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BORON AND TITANIUM(IV) HALIDE MEDIATED REACTIONS

A Dissertation
Presented for
the Doctor of Philosophy
Degree

The University of Tennessee, Knoxville

Michael Patrick Quinn
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DEDICATION

To my best friend and wife, Amber,
Thank you for all the support during this process,
You have been a tremendous source of strength and advice,
I could not have done this without your help.

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ABSTRACT

This dissertation summarizes research efforts focused on the use of boron and transition metal halides to form new carbon-carbon and carbon-halide bonds. The boron halide mediated alkyne-aldehyde coupling reaction to generate 1,3,5-triaryl-1,5-dihalo-1,4-dienes was reinvestigated in an attempt to explain the stereochemistry observed during changing of both the mode of addition and the reaction temperature. Either (*Z,Z*)-1,4-dienes or (*Z,E*)-1,4-dienes can be the predominant product depending on reaction conditions used. This mechanistic investigation also led to the discovery of several novel reactions. These include the stereoselective preparation of (*Z*)-3-chloroallylic ethers from the reaction of alkenylboron dichlorides with aryl aldehydes in the presence of an amine; the titanium(IV) halide coupling of alkoxides and alkynes; the haloallylation of aryl aldehydes with boron trihalide using different allylmetals; and the base induced elimination of the haloallylated products to form 1,3-dienes. The results of these studies strongly imply a cationic mechanism. The new reactions described herein can be characterized as atom-efficient, environmentally friendly, and capable of generating the desired products in good to excellent yields.

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LIST OF SYMBOLS AND ABBREVIATIONS

OAc	Acetate
α	Alpha
Anal. Calcd	Analytical Calculated
Å	Angstrom
Bn	Benzyl
β	Beta
9-BBN	9-Borabicyclo[3.3.1]nonane
<i>n</i> -BuLi	Butyl lithium
Cat.	Catalyst
C	Celsius
DCM	Dichloromethane
<i>J</i>	Coupling constant
°	degrees
CDCl ₃	Deuteriochloroform
d	doublet
dd	doublet of doublets
dt	doublet of triplets
Equiv.	Equivalents
Et	Ethyl
Et ₂ O	Diethyl ether
OTf	Trifluoromethanesulfonate

g	grams
Hz	Hertz
h	hours
THF	Tetrahydrofuran
MHz	Megahertz
Me	Methyl
OTs	4-Methylbenzenesulfonate
TMS	Tetramethylsilane
μm	micrometer
mg	milligram
mL	milliliter
mmol	millimole
min	minutes
<i>M</i>	Molar
m	multiplet
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
PhLi	Phenyl lithium
<i>n</i> -Pr	Propyl
q	quartet
s	singlet
t	triplet

Chapter 1. Lewis Acids in Organic Synthesis

1.1 Scope of this Dissertation

This dissertation focuses on Lewis acid (boron trihalide and titanium(IV) halide) mediated reactions involving alcohols, alcoholates, alkynes, and aldehydes. Several novel reactions have been developed. These include: (1) alkyne-aldehyde coupling reactions induced by boron trihalides; (2) titanium (IV) mediated coupling of alkoxides with alkynes; and (3) haloallylation of aryl aldehydes induced by boron trihalides in the presence of different allylmetals. Numerous applications of these novel reactions have been developed. These include the base mediated elimination of the haloallylated products to yield (*E*)-1,3-dienes and the preparation of (*Z*)-3-chloroallylic ethers resulting from the coupling of alkynes and aryl aldehydes. The discussion in the present chapter includes historical developments involving the use of the Lewis acids boron trihalide and titanium(IV) halide in organic synthesis as well as reactions pertaining to alkenylation and allylation of carbonyl compounds. Subsequent chapters contain discussions of the significance of these novel reactions as they relate to the literature and will provide mechanistic insights into these newly discovered reactions.

1.1.1 Historical Aspects of Boron and Transition Metal Halides in Organic Synthesis

A Lewis acid is a chemical substance that can accept a pair of electrons from an electron pair donor (Lewis base), a concept named for American physical chemist Gilbert Norton Lewis.¹ In valence bond formalism, trivalent boron reagents are Lewis acids because their valence shell is electron deficient, whereas, a Lewis base is electron rich. Chemistry occurs between the two

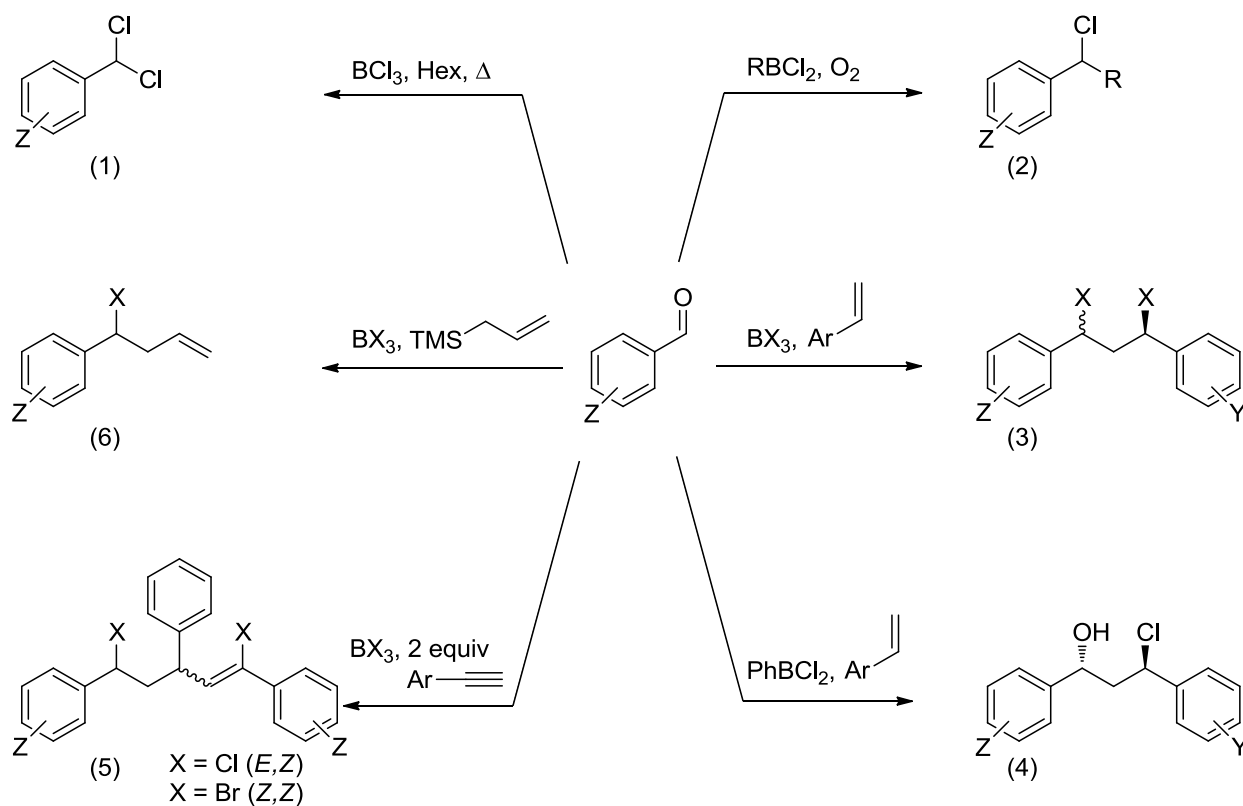
because the acceptance of electrons by the Lewis acid completes a full octet of electrons in the outer valence shell, resulting in the formation of a new bond. The Lewis acidic strength of boron trihalides increases as the halide becomes larger and less electronegative,²⁻³ counterintuitive on the basis of the relative σ -donor strengths of the halide ions. This discrepancy is explained by the overlap of a filled p-orbital on the halogen with the empty p-orbital on the boron that will be used to form a σ -bond.⁴ The p-orbital overlap between B-F is large and strong, whereas, p-orbital overlap in a B-I bond is negligible. This explains the increased Lewis acidity of BI_3 .

In transition metal Lewis acids, the more electron deficient or smaller d^n configurations are stronger Lewis acids than those with higher d^n configurations. Since titanium(IV) chloride and bromide form d^0 complexes, they are strong Lewis acids as compared to copper(II) chloride, a d^9 complex.

1.1.2 Reactions of Boron Trihalides in Organic Chemistry

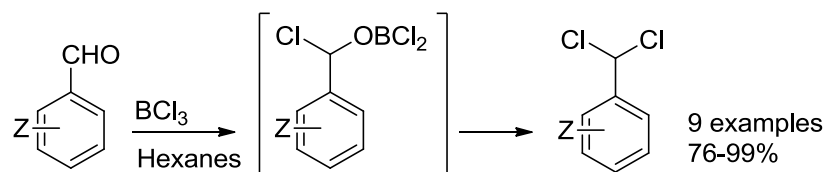
The synthetic applications of the boron trihalides have been known for over half a century.⁵⁻⁶ Ether cleavage by boron trihalides is a well-known reaction and widely used since reaction conditions are mild and the reactions proceed with high regio- and chemoselectivity.⁷⁻⁸ Other applications include the cleavage of acetals and esters,⁹⁻¹⁰ stereoselective glycosidation of glycols under mild conditions,¹¹ Aldol reactions,¹²⁻¹³ Friedel-Crafts alkylation and acylation reactions,¹⁴⁻¹⁵ Diels-Alder reactions,¹⁶⁻¹⁷ and other acid-induced reactions including rearrangements¹⁸ and cyclizations.¹⁹

In recent years, the Kabalka group has developed several novel reactions using boron halide Lewis acids as depicted in **Scheme 1-1**.²⁰⁻²⁶ These reactions serve as the background for the research presented in this dissertation.



Scheme 1-1 Boron Halide Induced Reactions of Aldehydes: (1) Dihalogenation, (2) Haloalkylation, (3) 1,3-Dihalo-1,3-diarylpropanes, (4) 3-Chloro-1,3-diarylpropanols, (5) Dialkenylation, and (6) Haloallylation.

At elevated reaction temperatures, the dihalogenation of aromatic aldehydes with BCl_3 occurs to form aryl dichloromethanes (Eq (1), **Scheme 1-1**). Based on a NMR study, the reaction proceeds through a benzyloxyboron dichloride intermediate that was the first indication that C-O bond cleavage occurs when boron trihalides coordinate with carbonyl groups as shown in **Scheme 1-2**.²⁷



Scheme 1-2 Dihalogenation of Aromatic Aldehydes.

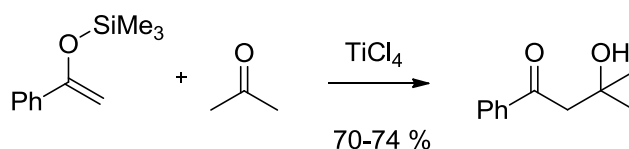
The reaction of dialkylboron chloride with aryl aldehydes in the presence of oxygen was found to produce excellent yields of alkylarylmethanols.²⁸ To increase atom economy, the use of monoalkylboron dichlorides was investigated and the reaction produced chloroalkylation products exclusively at room temperature (Eq (2), **Scheme 1-1**).²⁹ The Grignard-like alkylation of aldehydes and ketones using organoborane reagents offers several synthetic advantages that include mild reaction conditions normally not associated with more commonly used organometallic reagents including a tolerance of functional groups. The haloboration of styrenes using boron trihalides regioselectively produces diastereomeric mixtures of 1,3-dihalo-1,3-diaryl-propanes from aryl aldehydes (Eq. (3), **Scheme 1-1**). During examination of this reaction, the detection of chloroalcohols prompted an investigation into their synthesis. It was determined that if phenylboron dichloride was used instead of boron trichloride, *anti*-β-chloroalcohols were regioselectively produced in good to excellent yields (Eq (4), **Scheme 1-1**).²²

The dialkenylation and haloallylation of aryl aldehydes (Eq (5) and (6), **Scheme 1-1**) will be discussed in further detail in subsequent chapters, however, a brief review of alkenylation and allylation reactions is presented in this chapter.

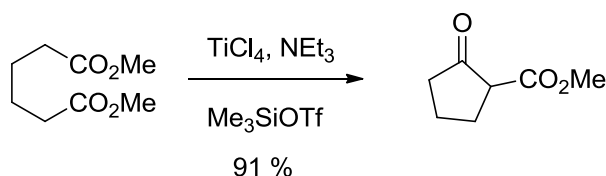
1.1.3 Reactions of Titanium(IV) Halides in Organic Chemistry

The titanium(IV) halides have been extensively studied and are useful reagents in organic synthesis.³⁰⁻³² The use of titanium(IV) halides to selectively form new carbon-carbon bonds has been demonstrated in a multitude of reactions, including Aldol condensations,³³⁻³⁶ Claisen condensations,³⁷⁻³⁹ and alkynylations of carbonyl compounds.⁴⁰ A few select examples of these reactions are provided in **Scheme 1-3**.

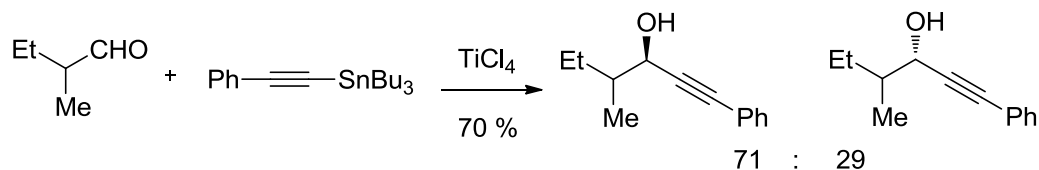
Aldol Condensation



Claisen Condensation



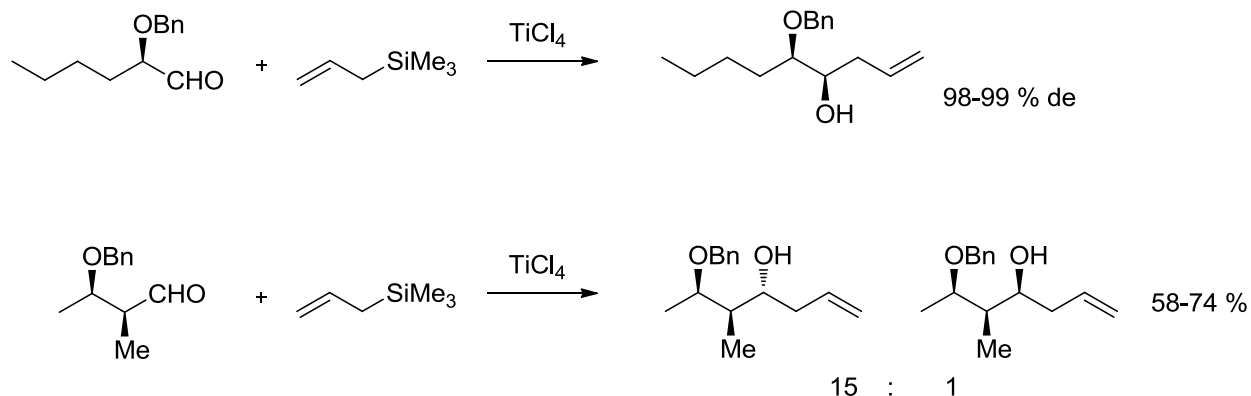
Alkynylation



Scheme 1-3 TiCl_4 Mediated Reactions forming Carbon-Carbon Bonds.

The reaction of titanium(IV) chloride with an allylmetal was first reported by Hosomi and Sakurai⁴¹ to yield homoallylic alcohols from aldehydes. The versatility of homoallylic compounds has generated tremendous interest in organic synthesis. Their preparation from aldehydes, ketones, mixed acetals, and α -keto esters have been investigated using titanium(IV)

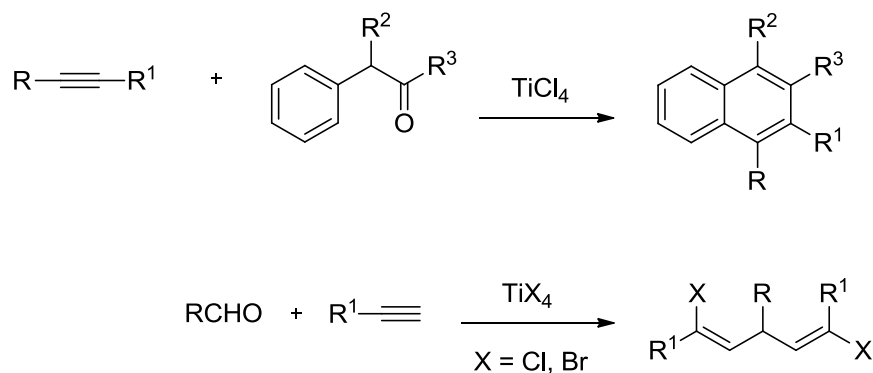
chloride assisted allylation.⁴²⁻⁵² Perhaps more important is the diastereoselective allylation of carbonyl and related compounds with allylsilanes mediated by TiCl_4 . A fundamental method used for the construction of stereogenic centers is the allyl addition to α - or β -oxyaldehydes in the presence of TiCl_4 .⁵³⁻⁵⁴ Examples are provided in **Scheme 1-4**.



Scheme 1-4 TiCl_4 Assisted Reaction of Oxyaldehydes with Allylsilanes.

Titanium(IV) chloride is also used in Claisen rearrangements,⁵⁵ Baylis-Hillman,⁵⁶⁻⁶³ and Friedel-Crafts⁶⁴⁻⁶⁶ reactions as well as organic functional group transformations. Some of the more common conversions include ethers to alcohols,⁶⁷⁻⁶⁸ ketals to carbonyl compounds,⁶⁹ and carbonyl compounds to acetals.⁷⁰

In recent years, the Kabalka group has developed several novel reactions using transition titanium halide⁷¹⁻⁷² as Lewis acid (**Scheme 1-5**). These reactions serve as the background for the research presented in this dissertation.



Scheme 1-5 Transition Metal Halide Reactions.

1.2 Alcohol Functional Group Conversion

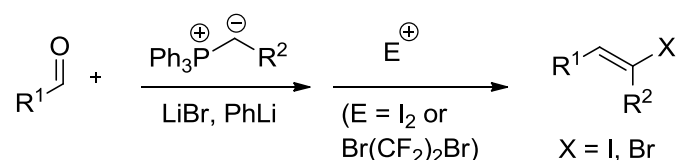
In the context of this dissertation, alcohols are converted into alkoxides and allowed to react with stereodefined haloalkenyl moieties in what can generally be considered the first transition-metal free nucleophilic substitution of hydroxyl groups. This will be discussed further in Chapter 3. Although the chemistry of alcohols is substantial, few results have been achieved involving the direct substitution of hydroxyl groups. Most substitution reactions require activation of the hydroxyl group which involve not only additional steps in the synthesis but the formation of large amounts of byproduct. Side reactions can also lead to unwanted byproducts during these conversions, decreasing atom efficiency and generating waste that creates environmental concerns. Encouraging results for the direct substitution of hydroxyl groups by nucleophiles have been achieved,⁷³⁻⁷⁷ but further developments remain a challenge.

1.3 Synthesis of Alkenyl Halides and Alkenylation of Carbonyl Groups

Developing efficient synthetic routes to stereodefined alkenyl halides is an important goal in synthetic organic chemistry due to their importance in transition-metal catalyzed cross-

coupling reactions. To this end, several reactions have been developed to facilitate the formation of stereodefined alkenyl halides from aldehydes and ketones.

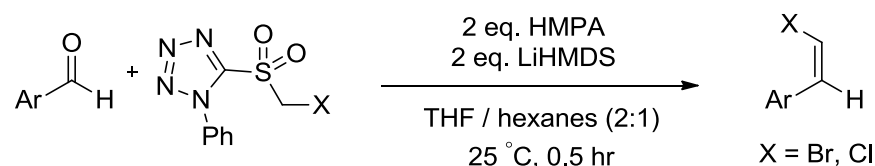
Recent advances in the formation of Wittig reagents, specifically β -oxido phosphonium ylides prepared *in situ* from aldehydes and Wittig reagents, include their reaction with electrophilic halogen sources to form predominantly *E*-bromo or iodosubstituted alkenes from aldehydes (**Scheme 1-6**).⁷⁸



Scheme 1-6 Reaction of β -Oxido Phosphonium Ylides with Electrophilic Halogen to Generate *E*-Halogen Substituted Alkenes.

The use of (PhO)₃P-halogen based reagents in Horner-Wadsworth-Emmons type reactions also allows the preparation of stereodefined vinyl halides and several modifications have been reported.⁷⁹⁻⁸⁰ The necessity to form either phosphonium ylides or phosphonate carbanion may be viewed as a limitation, especially considering the required use of strong base which limits application to reagents bearing labile functional groups.

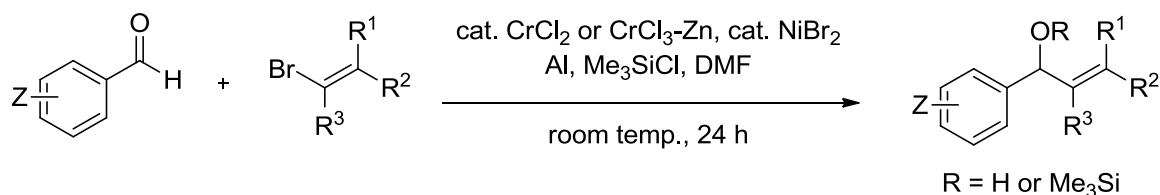
An interesting route to alkenyl halides was recently reported using α -halomethyl sulfones in an extension of the modified Julia olefination reaction (**Scheme 1-7**).⁸¹



Scheme 1-7 Modified Julia Olefination between α -Halomethyl Sulfones and Aldehydes to Yield Alkenyl Halides with High *E/Z* Stereoselectivities.

The necessary preparation of sulfones prior to olefination may prove inhibitory in selection of this method to obtaining the desired alkenyl halides two or three steps are required.

The general alkenylation of carbonyl compounds using alkenylmetal reagents such as alkenyllithium, -magnesium, -copper, or -chromium yields allylic alcohols.⁸²⁻⁸³ The alkenylation of carbonyl compounds promoted with Cr(II)/cat. Ni(II), known as the Nozaki-Hiyama-Kishi reaction, proceeds chemoselectively under very mild conditions and has been used in the synthesis of complex natural products.⁸⁴ Issues of toxicity have been addressed in more recent applications of this reaction using aluminum and catalytic amounts of chromium and nickel wherein aluminum acts as an electron source and CrCl₂ and NiBr₂ function as the electron-transfer catalysts (**Scheme 1-8**).⁸⁵

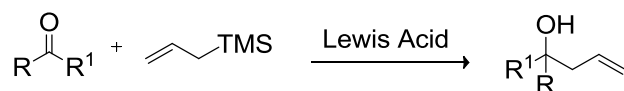


Scheme 1-8 Modified Nozaki-Hiyama-Kishi Reaction.

The Nozaki-Hiyama-Kishi reaction provides a method for alkenylation of aldehydes to yield allylic alcohols and exemplifies the importance of vinyl halides as important synthetic targets. The utility of allylic systems has been demonstrated in Claisen, Ireland-Claisen, and Alder-Ene rearrangements. The Prins reaction is another method for synthesizing allylic alcohols, however, the majority of methodology developed for allylation can be considered extensions of the Hosomi-Sakurai Reaction for the formation of homoallylic systems as discussed in the next section.

1.4 Allylation of Carbonyl Compounds

The Lewis acid mediated allylation of carbonyl compounds leading to homoallylic alcohols constitutes one of the most important synthetic reactions (**Scheme 1-9**).⁸⁶ Numerous allylic organometallic reagents and Lewis acids have been investigated and have proven to be enormously useful in the synthesis of open-chain systems bearing sequences of stereocenters.⁸⁷⁻⁹⁰ High degrees of diastereo- and enantioselectivity are observed for these reactions depending on allylmetal reagent selection. Furthermore, the products of these reactions offer substantial functionality in terms of alcohols and alkenes.

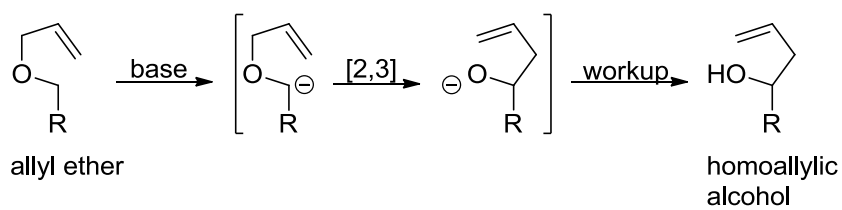


Scheme 1-9 Lewis-acid Assisted Allylation of Carbonyl Compounds to form Homoallylic Alcohols.

Asymmetric syntheses of homoallylic alcohols have been accomplished by incorporating chiral modifiers in allylic organometallic reagents such as the modified allylic borane⁹¹ or allylic titanium⁹² reagents. Considerable progress has been made in this area by Brown,⁹³ Roush,⁹⁴ Corey,⁹⁵ and Hafner and Duthaler,⁹⁶ among others.⁹⁷⁻⁹⁸ The use of other allylmetals has been extended to include allylic silanes and stannanes⁹⁹⁻¹⁰¹ and the reactions include low temperature boron halide mediated allylation of cyclic ketones using allylstannane to give homoallylic alcohols.¹⁰²

The Lewis acid-catalyzed allylation of acetals has been well documented as a synthetic route to homoallylic ethers.¹⁰³⁻¹⁰⁶ Many of these methods require a two-step conversion of

aldehydes into acetals and subsequent allylation of acetals to form the homoallylic ethers.¹⁰⁷ Various extensions of the Sakurai reaction to form homoallylic ethers from aldehydes in one-pot have also been reported.¹⁰⁸ The interest in generating homoallylic ethers indirectly stems from the preparation of optically active homoallylic alcohols, an area of continuing synthetic interest.¹⁰⁹⁻¹¹² The synthesis of chiral homoallylic ethers has also been used for the asymmetric synthesis of natural products like the immunosuppressant rapamycin.¹¹³ Furthermore, allylic ethers are also very interesting synthons because of base induced [2,3] Wittig rearrangements (**Scheme 1-10**).¹¹⁴⁻¹¹⁵



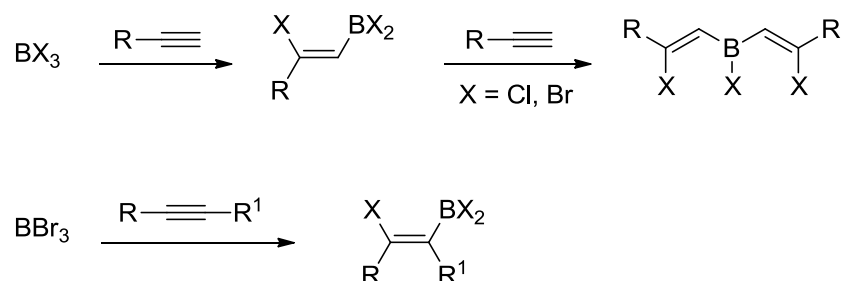
Scheme 1-10 [2,3] Wittig Rearrangement

Several applications in asymmetric syntheses have been reported utilizing the [2,3]-Wittig rearrangement as a critical step including the synthesis of Stork's prostaglandin intermediate and the total synthesis of the alkaloid, (+)-astrophylline.¹¹⁶⁻¹¹⁷

1.5 Boron Trihalide Haloboration of Alkynes

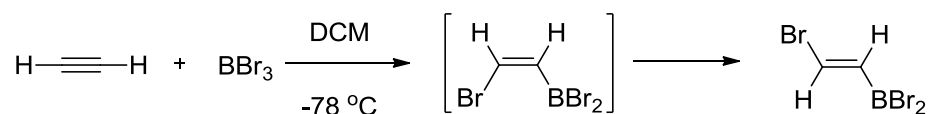
The haloboration of terminal alkynes using boron trihalides generates halovinylboron halides in a highly stereo- and regioselective manner.¹¹⁸ Depending on the quantity of alkyne used, selective haloboration of one equivalent of alkyne generates (Z)-halovinylboron dihalide whereas the (Z,Z)-di(halovinyl)boron halide results when two equivalents of the alkyne are used

(**Scheme 1-11**).¹¹⁹ The reactions leading to (*Z*)-halovinylboron dihalides occur rapidly at -78 °C and provide the desired products in high purity (>98 %). Haloboration of internal alkynes is also possible with boron tribromide.



Scheme 1-11 Haloboration of Alkynes.

Interestingly, the bromoboration of acetylene generates the unexpected (*E*)-2-bromethenylboron dibromide.¹²⁰ A spontaneous rearrangement from the *cis* to the *trans* isomer occurs immediately after the *syn* addition of the boron tribromide to the acetylene (**Scheme 1-12**).



Scheme 1-12 Bromoboration of Acetylene.

The halovinylboron halides are air and water- sensitive and are somewhat difficult to handle, but these shortcomings may be overlooked when considering their synthetic versatility resulting from the presence of vinylboron, vinyl halide, and alkene functional groups within the reagent.

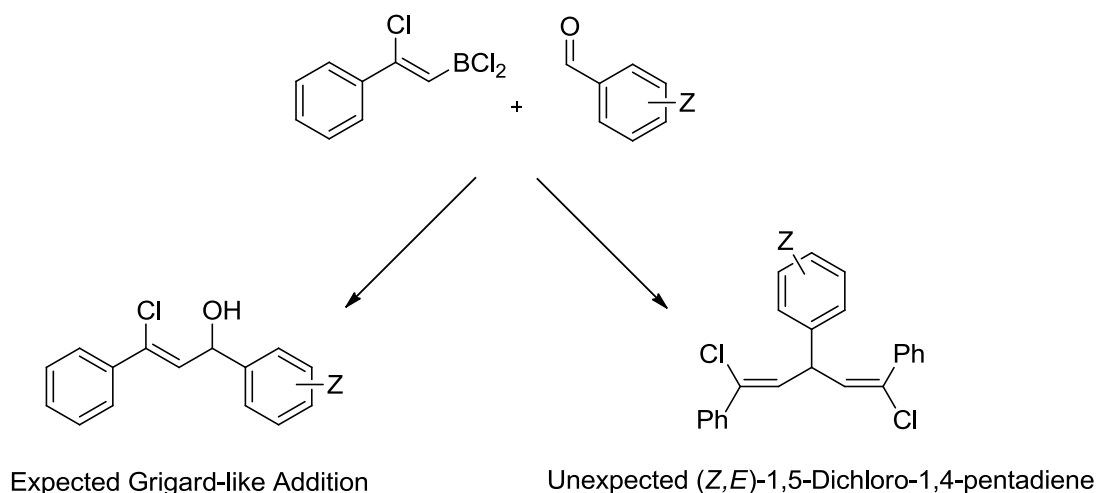
1.6 Statement of Problem

Lewis acids such as the boron trihalides and titanium(IV) halides can mediate reactions involving alkynes, aldehydes, and alcohols to generate compounds containing new carbon-carbon and carbon-halogen bonds. This dissertation is focused on a study of the reactions of boron halides and transition metal halides with carbonyl and hydroxy compounds. The boron halide mediated alkyne-aldehyde coupling reaction to generate 1,3,5-triaryl-1,5-dihalo-1,4-dienes was reinvestigated in an attempt to explain the stereochemistry observed during the changing of mode of addition and the reaction temperature. A mechanistic investigation was carried out in an effort to explain the observation that boron tribromide produces the (*Z,Z*)-1,4-diene isomer exclusively, while boron trichloride produces the (*Z,E*)-1,4-diene isomer (Chapter 2). The stereoselective preparation of (*Z*)-3-chloroallylic ethers from the reaction of alkenylboron dichlorides with aryl aldehydes in the presence of amine was investigated as a result of initial observations during the dialkenylation of aldehydes with vinylboron halides (Chapter 3). The alkenylation of allylic, benzylic, and propargylic alcohols using phenylacetylenes and titanium (IV) halides to afford high (*E,Z*) ratios of alkenylated products was investigated (Chapter 4). The previously unknown capture of a carbocation by alkynes generated from an unprecedented alkoxide C-O bond cleavage was investigated. The haloallylation of aryl aldehydes using boron trihalides further validates carbocation formation and is discussed in Chapter 5. The use of other allylmetals to facilitate haloallylation of aryl aldehydes was also previously not known and was investigated (Chapter 6). Synthesis of (*E*)-1,3-dienes from bromoallylated products using the haloallylation of aryl aldehydes was previously unknown (Chapter 7).

Chapter 2. Reaction Pathways Involved in Boron Trichloride Mediated Alkyne-Aldehyde Coupling under Varying Reaction Conditions

2.1 Introduction

Our research group has focused on the chemistry of organoboron halide derivatives for many years and the studies resulted in the first report of a Grignard-like alkylation of aryl aldehydes using dialkylboron chlorides²⁸ and alkylboron dichlorides.²⁹ In a continuation of this study, we investigated the feasibility of expanding the reaction to the addition of vinylboron dichloride reagents to aryl aldehydes.^{21, 121} Surprisingly, the reaction afforded (*Z,E*)-1,5-dichloro-1,4-pentadienes as major products instead of the expected Grignard-like addition products, if preformed (*Z*)-vinylphenylboron dichloride reagents were used (**Scheme 2-1**).²¹



Scheme 2-1 Formation of (*Z,Z*)-1,5-Dichloro-1,4-pentadiene vs Grignard-like Addition.

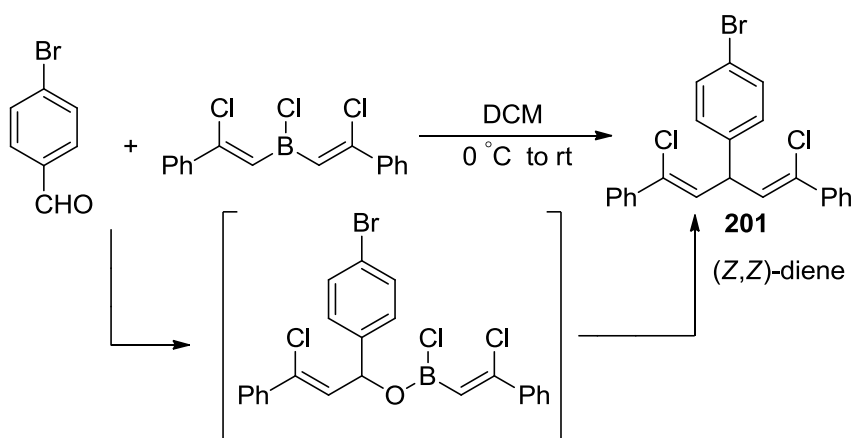
Since it has been reported that boron trichloride adds to terminal alkynes readily to generate (*Z*)-vinylboron dichloride,¹¹⁸ we decided to explore a one-pot reaction employing boron trichloride, phenylacetylene, and benzaldehyde at 0 °C. We found that a diene product formed but, unexpectedly, (*Z,E*)-1,5-dichloro-1,4-pentadiene was isolated as the major product instead of the expected (*Z,Z*)-1,5-dichloro-1,4-pentadiene. (None of the (*E,E*)-1,5-dichloro-1,4-pentadiene isomer was detected.)

Several novel reactions were then designed to probe the reaction mechanism.¹²²⁻¹³⁰ During these studies, we discovered novel reactions involving an unprecedented C-O bond cleavage in $R_1R_2CH-O-BX_nR_{3-n}$ intermediates; they included a transition-metal-free, formal Suzuki-coupling of alkoxides with vinylboron dichlorides,¹²² the boron trichloride mediated coupling of alkoxides with allylsilane,¹²³ and the boron trihalide mediated haloallylation of aryl aldehydes using allylmethyl compounds.¹³¹ In addition, we found that, at low temperature the reaction of boron chloride with two equivalents of terminal alkynes, yields only vinylboron dichloride instead of the reported divinylboron chloride.

Although the methodology required for the stereoselective boron trihalide mediated alkyne-aldehyde coupling reactions has been reported, the dramatic influence of reactant addition order and reaction temperature on the stereochemistry of the products had not been investigated in details. To fully explore these parameters, we chose the reaction of phenylacetylene with *p*-bromobenzaldehyde as a model system for probing these parameters.

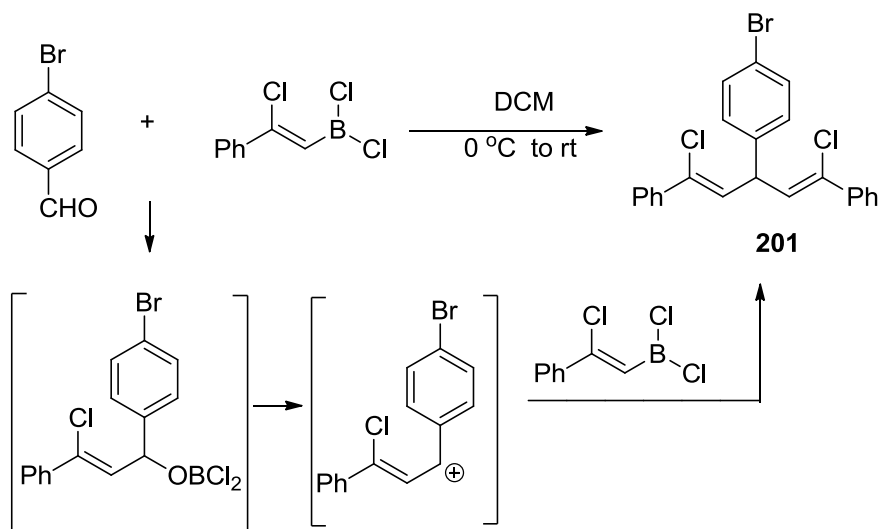
2.2 Results and Discussion

(*Z,Z*)-1,5-Dichloro-1,4-pentadiene (**201**) and (*Z,E*)-1,5-dichloro-1,4-pentadiene (**202**) were synthesized according to reported procedures.^{21, 121} In the reaction of (*Z,Z*)-di(chlorovinyl)boron chloride with *p*-bromobenzaldehyde (**Scheme 2-2**), the halovinyl group migrates from boron to carbon with retention of stereochemistry.¹²² Interestingly, racemization in chiral benzyloxide derivatives in the coupling reaction of benzyloxides and vinylboron dihalides suggest that a cationic mechanism is involved in this migration.¹²³



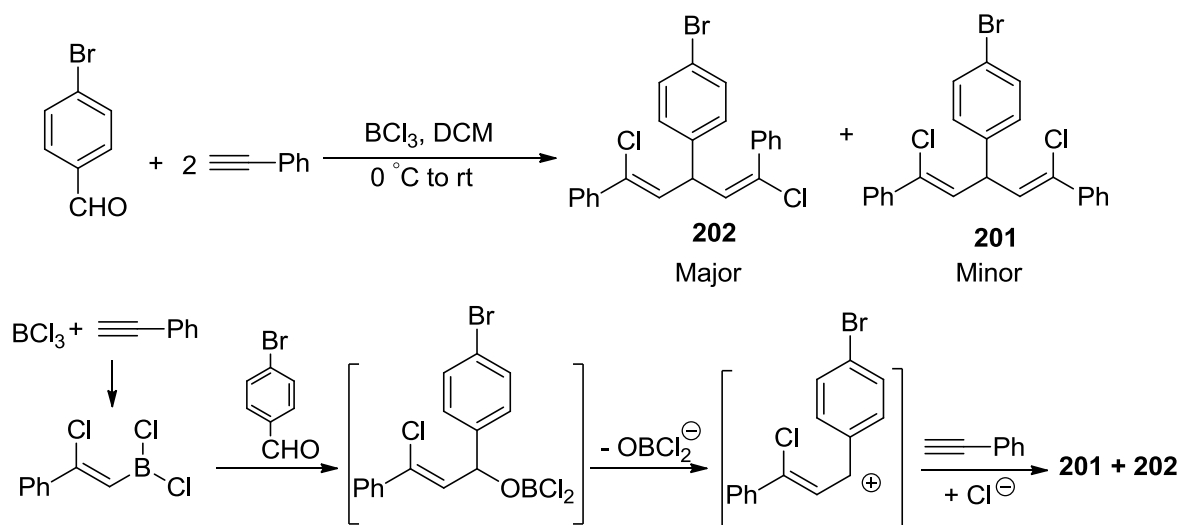
Scheme 2-2 Reaction of Aldehyde with (*Z,Z*)-Di(chlorovinyl)boron Chloride.

Alternatively, compound **201** can also be prepared by the reaction of *p*-bromobenzaldehyde with two equivalents of preformed (*Z*)-chlorovinylboron dichloride (**Scheme 2-3**). The Grignard-like addition of (*Z*)-halovinylboron dichloride to the aldehyde followed by a carbon-oxygen bond cleavage affords a carbocation intermediate. Then the cation adds to a second equivalent of the monovinylboron dichloride to generate the observed *Z,Z*-diene product. It has been demonstrated that electrophiles can add to vinylboron reagents stereoselectively with retention of configuration of the vinyl group.¹³²⁻¹³⁶



Scheme 2-3 Reaction of an Aldehyde with Two Equivalents of *Z*-Chlorovinylboron Dichloride.

(*Z,E*)-1,5-Dichloro-1,4-pentadiene (**202**) was prepared by adding boron trichloride to a mixture of the aldehyde and phenylacetylene at 0 °C (**Scheme 2-4**). Reaction of boron trichloride with the alkyne generates the (*Z*)-chlorovinylboron dichloride. Addition of (*Z*)-halovinylboron dichloride to the aldehyde followed by carbon-oxygen bond cleavage affords the carbocation intermediate which then adds to the second alkyne to generate the more thermodynamically stable (*Z,E*)-diene **202** as the major product.¹²⁹ The reactions outlined in **Scheme 2-4** presumably compete with those shown in **Scheme 2-3**. This assumption is strongly supported by two observations: the quantity of (*Z,Z*)-diene **201** increases when aldehyde is added to a mixture of phenylacetylene and boron trichloride which favors the formation of the vinylboron dichloride (**Scheme 2-3**), whereas adding boron trichloride to a mixture of aldehyde and excess phenylacetylene (3.0 equivalents) at 0 °C results in a higher ratio of **202** to **201**. Since (*Z,Z*)-di(chlorovinyl)boron chloride only forms at elevated temperature (refluxing dichloromethane),¹²⁵ the reaction pathway shown in **Scheme 2-2** should not be important in this investigation.



Scheme 2-4 BCl_3 -Mediated Coupling of Aryl Aldehydes and Alkynes.

After establishing the analytical GCMS conditions for analyzing stereoisomers **201** and **202** (see Experimental), we examined the addition of boron trichloride to a mixture of two equivalents of phenylacetylene and one equivalent of *p*-bromobenzaldehyde at various temperature (**Table 2-1**). The reaction mixtures were subjected to GCMS analyses after a simple workup (see Experimental). As illustrated in **Table 2-1**, (*Z,E*)-1,5-dichloro-1,4-pentadiene (**202**) was always the major product, indicating that the reaction pathway shown in **Scheme 2-4** played a predominant role. As the temperature was decreased from 0 °C to −42 °C, the ratio of the (*Z,E*) to (*Z,Z*) isomer increased due to the thermodynamic stability of the (*Z,E*)-1,5-dichloro-1,4-pentadiene product **202**. The reaction pathway shown in **Scheme 2-3** is also presumably involved but it would be expected to be minimal at temperatures approaching −60 °C, because the haloboration reaction would be less effective at very low temperatures. As a consequence of slow haloboration, the concentration of (*Z*)-chlorovinylboron dichloride remains low compared to that of phenylacetylene. Therefore, the reaction pathway (**Scheme 2-3**) leading to (*Z,Z*)-1,5-

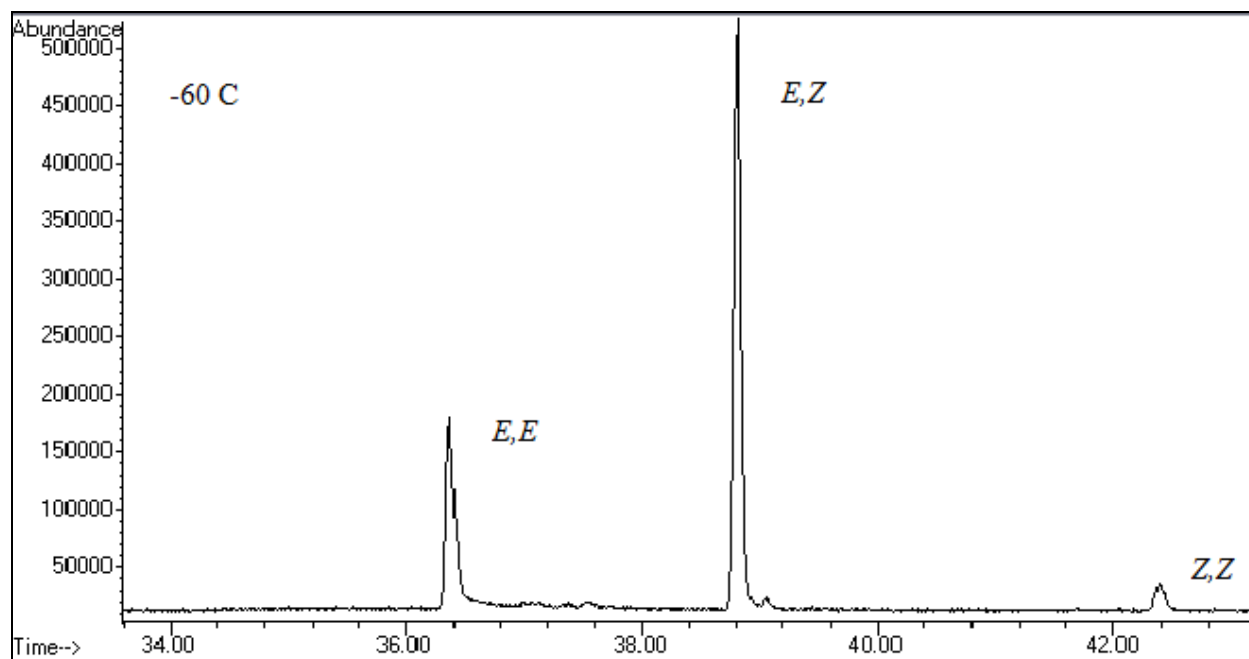


Figure 2-1 Chromatogram of isomers resulting from the addition of boron trichloride to a mixture of two equivalents of phenylacetylene and one equivalent of *p*-bromobenzaldehyde at -60°C . Retention times are 36.4, 38.8, and 42.4 minutes for the *E,E*, *E,Z*, and *Z,Z* isomers, respectively.

dichloro-1,4-pentadiene **201** is suppressed. A representative chromatogram for the reaction at -60°C is provided in **Figure 2-1**.

Interestingly, reactions run at or below -60°C produce an additional isomer (molecular weight 444, $R_t = 42.4$ min) which was later confirmed to be the (*E,E*)-1,5-dichloro-1,4-pentadiene **203**. At these low temperatures, the unreacted boron trichloride acts as a Lewis acid and initiates a competing reaction to generate (*E,E*)-1,5-dichloro-1,4-pentadiene **203** (**Scheme 2-5**). Addition of the alkyne to the boron trichloride activated carbonyl group, followed by C-O bond cleavage, to form a carbocation bearing a thermodynamically stable (*E*)-vinyl moiety. Addition of this cation to the second alkyne then generates the more thermodynamically stable (*E,E*)-diene product **203**.

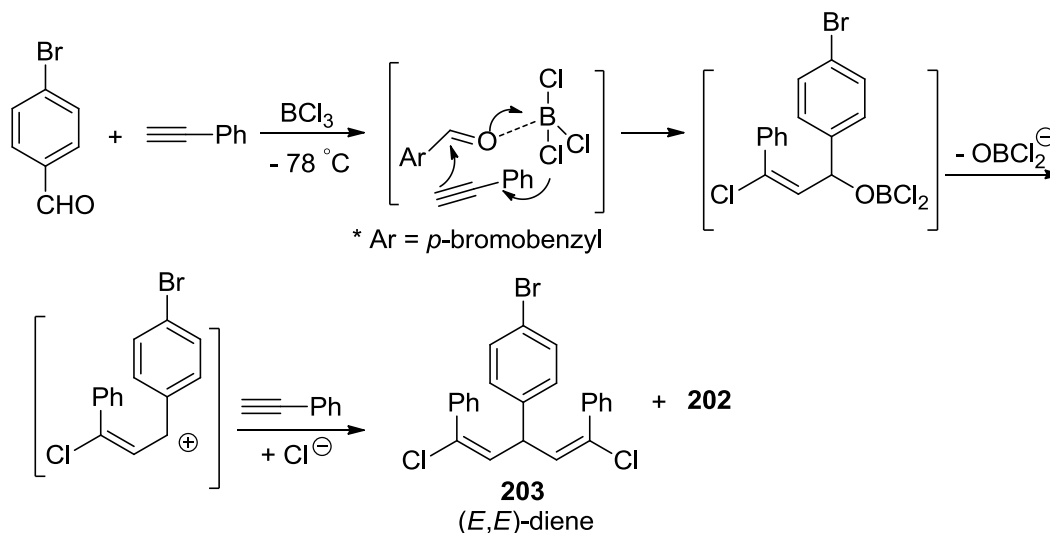
Table 2-1 The influence of reaction temperature on the ratio of isomers.^a

Reaction temperature	Ratio of (Z,Z)-: (Z,E)-: (E,E)- ^b
0 °C	~ 1 : 6 : 0
- 20 °C	~ 1 : 24 : 0
- 42 °C	~ 1 : 27 : 0
- 60 °C	~ 2 : 43 : 1
- 78 °C	~ trace : 9 : 1

^a See Experimental for reaction procedure.

^b The ratios shown in table are the average of multiple experiments.

To confirm the formation of **203**, it was isolated by column chromatography; the ¹H spectrum of the compound exhibited only one set of vinyl resonances which supports the formation of the symmetrical (*E,E*)-1,5-dichloride-1,4-pentadiene isomer. The structure was further confirmed by X-ray crystallography (**Figure 2-1**).



Scheme 2-5 Lewis Acid Boron Trichloride Initiated Alkyne-Aldehyde Coupling.

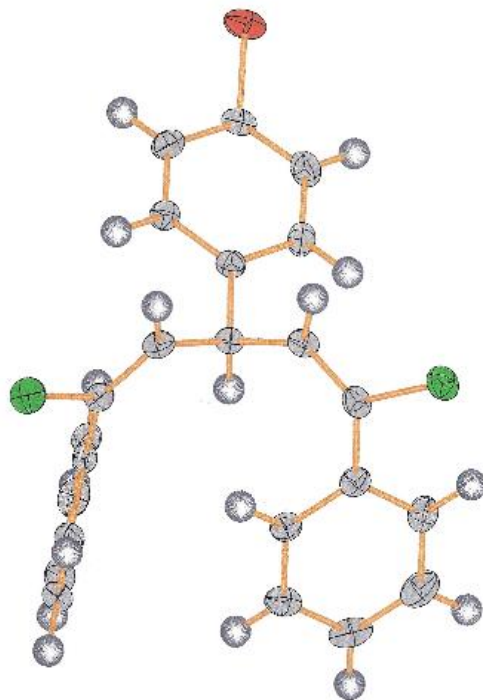


Figure 2-2 X-Ray Crystallography of **203** (see **Appendix A** for X-ray data).

The specific chemical shifts and coupling constants for vinyl and benzylic protons, as well as the and benzylic carbons, for the (Z,Z)-, (Z,E)-, (E,E)-isomers are tabulated in **Table 2-2**. As summarized in **Table 2-2**, both the vinyl and benzylic protons in the (E,E)-diene are upfield when compared to those in (Z,Z)-diene. Interestingly, the chemical shift difference in shifts of the benzylic proton in (E,E)-diene and (Z,Z)-diene approaches 1 ppm.

2.3 Conclusions

The reaction pathways involved in the reactions of phenylacetylene, *p*-bromobenzaldehyde and boron trichloride are discussed. Through the use of GC-MS, the ratios of (Z,Z)-, (Z,E)- and (E,E)-1,5-dichloro-1,4-diene isomers in the crude reaction mixtures obtained under different reaction conditions were determined. The investigation reveals that at temperatures greater than - 42 °C) the addition of boron trichloride to phenylacetylene occurs rapidly and boron trichloride

Table 2-2 Chemical Shift and Coupling Constants for Vinyl, Benzylic Proton and Benzylic Carbon.

Isomer	^1H NMR		^{13}C NMR
	Vinyl proton	Benzylic proton	Benzylic carbon
(<i>Z,Z</i>)-diene	6.30 (d, 2H, $J = 8.97$ Hz)	5.39 (t, 1H, $J = 8.97$ Hz)	45.3
(<i>Z,E</i>)-diene	6.21 (d, 1H, $J = 9.1$ Hz), 6.13 (d, 1H, $J = 10.5$ Hz)	4.81 (dd, 1H, $J = 10.5$ and 9.1 Hz)	45.0
(<i>E,E</i>)-diene	6.05 (d, 2H, $J = 10.7$ Hz)	4.34 (t, 1H, $J = 10.7$ Hz)	44.8

functions as a reactant. While, at relative lower temperature, the addition of boron trichloride to phenylacetylene becomes sluggish and the unreacted boron trichloride acts as a Lewis acid and leads to the (*E,E*)-diene.

2.4 Experimental

2.4.1 General Methods

All reagents were used as received. Column chromatography was performed using silica gel (60 Å, 230–400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical thin-layer chromatography was performed using 250 µm silica plates (Analtech, Inc., Newark, DE).

^1H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, respectively. Chemical shifts for ^1H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. Atlantic Microlab, Inc., Norcross, Georgia, performed microanalysis.

Gas Chromatography-Mass Spectroscopy studies were run on Hewlett Packard: HP 6890 series GC System with 5973 Mass Selective Detector; Column: Agilent 19091S-433E, 30.0mm

X 0.25mm X 0.25 μ m; Gas (He) flow rate: 0.8 mL/min; Initial temperature; 50 °C (hold 1 min); Ramp temperature rate: 7 °C/min to maximum 280 °C.

An APEX II CCD detector, radiation safety enclosure system, and a SMART APEX II 3-axis system incorporating a fixed-chi stage with a chi angle of approximately 54°, a phi drive with 360° rotation, and a freely rotating omega, with a Mo radiation source were used in the detection of X-Ray crystal data. SHELXTL based refinement software was used for analysis.

2.4.2 Typical Reaction Procedure

Phenylacetylene (204 mg, 2.00 mmol) and *p*-bromobenzaldehyde (185 mg, 1.00 mmol) were placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a stirring bar and dissolved in 15 mL dry CH₂Cl₂. The solution was cooled to the desired temperature, and boron trichloride (1.1 mmol, 1.1 mL of a 1.0 M CH₂Cl₂ solution) was added *via* syringe. The solution was allowed to stir for one hour at that temperature. The resulting mixture was hydrolyzed with water (20 mL) and extracted with hexanes (2 x 30 mL). The organic layer was separated and passed through a short silica gel column to remove the trace of water and acidic by-product.

2.4.3 Characterization of Compound 203

(*E,E*)-1,5-dichloro-1,5-diphenyl-3-(4-bromophenyl)-penta-1,4-diene (203): ¹H NMR (250 MHz, CDCl₃): δ 7.47-7.01 (m, 14H), 6.05 (d, 2H, *J* = 10.7 Hz), 4.34 (t, 1 H, *J* = 10.7 Hz). ¹³C NMR (CDCl₃): δ 140.6, 136.2, 132.9, 132.00, 128.8, 128.6, 128.2, 128.2, 121.0, 44.8. Confirmed by X-ray diffraction, refer to **Appendix A**. The crystals were developed at 4 °C for several days from a solution of hexanes.

Chapter 3. Stereoselective Preparation of (Z)-3-Chloroallylic Ethers: The reaction of Alkenylboron Dichlorides with Aryl Aldehydes in the Presence of Amine

3.1 Introduction

Allylic alcohol represents an important building block in synthetic organic chemistry. The synthesis of allylic alcohols can be achieved by α -cleavage of epoxides, allyl hydroxylation, and reduction of α,β -unsaturated carbonyl compounds.¹³⁷ The alkenylation of carbonyl compounds (the Nozaki-Hiyami-Kishi⁸³ reaction) can also be used to form allylic alcohols and has been used in the synthesis of complex natural products such as brefeldin,¹³⁸ ophiobolin C,¹³⁹ and polytoxin.¹⁴⁰ However, to reach the corresponding allylic ethers, an additional step is normally required. One of the few direct routes to allylic ethers is the synthesis of (*E*)-allylic TBS ethers based upon a unique Kocienski-Julia olefination reaction as reported by Pospisil and Marko.¹⁴¹ The use of allylic ethers as protecting groups¹⁴² illustrates their importance to the synthetic community, but they are also useful synthons in base induced [2,3]-Wittig rearrangements.¹¹⁴⁻¹¹⁵

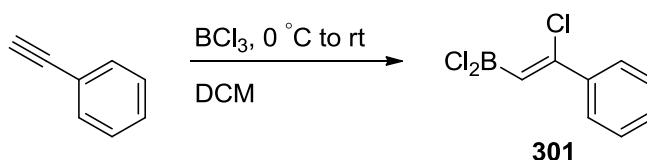
Herein, we report the synthesis of (*Z*)-3-chloroallylic ethers from aryl aldehydes *via* their reaction with alkenylboron dichlorides in the presence of triethylamine. These reactions are important not only because they represent a direct route to allylic ethers, but they also permit further synthetic manipulation of the vinyl chloride in chemistry such as metal-catalyzed coupling reactions (Heck, Kumada, Negishi, Stille, & Suzuki).

3.2 Results and Discussion

3.2.1 Generation of (Z)-3-Chloroallylic Alcohols

As discussed in Chapter 2, we recently reinvestigated the boron trihalide mediated reaction between aryl acetylenes and aryl aldehydes.¹⁴³ It was discovered that the reaction proceeded through different pathways depending on the reaction temperatures and order of reagent addition. For reactions below room temperature, the Grignard-like addition of stereodefined (Z)-2-halovinylboron dihalide to the aldehyde to form allyloxyboron halide was believed to be the first step. The subsequent C-O bond cleavage in the allyloxyboron halide intermediate then gives a carbocation which undergo further reaction with another equivalent of alkenylboron halide. The isolation of allylic alcohol (16% isolated yield from a reaction at 0 °C) from the reaction quenched prior to completion supported this mechanism.

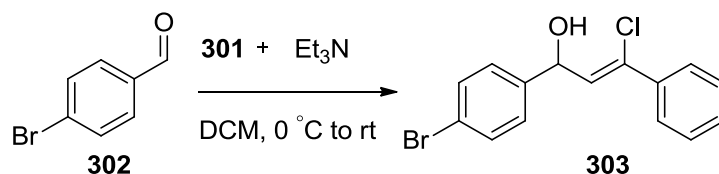
Considering the importance of the resultant multi-functionalized allylic alcohol, we decided to examine the feasibility of inhibiting the generation of carbocation from the allyloxyboron halide intermediate and thereby develop an efficient route to stereodefined haloallylic alcohols. It is well-known that the reaction of terminal alkynes with one equivalent of boron trichloride generates the stereodefined (Z)-2-chloro-1-alkenylboron dichloride, **301**, in quantitative yields as shown in **Scheme 3-1**.¹⁴⁴



Scheme 3-1 Formation of (Z)-2-Chloro-1-alkenylboron Dichloride.

Triethylamine was used to decrease the Lewis-acidic strength (or reactivity) of **301** via complexation, meanwhile hoping the similar complexation would also increase the stability of allyloxyboron intermediate and, thus, greatly slow down the generation of a carbocation.¹⁴⁵ Procedurally, after the formation of **301**, triethylamine was added to the reaction mixture. Immediately, a white cloud was observed due to the coordination of Et₃N and the alkenylboron dichloride. Even though the exact mechanism of the reaction is not clear, the results in **Table 3-1** clearly indicate that addition of triethylamine does favor the formation of the desired (Z)-3-chloroallylic alcohol.

Table 3-1 Efficiency of Addition of Triethylamine in Controlling (Z)- 3-Chloroallylic Alcohol Formation.^a



Entry	Et ₃ N (equiv).	Aldehyde 2 (equiv)	Product	Yield (%)
1	0.50	1.50	303	41
2	0.50	2.00	-	-
3	0.50	1.50	303	53
4	0.75	2.00	303	22
5	1.00	1.50	303	51
6	1.50	1.50	-	-

^a Certain amount of Triethylamine was added to **301**. The resulted reaction mixture then was added dropwise at 0 °C to 1.3 equivalents of aldehyde in 2 mL DCM (see Experimental for details).

^b Isolated yield based on phenylacetylene.

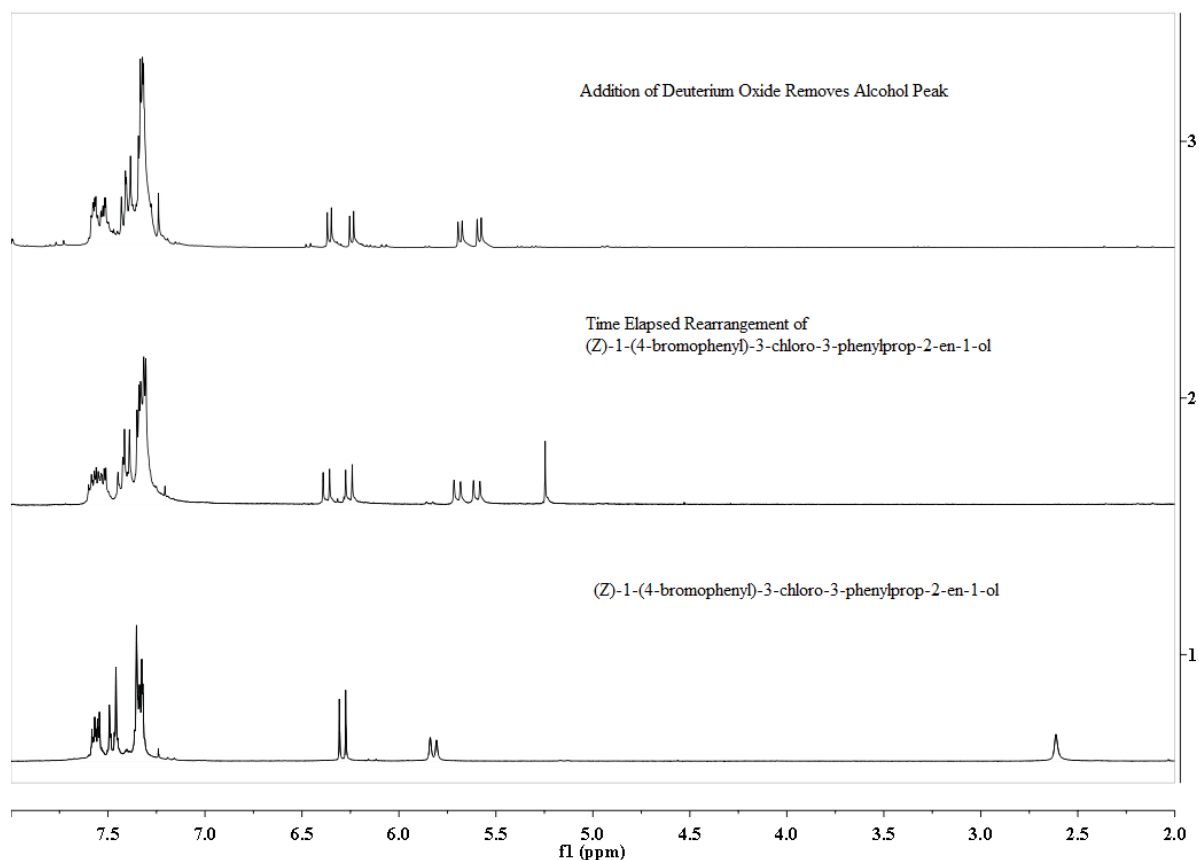
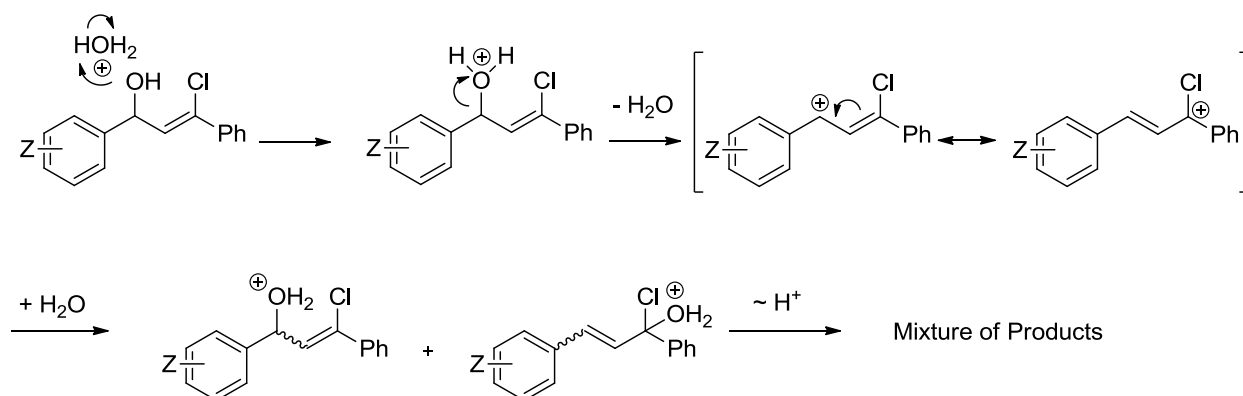


Figure 3-1 Time Elapsed Rearrangement of (Z) -1-(4-bromophenyl)-3-chloro-3-phenylprop-2-en-1-ol; Spectrum 1 is of the isolated (Z) -1-(4-bromophenyl)-3-chloro-3-phenylprop-2-en-1-ol, Spectrum 2 is the spectrum of the rearranged, and Spectrum 3 is the spectrum of the rearranged product after addition of deuterium oxide.

Isolation difficulties lead to yield discrepancies when comparing entries of **Table 3-1**. It was discovered that addition of 1% triethylamine to the eluent (5 hexanes : 1 ethyl acetate) facilitates isolation of the alcohol. However, once compound **303** was isolated it rearranged as evident by a comparison of ^1H NMR over time displayed in **Figure 3-1**.

An acid catalyzed mechanism for this rearrangement during isolation is proposed since the addition of triethylamine to the eluent during separation hindered the rearrangement leading to an increased yield of the intended product (**Scheme 3-2**). Proton integration support

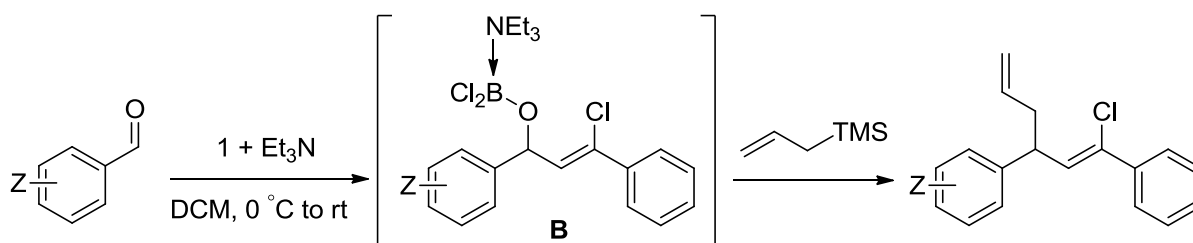
rearrangement for the isolated (Z)-3-chloroallylic alcohol rather than product degradation since the rearranged product integrates to an equivalent number of protons and also contains an alcohol (**Figure 3-1**). Unfortunately, full characterization of both the (Z)-3-chloroallylic alcohol and subsequent product from rearrangement has been hindered perhaps because of resonance stabilized carbocation formation.



Scheme 3-2 Plausible Mechanism for (Z)-3-chloroallylic Alcohol Rearrangement.

3.2.2 Allyltrimethylsilane

Allyltrimethylsilane has been successfully used as a carbocation scavenger.¹⁴⁶ Since the isolation of the (Z)-3-chloroallylic alcohol had proven difficult, capturing the carbocation with allyltrimethylsilane might produce the allylated product as shown in **Scheme 3-3**. This product would be less susceptible to acid-catalyzed carbocation formation during separation.



Scheme 3-3 Allylation of Alkenylboroloxo Dichloride Amine Intermediate.

Initially, the alkenylboron dichloride, **301**, was added to a cooled solution of aryl aldehyde and allyltrimethylsilane. This procedure resulted in the predominant formation of the haloallylated product. As a result, triethylamine was added to **301** and this solution was added dropwise to the aryl aldehyde and allowed to form intermediate **B** shown in **Scheme 3-3**. At that time, allyltrimethylsilane was added to the reaction. A mixture of products was detected by both NMR and GC-MS. The homoallylic alcohol was detected as the major product but other products included the haloallylated product, the dialkenylated product, and the desired allylated compound in miniscule amounts. Further investigations are underway.

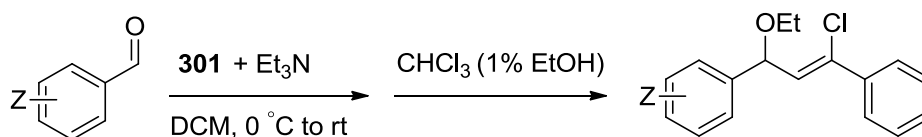
3.2.3 (Z)-3-Chloroallylic Ethers

The discovery of (Z)-3-chloroallylic ethers occurred during attempts to isolate the (Z)-3-chloroallylic alcohols using chloroform as an eluent for silica gel chromatography. NMR analysis of the isolated products revealed the characteristic splitting pattern for the (Z)-3-chloroallylic alcohol in addition to the presence of an ethyl group. At first, it was thought that residual triethylamine had co-eluted and not efficiently removed. The sample was placed under high vacuum but the ethyl group remained, as evident by NMR analysis.

IR analysis of the sample (**304d**, **Table 3-2**) validated the absence of an alcohol and confirmed the presence of an ethyl ether. After reading the literature, it was determined that trace amounts of ethanol used to stabilize the chloroform were reacting with the alkenylboroloxo dichloride amine intermediate **B** (**Scheme 3-3**) and capturing the resultant carbocation. The

addition of ethanol to products during the tosylation of alcohols had been documented and occurred as a result of using chloroform stabilized with ethanol.¹⁴⁷

Table 3-2 Generation of (*Z*)-3-chloroallylic Ethers.^a



Entry	Z	Time / hour	Product	Yield ^b (%)	Z : E ratio ^c
1	H	3	304a	77	99 : 1
2	4-Me	5	304b	49	99 : 1
3	4-Cl	3	304c	50	96 : 4
4	4-Br	9	304d	63	99 : 1
5	4-NO ₂	3	304e	37	98 : 2
6	3-Cl	4	304f	50	99 : 1
7	3-Br	11	304g	66	98 : 2
8	2-Br	12	304h	-	

^a 0.9 equivalent of triethylamine added to **301**. Then this solution is added dropwise at 0 °C to 1.3 equivalents of aldehyde in 2 mL DCM. After two hours at 0 °C, 25 mL of CHCl₃ (1% EtOH) is added at room temperature (see Experimental for details).

^b Isolated yield based on phenyl acetylene.

^c Determined by ¹H NMR spectroscopy.

Since the (*Z*)-3-chloroallylic ethers were stable when compared to the allylic alcohols, the procedure was modified to generate the ethyl ether products. After formation of **B**, chloroform with 1% ethanol was added and allowed to react, resulting in the formation of (*Z*)-3-chloroallylic

ethers. The products were easily isolated using silica gel chromatography using chloroform as an eluent and the results are presented in **Table 3-2**.

Based on the results provided in **Table 3-2**, the reaction is stereoselective for the formation of (*Z*)-3-chloroallylic ethers and tolerant of a variety of functional groups. Problems associated with the isolation of (*Z*)-3-chloroallylic alcohols are eliminated as a result of the conversion. *Ortho*-substituted aryl rings appear to sterically inhibit the reaction (entry 8 in **Table 3-2**).

3.3 Conclusions

In conclusion, a stereoselective formation of (*Z*)-3-chloroallylic ethers has been developed using the reaction of alkenylboron dichlorides with aryl aldehydes. Triethylamine was found to greatly slow down the dialkenylation of the aryl aldehyde. Reaction conditions are mild and the reagents are readily available. The application of this reaction to include other nucleophiles is of genuine interest, especially in the context of [2,3]-Wittig rearrangements of allylic ethers. The ability to increase the organic functionality of the vinyl chloride enhances this new route to (*Z*)-3-chloroallylic ethers.

3.4 Experimental

3.4.1 General Methods

All reagents were used as received. Column chromatography was performed using silica gel (60 Å, 230–400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical thin-layer chromatography was performed using 250 µm silica plates (Analtech, Inc., Newark, DE).

^1H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, respectively. Chemical shifts for ^1H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. Atlantic Microlab, Inc., Norcross, Georgia, performed microanalysis.

Gas Chromatography-Mass Spectroscopy studies were run on Hewlett Packard: HP 6890 series GC System with 5973 Mass Selective Detector; Column: Agilent 19091S-433E, 30.0mm X 0.25mm X 0.25 μm ; Gas (He) flow rate: 0.8 mL/min; Initial temperature; 50 $^{\circ}\text{C}$ (hold 1 min); Ramp temperature rate: 7 $^{\circ}\text{C}/\text{min}$ to maximum 280 $^{\circ}\text{C}$.

3.4.2 Typical Reaction Procedure for (Z)-3-Chloroallylic Alcohol

Phenylacetylene (1.50 mmol, 153 mg) and dry dichloromethane (10 mL) are placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a magnetic stirring bar. The solution is cooled to 0 $^{\circ}\text{C}$, and boron trichloride (1.65 mmol, 1.65 mL of a 1.00 M CH_2Cl_2) is added *via* syringe. After completion of the addition, the ice-bath is removed and the resulting solution is allowed to warm to room temperature for one hour. Triethylamine (1.35 mmol, 188 μL) is added to the solution and allowed to stir for an additional thirty minutes. In a separate flask, the aryl aldehyde (1.95 mmol) in dry dichloromethane (2 mL) is cooled to 0 $^{\circ}\text{C}$. The first solution is then added dropwise to the aldehyde *via* syringe and allowed to react for two hours. Once the solution has warmed to room temperature, the reaction mixture is hydrolyzed with water and extracted into dichloromethane. The organic layer is washed three times with a saturated solution of aqueous sodium bicarbonate, once with brine, then separated, and dried over anhydrous MgSO_4 . The solvents are removed *in vacuo* and the product purified by silica gel column chromatography using hexanes : ethyl acetate : triethylamine = 5:1:0.01.

3.4.3 Typical Reaction Procedure for (Z)-3-Chloroallylic Ether

Phenylacetylene (1.50 mmol, 153 mg) and dry dichloromethane (10 mL) are placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a magnetic stirring bar. The solution is cooled to 0 °C, and boron trichloride (1.65 mmol, 1.65 mL of a 1.00 M CH₂Cl₂) is added *via* syringe. After completion of the addition, the ice-bath is removed and the resulting solution is allowed to warm to room temperature for one hour. Triethylamine (1.35 mmol, 188 µL) is added to the solution and allowed to stir for an additional thirty minutes. In a separate flask, the aryl aldehyde (1.95 mmol) in dry dichloromethane (2 mL) is cooled to 0 °C. The first solution is then added dropwise to the aldehyde *via* syringe and allowed to react two hours. Once the solution has warmed to room temperature, 25 mL of chloroform stabilized with 1% ethanol is added to the reaction and the reaction allowed to proceed to completion. The solvents are removed *in vacuo* and the product purified by silica gel column chromatography using chloroform as an eluent.

3.4.4 Characterization of Compounds (Representative NMR spectra in Appendix C)

(Z)-1-(4-Bromophenyl)-3-chloro-3-phenylprop-2-en-1-ol (303): ¹H NMR (250 MHz, CDCl₃): δ 7.59 – 7.53 (m, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.30 (m, 5H), 6.29 (d, *J* = 8.1 Hz, 1H), 5.82 (d, *J* = 8.1 Hz, 1H), 2.61 (s, 1H). ¹³C NMR (63 MHz, CDCl₃): δ 141.0, 136.9, 134.4, 131.7, 129.2, 128.7, 128.4, 127.7, 126.6, 121.7, 71.1. HRMS-ESI⁺ (*m/z*): [M - OH]⁺ calcd for C₁₅H₁₂BrClO, 306.970; found, 306.971.

(Z)-(1-Chloro-3-ethoxyprop-1-ene-1,3-diyl)dibenzene (304a): ¹H NMR (250 MHz, CDCl₃): δ

7.60 – 7.51 (m, 2H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.29 (ddd, $J = 9.4, 7.2, 4.8$ Hz, 6H), 6.31 (d, $J = 8.3$ Hz, 1H), 5.49 (d, $J = 8.3$ Hz, 1H), 3.69 – 3.46 (m, 2H), 1.25 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (63 MHz, CDCl_3): δ 140.9, 137.3, 134.3, 129.0, 128.6, 128.6, 128.3, 127.8, 126.6, 78.9, 64.2, 15.4. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{ClO}$: C, 74.86; H, 6.28. Found: C, 74.87; H, 6.10.

(Z)-1-(3-Chloro-1-ethoxy-3-phenylallyl)-4-methylbenzene (304b): ^1H NMR (250 MHz, CDCl_3): δ 7.57 (dd, $J = 7.5, 2.3$ Hz, 2H), 7.38 – 7.26 (m, 5H), 7.16 (d, $J = 8.1$ Hz, 2H), 6.32 (d, $J = 8.3$ Hz, 1H), 5.44 (d, $J = 8.3$ Hz, 1H), 3.68 – 3.45 (m, 2H), 2.33 (s, 3H), 1.25 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (63 MHz, CDCl_3): δ 137.8, 137.5, 137.4, 133.9, 129.2, 128.9, 128.7, 128.3, 126.6, 126.5, 78.7, 64.0, 21.2, 15.4. Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{ClO}$: C, 74.38; H, 6.68. Found: C, 75.67; H, 6.65.

(Z)-1-Chloro-4-(3-chloro-1-ethoxy-3-phenylallyl)benzene (304c): ^1H NMR (250 MHz, CDCl_3): δ 7.61 – 7.53 (m, 2H), 7.42 – 7.30 (m, 7H), 6.26 (d, $J = 8.3$ Hz, 1H), 5.45 (d, $J = 8.2$ Hz, 1H), 3.70 – 3.45 (m, 2H), 1.26 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (63 MHz, CDCl_3): δ 139.3, 137.1, 134.6, 133.4, 129.0, 128.7, 128.3, 128.1, 127.9, 126.5, 78.1, 64.2, 15.3. HRMS-ESI $^+$ (m/z): $[\text{M} - \text{OEt}]^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{O}$, 261.023; found, 261.023.

(Z)-1-Bromo-4-(3-chloro-1-ethoxy-3-phenylallyl)benzene (304d): ^1H NMR (250 MHz, CDCl_3): δ 7.60 – 7.54 (m, 2H), 7.50 – 7.45 (m, 2H), 7.33 (ddd, $J = 6.1, 4.4, 2.1$ Hz, 5H), 6.25 (d, $J = 8.3$ Hz, 1H), 5.44 (d, $J = 8.2$ Hz, 1H), 3.57 (m, 2H), 1.26 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (63 MHz, CDCl_3): δ 139.9, 137.0, 134.6, 131.6, 129.1, 128.3, 128.2, 128.0, 126.5, 121.6, 78.2, 64.2, 15.3.

IR (cm^{-1}): 3058, 2974, 2918, 2872, 2849, 1633, 1591, 1486, 1445, 1397, 1330, 1244, 1220, 1134, 1105, 1086, 1073, 1011, 914, 866, 823, 759, 718, 692, 570, 514. $[\text{M} - \text{OEt}]^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{BrClO}$, 304.973; found, 304.972.

(Z)-1-(3-Chloro-1-ethoxy-3-phenylallyl)-4-nitrobenzene (304e): ^1H NMR (250 MHz, CDCl_3): δ 8.21 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.9 Hz, 2H), 7.58 (dd, J = 6.8, 3.0 Hz, 2H), 7.37 – 7.32 (m, 3H), 6.21 (d, J = 8.3 Hz, 1H), 5.59 (d, J = 8.3 Hz, 1H), 3.77 – 3.48 (m, 2H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C NMR (63 MHz, CDCl_3): δ 148.2, 147.4, 136.7, 135.7, 129.3, 128.4, 127.1, 126.5, 123.8, 77.9, 64.6, 15.3. HRMS-ESI $^+$ (m/z): $[\text{M} - \text{OEt}]^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{ClNO}_3$, 272.048; found, 272.047.

(Z)-1-Chloro-3-(3-chloro-1-ethoxy-3-phenylallyl)benzene (304f): ^1H NMR (250 MHz, CDCl_3): δ 7.57 (dd, J = 6.6, 3.1 Hz, 2H), 7.47 (s, 1H), 7.35 – 7.24 (m, 6H), 6.25 (d, J = 8.3 Hz, 1H), 5.46 (d, J = 8.3 Hz, 1H), 3.58 (tdd, J = 9.2, 7.0, 2.2 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H). ^{13}C NMR (63 MHz, CDCl_3): δ 142.9, 137.0, 134.9, 134.5, 129.8, 129.1, 128.3, 127.9, 126.6, 126.6, 124.7, 78.1, 64.3, 15.3. Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{O}$: C, 66.46; H, 5.25. Found: C, 66.34; H, 5.13.

(Z)-1-Bromo-3-(3-chloro-1-ethoxy-3-phenylallyl)benzene (304g): ^1H NMR (250 MHz, CDCl_3): δ 7.62 – 7.57 (m, 2H), 7.43 – 7.32 (m, 6H), 7.20 (d, J = 7.8 Hz, 1H), 6.25 (d, J = 8.4 Hz, 1H), 5.45 (d, J = 8.3 Hz, 1H), 3.70 – 3.47 (m, 2H), 1.27 (t, J = 7.0 Hz, 3H). ^{13}C NMR (63 MHz, CDCl_3): δ 143.2, 137.0, 134.9, 130.8, 130.1, 129.5, 129.1, 128.3, 127.8, 126.6, 125.1, 122.7, 78.1, 64.3, 15.3. HRMS-ESI $^+$ (m/z): $[\text{M} - \text{OEt}]^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{BrClO}$, 304.973; found, 304.972.

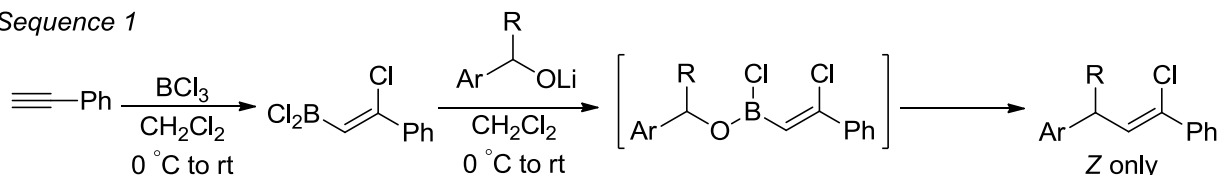
Chapter 4. Titanium(IV) Halide Mediated Coupling

of Alkoxides and Alkynes: An Efficient and Stereoselective Route to Trisubstituted (*E*)-Alkenyl Halides

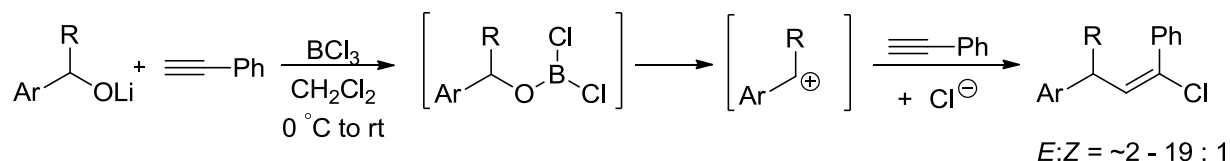
4.1 Introduction

In 2005, we reported the first transition-metal-free nucleophilic substitution of hydroxyl groups, through the corresponding alkoxides, by stereodefined haloalkenyl moieties (Sequence 1, **Scheme 4-1**).^{123, 131} The reaction involves the unprecedented C–O bond cleavage of an alkoxide in the presence of (*Z*)-halovinylboron dihalide and provides a practical route to trisubstituted (*Z*)-alkenyl halides. The stereochemistry is dependent on the formation of the (*Z*)-halovinylboron dihalide prior to addition to the alkoxide. The reaction proceeds quite well with alkoxides generated in situ from reactions of aldehydes and alkyllithium reagents which further adds versatility to the method.^{131, 148}

Sequence 1



Sequence 2



Scheme 4-1 Stereochemical Modification via Modification of Reagent Addition Sequence.

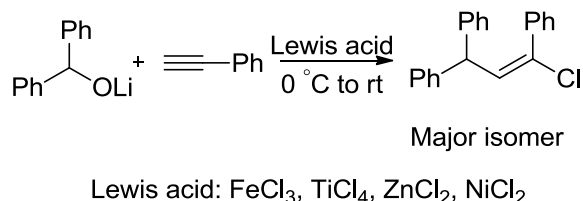
During ongoing mechanistic studies of the aldehyde-alkyne coupling reaction,¹²¹ we discovered that changing the mode of reagent addition greatly affects the stereochemistry of the product formed. It was determined that boron trihalide, when added to a mixture of alkoxide and alkyne, resulted in the coupling of alkoxides with terminal alkynes to yield trisubstituted (*E*)-alkenyl halides as the major products with moderate stereoselectivities.¹⁴⁹ In this case, we believe that carbocations are generated from alkoxides in the presence of boron trihalide and subsequently captured by the terminal alkynes (Sequence 2, **Scheme 4-1**).

4.2 Results and Discussion

Our recent study of boron tribromide-mediated aryl propargyl ether cleavage¹³⁰ suggests that the addition of boron trihalide to terminal alkynes is a very fast process. Methoxy groups (known to react with BBr₃) were found to survive the reaction conditions because of the high reactivity of BBr₃ toward the terminal alkynes. This observation led us to propose that the moderate stereoselectivity for the reaction shown in Sequence 2 (**Scheme 4-1**) resulted from a competitive reaction involving the facile formation of (*Z*)-vinylboron dihalide (giving the *Z*-isomer after coupling with the alkoxide). To minimize this undesired competitive reaction, we felt that replacement of boron trihalide with Lewis acids that do not undergo facile addition to alkynes might enhance the stereoselectivity of the overall coupling reaction. Previous studies from our group,^{71-72, 150} as well as other groups,¹⁵¹⁻¹⁵³ have demonstrated that C–O bond cleavage in alkoxide-type RC–OMX_n (M = Ti, Fe) intermediates can occur smoothly at room temperature. In 2008, Fuchter and Levy reported a one-pot method for the conversion of carbonyl electrophiles to allylic chlorides by activating the *in situ* generated magnesium alkoxides using TiCl₄.¹⁵⁴ Related work by Murai and co-workers documented successful C–S bond cleavage.¹⁵⁵⁻

¹⁵⁶ Herein, we report our preliminary results focused on the stereoselective synthesis of trisubstituted (*E*)-alkenyl halides.

The reaction of lithium diphenylmethanoxide with phenylacetylene was chosen as the model system (**Scheme 4-2**). Due to its low cost, FeCl₃ was initially used to test the feasibility of the coupling reaction.



Scheme 4-2 Lewis Acid Induced Coupling Reaction.

Several solvents were surveyed but the poor solubility of FeCl₃ led to modest yield even after twenty four hours at room temperature. Elevating the reaction temperature did increase the yield but led to decreased stereoselectivity. These results are consistent with a recent publication concerning the FeCl₃ mediated coupling of benzyl alcohols and aryl alkynes in refluxing CH₂Cl₂ which reports the formation of trisubstituted (*E*)-alkenyl halides as the major products but with only moderate stereoselectivities (*E/Z* = 8:1).¹⁵⁷ Notably, in 2008 Jana et al. reported that a FeCl₃ mediated reaction in nitromethane at 80 °C gives aryl ketones, rather than trisubstituted (*E*)-alkenyl halides.¹⁵⁸ Due to the poor solubility of FeCl₃ in organic solvents at room temperature, we decided to screen other metal halides. Fortunately, the desired reaction occurred smoothly at room temperature using TiCl₄; product **401a** was isolated in 78% yield and with excellent stereoselectivity (*E/Z* = 96:4). ZnCl₂ and NiCl₂ proved to be ineffective. The product's *E* stereochemistry was confirmed by X-ray analysis of compound **401d** shown in **Figure 4-1**.

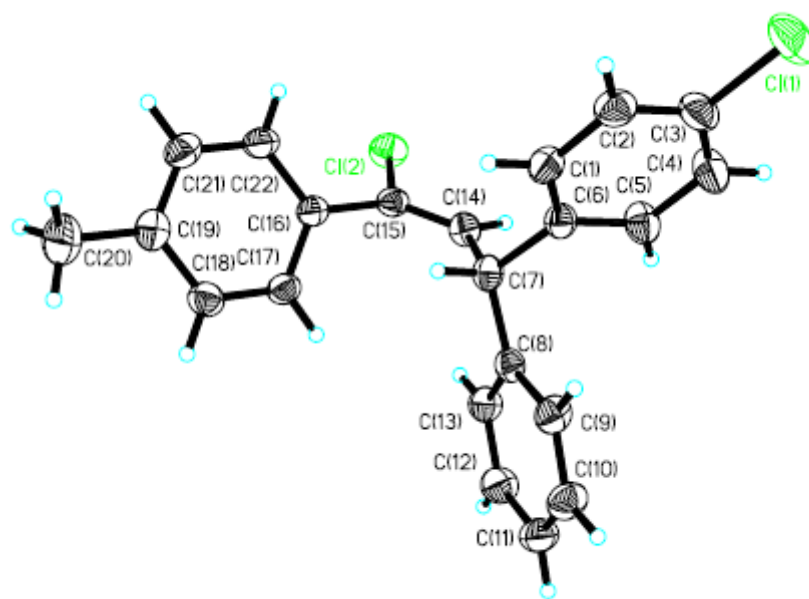
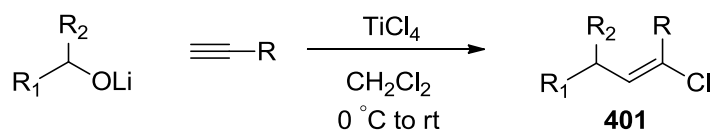


Figure 4-1 X-Ray Crystallography of **401d** (see **Appendix B** for crystal data).

To evaluate the scope and limitations of the reaction, a variety of benzylic, allylic, and propargylic alcohols were prepared and subjected to the new reaction conditions (**Table 4-1**). Several examples illustrate that ether moieties, double bonds, and triple bonds all tolerate the reaction conditions. The *E* products are produced in excellent stereochemical yields. Even lithium di(4-fluorobenzyl)methanoxide gives excellent stereoselectivity (entry 5, **Table 4-1**) using TiCl_4 . In our previous work, this reaction afforded very poor stereoselectivity (*E/Z* = 60:40) when BCl_3 was used.¹²⁶ Successful coupling using an aliphatic alkyne is notable, though the stereoselectivity is rather poor (*E/Z* = 70:30, entry 7). In recent reports,¹⁵⁷⁻¹⁵⁸ it was noted that the FeCl_3 mediated coupling reaction of benzylic alcohols with alkynes is only successful for aryl alkynes. The lower *E/Z* stereoselectivity for aliphatic alkynes is most likely due to the lack of steric bulk of the *n*-butyl group.

Table 4-1 Titanium(IV) Chloride Mediated Coupling of Alkoxides with Alkynes.^a

Entry	R ₁	R ₂	R	prod.	E:Z ^b	Yield (%) ^c
1	Ph	Ph	Ph	401a	96:4 (90:10) ^d	78 (84) ^d
2	2-MeC ₆ H ₄	Ph	Ph	401b	99:1	58
3	4-FC ₆ H ₄	4-FC ₆ H ₄	Ph	401c	98:2 (60:40) ^d	81 (80) ^d
4	4-ClC ₆ H ₄	Ph	4-MeC ₆ H ₄	401d	96:4	76
5	4-FC ₆ H ₄	4-FC ₆ H ₄	4-MeC ₆ H ₄	401e	98:2	76
6	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	Ph	401f	92:8	43
7	Ph	Ph	<i>n</i> -Bu	401g	70:30	62
8	(<i>E</i>)-PhCH=CH	Ph	Ph	401h	99:1	68
9	<i>n</i> -Bu—≡	4-ClC ₆ H ₄	Ph	401i	99:1	68
10	<i>n</i> -Bu—≡	4-MeC ₆ H ₄	Ph	401j	99:1	67
11	Ph—≡	Ph	Ph	401k	98:2	75
12	Ph—≡	<i>n</i> -Pr	Ph	401l	96:4	71

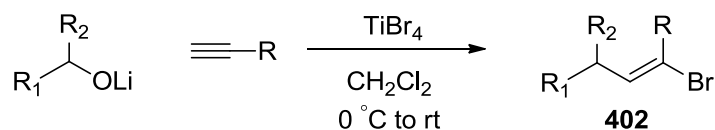
^a Reaction carried out at 0 °C for 10 min, then maintained at room temperature (see experimental section for details).

^b E:Z ratio determined by NMR.

^c Isolated yield based on alcohol.

^d E:Z stereoselectivity and yield using BCl₃ instead of TiCl₄.

Because of the synthetic potential of alkenyl bromides in transition metal catalyzed coupling reactions, we examined the use of TiBr₄ (**Table 4-2**). Again, the reaction proceeds readily at room temperature and good yields are obtained. We then examined the reactions of *in situ* generated lithium propargyloxides (from aryl aldehydes and lithium acetylide) with phenylacetylene (entries 4 and 5). High stereoselectivity and good yields were obtained in both cases.

Table 4-2 Titanium(IV) Bromide Mediated Coupling of Alkoxides with Alkynes.^a

Entry	R ₁	R ₂	R	prod.	E:Z ^b	Yield (%) ^c
1	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	4-MeC ₆ H ₄	402a	96:4	59
2	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	Ph	402b	96:4	64
3	Ph	Ph	4-MeC ₆ H ₄	402c	98:2	79
4 ^d	Ph—≡	Ph	Ph	402d	99:1	74
5 ^d	<i>n</i> -Bu—≡	Ph	Ph	402e	99:1	76
6	<i>n</i> -Bu—≡	Ph	4-MeC ₆ H ₄	402f	99:1	66
7	<i>n</i> -Bu—≡	4-ClC ₆ H ₄	Ph	402g	98:2	66

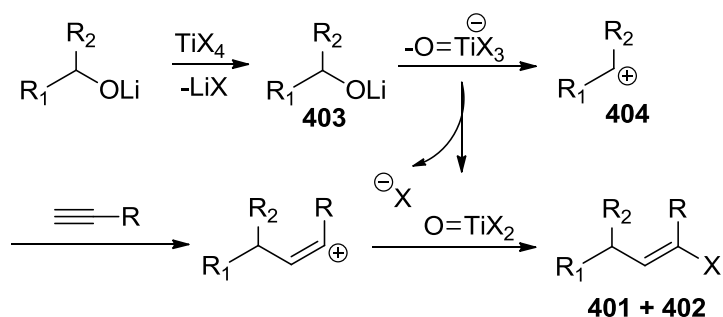
^a Reaction carried out at 0 °C for 10 min, then maintained at room temperature (see experimental for details).

^b E:Z ratio determined by NMR.

^c Isolated yield based on alcohol used.

^d Lithium alkoxide generated *in situ* from the reaction of benzaldehyde and lithium acetylide.

In view of the previously reported results^{121, 149} along with the dark purple color of reaction mixture, we postulate that the reactions proceed through a carbocation mechanism (**Scheme 4-3**). The reaction of the lithium alkoxide with TiX₄ first forms the intermediate R₁R₂CHO–TiCl₃. Carbocation **404** is then generated from either intermediate R₁R₂CHO–TiCl₃ or an oxonium ion intermediate [R₁R₂CHO–(TiCl₄)TiCl₃].^{128, 159-161} At present, there is insufficient data available to distinguish between these two pathways. Capture of carbocation **404** by the alkyne affords final product **401** or **402**. The carbocation nature of the reaction is supported by compounds **401** and **402** possessing the same stereochemistry as compounds that were obtained in a previously reported reaction of benzylic carbocations with alkynes.¹⁶²



Scheme 4-3 Proposed Reaction Mechanism.

4.3 Conclusions

In summary, a method for preparing trisubstituted (*E*)-alkenyl halide derivatives with high stereoselectivity is described. Both trisubstituted (*E*)-alkenyl halide and (*Z*)-alkenyl halide derivatives can now be prepared from readily available alkoxides and acetylenes. The feasibility of generating carbocations from alkoxides under Brønsted acid-free reaction conditions was further confirmed. Application of this new synthetic method is currently underway.

4.4 Experimental

4.4.1 General Methods

All glassware was dried in an oven at 120 °C and flushed with dry argon. All reactions were carried out under an argon atmosphere. CH₂Cl₂ was distilled over CaH₂. All alcohols and alkynes were purchased from commercial sources and used as received or synthesized following literature procedures. Titanium(IV) chloride and titanium(IV) bromide were diluted to 1.0 M in CH₂Cl₂. Products were purified by flash chromatography using silica gel (60 D, 230-400 mesh). ¹H NMR and ¹³C NMR were recorded in CDCl₃ at 250 MHz or 300 MHz with chemical shifts reported relative to TMS.

An APEX II CCD detector, radiation safety enclosure system, and a SMART APEX II 3-axis system incorporating a fixed-chi stage with a chi angle of approximately 54°, a phi drive with 360° rotation, and a freely rotating omega, with a Mo radiation source were used in the detection of X-Ray crystal data. SHELXTL based refinement software was used for analysis.

4.4.2 Representative Procedure for the Synthesis of (E)-Alkenyl Chlorides

(401a-l)

Diphenylmethanol (276 mg, 1.50 mmol) and dichloromethane (15 mL) were placed in a dry, argon-flushed, 100 mL round-bottomed flask equipped with a magnetic stirring bar. The solution was cooled to 0 °C in an ice bath and *n*-butyllithium (1.0 mL, 1.6 mmol of a 1.0 *M* hexanes solution) was added *via* syringe. The solution was allowed to stir for 10 minutes at 0 °C and then for 30 minutes at room temperature. Phenylacetylene (0.16 mL, 1.5 mmol) was added *via* syringe, followed by titanium(IV) chloride (1.65 mL g, 1.65 mmol of a 1.0 *M* dichloromethane solution). The reaction solution gradually turned dark purple and was allowed to react overnight. The resulting mixture was hydrolyzed with water (15 mL) and extracted into dichloromethane (3 x 15 mL). The organic layer was separated and dried over anhydrous MgSO₄. Product **401a** (356 mg, *E/Z* (96:4), 78% yield) was isolated by flash column chromatography using hexanes as eluent.

4.4.3 Representative procedure for the syntheses of (E)-Alkenyl Bromides (402a-g)

Bis(4-methoxyphenyl)methanol (0.37 g, 1.5 mmol) and dichloromethane (15 mL) were placed in a dry, argon-flushed, 100 mL round-bottomed flask equipped with a magnetic stirring bar. The solution was cooled to 0 °C in an ice bath and *n*-butyllithium (1.0 mL, 1.6 mmol of a 1.0 M hexane solution) was added *via* syringe. The solution was allowed to stir for 10 minutes at 0 °C and then for 30 minutes at room temperature. (Note: for **402d** and **402e**, lithium alkoxides were generated *in situ* from the reaction of benzaldehyde with lithium acetylide³). 1-Ethynyl-4-methylbenzene (0.19 mL, 1.5 mmol) was added *via* syringe, followed by titanium(IV) bromide (1.65 mL, 1.65 mmol of a 1.0 M dichloromethane solution). The reaction solution gradually turned dark purple and was allowed to react overnight. The resulting mixture was hydrolyzed with water (15 mL) and extracted with dichloromethane (3 x 15 mL). The organic layer was separated and dried over anhydrous MgSO₄. Product **402a** (0.31 g, 96:4 (*E/Z*), 59% yield) was isolated by flash column chromatography, using hexanes as eluent.

4.4.4 Characterization of Compounds 401a-l and 402a-g (Representative NMR spectra in Appendix D)

(E)-1-Chloro-1,3,3-triphenylprop-1-ene (401a)¹⁶²: ¹H NMR (250 MHz, CDCl₃): δ 7.08-7.36 (m, 15H); 6.45 (d, 1H, *J* = 11.0 Hz); 4.78 (d, 1H, *J* = 11.0 Hz). ¹³C NMR (CDCl₃): δ 143.3, 136.9, 131.5, 131.4, 128.9, 128.6, 128.3, 128.1, 126.6, 50.7. Anal. Calcd. for C₂₁H₁₇Cl: C, 82.75; H, 5.62. Found: C, 82.68; H, 5.63.

(E)-1-Chloro-1,3-diphenyl-3-(o-tolyl)prop-1-ene (401b): ^1H NMR (250 MHz, CDCl_3): δ 7.05-7.30 (m, 14H); 6.41 (d, 1H, $J = 10.7$ Hz); 4.94 (d, 1H, $J = 10.7$ Hz); 1.91 (s, 3H). ^{13}C NMR (CDCl_3): δ 143.2, 141.5, 136.9, 135.9, 131.4, 131.2, 130.7, 128.8, 128.6, 128.5, 128.3, 127.9, 126.7, 126.5, 126.4, 47.5, 20.5. Anal. Calcd. for $\text{C}_{22}\text{H}_{19}\text{Cl}$: C, 82.87; H, 6.01. Found: C, 83.17; H, 6.13.

(E)-1-Chloro-1-phenyl-3,3-di(*p*-fluorophenyl)prop-1-ene (401c)¹²⁶: ^1H NMR (250 MHz, CDCl_3): δ 7.28-7.32 (m, 5H); 6.96-7.10 (m, 8H); 6.36 (d, 1H, $J = 9.0$ Hz); 4.74 (d, 1H, $J = 9.0$ Hz). ^{13}C NMR (CDCl_3): δ 159.9, 138.9, 136.6, 130.9, 129.6, 129.5, 129.1, 128.5, 115.7, 115.4, 49.2. Anal. Calcd. for $\text{C}_{21}\text{H}_{15}\text{ClF}_2$: C, 74.01; H, 4.44. Found: C, 74.47; H, 4.45.

(E)-1-Chloro-1-(*p*-tolyl)-3-phenyl-3-(*p*-chlorophenyl)prop-1-ene (401d): ^1H NMR (250 MHz, CDCl_3): δ 7.00-7.30 (m, 13H); 6.35 (d, 1H, $J = 10.7$ Hz); 4.75 (d, 1H, $J = 10.7$ Hz); 2.33 (s, 3H). ^{13}C NMR (CDCl_3): δ 142.9, 141.9, 138.9, 133.8, 132.4, 130.4, 129.4, 129.1, 128.7, 128.4, 128.0, 126.8, 50.1, 21.3. Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{Cl}_2$: C, 74.79; H, 5.14. Found: C, 74.66; H, 5.32. Confirmed by X-ray diffraction, refer to **Appendix B**. The crystals were developed at 4 °C for several days from a solution of hexanes.

(E)-1-Chloro-1-(*p*-tolyl)-3,3-di(*p*-fluorophenyl)prop-1-ene (401e)¹³¹: ^1H NMR (250 MHz, CDCl_3): δ 6.94-7.24 (m, 12H); 6.31 (d, 1H, $J = 9.0$ Hz); 4.74 (d, 1H, $J = 9.0$ Hz); 2.35 (s, 3H). ^{13}C NMR (CDCl_3): δ 159.9, 139.1, 138.9, 133.7, 132.1, 130.5, 129.5, 129.1, 128.4, 115.6, 49.2, 21.3.

(E)-1-Chloro-1-phenyl-3,3-di(*p*-methoxyphenyl)prop-1-ene (401f)¹³¹: ^1H NMR (250 MHz, CDCl_3): δ 7.28-7.37 (m, 5H); 7.00-7.05 (m, 4H); 6.79-6.85 (m, 4H); 6.39 (d, 1H, $J = 11.0$ Hz); 4.68 (d, 1H, $J = 11.0$ Hz); 3.74 (s, 6H). ^{13}C NMR (CDCl_3): δ 158.2, 135.7, 131.9, 129.6, 128.7, 128.6, 128.3, 128.0, 126.6, 113.9, 55.1, 49.0.

(E)-1-Chloro-1-(n-butyl)-3,3-diphenylprop-1-ene (401g)¹⁶²: ¹H NMR (250 MHz, CDCl₃): δ 7.02- 7.32 (m, 20H); 6.09 (d, 1H, *J* = 10.2 Hz); 5.96 (d, 1H, *J* = 9.4 Hz); 5.22 (d, 1H, *J* = 9.4 Hz); 4.86 (d, 1H, *J* = 10.1 Hz); 2.36-2.47 (m, 4H); 1.47-1.62 (m, 4H); 1.10-1.41 (m, 4H); 0.80-0.98 (m, 6H). ¹³C NMR (CDCl₃): δ 143.5, 135.5, 129.9, 128.5, 128.2, 126.5, 126.3, 49.8, 39.3, 33.7, 29.4, 21.9, 13.9.

(E,E)-1-Chloro-1,3,5-triphenyl-1,4-pentadiene (401h): ¹H NMR (250 MHz, CDCl₃): δ 7.12-7.45 (m, 15H); 6.20-6.47 (m, 3H); 4.29-4.35 (m, 1H). ¹³C NMR (CDCl₃): δ 142.2, 136.9, 131.6, 131.2, 130.7, 128.8, 128.7, 128.5, 128.3, 127.6, 127.5, 126.8, 126.3, 48.4. Anal. Calcd For C₂₃H₁₉Cl: C, 83.50; H, 5.79. Found: C, 83.61; H, 5.97.

(E)-1-Chloro-1-phenyl-3-(p-chlorophenyl)non-1-en-4-yne (401i): ¹H NMR (250 MHz, CDCl₃): δ 7.19-7.52 (m, 9H); 5.97 (d, 1H, *J* = 10.4 Hz); 4.41 (d, 1H, *J* = 10.4 Hz); 2.23-2.30 (m, 2H); 1.39-1.57 (m, 4H); 0.90-0.96 (m, 3H). ¹³C NMR (CDCl₃): δ 138.6, 136.4, 132.6, 131.9, 129.4, 129.1, 128.7, 128.6, 128.5, 85.2, 78.3, 36.9, 30.9, 21.9, 18.6, 13.6. Anal. Calcd. for C₂₁H₂₀Cl₂: C, 73.47; H, 5.88. Found: C, 73.88; H, 6.02.

(E)-1-Chloro-1-phenyl-3-(p-tolyl)non-1-en-4-yne (401j)¹²²: ¹H NMR (250 MHz, CDCl₃): δ 7.09-7.54 (m, 9H); 6.01 (d, 1H, *J* = 10.5 Hz); 4.39 (d, 1H, *J* = 10.5 Hz); 2.31 (s, 3H); 2.21-2.35 (m, 2H); 1.32-1.59 (m, 4H); 0.88-0.96 (m, 3H). ¹³C NMR (CDCl₃): δ 137.2, 136.6, 131.3, 130.1, 129.4, 129.2, 128.9, 128.8, 128.4, 128.2, 127.1, 84.5, 79.0, 37.1, 30.9, 21.9, 20.9, 18.6

(E)-1-Chloro-1,3,5-triphenylpenta-1-en-4-yne (401k): ¹H NMR (250 MHz, CDCl₃): δ 7.15-7.54 (m, 15H); 6.09 (d, 1H, *J* = 10.4 Hz); 4.65 (d, 1H, *J* = 10.4 Hz). ¹³C NMR (CDCl₃): δ 137.9, 136.3, 133.1, 132.8, 131.7, 129.2, 128.8, 128.6, 128.3, 126.5, 122.9, 87.8, 84.8, 37.4. Anal. Calcd. for C₂₃H₁₇Cl: C, 84.01; H, 5.22. Found: C, 84.12; H, 4.87.

(E)-1-Chloro-1,5-diphenyl-3-(n-propyl)penta-1-en-4-yne (401l)¹²²: ¹H NMR (250 MHz, CDCl₃): δ 7.27-7.50 (m, 10H); 5.95 (d, 1H, *J* = 10.4 Hz); 3.33 (dt, 1H, *J* = 10.4 Hz); 1.37-1.65 (m, 4H); 0.82-0.88 (m, 3H). ¹³C NMR (CDCl₃): δ 131.9, 131.6, 129.7, 128.8, 128.7, 128.3, 128.2, 127.8, 126.6, 123.5, 90.3, 82.3, 37.9, 32.4, 20.1, 13.7.

(E)-1-Bromo-1-(p-tolyl)-3,3-di(p-methoxyphenyl)prop-1-ene (402a)¹³¹: ¹H NMR (250 MHz, CDCl₃): δ 7.23 (d, 2H, *J* = 8.2 Hz); 7.13 (d, 2H, *J* = 8.0 Hz); 7.02 (d, 4H, *J* = 8.5 Hz); 6.82 (d, 4H, *J* = 8.5 Hz); 6.58 (d, 1H, *J* = 10.7 Hz); 4.62 (d, 1H, *J* = 10.7 Hz); 3.76 (s, 6H); 2.34 (s, 3H). ¹³C NMR (CDCl₃): δ 158.2, 138.6, 135.7, 135.5, 129.1, 128.9, 128.6, 127.6, 120.9, 113.9, 55.2, 50.0, 21.3. HRMS. for C₂₄H₂₄BrO₂ (M+1 peak): 423.0786. Found: 423.0806.

(E)-1-Bromo-1-phenyl-3,3-di(p-methoxyphenyl)prop-1-ene (402b): ¹H NMR (250 MHz, CDCl₃): δ 7.32 (s, 5H); 7.02 (d, 4H, *J* = 8.6 Hz); 6.82 (d, 4H, *J* = 8.9 Hz); 6.61 (d, 1H, *J* = 11.0 Hz); 4.62 (d, 1H, *J* = 11.0 Hz); 3.75 (s, 6H). ¹³C NMR (CDCl₃): δ 158.2, 136.0, 135.4, 129.2, 128.7, 128.5, 128.2, 127.7, 120.6, 113.9, 55.2, 49.9. HRMS. for C₂₃H₂₂BrO₂ (M+1 peak): 409.0629. Found: 409.0643.

(E)-1-Bromo-1-(p-tolyl)-3,3-diphenylprop-1-ene (402c)¹³¹: ¹H NMR (250 MHz, CDCl₃): δ 7.08-7.27 (m, 14H); 6.65 (d, 1H, *J* = 11.0 Hz); 4.73 (d, 1H, *J* = 11.0 Hz); 2.30 (s, 3H). ¹³C NMR (CDCl₃): δ 143.0, 138.7, 135.4, 135.1, 128.9, 128.6, 128.5, 128.3, 128.1, 126.5, 121.5, 51.6, 21.3.

(E)-1-Bromo-1,3,5-triphenylpenta-1-en-4-yne (402d)¹³¹: ¹H NMR (250 MHz, CDCl₃): δ 7.21-7.53 (m, 15H); 6.37 (d, 1H, *J* = 10.3 Hz); 4.62 (d, 1H, *J* = 10.3 Hz). ¹³C NMR (CDCl₃): δ 139.2, 137.9, 132.9, 131.7, 129.0, 128.9, 128.7, 128.5, 128.3, 128.2, 127.3, 123.1, 122.0, 88.0, 84.5, 38.9.

(E)-1-Bromo-1,3-diphenylnon-1-en-4-yne (402e)¹²²: ¹H NMR (250 MHz, CDCl₃): δ 7.17-7.50 (m, 10H); 6.26 (d, 1H, J = 10.4 Hz); 4.37 (d, 1H, J = 10.4 Hz); 2.23-2.28 (m, 2H); 1.36-1.59 (m, 4H); 0.89-0.95 (m, 3H). ¹³C NMR (CDCl₃): δ 139.8, 137.9, 133.8, 128.9, 128.5, 128.4, 127.2, 126.9, 121.2, 84.9, 78.5, 38.4, 30.9, 21.9, 18.6, 13.6.

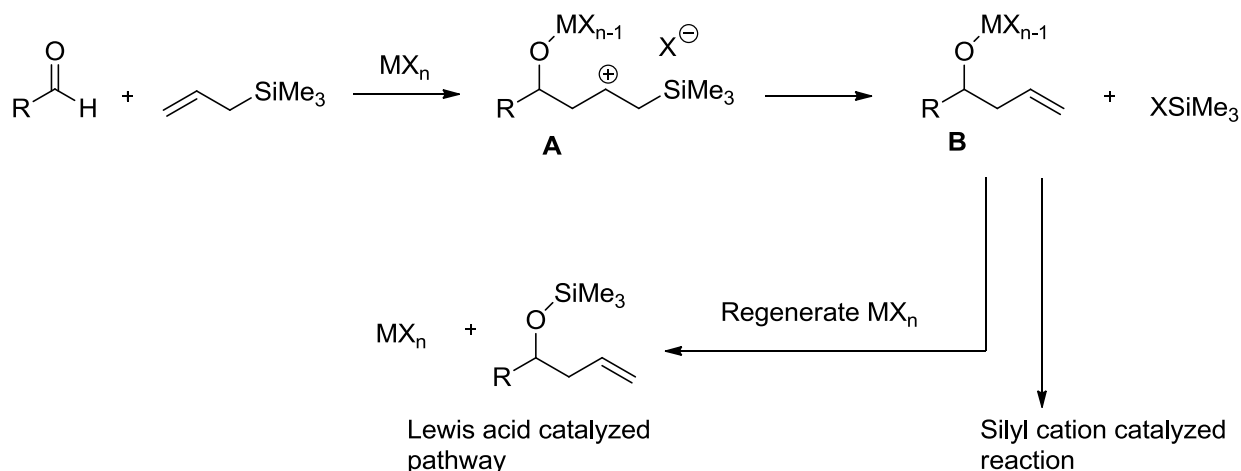
(E)-1-Bromo-1-(p-tolyl)-3-phenylnon-1-en-4-yne (402f): ¹H NMR (250 MHz, CDCl₃): δ 7.13-7.40 (m, 9H); 6.22 (d, 1H, J = 10.3 Hz); 4.39 (d, 1H, J = 10.3 Hz); 2.34 (s, 3H); 2.22-2.30 (m, 2H); 1.38-1.58 (m, 4H); 0.89-0.95 (m, 3H). ¹³C NMR (CDCl₃): δ 139.9, 138.8, 135.1, 133.5, 129.0, 128.8, 128.5, 127.2, 126.9, 121.5, 84.8, 78.6, 38.4, 30.9, 21.9, 21.2, 18.6, 13.6. Anal. Calcd. for C₂₂H₂₃Br: C, 71.94; H, 6.31. Found: C, 72.08; H, 6.45.

(E)-1-Bromo-1-phenyl-3-(p-chlorophenyl)non-1-en-4-yne (402g)¹²²: ¹H NMR (250 MHz, CDCl₃): δ 7.19-7.49 (m, 9H); 6.20 (d, 1H, J = 10.4 Hz); 4.33 (d, 1H, J = 10.4 Hz); 2.23-2.29 (m, 2H); 1.36-1.59 (m, 4H); 0.90-0.96 (m, 3H). ¹³C NMR (CDCl₃): δ 138.4, 137.8, 133.3, 132.8, 129.0, 128.8, 128.6, 128.5, 128.4, 121.7, 85.3, 78.1, 37.9, 30.9, 21.9, 18.6, 13.6. HRMS. for C₂₁H₂₁BrO₂ (M+1 peak): 389.0494. Found: 389.0485.

Chapter 5. Boron Trihalide Mediated Haloallylation of Aryl Aldehydes using Allylsilane Compounds

5.1 Introduction

The Lewis acid mediated allylation of carbonyl compounds leading to homoallylic alcohols constitutes one of the most important synthetic reactions.¹⁶³ Numerous allylic organometallic reagents and Lewis acids have been investigated. In recent years, asymmetric allylation reactions have also been studied extensively due to their importance in medicinal and natural product chemistry. Lewis acid mediated allylations have been shown to be stepwise processes, as shown in **Scheme 5-1**.

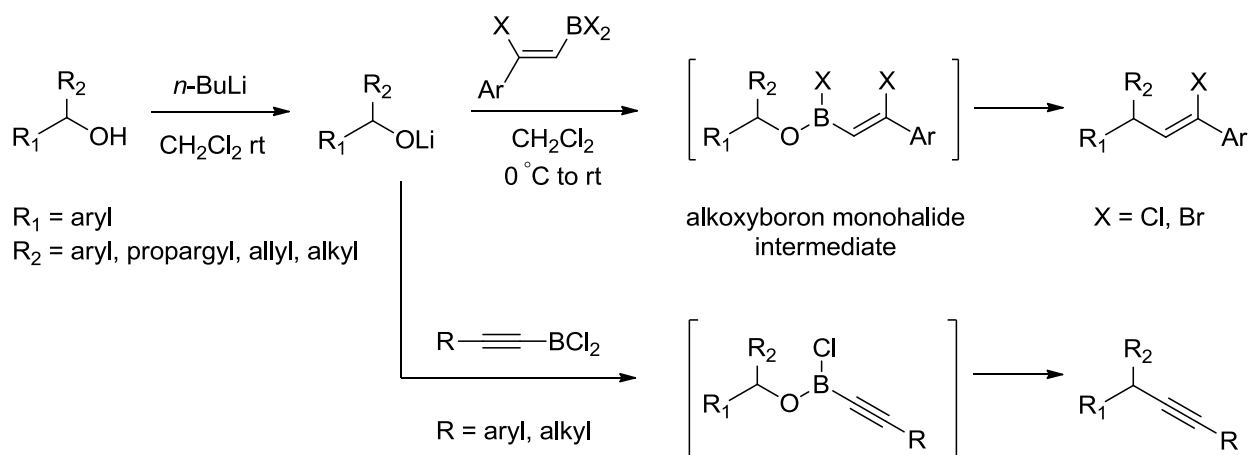


Scheme 5-1 Process of Lewis Acid Addition to Allyltrimethylsilane and an Aldehyde.

The addition of allylsilane to an activated aldehyde forms intermediate **A**. The silyl electrofuge cleavage then produces the metal homoallyloxide **B** and Me_3SiX . If the metal

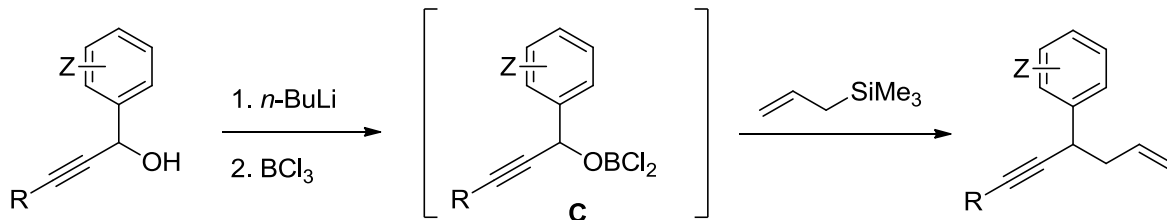
exchange between **B** and Me₃SiX occurs, Lewis acid MX_n is regenerated and the reaction is catalytic in nature. However, if the metal exchange does not occur, Me₃SiX could also induce further allylations (silyl cation catalyzed pathway). To achieve high enantioselectivity in chiral Lewis acid catalyzed allylations, minimizing the contribution from the silyl cation catalyzed pathway is required.

In the last decade, our group has developed a number of novel reactions using the chemistry of boron halide derivatives. These include, for example, the dialkenylation of aryl aldehydes by divinylboron halides,¹⁶⁴ a reaction that appears to occur *via* an unprecedented process: C—O bond cleavage in the alkoxyboron monohalide intermediate. This discovery led us to develop reactions in which the hydroxyl groups were substituted with stereodefined alkenyl^{24, 124, 165} and alkynyl¹⁶⁶ moieties using boron dihalides as represented in **Scheme 5-2**.



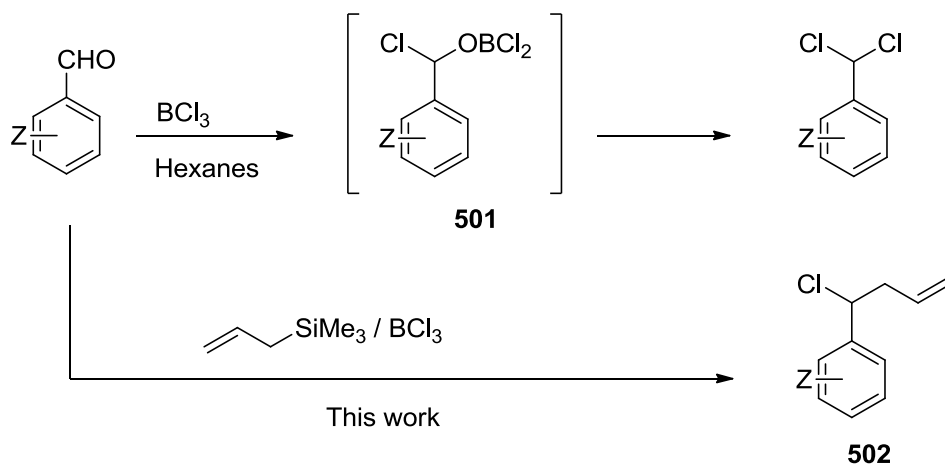
Scheme 5-2 Direct Substitution of Hydroxyl Groups with Stereodefined Alkenyl and Alkynyl Moieties using Boron Dihalides.

Very recently we found that C—O bond cleavage also occurs smoothly (**Scheme 5-3**) in propargyloxyboron dihalide **C**, an intermediate which is generated from alternative route (by reaction of alkoxide with BCl₃).¹⁴⁹⁻¹⁵⁰



Scheme 5-3 Allyltrimethylsilane Addition to a Propargyloxyboron Dihalide.

In an earlier study, we reported a novel method for dihalogenating aryl aldehydes (**Scheme 5-4**).¹⁶⁷ NMR study revealed that the reaction proceeds through the alkoxyboron dihalide intermediate **501**. The similarity between intermediates **C** and **501** led us to investigate the feasibility of capturing intermediate **501** with allyltrimethylsilane.



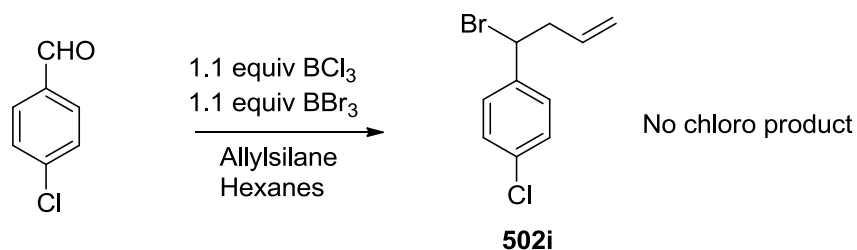
Scheme 5-4 Formation of Dichloro- and Chloroallylated Compounds from Aryl Aldehydes.

The mechanism shown in **Scheme 5-4** led us to postulate that the reaction of aryl aldehydes with allylsilane in the presence of a stoichiometric quantity of a boron halide would lead to haloallylated product **502** rather than the homoallylic alcohol. In fact, during a kinetic study of the reaction between a carbocation and allylsilane, Mayr and Gorath noted

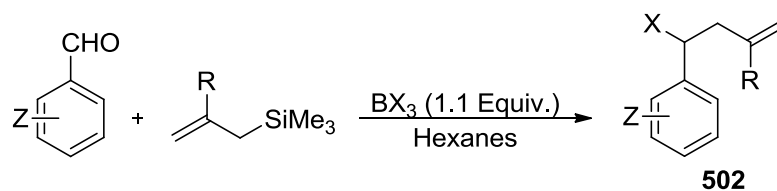
chloroallylation of aryl aldehydes in the presence of 2—4 equivalents of BCl_3 .¹⁶⁸ The sentence, “In the BCl_3 -promoted reaction of aldehydes with allyltrimethylsilanes, further halogenation by excess BCl_3 took place, and consecutive products were isolated instead of the corresponding alcohols” was used to describe the reaction mechanism. Herein are reported the results of a detailed study of this reaction, including a mechanistic discussion.

5.2 Results and Discussion

Due to its air and moisture sensitivity, 1.1 equivalents of BCl_3 were utilized for the reaction of benzaldehyde with allyltrimethylsilane. We found that the reaction proceeded readily in hexanes and gave the expected haloallylated product **502a** in 85% yield. A series of aryl aldehydes were subjected to the reaction, shown in **Table 5-1**. Essentially all of the aryl aldehydes investigated were successfully converted to the haloallylated products with the exception of *p*-anisaldehyde (the cleavage of the methoxy ether by BCl_3 and BBr_3 is well known).⁷ Generally, reactions with BBr_3 are faster than those using BCl_3 . Bromoallylated product **502i** formed exclusively when a mixture of BBr_3 and BCl_3 (1.1 equivalents each) was added to the *p*-chlorobenzaldehyde reaction, demonstrating a high chemoselectivity (**Scheme 5-5**).



Scheme 5-5 Chemoselective Bromoallylation of *p*-Chlorobenzaldehyde in the Presence of Equimolar Amounts of Boron Trihalide.

Table 5-1 Haloallylation of Aryl Aldehydes.^a

Entry	Z	R	X	Time/min	Product	Yield ^b (%)
1	H	H	Cl	30	502a	85
2	4-F	H	Cl	30	502b	62
3	4-Cl	H	Cl	20	502c	90
4	4-Br	H	Cl	30	502d	87
5	2-Me	H	Cl	20	502e	73
6	2-Br	H	Cl	180	502f	62
7	3,5-Br ₂	H	Cl	120	502g	61
8	4-F	Me	Cl	60	502h	94
9	4-Cl	Me	Cl	60	502i	92
10	3-Br	Me	Cl	60	502j	94
11	2-Me	Me	Cl	60	502k	69
12	2,3,4,5,6-F ₅	Me	Cl	180	502l^c	67
13	4-CF ₃	Me	Cl	120	502m	89
14	4-Cl	H	Br	10	502n	81
15	4-Cl	Me	Br	10	502o	72
16	4-Br	Me	Br	10	502p	78
17	3-Cl	Me	Br	20	502q	63

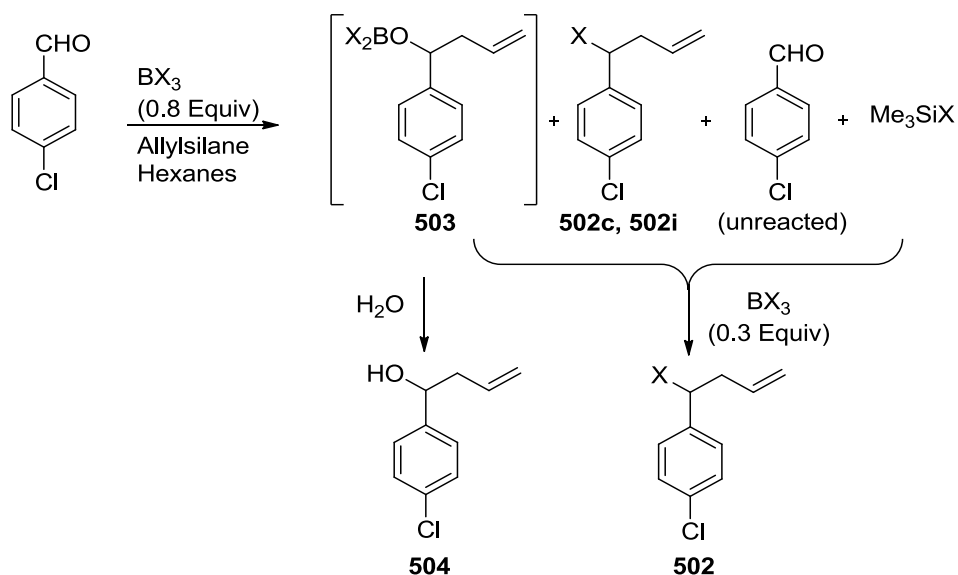
^a Boron halide was added at 0 °C and reaction mixture was warmed to room temperature until complete.

^b Isolated yield based on aldehyde.

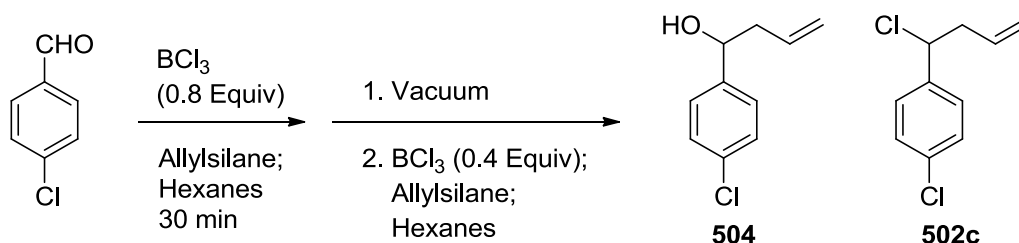
^c Refluxing is required for completion.

Several control experiments were performed to probe the reaction mechanism. First, the reaction of allyltrimethylsilane with *p*-chlorobenzaldehyde using a substoichiometric amount of boron trihalide (0.8 equivalent) was carried out to determine whether the reaction was catalytic (**Scheme 5-6**). *p*-Chlorobenzaldehyde was not completely consumed after 24 hours, clearly indicating that the reaction is not catalytic. Remarkably, the Me_3SiX ($\text{X} = \text{Cl}, \text{Br}$) generated in the reaction did not initiate a silyl cation catalyzed allylation. The discovery that Me_3SiX ($\text{X} = \text{Cl}, \text{Br}$) was not a catalyst in the non-polar solvent hexane could be significant for allylation reactions involving chiral Lewis acid catalysts. Hydrolysis of the reaction mixture at this stage revealed products **504** and **502**. Homoallylic alcohol **504** was isolated as the major product (70% yield) along with chloroallylated product **502c** (8% yield) when BCl_3 was employed. In contrast, bromoallylated product **502i** was the main product if boron tribromide was used; the yields of **504** and **502i** were 26% and 41%, respectively. In a separate experiment, an additional 0.3 equivalents of boron trihalide was added to the substoichiometric (0.8 equivalents) mediated reactions after they had been allowed to react for 24 hours. Both intermediate **503** and the unreacted *p*-chlorobenzaldehyde disappeared (no homoallylic alcohol **504** detected). Clearly the conversion of intermediate **503** to haloallylated product **502** occurred.

The complete conversion of intermediate **503** and unreacted *p*-chlorobenzaldehyde to haloallylated product **502** using only an additional 0.3 equivalent of boron trihalide (**Scheme 5-6**) was somewhat surprising. The isolation of homoallylic alcohol **504** in 53% yield from a modified reaction (**Scheme 5-7**) helps explain the earlier observation. Removal of the Me_3SiCl prior to addition of the extra BCl_3 inhibits the conversion of intermediate **503** to product **502c**.

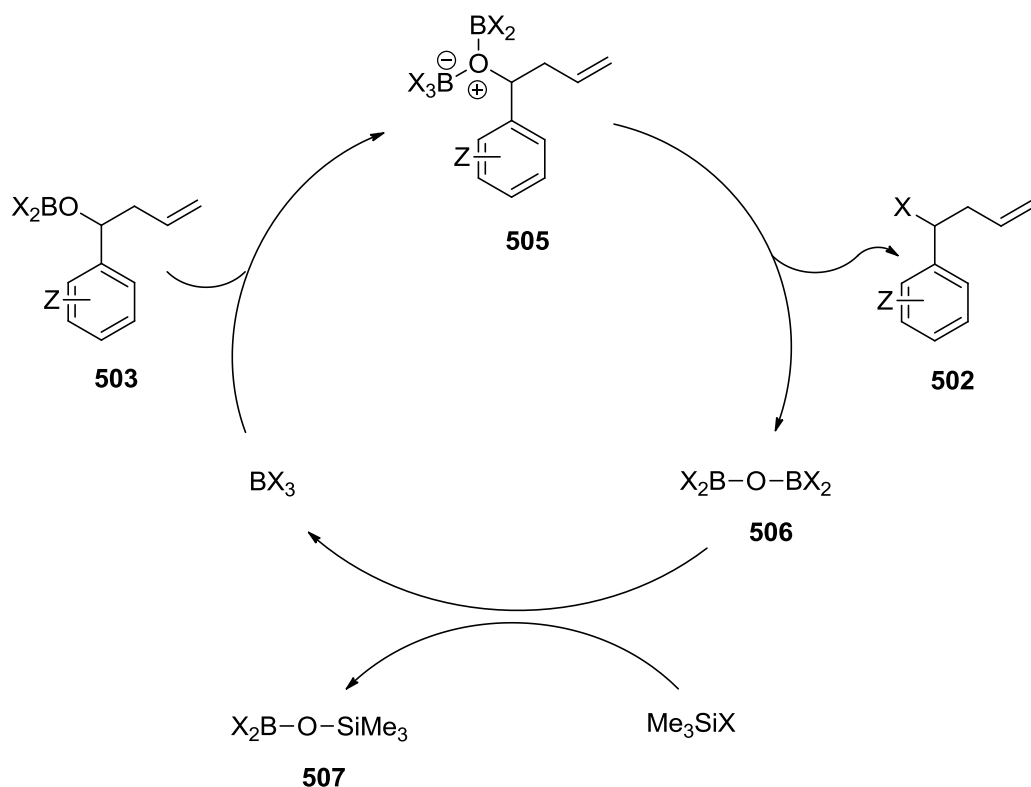


Scheme 5-6 Determination of Catalytic Nature of Reaction by Addition of Substoichiometric Amount of BX_3 .



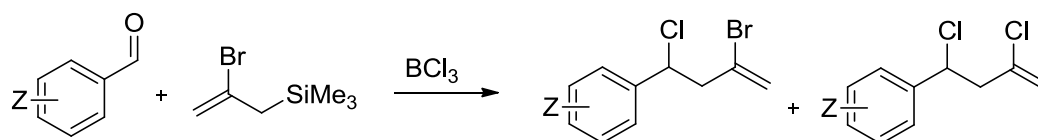
Scheme 5-7 Experimental Illustration of Me_3SiCl Removal.

Based on these experiments, a tentative mechanism was proposed to explain the boron trihalide catalyzed transformation of **503** to **502** (**Scheme 5-8**). Boron trihalide coordinates with the oxygen in intermediate **503** to form **505**. Rearrangement of **505** generates the desired product **502** along with $\text{X}_2\text{B}-\text{O}-\text{BX}_2$ (**506**). Exchange between **506** and Me_3SiX regenerates boron trihalide and mixed anhydride **507**.



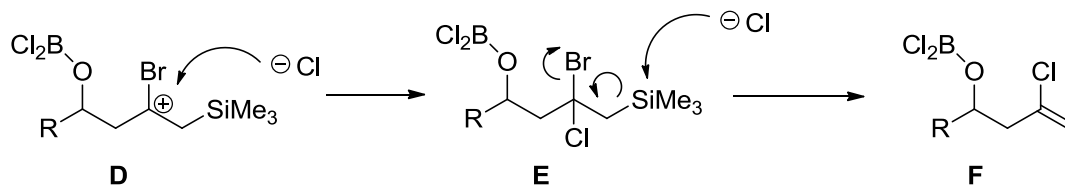
Scheme 5-8 Proposed Mechanistic Pathway for Formation of Haloallylated Product (502) from Intermediate 503.

Interestingly, the haloallylation of aryl aldehydes using 2-bromoallyltrimethylsilane generated a mixture of (3-bromo-1-chlorobut-3-en-1-yl)benzene derivatives along with unexpected (3-chloro-1-chlorobut-3-en-1-yl)benzene derivatives (**Scheme 5-9**), which are proved by GC-MS spectrum.



Scheme 5-9 Haloallylation of Aryl Aldehydes with 2-Bromoallyltrimethylsilane.

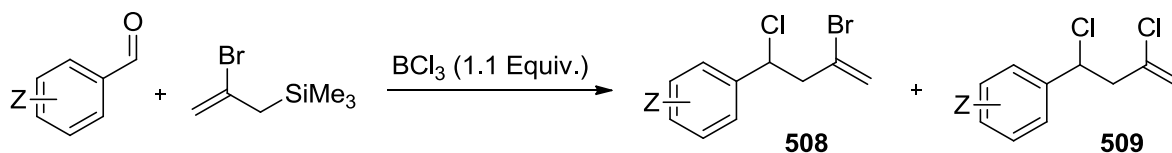
A mechanistic route to these unintended products is provided in **Scheme 5-10**. Similar to intermediate **A** (**Scheme 5-1**), intermediate **D** (**Scheme 5-8**) is generated by Lewis acid activation of aryl aldehydes with boron trichloride in the presence of 2-bromoallyltrimethylsilane. The subsequent chlorination of the carbocation of the metal homoalloxide intermediate **D** by chlorine forms intermediate **E**. Elimination of the more reactive bromine during silyl electrofuge cleavage produces intermediate **F**, resulting in the unintended (1,3-dichlorobut-3-en-1-yl)benzene compounds. Consequently, the haloallylation of aryl aldehydes using 2-bromoallyltrimethylsilane produces a mixture of inseparable 1,3-dihaloallylated products.



Scheme 5-10 Proposed Mechanistic Pathway for (1,3-Dichlorobut-3-en-1-yl)benzene Compounds.

The yields and product ratio for haloallylation of aryl aldehydes using 2-bromoallyltrimethylsilane are shown in **Table 5-2**. The percent of compound **508b** in **Table 5-2** suggests that steric hindrance slows the formation of the unintended chlorinated side product, **509b**.

Table 5-2 Haloallylation of Aryl Aldehydes using 2-Bromoallyltrimethylsilane Resulting in 1,3-Dihaloallylated Products.^a



Entry	Z	Time (min)	Product	Yield ^b of 8 (%)	Yield ^b of 9 (%)	Ratio of 8 : 9 ^c
1	naphthyl	60	508a + 509a	38	32	1.2 : 1
2	2-Me	60	508b + 509b	78	16	5.8 : 1
3	3-Br	60	508c + 509c	40	21	2.2 : 1
4	4-Cl	60	508d + 509d	69	29	2.8 : 1
5	4-Br	60	508e + 509e	48	25	2.2 : 1
6	4-NO ₂	120 ^c	508f + 509f	37	33	1.4 : 1

^a Boron trichloride was added at 0 °C and then the reaction mixture was warmed to room temperature until complete (see Experimental for details).

^b Yield based on aldehyde.

^c Ratio determined by ¹H NMR.

^d Refluxing required for completion.

5.3 Conclusions

In summary, a facile haloallylation of aryl aldehydes using boron trihalide is reported. A mechanistic study revealed the reaction involves two-steps: i) conversion of aldehydes to homoallyloxy borates in the presence of a stoichiometric amount of boron trihalides; ii) a boron trihalide catalyzed conversion of homoallyloxy borates into halogenated products in the presence of Me₃SiX (X = Cl, Br). The use of 2-bromoallyltrimethylsilane in the haloallylation of aryl aldehydes results in a mixture of 1,3-dihaloallylated products.

5.4 Experimental

5.4.1 General Methods

All reagents were used as received. Column chromatography was performed using silica gel (60 Å, 230–400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical thin-layer chromatography was performed using 250 µm silica plates (Analtech, Inc., Newark, DE).

^1H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, respectively. Chemical shifts for ^1H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. Atlantic Microlab, Inc., Norcross, Georgia, performed microanalysis.

Gas Chromatography-Mass Spectroscopy studies were run on Hewlett Packard: HP 6890 series GC System with 5973 Mass Selective Detector; Column: Agilent 19091S-433E, 30.0mm X 0.25mm X 0.25 µm; Gas (He) flow rate: 0.8 mL/min; Initial temperature; 50 °C (hold 1 min); Ramp temperature rate: 7 °C /min to maximum 280 °C.

5.4.2 Typical Reaction Procedure

Finely ground 4-chlorobenzaldehyde (210 mg, 1.5 mmol), allyltrimethylsilane (256 mg, 2.25 mmol) and dry hexanes (16 mL) were placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a magnetic stirring bar. The solution was cooled to 0 °C, and boron trichloride (1.65 mmol, 1.65 mL of a 1.0 M CH_2Cl_2 solution) was added *via* syringe. After completion of the addition, the ice-bath was removed and the resulting solution was allowed to warm to room temperature. The reaction mixture was hydrolyzed with water and extracted with hexanes. The organic layer was separated, dried over anhydrous MgSO_4 , the solvent removed

under reduced pressure, and the product isolated by flash column chromatography.

5.4.3 Reaction Procedure for Haloallylation of Aryl Aldehydes using

(2-Bromoallyl)trimethylsilane

Finely ground 4-chlorobenzaldehyde (70 mg, 0.50 mmol), (2-bromoallyl)trimethylsilane (116 mg, 0.60 mmol) and dry hexanes (10 mL) were placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a magnetic stirring bar. The solution was cooled to 0 °C, and boron trichloride (0.55 mmol, 0.55 mL of a 1.0 M CH₂Cl₂ solution) was added *via* syringe. After completion of the addition, the ice-bath was removed and the resulting solution was allowed to warm to room temperature. The reaction mixture was hydrolyzed with water and extracted with hexanes. The organic layer was separated, dried over anhydrous MgSO₄, the solvent removed under reduced pressure, and the product isolated by flash column chromatography.

5.4.4 Characterization of Compounds 502a-n (Representative NMR spectra in

Appendix E)

(1-Chlorobut-3-enyl)benzene (502a)¹⁶⁸: ¹H NMR (250 MHz, CDCl₃): δ 7.25-7.38 (m, 2H), 7.00–7.08 (m, 2H), 5.62-5.77 (m, 1H), 5.06-5.16 (m, 2H), 4.82 (t, *J* = 7.22 Hz, 1H), 2.72-2.85 (m, 2H). ¹³C NMR (CDCl₃): δ 138.1, 134.4, 129.0, 128.8, 128.6, 116.3, 56.7, 43.2.

1-(1-Chlorobut-3-enyl)-4-fluorobenzene (502b): ¹H NMR (250 MHz, CDCl₃): δ 7.25-7.38 (m, 2H), 7.00–7.08 (m, 2H), 5.65-5.79 (m, 1H), 5.08-5.15 (m, 2H), 4.83 (t, *J* = 7.27 Hz, 1H), 2.73-2.86 (m, 2H). ¹³C NMR (CDCl₃): δ 162.5, (¹*J*_{CF} = 246.5 Hz), 160.5, 137.4, 133.6, 128.8, (³*J*_{CF} =

7.7 Hz), 118.4, 115.5, ($^2J_{\text{CF}} = 21.2$ Hz), 61.3, 44.2. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{ClF}$: C, 65.05; H, 5.46. Found: C, 65.48; H, 5.61.

1-(1-Chlorobut-3-enyl)-4-chlorobenzene (502c)¹⁶⁸: ^1H NMR (250 MHz, CDCl_3): δ 7.29-7.33 (m, 4H), 5.63-5.77 (m, 1H), 5.06-5.14 (m, 2H), 4.86 (t, $J = 7.33$ Hz, 1H), 2.71-2.86 (m, 2H). ^{13}C NMR (CDCl_3): δ 139.7, 134.0, 133.5, 128.7, 128.4, 116.5, 61.7, 44.0.

1-(1-Chlorobut-3-enyl)-4-bromobenzene (502d)¹⁶⁹: ^1H NMR (250 MHz, CDCl_3): δ 7.44-7.47 (m, 2H), 7.21-7.25 (m, 2H), 5.63-5.76 (m, 1H), 5.06-5.13 (m, 2H), 4.81 (t, $J = 7.21$ Hz, 1H), 2.70-2.85 (m, 2H). ^{13}C NMR (CDCl_3): δ 140.1, 133.4, 131.7, 128.7, 118.5, 61.6, 43.9.

1-(1-Chlorobut-3-enyl)-2-methylbenzene (502e): ^1H NMR (250 MHz, CDCl_3): δ 7.14-7.50 (m, 4H), 5.74-5.80 (m, 1H), 5.07-5.17 (m, 3H), 2.81-2.91 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (CDCl_3): δ 139.1, 135.3, 134.2, 130.5, 128.1, 126.5, 118.1, 58.7, 43.0, 19.1. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{Cl}$: C, 73.12; H, 7.25. Found: C, 73.54; H, 7.37.

1-Bromo-2-(1-chlorobut-3-en-1-yl)benzene (502f)¹⁷⁰: ^1H NMR (250 MHz, CDCl_3): δ 7.58 (ddd, $J = 15.7, 7.9, 1.3$ Hz, 1H), 7.42 – 7.29 (m, 1H), 7.15 (td, $J = 8.0, 1.7$ Hz, 1H), 5.82 (ddt, $J = 23.3, 10.4, 6.9$ Hz, 1H), 5.42 (t, $J = 7.0$ Hz, 1H), 5.22 – 5.05 (m, 1H), 2.87 – 2.70 (m, 1H). ^{13}C NMR (CDCl_3): δ 133.3, 132.7, 129.5, 128.7, 127.9, 122.9, 118.5, 60.7, 43.1.

1,3-Dibromo-(1-chlorobut-3-enyl)benzene (502g): ^1H NMR (250 MHz, CDCl_3): δ 7.45-7.61 (m, 3H), 5.67-5.77 (m, 1H), 5.09-5.16 (m, 2H), 4.72-4.77 (m, 1H), 2.73-2.81 (m, 2H). ^{13}C NMR (CDCl_3): δ 133.9, 132.9, 129.0, 123.0, 119.1, 60.6, 43.9. HR-MS for $\text{C}_{10}\text{H}_9\text{Br}_2\text{Cl}$: 321.8760. Found: 321.8757.

1-(1-chloro-3-methylbut-3-en-1-yl)-4-fluorobenzene (502h)¹⁷¹: ^1H NMR (250 MHz, CDCl_3): δ 7.36 (dd, $J = 8.9, 5.3$ Hz, 2H), 7.02 (t, $J = 8.7$ Hz, 2H), 5.08 – 4.95 (m, 1H), 4.83 (s, 1H), 4.74 (s, 1H), 2.77 (ddd, $J = 21.3, 14.4, 7.5$ Hz, 2H), 1.70 (s, 3H). ^{13}C NMR (CDCl_3): δ 164.32,

160.39, 140.83, 137.35, 128.78, 128.64, 115.60, 115.26, 114.32, 60.48, 48.08, 22.11.

1-Chloro-4-(1-chloro-3-methylbut-3-enyl)benzene (502i): ^1H NMR (250 MHz, CDCl_3): δ 7.23-7.37 (m, 4H), 4.97 (dd, $J = 7.21, 7.19$ Hz, 1H), 4.83 (s, 1H), 4.73 (s, 1H), 2.71-2.83 (m, 2H), 1.69 (s, 3H). ^{13}C NMR (CDCl_3): δ 140.7, 140.0, 134.0, 128.7, 128.4, 114.4, 60.3, 47.9, 22.1. Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{Cl}_2$: C, 61.42; H, 5.62. Found: C, 61.19; H, 5.25.

1-Bromo-3-(1-chloro-3-methylbut-3-en-1-yl)benzene (502j)¹⁷¹: ^1H NMR (250 MHz, CDCl_3): δ 7.54 (s, 1H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.30 (d, $J = 7.3$ Hz, 1H), 7.19 (t, $J = 7.8$ Hz, 1H), 4.99 – 4.88 (m, 1H), 4.84 (s, 1H), 4.75 (s, 1H), 2.74 (qd, $J = 14.5, 7.5$ Hz, 2H), 1.70 (s, 3H). ^{13}C NMR (CDCl_3): δ 143.7, 140.6, 131.3, 130.1, 125.6, 122.5, 114.5, 60.2, 47.9, 22.1. Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{BrCl}$: C, 50.90; H, 4.66. Found: C, 50.64; H, 4.64.

1-(1-Chloro-3-methylbut-3-enyl)-2-methylbenzene (502k): ^1H NMR (250 MHz, CDCl_3): δ 7.14-7.51 (m, 4H), 5.30 (dd, $J = 6.43, 6.41$ Hz, 1H), 4.85 (s, 1H), 4.78 (s, 1H), 2.77-2.85 (m, 2H), 2.39 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (CDCl_3): δ 141.2, 139.4, 135.0, 130.5, 128.0, 126.6, 126.5, 114.0, 57.3, 46.7, 22.2, 19.1. HR-MS for $\text{C}_{12}\text{H}_{15}\text{Cl}$: 194.0862. Found: 194.0874.

1-(1-Chloro-3-methylbut-3-enyl)-2,3,4,5,6-pentafluorobenzene (502l): ^1H NMR (250 MHz, CDCl_3): δ 5.35 (t, $J = 8.08$ Hz, 1H), 4.81 (s, 1H), 4.74 (s, 1H), 2.95 (d, $J = 8.08$ Hz, 2H), 1.73 (s, 3H). ^{13}C NMR (CDCl_3): δ 147.0, 143.0, 140.2, 135.7, 120.8, 114.8, 112.7, 48.5, 45.0, 21.8. HR-MS for $\text{C}_{11}\text{H}_8\text{ClF}_5$: 270.0235. Found: 270.0237.

1-(1-Chloro-3-methylbut-3-enyl)-4-(trifluoromethyl)benzene (502m): ^1H NMR (250 MHz, CDCl_3): δ 7.35-7.50 (m, 4H), 4.90 (t, $J = 7.47$ Hz, 1H), 4.72 (s, 1H), 4.62 (s, 1H), 2.60-2.70 (m, 2H), 1.58 (s, 3H). ^{13}C NMR (CDCl_3): δ 145.4, 140.5, 130.7, 130.2, 127.4, 126.1, 125.6, 125.5, 114.6, 60.1, 48.0, 22.1. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{ClF}_3$: C, 57.96; H, 4.86. Found: C, 58.04; H, 4.91.

1-(1-Bromobut-3-enyl)-4-chlorobenzene (502n)¹⁶⁹: ¹H NMR (250 MHz, CDCl₃): δ 7.29 (s, 4H), 5.61-5.78 (m, 1H), 5.07-5.14 (m, 2H), 4.90 (t, J = 7.25 Hz, 1H), 2.81-3.04 (m, 2H). ¹³C NMR (CDCl₃): δ 140.0, 134.2, 128.8, 128.7, 127.8, 118.4, 52.6, 43.9.

1-(1-Bromo-3-methylbut-3-enyl)-4-chlorobenzene (502o): ¹H NMR (250 MHz, CDCl₃): δ 7.26-7.34 (m, 4H), 5.06 (t, J = 7.76 Hz, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 2.86-2.97 (m, 2H), 1.68 (s, 3H). ¹³C NMR (CDCl₃): δ 141.2, 140.3, 134.0, 128.7, 128.6, 114.3, 51.3, 47.9, 22.0. Anal. Calcd for C₁₁H₁₂BrCl: C, 50.90; H, 4.66. Found: C, 50.67; H, 4.32.

1-Bromo-4-(1-bromo-3-methylbut-3-enyl)benzene (502p): ¹H NMR (250 MHz, CDCl₃): δ 7.23-7.39 (m, 4H), 5.03 (t, J = 7.72 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 2.80-3.02 (m, 2H), 1.70 (s, 3H). ¹³C NMR (CDCl₃): δ 143.7, 141.1, 134.3, 129.9, 128.5, 127.5, 125.5, 114.4, 51.1, 47.8, 22.0. HR-MS for C₁₁H₁₂Br₂: C, 301.9306. Found: 301.9312.

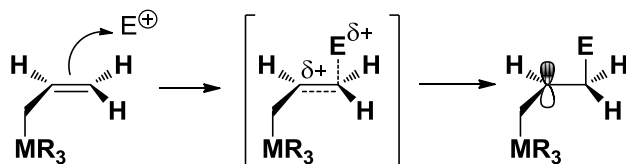
1-(1-Bromo-3-methylbut-3-enyl)-3-chlorobenzene (502q): ¹H NMR (250 MHz, CDCl₃): δ 7.45 (d, J = 8.48 Hz, 2H), 7.26 (d, J = 8.48 Hz, 2H), 5.05 (t, J = 7.73 Hz, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 2.81-3.04 (m, 2H), 1.68 (s, 3H). ¹³C NMR (CDCl₃): δ 141.2, 140.8, 131.8, 129.0, 122.2, 114.4, 51.3, 47.8, 22.0. Anal. Calcd for C₁₁H₁₂BrCl: C, 50.90; H, 4.66. Found: C, 51.07; H, 4.73.

Chapter 6. Boron Trihalide Mediated Haloallylation of Aryl Aldehydes using Allylmetal Compounds

6.1 Introduction

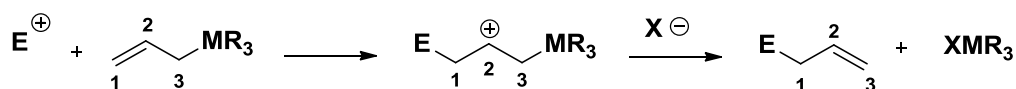
In the case of the group 14 congeners (Si, Ge, Sn), differences in nucleophilicity of allylmetals (as proposed in the reactions with aldehydes and acetals by Denmark¹⁷² and Yamamoto^{110, 173}) led us to investigate the use of various allylmetals in the reaction of aryl aldehydes using boron trihalides. Our interest is based, in part, on whether allylmetals other than allylsilane will produce haloallylated products. Similar to allylsilanes, the allylation of aldehydes using allylstannanes is a versatile synthetic method for the preparation of homoallylic alcohols and has been extensively investigated due to the usefulness of these products in the synthesis of natural products and pharmaceuticals.⁸⁶ However, the toxicity of organostannane compounds and, perhaps more significantly, difficulties in removing organostannane residues from the desired products, are disadvantages that limit their general use. Allylgermanium compounds tend to be less reactive than allylstannanes, do not pose the same drawbacks, but are more reactive than allylsilanes.¹⁷⁴ It was of interest to study their use in the haloallylation of aryl aldehydes. The order of reactivity increases by one order of magnitude from allyltriphenylsilane to allyltriphenylgermane and by two orders of magnitude from allyltriphenylgermane to allyltriphenylstannane, reflecting the relative ionization potentials of the allyltriphenylmetals as reported by Hagen and Mayr.¹⁷⁵

Asymmetric allylation of aldehydes, an area that has received considerable attention in the organic community, has been reported to proceed by diastereoselective allylmethyl addition to electrophiles and may utilize the orbital hyperconjugation effects between the metal and the β -carbon where electropositive carbenium ion is forming (**Scheme 6-1**).¹⁷⁶



Scheme 6-1 Stereochemistry of the Electrophilic Addition of Allyl Metals.

Regioselective reactions of allylmethyl reagents with electrophiles have been explained by the intermediate formation of carbenium ions, which are hyperconjugatively stabilized by the carbon-silicon, carbon-stannane, or carbon-germane bond in the β -position (**Scheme 6-2**).



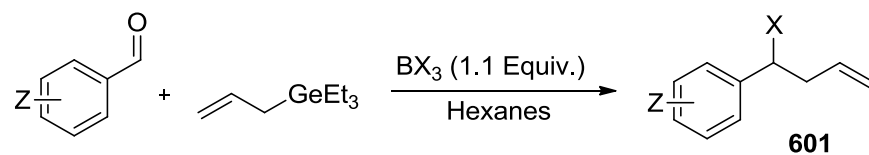
Scheme 6-2 Regioselective Allylation of Electrophiles with Allylmethyls: Generation of Carbenium Ion.

Mayr¹⁷⁷ and Brook¹⁷⁸ have determined that the β -cation stabilizing ability of silyl and stannyl groups increases in the order of $(\text{RO})_3\text{Si} < \text{Ar}_3\text{Si} < \text{R}_3\text{Si} < (\text{RO})_3\text{Sn} < \text{Ar}_3\text{Sn} < \text{R}_3\text{Sn}$. Therefore, determining whether germane and stannane reagents also react in the haloallylation of aryl aldehydes may provide new stereoselective haloallylation methodology in the future based on the strength of allylmethyl hyperconjugation with the developing carbenium ion during these reactions.

6.2 Results and Discussion

Due to its air and moisture sensitivity, a slight excess (1.1 equivalents) of boron trihalide was utilized for the reaction of benzaldehyde with allyltriethylgermane. We found that the reaction proceeded readily in hexanes and gave the expected haloallylated product **601a** in 95% yield, as compared to the 85% yield reported using allyltrimethylsilane. A series of aryl aldehydes were subjected to the reaction (**Table 6-1**). Essentially all of the aryl aldehydes investigated were successfully converted to the haloallylated products. Generally, reactions using BBr₃ are faster than those using BCl₃. Excellent yields are obtained for aryl aldehydes with electron donating groups as demonstrated by product **601i** (**Table 6-1**). Transformation of aryl aldehydes containing strong electron withdrawing groups is achieved by raising the reaction temperature to reflux, as represented by products **601e** and **601f** containing the *para* substituted nitrile and nitro groups, respectively. Both aldehydes present in the isophthalaldehyde are successfully converted by doubling the amount of other reactants as evidenced by formation of product **601h**. Overall, when compared to reactions incorporating allylsilane derivatives, haloallylation of aryl aldehydes using boron trihalides in the presence of allyltriethylgermane substantially increased the yield of haloallylated products.

The haloallylation of aryl aldehydes using allyltriphenylstannane is also tolerant of a wide variety of aromatic aldehydes as illustrated by **Table 6-2**. Electron withdrawing substituents are tolerated at *ortho*, *meta*, and *para* positions on the aryl ring. In the case of para-fluorobenzaldehyde, the yield increases from 62% for allyltrimethylsilane to 87% for allyltriethylgermane and finally to a quantitative transformation when allyltriphenylstannane is used. It is important to note that, although this trend applies for several other substituent's when

Table 6-1 Haloallylation of Aryl Aldehydes with Allyltriethylgermane.^a

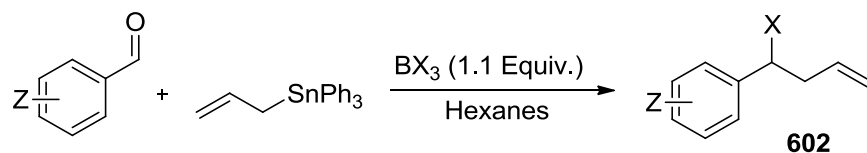
Entry	Z	X	Time (min)	Product	Yield ^b %
1	H	Cl	60	601a	95
2	4-F	Cl	60	601b	87
3	4-Cl	Cl	60	601c	99
4	4-Br	Cl	60	601d	99
5	4-CN	Cl	60 ^c	601e	59
6	4-NO ₂	Cl	60 ^c	601f	94
7	3-Br	Cl	180	601g	76
8	3-CHO	Cl	60	601h	84 ^d
9	2-Me	Cl	60	601i	97
10	naphthyl	Cl	180	601j	82
11	H	Br	30	601k	70
12	4-Cl	Br	30	601l	78

^a Boron halide was added under argon gas at 0 °C for twenty minutes and then the reaction mixture was warmed to room temperature until complete (see Experimental for details).

^b Isolated yield based on aldehyde.

^c Refluxing is required for completion.

^d An additional equivalent of boron trichloride and allyltriethylgermane were used.

Table 6-2 Haloallylation of Aryl Aldehydes with Allyltriphenylstannane.^a

Entry	Z	X	Time (min)	Product	Percent Yield ^b (%)
1	4-F	Cl	60	602a	99
2	4-Cl	Cl	60	602b	93
3	4-Br	Cl	60	602c	81
4	4-CN	Cl	120 ^c	602d	79
5	4-NO ₂	Cl	60 ^c	602e	65
6	3-Br	Cl	60	602f	93
7	3-CHO	Cl	60	602g	53 ^d
8	2-Me	Cl	60	602h	96
9	naphthyl	Cl	60	602i	82
10	2-Br	Cl	60	602j	68
11	4-Cl	Br	20	602k	74

^a Boron halide was added dropwise under argon gas at 0 °C for twenty minutes and then the reaction mixture was warmed to room temperature until complete (see Experimental for details).

^b Isolated yield based on aldehyde.

^c Refluxing is required for completion.

^d An additional equivalent of boron trichloride and allyltriphenylstannane were used.

comparing Ge, and Sn, namely 4-CN and 3-Br, it does not hold for others, specifically 4-Cl, 4-Br, and 4-NO₂. In the cases of 3-CHO and 2-Me, there are no appreciable changes.

A comparison of the reactivity of the allylmetal compounds, allyltriethylgermane and allyltriphenylstannane, may be explained by the different inductive effects of the alkyl and phenyl groups. When comparing the relative reactivities of allylgermanes and allylstannanes, the SnBu₃ group is three orders of magnitude more nucleophilic than the SnPh₃; similarly, the SiMe₃ is two orders of magnitude more nucleophilic than SiPh₃.¹⁷⁵ As a result, allyltriethylgermane and allyltriphenylstannane may be very similar in terms of reactivity since the more reactive allylstannane contains aryl groups, whereas, the less reactive allylgermane has considerably stronger electron donating alkyl groups. This could explain the overall lack of obvious trends when comparing yields between allyltriethylgermane and allyltriphenylstannane.

6.3 Conclusions

Both allyltriethylgermane and allyltriphenylstannane, when compared to allyltrimethylsilane, produce higher yields in reactions with aryl aldehydes mediated by boron trihalides to provide haloallylated products. As a result of the increased nucleophilicity of both reagents, aryl aldehydes containing strongly deactivating groups, such as the nitrile and nitro groups, are capable of generating haloallylated products using the procedures provided herein. The fact that allylmetal reagents containing -Si, -Ge, and -Sn furnish haloallylated products from aryl aldehydes in the presence of boron trihalides, provides the synthetic organic community a variety of options from which to choose. Further investigations of other allylmetals, as well as stereoselective haloallylation studies, are now possible given these results.

6.4 Experimental

6.4.1 General Methods

All reagents were used as received. Column chromatography was performed using silica gel (60 Å, 230–400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical thin-layer chromatography was performed using 250 µm silica plates (Analtech, Inc., Newark, DE).

^1H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, respectively. Chemical shifts for ^1H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. Atlantic Microlab, Inc., Norcross, Georgia, performed microanalysis.

6.4.2 Typical Reaction Procedure for Haloallylation of Aryl Aldehydes using Allyltriethylgermane

Finely ground 4-chlorobenzaldehyde (210 mg, 1.5 mmol), allyltriethylgermane (452 mg, 2.25 mmol) and dry hexanes (16 mL) were placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a magnetic stirring bar. The solution was cooled to 0 °C, and boron trichloride (1.65 mmol, 1.65 mL of a 1.00 M CH_2Cl_2 solution) was added *via* syringe. After completion of the addition, the ice-bath was removed and the resulting solution was allowed to warm to room temperature. The reaction mixture was hydrolyzed with water (5 mL) and extracted with hexanes. The organic layer was separated, dried over anhydrous MgSO_4 , the solvent removed under reduced pressure, and the product isolated by flash column chromatography.

6.4.3 Typical Reaction Procedure for Haloallylation of Aryl Aldehydes using

Allyltriphenylstannane

Finely ground 4-chlorobenzaldehyde (210 mg, 1.5 mmol), allyltriphenylstannane (645 mg, 1.65 mmol) and dry hexanes (16 mL) were placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a magnetic stirring bar. The solution was cooled to 0 °C, and boron trichloride (1.65 mmol, 1.65 mL of a 1.0 M CH₂Cl₂ solution) was added *via* syringe. After completion of the addition, the ice-bath was removed and the resulting solution was allowed to warm to room temperature. The reaction mixture was hydrolyzed with water (5 mL) and extracted with hexanes. The organic layer was separated, dried over anhydrous MgSO₄, the solvent removed under reduced pressure, and the product isolated by flash column chromatography.

6.4.4 Characterization of Compounds 601a - l and 602a - k . (Representative NMR spectra in Appendix F)

(1-Chlorobut-3-enyl)benzene (601a)¹⁶⁸: ¹H NMR (250 MHz, CDCl₃): δ 7.25-7.38 (m, 2H), 7.00–7.08 (m, 2H), 5.62-5.77 (m, 1H), 5.06-5.16 (m, 2H), 4.82 (t, *J* = 7.22 Hz, 1H), 2.72-2.85 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 138.1, 134.4, 129.0, 128.8, 128.6, 116.3, 56.7, 43.2.

1-(1-Chlorobut-3-enyl)-4-fluorobenzene (601b): ¹H NMR (250 MHz, CDCl₃): δ 7.25-7.38 (m, 2H), 7.00–7.08 (m, 2H), 5.65-5.79 (m, 1H), 5.08-5.15 (m, 2H), 4.83 (t, *J* = 7.27 Hz, 1H), 2.73-2.86 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 162.5, (¹*J*_{CF} = 246.5 Hz), 160.5, 137.4, 133.6, 128.8, (³*J*_{CF} = 7.7 Hz), 118.4, 115.5, (²*J*_{CF} = 21.2 Hz), 61.3, 44.2. Anal. Calcd for C₁₀H₁₀ClF: C, 65.05; H, 5.46. Found: C, 65.48; H, 5.61.

1-(1-Chlorobut-3-enyl)-4-chlorobenzene (601c)¹⁶⁸: ¹H NMR (250 MHz, CDCl₃): δ 7.29-7.33 (m, 4H), 5.63-5.77 (m, 1H), 5.06-5.14 (m, 2H), 4.86 (t, J = 7.33 Hz, 1H), 2.71-2.86 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 139.7, 134.0, 133.5, 128.7, 128.4, 116.5, 61.7, 44.0.

1-(1-Chlorobut-3-enyl)-4-bromobenzene (601d)¹⁶⁹: ¹H NMR (250 MHz, CDCl₃): δ 7.44-7.47 (m, 2H), 7.21-7.25 (m, 2H), 5.63-5.76 (m, 1H), 5.06-5.13 (m, 2H), 4.81 (t, J = 7.21 Hz, 1H), 2.70-2.85 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 140.1, 133.4, 131.7, 128.7, 118.5, 61.6, 43.9.

4-(1-Chlorobut-3-en-1-yl)benzonitrile (601e)¹⁷⁹: ¹H NMR (250 MHz, CDCl₃): δ 7.66 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 5.84 – 5.59 (m, 1H), 5.15 (s, 1H), 5.12 – 5.03 (m, 1H), 4.89 (t, J = 7.2 Hz, 1H), 2.98 – 2.66 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 146.1, 132.7, 132.4, 127.8, 119.1, 118.4, 112.1, 61.1, 43.8.

1-(1-Chlorobut-3-en-1-yl)-4-nitrobenzene (601f)¹⁷⁹: ¹H NMR (250 MHz, CDCl₃): δ 8.20 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 5.80 – 5.59 (m, 1H), 5.12 (s, 1H), 5.10 – 5.03 (m, 1H), 4.92 (t, J = 7.2 Hz, 1H), 2.94 – 2.68 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 148.0, 132.6, 128.0, 123.8, 119.2, 60.7, 43.9.

1-Bromo-3-(1-chlorobut-3-en-1-yl)benzene (601g): ¹H NMR (250 MHz, CDCl₃): δ 7.54 (t, J = 1.8 Hz, 1H), 7.43 (ddd, J = 7.7, 1.9, 1.3 Hz, 1H), 7.30 (dt, J = 7.7, 1.5 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 5.73 (ddt, J = 16.6, 9.7, 6.8 Hz, 1H), 5.14 (d, J = 4.2 Hz, 1H), 5.09 (s, 1H), 4.84 – 4.77 (m, 1H), 2.92 – 2.67 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 143.3, 133.4, 131.4, 130.1, 125.7, 122.5, 118.7, 61.5, 44.0. Anal. Calcd for C₁₀H₁₀BrCl: C, 48.51; H, 4.10. Found: C, 48.99; H, 4.03.

1,3-Bis(1-chlorobut-3-en-1-yl)benzene (601h): ¹H NMR (250 MHz, CDCl₃): δ 7.38 (s, 1H), 7.33 (d, J = 1.4 Hz, 3H), 5.86 – 5.63 (m, 2H), 5.18 – 5.10 (m, 2H), 5.08 (s, 2H), 4.88 (t, J = 7.2 Hz, 2H), 2.95 – 2.70 (m, 4H). ¹³C NMR (63 MHz, CDCl₃): δ 141.6, 133.7, 128.9, 126.9, 125.7,

118.4, 62.3, 62.3, 44.1, 44.1. Anal. Calcd for C₁₄H₁₆Cl₂: C, 65.89; H, 6.32. Found: C, 66.17; H, 6.41.

1-(1-Chlorobut-3-enyl)-2-methylbenzene (601i): ¹H NMR (250 MHz, CDCl₃): δ 7.14-7.50 (m, 4H), 5.74-5.80 (m, 1H), 5.07-5.17 (m, 3H), 2.81-2.91 (m, 2H), 2.38 (s, 3H). ¹³C NMR (63 MHz, CDCl₃): δ 139.1, 135.3, 134.2, 130.5, 128.1, 126.5, 118.1, 58.7, 43.0, 19.1. Anal. Calcd for C₁₁H₁₃Cl: C, 73.12; H, 7.25. Found: C, 73.54; H, 7.37.

1-(1-Chlorobut-3-en-1-yl)naphthalene (601j): ¹H NMR (250 MHz, CDCl₃): δ 8.14 (d, *J* = 8.1 Hz, 1H), 7.92 – 7.79 (m, 2H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.62 – 7.45 (m, 3H), 5.90 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.76 – 5.64 (m, 1H), 5.26 – 5.08 (m, 2H), 3.06 (tdd, *J* = 6.8, 2.9, 1.4 Hz, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 136.3, 134.2, 133.8, 130.4, 129.1, 129.0, 126.5, 125.8, 125.2, 124.6, 122.8, 118.9, 58.6, 42.8. Anal. Calcd for C₁₄H₁₃Cl: C, 77.59; H, 6.05. Found: C, 77.36; H, 5.99.

(1-Bromobut-3-en-1-yl)benzene (601k): ¹H NMR (250 MHz, CDCl₃): δ 7.41 – 7.24 (m, 5H), 5.73 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.19 – 5.03 (m, 2H), 5.01 – 4.88 (m, 1H), 3.09 – 2.85 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 141.6, 134.7, 128.6, 128.4, 127.3, 118.1, 54.0, 44.0.

1-(1-Bromobut-3-enyl)-4-chlorobenzene (601l)¹⁶⁹: ¹H NMR (250 MHz, CDCl₃): δ 7.29 (s, 4H), 5.61-5.78 (m, 1H), 5.07-5.14 (m, 2H), 4.90 (t, *J* = 7.25 Hz, 1H), 2.81-3.04 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 140.0, 134.2, 128.8, 128.7, 127.8, 118.4, 52.6, 43.9.

1-(1-Chlorobut-3-enyl)-4-fluorobenzene (602a): ¹H NMR (250 MHz, CDCl₃): δ 7.25-7.38 (m, 2H), 7.00–7.08 (m, 2H), 5.65-5.79 (m, 1H), 5.08-5.15 (m, 2H), 4.83 (t, *J* = 7.27 Hz, 1H), 2.73-2.86 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 162.5, (¹*J*_{CF} = 246.5 Hz), 160.5, 137.4, 133.6, 128.8, (³*J*_{CF} = 7.7 Hz), 118.4, 115.5, (²*J*_{CF} = 21.2 Hz), 61.3, 44.2. Anal. Calcd for C₁₀H₁₀ClF: C, 65.05; H, 5.46. Found: C, 65.48; H, 5.61.

1-(1-Chlorobut-3-enyl)-4-chlorobenzene (602b)¹⁶⁸: ¹H NMR (250 MHz, CDCl₃): δ 7.29-7.33 (m, 4H), 5.63-5.77 (m, 1H), 5.06-5.14 (m, 2H), 4.86 (t, J = 7.33 Hz, 1H), 2.71-2.86 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 139.7, 134.0, 133.5, 128.7, 128.4, 116.5, 61.7, 44.0.

1-(1-Chlorobut-3-enyl)-4-bromobenzene (602c)¹⁶⁹: ¹H NMR (250 MHz, CDCl₃): δ 7.44-7.47 (m, 2H), 7.21-7.25 (m, 2H), 5.63-5.76 (m, 1H), 5.06-5.13 (m, 2H), 4.81 (t, J = 7.21 Hz, 1H), 2.70-2.85 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 140.1, 133.4, 131.7, 128.7, 118.5, 61.6, 43.9.

4-(1-Chlorobut-3-en-1-yl)benzonitrile (602d)¹⁷⁹: ¹H NMR (250 MHz, CDCl₃): δ 7.66 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 5.84 – 5.59 (m, 1H), 5.15 (s, 1H), 5.12 – 5.03 (m, 1H), 4.89 (t, J = 7.2 Hz, 1H), 2.98 – 2.66 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 146.1, 132.7, 132.4, 127.8, 119.1, 118.4, 112.1, 61.1, 43.8.

1-(1-Chlorobut-3-en-1-yl)-4-nitrobenzene (602e)¹⁷⁹: ¹H NMR (250 MHz, CDCl₃): δ 8.20 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 5.80 – 5.59 (m, 1H), 5.12 (s, 1H), 5.10 – 5.03 (m, 1H), 4.92 (t, J = 7.2 Hz, 1H), 2.94 – 2.68 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 148.0, 132.6, 128.0, 123.8, 119.2, 60.72, 43.9.

1-Bromo-3-(1-chlorobut-3-en-1-yl)benzene (602f): ¹H NMR (250 MHz, CDCl₃): δ 7.54 (t, J = 1.8 Hz, 1H), 7.43 (ddd, J = 7.7, 1.9, 1.3 Hz, 1H), 7.30 (dt, J = 7.7, 1.5 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 5.73 (ddt, J = 16.6, 9.7, 6.8 Hz, 1H), 5.14 (d, J = 4.2 Hz, 1H), 5.09 (s, 1H), 4.84 – 4.77 (m, 1H), 2.92 – 2.67 (m, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 143.3, 133.4, 131.4, 130.1, 125.7, 122.5, 118.7, 61.5, 44.00. Anal. Calcd for C₁₀H₁₀BrCl: C, 48.51; H, 4.10. Found: C, 48.99; H, 4.03.

1,3-Bis(1-chlorobut-3-en-1-yl)benzene (602g): ¹H NMR (250 MHz, CDCl₃): δ 7.38 (s, 1H), 7.33 (d, J = 1.4 Hz, 3H), 5.86 – 5.63 (m, 2H), 5.18 – 5.10 (m, 2H), 5.08 (s, 2H), 4.88 (t, J = 7.2 Hz, 2H), 2.95 – 2.70 (m, 4H). ¹³C NMR (63 MHz, CDCl₃): δ 141.6, 133.7, 128.9, 126.9,

125.7, 118.4, 62.3, 62.3, 44.1, 44.1. Anal. Calcd for C₁₄H₁₆Cl₂: C, 65.89; H, 6.32. Found: C, 66.17; H, 6.41.

1-(1-Chlorobut-3-enyl)-2-methylbenzene (602h): ¹H NMR (250 MHz, CDCl₃): δ 7.14-7.50 (m, 4H), 5.74-5.80 (m, 1H), 5.07-5.17 (m, 3H), 2.81-2.91 (m, 2H), 2.38 (s, 3H). ¹³C NMR (CDCl₃): δ 139.1, 135.3, 134.2, 130.5, 128.1, 126.5, 118.1, 58.7, 43.0, 19.1. Anal. Calcd for C₁₁H₁₃Cl: C, 73.12; H, 7.25. Found: C, 73.54; H, 7.37.

1-(1-Chlorobut-3-en-1-yl)naphthalene (602i): ¹H NMR (250 MHz, CDCl₃): δ 8.14 (d, *J* = 8.1 Hz, 1H), 7.92 – 7.79 (m, 2H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.62 – 7.45 (m, 3H), 5.90 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.76 – 5.64 (m, 1H), 5.26 – 5.08 (m, 2H), 3.06 (tdd, *J* = 6.8, 2.9, 1.4 Hz, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 136.3, 134.2, 133.8, 130.4, 129.1, 129.0, 126.5, 125.8, 125.2, 124.6, 122.8, 118.2, 58.6, 42.8. Anal. Calcd for C₁₄H₁₃Cl: C, 77.59; H, 6.05. Found: C, 77.36; H, 5.99.

1-Bromo-2-(1-chlorobut-3-en-1-yl)benzene (602j)¹⁷⁰: ¹H NMR (250 MHz, CDCl₃): δ 7.58 (ddd, *J* = 15.7, 7.9, 1.3 Hz, 1H), 7.42 – 7.29 (m, 1H), 7.15 (td, *J* = 8.0, 1.7 Hz, 1H), 5.82 (ddt, *J* = 23.3, 10.4, 6.9 Hz, 1H), 5.42 (t, *J* = 7.0 Hz, 1H), 5.22 – 5.05 (m, 1H), 2.87 – 2.70 (m, 1H). ¹³C NMR (CDCl₃): δ 133.3, 132.7, 129.5, 128.7, 127.9, 122.9, 118.5, 60.7, 43.1.

1-(1-Bromobut-3-enyl)-4-chlorobenzene (602k)¹⁶⁹: ¹H NMR (250 MHz, CDCl₃): δ 7.29 (s, 4H), 5.61-5.78 (m, 1H), 5.07-5.14 (m, 2H), 4.90 (t, *J* = 7.25 Hz, 1H), 2.81-3.04 (m, 2H). ¹³C NMR (CDCl₃): δ 140.0, 134.2, 128.8, 128.7, 127.8, 118.4, 52.6, 43.9.

Chapter 7. A Two-pot Reaction Sequence to Aryl Dienes Based on a Boron Halide Mediated Haloallylation Followed by an Elimination using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)

7.1 Introduction

The synthesis of 1,3-dienes is an area of long-standing importance since this moiety is present in a wide range of bioactive materials including terpenoids,¹⁸⁰ fatty acid-derived lipids,¹⁸¹ pheromones,¹⁸² and polyketides.¹⁸³ Intramolecular cycloaddition reactions that use 1,3-dienes in Diels-Alder reactions have been found to offer solutions to many problems in complex natural product syntheses due to the exceptional regio- and stereochemical control of these reactions.¹⁸⁴ The utility of dienes as substrates for Ziegler-Natta polymerizations add to their importance in synthetic manipulations.¹⁸⁵ The development of methods for the stereoselective synthesis of dienes remains important to the organic synthetic community. Several routes to dienes can be employed including methods reported by Wittig,¹⁸⁶ Horner-Wadsworth-Emmons,¹⁸⁷ Julia,¹⁸⁸ and Peterson;¹⁸⁹ most produce mixtures of (*E*)- and (*Z*)-isomers although many subsequent derivations of these methods are aimed at producing a single stereoisomer.

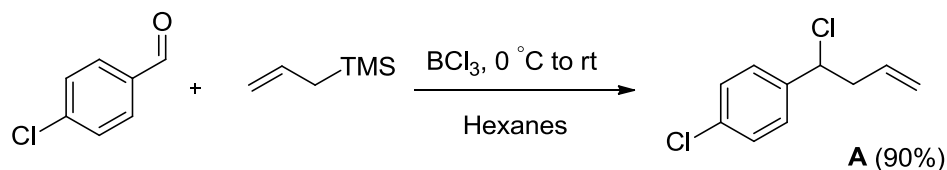
Using methodology developed for the haloallylation of aryl aldehydes mediated by boron trihalides, it has been determined that β -elimination in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), produces (*E*)-1,3-dienes stereoselectively. The facile synthesis of these compounds represents a mild two-pot reaction sequence.

7.2 Results and Discussion

7.2.1 Generation of Aryl Dienes from Haloallylation of Aryl Aldehydes

In last two chapters we described efficient routes to haloallylated products via the boron trihalide mediated haloallylation of aryl aldehydes.¹²⁸ Consider the importance of 1,3-diene in organic syntheses, we decided to investigate the feasibility of converting the haloallylated products to 1,3-dienes. Several bases were examined and it was found that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided the best route to (*E*)-alkenes. In addition, we discovered that (*E*)-1,3-diene syntheses can be fulfilled in a two-pot reaction sequence, a simple aqueous workup of haloallylation reaction followed by a 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) treatment.

We initiated the study by preparing chloroallylated product **A**, which was synthesized in high yield through the reaction of *p*-chlorobenzaldehyde with trimethylallylsilane in the presence of boron trichloride as presented in **Scheme 7-1**.



Scheme 7-1 Haloallylation of 4-Chlorobenzaldehyde.

Attempts at eliminating chlorine using a strong aqueous basic workups provided limited success. Exposure of the reaction mixture to a variety of inorganic bases resulted in either no reaction, degradation of the haloallylated product to several undesired by-products, or low yields of the expected diene with concomitant loss of stereochemistry. We suspected that the elimination, in

some cases, does not occur due to the insolubility of the inorganic bases in the reaction solvents, dichloromethane and hexane.

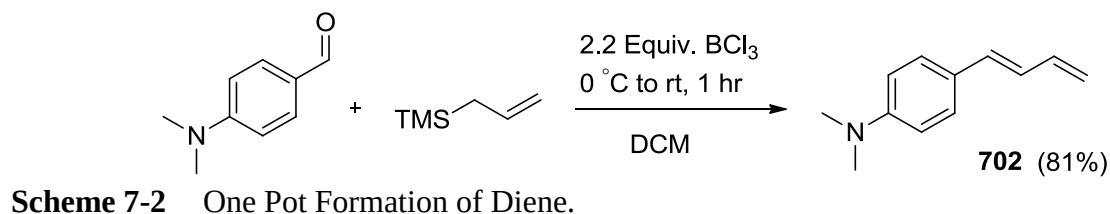
We then investigated a variety of organic bases: triethylamine, N,N-diisopropylethylamine, piperidine, pyridine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and found DBU to be superior in terms of stereochemical control and yield. During the course of this investigation, it was also determined that the bromoallylated products eliminated more rapidly than their chloroallylated counterparts due to the increased susceptibility of bromoallylated products to undergo base induced elimination.

As a continuation of this study, we discovered that comparable yields of 1,3-dienes could be obtained *via* treatment of the crude bromoallylated compounds with DBU. In this sequence, crude bromoallylated products were subjected to a mild basic aqueous wash using a solution of saturated sodium bicarbonate. This removes the acids (HCl and H₃BO₃) generated from the boron trihalide mediated haloallylation reaction step when the reaction is quenched with water. After this simple wash, 6 equivalents of DBU were added and the reaction directly gives 1,3-diene in comparable isolated yield with the reaction that used purified bromoallylated product. It is important to note that DBU is not soluble in hexanes, therefore, dichloromethane must be added to the reaction to facilitate its use. With reliable conditions in hand, we examined the scope of this mild two-step procedure. The results are presented in **Table 7-1**.

The bromoallylation-elimination sequence is tolerant of a wide variety of aromatic aldehydes. Substituents are tolerated at both the *meta* and *para* positions as shown by Entries 2-5 in **Table 7-1**. However, *ortho*-substituents appear to sterically inhibit the β -elimination by DBU and preliminary results indicated both poor yields and loss of stereochemistry. In the absence of *ortho* substituents, the diene products were formed quite stereoselectively, the *Z* isomer was

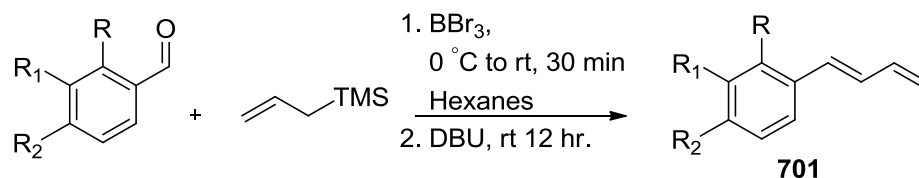
undetectable as identified by the vicinal coupling constants ($^3J_{\text{HH}}$) measured by NMR spectroscopy. Vicinal coupling constants when measured by NMR spectroscopy are typically larger for *trans*- (range: 12–18 Hz, typical: 15 Hz) than for *cis*- (range: 0–12 Hz, typical: 8 Hz) isomers.¹⁹⁰

Interestingly, the haloallylation of *para*-dimethylaminobenzaldehyde had proved to be problematic using previously reported procedures when only one equivalent of boron trihalide was used to generate the haloallylated product. As a result of the strong interaction between basic nitrogen with the boron Lewis acid, an extra equivalent of boron trichloride was then used to affect the transformation. To our surprise, the aryl diene was isolated in 81% yield, as opposed to the expected haloallylated product without the use of added base.



7.2.2 Generation of Aryl Trienes from Haloallylation of Aryl Aldehydes

Encouraged by the success of generating 1,3-diene, we were interested in the preparation of trienes using similar strategy. The boron trihalide mediated haloallylation of α -halocinnamaldehydes therefore was investigated. It was found that the reaction gave a mixture of products **703**, **704**, and **705**, as shown in **Scheme 7-3**, consisting of the haloallylation, diallylation, and triene isomers obtained from α -halocinnamaldehydes.

Table 7-1 A Two-pot Reaction Sequence to Generate Aryl Diene.^a

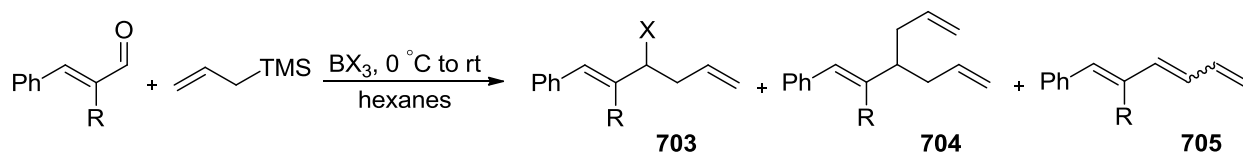
Entry	R	R ¹	R ²	Product	Yield ^b (%)
1	H	H	H	701a	60
2	H	H	Cl	701b	79
3	H	H	Br	701c	79
4	H	Cl	H	701d	80
5	H	Br	H	701e	80
6	Br	H	H	701f	-
7	H	H	NO ₂ ^c	701g	35
8	H	H	CN ^c	701h	10
9	H	CHO	H	701i	63 ^d
10	2,6-Me ₂	H	H	701j	-
11	Naphthyl		H	701k	92

^a Boron halide and allylsilane were added to the aldehyde under an argon atmosphere at 0 °C and then the reaction mixture was warmed to room temperature for 30 minutes, after simple aqueous work up, DBU was added (see Experimental for details).

^b Isolated yield based on aldehyde.

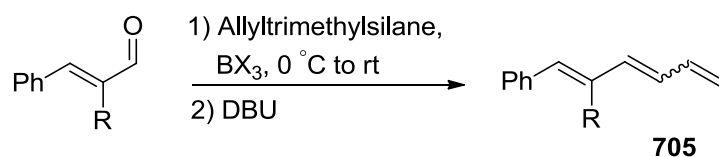
^c Refluxing is required for completion for the bromoallylation step.

^d An additional equivalent of boron trichloride and allyltrimethylsilane were used for bromoallylation step.

**Scheme 7-3** Haloallylation of α -Halocinnamaldehydes.

Interestingly, in the absence of any base triene **705** was formed in the haloallylation step most probably owe to its stable conjugation. Attempts to isolate the products by either column chromatography or distillation met with limited success. Therefore, we decided to examine the feasibility of converting the product **703** to triene **705** using the previously developed two-pot reaction sequence to 1,3-diene. As the data in **Table 7-2** illustrates, syntheses of trienes have been accomplished with moderate success but products were isolated as isomeric mixtures, as determined by NMR spectroscopy and GCMS. Similar to previous observations, the boron tribromide mediated reaction (Entry 1, **Table 7-2**) yields similar results in less time. The triene isomers are separable by column chromatography and it has been determined that the (*Z,E*)-triene is the major isomer formed during the reaction based on isolated yield.

Table 7-2 Synthesis of Trienes.^a



Entry	R	X	25 °C (hr)	Product ^b	Yield ^c (%)
1	Br	Br	2	705a	68
2	Cl	Cl	3	705b	70

^a Boron halide and allylsilane were added to the aldehyde under an argon atmosphere at 0 °C and then the reaction mixture was warmed to room temperature for 30 minutes, after simple aqueous workup DBU was added (see Experimental for details).

^b Isomeric Mixture.

^c Isolated yield based on aldehyde.

7.3 Conclusions

In conclusion, a stereoselective formation of aryl-(*E*)-1,3-butadienes in a simple two-pot reaction sequence was developed based on the boron trihalide mediated reactions of aryl aldehydes followed by the base induced β -elimination using DBU. This process may also be used to form isomeric mixtures of 1,3,5-trienes from α -halocinnamaldehydes that predominantly consist of (*Z,E*)-trienes. Reaction conditions are mild and reagents are readily commercial available.

7.4 Experimental

7.4.1 General Methods

All reagents were used as received. Column chromatography was performed using silica gel (60 Å, 230–400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical thin-layer chromatography was performed using 250 μ m silica plates (Analtech, Inc., Newark, DE).

^1H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, respectively. Chemical shifts for ^1H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. Atlantic Microlab, Inc., Norcross, Georgia, performed microanalysis.

Gas Chromatography-Mass Spectroscopy studies were run on Hewlett Packard: HP 6890 series GC System with 5973 Mass Selective Detector; Column: Agilent 19091S-433E, 30.0mm X 0.25mm X 0.25 μ m; Gas (He) flow rate: 0.8 mL/min; Initial temperature; 50 °C (hold 1 min); Ramp temperature rate: 7 °C/min to maximum 280 °C.

7.4.2 Typical Reaction Procedure for Aryl Dienes and Trienes

Finely ground 4-chlorobenzaldehyde (210 mg, 1.5 mmol), allyltrimethylsilane (256 mg, 2.25 mmol) and dry hexanes (16 mL) are placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a magnetic stirring bar. The solution is cooled to 0 °C, and boron tribromide (1.65 mmol, 1.65 mL of a 1.0 M CH₂Cl₂ solution) is added *via* syringe. After completion of the addition, the ice-bath is removed and the resulting solution is allowed to warm to room temperature until complete. The reaction mixture is hydrolyzed with water and extracted with dichloromethane. The organic layer is washed three times with a saturated solution of aqueous sodium bicarbonate, once with brine, then separated, and dried over anhydrous MgSO₄. After filtration, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.37 g, 9 mmol) is added neat and the mixture allowed to react until completion. Once complete, the organic layer is washed three times with an aqueous 1.0 M solution of hydrochloric acid, once with brine, and then dried over anhydrous MgSO₄. The solvent is removed under reduced pressure, and the product isolated by column chromatography using hexanes.

7.4.3 Procedure for One Pot Formation of (E)-4-(buta-1,3-dien-1-yl)-N,N-dimethylaniline

4-(Dimethylamino)benzaldehyde (224 mg, 1.5 mmol), allyltrimethylsilane (342 mg, 3.00 mmol) and dry dichloromethane (10 mL) are placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a magnetic stirring bar. The solution is cooled to 0 °C, and boron trichloride (3.3 mmol, 3.3 mL of a 1.0 M CH₂Cl₂ solution) is added *via* syringe. After completion of the addition, the ice-bath is removed and the resulting solution is allowed to warm to room

temperature until complete. The reaction mixture is hydrolyzed with a solution of saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer is washed three times with a saturated aqueous solution of sodium bicarbonate, once with brine, then separated, and dried over anhydrous MgSO_4 . The solvent is removed under reduced pressure, and the product isolated by column chromatography using hexanes:ethyl acetate :triethylamine (10:1:0.01) as the eluent.

7.4.4 Characterization of Compounds 701a - j, 702, and 705a - b. (Representative

NMR spectra in **Appendix G**)

(E)-Buta-1,3-dien-1-ylbenzene (701a)¹⁷¹: ^1H NMR (250 MHz, CDCl_3): δ 7.38 (d, J = 7.4 Hz, 2H), 7.29 (t, J = 7.2 Hz, 2H), 7.20 (dd, J = 8.2, 5.3 Hz, 1H), 6.78 (dd, J = 15.6, 10.6 Hz, 1H), 6.61 – 6.38 (m, 2H), 5.31 (d, J = 16.6 Hz, 1H), 5.16 (d, J = 9.2 Hz, 1H). ^{13}C NMR (63 MHz, CDCl_3): δ 137.2, 132.9, 129.6, 128.6, 127.6, 127.2, 126.4, 117.6.

(E)-1-(Buta-1,3-dien-1-yl)-4-chlorobenzene (701b)¹⁷¹: ^1H NMR (250 MHz, CDCl_3): δ 7.26 (d, J = 2.5 Hz, 4H), 6.72 (dd, J = 15.0, 10.9 Hz, 1H), 6.57 – 6.36 (m, 2H), 5.32 (d, J = 16.7 Hz, 1H), 5.18 (d, J = 9.7 Hz, 1H). ^{13}C NMR (63 MHz, CDCl_3): δ 136.8, 135.6, 133.1, 131.4, 130.1, 128.7, 127.5, 118.2.

(E)-1-Bromo-4-(buta-1,3-dien-1-yl)benzene (701c)¹⁷¹: ^1H NMR (250 MHz, CDCl_3): δ 7.39 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 6.72 (dd, J = 16.3, 10.3 Hz, 1H), 6.53 – 6.35 (m, 2H), 5.32 (d, J = 17.6 Hz, 1H), 5.18 (d, J = 9.9 Hz, 1H). ^{13}C NMR (63 MHz, CDCl_3): δ 136.9, 136.0, 131.7, 131.6, 130.2, 127.9, 121.4, 118.4.

(E)-1-(buta-1,3-dien-1-yl)-3-chlorobenzene (701d)¹⁹¹: ^1H NMR (250 MHz, CDCl_3): δ 7.37 (s, 1H), 7.27 – 7.13 (m, 3H), 6.76 (dd, J = 16.0, 10.6 Hz, 1H), 6.60 – 6.36 (m, 2H), 5.35 (d, J = 16.9

Hz, 1H), 5.21 (d, J = 10.6 Hz, 1H). ^{13}C NMR (63 MHz, CDCl_3): δ 139.0, 136.7, 134.5, 131.2, 130.9, 129.7, 127.4, 126.2, 124.6, 118.7.

(E)-1-Bromo-3-(buta-1,3-dien-1-yl)benzene (701e)¹⁹¹: ^1H NMR (250 MHz, CDCl_3): δ 7.53 (s, 1H), 7.30 (dd, J = 12.6, 7.8 Hz, 2H), 7.14 (t, J = 7.8 Hz, 1H), 6.75 (dd, J = 15.8, 10.2 Hz, 1H), 6.57 – 6.38 (m, 2H), 5.35 (d, J = 16.9 Hz, 1H), 5.21 (d, J = 9.3 Hz, 1H). ^{13}C NMR (63 MHz, CDCl_3): δ 139.3, 136.7, 131.1, 131.0, 130.3, 130.0, 129.1, 125.0, 122.8, 118.7.

(E)-1-(Buta-1,3-dien-1-yl)-4-nitrobenzene (701g)¹⁹²: ^1H NMR (250 MHz, CDCl_3): δ 8.17 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 6.93 (dd, J = 16.3, 10.3 Hz, 1H), 6.69 – 6.39 (m, 2H), 5.48 (d, J = 16.7 Hz, 1H), 5.34 (d, J = 9.7 Hz, 1H). ^{13}C NMR (63 MHz, CDCl_3): δ 143.6, 136.3, 133.9, 130.3, 129.1, 126.7, 124.0, 120.8, 116.8.

(E)-4-(Buta-1,3-dien-1-yl)benzonitrile (701h)¹⁹³: ^1H NMR (250 MHz, CDCl_3): δ 7.59 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 6.88 (dd, J = 15.3, 10.8 Hz, 1H), 6.64 – 6.37 (m, 2H), 5.44 (d, J = 16.2 Hz, 1H), 5.31 (d, J = 9.3 Hz, 1H). ^{13}C NMR (63 MHz, CDCl_3): δ 141.6, 136.4, 133.0, 132.3, 130.7, 126.7, 120.3, 119.9, 118.9.

1,3-Di((E)-buta-1,3-dien-1-yl)benzene (701i): ^1H NMR (250 MHz, CDCl_3): δ 7.40 (s, 1H), 7.31 – 7.16 (m, 3H), 6.79 (dd, J = 15.3, 10.7 Hz, 2H), 6.60 – 6.39 (m, 4H), 5.33 (d, J = 15.8 Hz, 2H), 5.17 (d, J = 8.4 Hz, 2H). ^{13}C NMR (63 MHz, CDCl_3): δ 137.4, 137.1, 132.6, 129.8, 128.8, 125.6, 124.6, 117.8. HRMS-ESI⁺ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{14}$, 183.117; found, 183.117.

(E)-1-(Buta-1,3-dien-1-yl)naphthalene (701k)¹⁷¹: ^1H NMR (250 MHz, CDCl_3): δ 8.08 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.1 Hz, 1H), 7.42 (dd, J = 4.7, 3.3 Hz, 2H), 7.32 (dd, J = 15.9, 11.9 Hz, 2H), 6.80 (dd, J = 15.0, 10.7 Hz, 1H), 6.71 – 6.47 (m, 1H), 5.33 (d, J = 16.7 Hz, 1H), 5.19 (d, J = 9.7 Hz, 1H). ^{13}C NMR (63 MHz, CDCl_3): δ 137.5, 134.6, 133.8, 132.5, 131.3, 129.7, 128.7, 128.1, 126.2, 125.9, 125.7, 123.7, 123.5, 118.0.

(E)-4-(Buta-1,3-dien-1-yl)-N,N-dimethylaniline (702)¹⁹⁴: ¹H NMR (250 MHz, CDCl₃): δ 7.18 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 8.9 Hz, 2H), 6.50 (d, *J* = 9.8 Hz, 1H), 6.38 (dt, *J* = 17.4, 10.4 Hz, 2H), 5.12 (d, *J* = 17.3 Hz, 1H), 4.94 (d, *J* = 9.0 Hz, 1H), 2.82 (s, 6H). ¹³C NMR (63 MHz, CDCl₃): δ 150.1, 137.9, 133.2, 127.6, 125.6, 115.0, 112.4, 40.4.

((1Z,3E)-2-Bromohexa-1,3,5-trien-1-yl)benzene (705a): ¹H NMR (250 MHz, CDCl₃): δ 7.40 – 7.25 (m, 5H), 7.11 (s, 1H), 6.78 (dd, *J* = 14.7, 10.7 Hz, 1H), 6.63 (d, *J* = 14.4 Hz, 1H), 6.43 (dt, *J* = 16.9, 10.2 Hz, 1H), 5.41 (d, *J* = 16.2 Hz, 1H), 5.25 (d, *J* = 10.7 Hz, 1H). ¹³C NMR (63 MHz, CDCl₃): δ 138.0, 136.3, 135.9, 134.3, 128.9, 128.4, 127.7, 127.3, 124.0, 120.5. HRMS-ESI⁺ (*m/z*): [M-Br]⁺ calcd for C₁₂H₁₁Br, 155.086; found, 155.085.

((1Z,3E)-2-Chlorohexa-1,3,5-trien-1-yl)benzene (705b): ¹H NMR (250 MHz, CDCl₃): δ 7.71 (d, *J* = 7.0 Hz, 2H), 7.35 (dd, *J* = 14.7, 7.3 Hz, 3H), 6.77 (dd, *J* = 14.3, 10.3 Hz, 1H), 6.67 (s, 1H), 6.48 (dt, *J* = 18.9, 11.8 Hz, 2H), 5.40 (d, *J* = 16.7 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H). ¹³C NMR (63 MHz, CDCl₃): δ 135.9, 134.9, 132.6, 131.9, 130.7, 129.6, 128.9, 128.2, 128.1, 119.7. HRMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₁₂H₁₁Cl, 191.063; found, 191.062.

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Appendices

Appendix A: X-ray Data for 203: (E, E)-1,5-dichloro-1,5-diphenyl-3-(4-bromophenyl)-penta-1,4-diene

Table A-1 Crystal Data and Structure Refinement for 203

Parameter	Output	
Identification code	203	
Empirical formula	C ₂₃ H ₁₇ Br Cl ₂	
Formula weight	444.18	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.730(2) Å	$\alpha = 90^\circ$
	b = 13.248(3) Å	$\beta = 95.957(4)^\circ$
	c = 16.912(4) Å	$\gamma = 90^\circ$
Volume	1945.4(8) Å ³	
Z	4	
Density (calculated)	1.517 Mg/m ³	
Absorption coefficient	2.392 mm ⁻¹	
F(000)	896	
Crystal size	0.39 x 0.22 x 0.20 mm ³	
Theta range for data collection	1.96 to 26.20°.	
Index ranges	-10 ≤ h ≤ 10, -16 ≤ k ≤ 16, -20 ≤ l ≤ 20	
Reflections collected	17368	
Independent reflections	3899 [R(int) = 0.0576]	
Completeness to theta = 26.20	99.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3899 / 0 / 235	
Goodness-of-fit on F ²	1.056	

Table A-1 continued

Parameter	Output
Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.0963
R indices (all data)	R1 = 0.0375, wR2 = 0.1008
Largest diff. peak and hole	0.843 and -0.383 e. ⁻³

Table A-2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (2×10^3) for **203**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

Atom	x	y	z	U(eq)
Br(1)	6530(1)	172(1)	8048(1)	40(1)
C(1)	5702(2)	1503(2)	7943(1)	29(1)
C(2)	5818(3)	2026(2)	7252(1)	34(1)
C(3)	5212(3)	2991(2)	7174(1)	32(1)
C(4)	4491(2)	3442(2)	7785(1)	24(1)
C(5)	4425(2)	2899(2)	8482(1)	29(1)
C(6)	5034(3)	1929(2)	8567(1)	31(1)
C(7)	3802(2)	4499(2)	7668(1)	24(1)
C(8)	2940(2)	4562(2)	6844(1)	26(1)
C(9)	3153(3)	5233(2)	6281(1)	26(1)
C(10)	4140(2)	6139(2)	6326(1)	25(1)
C(11)	5031(2)	6388(2)	5712(1)	33(1)
C(12)	5963(3)	7233(2)	5767(1)	40(1)
C(13)	6022(3)	7848(2)	6428(2)	39(1)
C(14)	5146(3)	7612(2)	7042(1)	34(1)
C(15)	4201(2)	6767(2)	6986(1)	27(1)
C(16)	2663(2)	4740(2)	8258(1)	26(1)
C(17)	2837(2)	5439(2)	8822(1)	24(1)

Table A-2 continued

Atom	x	y	z	U(eq)
C(18)	4187(2)	6085(2)	9049(1)	23(1)
C(19)	5654(2)	5663(2)	9191(1)	28(1)
C(20)	6922(2)	6286(2)	9395(1)	34(1)
C(21)	6741(3)	7314(2)	9449(1)	36(1)
C(22)	5286(3)	7742(2)	9311(1)	34(1)
C(23)	4015(2)	7129(2)	9120(1)	29(1)
Cl(2)	2124(1)	5031(1)	5340(1)	34(1)
Cl(3)	1277(1)	5655(1)	9382(1)	35(1)

Table A-3 Bond Lengths [Å] and Angles[°] for **203**

Br(1)-C(1)	1.906(2)	C(17)-C(18)	1.474(3)
C(1)-C(2)	1.372(3)	C(17)-Cl(3)	1.760(2)
C(1)-C(6)	1.378(3)	C(18)-C(19)	1.395(3)
C(2)-C(3)	1.385(3)	C(18)-C(23)	1.398(3)
C(2)-H(2)	0.95	C(19)-C(20)	1.395(3)
C(3)-C(4)	1.398(3)	C(19)-H(19)	0.95
C(3)-H(3)	0.95	C(20)-C(21)	1.376(4)
C(4)-C(5)	1.387(3)	C(20)-H(20)	0.95
C(4)-C(7)	1.529(3)	C(21)-C(22)	1.388(4)
C(5)-C(6)	1.392(3)	C(21)-H(21)	0.95
C(5)-H(5)	0.95	C(22)-C(23)	1.385(3)
C(6)-H(6)	0.95	C(22)-H(22)	0.95
C(7)-C(16)	1.515(3)	C(23)-H(23)	0.95
C(7)-C(8)	1.516(3)		
C(7)-H(7)	1	C(2)-C(1)-C(6)	121.3(2)
C(8)-C(9)	1.329(3)	C(2)-C(1)-Br(1)	119.04(16)
C(8)-H(8)	0.95	C(6)-C(1)-Br(1)	119.62(16)
C(9)-C(10)	1.475(3)	C(1)-C(2)-C(3)	119.1(2)
C(9)-Cl(2)	1.765(2)	C(1)-C(2)-H(2)	120.5
C(10)-C(15)	1.389(3)	C(3)-C(2)-H(2)	120.5
C(10)-C(11)	1.400(3)	C(2)-C(3)-C(4)	121.4(2)
C(11)-C(12)	1.381(4)	C(2)-C(3)-H(3)	119.3
C(11)-H(11)	0.95	C(4)-C(3)-H(3)	119.3

Table A-3 continued

C(12)-C(13)	1.380(4)	C(17)-C(16)-C(7)	125.99(19)
C(12)-H(12)	0.95	C(17)-C(16)-H(16)	117
C(13)-C(14)	1.388(3)	C(5)-C(4)-C(3)	117.9(2)
C(13)-H(13)	0.95	C(5)-C(4)-C(7)	122.37(18)
C(14)-C(15)	1.389(3)	C(3)-C(4)-C(7)	119.76(18)
C(14)-H(14)	0.95	C(4)-C(5)-C(6)	121.17(19)
C(15)-H(15)	0.95	C(4)-C(5)-H(5)	119.4
C(16)-C(17)	1.327(3)	C(6)-C(5)-H(5)	119.4
C(16)-H(16)	0.95	C(1)-C(6)-C(5)	119.1(2)
C(16)-C(7)-C(8)	107.30(17)	C(1)-C(6)-H(6)	120.4
C(16)-C(7)-C(4)	112.60(17)	C(5)-C(6)-H(6)	120.4
C(8)-C(7)-C(4)	108.74(17)	C(7)-C(16)-H(16)	117
C(16)-C(7)-H(7)	109.4	C(16)-C(17)-C(18)	128.34(18)
C(8)-C(7)-H(7)	109.4	C(16)-C(17)-Cl(3)	117.57(16)
C(4)-C(7)-H(7)	109.4	C(18)-C(17)-Cl(3)	114.09(14)
C(9)-C(8)-C(7)	127.02(19)	C(19)-C(18)-C(23)	119.10(19)
C(9)-C(8)-H(8)	116.5	C(19)-C(18)-C(17)	120.44(19)
C(7)-C(8)-H(8)	116.5	C(23)-C(18)-C(17)	120.46(18)
C(8)-C(9)-C(10)	129.22(19)	C(18)-C(19)-C(20)	119.7(2)
C(8)-C(9)-Cl(2)	116.60(17)	C(18)-C(19)-H(19)	120.1
C(10)-C(9)-Cl(2)	114.18(15)	C(20)-C(19)-H(19)	120.1
C(15)-C(10)-C(11)	118.5(2)	C(21)-C(20)-C(19)	120.6(2)
C(15)-C(10)-C(9)	120.10(18)	C(21)-C(20)-H(20)	119.7
C(11)-C(10)-C(9)	121.40(19)	C(19)-C(20)-H(20)	119.7
C(12)-C(11)-C(10)	120.6(2)	C(20)-C(21)-C(22)	120.1(2)
C(12)-C(11)-H(11)	119.7	C(20)-C(21)-H(21)	119.9
C(10)-C(11)-H(11)	119.7	C(22)-C(21)-H(21)	119.9
C(13)-C(12)-C(11)	120.4(2)	C(23)-C(22)-C(21)	119.8(2)
C(13)-C(12)-H(12)	119.8	C(23)-C(22)-H(22)	120.1
C(11)-C(12)-H(12)	119.8	C(21)-C(22)-H(22)	120.1
C(12)-C(13)-C(14)	119.8(2)	C(22)-C(23)-C(18)	120.6(2)
C(12)-C(13)-H(13)	120.1	C(22)-C(23)-H(23)	119.7
C(14)-C(13)-H(13)	120.1	C(18)-C(23)-H(23)	119.7
C(13)-C(14)-C(15)	119.9(2)		
C(13)-C(14)-H(14)	120		
C(15)-C(14)-H(14)	120		
C(14)-C(15)-C(10)	120.8(2)		
C(14)-C(15)-H(15)	119.6		
C(10)-C(15)-H(15)	119.6		

Table A-4 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **203**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	43(1)	23(1)	53(1)	-4(1)	-3(1)	5(1)
C(1)	29(1)	20(1)	36(1)	-3(1)	-1(1)	-1(1)
C(2)	39(1)	34(1)	29(1)	-6(1)	6(1)	5(1)
C(3)	40(1)	32(1)	24(1)	1(1)	6(1)	4(1)
C(4)	24(1)	22(1)	26(1)	-1(1)	2(1)	-3(1)
C(5)	32(1)	26(1)	29(1)	0(1)	9(1)	0(1)
C(6)	35(1)	27(1)	32(1)	5(1)	6(1)	-3(1)
C(7)	27(1)	21(1)	24(1)	-1(1)	3(1)	-3(1)
C(8)	26(1)	23(1)	29(1)	-3(1)	1(1)	-1(1)
C(9)	28(1)	27(1)	24(1)	-3(1)	-2(1)	5(1)
C(10)	24(1)	25(1)	27(1)	5(1)	1(1)	5(1)
C(11)	34(1)	35(1)	29(1)	5(1)	7(1)	9(1)
C(12)	34(1)	41(2)	45(1)	13(1)	12(1)	4(1)
C(13)	33(1)	29(1)	55(1)	12(1)	0(1)	-4(1)
C(14)	35(1)	26(1)	39(1)	0(1)	-3(1)	1(1)
C(15)	29(1)	24(1)	29(1)	3(1)	2(1)	3(1)
C(16)	24(1)	23(1)	31(1)	3(1)	5(1)	-2(1)
C(17)	22(1)	23(1)	27(1)	3(1)	7(1)	5(1)
C(18)	26(1)	25(1)	19(1)	1(1)	6(1)	1(1)
C(19)	29(1)	28(1)	27(1)	4(1)	6(1)	4(1)
C(20)	26(1)	46(2)	30(1)	5(1)	3(1)	0(1)
C(21)	37(1)	44(2)	28(1)	-4(1)	2(1)	-14(1)
C(22)	46(1)	27(1)	29(1)	-5(1)	6(1)	-5(1)
C(23)	32(1)	26(1)	27(1)	-1(1)	4(1)	4(1)
Cl(2)	40(1)	33(1)	28(1)	-3(1)	-6(1)	3(1)
Cl(3)	27(1)	36(1)	43(1)	0(1)	15(1)	5(1)

Table A-5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($^2 \times 10^3$)
for **203**

	x	y	z	U(eq)
H(2)	6307	1730	6832	41
H(3)	5287	3355	6696	38
H(5)	3957	3194	8909	34
H(6)	4989	1565	9048	38
H(7)	4649	5010	7717	29
H(8)	2163	4069	6716	32
H(11)	4994	5972	5252	39
H(12)	6566	7391	5348	47
H(13)	6660	8431	6462	47
H(14)	5194	8029	7502	40
H(15)	3589	6616	7403	33
H(16)	1740	4356	8222	31
H(19)	5788	4954	9149	33
H(20)	7919	5997	9497	41
H(21)	7614	7733	9581	44
H(22)	5162	8452	9348	41
H(23)	3018	7422	9036	34

Appendix B: X-ray Data for (E)-1-chloro-4-(3-chloro-1-phenyl-3-(p-tolyl)allyl)benzene, Compound 401d.

Table B-1 Crystal Data and Structure Refinement for **401d**

Identification code	401d	
Empirical formula	C ₂₂ H ₁₈ Cl ₂	
Formula weight	353.26	
Temperature	273(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.1068(10) Å	$\alpha = 83.794(2)^\circ$
	b = 9.9707(11) Å	$\beta = 77.895(2)^\circ$
	c = 10.3942(12) Å	$\gamma = 88.158(2)^\circ$
Volume	917.37(18) Å ³	
Z	2	
Density (calculated)	1.279 Mg/m ³	
Absorption coefficient	0.353 mm ⁻¹	
F(000)	368	
Crystal size	0.60 x 0.20 x 0.20 mm ³	
Theta range for data collection	2.01 to 27.85_	
Index ranges	-11 ≤ h ≤ 11, -13 ≤ k ≤ 12, -13 ≤ l ≤ 13	
Reflections collected	9505	
Independent reflections	4062 [R(int) = 0.0166]	
Completeness to theta = 27.85_	93.40%	
Max. and min. transmission	0.9327 and 0.8160	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4062 / 0 / 218	
Goodness-of-fit on F ²	1.037	
Final R indices [I > 2σ(I)]	R1 = 0.0545, wR2 = 0.1546	
R indices (all data)	R1 = 0.0705, wR2 = 0.1706	
Largest diff. peak and hole	1.058 and -0.223 e.Å ⁻³	

Table B-2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($C2x$ 103) for **401d**. $U(eq)$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(eq)$
C(1)	2514(3)	4374(2)	6959(3)	53(1)
C(2)	1647(3)	3359(3)	7738(3)	61(1)
C(3)	1649(3)	3155(3)	9066(3)	63(1)
C(4)	2523(4)	3941(3)	9623(3)	72(1)
C(5)	3387(3)	4946(3)	8821(3)	63(1)
C(6)	3380(3)	5191(2)	7482(2)	47(1)
C(7)	4257(3)	6352(2)	6616(2)	47(1)
C(8)	5901(3)	6379(2)	6729(2)	45(1)
C(9)	6734(3)	5183(2)	6747(3)	55(1)
C(10)	8249(3)	5189(3)	6730(3)	64(1)
C(11)	8981(3)	6385(3)	6712(3)	66(1)
C(12)	8168(3)	7570(3)	6716(3)	65(1)
C(13)	6650(3)	7572(2)	6721(3)	55(1)
C(14)	3407(3)	7641(2)	6953(2)	48(1)
C(15)	2875(2)	8520(2)	6114(2)	46(1)
C(16)	3093(2)	8551(2)	4657(2)	43(1)
C(17)	4523(3)	8482(2)	3878(2)	49(1)
C(18)	4723(3)	8479(3)	2533(3)	56(1)
C(19)	3514(3)	8561(2)	1906(3)	57(1)
C(20)	3725(5)	8496(4)	435(3)	89(1)
C(21)	2086(3)	8670(3)	2687(3)	58(1)
C(22)	1879(3)	8667(2)	4024(3)	54(1)
Cl(1)	578(1)	1866(1)	10045(1)	103(1)
Cl(2)	1757(1)	9853(1)	6784(1)	64(1)

Table B-3 Bond Lengths [C] and Angles[Å] for **401d**

C(1)-C(6)	1.378(3)	C(6)-C(1)-C(2)	121.6(2)
C(1)-C(2)	1.382(4)	C(3)-C(2)-C(1)	119.4(2)
C(2)-C(3)	1.373(4)	C(2)-C(3)-C(4)	120.8(2)
C(3)-C(4)	1.384(4)	C(2)-C(3)-Cl(1)	119.4(2)
C(3)-Cl(1)	1.738(3)	C(4)-C(3)-Cl(1)	119.8(2)
C(4)-C(5)	1.384(4)	C(5)-C(4)-C(3)	118.8(3)
C(5)-C(6)	1.388(3)	C(4)-C(5)-C(6)	121.5(2)
C(6)-C(7)	1.524(3)	C(1)-C(6)-C(5)	117.9(2)
C(7)-C(14)	1.514(3)	C(1)-C(6)-C(7)	120.5(2)
C(7)-C(8)	1.527(3)	C(5)-C(6)-C(7)	121.5(2)
C(8)-C(13)	1.388(3)	C(14)-C(7)-C(6)	107.18(19)
C(8)-C(9)	1.394(3)	C(14)-C(7)-C(8)	113.30(18)
C(9)-C(10)	1.377(4)	C(6)-C(7)-C(8)	113.47(17)
C(10)-C(11)	1.381(4)	C(13)-C(8)-C(9)	117.5(2)
C(11)-C(12)	1.374(4)	C(13)-C(8)-C(7)	122.5(2)
C(12)-C(13)	1.382(4)	C(9)-C(8)-C(7)	119.83(19)
C(14)-C(15)	1.322(3)	C(10)-C(9)-C(8)	121.1(2)
C(15)-C(16)	1.483(3)	C(9)-C(10)-C(11)	120.7(2)
C(15)-Cl(2)	1.762(2)	C(12)-C(11)-C(10)	118.8(3)
C(16)-C(17)	1.386(3)	C(11)-C(12)-C(13)	120.8(2)
C(16)-C(22)	1.396(3)	C(12)-C(13)-C(8)	121.1(2)
C(17)-C(18)	1.372(3)	C(15)-C(14)-C(7)	125.8(2)
C(18)-C(19)	1.389(4)	C(14)-C(15)-C(16)	128.8(2)
C(19)-C(21)	1.389(4)	C(14)-C(15)-Cl(2)	117.01(18)
C(19)-C(20)	1.508(4)	C(16)-C(15)-Cl(2)	114.22(15)
C(21)-C(22)	1.362(4)	C(17)-C(16)-C(22)	117.9(2)
		C(17)-C(16)-C(15)	120.54(19)
		C(22)-C(16)-C(15)	121.5(2)
		C(18)-C(17)-C(16)	120.5(2)
		C(17)-C(18)-C(19)	121.6(2)
		C(18)-C(19)-C(21)	117.6(2)
		C(18)-C(19)-C(20)	121.7(3)
		C(21)-C(19)-C(20)	120.7(3)
		C(22)-C(21)-C(19)	121.1(2)
		C(21)-C(22)-C(16)	121.2(2)

symmetry transformations used to generate equivalent atoms:

Table B-4 Anisotropic Displacement Parameters (C2x 103) for **401d**. The Anisotropic Displacement Factor Exponent Takes the Form: $-2p^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

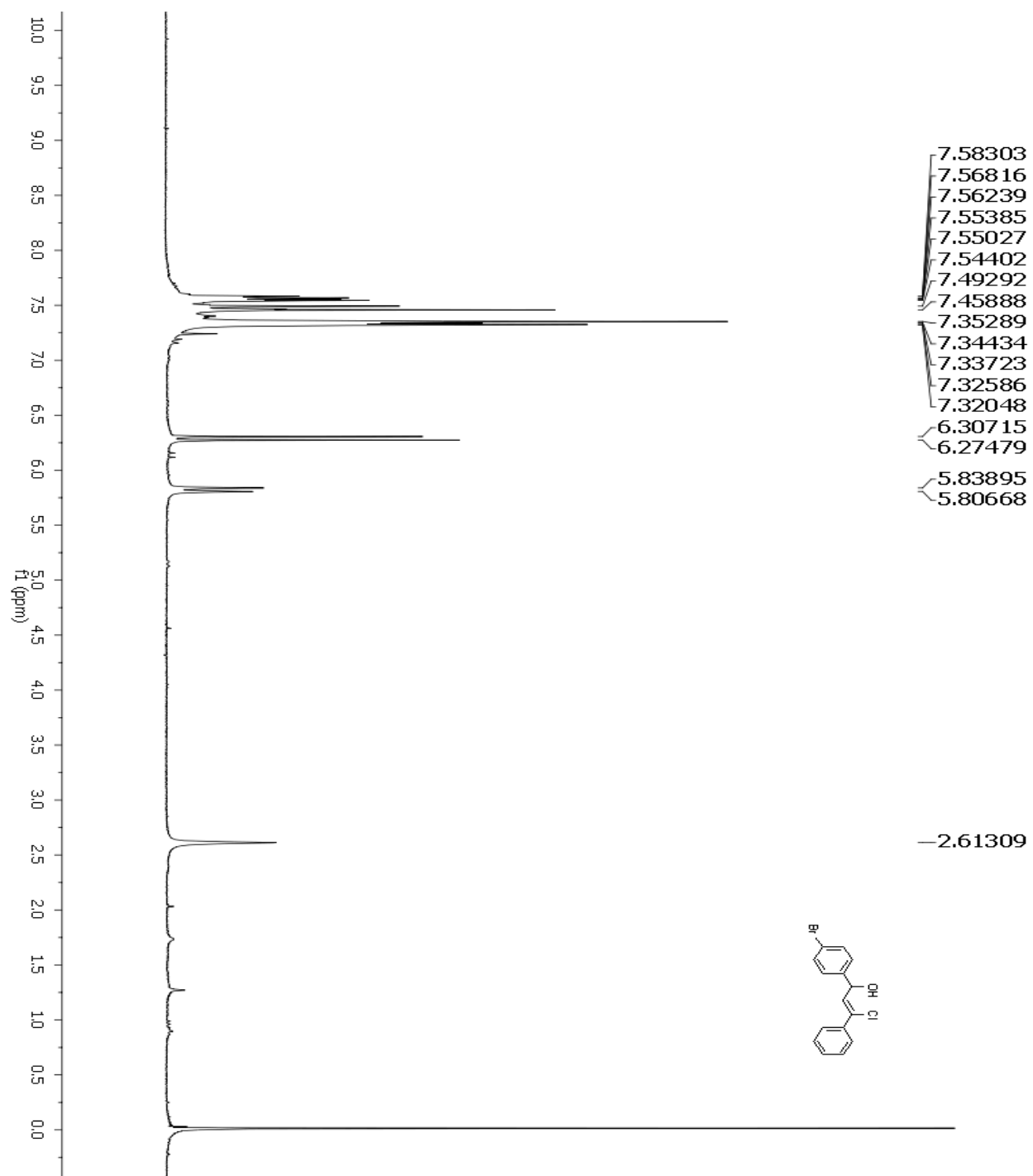
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	54(1)	50(1)	56(1)	-2(1)	-19(1)	2(1)
C(2)	54(1)	52(1)	81(2)	-3(1)	-23(1)	-8(1)
C(3)	57(1)	53(1)	73(2)	6(1)	-4(1)	-12(1)
C(4)	87(2)	72(2)	52(2)	4(1)	-10(1)	-21(2)
C(5)	78(2)	59(2)	54(1)	-1(1)	-18(1)	-20(1)
C(6)	50(1)	40(1)	50(1)	0(1)	-12(1)	1(1)
C(7)	56(1)	40(1)	45(1)	-2(1)	-12(1)	0(1)
C(8)	51(1)	39(1)	44(1)	1(1)	-8(1)	-1(1)
C(9)	61(1)	38(1)	67(2)	-3(1)	-17(1)	0(1)
C(10)	61(2)	51(1)	82(2)	-5(1)	-18(1)	12(1)
C(11)	49(1)	64(2)	82(2)	3(1)	-14(1)	-1(1)
C(12)	61(2)	49(1)	83(2)	5(1)	-13(1)	-12(1)
C(13)	58(1)	37(1)	67(2)	3(1)	-11(1)	0(1)
C(14)	54(1)	46(1)	45(1)	-6(1)	-8(1)	0(1)
C(15)	40(1)	41(1)	55(1)	-1(1)	-9(1)	-2(1)
C(16)	42(1)	32(1)	56(1)	1(1)	-12(1)	-1(1)
C(17)	43(1)	47(1)	58(1)	1(1)	-13(1)	2(1)
C(18)	50(1)	56(1)	58(1)	-2(1)	-5(1)	4(1)
C(19)	73(2)	44(1)	55(1)	-5(1)	-18(1)	-2(1)
C(20)	106(3)	104(3)	61(2)	-16(2)	-25(2)	-1(2)
C(21)	55(1)	58(1)	67(2)	-6(1)	-24(1)	-4(1)
C(22)	41(1)	53(1)	66(2)	-1(1)	-13(1)	-2(1)
Cl(1)	101(1)	93(1)	105(1)	26(1)	-11(1)	-47(1)
Cl(2)	58(1)	58(1)	74(1)	-15(1)	-8(1)	12(1)

Table B-5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **401d**.

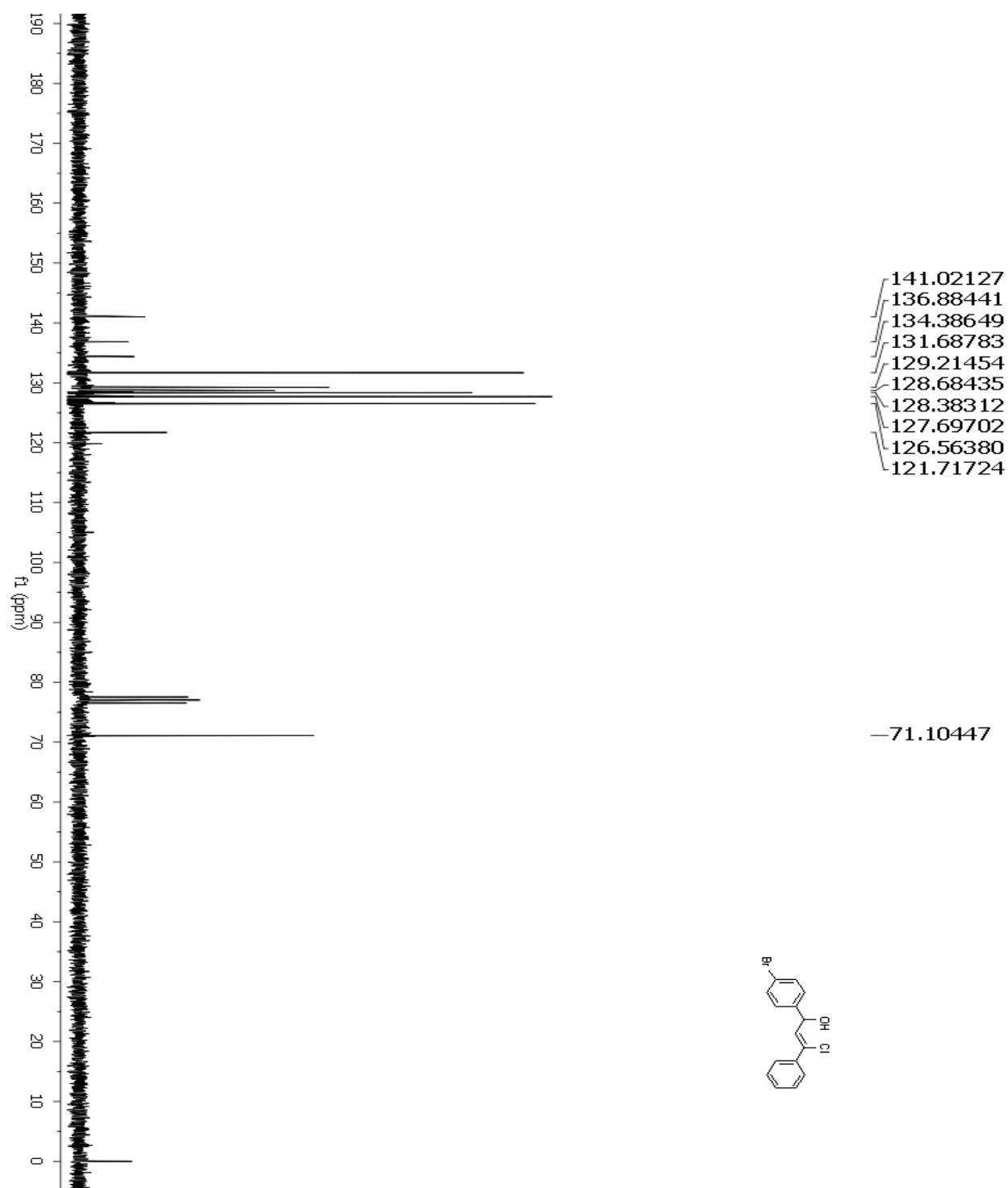
	x	y	z	U(eq)
H(1)	2513	4508	6059	63
H(2)	1068	2819	7368	73
H(4)	2528	3797	10521	86
H(5)	3987	5470	9187	76
H(7)	4239	6241	5694	56
H(9)	6258	4366	6771	66
H(10)	8786	4380	6732	77
H(11)	10006	6388	6697	79
H(12)	8646	8381	6714	78
H(13)	6121	8385	6720	66
H(14)	3244	7831	7828	58
H(17)	5355	8437	4270	59
H(18)	5692	8421	2029	67
H(20A)	3084	7815	271	133
H(20B)	4753	8275	78	133
H(20C)	3472	9355	21	133
H(21)	1257	8745	2291	70
H(22)	911	8744	4524	64

Appendix C: Representative NMR Spectra of compounds 303 and 304a-g for Chapter 3.

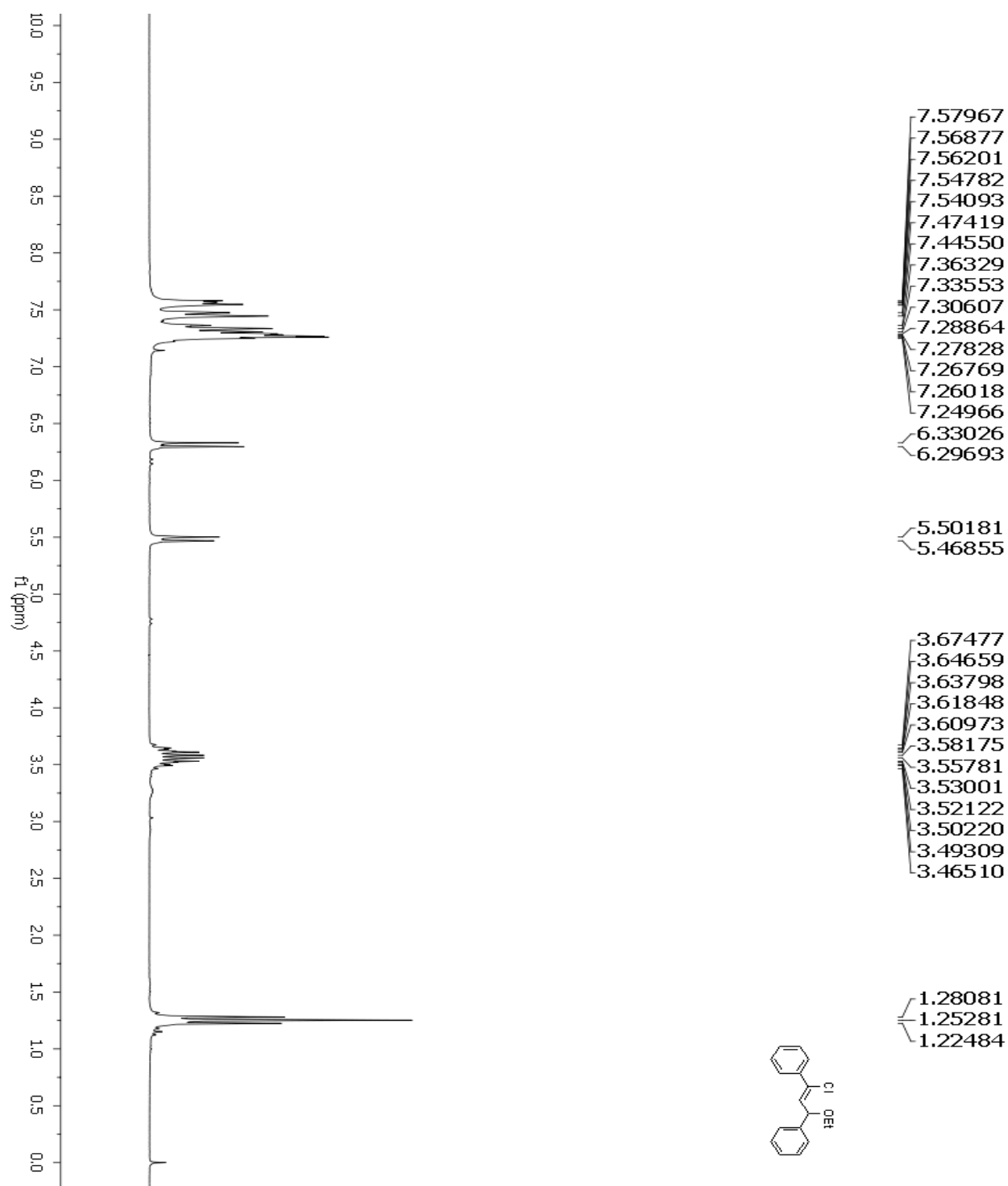
¹H spectrum of 303



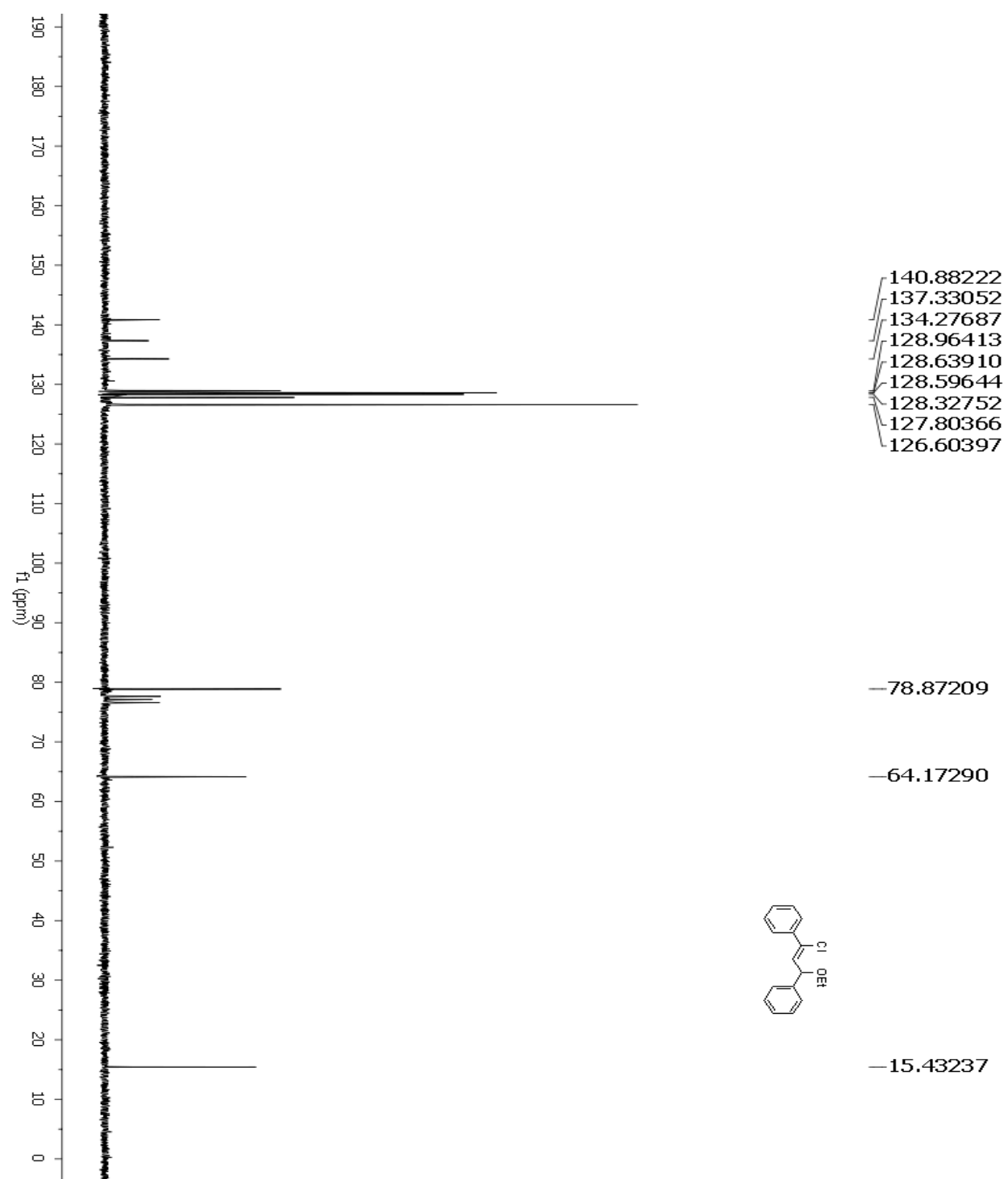
¹³C spectrum of 303



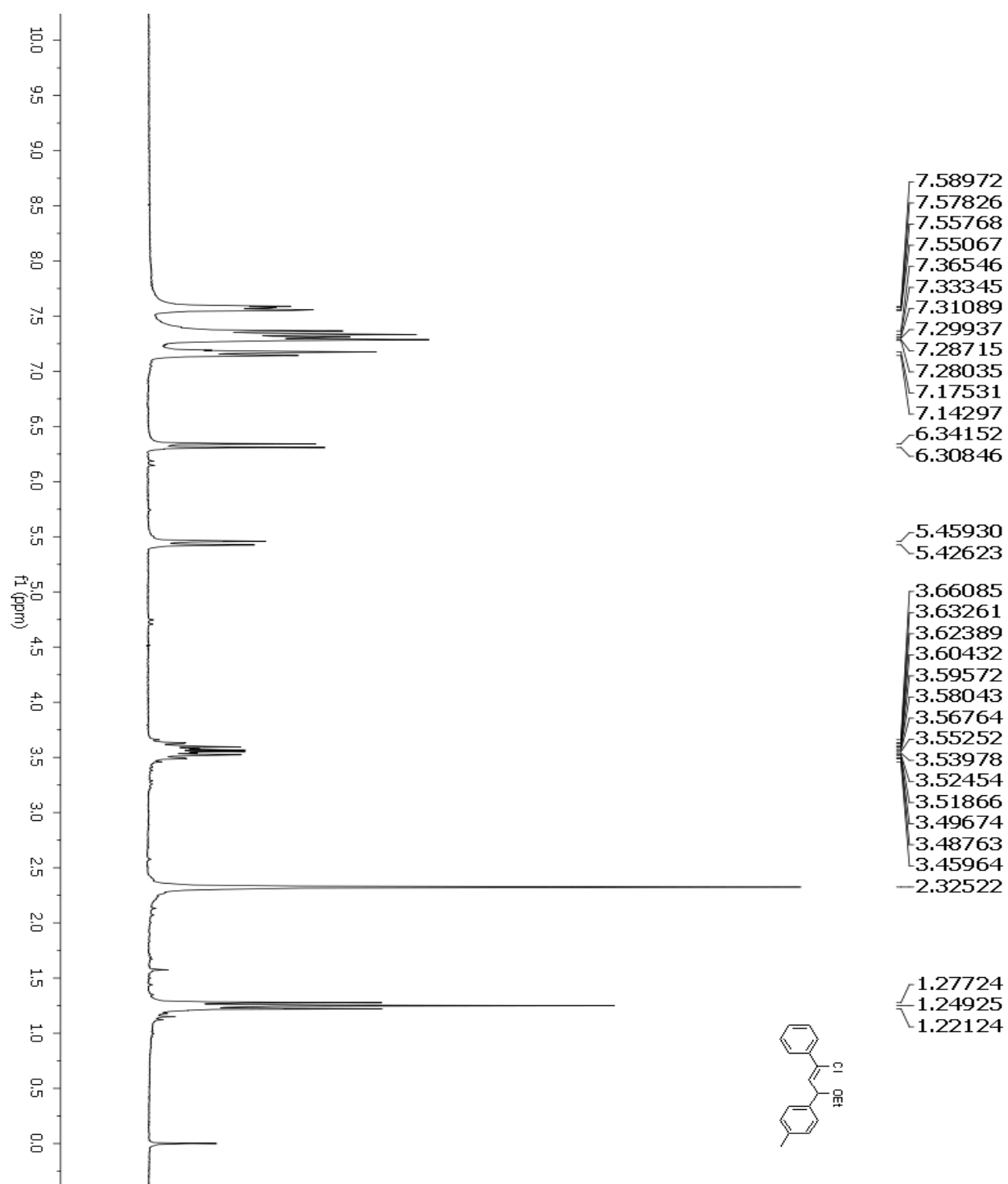
¹H spectrum of 304a



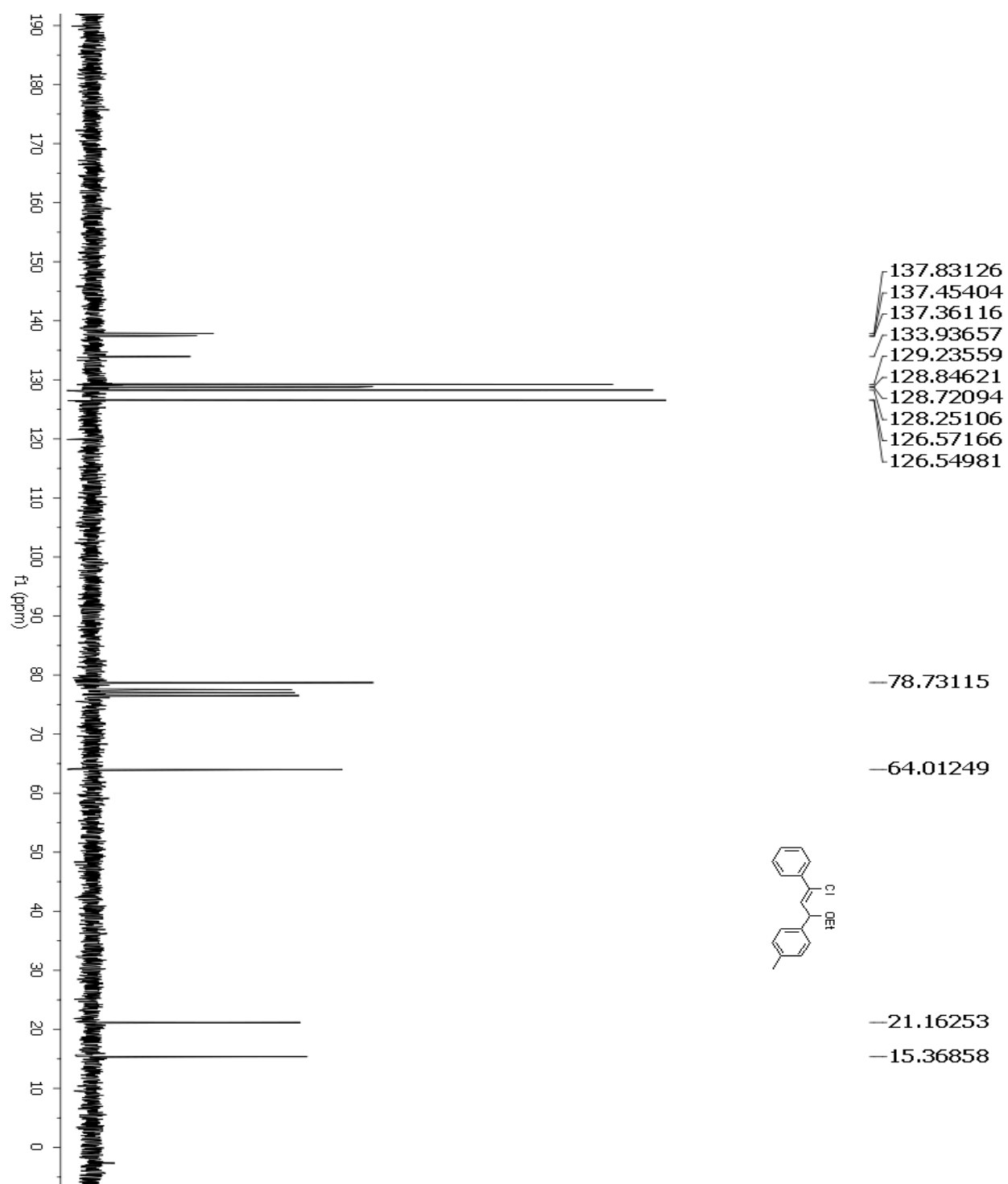
¹³C spectrum of 304a



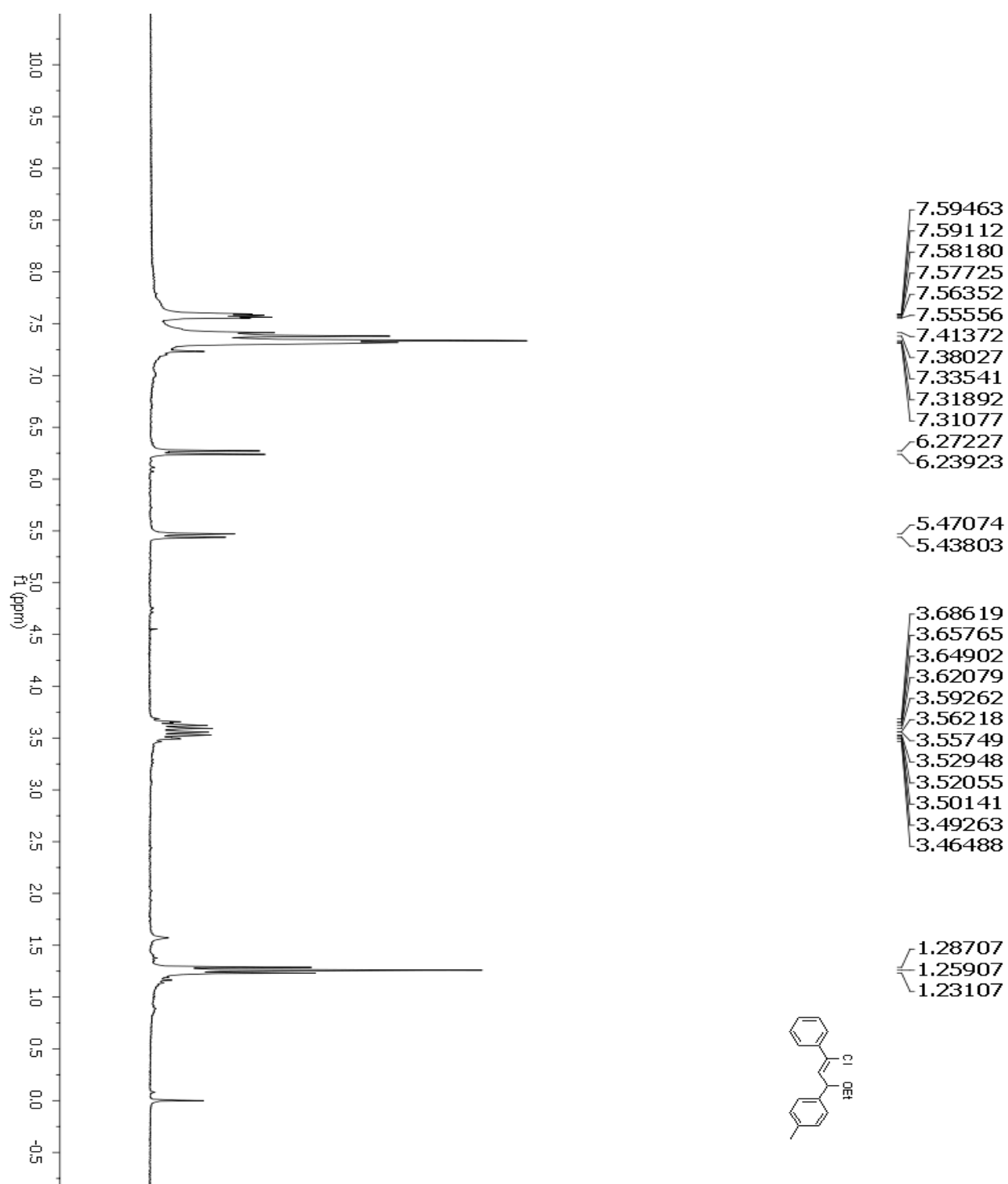
¹H spectrum of 304b



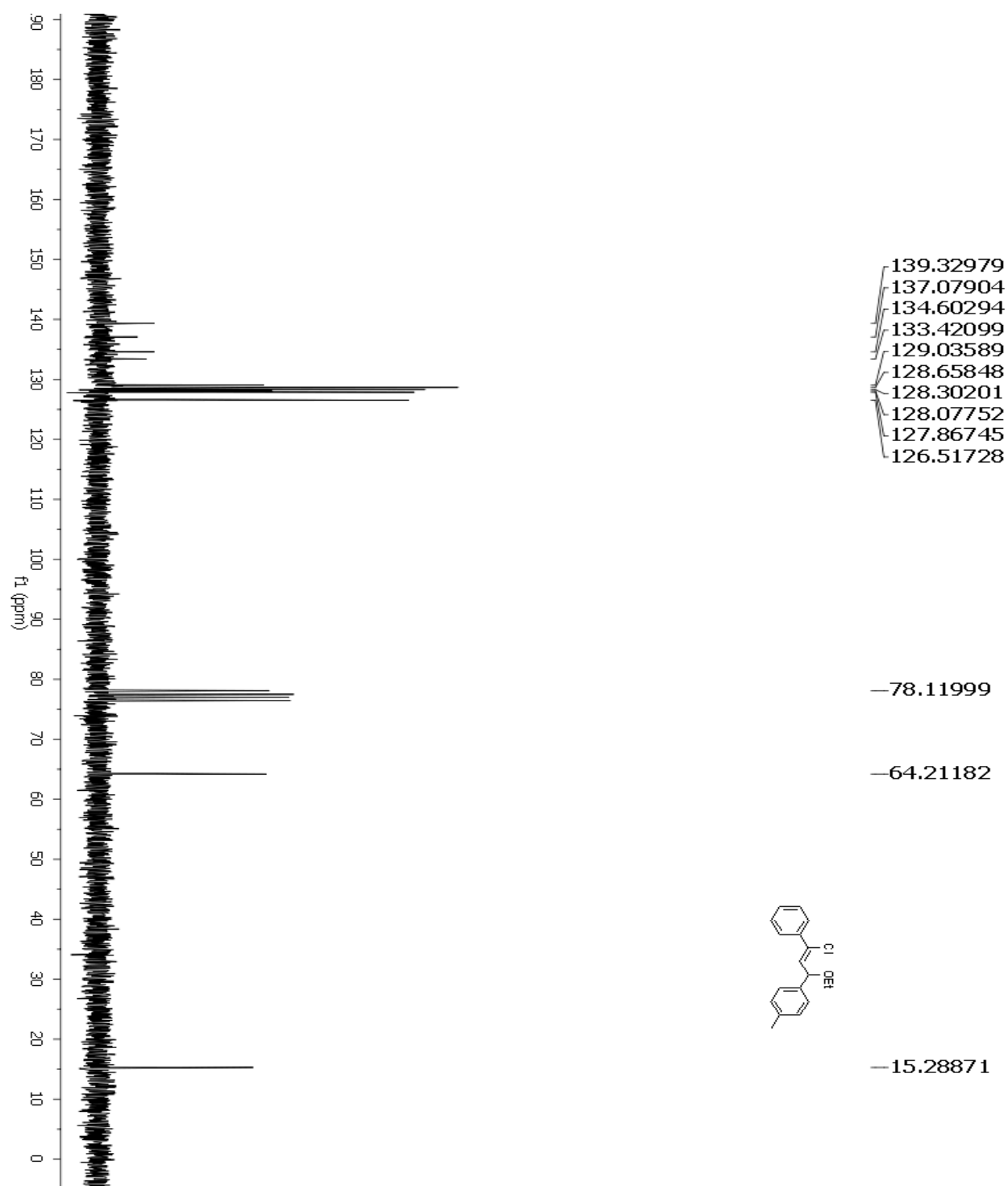
¹³C spectrum of 304b



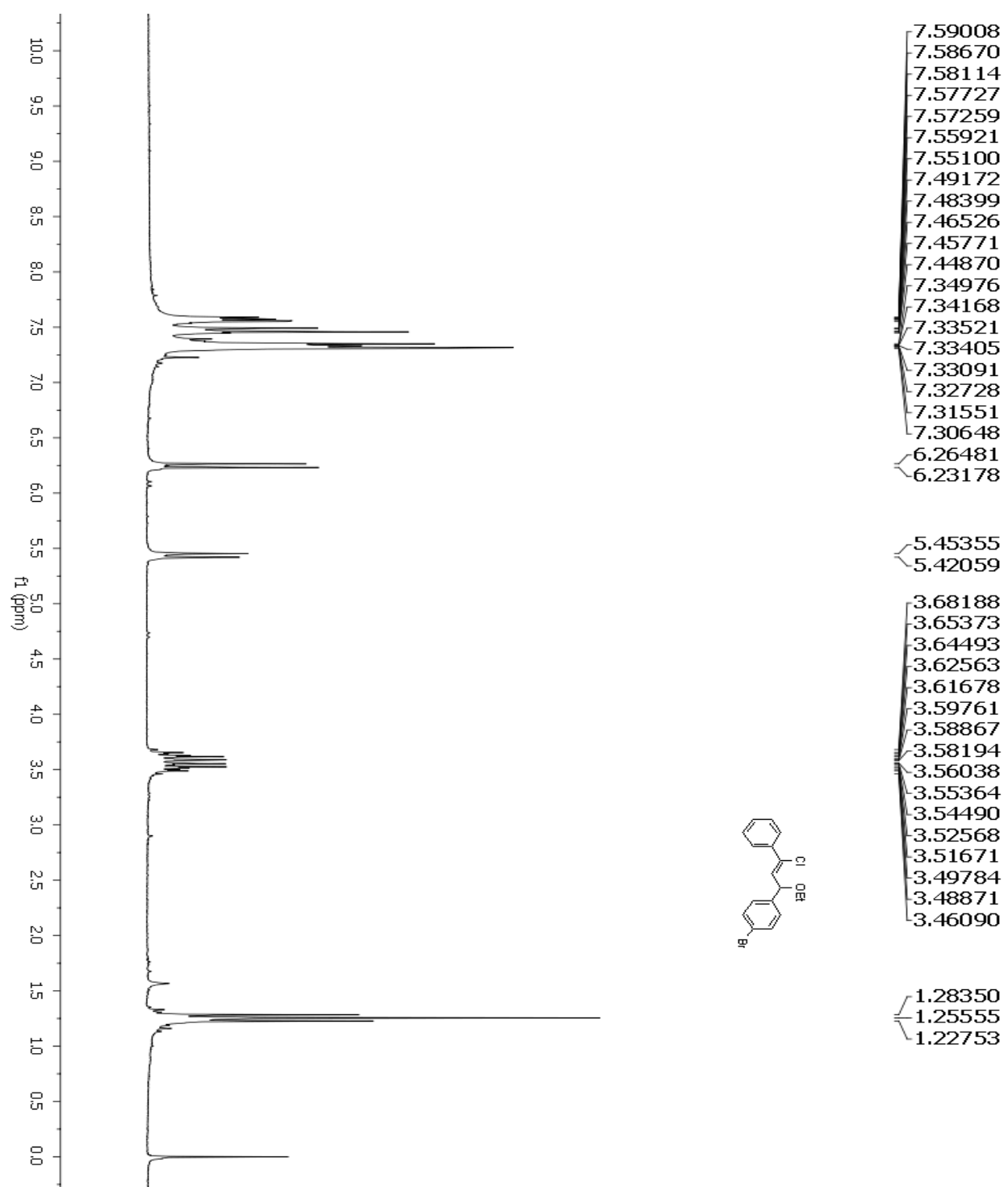
¹H spectrum of 304c



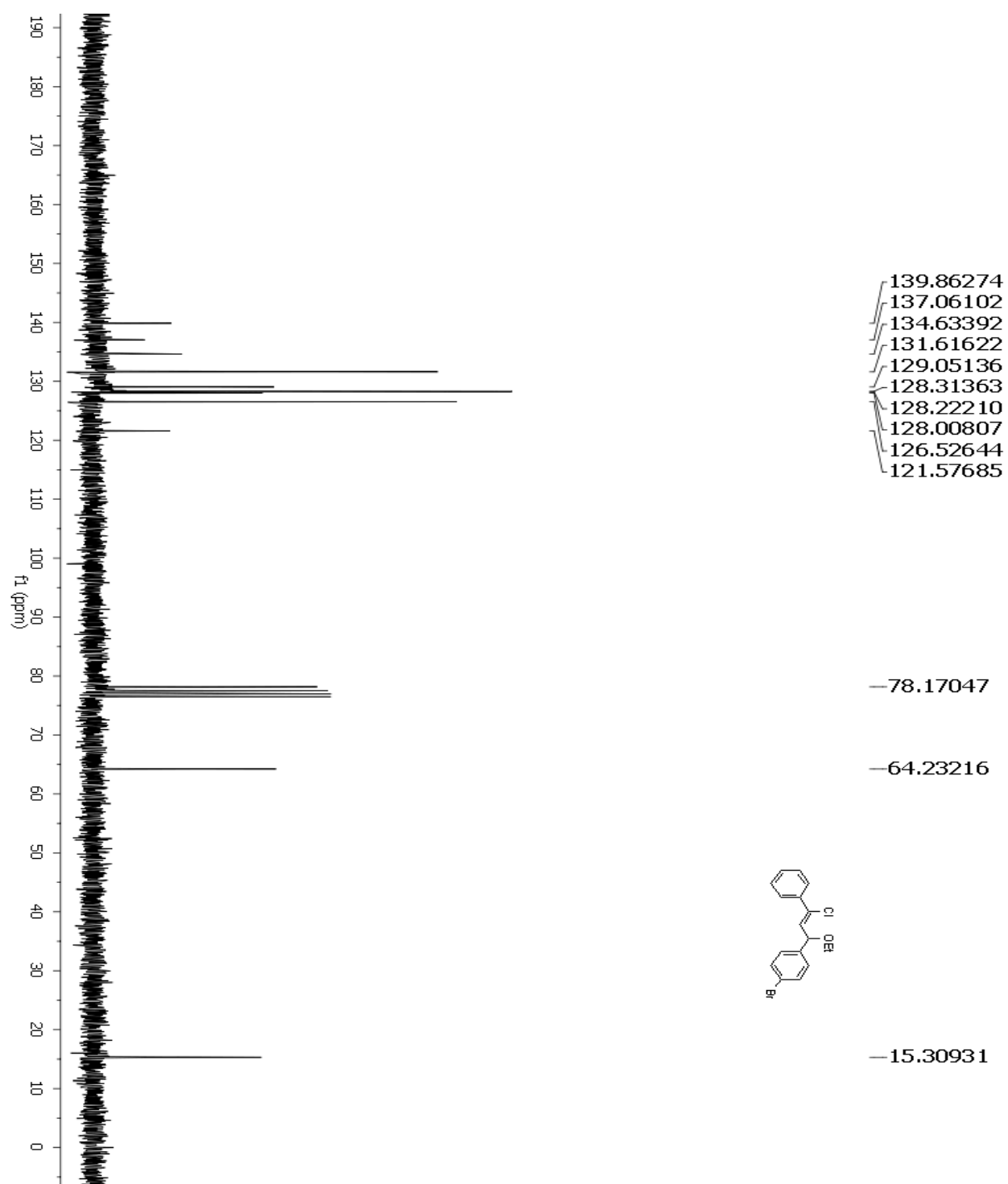
¹³C spectrum of 304c



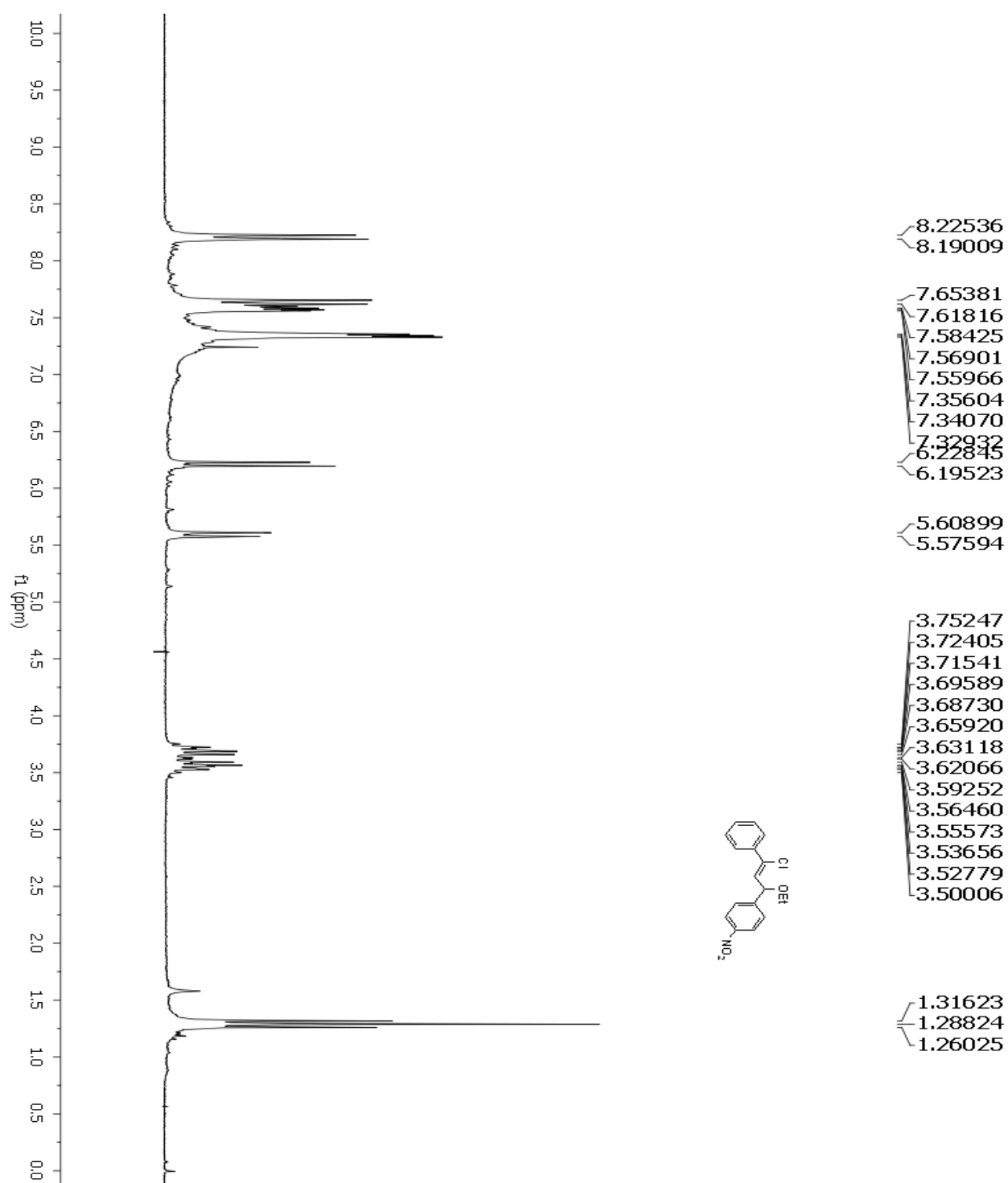
¹H spectrum of 304d



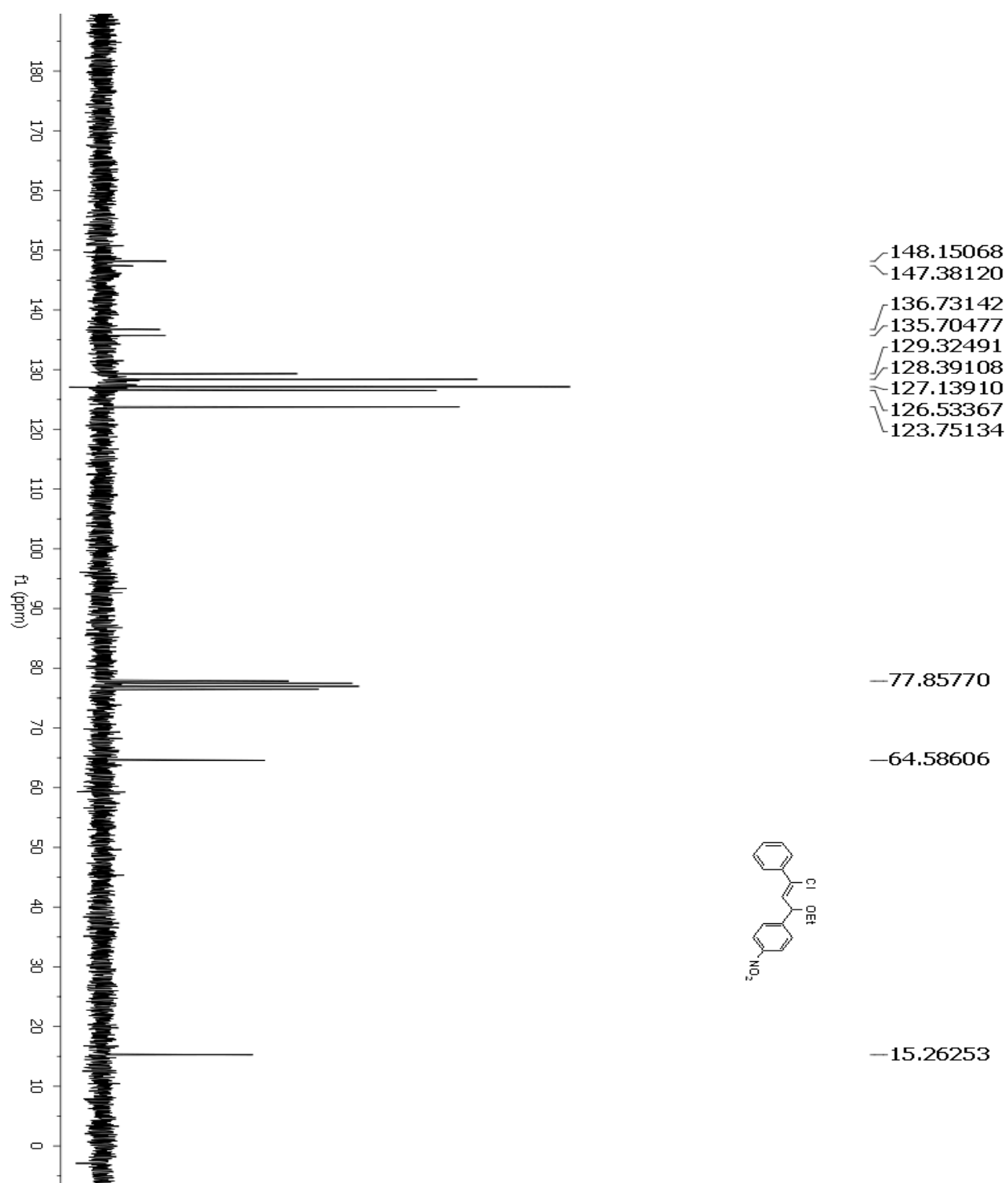
¹³C spectrum of 304d



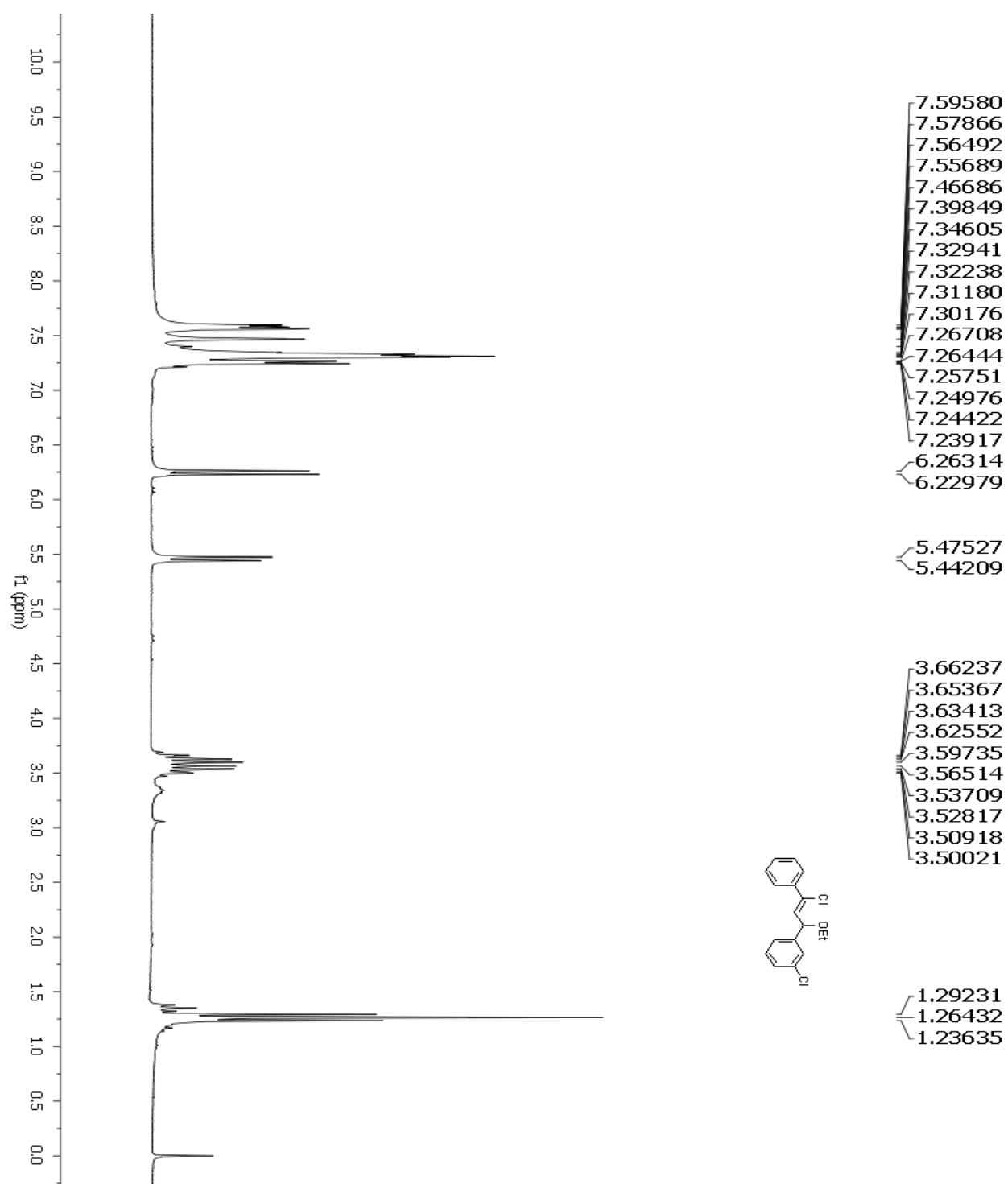
¹H spectrum of 304e



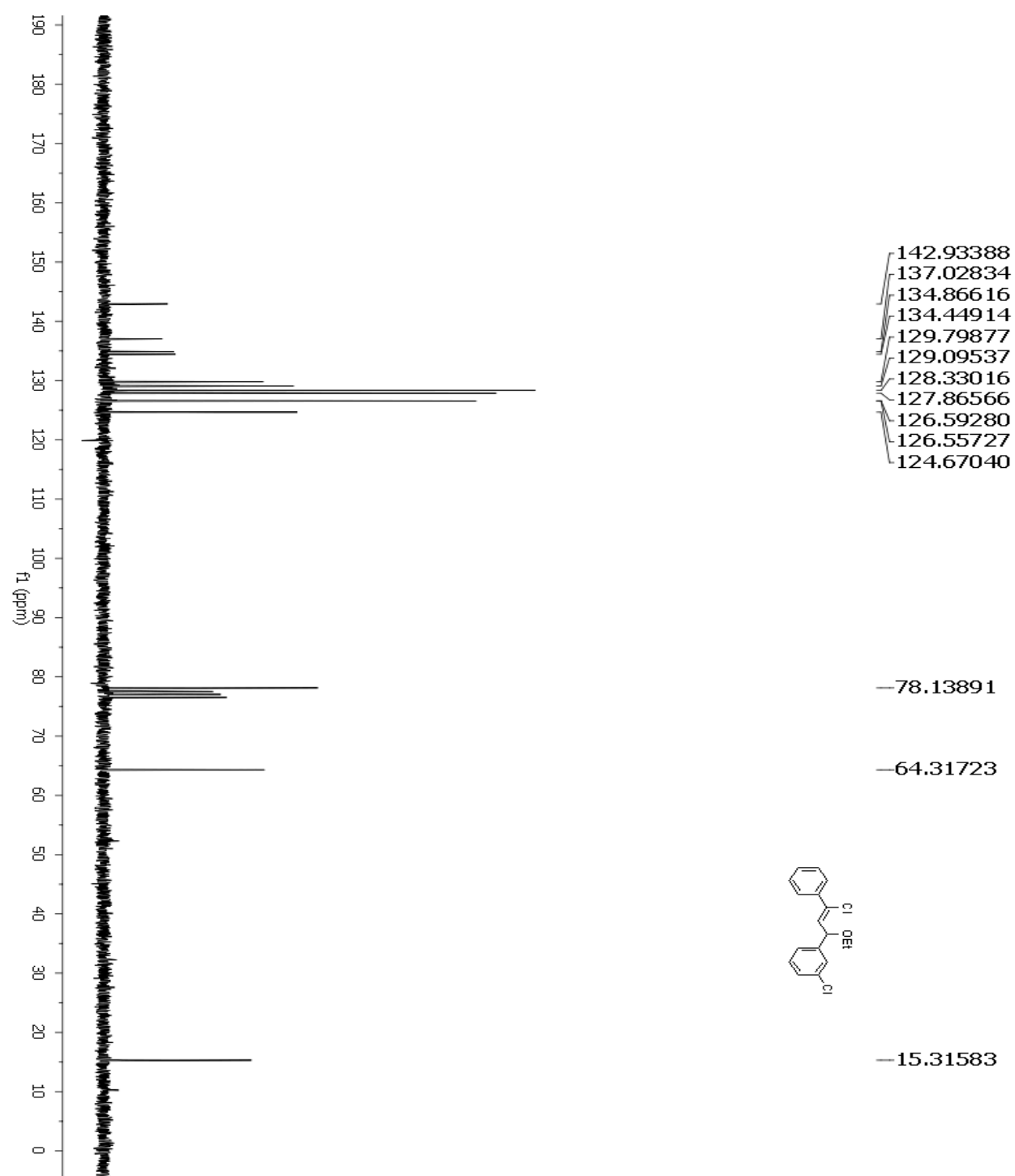
¹³C spectrum of 304e



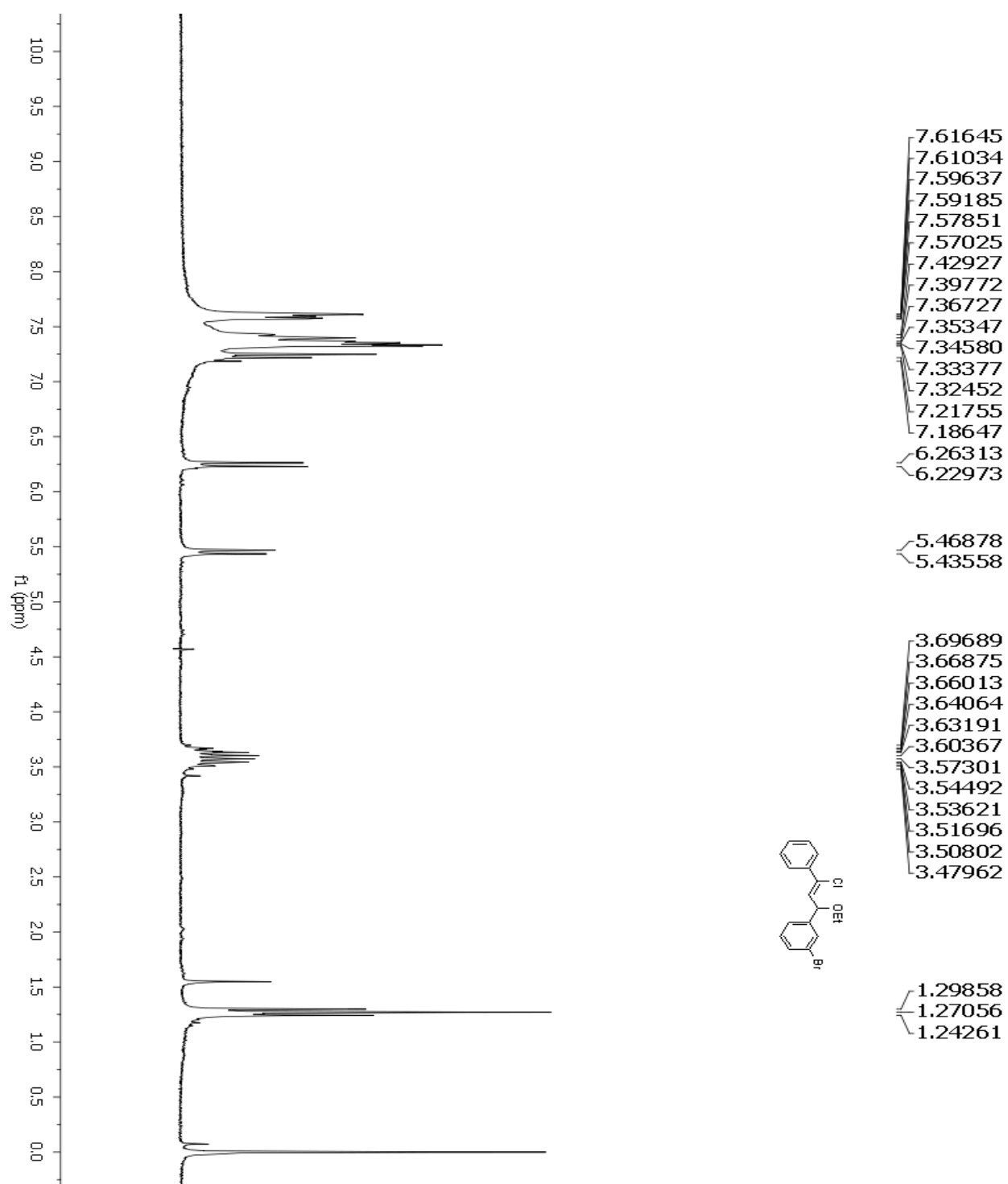
¹H spectrum of 304f



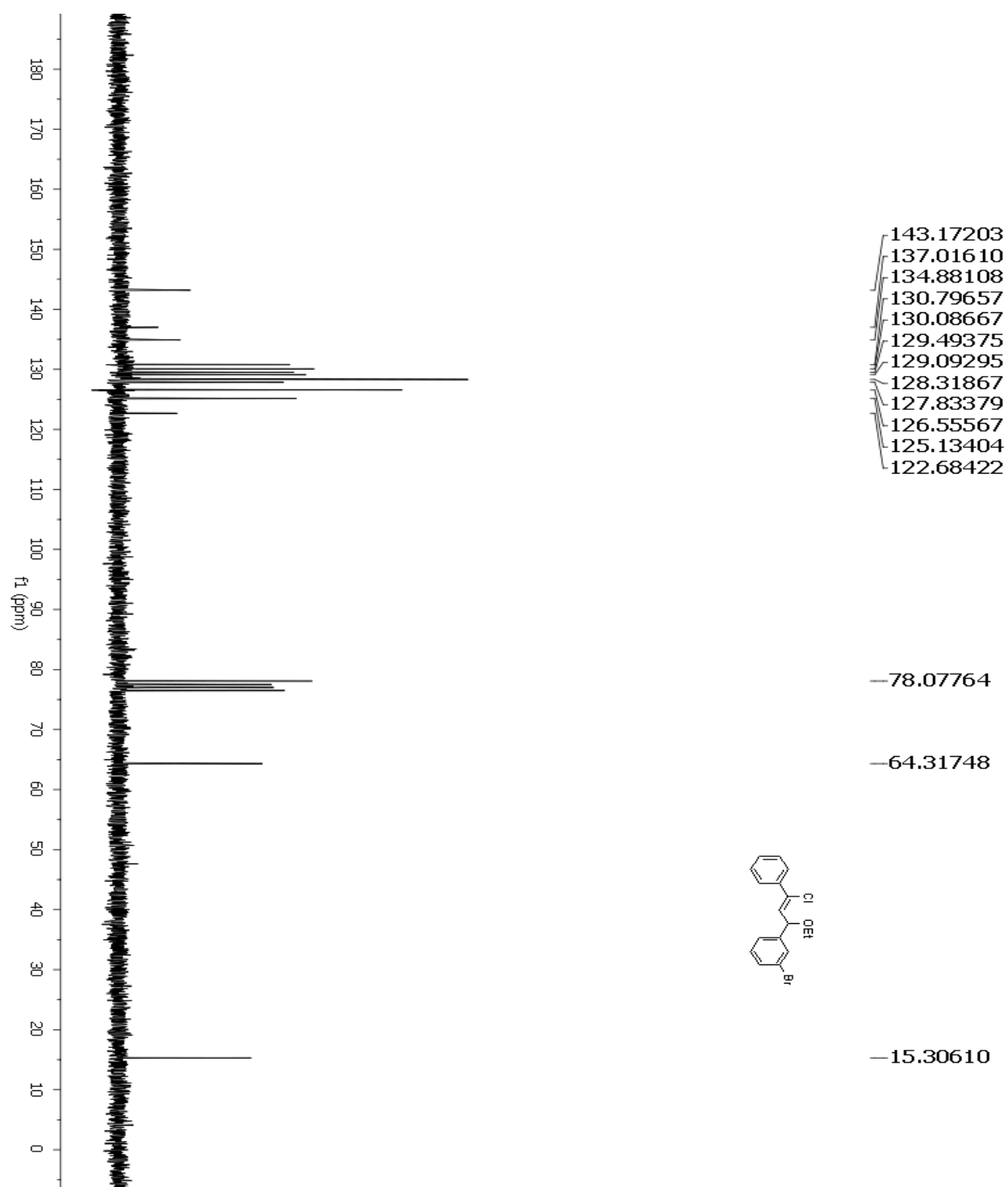
¹³C spectrum of 304f



¹H spectrum of 304g

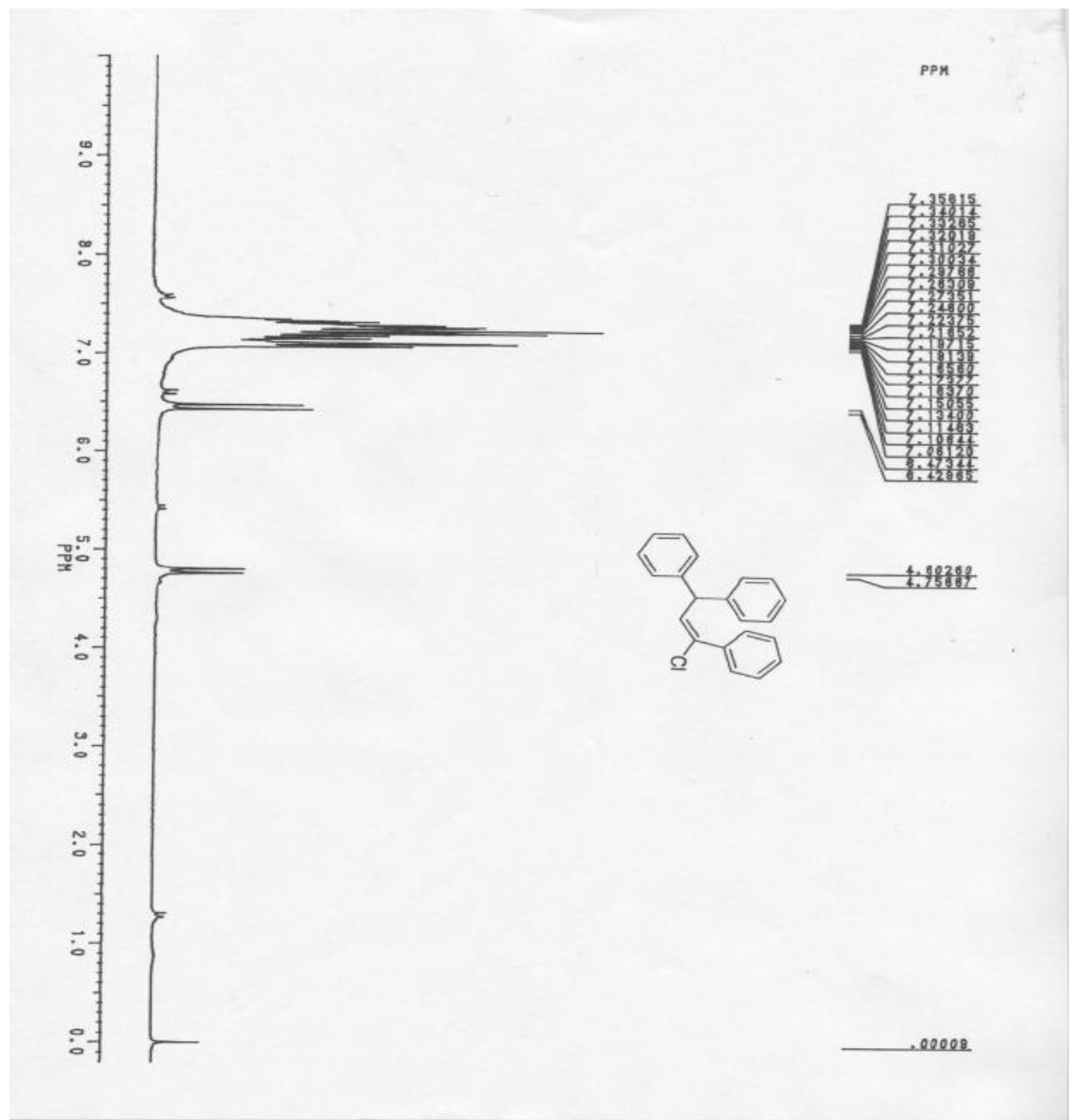


¹³C spectrum of 304g

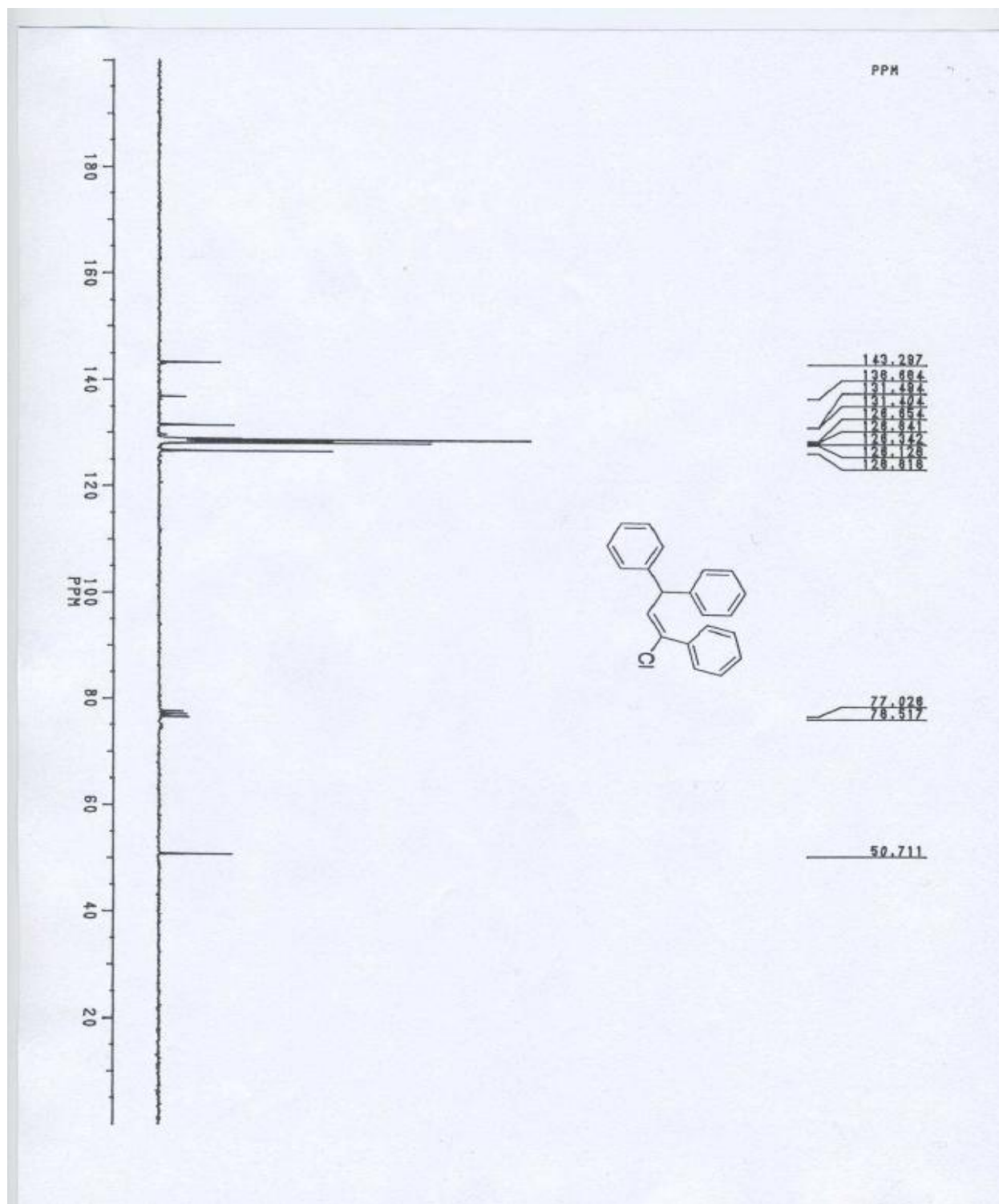


**Appendix D: Representative NMR Spectra of 401a-l and 402a-g
for Chapter 4.**

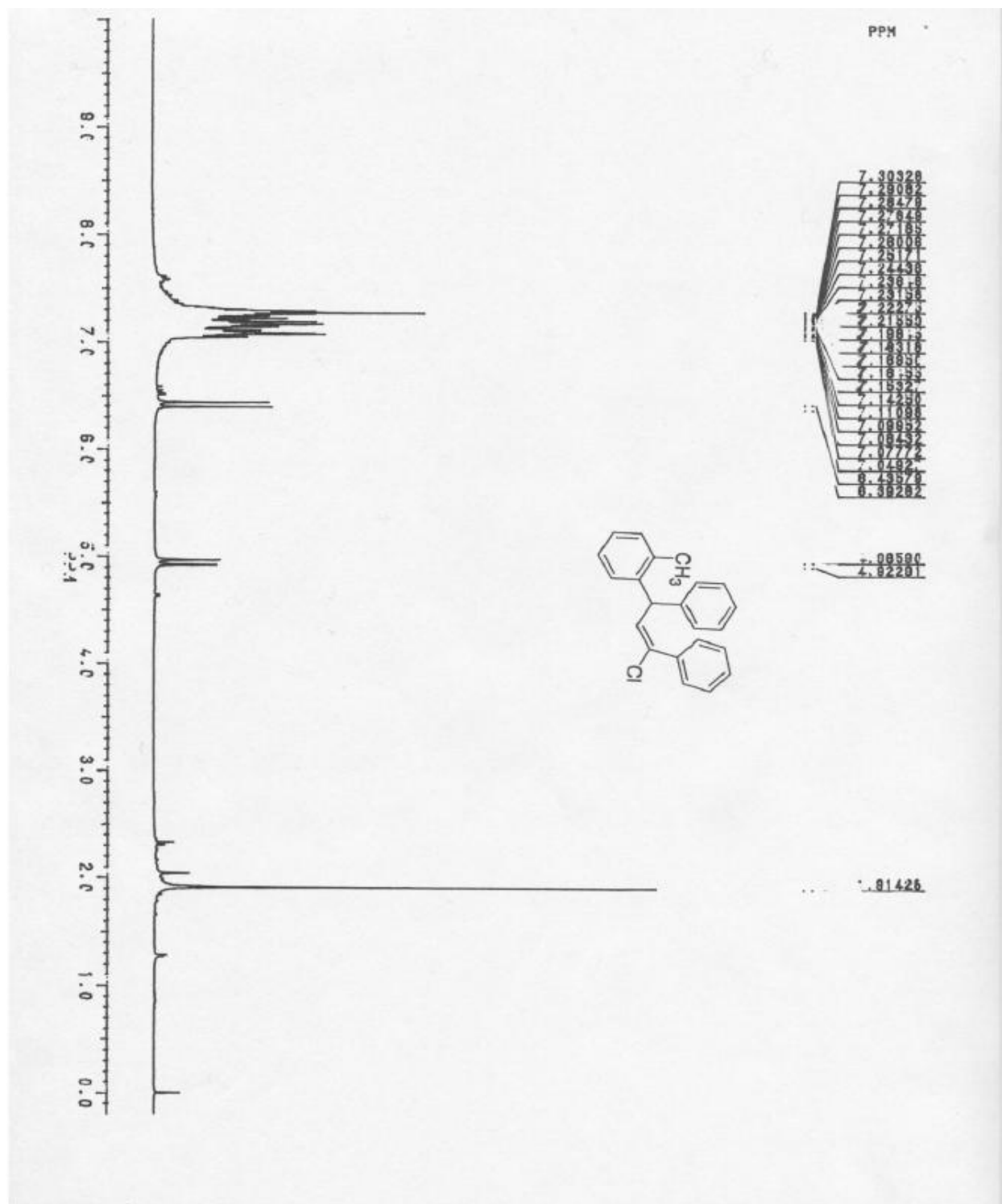
¹H spectrum of 401a



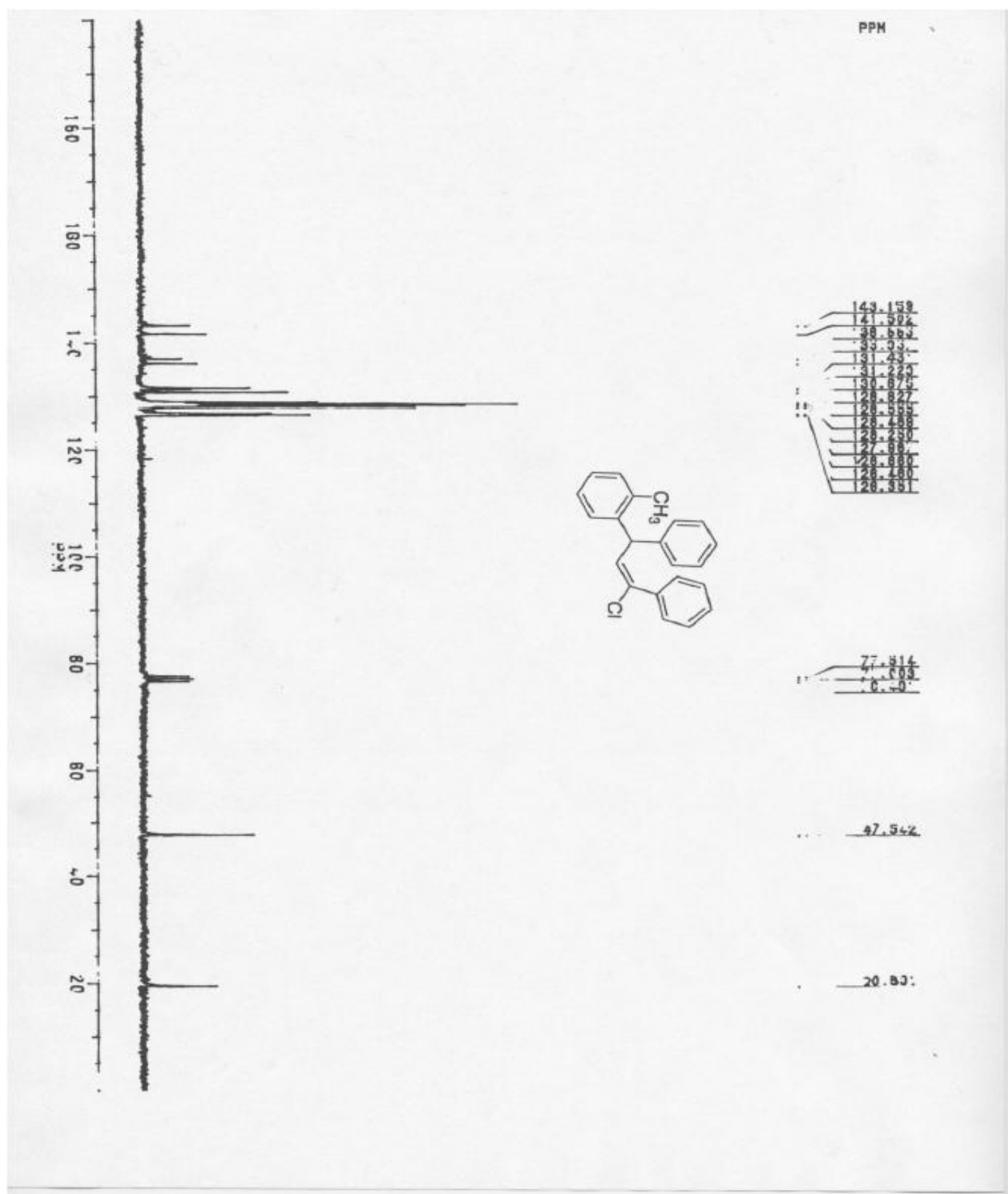
^{13}C spectrum of 401a



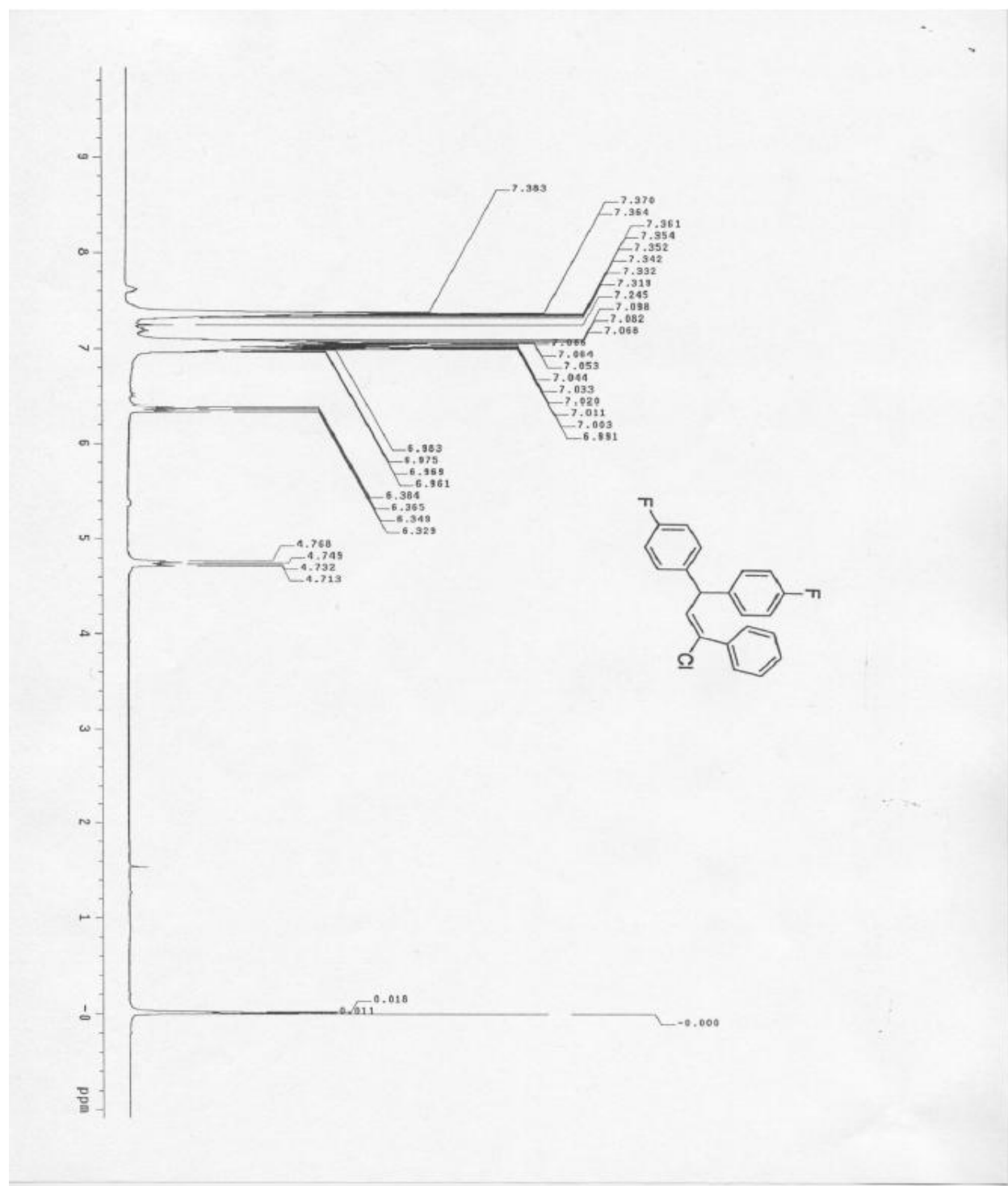
¹H spectrum of 401b



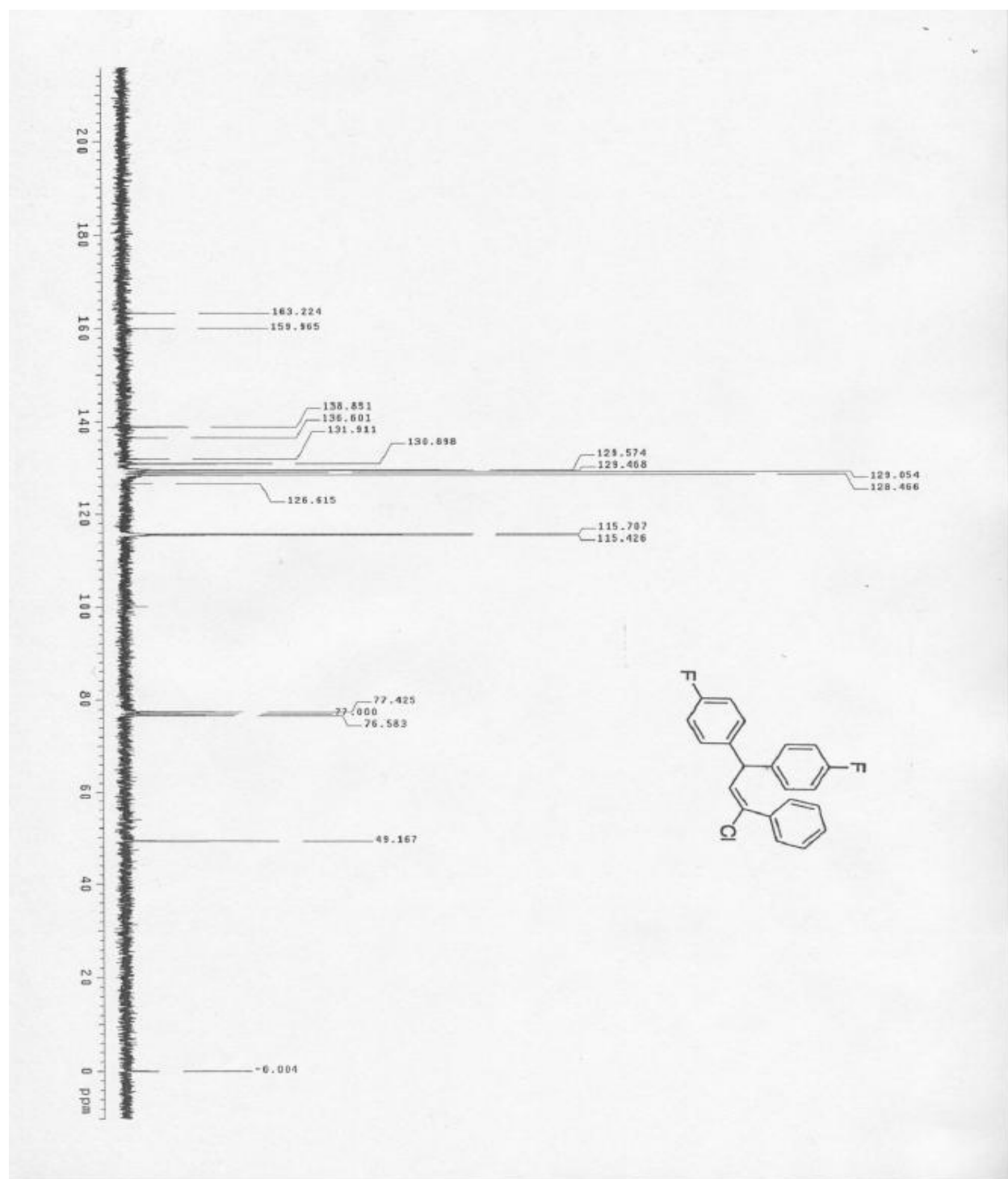
¹³C spectrum of 401b



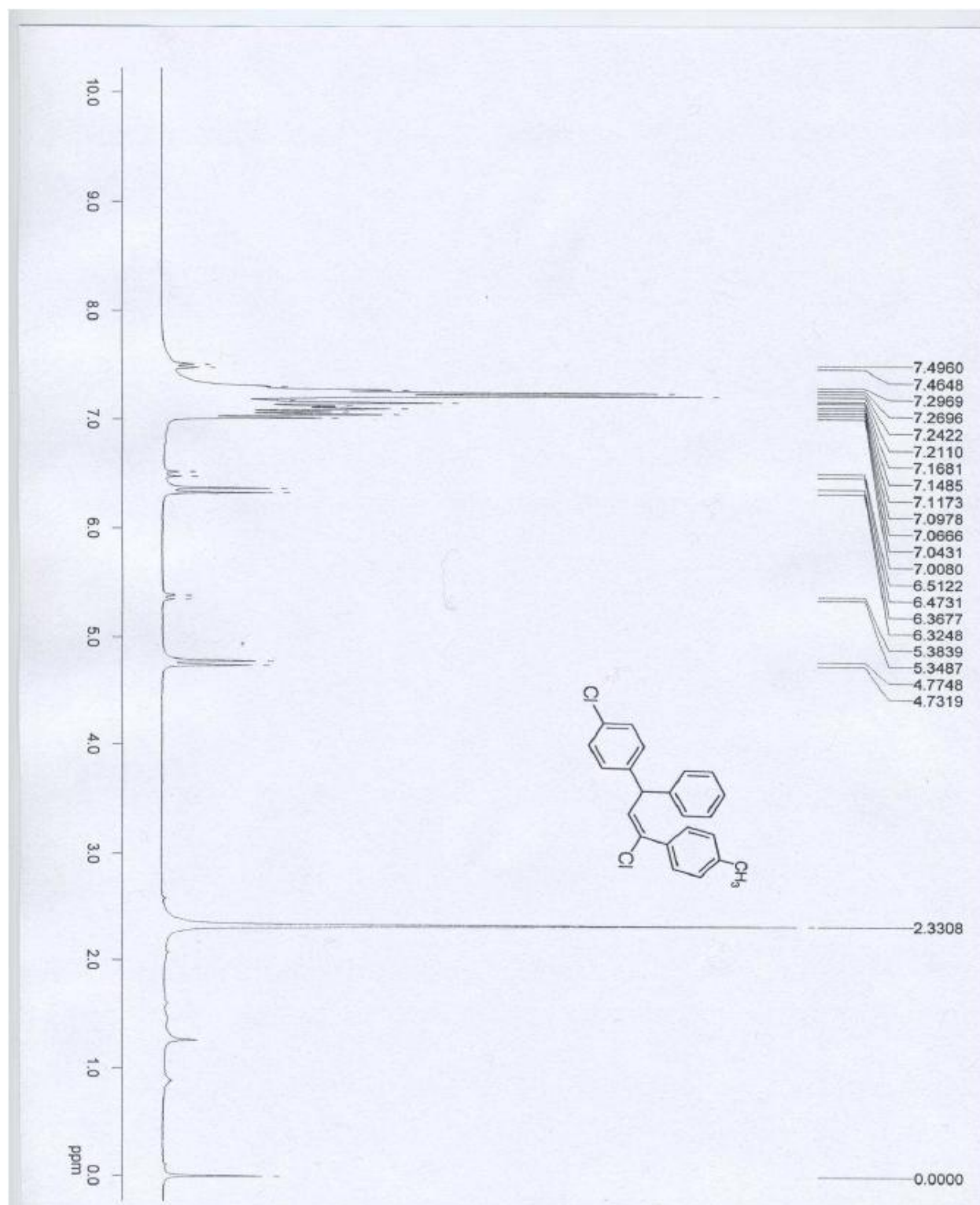
¹H spectrum of 401c



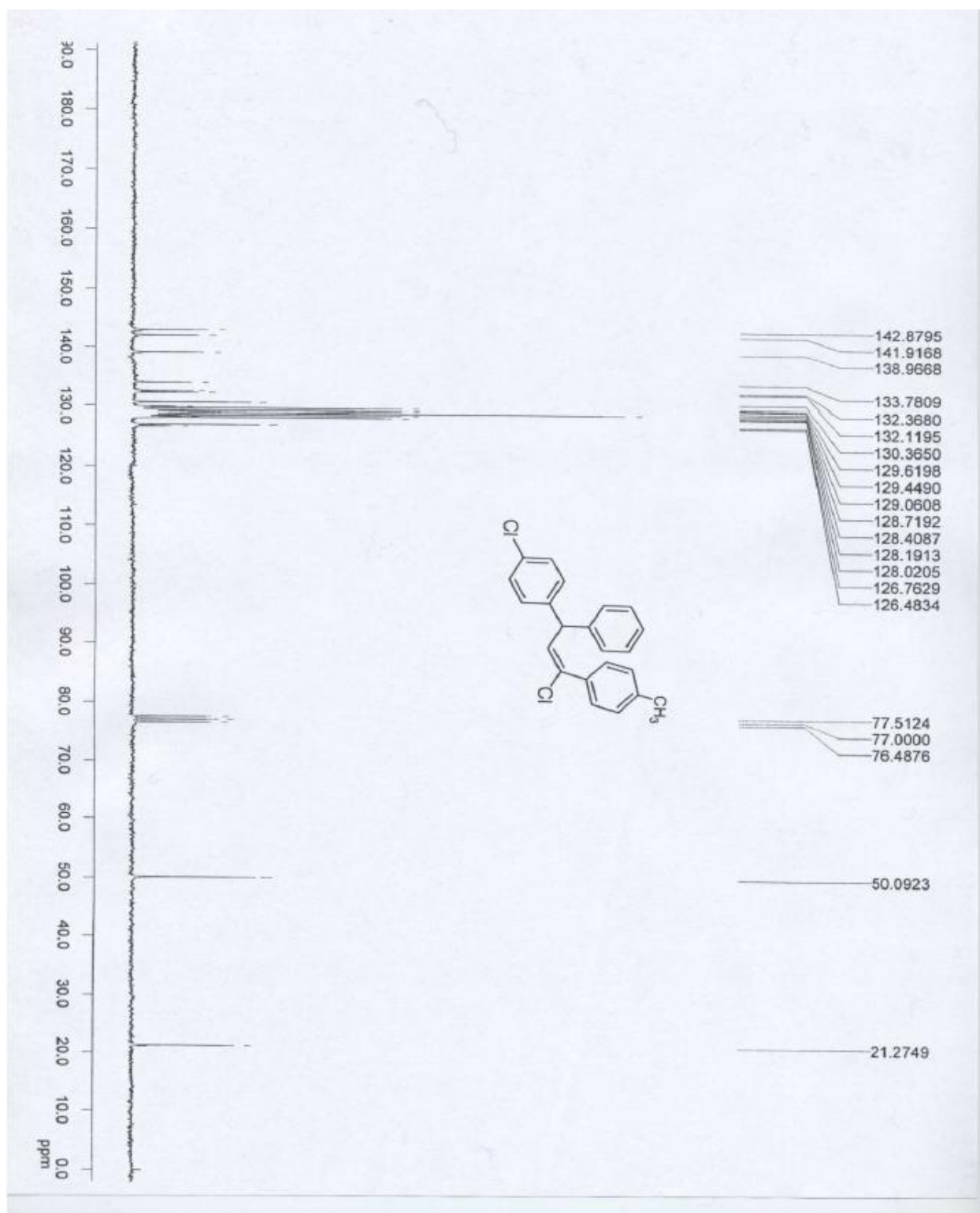
^{13}C spectrum of 401c



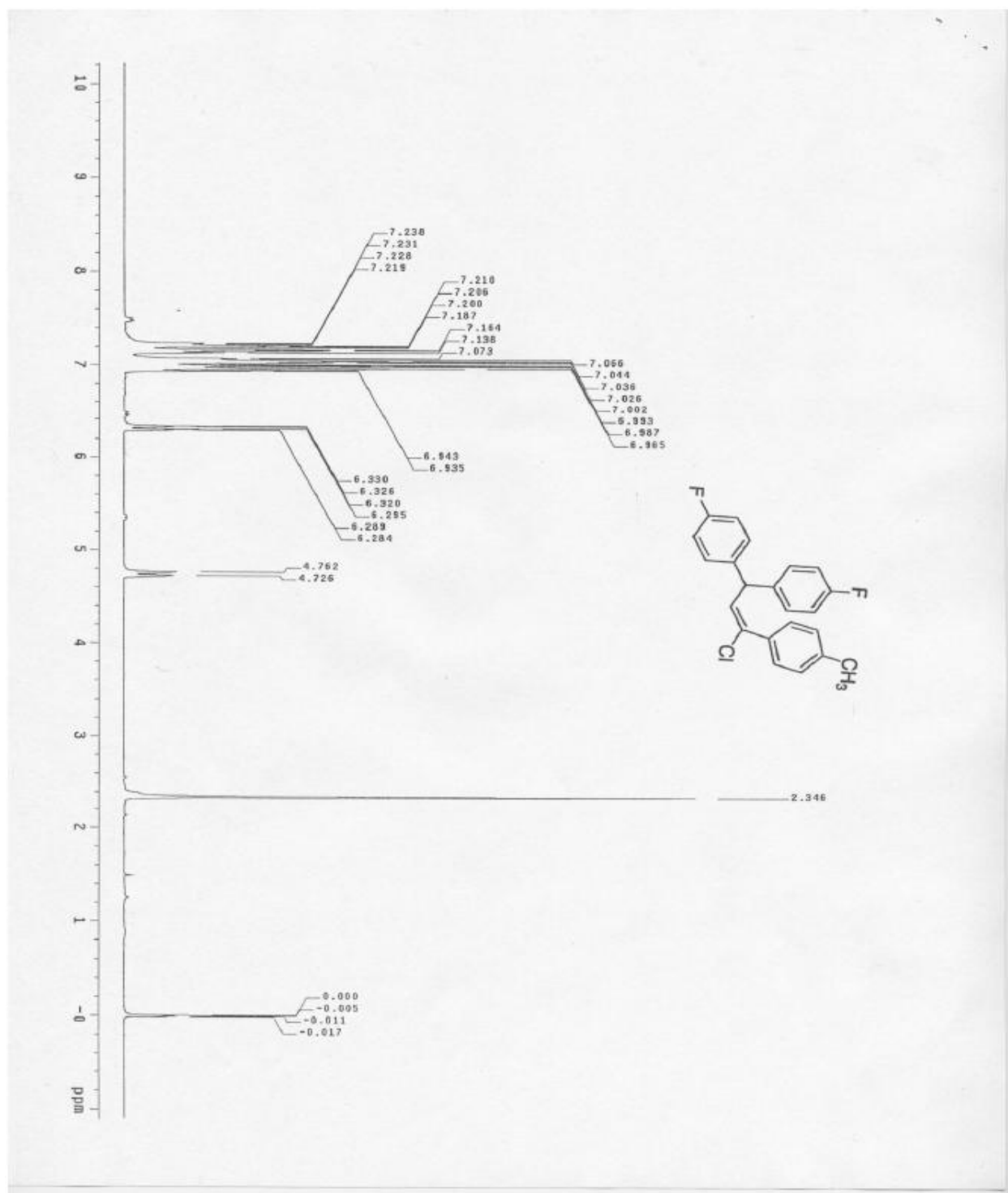
¹H spectrum of 401d



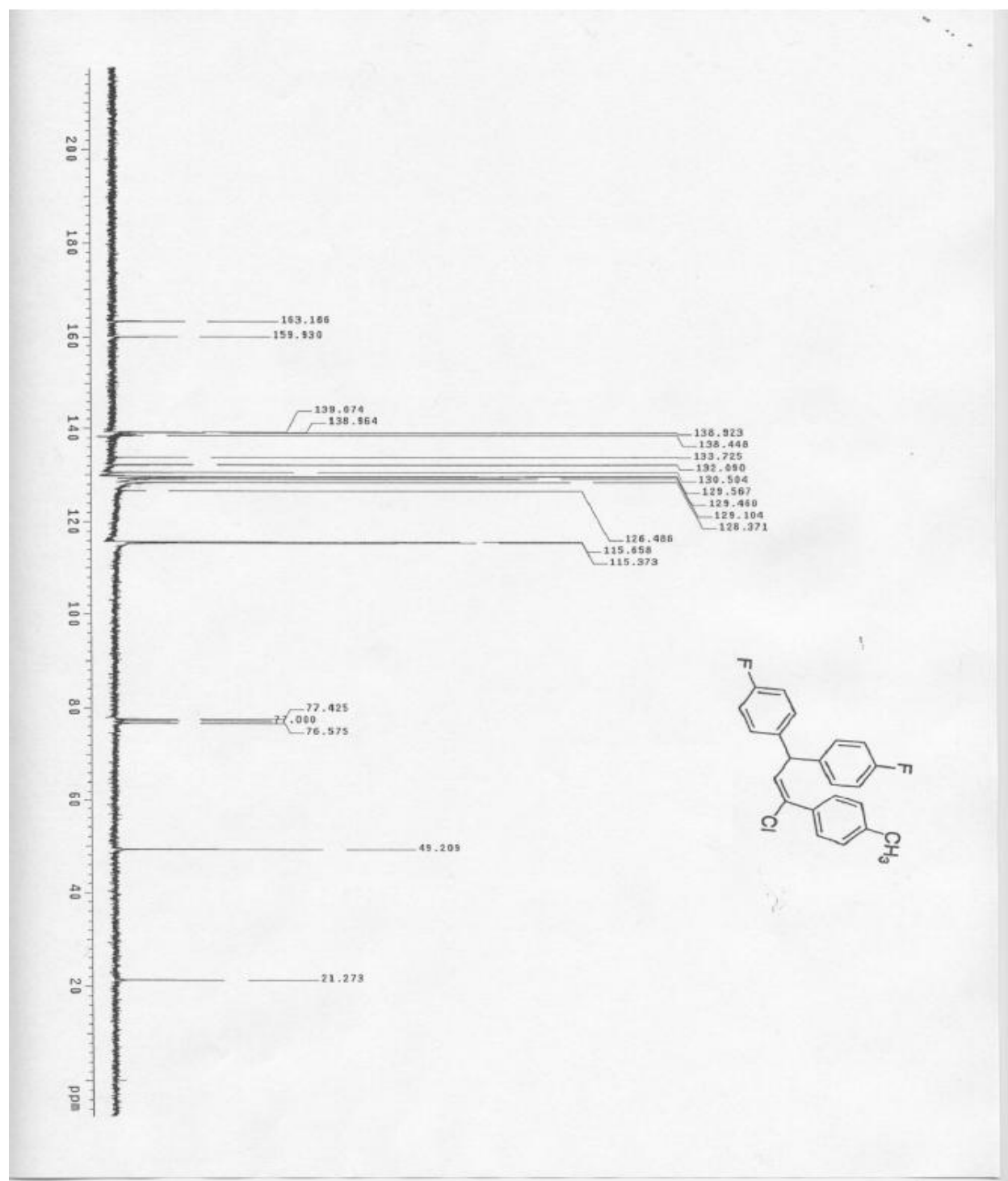
¹³C spectrum of 401d



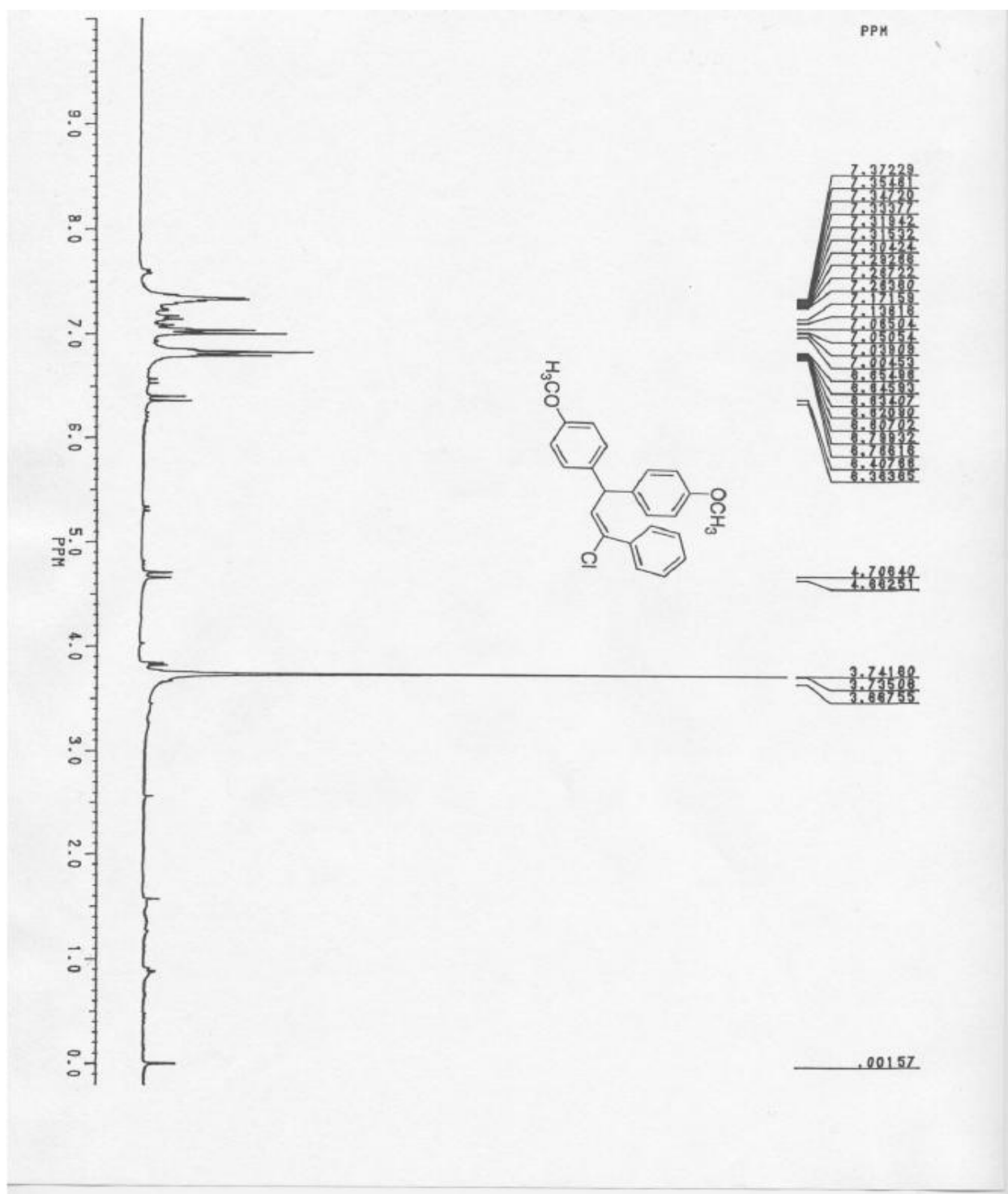
¹H spectrum of 401e



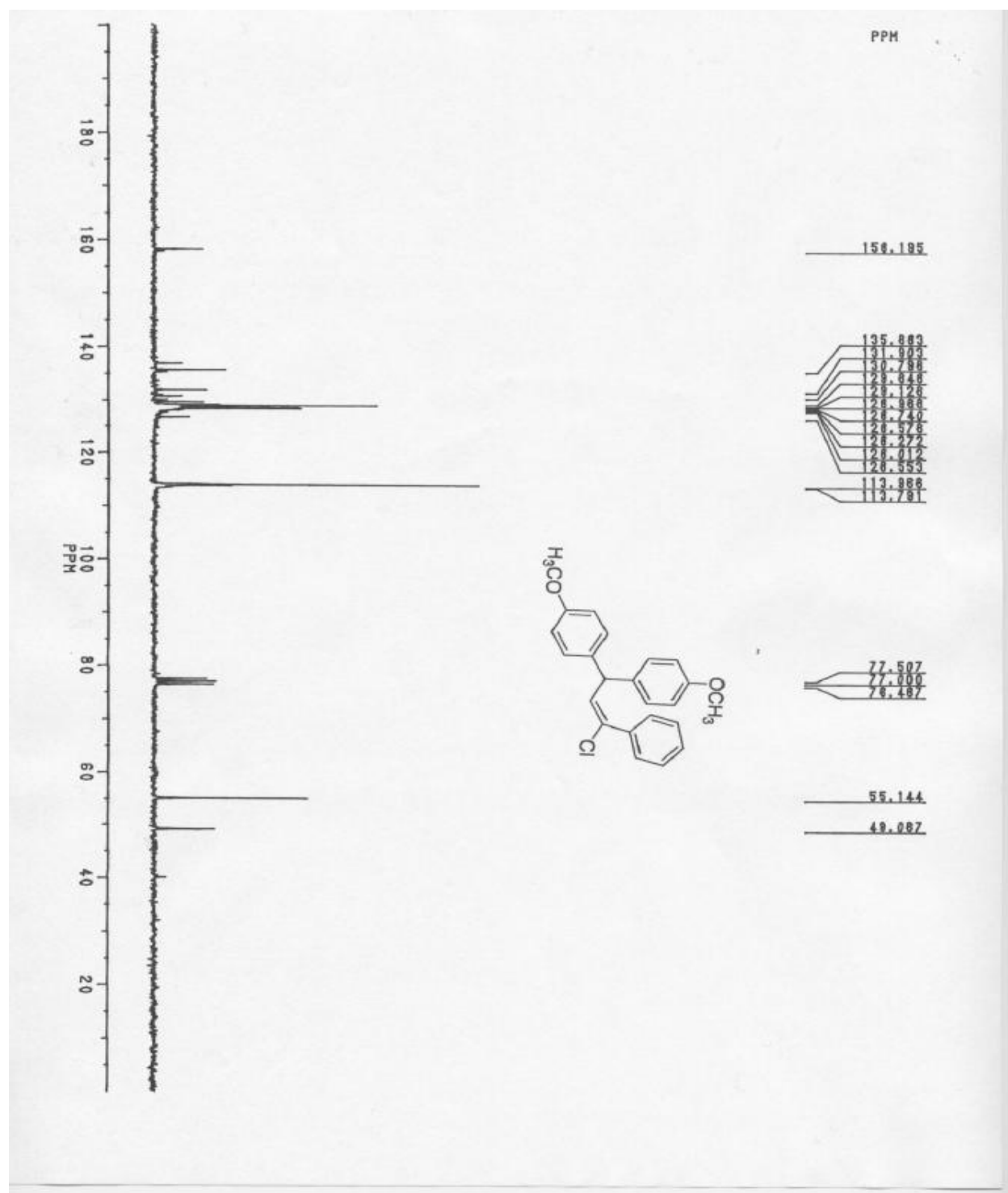
^{13}C spectrum of 401e



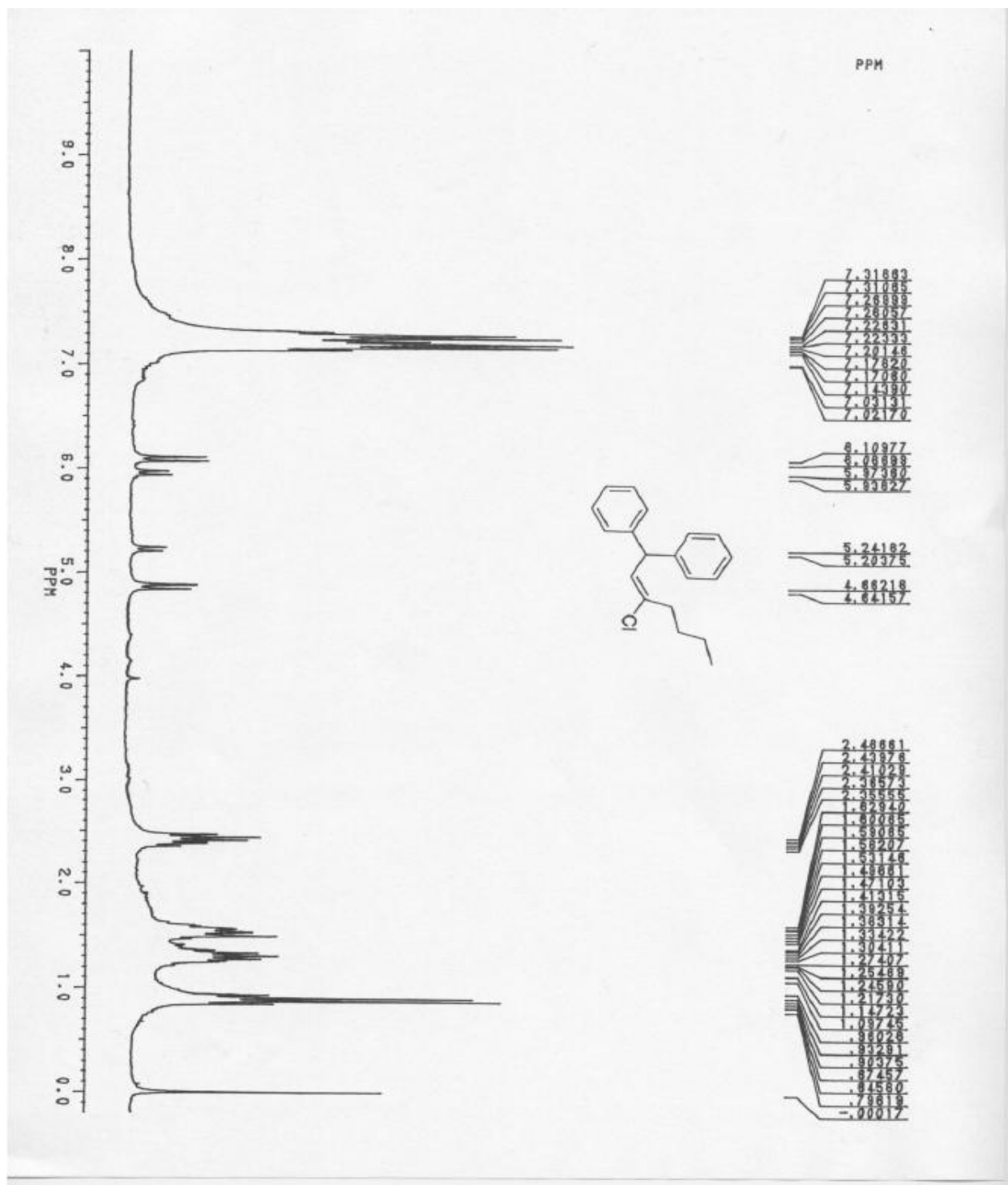
¹H spectrum of 401f



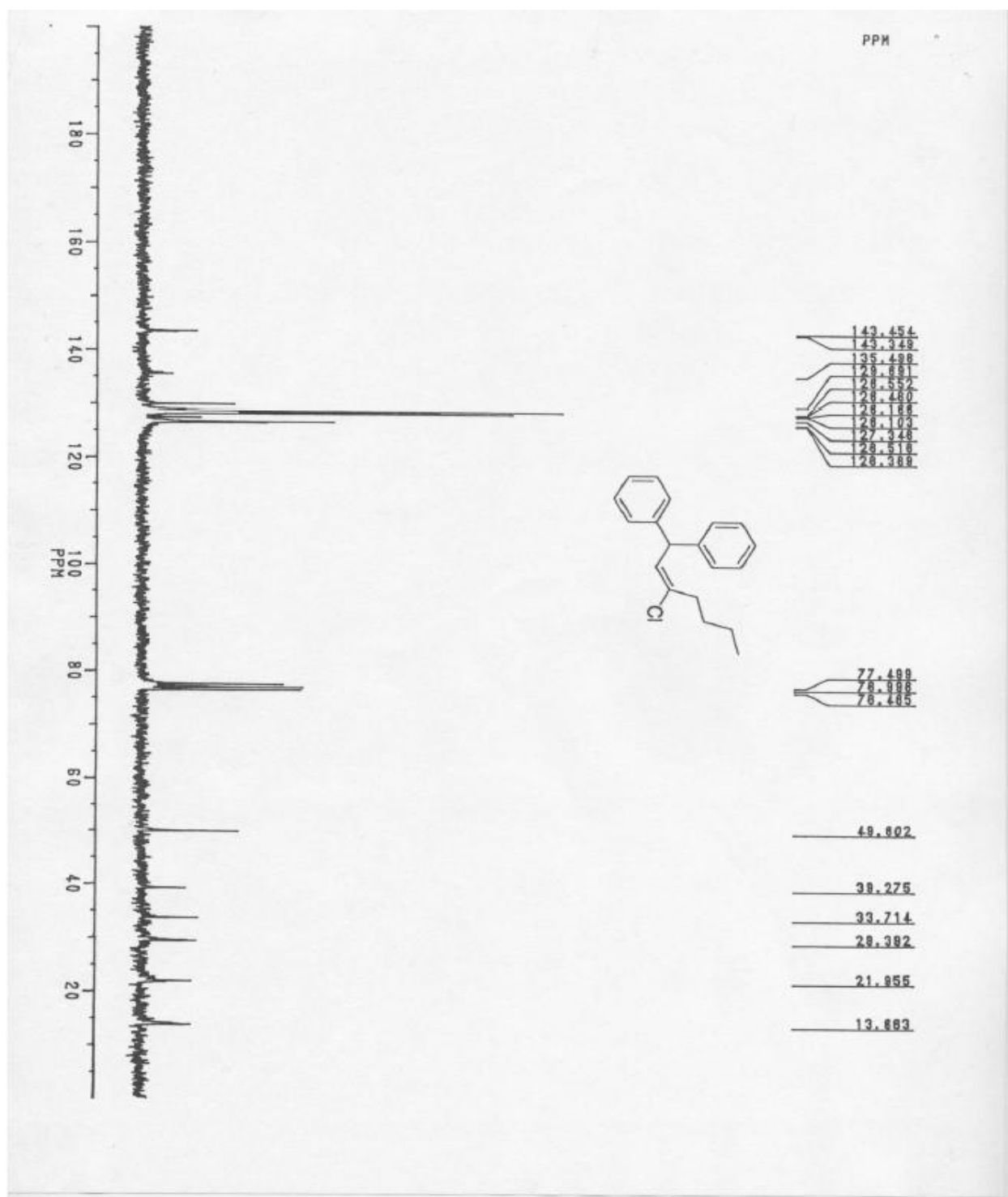
¹³C spectrum of 401f



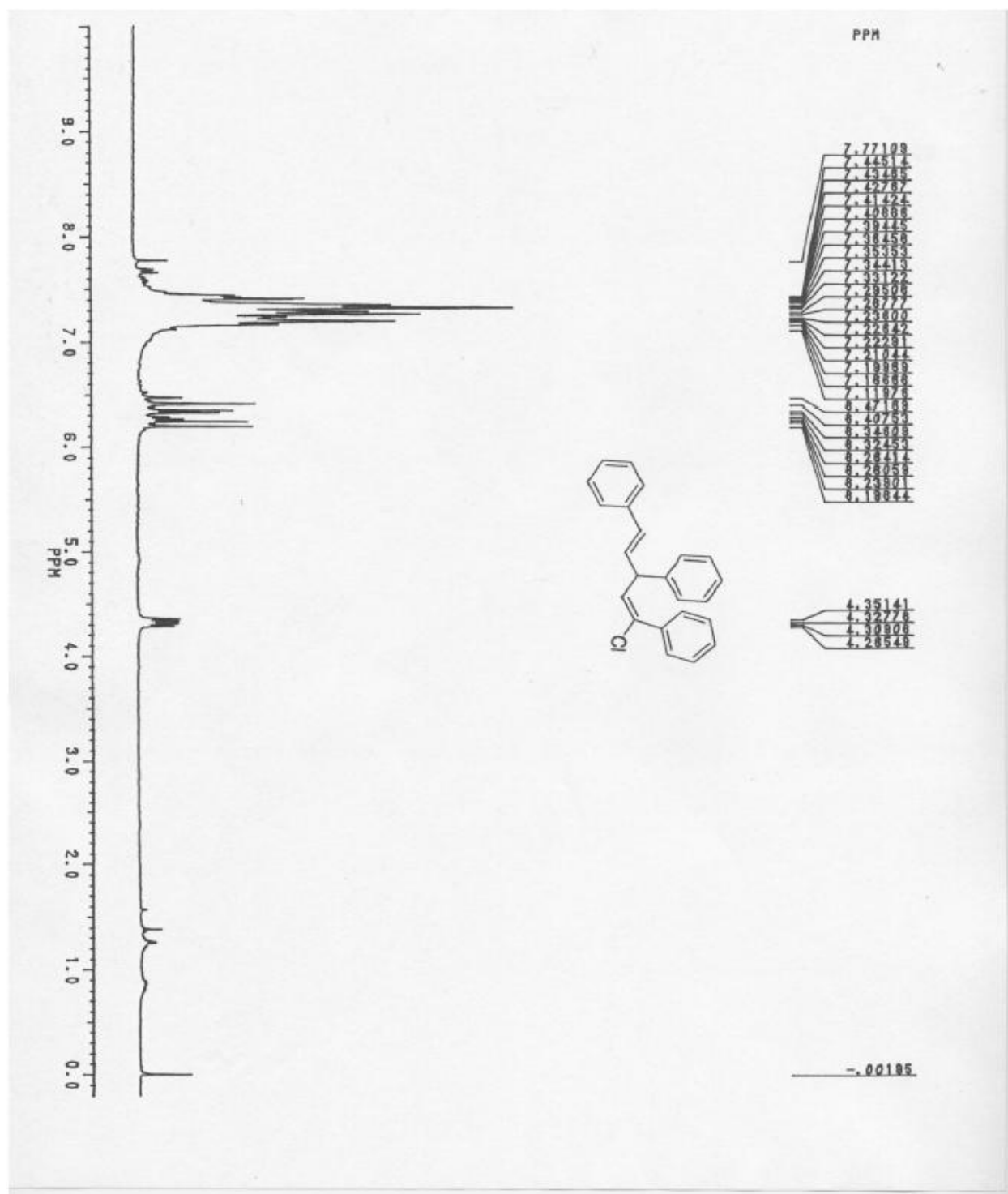
¹H spectrum of 401g



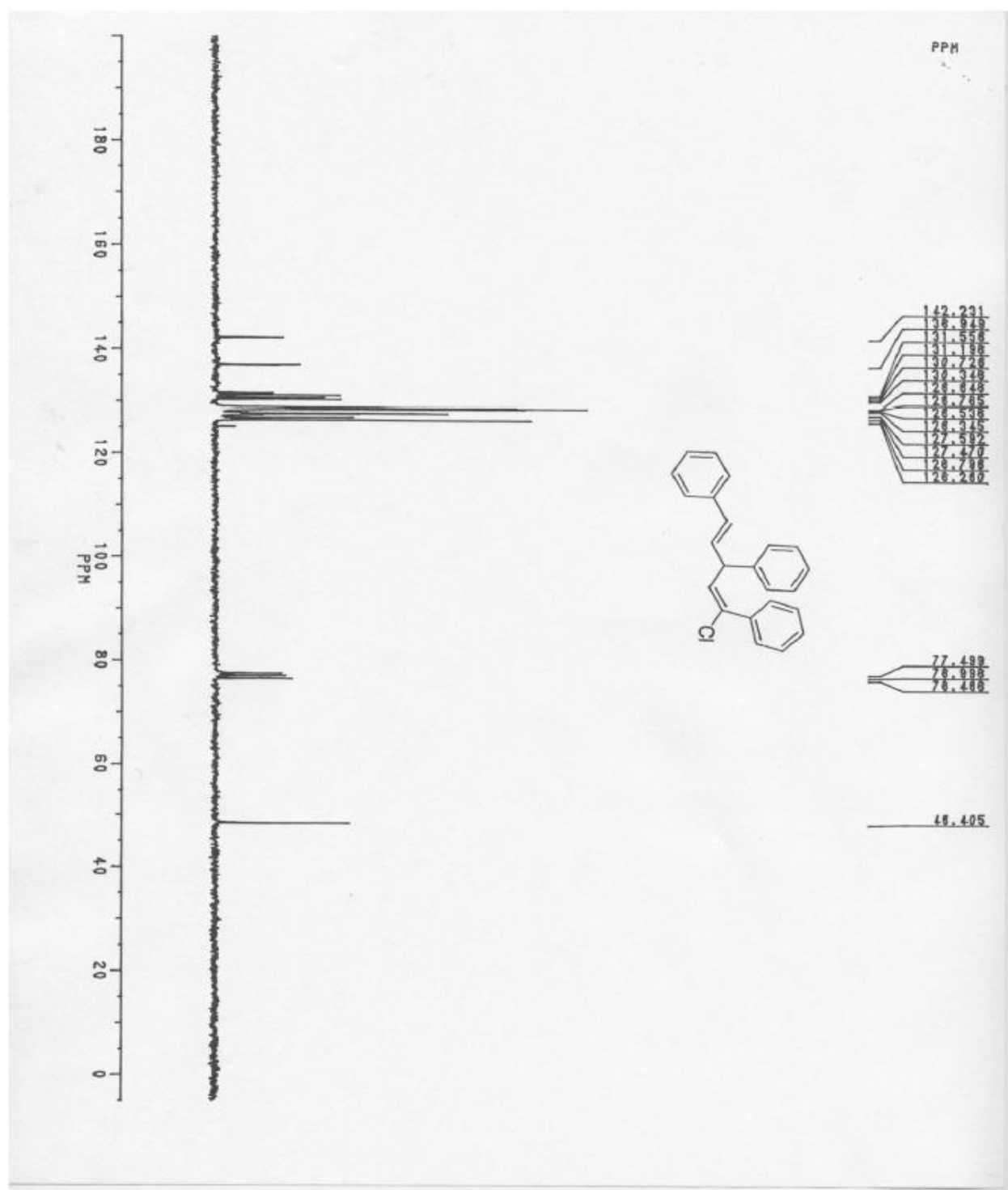
¹³C spectrum of 401g



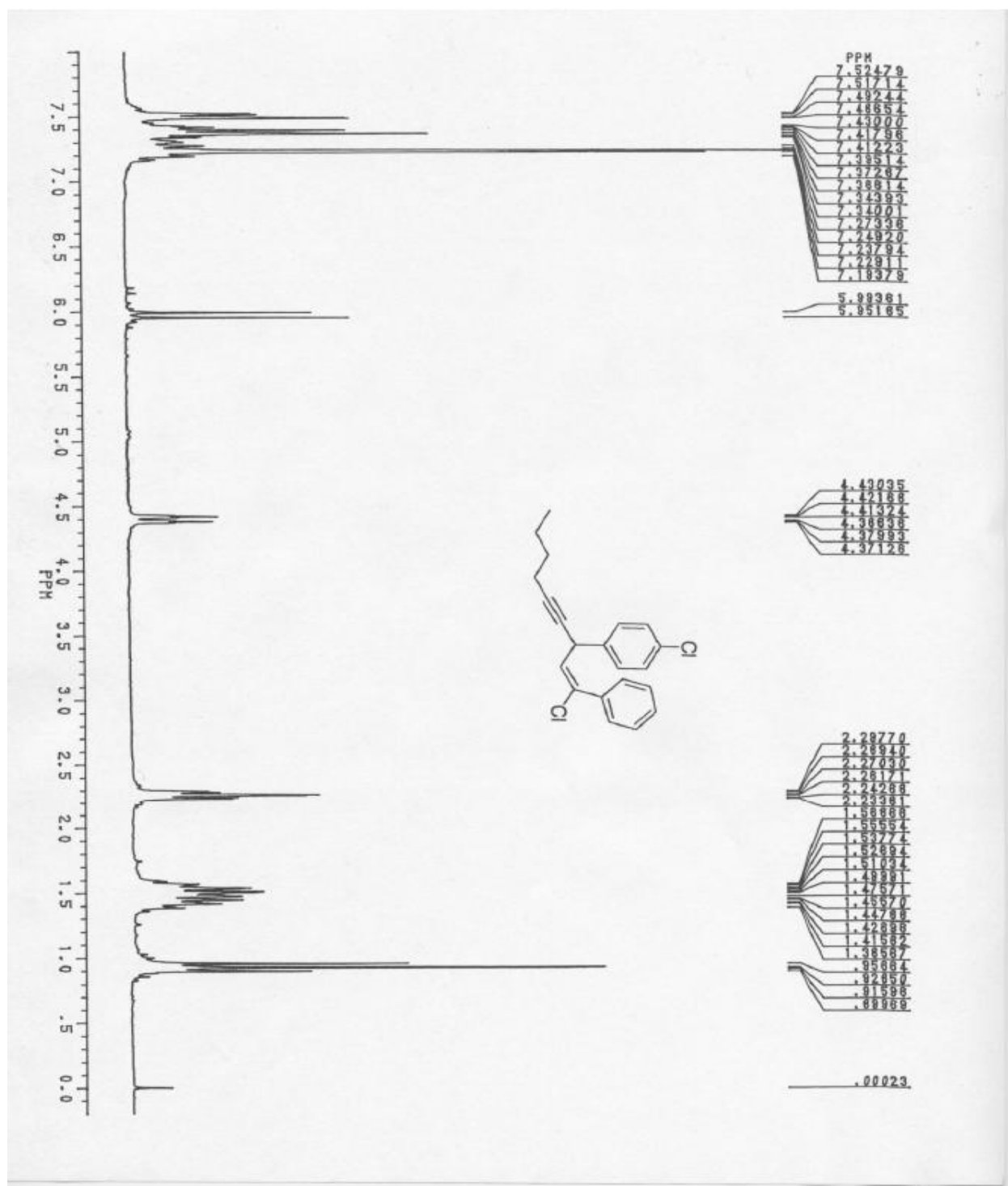
¹H spectrum of 401h



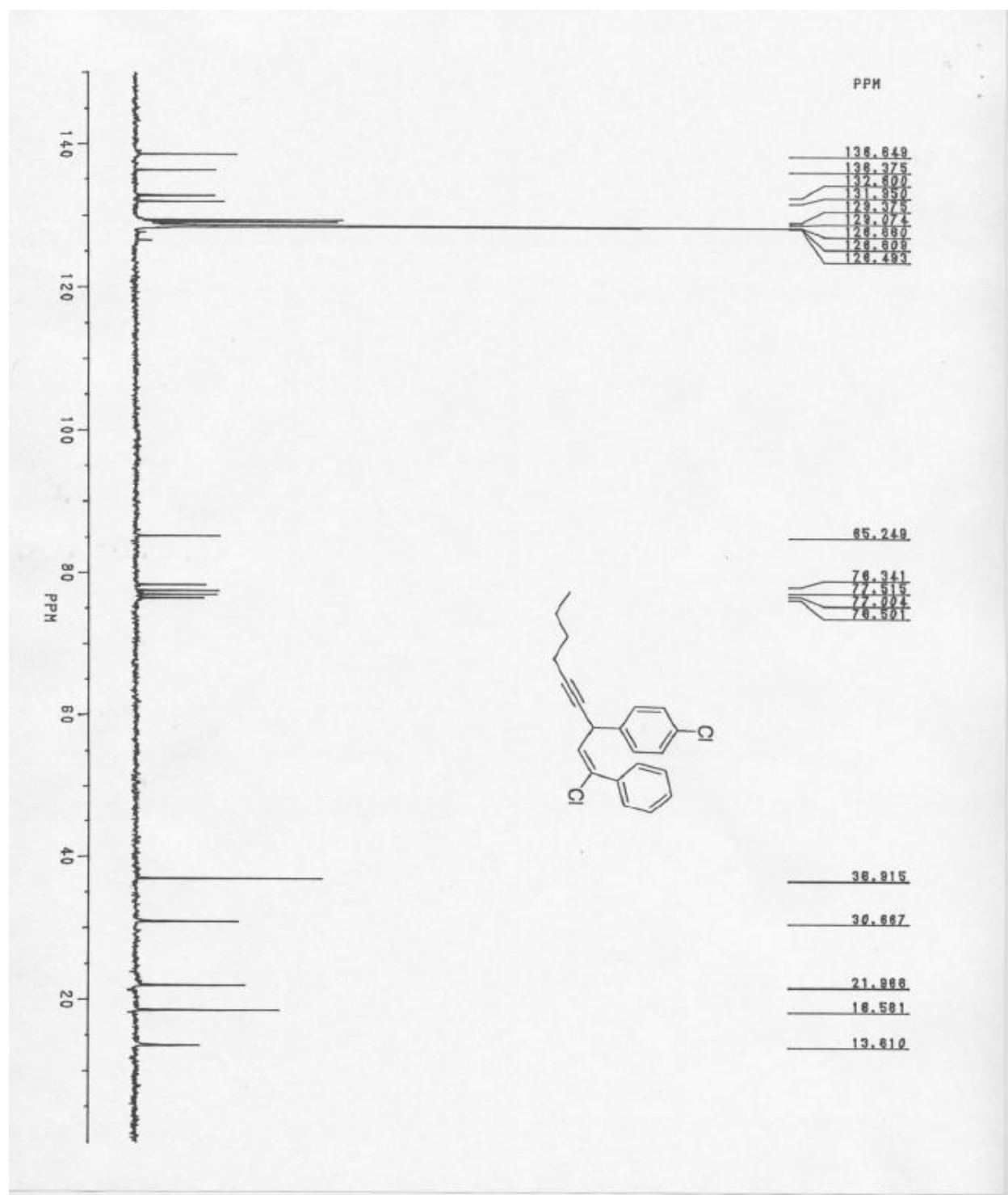
^{13}C spectrum of 401h



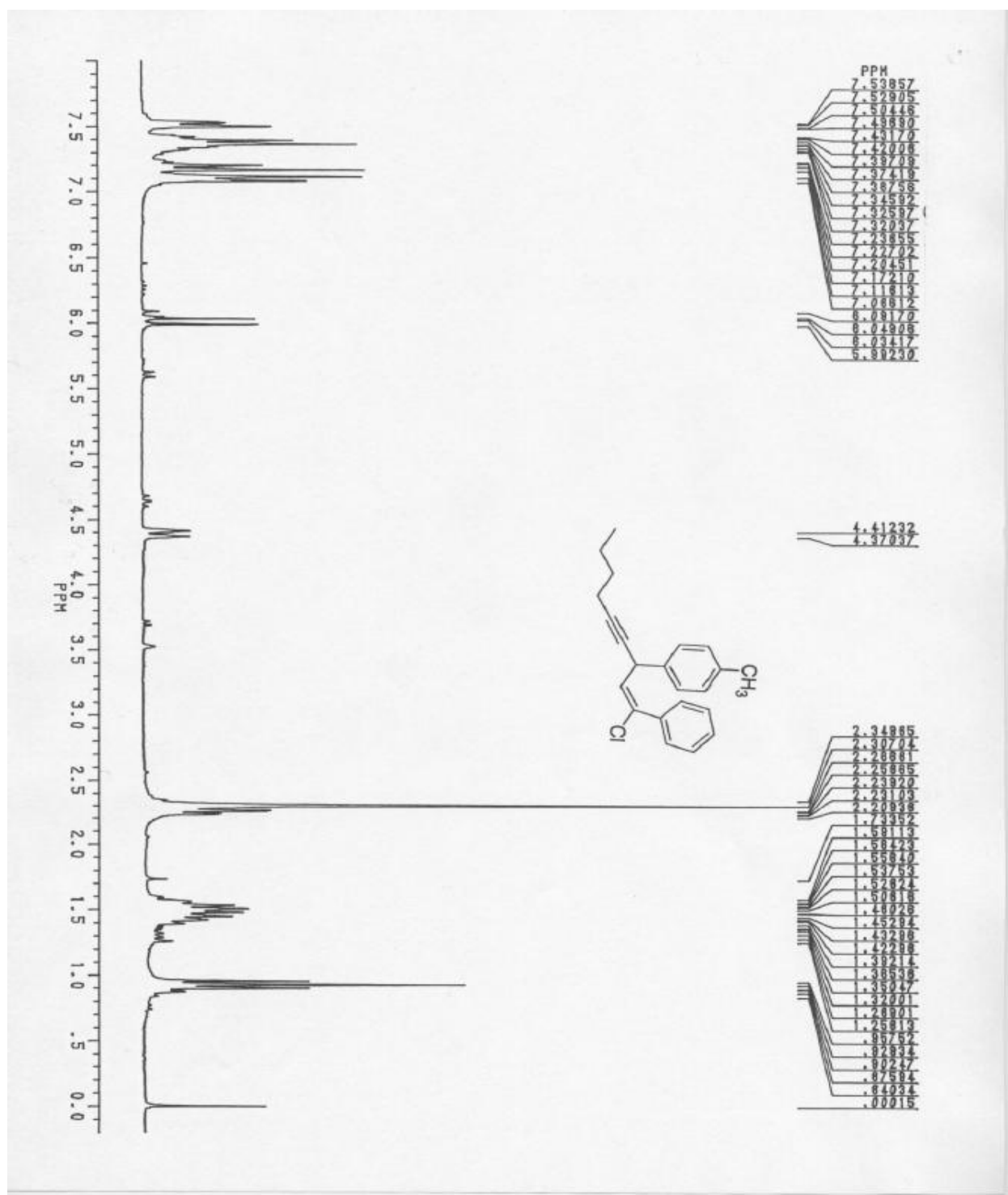
¹H spectrum of 401i



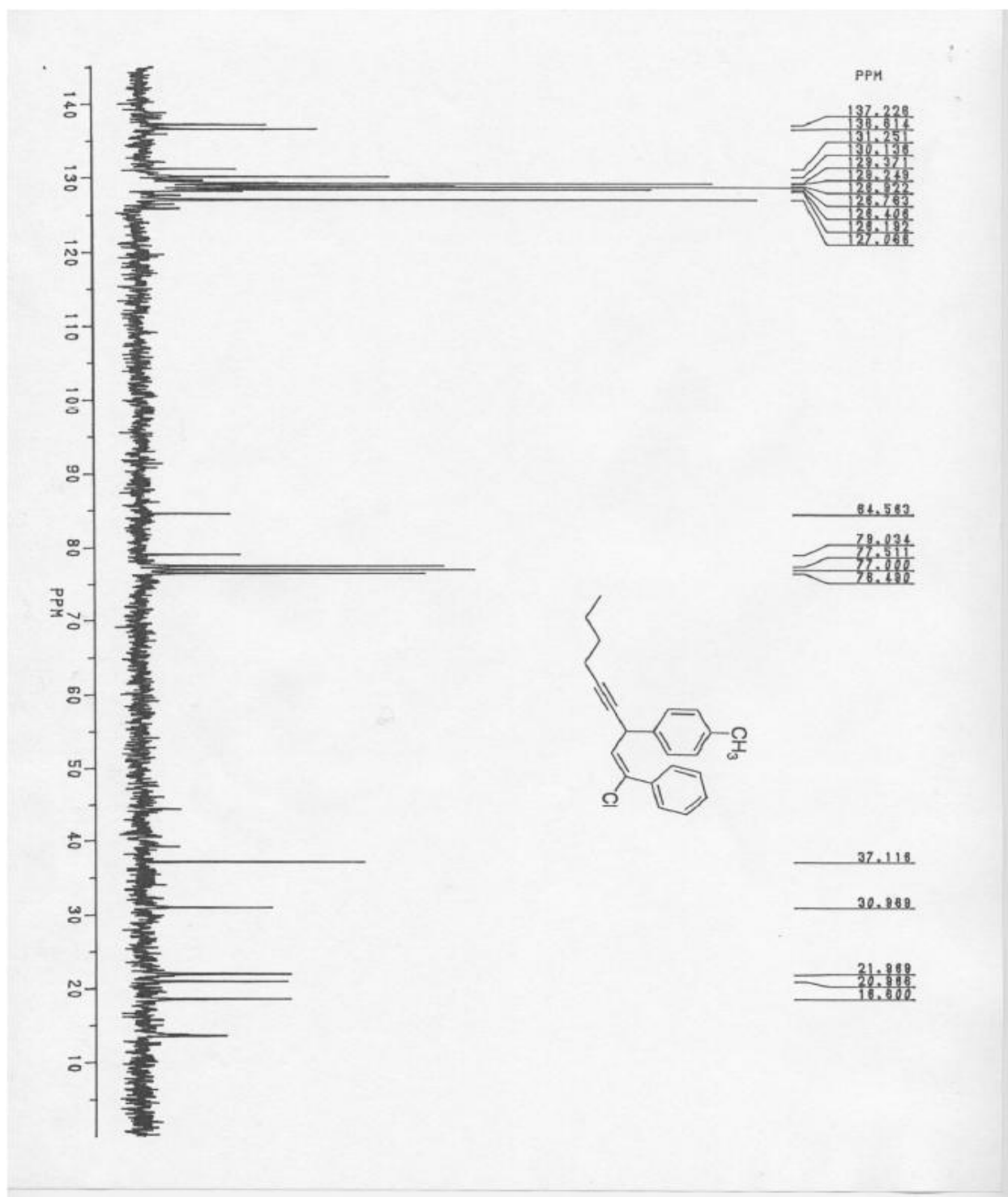
¹³C spectrum of 401i



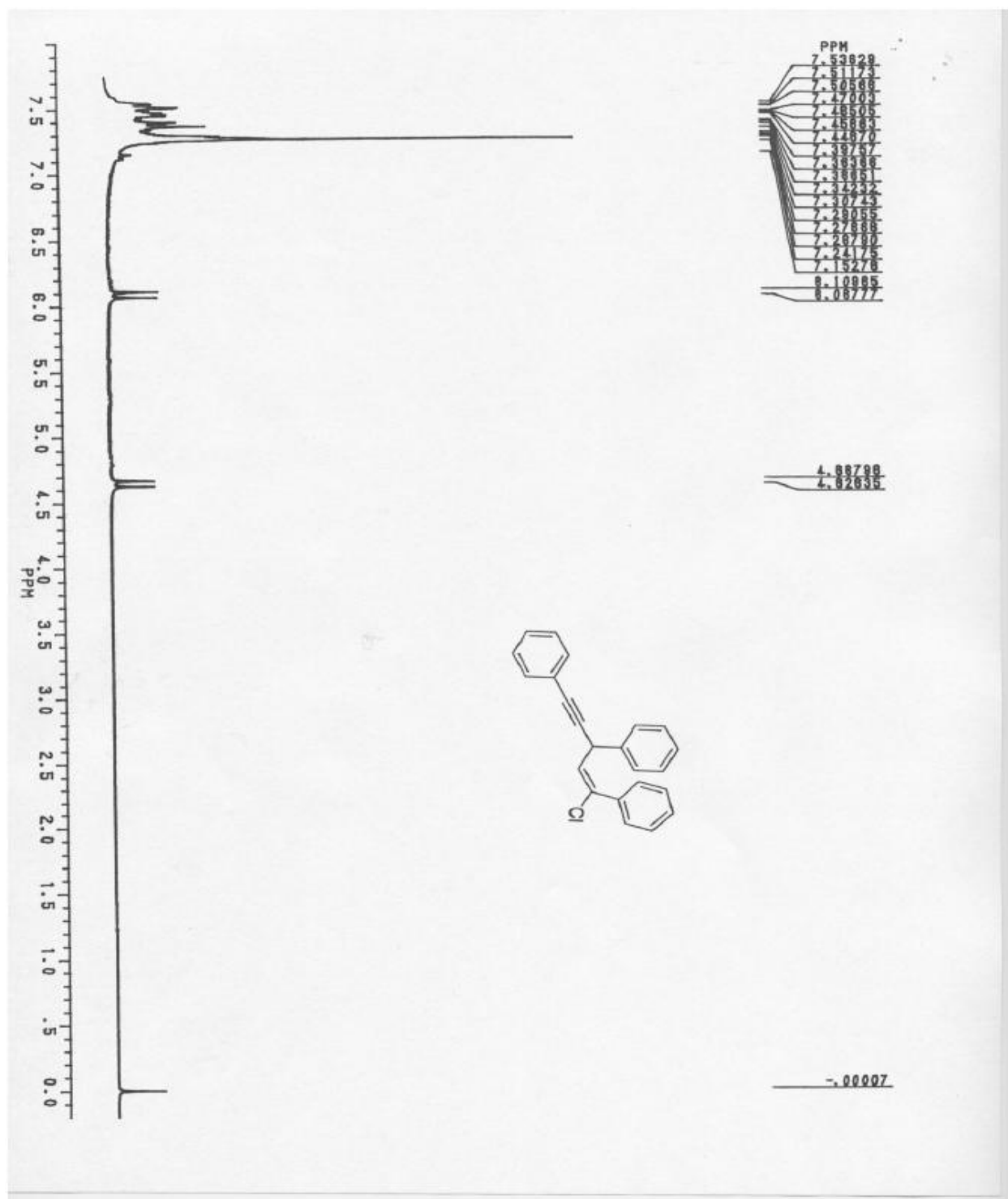
¹H spectrum of 401j



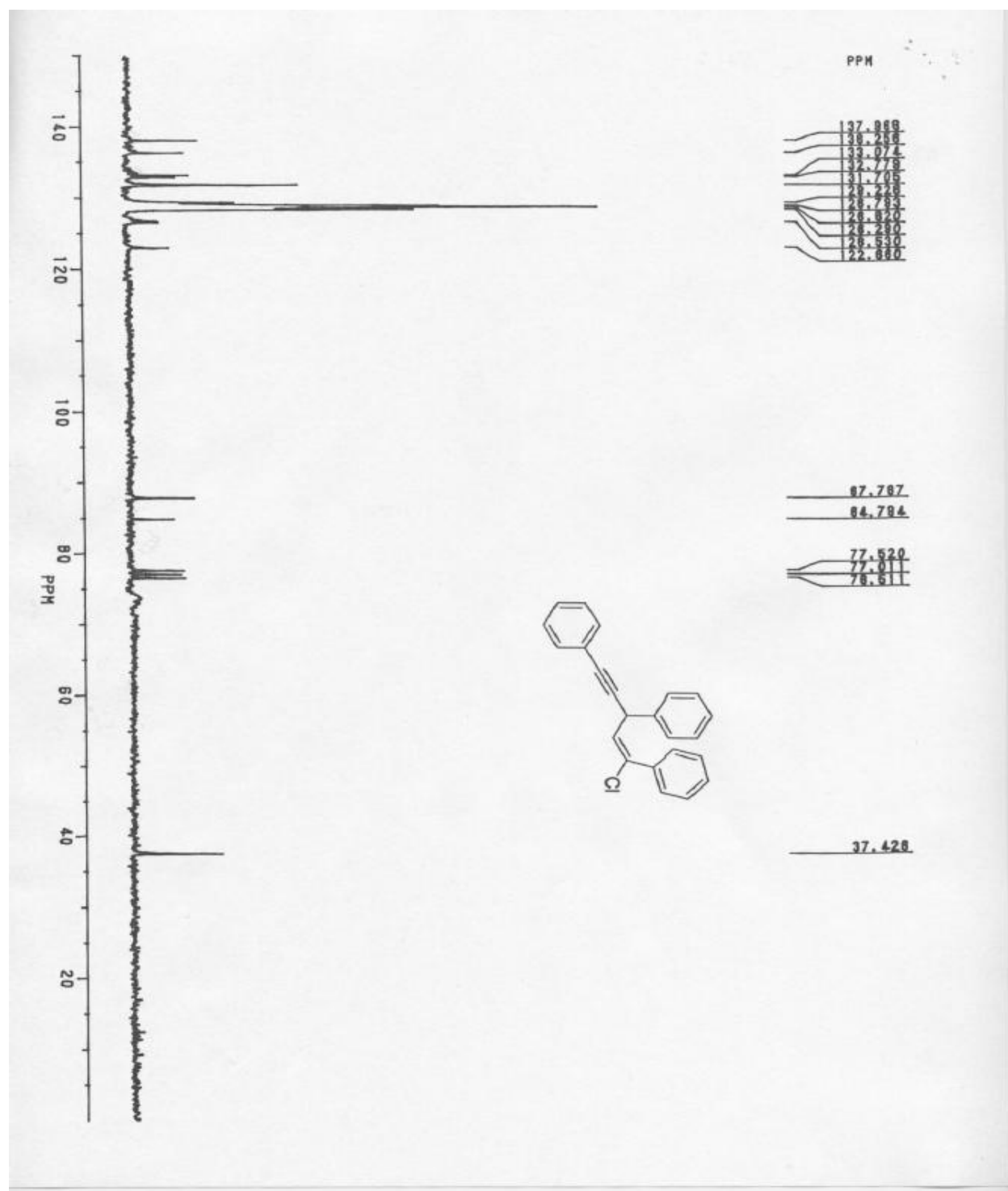
¹³C spectrum of 401j



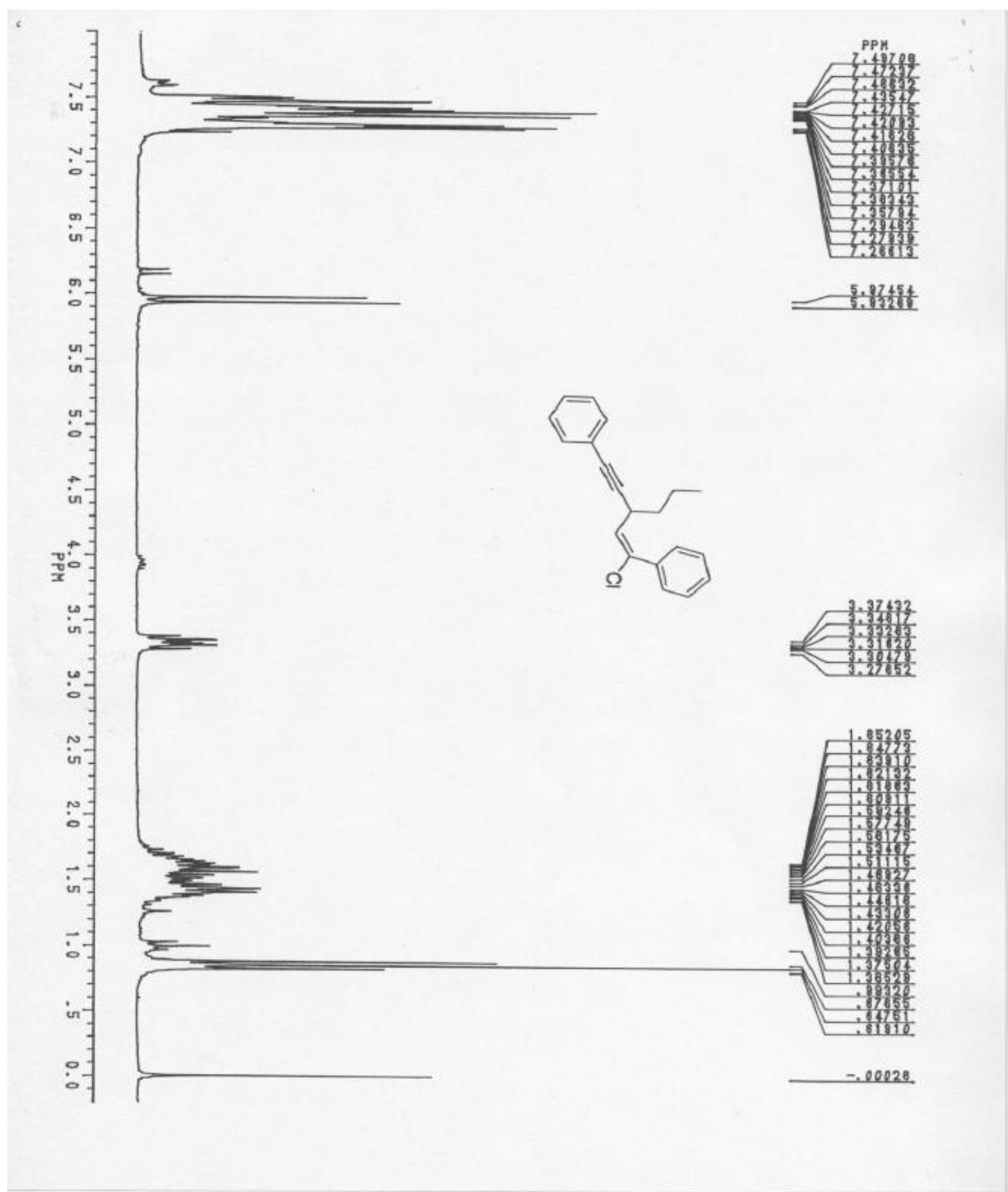
¹H spectrum of 401k



¹³C spectrum of 401k



^1H spectrum of 4011



140
130
120
110
100
90
80
70
60
50
40
30
20
10

PPM

131.857
131.856
130.878
128.852
128.875
128.210
128.186
127.878
127.862
127.388
127.499

80.272

62.337
77.493
78.893
78.482

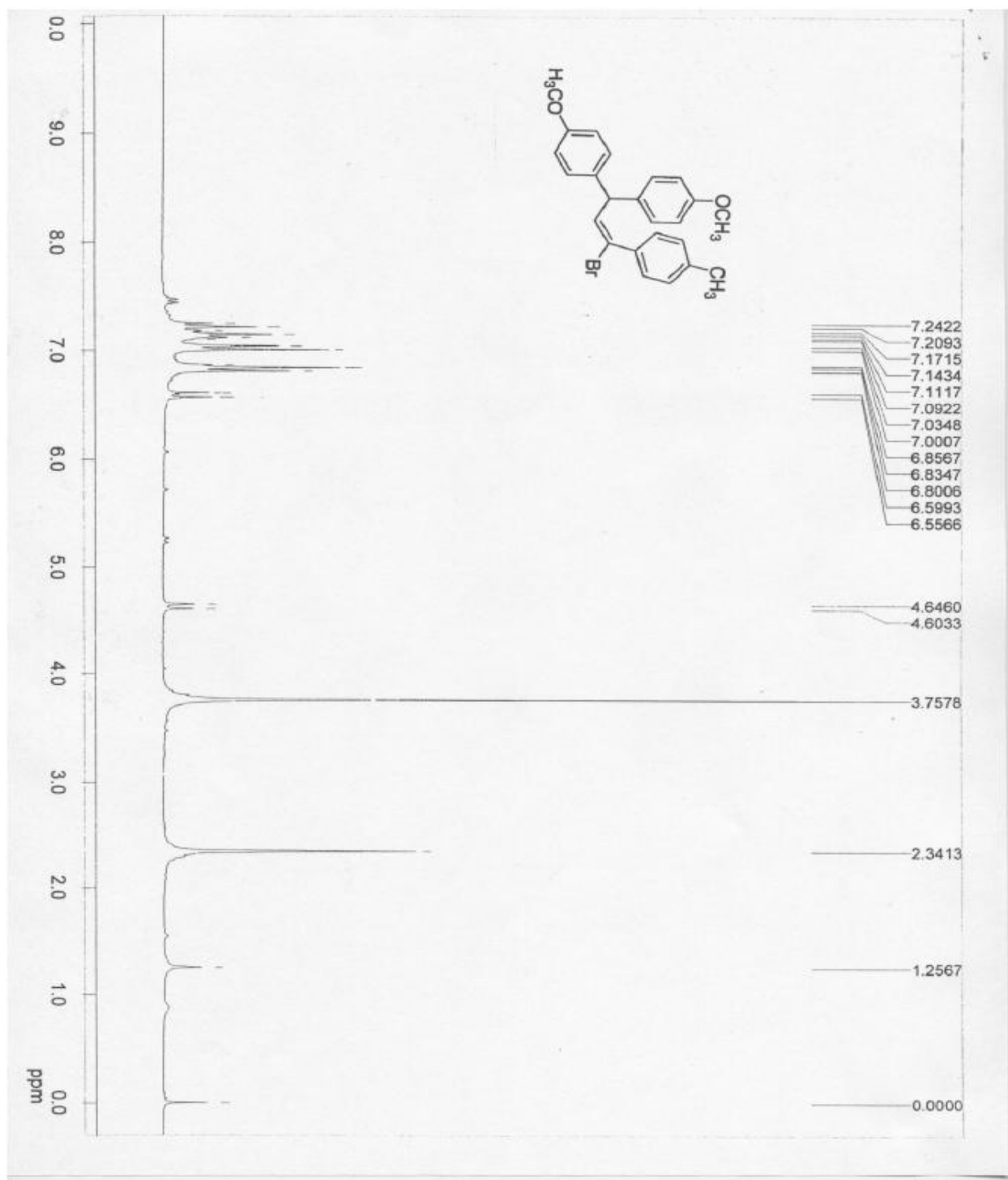
37.838
32.401

20.110
13.854

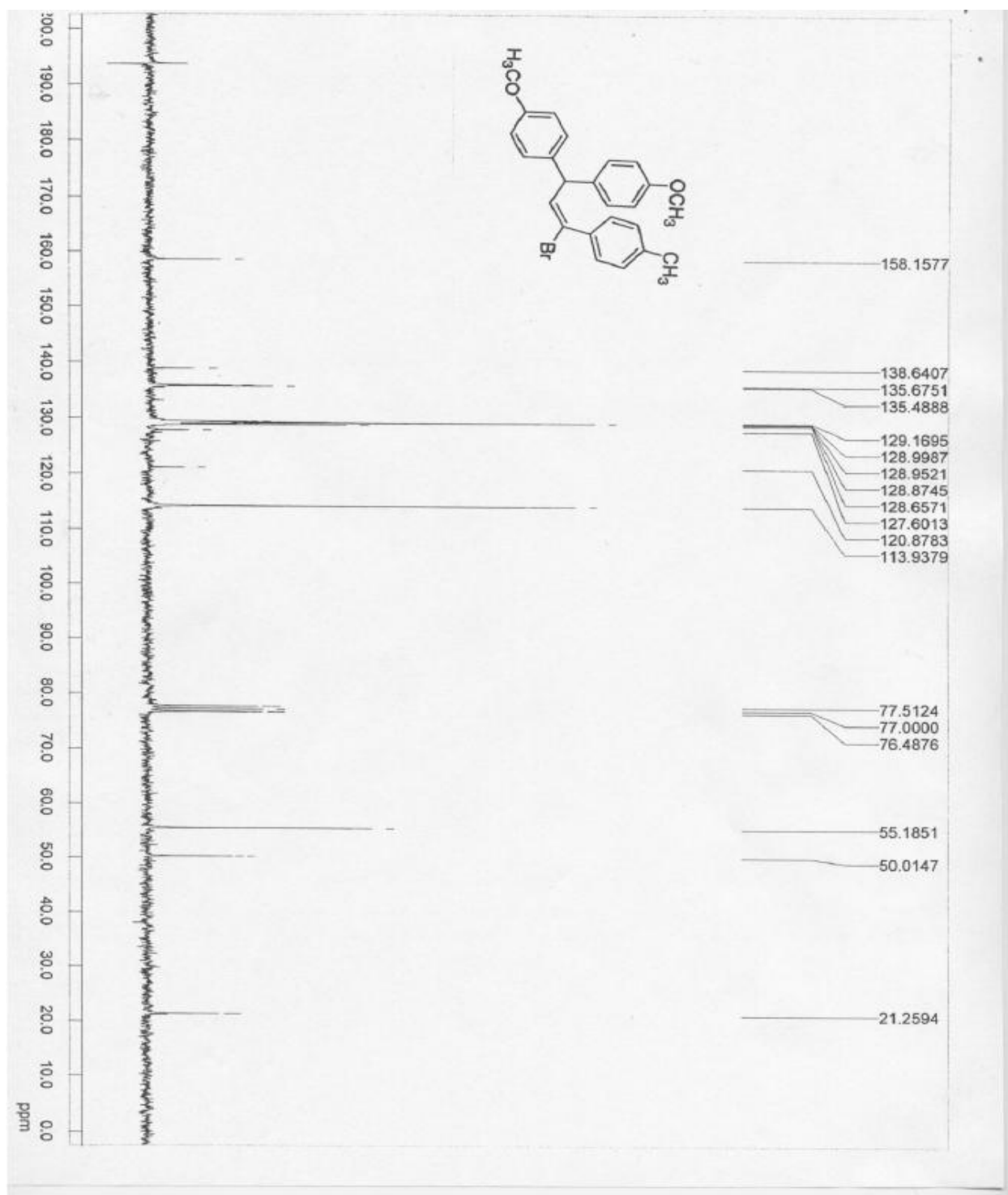
PPM

CCCC/C=C/C(Cl)=C/c1ccccc1

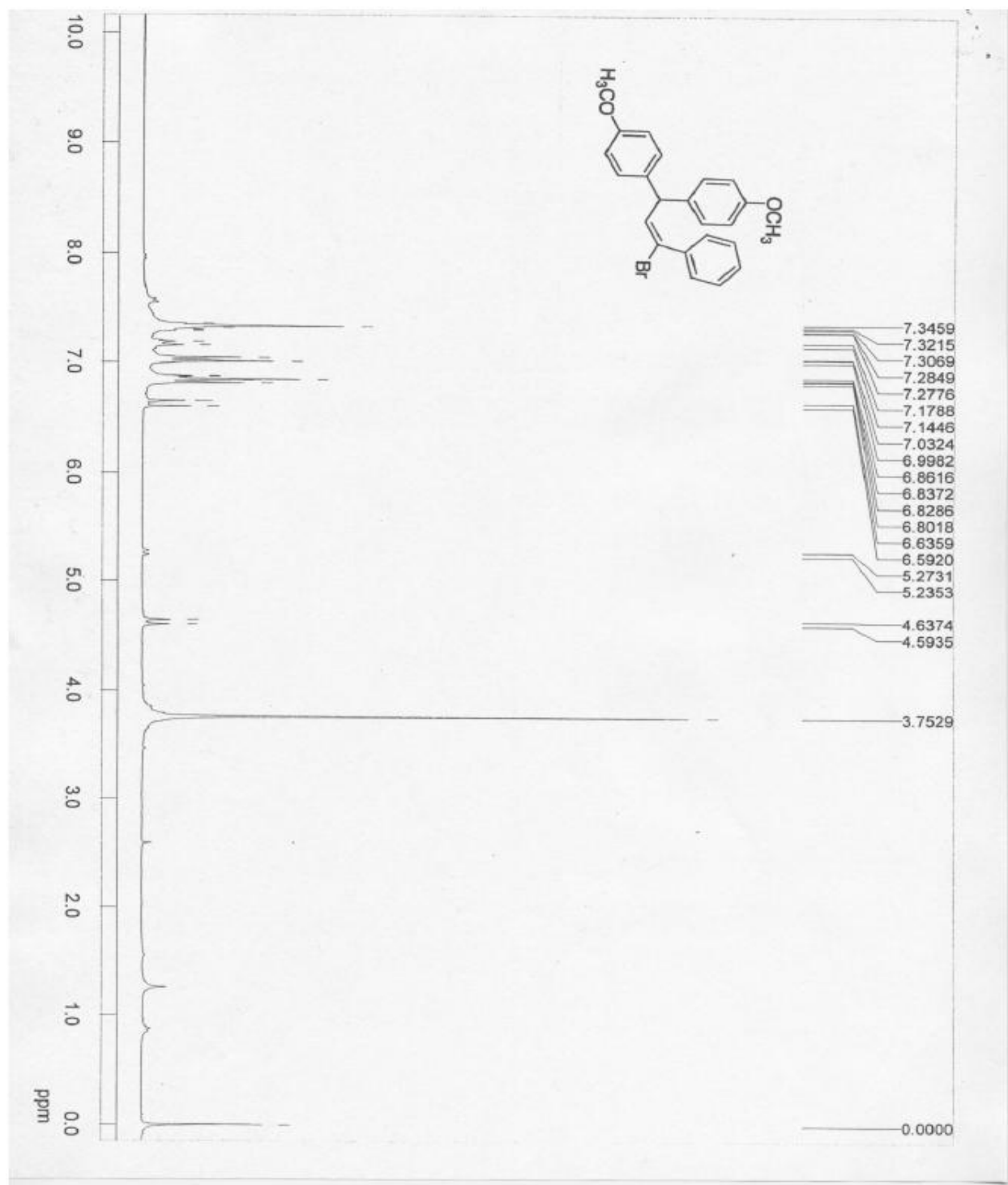
¹H spectrum of 402a



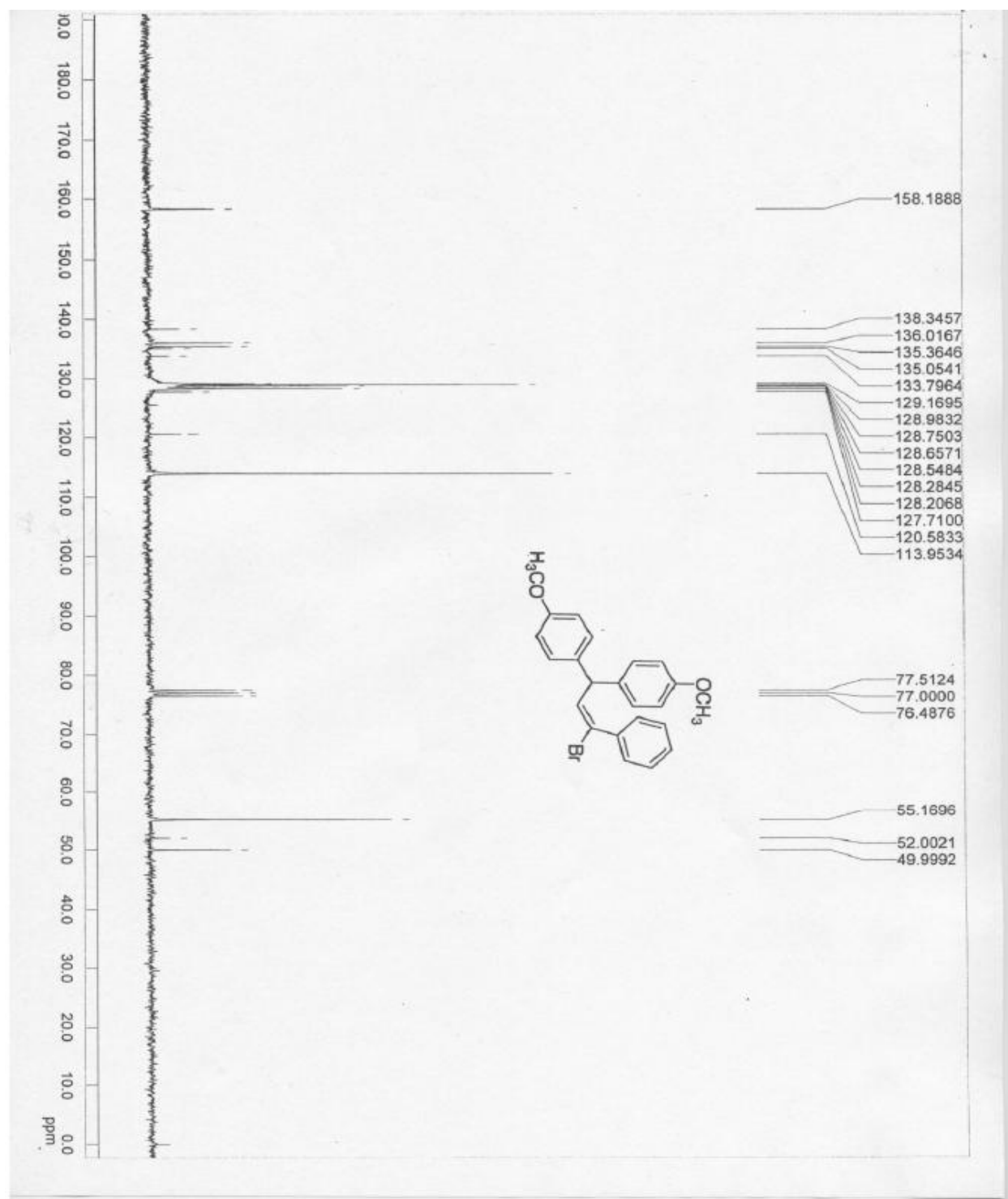
¹³C spectrum of 402a



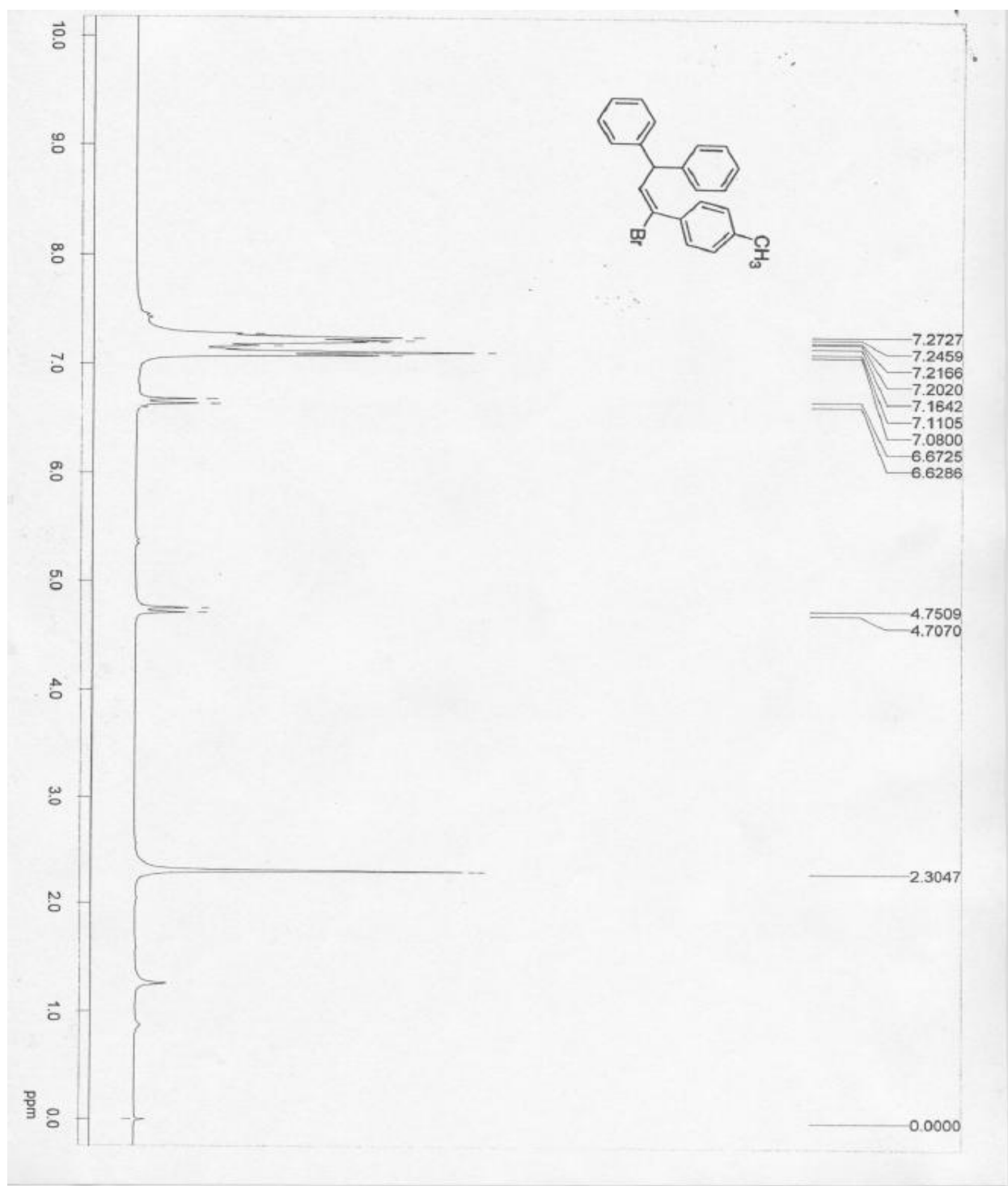
¹H spectrum of 402b



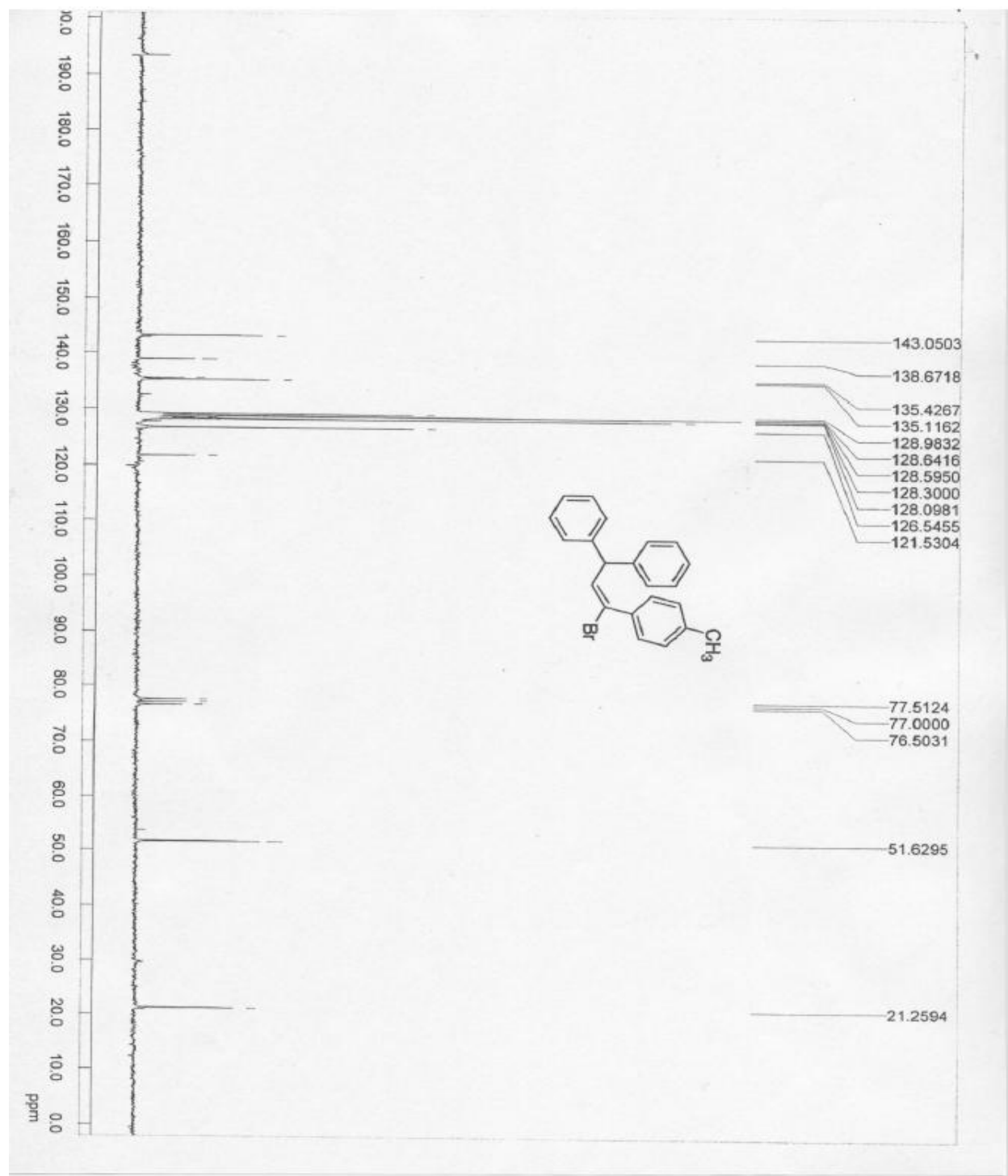
¹³C spectrum of 402b



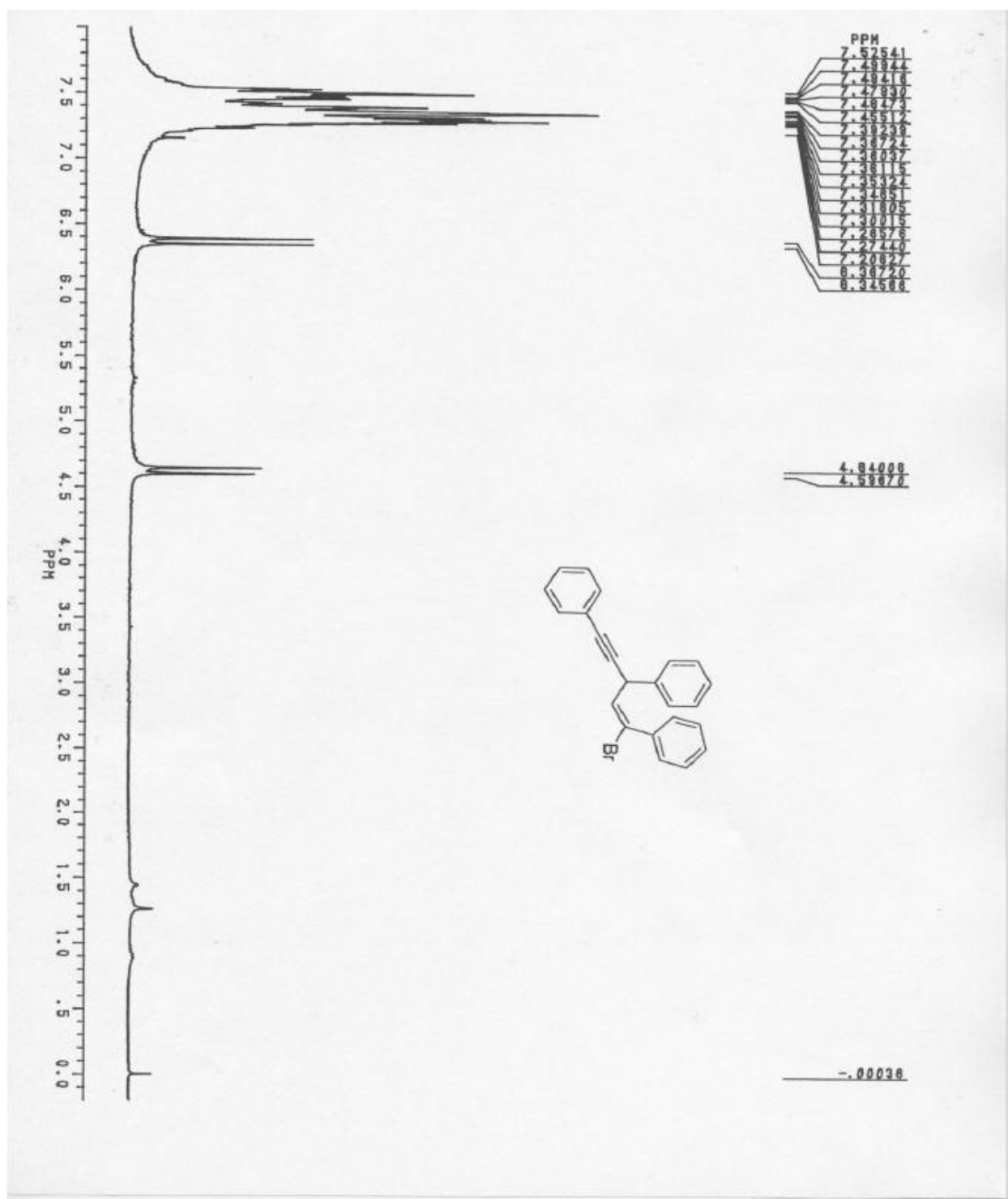
¹H spectrum of 402c



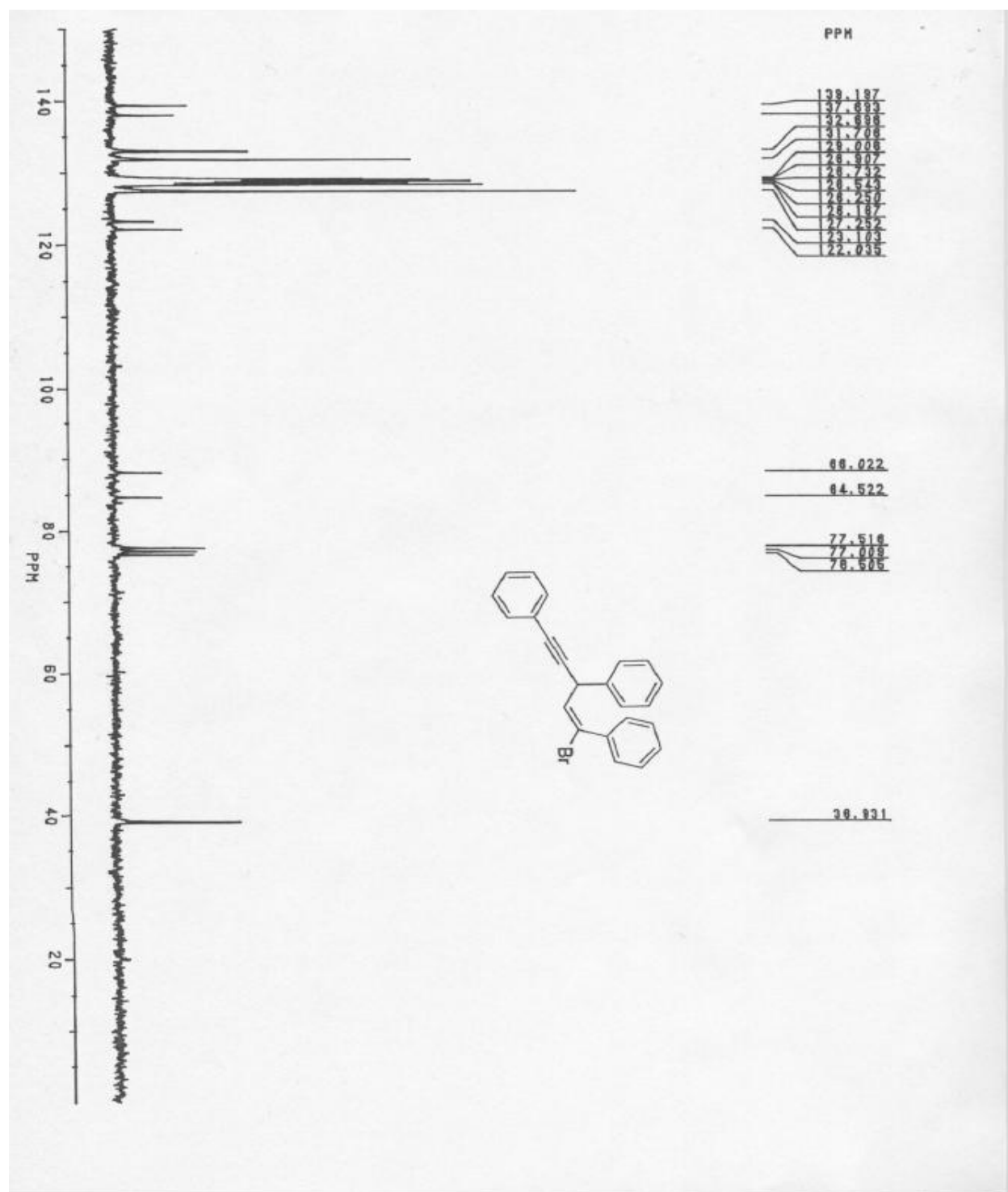
¹³C spectrum of 402c



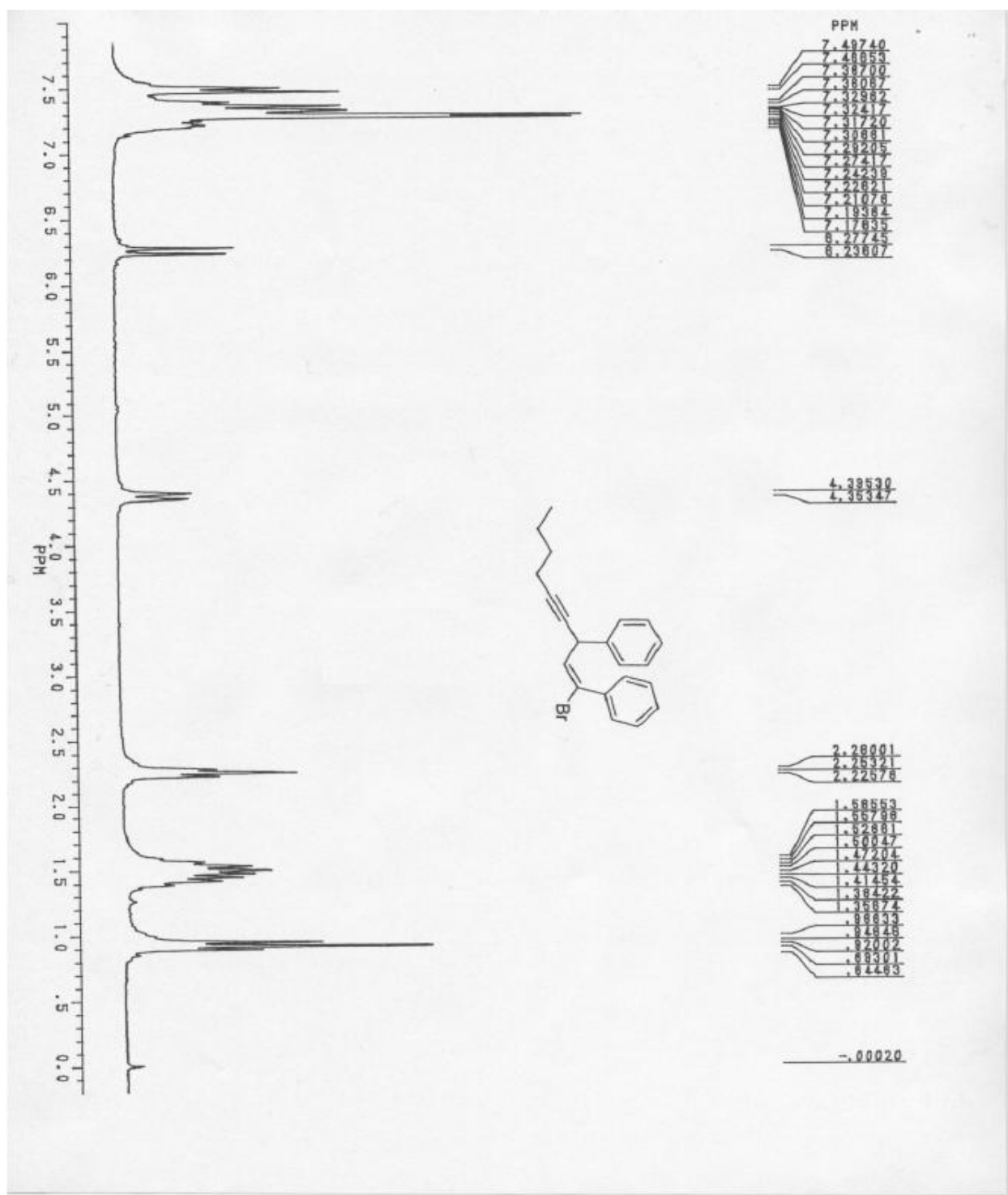
^1H spectrum of 402d



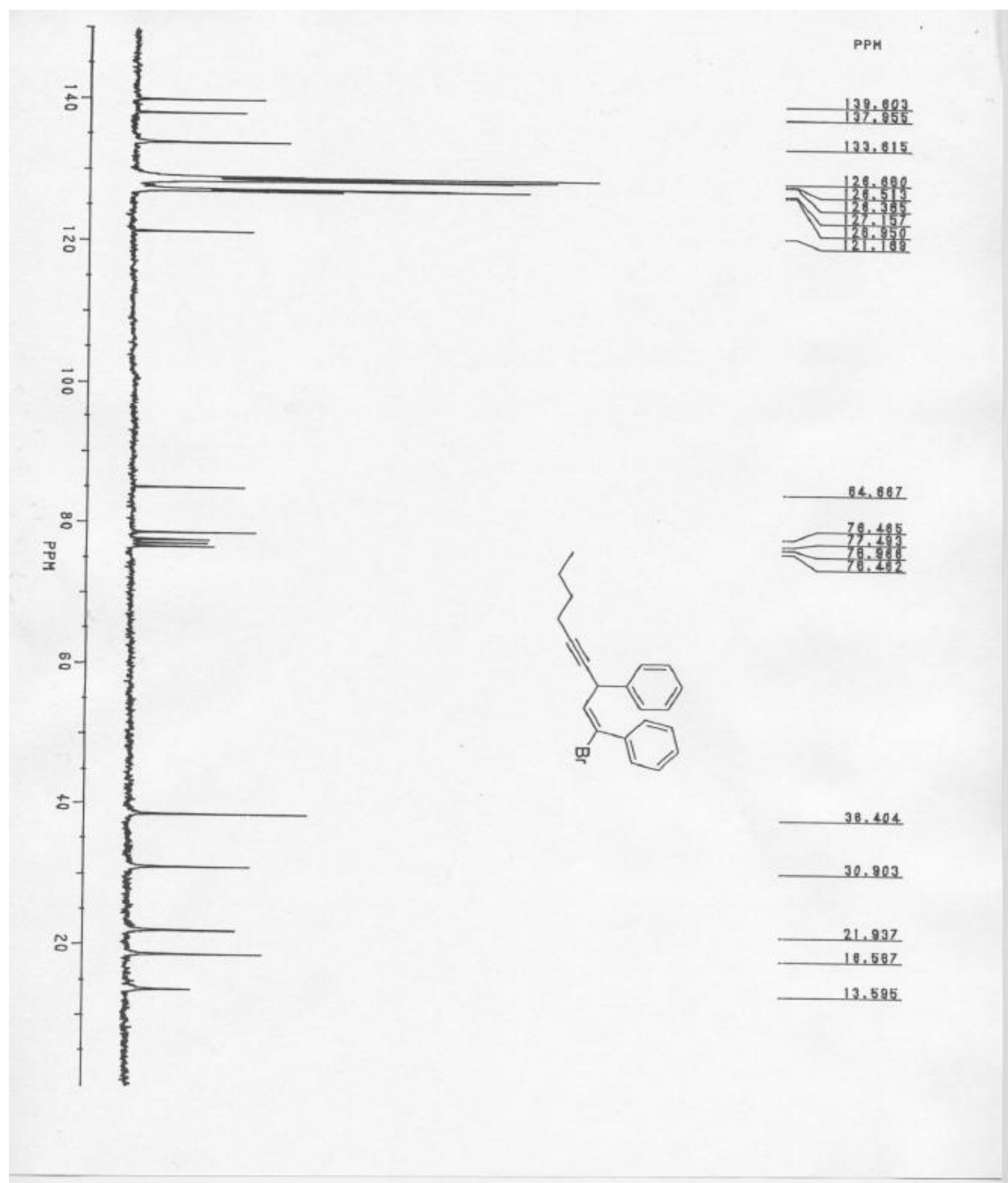
¹³C spectrum of 402d



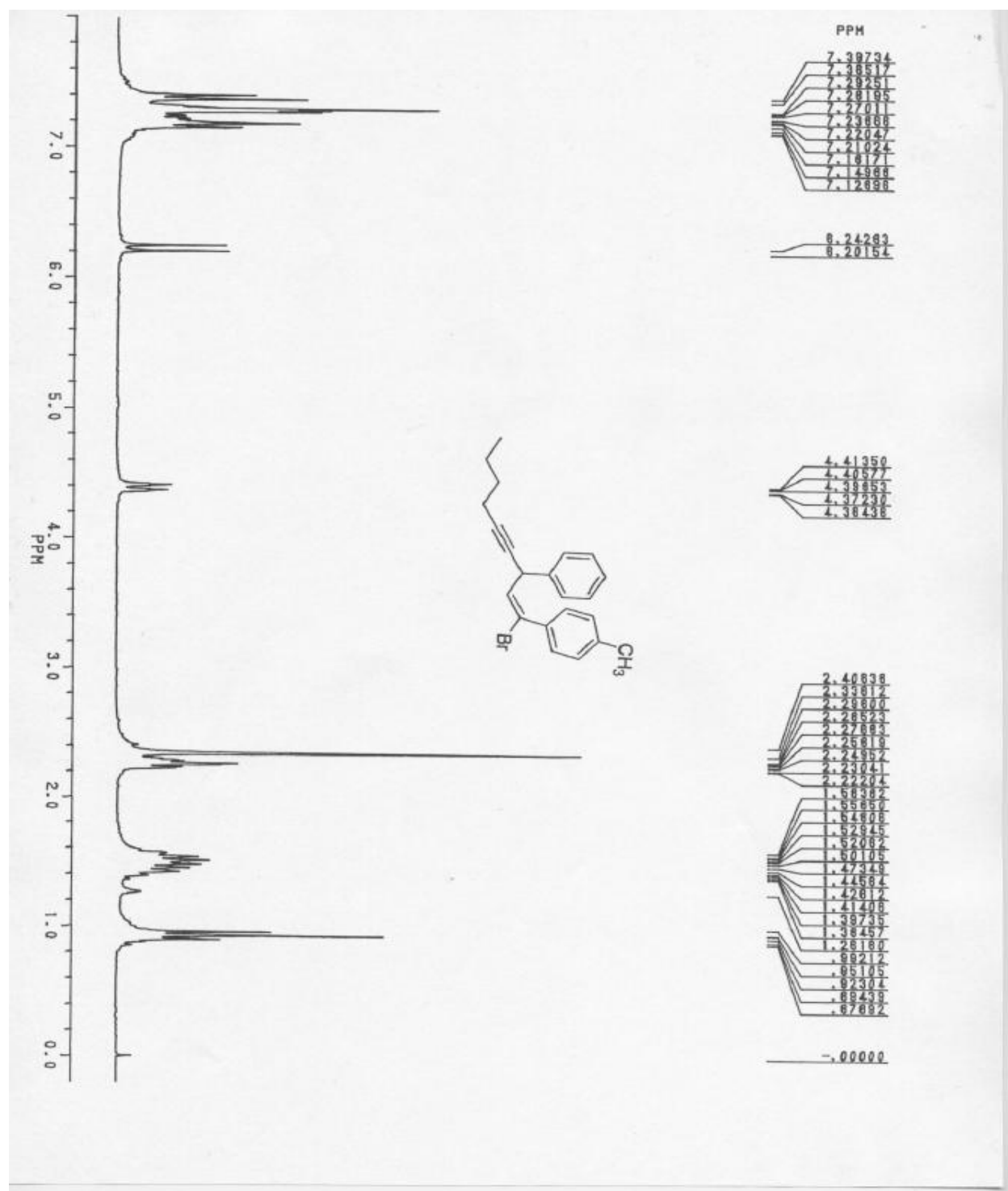
¹H spectrum of 402e



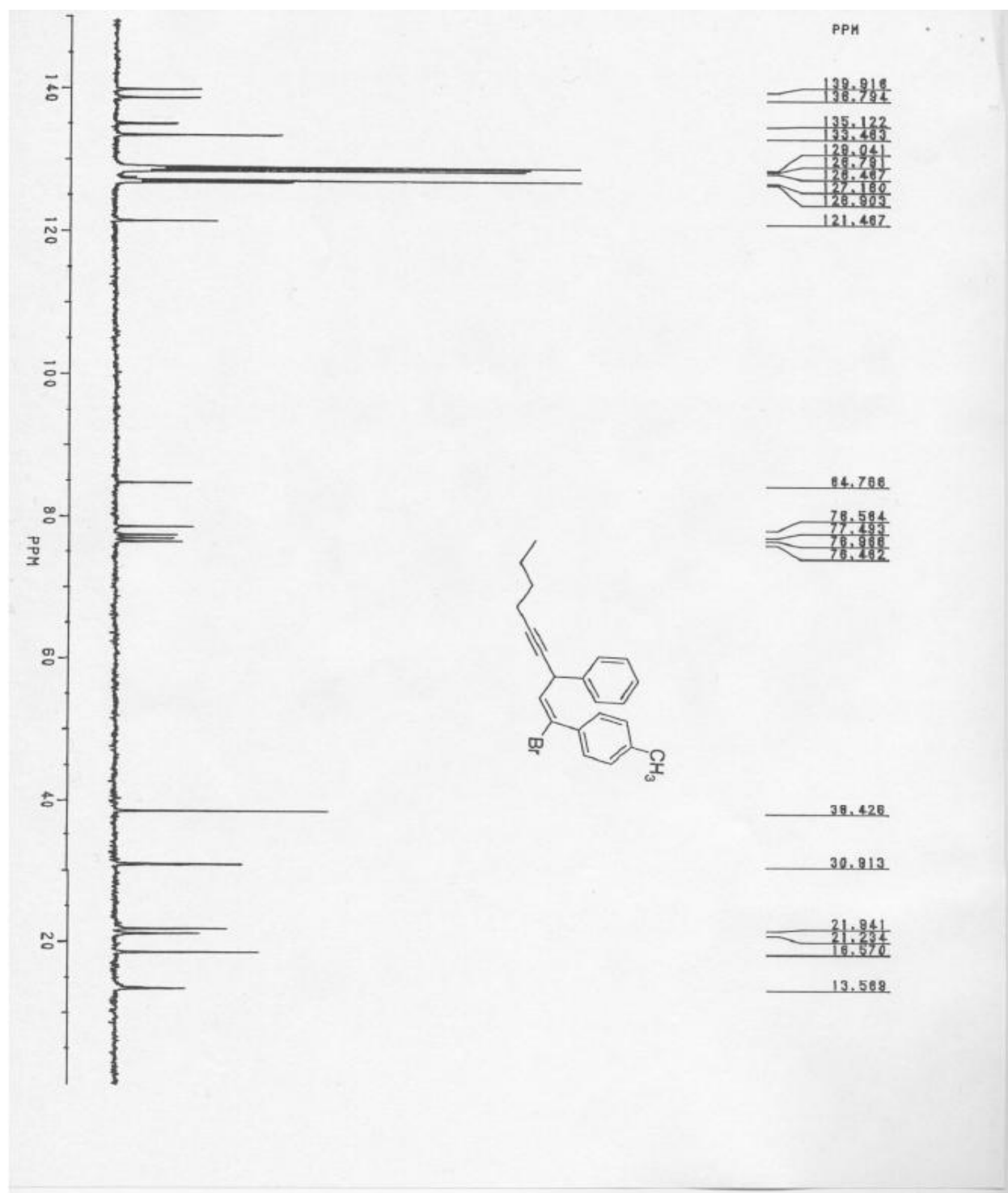
¹³C spectrum of 402e



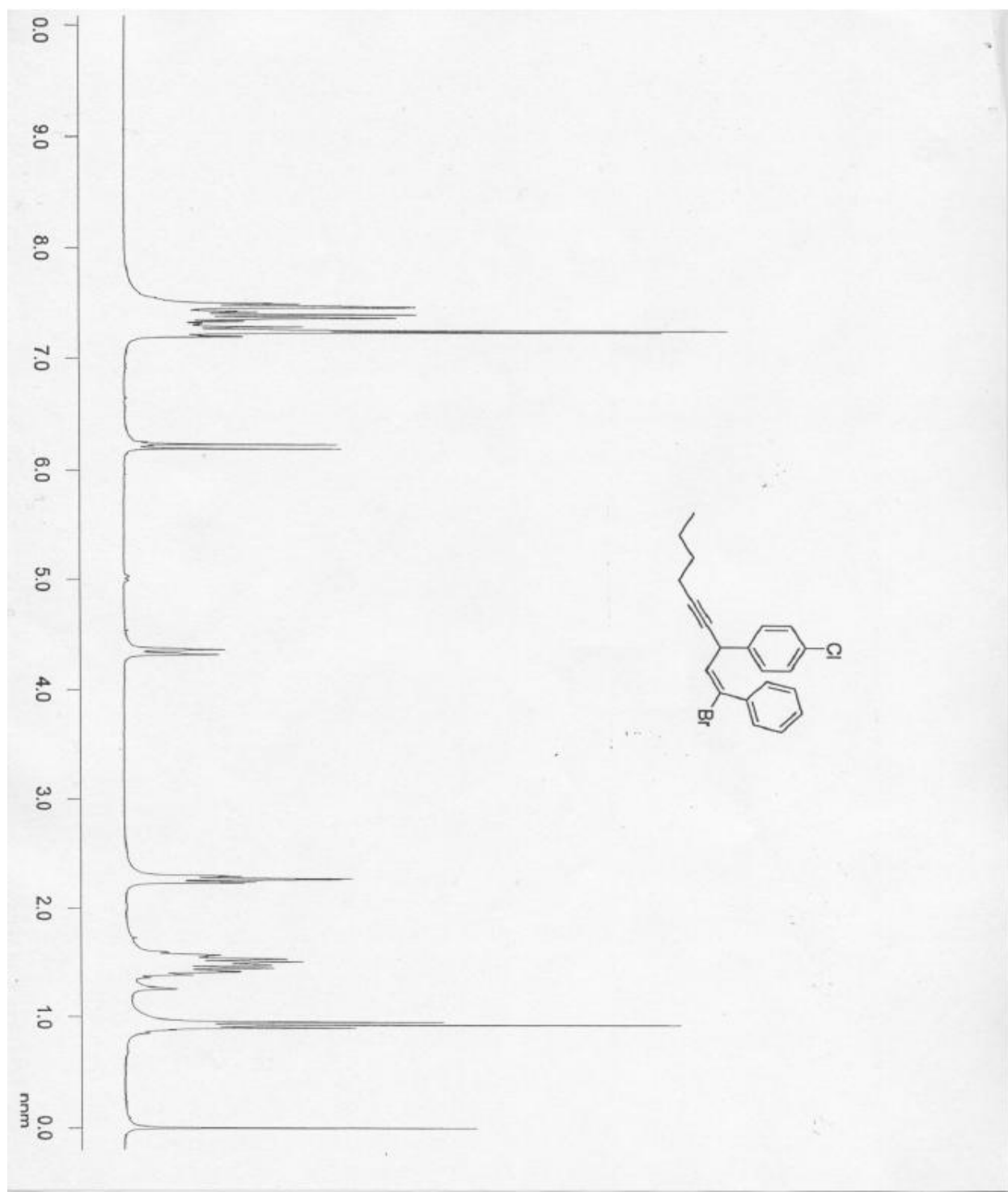
¹H spectrum of 402f



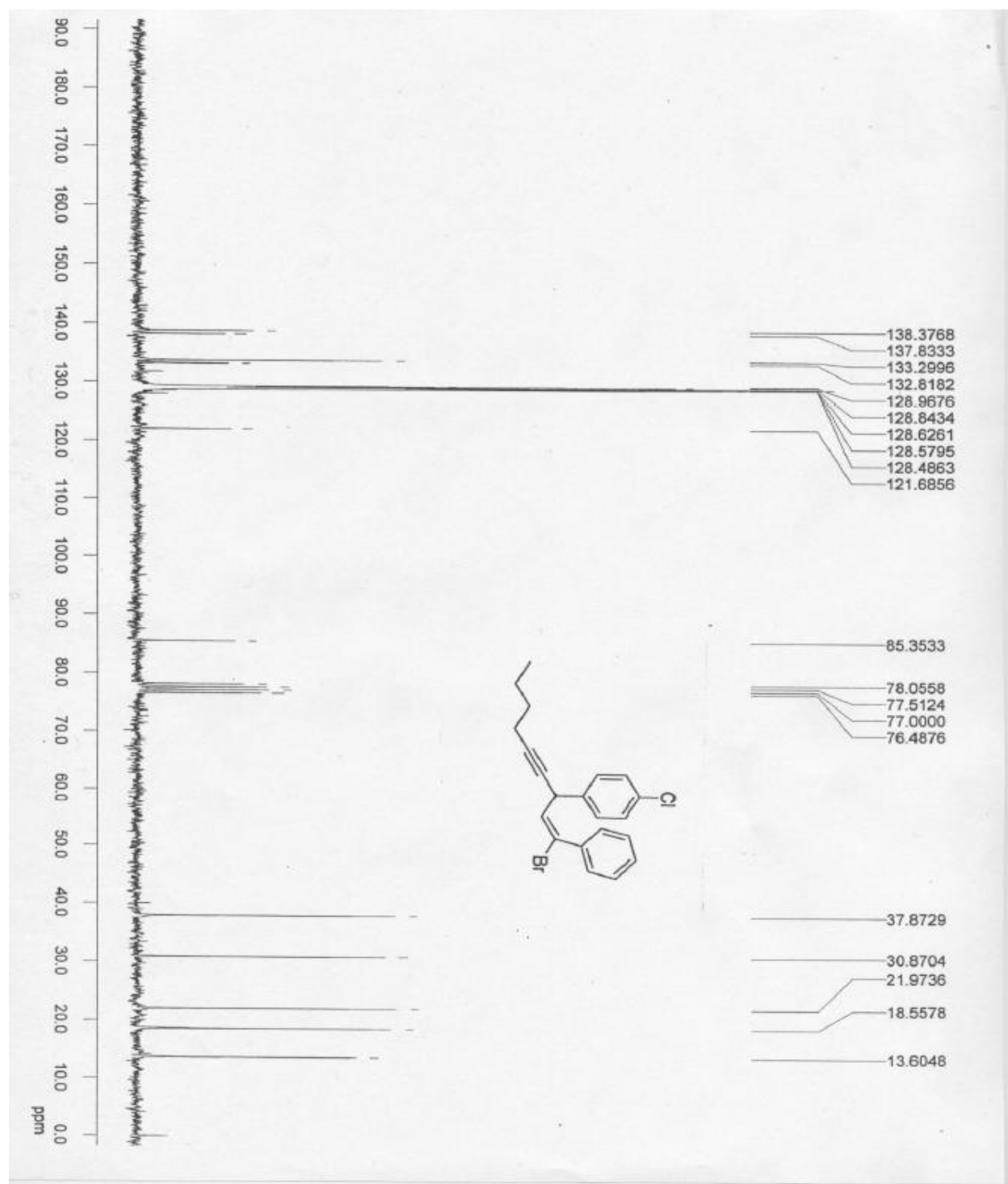
¹³C spectrum of 402f



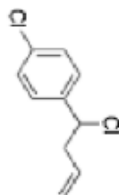
^1H spectrum of 402g



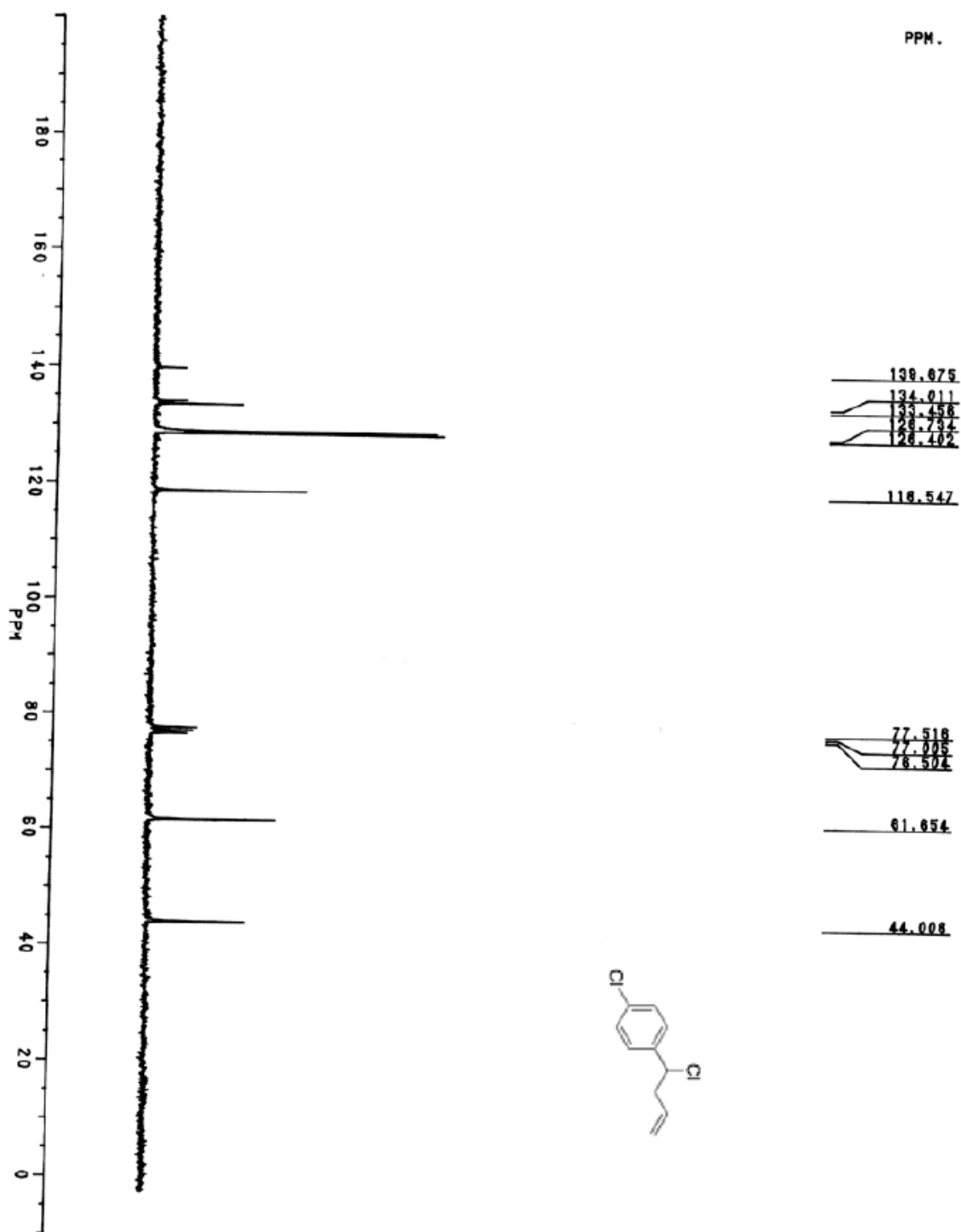
^{13}C spectrum of 402g



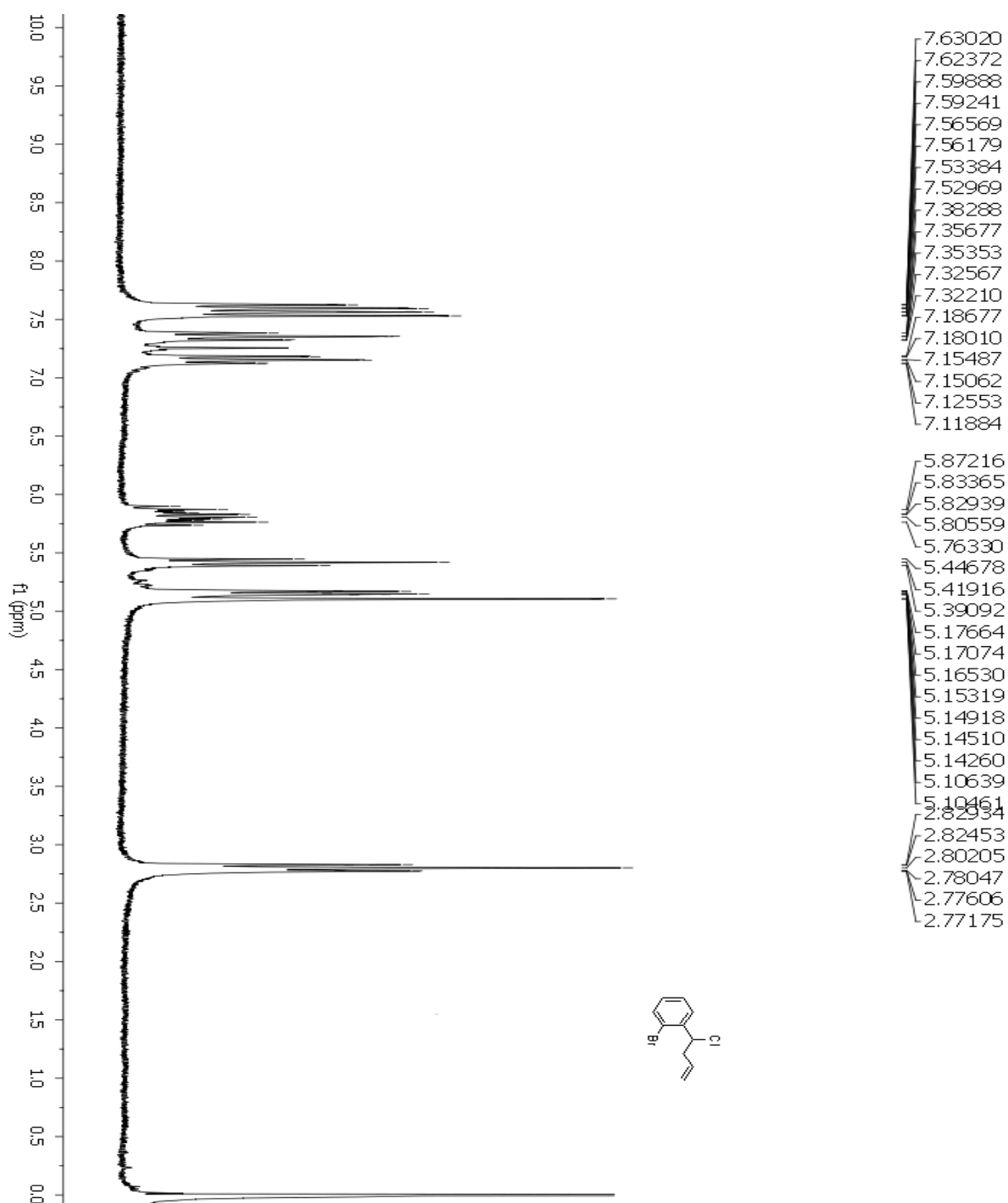
¹H spectrum of 502c



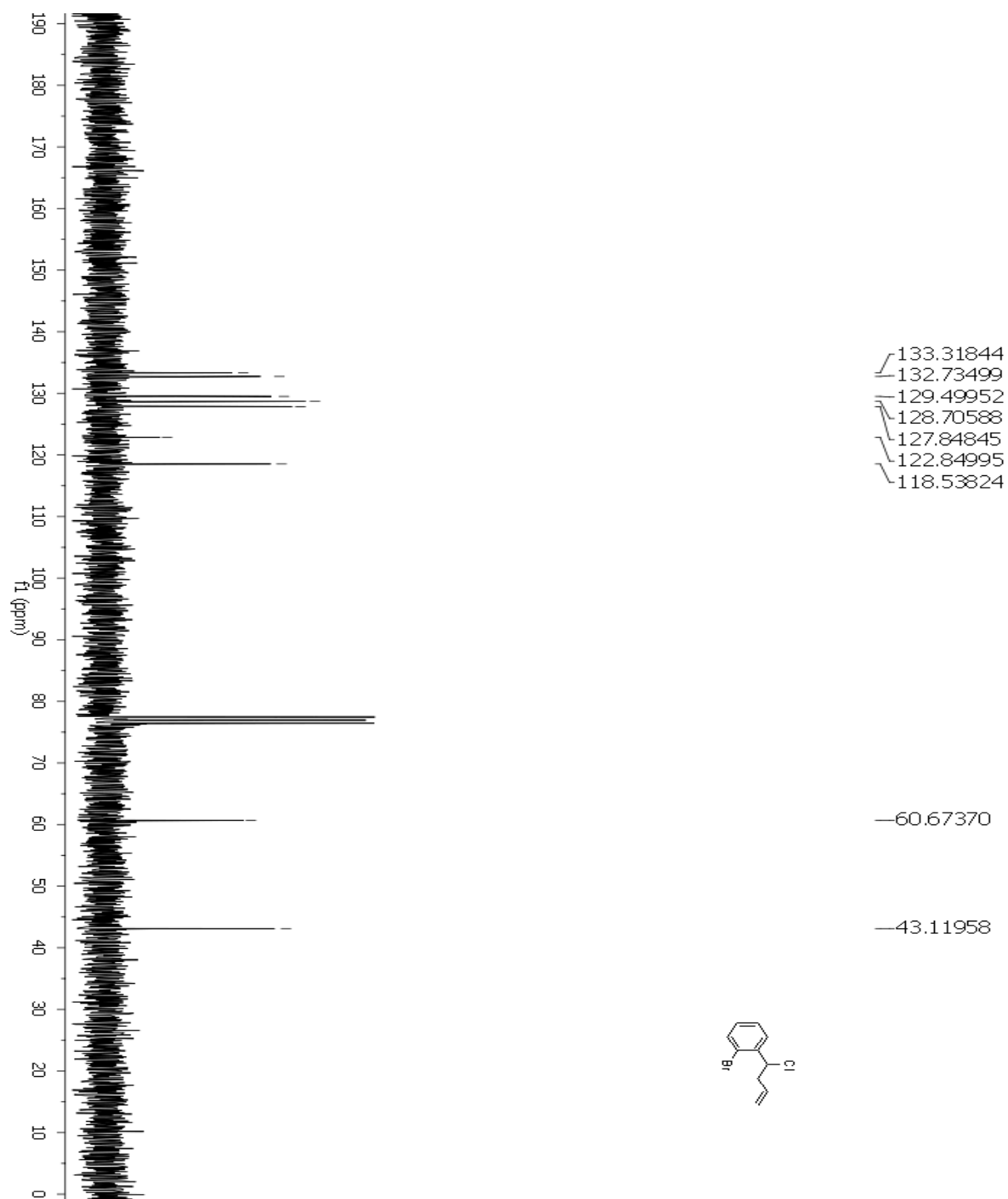
^{13}C spectrum of 502c



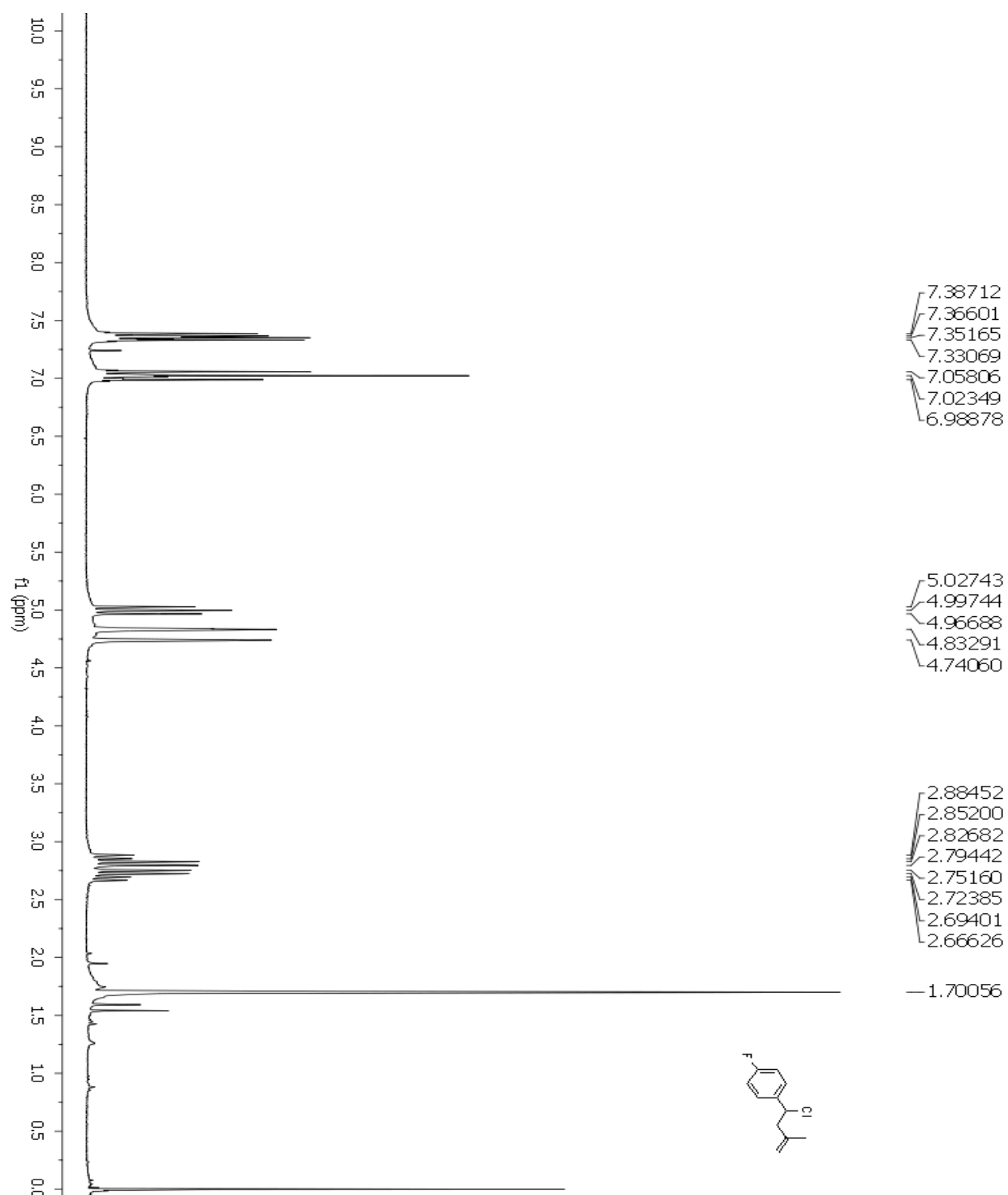
¹H spectrum of 502f



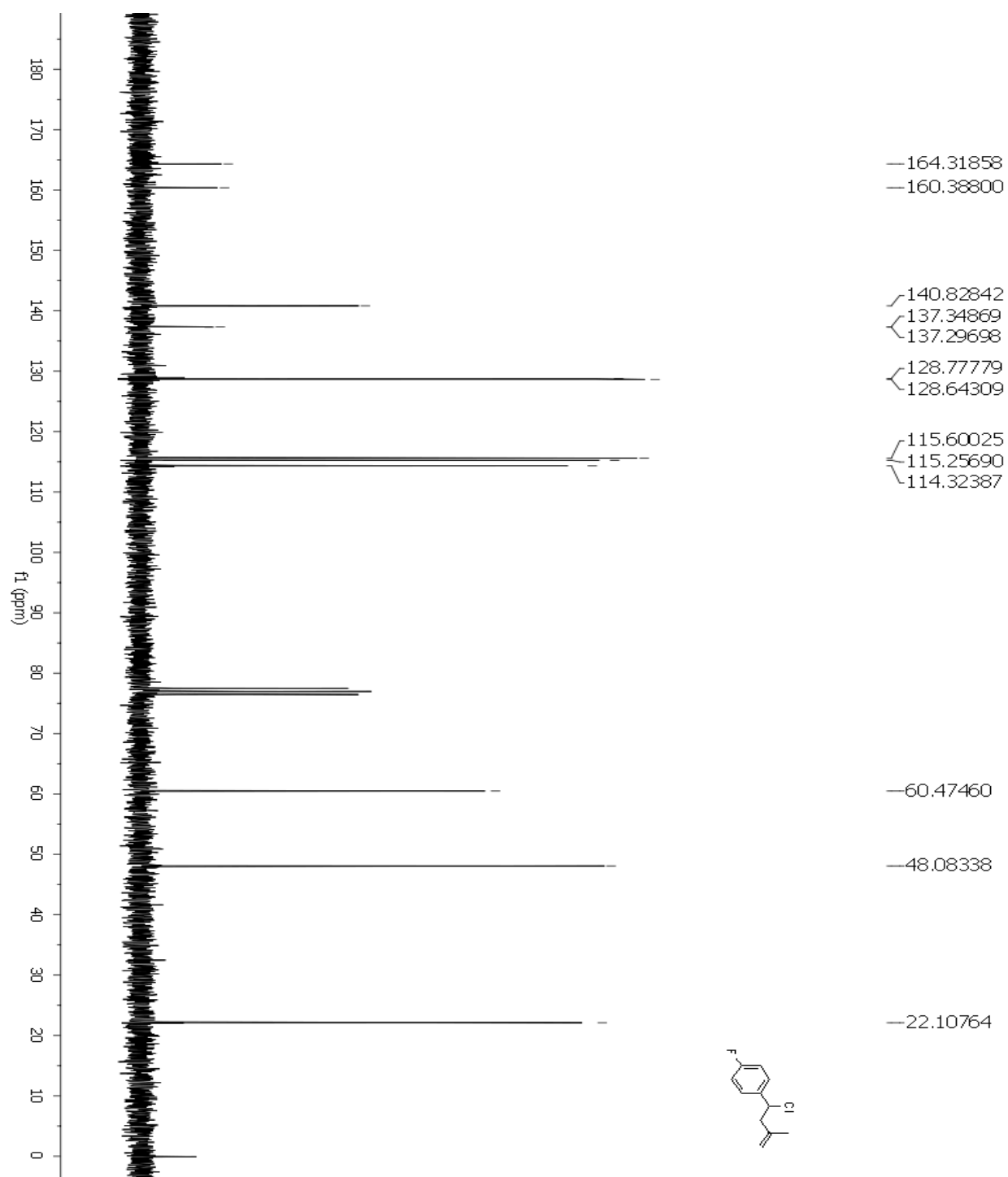
¹³C spectrum of 502f



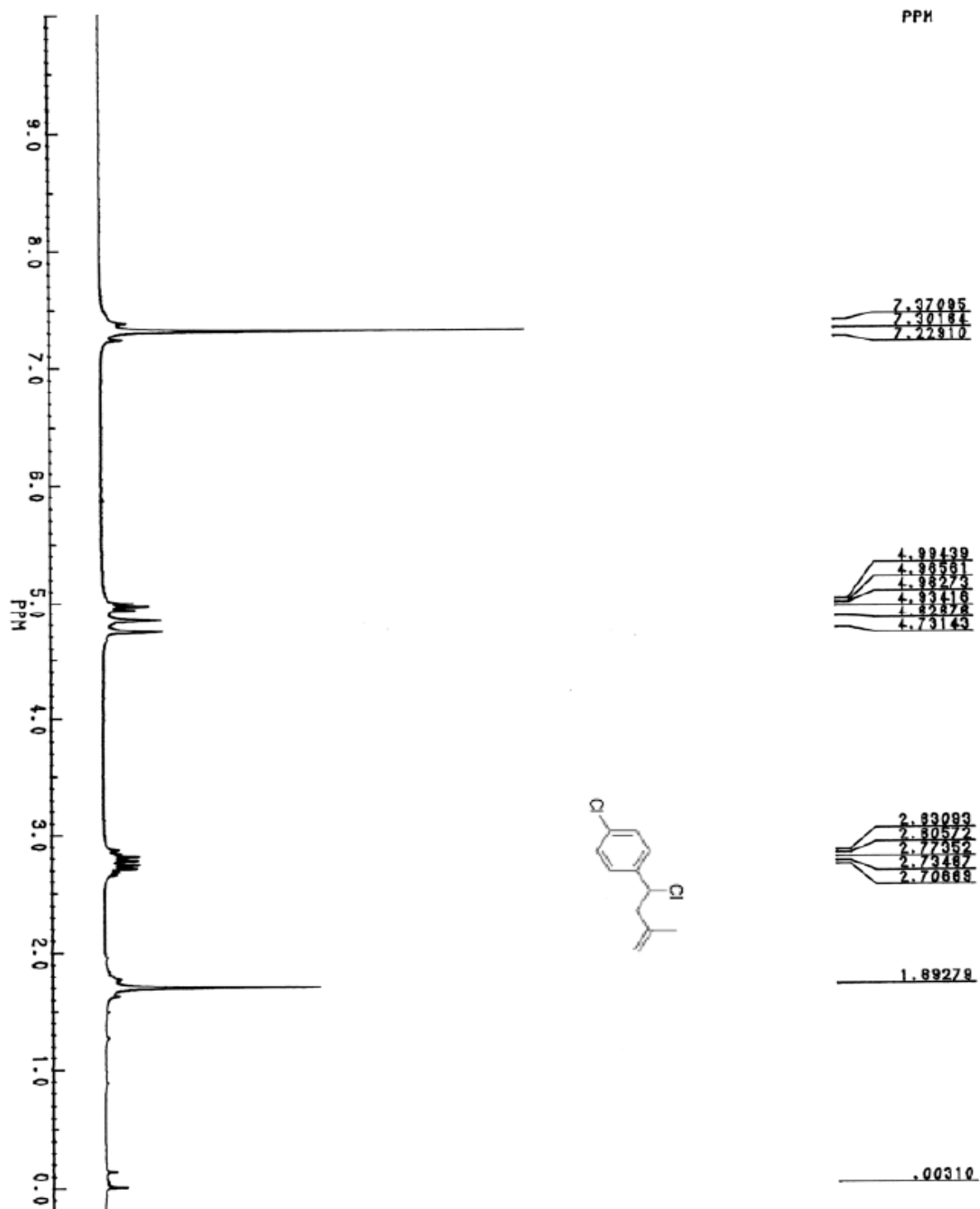
^1H spectrum of 502h



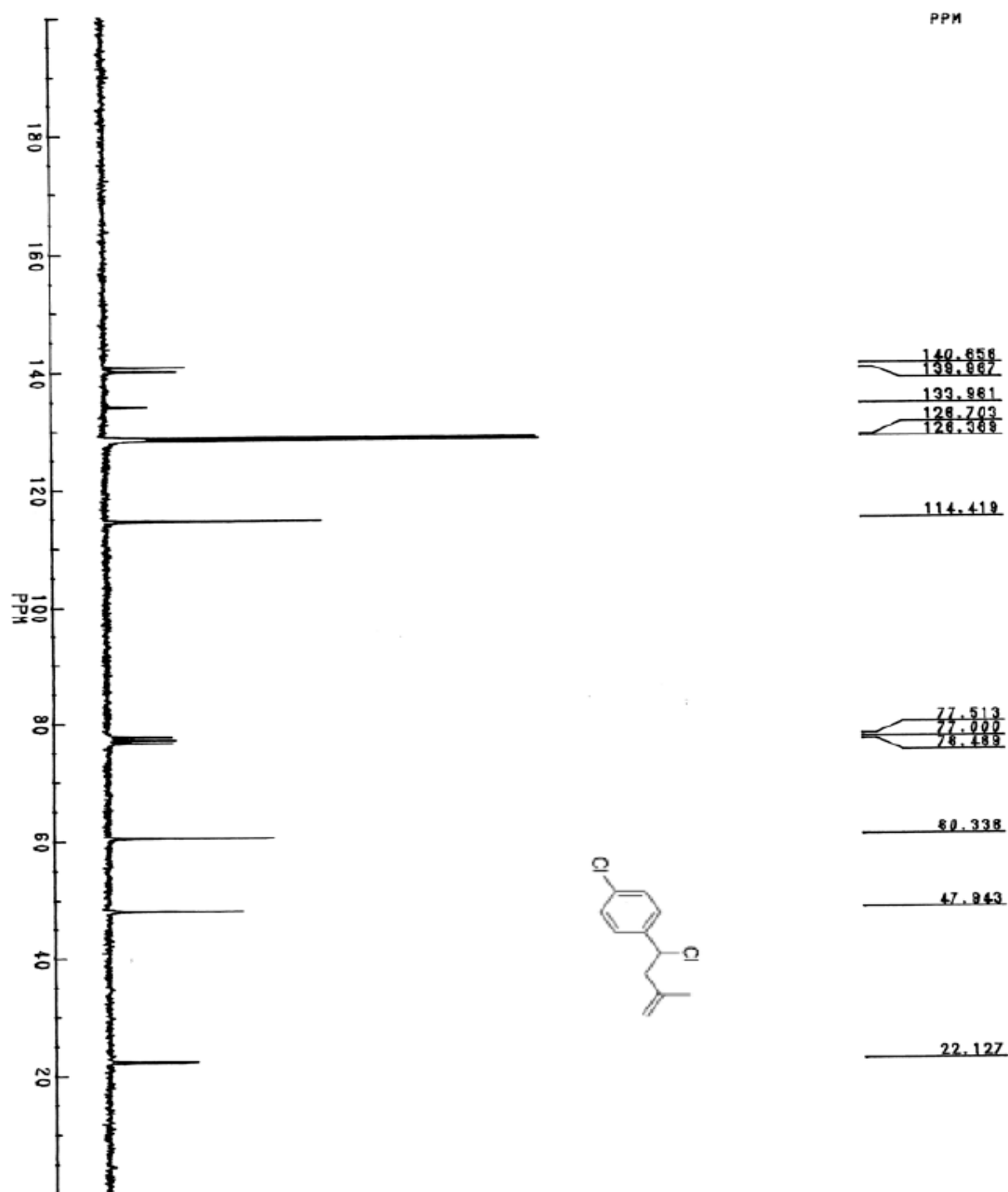
¹³C spectrum of 502h



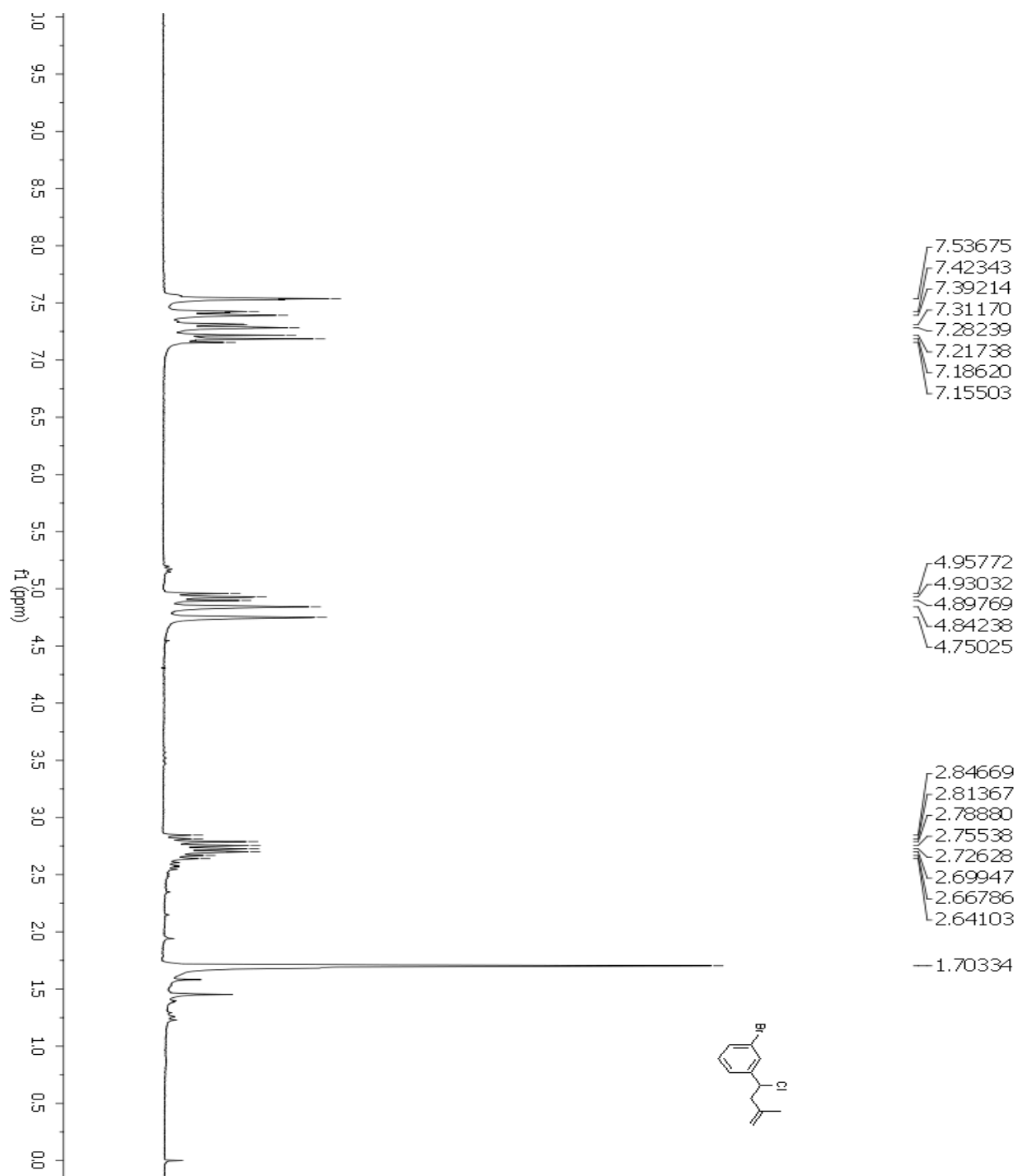
¹H spectrum of 502i



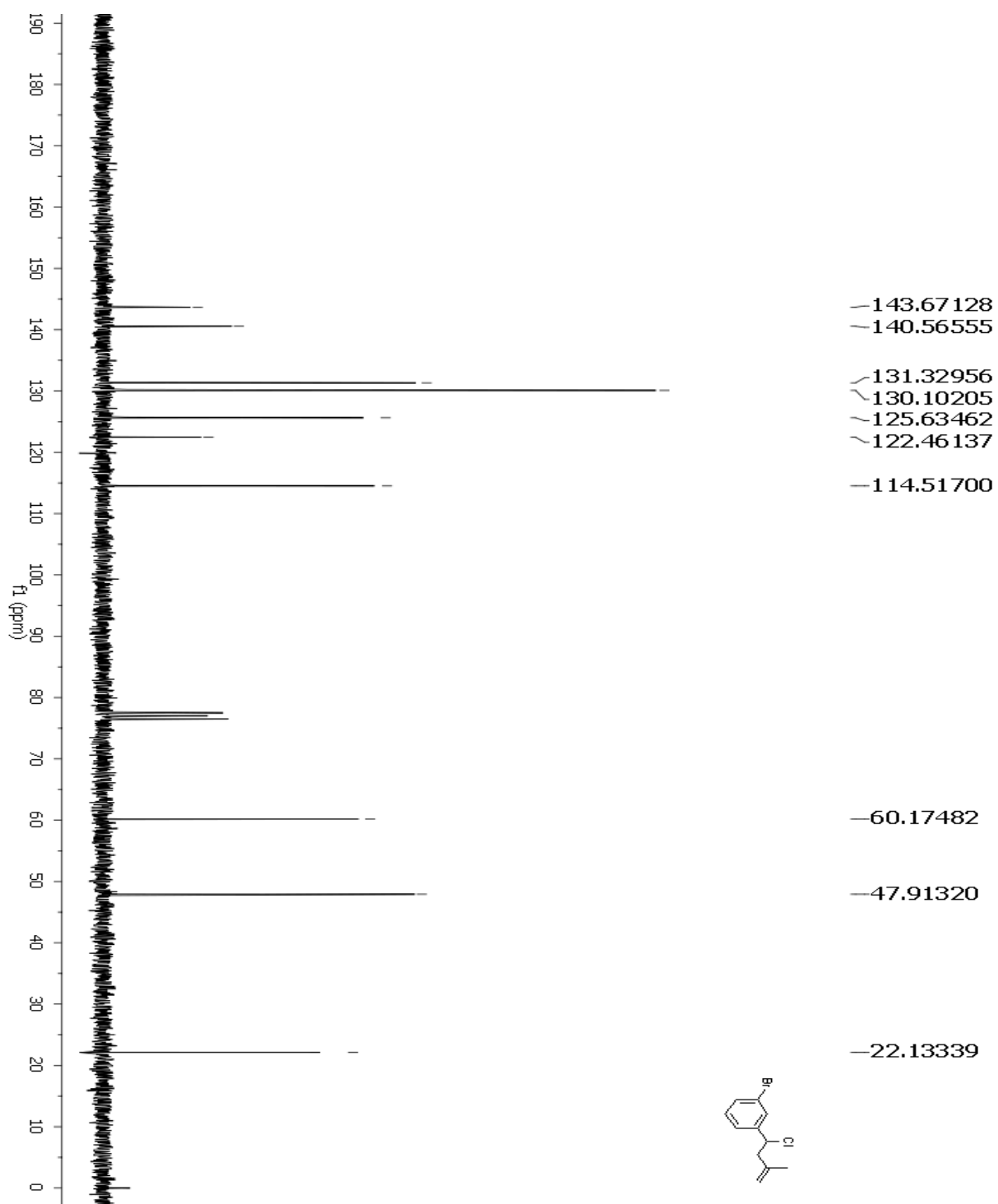
¹³C spectrum of 502i



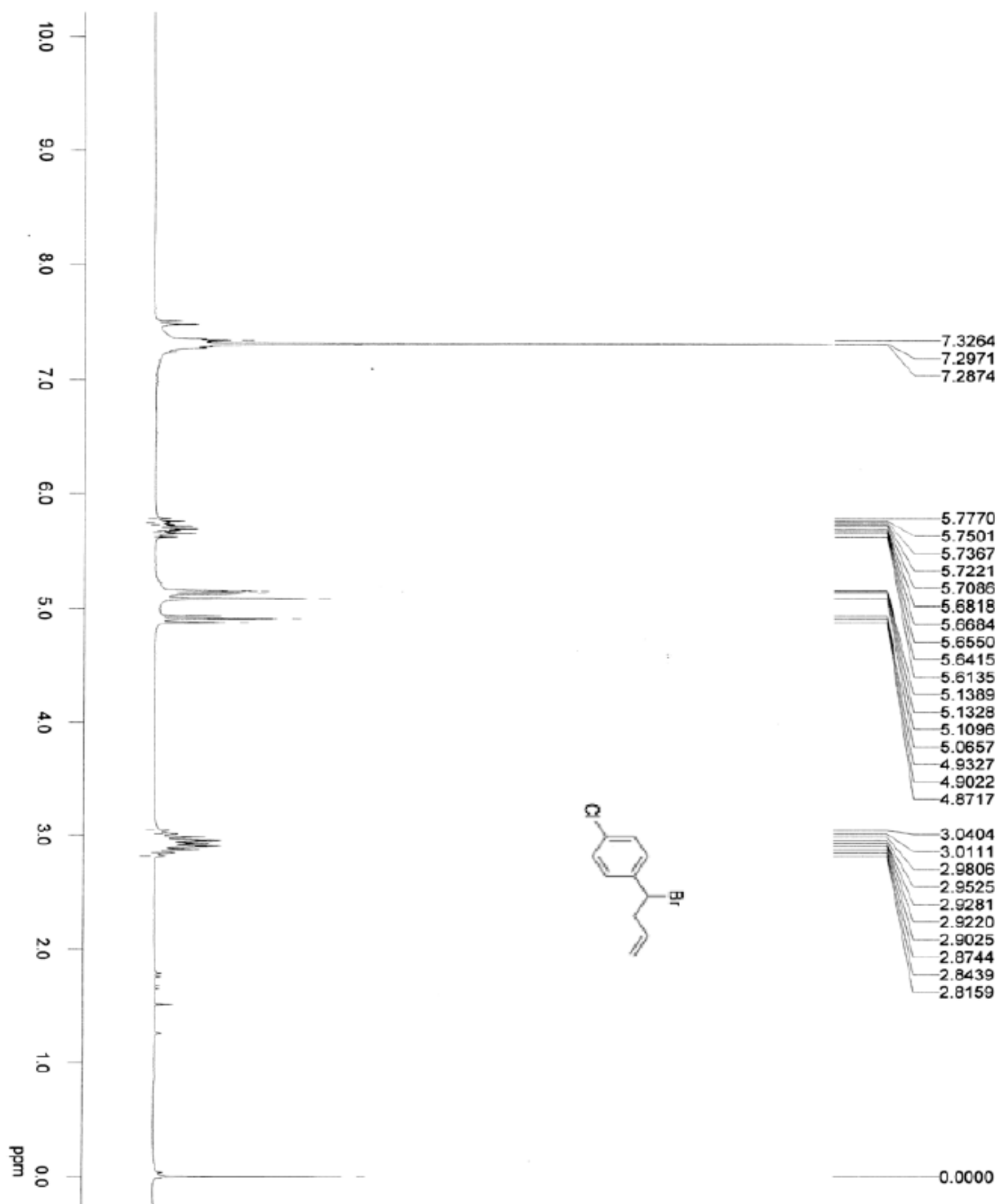
¹H spectrum of 502j



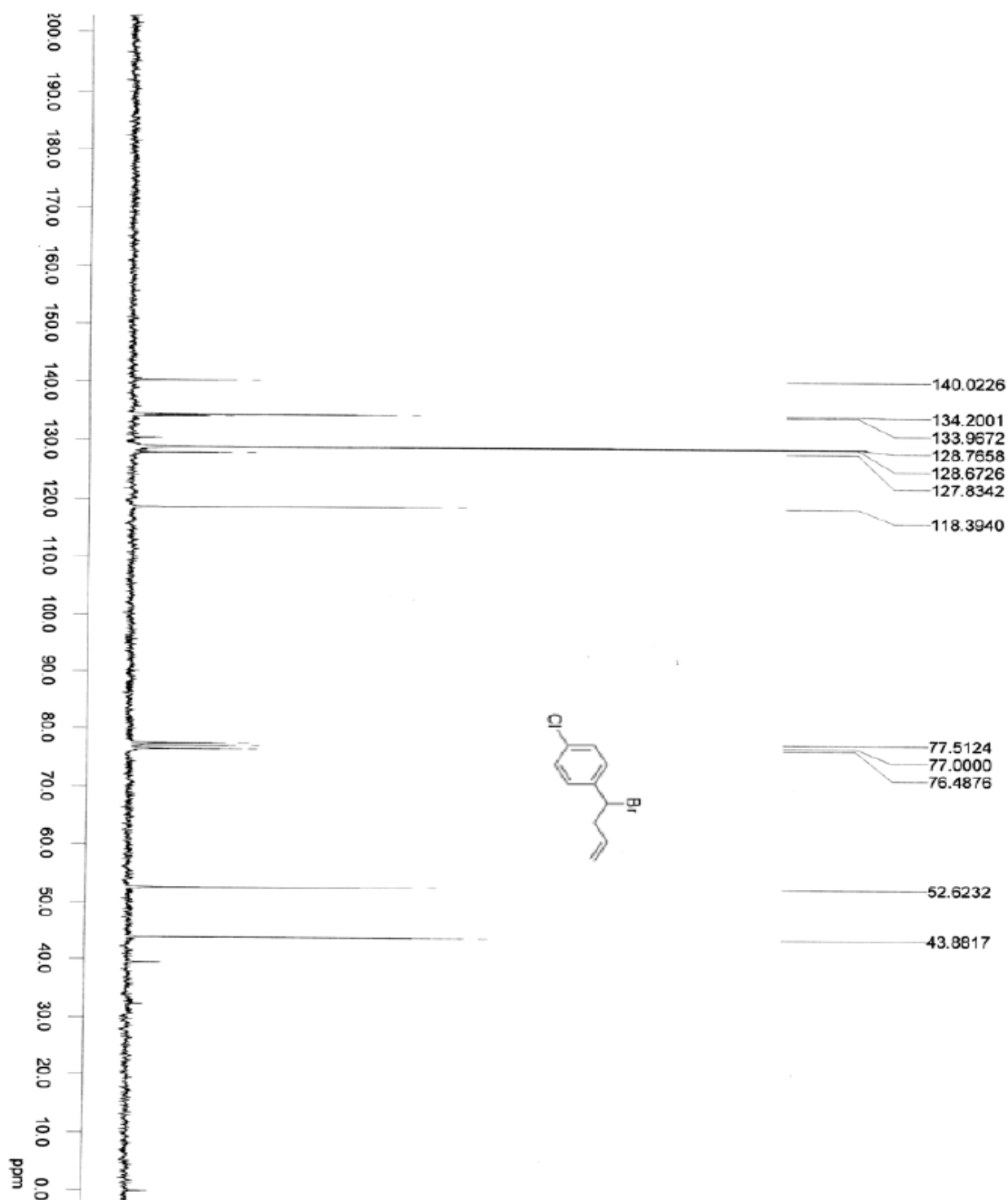
¹³C spectrum of 502j



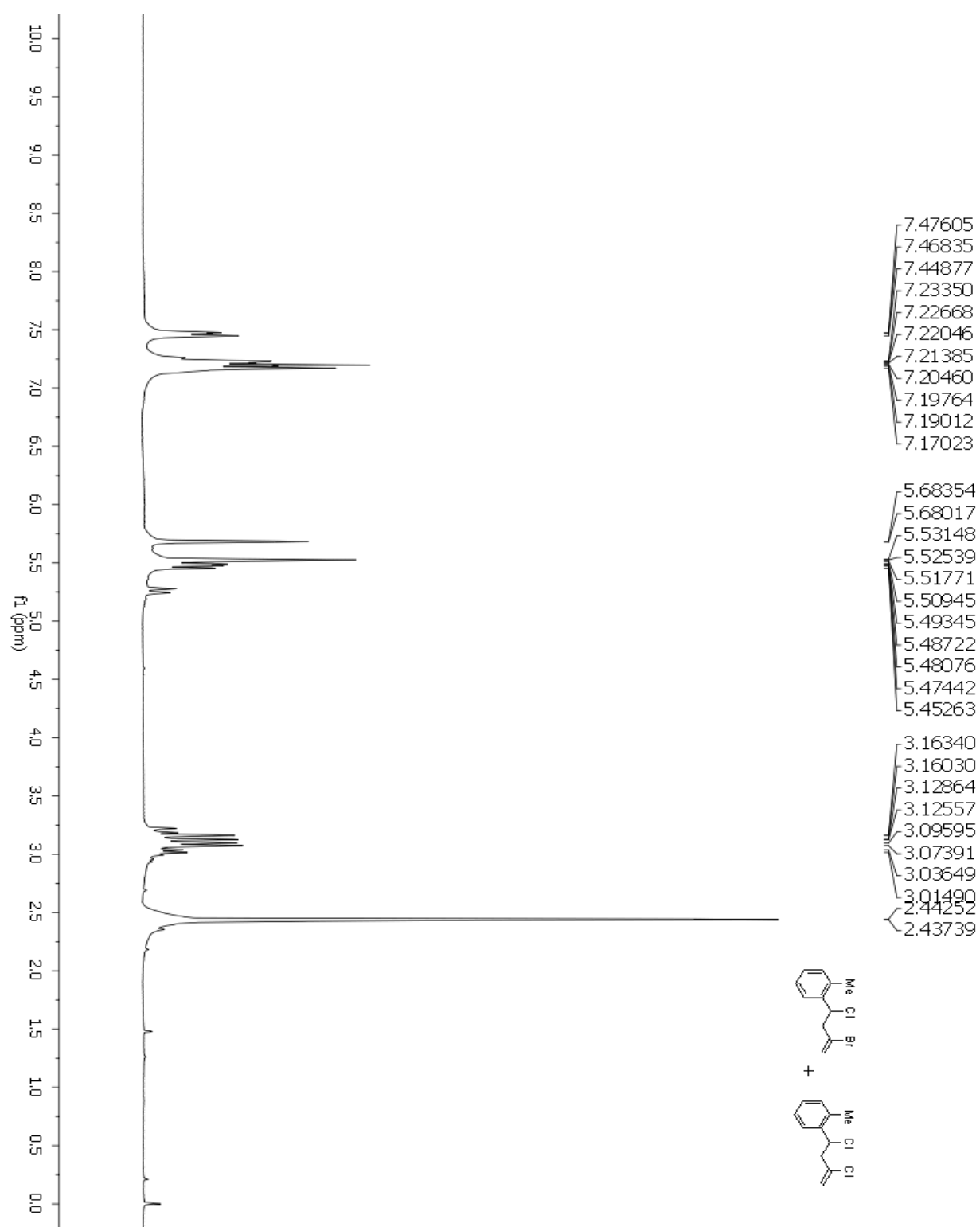
¹H spectrum of 502n



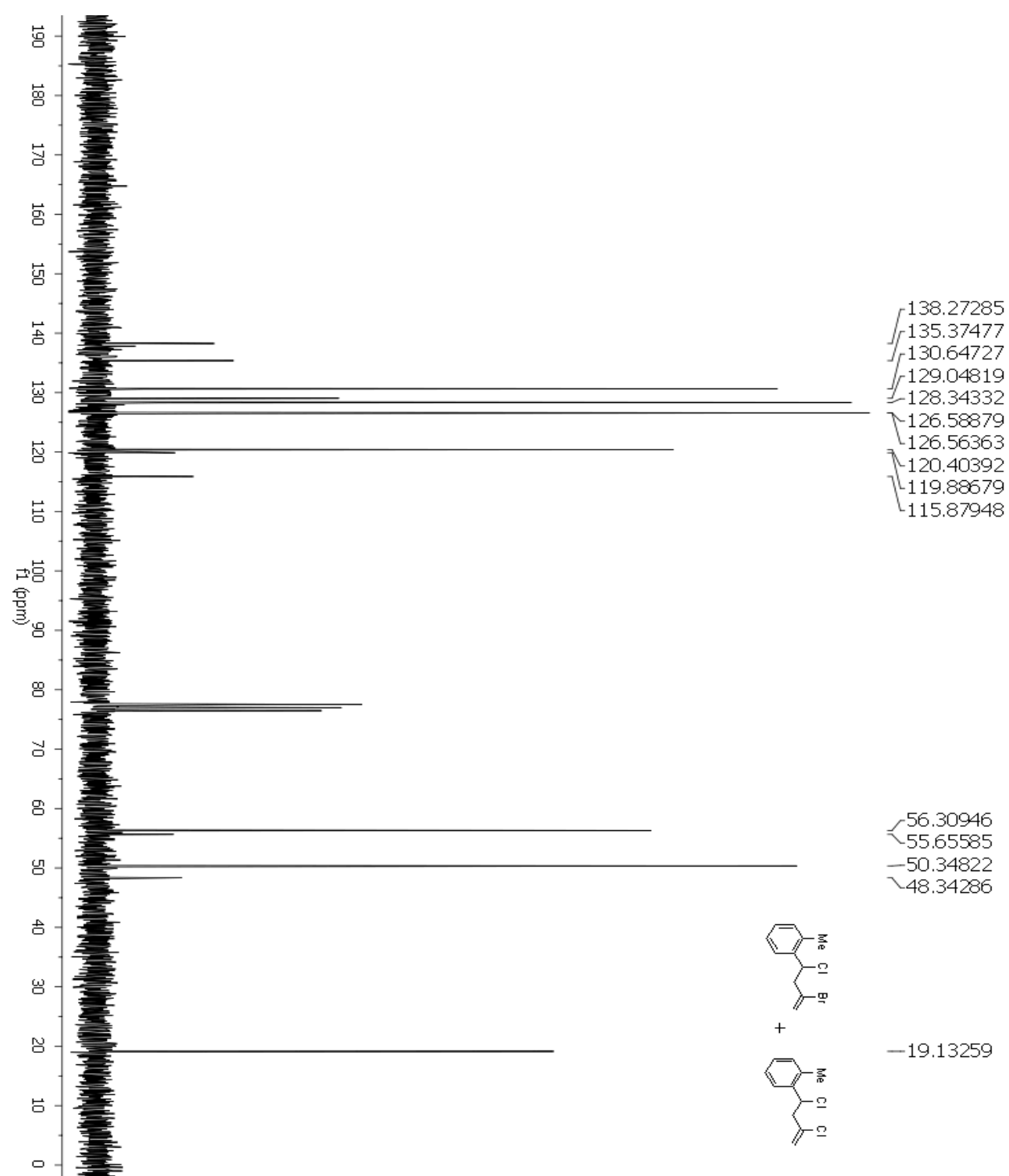
¹³C spectrum of 502n



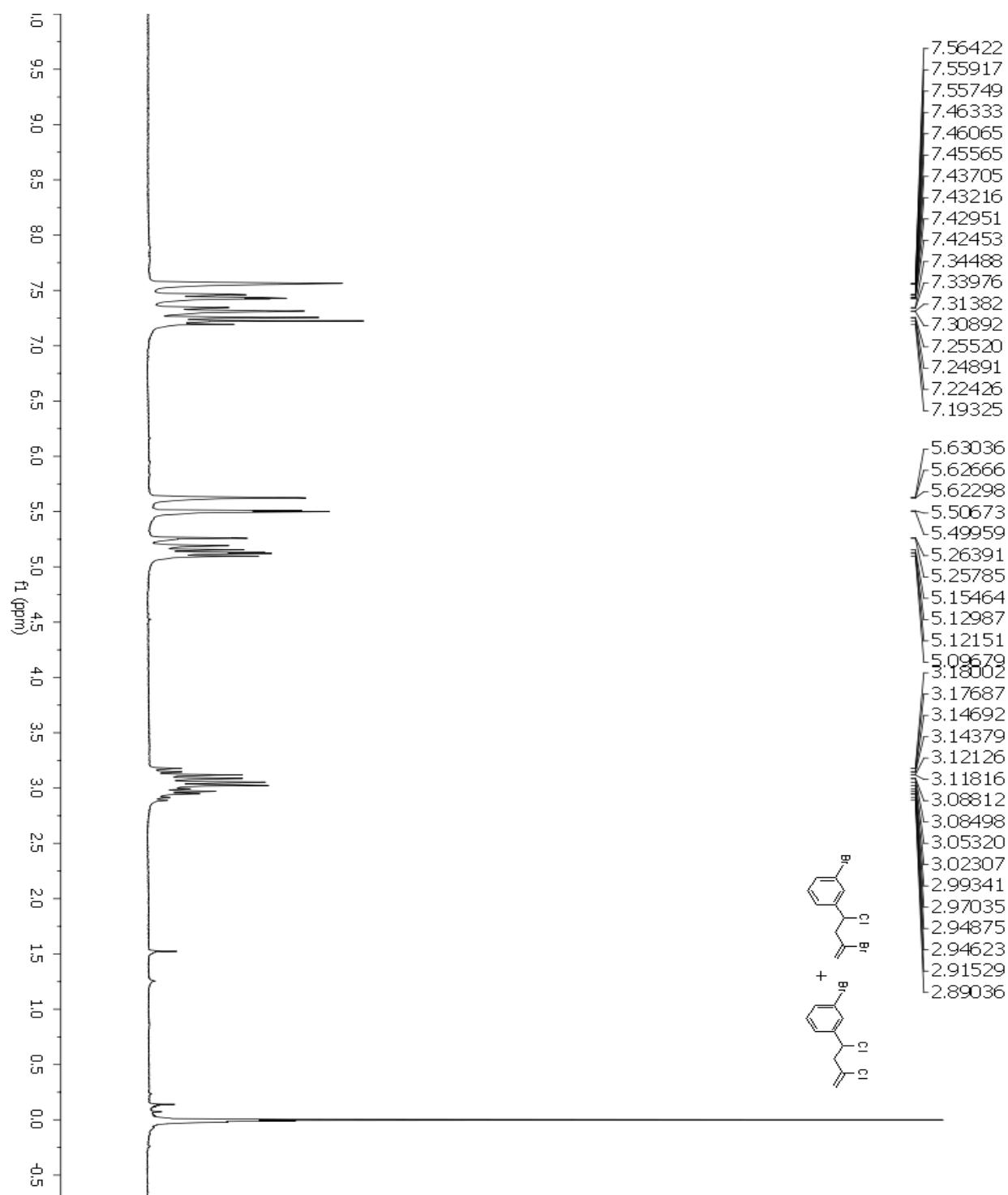
¹H spectrum of 508b and 509b



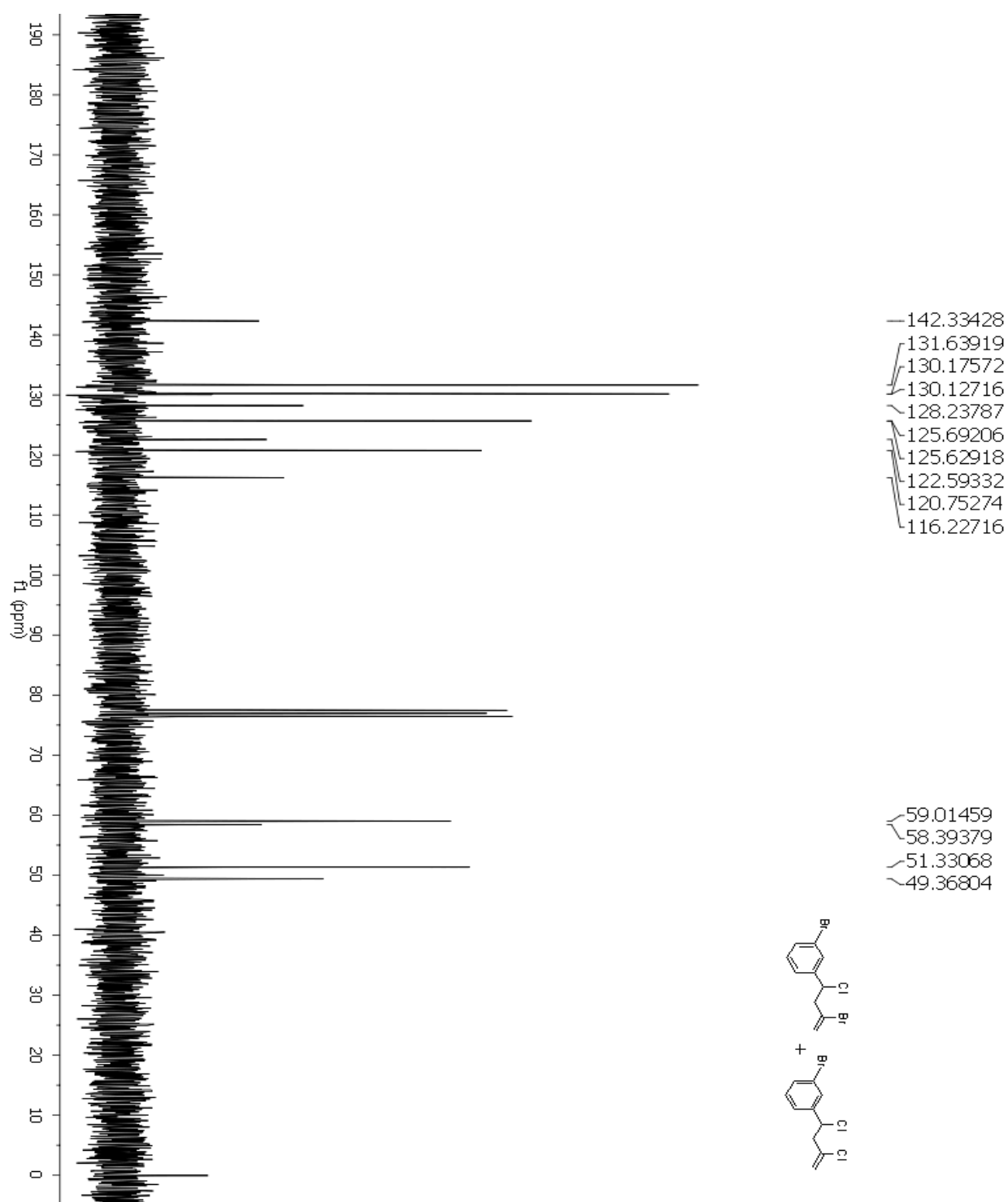
¹³C spectrum of 508b and 509b



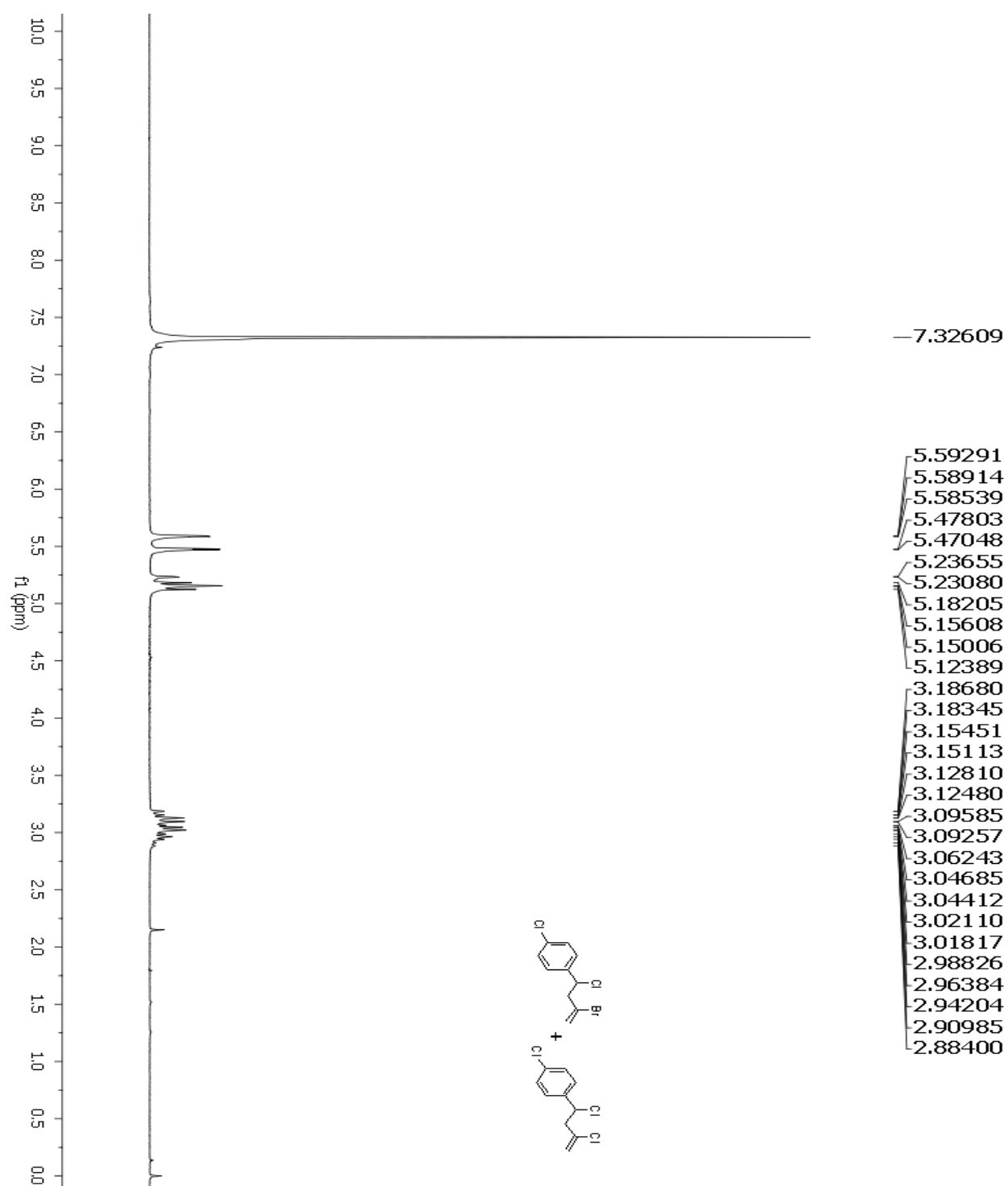
^1H spectrum of 508c and 509c



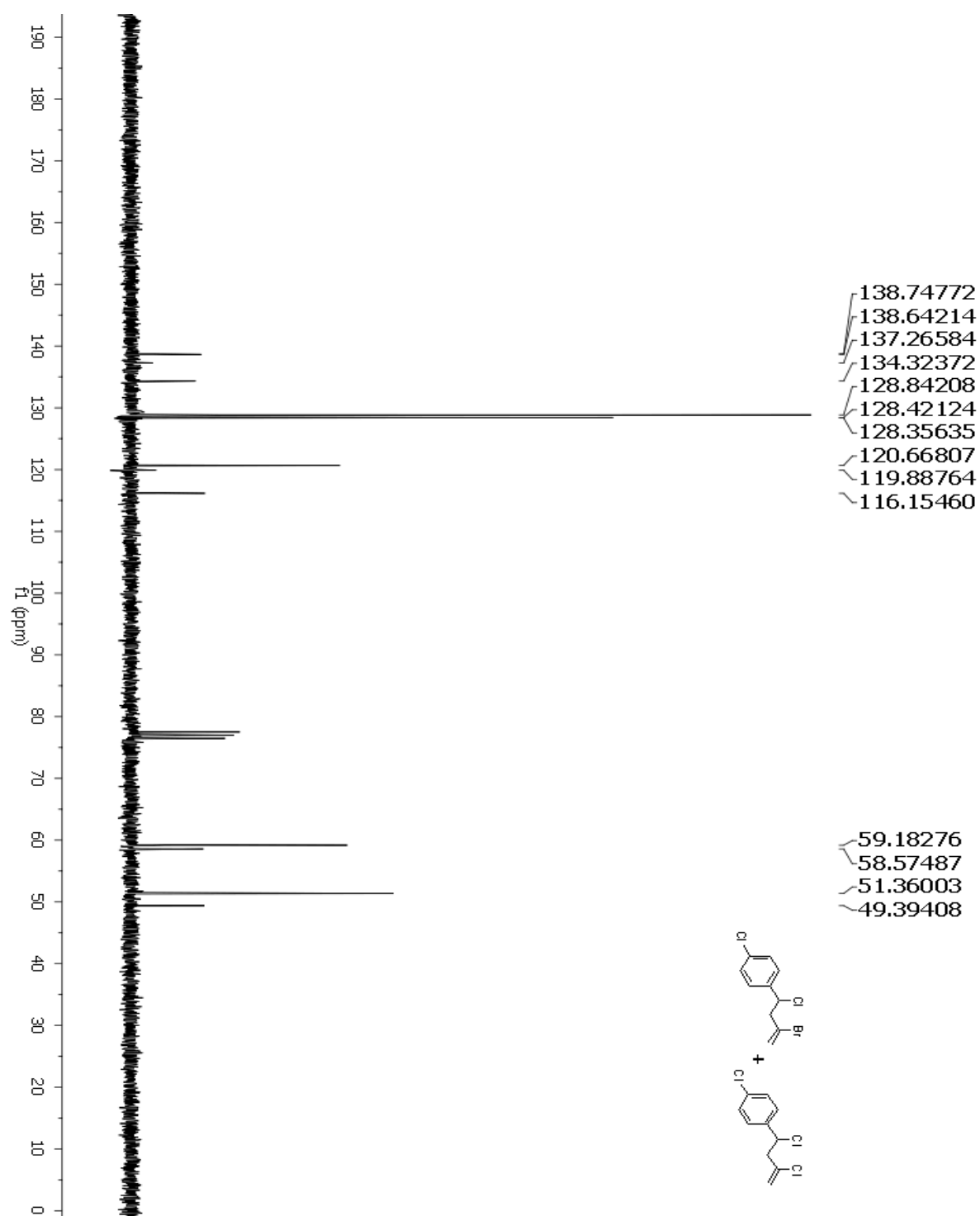
¹³C spectrum of 508c and 509c



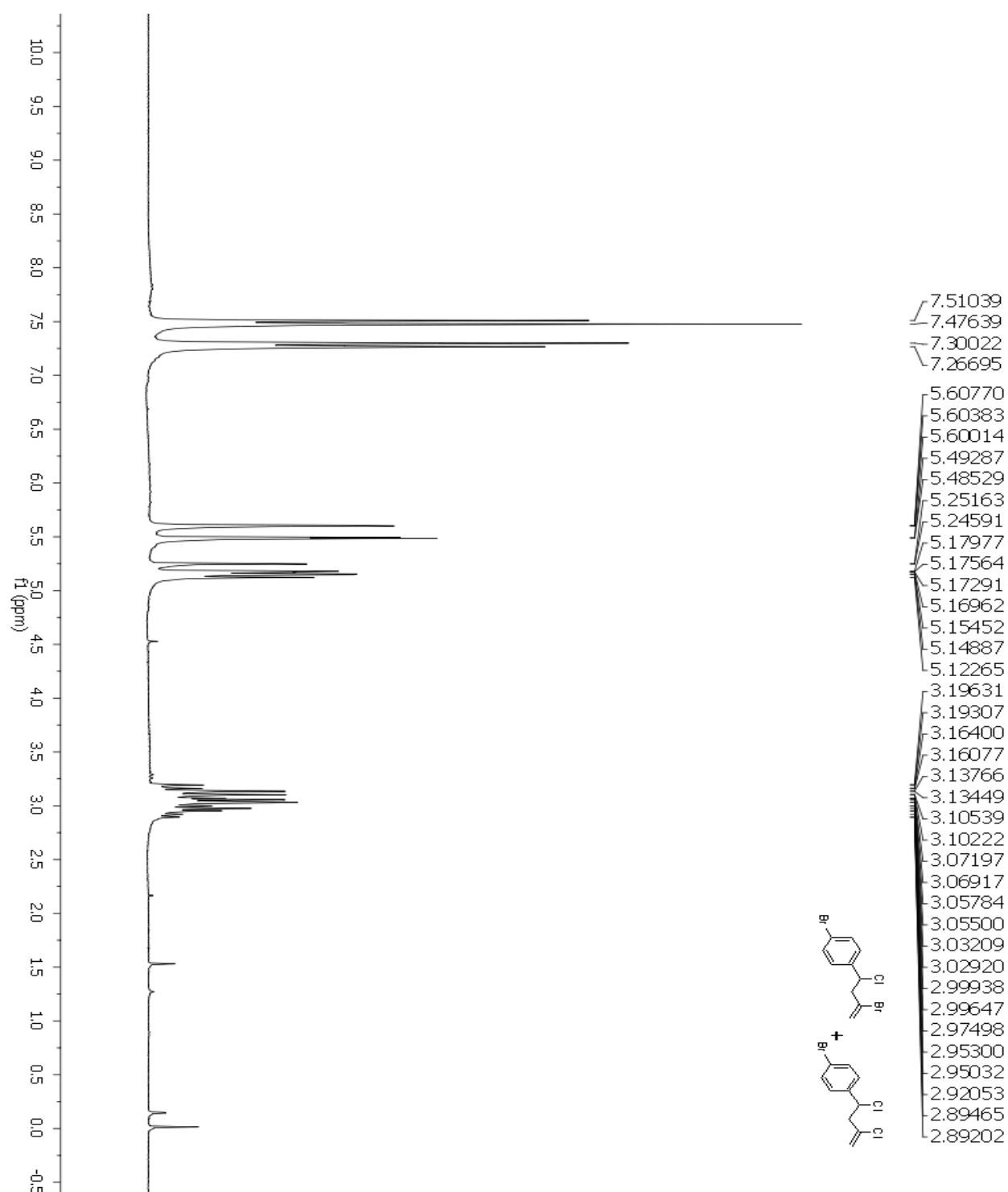
¹H spectrum of 508d and 509d



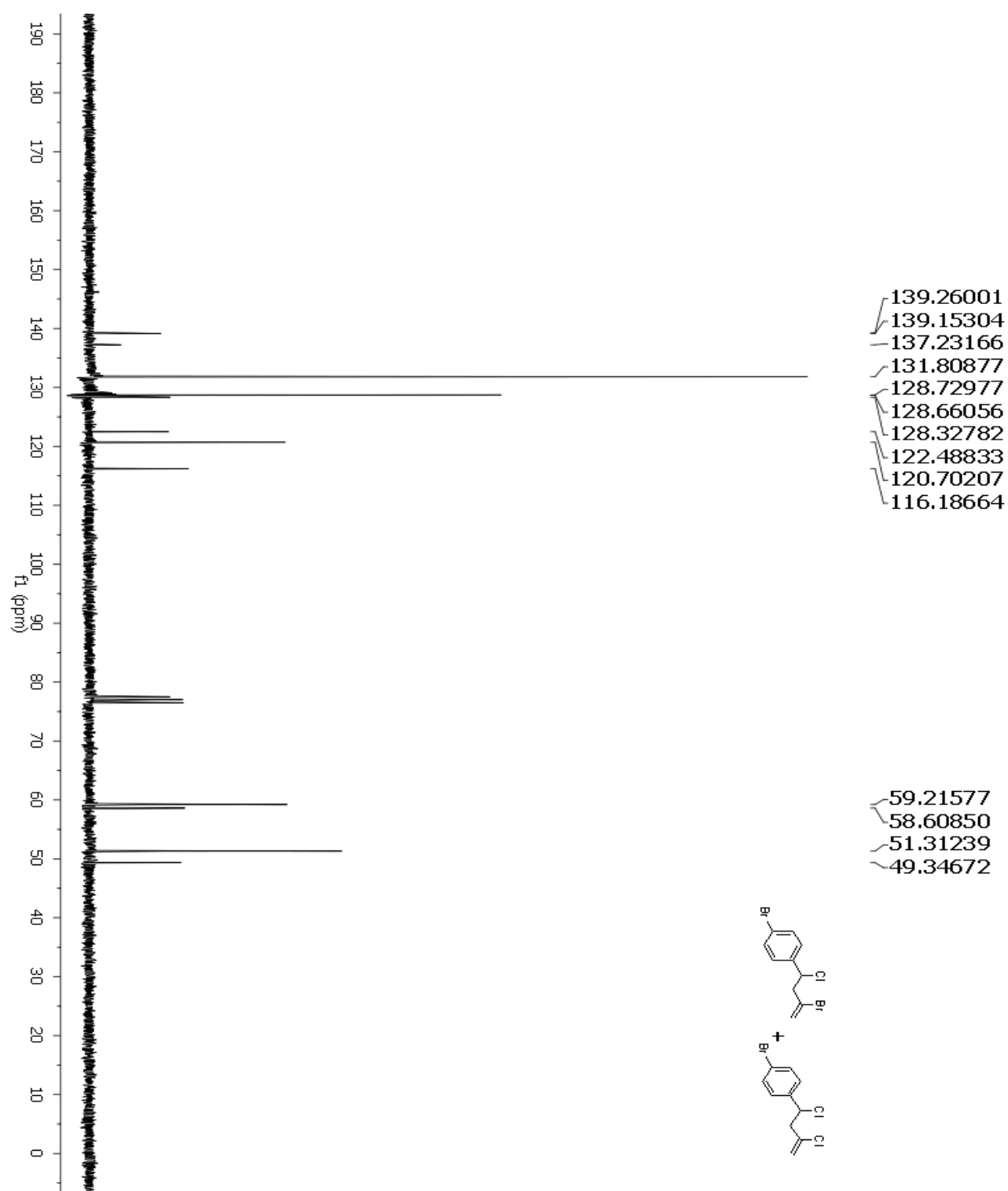
¹³C spectrum of 508d and 509d



¹H spectrum of 508e and 509e

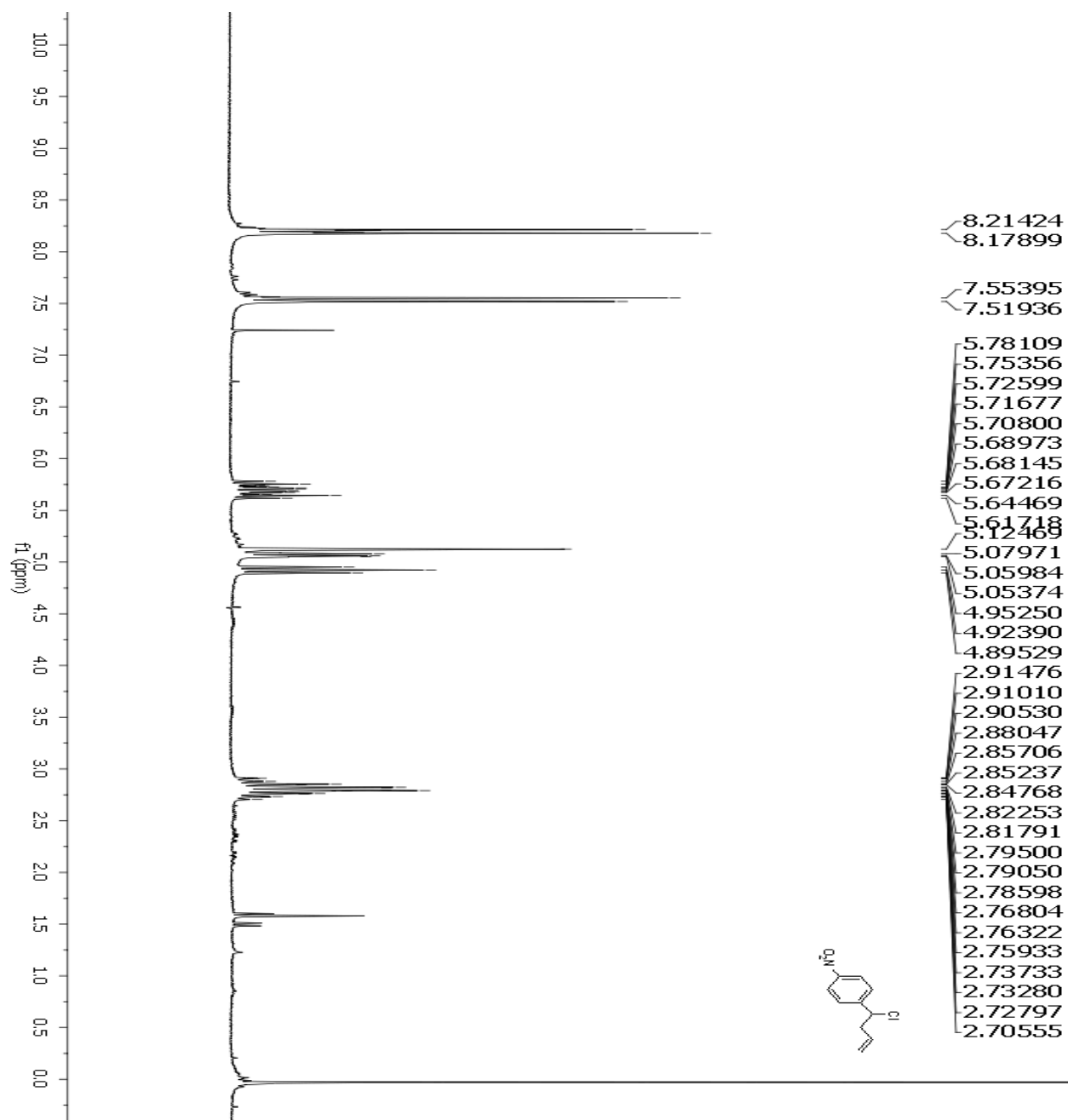


¹³C spectrum of 508e and 509e

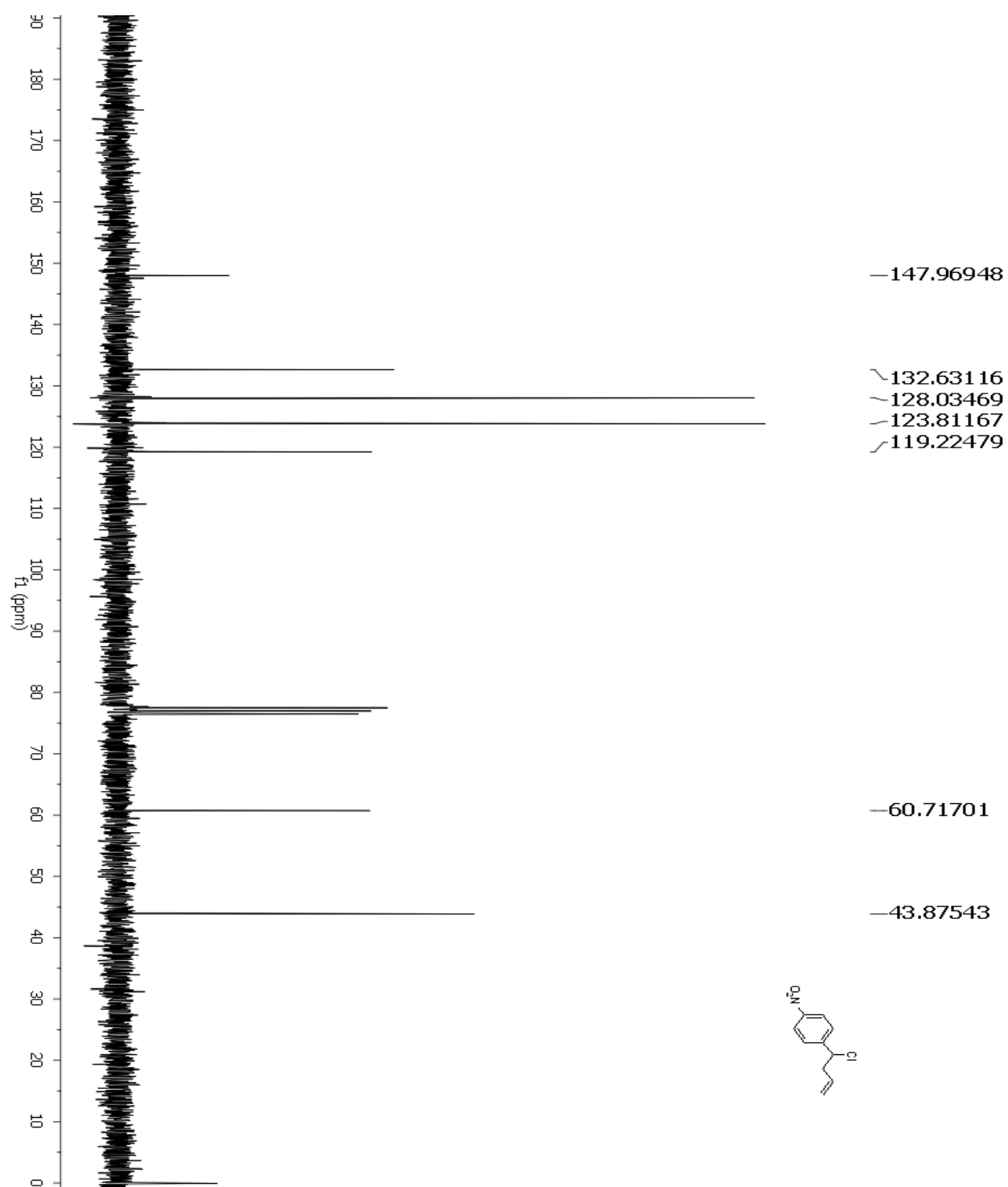


Appendix F: Representative NMR Spectra of compounds 601a-m and 602a-k for Chapter 6.

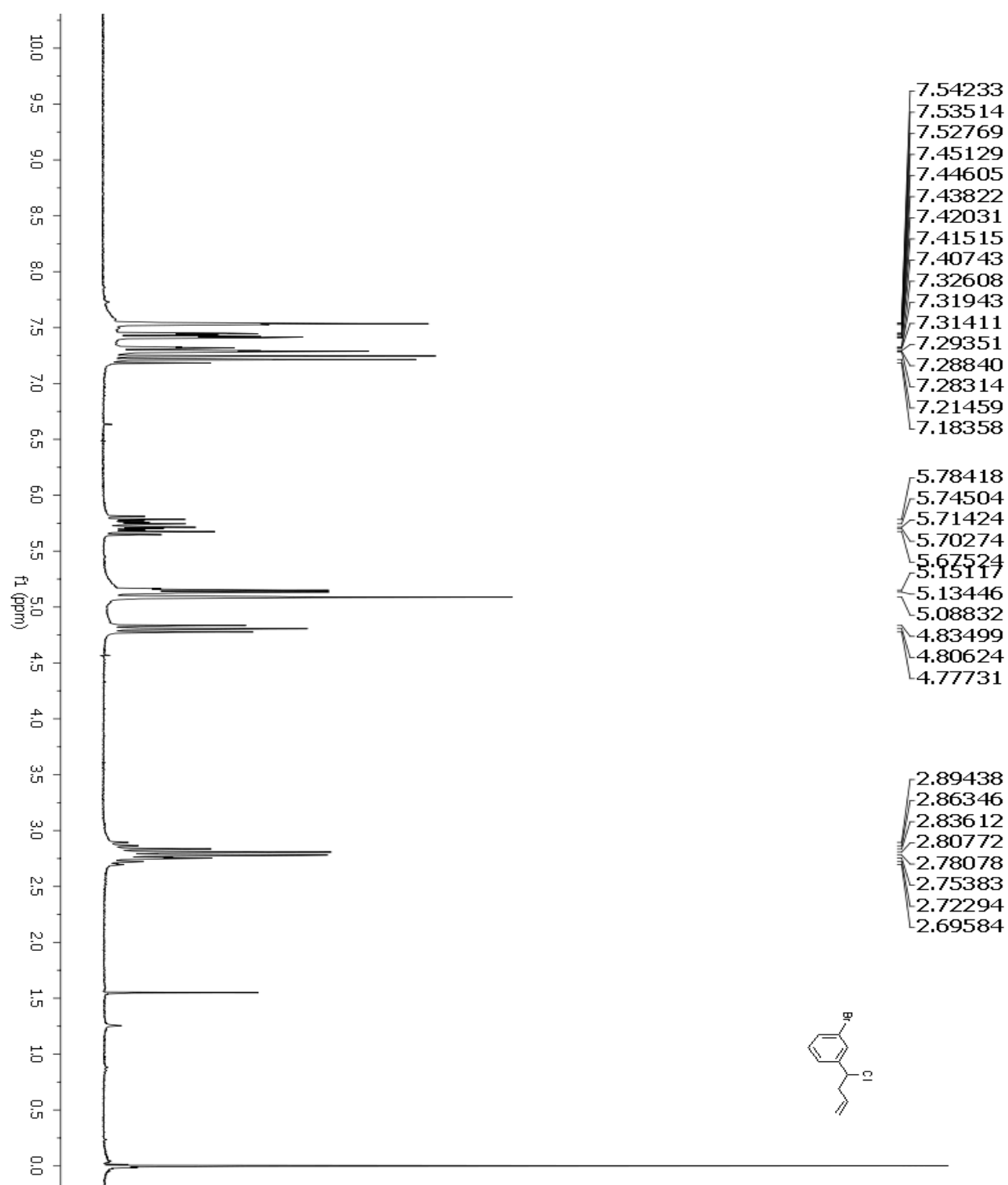
¹H spectrum of 601f



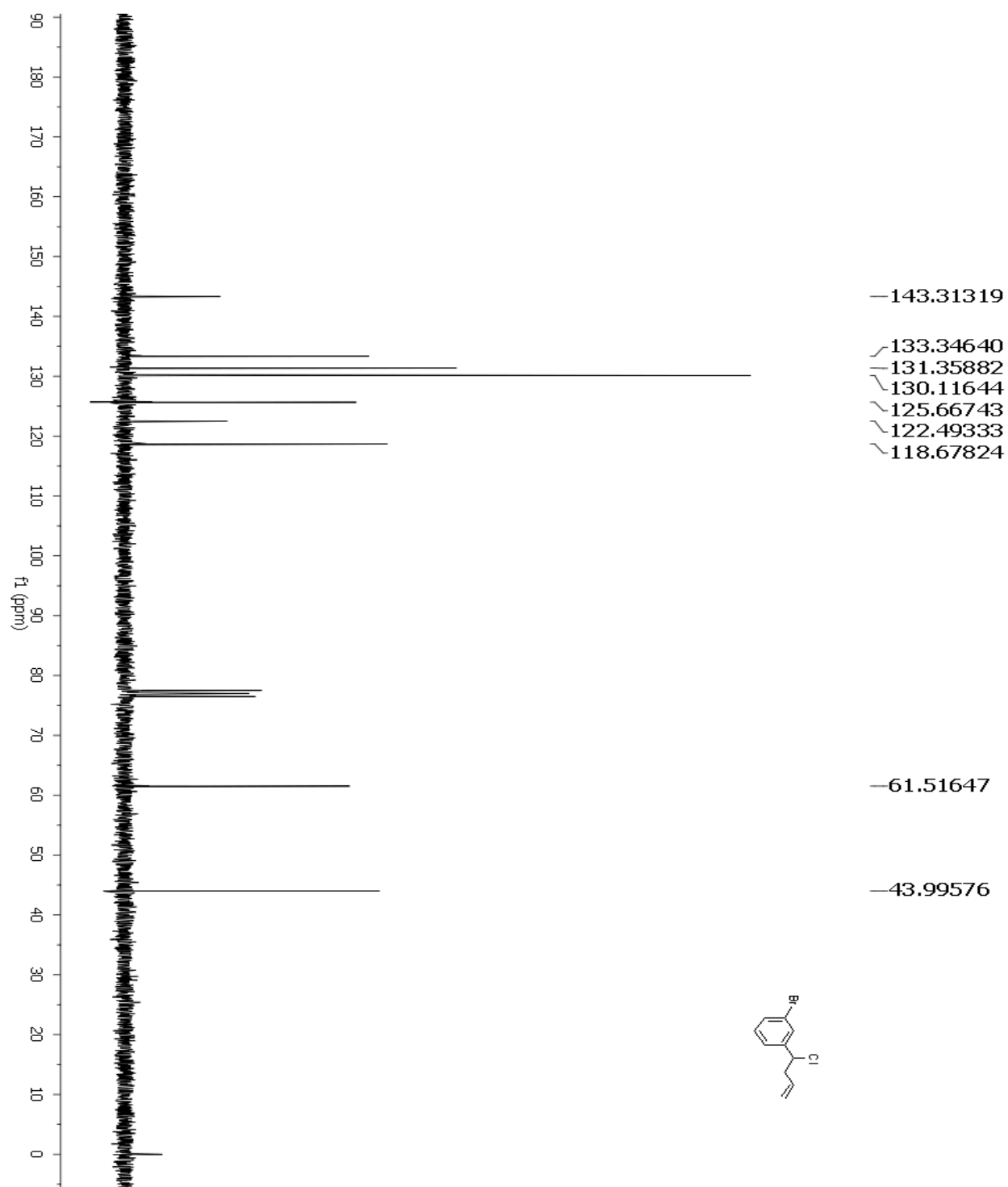
¹³C spectrum of 601f



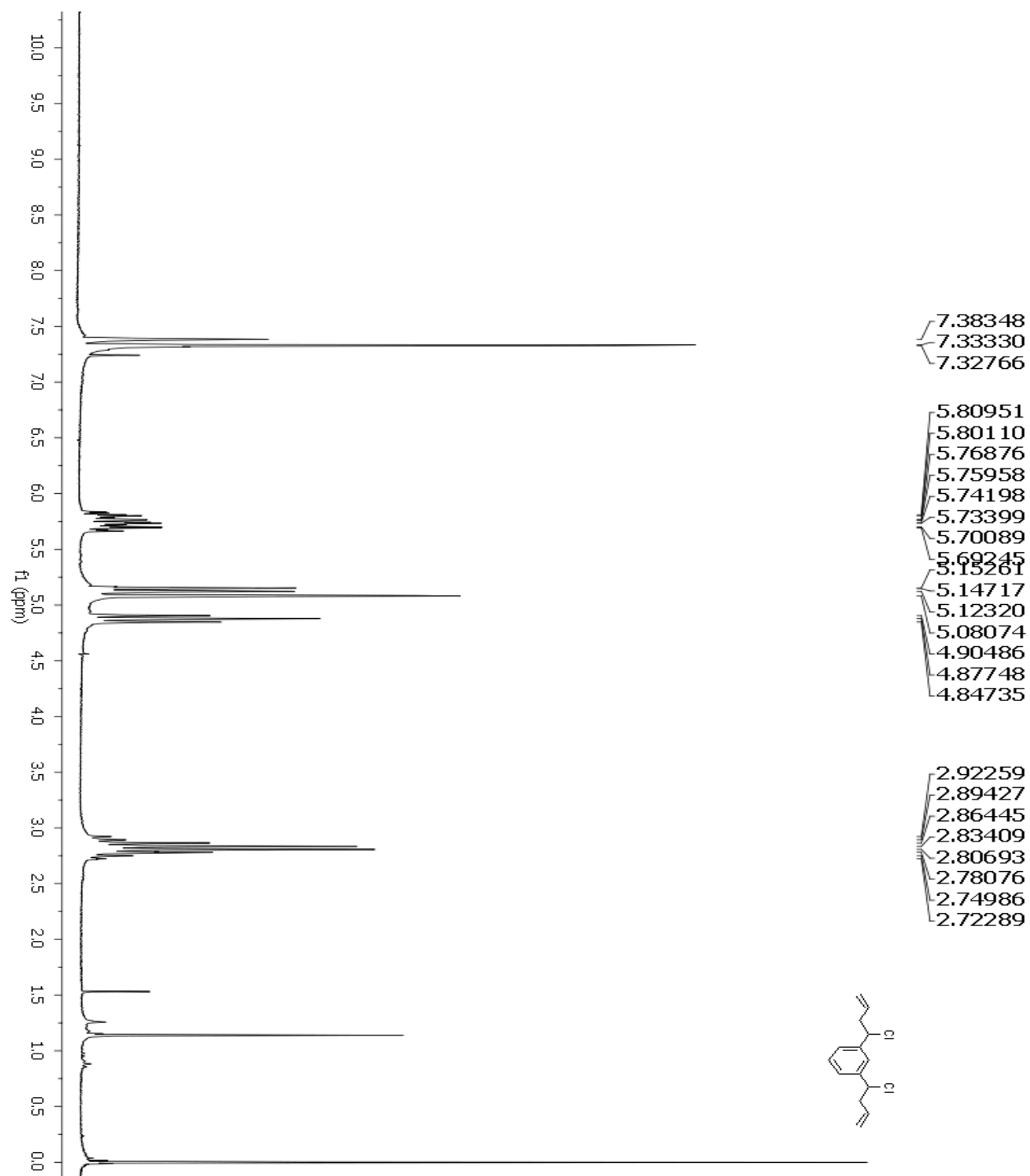
¹H spectrum of 601g



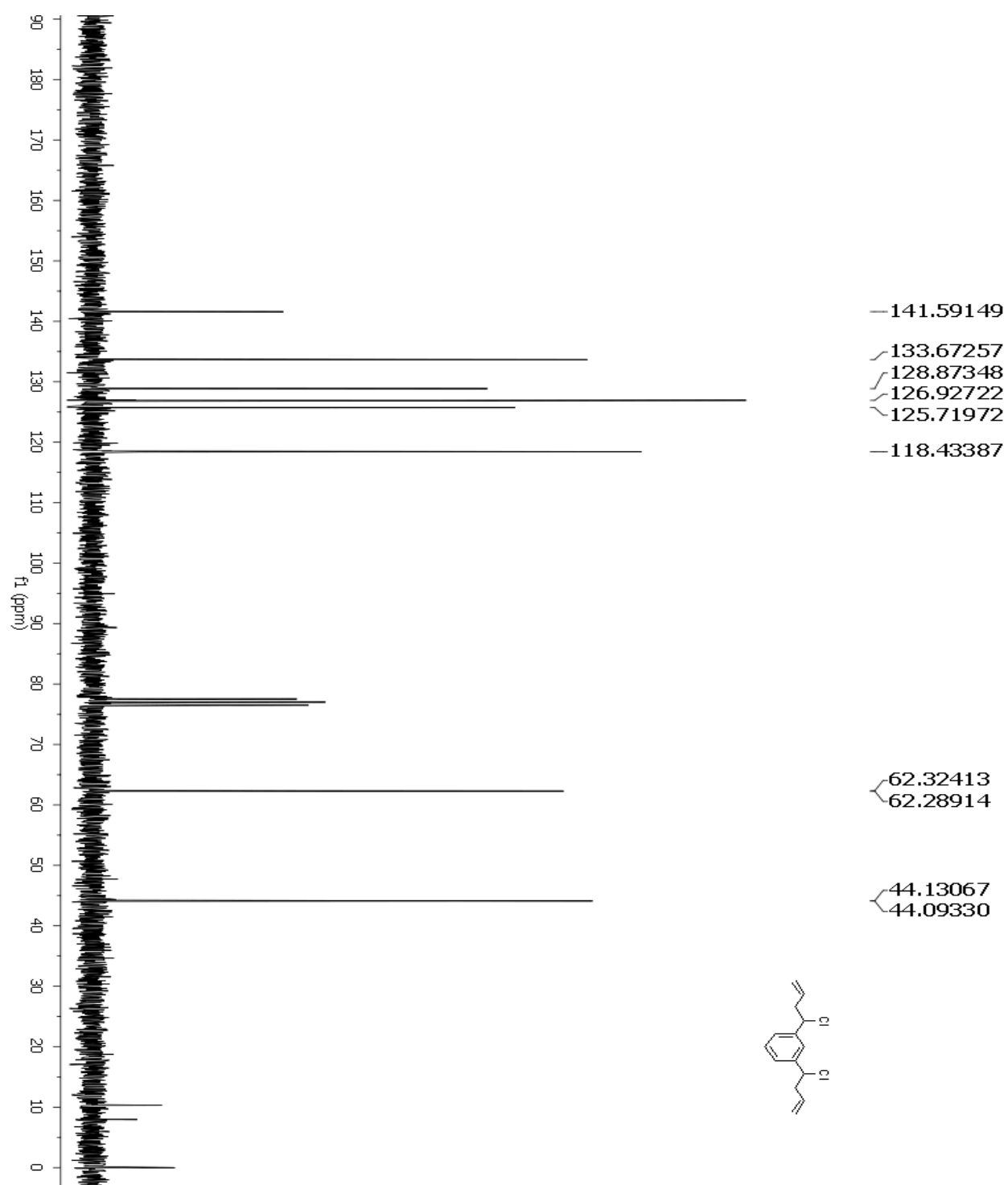
¹³C spectrum of 601g



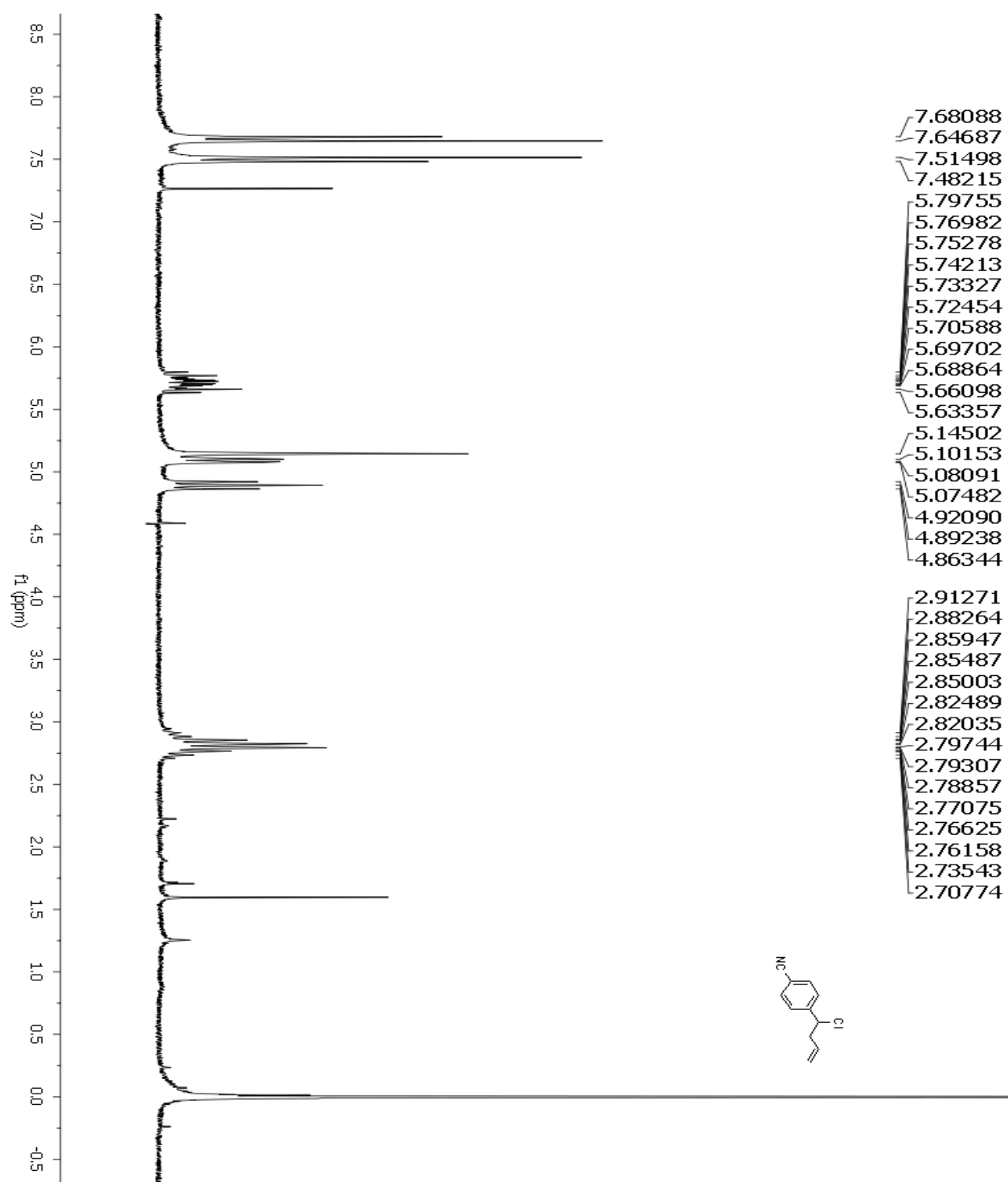
¹H spectrum of 601h



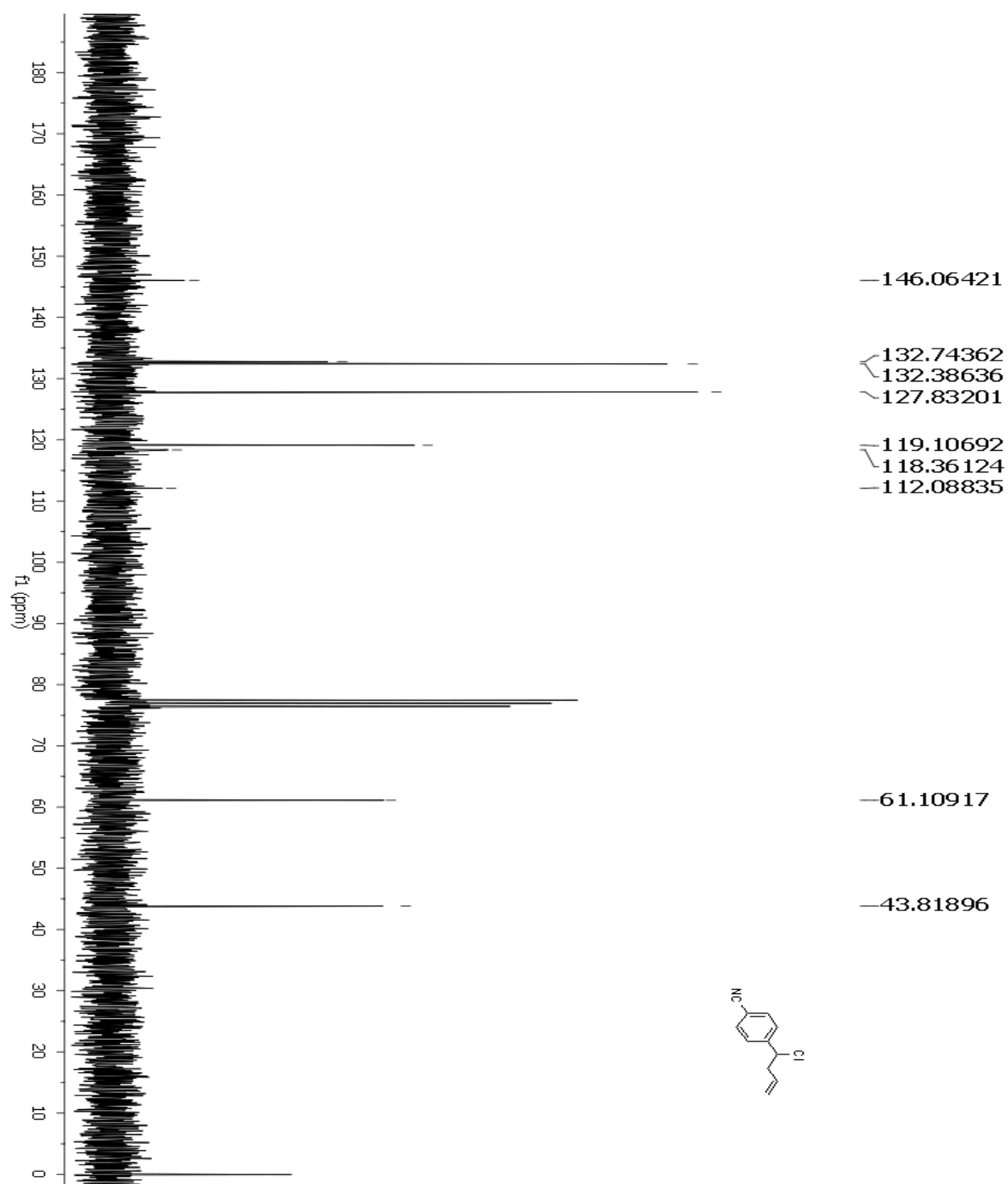
¹³C spectrum of 601h



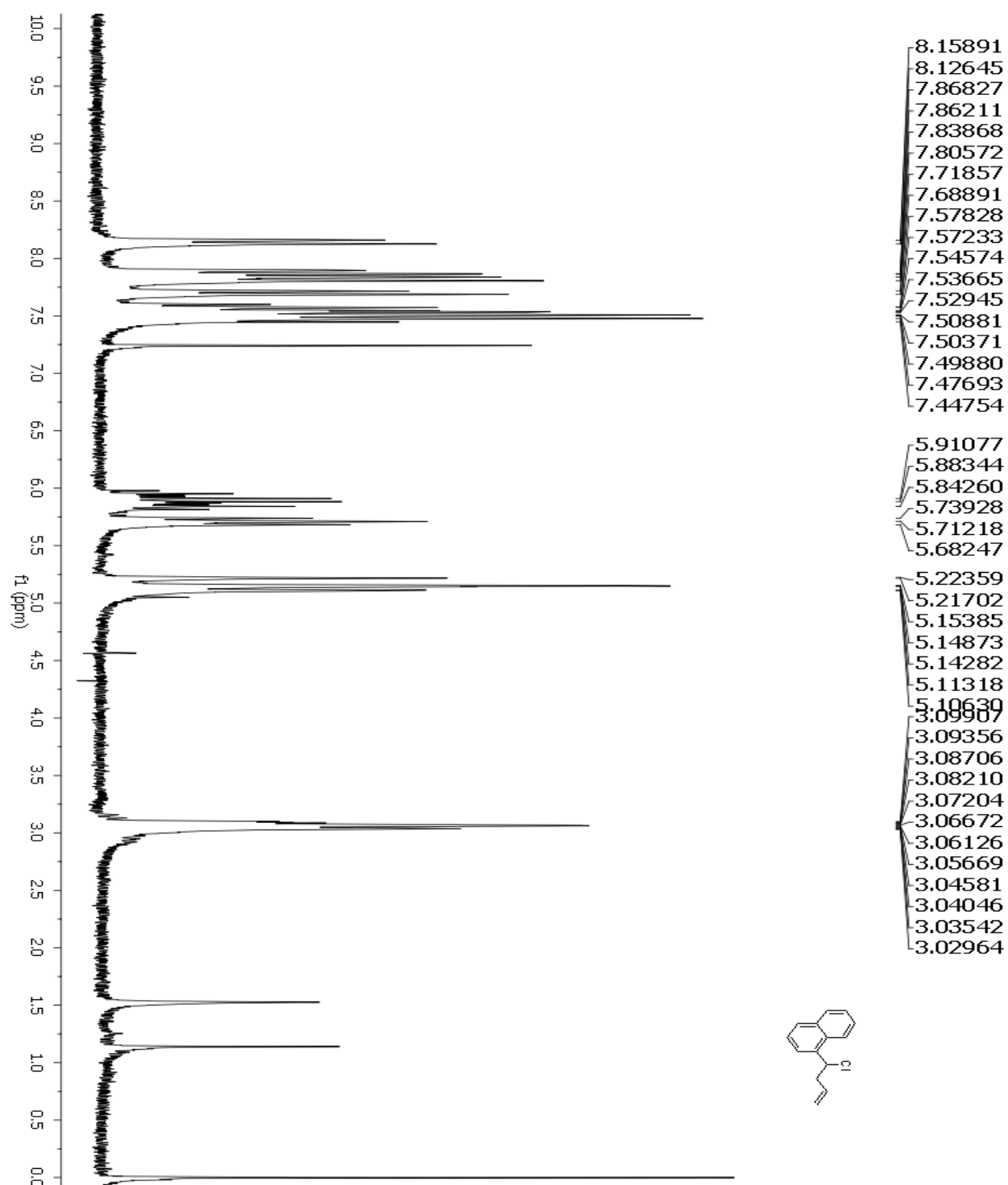
¹H spectrum of 602d



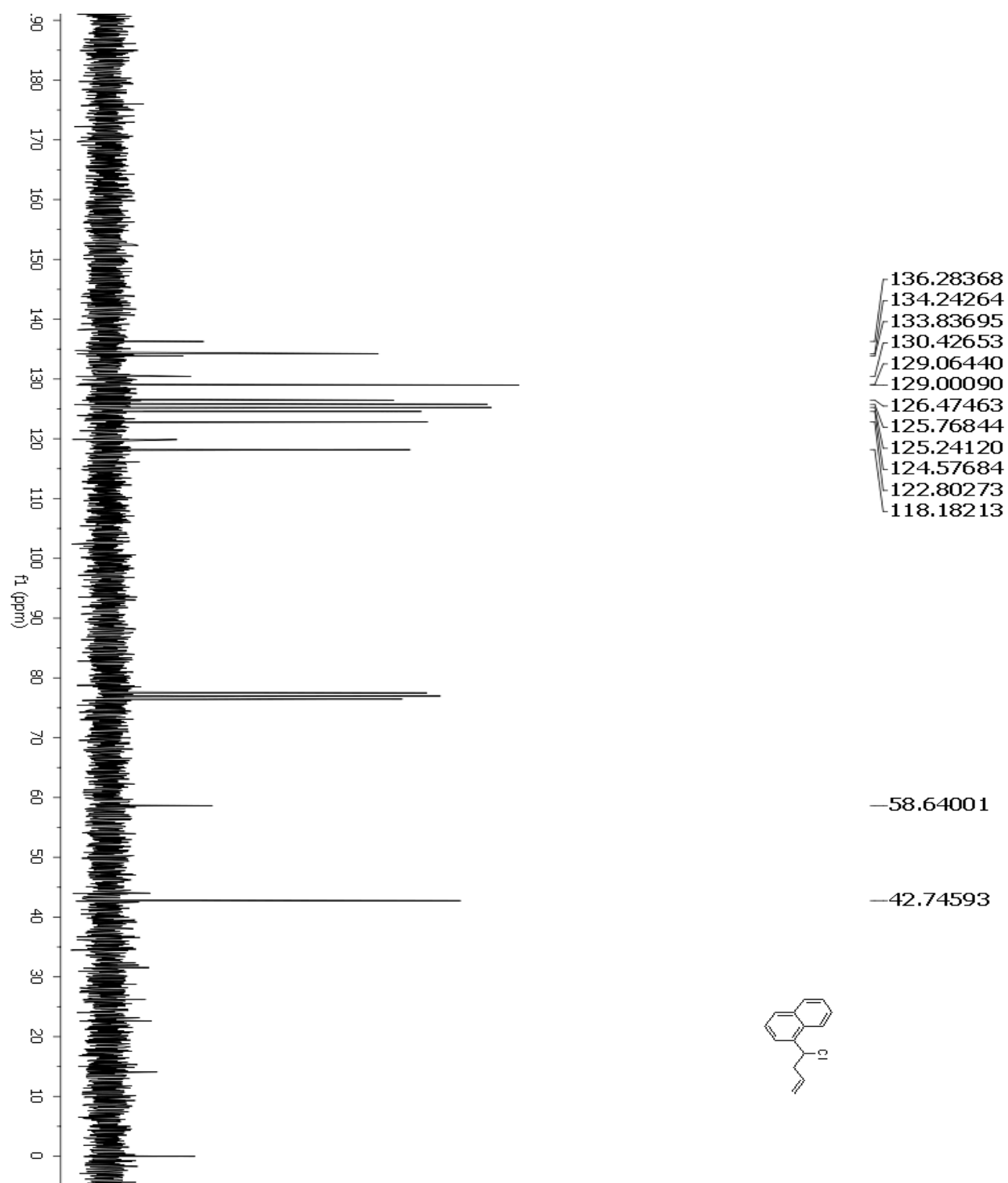
¹³C spectrum of 602d



¹H spectrum of 602i

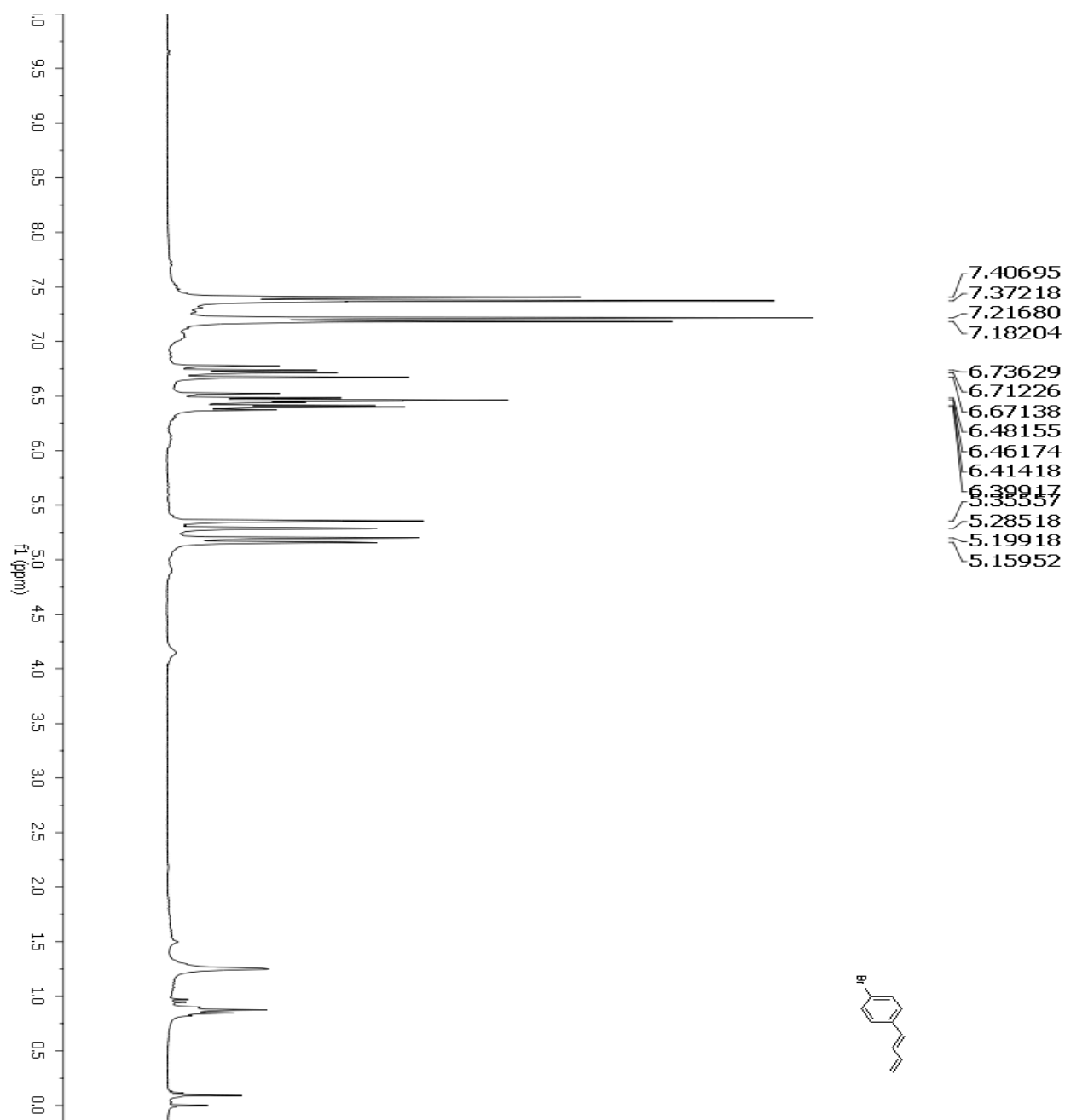


¹³C spectrum of 602i

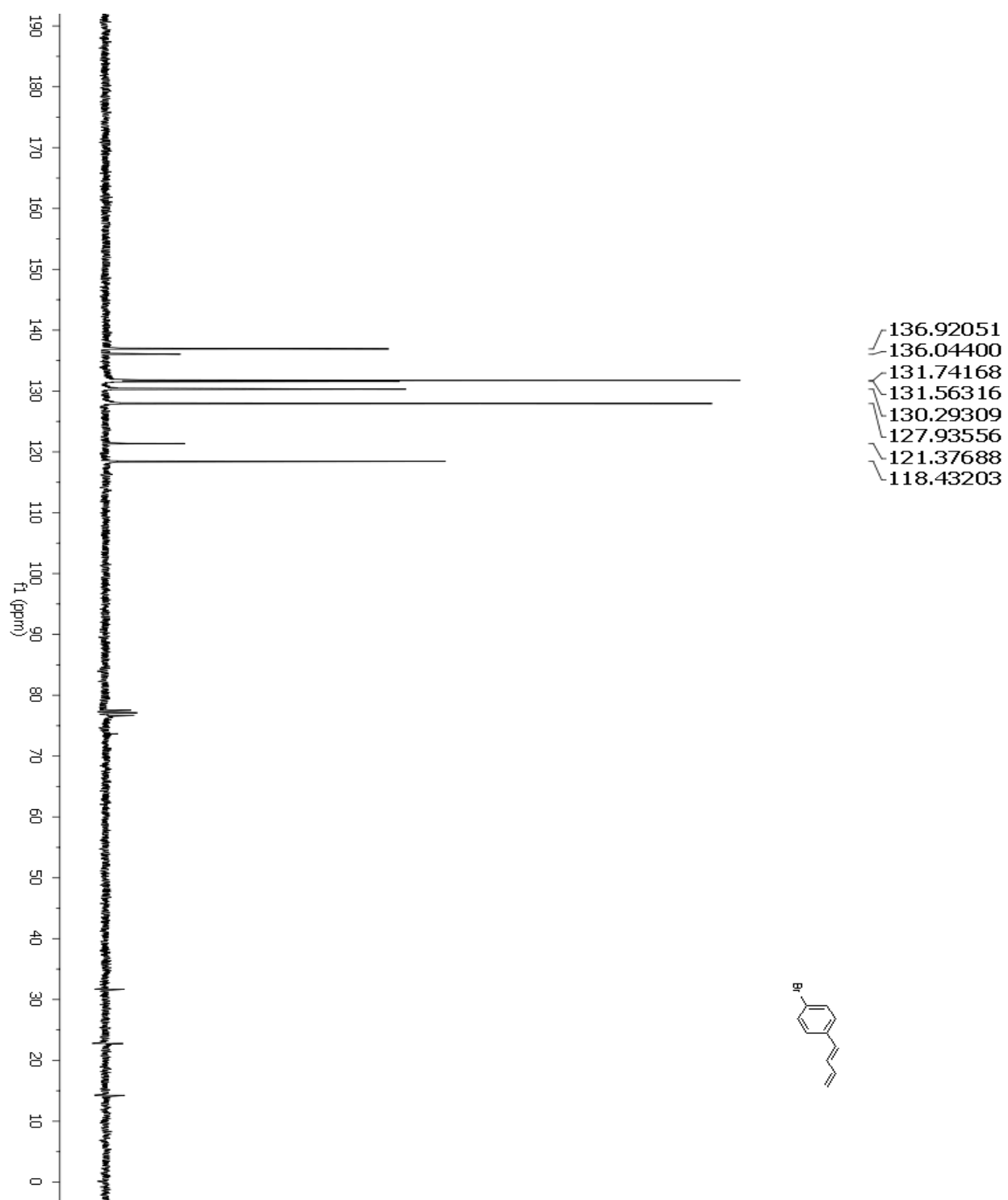


**Appendix G: Representative NMR Spectra of compounds 701a-j,
702, and 705a-b for Chapter 7.**

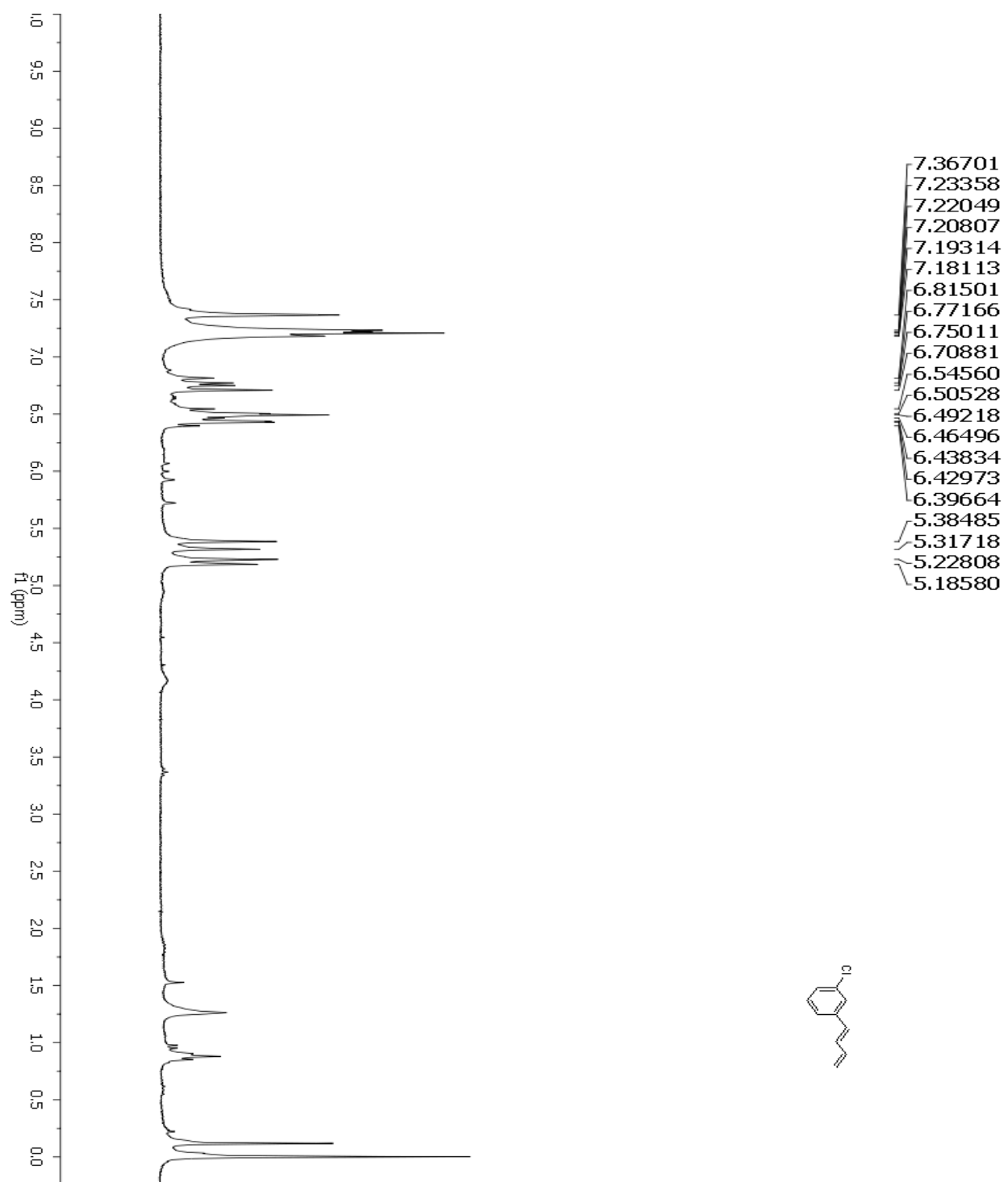
¹H spectrum of 701c



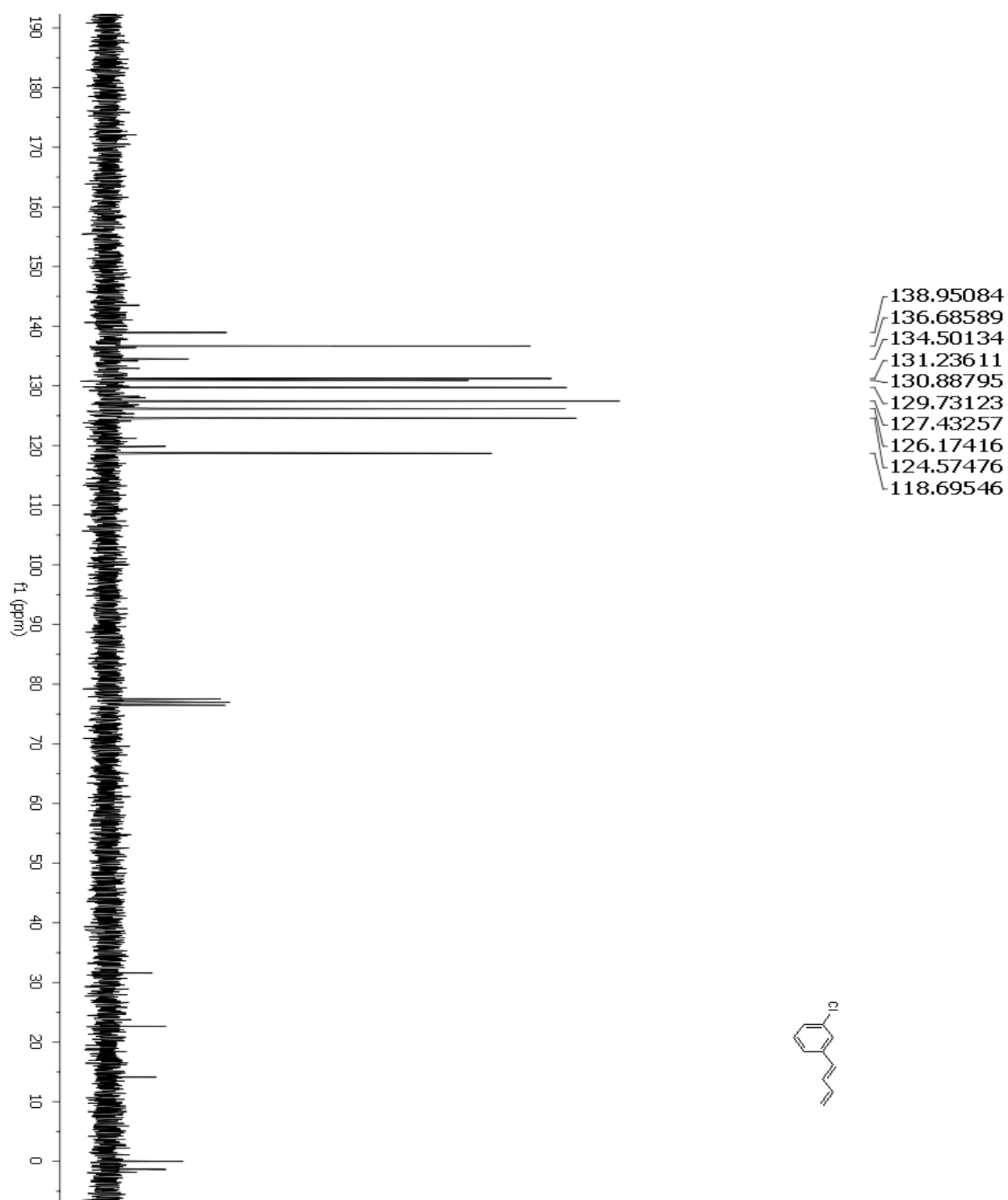
¹³C spectrum of 701c



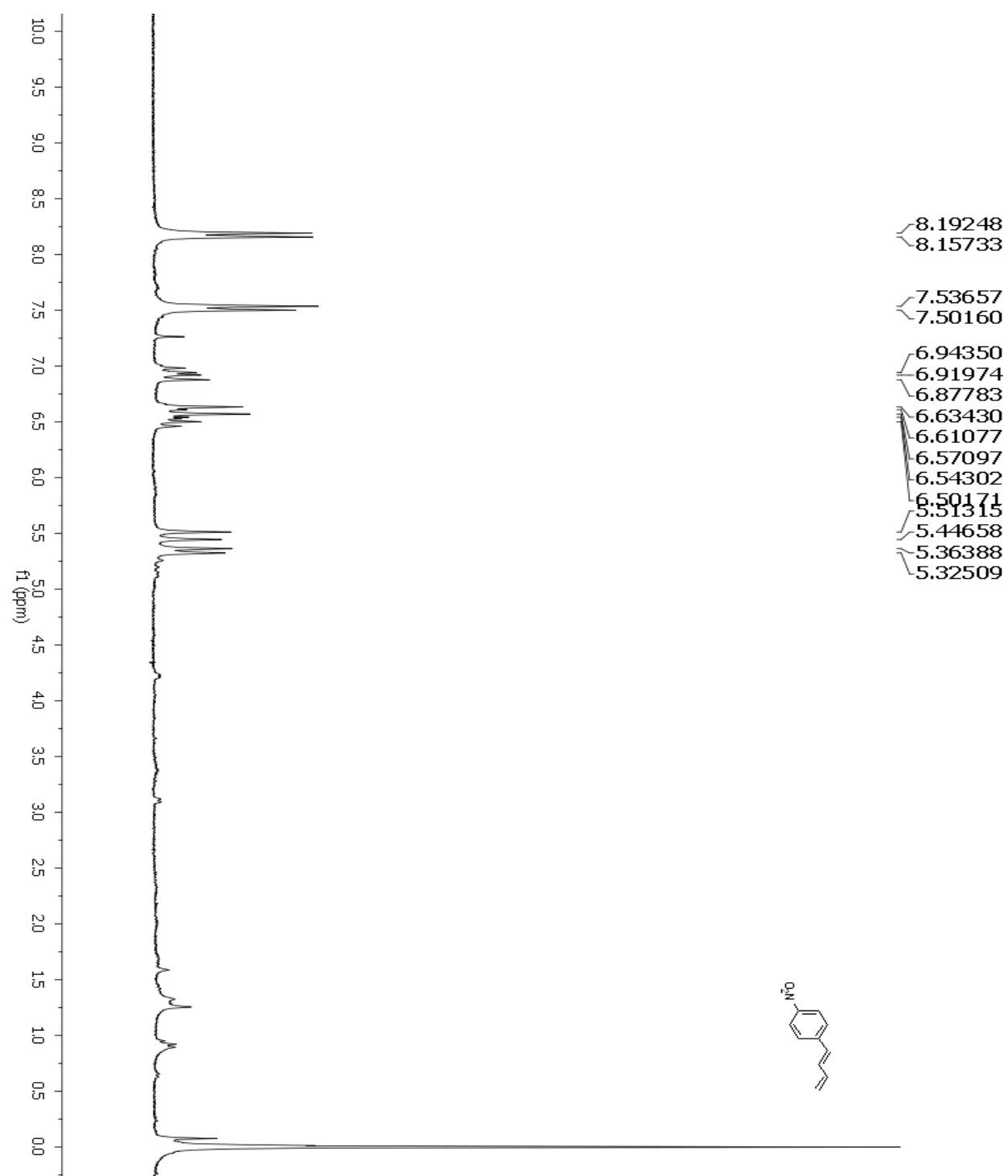
¹H spectrum of 701d



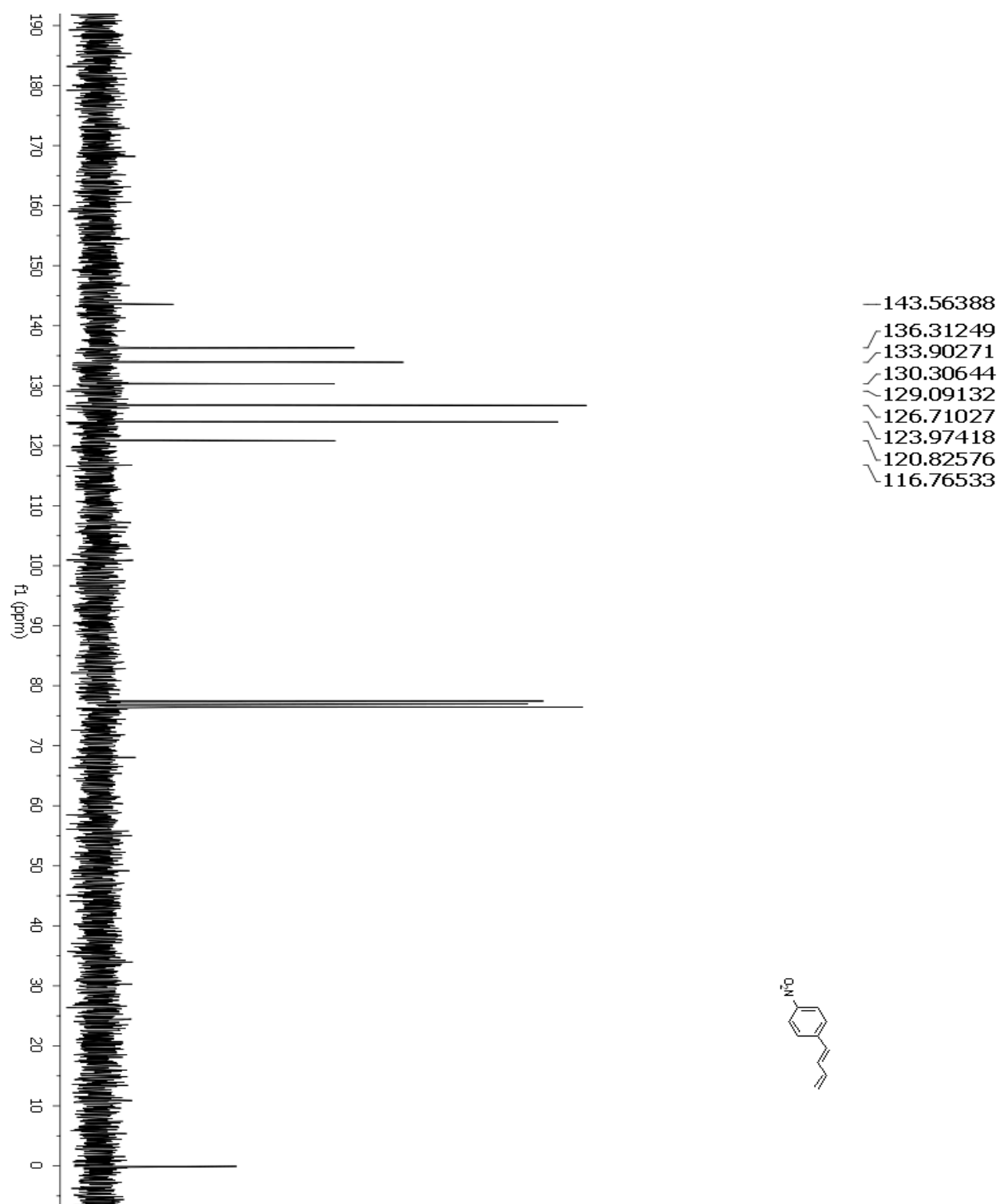
^{13}C spectrum of 701d



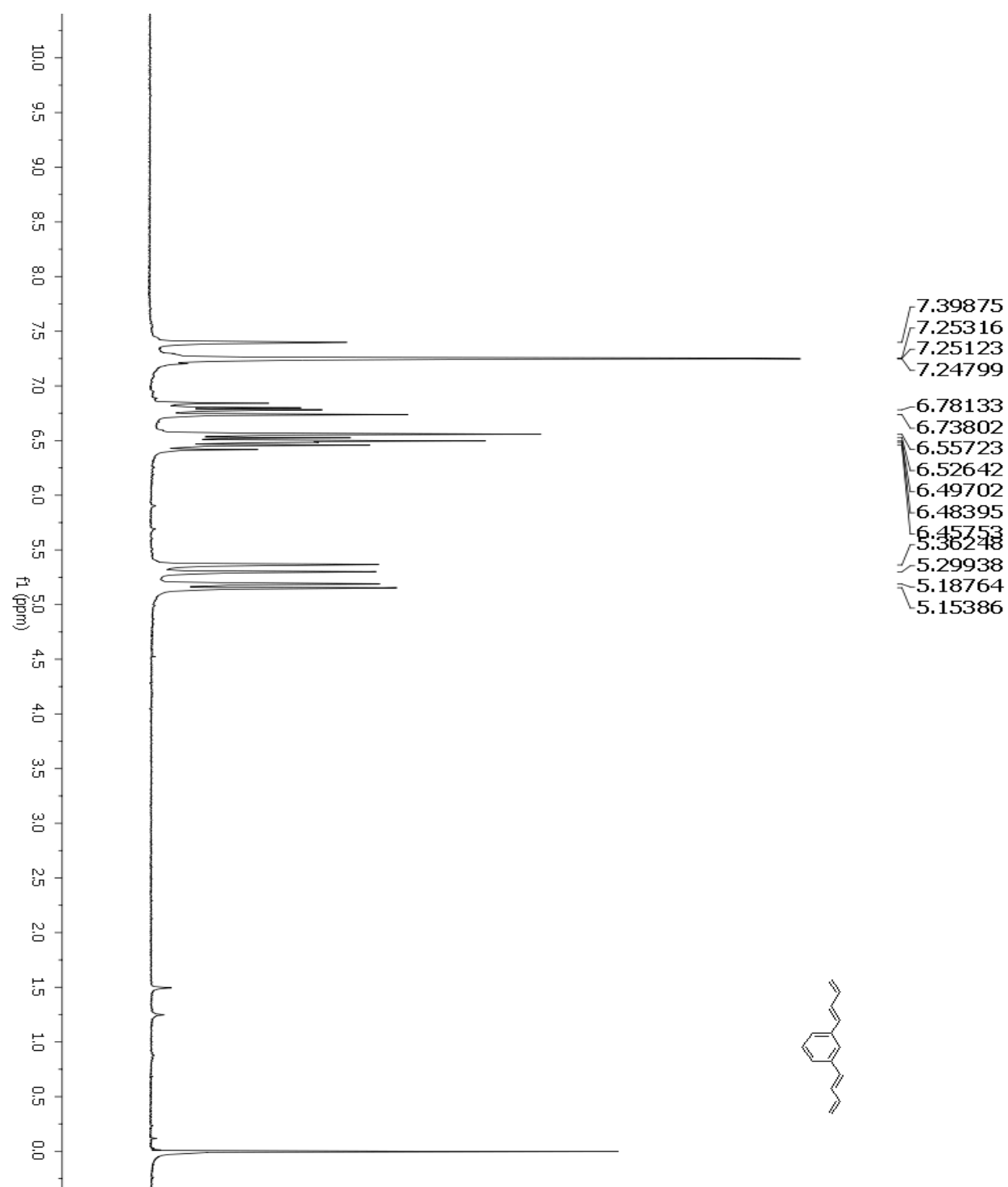
¹H spectrum of 701g



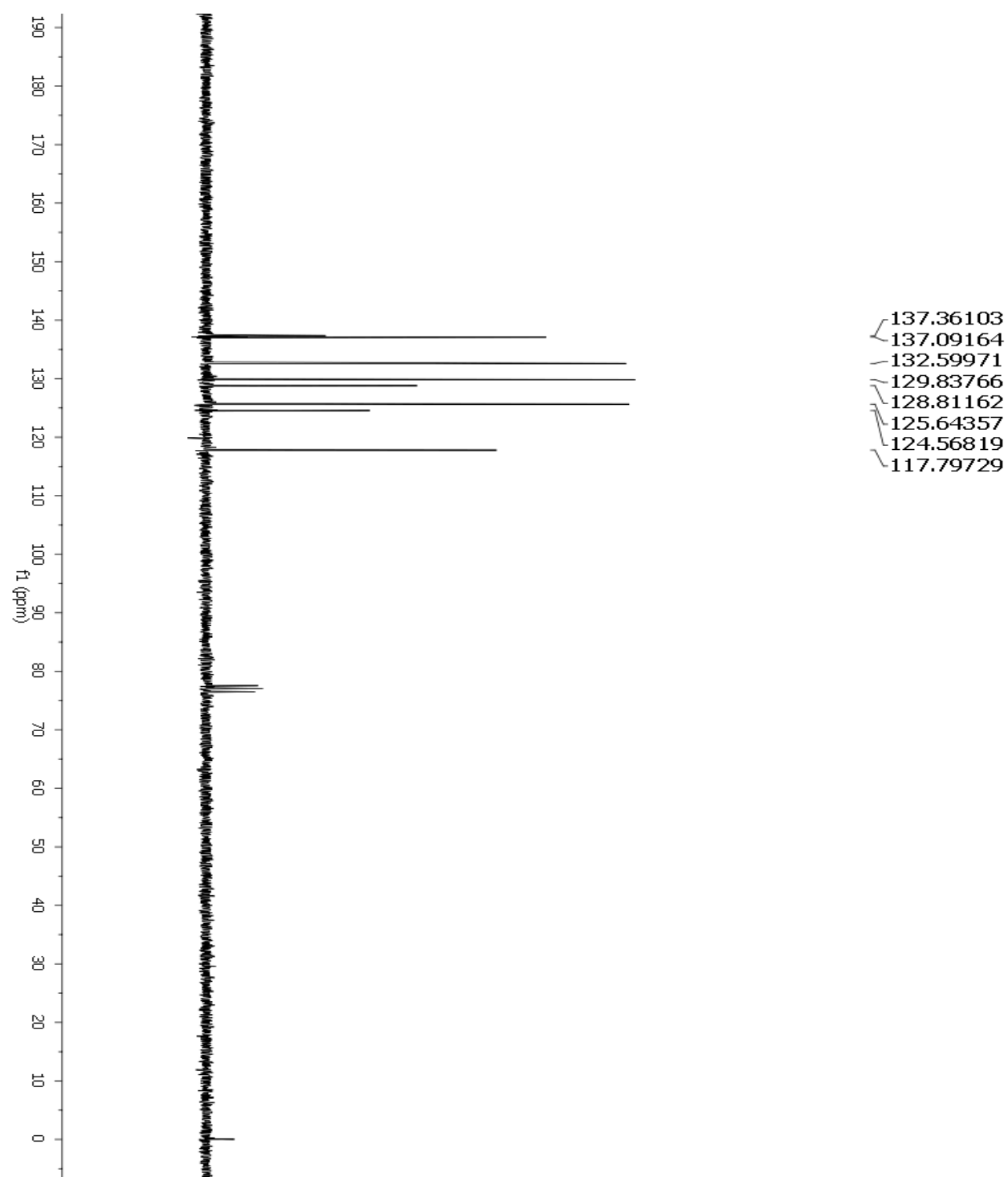
¹³C spectrum of 701g



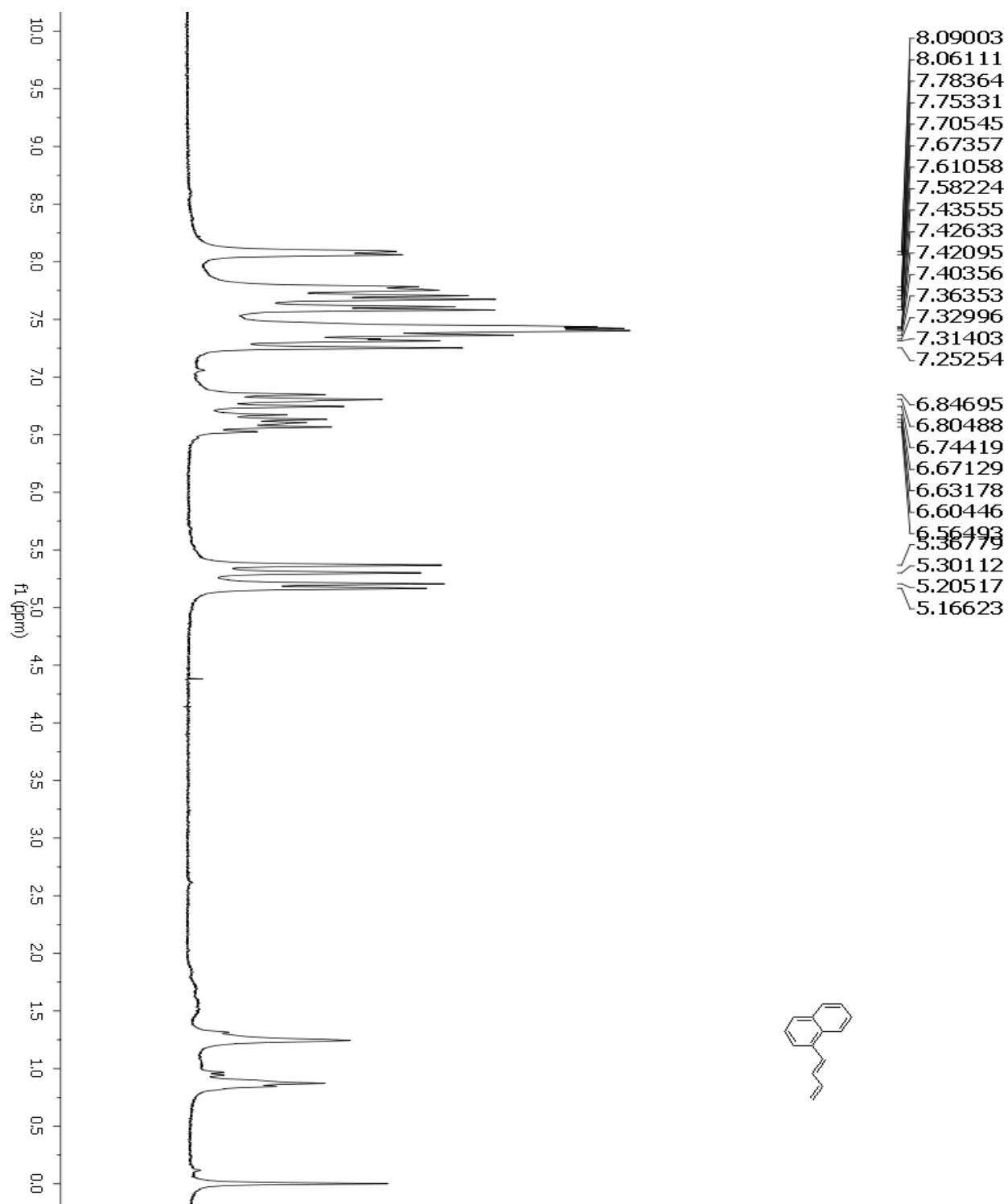
^1H spectrum of 701i



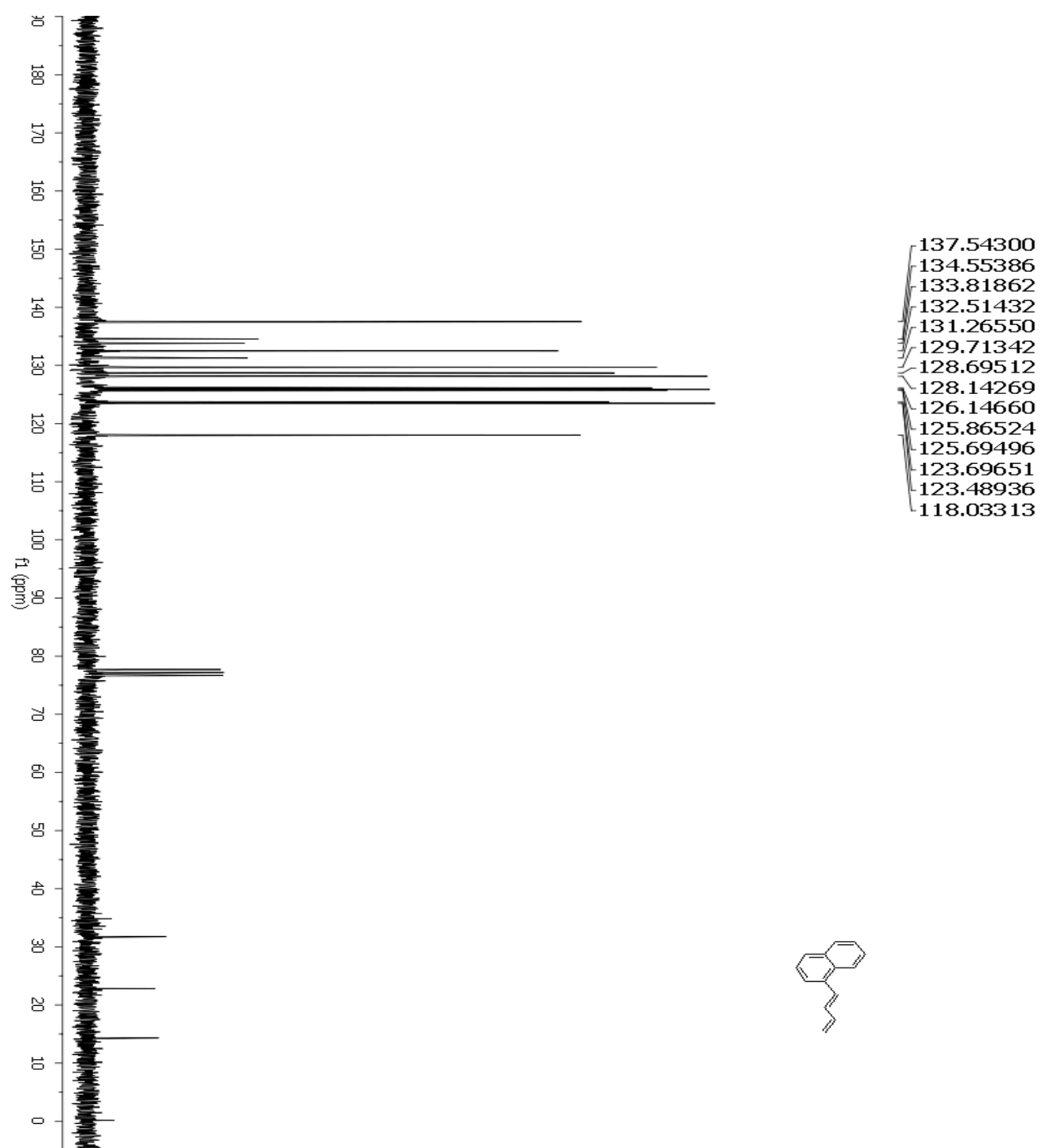
^{13}C spectrum of 701i



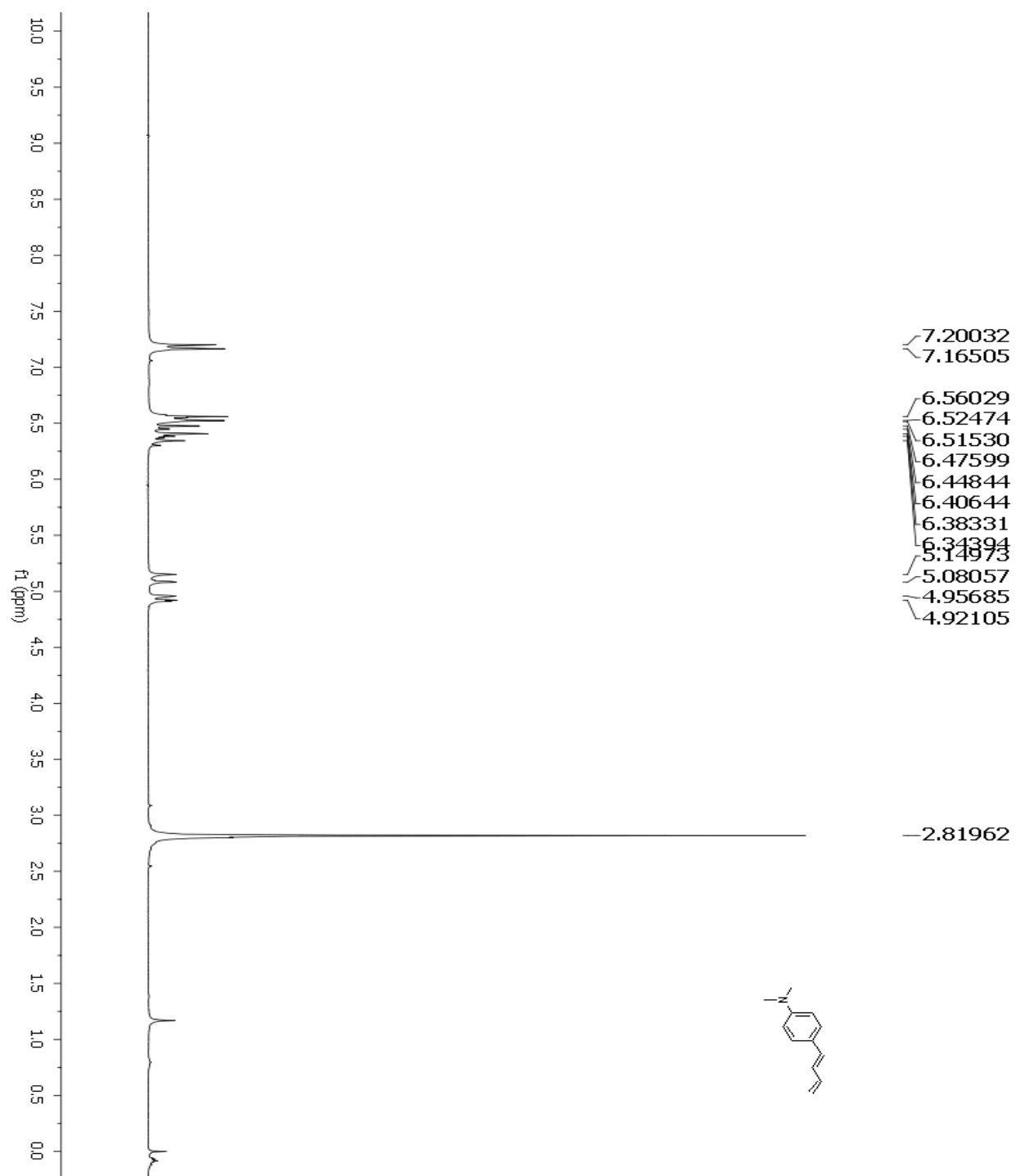
¹H spectrum of 701j



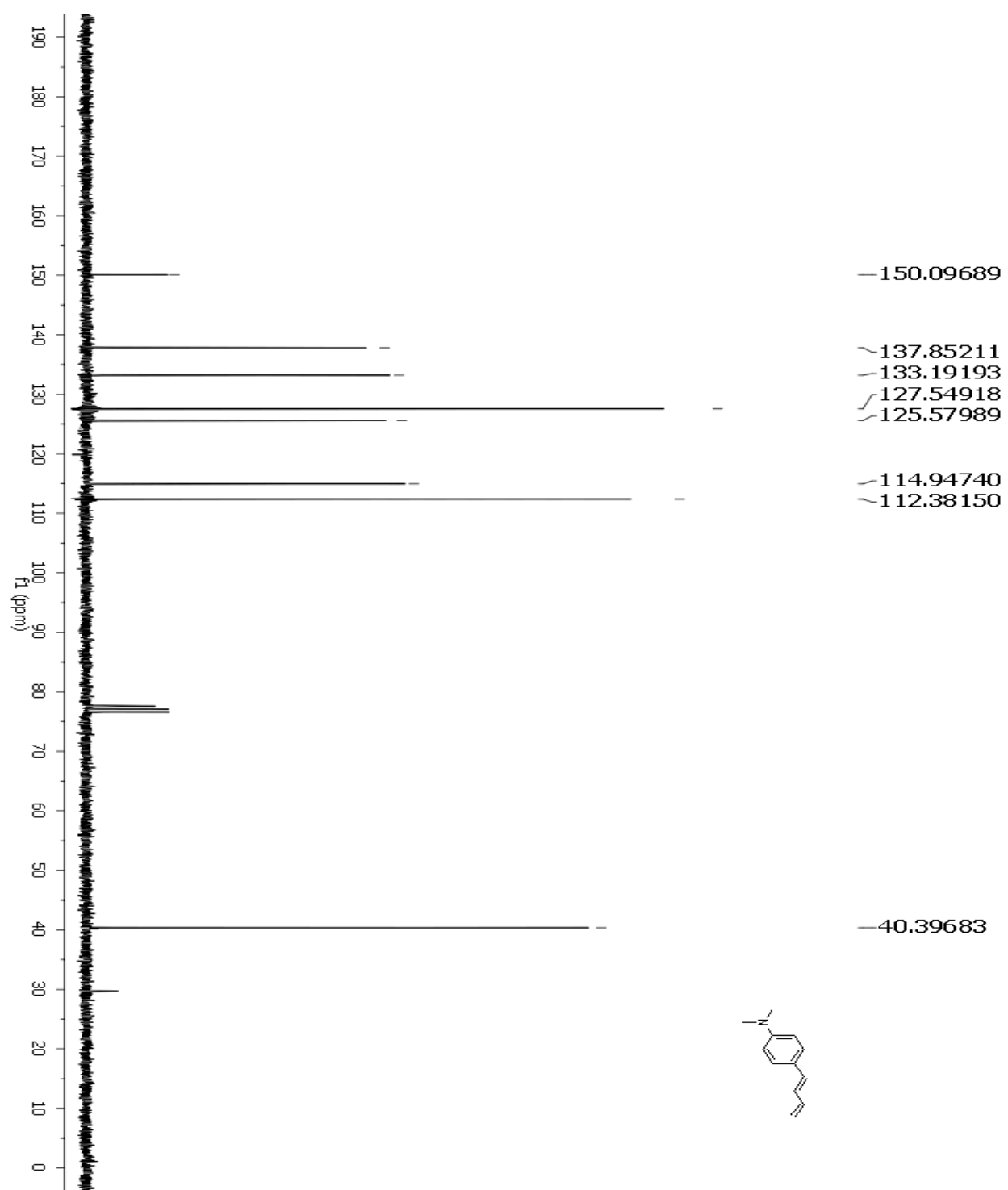
¹³C spectrum of 701j



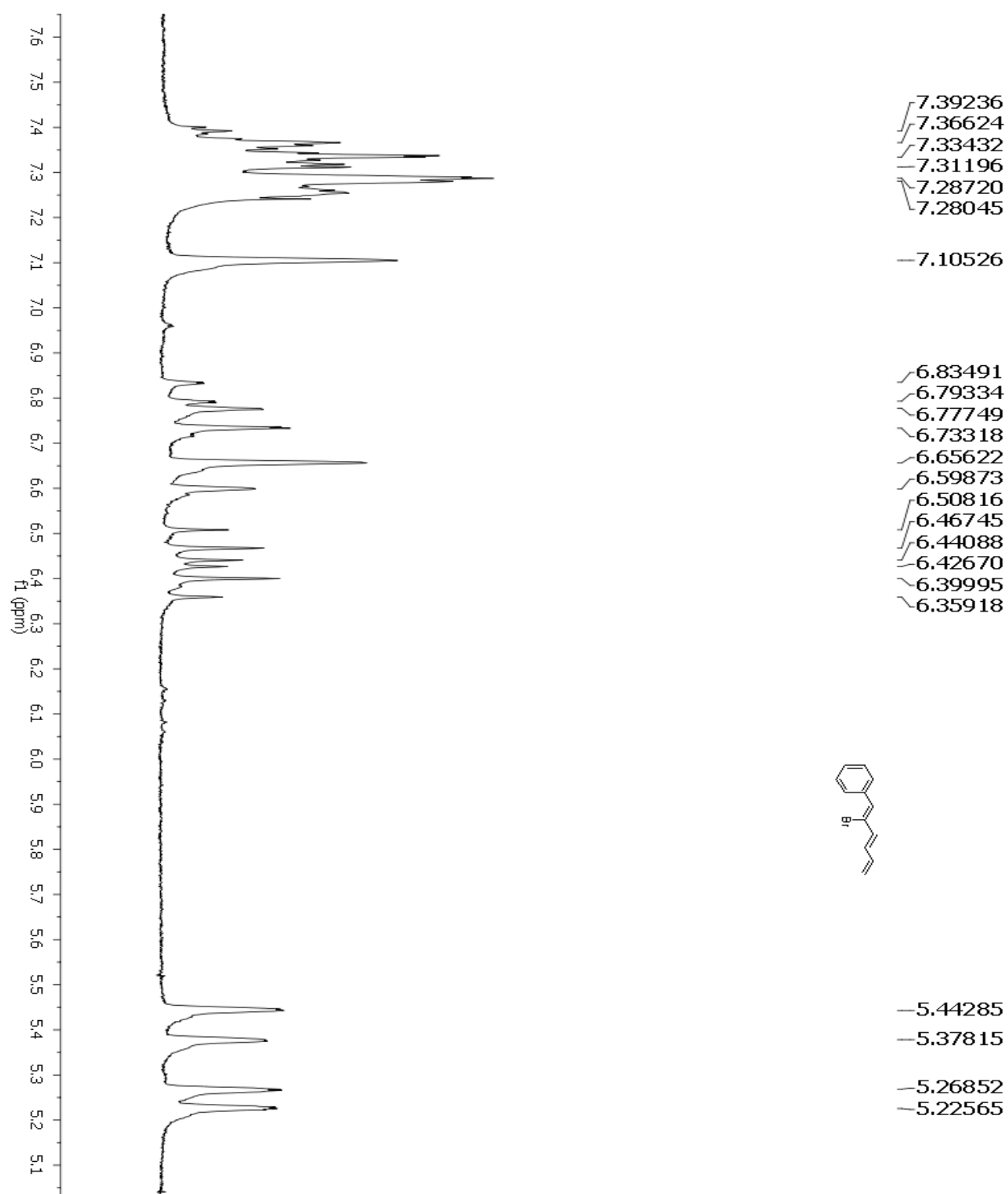
¹H spectrum of 702



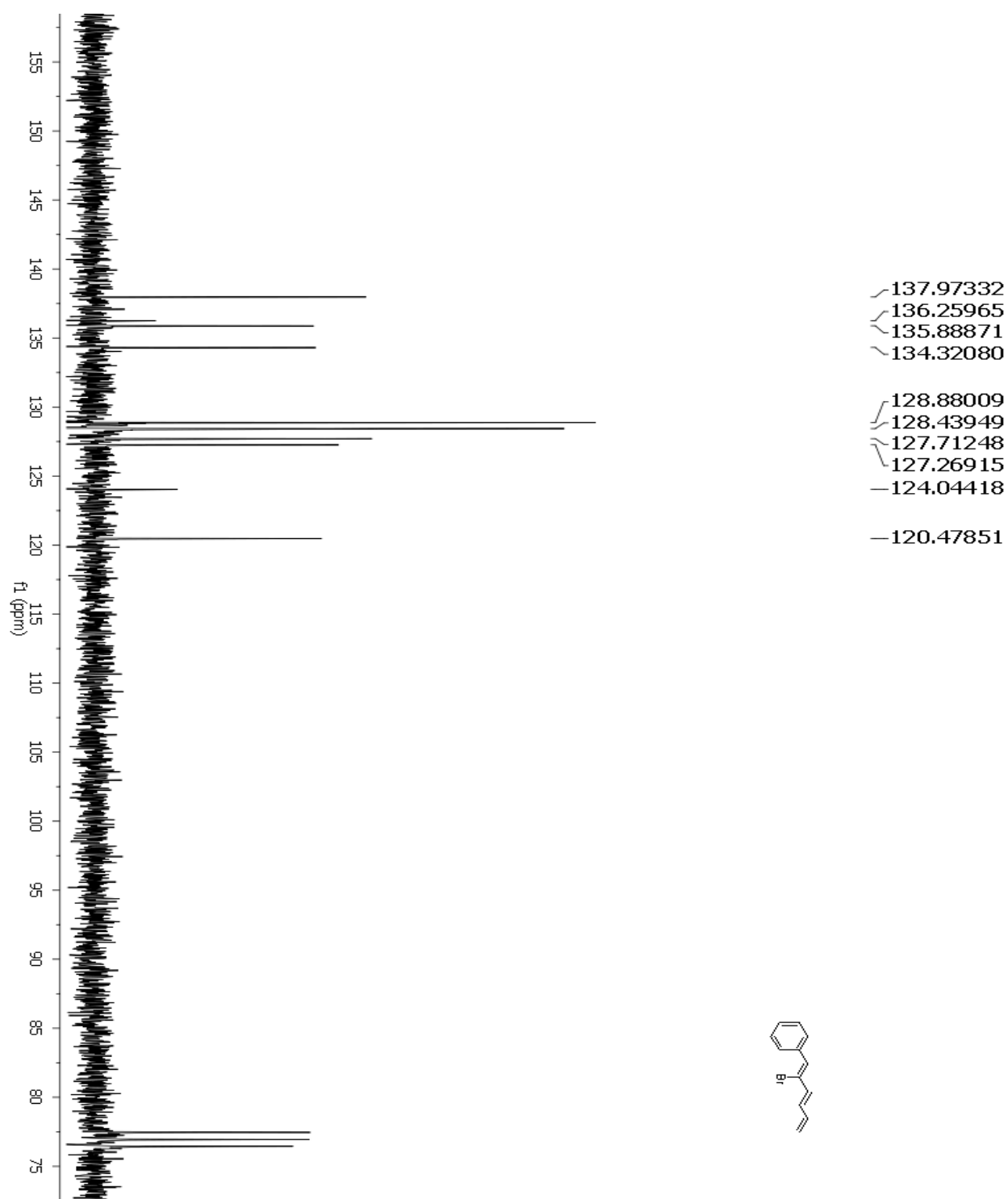
¹³C spectrum of 702



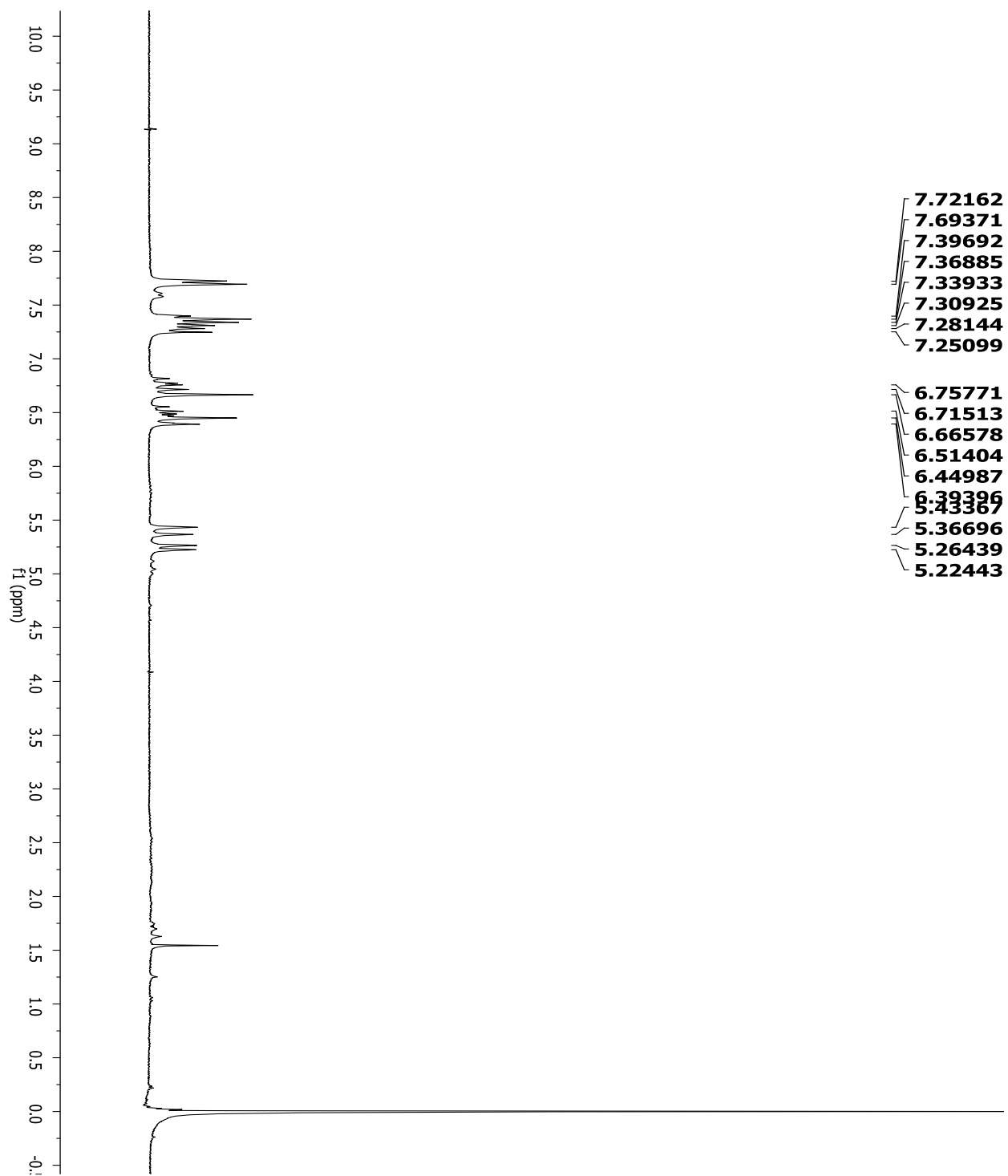
¹H spectrum of 705a



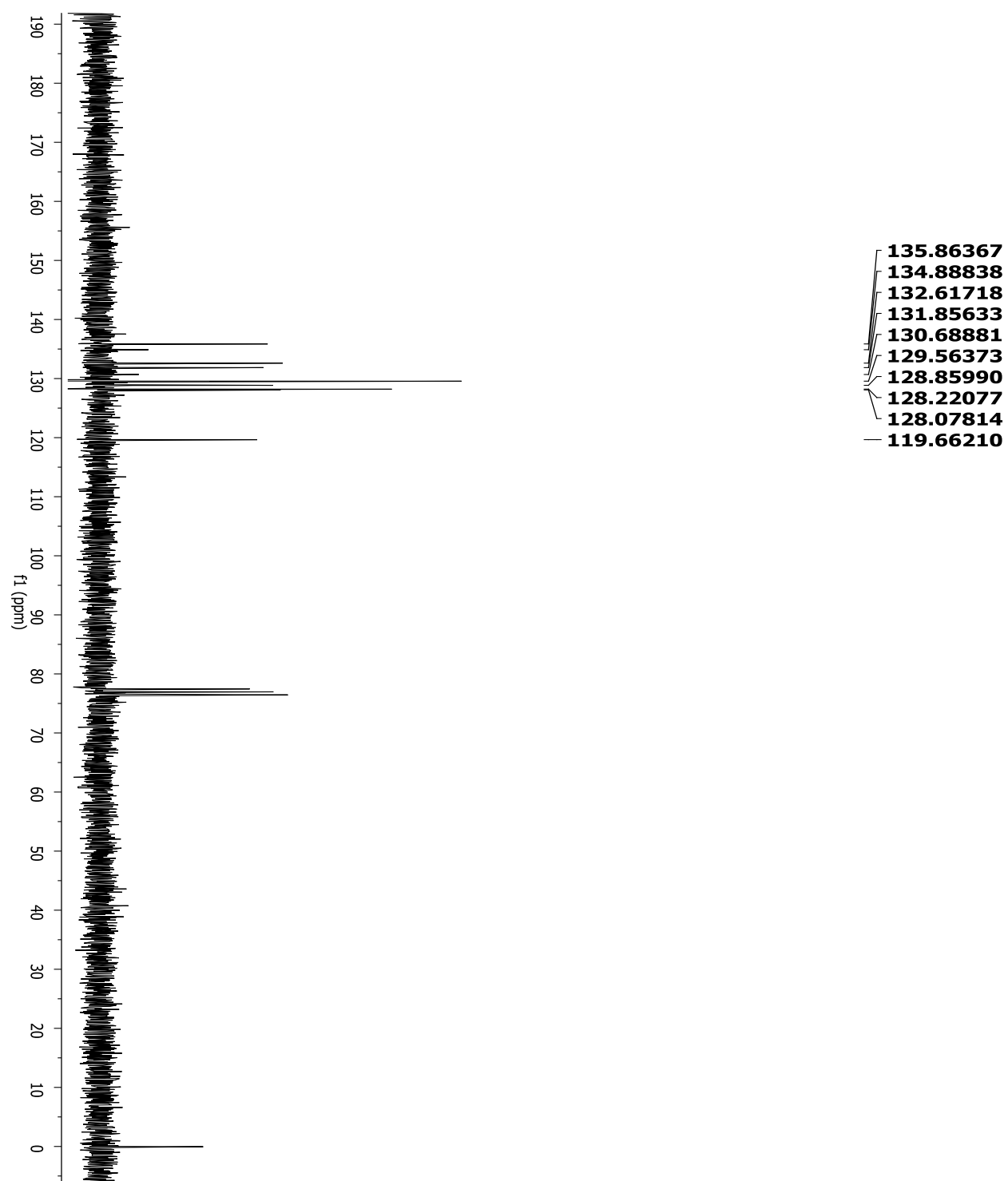
¹³C spectrum of 705a



^1H spectrum of 705b



^{13}C spectrum of 705b



VITA

Michael Patrick Quinn, son of Bruce Christopher and Patricia Ann Quinn, brother of Matthew Edward, Rebecca Katherine, Caitlin Mary, and Kevin Quentin Quinn, husband of Amber McCall Quinn, and father of Evelyn Anne Quinn, was born on April 3rd, 1979 at American River Hospital in Carmichael, California. In December of 1980, his family moved to Fall Branch, Tennessee where he attended grade school (K-5) at Saint Mary's Elementary in Johnson City. In the autumn of 1988, his family briefly moved back to California, but promptly returned to Johnson City, Tennessee in August 1989 where he attended Liberty Bell Middle School and Science Hill High School. After early graduation from Science Hill High School, he attended East Tennessee State University for a semester in the spring of 1997. In the fall of 1997, he was accepted to the University of Tennessee, Knoxville where he was awarded the Frank M. Roddy Scholarship for Mechanical Engineering in 1998 and consecutively thereafter until graduation in 2002. After graduating with a Bachelor of Science in Chemistry with a concentration in Mathematics, he went to work for Dr. Roger C. Carrol as a Senior Laboratory Technologist in the Department of Anesthesiology Research at the University of Tennessee Medical Center, Knoxville. In January of 2005, he moved to Houston, Texas to pursue a career in Environmental Project Management. In May of 2006, he and his future wife applied to graduate school at the University of Tennessee, Knoxville, where both accepted graduate positions. The joy of acceptance to graduate school and reunion with family led to the proposal and subsequent engagement to one Amber McCall Galbraith by Michael Patrick Quinn on February 4th, 2007. On August 9th, 2007 they were joined in holy matrimony and subsequently blessed by the arrival of Evelyn Anne Quinn on January 25th, 2008. In December of 2007, he

joined the research group of Dr. George W. Kabalka, and his work focused on developing new methodology using boron trihalides & titanium tetrahalides. In August of 2010, he received the Doctor of Philosophy in Chemistry.