SYNTHESIS OF α-β-UNSATURATED *N*-ARYL KETONITRONES AND USE AS PRECURSORS FOR SYNTHESIS OF C3-QUARTERNARY INDOLENINES

A Thesis

by

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ABSTRACT

Our group recently discovered and developed a diastereoselective reaction yielding C3-quaternary indolenines from the combination of α,β-unsaturated *N*-aryl ketonitrones and mono- or di-activated alkynes in toluene at 80 °C. This reaction builds a high level of complexity in a single step, and the C3-quaternary indolenines produced show promise as precursors to indole-containing molecules of biological and medicinal interest. However, we found our substrate scope was limited by the methods available for the synthesis of the α,β-unsaturated *N*-aryl ketonitrones necessary for the reaction.

As a result of this need, we sought to develop a new way to access these α,β-unsaturated *N*-aryl ketonitrones. Our priorities were to develop a method that was expedient with regard to time and number of steps, modular, general, and could rely on inexpensive commercially available starting materials. The method that we have reported proceeds in three steps: starting with a commercially available aniline derivative and α,β-unsaturated aldehyde an imine is synthesized and alkylated using an organolithium reagent. The resultant secondary amine is then oxidized using Oxone® to obtain the α,β-unsaturated *N*-aryl ketonitrone. Only the nitrone is subject to a discrete purification step, and it can generally be isolated in yields of 50-80%. Unfortunately, the nitrones generated using this technique would not react with activated alkynes to yield indolenines.

The two techniques discussed herein offer valuable insight into a poorly understood area of nitrone reactivity and are both synthetically useful in their own right. The studies

performed make it clear that nitrones are a very viable synthetic intermediate; many nitrones can be easily accessed and then used to create very complex molecules in a diastereoselective manner. Both of these synthetic techniques in combination offer a valuable alternative approach to many complex and biologically interesting indole containing alkaloids. It is hoped that this work will serve as fertile ground for further studies towards increasing the utility of this chemistry.

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CHAPTER I

INTRODUCTION

1.1 Structure and Nomenclature

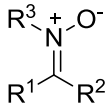


Figure 1. General structure of a nitrone.

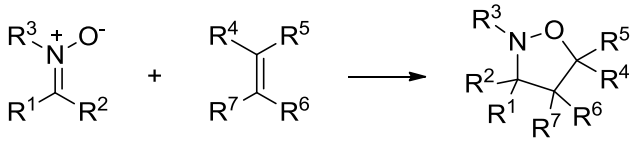
Nitrones are the *N*-oxides of imines (Figure 1). Pfeiffer derived the name nitrone from nitrogen ketone, based on his assumption that the reactivity of this new class of molecules would be analogous to ketones.[1] The central structural motif can be described as an N-oxide of an imine, although oxidation of imines is not a common strategy for preparing nitrones. Depending on whether the R^1 or R^2 are carbon containing moieties or one is a proton, the terms keto-nitrone and aldo-nitrone are used, respectively. In addition, there exists the possibility of (*E*)- and (*Z*)- isomerism about the C=N bond assuming that R^1 and R^2 are not identical.

1.2 History of Nitrones

As a class of compounds, nitrones have been known for a very long time. The term nitrone was first applied to this functional group by Pfeiffer in 1916 as described above, but the first were observed experimentally prior to this by Beckmann as well as Werner and Buss in the 1890s.[2] The name nitrone was given due to the anticipation that nitrones

would react analogously to ketones, with the carbon-nitrogen double bond displaying similar reactivity to the carbon-oxygen double bond. However, it was subsequently established that nitrones behave more like extended ketones; the carbon and oxygen are typically the two reactive sites.[3] Certain trends in nitrone reactivity are both very well known and well studied, with the 1,3-dipolar cycloaddition being a rather classic example. While discovery of novel avenues of reactivity of nitrones has been extremely sporadic over the long span of time since their discovery, many novel methods of synthesizing nitrones as well as new applications have been published recently.[4-10]

The 1,3-dipolar cycloaddition is a class of well-studied reactions characterized by the addition of a 1,3-dipole and a multiple bond dipolarophile to form a five-membered ring. Nitrones, potent 1,3-dipoles, are no exception; they will react efficiently with a fairly broad range of dipolarophiles, most notably alkenes and alkynes for the large amount of attention they have received over the years in methodology studies as well as applications in natural product total synthesis (Scheme 1).



Scheme 1. Reaction of a nitrone with a tetrasubstituted alkene to form an isoxazolidine.

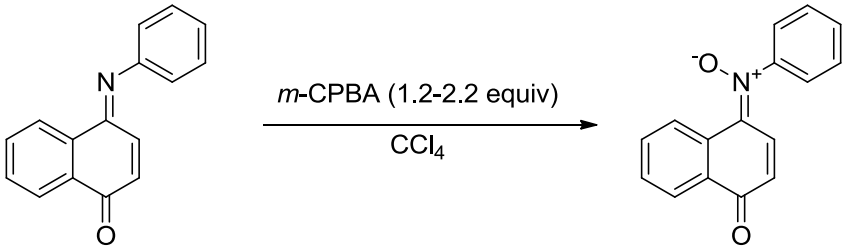
1.3 Synthesis of Nitrones

There are quite a few approaches to synthesize nitrones, which can be roughly divided into two major categories based on the reaction type, and then further with regard to the starting materials. The first major group involves oxidation of a nitrogenous starting material. Imines can be directly oxidized into nitrones in certain cases.[11] Nitrones can be obtained from a broad range of secondary amines when subjected to a variety of oxidative conditions.[12] Hydroxylamines, likely an intermediate in the oxidation of secondary amines to nitrones, can themselves be oxidized to nitrones.[13] The second major category of nitrone syntheses is comprised of addition reactions; carbonyl substrates can be converted to the desired nitrone by condensation with the appropriate primary hydroxylamine.[14]

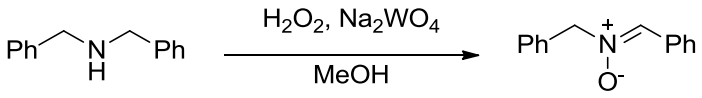
1.3.1 Nitrone Synthesis by Oxidation

Direct oxidation of imines is a straightforward approach to nitrones, though the scope of such a reaction appears at this time relatively limited. An example of a less sensitive imine substrate oxidized to the nitrone form by Forrester and colleagues is shown above (Scheme 2). Oxidation of imines with peroxyacids generally produces oxaziridines which may or may not rearrange to yield the nitrone.[15] In these cases the nitrone can be obtained as a side product or the sole product depending on the substrate and conditions[16]. Boyd et al. suggest that the ratio of oxaziridine to nitrone produced during peroxyacid oxidation is controlled by the relative frequency of peroxyacids attack on the carbon compared to attack by the nitrogen atom.[11] For example, dimethyl substitution adjacent to the imine carbon suppressed attack on the carbon and favored nitrone

formation. Conversely, use of methanol as a solvent greatly increased the yield of oxaziridine relative to chlorinated hydrocarbon solvents; this was theorized to result from inactivation of the imine nitrogen through hydrogen bonding.



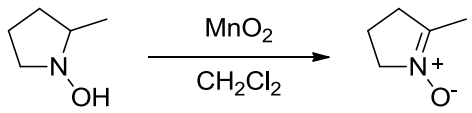
Scheme 2. Oxidation of quinone imines to quinone nitrone with *m*-CPBA.



Scheme 3. Oxidation of a secondary amine to the nitrone.

With the exception of select cases, primary amines cannot be reliably or cleanly oxidized to nitrones; complex mixtures are the most typical result.[15] The second commonly used oxidative strategy utilizes secondary amines as the starting material. The oxidation of secondary amines to nitrones is far more general than the same reaction for imines and can be achieved with a wide variety of different conditions. As a result of this, in many cases imines are first reduced or alkylated to yield secondary amines which are then oxidized to nitrones. One common set of conditions uses sodium tungstate as a catalyst along with excess hydrogen peroxide as oxidant (Scheme 3).[17] This set of

reaction conditions is not only clean but in almost all cases provides the nitrone in good yields. Variations of this scheme in which the sodium tungstate is replaced by other metal oxide catalysts have also been demonstrated to be serviceable.[12,18,19] Although the sodium tungstate-hydrogen peroxide oxidation is the most common, several non-catalytic oxidizing conditions have been used successfully as well. The urea-hydrogen peroxide complex serves as a successful stoichiometric oxidant,[12] as does dimethyldioxirane.[20]



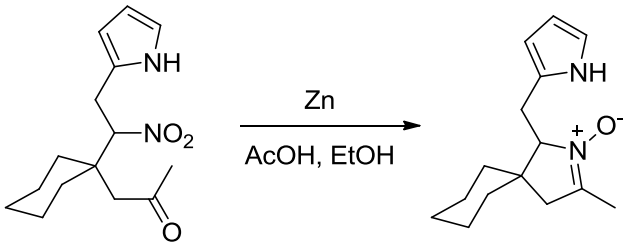
Scheme 4. Oxidation of a hydroxylamine to a nitrone using MnO_2.

Another functionality that can be oxidized to the nitrone is the hydroxylamine.[13] On a superficial level, the oxidation to the nitrone is relatively straightforward in contrast to imines. The conditions are milder than those required for imines or amines due to the oxidation state proximity of the hydroxylamine to the nitrone. There must be a hydrogen atom on the α-carbon of any hydroxylamine to be oxidized to the nitrone for obvious reasons. Unfortunately, however, the preparation of hydroxylamines is itself not always a trivial task; the reactions are usually plagued with a host of side products. In addition to these issues, the hydroxylamines are not usually particularly stable compounds. Many of the same oxidants that are used for imines and amines also affect the transformation

from hydroxylamine to nitrone,[15] and additionally mercury (II) oxide and Manganese (IV) oxide are also commonly used (Scheme 4).[21]

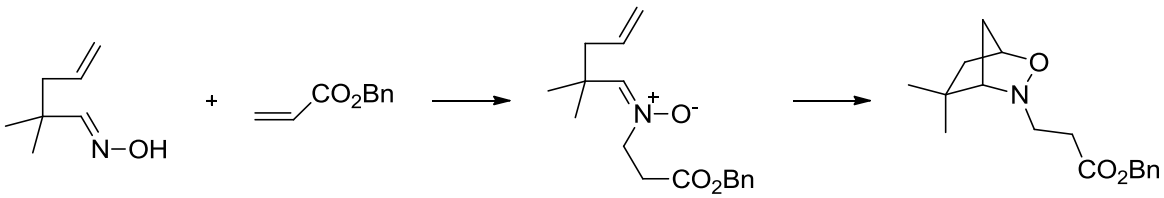
1.3.2 Nitrone Synthesis by Addition

The other major strategy aside from oxidation to access nitrones is addition. The first subcategory in this group is the condensation of carbonyl compounds with *N*-monosubstituted hydroxylamines. Hydroxylamines can be directly condensed with carbonyl compounds under water-removing conditions to yield nitrones. It has also been demonstrated that carbonyl compounds can be condensed with hydroxylamines generated in-situ by reduction of nitro compounds.[14] An intramolecular version of this reaction has also been demonstrated to be effective (Scheme 5).[22] In comparison to building a complex and probably unstable hydroxylamine to be oxidized, a simpler hydroxylamine can be prepared and the majority of complexity can be contained in the carbonyl partner.



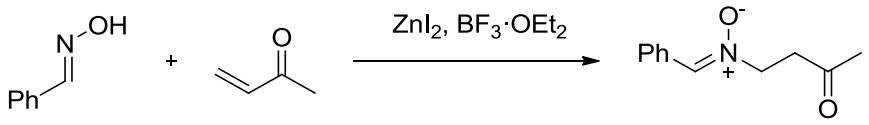
Scheme 5. In-situ hydroxylamine formation followed by intramolecular condensation with the ketone group to generate a cyclic nitrone.

The second method to access nitrones through addition reactions takes advantage of the functional similarity of oximes to nitrones. One common variety, sometimes known as Grigg's nitrone formation,[23] utilizes alkenes activated by electron withdrawing groups. The hydroxylamine undergoes a Michael addition to the alkene, at least formally. Despite the name of this reaction, the nitrone is often only an intermediate generated in situ for a 1,3-dipolar cycloaddition reaction with another the dipolarophile. This is the case in Grigg's original work; the nitrones generated reacted intramolecularly and spontaneously after formation to yield isoxazolidines (Scheme 6).



Scheme 6. Cyclization of nitrone generated from and oxime and an activated alkyne.

However, Heaney has shown that unsaturated oximes can be synthesized that will react in an intramolecular manner and stop reacting upon reaching the nitrone.[23] In addition, Nakama et al. have shown that nitrones can be formed terminally by the intermolecular Lewis Acid-catalyzed reaction between oximes and activated alkenes (Scheme 7).[24] Oximes with a large variety of side chains were successfully reacted with simple vinylic ketones, esters, aldehydes and carbamates, demonstrating the potential of this approach in synthetic applications.



Scheme 7. Lewis Acid-catalyzed condensation of an oxime and α,β-unsaturated ketone.

As a class of molecules, α,β-unsaturated nitrones are not well known in comparison to nitrones overall. Although there are several methods available to access different nitrones, as a subset α,β-unsaturated nitrones have received little attention. An excellent method, and one used to synthesize nitrones for use in our indolenine synthesis reaction (*vide infra*), is that developed by Bartoli et al. This method[25] allows one to make α,β-unsaturated *N*-aryl ketonitrones by treating nitroarenes with crotylmagnesium chloride. While this method offers access to a nitrones containing functionalized aryl groups in one step from commercially available materials, the researcher is limited by the Grignard reagent; few crotyl Grignard reagents are commercially available. In addition, preparation of unavailable nitro compounds is not necessarily trivial either.[26]

CHAPTER II

DIASTEREOSELECTIVE SYNTHESIS OF C-3 QUATERNARY INDOLENINES USING α,β-UNSATURATED *N*-ARYL KETONITRONES AND ACTIVATED ALKYNES

2.1 Introduction

Our group, in the course of conducting another study, discovered that C3-quaternary indolenines are produced by the reaction between α,β-unsaturated ketonitrones and activated alkynes. This avenue of research was pursued as it promised to provide a better solution for an important problem. The substituted C3-quaternary indole core is a common core structural motif in a large number of natural products. To date, few methods have been developed to prepare indolenines.[27] In contrast to this, a wide variety of methods to produce indoles are known.[28,29]

Some examples of indole containing alkaloids are shown below in Figure 2. Many of these compounds exhibit promising bioactivity. Communesin B, for example, has shown an ED_{50} value of 0.45 μg/mL in preliminary inihibition studies against murine lyphocytic leukemia cell line P-388.[30] A C3-quaternary indolenine could serve as a convenient starting point for further substitution of the five-membered ring, allowing access to the heavily substituted indole cores seen in these natural products. A facile preparation of a versatile precursor to these natural products, the indolenine, opens up a new avenue of different approaches towards the synthesis of these as well as other natural products.

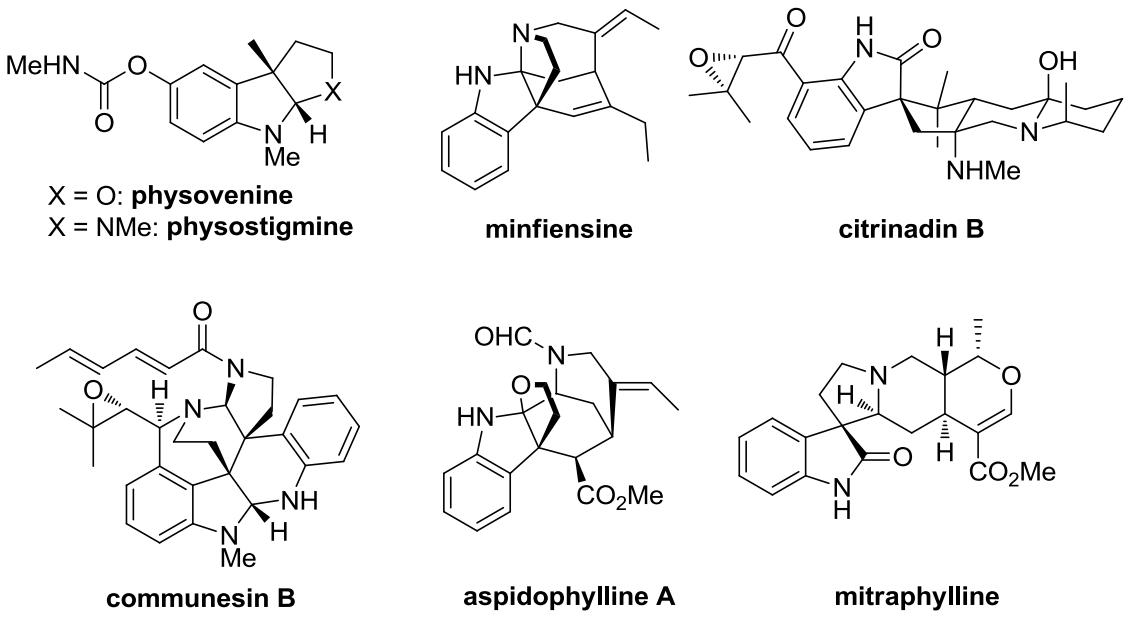
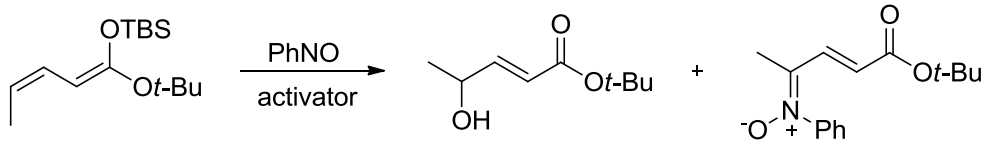


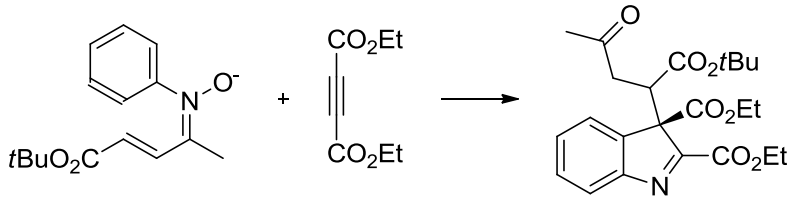
Figure 2. Examples of natural products containing highly substituted indole cores.

One of the research group's projects was a γ-oxygenation of α,β-unsaturated esters via a vinylogous *O*-nitroso Mukaiyama Aldol reaction.[31] Scheme 8 below shows this reaction, which was found to produce predominantly the α,β-unsaturated ketonitrone when carried out in methanol with acetic acid as an additive.



Scheme 8. The γ-oxygenation reaction developed in our lab showing nitrone side product.

The nitrone 1,3-dipolar cycloaddition has been known for quite a long time and is well studied.[32] However, during our study[33] of the reaction of α,β-unsaturated ketonitrones and activated alkynes, the actual product obtained was very much different from what was expected. It was determined that a C3-quaternary indolenine was created after characterizing the product through 1 and 2-D NMR studies as well as x-ray crystallography. Furthermore, it was apparent that the stereoisomer isolated was the major product by a large margin if not the only isomer produced in the reaction. This initial reaction is shown below in Scheme 9.



Scheme 9. Synthesis of C3-quaternary indolenine **2a** from α,β-unsaturated *N*-aryl ketonitrone **1a** and diethyl acetylenedicarboxylate.

2.2 Results and Discussion

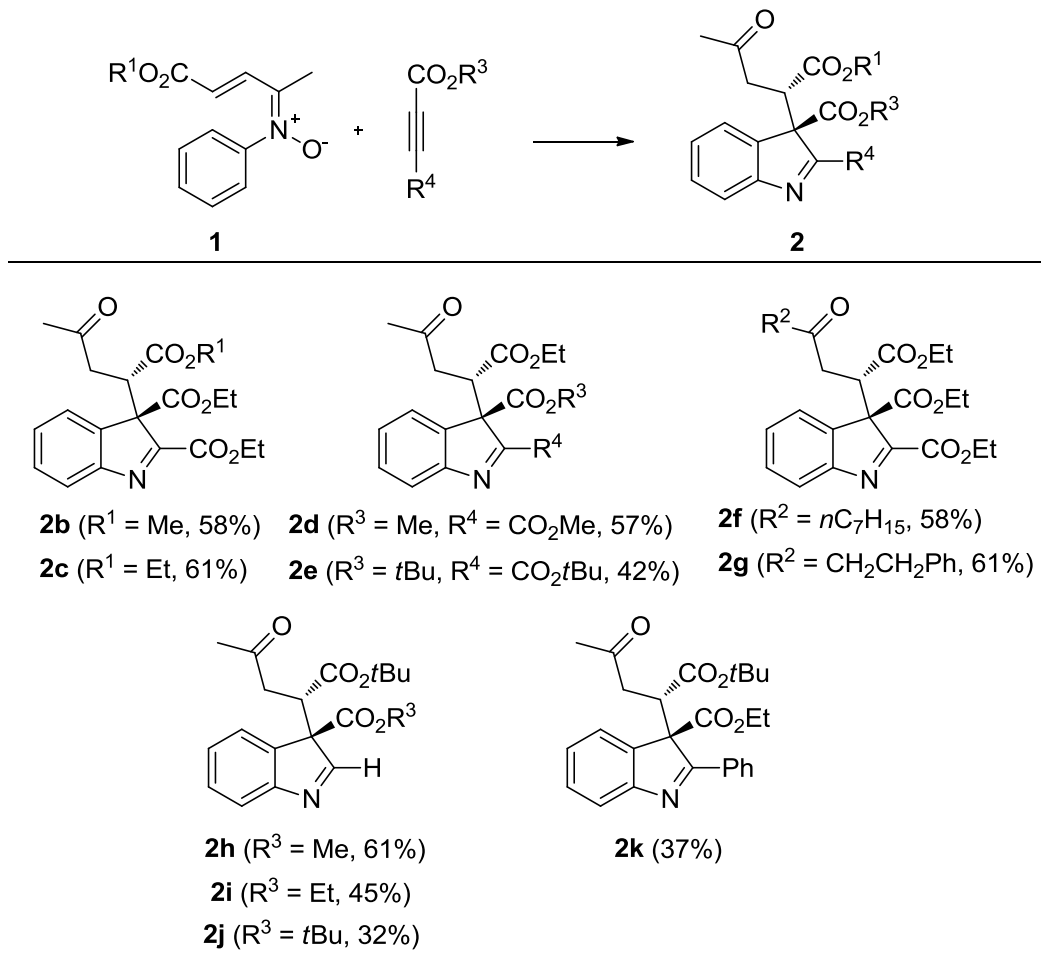
As this reaction displayed promise in the synthesis of indolenine precursors to indole-containing structures, optimization efforts were undertaken (Table 1).

Table 1. Optimization of C3-quaternary indolenine **2a** reaction conditions.

Entry	Solvent	T	Additive	Yield
1	CH_2Cl_2	RT	-	64
2	THF	RT	-	48
3	Ether	RT	-	21
4	DMF	RT	-	Trace
5	*i*PrOH	RT	-	Trace
6	Toluene	RT	-	68
7	Toluene	RT	HOAc	7
8	Toluene	RT	HOAc/H_2O	45
9	Toluene	RT	TFA	Trace
10	Toluene	RT	TfOH	15
11	Toluene	RT	$ZnCl_2$	Trace
12	Toluene	RT	$SnCl_4$	Trace
13	Toluene	RT	$FeCl_3$	Trace
14	Toluene	RT	$TiCl_4$	Trace
15	Toluene	40	-	73
16	Toluene	80	-	79

All of the reactions were carried out with 1 equiv of **1a**, 3 equiv of diethyl acetylenedicarboxylate, and 1.2 equiv of any additive if noted (0.2 equiv if HOAc). Using toluene as the solvent fared the best at room temperature (68% yield). Dichloromethane also proved to be an acceptable solvent giving **2a** in 64% yield. It was also determined that anhydrous toluene offered no advantage over undried toluene. The

reaction still progressed in ethereal solvents albeit with significantly decreased yield (entries 2 and 3). No significant quantity of product was observed in either DMF or isopropanol. Adding glacial acetic acid (entry 7) dramatically reduced the yield of **2a** to 7% while adding aqueous acetic acid (entry 8) only caused a drop to 45% yield. In both cases 0.2 equivalents of acetic acid were used, so the drastic difference between the two must be attributable to the addition of water. Though it is difficult to speculate this could be perhaps be due to the creation of a biphasic system, greatly reducing the amount of acetic acid available to interact with the reactants in the toluene phase. Conducting the reaction at a higher temperature (entries 15 and 16) in toluene also offered slightly improved yield; unless otherwise noted all subsequent reactions were conducted under the conditions listed in entry 16.

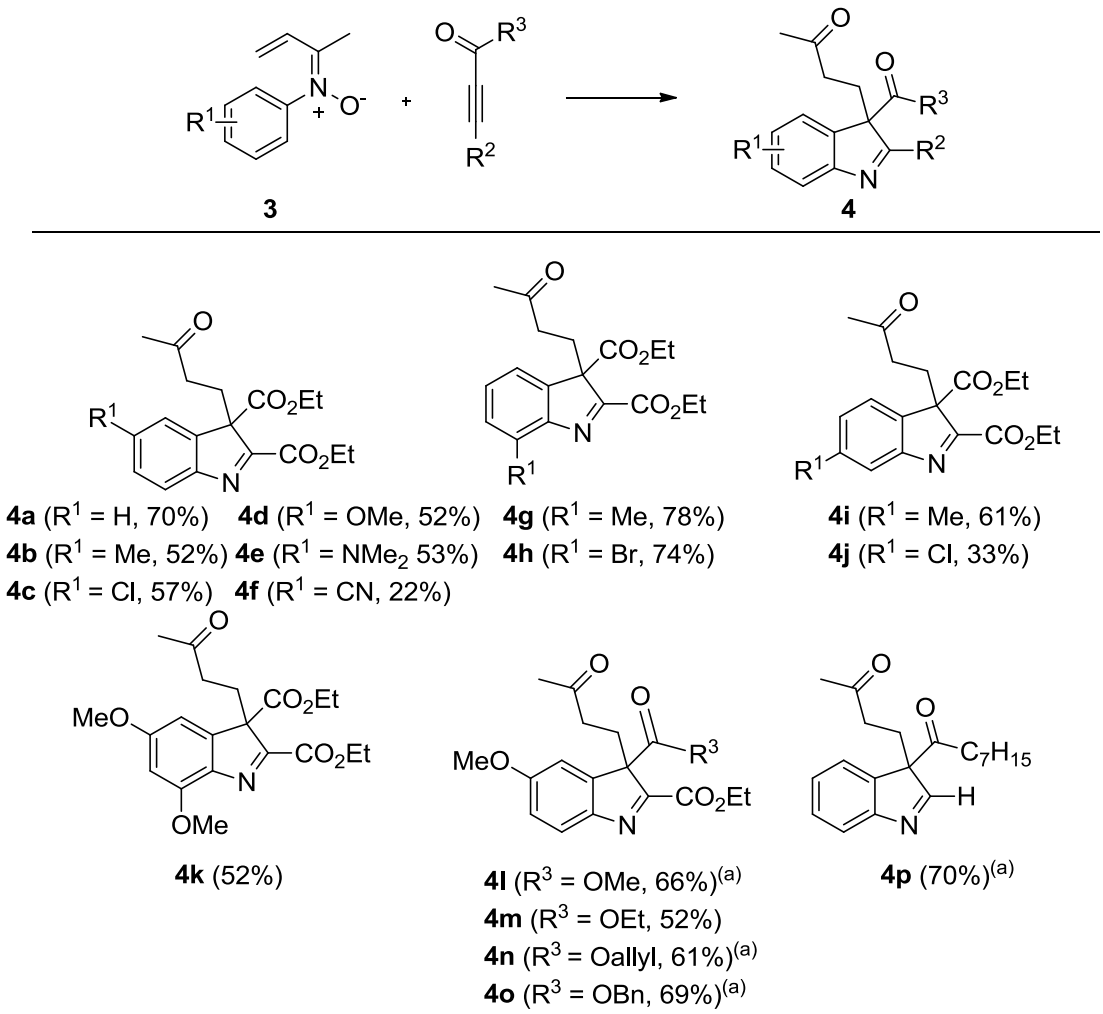


Scheme 10. Reaction of ketonitrones **1** with activated alkynes.

After optimizing the reaction, we then explored the scope of substrates (Scheme 10). The ketonitrone ester R-group was varied, and it was found that the *tert*-butyl ester provided a greater yield than the less bulky ethyl and methyl esters (**2a** vs. **2b** and **2c**). A variety of alkynes were tested. Unactivated alkynes, including phenylacetylene, diphenylacetylene and 6-dodecyne did not undergo the reaction at all. All other alkynes tested gave inferior yields when compared to the diethyl acetylene dicarboxylate used

initially. Monoactivated alkynes were found to undergo the reaction in moderate yields. Alkyl propiolates **2h**-**2j** display a strong trend of decreasing yield with increased steric bulk on the ester group; substituting a methyl group for a *tert*-butyl effectively cut the yield in half. Interestingly, this effect of steric bulk on the ester group of the activated alkyne is very much the opposite of that seen with the ketonitrone ester group. However, in an alkyne (**2e**) in which an alkyl group opposite the ester was increased in size as well, a less drastic drop in yield was observed (from **2d)**. This implies the increased steric bulk on the alkyne opposite the ester increases the reactivity of the alkyne. The same regioselectivity was still present with all substrates, and the reaction produced apparently only the *anti*- diastereomer. No isolable quantity of the other diastereomers was produced.

Next, in order to test the generality of the reaction with respect to the nitrone, we attempted to perform this reaction using *N*-aryl ketonitrones with a terminal alkene rather than the *β*-ester substituent (Scheme 11). We made these with the aforementioned convenient method developed by Bartoli[25] and coworkers in which nitrones are synthesized by the reaction of nitrobenzene and derivatives along with crotyl Grignard reagents.



Scheme 11. Reaction of ketonitrones **3** with activated alkynes. (a) These reactions were conducted at RT.

Nitrone group **3** reacted with diethyl acetylene dicarboxylate to form indolenine **4** in yields very much comparable to the nitrones tested previously. We varied the functionality on the aromatic ring to determine if it would have significantly impact the yield as well as assess the selectivity of the reaction with regard to substitutions on the ring. Using *meta*-tolyl ketonitrone gave only the 6-methyl indolenine; *ortho*- and *para*-

substitutions did not exhibit any unexpected effects and formed 5- and 7-methyl indolenines respectively. Although these substitutions generally resulted in yields of indolenine comparable to those lacking such substitutions, manipulating the identity of the substituent had quite a large impact on the reaction with yields ranging from 78% to 22% on otherwise similar substrate (**4g** versus **4f**). A wide variety of substituents were found to participate in the reaction, including alkoxy groups (**4l-4o**), methyl groups (**4b**, **4g** and **4i**), halides at 3' and 5' positions (**4c 4h** and **4j**), and an amine (**4e**). The least effective substrate was the *N*-phenyl ketonitrone containing a cyano group yielding indolenine **4f** with a cyano group at the *para* position. A quick test indicated that an indolenine (**4p**) is still produced when the only activating group on the alkyne is a ketone rather than an ester as used in all other examples.

2.3 Experimental

2.3.1 Synthetic Considerations

General experimental concerns

All non-aqueous reactions were carried out in flame-dried glassware under a N_2 atmosphere. Dichloromethane and diethyl ether were purified by passage through an activated molecular sieve solvent purification system. Tetrahydrofuran was freshly distilled over sodium and benzophenone. All other commercial reagents were used as received. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to $CDCl_3$ (7.26 ppm) or CD_3OD (4.57 ppm), coupling constants (*J*) are reported in Hertz (Hz), and multiplicity follows convention. Deuterochloroform ($CDCl_3$, 77.16 ppm) served as the internal standard for ^{13}C NMR spectra. Flash column chromatography was performed

using 60Å silica gel (Silicycle, 230-400 mesh) as the stationary phase. Mass spectra were obtained at the Center for Chemical Characterization and Analysis (Texas A&M University). Thin layer chromatography (TLC) was performed using pre-coated glass-backed TLC plates, Silica Gel 60 F254 (EMD, 250 μm thickness).

Synthesis of α,β-unsaturated *N*-aryl ketonitrones

The α,β-Unsaturated *N*-phenyl ketonitrones **1** were synthesized according to the procedure we previously described.[31] A solution of nitrosobenzene (51s mg, 0.48 mmol) in methanol (1 mL) was treated with acetic acid (14 mL, 0.24 mmol) and (((1Z,3Z)-1 (tert-butoxy)penta-1,3-dien-1-yl)oxy)(tert-butyl)dimethylsilane (54 mg, 0.20 mmol) at -78 °C. The reaction mixture was slowly allowed to room temperature over 2 h. The solvent was removed under vacuum and the residue was directly loaded onto a silica gel column for flash chromatography (petroleum ether/ethyl acetate ~ 2:1) to obtain **3** (33 mg, 64%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45 (s, 9H), 2.42 (s, 3H), 6.04 (d, J = 15.3 Hz, 1H), 7.24 (d, J = 15.3 Hz, 1H), 7.29-7.37 (m, 2H), 7.48-7.50 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.3, 28.0, 81.1, 122.7, 124.3, 129.5, 130.0, 134.3, 145.4, 146.0, 165.2; HRMS (ESI) calcd for $C_{15}H_{20}NO_3$ $(M+H)^+$ 262.1443, found 262.1437.

A general procedure for synthesis of α,β-unsaturated *N*-aryl ketonitrones 3

A solution of the nitroarene (0.16 M, 1 equiv.) in anhydrous THF was cooled to -78 ^{o}C and treated with a solution of crotylmagnesium chloride (1.6 M in THF, 1.1 equiv.) dropwise. The mixture was stirred at the same temperature for 15 min before the reaction was quenched with aq. NH_4Cl and extracted with diethyl ether (3x). The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced

pressure. The crude was purified by silica gel column chromatography (eluted with 100% ethyl acetate or 5% methanol in CH_2Cl_2) to give **3**.

A representative procedure for the synthesis of the C3-quaternary indolenines

A solution of the α,β-unsaturated *N*-aryl ketonitrone (0.2 M, 1 equiv.) and the activated alkyne (3 equiv.) in toluene was stirred at 80 ^oC until TLC indicated the reaction was complete. The homogenous solution was concentrated in vacuo and the residue was purified by silica gel column chromatography, eluted with hexanes–ethyl acetate, to give the C3-quaternary indolenines.

2.3.2 Spectral Data for New Compounds

Diethyl 3-(1-(tert-butoxy)-1,4-dioxopentan-2-yl)-*3H*-indole-2,3-dicarboxylate (2a)

Prepared according to the general procedure in 79% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.7 Hz, 1H), 7.54 – 7.35 (m, 3H), 4.58 – 4.36 (m, 2H), 4.23 (dd, J = 11.0, 2.6 Hz, 1H), 4.12 (dq, J = 10.8, 7.1 Hz, 1H), 3.95 (dq, J = 10.8, 7.1 Hz, 1H), 3.36 (dd, J = 17.5, 2.5 Hz, 1H), 3.13 (dd, J = 17.5, 11.0 Hz, 1H), 2.18 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H), 1.21 (s, 9H), 1.06 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, $CDCl_3$) δ 206.0, 169.6, 169.5, 167.9, 161.4, 154.5, 137.0, 130.0, 128.7, 123.9, 123.9, 82.3, 66.8, 62.4, 62.2, 44.0, 41.8, 30.1, 27.6, 14.4, 13.9. HRMS (ESI, m/z): $[M]^+$ calc.: 432.1083; found: 432.1090.

Diethyl 3-(1-methoxy-1,4-dioxopentan-2-yl)-*3H*-indole-2,3-dicarboxylate (2b)

Prepared according to the general procedure in 58% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.7 Hz, 1H), 7.55 – 7.35 (m, 3H), 4.46 (qd, J = 7.1, 1.7 Hz, 2H), 4.32 (dd, J = 10.9, 2.5 Hz, 1H), 4.21 – 3.91 (m, 4H), 3.54 (s, 3H), 3.01 (dd, J = 17.4,

11.0 Hz, 1H), 2.73 (dd, *J* = 17.5, 2.5 Hz, 1H), 2.10 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 171.1, 169.2, 167.7, 161.6, 153.9, 136.8, 130.2, 129.0, 123.9, 123.8, 67.0, 62.5, 62.4, 52.4, 43.6, 40.8, 30.1, 14.3, 13.8. HRMS (ESI, m/z): $[M]^+$ calc.: 390.1553; found: 390.1562.

Diethyl 3-(1-ethoxy-1,4-dioxopentan-2-yl)-*3H*-indole-2,3-dicarboxylate (2c)

Prepared according to the general procedure in 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.57 – 7.38 (m, 3H), 4.53 – 4.40 (m, 2H), 4.33 (dd, *J* = 10.8, 2.6 Hz, 1H), 4.23 – 4.07 (m, 2H), 4.07 – 3.89 (m, 2H), 3.05 (dd, *J* = 17.4, 10.8 Hz, 1H), 2.83 (dd, *J* = 17.5, 2.6 Hz, 1H), 2.12 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H), 1.12 (dt, *J* = 8.4, 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 170.6, 169.3, 167.8, 161.6, 154.1, 136.9, 130.2, 129.0, 124.0, 123.9, 67.1, 62.5, 62.3, 61.6, 43.64, 40.9, 30.1, 14.4, 13.9. HRMS (ESI, m/z): $[M]^+$ calc.: 404.1709; found: 404.1719.

Dimethyl 3-(1-ethoxy-1,4-dioxopentan-2-yl)-*3H*-indole-2,3-dicarboxylate (2d)

Prepared according to the general procedure in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.0 Hz, 1H), 7.56 – 7.37 (m, 3H), 4.32 (dd, *J* = 10.9, 2.6 Hz, 1H), 4.00 (s, 3H), 3.62 (s, 3H), 3.03 (dd, *J* = 17.4, 11.0 Hz, 1H), 2.73 (dd, *J* = 17.4, 2.5 Hz, 1H), 2.12 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); 13C NMR (75 MHz, $CDCl_3$) δ 205.7, 170.5, 168.7, 168.2, 161.9, 153.8, 136.7, 130.3, 129.2, 124.0, 123.9, 67.0, 61.6, 53.2, 53.2, 43.6, 40.6, 30.1, 13.8. HRMS (ESI, m/z): $[M]^+$ calc.: 376.1396; found: 376.1407.

Di-tert-butyl 3-(1-ethoxy-1,4-dioxopentan-2-yl)-*3H*-indole-2,3-dicarboxylate (2e)

Prepared according to the general procedure in 42% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.47 – 7.31 (m, 3H), 4.27 (dd, *J* = 11.0, 2.5 Hz,

1H), 4.00 – 3.78 (m, 2H), 3.33 (dd, *J* = 17.6, 2.5 Hz, 1H), 3.12 (dd, *J* = 17.6, 11.0 Hz, 1H), 2.15 (s, 3H), 1.63 (s, 9H), 1.23 (s, 9H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 *δ* 7.77 (m, 1H), 7.55-7.35 (m, 3MHz, $CDCl_3$) δ 206.1, 170.9, 170.7, 166.7, 160.1, 154.7, 137.2, 129.7, 128.3, 123.8, 123.4, 83.7, 82.8, 67.3, 61.4, 30.0, 28.1, 27.7, 13.9. HRMS (ESI, m/z): $[M]^+$ calc.: 460.2335; found: 460.2328.

Diethyl 3-(1-ethoxy-1,4-dioxoundecan-2-yl)-3*H*-indole-2,3-dicarboxylate (2f)

Prepared according to the general procedure in 70% yield. ^{1}H NMR (300MHz, $CDCl_3$) H), 4.55-3.90 (m, 7H), 3.00 (dd, *J* = 17.1, 10.5 Hz, 1H), 2.75 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.35 (m, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.35-1.17 (m, 10H), 1.13 (t, *J* = 6.9 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) *δ* 208.5, 170.9, 169.6, 168.0, 161.8, 154.2, 137.1, 130.3, 129.2, 124.1, 102.8 67.4, 62.7, 62.5, 61.8, 43.7, 43.1, 40.2, 32.0, 29.4, 29.3, 23.9, 22.9, 14.5, 14.4, 14.3, 14.0. HRMS (ESI, m/z): $[M+H]^+$ calc.: 460.2335; found: 460.2328.

Diethyl 3-(1-ethoxy-1,4-dioxo-6-phenylhexan-2-yl)-*3H*-indole-2,3-dicarboxylate (2g)

Prepared according to the general procedure in 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.75 (m, 1H), 7.52 – 7.34 (m, 3H), 7.29 – 7.10 (m, 5H), 4.53 – 4.40 (m, 2H), 4.36 (dd, *J* = 10.8, 2.7 Hz, 1H), 4.19 – 4.06 (m, 2H), 4.06 – 3.90 (m, 2H), 3.02 (dd, *J* = 17.3, 10.8 Hz, 1H), 2.88 – 2.76 (m, 2H), 2.76 – 2.64 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H), 1.12 (dt, *J* = 7.7, 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1, 170.6, 169.3, 167.7, 161.6, 154.0, 141.0, 136.9, 130.2, 129.0, 128.6, 128.6, 128.4, 126.2, 123.9, 123.9, 67.2, 62.5, 62.3, 61.6, 44.5, 43.6, 40.1, 29.6, 14.4, 13.9. HRMS (ESI, m/z): $[M]^+$ calc.: 494.2179; found: 494.2169.

Methyl 3-(1-(tert-butoxy)-1,4-dioxopentan-2-yl)-*3H*-indole-3-carboxylate (2h)

Prepared according to the general procedure in 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 4.11 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.68 (s, 3H), 2.35 (dd, *J* = 17.6, 8.3 Hz, 1H), 1.83 (s, 3H), 1.67 (dd, *J* = 17.6, 4.4 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 171.2, 171.1, 169.6, 155.4, 134.5, 129.9, 127.3, 123.7, 121.6, 82.7, 67.9, 53.1, 44.8, 39.5, 30.0, 28.0. HRMS (ESI, m/z): $[M]^+$ calc.: 346.1654; found: 346.1641.

Ethyl 3-(1-(tert-butoxy)-1,4-dioxopentan-2-yl)-*3H*-indole-3-carboxylate (2i)

Prepared according to the general procedure in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.31 – 7.22 (m, 1H), 4.21 – 4.02 (m, 3H), 2.34 (dd, *J* = 17.5, 8.4 Hz, 1H), 1.83 (s, 3H), 1.67 (dd, *J* = 17.6, 4.4 Hz, 1H), 1.46 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 171.4, 171.1, 168.9, 155.4, 134.6, 129.8, 127.2, 123.6, 121.6, 82.6, 68.0, 62.2, 44.7, 39.6, 30.0, 28.0, 14.0. HRMS (ESI, m/z): $[M]^+$ calc.: 360.1811; found: 360.1802.

tert-Butyl 3-(1-(tert-butoxy)-1,4-dioxopentan-2-yl)-*3H*-indole-3-carboxylate (2j)

Prepared according to the general procedure in 32% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.30 – 7.21 (m, 1H), 4.02 (dd, *J* = 8.3, 4.5 Hz, 1H), 2.32 (dd, *J* = 17.3, 8.3 Hz, 1H), 1.83 (s, 3H), 1.72 (dd, *J* = 17.4, 4.5 Hz, 1H), 1.45 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 172.0, 171.4, 167.7, 155.6, 135.0, 129.6, 127.0, 123.4, 121.5, 83.1, 82.5, 69.1, 44.8, 40.1, 30.0, 28.1, 27.9. HRMS (ESI, m/z): $[M]^+$ calc.: 388.2124; found: 388.2132.

Ethyl 3-(1-(tert-butoxy)-1,4-dioxopentan-2-yl)-2-phenyl-*3H*-indole-3-carboxylate (2k)

Prepared according to the general procedure in 37% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 – 8.06 (m, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.40 (m, 5H), 7.31 – 7.23 (m, 1H), 4.17 – 3.89 (m, 3H), 3.34 (dd, *J* = 17.5, 3.1 Hz, 1H), 3.16 (dd, *J* = 17.5, 10.3 Hz, 1H), 2.19 (s, 3H), 1.01 – 0.92 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 170.2, 169.2, 155.9, 137.6, 133.2, 131.0, 130.3, 129.7, 128.7, 128.6, 126.1, 123.3, 121.5, 81.6, 67.1, 62.2, 44.8, 42.3, 30.1, 27.3, 13.8. HRMS (MALDI, m/z): $[M]^+$ calc.: 436.2118; found: 436.2112.

(*E*)-*N*-(But-3-en-2-ylidene)aniline oxide (3a)

Prepared according to the general procedure in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.40 (m, 3H), 7.36 – 7.28 (m, 2H), 6.33 (dd, *J* = 17.1, 11.1 Hz, 1H), 5.51 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 11.1 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.9, 129.6, 129.5, 124.4, 123.6, 118.5, 12.8. HRMS (ESI, m/z): $[M]^+$ calc.: 162.0919; found: 162.0914.

(*E*)-*N*-(But-3-en-2-ylidene)-4-methylaniline oxide (3b)

Prepared according to the general procedure in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.17 (m, 4H), 6.36 (dd, *J* = 17.1, 11.1 Hz, 1H), 5.49 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 11.2 Hz, 1H), 2.39 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 130.0, 130.0, 124.2, 123.4, 118.1, 21.3, 12.8. HRMS (ESI, m/z): $[M]^+$ calc.: 176.1075; found: 176.1071.

(*E*)-*N*-(But-3-en-2-ylidene)-4-chloroaniline oxide (3c)

Prepared according to the general procedure in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.33 (dd, *J* = 17.1, 11.1 Hz, 1H), 5.54 (d, *J* = 17.1 Hz, 1H), 5.27 (d, *J* = 11.1 Hz, 1H), 2.39 (s, 3H); $_{13}$C NMR (75 MHz, $CDCl_3$) δ 135.4, 129.7, 129.5, 125.8, 125.1, 119.1, 12.8. HRMS (ESI, m/z): $[M]^+$ calc.: 196.0529; found: 196.0537.

(*E*)-*N*-(But-3-en-2-ylidene)-4-methoxyaniline oxide (3d)

Prepared according to the general procedure in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.38 (dd, *J* = 17.2, 11.1 Hz, 1H), 5.49 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 11.1 Hz, 1H), 3.83 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.1, 125.7, 118.1, 114.5, 55.7, 12.9. HRMS (ESI, m/z): $[M]^+$ calc.: 192.1025; found: 192.1028.

(*E*)-*N*-(But-3-en-2-ylidene)-4-(dimethylamino)aniline oxide (3e)

Prepared according to the general procedure in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 9.1 Hz, 2H), 6.67 (d, *J* = 9.1 Hz, 2H), 6.46 (dd, *J* = 17.2, 11.1 Hz, 1H), 5.45 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 11.1 Hz, 1H), 2.99 (s, 6H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.6, 125.3, 117.3, 111.8, 40.6, 13.1. HRMS (ESI, m/z): [M]+ calc.: 205.1341; found: 205.1333.

(*E*)-*N*-(But-3-en-2-ylidene)-4-cyanoaniline oxide (3f)

Prepared according to the general procedure in 20% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 6.20 (dd, *J* = 17.0, 11.1 Hz, 1H), 5.56 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 11.1 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 133.53, 128.68, 125.36, 120.23, 117.49, 113.46, 12.68. HRMS (ESI, m/z): $[M]^+$ calc.: 187.0871; found: 187.0876.

(*E*)-*N*-(But-3-en-2-ylidene)-2-methylaniline oxide (3g)

Prepared according to the general procedure in 70% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.15 (m, 4H), 6.15 (dd, *J* = 17.1, 11.1 Hz, 1H), 5.52 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 11.1 Hz, 1H), 2.41 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 131.5, 129.4, 129.2, 127.2, 124.2, 118.8, 16.7, 12.1. HRMS (ESI, m/z): $[M]^+$ calc.: 176.1075; found: 176.1071.

(*E*)-2-Bromo-*N*-(but-3-en-2-ylidene)aniline oxide (3h)

Prepared according to the general procedure in 67% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.46 – 7.27 (m, 3H), 6.11 (dd, *J* = 17.0, 11.1 Hz, 1H), 5.57 (d, *J* = 17.0 Hz, 1H), 5.28 (d, *J* = 11.1 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.9, 130.6, 128.9, 128.8, 126.1, 119.6, 117.5, 12.1. HRMS (ESI, m/z): $[M]^+$ calc.: 240.0024; found: 240.0021.

(*E*)-*N*-(But-3-en-2-ylidene)-3-methylaniline oxide (3i)

Prepared according to the general procedure in 70% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.07 (m, 3H), 6.35 (dd, *J* = 17.0, 11.2 Hz, 1H), 5.50 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 11.1 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.2, 130.0, 129.3, 124.9, 121.4, 118.3, 21.4, 12.7. HRMS (ESI, m/z): $[M]^+$ calc.: 176.1075; found: 176.1068.

(*E*)-*N*-(But-3-en-2-ylidene)-3-chloroaniline oxide (3j)

Prepared according to the general procedure in 48% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 3H), 7.24 – 7.19 (m,1H), 6.31 (dd, *J* = 17.1, 11.1 Hz, 1H), 5.54 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 11.1 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl^3$) δ 130.6, 129.8, 129.4, 124.9, 122.6, 119.3, 12.8. HRMS (ESI, m/z): $[M]^+$ calc.: 196.0529; found: 196.0532.

(*E*)-*N*-(But-3-en-2-ylidene)-2,4-dimethoxyaniline oxide (3k)

Prepared according to the general procedure in 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 9.5 Hz, 1H), 6.56 – 6.48 (m, 2H), 6.23 (dd, *J* = 17.2, 11.1 Hz, 1H), 5.48 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 11.2 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 153.0, 129.9, 126.4, 118.2, 104.8, 99.7, 56.1, 55.8, 12.4. HRMS (ESI, m/z): $[M]^+$ calc.: 222.1130; found: 222.1132.

Diethyl 3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4a)

Prepared according to the general procedure in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.50 – 7.36 (m, 3H), 4.44 (qd, *J* = 14.2, 7.1, 1.8 Hz, 2H), 4.14 (ddd, *J* = 17.9, 9.0, 5.3 Hz, 1H), 3.95 (dq, *J* = 14.2, 10.8, 7.1 Hz, 1H), 2.90 – 2.67 (m, 2H), 1.86 (s, 3H), 1.97 – 1.64 (m, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 170.0, 168.7, 161.4, 154.0, 138.5, 129.8, 129.2, 123.7, 122.7, 66.6, 62.4, 62.0, 37.1, 29.9, 27.0, 14.3, 13.9. HRMS (ESI, m/z): $[M]^+$ calc.: 332.1498; found: 332.1504.

Diethyl 5-methyl-3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4b)

Prepared according to the general procedure in 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.16 (m, 2H), 4.44 (qd, *J* = 7.1, 2.2 Hz, 2H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.95 (dq, *J* = 10.7, 7.1 Hz, 1H), 2.90 – 2.65 (m, 2H), 2.42 (s, 3H), 1.97 – 1.83 (m, 1H), 1.89 (s, 3H), 1.78 – 1.67 (m, 1H), 1.42 (t, *J* = 7.1Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 169.0, 169.0, 161.6, 151.9, 139.9, 138.7, 130.6, 123.4, 123.3, 66.3, 62.3, 62.0, 37.2, 30.0, 27.1, 21.9, 14.4, 14.0. HRMS (ESI, m/z): $[M]^+$ calc.: 346.1655; found: 346.1653.

Diethyl 5-chloro-3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4c)

Prepared according to the general procedure in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 1H), 7.49 – 7.37 (m, 2H), 4.45 (dq, *J* = 14.2, 7.1, 1.6 Hz, 2H), 4.18 (dq, *J* = 14.2, 10.8, 7.1 Hz, 1H), 3.98 (dq, *J* = 14.1, 10.6, 7.0 Hz, 1H), 2.92 – 2.63 (m, 2H), 1.92 (s, 3H), 1.98 – 1.77 (m, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 168.1, 161.2, 152.5, 140.2, 135.4, 130.2, 124.6, 123.3, 66.9, 62.6, 62.4, 37.1, 29.9, 27.1, 14.3, 13.9. HRMS (ESI, m/z): $[M]^+$ calc.: 366.1108; found: 366.1097.

Diethyl 5-methoxy-3-(3-oxobutyl)-3H-indole-2,3-dicarboxylate dicarboxylate (4d)

Prepared according to the general procedure in 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.5 Hz, 1H), 7.00 – 6.89 (m, 2H), 4.43 (dq, *J* = 7.1, 2.3 Hz, 2H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.96 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.84 (s, 3H), 2.84 (ddd, *J* = 14.2, 9.7, 6.1 Hz, 1H), 2.75 – 2.63 (m, 1H), 1.97 – 1.84 (m, 1H), 1.89 (s, 3H), 1.72 (ddd, *J* = 17.8, 9.7, 5.3 Hz, 1H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 206.8, 168.9, 167.6, 161.5, 161.1, 147.5, 140.6, 124.6, 115.4, 108.3, 66.5, 62.2, 62.1, 56.0, 37.1, 30.0, 27.3, 14.4, 14.0. HRMS (ESI, m/z): $[M]^+$ calc.: 362.1604; found: 362.1607.

Diethyl 5-(dimethylamino)-3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4e)

Prepared according to the general procedure in 53% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.7 Hz, 1H), 6.71 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 4.42 (qd, *J* = 7.1, 2.7 Hz, 2H), 4.19 (dq, *J* = 14.2, 10.8, 7.1 Hz, 1H), 3.94 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.04 (s, 6H), 2.83 (ddd, *J* = 14.1, 10.3, 5.8 Hz, 1H), 2.75 – 2.61 (m, 1H), 2.02 – 1.85 (m, 1H), 1.90 (s, 3H), 1.77 – 1.62 (m, 1H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 169.6, 164.0, 161.7, 151.4, 143.8, 141.1, 124.4, 112.4, 105.5, 65.9, 61.8, 61.8, 40.7, 37.1, 30.0, 27.6, 14.4, 14.0. HRMS (ESI, m/z): $[M]^+$ calc.: 375.1920; found: 375.1911.

Diethyl 5-cyano-3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4f)

Prepared according to the general procedure in 22% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.80 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.71 (d, *J* = 0.9 Hz, 1H), 4.49 (qd, *J* = 7.1, 0.9 Hz, 2H), 4.19 (dq, *J* = 14.2, 10.8, 7.1 Hz, 1H), 4.01 (dq, *J* = 14.2, 10.8, 7.1 Hz, 1H), 2.96 – 2.83 (m, 1H), 2.80 – 2.67 (m, 1H), 1.94 (s, 3H), 1.95 – 1.84 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); HRMS (ESI, m/z): $[M]^+$ calc.: 357.1450; found: 357.1442.

Diethyl 7-methyl-3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4g)

Prepared according to the general procedure in 78% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 3H), 4.46 (qd, *J* = 7.1, 0.9 Hz, 2H), 4.15 (dq, *J* = 10.8, 7.1 Hz,

1H), 3.95 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.89 – 2.68 (m, 2H), 2.67 (s, 1H), 1.89 (s, 1H), 1.96 – 1.82 (m, 1H), 1.79 – 1.65 (m, 1H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 169.0, 168.8, 161.6, 152.9, 138.5, 134.0, 131.2, 129.2, 120.0, 66.7, 62.4, 62.0, 37.2, 30.0, 27.1, 17.2, 14.3, 14.0. HRMS (ESI, m/z): $[M]^+$ calc.: 346.1655; found: 346.1646.

Diethyl 7-bromo-3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4h)

Prepared according to the general procedure in 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.38 – 7.21 (m, 2H), 4.45 (qd, *J* = 7.1, 1.7 Hz, 2H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.96 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.92 – 2.64 (m, 2H), 2.02 – 1.85 (m, 1H), 1.90 (s, 3H), 1.71 (ddd, *J* = 17.9, 9.7, 5.3 Hz, 1H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 170.9, 168.2, 161.3, 152.6, 140.0, 133.5, 130.4, 121.7, 117.7, 68.3, 62.6, 62.4, 37.0, 30.0, 27.2, 14.3, 13.9. HRMS (ESI, m/z): $[M]^+$ calc.: 410.0603; found: 410.0609.

Diethyl 6-methyl-3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4i)

Prepared according to the general procedure in 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.32 – 7.17 (m, 2H), 4.46 (dq, *J* = 7.1, 1.8 Hz, 2H), 4.15 (dq, *J* = 14.2, 10.8, 7.1 Hz, 1H), 3.95 (dq, 1H), 2.88 – 2.66 (m, 2H), 2.44 (s, 3H), 1.89 (s, 3H), 1.97 – 1.82 (m, 1H), 1.82 – 1.66 (m, 1H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 170.1, 168.9, 161.4, 154.3, 140.1, 135.5, 130.0, 124.3, 122.2, 66.2, 62.3, 61.9, 37.11, 29.9, 26.9, 21.7, 14.3, 13.9. HRMS (ESI, m/z): $[M]^+$ calc.: 352.1736; found: 352.1745.

Diethyl 6-chloro-3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4j)

Prepared according to the general procedure in 33% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 1.8, 0.5 Hz, 1H), 7.42 – 7.31 (m, 2H), 4.47 (qd, 2H), 4.16 (dq, *J* = 14.2, 10.7, 7.1 Hz, 1H), 3.98 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.92 – 2.67 (m, 2H), 1.91 (s, 3H), 1.98 – 1.75 (m, 2H), 1.44 (t, *J* = 7.1, 2.5 Hz, 3H), 1.11 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.31, 168.09, 161.05, 160.31, 154.98, 136.62, 135.45, 129.10, 123.90, 123.38, 66.47, 62.50, 62.18, 36.94, 29.80, 26.73, 14.15, 13.77. HRMS (ESI, m/z): $[M]^+$ calc.: 366.1108; found: 366.1104.

Diethyl 5,7-dimethoxy-3-(3-oxobutyl)-*3H*-indole-2,3-dicarboxylate (4k)

Prepared according to the general procedure in 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 6H), 4.45 – 4.32 (dq, 2H), 4.22 – 4.08 (dq, 1H), 3.96 (s, 3H), 4.01 – 3.88 (dq, 1H), 3.83 (s, 3H), 2.82 (ddd, *J* = 14.3, 10.4, 5.7 Hz, 1H), 2.71 – 2.57 (m, 1H), 1.99 – 1.83 (m, 1H), 1.90 (s, 3H), 1.75 – 1.60 (m, 1H), 1.37 (td, *J* = 7.1Hz, 3H), 1.07 (t, *J* = 7.1Hz, 3H). HRMS (ESI, m/z): $[M]^+$ calc.: 392.1709; found: 392.1717.

Methyl 5-methoxy-3-(3-oxobutyl)-*3H*-indole-3-carboxylate (4l)

Prepared according to the general procedure in 66% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.84 (s, 3H), 3.69 (s, 3H), 2.56 (ddd, *J* = 14.0, 9.3, 6.1 Hz, 1H), 2.46 – 2.32 (m, 1H), 2.21 – 2.01 (m, 2H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 170.1, 169.4, 159.3, 148.9, 137.8, 122.0, 114.3, 109.8, 66.9, 56.0, 53.1, 37.8, 30.1, 27.7. HRMS (ESI, m/z): $[M]^+$ calc.: 276.1236; found: 276.1241.

Ethyl 5-methoxy-3-(3-oxobutyl)-*3H*-indole-3-carboxylate (4m)

Prepared according to the general procedure in 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.25 – 4.02 (m, 2H), 3.82 (s, 3H), 2.54 (ddd, *J* = 14.1, 9.3, 6.1 Hz, 1H), 2.46 – 2.29 (m, 1H), 2.14 – 2.00 (m, 2H), 1.97 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 169.5, 169.4, 159.1, 148.7, 137.7, 121.7, 114.1, 109.7, 66.8, 62.0, 55.8, 37.6, 29.9, 27.6, 14.0. HRMS (ESI, m/z): $[M]^+$ calc.: 290.1393; found: 290.1397.

Allyl 5-methoxy-3-(3-oxobutyl)-3H-indole-3-carboxylate (4n)

Prepared according to the general procedure in 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.83 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.30 – 5.16 (m, 2H), 4.67 – 4.49 (m, 2H), 3.84 (s, 3H), 2.58 (ddd, *J* = 14.1, 9.4, 6.1 Hz, 1H), 2.49 – 2.32 (m, 1H), 2.15 – 2.01 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 169.3, 169.2, 159.3, 148.9, 137.7, 131.3, 122.0, 119.0, 114.4, 109.8, 66.9, 66.5, 55.9, 37.7, 30.1, 27.7. HRMS (ESI, m/z): $[M]^+$ calc.: 302.1392; found: 302.1386.

Benzyl 5-methoxy-3-(3-oxobutyl)-*3H*-indole-3-carboxylate (4o)

Prepared according to the general procedure in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.38 – 7.29 (m, 3H), 7.27 – 7.20 (m, 2H), 7.01 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.12 (q, *J* = 12.3 Hz, 2H), 3.81 (s, 3H), 2.56 (ddd, *J* = 14.0, 9.4, 6.0 Hz, 1H), 2.47 – 2.31 (m, 1H), 2.12 – 1.99 (m, 2H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 169.3, 159.3, 135.2, 128.7,

128.6, 128.2, 122.0, 114.6, 109.6, 67.6, 55.9, 37.7, 30.1, 27.7. HRMS (ESI, m/z): $[M]^+$ calc.: 352.1549; found: 352.1556.

1-(5-methoxy-3-(3-oxobutyl)-3H-indol-3-yl)octan-1-one (4p)

Prepared according to the general procedure in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 6.97 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.83 (d, *J* = 2.5 Hz, 1H), 3.83 (s, 3H), 2.64 – 2.50 (m, 1H), 2.44 – 2.30 (m, 1H), 2.06 – 1.88 (m, 7H), 1.38 (dt, *J* = 14.3, 7.2 Hz, 2H), 1.30 – 0.94 (m, 8H), 0.82 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 203.8, 169.5, 159.5, 150.3, 138.4, 122.4, 114.7, 109.0, 75.2, 55.9, 39.4, 37.8, 31.7, 30.1, 29.0, 28.9, 24.8, 23.7, 22.7, 14.2. HRMS (ESI, m/z): $[M]^+$ calc.: 344.2226; found: 344.2234.

2.3.3 Synthetic Procedures and Spectral Data for 5, 6, and 7

Methyl 5-methoxy-2-oxo-3-(3-oxobutyl)indoline-3-carboxylate (5)

A mixture of **4l** (210 mg, 0.76 mmol) and $NaHCO_3$ (64 mg, 0.76 mmol) in methylene chloride (10 mL) was treated with mCPBA (70%, 376 mg, 1.53 mmol) and stirred at room temperature until the reaction was complete as shown by TLC. The mixture was taken into ethyl acetate and washed with aq. $NaHSO_3$, $Na2CO_3$, and brine. The organic phase was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography, eluted with hexanes-ethyl acetate (1:3), to give **5** (148 mg, 67%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (s, 1H), 6.97 – 6.67 (m, 3H), 3.76 (s, 3H), 3.69 (s, 3H), 2.59 – 2.23 (m, 4H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 176.5, 169.5, 156.3, 134.5, 129.5, 114.3,

111.0, 110.6, 59.1, 55.9, 53.3, 37.81, 30.0, 28.1. HRMS (ESI, m/z): $[M]^+$ calc.: 298.1267; found: 298.1263.

Methyl 5-methoxy-3-(3-oxobutyl)indoline-3-carboxylate (6)

A solution of **4l** (38 mg, 0.14 mmol) and trifluoroacetic acid (27.6 μL, 41 mg, 0.36 mmol) in dichloromethane (1.5 mL) was treated with the Hantzsch ester (35 mg, 0.14 mmol) and stirred in the dark at room temperature overnight. After dilution with diethyl ether, the mixture was washed with aq. Na2CO3 and dried over anhydrous $MgSO_4$ before it was filtered and concentrated. The residue was purified by silica gel column chromatography eluting with hexanes-ethyl acetate (1:3) to give **6** (29 mg, 76%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, *J* = 2.5 Hz, 1H), 6.68 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 4.08 (d, *J* = 9.9 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.37 (d, *J* = 9.9 Hz, 1H), 2.53 – 2.18 (m, 4H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 174.1, 153.8, 144.7, 131.1, 114.5, 111.5, 111.2, 56.2, 56.1, 55.2, 52.6, 39.1, 31.6, 30.1. HRMS (ESI, m/z): $[M]^+$ calc.: 278.1392; found: 278.1384.

Ethyl 5-methoxy-1*H*-indole-3-carboxylate (7)

A solution of **4m** (50 mg, 0.17 mmol) in toluene (1 mL) was treated with pyrrolidine (28.9 mL, 24.4 mg, 0.34 mmol) and stirred at room temperature until the reaction was complete as shown by TLC. The residue was purified by silica gel column chromatography eluting with hexanes-ethyl acetate (1:3) to give **7** (38.3 mg, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (bs, 1H), 7.86 (d, *J* = 3.1 Hz, 1H), 7.68 (d, *J* = 2.5 Hz, 1H), 7.29 (dd, *J* = 8.8, 0.5 Hz, 1H), 6.94 – 6.88 (m, 1H), 4.39 (q, *J* = 7.1

Hz, 2H), 3.88 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 155.9, 131.4, 131.1, 126.9, 113.7, 112.5, 108.7, 102.9, 59.9, 55.8, 14.7.

CHAPTER III

A MODULAR APPROACH TO α,β-UNSATURATED *N*-ARYL KETONITRONES

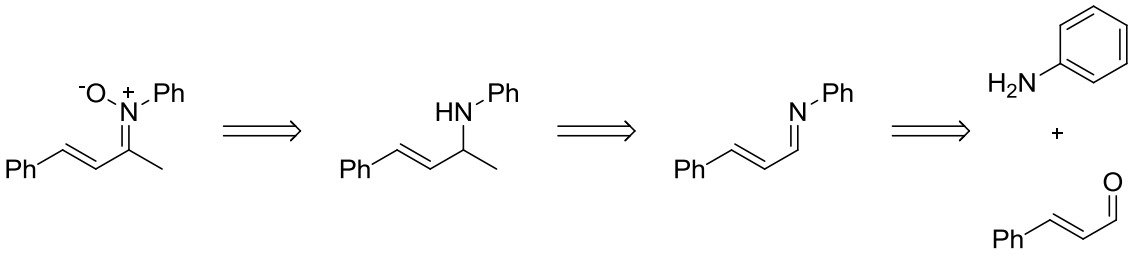
3.1 Introduction

Considering the starting materials, the indolenine synthesis described in the previous chapter builds considerable complexity with a high degree of selectivity in a single step. However, the ultimate utility of the reaction was limited somewhat by the difficulty in accessing the nitrones. The nitrones were synthesized using methods that ranged from inefficient with regard to steps or yield or both to unsuccessful outright. Furthermore, it was difficult to ascertain the purity and stability of the nitrone even after multiple purifications. This issue was partly alleviated by application of the Bartoli method as described above,[25] which provided straightforward access to nitrones with varying substitutions on the phenyl ring. Unfortunately, this reaction would not work with more complex crotyl Grignard reagents. It became clear that it was necessary to develop a more streamlined approach[34] to this class of nitrone to expand the scope of our study.

3.2 Synthetic Strategy Development

In designing our own approach to α,β-unsaturated *N*-aryl ketonitrones, we decided that the oxidation of secondary amines to the nitrones would be effective and general with regard to the substrate. Accessing the secondary amines required for our study, from commercially available materials, would be facile (Scheme 12). Thus, a straightforward approach to the secondary amine oxidation substrate was devised. It was envisioned that

the amine could be obtained from the alkylation of an imine, specifically an aldimine. The aldimine could, in turn, be accessed easily from a dehydration reaction between an aniline derivative and an α,β-unsaturated aldehyde. A wide variety of both starting materials was readily available, so for all substrates the imine synthesis would be the synthetic starting point.



Scheme 12. Retrosynthetic analysis from Nitrone.

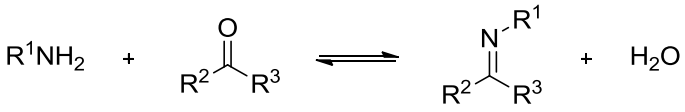
After examining the literature, a relevant oxidation method developed by Busqué and Figueredo[35] was found. It has been reported that Oxone® can be utilized to oxidize secondary amines to nitrones in good yield. Oxone®, or potassium peroxymonosulfate, is a commercially available oxidant that is both inexpensive and relatively stable. Many similar procedures use hydrogen peroxide as the oxidant and rely on metal catalysts such as selenium (IV) oxide[18] or sodium tungstate,[4] and others use oxidants such as DMDO[20] that are not commercially available.

3.3 Results and Discussion

The first issue we anticipated encountering was poor or incorrect regioselectivity during the alkylation of the imine. We anticipated that a hard nucleophile would favor

1,2-addition rather than 1,4-addition. A study by Pace[36] suggested that an additive such as LiBr was necessary for 1,2-addition to occur while a conflicting study by Tomioka[37] found that no such additive was necessary to attain 1,2-addition for certain imines. We found that no additive was necessary; no 1,4-addition product was ever observed in our experiments.

The synthesis of the imines was far less of a concern initially; the majority of the substrates we sought to synthesize were known, some as far back as Schiff's initial paper[38] regarding imines. As a class of molecules that has been known for nearly 150 years as of this writing, there are many different ways to synthesize imines. A general condensation reaction between an amine and carbonyl compound to synthesize an imine is shown below in Scheme 13.

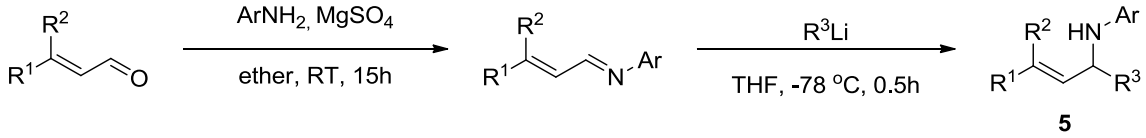


Scheme 13. General formation of an imine.

This scheme shows that the formation of the imine is reversible; a driving force must be imposed in order to push the reaction to completion. Water must be removed from the reaction by physical or chemical means. Physical removal of water is typically accomplished through azeotropic distillation, which imposes some important limitations. For one, obviously the boiling point of the solvent must be well below that of the reactants otherwise they will be lost. Several of the lower molecular weight aldehydes

that were to be used did not permit this approach, and less volatile aldehydes yielded unsatisfactory conversion and purity.

Removing water from the reaction mixture using a desiccant (anhydrous magnesium sulfate) provided a much more appealing solution. The desiccant could then be filtered off and the solution concentrated to provide the imine. This approach was adapted for synthesizing all of our substrates, with a few slight variations in order to obtain the purest material possible for the subsequent alkylation step without conducting a discrete purification step to streamline the process. The reaction sequence up into the secondary amine is shown in Scheme 14.



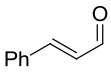
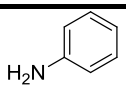
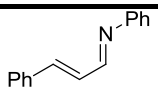
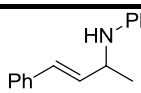
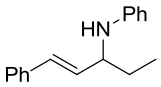
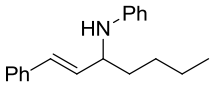
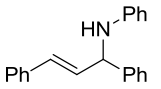
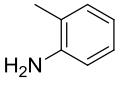
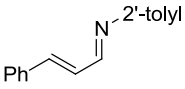
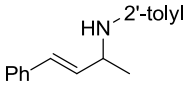
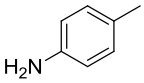
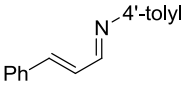
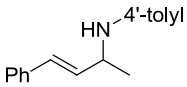
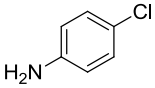
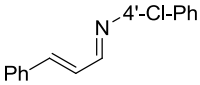
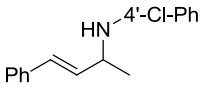
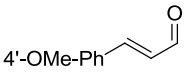
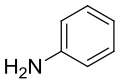
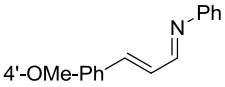
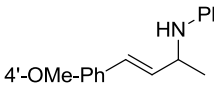
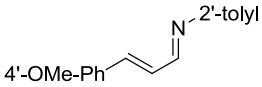
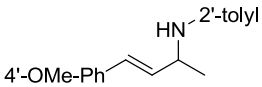
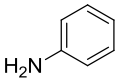
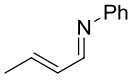
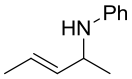
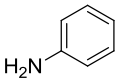
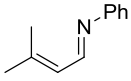
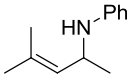
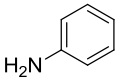
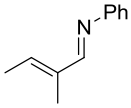
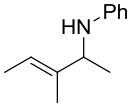
Scheme 14. Synthesis of **5**.

The results for the imine synthesis and subsequent alkylation step are shown in Table 2, with the combined yields for both steps listed. Filtration through silica gel was employed to simultaneously remove the spent desiccant and any unreacted aniline. Any imines synthesized from cinnamaldehyde and its derivatives (entries 1-9) could be isolated spectroscopically pure and in high yield by partially concentrating the filtrate and crystallizing them out of that concentrate. Excess aniline derivative was used in this case in order to minimize any aldehyde remaining after filtration.

Imines synthesized from non-aromatic aldehydes generally (entries 10-12) remained too soluble for this method to be applicable. Fortunately, any aldehyde remaining after filtration and concentration of the filtrate could be easily removed by co-evaporation with a high boiling solvent such as toluene. Excess aldehyde was used to force more complete conversion of the aniline derivative.

As imine formation is reversible, one can reasonably expect some degree of instability due to hydrolysis. It appeared to be the case that the unsaturated imines conjugated with an aromatic ring (i.e. those made from cinnamaldehyde derivatives) were mostly stable on the shelf in a sealed container. Those formed from enals lacking a phenyl group α- to the alkene, on the other hand, appeared to be less stable. These compounds were stored under nitrogen at -20 °C and were used as soon as possible; no discernible decomposition had occurred between isolation and alkylation by ^{1}H NMR under these storage conditions.

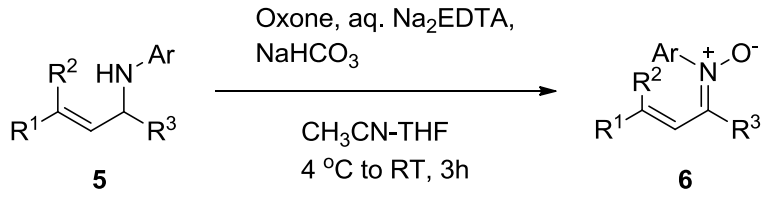
Table 2. Results for Imine synthesis and subsequent alkylation step.

Entry	Aldehyde	Aniline Derivative	Imine	Alkylating Agent	*N*-Allylideneaniline **5**	Yield
1				MeLi		**5a** (79%)
2				EtLi		**5b** (78%)
3				BuLi		**5c** (71%)
4				PhLi		**5d** (88%)
5				MeLi		**5e** (91%)
6				MeLi		**5f** (44%)
7				MeLi		**5g** (64%)
8				MeLi		**5h** (74%)
9				MeLi		**5i** (73%)
10				MeLi		**5j** (83%)
11				MeLi		**5k** (89%)
12				MeLi		**5l** (75%)

These imines were then alkylated with an organolithium reagent, also detailed above. These are shown in Table 2 as well; the yields given are the combined yields for the imine synthesis and subsequent alkylation step, which proceeded quantitatively in essentially all cases. The imine synthesis was a robust procedure, but nonetheless operationally sensitive due to the variation in substrate solubility and polarity. Some imines displayed diminished yield as a result of low solubility. During filtration, the less soluble imines were susceptible to loss along with the desiccant unless large quantities of solvent were used. The streamlined nature of the imine isolation procedure necessitates somewhat of a balancing act between isolating all of the product and obtaining the purest material possible.

The imine preparation and alkylation did not appear to be particularly sensitive to the aldehyde used; the lower molecular weight aldehydes (entries 10-12) lacking the phenyl functionality underwent the condensation to the imine and then alkylation to the *N*-allylideneaniline in very much comparable yields to the other substrates. However, while imines prepared from these substrates did not appear to be susceptible to loss during filtration, they were indeed much more difficult to obtain at the same level of purity as those containing the phenyl moiety.

The *N*-allylideneaniline substrates were then subject to oxidation by oxone (Scheme 15). A mixed solvent system of acetonitrile and THF was used, with disodium EDTA added as an aqueous solution. Sodium bicarbonate was then added at 4 °C. After the reaction was allowed to warm up to room temperature, the Oxone was added portionwise until the reaction was judged to be complete by TLC.



Scheme 15. Oxidation of *N*-allylideneaniline to the α,β-unsaturated *N*-aryl ketonitrone.

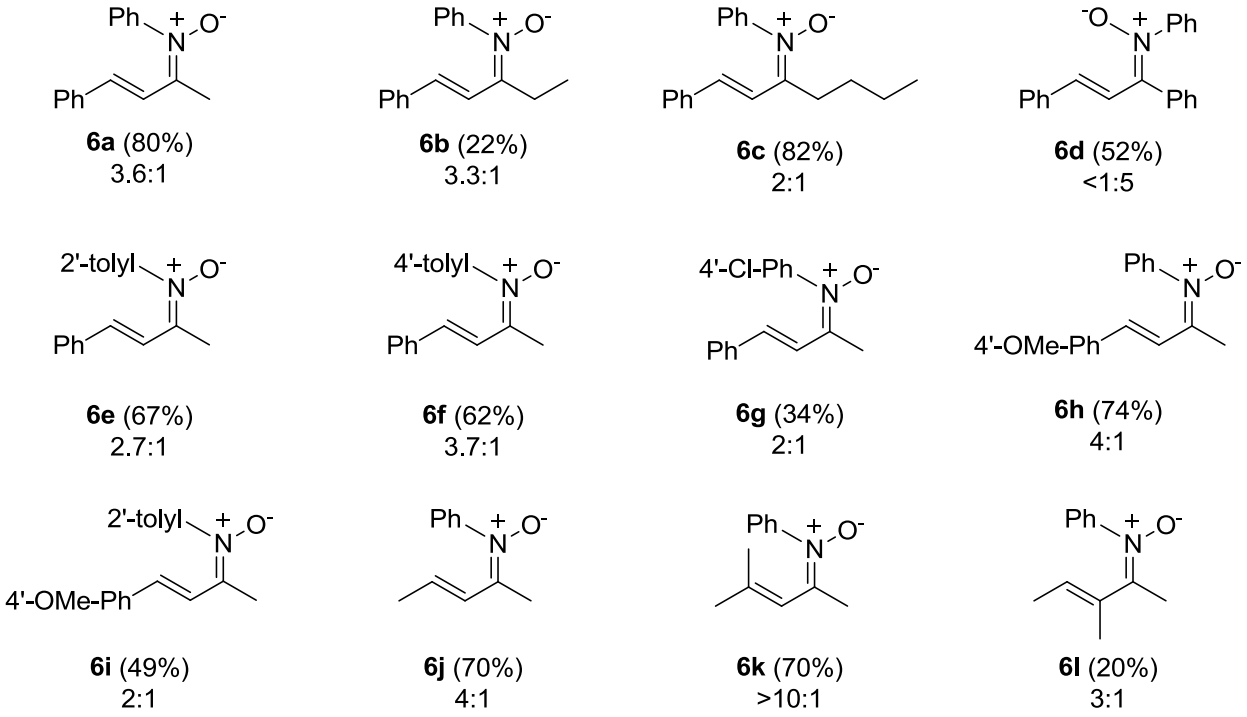


Figure 3. α,β-unsaturated *N*-aryl ketonitrones obtained using modular approach. Yields listed are isolated and ratios given are *E*:*Z*. Yields and ratios for **6j** and **6k** are estimated based on ^{1}H NMR spectra.

Our modular approach proved to be general with regard to the oxidation step as well, though yields varied from adequate to good depending on the substrate (Figure 3). Nitrones **6j-l** decomposed heavily during purification, so the yields and *E*:*Z* ratios were estimated from the crude ^{1}H NMR spectra. Oddly, **6b** was obtained with drastically decreased yield when compared to nitrones **6a** and **6c**, despite having an ethyl group α- to the nitrone rather than a methyl or *n*-butyl. Oxidation of chlorinated amine **5g** resulted in a poor yield of **6g** as well.

Bartoli et al. have proposed a method for identifying the configuration of the nitrone for α,β-unsaturated *N*-aryl ketonitrones with an Sα- methyl group;[25] it was reported that in the *E*- configuration the methyl group resonance peak would be found further downfield due to the deshielding effect of the nitrone oxygen. This shift difference was observed with the α,β-unsaturated *N*-aryl ketonitrones as well for all α-methyl species (all except **6b-d**). In these cases, the major isomer produced was assigned as *E*- due to the further downfield methyl group resonance compared to the minor isomer. Additional evidence in support of these assignments and the validity of this logic was provided by the vinyl proton resonances. In comparing the spectra of the two nitrone isomers of **6a** (Figure 4), it can be seen that the *Z*-isomer exhibits a differential deshielding effect on the two vinyl protons. In the *E*-isomer, the two vinyl proton resonances show a small chemical shift difference ($\Delta\delta \approx 0.1$ ppm) while the *Z*-isomer shows a much larger chemical shift difference ($\Delta\delta \approx 1$ ppm). The largest chemical shift difference was found in nitrone **6d** ($\Delta\delta = 1.5$ ppm); only the *Z*-isomer was observed.

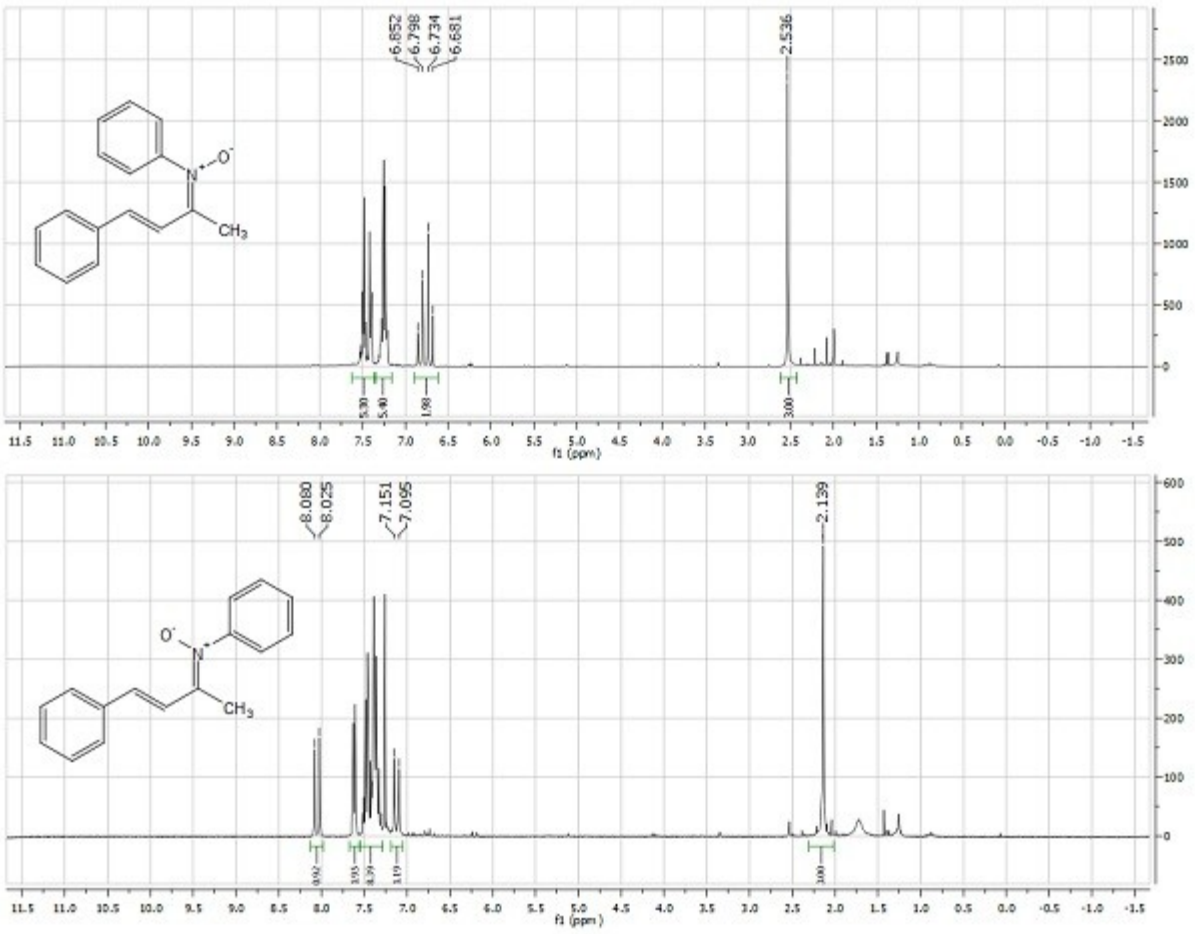


Figure 4. Spectra of *E*- and *Z*- isomers of nitrone **6a**.

This additional spectral characteristic made it possible to tentatively assign the remaining α,β-unsaturated nitrones with an α- substitution other than a methyl group. Based on the aforementioned support, the *E*-isomer was the major configuration produced (in some cases the only isomer observed), with the exception of nitrone **6d** with an α-phenyl group. Only one isomer was observed before and after purification, and based on the very large chemical shift difference between the vinyl protons the nitrone exists in the *Z*- configuration.

3.4 Experimental

3.4.1 Synthetic Considerations

General experimental concerns

All moisture- and air-sensitive reactions were carried out in flame-dried glassware under nitrogen atmosphere. Solvents were purified by passage through an activated alumina based solvent purification system. All commercial reagents were used as received. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to $CDCl_3$ (7.26 ppm), coupling constants (*J*) are reported in Hertz (Hz), and multiplicity follows convention. Deuterochloroform ($CDCl_3$) served as an internal standard (77.36 ppm) for all ^{13}C spectra. Flash column chromatography was performed using 60Å silica gel (Silicycle, 230 - 400 mesh) as the stationary phase. Thin layer chromatography (TLC) was performed using pre-coated glass-backed TLC plates, Silica Gel 60 F254 (EMD, 250 μm thickness).

Representative synthetic procedure

A solution of aniline (12.5 mmol) in diethyl ether (30 mL) was treated with anhydrous $MgSO_4$ (5.0 g) followed by dropwise addition of the α,β-unsaturated aldehyde (12 mmol for cinnamaldehyde/derivatives and 15 mmol for others). The suspension was stirred at room temperature for 15 h under a nitrogen atmosphere before the solid was removed by filtration. The filtrate was concentrated under reduced pressure to give the crude *N*-allylideneaniline **(4)** that was essentially pure by ^{1}H NMR spectrum. It was used in the next step without purification. The *N*-allylideneaniline (6.50 mmol) was taken into anhydrous THF in a flame-dried flask and cooled to –78 ^{o}C before it was treated

dropwise with an ethereal solution of the alkyl or phenyl lithium reagent (9.75 mmol). The mixture was stirred at the same temperature for 20-30 min before the reaction was quenched by dropwise addition of aq. NH_4Cl. The aqueous phase was extracted with ethyl acetate (2x). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used for the next step without purification. The *N*-allyl aniline (0.26 mmol) was taken into a mixed solvent of THF (0.75 mL), CH_3CN (2.9 mL), and 0.01 M aq. Na_2EDTA (2.9 mL). The mixture was cooled to 4 ^oC and treated with $NaHCO_3$ (0.108 g, 1.29 mmol). The mixture was warmed to RT and Oxone® (0.437 g, 0.71 mmol) was added in portions. It was stirred for an additional 20 min before ethyl acetate was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude nitrone, which was purified by silica gel column chromatography eluted with dichloromethane-methanol or ethyl acetate-acetone as a solvent system.

3.4.2 Spectral Data for New Compounds

(E)-N-((E)-3-phenylallylidene)aniline

Yield: 77%. Spectral data for this compound were consistent with those found in the literature.[39]

(E)-2-methyl-N-((E)-3-phenylallylidene)aniline

Yield: 95%. Spectral data for this compound were consistent with those found in the literature.[40]

(E)-4-methyl-N-((E)-3-phenylallylidene)aniline

Yield: 45%. Spectral data for this compound were consistent with those found in the literature.[40]

(E)-4-chloro-N-((E)-3-phenylallylidene)aniline

Yield: 65%. Spectral data for this compound were consistent with those found in the literature.[41]

(E)-N-((E)-3-(4-methoxyphenyl)allylidene)aniline

Yield: 75%. Spectral data for this compound were consistent with those found in the literature.[42]

(E)-N-((E)-3-(4-methoxyphenyl)allylidene)-2-methylaniline

Yield: 74%. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.12 (dd, J = 7.8, 0.6 Hz, 1H), 7.50 (m, 2H), 7.20 (m, 2H), 7.12(m, 1H), 7.07 (m, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.93 (m, 2H), 6.87 (m, 1H), 3.85 (s, 3H), 2.34 (s, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 161.7, 160.7, 151.5, 143.4, 131.6, 130.2, 129.0, 128.4, 126.7, 126.6, 125.4, 117.8, 114.3, 55.4, 17.9 Exact mass calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 251.1388. Found: 252.1396.

(E)-3-methoxy-N-(3-methylbut-2-en-1-ylidene)aniline

Yield: 93%. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.37 (d, J = 9.6 Hz, 1H), 7.25 (m, 1H), 6.78-6.66 (m, 3H), 6.21 (m, 1H), 3.82, (s, 3H), 2.02 (m, 3H), 1.97 (d, J = 1.2 Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 160.6, 159.3, 154.4, 150.9, 130.1, 126.5, 113.2, 111.6, 107.1, 55.6, 27.2, 19.3 Exact mass calcd for $C_{16}H_{16}NO$ $[M+H]^+$: 190.1232. Found: 190.1228.

(E)-N-((E)-2-methylbut-2-en-1-ylidene)aniline

Yield: 91%. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.37 (d, J = 9.6 Hz, 1H), 7.35 (m, 2H), 7.18 (m, 1H), 7.11 (m, 2H), 6.23 (m, 1H), 2.02 (m, 3H), 1.97 (m, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 159.2, 153.0, 150.6, 129.4, 126.6, 125.8, 121.2, 27.2, 19.3 Exact mass calcd for $C_{11}H_{14}N$ $[M+H]^+$: 160.1126. Found: 160.1121.

(E)-N-(4-phenylbut-3-en-2-yl)aniline (5a)

Yield: Quantitative. Spectral data for this compound were consistent with those found in the literature.[43]

(E)-2-methyl-N-(4-phenylbut-3-en-2-yl)aniline (5e)

Yield: 96%. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.40-7.12 (m, 5H), 7.08 (m, 2H), 6.67 (m, 2H), 6.59 (dd, J = 15.9, 1.2 Hz, 1H), 4.2 (m, 1H), 3.56 (br. S, 1H), 2.19 (s, 3H), 1.46 (d, J = 6.6 Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 145.7, 137.3, 133.7, 130.4, 129.6, 128.8, 127.7, 127.4, 126.7, 122.0, 117.2, 111.2, 51.0, 22.6, 18.0 $C_{17}H_{20}N$ $[M+H]^+$: 238.1596. Found: 238.1589.

(E)-4-methyl-N-(4-phenylbut-3-en-2-yl)aniline (5f)

Yield: 97%. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.98 (m, 2H), 6.58 (m, 3H), 6.23 (dd, J = 16.2, 6 Hz, 1H), 4.12 (m, 1H), 3.58 (br. s, 1H), 2.24 (s, 3H), 1.40 (d, J = 6.6 Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 145.4, 137.4, 133.8, 130.0, 129.5, 128.8, 127.6, 126.9, 126.6, 114.0, 51.5, 22.4, 20.7 Exact mass calcd for $C_{17}H_{20}N$ $[M+H]^+$: 138.1596. Found: 238.1601.

(E)-4-chloro-N-(4-phenylbut-3-en-2-yl)aniline (5g)

Yield: 99%. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.30 (m, 5H), 7.09 (m, 2H), 6.55 (m, 3H), 6.18 (dd, J = 15.9, 5.7 Hz, 1H), 4.10 (m, 1H), 3.73 (br. S, 1H), 1.41 (d, J = 6.6 Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 146.3, 137.1, 132.9, 129.9, 129.3, 128.9, 127.8, 126.7, 122.2, 114.8, 51.4, 22.4 Decomposed in mass spectrometry analysis.

(E)-N-(1-phenylpent-1-en-3-yl)aniline (5b)

Yield: 98%. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.4-7.13 (m, 7H), 6.67 (m, 3H), 6.59 (d, J = 15.9 Hz, 1H), 6.14 (dd, J = 15.9, 6.3 Hz, 1H), 3.90 (m, 1H), 3.75 (br. s, 1H), 1.73 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 148.0, 137.4, 132.3, 130.7, 128.8, 127.6, 126.7, 117.5, 113.7, 57.5, 29.4, 10.8. $C_{17}H_{20}N$ $[M+H]^+$: 238.1596. Found: 238.1607.

(E)-N-(1-phenylhept-1-en-3-yl)aniline (5c)

Yield: 91%. Spectral data for this compound were consistent with those found in the literature.[36]

(E)-N-(1,3-diphenylallyl)aniline (5d)

Yield: Quantitative. Spectral data for this compound were consistent with those found in the literature.[44]

(E)-N-(4-(4-methoxyphenyl)but-3-en-2-yl)aniline (5g)

Yield: 98%. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.16 (m, 2H), 6.84 (m, 2H), 6.66 (m, 3H), 6.52 (d, J = 15.9 Hz, 1H), 6.08 (dd, J = 15.9, 6 Hz, 1H), 4.13 (m, 1H), 3.80 (s, 3H), 3.70 (br. S, 1H), 1.40 (d, J = 6.6 Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ

159.4, 147.8, 131.3, 130.1, 129.5, 129.0, 127.8, 114.6, 114.3, 113.7, 55.6, 51.2, 22.5 $C_{17}H_{20}NO$ $[M+H]^+$: 254.1545. Found: 254.1548.

(E)-N-(4-(4-methoxyphenyl)but-3-en-2-yl)-2-methylaniline (5i)

Yield: 99%. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.08 (m, 2H), 6.84 (m, 2H), 6.66 (m, 2H), 6.53 (d, J = 15.9 Hz, 1H), 6.11 (dd, J = 15.9, 5.7 Hz, 1H), 4.18 (m, 1H), 3.80 (s, 3H), 3.55 (br. s, 1H), 2.18 (s, 3H), 1.44 (d, J = 6.6 Hz, 3H)) ^{13}C NMR (75MHz, $CDCl_3$) δ 159.4, 145.72, 131.5, 130.1, 129.0, 127.8, 127.4, 122.0, 117.1, 114.2, 111.2, 55.6, 51.1, 227, 18.0. Decomposed in mass spectrometry analysis.

(E)-N-(pent-3-en-2-yl)aniline (5j)

Yield: 91%. Spectral data for this compound were consistent with those found in the literature.[45]

3-methoxy-N-(4-methylpent-3-en-2-yl)aniline (5k)

Yield: 95%. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.05 (t, J = 8.1 Hz, 1H), 6.20 (m, 3H), 5.06 (m, 1H), 4.13 (m, 1H), 3.76 (m, 1H), 3.62 (br. S, 1H) 1.74 (d, J = 1.5 Hz, 3H), 1.70 (d, J = 2.4 Hz, 3H), 1.24 (d, J = 6.3 Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 161.0, 149.4, 133.0, 130.1, 129.7, 106.8, 102.6, 99.3, 55.3, 47.6, 26.0, 22.4, 18.5 $C_{12}H_{16}NO$ $[M+H]^+$: 206.1545. Found: 206.1554.

(E)-N-(3-methylpent-3-en-2-yl)aniline (5l)

Yield: 82%. Spectral data for this compound were consistent with those found in the literature.[46]

(Z)-N-((E)-4-phenylbut-3-en-2-ylidene)aniline oxide (*Z*-6a)

^{1}H NMR (300MHz, $CDCl_3$) δ 8.05 (d, 1H, J = 16.5 Hz), 7.62 (m, 2H), 7.29-7.52 (m, 8H), 7.12 (d, J = 16.8 Hz, 2H), 2.14 (s, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 138.1, 136.5, 129.9, 129.8, 129.7, 129.6, 129.2, 128.0, 128.0, 124.0, 120.8, 16.7 Exact mass calcd for $C_{16}H_{16}NO$ $[M+H]^+$: 238.1232. Found: 238.1221.

(E)-N-((E)-4-phenylbut-3-en-2-ylidene)aniline oxide (*E*-6a)

^{1}H NMR (300MHz, $CDCl_3$) δ 7.48 (m, 3H), 7.41 (m, 2H), 7.19-7.31 (m, 5H), 6.8 (d, J = 18 Hz, 1H), 6.71 (d, J = 15.9 Hz, 1H), 2.54 (s, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 148.4, 145.7, 136.3, 133.3, 129.8, 129.8, 129.2, 129.1, 127.2, 124.8, 121.3, 13.7 $C_{16}H_{16}NO$ $[M+H]^+$: 238.1232. Found: 238.1224

(E)-2-methyl-N-((E)-4-phenylbut-3-en-2-ylidene)aniline oxide (6e)

Yield: 51% 2.7:1 E:Z. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.40-7.15 (m, 9H), 6.82 (d, J = 15.9 Hz, 1H), 6.52 (d, J = 15.9 Hz, 1H), 2.54 (s, 3H), 2.25 (s, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 148.3, 144.6, 136.2, 133.4, 131.7, 129.6, 129.1, 129.1, 127.4, 127.2, 124.6, 120.6,17.0, 12.9 Exact mass calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388. Found: 252.1379.

(E)-4-methyl-N-((E)-4-phenylbut-3-en-2-ylidene)aniline oxide (6f)

Yield: 67%, 3.7:1 E:Z. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.26 (m, 9H), 6.77 (m, 2H), 2.51 (d, J = 2.1 Hz, 3H), 2.42 (d, J = 2.4 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 147.9, 143.4, 139.9, 136.4, 132.8, 130.2, 129.1, 129.0, 127.1. 124.5, 121.5. Exact mass calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388. Found: 252.1382.

(E)-4-chloro-N-((E)-4-phenylbut-3-en-2-ylidene)aniline oxide (6g)

Yield: 34%, 2:1 E:Z. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.36 (m, 2H), 7.27 (m, 4H), 6.84 (d, J =15.9 Hz, 1H), 6.69 (d, J = 15.9 Hz, 1H), 2.52 (s, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 148.5, 144.2, 136.1, 135.6, 133.6, 130.0, 129.4, 129.2, 127.3, 126.2, 120.9, 13.8. Exact mass calcd for $C_{16}H_{15}ClNO$ $[M+H]^+$: 272.0842. Found: 272.0831.

(E)-N-((E)-1-phenylpent-1-en-3-ylidene)aniline oxide (6b)

Yield: 22%, 3.3:1 E:Z. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.48 (m, 3H), 7.40 (m, 3H), 7.25 (m, 4H), 6.80 (d, J = 15.9, Hz, 1H), 6.64 (d, J = 16.2 Hz, 1H), 3.03 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5) ^{13}C NMR (75MHz, $CDCl_3$) δ 152.6, 145.9, 138.0, 132.4, 129.7, 129.7, 129.1, 127.2, 124.8, 120.4, 20.4, 10.4. Exact mass calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388. Found: 252.1371.

(Z)-N-((E)-1-phenylhept-1-en-3-ylidene)aniline oxide (*Z*-6c)

Yield: 82% 2:1 E:Z ^{1}H NMR (300MHz, $CDCl_3$) δ 7.92 (d, J = 16.8 Hz, 1H), 7.62 (m, 2H), 7.47 (m, 3H), 7.36 (m, 3H), 7.19 (d, J = 68 Hz, 1H), 2.46 (m, 2H), 1.51 (m, 2H), 1.25 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 149.8, 146.3, 138.1, 136.6, 129.8, 129.6, 129.5, 129.2, 127.9, 123.8, 119.6, 30.9, 29.6, 22.9, 13.8.

(E)-N-((E)-1-phenylhept-1-en-3-ylidene)aniline oxide (*E*-6c)

^{1}H NMR (300MHz, $CDCl_3$) δ 7.48 (m, 3H), 7.39 (m, 2H), 7.25 (m, 5H), 6.79 (d, J = 15.9 Hz, 1H), 6.65 (d, J = 15.9 Hz, 1H), 3.00 (m, 2H), 1.74 (m, 2H), 1.57 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 151.7, 145.7, 136.3, 132.5, 129.6, 129.6, 129.0, 129.0, 127.1, 124.7, 120.8, 28.0, 16.7, 23.3, 14.2. Exact mass calcd for $C_{19}H_{22}NO$ $[M+H]^+$: 280.1701. Found: 280.1704.

(E)-N-((E)-1,3-diphenylallylidene)aniline oxide (6d)

Yield: 52%, ≥5:1 E:Z. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.18 (d, J = 16.5 Hz, 1H), 7.53 (m, 3H), 7.38-7.14 (m, 12H), 6.71 (d, J = 16.2 Hz, 1H)) ^{13}C NMR (75MHz, $CDCl_3$) δ 150.2, 147.4, 141.2, 136.6, 133.1, 131.2, 129.7, 129.3, 129.1, 129.0, 128.9, 128.8, 128.0, 125.2, 122.3 Exact mass calcd for $C_{21}H_{18}NO$ $[M+H]^+$: 300.1388. Found: 300.1396.

(Z)-N-((E)-4-(4-methoxyphenyl)but-3-en-2-ylidene)aniline oxide (*Z*-6h)

Yield: 80%, 4:1 E:Z. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.93 (d, J = 16.5 Hz, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.44 (m, 5H), 7.08 (d, J = 16.5 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 2.11 (s, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 161.0, 146.6, 145.2, 137.9, 129.8, 129.5, 129.4, 129.3, 124.1, 118.6, 114.7, 55.7, 16.6 $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1338. Found: 268.1332.

(E)-N-((E)-4-(4-methoxyphenyl)but-3-en-2-ylidene)aniline oxide (*E*-6h)

^{1}H NMR (300MHz, $CDCl_3$) δ 7.45 (m, 5H), 7.17 (d, J = 8.7 Hz, 2H), 6.79 (m, 3H), 6.57 (d, J = 15.9 Hz), 3.78 (s, 3H), 2.52 (s, 3H)) ^{13}C NMR (75MHz, $CDCl_3$) δ 160.5, 148.4, 145.8, 132.9, 129.7, 129.7, 129.1, 128.7, 124.8, 119.3, 114.6, 55.6, 13.6. $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1338. Found: 268.1350.

(Z)-N-((E)-4-(4-methoxyphenyl)but-3-en-2-ylidene)-2-methylaniline oxide (*Z-6i*)

Yield: 49%, 2:1 E:Z. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.94 (d, J = 16.5 Hz, 1H), 7.57 (m, 2H), 7.30 (m, 3H), 7.22 (m, 1H), 7.08 (d, J = 16.5 Hz, 1H), 6.91 (m, 2H), 3.84 (s, 3H), 2.30 (s, 3H), 2.02 (s, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 161.0, 145.6, 145.5, 137.9, 131.8, 129.5, 129.3, 129.2, 127.5, 123.9, 118.1, 114.7, 55.7, 16.9, 15.7. Exact mass calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$: 282.1494. Found: 282.1502.

(E)-N-((E)-4-(4-methoxyphenyl)but-3-en-2-ylidene)-2-methylaniline oxide (*E*-6i)

^{1}H NMR (300MHz, $CDCl_3$) δ 7.32 (m, 4H), 7.15 (m, 2H), 6.78 (m, 3H), 6.37 (d, J = 14.7 Hz), 3.78 (s, 3H), 2.53 (s, 3H), 2.25 (s, 3H).

(E)-N-((E)-pent-3-en-2-ylidene)aniline oxide (6j)

Yield: 70% estimated, ≥5:1 E:Z. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.44 (m, 3H), 7.33 (m, 2H), 6.05 (m, 2H), 2.40 (s, 3H), 1.75 (d, J = 5.4 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 132.5, 129.8, 129.7, 129.5, 125.1, 124.6, 123.9, 19.3, 13.7. Exact mass calcd for $C_{11}H_{14}NO$ $[M+H]^+$: 176.1075. Found: 176.1079.

(E)-3-methoxy-N-(4-methylpent-3-en-2-ylidene)aniline oxide (6k)

Yield: 70% estimated, ≥5:1 E:Z. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.28 (m, 1H), 6.91 (m, 3H), 5.66 (m, 1H), 3.80 (s, 1H), 2.47 (s, 3H), 1.83 (d, J = 0.9 Hz, 3H), 1.70 (d, J = 1.2 Hz, 3H) Exact mass calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1545. Found: 206.1554.

(E)-N-((E)-3-methylpent-3-en-2-ylidene)aniline oxide (6k)

Yield: 20%. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.32 (m, 6H), 2.38 (t, J = 1.2 Hz, 3H), 1.52 (s, 3H), 1.46 (d, J = 6.6 Hz) ^{13}C NMR (75MHz, $CDCl_3$) δ 131.3, 129.7, 129.1, 129.0, 124.1, 123.6, 123.3 Exact mass calcd for $C_{12}H_{16}NO$ $[M+H]^+$: 190.1232. Found: 190.1239.

CHAPTER IV

SUMMARY

Our group recently discovered and developed a method for producing C3-quaternary indolenines in good yields from the reaction between α,β-Unsaturated *N*-aryl ketonitrones and activated alkynes. The reaction was optimized, and after exploring the substrate scope of the reaction it was found to be relatively general with varying yields. The α,β-Unsaturated *N*-aryl ketonitrones were synthesized using the aforementioned method developed in our lab as well as the one developed by Bartoli et al. Even with the use of these two very different approaches, we were very much limited in our range of nitrones, so we sought to develop an efficient and straightforward technique for accessing a wider range of nitrone substrates for this reaction as well as other potential synthetic applications. Unfortunately, after a brief investigation we found that these nitrones could not be used to synthesize C3-quaternary indolenines. It is hoped that with a deeper investigation a set of reaction conditions could be found to remedy this apparent lack of reactivity.

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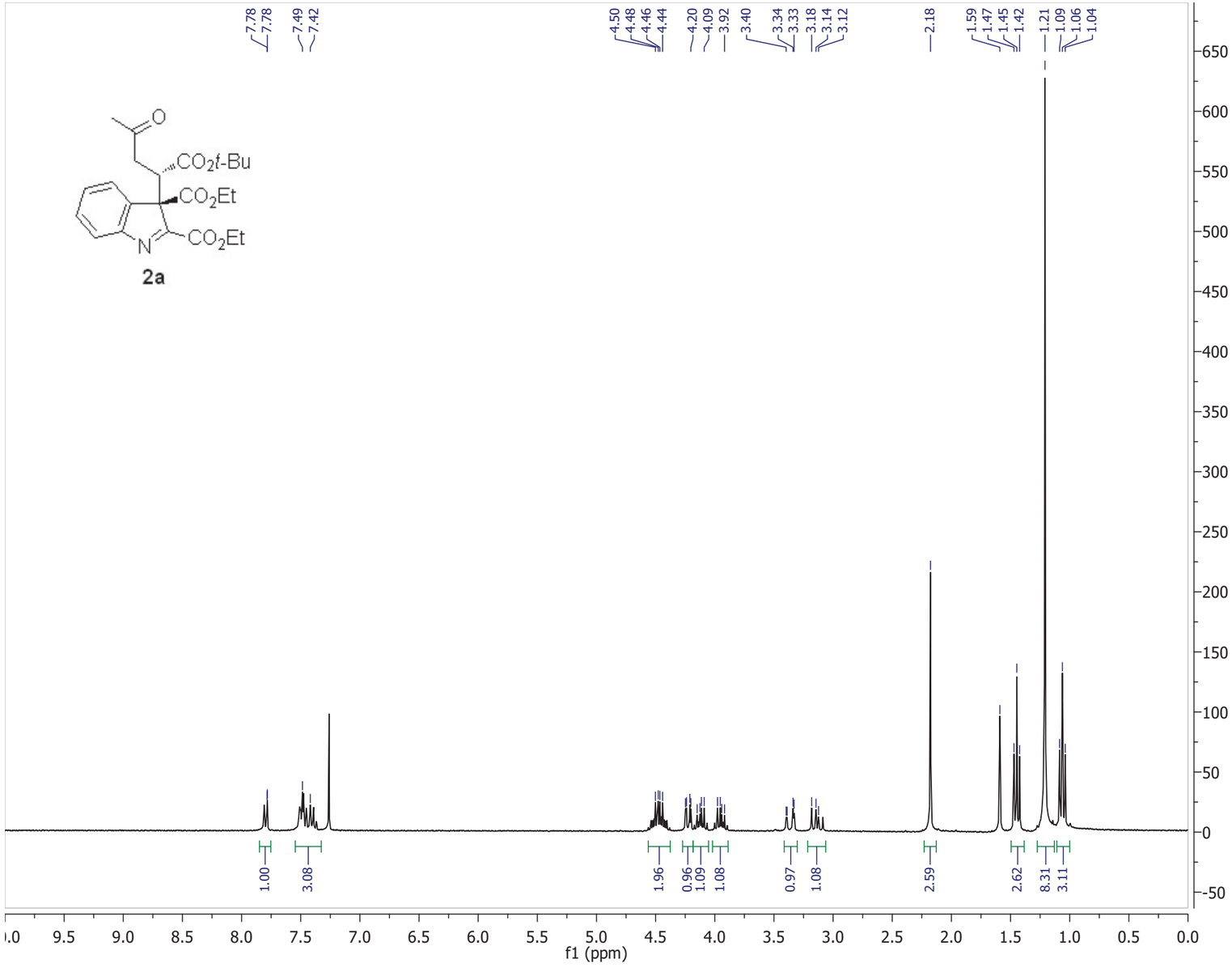
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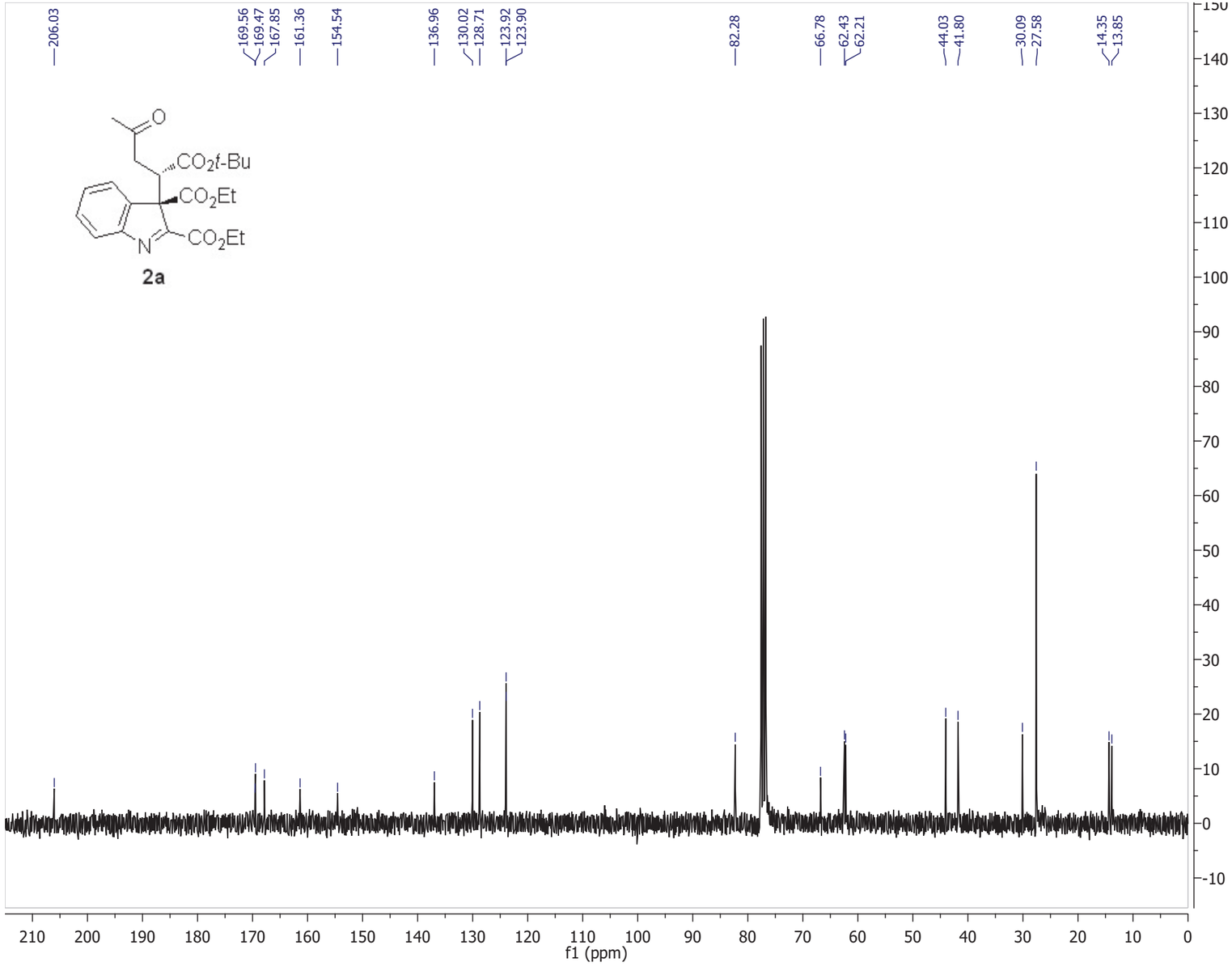
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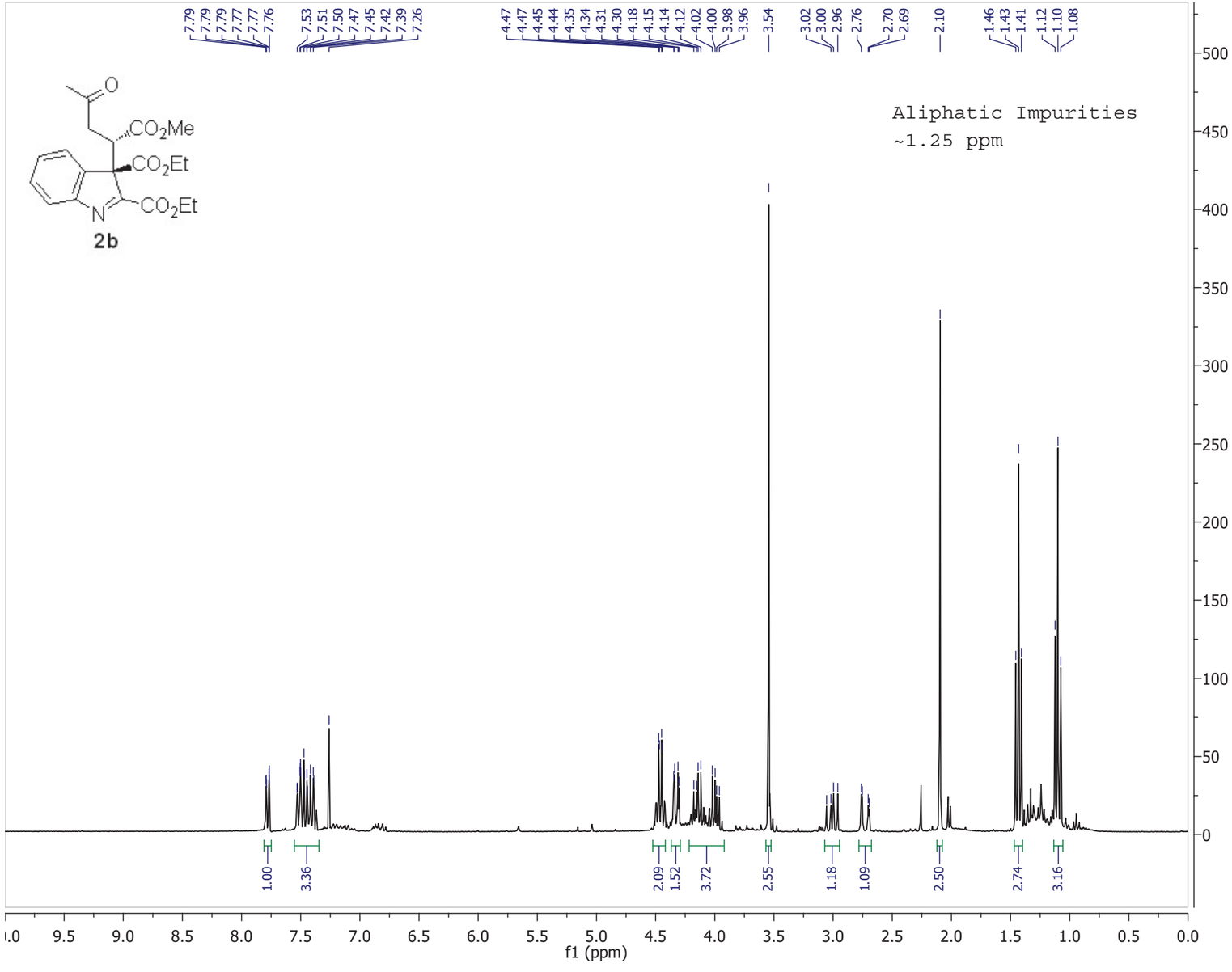
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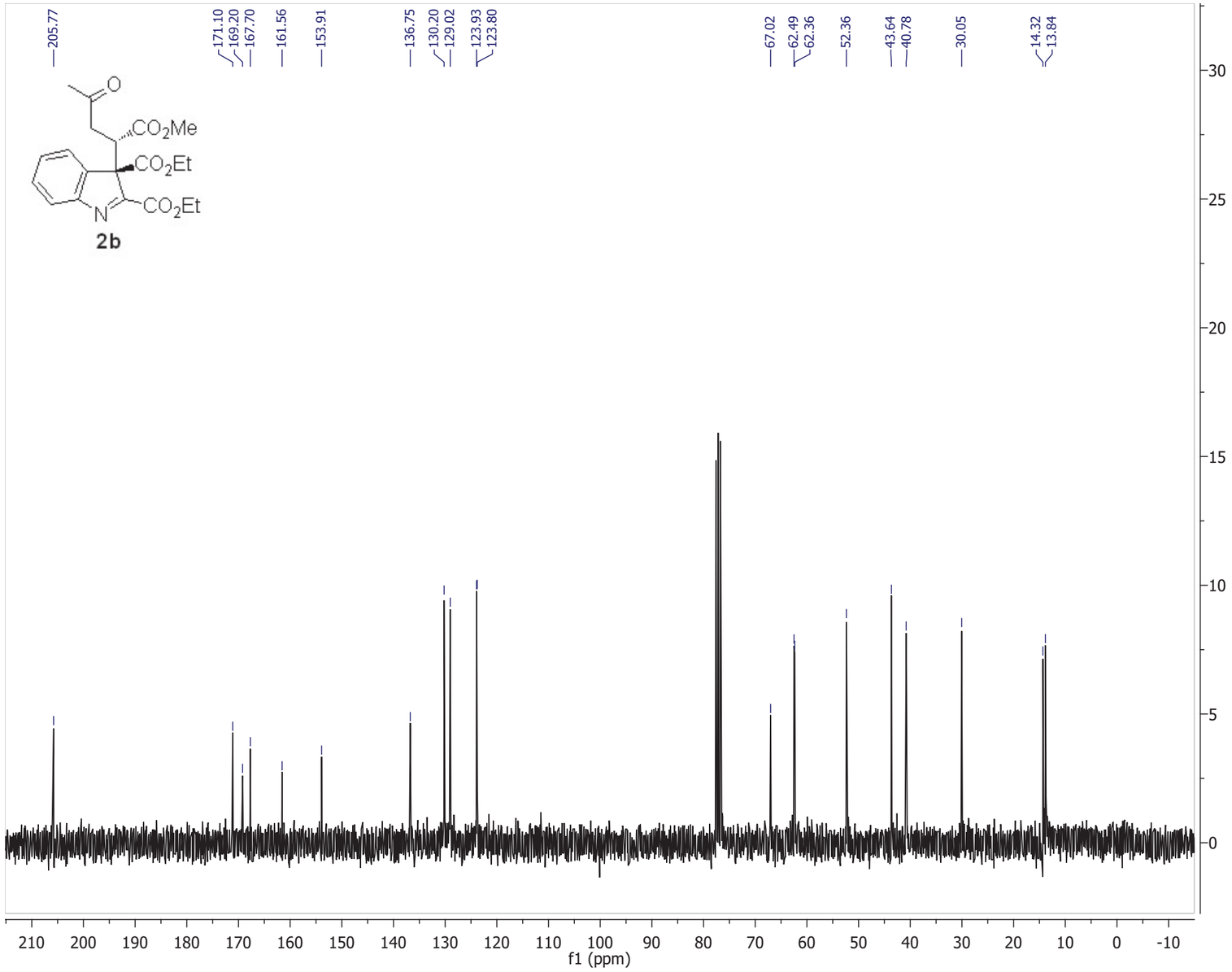
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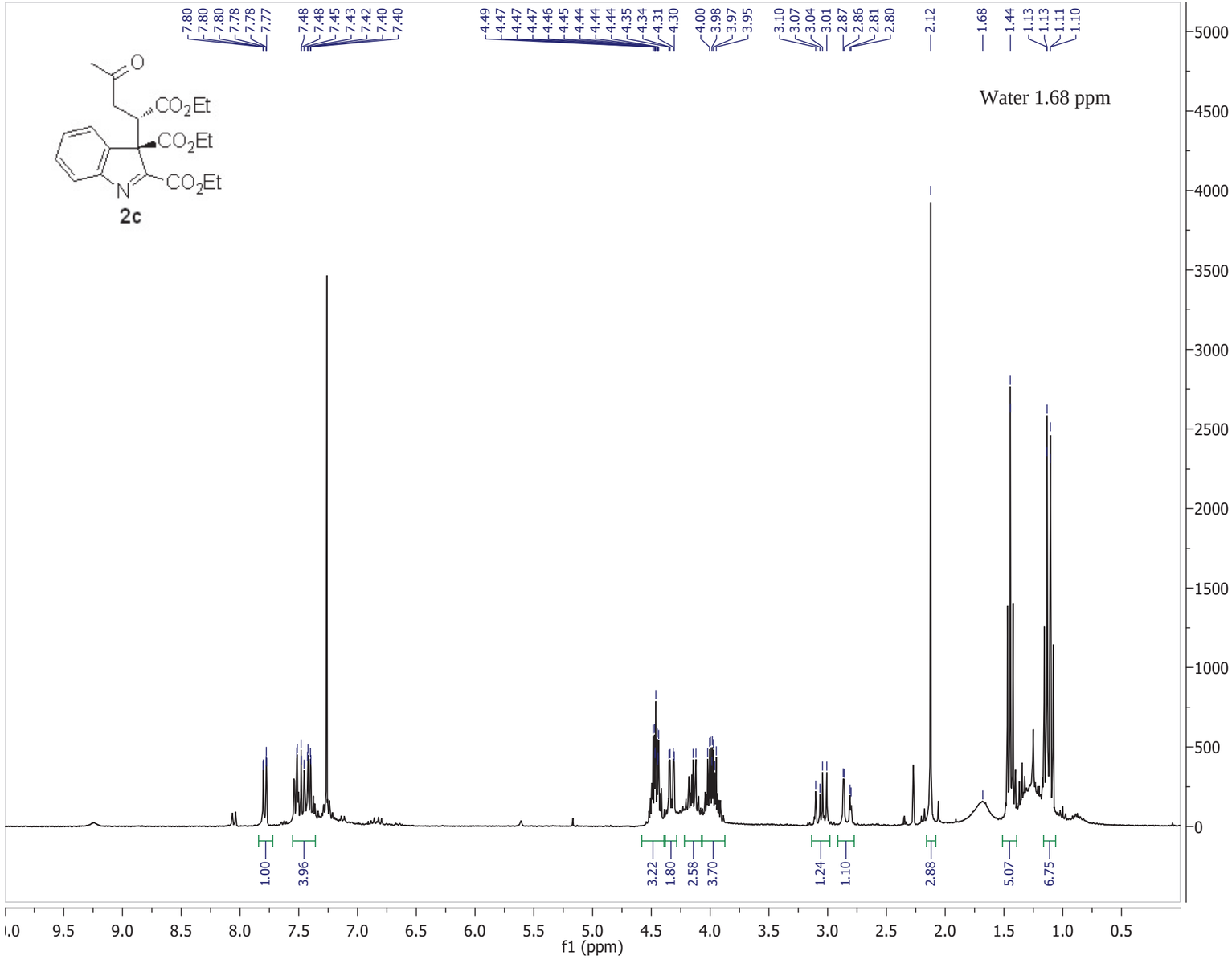
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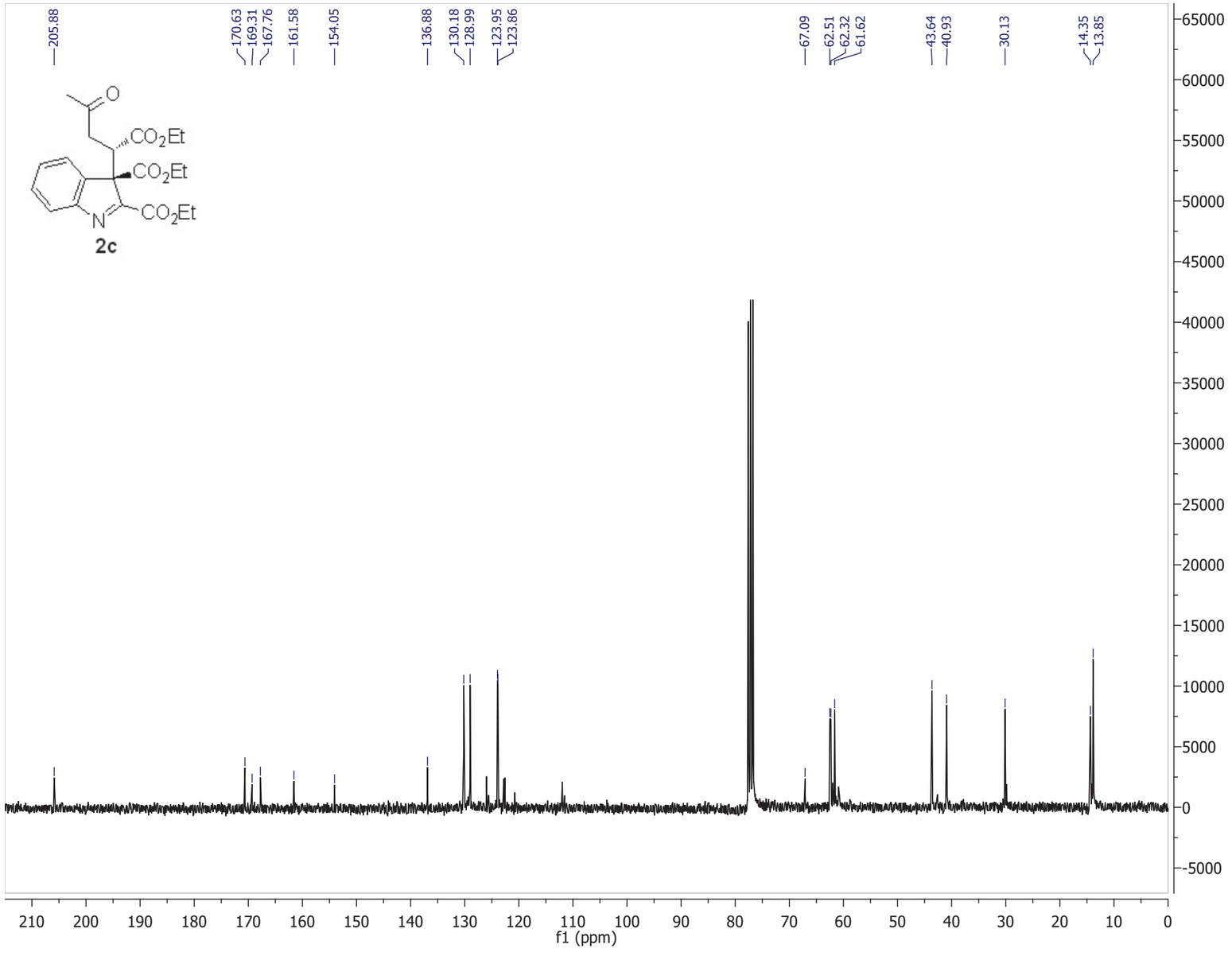
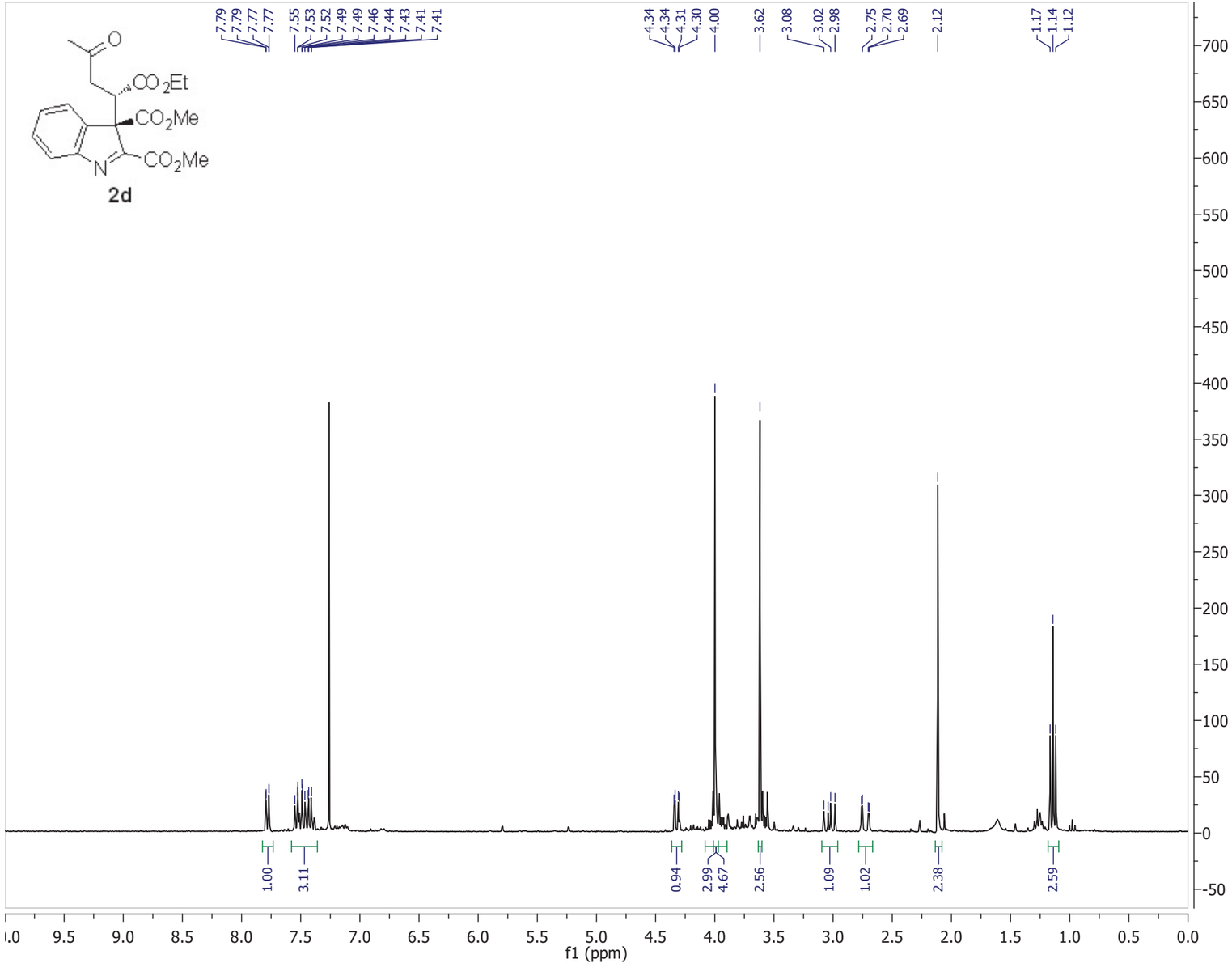
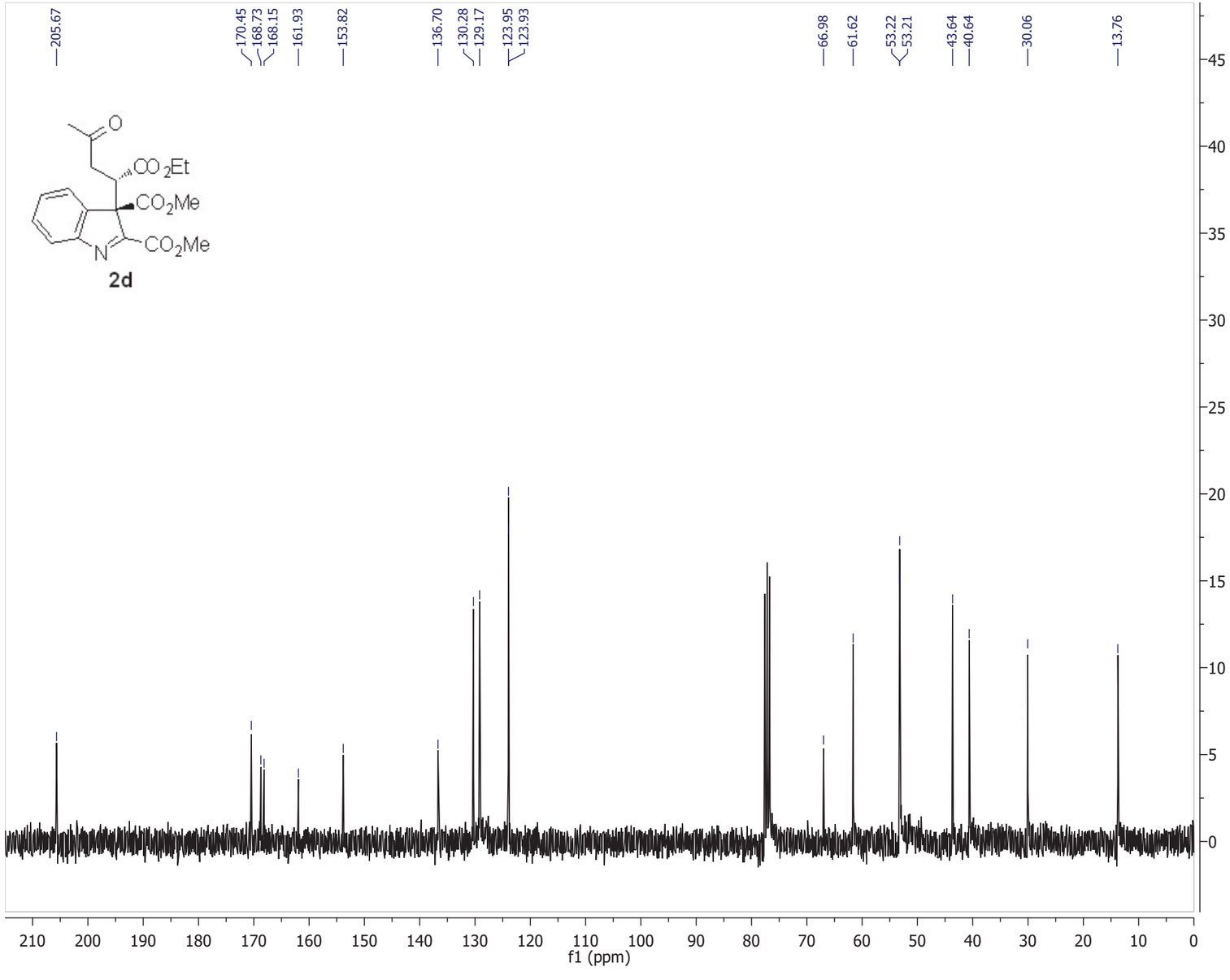
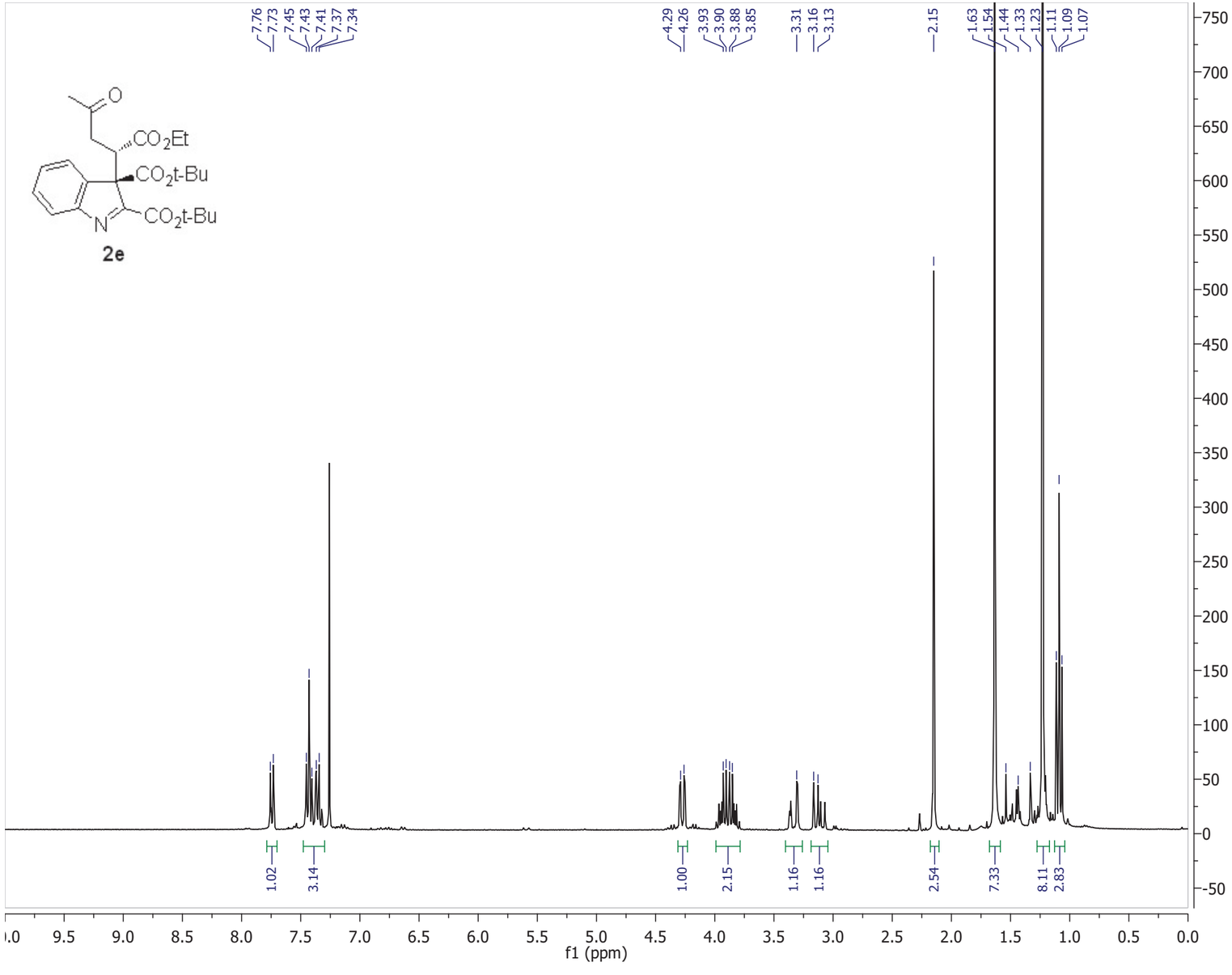
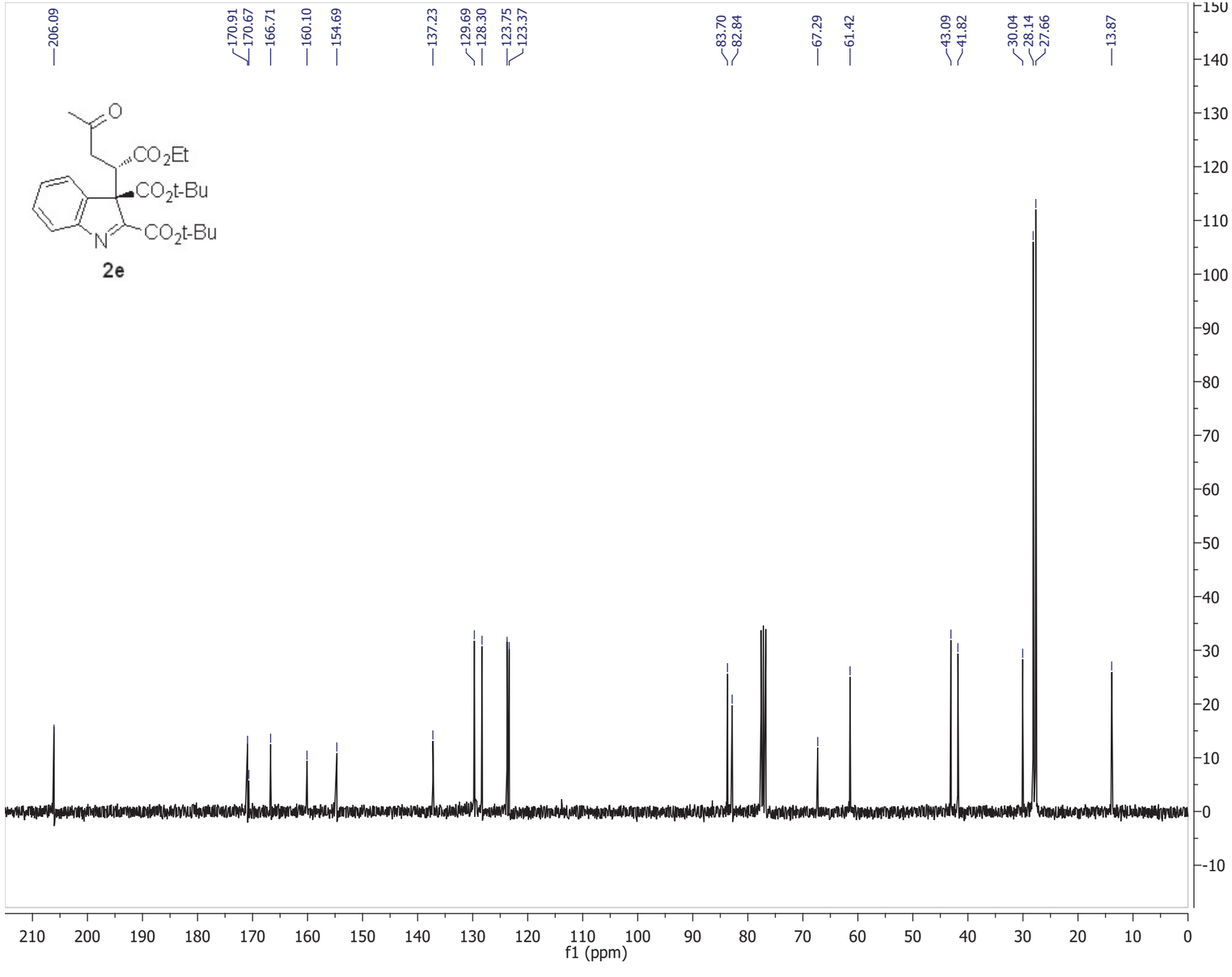
7.40
4.49
4.47
4.47
4.47
4.46
4.45
4.44
4.44
4.44
4.35
4.34
4.31
4.30
4.00
3.98
3.97
3.95
3.10
3.07
3.04
3.01
2.87
2.86
2.81
2.80
2.12
1.68
1.44
1.13
1.13
1.11
1.10
Water 1.68 ppm
O
CO2Et
CO2Et
CO2Et
N
2c
1.00
3.96
3.22
1.80
2.58
3.70
1.24
1.10
2.88
5.07
6.75
f1 (ppm)

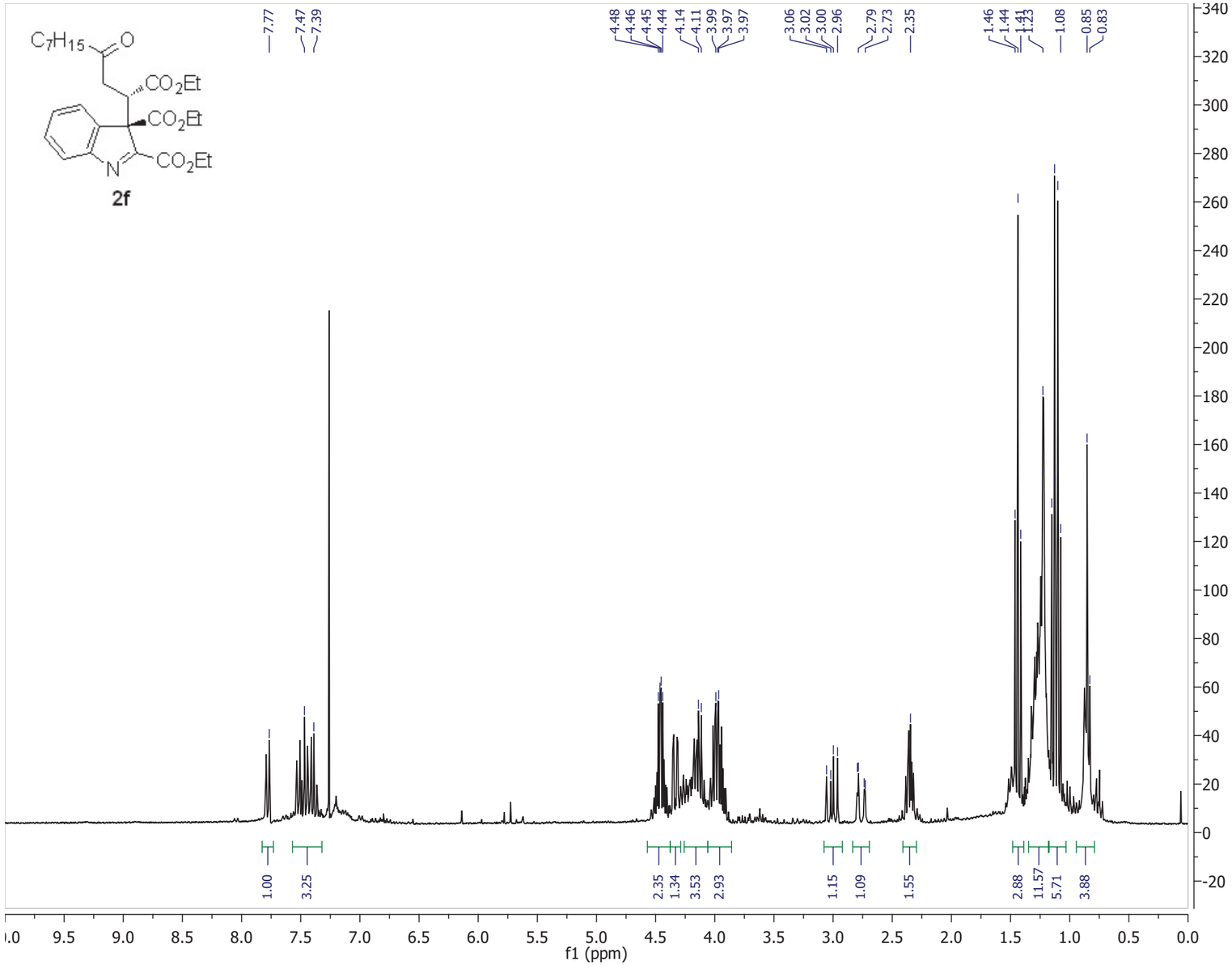

205.88
170.63
169.31
167.76
161.58
154.05
136.88
130.18
128.99
123.95
123.86
67.09
62.51
62.32
61.62
43.64
40.93
30.13
14.35
13.85
O
CO2Et
CO2Et
CO2Et
N
2c
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

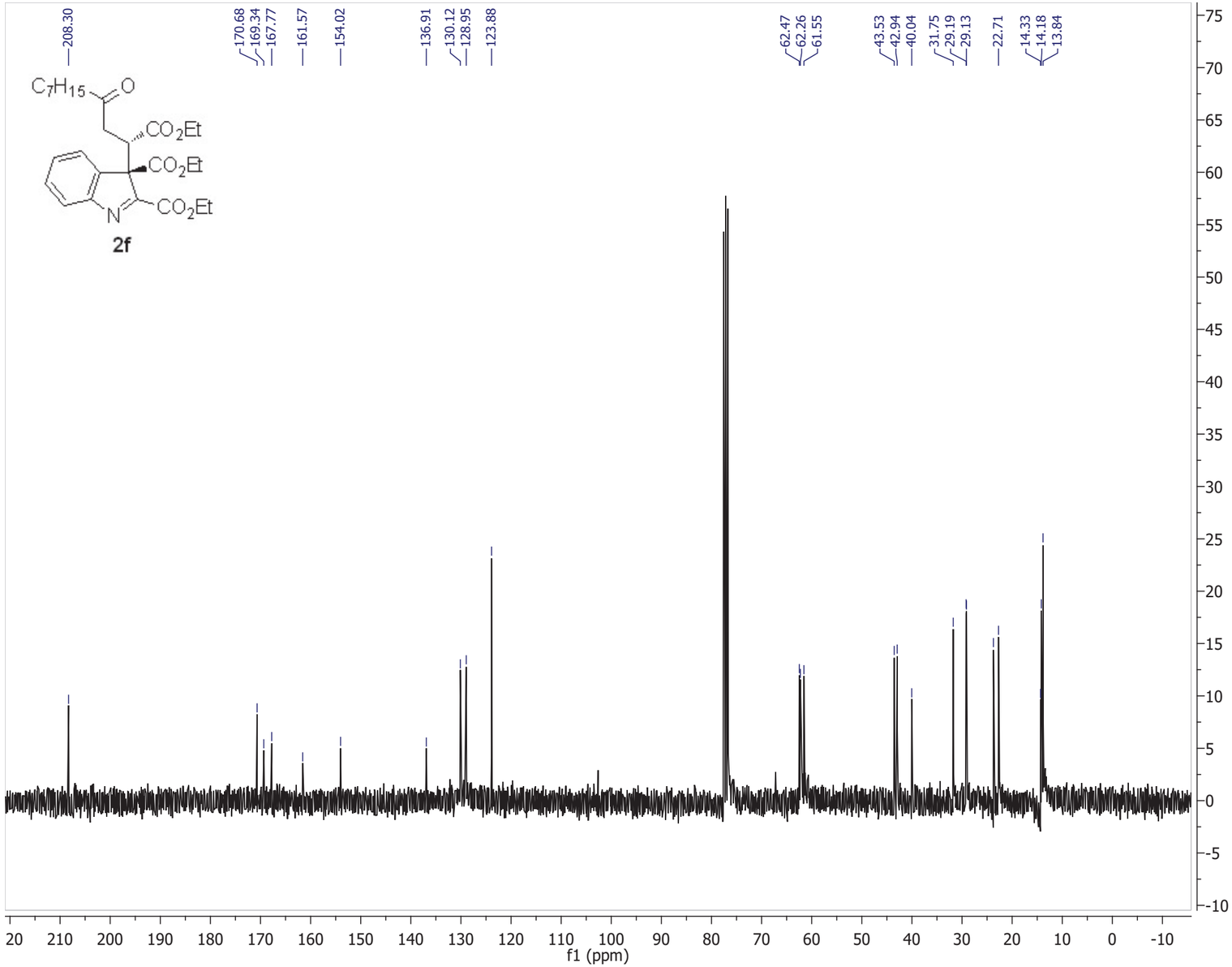

O
CO2Et
CO2Me
CO2Me
N
2d
7.79
7.79
7.77
7.77
7.55
7.53
7.52
7.49
7.49
7.46
7.44
7.43
7.41
7.41
4.34
4.34
4.31
4.30
4.00
3.62
3.08
3.02
2.98
2.75
2.70
2.69
2.12
1.17
1.14
1.12
1.00
3.11
0.94
2.99
4.67
2.56
1.09
1.02
2.38
2.59
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

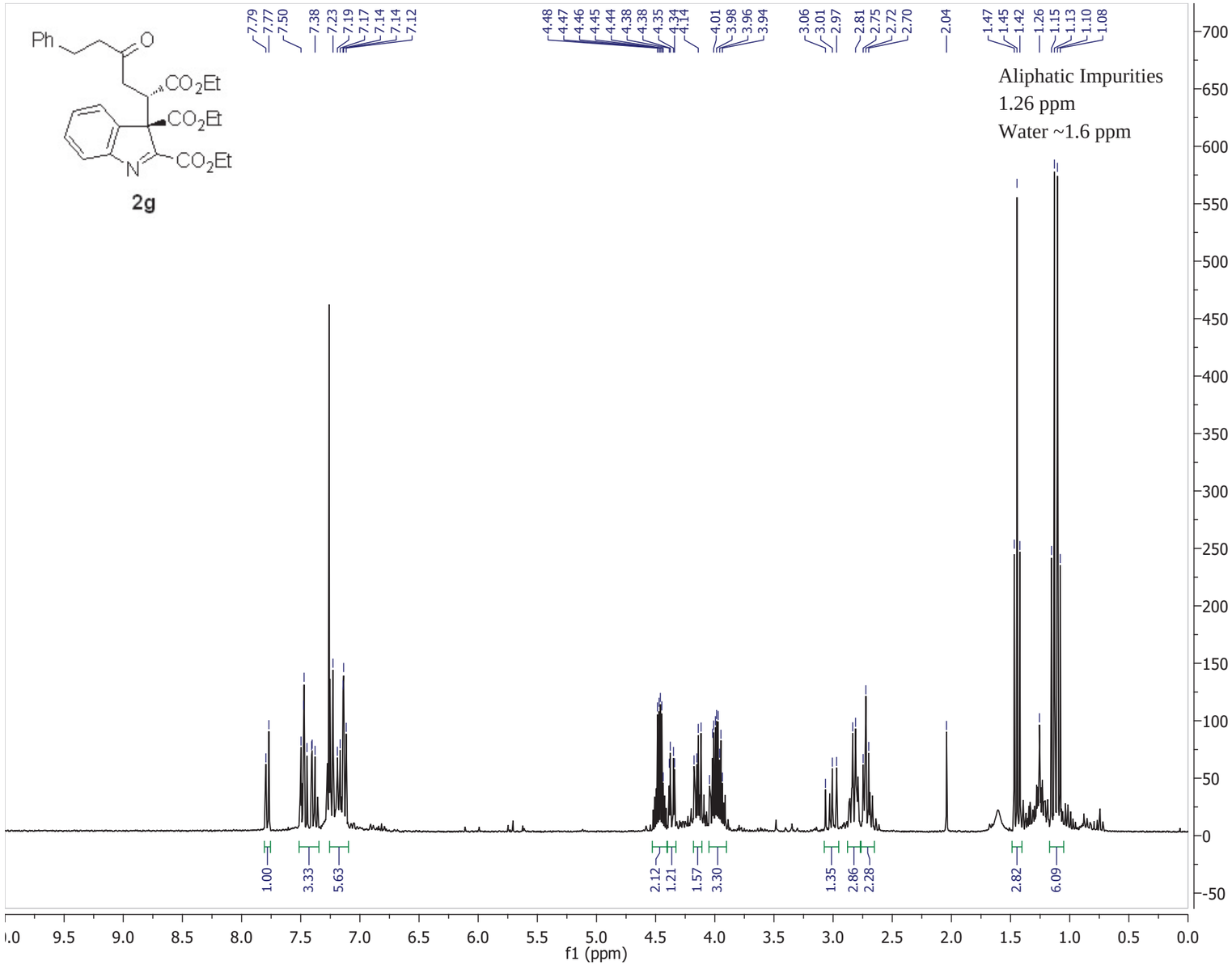

205.67
170.45
168.73
168.15
161.93
153.82
136.70
130.28
129.17
123.95
123.93
66.98
61.62
53.22
53.21
43.64
40.64
30.06
13.76
O
CO2Et
CO2Me
CO2Me
N
2d
45
40
35
30
25
20
15
10
5
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

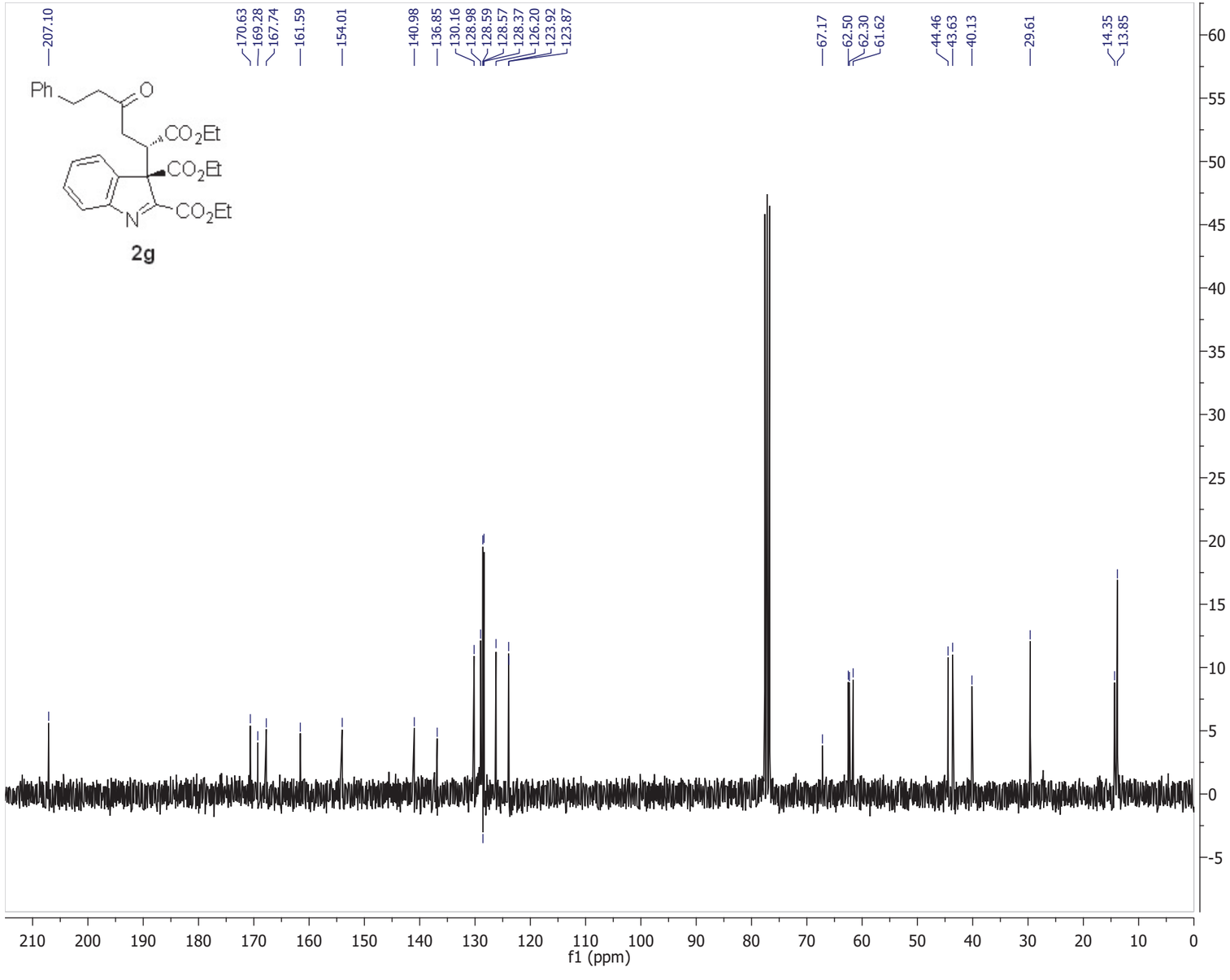

7.76
7.73
7.45
7.43
7.41
7.37
7.34
4.29
4.26
3.93
3.90
3.88
3.85
3.31
3.16
3.13
2.15
1.63
1.54
1.44
1.33
1.23
1.11
1.09
1.07
O
CO2Et
CO2t-Bu
CO2t-Bu
N
2e
1.02
3.14
1.00
2.15
1.16
1.16
2.54
7.33
8.11
2.83
f1 (ppm)

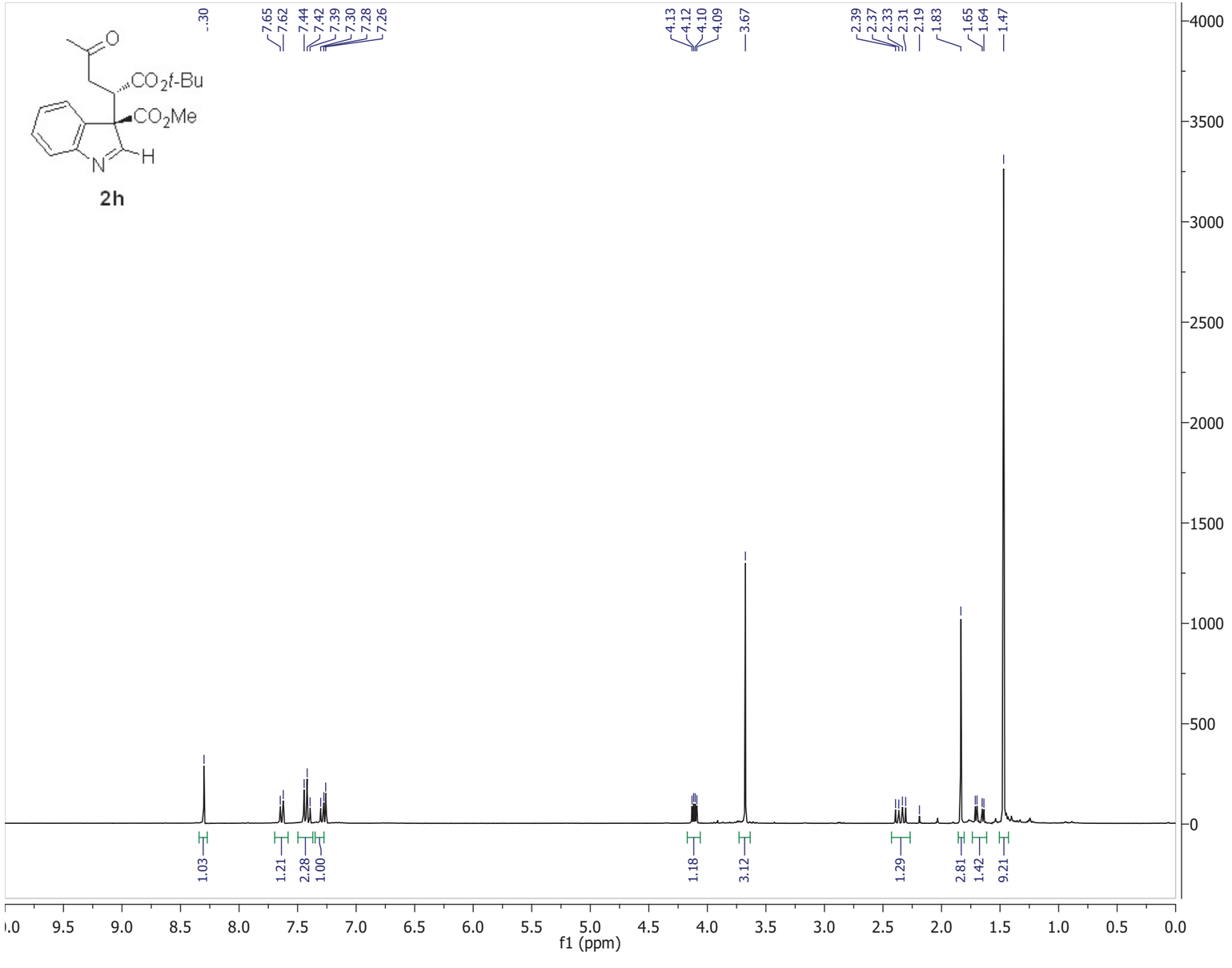

206.09
170.91
170.67
166.71
160.10
154.69
137.23
129.69
128.30
123.75
123.37
83.70
82.84
67.29
61.42
43.09
41.82
30.04
28.14
27.66
13.87
O
CO2Et
CO2t-Bu
CO2t-Bu
N
2e
f1 (ppm)

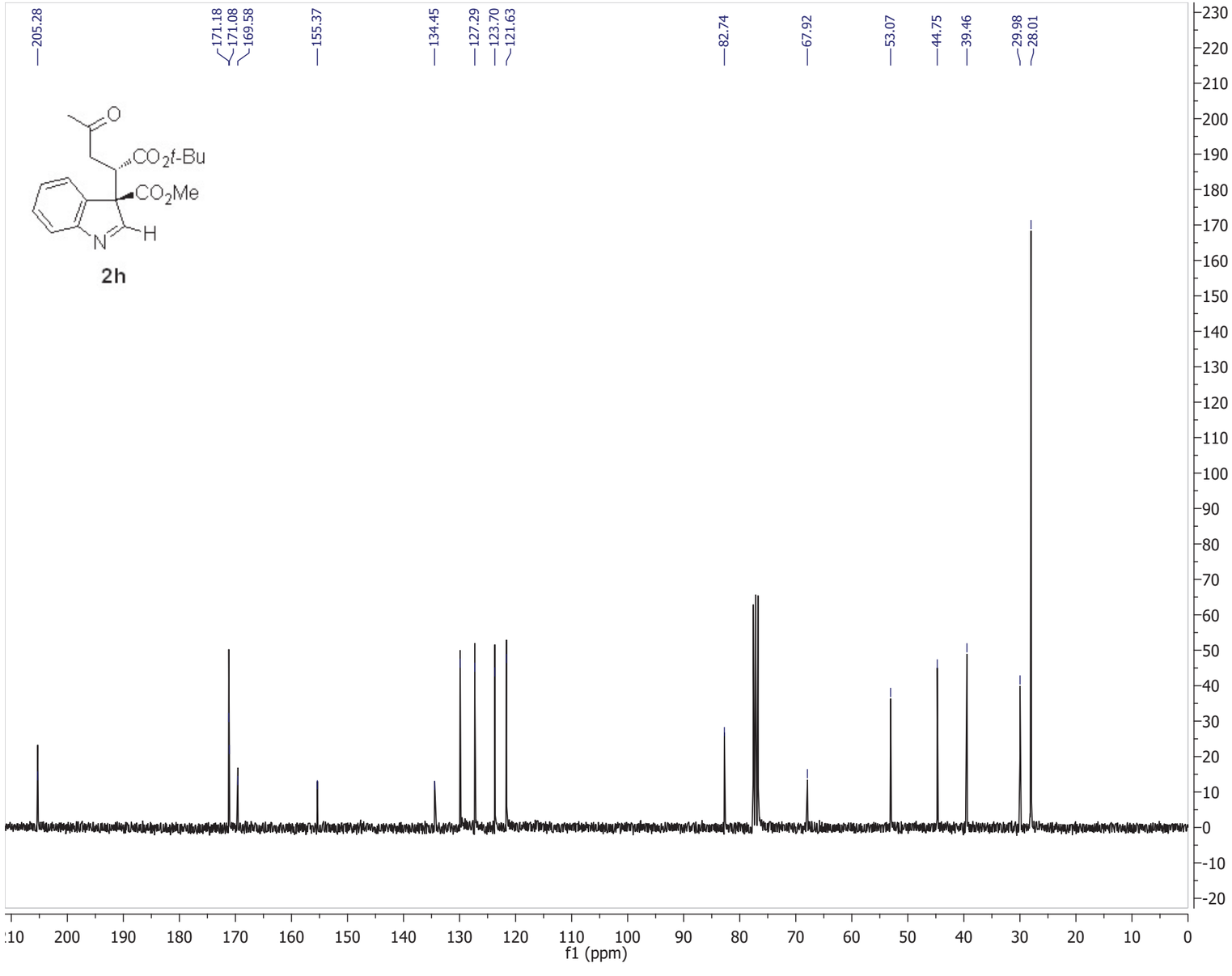

C7H15
O
CO2Et
CO2Et
CO2Et
N
2f
7.77
7.47
7.39
4.48
4.46
4.45
4.44
4.14
4.11
3.99
3.97
3.97
3.06
3.02
3.00
2.96
2.79
2.73
2.35
1.46
1.44
1.41
1.23
1.08
0.85
0.83
1.00
3.25
2.35
1.34
3.53
2.93
1.15
1.09
1.55
2.88
11.57
5.71
3.88
f1 (ppm)

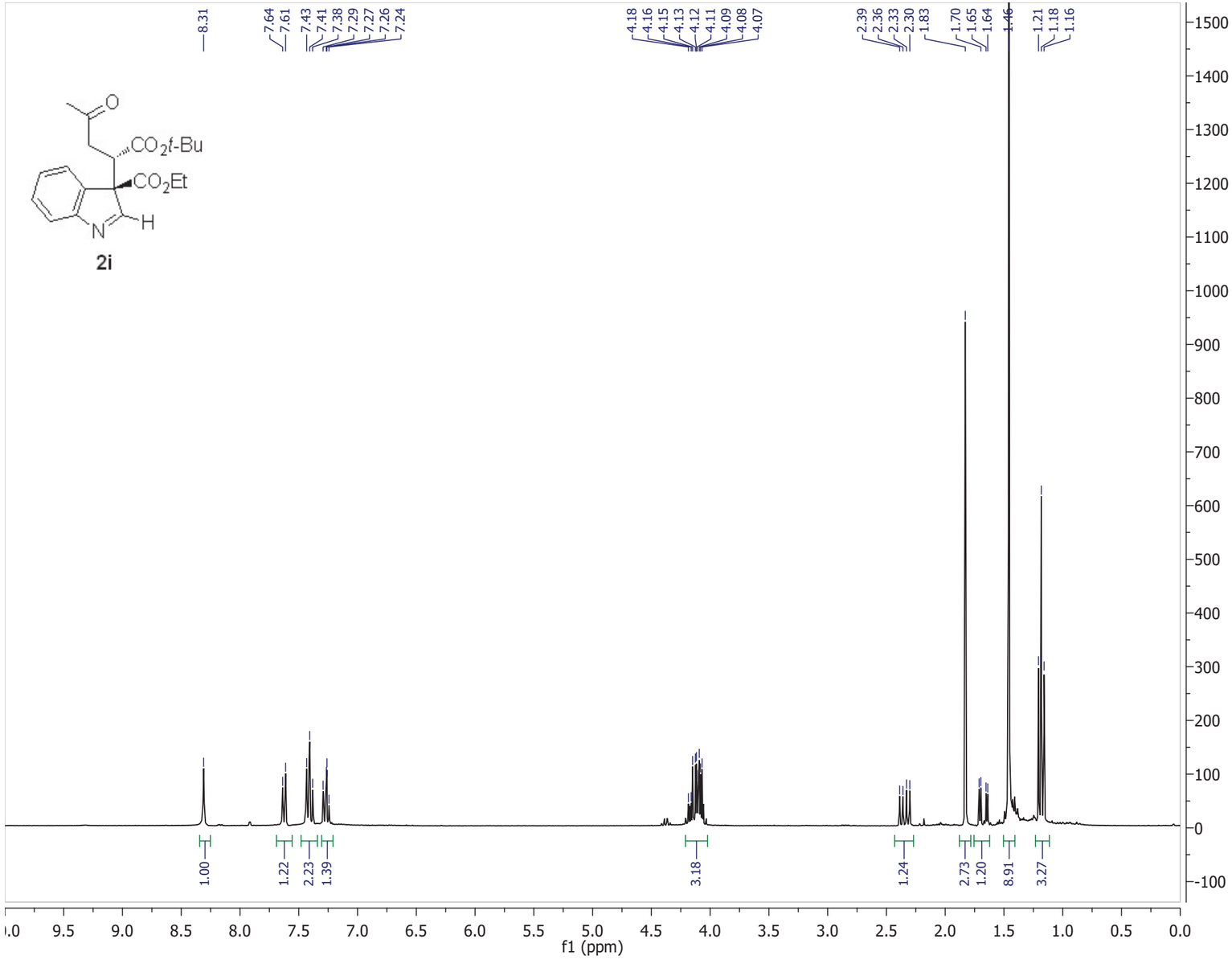

208.30
170.68
169.34
167.77
161.57
154.02
136.91
130.12
128.95
123.88
62.47
62.26
61.55
43.53
42.94
40.04
31.75
29.19
29.13
22.71
14.33
14.18
13.84
C7H15
O
CO2Et
CO2Et
CO2Et
N
2f
f1 (ppm)

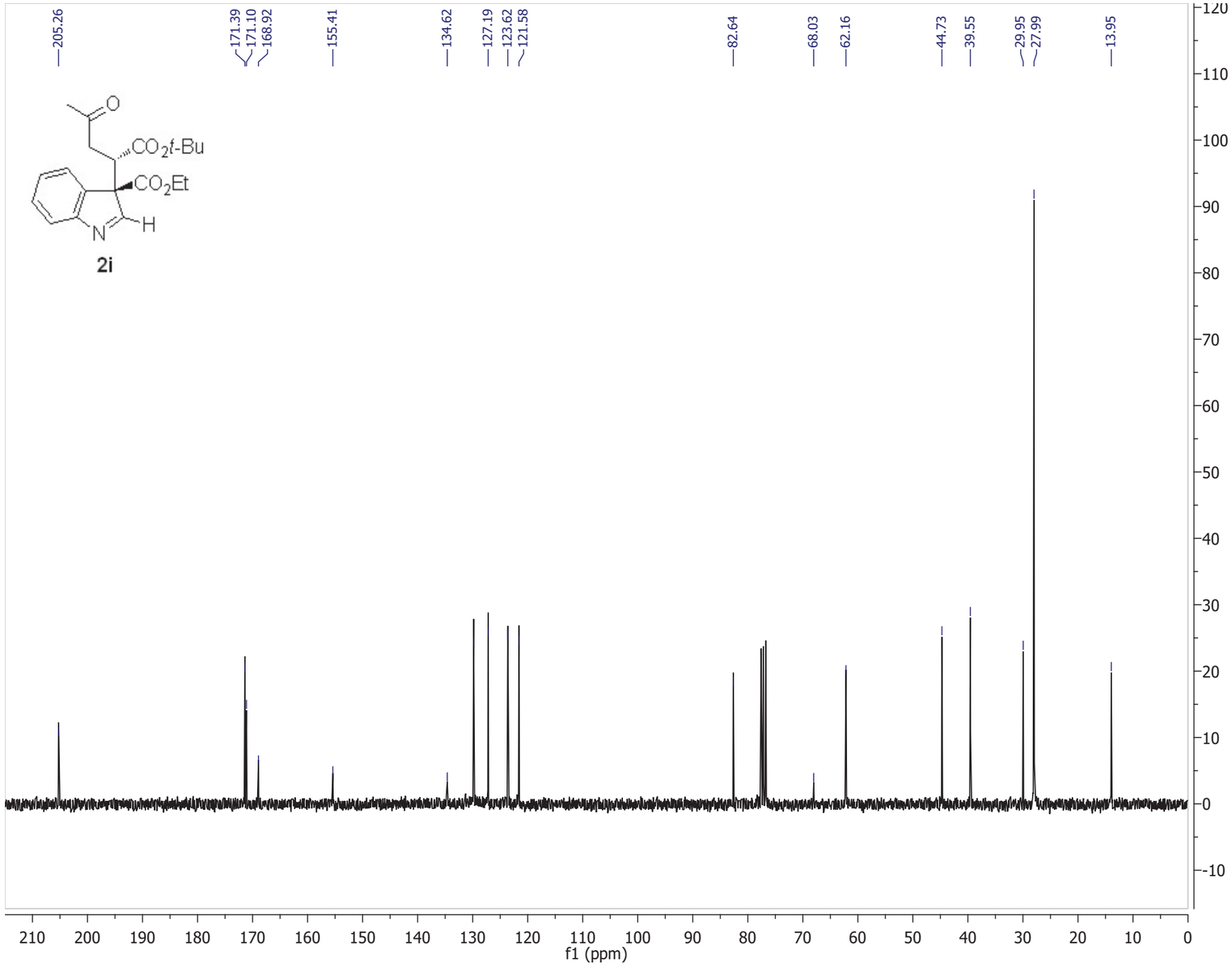

Ph
O
CO2Et
CO2Et
CO2Et
N
2g
Aliphatic Impurities
1.26 ppm
Water ~1.6 ppm
f1 (ppm)

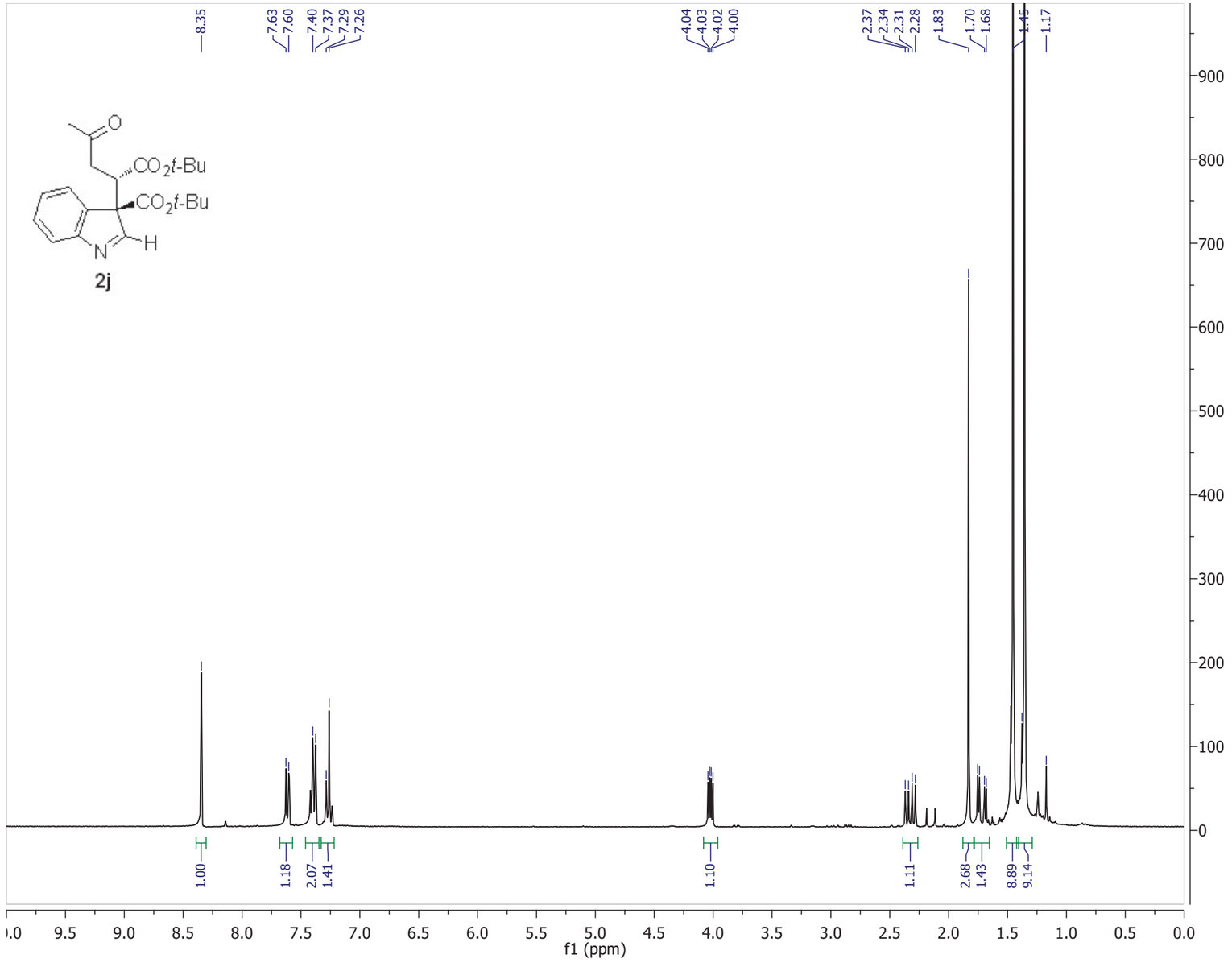

207.10
170.63
169.28
167.74
161.59
154.01
140.98
136.85
130.16
128.98
128.59
128.57
128.37
126.20
123.92
123.87
67.17
62.50
62.30
61.62
44.46
43.63
40.13
29.61
14.35
13.85
Ph
O
CO2Et
CO2Et
CO2Et
N
2g
f1 (ppm)

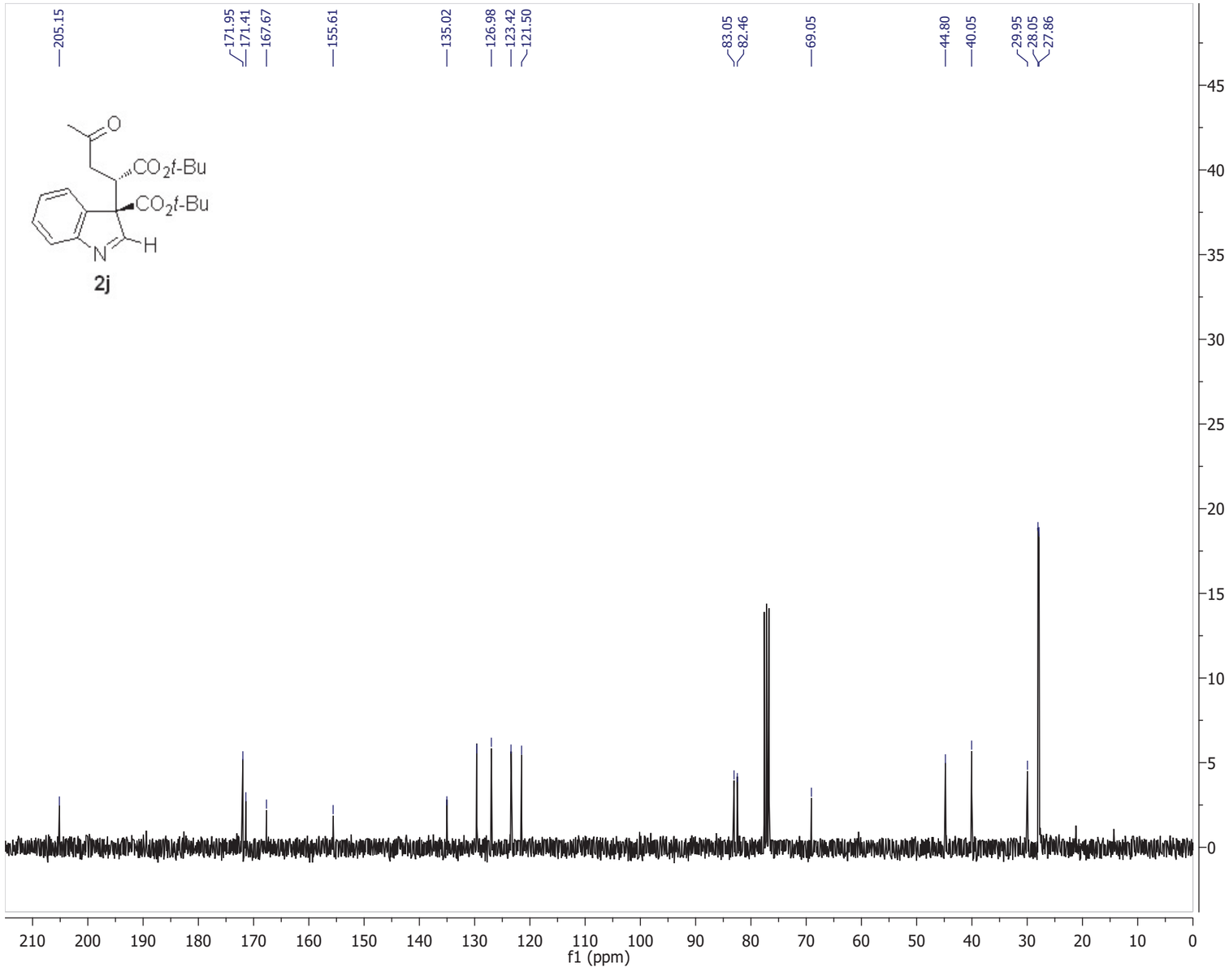

O
CO2t-Bu
CO2Me
H
N
2h
7.65
7.62
7.44
7.42
7.39
7.30
7.28
7.26
4.13
4.12
4.10
4.09
3.67
2.39
2.37
2.33
2.31
2.19
1.83
1.65
1.64
1.47
1.03
1.21
2.28
1.00
1.18
3.12
1.29
2.81
1.42
9.21
4000
3500
3000
2500
2000
1500
1000
500
0
f1 (ppm)

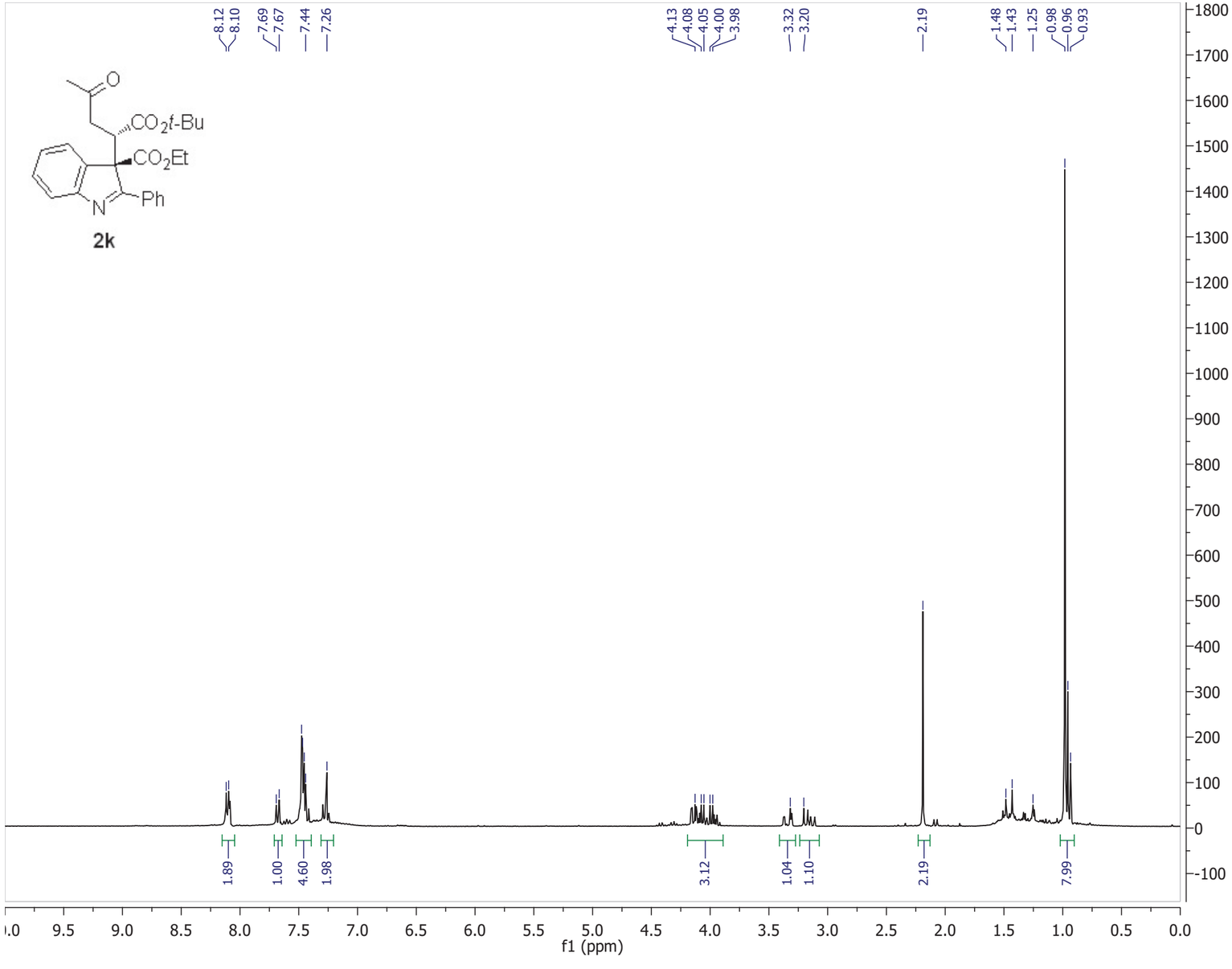

205.28
171.18
171.08
169.58
155.37
134.45
127.29
123.70
121.63
82.74
67.92
53.07
44.75
39.46
29.98
28.01
O
CO2t-Bu
CO2Me
H
N
2h
f1 (ppm)

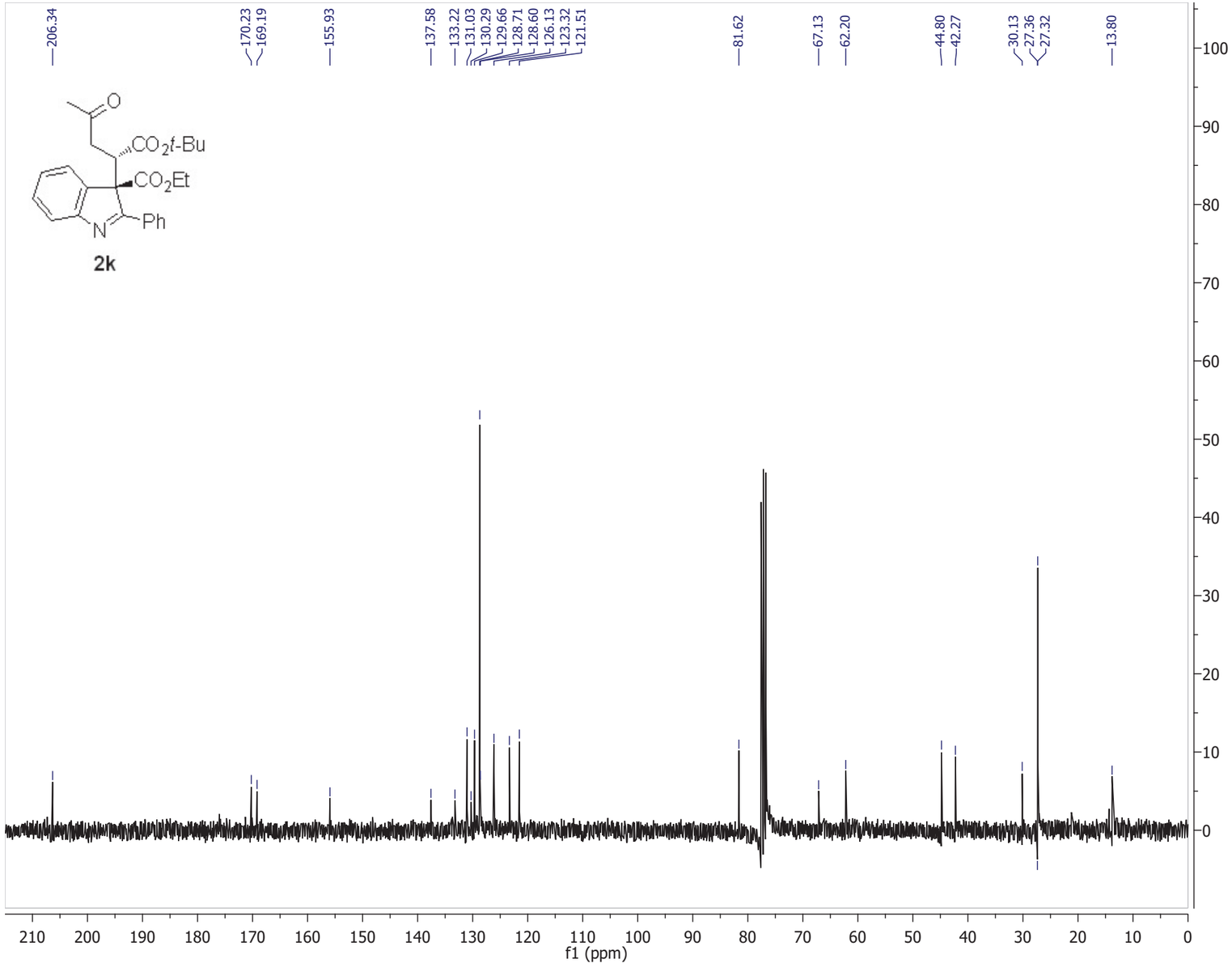

8.31
7.64
7.61
7.43
7.41
7.38
7.29
7.27
7.26
7.24
4.18
4.16
4.15
4.13
4.12
4.11
4.09
4.08
4.07
2.39
2.36
2.33
2.30
1.83
1.70
1.65
1.64
1.46
1.21
1.18
1.16
O
CO2t-Bu
CO2Et
N
H
2i
1.00
1.22
2.23
1.39
3.18
1.24
2.73
1.20
8.91
3.27
f1 (ppm)

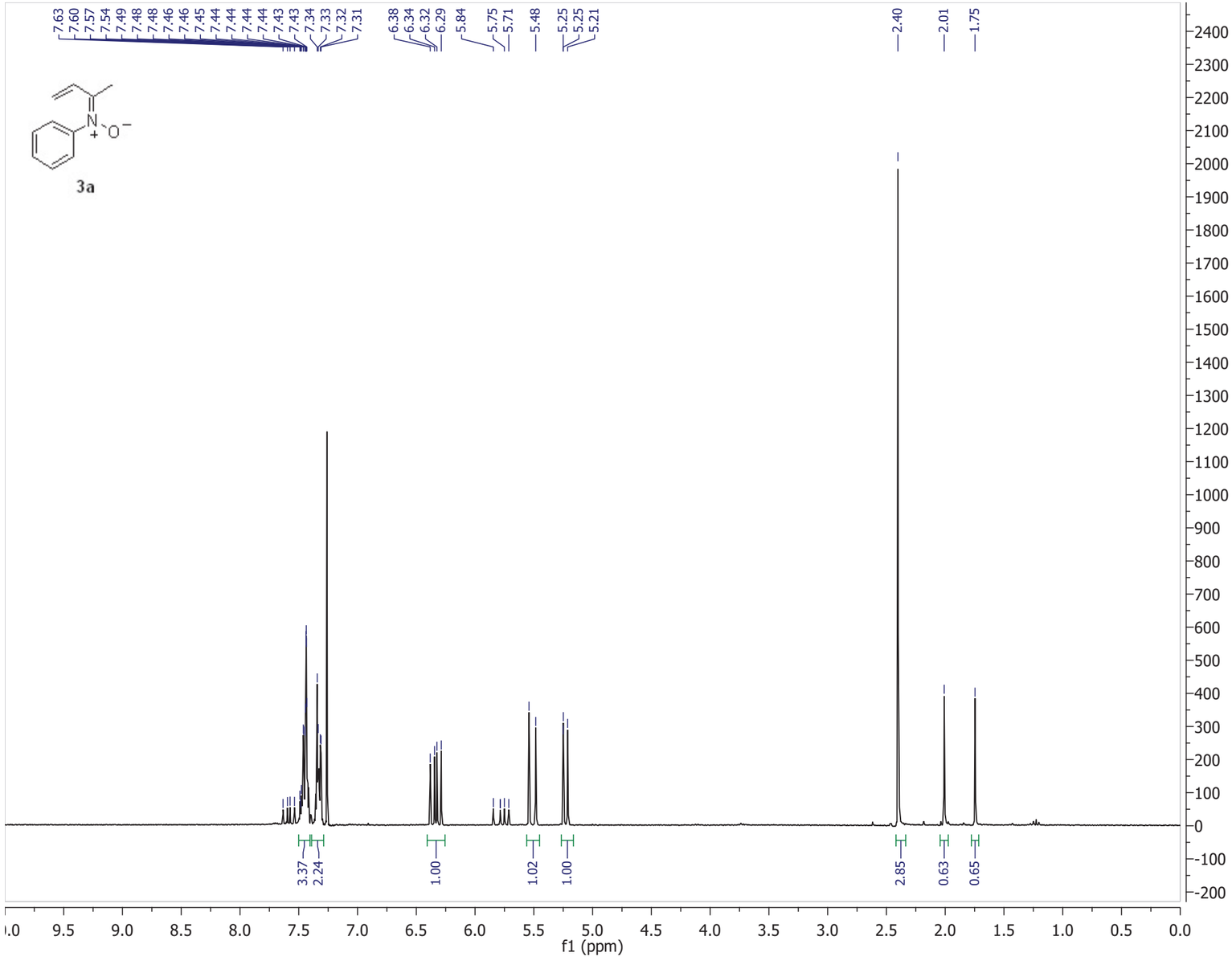

205.26
171.39
171.10
168.92
155.41
134.62
127.19
123.62
121.58
82.64
68.03
62.16
44.73
39.55
29.95
27.99
13.95
O
CO2t-Bu
CO2Et
N
H
2i
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.35
7.63
7.60
7.40
7.37
7.29
7.26
4.04
4.03
4.02
4.00
2.37
2.34
2.31
2.28
1.83
1.70
1.68
1.45
1.17
O
CO2t-Bu
CO2t-Bu
N
H
2j
1.00
1.18
2.07
1.41
1.10
1.11
2.68
1.43
8.89
9.14
f1 (ppm)

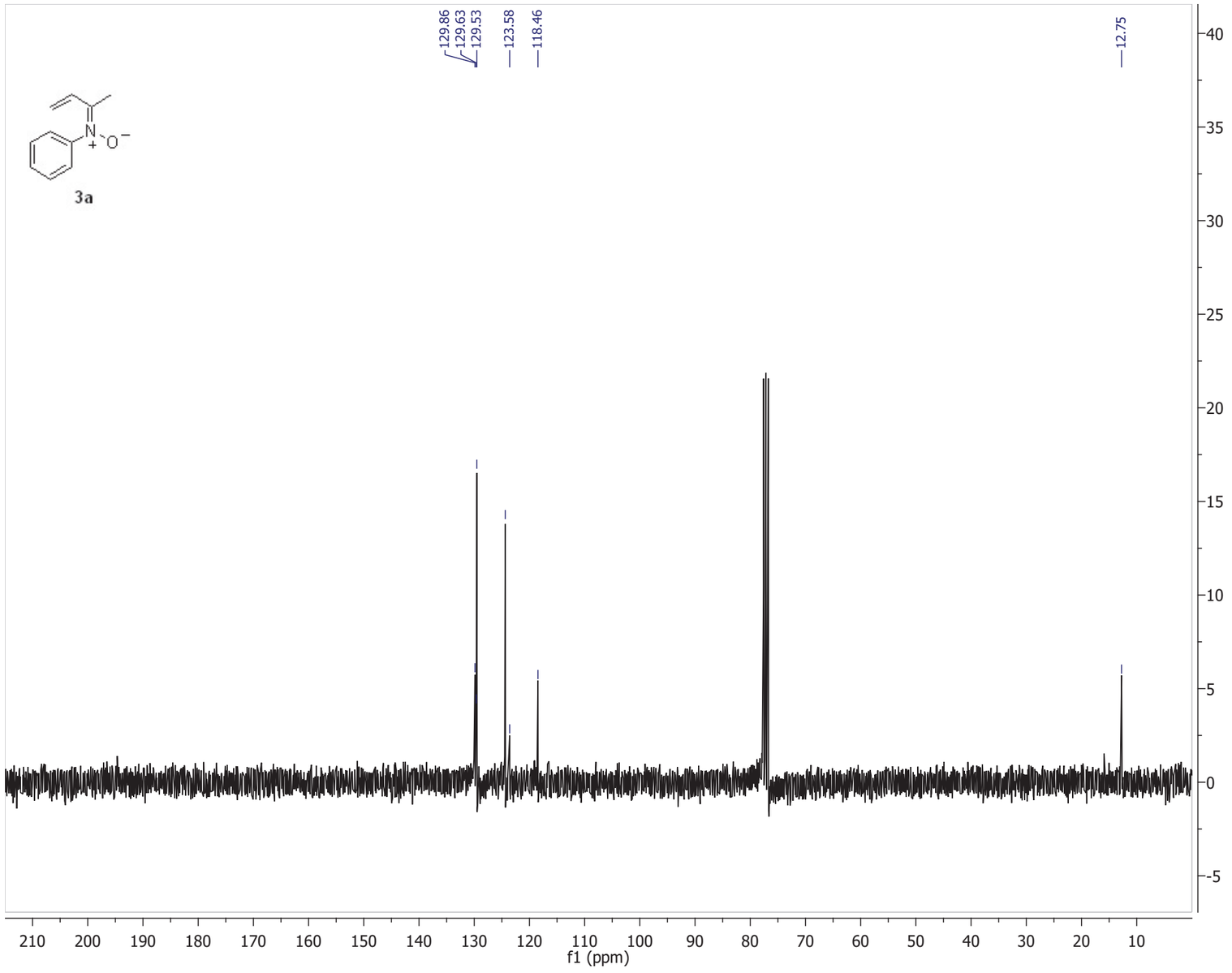

205.15
171.95
171.41
167.67
155.61
135.02
126.98
123.42
121.50
83.05
82.46
69.05
44.80
40.05
29.95
28.05
27.86
O
CO2t-Bu
CO2t-Bu
N
H
2j
45
40
35
30
25
20
15
10
5
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

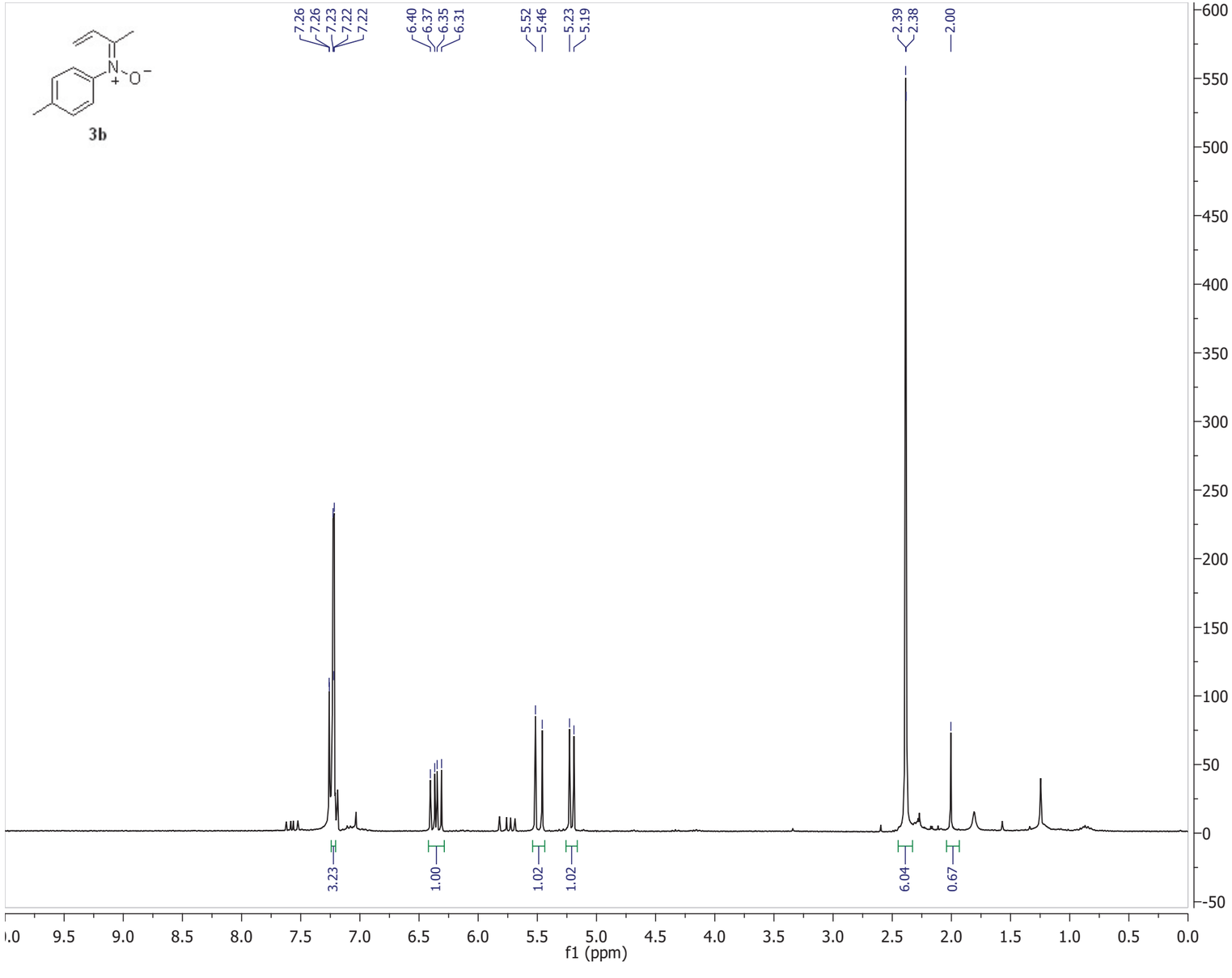

8.12
8.10
7.69
7.67
7.44
7.26
4.13
4.08
4.05
4.00
3.98
3.32
3.20
2.19
1.48
1.43
1.25
0.98
0.96
0.93
O
CO2t-Bu
CO2Et
N
Ph
2k
1.89
1.00
4.60
1.98
3.12
1.04
1.10
2.19
7.99
f1 (ppm)

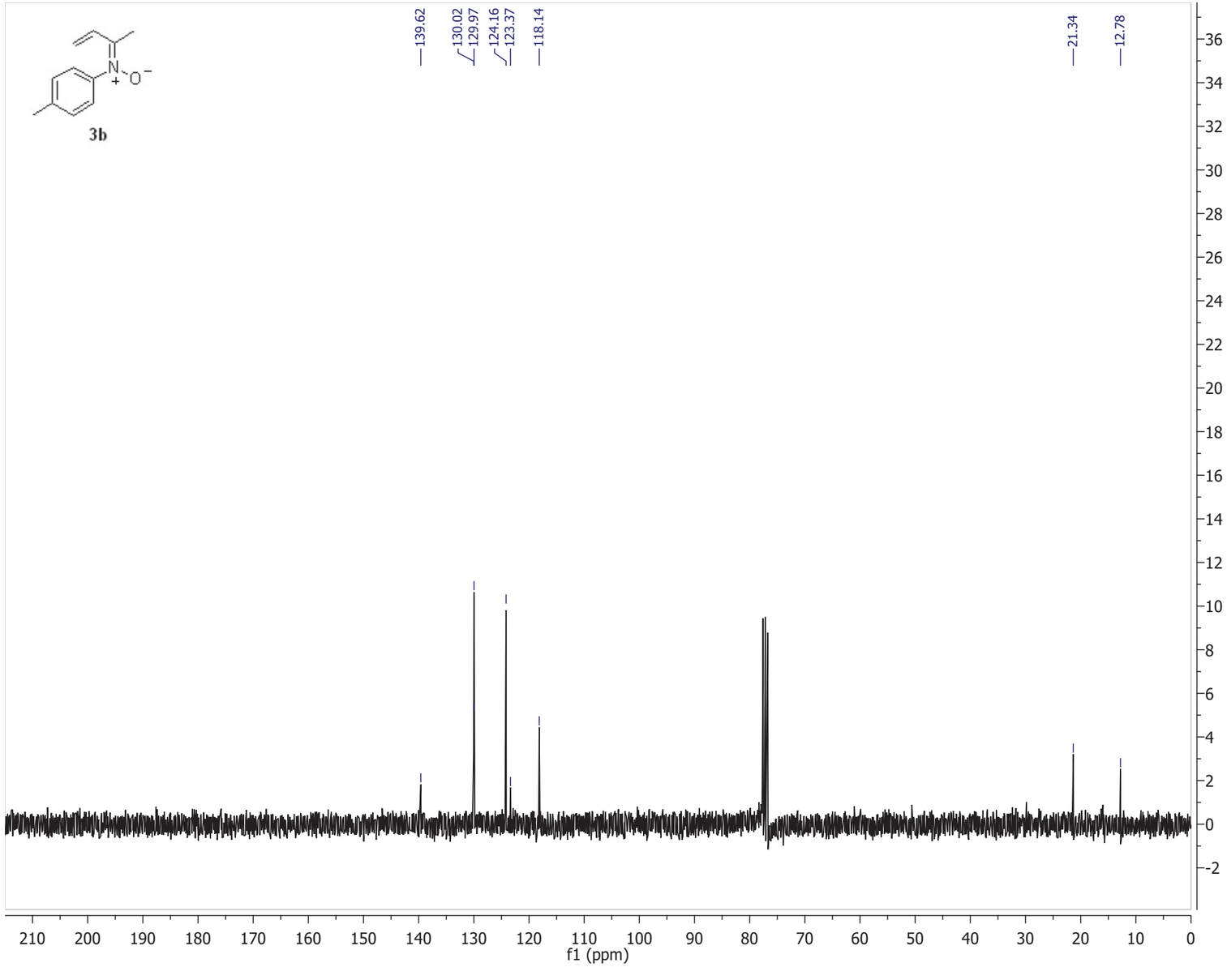

206.34
170.23
169.19
155.93
137.58
133.22
131.03
130.29
129.66
128.71
128.60
126.13
123.32
121.51
81.62
67.13
62.20
44.80
42.27
30.13
27.36
27.32
13.80
O
CO2t-Bu
CO2Et
N
Ph
2k
100
90
80
70
60
50
40
30
20
10
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

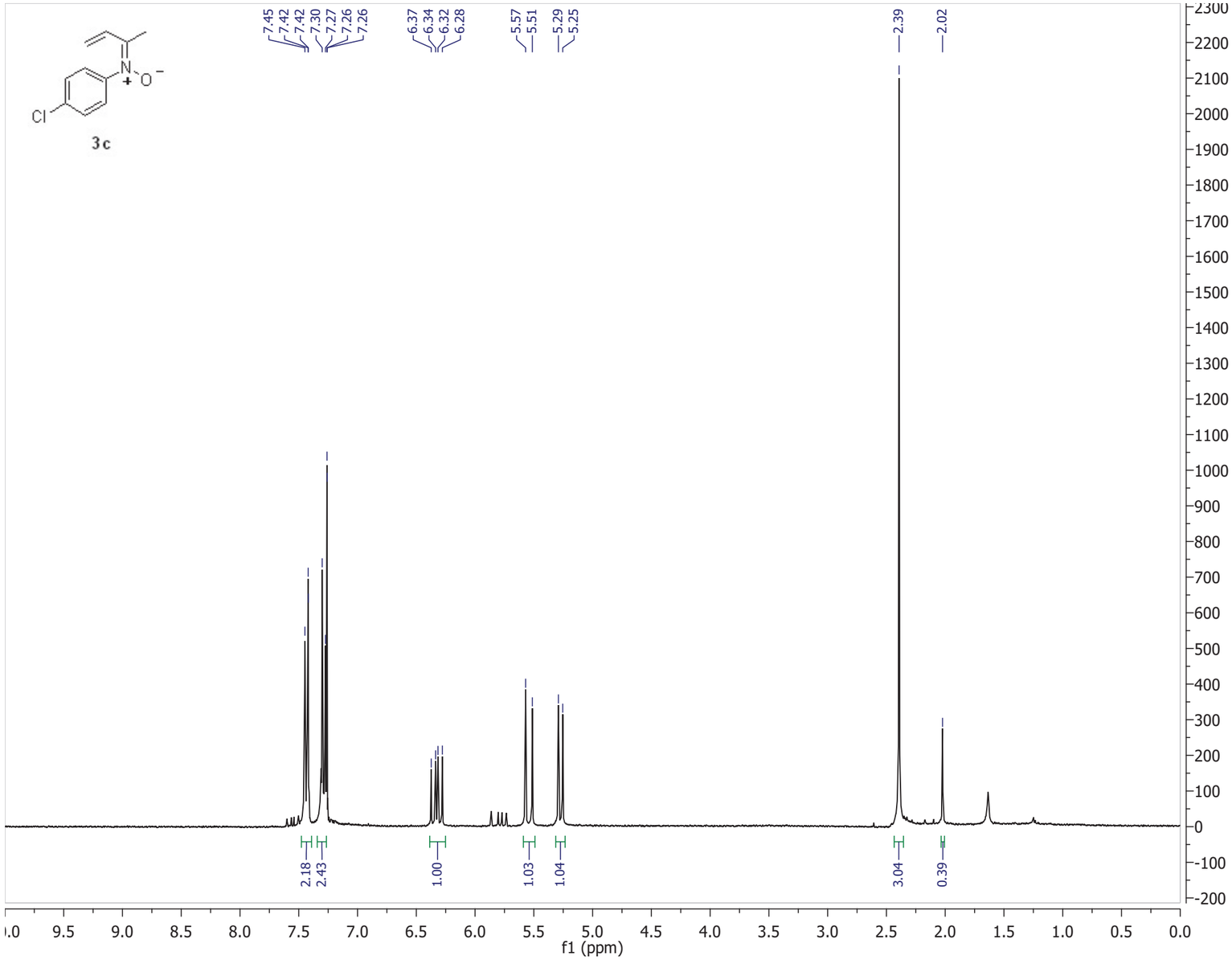

7.63
7.60
7.57
7.54
7.49
7.48
7.48
7.46
7.46
7.45
7.44
7.44
7.44
7.44
7.43
7.43
7.34
7.33
7.32
7.31
6.38
6.34
6.32
6.29
5.84
5.75
5.71
5.48
5.25
5.25
5.21
2.40
2.01
1.75
3.37
2.24
1.00
1.02
1.00
2.85
0.63
0.65
f1 (ppm)

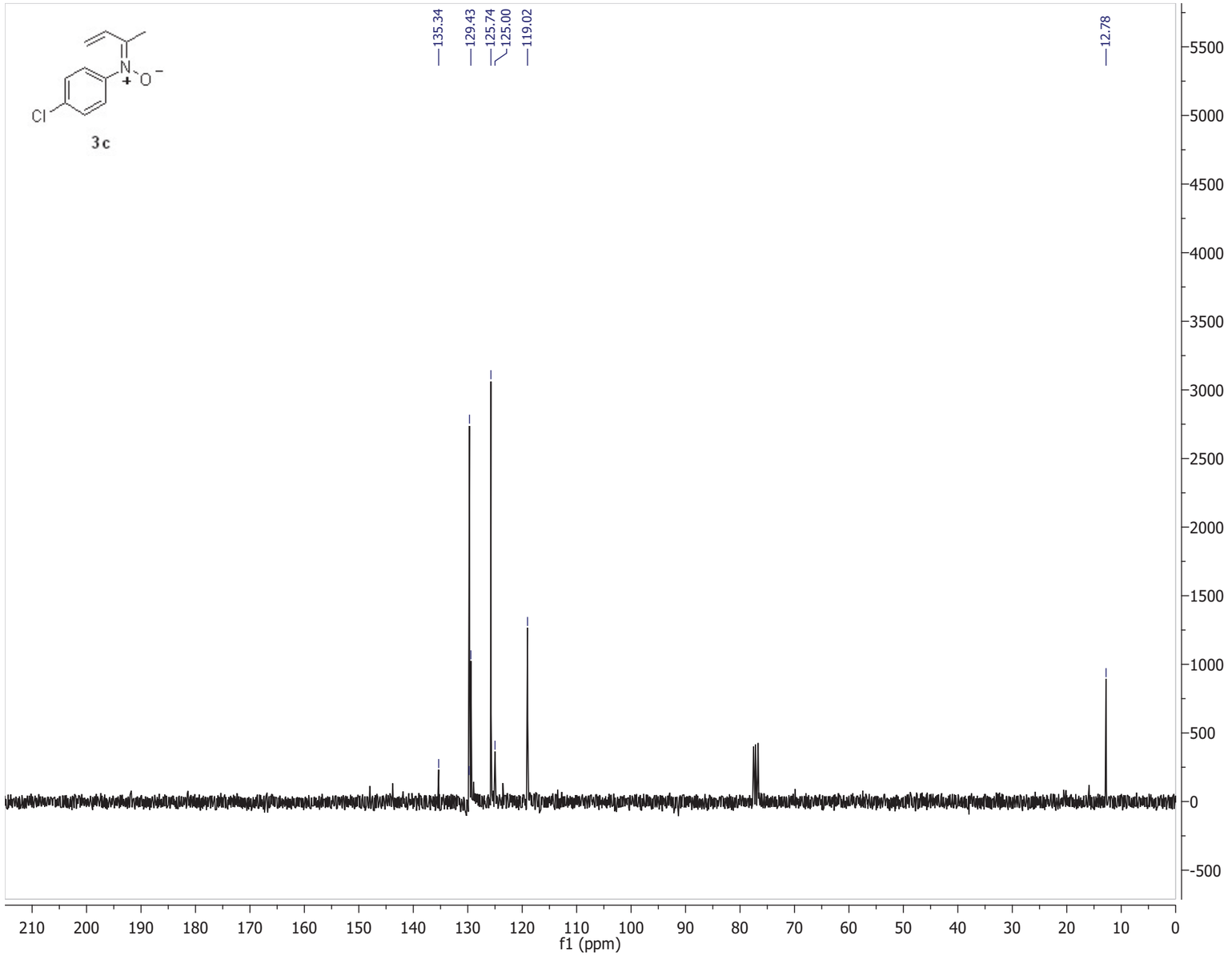
3a

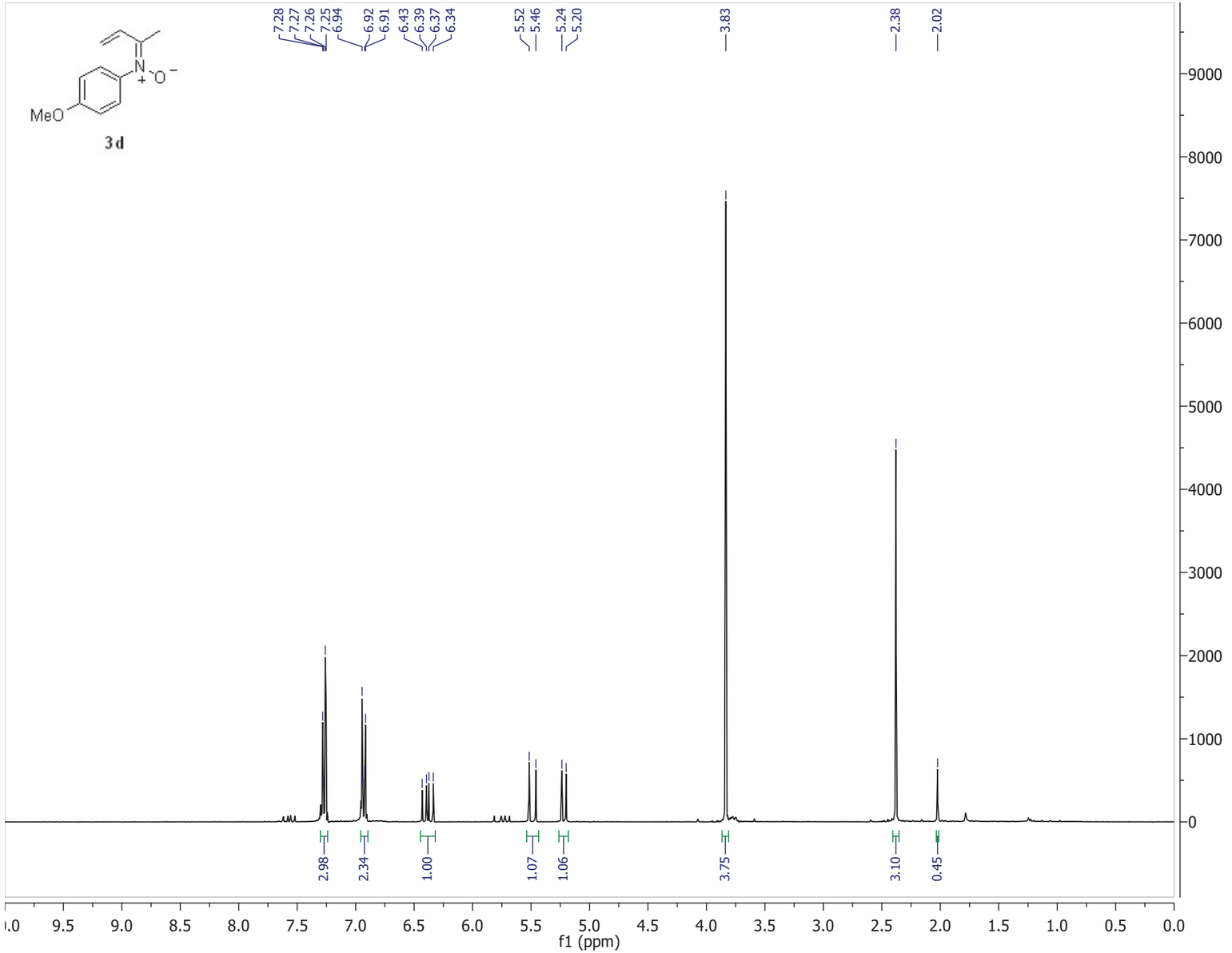

129.86
129.63
129.53
123.58
118.46
12.75
3a
40
35
30
25
20
15
10
5
0
-5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

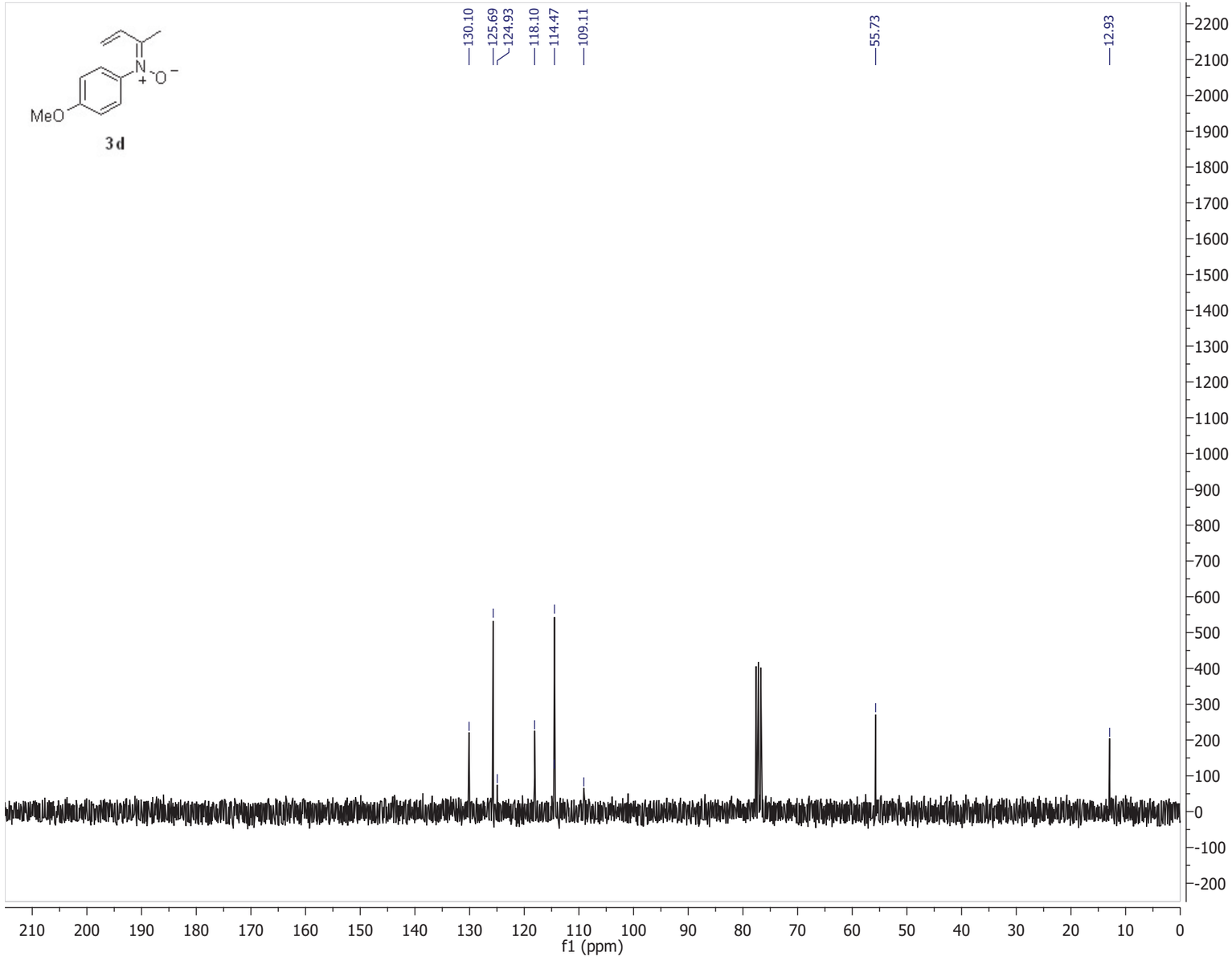

3b
7.26
7.26
7.23
7.22
7.22
6.40
6.37
6.35
6.31
5.52
5.46
5.23
5.19
2.39
2.38
2.00
3.23
1.00
1.02
1.02
6.04
0.67
f1 (ppm)

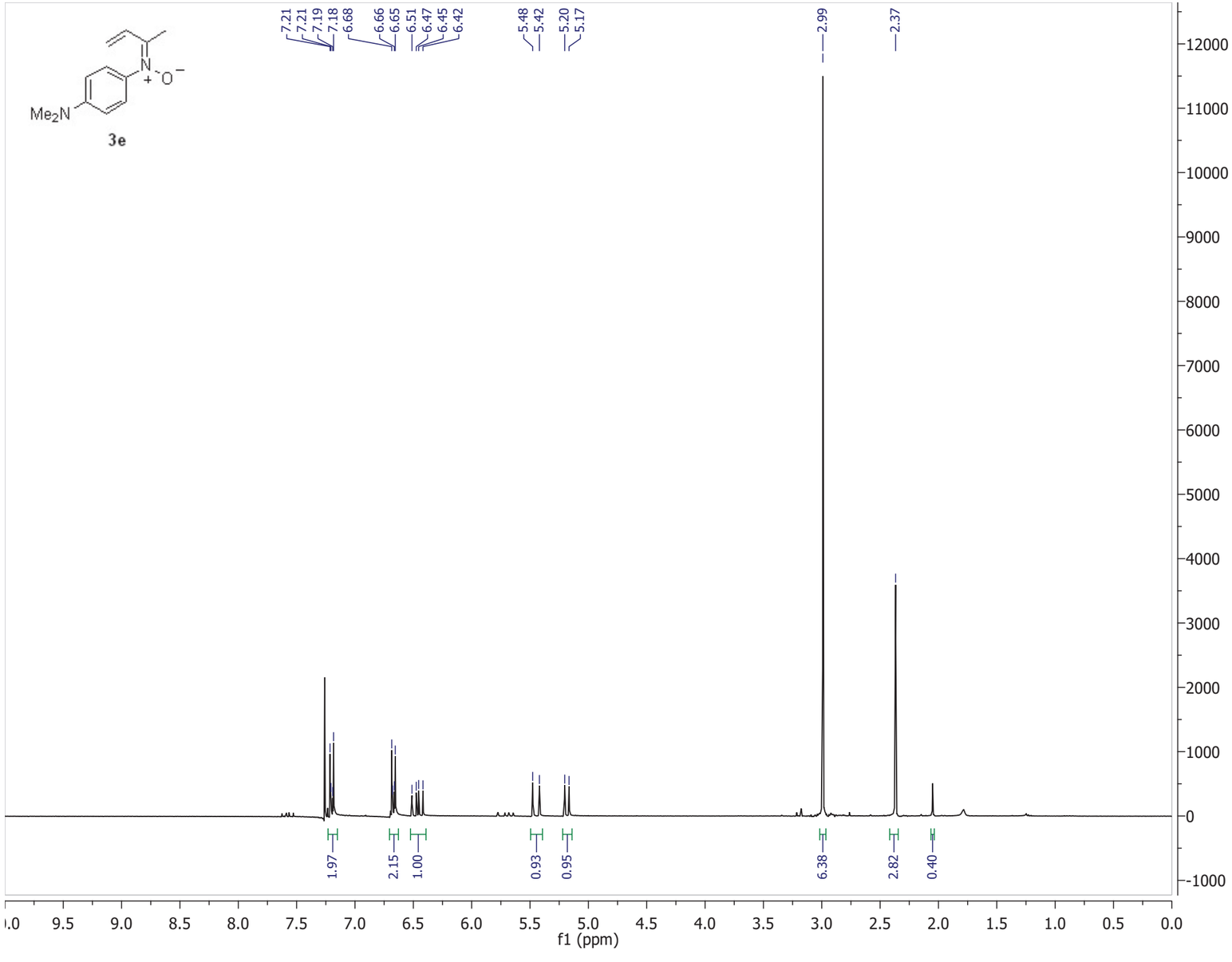

3b
139.62
130.02
129.97
124.16
123.37
118.14
21.34
12.78
f1 (ppm)

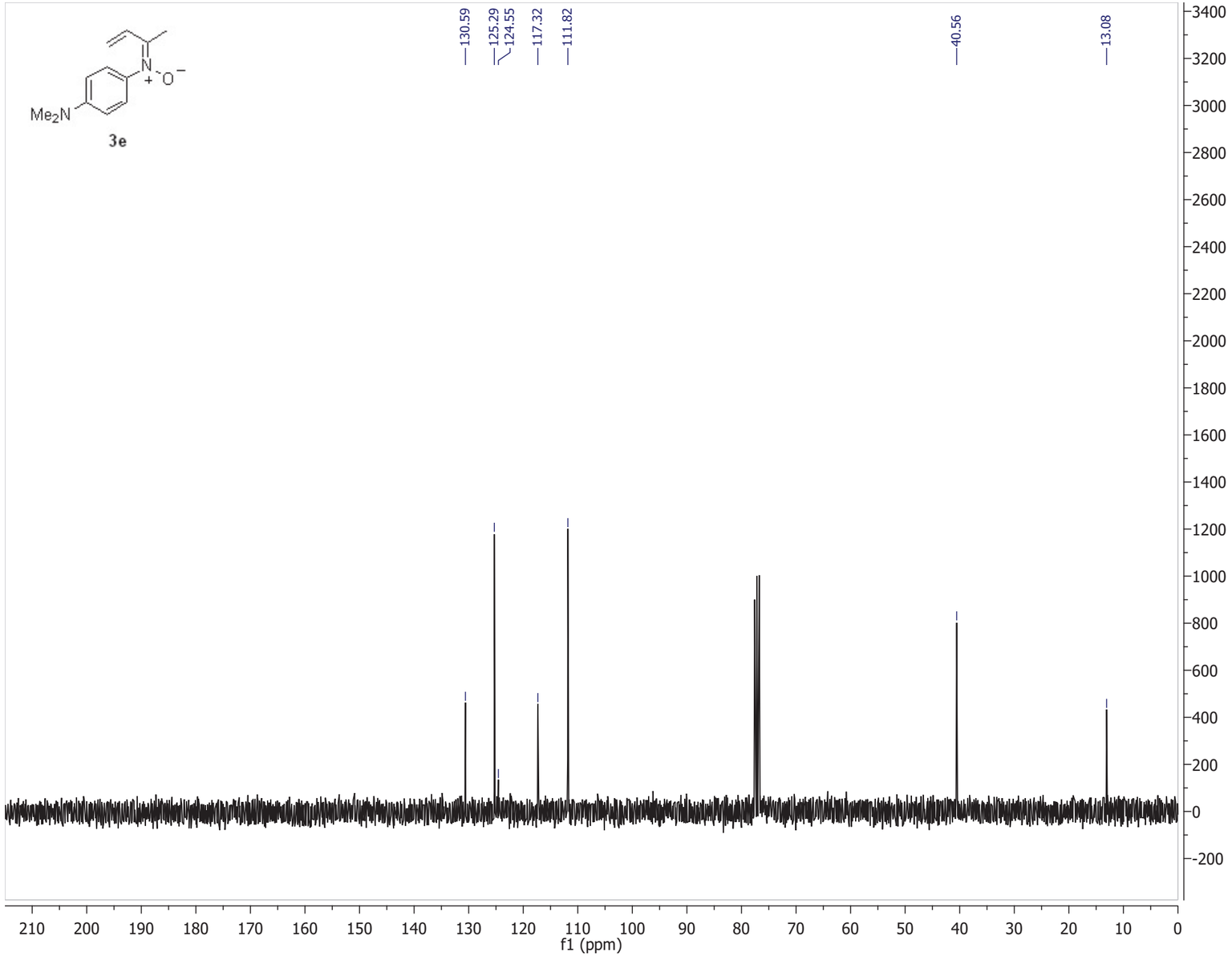

7.45
7.42
7.42
7.30
7.27
7.26
7.26
6.37
6.34
6.32
6.28
5.57
5.51
5.29
5.25
2.39
2.02
Cl
N
O
3c
2.18
2.43
1.00
1.03
1.04
3.04
0.39
f1 (ppm)

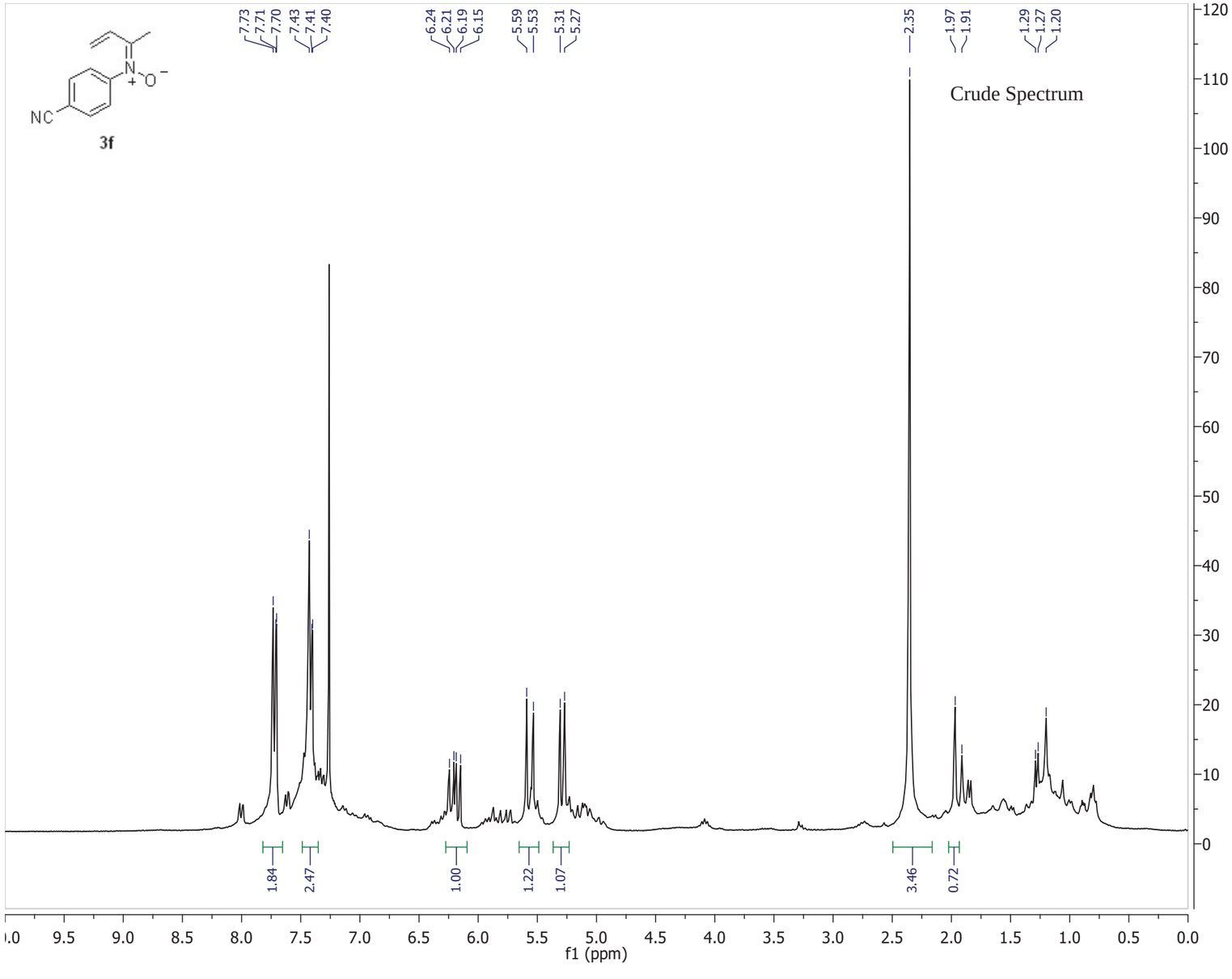

135.34
129.43
125.74
125.00
119.02
12.78
Cl
N
O
3c
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

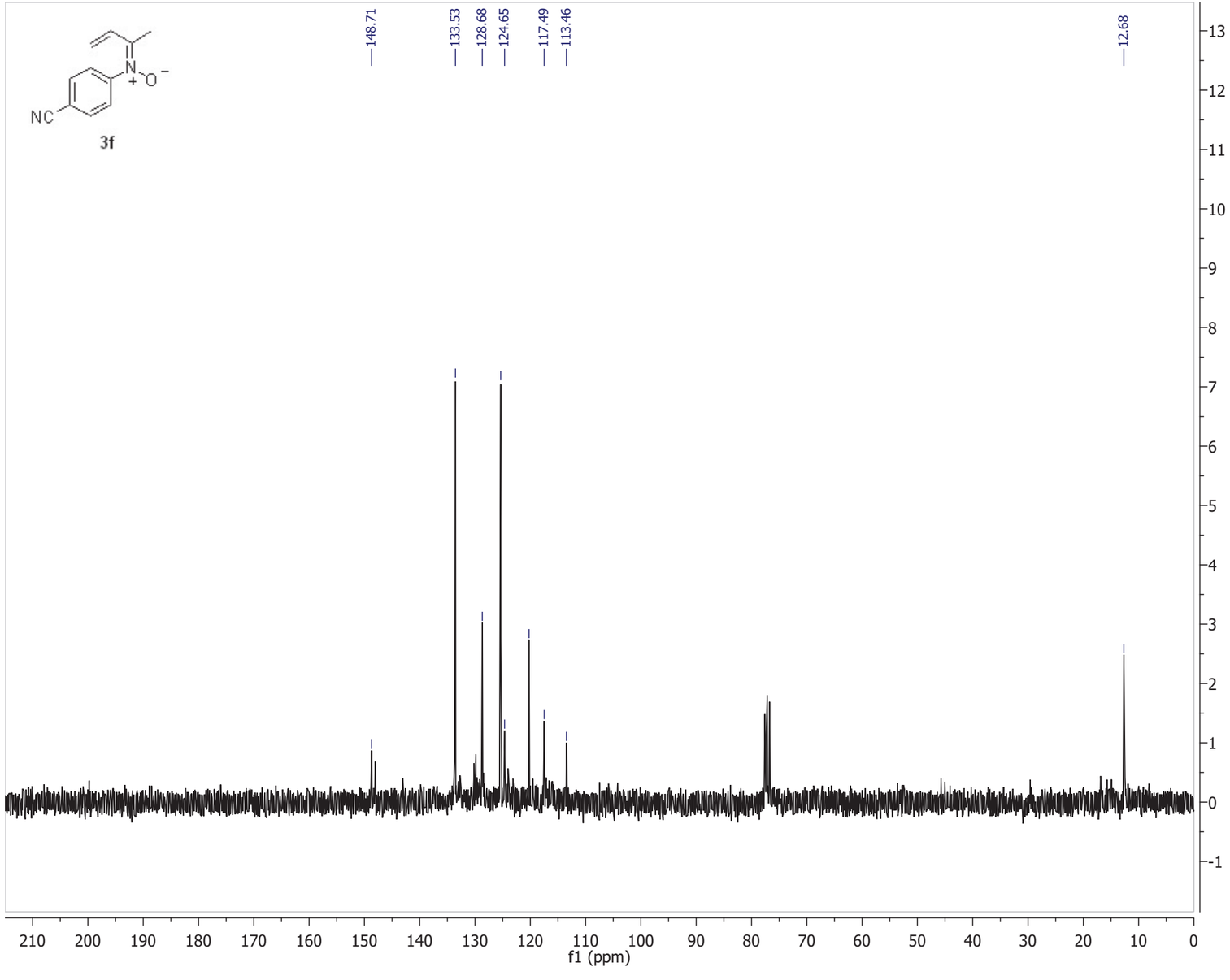

MeO
3d
7.28
7.27
7.26
7.25
6.94
6.92
6.91
6.43
6.39
6.37
6.34
5.52
5.46
5.24
5.20
3.83
2.38
2.02
2.98
2.34
1.00
1.07
1.06
3.75
3.10
0.45
f1 (ppm)

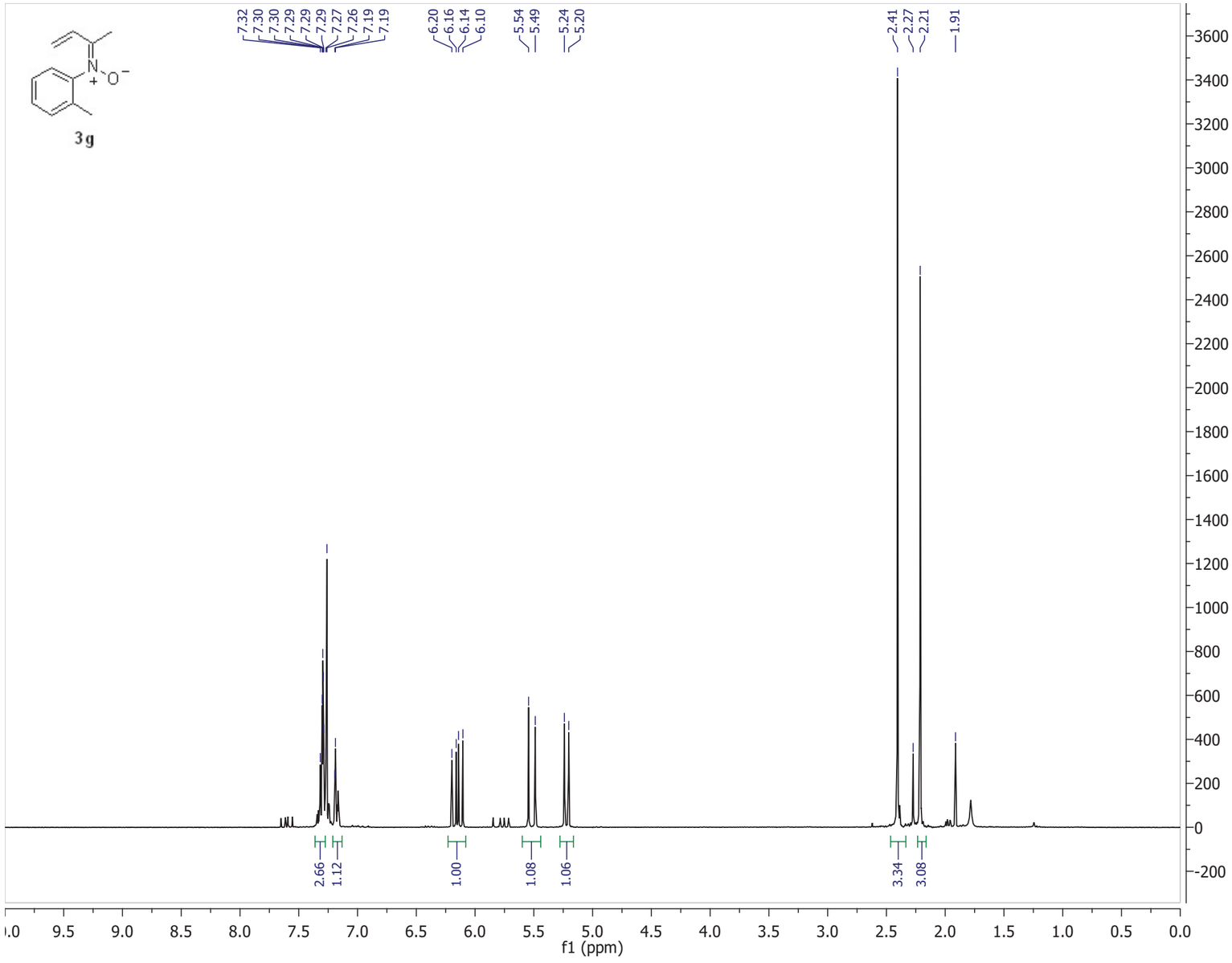

130.10
125.69
124.93
118.10
114.47
109.11
55.73
12.93
MeO
N
O
3d
f1 (ppm)

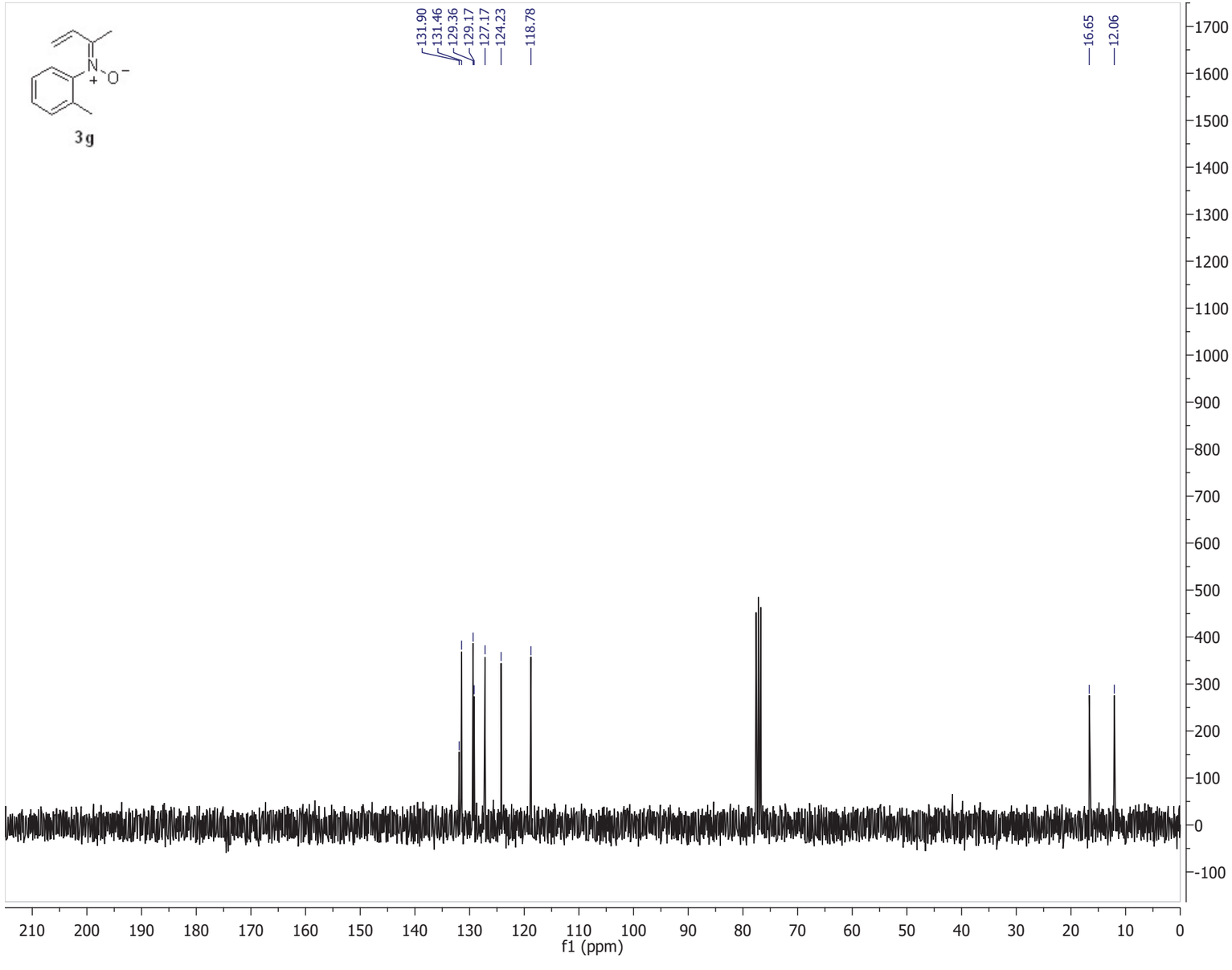

7.21
7.21
7.19
7.18
6.68
6.66
6.65
6.51
6.47
6.45
6.42
5.48
5.42
5.20
5.17
2.99
2.37
Me2N
N
O
3e
1.97
2.15
1.00
0.93
0.95
6.38
2.82
0.40
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

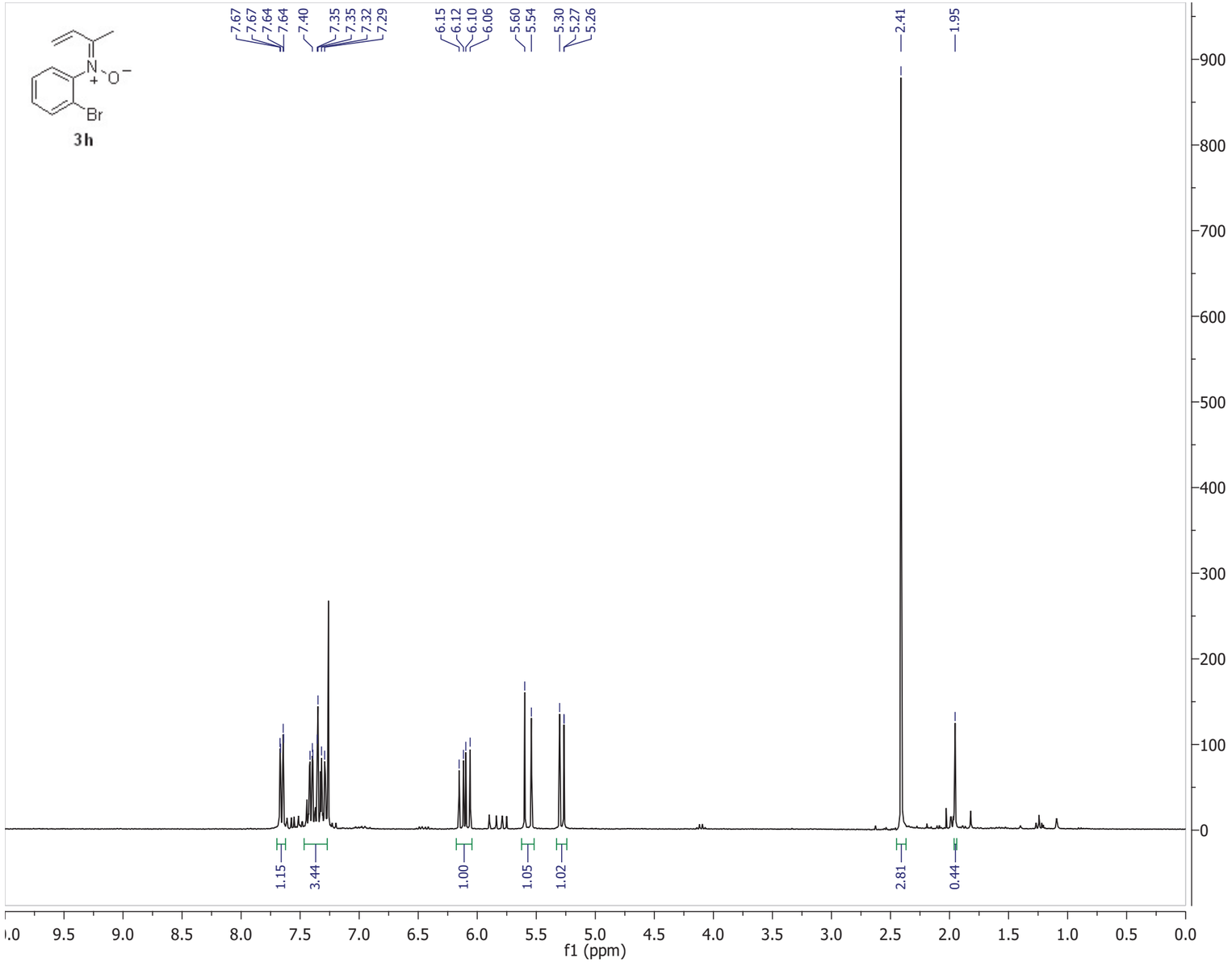

130.59
125.29
124.55
117.32
111.82
40.56
13.08
Me2N
3e
f1 (ppm)

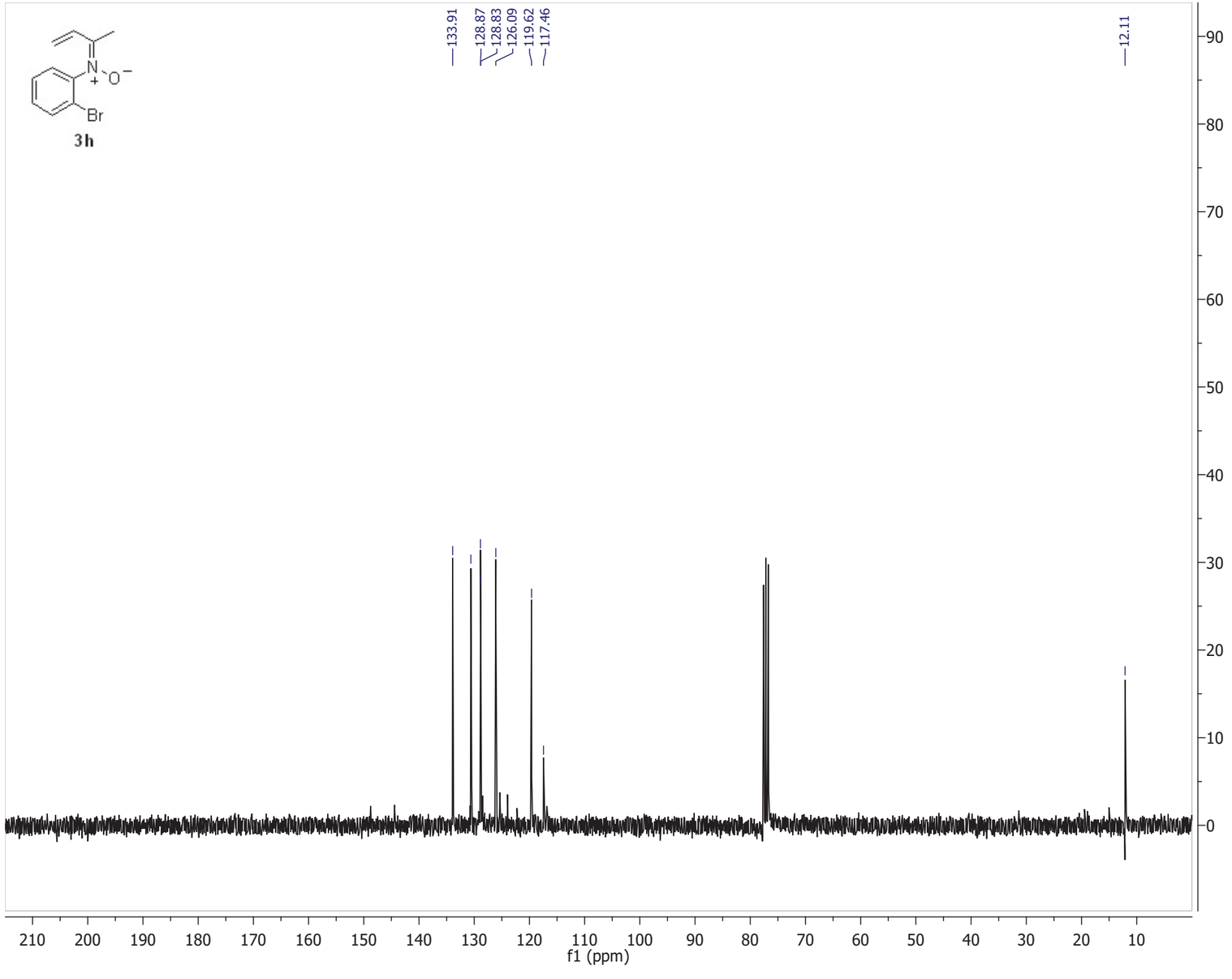

7.73
7.71
7.70
7.43
7.41
7.40
6.24
6.21
6.19
6.15
5.59
5.53
5.31
5.27
2.35
1.97
1.91
1.29
1.27
1.20
Crude Spectrum
NC
3f
1.84
2.47
1.00
1.22
1.07
3.46
0.72
f1 (ppm)

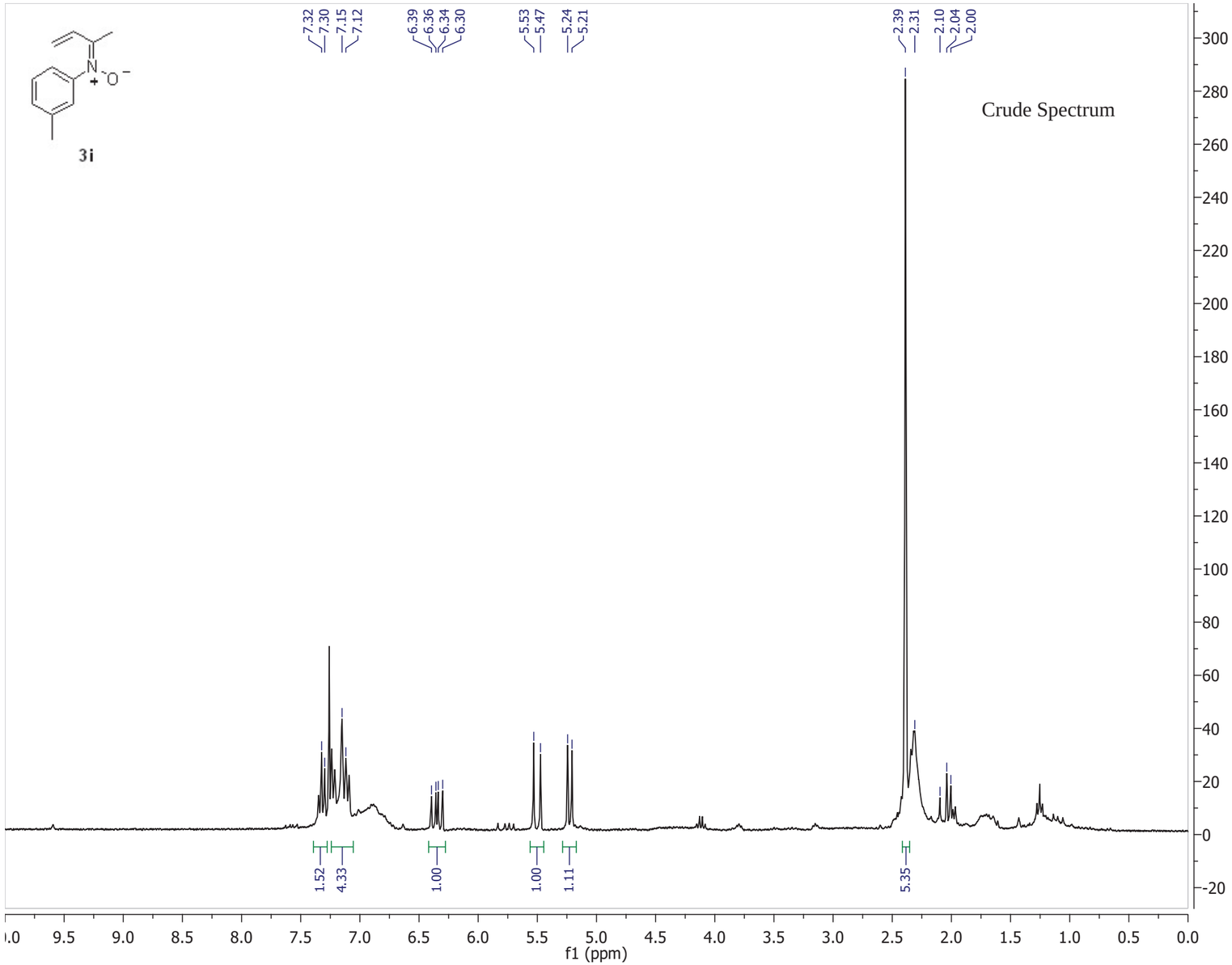

148.71
133.53
128.68
124.65
117.49
113.46
12.68
NC
3f
f1 (ppm)

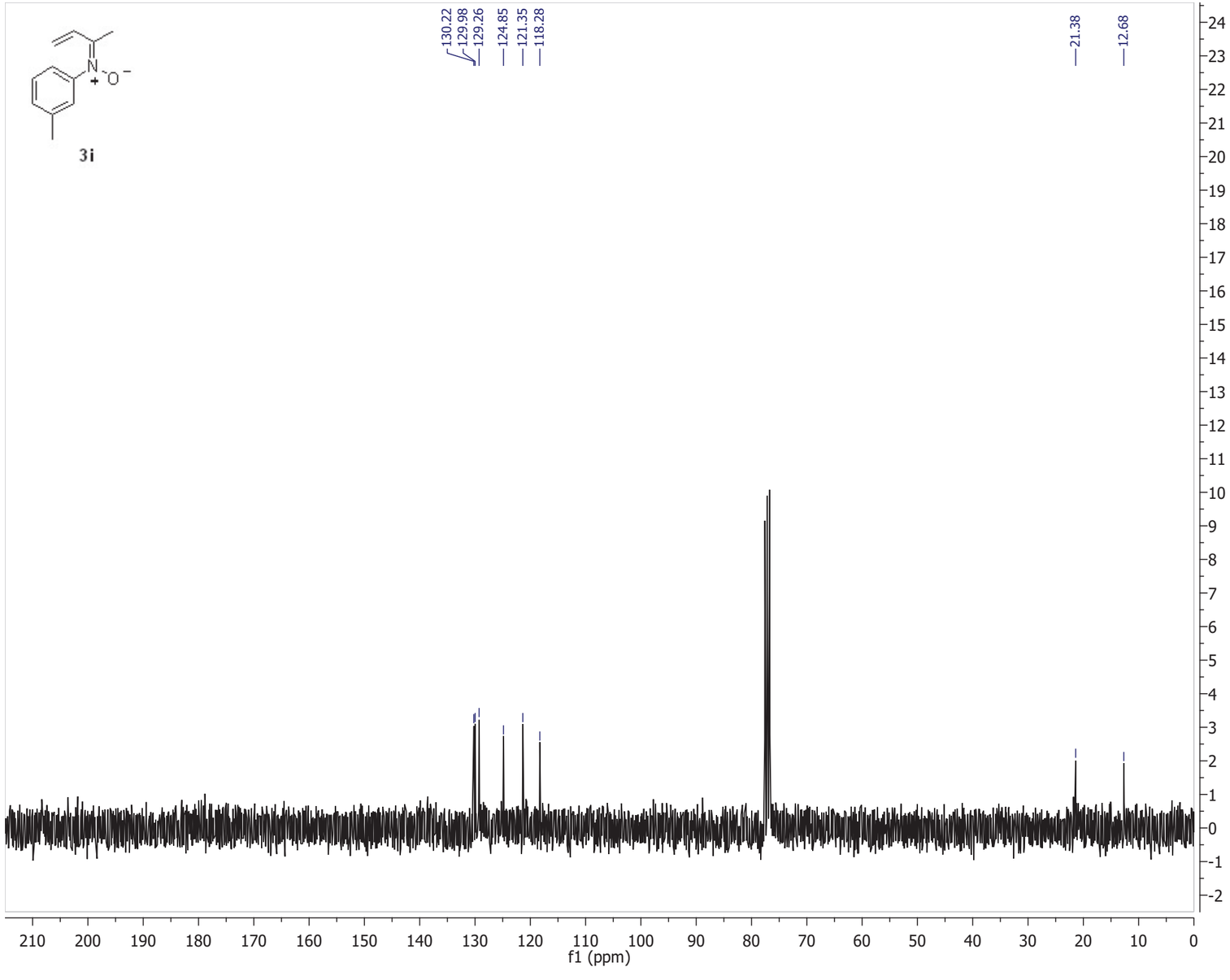

3g
7.32
7.30
7.30
7.29
7.29
7.29
7.27
7.26
7.19
7.19
6.20
6.16
6.14
6.10
5.54
5.49
5.24
5.20
2.41
2.27
2.21
1.91
2.66
1.12
1.00
1.08
1.06
3.34
3.08
f1 (ppm)

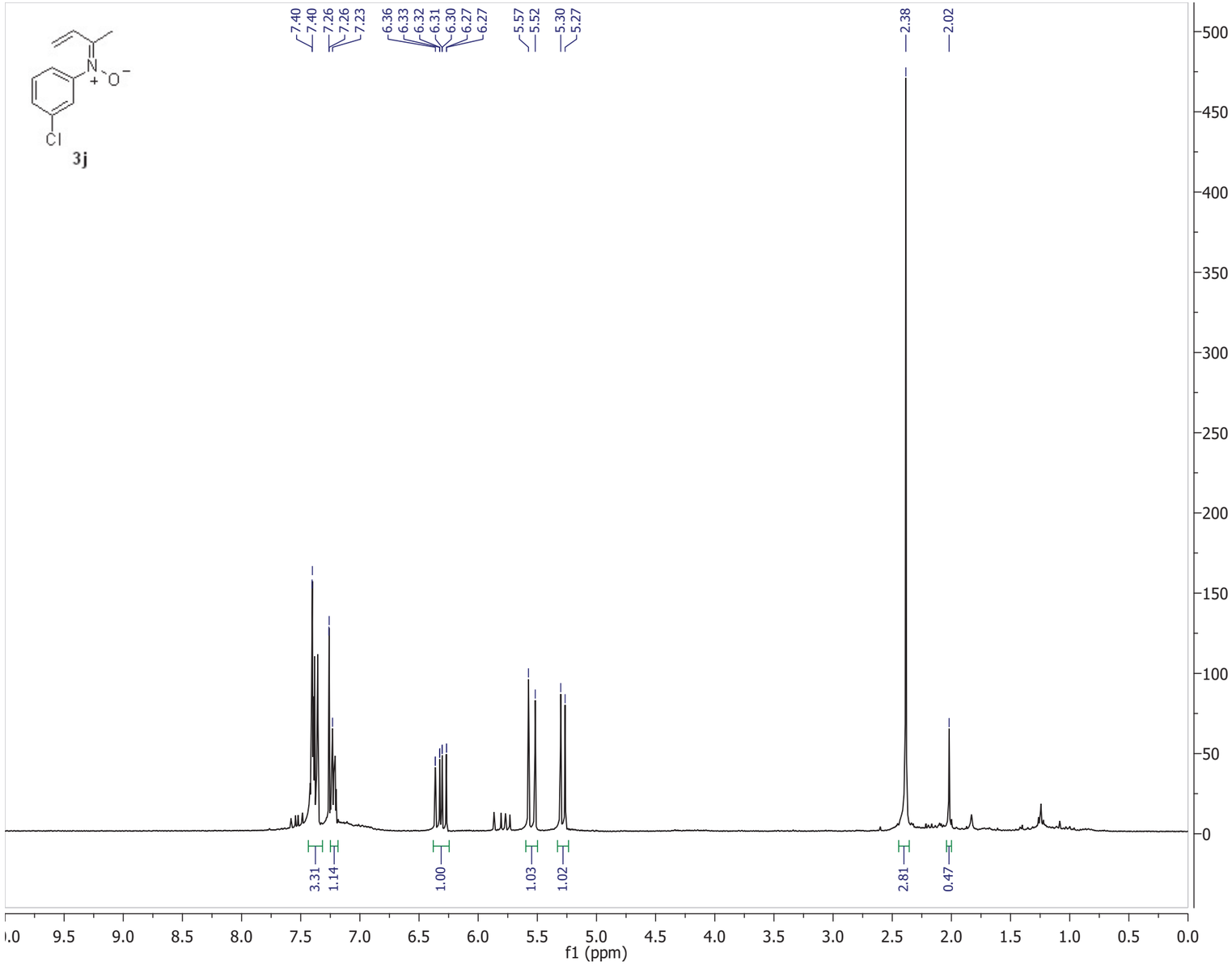

3g
131.90
131.46
129.36
129.17
127.17
124.23
118.78
16.65
12.06
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

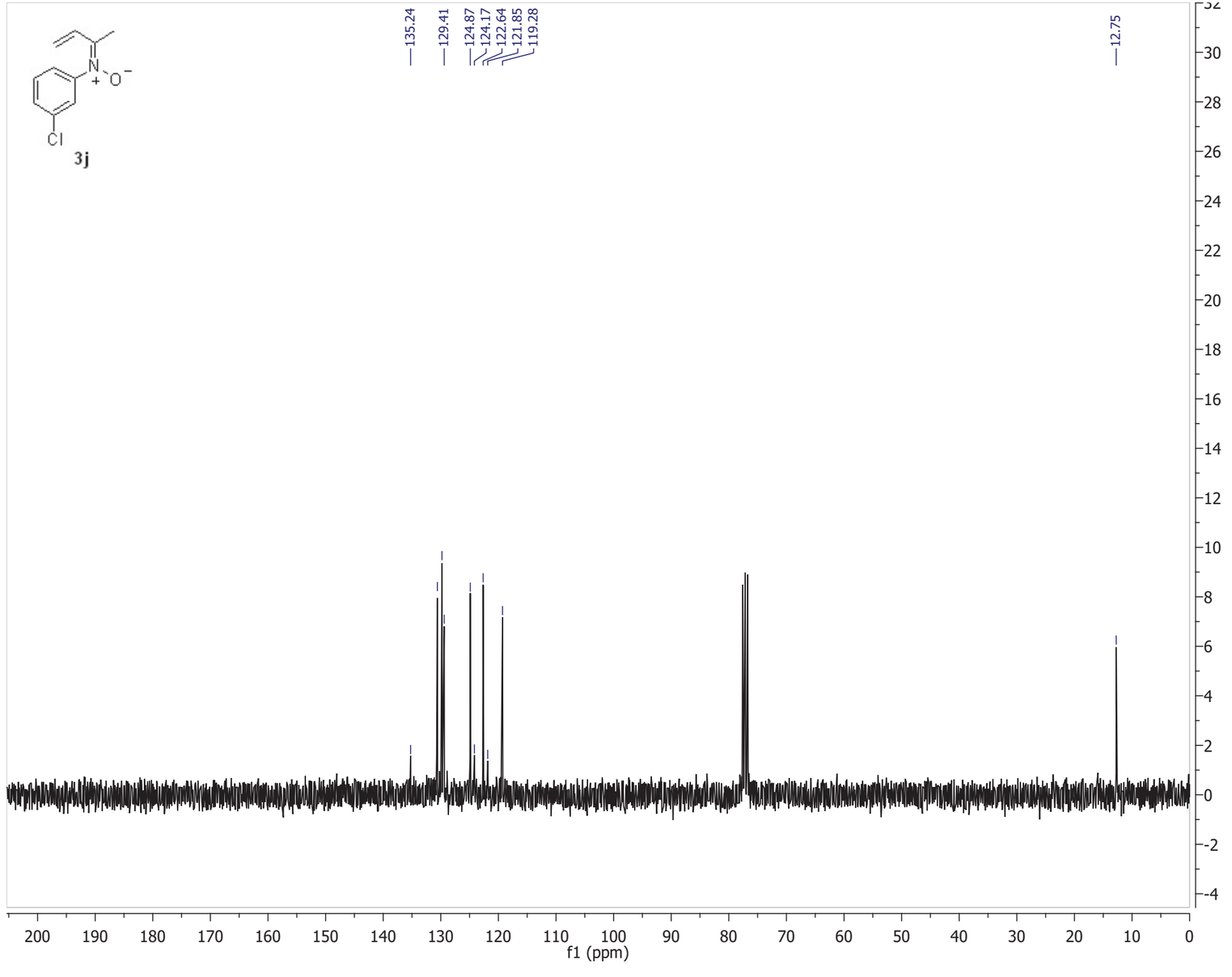

3h
7.67
7.67
7.64
7.64
7.40
7.35
7.35
7.32
7.29
6.15
6.12
6.10
6.06
5.60
5.54
5.30
5.27
5.26
2.41
1.95
1.15
3.44
1.00
1.05
1.02
2.81
0.44
f1 (ppm)

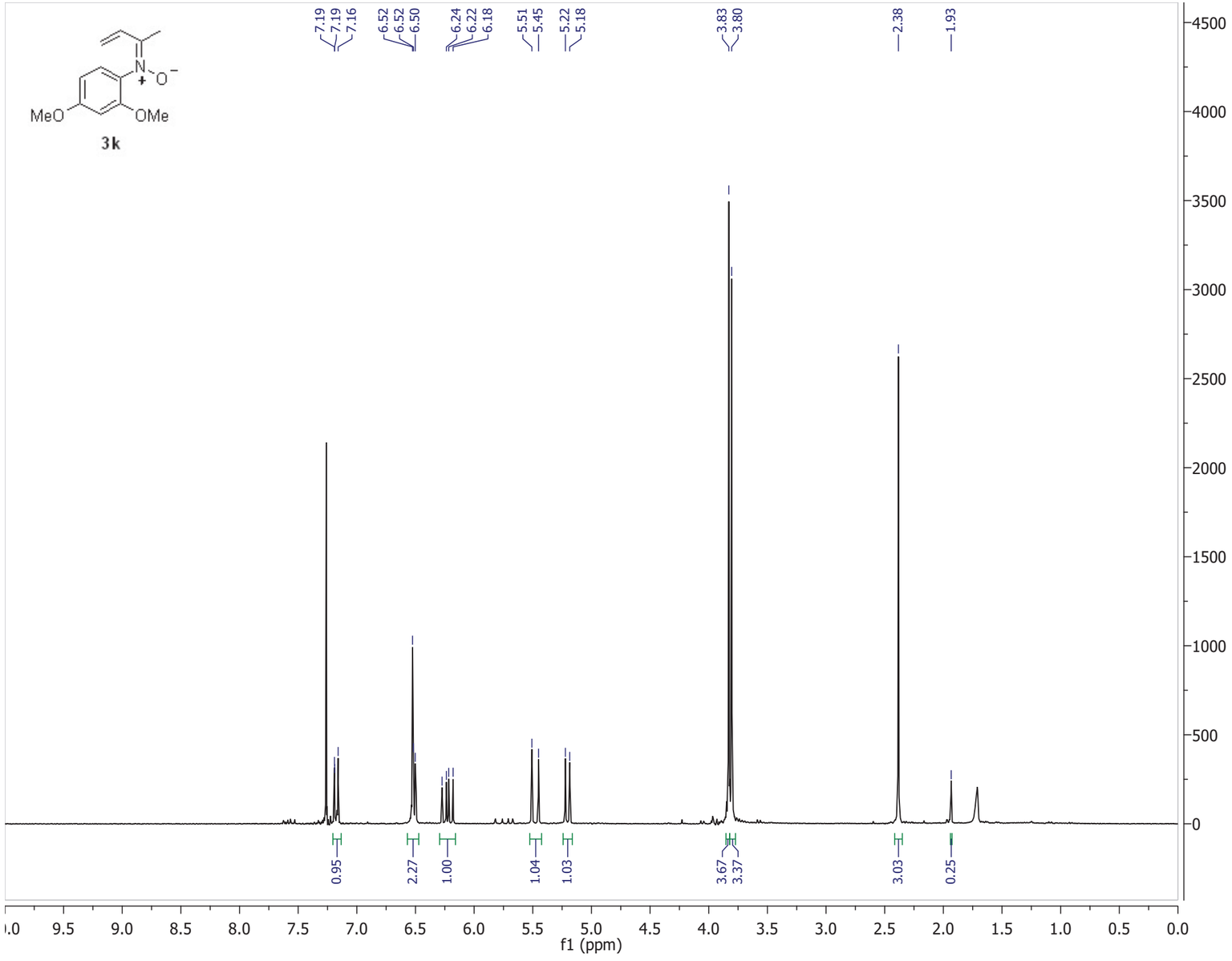

133.91
128.87
128.83
126.09
119.62
117.46
12.11
Br
3h
90
80
70
60
50
40
30
20
10
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

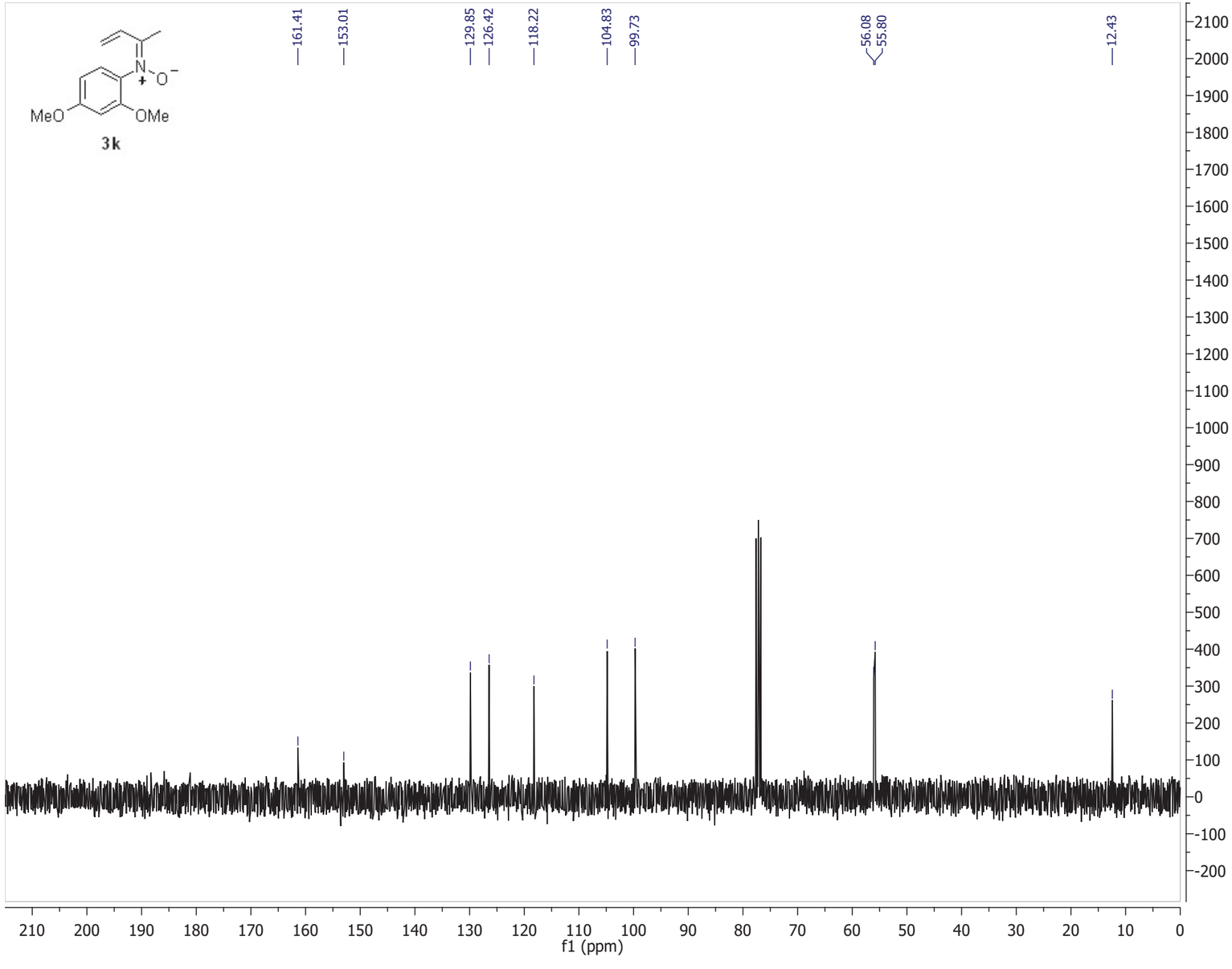

3i
7.32
7.30
7.15
7.12
6.39
6.36
6.34
6.30
5.53
5.47
5.24
5.21
2.39
2.31
2.10
2.04
2.00
Crude Spectrum
1.52
4.33
1.00
1.00
1.11
5.35
f1 (ppm)

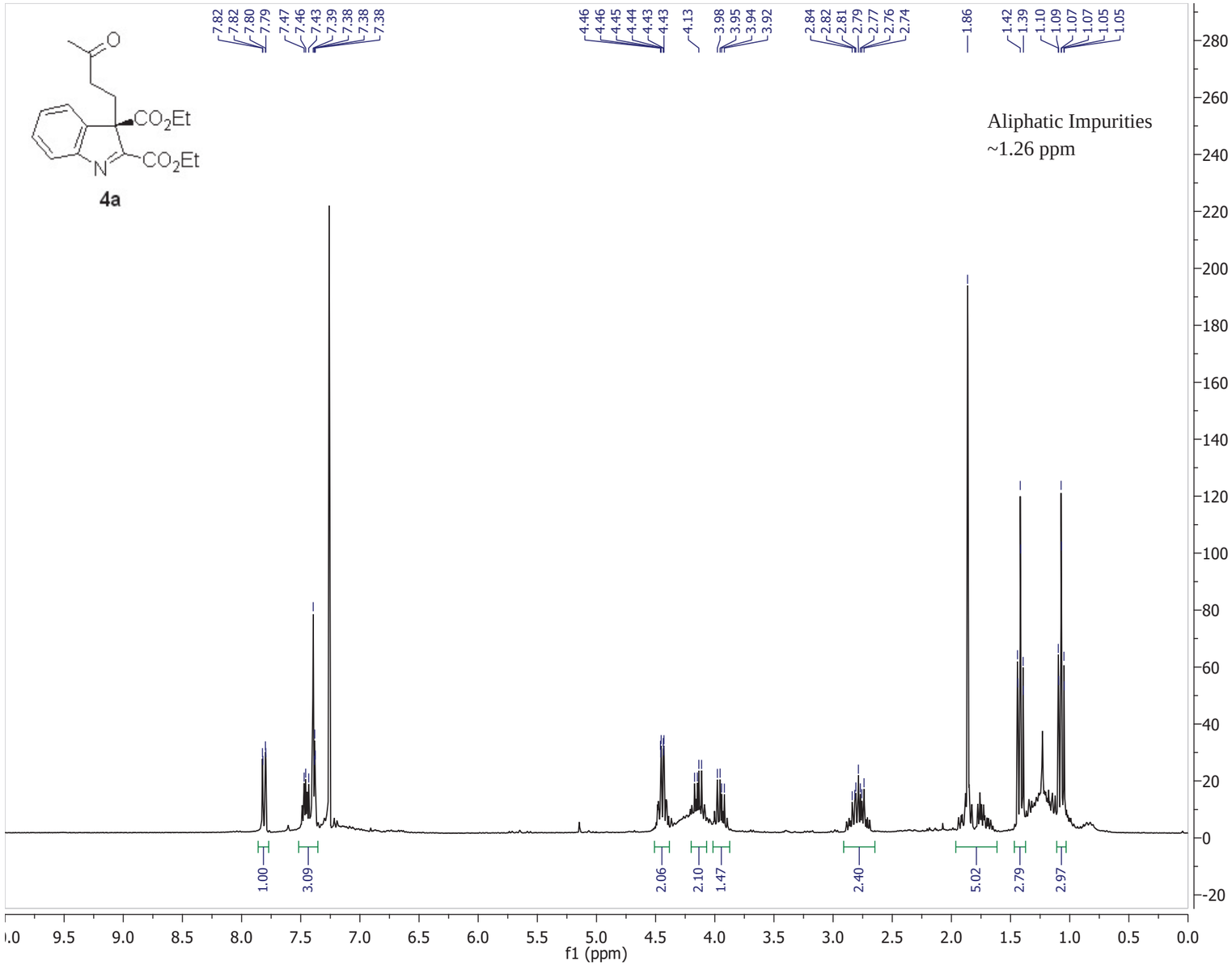

3i
130.22
129.98
129.26
124.85
121.35
118.28
21.38
12.68
f1 (ppm)

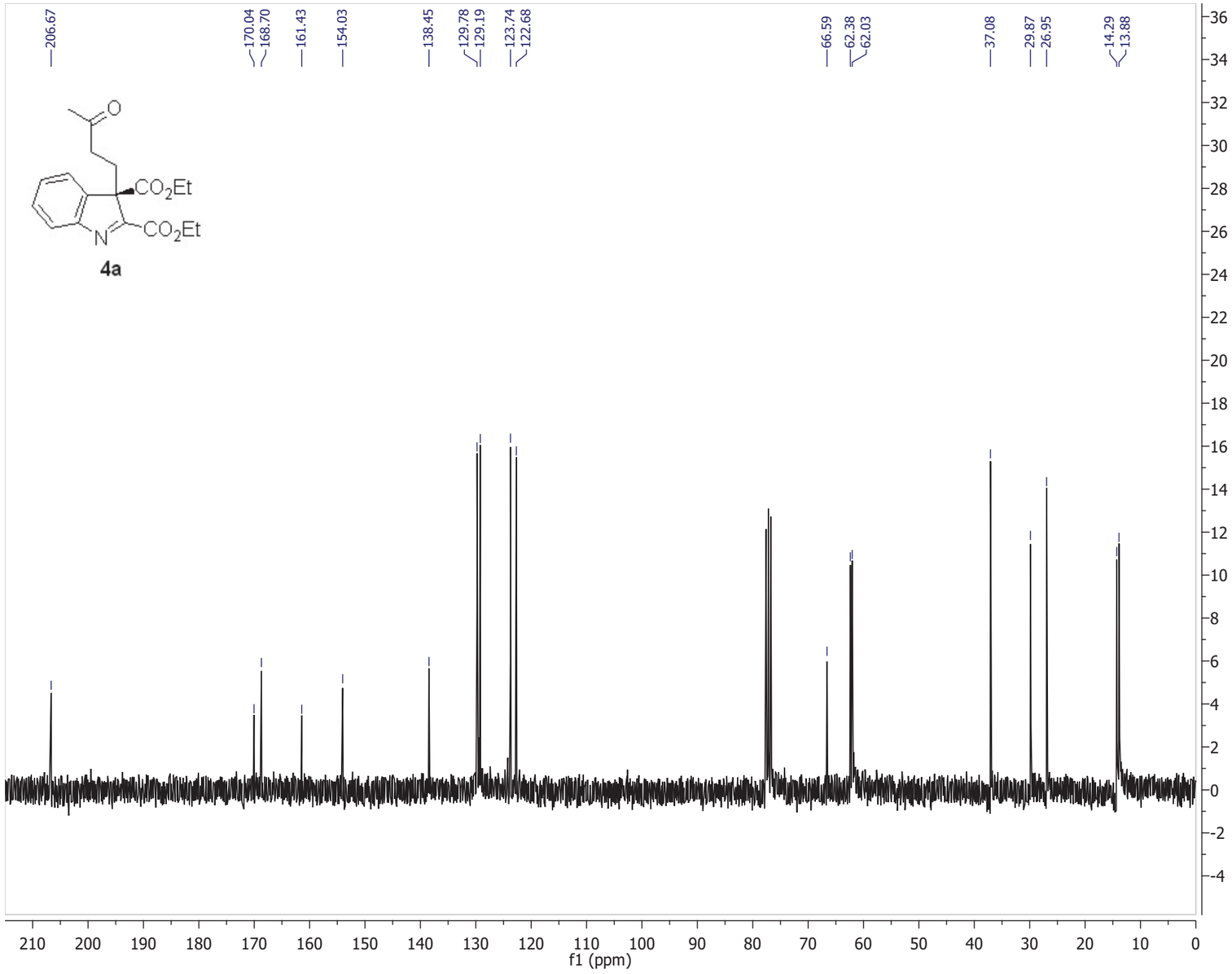

7.40
7.40
7.26
7.26
7.23
6.36
6.33
6.32
6.31
6.30
6.27
6.27
5.57
5.52
5.30
5.27
2.38
2.02
3j
Cl
3.31
1.14
1.00
1.03
1.02
2.81
0.47
f1 (ppm)

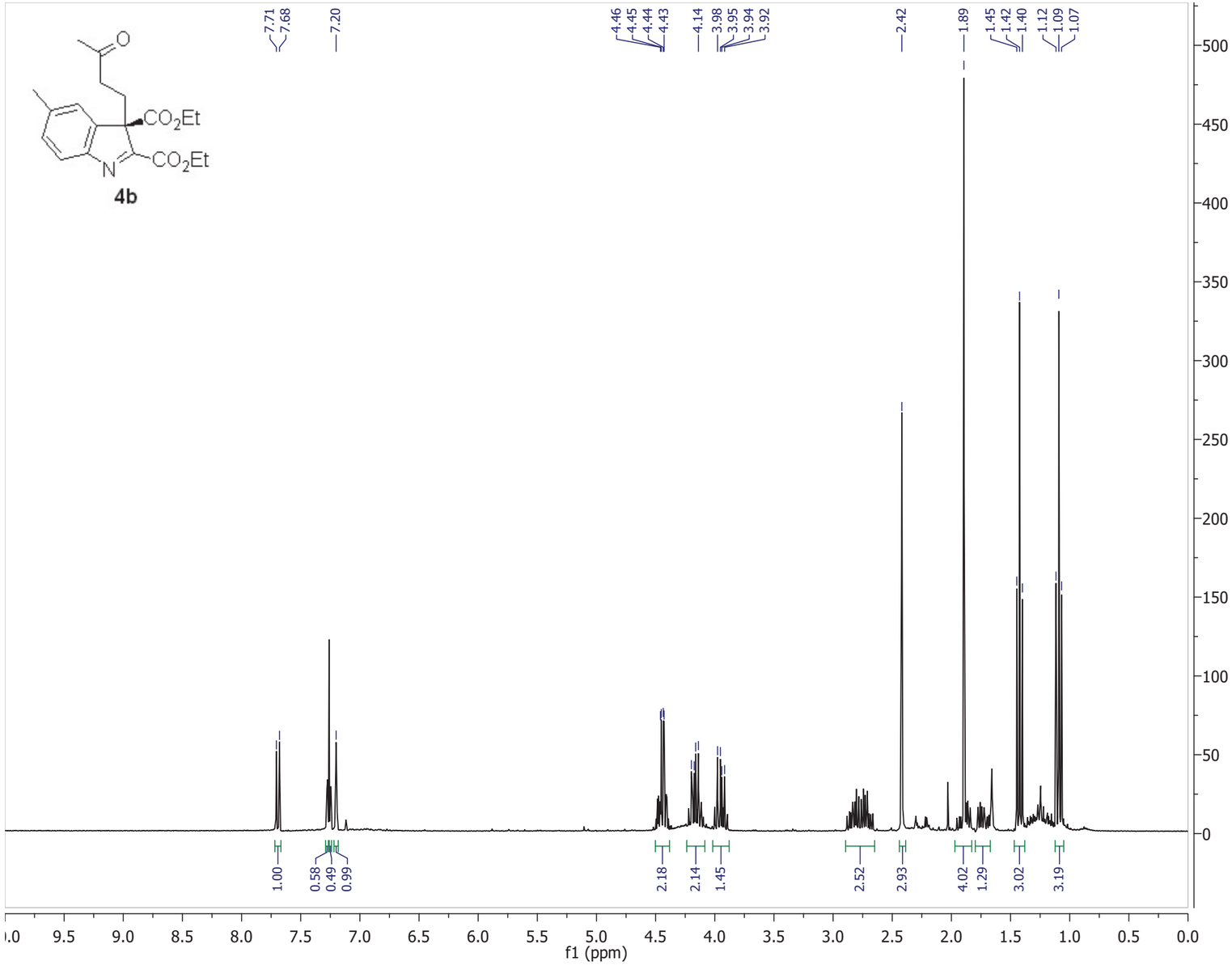

135.24
129.41
124.87
124.17
122.64
121.85
119.28
12.75
Cl
3j
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
-2
-4

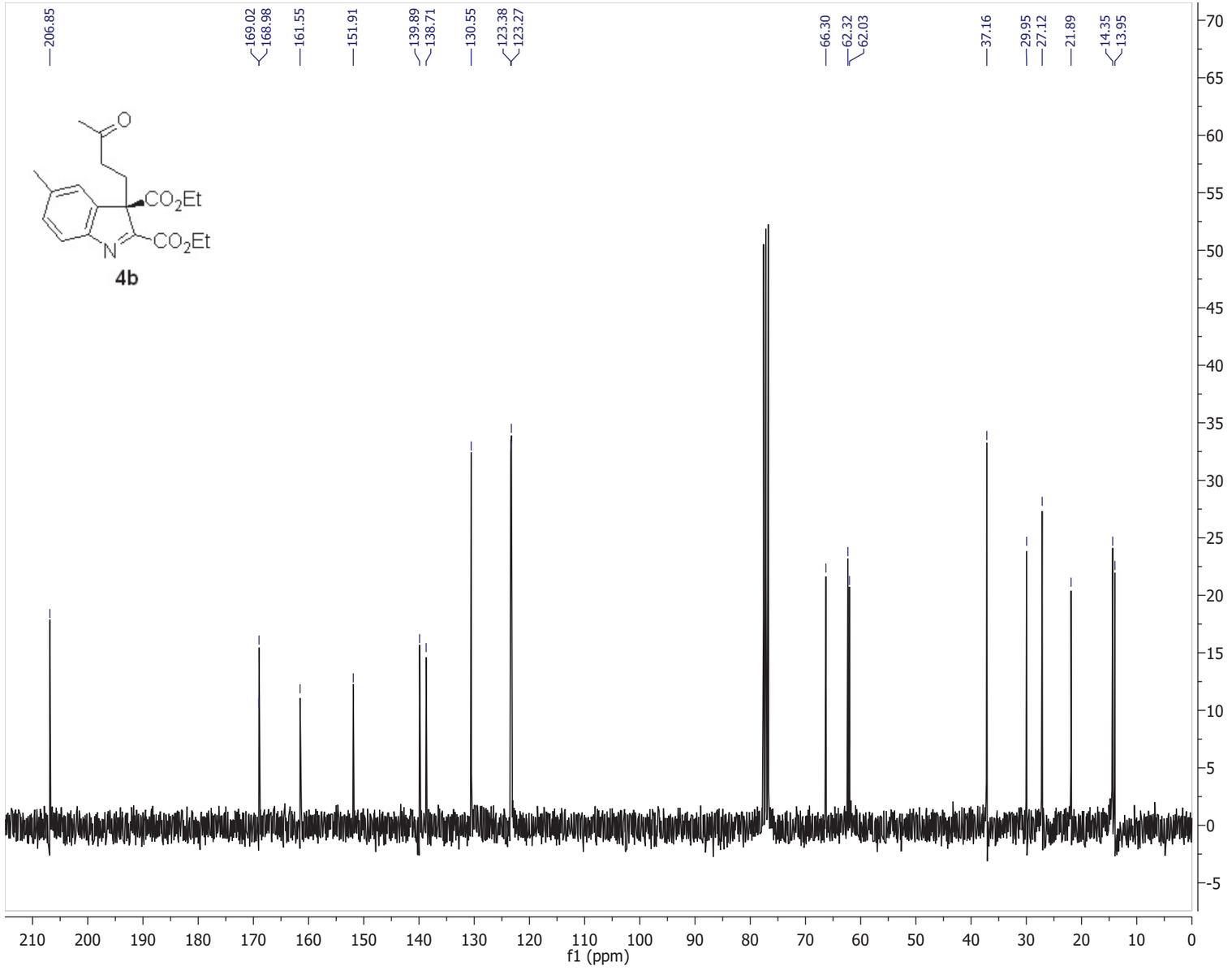

3k
7.19
7.19
7.16
6.52
6.52
6.50
6.24
6.22
6.18
5.51
5.45
5.22
5.18
3.83
3.80
2.38
1.93
0.95
2.27
1.00
1.04
1.03
3.67
3.37
3.03
0.25
f1 (ppm)

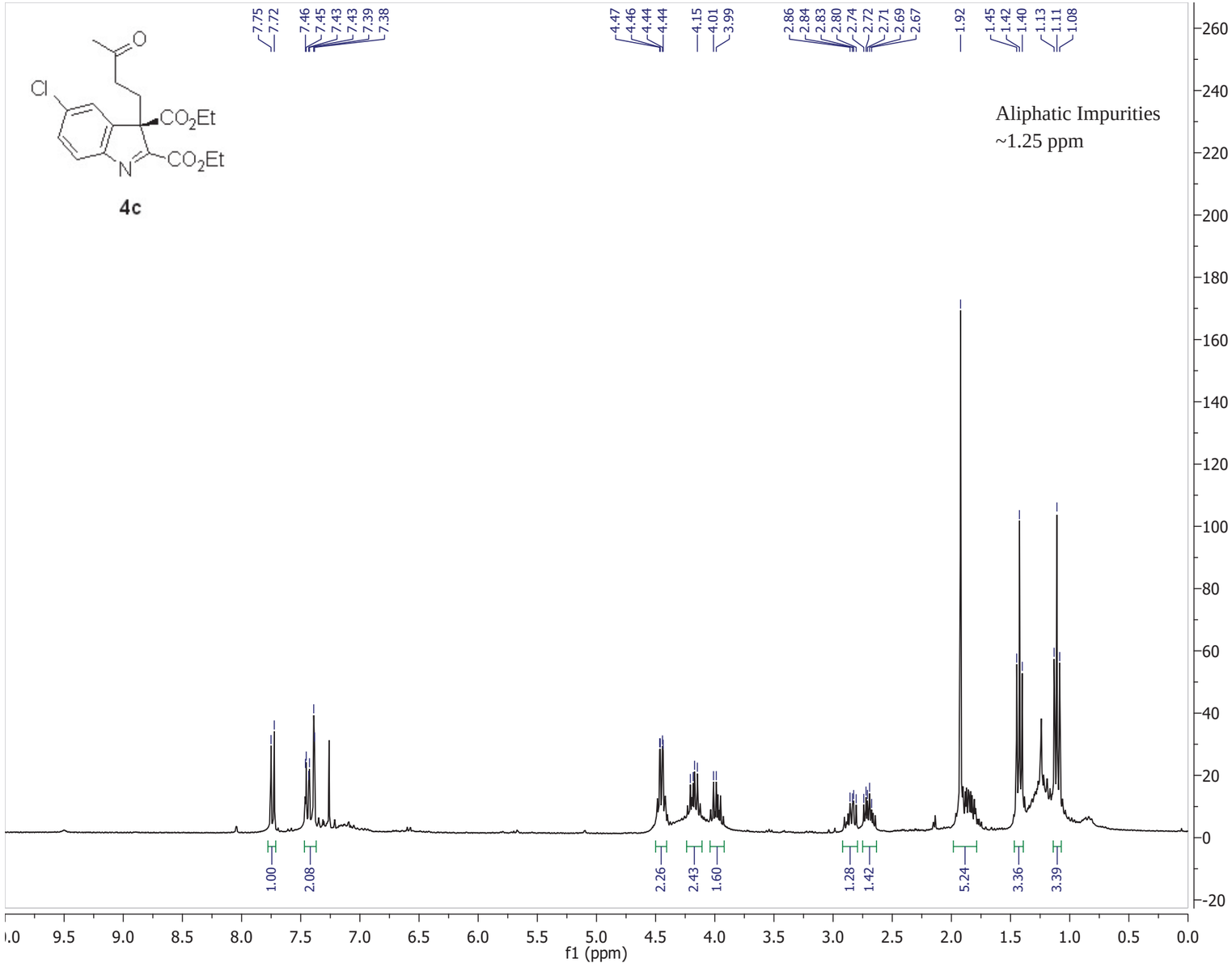

161.41
153.01
129.85
126.42
118.22
104.83
99.73
56.08
55.80
12.43
MeO
OMe
3k
f1 (ppm)

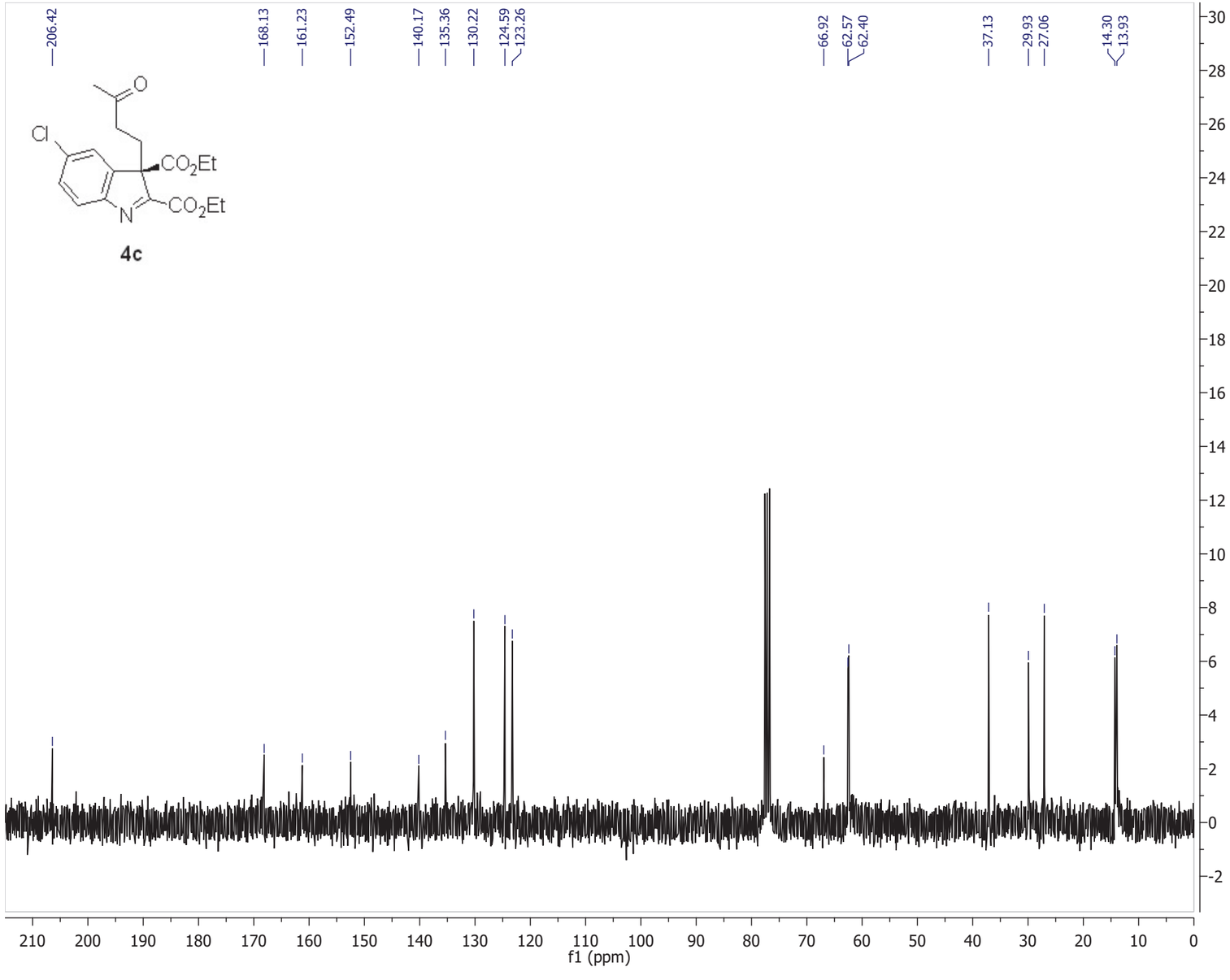

O
CO2Et
CO2Et
N
4a
7.82
7.82
7.80
7.79
7.47
7.46
7.43
7.39
7.38
7.38
7.38
4.46
4.46
4.45
4.44
4.43
4.43
4.13
3.98
3.95
3.94
3.92
2.84
2.82
2.81
2.79
2.77
2.76
2.74
1.86
1.42
1.39
1.10
1.09
1.07
1.07
1.05
1.05
Aliphatic Impurities
~1.26 ppm
1.00
3.09
2.06
2.10
1.47
2.40
5.02
2.79
2.97
f1 (ppm)

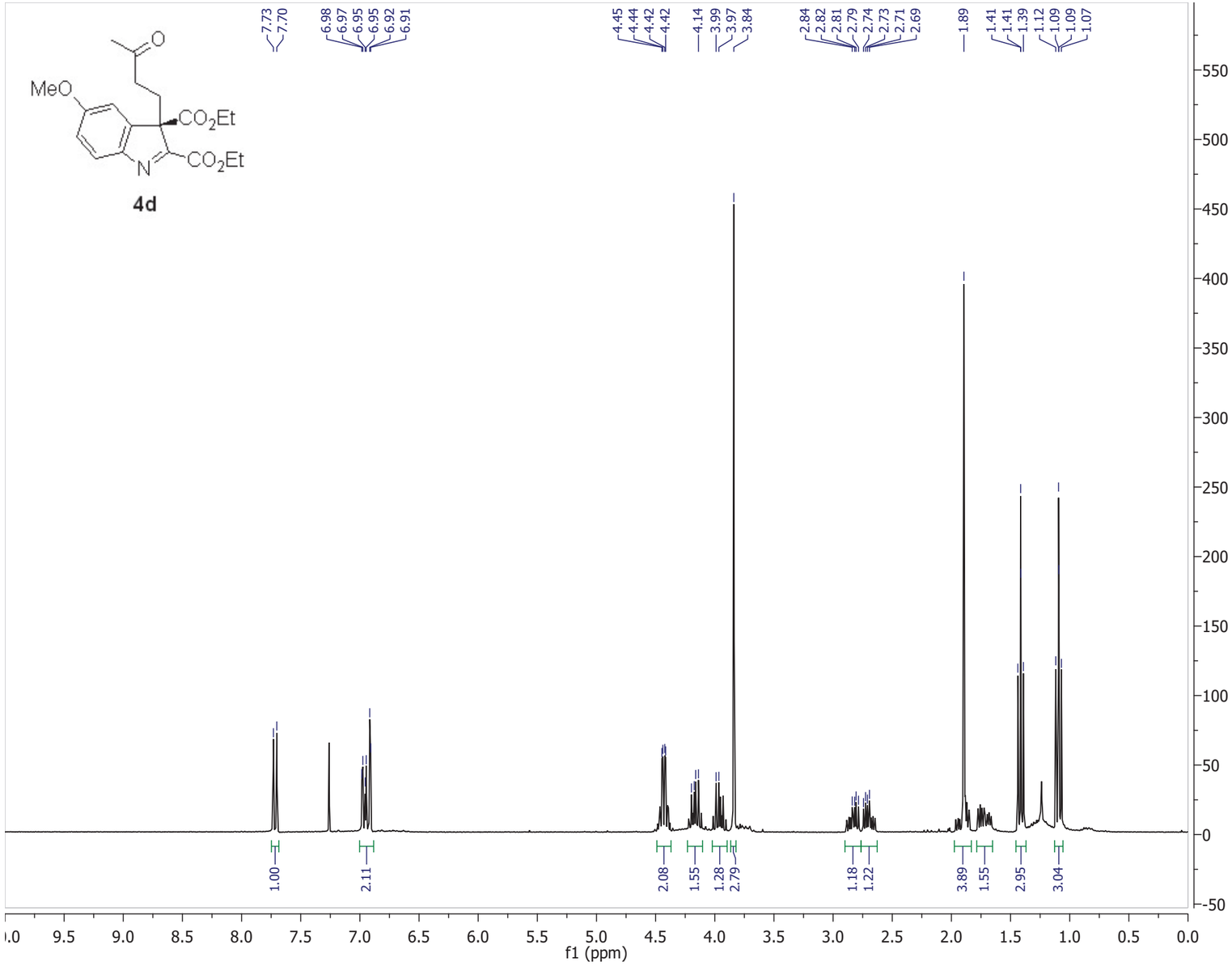

206.67
170.04
168.70
161.43
154.03
138.45
129.78
129.19
123.74
122.68
66.59
62.38
62.03
37.08
29.87
26.95
14.29
13.88
O
CO2Et
CO2Et
N
4a
f1 (ppm)

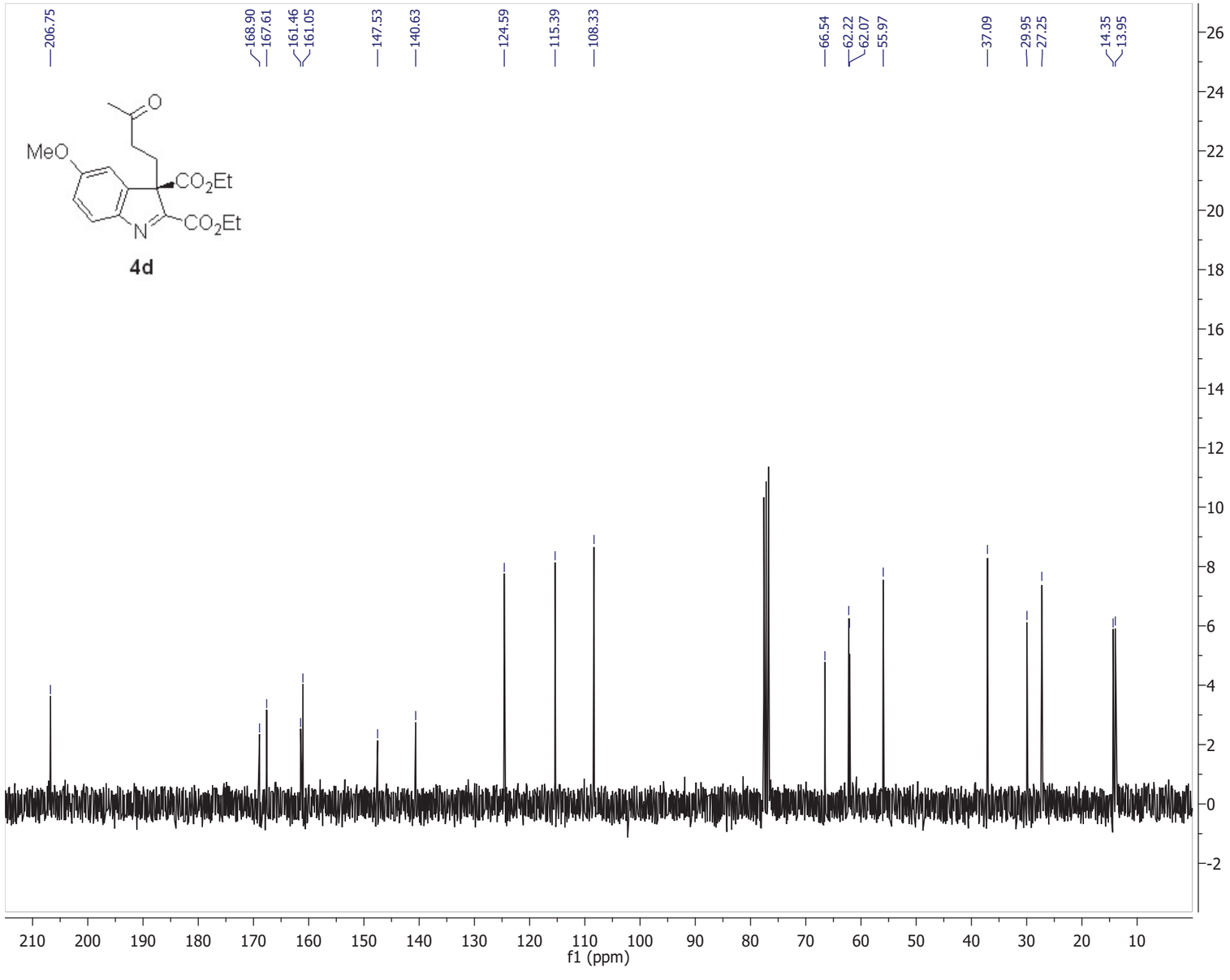

O
CO2Et
CO2Et
N
4b
7.71
7.68
7.20
4.46
4.45
4.44
4.43
4.14
3.98
3.95
3.94
3.92
2.42
1.89
1.45
1.42
1.40
1.12
1.09
1.07
1.00
0.58
0.49
0.99
2.18
2.14
1.45
2.52
2.93
4.02
1.29
3.02
3.19
f1 (ppm)

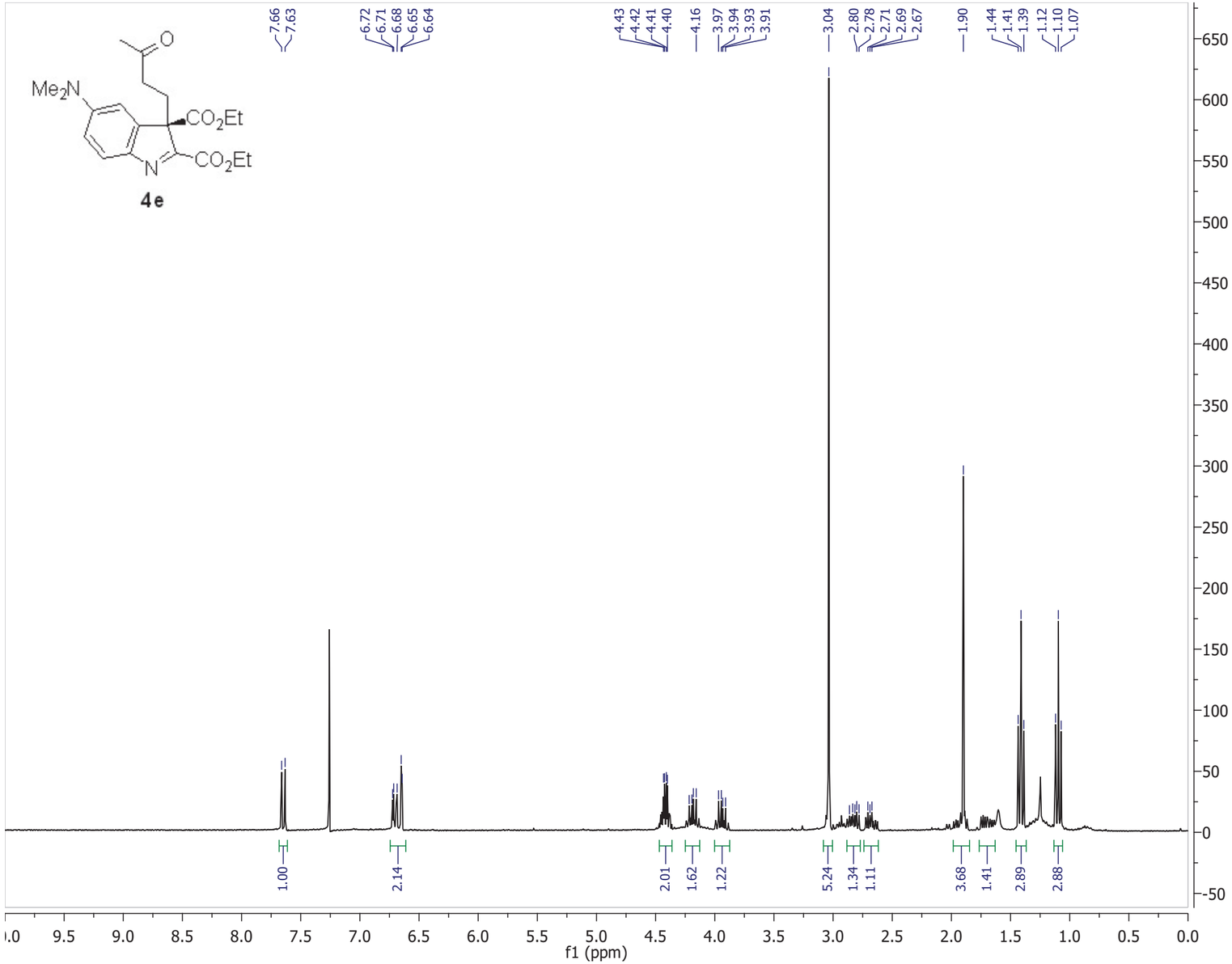

206.85
169.02
168.98
161.55
151.91
139.89
138.71
130.55
123.38
123.27
66.30
62.32
62.03
37.16
29.95
27.12
21.89
14.35
13.95
O
CO2Et
CO2Et
N
4b
f1 (ppm)

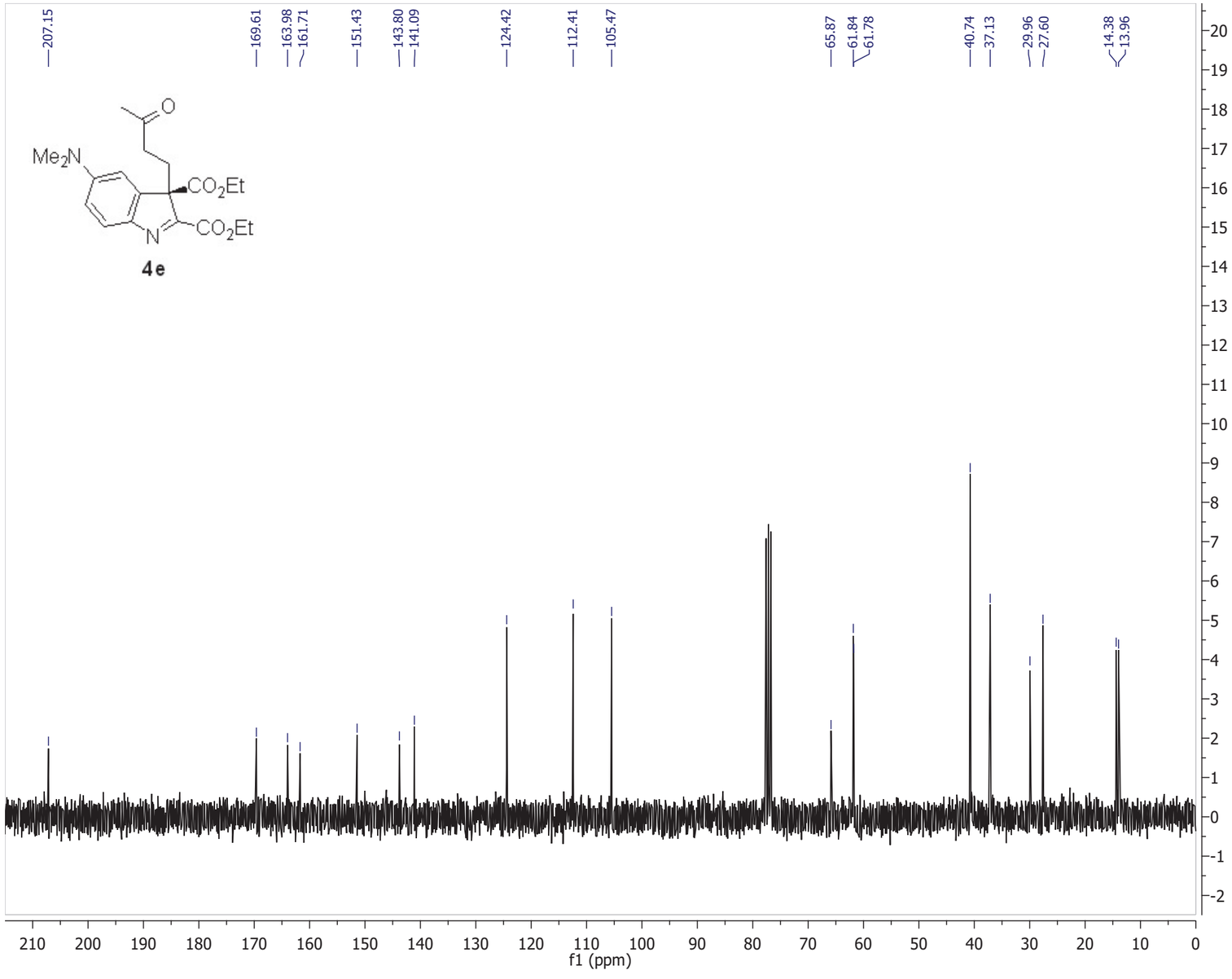

7.75
7.72
7.46
7.45
7.43
7.43
7.39
7.38
4.47
4.46
4.44
4.44
4.15
4.01
3.99
2.86
2.84
2.83
2.80
2.74
2.72
2.71
2.69
2.67
1.92
1.45
1.42
1.40
1.13
1.11
1.08
Cl
O
CO2Et
CO2Et
N
4c
Aliphatic Impurities
~1.25 ppm
1.00
2.08
2.26
2.43
1.60
1.28
1.42
5.24
3.36
3.39
f1 (ppm)

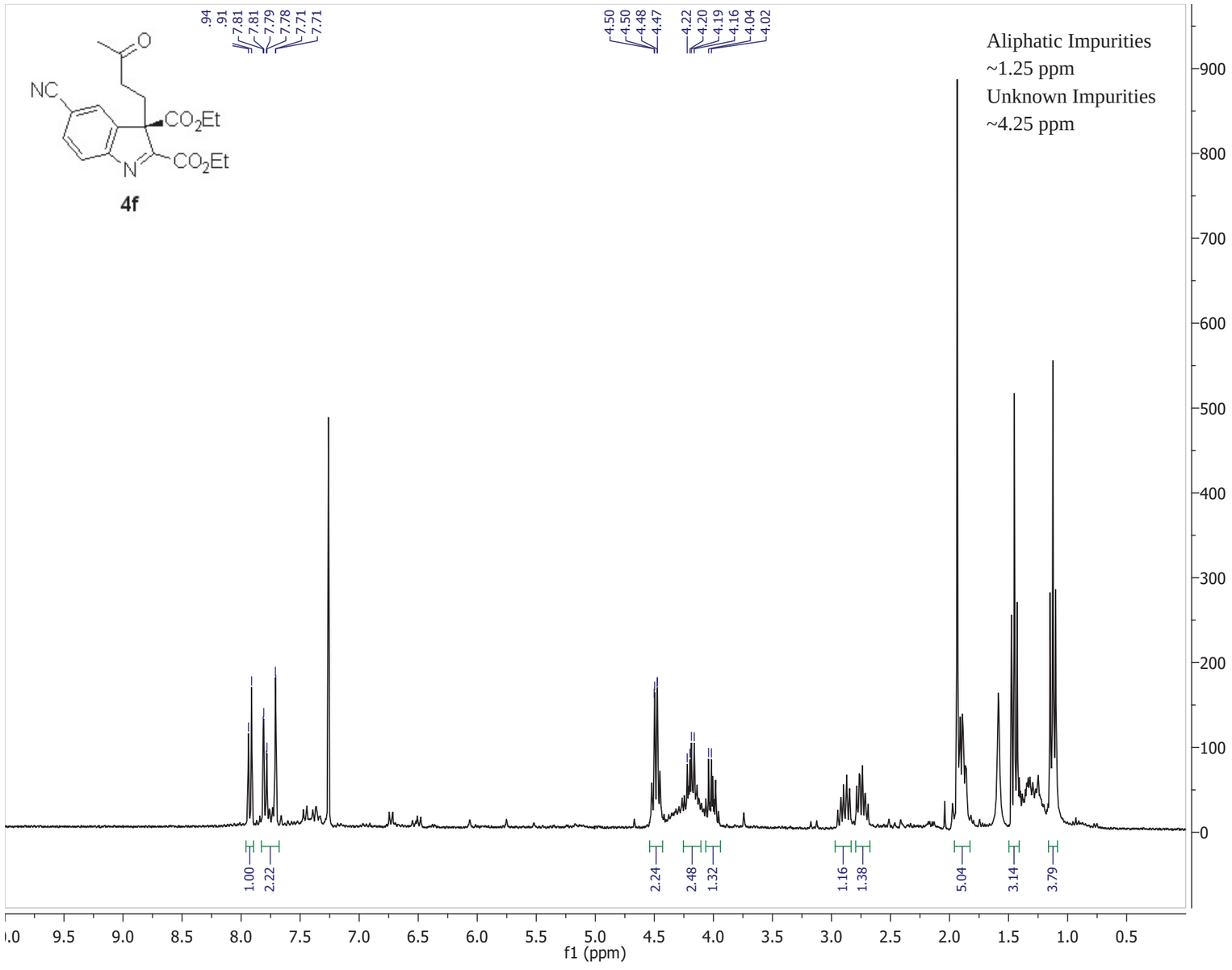

206.42
168.13
161.23
152.49
140.17
135.36
130.22
124.59
123.26
66.92
62.57
62.40
37.13
29.93
27.06
14.30
13.93
O
Cl
CO2Et
CO2Et
N
4c
f1 (ppm)

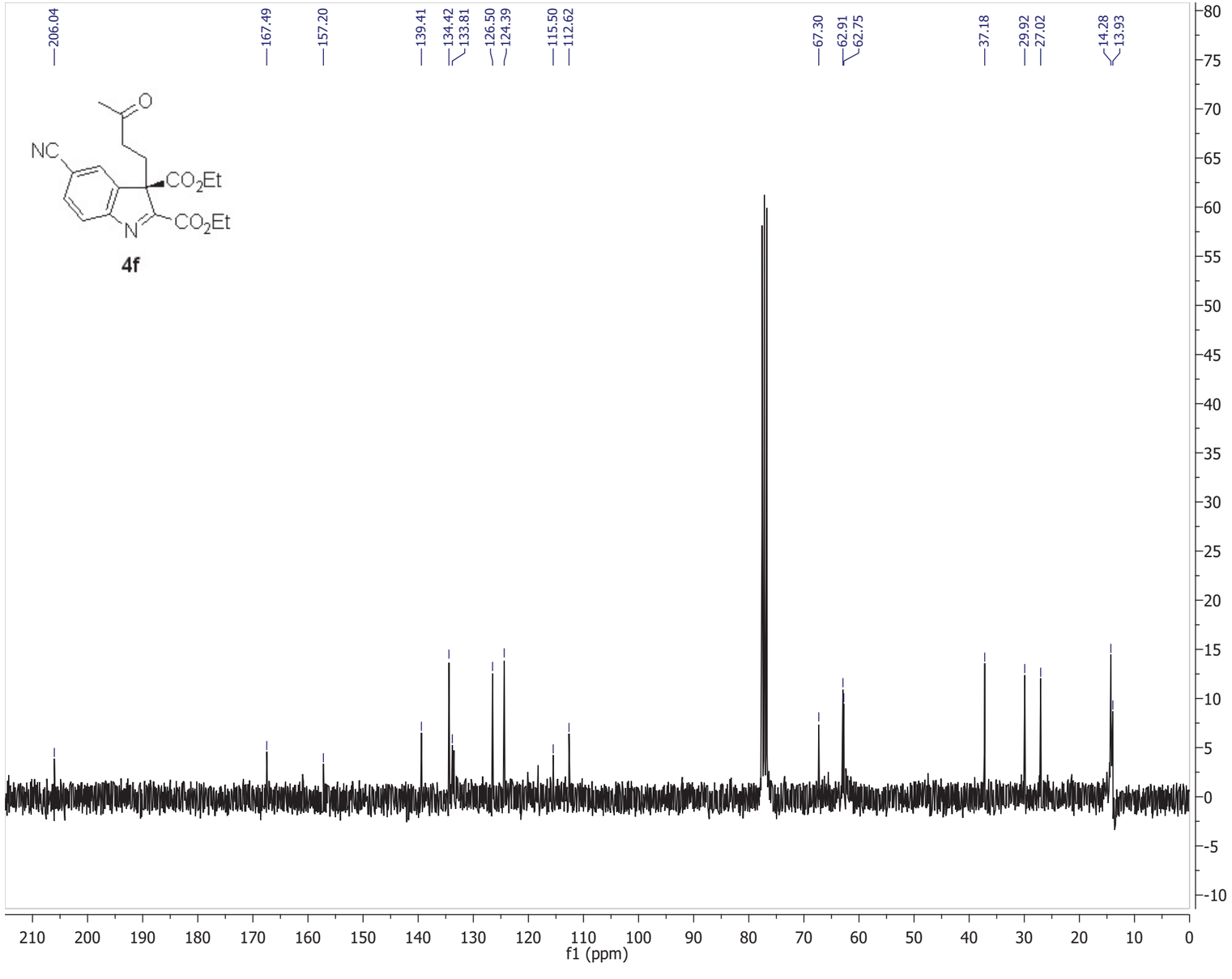

MeO
O
CO2Et
CO2Et
N
4d
7.73
7.70
6.98
6.97
6.95
6.95
6.92
6.91
4.45
4.44
4.42
4.42
4.14
3.99
3.97
3.84
2.84
2.82
2.81
2.79
2.74
2.73
2.71
2.69
1.89
1.41
1.41
1.39
1.12
1.09
1.09
1.07
1.00
2.11
2.08
1.55
1.28
2.79
1.18
1.22
3.89
1.55
2.95
3.04
f1 (ppm)

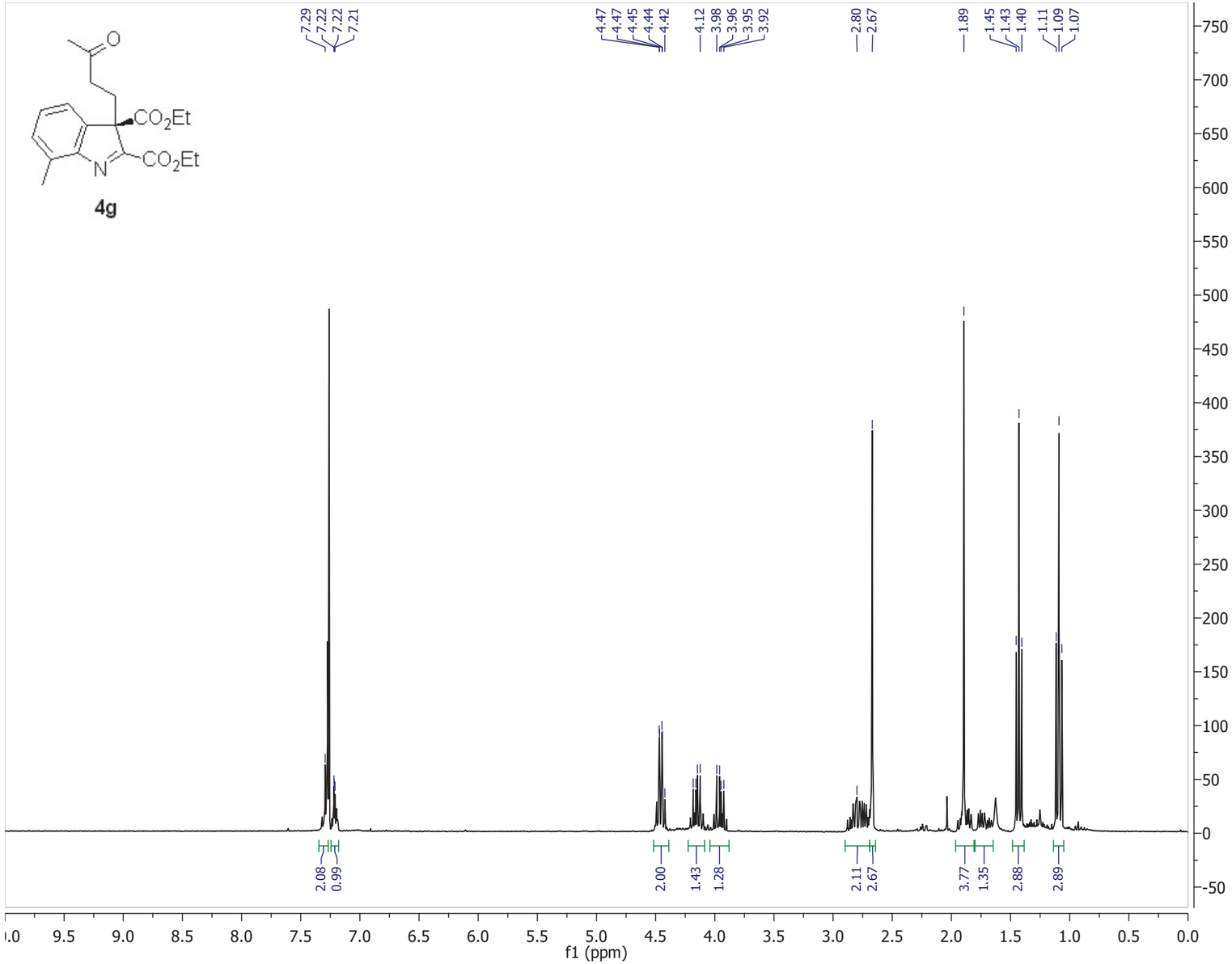

206.75
168.90
167.61
161.46
161.05
147.53
140.63
124.59
115.39
108.33
66.54
62.22
62.07
55.97
37.09
29.95
27.25
14.35
13.95
MeO
O
CO2Et
CO2Et
N
4d
f1 (ppm)

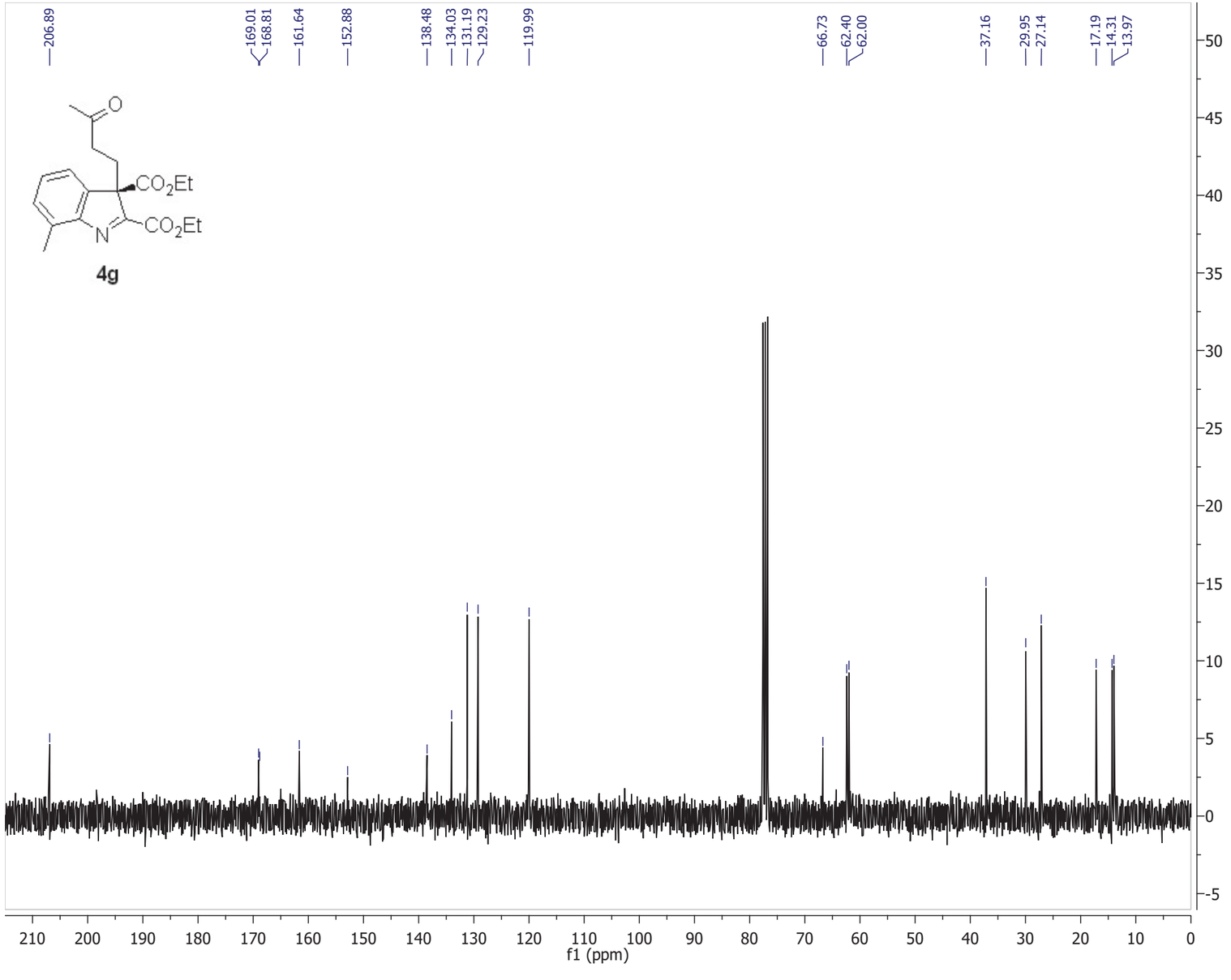

Me2N
O
CO2Et
CO2Et
N
4e
7.66
7.63
6.72
6.71
6.68
6.65
6.64
4.43
4.42
4.41
4.40
4.16
3.97
3.94
3.93
3.91
3.04
2.80
2.78
2.71
2.69
2.67
1.90
1.44
1.41
1.39
1.12
1.10
1.07
1.00
2.14
2.01
1.62
1.22
5.24
1.34
1.11
3.68
1.41
2.89
2.88
f1 (ppm)

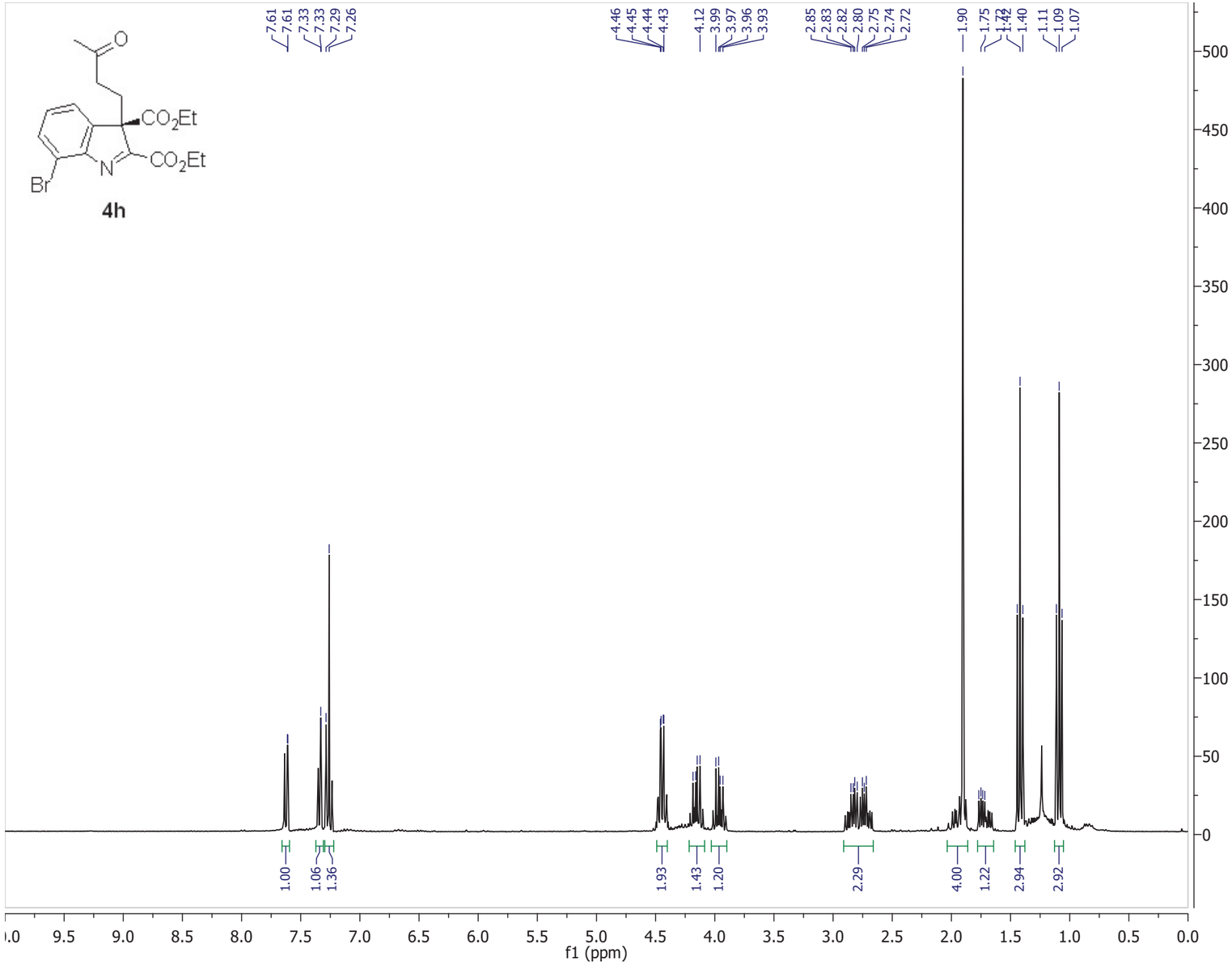

207.15
169.61
163.98
161.71
151.43
143.80
141.09
124.42
112.41
105.47
65.87
61.84
61.78
40.74
37.13
29.96
27.60
14.38
13.96
Me2N
CO2Et
CO2Et
O
N
4e
f1 (ppm)

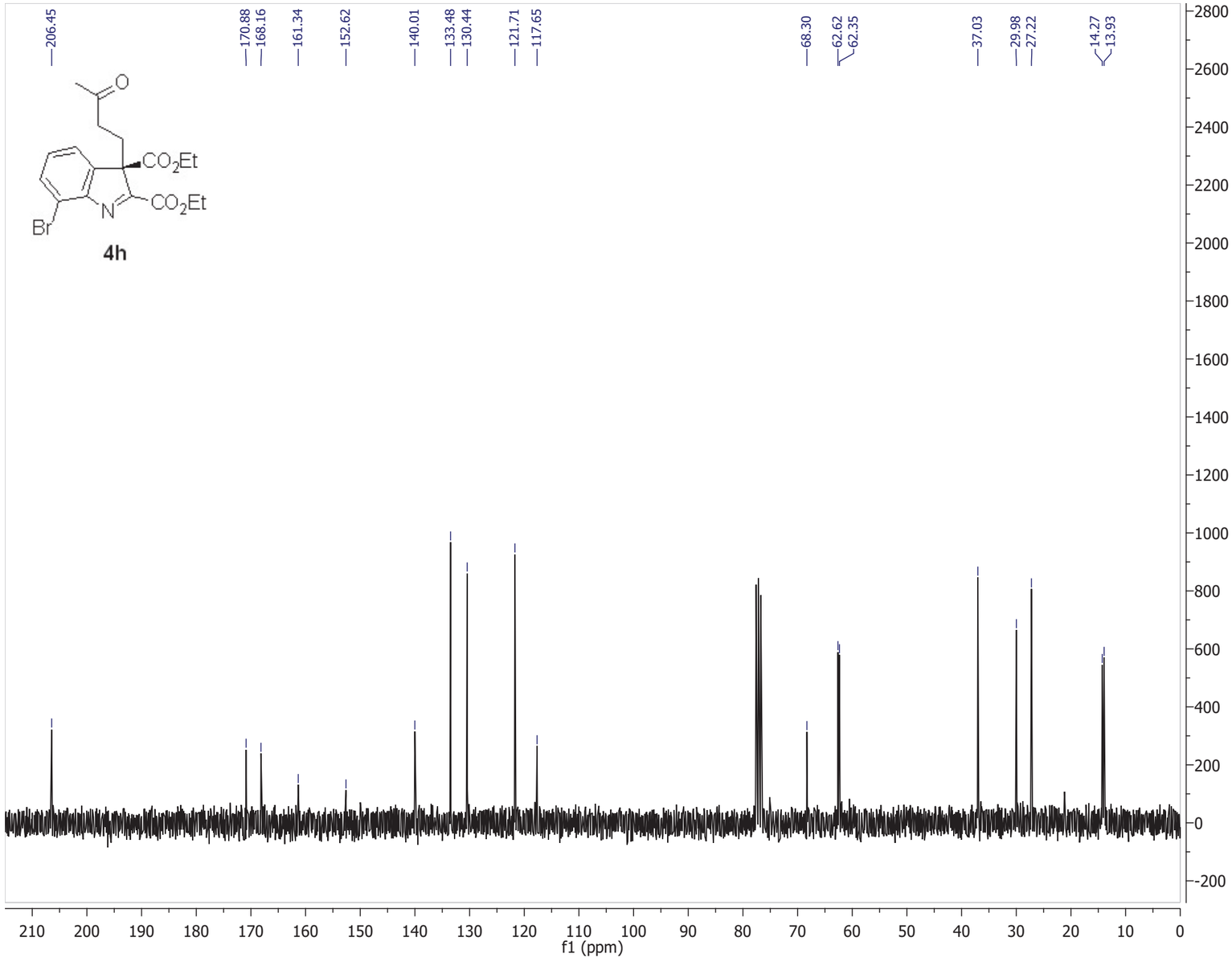

NC
O
CO2Et
CO2Et
N
4f
Aliphatic Impurities
~1.25 ppm
Unknown Impurities
~4.25 ppm
f1 (ppm)

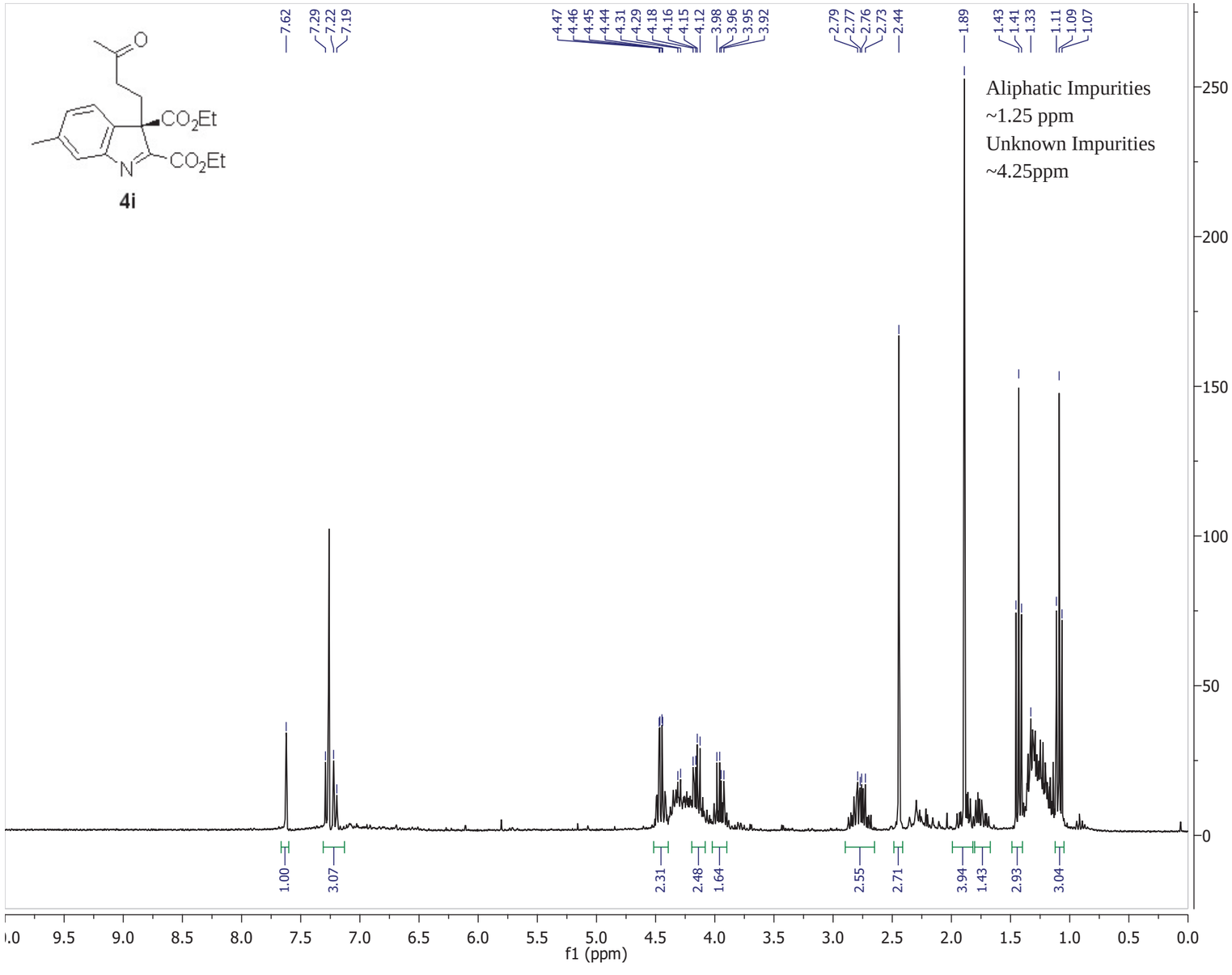

206.04
167.49
157.20
139.41
134.42
133.81
126.50
124.39
115.50
112.62
67.30
62.91
62.75
37.18
29.92
27.02
14.28
13.93
NC
O
CO2Et
CO2Et
N
4f
f1 (ppm)

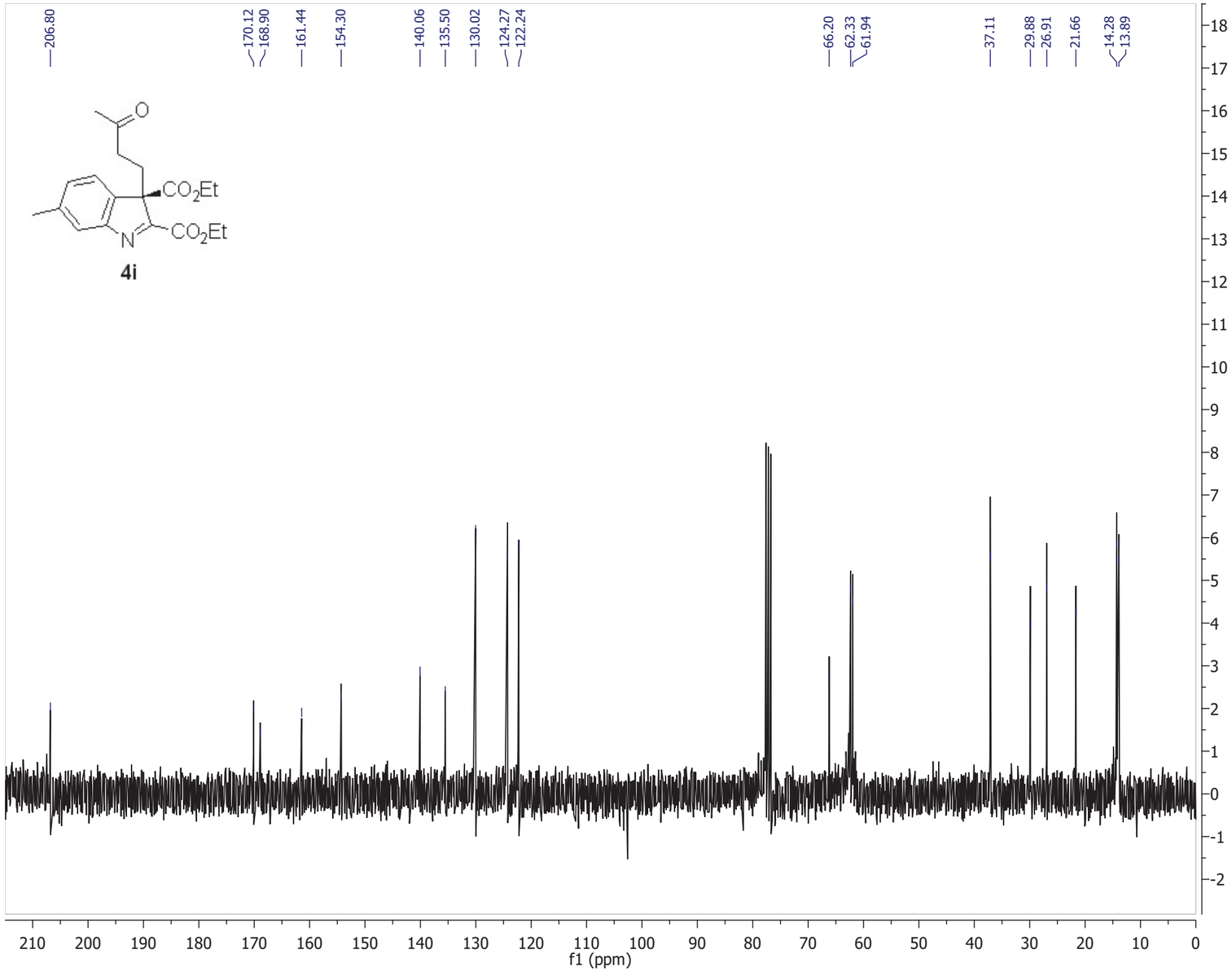

O
CO2Et
CO2Et
N
4g
7.29
7.22
7.22
7.21
4.47
4.47
4.45
4.44
4.42
4.12
3.98
3.96
3.95
3.92
2.80
2.67
1.89
1.45
1.43
1.40
1.11
1.09
1.07
2.08
0.99
2.00
1.43
1.28
2.11
2.67
3.77
1.35
2.88
2.89
f1 (ppm)

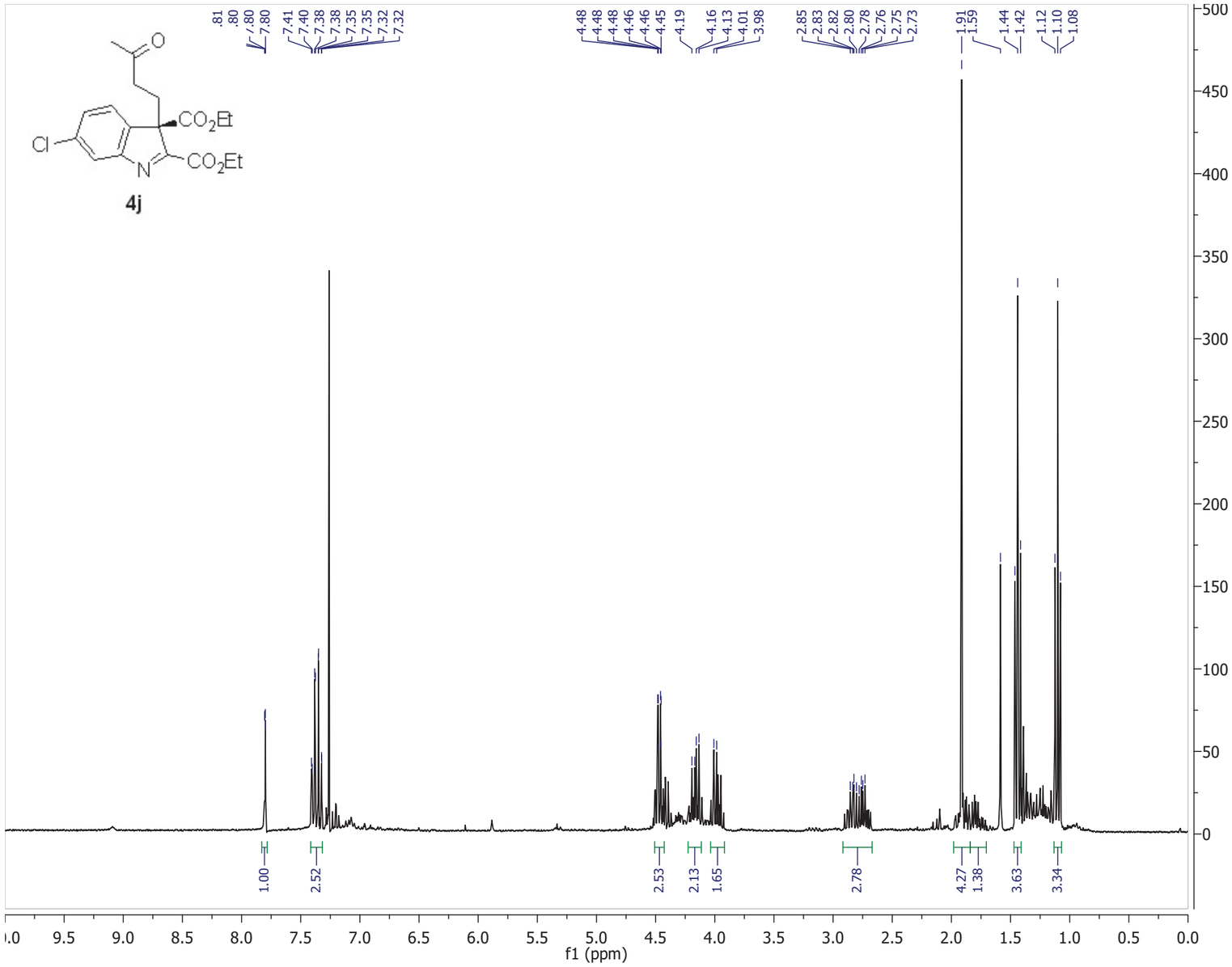

206.89
169.01
168.81
161.64
152.88
138.48
134.03
131.19
129.23
119.99
66.73
62.40
62.00
37.16
29.95
27.14
17.19
14.31
13.97
O
CO2Et
CO2Et
N
4g
50
45
40
35
30
25
20
15
10
5
0
-5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

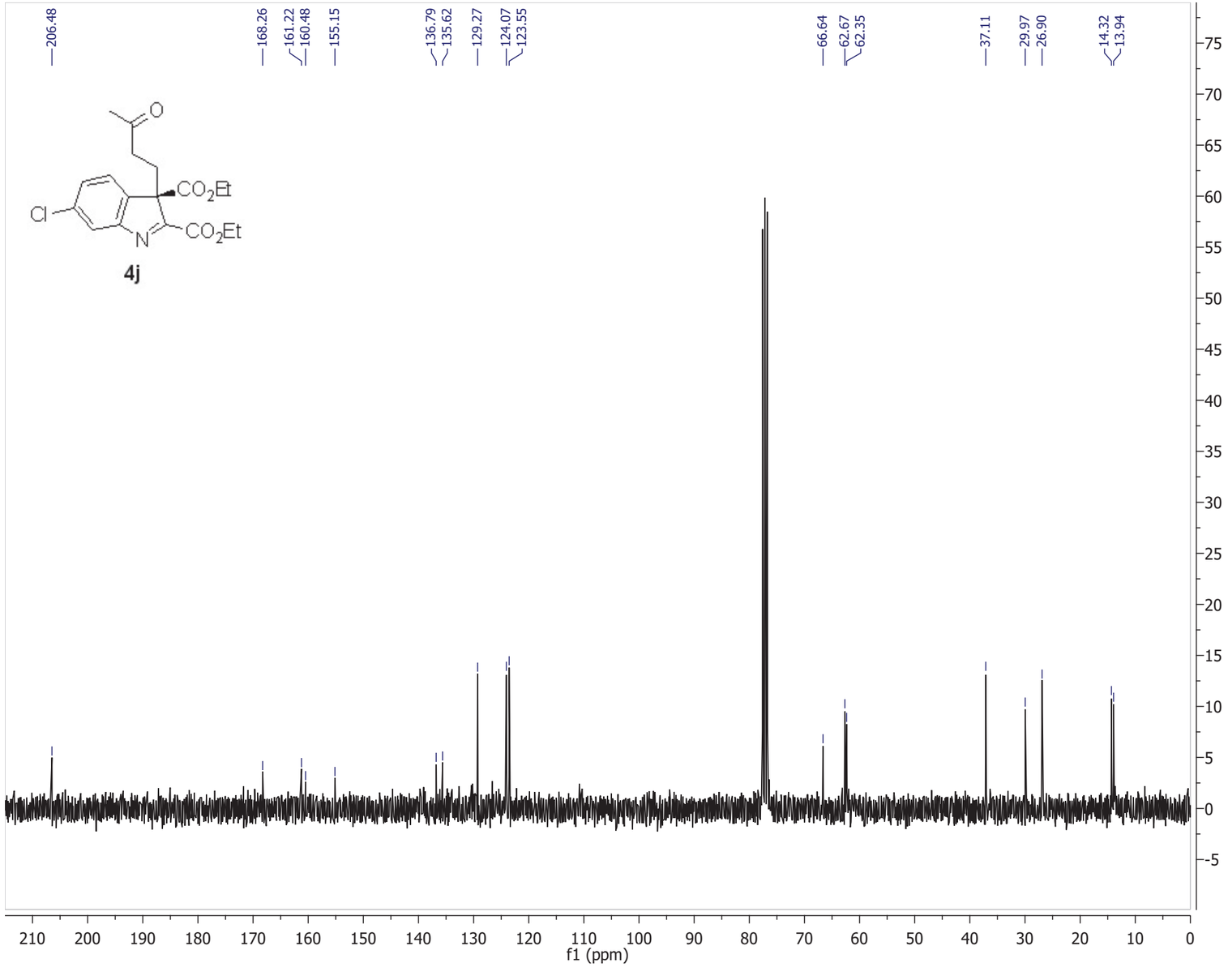

O
CO2Et
CO2Et
N
Br
4h
7.61
7.61
7.33
7.33
7.29
7.26
4.46
4.45
4.44
4.43
4.12
3.99
3.97
3.96
3.93
2.85
2.83
2.82
2.80
2.75
2.74
2.72
1.90
1.75
1.40
1.11
1.09
1.07
1.00
1.06
1.36
1.93
1.43
1.20
2.29
4.00
1.22
2.94
2.92
f1 (ppm)

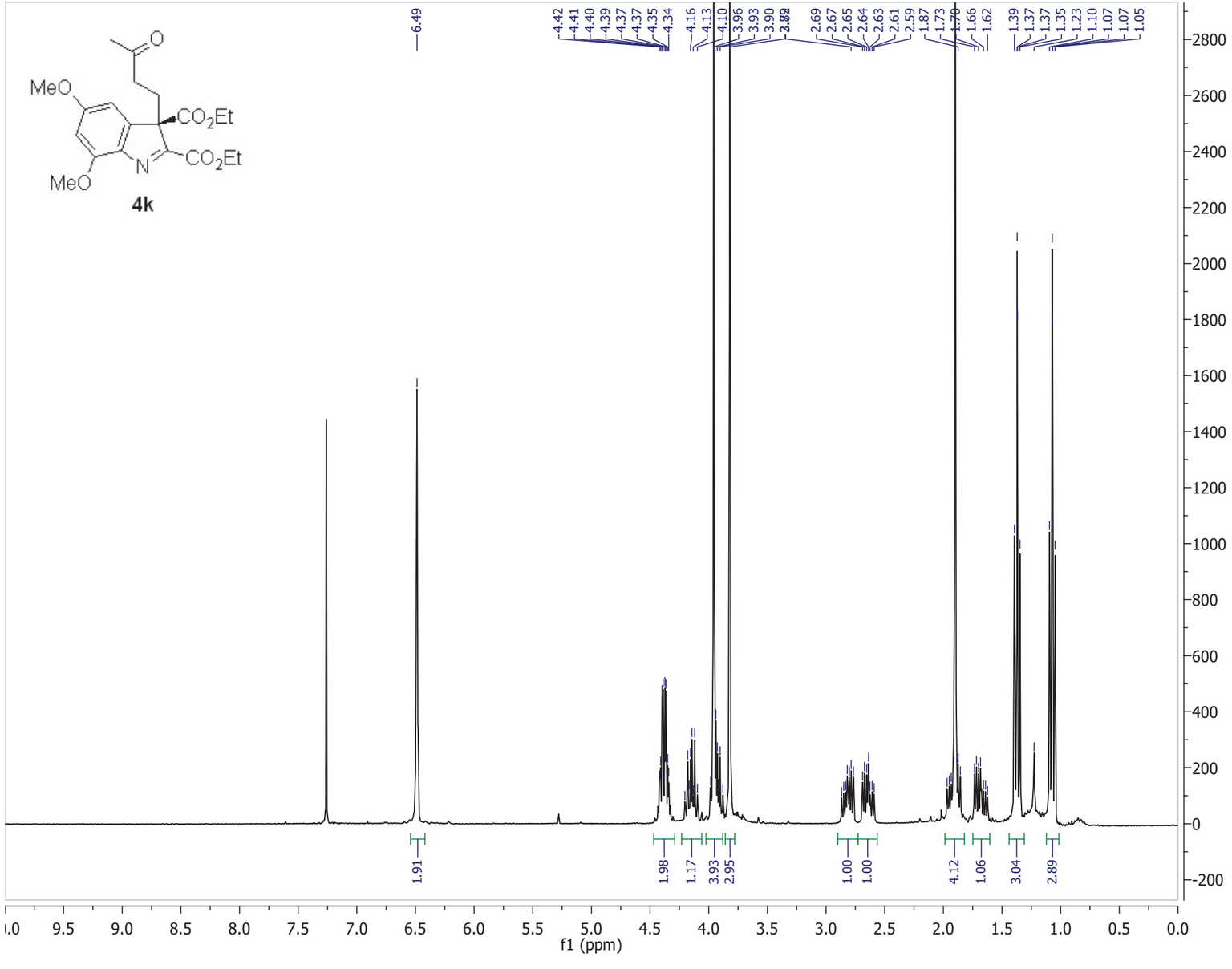

206.45
170.88
168.16
161.34
152.62
140.01
133.48
130.44
121.71
117.65
68.30
62.62
62.35
37.03
29.98
27.22
14.27
13.93
O
CO2Et
CO2Et
N
Br
4h
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

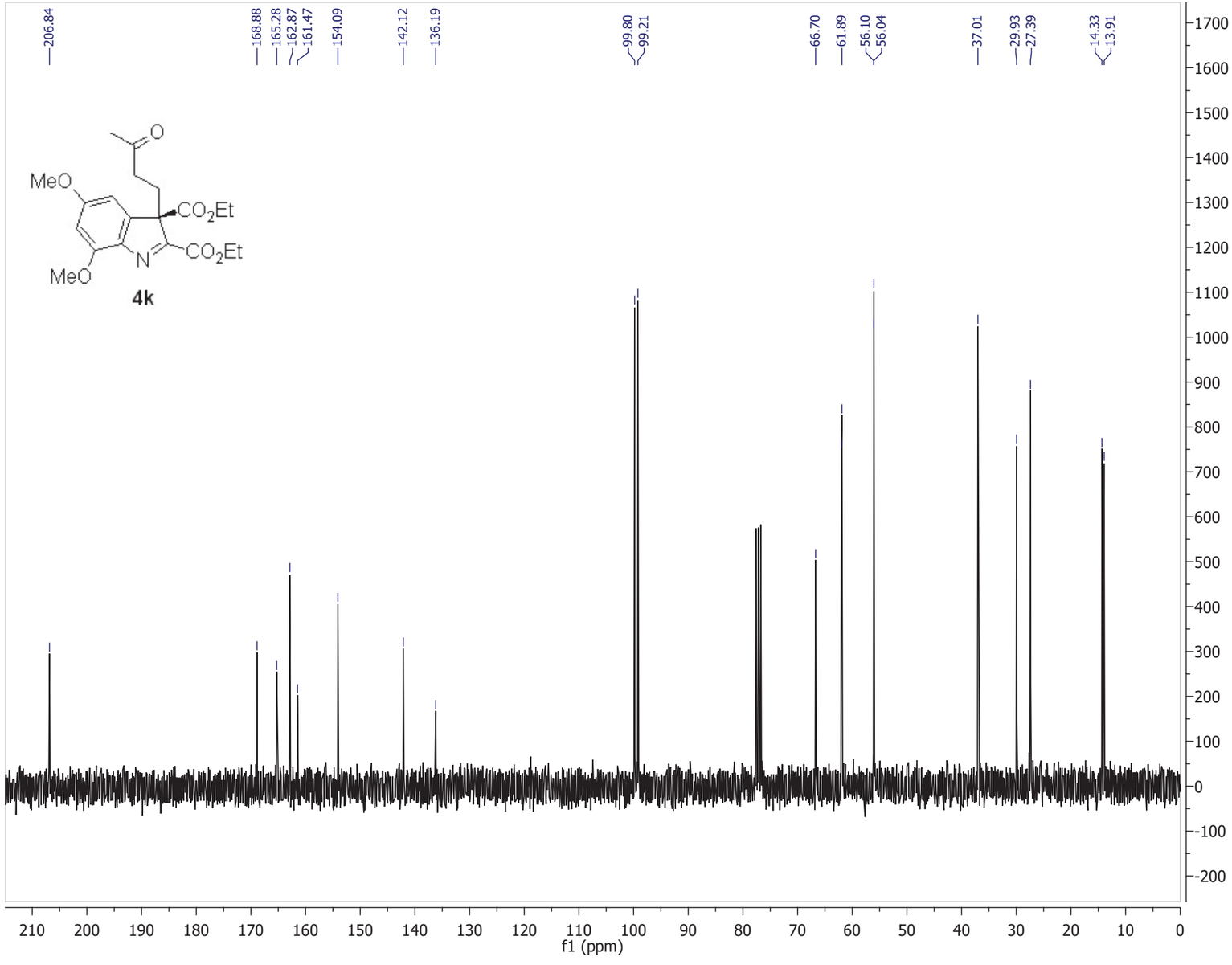

4i
7.62
7.29
7.22
7.19
4.47
4.46
4.45
4.44
4.31
4.29
4.18
4.16
4.15
4.12
3.98
3.96
3.95
3.92
2.79
2.77
2.76
2.73
2.44
1.89
1.43
1.41
1.33
1.11
1.09
1.07
Aliphatic Impurities
~1.25 ppm
Unknown Impurities
~4.25ppm
1.00
3.07
2.31
2.48
1.64
2.55
2.71
3.94
1.43
2.93
3.04
f1 (ppm)


206.80
170.12
168.90
161.44
154.30
140.06
135.50
130.02
124.27
122.24
66.20
62.33
61.94
37.11
29.88
26.91
21.66
14.28
13.89
O
CO2Et
CO2Et
N
4i
f1 (ppm)


O
CO2Et
Cl
CO2Et
N
4j
7.81
7.80
7.80
7.80
7.41
7.40
7.38
7.38
7.35
7.35
7.32
7.32
4.48
4.48
4.48
4.46
4.46
4.45
4.19
4.16
4.13
4.01
3.98
2.85
2.83
2.82
2.80
2.78
2.76
2.75
2.73
1.91
1.59
1.44
1.42
1.12
1.10
1.08
1.00
2.52
2.53
2.13
1.65
2.78
4.27
1.38
3.63
3.34
f1 (ppm)


206.48
168.26
161.22
160.48
155.15
136.79
135.62
129.27
124.07
123.55
66.64
62.67
62.35
37.11
29.97
26.90
14.32
13.94
O
CO2Et
Cl
N
CO2Et
4j
f1 (ppm)


MeO
O
CO2Et
CO2Et
N
MeO
4k
6.49
4.42
4.41
4.40
4.39
4.37
4.37
4.35
4.34
4.16
4.13
4.10
3.96
3.93
3.90
2.69
2.67
2.65
2.64
2.63
2.61
2.59
1.87
1.73
1.70
1.66
1.62
1.39
1.37
1.37
1.35
1.23
1.10
1.07
1.07
1.05
1.91
1.98
1.17
3.93
2.95
1.00
1.00
4.12
1.06
3.04
2.89
f1 (ppm)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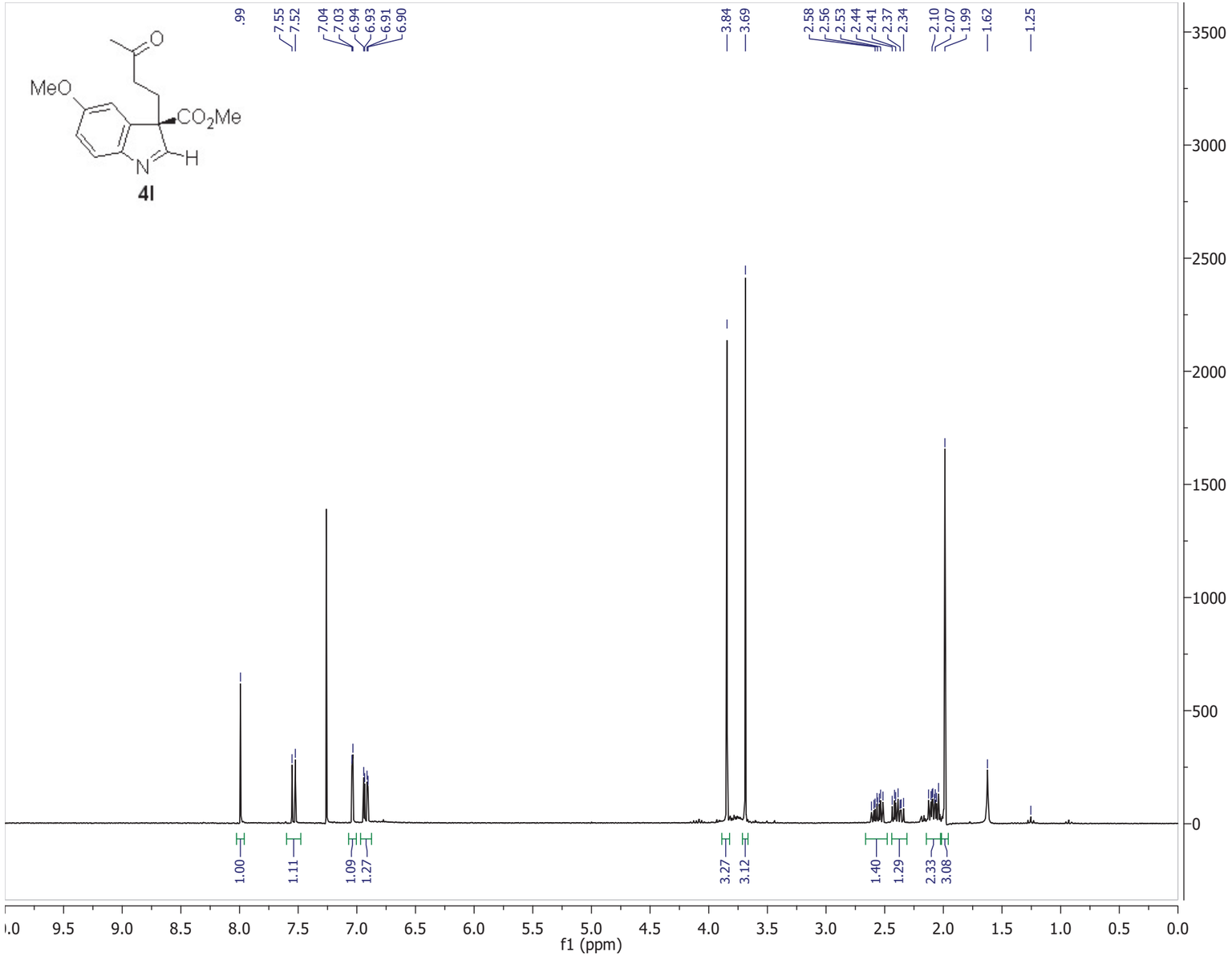
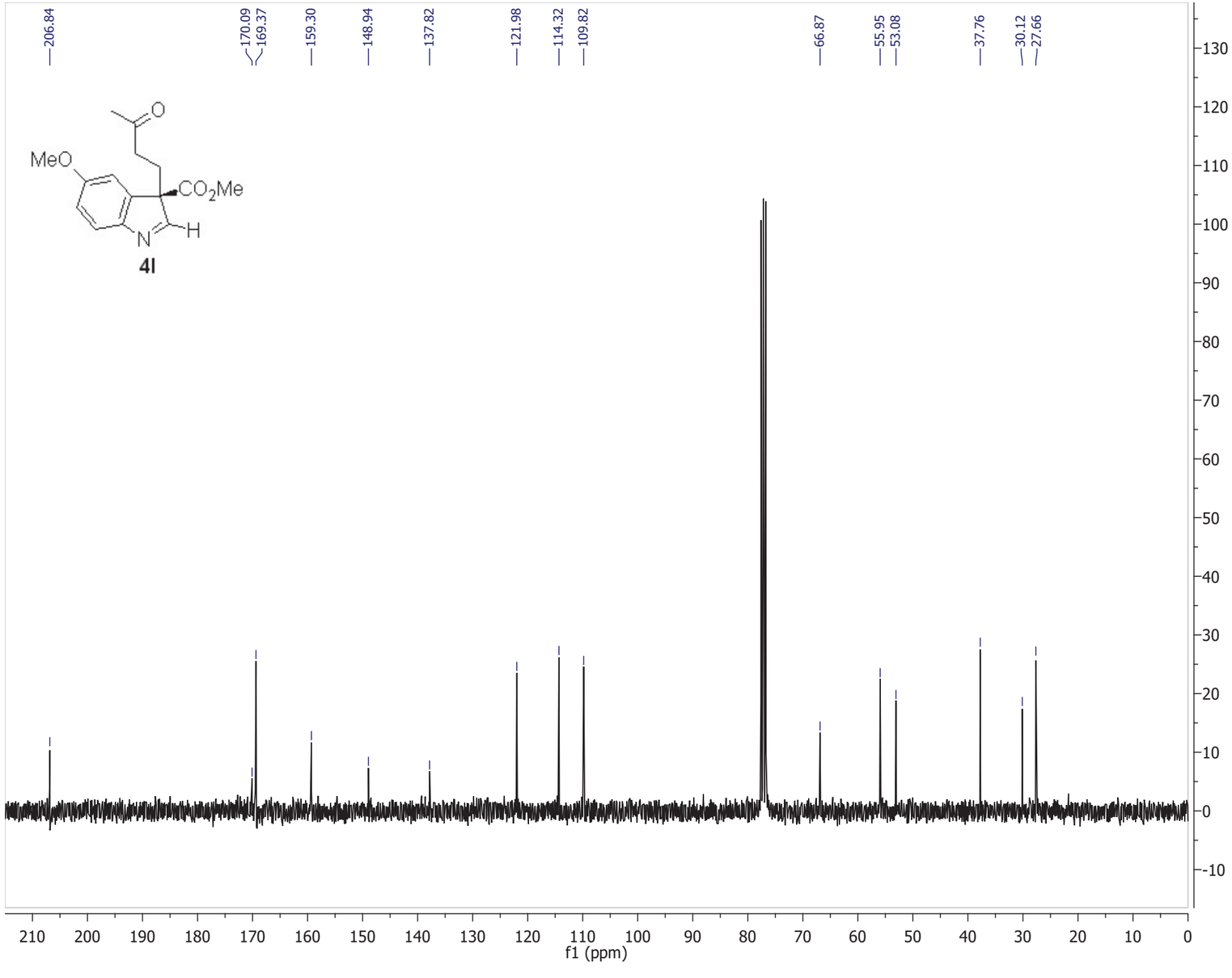
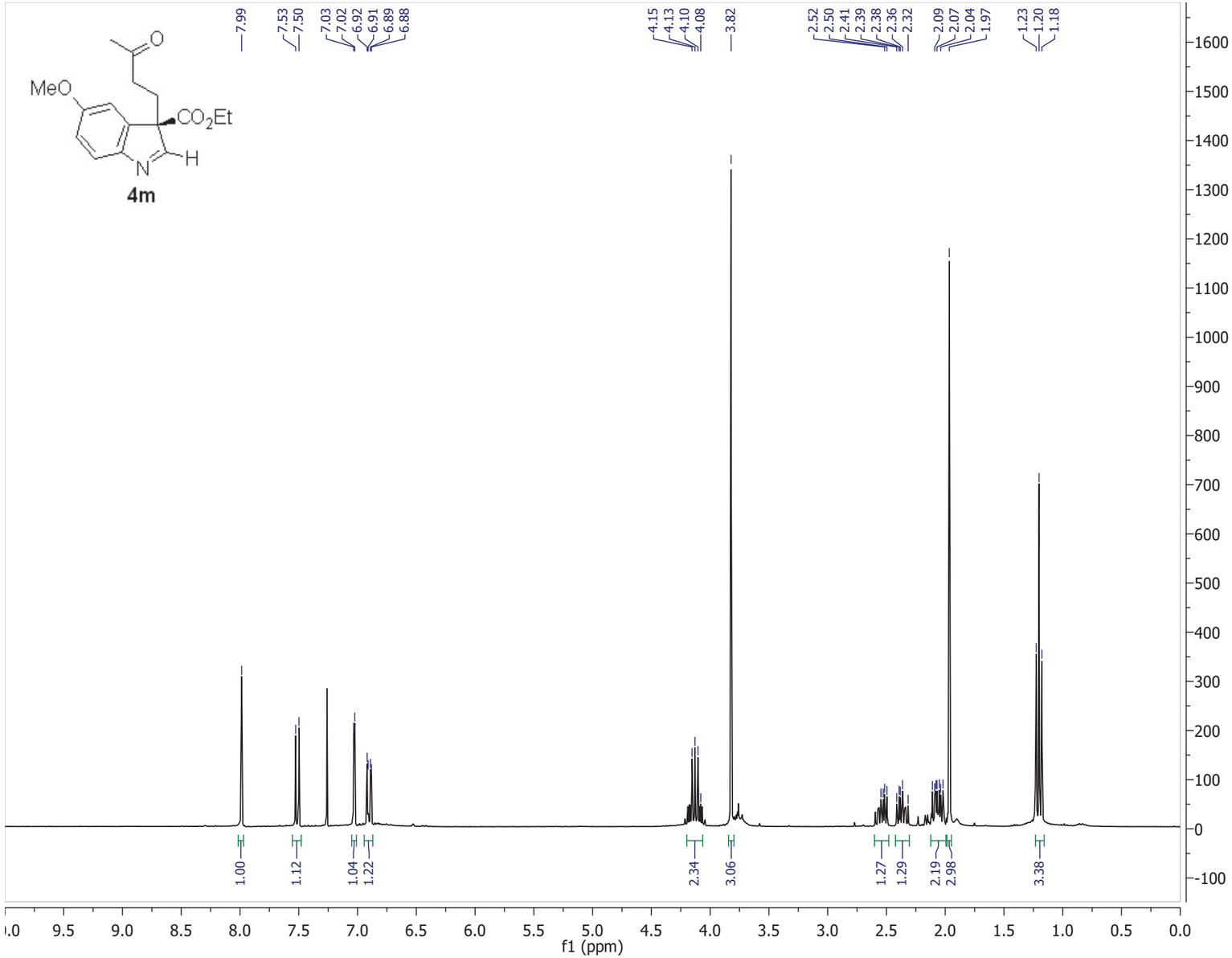
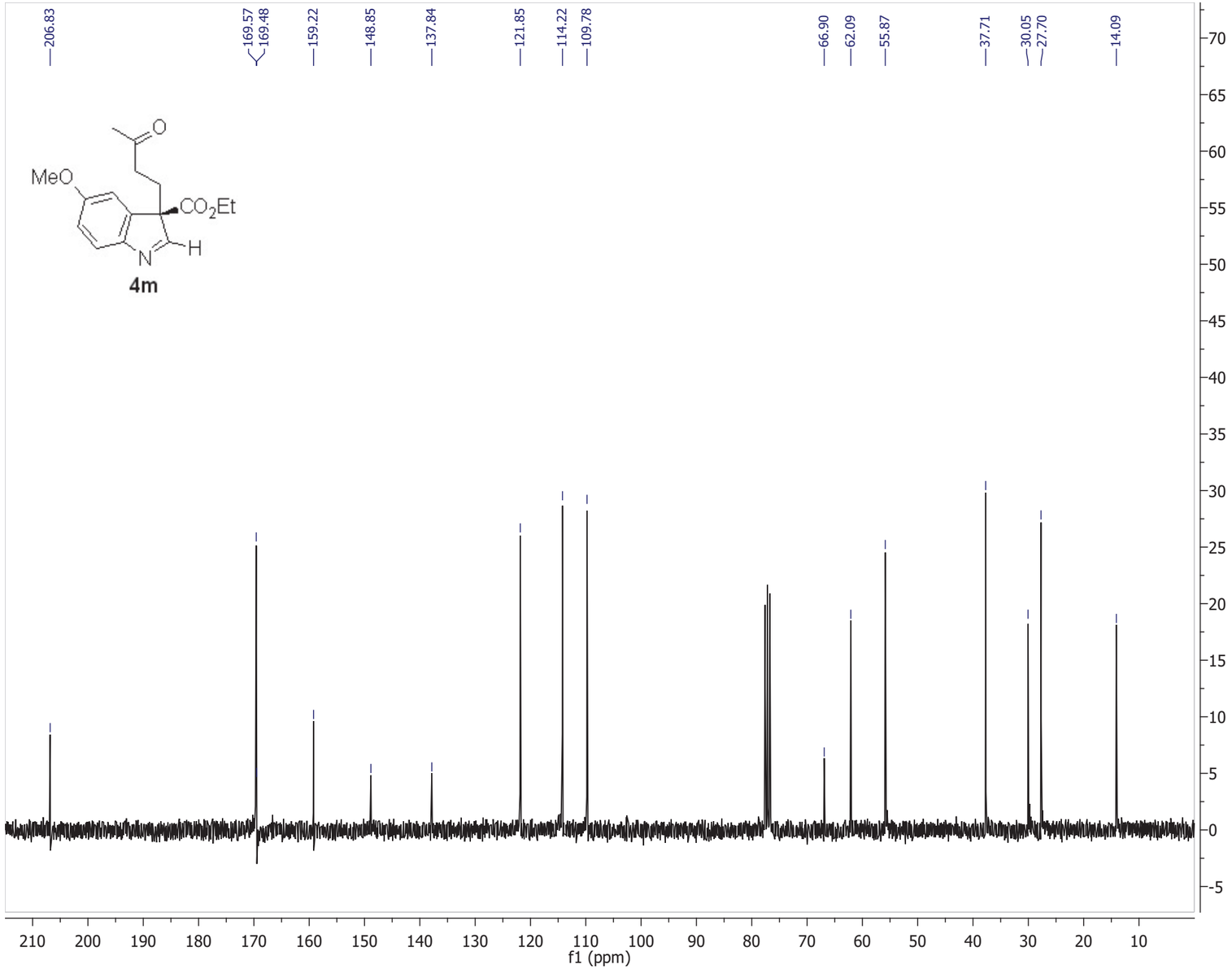
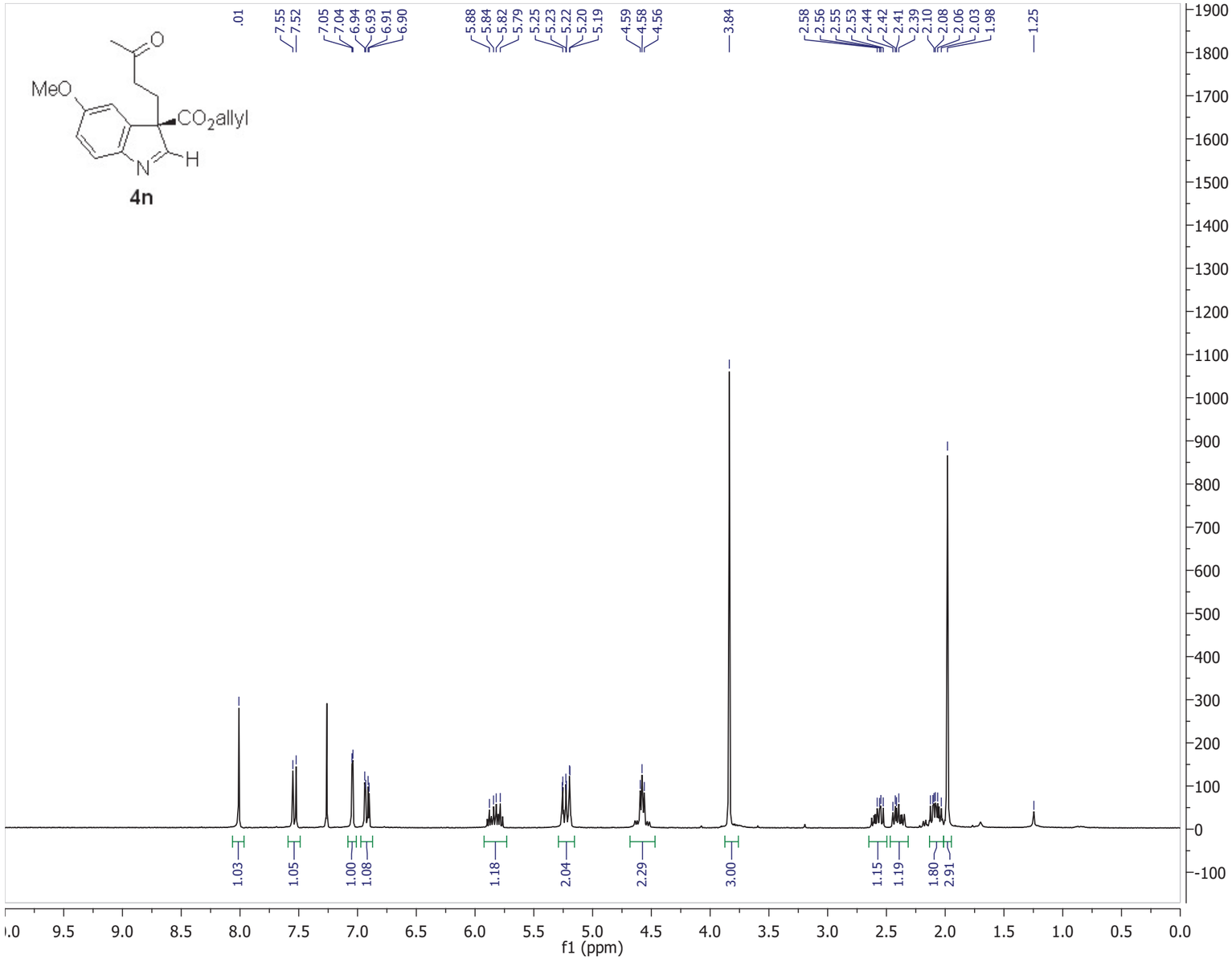
168.88
165.28
162.87
161.47
154.09
142.12
136.19
99.80
99.21
66.70
61.89
56.10
56.04
37.01
29.93
27.39
14.33
13.91
MeO
MeO
CO2Et
CO2Et
N
O
4k
f1 (ppm)

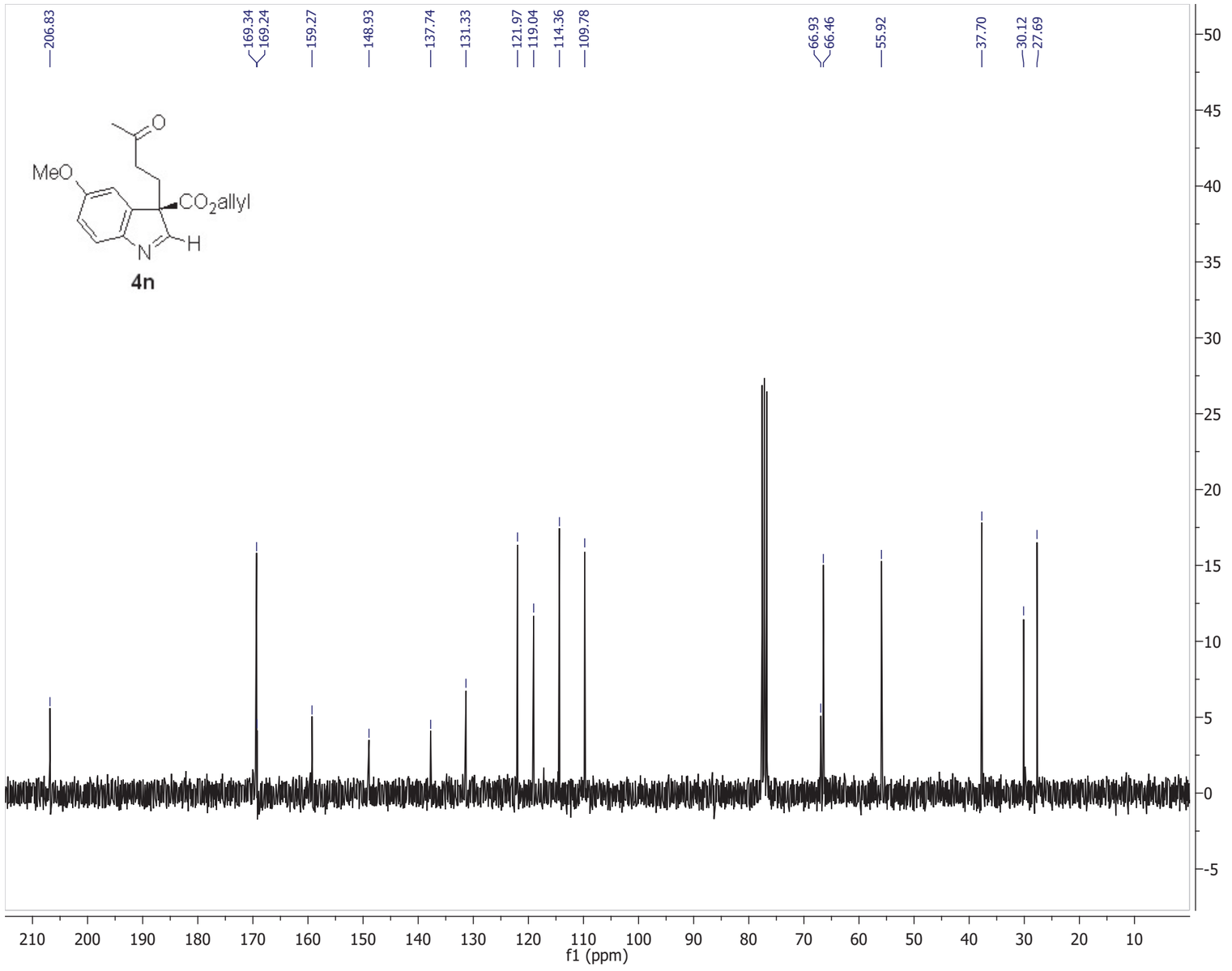

MeO
O
CO2Me
H
N
4l
.99
7.55
7.52
7.04
7.03
6.94
6.93
6.91
6.90
3.84
3.69
2.58
2.56
2.53
2.44
2.41
2.37
2.34
2.10
2.07
1.99
1.62
1.25
1.00
1.11
1.09
1.27
3.27
3.12
1.40
1.29
2.33
3.08
3500
3000
2500
2000
1500
1000
500
0
f1 (ppm)

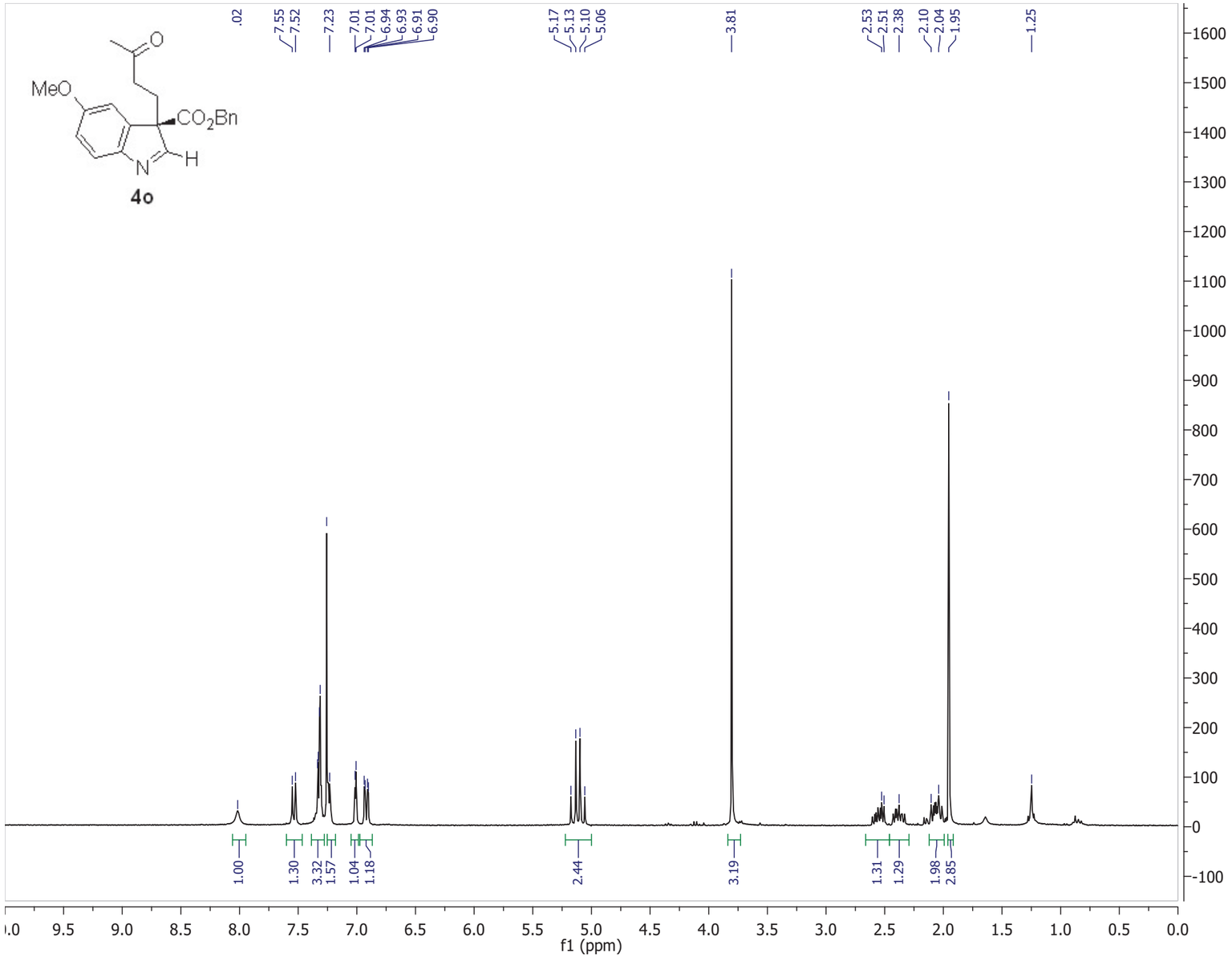

206.84
170.09
169.37
159.30
148.94
137.82
121.98
114.32
109.82
66.87
55.95
53.08
37.76
30.12
27.66
MeO
CO2Me
O
N
H
4l
f1 (ppm)

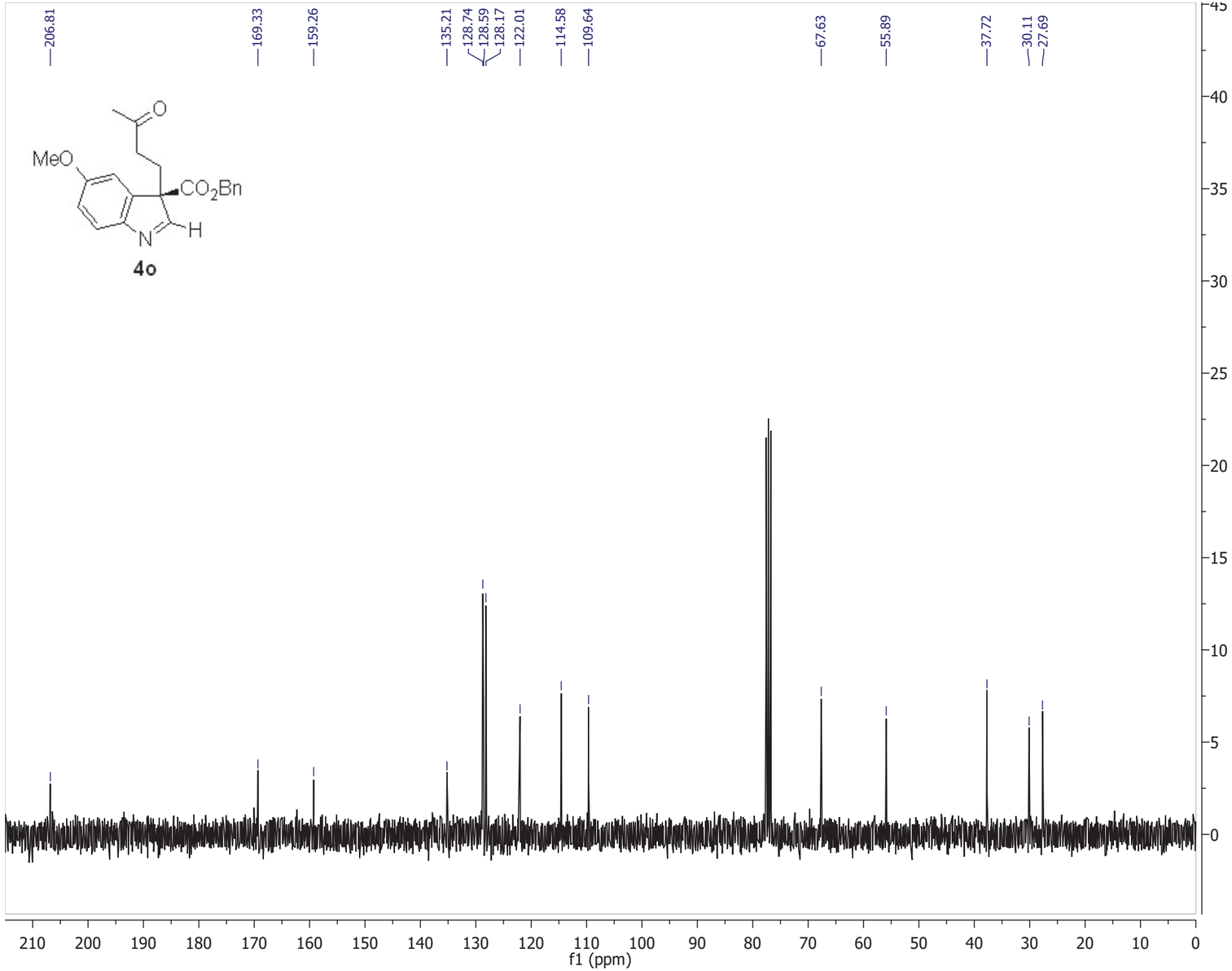

MeO
O
CO2Et
H
N
4m
7.99
7.53
7.50
7.03
7.02
6.92
6.91
6.89
6.88
4.15
4.13
4.10
4.08
3.82
2.52
2.50
2.41
2.39
2.38
2.36
2.32
2.09
2.07
2.04
1.97
1.23
1.20
1.18
1.00
1.12
1.04
1.22
2.34
3.06
1.27
1.29
2.19
2.98
3.38
f1 (ppm)

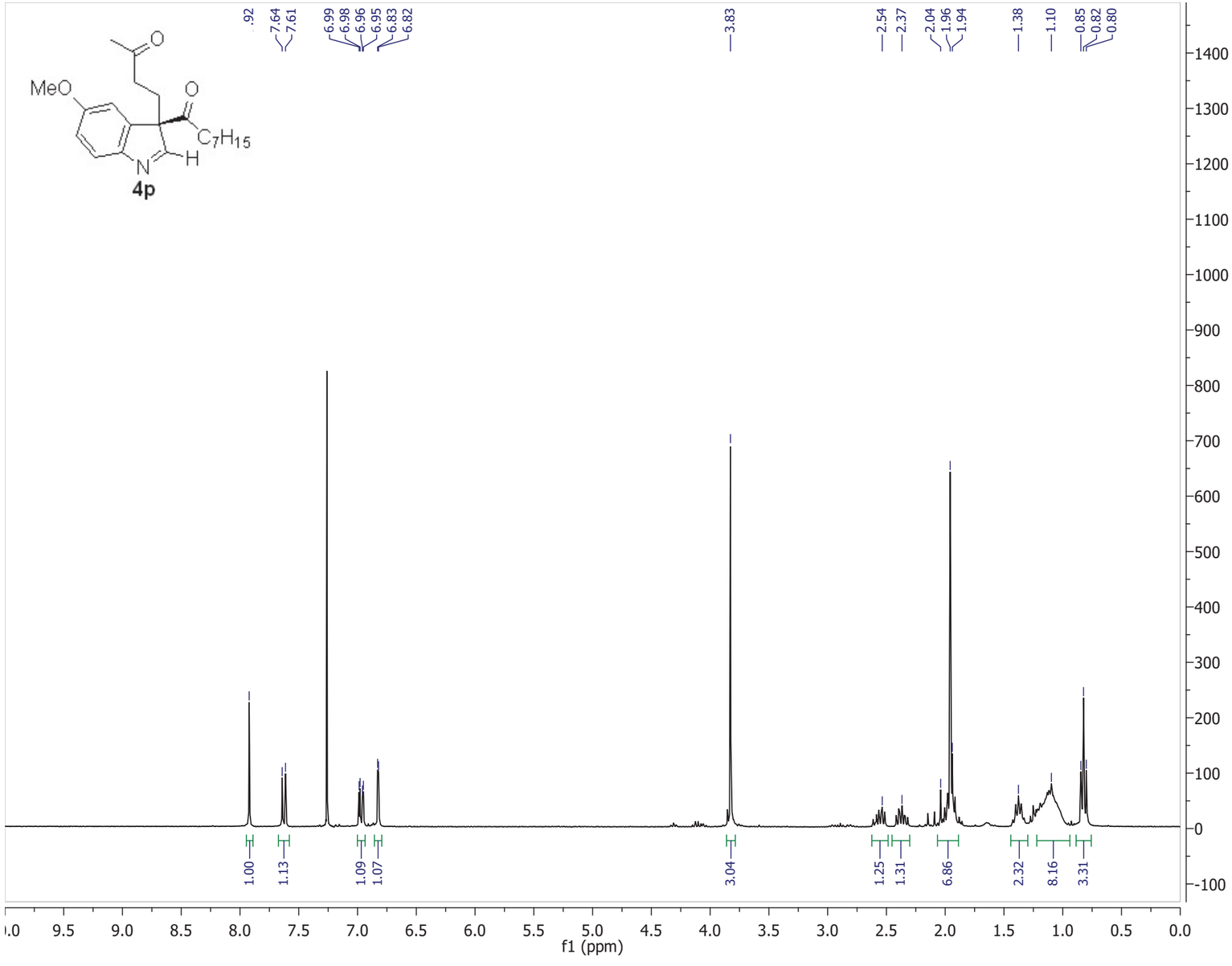

206.83
169.57
169.48
159.22
148.85
137.84
121.85
114.22
109.78
66.90
62.09
55.87
37.71
30.05
27.70
14.09
MeO
O
CO2Et
H
N
4m
f1 (ppm)

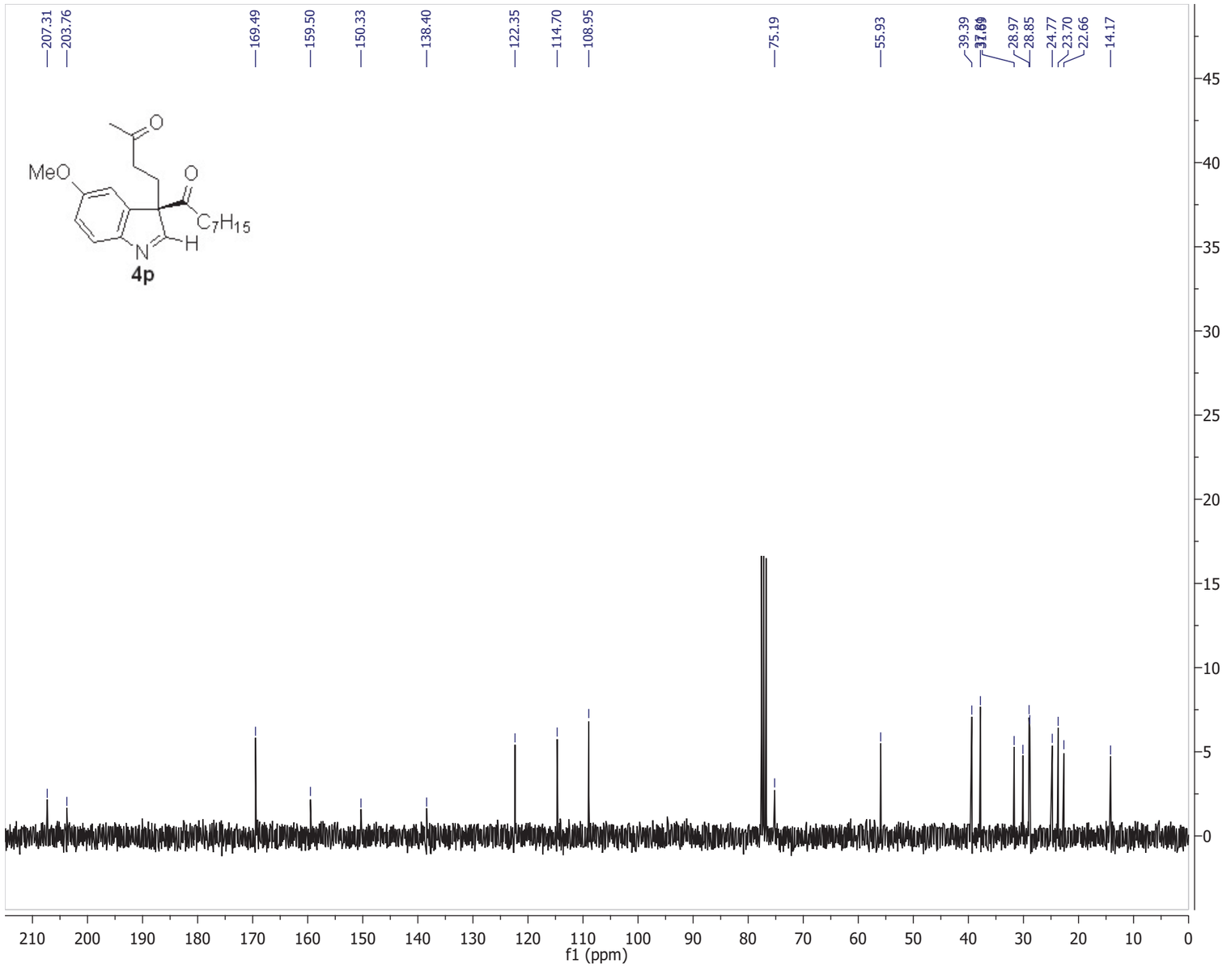

MeO
O
CO2allyl
H
N
4n
.01
7.55
7.52
7.05
7.04
6.94
6.93
6.91
6.90
5.88
5.84
5.82
5.79
5.25
5.23
5.22
5.20
5.19
4.59
4.58
4.56
3.84
2.58
2.56
2.55
2.53
2.44
2.42
2.41
2.39
2.10
2.08
2.06
2.03
1.98
1.25
1.03
1.05
1.00
1.08
1.18
2.04
2.29
3.00
1.15
1.19
1.80
2.91
f1 (ppm)

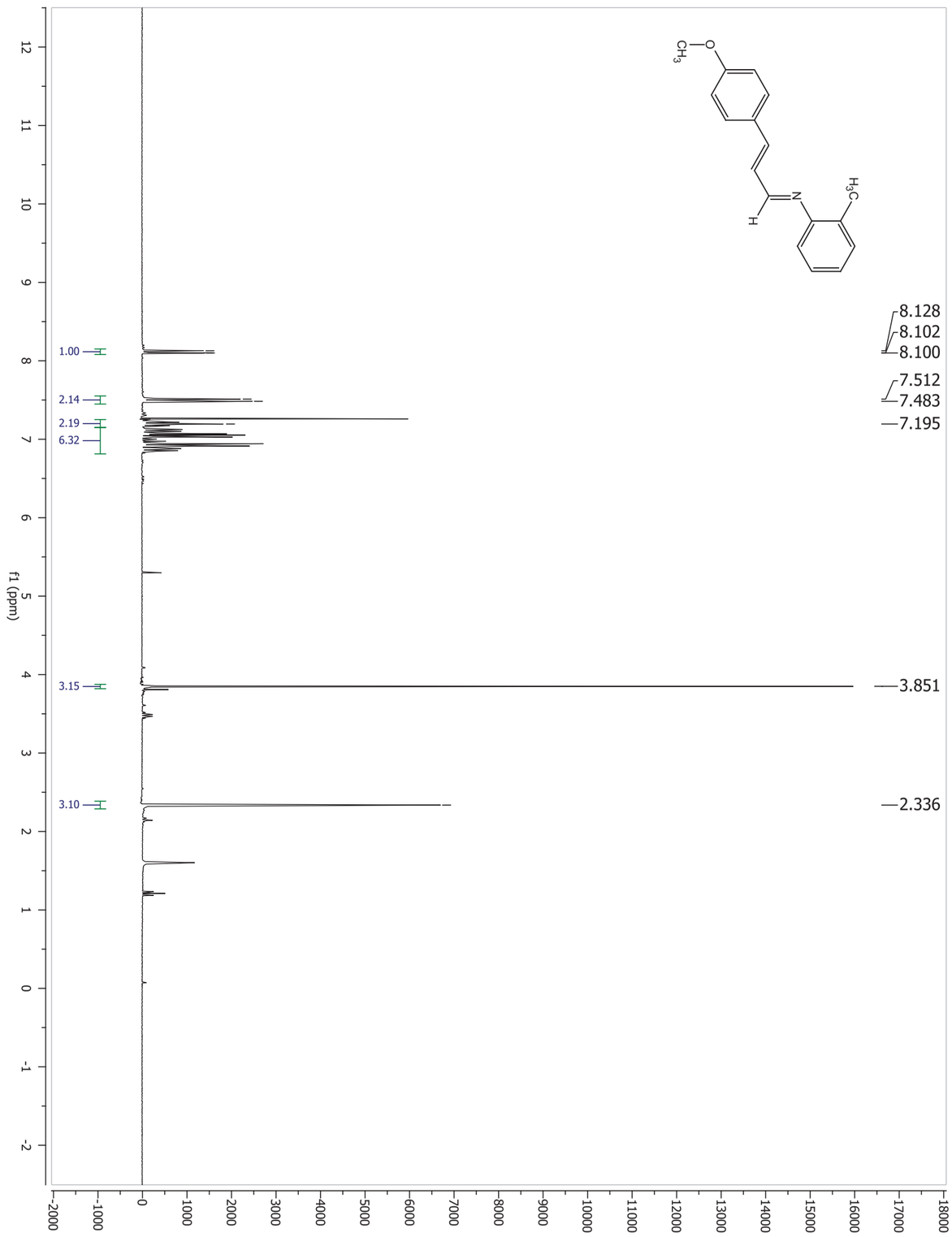

206.83
169.34
169.24
159.27
148.93
137.74
131.33
121.97
119.04
114.36
109.78
66.93
66.46
55.92
37.70
30.12
27.69
MeO
CO2allyl
N
H
O
4n
50
45
40
35
30
25
20
15
10
5
0
-5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

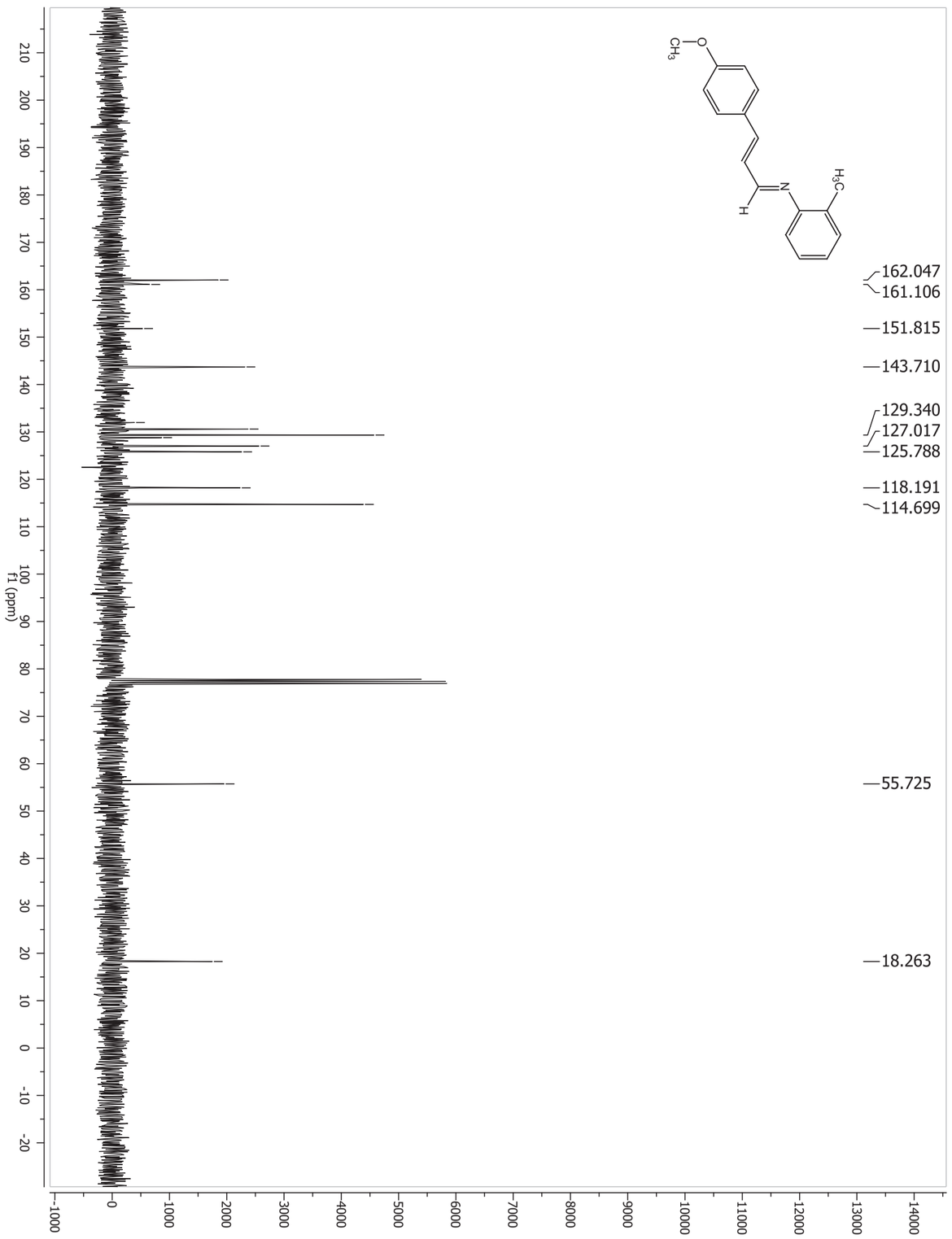

.02
7.55
7.52
7.23
7.01
7.01
6.94
6.93
6.91
6.90
5.17
5.13
5.10
5.06
3.81
2.53
2.51
2.38
2.10
2.04
1.95
1.25
MeO
O
CO2Bn
H
N
4o
1.00
1.30
3.32
1.57
1.04
1.18
2.44
3.19
1.31
1.29
1.98
2.85
f1 (ppm)

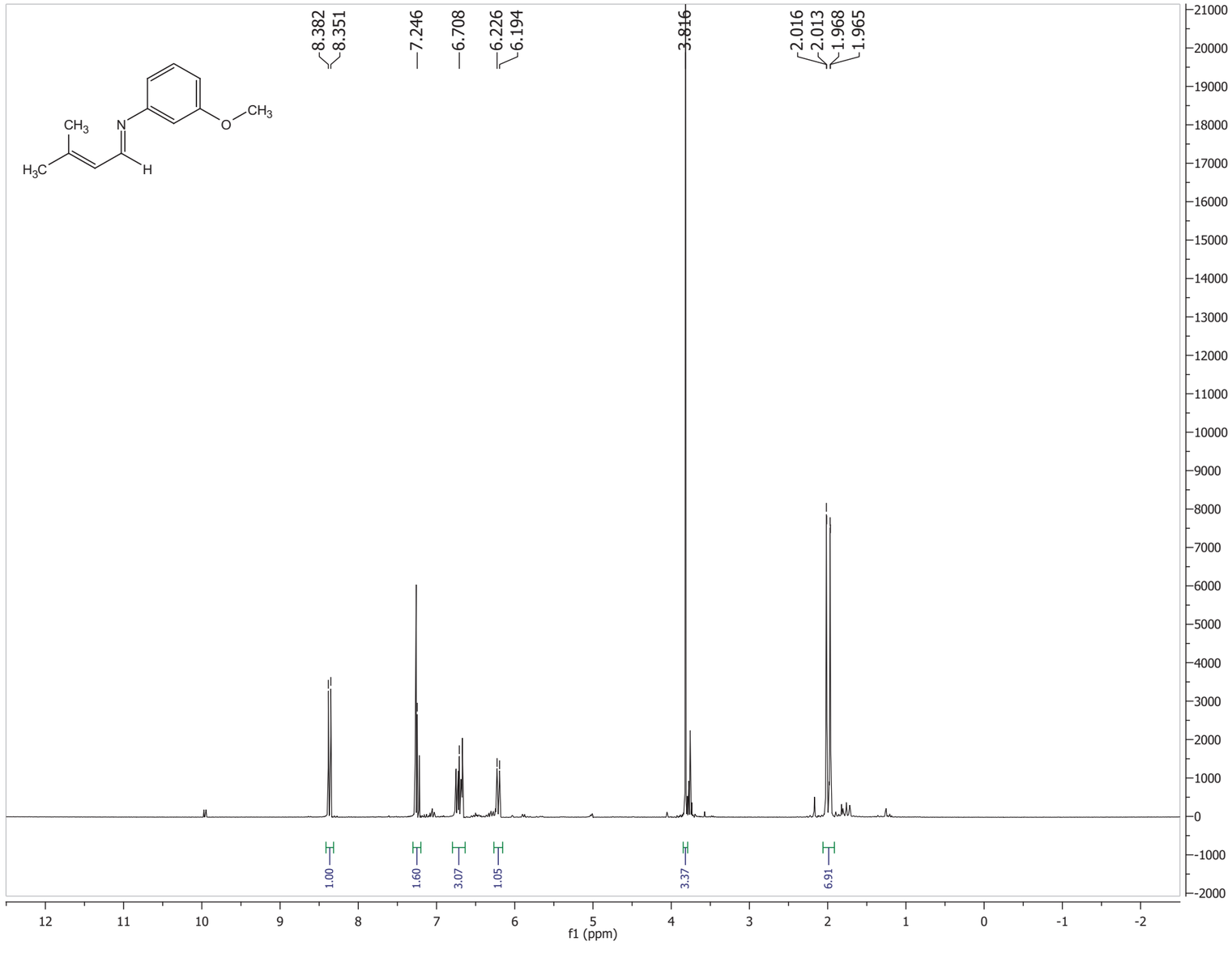

206.81
169.33
159.26
135.21
128.74
128.59
128.17
122.01
114.58
109.64
67.63
55.89
37.72
30.11
27.69
MeO
O
CO2Bn
H
N
4o
f1 (ppm)

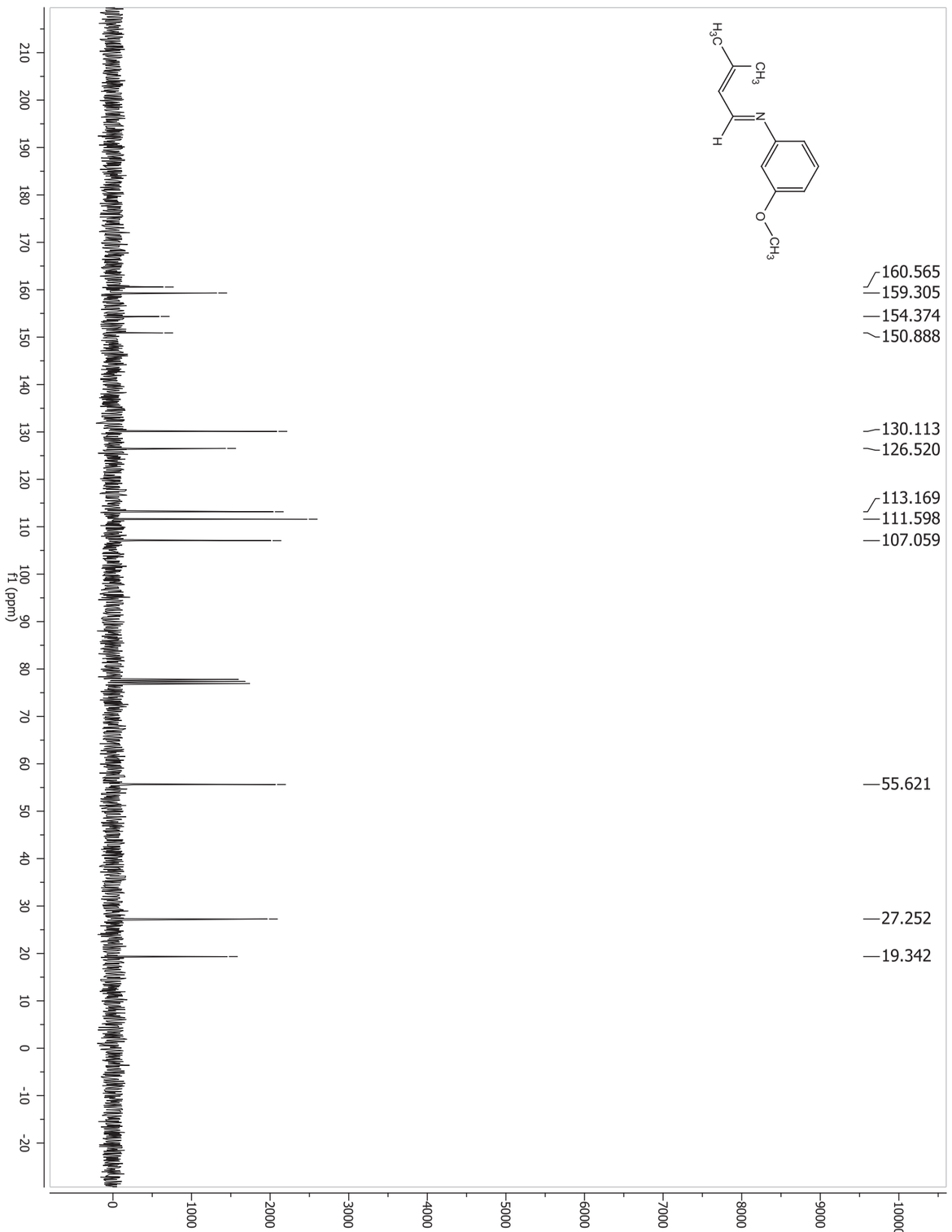

MeO
O
O
C_7H_{15}
H
N
4p
f1 (ppm)

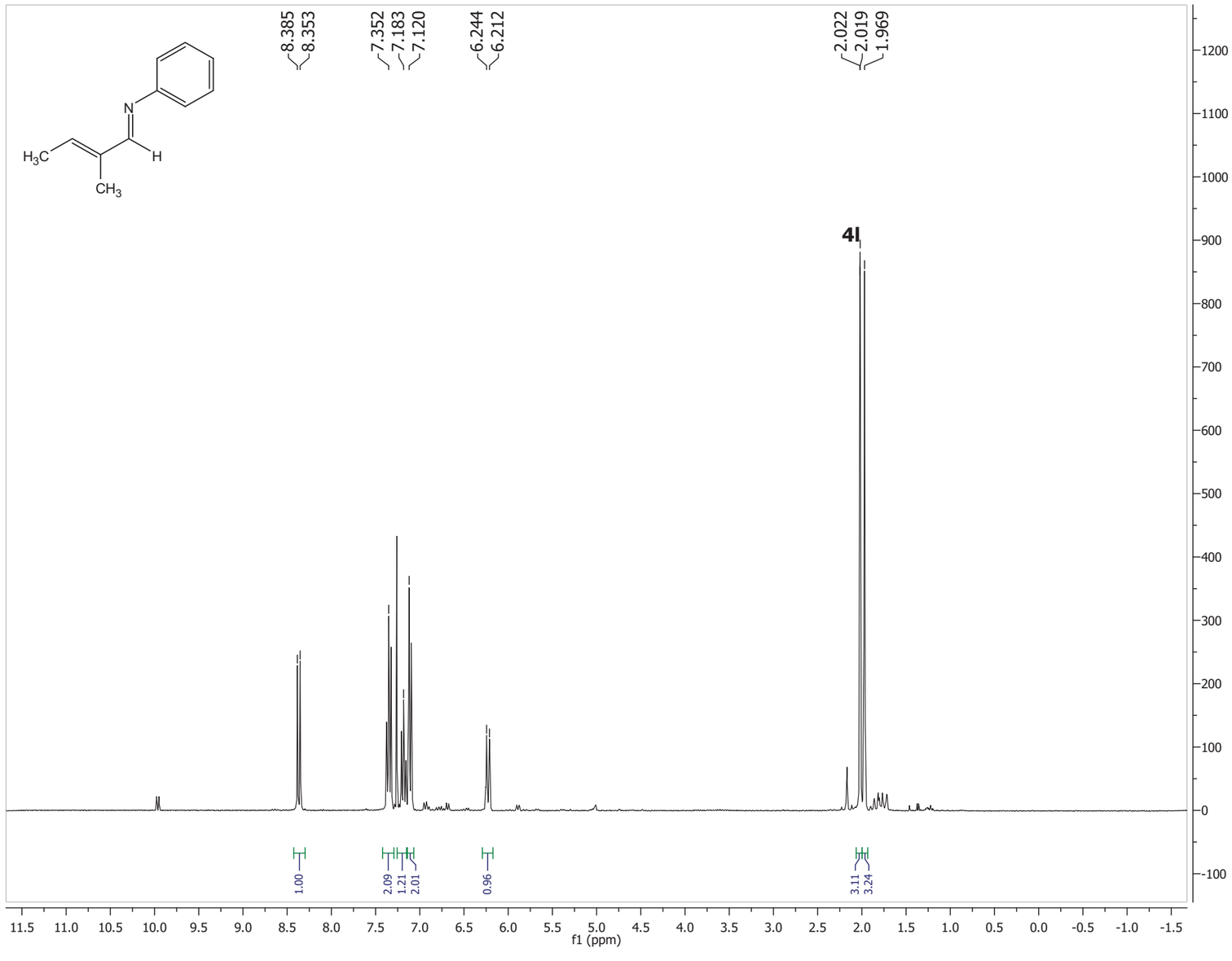

207.31
203.76
169.49
159.50
150.33
138.40
122.35
114.70
108.95
75.19
55.93
39.39
37.69
28.97
28.85
24.77
23.70
22.66
14.17
MeO
O
O
C7H15
N
H
4p
45
40
35
30
25
20
15
10
5
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

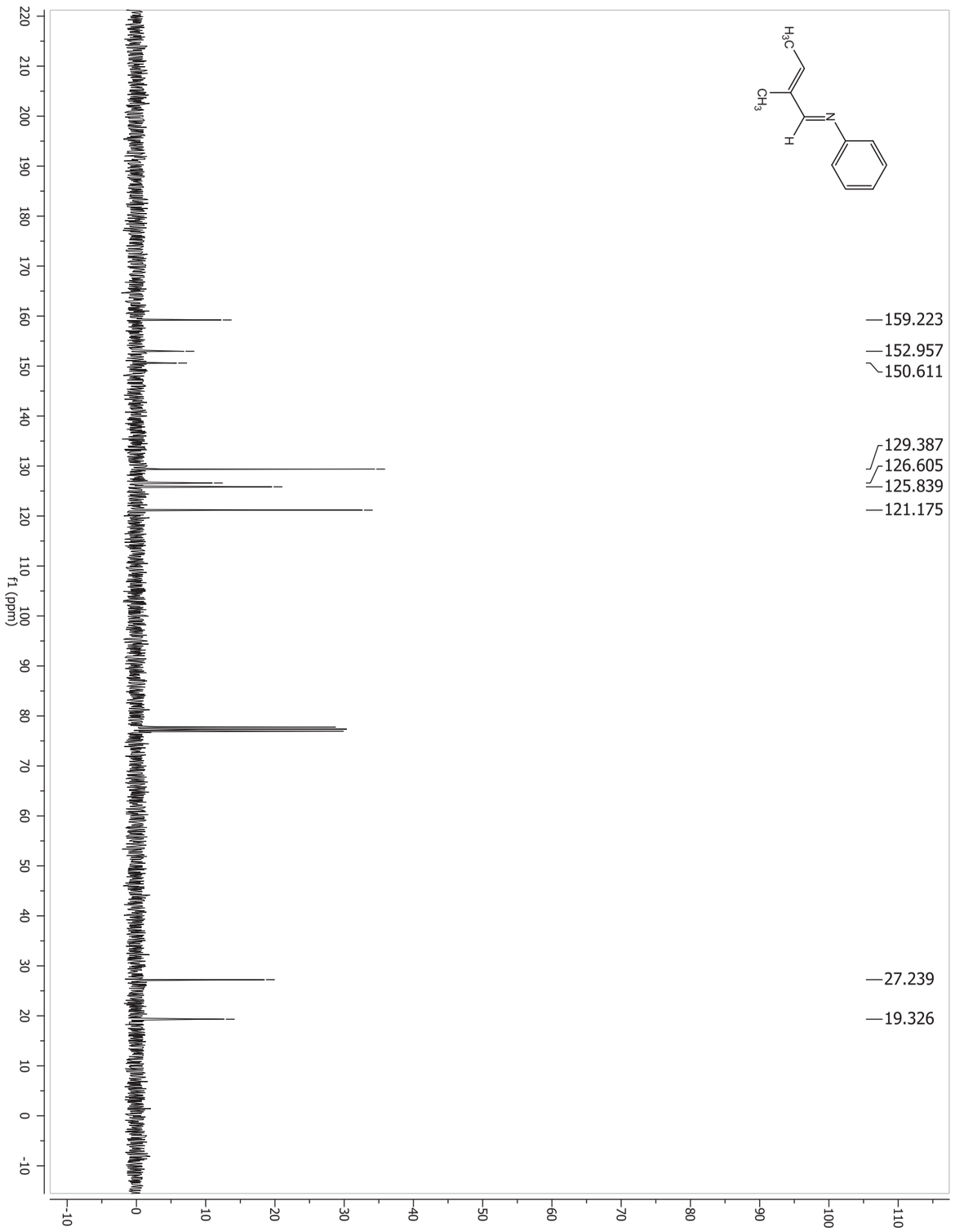

f1 (ppm)
1.00
2.14
2.19
6.32
3.15
3.10
8.128
8.102
8.100
7.512
7.483
7.195
3.851
2.336
O
CH3
N
H
H3C

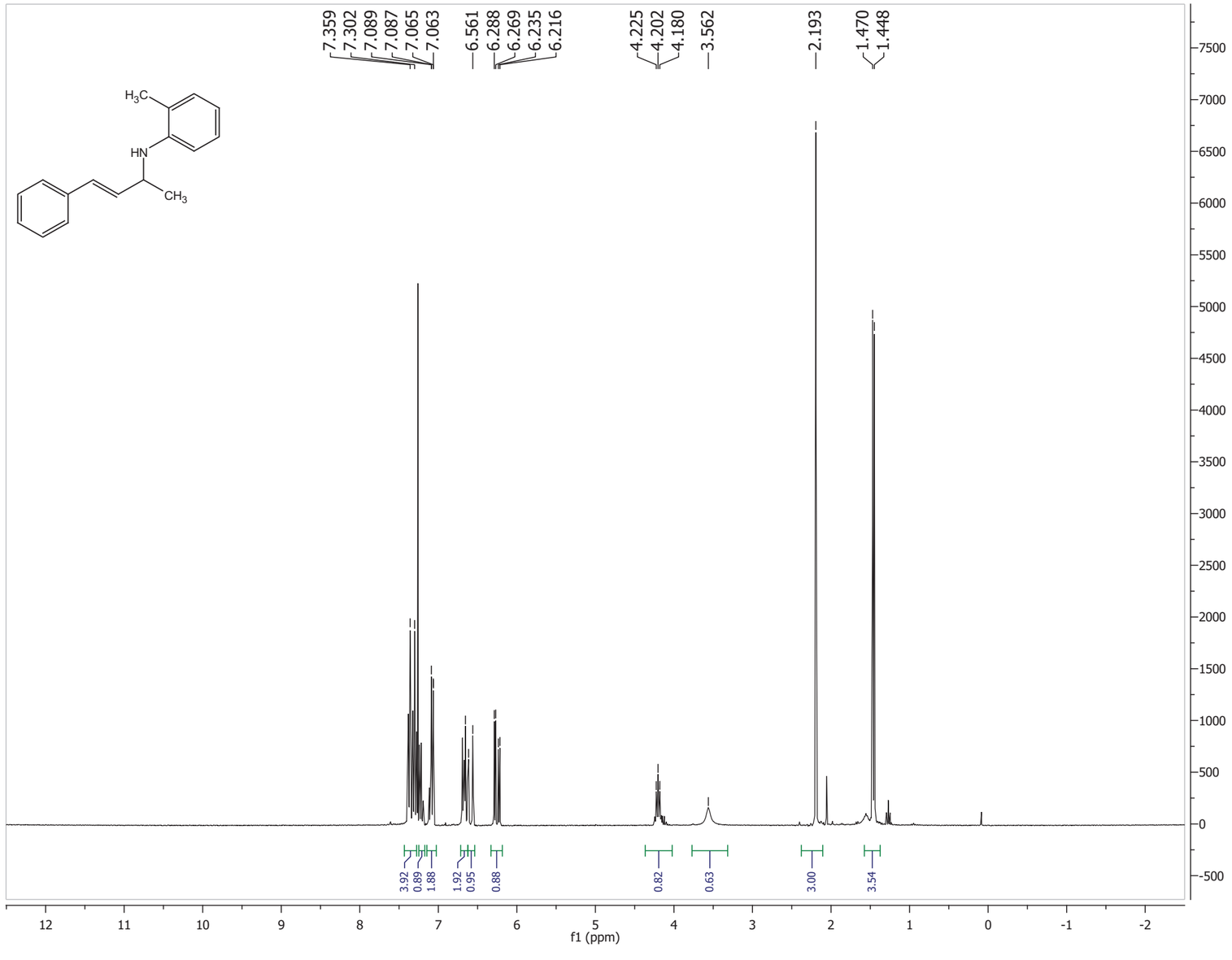

162.047
161.106
151.815
143.710
129.340
127.017
125.788
118.191
114.699
55.725
18.263
f1 (ppm)

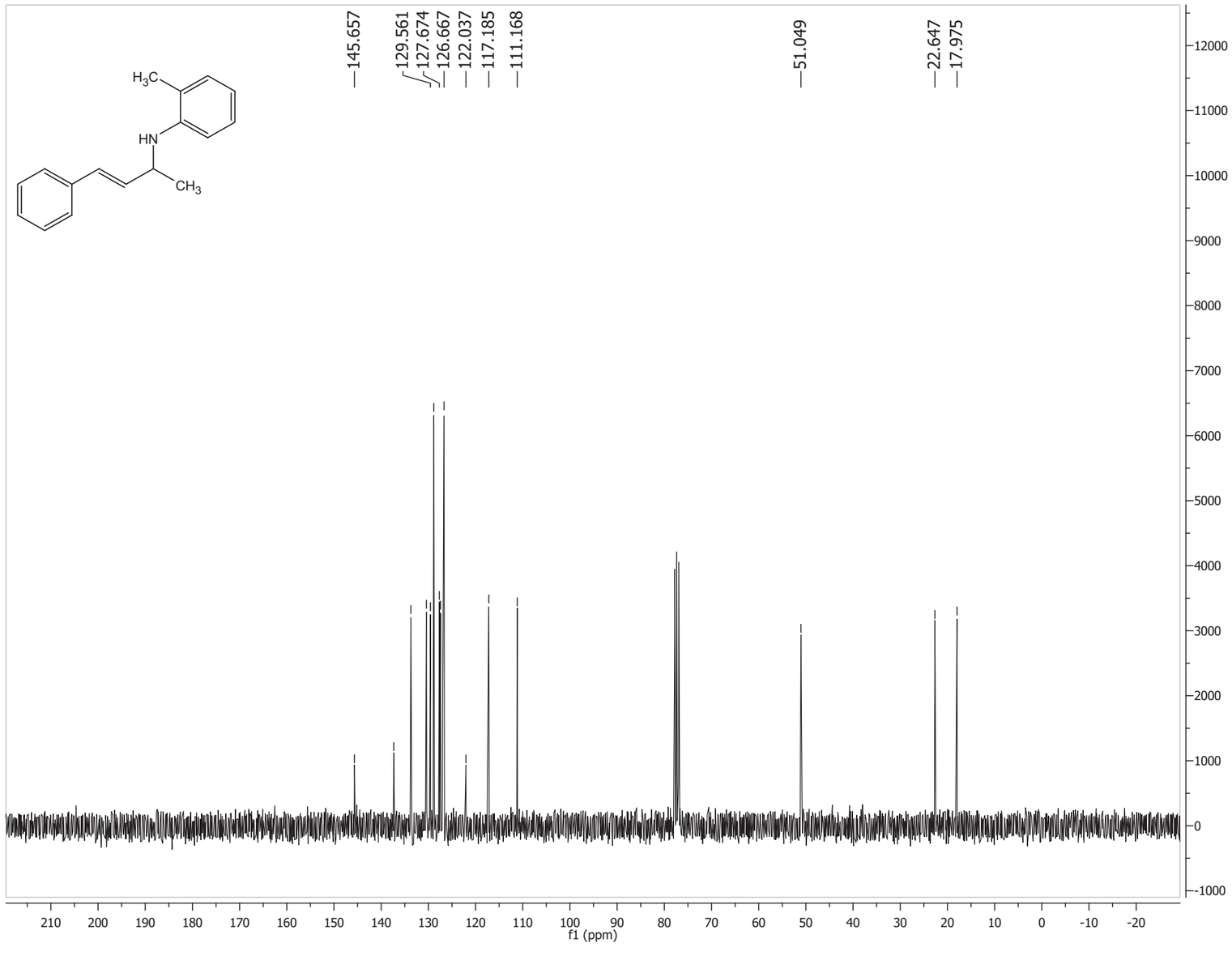

8.382
8.351
7.246
6.708
6.226
6.194
3.816
2.016
2.013
1.968
1.965
CH3
N
O
CH3
H3C
H
1.00
1.60
3.07
1.05
3.37
6.91
f1 (ppm)

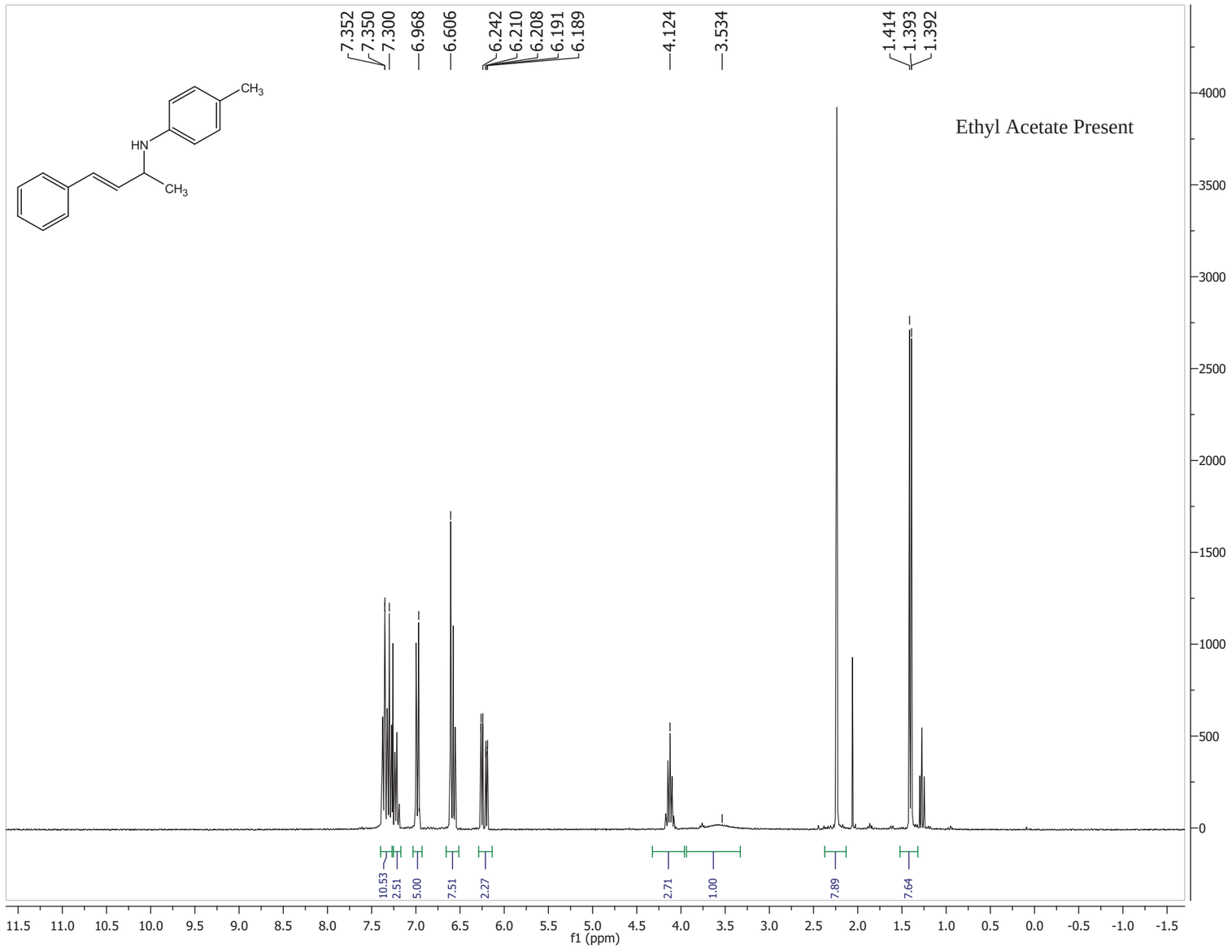

160.565
159.305
154.374
150.888
130.113
126.520
113.169
111.598
107.059
55.621
27.252
19.342
f1 (ppm)

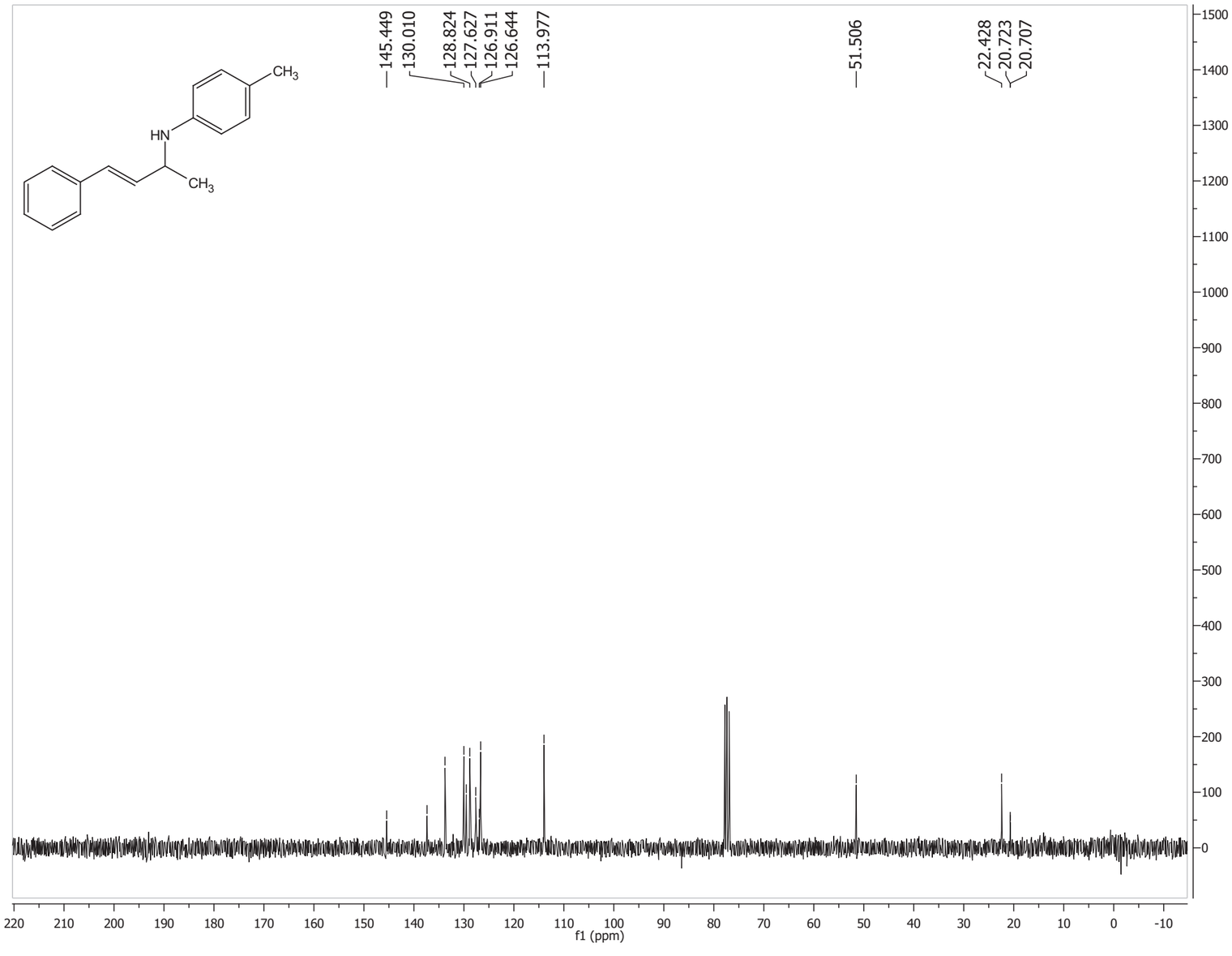

8.385
8.353
7.352
7.183
7.120
6.244
6.212
2.022
2.019
1.969
N
H
H_3C
CH_3
1.00
2.09
1.21
2.01
0.96
3.11
3.24
f1 (ppm)

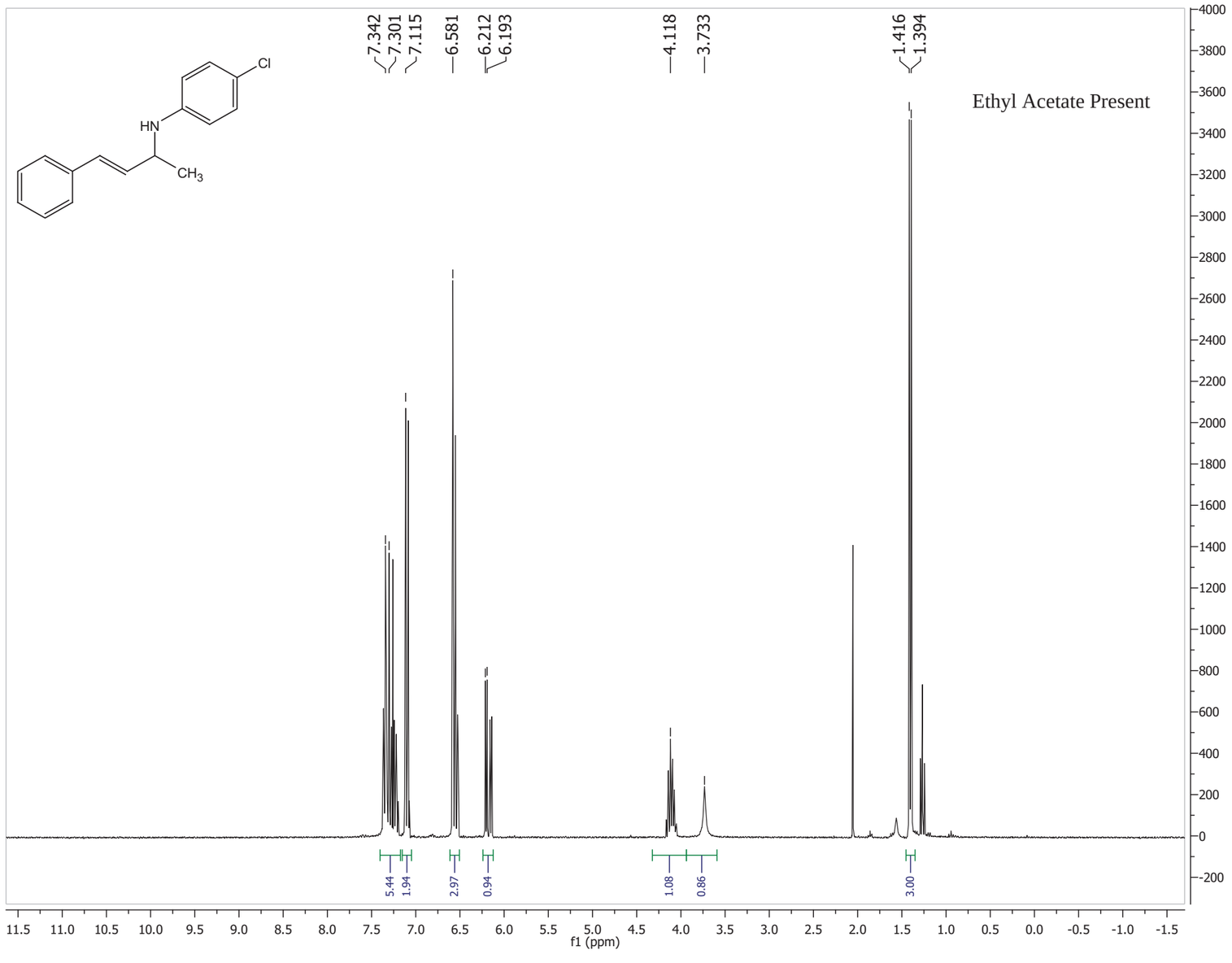

159.223
152.957
150.611
129.387
126.605
125.839
121.175
27.239
19.326
f1 (ppm)

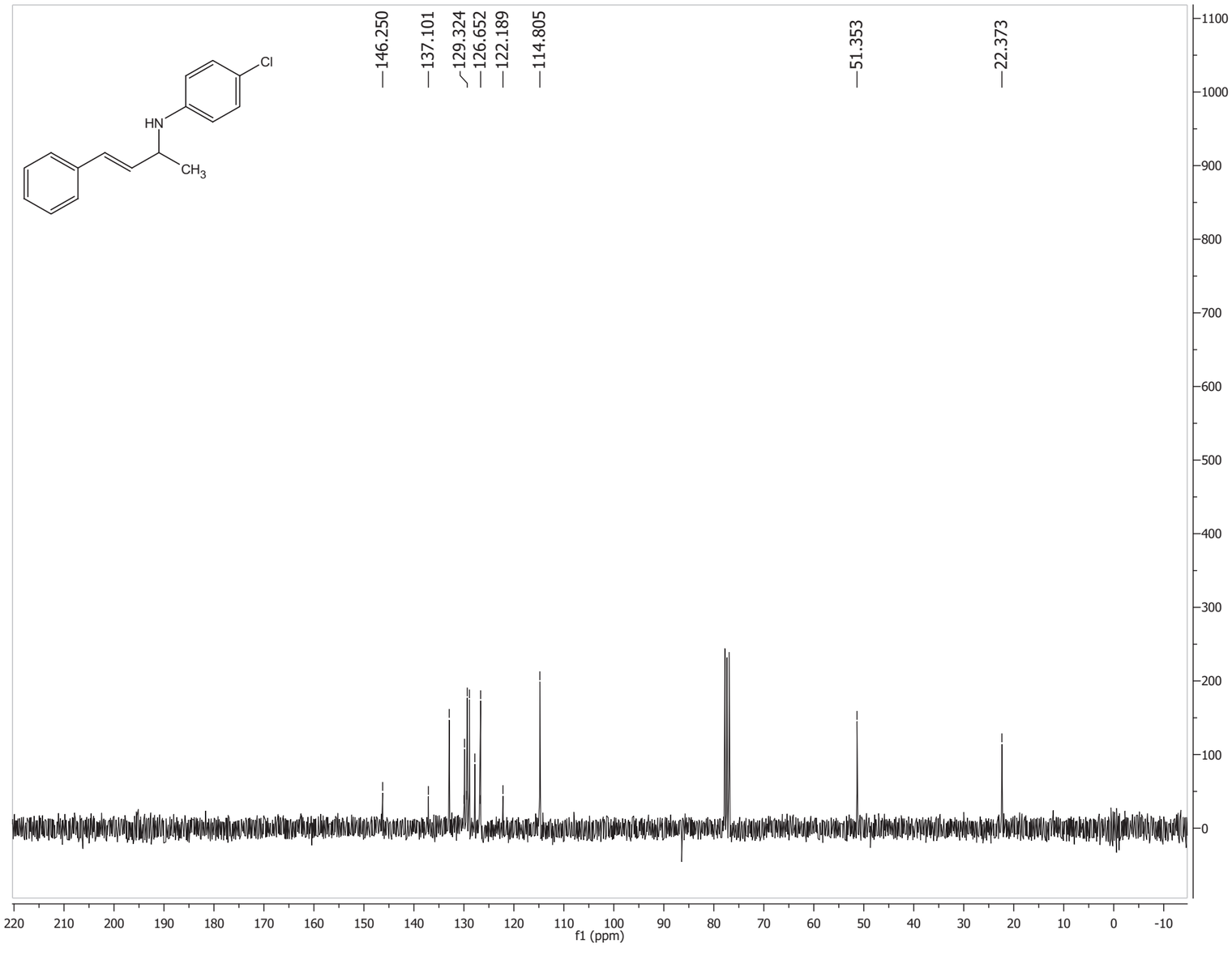

7.359
7.302
7.089
7.087
7.065
7.063
6.561
6.288
6.269
6.235
6.216
4.225
4.202
4.180
3.562
2.193
1.470
1.448
H3C
HN
CH3
3.92
0.89
1.88
1.92
0.95
0.88
0.82
0.63
3.00
3.54
f1 (ppm)

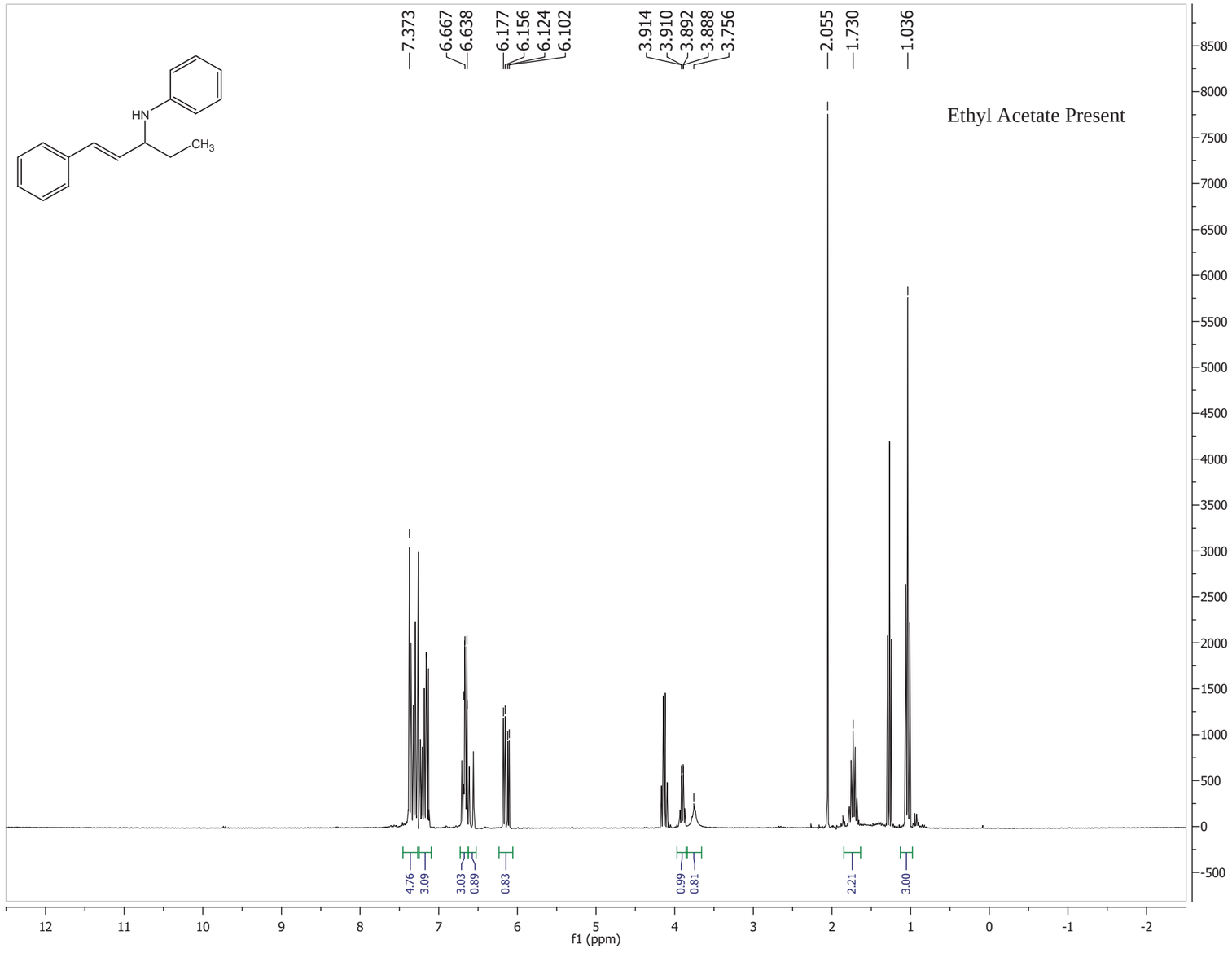

H3C
HN
CH3
145.657
129.561
127.674
126.667
122.037
117.185
111.168
51.049
22.647
17.975
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

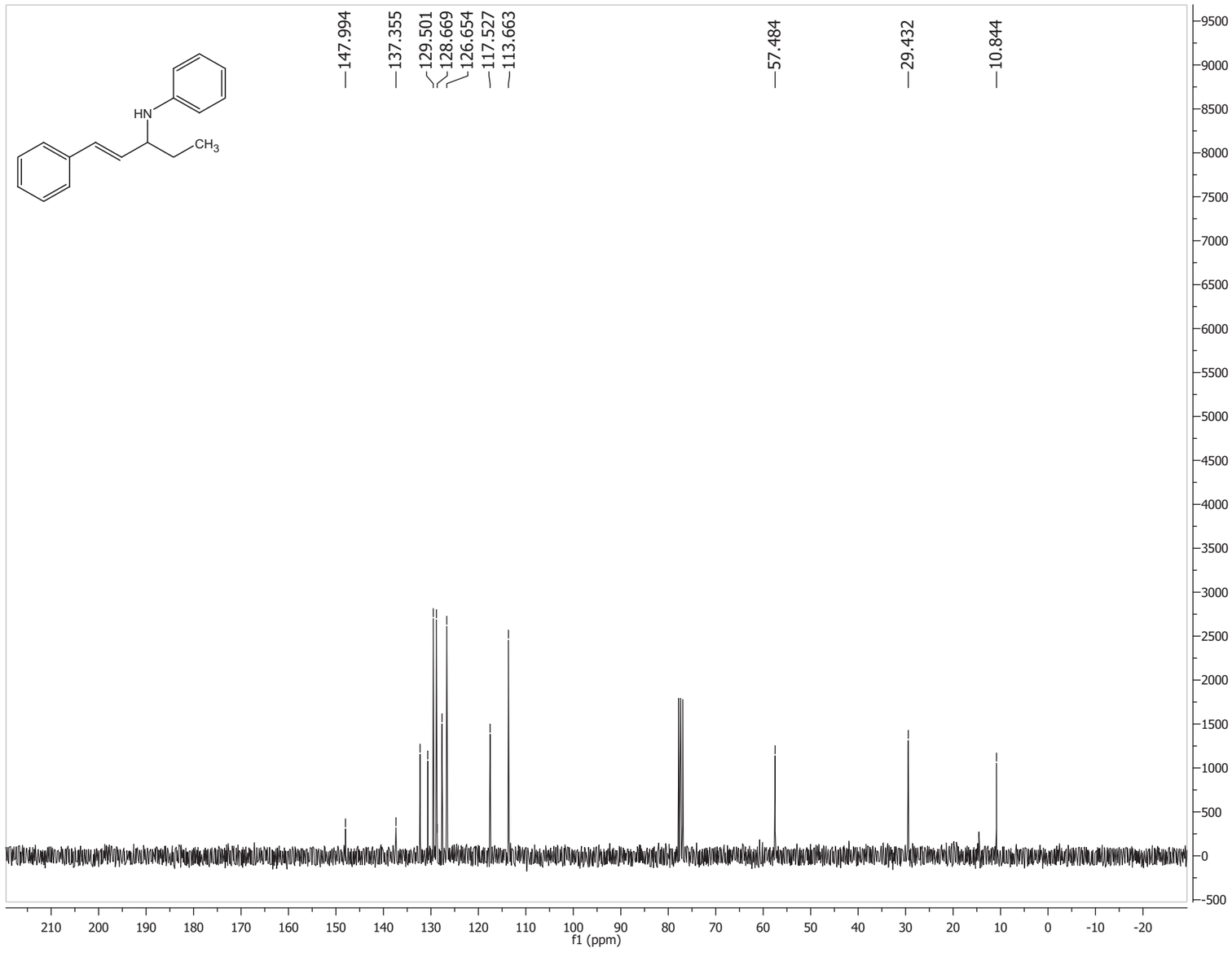

7.352
7.350
7.300
6.968
6.606
6.242
6.210
6.208
6.191
6.189
4.124
3.534
1.414
1.393
1.392
HN
CH3
CH3
Ethyl Acetate Present
10.53
2.51
5.00
7.51
2.27
2.71
1.00
7.89
7.64
f1 (ppm)

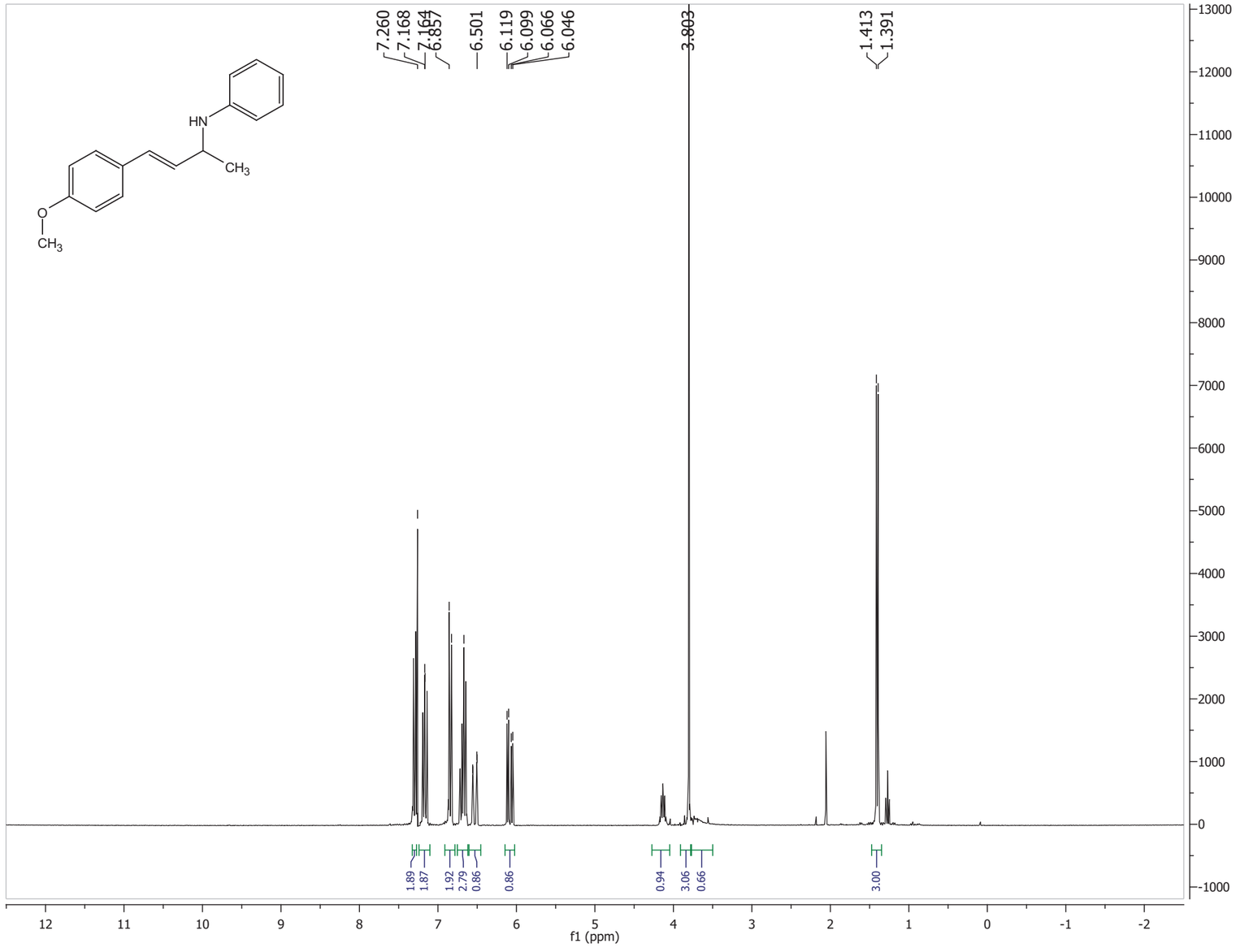

145.449
130.010
128.824
127.627
126.911
126.644
113.977
51.506
22.428
20.723
20.707
HN
CH3
CH3
f1 (ppm)

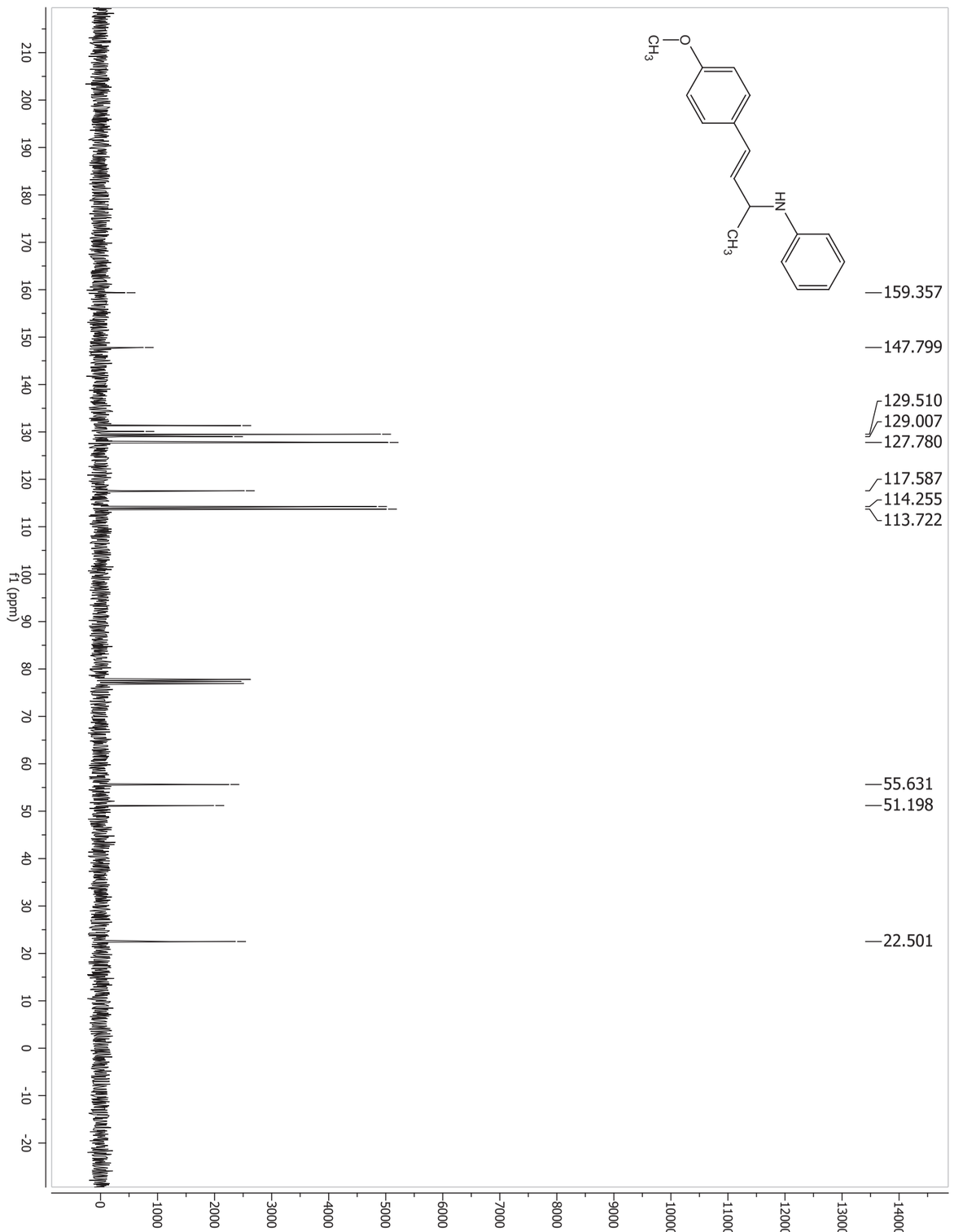

Cl
HN
CH3
7.342
7.301
7.115
6.581
6.212
6.193
4.118
3.733
1.416
1.394
Ethyl Acetate Present
5.44
1.94
2.97
0.94
1.08
0.86
3.00
f1 (ppm)

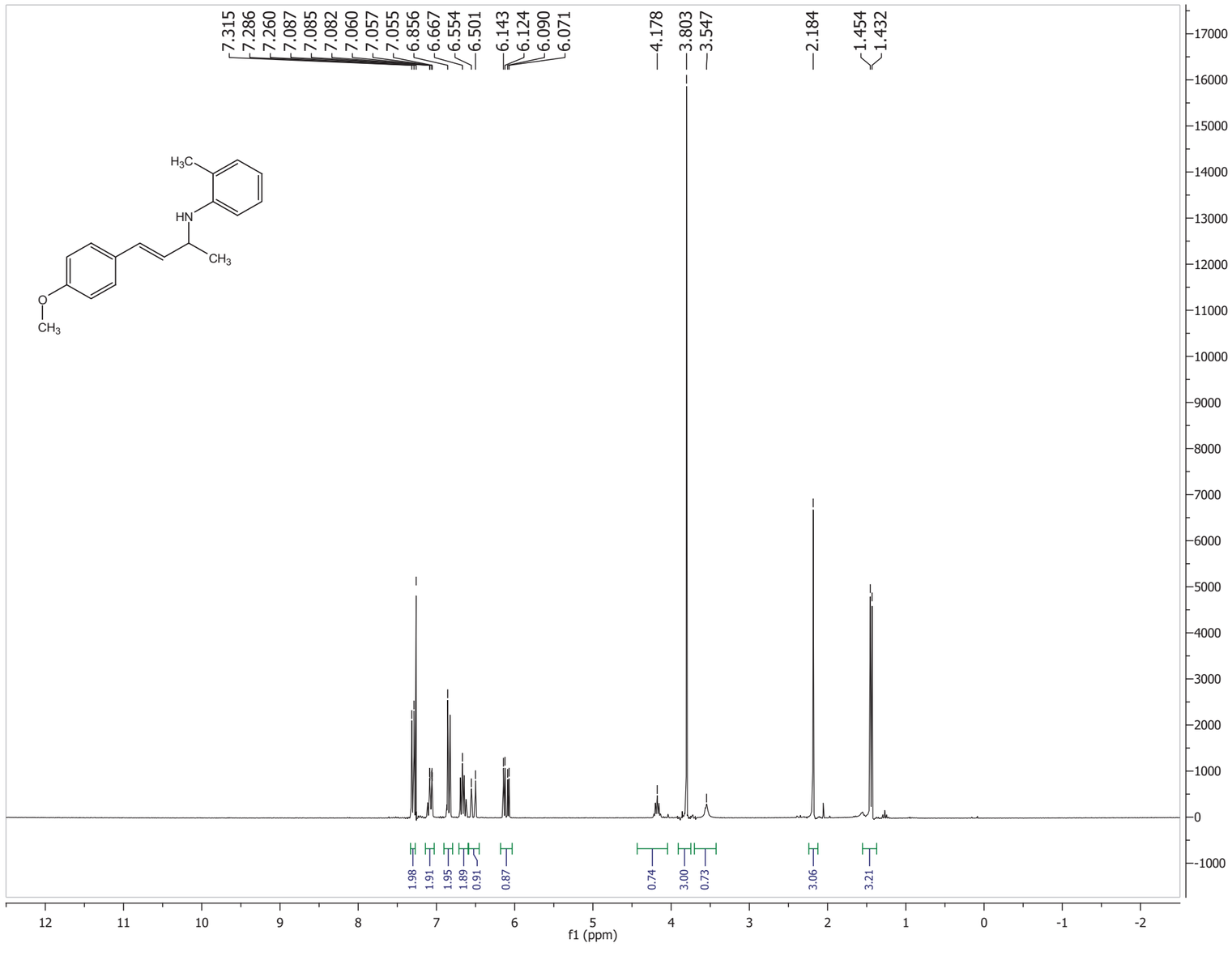

Cl
HN
CH3
146.250
137.101
129.324
126.652
122.189
114.805
51.353
22.373
1100
1000
900
800
700
600
500
400
300
200
100
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

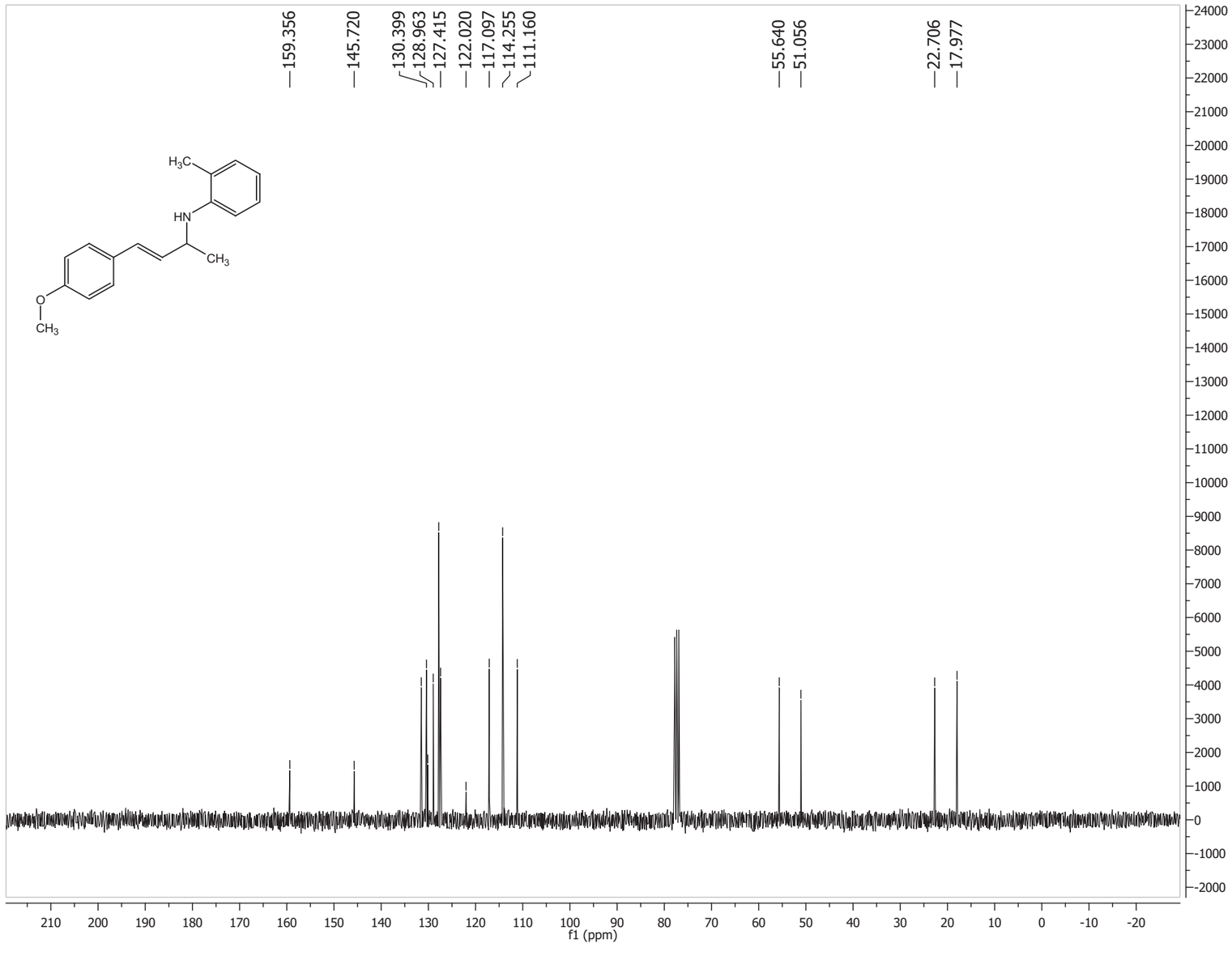

HN
CH3
7.373
6.667
6.638
6.177
6.156
6.124
6.102
3.914
3.910
3.892
3.888
3.756
2.055
1.730
1.036
Ethyl Acetate Present
4.76
3.09
3.03
0.89
0.83
0.99
0.81
2.21
3.00
f1 (ppm)

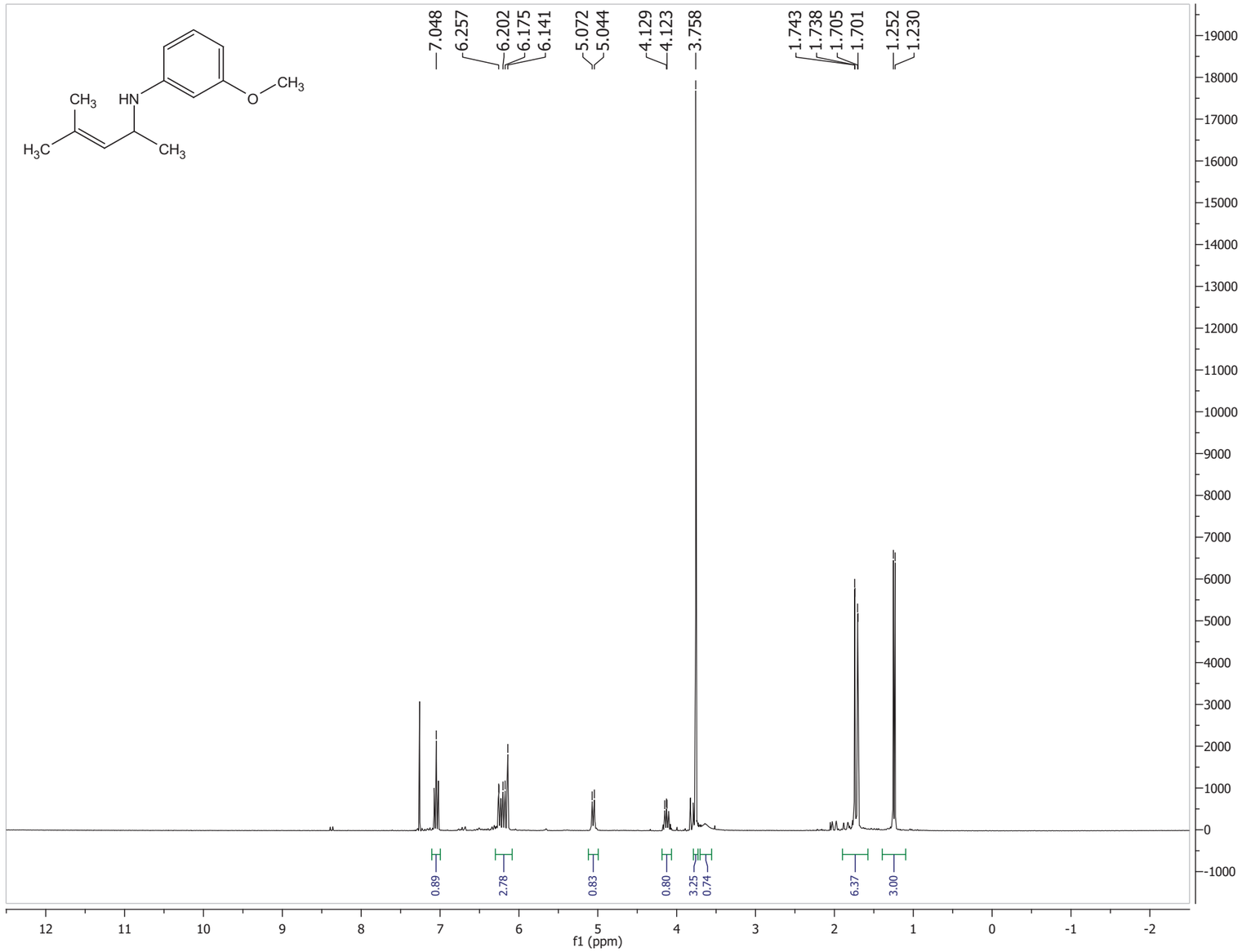

HN
CH3
147.994
137.355
129.501
128.669
126.654
117.527
113.663
57.484
29.432
10.844
f1 (ppm)

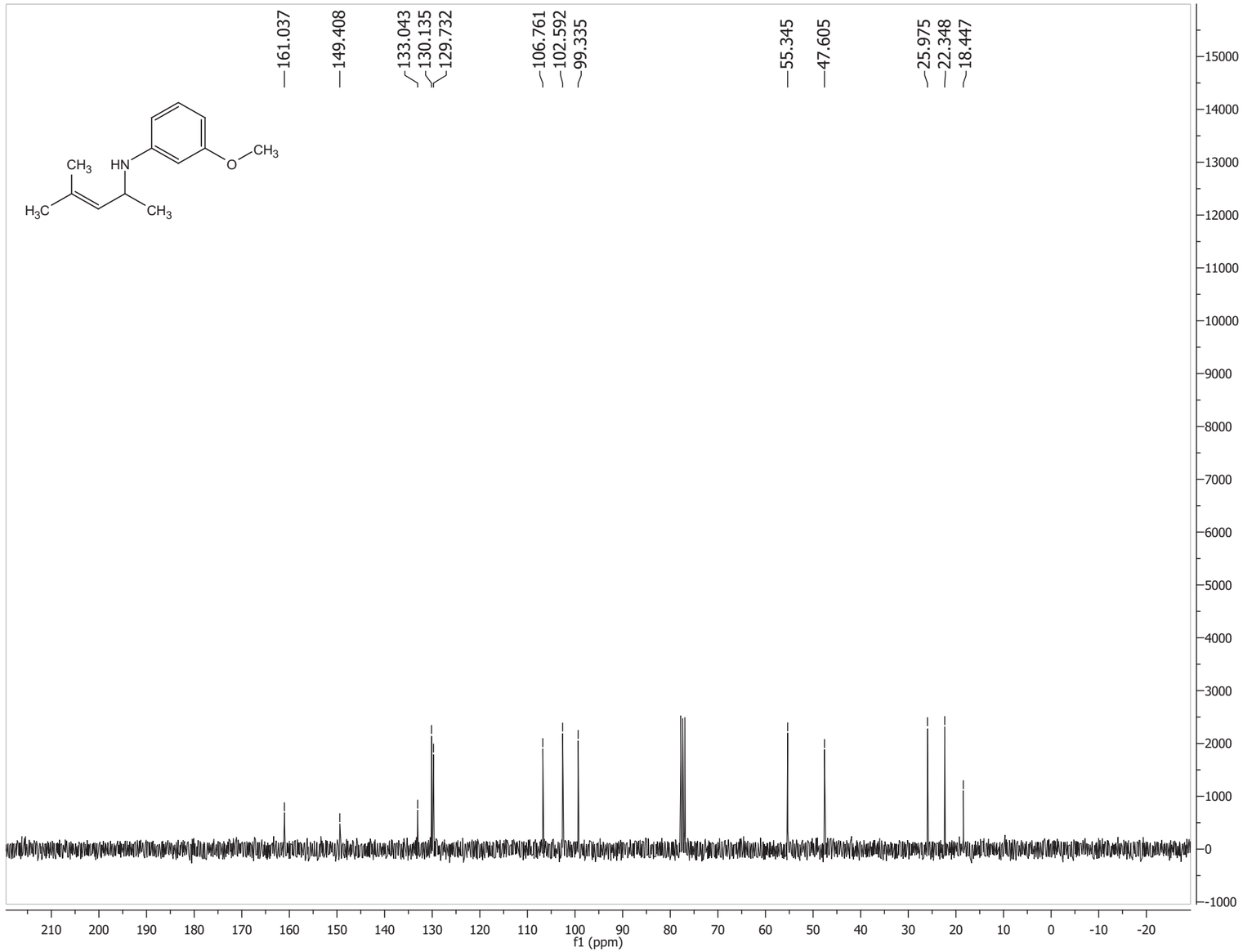

HN
CH3
O
CH3
7.260
7.168
7.164
6.857
6.501
6.119
6.099
6.066
6.046
3.803
1.413
1.391
1.89
1.87
1.92
2.79
0.86
0.86
0.94
3.06
0.66
3.00
f1 (ppm)

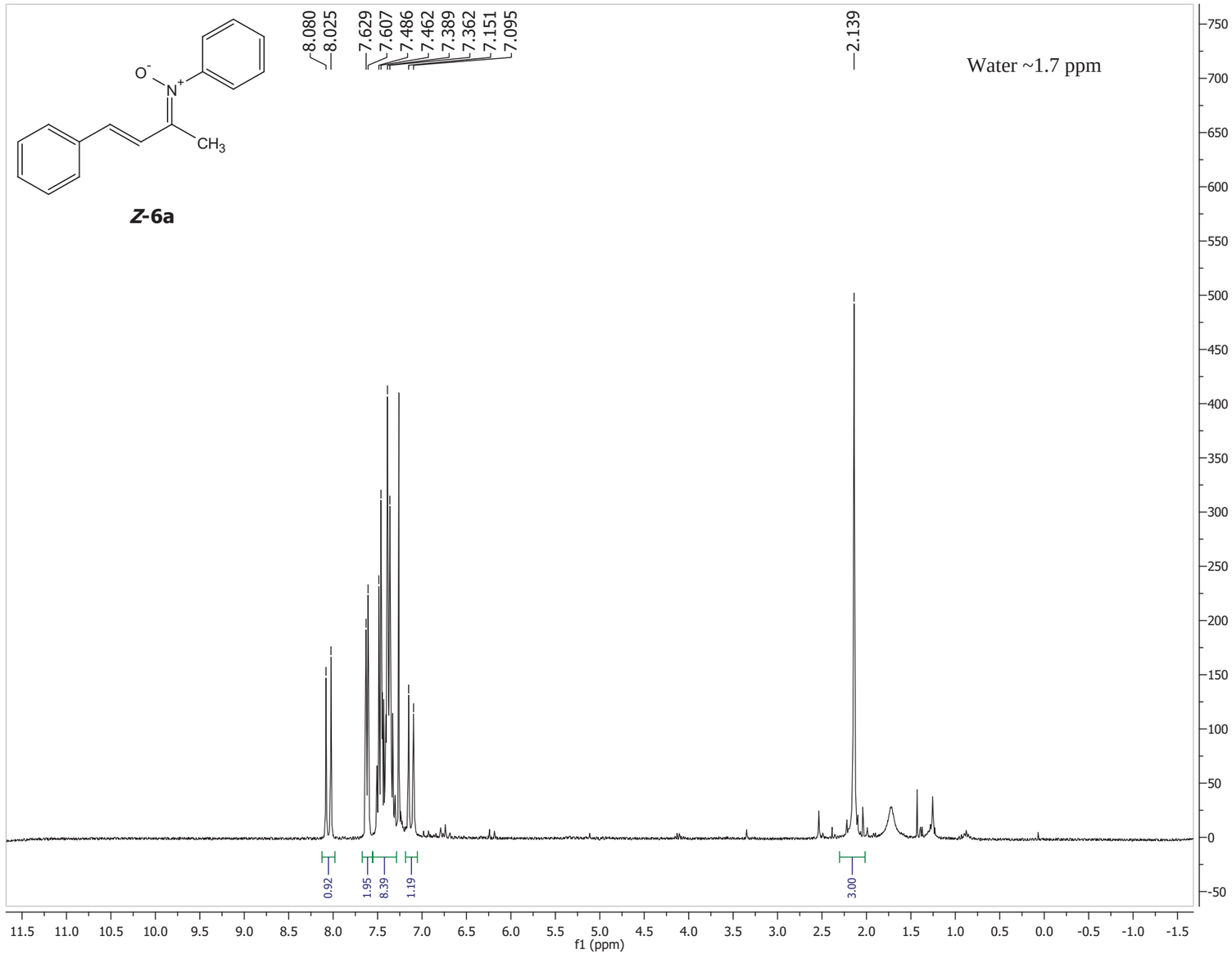

O
CH3
HN
CH3
159.357
147.799
129.510
129.007
127.780
117.587
114.255
113.722
55.631
51.198
22.501
f1 (ppm)

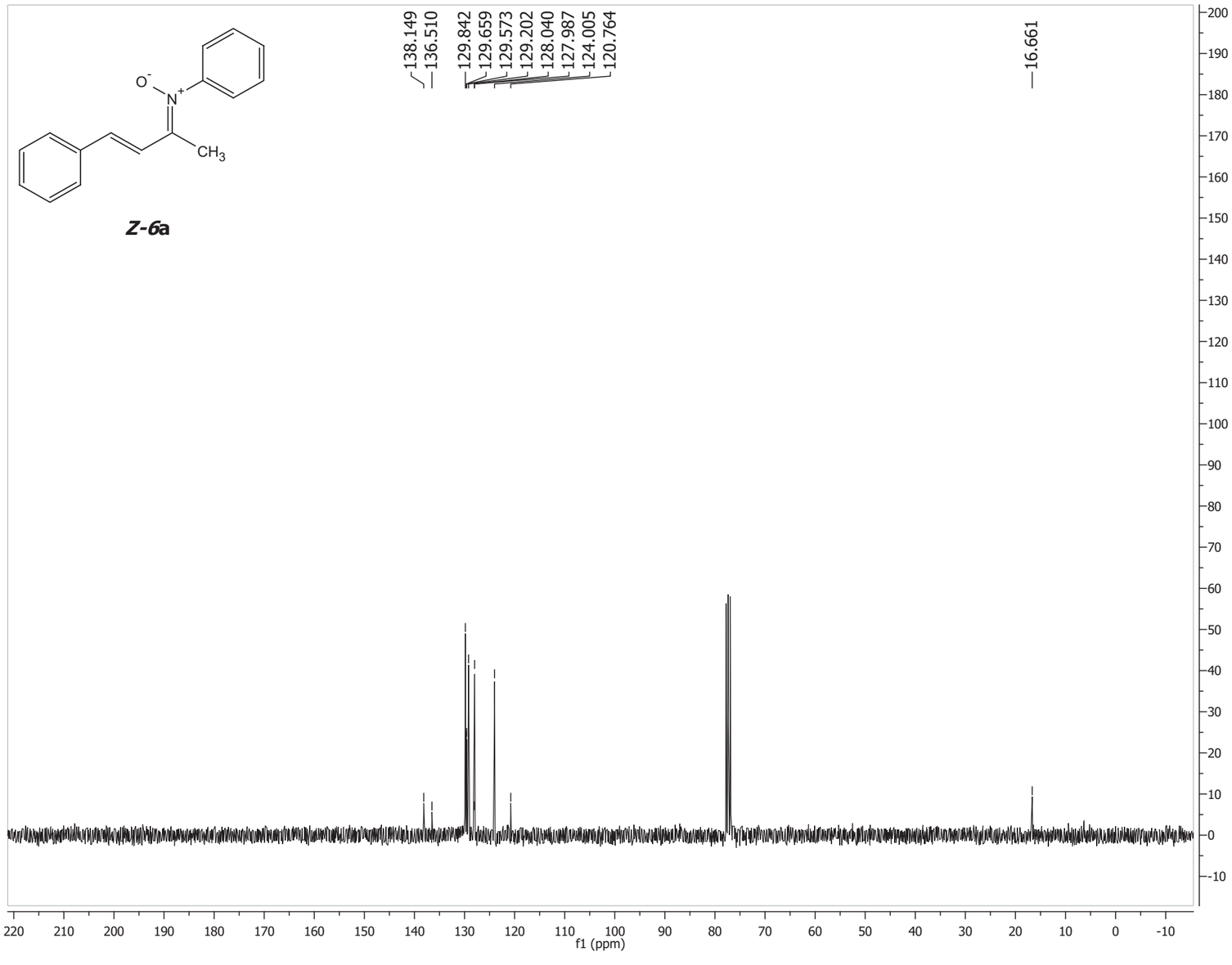

7.315
7.286
7.260
7.087
7.085
7.082
7.060
7.057
7.055
6.856
6.667
6.554
6.501
6.143
6.124
6.090
6.071
4.178
3.803
3.547
2.184
1.454
1.432
H3C
HN
CH3
O
CH3
1.98
1.91
1.95
1.89
0.91
0.87
0.74
3.00
0.73
3.06
3.21
f1 (ppm)


159.356
145.720
130.399
128.963
127.415
122.020
117.097
114.255
111.160
55.640
51.056
22.706
17.977
H3C
HN
CH3
O
CH3
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

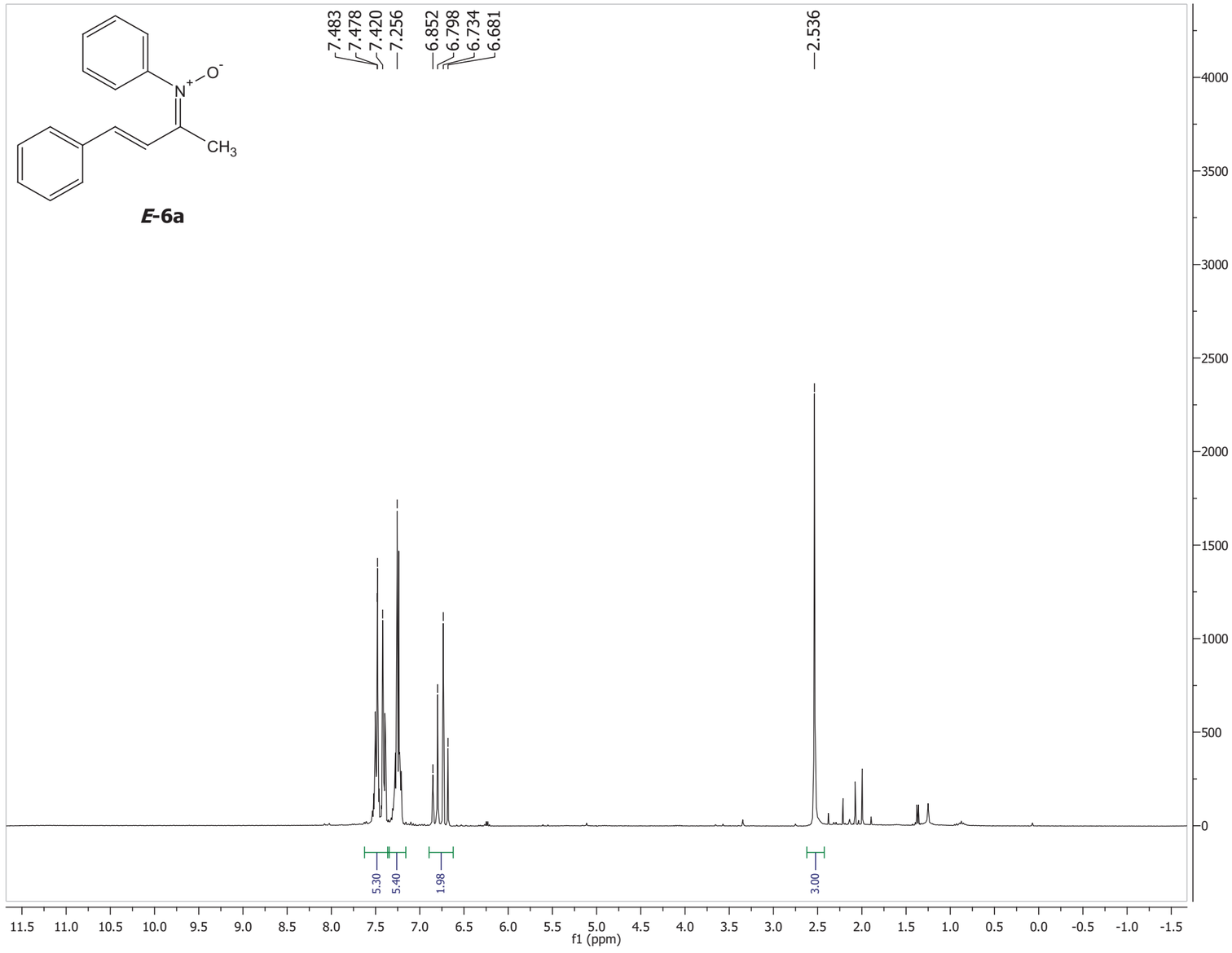

7.048
6.257
6.202
6.175
6.141
5.072
5.044
4.129
4.123
3.758
1.743
1.738
1.705
1.701
1.252
1.230
CH3
HN
O
CH3
H3C
CH3
0.89
2.78
0.83
0.80
3.25
0.74
6.37
3.00
f1 (ppm)

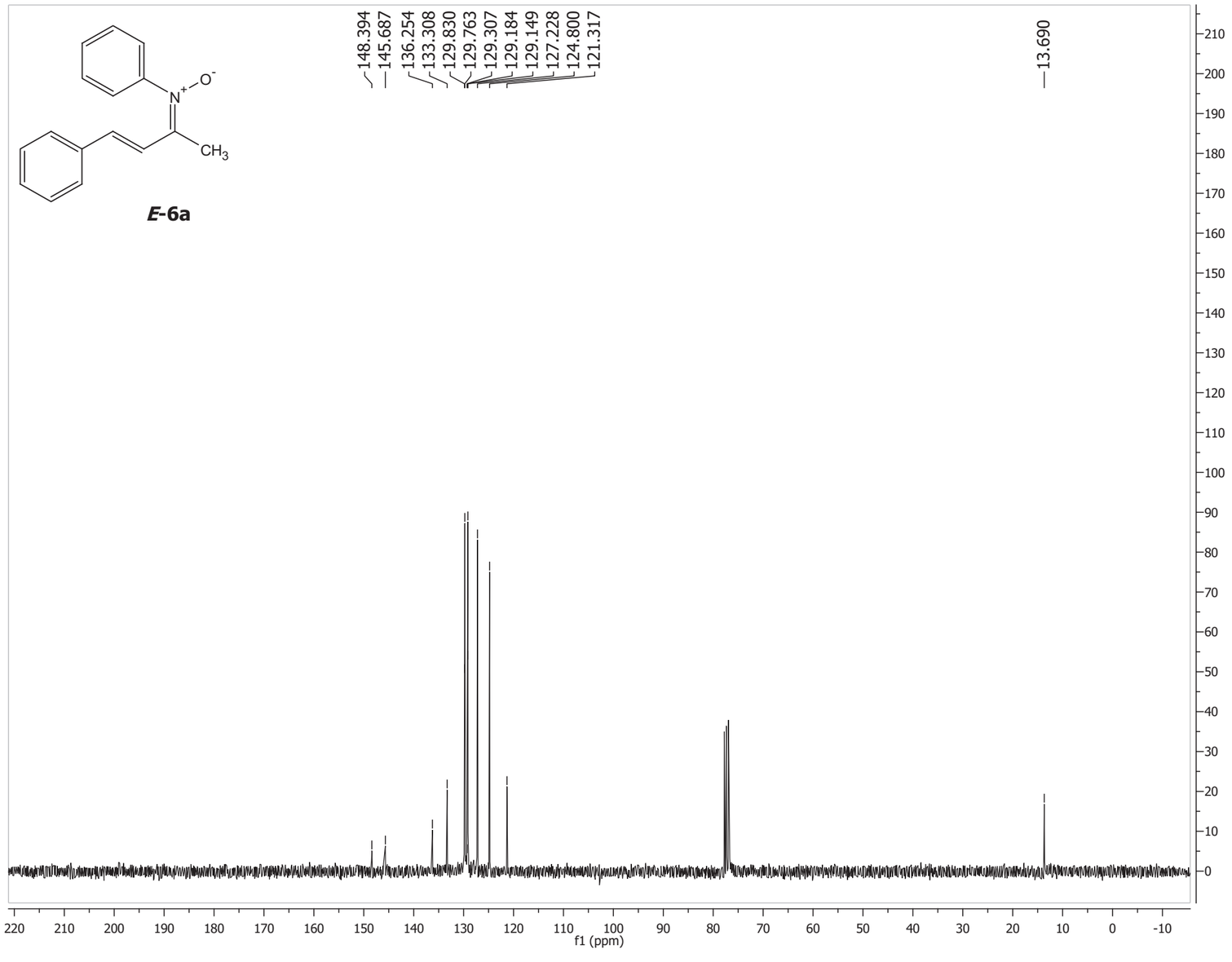

161.037
149.408
133.043
130.135
129.732
106.761
102.592
99.335
55.345
47.605
25.975
22.348
18.447
CH3
HN
O
CH3
H3C
CH3
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


8.080
8.025
7.629
7.607
7.486
7.462
7.389
7.362
7.151
7.095
2.139
Water ~1.7 ppm
O
N
CH3
Z-6a
0.92
1.95
8.39
1.19
3.00
f1 (ppm)

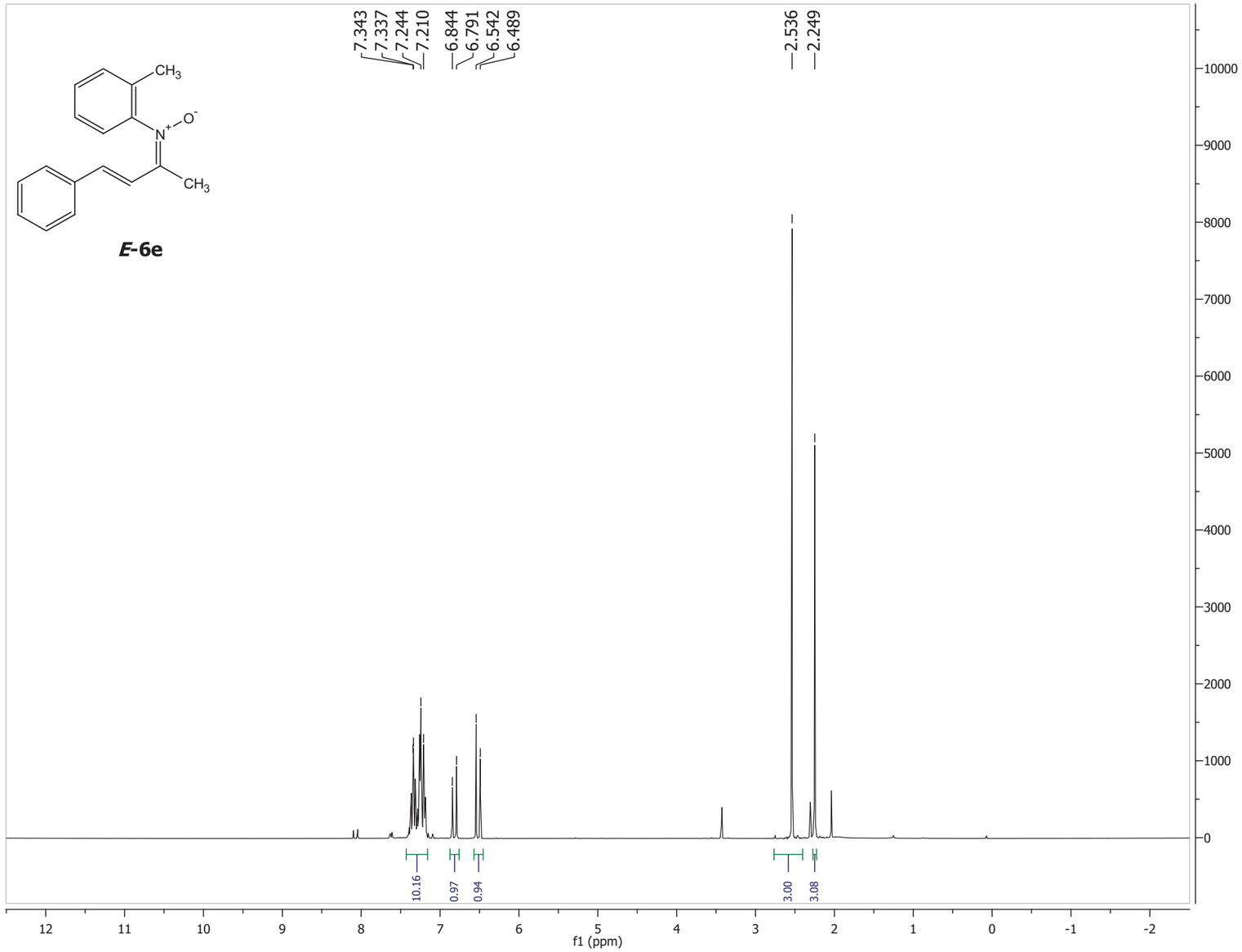

138.149
136.510
129.842
129.659
129.573
129.202
128.040
127.987
124.005
120.764
16.661
O
N
CH3
f1 (ppm)

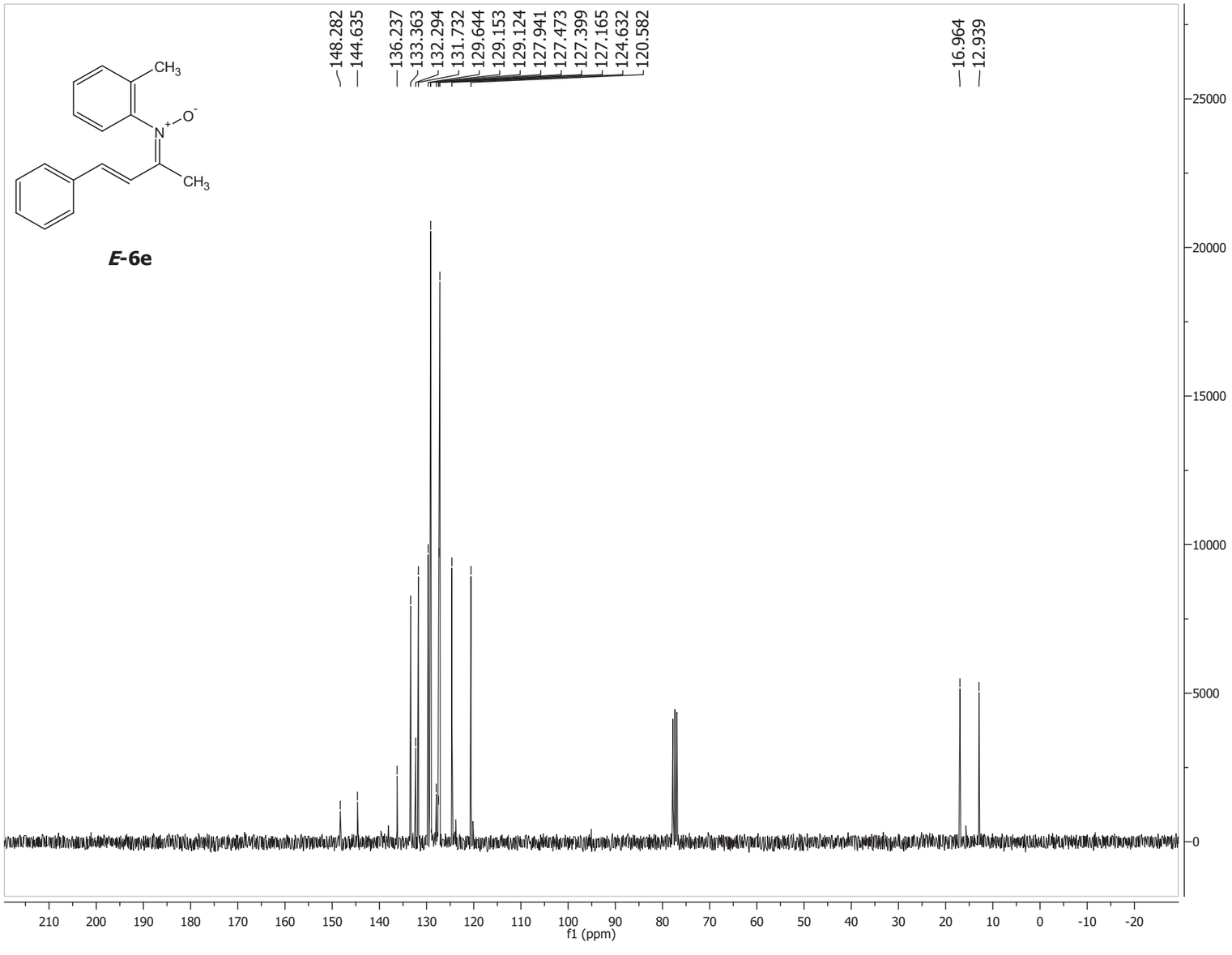
Z-6a


7.483
7.478
7.420
7.256
6.852
6.798
6.734
6.681
2.536
N+
O-
CH3
E-6a
5.30
5.40
1.98
3.00
f1 (ppm)

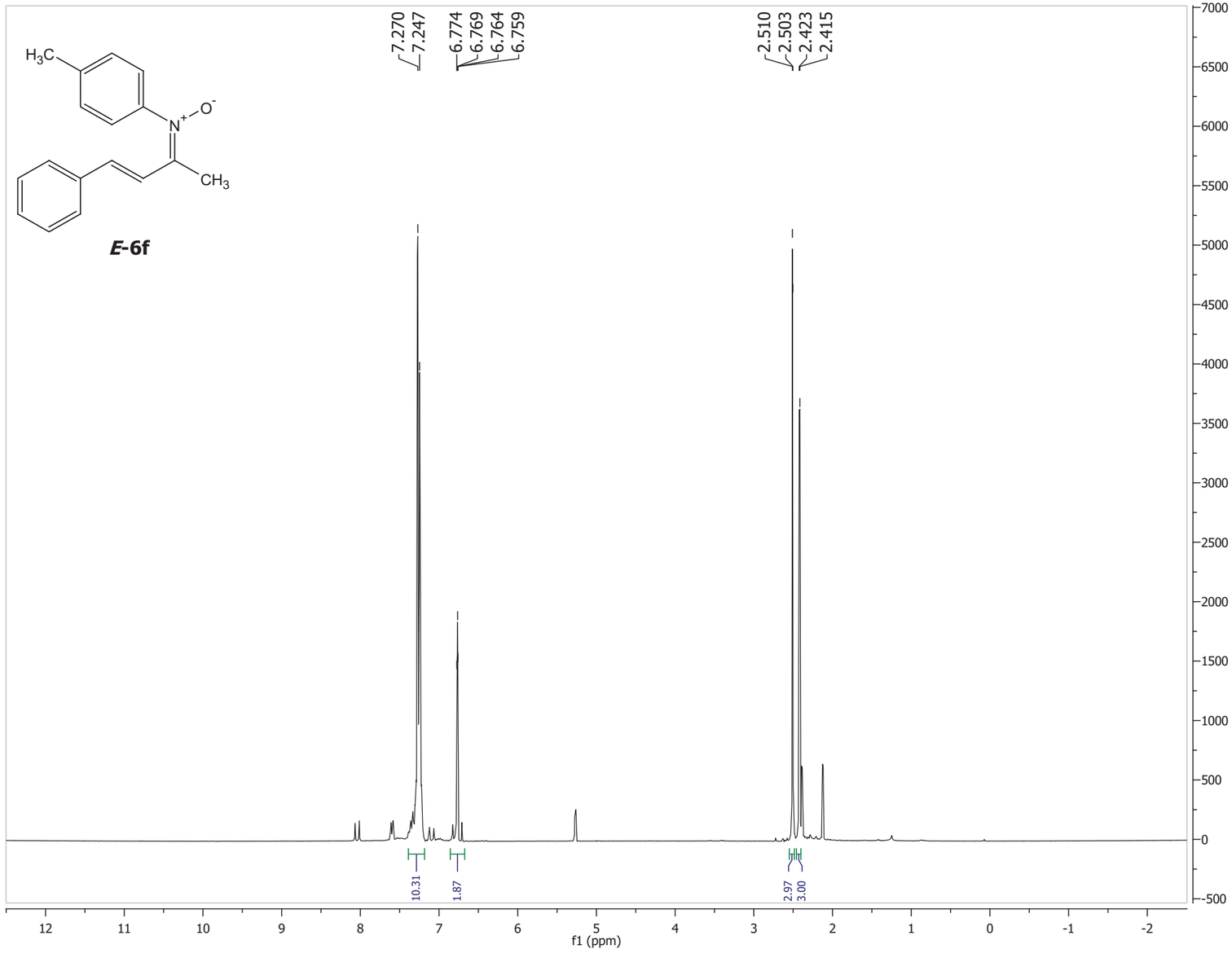

148.394
145.687
136.254
133.308
129.830
129.763
129.307
129.184
129.149
127.228
124.800
121.317
13.690
N+
O-
CH3
f1 (ppm)

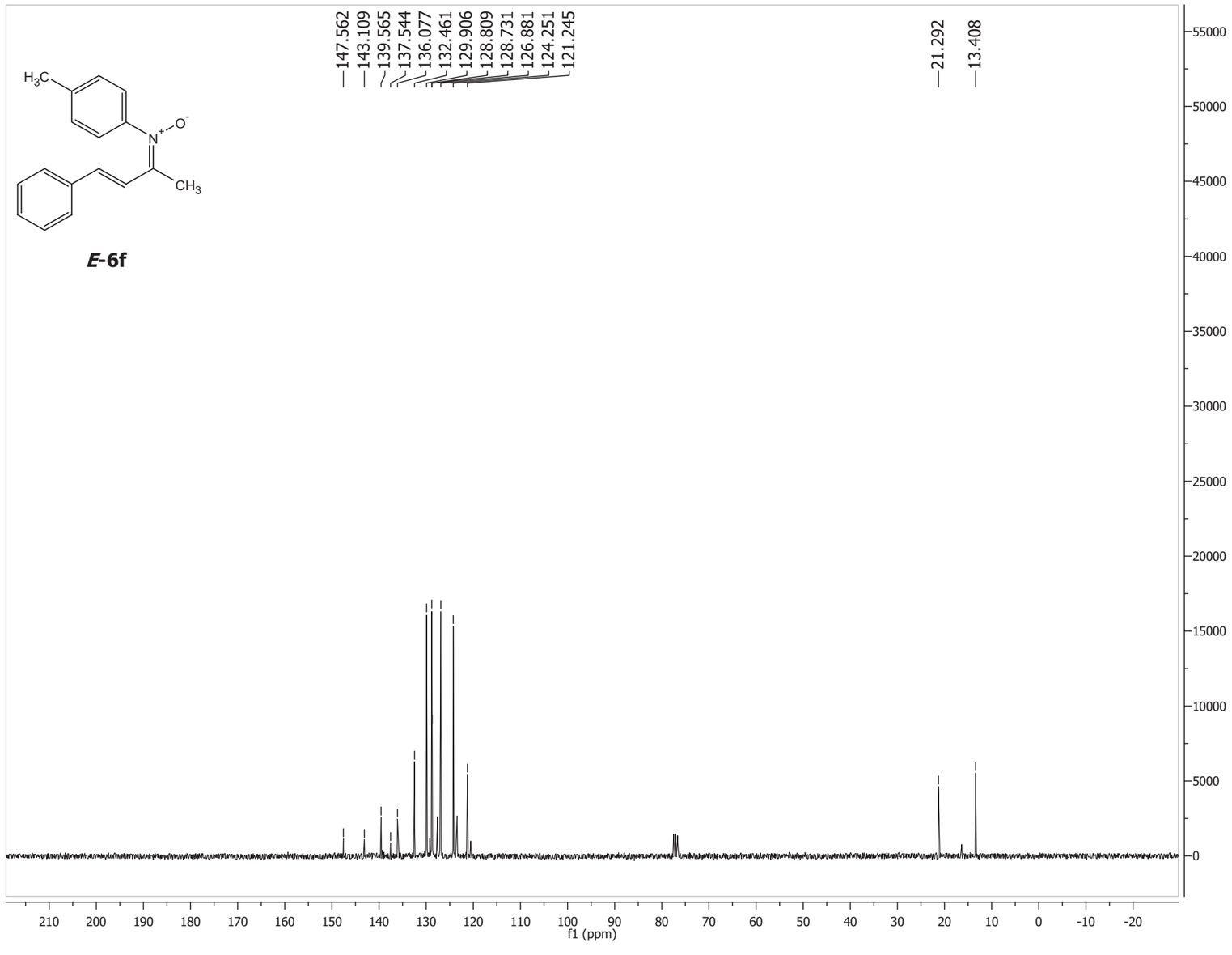
***E*-6a**


7.343
7.337
7.244
7.210
6.844
6.791
6.542
6.489
2.536
2.249
CH3
N+
O-
CH3
E-6e
10.16
0.97
0.94
3.00
3.08
f1 (ppm)

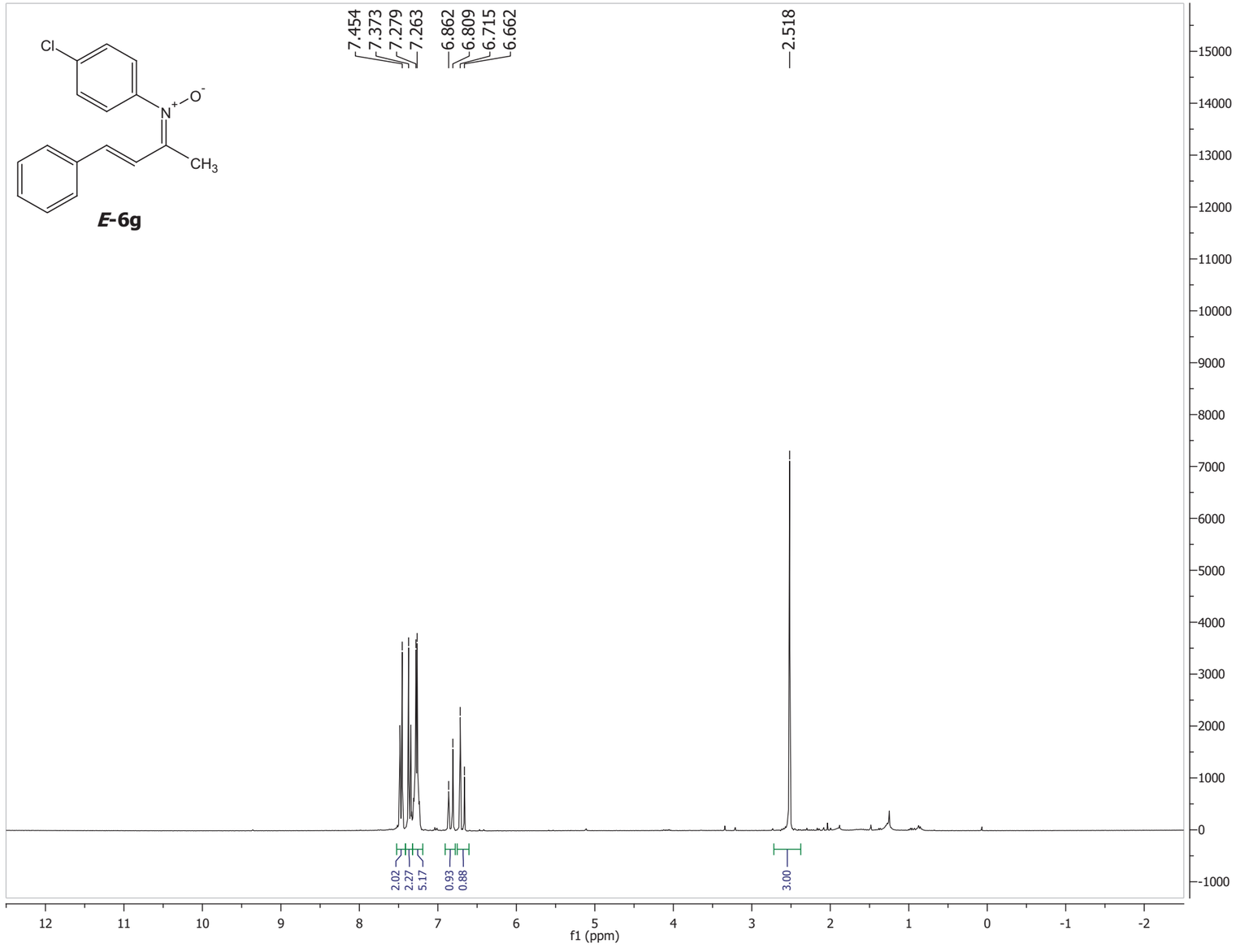

148.282
144.635
136.237
133.363
132.294
131.732
129.644
129.153
129.124
127.941
127.473
127.399
127.165
124.632
120.582
16.964
12.939
CH3
N+
O-
CH3
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

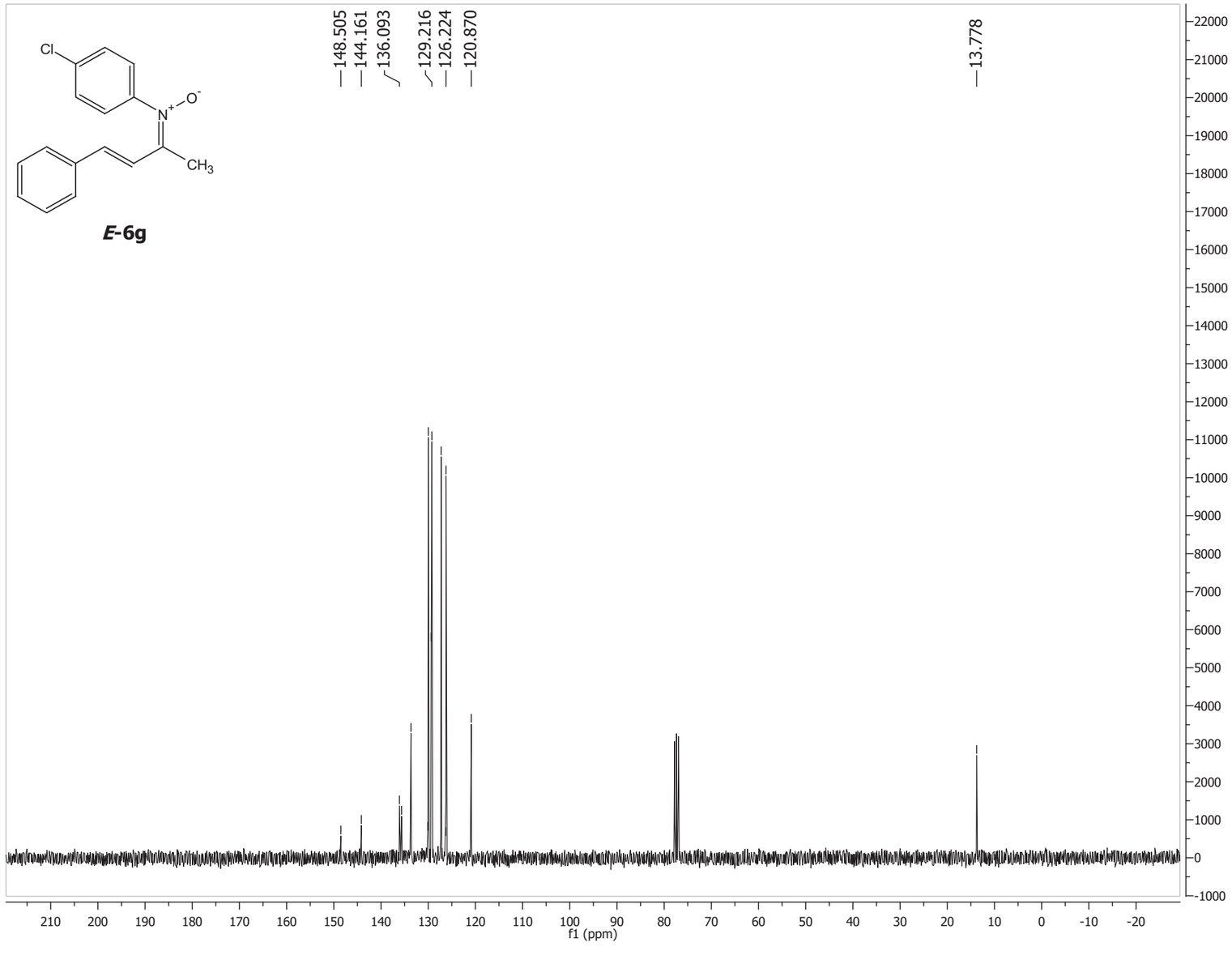
***E*-6e**

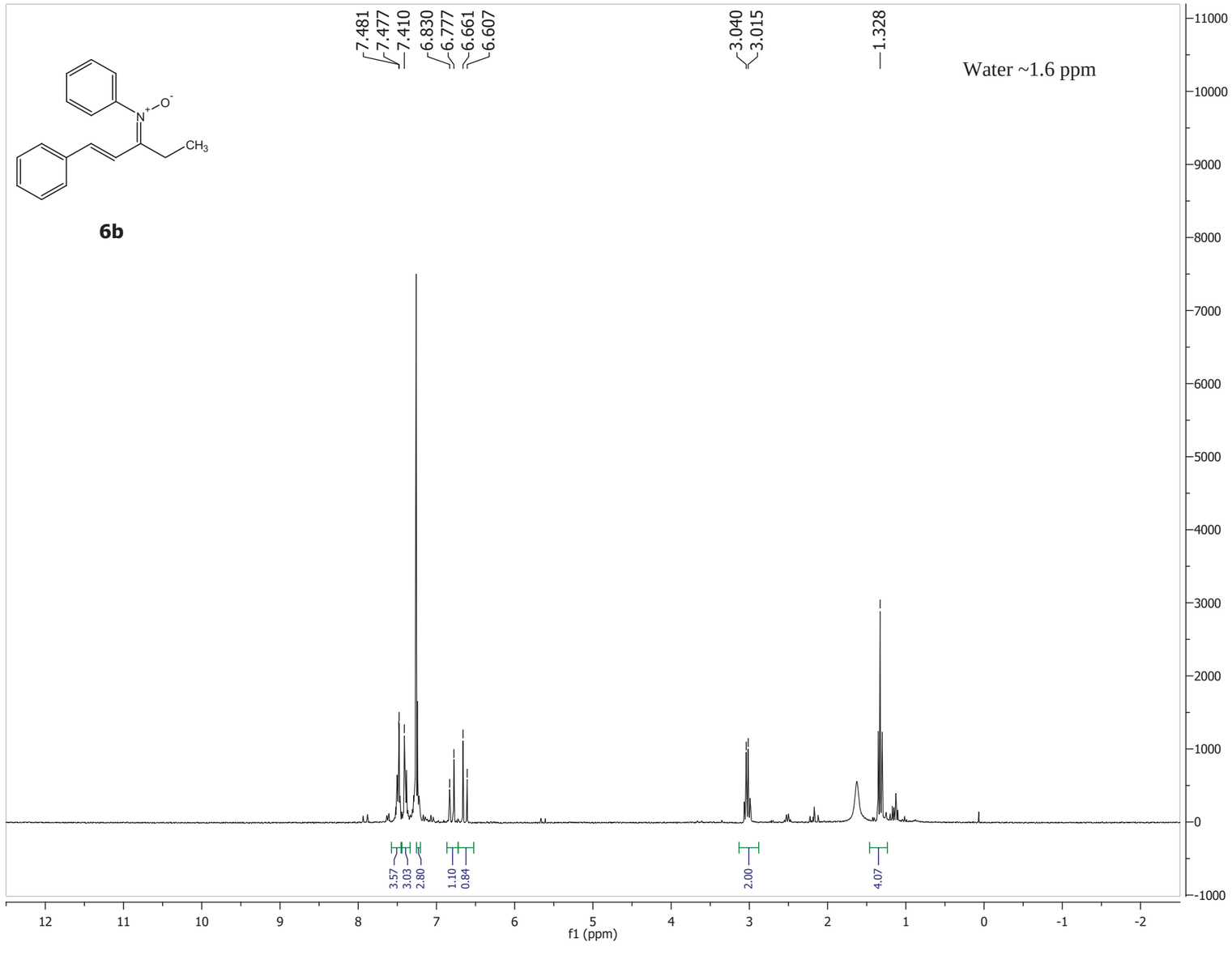

H3C
N+
O-
CH3
E-6f
7.270
7.247
6.774
6.769
6.764
6.759
2.510
2.503
2.423
2.415
10.31
1.87
2.97
3.00
f1 (ppm)

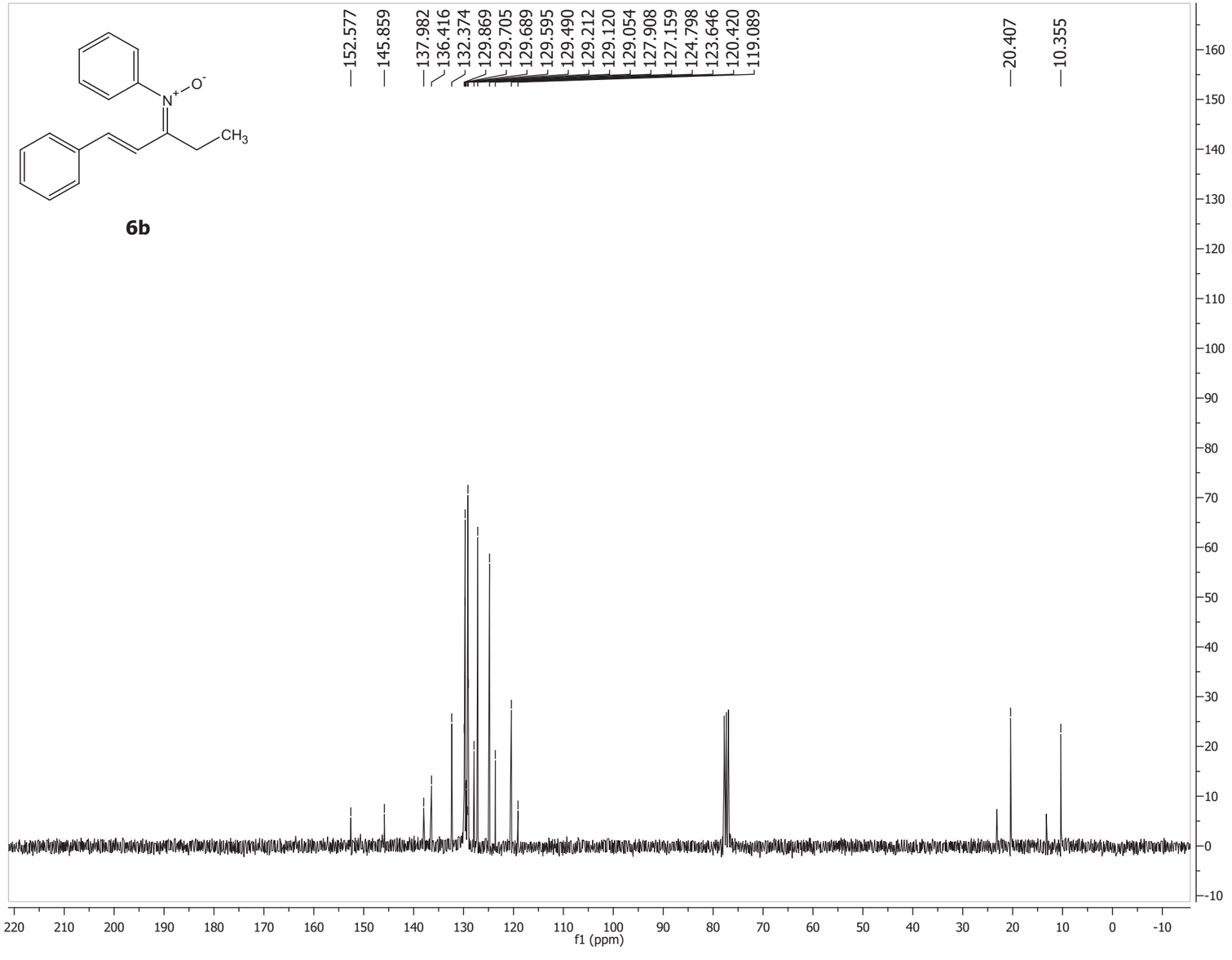

147.562
143.109
139.565
137.544
136.077
132.461
129.906
128.809
128.731
126.881
124.251
121.245
21.292
13.408
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

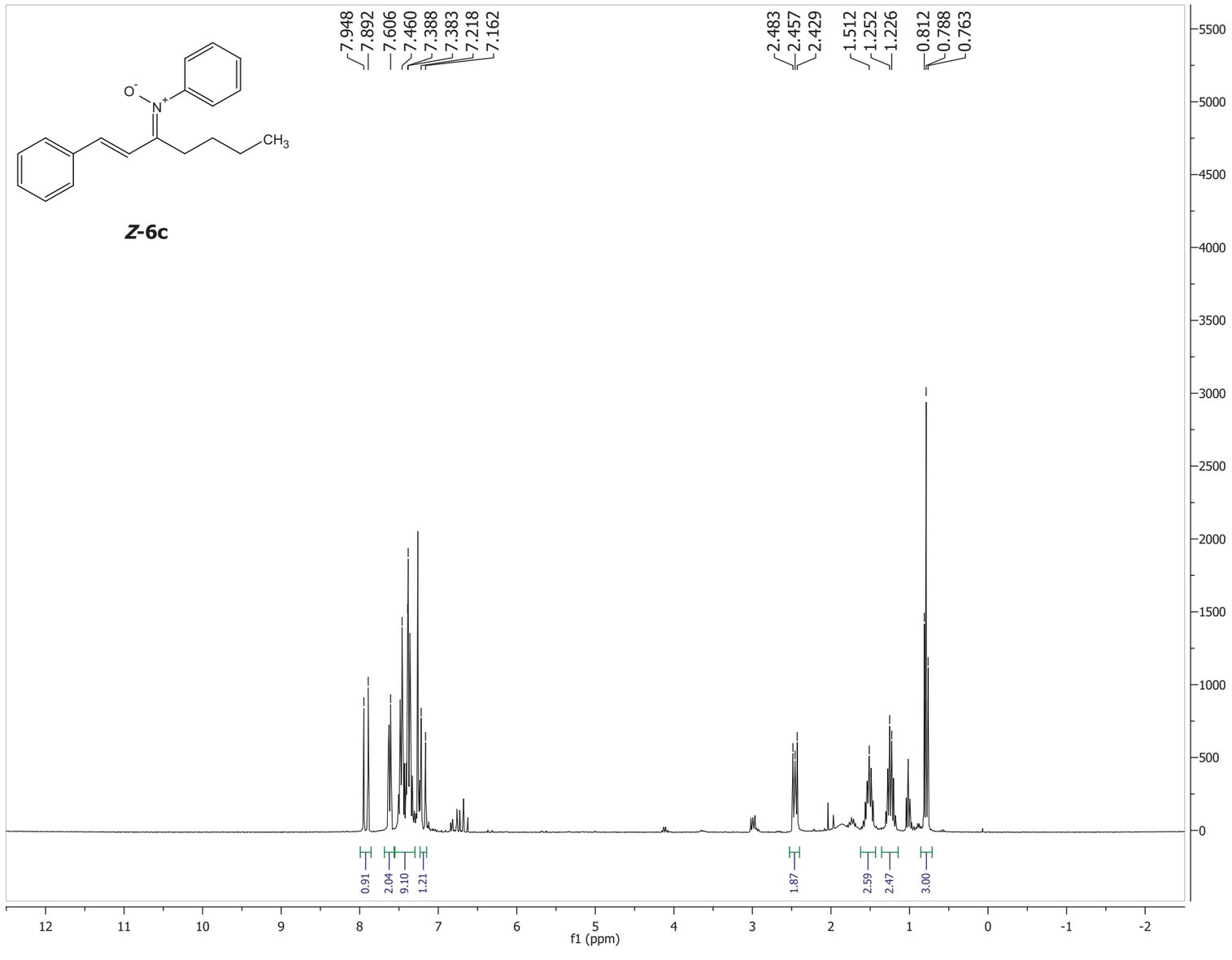
***E*-6f**


Cl
N+
O-
CH3
E-6g
7.454
7.373
7.279
7.263
6.862
6.809
6.715
6.662
2.518
2.02
2.27
5.17
0.93
0.88
3.00
f1 (ppm)

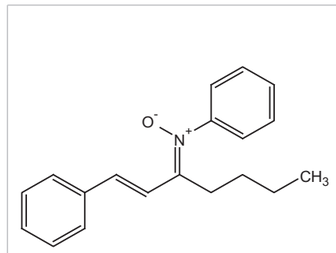

148.505
144.161
136.093
129.216
126.224
120.870
13.778
Cl
N+
O-
CH3
E-6g
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


7.481
7.477
7.410
6.830
6.777
6.661
6.607
3.040
3.015
1.328
Water ~1.6 ppm
6b
3.57
3.03
2.80
1.10
0.84
2.00
4.07
f1 (ppm)


152.577
145.859
137.982
136.416
132.374
129.869
129.705
129.689
129.595
129.490
129.212
129.120
129.054
127.908
127.159
124.798
123.646
120.420
119.089
20.407
10.355
N+
O-
CH3
6b
f1 (ppm)

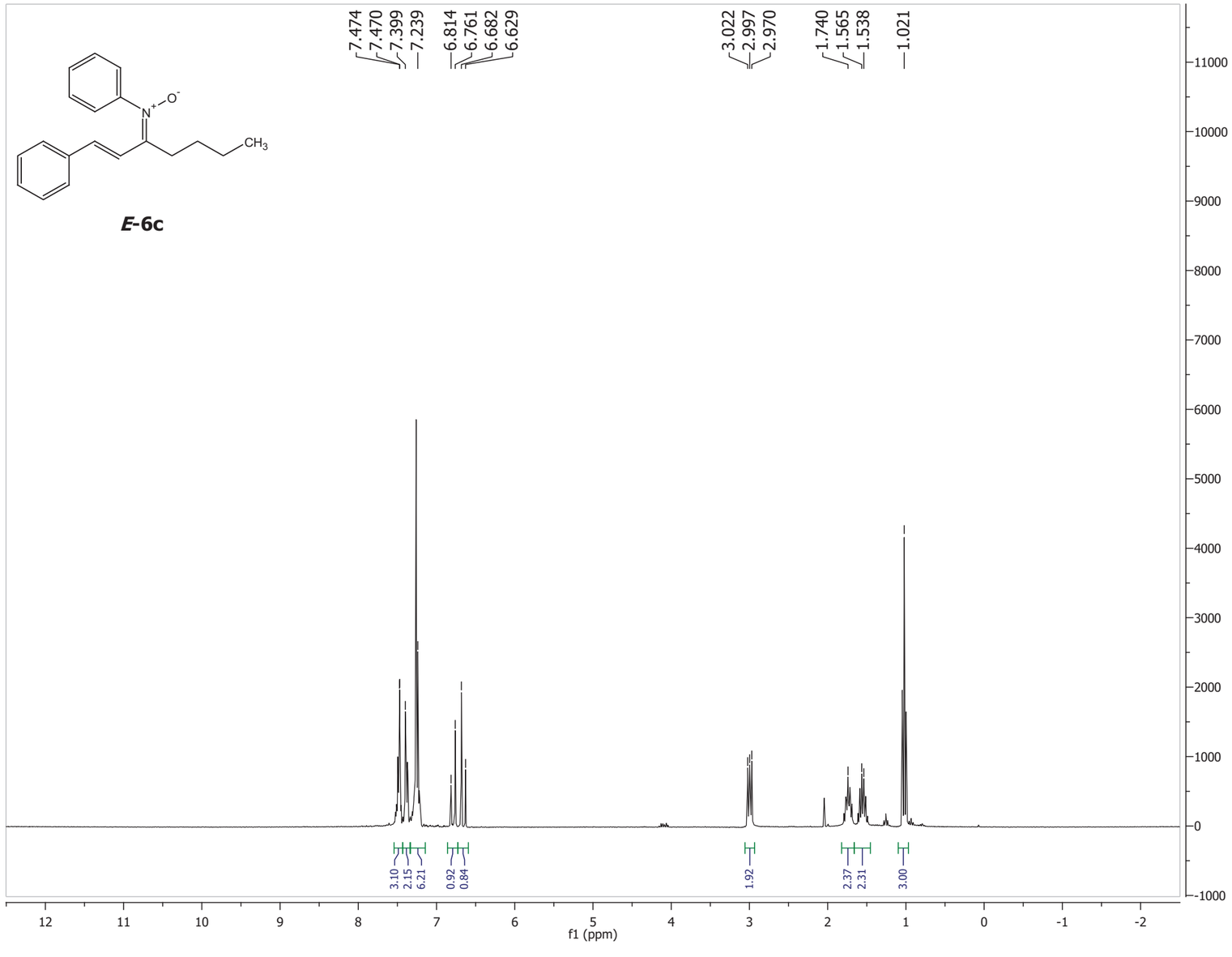

7.948
7.892
7.606
7.460
7.388
7.383
7.218
7.162
2.483
2.457
2.429
1.512
1.252
1.226
0.812
0.788
0.763
O
N
CH3
0.91
2.04
9.10
1.21
1.87
2.59
2.47
3.00
f1 (ppm)

***Z*-6c**

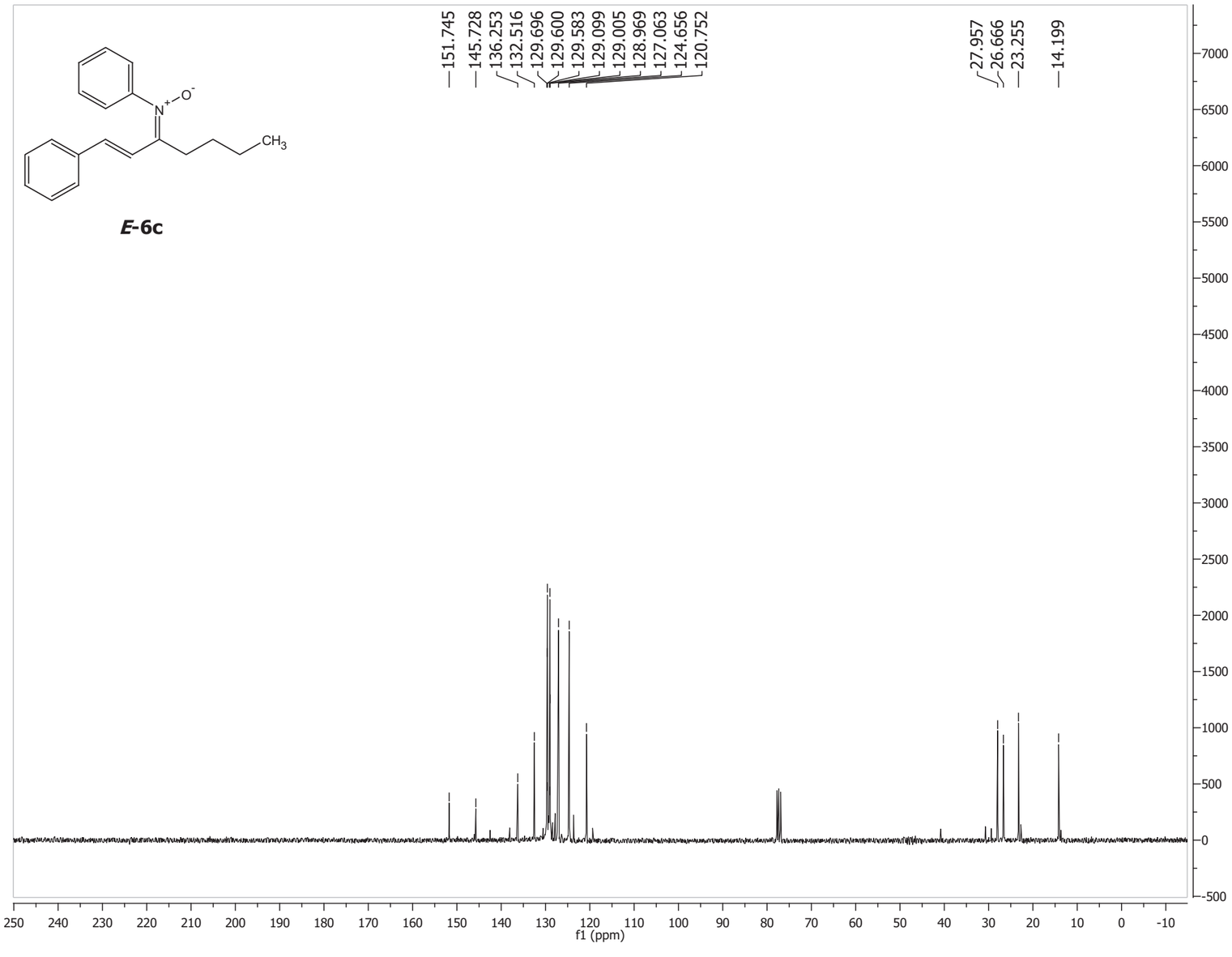

O
N
CH3

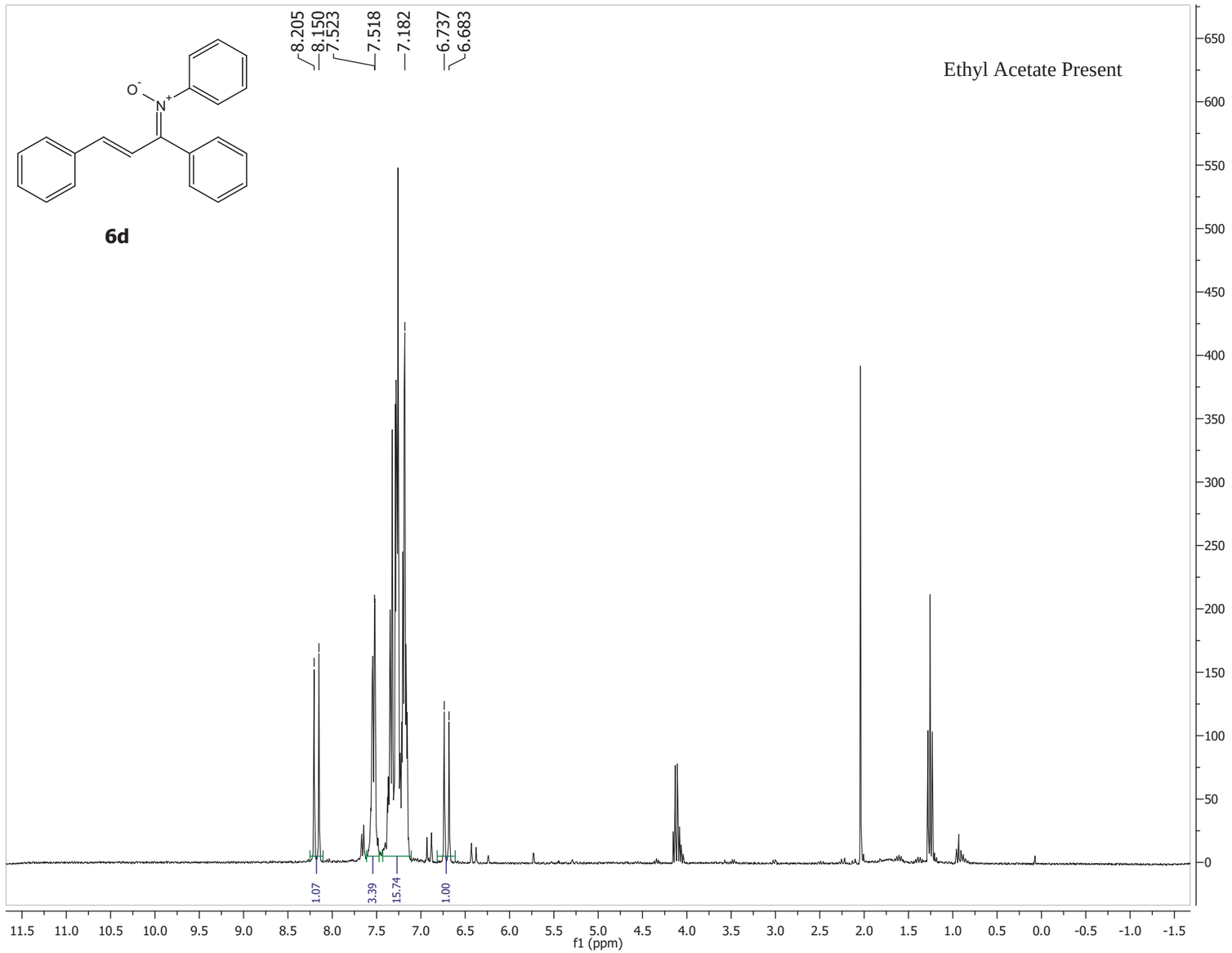
***Z*-6c**

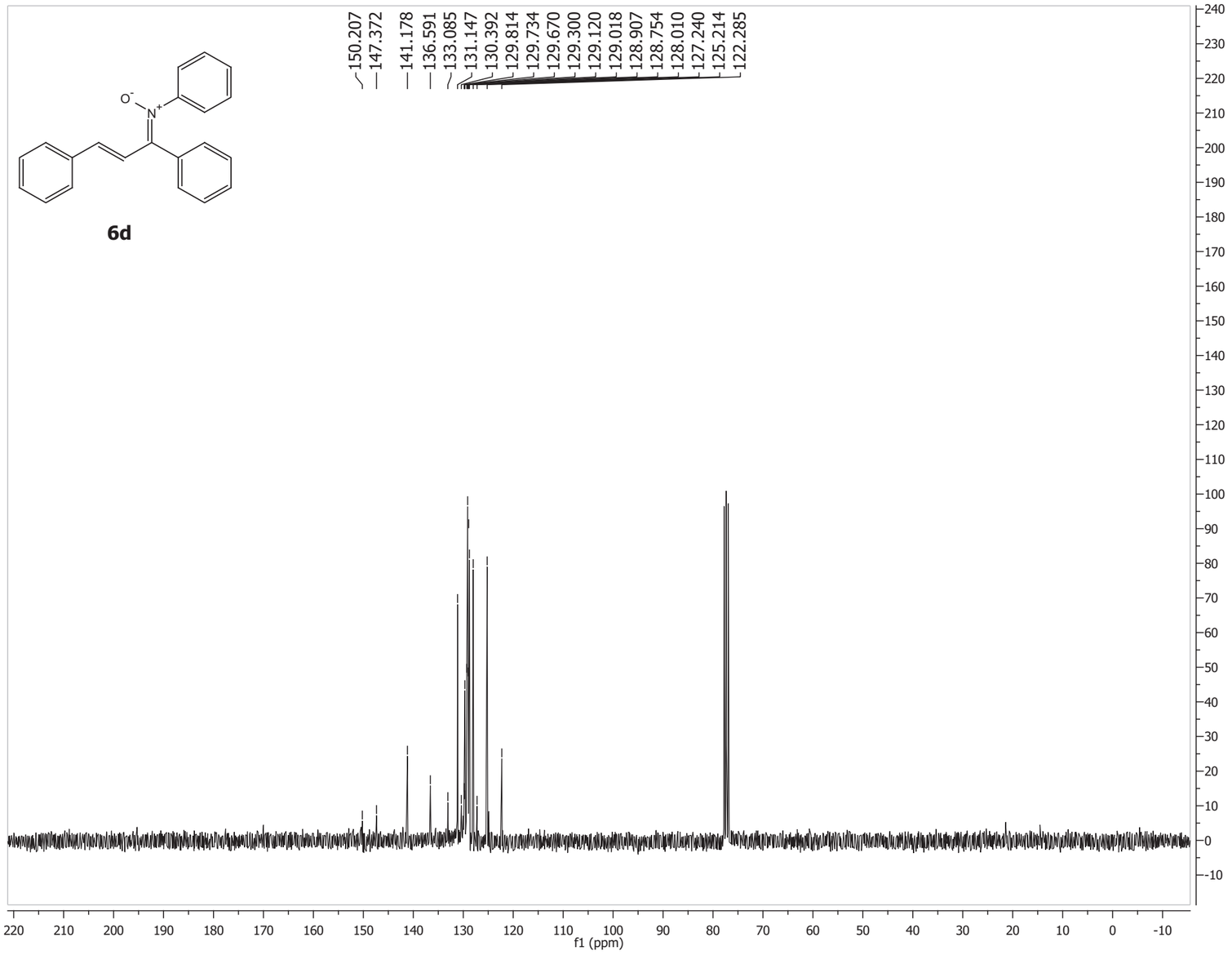
149.799
146.273
136.552
129.834
129.712
129.631
129.500
129.162
129.069
127.947
127.186
124.810
123.812
119.561
30.876
29.566
22.866
13.830
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

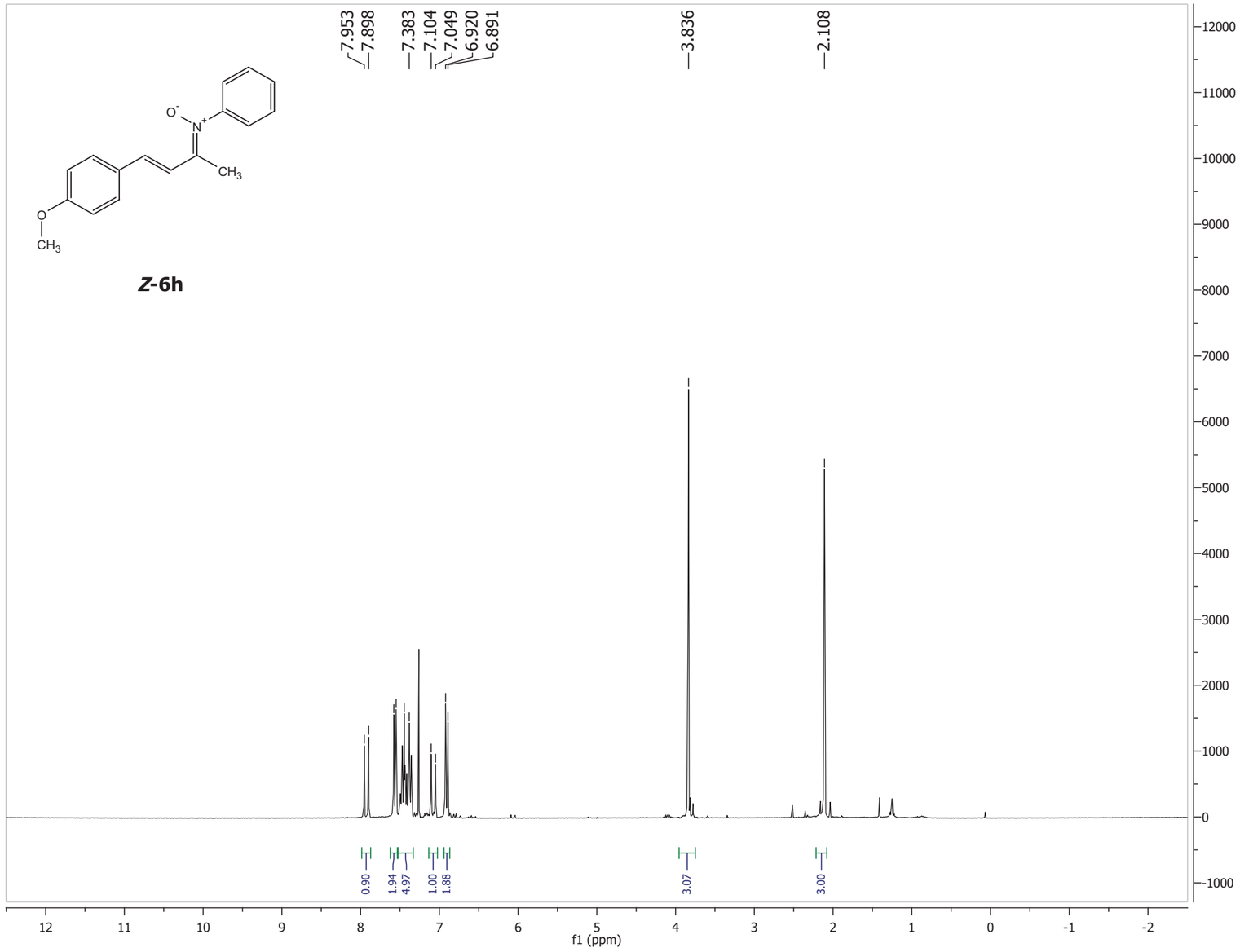

7.474
7.470
7.399
7.239
6.814
6.761
6.682
6.629
3.022
2.997
2.970
1.740
1.565
1.538
1.021
CH3
3.10
2.15
6.21
0.92
0.84
1.92
2.37
2.31
3.00
f1 (ppm)

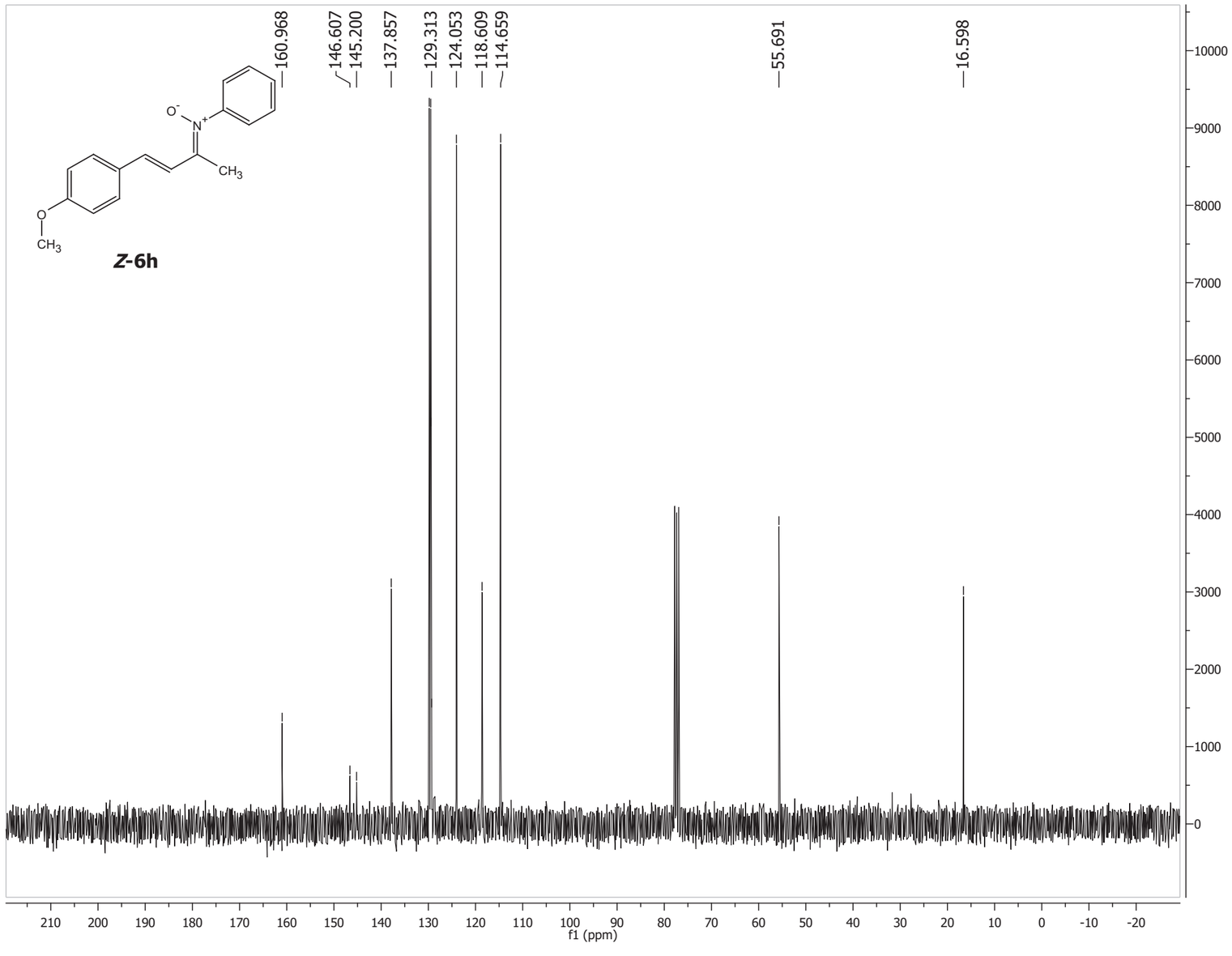
***E*-6c**

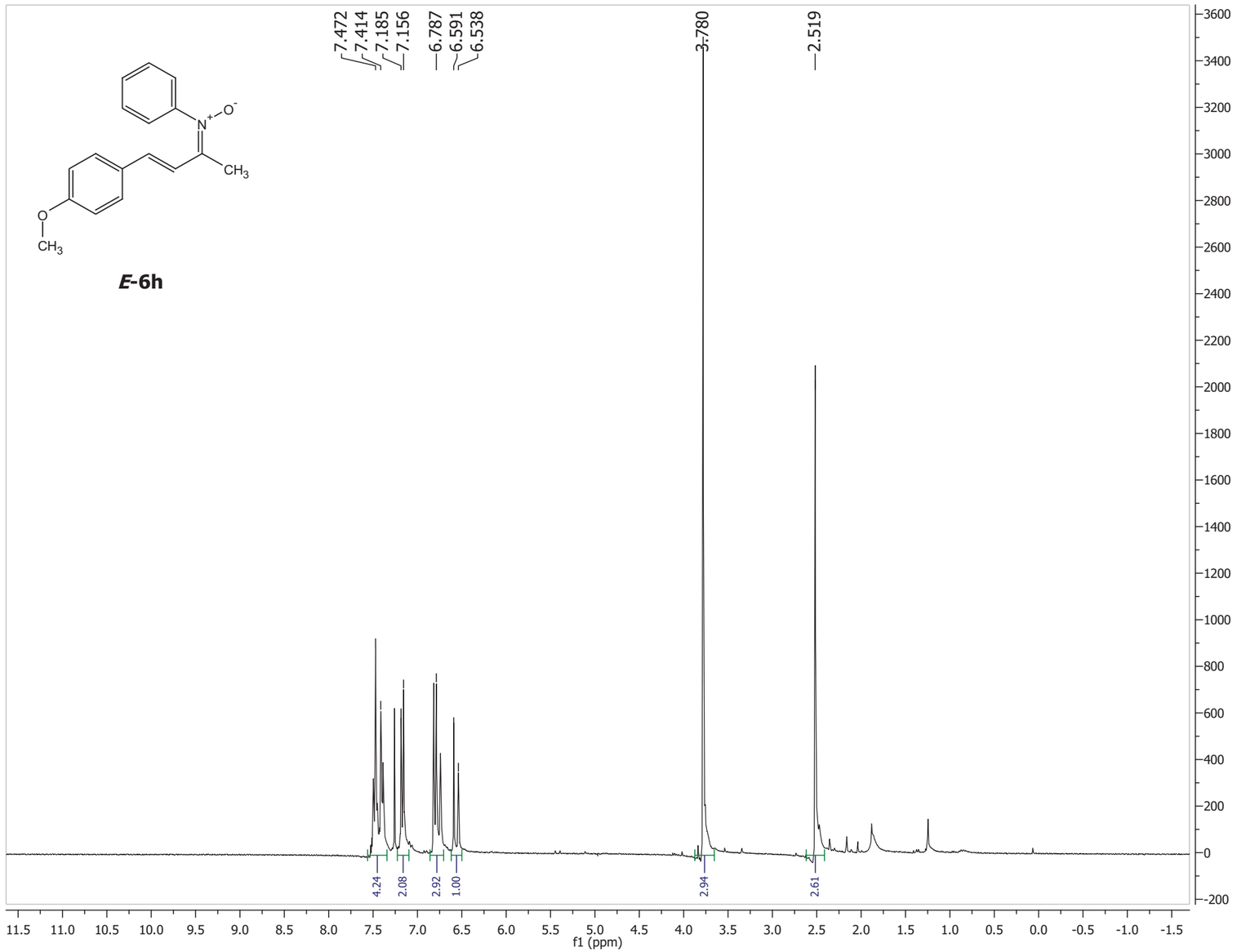

151.745
145.728
136.253
132.516
129.696
129.600
129.583
129.099
129.005
128.969
127.063
124.656
120.752
27.957
26.666
23.255
14.199
N+
O-
CH3
E-6c
f1 (ppm)


6d
8.205
8.150
7.523
7.518
7.182
6.737
6.683
Ethyl Acetate Present
1.07
3.39
15.74
1.00
f1 (ppm)

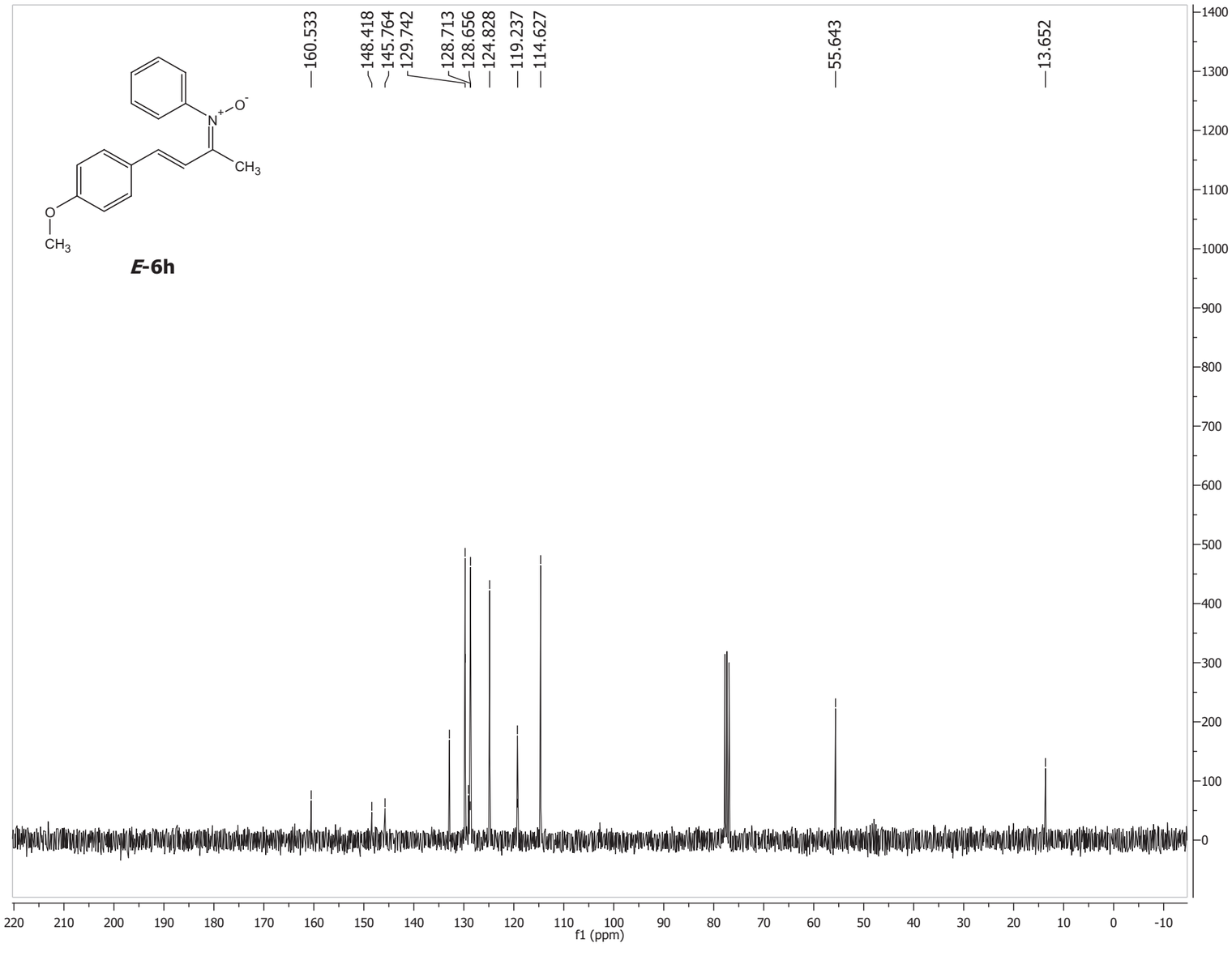

150.207
147.372
141.178
136.591
133.085
131.147
130.392
129.814
129.734
129.670
129.300
129.120
129.018
128.907
128.754
128.010
127.240
125.214
122.285
O
N
6d
f1 (ppm)

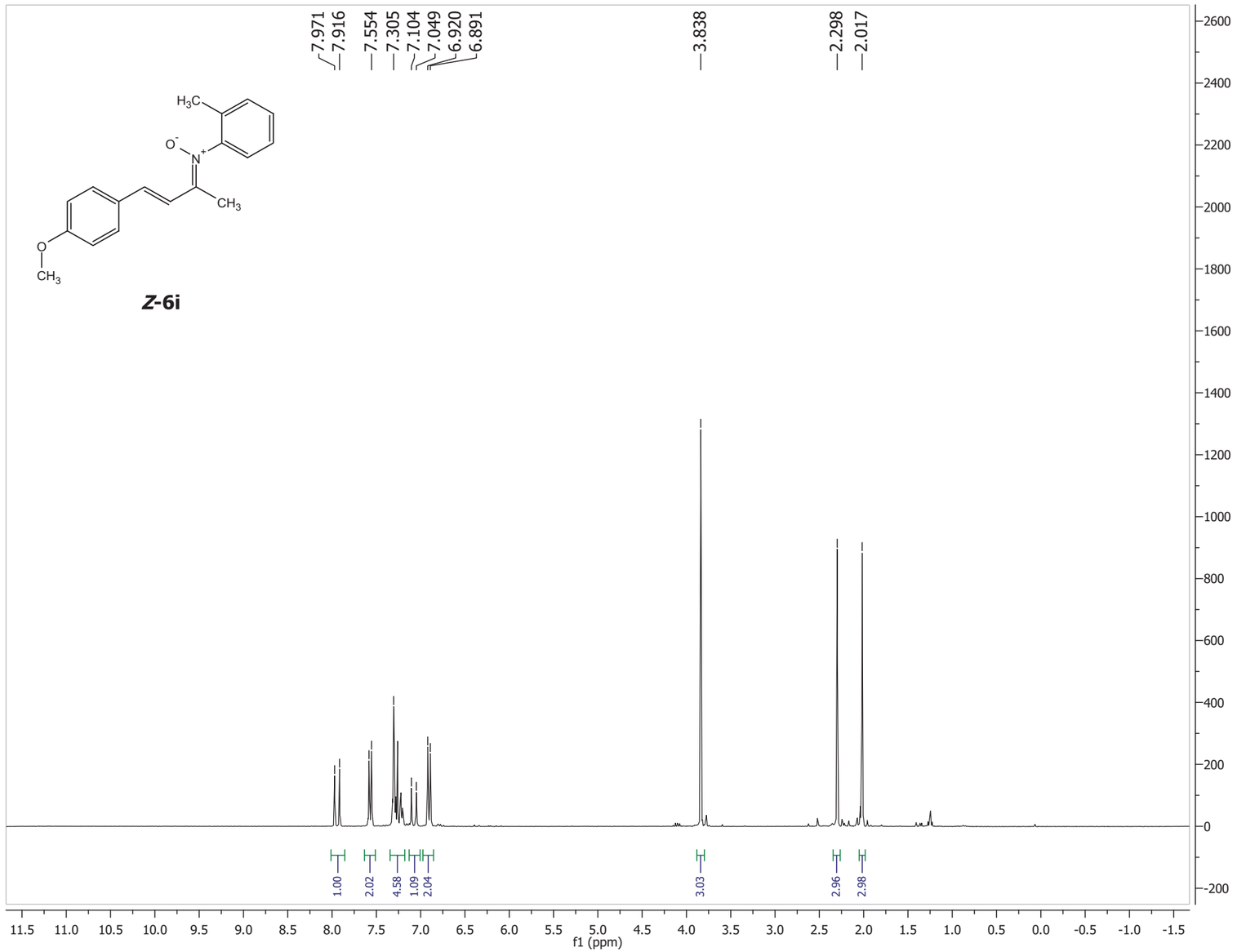

7.953
7.898
7.383
7.104
7.049
6.920
6.891
3.836
2.108
O
N
CH3
O
CH3
Z-6h
0.90
1.94
4.97
1.00
1.88
3.07
3.00
f1 (ppm)

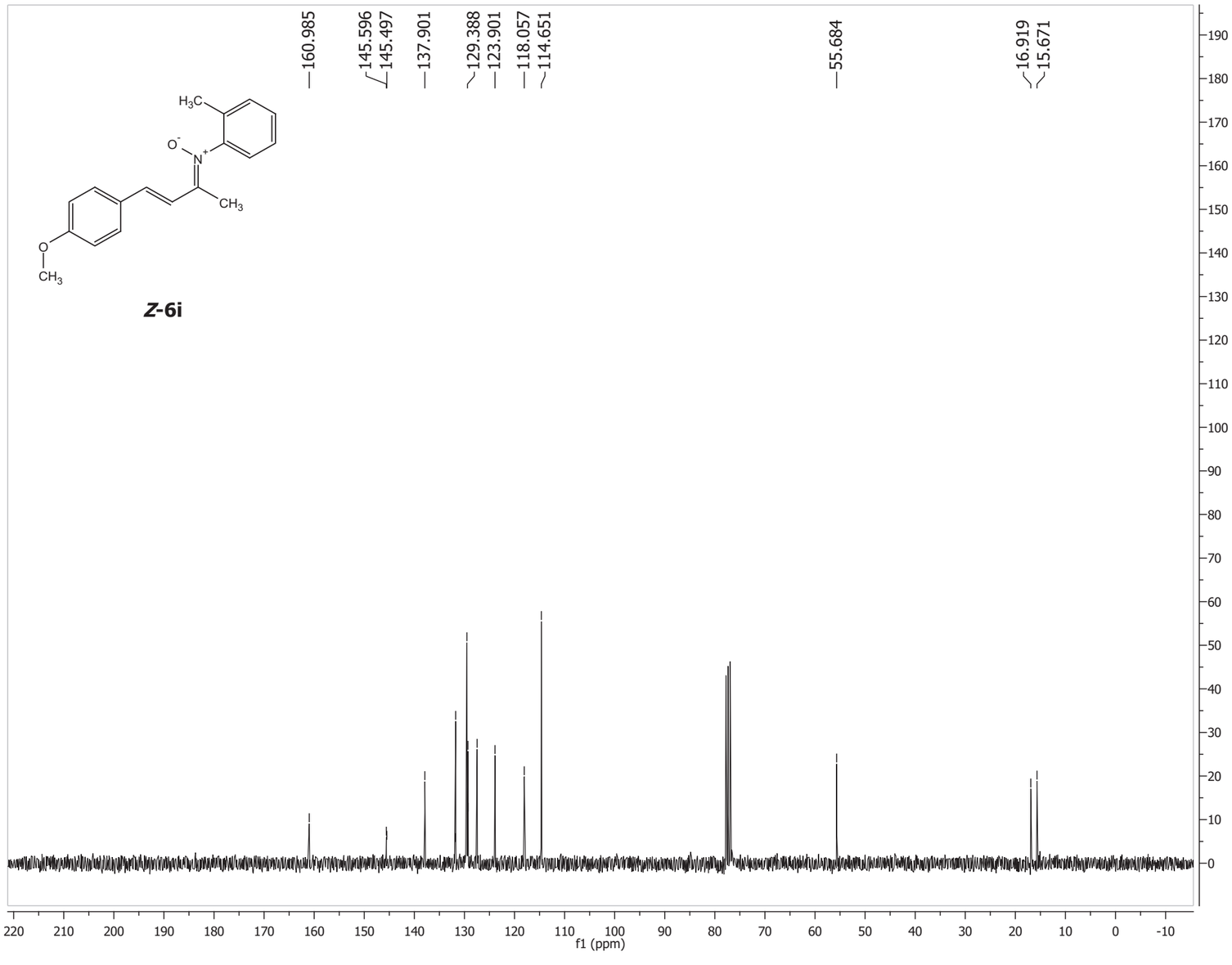

160.968
146.607
145.200
137.857
129.313
124.053
118.609
114.659
55.691
16.598
O
N
CH3
O
CH3
Z-6h
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


7.472
7.414
7.185
7.156
6.787
6.591
6.538
3.780
2.519
4.24
2.08
2.92
1.00
2.94
2.61
f1 (ppm)

***E*-6h**

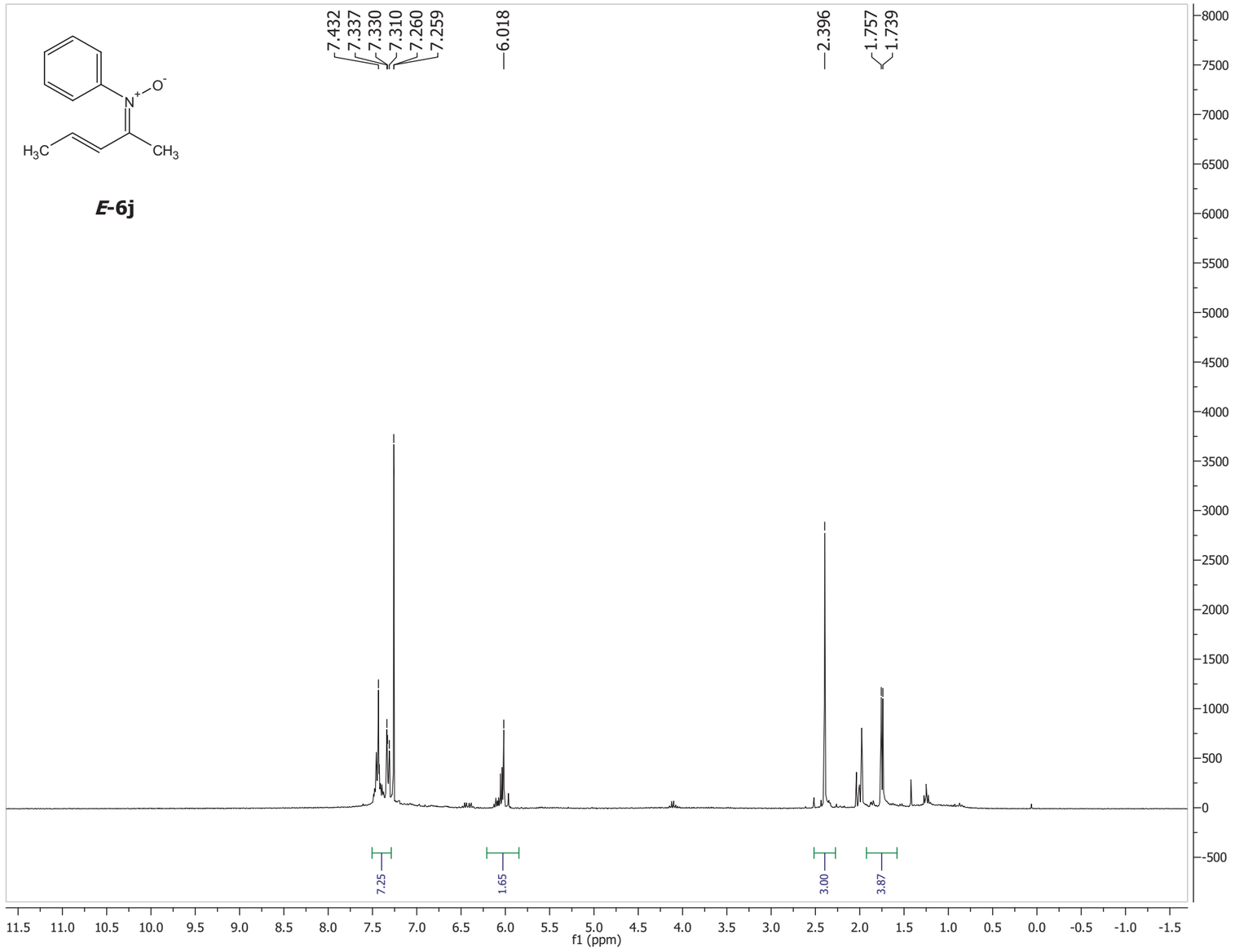

160.533
148.418
145.764
129.742
128.713
128.656
124.828
119.237
114.627
55.643
13.652
O
CH3
N+
O-
CH3
E-6h
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.971
7.916
7.554
7.305
7.104
7.049
6.920
6.891
3.838
2.298
2.017
H3C
O-
N+
CH3
O
CH3
Z-6i
1.00
2.02
4.58
1.09
2.04
3.03
2.96
2.98
f1 (ppm)

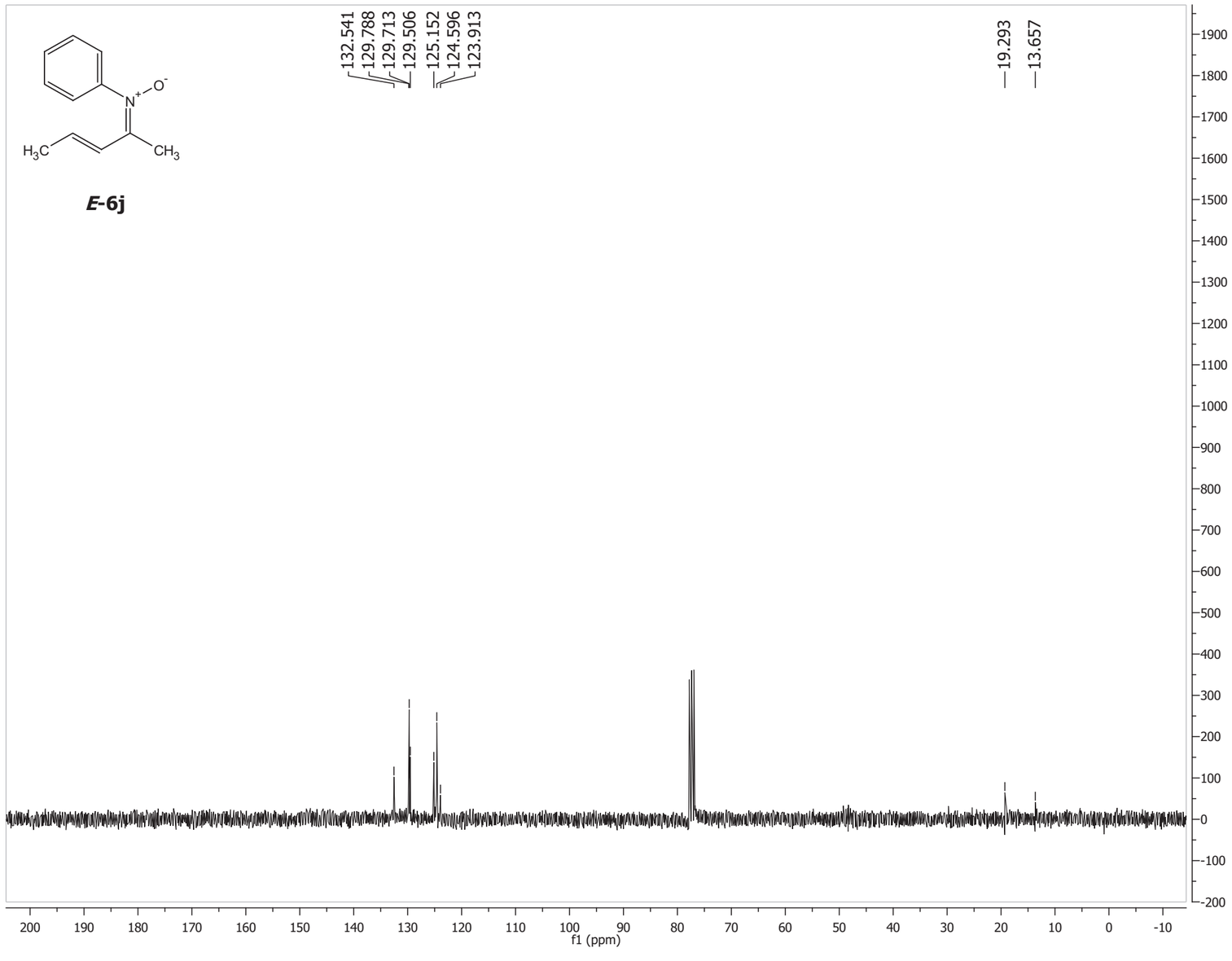

160.985
145.596
145.497
137.901
129.388
123.901
118.057
114.651
55.684
16.919
15.671
H3C
O-
N+
CH3
O
CH3
Z-6i
f1 (ppm)

7.620
7.591
7.193
6.814
6.431
6.378
3.813
2.560
2.281
CH3
N+
O-
CH3
O
CH3
0.29
0.77
4.26
3.12
3.69
0.80
3.00
2.82
2.95
f1 (ppm)

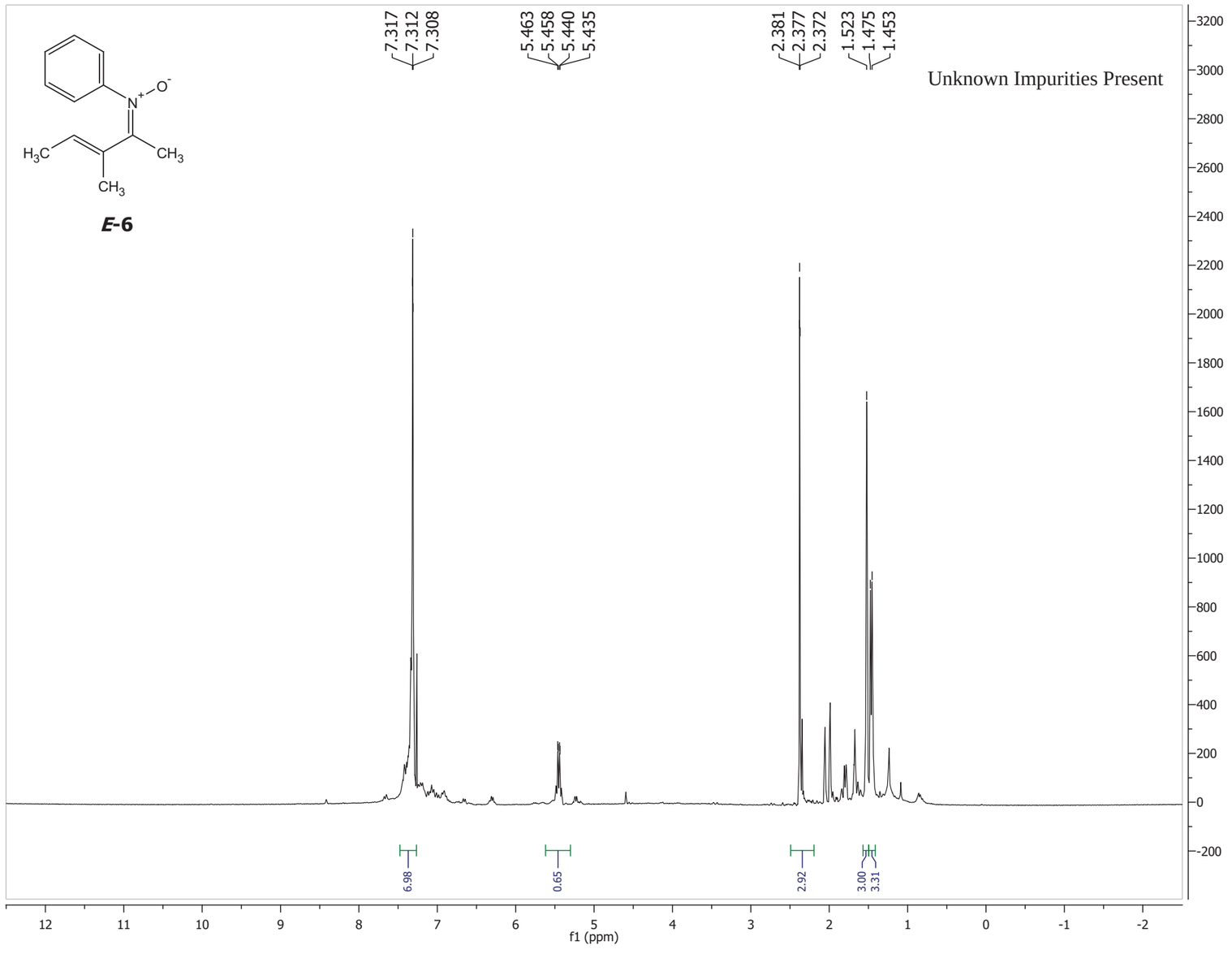
***E*-6i**


7.432
7.337
7.330
7.310
7.260
7.259
6.018
2.396
1.757
1.739
7.25
1.65
3.00
3.87
f1 (ppm)

***E*-6j**


132.541
129.788
129.713
129.506
125.152
124.596
123.913
19.293
13.657
f1 (ppm)

***E*-6j**


7.317
7.312
7.308
5.463
5.458
5.440
5.435
2.381
2.377
2.372
1.523
1.475
1.453
Unknown Impurities Present
6.98
0.65
2.92
3.00
3.31
f1 (ppm)

***E*-6**