The development and applications of unsymmetrical diboron compounds

Xi Guo

Dissertation submitted to the faculty of the Virginia Polytechnic Institute and State University in partial fulfillment of the requirements for the degree of

Doctor of Philosophy
In
Chemistry

Webster L. Santos, Chair
Felicia A. Etzkorn
David G. I. Kingston
James M. Tanko

November 6, 2014
Blacksburg, VA

Keywords: diboron compounds, conjugate addition, diboration, *o*-nitrobenzyl ligands

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ABSTRACT

Organoboron compounds have shown a wide variety of applications in both organic synthesis and the pharmaceutical field in the past decades. Transition metal-catalyzed boration of unsaturated compounds has been studied extensively as an efficient method to install C-B bonds. Most of the previous examples employed symmetrical diboron reagents such as $B_2(pin)_2$ (pin = pinacolate) and $B_2(cat)_2$ (cat = catecholate). There are, however, limited examples of boration using unsymmetrical diboron reagents. This dissertation discloses two transition metal-catalyzed borations of unsaturated compounds with unsymmetrical diboron compounds.

A Cu-catalyzed β-boration of electrophilic allenoates with a novel sp^2-sp^3 hybridized diboron reagent (PDIPA) is described. This unsymmetrical diboron reagent is preactivated and allows the boration to go smoothly under mild reaction conditions. The reaction provides β-borylated β,γ-unsaturated esters with exclusive (*Z*)-double bond geometry. These borylated products are useful intermediates for subsequent Suzuki-Miyaura cross-coupling reaction.

In order to install two C-B bonds in one reaction, a Pt-catalyzed diboration of allenes with a differentially protected diboron reagent (PDAN) is presented. This unsymmetrical diboron reagent is prepared from the sp^2-sp^3 hybridized diboron compound, and it reacts with a series of 1,1-disubstituted allenes chemo- and regioselectively. Steric control ensures that both boryl moieties add to the terminal double bond, and the pinacol boronate preferentially attaches to the sp-

hybridized carbon. The bis-boronyl products can be further converted to other functional groups as well as cross-coupling reactions.

A collaborative project with Department of Physics and Department of Chemical Engineering is also discussed. In this project, a series of *o*-nitrobenzyl ligands containing a disulfide group as the anchor to gold surfaces are synthesized. The *o*-nitrobenzyl group uncages an amine upon photoexcitation. Attempts to make a water soluble analog failed, however, the mixture of methanol and water as the solvent was sufficient to attach them on gold surfaces.

Acknowledgements

I would like to thank my advisor, Dr. Santos, for his guidance and support. He helped me out when I was struggling in the beginning of graduate school. He was patient when I was lost or slow in the project. He encouraged me when I had doubts about myself. He taught me how to think as a graduate student when I was doing the research, and how to think as an instructor when I was teaching the lecture class in the summer. He is always there willing to help. I still remember when he showed me our lab the first time, he said "you are going to be married to this lab for a few years". I am very glad that I joined this research group and I enjoy the nice working environment that he creates. I would not have made this far in graduate school without his help and encouragement. I especially appreciate his understanding and help when I am pregnant.

I would also like to thank my committee members, Dr. Etzkorn, Dr. Kingston, and Dr. Tanko. They taught me to read papers critically, think about research problems deeply, and pay attention to the fundamental principles. I would specifically like to thank Dr. Etzkorn for her support and help when I was teaching this summer.

I would like to thank my group members. Dr. Brandon Thorpe helped me get started in the lab, and he was always happy to answer my questions. Jing Sun helped me set up the hood and taught me the experimental techniques which I was not familiar with. I worked on the same project with Amanda Nelson. I enjoy discussing the research problems with her. She seems to have solutions for all the problems. Her comments on my writing helped me a lot. Emily Morris is a great life coach especially during my pregnancy. It is always nice talking to Molly Congdon and Beth Childress. I would also like to thank Dr. David Bryson, Dr. Ming Gao, Dr. Wenyu Zhang, Jessica Wynn, Cheryl Peck, Russell Snead, Dr. Jason Crumpton, Dr. Mithun Raje, Ken Knott,

Joseph Caldrone, Dr. Neeraj Patwardhan, Dr. Srinath Pashikanti, Sean Lafferty, and Hao Li for their help and support. It has been a pleasure to work with you all.

I would like to express my gratitude to my family for their unconditional love and support. Whenever I am frustrated, talking to my parents always cheers me up. Although they cannot visit me often like when I was in college, I can still feel their support and care. I would like to thank my husband, Zhengmian Chang, who stands by my side all the time. We have stayed together through ups and downs, and I look forward to the future with him.

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Chapter 1 Introduction to boronic acids and boronic acid derivatives

1.1 Structure and properties of boronic acids and boronic acid derivatives

1.1.1 Overview

Boronic acids are boron-containing compounds with one carbon substituent and two hydroxyl groups covalently attached to the boron atom (Figure 1.1). The trivalent boron atom is sp^2-hybridized and therefore adopts a trigonal planar geometry. The boron atom has six valence electrons and an empty p orbital which is perpendicular to the plane. The empty p orbital can accept electrons from other atoms, which makes boronic acids Lewis acidic. Boronic acids have low toxicity, and they will be ultimately oxidized into boric acids (**1.2**) in air. Boric acids are also relatively nontoxic.[1] Because of the Lewis acidity, low toxicity, and relatively stability, boronic acids are attractive and environmentally benign synthetic intermediates.[2]

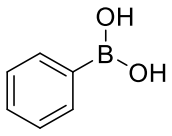
boronic acid **1.1** | boric acid **1.2** | boronic ester **1.3** | boroxine **1.4**

Figure 1.1 Structures of boronic acids and boronic acid derivatives.

When the two hydroxyl groups are protected by other alkyl or aryl groups, the resulting organoboron compounds are boronic esters (**1.3**). Without the presence of hydroxyl groups, boronic esters are more stable and easier to handle. Therefore, they are often preferred in organic reactions.

1.1.2 Structure and properties of boronic acids

The crystals of phenylboronic acid (**1.5**) were obtained by recrystallization from water, and their structure was determined by X-ray crystallography in 1977.[3] Each asymmetric unit of the crystals contains two molecules of phenylboronic acid which are connected by hydrogen bonding (Figure 1.3). The structures of several other boronic acids were elucidated by X-ray crystallographic analysis later, and they all show similar pattern to phenylboronic acids.[4,5] The average B-O bond length is around 1.36 Å, which is shorter than a typical C-O bond with the bond length of around 1.43 Å. Bond strength data also shows that B-O bond (124 kcal/mol) is much stronger than C-O bond (92 kcal/mol). It is believed that the B-O bond is shorter and stronger than the C-O bond because the lone pairs of electrons of oxygen can be donated to the empty p orbital of boron.[6] In this way, the B-O bond has a partial double bond character.



1.5

Figure 1.2 Structure of phenylboronic acid.

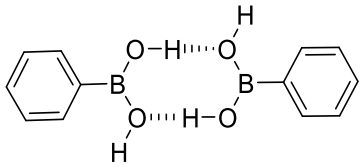
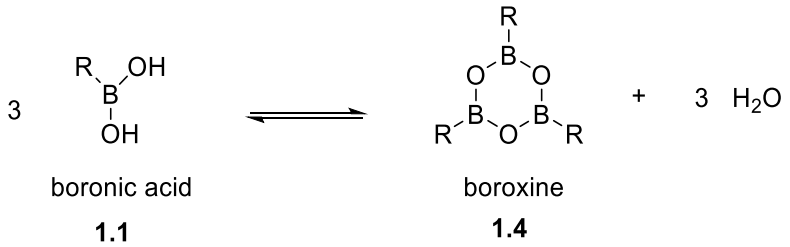


Figure 1.3 Structure of dimeric unit of phenylboronic acid.

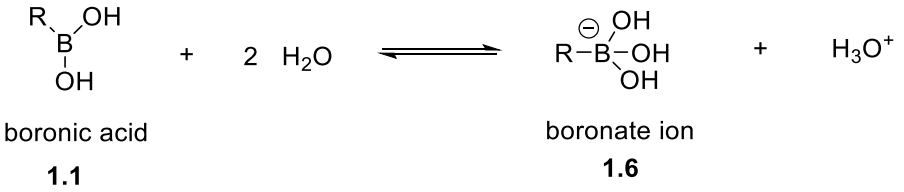
Most aromatic boronic acids are white crystalline solids and possess relative stability towards air and moisture compared to alkyl and some heteroaromatic boronic acids. These alkyl substituted and heteroaromatic boronic acids necessitate storage under an inert atmosphere to prevent the slow oxidation by air.[7] The formation of the stronger B-O bond (124 kcal/mol) from the B-C bond (77

kcal/mol) is the thermodynamic driving force for oxidation. Moreover, boronic acids tend to dehydrate and form the trimeric cyclic anhydrides, or boroxines (**1.4**) over time (Scheme 1.1). Thermodynamic studies in aqueous solution showed that the formation of boroxines is reversible, and the presence of electron-donating groups on boron helps drive the equilibrium further towards the boroxine formation.[8,9] Additionally, the increase of entropy by generation of three molecules of water is another driving force for this process.[9] Fortunately, both the free boronic acid and the boroxine derivatives will undergo most synthetic reactions in which boronic acids are employed as substrates such as in Suzuki-Miyaura cross-coupling reaction. In these transformations, the boronic acid is generally used in excess because there is no simple method to determine the exact amount of boronic acid present with the coexistence of boroxine.[10]



Scheme 1.1 Formation of boroxine from boronic acid.

Despite the fact that boronic acids have two hydroxyl groups, they still act as Lewis acids, accepting electrons into the vacant p orbital of the boron atom, instead of Brønsted acids in water. When the boron accepts electrons from a water molecule, it forms the anionic tetrahedral species, boronate ion (Scheme 1.2).[11] The formation of the boronate ion has been known for several decades, however, the crystal structure of a trihydroxyboronate salt was not reported until 2006.[12] The formation of the boronate ion with water makes most boronic acids amphiphilic, which can make their isolation and purification complicated.



Scheme 1.2 Formation of boroxine from boronic acid.

1.1.3 Structure and properties of boronic esters

The formation of boroxines and amphiphilicity of boronic acids can limit their utility in synthetic applications. When the two hydroxyl groups are substituted by alkoxy or aryloxy groups, boronic esters are obtained. This substitution protects the boronic acid, thereby solving the stoichiometry problem by preventing the formation of boroxines. Furthermore, boronic esters are less polar than boronic acids, and lose the ability to form hydrogen-bonds with water. Their solubility in water is therefore limited, which makes the isolation and purification of boronic esters easier than the corresponding boronic acids. Due to the advantages of boronic esters, they are often preferred in organic reactions. Some of the commonly used boronic esters are shown in Figure 1.4.

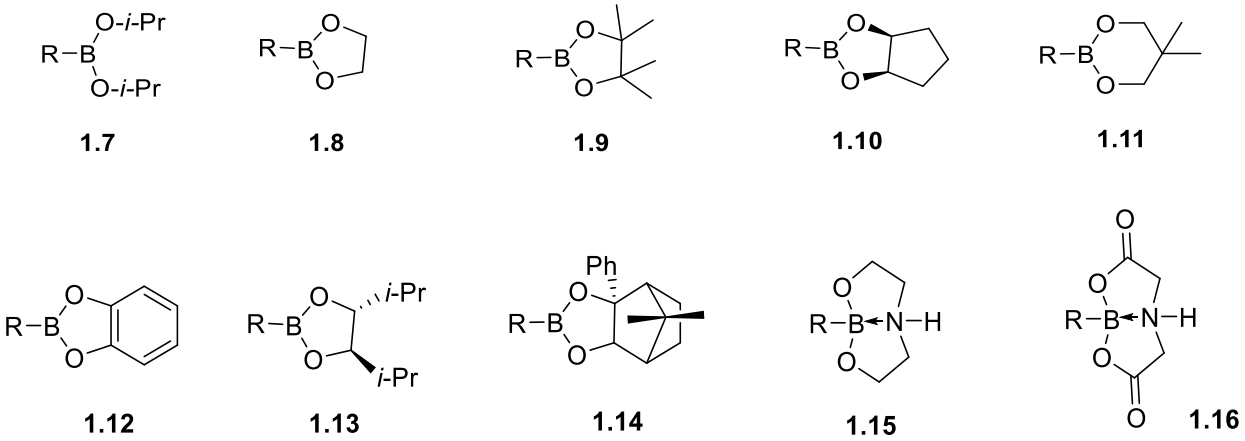
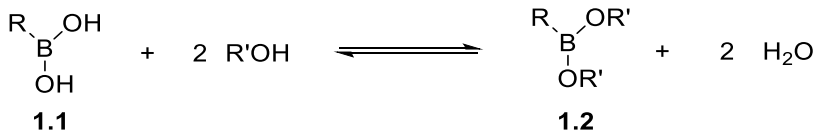


Figure 1.4 Structures of common boronic esters.

Boronic esters are prepared by treating boronic acids with the corresponding alcohols or diols (Scheme 1.3). The reaction is an equilibrium. Removal of water by azeotropic distillation with a Dean-Stark apparatus or addition of drying agents such as molecular sieves is used to drive the reaction in favor of the formation of boronic esters. The synthesis of cyclic boronic esters, such as **1.8**-**1.16**, is more favored than that of noncyclic ones like **1.7**. Among those cyclic boronic esters, the sterically hindered **1.9** is more stable than **1.8**, because sterics prevent water molecules from attacking the boron atom and converting back to the starting boronic acid.[13] Several chiral boronic esters (e.g. **1.10, 1.13, 1.14**) have been synthesized with chiral diols, and are useful for stereoselective transformations such as homologation reactions discussed later in this chapter.[14-16] Diethanolamine boronic esters (**1.15**) and other N-substituted boronic esters (**1.16**) were also prepared.[17] Compounds like **1.15** and **1.16** exhibit tetrahedral geometry, wherein electron donation from the nitrogen lone pair to the Lewis acidic boron center forms a dative bond. This dative bonding lengthens the B-O bond by approximately 0.1 Å as compared to the tricoordinate derivatives.[18] These compounds are normally white crystalline solids and do not dissolve in nonpolar solvents well. As a result, they can be easily purified by precipitation and filtration.



1.1 **1.2**

Scheme 1.3 Synthesis of boronic esters from boronic acids.

1.1.4 Diboron compounds

Diboron compounds comprise another class of synthetically useful boronic acid derivatives. Several examples of diboron compounds have been synthesized and employed in a wide variety of reactions.[19] The most commonly employed and extensively studied diboron compound is the commercially available bis(pinacolato)diboron or B_2pin_2 (pin = pinacolate, **1.17**).

Bis(catecholato)diboron or B_2cat_2 (cat = catecholate, **1.18**) is another commonly used diboron compound. Like most diboron compounds, it is prepared by reaction of tetrakis(dimethyamino)diboron, $B_2(Me_2N)_4$, with catechol.[20] The unsymmetrical diboron compound PDAN (pinB-Bdan, **1.19**) was first reported in 2010, and it was used for regioselective diboration of alkynes.[21] More recently, another unsymmetrical diboron compound **1.20** was prepared by Yamashita group and it can cleave an isonitrile C-N triple bond in the absence of transition metal at room temperature.[22]

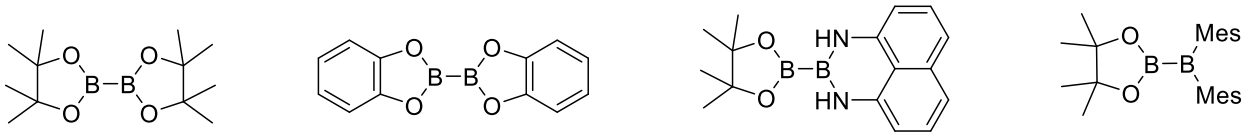


Figure 1.5 Structures of common diboron compounds.

Both boron atoms of compounds **1.17** to **1.20** are sp^2 hybridized. A novel sp^2-sp^3 hybridized diboron compound PDIPA diboron (**1.21**) was designed by Drs. Gao and Thorpe in our group.[23] The crystal structure showed that the B-B bond of PDIPA diboron is longer than that of B_2pin_2, therefore, PDIPA diboron can be considered as a preactivated diboron compound. It was employed for conjugate boration under mild reaction conditions.[24,25] Recently, Braunschweig and coworkers elegantly designed and synthesized another sp^2-sp^3 hybridized diboron compound (**1.22**), which was a phosphine adduct of 1,2-dibromo-1,2-dimesityldiborane.[26-28]

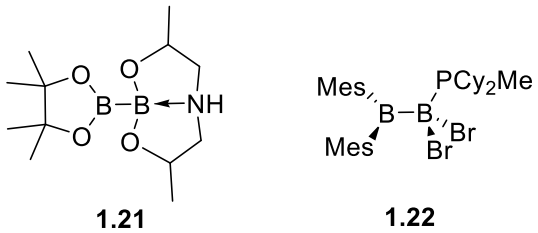
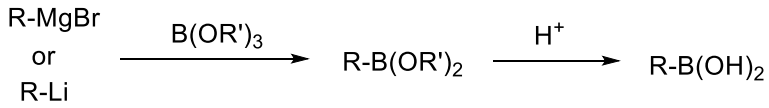


Figure 1.6 Structures of sp2-sp3 hybridized diboron compounds.

1.2 Preparation of organoboron compounds

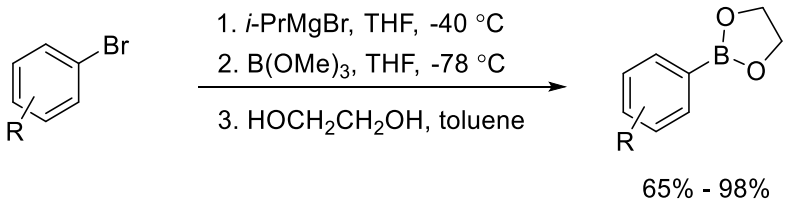
1.2.1 Trapping organometallic reagents with trialkylborates

The most traditional way to synthesize organoboron compounds is by treating trialkylborates with organometallic reagents, such as the Grignard or organolithium reagents (Scheme 1.4). Phenylboronic acid was the first organoboron compound prepared using this method.[29,30] In the reaction, phenylmagnesium bromide was added slowly to the ethereal solution of n-butylborate at -60 ℃. A workup later with cold sulfuric acid hydrolyzed the boronic ester to the corresponding boronic acid in 50% yield. In addition to arylboronic acids,[29,30] this method has been successfully applied to prepare alkenylboronic acids,[31,32] alkynlboronic acids,[33,34] and also alkylboronic acids.[35,36]



Scheme 1.4 Preparation of organoboronic acids with organometallic reagents.

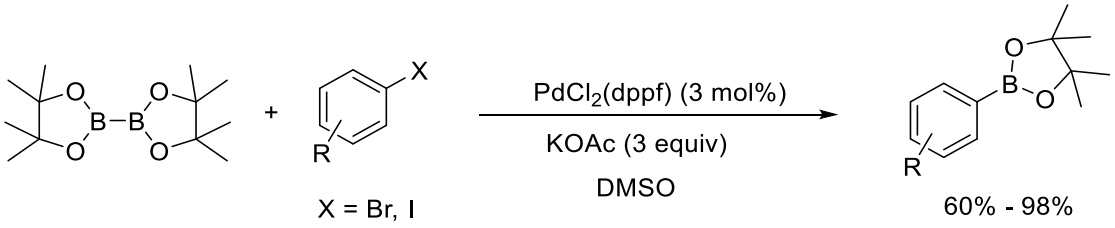
As mentioned previously, most boronic acids are partially soluble in water. Therefore, workup by an aqueous acid negatively affects the isolated yield. To address this problem, the synthesis of the more stable boronic esters is preferred.[37-39] Scheme 1.5 shows an example of employing a nonaqeuous workup procedure to prepare the arylboronic ester.[40] This procedure is effective for a variety of aryl bromides, and even sterically hindered ones, such as 2,4,6-trimethylphenylboronic ester, are obtained in high yields. 1,3-propanediol and pinacol are also suitable diols to perform the reaction.



Scheme 1.5 Preparation of arylboronic esters with nonaqueous workup procedure.

1.2.2 Coupling of aryl halides with diboronyl compounds

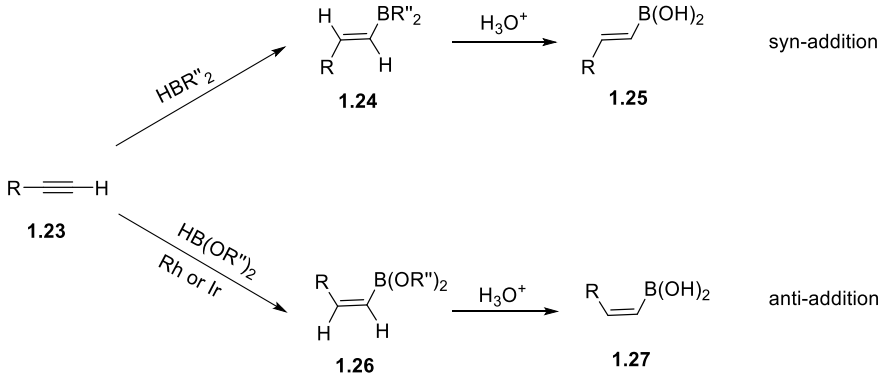
Although trapping Grignard or organolithium reagents with alkylborates has proved to be effective for preparation of numerous organoboron compounds, these organometallic reagents are sensitive to water and air. Handling them usually requires special precautions. Furthermore, the harsh reaction condition also limits the functional group tolerance, and thus a milder alternative approach needed to be explored. In 1995, Ishiyama et al. reported the first example of generating arylboronic esters by coupling of aryl halides with B_2pin_2 (Scheme 1.6).[41] They found that a catalytic amount of $PdCl_2$(dppf) in combination with the very weak base KOAc was the most efficient system for aryl bromides or iodides. Unlike the organometallic approach, this mild condition can tolerate functional groups such as esters, ketones and nitriles. Further experiments showed that when $PdCl_2$(dppf) was replaced with $Pd_2(dba)_3$ and the Buchwald ligand Xphos, a more reactive catalyst was generated to enable the synthesis of arylboronic esters from the more synthetically available aryl chlorides.[42] Similarly, boronic acids can be obtained directly from tetrahydroxydiboron $B_2(OH)_4$.[43]



Scheme 1.6 Synthesis of arylboronic esters by coupling of aryl halides with B_2pin_2.

1.2.3 Hydroboration

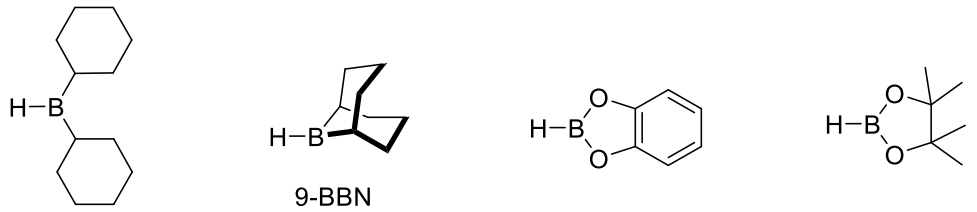
Another traditional method for preparation of organoboron compounds is the hydroboration of alkynes with organoboranes (Scheme 1.7). Syn-addition to the triple bond places both the hydride and the boron on the same side of the resulting double bond (**1.24**). For terminal alkynes, this step is regioselective, and the boron group is always added to the terminal carbon. Hydrolysis of the ester (**1.24**) with an acid provides trans-2-substituted alkenylboronic acids (**1.25**).[44,45]



Scheme 1.7 Preparation of boronic acids by hydroboration.

When bulky dialkylboranes such as dicyclohexylborane (**1.28**) and 9-BBN (**1.29**) are present, hydroboration of terminal alkynes can stop at the alkenylboronic ester (**1.24**) with great regioselectivity. Small organoboranes like BH_3, however, will undergo hydroboration twice and form undesired diborated alkanes.[46] On the other hand, dialkoxyboranes such as catecholborane (**1.30**) and pinacolborane (**1.31**) are also applicable for regioselective hydroboration. Although dialkoxyboranes afford robust organoboronic esters directly, they are less reactive, and usually require heating and take several hours to finish.[47-50] To improve the efficiency of the uncatalyzed reaction, late transition metal Rh (I) and Pd (II) complexes were investigated as catalysts in the early 1990s.[51] Unfortunately, decomposition of catecholborane and other catecholate-containing side products were still observed in those catalytic reactions.[52,53] Later experiments showed that

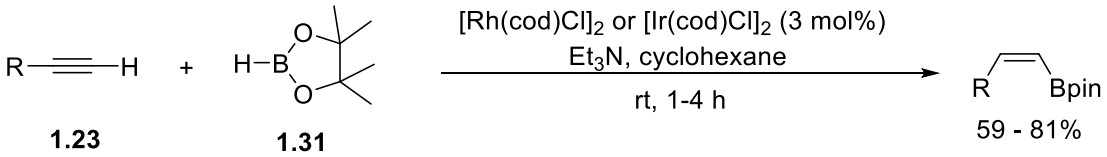
when the hydroboration was performed under the catalysis of dicarbonyltitanocene $Cp_2Ti(CO)_2$, near quantitative yields of alkenylboronic esters were obtained without decomposition of catecholborane.[54] This catalytic pathway also provided higher regioselectivity than noncatalytic one. Similarly, pinacolborane is a sluggish hydrobrating reagent. Addition of zirconocene chloride hydride $HZrCp_2Cl$ can help it proceed smoothly even at room temperature.[55,56]



1.28 **1.29** **1.30** **1.31**

Figure 1.7 Structures of common bulky dialkylboranes and dialkoxyboranes.

Both the uncatalyzed and catalyzed hydroborations discussed above follow anti-Markovnikov and syn-addition pathway to provide trans-alkenylboron compounds (**1.25**). To complement the selectivity, Miyaura and coworkers found that cis-alkenylboron compounds (**1.27**) can be accessed in the presence of Rh or Ir complexes and triethylamine (Scheme 1.8).[57] The first step of catalytic hydroboration is oxidative addition of the Rh or Ir catalyst to the alkyne. Mechanistic studies showed that the oxidative addition intermediate of syn-addition was not stable in the presence of triethylamine. As a result, the anti-addition pathway was followed and cis-alkenylboron compounds were obtained instead. This approach has been applied successfully as the key step in natural product synthesis.[58]

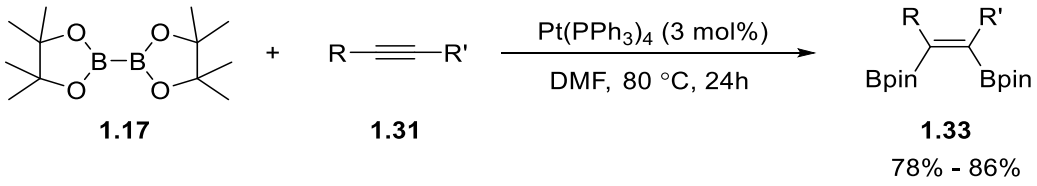


1.23 **1.31**

Scheme 1.8 Anti-addition to terminal alkynes catalyzed by Rh or Ir complexes.

1.2.4 Catalytic boration of unsaturated compounds

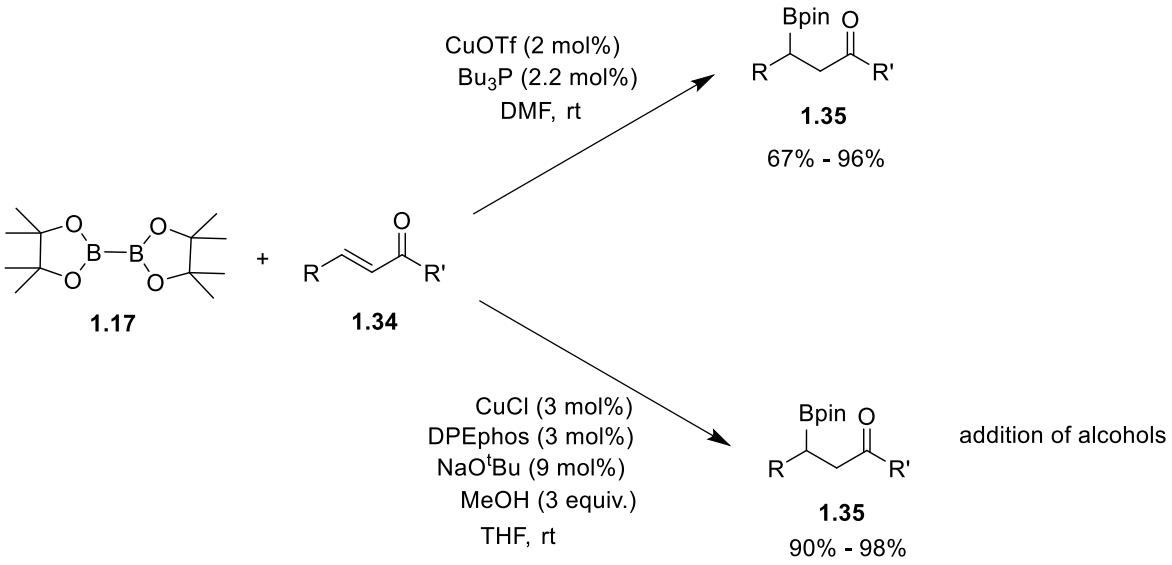
Besides coupling with aryl halides, diboronyl compounds can react with unsaturated compounds to prepare diborated or monoborated compounds. Ishiyama et al. reported the first example of diboration of alkynes with B_2pin_2.[59] Catalytic amounts of $Pt(PPh_3)_4$ in DMF at 80 ℃, generated the desired diborated product with good yields (Scheme 1.9). Other attempts using Pd, Rh, Ni or Co complexes failed to provide the diborated product. Both internal and terminal alkynes were suitable substrates for this reaction, whereas it did not work with the less reactive alkenes. Mechanistic studies revealed that the catalyst undergoes oxidative addition with B_2pin_2, followed by alkyne insertion, and finally reductive elimination to release the product and regenerates the catalyst. Diboration of alkenes is known to be challenging due to the competition of β-hydride elimination and the sluggish rate at which alkene insertion takes place.[60] To address these problems, more reactive catalysts were later developed. Employment of $Pt(dba)_2$,[61] $Pt(cod)_2$[62] and $RhCl(PPh_3)_4$[63] provided a successful diboration of alkenes, despite the presence of small amount of side products coming from β-hydride elimination.



Scheme 1.9 Diboration of alkynes with B_2pin_2.

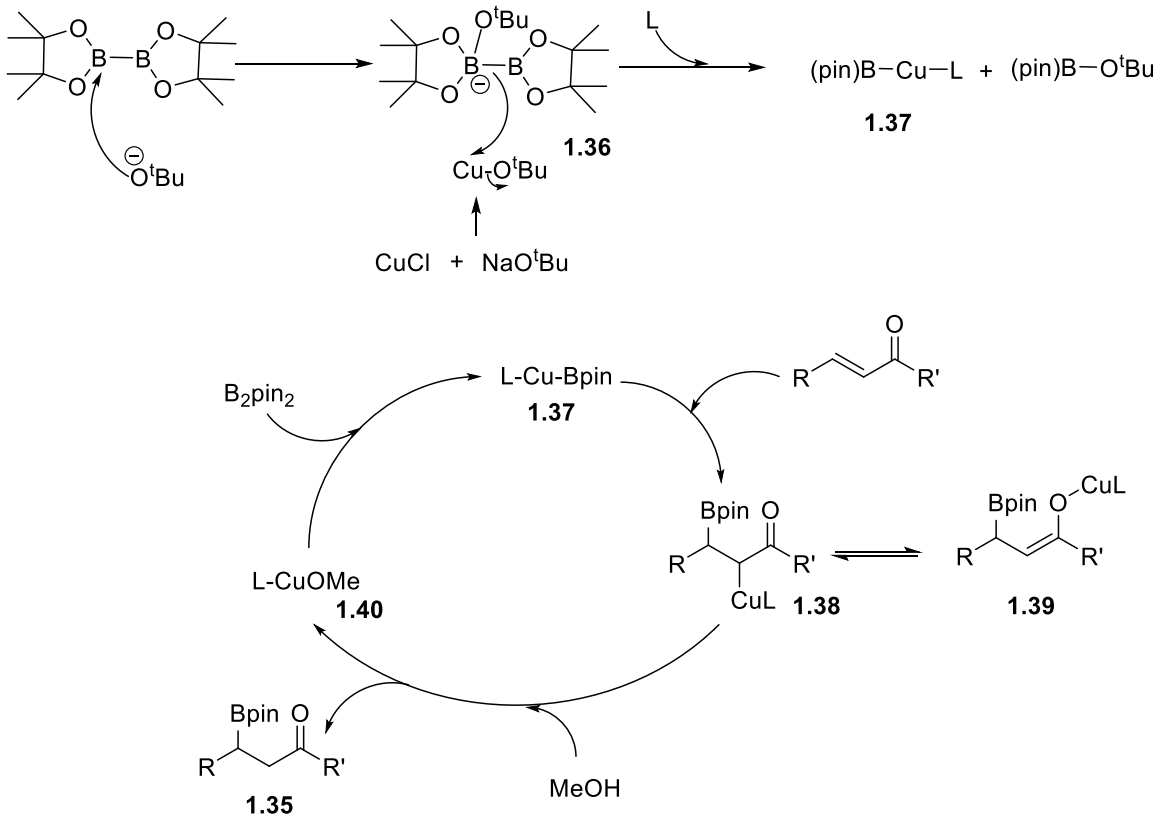
Conjugate boration of α,β-unsaturated compounds in the catalysis of Pt complexes was also described.[64] Further investigation for cheaper metals indicated that copper(I) can carry out this transformation with addition of tributylphosphine (Scheme 1.10).[65] The optimized reaction condition was selective for α,β-unsaturated ketones, and most substrates required longer than 20 hours to ensure good yields. In 2006, Yun's group found that addition of base and alcohol can

accelerate the conjugate boration dramatically.[66] Both α,β-unsaturated ketones and esters proceed smoothly and provide excellent yield in less than 14 hours. When a chiral ligand such as Josiphos was employed, asymmetric β-boration product can be obtained readily with still excellent yield and high enantiomeric excesses (82 – 92% ee).[67]



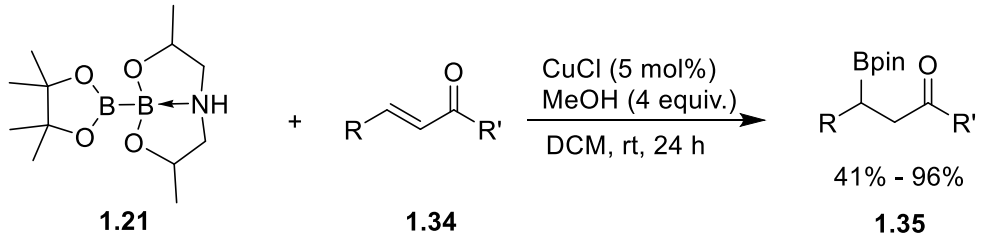
Scheme 1.10 Copper(I)-catalyzed conjugate boration of α,β-unsaturated compounds.

Mechanistic studies provided further insight that the Lewis acidic boron atom of B_2pin_2 can accept electrons from base to form a base adduct **1.36** (Scheme 1.11). As a result, the B-B bond of **1.36** becomes longer and more electron-rich, which can attack the electrophilic Cu(I) to yield the active catalytic species **1.37**.[68] This borylcuprate intermediate **1.37** is nucleophilic, and will undergo conjugate addition to α,β-unsaturated compounds, providing **1.38** and **1.39**. These two tautomers are in equilibrium, but metathesis of either with methanol will generate the final product **1.35** and compound **1.40** which reacts with B_2pin_2 to regenerate the active catalyst **1.37**.[69,66]



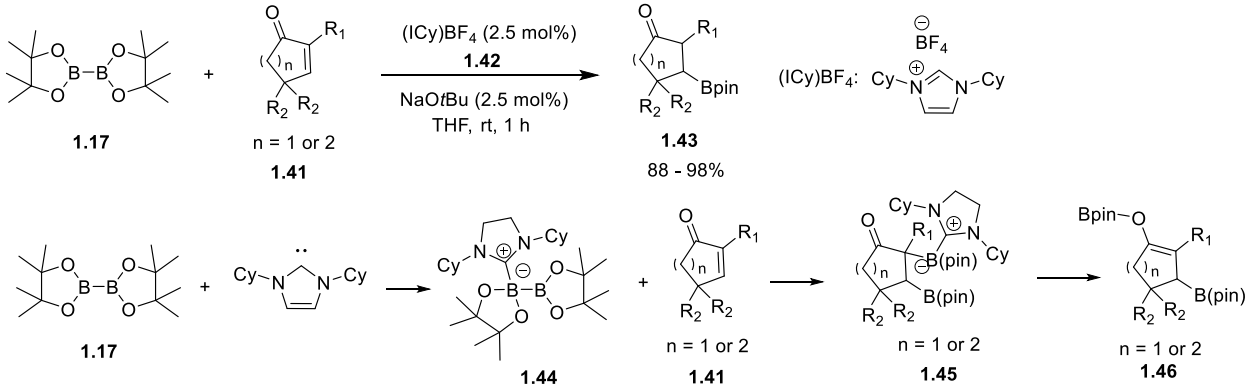
Scheme 1.11 Proposed mechanism for copper(I)-catalyzed conjugate boration.

Both base and alcohol are necessary to ensure short reaction times and high yields for conjugate boration. Consequently, the compounds with base-sensitive group cannot be borylated under these reaction conditions. Encouraged by the structure of base adduct **1.36**, Drs. Gao and Thorpe in our group designed a novel sp^2-sp^3 hybridized diboron compound PDIPA (**1.21**).[24] The B-B bond of PDIPA diboron is longer than that of B_2pin_2, therefore, PDIPA diboron can be considered as a preactivated diboron compound. It was hypothesized that if PDIPA diboron was used instead of B_2pin_2, the conjugate boration can take place without the presence of base. Fortunately, the following experiments proved that hypothesis, and provided an alternative approach to perform conjugate boration under mild reaction conditions (Scheme 1.12).



Scheme 1.12 Conjugate boration with PDIPA diboron.

In addition to the Pt and Cu catalysts, Rh[70] and Ni[71] complexes can also catalyze conjugate boration. More recently, a metal-free catalytic system was developed by Hoveyda and coworkers (Scheme 1.13).[72] An N-heterocyclic carbene (**1.42**) is used to catalytically activate B_2pin_2 through coordination to the Lewis acidic boron atom of B_2pin_2 (**1.44**). The resulting B-B bond of **1.44** becomes longer and more electron-rich, which will undergo conjugate addition to **1.41**, generating **1.45**. Then release of the N-heterocyclic carbene followed by tautomerization yields compound **1.46**, which will be converted into the desired product **1.43** under acidic workup.



Scheme 1.13 The reaction and proposed mechanism for metal-free conjugate boration.

1.3 Applications of organoboron compounds

Organoboron compounds have shown a wide variety of application in both the organic synthesis and pharmaceutical fields in the past decades.

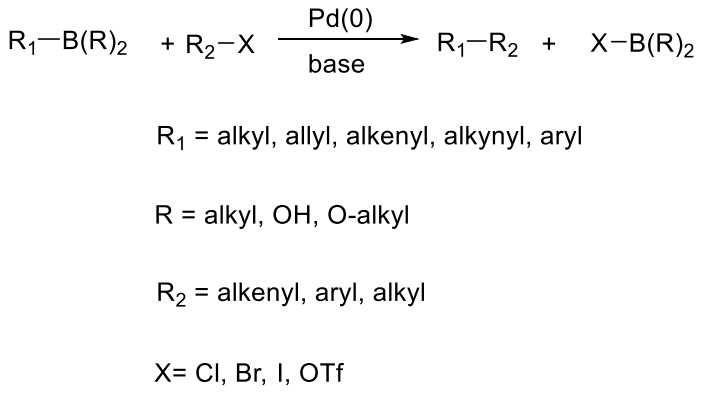
1.3.1 Synthetic intermediates

1.3.1.1 Oxidation

Organoboron compounds can be readily oxidized into corresponding alcohols, aldehydes or ketones. Oxidation of phenylboronic acids[73] and alkylboronic acids[74] into alcohols with hydrogen peroxide was first published in 1930s. Later experiments showed that this approach can be applied to convert alkenylboronic acids into aldehydes or ketones.[75,76] A number of chiral alcohols have been prepared by enantioselective hydroboration followed by oxidation.[77,78] Sodium perborate,[79] oxone,[80,81] and hydroxylamine[82] provide alternative oxidants for milder oxidation conditions.

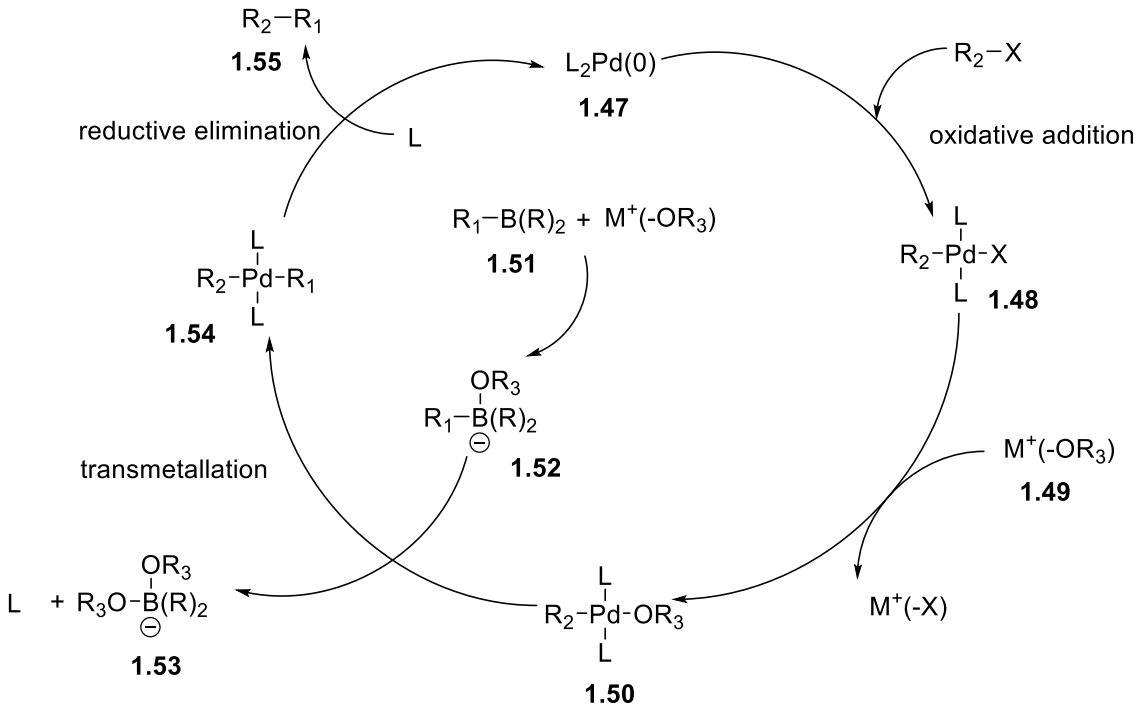
1.3.1.2 Suzuki-Miyaura cross-coupling reaction

Cross-coupling reactions are some of the most powerful methods to construct new carbon-carbon bonds. The early examples of cross-coupling reactions employed organometallic reagents such as magnesium,[83] aluminum[84] and zinc[85]. Miyaura et al. demonstrated a palladium-mediated cross-coupling reaction between organoboron compounds and haloarenes for the first time.[86] Following their discovery, this class of reactions, referred as the Suzuki-Miyaura cross-coupling (SMC) reaction, attracted great attention due to the commercial availability of organoboron compounds, mild reaction conditions, low toxicity of byproducts and the tolerance to a broad spectrum of functional groups (Scheme 1.14). As a result, it has become one of the most important methods to form new carbon-carbon bonds in organic synthesis, receiving acknowledgement by the 2010 Nobel Prize in Chemistry.[87-90]



Scheme 1.14 General scheme for the Suzuki-Miyaura cross-coupling reaction.

The SMC catalytic cycle is believed to proceed via oxidative addition of palladium catalyst (**1.47**) to haloarenes, ligand exchange between **1.48** and base (**1.49**), transmetallation of **1.50** with organoboronate (**1.52**), and finally reductive elimination of **1.54** to provide the desired product (**1.55**) and regenerate the catalytic species (Scheme 1.15). Mechanistic studies have found oxidative addition to be the rate-limiting step.[88] For this reason, organoiodides usually proceed faster than organobromides, which are faster than organochlorides. In the transmetallation step, the sp^2 boron compound **1.51** does not react with palladium(II) compound **1.50** readily because of the low nucleophilicity of organic groups bound to the sp^2 boron atom. However, the Lewis acidity of the sp^2 boron compound enables a base additive to generate a quaternary boron center **1.52**, which facilitates the transfer of the organic group to the organopalladium intermediate.



Scheme 1.15 General mechanism for SMC reaction.

The SMC reaction is widely used for construction of sp^2-sp^2 C-C bonds. Examples of SMC with alkyl halides are limited since the sp^3-hybridized carbon of the alkyl halide slows down the oxidative addition step.[91] Furthermore, β-hydride elimination side products are commonly observed due to the propensity of the metal to form interactions with the β-hydrogen.[92,93] Similarly, alkylboron compounds are more challenging than alkenyl or aryl organoboron compounds due to the competitive β-hydride elimination. Nevertheless, during the past decade significant advances have been made to overcome those difficulties. In the early 2000s, Fu and coworkers developed the effective catalytic systems for SMC of unactivated alkyl bromides,[94] chlorides[95] and tosylates[96] with 9-BBN derivatives. In the presence of $Pd(OAc)_2$, PCy_3 was the best ligand for alkyl bromides, whereas P*t*Bu_2Me proved to be the most effective one for alkyl tosylates. When they applied those conditions to alkyl chlorides, only trace product was obtained. The experimental data suggested that the steric difference between monophosphine ligands plays an important role in the success of

SMC reactions of alkyl halides, although the detailed mechanism is still unclear now. During the investigation of SMC reactions, the Buchwald group at M.I.T. designed a series of dialkylbiaryl phosphine ligands (Figure 1.8).[97] Based on the mechanistic studies they conducted, the properties of those ligands is tunable by rational modifications of the ligand structure. This new class of ligands benefitted the SMC reaction by enabling aryl chlorides to proceed smoothly at room temperature with as little as 1.0-1.5 mol% Pd and JohnPhos (**1.57**).[98] Both XPhos (**1.59**)[99] and RuPhos (**1.60**)[100] have also been employed in the stereoselective SMC of alkyl boronic esters.

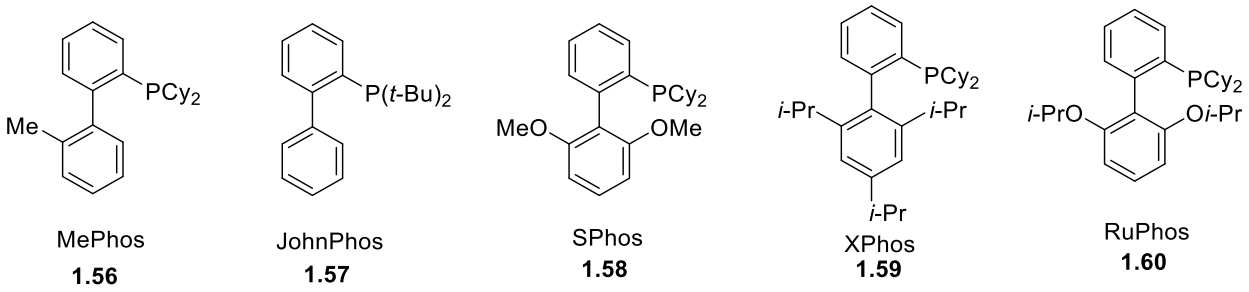


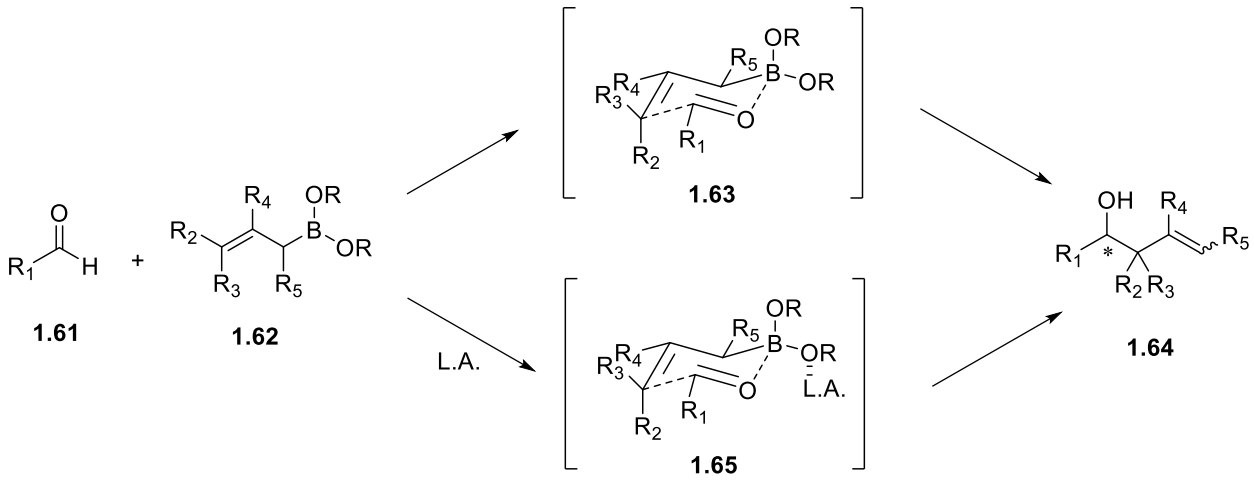
Figure 1.8 Structures of Buchwald ligands.

The recent success of organotrifluoroborates in challenging SMC reactions has attracted great attention.[10] Organotrifluoroborates are generally air and moisture stable, which arises from the tetracoordinate, sp^3 hybridized boron. Their preparation is quite straightforward (Scheme 1.16). Treatment of boronic acids with saturated aqueous KHF_2 provides organotrifluoroborates directly, which usually precipitate from solution, allowing purification by simple filtration.[101,102] Examples of SMC reactions with both primary[103,104] and secondary[105,106] alkyl trifluoroborates were reported lately.

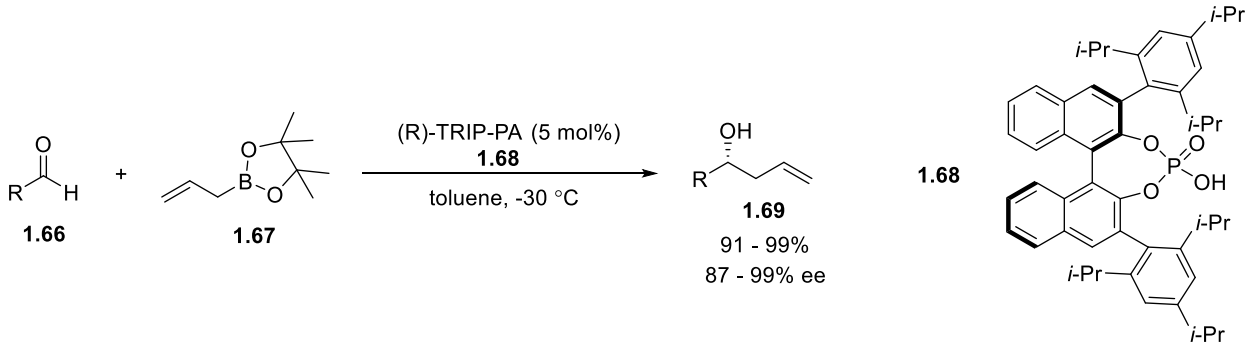
Scheme 1.16 Preparation of organotrifluoroborates from boronic acids.

1.3.1.3 Allylboration

The reaction between allylic boronates and aldehydes is a useful approach to access chiral homoallylic alcohols, such as those commonly found in natural products (Scheme 1.17).[107] This type of reaction is stereoselective because it proceeds via a six-membered chair-like transition state (**1.63**).[108] Early efforts for tuning the reactivity was focused on changing the solvents or boronate structures.[109] Additives such as Lewis acids were not promising in the beginning since they might interrupt the chair-like transition state and reduced the stereoselectivity. Surprisingly, Lewis acids such as $Sc(OTf)_3$,[110] $Cu(OTf)_2$[111] demonstrated their dramatic rate acceleration effect in recent reports. Interestingly, allylboration with or without Lewis acids provided the same product, which suggested that both methods had the same stereo-defined transition state. The rate enhancement is believed to arise from the coordination of the Lewis acidic metal ion to the equatorial oxygen atom on the organoboronates (**1.65**). The boron atom, therefore, becomes more electrophilic and thus more reactive towards allylboration.[112] Likewise Brønsted acid can also activate the electrophilic organoboronates by protonation of the oxygen atom.[113] Compared to uncatalyzed reactions, higher enantiomeric excesses can be obtained with chiral Brønsted acids, such as (R)-TRIP-PA (**1.68**, Scheme 1.18).[114,115]



Scheme 1.17 General scheme for allylboration.



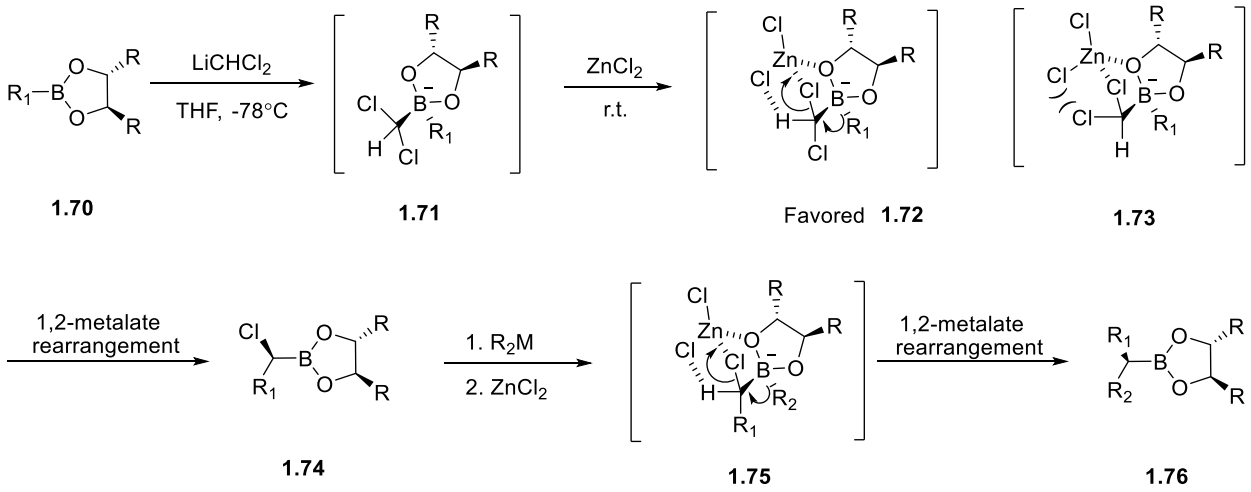
Scheme 1.18 Allylboration catalyzed by Chiral Brønsted acid.

Unlike allylboration with aldehydes, examples with ketones are limited due to both electronic and steric reasons.[116] The extra alkyl group of ketones is slightly electron-donating, which leads to less electrophilic carbonyl groups. Sterically, one of the alkyl groups of ketones is forced to occupy an axial position in the chair-like transition state, which increases the 1,3-diaxial interaction with the axial group on the boron atom. By forming a more reactive allylcopper intermediate, the presence of CuF_2 and $La(O\textit{i}Pr)_3$ can promote allylboration with ketones, although the enantioselectivity is highly dependent on the ketone structures.[117] Indium (I) iodide also promotes the reaction but without any stereoselectivity.[118] Both good yields and stereoselectivities

can be achieved by employing chiral diols as additives.[119] Chiral diols can induce enantioselectivity, and also activate the organoboron compounds as Brønsted acids.

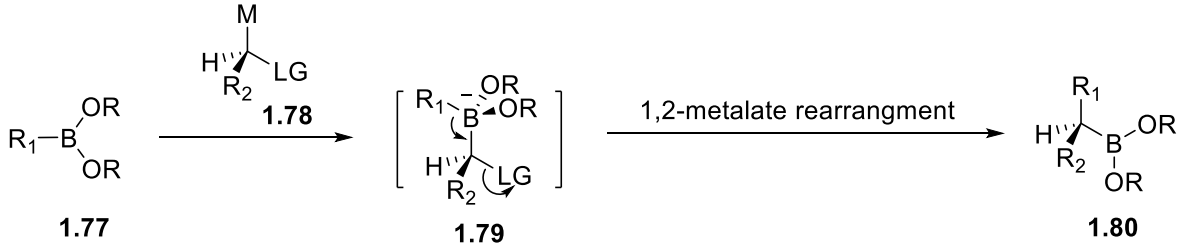
1.3.1.4 Asymmetric homologation

Since Matteson and Ray first published the highly diastereoselective homologation reaction starting from enantiopure boronic esters, it has become an important method for carbon chain extension in organic synthesis (Scheme 1.19).[120,79,121] An enantiopure boronic ester **1.70** reacts with (dichloromethyl)lithium to form the boronate complex **1.71** owing to the Lewis acidity of boronic ester. Then the nucleophilic alkyl group from boron atom attacks the adjacent carbon atom, as chloride leaves. This process is also called 1,2-metalate rearrangement, which provides (α-chloroalkyl)boronic ester **1.74**. The presence of zinc chloride can improve the diastereoselectivity from 90% to 99% due to the favored transition state **1.72**.[122] In the favored transition state, zinc is coordinated to the more accessible oxygen on the boron atom, and transfer of the alkyl group reduces the steric interaction between zinc chloride and one of the chlorides on α-carbon (**1.73**). Another nucleophile R_2M such as Grignard or organolithium reagent can undergo the similar reaction sequence of boronate complex **1.75** formation followed by 1,2-metalate rearrangement in the presence of zinc chloride. The structure of **1.75** has the same stabilized effect as **1.72**, and also the migrating alkyl group R_2 and leaving group chloride has to align anti-periplanar to each other, which lead to the homologated product **1.76** stereospecifically.[123] The preparation of a number of natural products via this pathway such as stegobinone,[124] japonilure[125] and microcarpalide[126] is indicative of its utility. The limitations of this approach include the availability of the starting boronic ester **1.70** and functional group tolerance to the extreme basicity of the organometallic reagents.



Scheme 1.19 General scheme for Matteson-type asymmetric homologation.

The stereoselectivity of Matteson-type asymmetric homologation originates from the enantiopure boronic esters (**1.70**). Thus it is a substrate-control approach. When achiral boronic esters (**1.77**) are employed, the stereoselectivity can be introduced by entioenriched reagents (**1.78**), such as lithiated chlorides[127-129] or carbamates.[130,131] Reaction of **1.77** with **1.78** generates a boronate complex (**1.79**), which then undergoes 1,2-metalate rearrangement to produce the homologated product **1.80** stereospecifically. This reagent controlled method has been applied successfully in the synthesis of several natural products such as (+)-faranal,[132] (-)-filiformin,[133] and (+)-giganin.[134]



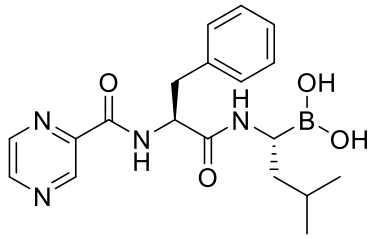
Scheme 1.20 General scheme for reagent controlled asymmetric homologation.

1.3.2 Pharmaceutical applications of boronic acids and their derivatives

The past several years bear witness to the rapid development of organoboron compounds in pharmaceutical molecules.[135,136] As discussed previously, boronic acids have low toxicity and are Lewis acids with pK_a in the range of 4-9. Therefore, many of them can accept electrons under physiological conditions.[137,138] In addition, the trivalent boron atom of boronic acids is sp^2-hybridized and thus adopts a trigonal planar geometry, which will form an anionic tetrahedral species, boronate ion, after accepting electrons. This sp^2 to sp^3 conversion of boron atom resembles the tetrahedral intermediate formed with carbonyl carbon when an amide bond is cleaved, which provides boronic acids the potential to be good transition state analogs for the inhibition of hydrolytic enzymes. The examples of boronic acids as inhibitors against chymotrypsin,[139] thrombin,[140] β-lactamases,[141,142] and dipeptidyl peptidase IV,[143] demonstrate this property. Moreover, boronic acids can form tight or reversible complexes with 1,2- and 1,3-diols, which make them great candidates of sensors and binders for carbohydrate-based biomarkers.[135]

The first example of a boronic acid as a pharmaceutical to hit the market in 2003 was with the antineoplastic drug bortezomib (PS-341, **1.81**). It is a proteasome inhibitor used for the treatment of relapsed and refractory multiple myeloma.[144] Bortezomib inhibits the 20S proteasome, which is responsible for inappropriate or accelerated protein degradation. The crystallographic structural analysis indicates that early tripeptide aldehyde inhibitors of 20S proteasome form hemi-acetal adducts with the threonine residues of the active β-subunits.[145] Interestingly, after the aldehyde group is replaced by boronic acid, the corresponding inhibitor exhibits dramatically enhanced potency compared to the original aldehyde inhibitor.[146] This promising inhibition is believed to be attributed to the formation of a tetrahedral intermediate of boronic acid with threonine residues of the active proteasome β-subunits.[147] Among all of the

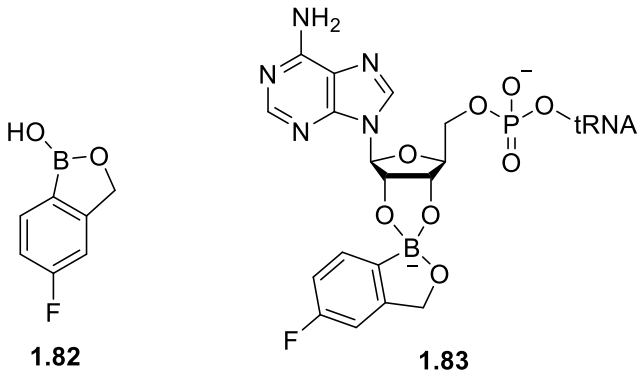
compounds synthesized, Bortezomib has the practical advantage of low molecular weight and facile synthesis.



1.81

Figure 1.9 The structure of bortezomib.

Another example is Tavaborole (AN2690, **1.82**), which is a benzoxaborole developed by Anacor. It is an antifungal agent that has been approved by FDA in 2014 for the treatment of onychomycosis.[148] Tavaborole inhibits yeast cytoplasmic leucyl-tRNA synthetase by forming a covalent adduct (**1.83**) with the 2'- and 3'-hydroxyl groups of the tRNA's 3'-terminal adenosine (Figure 1.10).[149-151] This adduct formation takes place in the editing site of the enzyme which prevents catalytic turnover, therefore, it can inhibit the synthesis of leucyl-tRNA and block protein synthesis.



1.82 **1.83**

Figure 1.10 The structure of Tavaborole and the complex of Tavaborole with tRNA.

1.4 Dissertation overview

Chapter 1 introduces the basic structures, physical properties and chemical stability of organoboron compounds. Some of the typical bond lengths and strengths are also included. Preparations of organoboron compounds are presented next, with an emphasis on modern catalytic methods. Selected mechanisms and limitations are analyzed. The applications of organoboron compounds as synthetic intermediates and pharmaceutical agents are discussed.

In chapter 2, a Cu(I)-catalyzed β-boration of allenoates with a novel sp^2-sp^3 hybridized diboron reagent is described. The novel diboron reagent is preactivated and allows the reaction to take place at mild condition. Only a single stereoisomer was obtained from racemic starting materials, and its structure was assigned based on 1D NOE experiments. A proposed mechanism and rational for the diastereoselectivity is also discussed. Finally, an application of the boration product in Suzuki-Miyaura cross-coupling reaction is investigated.

Chapter 3 discloses a Pt-catalyzed diboration of allenes with a differentially protected diboron reagent. This unsymmetrical diboron compound is prepared from the aforementioned sp^2-sp^3 hybridized diboron reagent in Chapter 2. Optimization with 1-phenylallene indicates the combination of $Pt(dba)_3$ and SPhos provides the best selectivity and modest yield. Both selectivity and yield are greatly improved when the optimized condition is applied to 1,1-diaryl allene substrates. Steric control ensures that both boryl moieties add to the terminal double bond, and the pinacol boronate preferentially attaches to the sp hybridized carbon. The structures of major isomers were confirmed by X-ray crystallography and 1D NOE experiments. Applications of the product in chemoselective Suzuki-Miyaura cross-coupling reactions and oxidations are examined.

Chapter 4 presents the synthesis of a series of photocleavable *o*-nitrobenzyl ligands with disulfide as the anchor to gold surface. Curtius rearrangement with different carboxylic acids is

the key step. A photoreaction pathway is proposed. Attempts to make a water soluble analog failed, so a mixture of methanol and water was used as the solvent instead.

In chapter 5, general methods, instrumentation, experimental procedures and product characterization data for chapters 2-4 are included. References for known compounds are also included.

1.5 References

(1) Weir Jr, R. J.; Fisher, R. S. Toxicologic Studies on Borax and Boric Acid. *Toxicol. Appl. Pharmacol.* **1972**, *23*, 351-364.

(2) Hall, D. G. *Boronic Acids: Preparation, Applications in Organic Synthesis, Medicine and Materials*; Wiley-VCH GmbH & Co.: Weinheim, 2011.

(3) Rettig, S. J.; Trotter, J. Crystal and Molecular Structure of Phenylboronic Acid, $C_6H_5B(OH)_2$. *Can. J. Chem.* **1977**, *55*, 3071-3075.

(4) Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. Functionalized Pyridylboronic Acids and Their Suzuki Cross-Coupling Reactions To Yield Novel Heteroarylpyridines. *J. Org. Chem.* **2002**, *67*, 7541-7543.

(5) Soundararajan, S.; Duesler, E. N.; Hageman, J. H. Structure of 4-Carboxy-2-nitrobenzeneboronic Acid. *Acta Crystallogr. C* **1993**, *49*, 690-693.

(6) Sana, M.; Leroy, G.; Wilante, C. Enthalpies of Formation and Bond Energies in Lithium, Beryllium, and Boron derivatives. A Theoretical Attempt for Data Rationalization. *Organometallics* **1991**, *10*, 264-270.

(7) Knapp, D. M.; Gillis, E. P.; Burke, M. D. A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates. *J. Am. Chem. Soc.* **2009**, *131*, 6961-6963.

(8) Korich, A. L.; Iovine, P. M. Boroxine Chemistry and Applications: A Perspective. *Dalton Trans.* **2010**, *39*, 1423-1431.

(9) Tokunaga, Y.; Ueno, H.; Shimomura, Y.; Seo, T. Formation of Boroxine: Its Stability and Thermodynamic Parameters in Solution. *Heterocycles* **2002**, *57*, 787-790.

(10) Molander, G. A.; Ellis, N. Organotrifluoroborates: Protected Boronic Acids That Expand the Versatility of the Suzuki Coupling Reaction. *Acc. Chem. Res.* **2007**, *40*, 275-286.

(11) Lorand, J. P.; Edwards, J. O. Polyol Complexes and Structure of the Benzeneboronate Ion. *J. Org. Chem.* **1959**, *24*, 769-774.

(12) Cammidge, A. N.; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Hughes, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A. J. Aryl Trihydroxyborates: Easily Isolated Discrete Species Convenient for Direct Application in Coupling Reactions. *Org. Lett.* **2006**, *8*, 4071-4074.

(13) Roy, C. D.; Brown, H. C. Stability of Boronic Esters – Structural Effects on the Relative Rates of Transesterification of 2-(Phenyl)-1,3,2-dioxaborolane. *J. Organomet. Chem.* **2007**, *692*, 784-790.

(14) Matteson, D. S.; Michnick, T. J. Stereoselective Reaction of an Enolate with Chiral α-Halo Boronic Acid Esters. *Organometallics* **1990**, *9*, 3171-3177.

(15) Matteson, D. S.; Soundararajan, R.; Ho, O. C.; Gatzweiler, W. (Alkoxyalkyl)boronic Ester Intermediates for Asymmetric Synthesis. *Organometallics* **1996**, *15*, 152-163.

(16) Matteson, D. S.; Tripathy, P. B.; Sarkar, A.; Sadhu, K. M. A Stereospecific Convergent Coupling of Nucleophilic and Electrophilic Chiral Carbons. *J. Am. Chem. Soc.* **1989**, *111*, 4399-4402.

(17) Letsinger, R. L.; Skoog, I. Organoboron Compounds. IV.1 Aminoethyl Diarylborinates. *J. Am. Chem. Soc.* **1955**, *77*, 2491-2494.

(18) Rettig, S. J.; Trotter, J. Crystal and Molecular Structure of B-Phenyl-diptychboroxazolidine. *Can. J. Chem.* **1975**, *53*, 1393-1401.

(19) Ishiyama, T.; Miyaura, N. Chemistry of Group 13 Element-transition Metal Linkage — the Platinum- and Palladium-catalyzed Reactions of (Alkoxo)diborons. *J. Organomet. Chem.* **2000**, *611*, 392-402.

(20) Lawlor, F. J.; Norman, N. C.; Pickett, N. L.; Robins, E. G.; Nguyen, P.; Lesley, G.; Marder, T. B.; Ashmore, J. A.; Green, J. C. Bis-Catecholate, Bis-Dithiocatecholate, and Tetraalkoxy Diborane(4) Compounds: Aspects of Synthesis and Electronic Structure. *Inorg. Chem.* **1998**, *37*, 5282-5288.

(21) Iwadate, N.; Suginome, M. Differentially Protected Diboron for Regioselective Diboration of Alkynes: Internal-Selective Cross-Coupling of 1-Alkene-1,2-diboronic Acid Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 2548-2549.

(22) Asakawa, H.; Lee, K.-H.; Lin, Z.; Yamashita, M. Facile Scission of Isonitrile Carbon–Nitrogen Triple Bond Using a Diborane(4) Reagent. *Nat Commun* **2014**, *5*.

(23) Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slebodnick, C.; Marder, T. B.; Santos, W. L. Structure and Reactivity of a Preactivated sp^2–sp^3 Diboron Reagent: Catalytic Regioselective Boration of α,β-Unsaturated Conjugated Compounds. *J. Org. Chem.* **2011**, *76*, 3997-4007.

(24) Gao, M.; Thorpe, S. B.; Santos, W. L. sp^2−sp^3 Hybridized Mixed Diboron: Synthesis, Characterization, and Copper-Catalyzed β-Boration of α,β-Unsaturated Conjugated Compounds. *Org. Lett.* **2009**, *11*, 3478-3481.

(25) Thorpe, S. B.; Guo, X.; Santos, W. L. Regio- and Stereoselective Copper-Catalyzed β-Borylation of Allenoates by a Preactivated Diboron. *Chem. Commun.* **2011**, *47*, 424-426.

(26) Braunschweig, H.; Damme, A.; Dewhurst, R. D.; Kramer, T.; Kupfer, T.; Radacki, K.; Siedler, E.; Trumpp, A.; Wagner, K.; Werner, C. Quaternizing Diboranes(4): Highly Divergent Outcomes and an Inorganic Wagner–Meerwein Rearrangement. *J. Am. Chem. Soc.* **2013**, *135*, 8702-8707.

(27) Braunschweig, H.; Damme, A.; Jimenez-Halla, J. O. C.; Kupfer, T.; Radacki, K. Phosphine Adducts of 1,2-Dibromo-1,2-dimesityldiborane(4): Between Bridging Halides and Rearrangement Processes. *Angew. Chem. Int. Ed.* **2012**, *51*, 6267-6271.

(28) Braunschweig, H.; Damme, A.; Kupfer, T. Synthesis of a Bicyclic Diborane by Selective Boron Carbon Bond Formation. *Chem. Commun.* **2013**, *49*, 2774-2776.

(29) Bean, F. R.; Johnson, J. R. Derivatives of Phenyboric Acic, Their Preparation and Action upon Bacteria. II. Hydroxyphenylboric Acids. *J. Am. Chem. Soc.* **1932**, *54*, 4415-4425.

(30) Seaman, W.; Johnson, J. R. Derivatives of Phenyboric Acic, Their Preparation and Action upon Bacteria. *J. Am. Chem. Soc.* **1931**, *53*, 711-723.

(31) Dieck, H. A.; Heck, R. F. Palladium-Catalyzed Conjugated Diene Synthesis from Vinylic Halides and Olefinic Compounds. *J. Org. Chem.* **1975**, *40*, 1083-1090.

(32) Uenishi, J. I.; Matsui, K.; Wada, A. Trienylboronic Acid, a Versatile Coupling Tool for Retinoid Synthesis; Stereospecific Synthesis of 13-Aryl Substituted (11*Z*)-Retinal. *Tetrahedron Lett.* **2003**, *44*, 3093-3096.

(33) Brown, H. C.; Bhat, N. G.; Srebnik, M. A Simple, General Synthesis of 1-Alkynyldiisopropoxyboranes. *Tetrahedron Lett.* **1988**, *29*, 2631-2634.

(34) Matteson, D. S.; Peacock, K. Dibutyl Acetyleneboronate: Preparation and Some Additions of Free Radicals. *J. Org. Chem.* **1963**, *28*, 369-371.

(35) Brown, H. C.; Cole, T. E. Organoboranes. 31. A Simple Preparation of Boronic Esters from Organolithium Reagents and Selected Trialkoxyboranes. *Organometallics* **1983**, *2*, 1316-1319.

(36) Sadhu, K. M.; Matteson, D. S. (Chloromethyl)lithium: Efficient Generation and Capture by Boronic Esters and a Simple Preparation of Diisopropyl (Chloromethyl)boronate. *Organometallics* **1985**, *4*, 1687-1689.

(37) Balma Tivola, P.; Deagostino, A.; Prandi, C.; Venturello, P. A New Synthesis of Butadienyl- and Styrylboronic Esters: Highly Reactive Intermediates for Suzuki Cross-Coupling. *Org. Lett.* **2002**, *4*, 1275-1277.

(38) Brown, H. C.; Bhat, N. G. A Simple Conversion of [*E*]- Into the Isomeric [*Z*]-2-(1-Substituted-1-alkenyl)-1,3,2-dioxaborinanes, Providing a Convenient Stereospecific Synthesis of Both [*E*]- and [*Z*]-1,2-Disubstituted vinyl bromides. *Tetrahedron Lett.* **1988**, *29*, 21-24.

(39) Garg, N. K.; Sarpong, R.; Stoltz, B. M. The First Total Synthesis of Dragmacidin D. *J. Am. Chem. Soc.* **2002**, *124*, 13179-13184.

(40) Wong, K. T.; Chien, Y. Y.; Liao, Y. L.; Lin, C. C.; Chou, M. Y.; Leung, M. K. Efficient and Convenient Nonaqueous Workup Procedure for the Preparation of Arylboronic Esters. *J. Org. Chem.* **2002**, *67*, 1041-1044.

(41) Ishiyama, T.; Murata, M.; Miyaura, N. Palladium(0)-Catalyzed Cross-Coupling Reaction of Alkoxydiboron with Haloarenes: A Direct Procedure for Arylboronic Esters. *J. Org. Chem.* **1995**, *60*, 7508-7510.

(42) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. Palladium-Catalyzed Borylation of Aryl Chlorides: Scope, Applications, and Computational Studies. *Angew. Chem. Int. Ed.* **2007**, *46*, 5359-5363.

(43) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. Palladium-Catalyzed, Direct Boronic Acid Synthesis from Aryl Chlorides: A Simplified Route to Diverse Boronate Ester Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 17701-17703.

(44) Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. Hydroboration. 45. New, Convenient Preparations of Representative Borane Reagents Utilizing Borane-Methyl Sulfide. *J. Org. Chem.* **1977**, *42*, 1392-1398.

(45) Brown, H. C.; Rao, B. C. S. A New Technique for the Conversion of Olefins Into Organoboranes and Related Alcohols. *J. Am. Chem. Soc.* **1956**, *78*, 5694-5695.

(46) Zweifel, G.; Brown, H. C. Hydroboration. XVI. The Hydroboration of Olefins, Acetylenes and Dienes with Thexylborane. *J. Am. Chem. Soc.* **1963**, *85*, 2066-2072.

(47) Arase, A.; Hoshi, M.; Mijin, A.; Nishi, K. Dialkylborane-Catalyzed Hydroboration of Alkynes with 1,3,2-Benzodioxaborole in Tetrahydrofuran. *Synth. Commun.* **1995**, *25*, 1957-1962.

(48) Brown, H. C.; Gupta, S. K. Catecholborane (1,3,2-benzodioxaorole) as a New, General Monohydroboration Reagent for Alkynes. Convenient Synthesis of Alkeneboronic Esters and Acids from Alkynes via Hydroboration. *J. Am. Chem. Soc.* **1972**, *94*, 4370-4371.

(49) Brown, H. C.; Gupta, S. K. Hydroboration. XXXIX. 1,3,2-Benzodioxaborole (catecholborane) as a New Hydroboration Reagent for Alkenes and Alkynes. General Synthesis of Alkane- and Alkeneboronic Acids and Esters via Hydroboration. Directive Effects in the Hydroboration of Alkenes and Alkynes with Catecholborane. *J. Am. Chem. Soc.* **1975**, *97*, 5249-5255.

(50) Tucker, C. E.; Davidson, J.; Knochel, P. Mild and Stereoselective Hydroborations of Functionalized Alkynes and Alkenes Using Pinacolborane. *J. Org. Chem.* **1992**, *57*, 3482-3485.

(51) Burgess, K.; Ohlmeyer, M. J. Transition-Metal Promoted Hydroborations of Alkenes, Emerging Methodology for Organic Transformations. *Chem. Rev.* **1991**, *91*, 1179-1191.

(52) Burgess, K.; Van der Donk, W. A.; Westcott, S. A.; Marder, T. B.; Baker, R. T.; Calabrese, J. C. Reactions of Catecholborane with Wilkinson's Catalyst: Implications for Transition Metal-Catalyzed Hydroborations of Alkenes. *J. Am. Chem. Soc.* **1992**, *114*, 9350-9359.

(53) Westcott, S. A.; Blom, H. P.; Marder, T. B.; Baker, R. T.; Calabrese, J. C. Nucleophile Promoted Degradation of Catecholborane: Consequences for Transition Metal-Catalyzed Hydroborations. *Inorg. Chem.* **1993**, *32*, 2175-2182.

(54) He, X.; Hartwig, J. F. True Metal-Catalyzed Hydroboration with Titanium. *J. Am. Chem. Soc.* **1996**, *118*, 1696-1702.

(55) Pereira, S.; Srebnik, M. Hydroboration of Alkynes with Pinacolborane Catalyzed by HZrCp2Cl. *Organometallics* **1995**, *14*, 3127-3128.

(56) Pereira, S.; Srebnik, M. A Study of Hydroboration of Alkenes and Alkynes with Pinacolborane Catalyzed by Transition Metals. *Tetrahedron Lett.* **1996**, *37*, 3283-3286.

(57) Ohmura, T.; Yamamoto, Y.; Miyaura, N. Rhodium- or Iridium-Catalyzed Trans-Hydroboration of Terminal Alkynes, Giving (Z)-1-Alkenylboron Compounds. *J. Am. Chem. Soc.* **2000**, *122*, 4990-4991.

(58) Gao, D.; O'Doherty, G. A. Total Synthesis of Fostriecin: Via a Regio- and Stereoselective Polyene Hydration, Oxidation, and Hydroboration Sequence. *Org. Lett.* **2010**, *12*, 3752-3755.

(59) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. Platinum(0)-Catalyzed Diboration of Alkynes. *J. Am. Chem. Soc.* **1993**, *115*, 11018-11019.

(60) Marder, T.; Norman, N. Transition Metal Catalysed Diboration. *Top. Catal.* **1998**, *5*, 63-73.

(61) Ishiyama, T.; Yamamoto, M.; Miyaura, N. Diboration of Alkenes with Bis(pinacolato)diboron Catalysed by a Platinum(0) Complex. *Chem. Commun.* **1997**, 689-690.

(62) Iverson, C. N.; Smith, M. R. Efficient Olefin Diboration by a Base-Free Platinum Catalyst. *Organometallics* **1997**, *16*, 2757-2759.

(63) Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. Transition Metal Catalyzed Diboration of Vinylarenes. *Angew. Chem. Int. Ed.* **1995**, *34*, 1336-1338.

(64) Lawson, Y.; Lesley, G.; Norman, N.; Rice, C.; Marder, T. Platinum Catalysed 1,4-Diboration of α,β-Unsaturated Ketones. *Chem. Commun.* **1997**, 2051-2052.

(65) Ito, H.; Yamanaka, H.; Tateiwa, J.-i.; Hosomi, A. Boration of an α,β-Enone Using a Diboron Promoted by a Copper(I)-Phosphine Mixture Catalyst. *Tetrahedron Lett.* **2000**, *41*, 6821-6825.

(66) Mun, S.; Lee, J. E.; Yun, J. Copper-Catalyzed β-Boration of α,β-Unsaturated Carbonyl Compounds: Rate Acceleration by Alcohol Additives. *Org. Lett.* **2006**, *8*, 4887-4889.

(67) Lee, J. E.; Yun, J. Catalytic Asymmetric Boration of Acyclic α,β-Unsaturated Esters and Nitriles. *Angew. Chem. Int. Ed.* **2008**, *47*, 145-147.

(68) Takahashi, K.; Ishiyama, T.; Miyaura, N. A Borylcopper Species Generated from Bis(pinacolato)diboron and its Additions to α,β-Unsaturated Carbonyl Compounds and Terminal Alkynes. *J. Organomet. Chem.* **2001**, *625*, 47-53.

(69) Dang, L.; Lin, Z.; Marder, T. B. DFT Studies on the Borylation of α,β-Unsaturated Carbonyl Compounds Catalyzed by Phosphine Copper(I) Boryl Complexes and Observations on the Interconversions between O- and C-Bound Enolates of Cu, B, and Si. *Organometallics* **2008**, *27*, 4443-4454.

(70) Kabalka, G. W.; Das, B. C.; Das, S. Rhodium-Catalyzed 1,4-Addition Reactions of Diboron Reagents to Electron Deficient Olefins. *Tetrahedron Lett.* **2002**, *43*, 2323-2325.

(71) Hirano, K.; Yorimitsu, H.; Oshima, K. Nickel-Catalyzed β-Boration of α,β-Unsaturated Esters and Amides with Bis(pinacolato)diboron. *Org. Lett.* **2007**, *9*, 5031-5033.

(72) Lee, K. S.; Zhugralin, A. R.; Hoveyda, A. H. Efficient C−B Bond Formation Promoted by N-Heterocyclic Carbenes: Synthesis of Tertiary and Quaternary B-Substituted Carbons through Metal-Free Catalytic Boron Conjugate Additions to Cyclic and Acyclic α,β-Unsaturated Carbonyls. *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255.

(73) Ainley, A. D.; Challenger, F. CCLXXX.-Studies of the Boron-Carbon Linkage. Part I. The Oxidation and Nitration of Phenylboric Acid. *J. Chem. Soc.* **1930**, 2171-2180.

(74) Snyder, H. R.; Kuck, J. A.; Johnson, J. R. Organoboron Compounds, and the Study of Reaction Mechanisms. Primary Aliphatic Boronic Acids. *J. Am. Chem. Soc.* **1938**, *60*, 105-111.

(75) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Lee, H. D.; Negishi, E.; Katz, J. J. Vinylic Organoboranes. 6. A General Synthesis of (E)-Disubstituted-Alkenes or Ketones via the (E)-(1-Substituted-1-alkenyl)boronic Esters. *J. Org. Chem.* **1986**, *51*, 5270-5276.

(76) Matteson, D. S.; Moody, R. J.; Jesthi, P. K. Reaction of Aldehydes and Ketones with a Boron-Substituted Carbanion, Bis(ethylenedioxyboryl)methide. Simple Aldehyde Homologation. *J. Am. Chem. Soc.* **1975**, *97*, 5608-5609.

(77) Brown, H. C.; Zweifel, G. Hydroboration. IX. The Hydroboration of Cyclic and Bicyclic Olefins—Stereochemistry of the Hydroboration Reaction. *J. Am. Chem. Soc.* **1961**, *83*, 2544-2551.

(78) Crudden, Cathleen M.; Edwards, D. Catalytic Asymmetric Hydroboration: Recent Advances and Applications in Carbon−Carbon Bond-Forming Reactions. *Eur. J. Org. Chem.* **2003**, *2003*, 4695-4712.

(79) Matteson, D. S.; Ray, R. Directed Chiral Synthesis With Pinanediol Boronic Esters. *J. Am. Chem. Soc.* **1980**, *102*, 7590-7591.

(80) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. C−H Activation/Borylation/Oxidation: A One-Pot Unified Route To Meta-Substituted Phenols Bearing Ortho-/Para-Directing Groups. *J. Am. Chem. Soc.* **2003**, *125*, 7792-7793.

(81) Webb, K. S.; Levy, D. A Facile Oxidation of Boronic Acids and Boronic Esters. *Tetrahedron Lett.* **1995**, *36*, 5117-5118.

(82) Kianmehr, E.; Yahyaee, M.; Tabatabai, K. A Mild Conversion of Arylboronic Acids and Their Pinacolyl Boronate Esters into Phenols Using Hydroxylamine. *Tetrahedron Lett.* **2007**, *48*, 2713-2715.

(83) Kumada, M. Nickel and Palladium Complex Catalyzed Cross-coupling Reactions of Organometallic Reagents with Organic Halides. *Pure Appl. Chem.* **1980**, *52*, 669-679.

(84) Baba, S.; Negishi, E. A Novel Stereospecific Alkenyl-Alkenyl Cross-Coupling by a Palladium- or Nickel-Catalyzed Reaction of Alkenylalanes with Alkenyl Halides. *J. Am. Chem. Soc.* **1976**, *98*, 6729-6731.

(85) Negishi, E.; King, A. O.; Okukado, N. Selective Carbon-Carbon Bond Formation via Transition Metal Catalysis. 3. A Highly Selective Synthesis of Unsymmetrical Biaryls and Diarylmethanes by the Nickel- or Palladium-Catalyzed Reaction of Aryl- and Benzylzinc Derivatives with Aryl Halides. *J. Org. Chem.* **1977**, *42*, 1821-1823.

(86) Miyaura, N.; Yanagi, T.; Suzuki, A. The Palladium-Catalyzed Cross-Coupling Reaction of Phenylboronic Acid with Haloarenes in the Presence of Bases *Synth. Commun.* **1981**, *11*, 513-519.

(87) Kotha, S.; Lahiri, K.; Kashinath, D. Recent Applications of the Suzuki-Miyaura Cross-Coupling Reaction in Organic Synthesis. *Tetrahedron* **2002**, *58*, 9633-9695.

(88) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457-2483.

(89) Suzuki, A. Organoborane Coupling Reactions (Suzuki Coupling). *Proceedings of the Japan Academy, Series B* **2004**, *80*, 359-371.

(90) Suzuki, A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles, 1995-1998. *J. Organomet. Chem.* **1999**, *576*, 147-168.

(91) Grushin, V. V.; Alper, H. Transformations of Chloroarenes, Catalyzed by Transition-Metal Complexes. *Chem. Rev.* **1994**, *94*, 1047-1062.

(92) Chen, G. S.; Labinger, J. A.; Bercaw, J. E. The Role of Alkane Coordination in C–H Bond Cleavage at a Pt(II) Center. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 6915-6920.

(93) Frisch, A. C.; Beller, M. Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides. *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688.

(94) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. Room-Temperature Alkyl−Alkyl Suzuki Cross-Coupling of Alkyl Bromides that Possess β Hydrogens. *J. Am. Chem. Soc.* **2001**, *123*, 10099-10100.

(95) Kirchhoff, J. H.; Dai, C.; Fu, G. C. A Method for Palladium-Catalyzed Cross-Couplings of Simple Alkyl Chlorides: Suzuki Reactions Catalyzed by [Pd2(dba)3]/PCy3. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945-1947.

(96) Netherton, M. R.; Fu, G. C. Suzuki Cross-Couplings of Alkyl Tosylates that Possess β Hydrogen Atoms: Synthetic and Mechanistic Studies. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910-3912.

(97) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

(98) Wolfe, J. P.; Buchwald, S. L. A Highly Active Catalyst for the Room-Temperature Amination and Suzuki Coupling of Aryl Chlorides. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413-2416.

(99) Awano, T.; Ohmura, T.; Suginome, M. Inversion or Retention? Effects of Acidic Additives on the Stereochemical Course in Enantiospecific Suzuki–Miyaura Coupling of α-(Acetylamino)benzylboronic Esters. *J. Am. Chem. Soc.* **2011**, *133*, 20738-20741.

(100) Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. Asymmetric Synthesis from Terminal Alkenes by Cascades of Diboration and Cross-Coupling. *Nature* **2014**, *505*, 386-390.

(101) Darses, S.; Genet, J.-P. Potassium Organotrifluoroborates: New Perspectives in Organic Synthesis. *Chem. Rev.* **2007**, *108*, 288-325.

(102) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. Conversion of Arylboronic Acids into Potassium Aryltrifluoroborates: Convenient Precursors of Arylboron Difluoride Lewis Acids. *J. Org. Chem.* **1995**, *60*, 3020-3027.

(103) Dreher, S. D.; Lim, S.-E.; Sandrock, D. L.; Molander, G. A. Suzuki−Miyaura Cross-Coupling Reactions of Primary Alkyltrifluoroborates with Aryl Chlorides. *J. Org. Chem.* **2009**, *74*, 3626-3631.

(104) Molander, G. A.; Ito, T. Cross-Coupling Reactions of Potassium Alkyltrifluoroborates with Aryl and 1-Alkenyl Trifluoromethanesulfonates. *Org. Lett.* **2001**, *3*, 393-396.

(105) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-y.; Dreher, S. D.; Molander, G. A. Stereospecific Cross-Coupling of Secondary Alkyl β-Trifluoroboratoamides. *J. Am. Chem. Soc.* **2010**, *132*, 17108-17110.

(106) van den Hoogenband, A.; Lange, J. H. M.; Terpstra, J. W.; Koch, M.; Visser, G. M.; Visser, M.; Korstanje, T. J.; Jastrzebski, J. T. B. H. Ruphos-Mediated Suzuki Cross-Coupling of Secondary Alkyl Trifluoroborates. *Tetrahedron Lett.* **2008**, *49*, 4122-4124.

(107) Hall, D. G. Lewis and Brønsted Acid Catalyzed Allylboration of Carbonyl Compounds: From Discovery to Mechanism and Applications. *Synlett* **2007**, *2007*, 1644-1655.

(108) Pratt, A. J.; Thomas, E. J. On the Use of E-1-Methoxymethoxybut-2-enyl(tri-n-butyl)stannane as a Threo-Selective, Homo-Enolate Equivalent. *J. Chem. Soc., Chem. Commun.* **1982**, 1115-1117.

(109) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. Organoboranes. 53. A High-Field Variable-Temperature Proton and Boron-11 NMR Study of the Effects of Solvent and Structure on Reactivity in Allylboration. *J. Org. Chem.* **1990**, *55*, 1868-1874.

(110) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. Acceleration Effect of Lewis Acid in Allylboration of Aldehydes: Catalytic, Regiospecific, Diastereospecific, and Enantioselective Synthesis of Homoallyl Alcohols†. *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415.

(111) Kennedy, J. W. J.; Hall, D. G. Dramatic Rate Enhancement with Preservation of Stereospecificity in the First Metal-Catalyzed Additions of Allylboronates. *J. Am. Chem. Soc.* **2002**, *124*, 11586-11587.

(112) Rauniyar, V.; Hall, D. G. Lewis Acids Catalyze the Addition of Allylboronates to Aldehydes by Electrophilic Activation of the Dioxaborolane in a Closed Transition Structure. *J. Am. Chem. Soc.* **2004**, *126*, 4518-4519.

(113) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. Brønsted Acid-Catalyzed Allylboration: Short and Stereodivergent Synthesis of All Four Eupomatilone Diastereomers with Crystallographic Assignments. *J. Am. Chem. Soc.* **2005**, *127*, 12808-12809.

(114) Jain, P.; Antilla, J. C. Chiral Brønsted Acid-Catalyzed Allylboration of Aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 11884-11886.

(115) Rauniyar, V.; Zhai, H.; Hall, D. G. Catalytic Enantioselective Allyl- and Crotylboration of Aldehydes Using Chiral Diol•SnCl4 Complexes. Optimization, Substrate Scope and Mechanistic Investigations. *J. Am. Chem. Soc.* **2008**, *130*, 8481-8490.

(116) Shibasaki, M.; Kanai, M. Asymmetric Synthesis of Tertiary Alcohols and α-Tertiary Amines via Cu-Catalyzed C−C Bond Formation to Ketones and Ketimines. *Chem. Rev.* **2008**, *108*, 2853-2873.

(117) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. Catalytic Enantioselective Allylboration of Ketones. *J. Am. Chem. Soc.* **2004**, *126*, 8910-8911.

(118) Schneider, U.; Kobayashi, S. Catalytic Activation of Pinacolyl Allylboronate with Indium(I): Development of a General Catalytic Allylboration of Ketones. *Angew. Chem. Int. Ed.* **2007**, *46*, 5909-5912.

(119) Lou, S.; Moquist, P. N.; Schaus, S. E. Asymmetric Allylboration of Ketones Catalyzed by Chiral Diols. *J. Am. Chem. Soc.* **2006**, *128*, 12660-12661.

(120) Matteson, D. S. Boronic Esters in Asymmetric Synthesis. *J. Org. Chem.* **2013**, *78*, 10009-10023.

(121) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. Homologation and Alkylation of Boronic Esters and Boranes by 1,2-Metallate Rearrangement of Boron Ate Complexes. *Chem. Rec.* **2009**, *9*, 24-39.

(122) Matteson, D. S.; Sadhu, K. M. Boronic Ester Homologation with 99% Chiral Selectivity and Its Use in Syntheses of the Insect Pheromones (3S,4S)-4-Methyl-3-heptanol and Exo-Brevicomin. *J. Am. Chem. Soc.* **1983**, *105*, 2077-2078.

(123) Matteson, D. S. α-Halo Boronic Esters in Asymmetric Synthesis. *Tetrahedron* **1998**, *54*, 10555-10607.

(124) Matteson, D. S.; Man, H.-W.; Ho, O. C. Asymmetric Synthesis of Stegobinone via Boronic Ester Chemistry. *J. Am. Chem. Soc.* **1996**, *118*, 4560-4566.

(125) Hiscox, W. C.; Matteson, D. S. Asymmetric Synthesis of the Japanese Beetle Pheromone via Boronic Esters. *J. Organomet. Chem.* **2000**, *614–615*, 314-317.

(126) Davoli, P.; Fava, R.; Morandi, S.; Spaggiari, A.; Prati, F. Enantioselective Total Synthesis of (-)Microcarpalide. *Tetrahedron* **2005**, *61*, 4427-4436.

(127) Blakemore, P. R.; Burge, M. S. Iterative Stereospecific Reagent-Controlled Homologation of Pinacol Boronates by Enantioenriched α-Chloroalkyllithium Reagents. *J. Am. Chem. Soc.* **2007**, *129*, 3068-3069.

(128) Blakemore, P. R.; Marsden, S. P.; Vater, H. D. Reagent-Controlled Asymmetric Homologation of Boronic Esters by Enantioenriched Main-Group Chiral Carbenoids. *Org. Lett.* **2006**, *8*, 773-776.

(129) Hoppe, D.; Hense, T. Enantioselective Synthesis with Lithium/(−)-Sparteine Carbanion Pairs. *Angewandte Chemie International Edition in English* **1997**, *36*, 2282-2316.

(130) O'Brien, P.; Bilke, J. L. Expanding the Synthetic Potential of Asymmetric Deprotonation: Arylation of Carbanions. *Angew. Chem. Int. Ed.* **2008**, *47*, 2734-2736.

(131) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. Lithiated Carbamates: Chiral Carbenoids for Iterative Homologation of Boranes and Boronic Esters. *Angew. Chem. Int. Ed.* **2007**, *46*, 7491-7494.

(132) Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. Stereocontrolled Synthesis of Carbon Chains Bearing Contiguous Methyl Groups by Iterative Boronic Ester Homologations: Application to the Total Synthesis of (+)-Faranal. *Angew. Chem. Int. Ed.* **2009**, *48*, 6317-6319.

(133) Blair, D. J.; Fletcher, C. J.; Wheelhouse, K. M. P.; Aggarwal, V. K. Stereocontrolled Synthesis of Adjacent Acyclic Quaternary-Tertiary Motifs: Application to a Concise Total Synthesis of (−)-Filiformin. *Angew. Chem. Int. Ed.* **2014**, *53*, 5552-5555.

(134) Fletcher, C. J.; Wheelhouse, K. M. P.; Aggarwal, V. K. Stereoselective Total Synthesis of (+)-Giganin and Its C10 Epimer by Using Late-Stage Lithiation–Borylation Methodology. *Angew. Chem. Int. Ed.* **2013**, *52*, 2503-2506.

(135) Jin, S.; Cheng, Y.; Reid, S.; Li, M.; Wang, B. Carbohydrate Recognition by Boronolectins, Small Molecules, and Lectins. *Med. Res. Rev.* **2010**, *30*, 171-257.

(136) Yang, W.; Gao, X.; Wang, B. Boronic Acid Compounds as Potential Pharmaceutical Agents. *Med. Res. Rev.* **2003**, *23*, 346-368.

(137) Babcock, L.; Pizer, R. Dynamics of Boron Acid Complexation Reactions. Formation of 1:1 Boron Acid-Ligand Complexes. *Inorg. Chem.* **1980**, *19*, 56-61.

(138) Yan, J.; Springsteen, G.; Deeter, S.; Wang, B. The Relationship Among pKa, pH, and Binding Constants in the Interactions Between Boronic Acids and Diols—It is not as Simple as it Appears. *Tetrahedron* **2004**, *60*, 11205-11209.

(139) Philipp, M.; Bender, M. L. Inhibition of Serine Proteases by Arylboronic Acids. *Proc. Natl. Acad. Sci. USA* **1971**, *68*, 478-480.

(140) Spencer, J.; Burd, A. P.; Goodwin, C. A.; Mérette, S. A. M.; Scully, M. F.; Adatia, T.; Deadman, J. J. Synthesis of Ortho-Modified Mercapto- and Piperazino-Methyl-Phenylboronic Acid Derivatives. *Tetrahedron* **2002**, *58*, 1551-1556.

(141) Ness, S.; Martin, R.; Kindler, A. M.; Paetzel, M.; Gold, M.; Jensen, S. E.; Jones, J. B.; Strynadka, N. C. J. Structure-Based Design Guides the Improved Efficacy of Deacylation Transition State Analogue Inhibitors of TEM-1 β-Lactamase. *Biochemistry* **2000**, *39*, 5312-5321.

(142) Strynadka, N. C. J.; Martin, R.; Jensen3, S. E.; Gold4, M.; Jones, J. B. Structure-Based Design of a Potent Transition State Analogue for TEM-1 Bold β-lactamase. *Nature Structural Biology* **1996**, *3*, 688-695.

(143) Flentke, G. R.; Munoz, E.; Huber, B. T.; Plaut, A. G.; Kettner, C. A.; Bachovchin, W. W. Inhibition of Dipeptidyl Aminopeptidase IV (DP-IV) by Xaa-BoroPro Dipeptides and Use of These Inhibitors to Examine the Role of DP-IV in T-Cell Function. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 1556-1559.

(144) Kane, R. C.; Bross, P. F.; Farrell, A. T.; Pazdur, R. Velcade®: U.S. FDA Approval for the Treatment of Multiple Myeloma Progressing on Prior Therapy. *Oncologist* **2003**, *8*, 508-513.

(145) Groll, M.; Ditzel, L.; Lowe, J.; Stock, D.; Bochtler, M.; Bartunik, H. D.; Huber, R. Structure of 20S Proteasome from Yeast at 2.4A Resolution. *Nature* **1997**, *386*, 463-471.

(146) Adams, J.; Behnke, M.; Chen, S.; Cruickshank, A. A.; Dick, L. R.; Grenier, L.; Klunder, J. M.; Ma, Y.-T.; Plamondon, L.; Stein, R. L. Potent and Selective Inhibitors of the Proteasome: Dipeptidyl Boronic Acids. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 333-338.

(147) Mc Cormack, T.; Baumeister, W.; Grenier, L.; Moomaw, C.; Plamondon, L.; Pramanik, B.; Slaughter, C.; Soucy, F.; Stein, R.; Zühl, F.; Dick, L. Active Site-Directed Inhibitors of Rhodococcus 20 S Proteasome: Kinetics and Mechanism. *J. Biol. Chem.* **1997**, *272*, 26103-26109.

(148) Baker, S. J.; Zhang, Y.-K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M. R. K.; Sanders, V.; Plattner, J. J. Discovery of a New Boron-Containing Antifungal Agent, 5-Fluoro-1,3-dihydro-1-hydroxy-2,1- benzoxaborole (AN2690), for the Potential Treatment of Onychomycosis. *J. Med. Chem.* **2006**, *49*, 4447-4450.

(149) Baker, S. J.; Tomsho, J. W.; Benkovic, S. J. Boron-containing Inhibitors of Synthetases. *Chem. Soc. Rev.* **2011**, *40*, 4279-4285.

(150) Rock, F. L.; Mao, W.; Yaremchuk, A.; Tukalo, M.; Crépin, T.; Zhou, H.; Zhang, Y.-K.; Hernandez, V.; Akama, T.; Baker, S. J.; Plattner, J. J.; Shapiro, L.; Martinis, S. A.; Benkovic, S. J.; Cusack, S.; Alley, M. R. K. An Antifungal Agent Inhibits an Aminoacyl-tRNA Synthetase by Trapping tRNA in the Editing Site. *Science* **2007**, *316*, 1759-1761.

(151) Seiradake, E.; Mao, W.; Hernandez, V.; Baker, S. J.; Plattner, J. J.; Alley, M. R. K.; Cusack, S. Crystal Structures of the Human and Fungal Cytosolic Leucyl-tRNA Synthetase Editing Domains: A Structural Basis for the Rational Design of Antifungal Benzoxaboroles. *J. Mol. Biol.* **2009**, *390*, 196-207.

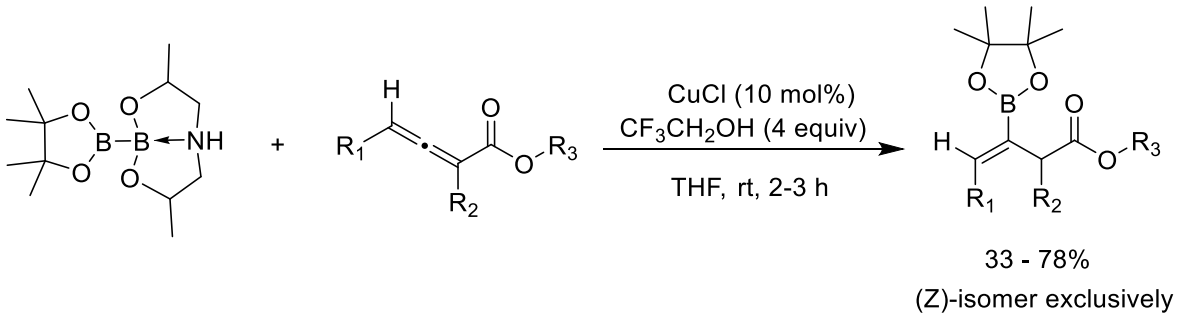
Chapter 2 Regio- and stereoselective copper-catalyzed β-borylation of allenoates by a preactivated diboron

2.1 Contributions

The work described in this chapter was conducted in collaboration with Dr. Brandon Thorpe. The allenoates were synthesized by a 3-step procedure. The author is responsible for all of the first two steps. Optimization experiments, substrate scope and application in cross-coupling reaction were run by Dr. Thorpe. The final manuscript was prepared by Dr. Webster L. Santos with major contribution by Dr. Thorpe. The author contributed greatly to the revision of the manuscript. This work has been published in *Chemical Communications* and is available online. [Thorpe, S. B.; Guo, X.; Santos, W. L. Regio- and Stereoselective Copper-Catalyzed β-Borylation of Allenoates by a Preactivated Diboron. *Chem. Commun.* **2011**, *47*, 424. Reproduced (adapted) with permission from The Royal Society of Chemistry.]

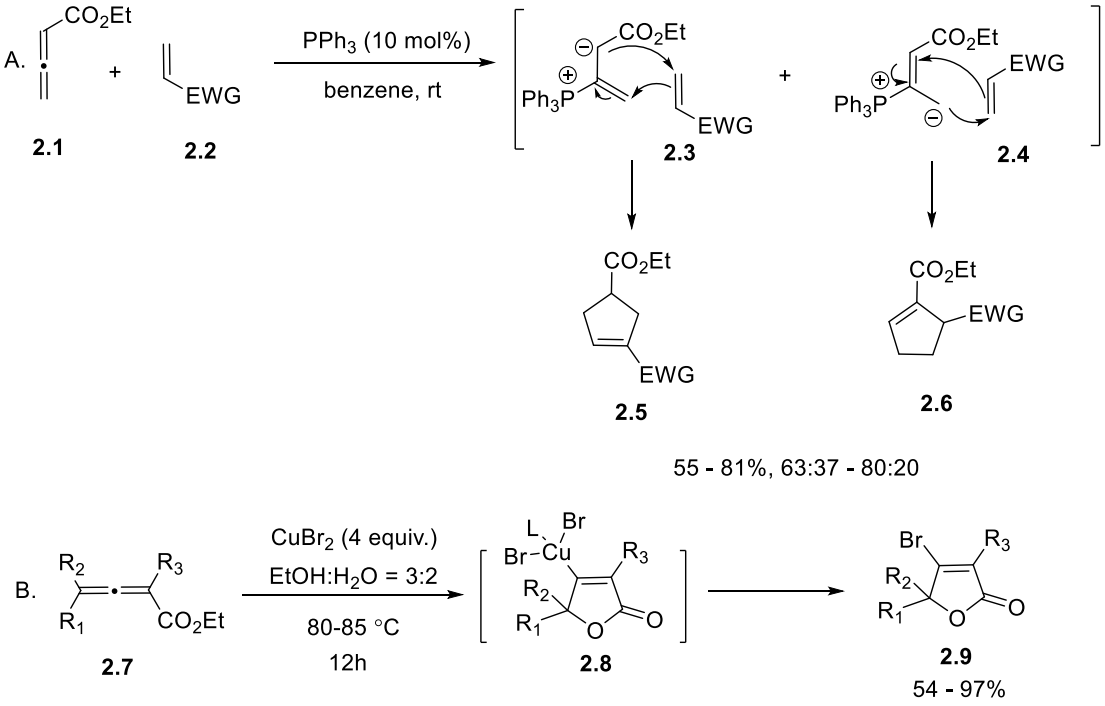
2.2 Abstract

Organoboron compounds are important synthetic intermediates in organic synthesis. Transition metal-catalyzed boration of α,β-unsaturated carbonyl compounds is an efficient method to install C-B bonds. Herein, the first copper-catalyzed β-boration of electrophilic allenoates with a preactivated diboron compound is reported. The mild boration goes smoothly with only 10 mol% of CuCl and 4 equiv. trifluoroethanol, and provides the (*Z*)-isomer exclusively.



2.3 Introduction

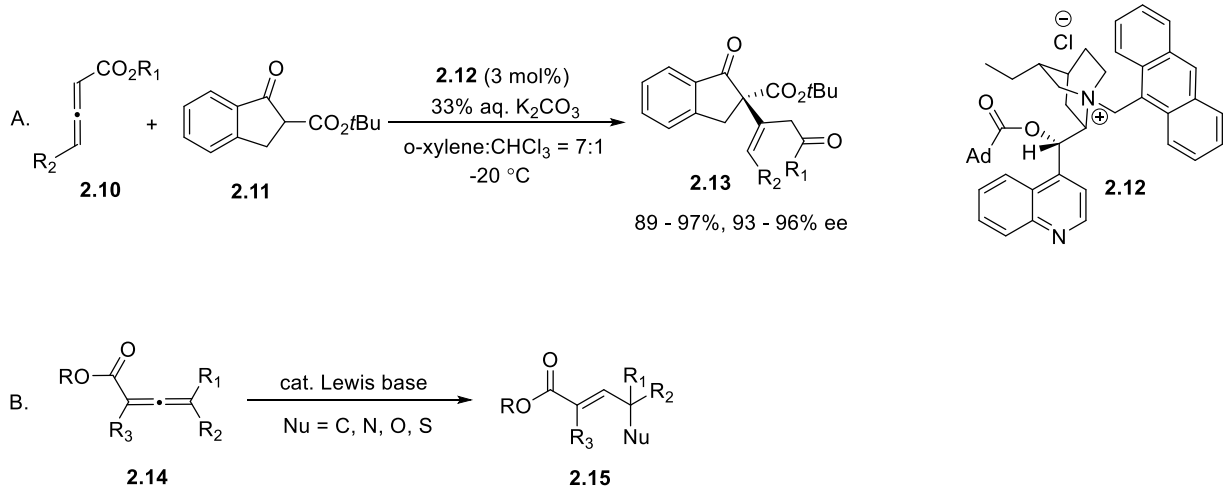
In recent years, allenes have become a promising precursor for construction of complex molecules, and their presence in natural products has shown intriguing biological activities.[1-4] Allenes can have up to four substituents because of the two cumulated C-C double bonds, and thus the reactivity of each carbon of the double bonds can be tuned by the substituent. In particular, allenoates as a class of electron-deficient allenes, have shown their unique reactivities.[5] For example, Zhang and Lu disclosed a novel annulation reaction with allenoates (**2.1**) and electron-deficient olefins (**2.2**) to produce cyclopentenes (**2.5**, **2.6**) via zwitterionic enolate intermediates (**2.3**, **2.4**), which later became the key step in synthesis of (-)-hinesol (Scheme 2.1A).[6,7] Allenoates can also undergo halolactonization with $CuBr_2$ (Scheme 2.1B).[8,9]



Scheme 2.1 A) Annulation and B) halolactonization.

Furthermore, the reactivity of allenoates in addition reactions can be further tuned to produce either β,γ-unsaturated carbonyl compounds or γ-addition products depending on the reaction

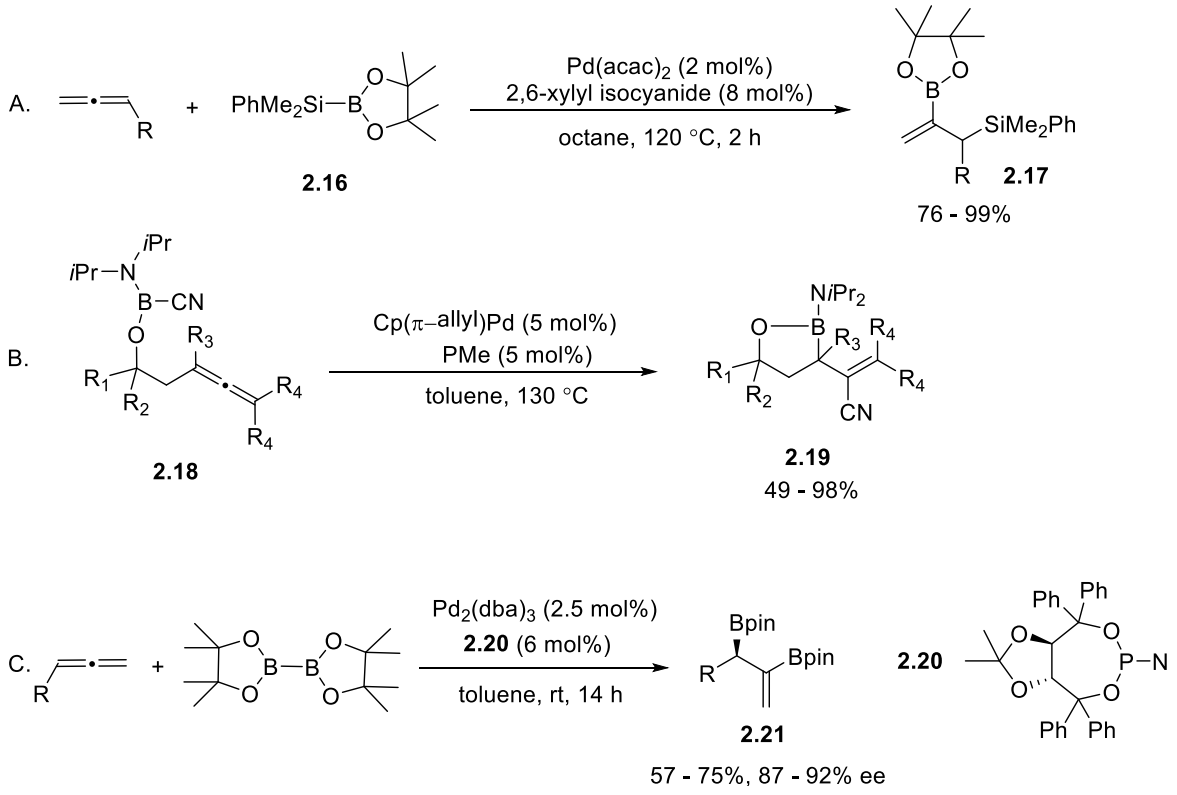
conditions. For example, Jorgensen et al. demonstrated organocatalytic asymmetric conjugate addition to electron-deficient allenes to form tertiary and quaternary stereogenic centers (Scheme 2.2A).[10] This reaction produces β,γ-unsaturated carbonyl compounds, and examples in the literature are limited. However, the regioselectivity of the reaction can be reversed. Lewis bases such as phosphines catalyze γ-additions of carbon, nitrogen, oxygen and sulfur nucleophiles to allenoates to produce α,β-unsaturated carbonyl compounds (Scheme 2.2B).[11-19]



Scheme 2.2 A) β-Addition of allenoates and B) γ-addition of allenoates.

As complementary reacting partners, organoboron compounds increasingly provide access to the formation of difficult C-C bonds. Indeed, the Suzuki-Miyaura coupling reaction, which employs a boronic acid and organohalide, is a powerful method for the construction of complex molecules partly because of its functional group tolerance.[20-23] Thus far, silaboration,[24-29] cyanoboration,[30] and diboration[31-35] have been achieved with allenes using transition metals. For example, the pioneering work of Suginome and coworkers showed regioselective silaboration of allenes in the catalysis of palladium complex (Scheme 2.3A).[27,28] Yamamoto et al. reported a palladium-catalyzed intramolecular cyanoboration of allenes to prepare β-cyanoallylboranes (**2.19**) regioselectively (Scheme 2.3B).[30] More recently, enantioselective diboration of allenes with

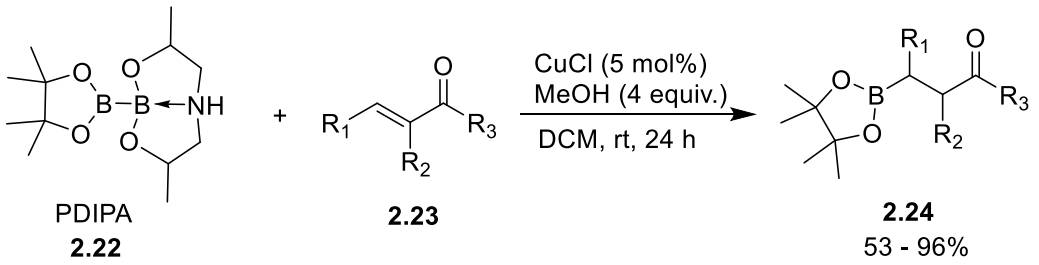
substituted TADDOL-derived phosphoramidites (**2.20**) was documented by Morken and coworkers.[31]



Scheme 2.3 A) Silaboration, B) cyanoboration and C) enantioselective diboration.

To date, however, direct boration of electron-deficient allenes has not been reported. We recently disclosed the synthesis of an internally activated, sp^2-sp^3 hybridized diboron compound, PDIPA diboron (pinacolato diisopropanolaminato diboron, **2.22**), and demonstrated its utility in the copper-catalyzed, β-boration of α,β-unsaturated carbonyl compounds (Scheme 2.4).[36] In pursuit of expanding the scope of this reaction to more intricate substrates, we investigated the utility of PDIPA diboron to the boration of electrophilic allenoates. There substrates are attractive because they give rise to β,γ-unsaturated carbonyl compounds, as opposed to acetylenic esters which produce α,β-unsaturated carbonyl compounds,[37] allowing for further functionalization of

the resulting nonconjugated olefin. In addition, we were excited by the possibility that a racemic mixture of the starting allenoate would form a product containing a defined double bond geometry and a vinyl boronic ester, which is potentially a Suzuki-Miyaura cross-coupling partner.[20-23]



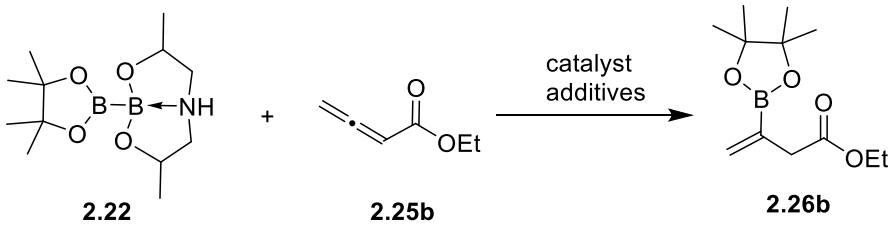
Scheme 2.4 β-Boration of α,β-unsaturated carbonyl compounds with PDIPA diboron.

2.4 Optimization of β-boration of allenoates

To explore the feasibility of the boration reaction, we investigated reaction conditions to generate β-borylated β,γ-unsaturated ethyl ester **2.26b** using ethyl 2,3-butadienoate (**2.25b**) as the substrate. As shown in Table 2.1, agents with strong sigma bond donor capacity to activate bis(pinacolato)diboron such as N-heterocyclic carbenes (NHC),[38] (IMe)CO_2[39] and (ICy)BF_4,[40] promoted the boration reaction with good yields (entries 1 and 2); however, the use of a strong base to generate the carbene can be a disadvantage for sensitive substrates. In addition, NHC ligands are expensive and difficult to handle. With the effort to use milder reaction conditions, we investigated whether a preactivated diboron[36] also effects the desired transformation. To our delight, treating allenoate **2.25b** with a catalytic amount of CuCl, trifluoroethanol (TFE) and **2.22** in dichloromethane produced **2.26b** in excellent yield (entry 3).[41] Running the reaction in the absence of TFE successfully provided the product (entries 4 and 12). Other additives such as base and phosphine ligand were effective although a copper stabilizing DPEphos dramatically decreased the product yield (entries 5-7). As expected, when the reaction was attempted without a

copper catalyst, the reaction was sluggish (entry 8). Evaluation of the effect of solvent revealed that the reaction was tolerant of aprotic solvents used, although the reaction performed in THF was most effective (entries 4, 9 and 10). We also screened the effect of temperature on the reaction and discovered that the boration reaction is efficient at room temperature in the presence of TFE (compare entries1-10 vs. 11). CuCl as the copper source appears to be important since CuBr or other Cu(II) sources afforded the product in moderate yields (entries 12-14). Finally, an examination of other transition metals such as Rh, Pt, Ni and Ag resulted in minor or undetectable product formation (entries 15-18). Thus, subsequent investigations used 10 mol% CuCl, 4 equiv. TFE, allenoate substrate and **2.22** in THF at room temperature.

Table 2.1 Optimization of reaction conditions.[a]



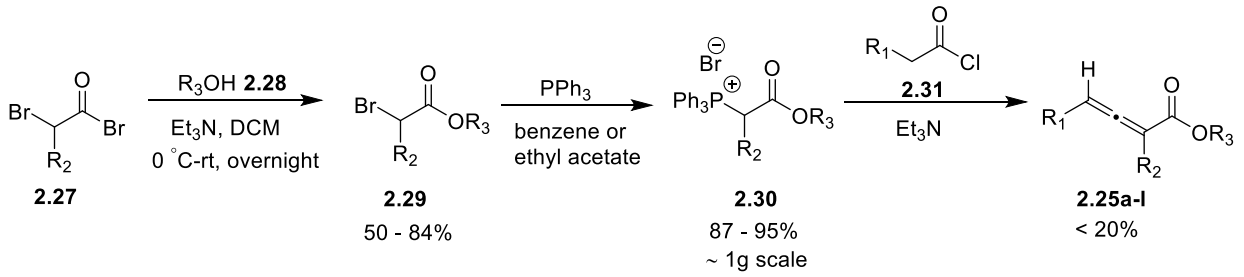
2.22 **2.25b** **2.26b**

entry	catalyst	solvent	additives (equiv.)	conv %[b]
1	CuCl[c]	ACN	(IMe)CO_2 (0.1)	81.3
2	CuCl[c]	THF	(ICy)BF_4 (0.05), NaO*t*Bu (0.1)	95.1
3	CuCl[d]	CH_2Cl_2	TFE (4)	96.9
4	CuCl[d]	CH_2Cl_2	—	96.4
5	CuCl[d]	CH_2Cl_2	NaO^{t}Bu (0.1)	98.3
6	CuCl[d]	CH_2Cl_2	DPEphos (0.1)	45.7
7	CuCl[d]	CH_2Cl_2	NaO*t*Bu (0.1), TFE (4)	97.5
8	—[d]	CH_2Cl_2	—	4.9
9	CuCl[d]	DMF	—	78.0
10	CuCl[e]	THF	—	98.3
11	CuCl[f]	THF	TFE (4)	96.7
12	CuBr[e]	THF	—	87.8
13	$CuBr_2$[e]	THF	—	76.6
14	$CuCl_2$[e]	THF	—	86.7
15	[Rh(cod)Cl]$_2$[e]	THF	—	ND
16	Pt(cod)Cl_2[e]	THF	—	ND
17	Ni(cod)[e]	THF	—	ND
18	Ag(NO_3)[e]	THF	—	1.5

[a] PDIPA diboron (**2.22**, 1.2 equiv), catalyst (0.1 equiv.), and additives were suspended in solvent and stirred for 5 minutes. Ethyl 2,3-butadienoate (1.0 equiv.) was then added and the reaction was stirred for 2 hours at room temperature. [b] Conversion was determined by GC analysis of the crude material. [c] The reaction was performed at rt and bis(pinacolato)diboron was used instead of **2.22**. [d] The reaction was heated to 40 ℃. [e] The reaction was heated to 70 ℃. [f] The reaction was performed at rt. Abbreviations: (IMe)CO_2 = 1,3-dimethylimidazolium carboxylate; (ICy)BF_4 = 1,3-dicyclohexylimidazolium tetrafluoroborate; TFE = 2,2,2-trifluoroethanol; ND = none detected.

2.5 Preparation of allenoates

With the optimized conditions in hand, we next investigated the scope of the reaction using various allenoates. Because ethyl 2,3-butadienoate (**2.25b**) was the only commercially available substrate, the rest of the allenoates were synthesized via a 3-step procedure, which was a slight modification from the literature (Scheme 2.5).[42] Acyl substitution of bromoacetyl bromide (**2.27**) with alcohol (**2.28**) provided the corresponding bromoester (**2.29**) in moderate to good yield. Nucleophilic substitution of bromoester (**2.29**) with triphenylphosphine yielded the phosphonium salt (**2.30**) in excellent yield. When a methyl group was attached to the α-carbon of the ester (R_2 = CH_3), ethyl acetate was employed as the solvent instead of benzene, since the polar intermediate of the substitution reaction could be stabilized better in ethyl acetate. Finally, a Wittig-type reaction of phosphophonium salt (**2.30**) with acetyl chloride (**2.31**) was used to prepare the desired racemic allenoates (**2.25**). The allenoates were purified by either column chromatography or bulb-to-bulb distillation. The low boiling points of them and presence of many side products made purification especially challenging. Not surprisingly, low yields were obtained at this step, which is known in the literature.[42-44] Figure 2.1 shows all the phosphonium salts that were synthesized by the author.



Scheme 2.5 Synthesis of allenoates.

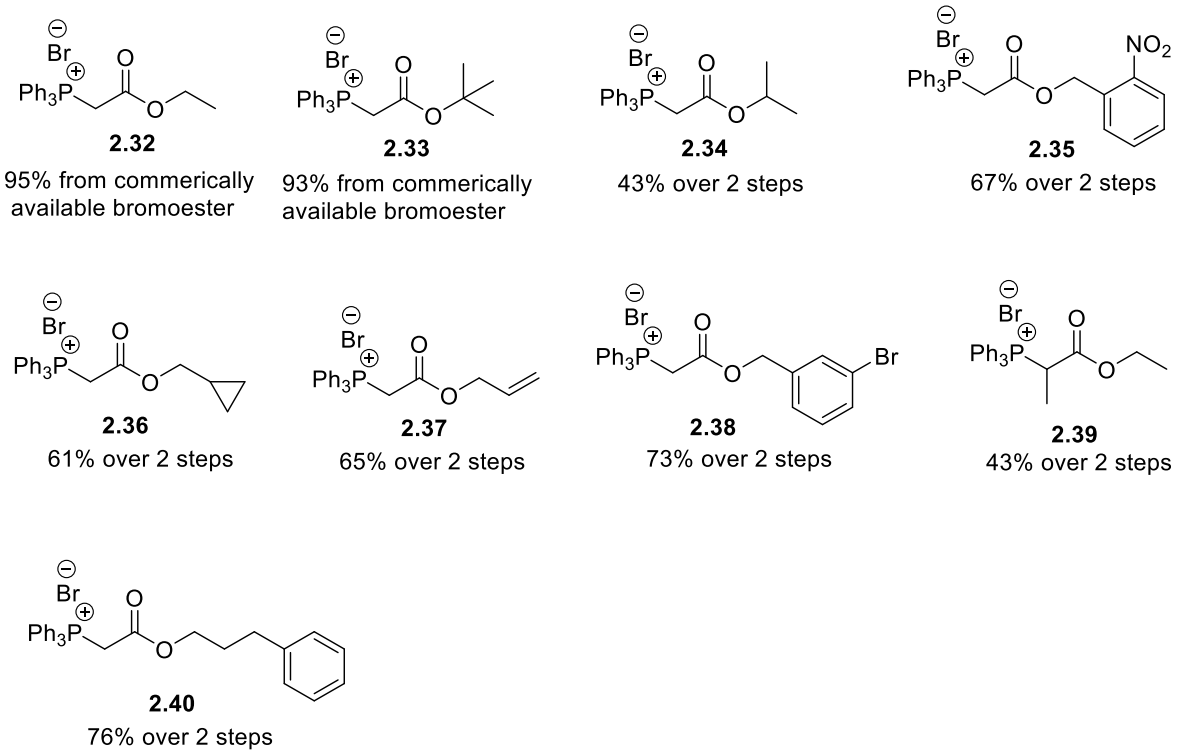


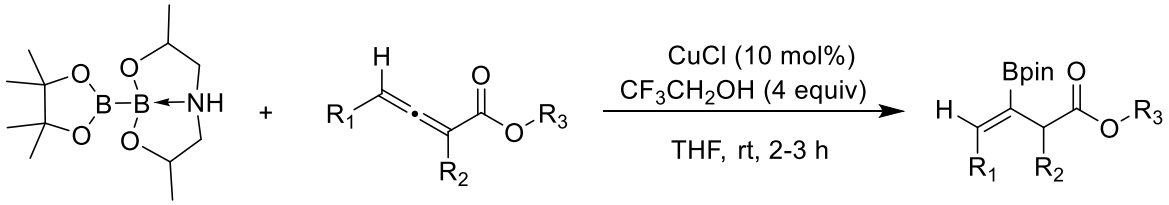
Figure 2.1 The structures of all the phosphonium salts that were synthesized.

2.6 Substrate scope of β-boration of allenoates

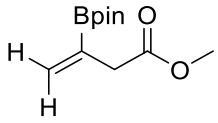
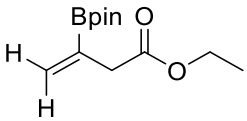
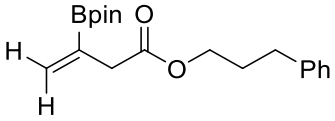
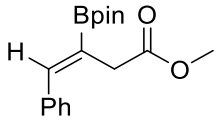
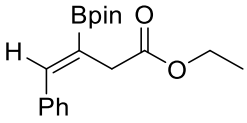
After various allenoates were synthesized, we investigated their possibility of β-boration with PDIPA diboron using our optimized conditions. The results of our study are summarized in Table 2.2. Increasing the size of the ester moiety from methyl to ethyl on unsubstituted allenoates provided the β-borylated β,γ-unsaturated esters **2.26a** and **b** in good yields (entries 1 and 2). A change to the bulkier 3-phenylpropyl ester **2.26c** resulted in slight decrease in yield with some unreacted starting material isolated (entry 3). Gratifyingly, the presence of a bulky phenyl substituent on the γ-position allowed the boration to proceed in moderate yields (entries 4-6). When the phenyl substituent was replaced with a less sterically demanding methyl group, the prouct was isolated in good yield (58 - 78%, entries 7-10). The presence of a bulky *o*-nitrobenzyl moiety resulted in a much lower yield in part because this group is sensitive to light (entry 11).

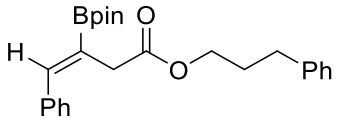
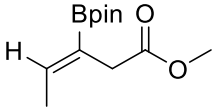
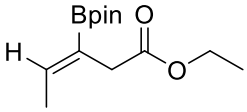
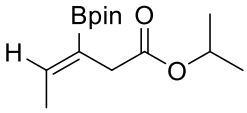
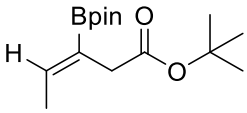
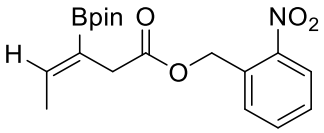
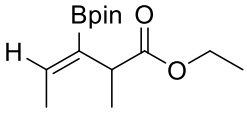
Finally, α,γ-disubstituted ethyl allenoate **2.26l** was converted to the product in moderate yield presumably because of the bulkiness of the substrate (entry 12).

Table 2.2 β-Boration of allenoates.[a]



2.22 **2.25a-l** **2.26a-l**

entry	product	**2.26**	*Z*/*E* [b]	% [c] yield (%)[d]
1		**2.26a**	—	59
2		**2.26b**	—	60
3		**2.26c**	—	41 (71)
4		**2.26d**	100:0	41
5		**2.26e**	100:0	46

6		**2.26f**	100:0	14 (45)
7		**2.26g**	100:0	72
8		**2.26h**	100:0	58
9		**2.26i**	100:0	78
10		**2.26j**	100:0	71
11		**2.26k**	100:0	33 (75)
12		**2.26l**	100:0	38[e] (81)

[a] PDIPA diboron (**2.22**, 1.2 equiv.) and CuCl (0.1 equiv.) were suspended in solvent and stirred for 5 minutes. Allenoate (1.0 equiv.) and TFE (4 equiv.) were then added and the reaction was stirred at room temperature until the starting material was consumed completely by TLC. [b] The ratio of Z/E isomers were determined by GC and the geometry of the product was assigned based on 1D NOE experiments. [c] Isolated Yield. [d] Corrected yield with recovered starting material. [e] Reaction was stirred 24 hours before workup. Product contaminated with 22% α,β-unsaturated isomer.

2.7 Rationale for diastereoselectivity and proposed mechanism

It is important to highlight that the copper-catalyzed β-boration reaction proceeded not only regioselectively but also diastereoselectively. In contrast with phosphine-catalyzed reactions to electrophilic allenoates that afford γ-substituted products,[11-19] the copper-catalyzed reaction regioselectively installed the boryl moiety on the β-position. In addition, under the reaction conditions of our investigation, we did not observe any cycloisomerization products seen in other copper-catalyzed reactions with allenoates.[8] Interestingly, the geometry of the double bond on the resulting product was determined to be Z based on NOESY experiments, and ^{1}H NMR and GC-MS analysis of the crude reaction mixture showed exclusive formation of this product. The stereoselectivity of the reaction can be rationalized by analysis of the approach of the boryl-copper intermediate (Figure 2.2). Since the two double bonds are orthogonal to each other, boryl addition to the β-carbon is expected to occur on the opposite side of the γ-substituent of the allenoate because of a strong steric interaction. Furthermore, 1,3-allylic strain in the (E)-isomer should favor the formation of the more stable (Z)-isomer. Indeed, only the (Z)-product was observed. Finally, we were pleased to find that although the allenoate substrates were used as racemic mixtures, the reaction provided a single product.

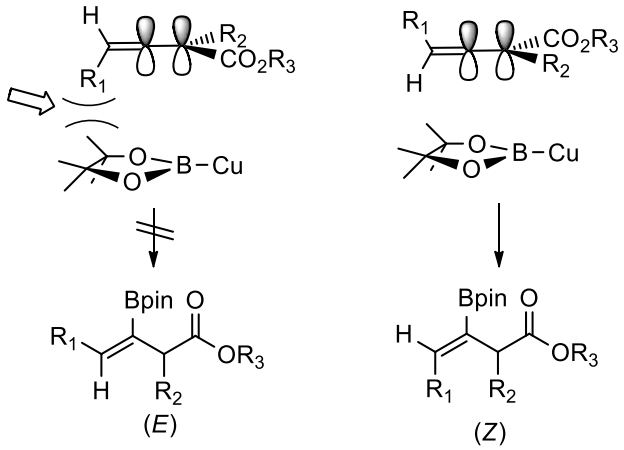
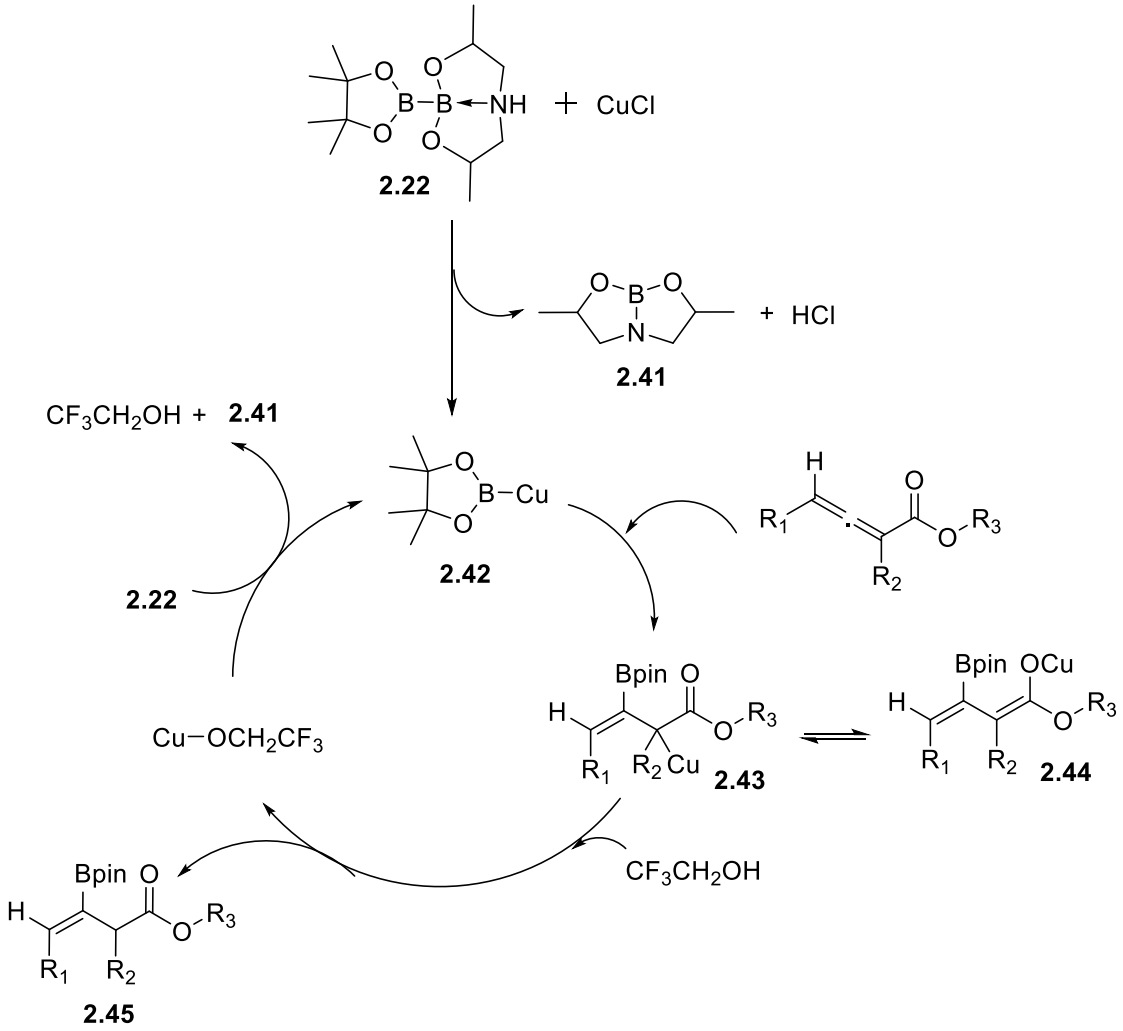


Figure 2.2 Steric interactions lead to exclusive formation of the (*Z*)-isomer.

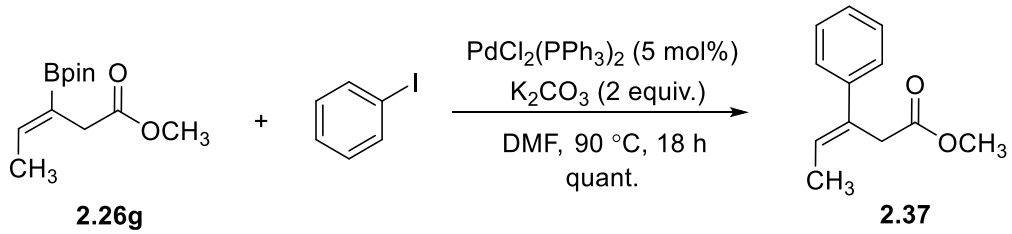
A possible catalytic cycle for the β-boration reaction is shown in Scheme 2.6. Preactivated sp^2-sp^3 hybridized diboron **2.22** is sufficiently activated to transmetalate with CuCl to generate nucleophilic boryl species **2.42**. DFT calculations on the copper-catalyzed boration of related α,β-unsaturated carbonyl compounds[45] suggest the formation of metalated intermediates **2.43**/**2.44** that can be protonated to yield the desired β-borylated β,γ-unsaturated ester **2.45**. Simultaneous regeneration of copper-alkoxide at this stage continues the catalytic cycle. The essential role of TFE is to accelerate the reaction by protonation of **2.43**/**2.44** and formation of copper-alkoxide.[41]



Scheme 2.6 Proposed mechanism for β-boration of allenoates.

2.8 Application of the β-borylated product

To demonstrate the utility of the regio- and stereoselective boration reaction, a Suzuki-Miyaura cross-coupling reaction between **2.26g** and iodobenzene was attempted. In this case, the coupled product **2.37** was isolated in quantitative yield (Scheme 2.7). In contrast, **2.37** was previously synthesized as a mixture of E/Z isomers at 52% yield from a cyclopropanone acetal derivative.[46]



Scheme 2.7 Coupling of β-boronic ester with iodobenzene.

2.9 Conclusion

In conclusion, an efficient and catalytic copper-catalyzed regioselective boration of allenoates was developed. To the best of our knowledge, this reaction is the first example of a boryl addition to electrophilic allenoates. The reaction provided β-borylated β,γ-unsaturated esters with exclusive (Z)-double bond geometry. These borylated products are useful intermediates for subsequent elaboration to more complex structures.

2.10 References

(1) Hoffmann-Röder, A.; Krause, N. Synthesis and Properties of Allenic Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196-1216.

(2) Ma, S. Some Typical Advances in the Synthetic Applications of Allenes. *Chem. Rev.* **2005**, *105*, 2829-2872.

(3) Ma, S. Transition Metal-Catalyzed/Mediated Reaction of Allenes with a Nucleophilic Functionality Connected to the α-Carbon Atom. *Acc. Chem. Res.* **2003**, *36*, 701-712.

(4) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. Palladium-Catalyzed Reactions of Allenes. *Chem. Rev.* **2000**, *100*, 3067-3126.

(5) Cowen, B. J.; Miller, S. J. Enantioselective Catalysis and Complexity Generation from Allenoates. *Chem. Soc. Rev.* **2009**, *38*, 3102-3116.

(6) Du, Y.; Lu, X. A Phosphine-Catalyzed [3+2] Cycloaddition Strategy Leading to the First Total Synthesis of (−)-Hinesol. *J. Org. Chem.* **2003**, *68*, 6463-6465.

(7) Zhang, C.; Lu, X. Phosphine-Catalyzed Cycloaddition of 2,3-Butadienoates or 2-Butynoates with Electron-Deficient Olefins. A Novel [3 + 2] Annulation Approach to Cyclopentenes. *J. Org. Chem.* **1995**, *60*, 2906-2908.

(8) Ma, S.; Wu, S. CuBr2-mediated direct aqueous bromolactonization of 2,3-allenoates. An efficient access to β-bromobutenolides. *Tetrahedron Lett.* **2001**, *42*, 4075-4077.

(9) Ma, S.; Wu, S. CuX2-Mediated Cyclization Reaction of 2,3-Allenoic Acids. An Efficient Route to β-Halobutenolides. *J. Org. Chem.* **1999**, *64*, 9314-9317.

(10) Elsner, P.; Bernardi, L.; Salla, G. D.; Overgaard, J.; Jørgensen, K. A. Organocatalytic Asymmetric Conjugate Addition to Allenic Esters and Ketones. *J. Am. Chem. Soc.* **2008**, *130*, 4897-4905.

(11) Chen, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. Asymmetric Formation of Quaternary Carbon Centers Catalyzed by Novel Chiral 2,5-Dialkyl-7-phenyl-7-phosphabicyclo[2.2.1]heptanes. *J. Org. Chem.* **1998**, *63*, 5631-5635.

(12) Chung, Y. K.; Fu, G. C. Phosphine-Catalyzed Enantioselective Synthesis of Oxygen Heterocycles. *Angew. Chem. Int. Ed.* **2009**, *48*, 2225-2227.

(13) Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. Phosphine-Catalyzed Annulation of Thioamides and 2-Alkynoates: A New Synthesis of Thiazolines. *J. Org. Chem.* **2002**, *67*, 4595-4598.

(14) Lu, C.; Lu, X. Tandem Reactions to Construct Heterocycles via Phosphine-Catalyzed Umpolung Addition and Intramolecular Conjugate Addition. *Org. Lett.* **2002**, *4*, 4677-4679.

(15) Smith, S. W.; Fu, G. C. Asymmetric Carbon−Carbon Bond Formation γ to a Carbonyl Group: Phosphine-Catalyzed Addition of Nitromethane to Allenes. *J. Am. Chem. Soc.* **2009**, *131*, 14231-14233.

(16) Sun, J.; Fu, G. C. Phosphine-Catalyzed Formation of Carbon−Sulfur Bonds: Catalytic Asymmetric Synthesis of γ-Thioesters. *J. Am. Chem. Soc.* **2010**, *132*, 4568-4569.

(17) Trost, B. M.; Li, C.-J. Novel "Umpolung" in C-C Bond Formation Catalyzed by Triphenylphosphine. *J. Am. Chem. Soc.* **1994**, *116*, 3167-3168.

(18) Trost, B. M.; Li, C.-J. Phosphine-Catalyzed Isomerization-Addition of Oxygen Nucleophiles to 2-Alkynoates. *J. Am. Chem. Soc.* **1994**, *116*, 10819-10820.

(19) Zhang, C.; Lu, X. Umpolung Addition Reaction of Nucleophiles to 2,3-Butadienoates Catalyzed by a Phosphine. *Synlett* **1995**, *1995*, 645-646.

(20) Kotha, S.; Lahiri, K.; Kashinath, D. Recent Applications of the Suzuki-Miyaura Cross-Coupling Reaction in Organic Synthesis. *Tetrahedron* **2002**, *58*, 9633-9695.

(21) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457-2483.

(22) Suzuki, A. Organoborane Coupling Reactions (Suzuki Coupling). *Proceedings of the Japan Academy, Series B* **2004**, *80*, 359-371.

(23) Suzuki, A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles, 1995-1998. *J. Organomet. Chem.* **1999**, *576*, 147-168.

(24) Chang, K.; Rayabarapu, D.; Yang, F.; Cheng, C. Unusual Palladium-Catalyzed Silaboration of Allenes Using Organic Iodides as Initiators: Mechanism and Application. *J. Am. Chem. Soc.* **2004**, *127*, 126-131.

(25) Onozawa, S.; Hatanaka, Y.; Tanaka, M. Palladium-Catalysed Borylsilylation and Borylstannylative Dimerization of 1,2-Dienes. *Chem. Commun.* **1999**, 1863-1864.

(26) Suginome, M.; Ito, Y. Regio- and Stereoselective Synthesis of Boryl-Substituted Allylsilanes via Transition Metal-Catalyzed Silaboration. *J. Organomet. Chem.* **2003**, *680*, 43-50.

(27) Suginome, M.; Ohmori, Y.; Ito, Y. Highly Regioselective Silaboration of 3-Substituted 1,2-Dienes Catalyzed by Palladium/2,6-Xylyl Isocyanide. *Synlett* **1999**, *1999*, 1567-1568.

(28) Suginome, M.; Ohmori, Y.; Ito, Y. Palladium-Catalyzed Regioselective Silaboration of 1,2-Dienes. *J. Organomet. Chem.* **2000**, *611*, 403-413.

(29) Suginome, M.; Ohmura, T.; Miyake, Y.; Mitani, S. i.; Ito, Y.; Murakami, M. Enantioface-Selective Palladium-Catalyzed Silaboration of Allenes via Double Asymmetric Induction. *J. Am. Chem. Soc.* **2003**, *125*, 11174-11175.

(30) Yamamoto, A.; Ikeda, Y.; Suginome, M. Palladium-Catalyzed Intramolecular Cyanoboration of Allenes Leading to the Regioselective Synthesis of β-Cyanoallylboranes. *Tetrahedron Lett.* **2009**, *50*, 3168-3170.

(31) Burks, H. E.; Liu, S.; Morken, J. P. Development, Mechanism, and Scope of the Palladium-Catalyzed Enantioselective Allene Diboration. *J. Am. Chem. Soc.* **2007**, *129*, 8766-8773.

(32) Ishiyama, T.; Kitano, T.; Miyaura, N. Platinum(0)-Catalyzed Diboration of Allenes with Bis(pinacolato)Diboron. *Tetrahedron Lett.* **1998**, *39*, 2357-2360.

(33) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. Palladium-Catalyzed Enantioselective Diboration of Prochiral Allenes. *J. Am. Chem. Soc.* **2004**, *126*, 16328-16329.

(34) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. Concatenated Catalytic Asymmetric Allene Diboration/Allylation/Functionalization. *Org. Lett.* **2005**, *7*, 5505-5507.

(35) Yang, F.; Cheng, C. Unusual Diboration of Allenes Catalyzed by Palladium Complexes and Organic Iodides: A New Efficient Route to Biboronic Compounds. *J. Am. Chem. Soc.* **2001**, *123*, 761-762.

(36) Gao, M.; Thorpe, S. B.; Santos, W. L. sp2−sp3 Hybridized Mixed Diboron: Synthesis, Characterization, and Copper-Catalyzed β-Boration of α,β-Unsaturated Conjugated Compounds. *Org. Lett.* **2009**, *11*, 3478-3481.

(37) Lee, J.; Kwon, J.; Yun, J. Copper-Catalyzed Addition of Diboron Reagents to α,β-Acetylenic Esters: Efficient Synthesis of β-Boryl-α,β-Ethylenic Esters. *Chem. Commun.* **2008**, 733-734.

(38) Bonet, A.; Gulyás, H.; Fernández, E. Metal-Free Catalytic Boration at the β-Position of α,β-Unsaturated Compounds: A Challenging Asymmetric Induction. *Angew. Chem. Int. Ed.* **2010**, *49*, 5130-5134.

(39) Voutchkova, A. M.; Feliz, M.; Clot, E.; Eisenstein, O.; Crabtree, R. H. Imidazolium Carboxylates as Versatile and Selective N-Heterocyclic Carbene Transfer Agents: Synthesis, Mechanism, and Applications. *J. Am. Chem. Soc.* **2007**, *129*, 12834-12846.

(40) Lee, K.; Zhugralin, A. R.; Hoveyda, A. H. Efficient C−B Bond Formation Promoted by N-Heterocyclic Carbenes: Synthesis of Tertiary and Quaternary B-Substituted Carbons through Metal-Free Catalytic Boron Conjugate Additions to Cyclic and Acyclic α,β-Unsaturated Carbonyls. *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255.

(41) Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slebodnick, C.; Marder, T. B.; Santos, W. L. Structure and Reactivity of a Preactivated sp2–sp3 Diboron Reagent: Catalytic Regioselective Boration of α,β-Unsaturated Conjugated Compounds. *J. Org. Chem.* **2011**, *76*, 3997-4007.

(42) Creech, G. S.; Kwon, O. Alcohol-Assisted Phosphine Catalysis: One-Step Syntheses of Dihydropyrones from Aldehydes and Allenoates. *Org. Lett.* **2008**, *10*, 429-432.

(43) Harvey, G. R.; Ratts, K. W. Synthesis of Azirenes from Allenic Esters. *J. Org. Chem.* **1966**, *31*, 3907-3910.

(44) Zhu, X.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. Phosphine-Catalyzed Synthesis of 1,3-Dioxan-4-ylidenes. *Org. Lett.* **2005**, *7*, 1387-1390.

(45) Dang, L.; Lin, Z.; Marder, T. B. DFT Studies on the Borylation of α,β-Unsaturated Carbonyl Compounds Catalyzed by Phosphine Copper(I) Boryl Complexes and Observations on the Interconversions between O- and C-Bound Enolates of Cu, B, and Si. *Organometallics* **2008**, *27*, 4443-4454.

(46) Oku, A.; Abe, M.; Iwamoto, M. Electron Transfer Profile of Cyclopropanone Acetals in the Nonirradiated Reaction with Tetracyanoethylene, Chloranil, and Dicyanodichlorobenzoquinone. *J. Org. Chem.* **1994**, *59*, 7445-7452.

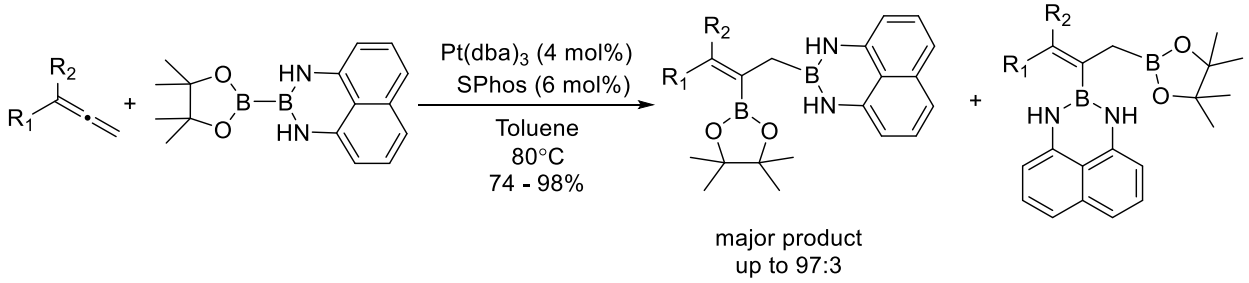
Chapter 3 Chemo-, regio- and stereoselective diboration of allenes with differentially protected diboron

3.1 Contributions

The work described in this chapter was conducted in collaboration with Amanda Nelson. The author is singly responsible for optimization experiments and application of the product. Substrate scope was run in duplicate with Amanda Nelson. Allenes were synthesized by Amanda Nelson. Crystals of **3.34** were obtained by the author, and crystals of **3.44b** and **3.45b** were obtained by Amanda Nelson. The crystal data collection was done by Dr. Carla Slebodnick.

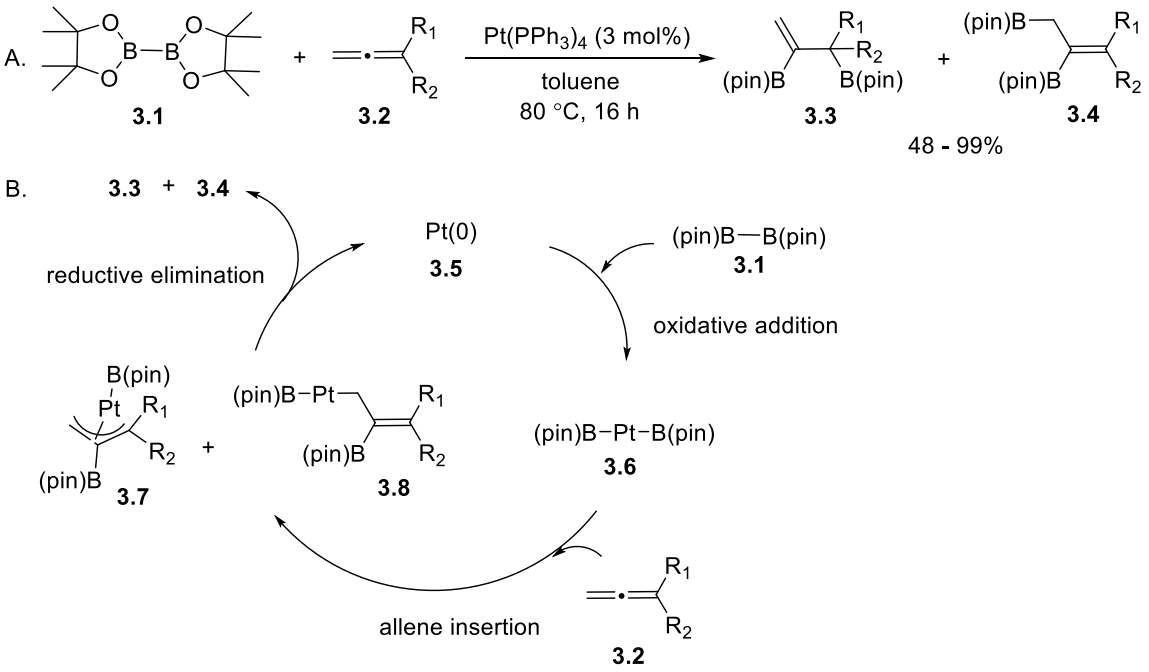
3.2 Abstract

Allenes have proven to be versatile substrates for transition metal-catalyzed diboration reactions. Although symmetrical diboron reagents such as $B_2(pin)_2$ (pin = pinacolate) and $B_2(cat)_2$ (cat = catecholate) are widely used in these reactions, there are limited examples of diboration with unsymmetrical diboron reagents. In this work, an unsymmetrical diboron reagent, (pin)B-B(dan) (dan = naphthalene-1,8-diaminate) was reacted with a series of 1,1-disubstituted allenes chemo- and regioselectively. A catalyst and ligand screening found the combination of $Pt(dba)_3$ and SPhos provided the best selectivity with good yields. These optimized reaction conditions tolerate both electron withdrawing and donating groups on the 1,1-diaryl allene substrates. Steric control ensures that both boryl moieties add to the terminal double bond. Moreover, the pinacol boronate preferentially attaches to the sp-hybridized carbon. The structures of the major isomers were confirmed by X-ray crystallography and 1D NOE experiment. We further demonstrate the application of these intermediates in the chemoselective Suzuki cross-coupling reaction of the pinacol protected over the 1,8-diaminonaphathelene protected boronate moiety to afford a trisubstituted alkene.



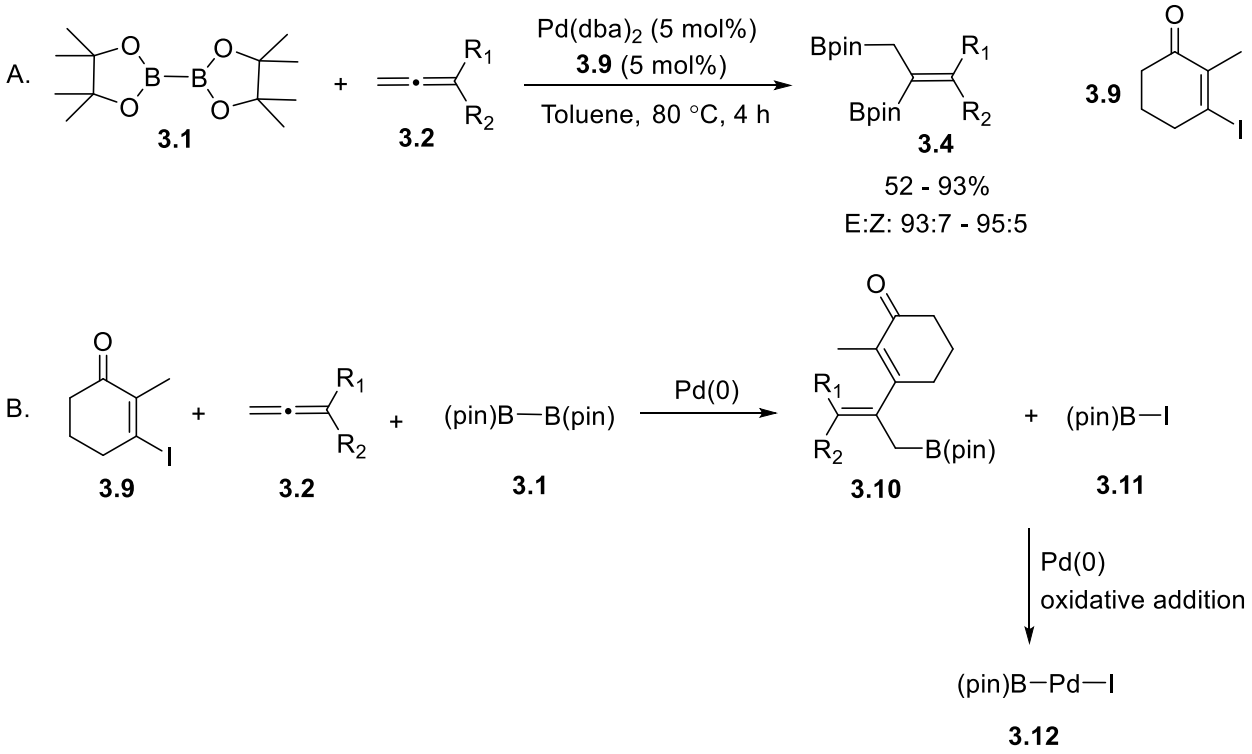
3.3 Introduction

Organoboron compounds have shown a wide variety of applications in both organic synthesis and the pharmaceutical field in the past decades.[1-3] Transition metal-catalyzed diboration of unsaturated compounds has been studied extensively as an efficient method to install C-B bonds.[4-8] Among those unsaturated compounds, allenes are attractive substrates given that the diboration process provides a product bearing both vinyl and allylic boronates.[9,10] The orthogonal reactivity of each C-B bond allows for chemoselective transformations to other valuable functional groups to be performed and achieve rapid construction of complex molecular scaffolds.[11,12] Ishiyama and coworkers first reported a platinum-catalyzed diboration of allenes with $B_2(pin)_2$ (pin = pinacolate; Scheme 3.1A).[13] Diboration with this method preferentially added to the internal double bond to provide product **3.3** when monosubstituted allenes were employed. By employing bulky phosphine ligands such as tricyclohexylphosphine, modest selectivity for the terminal double bond addition product (**3.4**) was achieved. This type of reaction is proposed to proceed via the catalytic cycle of oxidative addition of diboron compound **3.1** to platinum catalyst, allene insertion into the platinum complex **3.6** to yield π-allyl (**3.7**) or vinyl (**3.8**) platinum species, and finally reductive elimination to provide the diborated product (**3.3** and **3.4**) and regenerate the active catalyst (**3.5**, Scheme 3.1B).



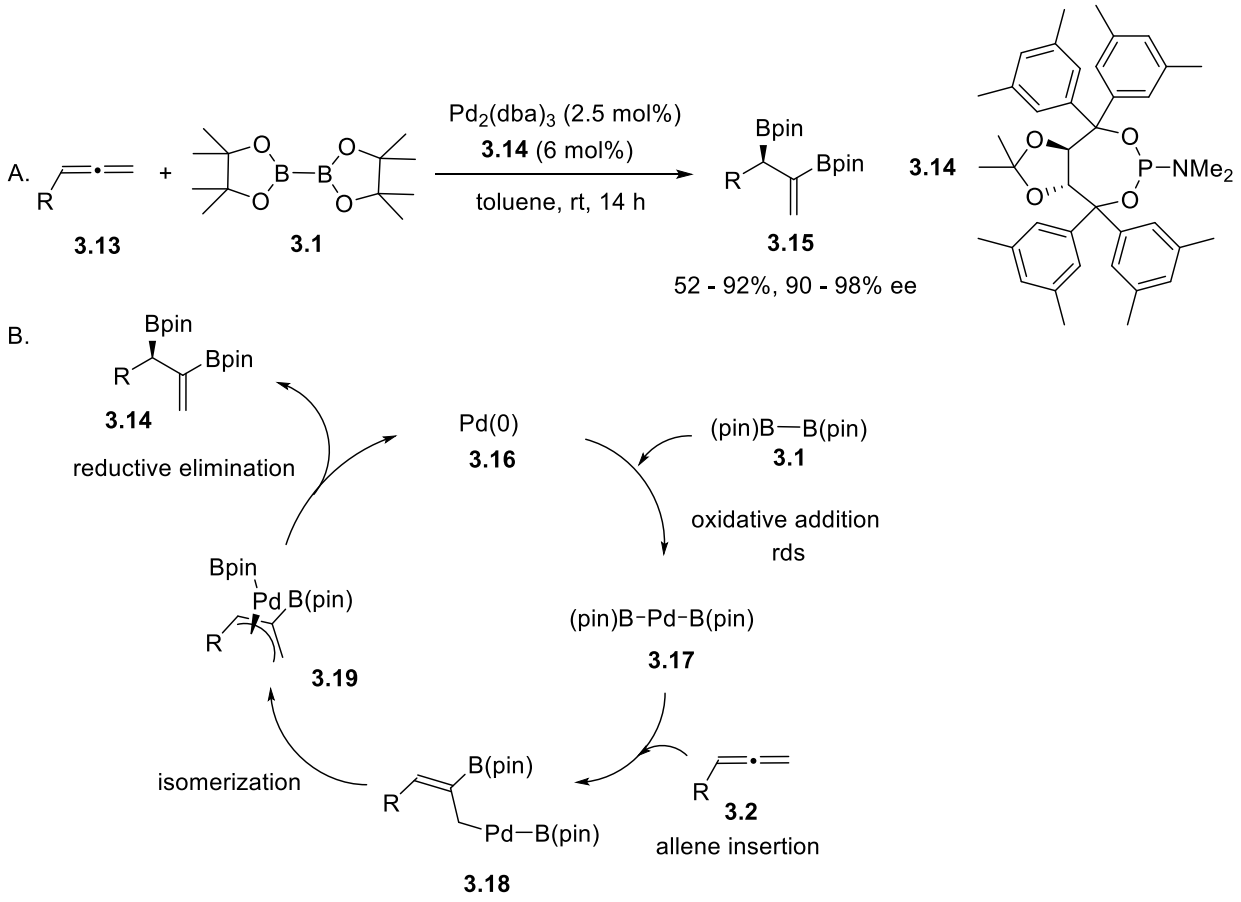
Scheme 3.1 A) Reaction and B) mechanism of platinum-catalyzed diboration of allenes.

Compared with platinum catalysts, diboration of allenes with palladium catalysts is challenging because the oxidative addition product to palladium is not stable.[14-18] To solve this problem, Yang and Cheng developed a catalytic pathway using alkenyl iodide (**3.9**) as the co-catalyst in the presence of $Pd(dba)_2$ (Scheme 3.2A).[19] In this way, iodo(pinacolato)boron (**3.11**) is generated first, and then the oxidative addition of the B-I bond instead of B-B bond to the palladium catalyst takes place to initiate the catalytic cycle (Scheme 3.2B). Interestingly, even with monosubstituted allenes, this approach provides the terminal addition product (**3.4**) exclusively.



Scheme 3.2 A) Reaction of palladium-catalyzed diboration of allenes and B) formation of iodo(pinacolato)boron for oxidative addtion.

To complement the regioselectivity of the above palladium-catalyzed reaction, Morken et al. disclosed that the internal addition product can be achieved enantioselectively by addition of external Lewis basic ligands such as TADDOL(α,α,α,α-tetraaryl-1,3-dioxolane-4,5- dimethanols)-derived phosphoramidites (**3.14**; Scheme 3.3A).[20-22] Although only monosubstituted allenes are investigated under the optimized condition, both aliphatic and aromatic allenes undergo this diboration reaction smoothly with high enantioselectivity, and no terminal addition products are obtained. Mechanistic studies showed that the palladium complexes (**3.17**) generated after oxidative addition add to the more accessible terminal double bond first, and then **3.18** isomerizes to form π-allyl palladium species (**3.19**; Scheme 3.3B).



Scheme 3.3 A) Reaction and B) mechanism of palladium-catalyzed enantioselective diboration of allenes.

As the other diboration partner, symmetrical diboron reagents such as $B_2(pin)_2$ (**3.1**) and $B_2(cat)_2$ (cat = catecholate, **3.20**) are widely used in transition metal-catalyzed boration reactions.[4-8] There are, however, few examples of diboration using unsymmetrical diboron reagents.[23-25] Earlier work in our group demonstrated the internally activated, sp^2-sp^3 hybridized diboron compound, pinacolato diisopropanolaminato diboron (PDIPA diboron, **3.21**), is a particularly effective reagent for a mild, copper-catalyzed β-boration of α,β-unsaturated carbonyl compounds[23] and allenoates[25]. Recently, Iwadate and Suginome reported an unsymmerical diboron reagent, B(pin)-B(dan) (PDAN diboron, dan = naphthalene-1,8-diaminate, **3.22**), that was used for a regioselective diboration of alkynes (Scheme 3.4).[24] In this example, the B(pin) and B(dan) groups

showed different reactivity in subsequent cross-coupling and oxidation reactions, with the Bpin group reacting preferentially. To date, no literature precedent for diboration of allenes with unsymmetrical diboron reagents exist. Herein, we disclose the first diboration of allenes with the unsymmetrical diboron reagent B(pin)-B(dan) in a chemo- and regioselective manner. With diarylsubstituted allenes, both boryl moieties add to the terminal double bond. Moreover, the pinacol boronate preferentially attaches to the sp hybridized carbon. The resulting B(pin) and B(dan) boronates allow for further chemoselective cross-coupling reactions.

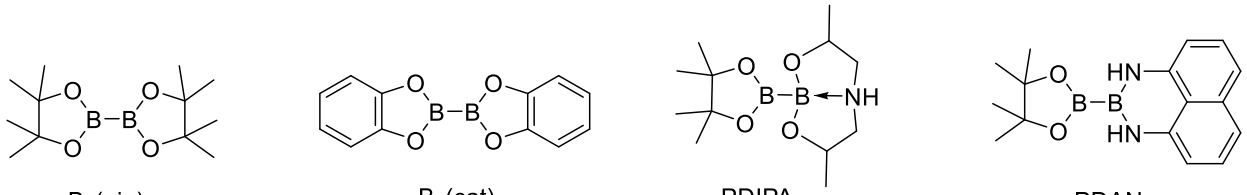
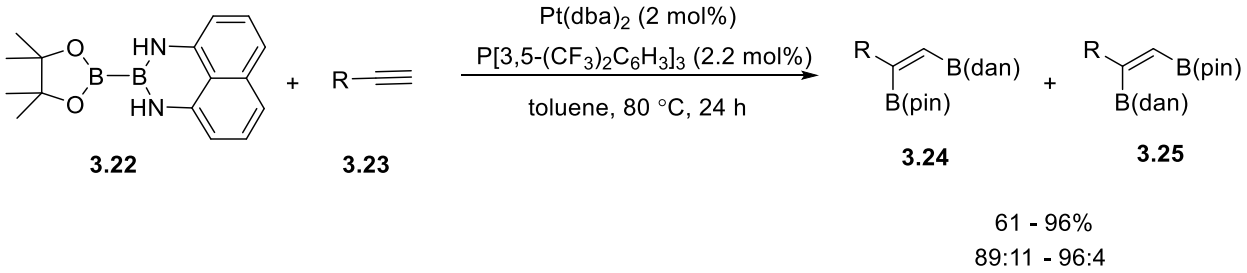


Figure 3.1 Structures of diboron reagents.

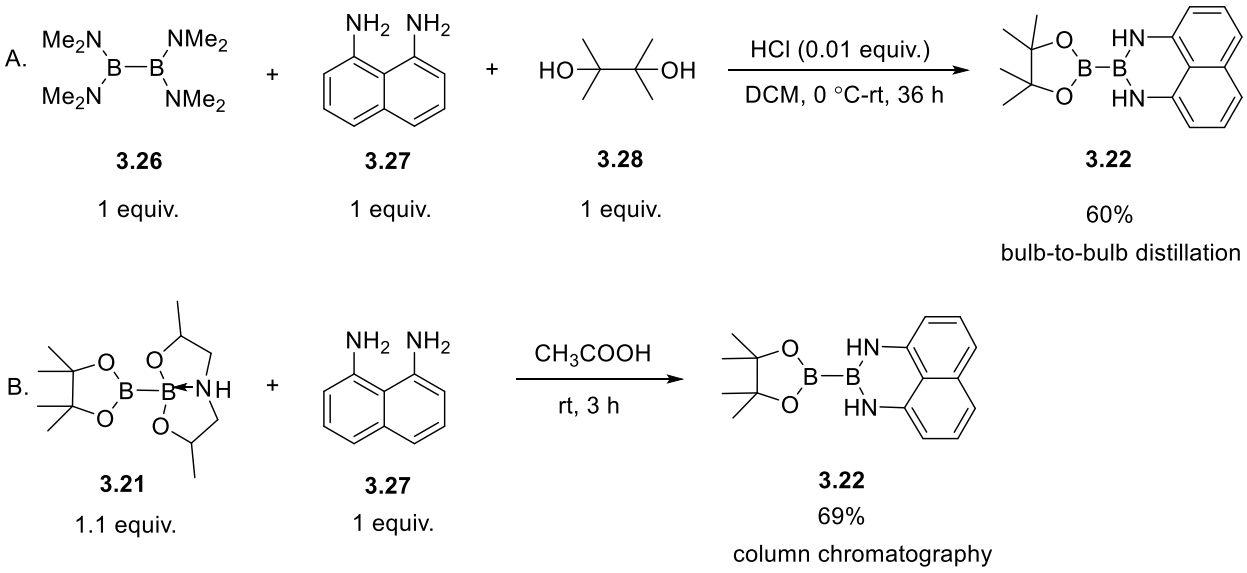


Scheme 3.4 Platinum-catalyzed regioselective diboration of alkynes.

3.4 Synthesis of PDAN diboron

The literature method for synthesis of PDAN diboron employs tetrakis(dimethylamino)diboron (**3.26**), 1,8-diaminonaphthalene (**3.27**) and pinacol (**3.28**; Scheme 3.5A).[24] The ratio of those three reagents needs to be controlled at 1:1:1 stoichiometry carefully. The reaction goes to completion after 36 hours, and bulb-to-bulb distillation affords PDAN

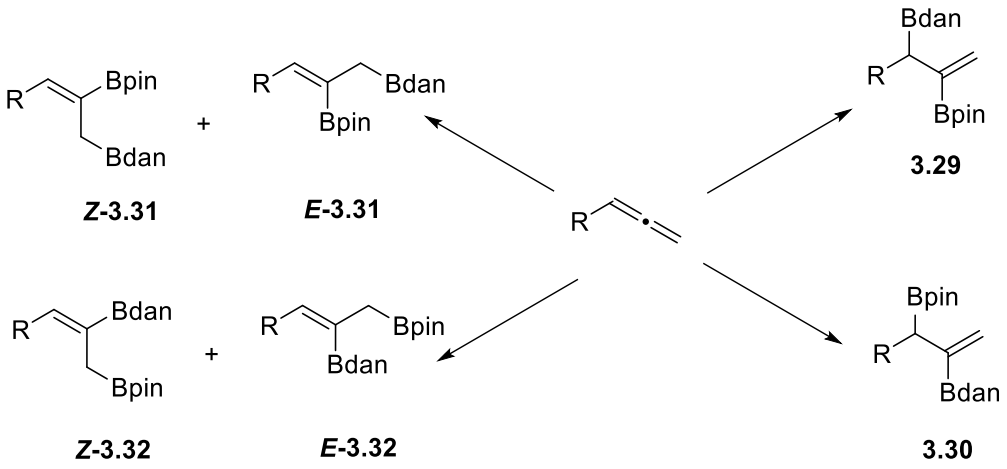
diboron in 60% yield. In order to reduce the reaction time and improve the yield, we designed a new route to prepare PDAN diboron starting from PDIPA diboron (Scheme 3.5B). Simply stirring PDIPA diboron and **3.27** in acetic acid for 3 hours, followed by extraction and column chromatography, provides PDAN diboron as a white solid in 69% yield. Using this method, PDAN diboron can be prepared easily in large scale reactions (1-2 g).



Scheme 3.5 A) Previous method and B) our improved method to synthesize PDAN diboron.

3.5 Optimization of diboration with phenylallene

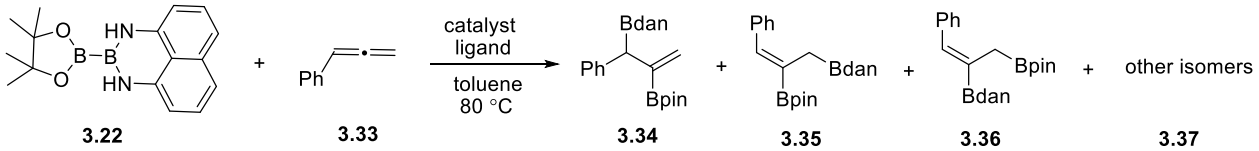
After we optimized our procedure to prepare PDAN diboron, we explored the feasibility of diboration of allenes with PDAN diboron using phenylallene (**3.33**) as the substrate. Diboration of a substituted allene with an unsymmetrical diboron reagent inherently presents a significant regio- and stereoselectivity concern; in principle, the possibility of obtaining up to six constitutional and stereoisomers must be controlled (Scheme 3.6). **3.29** and **3.30** are the internal addition products, whereas *Z*/*E*-**3.31** and *Z*/*E*-**3.32** are the terminal addition products. To address this selectivity challenge, we aimed to obtain regioselectivity for the internal double bond of phenylallene by



Scheme 3.6 Possible diboration products of an allene with PDAN diboron.

exploring previously established catalytic conditions which favored the internal diboration of monosubstituted allenes with symmetrical diboron reagents.[13] As shown in Table 3.1, similar to the initial reports, reactions with $Pt(dba)_3$ favored addition to the internal double bond (entries 1-3). Only two isomers were produced under these conditions, and interestingly, an exclusive regioselectivity to attach the B(dan) moiety to the sp^3 carbon was also observed. Altering the catalyst loading did not significantly affect the selectivity, but negatively impacted the overall yield of the reaction (entries 2 and 3). Then a series of phosphine ligands were screened. Triphenylphosphine improved the yield slightly from 56% to 63%, but at the expense of selectivity (entry 4). The more sterically hindered tricyclohexylphosphine afforded a better selectivity of 80:20 but in low yields (entry 5). It was previously reported that $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ provided the optimal regioselectivity for the diboration of alkynes with PDAN diboorn.[24] We observed a high yield but very little selectivity with the same ligand (entry 6). Regioselectivity for the internal double bond and exclusive chemoselectivity for the B(dan) moiety to attach to the sp^3 carbon was achieved with Buchwald's ligand, SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, **3.38**; entry 7).[26] It preferred product **3.34** with 90% selectivity, although the overall yield (36%)

Table 3.1 Optimization of reaction conditions.[a]



3.22 + 3.33 → 3.34 + 3.35 + 3.36 + 3.37

entry	catalyst (mol%)	ligand (mol%)	yield[b]	product ratio **3.34**:**3.35**:**3.36**:**3.37**[c]
1	$Pt(dba)_3$ (4)	—	56	78:22:0:0
2	$Pt(dba)_3$ (2)	—	16	73:27:0:0
3	$Pt(dba)_3$ (8)	—	45	76:24:0:0
4	$Pt(dba)_3$ (4)	PPh_3(6)	63	67:16:5:12
5	$Pt(dba)_3$ (4)	PCy_3 (6)	34	80:20:0:0
6	$Pt(dba)_3$ (4)	$P[3,5\text{-}(CF_3)_2C_6H_3]_3$ (6)	72	45:5:28:22[d]
7	$Pt(dba)_3$ (4)	SPhos (6)	36	90:10:0:0[e]
8	$Pt(dba)_3$ (4)	RuPhos (6)	NR[f]	—
9	$Pt(dba)_3$ (4)	$P(OEt)_3$ (6)	68	68:19:9:4
10	$Pt(dba)_3$ (4)	$P(OPh)_3$ (6)	trace	—
11	$Pt(dba)_3$ (4)	Xantphos (6)	66	3:62:35:0
12	$Pt(dba)_3$ (4)	Dppe (6)	NR[f]	—
13	$Pt(dba)_3$ (4)	DPEPhos (6)	NR[f]	—
14	$[Ir(cod)Cl]_2$ (2.5)	—	12	0:100:0:0
15	$[Ir(cod)Cl]_2$ (2.5)	PPh_3 (6)	NR[f]	—
16	$[Rh(cod)Cl]_2$ (2.5)	—	NR[f]	—
17	$[Rh(cod)Cl]_2$ (2.5)	PPh_3 (6)	NR[f]	—
18	$Pd_2(dba)_3$ (2.5)	—	NR[f]	—

[a] Catalyst and ligand were added to a flask and purged with nitrogen first. Toluene was added and the suspension was stirred for 15 min. PDAN diboron (1.0 equiv) and phenylallene (1.2 equiv.) were added sequentially. The reaction was heated to 80 ℃ and followed by TLC until the starting material is consumed completely. [b] Isolated yields of all isomers. [c] Determined by GC analysis of the crude reaction mixture. [d] Reaction did not work in dioxane or DMF. [e] The same isomeric ratio and yield were obtained at 100 ℃. [f] NR = no reaction.

was low. A similar ligand, RuPhos (2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl, **3.39**), gave no reaction at all (entry 8). Phosphite ligands were investigated as well.[20] Triethylphosphite provided a comparable yield, but all six isomers were obtained and only a moderate selectivity for product **3.34** was observed (entry 9). Unfortunately, the more bulky triphenylphosphite did not catalyze the boration (entry 10). Not surprisingly, a reversal of the regioselective preference for addition to the internal double bond was observed when the bidentate ligand, Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, **3.40**), was used (entry 11). Dppe (1,2-bis(diphenylphosphino)ethane, **3.41**) and DPEPhos (bis[(2-diphenylphosphino)phenyl] ether, **3.42**) were also examined; however, no reaction took place under the reaction conditions (entries 12 and 13). Finally, other metal catalysts including iridium, rhodium, and palladium were screened for catalytic activity (entries 14-18). While catalysis was only observed in the case of iridium, it is most noteworthy that these conditions provided excellent regio- and chemoselective addition to the terminal double bond to afford product **3.35** exclusively, albeit in low yield (entry 14). Despite altering the ligand and raising the temperature, the yield could not be improved (entry 7). Changing the solvent to DMF or 1,4-dioxane was detrimental to the boration (entry 6).

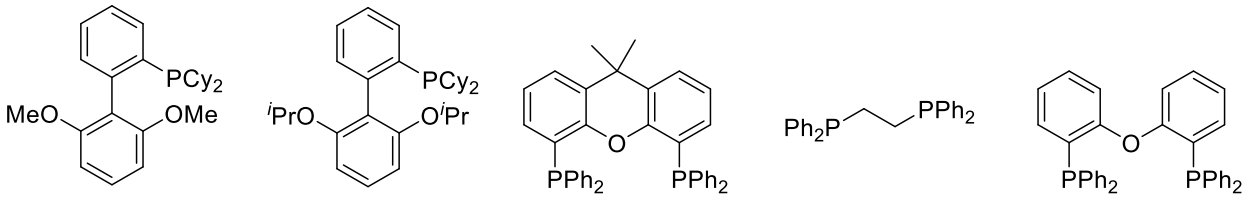


Figure 3.2 Structures of ligands used in Table 3.1

3.6 Structure determination of the diboration product with phenylallene

The crystals of the internal addition product (**3.34**) were obtained from hexane, and their structure was determined by X-ray crystallography shown in Figure 3.3. Although the attempts to obtain crystals of the terminal addition products (**3.35** and **3.36**) failed, their structures were confirmed based on 1D NOE experiments (Figures 3.4 and 3.5).

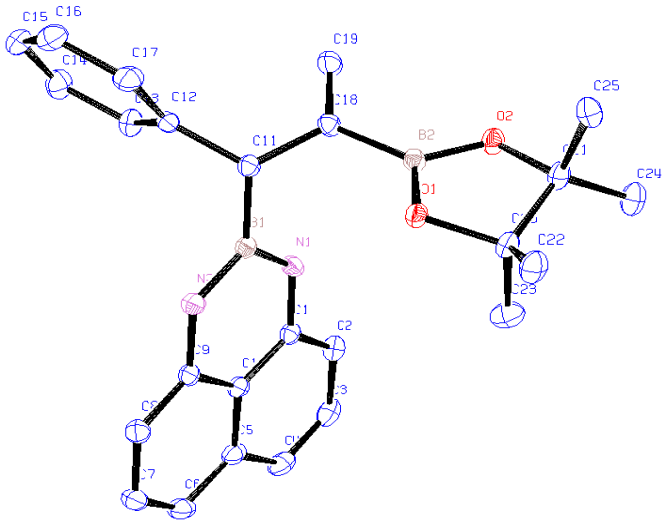
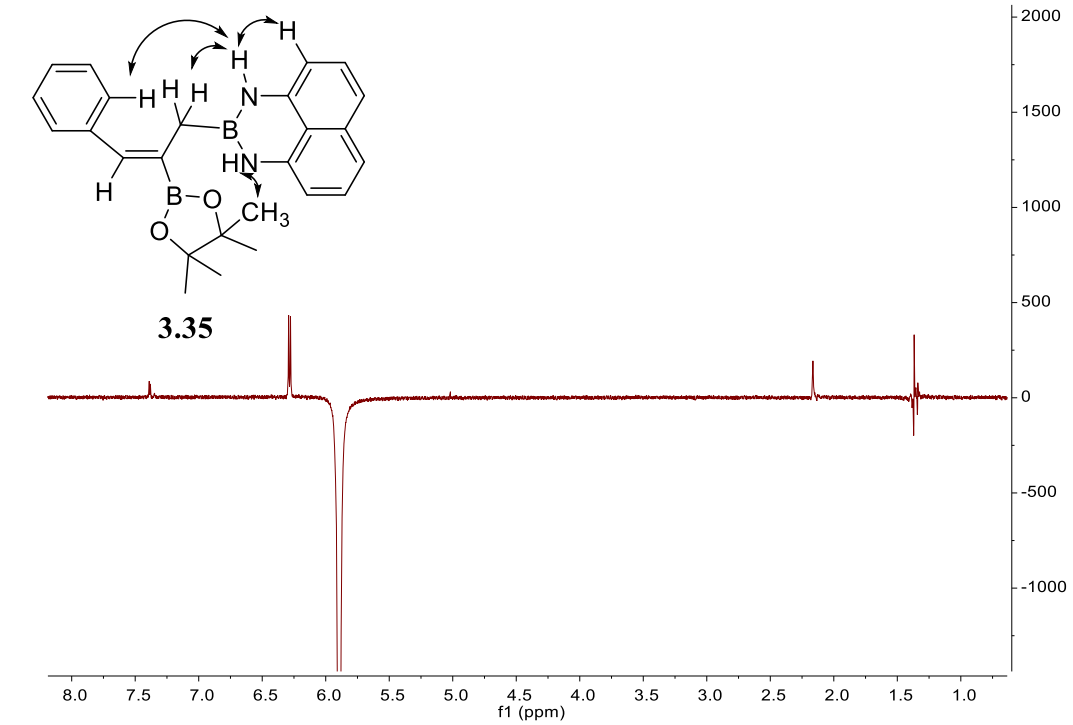


Figure 3.3 ORTEP plot of the crystal structure of **3.34**.



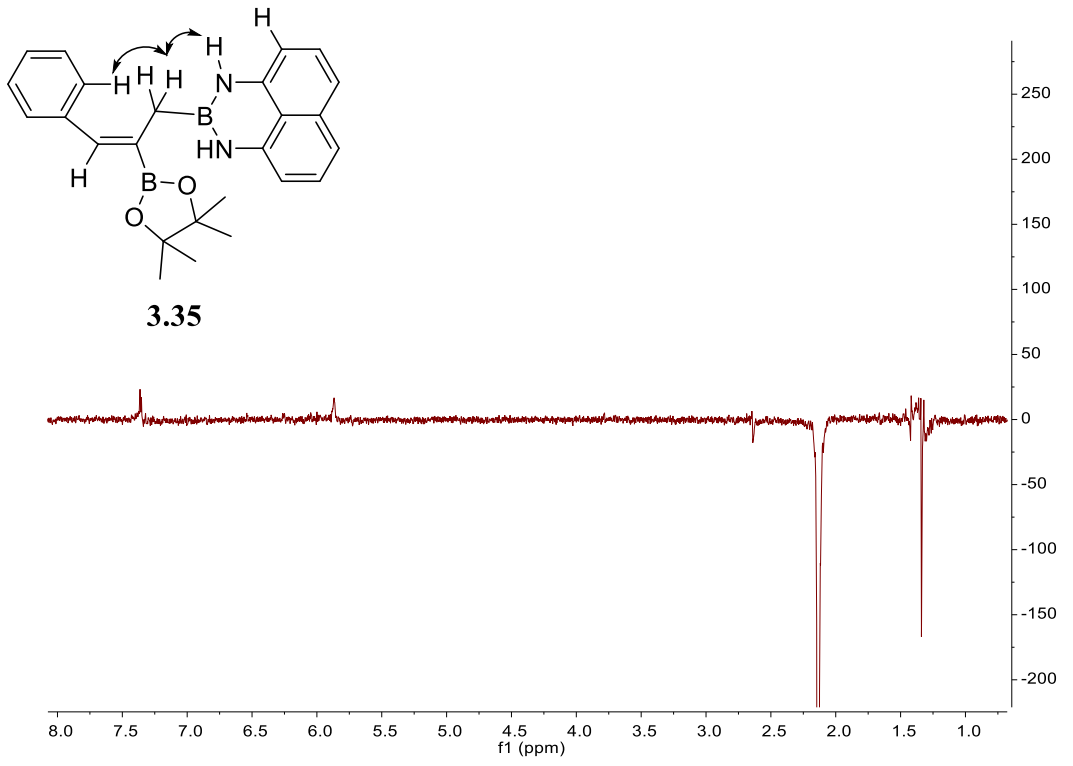
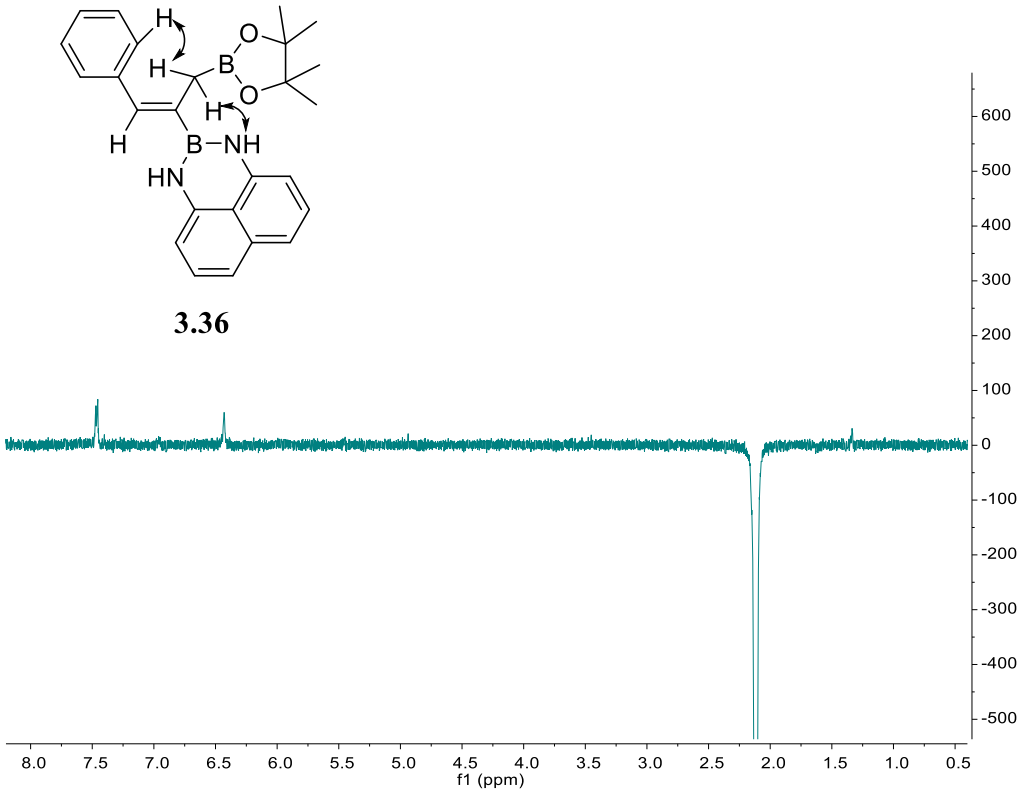


Figure 3.4 1D NOE experiments of terminal addition product **3.35**.



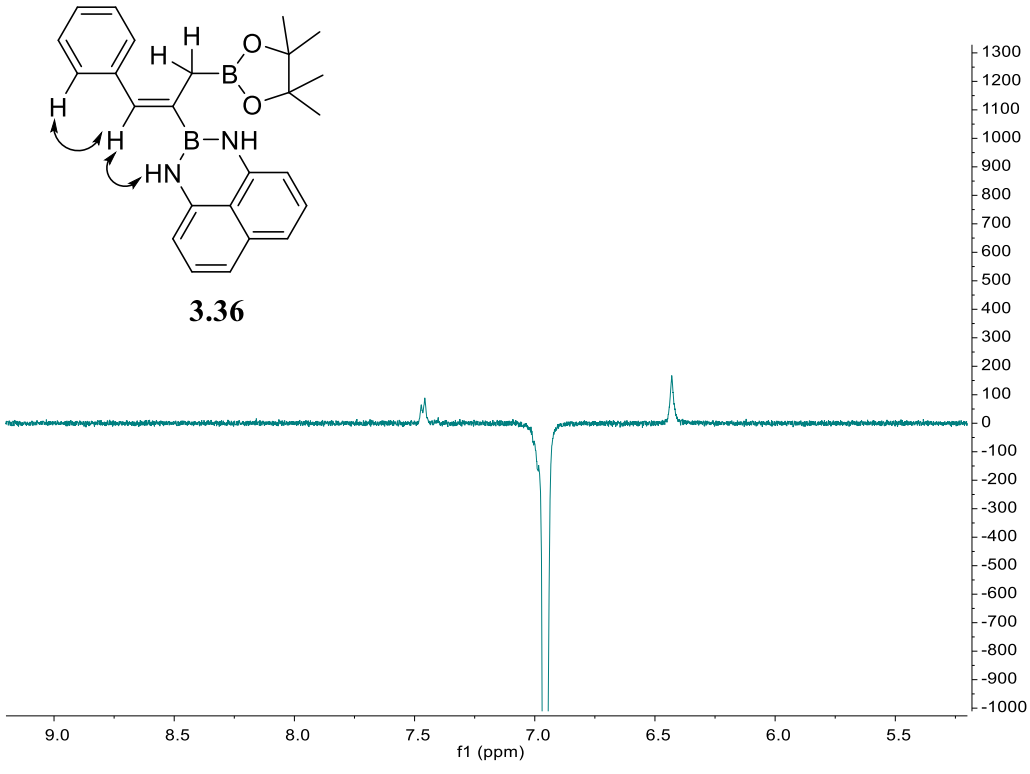
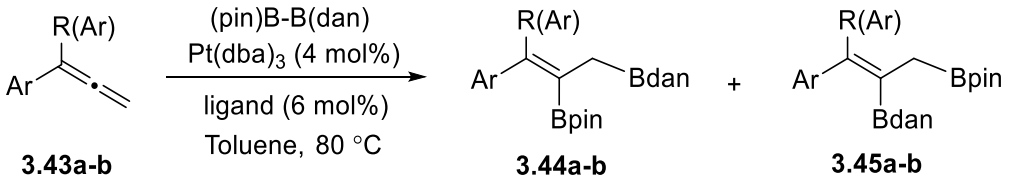


Figure 3.5 1D NOE experiments of terminal addition product **3.36**.

3.7 Ligand screening with doubly substituted allenes

The excellent selectivity of SPhos ligand with phenylallene inspired us to probe these conditions on doubly substituted allenes (entry 7 in Table 3.1). Since the B(dan) moiety is more bulky than the B(pin) moiety, we rationalized that when a more substituted allene was introduced, a preference for diboration of the terminal double bond would be observed. Indeed, when the same reaction conditions were applied to 1-methyl-1-phenylallene (**3.43a**) and 1,1-diphenylallene (**3.43b**), high regio- and chemoselectivity for the terminal double bond was observed in good yields (Table 3.2). A single stereoisomer was isolated with 94% selectivity in the reaction of 1-methyl-1-phenylallene despite the fact that all four possible isomers of terminal addition products were observed (entry 1). Similar selectivity was obtained with 1,1-diphenylallene (**3.43b**, entry 2). For this substrate, only two isomers (**3.44b** and **3.45b**) were produced with SPhos, and both of their structures were confirmed by X-ray crystallography (Figure 3.6). The $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ ligand, which provided a good yield for diboration of phenylallene (entry 6 in Table 3.1), was also tested with the disubstituted allenes. Although yield was improved slightly, poor selectivity was observed for this catalytic system (entries 3 and 4). Interestingly, the employment of either ligand preferred the same product (**3.44a**) for 1-methyl-1-phenylallene, whereas different products (**3.44b** vs. **3.45b**) were favored for 1,1-diphenylallene. Therefore, the subsequent investigation used SPhos as the ligand.

Table 3.2 Ligand screening of disubstituted allenes.[a]



3.43a-b **3.44a-b** **3.45a-b**

entry	allene	R(Ar)	Ar	ligand	yield[b]	product ratio **3.44**:**3.45**[c]
1	**3.43a**	Me	Ph	SPhos	75	94:6[d]
2	**3.43b**	Ph	Ph	SPhos	85	94:6
3	**3.43a**	Me	Ph	P[3,5-$(CF_3)_2C_6H_3$]$_3$	76	76:24[e]
4	**3.43b**	Ph	Ph	P[3,5-$(CF_3)_2C_6H_3$]$_3$	91	33:67

[a] $Pt(dba)_3$ (4 mol%) and ligand (6 mol%) were added to a flask and purged with nitrogen first. Toluene was added and the suspension was stirred for 15 min. PDAN diboron (1.0 equiv) and disubstituted allene (1.2 equiv.) were added sequentially. The reaction was heated to 80 ℃ and followed by TLC until the starting material is consumed completely. [b] Isolated yields of all isomers. [c] Determined by GC analysis of the crude reaction mixture. [d] All four terminal addition products were observed with GC; 94% refers to **3.44a**. [e] All four terminal addition products were observed with GC; 76% refers to **3.44a**.

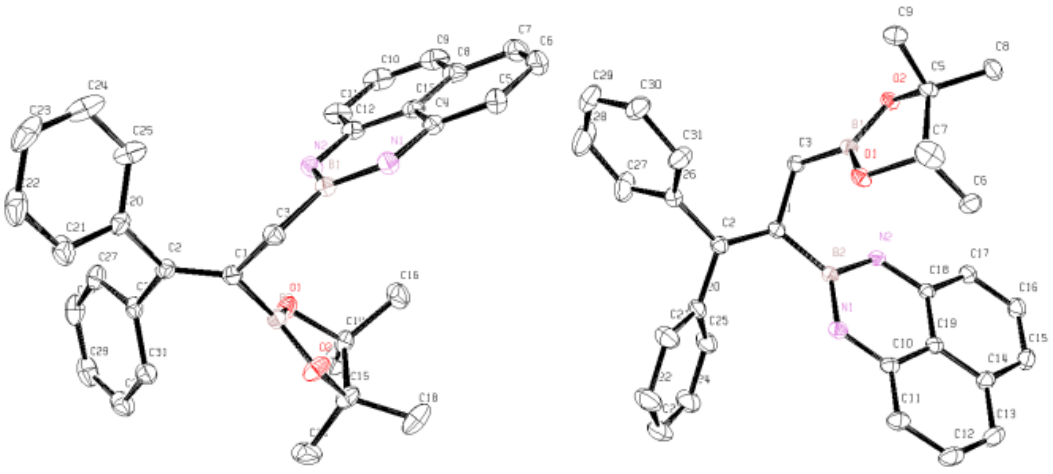
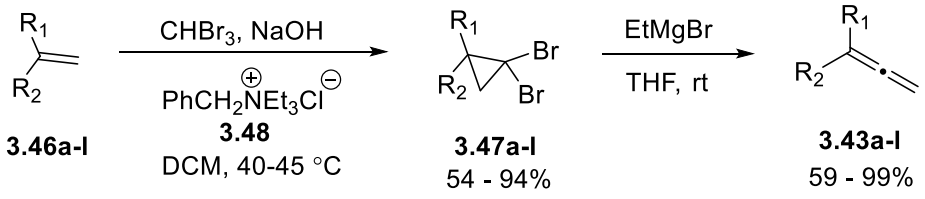


Figure 3.6 ORTEP plot of the crystal structures of **3.44b** and **3.45b**.

3.8 Preparation of allenes

With the optimized reaction conditions in hand, we next examined the scope of the reaction with various disubstituted allenes. They are, however, not commercially available. Fortunately, Yamazaki and coworkers established a synthetic procedure to prepare disubstituted allenes (**3.43a-l**) from commercially or synthetically available alkenes (**3.46a-l**; Scheme 3.7).[27] Carbene insertion to alkenes (**3.46a-l**) in the presence of a phase transfer catalyst (**3.48**) in refluxing DCM provided 1,1-dibromocyclopropanes (**3.47a-l**) in good yields (54 - 94%). Bromine-magnesium exchange using Grignard reagents, followed by cyclopropane ring opening, afforded the desired disubstituted allenes (**3.43a-l**) in good to excellent yields (59 - 99%).[28] Figure 3.7 shows all the allenes that were synthesized using this method and the yields over two steps.



Scheme 3.7 Preparation of allenes.

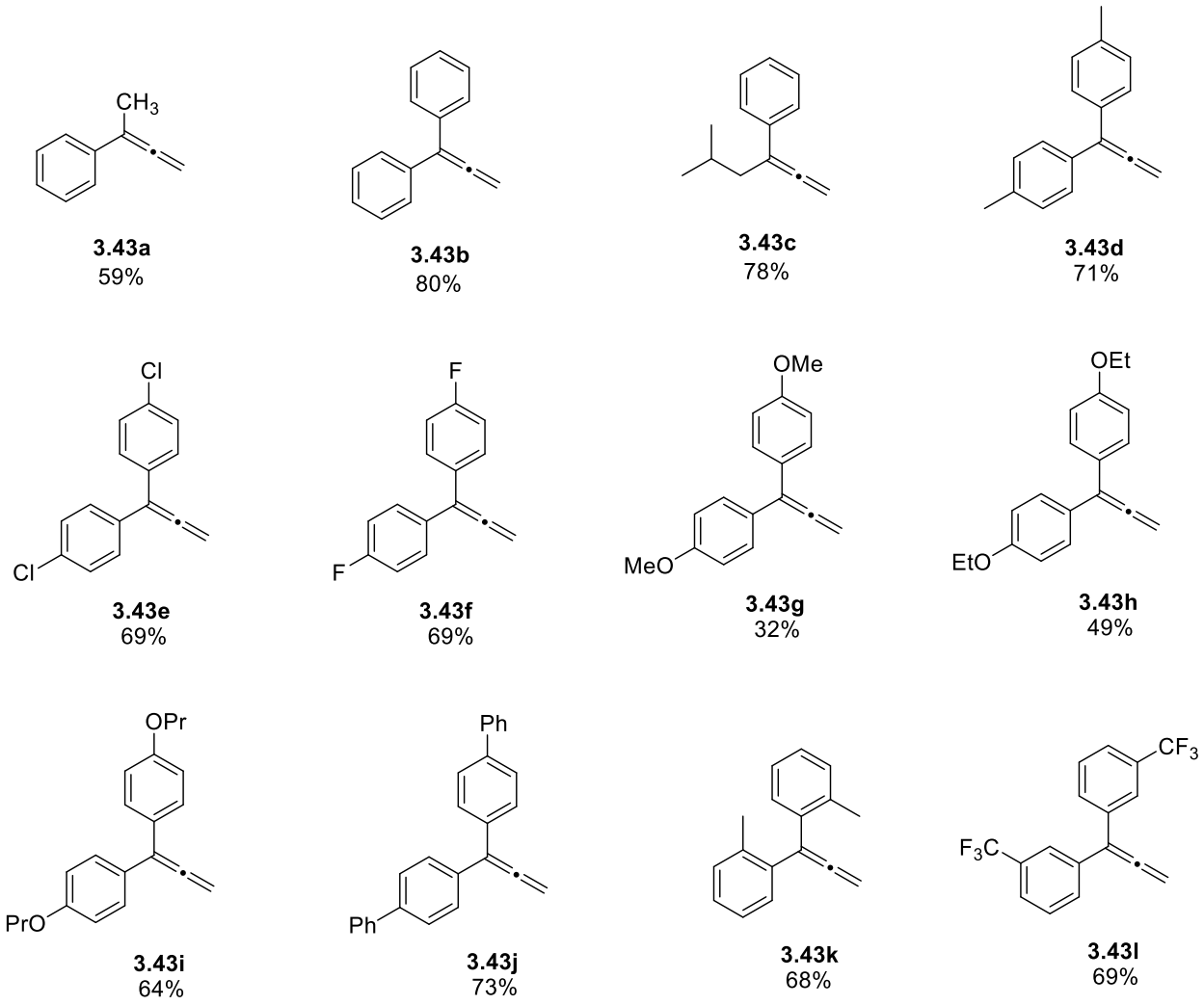


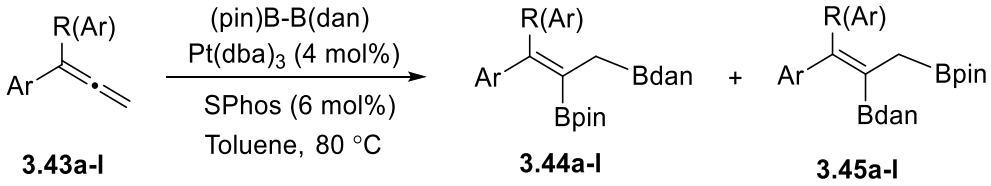
Figure 3.7 The structures of allenes that were synthesized.

3.9 Substrate scope of diboration of allenes

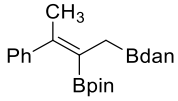
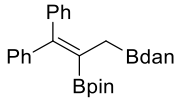
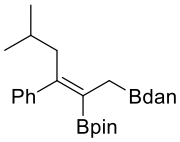
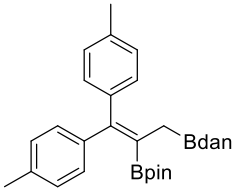
After the disubstituted allenes were synthesized, we investigated the scope of the developed diboration conditions using these as substrates. Indeed, as can be seen in Table 3.3, 1,1-diaryl allenes continued to provide high yields with excellent selectivity of the desired product. The reaction was found to be tolerant of halogen atoms in the *para* positions (entries 5 and 6). Using the inductively electron-withdrawing *meta*-trifluoromethyl substituent, a near quantitative yield of

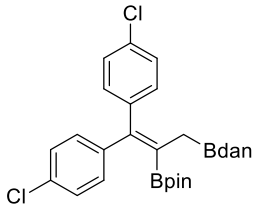
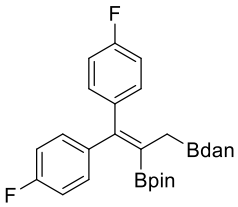
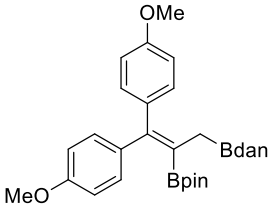
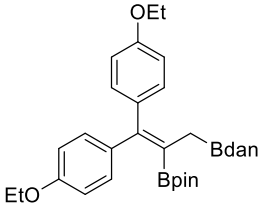
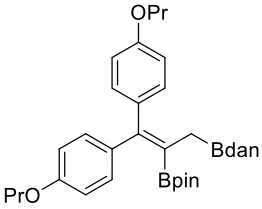
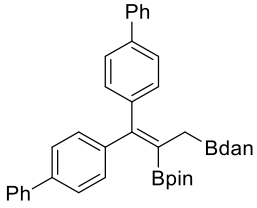
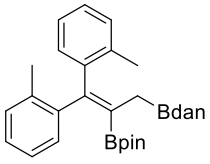
the major isomer was achieved (entry 12). Entries 7 and 8 indicated that electron-donating substituents in the *para* positions also provided high yields, but the selectivity decreased slightly. Both yield and selectivity of the reaction were compromised when bulkier *para*-substituents were introduced (entries 9 and 10). While a methyl substituent in the *para* position provided a similar yield and selectivity to 1,1-diphenyl allene (entry 4 vs. entry 2), when these methyl substituents were placed in the *ortho* position, selectivity for the desired product decreased substantially (entry 11).

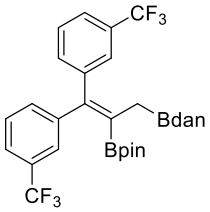
Table 3.3 Diboration of disubstituted allenes with PDAN diboron.[a]



3.43a-l **3.44a-l** **3.45a-l**

entry	Major product	**3.44**	yield[b]	product ratio **3.44**:**3.45**[c]
1		**3.44a**	75	94:6[d]
2		**3.44b**	85	94:6
3		**3.44c**	95	68:32[e]
4		**3.44d**	82	92:8

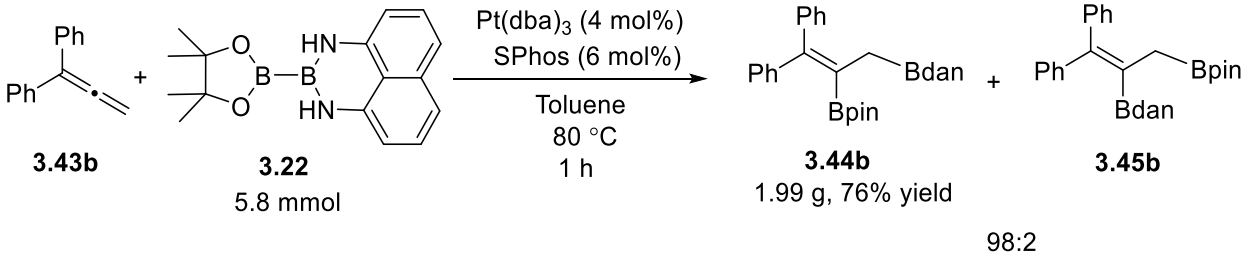
5		**3.44e**	86	94:6
6		**3.44f**	90	95:5
7		**3.44g**	94	90:10
8		**3.44h**	93	90:10
9		**3.44i**	74	84:16[f]
10		**3.44j**	76	81:19[f]
11		**3.44k**	96	70:30

12		**3.44l**	98	97:3

[a] $Pt(dba)_3$ (4 mol%) and SPhos (6 mol%) were added to a flask and purged with nitrogen first. Toluene was added and the suspension was stirred for 15 min. PDAN diboron (1.0 equiv) and disubstituted allene (1.2 equiv.) were added sequentially. The reaction was heated to 80 ℃ and followed by TLC until the starting material is consumed completely. [b] Isolated yields of all isomers. [c] Determined by GC analysis of the crude reaction mixture, unless otherwise noted. [d] All four terminal addition products were observed with GC; 94% refers to **3.44a**. [e] All four terminal addition products were observed with GC; 68% refers to **3.44c**. [f] Determined by ^{1}H-NMR analysis of the crude reaction mixture.

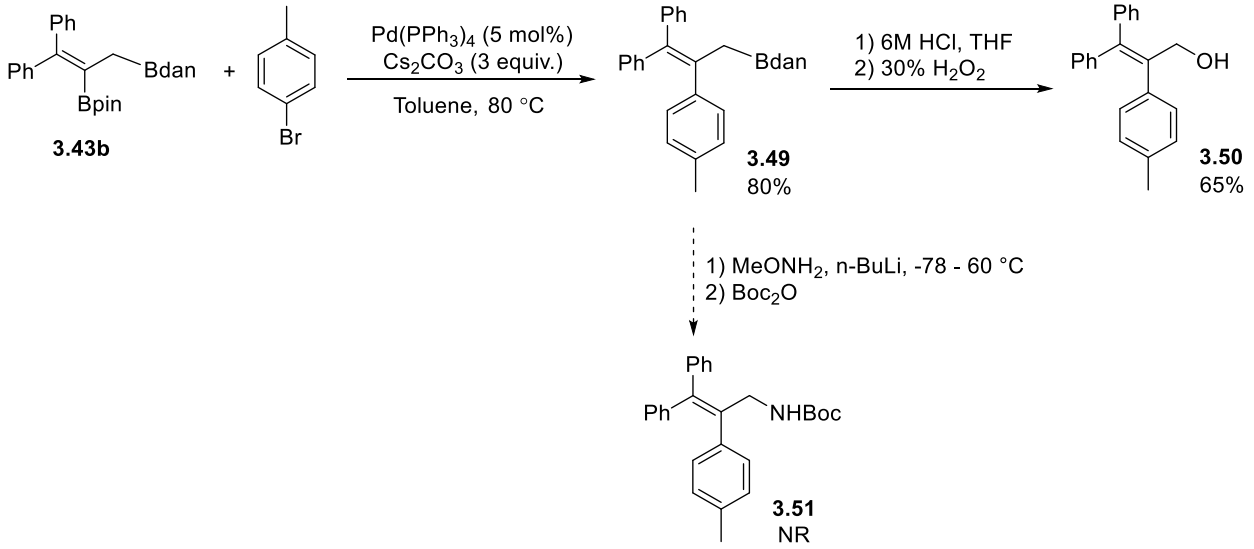
3.10 Application of the diboration product

The optimized conditions can be applied to large-scale reactions. The reaction with 5.8 mmol PDAN diboron reached completion within one hour and provided 1.99 grams of the major product **3.44b** in 76% yield with excellent 98:2 selectivity (Scheme 3.8).



Scheme 3.8 Large-scale diboration of allenes with PDAN diboron.

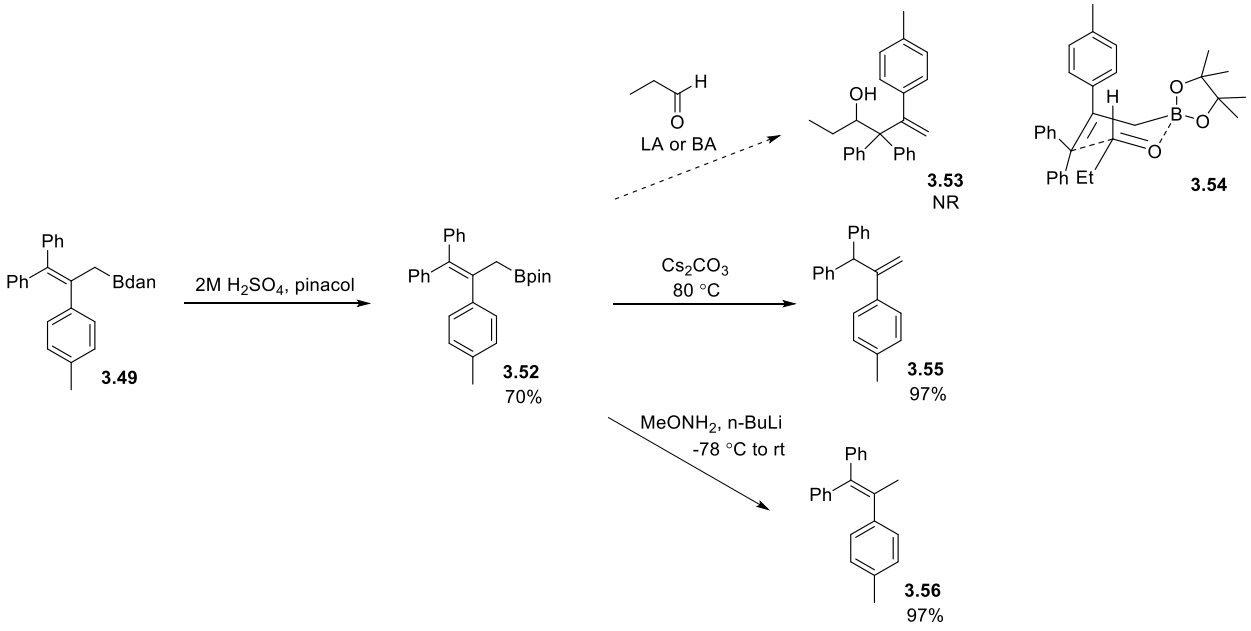
To further explore the utility of our diboration product, compound **3.44b** was first subjected to the typical Suzuki-Miyaura cross-coupling conditions (Scheme 3.9).[12,29,30] Pioneering work by Suginome and coworkers have shown that 1,8-diaminonaphathelene protected boron is not reactive towards cross-coupling reactions.[24,31,32] Indeed, under the cross-coupling conditions, only the pinacol protected boron of **3.44b** reacted while the 1,8-diaminonaphathelene protected moiety remained intact. Further deprotection and oxidation with hydrogen peroxide provided an allylic alcohol **3.50**; however, oxidative amination followed by Boc protection failed to afford product **3.51**.[33]



Scheme 3.9 Chemoselective cross-coupling reaction followed by oxidation.

Alternatively, the 1,8-diaminonaphathelene protected boron moiety of compound **3.49** can be easily converted into a boron pinacolate (**3.52**; Scheme 3.10).[34] Further transformation of this allylic boronate was attempted. First, allylboration of compound **3.52** with an aldehyde was examined.[35,36] Unfortunately, no reaction was observed even with the addition of an external Lewis acids[37-39] or Brønsted acids.[40-42] This is likely due to the sterics in the six-membered chair-like transition state (**3.54**).[35,43,44] To determine the utility of these products, an allylic cross-coupling

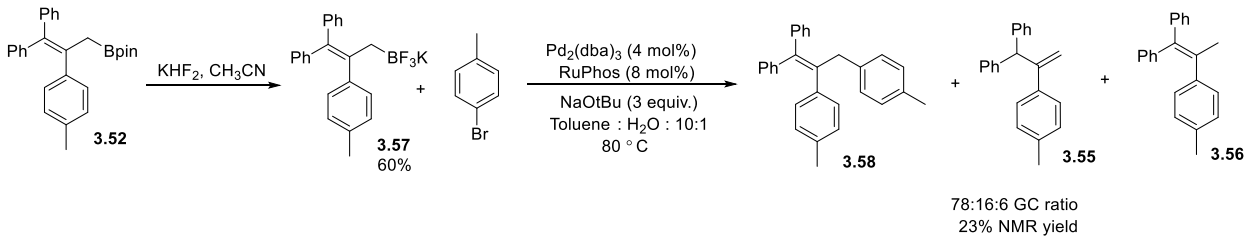
reaction with **3.52** was investigated.[12,29,30] Unfortunately, no desired cross-coupling product was obtained. However, we found that compound **3.52** was converted into a terminal alkene **3.55** in the presence of cesium carbonate within one hour in almost quantitative yield. Further experiments showed that the presence of Pd catalyst had no effect on the formation of compound **3.55**. Reaction of **3.52** and a mild base such as Cs_2CO_3 without addition of a Pd complex still led to compound **3.55** in excellent yield. The formation of the alkene **3.55** could be the result of a 1,3-boron shift followed by protodeboronation.[45] Direct protodeboronation to yield a tetrasubstituted alkene **3.56** was observed when lithiated alkoxy amine was used.



Scheme 3.10 Formation and application of pinacol boronate **3.52**.

As mentioned above, the allylic cross-coupling reaction with **3.52** failed to provide the desired product. A more robust, yet reactive trifluoroborate **3.57** was synthesized next and subjected to the cross-coupling reaction condition (Scheme 3.11).[46,47] Fortunately, employment of $Pd_2(dba)_3$ and RuPhos afforded the desired cross-coupling product **3.58**, although the yield was low.[48,49]

Purification of compound **3.58** was challenging due to the formation of the aforementioned alkenes **3.55** and **3.56**.



Scheme 3.11 Formation and application of trifluoroborate **3.57**.

3.11 Conclusion

In conclusion, the first diboration of allenes with the unsymmetrical diboron reagent (pin)B-B(dan) was achieved regio- and chemoselectively. In the catalysis of $Pt(dba)_3$ and SPhos, the terminal addition product was exclusively obtained with diarylsubstituted allenes. Our investigations suggest that the pinacol protected boron moiety preferentially attached to the sp-hybridized carbon while the 1,8-diaminonaphthalene group was installed in the sp^2 carbon. We further demonstrate the utility of bis-boronyl products in conversions to other functional groups as well as in cross-coupling reactions.

3.12 References

(1) Hall, D. G. *Boronic Acids: Preparation, Applications in Organic Synthesis, Medicine and Materials*; Wiley-VCH GmbH & Co.: Weinheim, 2011.

(2) Jin, S.; Cheng, Y.; Reid, S.; Li, M.; Wang, B. Carbohydrate Recognition by Boronolectins, Small Molecules, and Lectins. *Med. Res. Rev.* **2010**, *30*, 171-257.

(3) Yang, W.; Gao, X.; Wang, B. Boronic Acid Compounds as Potential Pharmaceutical Agents. *Med. Res. Rev.* **2003**, *23*, 346-368.

(4) Dembitsky, V. M.; Abu Ali, H.; Srebnik, M. In *Adv. Organomet. Chem.*; Robert, W., Anthony, F. H., Eds.; Academic Press: 2004; Vol. 51, p 193-250.

(5) Dembitsky, V. M.; Abu Ali, H.; Srebnik, M. Recent Developments in Bisdiborane Chemistry: B-C-B, B-C-C-B, B-C=C-B and B-C≡C-B compounds. *Appl. Organomet. Chem.* **2003**, *17*, 327-345.

(6) Ishiyama, T.; Miyaura, N. Chemistry of Group 13 Element-Transition Metal Linkage — the Platinum- and Palladium-Catalyzed Reactions of (Alkoxo)diborons. *J. Organomet. Chem.* **2000**, *611*, 392-402.

(7) Ishiyama, T.; Miyaura, N. Metal-Catalyzed Reactions of Diborons for Synthesis of Organoboron Compounds. *Chem. Rec.* **2004**, *3*, 271-280.

(8) Marder, T.; Norman, N. Transition Metal Catalysed Diboration. *Top. Catal.* **1998**, *5*, 63-73.

(9) Ma, S. Some Typical Advances in the Synthetic Applications of Allenes. *Chem. Rev.* **2005**, *105*, 2829-2872.

(10) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. Palladium-Catalyzed Reactions of Allenes. *Chem. Rev.* **2000**, *100*, 3067-3126.

(11) Cowen, B. J.; Miller, S. J. Enantioselective Catalysis and Complexity Generation from Allenoates. *Chem. Soc. Rev.* **2009**, *38*, 3102-3116.

(12) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457-2483.

(13) Ishiyama, T.; Kitano, T.; Miyaura, N. Platinum(0)-Catalyzed Diboration of Allenes with Bis(pinacolato)Diboron. *Tetrahedron Lett.* **1998**, *39*, 2357-2360.

(14) Cui, Q.; Musaev, D. G.; Morokuma, K. Density Functional Study on the Mechanism of Palladium(0)-Catalyzed Thioboration Reaction of Alkynes. Differences between Pd(0) and Pt(0) Catalysts and between Thioboration and Diboration. *Organometallics* **1998**, *17*, 1383-1392.

(15) Cui, Q.; Musaev, D. G.; Morokuma, K. Molecular Orbital Study of the Mechanism of Platinum(0)-Catalyzed Alkene and Alkyne Diboration Reactions. *Organometallics* **1997**, *16*, 1355-1364.

(16) Cui, Q.; Musaev, D. G.; Morokuma, K. Why Do $Pt(PR_3)_2$ Complexes Catalyze the Alkyne Diboration Reaction, but Their Palladium Analogues Do Not? A Density Functional Study. *Organometallics* **1998**, *17*, 742-751.

(17) Irvine, G. J.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R.; Robins, E. G.; Roper, W. R.; Whittell, G. R.; Wright, L. J. Transition Metal−Boryl Compounds: Synthesis, Reactivity, and Structure. *Chem. Rev.* **1998**, *98*, 2685-2722.

(18) Sakaki, S.; Kikuno, T. Reaction of BX_2−BX_2 (X = H or OH) with $M(PH_3)_2$ (M = Pd or Pt). A Theoretical Study of the Characteristic Features. *Inorg. Chem.* **1997**, *36*, 226-229.

(19) Yang, F.; Cheng, C. Unusual Diboration of Allenes Catalyzed by Palladium Complexes and Organic Iodides: A New Efficient Route to Biboronic Compounds. *J. Am. Chem. Soc.* **2001**, *123*, 761-762.

(20) Burks, H. E.; Liu, S.; Morken, J. P. Development, Mechanism, and Scope of the Palladium-Catalyzed Enantioselective Allene Diboration. *J. Am. Chem. Soc.* **2007**, *129*, 8766-8773.

(21) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. Palladium-Catalyzed Enantioselective Diboration of Prochiral Allenes. *J. Am. Chem. Soc.* **2004**, *126*, 16328-16329.

(22) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. Concatenated Catalytic Asymmetric Allene Diboration/Allylation/Functionalization. *Org. Lett.* **2005**, *7*, 5505-5507.

(23) Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slebodnick, C.; Marder, T. B.; Santos, W. L. Structure and Reactivity of a Preactivated sp^2–sp^3 Diboron Reagent: Catalytic Regioselective Boration of α,β-Unsaturated Conjugated Compounds. *J. Org. Chem.* **2011**, *76*, 3997-4007.

(24) Iwadate, N.; Suginome, M. Differentially Protected Diboron for Regioselective Diboration of Alkynes: Internal-Selective Cross-Coupling of 1-Alkene-1,2-diboronic Acid Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 2548-2549.

(25) Thorpe, S. B.; Guo, X.; Santos, W. L. Regio- and Stereoselective Copper-Catalyzed β-Borylation of Allenoates by a Preactivated Diboron. *Chem. Commun.* **2011**, *47*, 424-426.

(26) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

(27) Yamazaki, S.; Yamamoto, Y.; Fukushima, Y.; Takebayashi, M.; Ukai, T.; Mikata, Y. Lewis Acid Promoted Reactions of Ethenetricarboxylates with Allenes: Synthesis of Indenes and γ-Lactones via Conjugate Addition/Cyclization Reaction. *J. Org. Chem.* **2010**, *75*, 5216-5222.

(28) Baird, M. S.; Nizovtsev, A. V.; Bolesov, I. G. Bromine–magnesium exchange in gem-dibromocyclopropanes using Grignard reagents. *Tetrahedron* **2002**, *58*, 1581-1593.

(29) Suzuki, A. Organoborane Coupling Reactions (Suzuki Coupling). *Proc. Jpn Acad., Ser. B* **2004**, *80*, 359-371.

(30) Suzuki, A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles, 1995-1998. *J. Organomet. Chem.* **1999**, *576*, 147-168.

(31) Noguchi, H.; Hojo, K.; Suginome, M. Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki−Miyaura Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 758-759.

(32) Noguchi, H.; Shioda, T.; Chou, C. M.; Suginome, M. Differentially Protected Benzenediboronic Acids: Divalent Cross-Coupling Modules for the Efficient Synthesis of Boron-Substituted Oligoarenes. *Org. Lett.* **2008**, *10*, 377-380.

(33) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. Direct Stereospecific Amination of Alkyl and Aryl Pinacol Boronates. *J. Am. Chem. Soc.* **2012**, *134*, 16449-16451.

(34) Lee, J. C. H.; McDonald, R.; Hall, D. G. Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds. *Nat Chem* **2011**, *3*, 894-899.

(35) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. Organoboranes. 53. A High-Field Variable-Temperature Proton and Boron-11 NMR Study of the Effects of Solvent and Structure on Reactivity in Allylboration. *J. Org. Chem.* **1990**, *55*, 1868-1874.

(36) Hall, D. G. Lewis and Brønsted Acid Catalyzed Allylboration of Carbonyl Compounds: From Discovery to Mechanism and Applications. *Synlett* **2007**, *2007*, 1644-1655.

(37) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. Acceleration Effect of Lewis Acid in Allylboration of Aldehydes: Catalytic, Regiospecific, Diastereospecific, and Enantioselective Synthesis of Homoallyl Alcohols. *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415.

(38) Kennedy, J. W. J.; Hall, D. G. Dramatic Rate Enhancement with Preservation of Stereospecificity in the First Metal-Catalyzed Additions of Allylboronates. *J. Am. Chem. Soc.* **2002**, *124*, 11586-11587.

(39) Rauniyar, V.; Hall, D. G. Lewis Acids Catalyze the Addition of Allylboronates to Aldehydes by Electrophilic Activation of the Dioxaborolane in a Closed Transition Structure. *J. Am. Chem. Soc.* **2004**, *126*, 4518-4519.

(40) Jain, P.; Antilla, J. C. Chiral Brønsted Acid-Catalyzed Allylboration of Aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 11884-11886.

(41) Rauniyar, V.; Zhai, H.; Hall, D. G. Catalytic Enantioselective Allyl- and Crotylboration of Aldehydes Using Chiral Diol•SnCl4 Complexes. Optimization, Substrate Scope and Mechanistic Investigations. *J. Am. Chem. Soc.* **2008**, *130*, 8481-8490.

(42) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. Brønsted Acid-Catalyzed Allylboration: Short and Stereodivergent Synthesis of All Four Eupomatilone Diastereomers with Crystallographic Assignments. *J. Am. Chem. Soc.* **2005**, *127*, 12808-12809.

(43) Pratt, A. J.; Thomas, E. J. On the Use of E-1-Methoxymethoxybut-2-Enyl(tri-n-butyl)stannane as a Threo-Selective, Homo-Enolate Equivalent. *J. Chem. Soc., Chem. Commun.* **1982**, 1115-1117.

(44) Raducan, M.; Alam, R.; Szabó, K. J. Palladium-Catalyzed Synthesis and Isolation of Functionalized Allylboronic Acids: Selective, Direct Allylboration of Ketones. *Angew. Chem. Int. Ed.* **2012**, *51*, 13050-13053.

(45) Gridnev, I. D.; Gurskii, M. E.; Ignatenko, A. V.; Bubnov, Y. N.; Il'ichev, Y. V. A Series of Sigmatropic Rearrangements in 2,4,6-Heptatrienyldipropylborane. Kinetic Study of a 1,7-Hydrogen Shift Facilitated by 1,3-Boron Shifts. *Organometallics* **1993**, *12*, 2487-2495.

(46) Darses, S.; Genet, J.-P. Potassium Organotrifluoroborates: New Perspectives in Organic Synthesis. *Chem. Rev.* **2007**, *108*, 288-325.

(47) Molander, G. A.; Ellis, N. Organotrifluoroborates: Protected Boronic Acids That Expand the Versatility of the Suzuki Coupling Reaction. *Acc. Chem. Res.* **2007**, *40*, 275-286.

(48) Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. Asymmetric Synthesis from Terminal Alkenes by Cascades of Diboration and Cross-Coupling. *Nature* **2014**, *505*, 386-390.

(49) Yang, C. T.; Zhang, Z. Q.; Tajuddin, H.; Wu, C. C.; Liang, J.; Liu, J. H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. Alkylboronic Esters from Copper-Catalyzed Borylation of Primary and Secondary Alkyl Halides and Pseudohalides. *Angew. Chem. Int. Ed.* **2012**, *51*, 528-532.

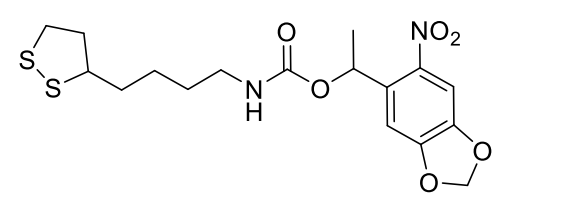
Chapter 4 Synthesis of photoreactive *o*-nitrobenzyl ligands on gold nanoparticles

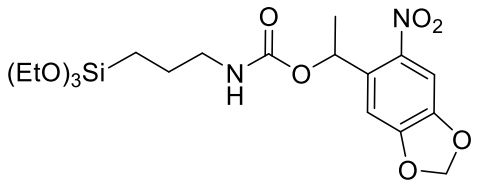
4.1 Contributions

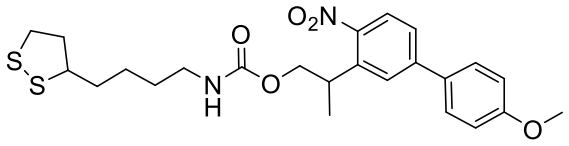
The work described in this chapter was conducted in collaboration with the groups of Professor Hans Robinson of the Department of Physics and Professor Rickey Davis of the Department of Chemical Engineering. This collaborative project is still continuing, and the author is responsible for the synthesis of the *o*-nitrobenzyl ligands. Photoreactivity studies of these ligands on gold surfaces, silicon surfaces or in aqueous media are being conducted by the Robinson group and the Davis group. A part of this project has been published in *The Journal of Physical Chemistry C* and is available online. [Reprinted with permission from Daengngam, C.; Thorpe, S. B.; Guo, X.; Stoianov, S. V.; Santos, W. L.; Morris, J. R.; Robinson, H. D. High Photoreactivity of o-Nitrobenzyl Ligands on Gold. *J. Phys. Chem. C* **2013**, *117*, 14165-14175. Copyright 2014 American Chemical Society.]

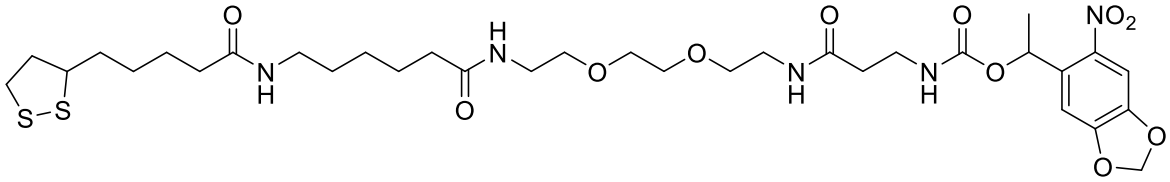
4.2 Abstract

A series of *o*-nitrobenzyl ligands were synthesized, and their photoreactivity on gold surfaces, silicon surfaces or in aqueous media are being investigated. *o*-Nitrobenzyl group uncages an amine upon photoexcitation, which is positively charged at sufficiently low pH. The positively charged amine binds to negatively charged gold nanoparticles irreversibly.









4.3 Introduction

The cleanest way to photolithographically pattern a surface is perhaps to functionalize it with a monolayer of a photoreactive ligand. When the surface is exposed to light, typically at ultraviolet wavelengths, surface properties such as adhesion and wettability change locally so that the surface can be patterned without the use of a photoresist that would need to be removed with harsh solvents. This makes it possible to build structures out of entities such as cells that otherwise would be incompatible with the photoresist removal.

We can distinguish two categories of photoreactions used for such surface patterning. The first category includes compounds sensitive to longer (generally ≥ 300 nm) wavelengths that rely on dedicated groups that cleave to reveal (or "uncage") functional groups such as carboxyls or amines. *o*-Nitrobenzyl-based ligands are by far the most studied,[1-14] but a host of other chemistries (including benzoin,[15,16] (coumarin-4-yl)-methyl,[17] aryl ester,[18] 7-nitroindoine,[19] p-hydroxyphenacyl,[19] Ru bipyridyl,[20] benzophenone,[21] spirobenzopyran,[22] and diazoketo[23] derivatives) have also been used. The second category uses mostly deep UV light to induce less specific reactions that degrade or remove the ligands in the exposed areas, by processes such as photo-oxidation of a metal-sulfur bond,[24-27] by breaking of Si-C,[28-30] C-N,[31] or C-C[32] bonds, or by thermal decomposition.[33] The variety of available photochemistries makes it possible to simultaneously pattern as many as four orthogonal functionalities on a surface, each activated by different wavelengths of light.[15,17] These techniques have been used to photolithographically guide the surface deposition of, among other things, cells,[7,10,13] proteins,[1,11,13] DNA,[8,16] colloidal particles,[6,8,9,22] and fluorophores.[8,16,17] They have also been applied in the fabrication of microfluidic devices[21] and in metal deposition.[31]

In this chapter, we aim to study the photo-uncaging properties of *o*-nitrobenzyl ligands **4.1**-**4.3** when bound to gold surface in the form of a self-assembled monolayer (SAM). These ligands are anchored to the gold by way of a disulfide group derived from the lipoic acid moiety that forms the anchor and linker parts of the molecule. Because the disulfide forms a dual thiol anchor when it binds to gold surfaces the attachment to the surface should be more robust than with a simple thiol ligand. The photosensitive part of all the ligands shown in Figure 4.1 is an *o*-nitrobenzyl group which uncages an amine upon photoexcitation. The amine is positively charged at sufficiently low pH, so we can visualize the exposed regions of the substrate by submersion in a suspension of negatively charged gold nanoparticles. The particles are attracted to the amines and bind to them irreversibly. Measurements are also performed on a silicon surface with ligand **4.4** as a control.

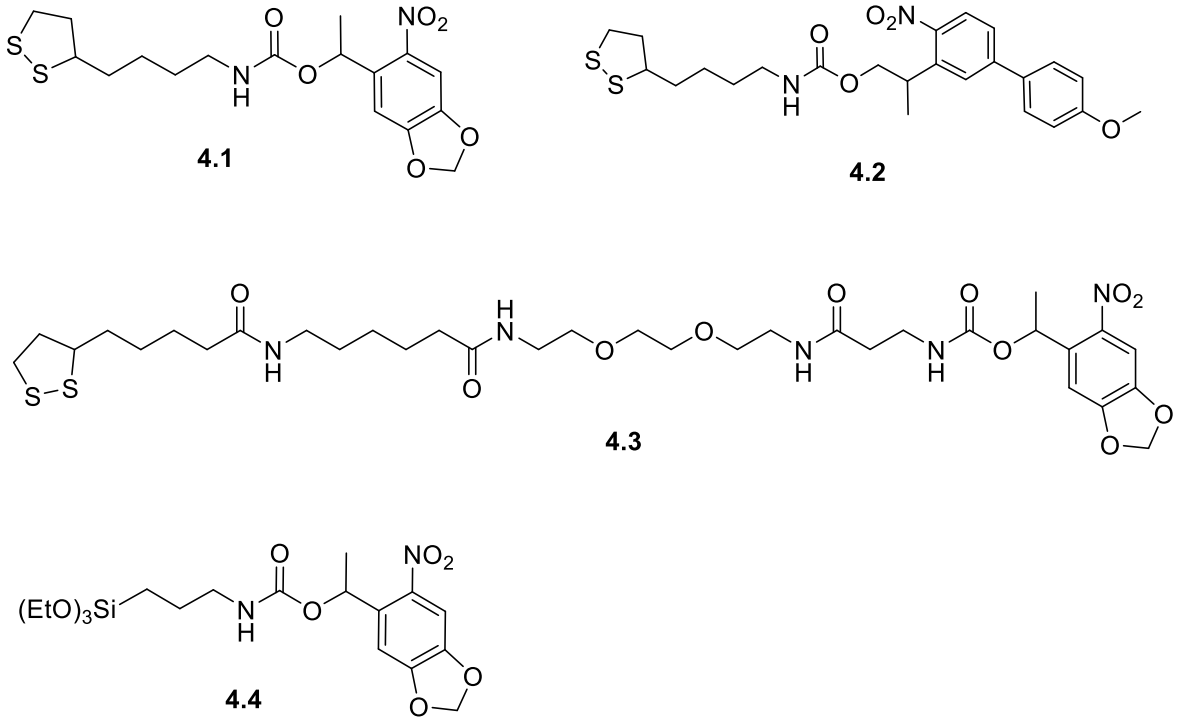
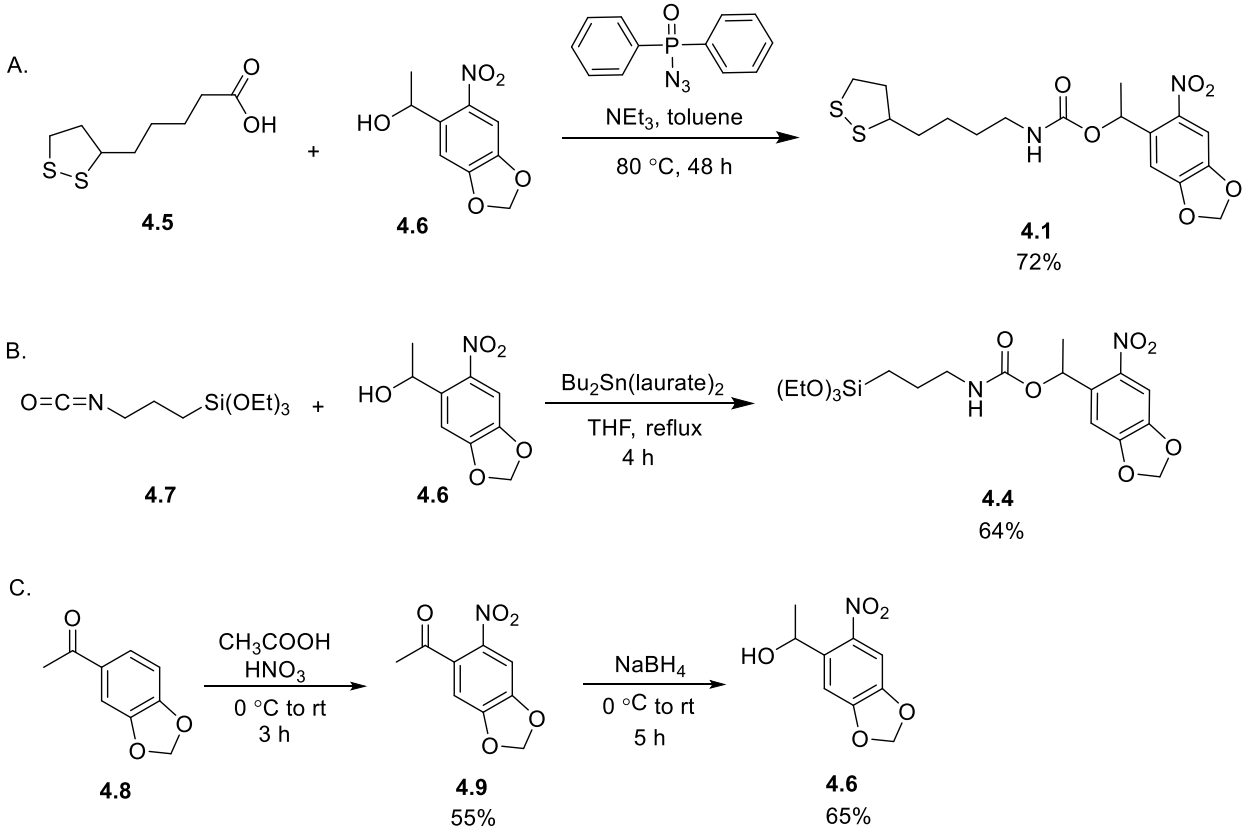


Figure 4.1 Structures of o-nitrobenzyl ligands.

4.4 Synthesis of *o*-nitrobenzyl ligands to gold or silicon surfaces

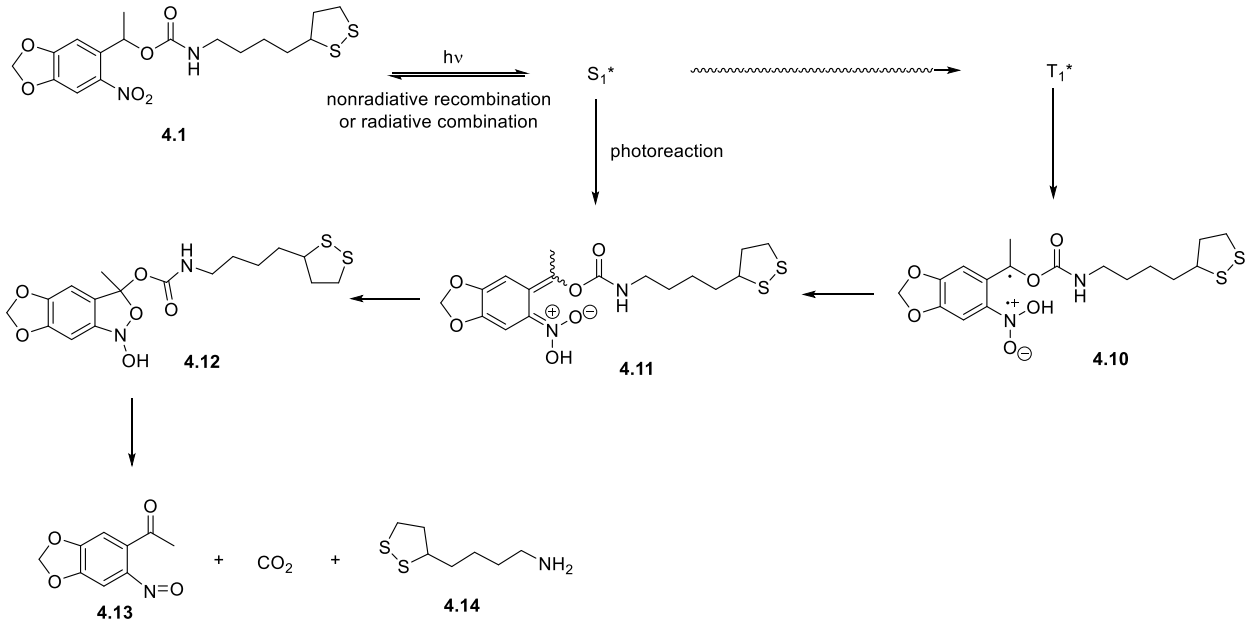
o-Nitrobenzyl ligands with disulfide (**4.1**) as the anchor to gold surfaces and silane (**4.4**) as the anchor to glass surfaces were both synthesized from 1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethan-1-ol (**4.6**, Scheme 4.1A and 4.1B). Compound **4.6** was prepared in large scale reactions via a 2-step procedure, which was a slight modification from the literature (Scheme 4.1C).[34] The nitro group was introduced by nitration of commercially available ketone **4.8** in an ice bath. Then mild reduction of **4.9** with sodium borohydride provided the desired alcohol **4.6** in good yield. With compound **4.6** in hand, the disulfide anchor was installed by a Curtius-type rearrangement with lipoic acid (**4.5**). The silane anchor was introduced through a dibutyltin dilaurate-catalyzed nucleophilic addition of **4.6** to the isocyanate **4.7**.



Scheme 4.1 Synthesis of o-nitrobenzyl ligands to gold or silicon surfaces.

4.5 Photoreaction pathway of 4.1

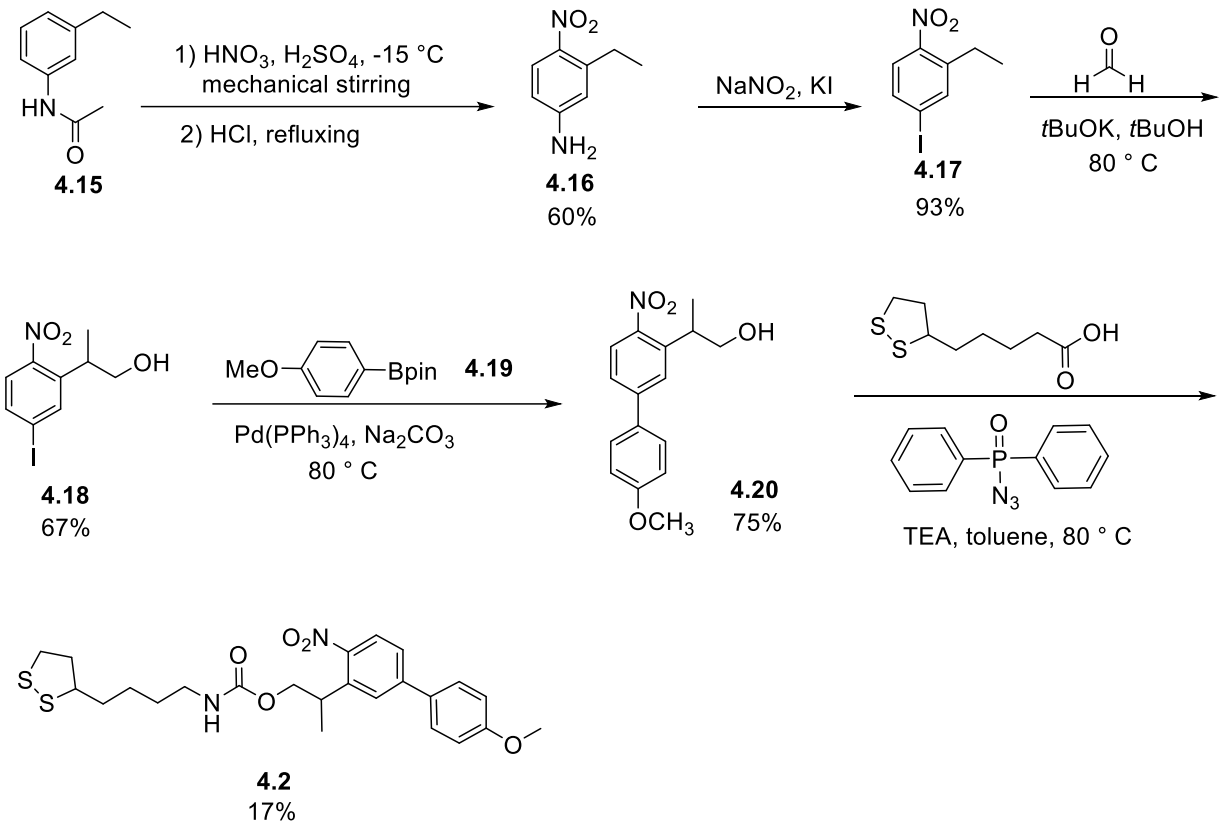
The proposed photoreaction pathway of **4.1** is shown in Scheme 4.2.[35,36] Once the molecule is in the excited state, it rapidly thermalizes to the lowest excited singlet state S_1*. From there, it can return to the ground state through either nonradiative recombination or radiative recombination. If it does not recombine, the molecule can proceed either to the *o*-quinolone intermediary (**4.11**) or undergo intersystem crossing to the triplet state T_1*. The *o*-quinolone moiety cyclizes to **4.12**, which decomposes into nitroso compound **4.13**, accompanied by the desired amine uncaging. The T_1* state decays into the biradical (**4.10**), which then further decays into *o*-quinolone intermediary **4.11** or **4.12**. It is assumed that once **4.10** or **4.11** has formed, the process is irreversible and that the original nitrobenzyl moiety is never regenerated.



Scheme 4.2 Proposed photoreaction pathway of **4.1**.

4.6 Synthesis of a more photoreactive ligand

During the investigation of the photoreactivity of **4.1** the gold surface, we found that sometimes it decomposed before undergoing the desired photoreaction pathway, leading to a relatively low photoreactive efficiency. Previous work by Sylvestre et al. showed that elongation of the conjugated π-system by two directly linked phenyl rings increases the efficiency of the photochemical reaction.[37] Therefore, we hypothesized that if a biaryl ring system is introduced into compound **4.1**, the photochemical efficiency would be improved. Based on this hypothesis, compound **4.2** was designed and synthesized from N-(3-ethylphenyl)acetamide (**4.15**; Scheme 4.3).[38] Introduction of a nitro group followed by deprotection with HCl provided free amine **4.16**. Mechanical stirring at -15 ℃ was essential for the success of the nitration step. Amine **4.16** then underwent a Sandmeyer reaction to generate compound **4.17** in excellent yield. Treating compound **4.17** with paraformaldehyde in basic conditions yielded the alcohol **4.18**, which reacted with para-methoxylphenylboron pinacolate (**4.19**) through a palladium-catalyzed cross-coupling reaction to produce compound **4.20**. Finally, the disulfide anchor was installed through a Curtius-type rearrangement with lipoic acid. The yield of this step was low because several side products were obtained, and two of them co-eluted with **4.2** during column chromatography. Moreover, compound **4.2** needed to be purified rapidly by chromatography on a column covered with aluminum foil to minimize decomposition under light. The photoreactivity of **4.2** on the gold surface is currently under investigation by the Robinson group.

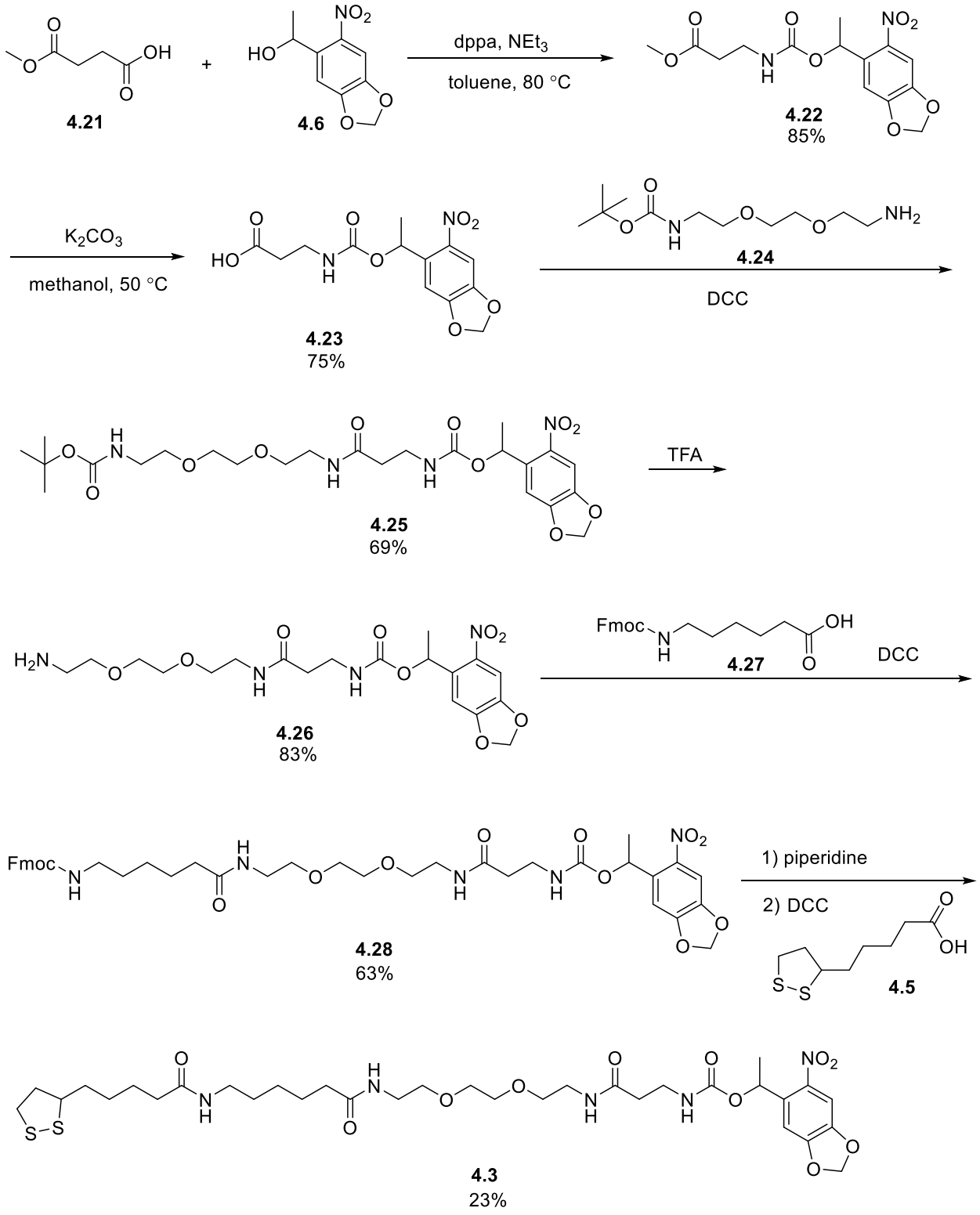


Scheme 4.3 Synthesis of compound **4.2**.

4.7 Design and synthesis of water soluble ligands with disulfide anchor

In order to examine the photoreactivity of *o*-nitrobenzyl ligands on gold surfaces in aqueous solution, a water soluble ligand **4.3** was designed and prepared according to the following synthetic route (Scheme 4.4). The 6-aminohexanoic acid was installed in the middle so that it could prevent ligand aggregation on the gold surface. The *o*-nitrobenzyl group was introduced first via a Curtius-type rearrangement of **4.21** and **4.6** to generate the carbamate **4.22**, which was treated with potassium carbonate in hot methanol to produce the free carboxylic acid **4.23**. Coupling of **4.23** and **4.24** with DCC followed by Boc deprotection with trifluoroacetic acid produced the free amine **4.26**.[39] Compound **4.26** was coupled with the Fmoc protected carboxylic acid **4.27** to provide **4.28**. Finally, compound **4.28** was treated with piperidine to remove the Fmoc group followed by

coupling with lipoic acid **4.5** to yield the desired compound **4.3**. The low yield obtained from this step was due to the polarity of the Fmoc deprotection product, making it hard to purify by column chromatography. Unfortunately, compound **4.3** did not dissolve well in water, however, it dissolved in a mixture of methanol and water in a 1:1 ratio.



Scheme 4.4 Synthesis of compound **4.3**.

4.8 Conclusion

In conclusion, a series of *o*-nitrobenzyl ligands containing a disulfide group derived from lipoic acid were synthesized. The disulfide group forms a dual thiol anchor when it binds to gold surfaces. The *o*-nitrobenzyl group uncages an amine upon photoexcitaion. Curtius-type rearrangement with different carboxylic acids is the key step. Attempts to make water soluble analogs failed, however, the mixture of methanol and water was used as the solvent instead.

4.9 References

(1) Alonso, J. M.; Reichel, A.; Piehler, J.; del Campo, A. Photopatterned Surfaces for Site-Specific and Functional Immobilization of Proteins. *Langmuir* **2007**, *24*, 448-457.

(2) Álvarez, M.; Best, A.; Unger, A.; Alonso, J. M.; del Campo, A.; Schmelzeisen, M.; Koynov, K.; Kreiter, M. Near-Field Lithography by Two-Photon Induced Photocleavage of Organic Monolayers. *Adv. Funct. Mater.* **2010**, *20*, 4265-4272.

(3) Critchley, K.; Jeyadevan, J. P.; Fukushima, H.; Ishida, M.; Shimoda, T.; Bushby, R. J.; Evans, S. D. A Mild Photoactivated Hydrophilic/Hydrophobic Switch. *Langmuir* **2005**, *21*, 4554-4561.

(4) Critchley, K.; Zhang, L.; Fukushima, H.; Ishida, M.; Shimoda, T.; Bushby, R. J.; Evans, S. D. Soft-UV Photolithography using Self-Assembled Monolayers. *J. Phys. Chem. B* **2006**, *110*, 17167-17174.

(5) Fodor, S.; Read, J.; Pirrung, M.; Stryer, L.; Lu, A.; Solas, D. Light-Directed, Spatially Addressable Parallel Chemical Synthesis. *Science* **1991**, *251*, 767-773.

(6) Jonas, U.; del Campo, A.; Krüger, C.; Glasser, G.; Boos, D. Colloidal assemblies on patterned silane layers. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5034-5039.

(7) Kaneko, S.; Nakayama, H.; Yoshino, Y.; Fushimi, D.; Yamaguchi, K.; Horiike, Y.; Nakanishi, J. Photocontrol of Cell Adhesion on Amino-Bearing Surfaces by Reversible Conjugation of Poly(ethylene glycol) via a Photocleavable Linker. *Phys. Chem. Chem. Phys.* **2011**, *13*, 4051-4059.

(8) Manning, B.; Leigh, S. J.; Ramos, R.; Preece, J. A.; Eritja, R. Fabrication of Patterned Surfaces by Photolithographic Exposure of DNA Hairpins Carrying a Novel Photolabile Group. *J. Exp. Nanosci.* **2010**, *5*, 26-39.

(9) Nakagawa, M.; Ichimura, K. Photopatterning of Self-Assembled Monolayers to Generate Aniline Moieties. *Colloids Surf., A* **2002**, *204*, 1-7.

(10) Petersen, S.; Alonso, J. M.; Specht, A.; Duodu, P.; Goeldner, M.; del Campo, A. Phototriggering of Cell Adhesion by Caged Cyclic RGD Peptides. *Angew. Chem. Int. Ed.* **2008**, *47*, 3192-3195.

(11) Pirrung, M. C.; Huang, C.-Y. A General Method for the Spatially Defined Immobilization of Biomolecules on Glass Surfaces Using "Caged" Biotin. *Bioconjugate Chem.* **1996**, *7*, 317-321.

(12) Ryan, D.; Parviz, B. A.; Linder, V.; Semetey, V.; Sia, S. K.; Su, J.; Mrksich, M.; Whitesides, G. M. Patterning Multiple Aligned Self-Assembled Monolayers Using Light. *Langmuir* **2004**, *20*, 9080-9088.

(13) Stegmaier, P.; del Campo, A. Photoactive Branched and Linear Surface Architectures for Functional and Patterned Immobilization of Proteins and Cells onto Surfaces: A Comparative Study. *ChemPhysChem* **2009**, *10*, 357-369.

(14) Zhao, B.; Moore, J. S.; Beebe, D. J. Principles of Surface-Directed Liquid Flow in Microfluidic Channels. *Anal. Chem.* **2002**, *74*, 4259-4268.

(15) del Campo, A.; Boos, D.; Spiess, H. W.; Jonas, U. Surface Modification with Orthogonal Photosensitive Silanes for Sequential Chemical Lithography and Site-Selective Particle Deposition. *Angew. Chem. Int. Ed.* **2005**, *44*, 4707-4712.

(16) Pirrung, M. C.; Fallon, L.; McGall, G. Proofing of Photolithographic DNA Synthesis with 3',5'-Dimethoxybenzoinyloxycarbonyl-Protected Deoxynucleoside Phosphoramidites. *J. Org. Chem.* **1998**, *63*, 241-246.

(17) Stegmaier, P.; Alonso, J. M.; Campo, A. d. Photoresponsive Surfaces with Two Independent Wavelength-Selective Functional Levels. *Langmuir* **2008**, *24*, 11872-11879.

(18) Höfler, T.; Track, A. M.; Pacher, P.; Shen, Q.; Flesch, H.-G.; Hlawacek, G.; Koller, G.; Ramsey, M. G.; Schennach, R.; Resel, R.; Teichert, C.; Kern, W.; Trimmel, G.; Griesser, T. Photoreactive Molecular Layers Containing Aryl Ester Units: Preparation, UV Patterning and Post-Exposure Modification. *Mater. Chem. Phys.* **2010**, *119*, 287-293.

(19) San Miguel, V.; Bochet, C. G.; del Campo, A. Wavelength-Selective Caged Surfaces: How Many Functional Levels Are Possible? *J. Am. Chem. Soc.* **2011**, *133*, 5380-5388.

(20) Álvarez, M.; Alonso, J. M. a.; Filevich, O.; Bhagawati, M.; Etchenique, R.; Piehler, J.; del Campo, A. n. Modulating Surface Density of Proteins via Caged Surfaces and Controlled Light Exposure. *Langmuir* **2011**, *27*, 2789-2795.

(21) Besson, E.; Gue, A.-M.; Sudor, J.; Korri-Youssoufi, H.; Jaffrezic, N.; Tardy, J. A Novel and Simplified Procedure for Patterning Hydrophobic and Hydrophilic SAMs for Microfluidic Devices by Using UV Photolithography. *Langmuir* **2006**, *22*, 8346-8352.

(22) Piech, M.; George, M. C.; Bell, N. S.; Braun, P. V. Patterned Colloid Assembly by Grafted Photochromic Polymer Layers. *Langmuir* **2006**, *22*, 1379-1382.

(23) Ganesan, R.; Yoo, S. Y.; Choi, J.; Lee, S. Y.; Kim, J. Simple Micropatterning of Biomolecules on a Diazoketo-Functionalized Photoresist. *J. Mater. Chem.* **2008**, *18*, 703-709.

(24) Brewer, N. J.; Rawsterne, R. E.; Kothari, S.; Leggett, G. J. Oxidation of Self-Assembled Monolayers by UV Light with a Wavelength of 254 nm. *J. Am. Chem. Soc.* **2001**, *123*, 4089-4090.

(25) Huang, J.; Hemminger, J. C. Photooxidation of Thiols in Self-Assembled Monolayers on Gold. *J. Am. Chem. Soc.* **1993**, *115*, 3342-3343.

(26) Hutt, D. A.; Cooper, E.; Leggett, G. J. Structure and Mechanism of Photooxidation of Self-assembled Monolayers of Alkylthiols on Silver Studied by XPS and Static SIMS. *J. Phys. Chem. B* **1998**, *102*, 174-184.

(27) Tarlov, M. J.; Burgess, D. R. F.; Gillen, G. UV Photopatterning of Alkanethiolate Monolayers Self-Assembled on Gold and Silver. *J. Am. Chem. Soc.* **1993**, *115*, 5305-5306.

(28) Dressick, W. J.; Calvert, J. M. Patterning of Self-Assembled Films Using Lithographic Exposure Tools. *Jpn. J. Appl. Phys.* **1993**, *32*, 5829.

(29) Dulcey, C.; Georger, J.; Krauthamer, V.; Stenger, D.; Fare, T.; Calvert, J. Deep UV Photochemistry of Chemisorbed Monolayers: Patterned Coplanar Molecular Assemblies. *Science* **1991**, *252*, 551-554.

(30) Lee, J. P.; Sung, M. M. A New Patterning Method Using Photocatalytic Lithography and Selective Atomic Layer Deposition. *J. Am. Chem. Soc.* **2003**, *126*, 28-29.

(31) Chen, M. S.; Dulcey, C. S.; Chrisey, L. A.; Dressick, W. J. Deep-UV Photochemistry and Patterning of (Aminoethylaminomethyl)phenethylsiloxane Self-Assembled Monolayers. *Adv. Funct. Mater.* **2006**, *16*, 774-783.

(32) Ye, T.; McArthur, E. A.; Borguet, E. Mechanism of UV Photoreactivity of Alkylsiloxane Self-Assembled Monolayers. *J. Phys. Chem. B* **2005**, *109*, 9927-9938.

(33) Balgar, T.; Franzka, S.; Hartmann, N. Laser-Assisted Decomposition of Alkylsiloxane Monolayers at Ambient Conditions: Rapid Patterning Below the Diffraction Limit. *Appl. Phys. A* **2006**, *82*, 689-695.

(34) McGall, G. H.; Barone, A. D.; Diggelmann, M.; Fodor, S. P. A.; Gentalen, E.; Ngo, N. The Efficiency of Light-Directed Synthesis of DNA Arrays on Glass Substrates. *J. Am. Chem. Soc.* **1997**, *119*, 5081-5090.

(35) Daengngam, C.; Thorpe, S. B.; Guo, X.; Stoianov, S. V.; Santos, W. L.; Morris, J. R.; Robinson, H. D. High Photoreactivity of o-Nitrobenzyl Ligands on Gold. *J. Phys. Chem. C* **2013**, *117*, 14165-14175.

(36) Yip, R. W.; Wen, Y. X.; Gravel, D.; Giasson, R.; Sharma, D. K. Photochemistry of the o-Nitrobenzyl System in Solution: Identification of the Biradical Intermediate in the Intramolecular Rearrangement. *J. Phys. Chem.* **1991**, *95*, 6078-6081.

(37) Gug, S.; Charon, S.; Specht, A.; Alarcon, K.; Ogden, D.; Zietz, B.; Léonard, J.; Haacke, S.; Bolze, F.; Nicoud, J.-F.; Goeldner, M. Photolabile Glutamate Protecting Group with High One- and Two-Photon Uncaging Efficiencies. *ChemBioChem* **2008**, *9*, 1303-1307.

(38) Bühler, S.; Lagoja, I.; Giegrich, H.; Stengele, K.-P.; Pfleiderer, W. New Types of Very Efficient Photolabile Protecting Groups Based upon the [2-(2-Nitrophenyl)propoxy]carbonyl (NPPOC) Moiety. *Helv. Chim. Acta* **2004**, *87*, 620-659.

(39) Marom, H.; Miller, K.; Bechor-Bar, Y.; Tsarfaty, G.; Satchi-Fainaro, R.; Gozin, M. Toward Development of Targeted Nonsteroidal Antiandrogen-1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic Acid−Gadolinium Complex for Prostate Cancer Diagnostics. *J. Med. Chem.* **2010**, *53*, 6316-6325.

Chapter 5 Experimental

5.1 General methods

All reactions in Chapters 2-4 were carried out in oven-dried glassware under a nitrogen atmosphere, unless otherwise noted. Solvents were purchased from Fisher Scientific or Spectrum. Tetrahydrofuran, toluene, acetonitrile, dichloromethane, and dimethylformamide were dried using an Innovative Technologe Pure Solv-MD solvent purification system. Bis(pinacolato)diboron was purchased from Boron Molecular or donated by Allychem. Commercially available reagents and catalysts were purchased and used as received. The TLC analyses were performed using EMD silica gel $60F_{254}$ plates and spots were visualized with permanganate or aqueous phosphomolybdic acid (PMA) stain.

5.2 Instrumentation

^{1}H NMR spectra were recorded on a Bruker Advance II-500 (500 MHz), Agilent 400-MR (400 MHz), JOEL EclipsePlus-500 (500 MHz), or Varian Inova-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Bruker Advance II-500 (125 MHz), Agilent 400-MR (100 MHz), JOEL EclipsePlus-500 (125 MHz), or Varian Inova-400 (100 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm). The carbon atoms directly attached to boron are not observed due to quadruple relaxation. ^{11}B NMR spectra were recorded on a Bruker Advance II-500 (160 MHz), Agilent 400-MR (128 MHz), or

JOEL EclipsePlus-500 (160 MHz) spectrometer. Chemical shifts are reported in ppm with boron trifluoride diethyl etherate as an external standard ($BF_3(OC_2H_5)_2$: 0 ppm). High resolution mass spectra (HRMS) were performed on an Agilent LC-ESI-TOF. Gas chromatography (GC) analyses were performed on a Hewlett Packard 6890 Series GC system coupled to a HP 5973 Mass Selective Detector. The column was an Agilent DB-5MS with a length of 30 m, I.D. of 250 μm, and film thickness of 0.25 μm. Elemental Microanalyses were performed by Atlantic Microlab, Georgia. Melting points were measured on Büchi Melting Point B-540.

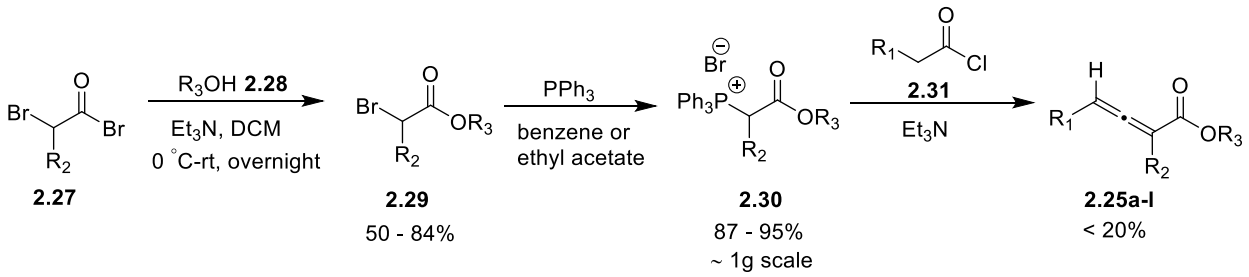
5.3 Synthetic procedures and characterization of products for Chapter 2

General procedure for synthesis of phosphonium salts 2.30 (General Procedure A):

The following procedure was a slight modification from the literature.[1] Alcohol **2.28** (1 equiv.) and triethylamine (1 equiv.) were added in a 25 mL round bottom flask. The flask was purged with nitrogen. DCM was added to give 0.6 M solution of **2.28** and the reaction mixture was cooled to 0 ℃ in an ice bath. Bromoacetyl bromide **2.27** (1.5 equiv.) was added slowly over 30 min in an ice bath. Then the contents were warmed up to r.t. and stirred overnight. The resulting mixture was quenched with water and extracted with EtOAc twice. The organic layer was washed with brine, dried over sodium sulfate, filtered, concentrated in vacuo, and purified by column chromatography to yield the bromoester **2.29** (50 - 84% yield). The bromoester **2.29** (1 equiv.) was dissolved in benzene, and triphenylphosphine (1 equiv.) was added to the solution. The contents were stirred at r.t. overnight and white precipitate formed. The white precipitate was filtered off, washed with benzene, and dried under high vacuum to afford the phosphonium salt **2.30** in excellent yield (87 - 95%).

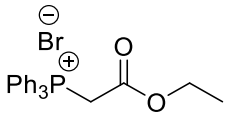
General procedure for synthesis of allenoates 2.25a-l (General Procedure B):

The following procedure was a slight modification from the literature.[1] A mixture of DCM and hexane (2:1) was added to the phosphonium salt **2.30** (1 equiv.). The mixture was cooled to 0 ℃ in an ice bath, and then triethylamine (1.1 equiv.) was added. The contents were stirred for 2 h, and another 1.1 equiv. of triethylamine was added. Then acetyl chloride **2.31** (1.1 equiv.) was added slowly over 30 min. The resulting mixture was stirred overnight in an ice bath. The suspension was filtered through a pad of silica gel and washed with DCM several times. The filtrate was concentrated in vacuo and purified by either column chromatography or bulb-to-bulb distillation to yield the allenoates **2.25**.



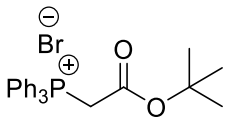
Characterization of phosphonium salts 2.32-2.40:

(2-ethoxy-2-oxoethyl)triphenylphosphonium bromide (2.32):



Compound **2.32** was synthesized using General Procedure A. Spectral data are consistent with the literature.[2] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 13.4, 7.4 Hz, 6H), 7.77 – 7.70 (m, 3H), 7.63 (dd, *J* = 8.0, 3.6 Hz, 6H), 5.42 (d, *J* = 13.8 Hz, 2H), 3.96 (d, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 135.2 (d, *J* = 3.0 Hz), 134.0 (d, *J* = 10.7 Hz), 130.3 (d, *J* = 13.2 Hz), 117.9 (d, *J* = 89.0 Hz), 62.8 , 33.2 (d, *J* = 56.2 Hz), 13.7.

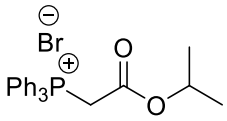
(2-(tert-butoxy)-2-oxoethyl)triphenylphosphonium bromide (2.33):



Compound **2.33** was synthesized using General Procedure A. Spectral data

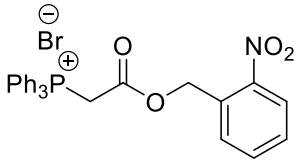
are consistent with the literature.[3] White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 6H), 7.79 – 7.72 (m, 3H), 7.68 – 7.61 (m, 6H), 5.27 (d, *J* = 14.1 Hz, 2H), 1.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0, 135.1 (d, *J* = 3.4 Hz), 133.9 (d, *J* = 10.9 Hz), 130.2 (d, *J* = 13.3 Hz), 118.0 (d, *J* = 88.9 Hz), 84.7, 34.1 (d, *J* = 54.8 Hz), 27.5.

(2-isopropoxy-2-oxoethyl)triphenylphosphonium bromide (2.34):



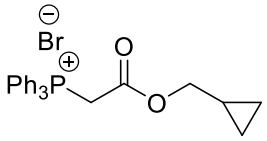
Compound **2.34** was synthesized using General Procedure A. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 13.4, 8.0 Hz, 6H), 7.77 – 7.72 (m, 3H), 7.64 (dd, *J* = 7.7, 3.5 Hz, 6H), 5.36 (d, *J* = 14.0 Hz, 2H), 4.83 – 4.68 (m, 1H), 0.96 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 135.1 (d, *J* = 3.1 Hz), 133.8 (d, *J* = 10.7 Hz), 130.1 (d, *J* = 13.2 Hz), 117.7 (d, *J* = 88.9 Hz), 71.1, 33.1 (d, *J* = 54.7 Hz), 21.1.

(2-((2-nitrobenzyl)oxy)-2-oxoethyl)triphenylphosphonium bromide (2.35):



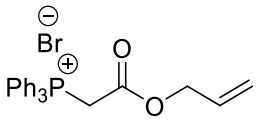
Compound **2.35** was synthesized using General Procedure A. Slightly yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.93 (m, 1H), 7.86 – 7.76 (m, 7H), 7.72 – 7.64 (m, 3H), 7.65 – 7.52 (m, 7H), 7.43 – 7.34 (m, 1H), 5.74 (d, *J* = 13.4 Hz, 2H), 5.34 (s, 2H).

(2-(cyclopropylmethoxy)-2-oxoethyl)triphenylphosphonium bromide (2.36):



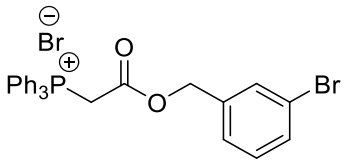
Compound **2.36** was synthesized using General Procedure A. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.87 (m, 6H), 7.81 – 7.74 (m, 3H), 7.71 – 7.63 (m, 6H), 5.59 (d, *J* = 13.9 Hz, 2H), 3.80 (d, *J* = 7.5 Hz, 2H), 0.94 – 0.83 (m, 1H), 0.46 – 0.38 (m, 2H), 0.13 – 0.06 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 135.2 (d, *J* = 3.3 Hz), 134.2 (d, *J* = 10.9 Hz), 130.4 (d, *J* = 13.3 Hz), 118.2 (d, *J* = 88.9 Hz), 71.8, 33.4 (d, *J* = 55.9 Hz), 9.5, 3.6.

(2-(allyloxy)-2-oxoethyl)triphenylphosphonium bromide (2.37):



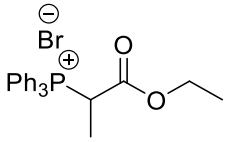
Compound **2.37** was synthesized using General Procedure A. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 6H), 7.82 – 7.74 (m, 3H), 7.70 – 7.64 (m, 6H), 5.68 (d, *J* = 12.7 Hz, 2H), 5.67 – 5.58 (m, 1H), 5.20 – 5.11 (m, 2H), 4.47 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 135.3 (d, *J* = 3.2 Hz), 134.2 (d, *J* = 10.8 Hz), 130.4 (d, *J* = 13.3 Hz), 128.5, 119.9, 118.1 (d, *J* = 89.1 Hz), 67.4, 33.4 (d, *J* = 57.0 Hz).

(2-((3-bromobenzyl)oxy)-2-oxoethyl)triphenylphosphonium bromide (2.38):



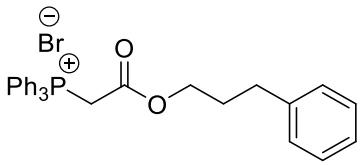
Compound **2.38** was synthesized using General Procedure A. Slightly yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 6H), 7.71 – 7.64 (m, 3H), 7.60 – 7.50 (m, 6H), 7.33 (dd, *J* = 6.9, 2.2 Hz, 1H), 7.13 – 7.10 (m, 1H), 7.08 – 7.00 (m, 2H), 5.52 (d, *J* = 13.9 Hz, 2H), 4.88 (s, 2H).

(1-ethoxy-1-oxopropan-2-yl)triphenylphosphonium bromide (2.39):



Compound **2.39** was synthesized using General Procedure A. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.85 (m, 6H), 7.77 – 7.70 (m, 3H), 7.68 – 7.59 (m, 6H), 6.71 – 6.51 (m, 1H), 4.04 – 3.82 (m, 2H), 1.62 (dd, *J* = 18.5, 7.1 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 135.0 (d, *J* = 3.0 Hz), 134.3 (d, *J* = 10.0 Hz), 130.2 (d, *J* = 12.9 Hz), 117.7 (d, *J* = 86.3 Hz), 62.9, 36.7 (d, *J* = 50.2 Hz), 13.6, 13.0.

(2-oxo-2-(3-phenylpropoxy)ethyl)triphenylphosphonium bromide (2.40):

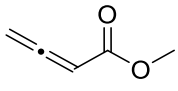


Compound **2.40** was synthesized using General Procedure A. White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 6H), 7.73 – 7.65 (m, 3H), 7.64 – 7.53 (m, 6H), 7.19 – 7.10 (m, 2H), 7.10 – 7.03 (m, 1H), 7.00 – 6.93 (m, 2H), 5.42 (d, *J* = 13.8 Hz, 2H), 3.88 (t, *J* = 6.4 Hz, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 1.72 – 1.56 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 140.4, 135.1 (d, *J* = 3.1 Hz),

133.8 (d, *J* = 10.8 Hz), 130.2 (d, *J* = 13.2 Hz), 128.2 (d, *J* = 8.7 Hz), 125.9, 117.6 (d, *J* = 89.0 Hz), 66.0, 33.0 (d, *J* = 56.1 Hz), 31.6, 29.4.

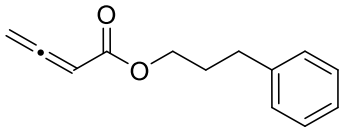
Characterization of allenoates 2.25a-l:

methyl buta-2,3-dienoate (2.25a):



Compound **2.25a** was synthesized using General Procedure B. Spectral data are consistent with the literature.[4]

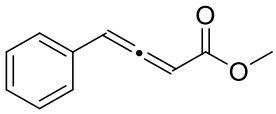
3-phenylpropyl buta-2,3-dienoate (2.25c):



Compound **2.25c** was synthesized using General Procedure B.

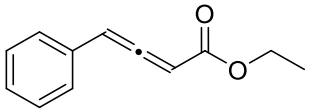
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.19 (m, *J* = 7.6 Hz, 3H), 5.65 (t, *J* = 6.5 Hz, 1H), 5.23 (d, *J* = 6.5 Hz, 2H), 4.17 (t, *J* = 6.5 Hz, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 2.03 – 1.96 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.0, 165.9, 141.3, 128.6, 128.6, 126.2, 88.1, 79.4, 64.4, 32.2, 30.3; HRMS (APCI+): Calcd for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1072, Found 203.1080; TLC: 1:9 / EtOAc:Hexanes, R_f 0.39.

methyl 4-phenylbuta-2,3-dienoate (2.25d):



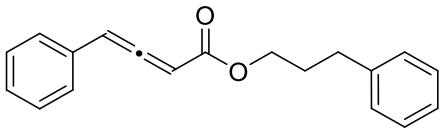
Compound **2.25d** was synthesized using General Procedure B. Spectral data are consistent with the literature.[5]

ethyl 4-phenylbuta-2,3-dienoate (2.25e):



Compound **2.25e** was synthesized using General Procedure B. Spectral data are consistent with the literature.[6]

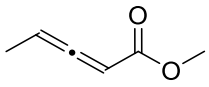
3-phenylpropyl 4-phenylbuta-2,3-dienoate (2.25f):



Compound **2.25f** was synthesized using General Procedure

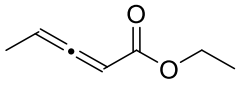
B. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.13 (m, 10H), 6.64 (d, *J* = 6.4 Hz, 1H), 6.03 (d, *J* = 6.4 Hz, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.06 - 1.94 (m, 2H); HRMS (APCI+): Calcd for $C_{19}H_{19}O_2$ $[M+H]^+$: 279.1380, Found 279.1386; TLC: 1:9 / EtOAc:Hexanes, R_f 0.37.

methyl penta-2,3-dienoate (2.25g):



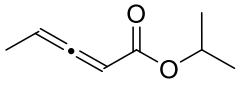
Compound **2.25g** was synthesized using General Procedure B. Spectral data are consistent with the literature.[5]

ethyl penta-2,3-dienoate (2.25h):



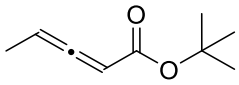
Compound **2.25h** was synthesized using General Procedure B. Spectral data are consistent with the literature.[7]

isopropyl penta-2,3-dienoate (2.25i):



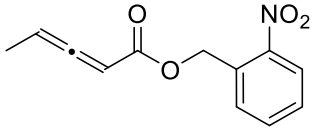
Compound **2.25i** was synthesized using General Procedure B. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 – 5.51 (m, 1H), 5.11 – 4.99 (m, 1H), 3.19 (q, *J* = 2.6 Hz, 1H), 1.84 – 1.77 (m, 3H), 1.27 – 1.24 (m, 6H); HRMS (APCI+): Calcd for $C_{18}H_{13}O_2$ $[M+H]^+$: 141.0910, Found 141.0909; TLC: 1:9 / EtOAc:Hexanes, R_f 0.45.

tert-butyl penta-2,3-dienoate (2.25j):



Compound **2.25j** was synthesized using General Procedure B. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 – 5.44 (m, 1H), 3.14 (q, *J* = 2.5 Hz, 1H), 1.87 – 1.72 (m, 3H), 1.47 (d, *J* = 6.5 Hz, 9H); GC/MS (EI+): Calcd for $C_9H_{14}O_2$: 154, Found 154; TLC: 1:9 / EtOAc:Hexanes, R_f 0.50.

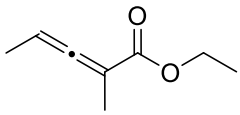
2-nitrobenzyl penta-2,3-dienoate (2.25k):



Compound **2.25k** was synthesized using General Procedure B. White

solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (t, *J* = 7.6 Hz, 1H), 7.69 – 7.58 (m, 2H), 7.53 – 7.46 (m, 1H), 5.59 (d, *J* = 5.6 Hz, 2H), 3.34 (q, *J* = 2.5 Hz, 1H), 1.95 – 1.77 (m, 3H); HRMS (APCI+): Calcd for $C_{12}H_{12}NO_4$ $[M+H]^+$: 234.0761, Found 234.0764; TLC: 1:4 / EtOAc:Hexanes, R_f 0.35.

ethyl 2-methylpenta-2,3-dienoate (2.25l):



Compound **2.25l** was synthesized using General Procedure B. Spectral data are consistent with the literature.[5]

General procedure for the optimization of the β-boration of ethyl-2,3-butadienoate (General Procedure C; Table 2.1):

Method 1 (Entry 1). 1,3-Dimethylimidazolium-2-carboxylate (2.5 mg, 0.018 mmol) and copper(I) chloride (1.8 mg, 0.018 mmol) were added to a 10 mL, 2-neck, round-bottomed flask. ACN (2 ml) was added and the reaction was stirred for 15 min. Bis(pinacolato)diboron (100 mg, 0.394 mmol) in ACN (2 mL) was added, followed by ethyl 2,3-butadienoate (0.042 ml, 0.358 mmol) and the black reaction mixture was stirred at room temperature for 2 h.[8]

Method 2 (Entry 2). 1,3-dicyclohexylimidazolium tetrafluoroborate (5.7 mg, 0.018 mmol), sodium tert-butoxide (3.4 mg, 0.036 mmol) and copper(I) chloride (1.8 mg, 0.018 mmol) were added to a 10 mL, 2-neck, round-bottomed flask. THF (3 mL) was added and the reaction was stirred for 2.5 hr. Bis(pinacolato)diboron (100 mg, 0.392 mmol) in THF (1 mL) was added via syringe. After 10 minutes. ethyl 2,3-butadienoate (0.041 ml, 0.357 mmol) was added and the reaction was stirred at room temperature for 2 hr.[9]

Method 3 (Entries 3-8). Copper(I) chloride (3.5 mg, 0.036 mmol) was added to a 10 mL, 2-neck, round-bottomed flask fitted with a reflux condenser (for entries 5-6, NaO*t*Bu and DPEphos were also added at this time). DCM (0.5 mL) was added and the reaction was stirred for 2 min. PDIPA diboron (115 mg, 0.428 mmol) in DCM (4 mL) was injected via syringe. After 10 minutes, ethyl

2,3-butadienoate (0.041 mL, 0.357 mmol) was added and the reaction was stirred at reflux for 2 hours (for entries 3 and 7, TFE was added directly after the allenoate).

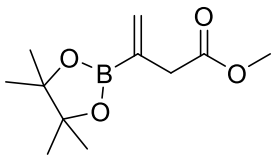
Method 4 (Entries 9-18). Copper(I) chloride (3.5 mg, 0.036 mmol) and PDIPA diboron (115 mg, 0.428 mmol) were added to a 10 mL, 2-neck, round-bottomed flask fitted with a reflux condenser. THF (4.5 mL) was added (for entry 9, DMF was used instead). After 10 minutes, ethyl 2,3-butadienoate (0.041 mL, 0.357 mmol) was added and the reaction was stirred at the indicated temperature for 2 hours. For entries 12-18, copper(I) chloride was substituted for the indicated catalyst.

General procedure for the β-boration of allenoates (General Procedure D; Table 2.2):

Copper(I) chloride (3.53 mg, 0.036 mmol) and PDIPA diboron (115 mg, 0.428 mmol) were added to a 10 mL, 2-neck, round-bottomed flask and purged with vacuum / nitrogen. THF (2.5 mL) was added and the suspension was stirred for 5 min, producing a black mixture. Ethyl 2,3-butadienoate (40 mg, 0.357 mmol) dissolved in THF (0.5 ml) was added, washing once more with THF (0.5 mL), and the reaction was stirred at r.t. and followed by TLC until the starting material was gone (typically 2-3 hr). The contents were then filtered through celite, washing with diethyl ether, and concentrated by rotary evaporation. Compounds **2.26a, b, g, h, i**, and **j** were purified by vacuum distillation and compounds **2.26c, d, e, f,** and **k** were purified by flash chromatography on silica gel.

Characterization of compounds 2.26a-l:

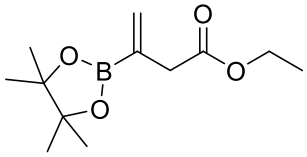
methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enoate (2.26a):



Compound **2.26a** was synthesized using General Procedure D. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (d, *J* = 2.9 Hz, 1H), 5.69 (s, 1H), 3.66 (s, 3H), 3.19 (s, 2H), 1.26 (d, *J* = 4.7 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 132.0,

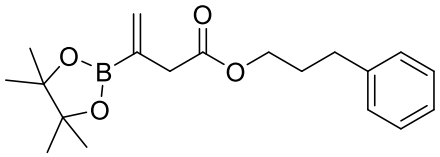
83.9, 51.8, 40.6, 24.8; ^{11}B NMR (160 MHz) δ 29.58; HRMS (ESI+): Calcd for $C_{11}H_{20}BO_4$ $[M+H]^+$: 227.1449, Found 227.1444; Calcd for $C_{11}H_{23}BNO_4$ $[M+ NH_4]^+$: 244.1715, Found: 244.1718; TLC: 1:9 / EtOAc:Hexanes, R_f 0.28.

ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enoate (2.26b):



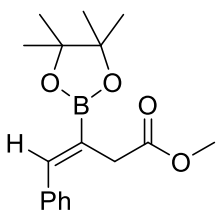
Compound **2.26b** was synthesized using General Procedure D. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (d, *J* = 2.9 Hz, 1H), 5.69 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.17 (s, 2H), 1.26 (s, 12H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 131.9, 83.9, 60.6, 40.8, 24.8, 14.4; ^{11}B NMR (160 MHz) δ 29.57; HRMS (ESI+): Calcd for $C_{12}H_{22}BO_4$ $[M+H]^+$: 241.1606, Found: 241.1600; Calcd for $C_{12}H_{21}BNaO_4$ $[M+Na]^+$: 263.1425, Found: 263.1435; TLC: 1:9 / EtOAc:Hexanes, R_f 0.35.

3-phenylpropyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enoate (2.26c):



Compound **2.26c** was synthesized using General Procedure D. Light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.21 – 7.17 (m, 3H), 5.92 (d, *J* = 2.9 Hz, 1H), 5.71 (s, 1H), 4.10 (t, *J* = 6.6 Hz, 2H), 3.19 (s, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 1.99 – 1.92 (m, 2H), 1.26 (s, 12H); ^{13}C NMR (126 MHz) δ 172.4, 141.4, 132.1, 128.6, 128.6, 126.1, 83.9, 63.9, 40.7, 32.3, 30.4, 24.9; ^{11}B NMR (160 MHz) δ 29.69; HRMS (ESI+): Calcd for $C_{19}H_{28}BO_4$ $[M+H]^+$: 331.2075, Found: 331.2083; Calcd for $C_{19}H_{27}BNaO_4$ $[M+Na]^+$: 353.1895, Found: 353.1917; TLC: 1:9 / EtOAc:Hexanes, R_f 0.34.

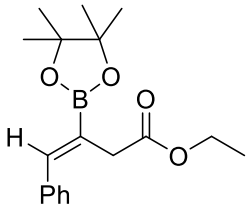
methyl (Z)-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enoate (2.26d):



Compound **2.26d** was synthesized using General Procedure D. Light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 6H), 3.68 (s, 3H), 3.41 (d,

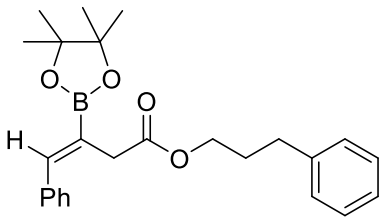
J = 1.3 Hz, 2H), 1.30 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 144.4, 137.0, 129.0, 128.4, 127.8, 83.9, 51.9, 35.1, 24.9; ^{11}B NMR (160 MHz) δ 30.19; HRMS (ESI+): Calcd for $C_{17}H_{24}BO_4$ $[M+H]^+$: 303.1762, Found: 303.1779; Calcd for $C_{17}H_{23}BNaO_4$ $[M+Na]^+$: 325.1582, Found: 325.1596; TLC: 1:9 / EtOAc:Hexanes, R_f 0.31.

ethyl (Z)-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enoate (2.26e):



Compound **2.26e** was synthesized using General Procedure D. Light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 6H), 4.14 (q, J = 7.1 Hz, 2H), 3.39 (d, J = 1.3 Hz, 2H), 1.31 (s, 12H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 144.3, 137.1, 129.1, 128.4, 127.7, 83.9, 60.7, 35.3, 24.9, 14.4; ^{11}B NMR (160 MHz) δ 30.20; HRMS (ESI+): Calcd for $C_{18}H_{26}BO_4$ $[M+H]^+$: 317.1924, Found: 317.1883; Calcd for $C_{18}H_{25}BNaO_4$ $[M+Na]^+$: 339.1738, Found: 339.1713; TLC: 1:9 / EtOAc:Hexanes, R_f 0.33.

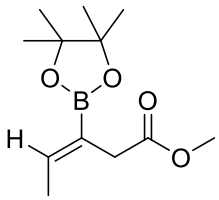
3-phenylpropyl (Z)-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enoate (2.26f):



Compound **2.26f** was synthesized using General Procedure D. Light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.14 (m, 11H), 4.11 (t, J = 6.5 Hz, 2H), 3.41 (s, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.00 – 1.90 (m, 2H), 1.30 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 144.5, 141.4, 137.1, 129.1, 128.6, 128.6, 128.4, 127.8, 126.1, 83.9, 64.0, 35.3, 32.3, 30.4, 24.9; ^{11}B NMR (160 MHz)

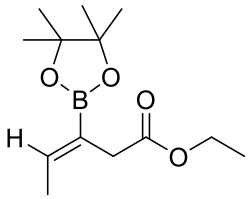
δ 30.19; HRMS (ESI+): Calcd for $C_{25}H_{32}BO_4$ $[M+H]^+$: 407.2388, Found: 407.2416; Calcd for $C_{25}H_{31}BKO_4$ $[M+K]^+$: 445.1947, Found: 445.1961; TLC: 1:9 / EtOAc:Hexanes, R_f 0.31.

methyl (Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-enoate (2.26g):



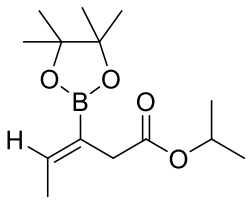
Compound **2.26g** was synthesized using General Procedure D. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (q, *J* = 6.8, 1H), 3.65 (s, 3H), 3.20 (s, 2H), 1.73 (d, *J* = 6.8 Hz, 3H), 1.25 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 143.2, 83.6, 51.8, 33.5, 24.8, 14.7; ^{11}B NMR (160 MHz) δ 30.12; HRMS (ESI+): Calcd for $C_{12}H_{22}BO_4$ [M+H]+: 241.1606, Found: 241.1618; Calcd for $C_{12}H_{21}BNaO_4$ [M+Na]+: 263.1425, Found: 263.1440; TLC: 1:9 / EtOAc:Hexanes, Rf 0.33.

ethyl (Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-enoate (2.26h):



Compound **2.26h** was synthesized using General Procedure D. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (q, *J* = 6.8 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.18 (s, 2H), 1.73 (t, *J* = 5.0 Hz, 3H), 1.25 – 1.22 (m, 15H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 143.2, 83.5, 60.5, 33.8, 24.9, 14.7, 14.4; ^{11}B NMR (160 MHz) δ 29.98; HRMS (ESI+): Calcd for $C_{13}H_{24}BO_4$ $[M+H]^+$: 255.1762, Found: 255.1753; Calcd for $C_{13}H_{23}BNaO_4$ $[M+Na]^+$: 277.1582, Found: 277.1589; TLC: 1:9 / EtOAc:Hexanes, R_f 0.34.

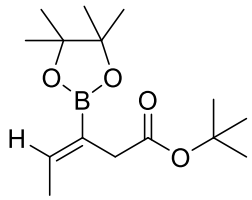
isopropyl (Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-enoate (2.26i):



Compound **2.26i** was synthesized using General Procedure D. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 – 6.51 (m, 1H), 4.96 (m, 1H), 3.13 (s, 2H), 1.73 (d, J = 6.8 Hz, 3H), 1.24 (s, 12H), 1.20 (d, *J* – 6.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 143.1, 83.5, 67.7, 34.1, 24.9, 22.0, 14.7; ^{11}B NMR (160

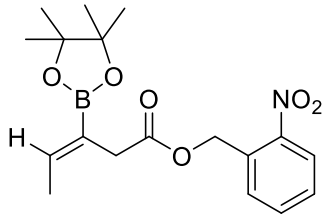
MHz) δ 30.01; HRMS (ESI+): Calcd for $C_{14}H_{26}BO_4$ $[M+H]^+$: 269.1919, Found: 269.1893; TLC: 1:9 / EtOAc:Hexanes, Rf 0.37.

tert-butyl (Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-enoate (2.26j):



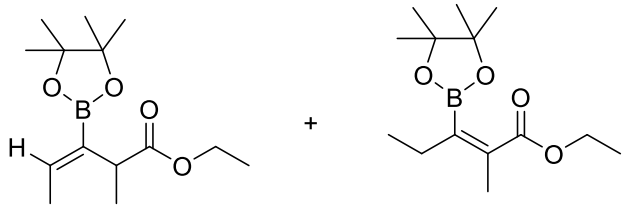
Compound **2.26j** was synthesized using General Procedure D. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 – 6.51 (m, 1H), 3.09 (s, 2H), 1.73 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 9H), 1.24 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 142.7, 83.4, 80.0, 34.9, 28.1, 24.8, 14.6; ^{11}B NMR (160 MHz) δ 30.05; HRMS (ESI+): Calcd for $C_{15}H_{28}BO_4$ $[M+H]^+$: 283.2075, Found: 283.2081; Calcd for $C_{15}H_{27}BNaO_4$ $[M+Na]^+$: 305.1895, Found: 305.1894; TLC: 1:9 / EtOAc:Hexanes, R_f 0.44.

2-nitrobenzyl (Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-enoate (2.26k):



Compound **2.26k** was synthesized using General Procedure D. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 3.9 Hz, 2H), 7.50 – 7.54 (m, 1H), 6.62 (q, *J* = 7.0 Hz, 1H), 5.53 (s, 2H), 3.32 (s, 2H), 1.77 (d, J = 6.8 Hz, 3H), 1.22 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 147.7, 144.0, 133.8, 128.7, 128.6, 125.1, 83.6, 62.9, 33.6, 24.9, 14.8; ^{11}B NMR(160 MHz) δ 29.88; HRMS (ESI+): Calcd for $C_{18}H_{25}BNO_6$ $[M+H]^+$: 362.1769, Found: 362.1746; Calcd for $C_{18}H_{24}BNNaO_6$ $[M+Na]^+$: 384.1589, Found: 384.1565; TLC: 1:4 / EtOAc:Hexanes, Rf 0.38.

ethyl (Z)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-enoate (2.26l):

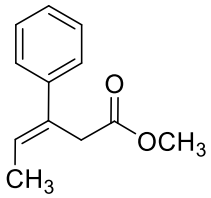


Compound **2.26l** was synthesized using General Procedure D. Colorless oil; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 6.45 (q, *J* = 6.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 0.5H), 4.17 – 4.04 (m, 2H), 3.47 (q, *J* = 7.1 Hz, 1H), 2.29 – 2.21 (m, 0.5H), 1.80 (s, 0.75H), 1.74 (d, *J* = 6.8 Hz, 3H), 1.34 (s, 3H), 1.30– 1.19 (m, 22H), 1.05 (t, *J* = 7.7 Hz, 0.75H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 171.1, 140.6, 131.7, 83.3, 83.2, 68.1, 61.6, 60.5, 38.9, 25.8, 25.1, 24.8, 16.6, 14.4, 14.3, 12.4, 11.8; ^{11}B NMR (160 MHz) δ 30.05; HRMS (ESI+): Calcd for $C_{14}H_{26}BO_4$ $[M+H]^+$: 269.1919, Found: 269.1924; Calcd for $C_{14}H_{25}BNaO_4$ $[M+Na]^+$: 291.1738, Found: 291.1737; TLC: 1:9 / EtOAc:Hexanes, Rf 0.34.

Application of the β-borylated product:

methyl (E)-3-phenylpent-3-enoate (2.37):



$PdCl_2(PPh_3)_2$ (4 mg, 0.05 equiv.) and K_2CO_3 (28 mg, 2 equiv.) were added to a 10 mL, 2-neck, round-bottomed flask fitted with a reflux condenser and purged several times with vacuum and nitrogen. DMF (2 mL) was added. Iodobenzene (22 µl, 2 equiv.) followed by **2.26g** (24 mg, 1 equiv.) dissolved in DMF (1 mL) was added, washing with additional DMF, and the reaction was heated to 90 ℃ and stirred for 18 hr. The crude mixture was diluted with diethyl ether (10 mL) and DMF was removed by washing with saturated LiBr (3 × 5 mL). The organic layer was dried over sodium sulfate, filtered, concentrated by rotary evaporation, and purified by flash chromatography on silica gel to afford the title compound as a light yellow oil (19 mg, 100%). Spectral data are consistent with the literature.[10]

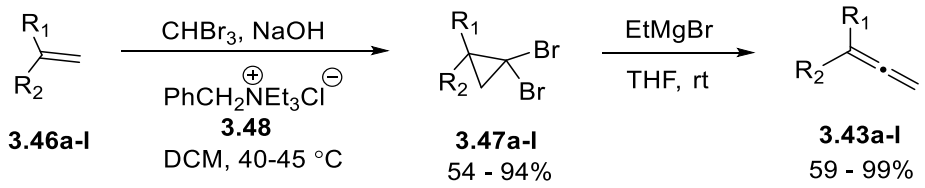
5.4 Synthetic procedures and characterization of products for Chapter 3

Preparation of (pin)B-B(dan):

PDIPA diboron (0.56 g, 2.08 mmol)[11,12] and 1,8-diaminonaphthalene (0.299 g, 1.89 mmol) were added in a 25 mL round bottom flask. The flask was purged with nitrogen. Acetic acid (6.50 ml, 114 mmol) was added later and the reaction solution was stirred at room temperature for 3 h. The mixture was concentrated in vacuo, and then diluted with EtOAc. The organic mixture was washed with water several times, dried over sodium sulfate, filtered, concentrated in vacuo, and purified by flash column chromatography (hexanes/EtOAc = 9:1) to yield (pin)B-B(dan) (0.383 g, 69%) as a white solid. Spectral data are consistent with the literature.[13]

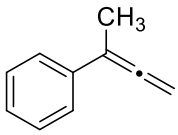
General procedure for synthesis of allenes 3.43a-l (General Procedure A):

The following procedure was a slight modification from the literature.[14] Alkene **3.46** (1 equiv.), bromoform (1.5 equiv.), and triethylbenzylammonium chloride (0.2 equiv.) were added to a round-bottomed flask and purged with nitrogen. DCM was added later followed by a solution of sodium hydroxide in water (1g/mL, 40 equiv.). The contents were stirred vigorously at 40 – 45 ℃ overnight. After the reaction mixture was cooled to r.t., water was added to quench the reaction. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over sodium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (hexanes/EtOAc = 7:3) to afford the 1,1-dibromocyclopropanes **3.47** (54 - 97%). To a stirred solution of 1,1-dibromocyclopropanes **3.47** (1 equiv.) in dry THF was added ethyl magnesium bromide (0.9M in THF, 1.7 equiv.) under nitrogen. The contents were stirred at r.t. for 0.5 h. 6M HCl was added to quench the reaction. The resulting mixture was extracted with EtOAc. The organic layer was washed with water, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by column chromatography to yield the allenes **3.43a-l** (59 - 99%).



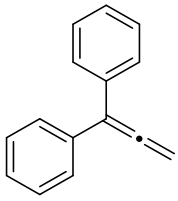
Characterization of allenes 3.43a-l:

buta-2,3-dien-2-ylbenzene (3.43a):



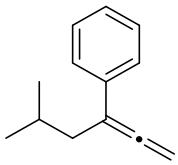
Compound **3.43a** was synthesized using General Procedure A. Spectral data are consistent with the literature.[15]

propa-1,2-diene-1,1-diyldibenzene (3.43b):



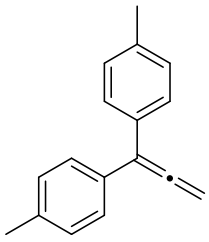
Compound **3.43b** was synthesized using General Procedure A. Spectral data are consistent with the literature.[16]

(5-methylhexa-1,2-dien-3-yl)benzene (3.43c):



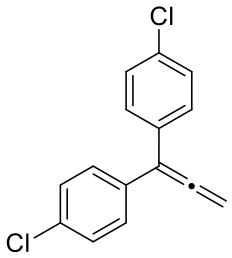
Compound **3.43c** was synthesized using General Procedure A. Clear liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.33 – 7.27 (m, 2H), 7.20 – 7.15 (m, 1H), 5.02 (t, *J* = 2.8 Hz, 2H), 2.30 (dt, *J* = 7.0, 2.8 Hz, 2H), 1.91 – 1.79 (m, 1H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 136.7, 128.5, 126.6, 126.3, 104.0, 77.3, 39.5, 27.0, 22.8; TLC: 100% Hexanes, Rf 0.57.

4,4'-(propa-1,2-diene-1,1-diyl)bis(methylbenzene) (3.43d):



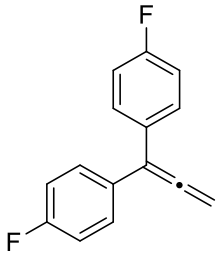
Compound **3.43d** was synthesized using General Procedure A. Spectral data are consistent with the literature.[14]

4,4'-(propa-1,2-diene-1,1-diyl)bis(chlorobenzene) (3.43e):



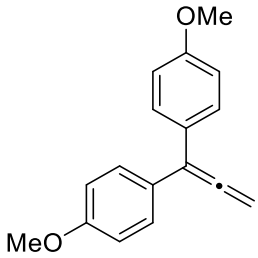
Compound **3.43e** was synthesized using General Procedure A. Spectral data are consistent with the literature.[14]

4,4'-(propa-1,2-diene-1,1-diyl)bis(fluorobenzene) (3.43f):



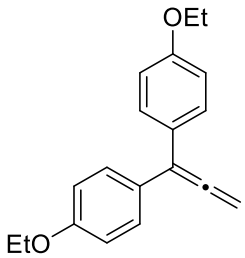
Compound **3.43f** was synthesized using General Procedure A. White solid; mp 68 – 69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 4H), 7.07 – 7.01 (m, 4H), 5.26 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 163.3, 160.9, 132.0, 132.0, 129.9, 129.8, 115.5, 115.3, 107.5, 78.4; HRMS (APCI+): Calcd for $C_{15}H_{11}F_2$ $[M+H]^+$: 229.0823, Found 229.0823; TLC: 100% Hexanes, Rf 0.45.

4,4'-(propa-1,2-diene-1,1-diyl)bis(methoxybenzene) (3.43g):



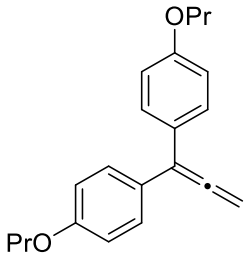
Compound **3.43g** was synthesized using General Procedure A. Spectral data are consistent with the literature.[14]

4,4'-(propa-1,2-diene-1,1-diyl)bis(ethoxybenzene) (3.43h):



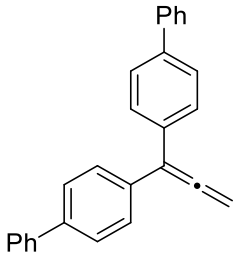
Compound **3.43h** was synthesized using General Procedure A. Slightly yellow solid; mp 71 – 72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 4H), 6.90 – 6.83 (m, 4H), 5.21 (s, 2H), 4.05 (q, *J* = 7.0 Hz, 4H), 1.42 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6, 158.4, 129.6, 128.7, 114.5, 108.4, 77.8, 63.6, 15.0; HRMS (ESI+): Calcd for $C_{19}H_{21}O_2$ $[M+H]^+$: 281.1536, Found 281.1548; TLC: 19:1 / Hexanes:EtOAc, Rf 0.34.

4,4'-(propa-1,2-diene-1,1-diyl)bis(propoxybenzene) (3.43i):



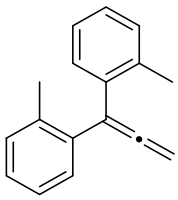
Compound **3.43i** was synthesized using General Procedure A. Yellow solid; mp 59 – 61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.33 – 7.23 (m, 4H), 6.97 – 6.83 (m, 4H), 5.22 (s, 2H), 3.95 (t, *J* = 6.6 Hz, 4H), 1.89 – 1.78 (m, 4H), 1.06 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6, 158.6, 129.6, 128.7, 114.6, 108.4, 77.8, 69.7, 22.8, 10.7; HRMS (ESI+): Calcd for $C_{21}H_{25}O_2$ $[M+H]^+$: 309.1849, Found 309.1862; TLC: 19:1 / Hexanes:EtOAc, Rf 0.45.

4,4''-(propa-1,2-diene-1,1-diyl)di-1,1'-biphenyl (3.43j):



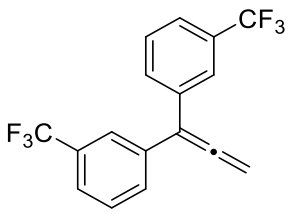
Compound **3.43j** was synthesized using General Procedure A. White solid; mp 150 – 151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.65 – 7.58 (m, 8H), 7.50 – 7.42 (m, 8H), 7.38 – 7.32 (m, 2H), 5.34 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.2, 140.9, 140.3, 135.3, 129.0, 128.9, 127.5, 127.3, 127.2, 108.8, 78.5; HRMS (ESI+): Calcd for $C_{27}H_{21}$ $[M+H]^+$: 345.1638, Found 345.1643; TLC: 4:1 / Hexanes:DCM, Rf 0.35.

2,2'-(propa-1,2-diene-1,1-diyl)bis(methylbenzene) (3.43k):



Compound **3.43k** was synthesized using General Procedure A. White solid; mp 75 – 76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.22 – 7.06 (m, 8H), 5.03 (s, 2H), 2.26 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3, 137.1, 136.6, 130.9, 129.6, 127.3, 126.1, 106.4, 76.1, 20.8; TLC: 100% Hexanes, Rf 0.43.

3,3'-(propa-1,2-diene-1,1-diyl)bis((trifluoromethyl)benzene) (3.43l):



Compound **3.43l** was synthesized using General Procedure A. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.63 – 7.46 (m, 8H), 5.40 (s, 2H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ 210.2, 136.7, 131.6 (d, *J* = 1.2 Hz), 131.2, 129.2, 125.5, 125.2 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 3.8 Hz), 122.8, 79.8; TLC: 100% Hexanes, Rf 0.45.

General procedure for optimization of the catalyzed diboration of phenylallene (General Procedure B; Table 3.1):

Method 1 (entries 1-3). Pt catalyst was added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min. (Dan)B-B(pin) (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material is consumed completely. The resultant solution was analyzed by GC to determine the isomeric ratio. The contents were then concentrated in vacuo and purified by flash chromatography on silica gel.

Method 2 (entries 4-13). $Pt(dba)_3$ (4.8 mg, 5.35 μmol) and ligand (8.16 μmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min, producing a purple mixture. (Dan)B-B(pin) (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material is consumed completely. The resultant solution was analyzed by GC to determine the isomeric ratio. The contents were then concentrated in vacuo and purified by flash chromatography on silica gel.

Method 3 (entries 14-15). $[IrCl(cod)]_2$ (2.3 mg, 3.40 μmol) and ligand (0 or 8.16 μmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min. (Dan)B-B(pin) (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material is consumed completely. The resultant solution was

analyzed by GC to determine the isomeric ratio. The contents were then concentrated in vacuo and purified by flash chromatography on silica gel.

Method 4 (entries 16-17). $[RhCl(cod)]_2$ (1.7 mg, 3.40 μmol) and ligand (0 or 8.16 μmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min. (Dan)B-B(pin) (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material is consumed completely. The resultant solution was analyzed by GC to determine the isomeric ratio. The contents were then concentrated in vacuo and purified by flash chromatography on silica gel.

Method 5 (entry 18). $Pd_2(dba)_3$ (3.1 mg, 3.40 μmol) was added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min. (Dan)B-B(pin) (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material is consumed completely. The resultant solution was analyzed by GC to determine the isomeric ratio. The contents were then concentrated in vacuo and purified by flash chromatography on silica gel.

General procedure for ligand screening of disubstituted allenes (General Procedure C; Table 3.2):

$Pt(dba)_3$ (4.8 mg, 5.35 μmol) and SPhos (3.4 mg, 8.16 μmol) or $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ (5.5 mg, 8.16 μmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min, producing a purple mixture. (Dan)B-B(pin) (40 mg, 0.136 mmol) and disubstituted allene (0.163 mmol) were added sequentially. The contents were heated to 80 °C and followed by TLC until the starting material is consumed completely. The

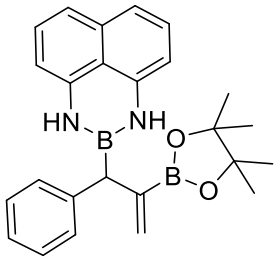
resultant solution was analyzed by GC or ^{1}H NMR to determine the isomeric ratio. The reaction mixture was concentrated in vacuo and purified by flash column chromatography to yield the diboration product.

General procedure for diboration of disubstituted allenes with PDAN diboron (General Procedure D; Table 3.3):

$Pt(dba)_3$ (4.8 mg, 5.35 μmol) and SPhos (3.4 mg, 8.16 μmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min, producing a purple mixture. (Dan)B-B(pin) (40 mg, 0.136 mmol) and disubstituted allene (0.163 mmol) were added sequentially. The contents were heated to 80 °C and followed by TLC until the starting material is consumed completely. The resultant solution was analyzed by GC or ^{1}H NMR to determine the isomeric ratio. The reaction mixture was concentrated in vacuo and purified by flash column chromatography to yield the diboration product.

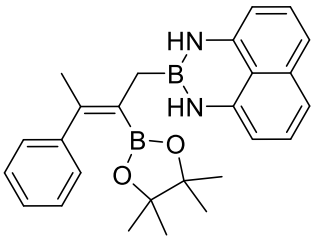
Characterization of diboration products 3.34, 3.44a-l:

2-(1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.34):



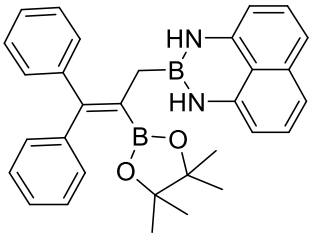
Compound **3.34** was synthesized using General Procedure B. White solid; mp 172 – 174 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.08 (m, 5H), 7.05 – 6.97 (m, 2H), 6.96 – 6.89 (m, 2H), 6.18 (d, *J* = 7.2 Hz, 2H), 5.85 (d, *J* = 2.9 Hz, 1H), 5.81 (s, 2H), 5.47 (d, *J* = 2.6 Hz, 1H), 3.42 (s, 1H), 1.15 (s, 6H), 1.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 141.4, 136.4, 129.8, 129.7, 128.6, 127.7, 125.8, 119.8, 117.5, 105.8, 84.0, 25.0, 24.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.60; HRMS (ESI+): Calcd for $C_{25}H_{29}B_2N_2O_2$ $[M+H]^+$: 411.2410, Found 411.2425; TLC: 19:1 / Hexanes:EtOAc, Rf 0.35.

(E)-2-(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-en-1-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44a):



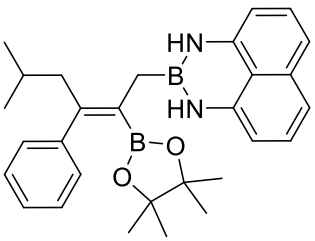
Compound **3.44a** was synthesized using General Procedure D. White solid; mp 139 – 140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 1H), 7.26 – 7.20 (m, 4H), 7.12 – 7.07 (m, 2H), 7.03 – 6.97 (m, 2H), 6.30 (d, *J* = 7.3 Hz, 2H), 6.05 (s, 2H), 2.06 (s, 3H), 1.98 (s, 2H), 1.11 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 145.9, 141.6, 136.5, 128.0, 127.9, 127.7, 126.8, 119.8, 117.4, 105.6, 83.5, 24.7, 20.4; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.00; HRMS (ESI+): Calcd for $C_{26}H_{31}B_2N_2O_2$ $[M+H]^+$: 425.2566, Found 425.2572; TLC: 9:1 / Hexanes:EtOAc, Rf 0.4.

2-(3,3-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44b):



Compound **3.44b** was synthesized using General Procedure D. White solid; mp 183 – 185 °C; ^{1}H NMR (500 MHz, CDCl3) δ 7.34 – 7.28 (m, 2H), 7.26 – 7.18 (m, 6H), 7.17 – 7.06 (m, 4H), 7.02 – 6.97 (m, 2H), 6.26 (d, J = 7.1 Hz, 2H), 5.90 (s, 2H), 1.95 (s, 2H), 1.18 (s, 12H); ^{13}C NMR (126 MHz, CDCl3) δ 150.6, 144.5, 142.3, 141.5, 136.5, 129.6, 129.4, 128.3, 127.9, 127.7, 127.2, 127.0, 119.8, 117.4, 105.6, 83.9, 24.8; ^{11}B NMR (128 MHz, CDCl3) δ 35.51; HRMS (ESI+): Calcd for $C_{31}H_{33}B_2N_2O_2$ [M+H]+: 487.2723, Found 487.2734; TLC: 9:1 / Hexanes:EtOAc, Rf 0.38.

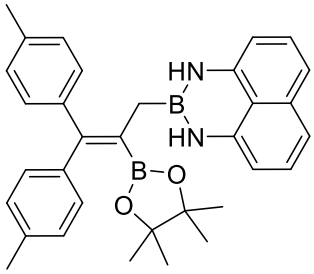
(E)-2-(5-methyl-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-2-en-1-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44c):



Compound **3.44c** was synthesized using General Procedure D. White

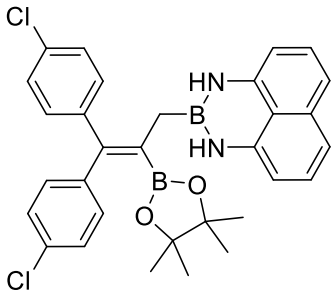
solid; mp 147 - 149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 1H), 7.26 – 7.19 (m, 4H), 7.12 – 7.07 (m, 2H), 7.01 – 6.95 (m, 2H), 6.31 (dd, *J* = 7.3, 1.0 Hz, 2H), 6.06 (s, 2H), 2.36 (d, *J* = 7.3 Hz, 2H), 2.02 (s, 2H), 1.49 (m, 1H), 1.06 (s, 12H), 0.82 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 145.3, 141.6, 136.5, 128.6, 127.9, 127.7, 126.7, 119.8, 117.3, 105.6, 83.5, 42.2, 27.0, 24.7, 22.7; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.15; HRMS (ESI+): Calcd for $C_{29}H_{37}B_2N_2O_2$ $[M+H]^+$: 467.3036, Found 467.3064; Calcd for $C_{29}H_{36}B_2N_2NaO_2$ $[M+Na]^+$: 489.2855, Found 489.2875; TLC: 19:1 / Hexanes:EtOAc, Rf 0.29.

2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3-di-p-tolylallyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44d):



Compound **3.44d** was synthesized using General Procedure D. White solid; mp 215 – 217 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 6.97 (m, 12H), 6.26 (d, *J* = 7.3 Hz, 2H), 5.90 (s, 2H), 2.33 (d, *J* = 8.8 Hz, 4H), 1.95 (s, 2H), 1.19 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 142.0, 141.7, 139.8, 136.7, 136.6, 136.5, 129.5, 129.3, 129.0, 128.5, 127.7, 119.9, 117.4, 105.6, 83.9, 24.9, 21.3, 21.3; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.21; HRMS (ESI+): Calcd for $C_{31}H_{31}B_2F_2N_2O_2$ $[M+H]^+$: 515.3036, Found 515.3060; TLC: 9:1 / Hexanes:EtOAc, Rf 0.35.

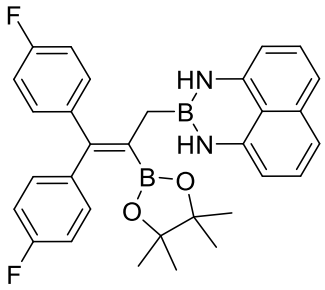
2-(3,3-bis(4-chlorophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44e):



Compound **3.44d** was synthesized using General Procedure D. White solid; mp 185 – 187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.31 – 7.27 (m, 2H), 7.25 – 7.20 (m, 2H), 7.14 – 6.99 (m, 8H), 6.27 (d, *J* = 7.2 Hz, 2H), 5.89 (s, 2H), 1.93 (s, 2H), 1.20 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 142.5, 141.3, 140.2, 136.4, 133.3, 133.1, 131.0, 130.7, 128.6, 128.1,

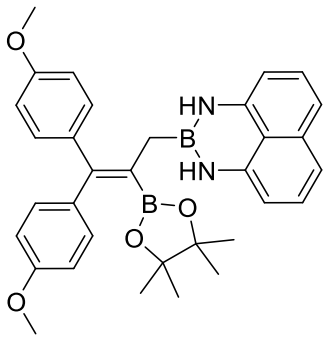
127.7, 119.8, 117.6, 105.7, 84.2, 24.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 35.69; HRMS (ESI+): Calcd for $C_{31}H_{31}B_2Cl_2N_2O_2$ $[M+H]^+$: 555.1943, Found 555.1958; TLC: 9:1 / Hexanes:EtOAc, Rf 0.30.

2-(3,3-bis(4-fluorophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44f):



Compound **3.44f** was synthesized using General Procedure D. White solid; mp 190 – 191.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.14 (m, 2H), 7.13 – 7.06 (m, 4H), 7.04 – 6.91 (m, 6H), 6.27 (d, *J* = 7.3 Hz, 2H), 5.90 (s, 2H), 1.93 (s, 2H), 1.19 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (d, *J* = 42.0 Hz), 160.9 (d, *J* = 42.2 Hz), 148.4, 141.3, 140.5 (d, *J* = 3.3 Hz), 138.0 (d, *J* = 3.3 Hz), 136.5, 131.2 (d, *J* = 7.9 Hz), 131.0 (d, *J* = 8.0 Hz), 127.7, 119.8, 117.6, 115.3 (d, *J* = 21.3 Hz), 114.8 (d, *J* = 21.3 Hz), 105.7, 84.1, 24.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.01; HRMS (ESI+): Calcd for $C_{31}H_{31}B_2F_2N_2O_2$ $[M+H]^+$: 523.2534, Found 523.2538; TLC: 9:1 / Hexanes:EtOAc, Rf 0.30.

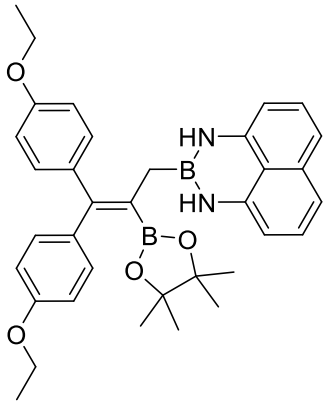
2-(3,3-bis(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44g):



Compound **3.44g** was synthesized using General Procedure D. White solid; mp 181 – 182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.03 (m, 6H), 7.02 – 6.98 (m, 2H), 6.87 – 6.82 (m, 2H), 6.81 – 6.77 (m, 2H), 6.27 (d, *J* = 8.2 Hz, 2H), 5.92 (s, 2H), 3.80 (s, 6H), 1.97 (s, 2H), 1.21 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 158.6, 149.9, 141.6, 137.6, 136.5, 135.0, 130.9, 130.6, 127.7, 119.8, 117.4, 113.6, 113.3, 105.6, 83.8, 55.4, 55.3, 24.9; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.40; HRMS (ESI+): Calcd for $C_{33}H_{37}B_2N_2O_4$ $[M+H]^+$:

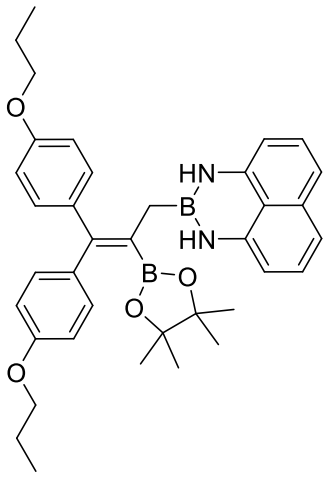
547.2934, Found 547.2963; Calcd for $C_{33}H_{36}B_2N_2NaO_4$ $[M+Na]^+$: 569.2753, Found 569.2744; TLC: 9:1 / Hexanes:EtOAc, Rf 0.20.

2-(3,3-bis(4-ethoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.29h):



Compound **3.44h** was synthesized using General Procedure D. White solid; mp 163.5 – 165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.07 (m, 4H), 7.04 – 6.97 (m, 4H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.27 (d, *J* = 7.3 Hz, 2H), 5.91 (s, 2H), 4.01 (q, *J* = 7.0 Hz, 4H), 1.96 (s, 2H), 1.40 (m, 6H), 1.20 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 157.9, 150.0, 141.6, 137.5, 136.5, 134.8, 130.9, 130.6, 127.7, 119.8, 117.3, 114.0, 113.9, 105.6, 83.8, 63.6, 63.5, 24.9, 15.0, 15.0; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.19; HRMS (ESI+): Calcd for $C_{35}H_{41}B_2N_2O_4$ $[M+H]^+$: 575.3247, Found 575.3289; Calcd for $C_{35}H_{40}B_2N_2NaO_4$ $[M+Na]^+$: 597.3066, Found 597.3099; TLC: 9:1 / Hexanes:EtOAc, Rf 0.25.

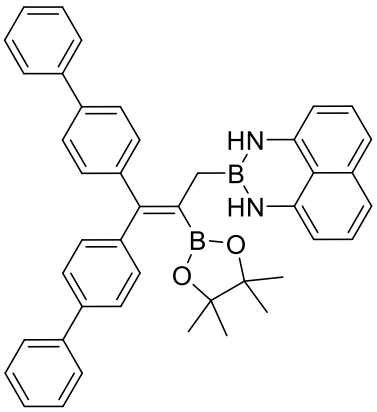
2-(3,3-bis(4-propoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44i):



Compound **3.44i** was synthesized using General Procedure D. White solid; mp 179.5 - 181°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 6.97 (m, 8H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.27 (d, *J* = 7.3 Hz, 2H), 5.91 (s, 2H), 3.90 (t, *J* = 6.6 Hz, 4H), 1.96 (s, 2H), 1.80 (m, 4H), 1.20 (s, 12H), 1.03 (td, *J* = 7.4, 2.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 158.1, 150.1, 141.6, 137.5, 136.5, 134.8,

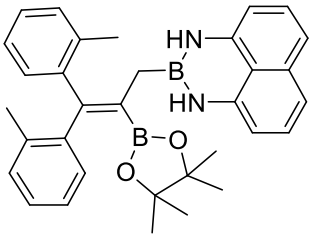
130.9, 130.6, 127.7, 119.8, 117.3, 114.1, 113.9, 105.6, 83.8, 69.7, 69.6, 24.9, 22.8, 22.8, 10.7, 10.7; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.62; HRMS (ESI+): Calcd for $C_{37}H_{45}B_2N_2O_4$ $[M+H]^+$: 603.3560, Found 603.3581; Calcd for $C_{37}H_{44}B_2N_2NaO_4$ $[M+Na]^+$: 625.3379, Found 625.3391; TLC: 9:1 / Hexanes:EtOAc, Rf 0.32.

2-(3,3-di([1,1'-biphenyl]-4-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44j):



Compound **3.44j** was synthesized using General Procedure D. White solid; mp 186 - 187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 6H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 4H), 7.37 – 7.32 (m, 4H), 7.27 (d, *J* = 7.7 Hz, 2H), 7.11 (t, *J* = 7.8 Hz, 2H), 7.02 (m, 2H), 6.29 (d, *J* = 7.3 Hz, 2H), 5.96 (s, 2H), 2.05 (s, 2H), 1.23 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 143.5, 141.5, 141.2, 141.1, 140.9, 140.1, 139.8, 136.5, 130.1, 129.9, 128.9, 128.9, 127.7, 127.4, 127.3, 127.2, 127.1, 127.0, 126.7, 119.8, 117.5, 105.7, 84.0, 24.9; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.73; HRMS (ESI+): Calcd for $C_{43}H_{41}B_2N_2O_4$ $[M+H]^+$: 639.3349, Found 639.3392; TLC: 9:1 / Hexanes:EtOAc, Rf 0.24.

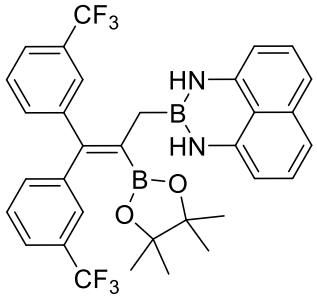
2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3-di-o-tolylallyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44k):



Compound **3.44k** was synthesized using General Procedure D. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 1H), 7.18 – 7.03 (m, 9H), 6.98 (d, *J* = 9.1 Hz, 2H), 6.21 (d, *J* = 8.2 Hz, 2H), 5.92 (s, 2H), 2.23 (d, *J* = 5.3 Hz, 6H), 1.81 (s, 2H), 1.07 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 143.5, 141.6, 140.7, 136.5, 136.5, 136.1, 131.3, 130.5, 130.4, 130.2,

127.7, 127.0, 126.9, 125.4, 125.1, 119.7, 117.2, 105.5, 83.6, 24.7, 21.1, 20.7; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.87; HRMS (ESI+): Calcd for $C_{33}H_{37}B_2N_2O_2$ $[M+H]^+$: 515.3036, Found 515.3067; TLC: 9:1 / Hexanes:EtOAc, Rf 0.38.

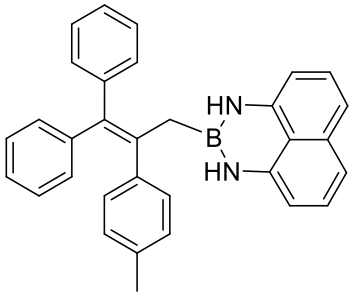
2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3-bis(3-(trifluoromethyl)phenyl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.44l):



Compound **3.44l** was synthesized using General Procedure D. White solid; mp 182.5 - 184.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.30 (m, 8H), 7.16 – 7.05 (m, 2H), 7.05 – 6.99 (m, 2H), 6.28 (d, *J* = 7.3 Hz, 2H), 5.94 (s, 2H), 1.93 (s, 2H), 1.18 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 144.2, 142.4, 141.2, 136.5, 132.9 – 132.8 (m), 132.8 (d, *J* = 1.1 Hz), 131.1, 130.8, 130.6, 130.2, 129.1, 128.6, 127.7, 126.3 – 125.9 (m), 125.6 (d, *J* = 14.1 Hz), 124.4 – 124.0 (m), 122.9 (d, *J* = 14.4 Hz), 119.8, 117.7, 105.8, 84.3, 24.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.76; HRMS (ESI+): Calcd for $C_{33}H_{31}B_2F_6N_2O_2$ $[M+H]^+$: 623.2470, Found 623.2501; Calcd for $C_{33}H_{30}B_2F_6N_2NaO_2$ $[M+Na]^+$: 645.2290, Found 645.2273; TLC: 9:1 / Hexanes:EtOAc, Rf 0.35.

<u>Procedures for applications of diboration products and Characterization of the compounds:</u>

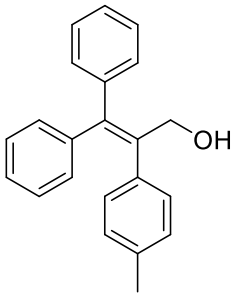
2-(3,3-diphenyl-2-(p-tolyl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.49):



Tetrakis(triphenylphosphine) palladium(0) (3.6 mg, 3.09 μmol), cesium carbonate (60.3 mg, 0.185 mmol), 1-bromo-4-methylbenzene (15.2 μl, 0.123 mmol) and diboration product **3.44b** (30 mg, 0.062 mmol) were placed in a flask and purged with nitrogen. Then toluene (1 mL) was added, and the mixture was stirred at 80 °C overnight. The reaction mixture was concentrated in vacuo and purified by flash column chromatography

(hexanes/EtOAc = 19:1) to yield the title compound (22.2 mg, 80%) as a white solid. mp 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.29 – 7.23 (m, 4H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.08 – 6.91 (m, 10H), 6.14 (d, *J* = 8.1 Hz, 2H), 5.42 (s, 2H), 2.29 (s, 3H), 2.23 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 143.2, 141.2, 140.9, 138.5, 137.5, 136.5, 136.4, 131.1, 130.0, 129.5, 129.2, 128.5, 127.7, 127.6, 126.8, 125.9, 119.7, 117.6, 105.7, 21.3; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.17; HRMS (ESI+): Calcd for $C_{32}H_{28}BN_2$ $[M+H]^+$: 451.234, Found 451.2322; TLC: 19:1 / Hexanes:EtOAc, Rf 0.31.

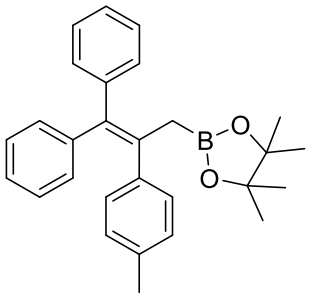
3,3-diphenyl-2-(p-tolyl)prop-2-en-1-ol (3.50):



To a solution of cross-coupling product **3.49** (40 mg, 0.089 mmol) in THF (0.8 mL) was added 6 M HCl (89 µl, 0.533 mmol). The mixture was stirred at r.t. for a few hours until the coupling product was reacted completely by TLC. Water was added and the resulting mixture was extracted with diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude mixture was dissolved in MeOH (1.4 mL) and THF (1.4 mL), and then hydrogen peroxide 35% (272 µl, 8.87 mmol) was added in an ice bath. The contents were stirred in ice bath for 30 min and then at room temperature overnight. Aqueous $Na_2S_2O_3$ was added to the reaction mixture, and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, filtered, concentrated, and purified by flash chromatography (hexanes/EtOAc = 9:1) to yield the title compound (17.3 mg, 65%) as a white solid. mp 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 7.13 – 6.99 (m, 7H), 6.96 – 6.91 (m, 2H), 4.47 (d, *J* = 6.1 Hz, 2H), 2.28 (s, 3H), 1.47 – 1.42 (t, *J* = 6.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 142.5, 138.6, 137.2, 136.7, 130.8, 129.9, 129.8, 129.2, 128.4, 127.7, 127.4, 126.5, 65.2,

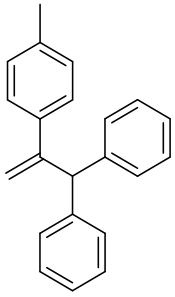
21.3; HRMS (ESI+): Calcd for $C_{22}H_{19}$ [M-OH]$^+$: 283.1481, Found 283.1475; TLC: 9:1 / Hexanes:EtOAc, Rf 0.25.

2-(3,3-diphenyl-2-(p-tolyl)allyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.52):



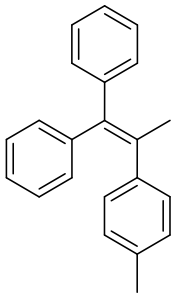
The following procedure was a slight modification from the literature.[17] The cross-coupling product **3.49** (42 mg, 0.093 mmol) was dissolved in THF (1 mL), and then 2M sulfuric acid (0.28 mL, 0.56 mmol) and pinacol (55.1 mg, 0.466 mmol) were added sequentially. The contents were stirred at r.t. for 24 h. Water was added and the mixture was extracted with diethyl ether. The organic layer was dried over magnesium sulfate, filtered, concentrated in vacuo and purified by flash chromatography (hexanes/EtOAc = 19:1) to yield the title compound (26.8 mg, 70%) as a white solid; mp 107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 4H), 7.25 – 7.20 (m, 1H), 7.06 – 6.97 (m, 5H), 6.95 – 6.90 (m, 4H), 2.24 (s, 3H), 2.14 (s, 2H), 1.10 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2, 143.6, 141.1, 137.8, 137.3, 135.5, 131.1, 130.2, 129.6, 128.4, 128.2, 127.4, 126.5, 125.5, 83.3, 24.8, 21.3; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.40; HRMS (ESI+): Calcd for $C_{28}H_{32}BO_2$ [M+H]$^+$: 411.2490, Found 411.2493; TLC: 19:1 / Hexanes:EtOAc, Rf 0.34.

(2-(p-tolyl)prop-2-ene-1,1-diyl)dibenzene (3.55):



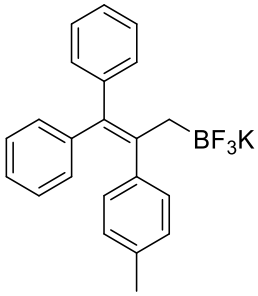
Cesium carbonate (42.9 mg, 0.132 mmol) and compound **3.52** (18 mg, 0.044 mmol) were placed in a flask and purged with nitrogen. Toluene (0.5 mL) was added, and the reaction mixture was stirred at 80 ℃ for 3 h. The crude mixture was concentrated in vacuo and purified by flash chromatography (100% hexane) to yield the title compound (12.1 mg, 97%). Spectral data are consistent with the literature.[18]

(2-(p-tolyl)prop-1-ene-1,1-diyl)dibenzene (3.56):



O-Methylhydroxylamine solution[19] (1.4 mL, 0.132 mmol, 0.094 M in THF) was added to a flame-dried flask, and the mixture was cooled to -78 ℃. A solution of *n*-butyl lithium in hexanes (0.012 mL, 0.132 mmol, 2.5 M) was added dropwise and the reaction was stirred at -78 ℃ for 30 min. Compound **3.52** (18 mg, 0.044 mmol) in THF (0.5 mL) solution was added dropwise to the deprotonated O-methylhydroxylamine solution. The reaction mixture was warmed to r.t. and heated to 60 ℃ for 10 h. Water was added and the mixture was extracted with EtOAc. The organic layer was dried over sodium sulfate, filtered, concentrated and purified by flash column chromatography (100% hexane) to yield the title compound (12 mg, 97%). Spectral data are consistent with the literature.[20]

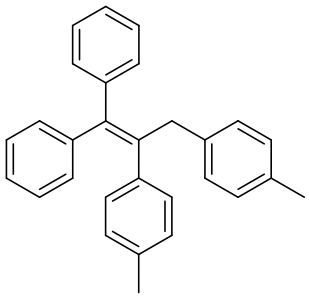
Potassium (3,3-diphenyl-2-(p-tolyl)allyl)trifluoroborate (3.57):



The following procedure was a slight modification from the literature.[17] Compound **3.52** (48.4 mg, 0.118 mmol) was dissolved in acetonitrile (1 mL), and then saturated aqueous KHF_2 (4.5 M, 105 µl, 0.472 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 3 h. The solvent was removed in vacuo, and the residual solid was dried under high vacuum overnight. The resulting mixture was then extracted with hot acetonitrile, filtered, and concentrated in vacuo. Diethyl ether was added to the crude mixture, and it formed a suspension of white solid in the solution. The white solid was filtered off, washed thoroughly with diethyl ether and dried under vacuum (27.4 mg, 60%). mp > 280 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.51 – 7.47 (m, 2H), 7.22 – 7.17 (m, 2H), 7.12 – 7.07 (m, 1H), 7.06 – 7.01 (m, 2H), 6.94 – 6.89 (m, 2H), 6.88 – 6.77 (m, 5H), 2.16 (s, 3H), 1.71 – 1.65 (m, 2H); ^{13}C NMR (126 MHz, acetone-d_6) δ146.7, 146.5, 146.2, 144.8, 134.3, 134.0, 132.3, 131.7, 130.7, 128.3, 128.0, 127.7, 125.9, 125.1, 21.1; ^{11}B NMR (128

MHz, acetone-d_6) δ 0.16; ^{19}F NMR (376 MHz, acetone-d_6) δ -135.65; HRMS (ESI-): Calcd for $C_{22}H_{19}BF_3$ [M-K$^+$]: 351.1537, Found 351.1549.

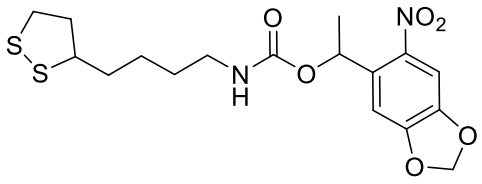
4,4'-(3,3-diphenylprop-2-ene-1,2-diyl)bis(methylbenzene) (3.58):



The following procedure was a slight modification from the literature.[21] $Pd_2(dba)_3$ (3.57 mg, 3.89 μmol), sodium tert-butoxide (28.1 mg, 0.292 mmol), RuPhos (3.63 mg, 7.79 μmol) and trifluoroborate **3.57** (38 mg, 0.097 mmol) were placed in a flask and purged with nitrogen. Then toluene (1 mL), water (0.1 mL), and 1-bromo-4-methylbenzene (24 μl, 0.195 mmol) were added. The contents were stirred at 80 ℃ overnight. The reaction mixture was then concentrated in vacuo and purified by flash column chromatography (100% hexanes) to yield the title compound (8.4 mg, 23%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 4H), 7.25 – 7.22 (m, 1H), 7.07 – 6.93 (m, 11H), 6.89 – 6.84 (m, 2H), 3.84 (s, 2H), 2.27 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 143.3, 141.3, 139.2, 138.1, 137.3, 135.8, 135.2, 130.9, 129.9, 129.6, 129.0, 128.7, 128.6, 128.3, 127.6, 126.9, 126.0, 41.1, 21.3, 21.1; HRMS (EI+): Calcd for $C_{29}H_{26}$ [M]$^+$: 374, Found 374; TLC: 98:2 / Hexanes:EtOAc, Rf 0.41.

5.5 Synthetic procedures and characterization of products for Chapter 4

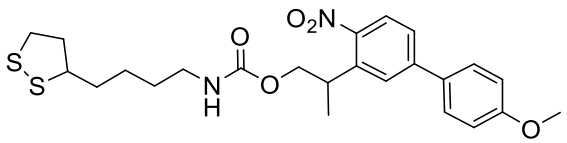
1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethyl (4-(1,2-dithiolan-3-yl)butyl)carbamate (4.1):



A 10 mL round-bottomed flask was charged with lipoic acid (500 mg, 2.432 mmol) and purged with nitrogen. Toluene (5 mL) was added to dissolve the solid. Triethylamine (0.507mL, 3.64 mmol) and diphenylphosphoryl azide (0.574 mL, 2.67 mmol) were added carefully, and the contents were stirred for 3 h at room temperature. 1-(6-

Nitrobenzo[d][1,3]dioxol-5-yl)ethan-1-ol (614 mg, 2.91 mmol) was added, and the contents were heated to 80 ℃ and stirred for 2 days. The solution was allowed to cool slightly and was then concentrated in vacuo. The compound was isolated by column chromatography on silica gel in 72% yield (707 mg) using RediSep Rf Gold media as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 6.99 (s, 1H), 6.24 (q, *J* = 6.4 Hz, 1H), 6.09 (s, 2H), 4.81 (t, *J* = 6.2 Hz, 1H), 3.57 – 3.48 (m, 1H), 3.28 – 2.97 (m, 4H), 2.47 – 2.39 (m, 1H), 1.97 – 1.79 (m, 1H), 1.74 – 1.33 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 152.4, 147.1, 141.5, 136.7, 105.7, 105.4, 103.1, 68.9, 56.5, 40.8, 40.3, 38.6, 34.5, 29.8, 26.4, 22.3; HRMS (ESI+): Calcd for $C_{17}H_{23}N_2O_6S_2$ $[M+H]^+$: 415.0998, Found 415.0994; Calcd for $C_{17}H_{22}N_2O_6S_2Na$ $[M+Na]^+$: 437.0817, Found 437.0814; TLC: 2:1 / Hexanes:EtOAc Rf = 0.32.

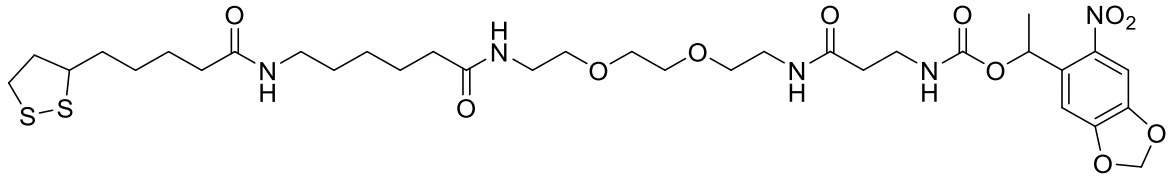
2-(4'-methoxy-4-nitro-[1,1'-biphenyl]-3-yl)propyl (4-(1,2-dithiolan-3-yl)butyl)carbamate (4.2):



A 10 mL round-bottomed flask was charged with lipoic acid (86 mg, 0.42 mmol) and purged with nitrogen. Toluene (2 mL) was added to dissolve the solid. Triethylamine (0.073 mL, 0.52 mmol) and diphenylphosphoryl azide (0.083 mL, 0.38 mmol) were added carefully, and the reaction mixture was stirred for 3 h at r.t. Compound **4.20** (100 mg, 0.35 mmol) was added later, and the mixture was heated to 80 ℃ and stirred for 3 days. The resulting solution was cooled to r.t. and then concentrated in vacuo. The crude mixture was purified by column chromatography (hexanes/EtOAc = 3:1) to yield the title compound (29 mg, 17%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 1H), 7.61 – 7.47 (m, 4H), 7.04 – 6.98 (m, 2H), 4.60 (s, 1H), 4.33 – 4.26 (m, 1H), 4.15 (t, *J* = 9.8 Hz, 1H), 3.87 – 3.81 (m, 4H), 3.55 – 3.50 (m, 1H), 3.20 – 3.04 (m, 4H), 2.50 – 2.38 (m, 1H), 1.92 – 1.86 (m, 1H), 1.71 – 1.32 (m, 9H); ^{13}C NMR (126 MHz,

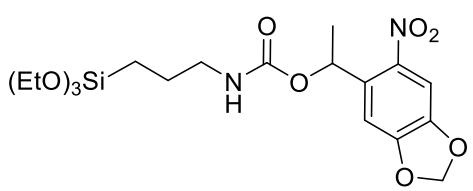
$CDCl_3$) δ 160.4, 156.3, 149.1, 145.5, 138.4, 131.5, 128.6, 126.0, 125.4, 125.1, 114.7, 68.8, 56.5, 55.6, 40.8, 40.4, 38.6, 34.6, 33.5, 29.8, 26.4 17.6; HRMS (ESI+): Calcd for $C_{24}H_{30}N_2O_5S_2Na$ $[M+Na]^+$: 513.1488, Found 513.1512; TLC: 2:1 / Hexanes:EtOAc Rf = 0.32.

1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethyl (25-(1,2-dithiolan-3-yl)-3,14,21-trioxo-7,10-dioxa-4,13,20-triazapentacosyl)carbamate (4.3):



Piperidine (91 µl, 0.92 mmol) was added to the solution of compound **4.26** (364.6 mg, 0.46 mmol) in DCM (5 mL). The contents were stirred at r.t. for 12 h. The solvent was removed in vacuo. The crude mixture was purified by column chromatography (DCM/MeOH = 4:1 with addition of 1% TEA) to obtain a yellow oil. The yellow oil and lipoic acid (142 mg, 0.69 mmol) were dissolved in DCM (4 mL). Then DCC (380 mg, 1.84 mmol) was added portion-wise. The contents were stirred for 12 h at r.t. The resulting mixture was cooled to 0 ℃, filtered, and washed with DCM. The organic solution was concentrated in vacuo. The crude mixture was purified by column chromatography (DCM/MeOH = 95:5) to yield the title compound (81.3 mg, 23%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.01 (s, 1H), 6.32 (br, 1H), 6.24 (d, *J* = 6.5 Hz, 2H), 6.10 (q, *J* = 1.2 Hz, 2H), 5.72 (br, 1H), 5.65 (br, 1H), 3.61 (s, 4H), 3.59 – 3.52 (m, 5H), 3.49 – 3.34 (m, 6H), 3.30 – 3.05 (m, 4H), 2.53 – 2.35 (m, 3H), 2.17 (q, *J* = 7.7 Hz, 4H), 1.96 – 1.84 (m, 1H), 1.74 – 1.59 (m, 6H), 1.55 (d, *J* = 5.5 Hz, 3H), 1.52 – 1.28 (m, 6H); HRMS (ESI+): Calcd for $C_{33}H_{52}N_5O_{11}S_2$ $[M+H]^+$: 758.3099, Found 758.3129; TLC: 95:5 / DCM:MeOH Rf = 0.34.

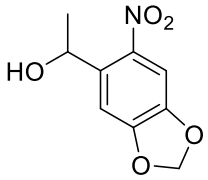
1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethyl (3-(triethoxysilyl)propyl)carbamate (4.4):



To a solution of triethoxy(3-isocyanatopropyl)silane (469

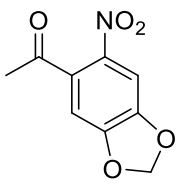
μL, 1.894 mmol) and 1-(6-Nitrobenzo[d][1,3]dioxol-5-yl)ethan-1-ol (200 mg, 0.947 mmol) in dry THF, dibutyltin dilaurate (11.29 μL, 0.019 mmol) was carefully added dropwise. The mixture was stirred at 70 ℃ for 4 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (hexanes/EtOAc = 3:1) to yield the title compound (0.278 g, 64%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.00 (s, 1H), 6.25 (q, *J* = 6.5 Hz, 1H), 6.12 - 6.05 (dd, *J* = 4.3, 1.2 Hz, 2H), 5.04 (s, 1H), 3.82 (q, *J* = 7.0 Hz, 6H), 3.24 – 3.03 (m, 2H), 1.63-1.52 (m, 5H), 1.22 (t, *J* = 7.0Hz, 9H), 0.60 (t, *J* = 8.1 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.3, 152.4, 147.1, 141.6, 136.9, 105.8, 105.4, 103.0, 68.8, 58.6, 43.5, 23.3, 22.4, 18.4, 7.8; HRMS (ESI+): Calcd for $C_{19}H_{31}N_2O_9Si$ $[M+H]^+$: 459.1793, Found 459.1759; Calcd for $C_{19}H_{30}N_2O_9SiNa$ $[M+Na]^+$: 481.1613, Found 481.1584; TLC: 7:3 / Hexanes:EtOAc Rf = 0.34.

1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethan-1-ol (4.6):



The following procedure was a slight modification from the literature.[22] Sodium borohydride (0.158 g, 4.19 mmol) was added over 10 minutes to a suspension of compound **4.9** (1.751 g, 8.37 mmol) in 10 mL methanol in an ice bath. The mixture was then stirred at room temperature for 5 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with DCM. The organic layer was washed with brine, dried over sodium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (hexanes/EtOAc = 2:1) to yield the title compound (1.149 g, 65%) as a yellow solid. Spectral data are consistent with the literature.[22]

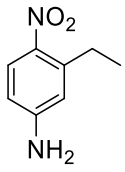
1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethan-1-one (4.9):



The following procedure was a slight modification from the literature.[22] A solution of 1-(benzo[d][1,3]dioxol-5-yl)ethanone (5 g, 30.5 mmol) in acetic acid (20 ml,

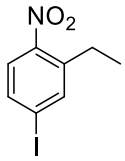
349 mmol) was added dropwise over 20 minutes to nitric acid (40 ml, 627 mmol) in an ice bath. The solution was stirred in the ice bath throughout the addition and for another 60 minutes afterward. The mixture was warmed up to room temperature and stirred for another 6 h at room temperature. The crude mixture was then quenched with ice and extracted with EtOAc. The organic layer was dried over sodium sulfate, filtered, concentrated, and purified by column chromatography (hexanes/EtOAc = 2:1) to yield the title compound (3.5 g, 55%) as a yellow solid. Spectral data are consistent with the literature.[22]

3-ethyl-4-nitroaniline (4.16):



The following procedure was a slight modification from the literature.[23] N-(3-ethylphenyl)acetamide (2.043 g, 12.52 mmol) was added slowly to concentrated sulfuric acid (6.67 ml, 125 mmol) under mechanical stirring. The solution was cooled to -15 ℃, and then concentrated nitric acid (0.617 ml, 9.39 mmol) was added dropwise. The mixture was stirred at -15 ℃ for 2 h. The reaction mixture was quenched with ice and extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate, filtered, concentrated in vacuo. The crude oil was heated with concentrated HCl solution (6 mL) under reflux for 3 h. A yellow solid precipitated after 3 h. The precipitate was filtered off, washed with water, suspended in 1M NaOH, and extracted with ether. The organic layer was dried over sodium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (hexanes/EtOAc = 7:3) to yield the title compound (1.231 g, 60%) as a yellow solid. Spectral data are consistent with the literature.[23]

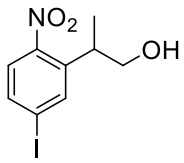
2-ethyl-4-iodo-1-nitrobenzene (4.17):



The following procedure was a slight modification from the literature.[23] Compound

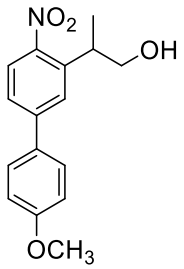
4.16 (0.3 g, 1.81 mmol) was added to concentrated H_2SO_4 solution (0.54 mL) and water (6 mL) at 60 ℃. The solution was cooled to 0 ℃. A solution of sodium nitrite (0.14 g, 2.03 mmol) in water (0.72 mL) was added to the mixture in an ice bath. The resulting mixture was stirred for 15 min at 0 ℃. Urea was added and the mixture was stirred for another 15 min. The mixture was added to a stirred solution of potassium iodide (0.45 g, 2.71 mmol) in water (1.7 mL). The mixture was stirred for 2 h at r.t., and then extracted with EtOAc. The organic layer was washed with 1M NaOH and water, dried over sodium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (100% hexanes) to yield the title compound (0.467 g, 93%) as a red oil. Spectral data are consistent with the literature.[23]

2-(5-iodo-2-nitrophenyl)propan-1-ol (4.18):



The following procedure was a slight modification from the literature.[23] A mixture of **4.17** (300 mg, 1.08 mmol) and paraformaldehyde (35.8 mg, 1.19 mmol) in dry DMF (2 mL) was treated with potassium *t*-butoxide (17.01 mg, 0.15 mmol) in *t*-Butanol (0.83 mL, 8.68 mmol). After stirring for 30 min at r.t. and 2 h at 80 ℃, the mixture was neutralized with 1M HCl, diluted with sat. NaCl solution, and extracted with EtOAc. The organic layer was dried over sodium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (hexanes/EtOAc = 8:2) to yield the title compound (0.224 g, 67%) as a yellow oil. Spectral data are consistent with the literature.[23]

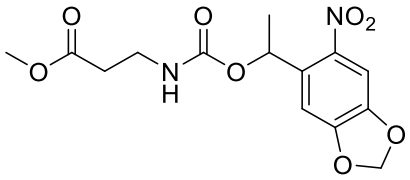
2-(4'-methoxy-4-nitro-[1,1'-biphenyl]-3-yl)propan-1-ol (4.20):



The following procedure was a slight modification from the literature.[24] Compound **4.18** (620 mg, 2.02 mmol) and tetrakis(triphenylphosphine) palladium(0) (233 mg, 0.20 mmol) were dissolved in toluene (9 mL) under

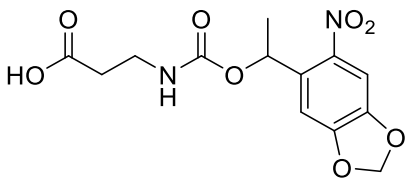
nitrogen. A saturated solution of Na_2CO_3 (9 mL) was added and the mixture was heated to 110 ℃. 2-(4-methoxyphenyl)-4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (539 mg, 2.30 mmol) dissolved in ethanol (3 mL) was added to the mixture dropwise. The mixture was stirred at 110 ℃ for 9 h. The reaction mixture was diluted with sat. NaCl and extracted with EtOAc. The organic layer was dried over sodium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (hexanes/EtOAc = 7:3) to yield the title compound (0.432 g, 75%) as a yellow solid. Spectral data are consistent with the literature.[24]

methyl 3-(((1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethoxy)carbonyl)amino)propanoate (4.22):



4-Methoxy-4-oxobutanoic acid (337 mg, 2.55 mmol) was dissolved in toluene (5 ml) and triethylamine (0.534 ml, 3.83 mmol) followed by diphenylphosphoryl azide (0.605 ml, 2.81 mmol) were added carefully. The contents were stirred for 6 hours. Compound **4.6** (646.7 mg, 3.06 mmol) was added later. The mixture was heated to 80 ℃ and stirred for 3 days. The resulting solution was cooled to r.t. and then concentrated in vacuo. The crude mixture was purified by column chromatography (hexanes/EtOAc = 7:3) to yield the title compound (0.738 g, 85%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 6.95 (s, 1H), 6.20 (q, *J* = 6.5 Hz, 1H), 6.05 (q, *J* = 1.3 Hz, 2H), 5.42 (t, *J* = 6.3 Hz, 1H), 3.64 (s, 3H), 3.41 – 3.26 (m, 2H), 2.56 – 2.39 (m, 2H), 1.50 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1 , 155.3, 152.4, 147.1, 141.6, 136.6, 105.8, 105.4, 103.1, 69.1, 52.0, 36.6, 34.2, 22.4; HRMS (ESI+): Calcd for $C_{14}H_{17}N_2O_8$ $[M+H]^+$: 341.0979, Found 341.0978; Calcd for $C_{14}H_{16}N_2O_8Na$ $[M+Na]^+$: 363.0799, Found 363.0807; TLC: 7:3 / Hexanes:EtOAc Rf = 0.28.

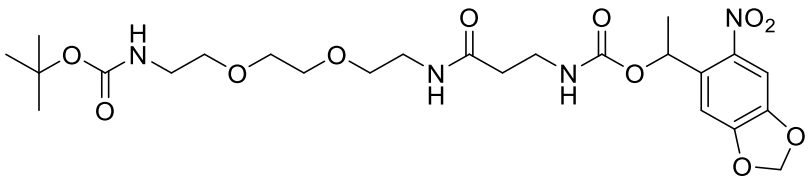
3-(((1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethoxy)carbonyl)amino)propanoic acid (4.23):



Compound **4.22** (738 mg, 2.17 mmol) was suspended in a

mixture of methanol (8 mL) and water (4 mL). Potassium carbonate (899 mg, 6.51 mmol) was added later. The contents were heated to 50 ℃ and stirred for 14 h. The solvent was removed in vacuo, and the mixture was added to 1M HCl solution until to pH 4. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was washed with diethyl ether and n-hexane to yield the title compound (0.530 g, 75%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.00 (s, 1H), 6.26 (q, *J* = 6.4 Hz, 1H), 6.09 (s, 2H), 5.40 – 5.31 (m, 1H), 3.49 – 3.34 (m, 2H), 2.56 (td, *J* = 5.4, 2.4 Hz, 2H), 1.57 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 155.4, 152.5, 147.2, 141.6, 136.3, 105.8, 105.4, 103.1, 69.3, 36.4, 34.2, 22.3; HRMS (ESI+): Calcd for $C_{13}H_{15}N_2O_8$ $[M+H]^+$: 327.0823, Found 327.0805; Calcd for $C_{14}H_{16}N_2O_8Na$ $[M+Na]^+$: 349.0642, Found 349.0629.

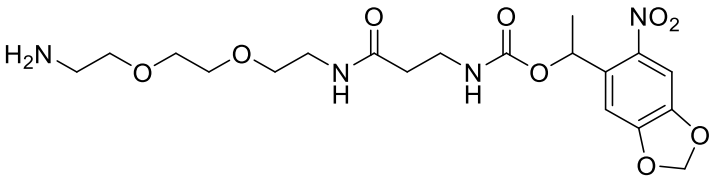
1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethyl (2,2-dimethyl-4,15-dioxo-3,8,11-trioxa-5,14-diazaheptadecan-17-yl)carbamate (4.25):



Compound **4.23** (84.8 mg, 0.26 mmol) and tert-butyl (2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamate (67.1 mg, 0.27 mmol) were dissolved in DCM (4 mL). Then DCC (64.4 mg, 0.31 mmol) was added portion-wise. The contents were stirred for 3 h at r.t. The resulting mixture was cooled to 0 ℃, filtered, and washed with DCM. The organic solution was concentrated in vacuo. The crude mixture was purified by column chromatography (DCM/MeOH = 95:5) to yield the title compound (100.4 mg, 69%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 6.98 (s, 1H), 6.28 – 6.17 (dd, m, 2H), 6.06 (s, 2H), 5.70 (br, 1H), 5.03 (br, 1H), 3.60 – 3.55 (m, 4H), 3.54 – 3.49 (m, 4H), 3.46 – 3.32 (m, 4H), 3.29 – 3.25 (m, 2H), 2.35 (td, *J* = 5.5,

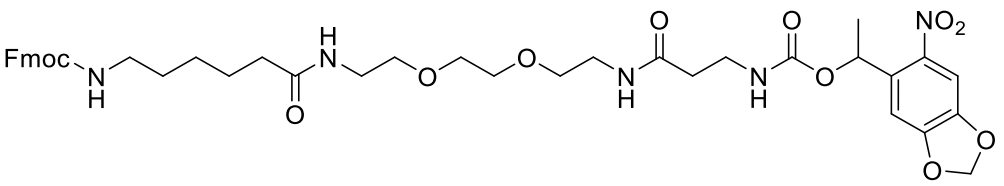
2.2 Hz, 2H), 1.51 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 156.3, 155.4, 152.4, 147.2, 141.8, 136.6, 106.0, 105.3, 103.0, 70.4, 70.2, 69.7, 68.8, 40.4, 39.3, 37.2, 35.7, 34.0, 28.5, 25.0, 22.3; HRMS (ESI+): Calcd for $C_{24}H_{37}N_4O_{11}$ $[M+H]^+$: 557.2453, Found 557.2489; TLC: 95:5 / DCM:MeOH Rf = 0.46.

1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethyl (3-((2-(2-(2-aminoethoxy)ethoxy)ethyl)amino)-3-oxopropyl)carbamate (4.26):



Compound **4.25** (453.5 mg, 0.82 mmol) was dissolved in DCM (5 mL) and trifluoroacetic acid (942 µl, 12.22 mmol) was added dropwise. The contents were stirred at r.t. for 2 h. The resulting mixture was concentrated in vacuo and extracted with DCM. The organic layer was washed with sat. NaOH, dried over sodium sulfate, and filtered. The solvent was evaporated to yield the title compound (0.310 g, 83%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.01 (s, 1H), 6.55 (br, 1H), 6.29 – 6.20 (m, 1H), 6.09 (s, 2H), 5.70 (br, 1H), 3.62 (s, 4H), 3.58 – 3.50 (m, 4H), 3.48 – 3.35 (m, 4H), 2.87 (t, *J* = 5.2 Hz, 2H), 2.38 (dt, *J* = 6.4, 3.0 Hz, 2H), 1.60 (br, 2H), 1.55 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 155.5, 152.5, 147.1, 141.6, 136.7, 105.9, 105.3, 103.1, 76.8, 73.4, 70.5, 70.0, 68.9, 41.8, 39.3, 37.2, 35.7, 22.4; HRMS (ESI+): Calcd for $C_{19}H_{28}N_4O_9Na$ $[M+Na]^+$: 479.1748, Found 479.1762.

(9H-fluoren-9-yl)methyl (1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethyl) (3,14-dioxo-7,10-dioxa-4,13-diazanonadecane-1,19-diyl)dicarbamate (4.28):



6-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)hexanoic acid (35.2 mg, 0.10 mmol) and **4.26** (47.3 mg, 0.104 mmol) were dissolved in DCM (4 mL). Then DCC (24.7 mg, 0.12 mmol) was added portion-wise. The contents were stirred for 4 h at r.t. The resulting mixture was cooled to 0 ℃, filtered, and washed with DCM. The organic solution was concentrated in vacuo. The crude mixture was purified by column chromatography (DCM/MeOH = 95:5) to yield the title compound (49.7 mg, 63%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.58 (dd, *J* = 7.3, 1.1 Hz, 2H), 7.44 (s, 1H), 7.41 – 7.36 (m, 2H), 7.33 – 7.27 (m, 2H), 6.99 (s, 1H), 6.29 (br, 1H), 6.26 – 6.20 (m, 1H), 6.10 (br, 1H), 6.05 (s, 2H), 5.66 (br, 1H), 5.05 (br, 1H), 4.38 (d, *J* = 6.8 Hz, 2H), 4.19 (t, *J* = 6.9 Hz, 1H), 3.60 – 3.49 (m, 8H), 3.45 – 3.30 (m, 6H), 3.17 (q, *J* = 6.5 Hz, 2H), 2.36 (td, *J* = 5.8, 2.6 Hz, 2H), 2.17 (t, *J* = 7.3 Hz, 2H), 1.68 – 1.59 (m, 3H), 1.53 (d, *J* = 6.3 Hz, 3H), 1.39 – 1.29 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 171.6, 156.6, 155.5, 152.5, 147.1, 144.1, 141.5, 141.4, 136.5, 127.8, 127.2, 125.1, 120.1, 105.9, 105.3, 103.1, 70.4, 70.3, 70.0, 69.7, 68.9, 66.6, 47.4, 40.9, 39.3, 39.3, 37.3, 36.5, 35.9, 29.7, 26.4, 25.3, 22.3; HRMS (ESI+): Calcd for $C_{40}H_{50}N_5O_{12}$ $[M+H]^+$: 792.3450, Found 792.3392; TLC: 95:5 / DCM:MeOH Rf = 0.34.

5.6 References

(1) Creech, G. S.; Kwon, O. Alcohol-Assisted Phosphine Catalysis: One-Step Syntheses of Dihydropyrones from Aldehydes and Allenoates. *Org. Lett.* **2008**, *10*, 429-432.

(2) Xiao, Y.; Liu, P. IspH Protein of the Deoxyxylulose Phosphate Pathway: Mechanistic Studies with C1-Deuterium-Labeled Substrate and Fluorinated Analogue. *Angew. Chem. Int. Ed.* **2008**, *47*, 9722-9725.

(3) Etzenhouser, B.; Hansch, C.; Kapur, S.; Selassie, C. D. Mechanism of Toxicity of Esters of Caffeic and Dihydrocaffeic Acids. *Biorg. Med. Chem.* **2001**, *9*, 199-209.

(4) Andrews, S. D.; Day, A. C.; Inwood, R. N. Cycloadditions. Part III. Steric Effects in the Addition of 2-Diazopropane to Conjugated Allenic Esters and Nitriles. *J. Chem. Soc. C* **1969**, 2443-2449.

(5) Lang, R. W.; Hansen, H. J. Eine einfache Allencarbonsäureester-Synthese Mittels der Wittig-Reaktion. *Helv. Chim. Acta* **1980**, *63*, 438-455.

(6) Li, C.; Wang, X.; Sun, X.; Tang, Y.; Zheng, J.; Xu, Z.; Zhou, Y.; Dai, L. Iron Porphyrin-Catalyzed Olefination of Ketenes with Diazoacetate for the Enantioselective Synthesis of Allenes. *J. Am. Chem. Soc.* **2007**, *129*, 1494-1495.

(7) Lang, R.; Hansen, H. α-Allenic Esters from α-Phosphoranylidene Esters and Acid Chlorides: Ethyl 2,3-Pentadienoate. *Org. Synth.* **1984**, *62*, 202.

(8) Voutchkova, A. M.; Feliz, M.; Clot, E.; Eisenstein, O.; Crabtree, R. H. Imidazolium Carboxylates as Versatile and Selective N-Heterocyclic Carbene Transfer Agents: Synthesis, Mechanism, and Applications. *J. Am. Chem. Soc.* **2007**, *129*, 12834-12846.

(9) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. Catalytic Diboration of Aldehydes via Insertion into the Copper−Boron Bond. *J. Am. Chem. Soc.* **2006**, *128*, 11036-11037.

(10) Oku, A.; Abe, M.; Iwamoto, M. Electron Transfer Profile of Cyclopropanone Acetals in the Nonirradiated Reaction with Tetracyanoethylene, Chloranil, and Dicyanodichlorobenzoquinone. *J. Org. Chem.* **1994**, *59*, 7445-7452.

(11) Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slebodnick, C.; Marder, T. B.; Santos, W. L. Structure and Reactivity of a Preactivated sp^2–sp^3 Diboron Reagent: Catalytic Regioselective Boration of α,β-Unsaturated Conjugated Compounds. *J. Org. Chem.* **2011**, *76*, 3997-4007.

(12) Gao, M.; Thorpe, S. B.; Santos, W. L. sp^2−sp^3 Hybridized Mixed Diboron: Synthesis, Characterization, and Copper-Catalyzed β-Boration of α,β-Unsaturated Conjugated Compounds. *Org. Lett.* **2009**, *11*, 3478-3481.

(13) Iwadate, N.; Suginome, M. Differentially Protected Diboron for Regioselective Diboration of Alkynes: Internal-Selective Cross-Coupling of 1-Alkene-1,2-diboronic Acid Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 2548-2549.

(14) Yamazaki, S.; Yamamoto, Y.; Fukushima, Y.; Takebayashi, M.; Ukai, T.; Mikata, Y. Lewis Acid Promoted Reactions of Ethenetricarboxylates with Allenes: Synthesis of Indenes and γ-Lactones via Conjugate Addition/Cyclization Reaction. *J. Org. Chem.* **2010**, *75*, 5216-5222.

(15) Baird, M. S.; Nizovtsev, A. V.; Bolesov, I. G. Bromine–magnesium exchange in gem-dibromocyclopropanes using Grignard reagents. *Tetrahedron* **2002**, *58*, 1581-1593.

(16) Ma, S.; Zhang, A. Efficient Synthesis of 1,1-Diaryl 1,2-Dienes via Pd(0)-Catalyzed Coupling of Aryl Halides with Allenic/Propargylic Zinc Reagents. *J. Org. Chem.* **1998**, *63*, 9601-9604.

(17) Lee, J. C. H.; McDonald, R.; Hall, D. G. Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds. *Nat Chem* **2011**, *3*, 894-899.

(18) Gauthier, D.; Beckendorf, S.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. A Ligand Free and Room Temperature Protocol for Pd-Catalyzed Kumada−Corriu Couplings of Unactivated Alkenyl Phosphates. *J. Org. Chem.* **2009**, *74*, 3536-3539.

(19) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. Direct Stereospecific Amination of Alkyl and Aryl Pinacol Boronates. *J. Am. Chem. Soc.* **2012**, *134*, 16449-16451.

(20) Ackermann, L.; Kapdi, A. R.; Fenner, S.; Kornhaaß, C.; Schulzke, C. Well-Defined Air-Stable Palladium HASPO Complexes for Efficient Kumada–Corriu Cross-Couplings of (Hetero)Aryl or Alkenyl Tosylates. *Chem. Eur. J.* **2011**, *17*, 2965-2971.

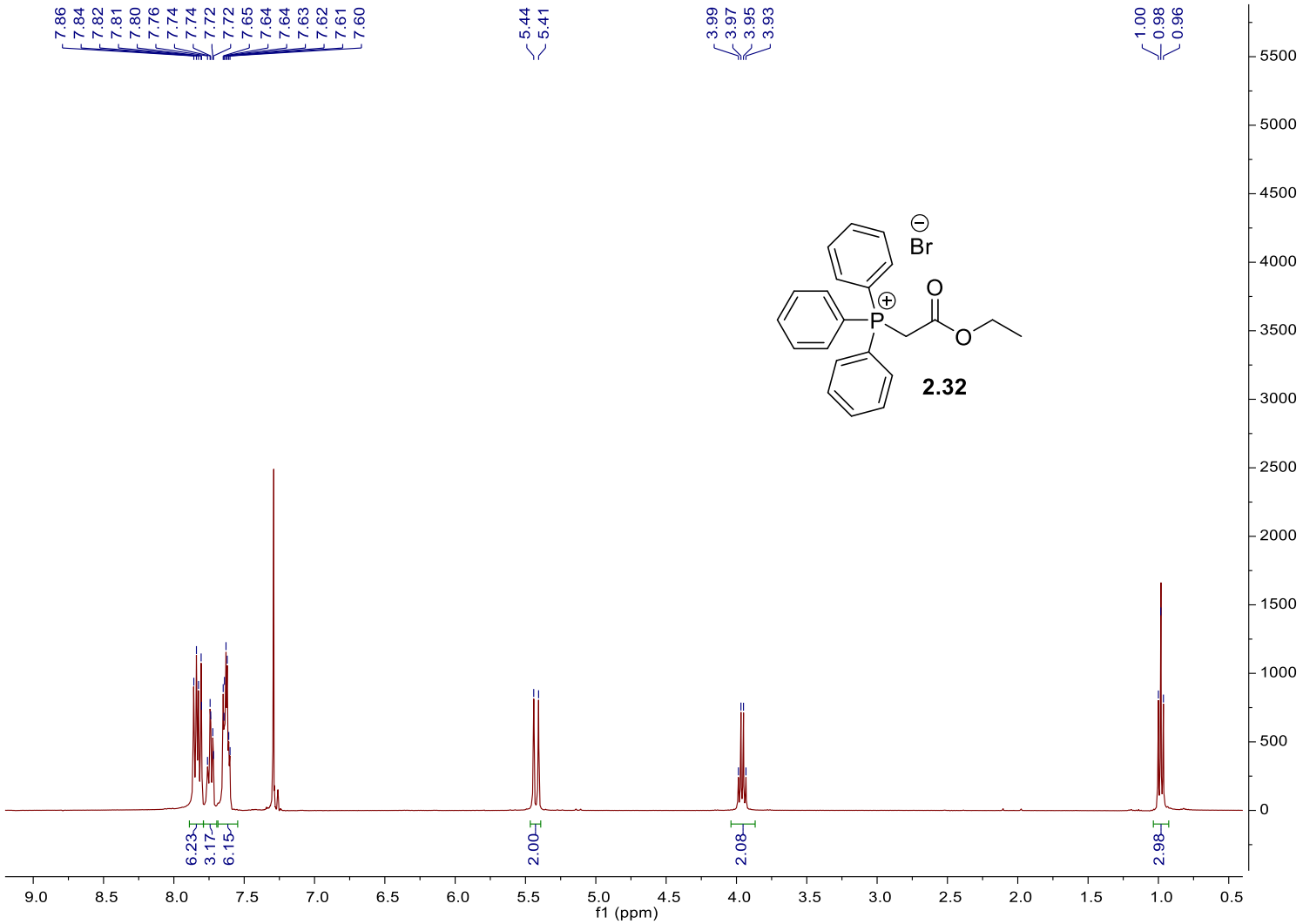
(21) Yang, C. T.; Zhang, Z. Q.; Tajuddin, H.; Wu, C. C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. Alkylboronic Esters from Copper-Catalyzed Borylation of Primary and Secondary Alkyl Halides and Pseudohalides. *Angew. Chem. Int. Ed.* **2012**, *51*, 528-532.

(22) McGall, G. H.; Barone, A. D.; Diggelmann, M.; Fodor, S. P. A.; Gentalen, E.; Ngo, N. The Efficiency of Light-Directed Synthesis of DNA Arrays on Glass Substrates. *J. Am. Chem. Soc.* **1997**, *119*, 5081-5090.

(23) Bühler, S.; Lagoja, I.; Giegrich, H.; Stengele, K. P.; Pfleiderer, W. New Types of Very Efficient Photolabile Protecting Groups Based upon the [2-(2-Nitrophenyl)propoxy]carbonyl (NPPOC) Moiety. *Helv. Chim. Acta* **2004**, *87*, 620-659.

(24) Gug, S.; Charon, S.; Specht, A.; Alarcon, K.; Ogden, D.; Zietz, B.; Léonard, J.; Haacke, S.; Bolze, F.; Nicoud, J. F.; Goeldner, M. Photolabile Glutamate Protecting Group with High One- and Two-Photon Uncaging Efficiencies. *ChemBioChem* **2008**, *9*, 1303-1307.

Appendix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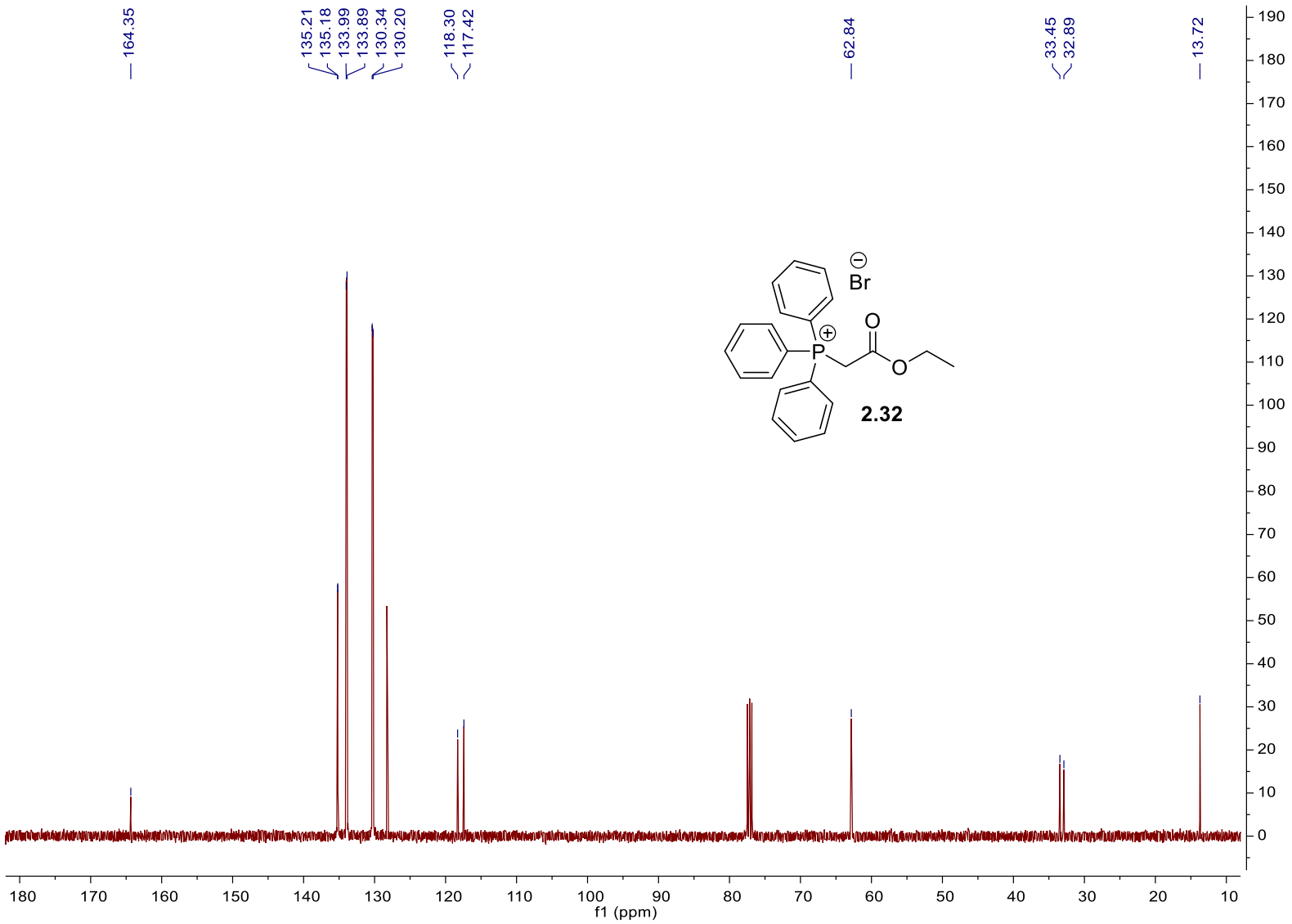
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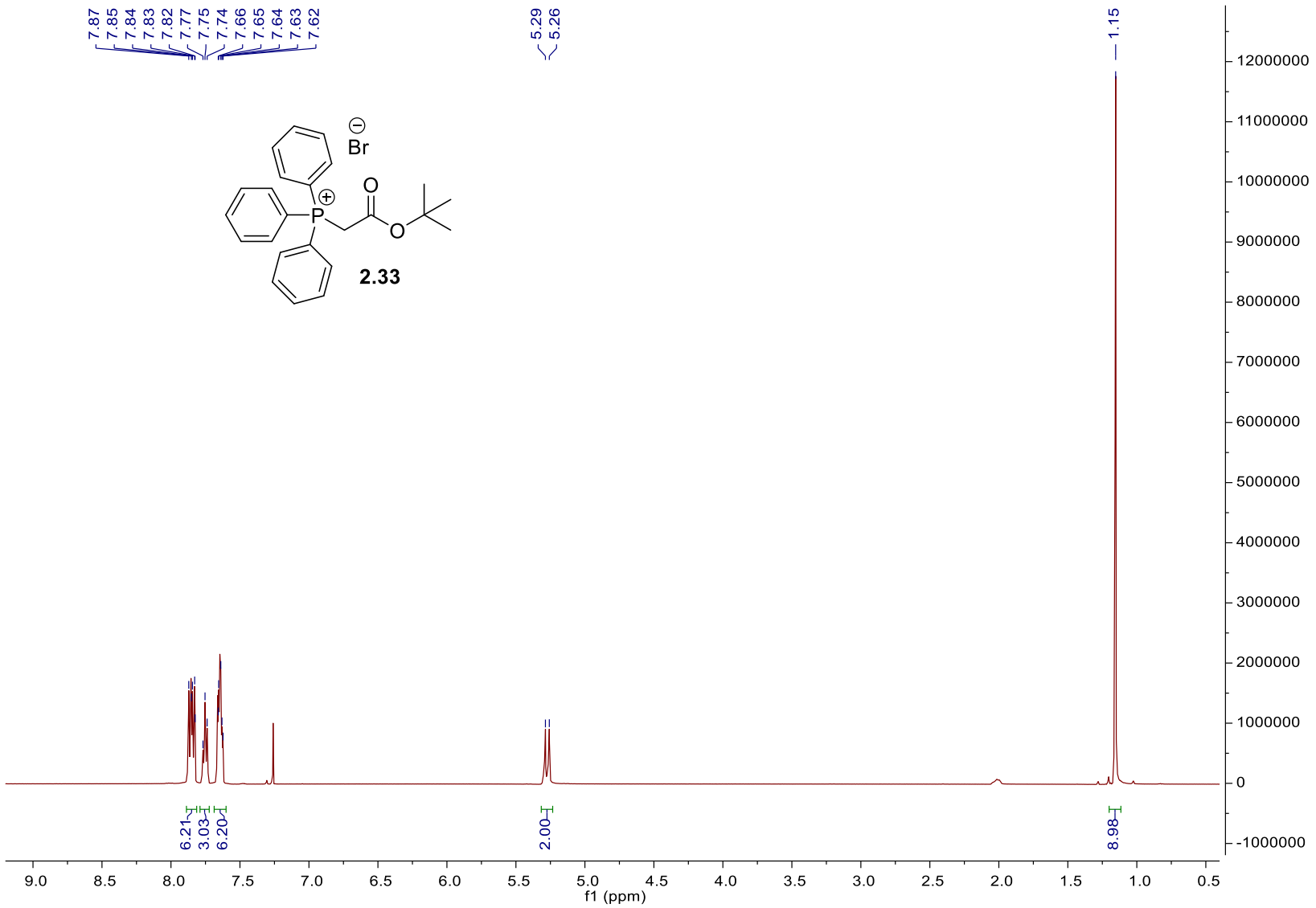
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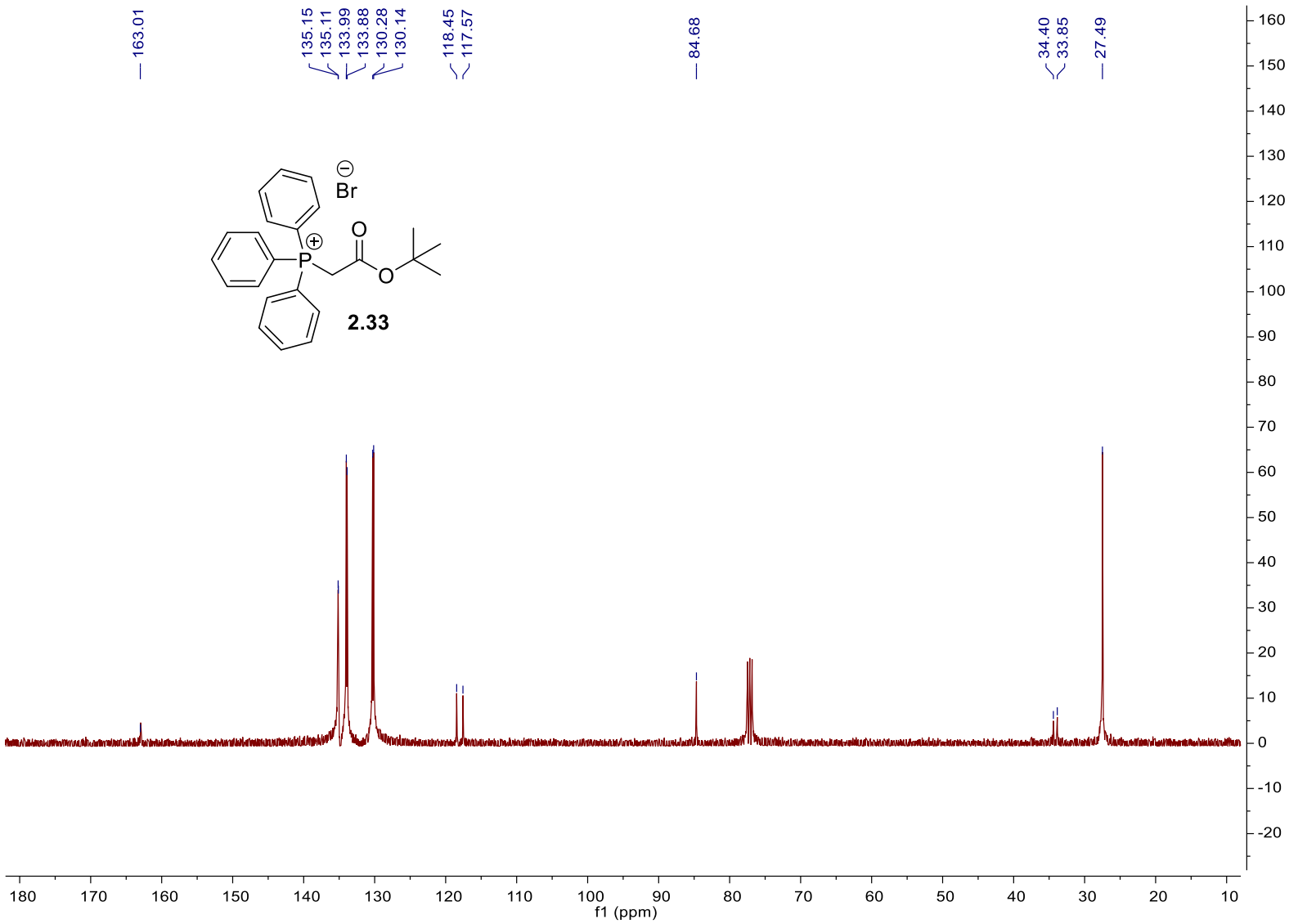
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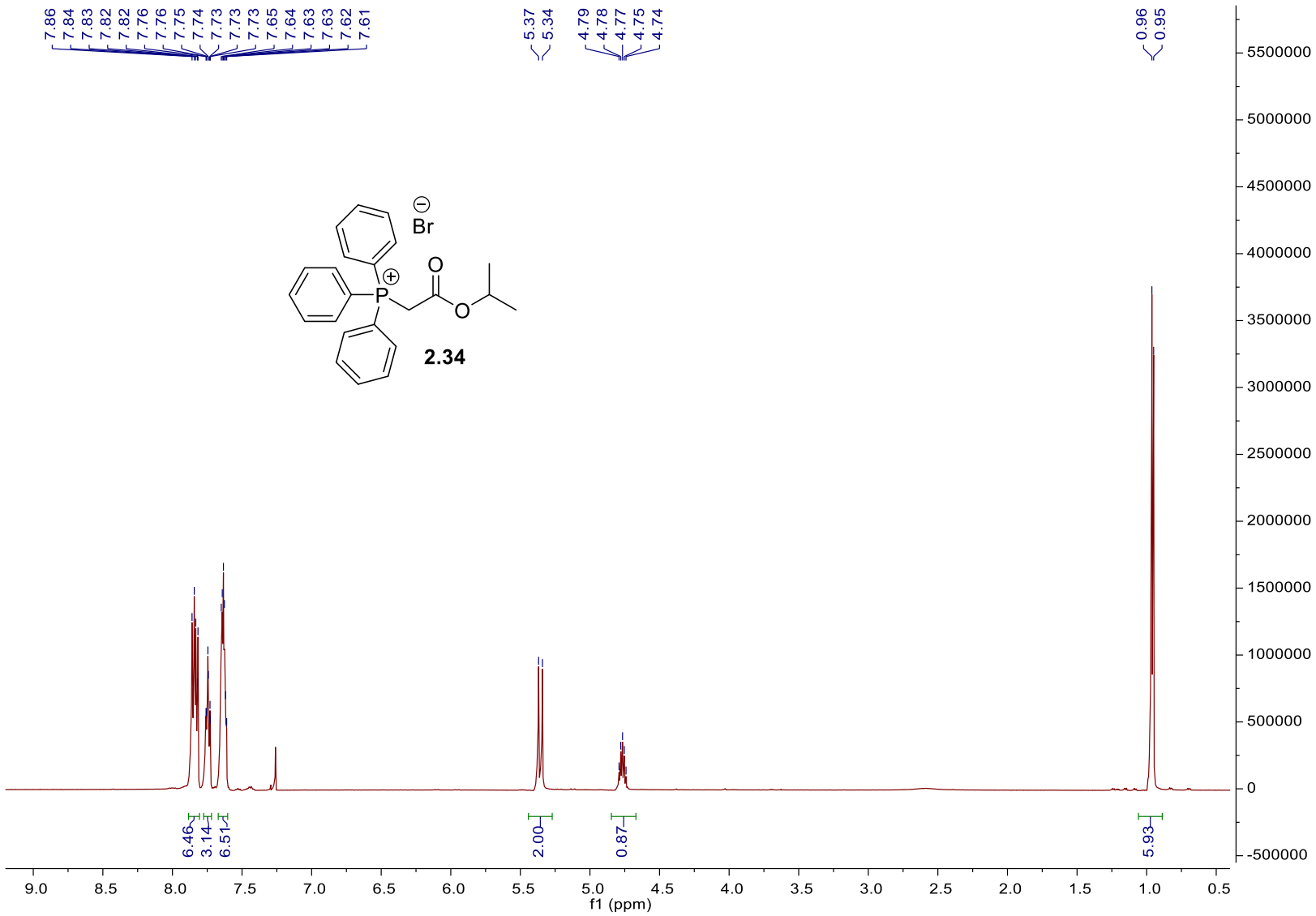
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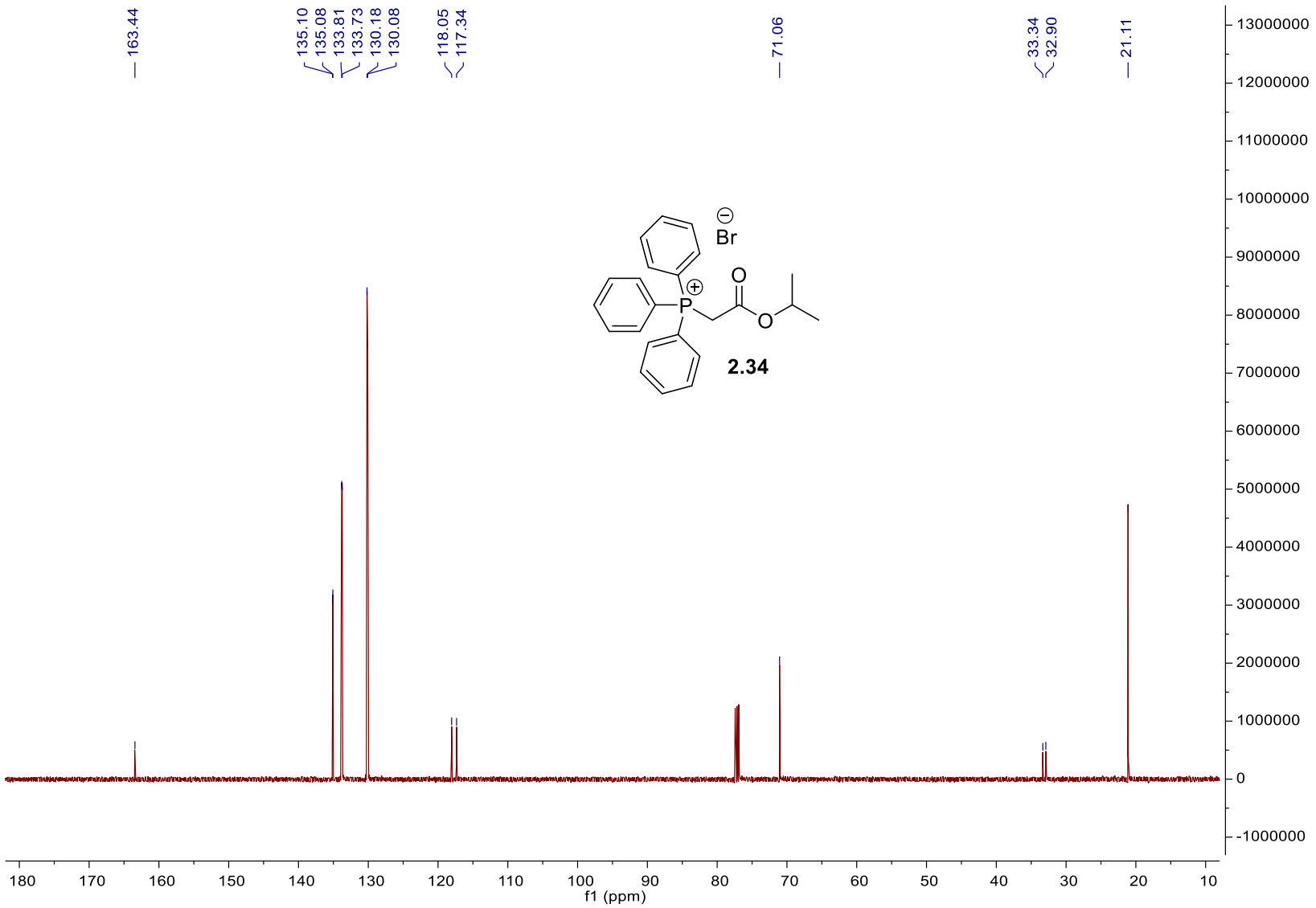
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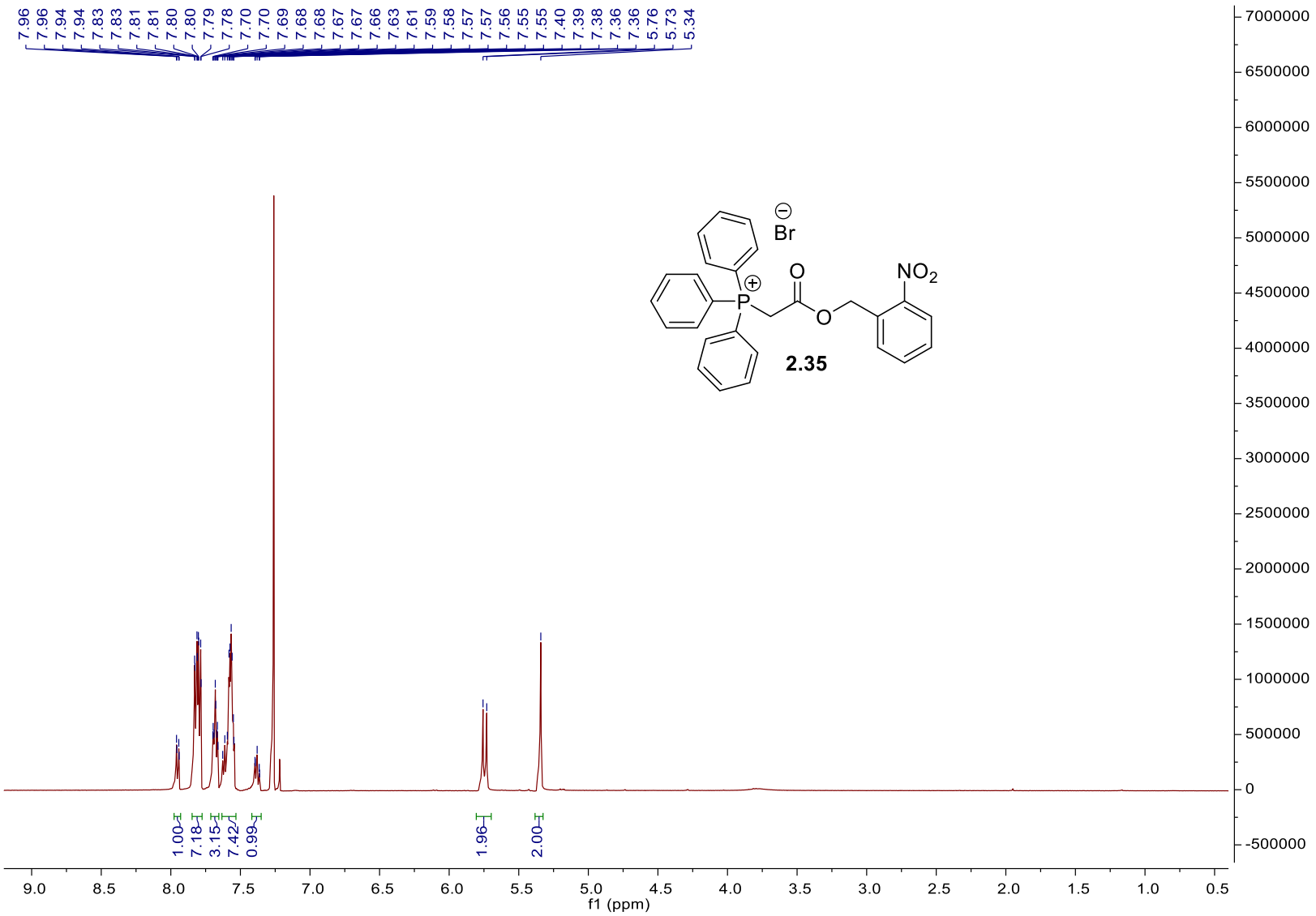
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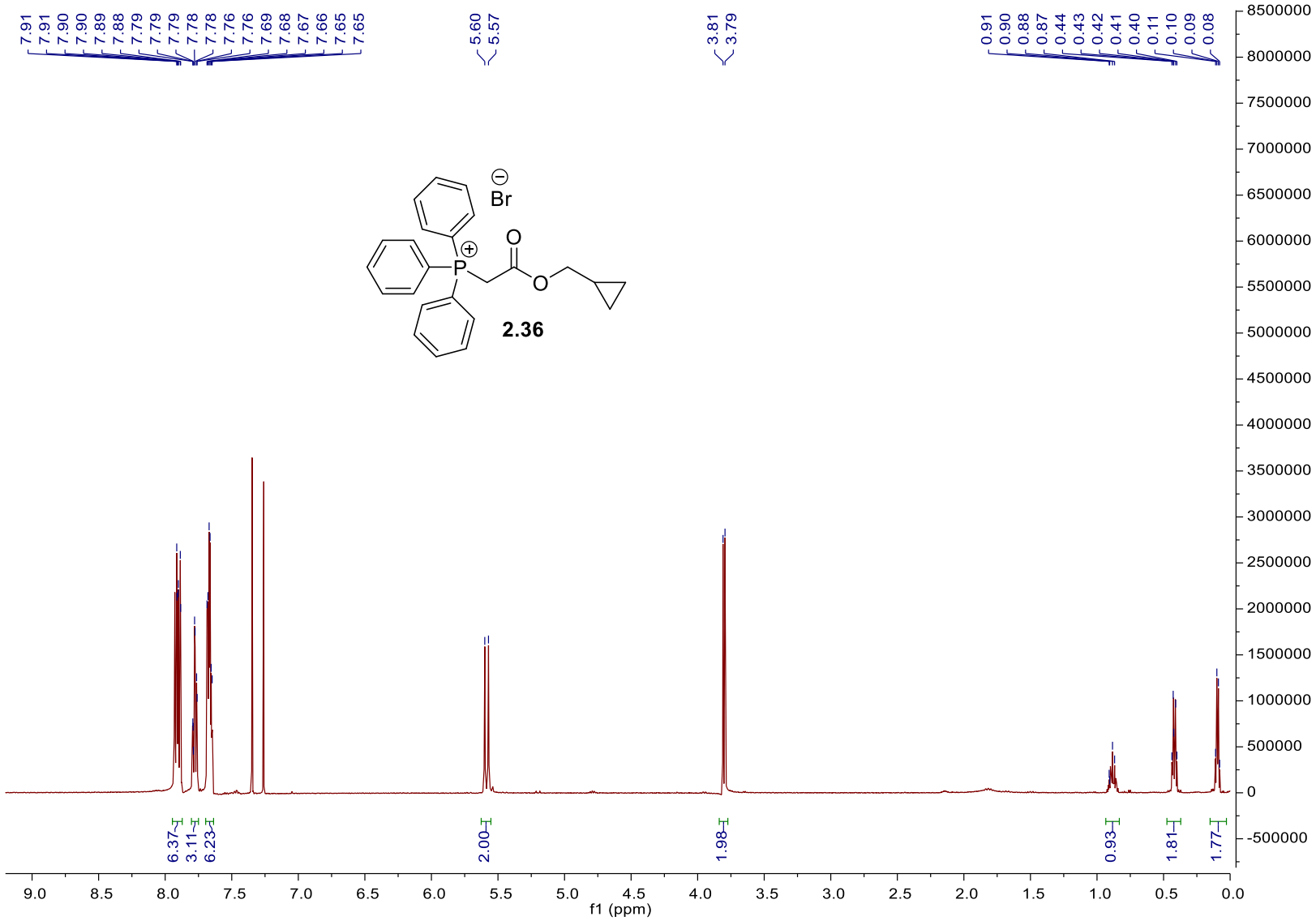
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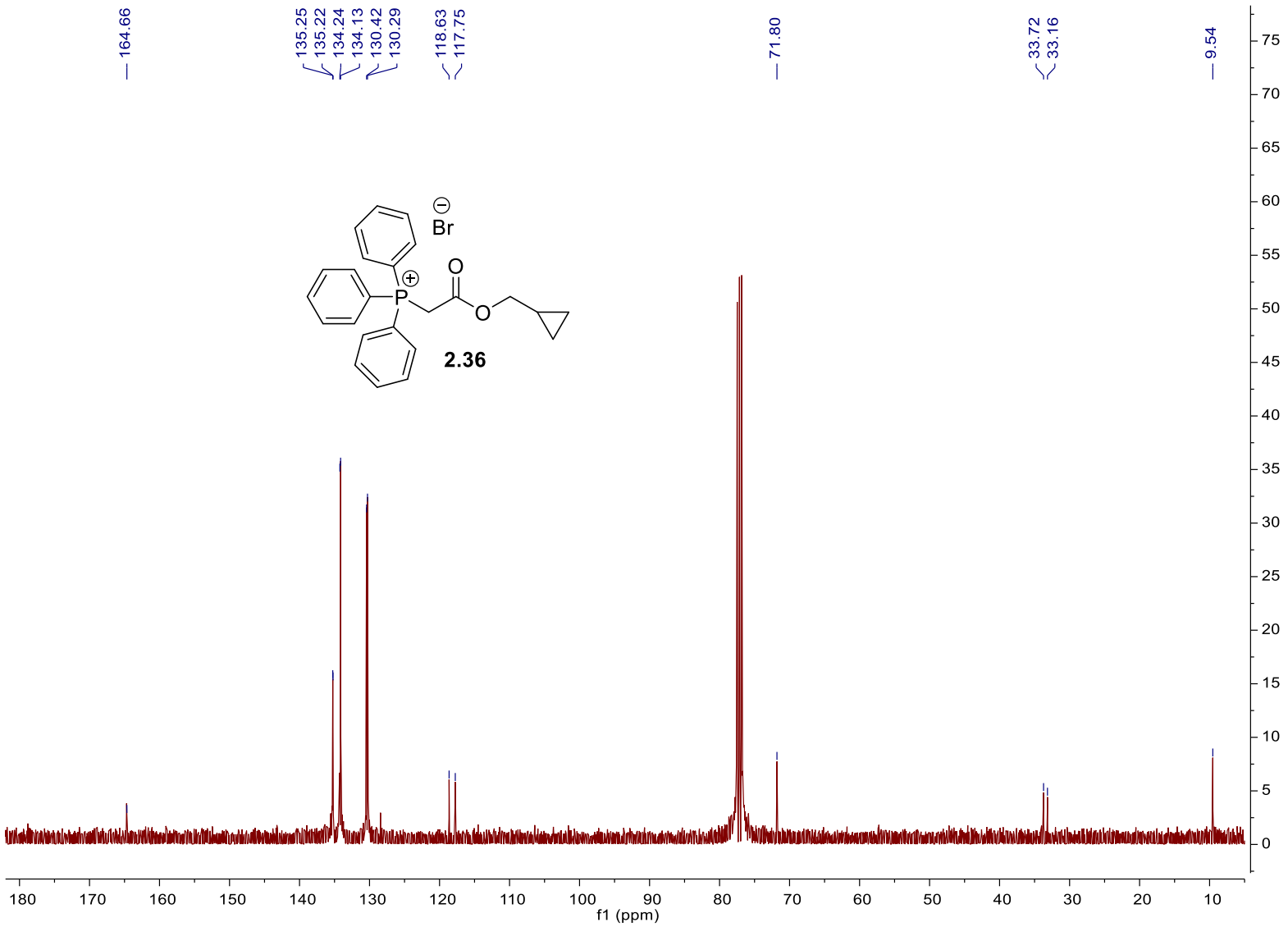
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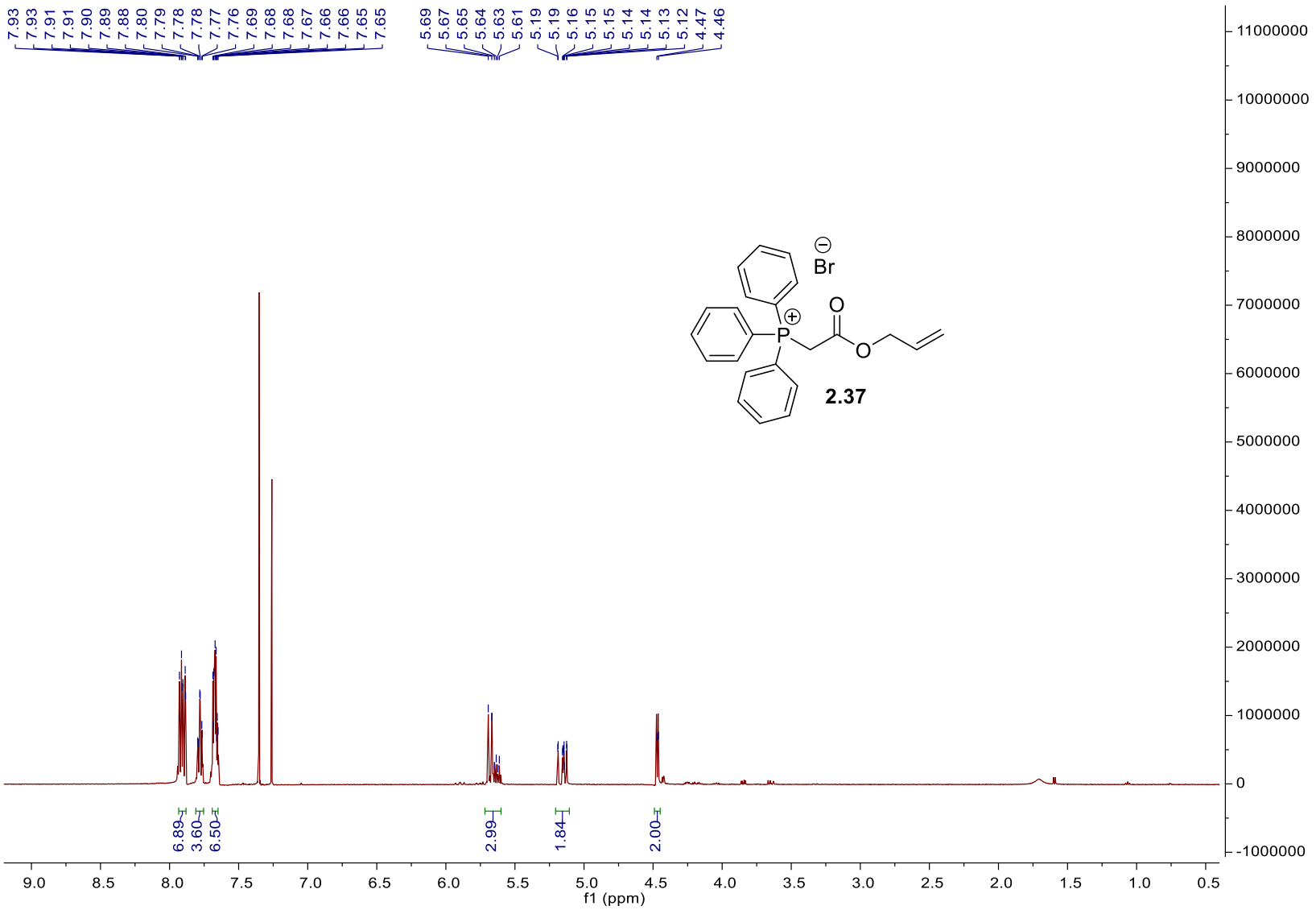
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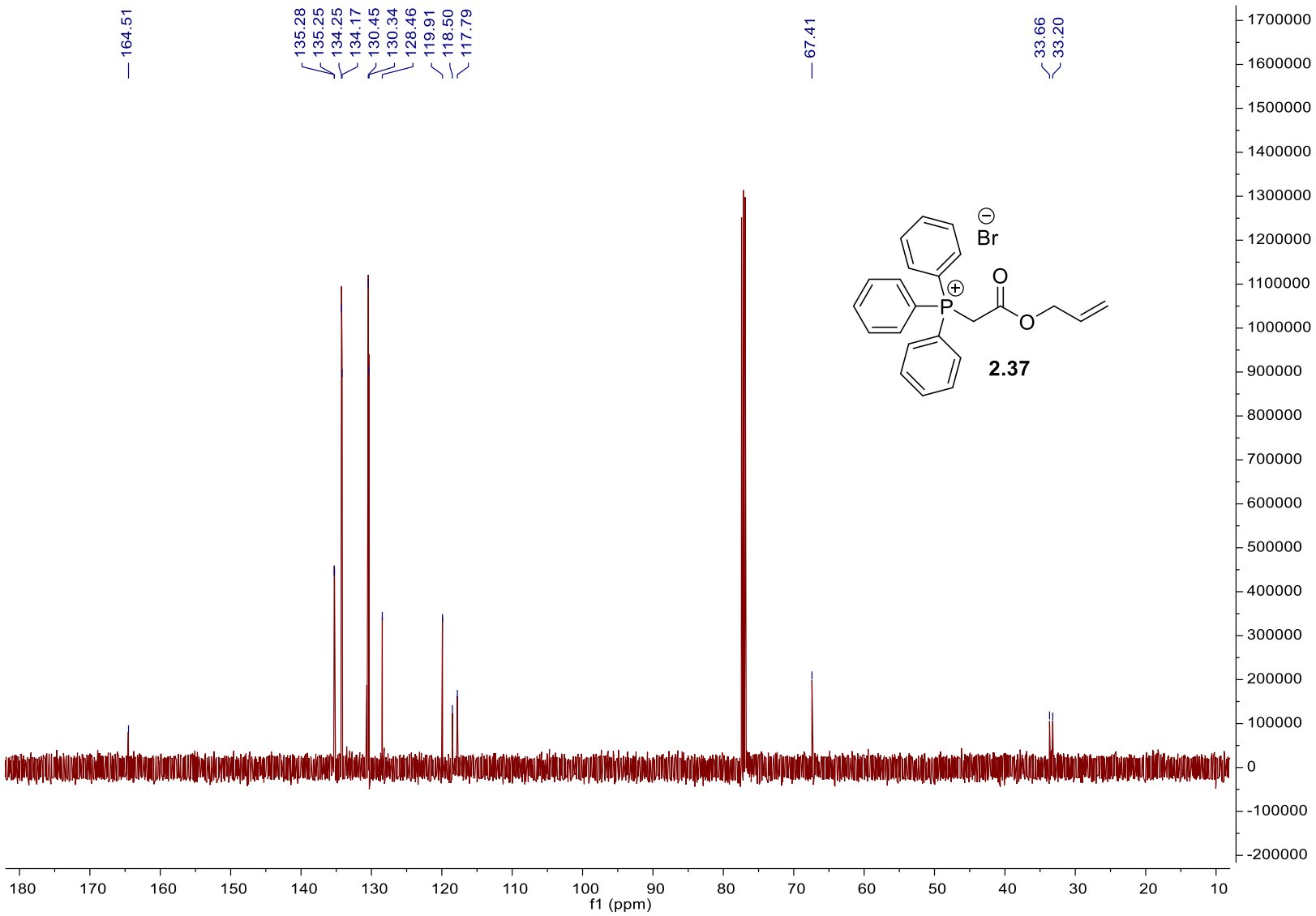
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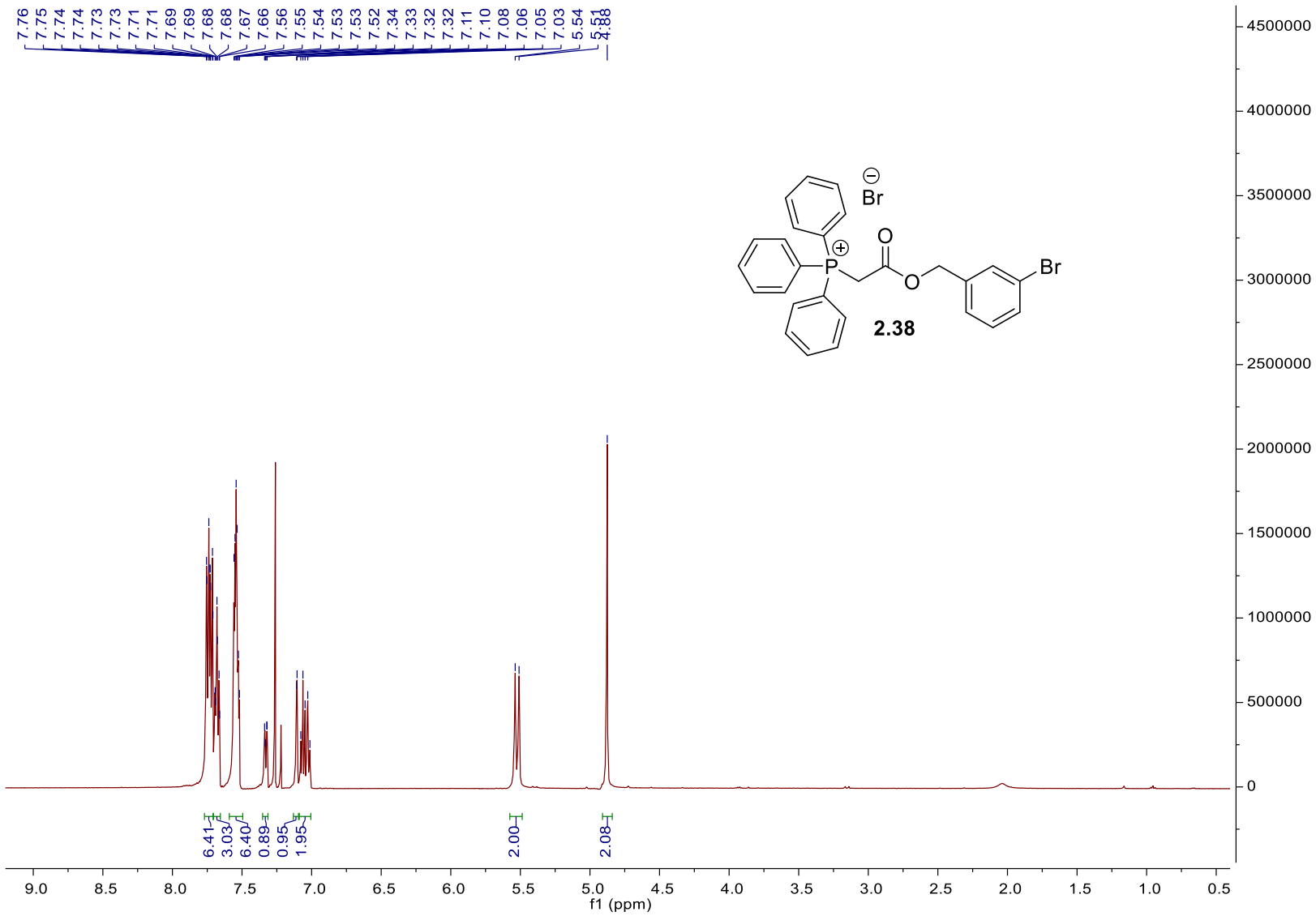
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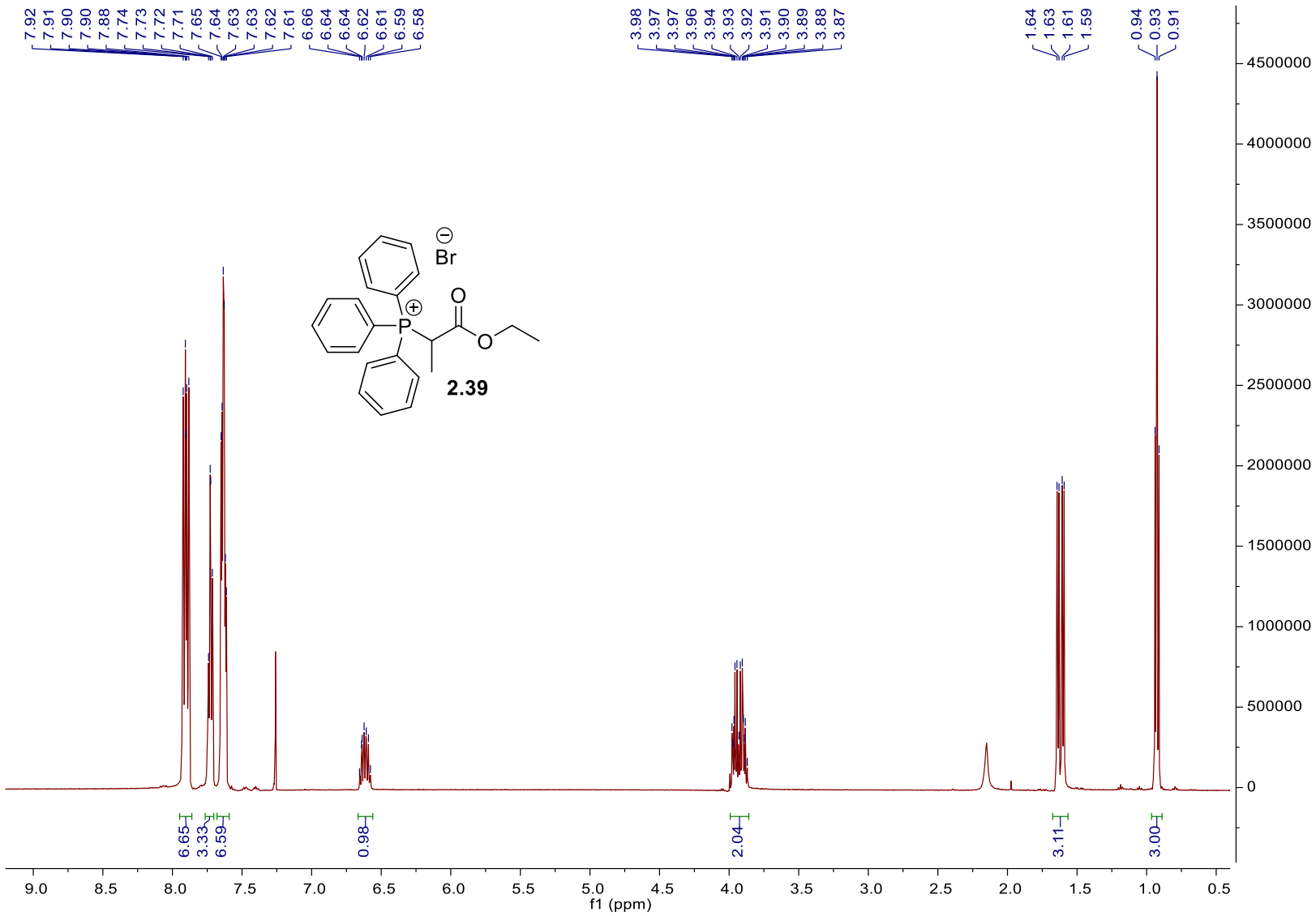
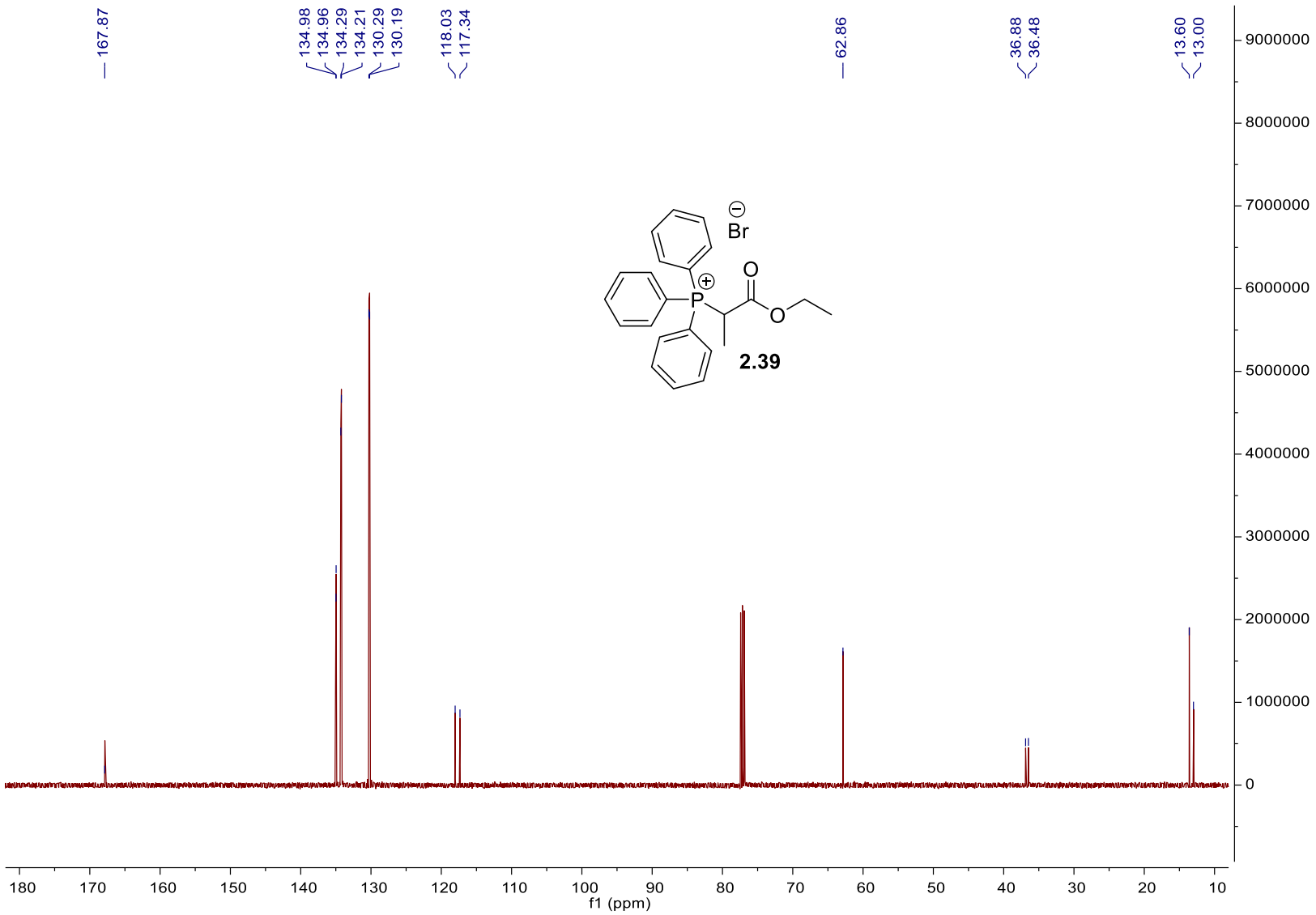
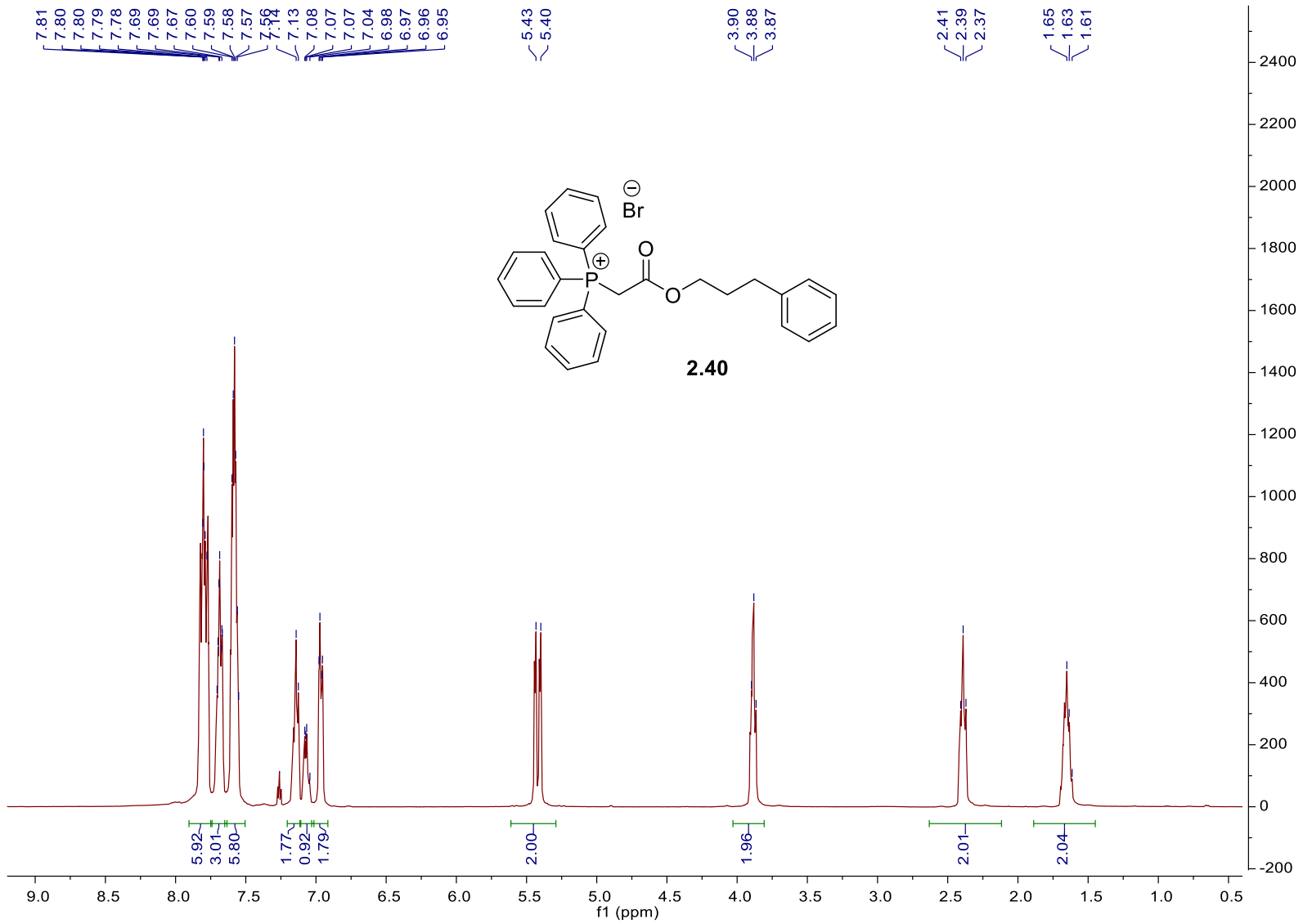
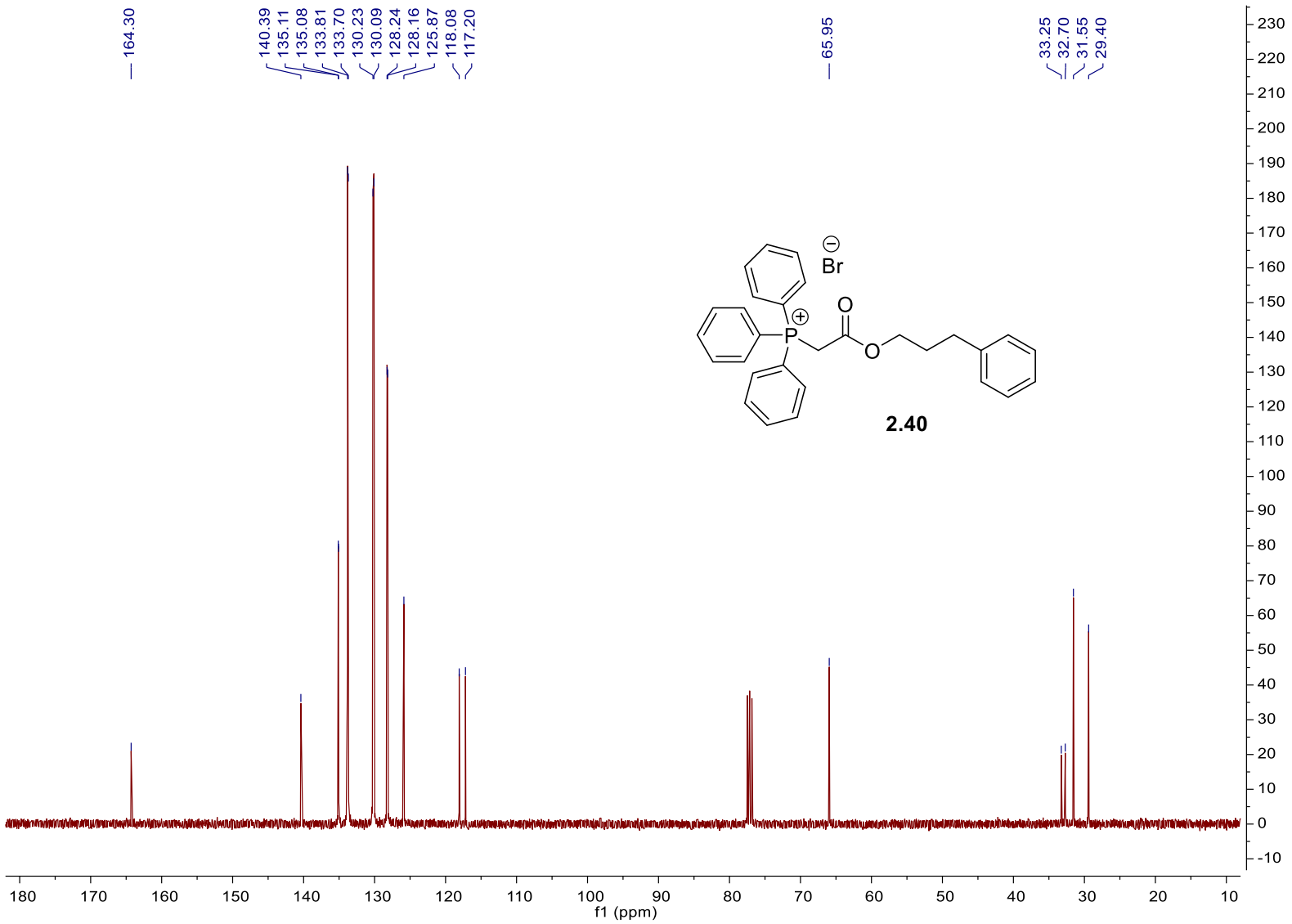
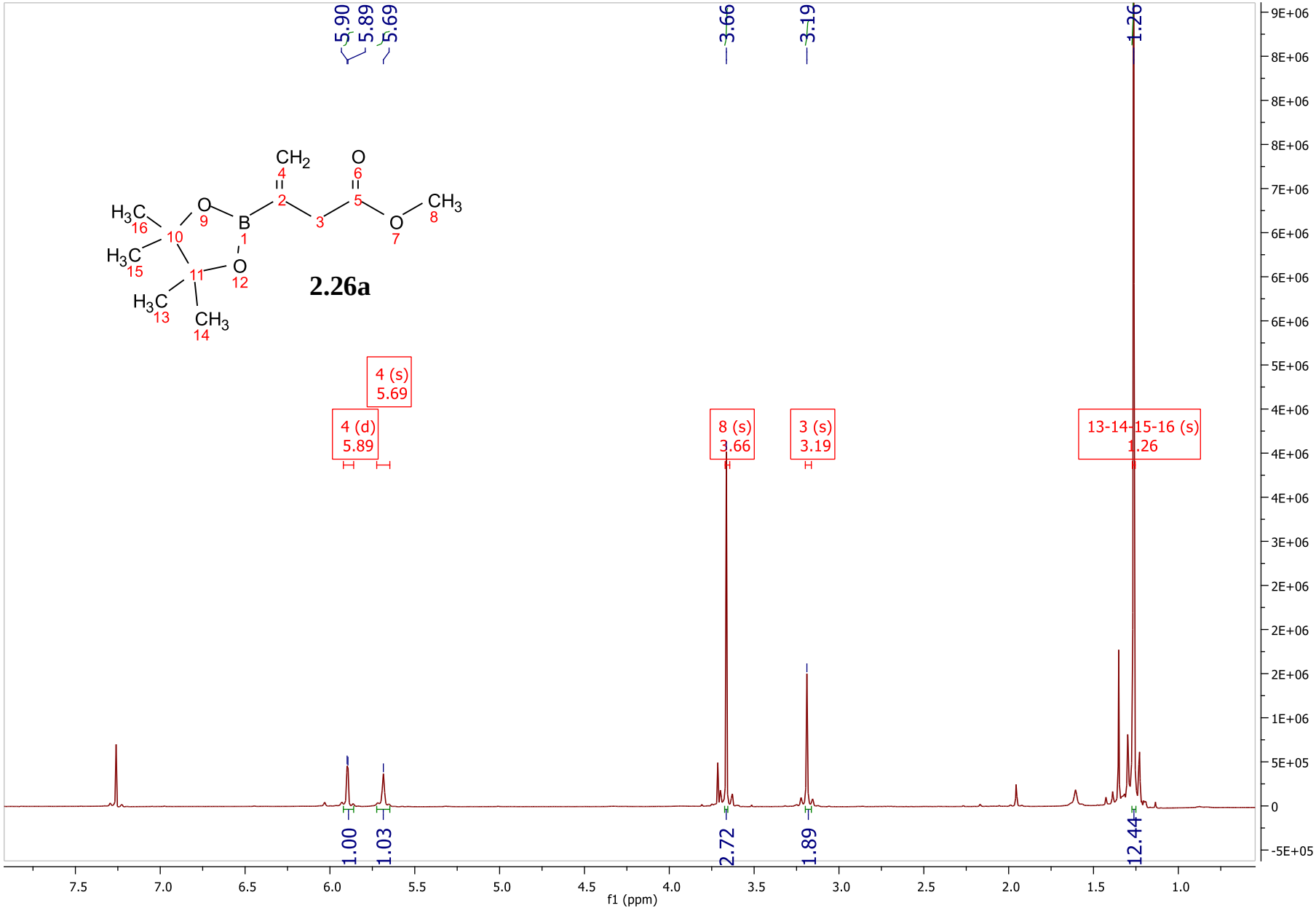
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

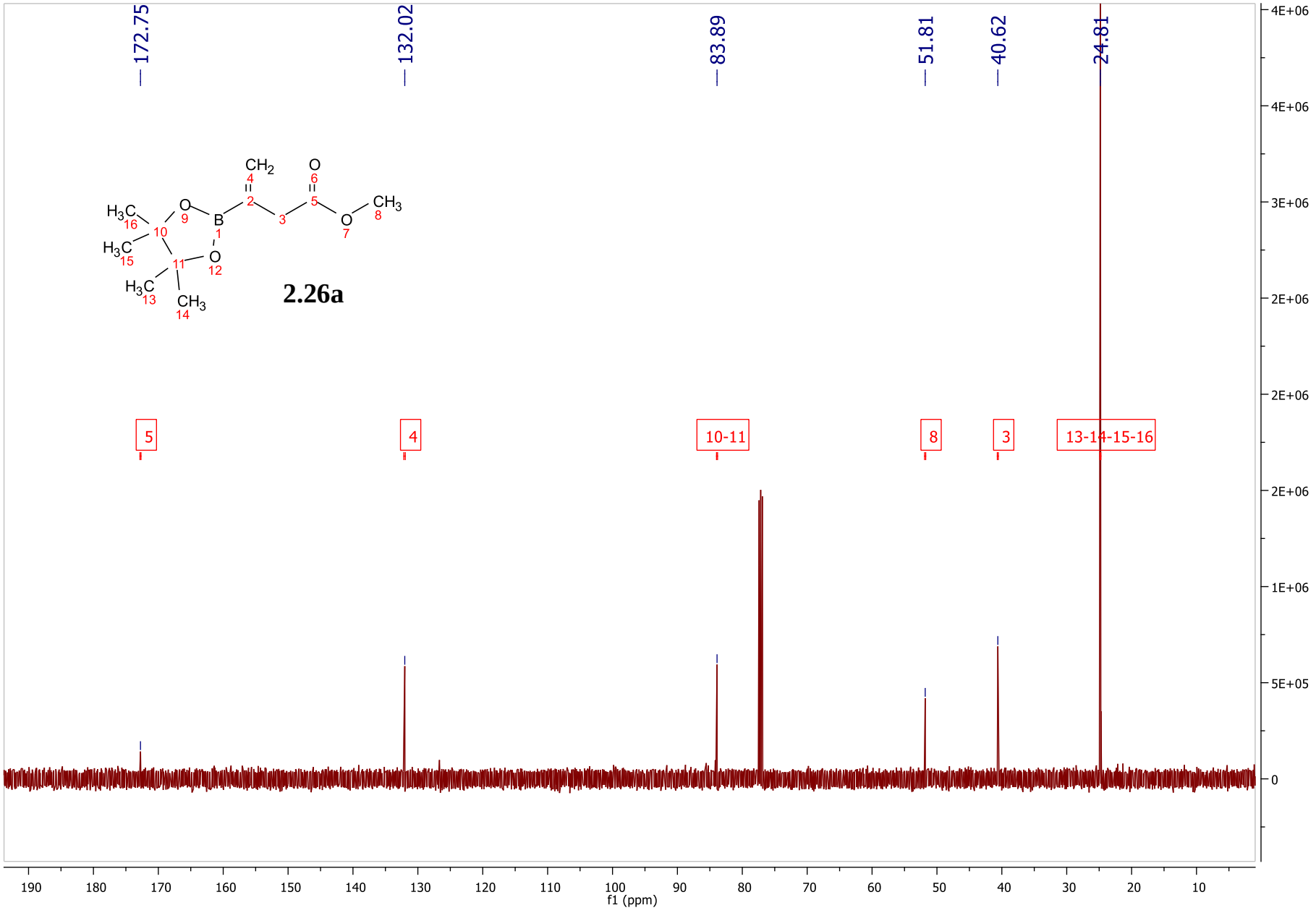

7.92
7.91
7.90
7.90
7.88
7.74
7.73
7.72
7.71
7.65
7.64
7.63
7.63
7.62
7.61
6.66
6.64
6.64
6.62
6.61
6.59
6.58
3.98
3.97
3.97
3.96
3.94
3.93
3.92
3.91
3.90
3.89
3.88
3.87
1.64
1.63
1.61
1.59
0.94
0.93
0.91
Br
O
P
O
2.39
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
6.65
3.33
6.59
0.98
2.04
3.11
3.00
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
f1 (ppm)

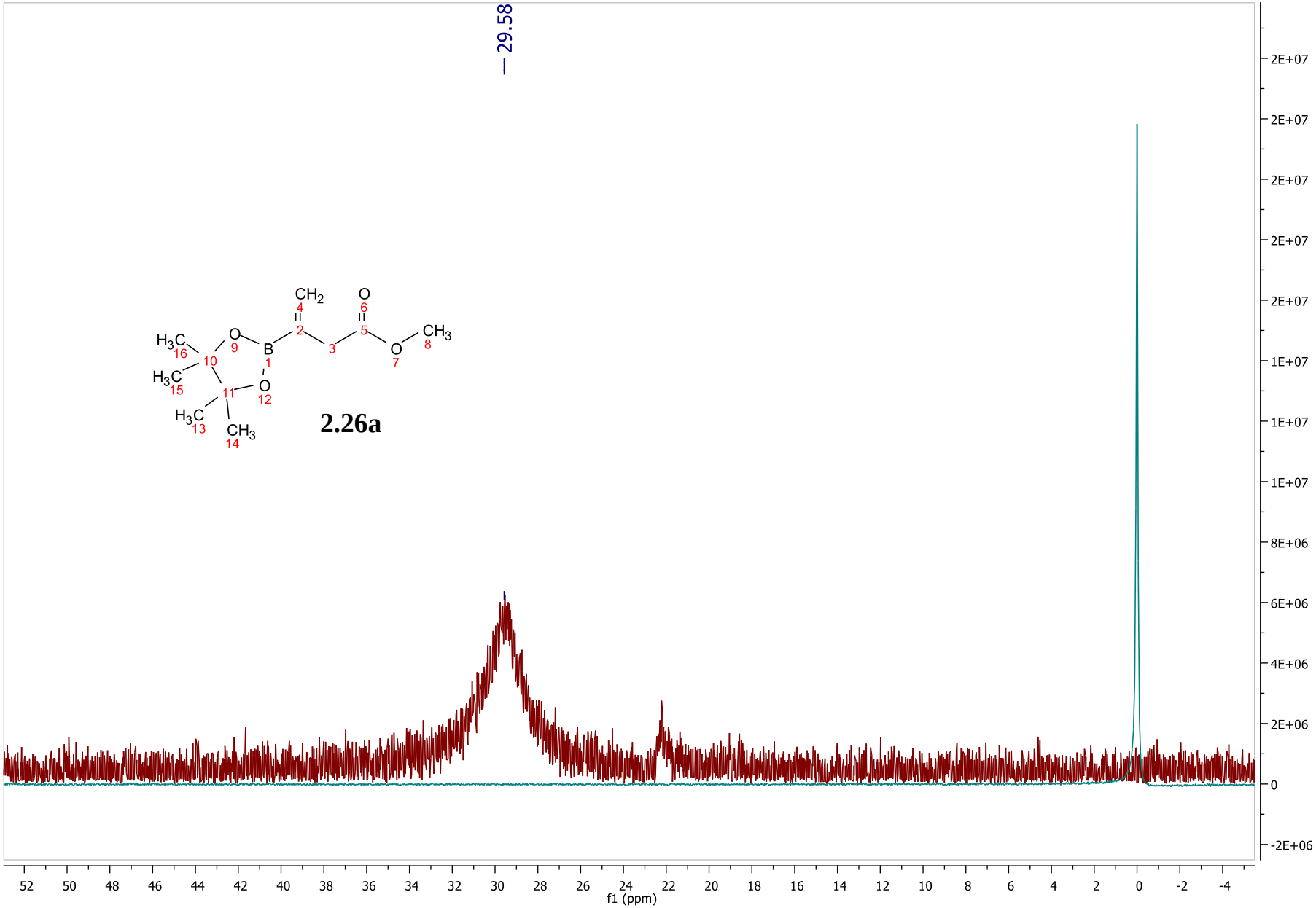

167.87
134.98
134.96
134.29
134.21
130.29
130.19
118.03
117.34
62.86
36.88
36.48
13.60
13.00
Br
O
P
O
2.39
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.81
7.80
7.80
7.79
7.78
7.69
7.69
7.67
7.60
7.59
7.58
7.57
7.56
7.14
7.13
7.08
7.07
7.07
7.04
6.98
6.97
6.96
6.95
5.43
5.40
3.90
3.88
3.87
2.41
2.39
2.37
1.65
1.63
1.61
Br
O
P
O
2.40
5.92
3.01
5.80
1.77
0.92
1.79
2.00
1.96
2.01
2.04
f1 (ppm)

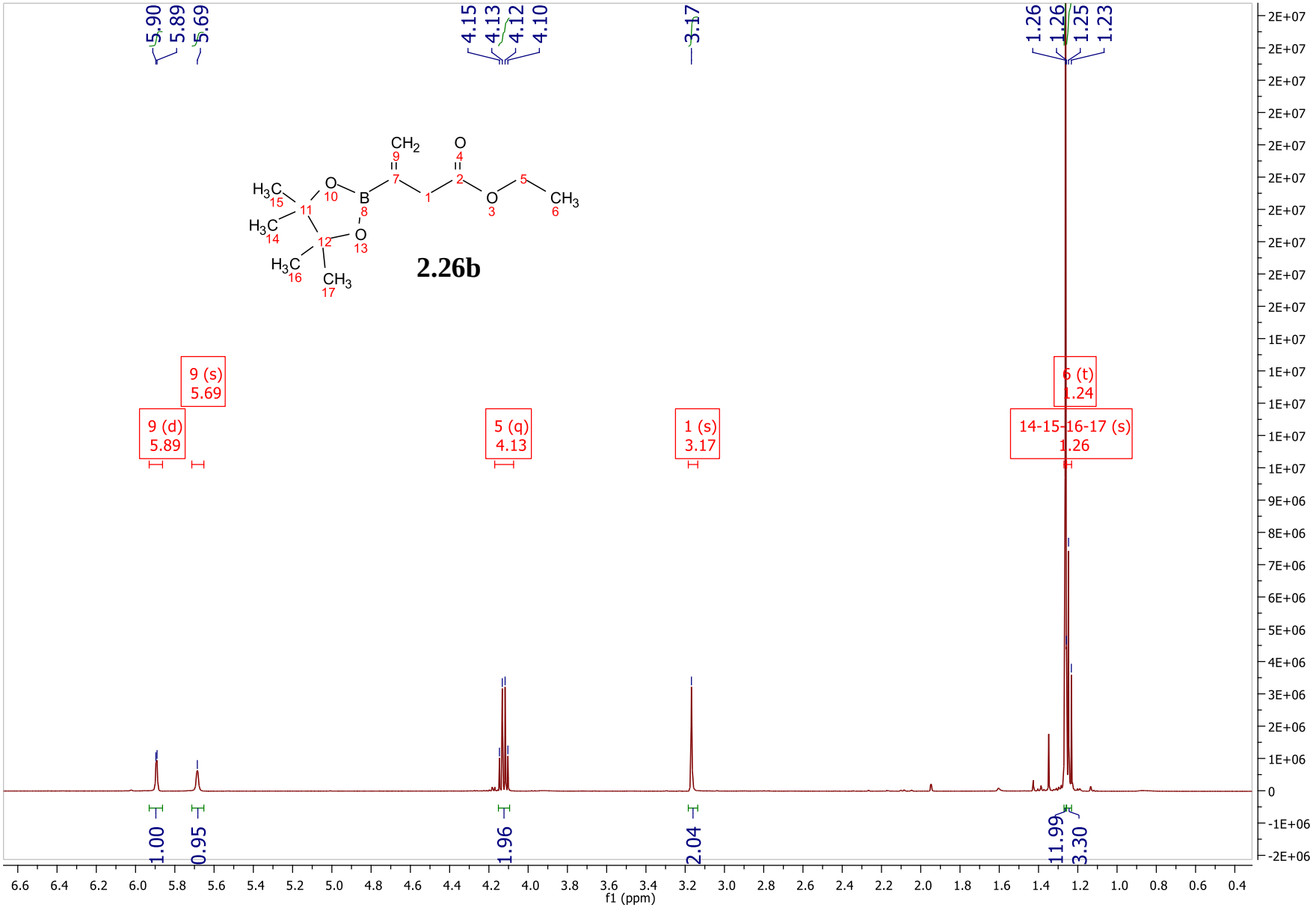

164.30
140.39
135.11
135.08
133.81
133.70
130.23
130.09
128.24
128.16
125.87
118.08
117.20
65.95
33.25
32.70
31.55
29.40
Br
O
P
O
2.40
f1 (ppm)

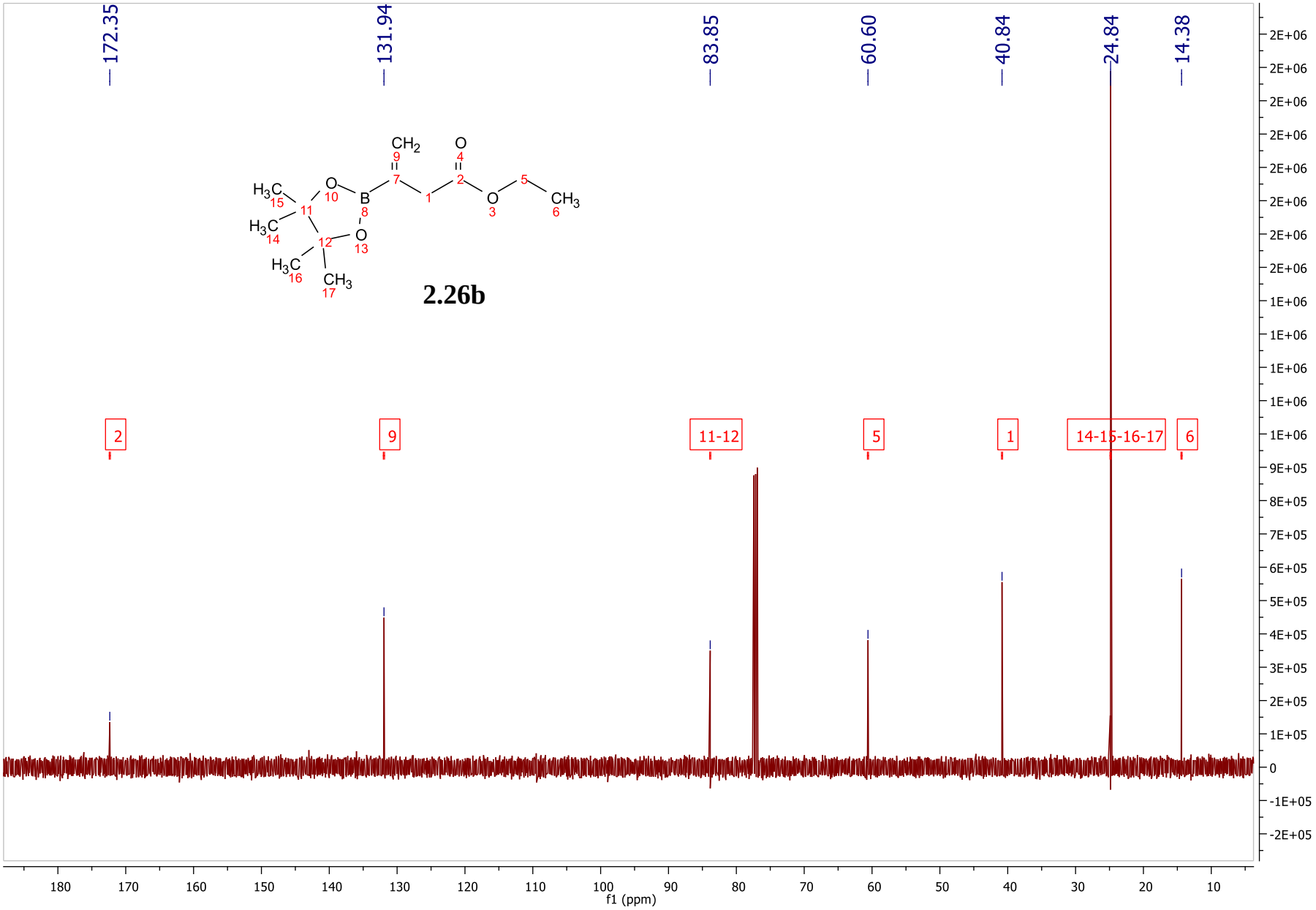

5.90
5.89
5.69
3.66
3.19
1.26
CH2
O
4
6
2
5
H3C
16
O
9
B
1
3
O
7
CH3
8
10
H3C
15
11
O
12
H3C
13
CH3
14
2.26a
4 (s)
5.69
4 (d)
5.89
8 (s)
3.66
3 (s)
3.19
13-14-15-16 (s)
1.26
1.00
1.03
2.72
1.89
12.44
9E+06
8E+06
8E+06
8E+06
7E+06
6E+06
6E+06
6E+06
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
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
f1 (ppm)

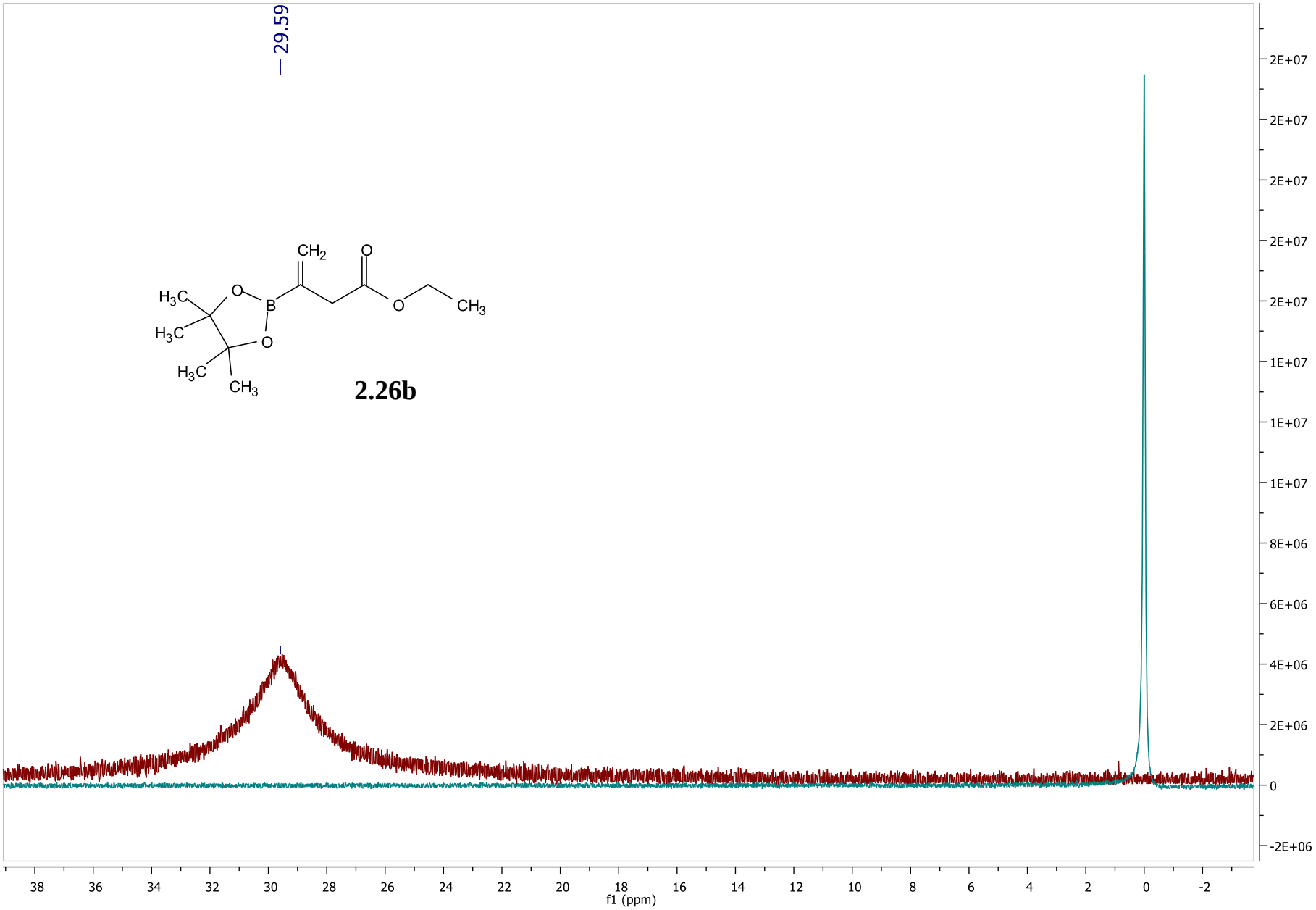

172.75
132.02
83.89
51.81
40.62
24.81
5
4
10-11
8
3
13-14-15-16
2.26a
f1 (ppm)

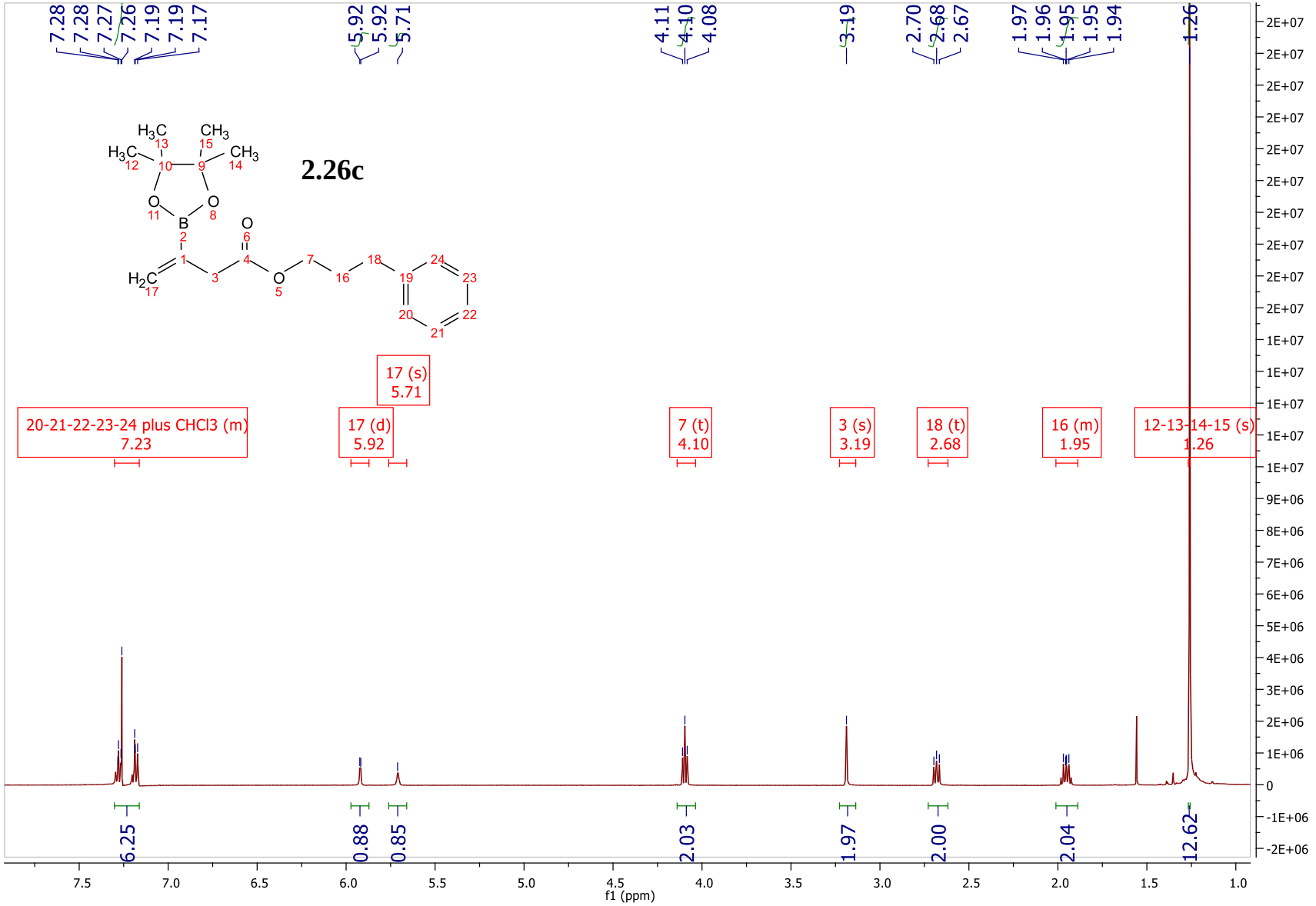

29.58
2E+07
2E+07
2E+07
2E+07
2E+07
1E+07
1E+07
1E+07
8E+06
6E+06
4E+06
2E+06
0
-2E+06
52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2 -4
f1 (ppm)

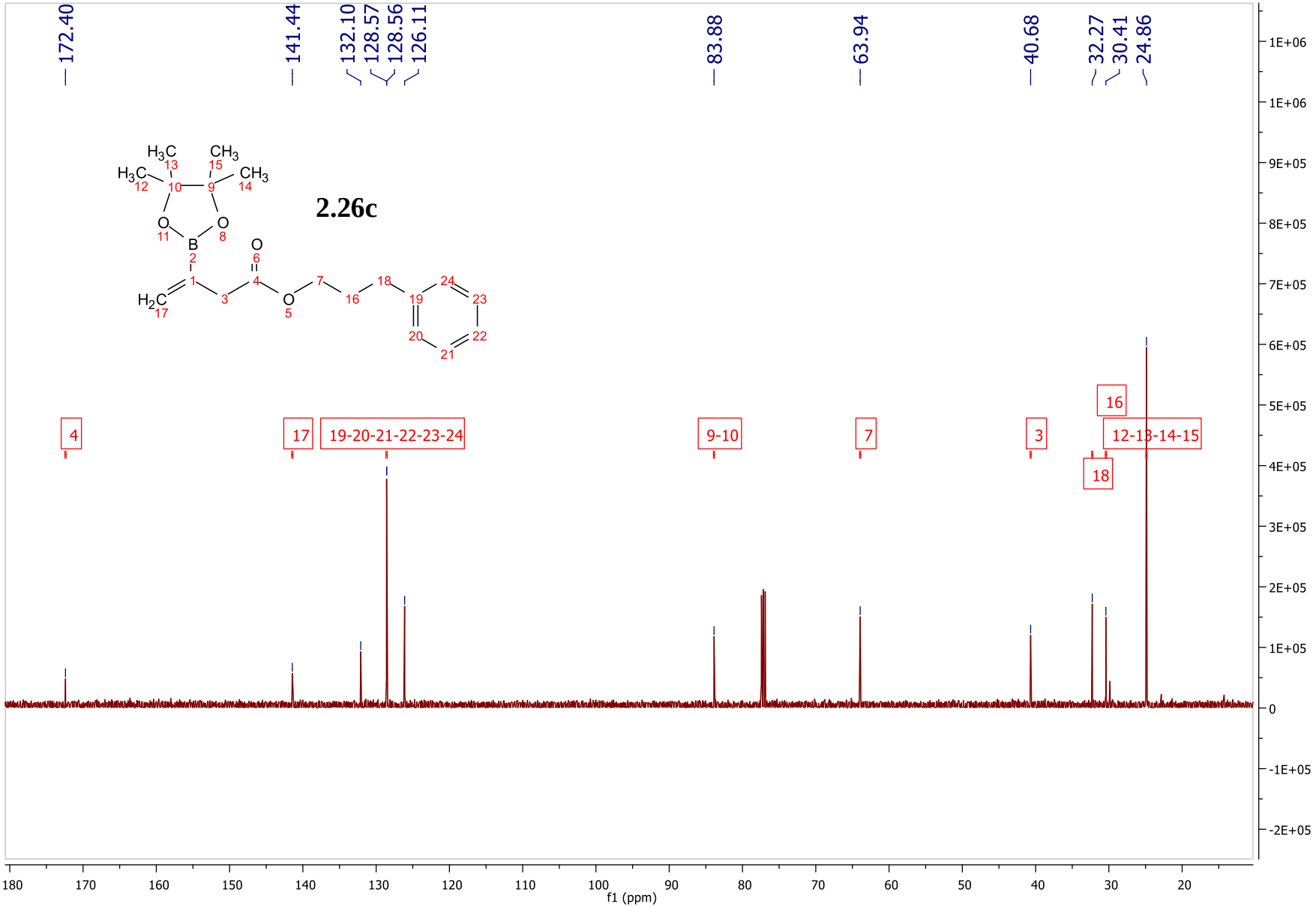
2.26a

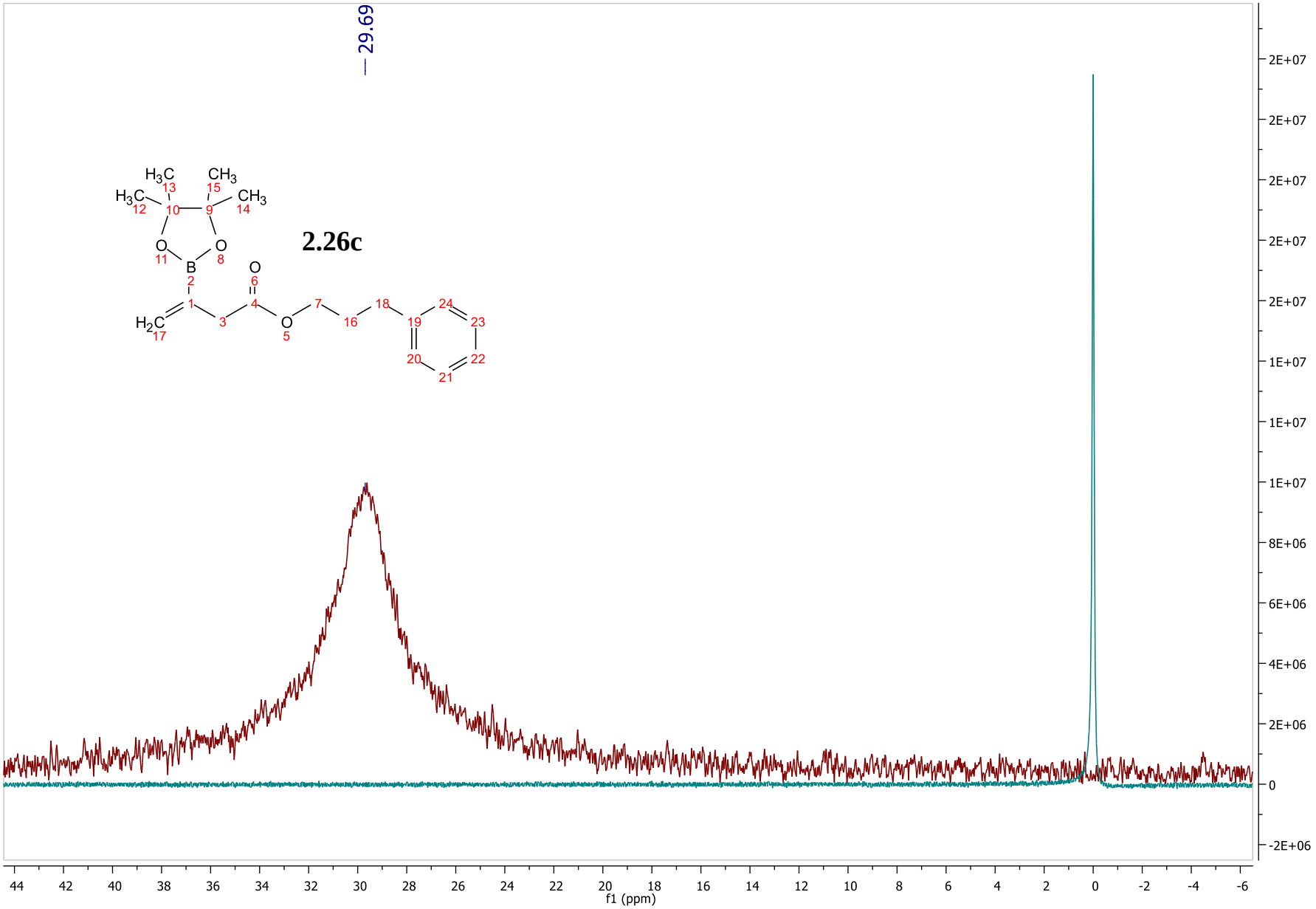

5.90
5.89
5.69
4.15
4.13
4.12
4.10
3.17
1.26
1.26
1.25
1.23
2.26b
9 (s)
5.69
9 (d)
5.89
5 (q)
4.13
1 (s)
3.17
6 (t)
1.24
14-15-16-17 (s)
1.26
1.00
0.95
1.96
2.04
11.99
3.30
f1 (ppm)

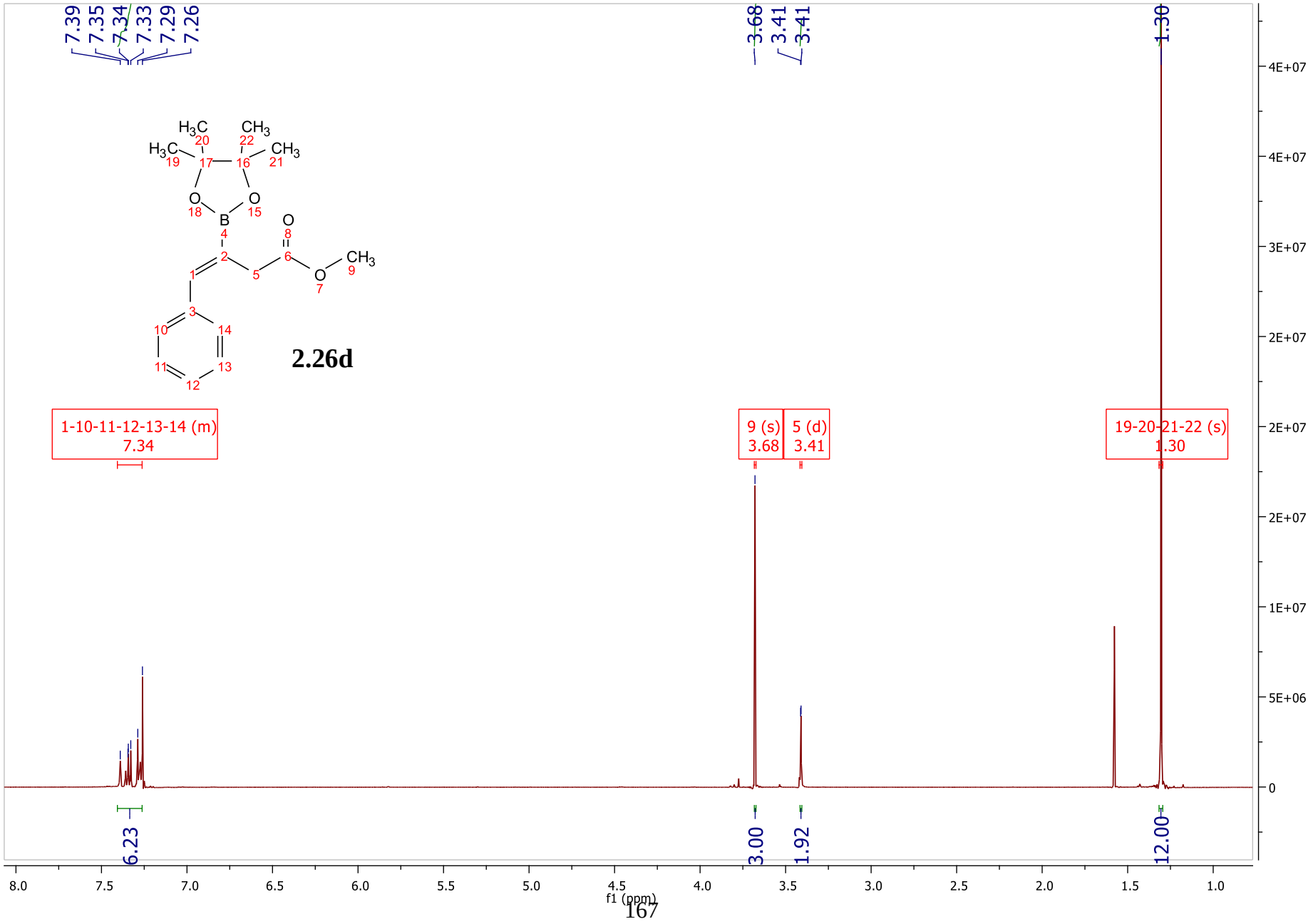

172.35
131.94
83.85
60.60
40.84
24.84
14.38
2
9
11-12
5
1
14-15-16-17
6
2.26b
f1 (ppm)

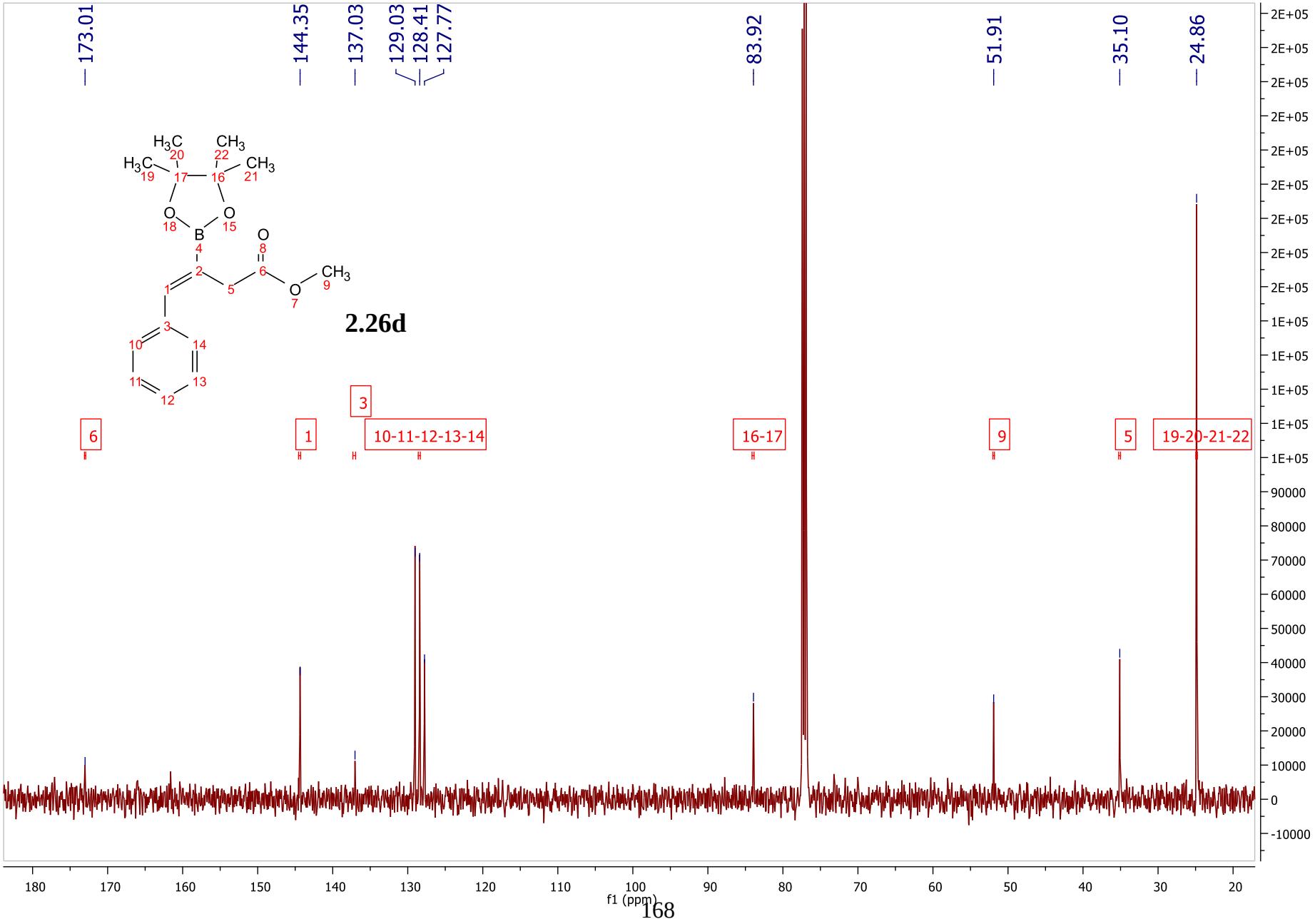

29.59
CH2
O
H3C
O
B
O
CH3
H3C
O
H3C
CH3
2.26b
2E+07
2E+07
2E+07
2E+07
2E+07
1E+07
1E+07
1E+07
8E+06
6E+06
4E+06
2E+06
0
-2E+06
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
-2
f1 (ppm)

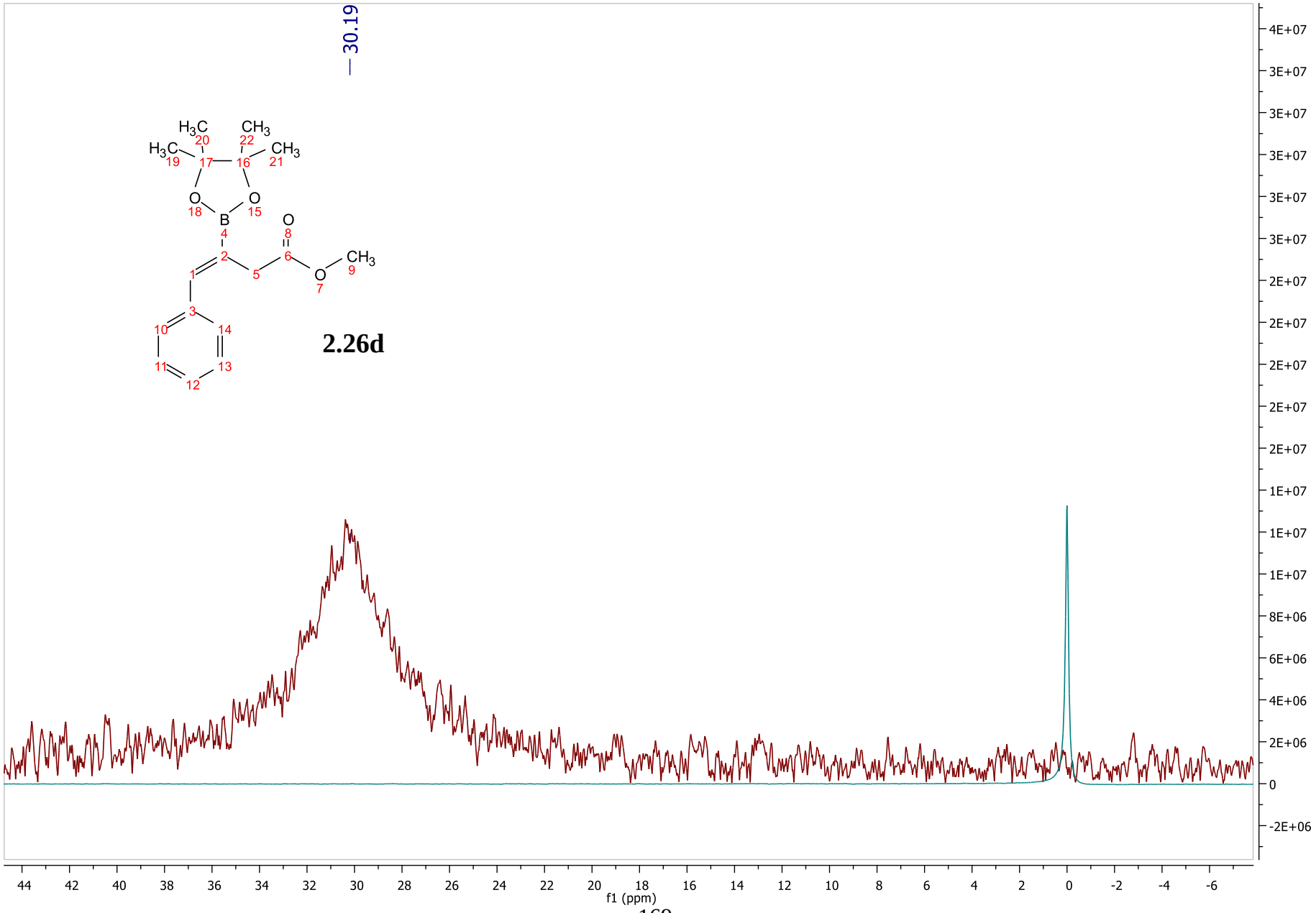

2.26c
7.28
7.28
7.27
7.26
7.19
7.19
7.17
5.92
5.92
5.71
4.11
4.10
4.08
3.19
2.70
2.68
2.67
1.97
1.96
1.95
1.95
1.94
1.26
17 (s)
5.71
20-21-22-23-24 plus CHCl3 (m)
7.23
17 (d)
5.92
7 (t)
4.10
3 (s)
3.19
18 (t)
2.68
16 (m)
1.95
12-13-14-15 (s)
1.26
6.25
0.88
0.85
2.03
1.97
2.00
2.04
12.62
f1 (ppm)

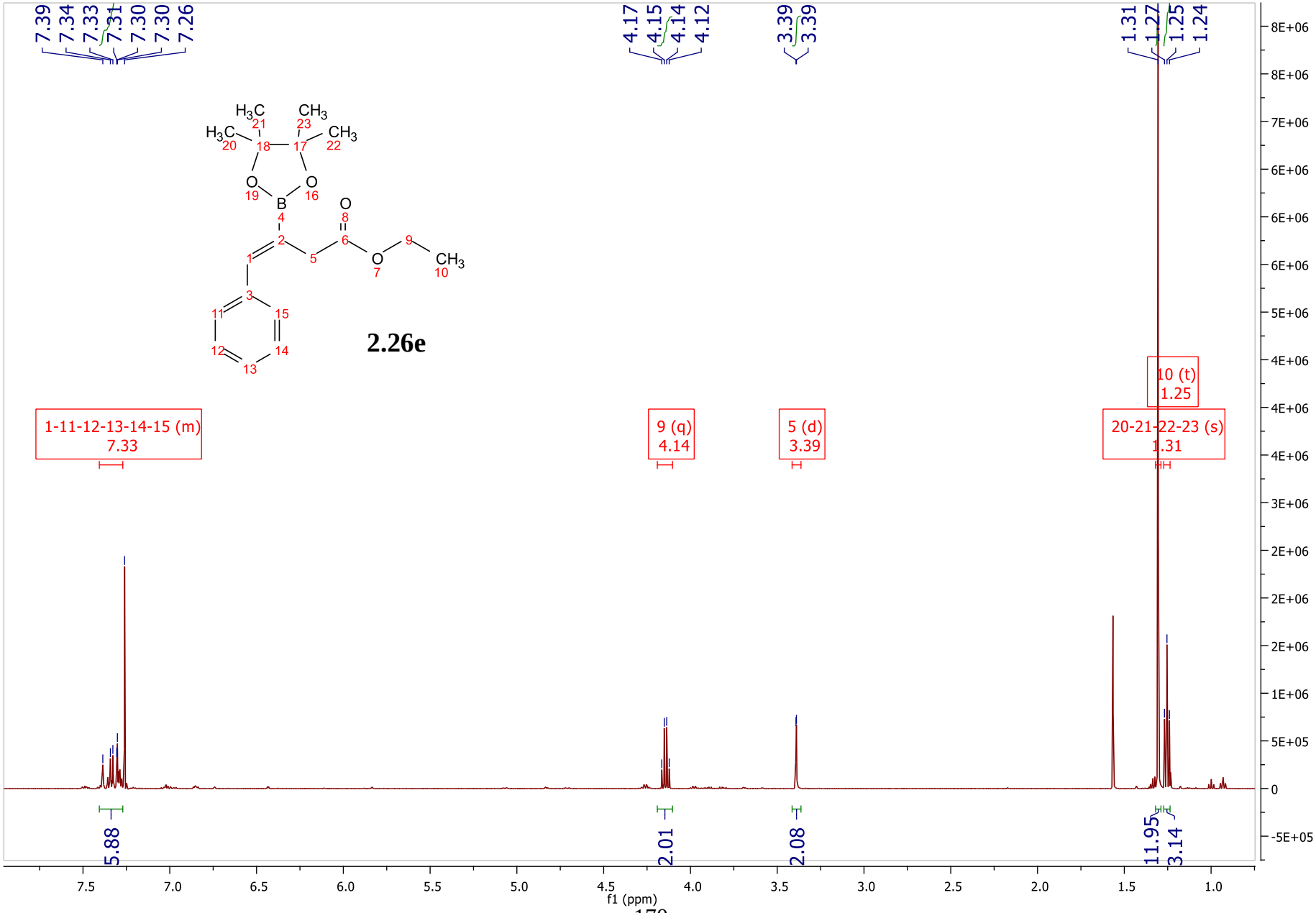

172.40
141.44
132.10
128.57
128.56
126.11
83.88
63.94
40.68
32.27
30.41
24.86
2.26c
4
17
19-20-21-22-23-24
9-10
7
3
16
18
12-13-14-15
1E+06
9E+05
8E+05
7E+05
6E+05
5E+05
4E+05
3E+05
2E+05
1E+05
0
-1E+05
-2E+05
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

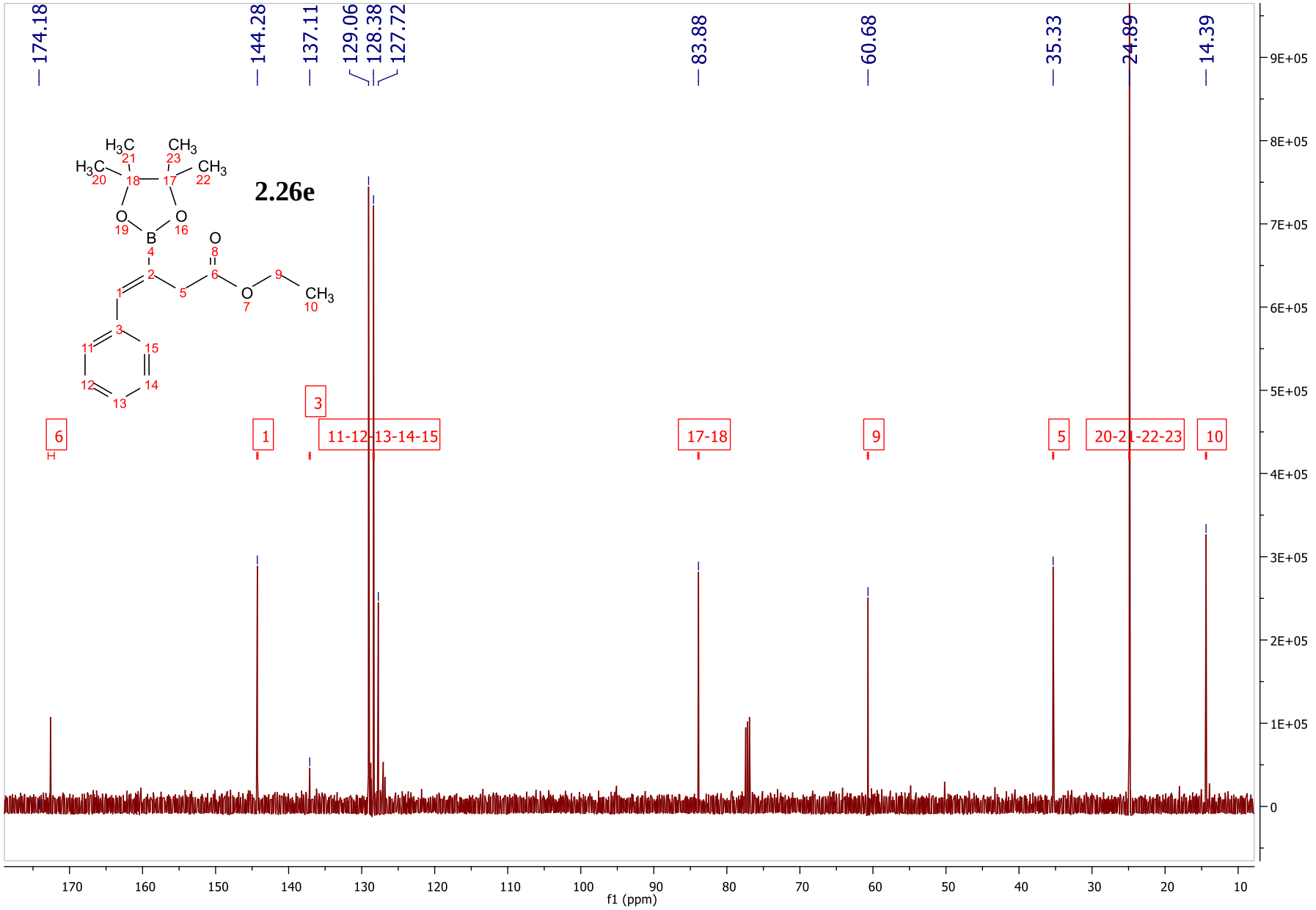

29.69
2.26c
f1 (ppm)

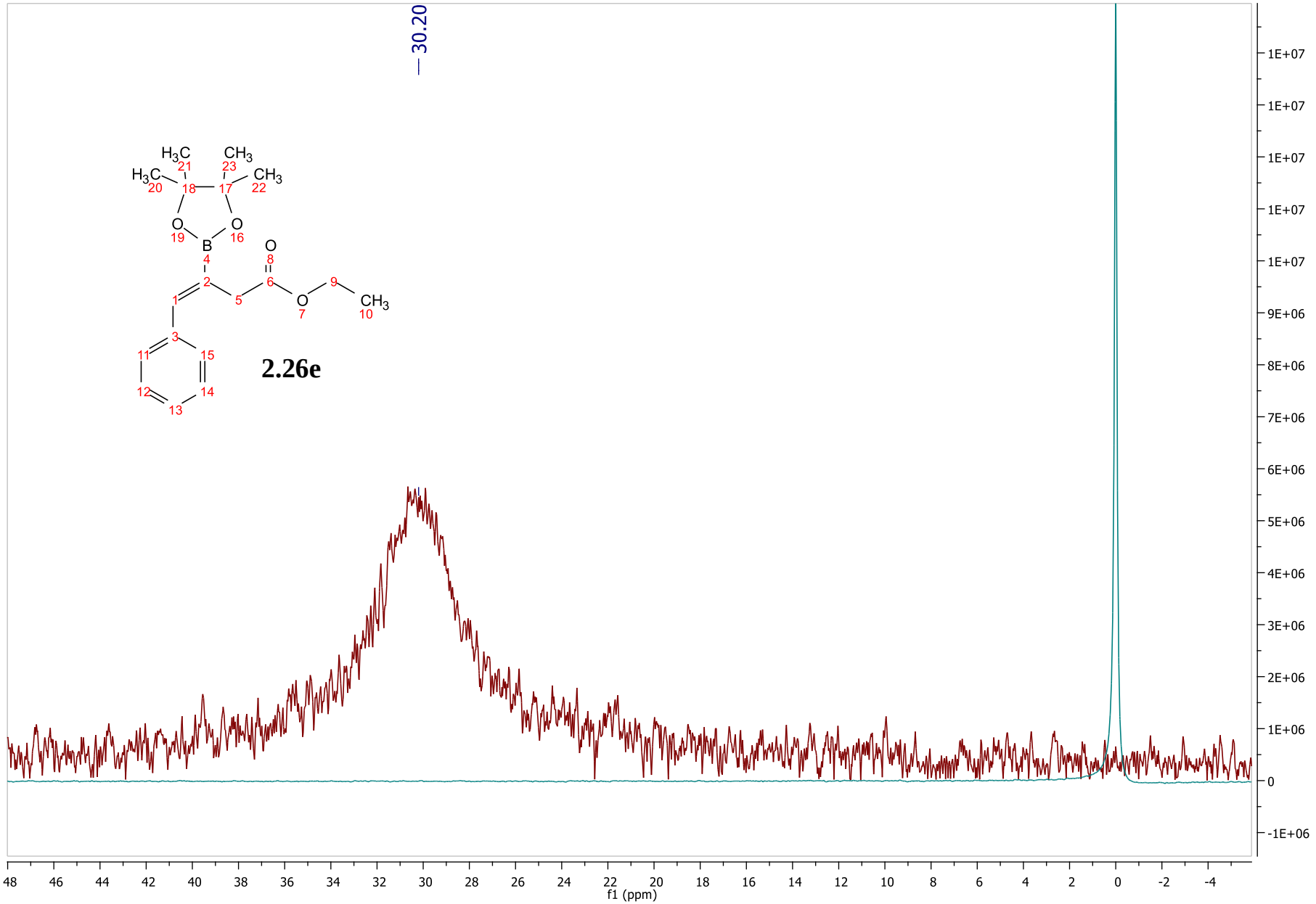

7.39
7.35
7.34
7.33
7.29
7.26
3.68
3.41
3.41
1.30
2.26d
1-10-11-12-13-14 (m)
7.34
9 (s)
3.68
5 (d)
3.41
19-20-21-22 (s)
1.30
6.23
3.00
1.92
12.00
f1 (ppm)

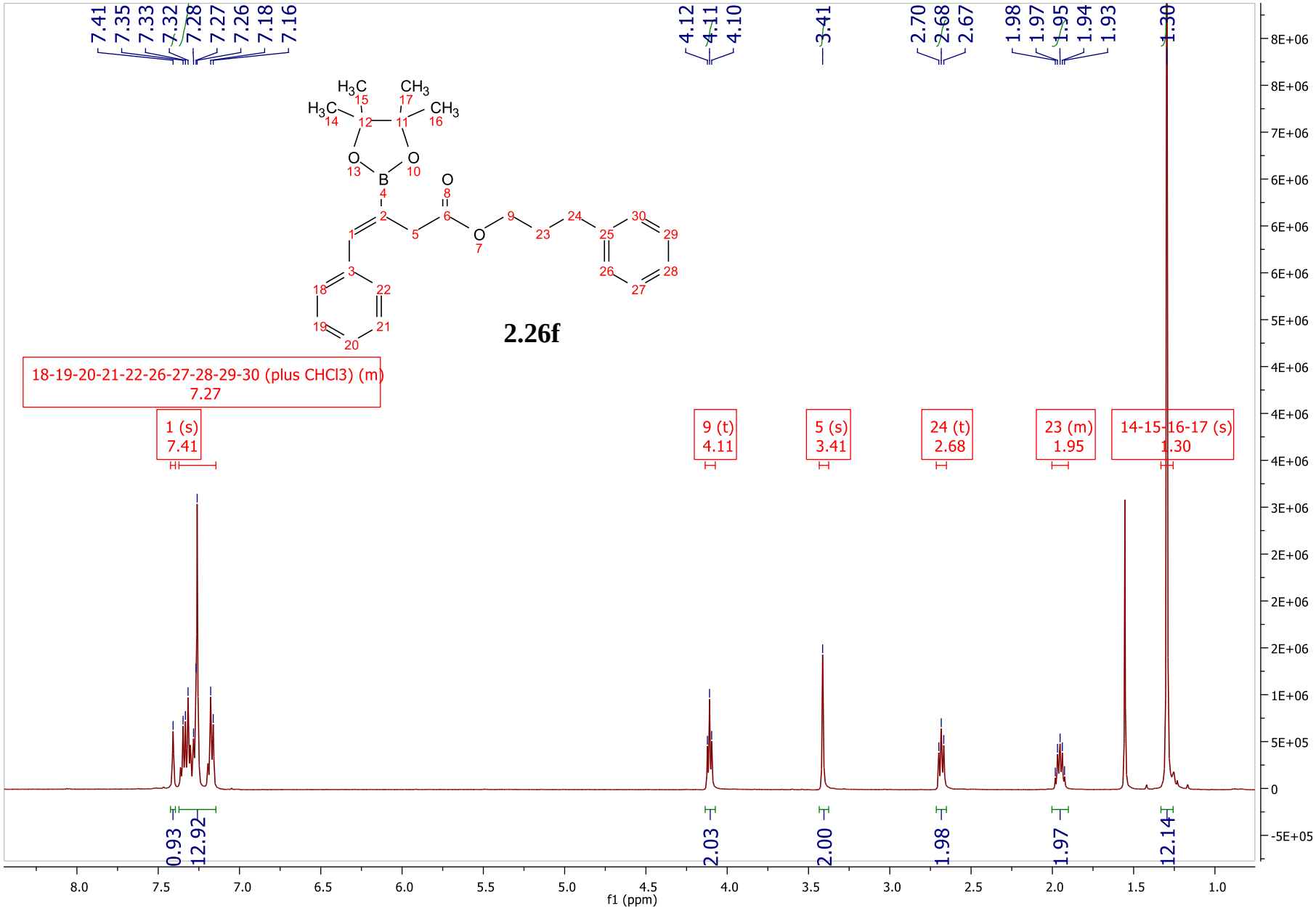

173.01
144.35
137.03
129.03
128.41
127.77
83.92
51.91
35.10
24.86
2.26d
6
1
3
10-11-12-13-14
16-17
9
5
19-20-21-22
f1 (ppm)

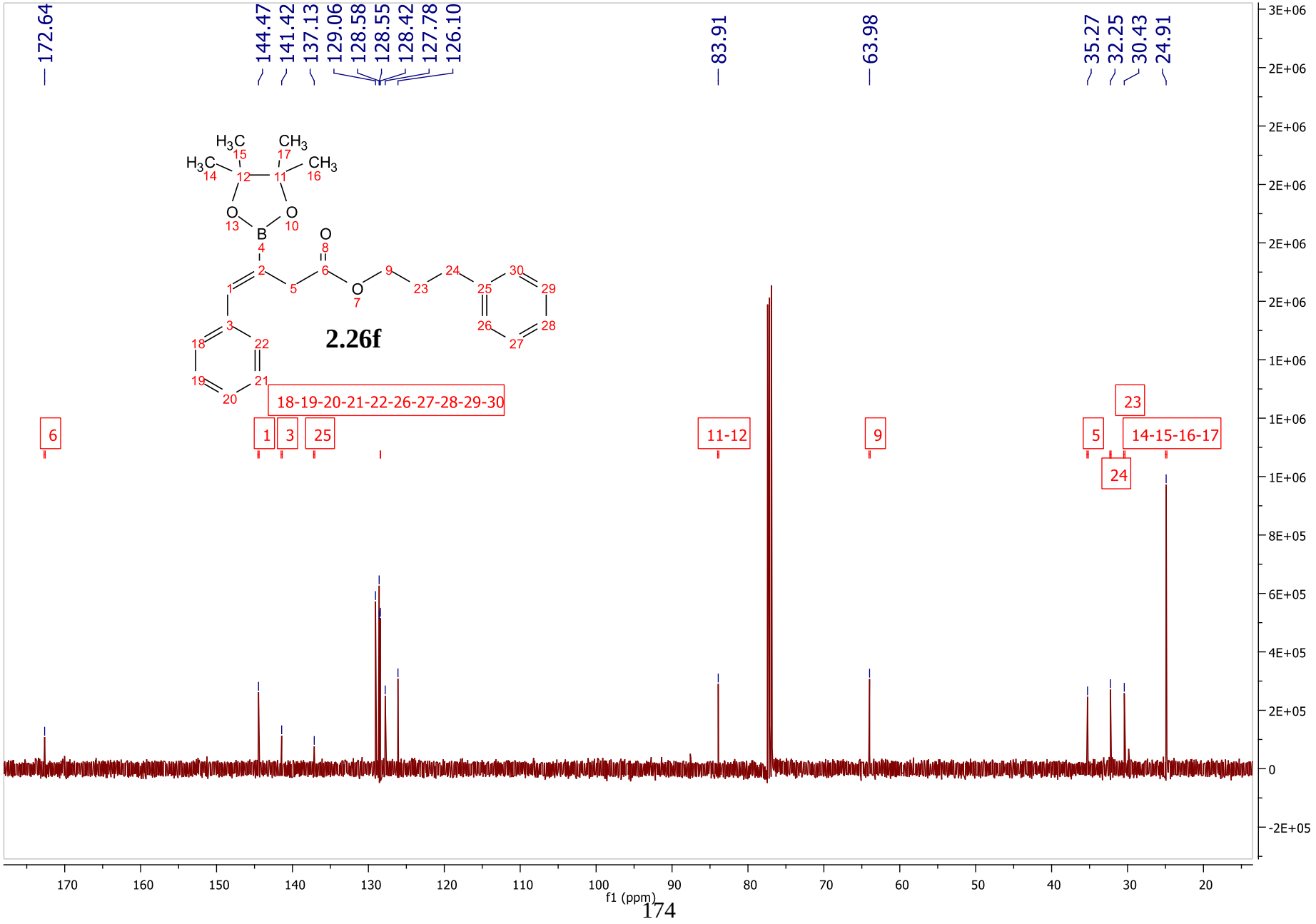

30.19
2.26d
f1 (ppm)

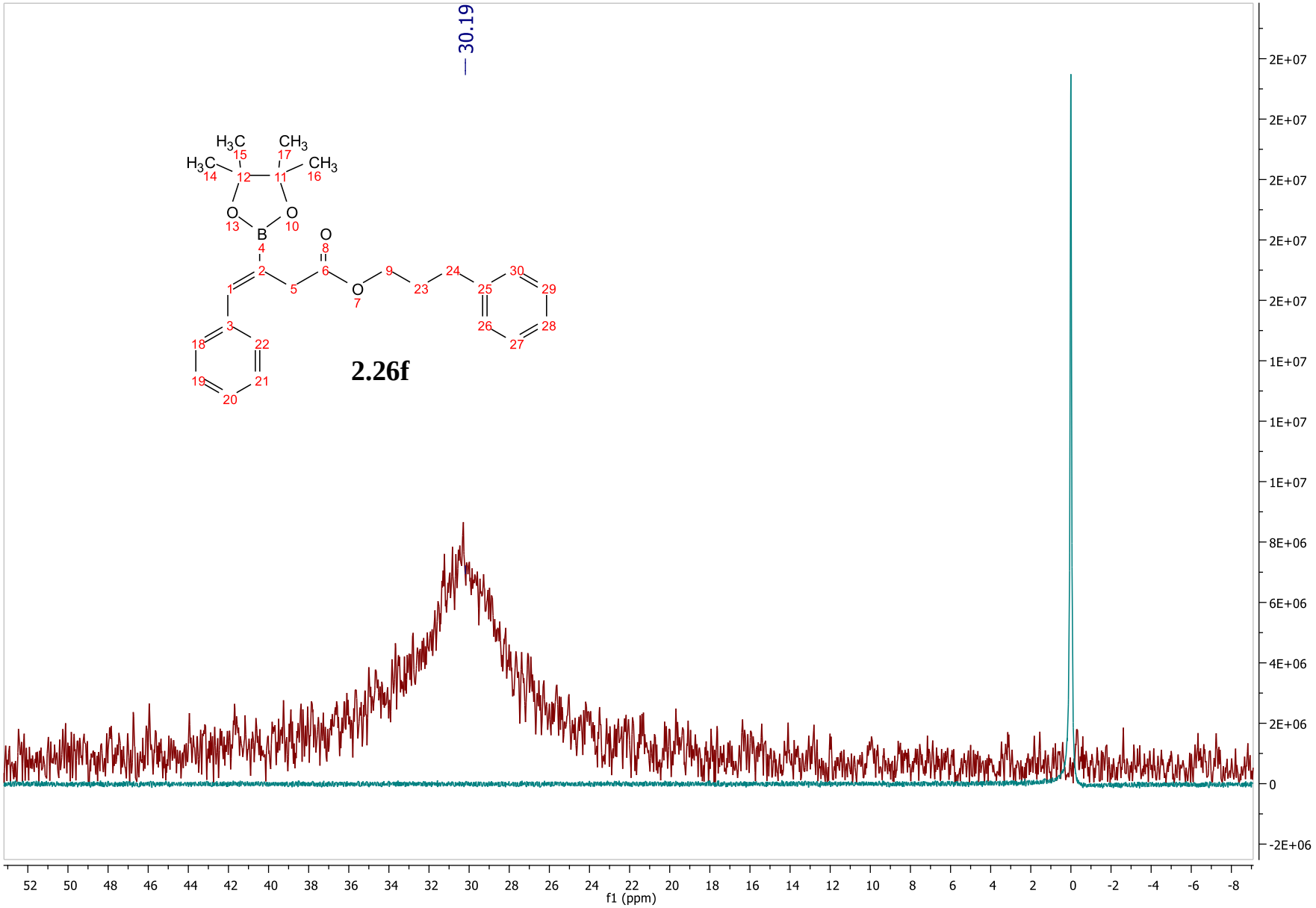

7.39
7.34
7.33
7.31
7.30
7.30
7.26
4.17
4.15
4.14
4.12
3.39
3.39
1.31
1.27
1.25
1.24
2.26e
1-11-12-13-14-15 (m)
7.33
9 (q)
4.14
5 (d)
3.39
10 (t)
1.25
20-21-22-23 (s)
1.31
5.88
2.01
2.08
11.95
3.14
f1 (ppm)

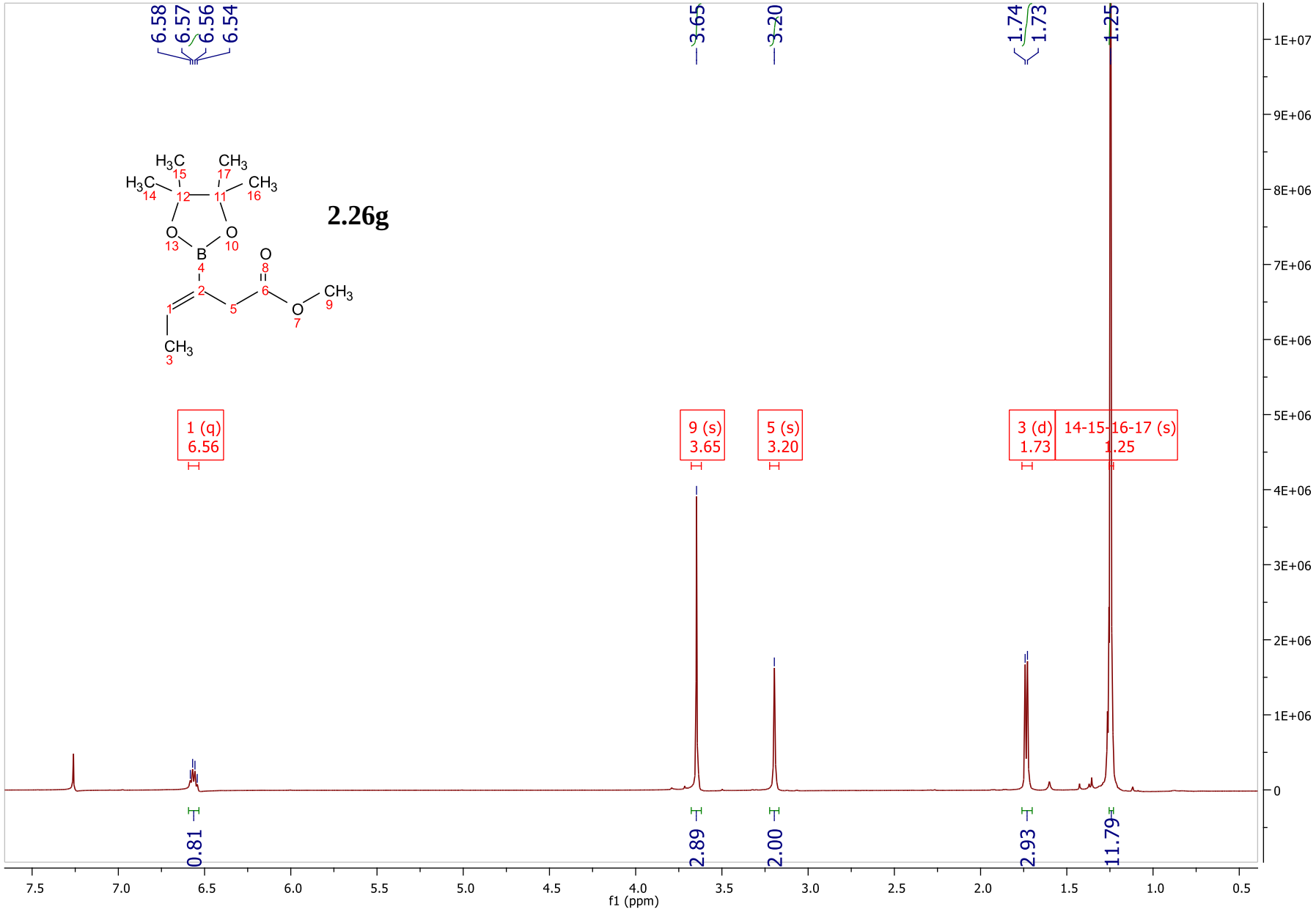

174.18
144.28
137.11
129.06
128.38
127.72
83.88
60.68
35.33
24.89
14.39
2.26e
6
1
3
11-12-13-14-15
17-18
9
5
20-21-22-23
10
9E+05
8E+05
7E+05
6E+05
5E+05
4E+05
3E+05
2E+05
1E+05
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

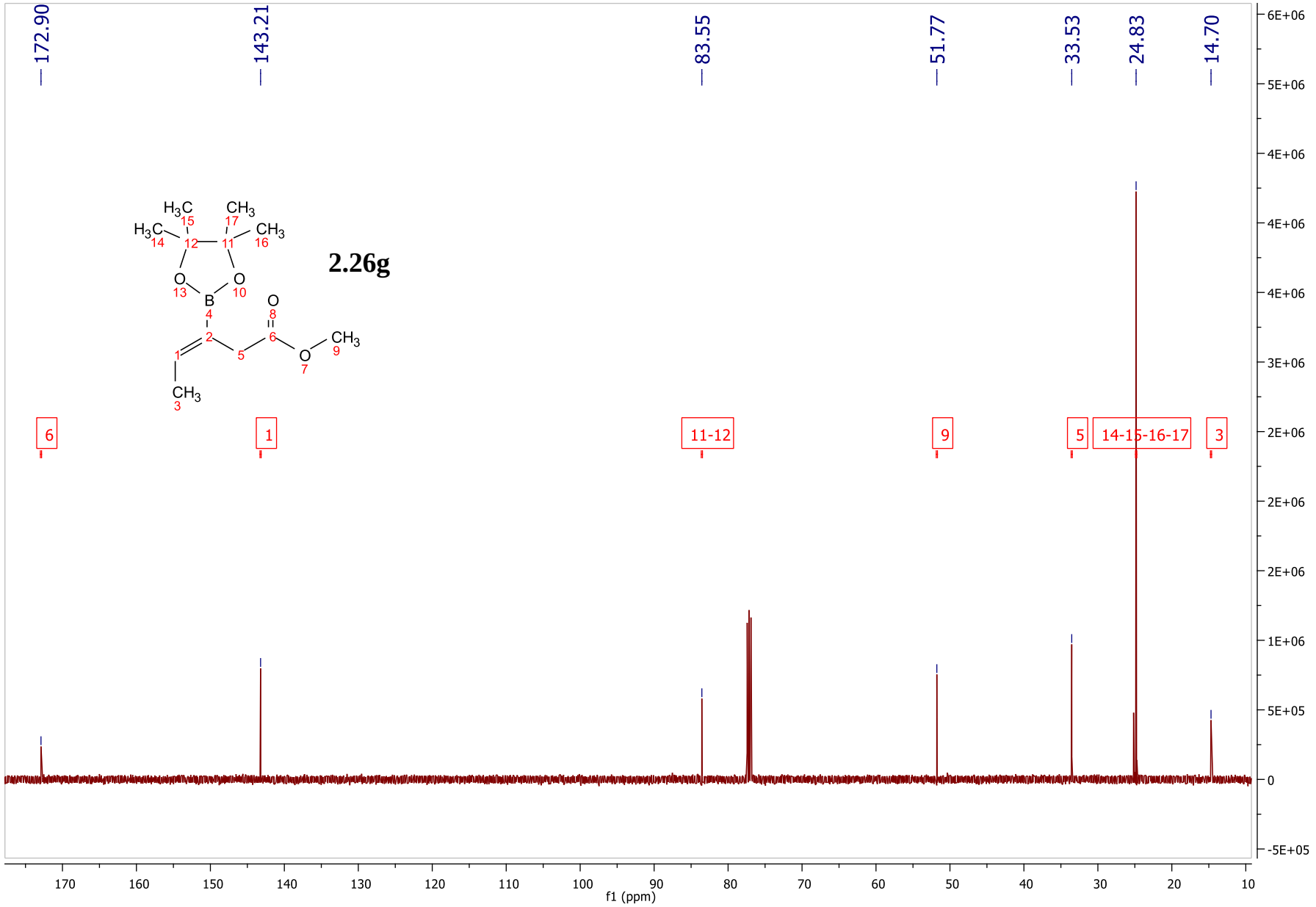

30.20
2.26e
1E+07
1E+07
1E+07
1E+07
1E+07
9E+06
8E+06
7E+06
6E+06
5E+06
4E+06
3E+06
2E+06
1E+06
0
-1E+06
48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2 -4
f1 (ppm)

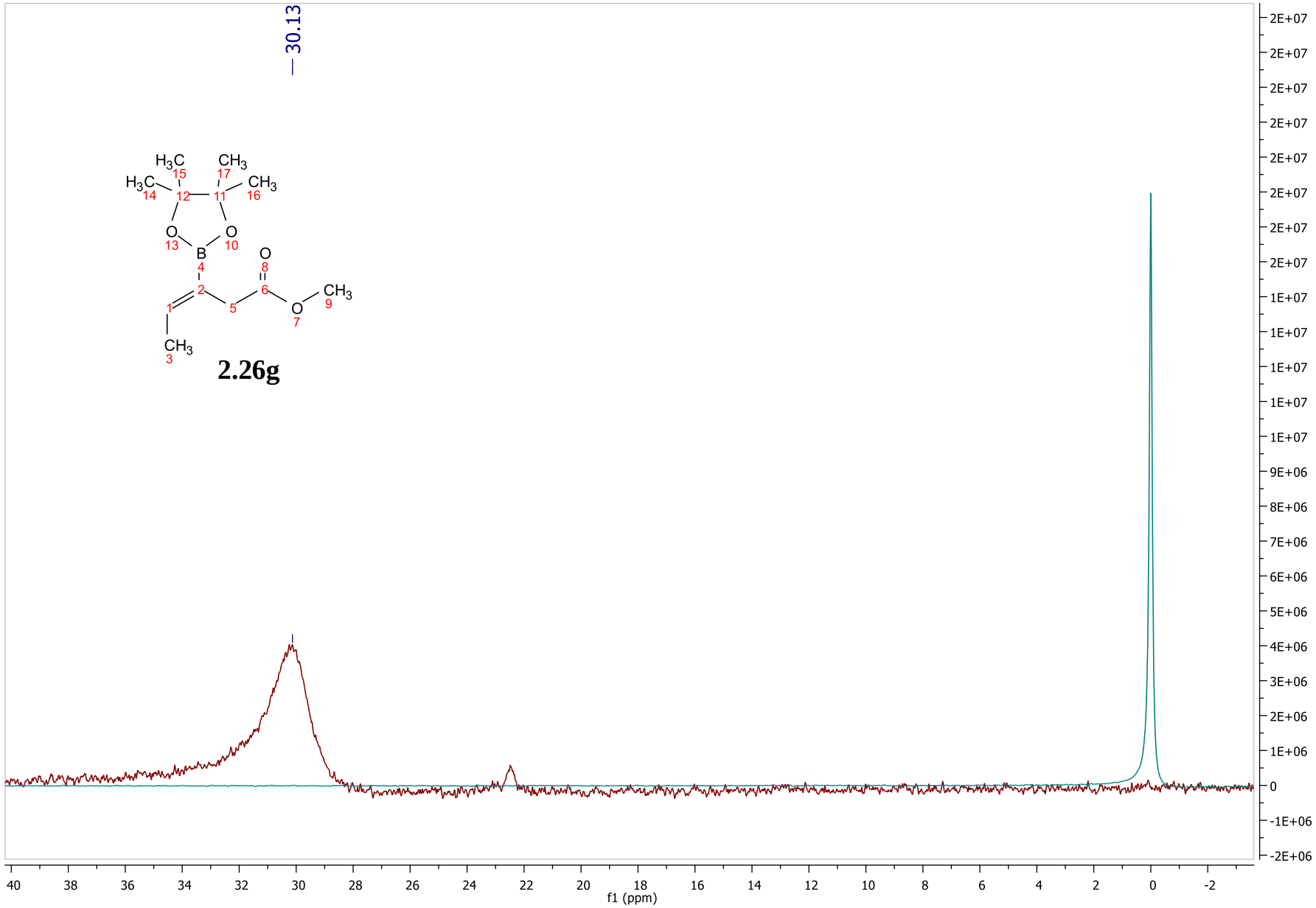

7.41
7.35
7.33
7.32
7.28
7.27
7.26
7.18
7.16
4.12
4.11
4.10
3.41
2.70
2.68
2.67
1.98
1.97
1.95
1.94
1.93
1.30
2.26f
18-19-20-21-22-26-27-28-29-30 (plus CHCl3) (m)
7.27
1 (s)
7.41
9 (t)
4.11
5 (s)
3.41
24 (t)
2.68
23 (m)
1.95
14-15-16-17 (s)
1.30
0.93
12.92
2.03
2.00
1.98
1.97
12.14
f1 (ppm)

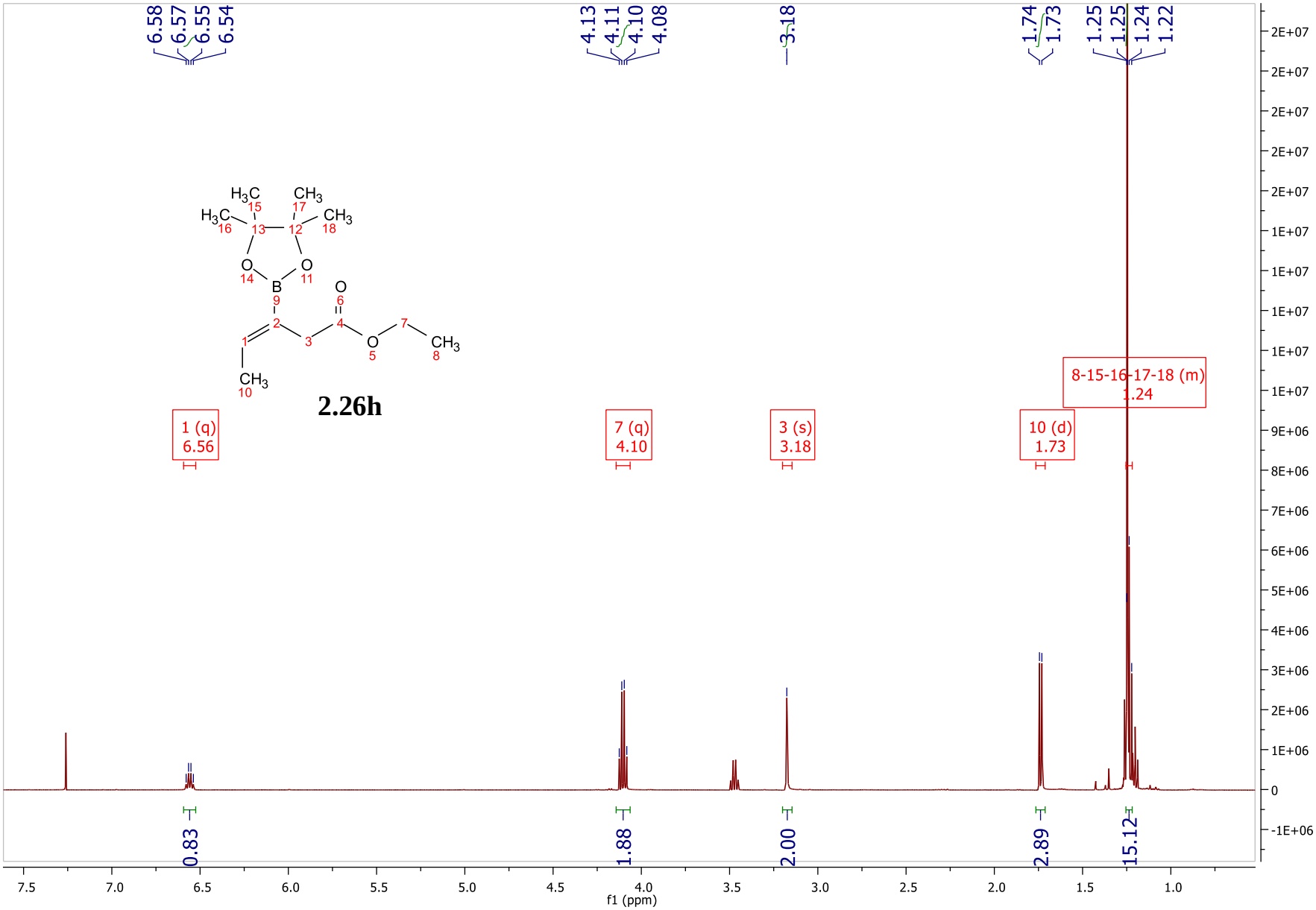

172.64
144.47
141.42
137.13
129.06
128.58
128.55
128.42
127.78
126.10
83.91
63.98
35.27
32.25
30.43
24.91
2.26f
18-19-20-21-22-26-27-28-29-30
6
1
3
25
11-12
9
5
23
14-15-16-17
24
f1 (ppm)

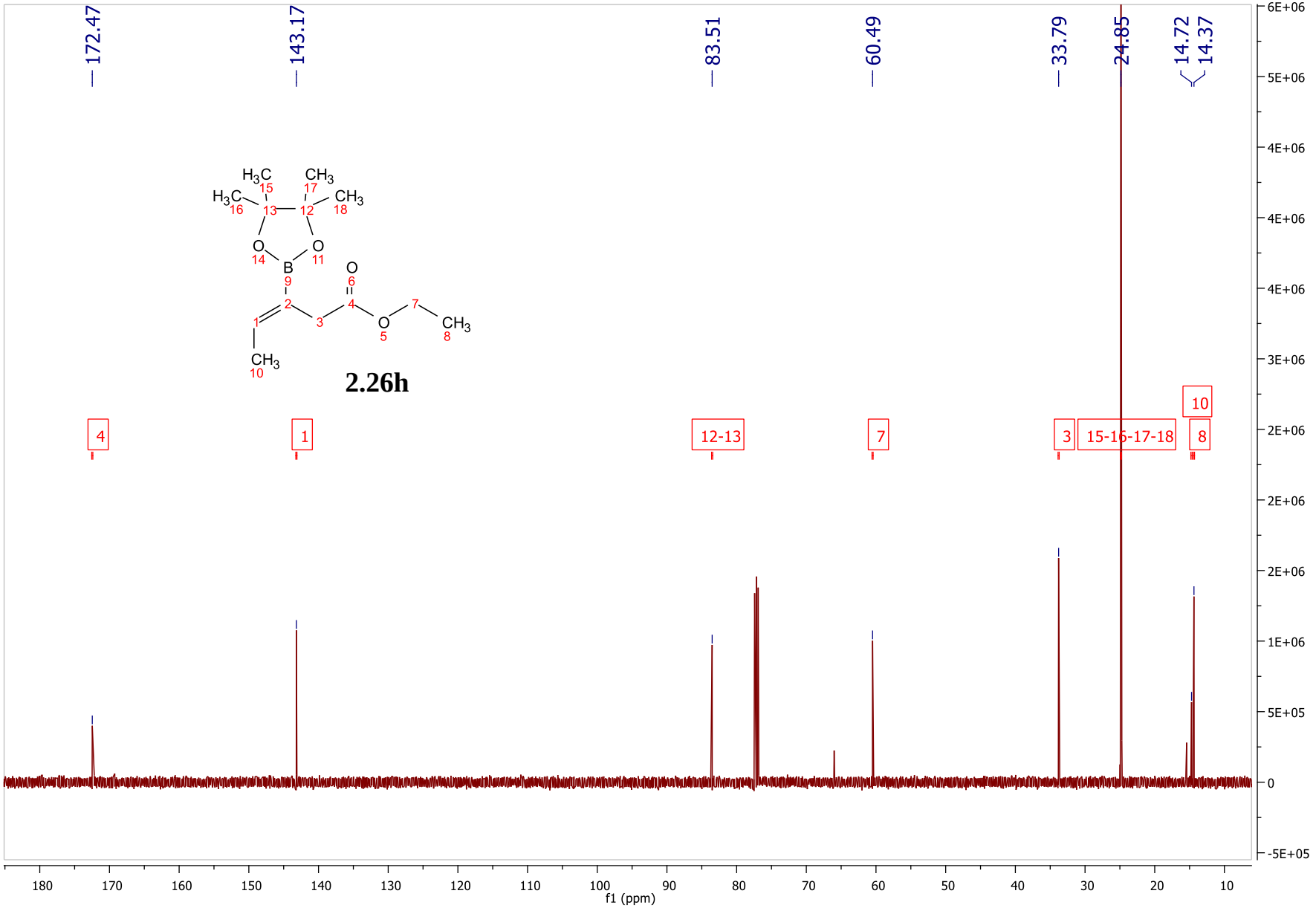

30.19
2.26f
2E+07
2E+07
2E+07
2E+07
2E+07
1E+07
1E+07
1E+07
8E+06
6E+06
4E+06
2E+06
0
-2E+06
52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2 -4 -6 -8
f1 (ppm)

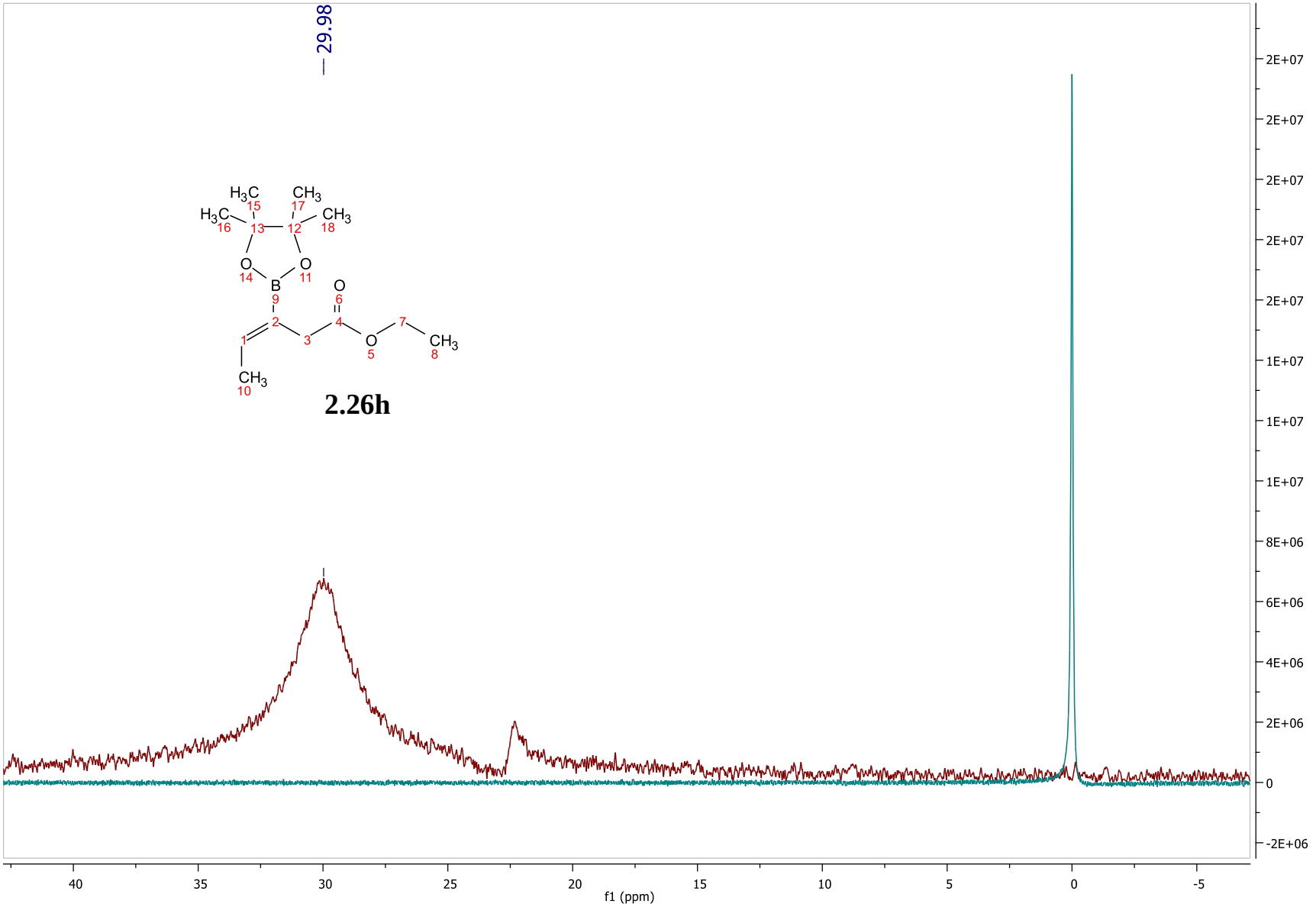

6.58
6.57
6.56
6.54
3.65
3.20
1.74
1.73
1.25
2.26g
1 (q)
6.56
9 (s)
3.65
5 (s)
3.20
3 (d)
1.73
14-15-16-17 (s)
1.25
0.81
2.89
2.00
2.93
11.79
f1 (ppm)

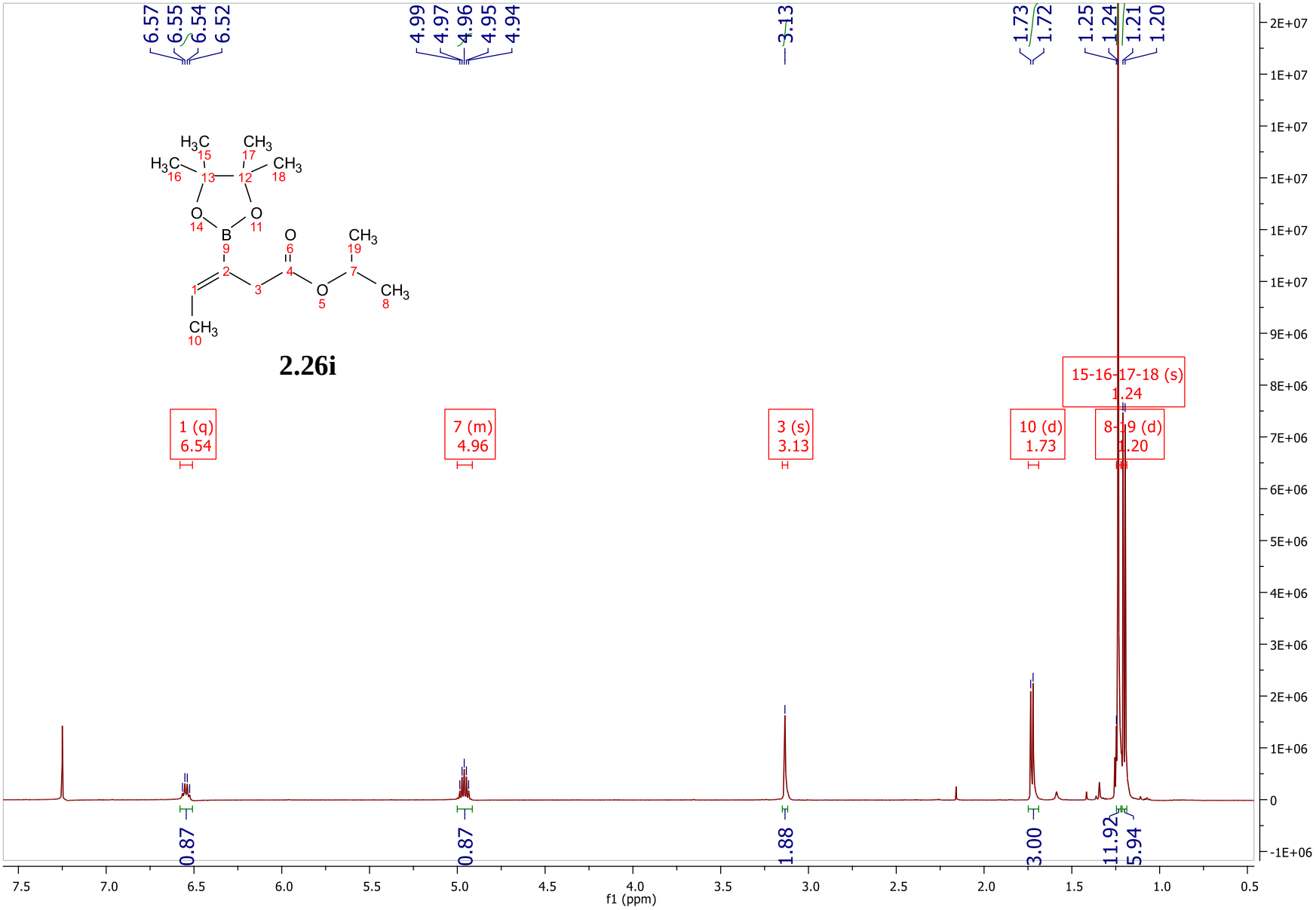

172.90
143.21
83.55
51.77
33.53
24.83
14.70
2.26g
6
1
11-12
9
5
14-15-16-17
3
f1 (ppm)

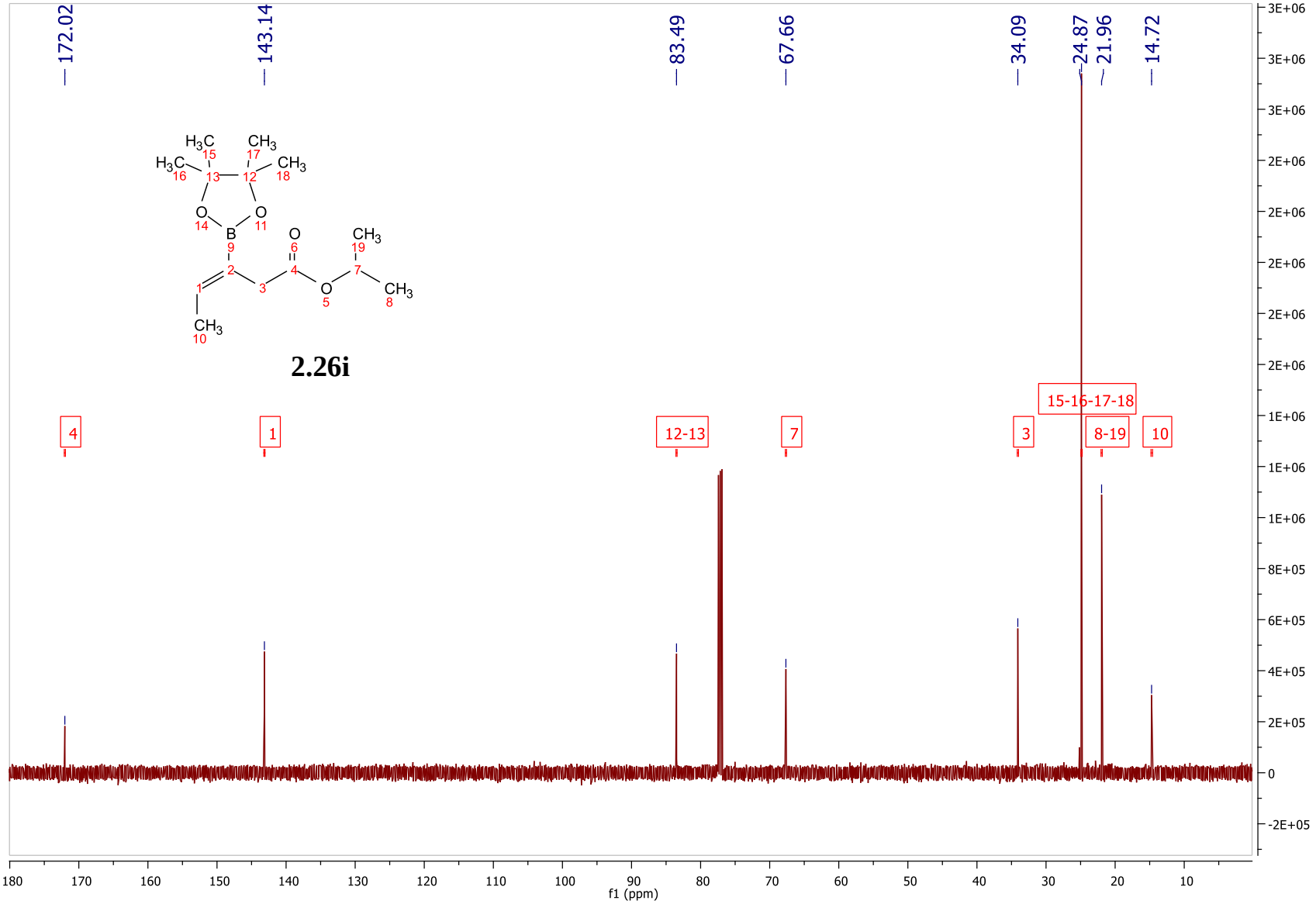

30.13
2.26g
f1 (ppm)

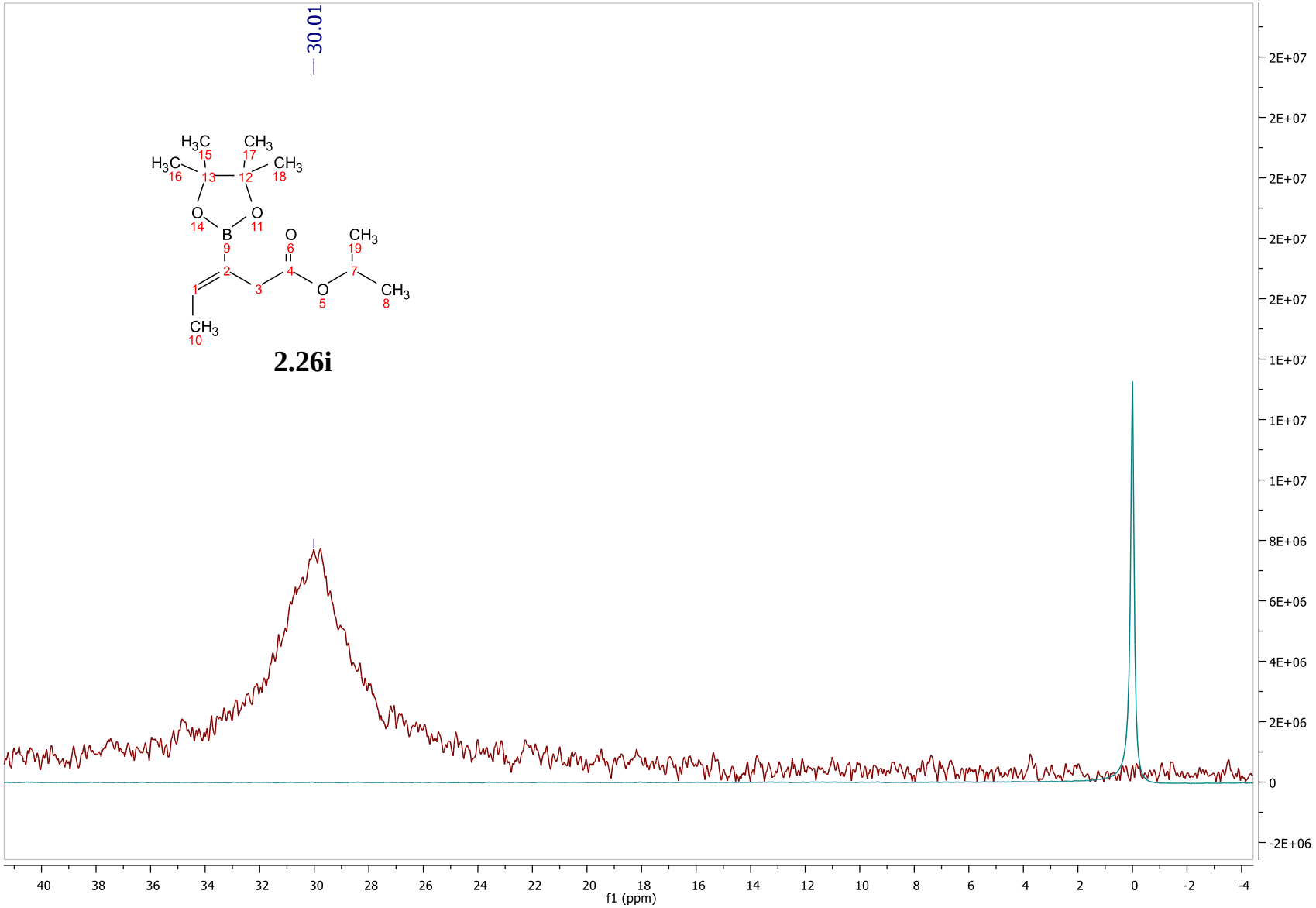

6.58
6.57
6.55
6.54
4.13
4.11
4.10
4.08
3.18
1.74
1.73
1.25
1.25
1.24
1.22
2.26h
1 (q)
6.56
7 (q)
4.10
3 (s)
3.18
10 (d)
1.73
8-15-16-17-18 (m)
1.24
0.83
1.88
2.00
2.89
15.12
f1 (ppm)


172.47
143.17
83.51
60.49
33.79
24.85
14.72
14.37
2.26h
4
1
12-13
7
3
15-16-17-18
10
8
f1 (ppm)

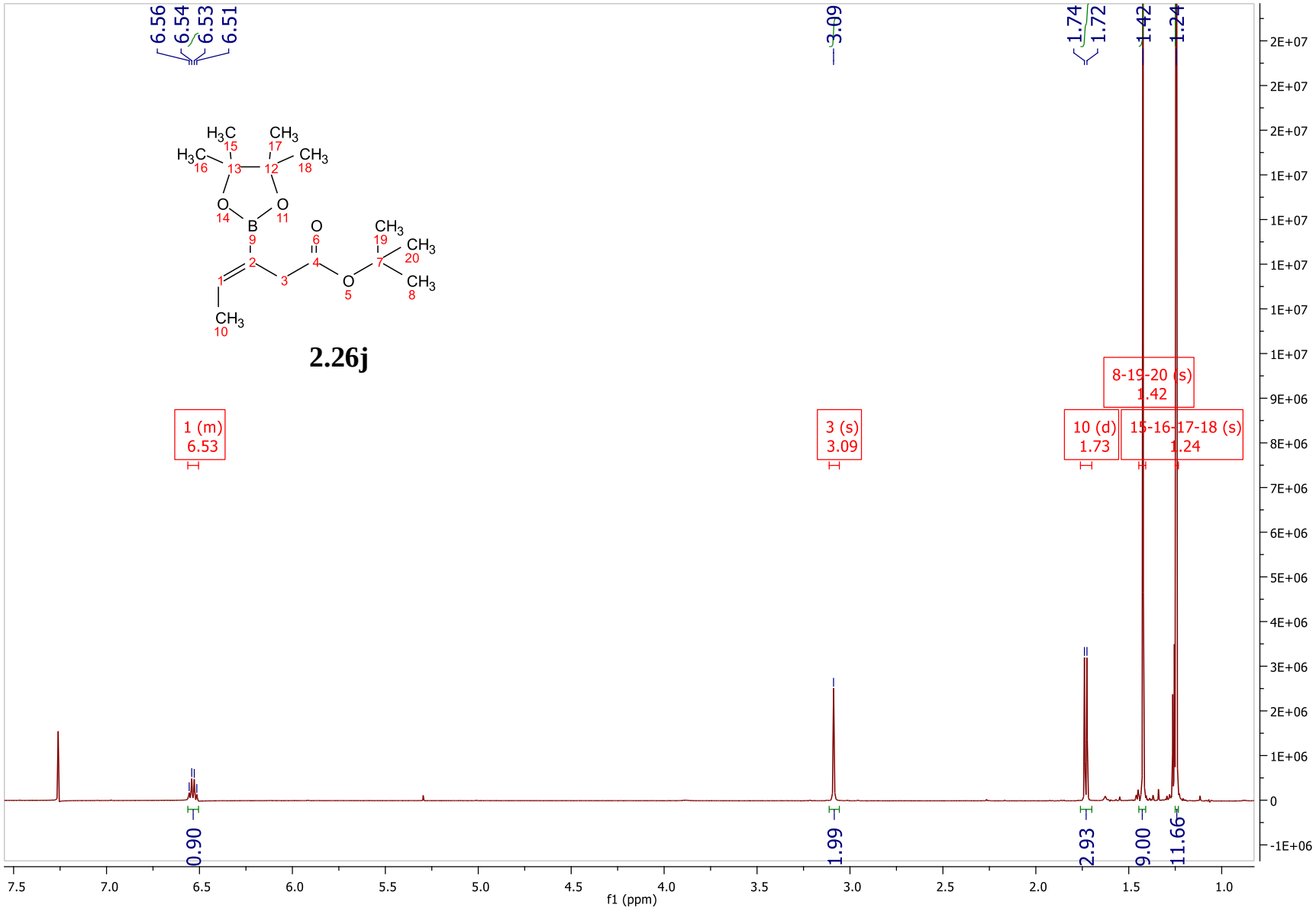

29.98
2.26h
2E+07
2E+07
2E+07
2E+07
2E+07
1E+07
1E+07
1E+07
8E+06
6E+06
4E+06
2E+06
0
-2E+06
40
35
30
25
20
15
10
5
0
-5
f1 (ppm)

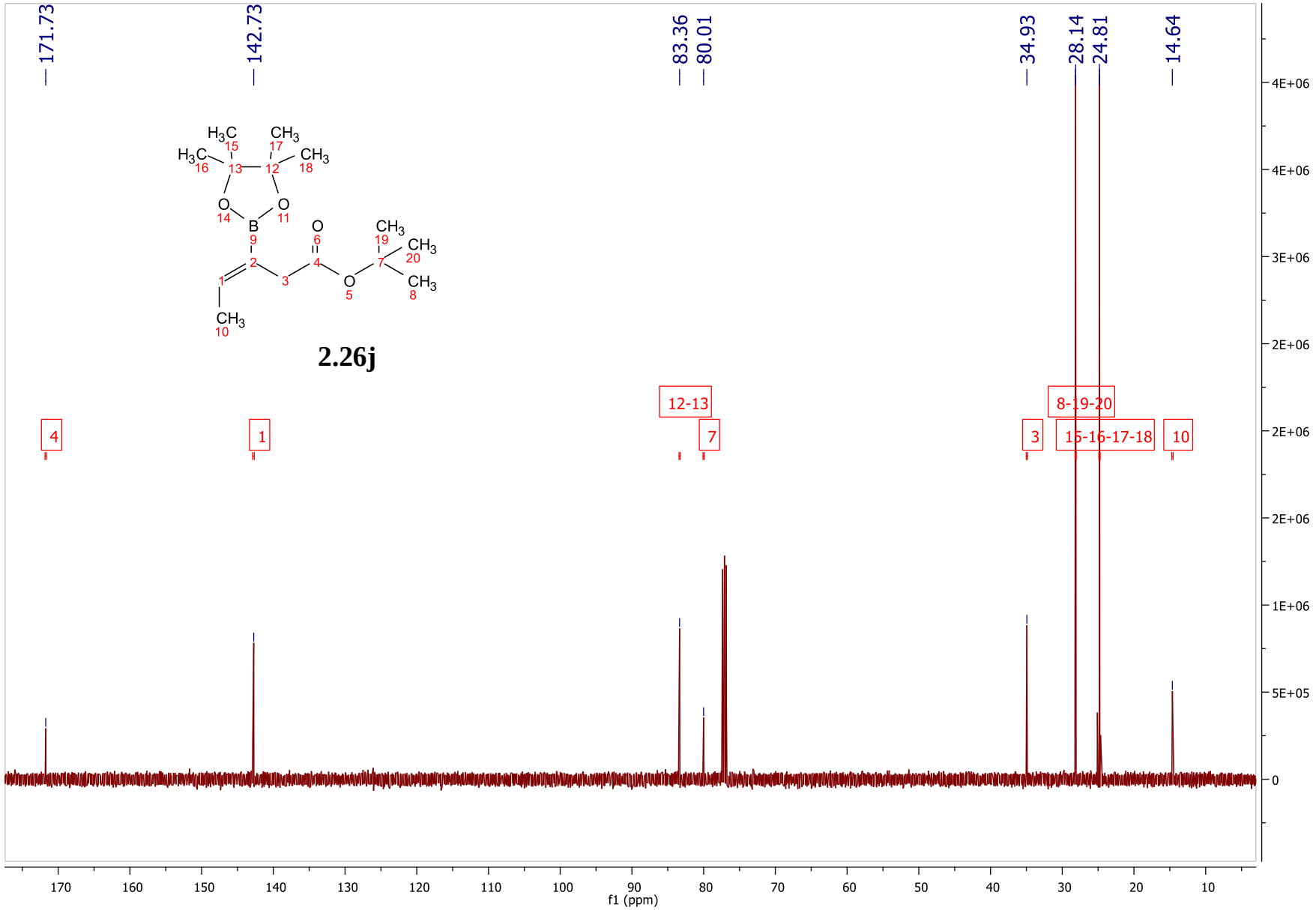

6.57
6.55
6.54
6.52
4.99
4.97
4.96
4.95
4.94
3.13
1.73
1.72
1.25
1.24
1.21
1.20
2.26i
1 (q)
6.54
7 (m)
4.96
3 (s)
3.13
10 (d)
1.73
15-16-17-18 (s)
1.24
8-19 (d)
1.20
0.87
0.87
1.88
3.00
11.92
5.94
f1 (ppm)

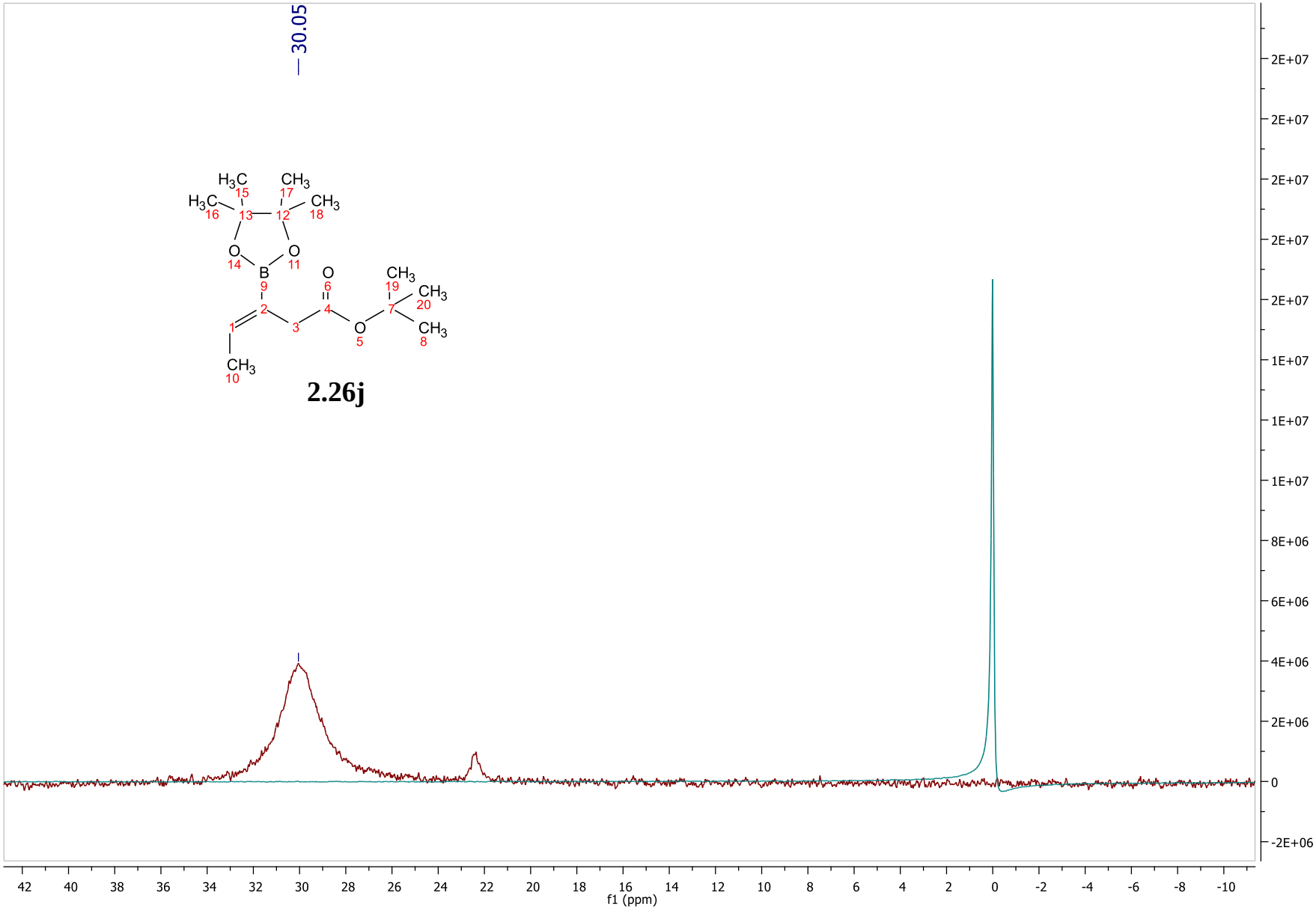

172.02
143.14
83.49
67.66
34.09
24.87
21.96
14.72
2.26i
4
1
12-13
7
3
15-16-17-18
8-19
10
f1 (ppm)


30.01
2E+07
2E+07
2E+07
2E+07
2E+07
1E+07
1E+07
1E+07
8E+06
6E+06
4E+06
2E+06
0
-2E+06
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
-2
-4
f1 (ppm)

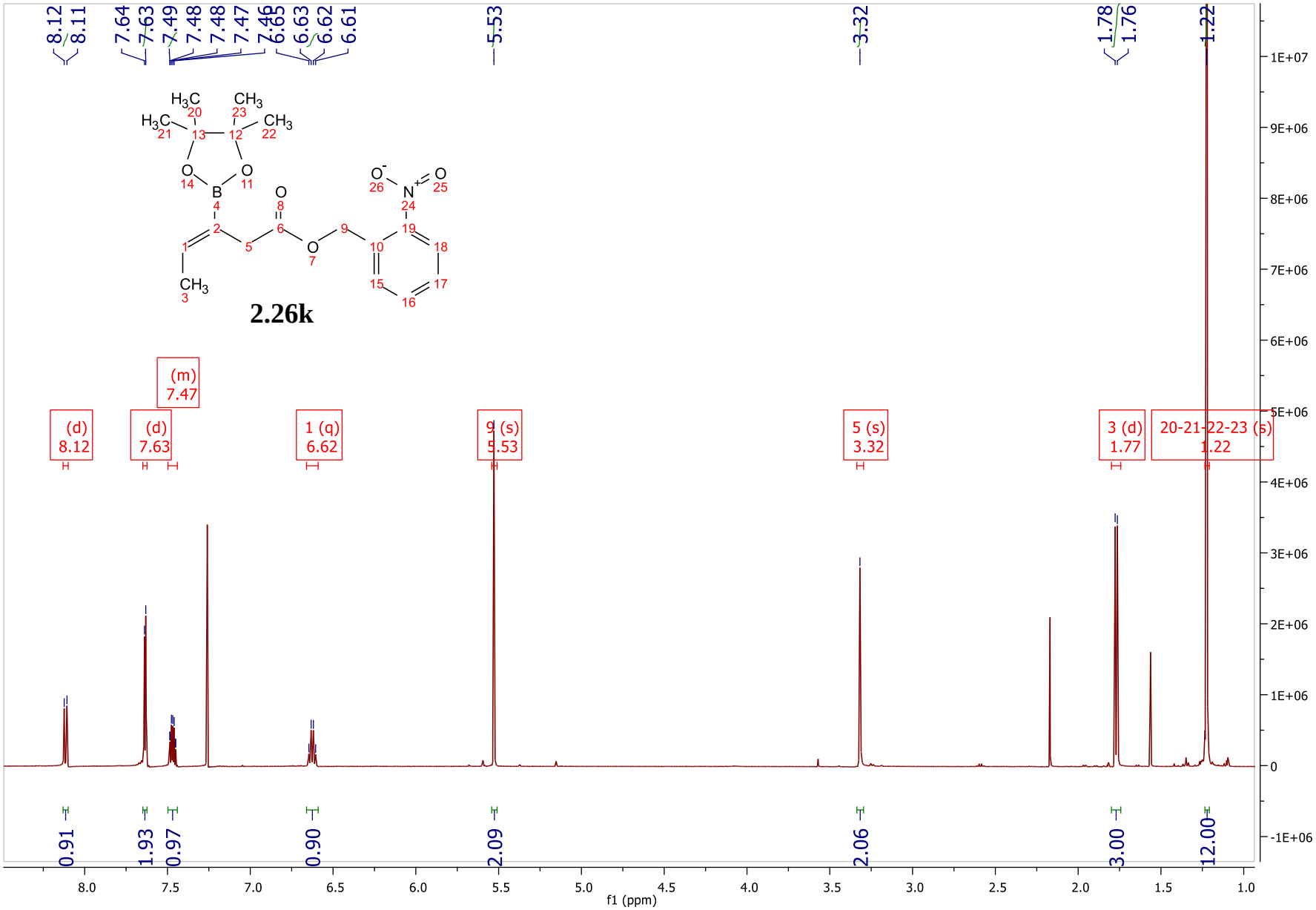
2.26i

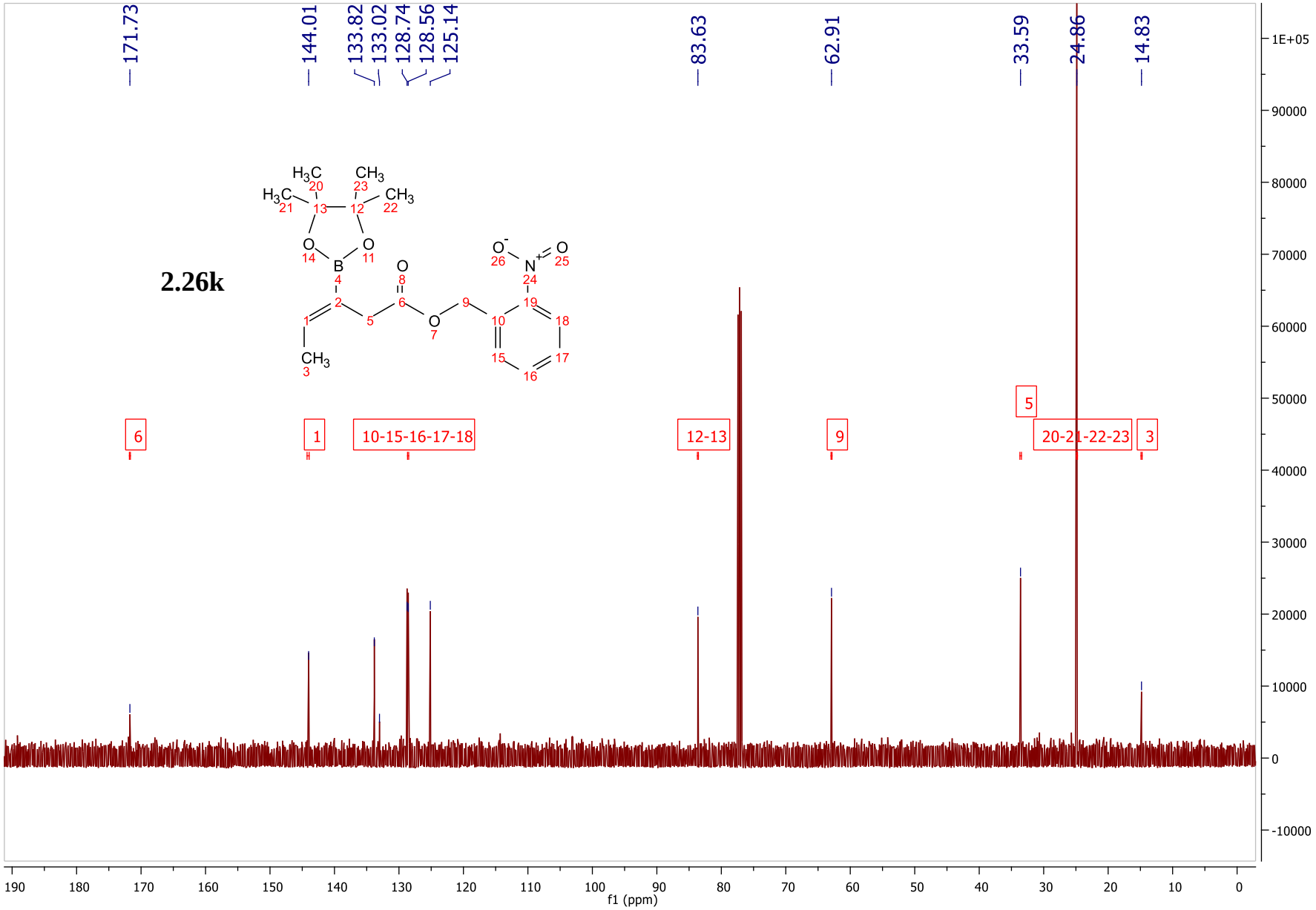

6.56
6.54
6.53
6.51
3.09
1.74
1.72
1.42
1.24
2.26j
1 (m)
6.53
3 (s)
3.09
10 (d)
1.73
8-19-20 (s)
1.42
15-16-17-18 (s)
1.24
0.90
1.99
2.93
9.00
11.66
f1 (ppm)

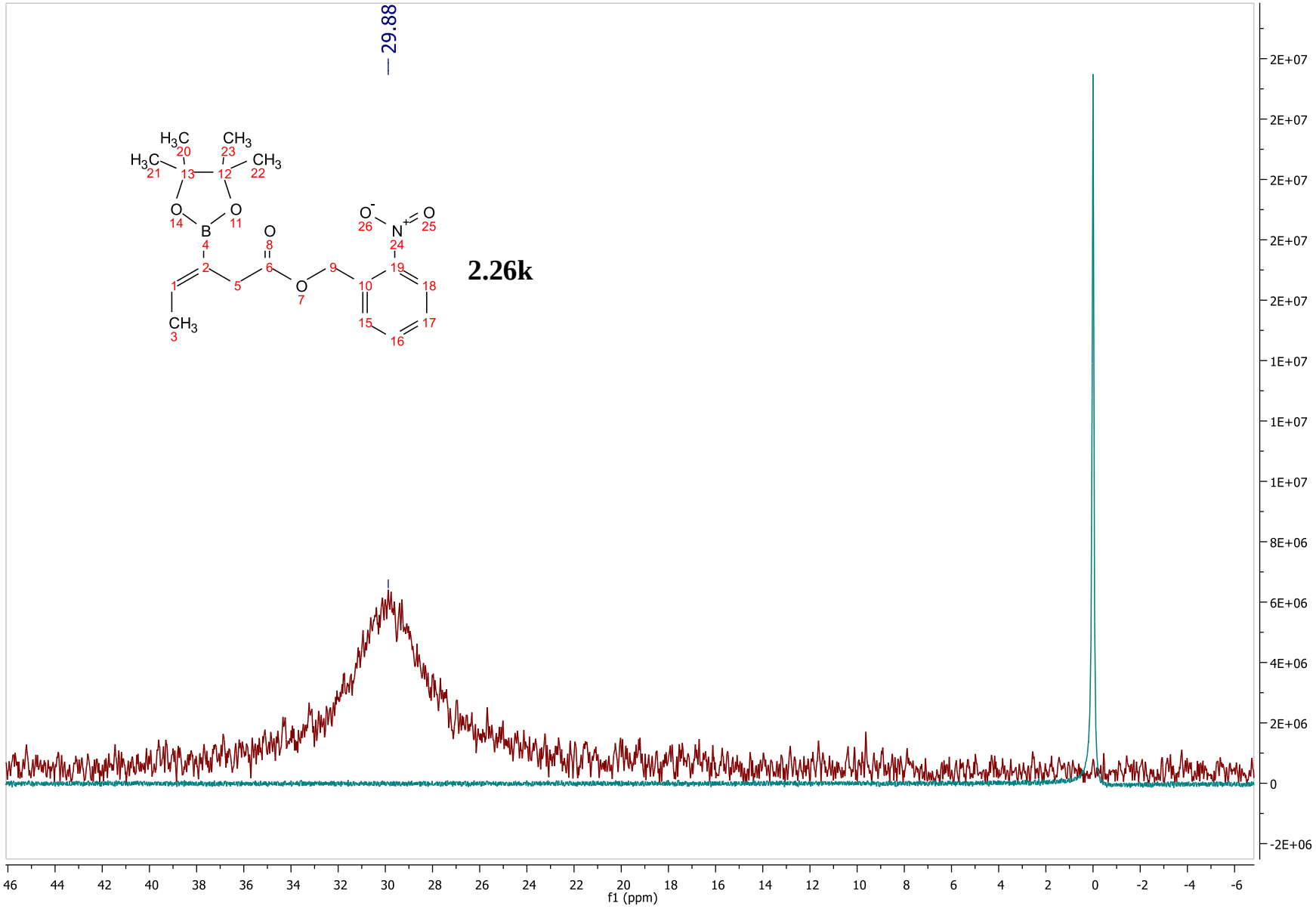

171.73
142.73
83.36
80.01
34.93
28.14
24.81
14.64
2.26j
4
1
12-13
7
3
8-19-20
15-16-17-18
10
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

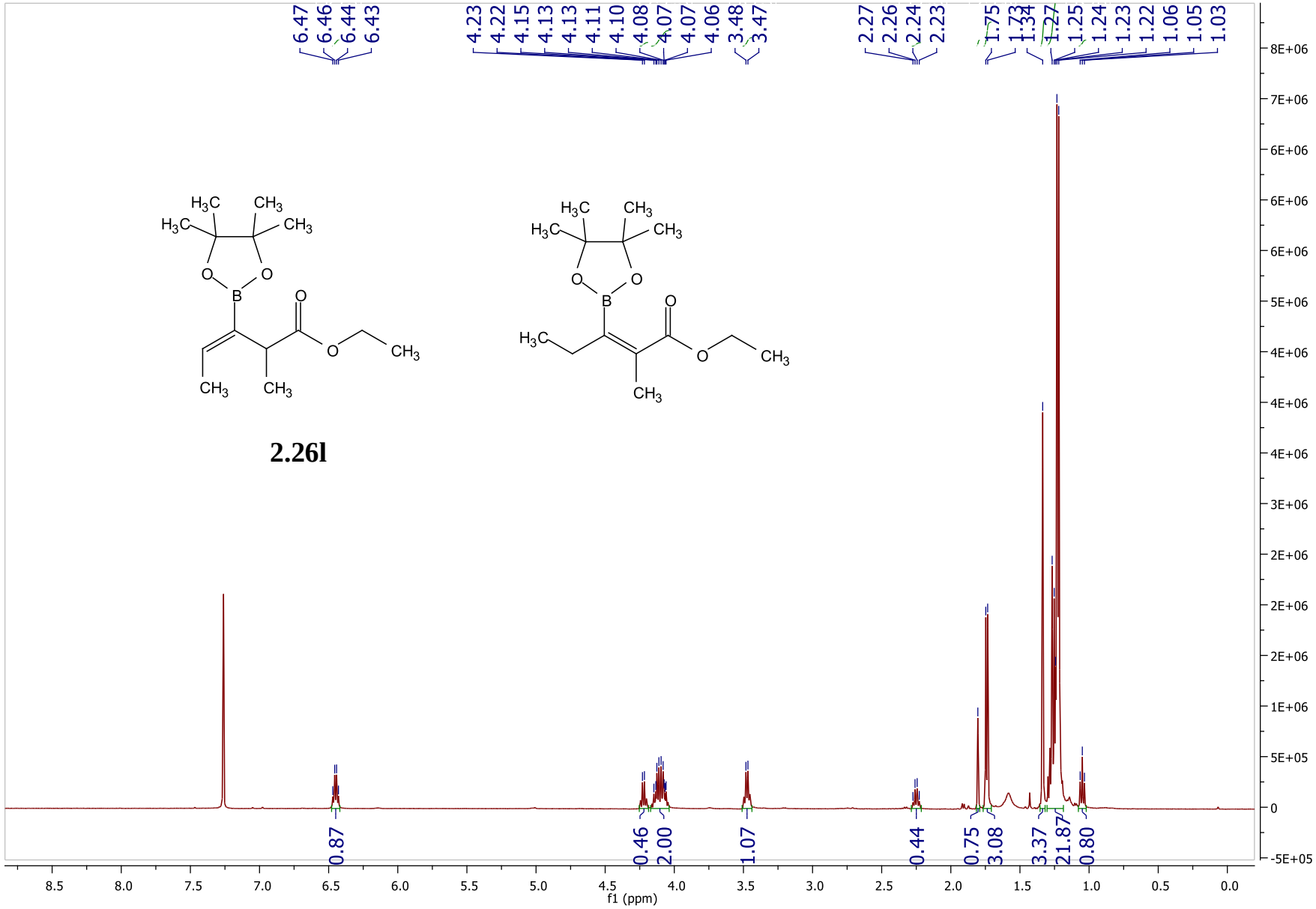

30.05
2E+07
2E+07
2E+07
2E+07
2E+07
1E+07
1E+07
1E+07
8E+06
6E+06
4E+06
2E+06
0
-2E+06
42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2 -4 -6 -8 -10
f1 (ppm)

2.26j

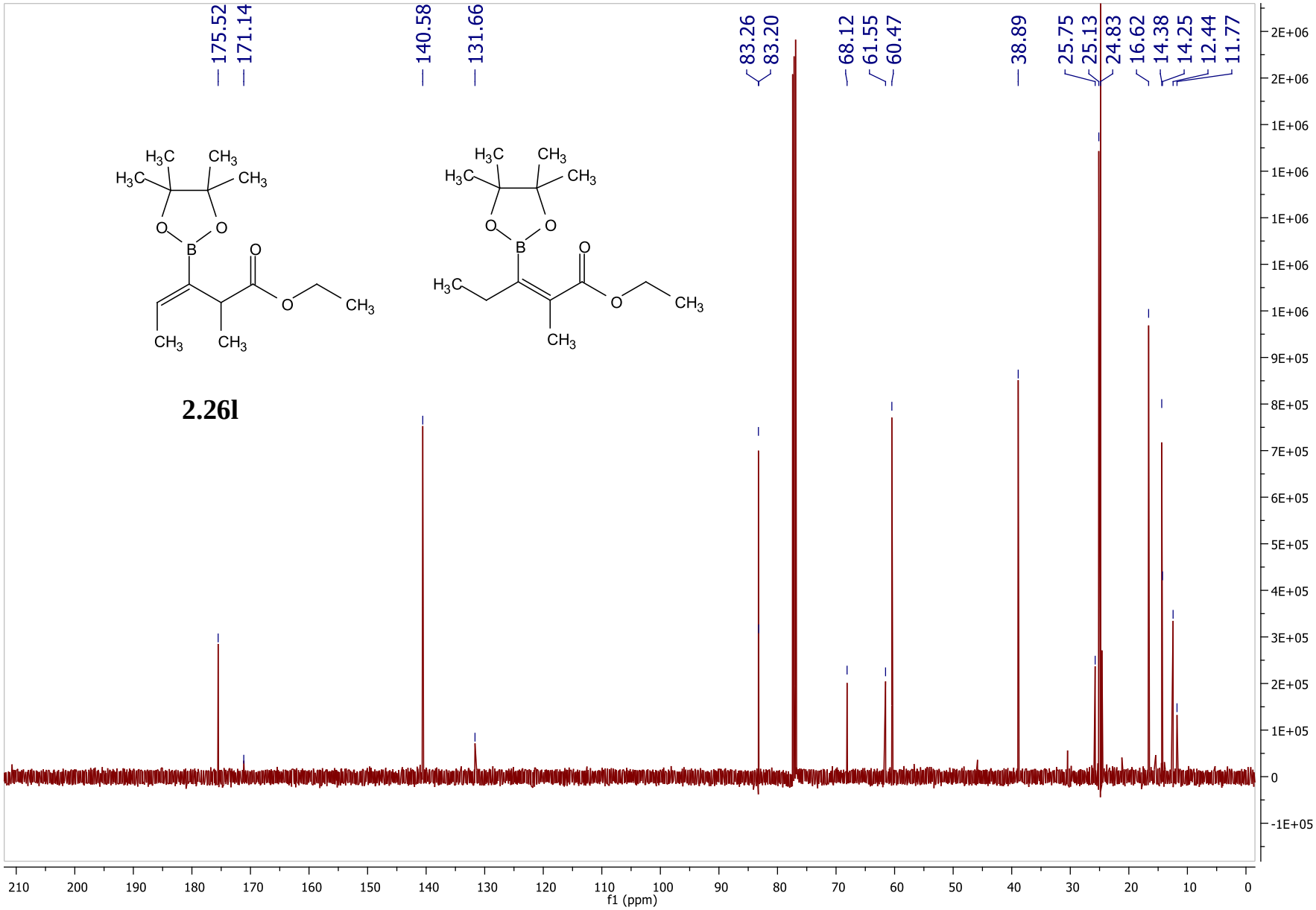

8.12
8.11
7.64
7.63
7.49
7.48
7.48
7.47
7.46
6.65
6.63
6.62
6.61
5.53
3.32
1.78
1.76
1.22
2.26k
(d)
8.12
(d)
7.63
(m)
7.47
1 (q)
6.62
9 (s)
5.53
5 (s)
3.32
3 (d)
1.77
20-21-22-23 (s)
1.22
0.91
1.93
0.97
0.90
2.09
2.06
3.00
12.00
f1 (ppm)

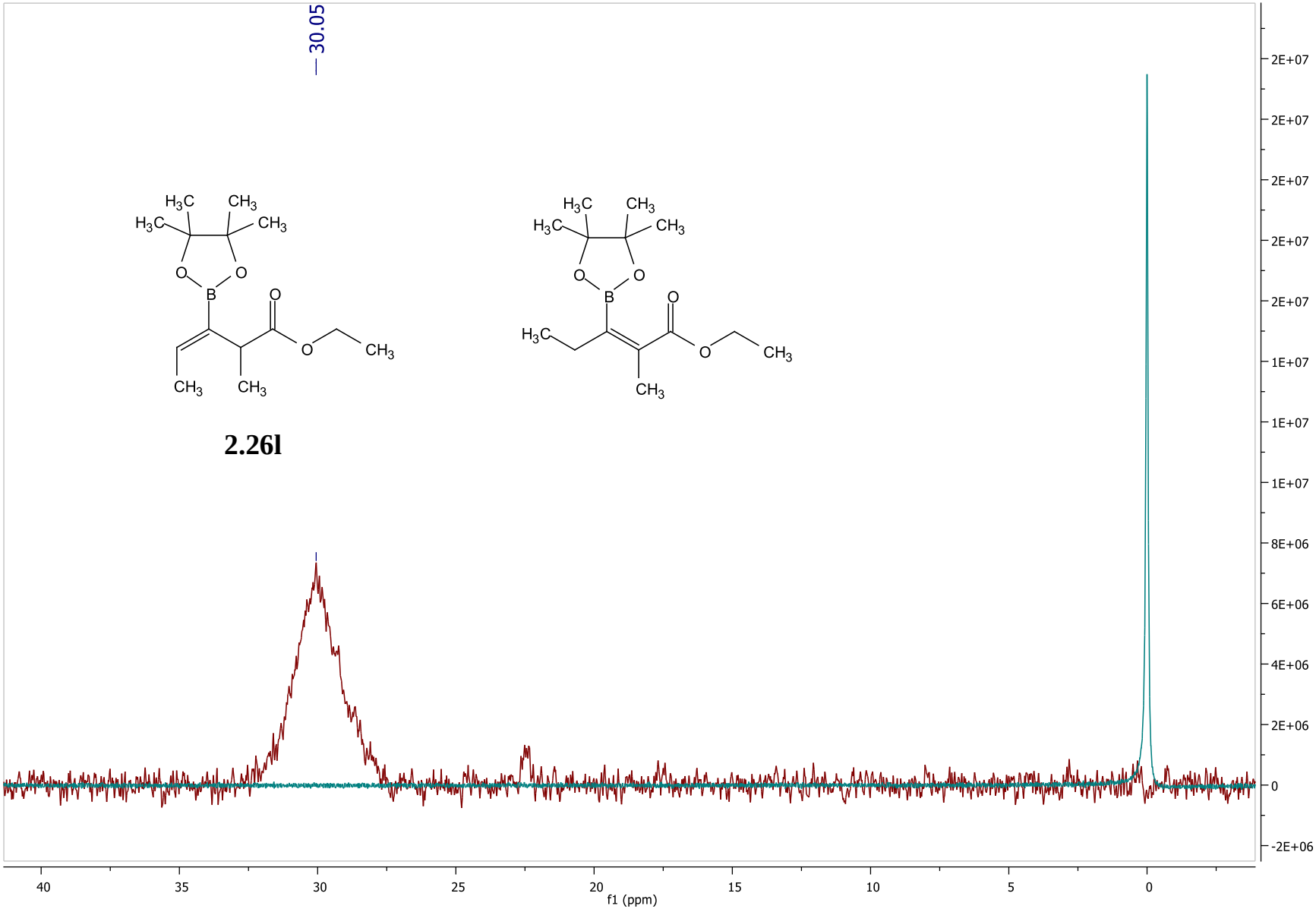

171.73
144.01
133.82
133.02
128.74
128.56
125.14
83.63
62.91
33.59
24.86
14.83
2.26k
6
1
10-15-16-17-18
12-13
9
5
20-21-22-23
3
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


29.88
2.26k
f1 (ppm)


6.47
6.46
6.44
6.43
4.23
4.22
4.15
4.13
4.13
4.11
4.10
4.08
4.07
4.07
4.06
3.48
3.47
2.27
2.26
2.24
2.23
1.75
1.73
1.34
1.27
1.25
1.24
1.23
1.22
1.06
1.05
1.03
0.87
0.46
2.00
1.07
0.44
0.75
3.08
3.37
21.87
0.80
f1 (ppm)

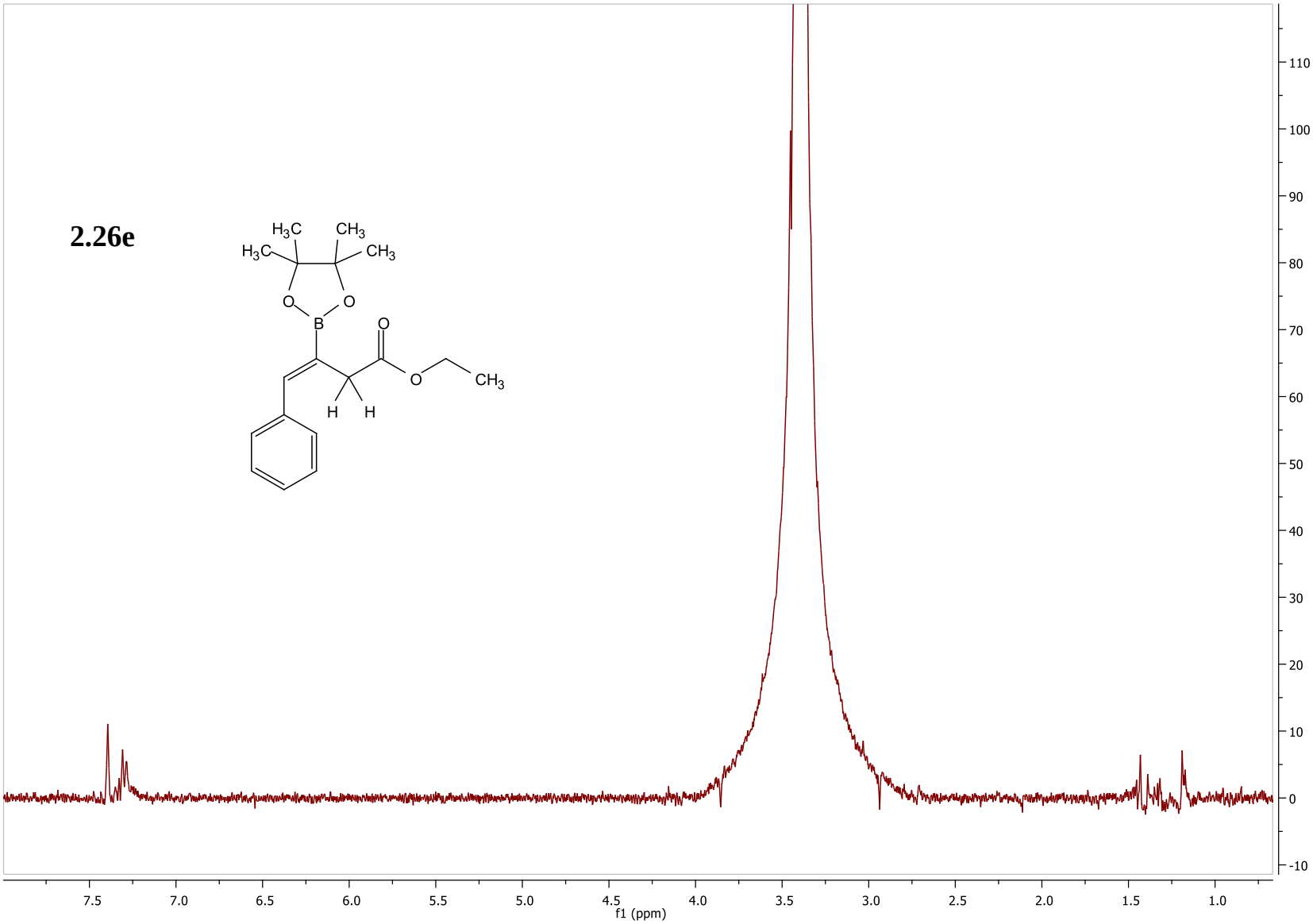
2.26l


175.52
171.14
140.58
131.66
83.26
83.20
68.12
61.55
60.47
38.89
25.75
25.13
24.83
16.62
14.38
14.25
12.44
11.77
2.26l
f1 (ppm)

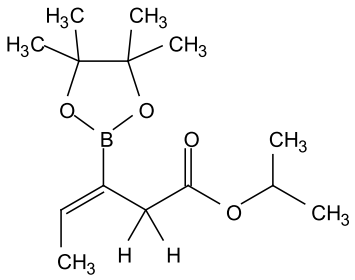

30.05
2E+07
2E+07
2E+07
2E+07
2E+07
1E+07
1E+07
1E+07
8E+06
6E+06
4E+06
2E+06
0
-2E+06
40
35
30
25
20
15
10
5
0
f1 (ppm)

2.26l

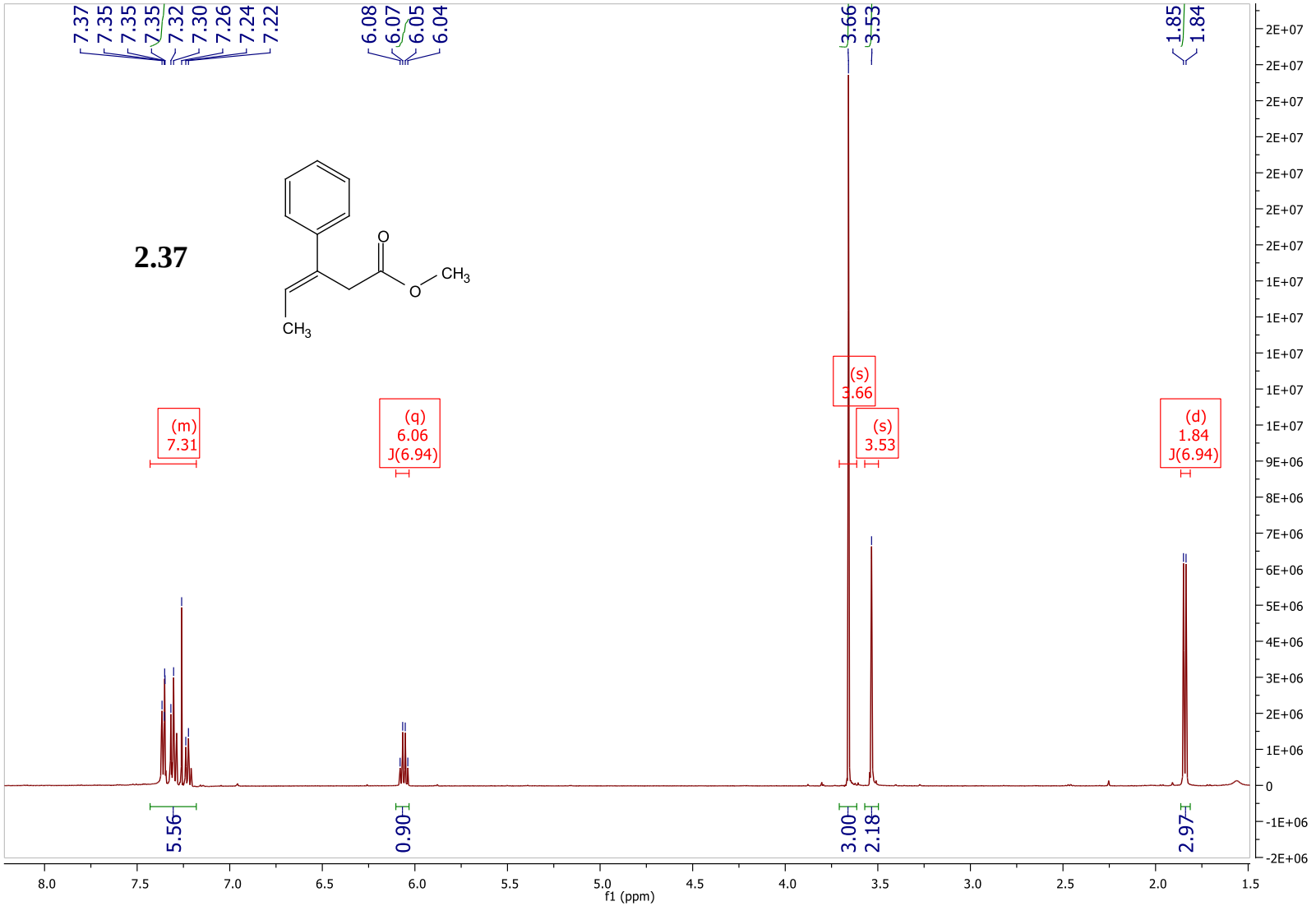
Examples of 1D NOESY experiments:

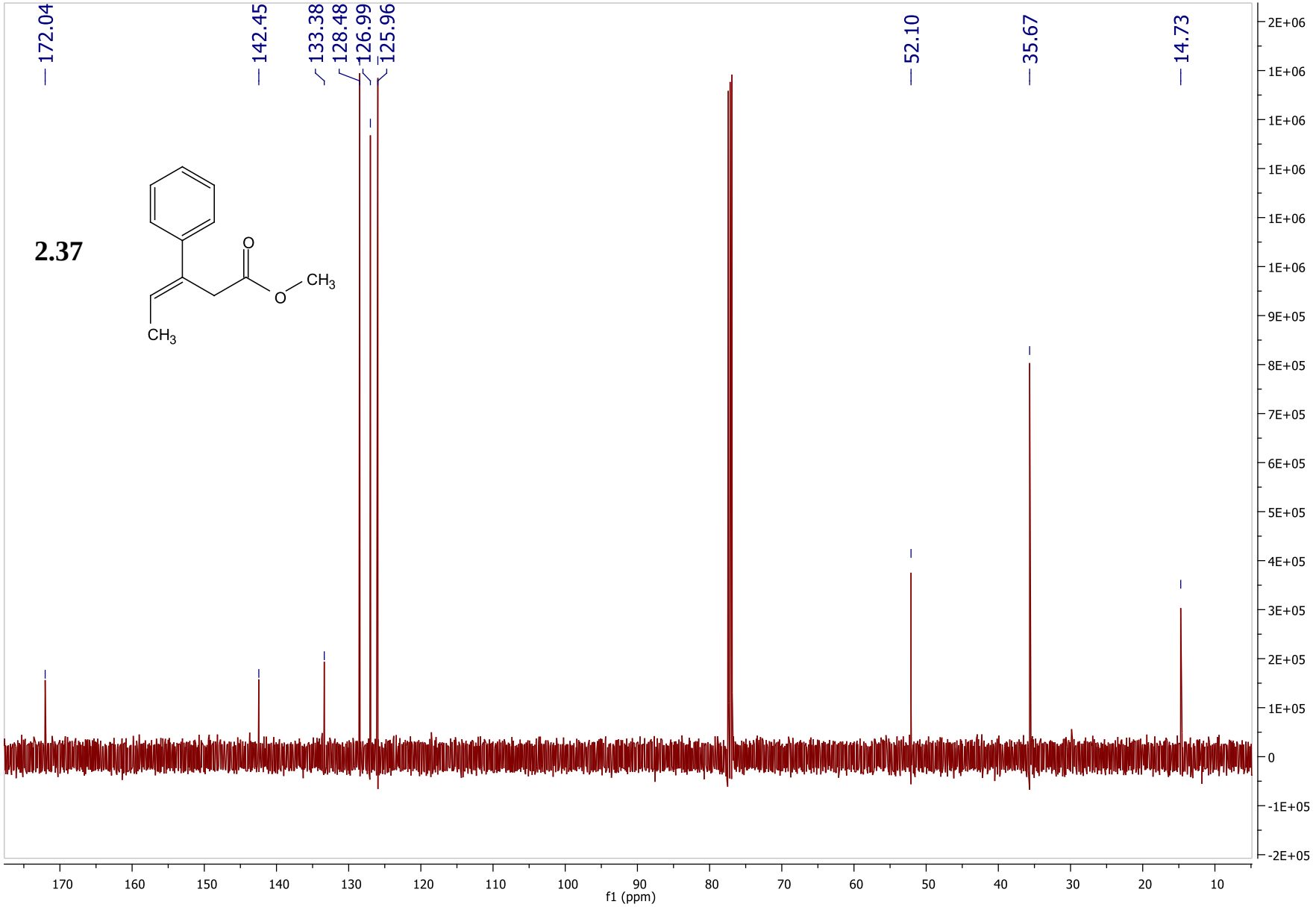


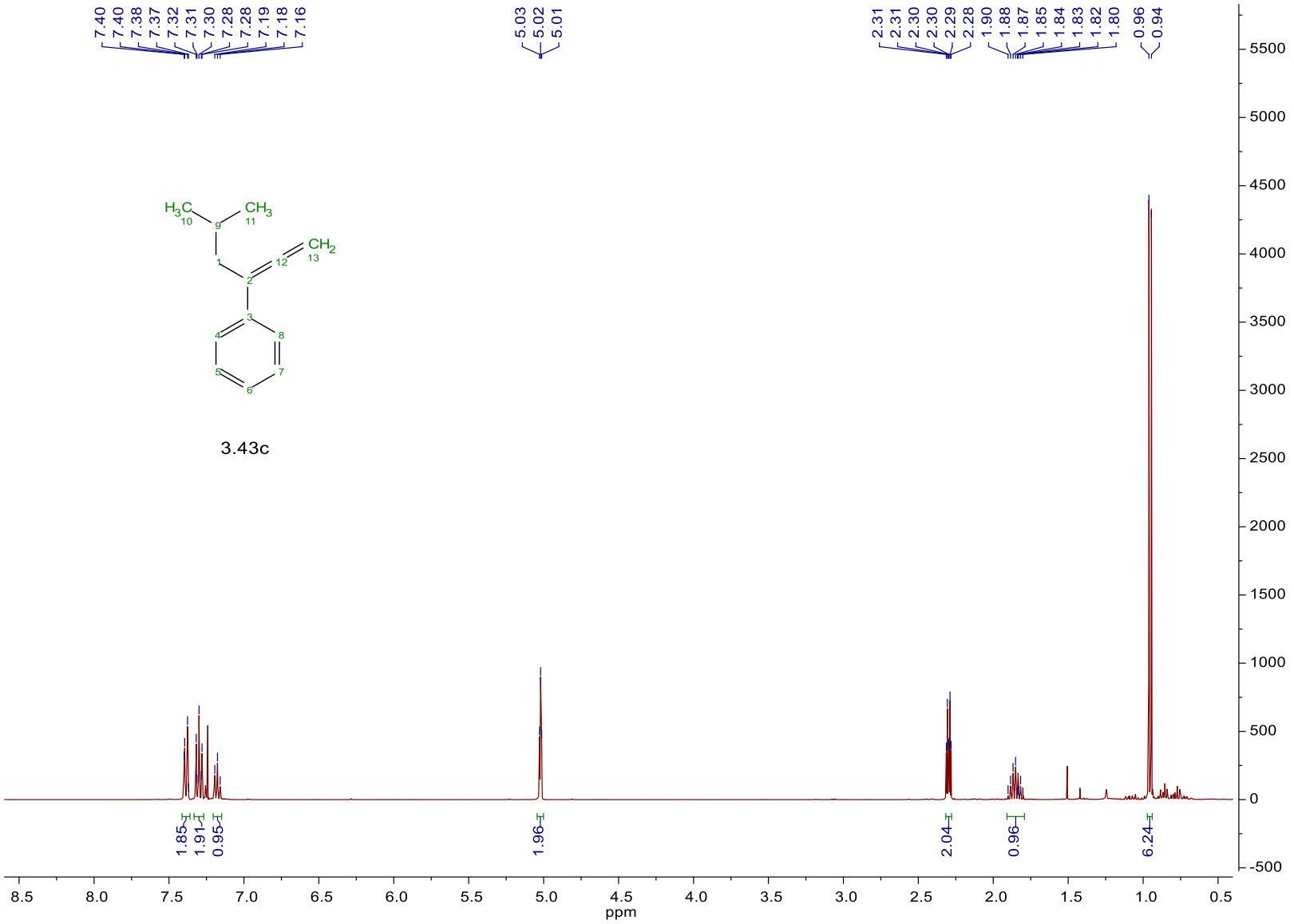
2.26i

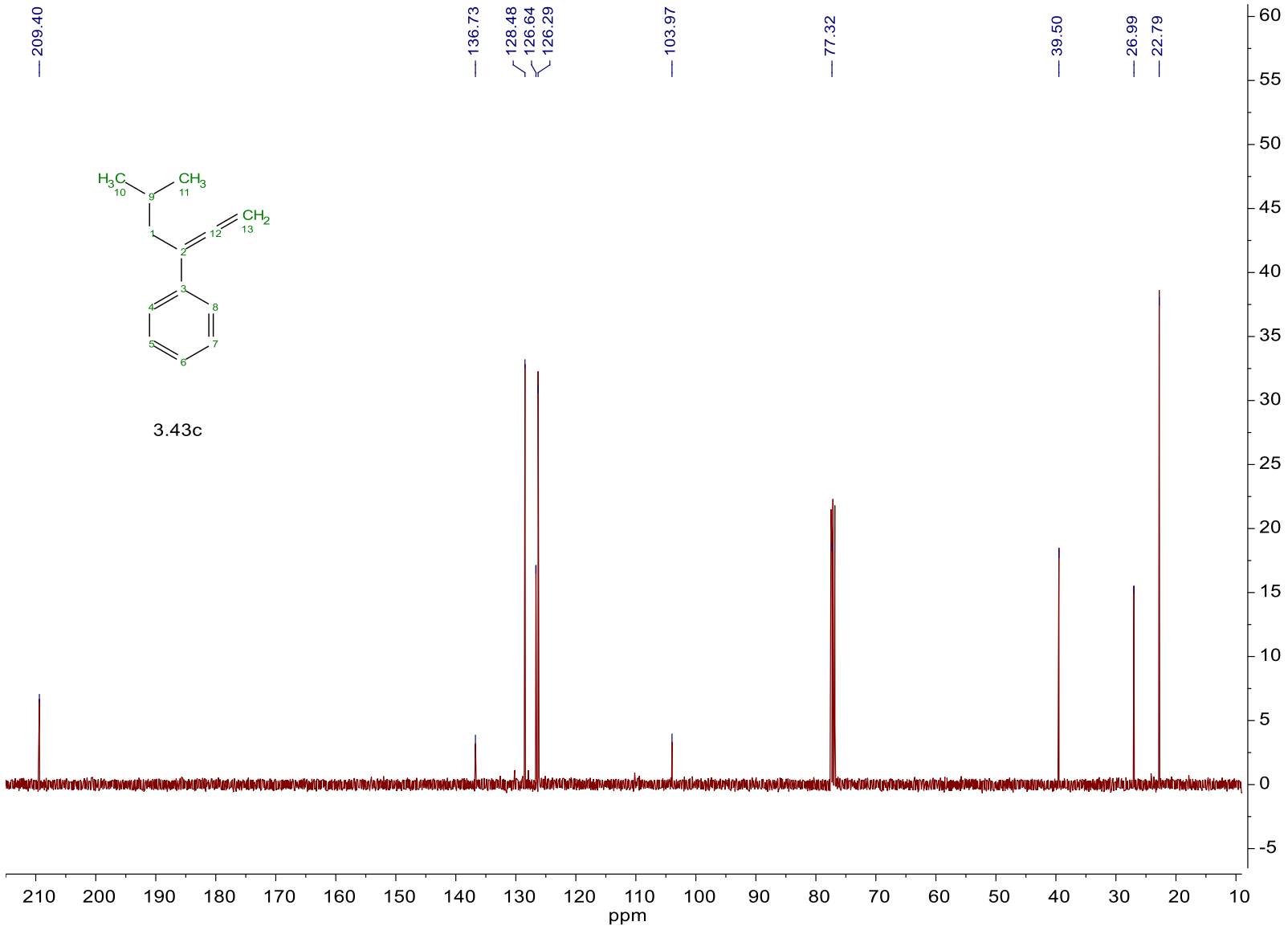

H3C
CH3
H3C
CH3
O
O
B
O
CH3
O
CH3
CH3
H
H

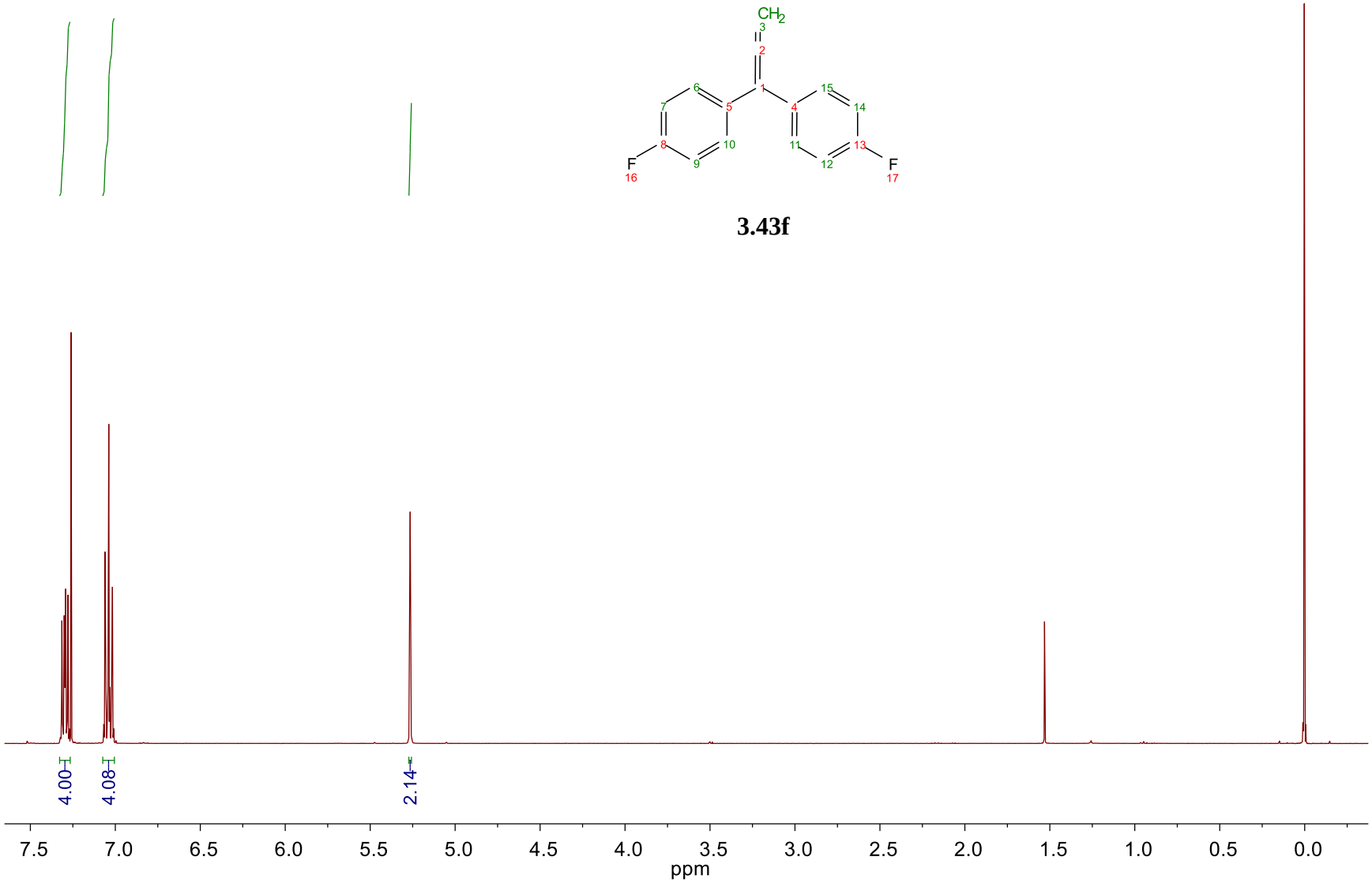
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.37
7.35
7.35
7.35
7.32
7.30
7.26
7.24
7.22
6.08
6.07
6.05
6.04
3.66
3.53
1.85
1.84
2.37
O
O
CH3
CH3
(m)
7.31
(q)
6.06
J(6.94)
(s)
3.66
(s)
3.53
(d)
1.84
J(6.94)
5.56
0.90
3.00
2.18
2.97
f1 (ppm)

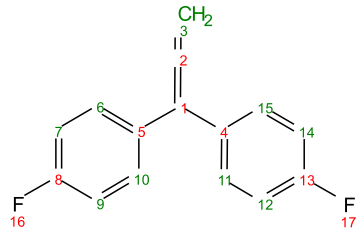

172.04
142.45
133.38
128.48
126.99
125.96
52.10
35.67
14.73
2.37
O
O
CH3
CH3
2E+06
1E+06
1E+06
1E+06
1E+06
1E+06
1E+06
9E+05
8E+05
7E+05
6E+05
5E+05
4E+05
3E+05
2E+05
1E+05
0
-1E+05
-2E+05
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.40
7.40
7.38
7.37
7.32
7.31
7.30
7.28
7.28
7.19
7.18
7.16
5.03
5.02
5.01
2.31
2.31
2.30
2.30
2.29
2.28
1.90
1.88
1.87
1.85
1.84
1.83
1.82
1.80
0.96
0.94
H3C
10
CH3
11
9
1
2
12
CH2
13
3
4
8
5
7
6
3.43c
1.85
1.91
0.95
1.96
2.04
0.96
6.24
ppm


209.40
136.73
128.48
126.64
126.29
103.97
77.32
39.50
26.99
22.79
3.43c
ppm

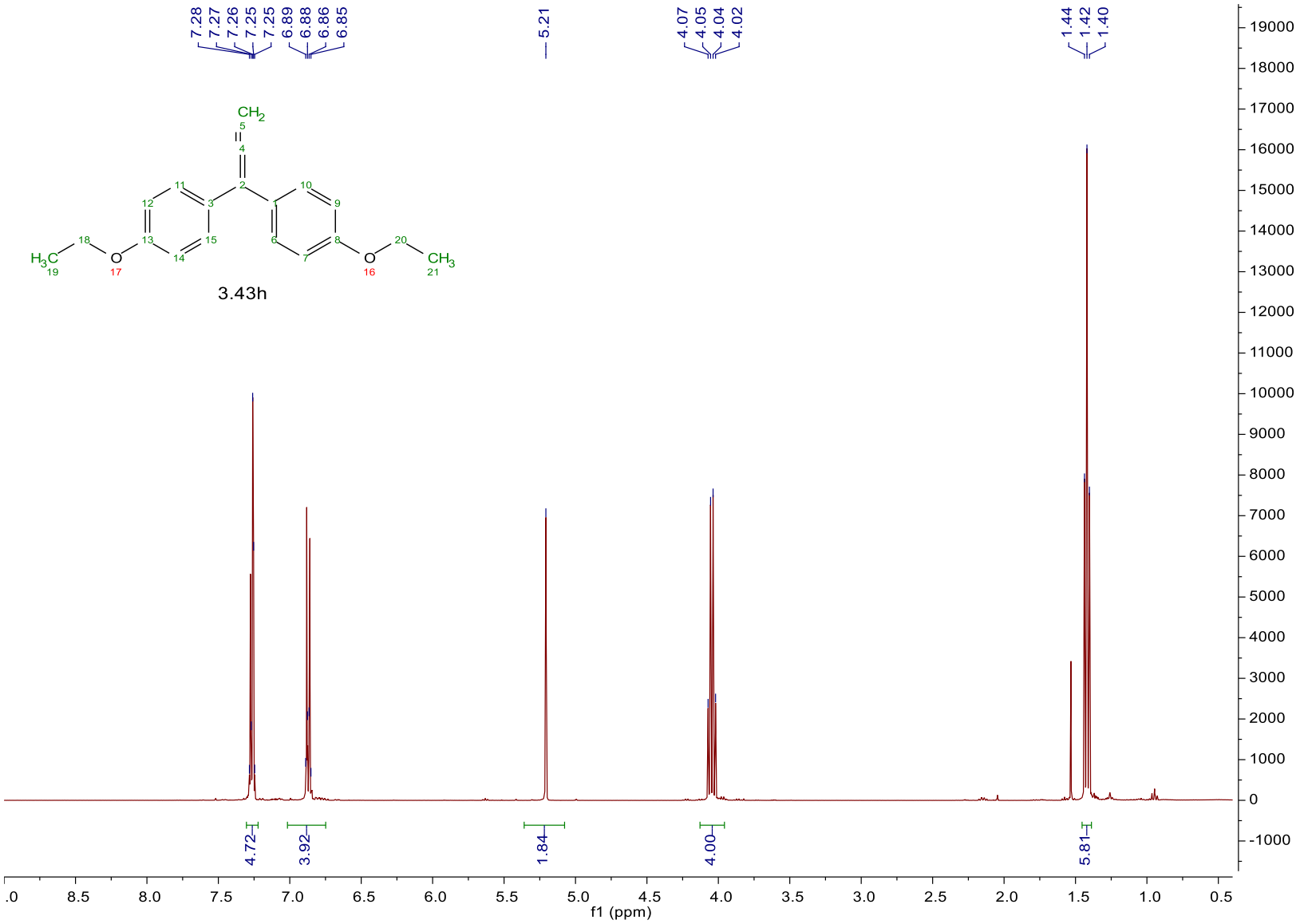

CH2
3
2
6
1
15
7
5
4
14
8
10
11
13
F
16
9
12
F
17
4.00
4.08
2.14
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

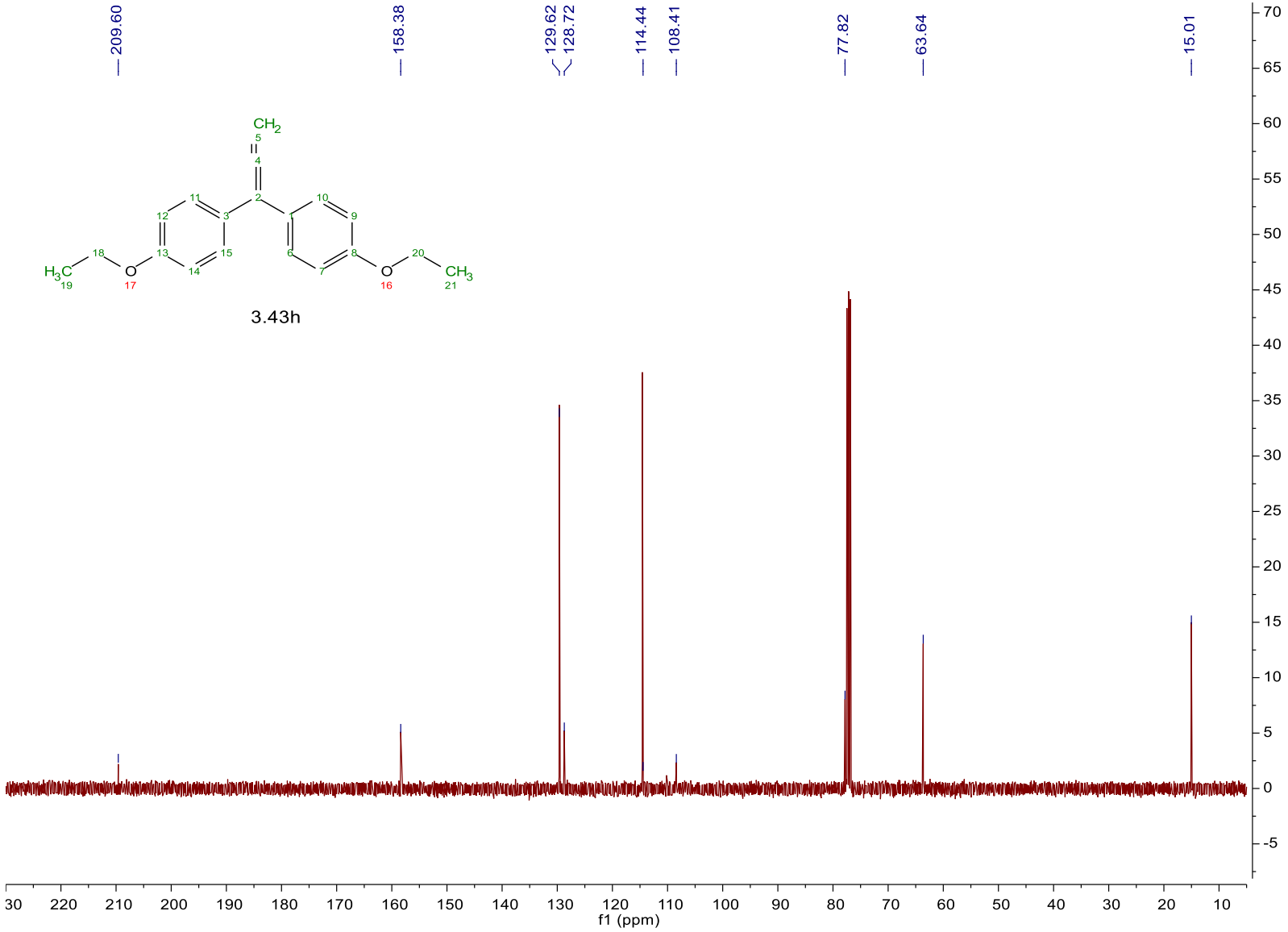
3.43f

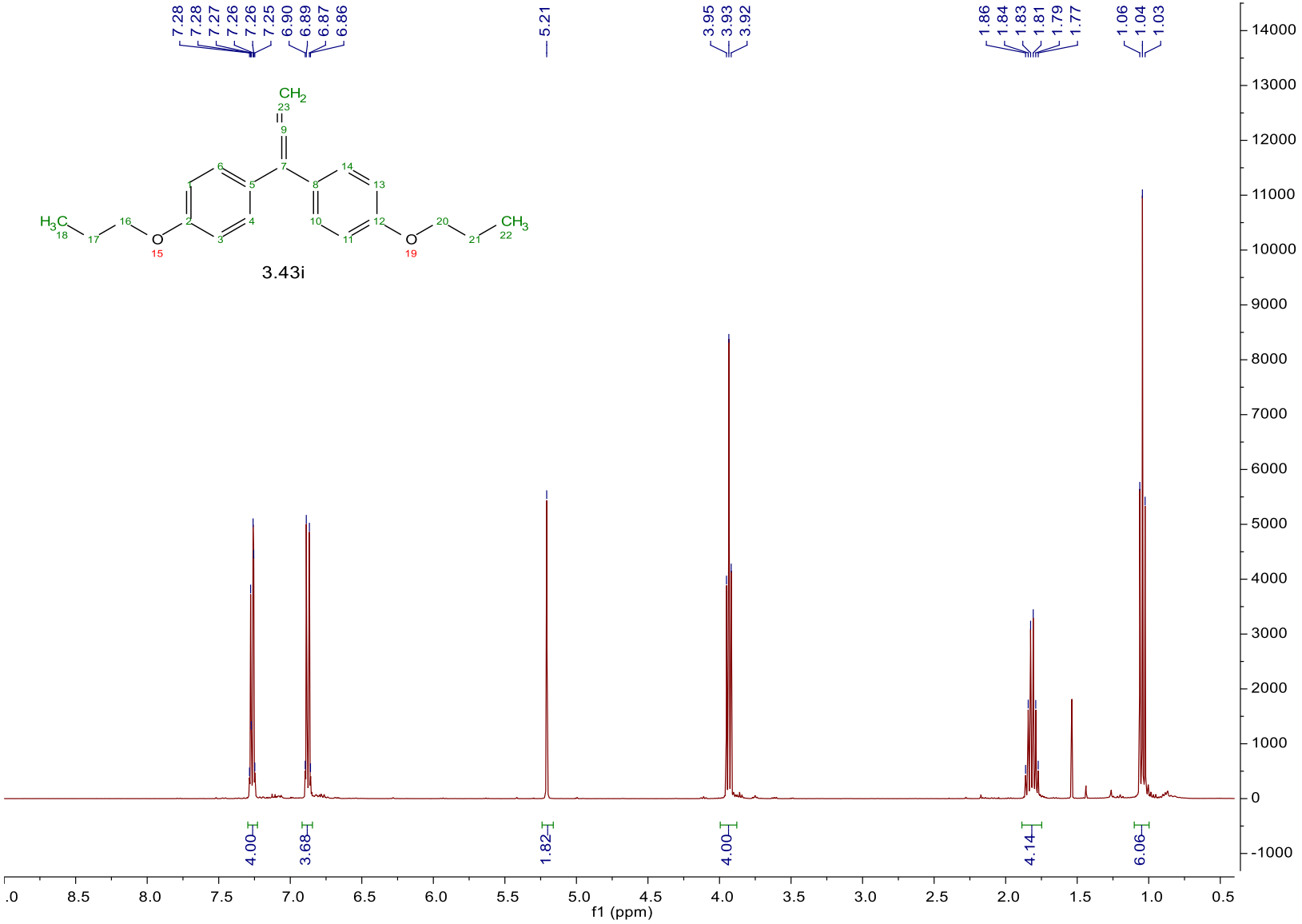

CH2
3
2
1
6
5
4
15
14
7
8
10
11
13
9
12
F
16
F
17

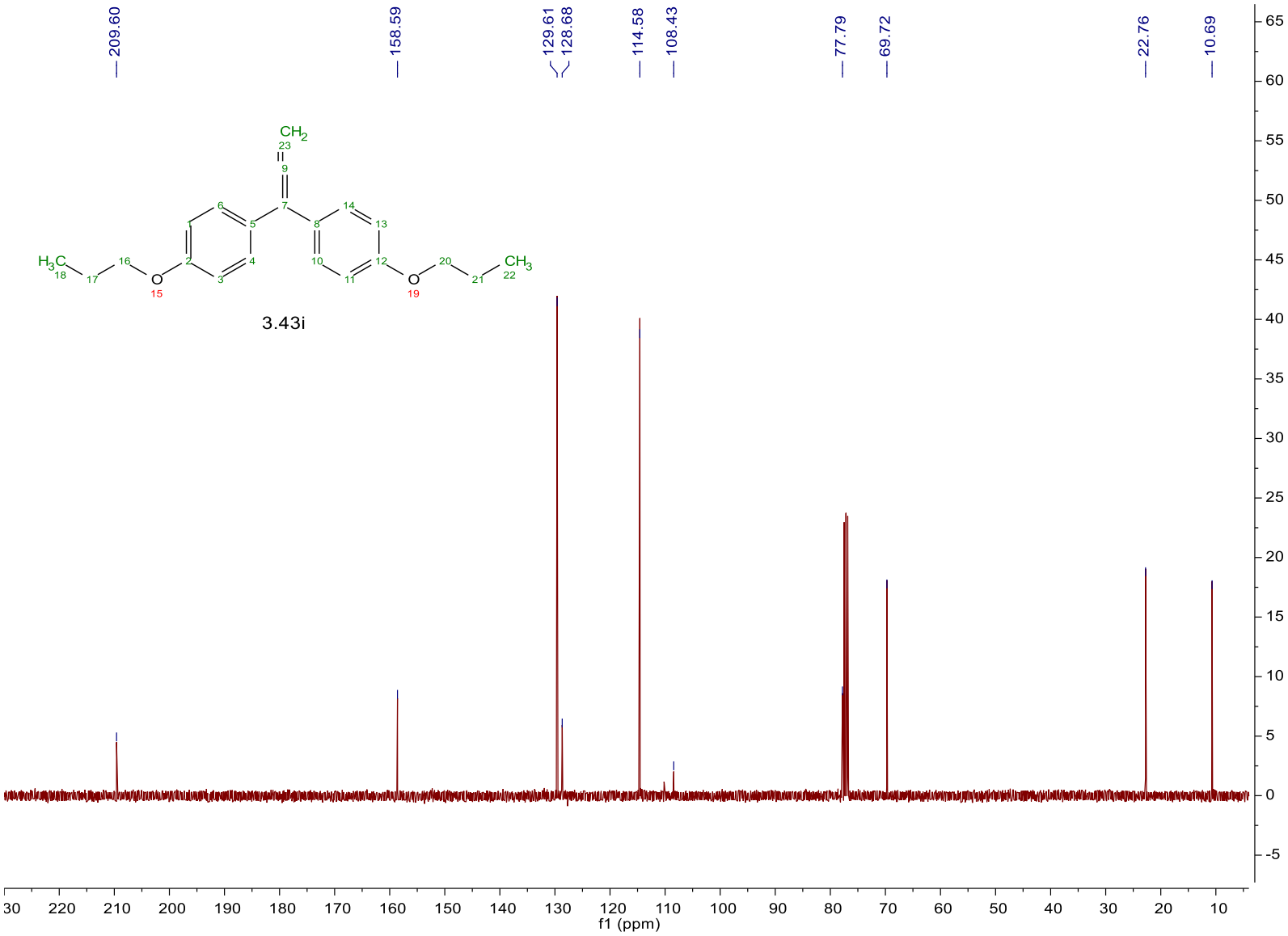
3.43f

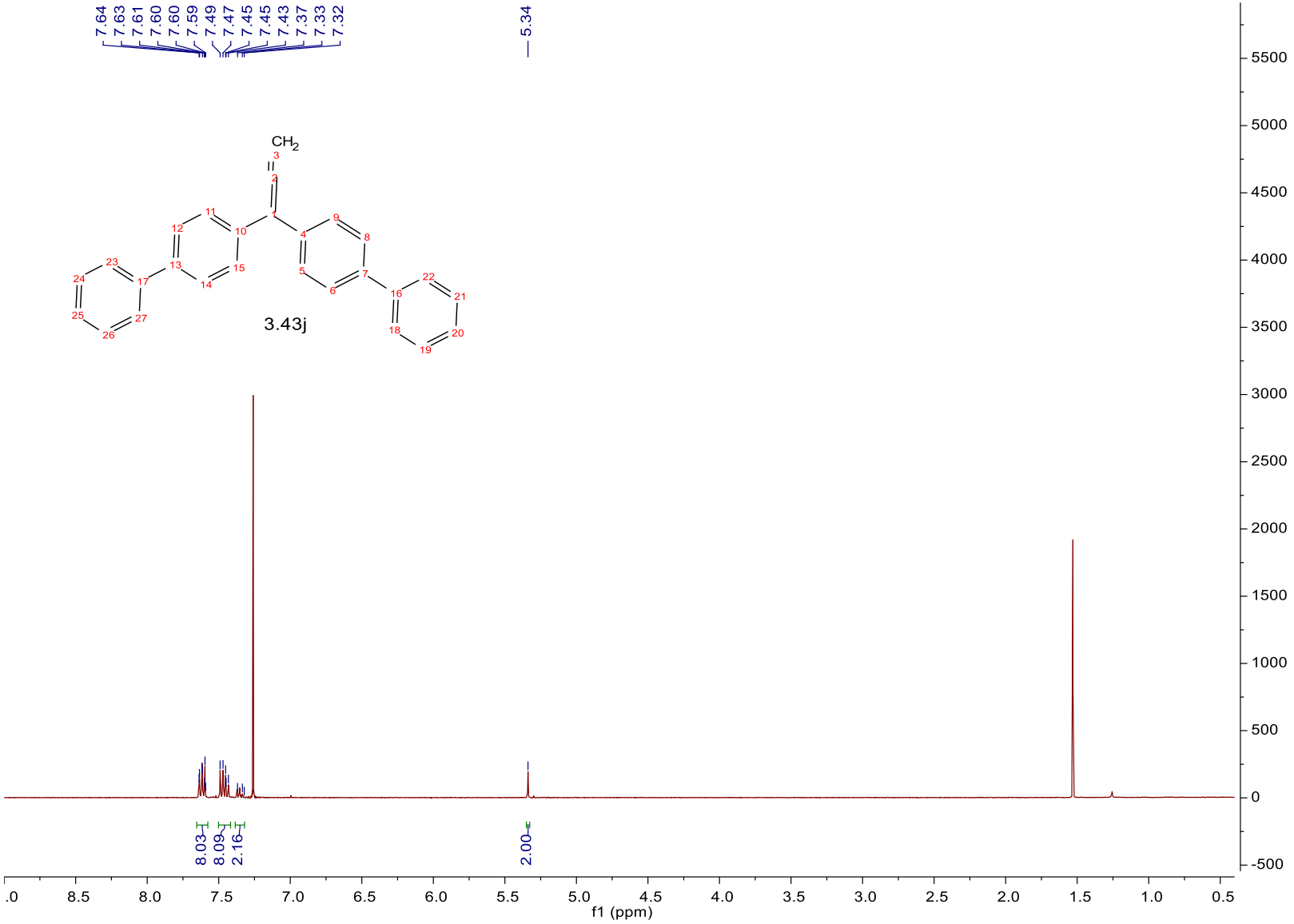
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

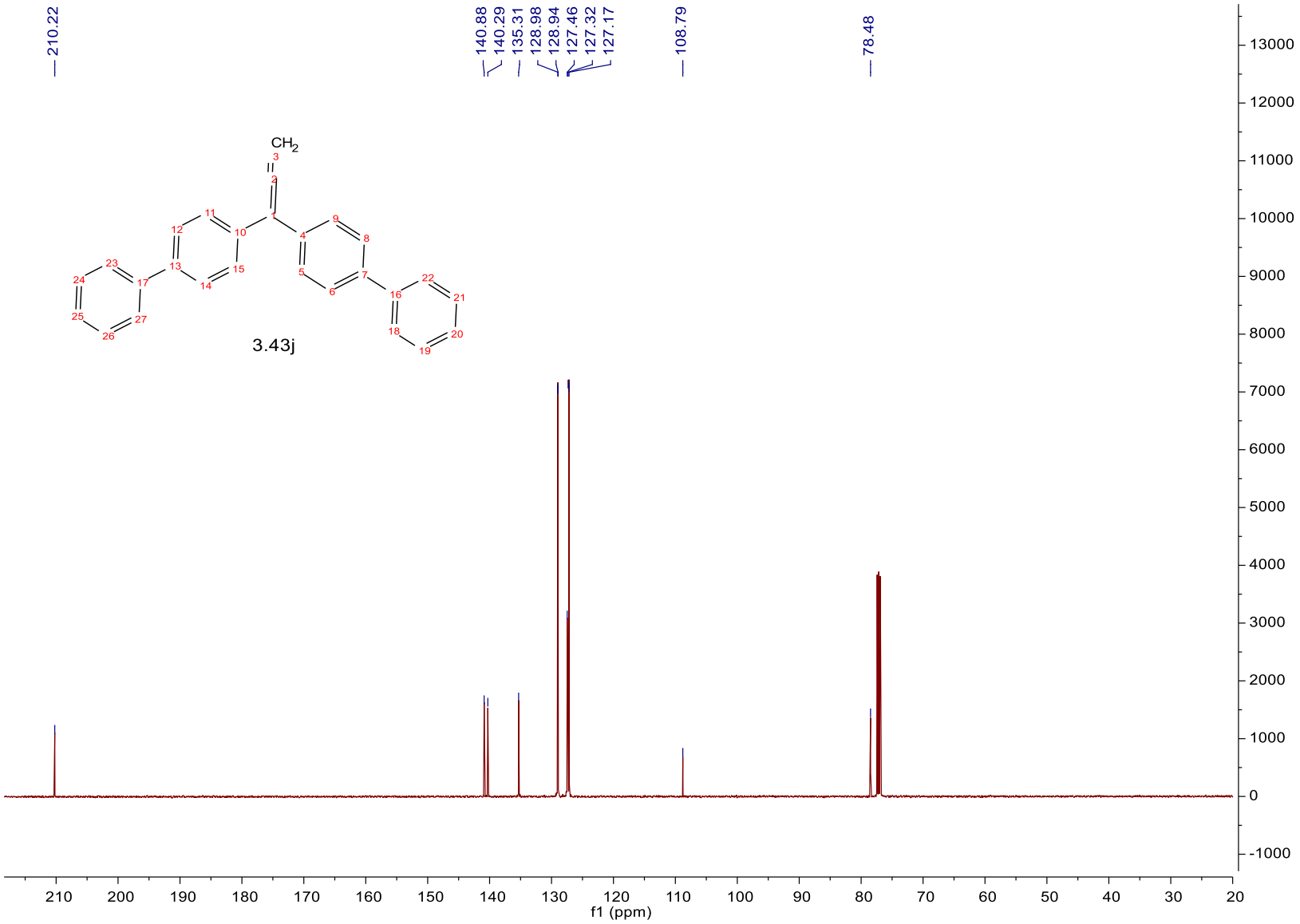

7.28
7.27
7.26
7.25
7.25
6.89
6.88
6.86
6.85
5.21
4.07
4.05
4.04
4.02
1.44
1.42
1.40
3.43h
4.72
3.92
1.84
4.00
5.81
f1 (ppm)

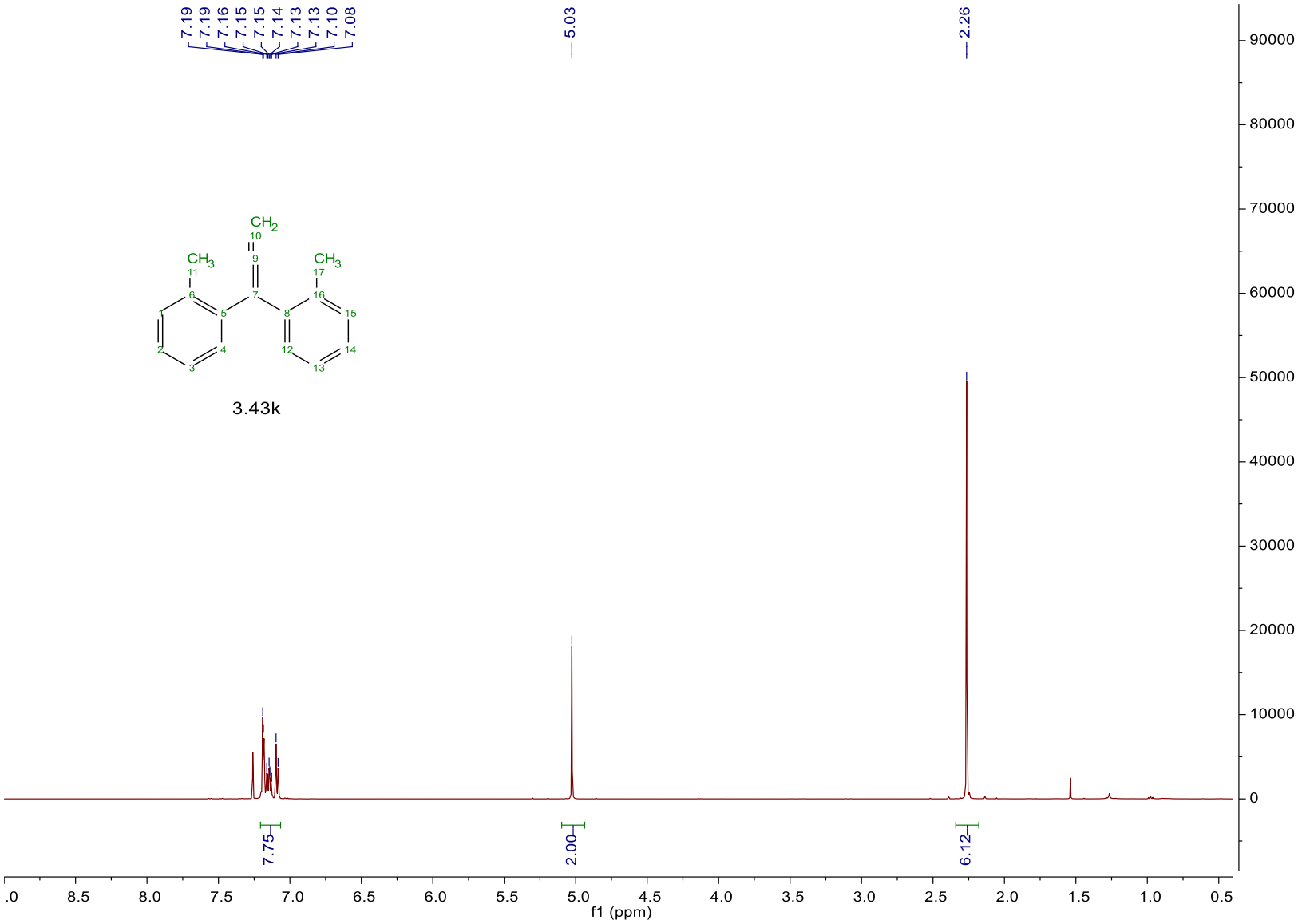

209.60
158.38
129.62
128.72
114.44
108.41
77.82
63.64
15.01
3.43h
f1 (ppm)

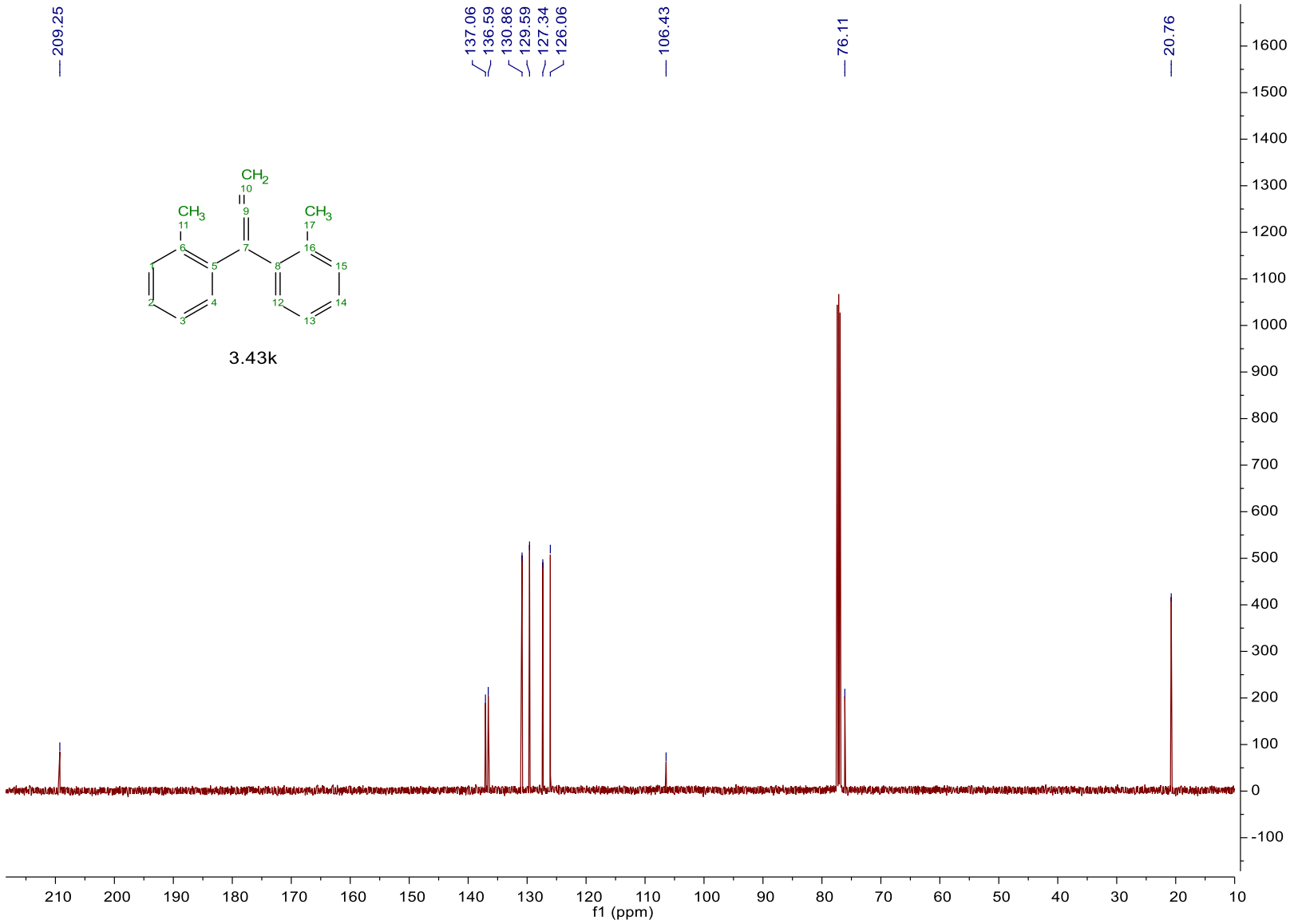

7.28
7.28
7.27
7.26
7.26
7.25
6.90
6.89
6.87
6.86
5.21
3.95
3.93
3.92
1.86
1.84
1.83
1.81
1.79
1.77
1.06
1.04
1.03
CH2
23
9
6
5
7
14
13
1
8
2
4
3
10
12
11
H3C
18
17
16
O
15
O
19
20
21
CH3
22
3.43i
4.00
3.68
1.82
4.00
4.14
6.06
f1 (ppm)

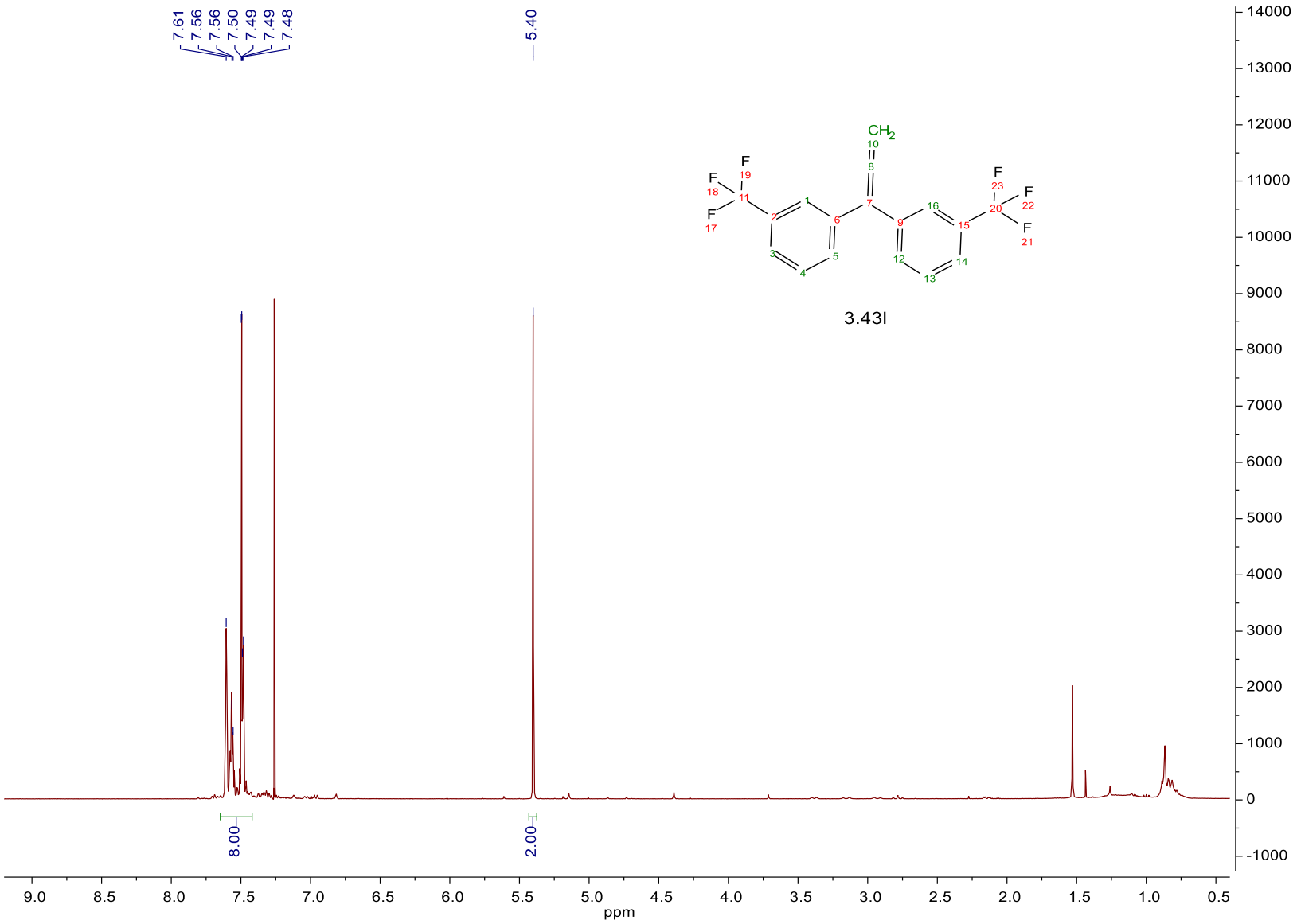

209.60
158.59
129.61
128.68
114.58
108.43
77.79
69.72
22.76
10.69
CH2
23
9
H3C
18
17
16
O
15
2
3
4
6
5
7
8
14
13
10
11
12
O
19
20
21
CH3
22
3.43i
f1 (ppm)

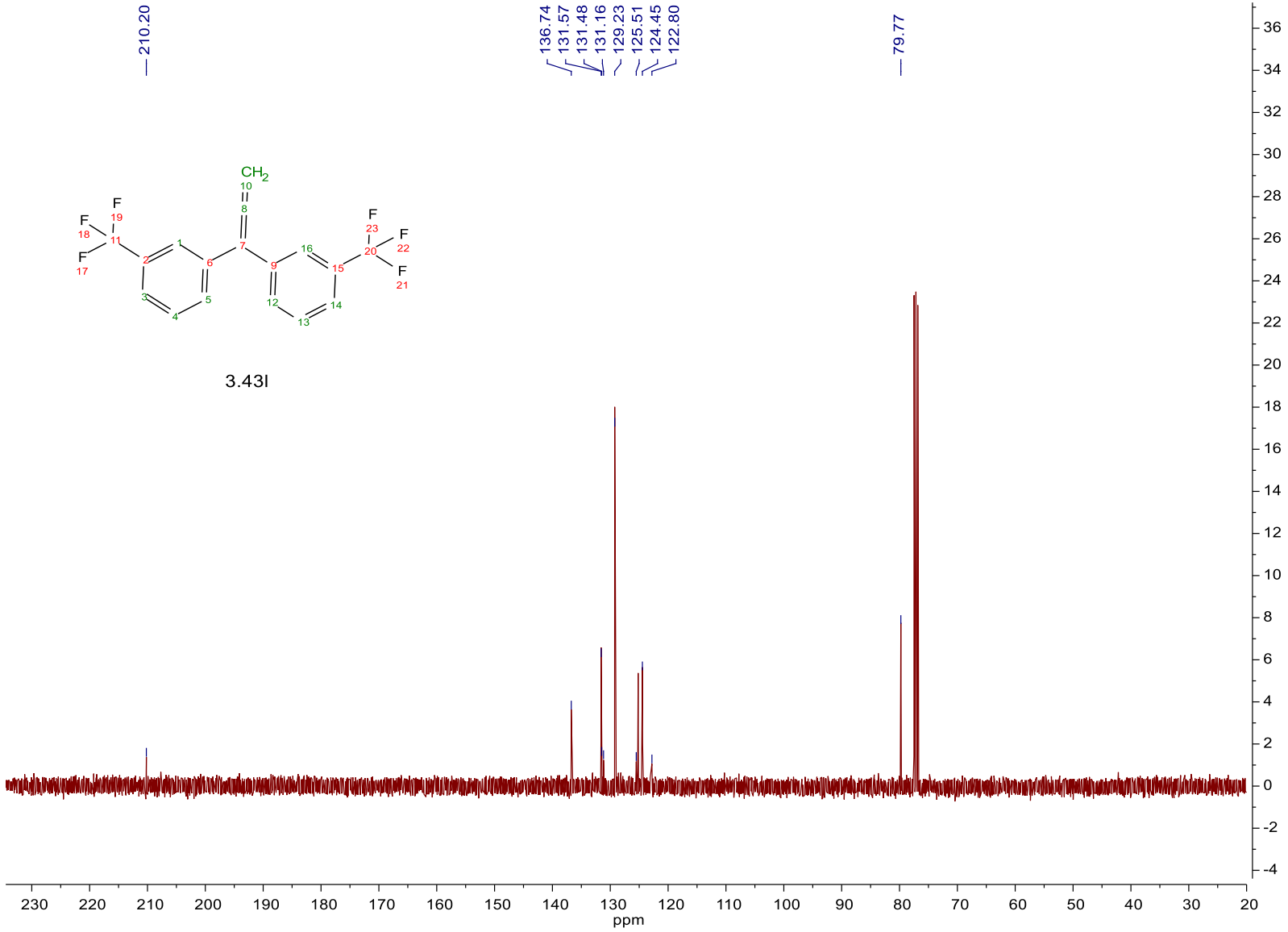

7.64
7.63
7.61
7.60
7.60
7.59
7.49
7.47
7.45
7.45
7.43
7.37
7.33
7.32
5.34
CH2
3.43j
8.03
8.09
2.16
2.00
f1 (ppm)

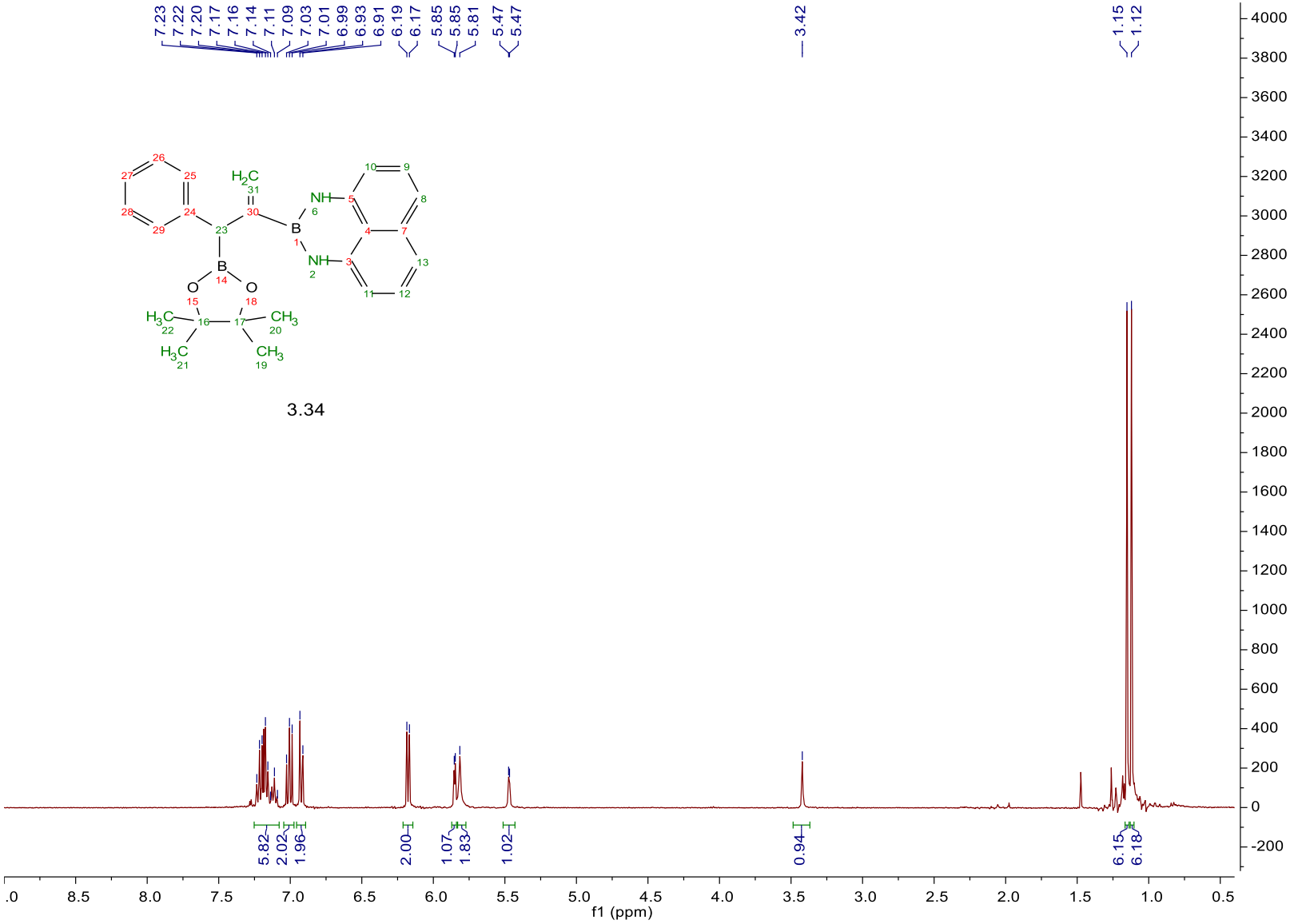

210.22
140.88
140.29
135.31
128.98
128.94
127.46
127.32
127.17
108.79
78.48
CH2
3.43j
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

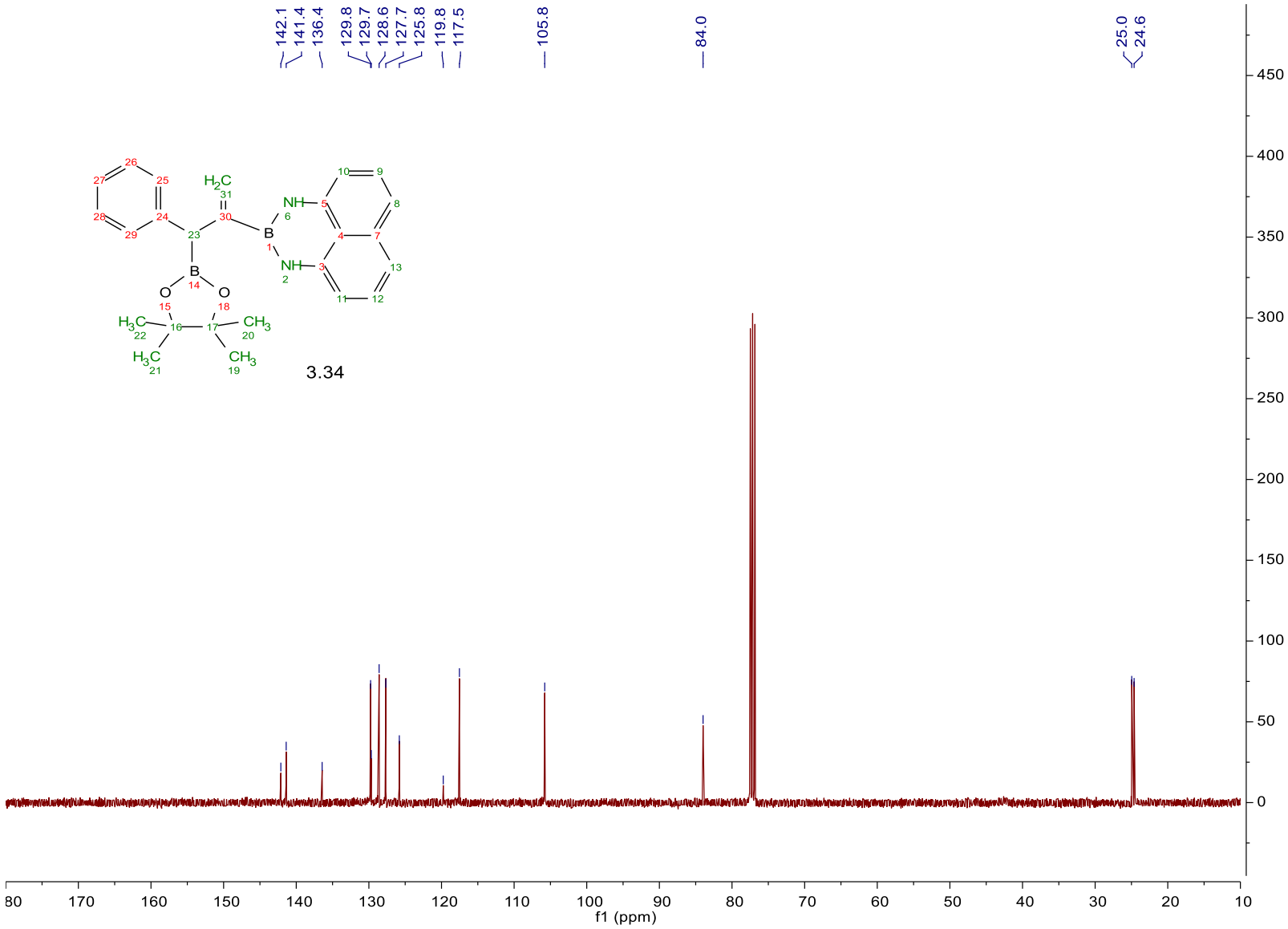

7.19
7.19
7.16
7.15
7.15
7.14
7.13
7.13
7.10
7.08
5.03
2.26
CH2
10
CH3
11
CH3
17
3.43k
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
7.75
2.00
6.12
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

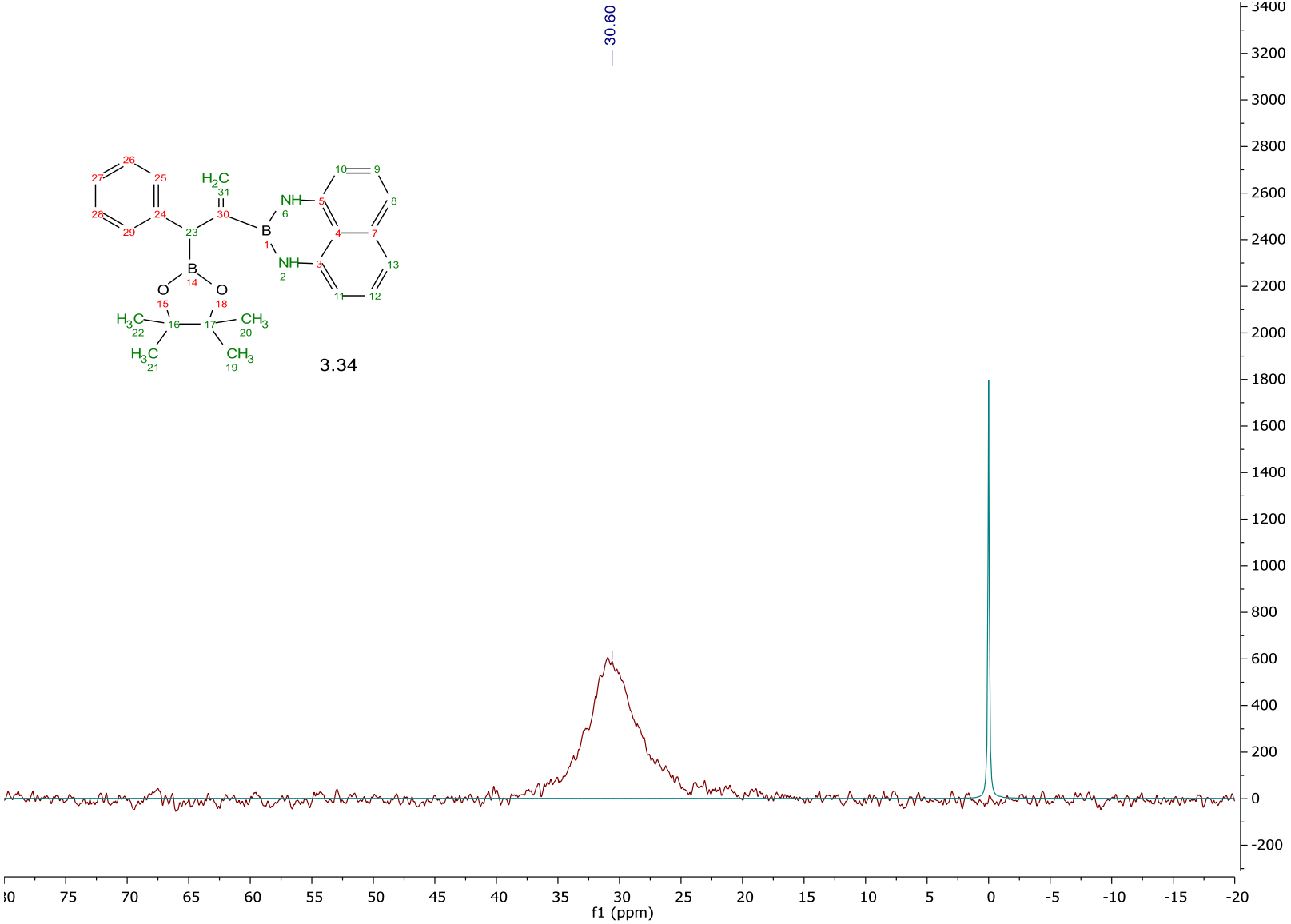

209.25
137.06
136.59
130.86
129.59
127.34
126.06
106.43
76.11
20.76
CH2
10
CH3
11
CH3
17
9
6
7
16
5
8
15
1
2
4
12
14
3
13
3.43k
f1 (ppm)

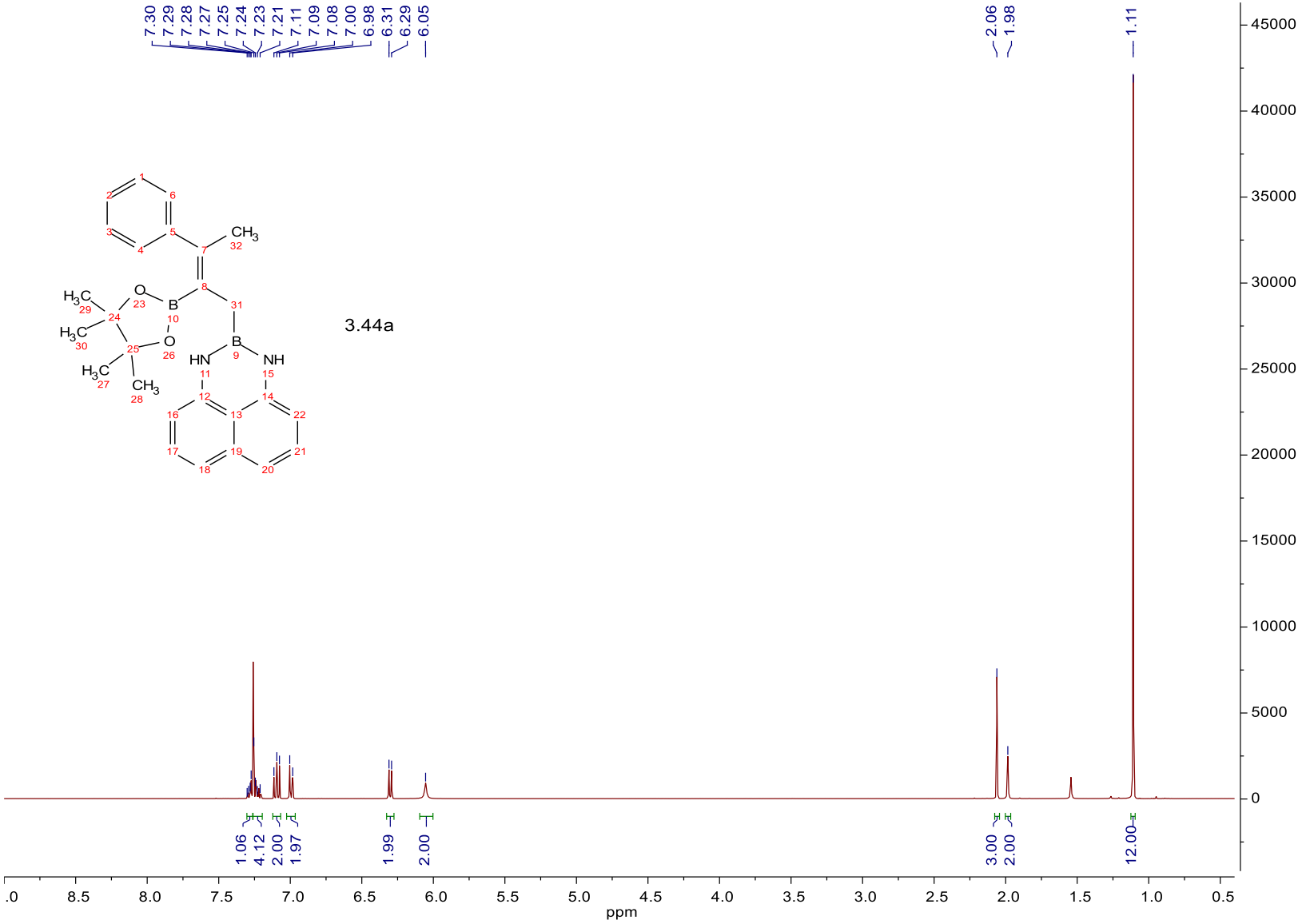

7.61
7.56
7.56
7.50
7.49
7.49
7.48
5.40
CH2
10
8
F
19
F
18
11
F
17
1
2
6
7
9
16
15
20
F
23
F
22
F
21
3
4
5
12
13
14
3.43l
8.00
2.00
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

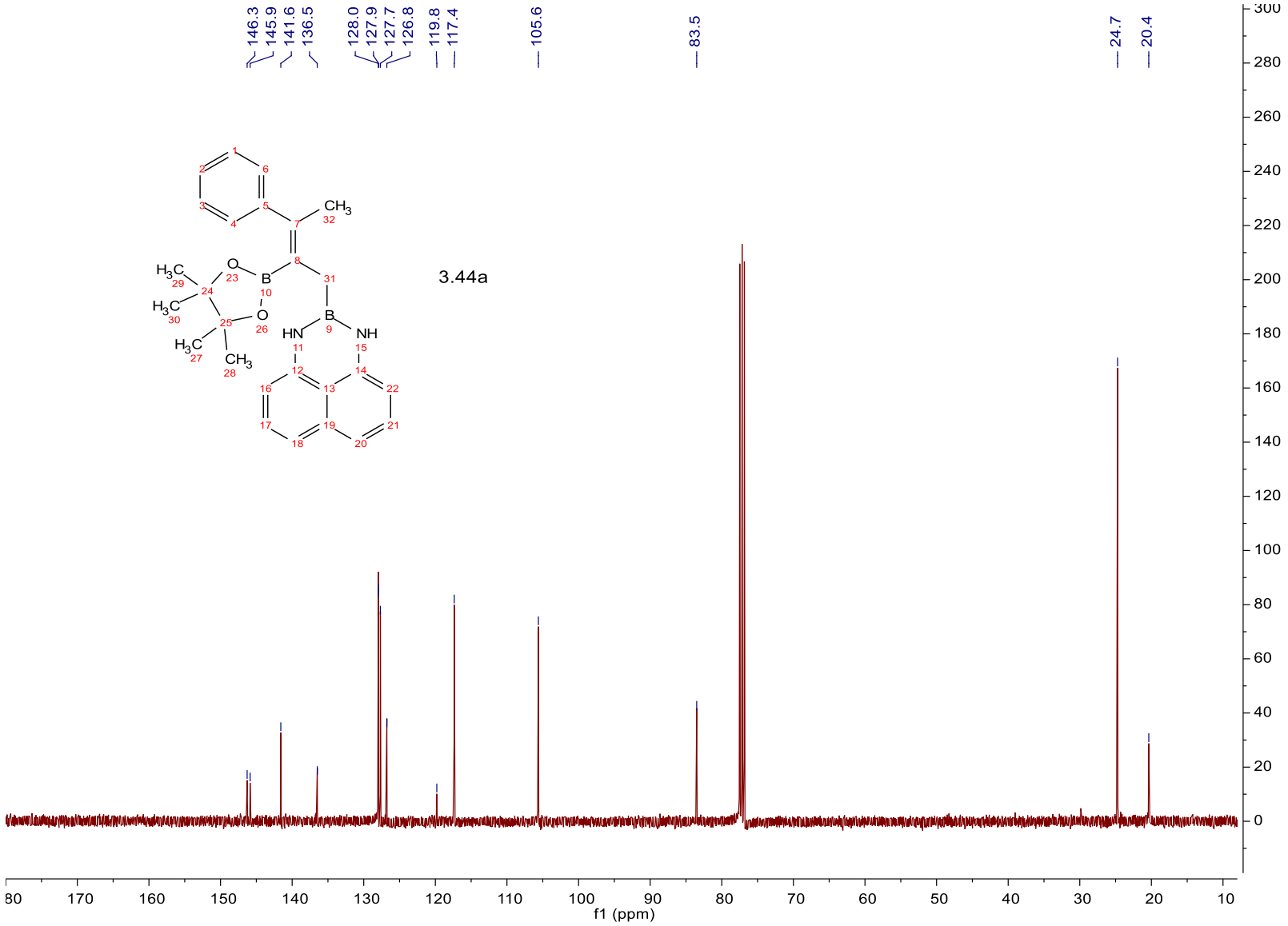

210.20
136.74
131.57
131.48
131.16
129.23
125.51
124.45
122.80
79.77
CH2
10
8
F
19
F
18
11
F
17
1
2
6
7
9
16
15
20
F
23
F
22
F
21
3
4
5
12
13
14
3.43l
ppm

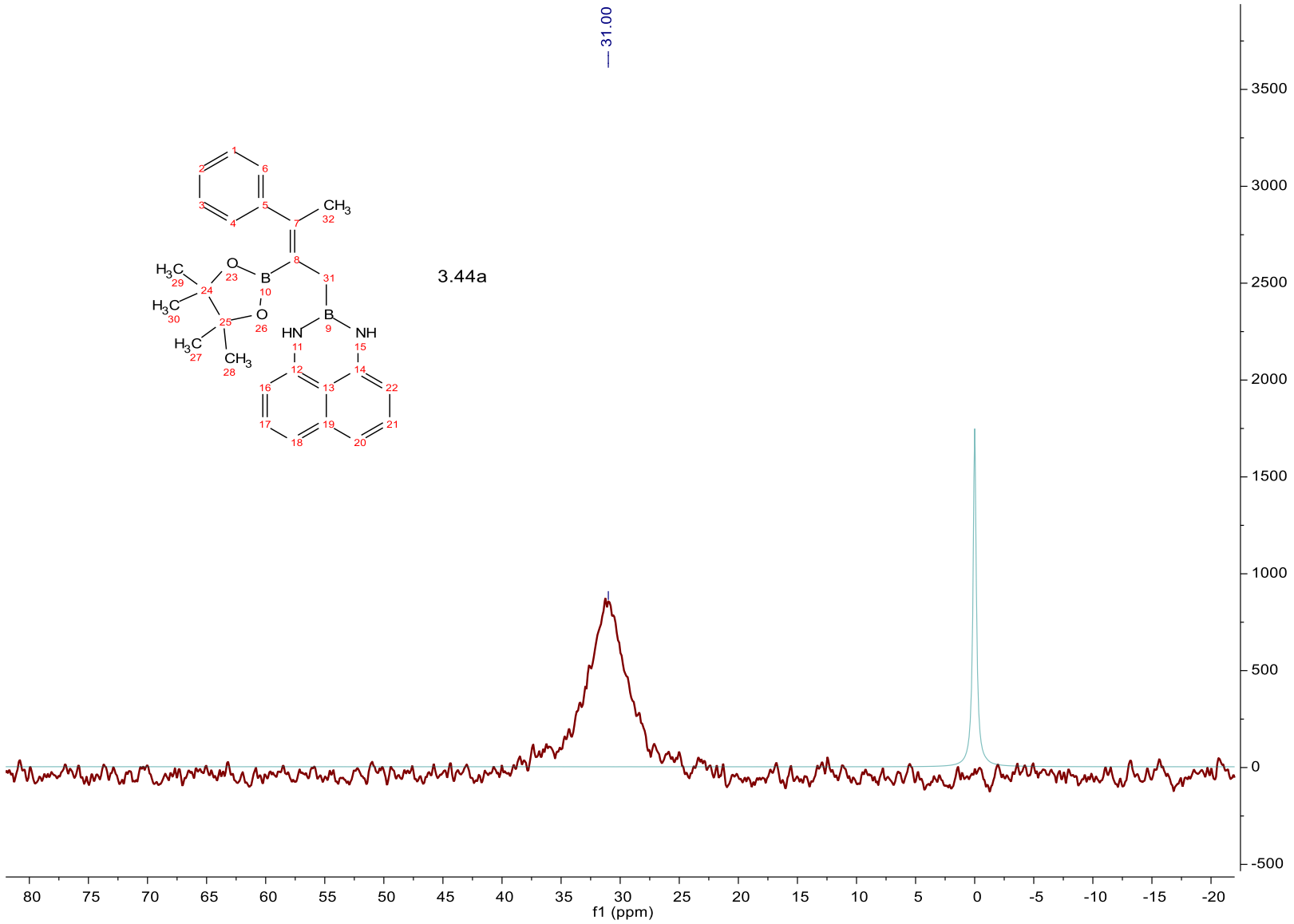

7.23
7.22
7.20
7.17
7.16
7.14
7.11
7.09
7.03
7.01
6.99
6.93
6.91
6.19
6.17
5.85
5.85
5.81
5.47
5.47
3.42
1.15
1.12
3.34
5.82
2.02
1.96
2.00
1.07
1.83
1.02
0.94
6.15
6.18
f1 (ppm)

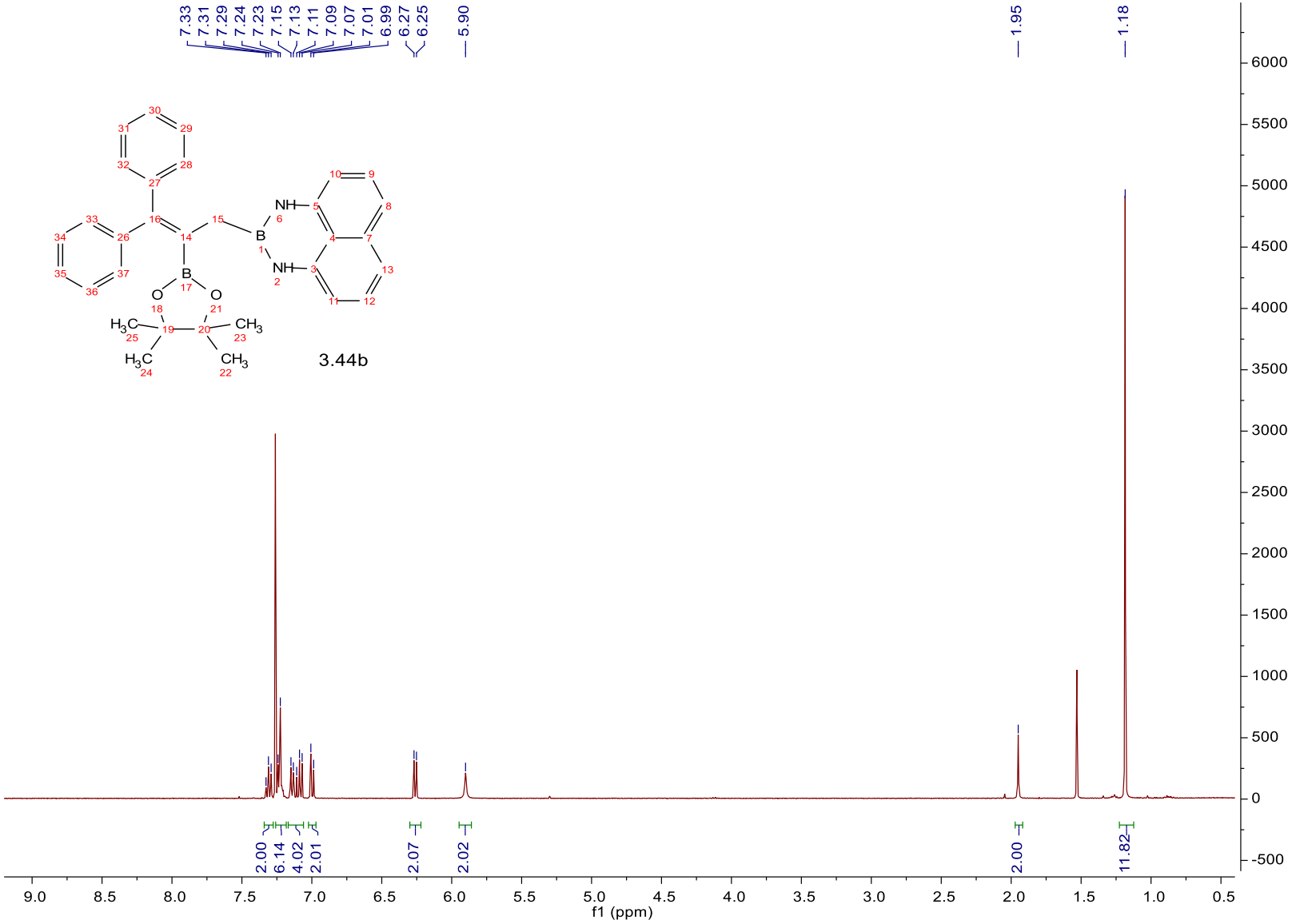

142.1
141.4
136.4
129.8
129.7
128.6
127.7
125.8
119.8
117.5
105.8
84.0
25.0
24.6
3.34
f1 (ppm)

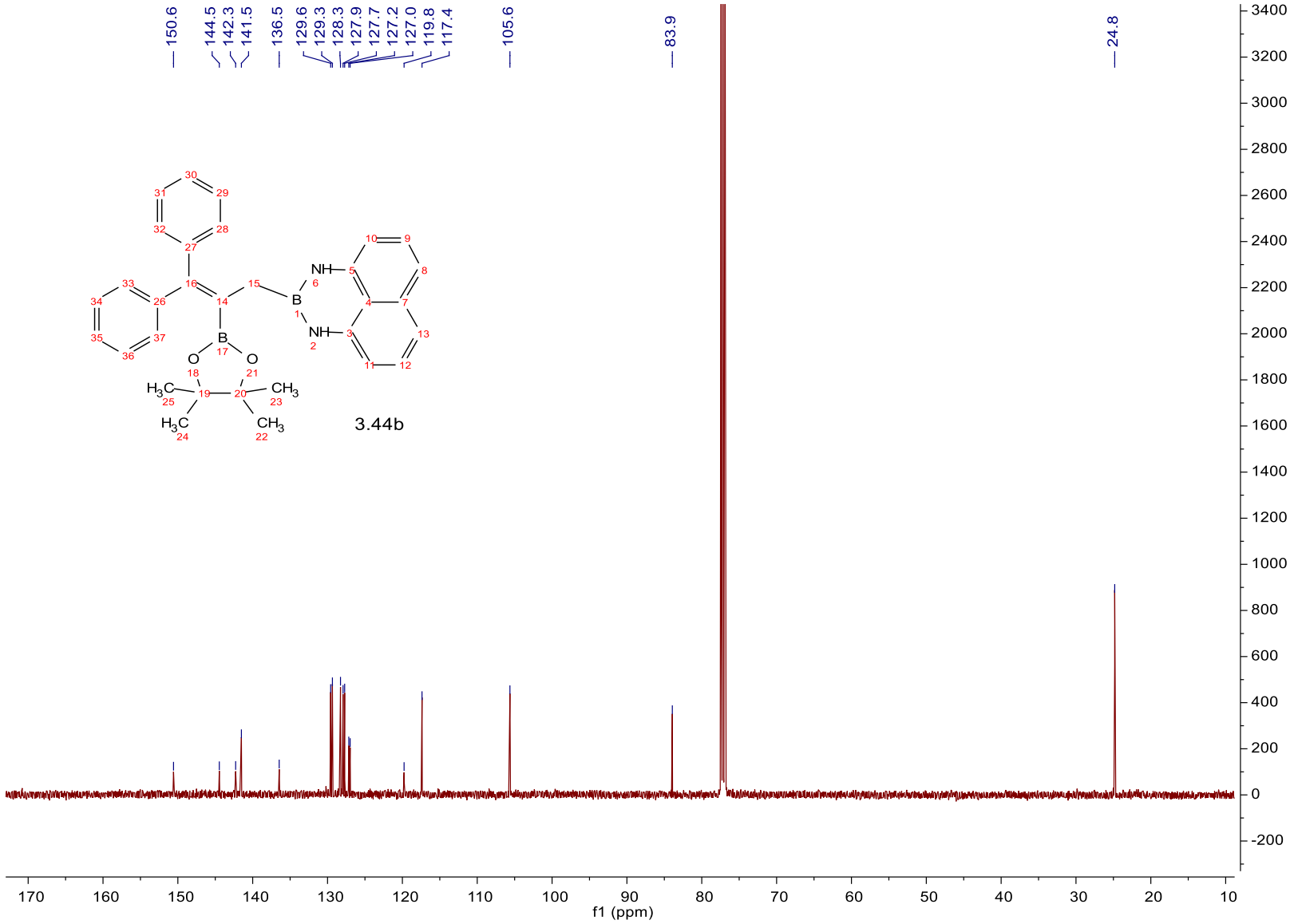

30.60
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
f1 (ppm)
3.34

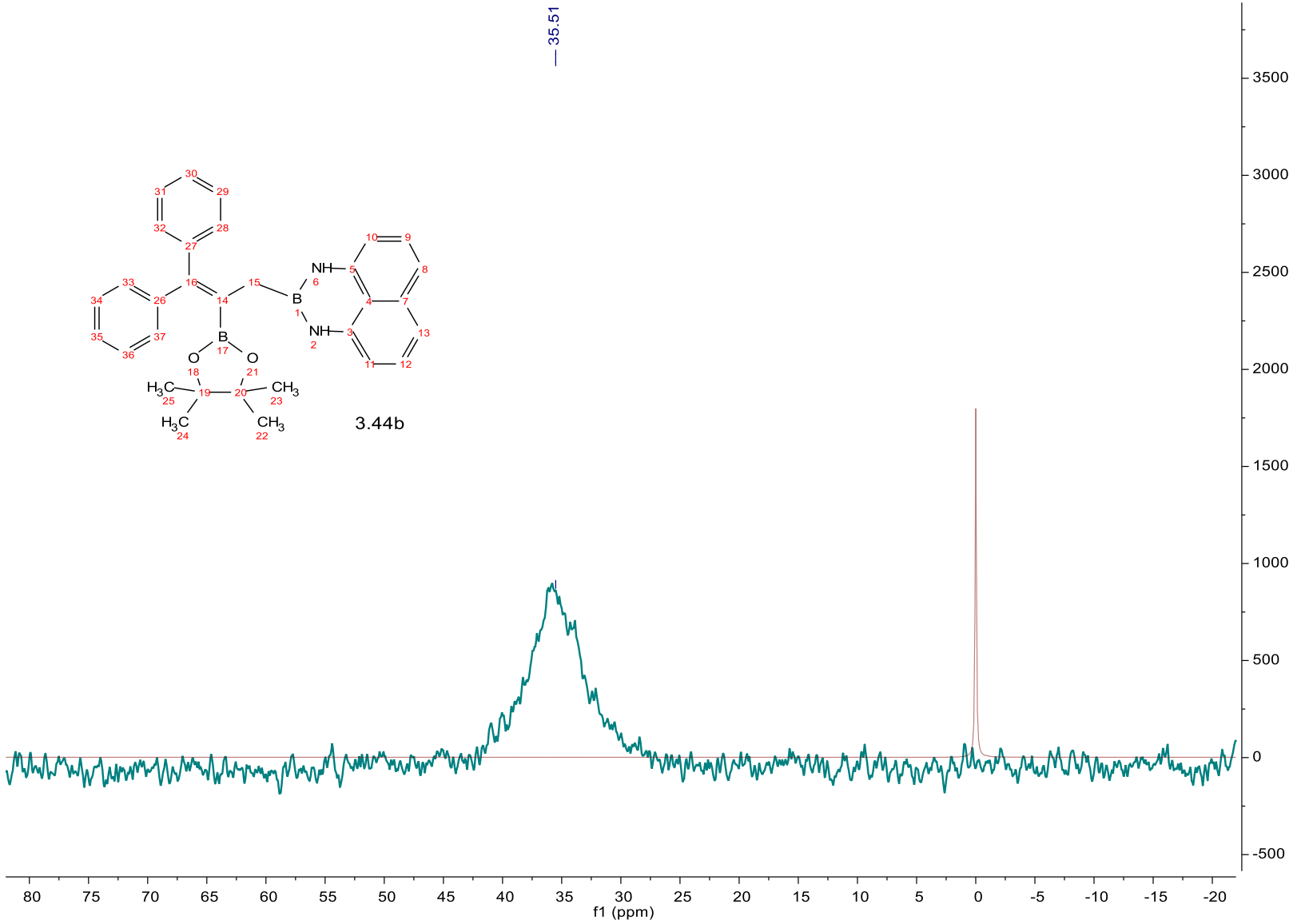

7.30
7.29
7.28
7.27
7.25
7.24
7.23
7.21
7.11
7.09
7.08
7.00
6.98
6.31
6.29
6.05
2.06
1.98
1.11
3.44a
1.06
4.12
2.00
1.97
1.99
2.00
3.00
2.00
12.00
ppm

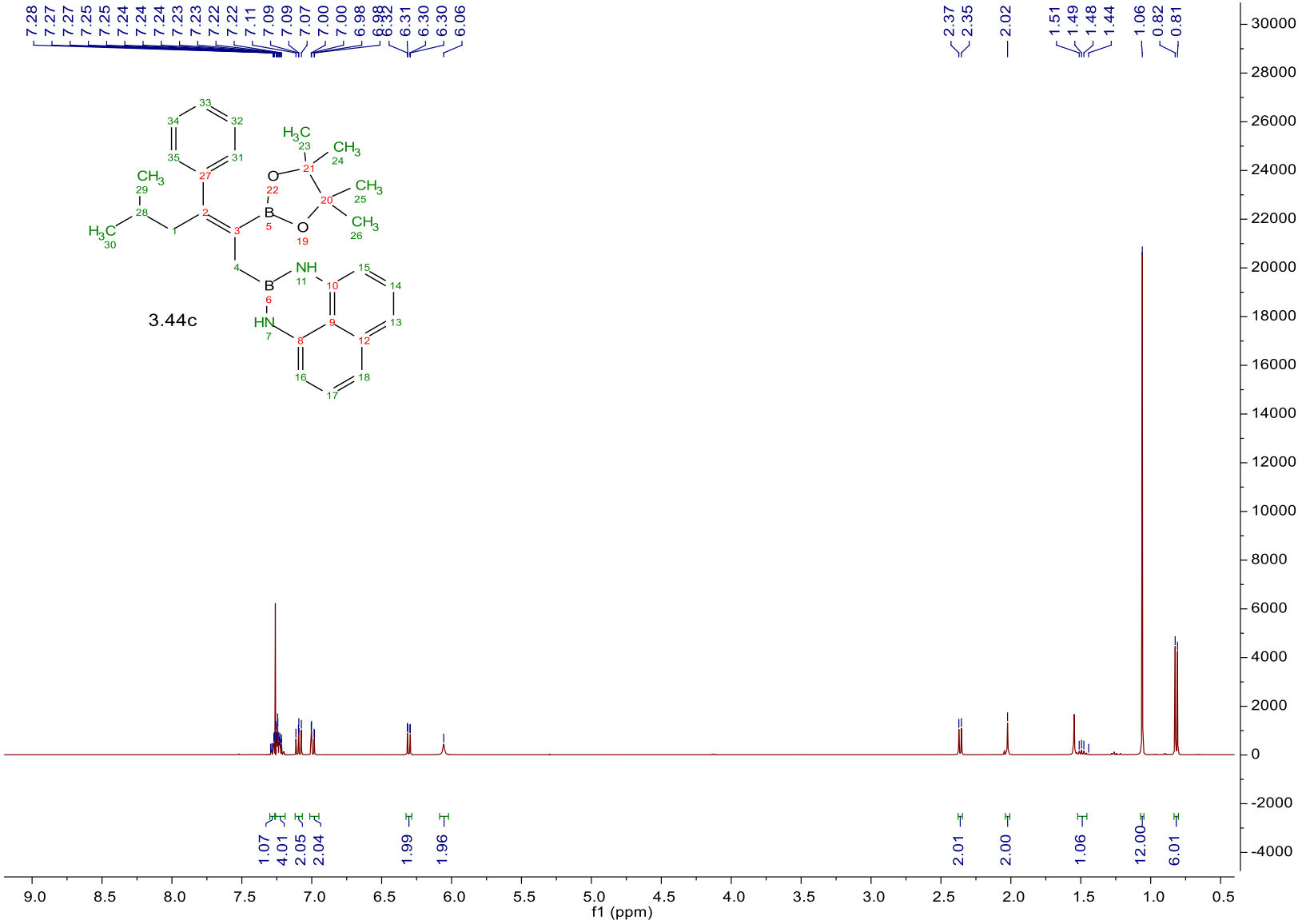

146.3
145.9
141.6
136.5
128.0
127.9
127.7
126.8
119.8
117.4
105.6
83.5
24.7
20.4
3.44a
f1 (ppm)

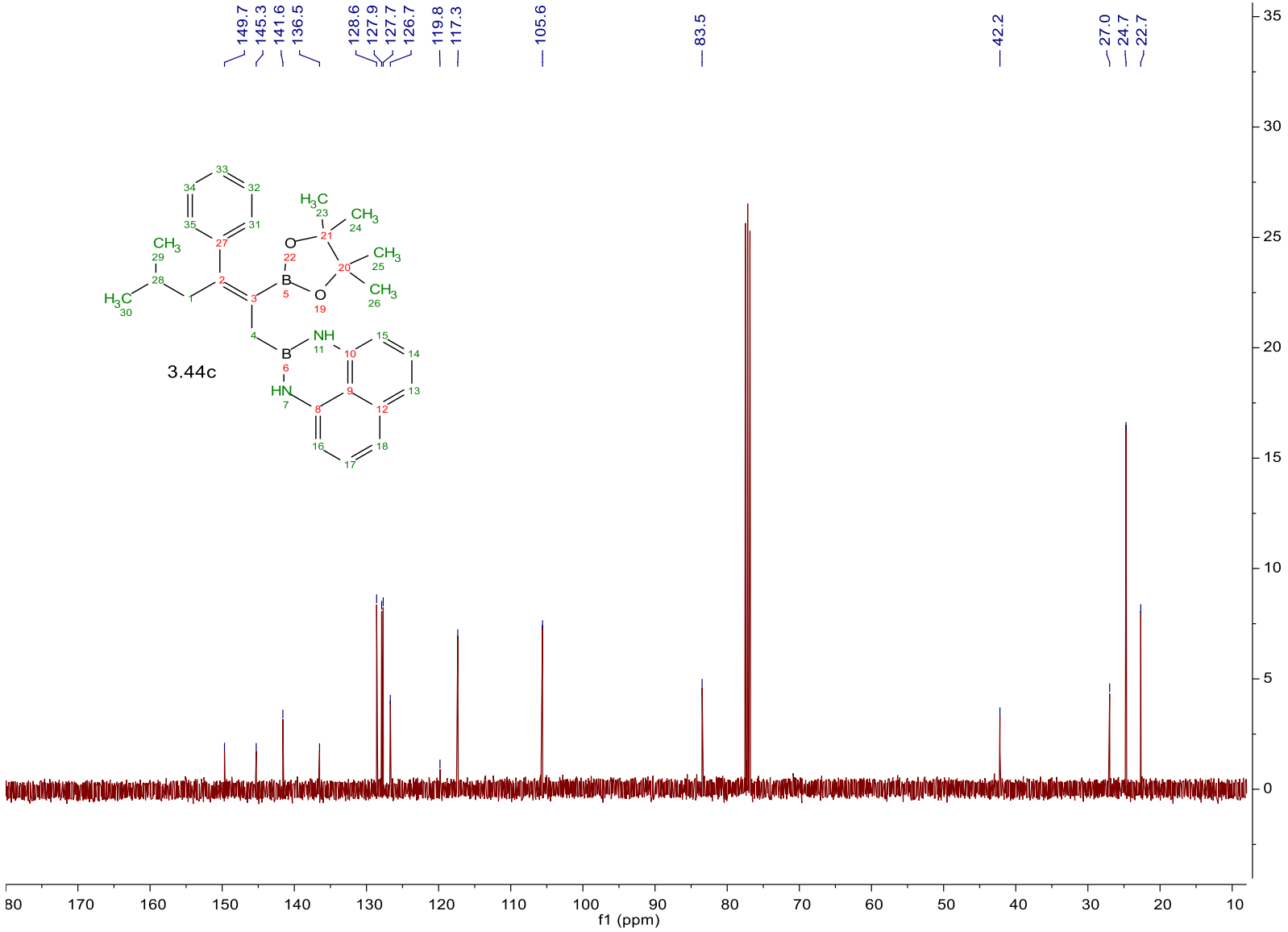

31.00
3.44a
3500
3000
2500
2000
1500
1000
500
0
-500
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20
f1 (ppm)

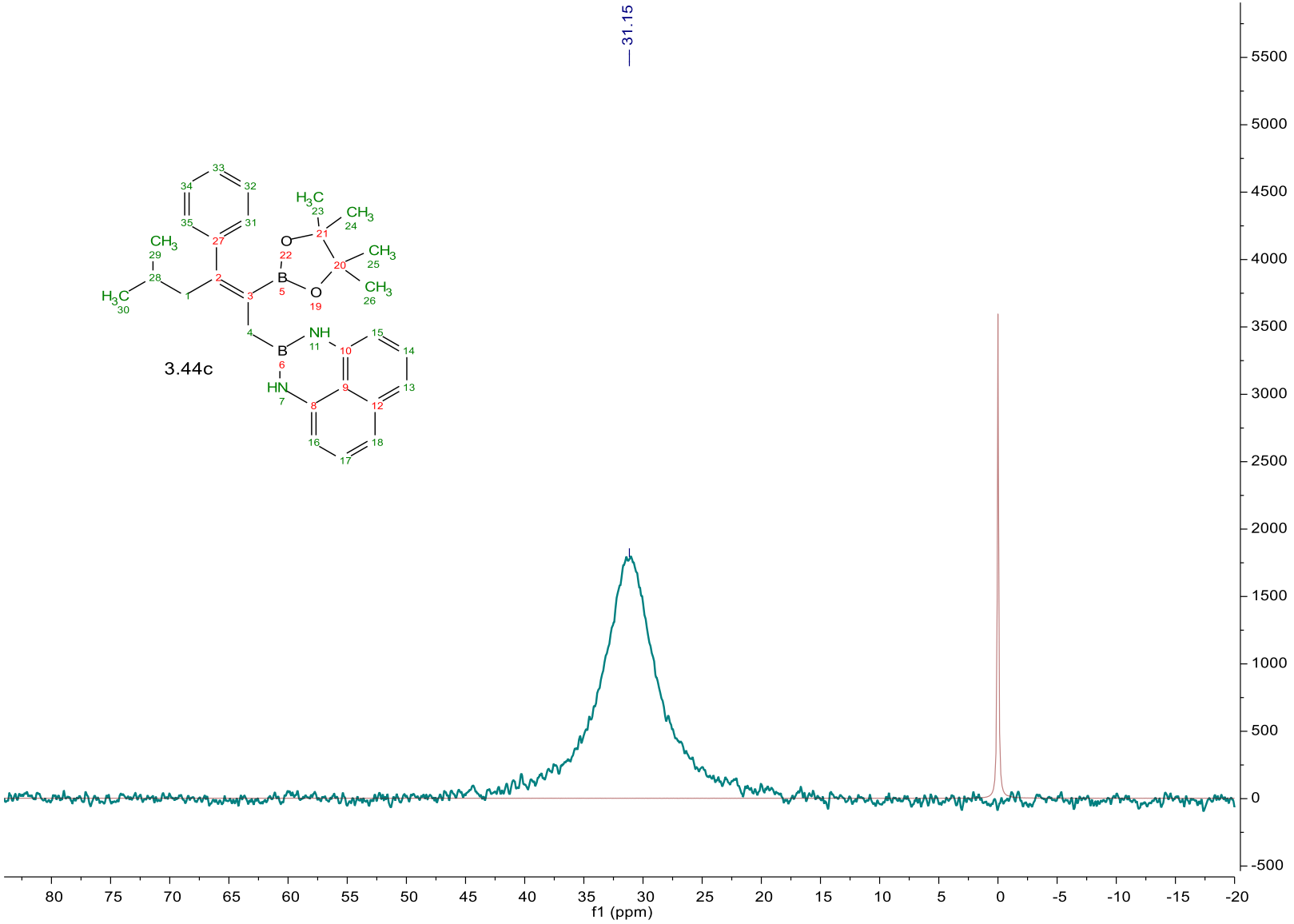

7.33
7.31
7.29
7.24
7.23
7.15
7.13
7.11
7.09
7.07
7.01
6.99
6.27
6.25
5.90
1.95
1.18
3.44b
2.00
6.14
4.02
2.01
2.07
2.02
2.00
11.82
f1 (ppm)

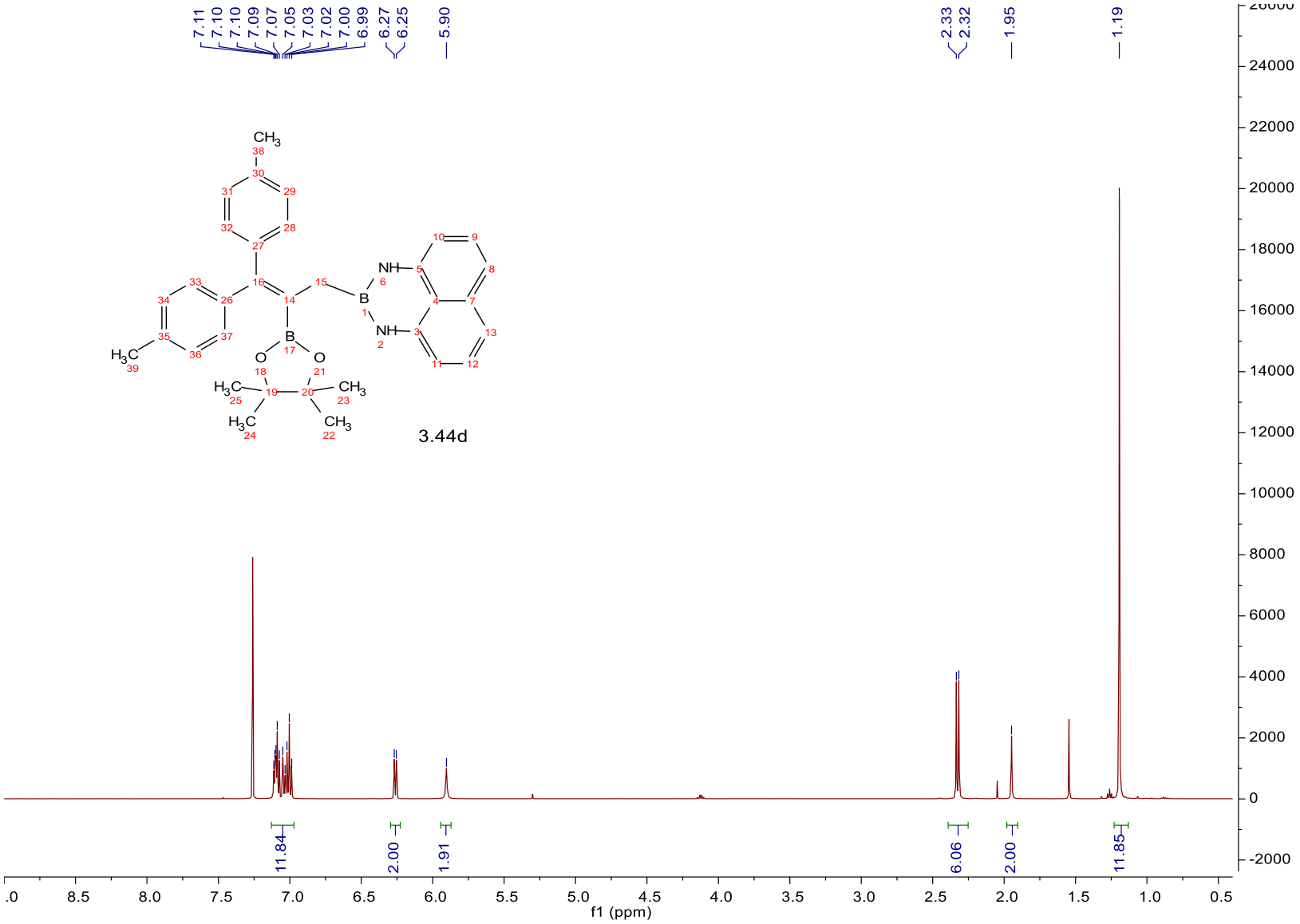

150.6
144.5
142.3
141.5
136.5
129.6
129.3
128.3
127.9
127.7
127.2
127.0
119.8
117.4
105.6
83.9
24.8
3.44b
f1 (ppm)

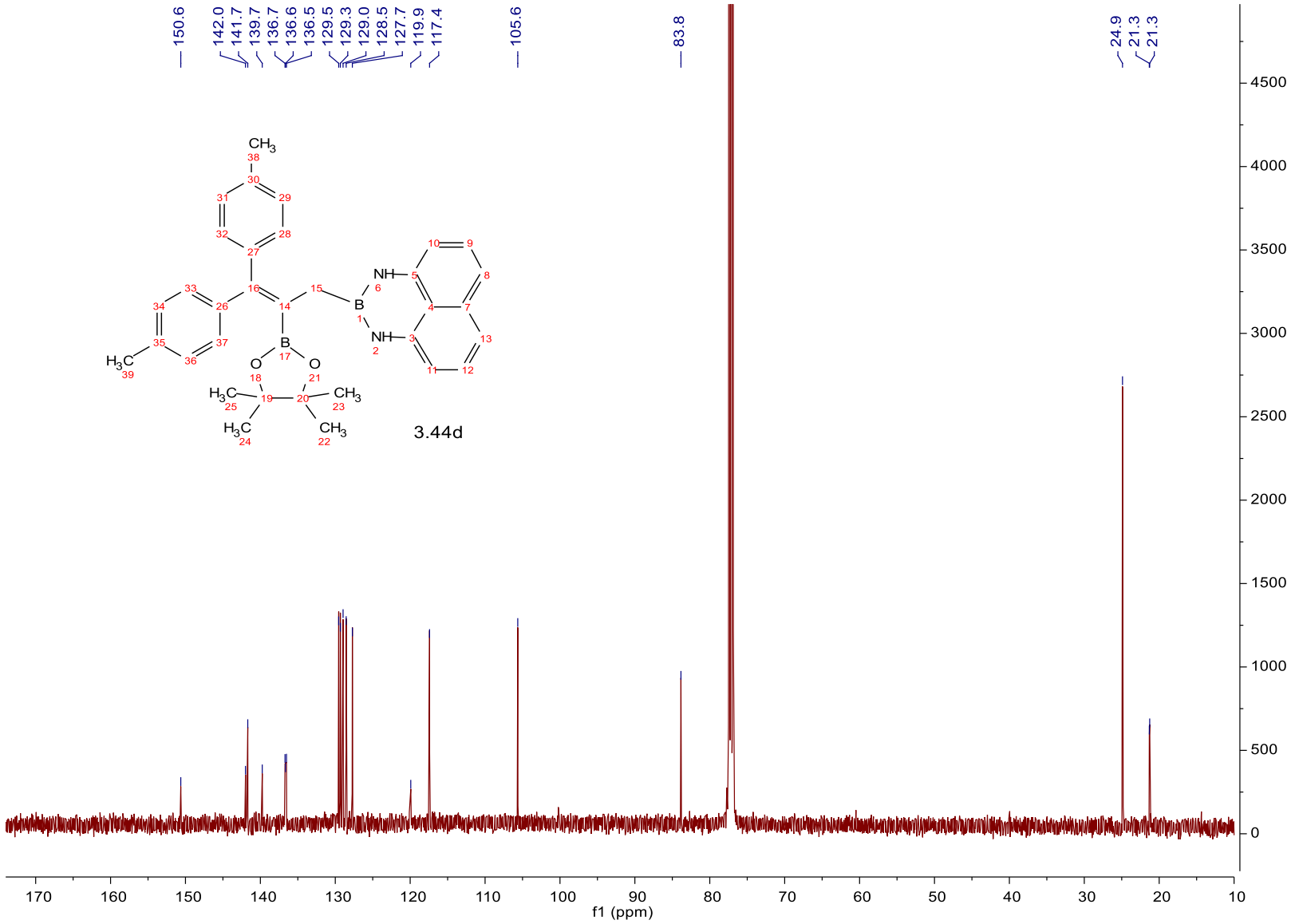

35.51
3500
3000
2500
2000
1500
1000
500
0
-500
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
f1 (ppm)
NH
NH
B
B
O
O
H_3C
CH_3
H_3C
CH_3
3.44b

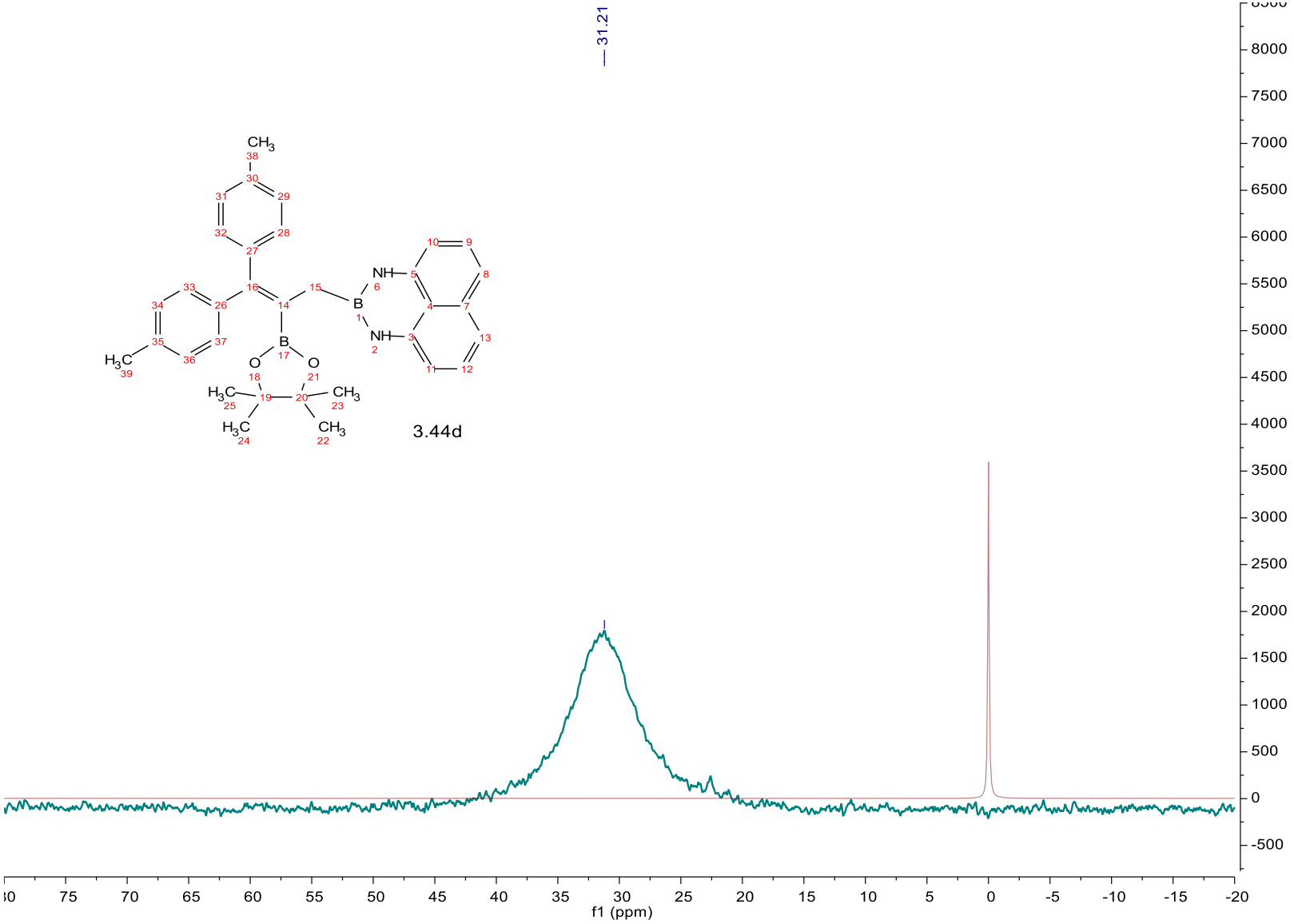

7.28 7.27 7.27 7.25 7.25 7.24 7.24 7.24 7.23 7.23 7.22 7.22 7.11 7.09 7.09 7.07 7.00 7.00 6.98 6.31 6.30 6.30 6.06
2.37 2.35 2.02 1.51 1.49 1.48 1.44 1.06 0.82 0.81
3.44c
1.07 4.01 2.05 2.04 1.99 1.96 2.01 2.00 1.06 12.00 6.01
f1 (ppm)

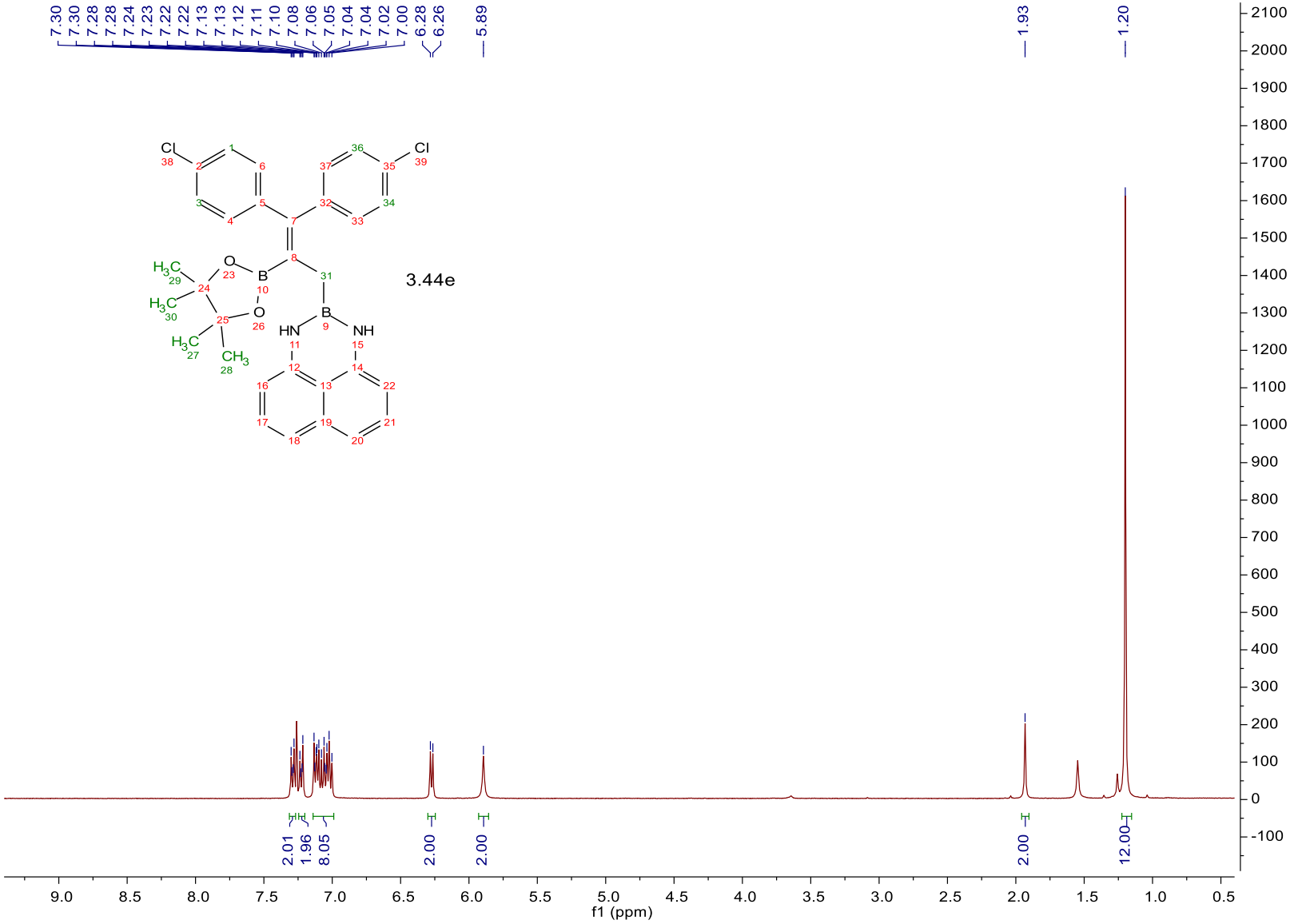

149.7
145.3
141.6
136.5
128.6
127.9
127.7
126.7
119.8
117.3
105.6
83.5
42.2
27.0
24.7
22.7
3.44c
f1 (ppm)

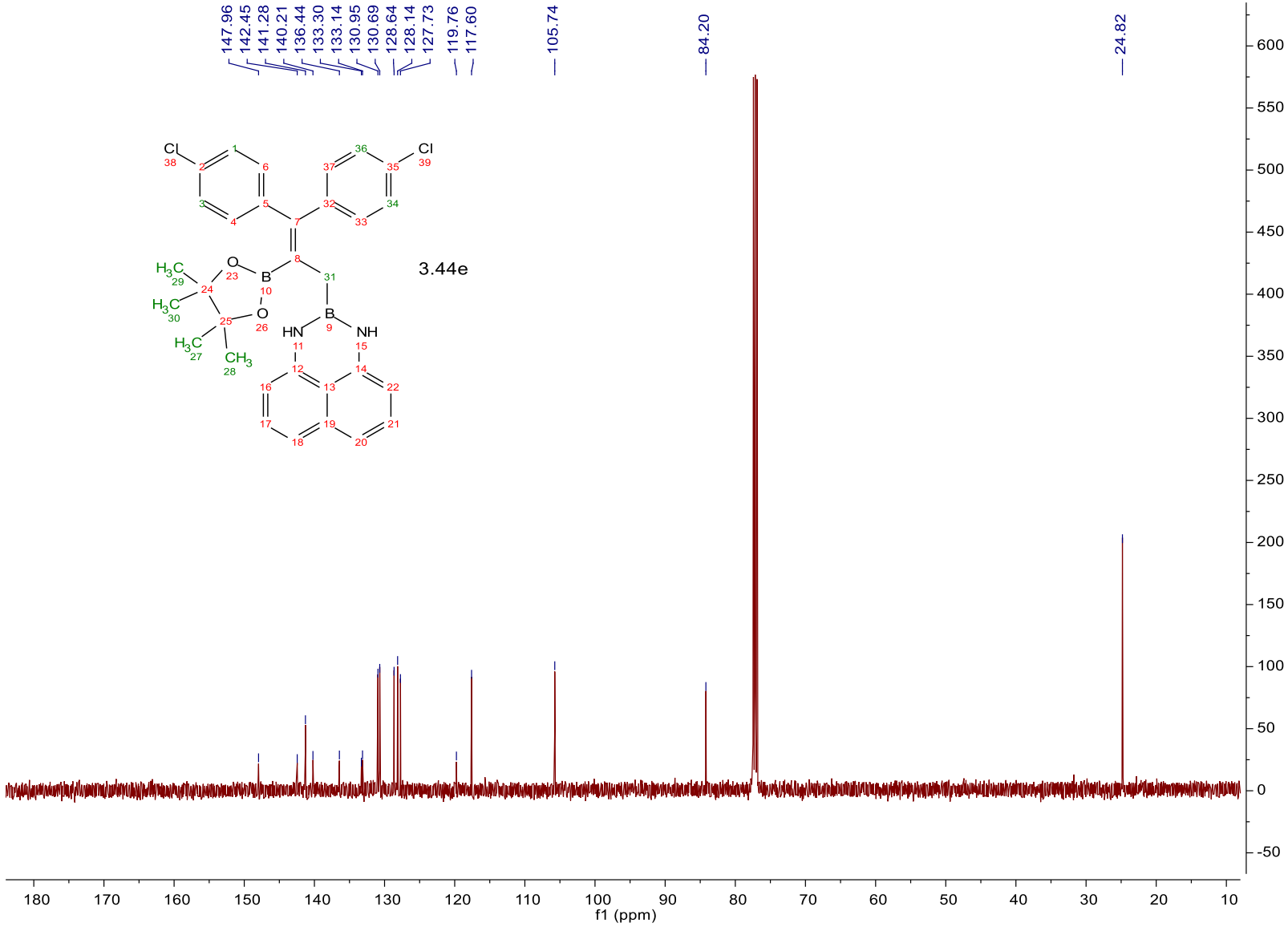

31.15
3.44c
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
f1 (ppm)

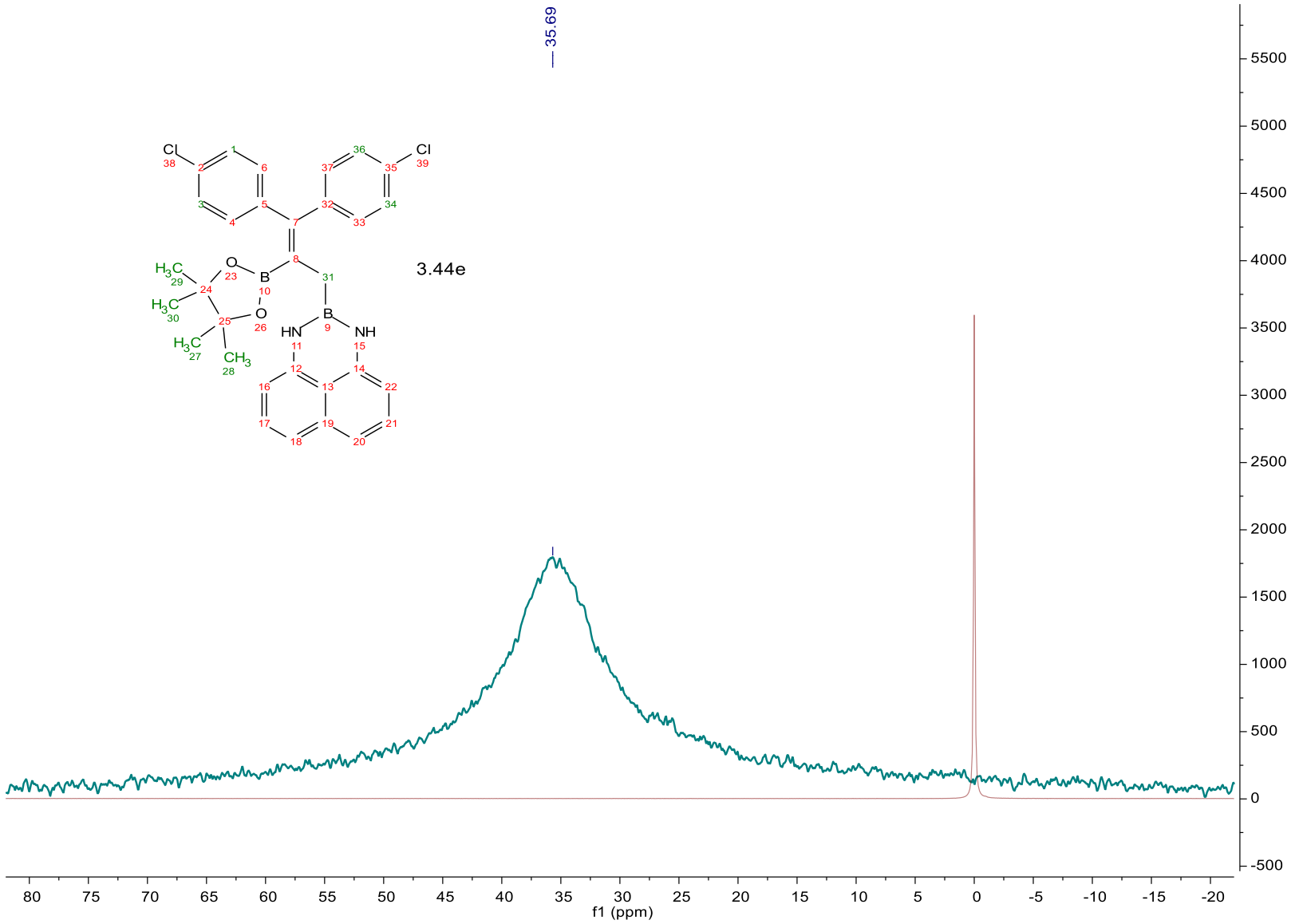

7.11
7.10
7.10
7.09
7.07
7.05
7.03
7.02
7.00
6.99
6.27
6.25
5.90
2.33
2.32
1.95
1.19
3.44d
11.84
2.00
1.91
6.06
2.00
11.85
f1 (ppm)

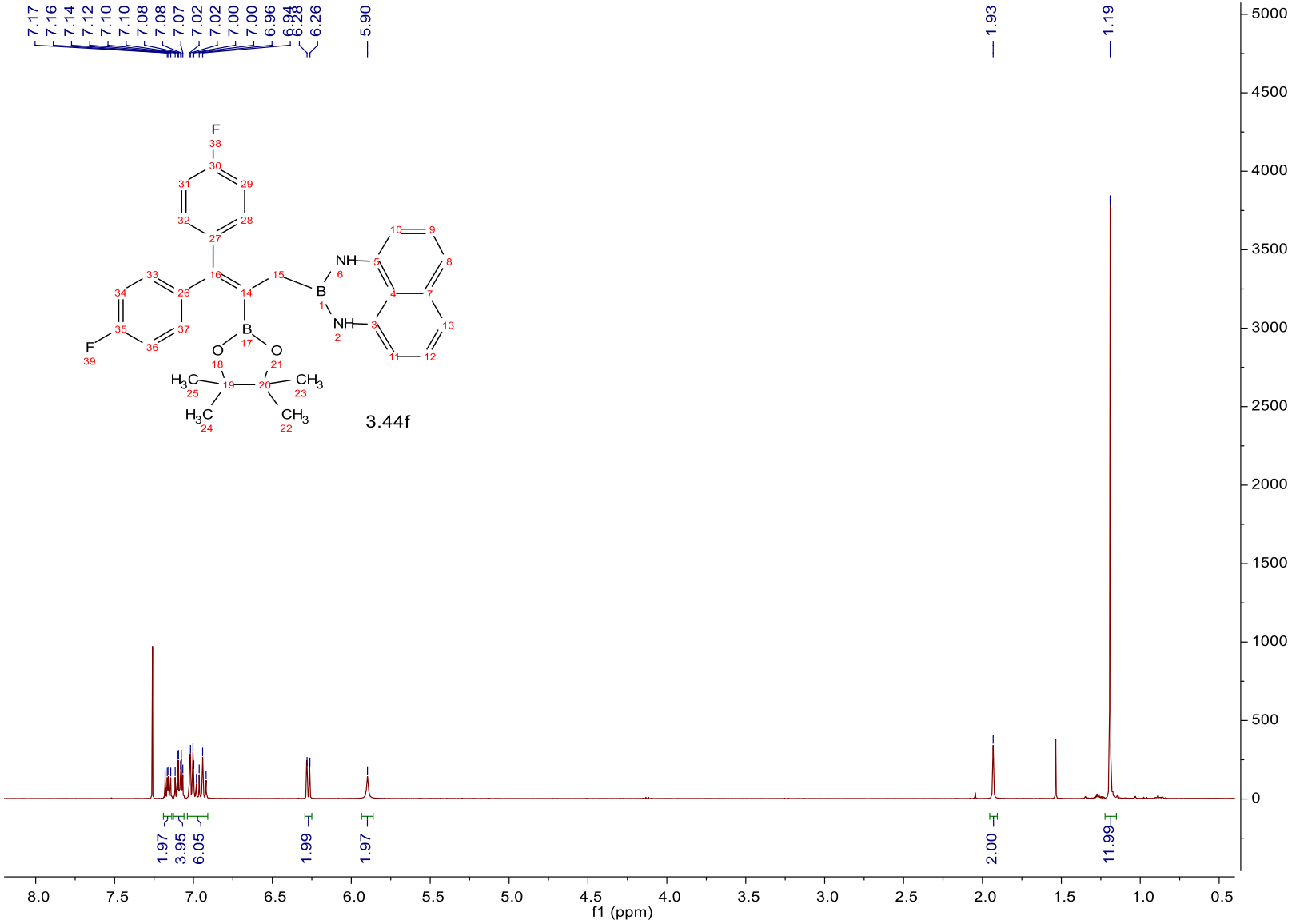

150.6
142.0
141.7
139.7
136.7
136.6
136.5
129.5
129.3
129.0
128.5
127.7
119.9
117.4
105.6
83.8
24.9
21.3
21.3
3.44d
4500
4000
3500
3000
2500
2000
1500
1000
500
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

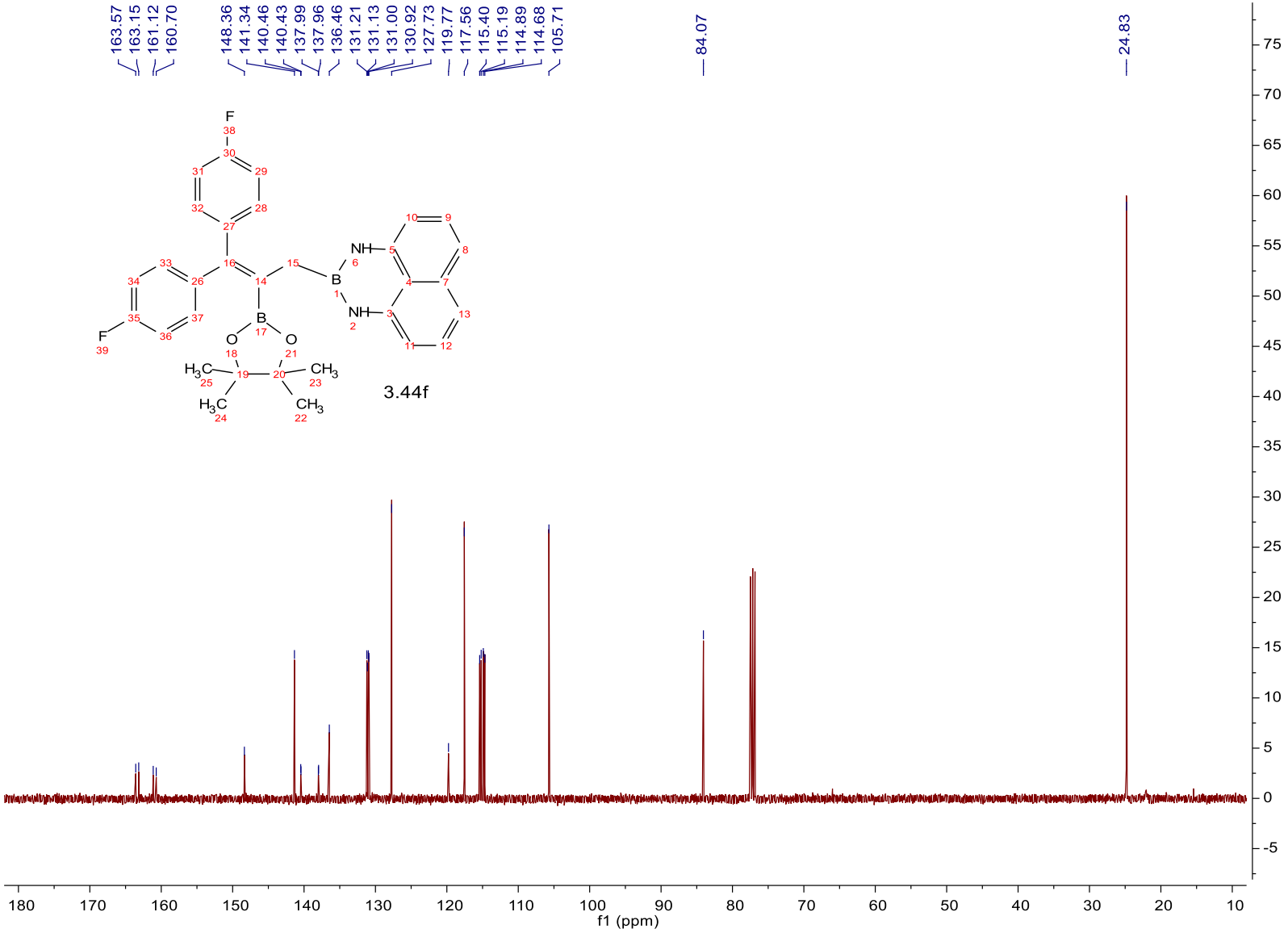

31.21
3.44d
f1 (ppm)

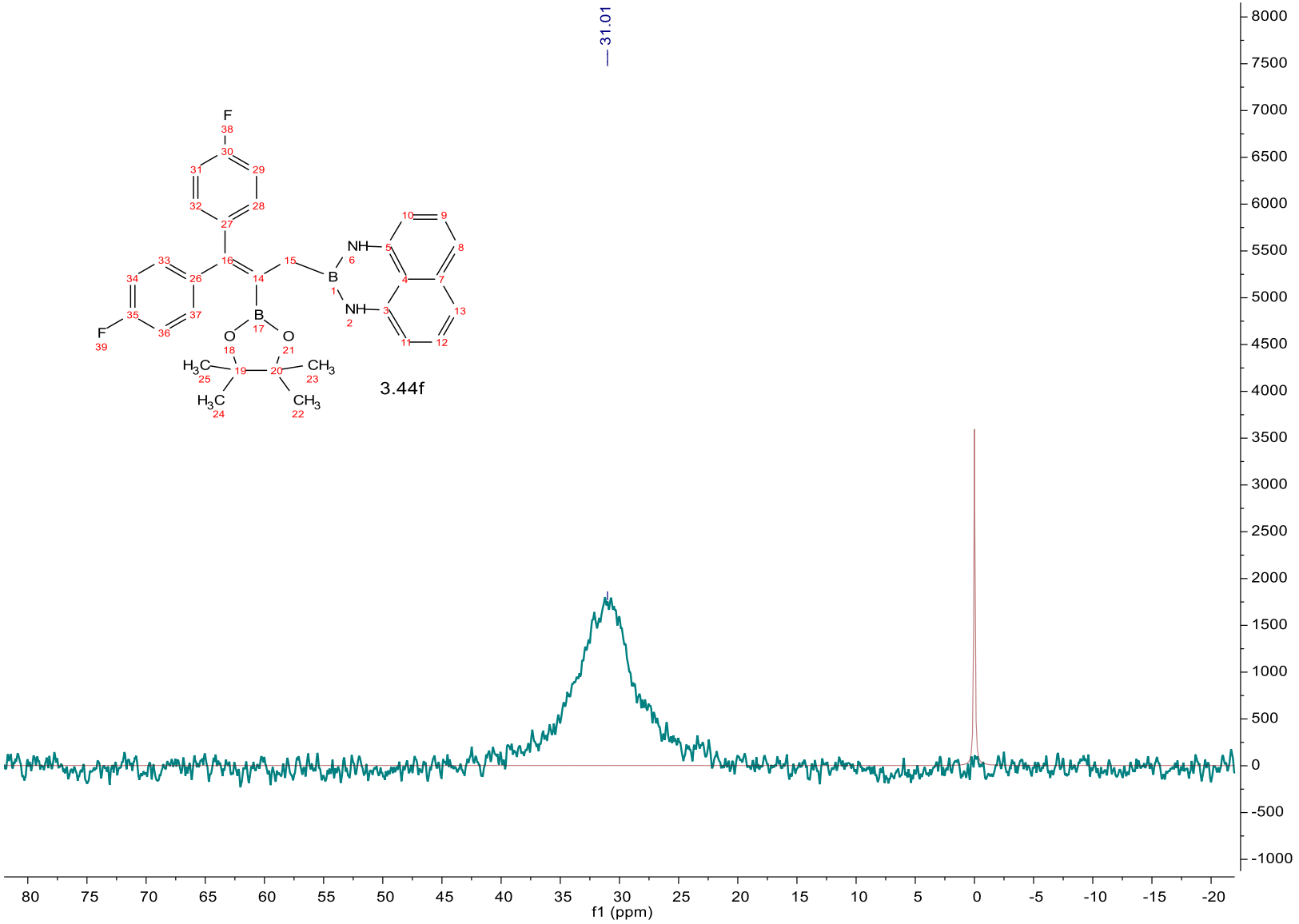

7.30
7.30
7.28
7.28
7.24
7.23
7.22
7.22
7.13
7.13
7.12
7.11
7.10
7.08
7.06
7.05
7.04
7.04
7.02
7.00
6.28
6.26
5.89
1.93
1.20
3.44e
2.01
1.96
8.05
2.00
2.00
2.00
12.00
f1 (ppm)

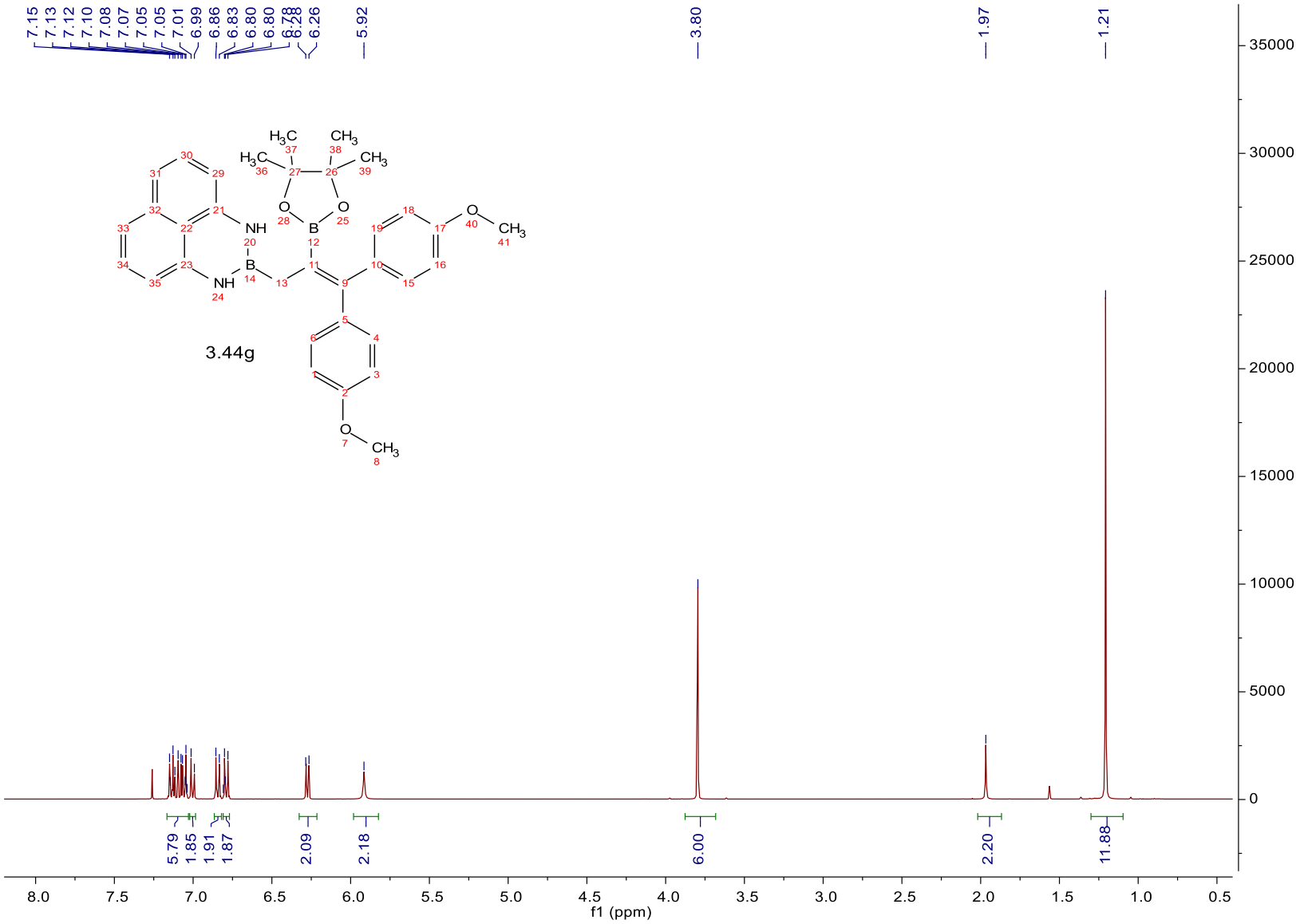

147.96
142.45
141.28
140.21
136.44
133.30
133.14
130.95
130.69
128.64
128.14
127.73
119.76
117.60
105.74
84.20
24.82
3.44e
f1 (ppm)

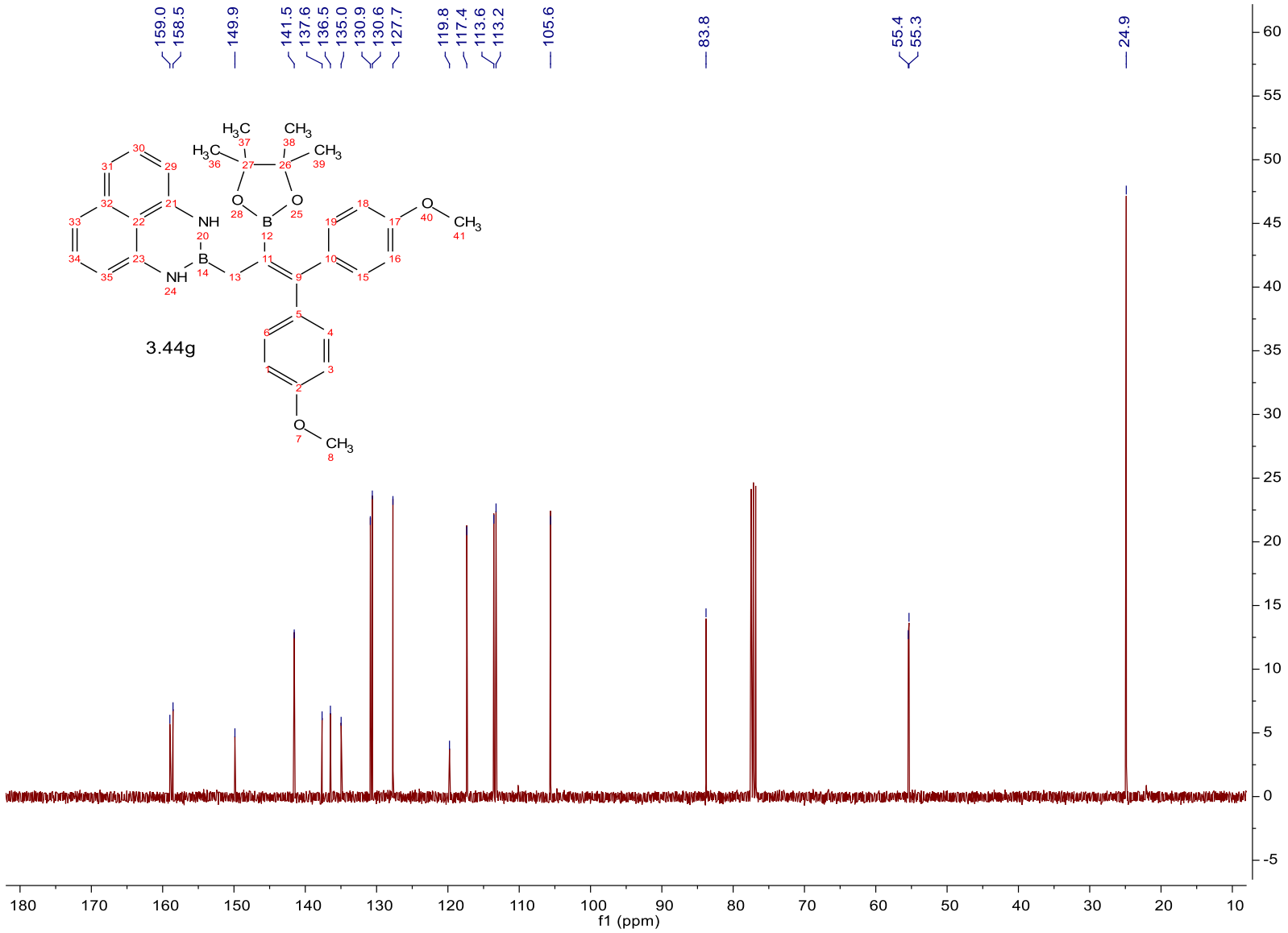

35.69
3.44e
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20
f1 (ppm)

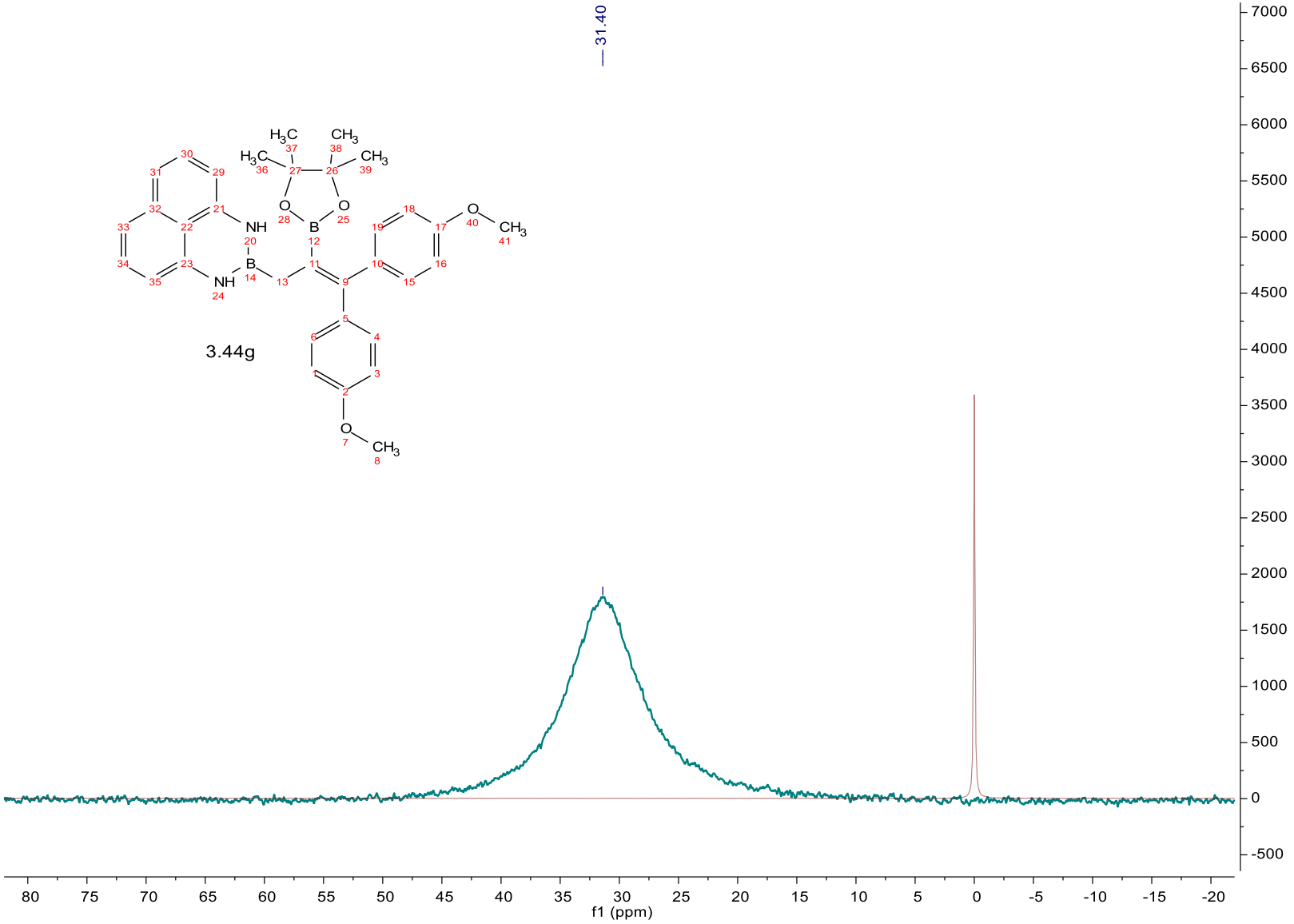

7.17
7.16
7.14
7.12
7.10
7.10
7.08
7.08
7.07
7.02
7.02
7.00
7.00
6.96
6.94
6.28
6.26
5.90
1.93
1.19
F
38
30
31
29
32
28
27
16
15
14
B
1
NH
6
NH
2
10
9
8
5
4
7
3
13
11
12
33
34
26
35
37
36
F
39
B
17
O
18
O
21
H3C
25
19
20
CH3
23
H3C
24
CH3
22
3.44f
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.97
3.95
6.05
1.99
1.97
2.00
11.99
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
f1 (ppm)

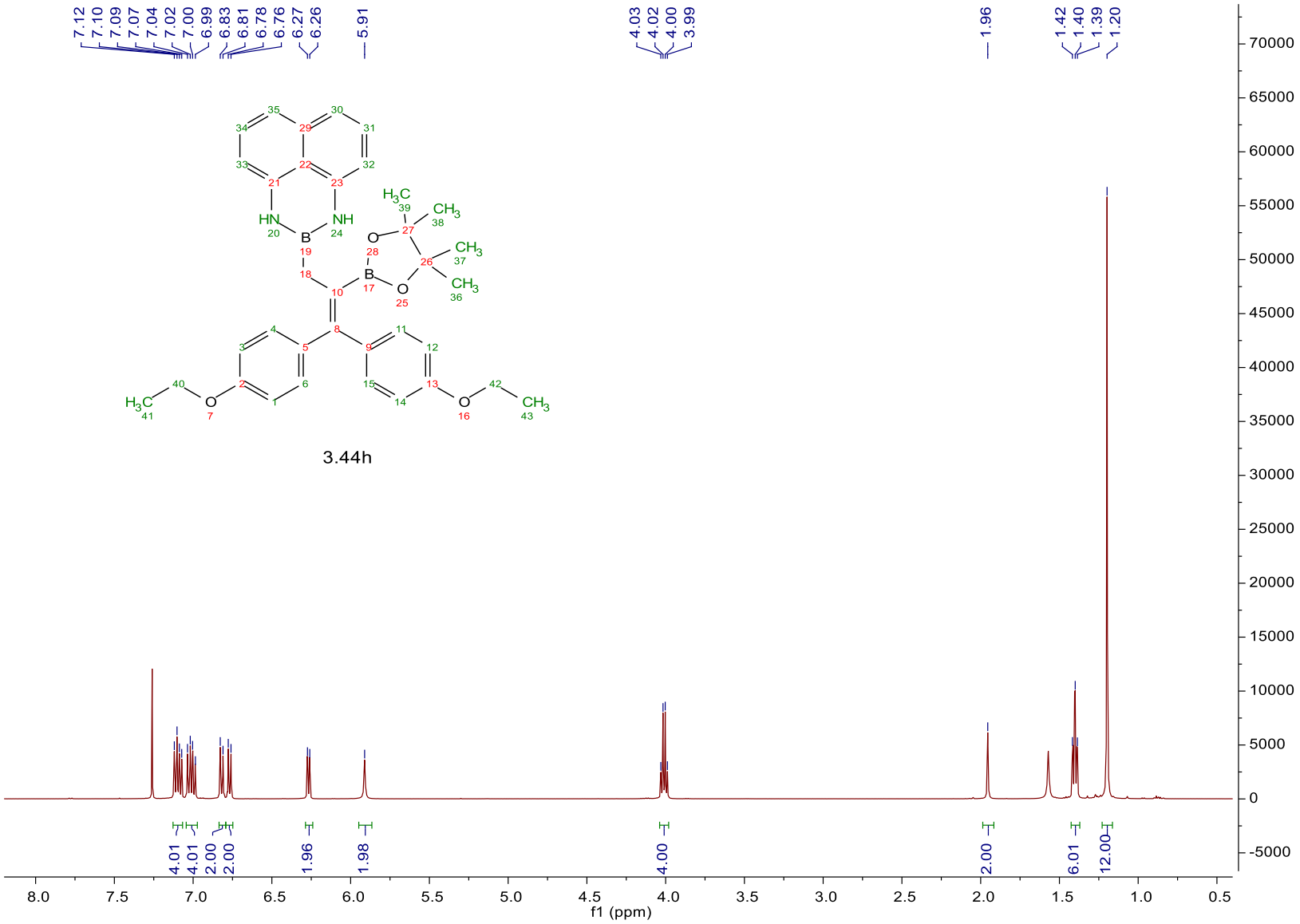

163.57
163.15
161.12
160.70
148.36
141.34
140.46
140.43
137.99
137.96
136.46
131.21
131.13
131.00
130.92
127.73
119.77
117.56
115.40
115.19
114.89
114.68
105.71
84.07
24.83
3.44f
f1 (ppm)

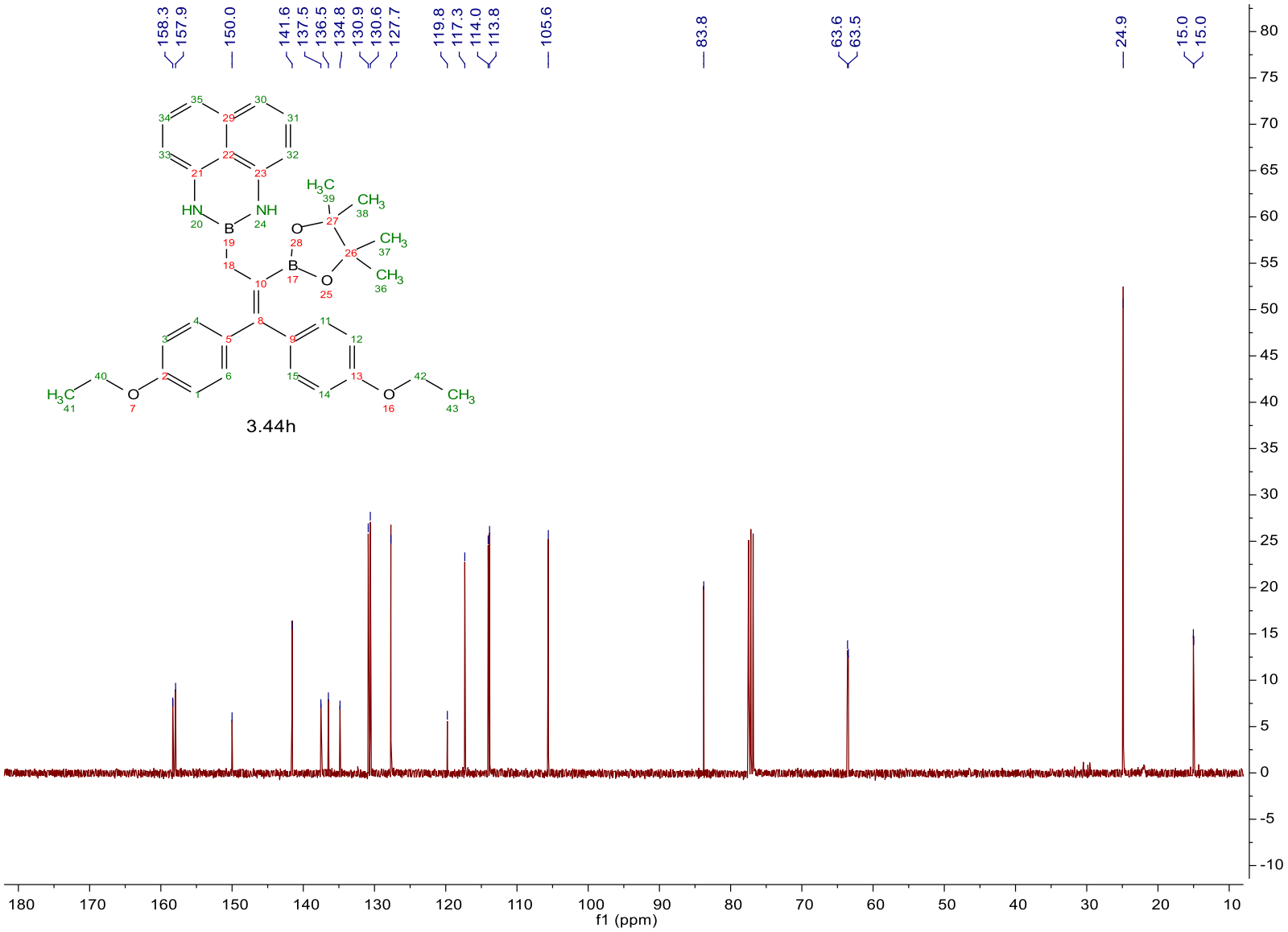

31.01
F
38
30
31
29
32
28
27
16
33
34
26
14
15
B
1
NH
6
10
9
5
8
4
7
NH
3
2
13
11
12
35
37
B
17
F
39
36
O
18
O
21
H3C
25
19
20
CH3
23
H3C
24
CH3
22
3.44f
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
f1 (ppm)

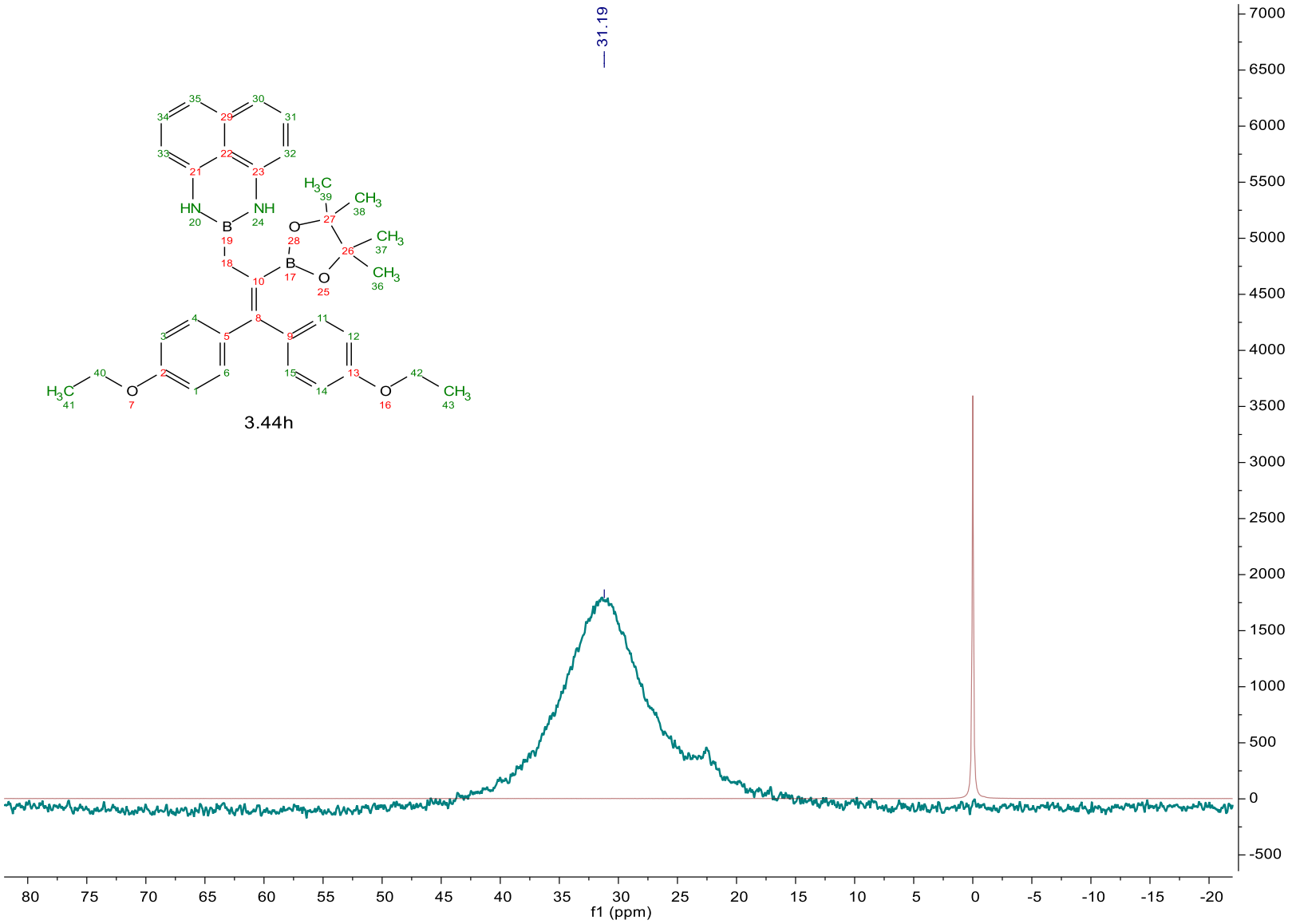

7.15
7.13
7.12
7.10
7.08
7.07
7.05
7.05
7.01
6.99
6.86
6.83
6.80
6.80
6.78
6.28
6.26
5.92
3.80
1.97
1.21
3.44g
35000
30000
25000
20000
15000
10000
5000
0
5.79
1.85
1.91
1.87
2.09
2.18
6.00
2.20
11.88
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

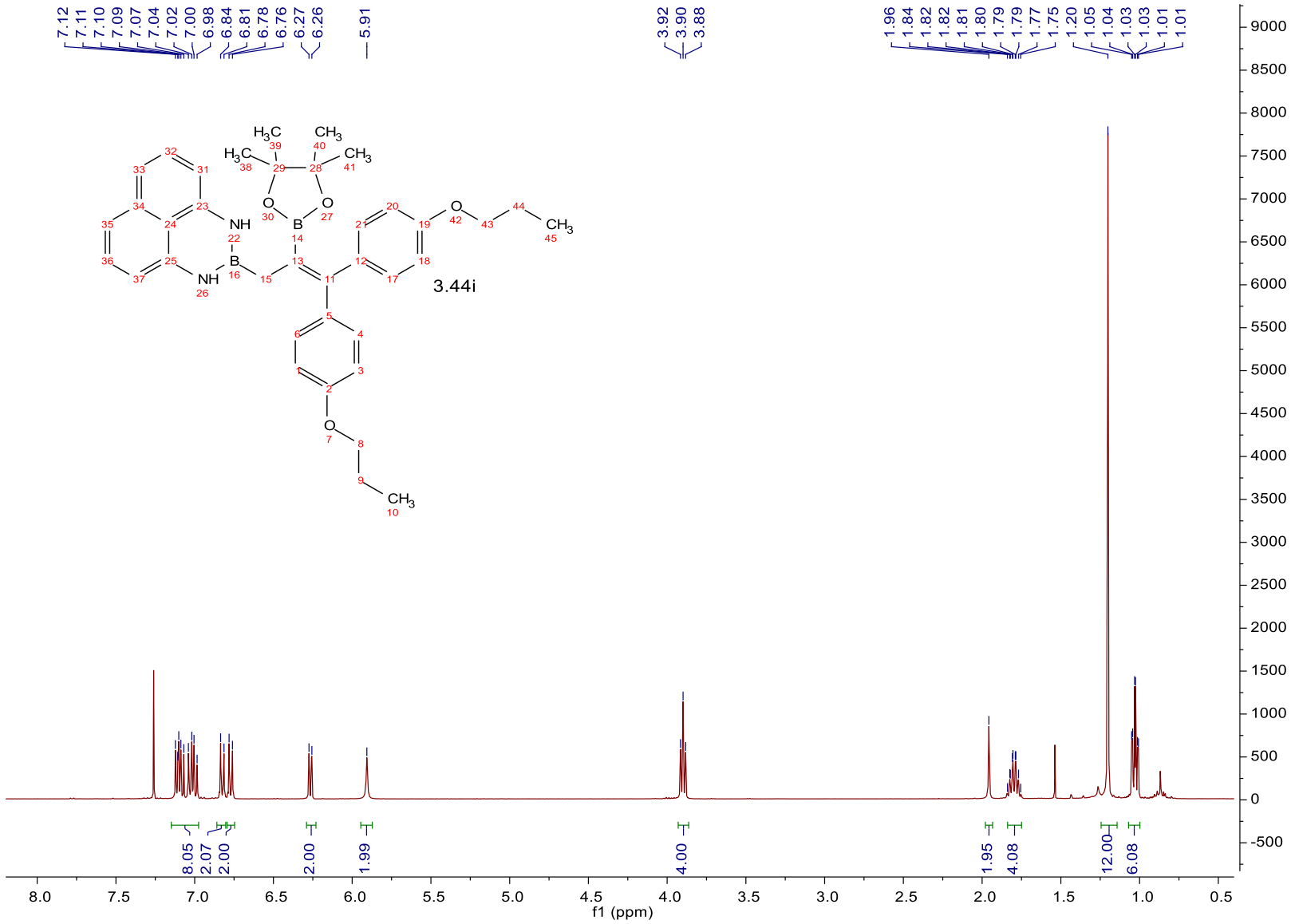

159.0
158.5
149.9
141.5
137.6
136.5
135.0
130.9
130.6
127.7
119.8
117.4
113.6
113.2
105.6
83.8
55.4
55.3
24.9
3.44g
f1 (ppm)


31.40
3.44g
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20
f1 (ppm)


7.12
7.10
7.09
7.07
7.04
7.02
7.00
6.99
6.83
6.81
6.78
6.76
6.27
6.26
5.91
4.03
4.02
4.00
3.99
1.96
1.42
1.40
1.39
1.20
3.44h
4.01
4.01
2.00
2.00
1.96
1.98
4.00
2.00
6.01
12.00
f1 (ppm)


158.3
157.9
150.0
141.6
137.5
136.5
134.8
130.9
130.6
127.7
119.8
117.3
114.0
113.8
105.6
83.8
63.6
63.5
24.9
15.0
15.0
3.44h
f1 (ppm)


31.19
3.44h
f1 (ppm)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7.11
7.10
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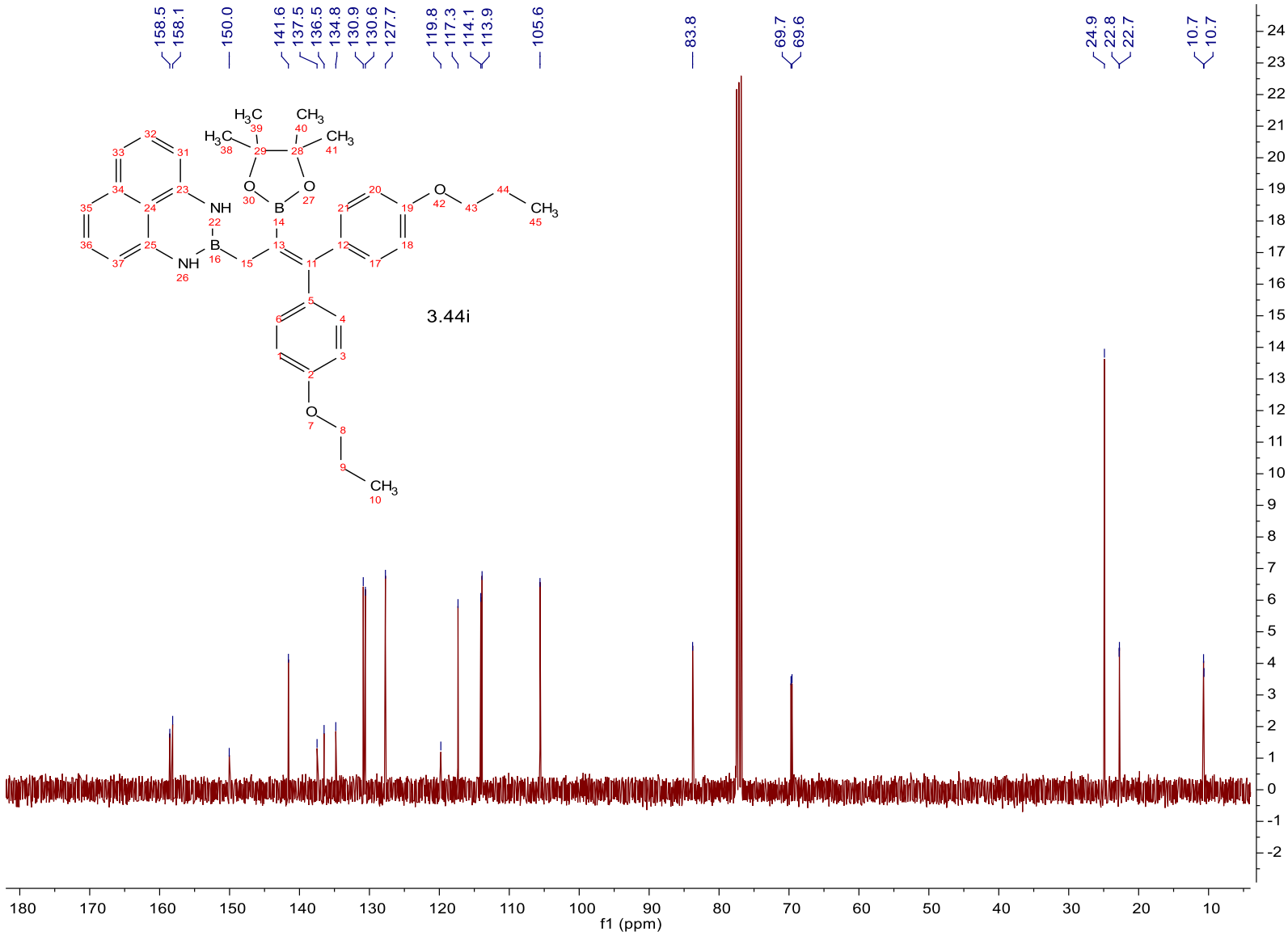
7.07
7.04
7.02
7.00
6.98
6.84
6.81
6.78
6.76
6.27
6.26
5.91
3.92
3.90
3.88
1.96
1.84
1.82
1.82
1.81
1.80
1.79
1.79
1.77
1.75
1.20
1.05
1.04
1.03
1.03
1.01
1.01
3.44i
8.05
2.07
2.00
2.00
1.99
4.00
1.95
4.08
12.00
6.08
f1 (ppm)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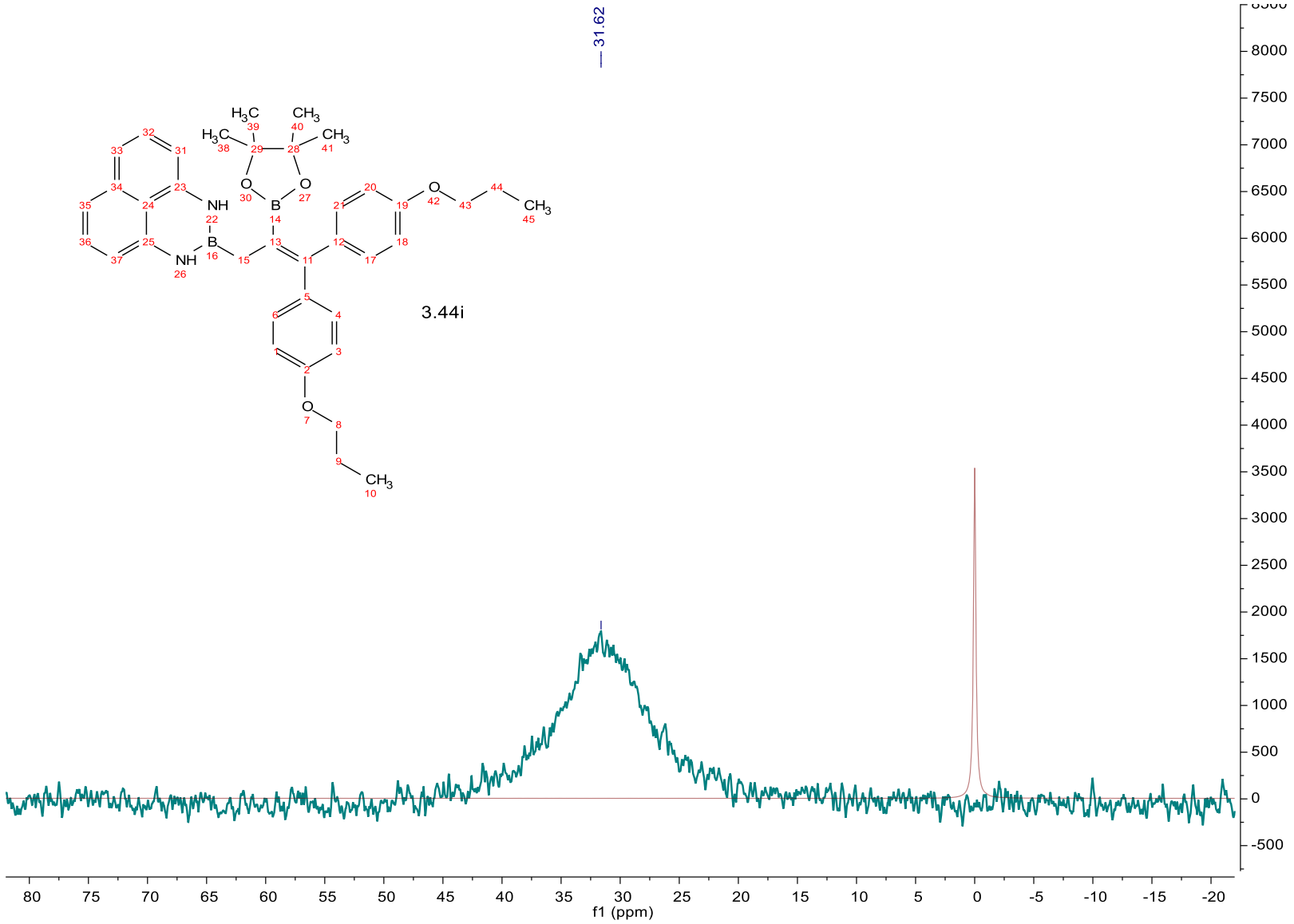
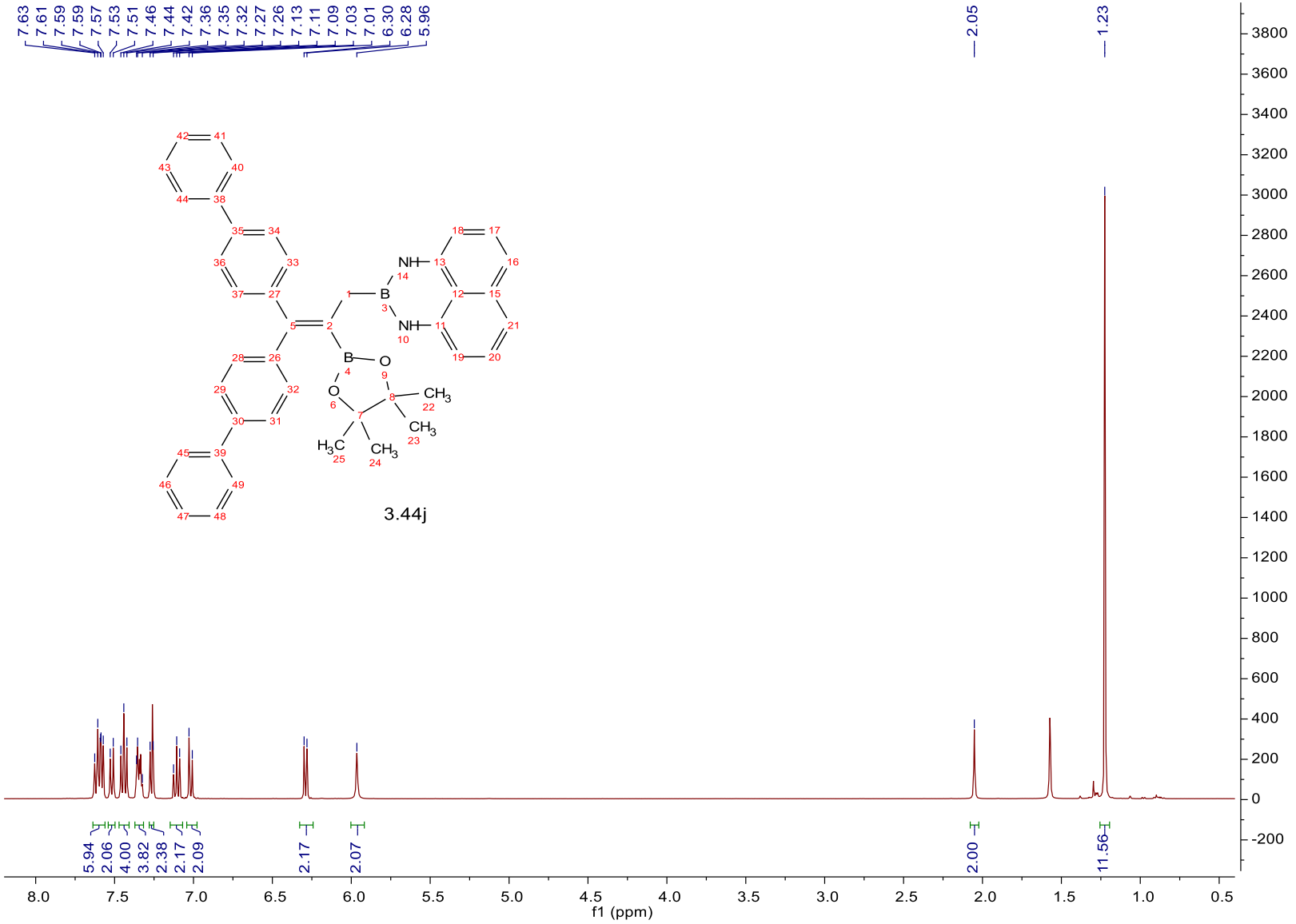
158.1
150.0
141.6
137.5
136.5
134.8
130.9
130.6
127.7
119.8
117.3
114.1
113.9
105.6
83.8
69.7
69.6
24.9
22.8
22.7
10.7
10.7
3.44i
f1 (ppm)


31.62
3.44i
f1 (ppm)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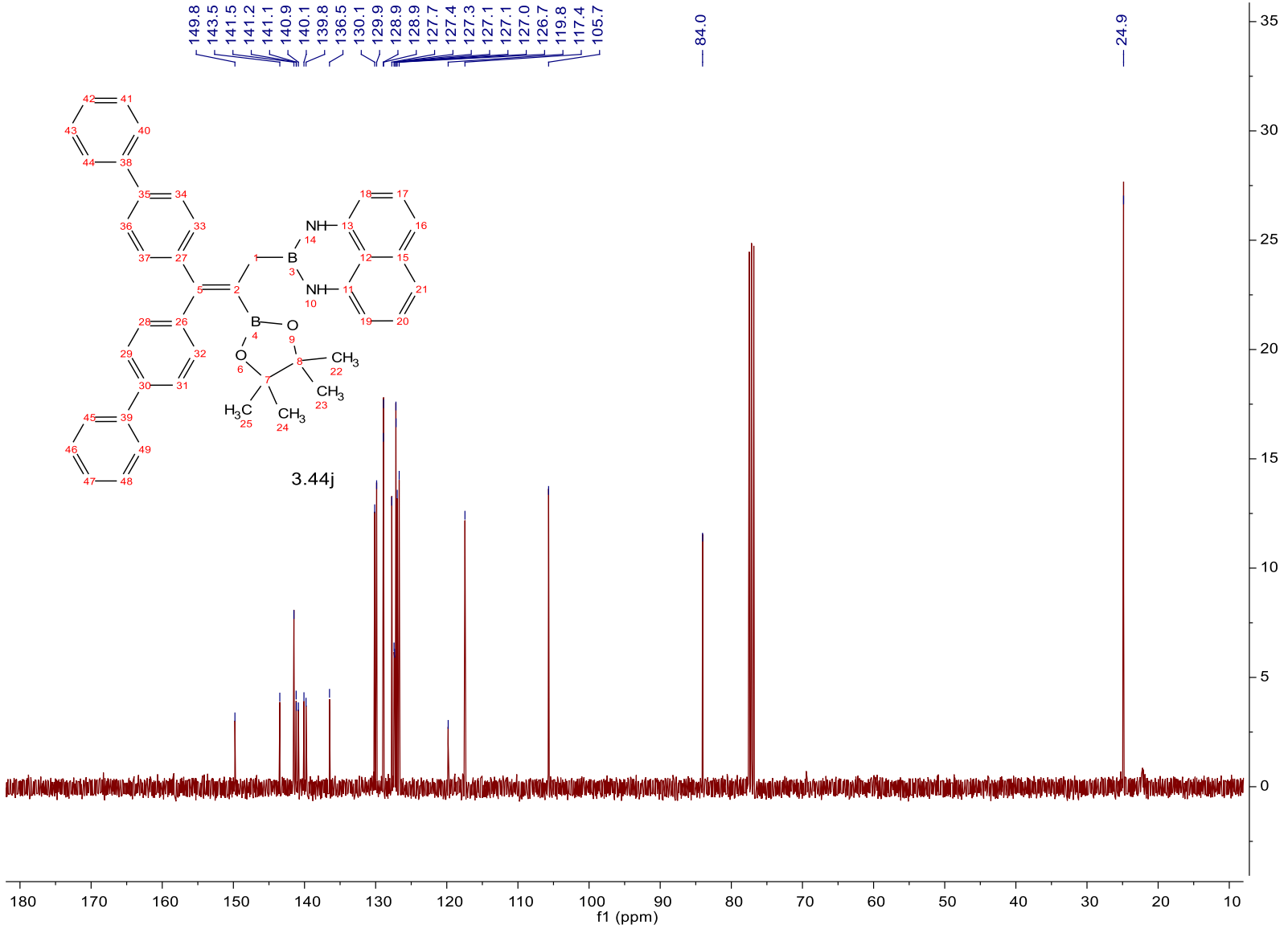
7.61
7.59
7.59
7.57
7.53
7.51
7.46
7.44
7.42
7.36
7.35
7.32
7.27
7.26
7.13
7.11
7.09
7.03
7.01
6.30
6.28
5.96
2.05
1.23
3.44j
5.94
2.06
4.00
3.82
2.38
2.17
2.09
2.17
2.07
2.00
11.56
f1 (ppm)


149.8
143.5
141.5
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141.1
140.9
140.1
139.8
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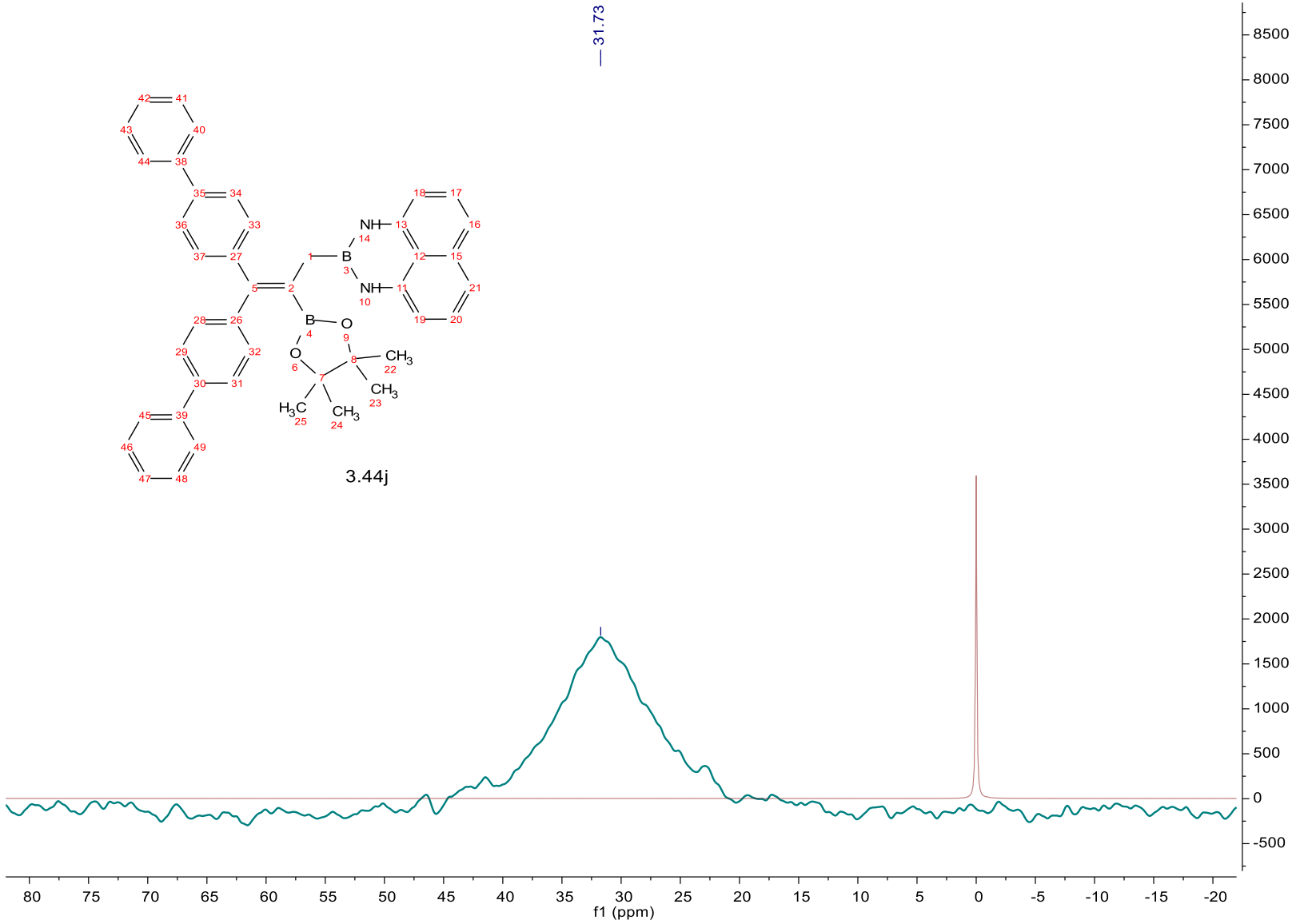
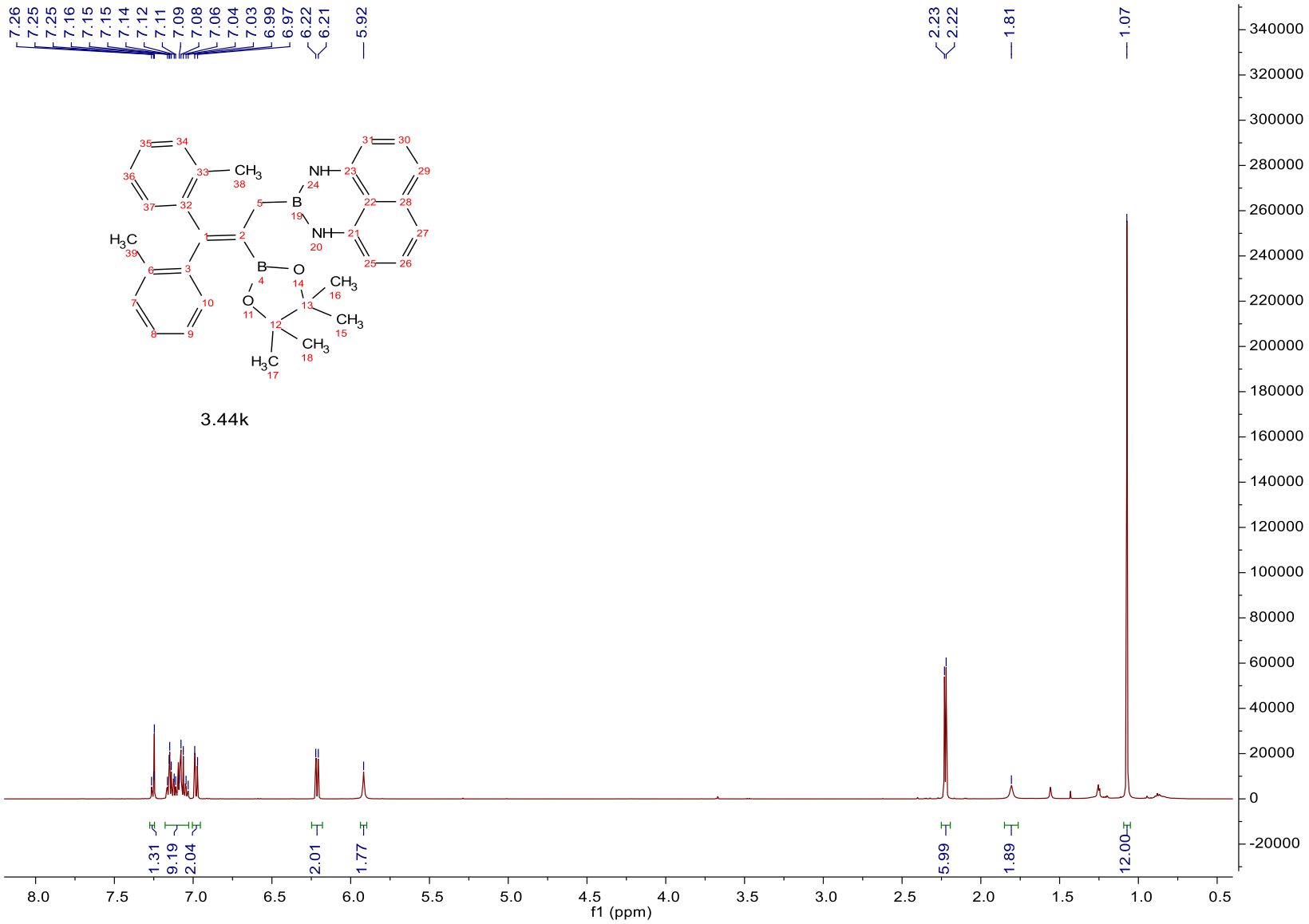
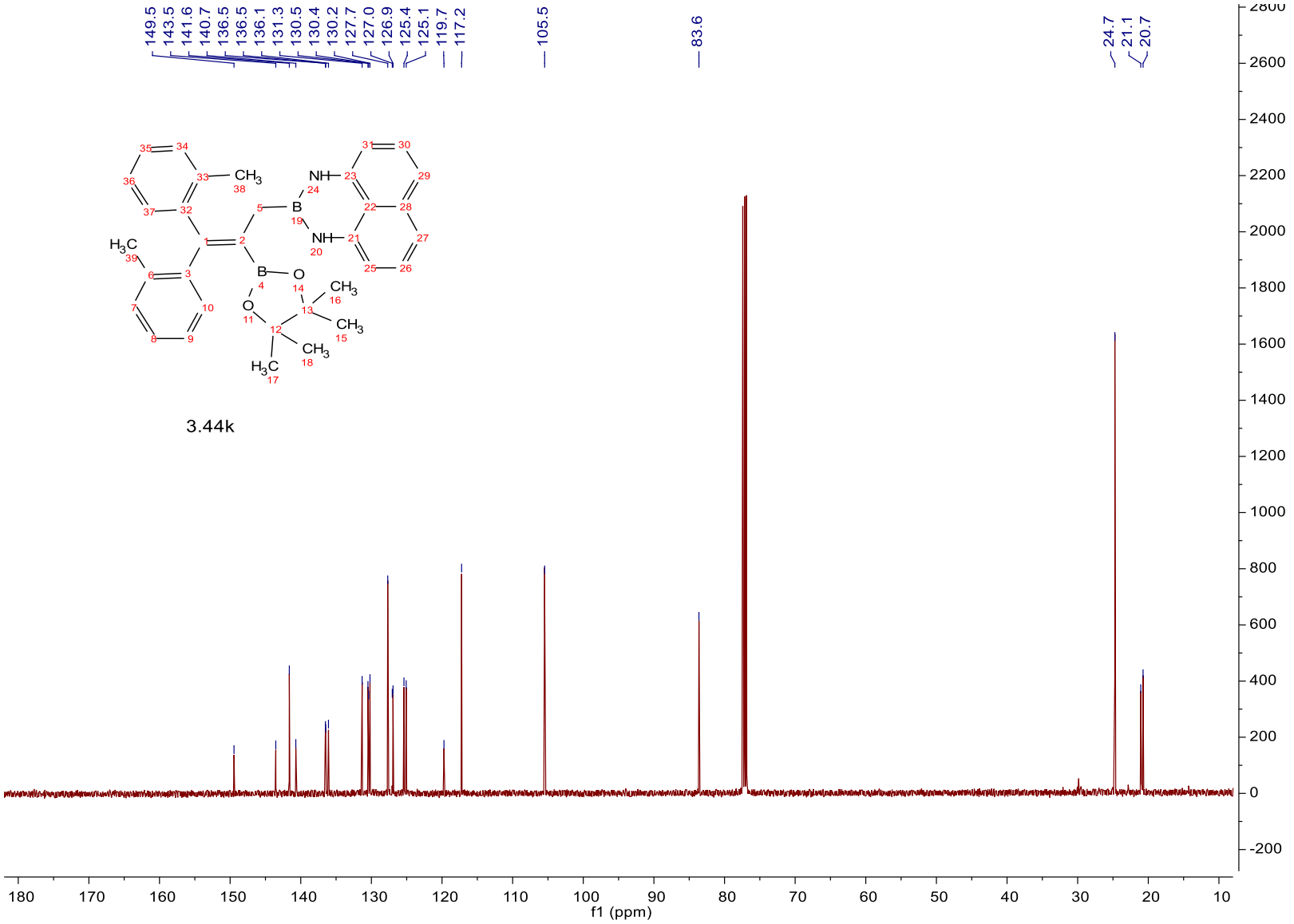
130.1
129.9
128.9
128.9
127.7
127.4
127.3
127.1
127.1
127.0
126.7
119.8
117.4
105.7
84.0
24.9
3.44j
f1 (ppm)


31.73
3.44j
f1 (ppm)


7.26
7.25
7.25
7.16
7.15
7.15
7.14
7.12
7.11
7.09
7.08
7.06
7.04
7.03
6.99
6.97
6.22
6.21
5.92
2.23
2.22
1.81
1.07
3.44k
f1 (ppm)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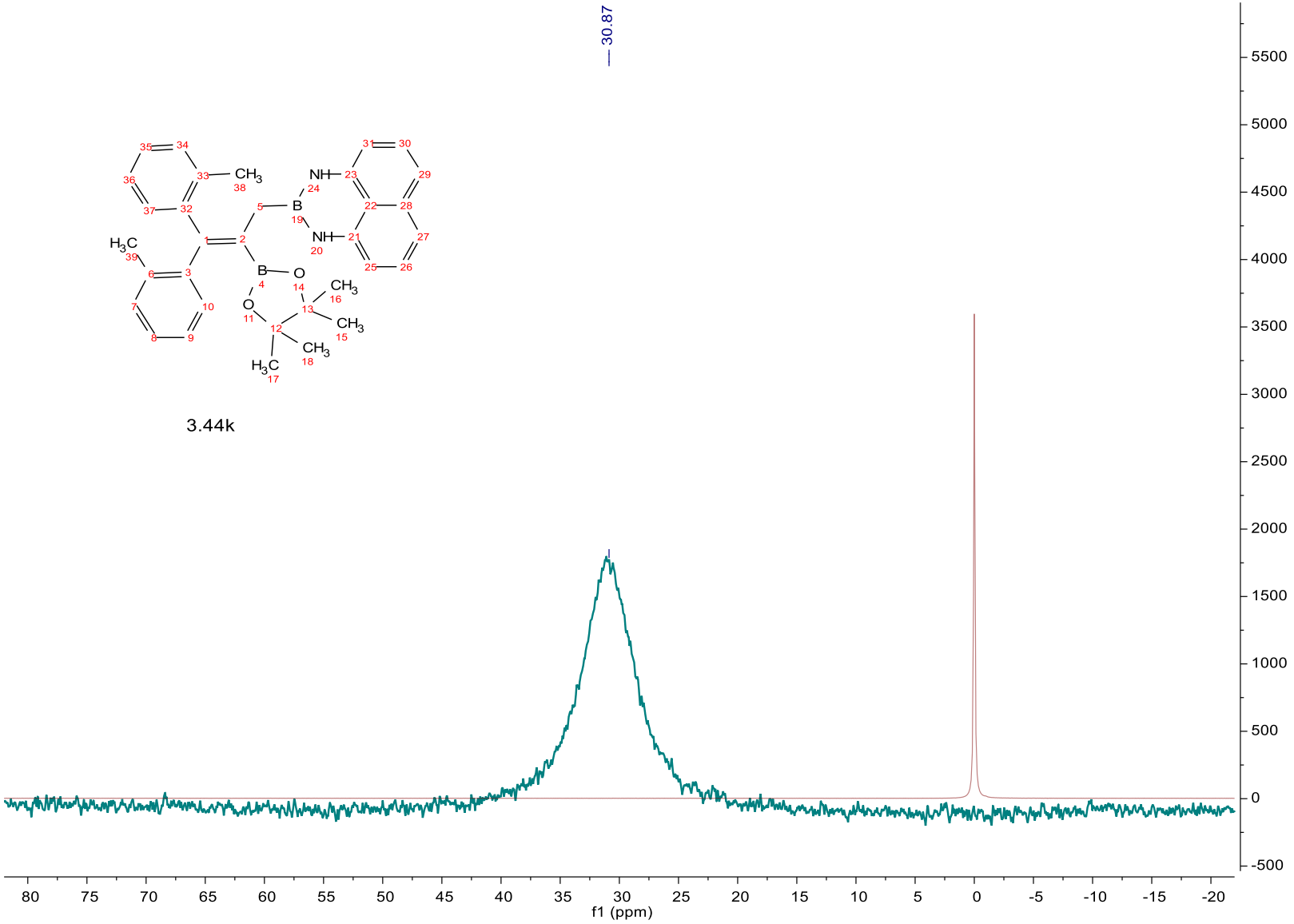
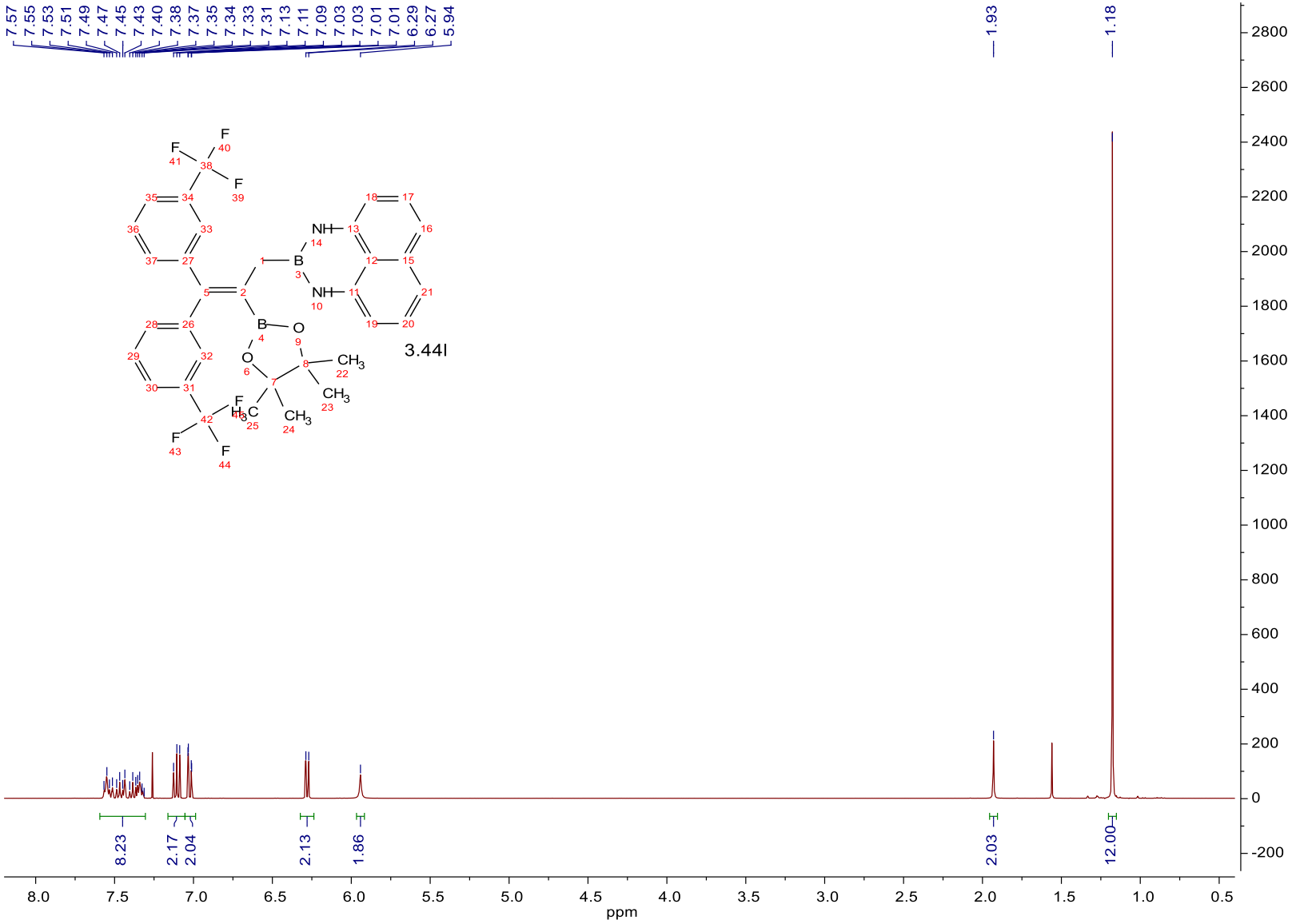
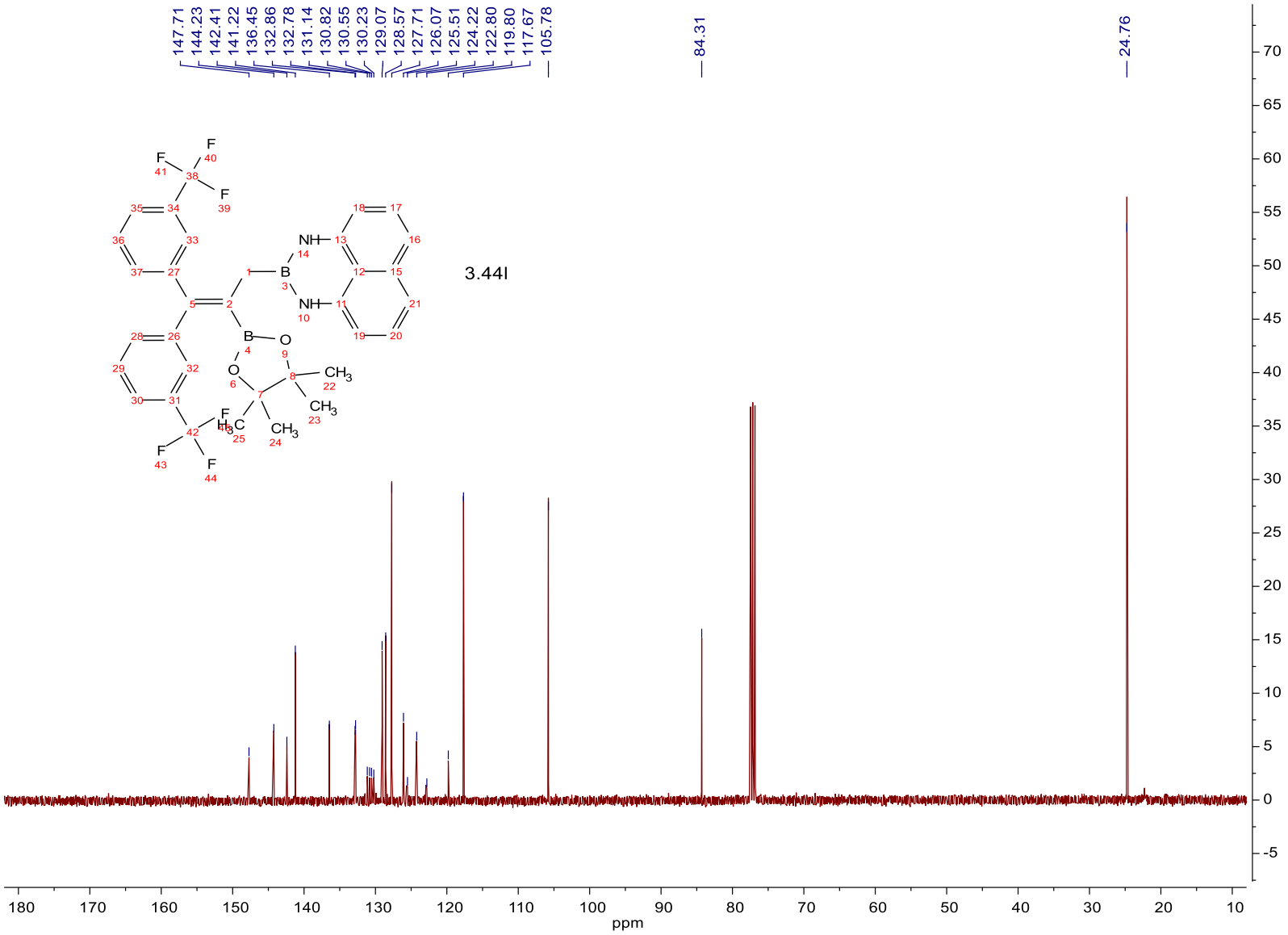
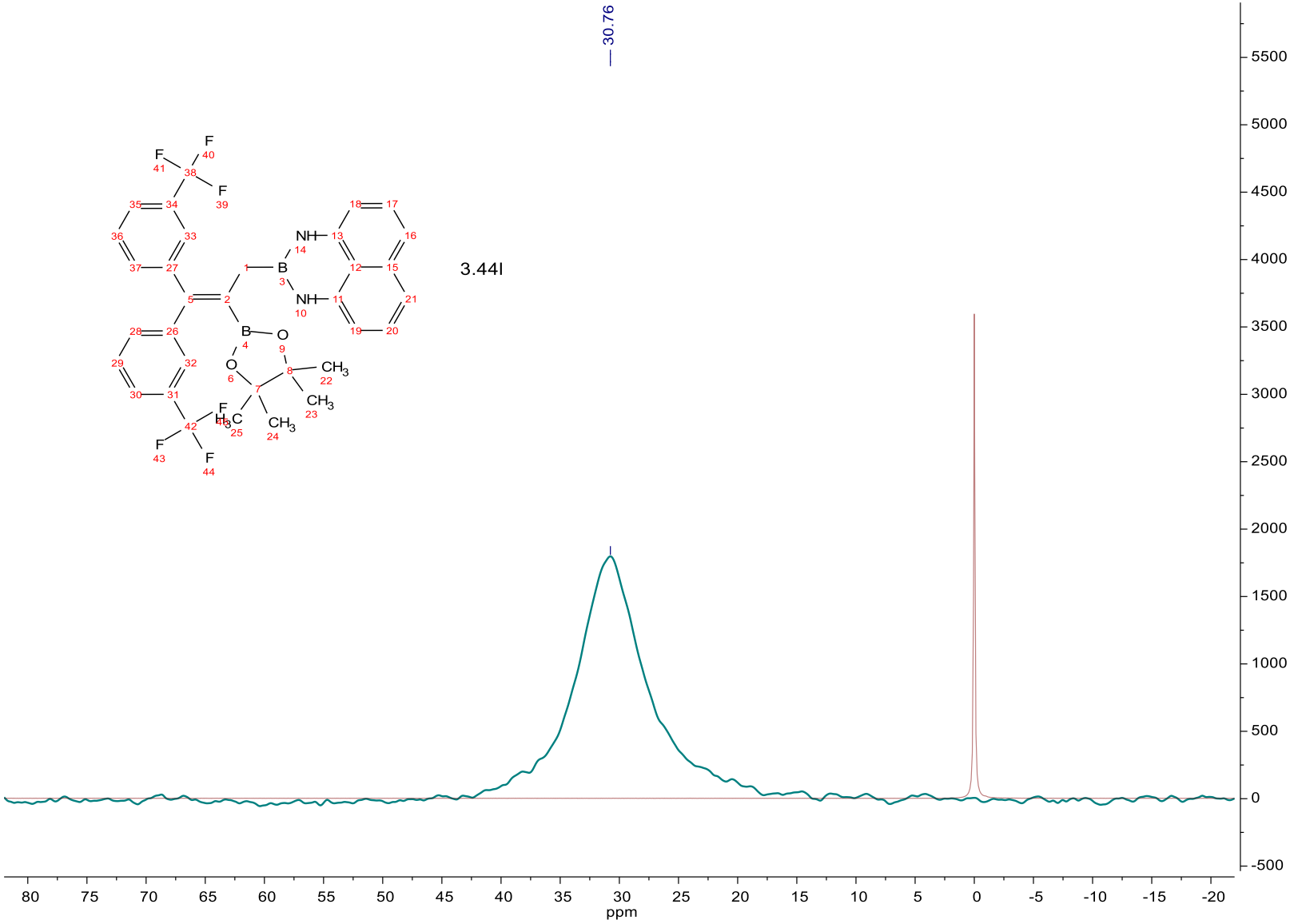
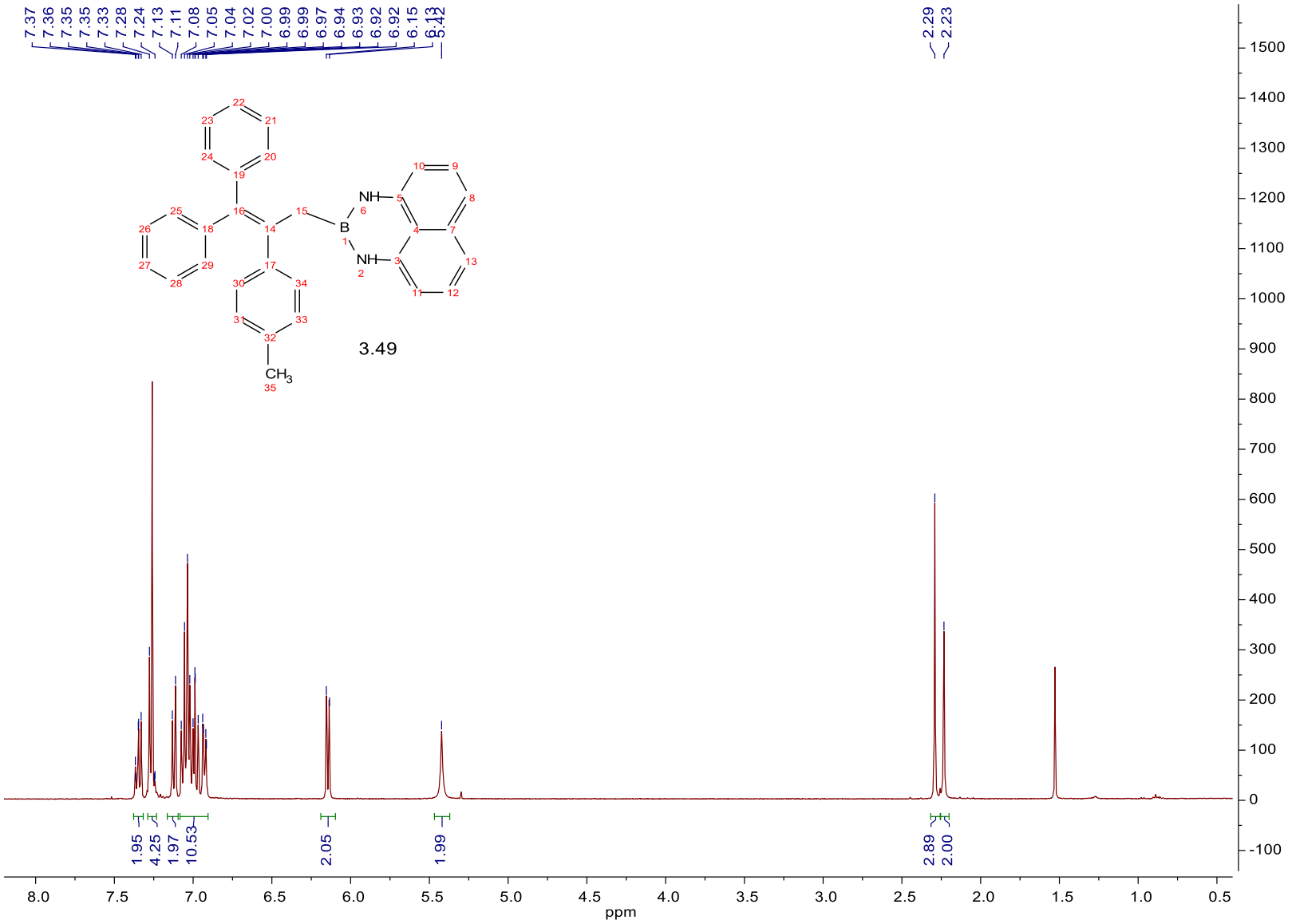
143.5
141.6
140.7
136.5
136.5
136.1
131.3
130.5
130.4
130.2
127.7
127.0
126.9
125.4
125.1
119.7
117.2
105.5
83.6
24.7
21.1
20.7
3.44k
f1 (ppm)

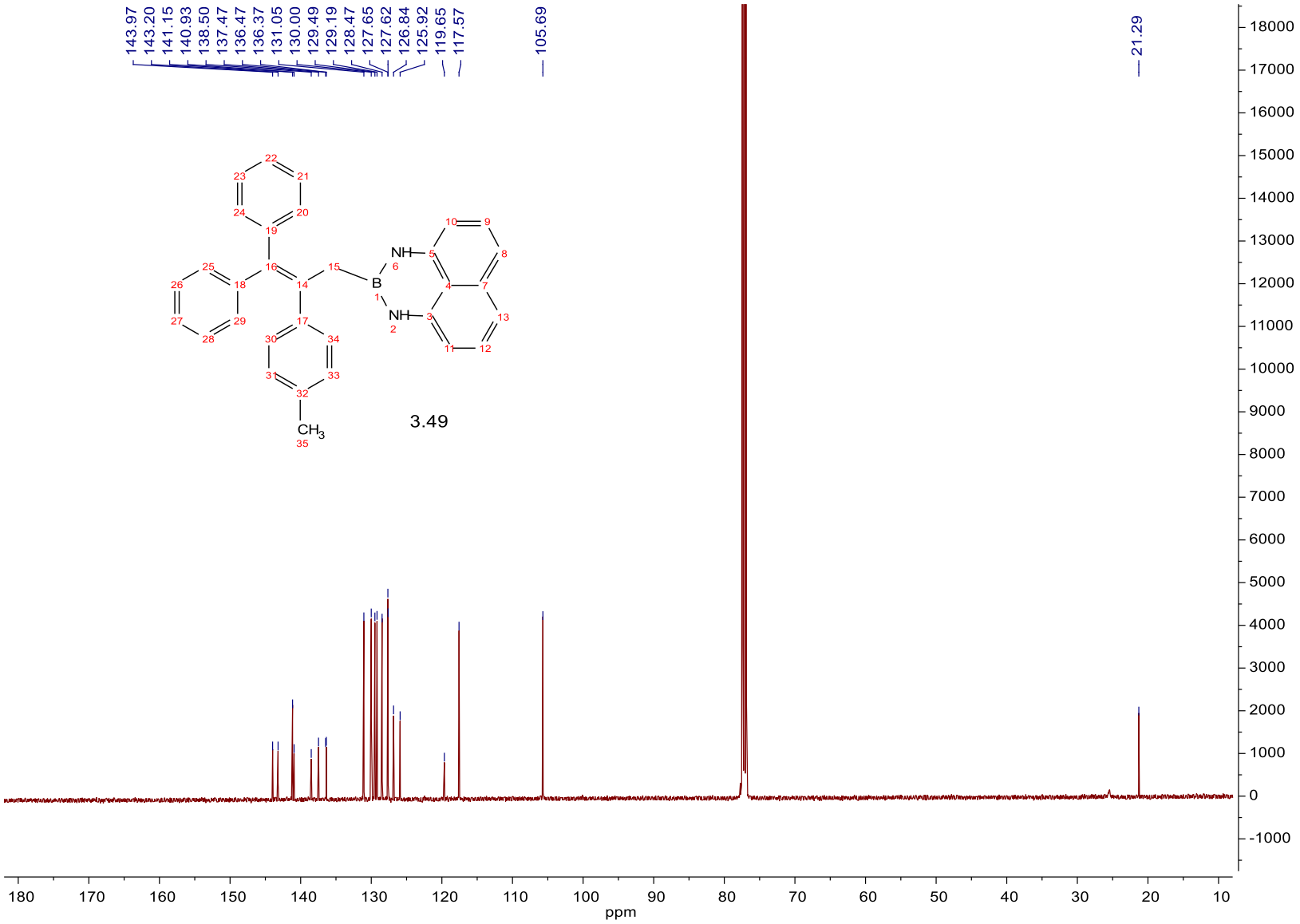

30.87
3.44k
f1 (ppm)


7.57
7.55
7.53
7.51
7.49
7.47
7.45
7.43
7.40
7.38
7.37
7.35
7.34
7.33
7.31
7.13
7.11
7.09
7.03
7.03
7.01
7.01
6.29
6.27
5.94
1.93
1.18
3.44l
8.23
2.17
2.04
2.13
1.86
2.03
12.00
ppm


147.71
144.23
142.41
141.22
136.45
132.86
132.78
131.14
130.82
130.55
130.23
129.07
128.57
127.71
126.07
125.51
124.22
122.80
119.80
117.67
105.78
84.31
24.76
3.44l
ppm


30.76
3.44l
ppm


7.37
7.36
7.35
7.35
7.33
7.28
7.24
7.13
7.11
7.08
7.05
7.04
7.02
7.00
6.99
6.99
6.97
6.94
6.93
6.92
6.92
6.15
6.13
5.42
2.29
2.23
NH
NH
B
CH3
3.49
1.95
4.25
1.97
10.53
2.05
1.99
2.89
2.00
ppm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137.47
136.47
136.37
131.05
130.00
129.49
129.19
128.47
127.65
127.62
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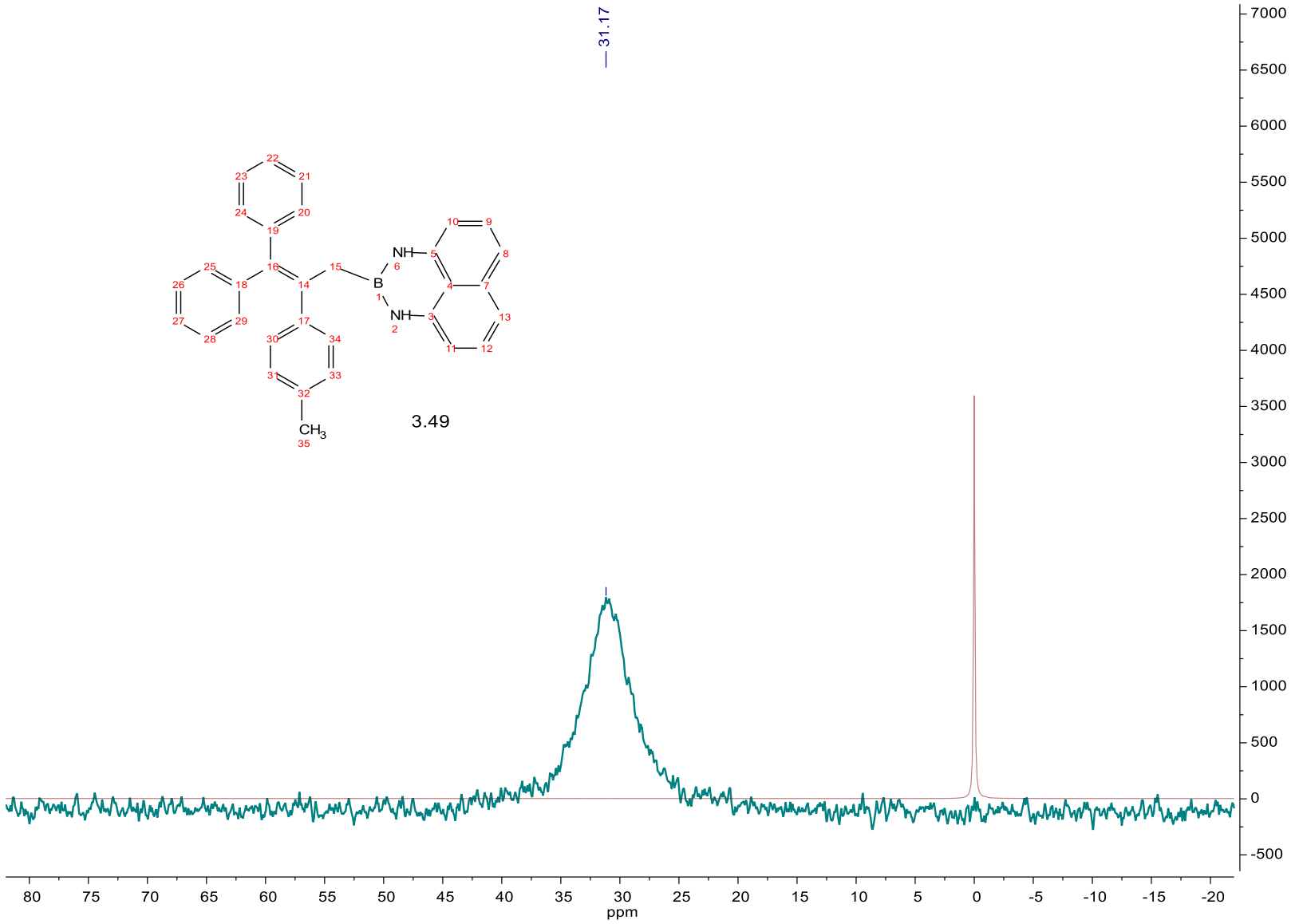
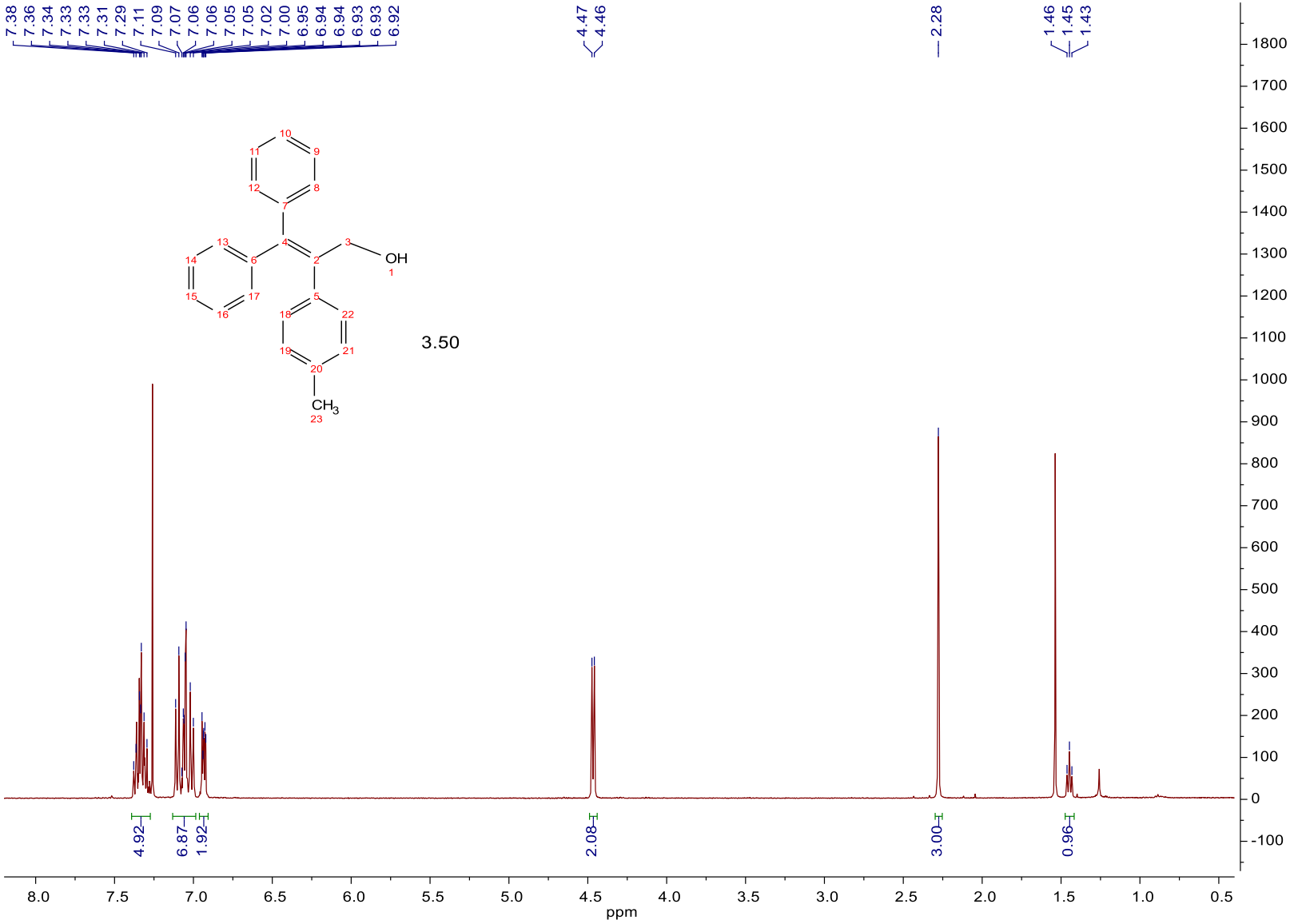
125.92
119.65
117.57
105.69
21.29
NH
B
NH
CH3
3.49
ppm


31.17
3.49
NH
B
NH
CH3
ppm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7.36
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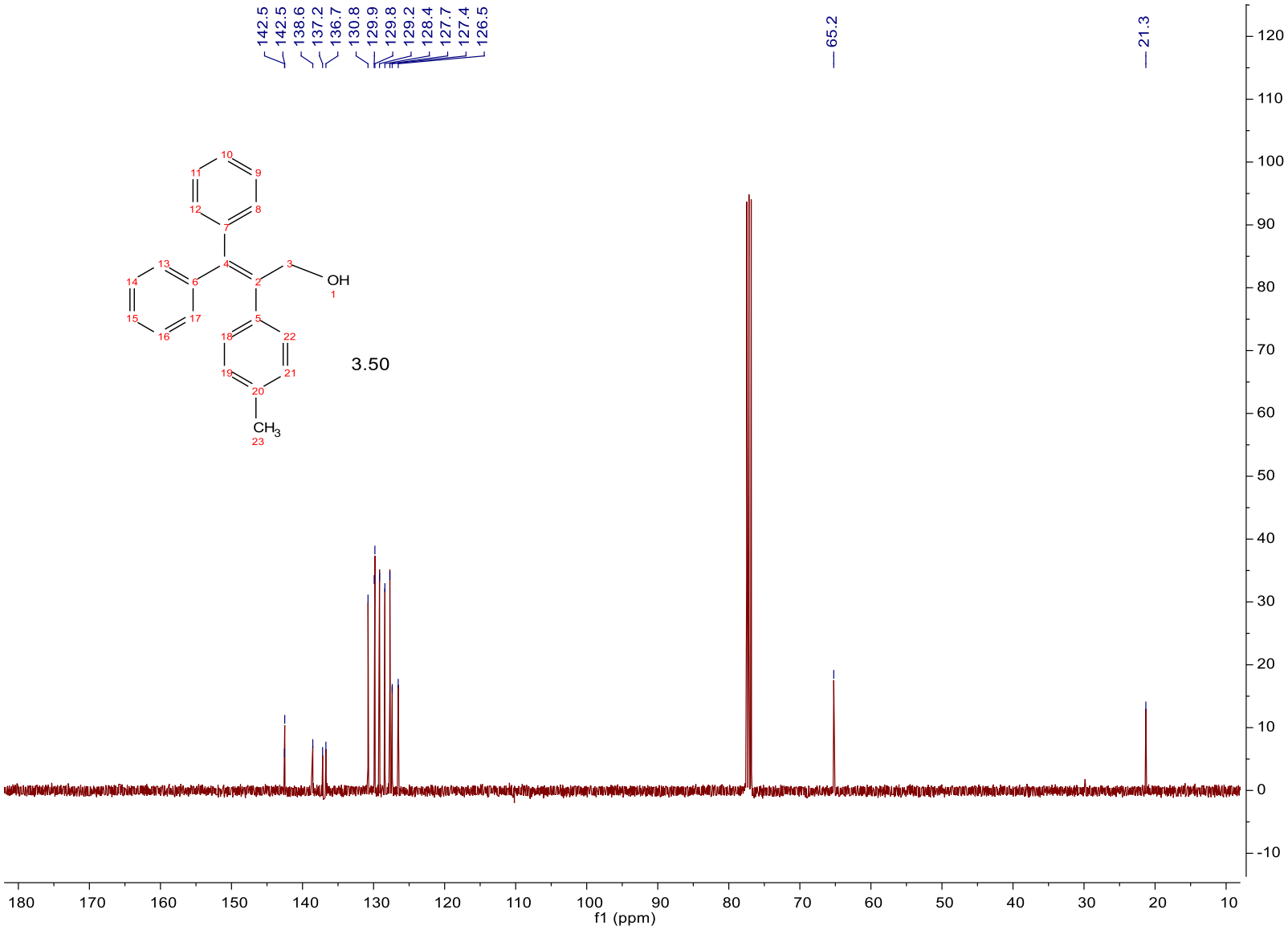
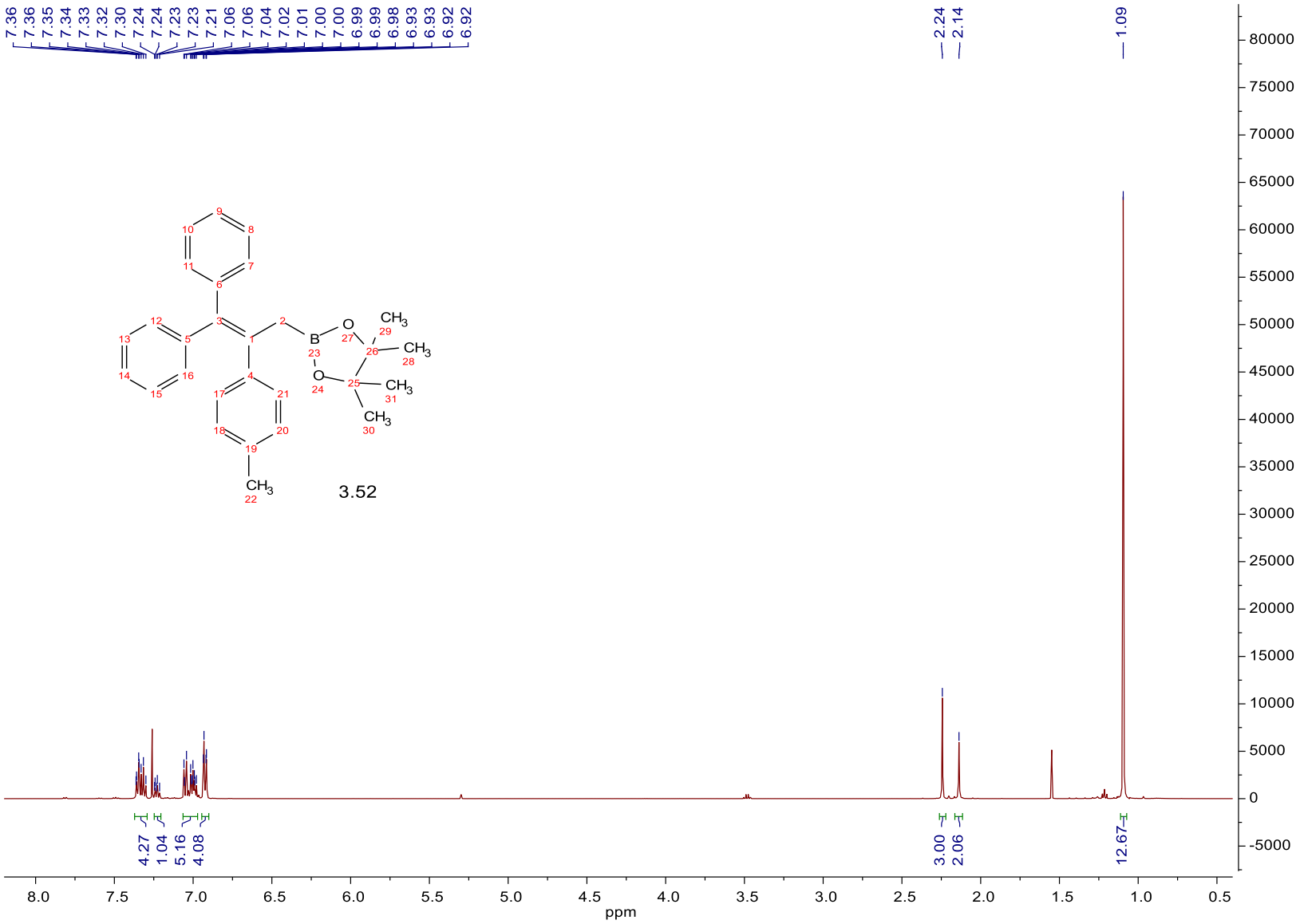
7.33
7.31
7.29
7.11
7.09
7.07
7.06
7.06
7.05
7.05
7.02
7.00
6.95
6.94
6.94
6.93
6.93
6.92
4.47
4.46
2.28
1.46
1.45
1.43
OH
3.50
4.92
6.87
1.92
2.08
3.00
0.96
ppm


142.5
142.5
138.6
137.2
136.7
130.8
129.9
129.8
129.2
128.4
127.7
127.4
126.5
65.2
21.3
OH
3.50
CH3
f1 (ppm)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7.36
7.35
7.34
7.33
7.32
7.30
7.24
7.24
7.23
7.23
7.21
7.06
7.06
7.04
7.02
7.01
7.00
7.00
6.99
6.99
6.98
6.93
6.93
6.92
6.92
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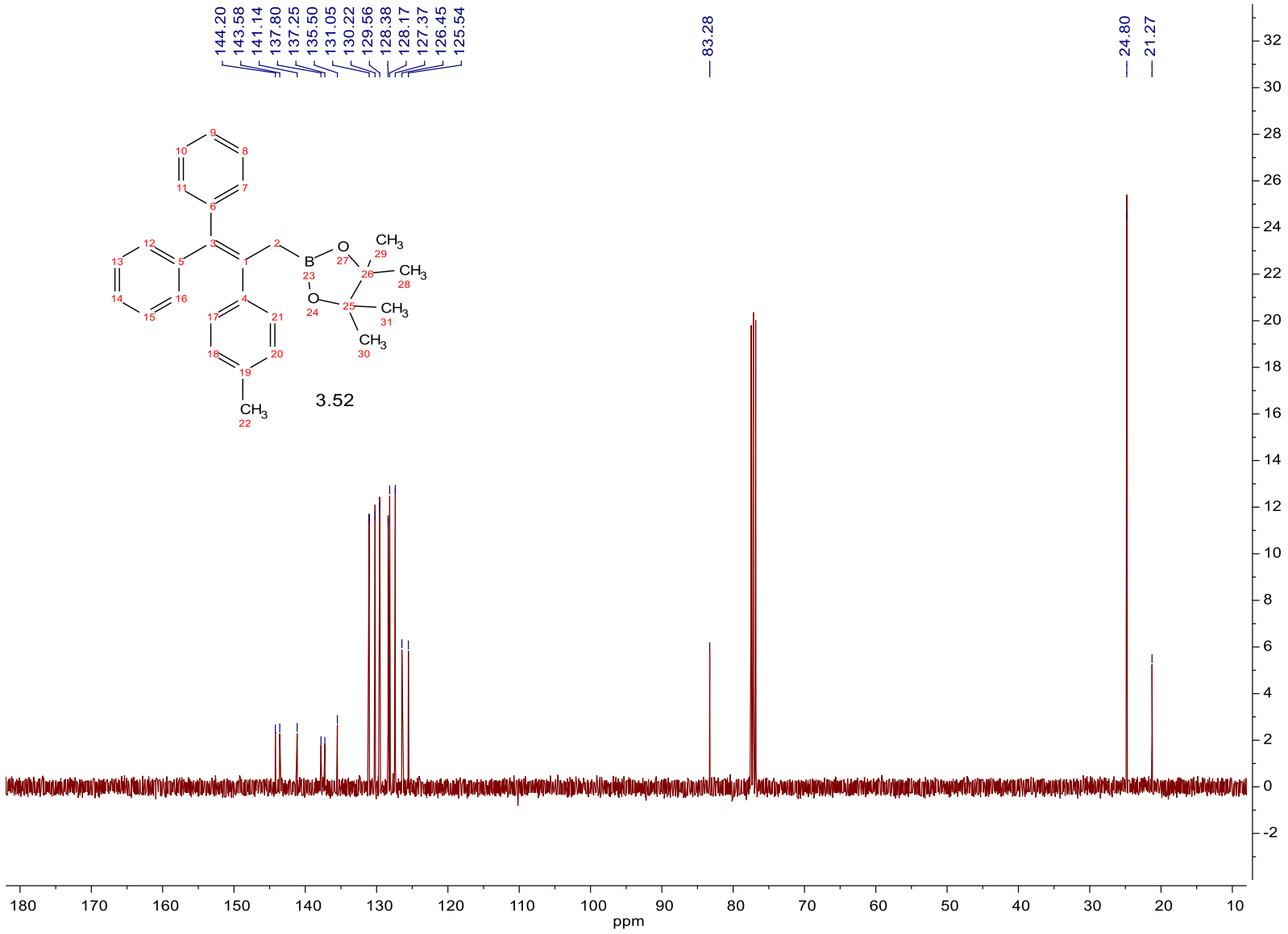
1.09
3.52
4.27
1.04
5.16
4.08
3.00
2.06
12.67
ppm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143.58
141.14
137.80
137.25
135.50
131.05
130.22
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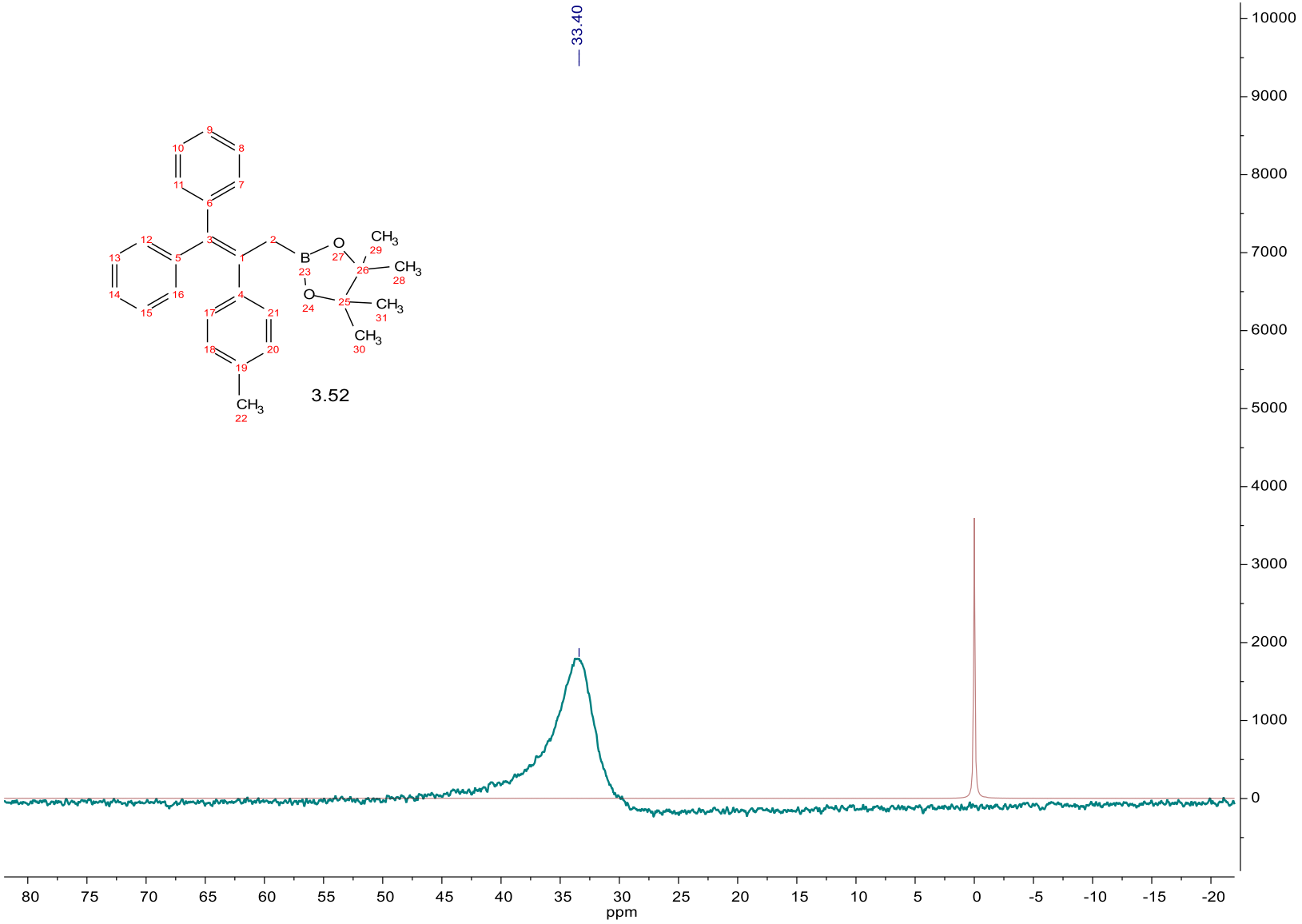
128.38
128.17
127.37
126.45
125.54
83.28
24.80
21.27
3.52
ppm


33.40
3.52
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
80
75
70
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60
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45
40
35
30
25
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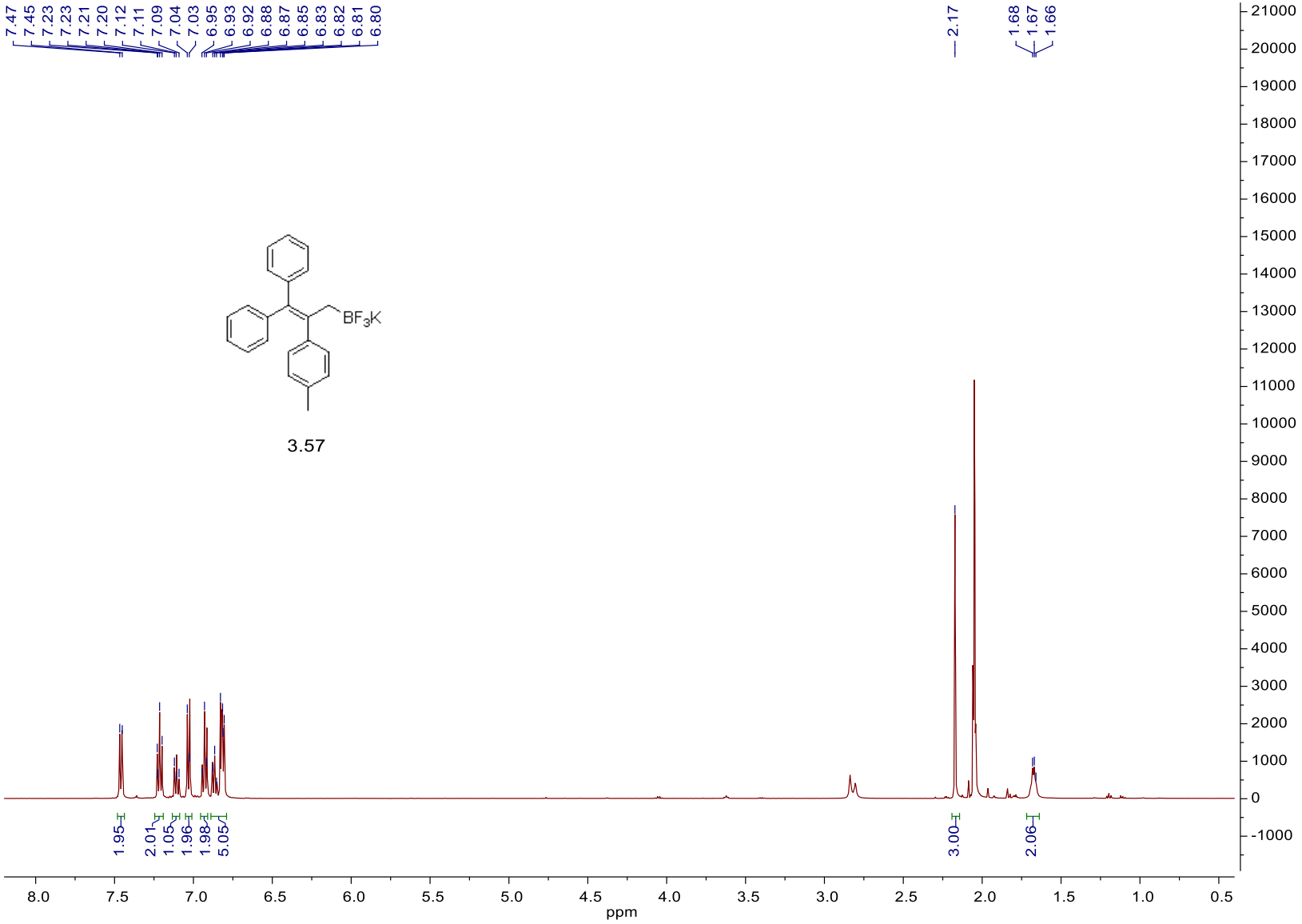
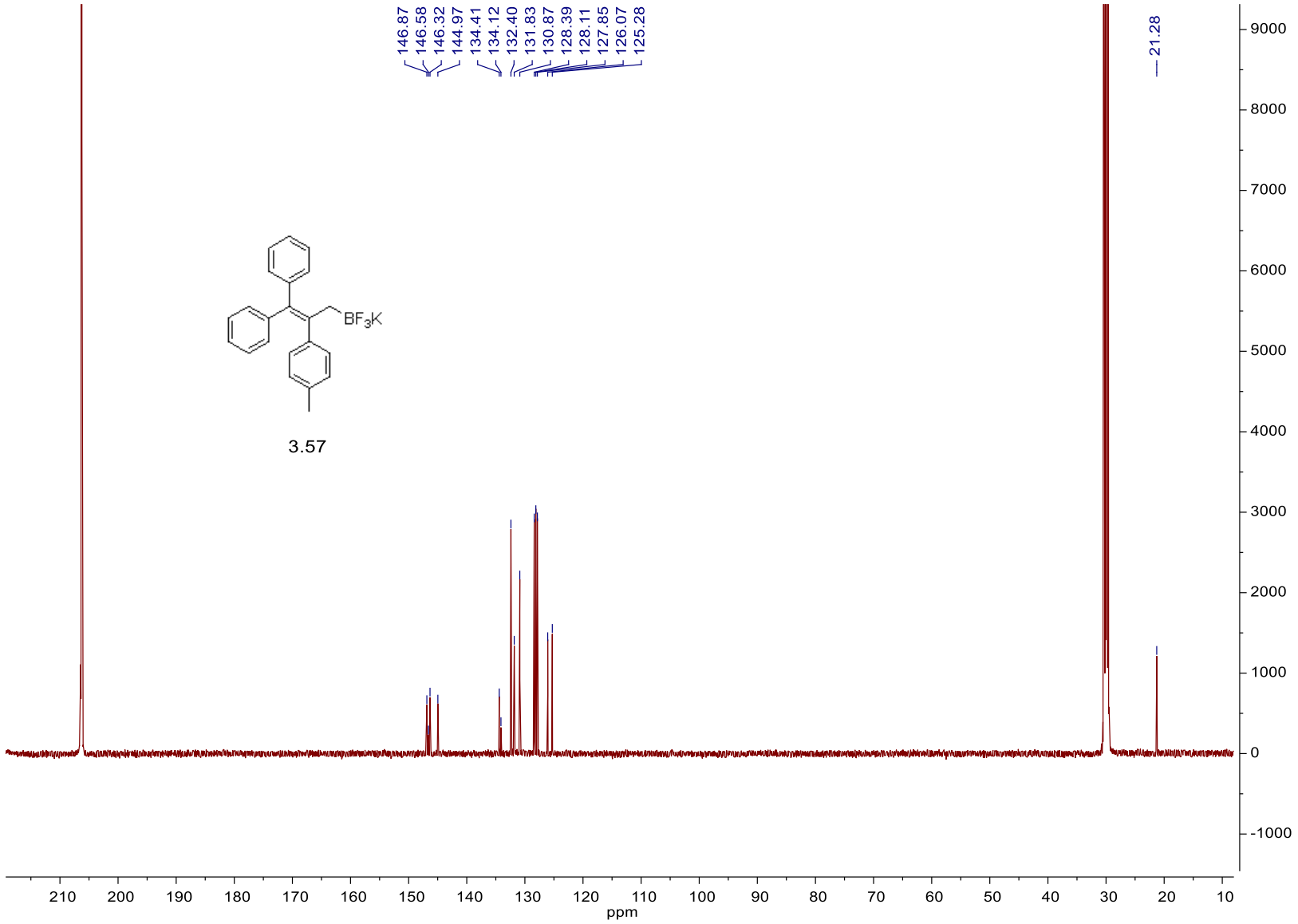
5
0
-5
-10
-15
-20
ppm


7.47
7.45
7.23
7.23
7.21
7.20
7.12
7.11
7.09
7.04
7.03
6.95
6.93
6.92
6.88
6.87
6.85
6.83
6.82
6.81
6.80
2.17
1.68
1.67
1.66
BF3K
3.57
1.95
2.01
1.05
1.96
1.98
5.05
3.00
2.06
ppm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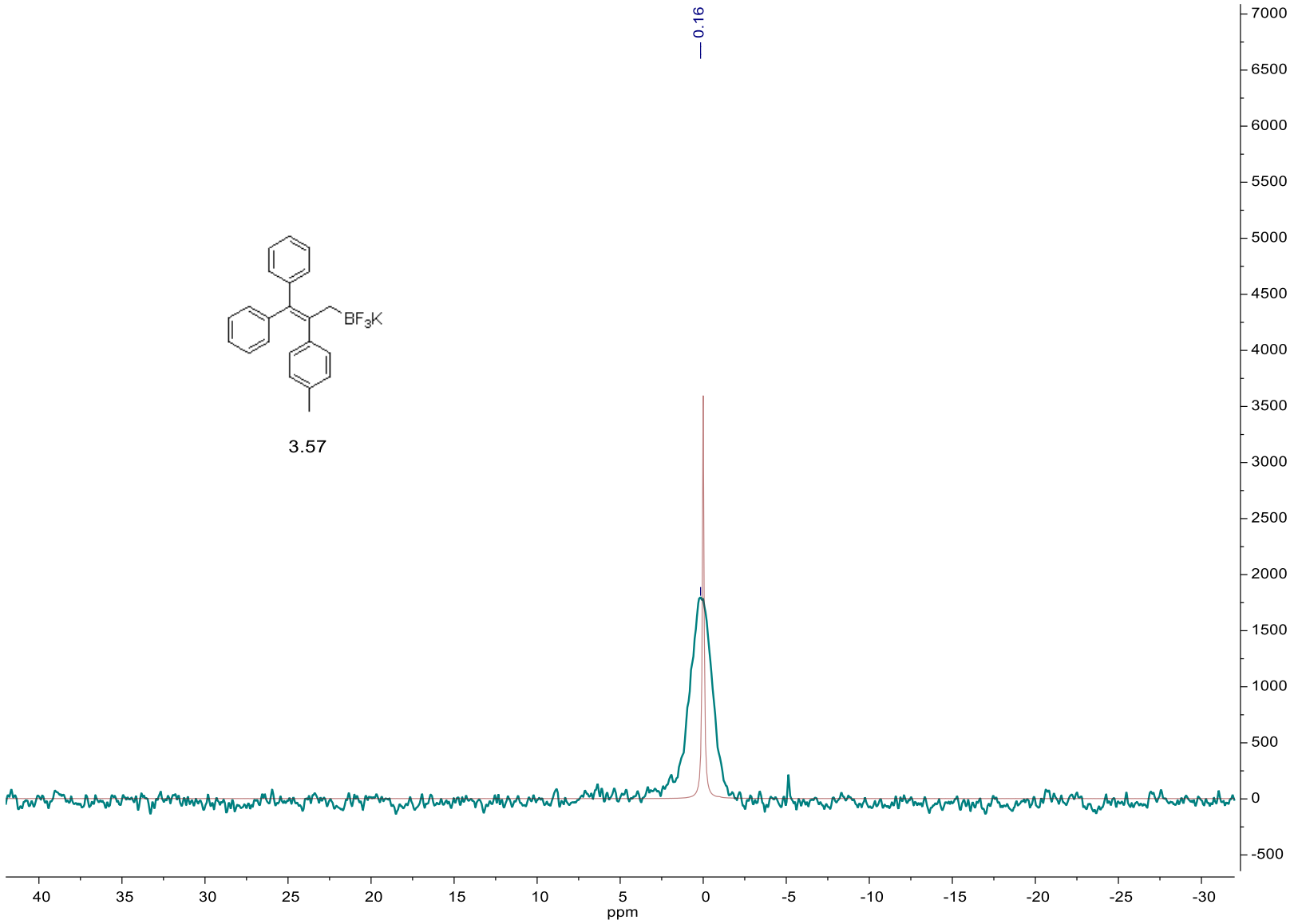
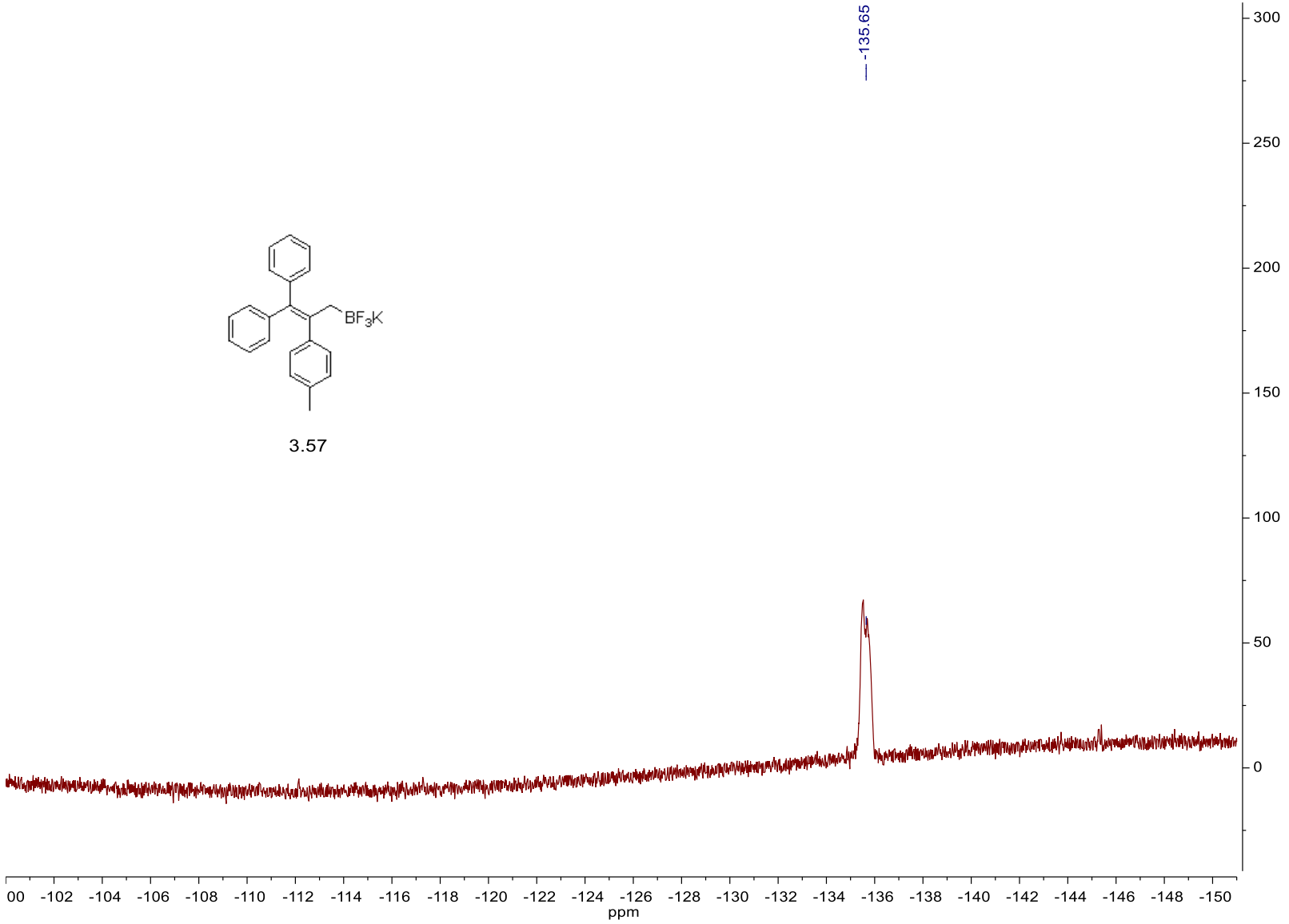
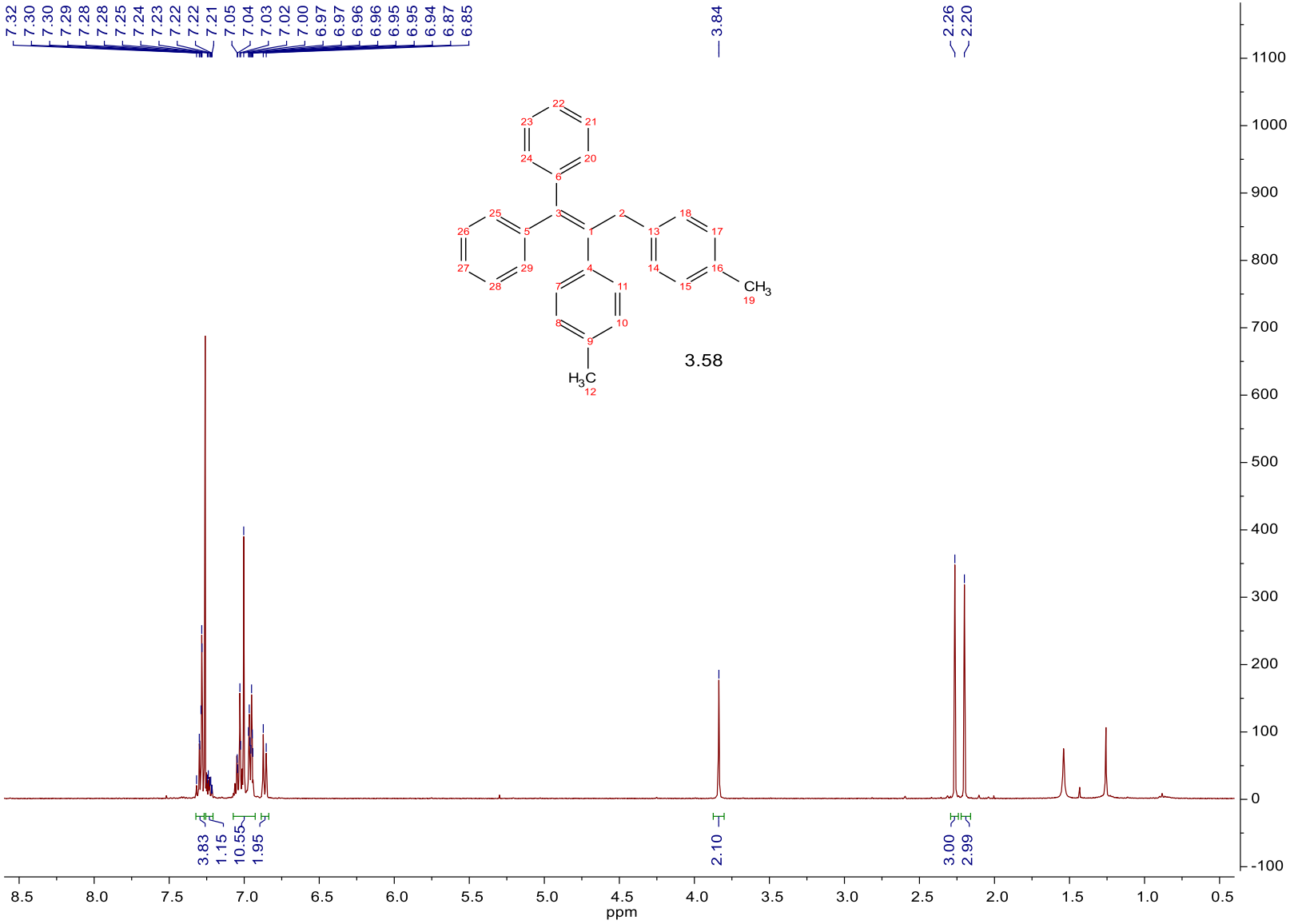
144.97
134.41
134.12
132.40
131.83
130.87
128.39
128.11
127.85
126.07
125.28
21.28
BF3K
3.57
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


0.16
BF3K
3.57
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
ppm


-135.65
300
250
200
150
100
50
0
BF3K
00 -102 -104 -106 -108 -110 -112 -114 -116 -118 -120 -122 -124 -126 -128 -130 -132 -134 -136 -138 -140 -142 -144 -146 -148 -150
ppm

3.57


7.32
7.30
7.30
7.29
7.28
7.28
7.25
7.24
7.23
7.22
7.22
7.21
7.05
7.04
7.03
7.02
7.00
6.97
6.97
6.96
6.96
6.95
6.95
6.94
6.87
6.85
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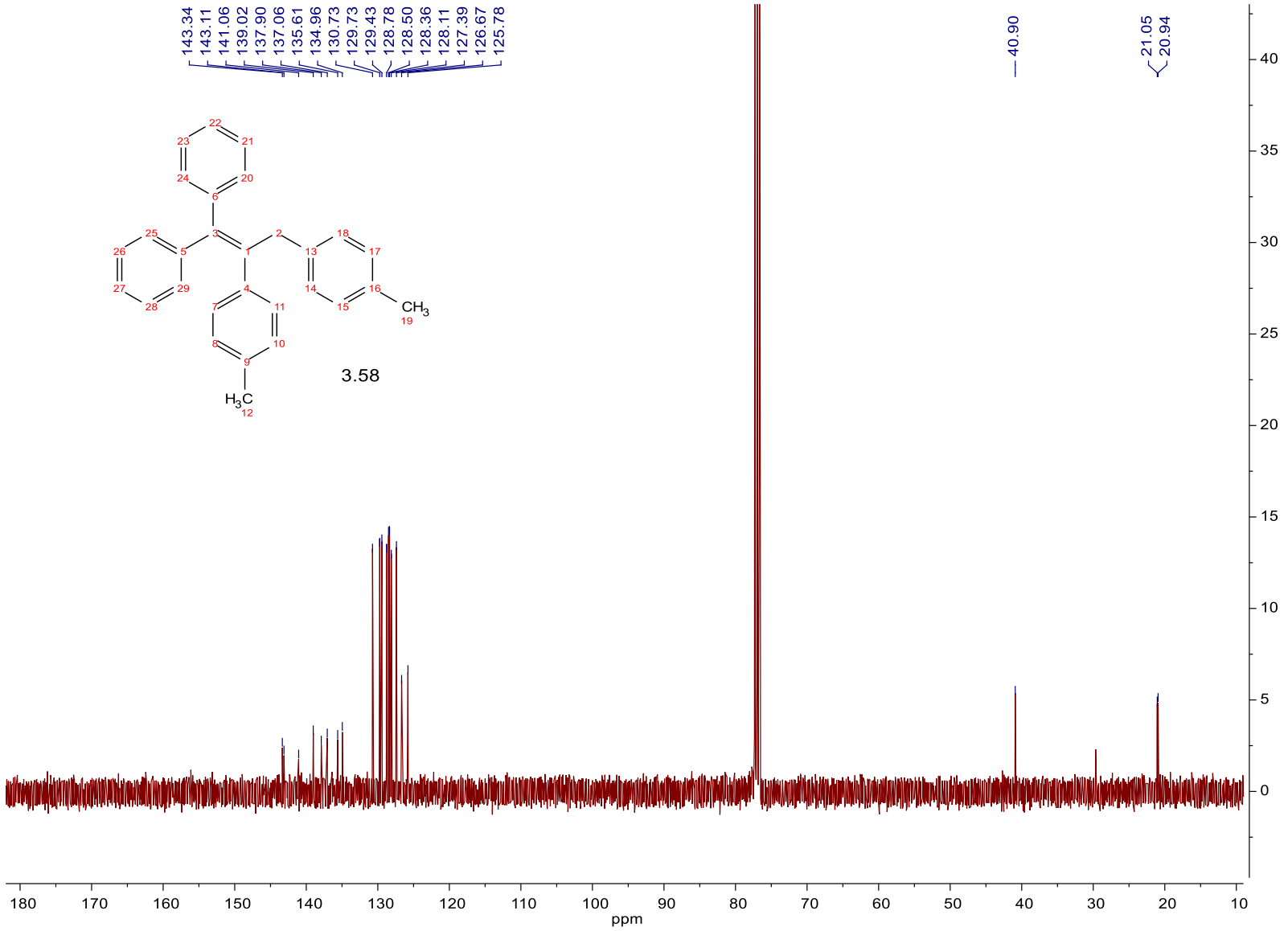
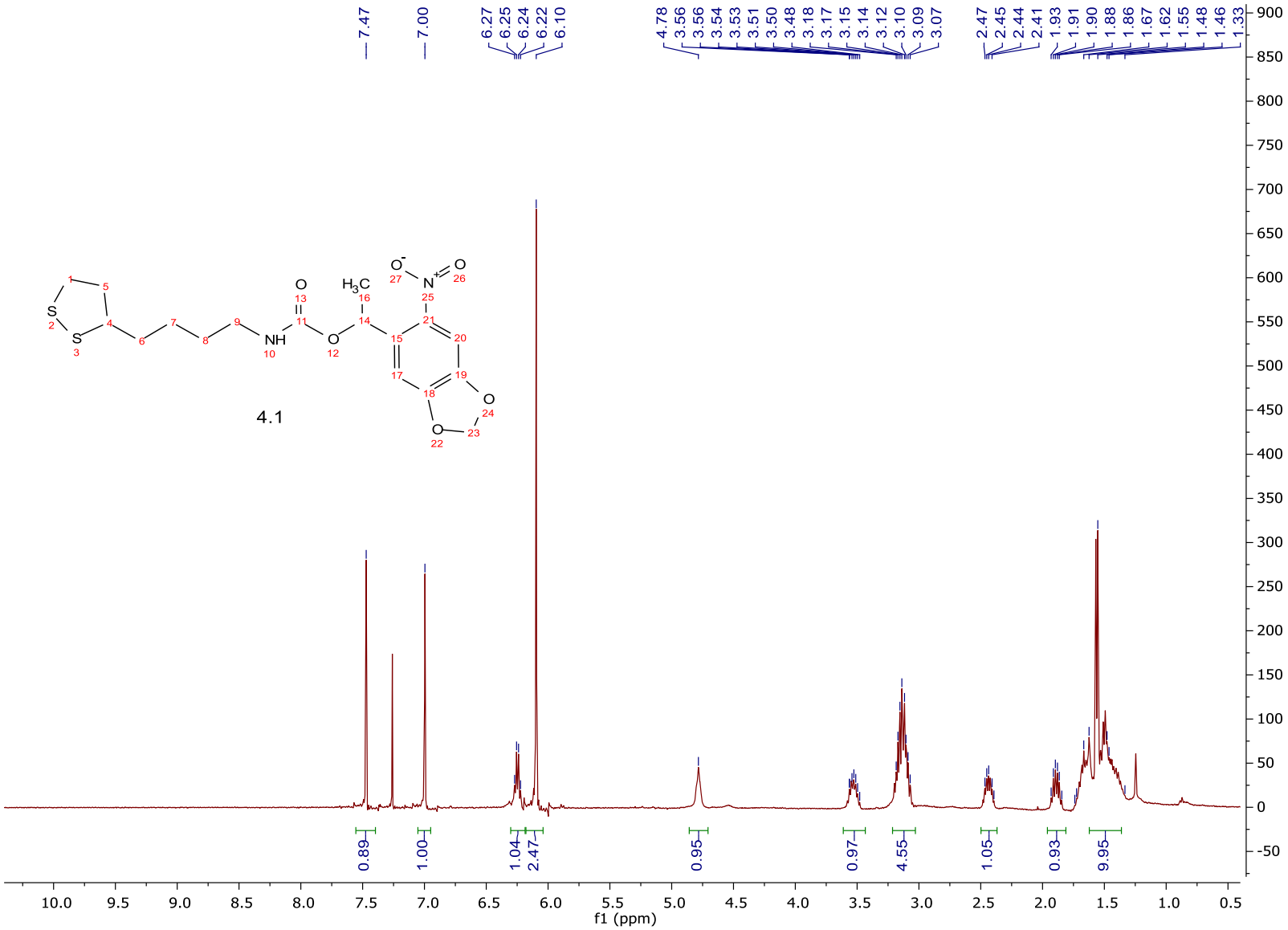
2.20
3.58
3.83
1.15
10.55
1.95
2.10
3.00
2.99
ppm


143.34
143.11
141.06
139.02
137.90
137.06
135.61
134.96
130.73
129.73
129.43
128.78
128.50
128.36
128.11
127.39
126.67
125.78
40.90
21.05
20.94
3.58
CH3
H3C
ppm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6.25
6.24
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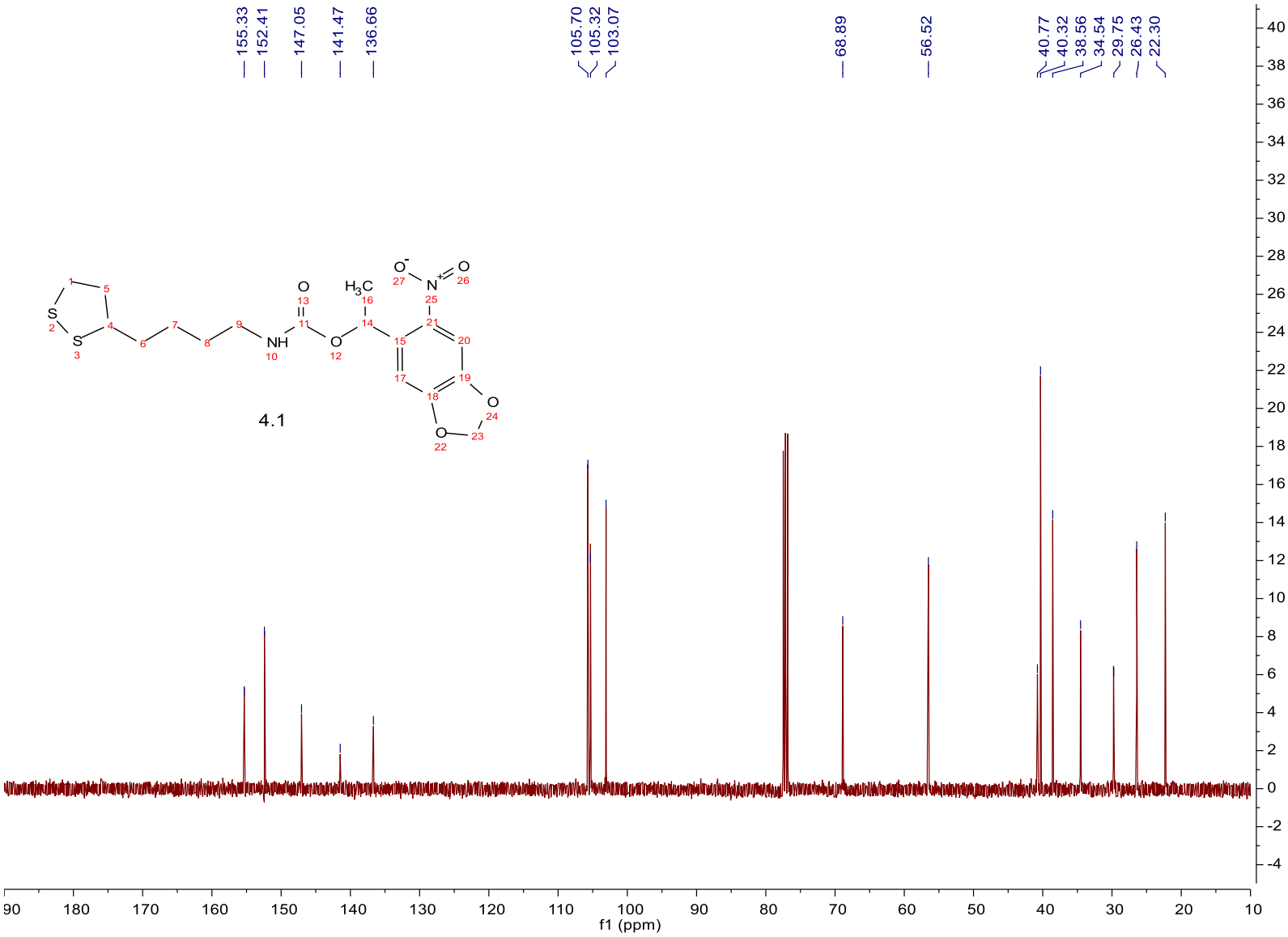
6.10
4.78
3.56
3.56
3.54
3.53
3.51
3.50
3.48
3.18
3.17
3.15
3.14
3.12
3.10
3.09
3.07
2.47
2.45
2.44
2.41
1.93
1.91
1.90
1.88
1.86
1.67
1.62
1.55
1.48
1.46
1.33
4.1
0.89
1.00
1.04
2.47
0.95
0.97
4.55
1.05
0.93
9.95
f1 (ppm)


155.33
152.41
147.05
141.47
136.66
105.70
105.32
103.07
68.89
56.52
40.77
40.32
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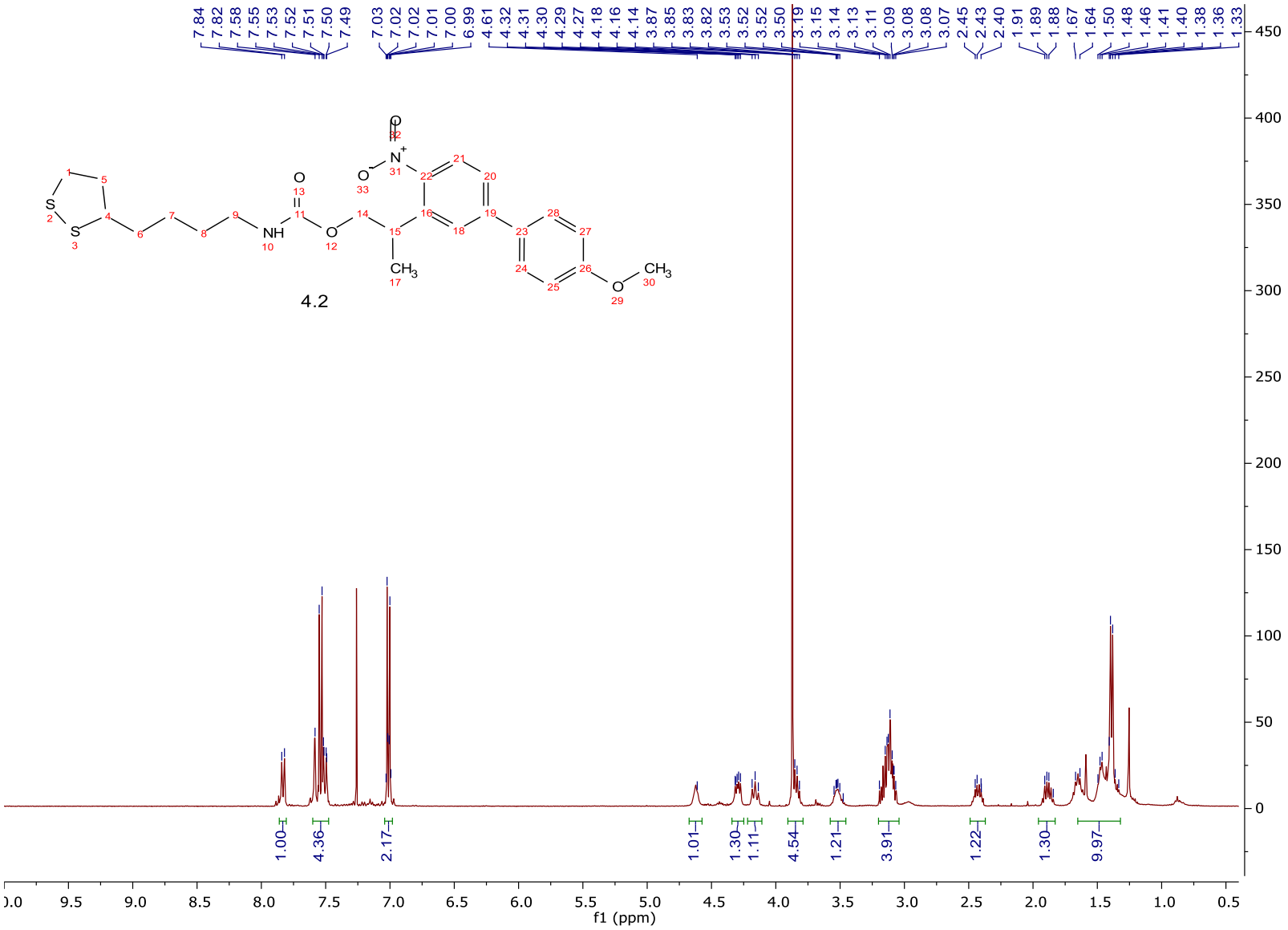
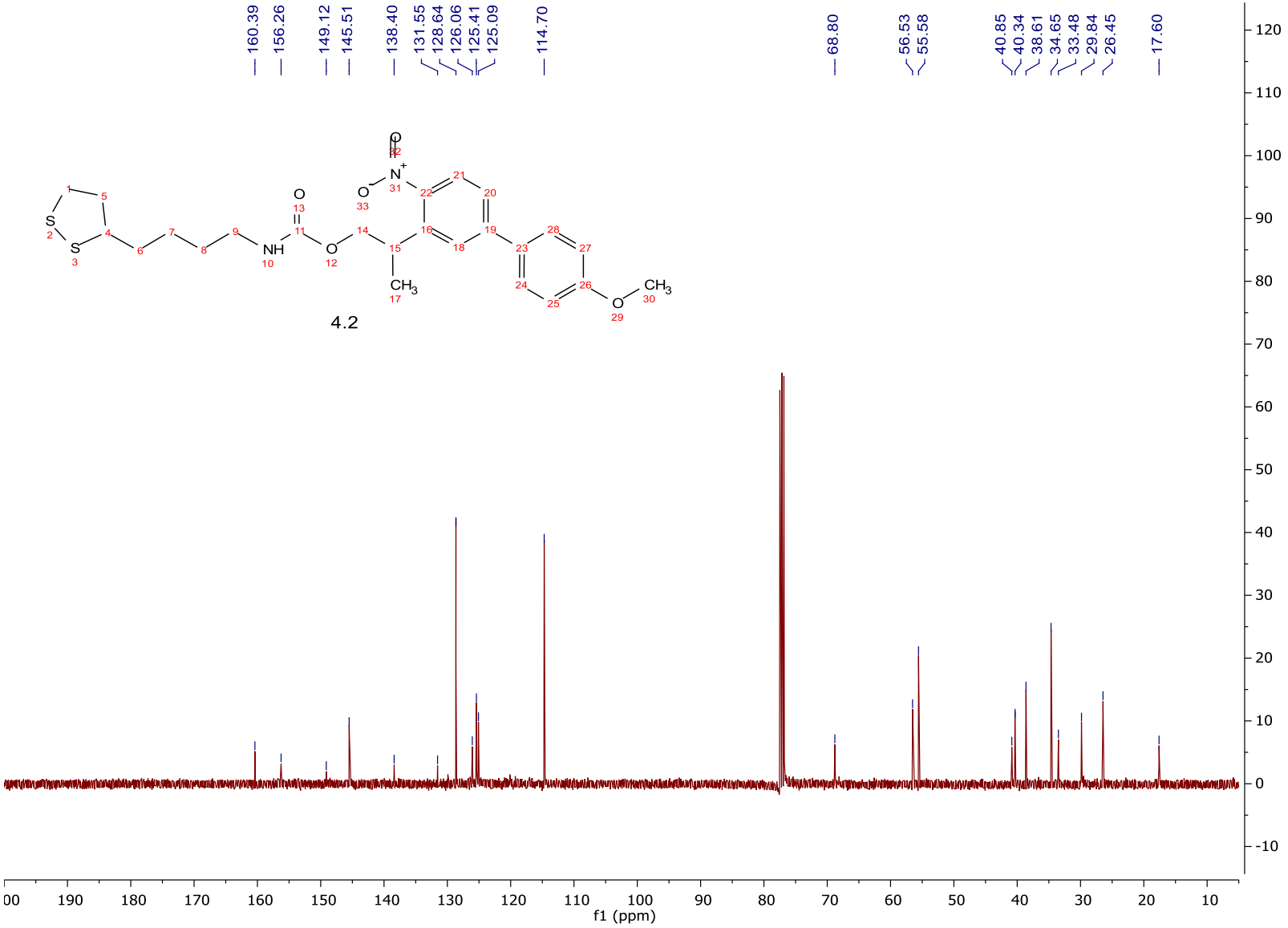
34.54
29.75
26.43
22.30
4.1
f1 (ppm)


7.84 7.82 7.58 7.55 7.53 7.52 7.51 7.50 7.49 7.03 7.02 7.02 7.01 7.00 6.99 4.61 4.32 4.31 4.30 4.29 4.27 4.18 4.16 4.14 3.87 3.85 3.83 3.82 3.53 3.52 3.52 3.50 3.19 3.15 3.14 3.13 3.11 3.09 3.08 3.08 3.07 2.45 2.43 2.40 1.91 1.89 1.88 1.67 1.64 1.50 1.48 1.46 1.41 1.40 1.38 1.36 1.33
4.2
1.00 4.36 2.17 1.01 1.30 1.11 4.54 1.21 3.91 1.22 1.30 9.97
f1 (ppm)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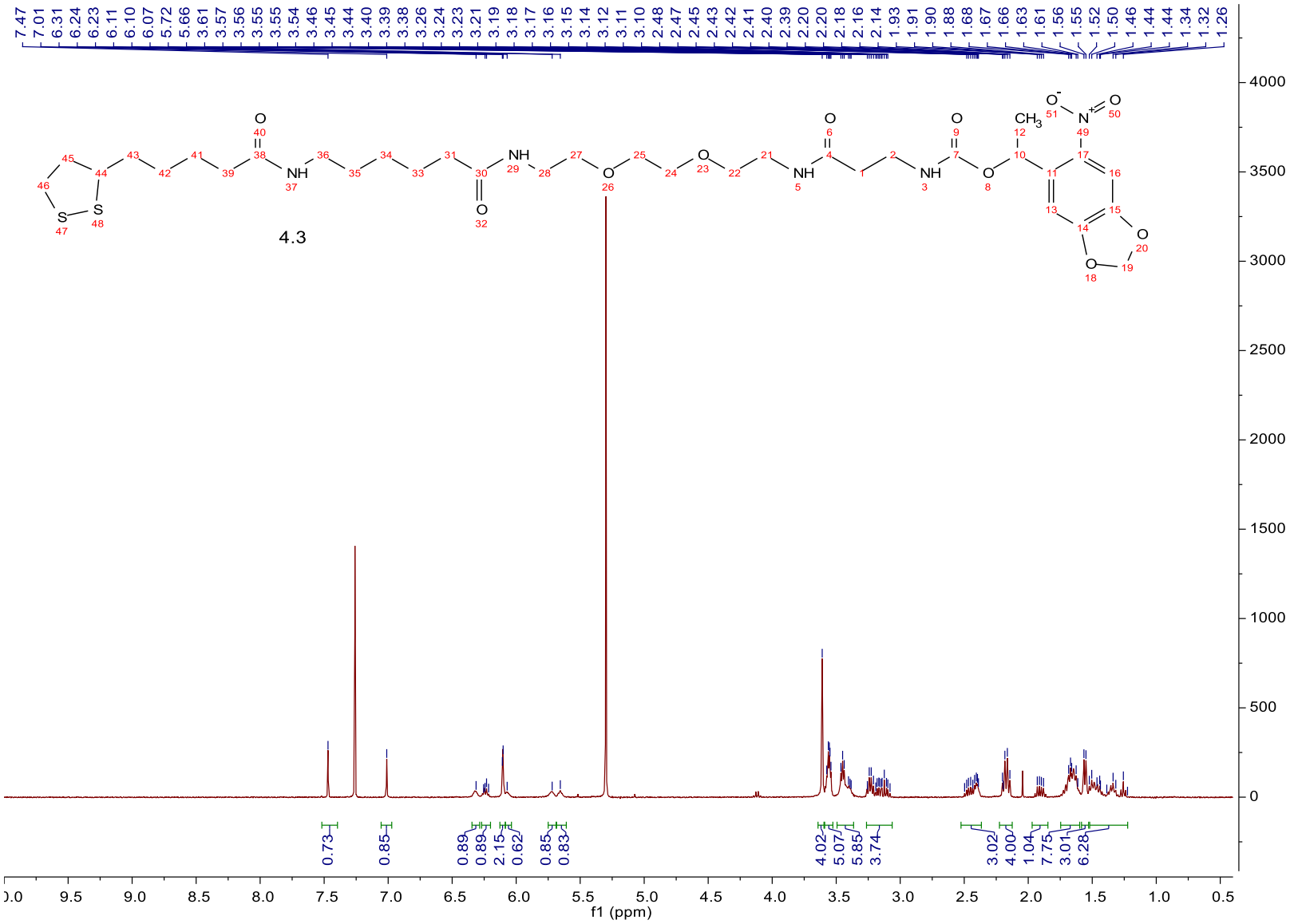
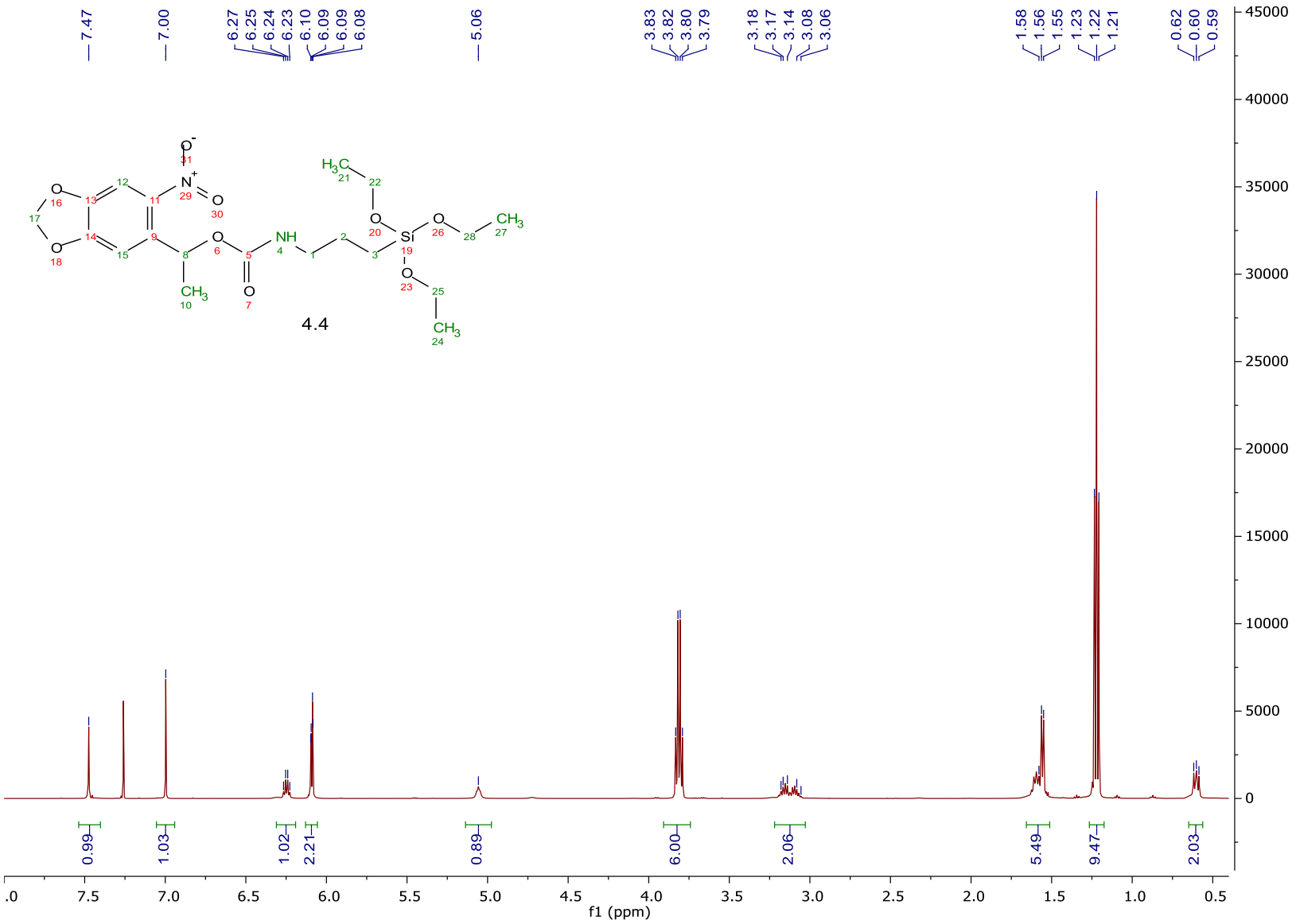
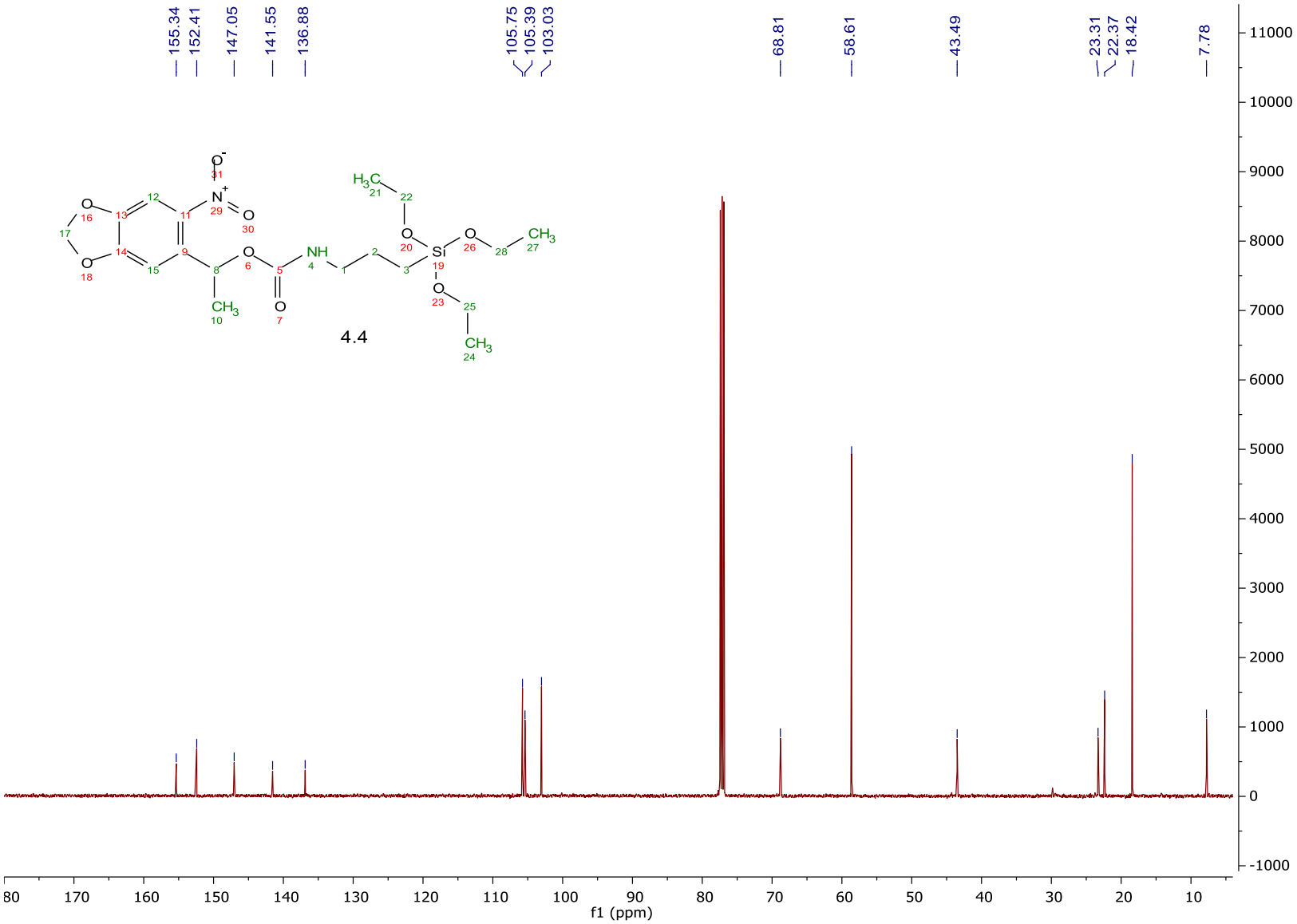
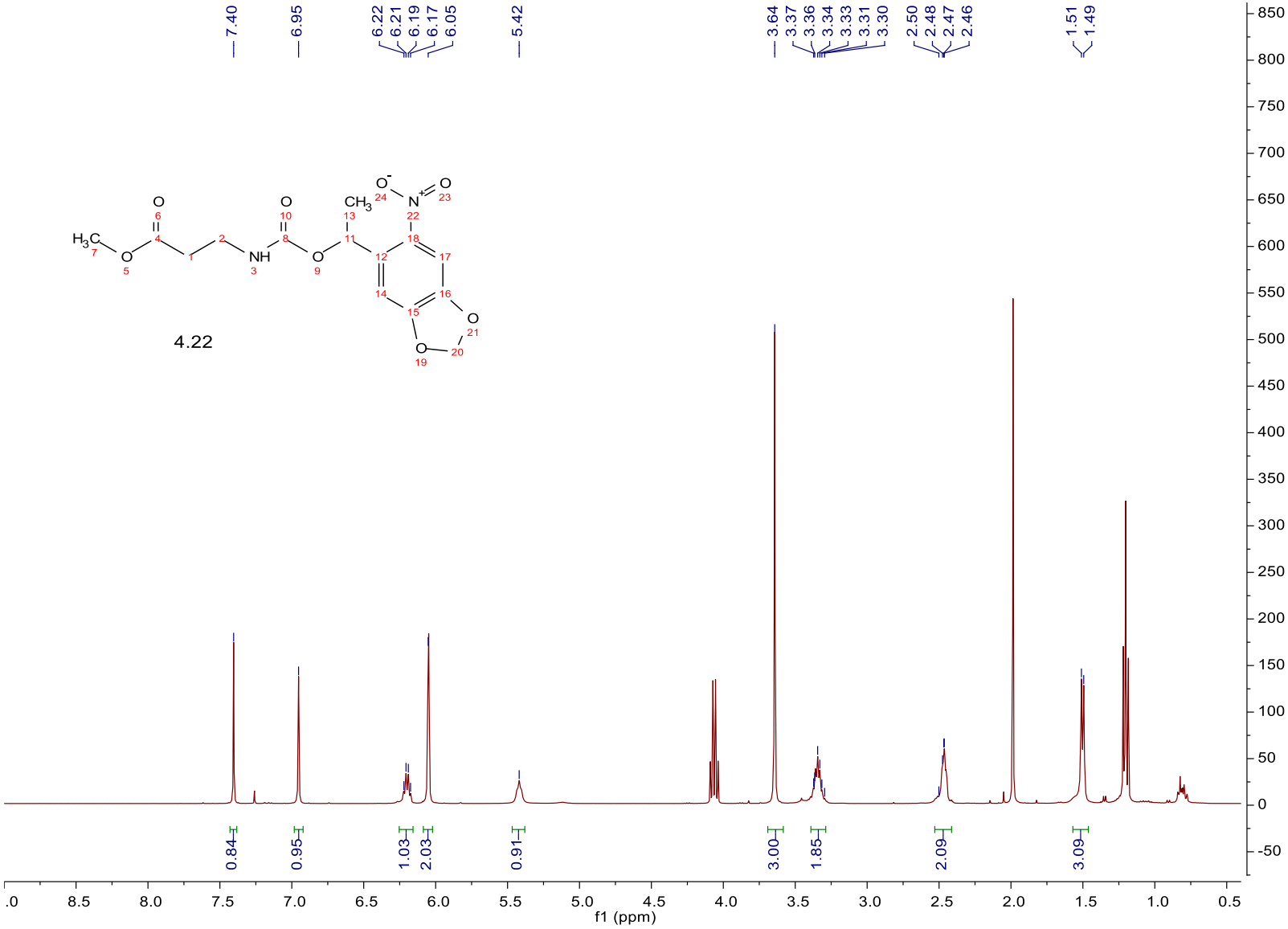
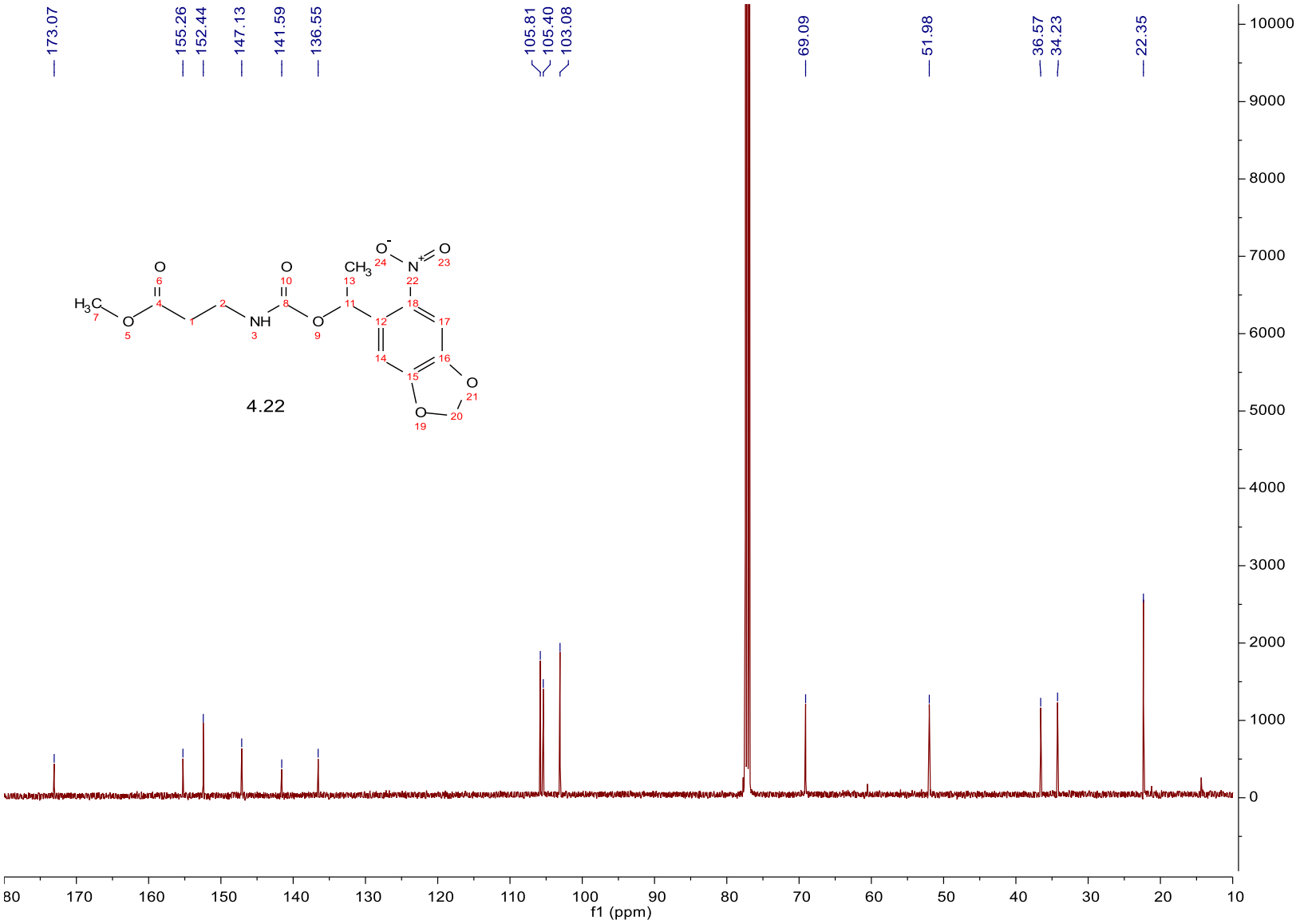
145.51
138.40
131.55
128.64
126.06
125.41
125.09
114.70
68.80
56.53
55.58
40.85
40.34
38.61
34.65
33.48
29.84
26.45
17.60
4.2
f1 (ppm)

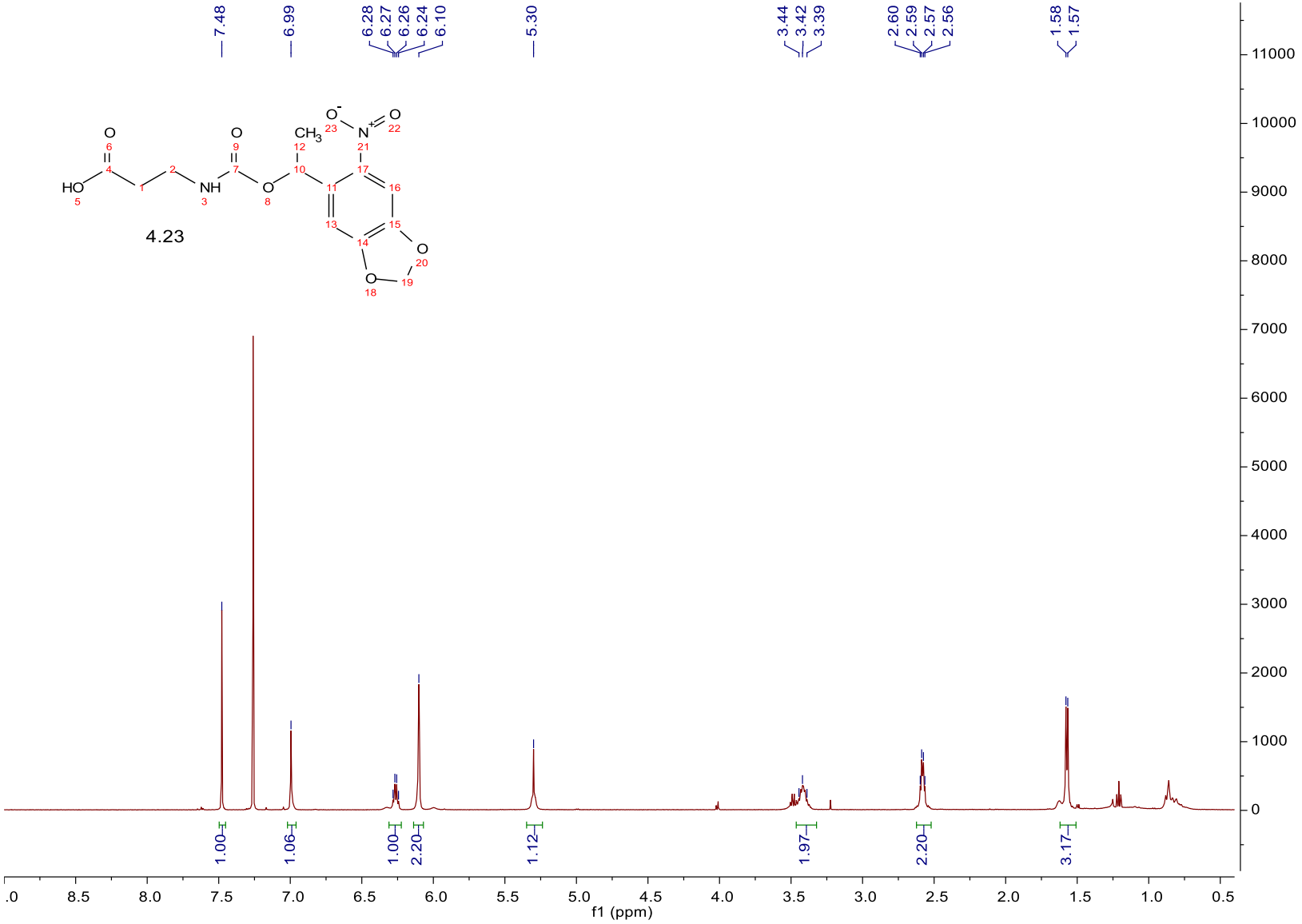

7.47 7.01 6.31 6.24 6.23 6.11 6.10 6.07 5.72 5.66 3.61 3.57 3.56 3.55 3.55 3.54 3.46 3.45 3.44 3.40 3.39 3.38 3.26 3.24 3.23 3.21 3.19 3.18 3.17 3.16 3.15 3.14 3.12 3.11 3.10 2.48 2.47 2.45 2.43 2.42 2.41 2.40 2.39 2.20 2.20 2.18 2.16 2.14 1.93 1.91 1.90 1.88 1.68 1.67 1.66 1.63 1.61 1.56 1.55 1.52 1.50 1.46 1.44 1.44 1.34 1.32 1.26
4.3
0.73 0.85 0.89 0.89 2.15 0.62 0.85 0.83 4.02 5.07 5.85 3.74 3.02 4.00 1.04 7.75 3.01 6.28
f1 (ppm)

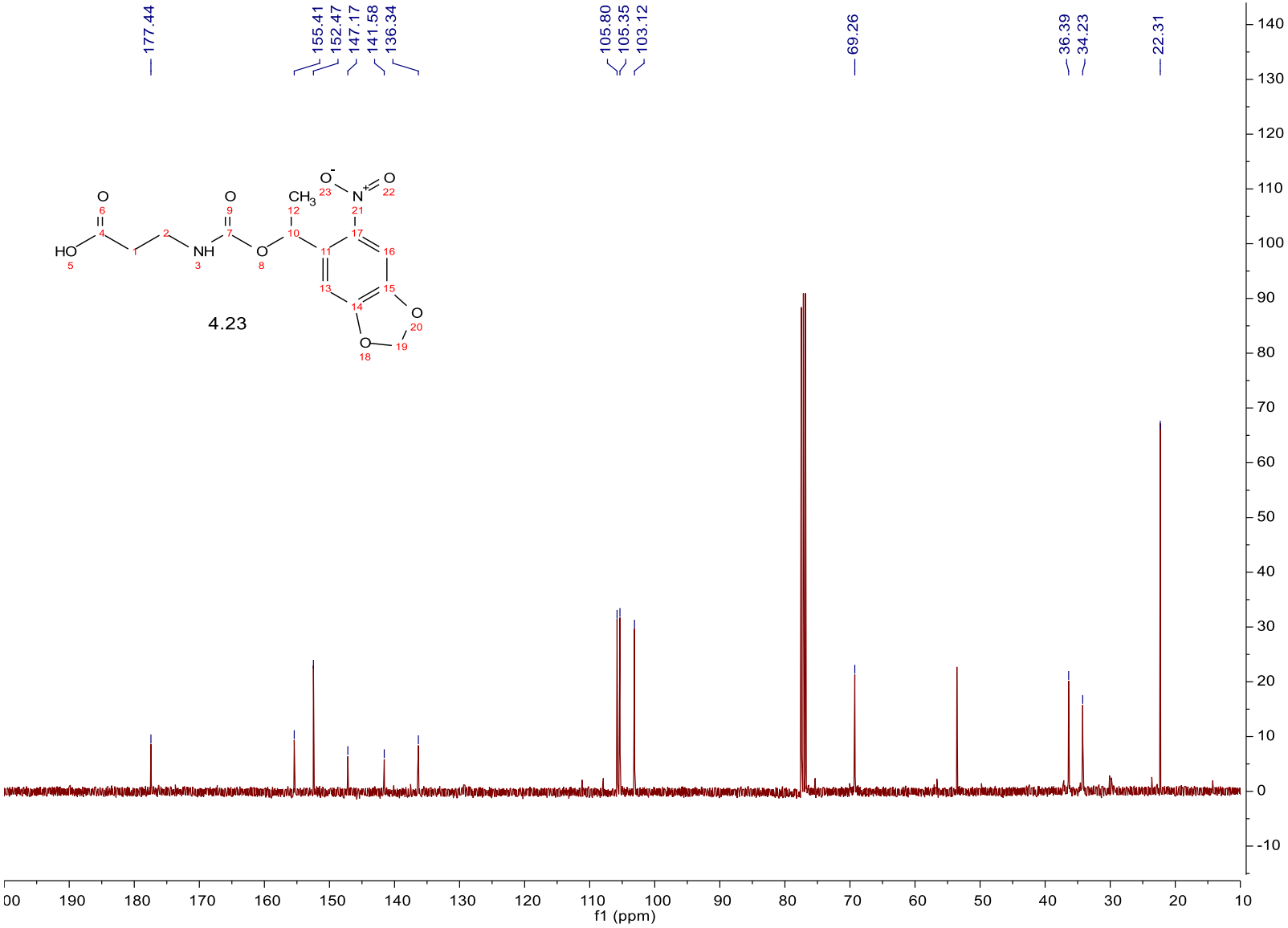

7.47
7.00
6.27
6.25
6.24
6.23
6.10
6.09
6.09
6.08
5.06
3.83
3.82
3.80
3.79
3.18
3.17
3.14
3.08
3.06
1.58
1.56
1.55
1.23
1.22
1.21
0.62
0.60
0.59
4.4
0.99
1.03
1.02
2.21
0.89
6.00
2.06
5.49
9.47
2.03
f1 (ppm)

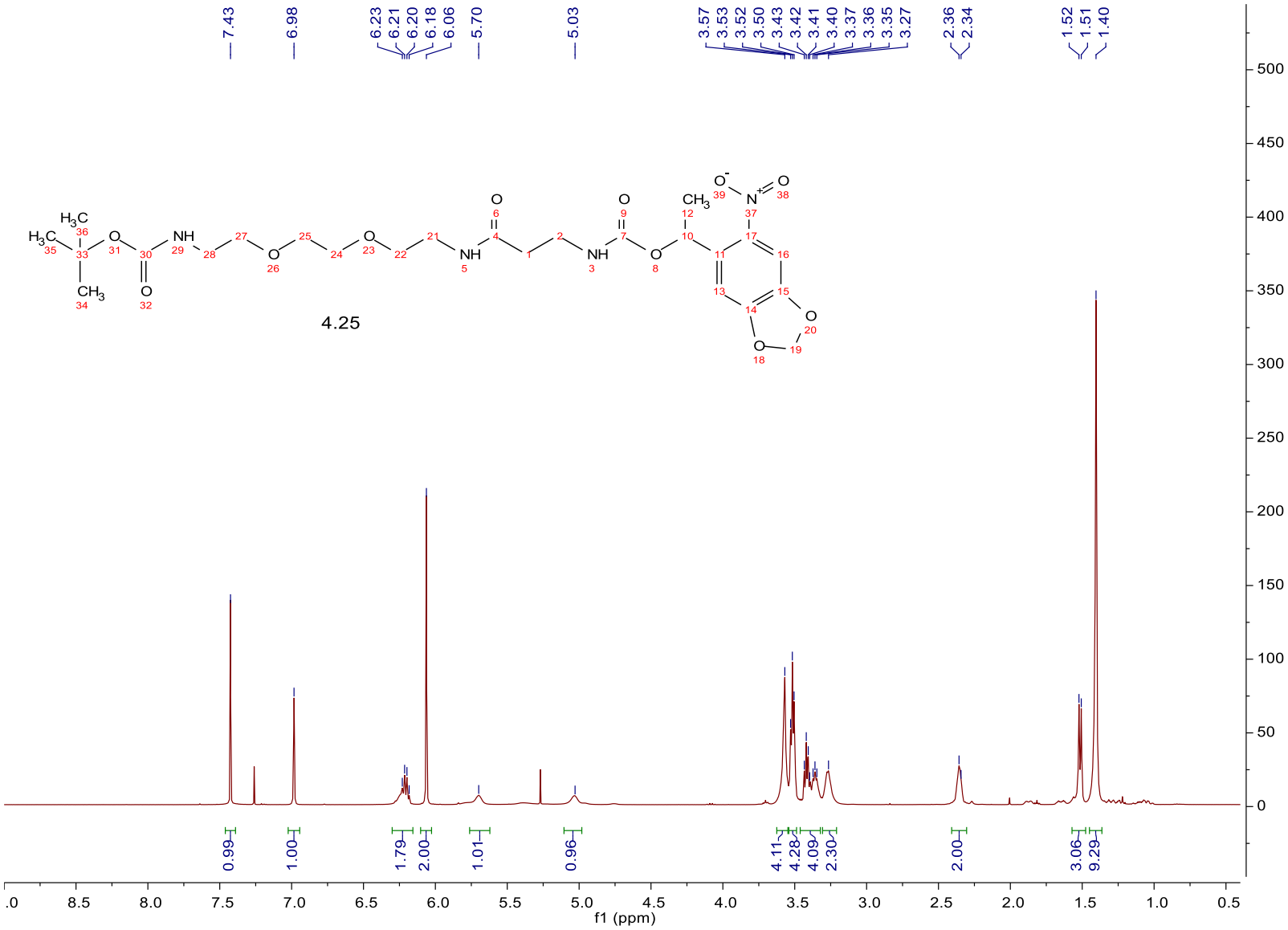

155.34
152.41
147.05
141.55
136.88
105.75
105.39
103.03
68.81
58.61
43.49
23.31
22.37
18.42
7.78
4.4
f1 (ppm)

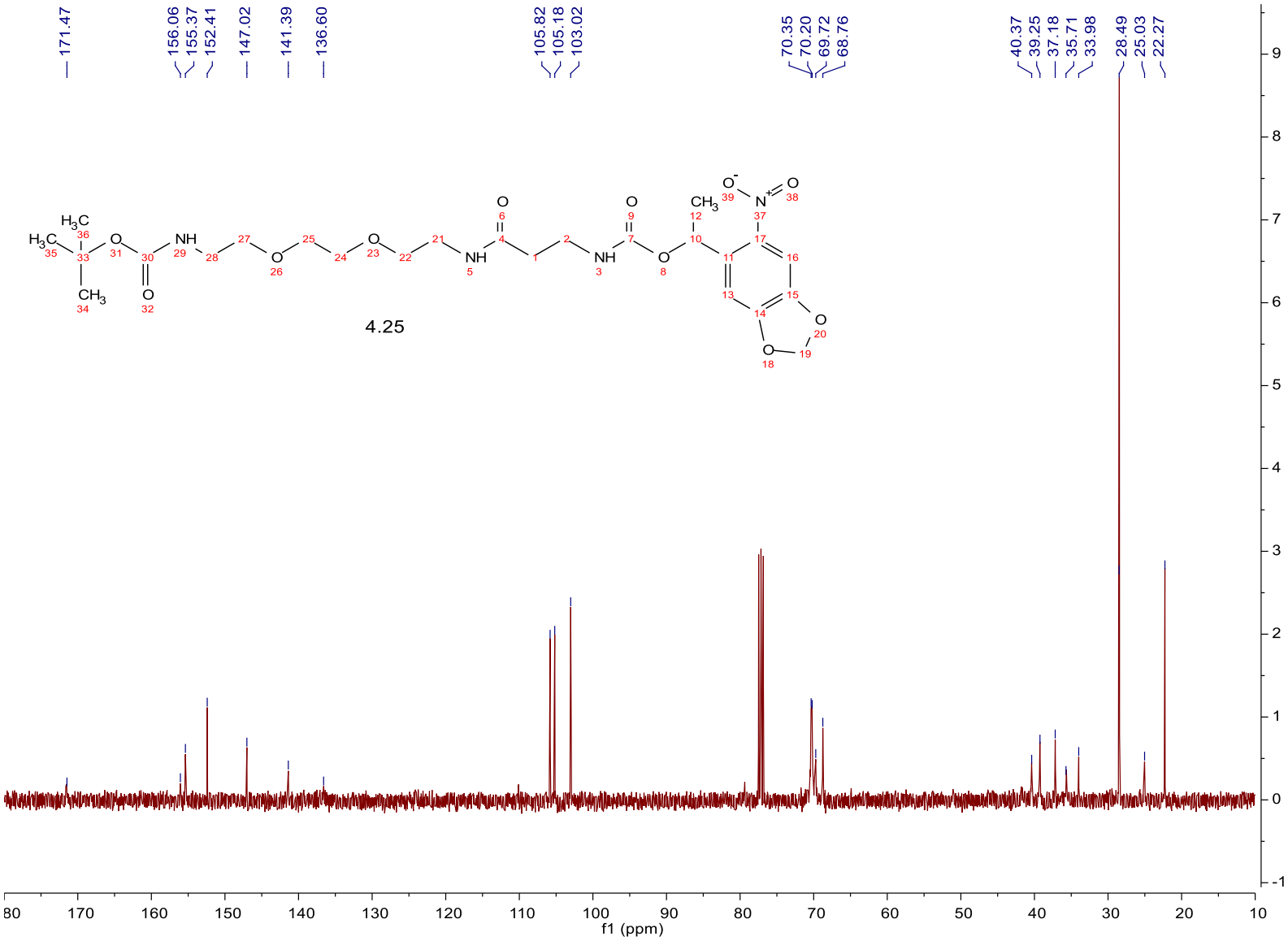

7.40
6.95
6.22
6.21
6.19
6.17
6.05
5.42
3.64
3.37
3.36
3.34
3.33
3.31
3.30
2.50
2.48
2.47
2.46
1.51
1.49
4.22
0.84
0.95
1.03
2.03
0.91
3.00
1.85
2.09
3.09
f1 (ppm)

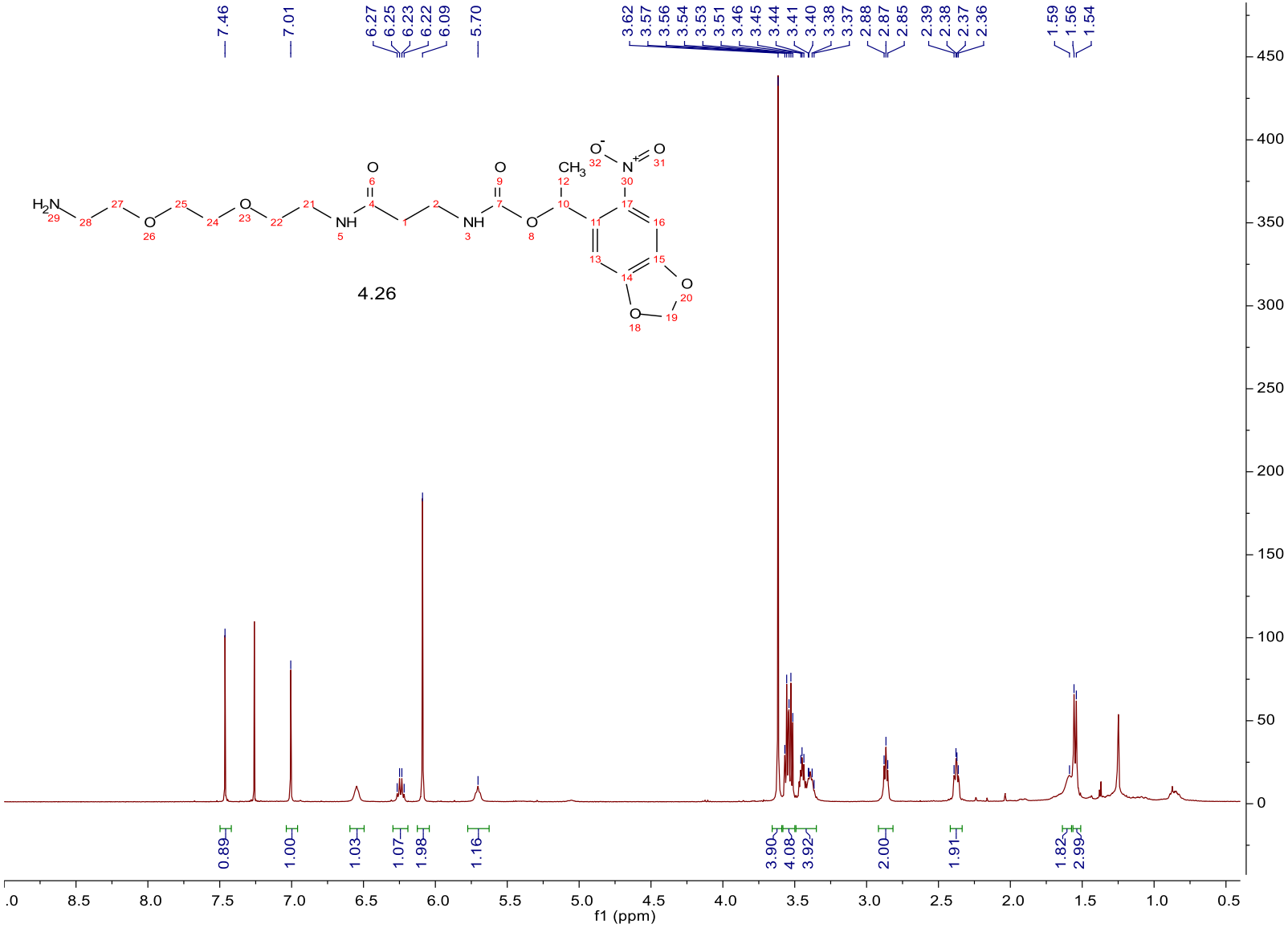

173.07
155.26
152.44
147.13
141.59
136.55
105.81
105.40
103.08
69.09
51.98
36.57
34.23
22.35
4.22
f1 (ppm)

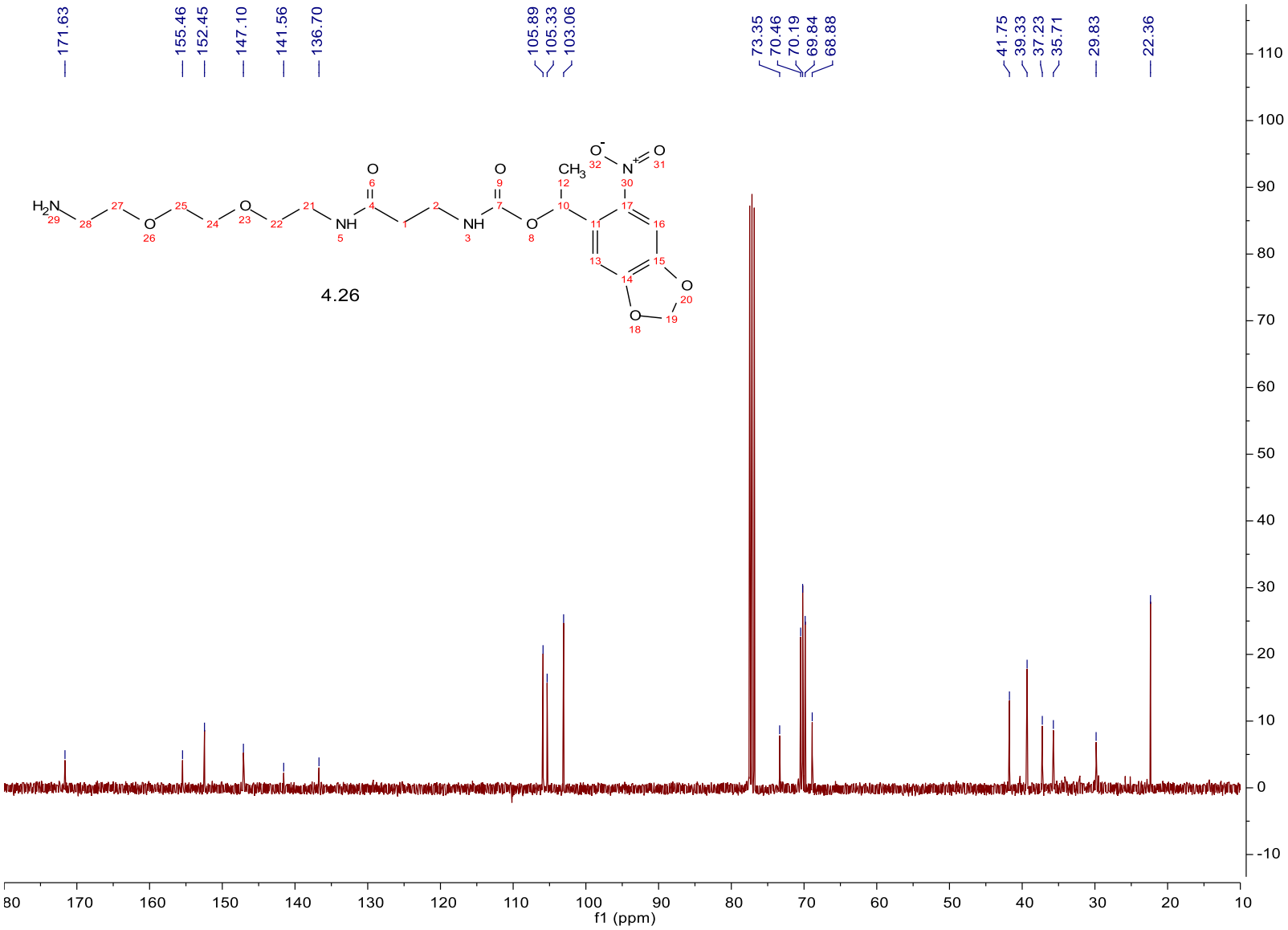

7.48
6.99
6.28
6.27
6.26
6.24
6.10
5.30
3.44
3.42
3.39
2.60
2.59
2.57
2.56
1.58
1.57
4.23
1.00
1.06
1.00
2.20
1.12
1.97
2.20
3.17
f1 (ppm)

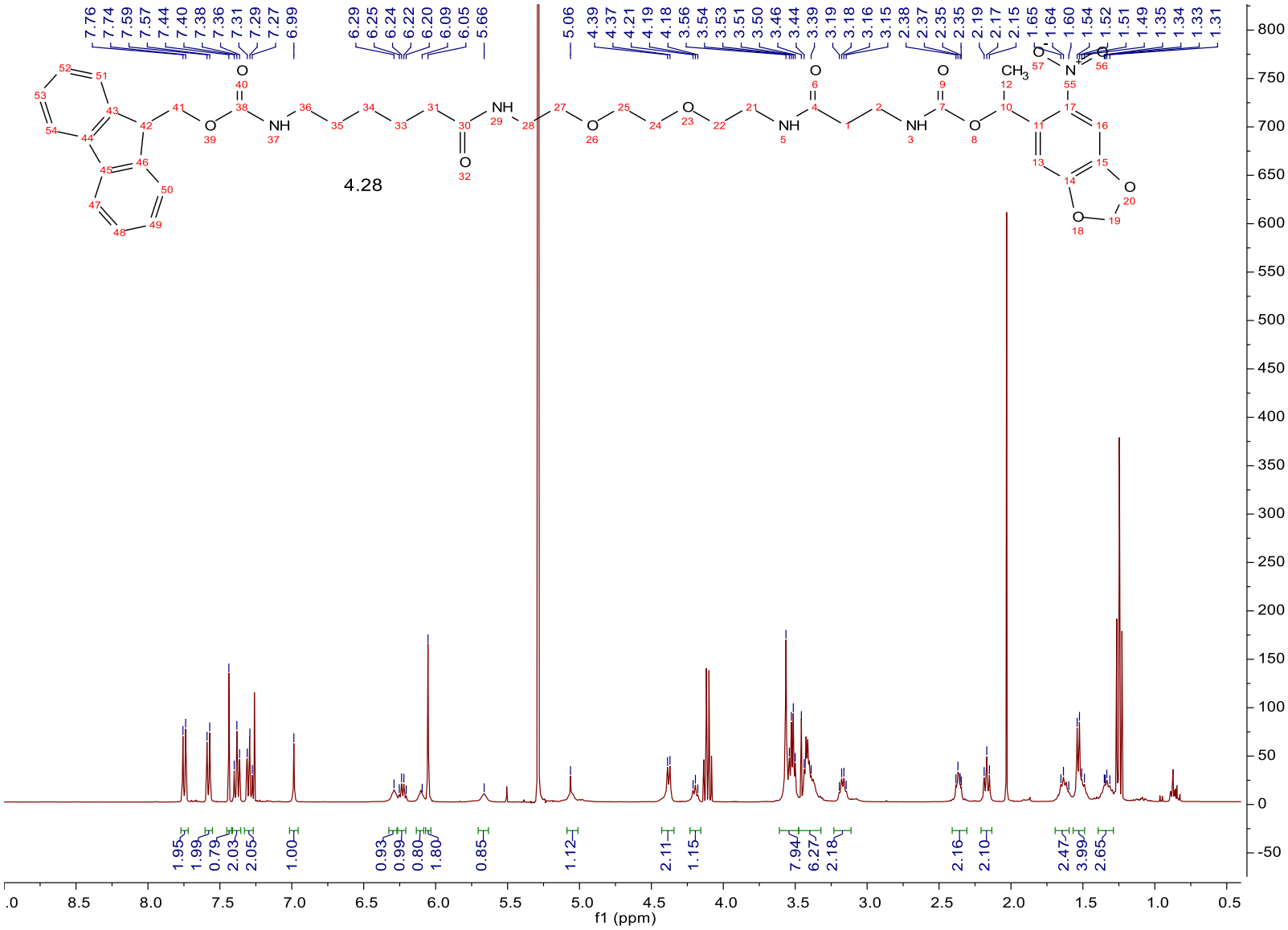

177.44
155.41
152.47
147.17
141.58
136.34
105.80
105.35
103.12
69.26
36.39
34.23
22.31
4.23
f1 (ppm)

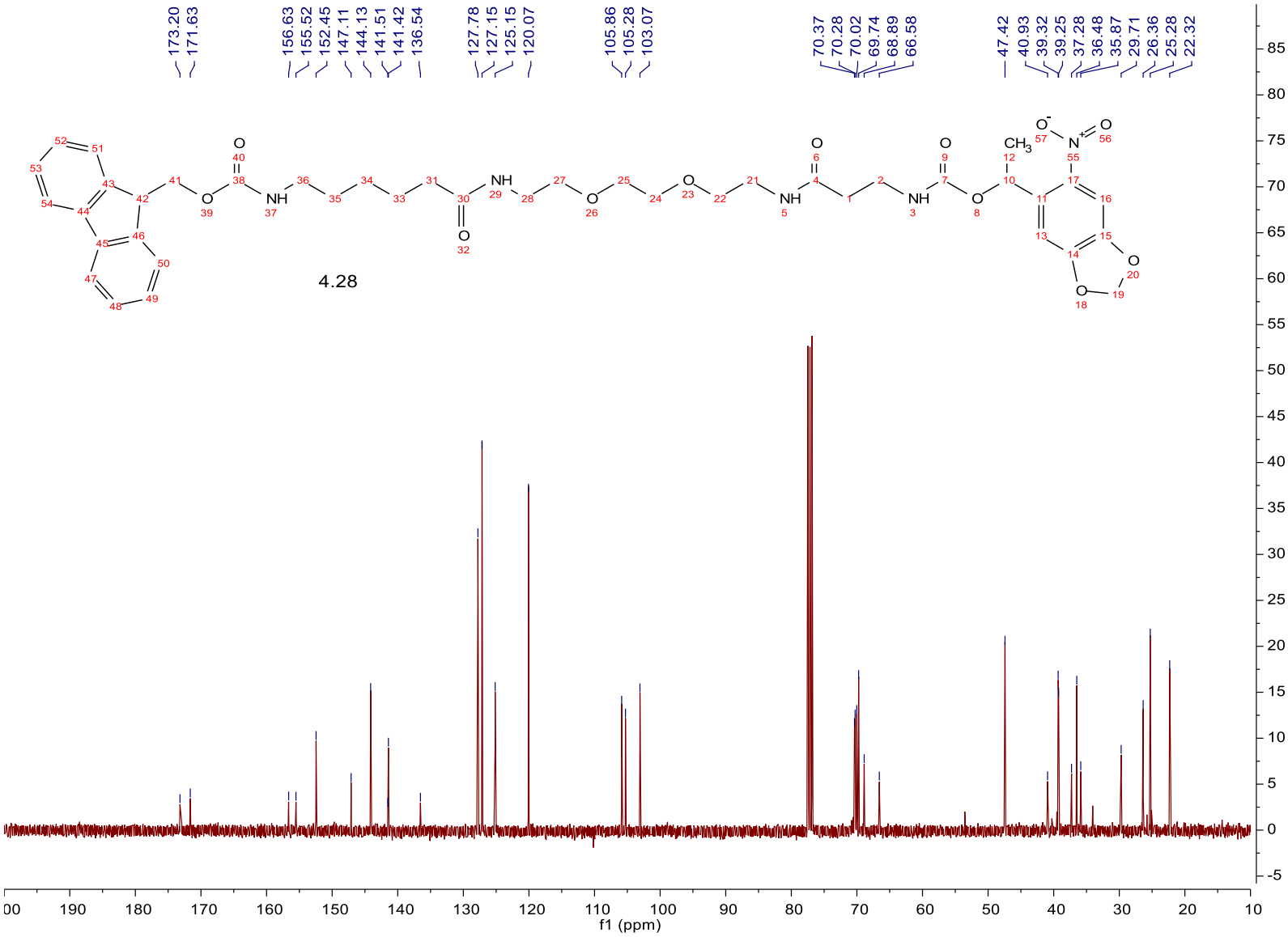

7.43
6.98
6.23
6.21
6.20
6.18
6.06
5.70
5.03
3.57
3.53
3.52
3.50
3.43
3.42
3.41
3.40
3.37
3.36
3.35
3.27
2.36
2.34
1.52
1.51
1.40
4.25
0.99
1.00
1.79
2.00
1.01
0.96
4.11
4.28
4.09
2.30
2.00
3.06
9.29
f1 (ppm)


171.47
156.06
155.37
152.41
147.02
141.39
136.60
105.82
105.18
103.02
70.35
70.20
69.72
68.76
40.37
39.25
37.18
35.71
33.98
28.49
25.03
22.27
4.25
f1 (ppm)


7.46
7.01
6.27
6.25
6.23
6.22
6.09
5.70
3.62
3.57
3.56
3.54
3.53
3.51
3.46
3.45
3.44
3.41
3.40
3.38
3.37
2.88
2.87
2.85
2.39
2.38
2.37
2.36
1.59
1.56
1.54
4.26
0.89
1.00
1.03
1.07
1.98
1.16
3.90
4.08
3.92
2.00
1.91
1.82
2.99
f1 (ppm)


171.63
155.46
152.45
147.10
141.56
136.70
105.89
105.33
103.06
73.35
70.46
70.19
69.84
68.88
41.75
39.33
37.23
35.71
29.83
22.36
4.26
f1 (ppm)


7.76 7.74 7.59 7.57 7.44 7.40 7.38 7.36 7.31 7.29 7.27 6.99
6.29 6.25 6.24 6.22 6.20 6.09 6.05 5.66
5.06
4.39 4.37 4.21 4.19 4.18 3.56 3.54 3.53 3.51 3.50 3.46 3.44 3.39 3.19 3.18 3.16 3.15 2.38 2.37 2.35 2.35 2.19 2.17 2.15 1.65 1.64 1.60 1.54 1.52 1.51 1.49 1.35 1.34 1.33 1.31
4.28
1.95 1.99 0.79 2.03 2.05 1.00 0.93 0.99 0.80 1.80 0.85 1.12 2.11 1.15 7.94 6.27 2.18 2.16 2.10 2.47 3.99 2.65
f1 (ppm)


173.20
171.63
156.63
155.52
152.45
147.11
144.13
141.51
141.42
136.54
127.78
127.15
125.15
120.07
105.86
105.28
103.07
70.37
70.28
70.02
69.74
68.89
66.58
47.42
40.93
39.32
39.25
37.28
36.48
35.87
29.71
26.36
25.28
22.32
4.28
f1 (ppm)