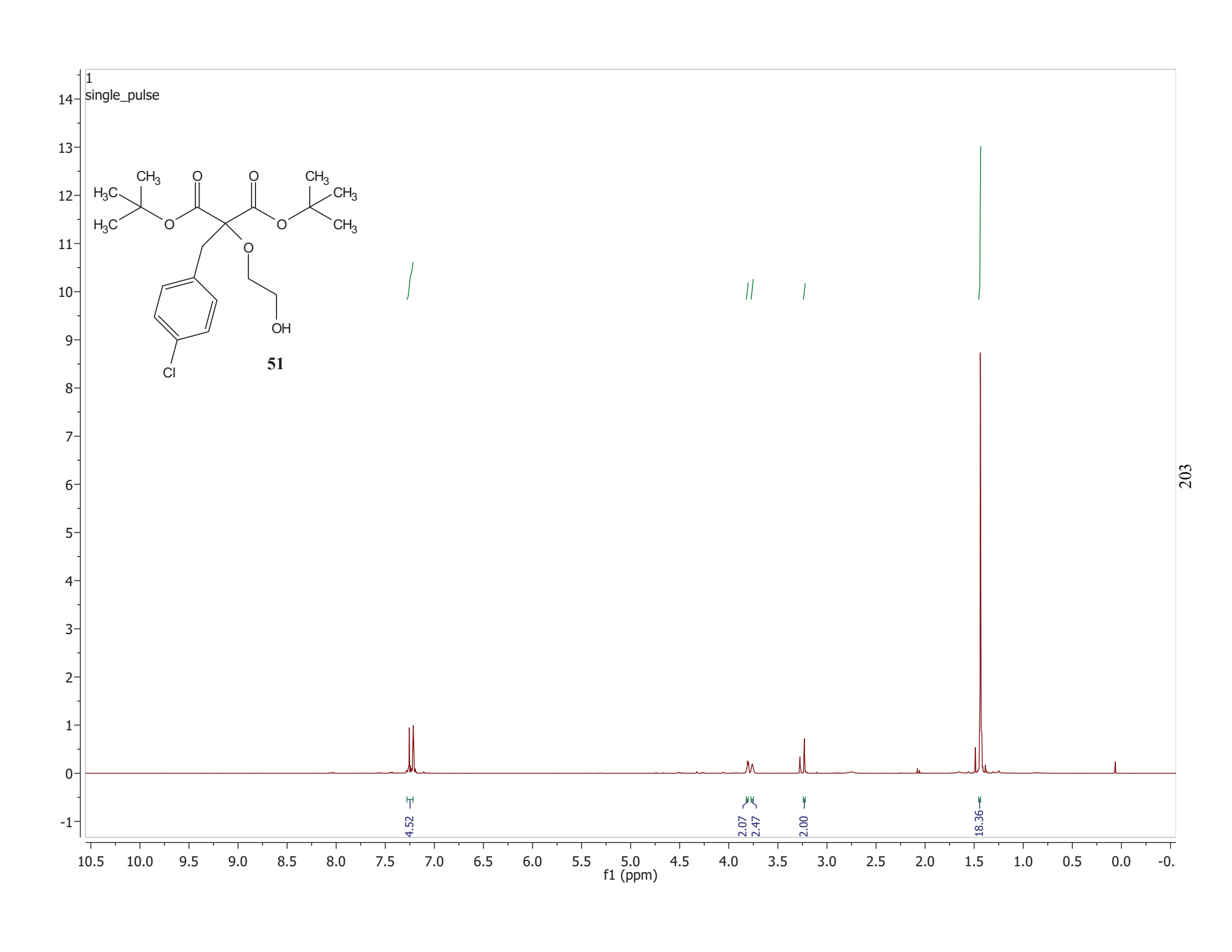

AMK-2019-2
168.24
87.74
82.86
69.08
62.49
35.09
28.09
17.39
49
f1 (ppm)

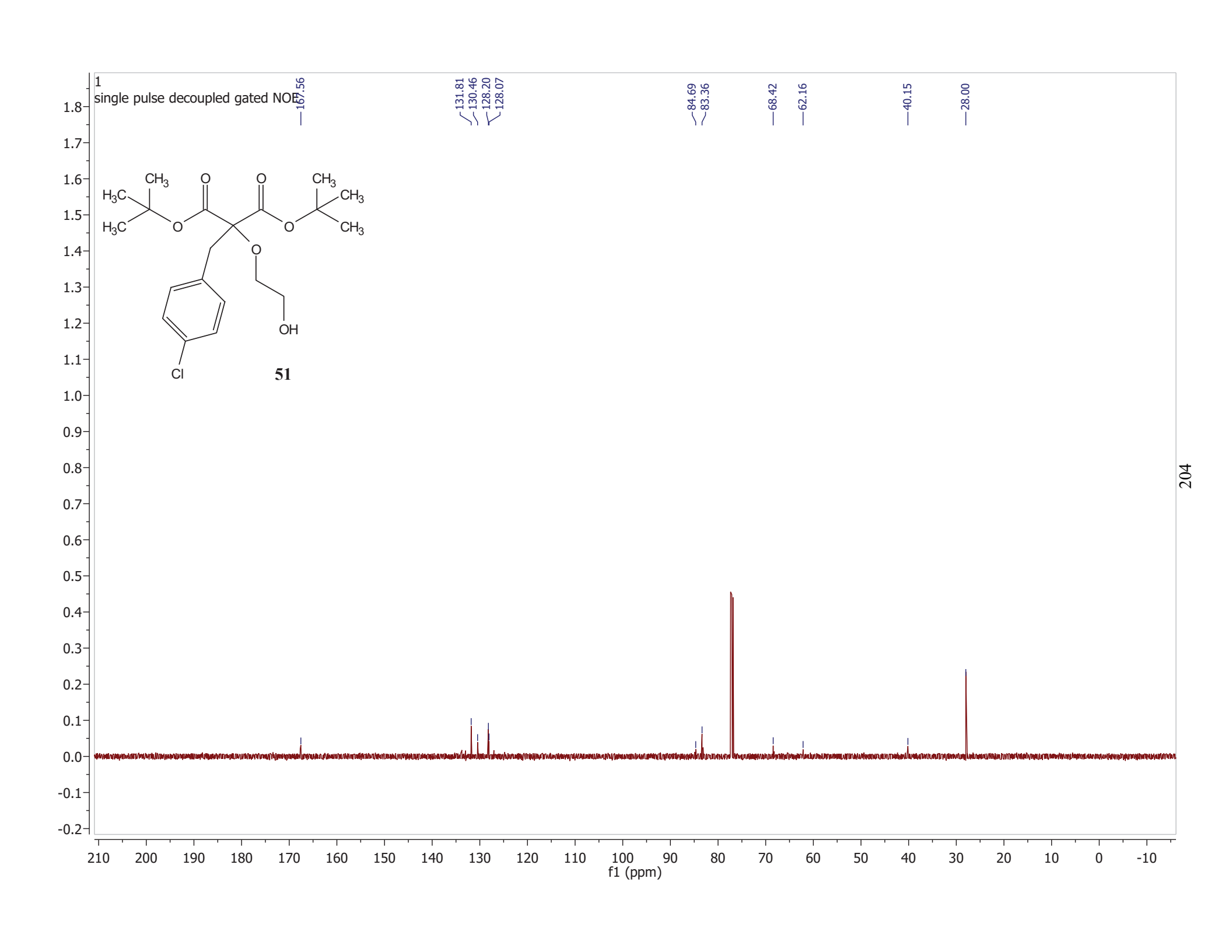

AMK-2019_6_3-7
CH3
H3C
H3C
O
O
O
H3C
O
O
CH3
50
1.00
1.00
0.99
1.02
0.94
8.92
3.02
3.06
f1 (ppm)
199

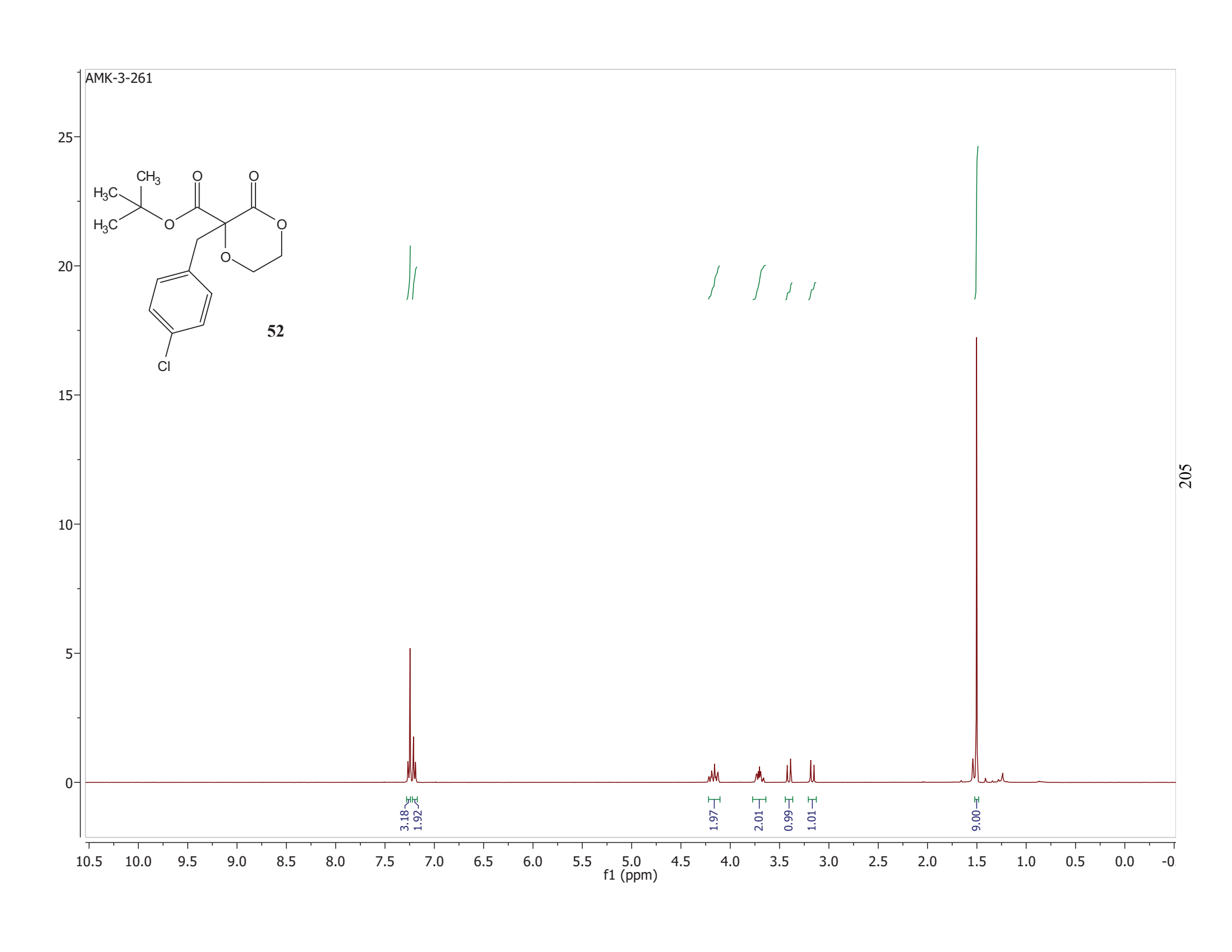

AMK-2019_6_3-7
167.08
165.92
86.55
83.50
68.38
61.20
35.69
27.89
17.17
16.16
CH3
H3C
H3C
O
O
O
H3C
O
CH3
50
200
f1 (ppm)

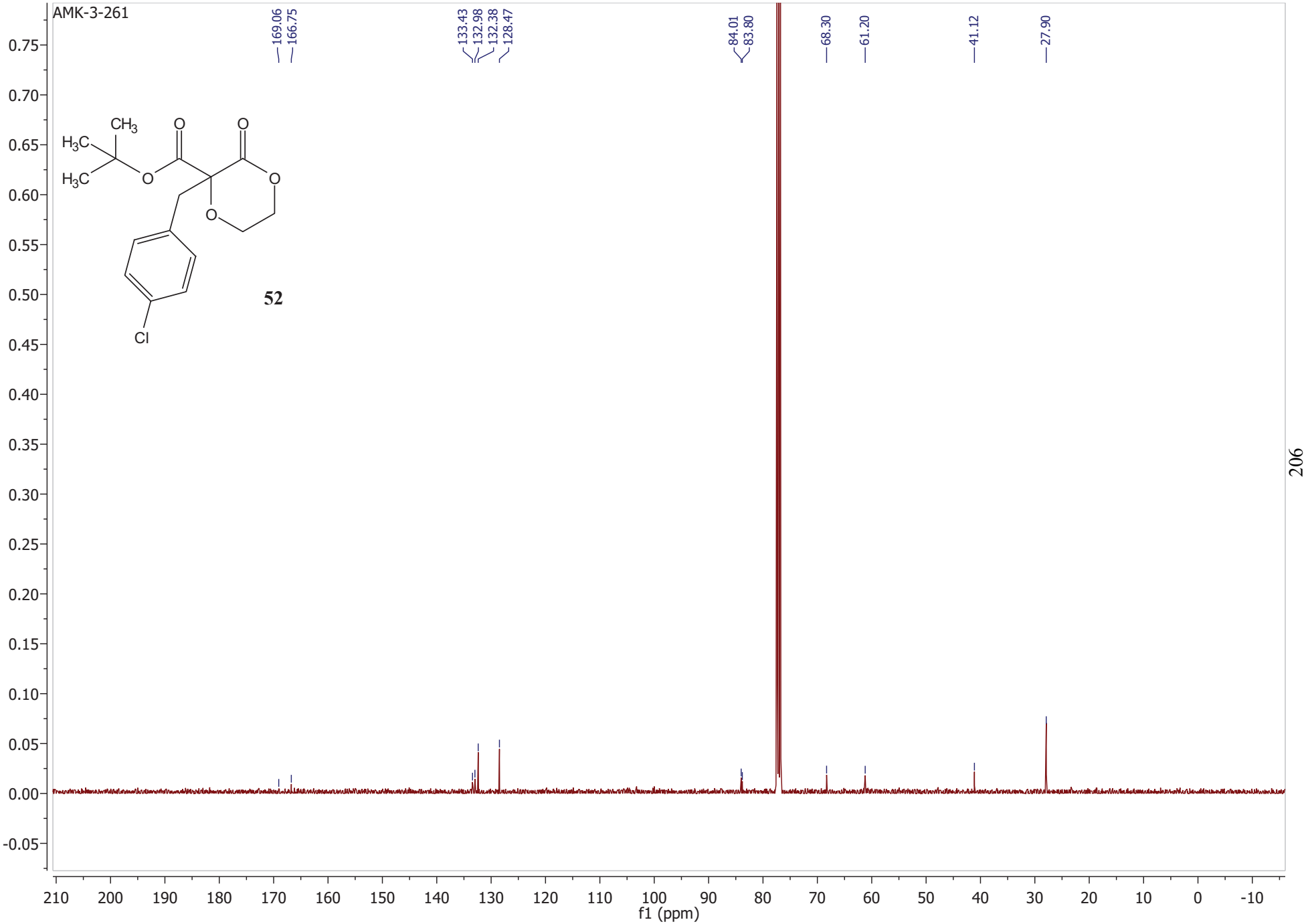

AK-3-215_proton
CH3
H3C
H3C
O
O
O
O
CH3
CH3
CH3
O
O
Cl
5.30
1.85
1.94
2.38
2.03
2.02
2.01
18.00
f1 (ppm)
201

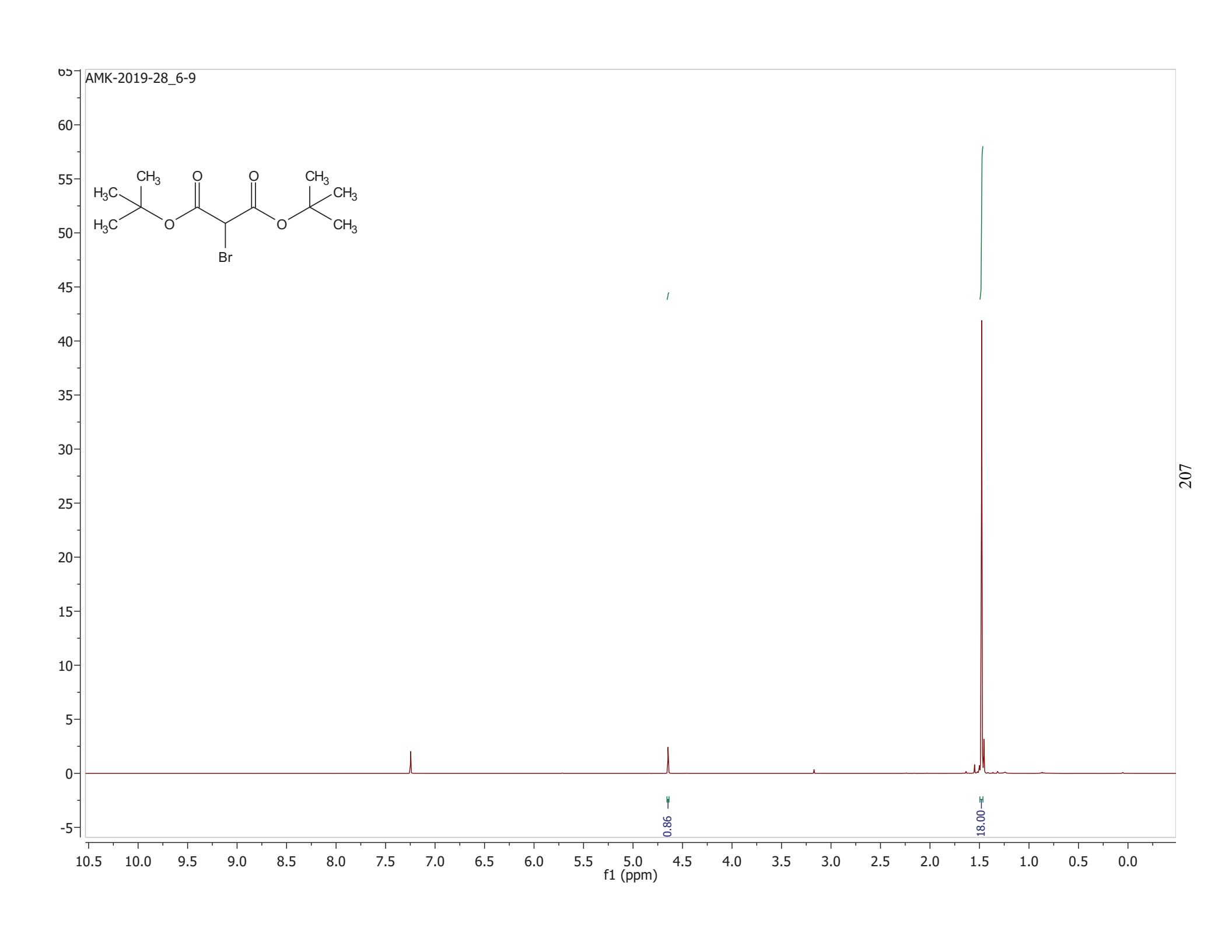

AK-3-215_carbon
167.32
138.47
134.09
132.70
132.01
128.45
127.99
127.83
127.66
84.94
82.79
73.37
69.56
66.02
39.51
27.99
CH3
H3C
H3C
O
O
O
CH3
CH3
CH3
O
O
Cl
202
f1 (ppm)

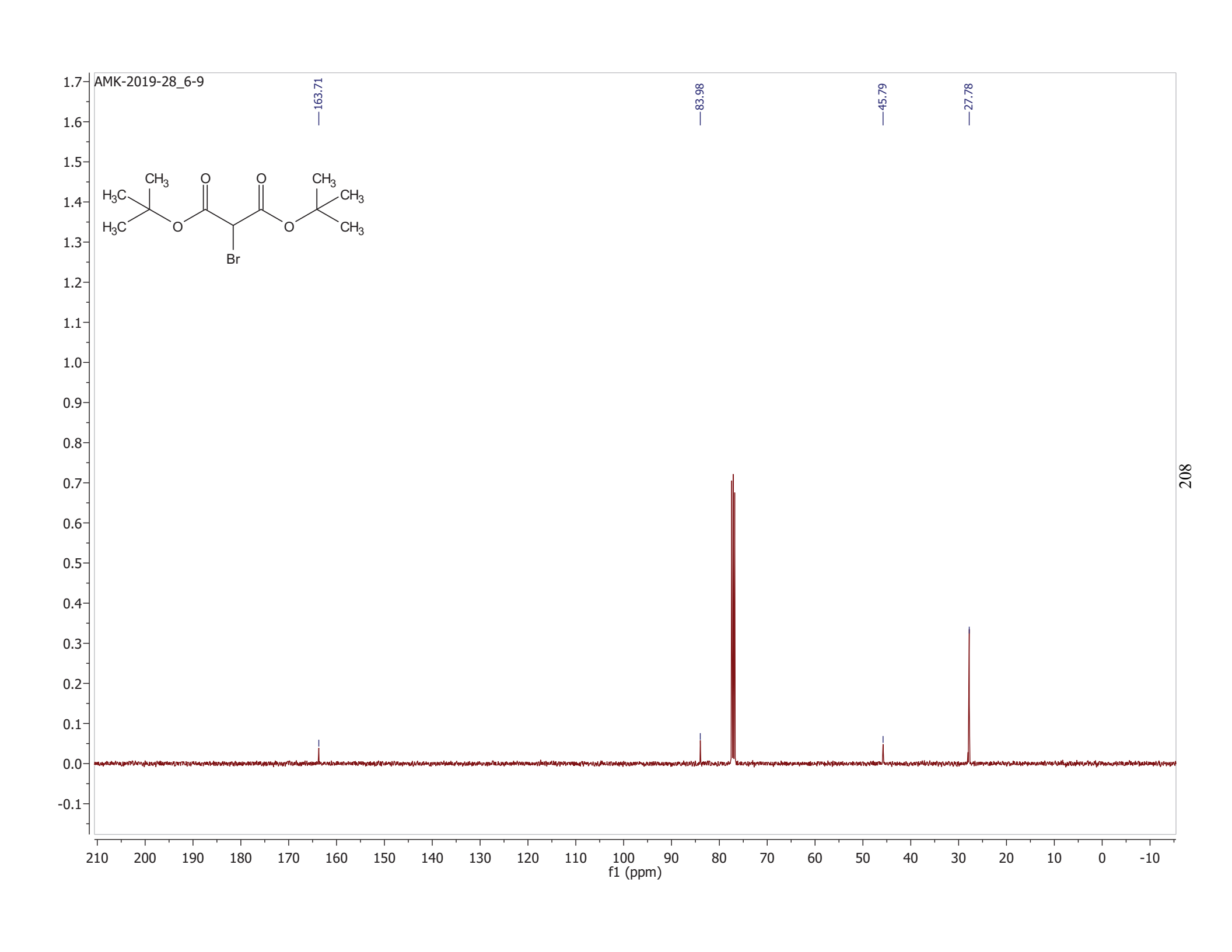

1
single_pulse
CH3
H3C
H3C
O
O
O
O
CH3
CH3
CH3
O
OH
Cl
51
4.52
2.07
2.47
2.00
18.36
f1 (ppm)
203

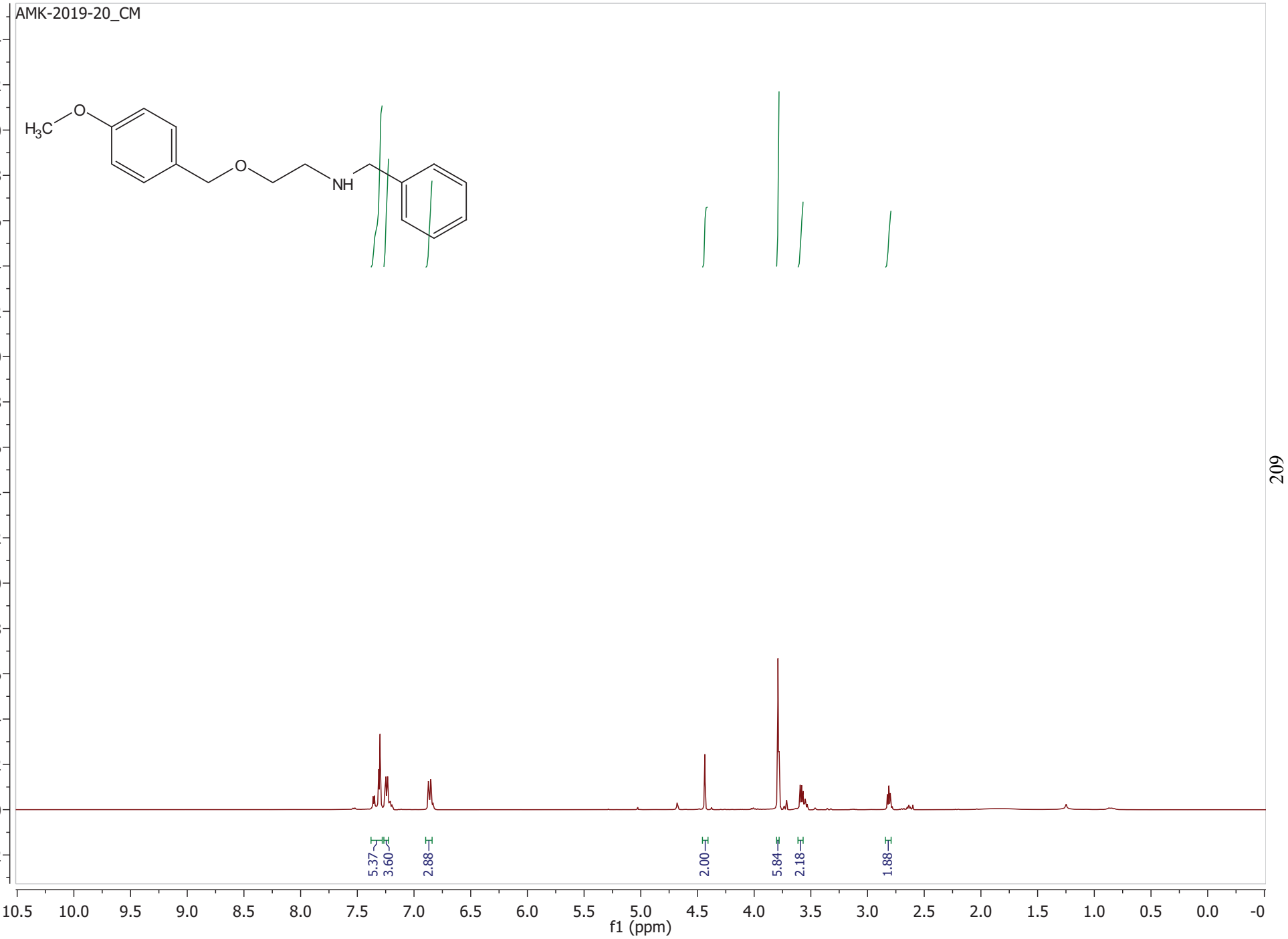

1
single pulse decoupled gated NOE
167.56
131.81
130.46
128.20
128.07
84.69
83.36
68.42
62.16
40.15
28.00
CH3
H3C
H3C
O
O
O
CH3
CH3
CH3
O
OH
Cl
51
204
f1 (ppm)

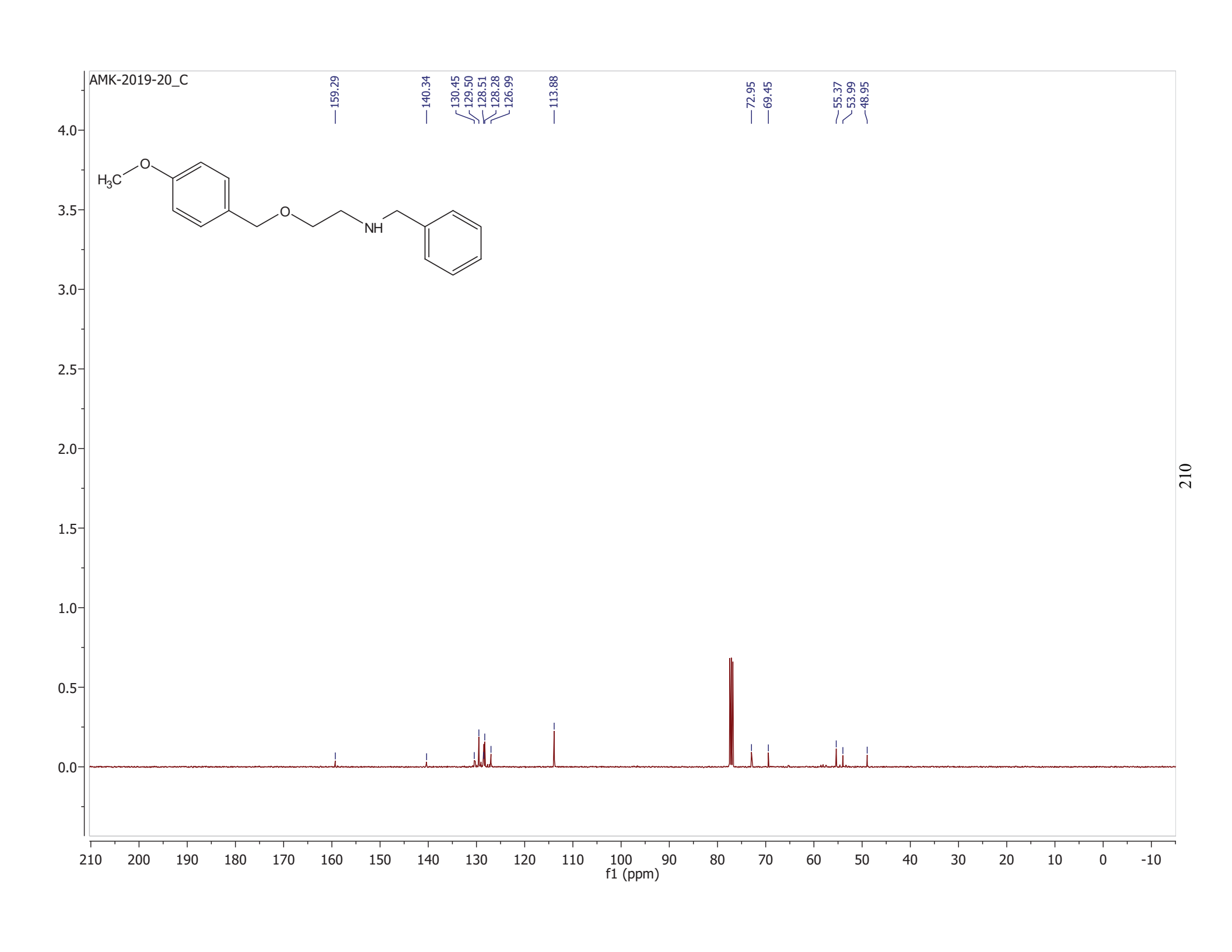

AMK-3-261
CH3
H3C
H3C
O
O
O
O
O
Cl
52
25
20
15
10
5
0
3.18
1.92
1.97
2.01
0.99
1.01
9.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)
205

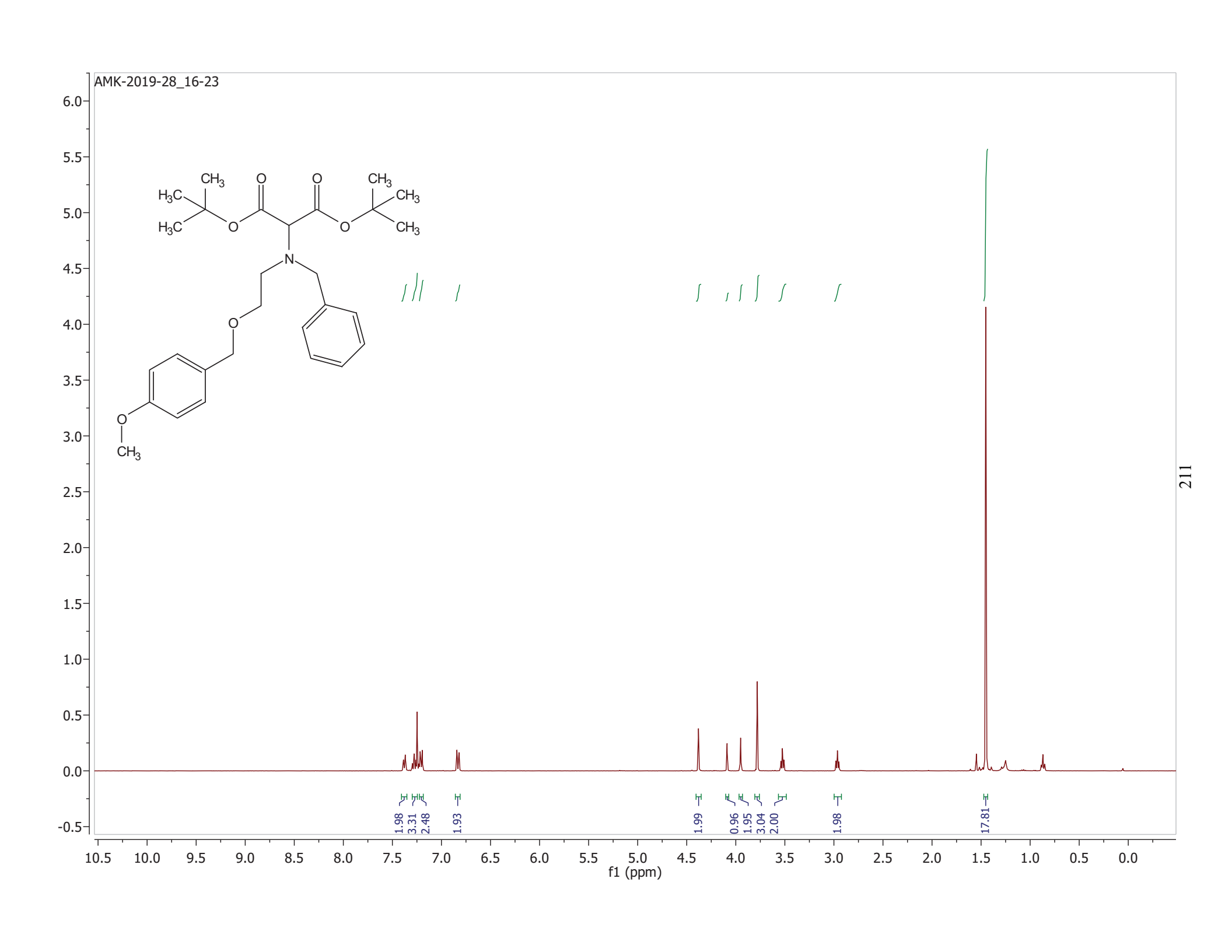

AMK-3-261
169.06
166.75
133.43
132.98
132.38
128.47
84.01
83.80
68.30
61.20
41.12
27.90
CH3
H3C
H3C
O
O
O
O
O
Cl
52
206
f1 (ppm)

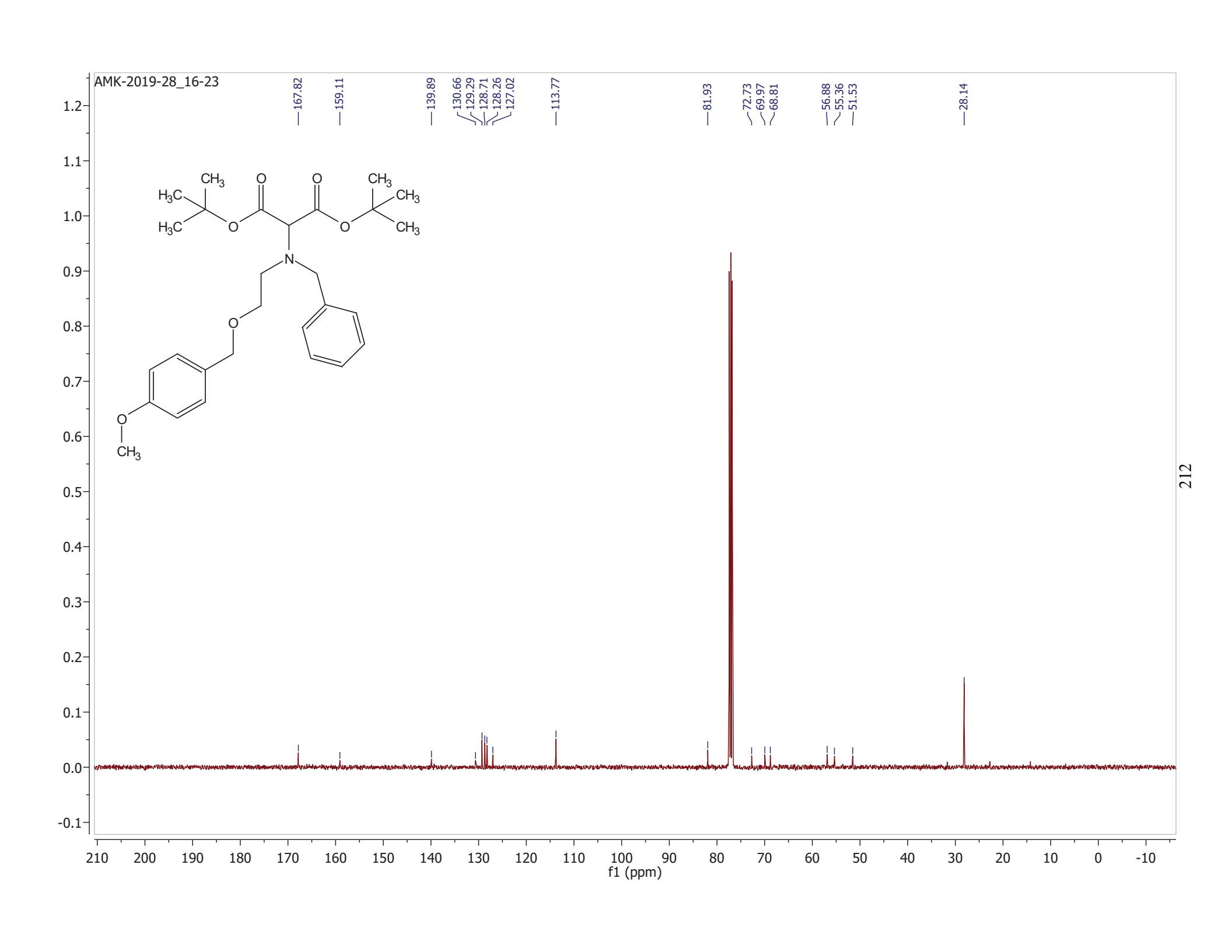

AMK-2019-28_6-9
CH3
O
O
CH3
H3C
CH3
H3C
O
O
CH3
Br
0.86
18.00
f1 (ppm)
207

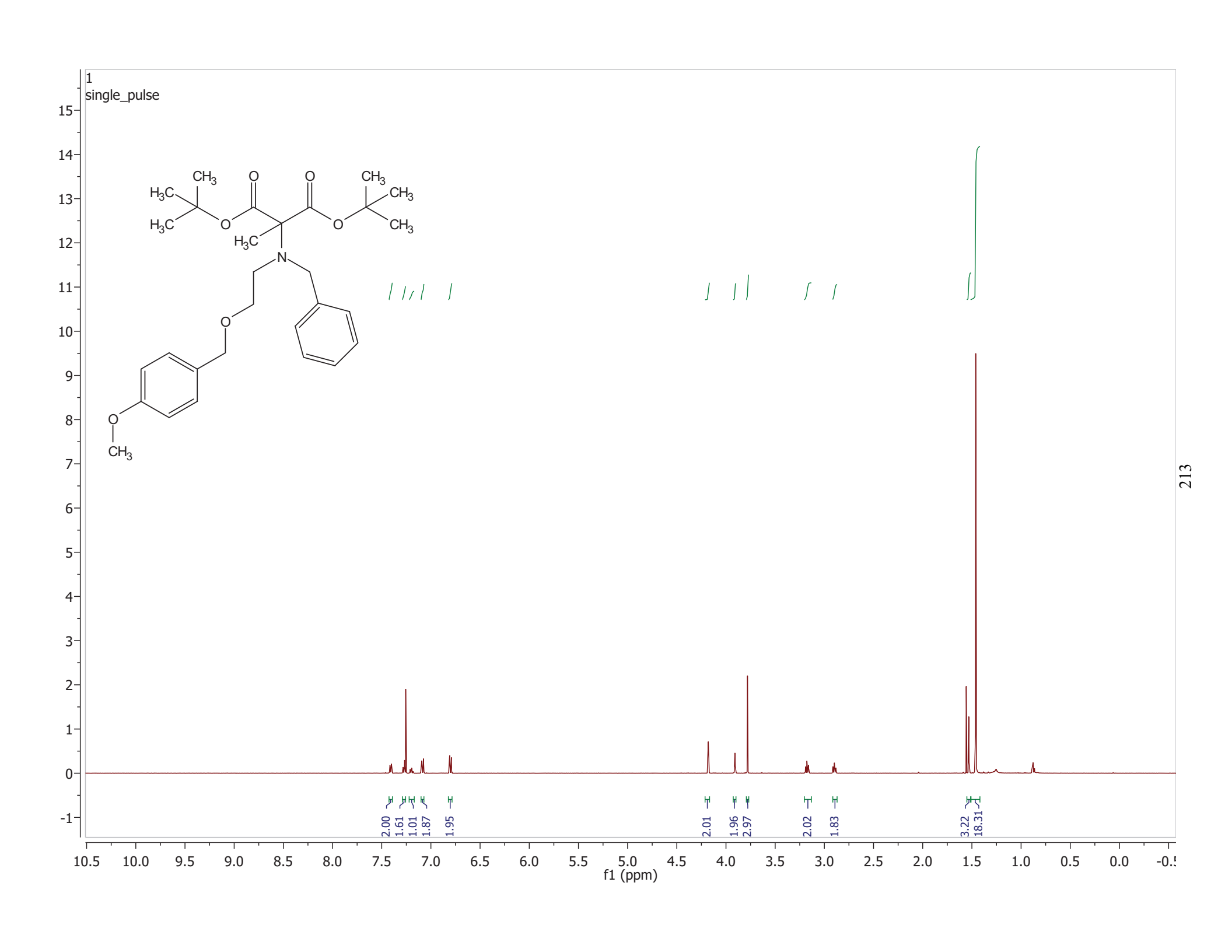

AMK-2019-28_6-9
163.71
83.98
45.79
27.78
208
f1 (ppm)

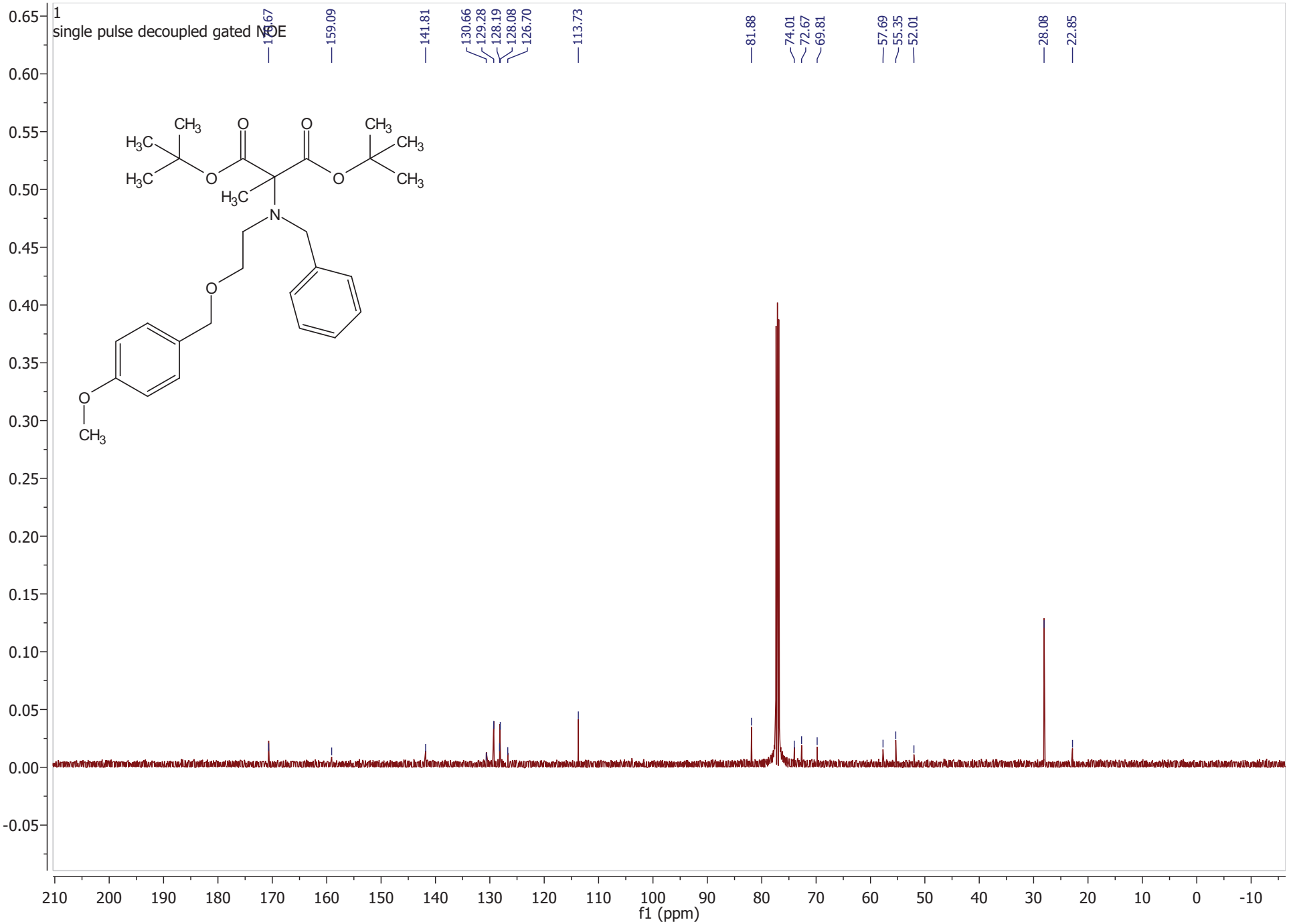

AMK-2019-20_CM
O
H3C
O
NH
5.37
3.60
2.88
2.00
5.84
2.18
1.88
f1 (ppm)
209

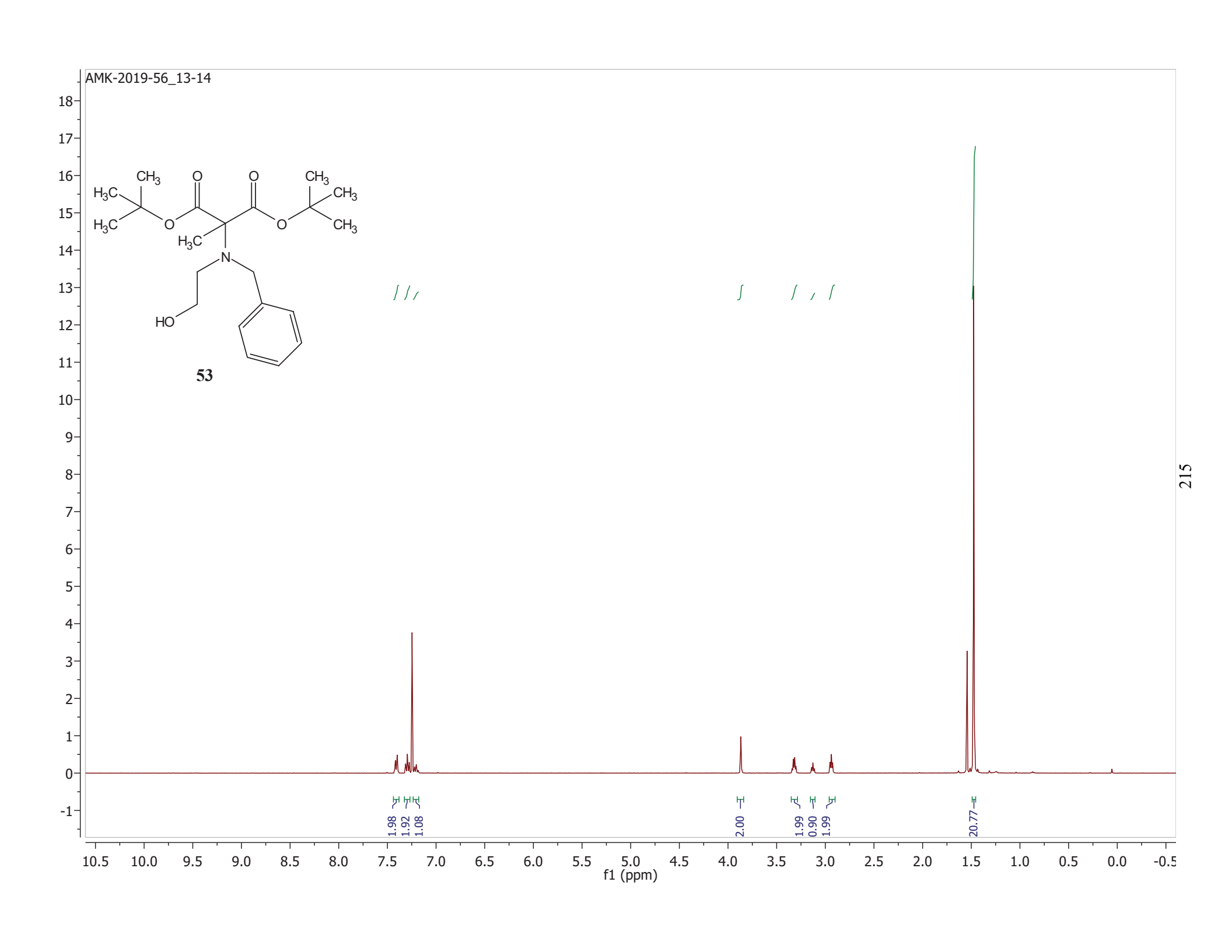

AMK-2019-20_C
159.29
140.34
130.45
129.50
128.51
128.28
126.99
113.88
72.95
69.45
55.37
53.99
48.95
O
H3C
O
NH
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
210

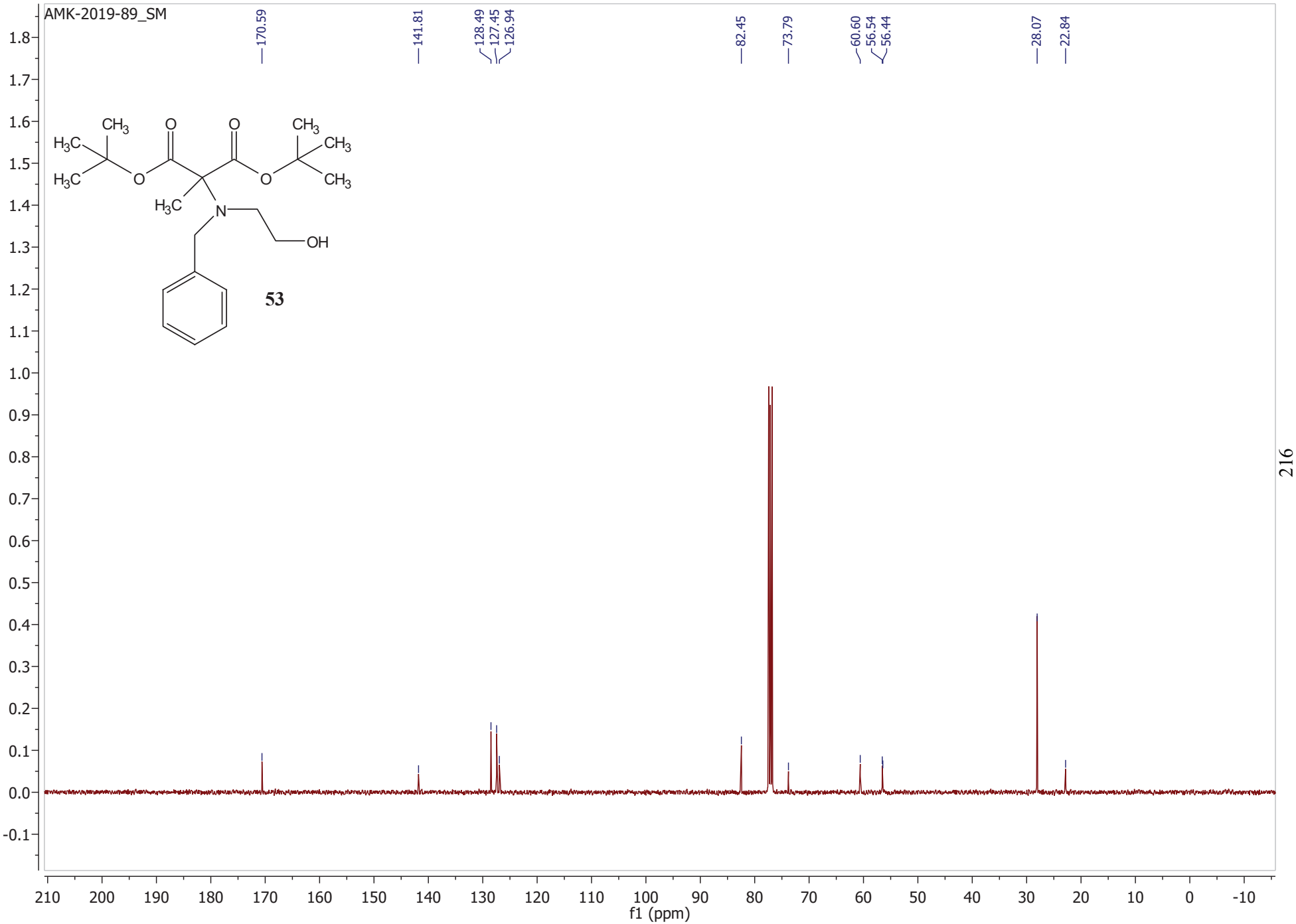

AMK-2019-28_16-23
f1 (ppm)
211
1.98
3.31
2.48
1.93
1.99
0.96
1.95
3.04
2.00
1.98
17.81

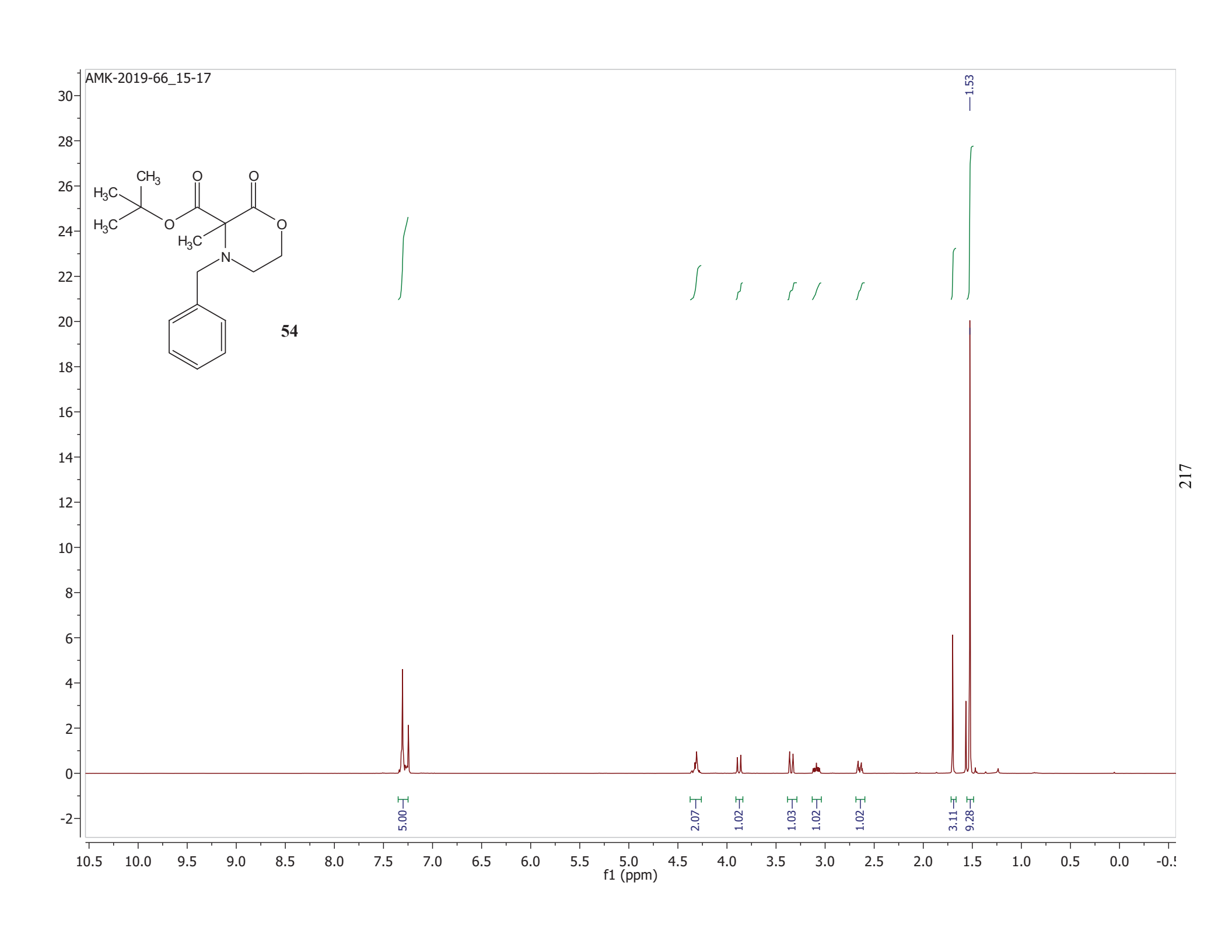

AMK-2019-28_16-23
167.82
159.11
139.89
130.66
129.29
128.71
128.26
127.02
113.77
81.93
72.73
69.97
68.81
56.88
55.36
51.53
28.14
f1 (ppm)
212

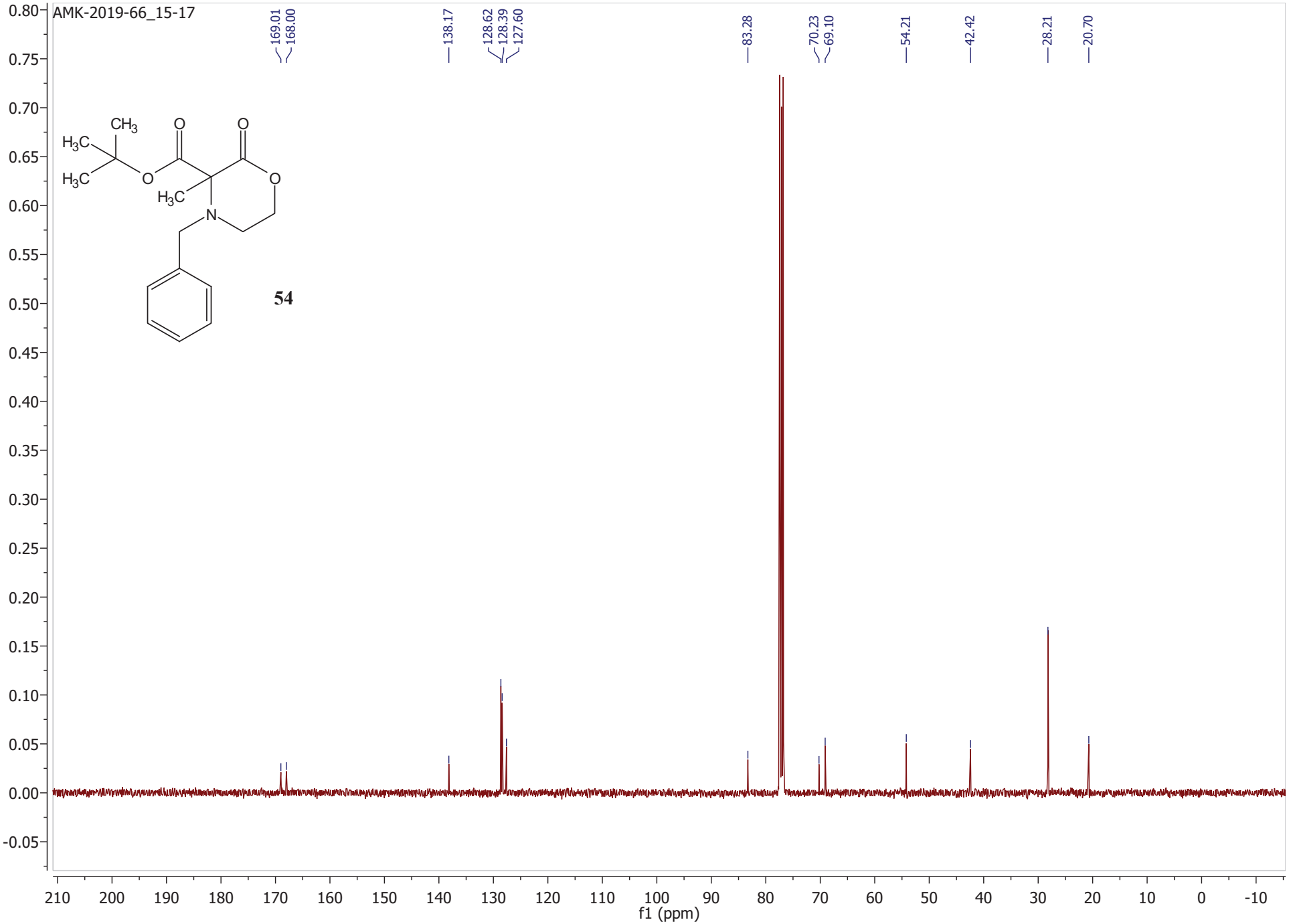

1
single_pulse
213
f1 (ppm)
2.00
1.61
1.01
1.87
1.95
2.01
1.96
2.97
2.02
1.83
3.22
18.31

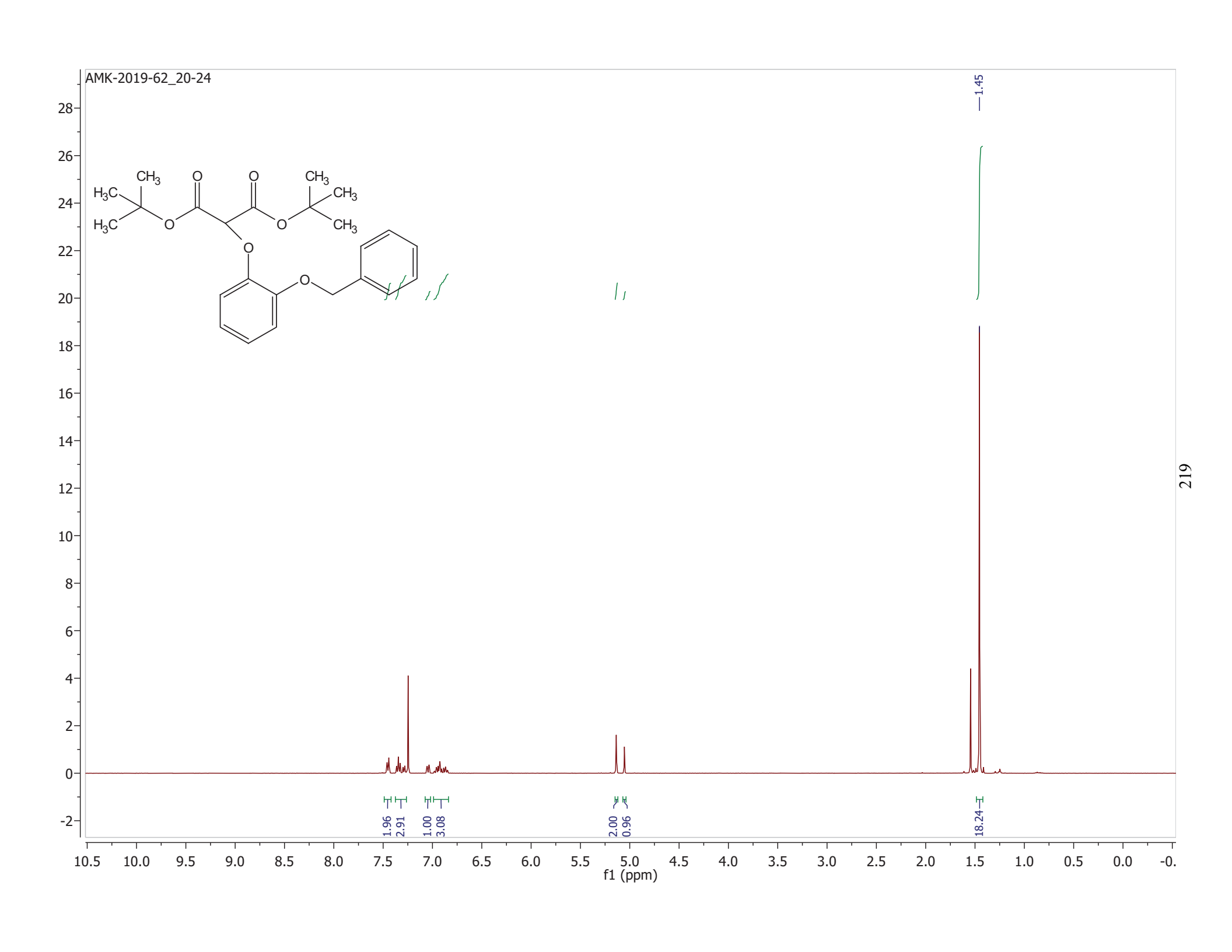

1
single pulse decoupled gated NOE
170.67
159.09
141.81
130.66
129.28
128.19
128.08
126.70
113.73
81.88
74.01
72.67
69.81
57.69
55.35
52.01
28.08
22.85
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
214

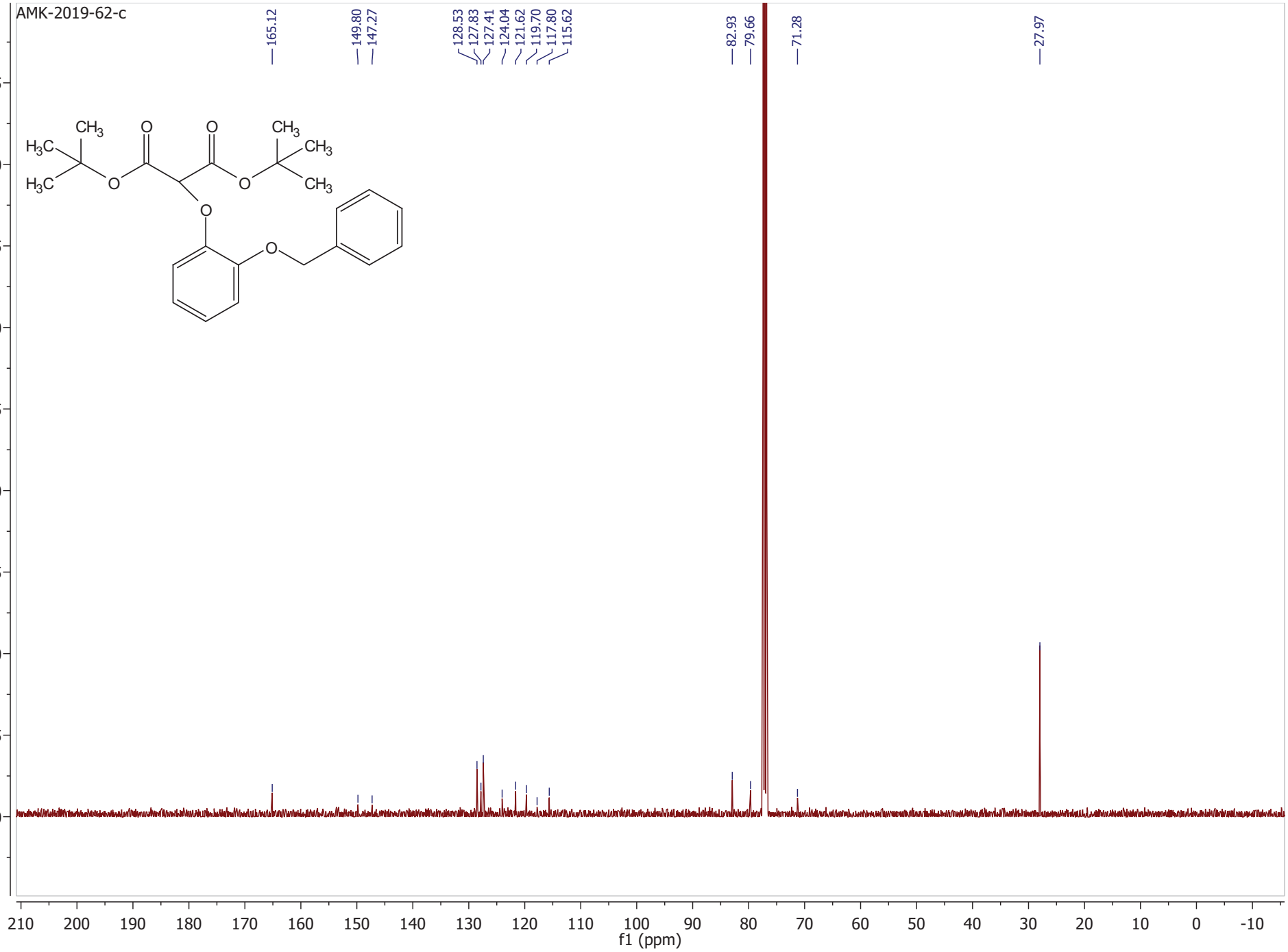

AMK-2019-56_13-14
CH3
O
O
CH3
H3C
CH3
H3C
O
O
CH3
H3C
N
HO
53
1.98
1.92
1.08
2.00
1.99
0.90
1.99
20.77
f1 (ppm)
215

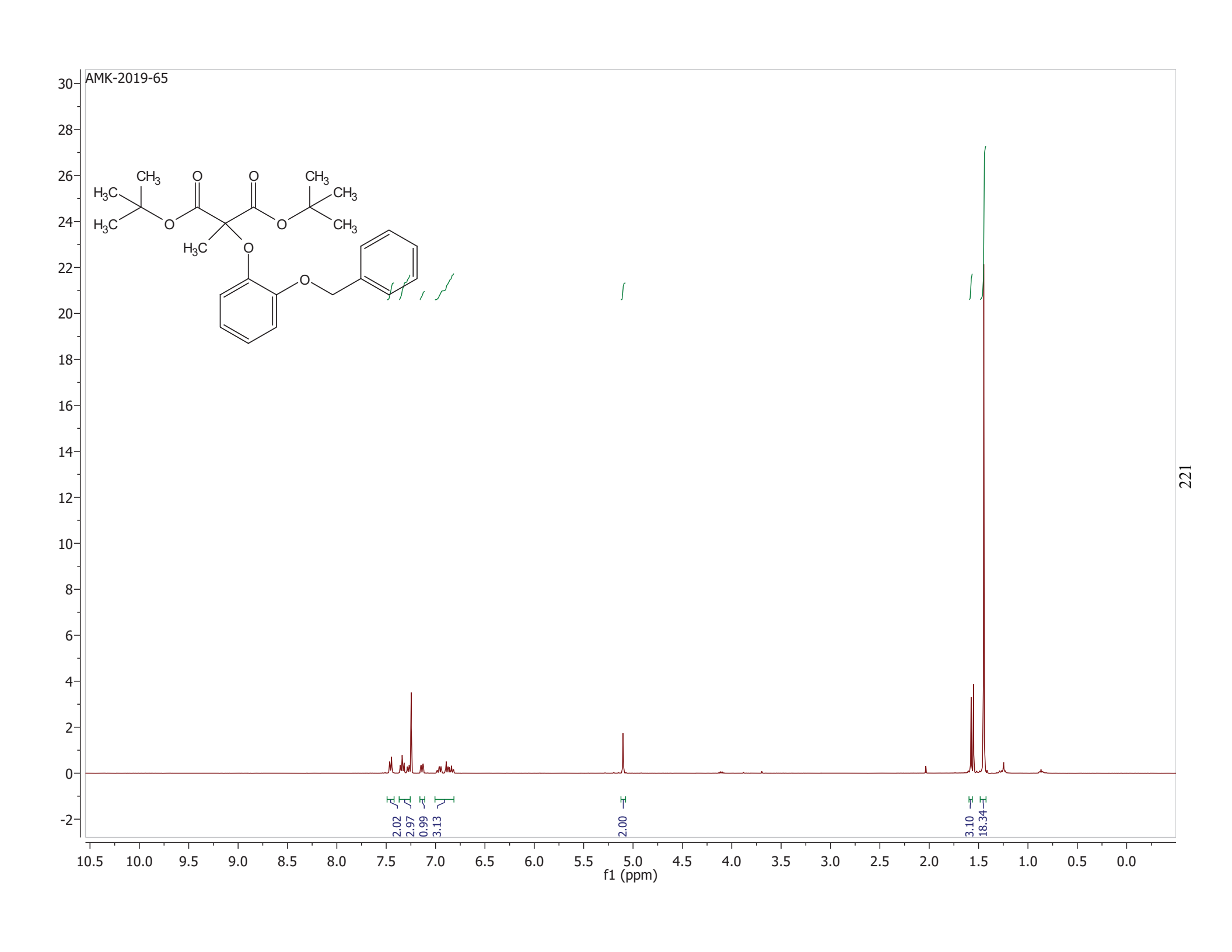

AMK-2019-89_SM
170.59
141.81
128.49
127.45
126.94
82.45
73.79
60.60
56.54
56.44
28.07
22.84
CH3
O
O
CH3
H3C
CH3
H3C
O
O
CH3
H3C
N
OH
53
f1 (ppm)

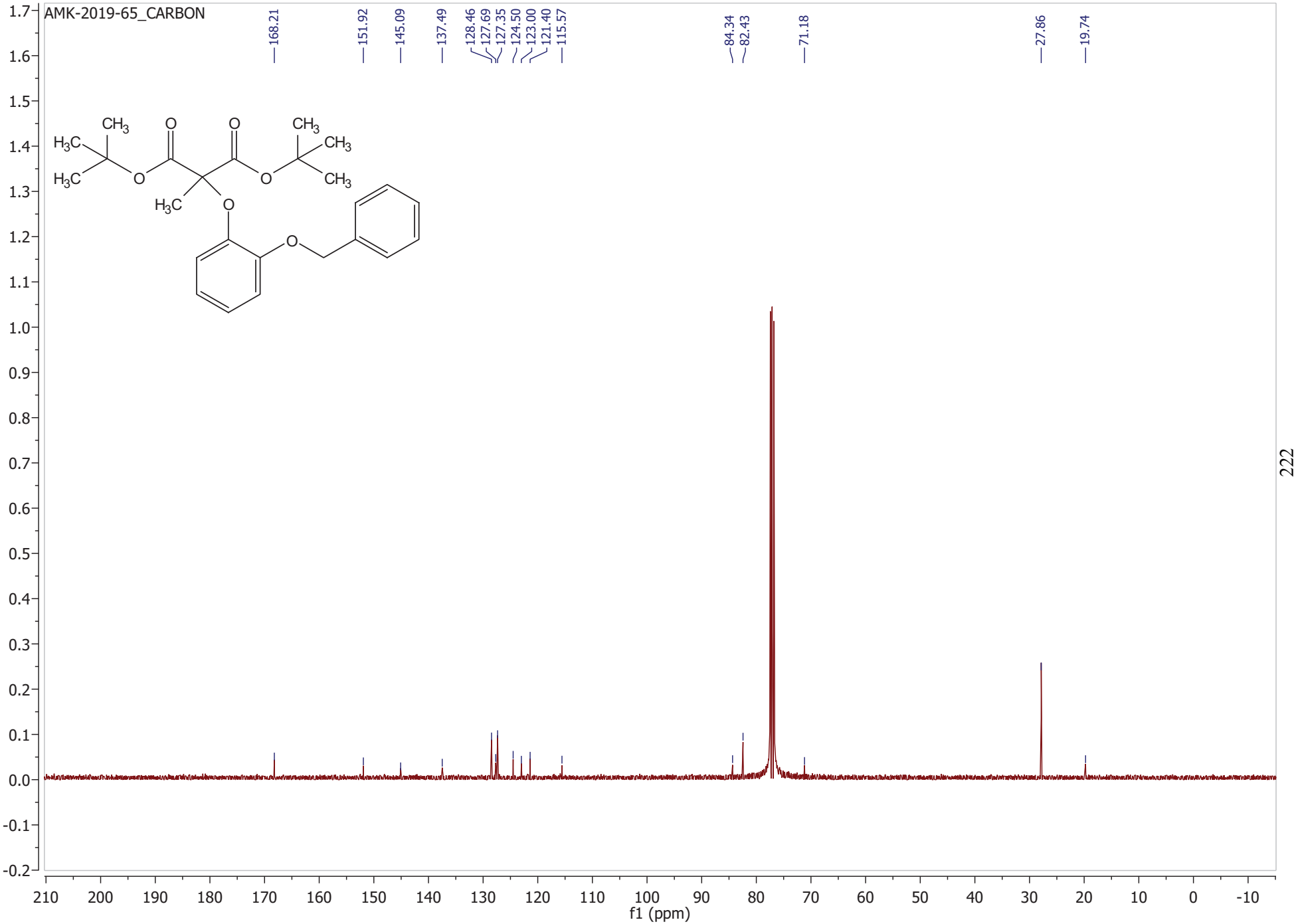

AMK-2019-66_15-17
1.53
5.00
2.07
1.02
1.03
1.02
1.02
3.11
9.28
f1 (ppm)
54
217

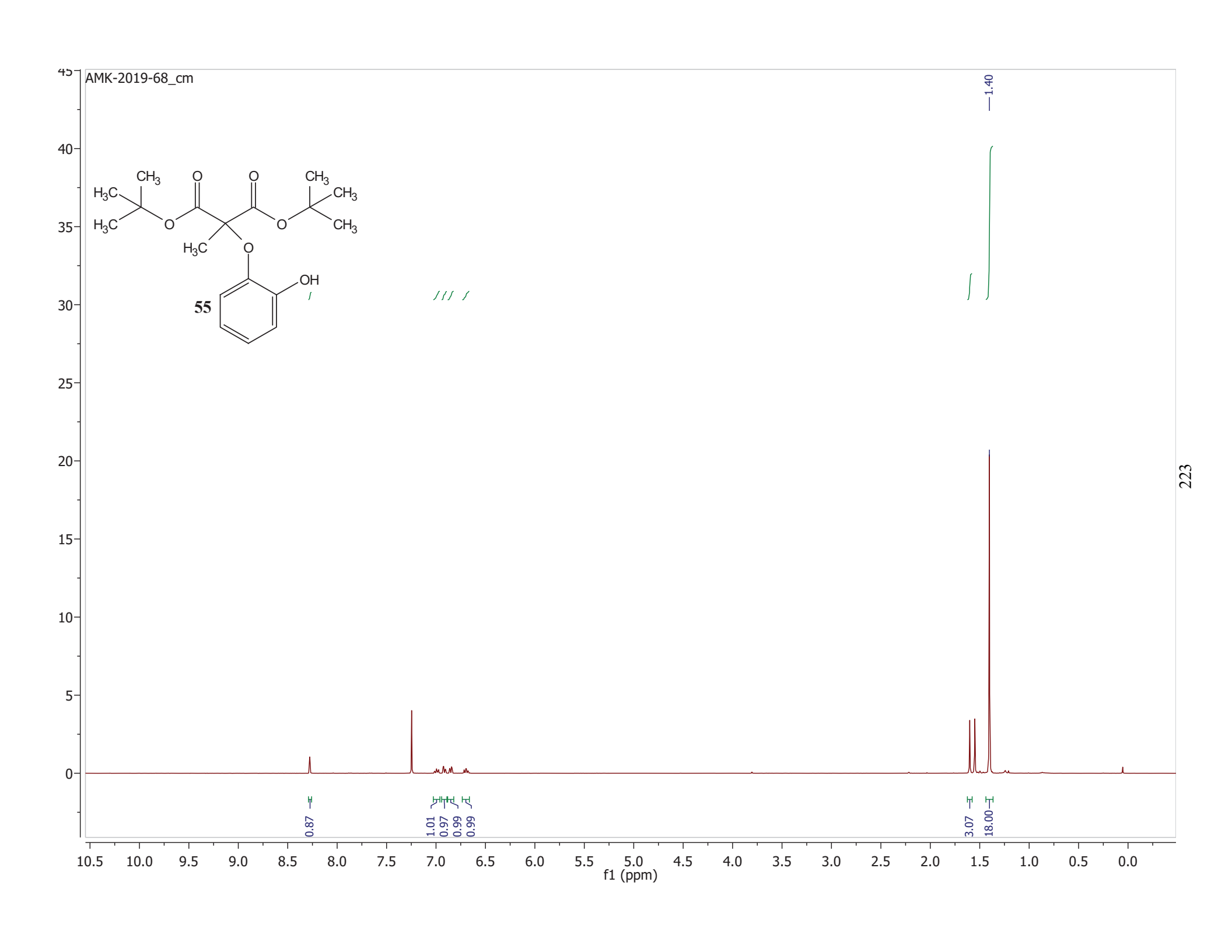

AMK-2019-66_15-17
169.01
168.00
138.17
128.62
128.39
127.60
83.28
70.23
69.10
54.21
42.42
28.21
20.70
54
f1 (ppm)

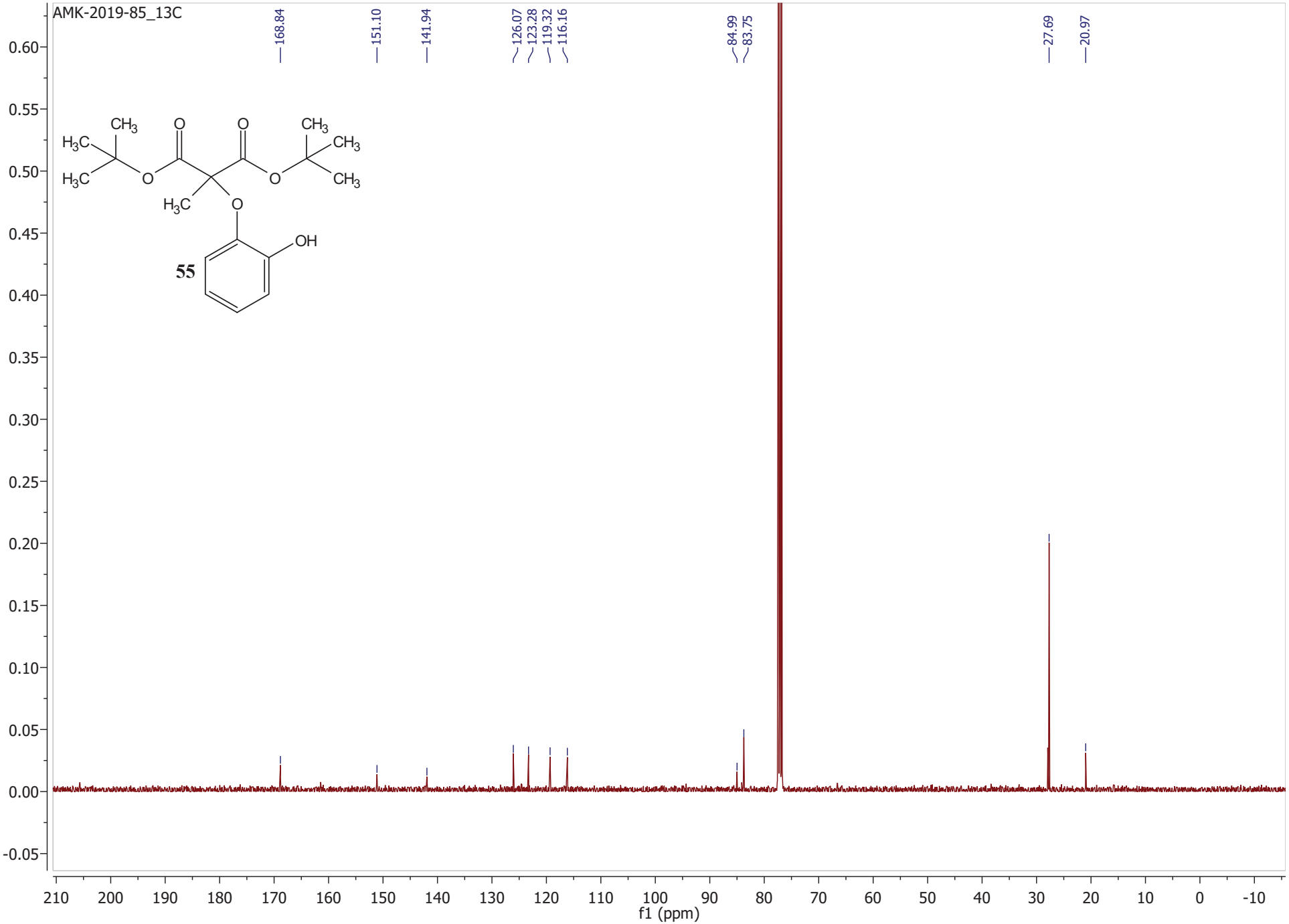

AMK-2019-62_20-24
1.45
1.96
2.91
1.00
3.08
2.00
0.96
18.24
f1 (ppm)
219

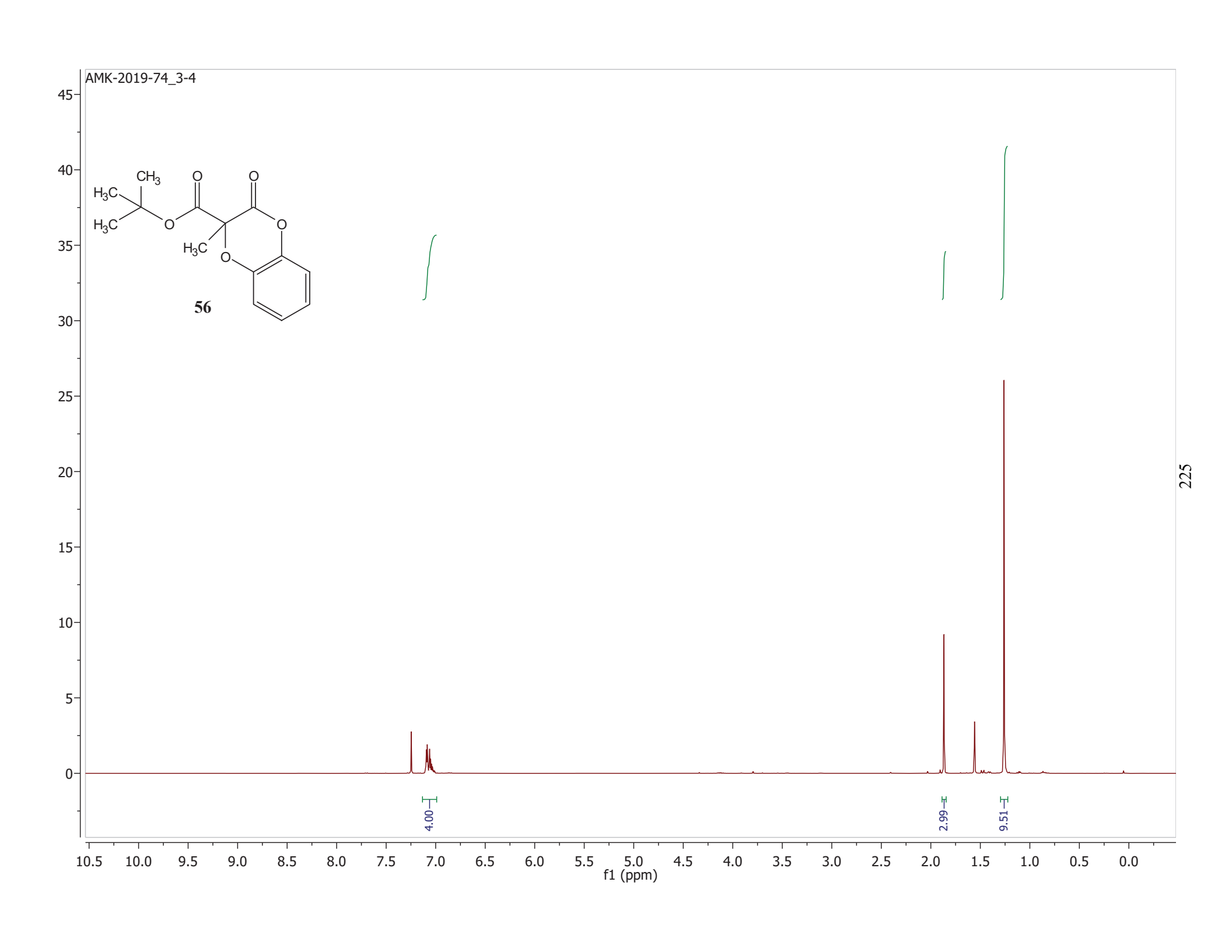

AMK-2019-62-c
165.12
149.80
147.27
128.53
127.83
127.41
124.04
121.62
119.70
117.80
115.62
82.93
79.66
71.28
27.97
CH3
H3C
H3C
O
O
O
CH3
CH3
CH3
O
O
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
220

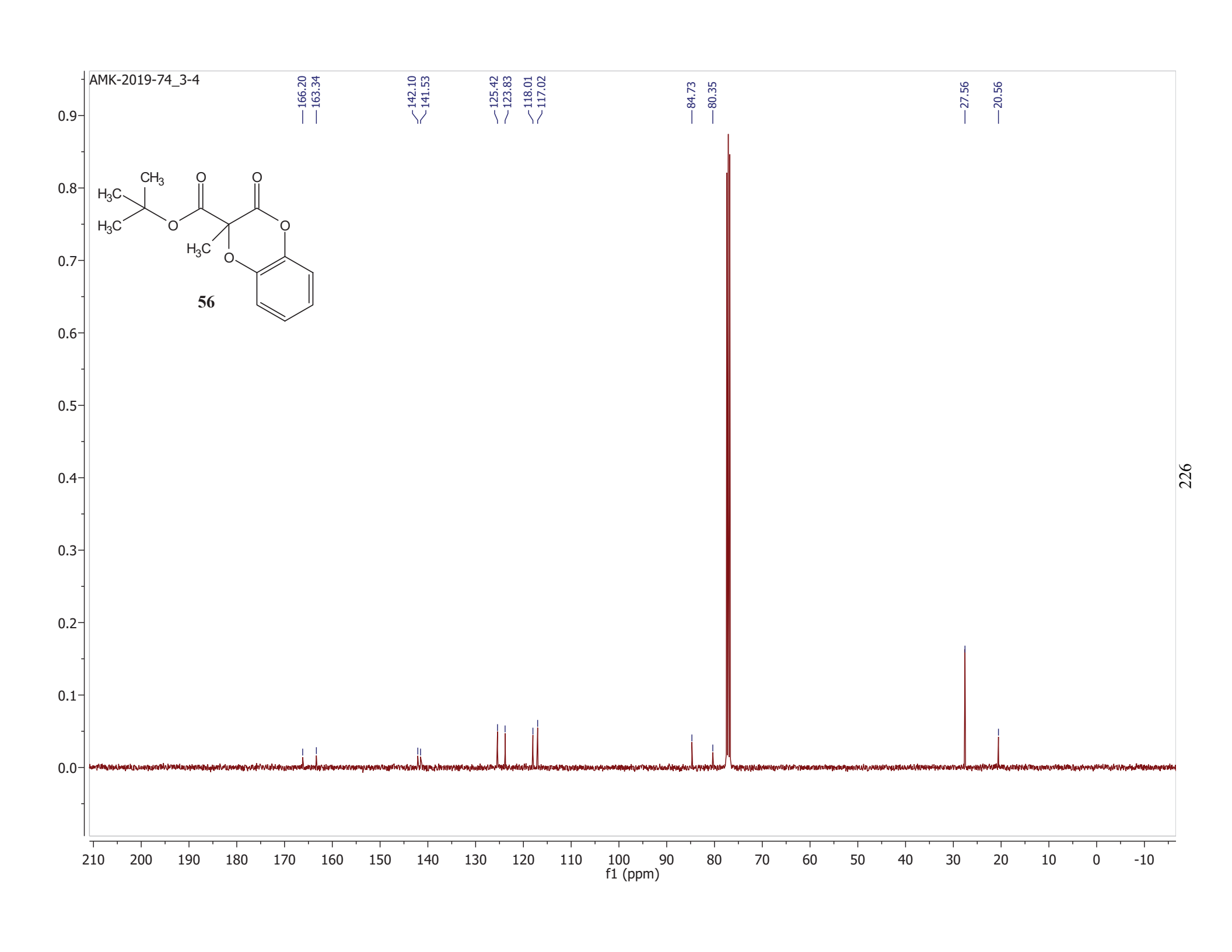

AMK-2019-65
221
f1 (ppm)
2.02
2.97
0.99
3.13
2.00
3.10
18.34

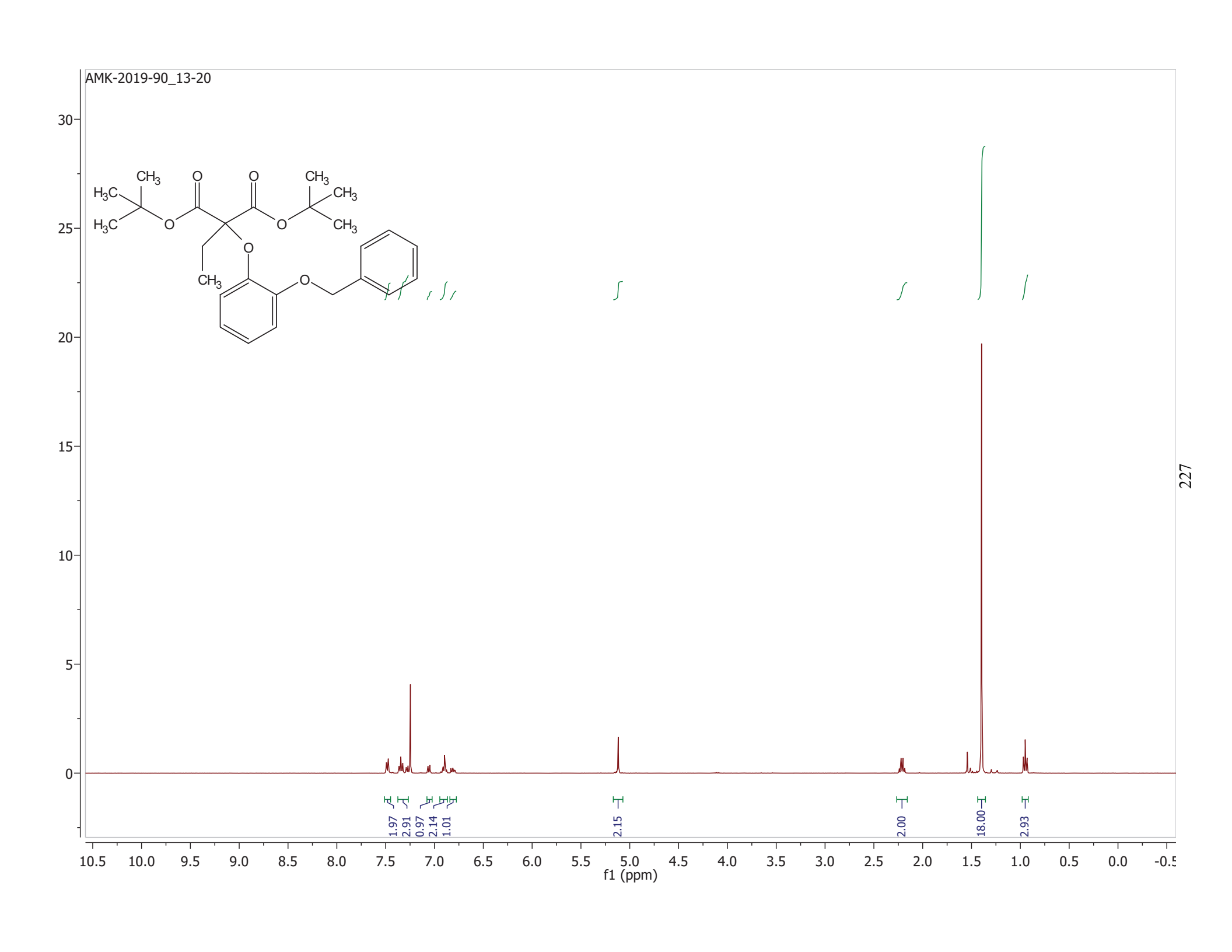

AMK-2019-65_CARBON
168.21
151.92
145.09
137.49
128.46
127.69
127.35
124.50
123.00
121.40
115.57
84.34
82.43
71.18
27.86
19.74
CH3
O
O
CH3
H3C
CH3
H3C
O
O
CH3
H3C
O
O
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
222

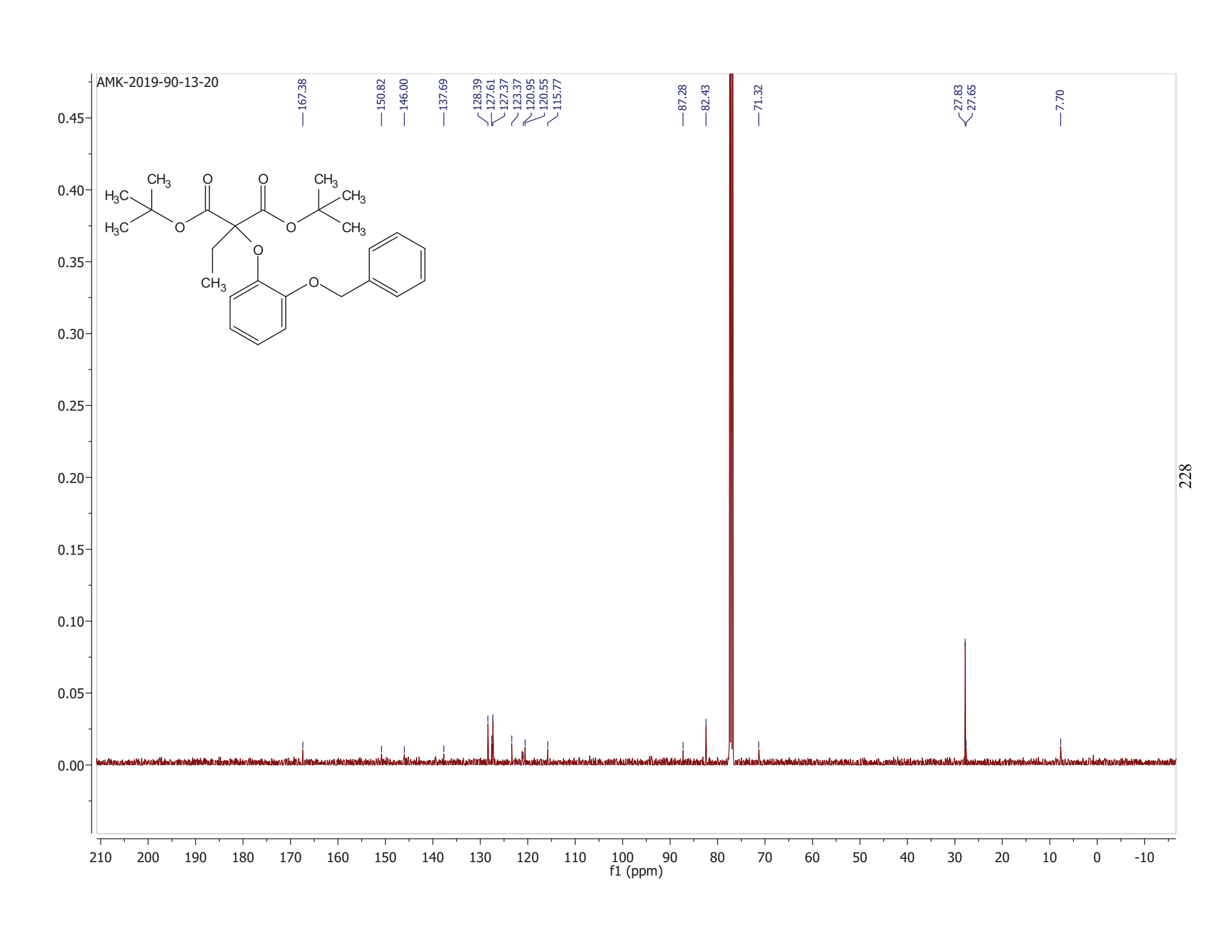

AMK-2019-68_cm
1.40
55
OH
0.87
1.01
0.97
0.99
0.99
3.07
18.00
f1 (ppm)
223

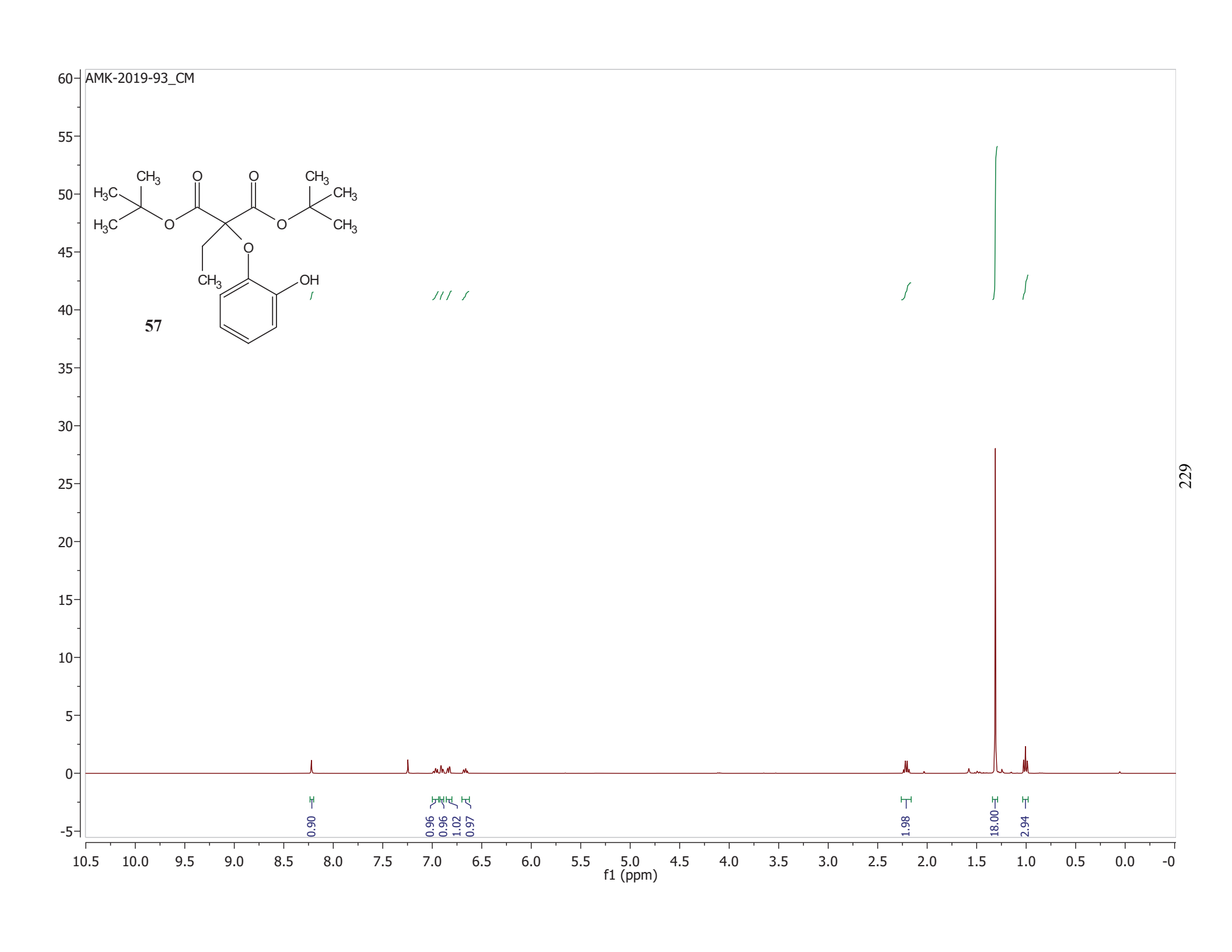

AMK-2019-85_13C
168.84
151.10
141.94
126.07
123.28
119.32
116.16
84.99
83.75
27.69
20.97
55
OH
f1 (ppm)
224

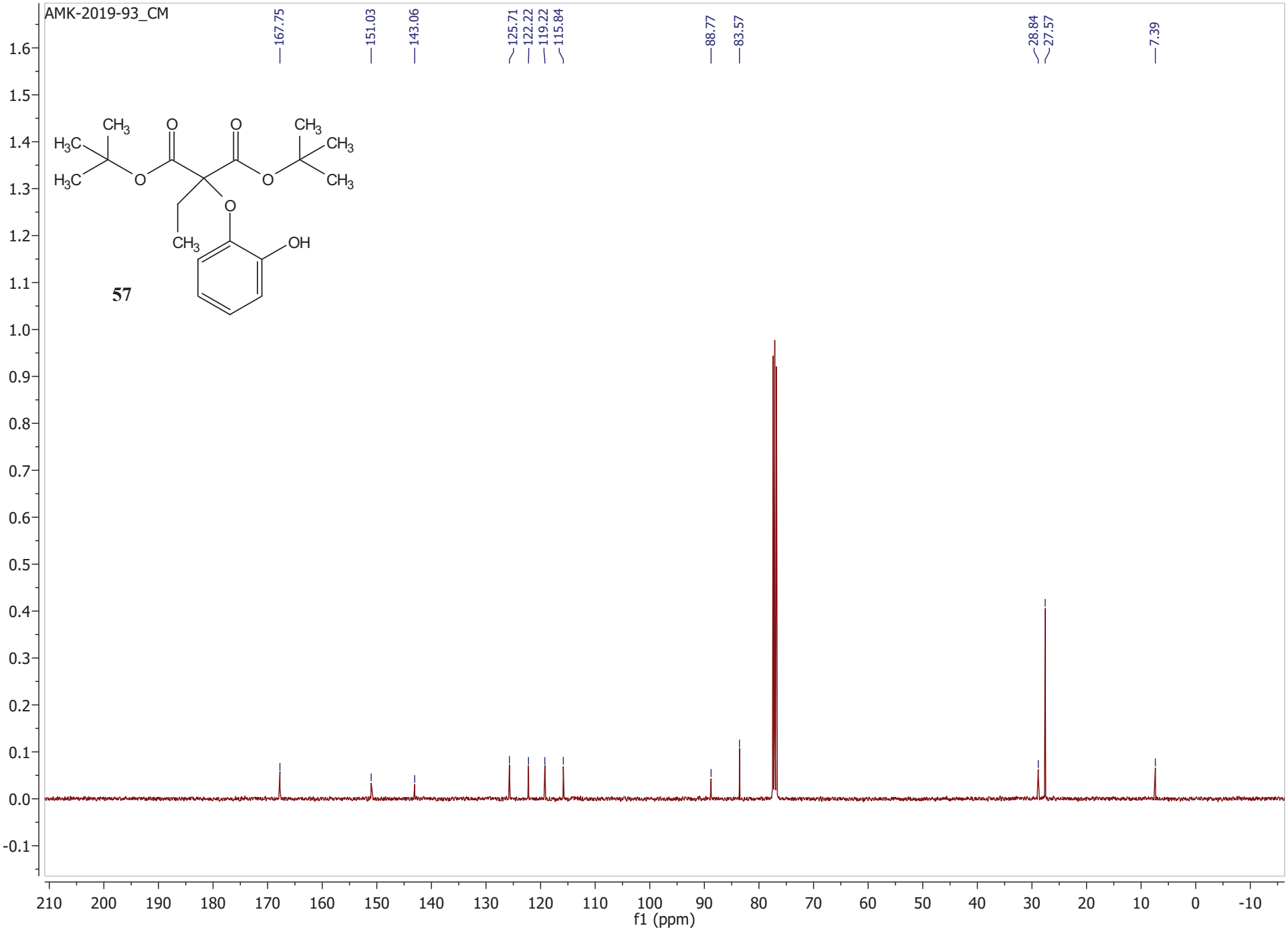

AMK-2019-74_3-4
CH3
H3C
H3C
O
O
O
O
H3C
O
56
4.00
2.99
9.51
f1 (ppm)
225

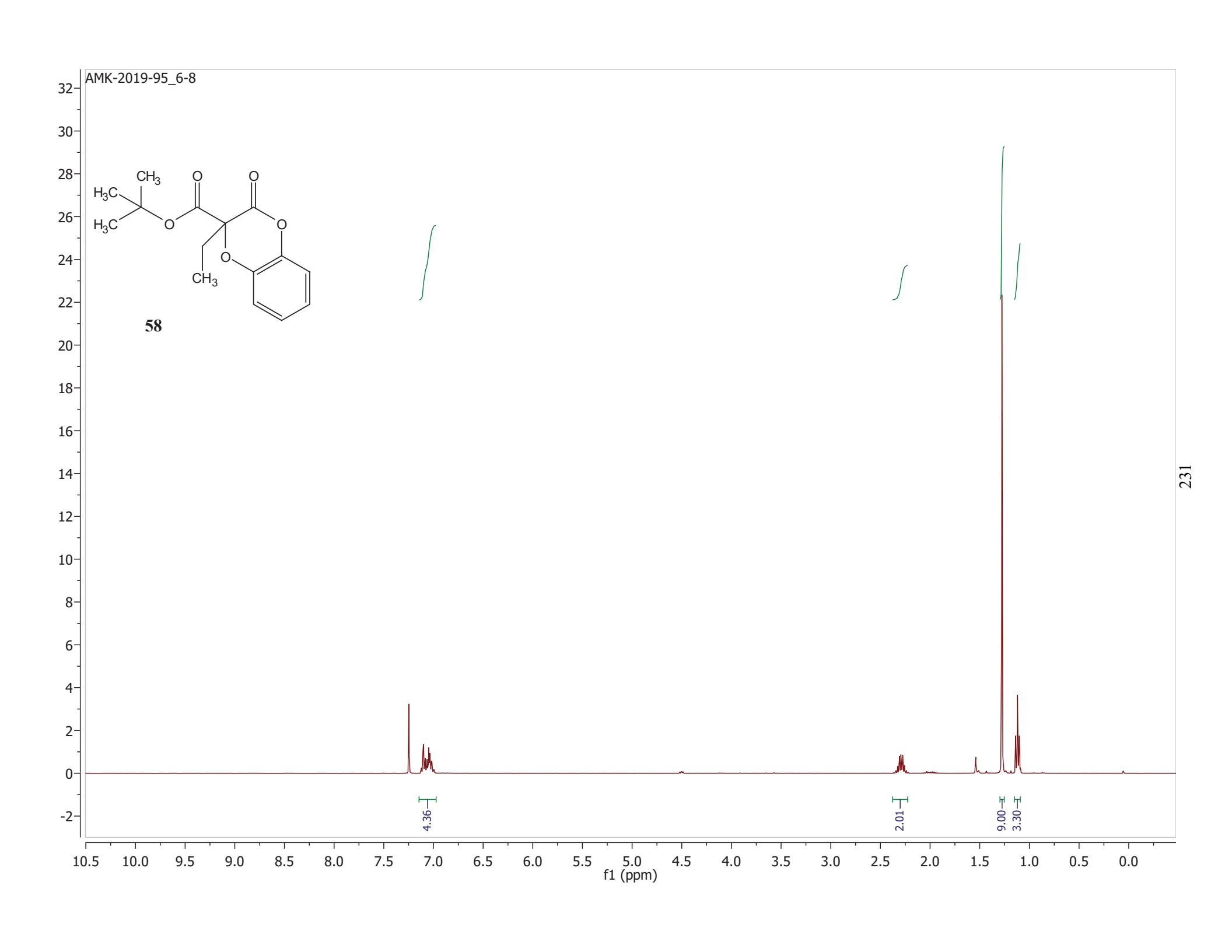

AMK-2019-74_3-4
166.20
163.34
142.10
141.53
125.42
123.83
118.01
117.02
84.73
80.35
27.56
20.56
56
f1 (ppm)
226

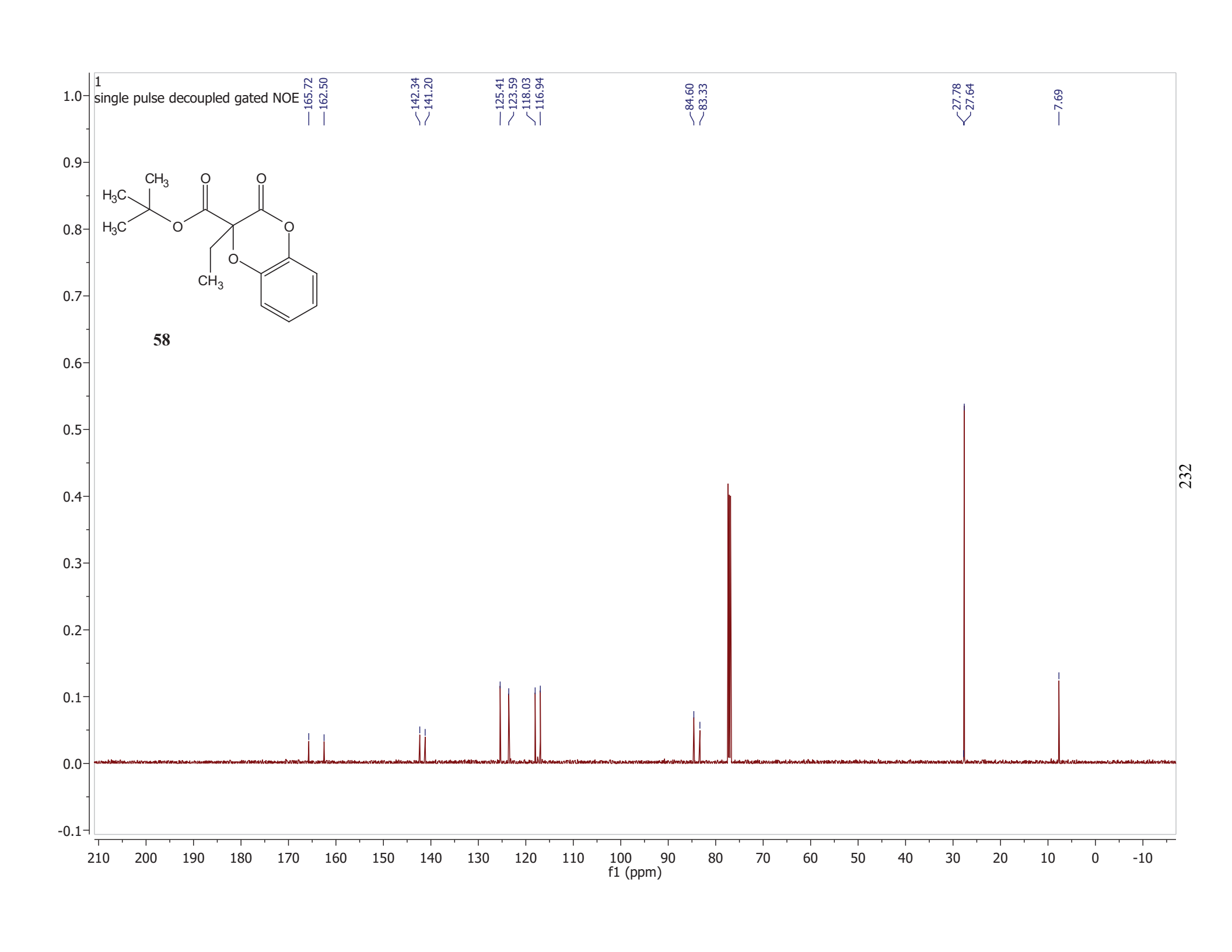

AMK-2019-90_13-20
227
f1 (ppm)
1.97
2.91
0.97
2.14
1.01
2.15
2.00
18.00
2.93


AMK-2019-90-13-20
167.38
150.82
146.00
137.69
128.39
127.61
127.37
123.37
120.95
120.55
115.77
87.28
82.43
71.32
27.83
27.65
7.70
CH3
H3C
H3C
O
O
O
CH3
CH3
CH3
O
CH3
O
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
228

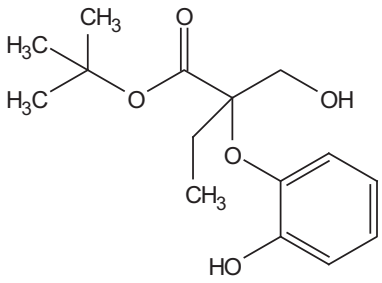

AMK-2019-93_CM
57
f1 (ppm)
229


AMK-2019-93_CM
167.75
151.03
143.06
125.71
122.22
119.22
115.84
88.77
83.57
28.84
27.57
7.39
CH3
H3C
H3C
O
O
O
O
CH3
CH3
CH3
CH3
OH
57
f1 (ppm)
230


AMK-2019-95_6-8
CH3
H3C
H3C
O
O
O
O
O
CH3
58
4.36
2.01
9.00
3.30
f1 (ppm)
231

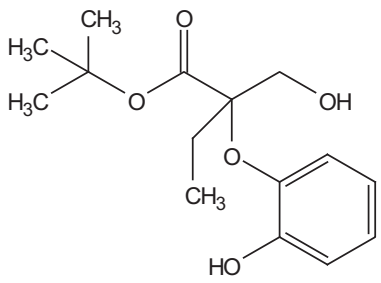

1
single pulse decoupled gated NOE
165.72
162.50
142.34
141.20
125.41
123.59
118.03
116.94
84.60
83.33
27.78
27.64
7.69
CH3
H3C
H3C
O
O
O
O
O
CH3
58
232
f1 (ppm)

S#495681
single_pulse



58'

S#497113
single pulse decoupled gated NOE

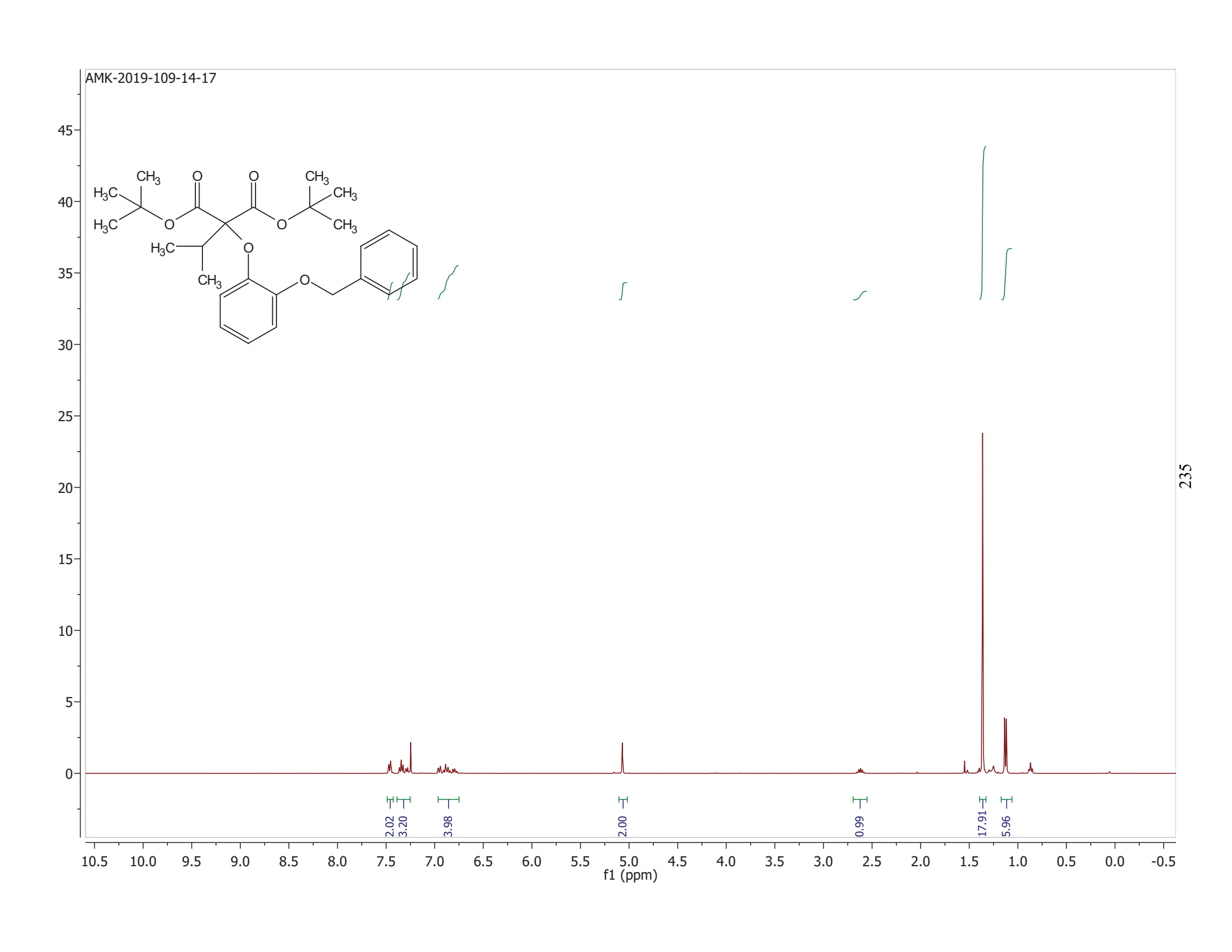


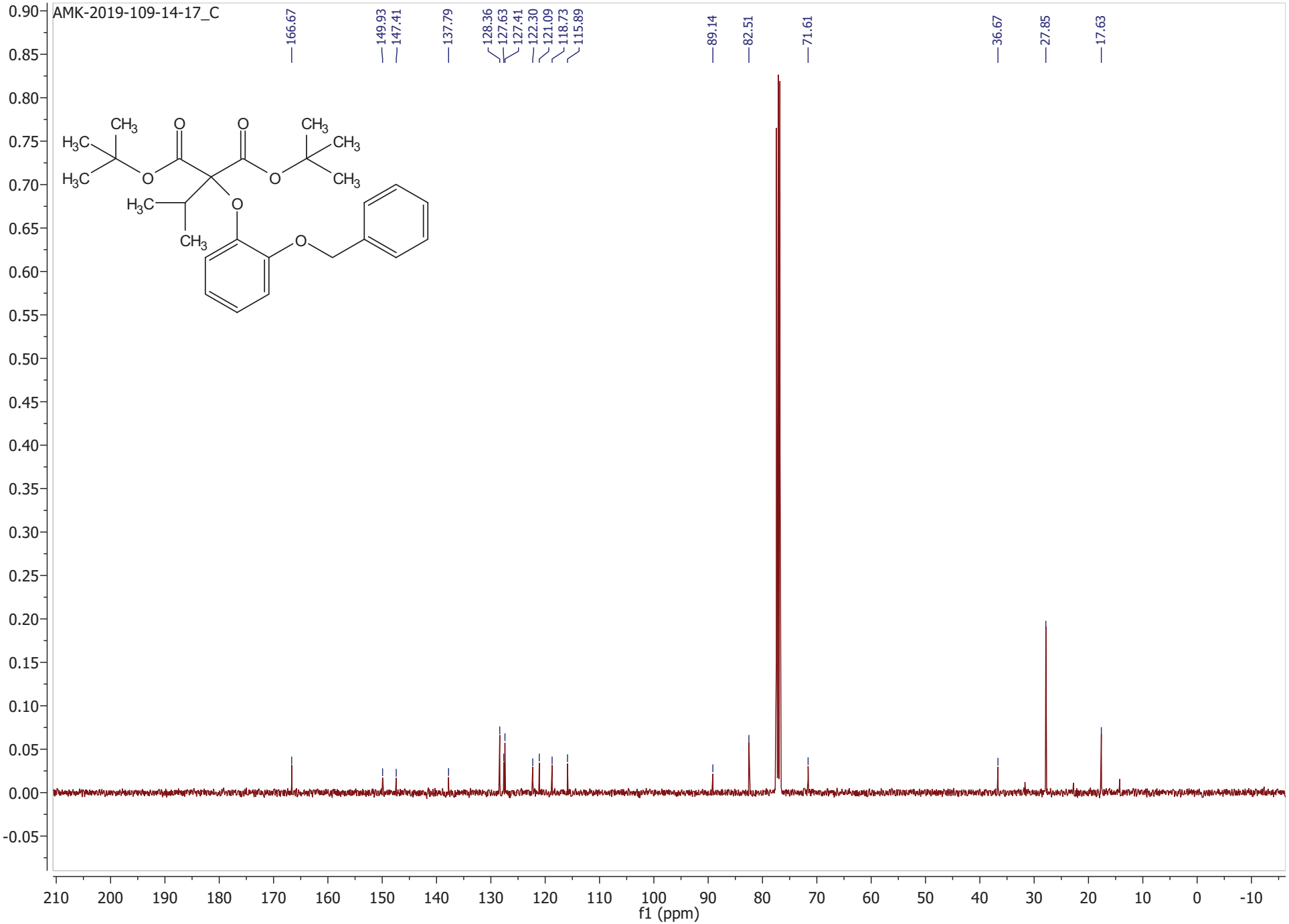
58'

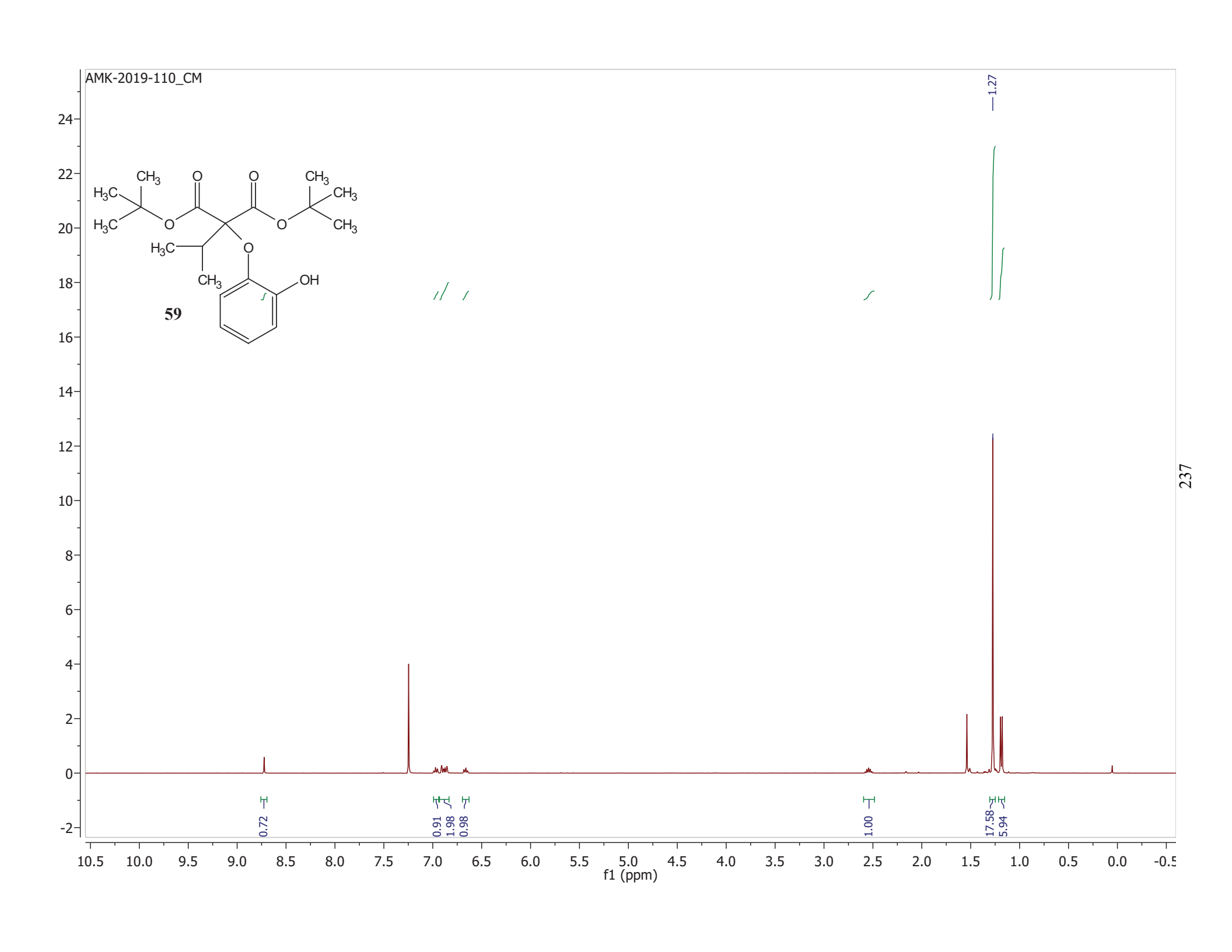
173.05
151.06
141.58
125.83
123.57
119.45
116.69
87.85
83.95
65.85
28.04
26.64
8.12

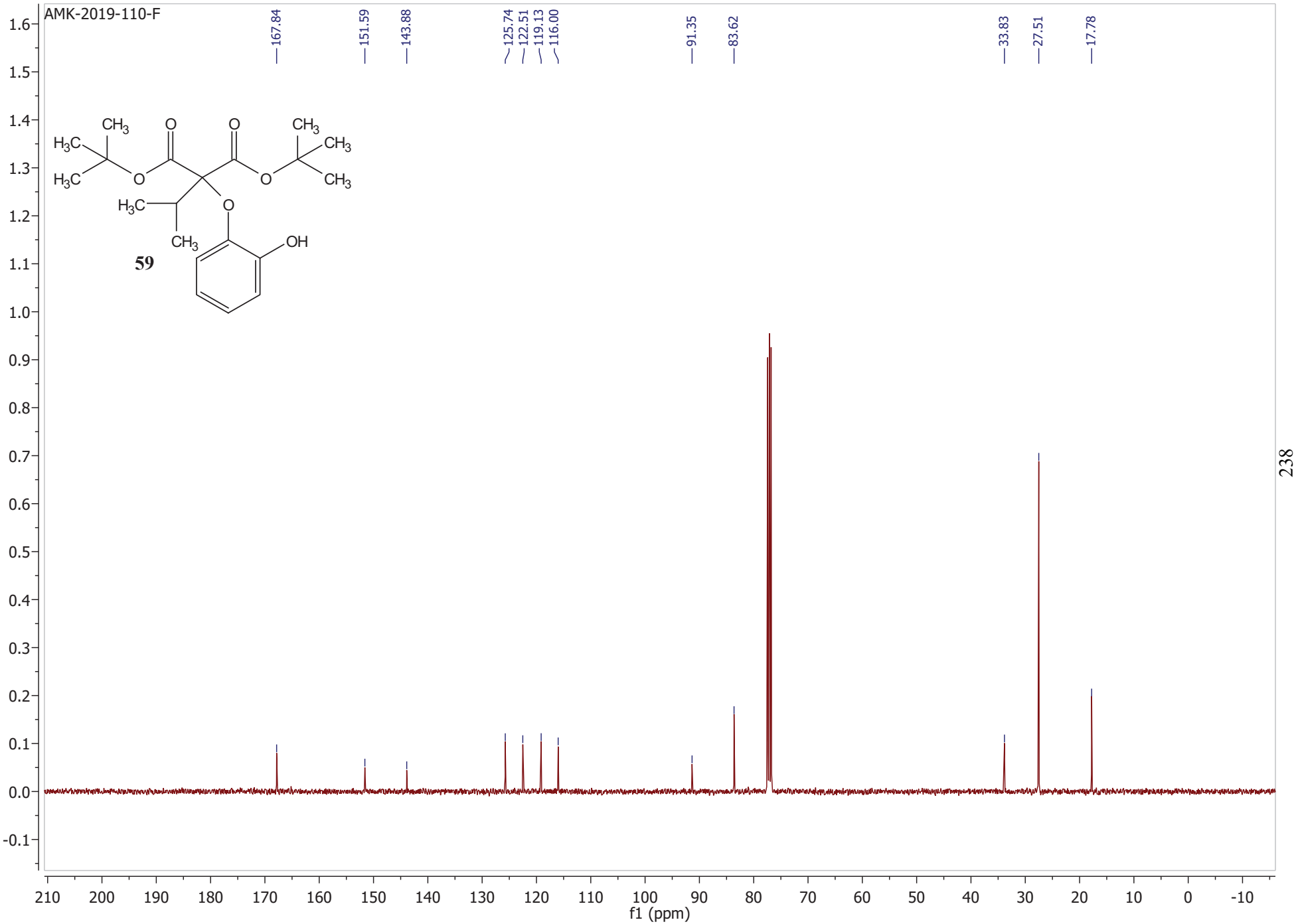
234

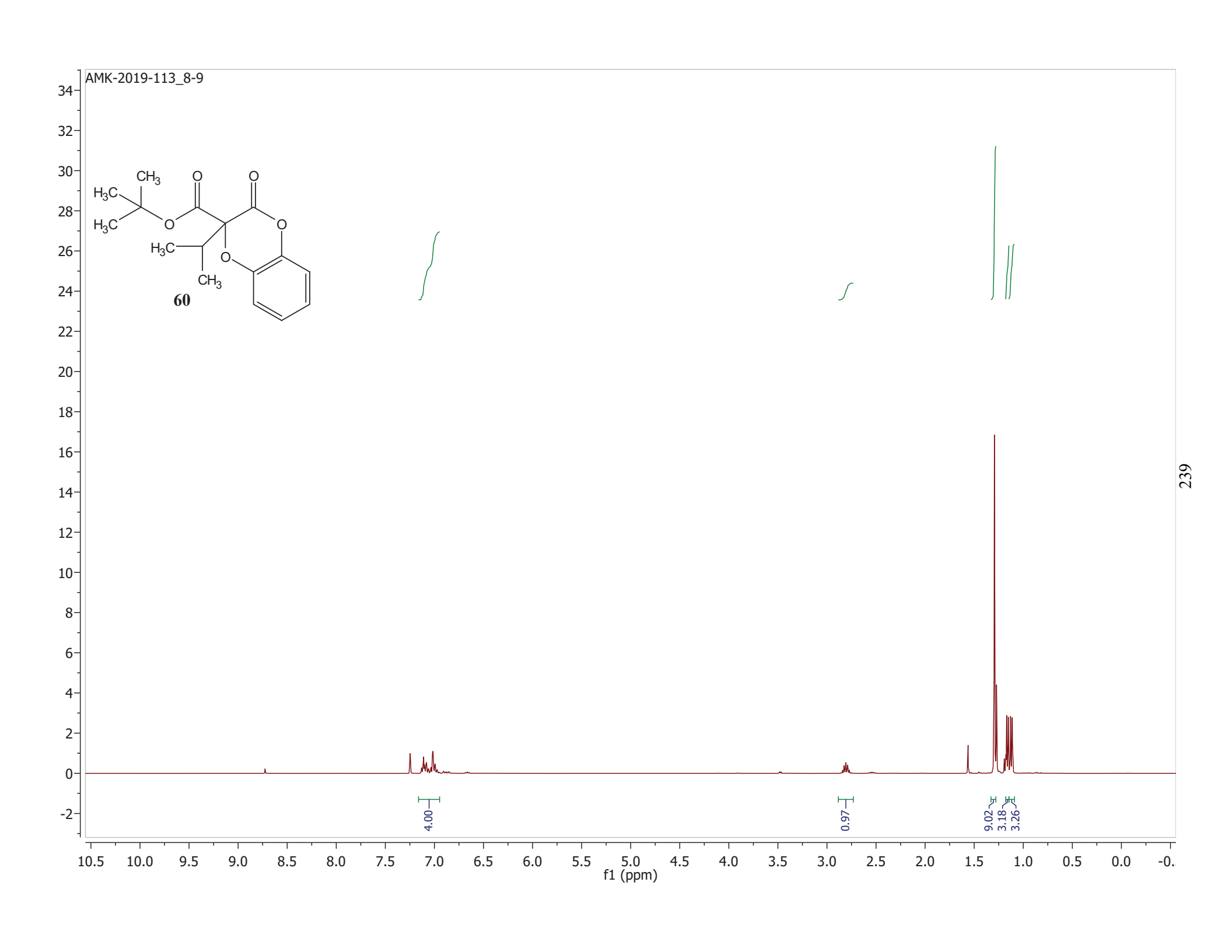
f1 (ppm)

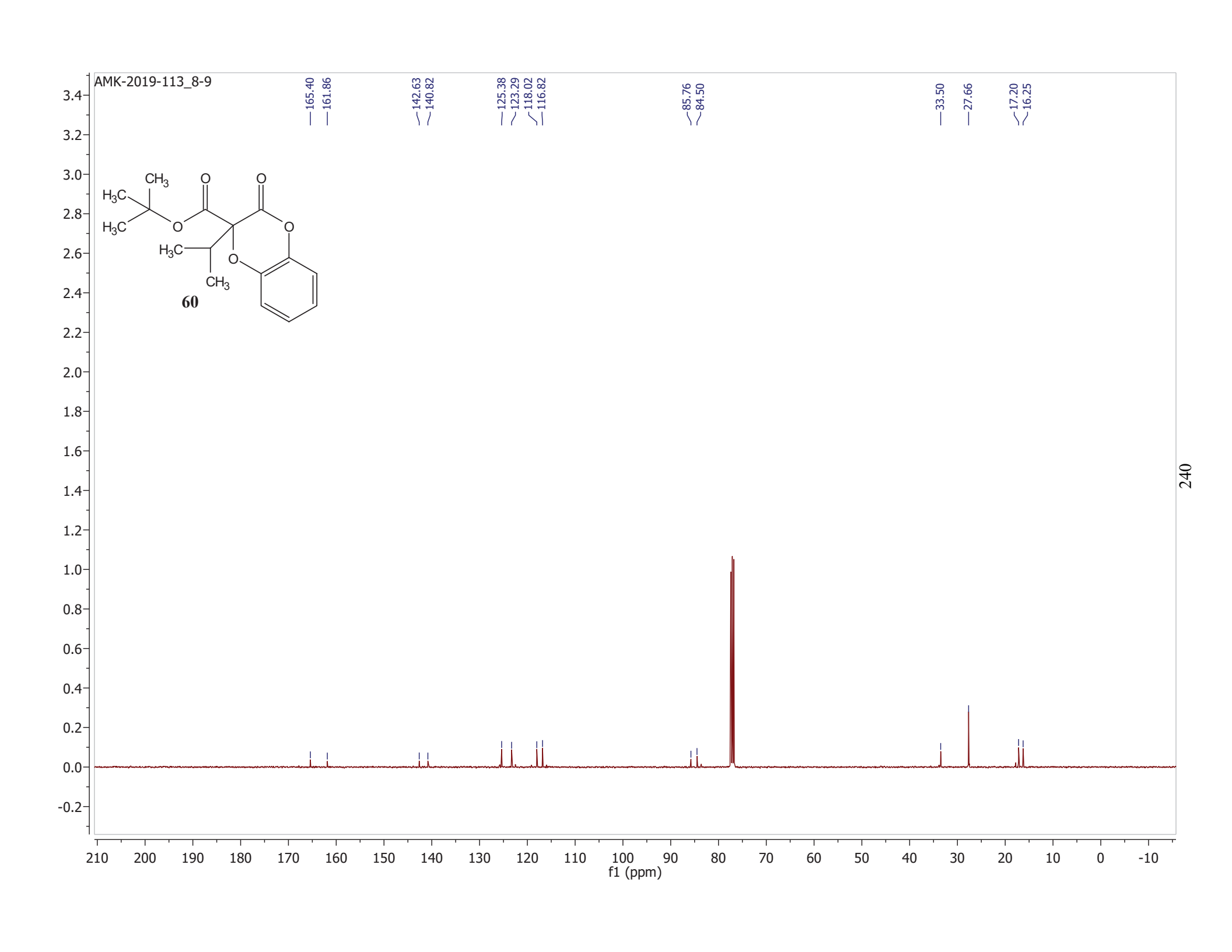

AMK-2019-109-14-17
235
2.02
3.20
3.98
2.00
0.99
17.91
5.96
f1 (ppm)

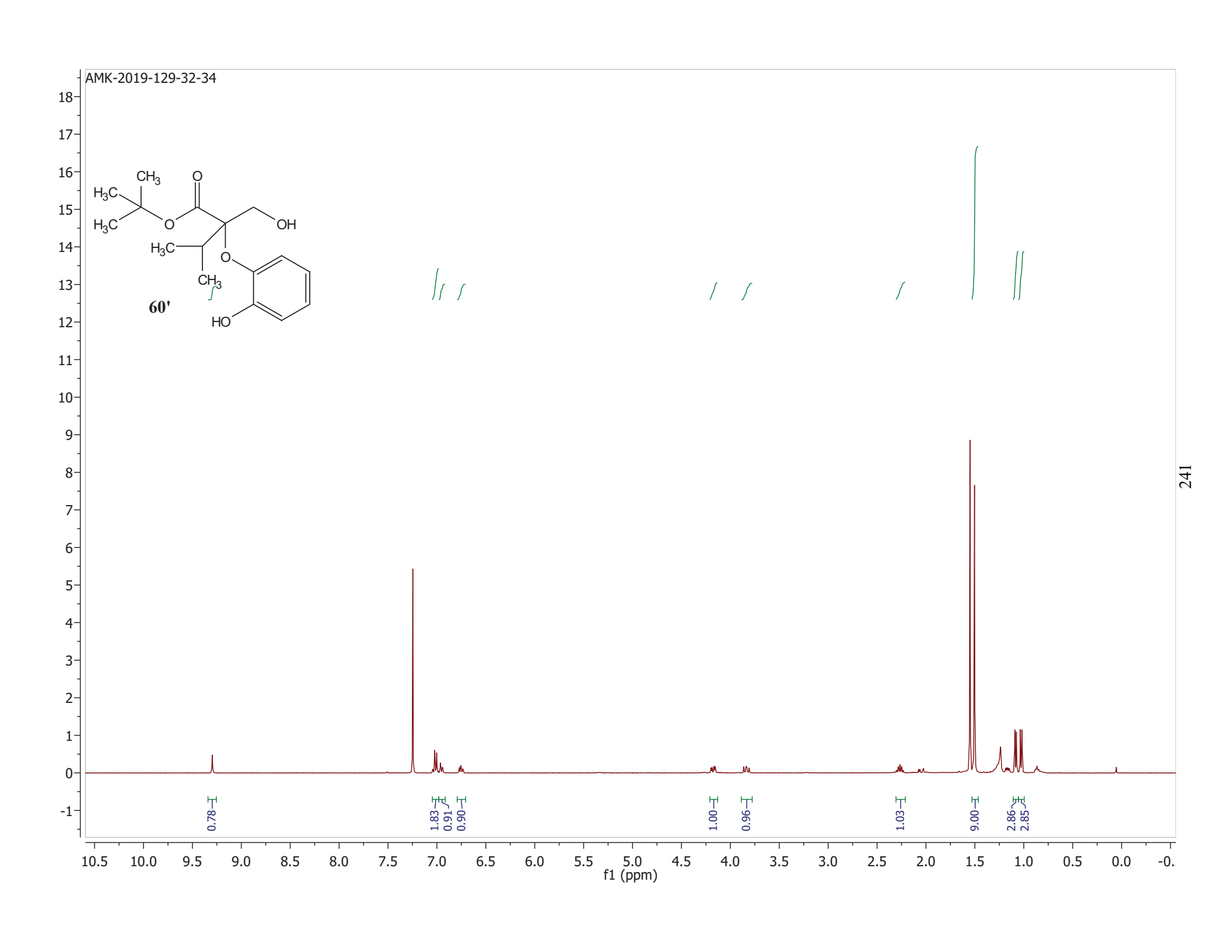

AMK-2019-109-14-17_C
166.67
149.93
147.41
137.79
128.36
127.63
127.41
122.30
121.09
118.73
115.89
89.14
82.51
71.61
36.67
27.85
17.63
f1 (ppm)

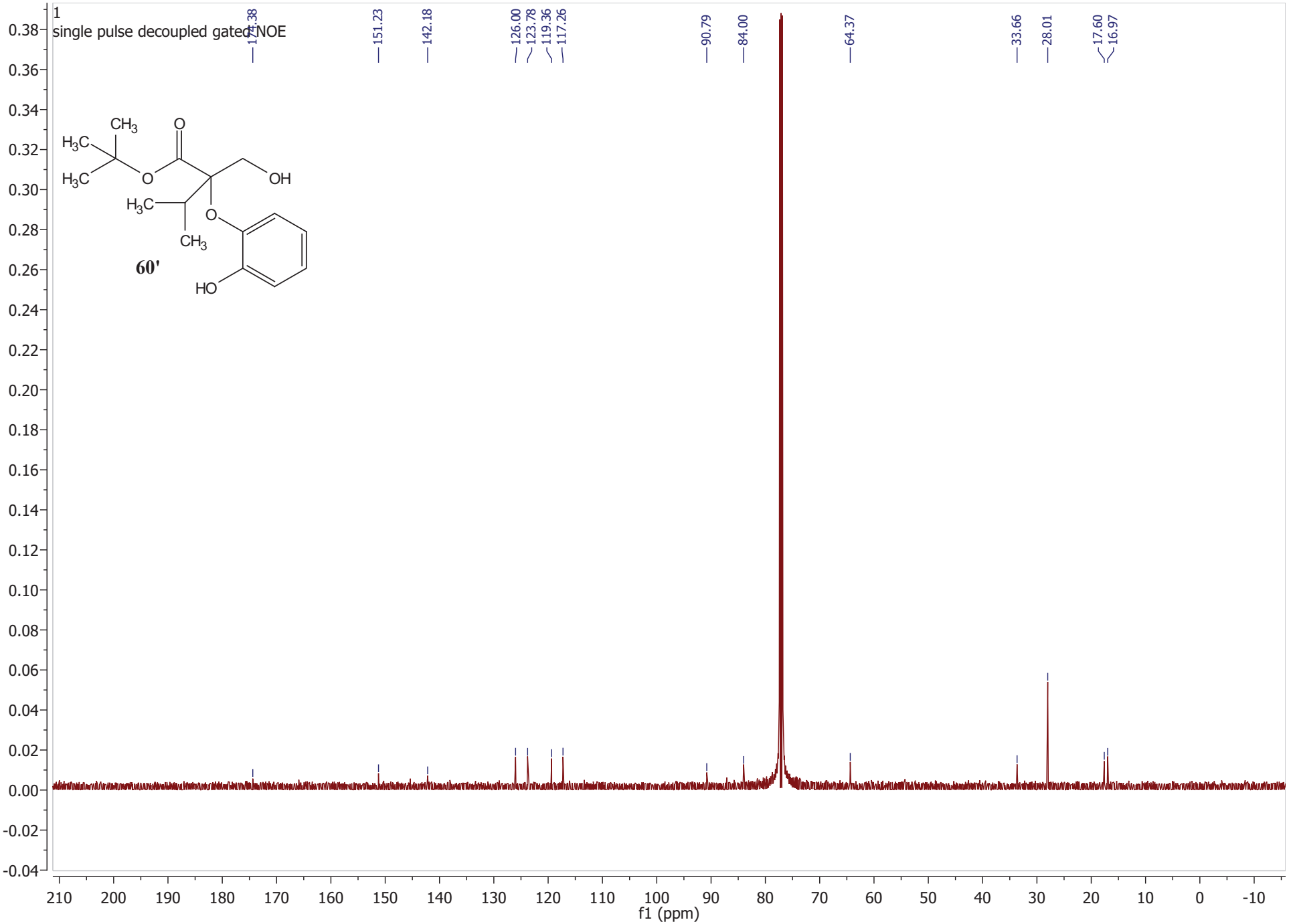

AMK-2019-110_CM
1.27
59
0.72
0.91
1.98
0.98
1.00
17.58
5.94
f1 (ppm)
237

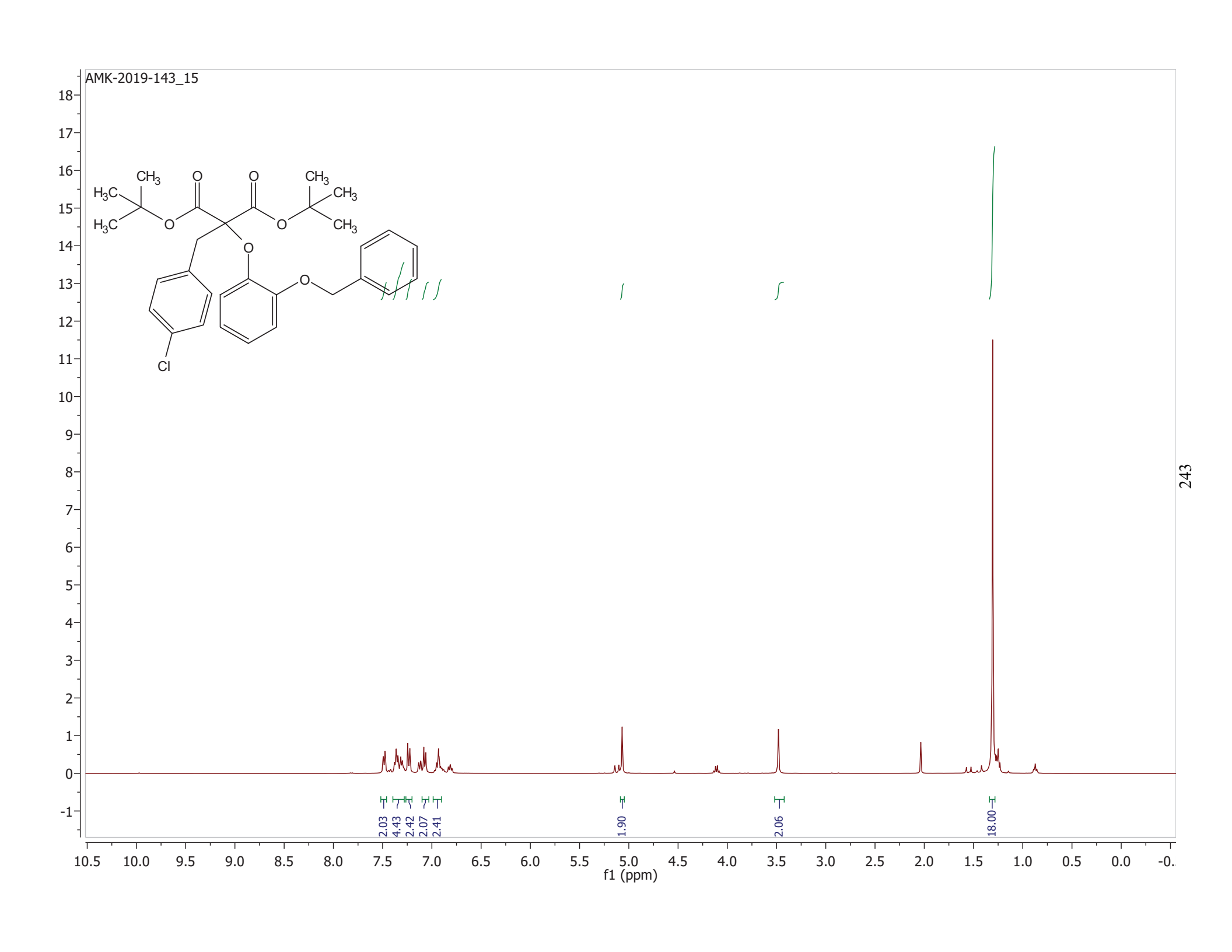

AMK-2019-110-F
167.84
151.59
143.88
125.74
122.51
119.13
116.00
91.35
83.62
33.83
27.51
17.78
59
f1 (ppm)
238

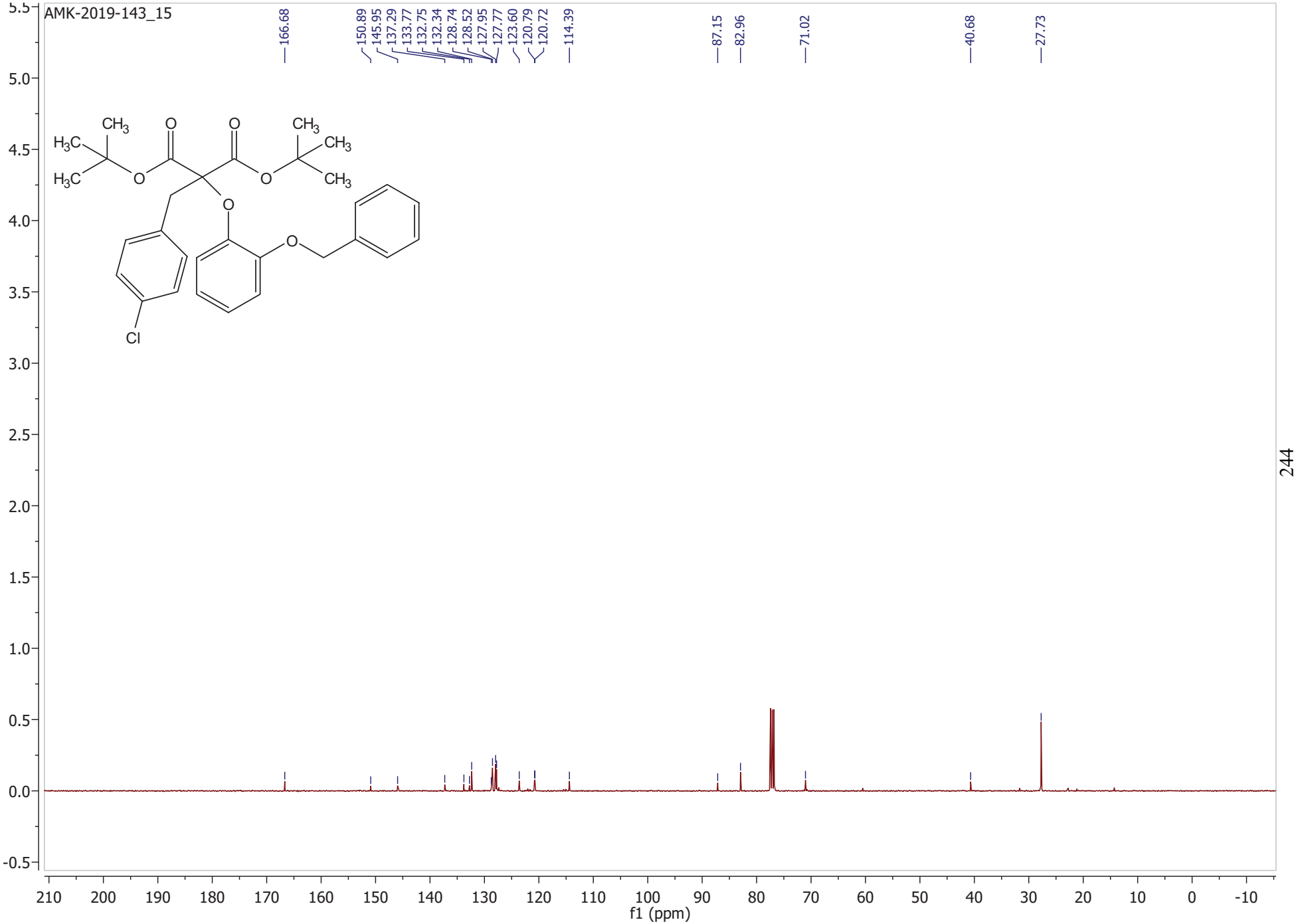

AMK-2019-113_8-9
60
4.00
0.97
9.02
3.18
3.26
f1 (ppm)
239

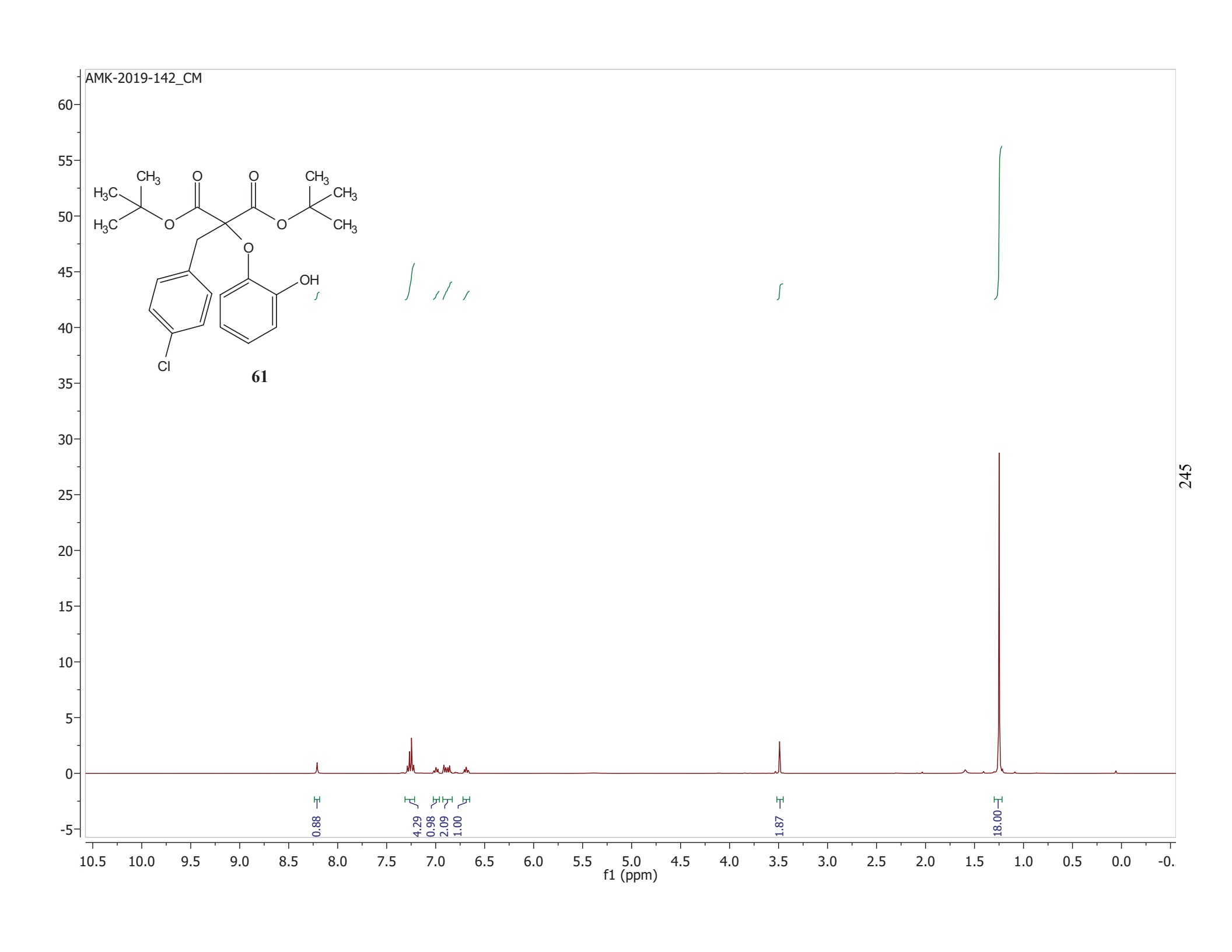

AMK-2019-113_8-9
165.40
161.86
142.63
140.82
125.38
123.29
118.02
116.82
85.76
84.50
33.50
27.66
17.20
16.25
60
240
f1 (ppm)

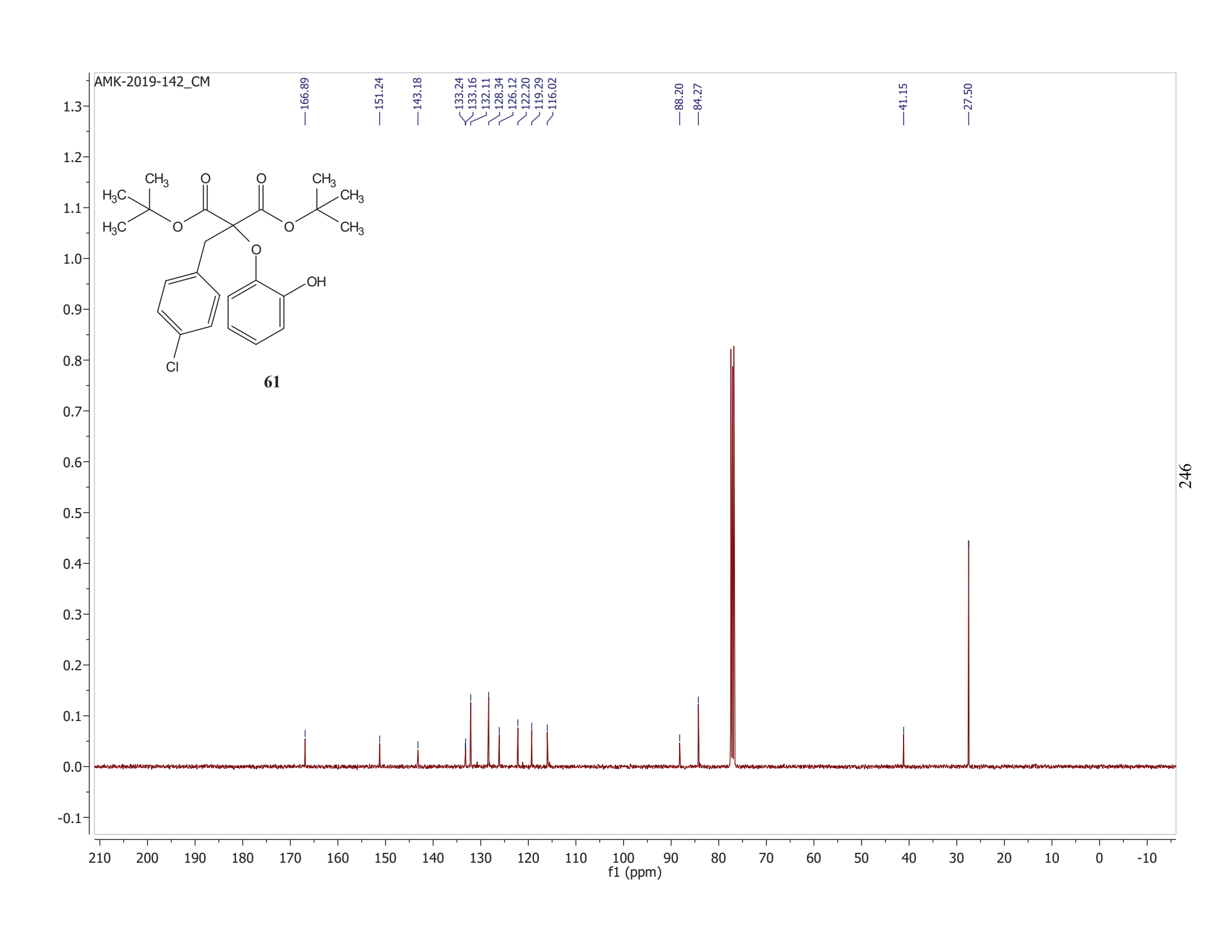

AMK-2019-129-32-34
60'
f1 (ppm)
241


1
single pulse decoupled gated NOE
171.38
151.23
142.18
126.00
123.78
119.36
117.26
90.79
84.00
64.37
33.66
28.01
17.60
16.97
60'
242
f1 (ppm)

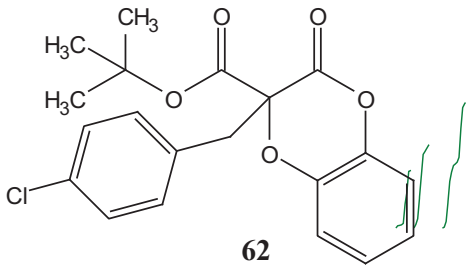

AMK-2019-143_15
CH3
H3C
H3C
O
O
O
O
CH3
CH3
CH3
O
O
Cl
243
2.03
4.43
2.42
2.07
2.41
1.90
2.06
18.00
f1 (ppm)


AMK-2019-143_15
166.68
150.89
145.95
137.29
133.77
132.75
132.34
128.74
128.52
127.95
127.77
123.60
120.79
120.72
114.39
87.15
82.96
71.02
40.68
27.73
CH3
H3C
H3C
O
O
O
CH3
CH3
CH3
O
O
Cl
244
f1 (ppm)


AMK-2019-142_CM
CH3
O
O
CH3
H3C
CH3
H3C
O
O
CH3
O
OH
Cl
61
0.88
4.29
0.98
2.09
1.00
1.87
18.00
f1 (ppm)
245


AMK-2019-142_CM
166.89
151.24
143.18
133.24
133.16
132.11
128.34
126.12
122.20
119.29
116.02
88.20
84.27
41.15
27.50
CH3
H3C
H3C
O
O
O
CH3
CH3
CH3
O
OH
Cl
61
246
f1 (ppm)

1
single_pulse

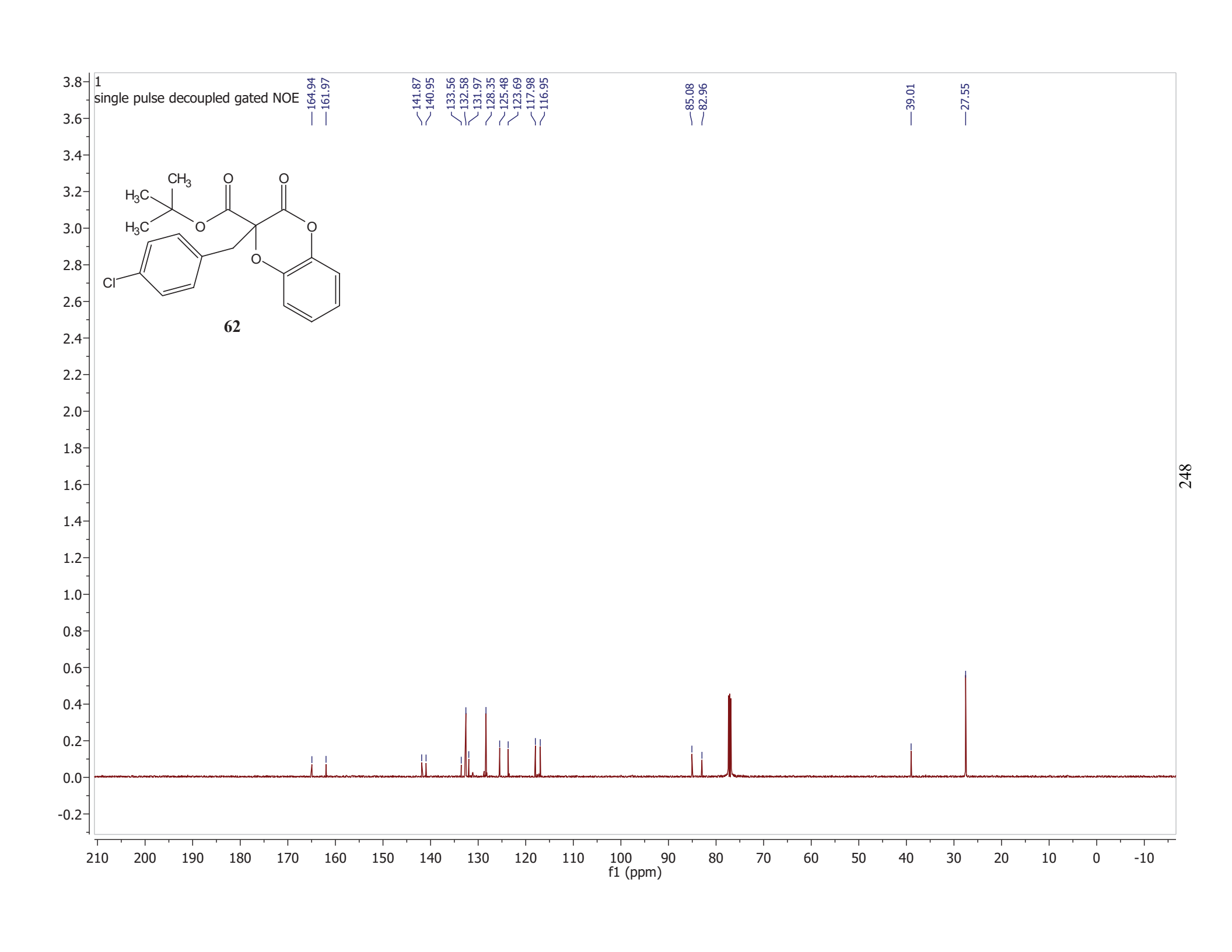


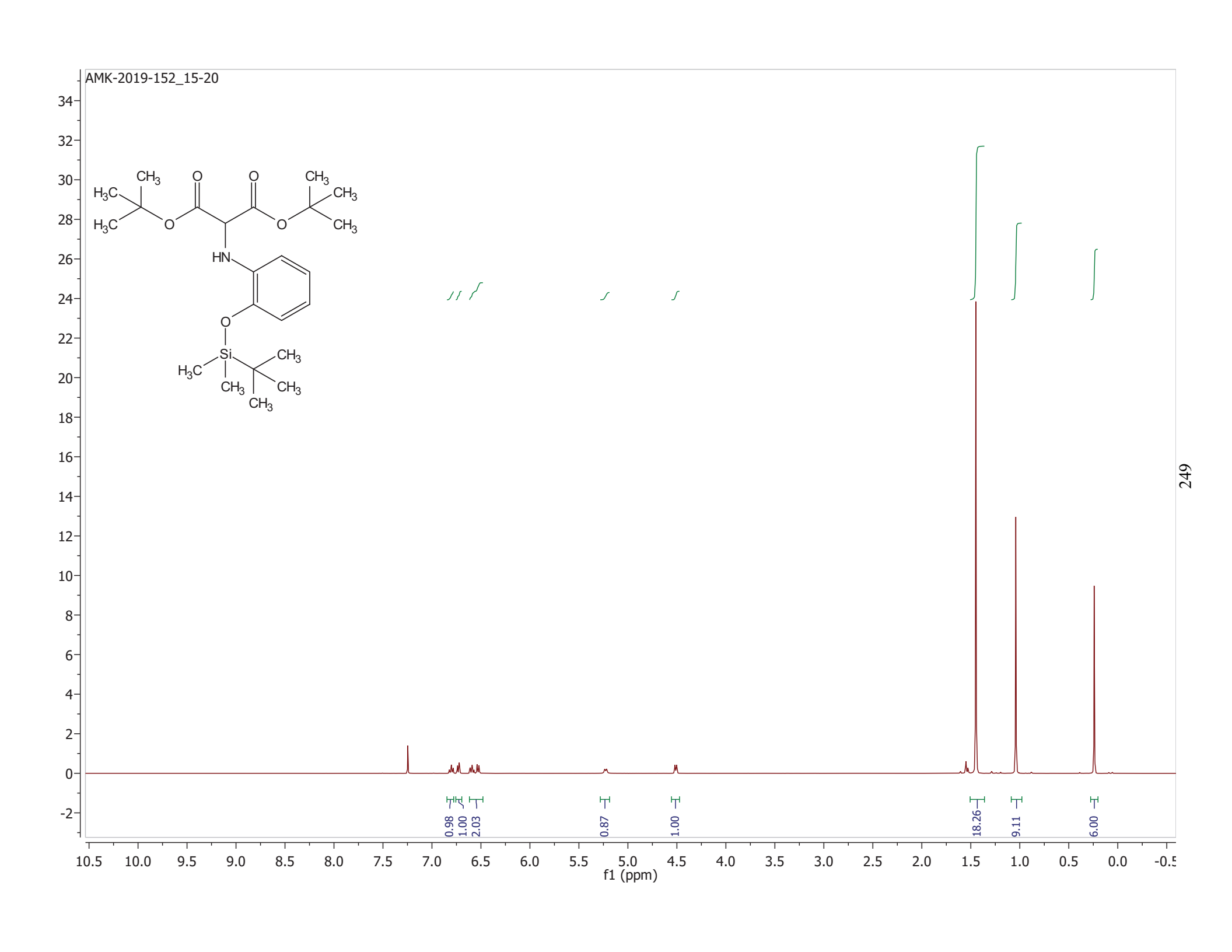
62

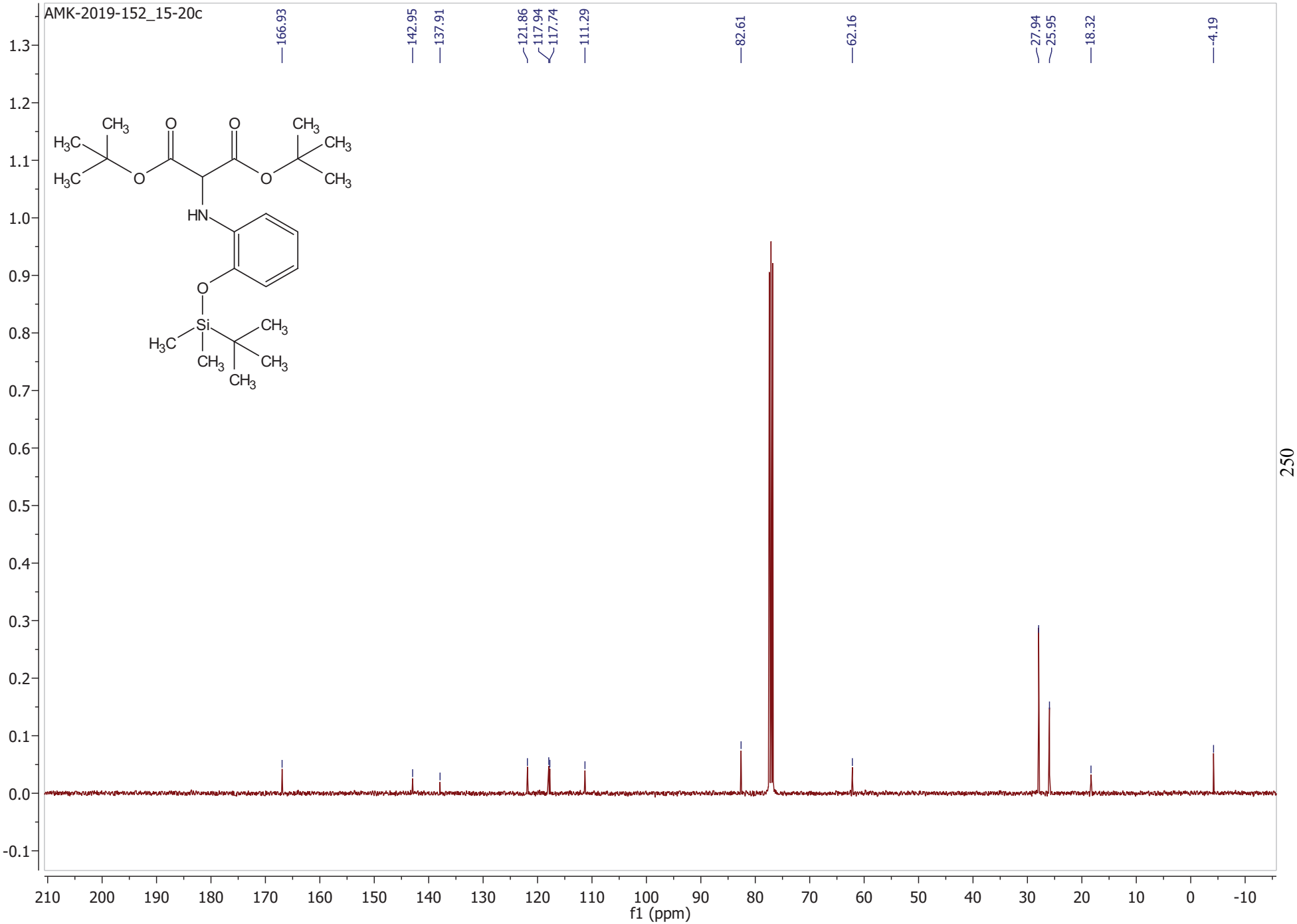
1.98
2.86
4.31
2.07
9.00

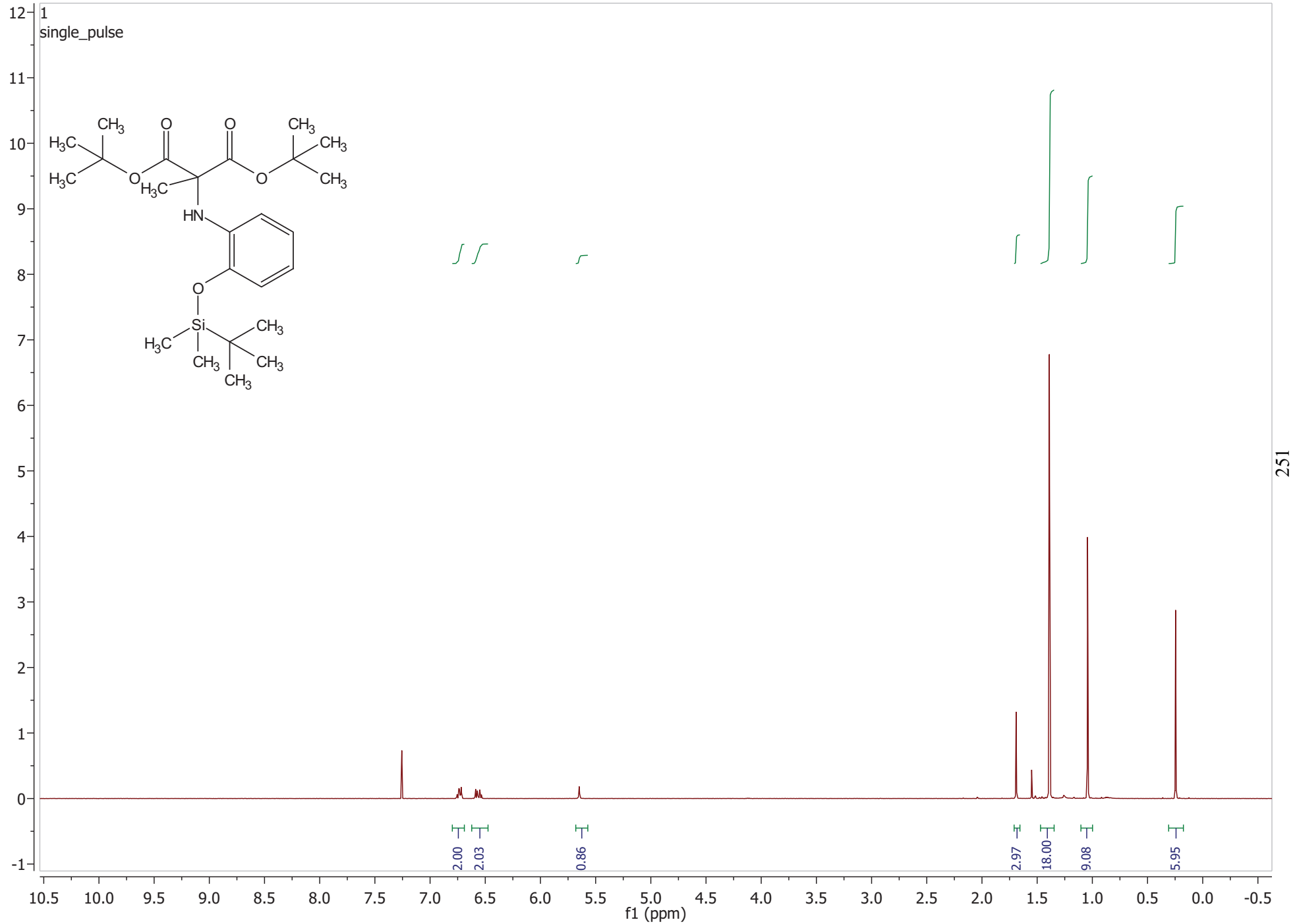
f1 (ppm)

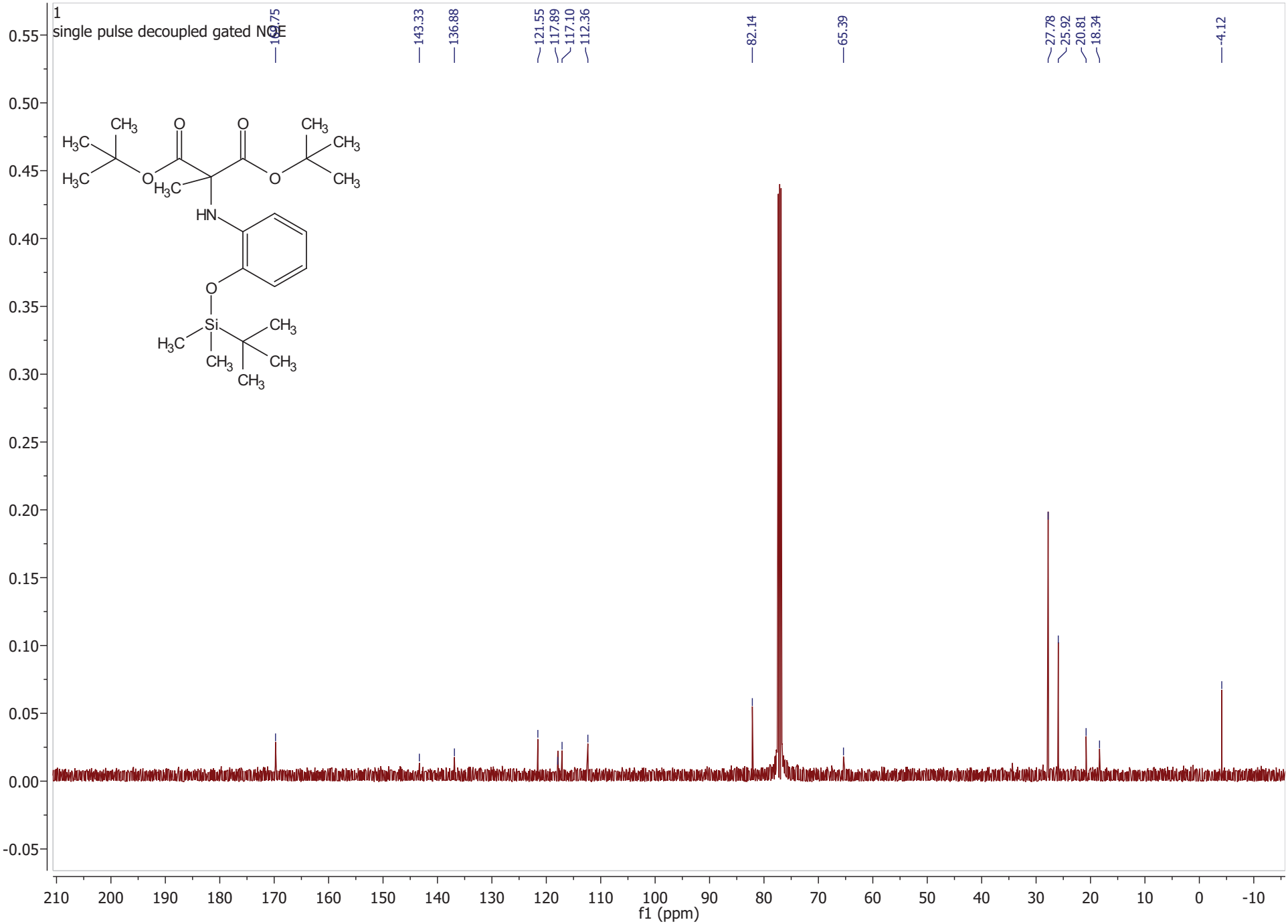
247

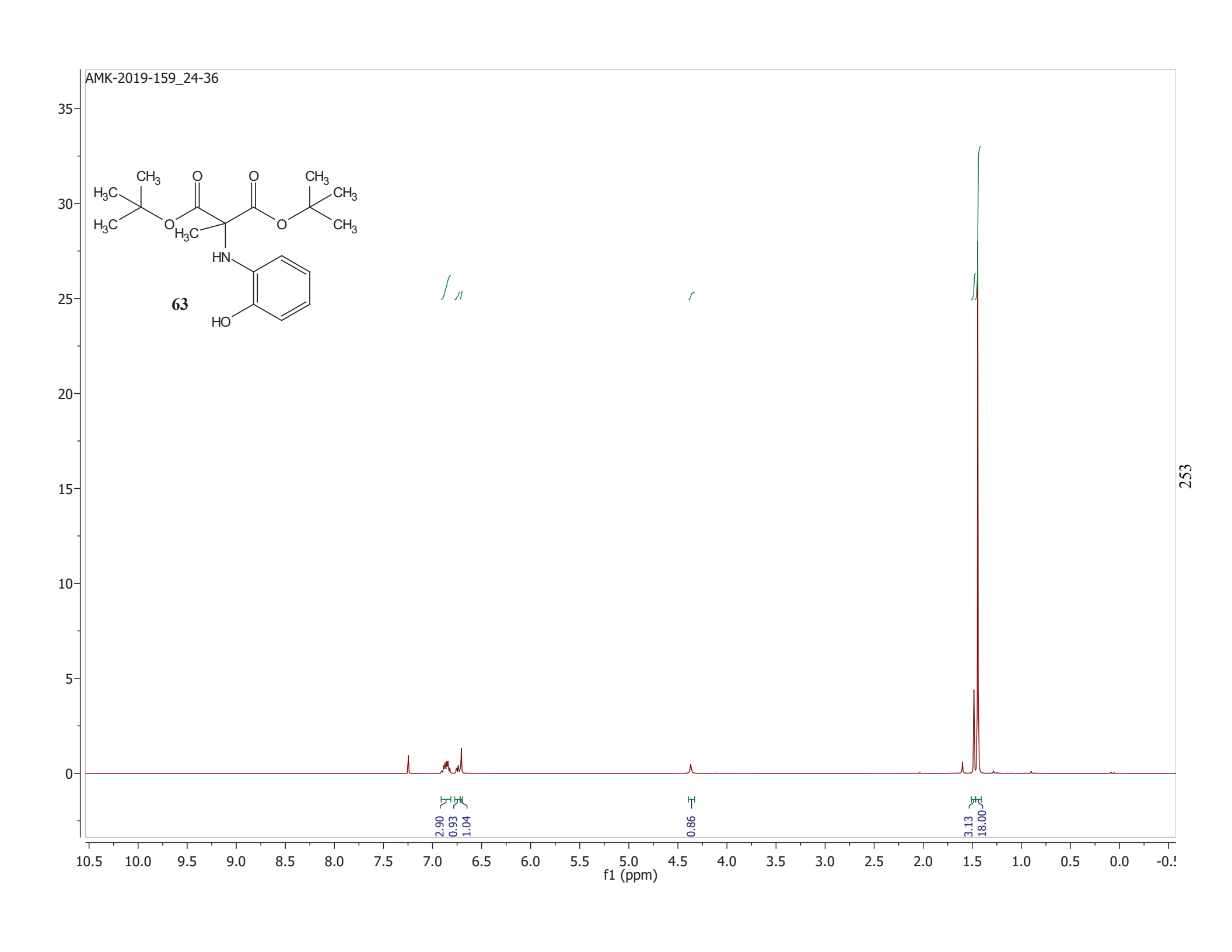

1
single pulse decoupled gated NOE
164.94
161.97
141.87
140.95
133.56
132.58
131.97
128.35
125.48
123.69
117.98
116.95
85.08
82.96
39.01
27.55
CH3
H3C
H3C
O
O
O
O
O
Cl
62
248
f1 (ppm)

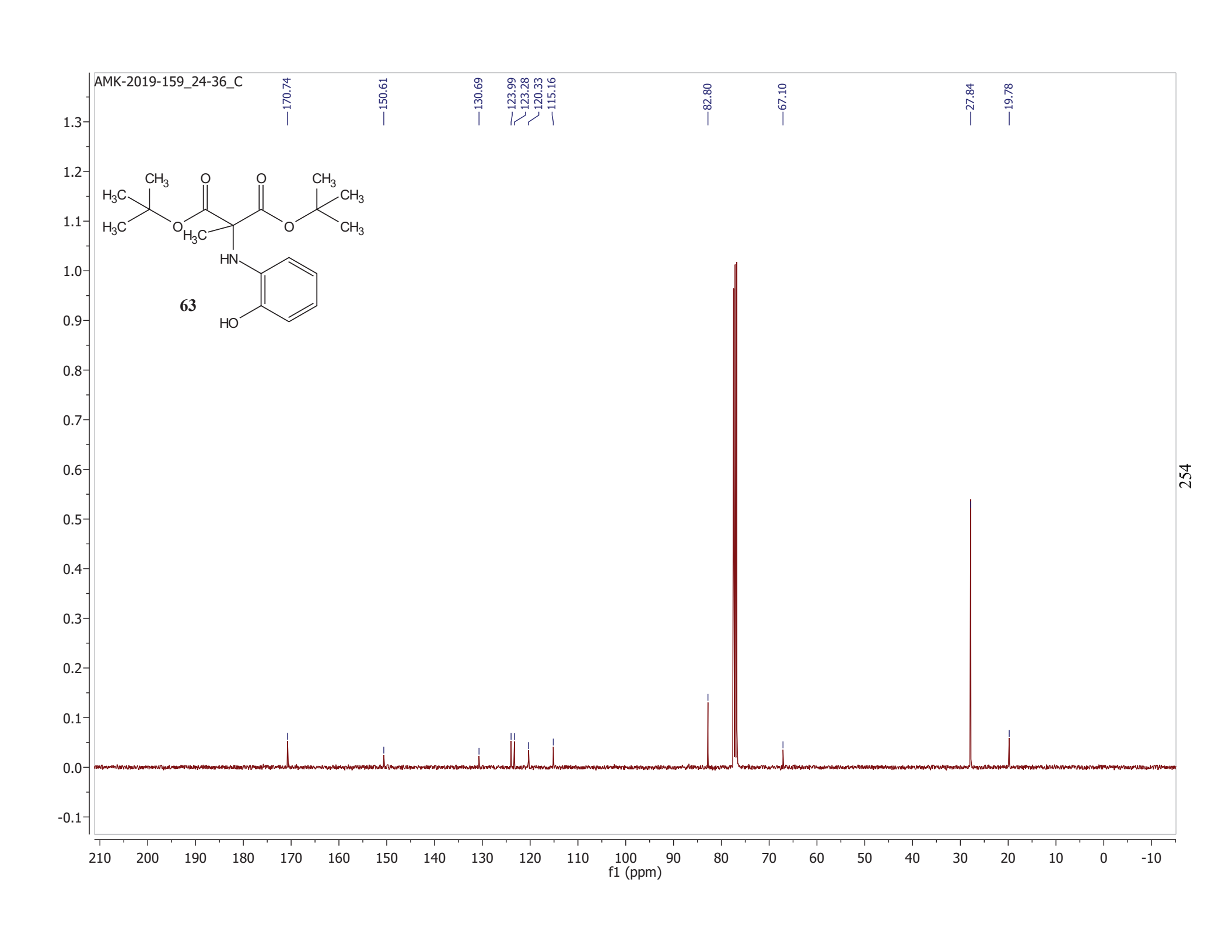

AMK-2019-152_15-20
249
f1 (ppm)
0.98
1.00
2.03
0.87
1.00
18.26
9.11
6.00

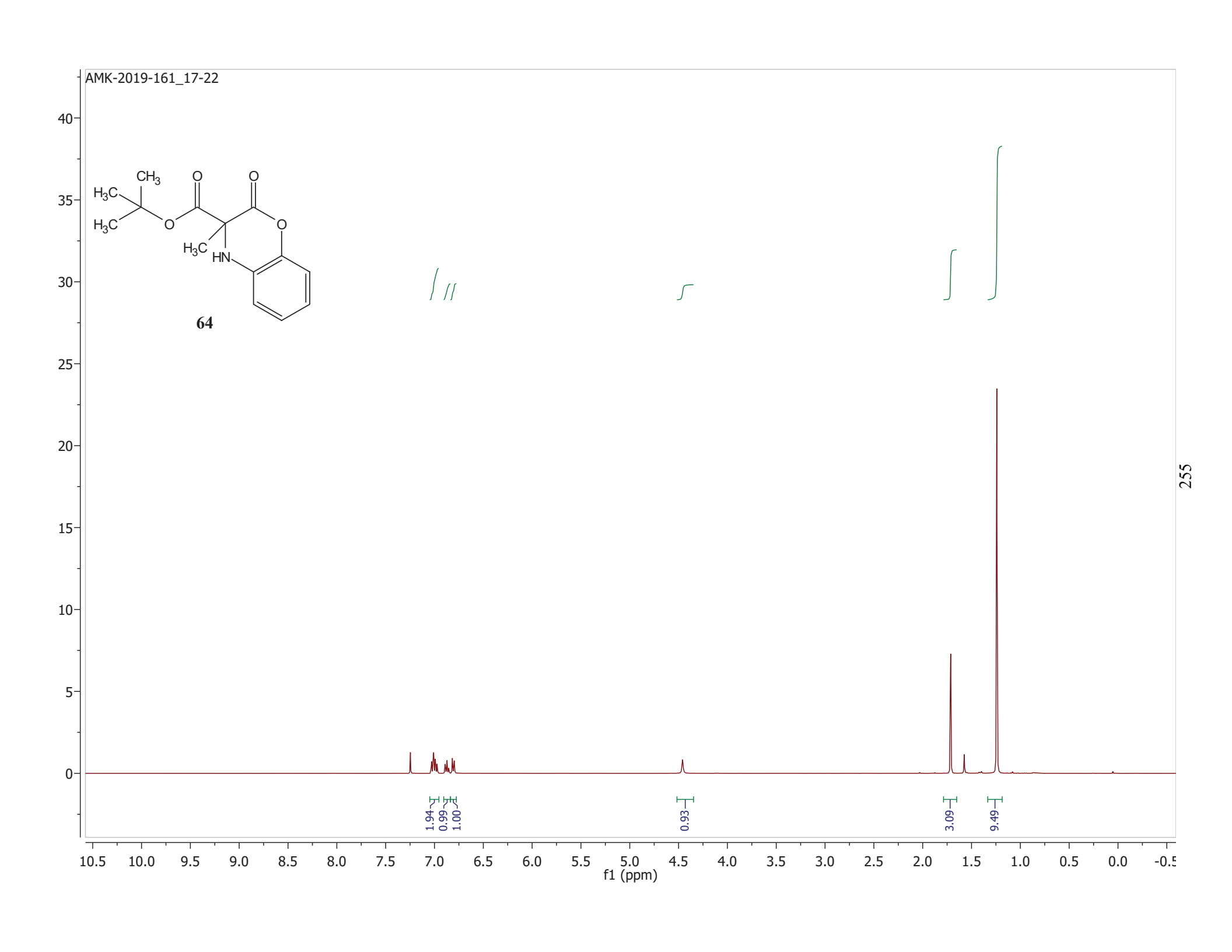

AMK-2019-152_15-20c
166.93
142.95
137.91
121.86
117.94
117.74
111.29
82.61
62.16
27.94
25.95
18.32
-4.19
250
f1 (ppm)

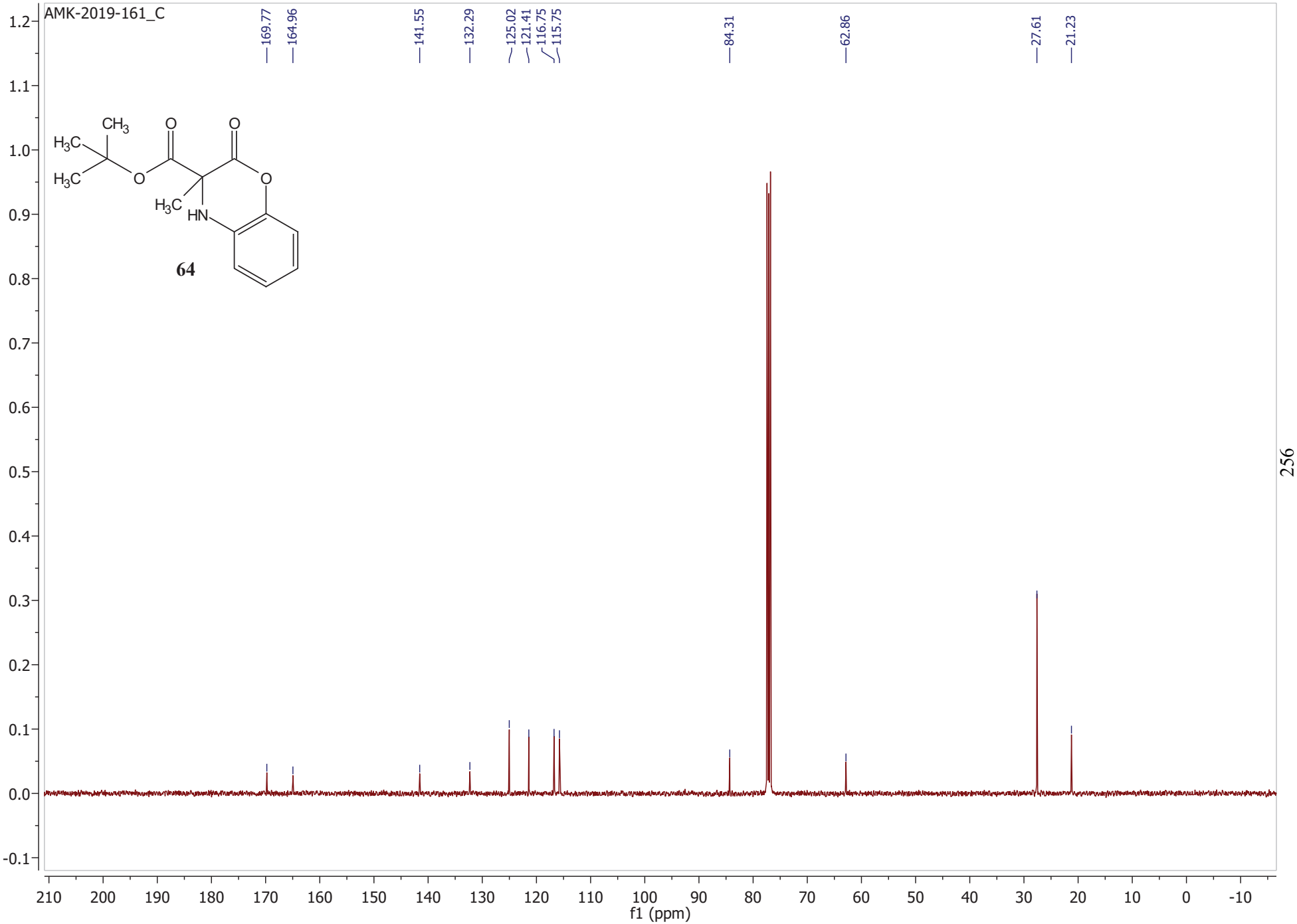

1
single_pulse
CH3
O
O
CH3
H3C
CH3
H3C
O
O
CH3
H3C
HN
O
Si
CH3
H3C
CH3
CH3
CH3
CH3
2.00
2.03
0.86
2.97
18.00
9.08
5.95
f1 (ppm)
251

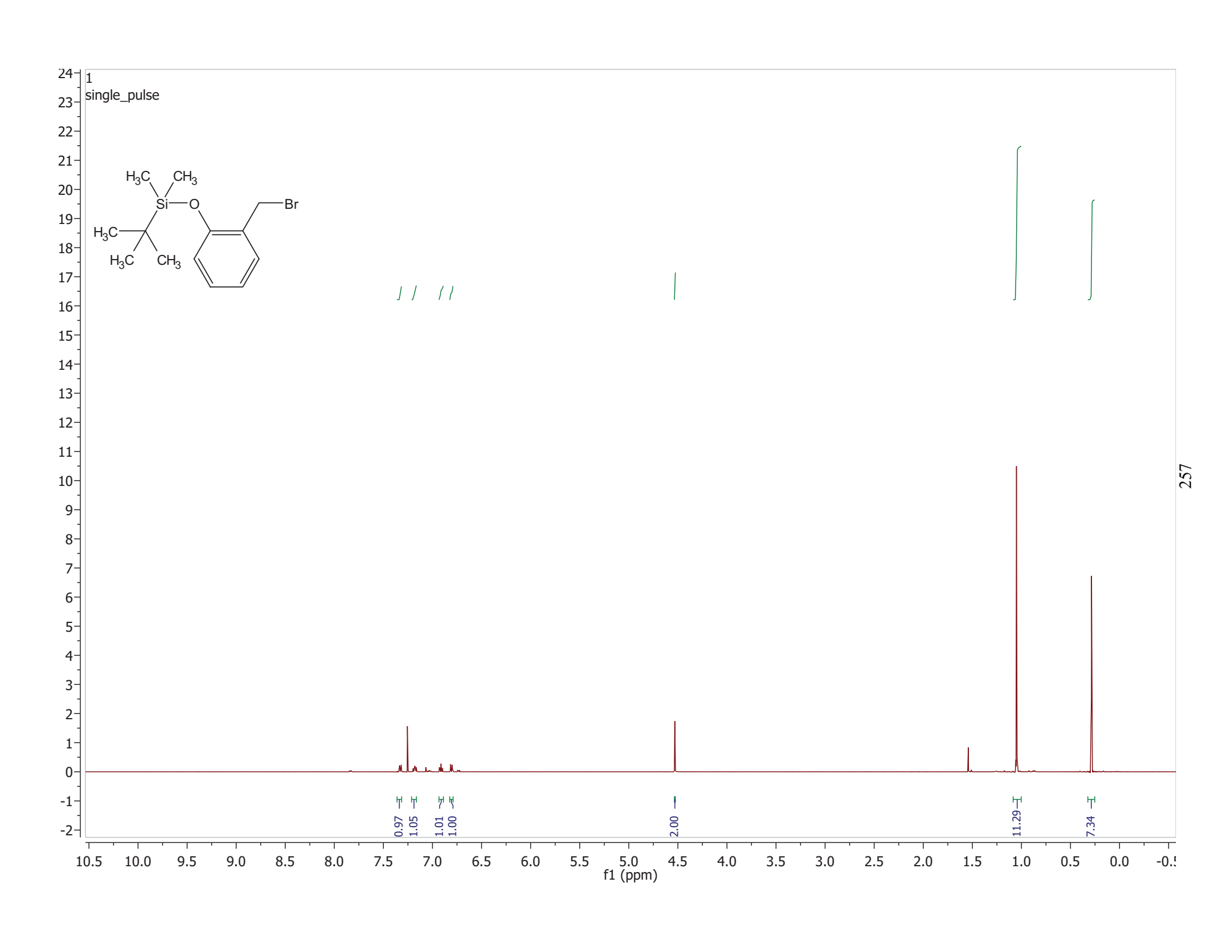

1
single pulse decoupled gated NOE
169.75
143.33
136.88
121.55
117.89
117.10
112.36
82.14
65.39
27.78
25.92
20.81
18.34
-4.12
252
f1 (ppm)

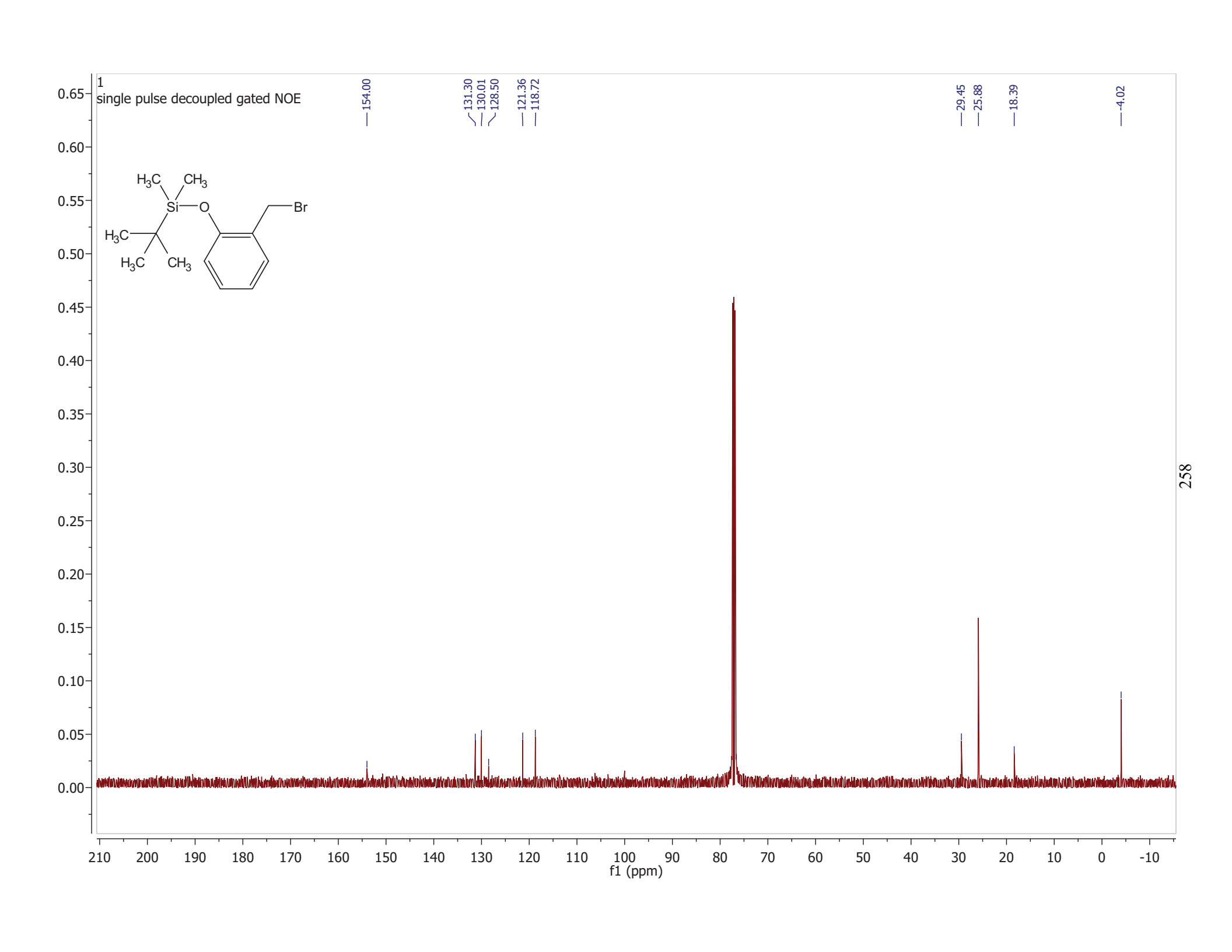

AMK-2019-159_24-36
63
2.90
0.93
1.04
0.86
3.13
18.00
f1 (ppm)
253

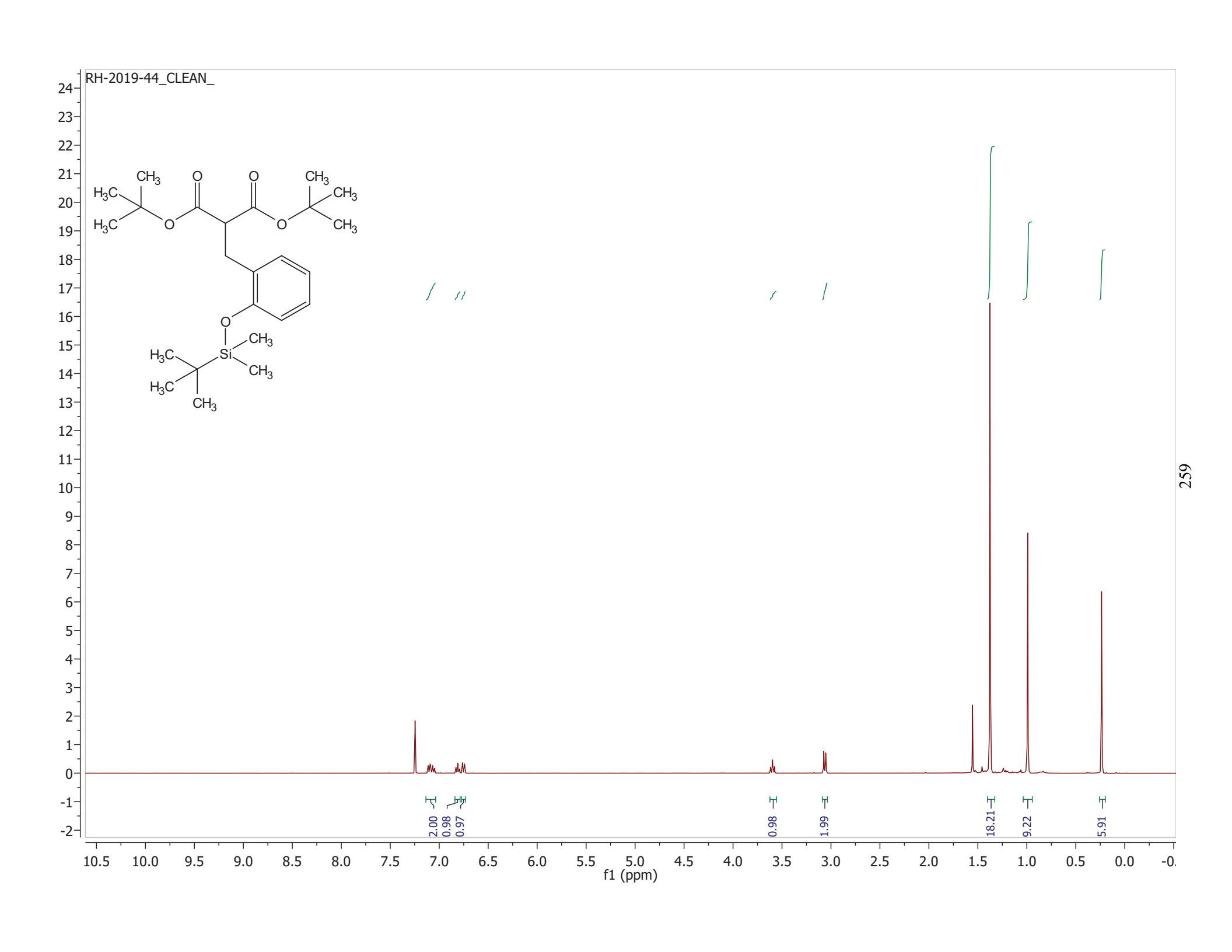

AMK-2019-159_24-36_C
170.74
150.61
130.69
123.99
123.28
120.33
115.16
82.80
67.10
27.84
19.78
63
254
f1 (ppm)

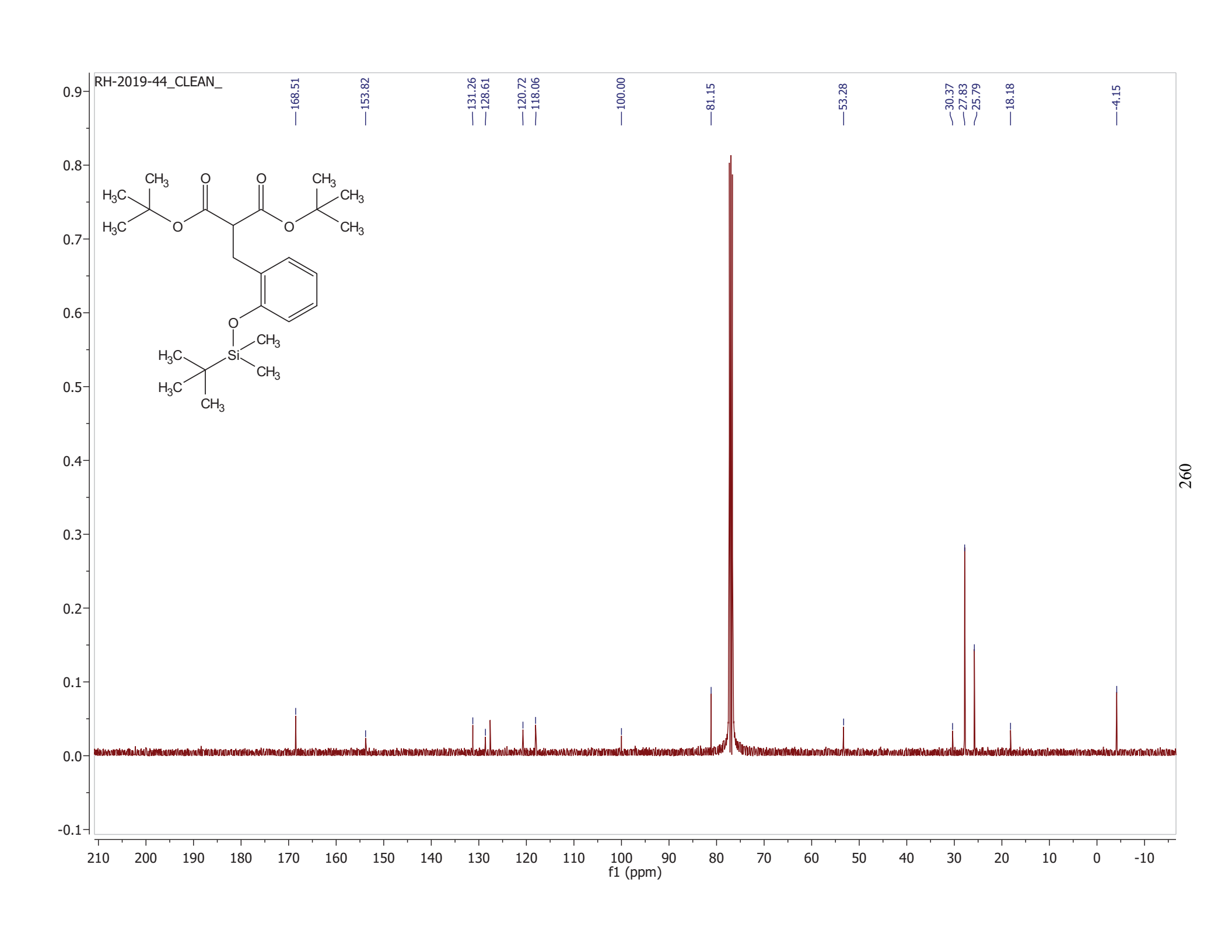

AMK-2019-161_17-22
CH3
H3C
H3C
O
O
O
O
H3C
HN
64
1.94
0.99
1.00
0.93
3.09
9.49
f1 (ppm)
255

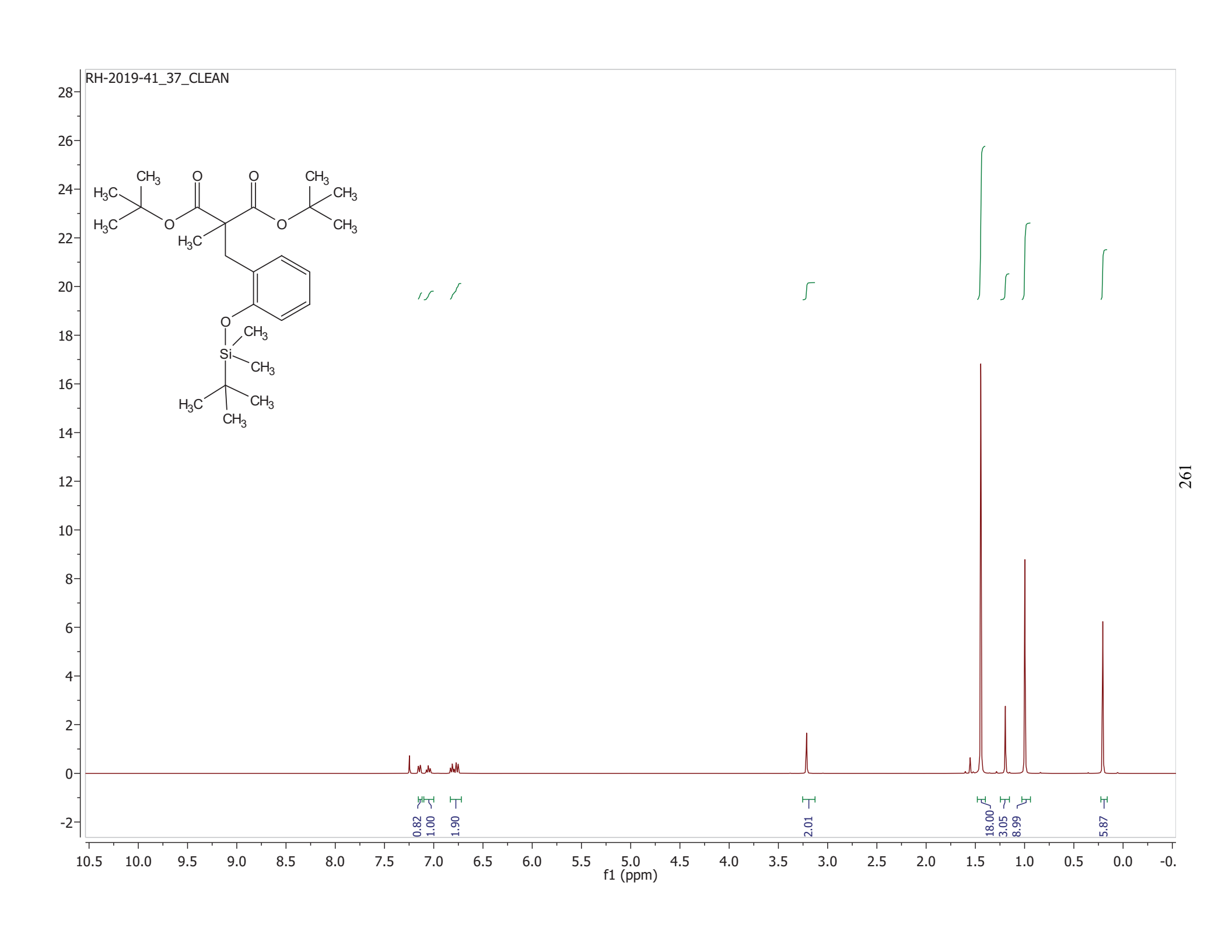

AMK-2019-161_C
169.77
164.96
141.55
132.29
125.02
121.41
116.75
115.75
84.31
62.86
27.61
21.23
CH3
H3C
H3C
O
O
O
O
H3C
HN
64
256
f1 (ppm)

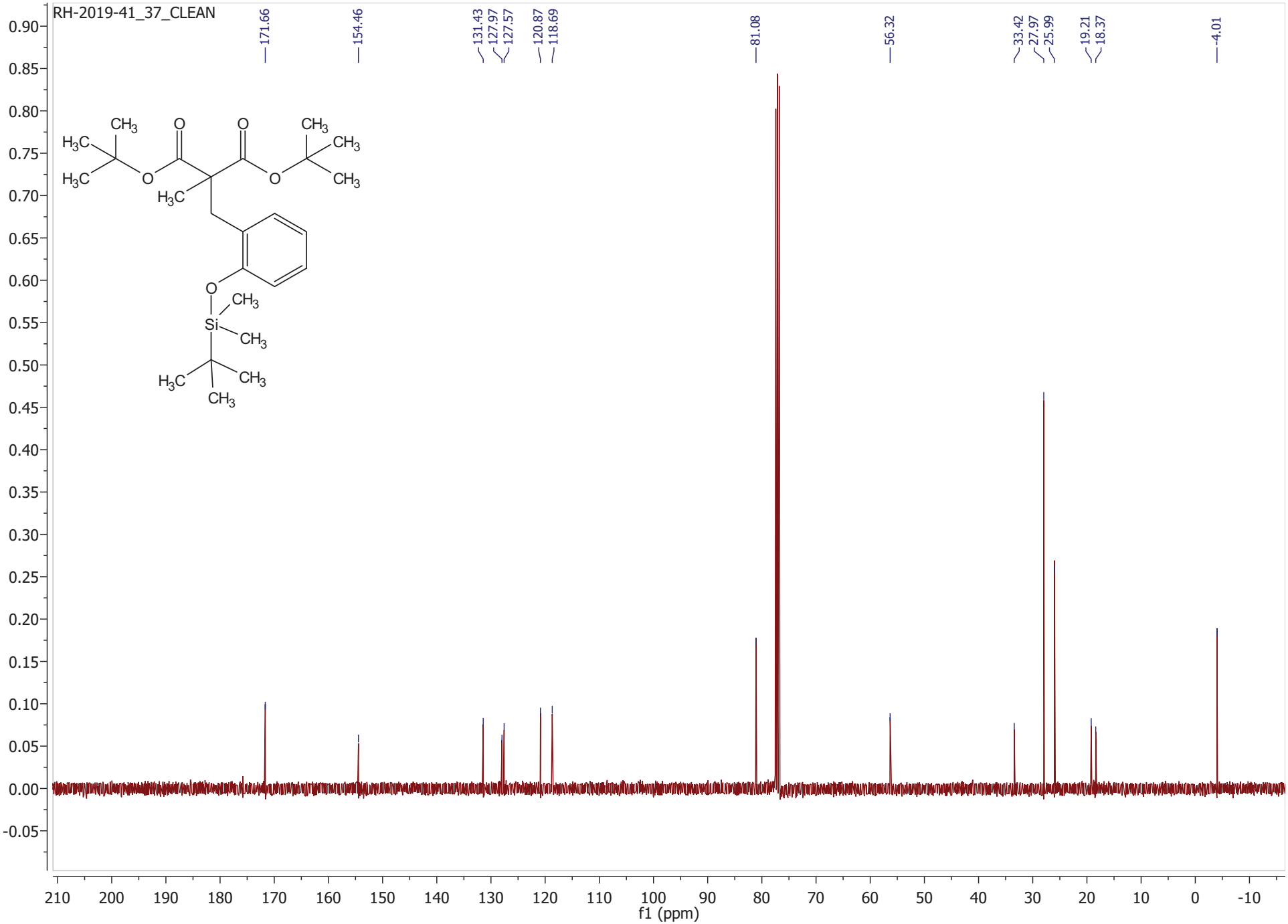

1
single_pulse
H3C
CH3
Si
O
Br
H3C
H3C
CH3
257
0.97
1.05
1.01
1.00
2.00
11.29
7.34
f1 (ppm)


1
single pulse decoupled gated NOE
154.00
131.30
130.01
128.50
121.36
118.72
29.45
25.88
18.39
-4.02
H3C
CH3
Si
O
Br
H3C
H3C
CH3
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
258

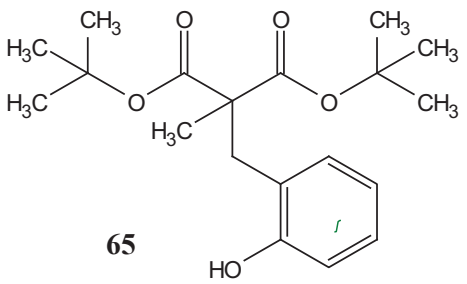

RH-2019-44_CLEAN_
259
f1 (ppm)
2.00
0.98
0.97
0.98
1.99
18.21
9.22
5.91


RH-2019-44_CLEAN_
168.51
153.82
131.26
128.61
120.72
118.06
100.00
81.15
53.28
30.37
27.83
25.79
18.18
-4.15
260
f1 (ppm)


RH-2019-41_37_CLEAN
261
f1 (ppm)
0.82
1.00
1.90
2.01
18.00
3.05
8.99
5.87


RH-2019-41_37_CLEAN
171.66
154.46
131.43
127.97
127.57
120.87
118.69
81.08
56.32
33.42
27.97
25.99
19.21
18.37
-4.01
262
f1 (ppm)

RH-2019-34-42_CLEAN_METHYL

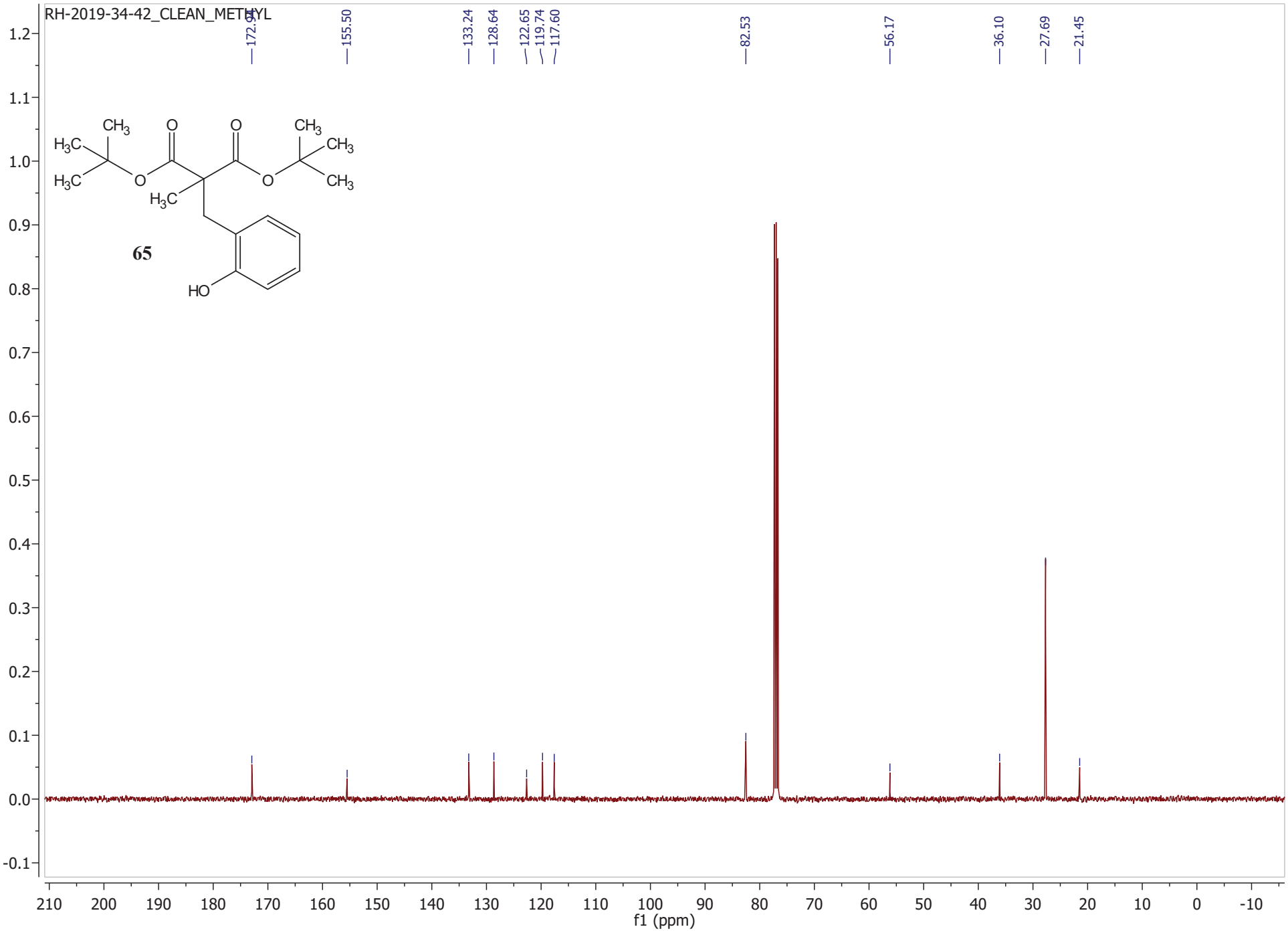


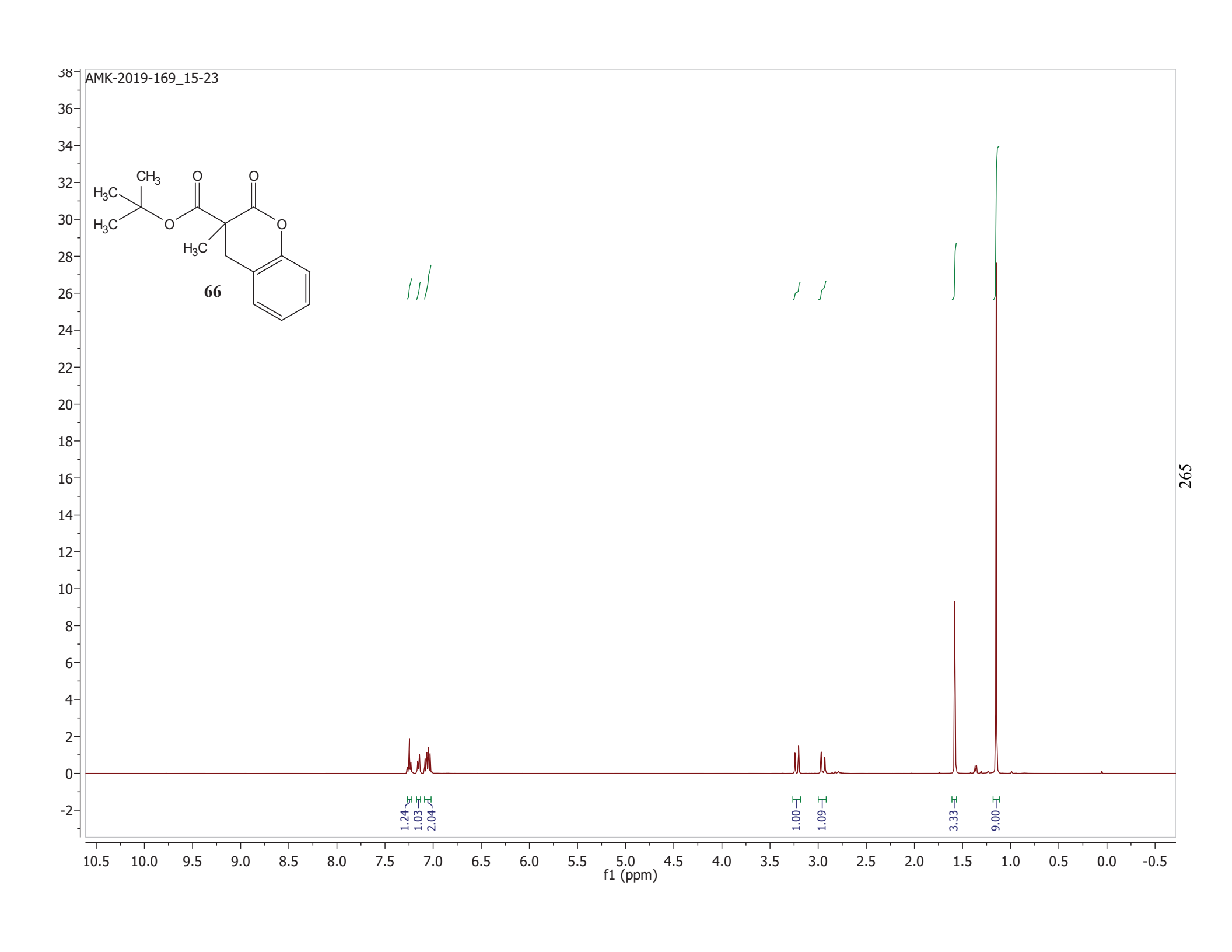
65

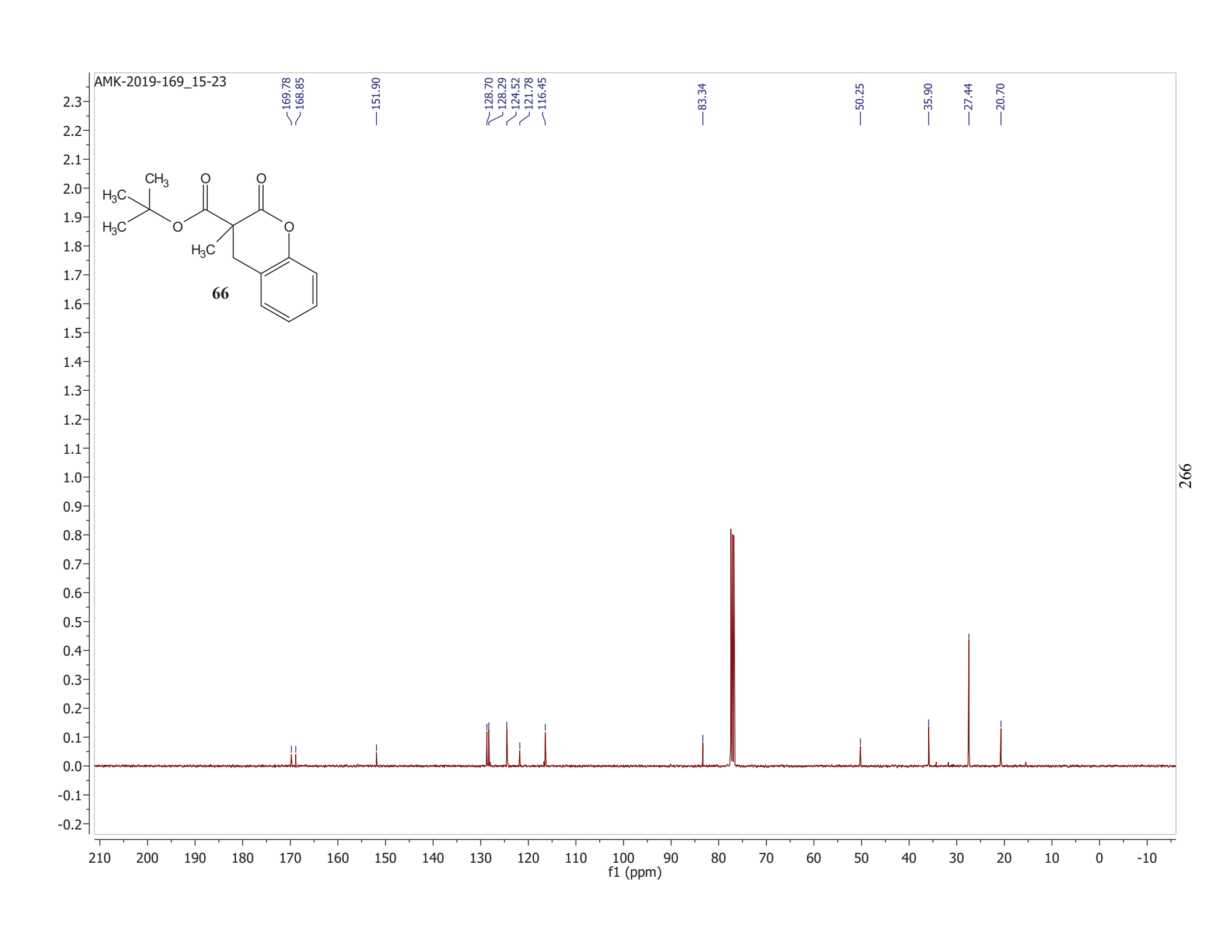
1.00 1.08 1.08 1.01 1.09 2.19 22.93

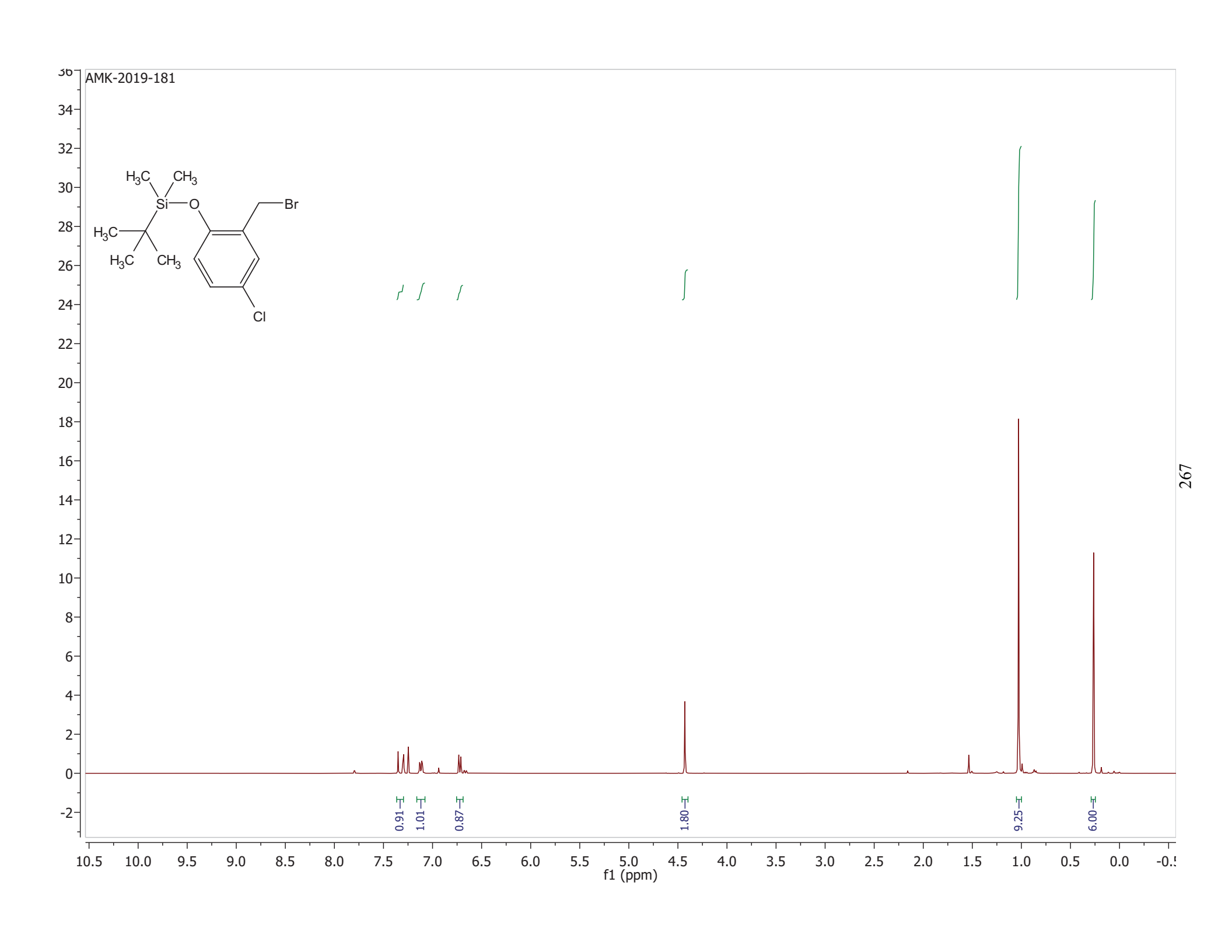
f1 (ppm)

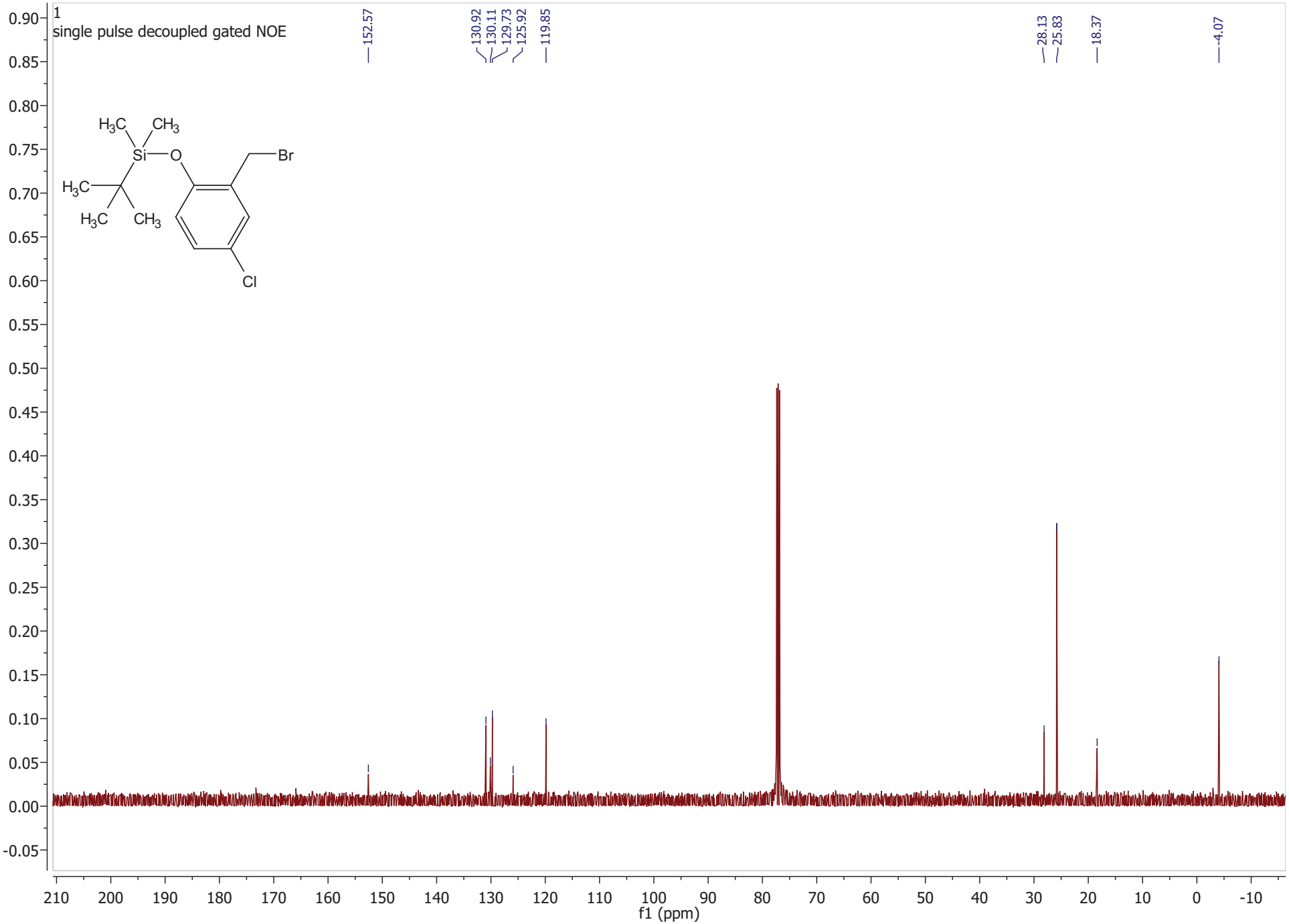
263

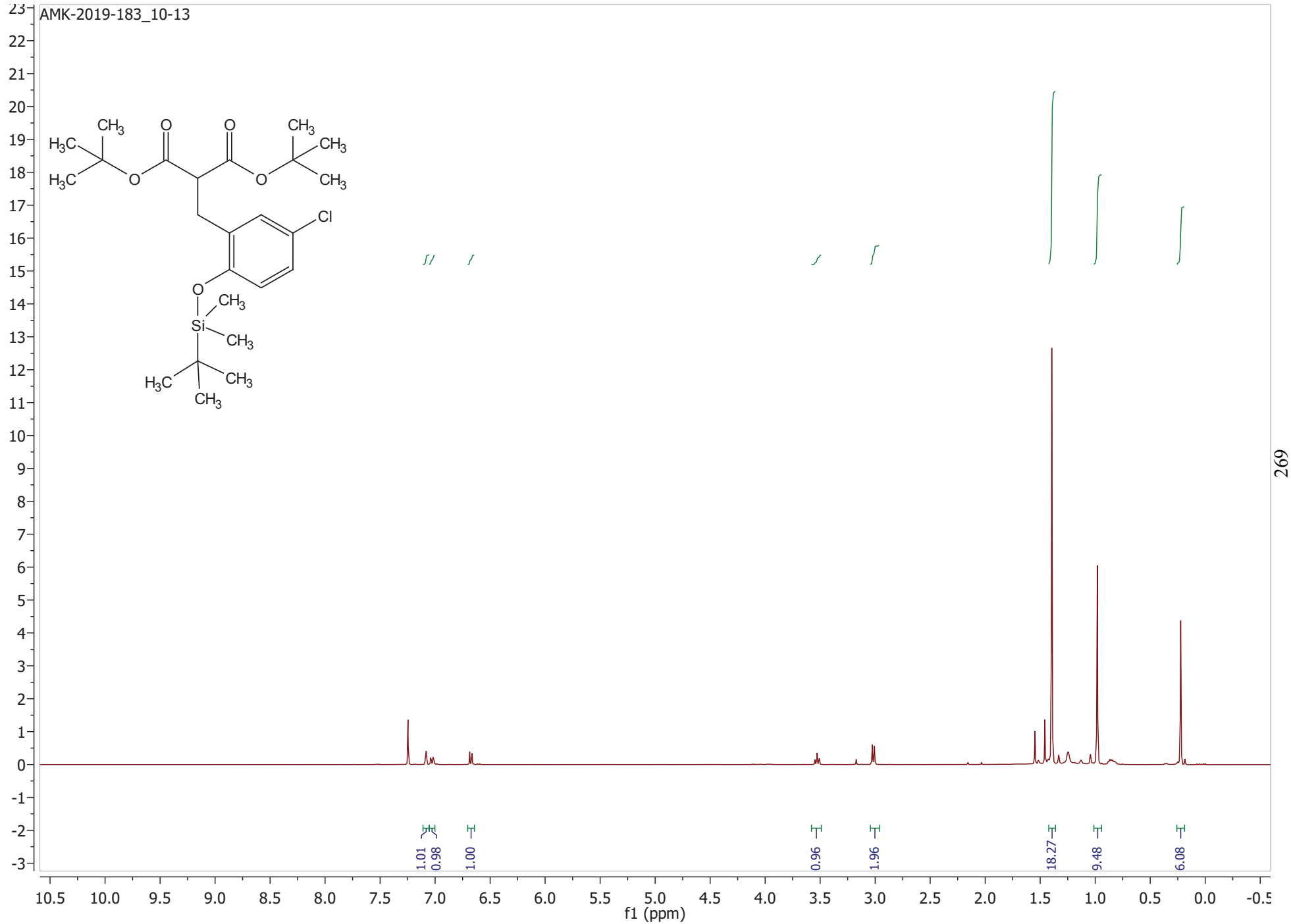

RH-2019-34-42_CLEAN_METHYL
172.95
155.50
133.24
128.64
122.65
119.74
117.60
82.53
56.17
36.10
27.69
21.45
65
f1 (ppm)
264

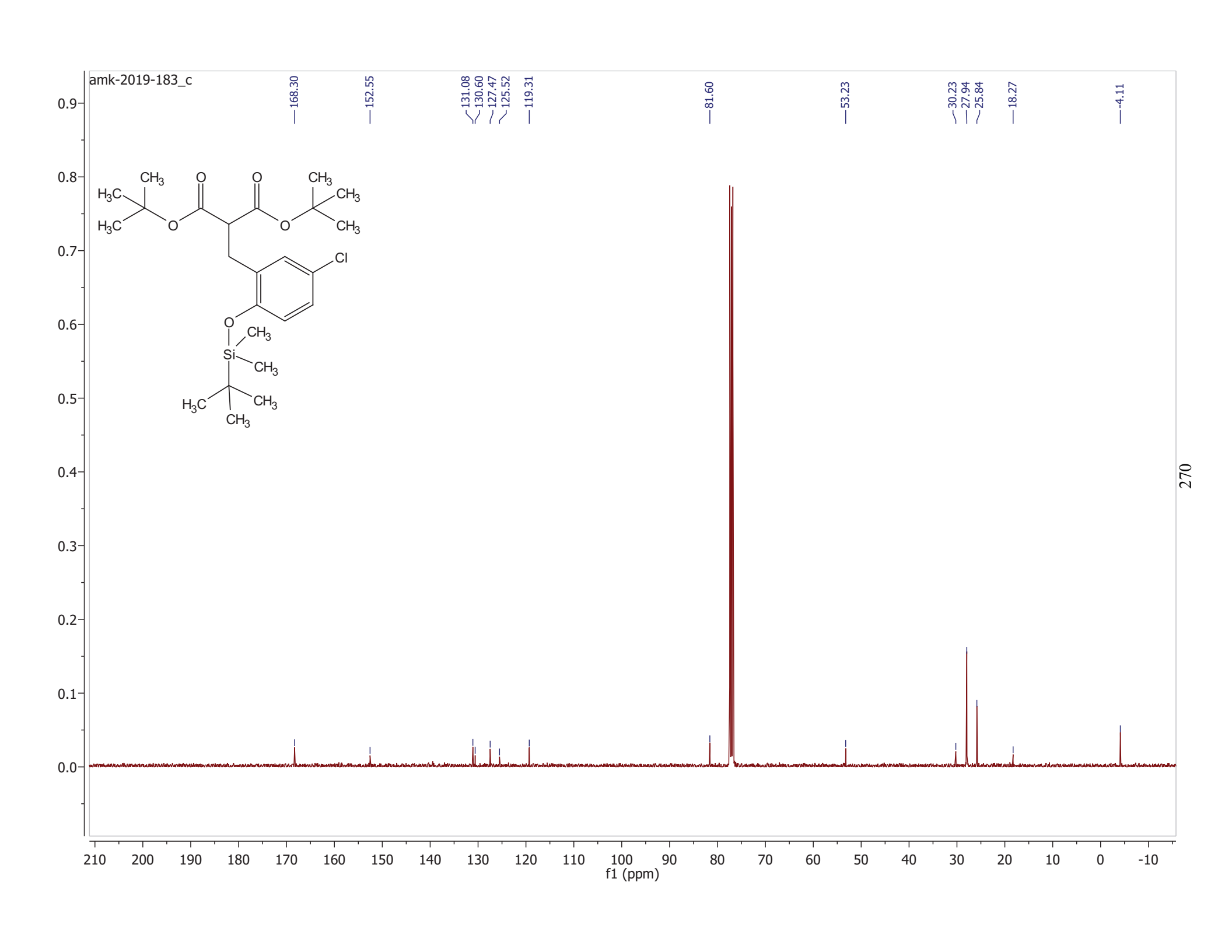

AMK-2019-169_15-23
CH3
H3C
H3C
O
O
O
O
H3C
66
1.24
1.03
2.04
1.00
1.09
3.33
9.00
f1 (ppm)
265

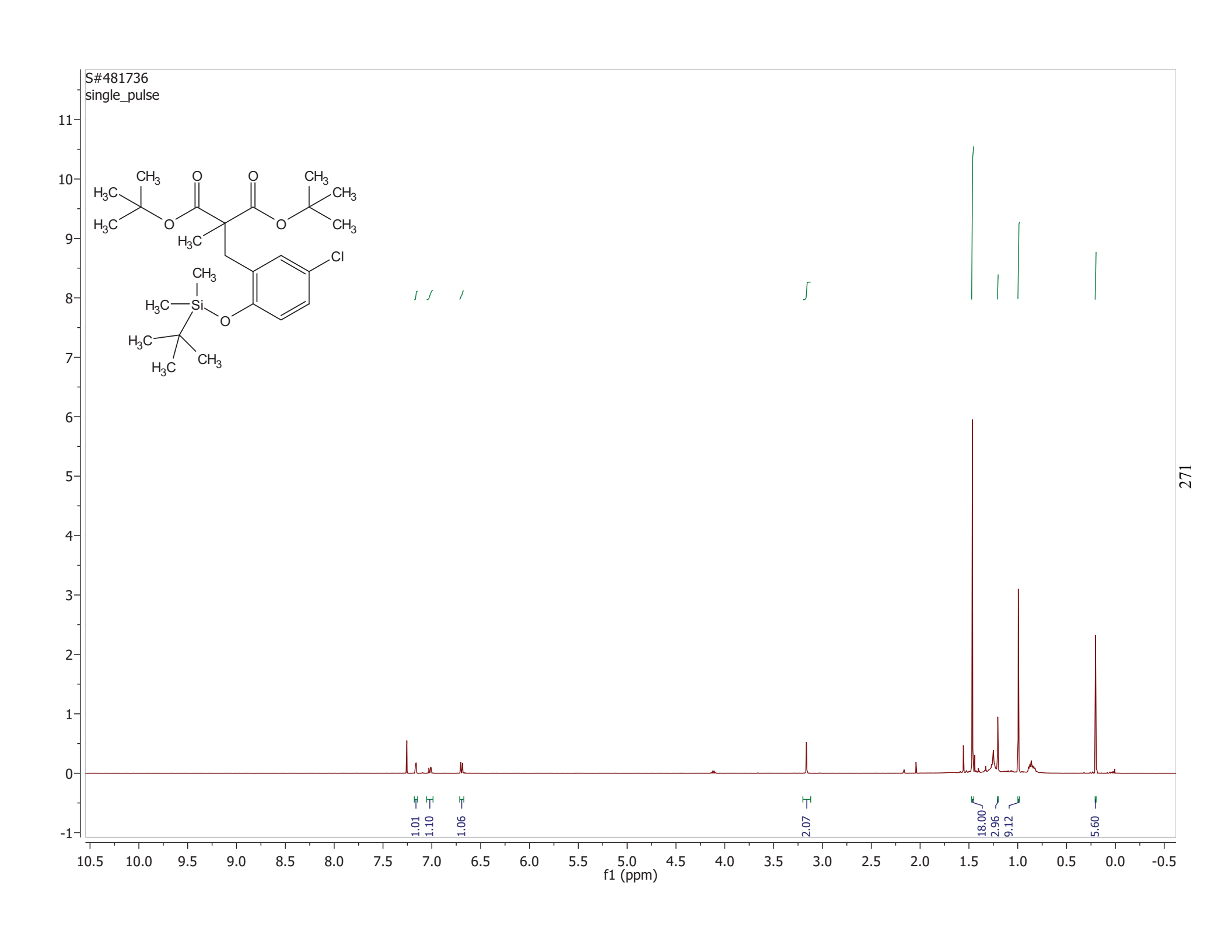

AMK-2019-169_15-23
169.78
168.85
151.90
128.70
128.29
124.52
121.78
116.45
83.34
50.25
35.90
27.44
20.70
66
f1 (ppm)
266

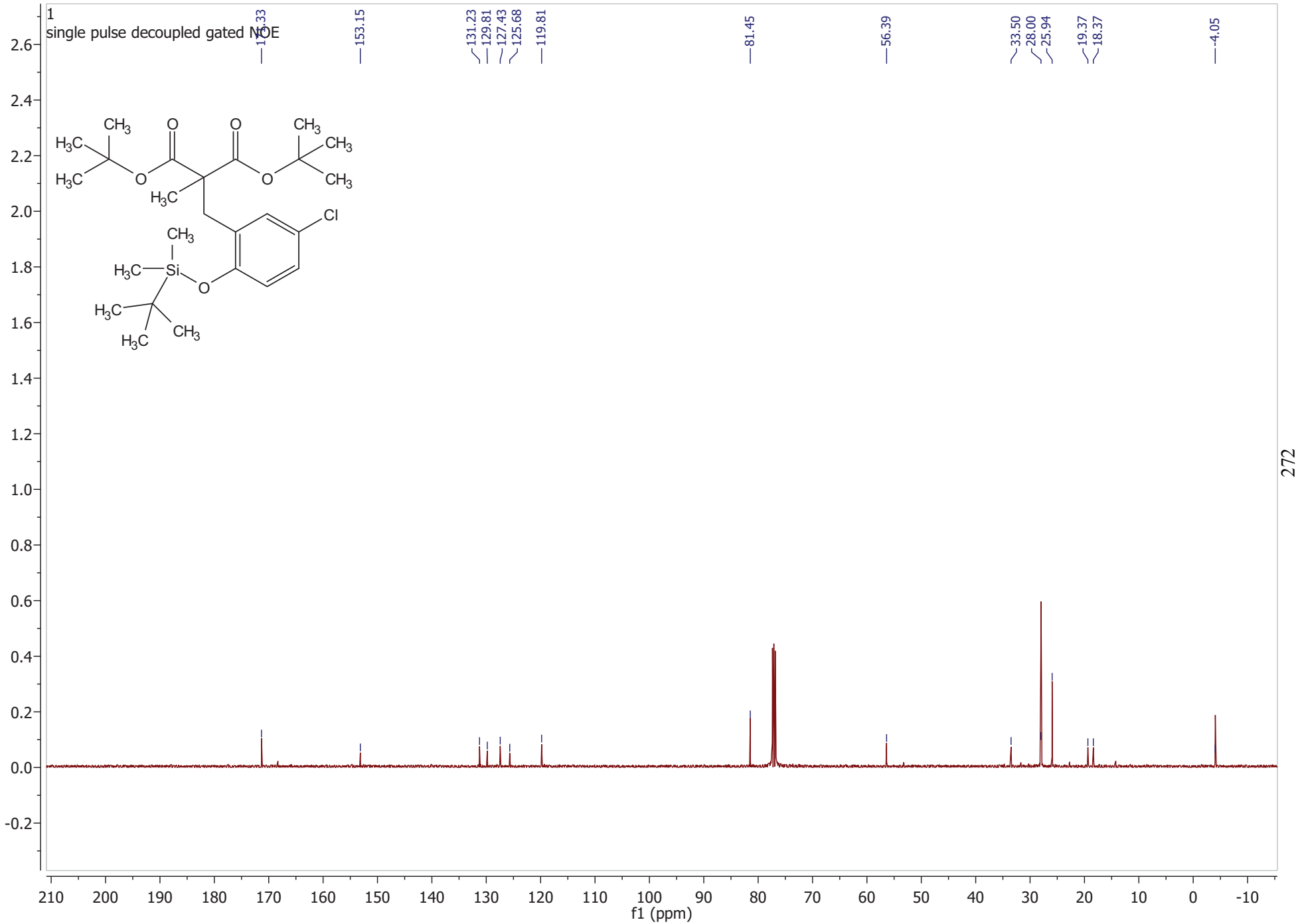

AMK-2019-181
H3C
CH3
Si
O
Br
H3C
H3C
CH3
Cl
0.91
1.01
0.87
1.80
9.25
6.00
f1 (ppm)
267

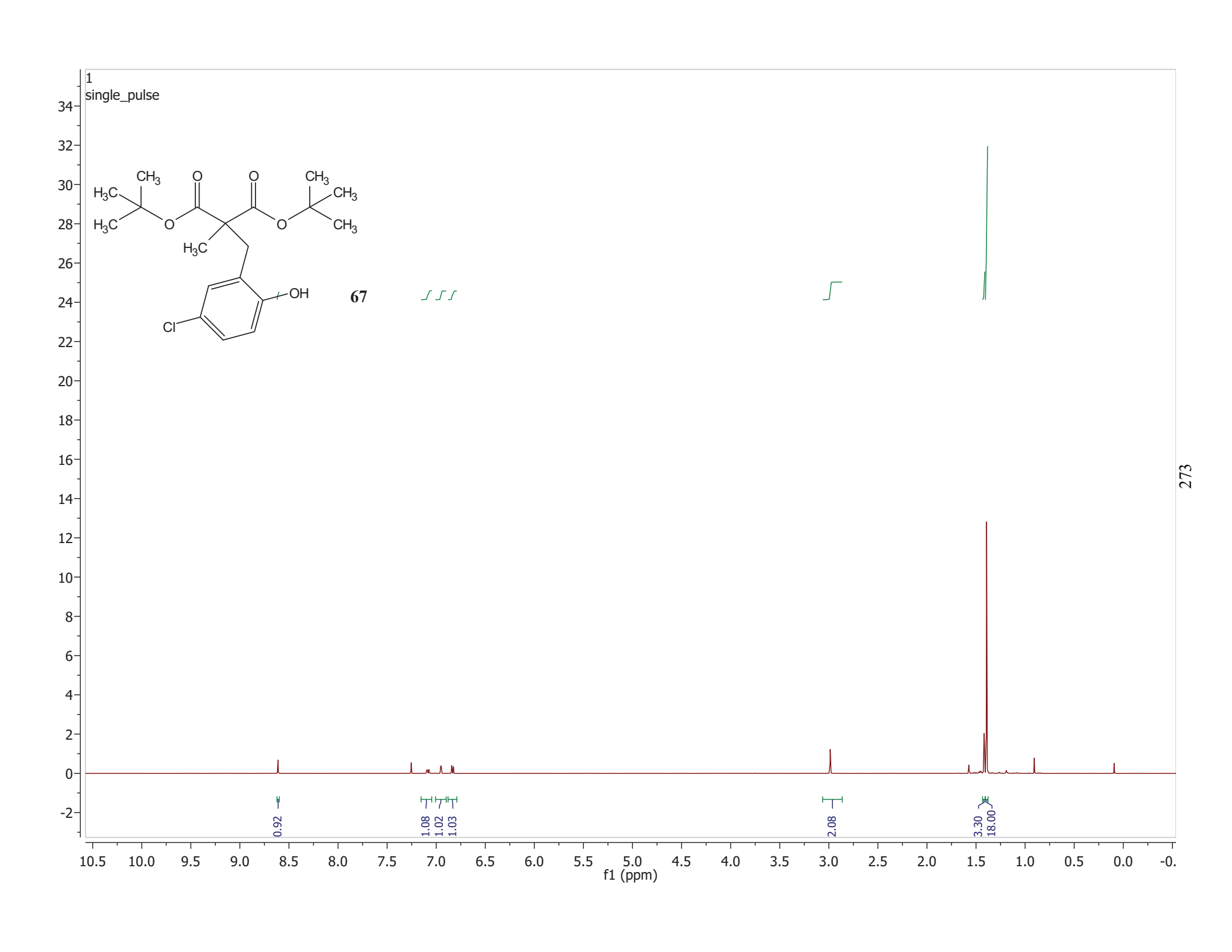

1
single pulse decoupled gated NOE
152.57
130.92
130.11
129.73
125.92
119.85
28.13
25.83
18.37
-4.07
H3C
CH3
Si
O
Br
H3C
H3C
CH3
Cl
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
268

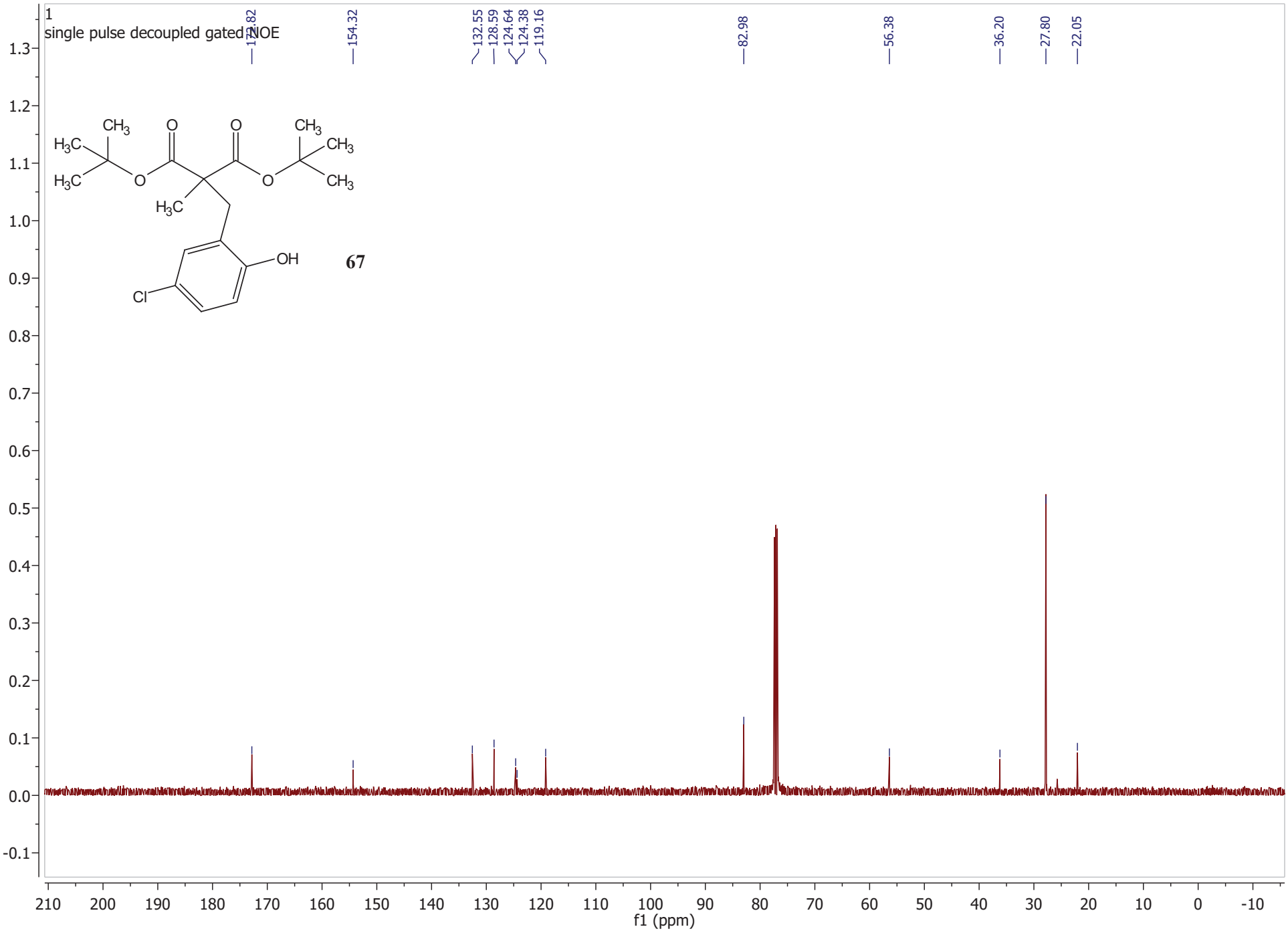

AMK-2019-183_10-13
269
1.01
0.98
1.00
0.96
1.96
18.27
9.48
6.08
f1 (ppm)

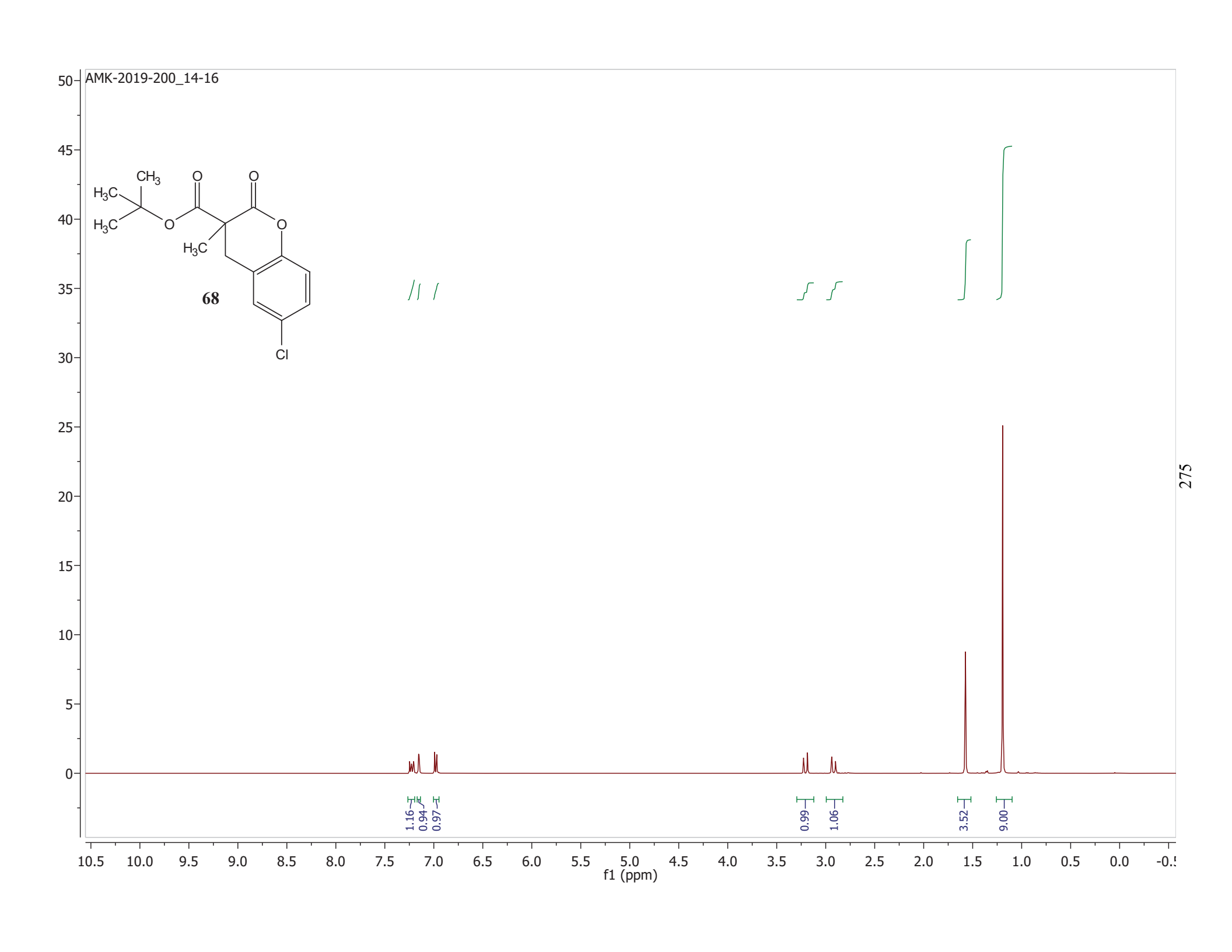

amk-2019-183_c
168.30
152.55
131.08
130.60
127.47
125.52
119.31
81.60
53.23
30.23
27.94
25.84
18.27
-4.11
Cl
Si
f1 (ppm)
270

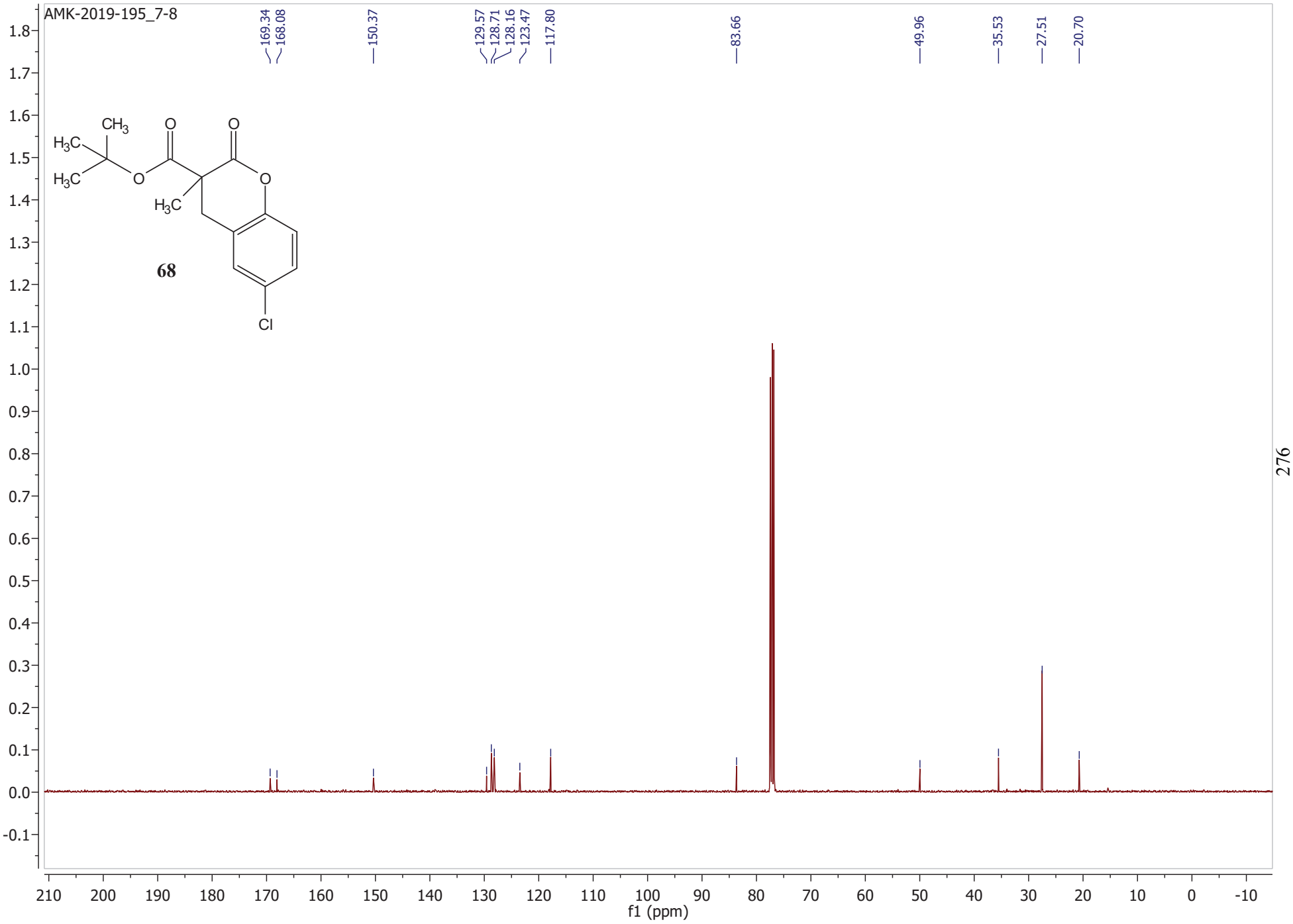

S#481736
single_pulse
271
f1 (ppm)
1.01
1.10
1.06
2.07
18.00
2.96
9.12
5.60

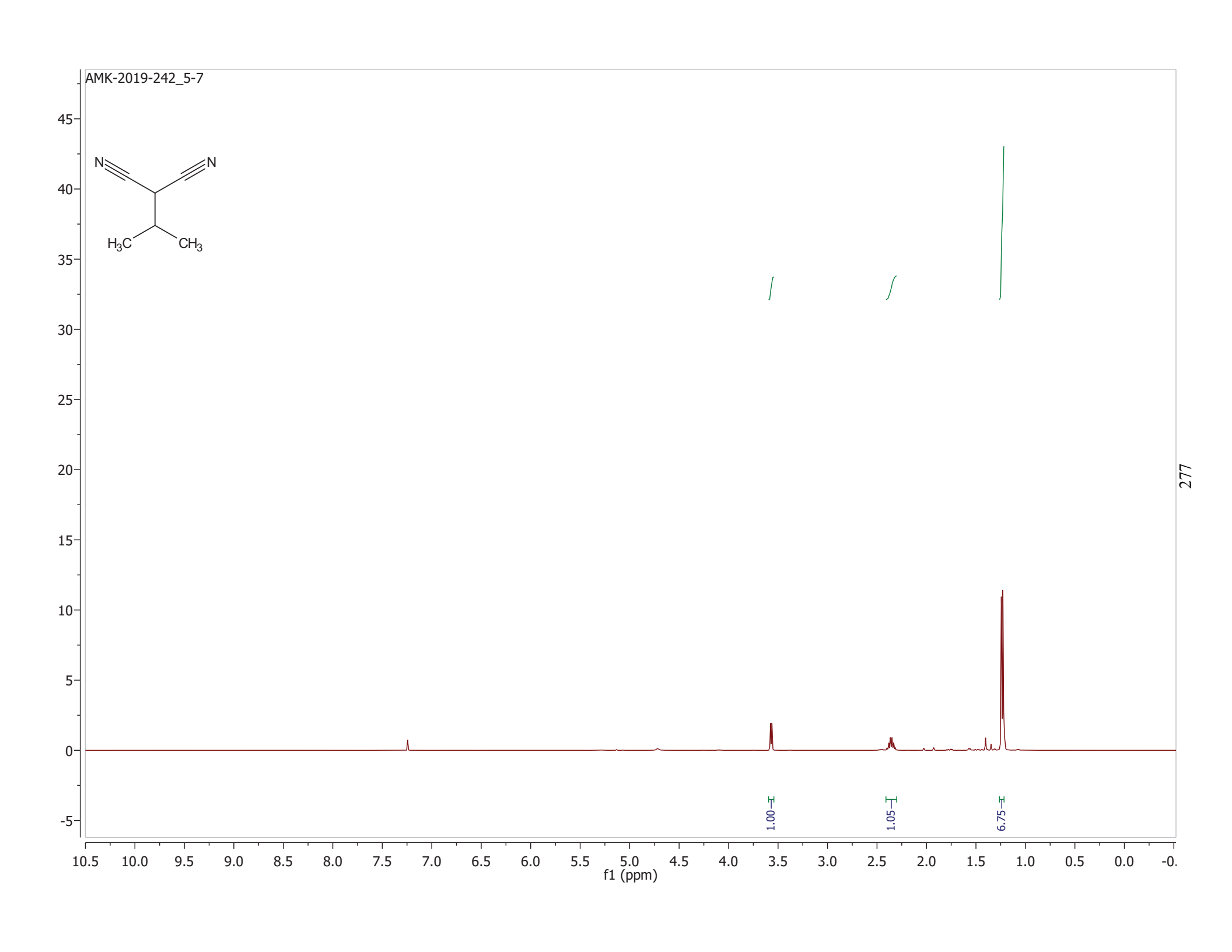

1
single pulse decoupled gated NOE
171.33
153.15
131.23
129.81
127.43
125.68
119.81
81.45
56.39
33.50
28.00
25.94
19.37
18.37
-4.05
272
f1 (ppm)

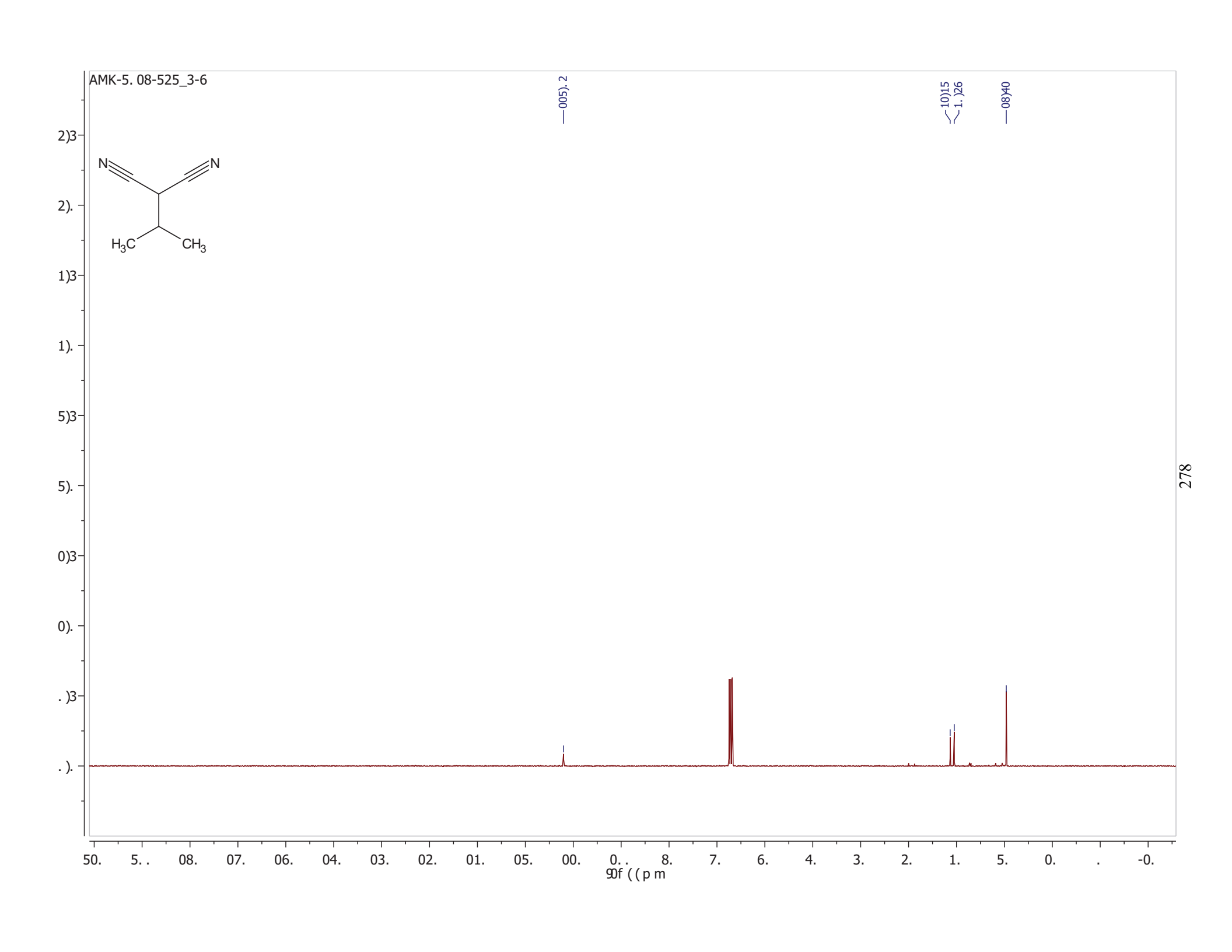

1
single_pulse
67
OH
Cl
0.92
1.08
1.02
1.03
2.08
3.30
18.00
f1 (ppm)
273

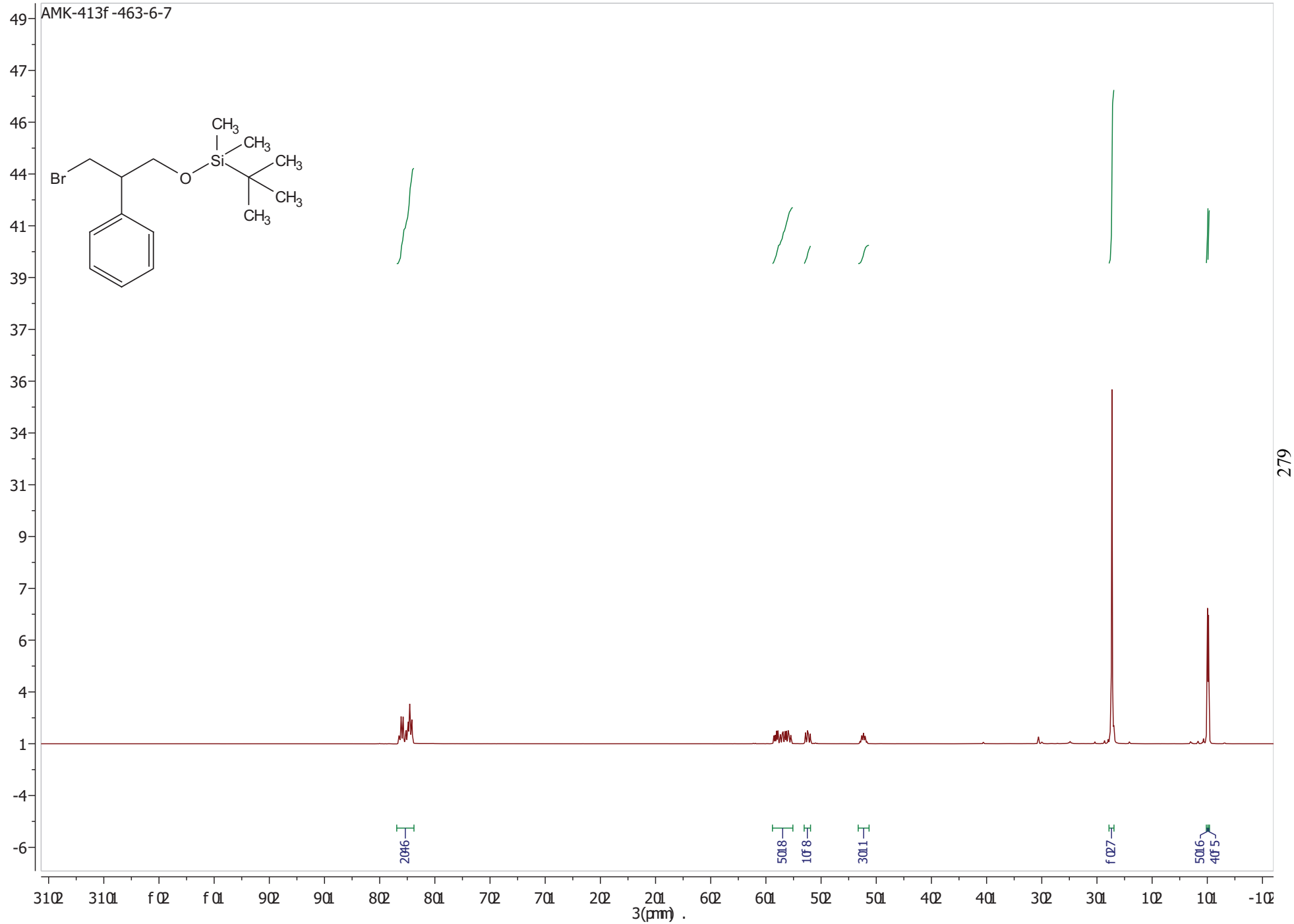

1
single pulse decoupled gated NOE
172.82
154.32
132.55
128.59
124.64
124.38
119.16
82.98
56.38
36.20
27.80
22.05
CH3
O
O
CH3
H3C
CH3
H3C
O
O
CH3
H3C
OH
Cl
67
274
f1 (ppm)

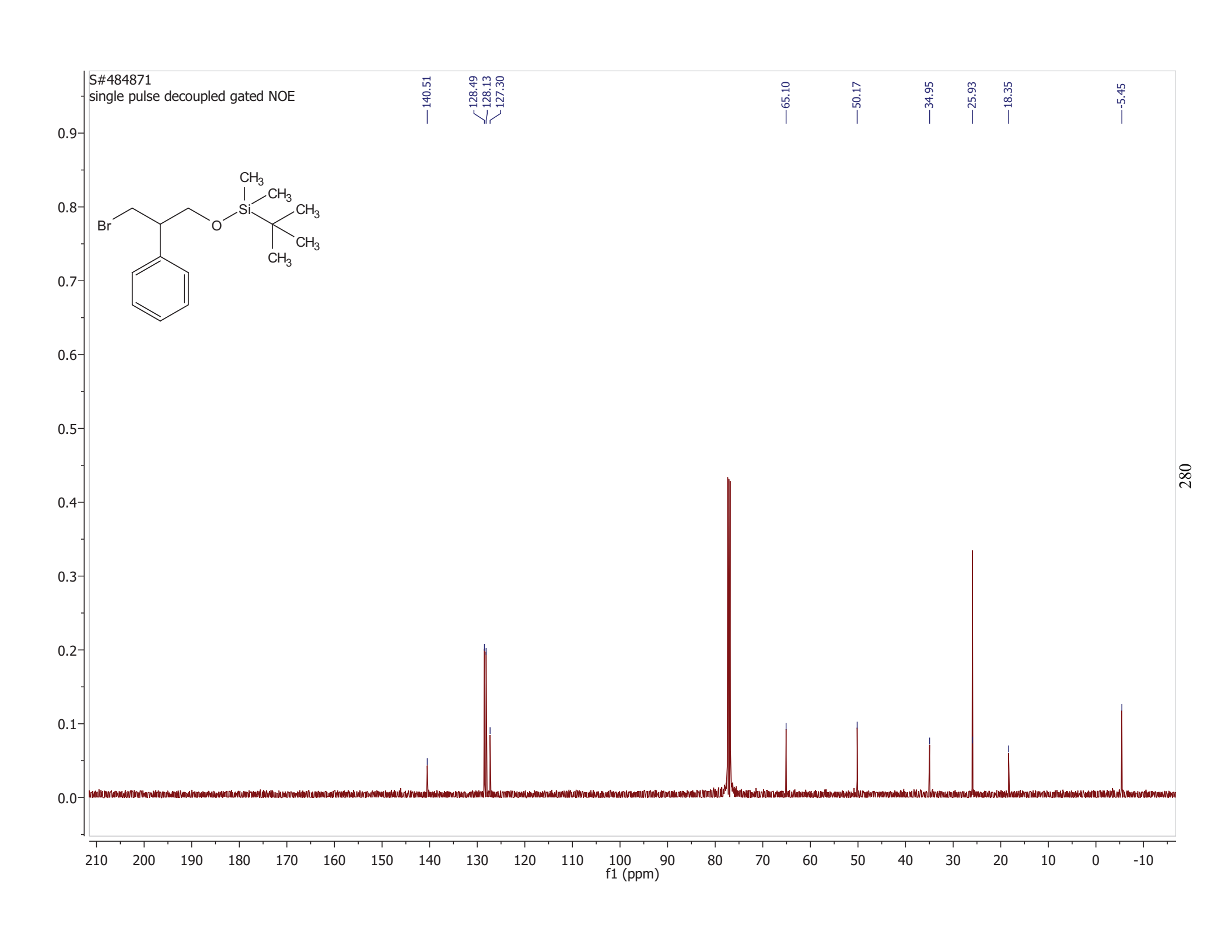

AMK-2019-200_14-16
CH3
H3C
H3C
O
O
O
O
H3C
68
Cl
1.16
0.94
0.97
0.99
1.06
3.52
9.00
f1 (ppm)
275

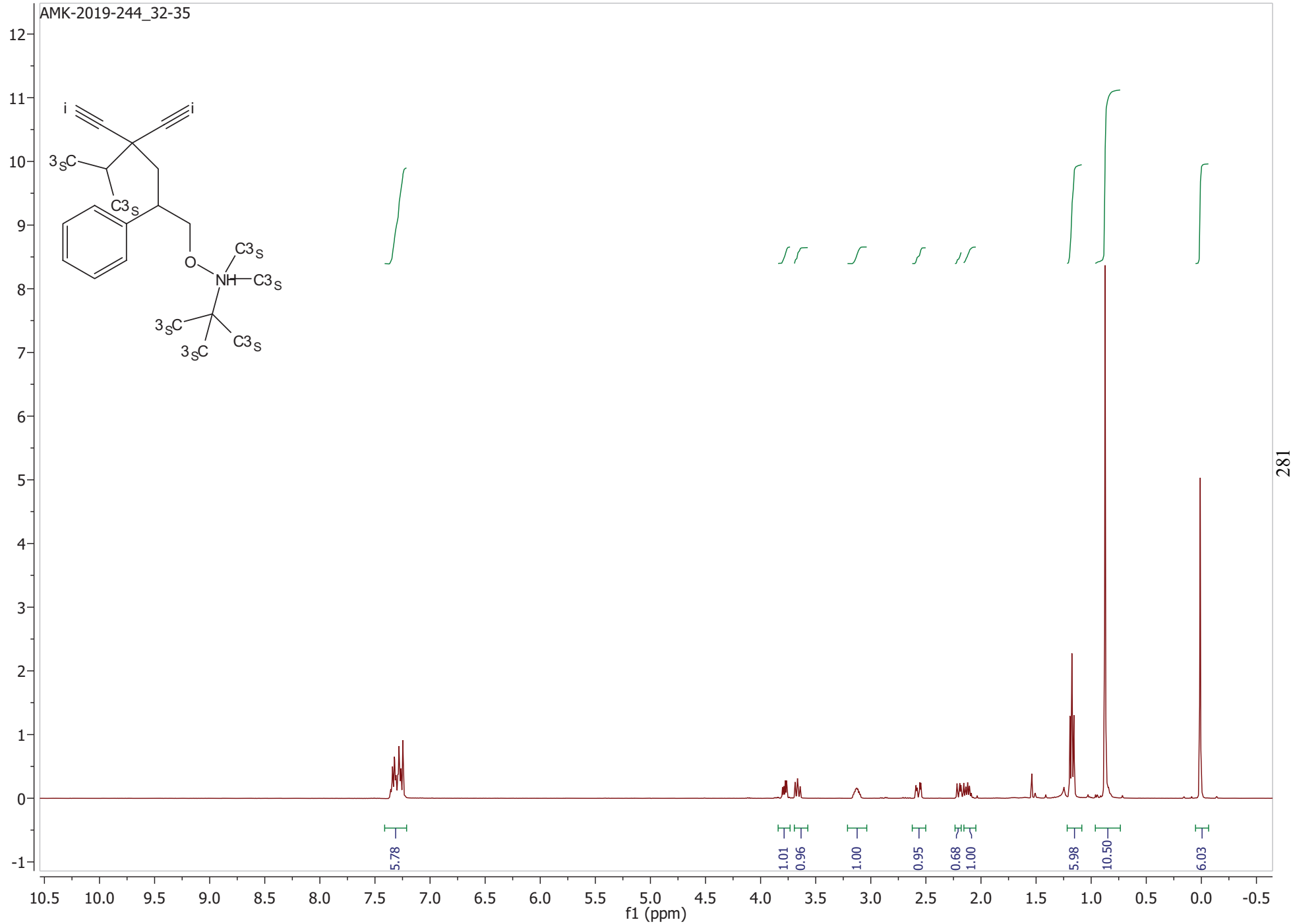

AMK-2019-195_7-8
169.34
168.08
150.37
129.57
128.71
128.16
123.47
117.80
83.66
49.96
35.53
27.51
20.70
68
Cl
f1 (ppm)
276

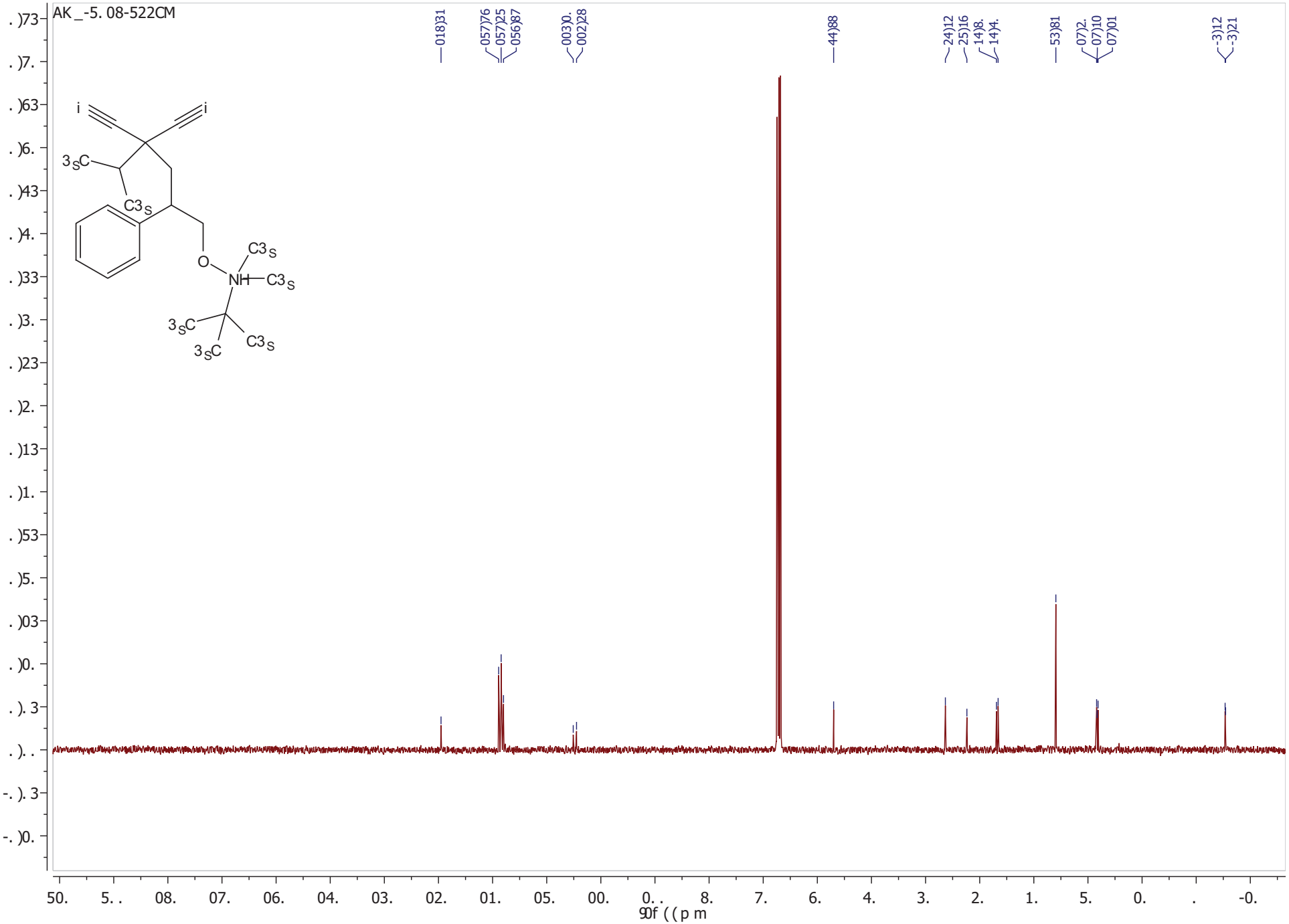

AMK-2019-242_5-7
N
N
H3C
CH3
45
40
35
30
25
20
15
10
5
0
-5
1.00
1.05
6.75
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
277

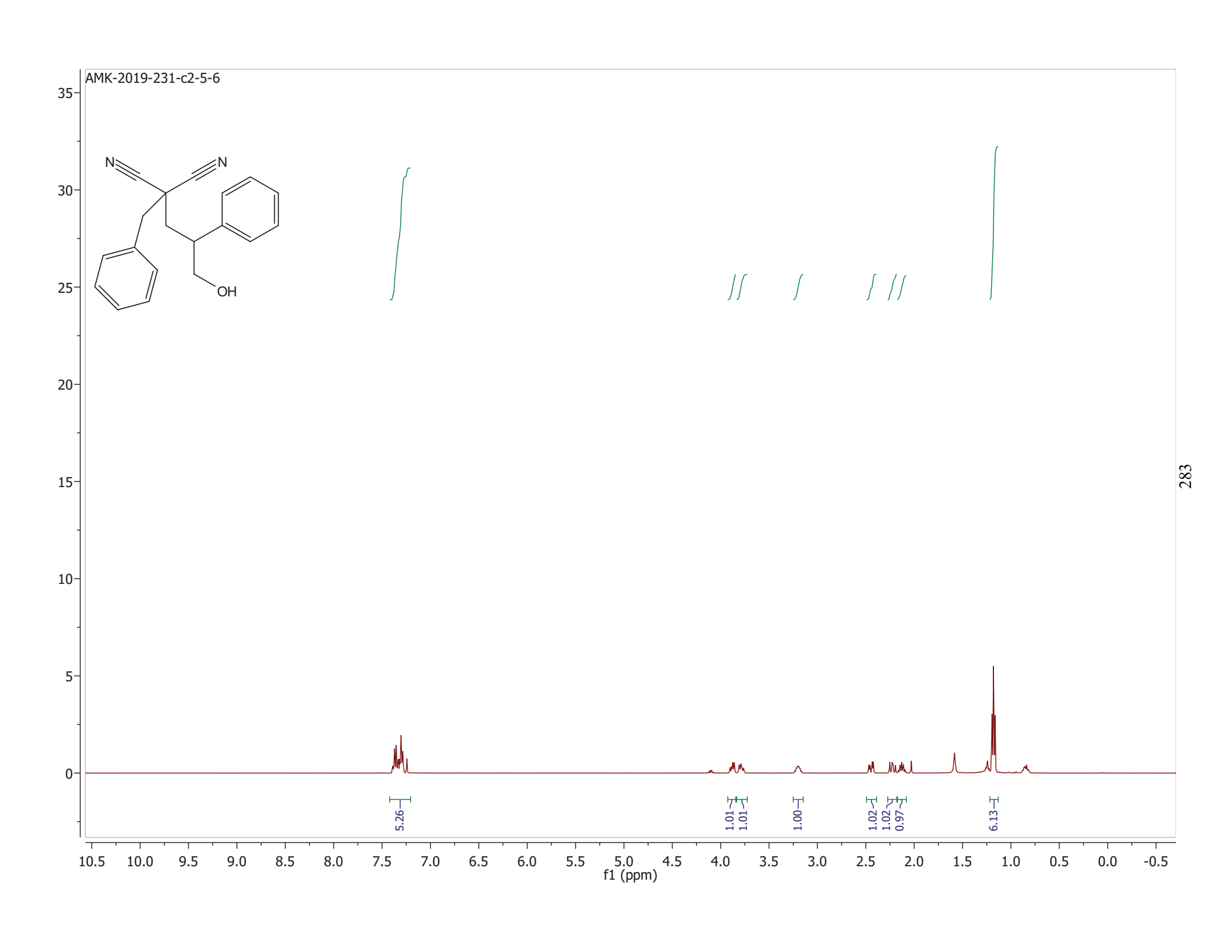

AMK-5. 08-525_3-6
005). 2
10)15
1.)26
08)40
N
N
H3C
CH3
2)3
2).
1)3
1).
5)3
5).
0)3
0).
.)3
.).
50.
5. .
08.
07.
06.
04.
03.
02.
01.
05.
00.
0. .
8.
7.
6.
4.
3.
2.
1.
5.
0.
.
-0.
90f ((p m
278

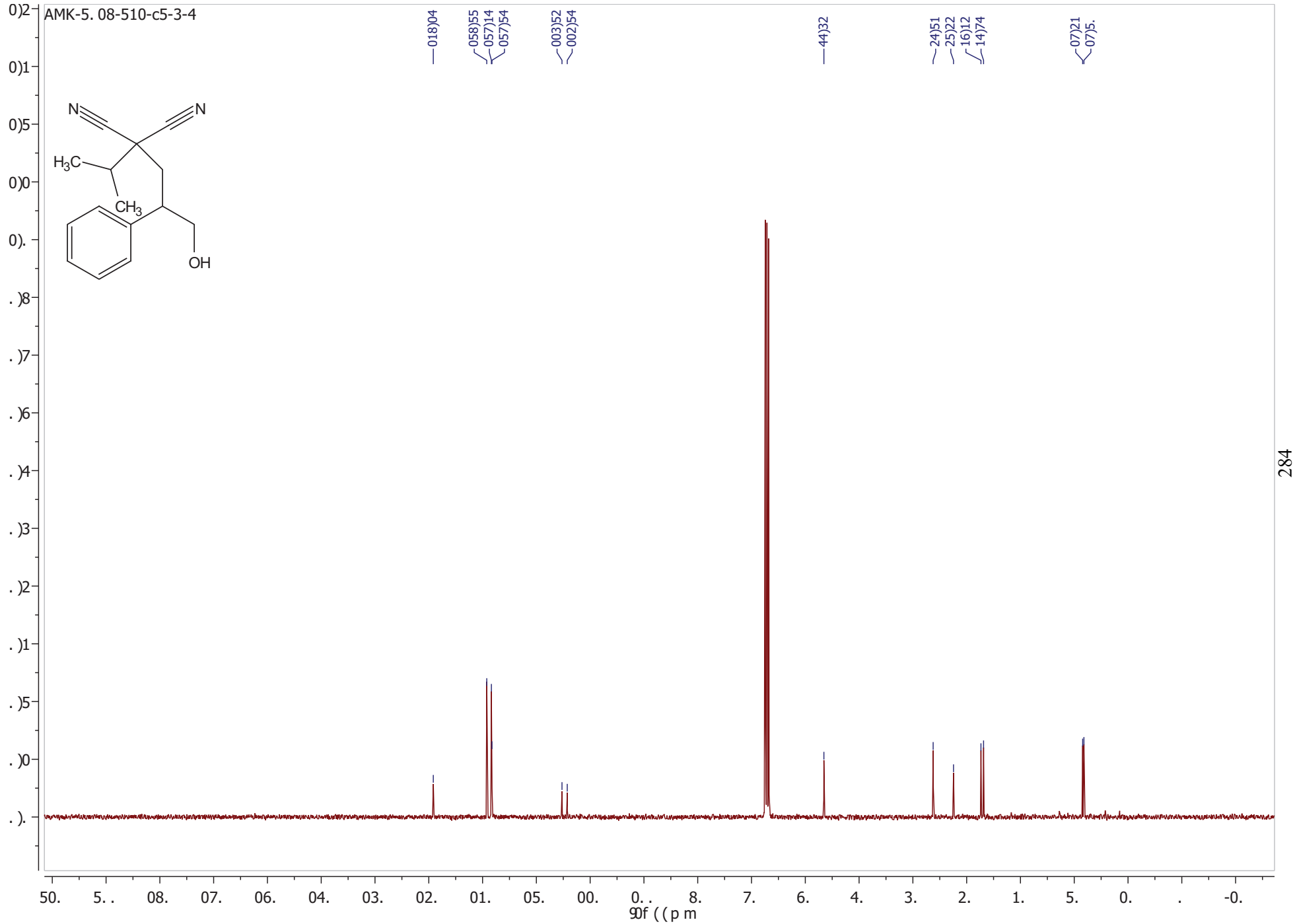

AMK-413f -463-6-7
Br
O
Si
CH3
CH3
CH3
CH3
CH3
CH3
2.46
5.18
1.08
3.01
f.02.7
5.16
4.05
3(ppm)
279

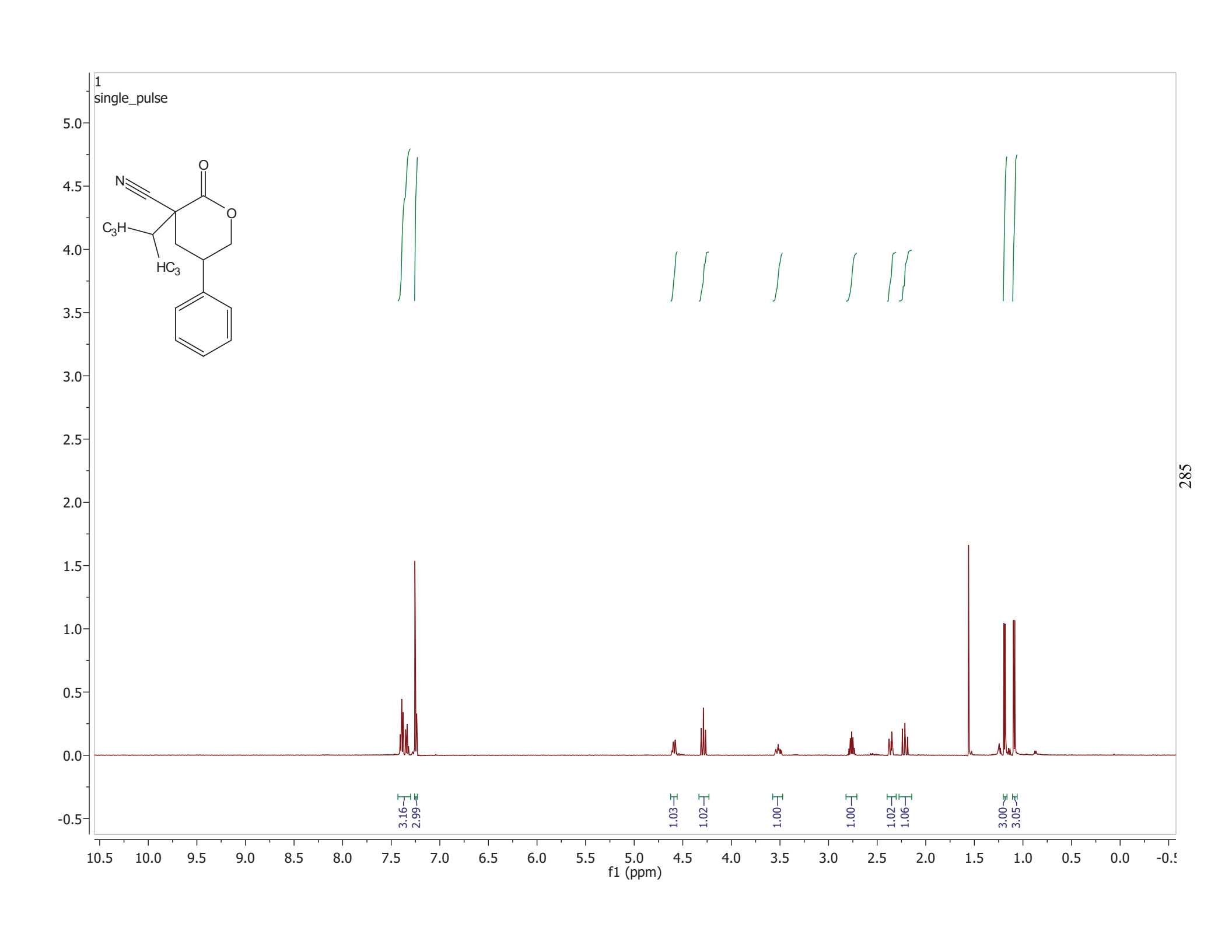

S#484871
single pulse decoupled gated NOE
140.51
128.49
128.13
127.30
65.10
50.17
34.95
25.93
18.35
-5.45
Br
O
Si
CH3
CH3
CH3
CH3
CH3
280
f1 (ppm)

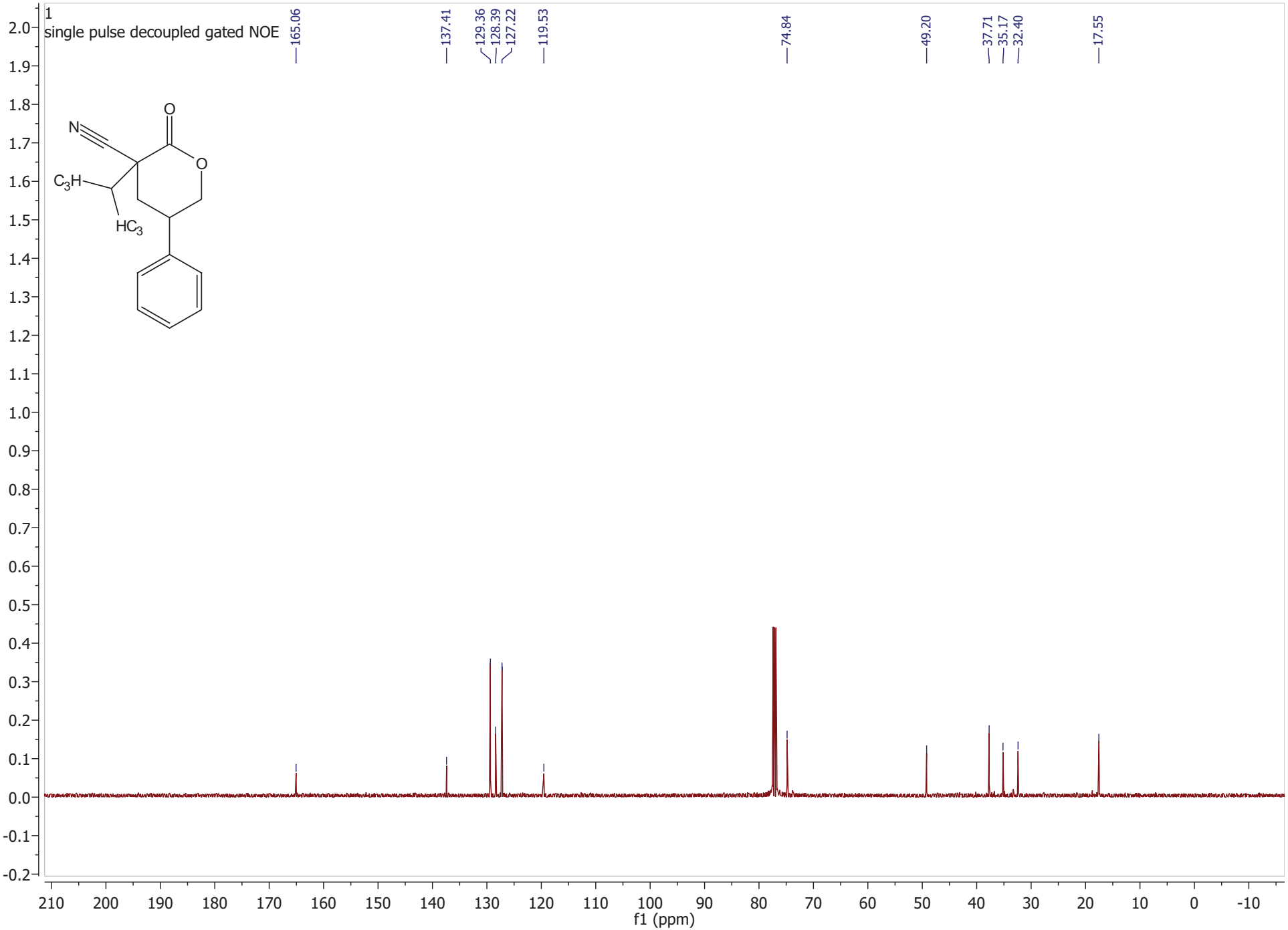

AMK-2019-244_32-35
281
f1 (ppm)
5.78
1.01
0.96
1.00
0.95
0.68
1.00
5.98
10.50
6.03

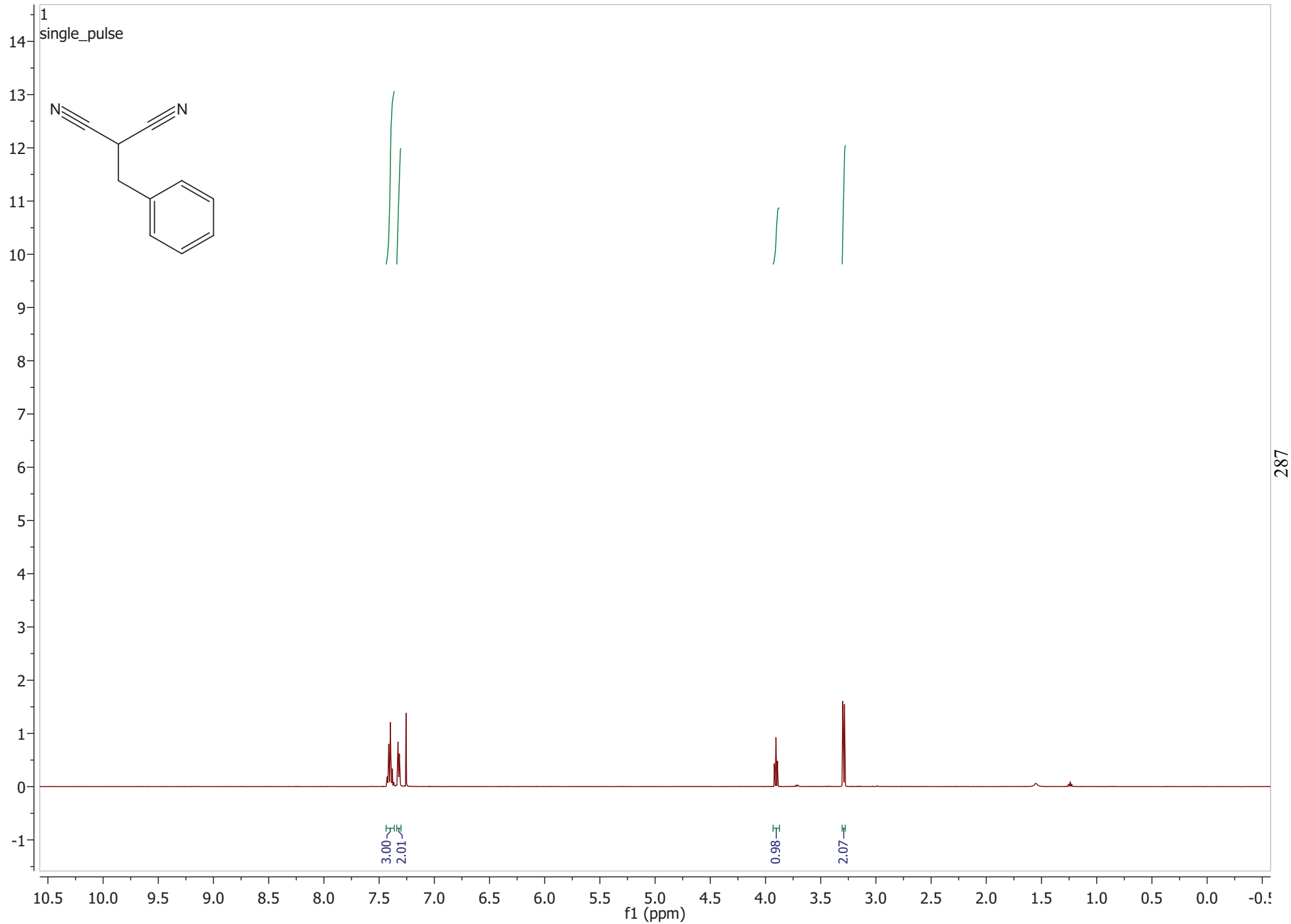

AK_-5. 08-522CM
018)31
057)76
057)25
056)87
003)0.
002)28
44)88
24)12
25)16
14)8.
14)4.
53)81
07)2.
07)10
07)01
-3)12
-3)21
i
i
3SC
C3S
C3S
O
NH
C3S
3SC
C3S
3SC
282
90f ((p m

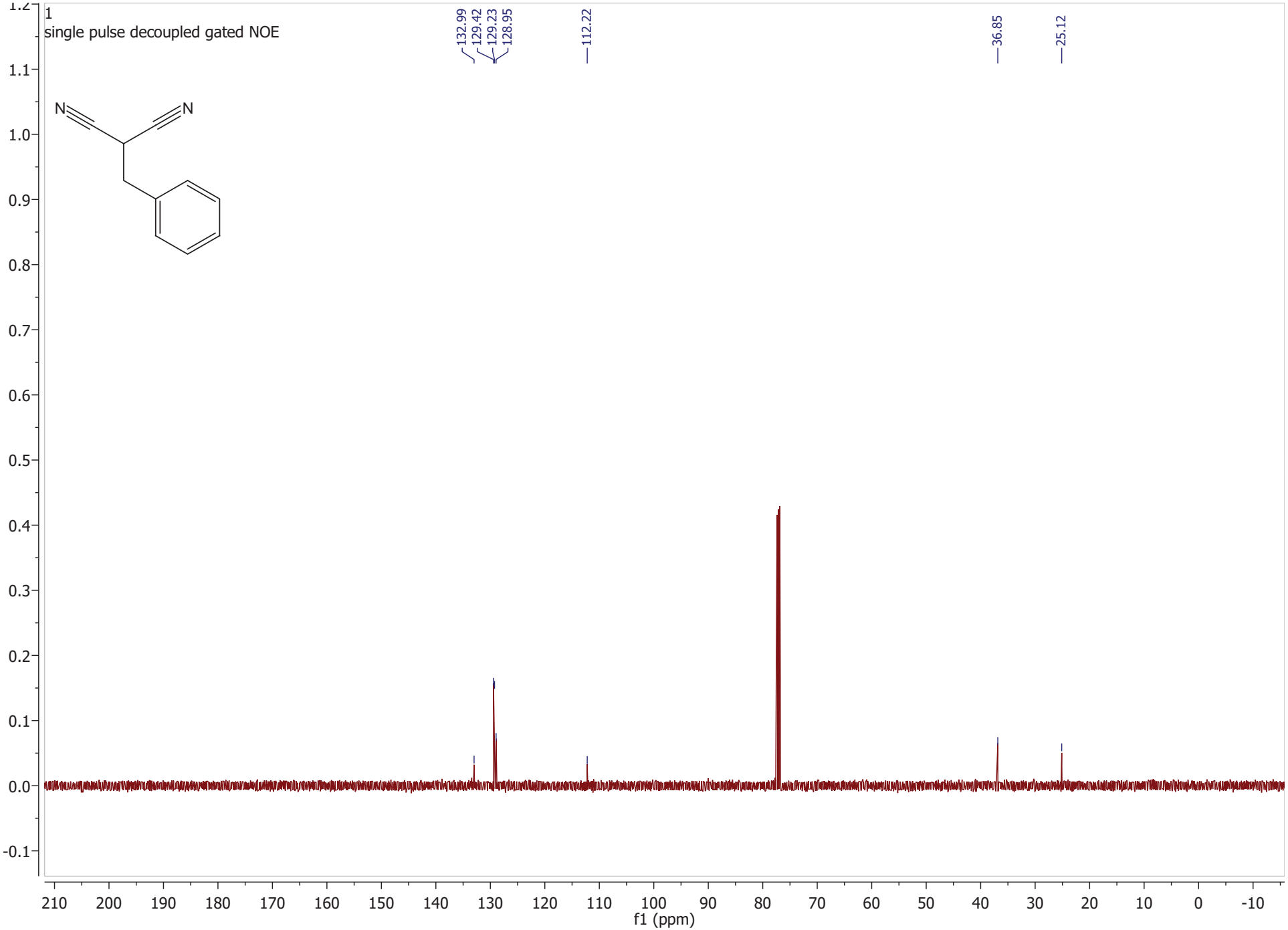

AMK-2019-231-c2-5-6
N
N
OH
35
30
25
20
15
10
5
0
5.26
1.01
1.01
1.00
1.02
1.02
0.97
6.13
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
283

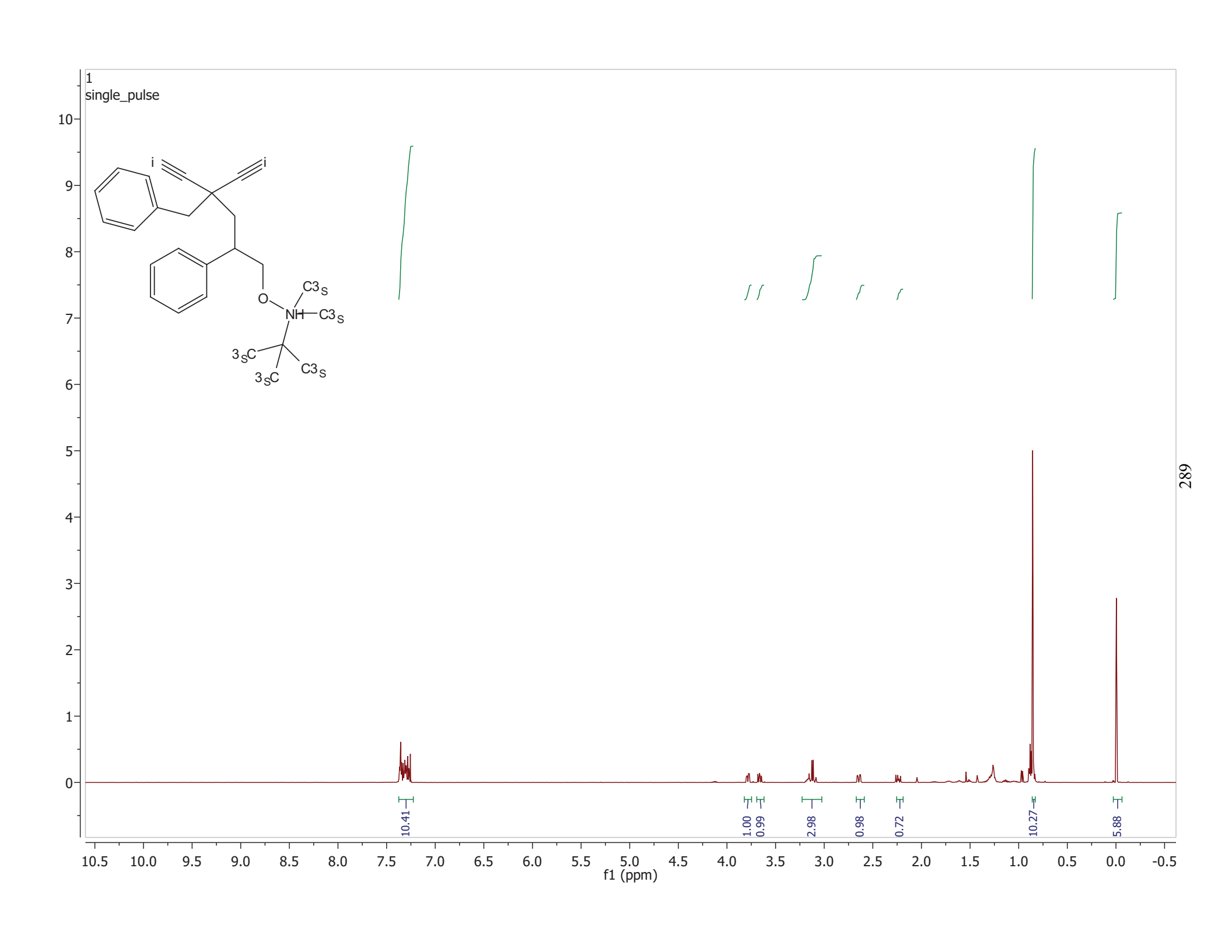

AMK-5. 08-510-c5-3-4
018)04
058)55
057)14
057)54
003)52
002)54
44)32
24)51
25)22
16)12
14)74
07)21
07)5.
N
N
H3C
CH3
OH
284
50.
5. .
08.
07.
06.
04.
03.
02.
01.
05.
00.
0. .
8.
7.
6.
4.
3.
2.
1.
5.
0.
.
-0.
90f ((p m

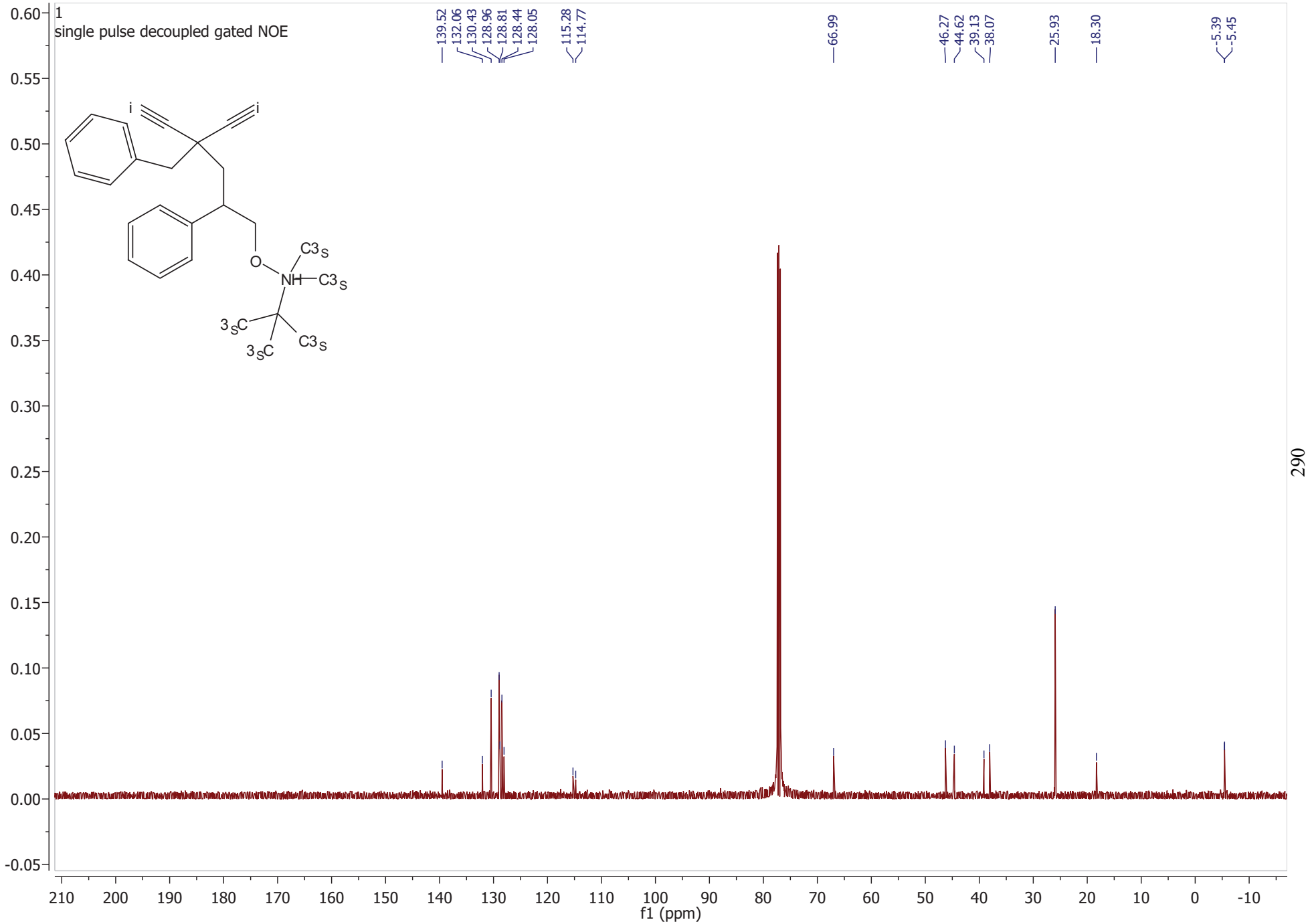

1
single_pulse
O
N
O
C3H
HC3
285
3.16
2.99
1.03
1.02
1.00
1.00
1.02
1.06
3.00
3.05
f1 (ppm)

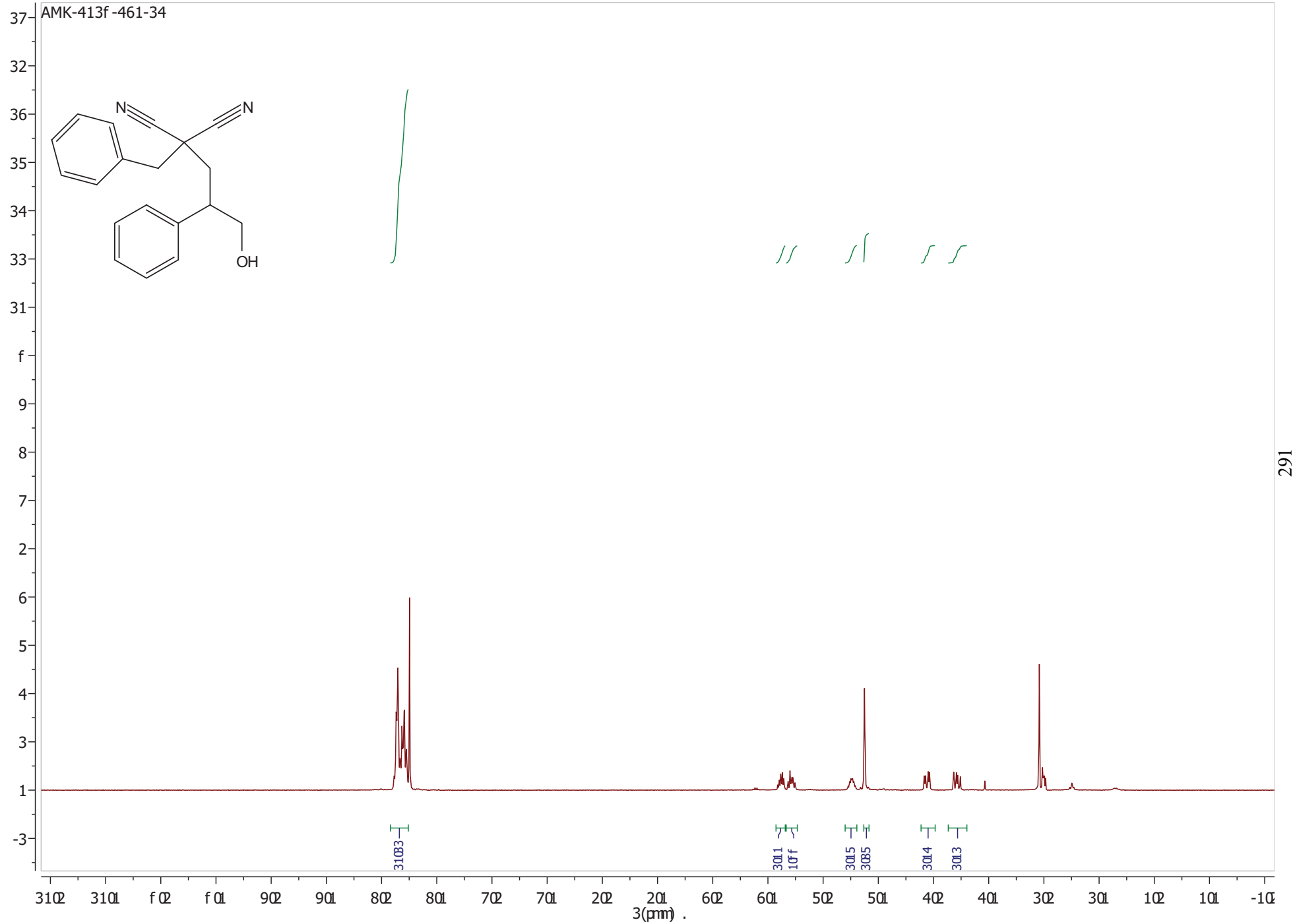

1
single pulse decoupled gated NOE
165.06
137.41
129.36
128.39
127.22
119.53
74.84
49.20
37.71
35.17
32.40
17.55
N
O
O
C3H
HC3
f1 (ppm)

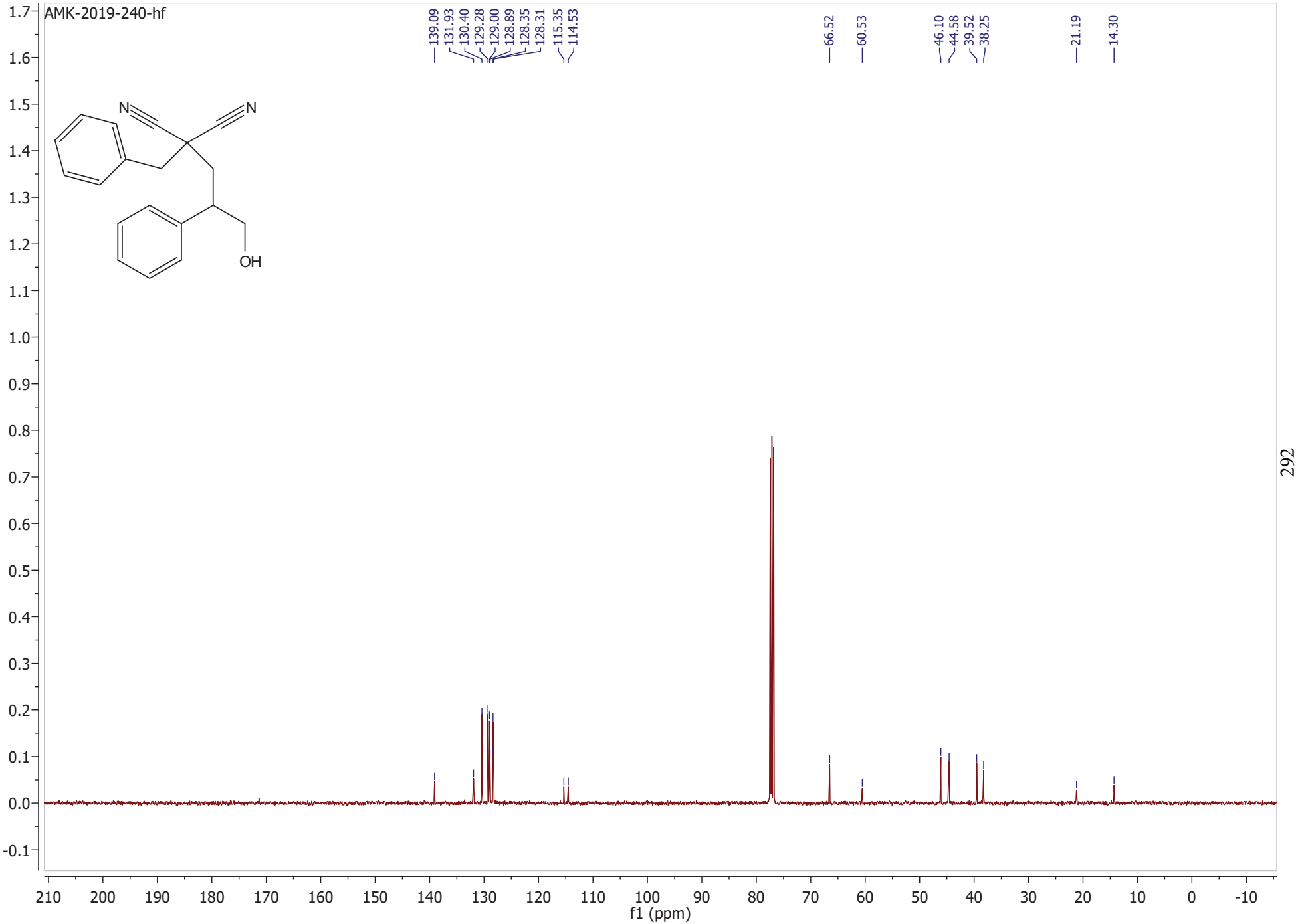

1
single_pulse
N
N
3.00
2.01
0.98
2.07
f1 (ppm)
287

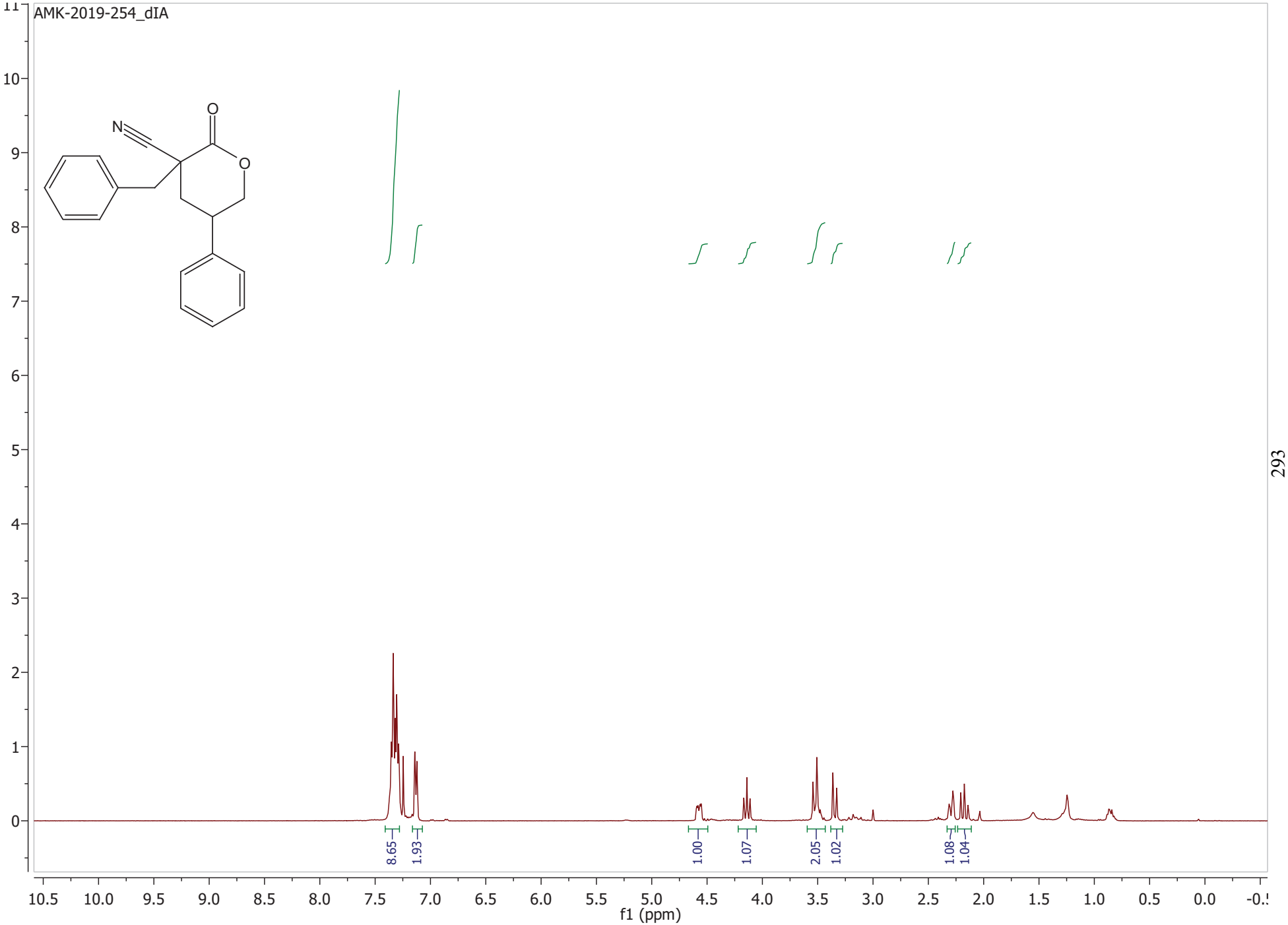

1
single pulse decoupled gated NOE
132.99
129.42
129.23
128.95
112.22
36.85
25.12
N
N
288
f1 (ppm)

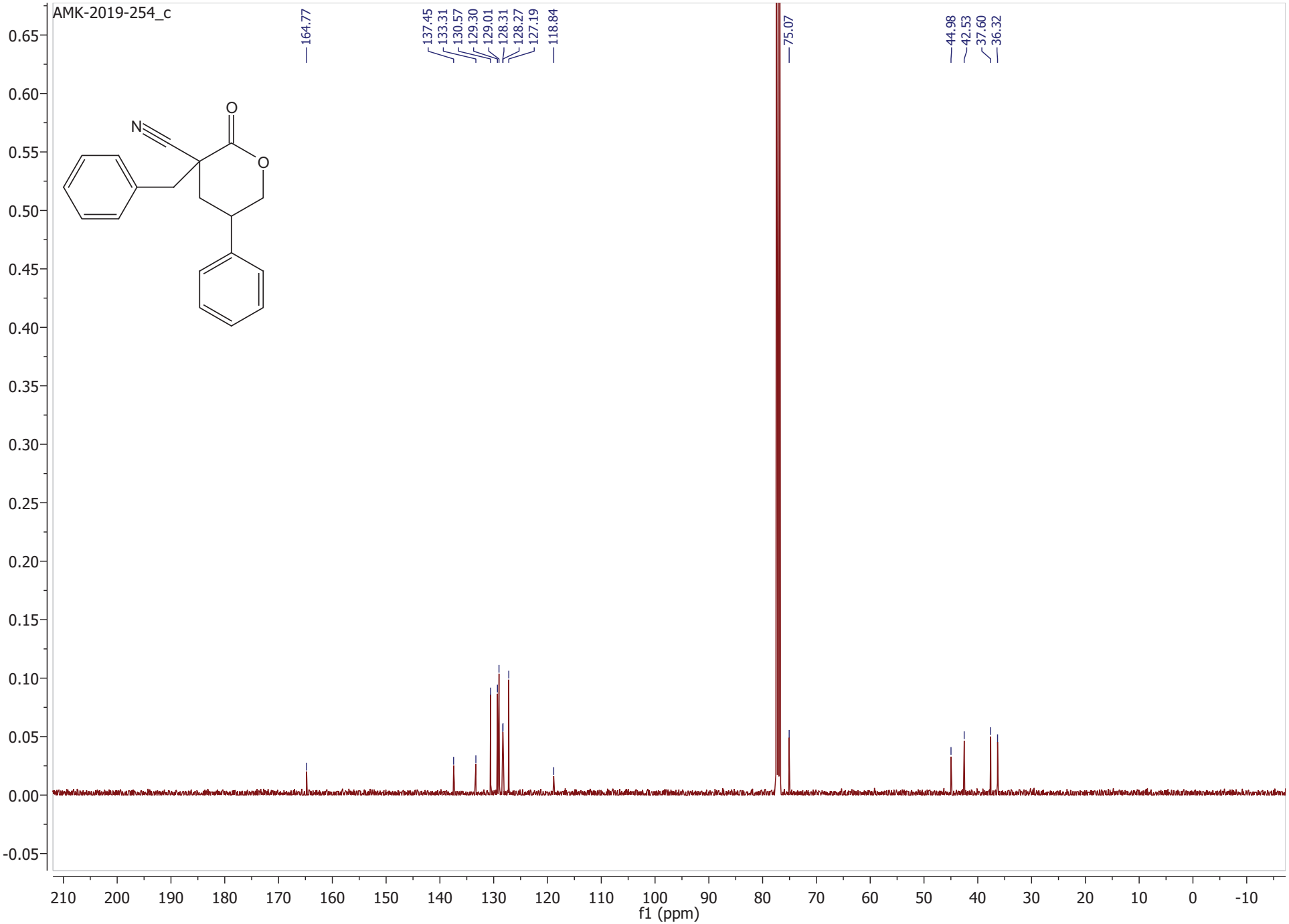

1
single_pulse
i
i
O
NH
C3S
C3S
3SC
3SC
C3S
289
10.41
1.00
0.99
2.98
0.98
0.72
10.27
5.88
f1 (ppm)

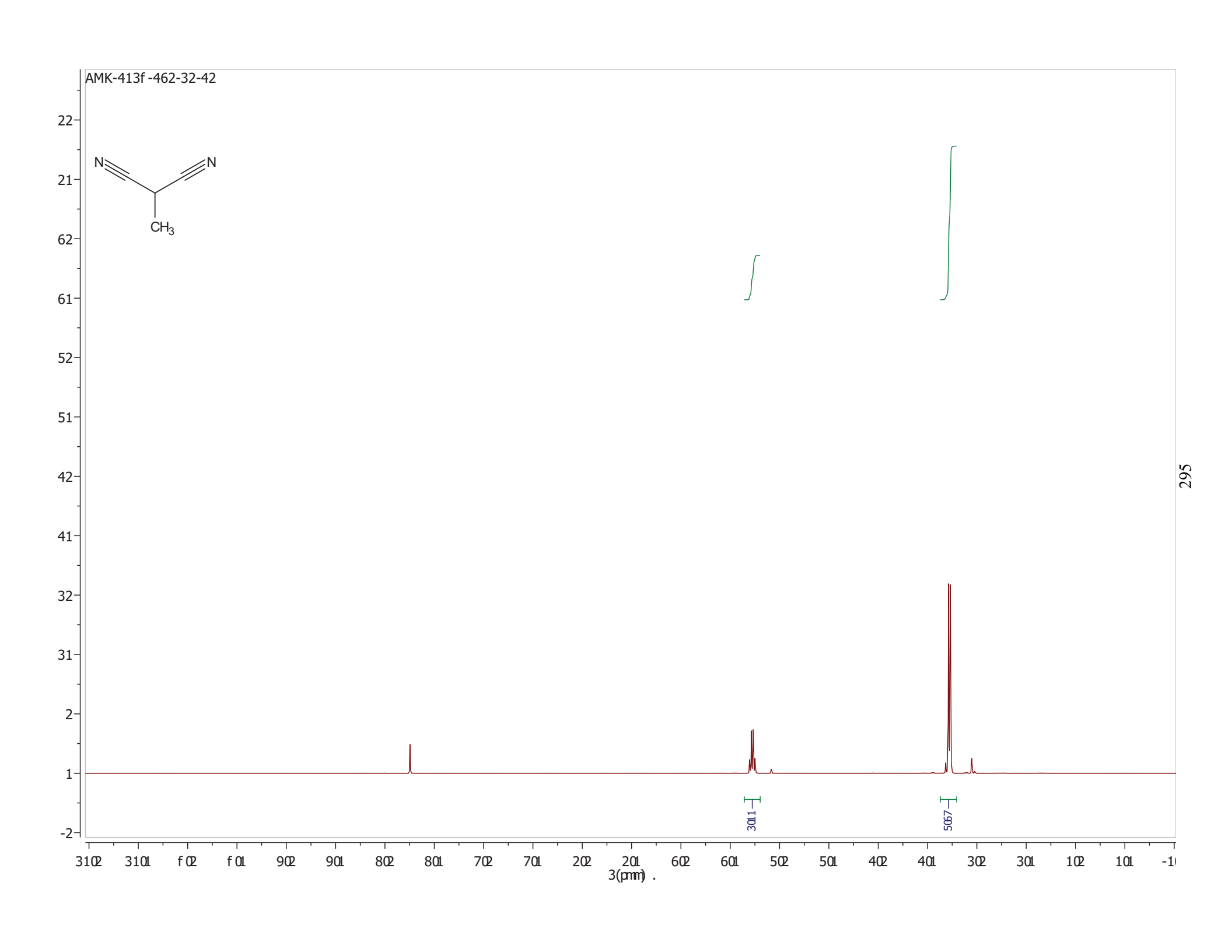

1
single pulse decoupled gated NOE
139.52
132.06
130.43
128.96
128.81
128.44
128.05
115.28
114.77
66.99
46.27
44.62
39.13
38.07
25.93
18.30
-5.39
-5.45
i
i
O
NH
C3S
C3S
3SC
3SC
C3S
f1 (ppm)

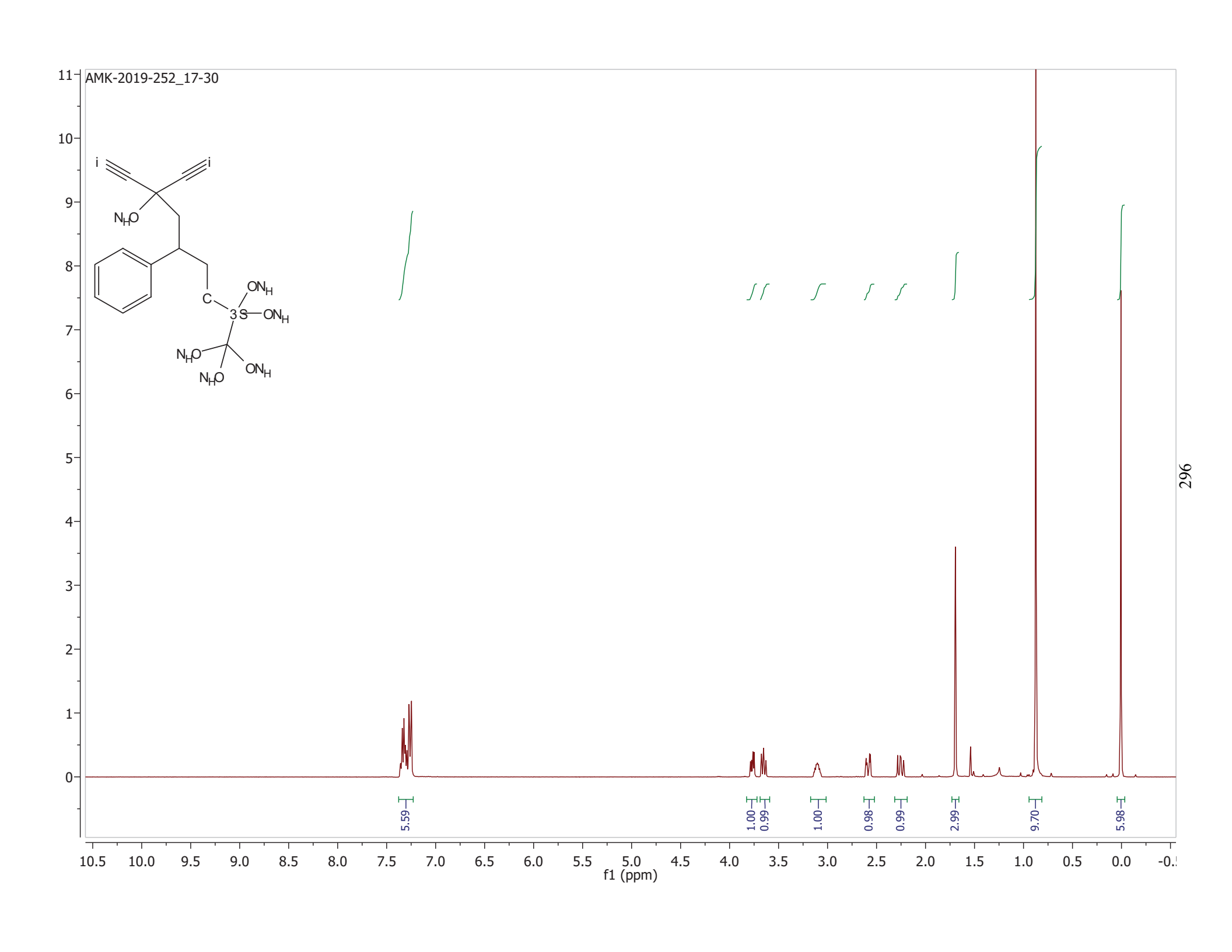

AMK-413f -461-34
N
N
OH
291
3(ppm) .

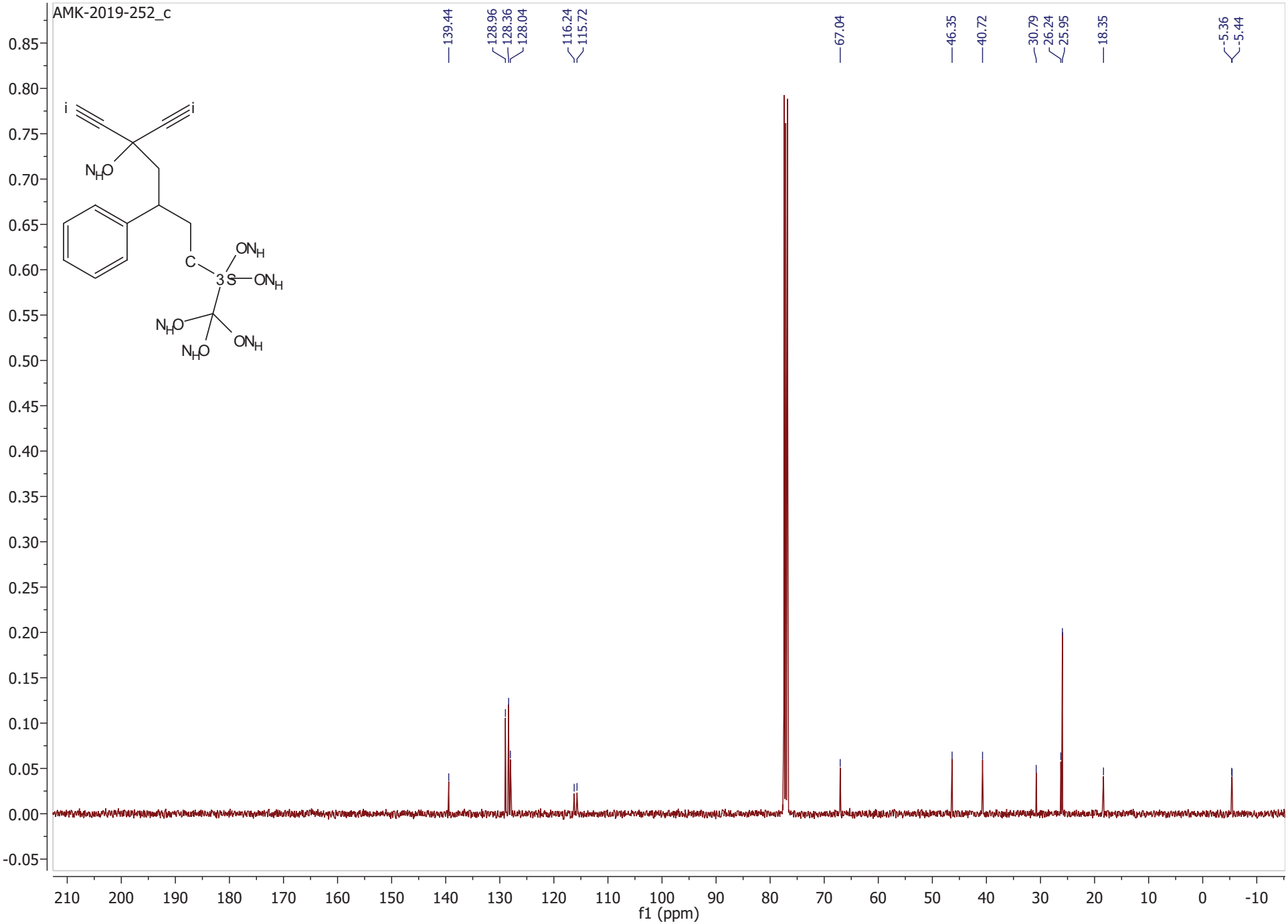

AMK-2019-240-hf
139.09
131.93
130.40
129.28
129.00
128.89
128.35
128.31
115.35
114.53
66.52
60.53
46.10
44.58
39.52
38.25
21.19
14.30
N
N
OH
292
f1 (ppm)

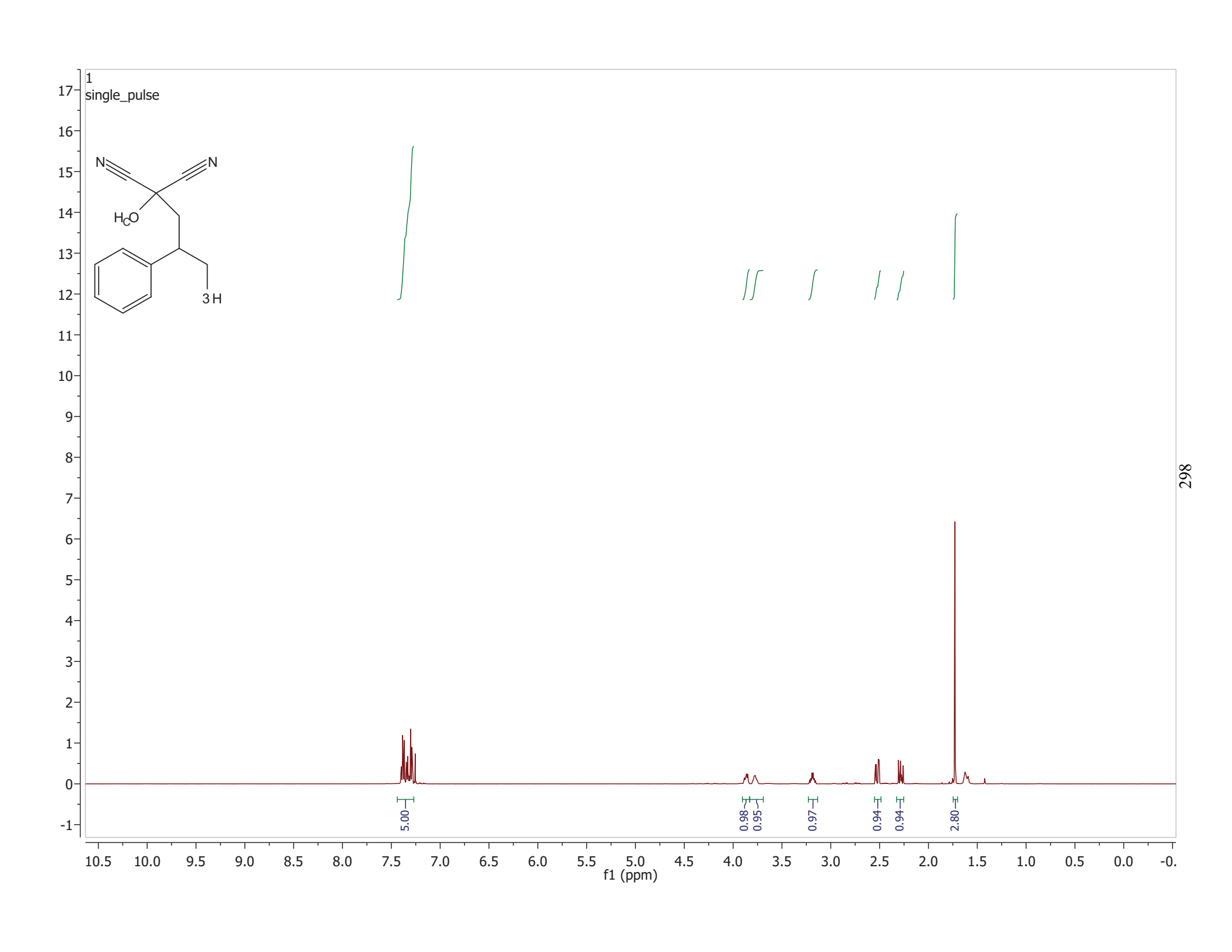

AMK-2019-254_dIA
N
O
O
8.65
1.93
1.00
1.07
2.05
1.02
1.08
1.04
f1 (ppm)
293

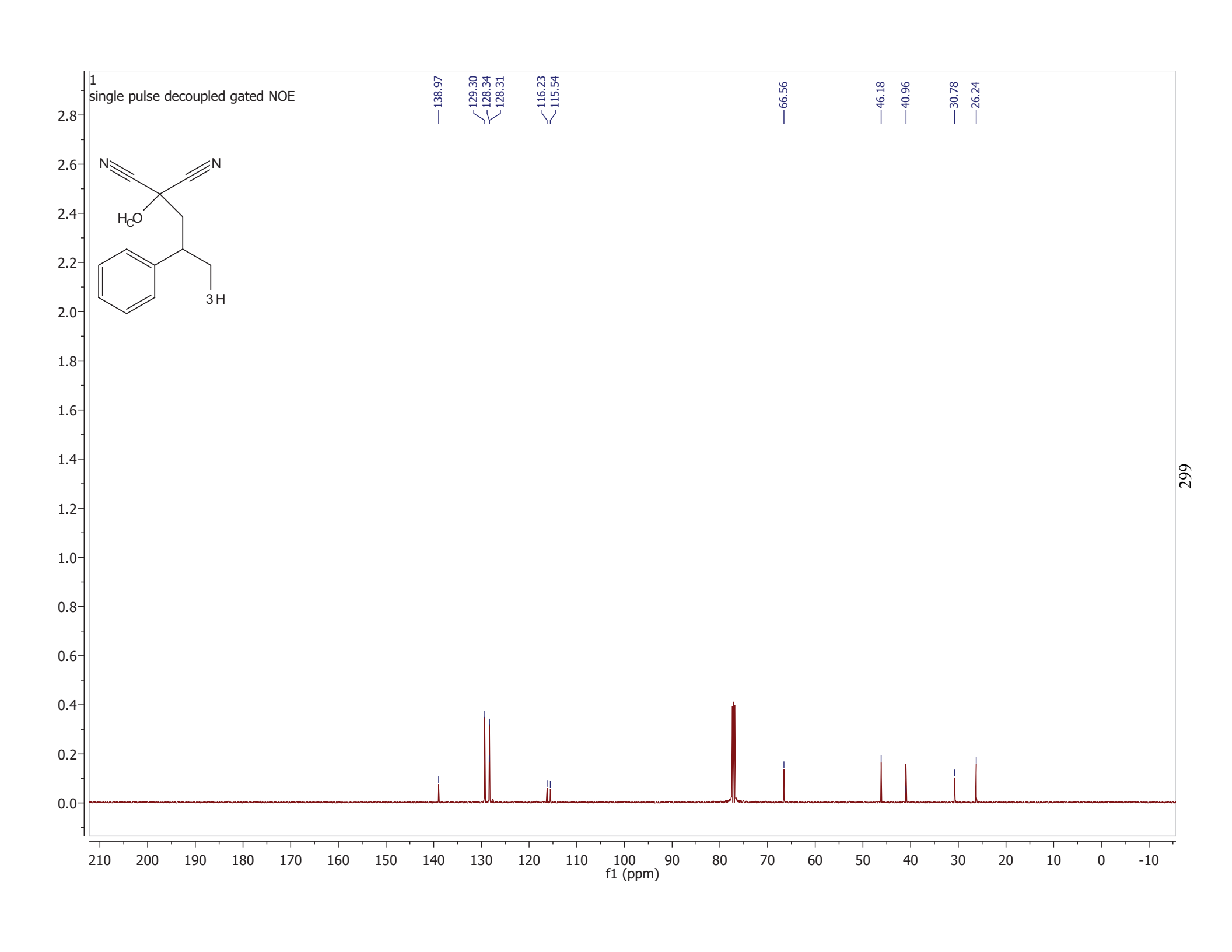

AMK-2019-254_c
164.77
137.45
133.31
130.57
129.30
129.01
128.31
128.27
127.19
118.84
75.07
44.98
42.53
37.60
36.32
N
O
O
f1 (ppm)

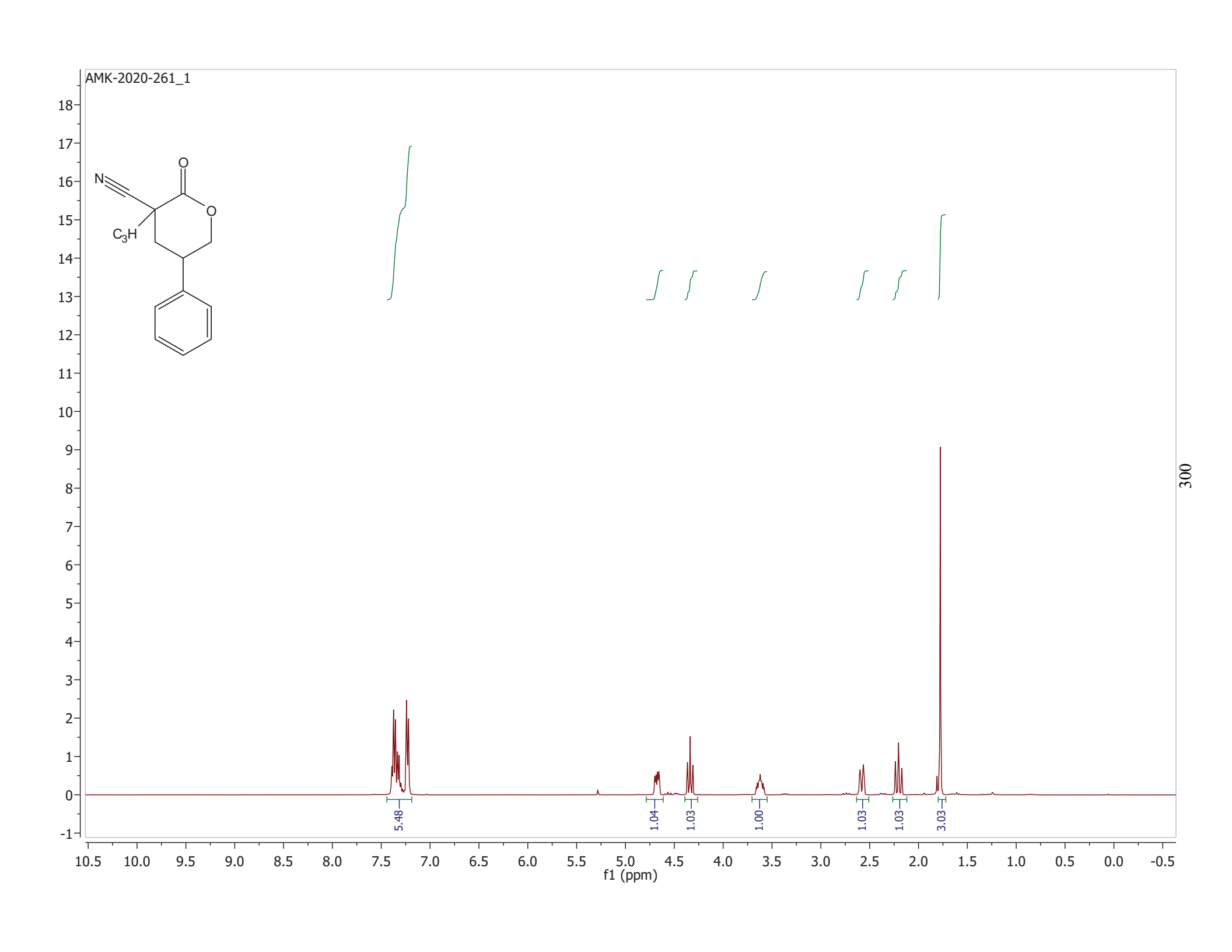

AMK-413f -462-32-42
N
N
CH3
3.01
5.67
3(ppm)

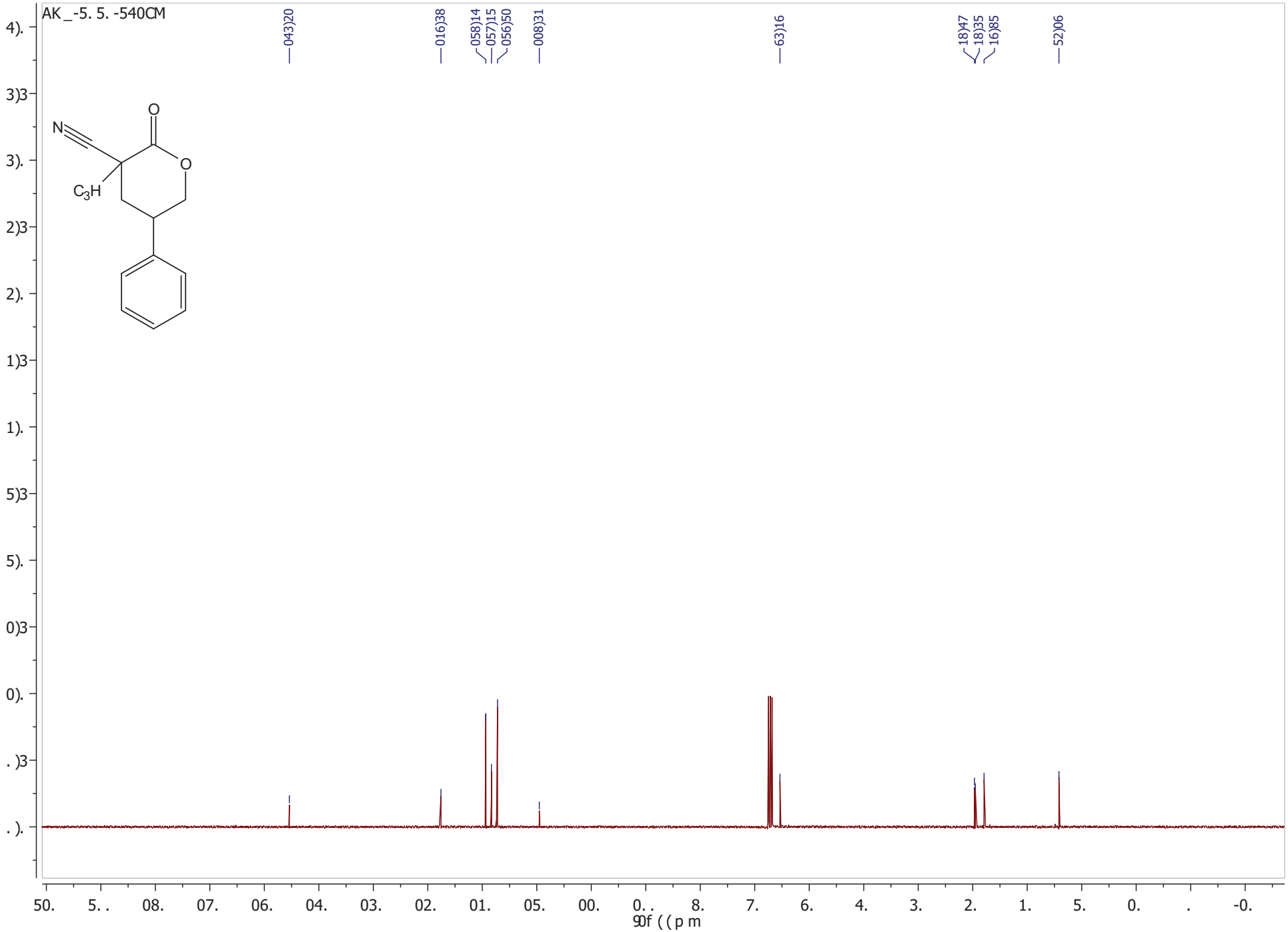

AMK-2019-252_17-30
296
f1 (ppm)
5.59
1.00
0.99
1.00
0.98
0.99
2.99
9.70
5.98

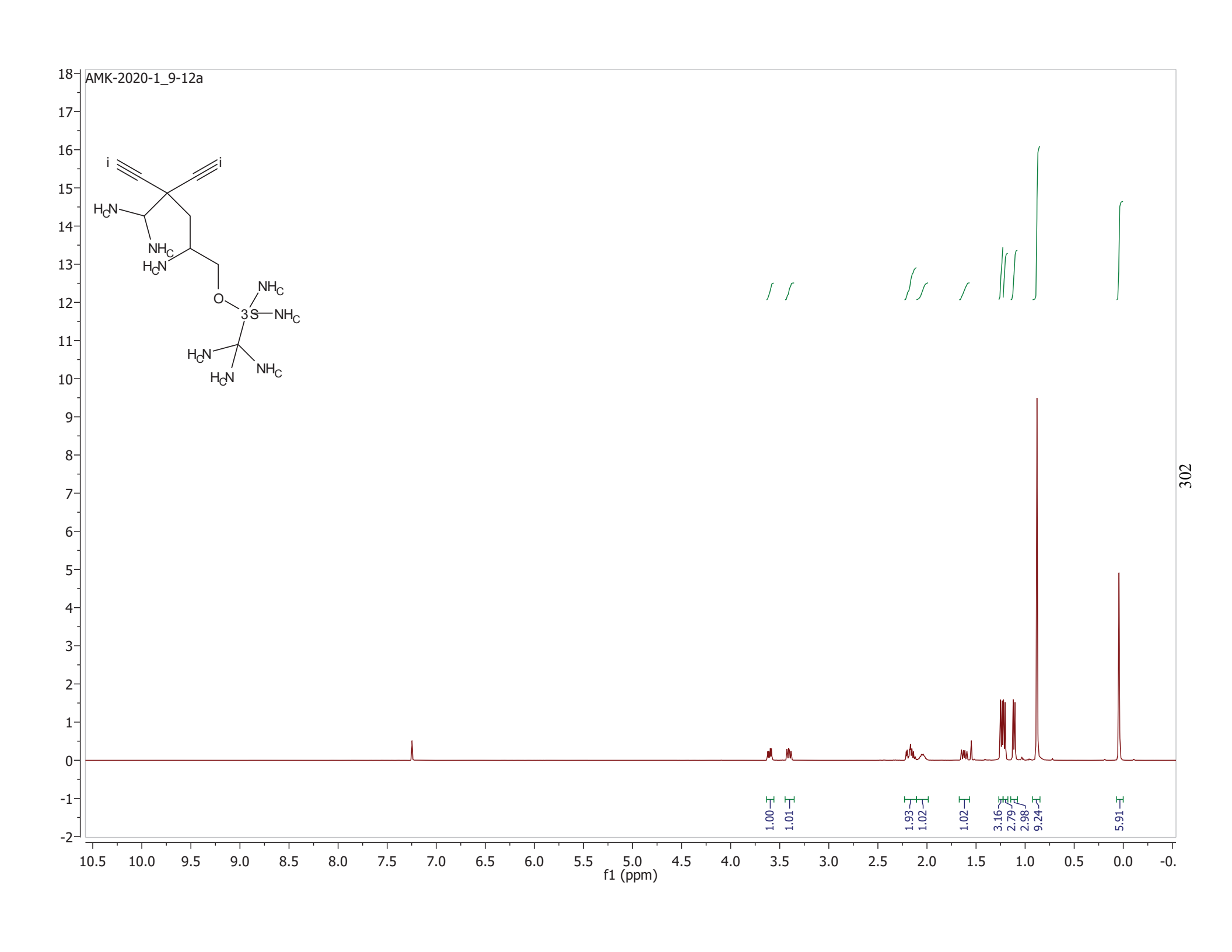

AMK-2019-252_c
139.44
128.96
128.36
128.04
116.24
115.72
67.04
46.35
40.72
30.79
26.24
25.95
18.35
-5.36
-5.44
297
f1 (ppm)

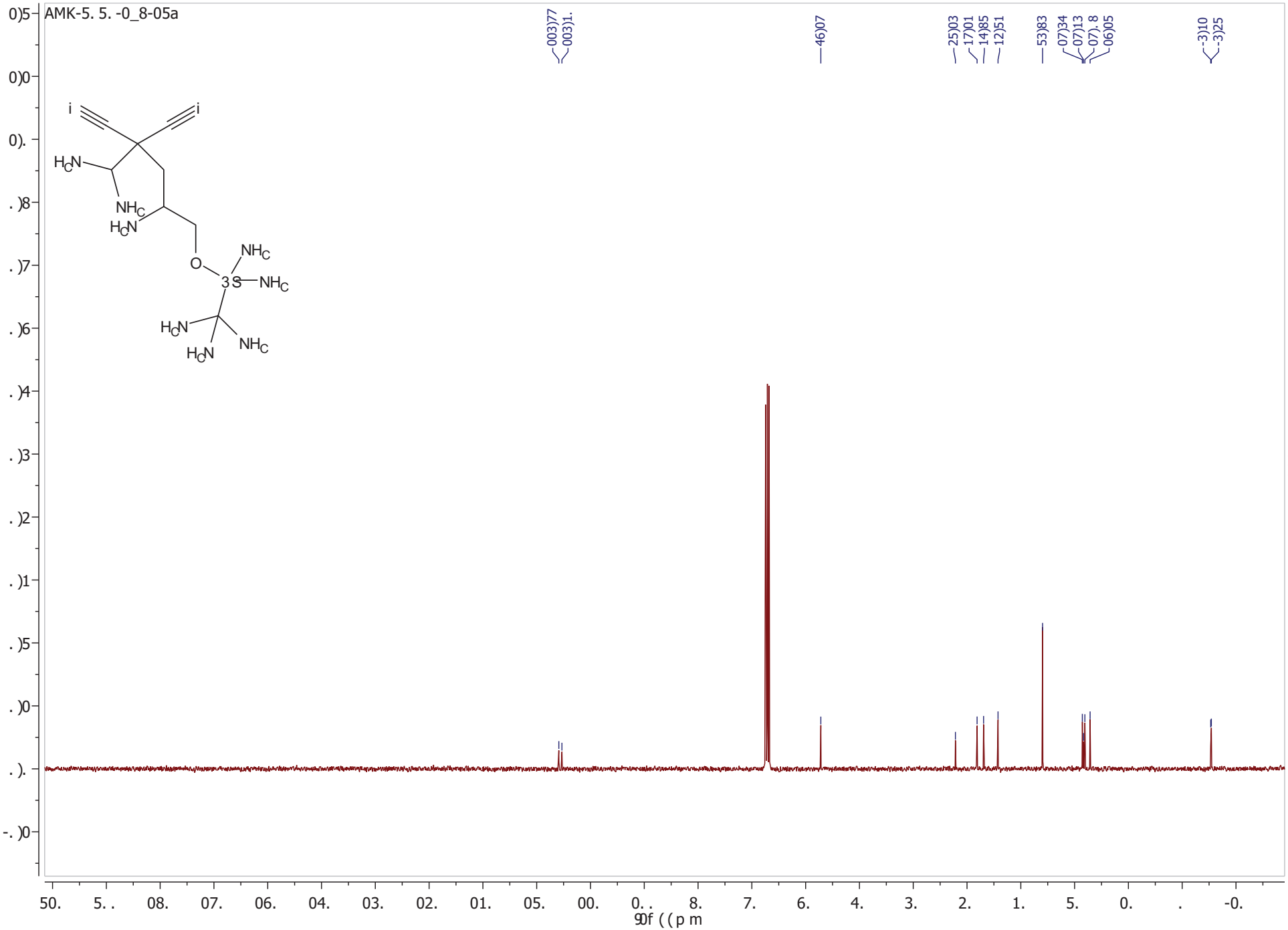

1
single_pulse
N
N
H3C
O
3 H
5.00
0.98
0.95
0.97
0.94
0.94
2.80
f1 (ppm)
298

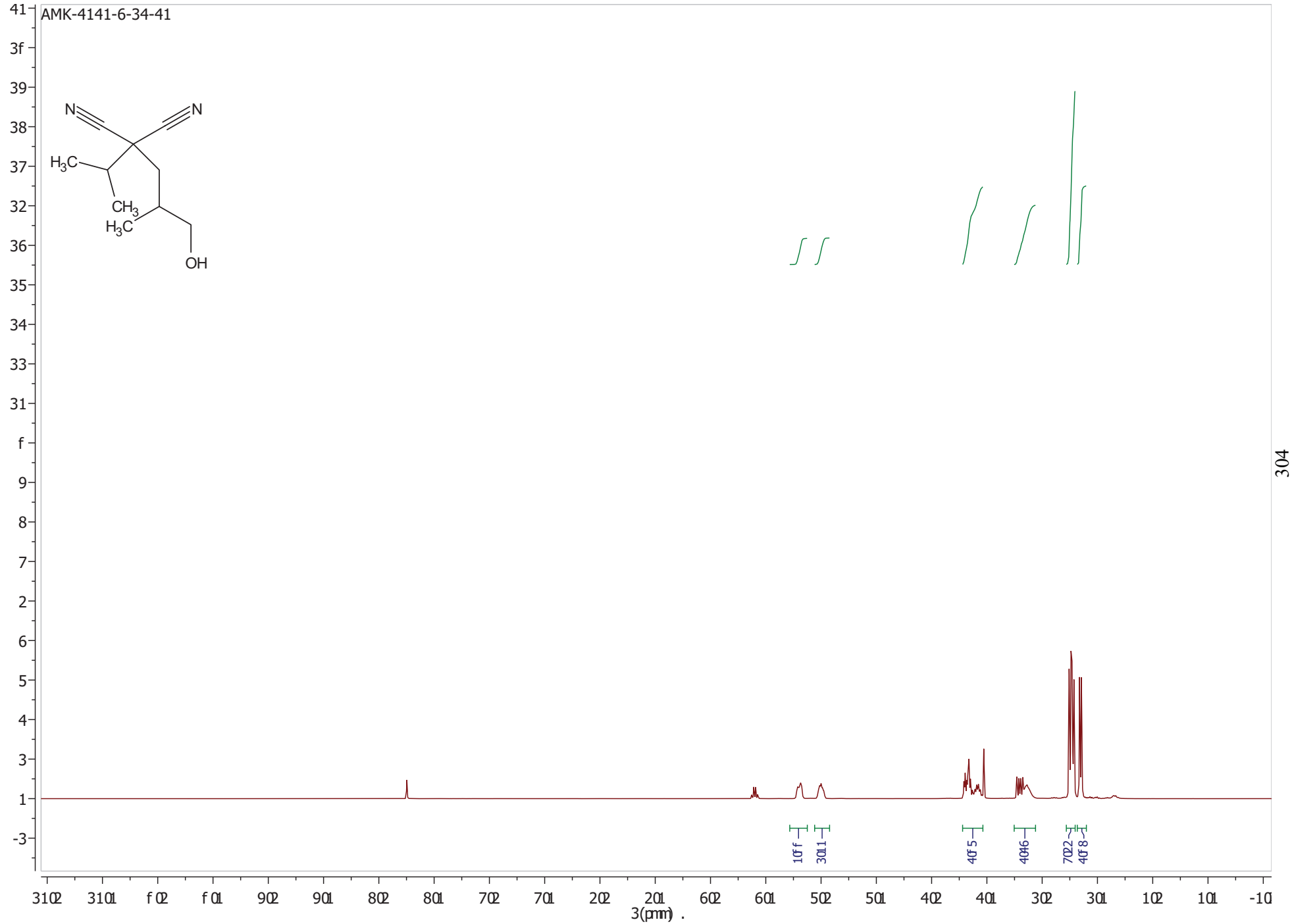

1
single pulse decoupled gated NOE
138.97
129.30
128.34
128.31
116.23
115.54
66.56
46.18
40.96
30.78
26.24
N
N
H
C
O
3 H
f1 (ppm)

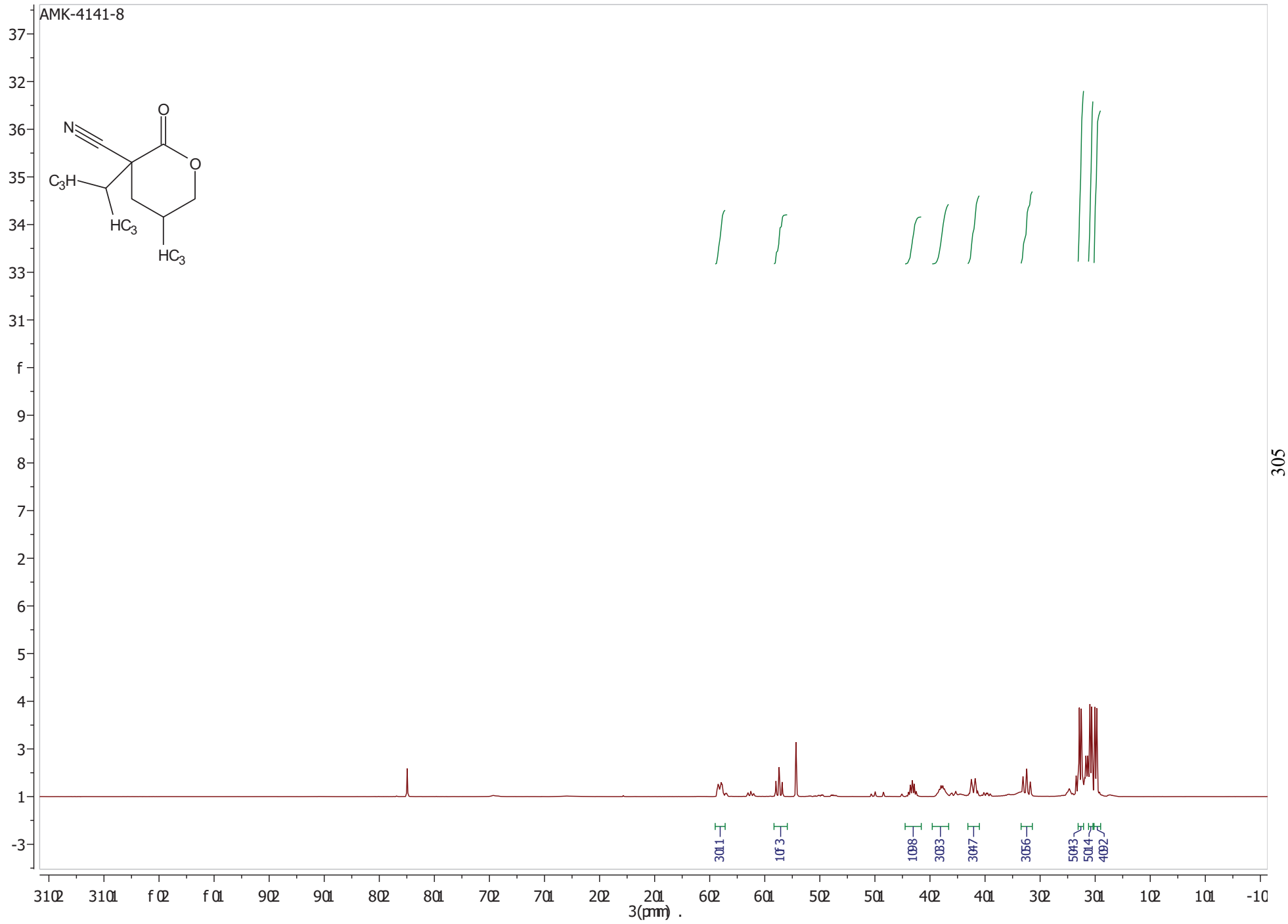

AMK-2020-261_1
N
O
O
C3H
5.48
1.04
1.03
1.00
1.03
1.03
3.03
f1 (ppm)
300

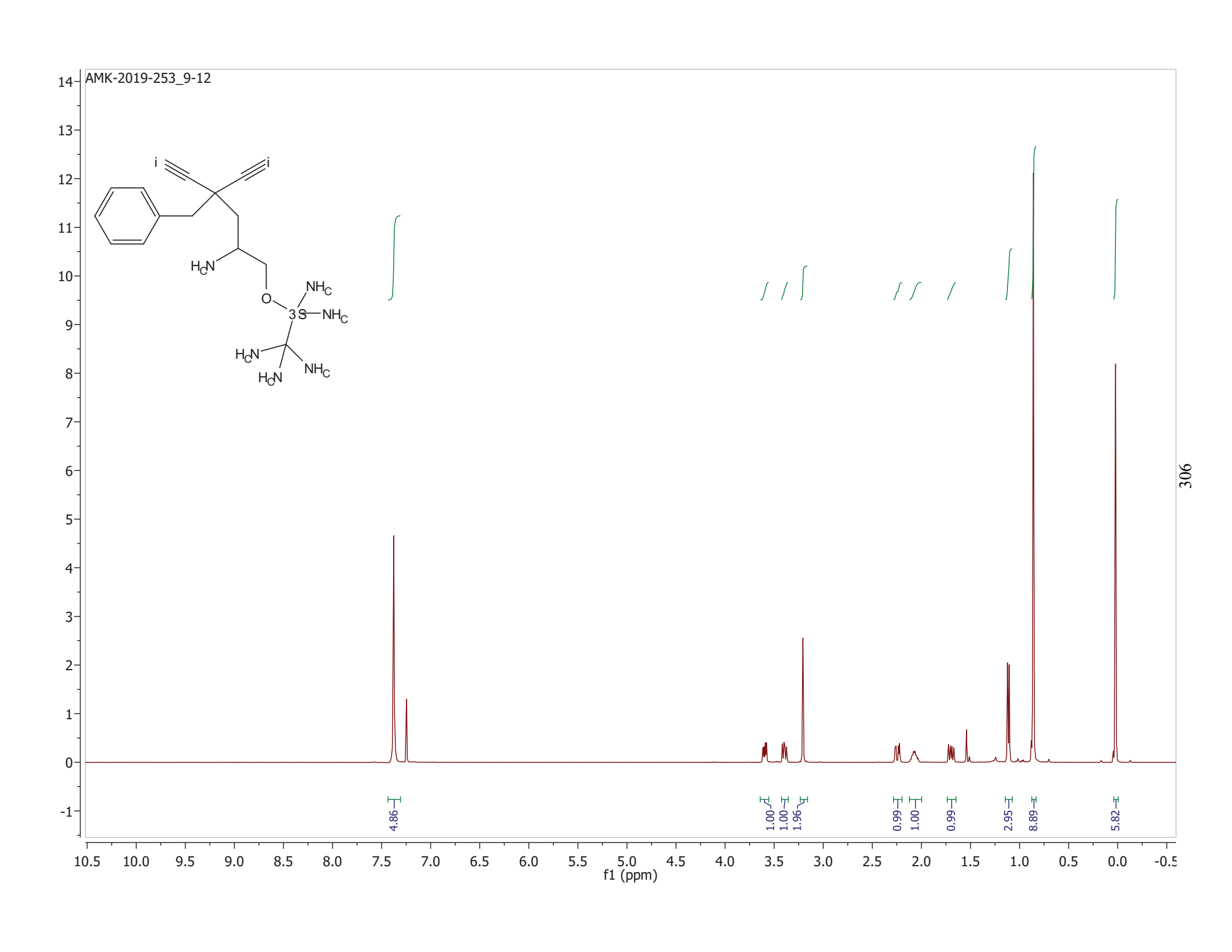

AK_-5. 5. -540CM
043)20
016)38
058)14
057)15
056)50
008)31
63)16
18)47
18)35
16)85
52)06
O
N
O
C3H
4).
3)3
3).
2)3
2).
1)3
1).
5)3
5).
0)3
0).
.)3
.).
50.
5. .
08.
07.
06.
04.
03.
02.
01.
05.
00.
0. .
8.
7.
6.
4.
3.
2.
1.
5.
0.
.
-0.
90f ((p m
301

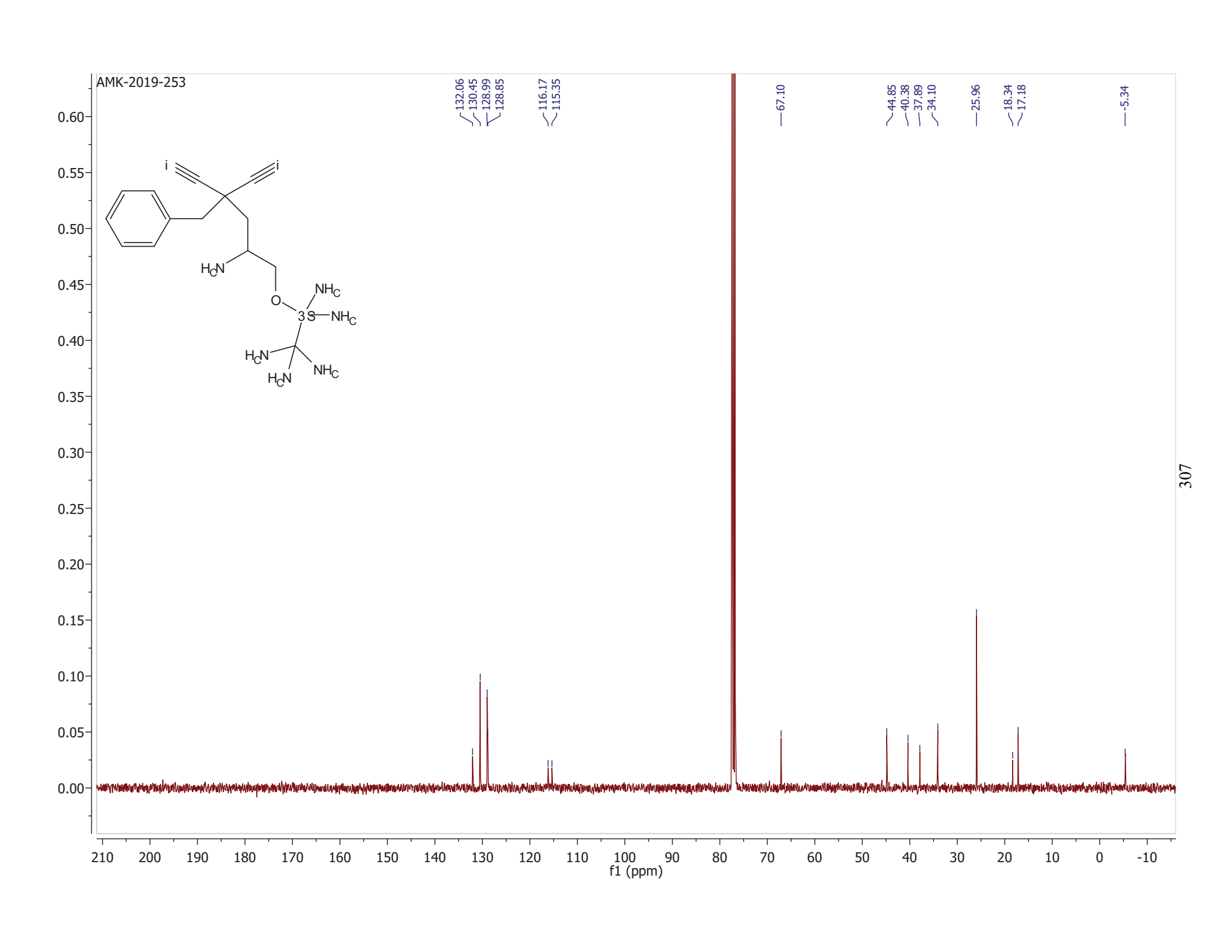

AMK-2020-1_9-12a
f1 (ppm)
1.00
1.01
1.93
1.02
1.02
3.16
2.79
2.98
9.24
5.91
302

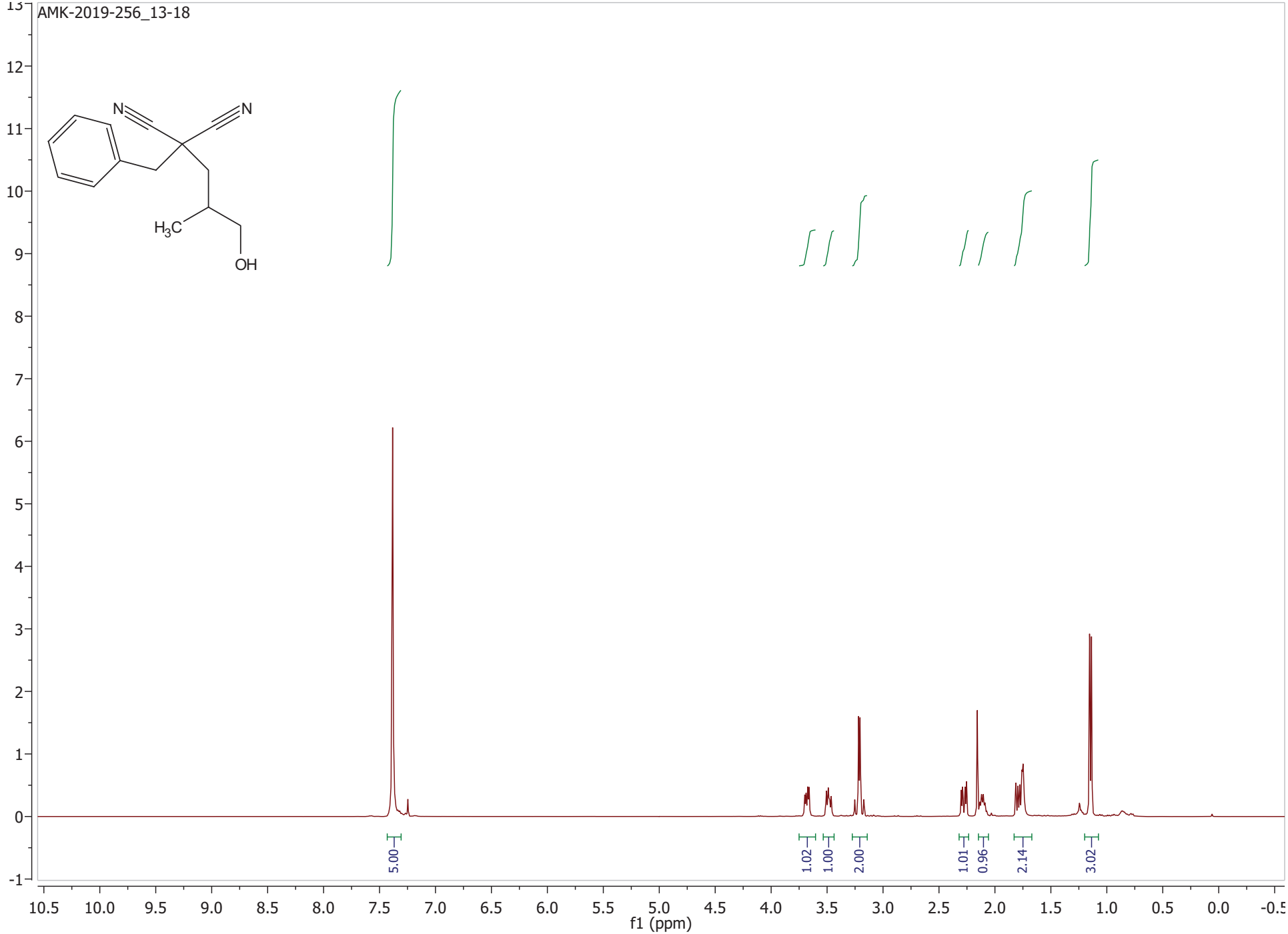

AMK-5. 5. -0_8-05a
003)77
003)1.
46)07
25)03
17)01
14)85
12)51
53)83
07)34
07)13
07). 8
06)05
-3)10
-3)25
303
90f ((p m

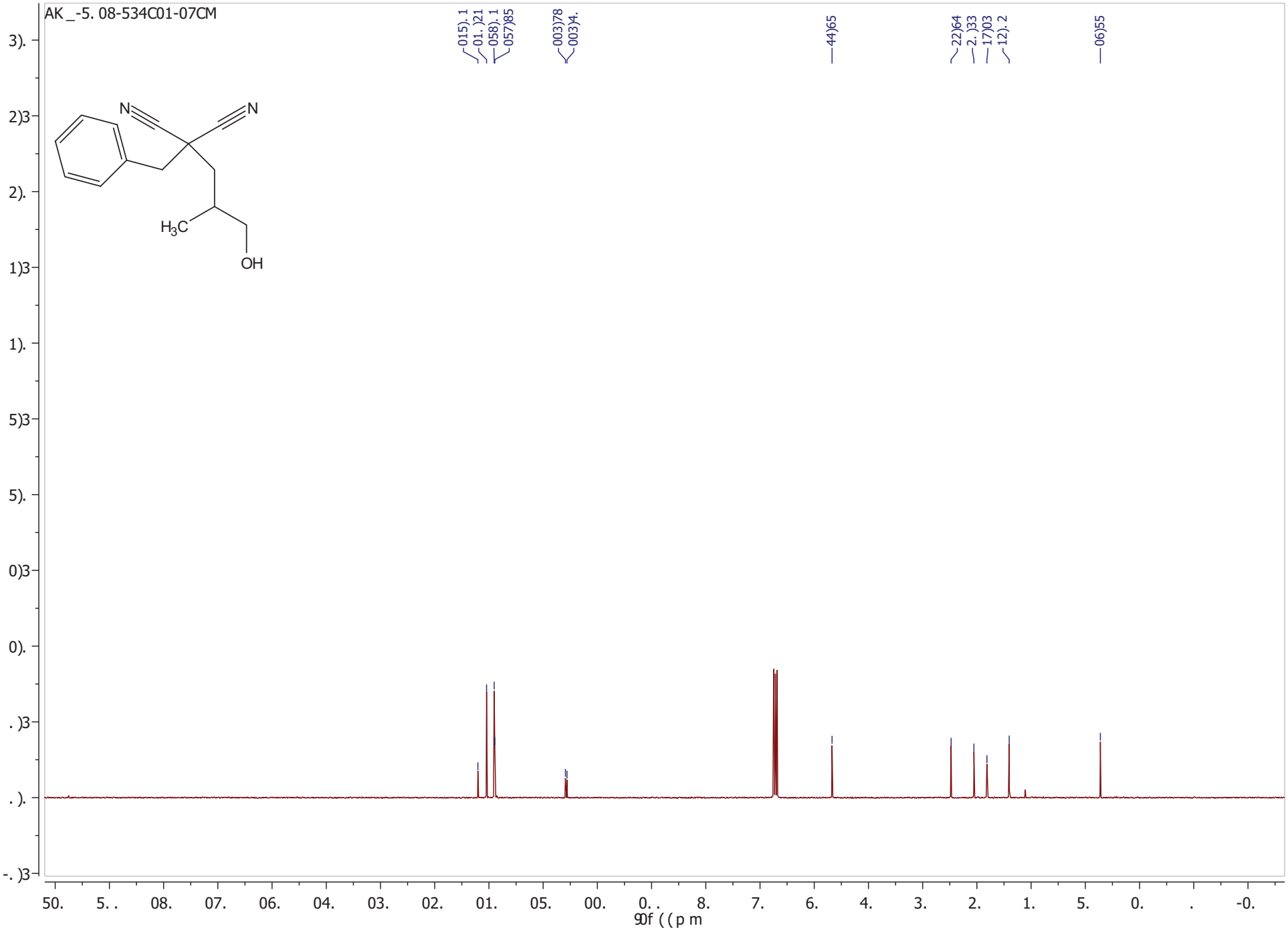

AMK-4141-6-34-41
N
N
H3C
CH3
H3C
OH
304
1.0f
3.01
4.05
4.06
7.02
4.08
3(ppm)

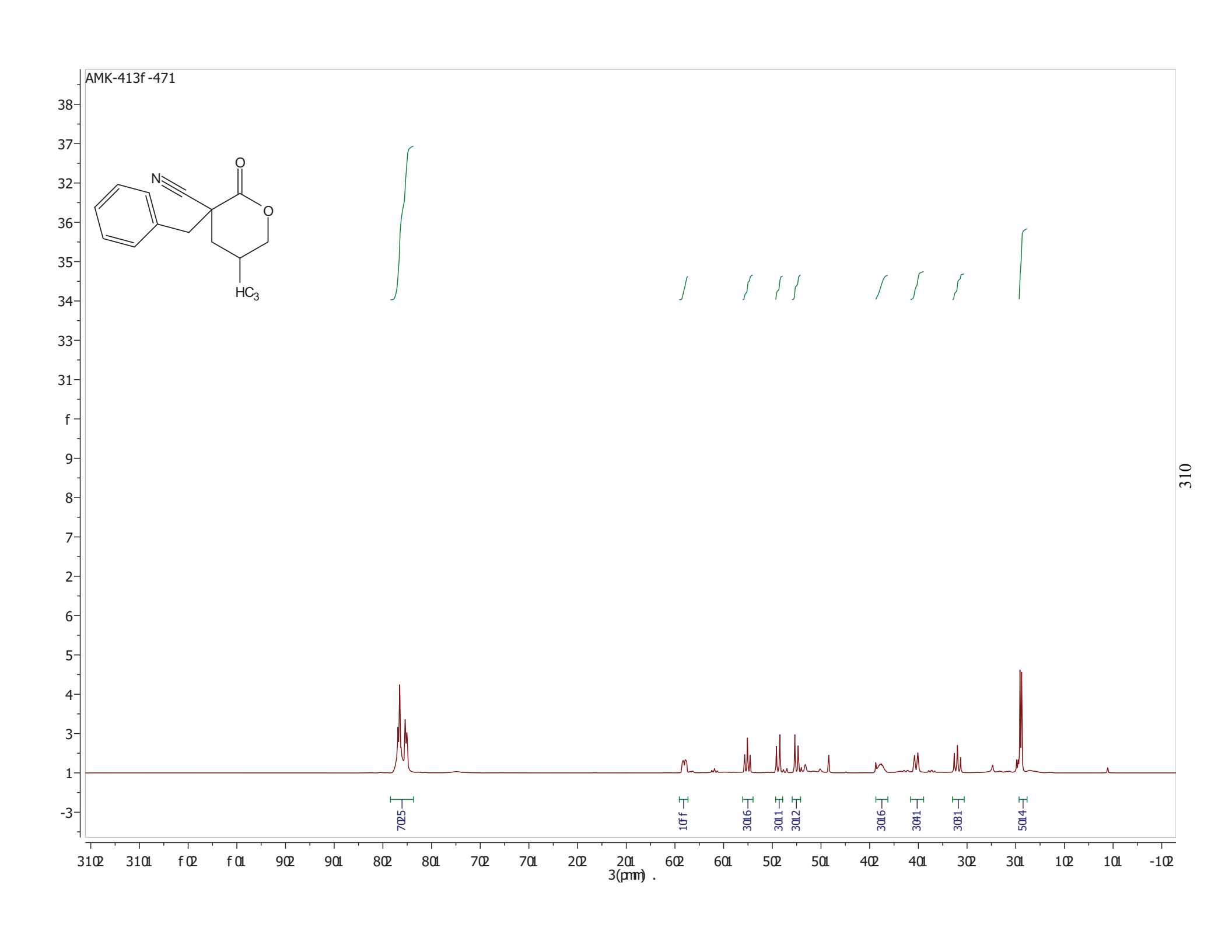

AMK-4141-8
O
N
O
C3H
HC3
HC3
305
3(ppm)

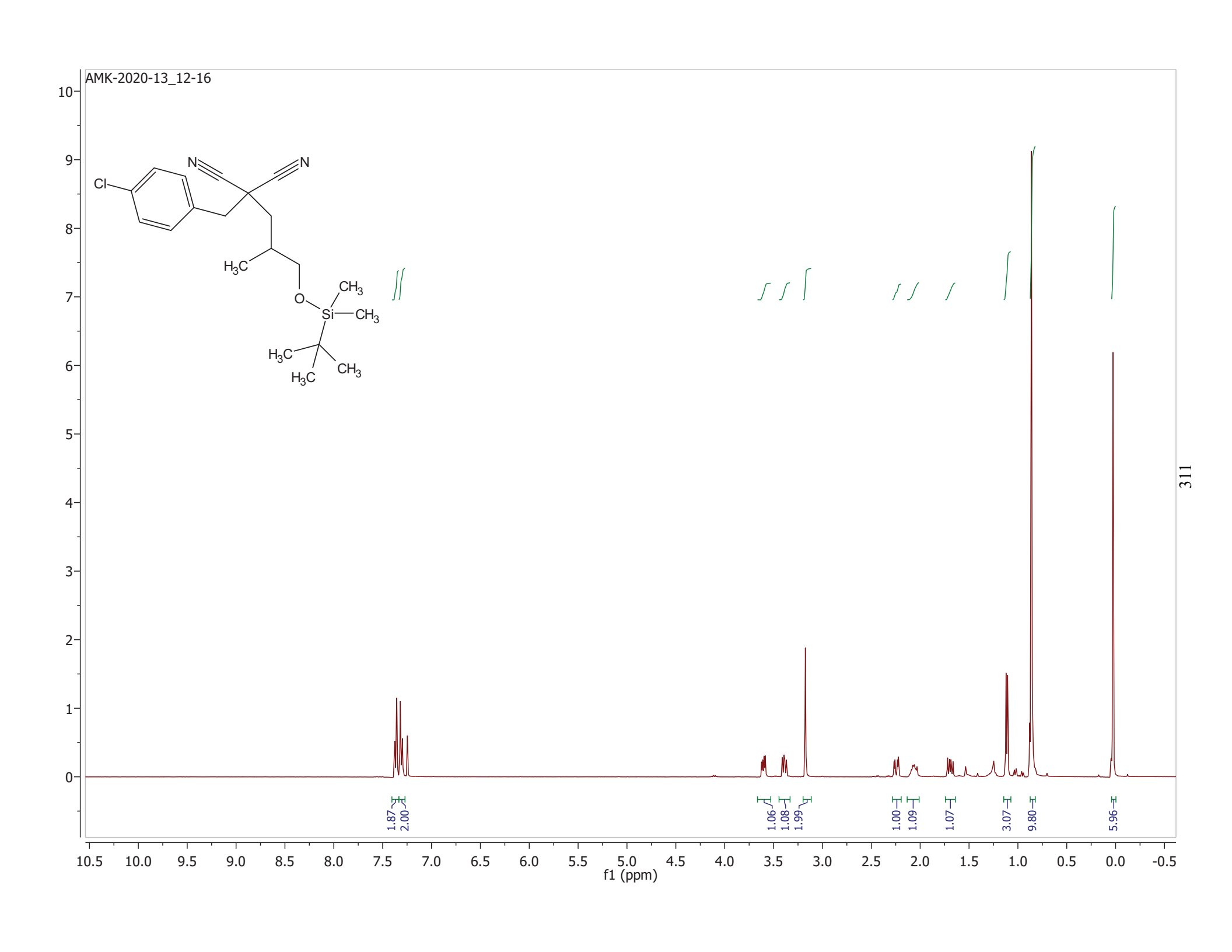

AMK-2019-253_9-12
306
f1 (ppm)
4.86
1.00
1.00
1.96
0.99
1.00
0.99
2.95
8.89
5.82

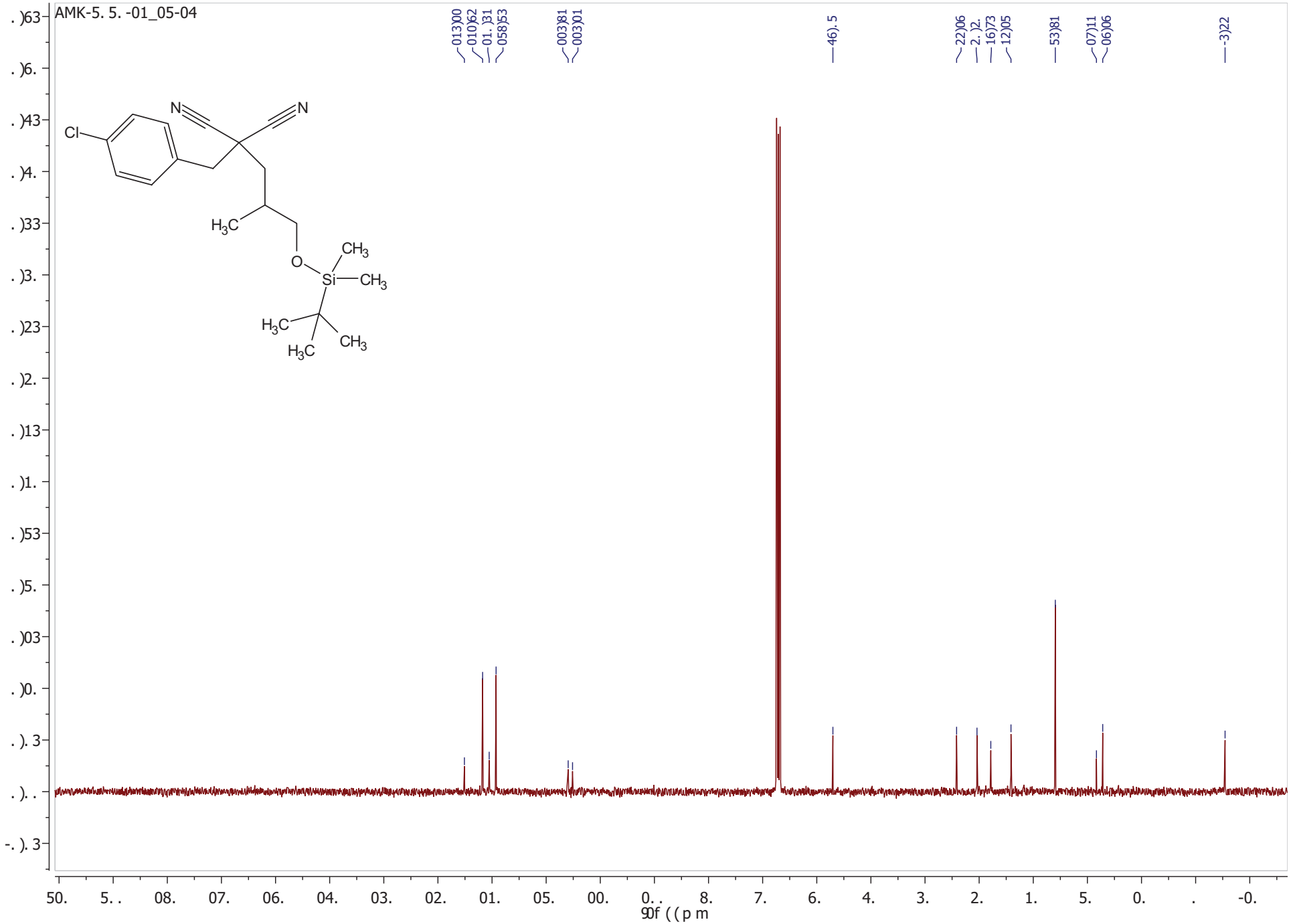

AMK-2019-253
132.06
130.45
128.99
128.85
116.17
115.35
67.10
44.85
40.38
37.89
34.10
25.96
18.34
17.18
-5.34
307
f1 (ppm)

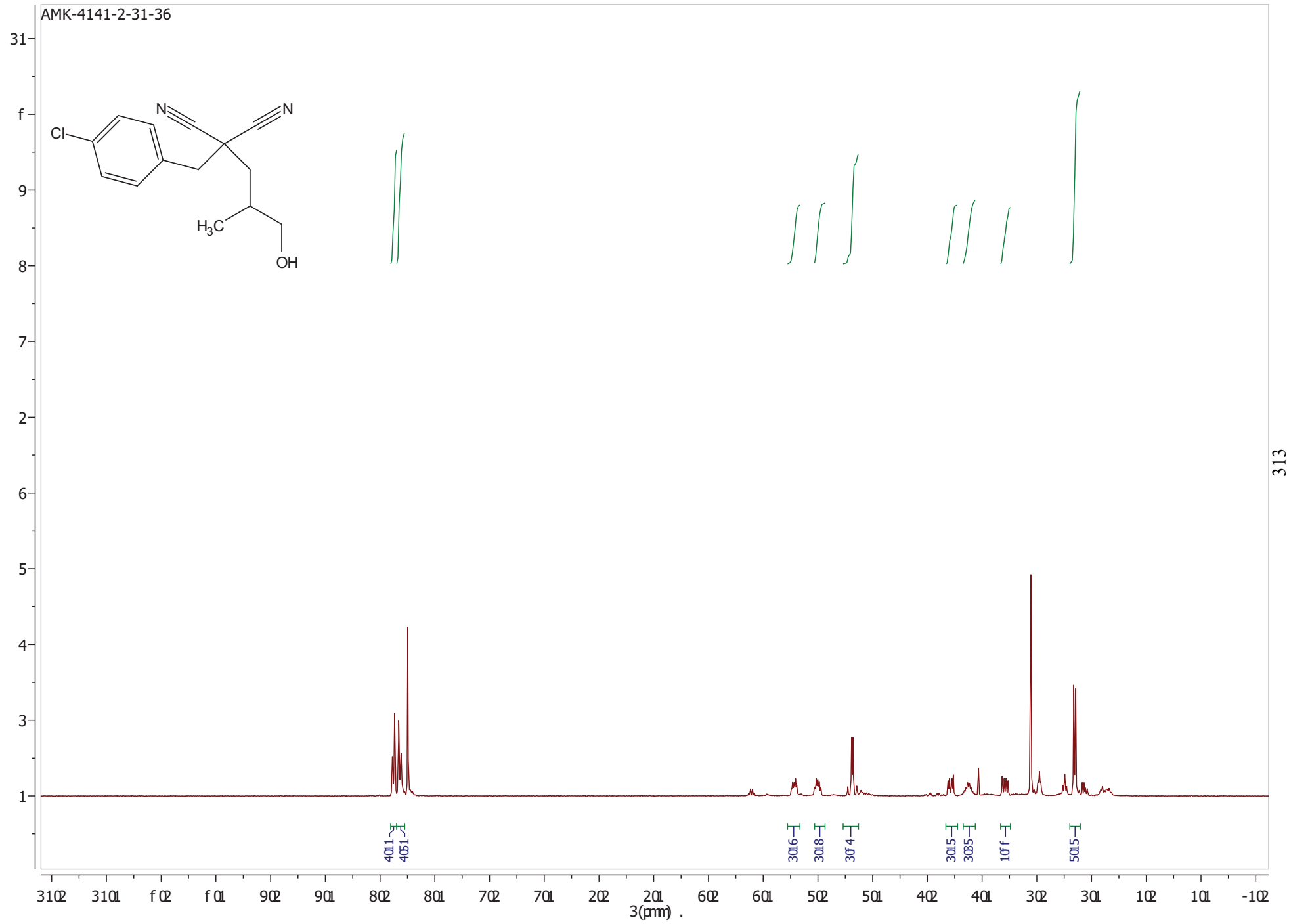

AMK-2019-256_13-18
N
N
H3C
OH
5.00
1.02
1.00
2.00
1.01
0.96
2.14
3.02
f1 (ppm)
308

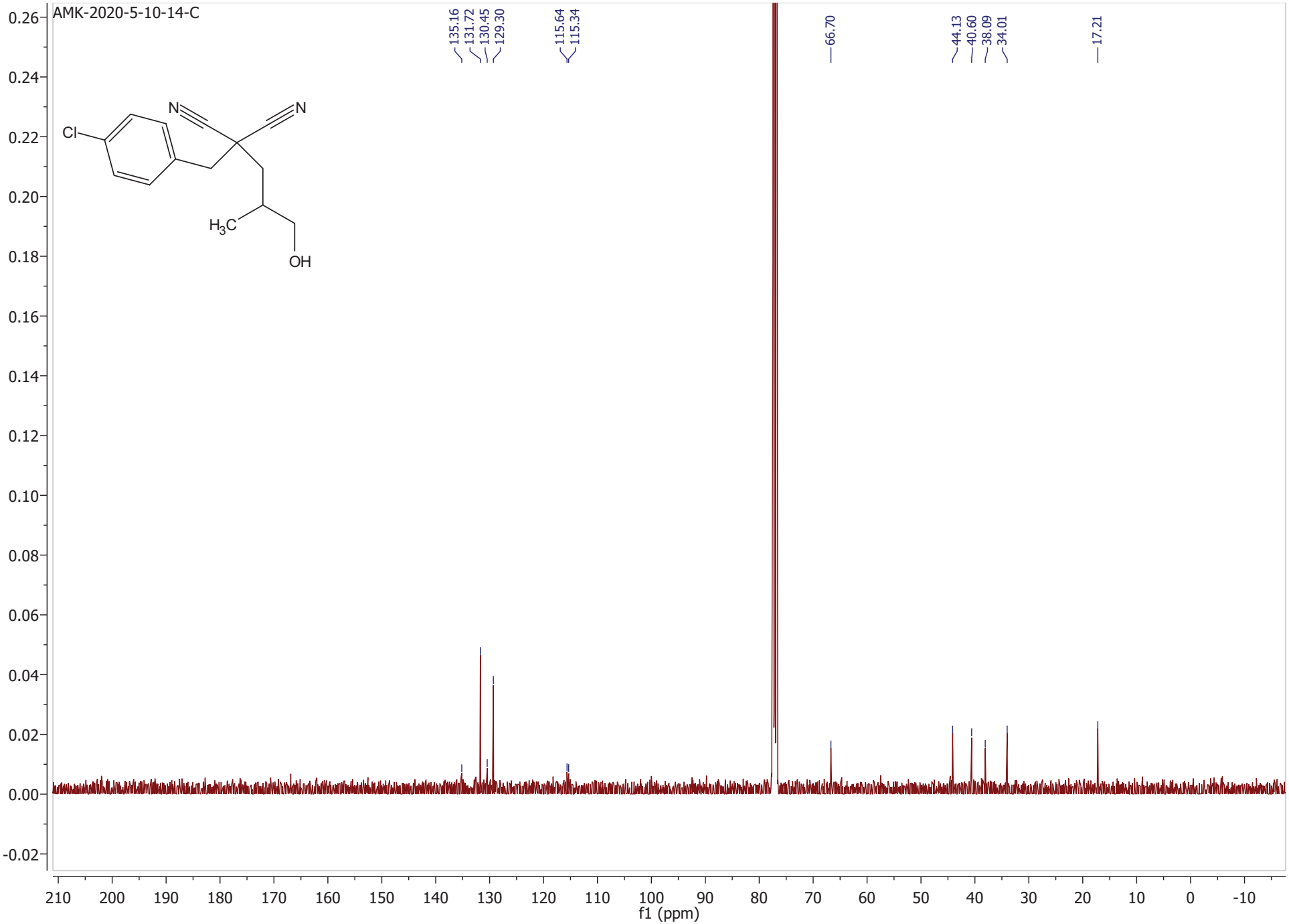

AK _-5. 08-534C01-07CM
015). 1
01.)21
058). 1
057)85
003)78
003)4.
44)65
22)64
2.)33
17)03
12). 2
06)55
N
N
H3C
OH
3).
2)3
2).
1)3
1).
5)3
5).
0)3
0).
.)3
.).
-.)3
50.
5. .
08.
07.
06.
04.
03.
02.
01.
05.
00.
0. .
8.
7.
6.
4.
3.
2.
1.
5.
0.
.
-0.
90f ((p m

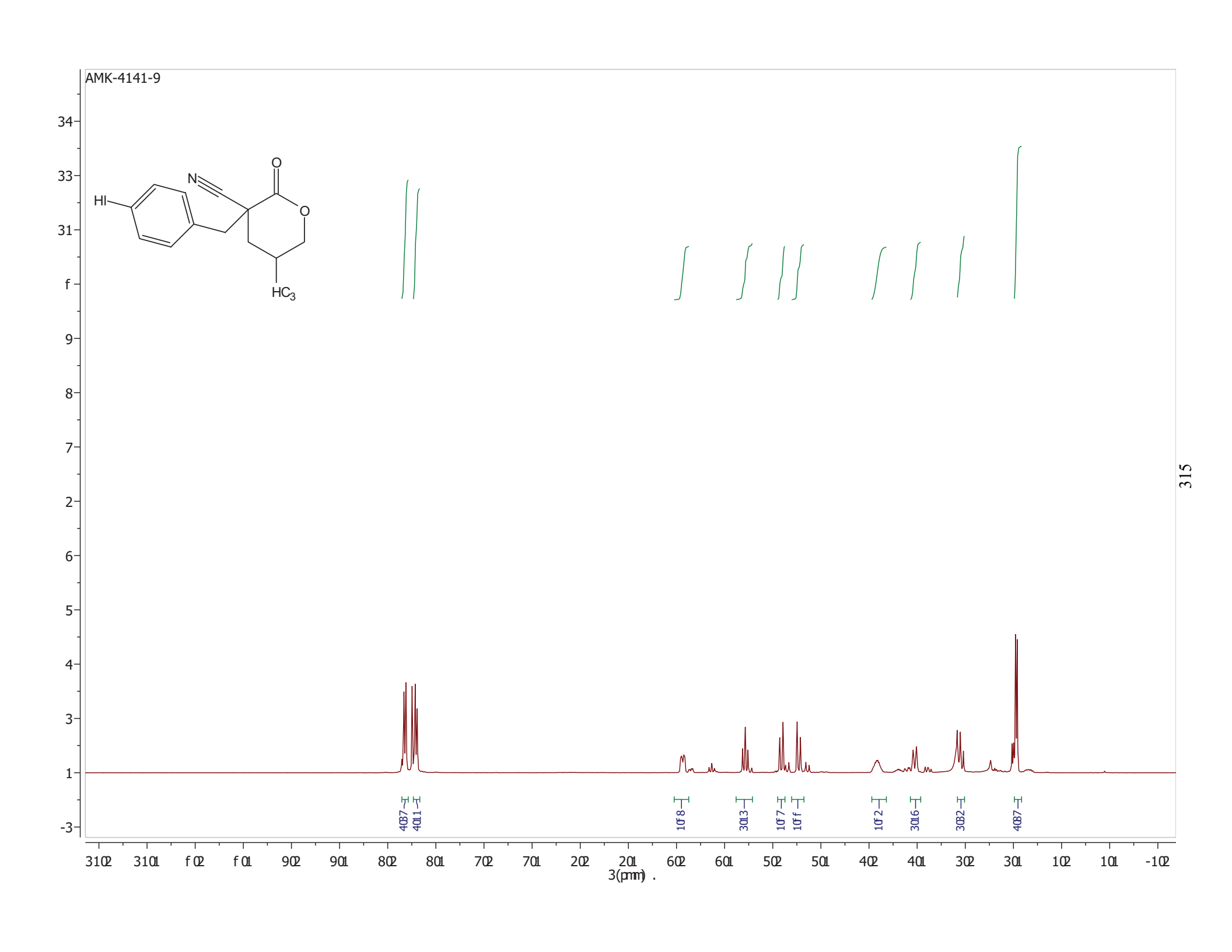

AMK-413f -471
N
O
O
HC3
7.25
1.0 f
3.01 6
3.01 1
3.01 2
3.01 6
3.04 1
3.03 1
5.01 4
3(ppm) .
310


AMK-2020-13_12-16
N
N
Cl
H3C
O
Si
CH3
CH3
H3C
H3C
CH3
1.87
2.00
1.06
1.08
1.99
1.00
1.09
1.07
3.07
9.80
5.96
f1 (ppm)
311


AMK-5. 5. -01_05-04
013)00
010)62
01.)31
058)53
003)81
003)01
46). 5
22)06
2.)2.
16)73
12)05
53)81
07)11
06)06
-3)22
Cl
N
N
H3C
O
Si
CH3
CH3
H3C
CH3
H3C
50.
5. .
08.
07.
06.
04.
03.
02.
01.
05.
00.
0. .
8.
7.
6.
4.
3.
2.
1.
5.
0.
.
-0.
9pf ((p m


AMK-4141-2-31-36
Cl
N
N
H3C
OH
3(ppm)


AMK-2020-5-10-14-C
135.16
131.72
130.45
129.30
115.64
115.34
66.70
44.13
40.60
38.09
34.01
17.21
N
N
Cl
H3C
OH
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

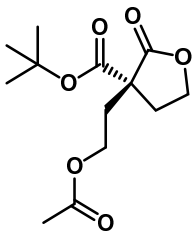

AMK-4141-9
HI
N
O
O
HC3
4.087
4.011
1.018
3.013
1.017
1.01f
1.012
3.016
3.032
4.087
3(ppm)
315

APPENDIX B

CHROMATOGRAMS

GC chromatograms were obtained using an Agilent 7890A. The chiral column used was a Supelco Betadex 110 Fused Silica Capillary Column (30m x 0.25mm x 0.25 μm). HPLC chromatograms were obtained using an Agilent 1260 Infinity. The chiral columns used were CHIRALCEL OJ-H (4.6 mm x 250 mm x 5 μm), CHIRALCEL OD-H (4.6 mm x 250 mm x 5 μm), CHIRALCEL AD-H (4.6 mm x 250 mm x 5 μm). Analysis details can be found with each chromatogram.

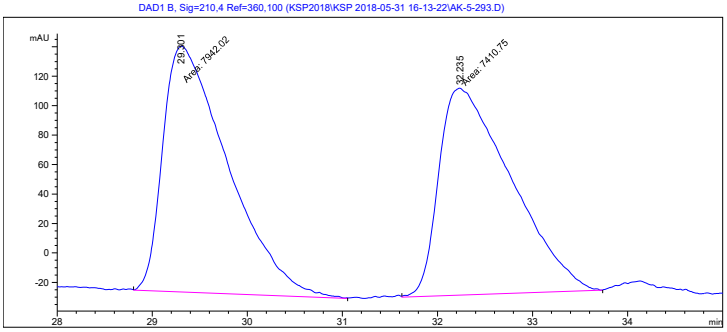
Table 1. Substrate 35a



35a

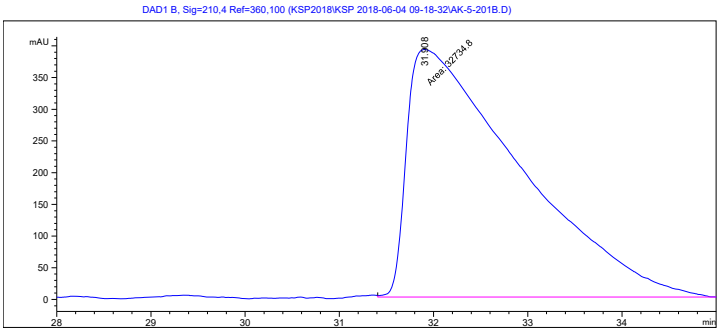
HPLC Conditions: Chiralcel OD-H; 4.6 mm x 250 mm x 5 µm; Eluent Rate: 1mL/min; Eluent: 1% IPA/hexane; Monitoring wave: 210 nm

Racemic



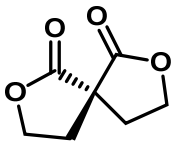
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	29.301	1	MM	7942.02100	166.91513	51.7302
2	32.235	1	MM	7410.75439	140.53903	48.2698

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	31.908	1	MM	3.27348e4	390.80692	100.0000

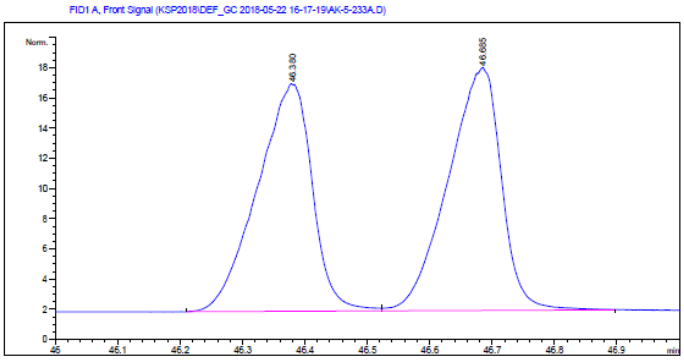
Table 1. Substrate 36a



36a

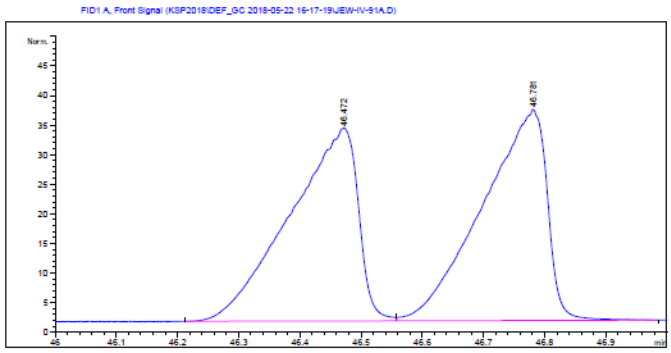
GC Conditions: Column: Beta Dex™ 110, 30m x 0.25mm x 0.25µm; Eluent Rate: 2.734 mL/min;Tempurature Ramp: 100° C for 20 min, ramp 2° C/min to 170° C, 170° C for 20 min.

Racemic



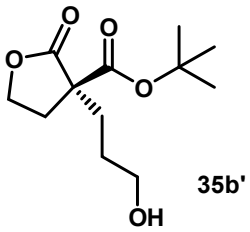
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	46.380	1	BV	92.02161	15.04099	49.14475
2	46.685	1	VB	95.22444	16.05278	50.85525

Enantioenriched



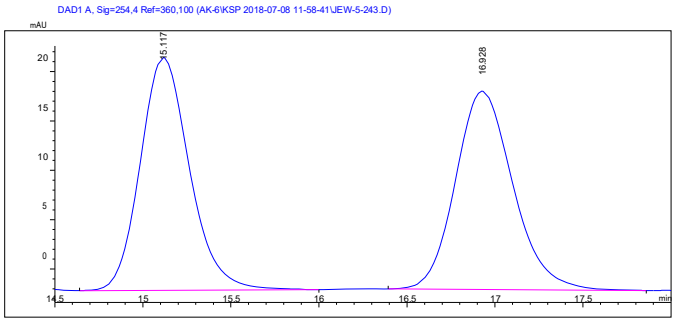
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	46.472	1	BV	253.70522	32.56509	49.18430
2	46.781	1	VB	262.12042	35.64466	50.81570
Totals :				515.82564	68.20975	

Table 1. Substrate **35b'**



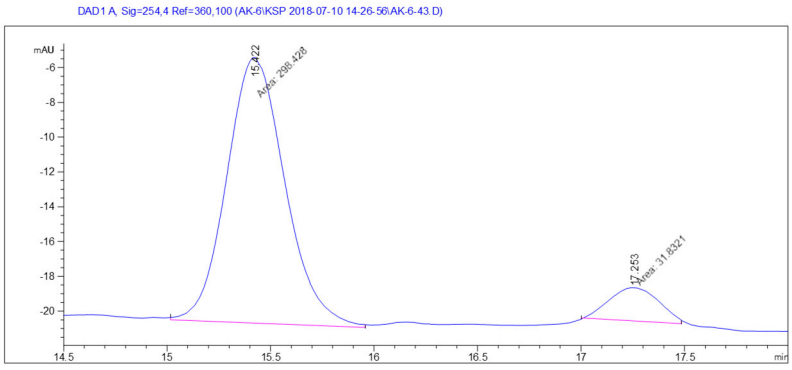
HPLC Conditions: Column: HPLC AD-H 4.6 mm x 250 mm x 5 µm; Eluent Rate: 1mL/min; Eluent: 5% IPA/hexane; Monitoring wave: 210 nm

Racemic



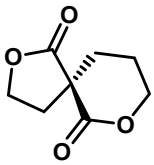
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	15.117	1	BB	459.11713	23.58135	50.1869
2	16.928	1	BB	455.69757	20.09037	49.8131
Totals :				914.81470	43.67172	

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	15.422	1	MM	298.42813	15.27881	90.3615
2	17.253	1	MM	31.83207	1.91101	9.6385
Totals :				330.26020	17.18982	

Table 1. Substrate **36b**

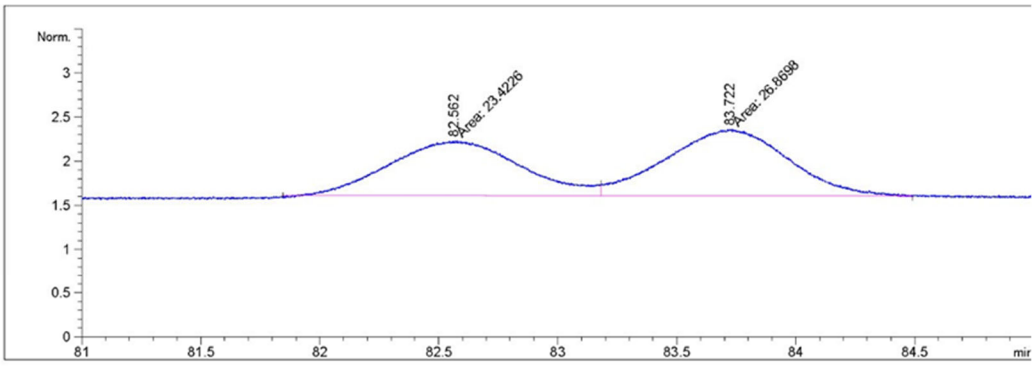


36b

GC Conditions: Column: Beta Dex™ 110, 30m x 0.25mm x 0.25µm; Eluent Rate: 2.734 mL/min;

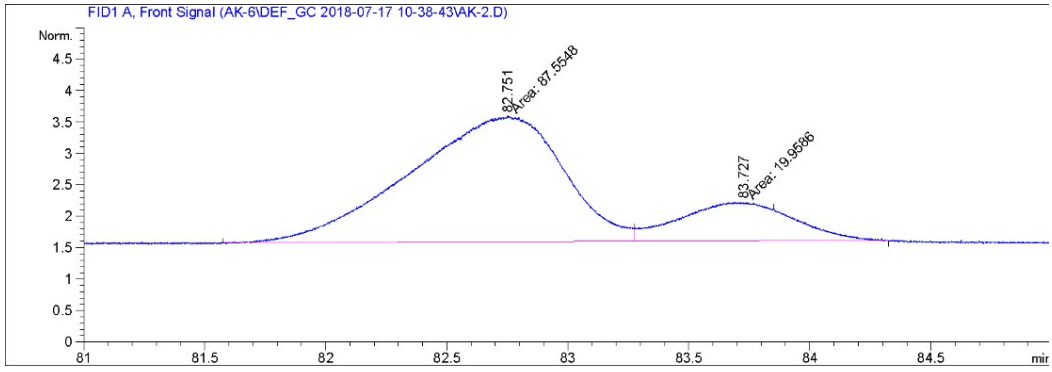
Tempurature Ramp: 125° C for 100 min, ramp 2° C to 170° C, 170° C for 20 min.

Racemic



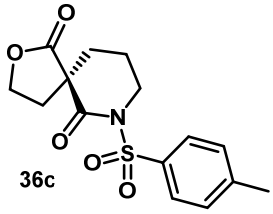
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	82.562	1	MF	23.42256	6.21933e-1	46.57277
2	83.722	1	FM	26.86983	7.55452e-1	53.42723
Totals :				50.29238	1.37739	

Enantioenriched



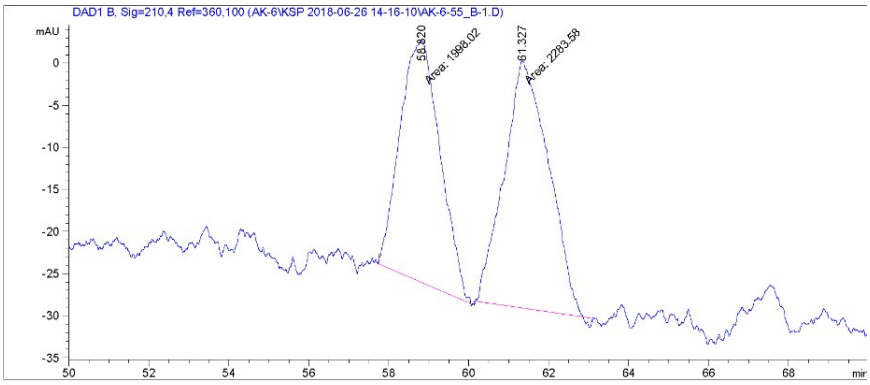
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	82.751	1	MF	87.55479	1.99870	81.43619
2	83.727	1	FM	19.95858	6.13417e-1	18.56381
Totals :				107.51337	2.61211	

Table 1. Substrate **36c**



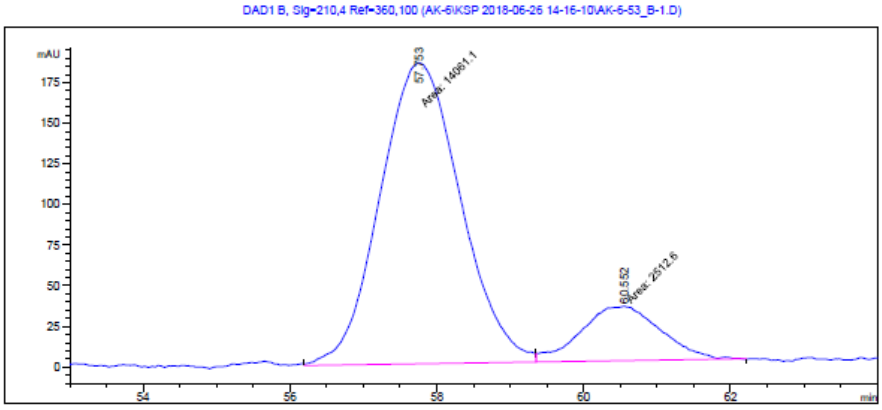
HPLC Conditions: Column: HPLC AD-H 4.6 mm x 250 mm x 5 Î¼m; Eluent Rate: 1mL/min; Eluent: 10% IPA/hexane; Monitoring wave: 210 nm

Racemic



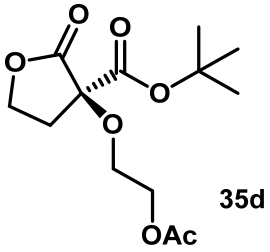
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	58.820	1	MM	1998.01978	28.75615	46.6653
2	61.327	1	MM	2283.57837	29.31816	53.3347
Totals :				4281.59814	58.07431	

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	57.753	1	MF	1.40611e4	185.12003	84.8398
2	60.552	1	FM	2512.60278	33.45011	15.1602

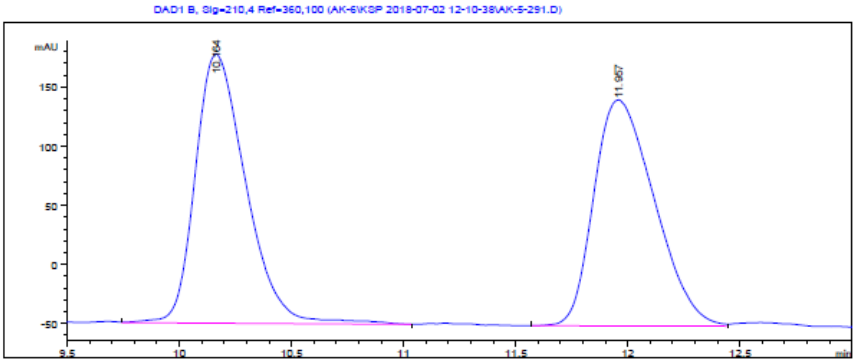
Table 1. Substrate **35d**



35d

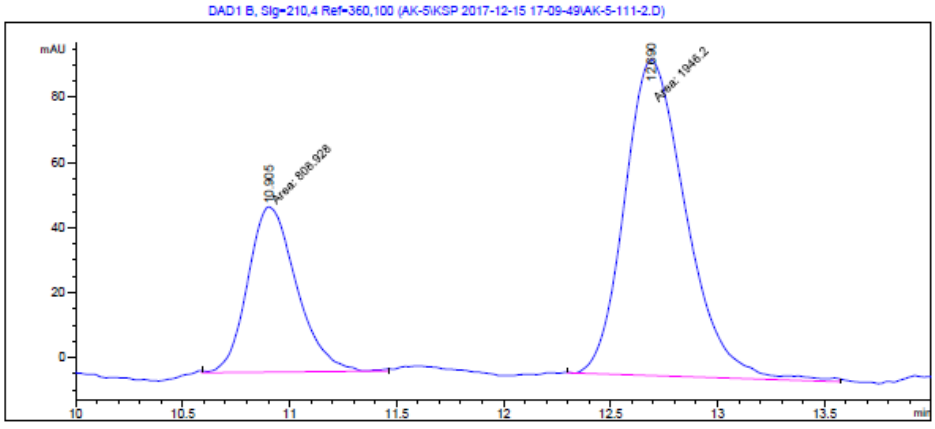
HPLC Conditions: Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 5% IPA/hexane; Monitoring wave: 210 nm

Racemic



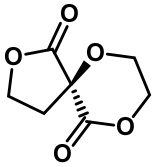
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	10.164	1	VB	3595.38208	228.11392	49.9729
2	11.957	1	BV	3599.27808	191.49210	50.0271

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	10.905	1	MM	808.92816	50.85793	29.3608
2	12.690	1	MM	1946.19702	97.29915	70.6392

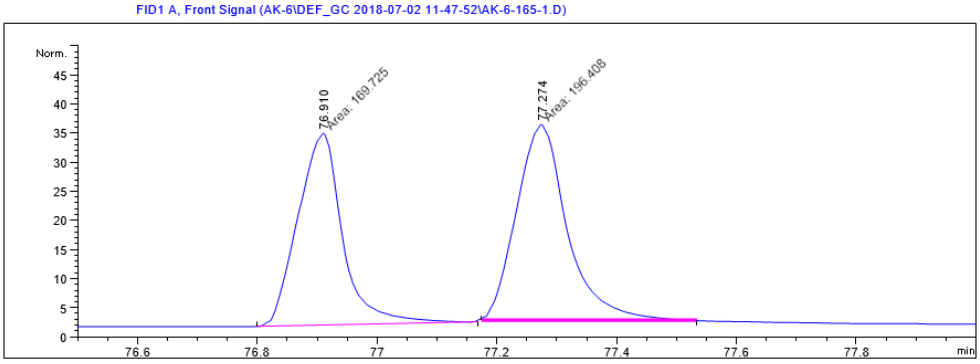
Table 1. Substrate **36d**



36d

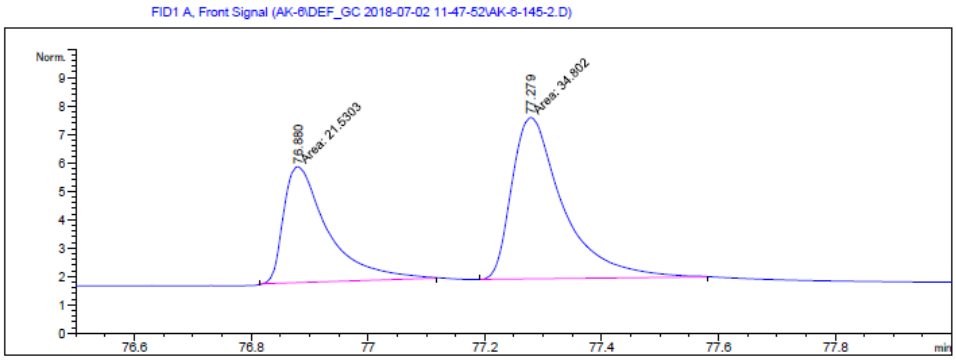
GC Conditions: Column: Beta Dex™ 110, 30m x 0.25mm x 0.25µm; Eluent Rate: 2.734 mL/min; Tempurature Ramp: 50° C for 30 min, ramp 20° C to 170° C, 170° C for 10 min.

Racemic



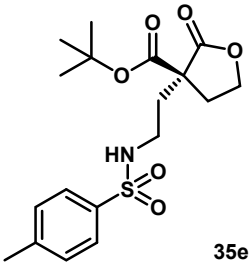
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	76.910	1	MM	169.72528	32.96133	46.35621
2	77.274	1	MM	196.40752	33.46372	53.64379

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	76.880	1	MM	21.53029	4.08600	38.22013
2	77.279	1	MM	34.80203	5.68204	61.77987

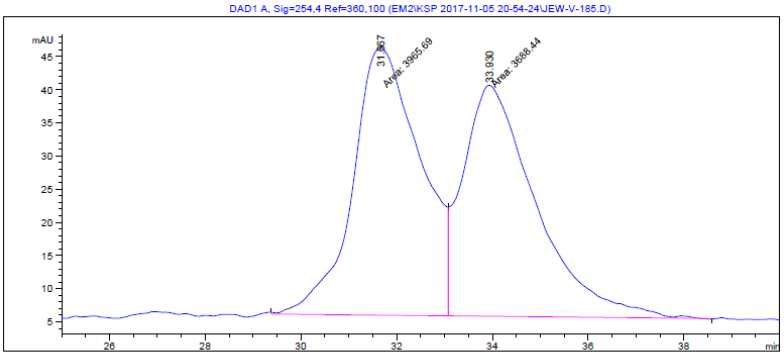
Table 1. Substrate **35e**



35e

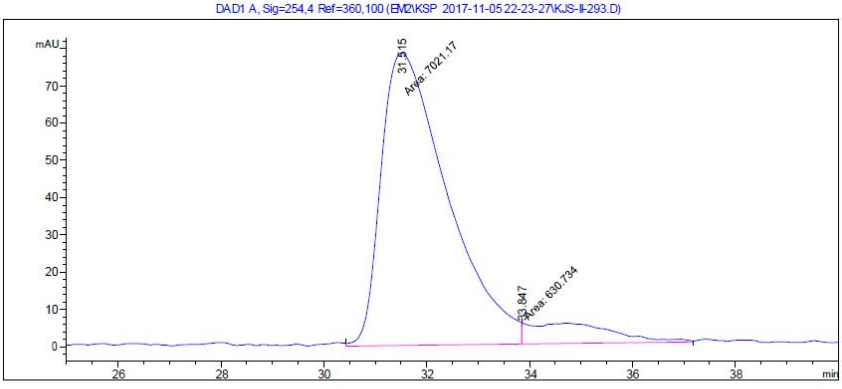
HPLC Conditions: Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 10% IPA/hexane; Monitoring wave: 210 nm

Racemic



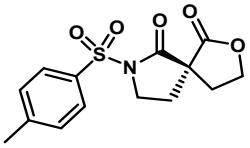
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	31.667	1	MF	3965.68652	40.27905	51.8111
2	33.930	1	FM	3688.44409	34.82159	48.1889

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	31.515	1	MF	7021.16748	78.45442	91.7572
2	33.847	1	FM	630.73370	5.70773	8.2428

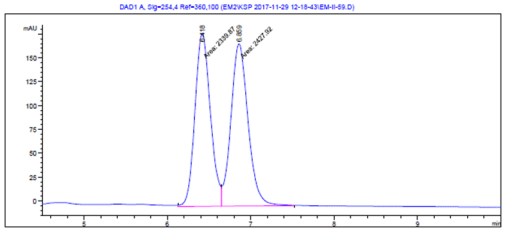
Table 1. Substrate **36e**



36e

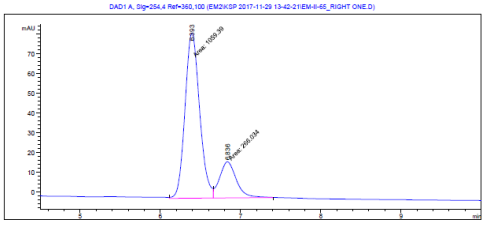
HPLC Conditions: Column: HPLC OD-RH; Eluent Rate: 1mL/min.Eluent: 40% Acetonitrile/Aqueous; Monitoring wave: 254 nm

Racemic



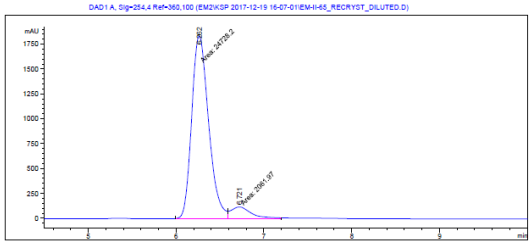
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	6.419	1	MF	2399.87256	181.26688	49.0767
2	6.859	1	FM	2427.91797	170.05028	50.9233

Enantioenriched (Before Recrystallization)



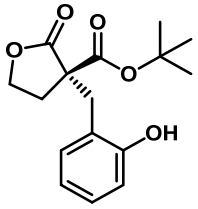
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	6.399	1	MF	1089.89089	83.70535	79.9284
2	6.896	1	FM	266.09412	18.34127	20.0716

Enantioenriched (After Recrystallization)



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	6.262	1	MF	2.47282e4	1696.97388	92.3033
2	6.721	1	FM	2061.96826	122.31849	7.6967

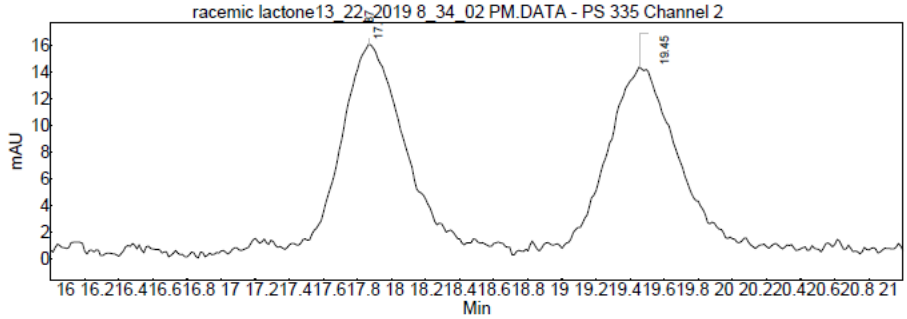
Table 1. Substrate **35f'**



35f'

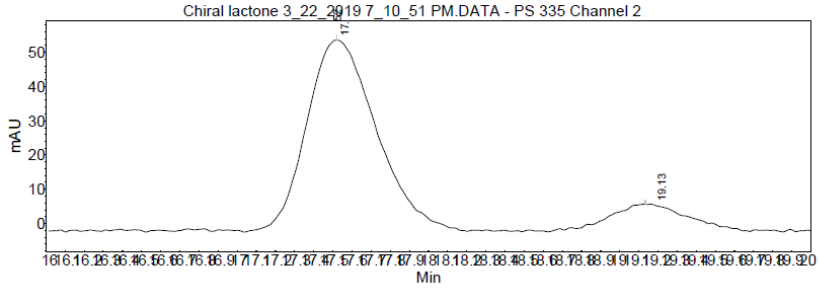
HPLC Conditions: Column: HPLC AD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 5% IPA/hexane; Monitoring wave: 254 nm

Racemic



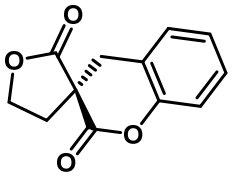
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17.87	49.91	15.2	6.4	49.913
2	UNKNOWN	19.45	50.09	13.6	6.4	50.087
Total			100.00	28.8	12.7	100.000

Enantioenriched



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17.52	87.77	55.8	23.4	87.771
2	UNKNOWN	19.13	12.23	7.3	3.3	12.229
Total			100.00	63.0	26.6	100.000

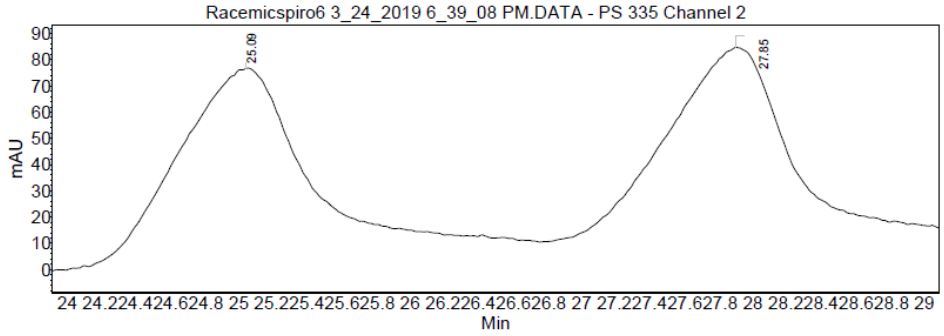
Table 1. Substrate **36f**



36f

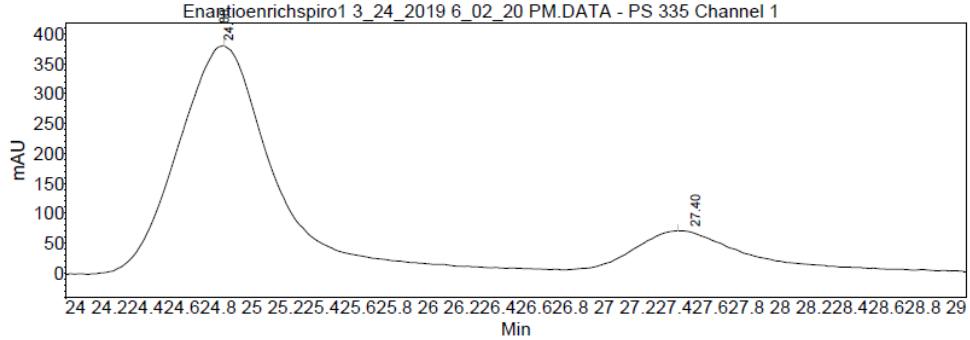
HPLC Conditions: Column: HPLC AD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 10% IPA/hexane; Monitoring wave: 220 nm

Racemic



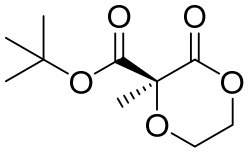
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	25.09	49.83	65.8	46.2	49.831
2	UNKNOWN	27.85	50.17	67.1	46.5	50.169
Total			100.00	132.9	92.6	100.000

Enantioenriched



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24.88	85.99	375.1	214.6	85.993
2	UNKNOWN	27.40	14.01	61.0	35.0	14.007
Total			100.00	436.1	249.6	100.000

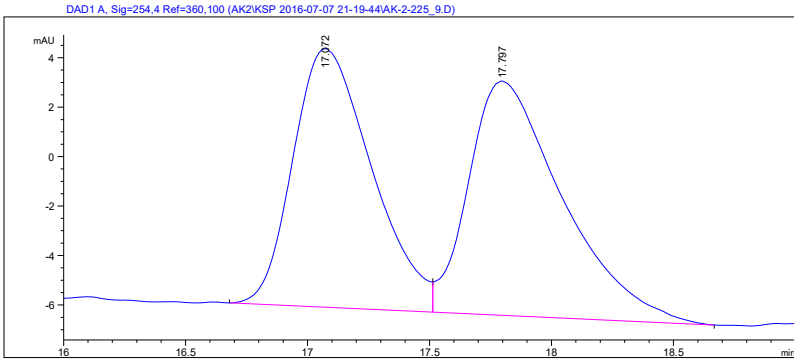
Table 3. Substrate **46**



46

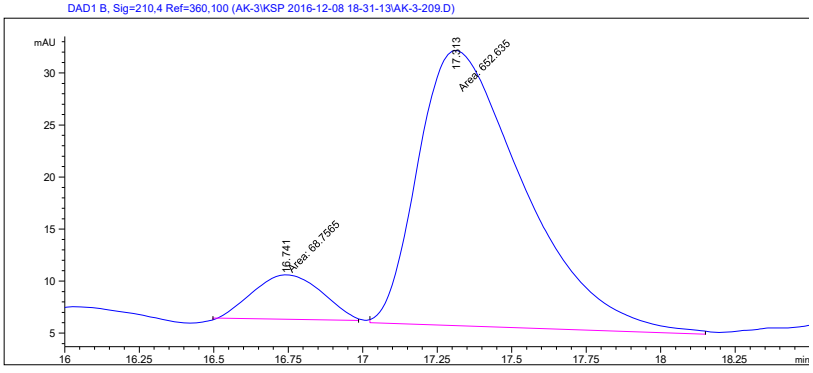
HPLC Conditions: Column: HPLC Chiralcel OD-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 1% IPA/hexane; Monitoring wave 254 nm

Racemic



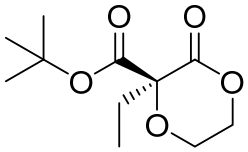
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	17.072	1	BV	235.26595	10.45789	48.1084
2	17.797	1	VB	253.76672	9.48096	51.8916

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	16.741	1	MM	68.75646	4.26214	9.5311
2	17.313	1	MM	652.63550	26.43526	90.4689

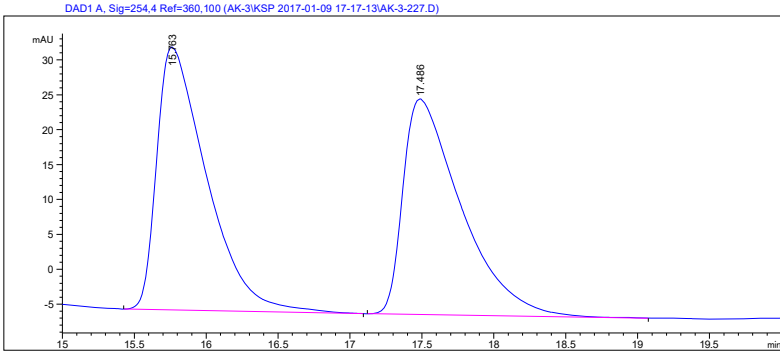
Table 3. Substrate **48**



48

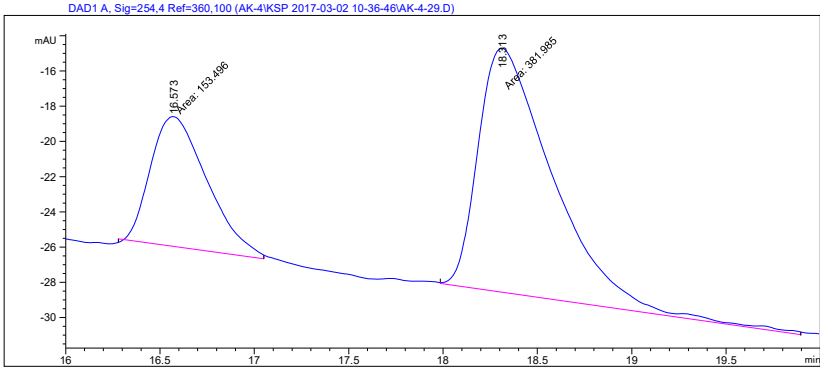
HPLC Conditions: Column: HPLC Chiralcel OJ-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 3% IPA/hexane; Monitoring wave 254 nm

Racemic



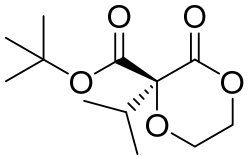
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	15.763	1	BB	905.82007	37.65872	51.0975
2	17.486	1	BB	866.90961	30.88494	48.9025

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	16.573	1	MM	153.49565	7.37346	28.6650
2	18.313	1	MM	381.98520	13.85821	71.3350

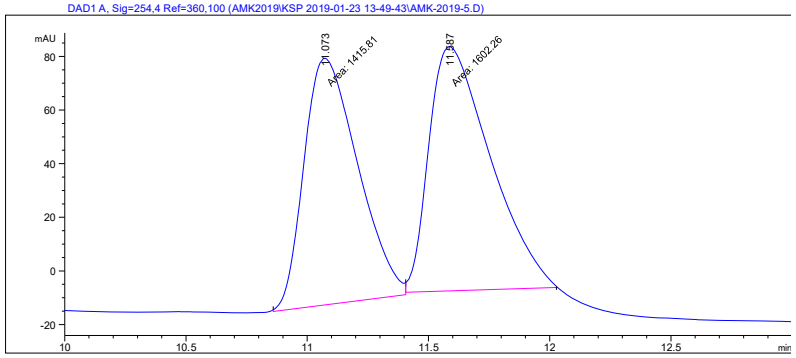
Table 3. Substrate **50**



50

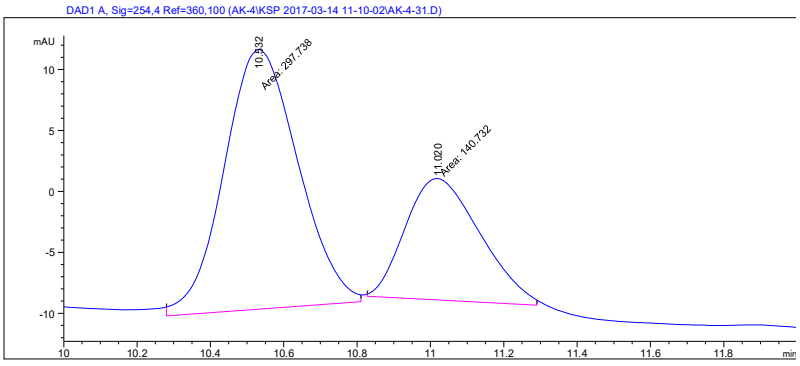
HPLC Conditions: Column: HPLC Chiralcel OD-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 1% IPA/hexane; Monitoring wave 254 nm

Racemic



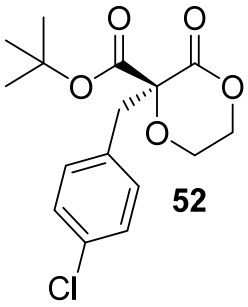
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	11.073	1	MM	1415.81165	92.04710	46.9111
2	11.587	1	MM	1602.26282	91.13145	53.0889

Enantioenriched



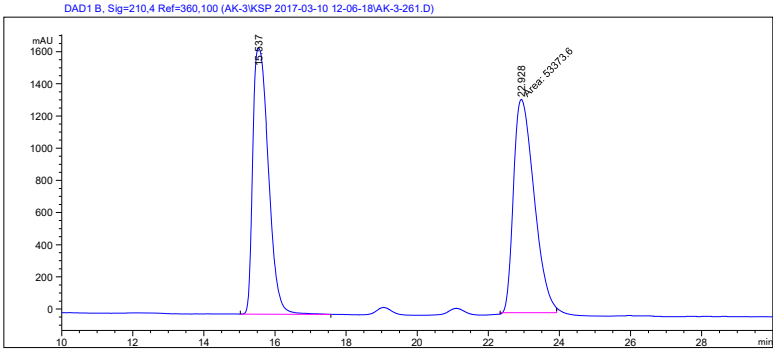
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	10.532	1	MM	297.73779	21.31725	67.9038
2	11.020	1	MM	140.73250	9.95236	32.0962

Table 3. Substrate **52**



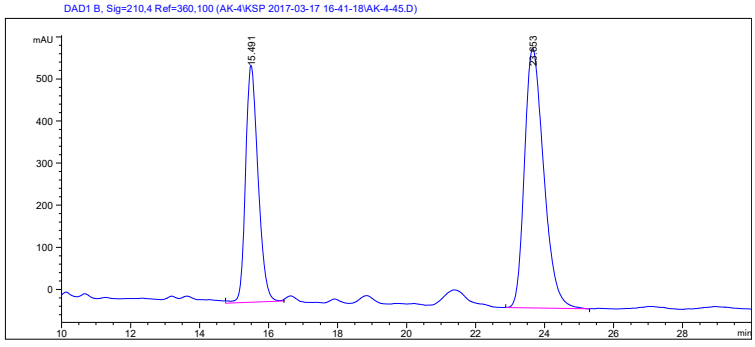
HPLC Conditions: Column: HPLC Chiralcel OD-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 1% IPA/hexane; Monitoring wave 210 nm

Racemic



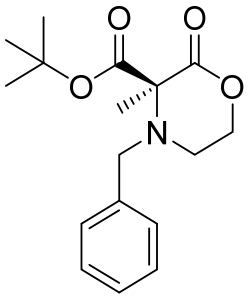
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	15.537	1	BB	5.03016e4	1655.07080	48.5185
2	22.928	1	MM	5.33736e4	1325.70850	51.4815

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	15.491	1	MM	1.41588e4	562.65771	37.2320
2	23.653	1	BB	2.38698e4	617.04285	62.7680

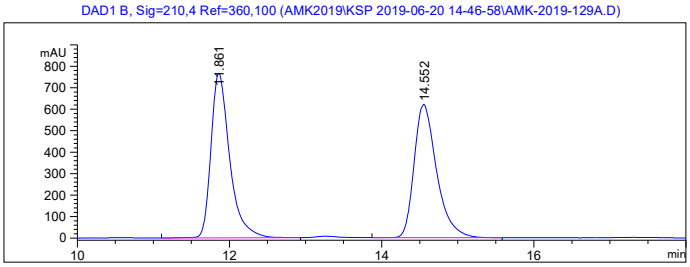
Table 3. Substrate **54**



54

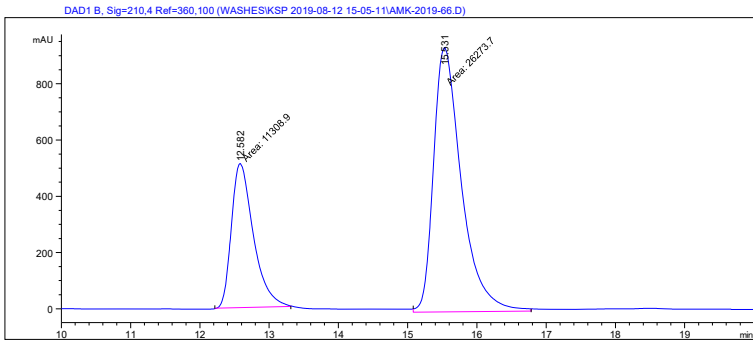
HPLC Conditions: Column: HPLC Chiralcel OJ-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 1% IPA/hexane; Monitoring wave 210 nm

Racemic



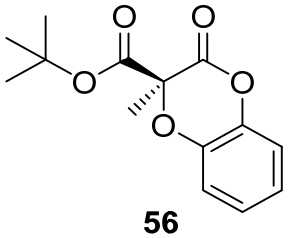
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	11.861	1	BV	1.31330e4	765.71539	50.6961
2	14.552	1	BB	1.27724e4	621.24536	49.3039

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	12.582	1	MM	1.13089e4	512.75830	30.0908
2	15.531	1	MM	2.62737e4	939.60724	69.9092

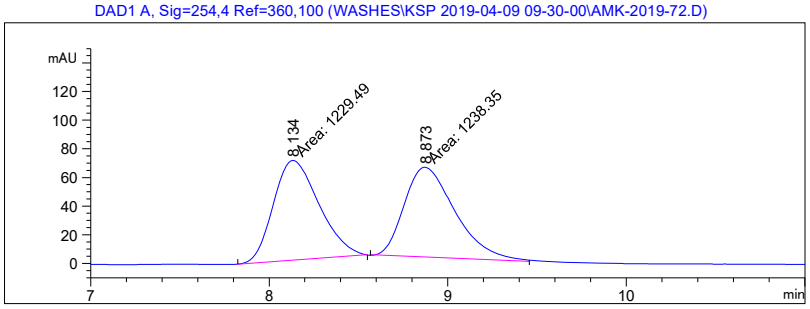
Table 4. Substrate **56**



56

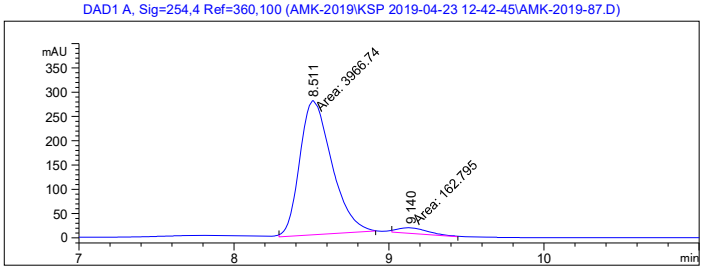
HPLC Conditions: Column: HPLC Chiralcel OJ-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 1% IPA/hexane; Monitoring wave 254 nm

Racemic



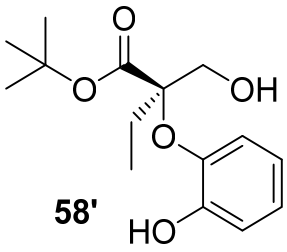
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	8.134	1	MM	1229.49121	69.55069	49.8206
2	8.873	1	MM	1238.34534	62.52538	50.1794

Enantioenriched



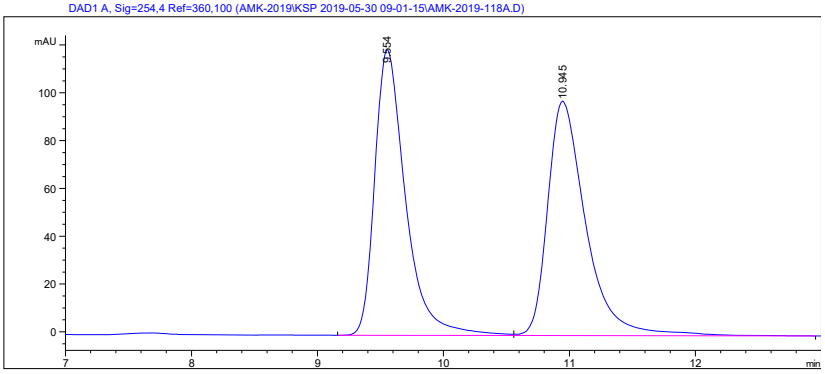
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	8.511	1	MM	3966.73755	276.26147	96.0578
2	9.140	1	MM	162.79495	11.67375	3.9422

Table 4. Substrate **58'**



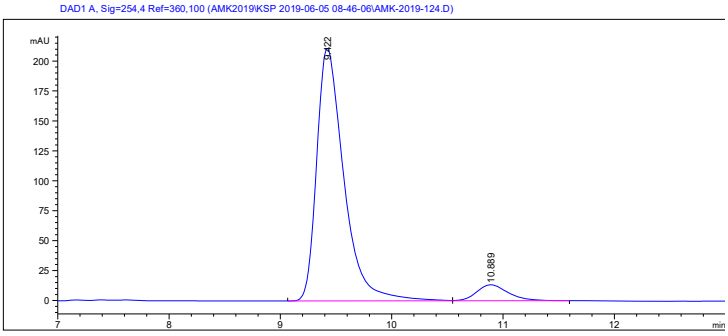
HPLC Conditions: Column: HPLC Chiralcel OJ-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 5% IPA/hexane; Monitoring wave 254 nm

Racemic



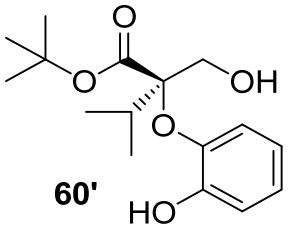
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	9.554	1	BV	2027.19287	119.55624	49.6019
2	10.945	1	VB	2059.73169	98.07139	50.3981

Enantioenriched



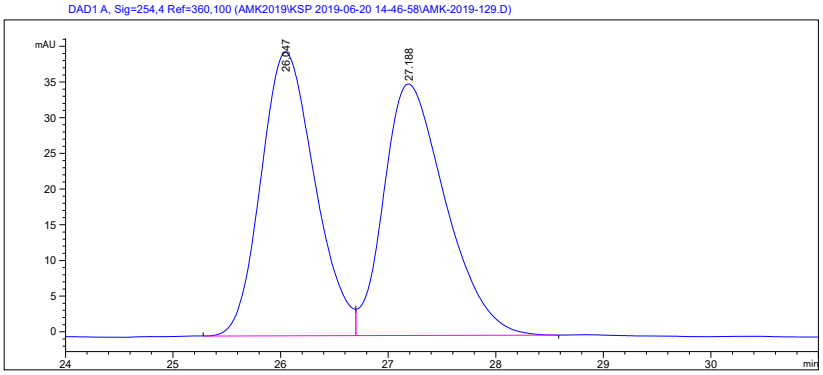
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	9.422	1	BV	3583.19995	211.11469	93.0684
2	10.889	1	VB	266.87100	13.42093	6.9316

Table 4. Substrate **60'**



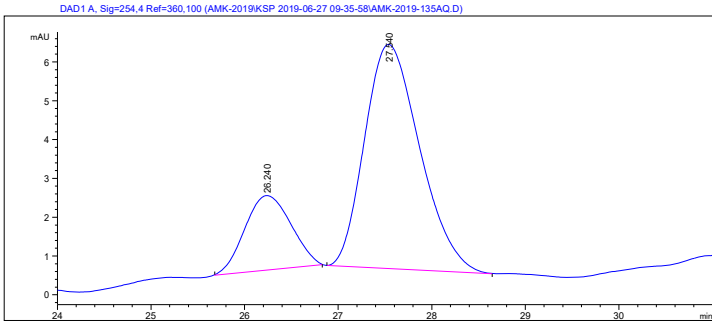
HPLC Conditions: Column: HPLC Chiralcel AD-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 1% IPA/hexane; Monitoring wave 254 nm

Racemic



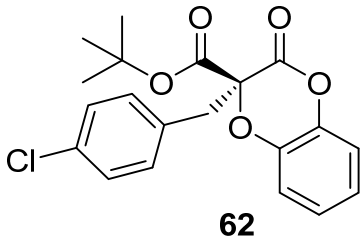
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	26.047	1	BV	1380.66492	39.70302	49.5230
2	27.188	1	VB	1407.25952	35.24186	50.4770

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	26.240	1	MM	65.65859	1.91902	21.7512
2	27.540	1	BB	236.20398	5.77290	78.2488

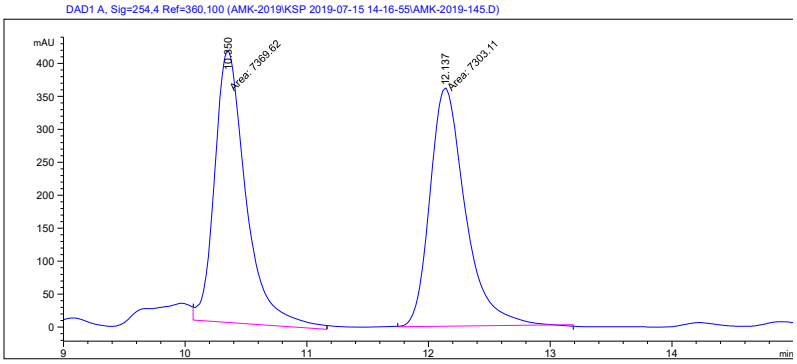
Table 4. Substrate **62**



62

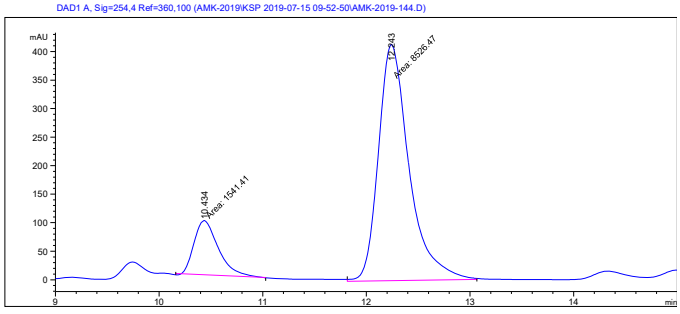
HPLC Conditions: Column: HPLC Chiralcel AD-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 1% IPA/hexane; Monitoring wave 254 nm

Racemic



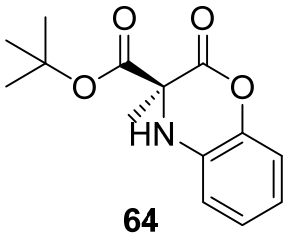
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	10.350	1	MM	7369.62305	412.28485	50.2267
2	12.137	1	MM	7303.11035	361.74759	49.7733

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	10.434	1	MM	1541.41150	94.89913	15.3102
2	12.243	1	MM	8526.47168	414.27527	84.6898

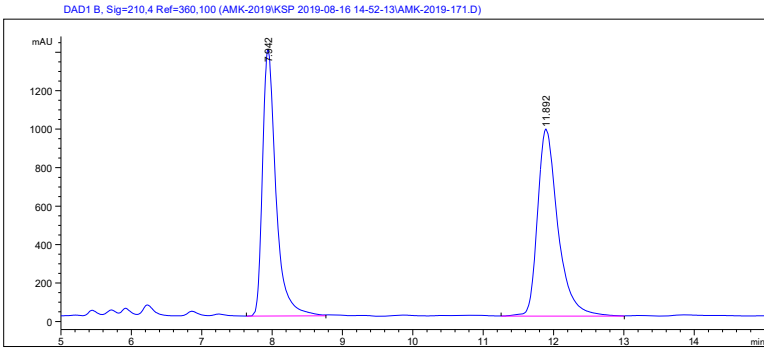
Table 4. Substrate **64**



64

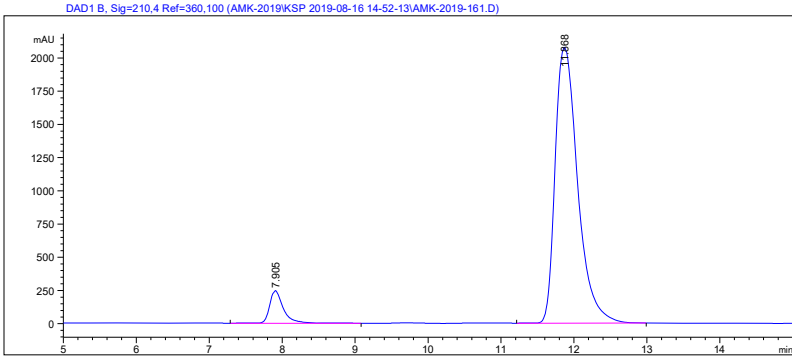
HPLC Conditions: Column: HPLC Chiralcel AD-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 5% IPA/hexane; Monitoring wave 210 nm

Racemic



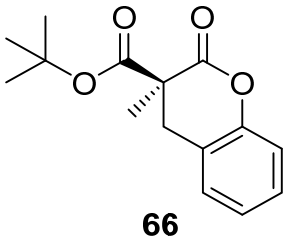
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	7.942	1	BV	1.82850e4	1384.57825	48.3322
2	11.892	1	VV	1.95469e4	972.62482	51.6678

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	7.905	1	BB	3200.58447	245.66026	6.7123
2	11.868	1	BB	4.44818e4	2075.77539	93.2877

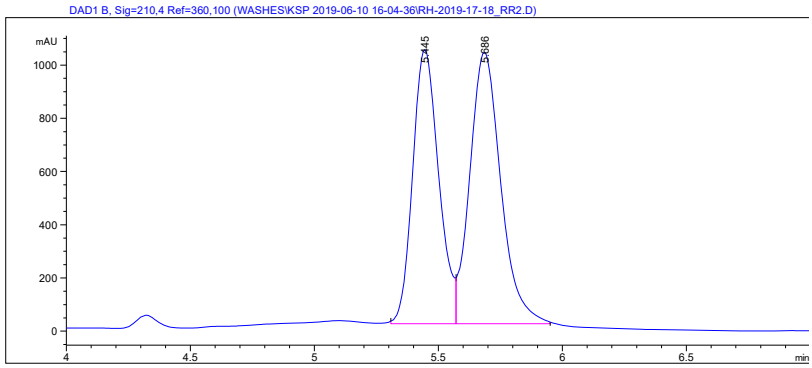
Table 4. Substrate **66**



66

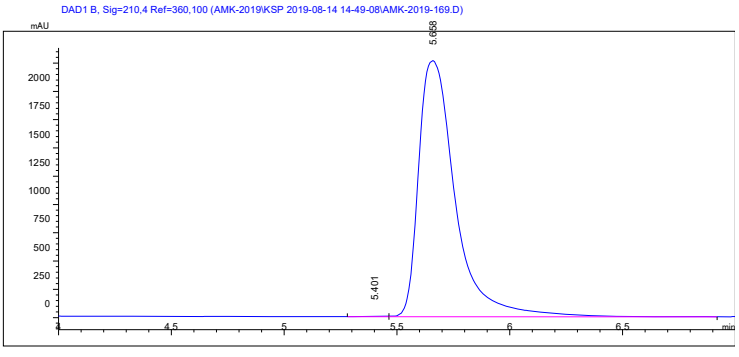
HPLC Conditions: Column: HPLC Chiralcel AD-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 5% IPA/hexane; Monitoring wave 210 nm

Racemic



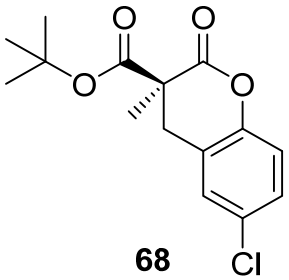
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	5.445	1	MF	7545.57129	1030.93115	46.1584
2	5.686	1	FM	8801.53711	1021.01306	53.8416

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	5.401	1	BV	27.17055	3.99311	0.1058
2	5.658	1	VB	2.56564e4	2265.89648	99.8942

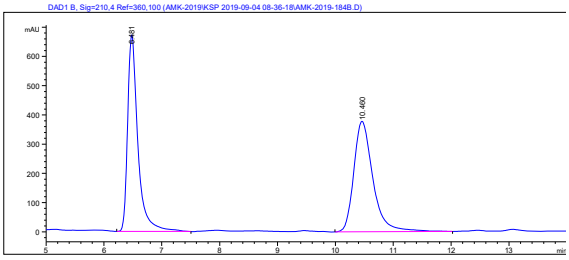
Table 4. Substrate **68**



68

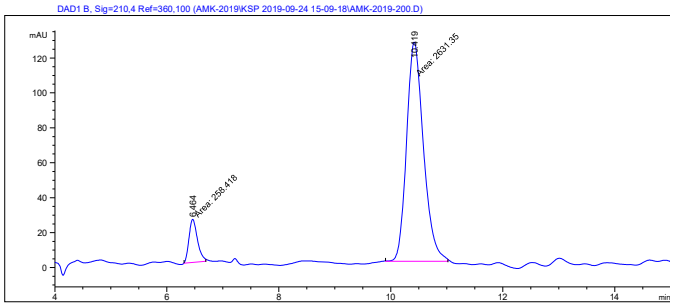
HPLC Conditions: Column: HPLC Chiralcel OJ-H 4.6 mm x 250 mm x 5 µm: Eluent Rate: 1 mL/min: Eluent 10% IPA/hexane; Monitoring wave 210 nm

Racemic



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	6.481	1	BB	8263.93066	672.09711	48.8527
2	10.460	1	BB	8652.09473	377.69562	51.1473

Enantioenriched



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	6.464	1	MM	258.41794	24.69413	8.9425
2	10.419	1	MM	2631.34790	125.40757	91.0575

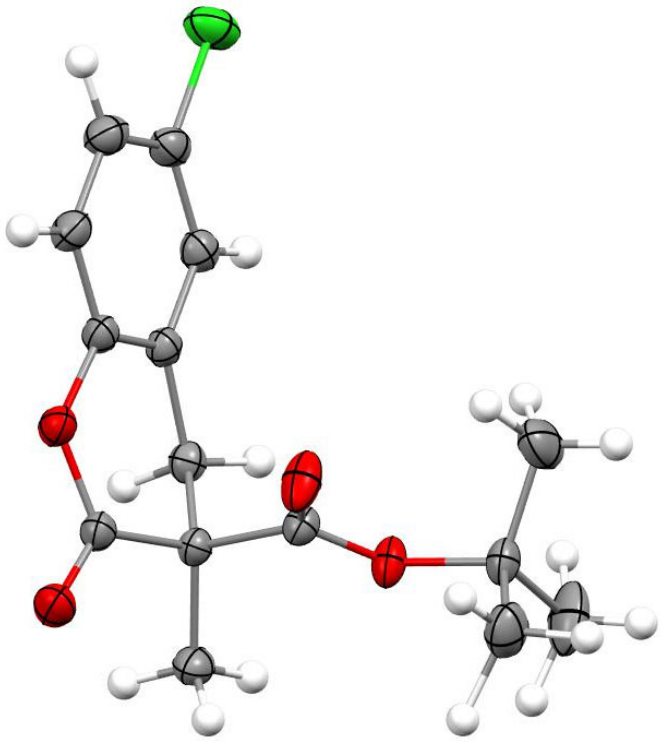
APPENDIX C

X-RAY DATA

UNC CHAPEL HILL DEPARTMENT OF CHEMISTRY

X-ray Core Laboratory

Report No. 19077



$C_{15}\ H_{17}\ Cl_1\ O_4$

Prepared for
Amber Kelley and Prof. K. Petersen

by
C. Chen

October 21, 2019

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

The sample was submitted by Amber Kelley (research group of Petersen, Department of Chemistry, the University of North Carolina at Greensboro). A colorless crystal (approximate dimensions 0.150 x 0.100 x 0.100 mm^3) was placed onto the tip of MiTeGen and mounted on a Bruker SMART Apex II diffractometer and measured at 293 K.

Data collection

A preliminary set of cell constants was calculated from reflections harvested from three sets of 12 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 148 reflections. The data collection was carried out using Cu Kα radiation (graphite monochromator) with theta-dependent frame time of 10-20 seconds and a detector distance of 4.0 cm. A randomly oriented region of reciprocal space was surveyed to achieve complete data with a redundancy of 4. Sections of frames were collected with 0.50º steps in ω and ϕ scans. Data to a resolution of 0.81 Å were considered in the reduction. Final cell constants were calculated from the xyz centroids of 8197 strong reflections from the actual data collection after integration (SAINT).[1] The intensity data were corrected for absorption (SADABS).[2] Please refer to Table 1 for additional crystal and refinement information.

Structure solution and refinement

The space group $P2_12_12_1$ was determined based on intensity statistics and systematic absences. The structure was solved using Superflip[3] and refined (full-matrix-least squares) using the Oxford University Crystals for Windows system.[4] The charge-flipping solution provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed, which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were placed in ideal positions and refined with individual relative isotropic displacement parameters. The final full matrix least squares refinement converged to R1 = 0.0352 and wR2 = 0.0913 (F^2, all data).

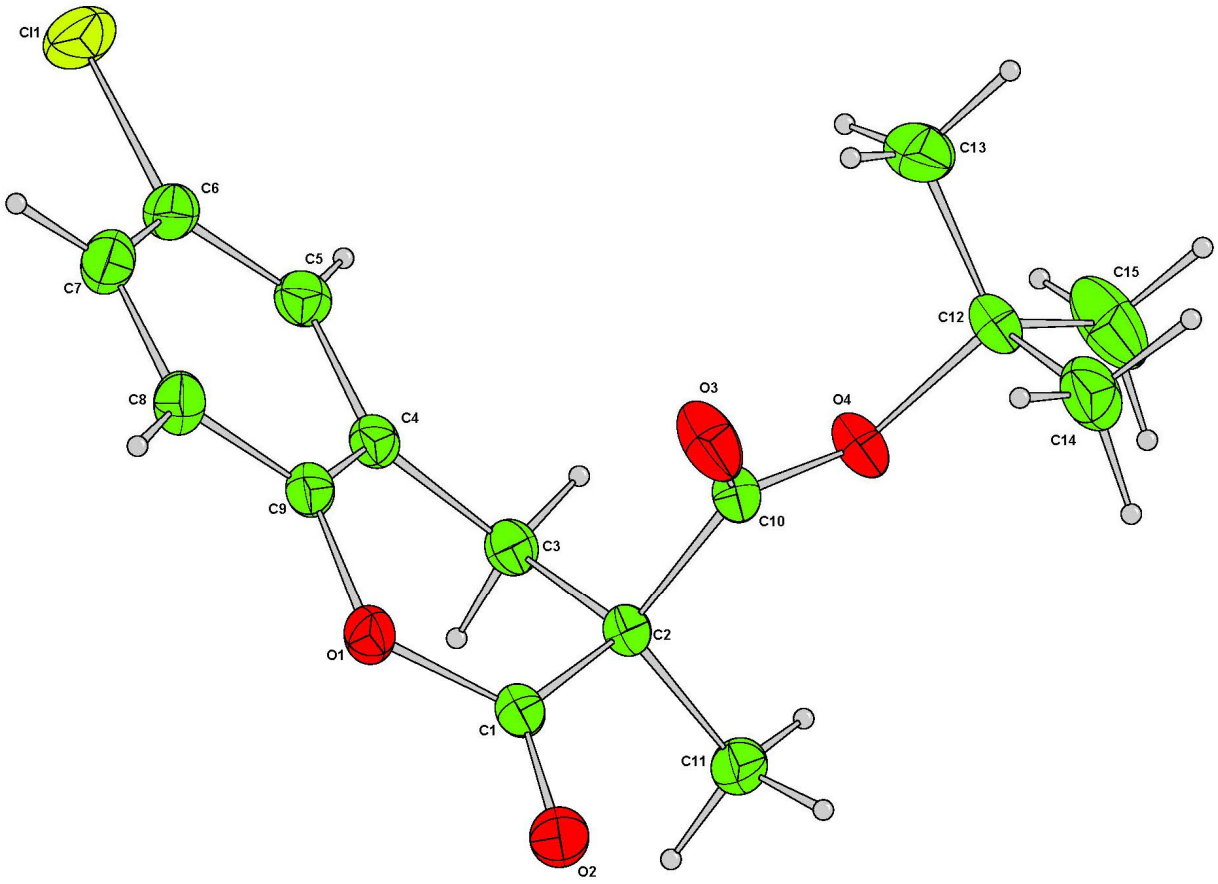
Structure description

The structure was found as proposed.

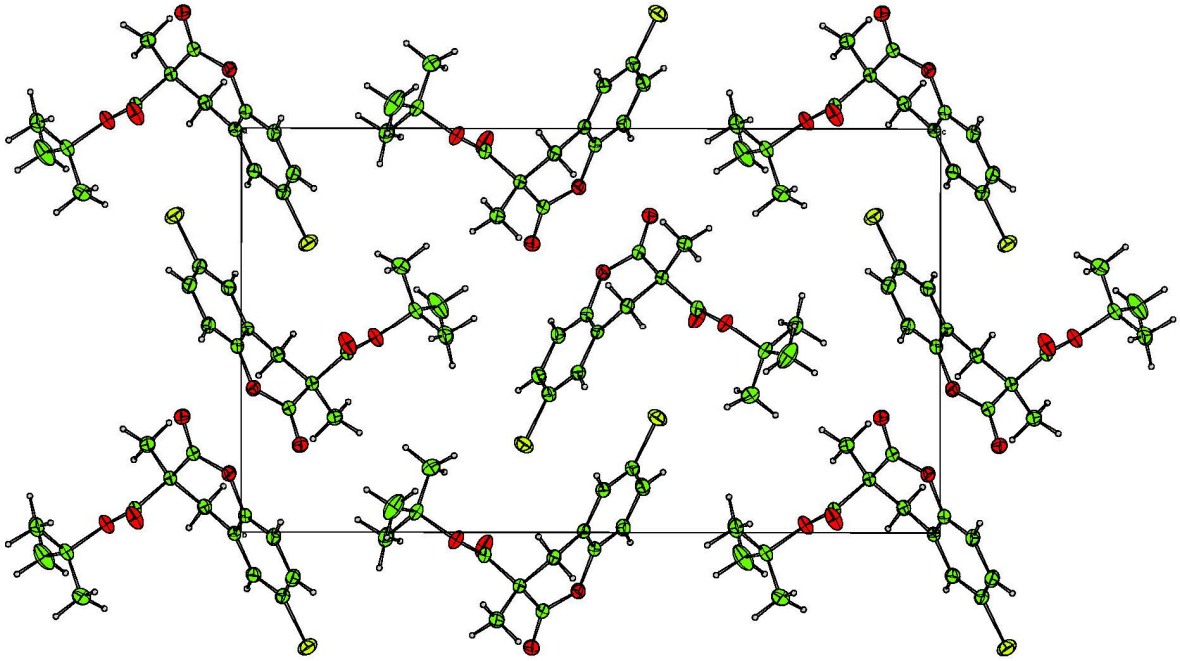
[1] SAINT, Bruker Analytical X-Ray Systems, Madison, WI, current version.

[2] An empirical correction for absorption anisotropy, R. Blessing, Acta Cryst. A51, 33 - 38

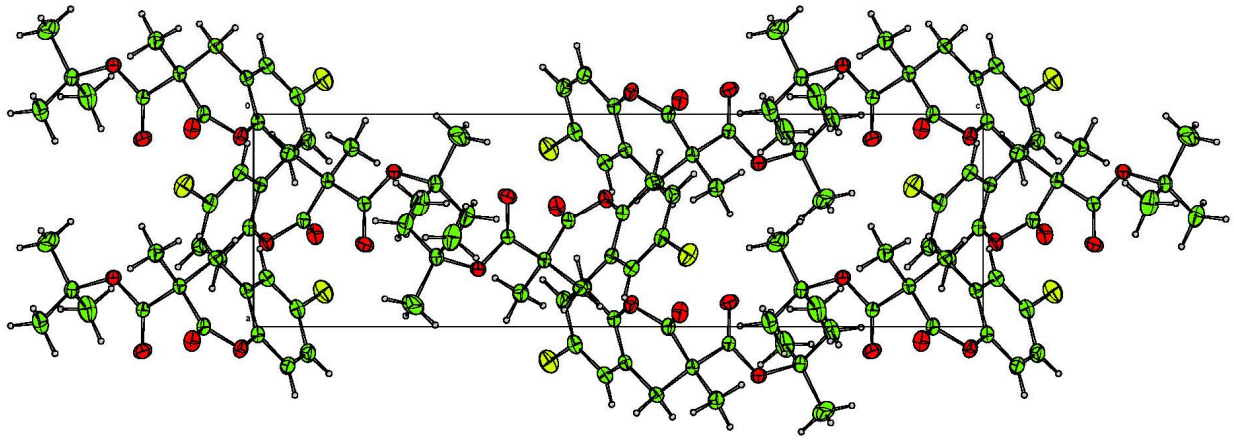
(1995).
[3] Palatinus L., Chapuis G. (2007): Superflip - a computer program for the solution of crystal structures by charge flipping in arbitrary dimensions. J. Appl. Cryst. 40, 786-790.
[4] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. J. Appl. Cryst. 2003, 36, 1487.



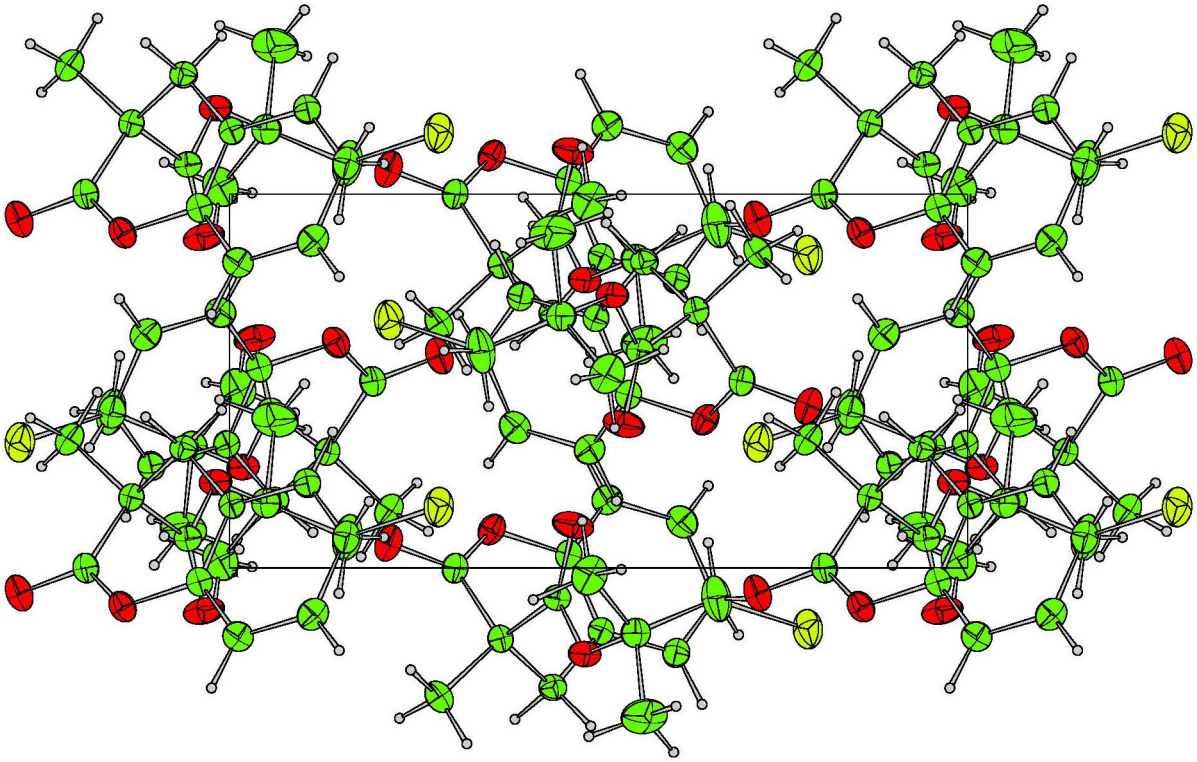
Molecular structure with labels on the asymmetric unit



Cell plot, viewed along a- axis



Cell plot, viewed along b- axis



Cell plot, viewed along c- axis

Table 1. Crystal data and structure refinement for 19077.

Empirical formula	C15 H17 Cl1 O4	
Formula weight	296.75	
Crystal color, shape, size	colorless plate fragment, 0.150 x 0.100 x 0.100 mm^3	
Temperature	293 K	
Wavelength	1.54178 Å	
Crystal system, space group	Orthorhombic, $P2_12_12_1$	
Unit cell dimensions	a = 6.03660(10) Å	α= 90°.
	b = 11.9785(2) Å	β= 90°.
	c = 20.7058(4) Å	γ = 90°.
Volume	1497.22(5) $Å^3$	
Z	4	
Density (calculated)	1.316 Mg/m^3	
Absorption coefficient	2.355 mm^{-1}	
F(000)	624	
Data collection		
Diffractometer	Bruker Apex Kappa Duo, Bruker	
Theta range for data collection	4.264 to 72.169°.	
Index ranges	-7<=h<=7, -14<=k<=14, -25<=l<=25	
Reflections collected	29628	
Independent reflections	2955 [R(int) = 0.043]	
Observed Reflections	2723	
Completeness to theta = 72.169°	100.0 %	
Solution and Refinement		
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.79 and 0.79	
Solution	Charge-Flipping methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting scheme	$w = [\sigma^2Fo^2 + AP^2 + BP]^{-1}$, with	
	$P = (Fo^2 + 2\,Fc^2)/3$, A = 0.057, B = 0.123	
Data / restraints / parameters	2942 / 0 / 182	
Goodness-of-fit on F^2	1.0199	
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0900	
R indices (all data)	R1 = 0.0372, wR2 = 0.0913	
Absolute structure parameter	0.032(16)	
Largest diff. peak and hole	0.17 and -0.27 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 19077. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl1	1635(1)	7835(1)	4045(1)	78
O1	-1032(2)	3554(1)	5175(1)	51
O2	-666(3)	2155(1)	5844(1)	63
O3	-1148(2)	4656(2)	6522(1)	74
O4	2299(2)	4813(1)	6923(1)	53
C1	3(3)	3058(1)	5685(1)	46
C2	1891(3)	3675(1)	6015(1)	42
C3	3190(3)	4381(1)	5522(1)	45
C4	1688(3)	5035(1)	5094(1)	43
C5	2269(3)	6054(2)	4819(1)	49
C6	823(4)	6583(2)	4403(1)	54
C7	-1236(4)	6130(2)	4257(1)	59
C8	-1830(3)	5121(2)	4532(1)	54
C9	-366(3)	4596(1)	4942(1)	45
C10	794(3)	4439(2)	6516(1)	43
C11	3443(4)	2840(2)	6340(1)	55
C12	1737(3)	5503(2)	7493(1)	52
C13	832(6)	6600(2)	7282(1)	88
C14	193(5)	4881(2)	7924(1)	78
C15	3959(5)	5621(3)	7815(2)	105

Table 3. Bond lengths [Å] and angles [°] for 19077.

Cl1-C6	1.7436(19)	O1-C1	
1.364(2)	O1-C9	1.396(2)	
O2-C1	1.200(2)	O3-C10	
1.201(2)	O4-C10	1.318(2)	
O4-C12	1.4801(19)	C1-C2	
1.521(2)	C2-C3	1.540(2)	
C2-C10	1.533(2)	C2-C11	
1.527(2)	C3-C4	1.490(2)	
C3-H31	0.989	C3-H32	
0.978	C4-C5	1.392(2)	
C4-C9	1.383(2)	C5-C6	
1.380(3)	C5-H51	0.947	
C6-C7	1.389(3)	C7-C8	
1.383(3)	C7-H71	0.942	
C8-C9	1.377(3)	C8-H81	
0.960	C11-H111	0.966	
C11-H112	0.960	C11-H113	
0.969	C12-C13	1.489(3)	
C12-C14	1.490(3)	C12-C15	
1.504(3)	C13-H131	0.956	
C13-H132	0.962	C13-H133	
0.994	C14-H141	0.988	
C14-H142	1.016	C14-H143	
0.976	C15-H151	0.965	
C15-H152	0.975	C15-H153	0.981

C1-O1-C9	121.66(13)	C10-O4-C12	
122.86(14)	O1-C1-O2	116.78(16)	
O1-C1-C2	118.64(14)	O2-C1-C2	
124.58(16)	C1-C2-C3	110.54(13)	
C1-C2-C10	105.69(13)	C3-C2-C10	
109.90(13)	C1-C2-C11	109.81(14)	
C3-C2-C11	109.84(14)	C10-C2-C11	
110.99(13)	C2-C3-C4	111.91(14)	
C2-C3-H31	110.9	C4-C3-H31	
109.4	C2-C3-H32	107.6	

C4-C3-H32	108.1	H31-C3-H32	
108.8	C3-C4-C5	123.42(16)	
C3-C4-C9	118.74(15)	C5-C4-C9	
117.80(16)	C4-C5-C6	119.91(17)	
C4-C5-H51	121.6	C6-C5-H51	
118.5	Cl1-C6-C5	118.83(16)	
Cl1-C6-C7	119.65(15)	C5-C6-C7	
121.51(18)	C6-C7-C8	118.88(18)	
C6-C7-H71	121.0	C8-C7-H71	
120.1	C7-C8-C9	119.13(19)	
C7-C8-H81	122.2	C9-C8-H81	
118.6	O1-C9-C4	121.30(16)	
O1-C9-C8	115.87(16)	C4-C9-C8	
122.76(16)	C2-C10-O4	109.77(14)	
C2-C10-O3	123.91(16)	O4-C10-O3	
126.32(16)	C2-C11-H111	110.9	
C2-C11-H112	111.6	H111-C11-H112	
105.4	C2-C11-H113	111.2	
H111-C11-H113	107.4	H112-C11-H113	
110.1	O4-C12-C13	109.99(15)	
O4-C12-C14	109.97(16)	C13-C12-C14	
112.8(2)	O4-C12-C15	101.64(16)	
C13-C12-C15	112.0(2)	C14-C12-C15	
109.9(2)	C12-C13-H131	108.4	
C12-C13-H132	108.3	H131-C13-H132	
109.3	C12-C13-H133	109.2	
H131-C13-H133	113.1	H132-C13-H133	
108.5	C12-C14-H141	107.9	
C12-C14-H142	108.9	H141-C14-H142	
109.7	C12-C14-H143	111.6	
H141-C14-H143	109.9	H142-C14-H143	
108.8	C12-C15-H151	105.5	
C12-C15-H152	107.5	H151-C15-H152	
112.0	C12-C15-H153	106.5	
H151-C15-H153	112.2	H152-C15-H153	112.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 19077. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	102(1)	57(1)	75(1)	21(1)	20(1)	3(1)
O1	61(1)	50(1)	42(1)	1(1)	-8(1)	-12(1)
O2	84(1)	50(1)	53(1)	3(1)	-4(1)	-16(1)
O3	46(1)	110(1)	66(1)	-37(1)	-10(1)	16(1)
O4	42(1)	69(1)	48(1)	-23(1)	-2(1)	3(1)
C1	57(1)	44(1)	37(1)	-4(1)	0(1)	-2(1)
C2	48(1)	42(1)	35(1)	-2(1)	2(1)	2(1)
C3	44(1)	49(1)	42(1)	-3(1)	4(1)	1(1)
C4	48(1)	44(1)	36(1)	-3(1)	4(1)	-1(1)
C5	54(1)	48(1)	47(1)	-2(1)	9(1)	-2(1)
C6	70(1)	48(1)	44(1)	4(1)	11(1)	4(1)
C7	67(1)	64(1)	46(1)	8(1)	-1(1)	9(1)
C8	57(1)	62(1)	42(1)	2(1)	-6(1)	-2(1)
C9	54(1)	45(1)	35(1)	-1(1)	1(1)	-3(1)
C10	42(1)	50(1)	36(1)	-3(1)	-2(1)	1(1)
C11	64(1)	53(1)	49(1)	0(1)	-2(1)	14(1)
C12	56(1)	57(1)	42(1)	-16(1)	-1(1)	-1(1)
C13	134(3)	58(1)	71(1)	-9(1)	14(2)	17(2)
C14	101(2)	82(2)	50(1)	-10(1)	16(1)	-11(1)
C15	77(2)	141(3)	95(2)	-57(2)	-23(2)	-9(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for 19077.

	x	y	z	U(eq)
H31	4224	4896	5743	52
H32	4044	3869	5252	54
H51	3641	6402	4912	59
H71	-2200	6488	3965	70
H81	-3205	4757	4433	64
H111	4697	3216	6532	82
H112	2725	2458	6690	82
H113	4017	2305	6031	82
H131	827	7093	7645	132
H132	1791	6896	6953	132
H133	-664	6486	7092	134
H141	37	5310	8329	115
H142	848	4117	8021	118
H143	-1256	4780	7723	115
H151	3689	6049	8202	155
H152	4497	4871	7912	156
H153	4915	6018	7509	156

Table 6. Torsion angles [°] for 19077.

C9-O1-C1-O2	-178.88(16)	C9-O1-C1-C2	
1.6(2)	C1-O1-C9-C4	17.5(2)	
C1-O1-C9-C8	-165.47(15)	C12-O4-C10-O3	
5.3(3)	C12-O4-C10-C2	-175.24(14)	
C10-O4-C12-C13	-65.6(2)	C10-O4-C12-C14	
59.3(2)	C10-O4-C12-C15	175.62(19)	
O1-C1-C2-C3	-33.2(2)	O1-C1-C2-C10	
85.67(17)	O1-C1-C2-C11	-154.56(15)	
O2-C1-C2-C3	147.26(18)	O2-C1-C2-C10	-
93.9(2)	O2-C1-C2-C11	25.9(2)	
C1-C2-C3-C4	46.44(18)	C10-C2-C3-C4	-
69.84(17)	C11-C2-C3-C4	167.78(14)	
C1-C2-C10-O3	-14.8(2)	C1-C2-C10-O4	
165.67(14)	C3-C2-C10-O3	104.5(2)	
C3-C2-C10-O4	-75.02(17)	C11-C2-C10-O3	-
133.8(2)	C11-C2-C10-O4	46.7(2)	
C2-C3-C4-C5	150.76(15)	C2-C3-C4-C9	-
31.5(2)	C3-C4-C5-C6	177.00(16)	
C9-C4-C5-C6	-0.8(2)	C3-C4-C9-O1	
-0.8(2)	C3-C4-C9-C8	-177.67(16)	
C5-C4-C9-O1	177.09(15)	C5-C4-C9-C8	
0.3(3)	C4-C5-C6-Cl1	-177.88(14)	
C4-C5-C6-C7	1.0(3)	Cl1-C6-C7-C8	
178.30(15)	C5-C6-C7-C8	-0.6(3)	
C6-C7-C8-C9	0.0(3)	C7-C8-C9-O1	-
176.84(16)	C7-C8-C9-C4	0.2(3)	

Symmetry transformations used to generate equivalent atoms: