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Molecular chirality plays a key role in chemical and biological reactivity of molecules. The handedness of a particular molecule, for example, can have drastic effects on its biological or pharmaceutical properties. Synthesis of stereoenriched chiral molecules is challenging, especially molecules containing all-carbon quaternary centers. Desymmetrizations are a method that takes advantage of a prochiral moiety to generate stereoenriched compounds without the drawbacks of other classical asymmetric methods.

Lactones are synthetically important target moieties, as they are replete throughout natural products and biological chemistry spaces. Indeed, chiral lactones are key to the functioning of several bioactive molecules, including molecules with anti-cancer activity. Methods for the synthesis of chiral lactones, then, present an important challenge for synthetic chemists.

This work builds on previous methods for the synthesis of chiral lactones via desymmetrizations. It introduces new stereoselective uses for known reactions, and builds on methodology to develop a cascade reaction that streamlines our synthetic pathway. Finally, this work delineates a new co-catalytic cascade desymmetrization enhances the rescues the reactivity of chiral phosphoric acid catalysts. These methods add new tools in the synthetic chemist's toolbox for synthesis of chiral molecules, and particularly chiral lactones.

STEREOSELECTIVE LACTONE SYNTHESIS VIA CHIRAL BRONSTED ACID CATALYSIS

by

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Approved by

Dr. Kimberly S. Petersen
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DEDICATION

When I began my doctoral education in August 2019, the world was entirely different than it is today. Four months later, I would be asking my father-in-law, a medical professional, his thoughts on the burgeoning respiratory illness taking Asia by storm. By early March, Spring Break would get extended for a week, to help curb the spread of Covid-19. I would not return to campus until the summer, several months later, under strict distancing and masking protocols. The world had officially changed.

Getting a Ph.D. during a pandemic and the resulting fallout is no easy task, and is only made possible by the incredible support of family, friends, and faculty. First, I would like to thank my friends who have supported me throughout my entire scientific and academic journey. In particular, my two good friends Kala Youngblood and Abbie Horchar. From the first time the group text appeared (in group meeting no less) to the Halloween costumes and beyond, I am thankful for your love, support, and encouragement.

To Dr. Petersen, thank you for continually pushing me to be the best scientist and chemist that I could be. When I chose to go back into science, I knew it had to be in your lab. Thank you for supporting and mentoring me these past five years.

To my family, who saw my love of science and lent nothing but support and encouragement, I cannot thank you enough. Even though I have changed my mind several times about what kind of scientist I wanted to be, you have stuck with me and supported me on this long journey. I would not have gotten this far without your love and your constant pushing me to be the best that I could be.

To my kids, I hope this work inspires you and reminds you to constantly challenge and push yourself. You are capable of everything you set your minds to, and I am lucky to have all of you in my life.

Finally, to my lovely wife Morgan – you are my reason for everything. Your constant love and support these five years and beyond has been my rock through challenging times. You inspire me daily, and I cannot imagine doing this undertaking without you to encourage me every step of the way. You paved the way for me to do this, and without you I would not be at the finish line here.

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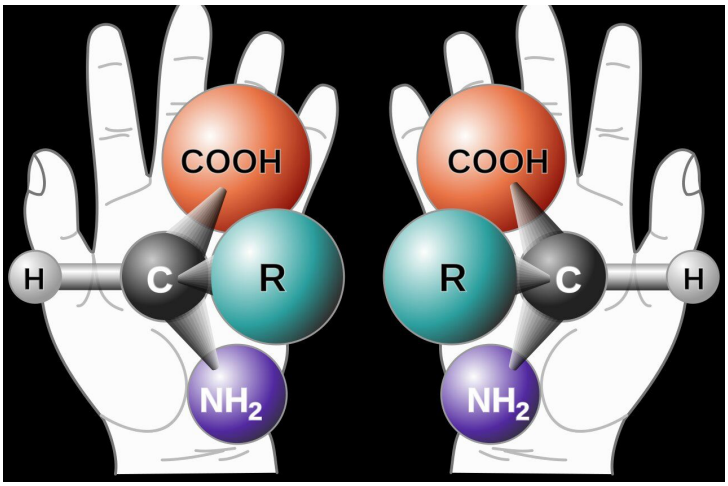
CHAPTER I: INTRODUCTION TO STEREOSELECTIVE SYNTHESIS

Molecular Chirality in Biological Synthesis

Molecular chirality plays a fundamental role throughout chemistry and biology. Chirality, from the Greek "hand," is a property of asymmetry where a molecule differs in its orientation in three-dimensional space. Many common objects possess chirality – including left and right hands. Objects are said to be chiral if they have mirror images which cannot be superimposed on the other. In the example of left and right hands, each hand is a mirror of each other, but they cannot be superimposed (i.e. "layered" on top of each other). Therefore, the objects are said to be chiral (Figure 1).

Figure 1. Handedness of Chirality.

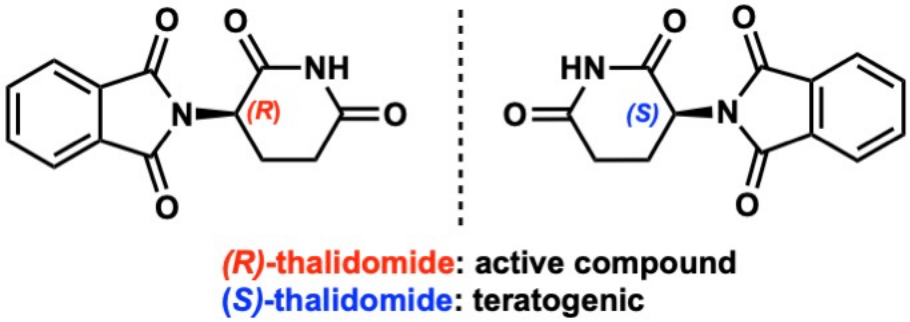


This lack of symmetry is crucial in throughout organic and biochemistry. Chiral molecules interact in unique ways depending on the chirality of the substrate or environment. For example, the amino acids which serve as the building blocks of proteins are enantiopure and exist in the *L* or *levorotary* stereoisomer.

The chirality of pharmaceutical agents plays a key role in their biological activity. The classic example of this is the drug molecule thalidomide. Thalidomide was an antiemetic drug

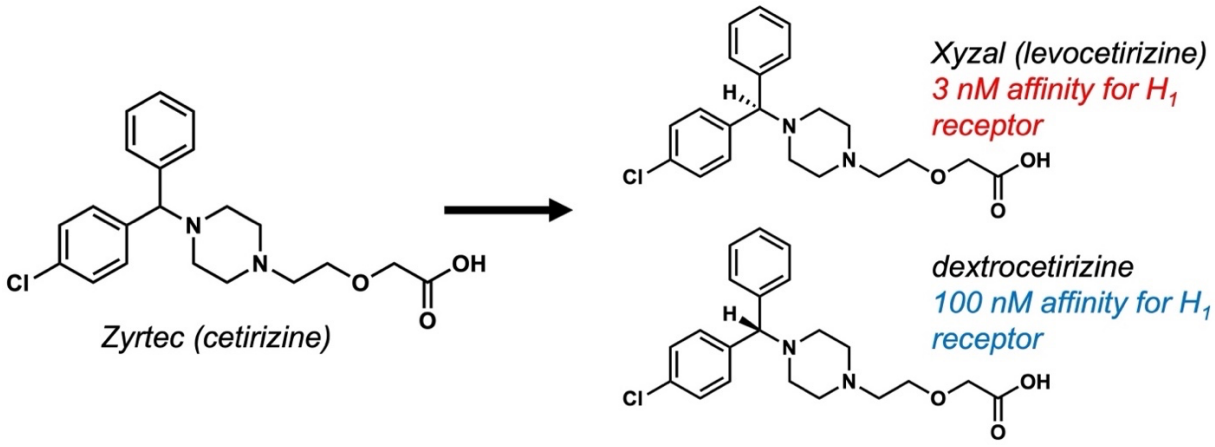
given to pregnant women throughout the 1950s to treat morning sickness. However, it was noted that children born after women took thalidomide had severe birth defects. This teratogenicity was quickly attributed to thalidomide and the drug was removed from use in pregnant women. Thalidomide exists as a mixture of enantiomers (Figure 2). The *R* enantiomer of thalidomide is responsible for the therapeutic effects seen when used as an antiemetic. The *S* enantiomer, however, causes severe teratogenic side effects when taken while pregnant.[1] The only difference between these two molecules is their orientation in three dimensional space, but their effects in a chiral environment such as the body are drastic.

Figure 2. Thalidomide enantiomers.



Additionally, chiral molecules have varying degrees of on-target therapeutic effectiveness. For example, the compound cetirizine (brand name Zyrtec) is a common antihistamine drug given to treat allergic reactions. Cetirizine itself is a mixture

Figure 3. Cetirizine effectiveness per enantiomer.



of *R* and *S* enantiomers. Levocetirizine, the *R* enantiomer, has a greater affinity for the histamine H_1 receptor than dextrocetirizine, the *S* enantiomer. Dextrocetirizine as a result is largely inactive and has no antihistamine effect. Zyrtec was originally marketed as a mixture of both enantiomers, while Xyzal, is comprised of only the active enantiomer.[2]

Stereoselective Synthesis

The targeted synthesis of particular stereoisomers is a challenge to synthetic chemists. Asymmetric methodologies focuses on methods to synthesize of particular enantiomers or diastereomers of molecules. Given the importance of particular enantiomers in biological systems and pharmaceutical spaces, and the particular reactivity of stereoenriched molecules, accurate synthesis of stereoisomers is of utmost importance.

Types of Asymmetric Syntheses

There are several ways to obtain a specific enantiomer or diastereomer. For asymmetric synthesis, the ideal methodology is one in which all (or a large majority) of the product generated is the desired enantiomer or diastereomer. The simplest method would be to ignore stereospecific methods and synthesize a racemic mixture of molecules. This racemic mixture

could be purified via chromatography with a chiral stationary phase. This method, however, is wasteful as the maximum yield for a racemic mixture of enantiomers is 50%.

Resolutions

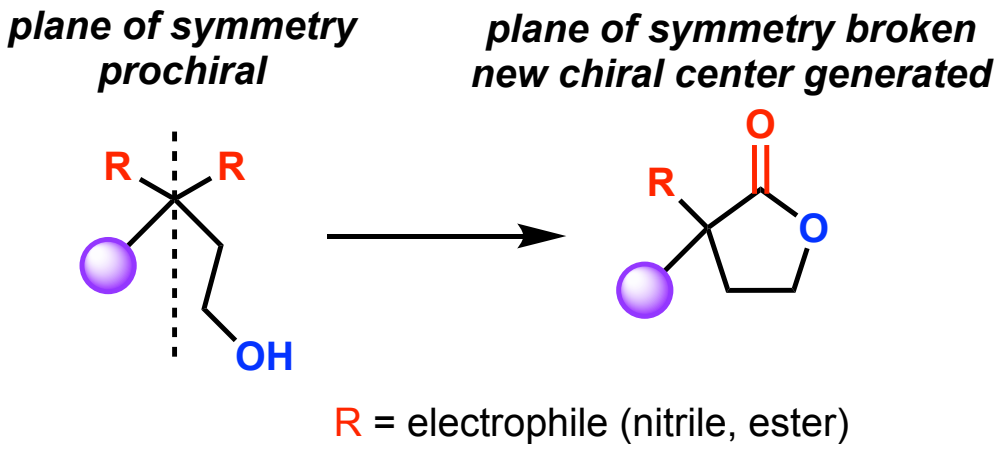
Chiral resolutions are another means by which stereospecific molecules can be obtained.[3] There are a variety of types of resolutions. For example, utilization of a chiral auxiliary can create a mixture of diastereomers which, given their distinct chemical properties, can be separated by traditional means and isolated. Ideally, the chiral auxiliary can then be removed, furnishing the enantiopure isomer. Kinetic resolutions are another means by which stereospecific compounds can be separated. In a kinetic resolution, the relative reaction rate of a racemate with an external compound to form diastereomers is utilized. Generally, only one diastereomer is formed and the resulting compounds can be separated and characterized.

While important, these resolutions suffer from several drawbacks. As the stereoisomers start in racemic mixtures, resolutions are still limited by yields, as only 50% of a particular stereoisomer can be isolated. Auxiliaries additionally introduce extra steps to the methodology and can cause overall yields to suffer as a result.

Desymmetrizations

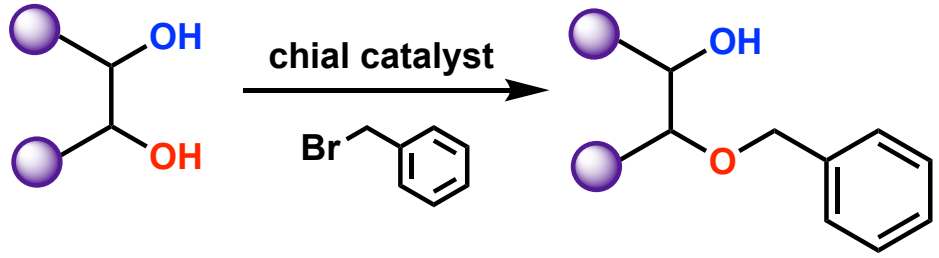
Desymmetrizations are a powerful methodology used to generate asymmetric molecules.[4] Desymmetrizations can occur when a prochiral molecule – a molecule where altering one symmetric element will generate a chiral molecule – is reacted to break the existing plane of symmetry.

Figure 4. General desymmetrizations of malonates.



A simple example of this is a symmetric diol molecule. In this scenario, the diol is symmetric and achiral due to the plane of symmetry bisecting the two alcohol groups. However, if the diol were subjected to conditions such that only one alcohol reacted with a chemical (e.g. benzyl bromide to generate the ether), the plane of symmetry would be broken, and the resulting molecule would be chiral.

Figure 5. Example hypothetical desymmetrization of diols.



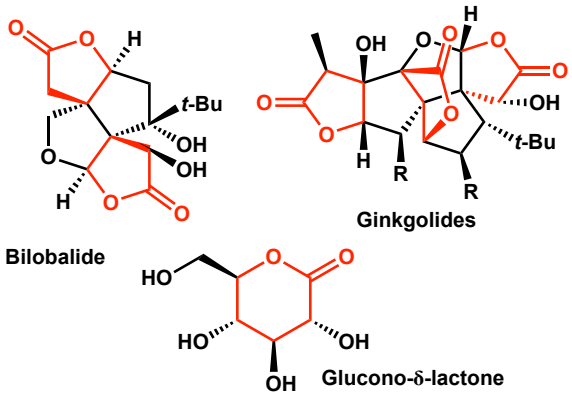
Desymmetrizations improve on other asymmetric methods in that they do not necessarily suffer from yield limitations (more than 50% of an enantiomer can be generated, as opposed to some resolutions). However, to utilize desymmetrizations as an asymmetric methodology, the starting molecule must be prochiral and one of the prochiral groups must be reactive to the set

conditions. This limits some of the molecular complexity of the starting molecule for desymmetrization.

Lactones as Synthetic Targets

Lactones are cyclic esters common throughout the natural products and pharmaceutical chemistry spaces. Examples of lactones with chiral motifs are replete in the literature. For example, extracts of the leaves of the Ginkgo tree are used as dietary supplements to improve mental functioning. These Ginkgo extracts comprise chiral lactone containing molecules, including bilobalide and various ginkgolides.[5] In addition, dietary intake of glucono-δ-lactone, a common additive in honey and wine, has been shown to lessen skin inflammation.[6]

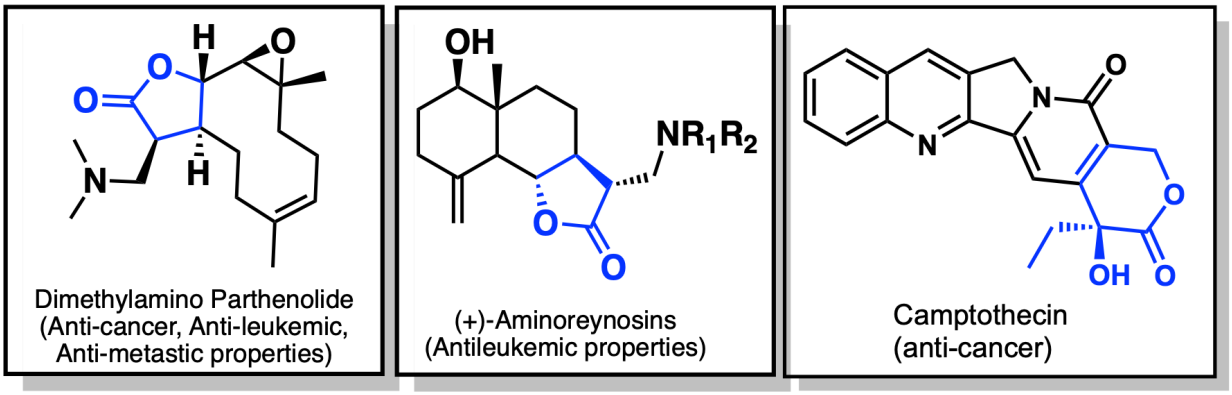
Figure 6. Chiral lactone natural products.



Molecules containing chiral lactone moieties have seen extensive use throughout the pharmaceutical space. α-chiral lactones, in particular, play a prevalent functional group role in natural product chemistry. The aminoreynosin and parthenolide natural products, for example, contain a γ-lactone with a chiral alpha carbon and a beta amino moiety. These natural products and their derivatives are currently being investigated broadly for their anti-cancer and cytotoxic effects.[7,8]

Camptothecin is a natural product compound isolated from the bark and stem of *Camptotheca acuminata*.[9] Camptothecin is a topoisomerase inhibitor and is active against several cancer cell lines.[10] Camptothecin and the camptothecin analogues provide the most stark example of the chiral lactone motif in the pharmaceutical chemistry space, as the lactone "E" ring provides most of the molecule's activity against cancer cells. The lactone ring and oxygen atoms provide several hydrogen-bonding interactions which stabilize the intracellular interaction of camptothecin and camptothecin analogues with topoisomerase, preventing DNA ligation and causing apoptosis.[11]

Figure 7. Bioactive chiral lactones with pharmaceutical importance.



Given the prominence of chiral lactone motifs in these natural product and pharmaceutical compounds, accurate synthesis of these molecules is an important undertaking. Stereoselective synthesis of lactones allows for generation of compounds that could be useful in determination of structure activity relationships, as well as the total synthesis of complex molecules with potentially beneficial properties.

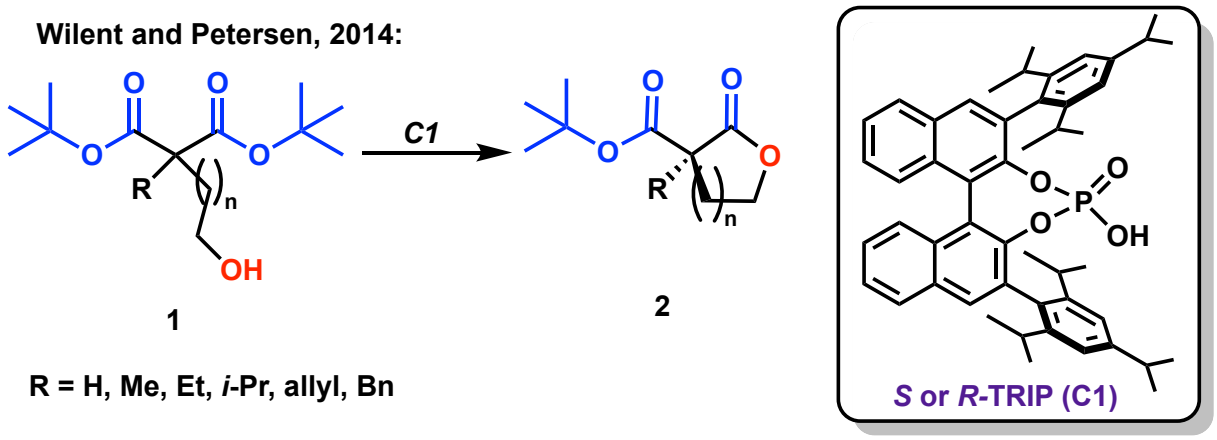
Asymmetric Lactone Synthesis via Desymmetrization

Synthesis of chiral lactones can be challenging, particularly with substitutions on the lactone ring. The Petersen group has been developing methods for the stereoselective synthesis

of α-chiral lactones via a stereoselective desymmetrization reaction. These desymmetrizations make use of a prochiral diester malonate, which is susceptible to desymmetrization via an acid-catalyzed intramolecular cyclization. This transesterification reaction generates a new lactone moiety and generates a chiral center at the α-carbon of the ring.

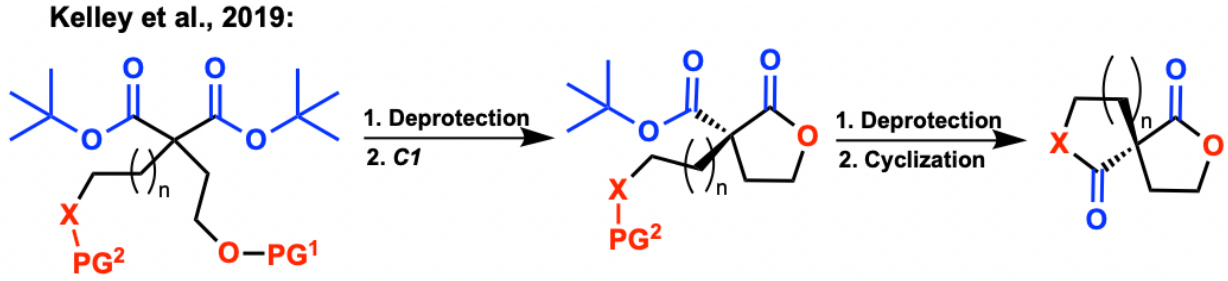
The Petersen group has used this transformation to great effect in synthesizing chiral lactones with fully substituted quaternary centers. One of the first examples we reported of this transformation was detailed in by Dr. Jennifer Wilent and coworkers in the *Journal of Organic Chemistry*. Building on previous methods development in the Petersen group,[12] this work utilized the chiral Brønsted acid TRIP (3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate) to desymmetrize prochiral di-*t*-butyl malonates to their corresponding lactones. These lactones were able to be generated in good yields (up to 96%) and good enantioselectivities (up to 98% ee) for a variety of alkyl and aryl fully substituted chiral quaternary centers. In particular, synthesis of these chiral lactones with all carbon quaternary centers at the α-carbon of the ring is challenging, and this methodology provides another tool for the synthesis of such molecules.

Figure 8. Previous desymmetrizations of diesters.



Other desymmetrizations have been reported by the Petersen group that build on this methodology and aimed to synthesize increasingly complex chiral lactone molecules. Dr. Amber Kelley and coworkers in 2019 published a method for the synthesis of stereoenriched spirocyclic lactones utilizing the Brønsted acid TRIP.[13] The spirocyclic ring system is privileged and the synthesis of stereoenriched spirocycles is challenging. Additionally, the Petersen group has published work detailing the synthesis of coumarin and coumarin-like molecules, which represent the core structure of several bioactive natural product molecules.[14]

Figure 9. Desymmetrizations to form spirocycles.



This Work

This work builds on the work done by the Petersen group by expanding the synthetic methodology to new reactions and refining the existing methodology to potentially allow for more targeted and expanded syntheses.

Chapter II delves into an expansion of the methodology to the Pinner Reaction. The Pinner Reaction is an underutilized synthetic transformation of a nitrile to an ester in the presence of an alcohol. This acid-catalyzed esterification has yet to have been made stereoselective. In our hands, we were able to take a prochiral dinitrile and effect a diastereoselective intramolecular desymmetrization cyclization to form lactones with an α-cyano moiety. To the best of our knowledge, this represents the first stereoselective Pinner Reaction to have been reported in the literature.

Chapter III investigates a discovery stemming from our work in Chapter II. In attempting to design a method to synthesize γ-lactones stereoselectively via the Pinner Reaction, we discovered that use of an acid-labile alcohol protecting group with a different chiral Brønsted acid caused a cascade reaction to occur, generating the enantioenriched lactones from diester malonates in good yields and good enantioselectivities. To the best of our knowledge, this represents one of the first stereoselective deprotection cascade reactions of protected alcohols using a chiral Brønsted acid catalyst. This particular method improves on our previous methodology by removing a yield-costly alcohol deprotection step.

Chapter IV builds on methodology developed in Chapter III. In the process of developing our methods for Chapter III, we discovered that THP-protected alcohols, which were previously unavailable for participation in the cascade reaction due to rate constraints, had reactivity with our chiral phosphoric acid TRIP when reacted with an acid co-catalyst. The work in this chapter summarizes our current findings and includes next steps for investigation of this methodology to make it more broadly applicable to the synthetic organic community.

CHAPTER II: STEREOSELECTIVE DESYMMETRIZATION OF DINITRILES TO FORM LACTONES

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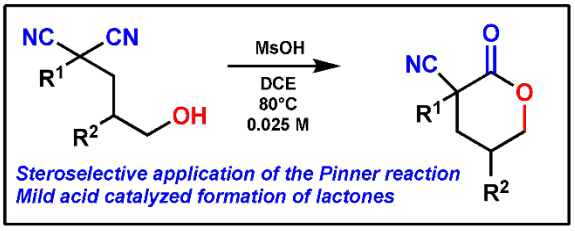
Abstract/Summary

Nitriles are important organic functional groups, allowing for installation of nitrogen in organic synthesis. The Pinner reaction transforms nitriles into esters via the imidate group, but in general has previously necessitated harsh acid conditions. Additionally, stereoselective reports of Pinner reactions are minimal and represent an underutilized space in the chemical literature. This work builds on the utility of the Pinner reaction through a stereoselective desymmetrization of dinitriles to form γ- and δ-lactones in good yields and diastereoselectivites.

Figure 10. Stereoselective Pinner lactonization abstract.



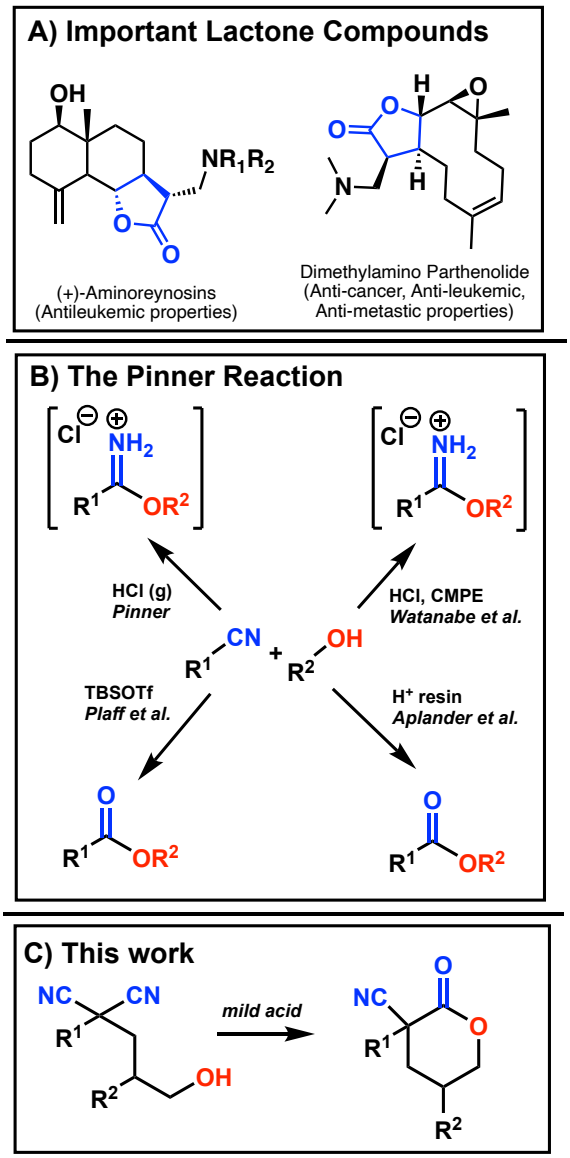
Introduction

Lactones as Synthetic Targets

Lactones that contain multiple stereocenters are key frameworks in many bioactive compounds.[15] For instance, the lactone derivatives of parthenolide natural products have many anti-cancer properties and are valuable synthetic targets due to this utility (Figure 11).[7,8,16] To

fully unlock the usefulness of these compounds, especially in medicinal or pharmaceutical spaces, synthetic routes giving chiral lactones must be developed. While not usually considered as a substrate, the electrophilic carbon of a nitrile functional group can serve as a template for the formation of chiral lactones.[17,18]

Figure 11. Pinner lactonization background.



The Pinner Reaction

The Pinner reaction is an underutilized organic transformation of an electrophilic nitrile source (Figure 11B). Here, the nucleophilic attack of an alcohol with an acid forms an imidate salt (Pinner salt).[19] Pinner salts can undergo a second nucleophilic attack – such as the hydrolysis of the imidate to form an ester. Due to the harsh conditions of the Pinner reaction, there have been select examples utilizing reaction alternatives (Figure 11B). Watanabe and coworkers used an alternative solvent CMPE which allowed facile isolation of the Pinner salt product by filtration.[20] Plaff and coworkers used the Lewis acid TBSOTf to yield the ester, although the conditions require the reaction to be neat in either the nitrile or the alcohol, limiting substrate diversification.[21]

To our knowledge the only systematic study of the use of an intramolecular lactonization of the Pinner/hydrolysis was reported by Aplander and coworkers using a cationic exchange resin in water.[22] A select example of an intramolecular Pinner/hydrolysis includes a lactonization forming Cleistantoxin derivatives using HCl in dioxane.[23] Extensive study of mild Pinner/hydrolysis mediators has not been investigated to this point. Mild conditions allow for the exploration of stereoselective desymmetrizations without potential disruption of the nascent stereocenter.

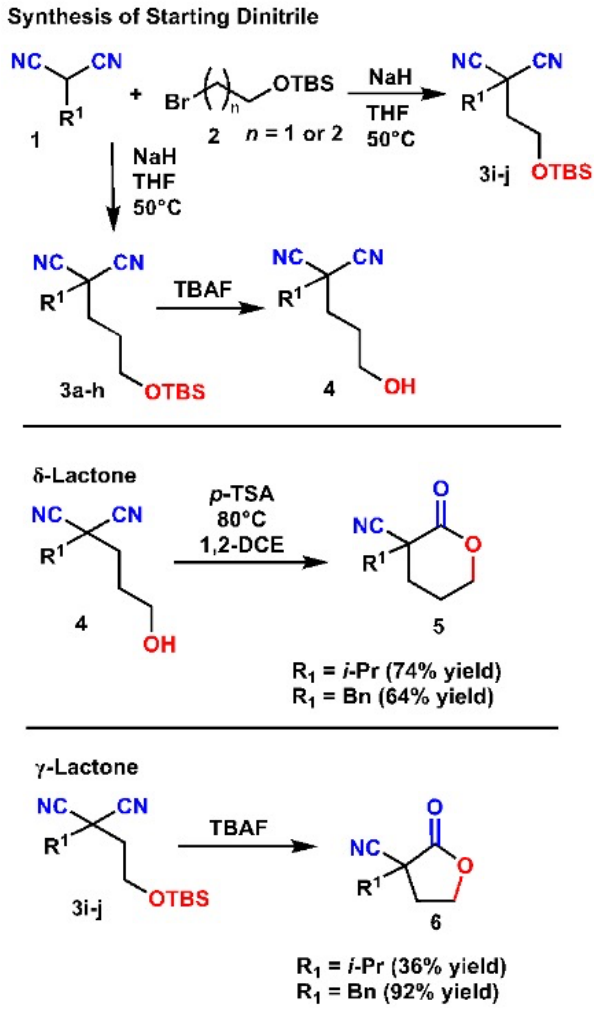
To our understanding, there have been no reports of a nitrile being used as a direct electrophile in the presence of a Brønsted acid stereoselectively. The stereoselective examples are of domino reactions that are Michael/Pinner isomerization reactions to chromene-type compounds.[24] While these reactions utilize a Pinner reaction, the Pinner reaction step is not stereoselective. Thus, this work represents the first instance of a stereoseletive Pinner reaction.

Previously, the Petersen lab has reported enantioselective desymmetrizations of diesters to synthesize lactones.[13,14] This methodology takes a similar approach but extends these procedures to nitriles which can undergo a diastereoselective intramolecular desymmetrizing cyclization. Here, we present a diastereoselective desymmetrization that generates cyanolactones in good yields and diastereoselectivities.

Results and Discussion

Our investigation began by establishing a general protocol for the cyclization of hydroxy dinitriles to both γ- and δ-lactones (Figure 12). δ-Lactones II-**5** were readily prepared from the corresponding hydroxy dinitrile II-**4** with *para*-toluensulfonic acid in good yields. Spontaneous cyclization of TBS protected hydroxy dinitrile II-**3i-j** under deprotection conditions yielded γ-lactones II-**6** in a single step.

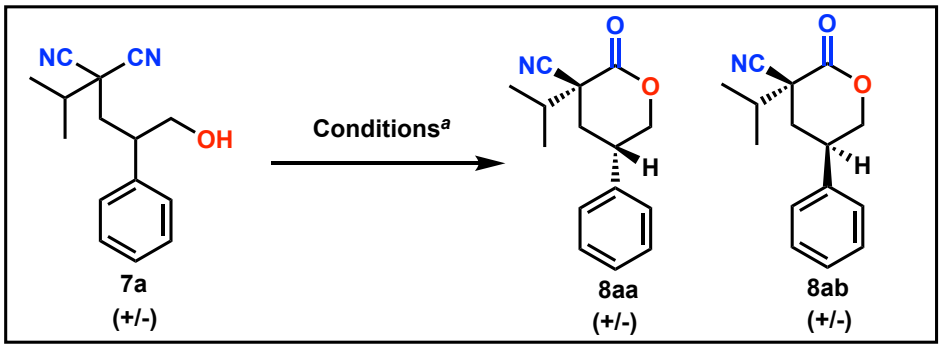
Figure 12. General method for synthesis of dinitrile starting materials.



Next, a diastereoselective cyclization of hydroxy dinitriles with a pre-existing stereocenter was tested. Initial efforts focused on the optimization of the stereoselective cyclization of dinitrile II-(±)-**7a** to yield lactones II-(±)-**8aa** and II-(±)-**8ab** (Figure 13). Various Brønsted acids were investigated, including several sulfonic acids and trifluoroacetic acid (entry 1-4). These were chosen due to their pK_A similarity to chiral acids previously used for stereoselective desymmetrizations, as well as their overall ease of use and accessibility. Based on X-ray analysis, sulfonic acids yielded predominately diastereomer II-**8aa** where the nitrile is *cis* to the hydrogen (entries 1-3, 5-15). Interestingly, trifluoroacetic acid (entry 4) resulted in

formation of the opposite diastereomer II-**8ab**. Methanesulfonic acid was chosen for additional optimization due to the best combination of yield and diastereoselectivity ratio in our initial screen. Reaction time was found to play an important role in the overall diastereoselectivity of the reaction. Longer reaction times would result in lower diastereoselectivity. We hypothesize that this reaction is reversible, allowing for racemization with longer reaction times. The concentration was lowered to avoid undesired intermolecular dimerization which lowered yields. The optimal reaction conditions occurred with methanesulfonic acid in dichloroethane at 80 ºC for one hour (entry 10).

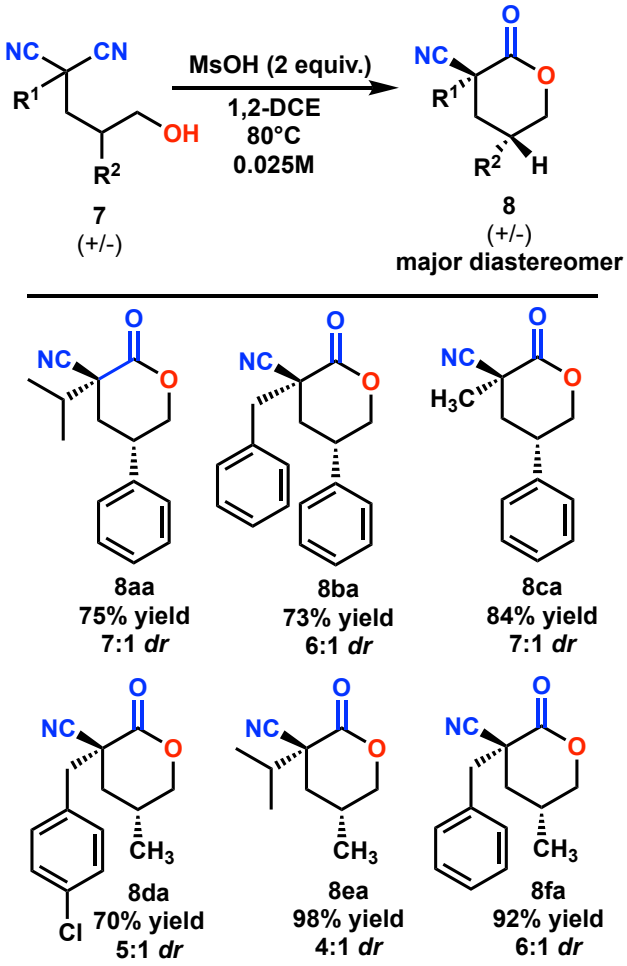
Figure 13. Optimization of Pinner lactonization conditions.



Entry	Acid	Temp. (°C)	Solvent	Conc. (M)	Time (hr)	Yield (%)[b]	8aa:8ab[c]
1	CSA	RT	DCE	0.1	72	32	3:1
2	TsOH	RT	DCE	0.1	72	45	5:1
3	MsOH	RT	DCE	0.1	72	51	5:1
4	TFA	RT	DCE	0.1	72	82	1:4
5[d]	MsOH	RT	DCE	0.1	2	20	9:1
6[d]	MsOH	RT	DCE	0.1	4	32	7.5:1
7[d]	MsOH	RT	DCE	0.1	18	57	7:1
8[d]	MsOH	RT	DCE	0.1	42	61	6:1
9	MsOH	50	DCE	0.025	1	35	5:1
10	MsOH	80	DCE	0.025	1	75	7:1
11	MsOH	80	DCE	0.025	0.5	60	7:1
12[e]	MsOH	80	DCE	0.025	1	58	6:1
13	MsOH	80	DCE/H_2O (20:1)	0.025	1	Trace	—
14	MsOH	80	DCE	0.01	1	54	4:1
15	MsOH	80	Toluene	0.025	1	73	4:1

In order to explore the scope of this diastereoselective cyclization, various substitution patterns were explored (Figure 14). The cyclization of dinitriles that contained a phenyl group in the R^2 position were shown to yield lactone products in good yields and diastereoselectivity (compounds II-**8aa-ca**). The reaction of methanesuflonic acid and dinitriles that contained a methyl group in R^2 resulted in excellent yields and good stereoselectivities (compounds II-**8da-fa**).

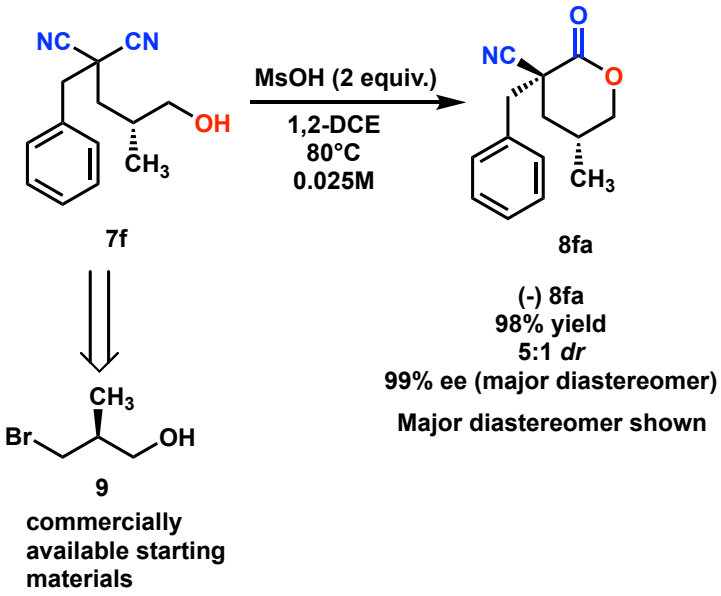
Figure 14. Scope of Pinner lactonization.



Next, synthesis of a single enantiomer of a lactone was accomplished by using the commercially available enantioenriched bromide II-**9**. Diastereoselective intramolecular

cyclization of hydroxy dinitrile II-**7f** using our optimized reaction conditions yielded enantioenriched lactone II-**8fa** in excellent yields and 99% ee (Figure 15). The diastereomer of this enantioenriched compound, additionally, was able to be separated via silica gel column chromatography.

Figure 15. Synthesis of optically pure lactones via Pinner Reaction.



Conclusions

Here, we have described a stereoselective intramolecular Pinner reaction which forms a lactone in good yields and diastereoselectivites. Additionally, we were able to accomplish this transformation using a mild acid as a catalyst, as opposed to the standard Pinner reaction conditions of HCl. This mild acid catalysis opens the door for further investigation into this method for the synthesis of complex natural product lactones – especially products with beta nitrogen moieties.

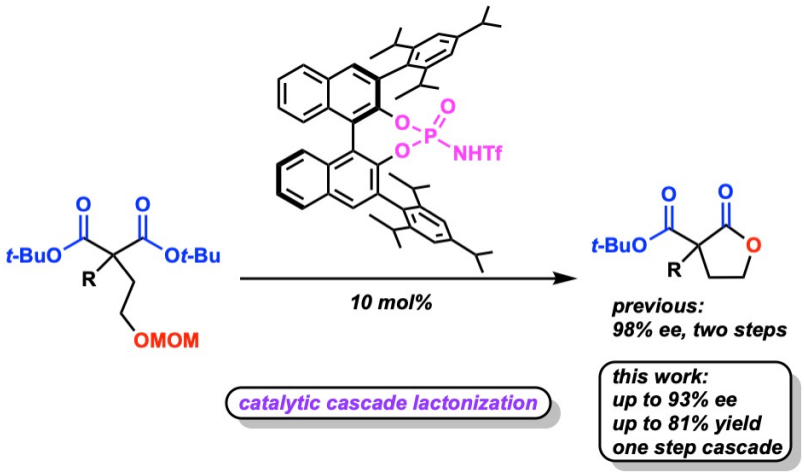
CHAPTER III: CHIRAL BRØNSTED ACID CATALYZED CASCADE ALCOHOL DEPROTECTION AND ENANTIOSELECTIVE CYCLIZATION

This chapter is published as: **Frost, J.A.;** Korb, S.M.; Green, F.E.; Youngblood, K.C.; Petersen, K.S.; Chiral Brønsted Acid Catalyzed Cascade Alcohol Deprotection and Enantioselective Cyclization. *ACS Omega*, **2024**, *9*, 2962-2969. https://doi.org/10.1021/acsomega.3c08869.

Abstract/Summary

The protection/deprotection sequence is vital to organic synthesis. Here, we describe a novel catalytic cascade where a chiral Brønsted acid selectively removes ether protecting groups and catalyzes an intramolecular cyclization in one pot. We test three model substrates from our previous work and investigate the rate of deprotection through GC studies. This work builds on our stereoselective synthesis of lactones by streamlining our synthesis. It also opens the door for additional investigations into other catalytic cascade reactions using chiral Brønsted acid catalysts.

Figure 16. Cascade deprotection/cyclization abstract.



Introduction

Chemical Protecting Groups

Chemical protecting groups have seen ubiquitous use throughout organic synthesis. Protection and deprotection of alcohol functional groups has been studied extensively, and the advancement of alcohol protection/deprotection sequences has allowed for chemoselective reaction development. Alcohol groups are commonly converted to ethers to mask their reactivity, varying from silyl ether protection to carbon-based ethers like tetrahydropyranyl ethers.[25,26] While protecting groups allow for better selectivity, their use is not without drawbacks, including the addition of multiple synthetic steps and potential effects on overall yields of reaction sequences.

Cascade Deprotections

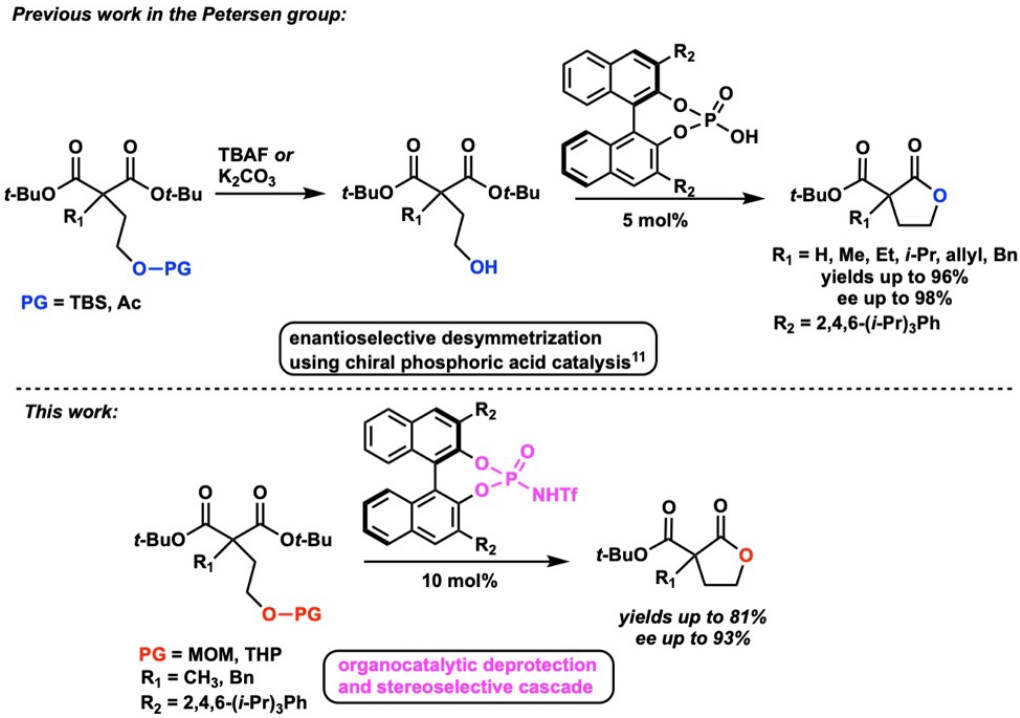
Chiral Brønsted acid catalyzed domino lactonizations are known in the literature. Bartoccini and coworkers reported stereoselective formation of benzo and naphthofuranones using chiral phosphoric acid catalysis.[27] Furthermore, catalytic deprotections are well known to the chemical literature. Many involve the use of metal or Lewis acid-catalyzed reagents to accomplish this transformation. For example, cerium(III),[28] cerium(IV),[29] and bismuth(III)[30] compounds have been used in the catalytic removal of acetal protecting groups. For the catalytic deprotection of alcohols, specifically, $Ce(OTf)_4$[31] has been used to remove trityl ethers catalytically. Additionally, catalytic removals of silyl ethers to form alcohols have been reported.[32,33]

Reports of Brønsted acid catalyzed deprotections are rarer in the literature. Karimi and Zareyee reported removal of silyl ethers via sulfuric acid-functionalized nanoporous silica.[34] Similarly, Iimura et al. reported removal of silyl-protected alcohol groups via polystyrene-

supported sulfuric acids.[35] Despite these, the literature surrounding Brønsted acid catalyzed alcohol deprotections is extremely limited. Here, we have developed an organocatalytic deprotection and stereoselective cascade cyclization of ether protected alcohols to form lactones.

To the best of our knowledge, this represents the first use of an organic Brønsted acid to catalyze both an alcohol deprotection and stereoselective cyclization in one pot. This reaction methodology builds on previous Petersen group methodology for the synthesis of lactones (Figure 17). Whereas previous Petersen group methodology was limited to a deprotection to a free alcohol followed by diester lactonization, this methodology outlines a reaction that uses a stronger chiral Brønsted acid that allows for a unique cascade transformation from protected alcohol to lactonization to occur. The development of this methodology presents a potential opportunity for the growth of cascade deprotection reactions for further use in organic synthesis.

Figure 17. Overview of cascade work: previous work vs. new cascade reaction.



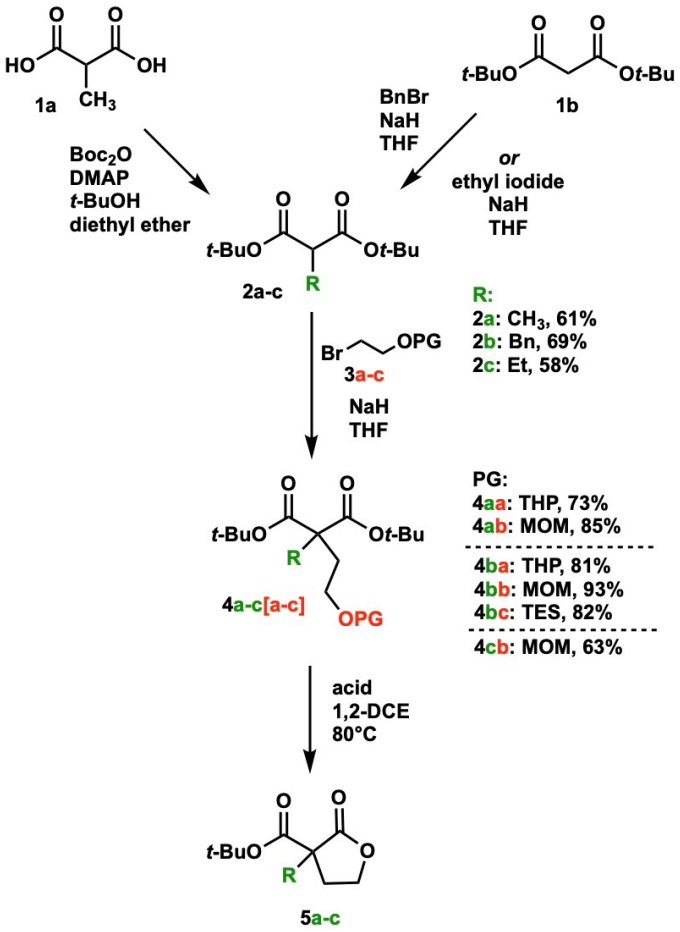
Results and Discussion

Our investigation began by envisioning a more elegant reaction pathway than our initial reaction pathway – involving an acid-labile protecting group that is removed in one pot by our chiral acid.

Starting Material Synthesis

We initially α-substituted diesters to test the feasibility of the cascade. The enantioselectivity of these substrates had been established by previously published reactions in the Petersen group.[36] As such, we chose the methyl, ethyl, and benzyl substituted esters III-**4a-c** as representative examples for a novel cascade reaction. The starting methyl malonate III-**2a** was synthesized readily from the diacid following our previously published procedure.[37] The malonate was further alkylated with a protected alcohol III-**3a-b**, giving compounds III-**4a[a-b]**.

Figure 18. Malonate starting material synthesis.



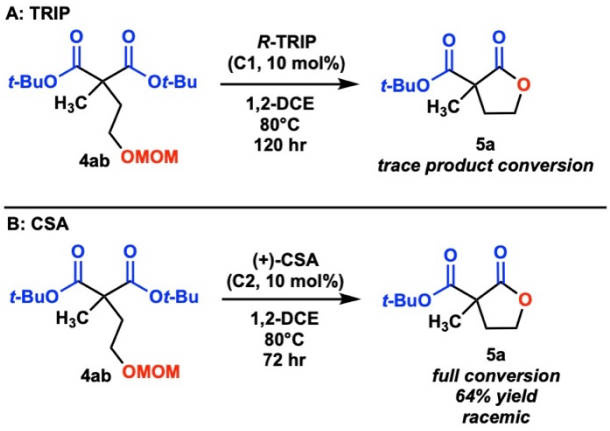
In a similar fashion, malonates III-**4b-c[a-c]** were synthesized from the starting unsubstituted malonate III-**1b** following a first alkylation with benzyl bromide or iodoethane to give III-**2b** and III-**2c** and a second alkylation with the protected alkylating agent III-**3a-c** (Figure 18).

These tetrahydropyranyl (THP), methoxymethyl (MOM), and triethylsilyl (TES) protected alcohols were chosen both based on their lability towards Brønsted acids but also to evaluate whether such stereoselective deprotection/cyclization cascades are selective only towards ether protecting groups or if silyl groups could be subjected to this cascade.

Cascade Investigation

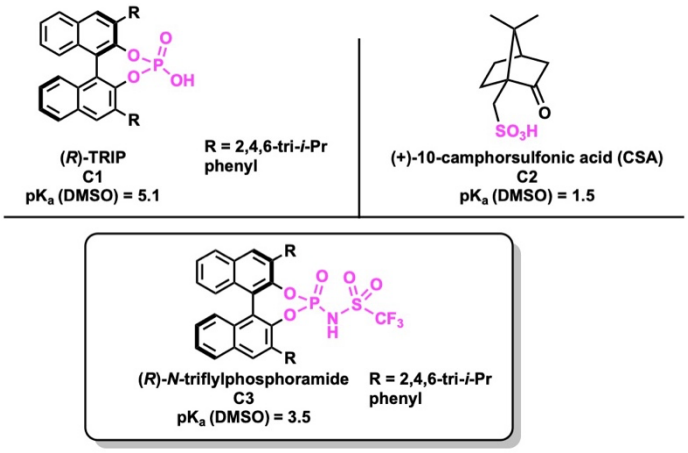
Initially, we investigated the conversion of methyl-substituted MOM-protected alcohol III-**4ab** to lactone III-**5a** with 10 mol% of the chiral phosphoric acid TRIP, **C1**, which we had used in our previous work. After several days, though, only trace conversion was seen (Figure 19A). However, when reacted with 10 mol% of (+)-camphorsulfonic acid, **C2**, full conversion to III-**5a** was observed, but the product was racemic (Figure 19B).

Figure 19. Initial investigations into the cascade reaction.



Given these data, we hypothesized that a difference in pK_a between **C1** and **C2** led to the observed difference in reactivity, and that a stronger chiral phosphoric acid catalyst might accomplish the transformation to III-**5a** (Figure 20), but still allow for enantioselectivity.

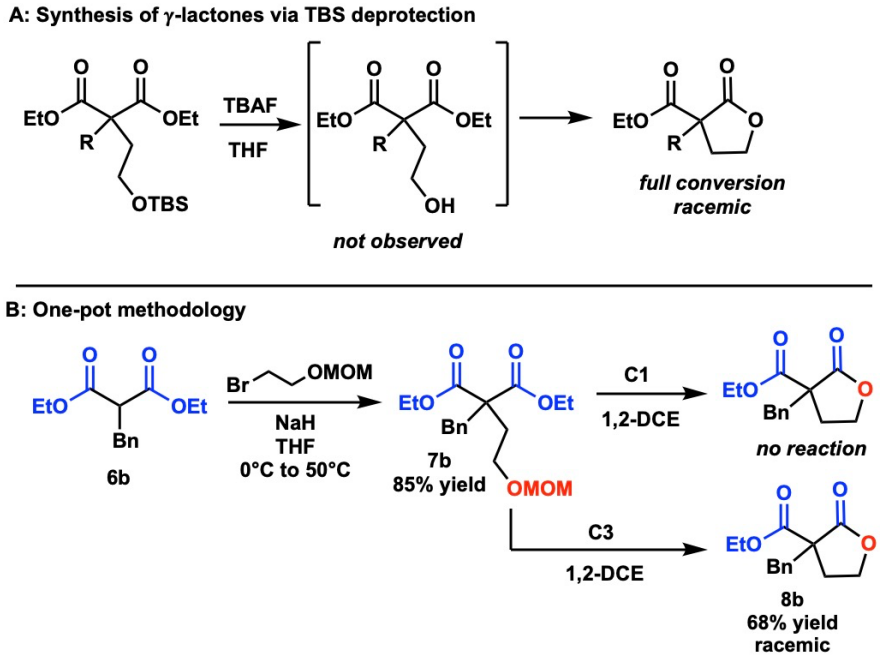
Figure 20. Acidity differences between chiral acids used.



Substrate Investigation

We next evaluated smaller esters in cascade to enantioenriched lactones. Previously, stereoselective cyclization of these esters was impossible with our desymmetrization, due to the rapid rate at which the deprotected alcohol reacts with smaller esters, even without the presence of an acid catalyst (Figure 21A). For comparison, compound III-**7b** was readily synthesized from the commercially available III-**6b**. With **C1**, no conversion was observed to III-**7b** and only led to recovery of starting material.

Figure 21. Investigation of one-pot methodology on smaller ester malonates.

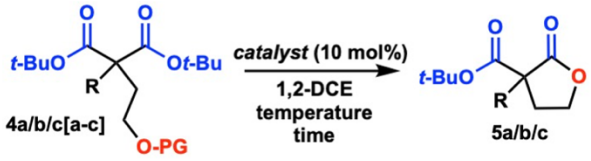


With **C3,** however, III-**7b** was able to convert to lactone **8b**, but no enantioenrichment of the product was observed (Figure 21B). This data led us to the hypothesis that the rate determining step of the cascade is the removal of the protecting group and that a stronger acid is required for protecting group removal.

We next turned our attention to the tert-butyl esters required in our previous work and investigated the conversion of the protected compounds III-**4a/b[a-c]** into lactones III-**5a/b** (Figure 22). Methyl and benzyl THP-protected alcohols III-**4aa** and III-**4ba** (Entries 1 and 2) did not lead to removal of the protecting group with **C1**, even at elevated temperatures (Entry 3), and only starting material was recovered. With the stronger acid **C3**, however, benzyl THP-protected alcohol III-**4ba** (Entry 4) saw full removal of the THP protecting group and cyclized to form lactone III-**5b**, but in racemic mixtures, even at room temperature. Turning to the more stable MOM protecting group, with catalyst **C1** methyl or benzyl MOM-protected alcohols III-**4ab** and III-**4bb** were unable to form product III-**5a** or III-**5b** (Entries 5 and 6) with only recovered

starting material obtained, even at elevated temperatures. At room temperature, methyl MOM-protected alcohol III-**4ab** converted to III-**5a** with **C3** (Entry 7) only at small scale (5 mg) and could not be isolated. Gratifyingly, however, methyl, ethyl, and benzyl MOM-protected alcohols III-**4ab** through III-**4cb** (Entries 8-10) were converted to their target lactones III-**5a** through III-**5c** with catalyst **C3** in good yields and good enantioselectivities when heated to 80 °C. Additionally, the benzyl TES-protected alcohol III-**4bc** was unable to be removed with **C3** (Entry 10) resulting in recovery of starting material.

Figure 22. Optimization and investigation of cascade reaction conditions.

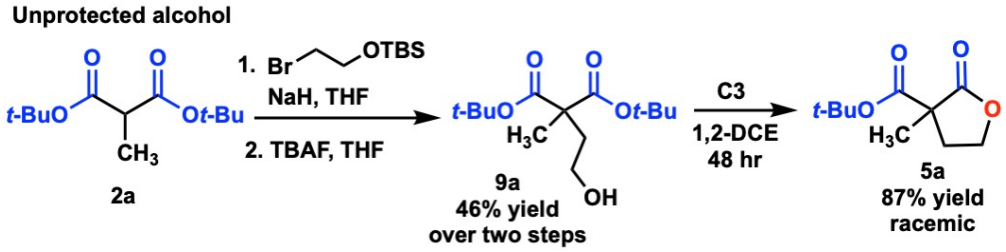


Entry	Cpd.	PG	Catalyst	R	Temp. (°C)	Time (h)	Yield (%)	%ee
1	**4aa**	THP	C1	CH_3	25	120	--	--
2	**4ba**	THP	C1	Bn	25	120	--	--
3	**4ba**	THP	C1	Bn	80	120	--	--
4	**4ba**	THP	C3	Bn	25	120	82	0
5	**4ab**	MOM	C1	CH_3	80	120	--	--
6	**4bb**	MOM	C1	Bn	80	120	--	--
7	**4ab**	MOM	C3	CH_3	25	120	44[a]	0
8	**4bb**	MOM	C3	Bn	80	72	81	67
9	**4ab**	MOM	C3	CH_3	80	72	80	93
10	**4cb**	MOM	C3	Et	80	72	84	-60[b]
11	**4bc**	TES	C3	Bn	80	120	--	--

Additionally, we tested catalyst **C3** on a previously published reaction from the Petersen group that achieved 98% *ee* with catalyst **C1**. To our surprise, catalyst **C3** readily converted III-**9a** to lactone III-**5a** utilizing our standard conditions (80°C), but as a racemic mixture (Figure

23). Furthermore, racemic mixtures were also obtained when reaction temperatures were lowered to both 25°C and 0°C.

Figure 23. Investigation of unprotected alcohol with phosphoramide catalyst.

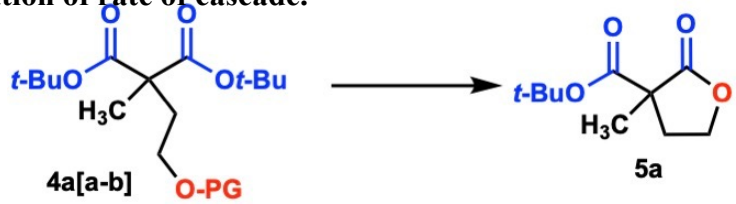


Mechanistic Exploration

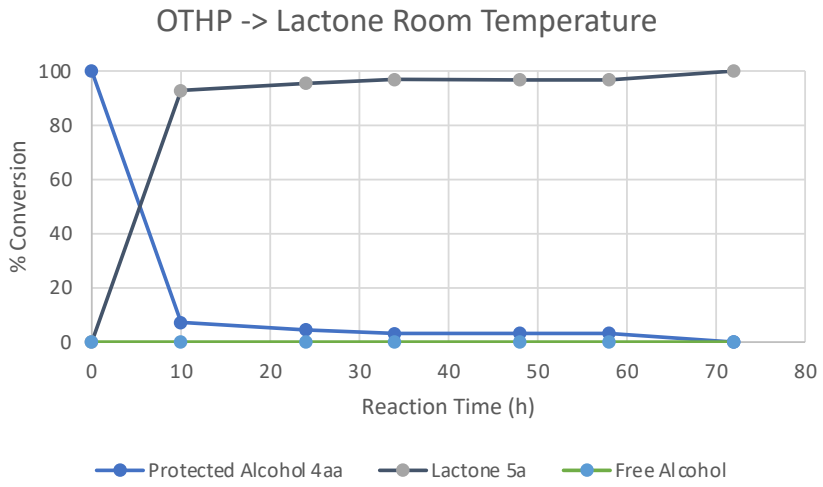
To further understand the mechanism and investigate the rate of deprotection, we continuously monitored each conversion of THP and MOM-protected alcohols to their corresponding lactone III-**5a** via GC. At room temperature, THP-protected III-**4aa** converted readily to lactone III-**5a**, with 92% conversion at the 10-hour mark. Meanwhile, MOM-protected III-**4ab** reacted significantly more slowly, reaching only 44% conversion to III-**5a** by 72 hours (Figure 24A). Additionally, we performed an experiment where 0.2 equivalent aliquots of III-**4aa/ab** were added sequentially over the course of 72 hours to a solution 10 mol% catalyst (relative to 1 equivalent of III-**4aa/ab**) in DCE at 80°C. After each addition, reaction progress was measured via GC. With THP-protected III-**4aa**, we saw full conversion of each aliquot to lactone III-**5a** at each time point, pointing to a rapid rate of deprotection and cyclization. However, with MOM-protected III-**4ab**, conversion to III-**5a** of each aliquot was not complete, even at more stochiometric catalyst-substrate ratios (Figure 24B). Finally, no concentration of free alcohol was detected while running either GC experiment, pointing to the cyclization step as the fast step in the cascade. These data point to a slower rate of MOM-deprotection in our reaction system, particularly when compared to THP-protected alcohol.

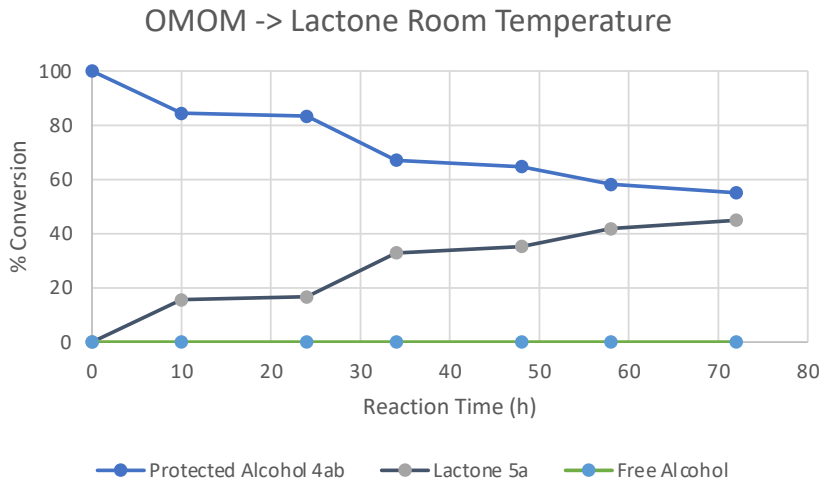
Taken together, we hypothesize that the mechanism and the observed stereoselectivity relies on the acidity of the catalyst, the rate at which the catalyst both deprotects and cyclizes the substrate, and the protecting group used. We observed that THP protecting groups were more labile to acid cleavage than MOM protecting groups, supported by our GC studies. This is further supported in the literature, where equivalent substrates with MOM or THP protected alcohols need longer or harsher

Figure 24. Gas chromatography investigation of rate of cascade.

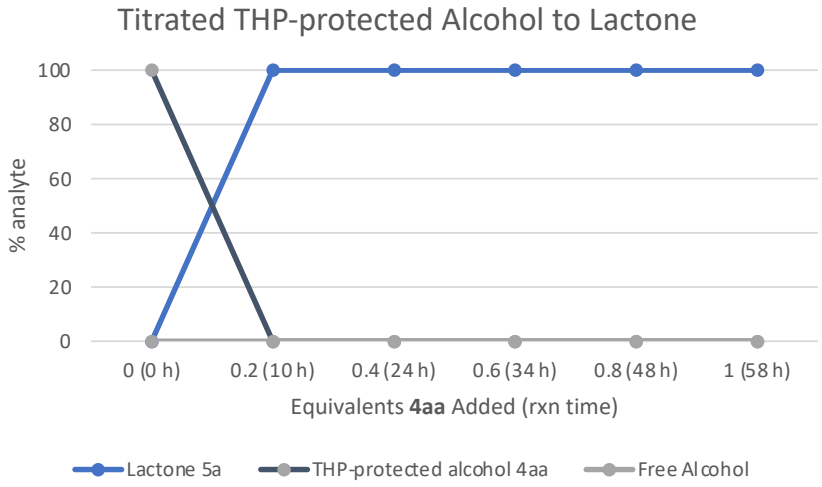


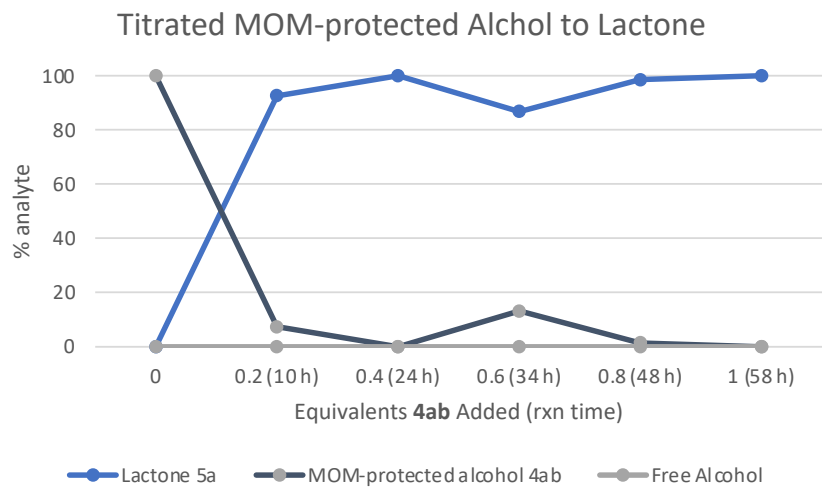
A:





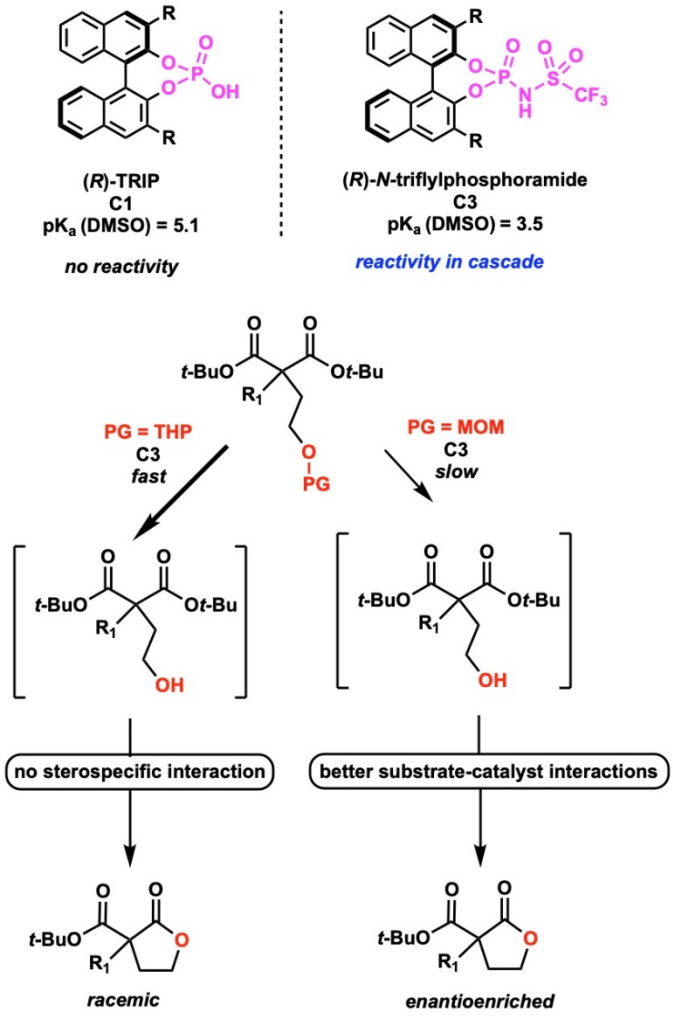
B:





conditions to deprotect MOM protected alcohols versus THP protected alcohols.[38,39] We also hypothesize that the lower pK_a of **C3** with respect to **C1** causes a significant increase in reaction rate, and with more labile THP protected alcohols, this increased reaction rate does not allow enough time for the catalyst to selectively interact with the substrate. Similarly, based on this data we observe that the rate determining step of this reaction is the initial deprotection step. Thus, with less labile MOM protected substrates, the deprotection by the catalyst is slow enough to allow for sufficient catalyst-substrate interaction, giving the observed stereoselectivity.

Figure 25. Current mechanistic hypothesis for observed cascade enantioselectivity.



Conclusions

Here, we have presented a Brønsted acid catalyzed deprotection and stereoselective cyclization cascade reaction. To the best of our knowledge, this represents the first such catalytic cascade reaction where the chiral Brønsted acid catalyst acts to both remove the protecting group and stereoselectively introduce an intramolecular cyclization reaction. This Brønsted acid catalyzed deprotection cascade represents a promising new tool for asymmetric synthesis and we have begun work to further elucidate the reaction mechanism and explore new applications for this cascade.

CHAPTER IV: CO-CATALYTIC ACID CASCADE WITH CHIRAL BRØNSTED ACIDS TO FORM LACTONES

Abstract/Summary

The use of chiral phosphoric acids and their derivatives has seen abundant use throughout the asymmetric synthetic space. We have discovered a co-catalytic system that appears to rescue the reactivity of a common chiral phosphoric acid (TRIP) by use of a catalytic amount of achiral Brønsted acid. The addition of a co-catalyst allows our previously discovered cascade reaction to occur with THP-protected alcohols to form lactones. Additionally, preliminary data shows that this co-catalytic system rescues other chiral phosphoric acids. Further investigation will focus on broader applicability of this co-catalytic system.

Introduction: BINOL Chiral Phosphoric Acids

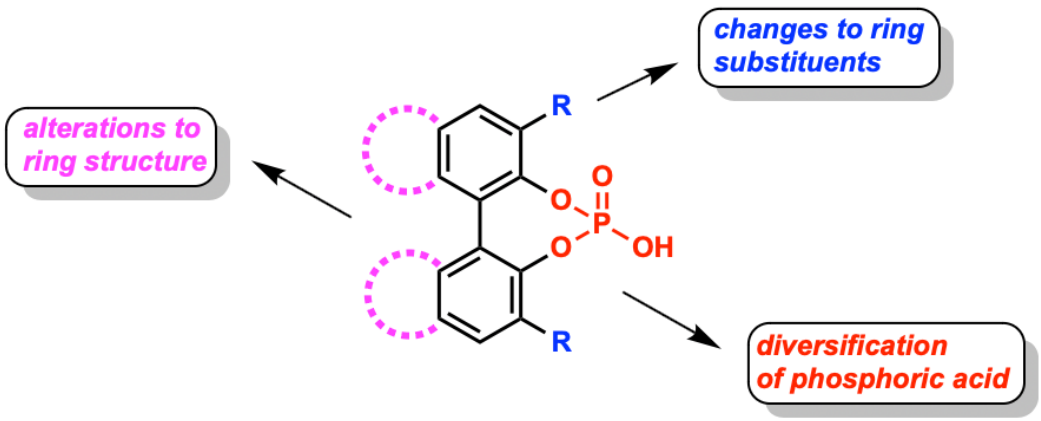
Over the past two decades, the use of binaphthyl (BINOL) based chiral phosphoric acids has grown significantly in popularity. The ability of these acids to catalyze a host of asymmetric reactions has increased exponentially. These reactions include a host of characteristic organic transformations, from Diels-Alder cycloadditions[40] to simple protonations.[41] Indeed, BINOL based phosphoric acid catalysts are frequently cited and well used in the asymmetric chemist's toolbox.

Part of the attractiveness of these BINOL phosphoric acid catalysts resides in the diverse functionalization that these catalysts can inhabit. For instance, there are a host of interactions within the structure of the phosphoric acid itself that can lead to different mechanistic and synthetic outcomes. The classical Brønsted acidic proton can function both as a hydrogen donor or the conjugate base phosphate can act as an ion pair acceptor. Additionally, a dual mode of

activation exists where two points of contact are made with the catalyst – one with the Brønsted acidic proton and the other with a proton hydrogen bonding or coordinating with the Lewis basic oxygen bonded to the phosphorus. These various modes of activation diversify the scope of reactions these BINOL phosphoric acid catalysts can catalyze.[42]

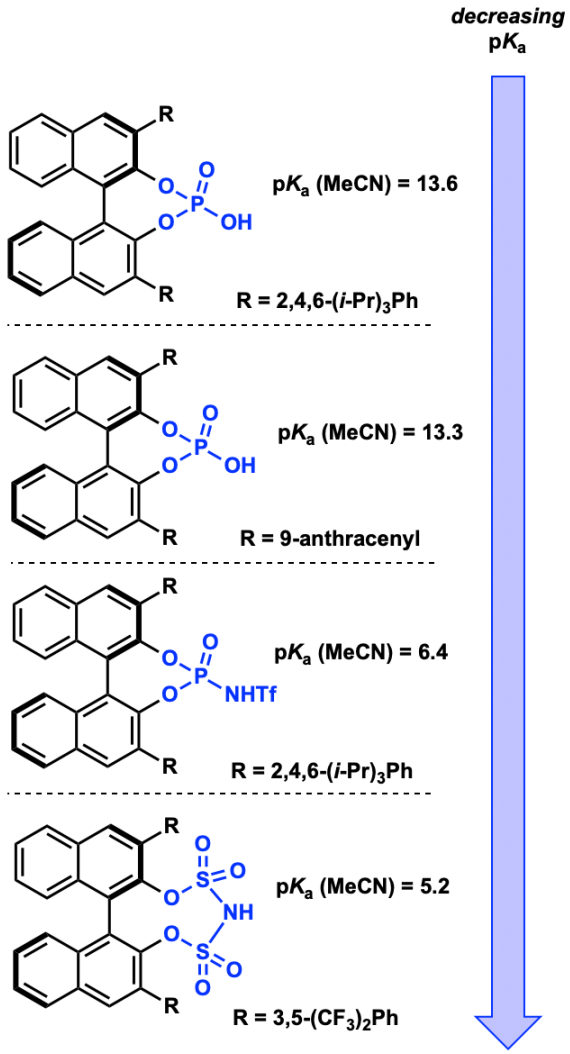
Similarly, the diversity of BINOL phosphoric acid catalysts is lent in part to the functionalizability of the core structure. A host of different groups can be added to the BINOL core, altering sterics and electronics to give different catalytic environments. For example, modifications to the 3 and 3' positions of the BINOL ring system give rise to common chiral phosphoric acids, including TRIP and its derivatives.

Figure 26. Alterations to BINOL structure influence acidity and reactivity.



The acidity of the acidic proton can be tuned through changes to the structure of the ring system, substitution of the ring, and changes to the phosphoric acid itself can tune acidity of the proton. In acetonitrile, the acidity of BINOL phosphoric acid protons can vary widely, from a pK_a of 14 for TRIP derivatives to as low as 5.3 for sulfonyl imide derivatives (HCl, for comparison, has a pK_a in acetonitrile of 10.3).[42]

Figure 27. Varying acidity of BINOL acid derivatives.

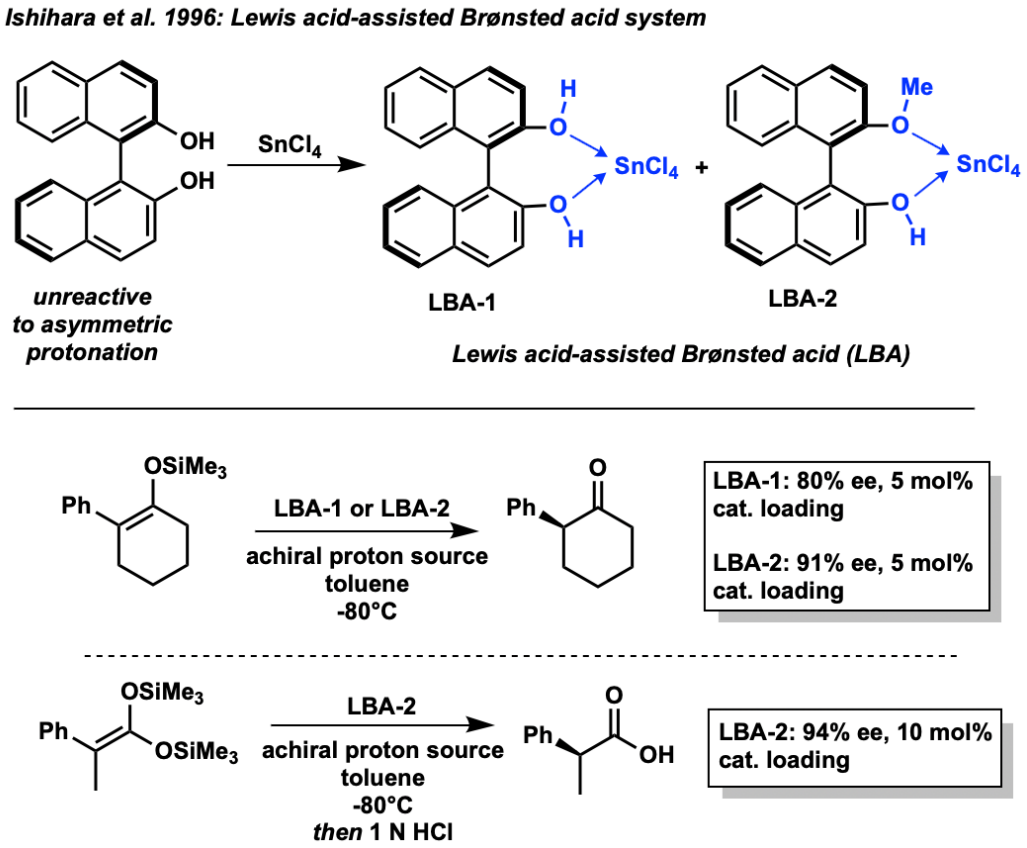


More Challenging Substrates: Tuning Acidity

One of the challenges of using BINOL chiral phosphoric acid catalysts – and one of the areas of further development for these molecules – is tuning acidity to allow for more challenging transformations. To this end, tuning acidity and reactivity has focused on creation of "designer acids"[43] or combinations of different acids to achieve greater reactivity. For example, the addition of a Lewis acid to a chiral Brønsted catalyst or backbone (the addition of $SnCl_4$ to

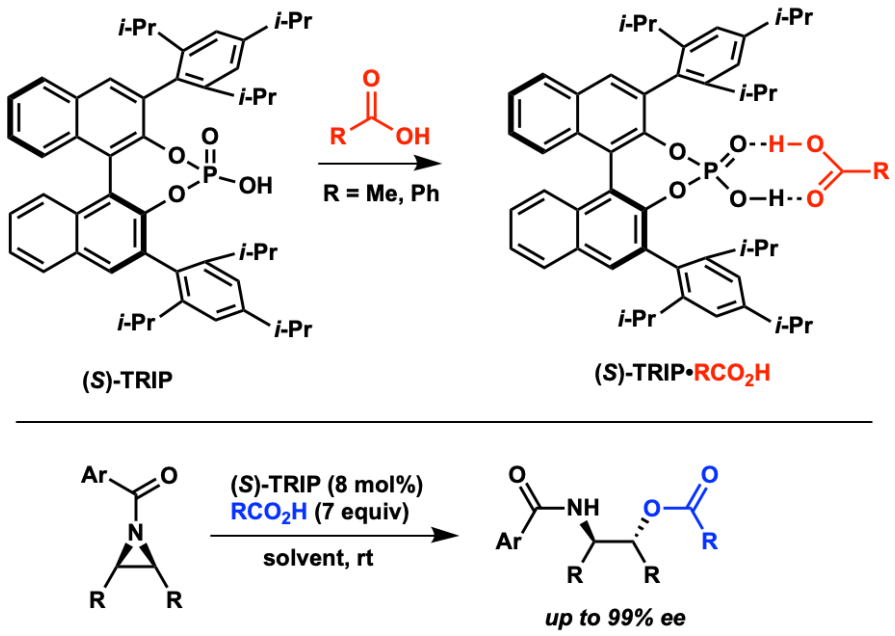
binaphthol, as an example[44]) increases the reactivity of the Brønsted acid and allows for investigation of new reactions.

Figure 28. Lewis acid-assisted Brønsted acid catalyzed reactions.



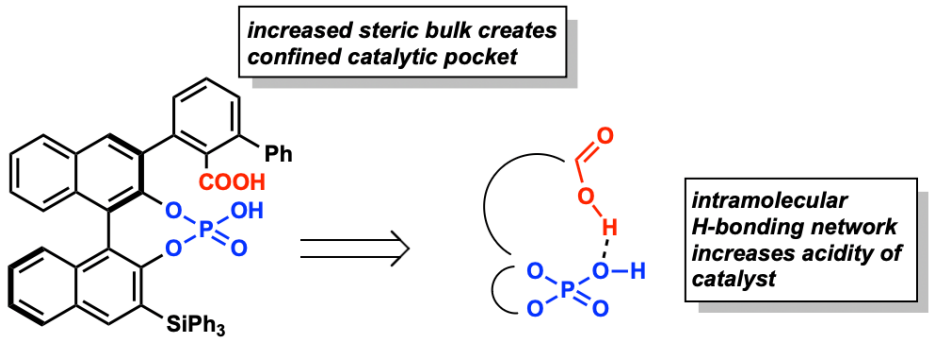
Brønsted-acid assisted Brønsted-acid catalysis examples involving BINOL phosphoric acids are also known in the literature.[45] These examples often rely on a heterodimeric system where hydrogen bonding interactions between molecules of catalyst generate a stronger catalytic system (often a stronger Brønsted acid). For example, the List group reported in 2016 a heterodimeric system based on carboxylic acid and thiolate co-catalysts, forming a heterodimer with the chiral phosphoric acid TRIP to catalyze several stereoselective reactions.[46] The dimers they formed with achiral acids provided a more acidic catalyst (and more nucleophilic carboxylic acid) to accomplish several sets of transformations.

Figure 29. Carboxolysis of aziridines with BINOL phosphoric acid heterodimers.



Other examples exist, often with the assisting Brønsted acid bound to the catalytic Brønsted acid. For example, several BINOL derivatives exist where an extra bound carboxylic acid to the 3' phenyl group creates a hydrogen bonding network that increases the activity of the catalyst through a more acidic proton and a more confined catalytic pocket.[45] A more recent example involves the use of such a heterodimeric system with achiral Brønsted acid assistance to catalyze a C-H activation/C-N cleavage.[47]

Figure 30. Linked H-bonded carboxylic acid co-catalysts.

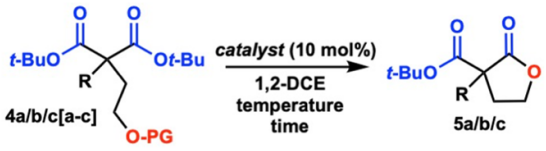


To the best of our knowledge, though, the use of an achiral Brønsted acid co-catalytically with a chiral Brønsted acid to rescue the reactivity of a chiral catalyst has remained unexplored. Recently, while investigating the cascade reaction reported in Chapter III, we noticed that trace amounts of acid appeared to catalyze a transformation that previously gave no reaction under the standard conditions. Our chiral phosphoric acid TRIP was unable to affect a cascade reaction with our reported conditions. However, we noticed that other conditions ($CDCl_3$ and heating) gave rise to enantioenriched products with TRIP. Here, we report the initial stages of development of a new co-catalytic system involving BINOL chiral phosphoric acid catalysis with an achiral Brønsted acid co-catalyst. Preliminary evidence shows that we are able to catalyze the cascade deprotection and enantioselective cyclization of a THP-protected alcohol to form a lactone in good enantioselectivities with a TRIP and HCl co-catalytic system. Moreover, additional preliminary evidence points to the fact that this co-catalytic system is able to rescue the reactivity of other BINOL chiral phosphoric acid catalysts. Further work is ongoing to investigate the scope of this reaction and to ascertain whether this system can be applied to other reactions where the BINOL chiral phosphoric acid (i.e. TRIP) is unreactive.

Preliminary Results and Discussion

Recalling from our previous work, we found that THP-protected substrates were unavailable for reactivity in the cascade reaction delineated in Chapter III.[48] We reported that THP-protected substrates III-**4aa-4ba** were not labile to TRIP (**C1**) and were unreactive. These substrates III-**4ba** reacted quickly with the *N*-triflylphosphoramide (**C3**) but the lactone was isolated in racemic mixtures.

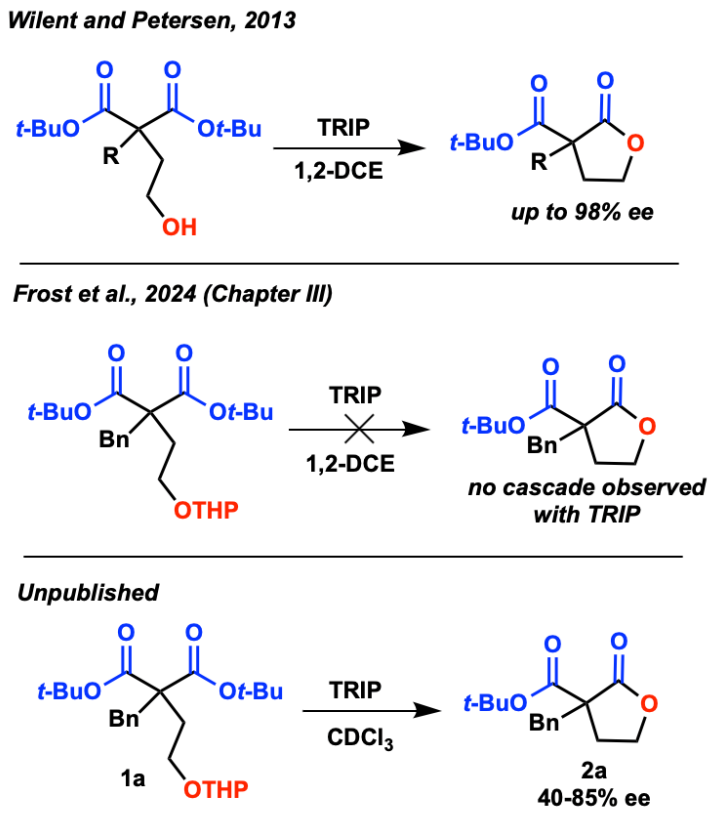
Figure 31. THP-protected substrates to not participate in stereoselective cascade.



Entry	Cpd.	PG	Catalyst	R	Temp. (°C)	Time (h)	Yield (%)	%ee
1	**4aa**	THP	C1	CH_3	25	120	--	--
2	**4ba**	THP	C1	Bn	25	120	--	--
3	**4ba**	THP	C1	Bn	80	120	--	--
4	**4ba**	THP	C3	Bn	25	120	82	0

Serendipitously, we noticed that when THP-protected alcohol substrates IV-**1a** were exposed to deuterated chloroform for elongated periods of time, we were able to obtain the cascade reaction product IV-**2a** with variable enantioselectivities.

Figure 32. Initial results with THP-protected substrates.

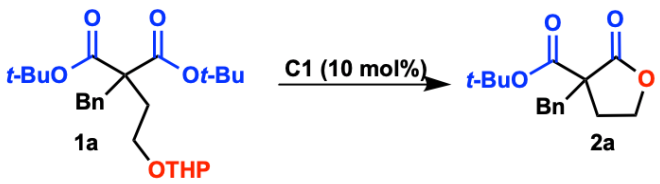


We initially wondered whether this observed stereoselectivity was particular to the deuterated chloroform or some other unrecognized mechanism. Deuterated chloroform is known to be slightly acidic, particularly in the presence of oxygen and light, where chloroform can breakdown to form phosgene and HCl.[49,50] While trace amounts of HCl (or DCl in the case of deuterated chloroform) would make sense to generate reactivity for the acid-sensitive cascade, it does not necessarily explain the observed stereoselectivity.

Nevertheless, we first decided to test whether this observed phenomenon was due to chloroform in particular or some outside mechanism. Initially, we tested whether $CHCl_3$ could effect the same transformation of IV-**1a** to IV-**2a**. At both room temperature and reflux, no conversion was observed with $CHCl_3$ (entries 1 and 2). Next, based on the knowledge that trace

acid impurities could be found in deuterated chloroform samples, we tested whether addition of several varying amounts of HCl additive could mimic the effects seen with deuterated chloroform samples. Somewhat unsurprisingly, addition of 1% HCl is able to catalyze the transformation, but the reaction is not stereoselective (entry 3). Addition of 0.1% HCl, however, catalyzes the cascade reaction and generates the benzyl lactone with 93% ee, albeit with low conversion (entry 4). Furthermore, addition of 0.01% HCl is not enough to cause reactivity under the timescale monitored (entry 5). We also deacidified the deuterated chloroform following standard procedures set by Cambridge Isotope Laboratories;[51] and the deacidified solvent showed no reactivity (entry 6). Finally, we tested whether this transformation was unique to chloroform or could be extended to other solvents. Gratifyingly, both DCE and toluene were tolerated by this co-catalytic system and produced similar enantioselectivity with better conversion when heated to 50°C (entries 7 and 8).

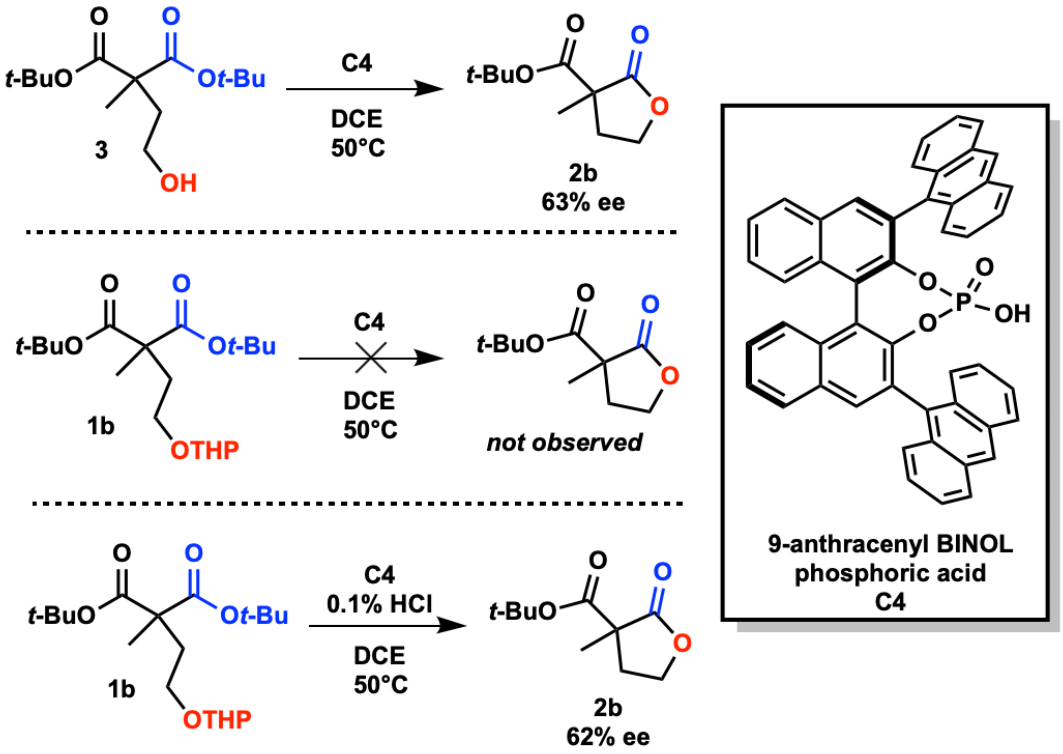
Figure 33. Solvent and additive screen.



Entry	Solvent	Temp. (°C)	Time (h)	% ee	Conv.
1	$CHCl_3$	r.t.	168	--	--
2	$CHCl_3$	50	168	--	--
3	$CHCl_3$ + 1% HCl	50	168	0	30%
4	$CHCl_3$+ 0.1% HCl	50	168	93	30%
5	$CHCl_3$+ 0.01% HCl	50, then 70	168	--	--
6	$CDCl_3$, deacidified	50	120	--	--
7	DCE + 0.1% HCl	50	120	91	100%
8	Toluene + 0.1% HCl	50	120	81	100%

Next, we turned our attention to whether other catalysts could affect the same transformation when paired with our co-catalytic system. To this, we turned to the 9-anthracenyl phosphoric acid catalyst **C4**, which had previously been assessed in the Petersen group for reactivity in a kinetic resolution.[12] For this, we assessed whether reactivity of **C4** could be rescued in our co-catalytic system. With the free alcohol IV-**3**, the lactonization proceeds in 63% ee. With THP-protected substrates, **C4** is unreactive. However, when an HCl additive is introduced, the catalytic system is regenerated and **C4** can catalyze the cascade transformation to IV-**2b** with similar enantioselectivity.

Figure 34. Applicability to other catalysts.



Future Directions and Investigations

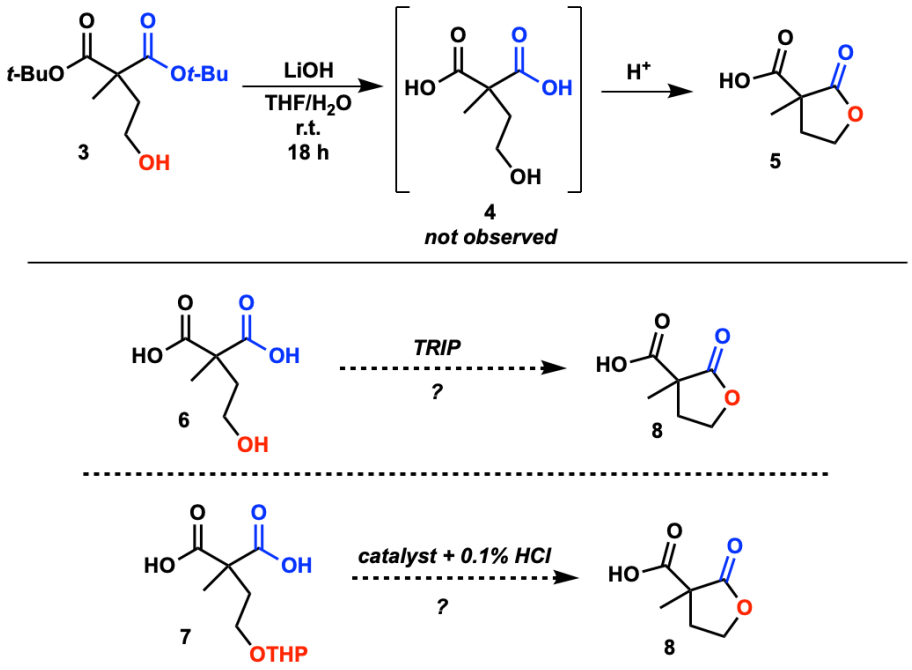
There are several future directions envisioned with these preliminary data. Primarily, they probe the mechanism and the further applicability of the co-catalytic system.

Carboxylic Acid Intermediate?

Given the addition of an acid additive to the catalytic system, we wondered whether the lactonization might be proceeding through a carboxylic acid intermediate IV-**7**. Initial data does not rule out this potential hypothesis – LiOH mediated saponification of the *tert*-butyl ester IV-**3** followed by workup generates the carboxylic acid lactone IV-**5**. Moreover, this transformation is not base-mediated; the carboxylic acid lactone is only generated following an acid workup to quench the LiOH. A few questions are pertinent with this experiment to determine if the reaction proceeds through the carboxylic acid as an intermediate. Will IV-**6** react with TRIP to form IV-

8? If TRIP reacts with IV-**6**, will this reactivity change when subjected to IV-**7** and our cascade conditions?

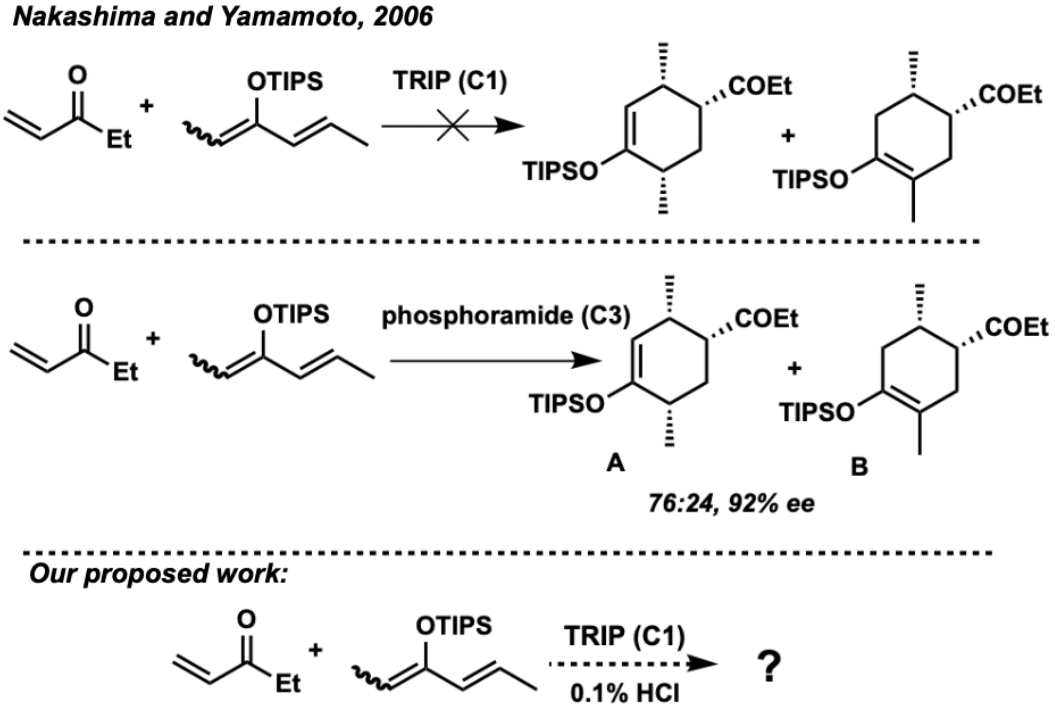
Figure 35. Investigation of potential carboxylic acid intermediate.



Other Reactions

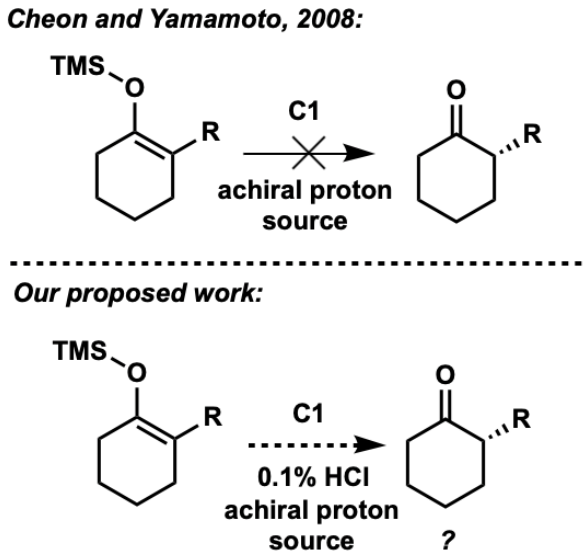
While applicability to our cascade lactonization is interesting, broader applicability to other reactions where BINOL phosphoric acids like TRIP are unreactive is an important future direction. For example, the seminal paper on the publication of the *N*-triflylphosphoramide **C3** showed that **C3** was reactive to a Diels-Alder cycloaddition whereas **C1** was not reactive under similar conditions.[40] Given this, work is currently underway investigating whether the co-catalytic system we developed is reactive and can rescue the reactivity of the Diels-Alder.

Figure 36. Potential applicability to Diels-Alder reaction.



Similarly, we envision testing the co-catalytic system on additional stereoselective reactions where **C1** is unreactive. For example, the asymmetric protonation reaction published by Yamamoto does not proceed with **C1**, but does with **C3**.[41] Future work is ongoing to investigate whether the co-catalytic system can rescue the stereoselective reactivity of **C1** for the protonation reaction.

Figure 37. Potential applicability to stereoselective protonation.



Conclusions

Here, we present preliminary findings of a Brønsted acid assisted Brønsted acid catalyzed system where addition of HCl rescues reactivity for THP-protected alcohols participating in a cascade deprotection/cyclization. Further work is ongoing into investigating our current mechanistic understanding and broader applicability of the system, which could highlight a new synthetic use for BINOL chiral phosphoric acid catalysts.

CHAPTER V: EXPERIMENTAL DATA

General Remarks

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 $CDCl_3$ as solvent at room temperature. 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 on an Orbitrap XL MS system. The specific rotations were acquired on an analytical polarimeter.

Experimental Procedures

Typical Procedure for Malononitrile Formation

To a mixture of alkene malononitrile (1 equivalent) in ethanol (0.25 M), $NaBH_4$ (1 equivalent) was slowly added at 0° C. After stirring for 10 min, the reaction was added to cold water, and 5 M HCl was added until the crude mixture no longer bubbled. The aqueous mixture was extracted with dichloromethane, and the organic layer was dried with $MgSO_4$, filtered and concentrated. The crude material was purified through a silica gel column (20% ethyl acetate/hexanes) to afford the desired product.

2-isopropylmalononitrile (II-**1a**)*:* colorless oil (823 mg, 81% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (d, J = 5.4 Hz, 1 H), 2.36 (m, 1 H), 1.24 (d, J = 6.4 Hz, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.0, 31.3, 30.5, 19.6 ppm. Characterization data matches previously reported.

2-benzylmalononitrile (II-**1b**): white solid (172 mg, 92% yield): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (m, 3 H), 7.32 (m, 2 H), 3.90 (t, *J* = 7.0 Hz, 1 H), 3.28 (t, *J* = 7.0 Hz, 2 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 133.0, 129.4, 129.2, 129.0, 112.2, 36.9, 25.1 ppm. Characterization data matches previously reported.

Typical Procedure for Methyl and Chlorobenzyl Malononitrile Formation

To a mixture of NaH (60% dispersion, 1 equivalent) in THF (0.75 M), malononitrile (1 equivalent) was slowly added at 0° C, followed by methyl iodide or 4-chlorobenzyl chloride (1 equivalent). The reaction was allowed to warm to room temperature and stir overnight. The reaction was quenched with water and then extracted with ethyl acetate. 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 product.

2-methylmalononitrile (II-**1c**)*:* white solid (407 mg, 35% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 3.77 (q, *J* = 7.5 Hz, 1 H), 1.78 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 113.3, 31.1, 17.1, 17.1 ppm. Characterization data matches previously reported.

2-(4-chlorobenzyl)malononitrile (II-**1d**)*:* white solid (1.29 g, 45% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.9 Hz, 2 H), 7.26 (d, *J* = 8.7 Hz, 2 H), 3.89 (t, *J* = 6.8 Hz, 1 H), 3.25 (d, *J* = 6.7 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 131.3, 130.6,129.6, 129.4, 111.9, 36.1, 24.9 ppm. Characterization data matches previously reported.

Typical Procedure for TBS-Protected Methyl Halide Alcohols

To a mixture of diol (1 equivalent) in dichloromethane (0.1 M), N-bromosuccinimide (1 equivalent) and triphenylphosphine (1 equivalent) 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

monobrominated alcohol. The alcohol was used in the next reaction. To a mixture of unprotected alcohol (1 equivalent) in THF (0.2 M), TBSCl (2 eqvuivalents) and imidazole were added (3 equivalents). The reaction stirred overnight and then quenched with water and extracted with ethyl acetate. The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography (20% ethyl acetate/hexanes) to yield the desired product.

(3-Bromo-2-phenylpropoxy)(tert-butyl)dimethylsilane (II-**2a**): colorless oil (2.6 g, 62% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 5 H), 3.77-3.95 (m, 3 H), 3.62 (m, 1 H), 3.12 (m, 1 H), 0.87 (s, 9 H), 0.01 (s, 3 H), -0.01 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) 140.5, 128.5, 128.1, 127.3, 65.1, 50.2, 34.9, 25.9, 18.4, -5.4 ppm; HRMS ($C_{15}H_{25}BrOSi$, ESI): calcd. 329.0931, $[M+H]^+$ found 329.0945.

(3-Bromo-2-methylpropoxy)(tert-butyl)dimethylsilane (II-**2b**): colorless oil (3.3 g, 60% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.55 (m, 1 H), 3.45 (m, 3 H), 1.96 (m, 1 H), 0.97 (d, J = 7.1 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 65.3, 39.1, 37.8, 25.9, 18.3, 15.5, 5.3 ppm. Characterization data matches previously reported.

(3-bromopropoxy)(tert-butyl)dimethylsilane (II-**2c**): colorless oil (5.4 g, 54% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (t, J = 5.7 Hz, 2 H), 3.50 (t, J = 6.3 Hz, 2 H), 2.02 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 60.4, 35.6, 30.8, 25.9, 18.4, 5.2 ppm. Characterization data matches previously reported.

Typical Procedure for Alkylation with Halide Alcohols

To a slurry of NaH (60% dispersion, 1 equivalent) in DMF (0.25 M), the reduced malononitrile II-**1** (1 equivalent) was added slowly followed by alkylating agent II-**2** (0.5 equivalents) at 0° C. The reaction was allowed to warm to room temperature overnight after which

it was quenched with water and extracted with ethyl acetate. 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 desired product.

2-(3-((tert-butyldimethylsilyl)oxy)-2-phenylpropyl)-2-isopropylmalononitrile (II-**3a**): colorless liquid (826 mg, 63% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 5 H), 3.79 (m, 1 H), 3.67 (m, 1 H), 3.13 (m, 1 H), 2.57 (m, 1 H), 2.16 (m, 2 H), 1.18 (d, J = 7.3 Hz, 6 H), 0.88 (s, 9 H), 0.02 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 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 ($C_{21}H_{32}N_2OSi$, ESI): calcd. 357.2357, $[M+H]^+$ found 357.2357.

2-benzyl-2-(3-((tert-butyldimethylsilyl)oxy)-2-phenylpropyl)malononitrile (II-**3b**): colorless oil (380 mg, 33% yield): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.38 (m, 10 H), 3.79 (m, 1 H), 3.66 (m, 1 H), 3.08-3.20 (m, 3 H), 2.64 (m, 1 H), 2.24 (m, 1 H), 0.86 (s, 9 H), -0.01 (s, 6 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): 139.5, 132.1, 130.4, 129.0, 128.9, 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 ($C_{25}H_{32}N_2OSi$, ESI): calcd. 405.2356, $[M+H]^+$ found 405.2346.

2-(3-((tert-butyldimethylsilyl)oxy)-2-phenylpropyl)-2-methylmalononitrile (II-**3c**): colorless oil (620 mg, 52% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5 H), 3.77 (m, 1 H), 3.65 (m, 1 H), 3.10 (m, 1 H), 2.59 (m, 1 H), 2.25 (m, 1 H), 1.70 (s, 3 H), 0.87 (s, 9 H), 0.01 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 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 ($C_{19}H_{28}N_2OSi$, ESI): calcd. 329.2043, $[M+H]^+$ found 329.2039.

2-(3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-2-isopropylmalononitrile (II-**3d**): colorless liquid (920 mg, 91% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (m, 1 H), 3.40 (m, 1 H),

2.17 (m, 2 H), 2.05 (m, 1 H), 1.62 (m, 1 H), 1.24 (d, *J* = 6.3 Hz, 3 H), 1.21 (d, *J* = 6.7 Hz, 3 H) 1.11 (d, *J* = 6.7 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H) 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; HRMS ($C_{16}H_{30}N_2OSi$, ESI): calcd. 295.2200, $[M+H]^+$ found 295.2195.

2-benzyl-2-(3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)malononitrile (II-**3e**): colorless liquid (178 mg, 32% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 5 H), 3.59 (m, 1 H), 3.39 (m, 1 H), 3.20 (s, 2 H), 2.25 (m, 1 H), 2.07 (m, 1 H), 1.69 (m, 1 H), 1.11 (d, *J* = 7.2 Hz, 3 H), 0.86 (s, 9 H) 0.02 (s, 6 H) 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; HRMS ($C_{20}H_{30}N_2OSi$, ESI): calcd. 343.2200, $[M+H]^+$ found 343.2196.

2-(3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(4-chlorobenzyl)malononitrile (II-**3f**): colorless oil (465 mg, 46% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 2 H), 7.31 (m, 2 H), 3.60 (m, 1 H), 3.39 (m, 1 H), 3.17 (s, 2 H), 2.24 (m, 1 H), 2.07 (m, 1 H), 1.69 (m, 1 H), 1.11 (d, *J* = 6.7 Hz, 3 H), 0.86 (s, 9 H) 0.03 (s, 6 H) 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; HRMS ($C_{20}H_{29}ClN_2O$, ESI): calcd. 377.1810, $[M+H]^+$ found 377.1806.

2-(3-((tert-butyldimethylsilyl)oxy)propyl)-2-isopropylmalononitrile (II-**3g**): colorless oil (612 mg, 46% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70 (t, *J* = 5.6 Hz, 2 H), 2.17 (m, 1 H), 2.01 (m, 2 H), 1.86 (m, 2 H), 1.23 (d, *J* = 6.7 Hz, 6 H), 0.88 (s, 9 H), 0.05 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.3, 61.5, 43.7, 35.5, 32.3, 29.0, 25.9, 18.4, -5.3 ppm; HRMS ($C_{15}H_{28}N_2OSi$, ESI): calcd. 281.2043, $[M + H]^+$ found: 281.2042.

2-benzyl-2-(3-((tert-butyldimethylsilyl)oxy)propyl) malononitrile (II-**3h**): white solid (230 mg, 22% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 5 H), 3.69 (t, *J* = 5.6 Hz, 2 H), 3.21 (s,

2 H), 2.05 (m, 2 H), 1.90 (m, 2 H), 0.86 (s, 9 H), 0.03 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.1, 130.3, 129.0, 128.9, 115.4, 61.4, 43.5, 39.2, 34.5, 28.9, 26.0, 18.3, -5.3 ppm; MP = 59.4 - 63.4 °C; HRMS ($C_{19}H_{28}N_2OSi$, ESI): calcd. 329.2043, $[M + H]^+$ found: 329.2040.

Typical Procedure for Alkylation with Halide Alcohols (2 carbon chain)

Alkylated malononitrile II-**1** (1 equivalent) was added to DMF (0.15 M) at 0° C, followed by slow addition of NaH (60% dispersion, 2 equivalents. 2-Bromobutoxy-TBS (2 equivalents) was added, the reaction was brought to room temperature and then added to a 50°C oil bath. The solution was reacted overnight then quenched with water. The solution was extracted with ethyl acetate and dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (10% ethyl acetate/hexanes) to afford the desired product as a colorless oil.

2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-isopropylmalononitrile (II-**3i**): colorless oil (188 mg, 40% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (t *J* = 6.0 Hz, 2 H), 2.23 (sept, *J* = 6.5 Hz, 1 H), 2.11 (t, *J* = 6.0 Hz, 2 H), 1.24 (d, *J* = 6.9 Hz, 6 H), 0.91 (s, 9 H), 0.1 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.0, 59.5, 41.1, 37.3, 36.2, 25.8, 18.3, 5.5 ppm; HRMS ($C_{14}H_{26}N_2O_2Si$, ESI): calcd. 267.1894, $[M + H]^+$ found: 267.1887.

2-benzyl-2-(2-((tert-butyldimethylsilyl)oxy)ethyl)malononitrile (II-**3j**): colorless oil (933 mg, 92% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 5 H), 3.97 (t, *J* = 5.9 Hz, 2 H), 3.28 (s, 2 H) , 2.17 (t, *J* = 5.9 Hz, 2 H), 0.91 (s, 9 H), 0.1 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.1, 130.5, 128.9, 128.8, 115.2, 59.3, 44.0, 39.1, 36.9, 25.9, 18.3, -5.5 ppm; HRMS ($C_{18}H_{26}N_2O_2Si$, ESI): calcd. 315.1887, $[M + H]^+$ found: 315.1886.

Typical Procedure for δ Lactones

To a mixture of alkylated malononitrile II-**1** (1 equivalent) in THF (0.2 M), TBAF (1M THF, 3 equivalents) was added at 0° C. The reaction was stirred at 0° C for 1 hour, and the reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purified crude material through a silica gel column to afford the desired product. To a mixture of the above product (1 equivalent) in 1,2-dichloroethane (0.025 M), methyl sulfonic acid (2 equivalents) was added. The reaction was stirred for one hour at 80° C. The reaction mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified through a short plug of silica and rinsed with dichloromethane to afford lactone as a colorless oil. The NMR of the major diastereomer is reported.

3-isopropyl-2-oxo-5-phenyltetrahydro-2H-pyran-3-carbonitrile (II-**8aa**): colorless oil (86 mg, 75% yield): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.42 (m, 3 H), 7.24 (m, 2 H), 4.59 (m, 1 H), 4.29 (t, *J* = 5.7 Hz, 1 H), 3.52 (m, 1 H), 2.76 (m, 1 H), 2.36 (m, 1 H), 2.21 (t, *J* = 6.8, 1 H), 1.19 (d, *J* = 6.5 Hz, 3 H), 1.09 (d, *J* = 6.7 Hz, 3 H) 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 ($C_{15}H_{17}NO_2$, ESI): calcd. 244.0896, $[M+H]^+$ found 244.0886.

3-benzyl-2-oxo-5-phenyltetrahydro-2H-pyran-3-carbonitrile (II-**8ba**)*:* white solid (66 mg, 73% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 8 H), 7.13 (m, 2 H), 4.57 (m, 1 H), 4.14 (m, 1 H), 3.51 (m, 2 H), 3.34 (d, *J* = 14.4 Hz, 1 H), 2.29 (m, 1 H), 2.17 (m, 1 H) 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; MP = 152.5-155.6 °C; HRMS ($C_{19}H_{17}N_2O$, ESI): calcd. 292.1332, $[M+H]^+$ found 292.1239.

3-methyl-2-oxo-5-phenyltetrahydro-2H-pyran-3-carbonitrile (II-**8ca**)*:* white solid (37 mg, 70% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.19 (m, 5 H), 4.66 (m, 1 H), 4.33 (m, 1 H), 3.61 (m, 1 H), 2.57 (m, 1 H), 2.21 (m, 1 H), 1.77 (s, 3 H) 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; MP = 135.6-137.0 °C; HRMS ($C_{13}H_{13}NO_2$, ESI): calc. 216.1019, $[M+H]^+$ found 216.1018.

3-(4-chlorobenzyl)-5-methyl-2-oxotetrahydro-2H-pyran-3-carbonitrile (II-**8da**)*:* white solid (37 mg, 70% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 2 H), 7.22 (m, 2 H), 4.44 (m, 1 H), 3.79 (m, 1 H), 3.41 (d, *J* = 14.0 Hz, 1 H), 3.23 (d, *J* = 13.9 Hz, 1 H), 2.42 (m, 1 H), 2.02 (m, 1 H), 1.55 (m, 1 H), 0.97 (d, *J* = 6.8 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 134.2, 131.8, 129.1, 126.7, 118.8, 76.1, 44.6, 41.7, 37.6, 26.4, 16.1 ppm; MP = 164.4 – 170.7 °C; HRMS ($C_{14}H_{14}ClNO_2$, ESI): calcd. 296.1048, $[M+H+CH_3CH_3OH]^+$ found 296.1047.

3-isopropyl-5-methyl-2-oxotetrahydro-2H-pyran-3-carbonitrile (II-**8ea**): white solid (147 mg, 98% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.40 (m, 1 H), 3.87 (m, 1 H), 2.66 (m, 1 H), 2.39 (m, 1 H), 2.11 (m, 1 H), 1.62 (m, 1 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.7, 75.8, 48.8, 35.0, 33.6, 26.6, 17.4, 16.1 ppm; HRMS ($C_{10}H_{15}NO_2$, ESI): calc. 182.1176, $[M+H]^+$ found 182.1179.

3-benzyl-5-methyl-2-oxotetrahydro-2H-pyran-3-carbonitrile (II-**8fa**)*:* white solid (racemic: 55 mg, 92% yield; enantioenriched: 216 mg, 98% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 5 H), 4.40 (m, 1 H), 3.75 (m, 1 H), 3.44 (d, *J* = 14.0 Hz, 1 H), 3.25 (d, *J* = 14.1 Hz, 1 H), 2.38 (m, 1 H), 2.02 (m, 1 H), 1.59 (m, 1 H), 0.94 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}CNMR (100 MHz, $CDCl_3$): δ 165.0, 133.4, 130.5, 128.9, 128.1, 119.1, 76.1, 49.7, 42.5, 37.6, 26.4, 16.1 ppm; MP = 132.76-137.9 °C; HRMS ($C_{14}H_{15}NO_2$, ESI): calcd. 230.1176, $[M+H]^+$ found 230.1183.

$[\alpha]_D^{23}$ = -18.4 (c = 0.5 in chloroform). %ee = 99%, HPLC: 30.372 min. Spectral data given for enantioenriched compound.

3-isopropyl-2-oxotetrahydro-2H-pyran-3-carbonitrile (II-**5a**)*:* colorless oil (93 mg, 74%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.55 (m, 1 H), 4.34 (m, 1 H), 2.61 (sept, 1 H), 1.95-2.27 (m, 4 H), 1.16 (d, *J* = 7.0 Hz, 3 H), 1.03 (d, *J* = 6.7 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 119.2, 70.5, 49.0, 34.2, 26.2, 20.4, 17.8, 17.5 ppm; HRMS ($C_9H_{13}NO_2$, ESI): calcd. 168.1019, $[M + H]^+$ found: 168.1015.

3-benzyl-2-oxotetrahydro-2H-pyran-3-carbonitrile (II-**5b**)*:* white solid (53 mg, 64% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 4.52 (m, 1 H), 4.29 (m, 1 H), 3.44 (d, *J* = 13.8 Hz, 1 H), 3.25 (d, *J* = 13.9 Hz, 1 H), 2.11 (m, 2 H), 1.95 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 133.4, 130.5, 128.9, 128.2, 118.9, 70.6, 44.7, 42.1, 29.4, 20.0 ppm; MP = 83.4 - 86.3 °C; HRMS ($C_{13}H_{13}NO_2$, ESI): calcd. 238.0839, $[M + Na]^+$ found: 238.0837.

Typical Procedure for γ Lactones

TBS protected alkylated malononitrile II-**3i** or II-**3j** (1 equivalent) was added to THF (0.13 M) at 0° C, followed by TBAF (1M THF, 3 equivalents). The reaction was allowed to proceed for 1 hour and quenched with water. The solution was extracted with ethyl acetate, dried with $MgSO_4$ then concentrated in vacuo. The crude material was purified with silica gel chromatography (30% ethyl acetate/hexanes) to yield the colorless oil as the product.

3-isopropyl-2-oxotetrahydrofuran-3-carbonitrile (II-**6a**)*:* colorless oil (140 mg, 36% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.40 (m, 2 H), 2.63 (m, 1 H), 2.45 (m, 1 H), 2.32 (m, 1 H), 1.23 (d, *J* = 6.8, 3 H), 1.07 (d, *J* = 6.7, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 117.2, 65.7, 47.6, 32.7, 30.4, 18.2, 17.9 ppm; HRMS ($C_8H_{11}NO_2$, ESI): calcd. 154.0862, $[M + H]^+$ found: 154.0856.

3-benzyl-2-oxotetrahydrofuran-3-carbonitrile (II-**6b**)*:* colorless oil (84 mg, 82% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 5 H), 4.36 (m 1 H), 4.05 (m 1 H), 3.34 (d, J = 13.8 Hz, 1 H), 3.17 (d, J = 13.8 Hz, 1 H), 2.58 (m, 1 H), 2.44 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 133.1, 130.0, 129.2, 128.5, 117.4, 65.9, 43.9, 40.2, 32.4 ppm; HRMS ($C_{12}H_{11}NO_2$, ESI): calcd. 202.0862, $[M+H]^+$ found 202.0861.

Procedure for Diesterification

Compound (III-**2a**): To a mixture of methyl malonic acid (0.6 g, 4.8 mmol) **1a** in diethyl ether (2.5 mL) was added 4-(dimethylamino)pyridine (0.06 g, 0.4 mmol), *t*-butyl alcohol (7.5 mL), and di-*t*-butyl dicarbonate (2.4 g, 10.7 mmol). The mixture was stirred at room temperature for 48 hours, after which the reaction mixture was quenched with water (20 mL) and 1M HCl (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with 0.5M NaOH (2 x 20 mL). The organic layer was dried over magnesium sulfate and concentrated, affording the product III-**2a** as a colorless oil (687 mg, 61% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.21 (q, J = 7.2 Hz, 1H), 1.45 (s, 18H), 1.31 (d, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 81.3, 48.2, 27.9, 13.5; Data matches previously reported.[37]

Procedure for Protection Reactions

Compound (III-**3a**): To a solution of 2-bromoethanol (1.5 mL, 21.2 mmol) in CH_2Cl_2 (21 mL) at 0°C was added pyridinium *p*-toluene sulfonate (0.5 g, 2.1 mmol). 3,4-Dihydro-2H-pyran (2.9 mL, 31.8 mmol) was added, and the reaction allowed to warm to room temperature for 16 h. The reaction was quenched with 20 mL of deionized water, extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The crude oil was purified via flash chromatography (10% ethyl acetate in hexanes) to afford III-**3a** as a colorless oil (4.23 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (m, 1H), 3.99 (m, 1H), 3.86

(m, 1H), 3.74 (m, 1H), 3.49 (m, 3H), 1.47-1.88 (br m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.0, 67.6, 62.3, 30.9, 29.9, 25.4, 19.3; Data matches previously reported.[52]

Compound III-**3c**: To a solution of 2-bromoethanol (0.3 mL, 4.4 mmol) in CH_2Cl_2 (10 mL) at room temperature was added triethylamine (1.5 mL, 11.1 mmol) and chlorotriethylsilane (0.7 mL, 4.43 mmol). The reaction mixture was stirred for 16 h. The reaction was quenched with 10 mL deionized water, extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were dried over magnesium sulfate and concentrated to afford **3c** as a colorless oil (1.01 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (t, J = 6.7 Hz, 2H), 3.39 (t, J = 6.6 Hz, 2H), 0.95 (t, J = 7.9 Hz, 9H), 0.61 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.3, 33.2, 6.7, 4.4; Data matches previously reported.[53]

Typical Procedure for Alkylation Reactions

To a solution of malonate starting material (1.1 equiv.) in THF (0.3 M) in an ice bath is added NaH (60% dispersion in mineral oil, 2 equiv.). After 5 minutes, the alkylating agent (1 equiv.) is added, and the reaction mixture moved to a 50°C oil bath and allowed to stir for 24 hours, or until completion is observed via TLC. The reaction mixture is quenched with a saturated brine solution (20 mL), extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were dried over magnesium sulfate and concentrated. The crude material was purified via flash column chromatography (10% ethyl acetate in hexanes) to afford the alkylated malonate.

Compound III-**2b**: colorless oil (1.23 g, 69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 3H), 7.19 (m, 2H), 3.45 (t, J = 8 Hz, 1H), 3.11 (d, J = 8 Hz, 2H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 138.3, 129.0, 128.4, 126.5, 81.6, 55.6, 34.6, 27.9; Data matches previously reported.[36]

Compound III-**4aa**: yellowish oil (125 mg, 73% yield);^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (m, 1H), 3.80 (m, 2H), 3.45 (m, 2H), 2.13 (m, 2H), 1.74 (m, 2H), 1.55 (m, 2H), 1.49 (m, 2H), 1.47 (s, 3H), 1.44 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 98.9, 81.1, 63.7, 62.2, 53.3, 34.9, 30.6, 27.9, 25.5, 19.9, 19.5; HRMS ($C_{19}H_{34}O_6$, ESI) calcd 359.2428 $[M + H]^+$, found 359.2424.

Compound III-**4ab**: colorless oil (105 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (s, 2H), 3.55 (t, J = 7.0 Hz, 2H), 3.33 (s, 3 H), 2.11 (t, J = 7.0 Hz, 2H), 1.43 (s, 18H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 96.3, 81.1, 63.7, 55.3, 53.2, 34.9, 27.9, 19.7; HRMS ($C_{16}H_{30}O_6$, ESI) calcd 341.1935 $[M + Na]^+$, found 341.1934.

Compound III-**4ba**: colorless oil (171 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 3H), 7.18 (m, 2H), 4.66 (m, 1H), 4.00 (m, 1H), 3.88 (m, 1H), 3.75 (m, 1H), 3.50 (m, 3H), 3.11 (d, J = 7.1 Hz, 2H), 1.83 (m, 1H), 1.72 (m, 2H), 1.53 (m, 4H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 138.3, 129.0, 128.4, 126.5, 99.0, 81.6, 67.6, 62.3, 55.6, 34.6, 27.9, 27.7, 25.4, 19.3; HRMS ($C_{25}H_{38}O_6$, ESI) calcd 435.2741 $[M + H]^+$, found 435.2743.

Compound III-**4bb**: colorless oil (543 mg, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 5H), 4.57 (s, 2H), 3.61 (t, J = 7.0 Hz, 2H), 3.34 (s, 3H), 3.21 (s, 2H), 2.04 (t, J = 6.9 Hz, 2H), 1.44 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 136.5, 130.3, 128.2, 126.8, 96.3, 81.6, 63.7, 57.9, 55.3, 38.0, 31.5, 27.9; HRMS ($C_{22}H_{34}O_6$, ESI) calcd 395.2428 $[M + H]^+$, found 395.2430.

Compound III-**4bc**: colorless oil (159 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 5H), 3.66 (t, J = 7.6 Hz, 2H), 3.19 (s, 2H), 2.00 (t, J = 7.6 Hz, 2H), 1.43 (s, 18H), 0.93 (t, J = 7.9 Hz, 9H), 0.57 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 136.7, 130.4,

128.1, 126.7, 81.5, 59.3, 58.0, 38.4, 34.4, 27.9, 6.8, 4.3; HRMS ($C_{26}H_{44}O_5Si$, ESI) calcd 465.3031 $[M + H]^+$, found 465.3033.

Compound III-**4cb**: yellowish oil (268 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (s, 2H), 3.49 (t, 2H), 3.32 (s, 3H), 2.12 (t, 2H), 1.86 (q, 2H), 1.42 (s, 1H), 0.80 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 96.3, 81.1, 63.5, 57.2, 55.3, 30.9, 27.9, 24.9, 8.4; HRMS ($C_{17}H_{32}O_6$, ESI) calcd 332.2199 $[M + H]^+$, found 332.2197.

Compound III-**7b**: yellowish oil (848 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 3H), 7.09 (m, 2H), 4.55 (s, 2H), 4.16 (q, J = 7.2 Hz, 4H), 3.62 (t, J = 6.7 Hz, 2H), 3.34 (s, 3H), 3.28 (s, 2H), 2.10 (t, J = 6.6 Hz, 2H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 136.1, 130.1, 128.3, 127.0, 96.4, 63.6, 61.3, 57.1, 55.3, 38.5, 31.8, 14.0; HRMS ($C_{18}H_{26}O_6$, ESI) calcd 339.1802 $[M + H]^+$, found 339.1806.

Compound III-**9a**: colorless oil (651 mg, 46% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (t, J = 6.4 Hz, 2H), 2.04 (t, J = 6.4 Hz, 2H), 1.44 (s, 18H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 81.6, 59.0, 53.7, 38.2, 27.9, 20.2; Data matches previously reported.[36]

Typical Procedure for Deprotection/Cyclization Cascade

To a solution of dialkylated protected starting material (1 equiv.) in 1,2-dichloroethane (0.025 M) at room temperature is added catalyst (**C1**-**C3**, 0.1 equiv.) and transferred to an 80°C oil bath and stirred for 72 hours or until reaction completion is determined by TLC analysis. The reaction mixture is quenched with deionized water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers are washed with brine (1 x 10 mL), dried over magnesium sulfate, and concentrated. The crude material was purified via flash column chromatography (20% ethyl acetate in hexanes) to afford the cyclized product.

Compound III-**5a**: colorless oil (10 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (m, 2H), 2.66 (m, 1H), 2.15 (m, 1H), 1.45 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 169.5, 82.9, 65.9, 50.5, 35.2, 27.8, 20.1; 93% ee; $[\alpha]_D^{23}$ = – 2.9 (c = 1.1, $CHCl_3$); Data matches previously reported.[36]

Compound III-**5b**: yellowish oil (11 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 3H), 7.18 (m, 2H), 4.20 (q, J = 8.2 Hz, 1H), 3.84 (td, J = 8.7, 4.1 Hz, 1H), 3.30 (m, 2H), 2.62 (m, 1H), 2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 170.0, 135.3, 130.1, 128.8, 127.5, 66.3, 55.5, 53.4, 39.3, 30.5; 67% ee; $[\alpha]_D^{23}$ = + 15.1 (c = 1.7, $CHCl_3$); Data matches previously reported.[36]

Compound III-**5c**: yellowish oil (x mg, x yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (m, 2H), 2.64 (m, 1H), 2.18 (m, 1H), 2.05 (m, 1H), 1.79 (m, 1H), 1.46 (s, 9H), 0.95 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ; 60% ee; $[\alpha]_D^{23}$ = - 1.1 (c = 1.9, $CHCl_3$); Data matches previously reported.[36] Opposite enantiomer catalyst used.

Compound III-**8b**: colorless oil (14 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 3H), 7.20 (m, 2H), 4.26 (m, 2H), 3.85 (td, J = 8.7, 4.0 Hz, 1H), 3.29 (m, 2H), 2.62 (m, 1H), 2.28 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 169.6, 135.4, 130.1, 128.8, 127.5, 66.3, 62.5, 55.5, 39.1, 30.6, 14.1; HRMS ($C_{14}H_{16}O_4$, ESI) calcd 249.1121 $[M + H]^+$, found 249.1116.

Gas Chromatography Experiments

GC Conditions: Column: Agilent 19091G-B213; 0 m x 320 μm x 0.25 μm; Flow Rate: 1 mL/min; Temperature Ramp: 75°C for 5 min, ramp 15°C/min → 300°C, 300°C for 30 min.

Rate Experiment. For the rate experiment, a 15 mg sample of III-**4aa** or III-**4ab** was dissolved in DCE and 10 mol% **C3** was added, and the reaction allowed to proceed at room

temperature. A GC sample was taken at 0, 10, 24, 34, 48, 58, and 72 hours to assess overall conversion. Controls of III-**4aa/ab**, III-**5a**, and III-**9a** were used as standards in the experiment.

Titration Experiment. For the titration experiment, a sample of 10 mol% (relative to 15 mg III-**4aa/ab**) was dissolved in DCE and allowed to stir at 80°C. 0.2 equivalents of III-**4aa** or III-**4ab** were added every 12 hours, up to 1 equivalent of III-**4aa/ab**. GC samples were taken prior to addition of III-**4aa/ab** and prior to every subsequent addition of 0.2 equivalents.

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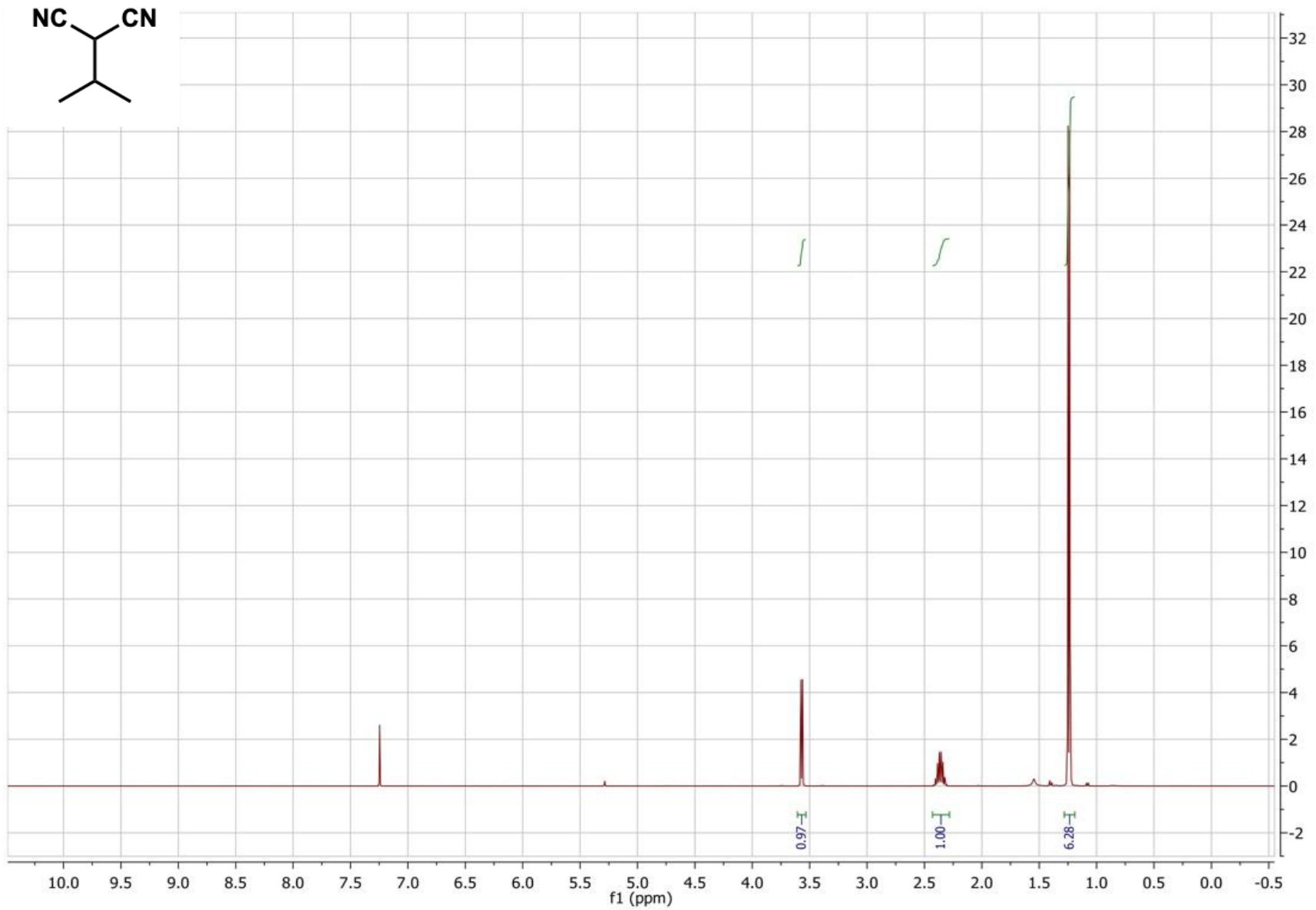
APPENDIX A: NMR SPECTRA

The 1H and 13C nuclear magnetic resonance (NMR) spectra were plotted on 400 and 500 MHz spectrometer using CDCl3 as a solvent at rt. The NMR chemical shifts (δ) are reported in ppm.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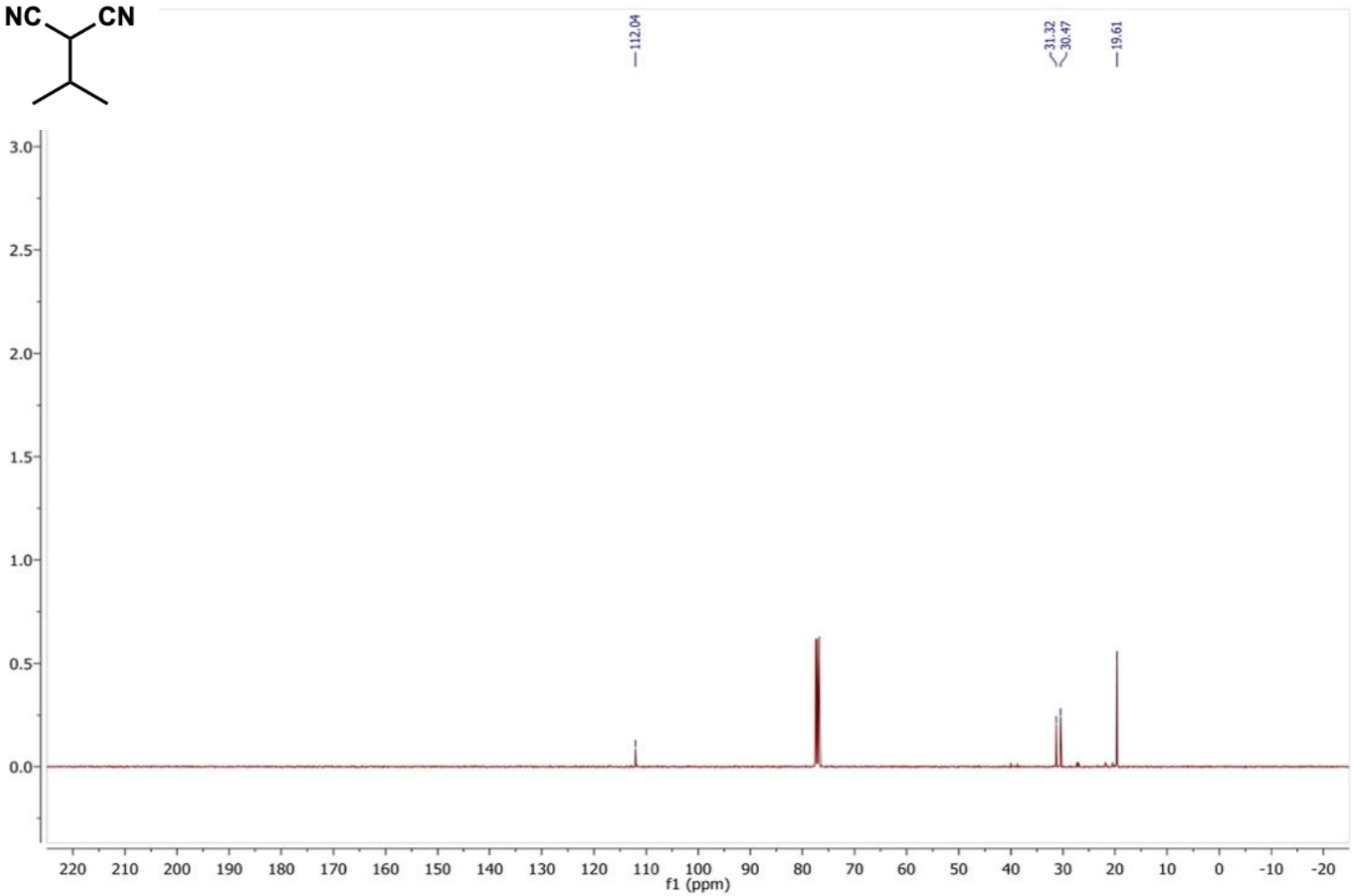
6.28
f1 (ppm)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CN
112.04
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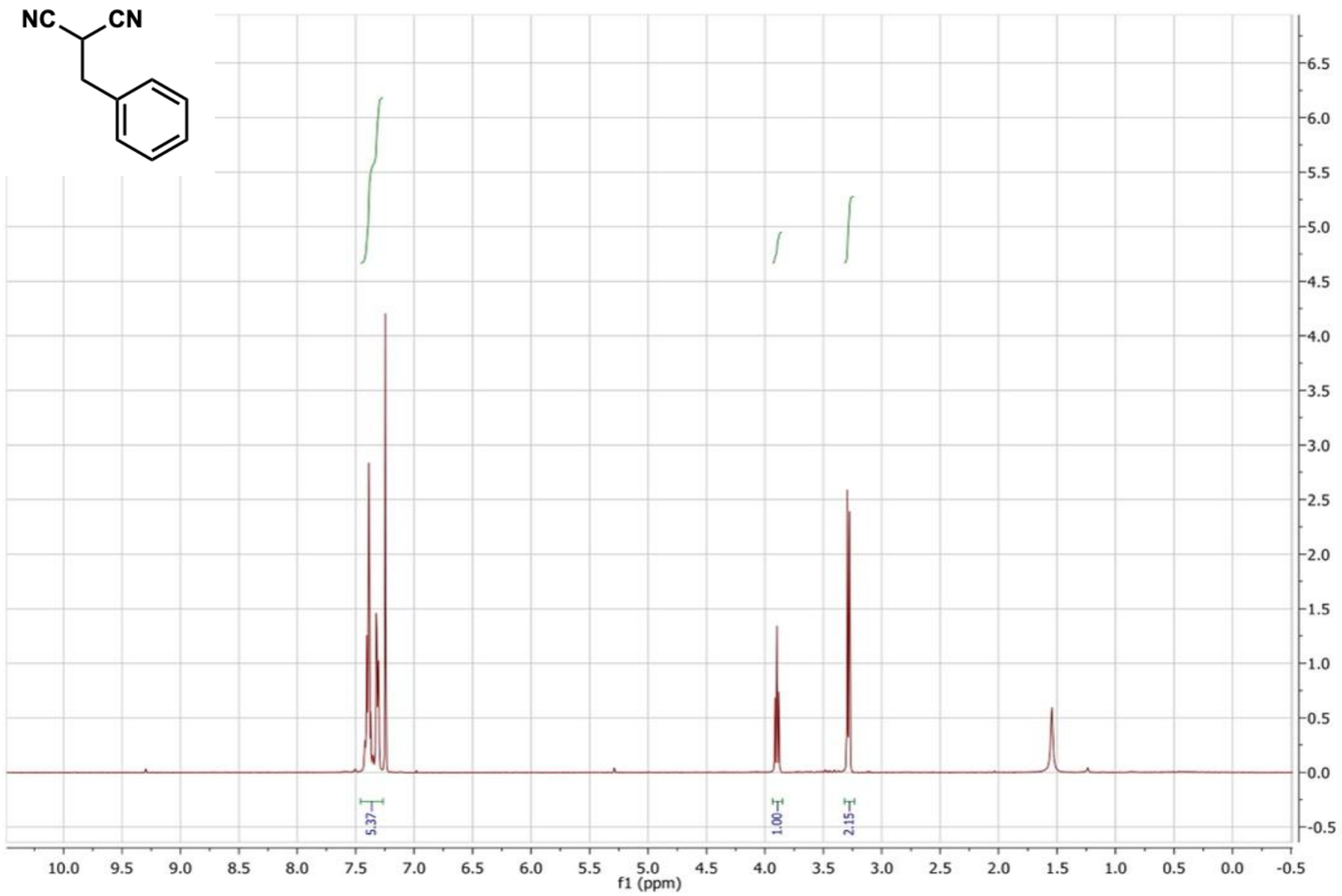
19.61
3.0
2.5
2.0
1.5
1.0
0.5
0.0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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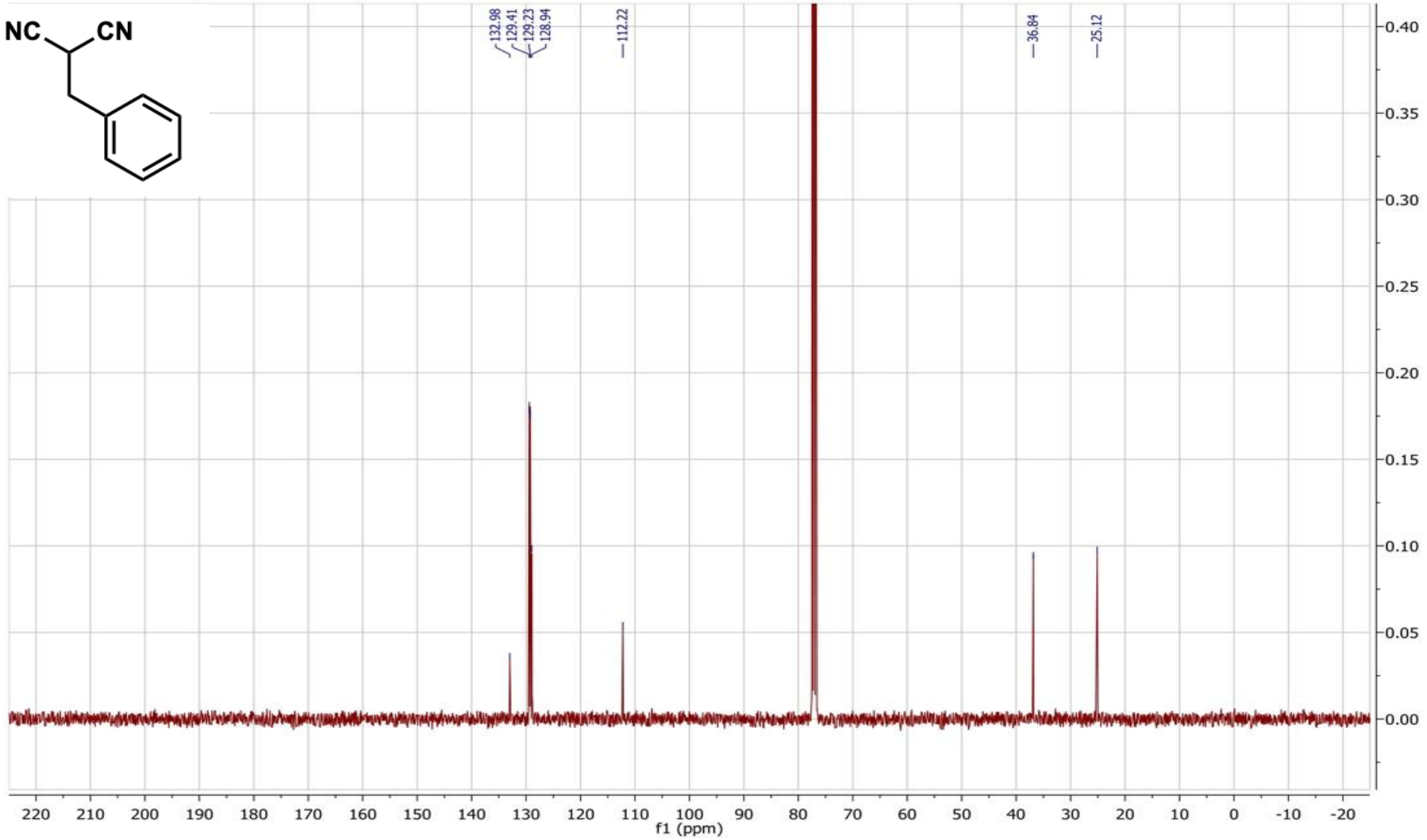
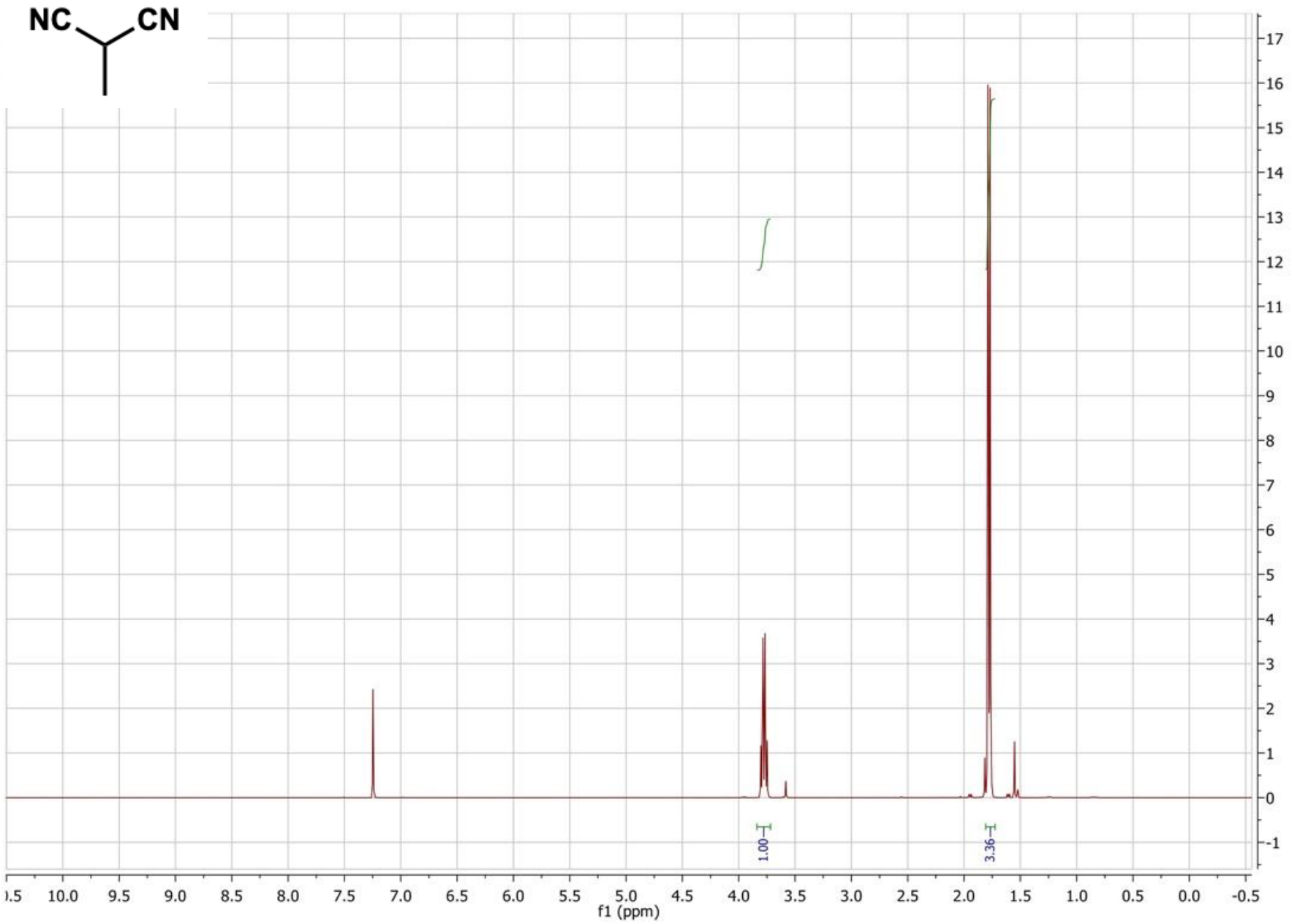
2.15
f1 (ppm)


NC
CN
132.98
129.41
129.23
128.94
112.22
36.84
25.12
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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CN
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3.36
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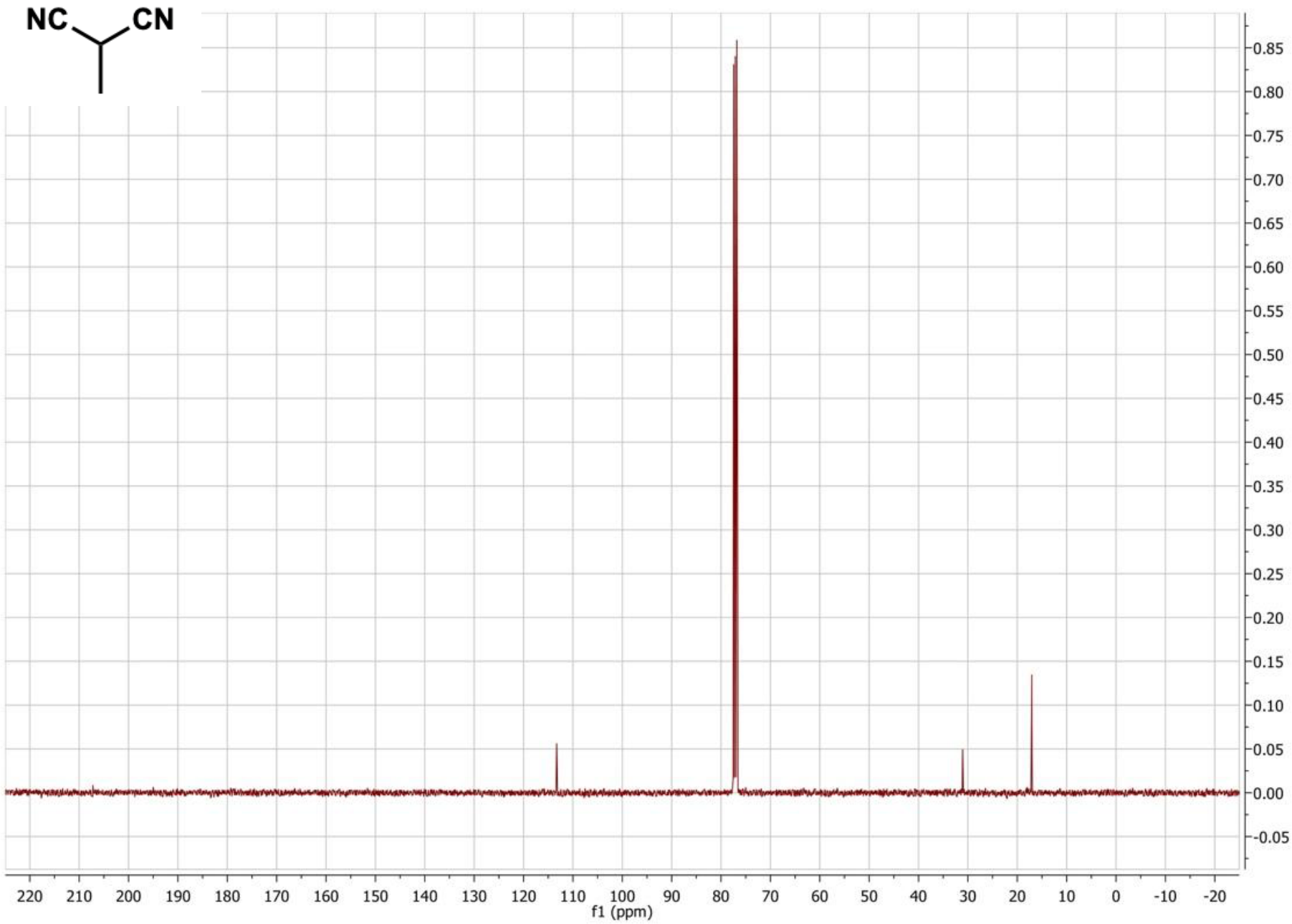
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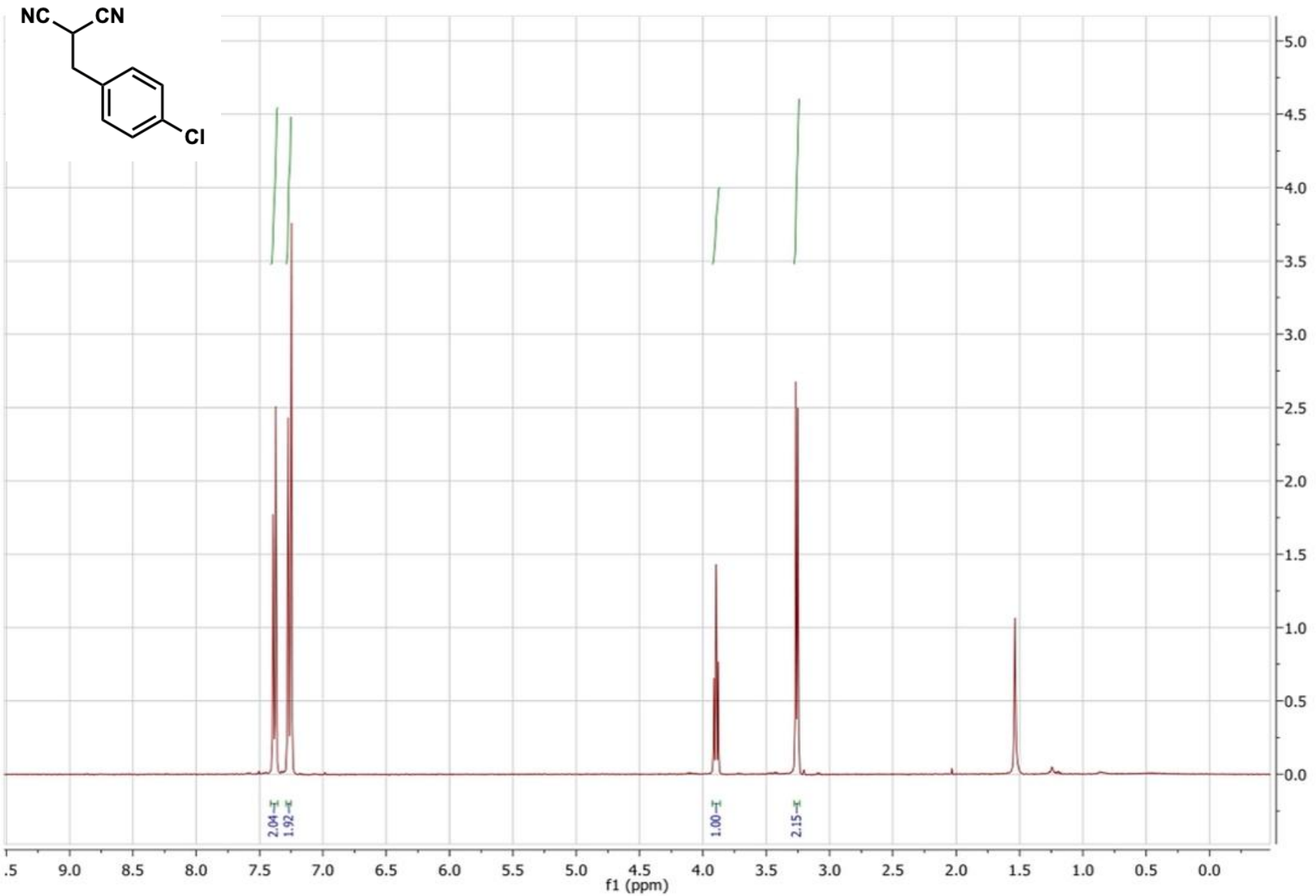
CN
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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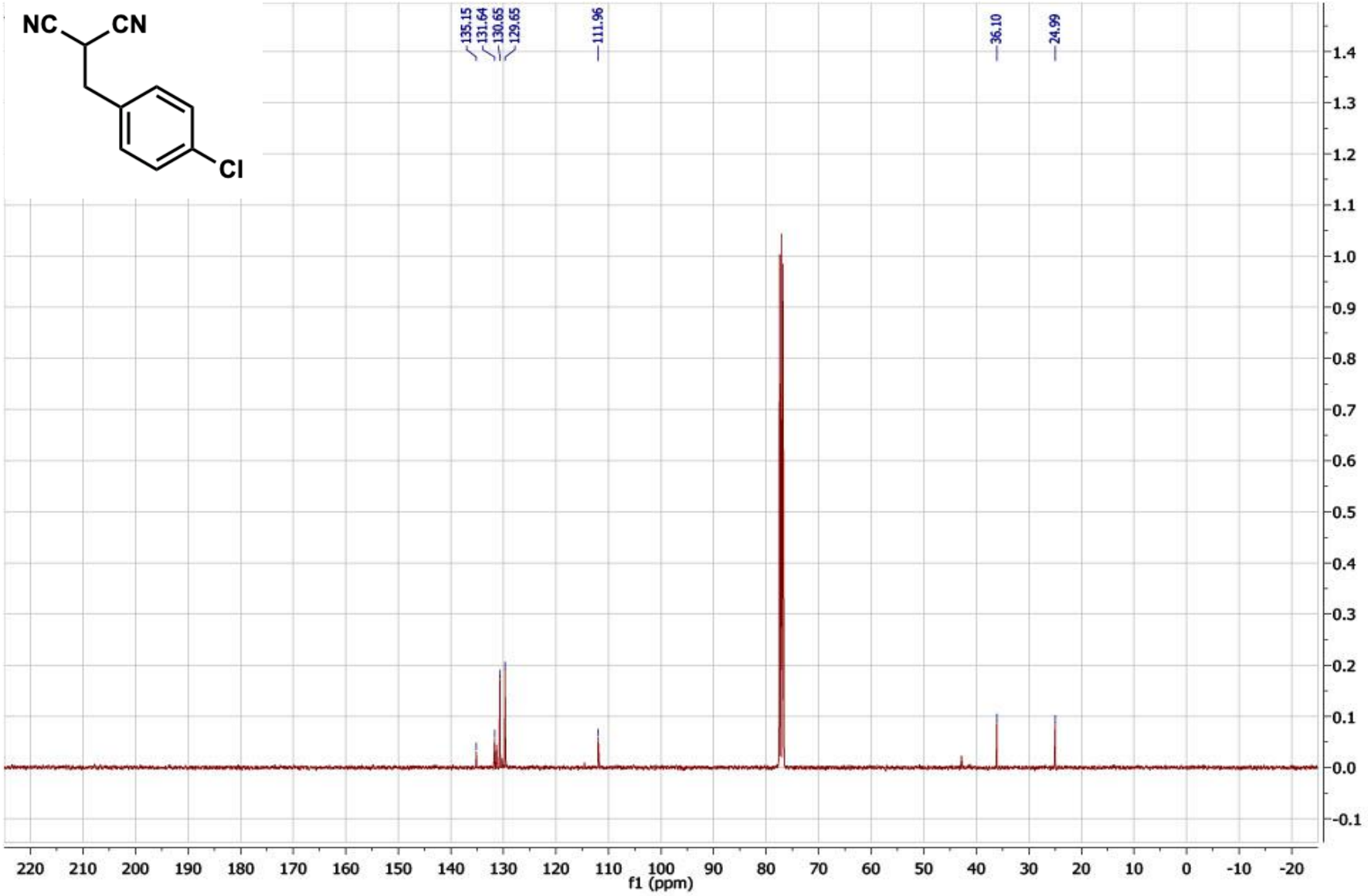
2.15
f1 (ppm)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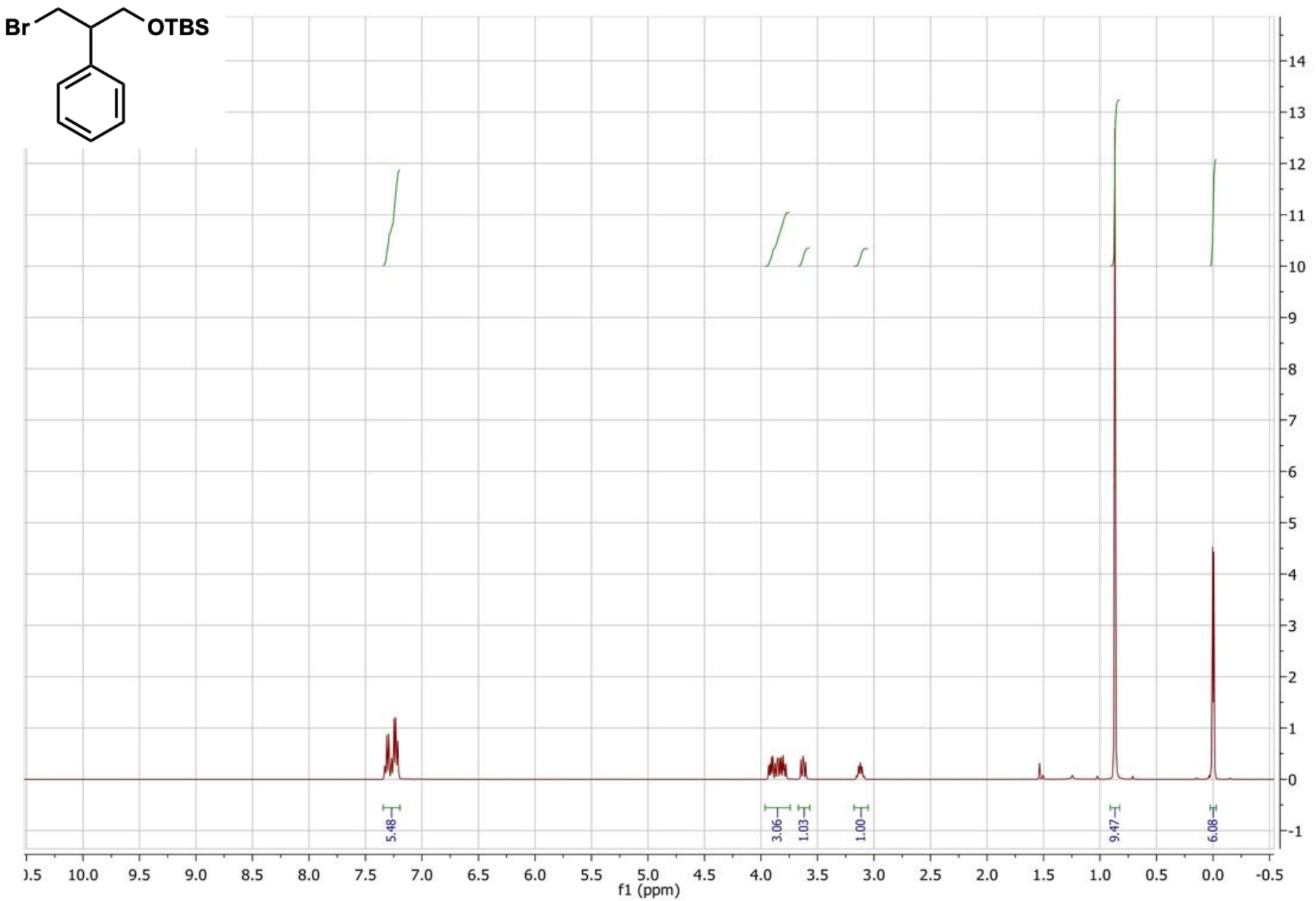
129.65
111.96
36.10
24.99
f1 (ppm)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9.47
6.08
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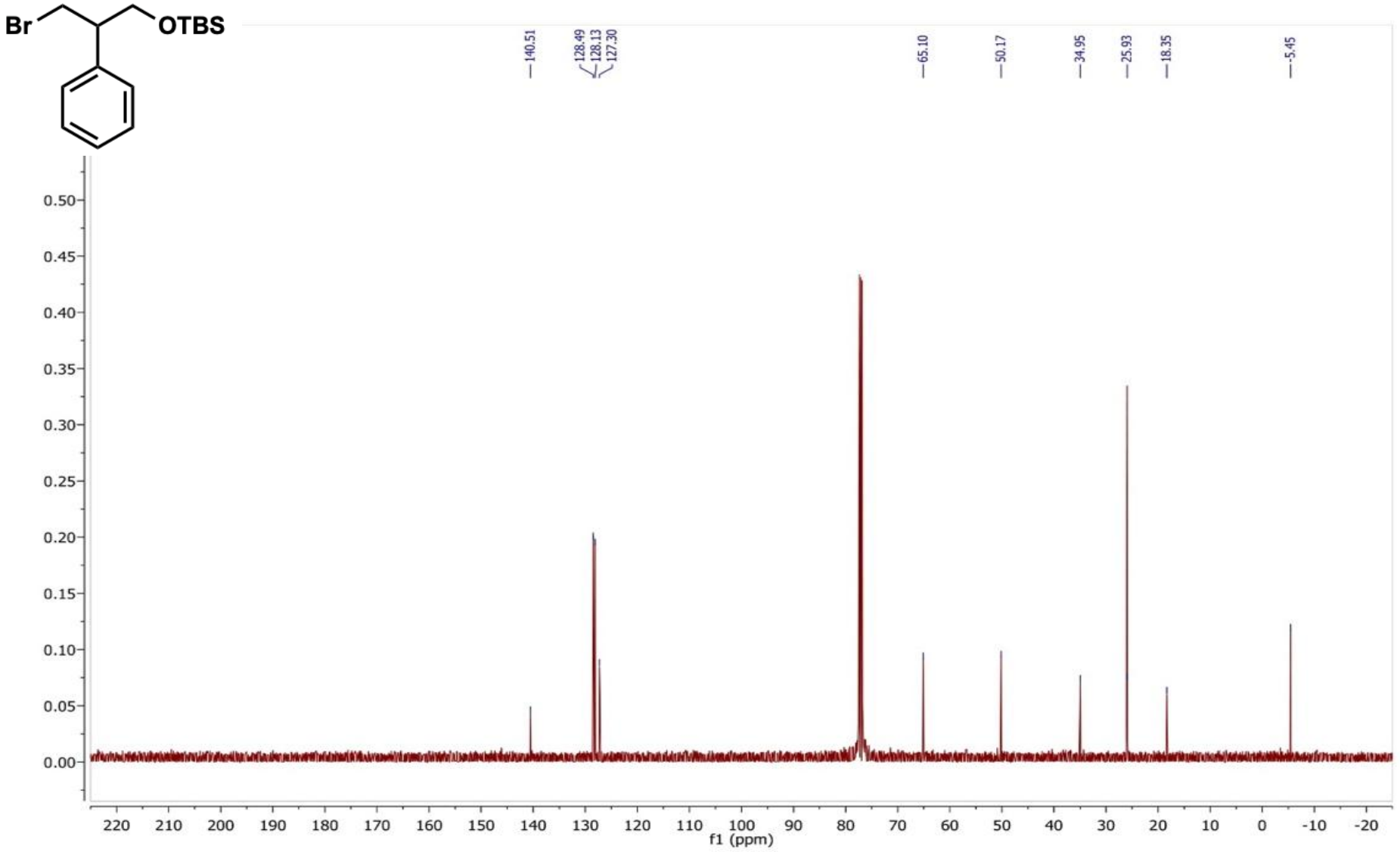
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OTBS
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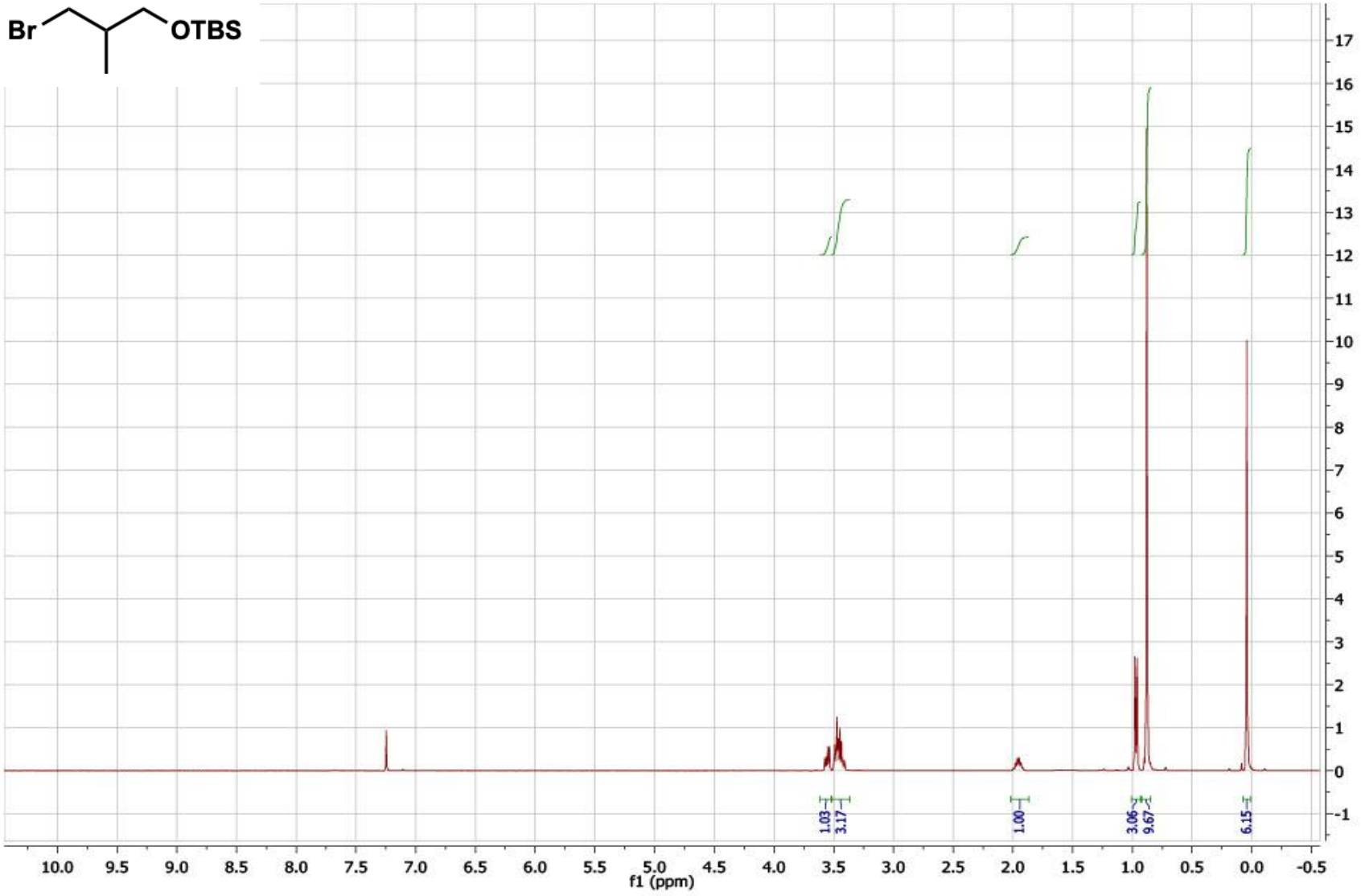
128.49
128.13
127.30
65.10
50.17
34.95
25.93
18.35
-5.45
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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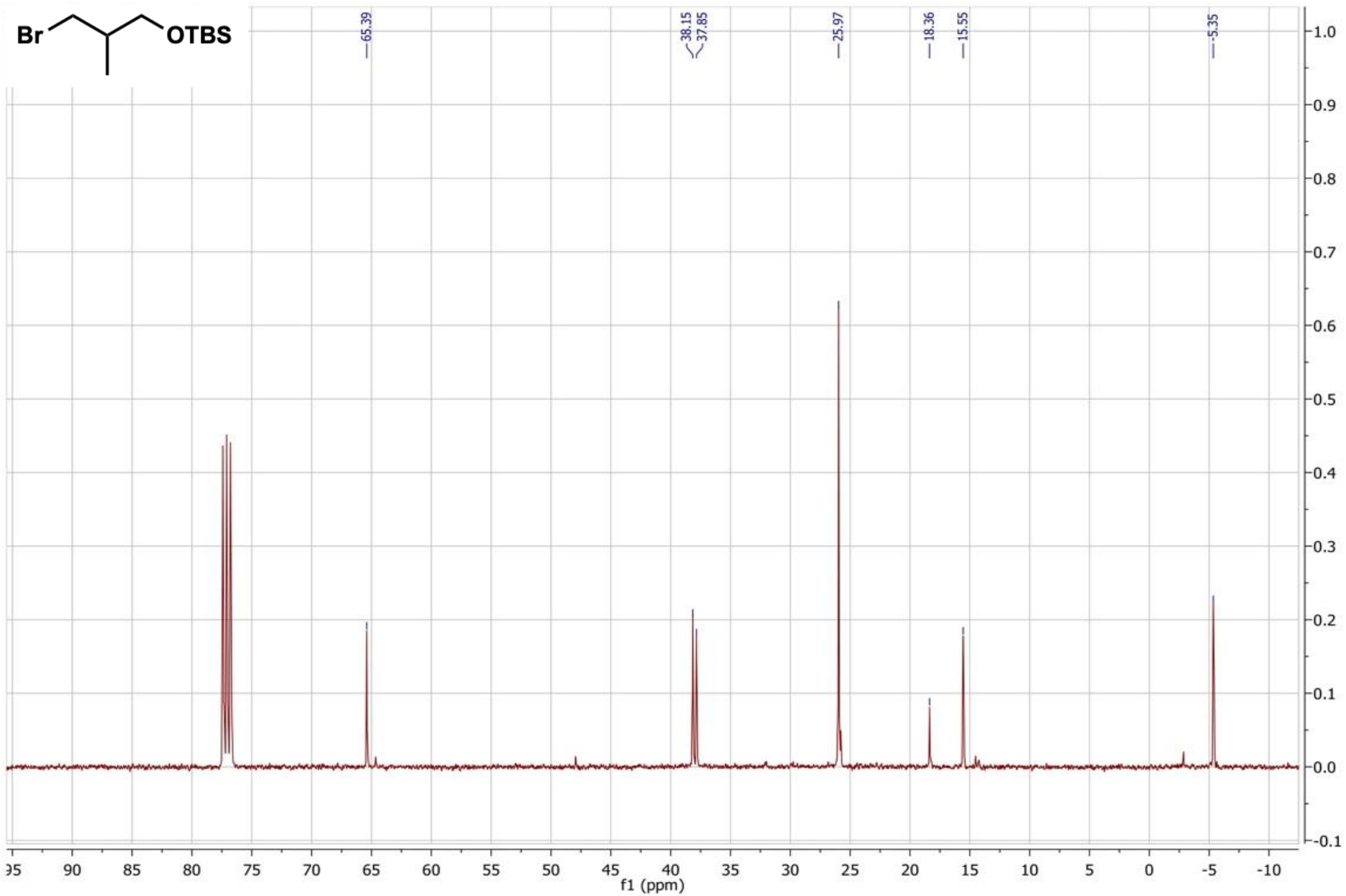
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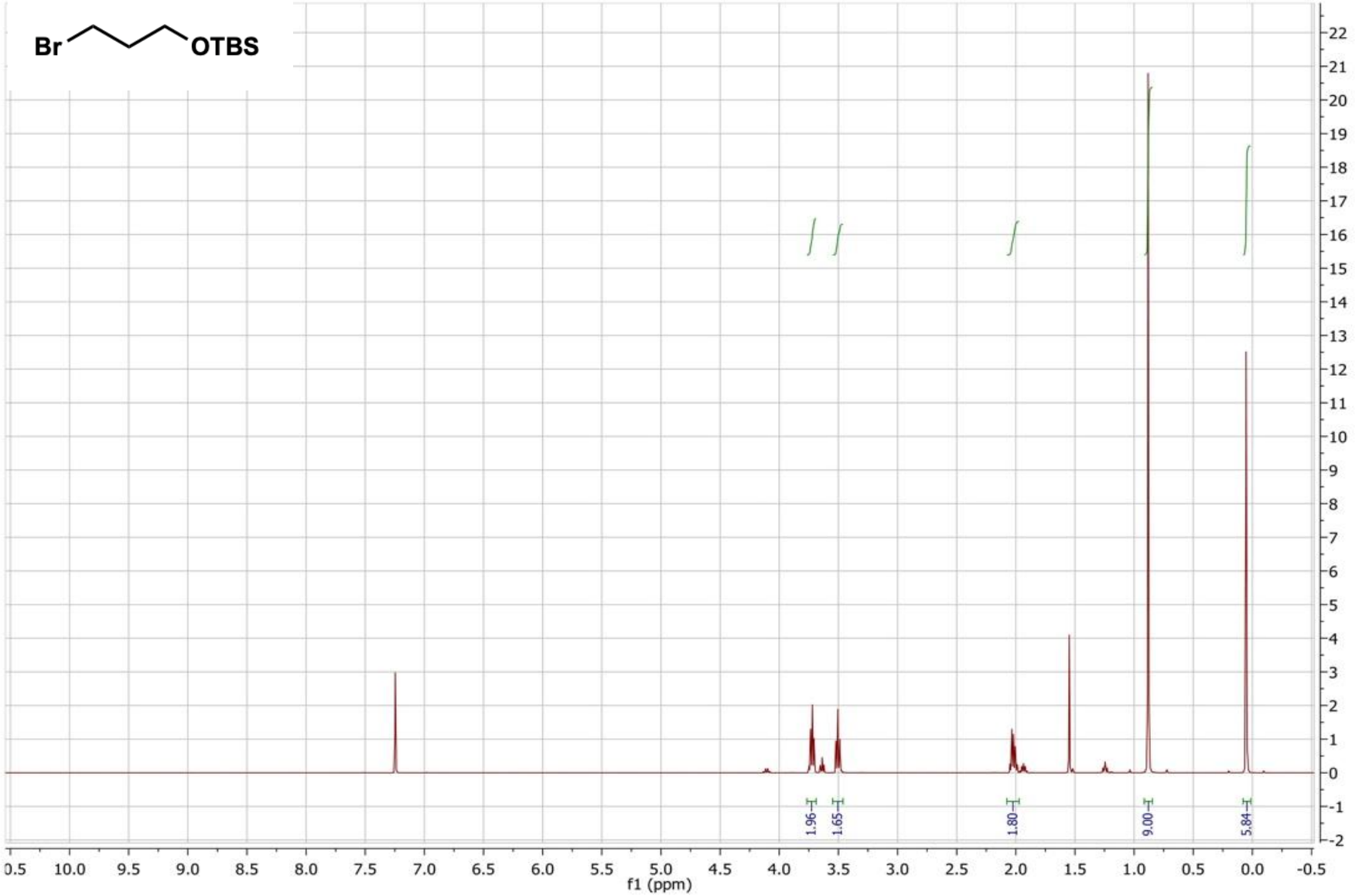
-5.35
f1 (ppm)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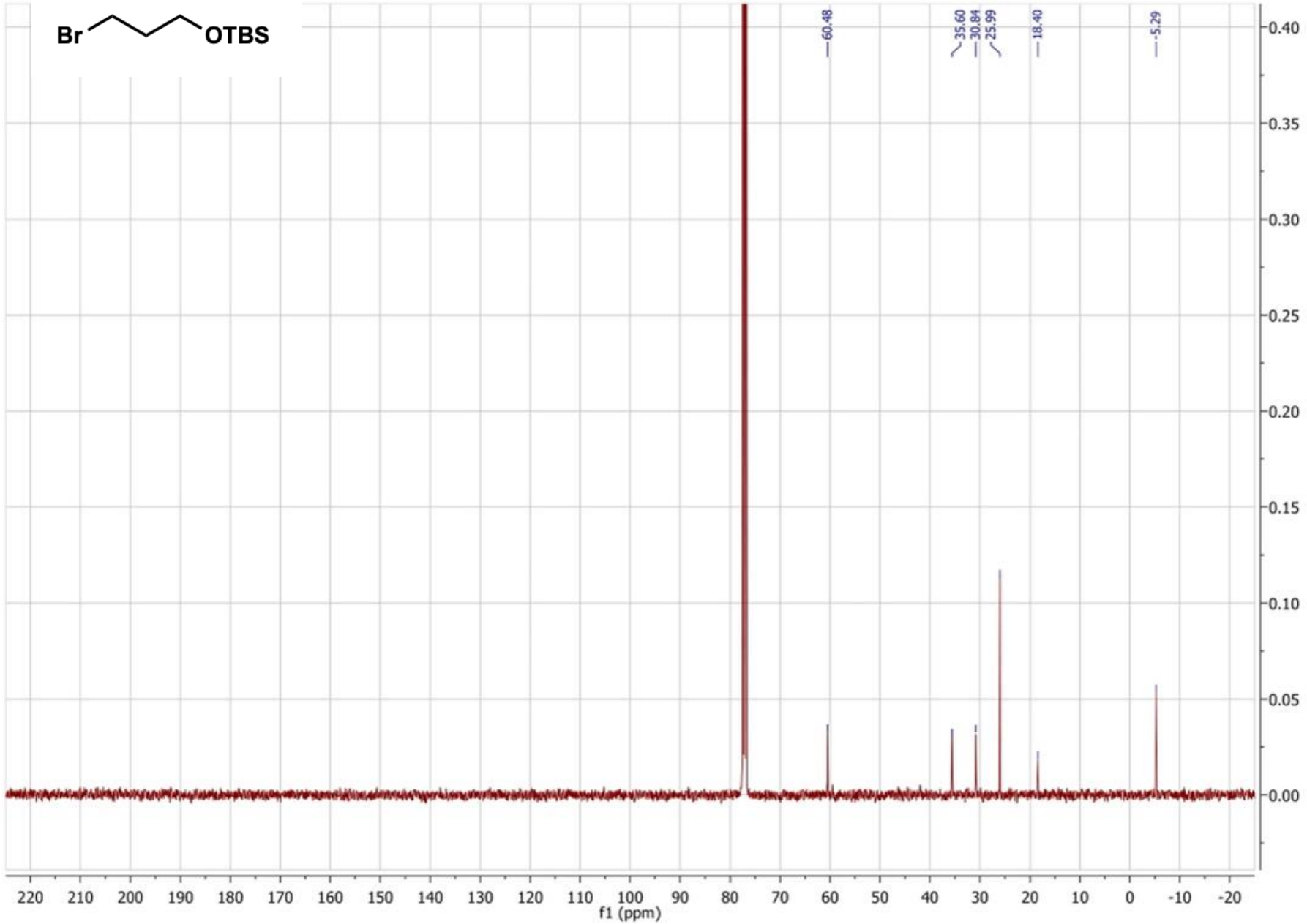
5.84
f1 (ppm)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35.60
30.84
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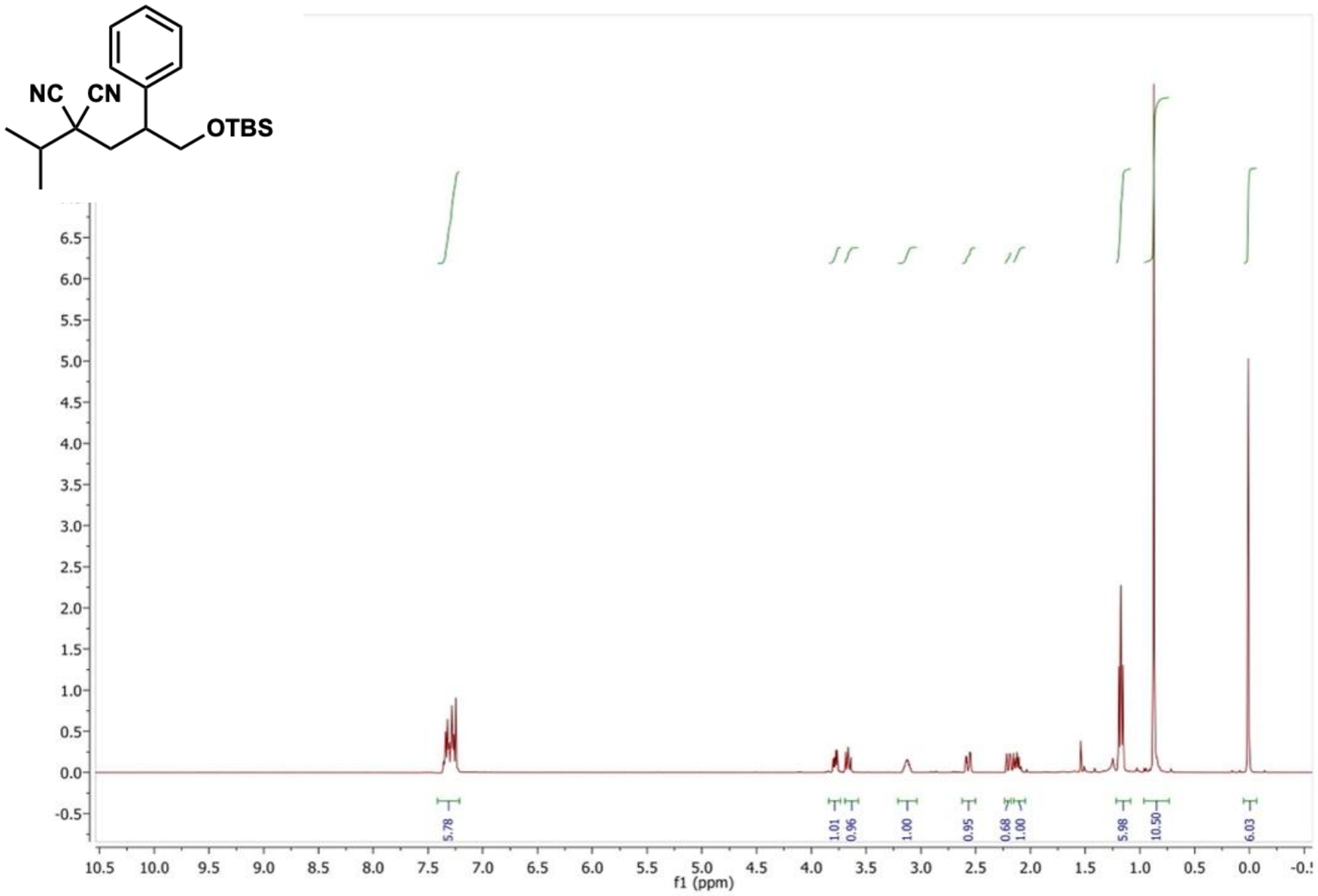
18.40
-5.29
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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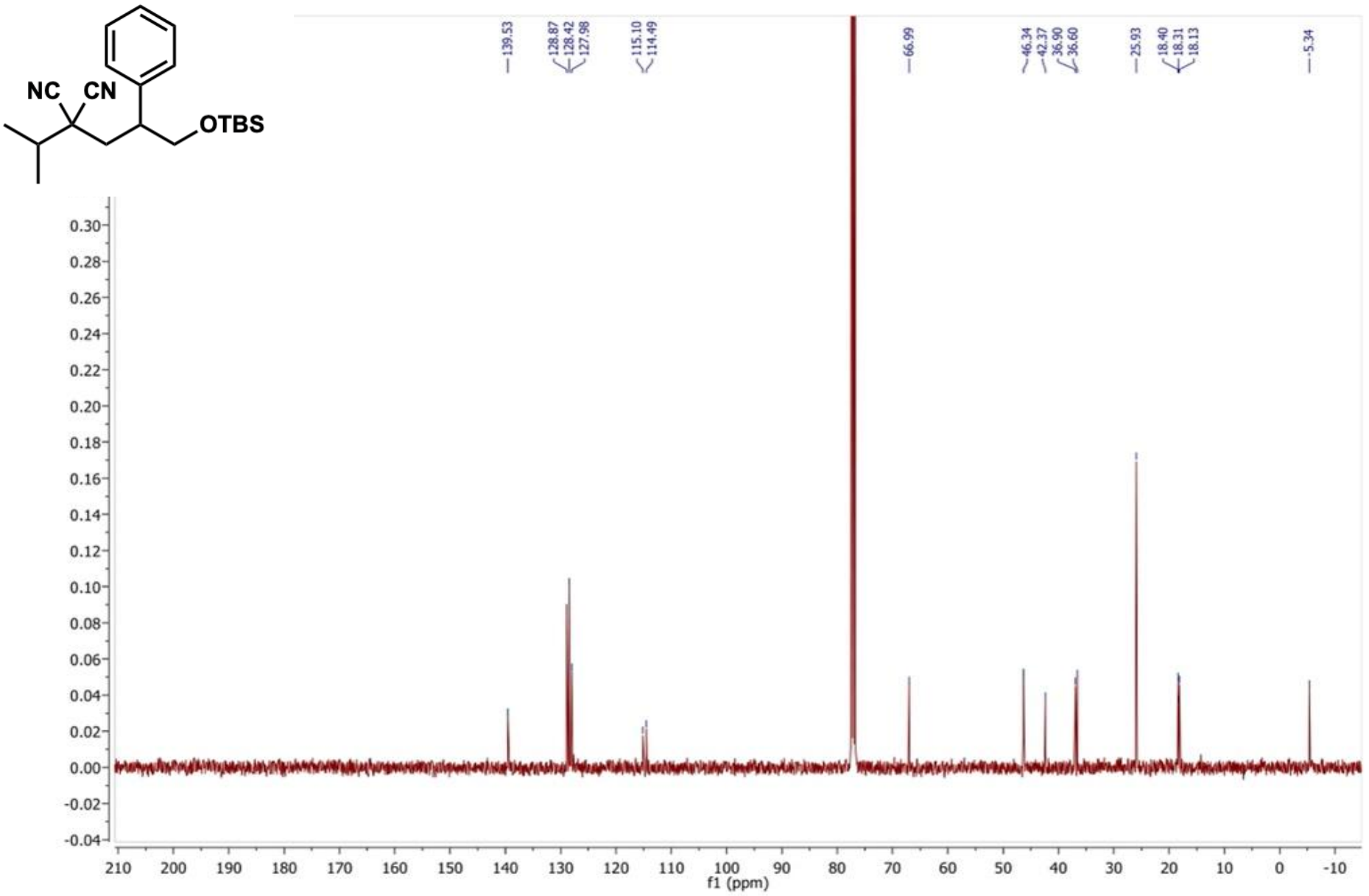
f1 (ppm)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18.31
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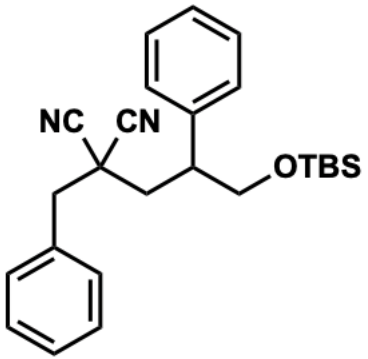
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CN
OTBS

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2.98
0.98
0.72
10.27
5.88
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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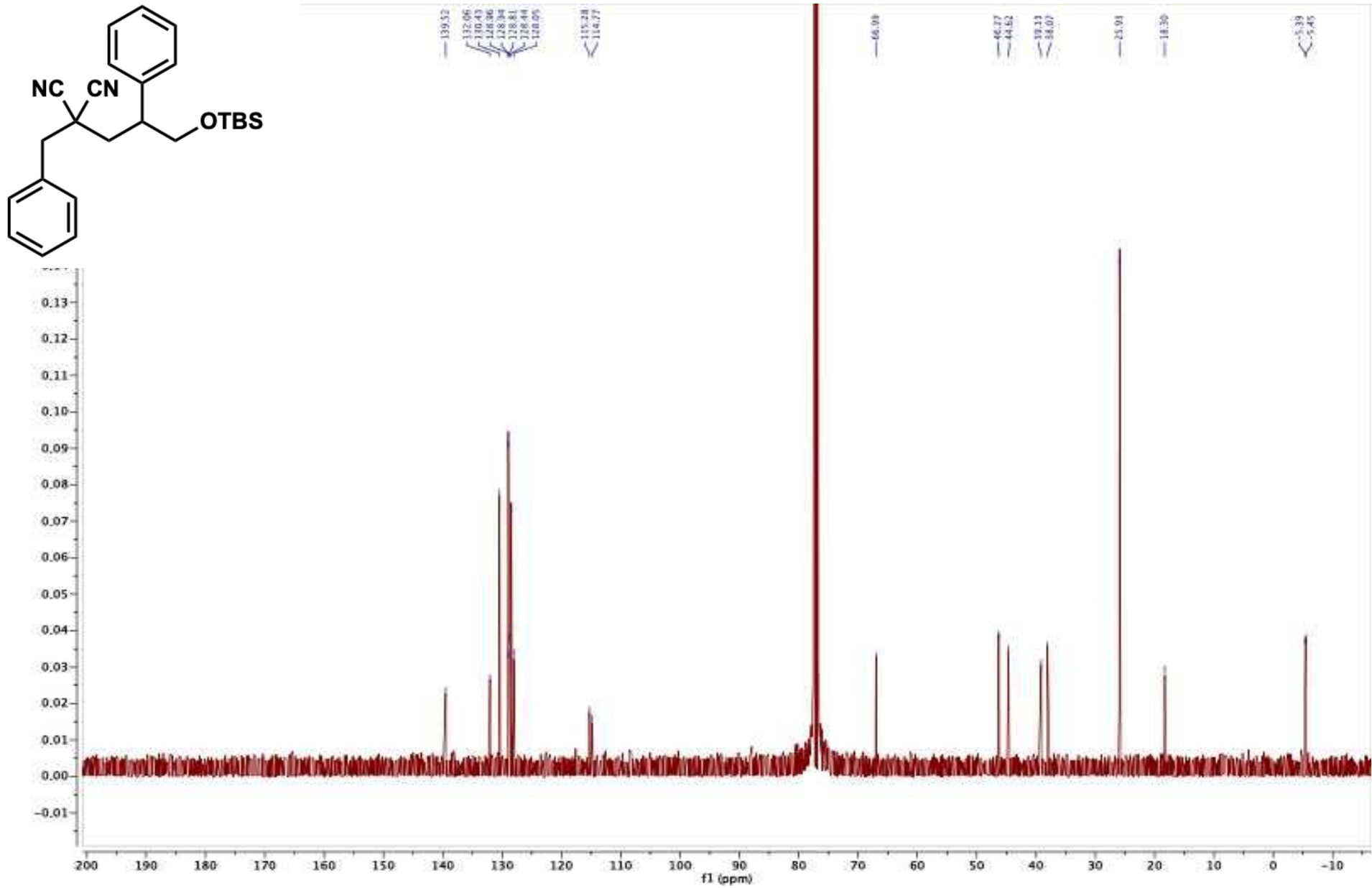
0.0
-0.
f1 (ppm)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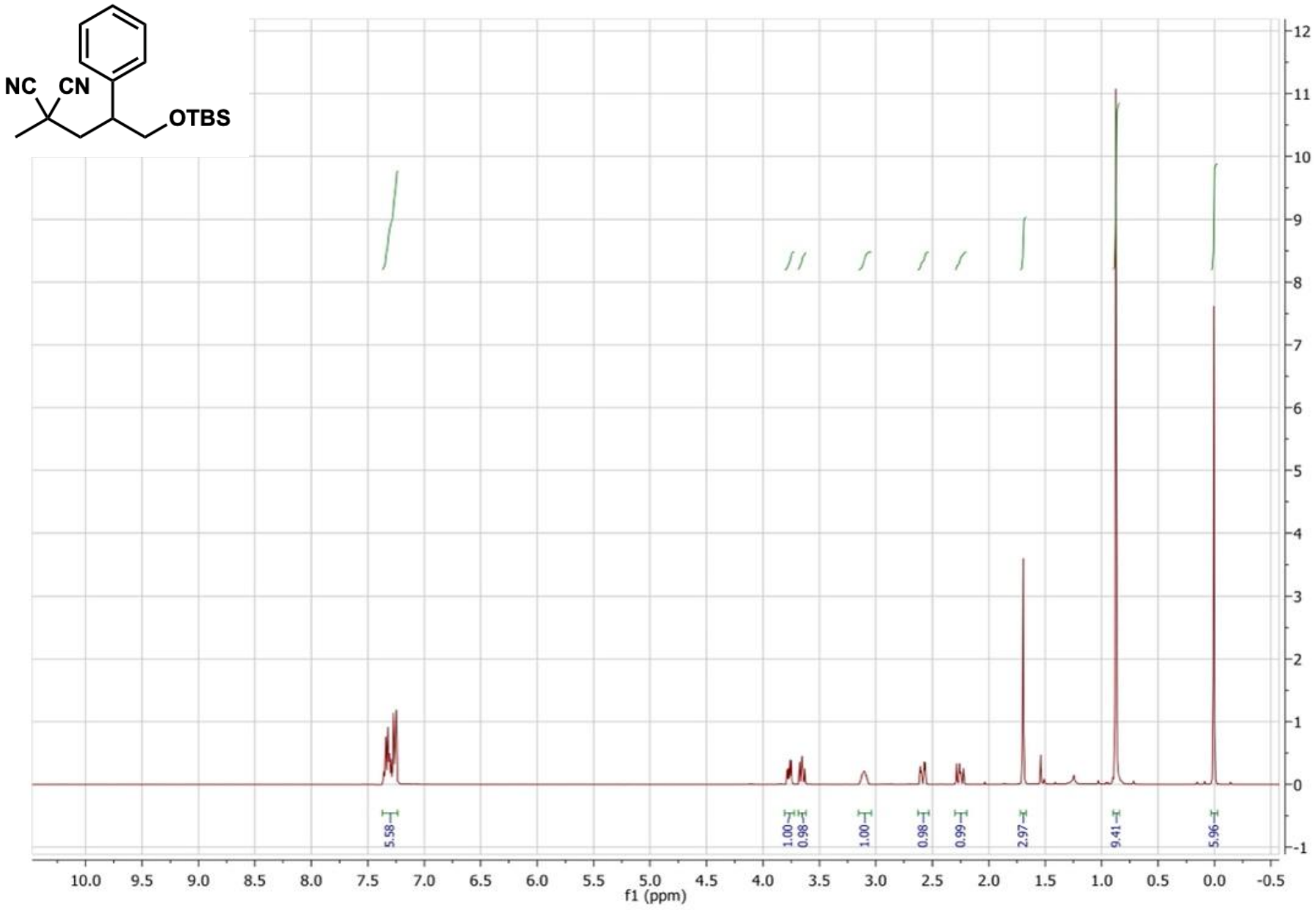
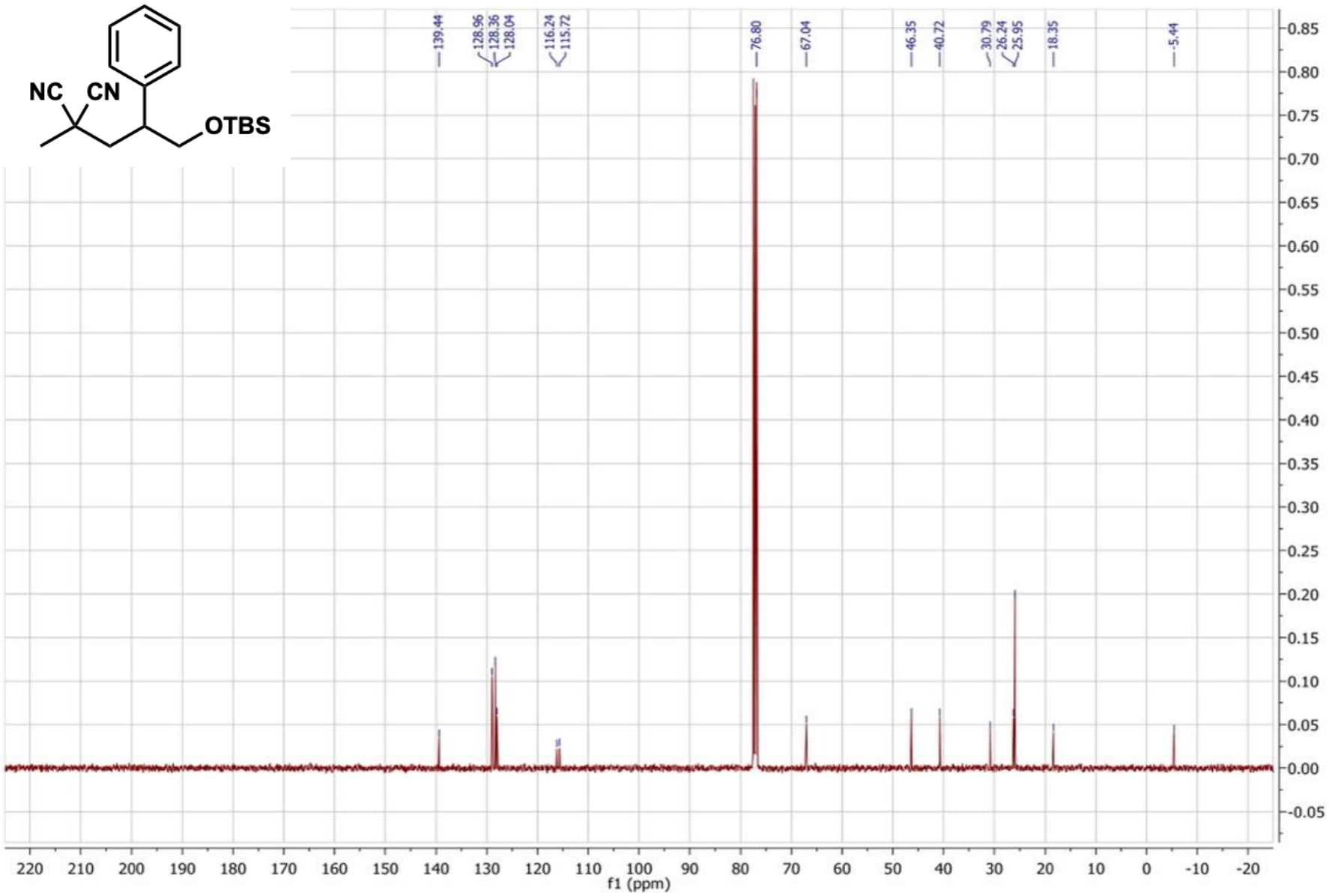
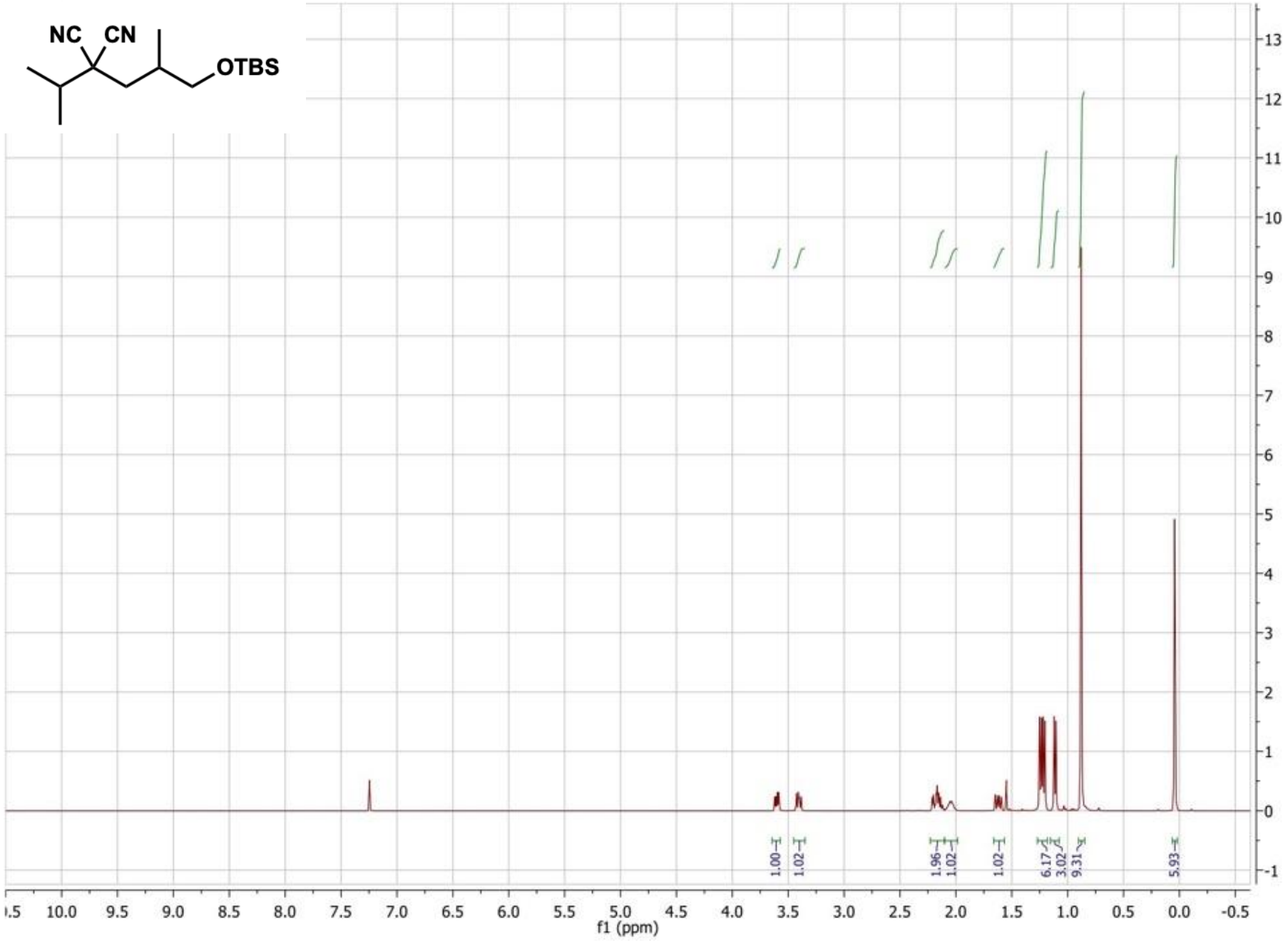
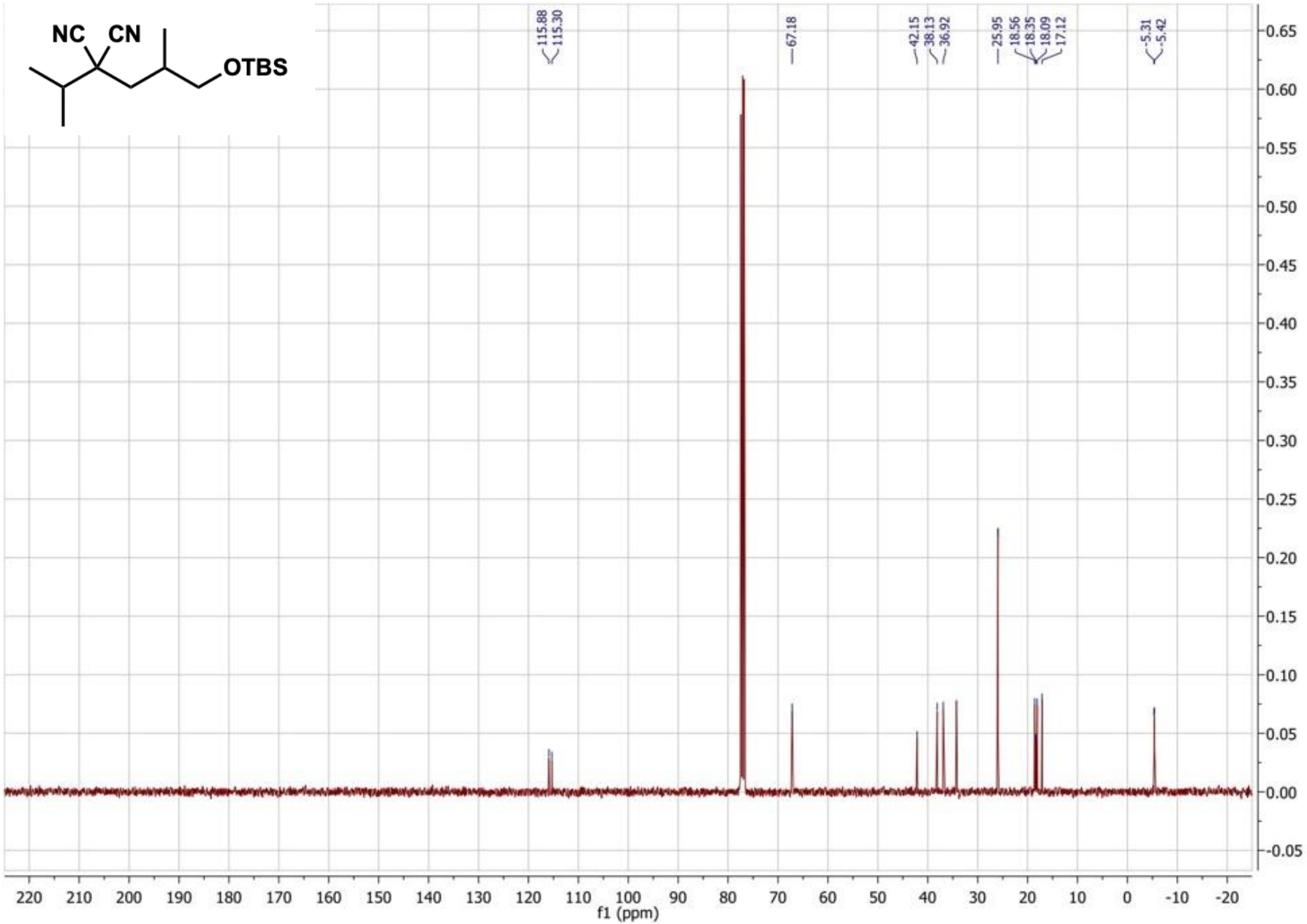
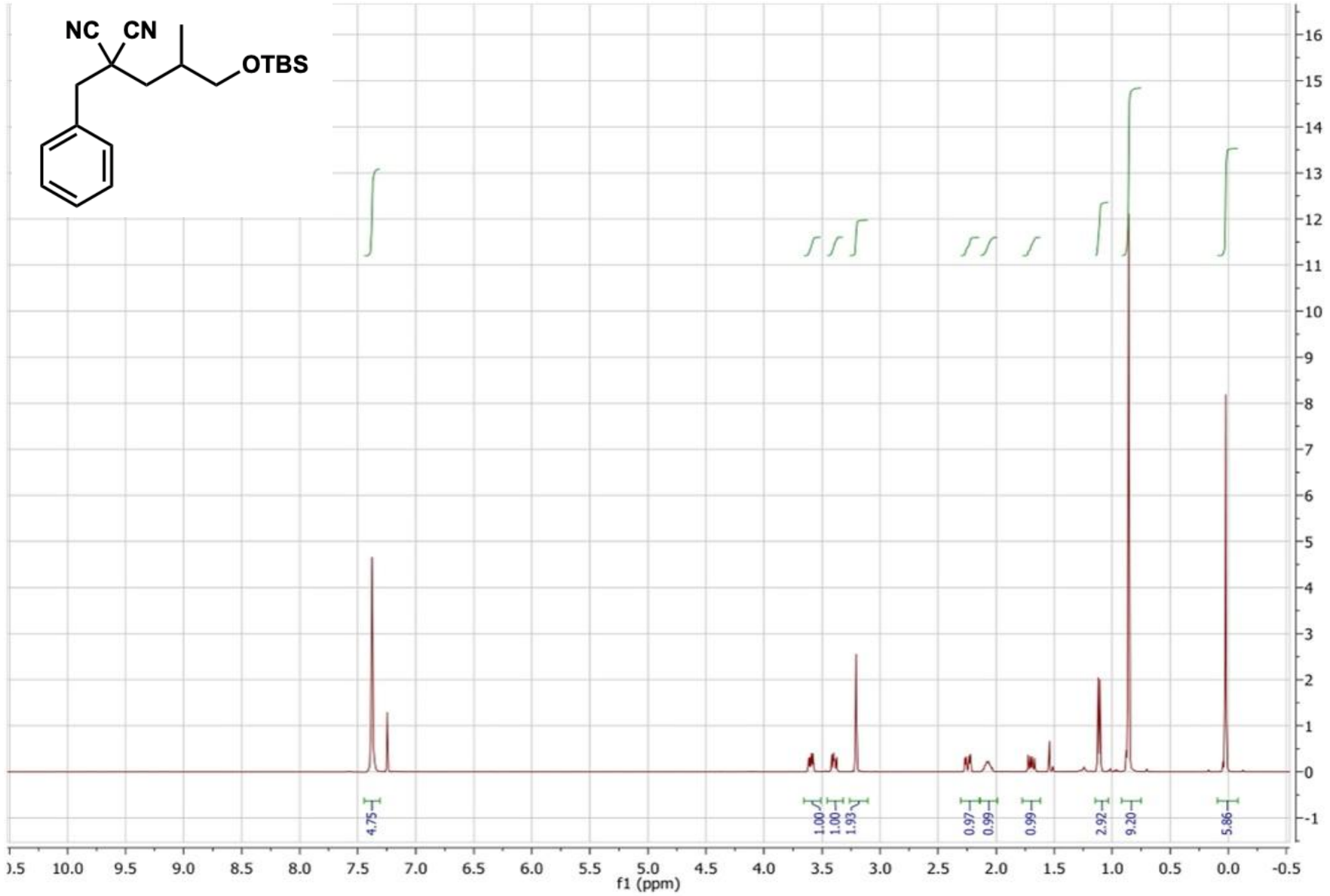
CN
OTBS
f1 (ppm)

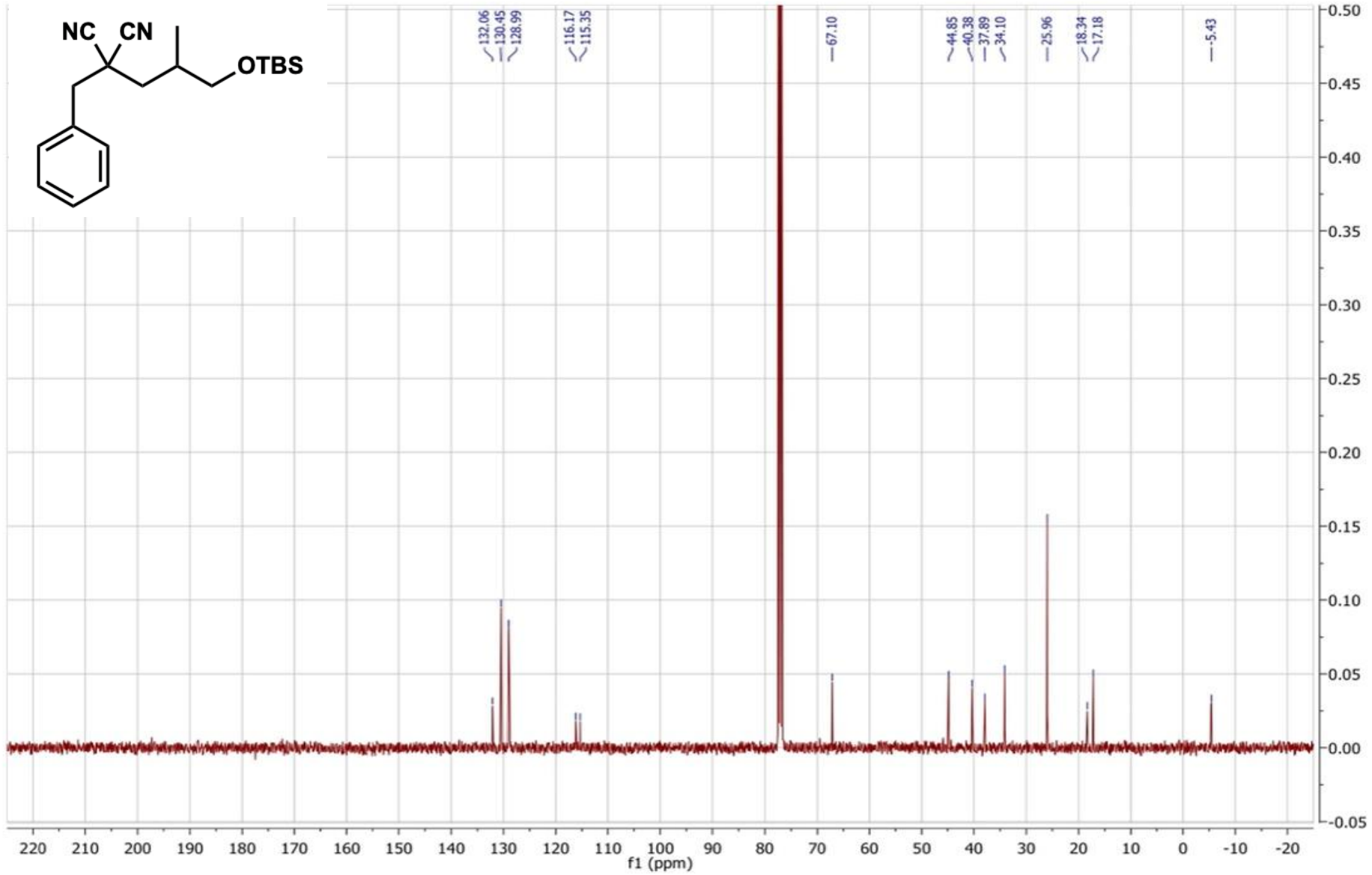

NC
CN
OTBS
5.58
1.00
0.98
1.00
0.98
0.99
2.97
9.41
5.96
f1 (ppm)

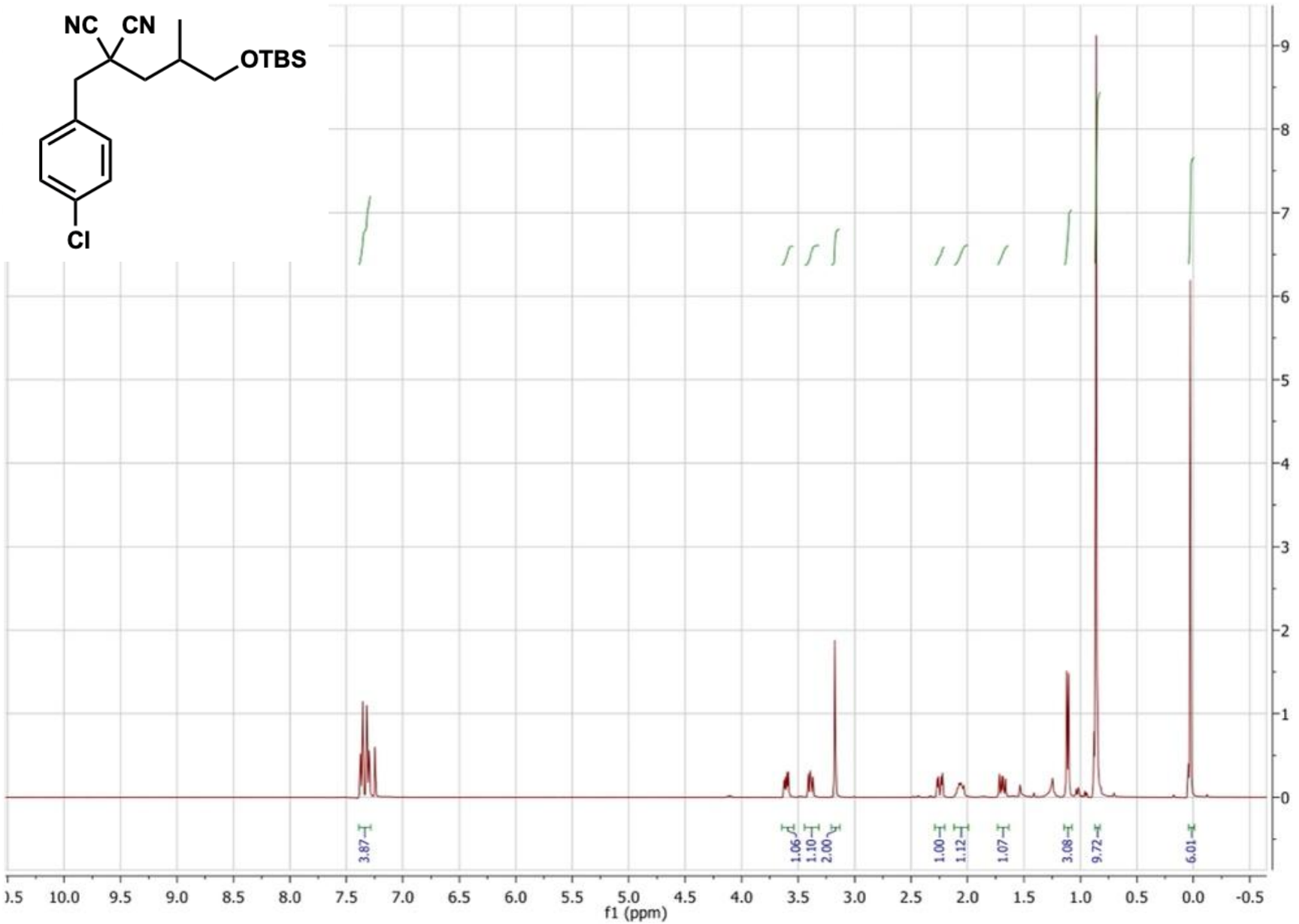

NC
CN
OTBS
139.44
128.96
128.36
128.04
116.24
115.72
76.80
67.04
46.35
40.72
30.79
26.24
25.95
18.35
-5.44
f1 (ppm)

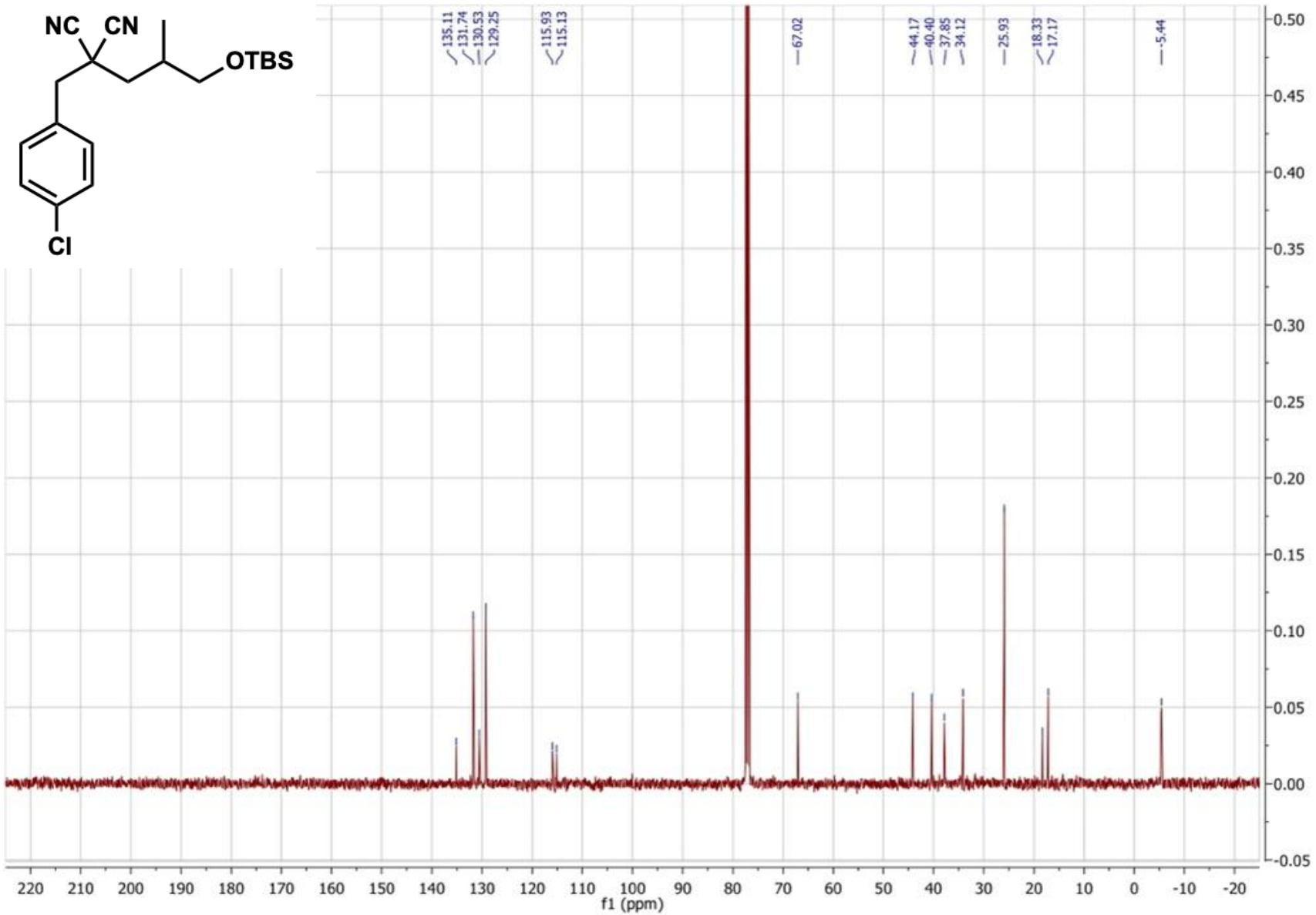

NC
CN
OTBS
1.00
1.02
1.96
1.02
1.02
6.17
3.02
9.31
5.93
f1 (ppm)


NC
CN
OTBS
115.88
115.30
67.18
42.15
38.13
36.92
25.95
18.56
18.35
18.09
17.12
-5.31
-5.42
f1 (ppm)


NC
CN
OTBS
4.75
1.00
1.00
1.93
0.97
0.99
0.99
2.92
9.20
5.86
f1 (ppm)


NC
CN
OTBS
132.06
130.45
128.99
116.17
115.35
67.10
44.85
40.38
37.89
34.10
25.96
18.34
17.18
-5.43
f1 (ppm)


NC
CN
OTBS
Cl
3.87
1.06
1.10
2.00
1.00
1.12
1.07
3.08
9.72
6.01
f1 (ppm)


NC
CN
OTBS
Cl
135.11
131.74
130.53
129.25
115.93
115.13
67.02
44.17
40.40
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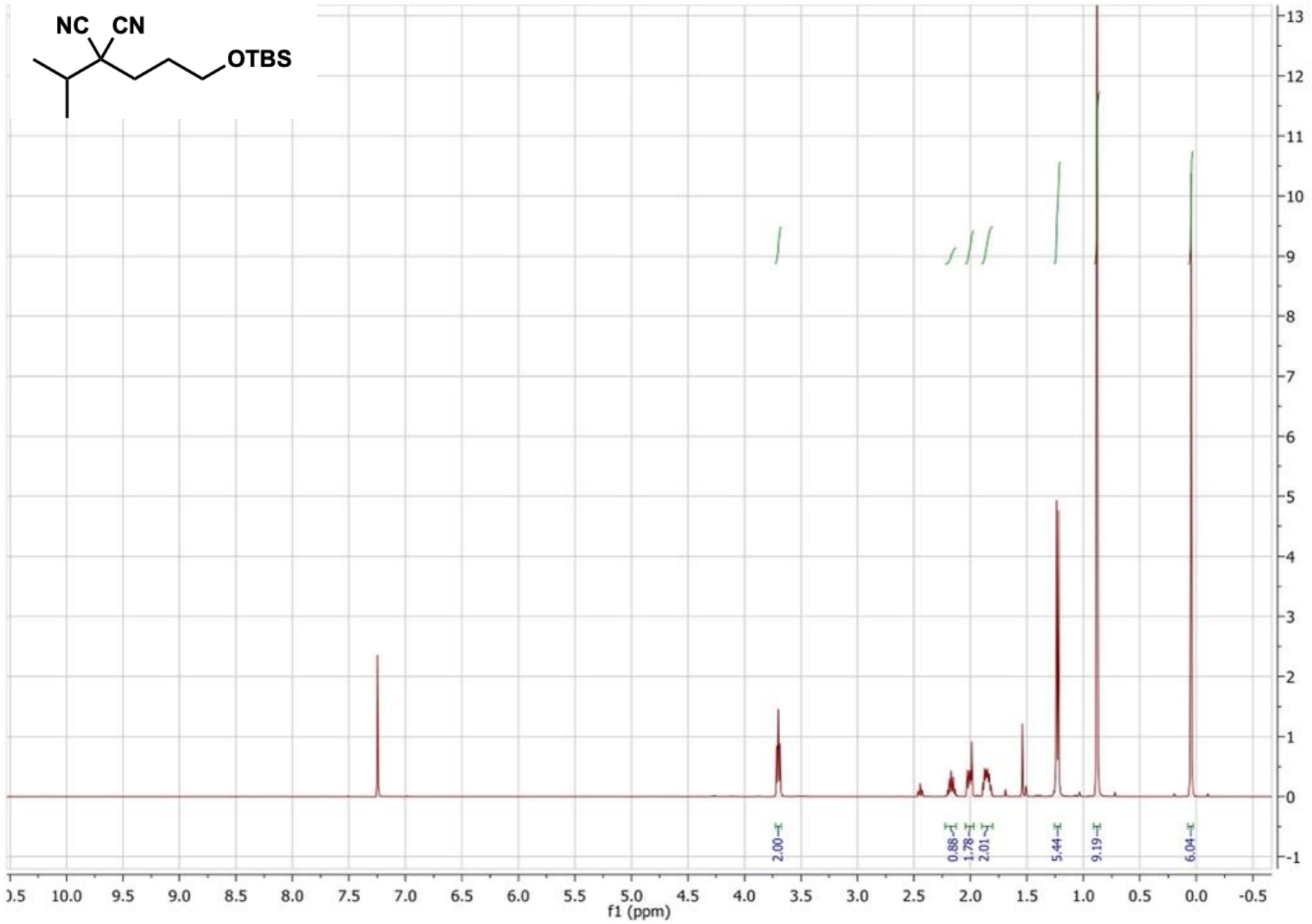
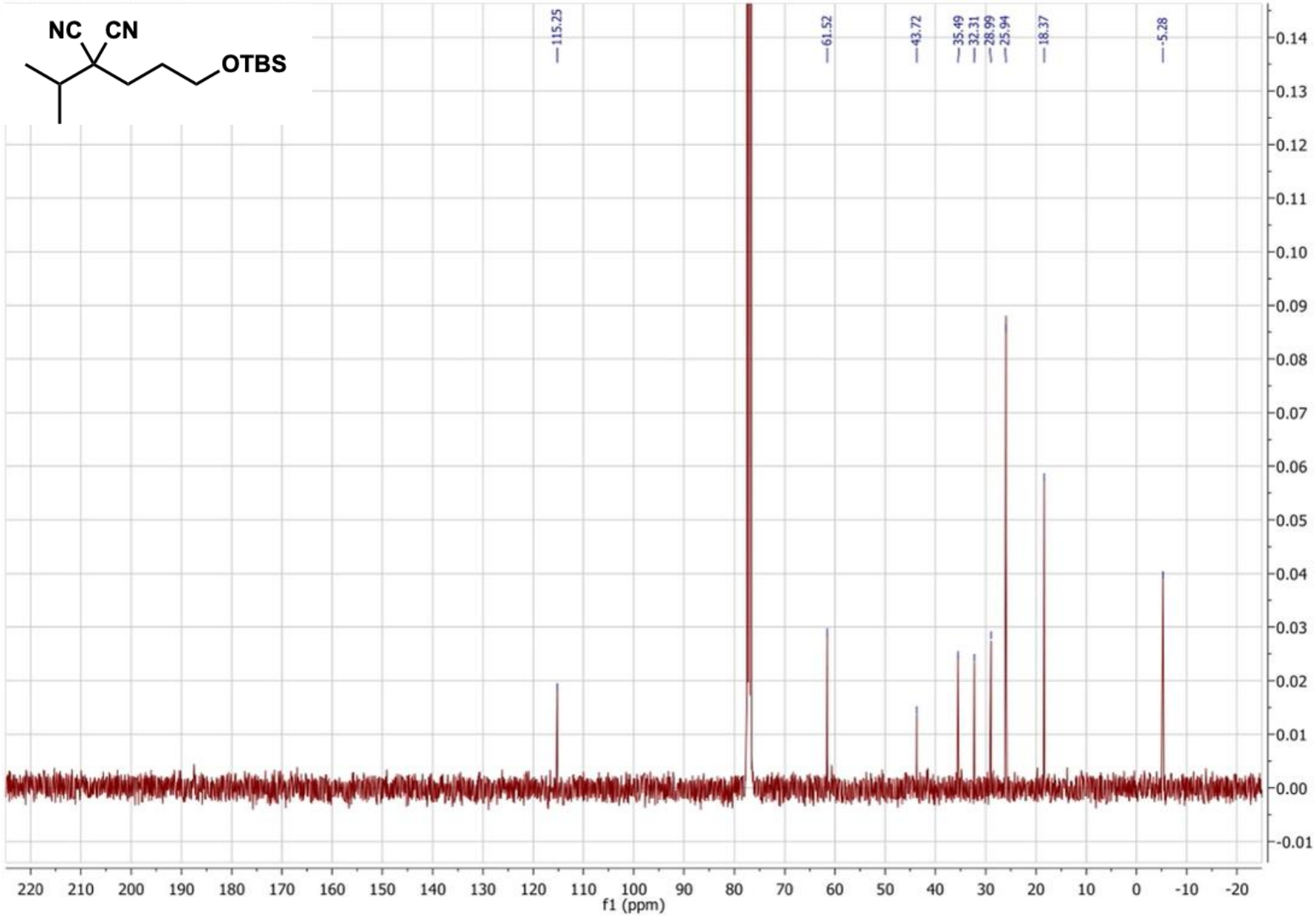
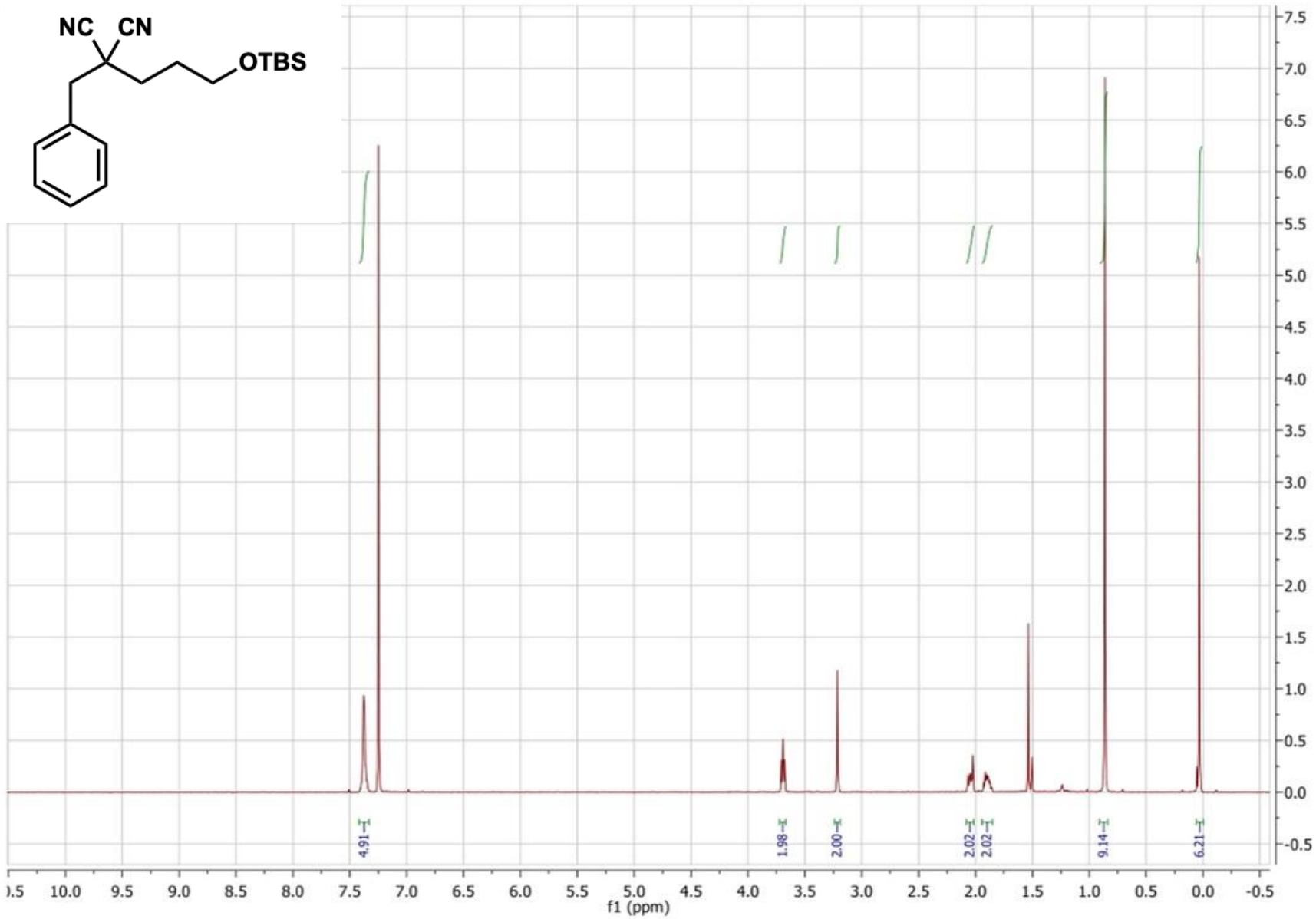
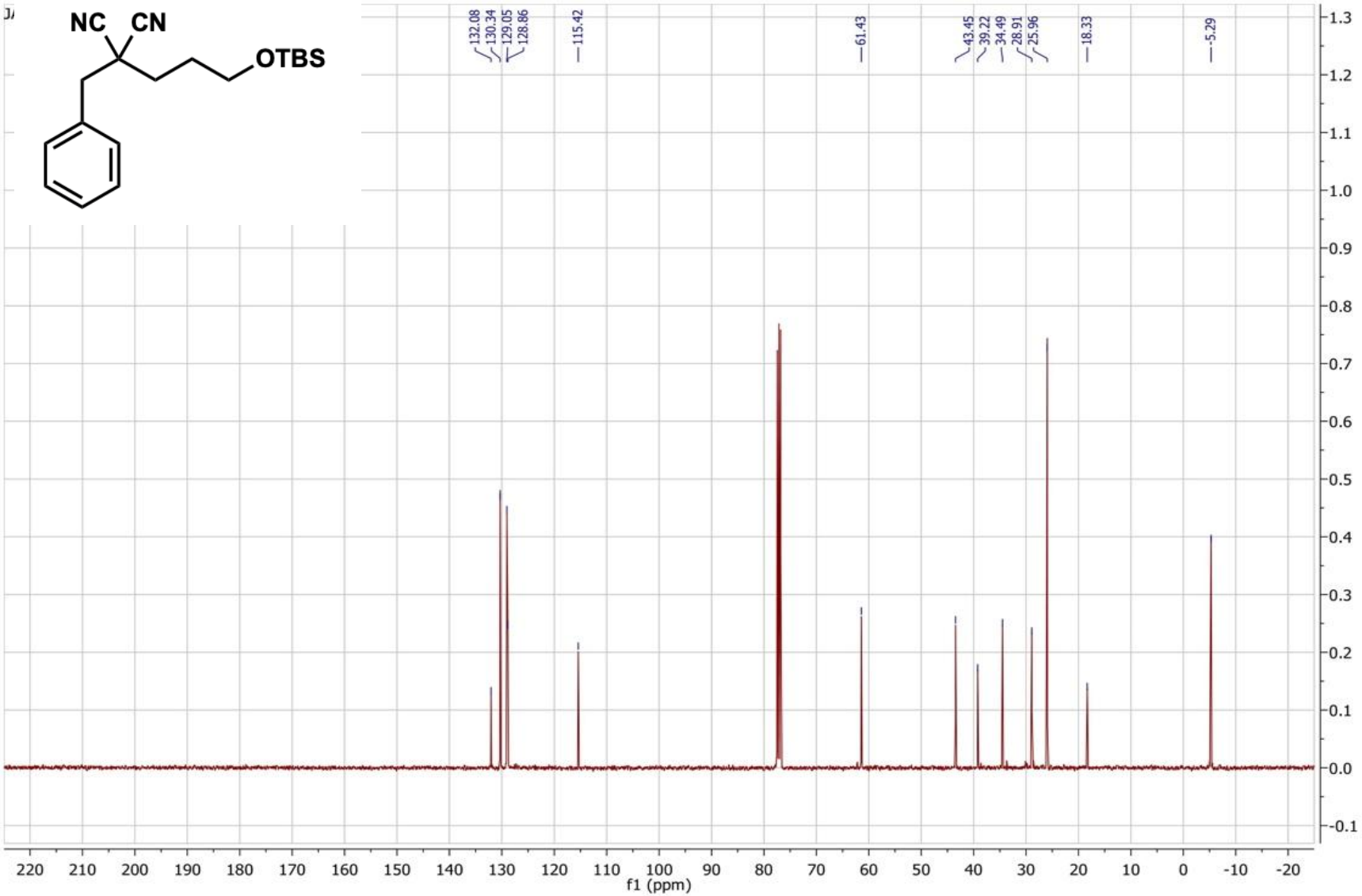
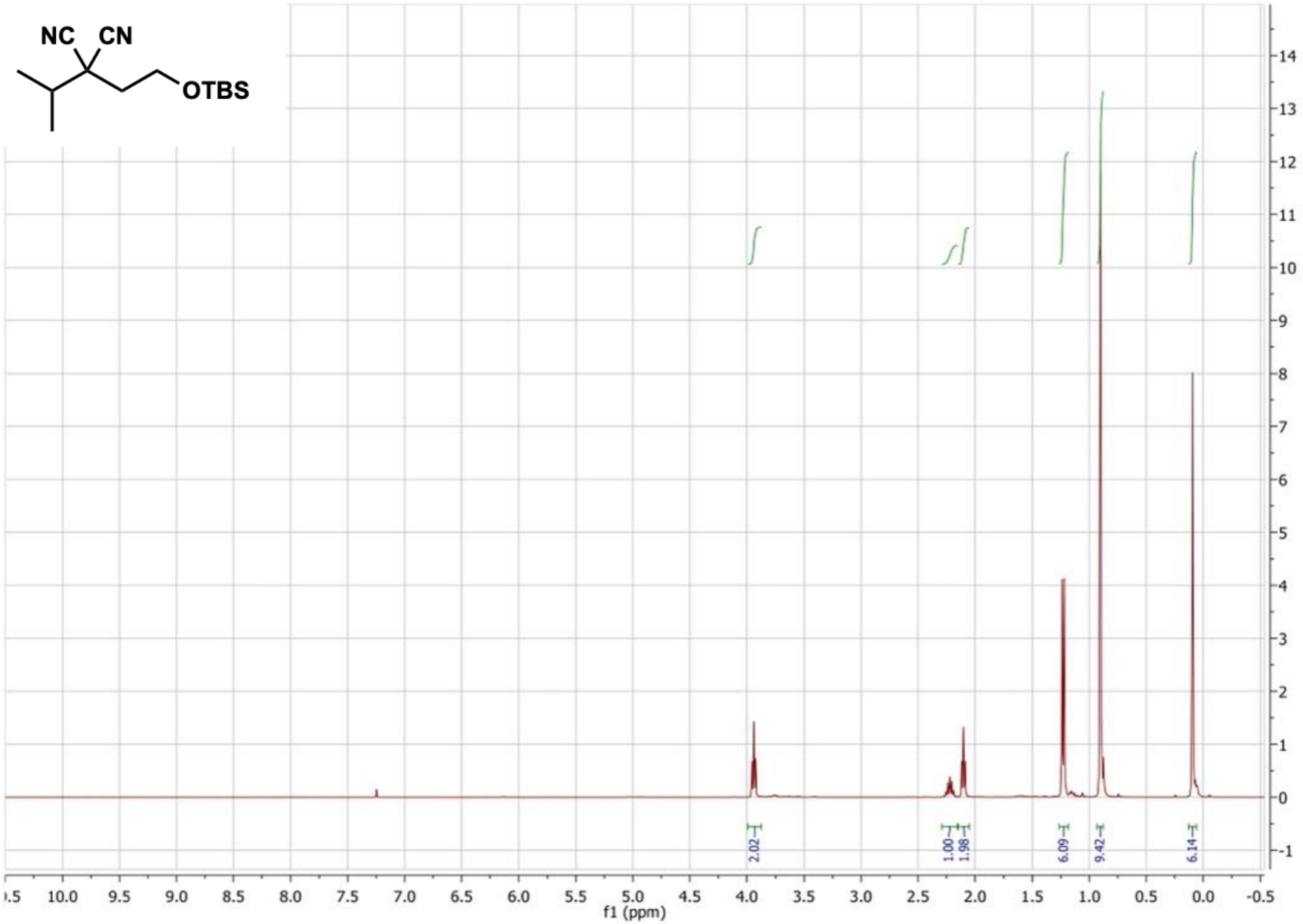
25.93
18.33
17.17
-5.44
f1 (ppm)

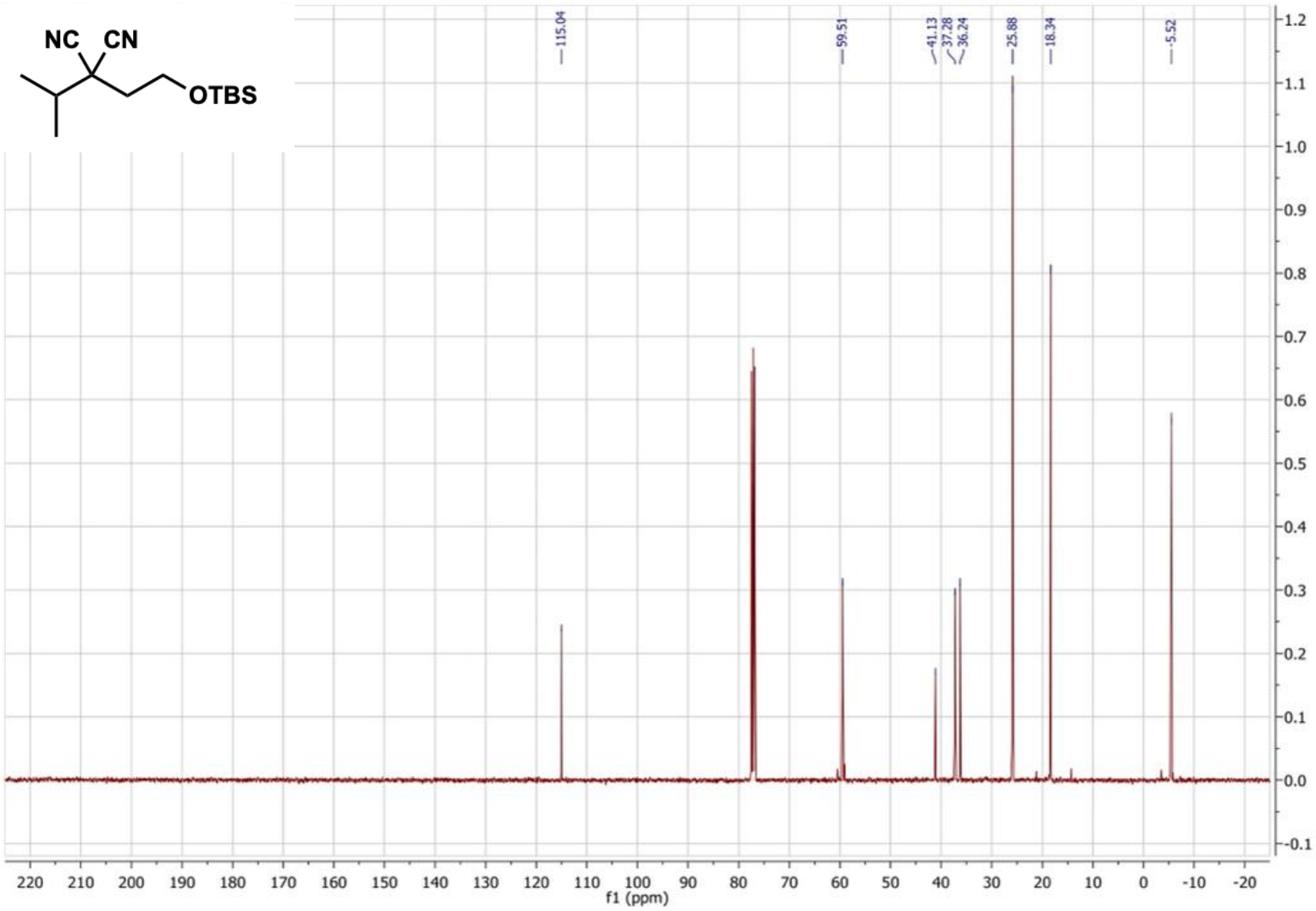

NC
CN
OTBS
2.00
0.88
1.78
2.01
5.44
9.19
6.04
f1 (ppm)

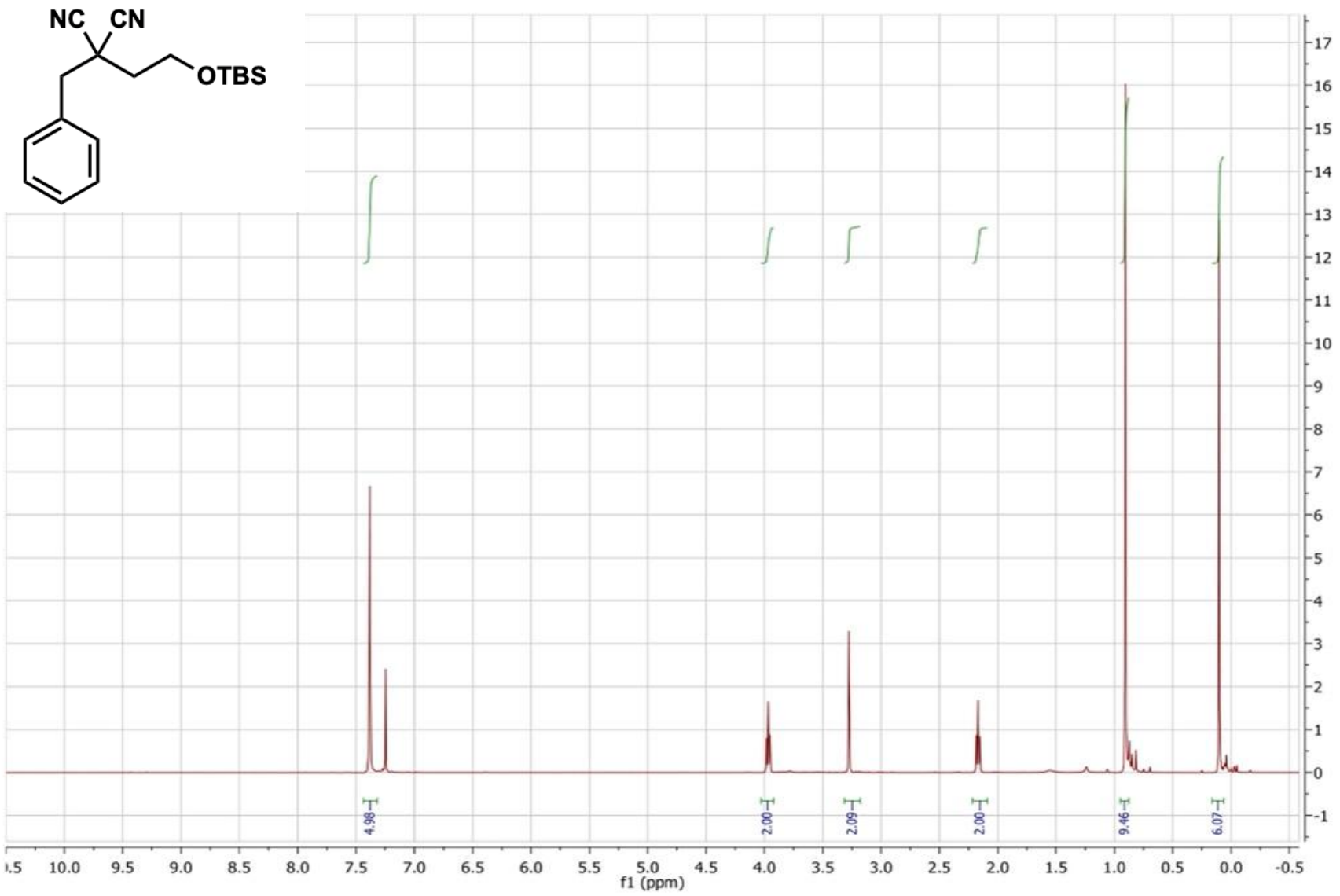

NC
CN
OTBS
115.25
61.52
43.72
35.49
32.31
28.99
25.94
18.37
-5.28
f1 (ppm)

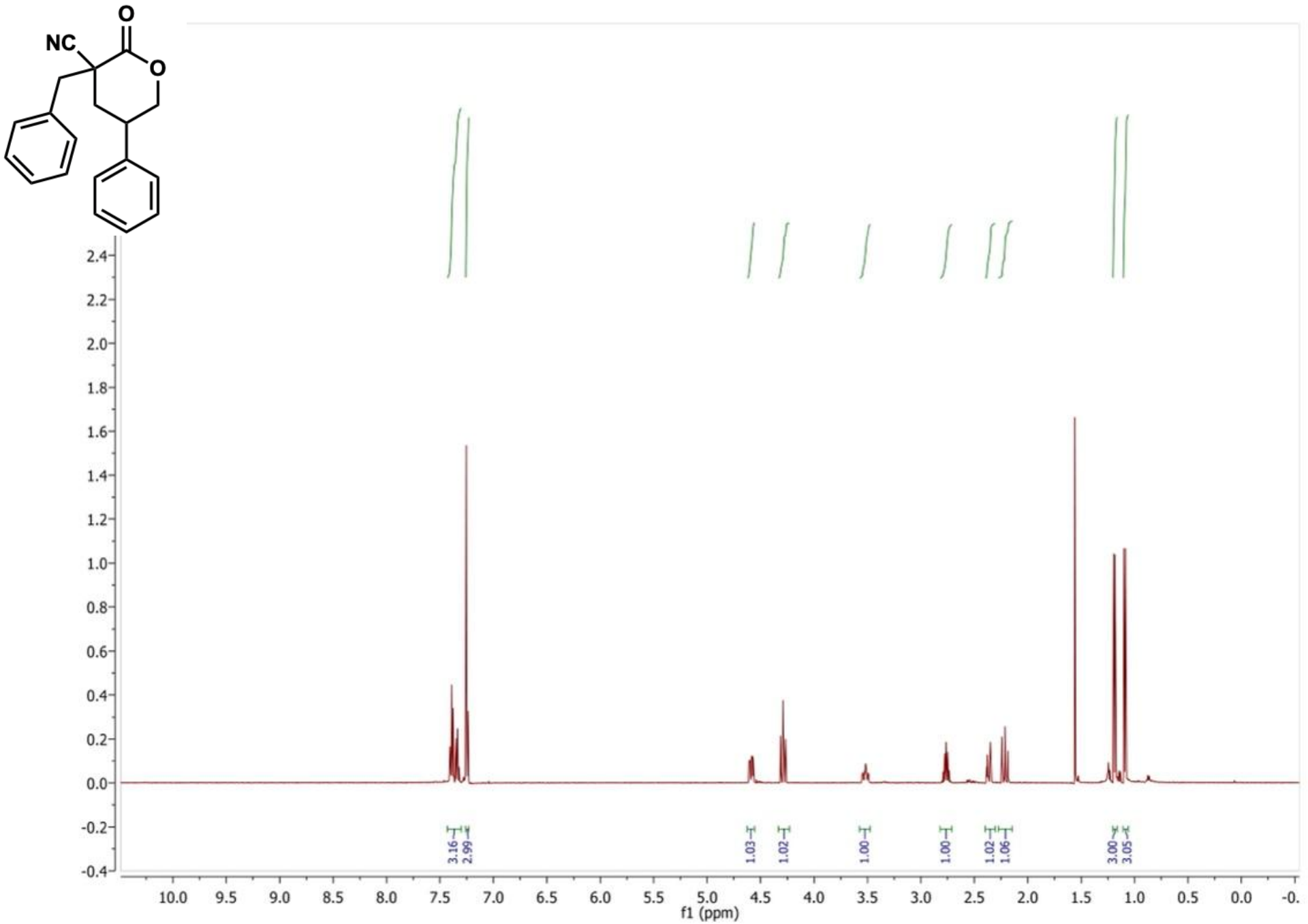

NC
CN
OTBS
4.91
1.98
2.00
2.02
2.02
9.14
6.21
f1 (ppm)

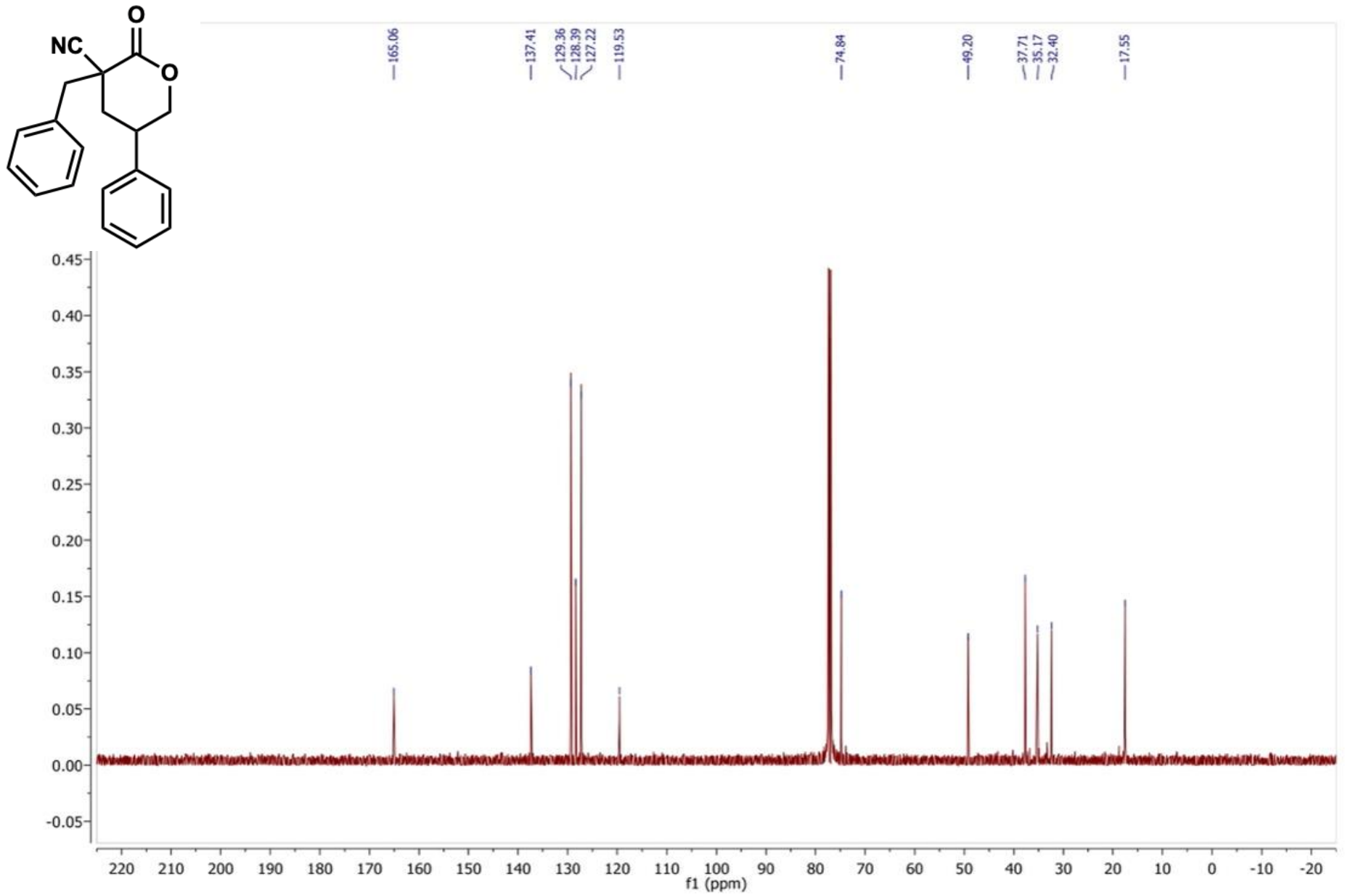

NC
CN
OTBS
132.08
130.34
129.05
128.86
115.42
61.43
43.45
39.22
34.49
28.91
25.96
18.33
-5.29
f1 (ppm)

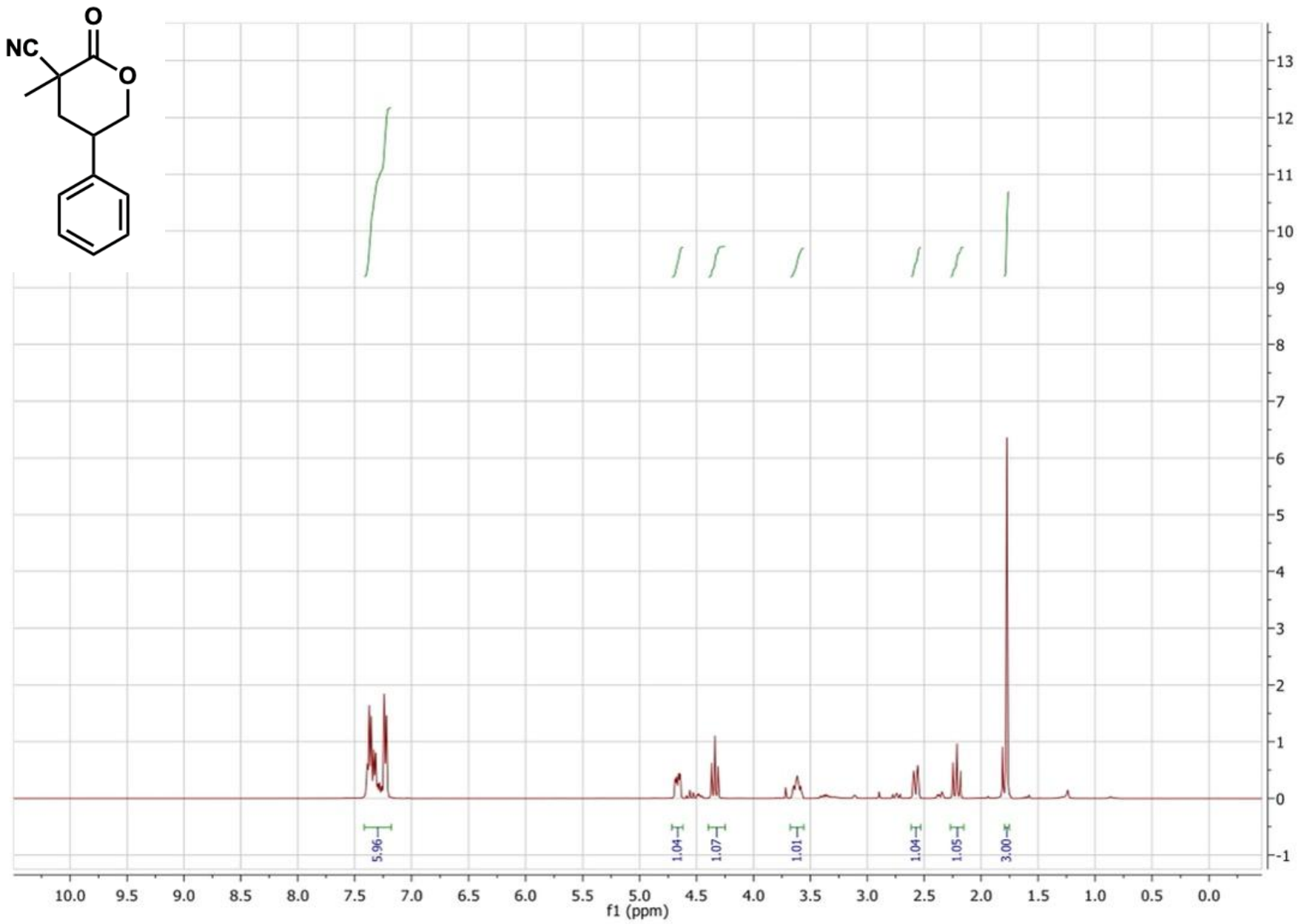

NC
CN
OTBS
2.02
1.00
1.98
6.09
9.42
6.14
f1 (ppm)

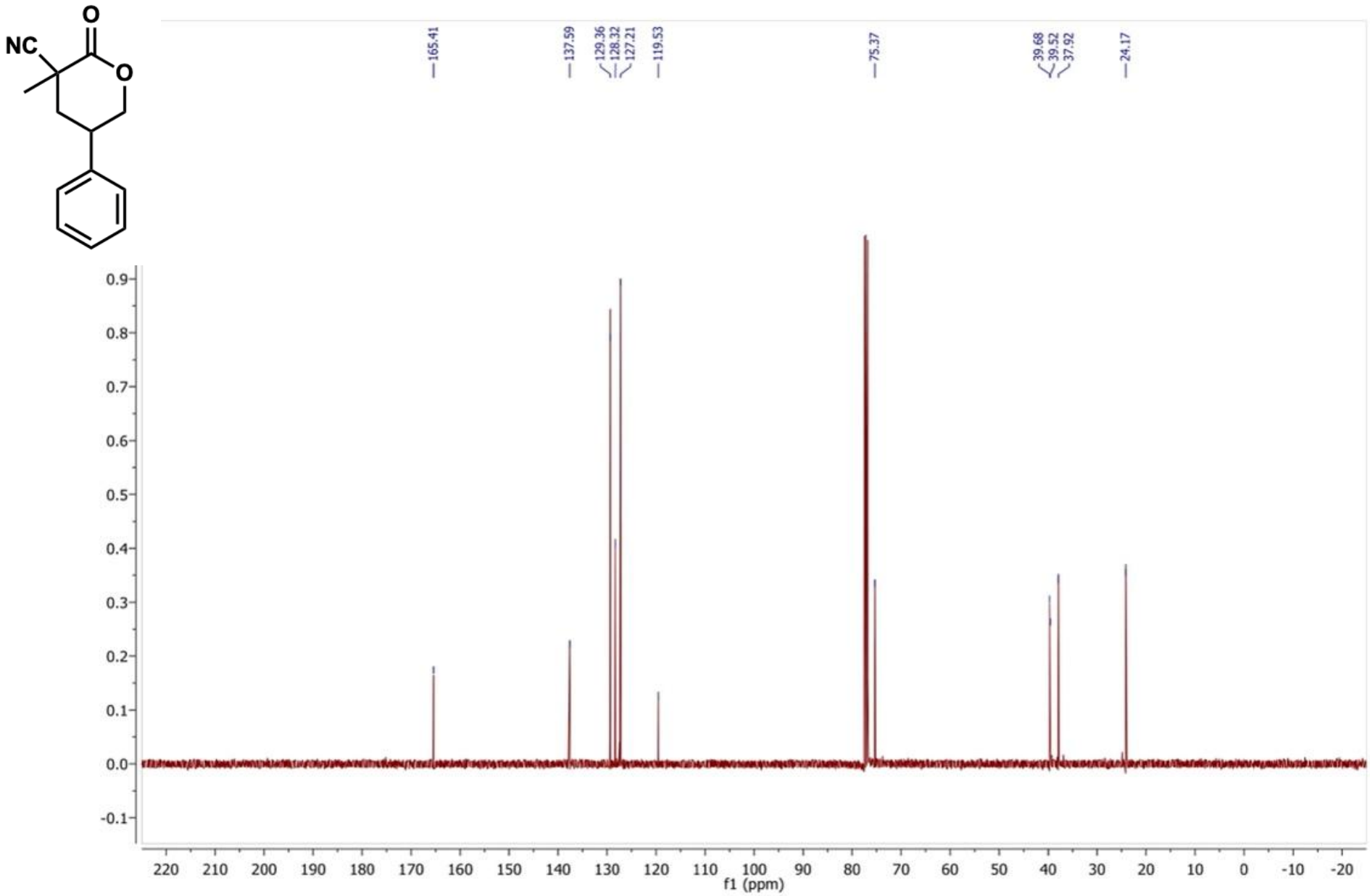

NC
CN
OTBS
115.04
59.51
41.13
37.28
36.24
25.88
18.34
-5.52
f1 (ppm)

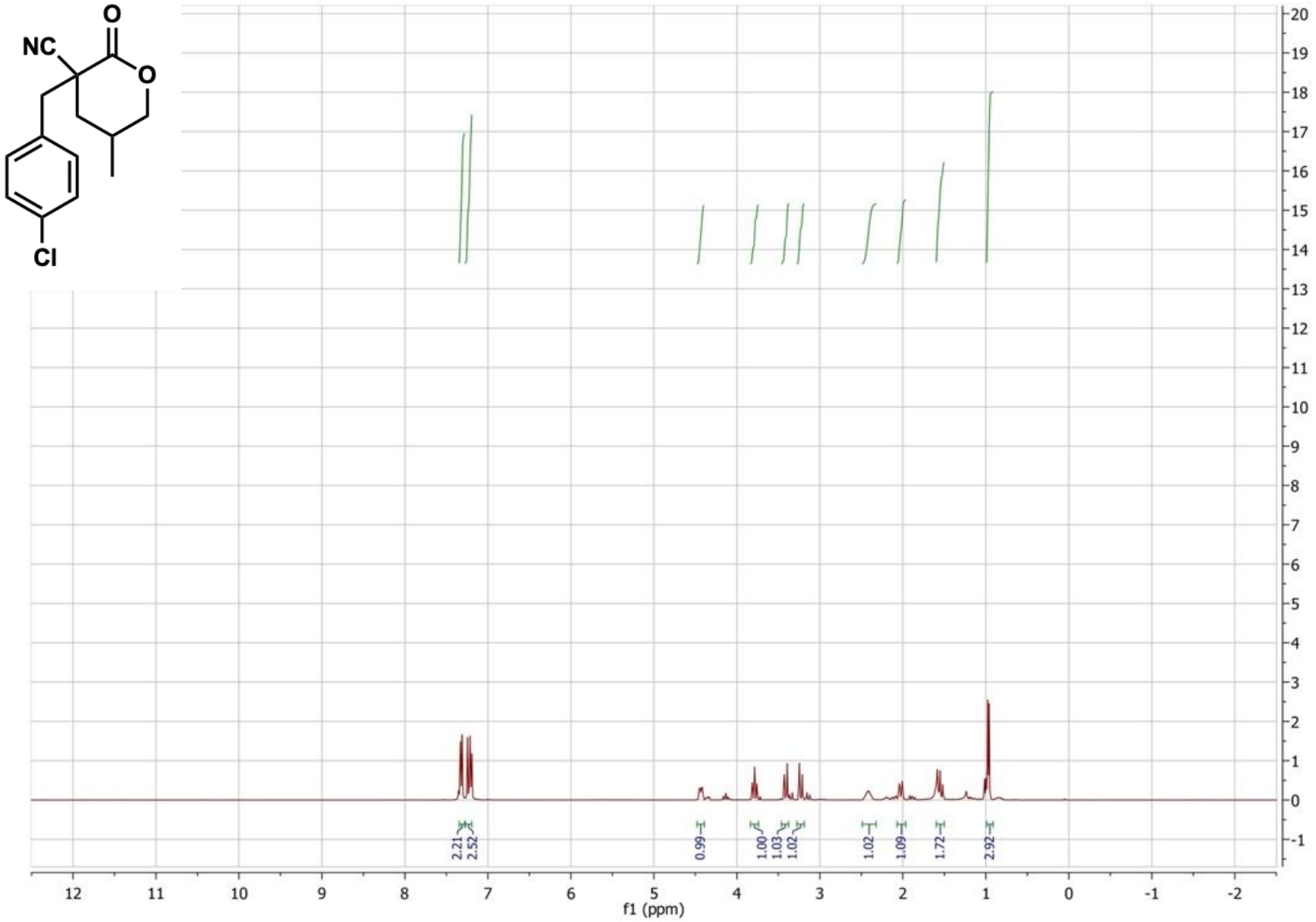

NC
CN
OTBS
4.98
2.00
2.09
2.00
9.46
6.07
f1 (ppm)

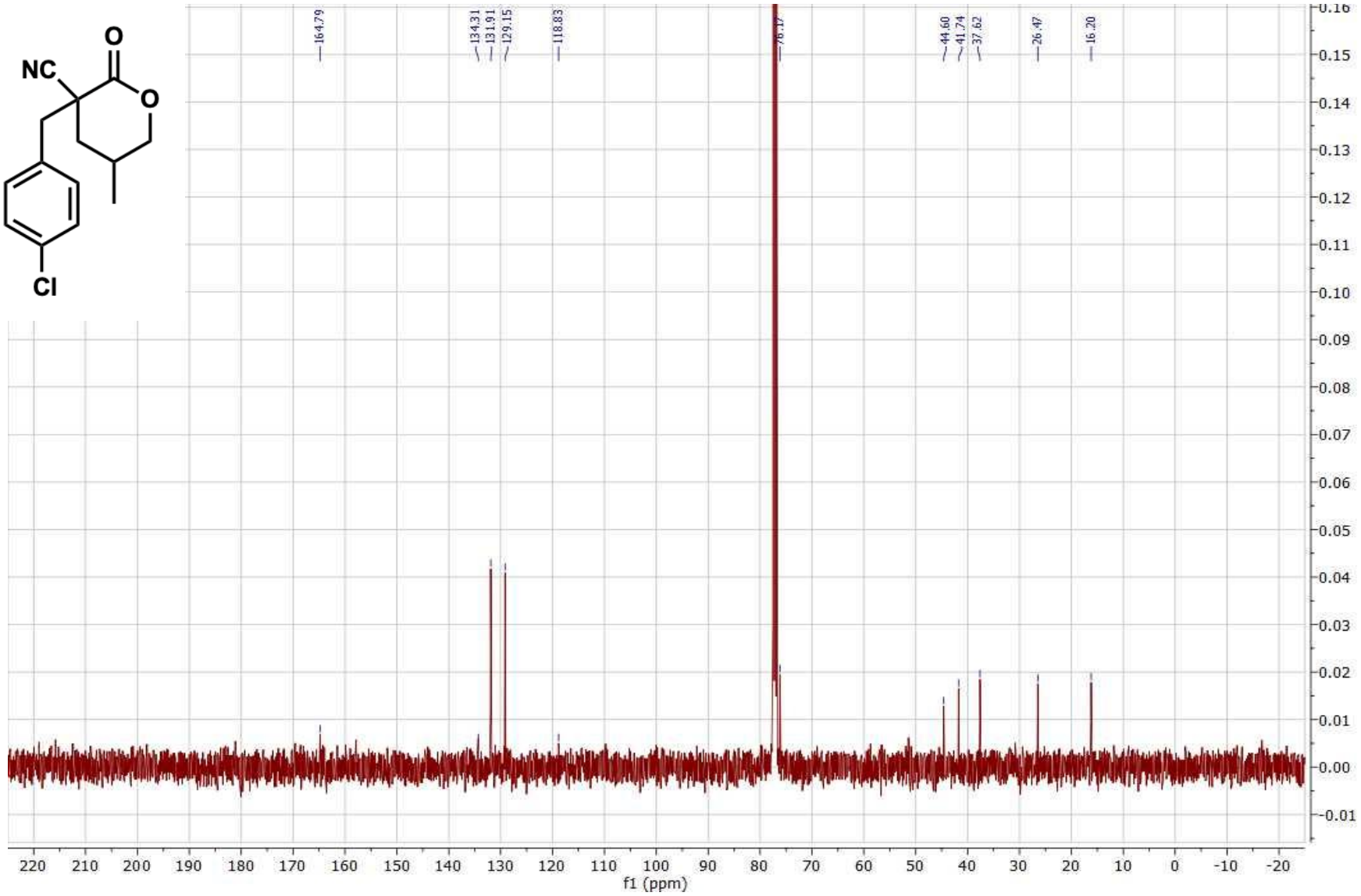

NC
O
O
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
3.16
2.99
1.03
1.02
1.00
1.00
1.02
1.06
3.00
3.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

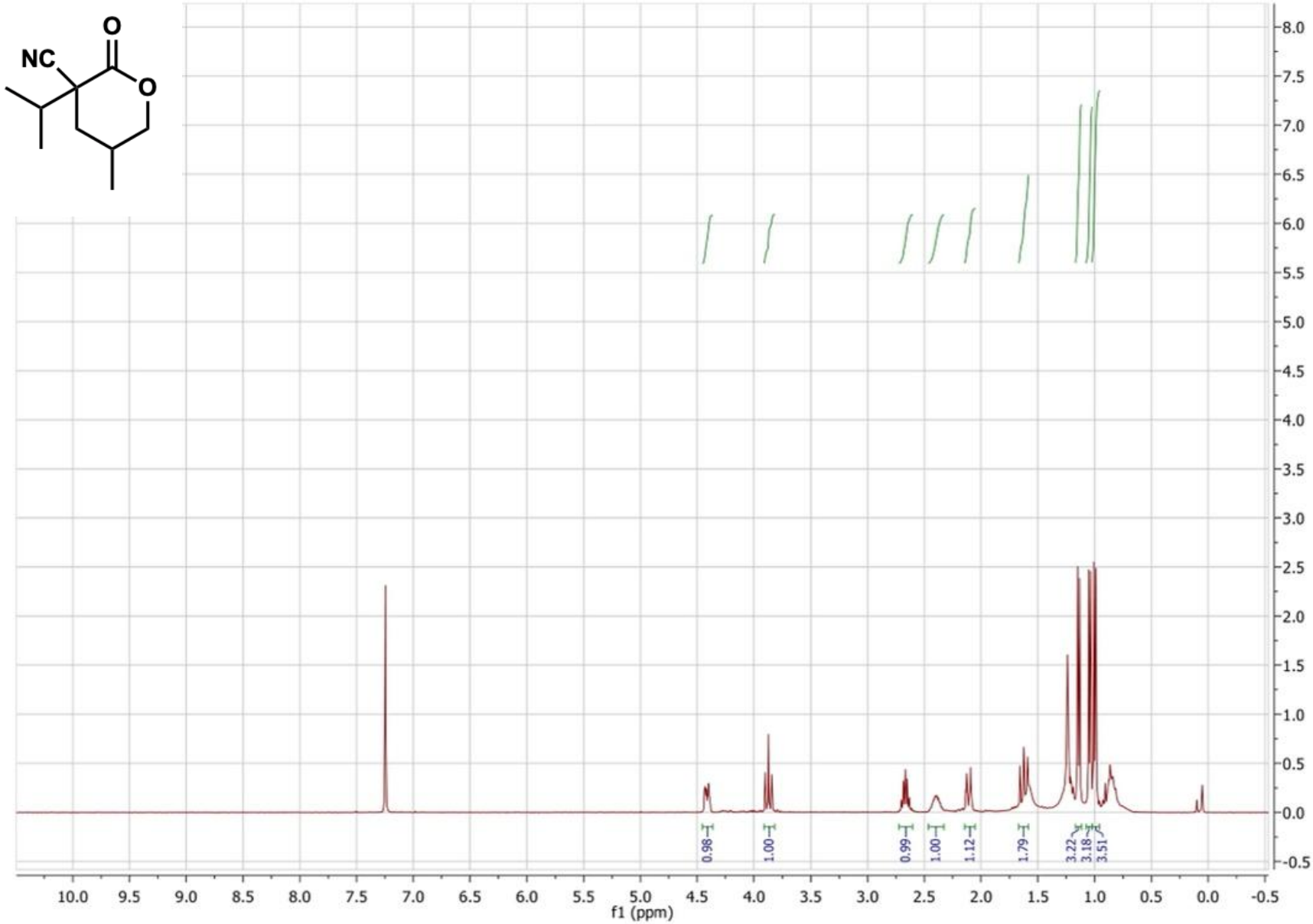

NC
O
O
165.06
137.41
129.36
128.39
127.22
119.53
74.84
49.20
37.71
35.17
32.40
17.55
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

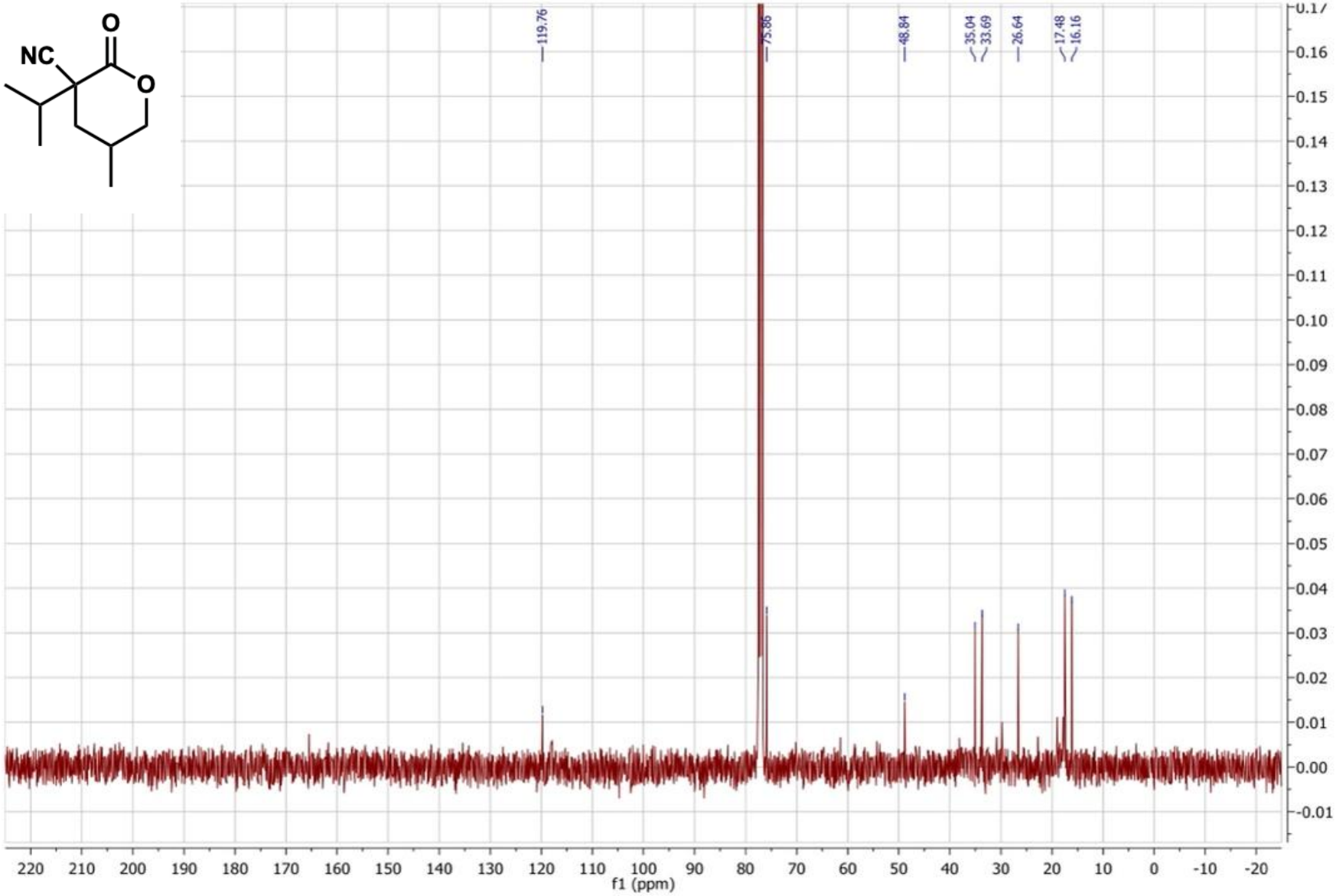

NC
O
O
5.96
1.04
1.07
1.01
1.04
1.05
3.00
f1 (ppm)

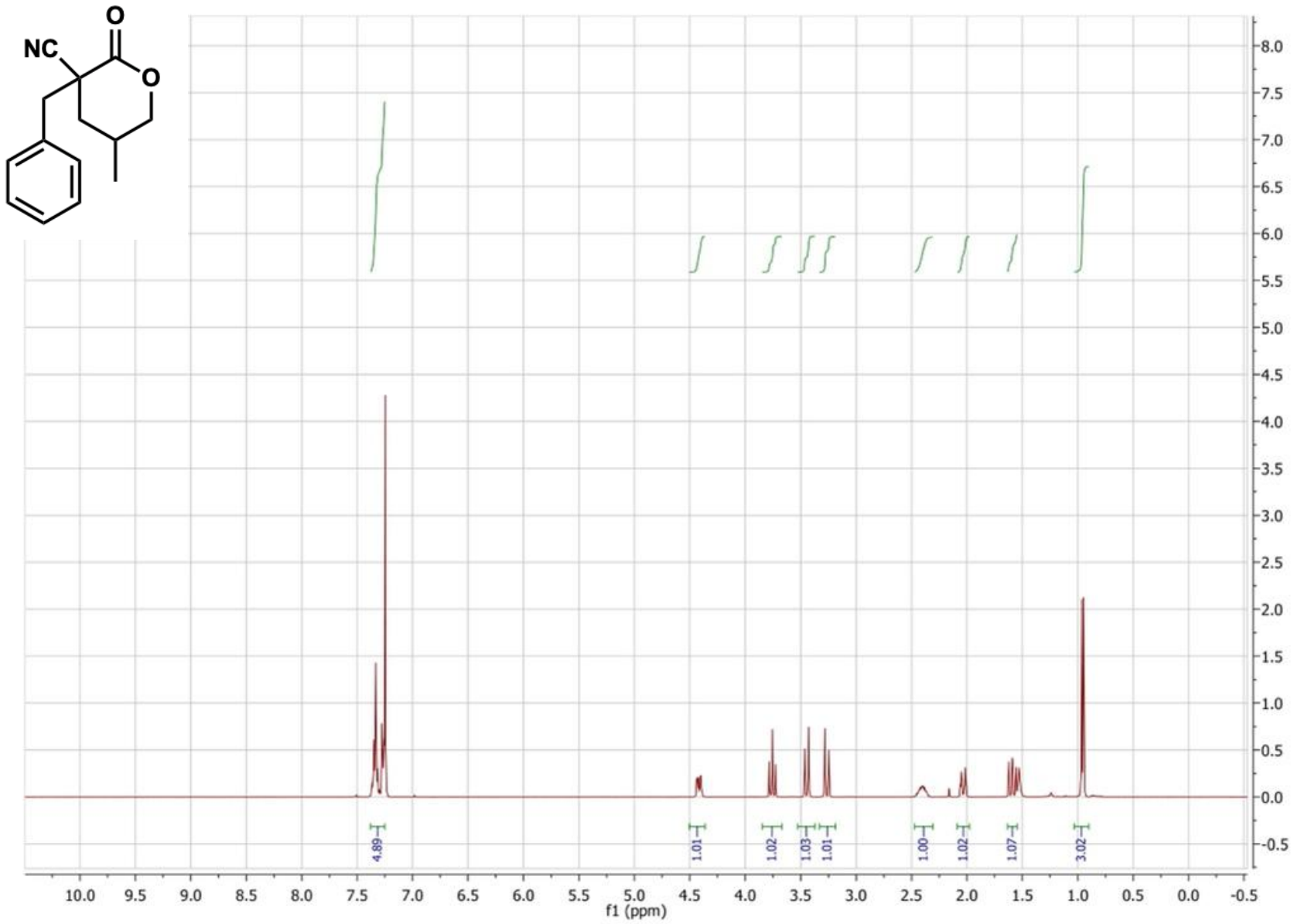

NC
O
O
165.41
137.59
129.36
128.32
127.21
119.53
75.37
39.68
39.52
37.92
24.17
f1 (ppm)

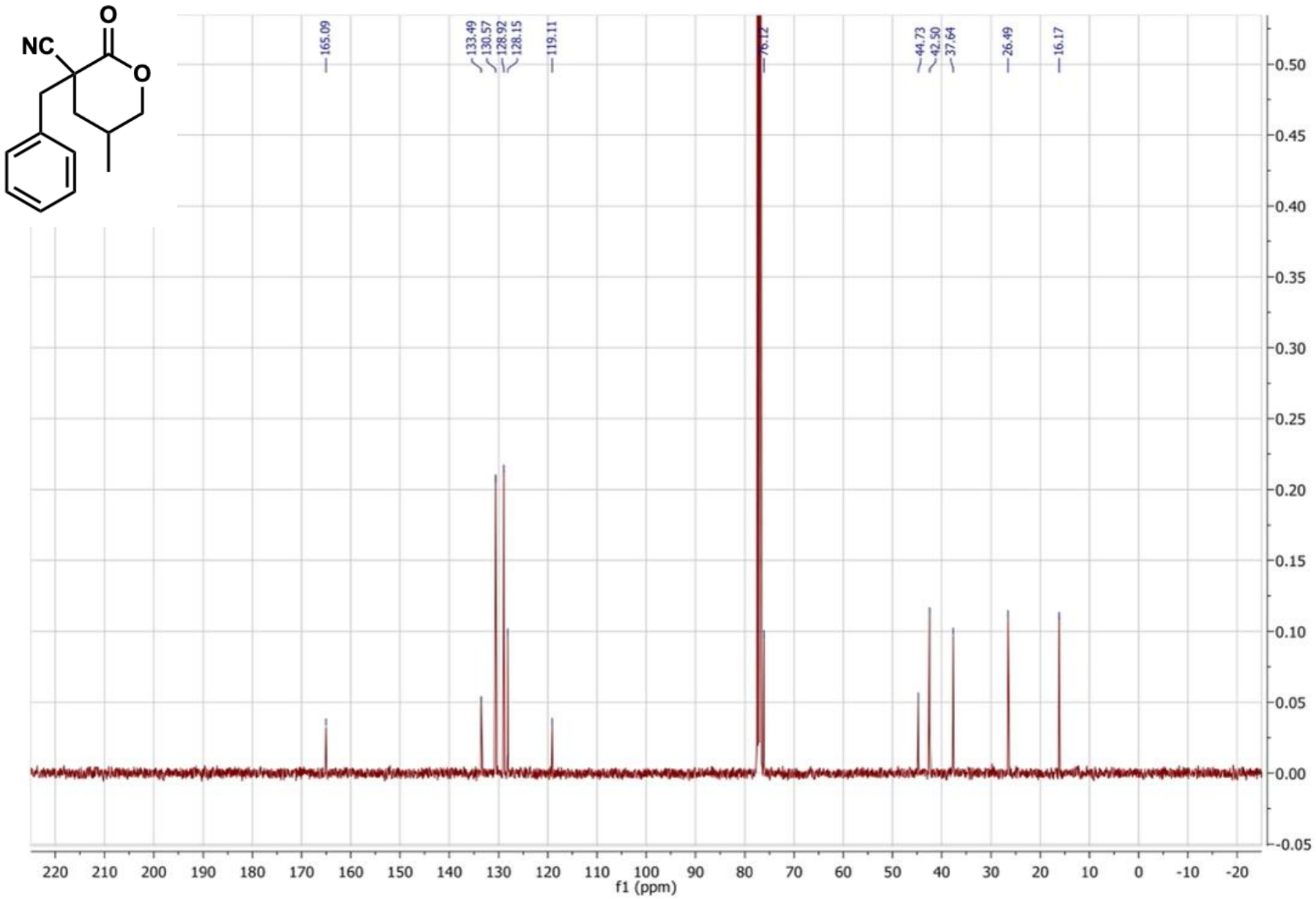

NC
O
O
Cl
2.21
2.52
0.99
1.00
1.03
1.02
1.02
1.09
1.72
2.92
f1 (ppm)

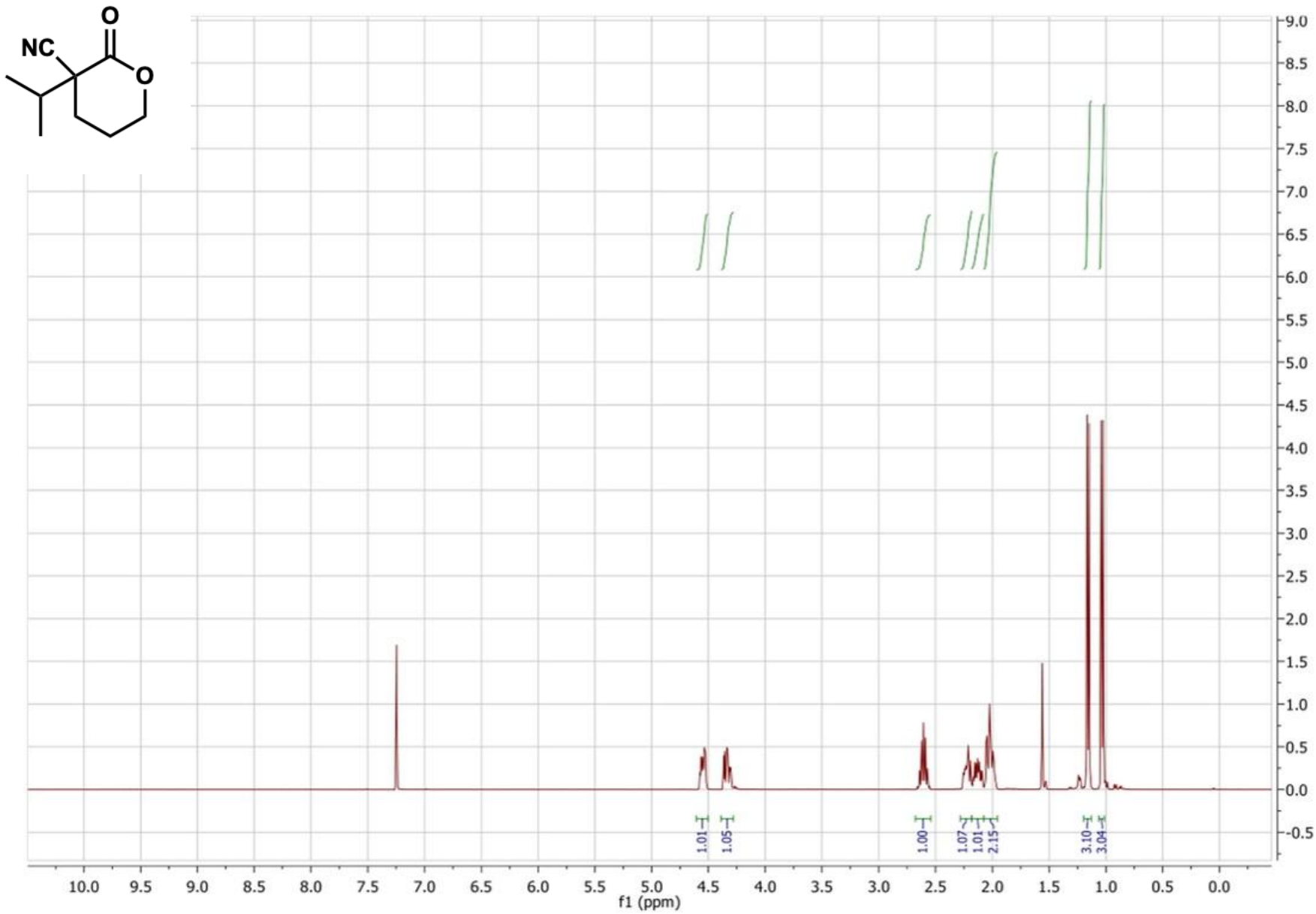

NC
O
O
Cl
164.79
134.31
131.91
129.15
118.83
76.17
44.60
41.74
37.62
26.47
16.20
f1 (ppm)

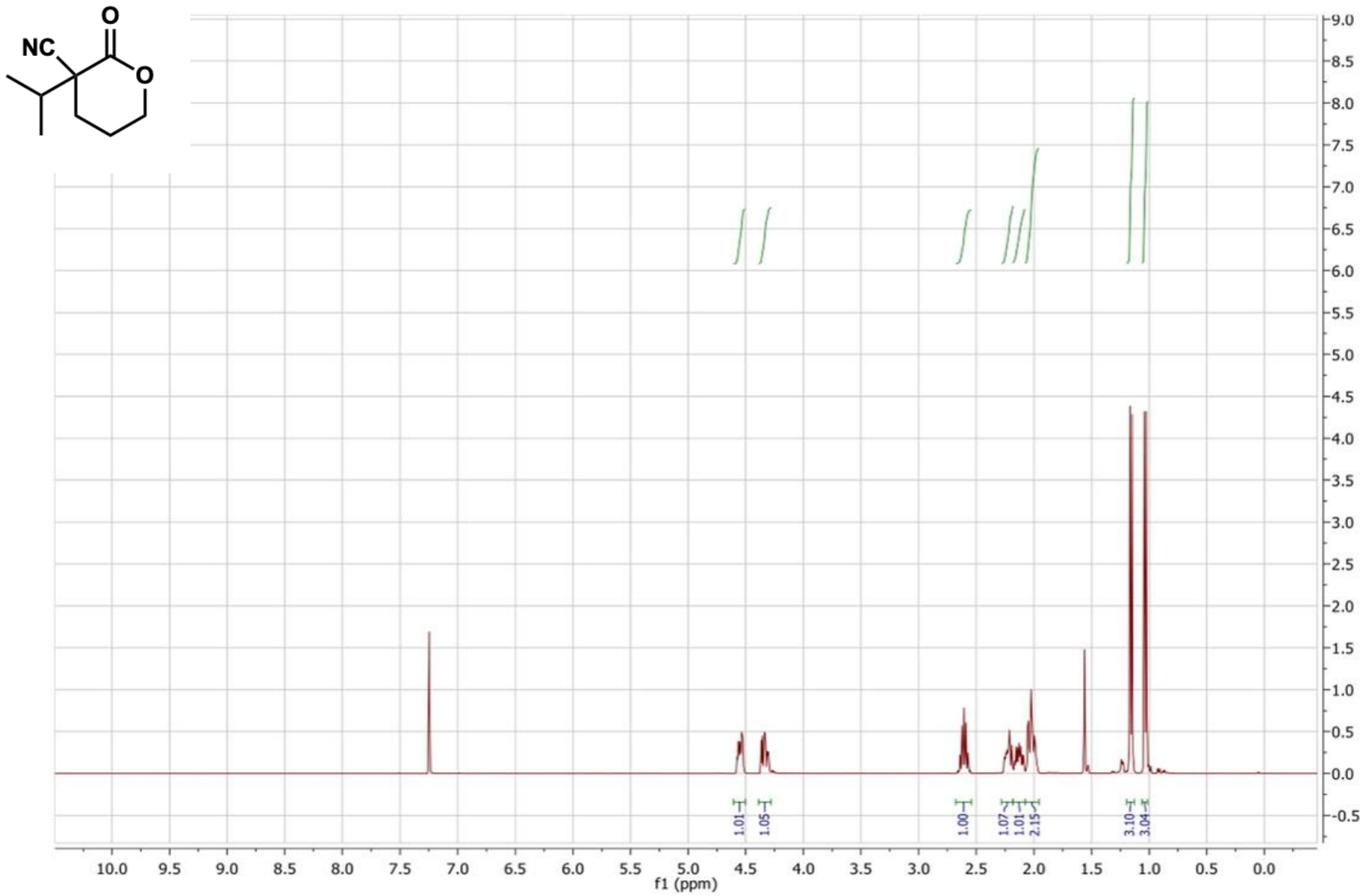

NC
O
O
0.98
1.00
0.99
1.00
1.12
1.79
3.22
3.18
3.51
f1 (ppm)

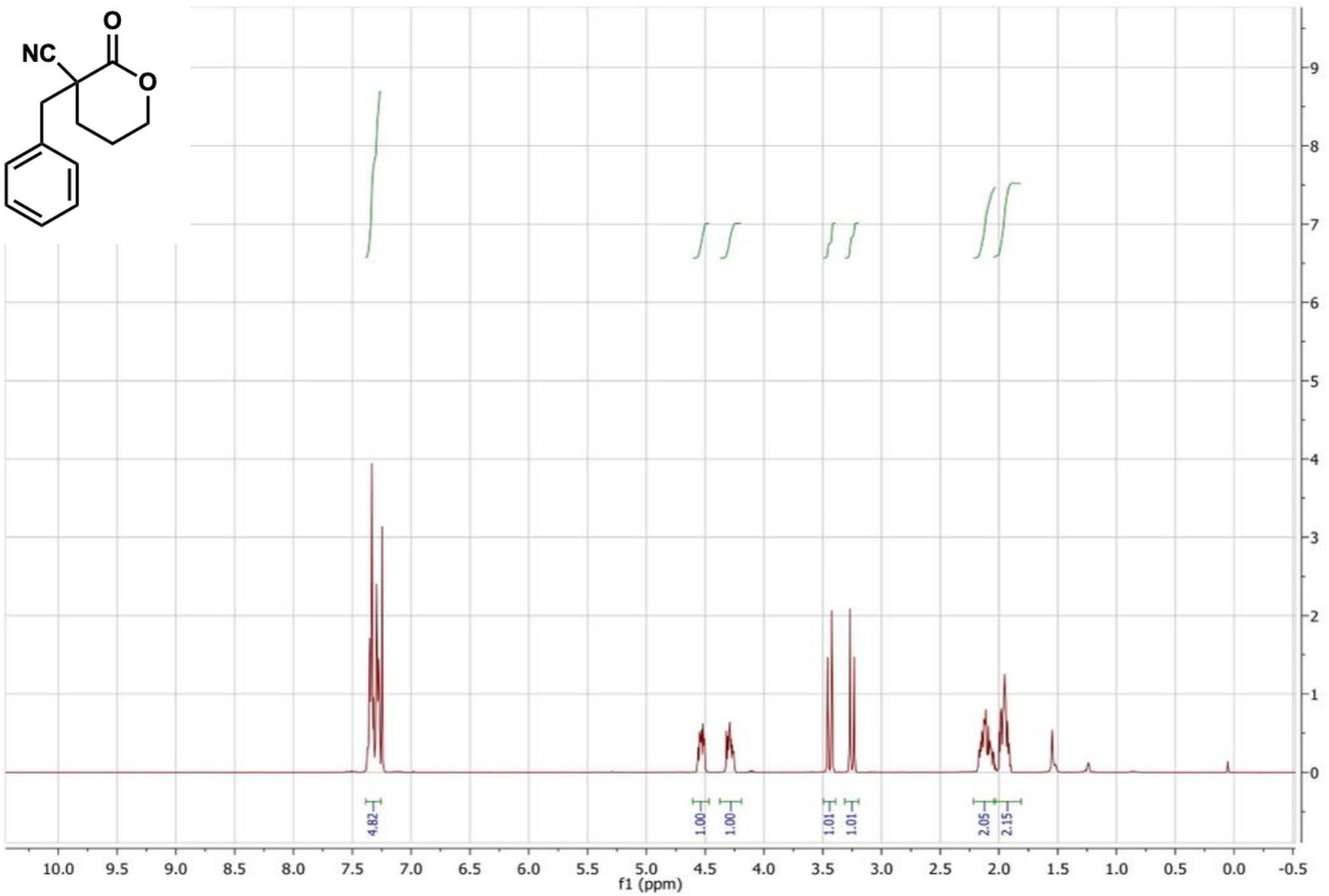

NC
O
O
119.76
75.86
48.84
35.04
33.69
26.64
17.48
16.16
f1 (ppm)

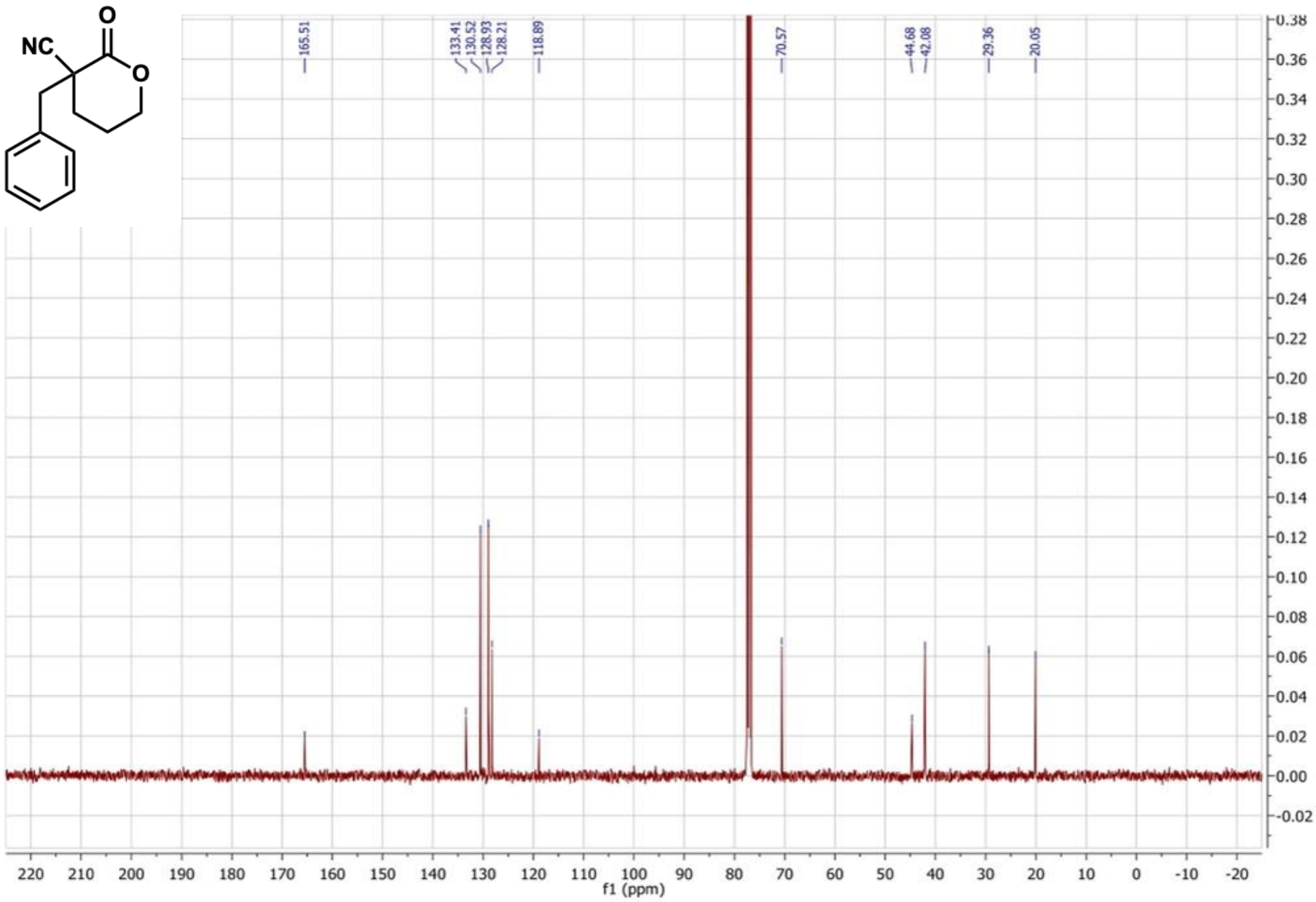

NC
O
O
4.89
1.01
1.02
1.03
1.01
1.00
1.02
1.07
3.02
f1 (ppm)

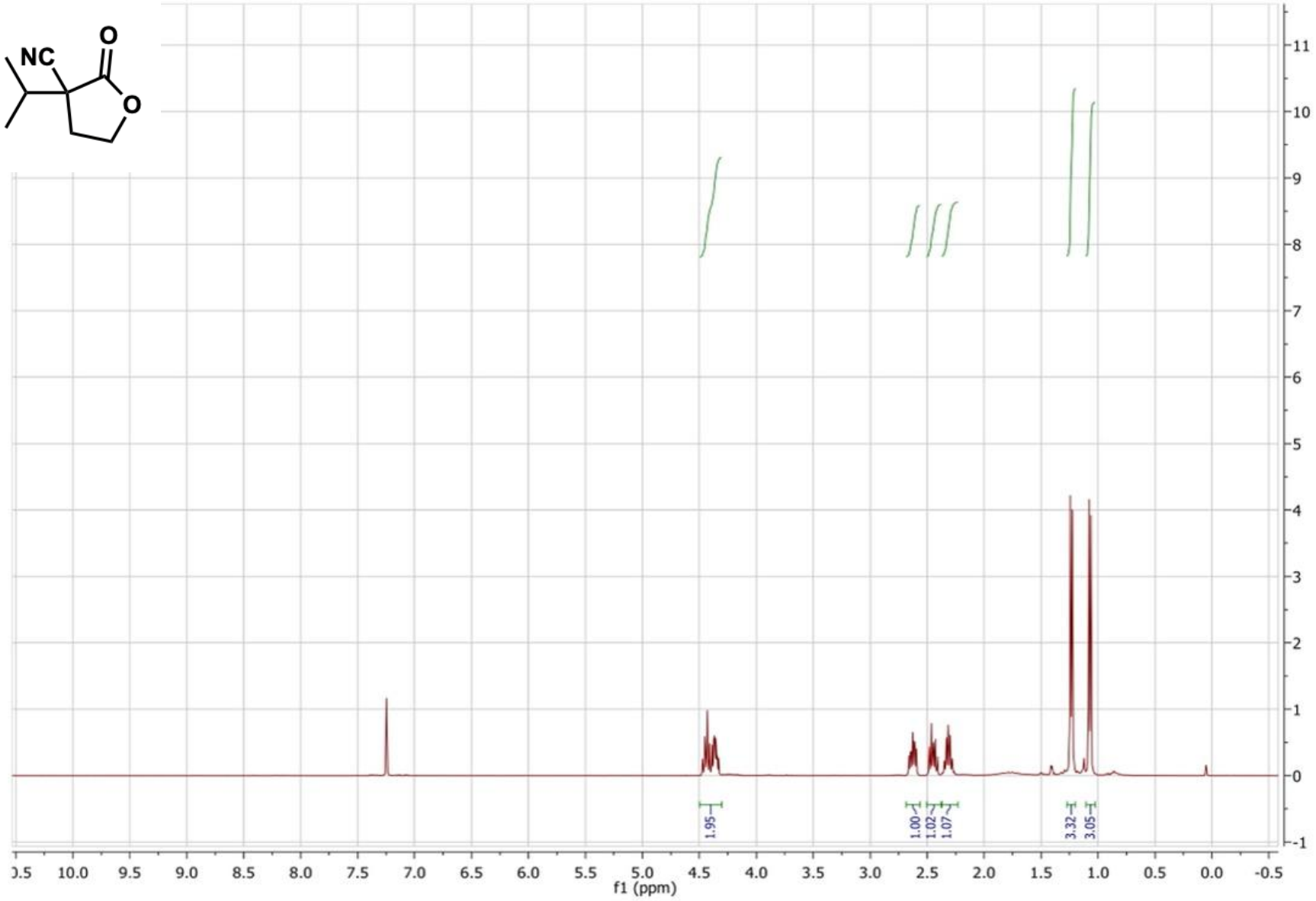

NC
O
O
165.09
133.49
130.57
128.92
128.15
119.11
44.73
42.50
37.64
26.49
16.17
f1 (ppm)

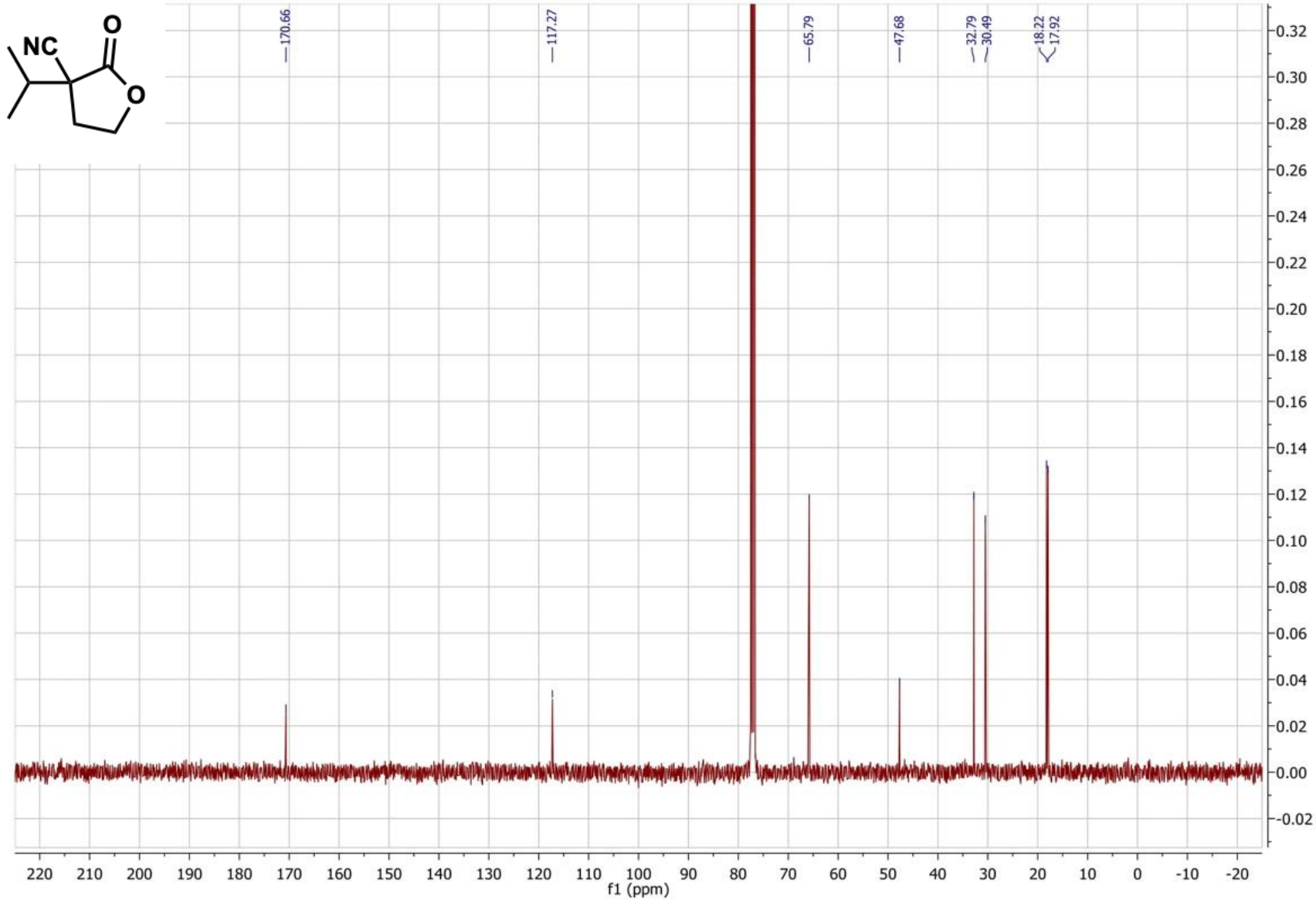

NC
O
O
1.01
1.05
1.00
1.07
1.01
2.15
3.10
3.04
f1 (ppm)

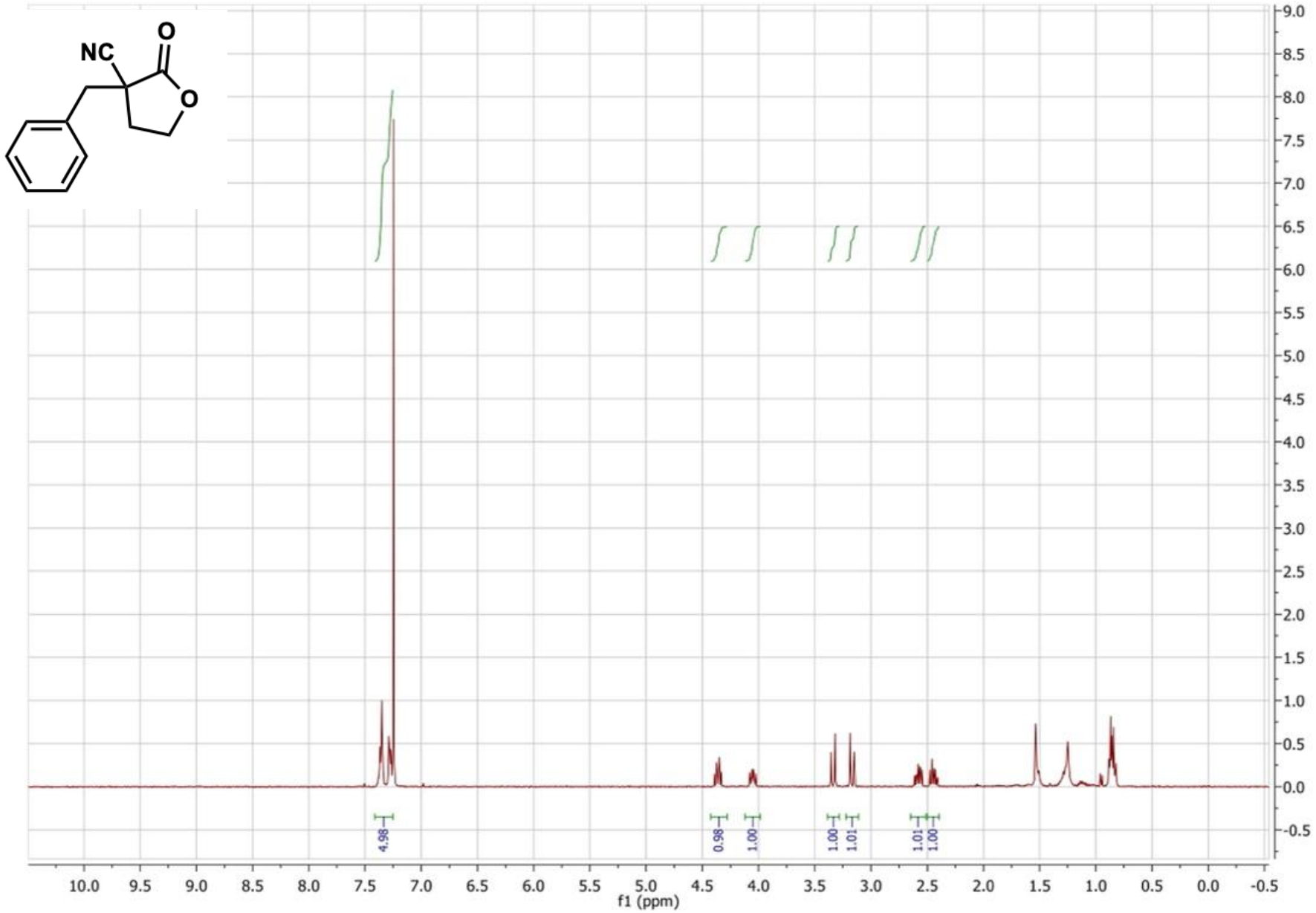

NC
O
O
1.01
1.05
1.00
1.07
1.01
2.15
3.10
3.04
f1 (ppm)

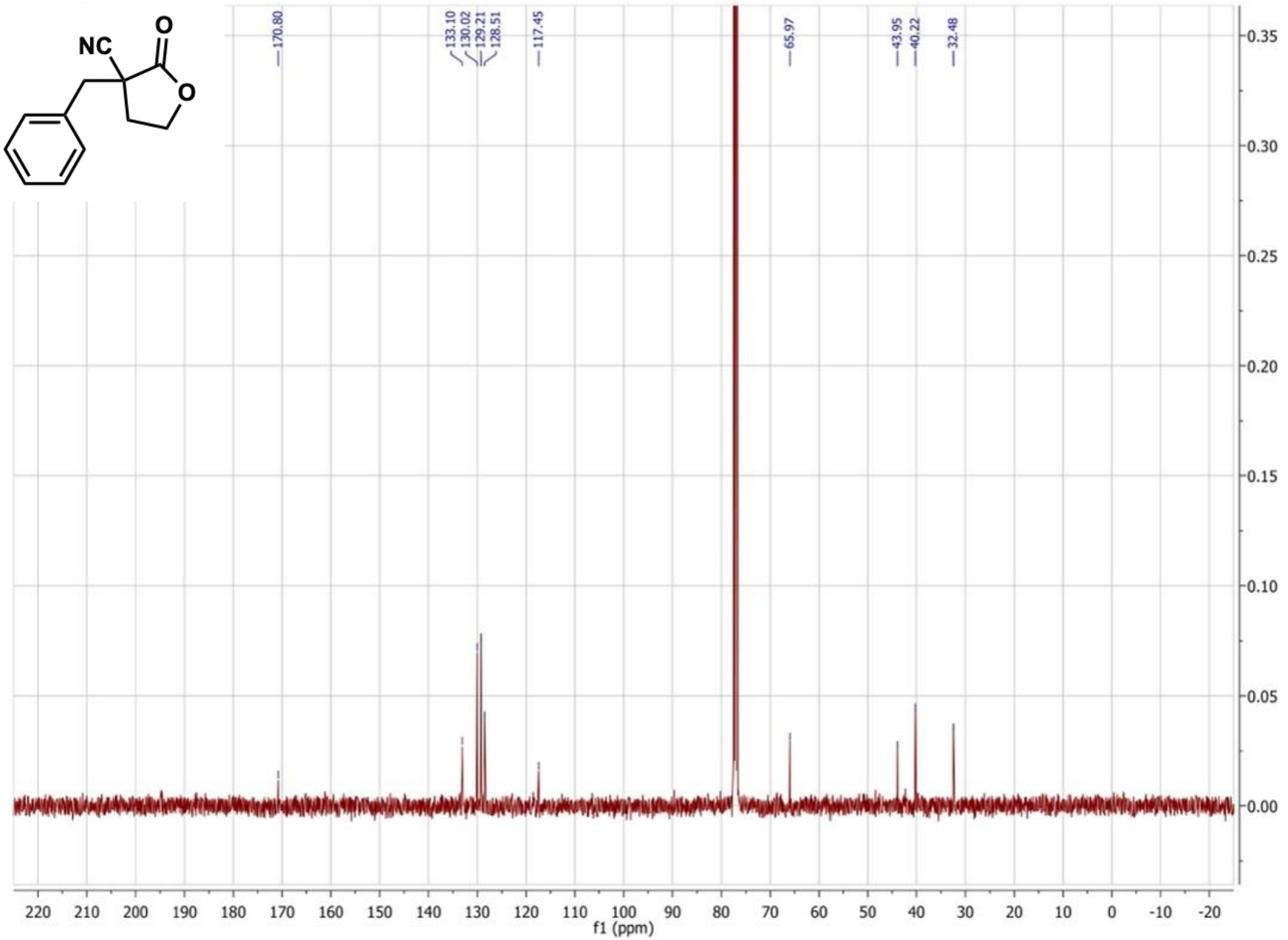

NC
O
O
4.82
1.00
1.00
1.01
1.01
2.05
2.15
f1 (ppm)

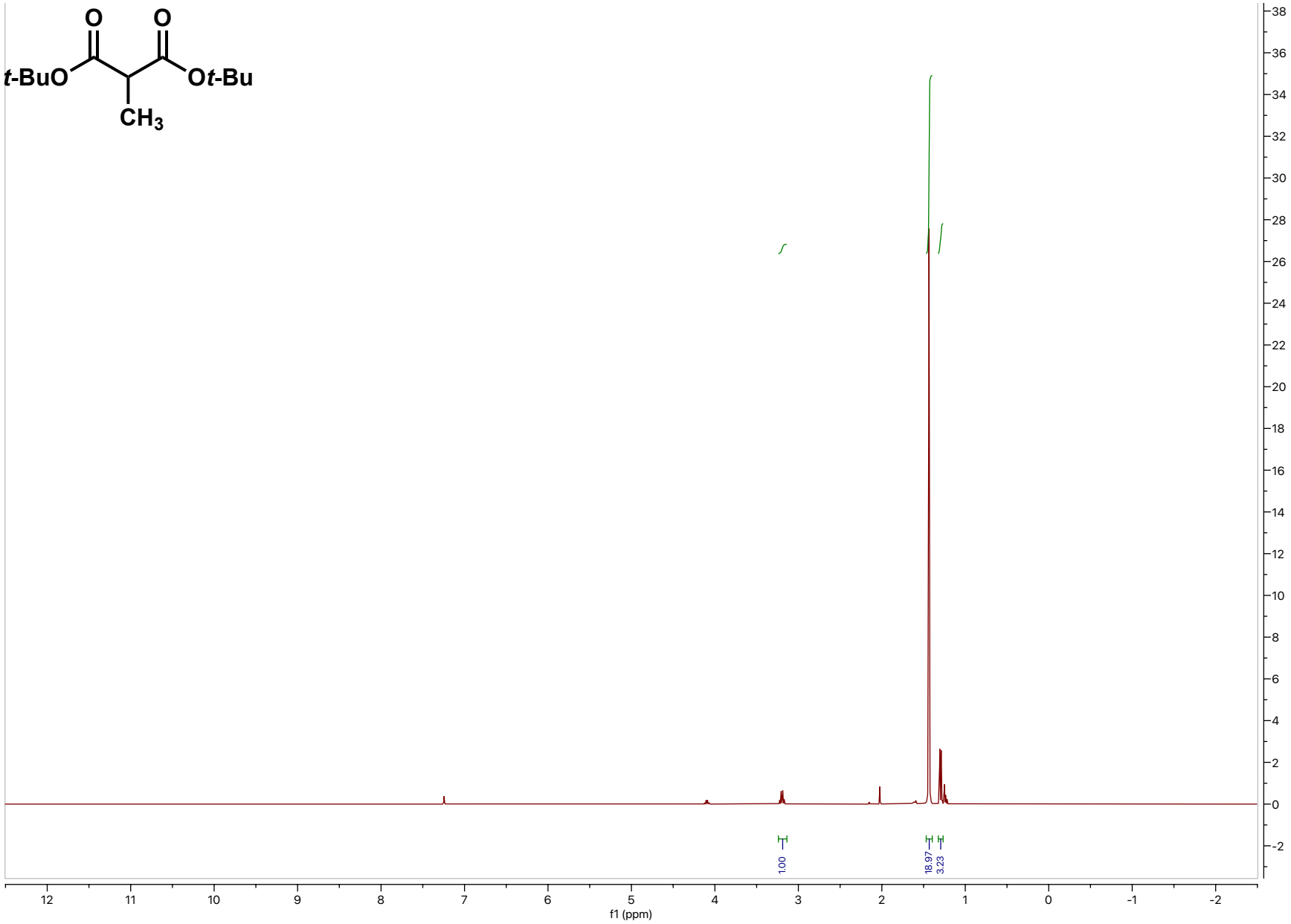

NC
O
O
165.51
133.41
130.52
128.93
128.21
118.89
70.57
44.68
42.08
29.36
20.05
f1 (ppm)

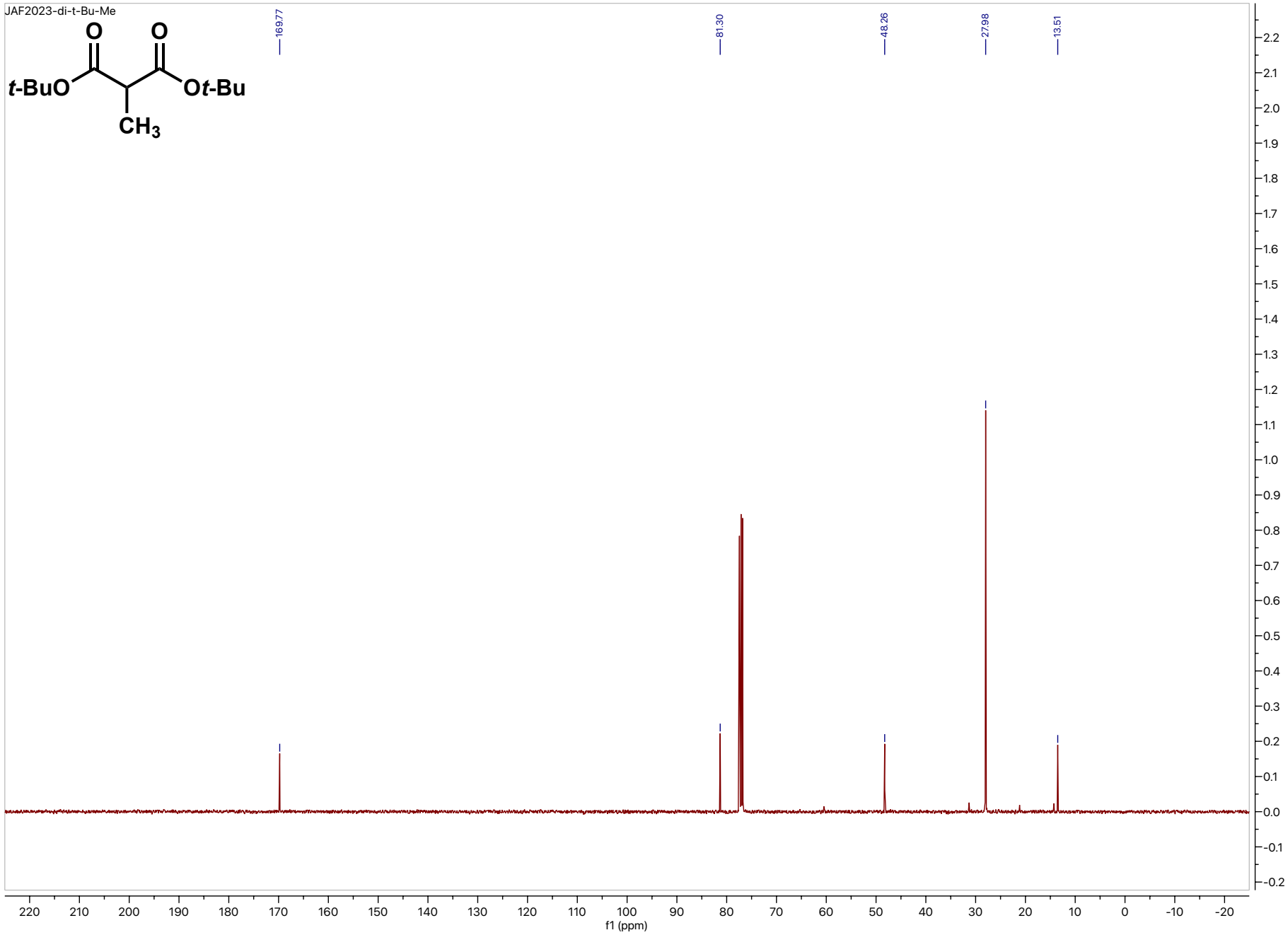

NC
O
O
1.95
1.00
1.02
1.07
3.32
3.05
f1 (ppm)

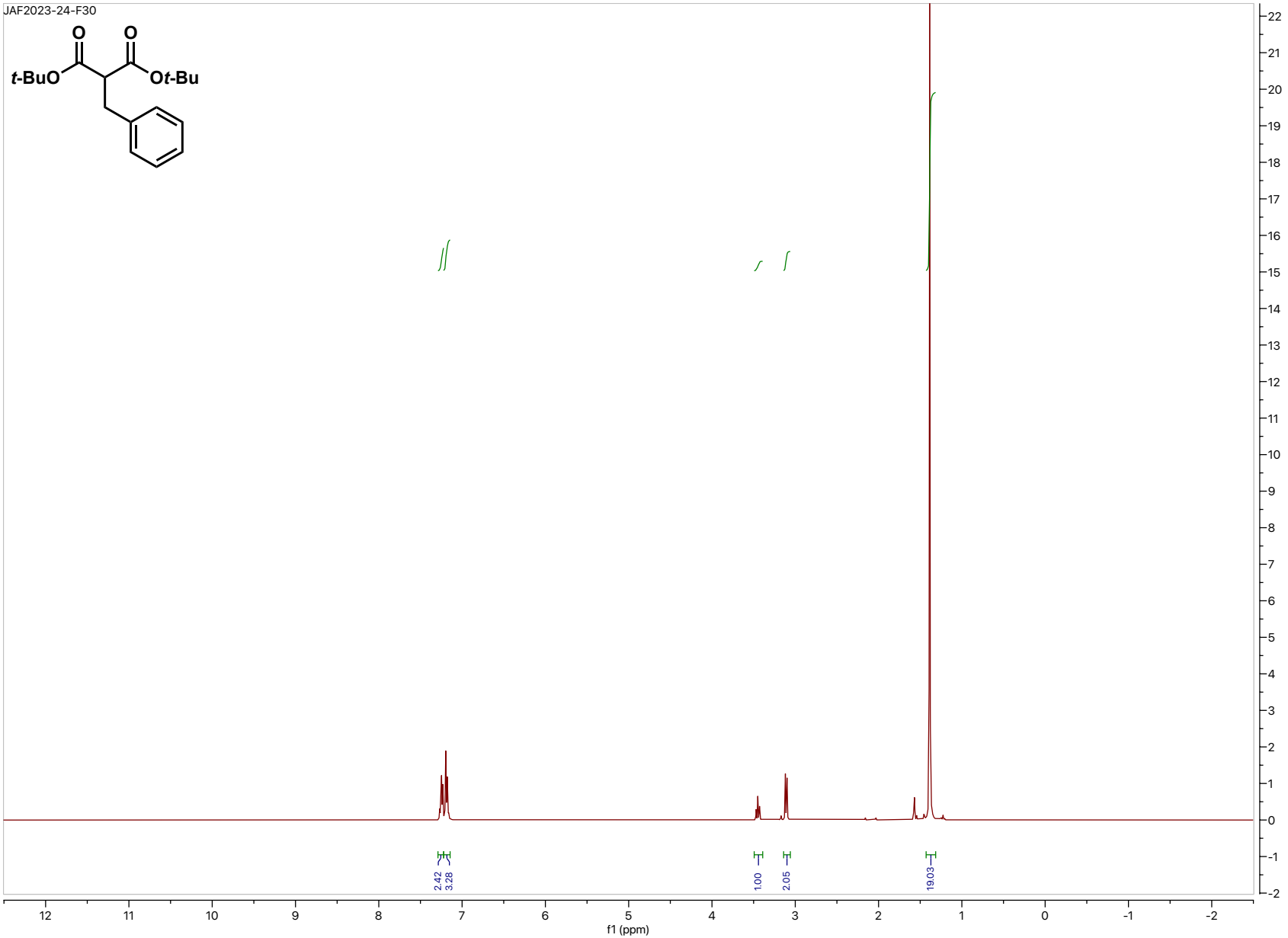

NC
O
O
170.66
117.27
65.79
47.68
32.79
30.49
18.22
17.92
0.32
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

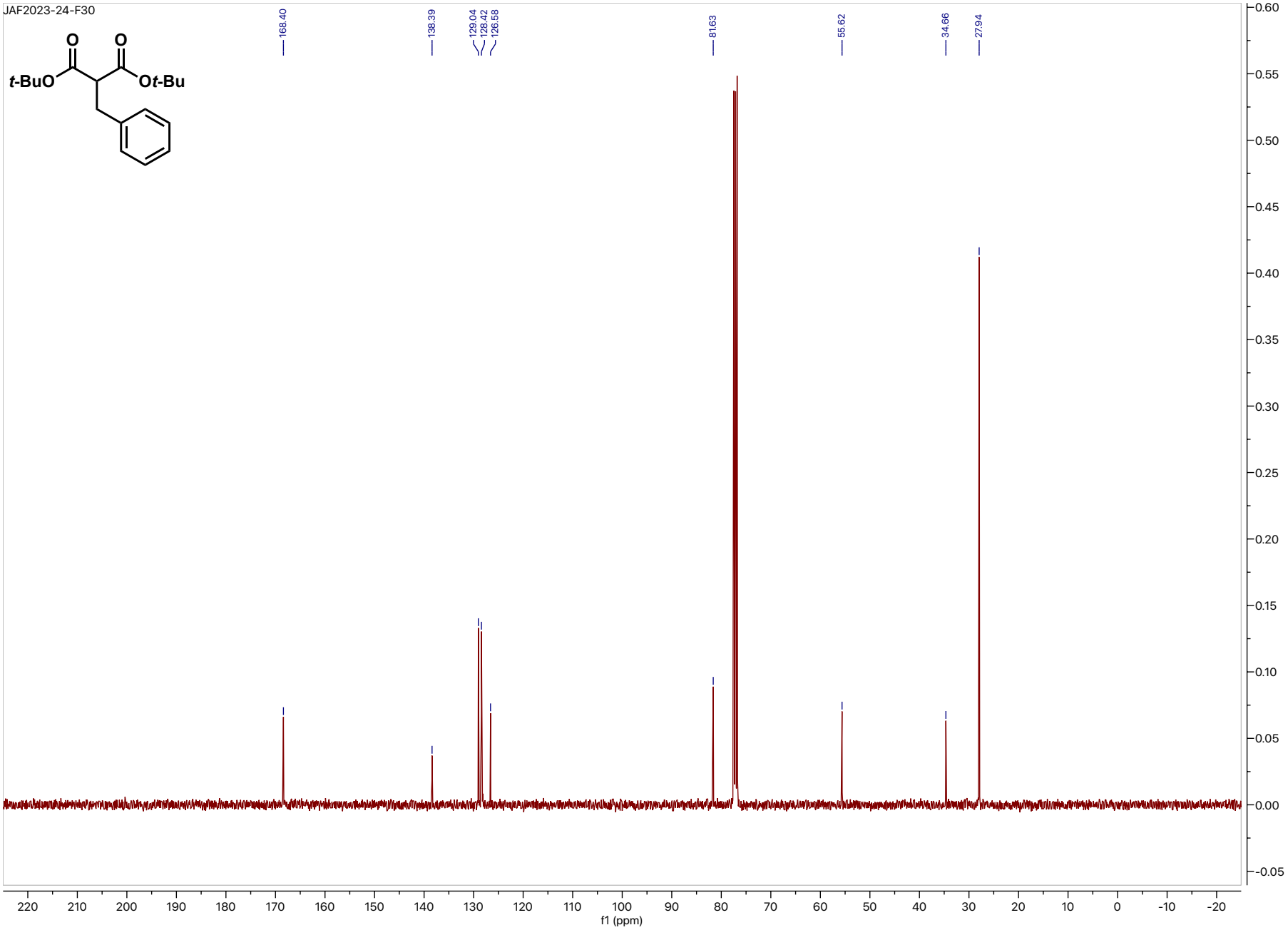

NC
O
O
4.98
0.98
1.00
1.00
1.01
1.01
1.00
f1 (ppm)

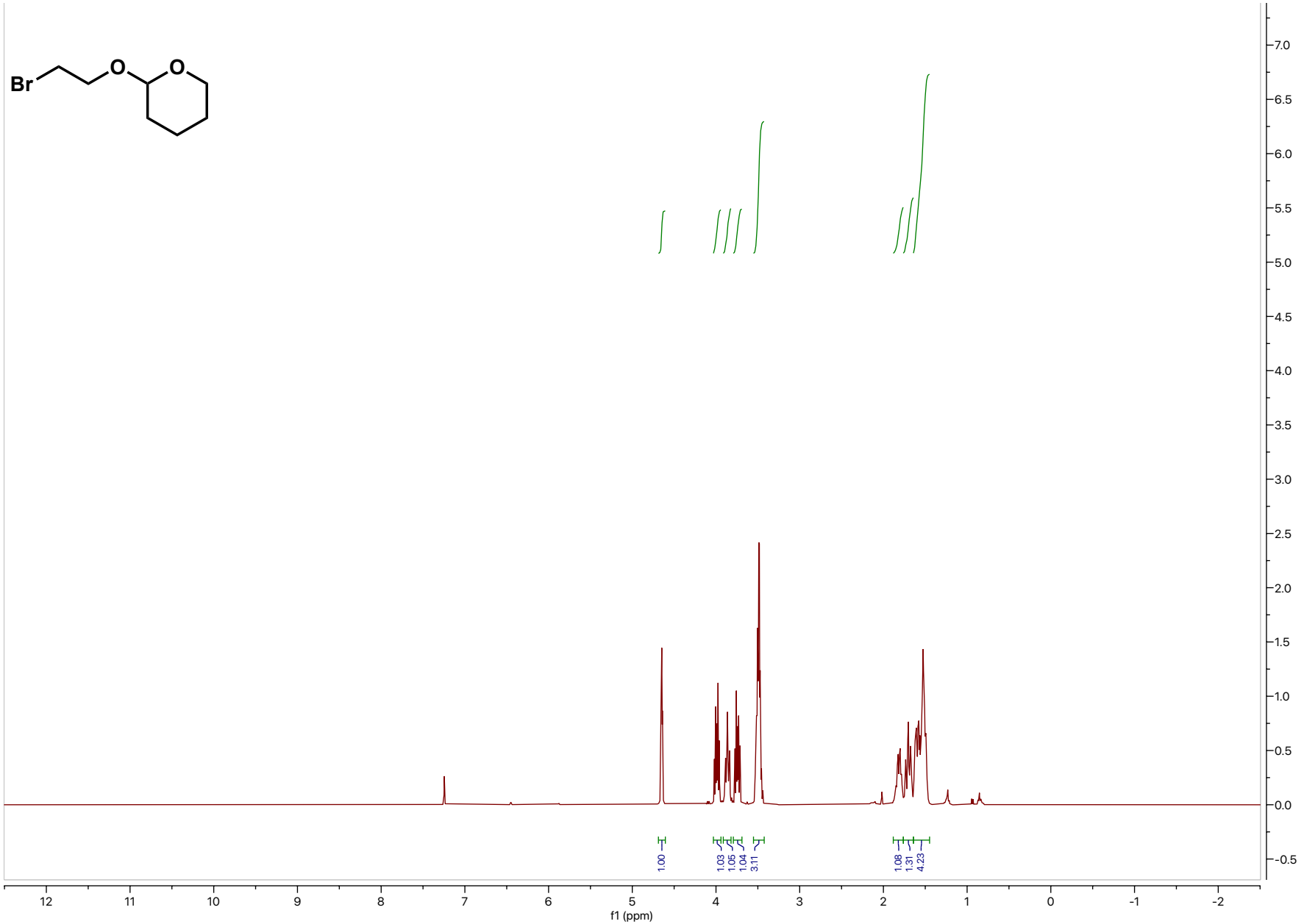

NC
O
O
170.80
133.10
130.02
129.21
128.51
117.45
65.97
43.95
40.22
32.48
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

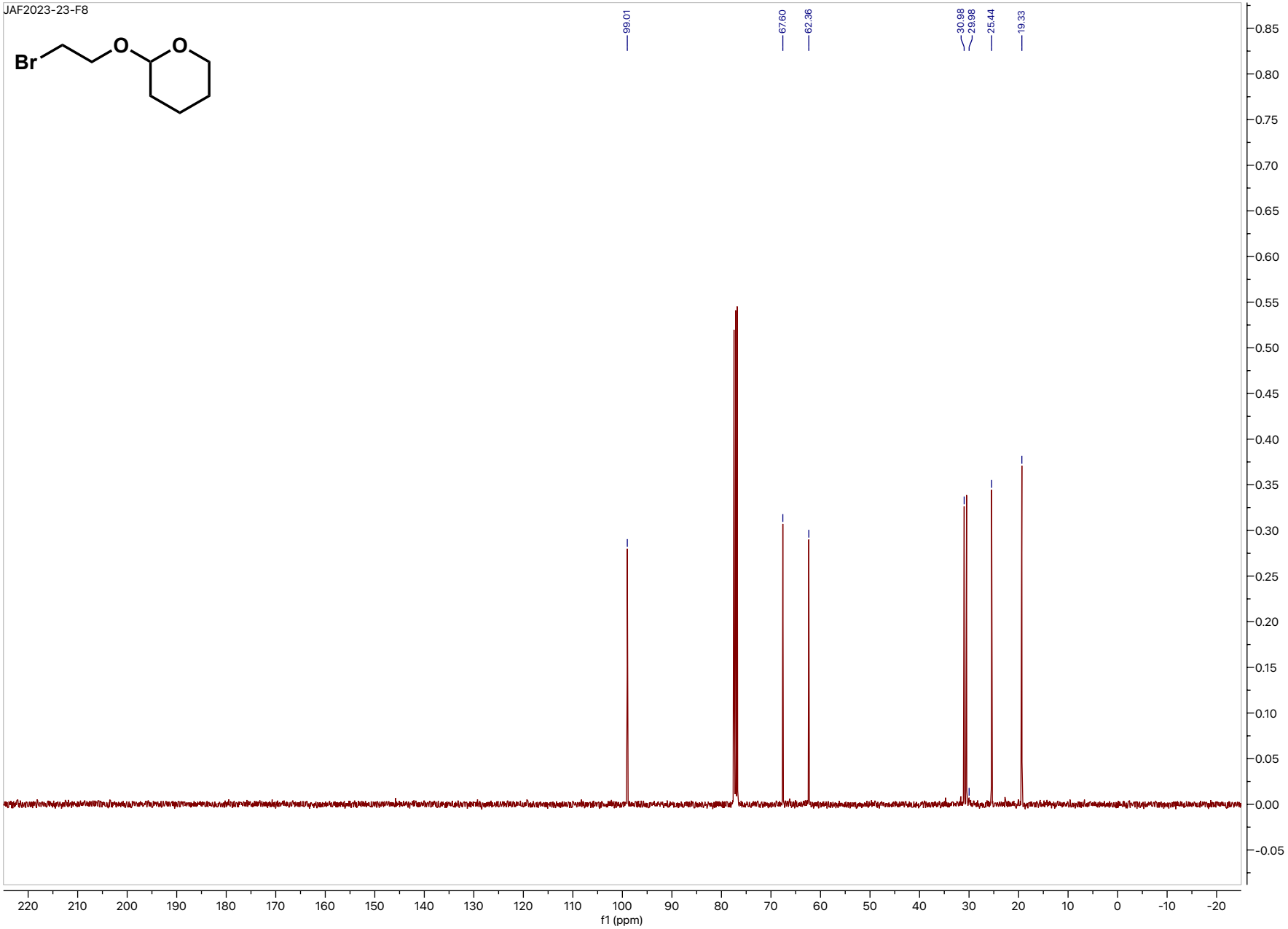

O
O
t-BuO
Ot-Bu
CH3
1.00
18.97
3.23
f1 (ppm)

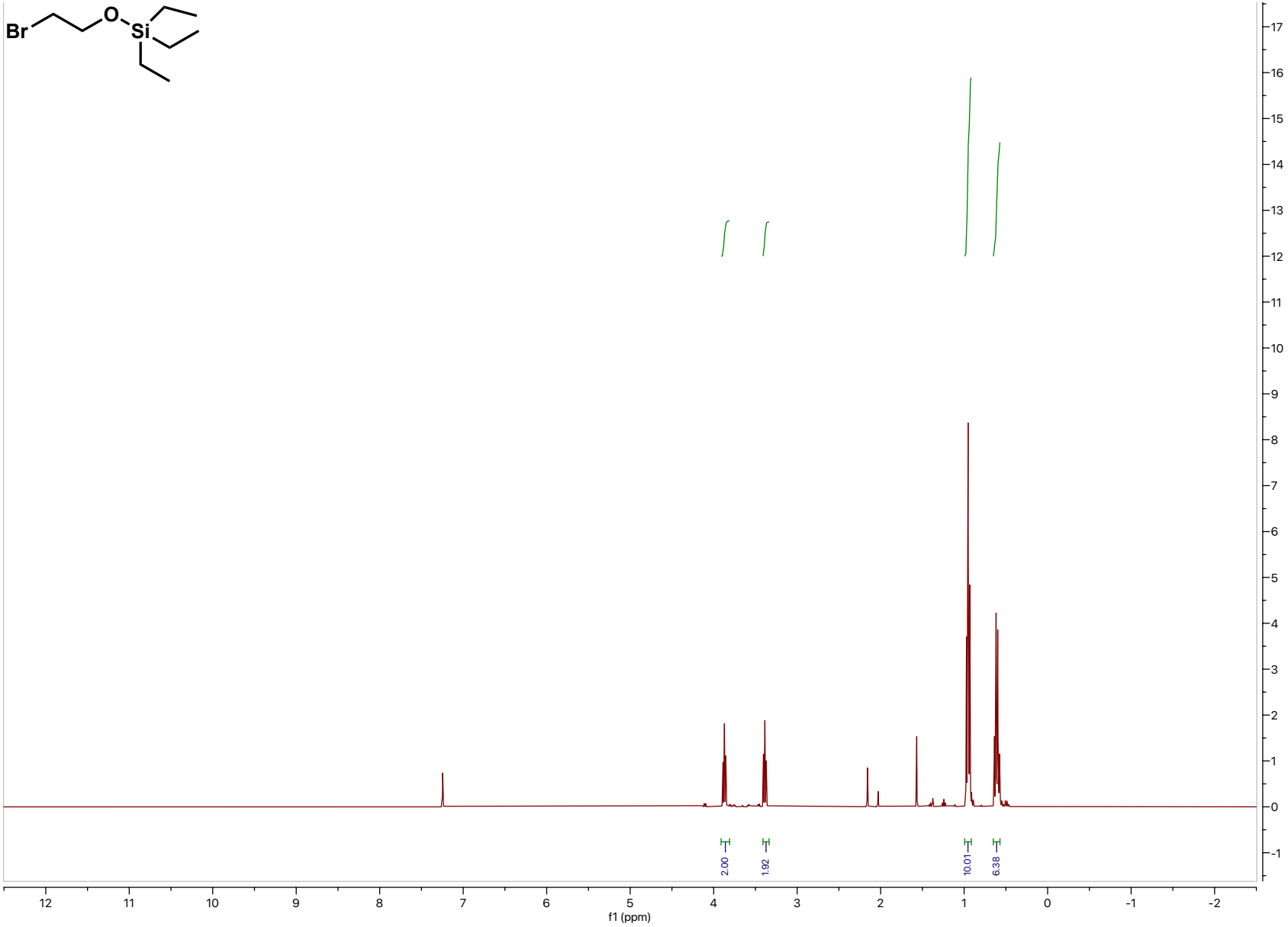

JAF2023-di-t-Bu-Me
O
O
t-BuO
Ot-Bu
CH3
169.77
81.30
48.26
27.98
13.51
f1 (ppm)

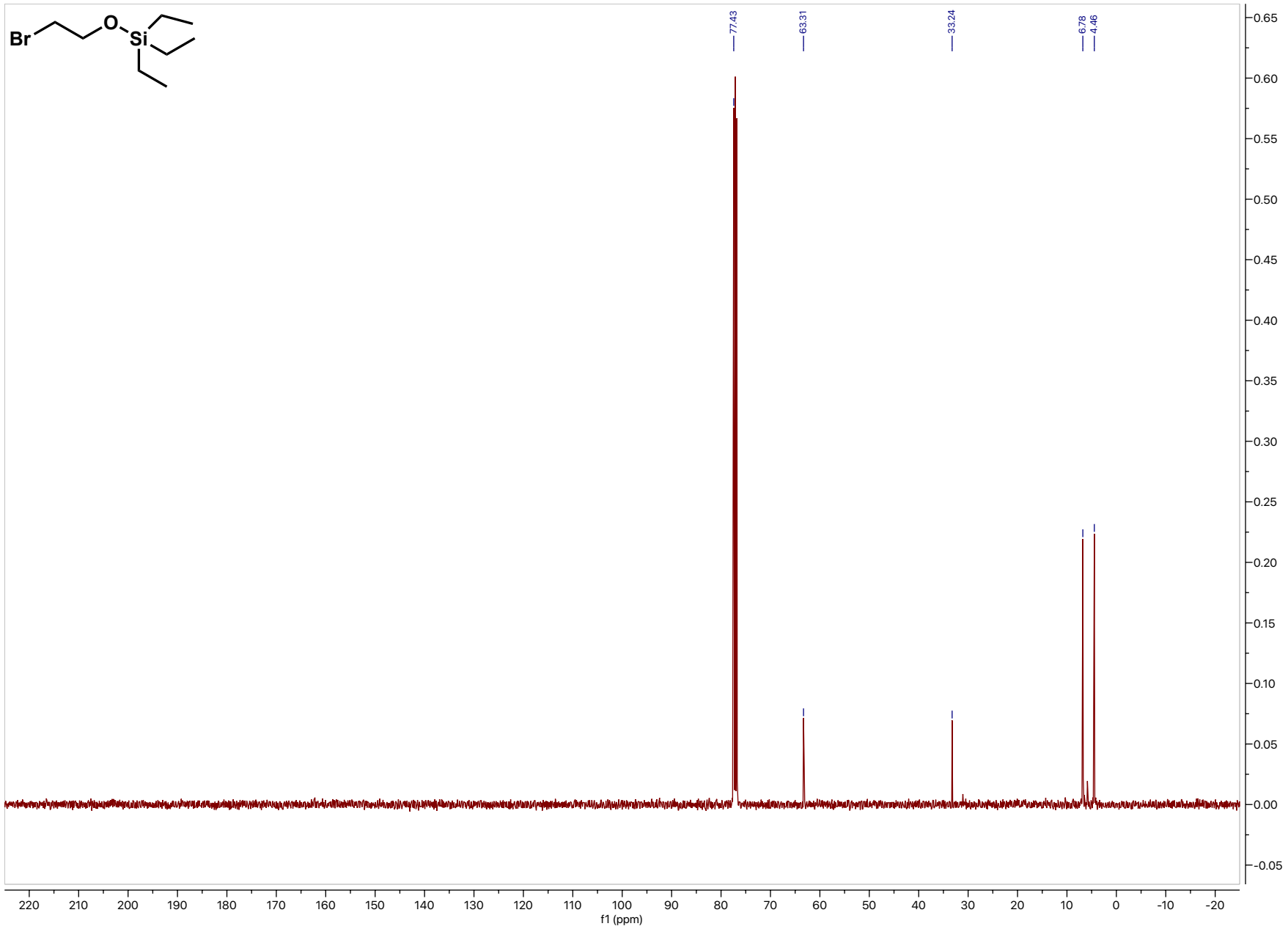

JAF2023-24-F30
O
O
t-BuO
Ot-Bu
2.42
3.28
1.00
2.05
19.03
f1 (ppm)

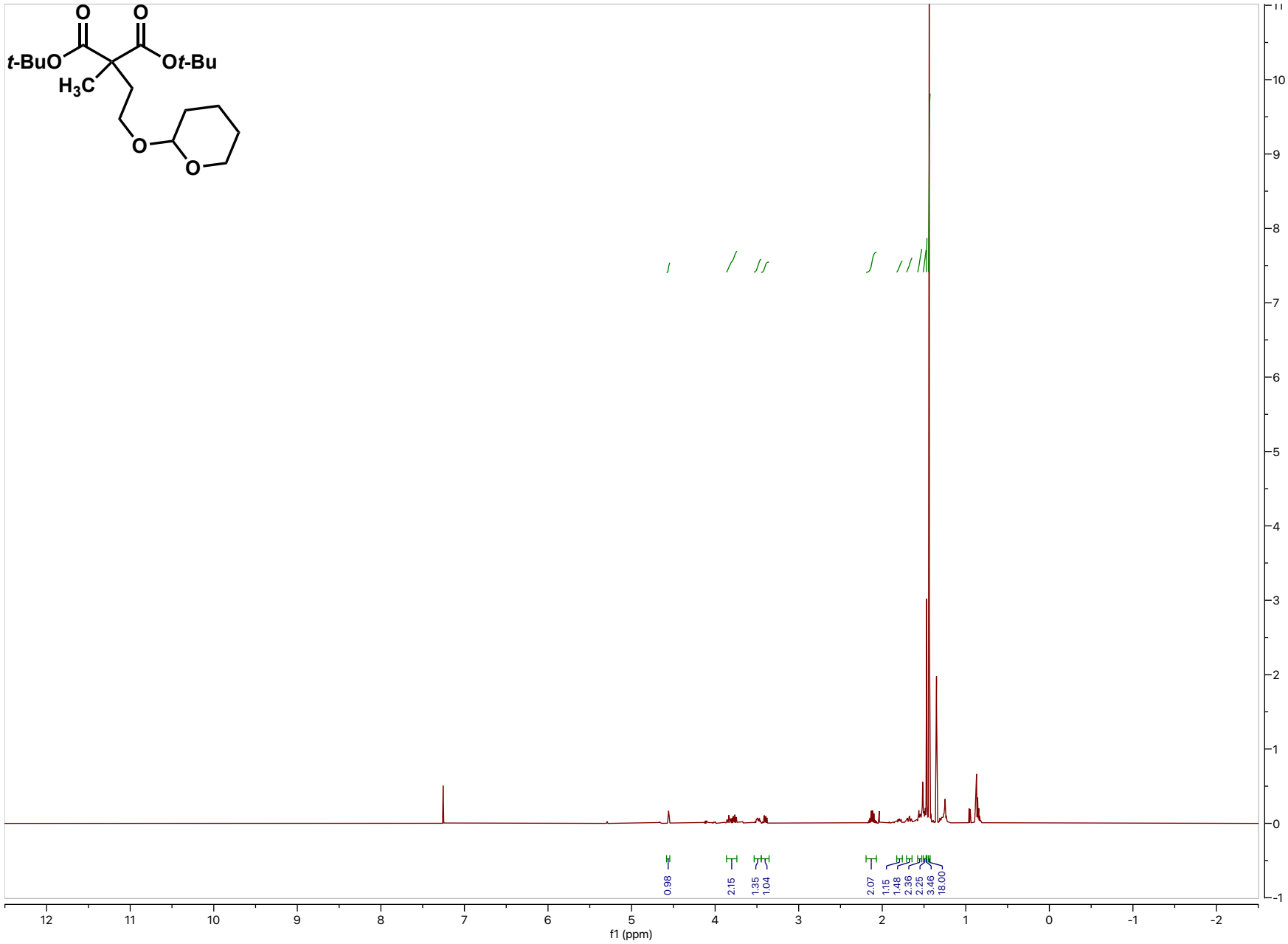

JAF2023-24-F30
t-BuO
O
O
Ot-Bu
168.40
138.39
129.04
128.42
126.58
81.63
55.62
34.66
27.94
f1 (ppm)

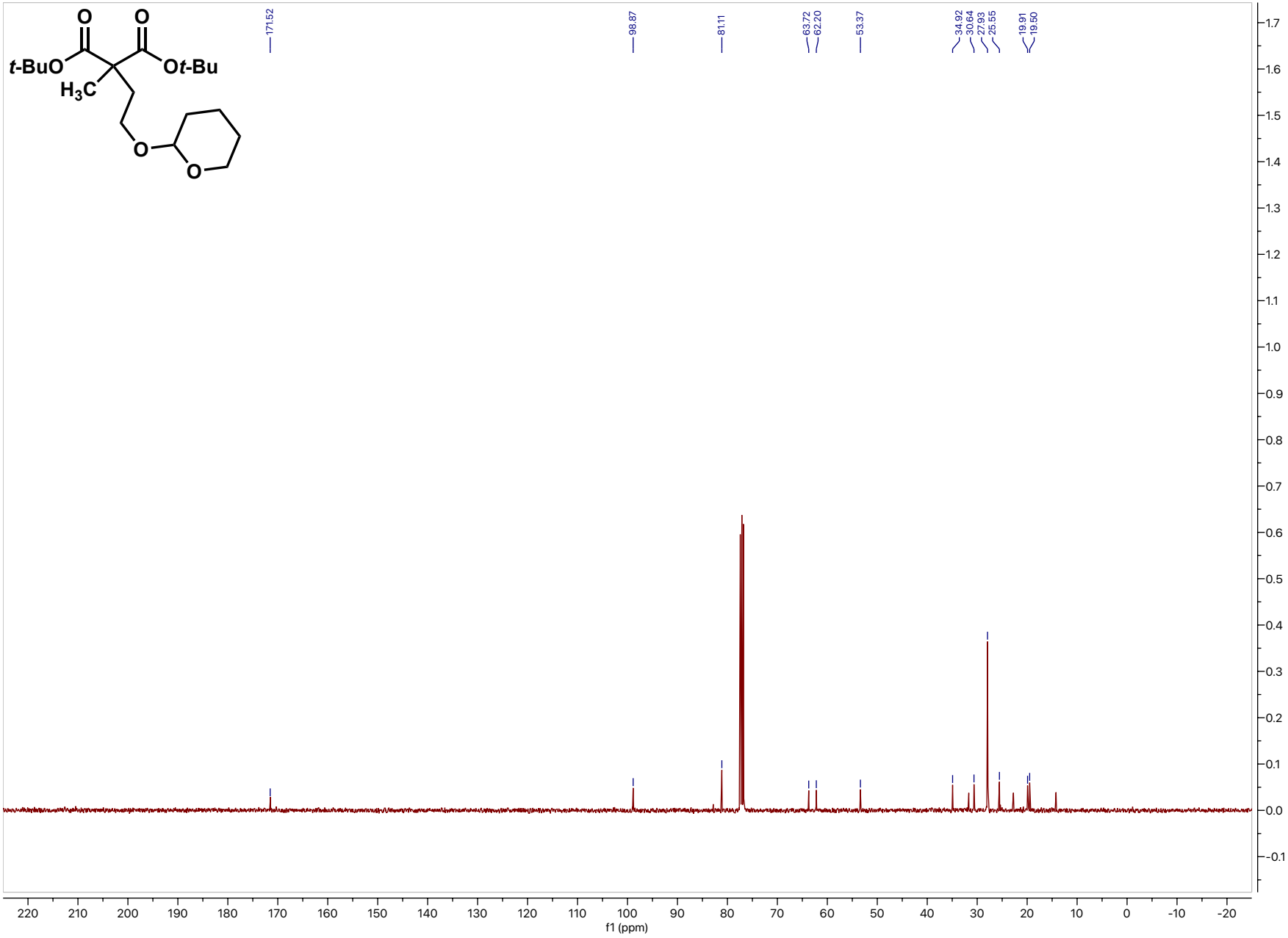

Br
O
O
1.00
1.03
1.05
1.04
3.11
1.08
1.31
4.23
f1 (ppm)

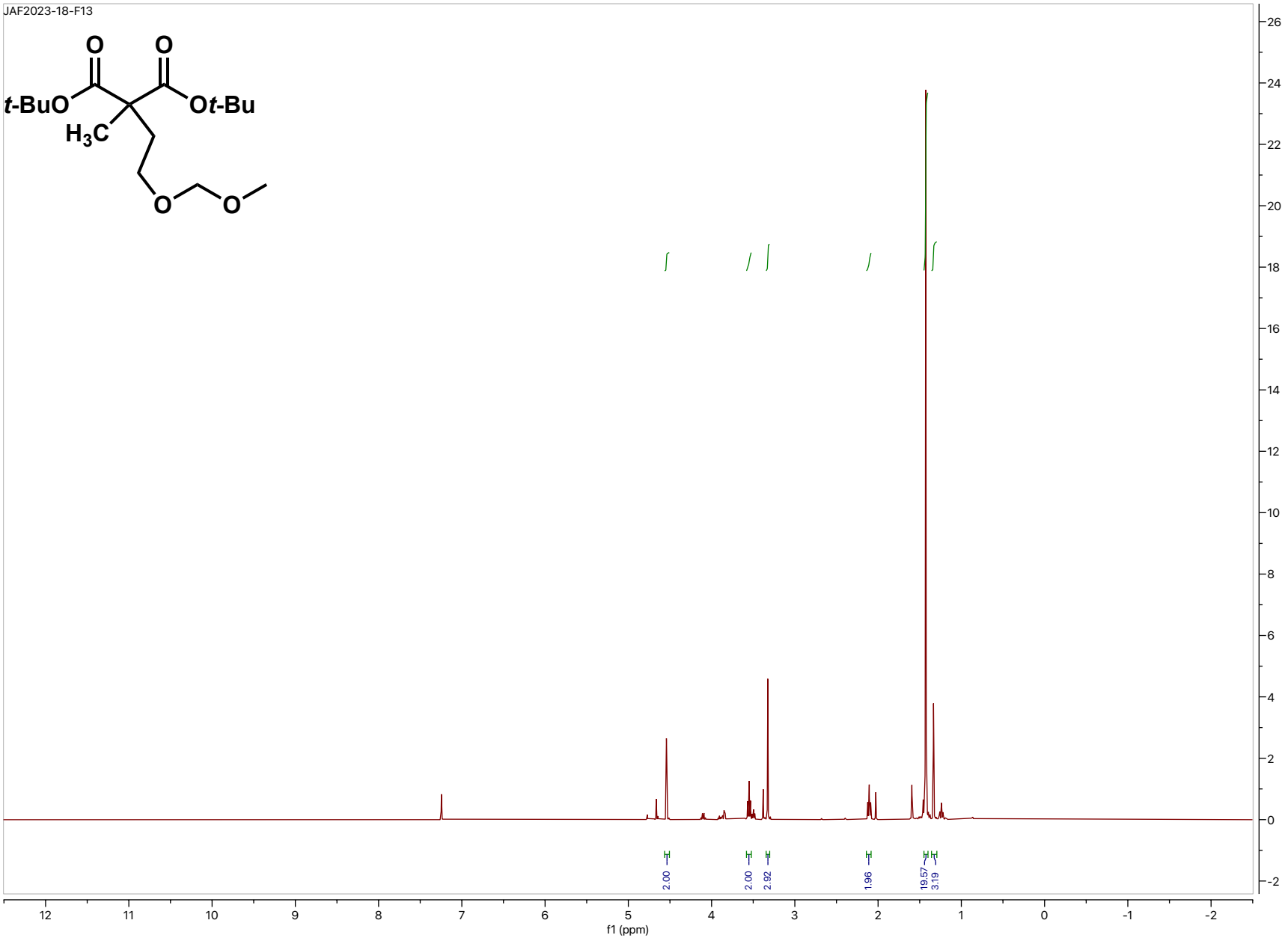

JAF2023-23-F8
Br
O
O
99.01
67.60
62.36
30.98
29.98
25.44
19.33
f1 (ppm)

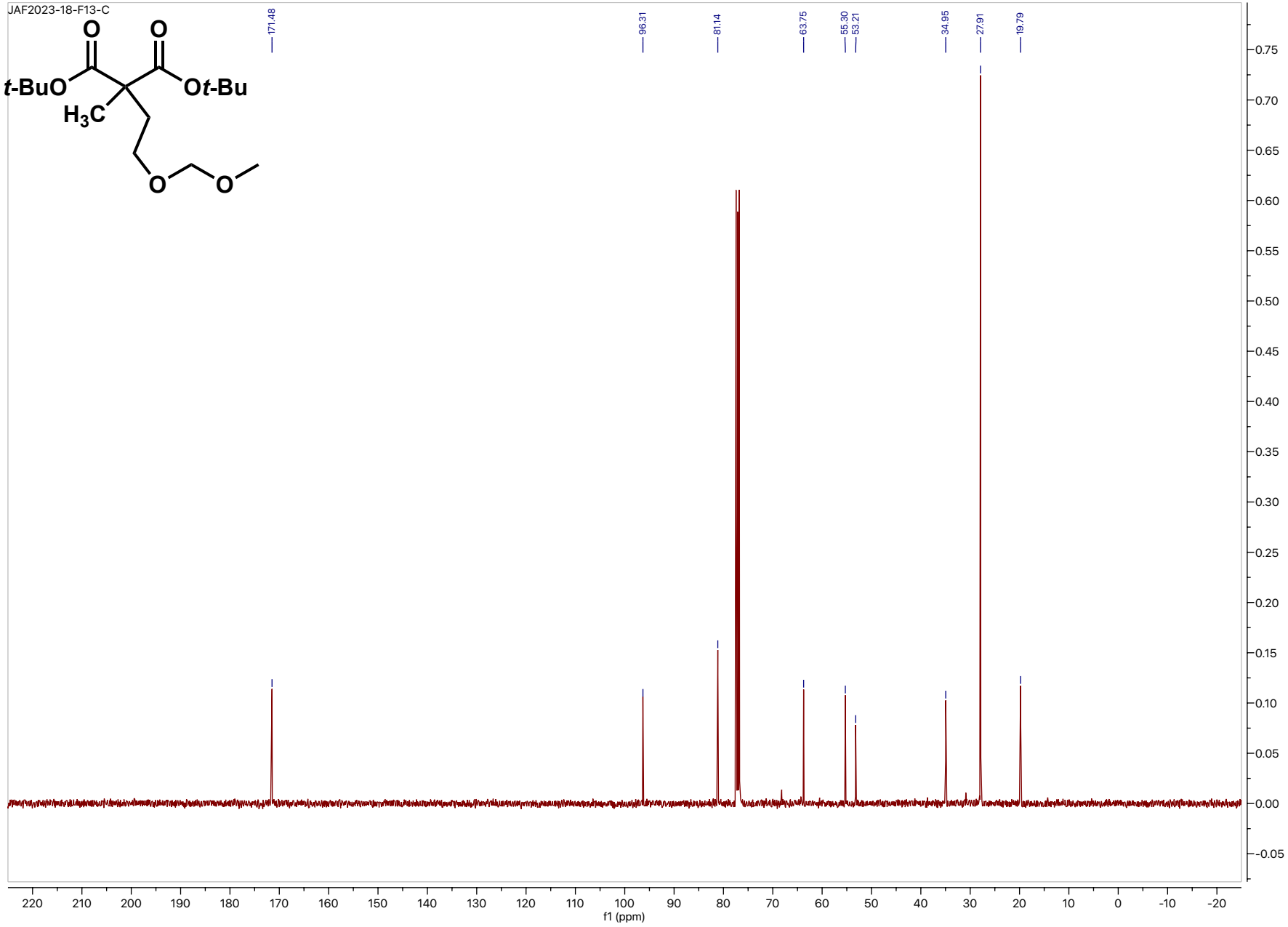

Br
O
Si
2.00
1.92
10.01
6.38
f1 (ppm)

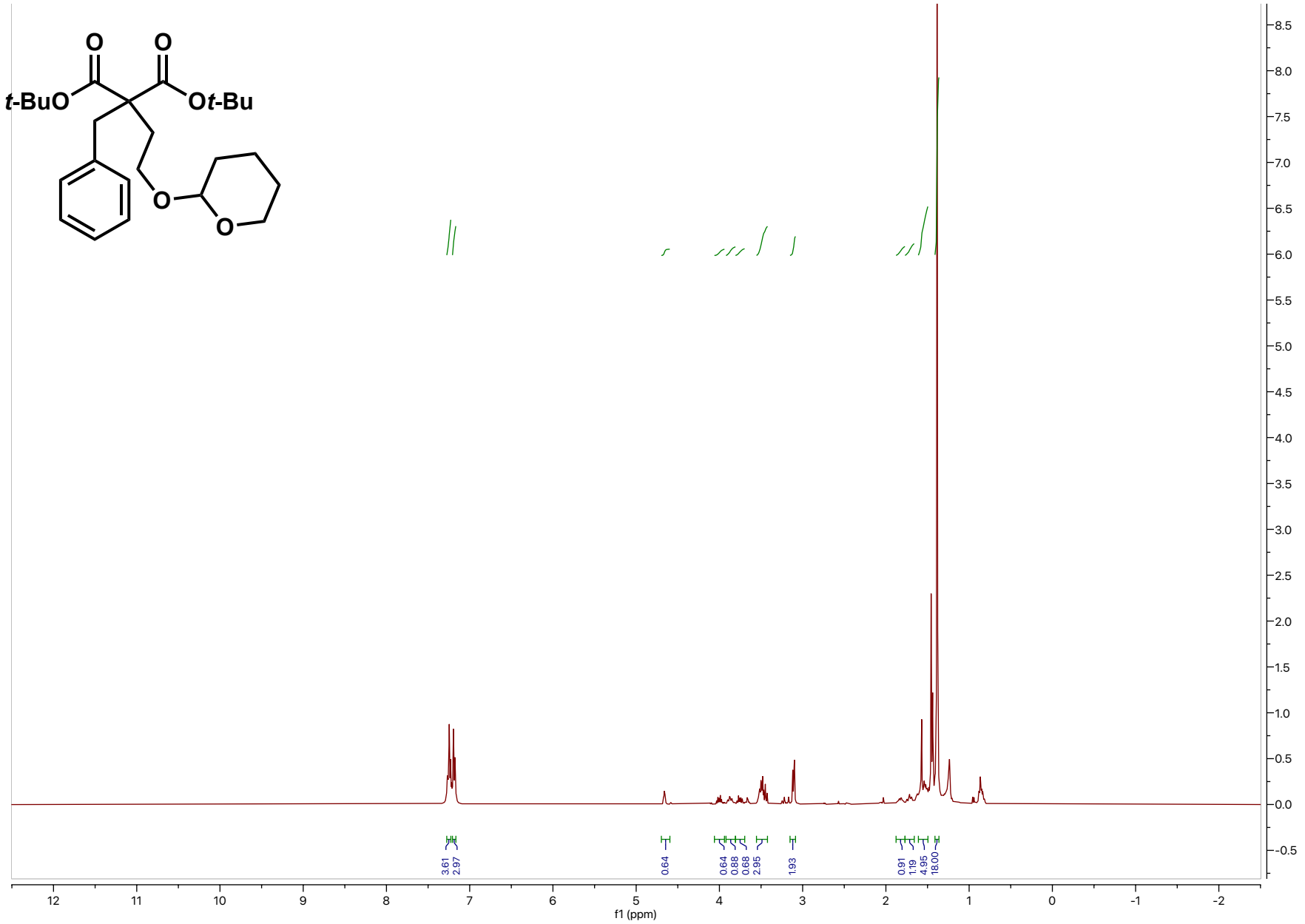

Br
O
Si
77.43
63.31
33.24
6.78
4.46
f1 (ppm)

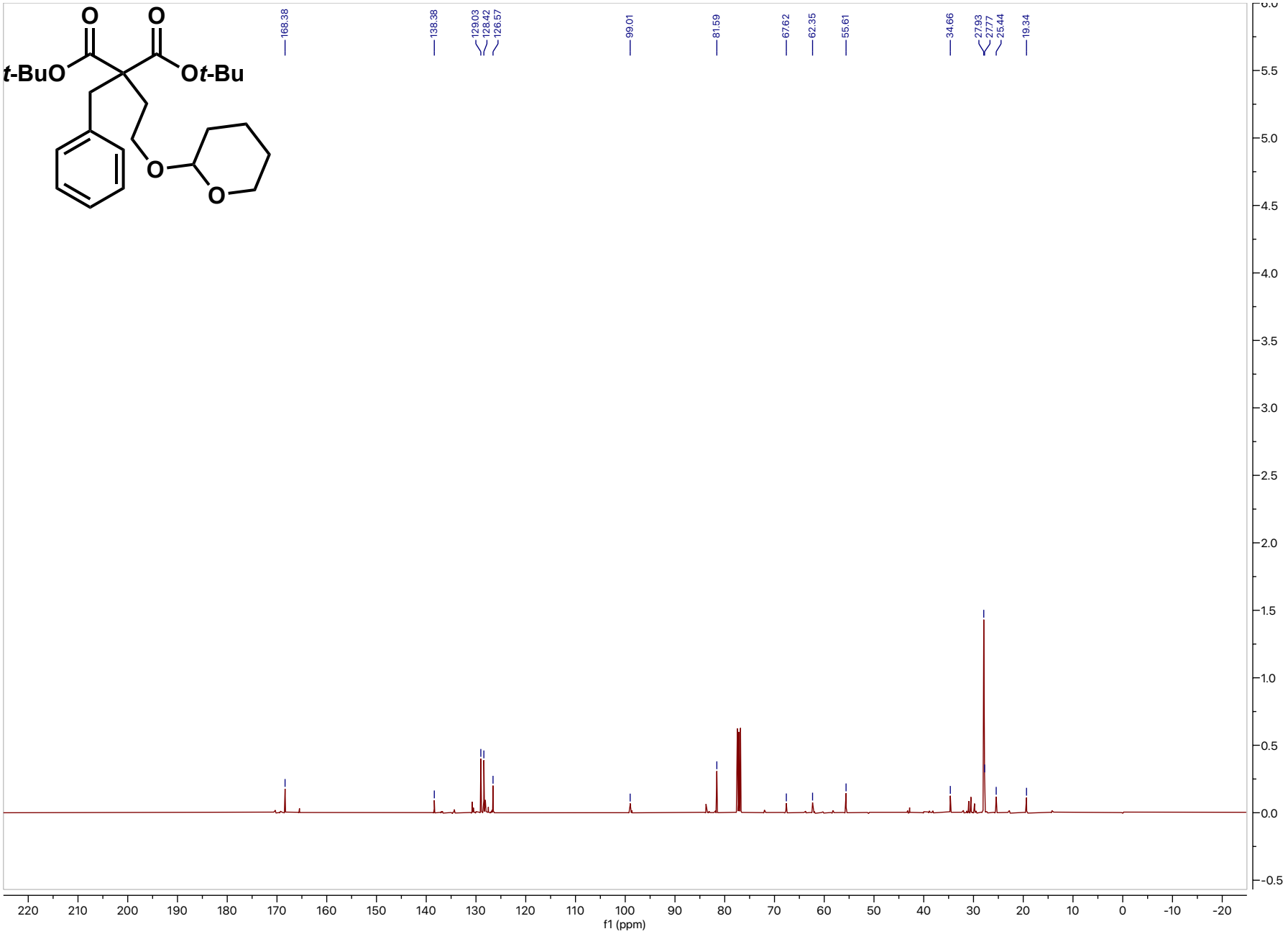

t-BuO
Ot-Bu
H3C
O
O
O
O
0.98
2.15
1.35
1.04
2.07
1.15
1.48
2.36
2.25
3.46
18.00
f1 (ppm)

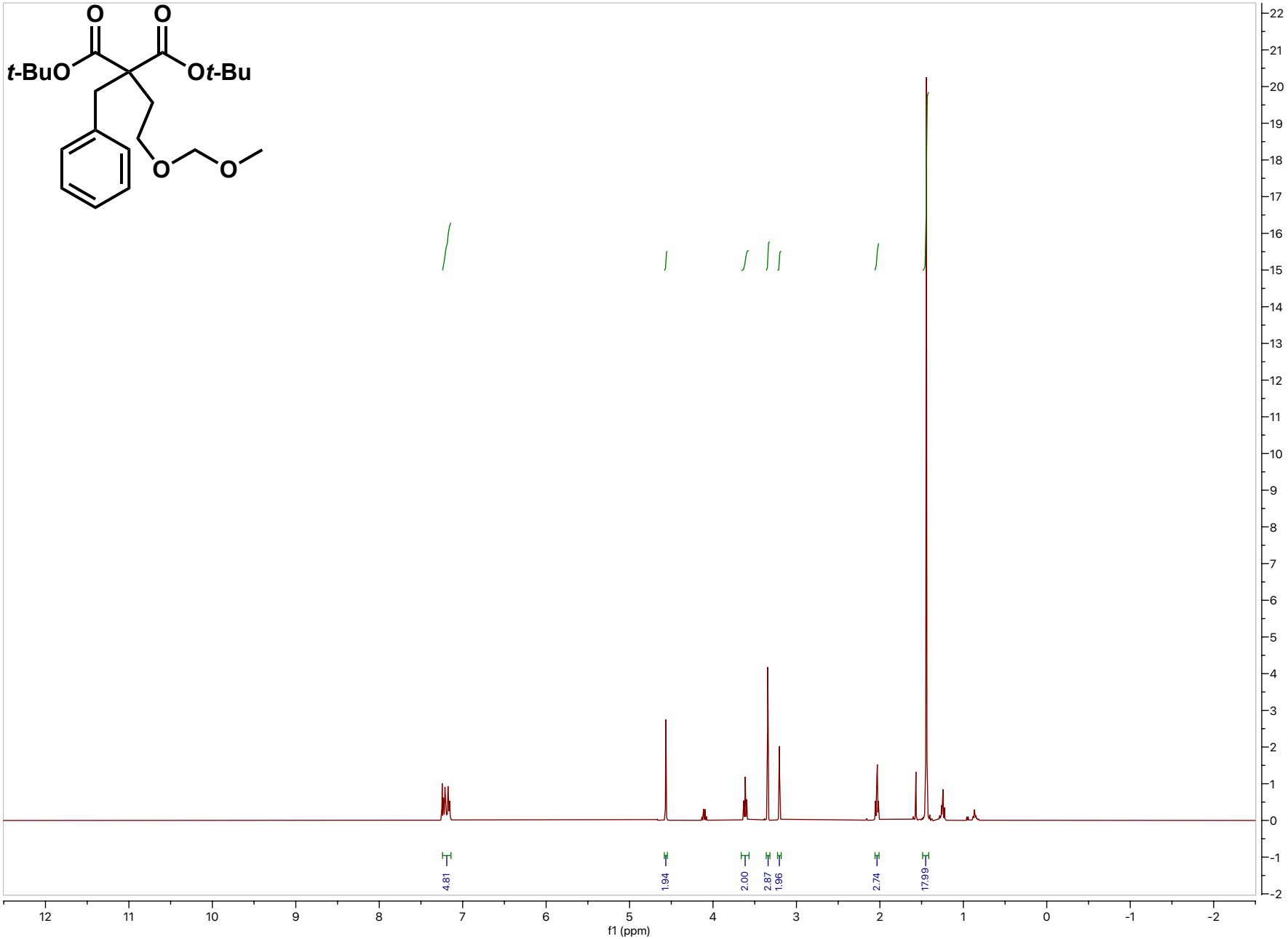

t-BuO
Ot-Bu
H3C
O
O
O
O
171.52
98.87
81.11
63.72
62.20
53.37
34.92
30.64
27.93
25.55
19.91
19.50
f1 (ppm)

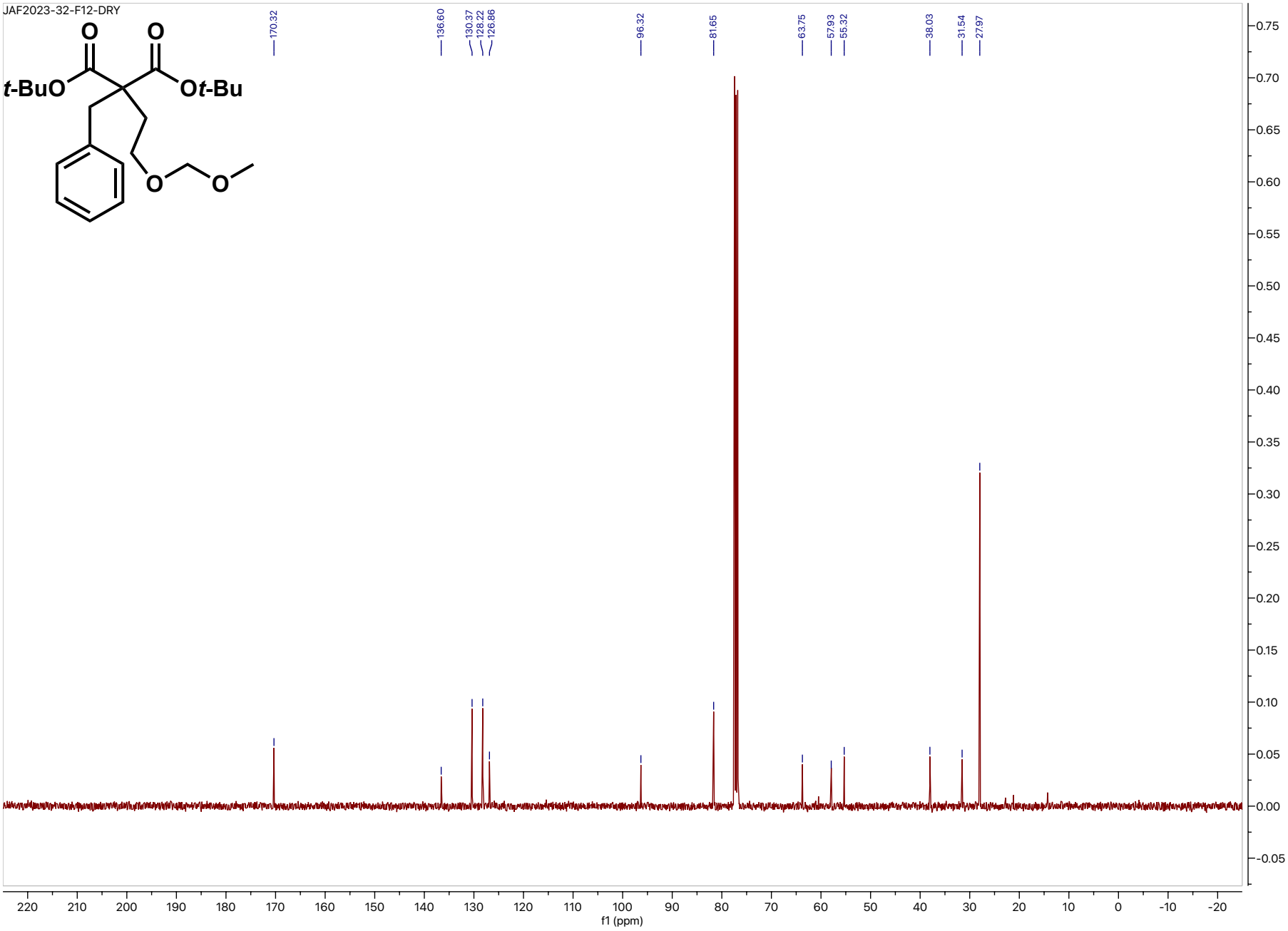

JAF2023-18-F13
O
O
t-BuO
Ot-Bu
H3C
O
O
2.00
2.00
2.92
1.96
19.57
3.19
f1 (ppm)

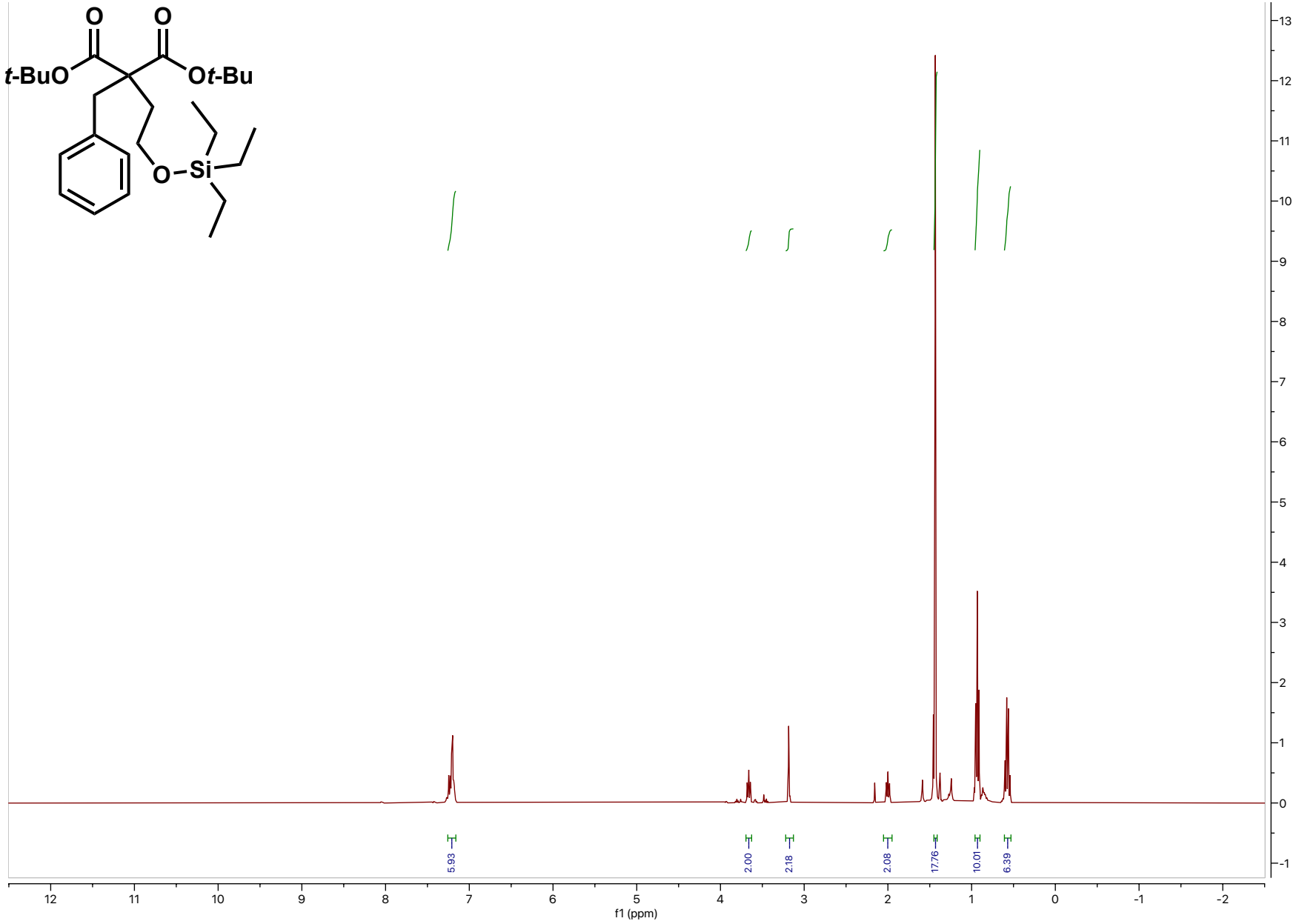

JAF2023-18-F13-C
O
O
t-BuO
Ot-Bu
H3C
O
O
171.48
96.31
81.14
63.75
55.30
53.21
34.95
27.91
19.79
f1 (ppm)

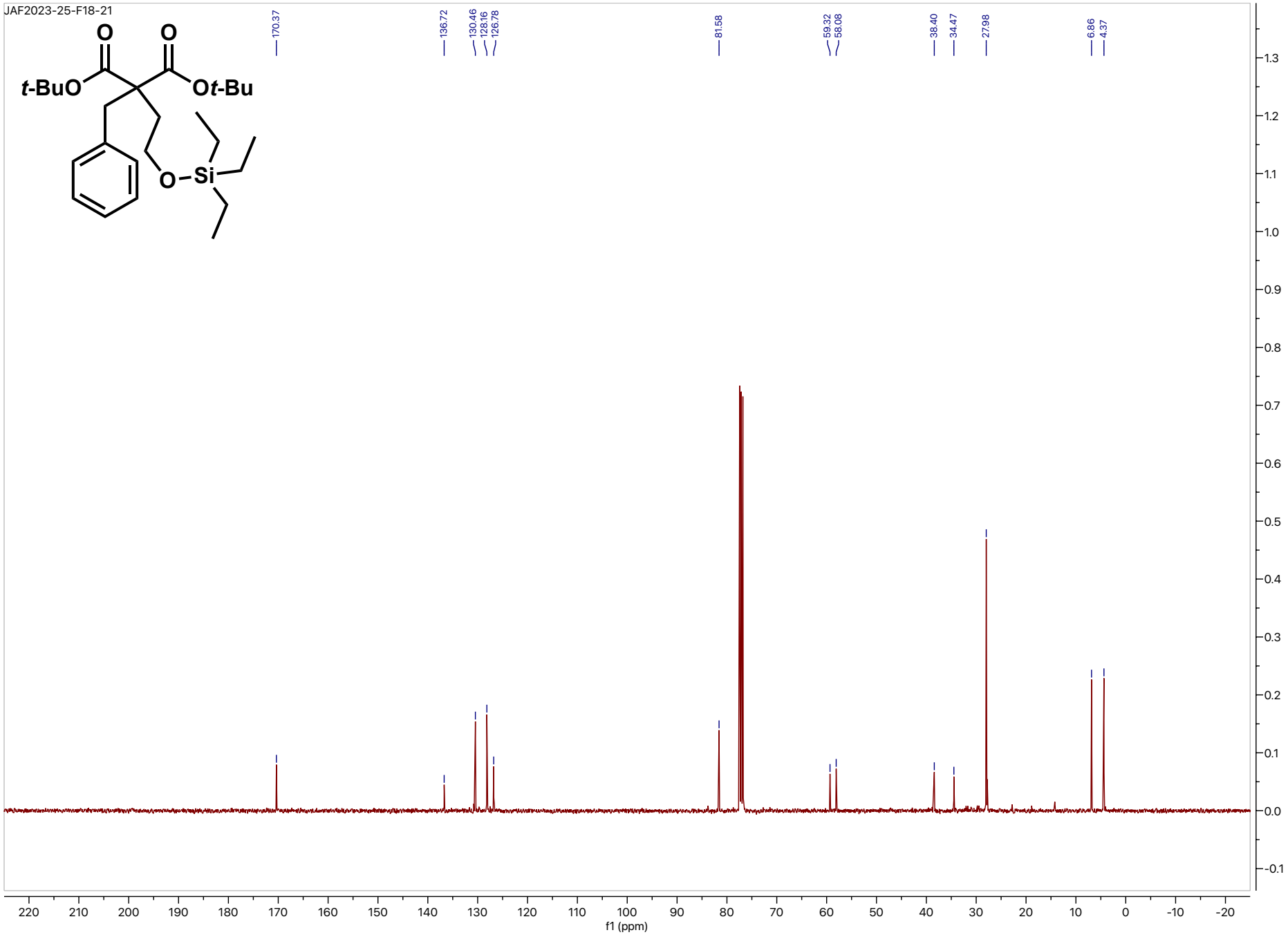

t-BuO
O
O
Ot-Bu
O
O
3.61
2.97
0.64
0.64
0.88
0.88
2.95
1.93
0.91
1.19
4.95
18.00
f1 (ppm)

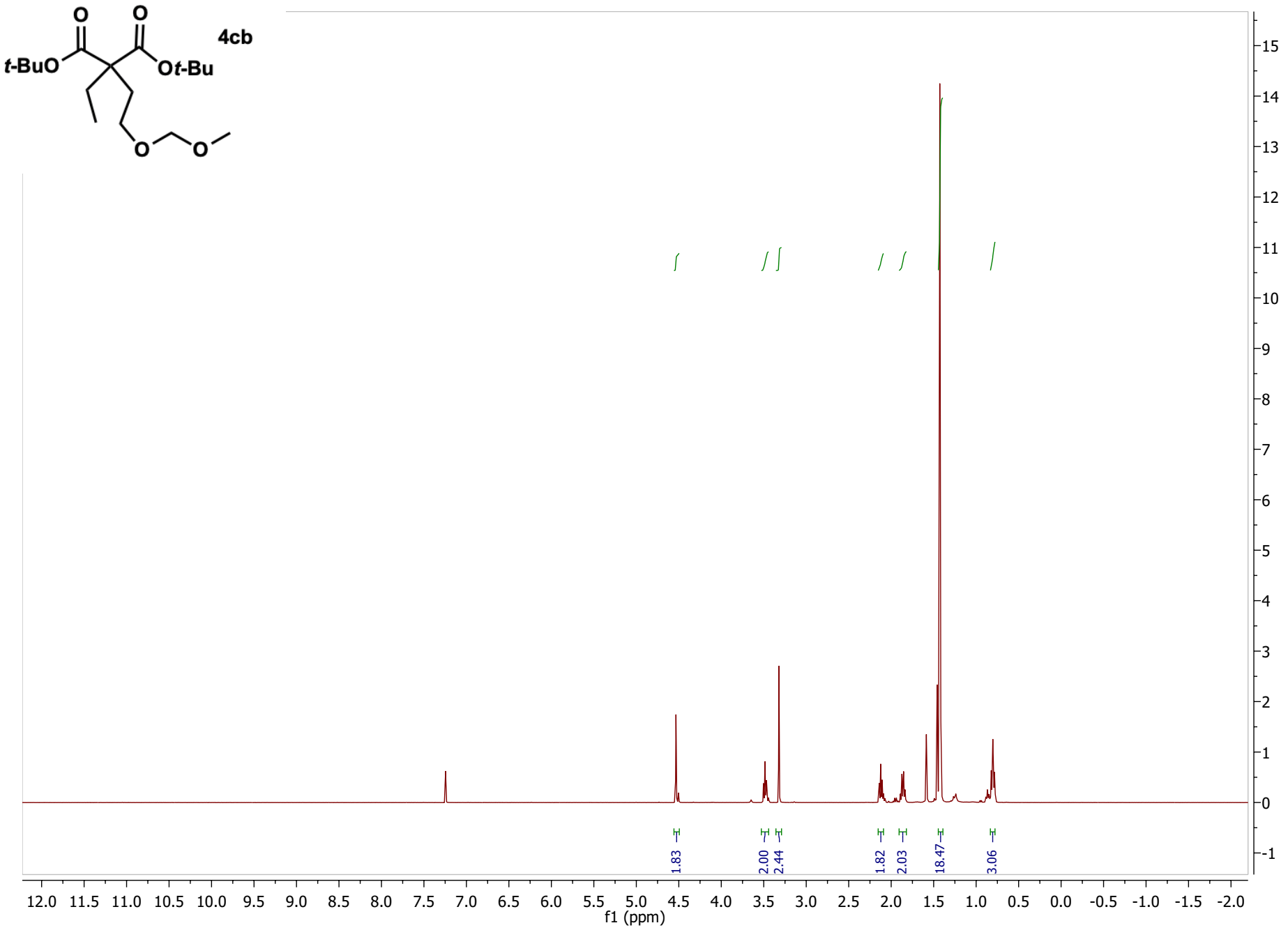

t-BuO
Ot-Bu
O
O
O
O
168.38
138.38
129.03
128.42
126.57
99.01
81.59
67.62
62.35
55.61
34.66
27.93
27.77
25.44
19.34
f1 (ppm)

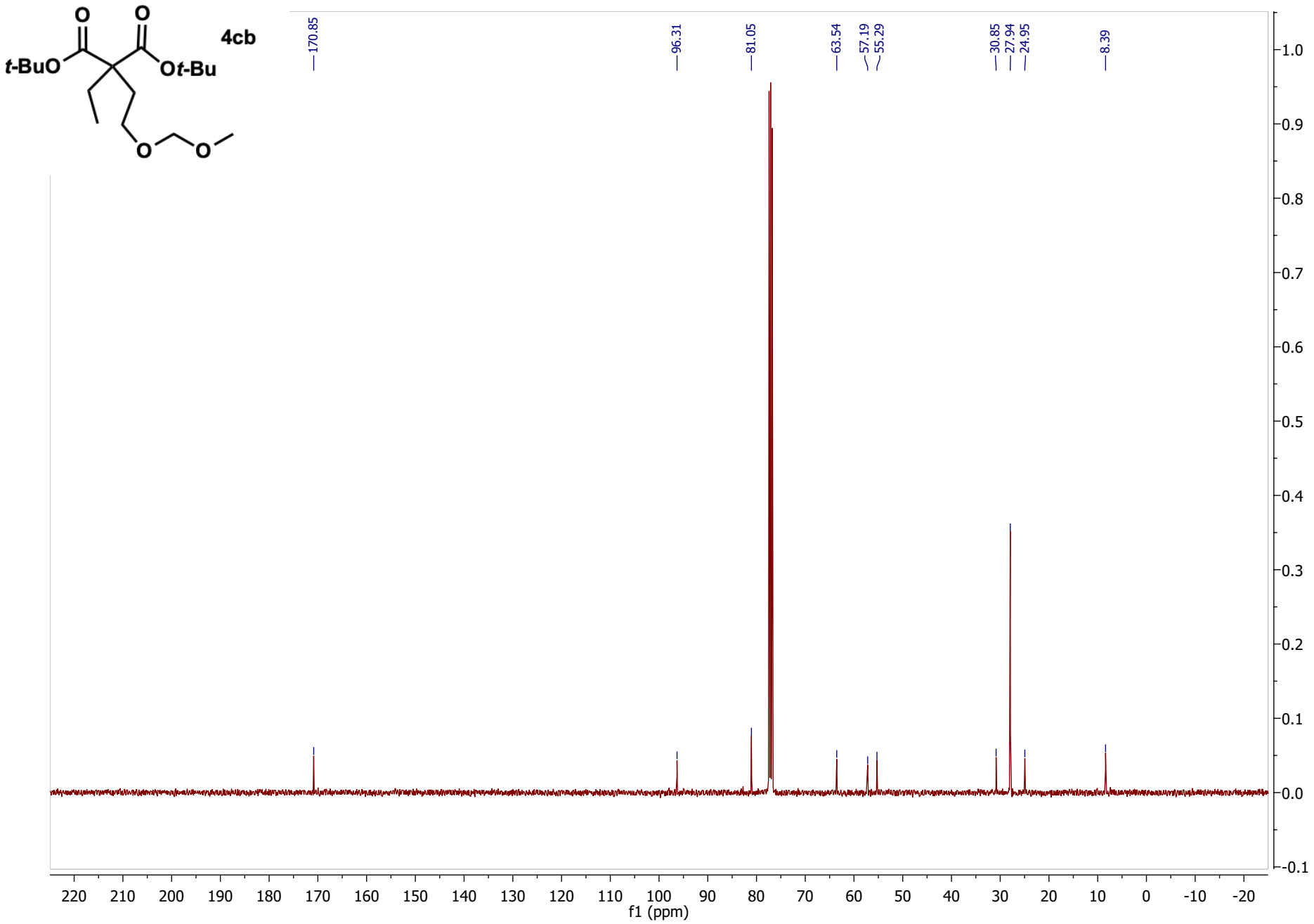

O
O
t-BuO
Ot-Bu
O
O
4.81
1.94
2.00
2.87
1.96
2.74
17.99
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

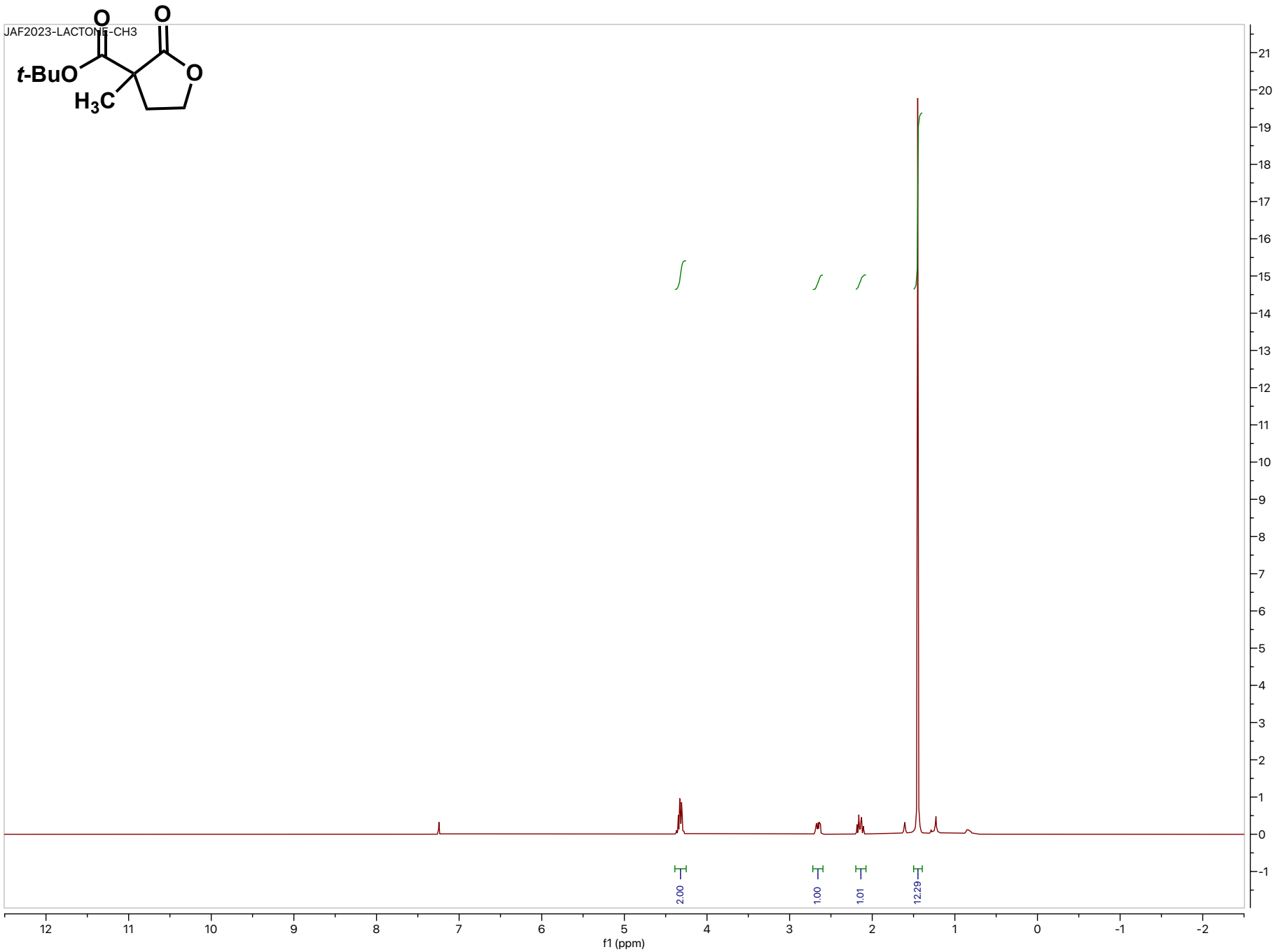

JAF2023-32-F12-DRY
t-BuO
Ot-Bu
O
O
O
O
170.32
136.60
130.37
128.22
126.86
96.32
81.65
63.75
57.93
55.32
38.03
31.54
27.97
f1 (ppm)

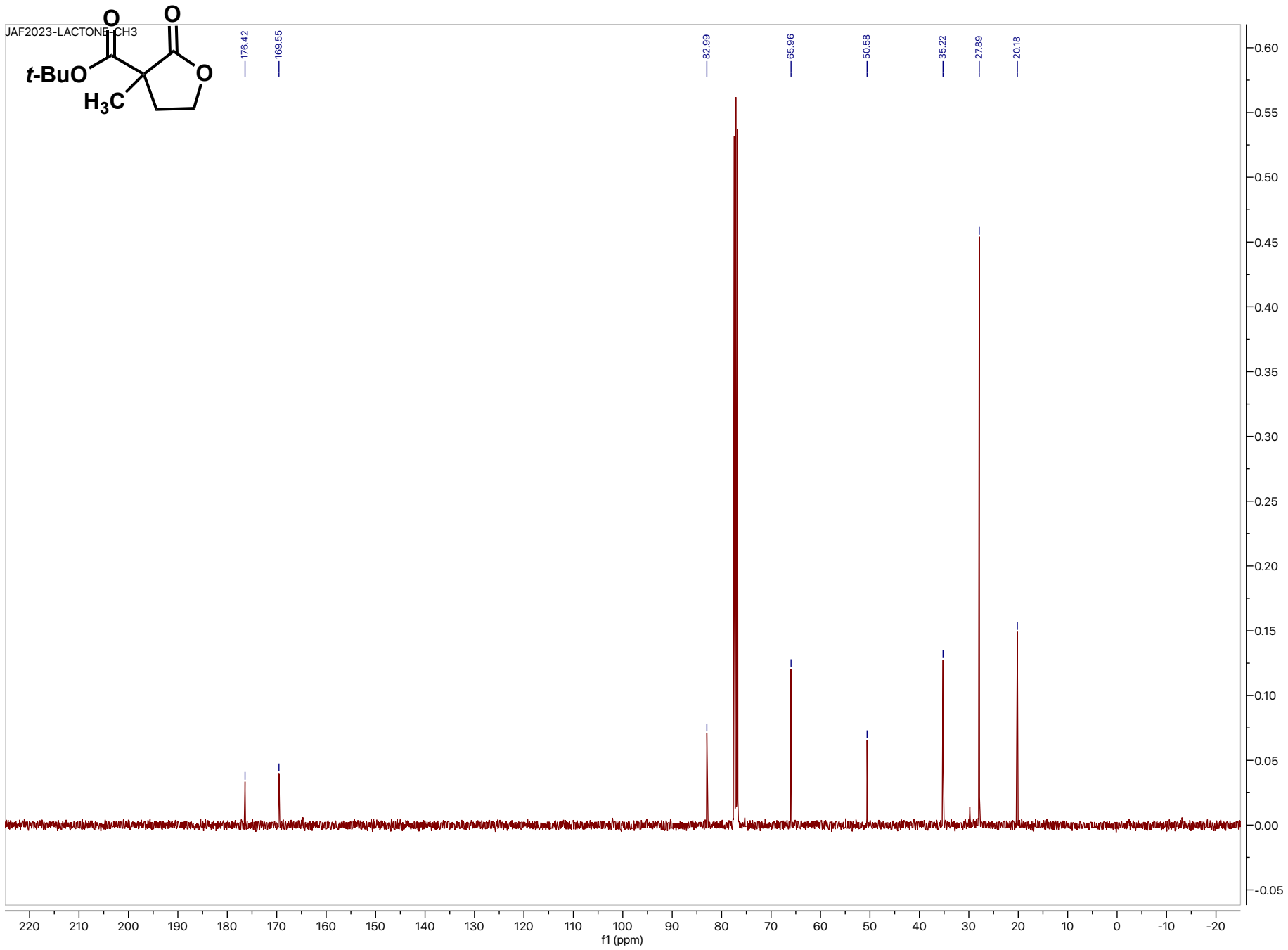

O
O
t-BuO
Ot-Bu
O
Si
5.93
2.00
2.18
2.08
17.76
10.01
6.39
f1 (ppm)

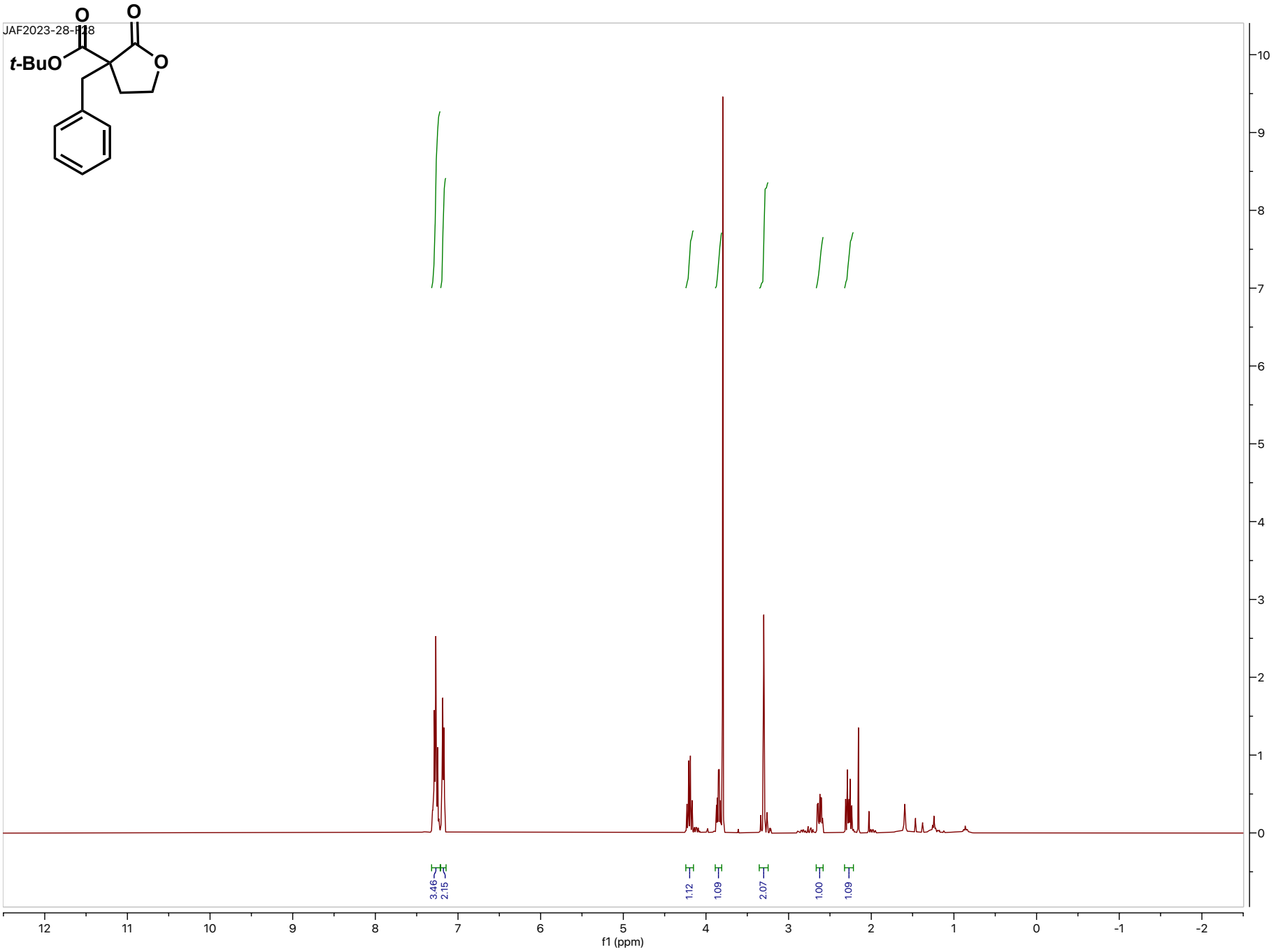

JAF2023-25-F18-21
t-BuO
Ot-Bu
O
O
O
O
Si
170.37
136.72
130.46
128.16
126.78
81.58
59.32
58.08
38.40
34.47
27.98
6.86
4.37
f1 (ppm)

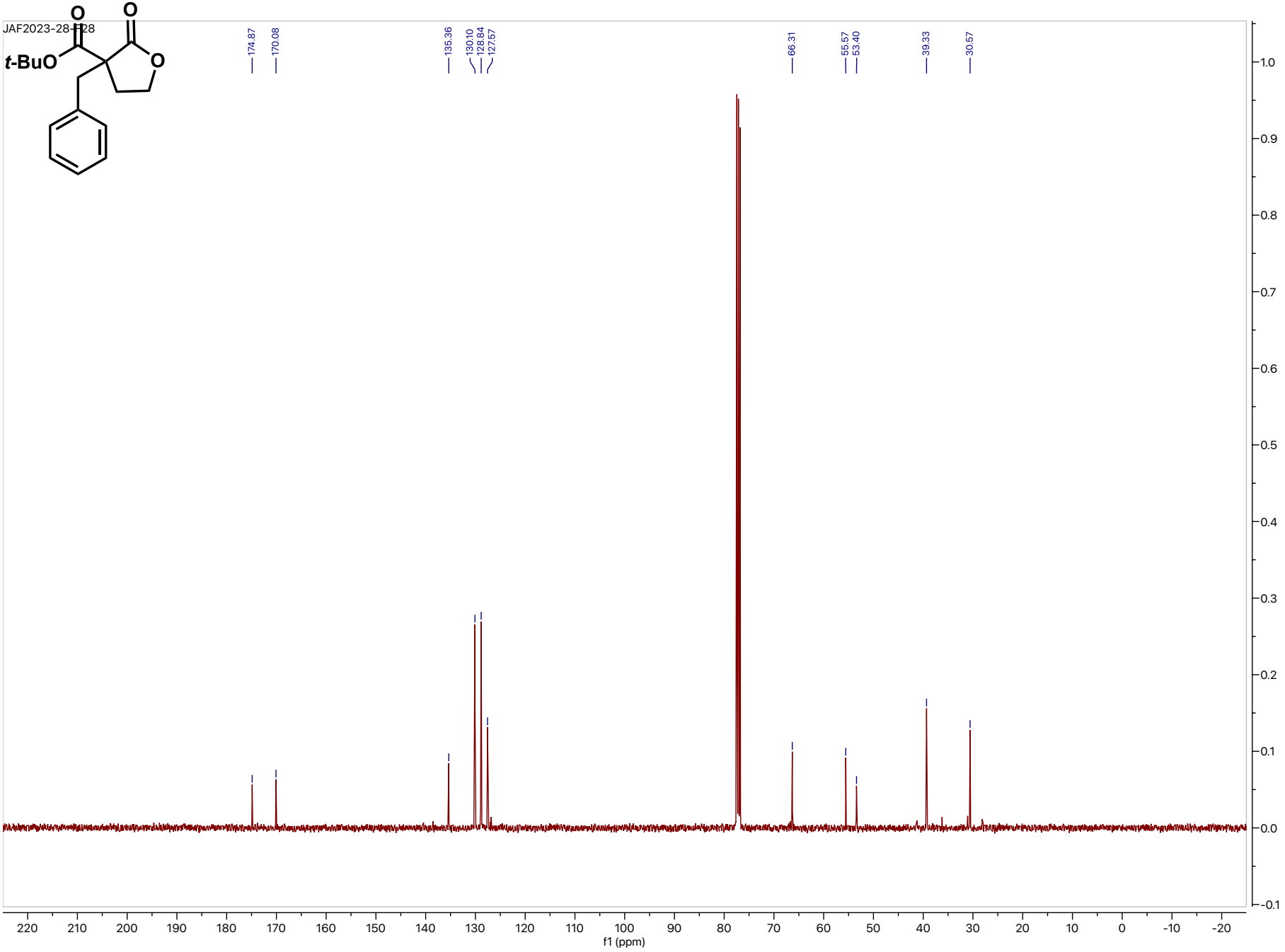

4cb
t-BuO
Ot-Bu
O
O
O
O
1.83
2.00
2.44
1.82
2.03
18.47
3.06
f1 (ppm)

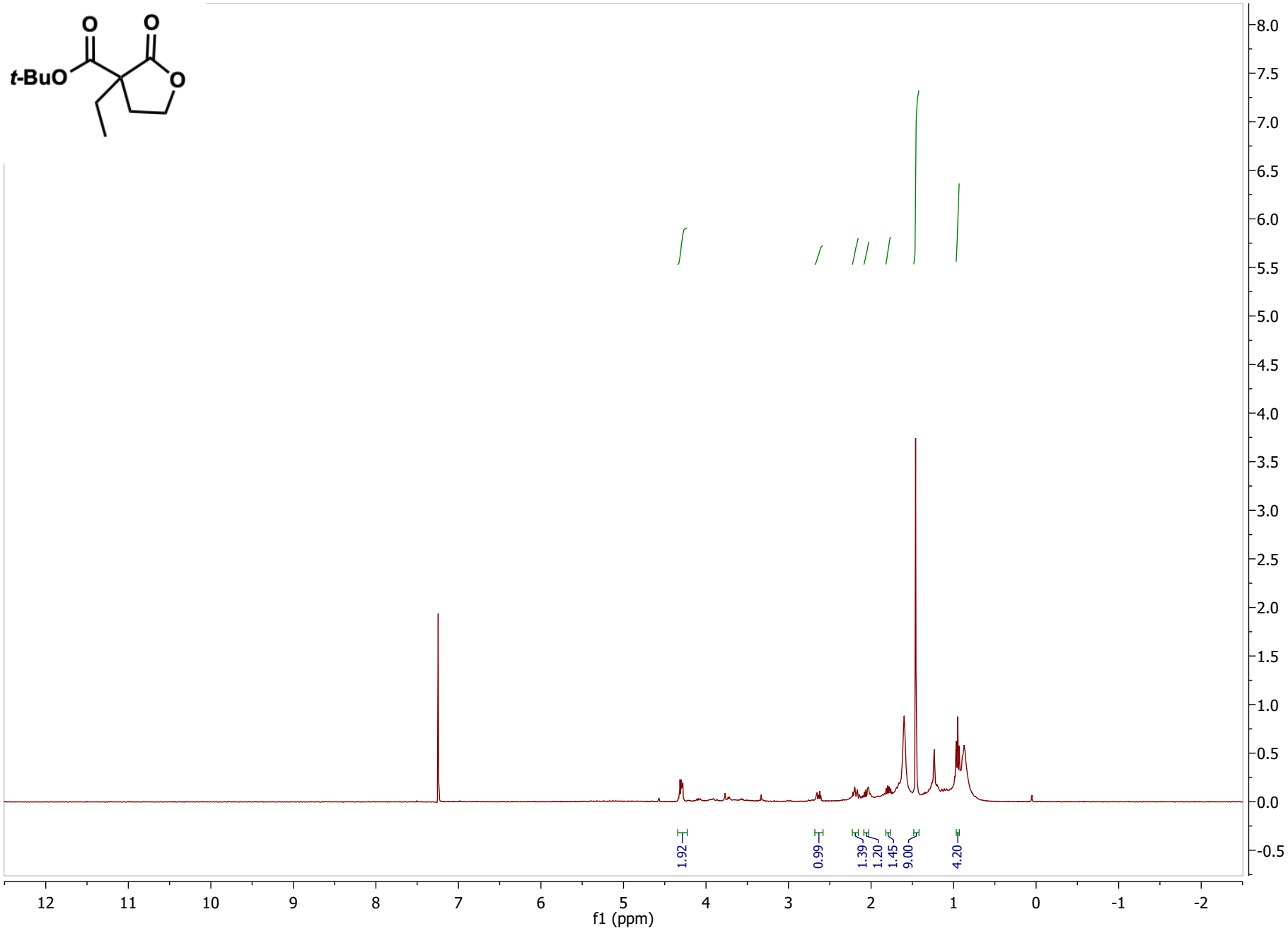

4cb
t-BuO
Ot-Bu
O
O
O
O
170.85
96.31
81.05
63.54
57.19
55.29
30.85
27.94
24.95
8.39
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

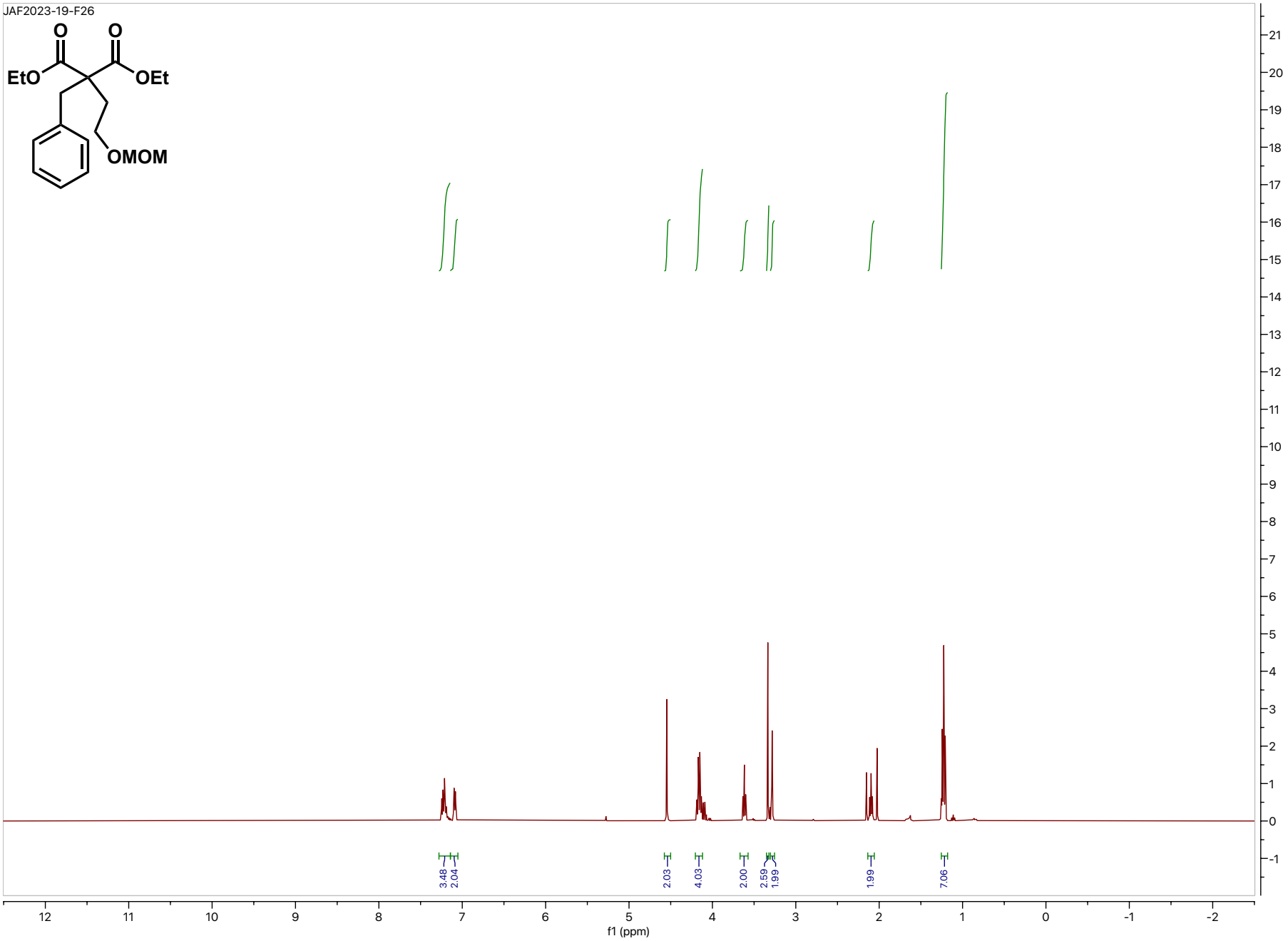

JAF2023-LACTONE-CH3
t-BuO
O
O
O
H3C
2.00
1.00
1.01
12.29
f1 (ppm)

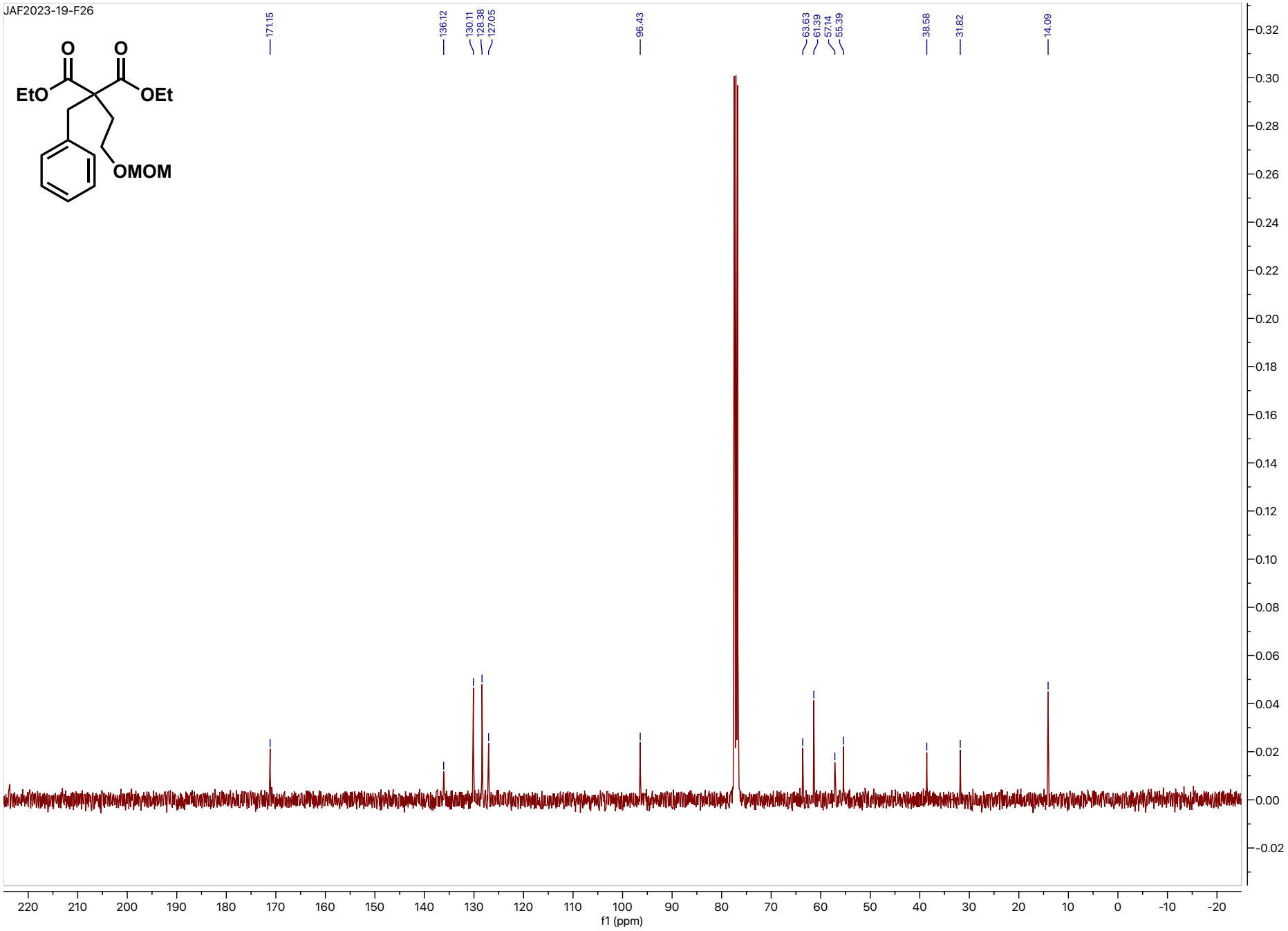

JAF2023-LACTONE-CH3
t-BuO
H3C
O
O
O
176.42
169.55
82.99
65.96
50.58
35.22
27.89
20.18
f1 (ppm)

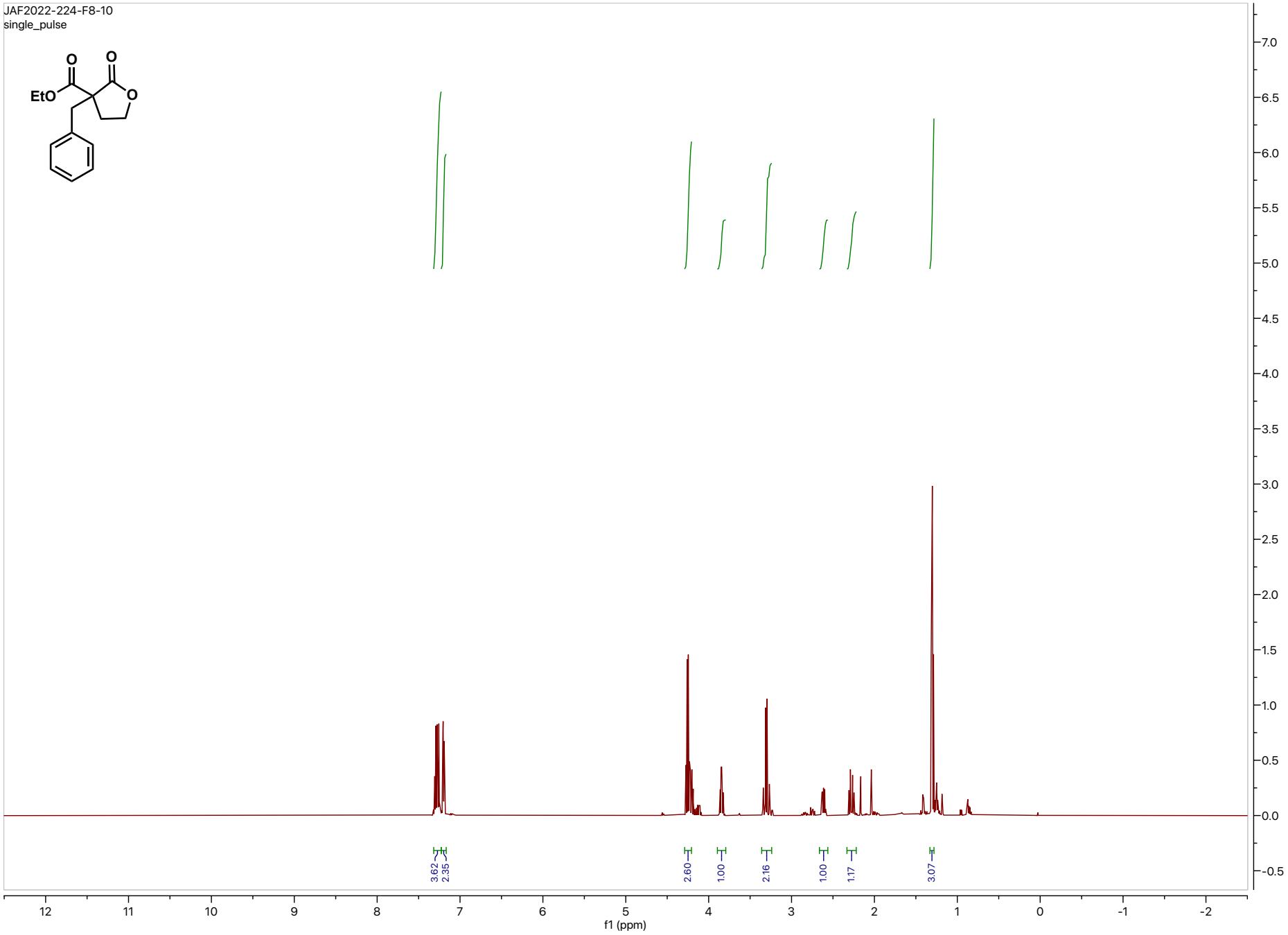

JAF2023-28-118
t-BuO
O
O
O
3.46
2.15
1.12
1.09
2.07
1.00
1.09
f1 (ppm)

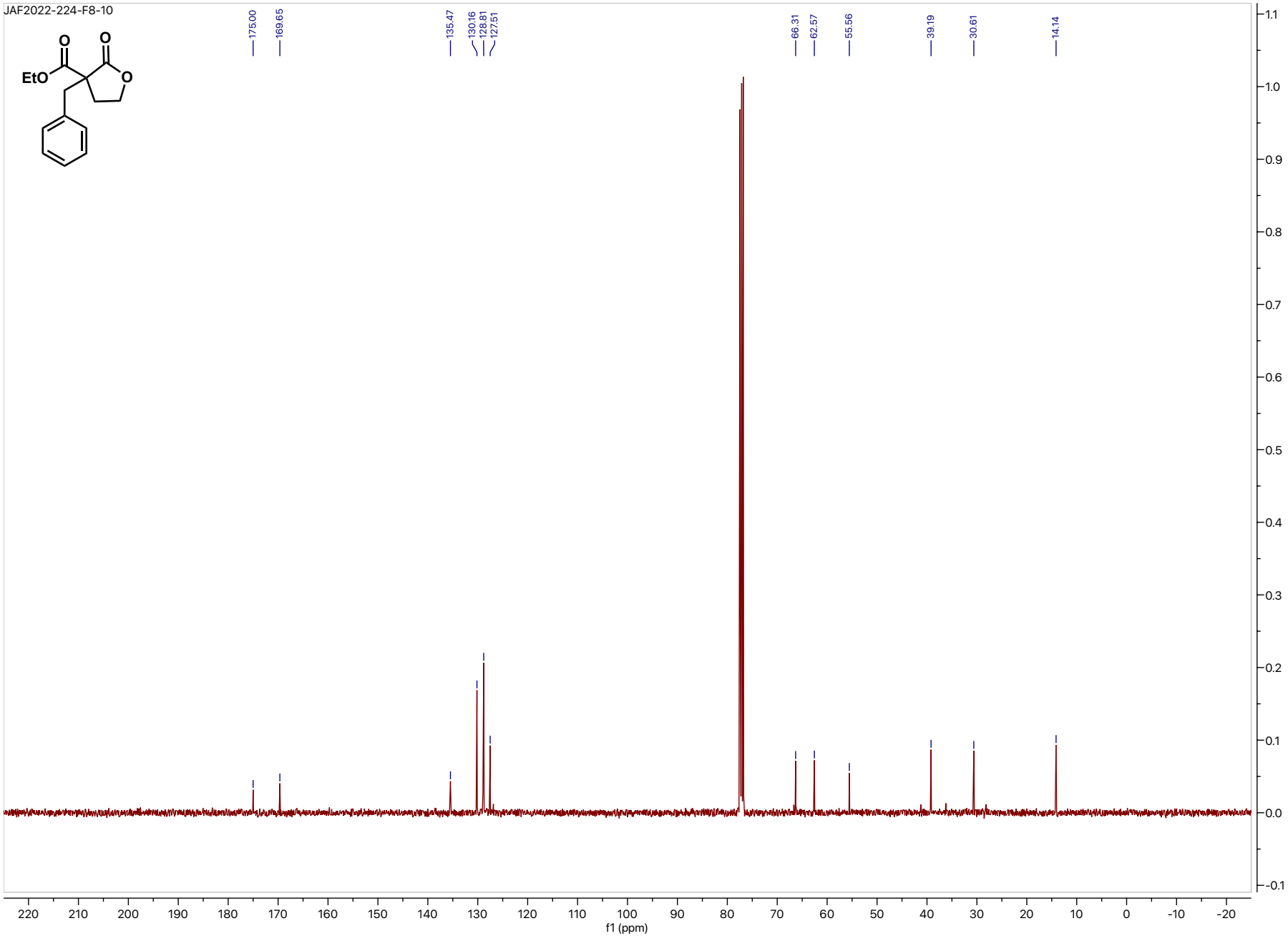

JAF2023-28-128
t-BuO
O
O
O
174.87
170.08
135.36
130.10
128.84
127.57
66.31
55.57
53.40
39.33
30.57
f1 (ppm)

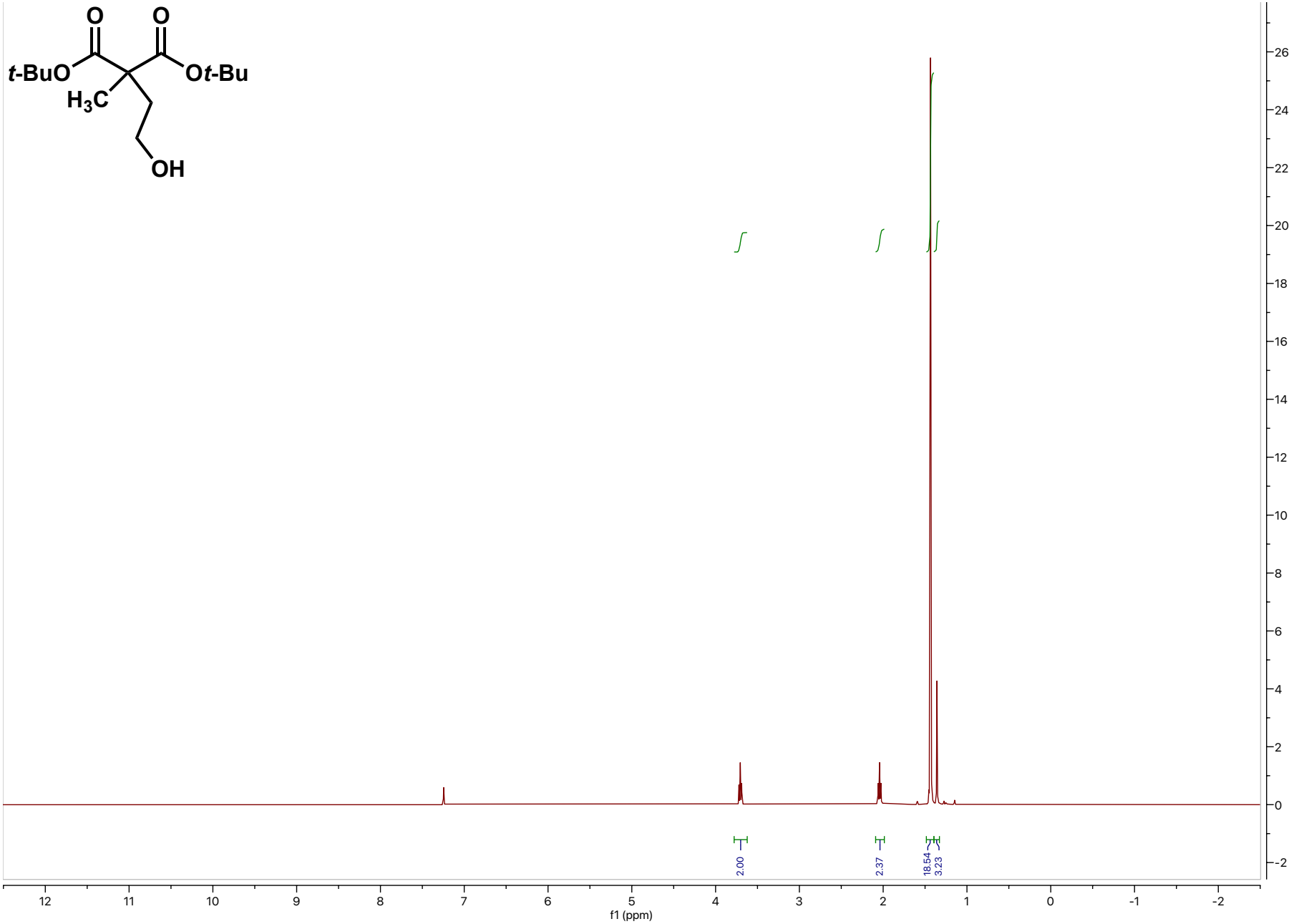

t-BuO
O
O
O
1.92
0.99
1.39
1.20
1.45
9.00
4.20
f1 (ppm)

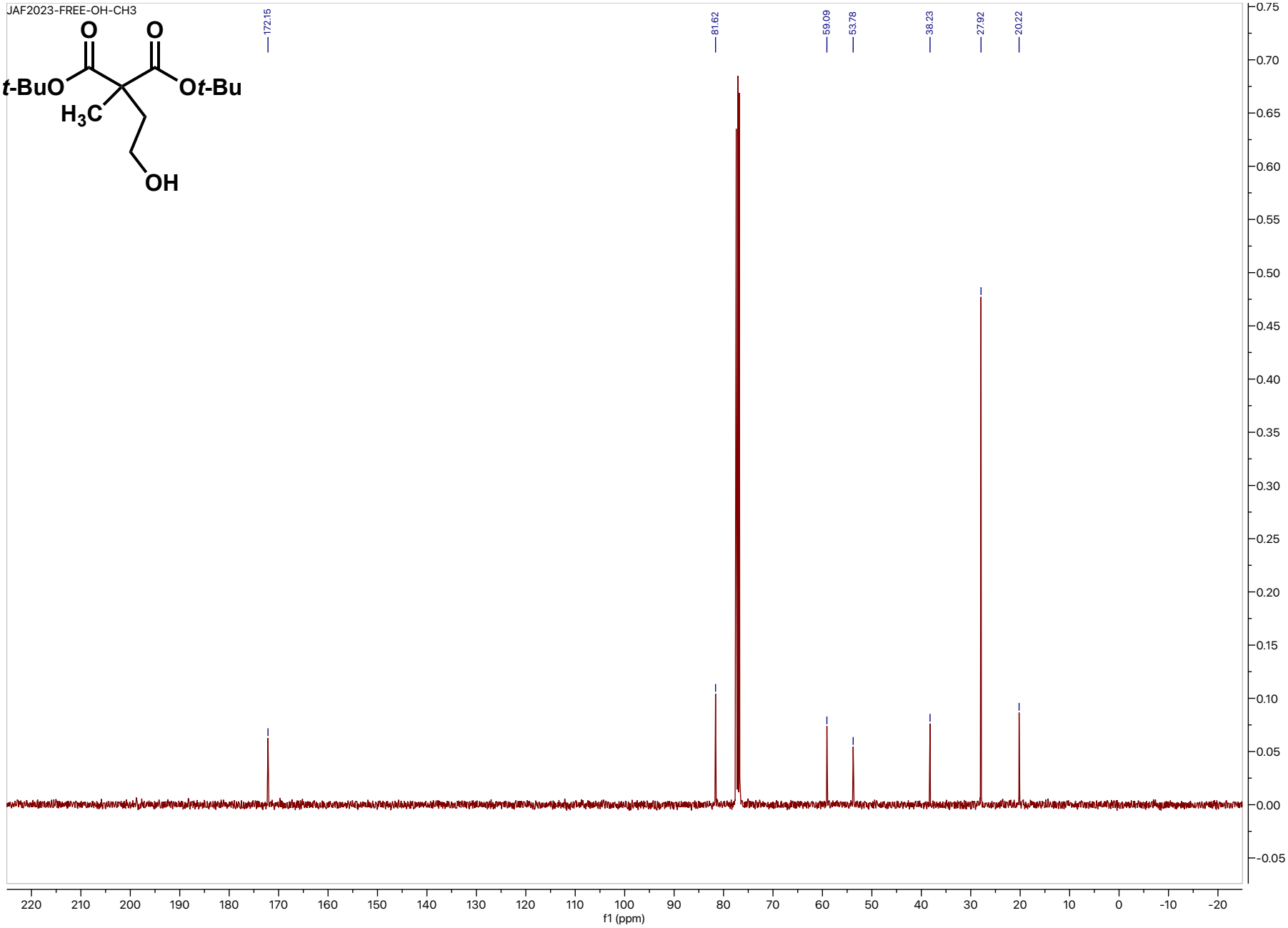

JAF2023-19-F26
O
O
EtO
OEt
OMOM
3.48
2.04
2.03
4.03
2.00
2.59
1.99
1.99
7.06
f1 (ppm)


JAF2023-19-F26
171.15
136.12
130.11
128.38
127.05
96.43
63.63
61.39
57.14
55.39
38.58
31.82
14.09
EtO
OEt
OMOM
f1 (ppm)


JAF2022-224-F8-10
single_pulse
EtO
O
O
O
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
3.62
2.35
2.60
1.00
2.16
1.00
1.17
3.07
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


JAF2022-224-F8-10
EtO
O
O
O
175.00
169.65
135.47
130.16
128.81
127.51
66.31
62.57
55.56
39.19
30.61
14.14
f1 (ppm)

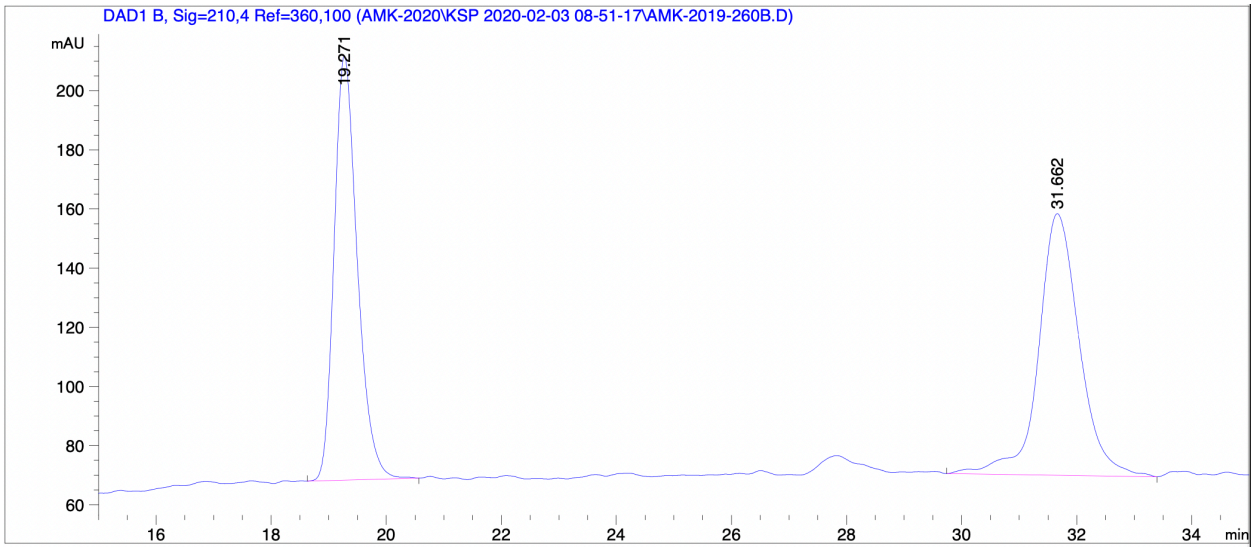

O
O
t-BuO
Ot-Bu
H3C
OH
2.00
2.37
18.54
3.23
f1 (ppm)


JAF2023-FREE-OH-CH3
O
O
t-BuO
Ot-Bu
H3C
OH
172.15
81.62
59.09
53.78
38.23
27.92
20.22
f1 (ppm)

APPENDIX B: CHROMATOGRAMS

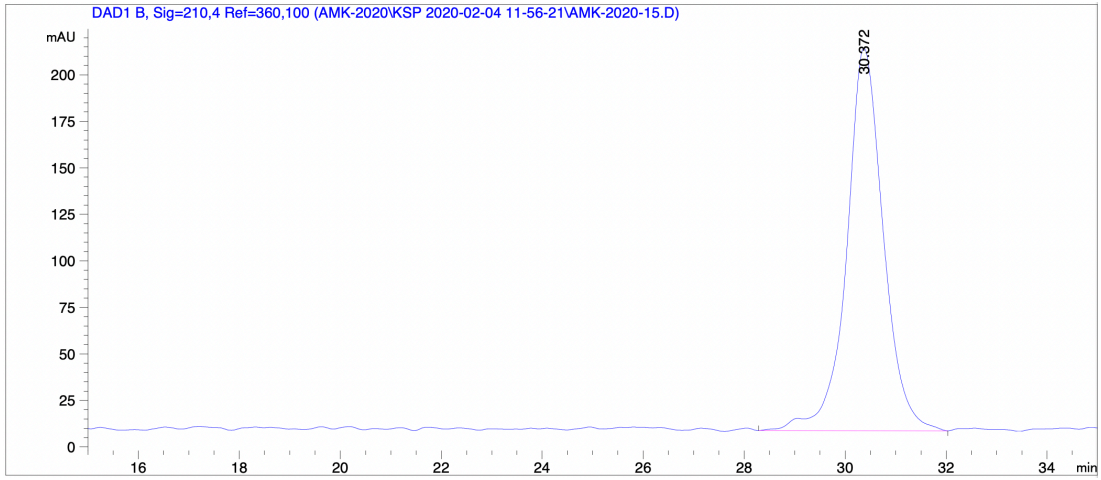
Column: Chiralpak AD-H 4.6 mm x 250 mm x 5 µm; Eluent Rate: 1 mL/min; Eluent: 10% IPA/hexanes; Monitoring wave: 210 nm.

Racemic Compound II-**8fa**



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	19.271	1	BB	4015.41333	143.46841	47.9306
2	31.662	1	BB	4362.14063	88.46686	52.0694

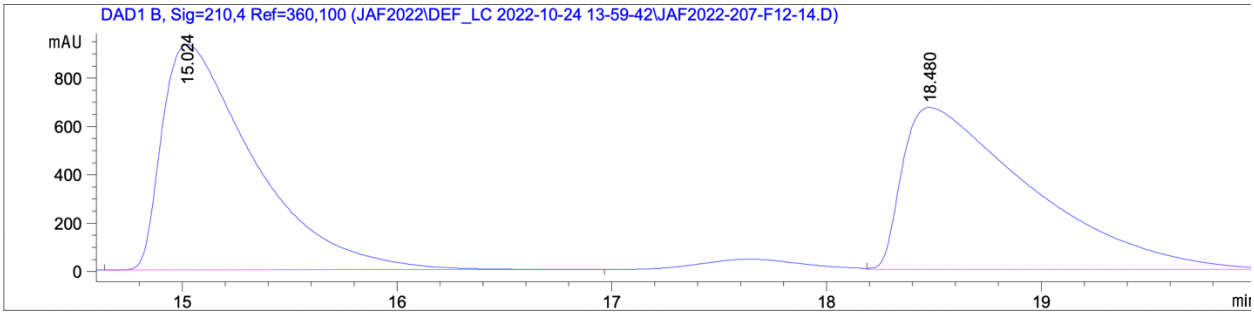
Enantioenriched Compound II-**8fa**



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	30.372	1	BB	1.03933e4	205.67062	100.0000

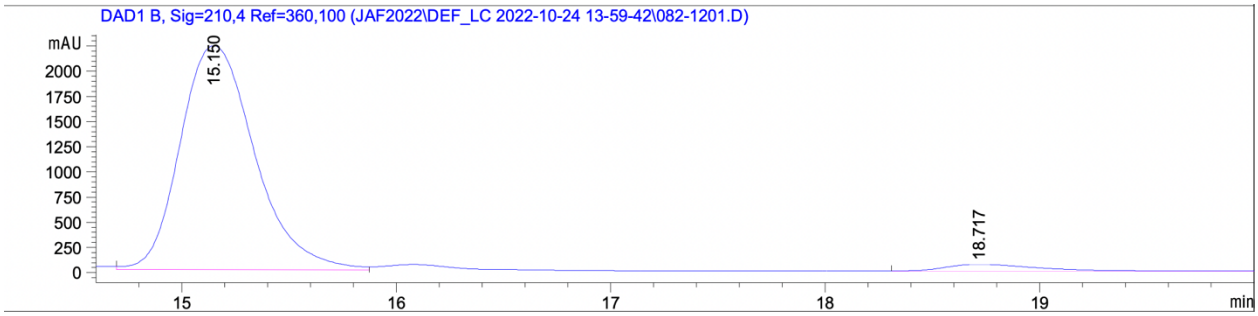
Column: Chiralpak AD-H 4.6 mm x 250 mm x 5 µm; Eluent Rate: 1 mL/min; Eluent: 5% IPA/hexanes; Monitoring wave: 210 nm.

Racemic III-**5a**



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	15.024	2	BB	2.77790e4	932.40704	47.4826
2	18.480	2	VV	2.79479e4	671.18896	47.7713

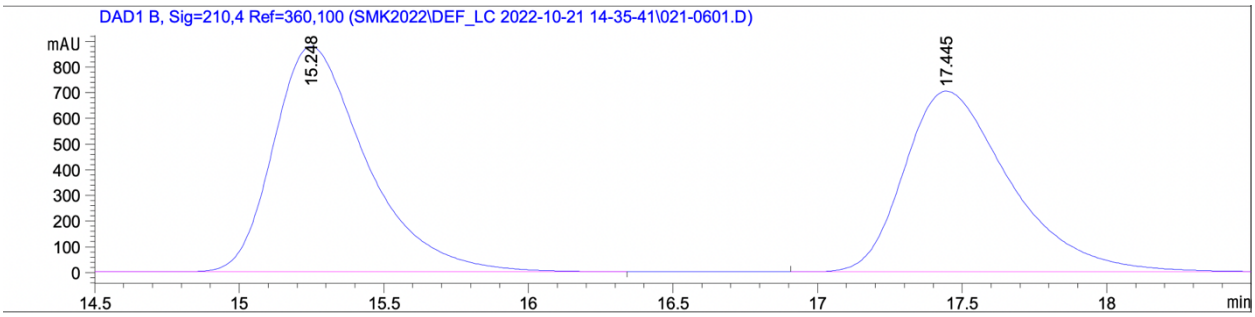
Enantioenriched III-**5a**



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	15.150	2	VV	5.38423e4	2225.26074	96.3389
2	18.717	2	VB	2048.12451	67.81987	3.6647

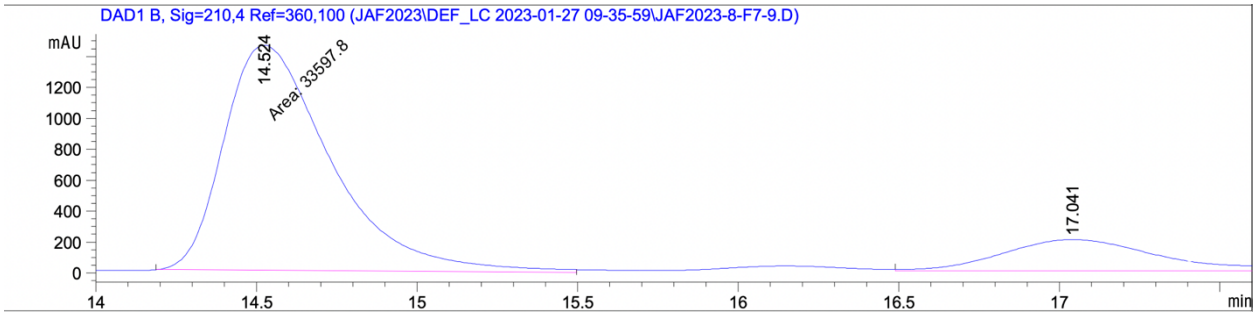
Column: Chiralpak AD-H 4.6 mm x 250 mm x 5 µm; Eluent Rate: 1 mL/min; Eluent: 5% IPA/hexanes; Monitoring wave: 210 nm.

Racemic III-**5b**



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	15.248	2	BB	1.95923e4	878.13434	49.4549
2	17.445	2	BB	1.78330e4	703.38556	45.0140

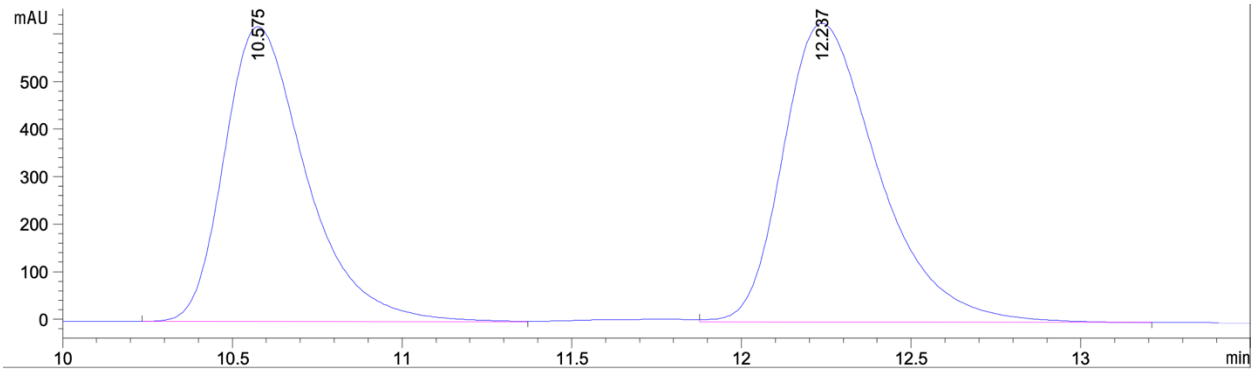
Enantioenriched III-**5b**



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	14.524	2	MM	3.35978e4	1453.78284	83.4784
2	17.041	2	VV	6651.47314	202.05029	16.5265

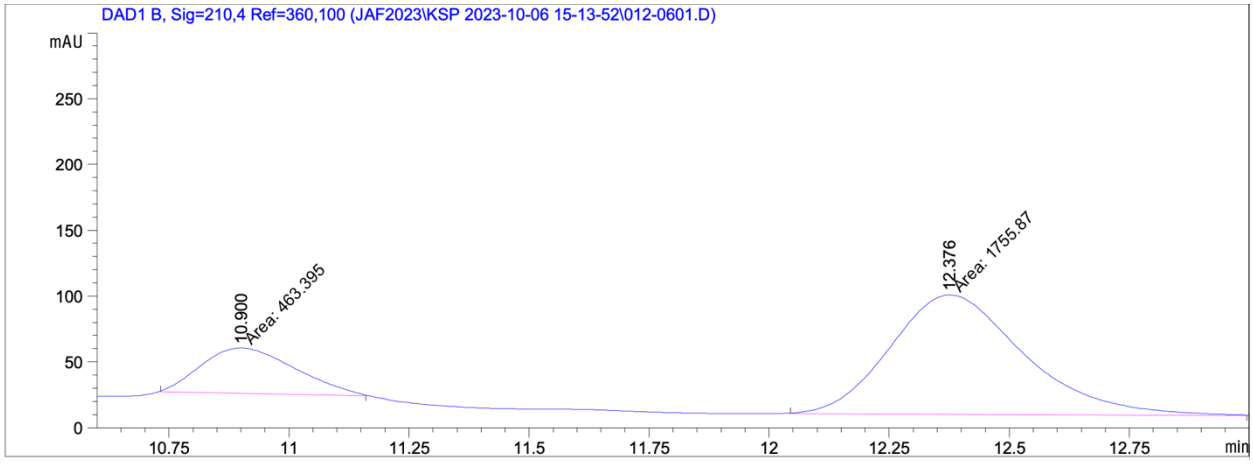
Column: Chiralpak AD-H 4.6 mm x 250 mm x 5 µm; Eluent Rate: 1 mL/min; Eluent: 1% IPA/hexanes; Monitoring wave: 210 nm.

Racemic III-**5c**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.575	BV	0.2560	1.04079e4	619.55042	45.7817
2	12.237	VV	0.3030	1.23258e4	627.91461	54.2183

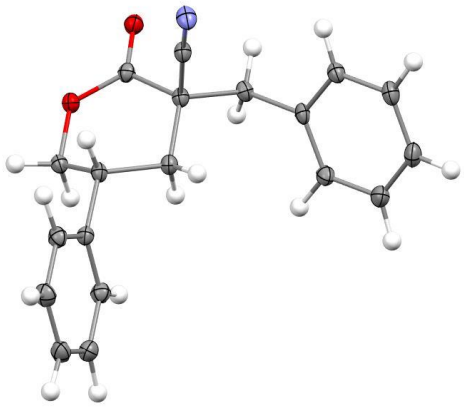
Enantioenriched III-**5c**



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	10.900	2	MM	463.39502	34.30749	20.8994
2	12.376	2	MM	1755.87048	90.67243	79.1908

APPENDIX C: X-RAY CRYSTAL DATA

*Compound II-**8ba***: A colorless crystal (approximate dimensions 0.300 x 0.100 x 0.030 mm3) was placed onto the tip of MiTeGen and mounted on a Bruker SMART Apex II diffractometer and measured at 150 K. 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 76 reflections. The data collection was carried out using Cu K_α radiation (graphite monochromator) with theta-dependent frame window of 10-70 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 1.90º steps ω and Φ scans. Data to a resolution of 0.84 Å were considered in the reduction. Final cell constants were calculated from the xyz centroids of 1767 strong reflections from the actual data collection after integration (SAINT). The intensity data were corrected for absorption (SADABS).



*Compound II-**8ca***: A colorless crystal (approximate dimensions 0.150 x 0.050 x 0.020 mm3) was placed onto the tip of MiTeGen and mounted on a Bruker SMART Apex II diffractometer and measured at 150 K. 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 48 reflections. The data collection was carried out using Cu K_α radiation (graphite monochromator) with a frame time of 10-60 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 2.0º steps ω and Φ scans. Data to a resolution of 0.84 Å were considered in the reduction. Final cell constants were calculated from the xyz centroids of 1476 strong reflections from the actual data collection after integration (SAINT). The intensity data were corrected for absorption (SADABS).