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Boron and Metal Catalyzed C-C and C-H Bond Formation

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To the Graduate Council:

I am submitting herewith a dissertation written by Adam Barret Pippin entitled "Boron and Metal Catalyzed C-C and C-H Bond Formation." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

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Boron and Metal Catalyzed C-C and C-H Bond Formation

A Dissertation
Presented for the
The Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Adam Barret Pippin
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DEDICATION

To my wife, Stacey,

You have been my support through the good and bad.

Thank you for your unconditional love.

I will always be your “chem-god.”

To my parents,

Without your love, support, and encouragement,

I might not have made it through graduate school.

Thank you for always being there for me.

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ABSTRACT

Research efforts focused on the use of boron and metals to form new carbon-carbon and carbon-hydrogen bonds are summarized in this dissertation. Several novel reactions have been developed. These include: the deoxygenation of benzylic alcohols using chloroboranes, alkenylation of benzylic alcohols using boron trichloride, and dialkynylation of aryl aldehydes using dialkynylboron chloride. Numerous applications of these novel reactions have been developed. These include alternate routes to diphenylmethanes and 1,4-diynes from easily prepared dialkynylboron chlorides. In addition, *E* and *Z* alkenyl halides can now be prepared using boron trichloride without the use of butyllithium. The stereochemistry of the alkenyl halide can be altered using various reaction conditions. This type of methodology and previously reported indium allylation chemistry was applied to the synthesis of naturally occurring lactones.

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LIST OF SYMBOLS AND ABBREVIATIONS

Ac_2O	Acetic Anhydride
OAc	Acetyl
α	Alpha
Bn	Benzyl
Bz	Benzoyl
β	Beta
BuLi	*n*-Butyllithium
Cat.	Catalyst
°C	Degrees Celsius
DCM	Dichloromethane
DME	Dimethoxyethanol
J	Coupling constant
$CDCl_3$	Deutero chloroform
d	Doublet
dd	Doublet of doublets
dt	Doublet of triplets
Eq.	Equivalents
Et	Ethyl
Et_3SiH	Triethylsilane
Et_2O	Diethyl Ether

OTf	Trifluoromethanesulfonate
OTs	4-Methylbenzenesulfonate
MOM	Methyoxymethyl-
g	Grams
Hz	Hertz
hr	Hour
Hxn	Hexane
iPrOH	2-Propanol
THF	Tetrahydrofuran
LDA	Lithium diisopropylamide
mCPBA	*meta*-Chloroperbenzoic acid
MHz	Megahertz
Me	Methyl
TMS	Trimethylsilane
TMSCl	Trimethylsilyl chloride
min	Minute
µm	Micrometer
mg	Milligrams
mL	Milliliters
mol	Mols

mmol	Millimol
M	Molar
m	Multiplet
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
PPh_3	Triphenylphosphine
q	Quartet
r.t.	Room temperature
s	Singlet
t	Triplet
TBS	Tributylsilane

CHAPTER 1 - INTRODUCTION

1.1 Scope of this Dissertation

Use of Lewis acids (BCl_3, $HBCl_2$, H_2BCl) and metals (indium) to form C-C and C-H bonds is a focus of this dissertation. Several novel reactions have been developed. These include: (II) deoxygenation of benzylic alcohols using chloroboranes; (III) alkenylation of benzylic alcohols using boron trichloride; and (IV) dialkynylation of aryl aldehydes using dialkynylboron chloride. Numerous applications of these novel reactions have been developed. These include alternate routes to diphenylmethanes and 1,4-diynes from easily prepared dialkynylboron chlorides. In addition, the use of indium is discussed as a way of forming α-methylenebis-γ-lactones, a common structural feature in many natural products. Subsequent chapters contain discussions of the significance of these reactions as they relate to the literature and will provide mechanistic insight into newly discovered and previously known organic reactions.

1.1.1 Historical Aspects of C-C and C-H bond formation

Carbon compounds form the basis of all known life on Earth. Carbon-carbon bond formation represents the fundamental aspect of organic chemistry, a sub discipline of chemistry involving the study of structure, properties and reactions of carbon-based compounds. The term "organic", which dates back to the 1st century, was used to describe complex compounds that could only be synthesized by "life forces" using the classical elements – earth, water, air and fire.[1] Today, we know organic compounds to be

primarily composed of C-C and C-H bonds. These types of bonds make up the skeletal backbone of the materials required to sustain life. Development of reactions forming C-C and C-H bonds is essential for producing many of the pharmaceuticals, foods, dyes, polymers, and other materials needed in daily life.

1.1.2 Historical Aspects of Boron and Metals in Organic Synthesis

The formation of C-C and C-H bonds typically requires a method for lowering activation energy barriers. In particular, boron-containing compounds accomplish this by acting as a Lewis Acid. In 1923, Gilbert Norton Lewis described the theory of Lewis acidity, as "An acid substance is one which can employ an electron lone pair from another molecule in completing the stable group of one of its own atoms".[2] Previously, the term "acid" referred to a substance that donated H^+ ions and a "base" as a substance that accepted H^+ ions.[3] The older definition did not take into account that salts that could form when an electron pair donor is reacted with an electron deficient atom such as boron. A reaction occurs between the two because of the acceptance of electrons by the Lewis acid completes a full octet in the outer valence shell, resulting in the formation of a new bond. In boron halides, the Lewis acid strength increases as the halide becomes larger and less electronegative.[4] This is counterintuitive on the basis of the relative σ-donor strengths of halides, which increases with electronegativity. This discrepancy is explained by the overlap of an empty *p* orbital on the boron with a pair of unshared electrons on the halogen.[5] The *p* orbital overlap between boron and fluorine is large and

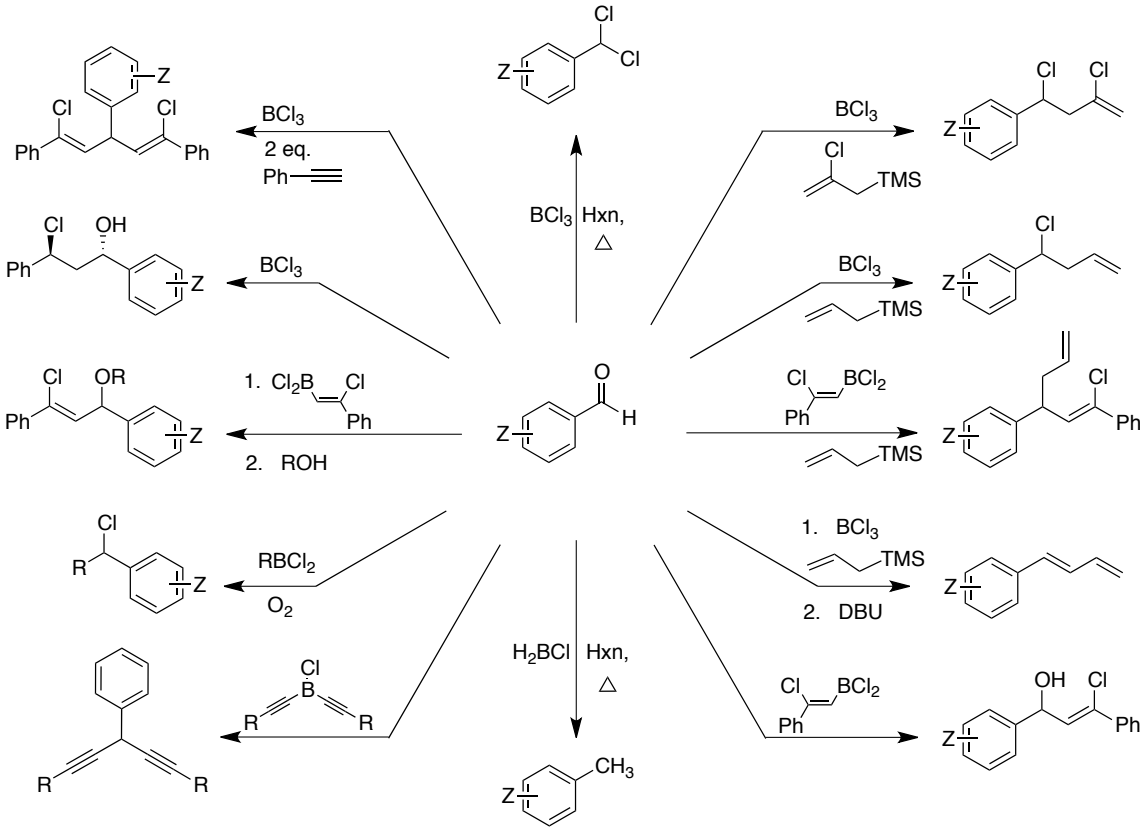
strong, where as the overlap in a B-I bond is negligible. This explains why BI_3 is a stronger Lewis acid than BF_3.

The Lewis acidity of transition metals is a function of electron deficiency in their d orbitals. The metals with lower d^n configurations are stronger Lewis acids than those with high d^n configurations.[6] In addition, metals can lose electrons easily to allow for reduction and oxidation reactions. Active metals will react with oxygen and moisture in the air to form oxides on the surface of the metal. Removal of the oxide is usually necessary to restore activity.

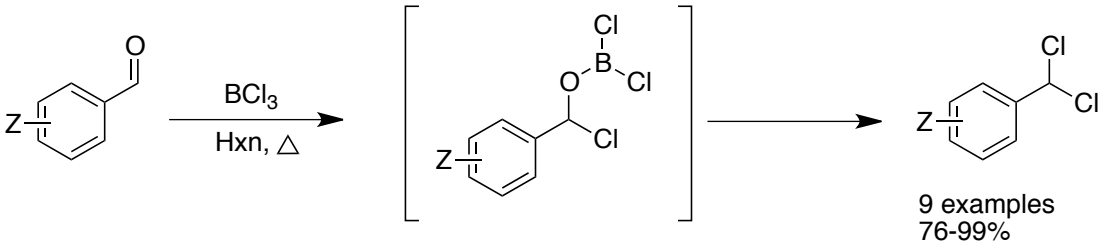
1.1.3 Reactions of Boron Trihalides in Organic Chemistry

The synthetic utility of boron lies in its Lewis acidity and its ability to form a negatively charged tetrahedral intermediate and complex with a Lewis base. Boron trihalides, in particular, are widely used in organic synthesis due to their availability, low price, and high regio- and chemoselectivity.[7] Many applications exist including: cleavage of esters and acetals,[8] stereoselective glycosidation of glycols,[9] asymmetric Aldol reactions,[10] Friedel-Crafts alkylation and acylation,[11] alkenylation,[12] alkynylation,[13] allylation,[14] and many acid-induced rearrangements.

Over the past decade, the Kabalka group has developed several novel reactions using boron and transition metals.[15,16,17] Reactions using boron halides can facilitate di-substitution of aldehydes and mono-substitution of alcohols via an unprecedented C-O bond cleavage (**Scheme 1-1**).[13, 16, 18] These reactions serve as the background for the research presented in this dissertation.



Scheme 1-1 Boron Halide Reactions of Aryl Aldehydes Developed by Kabalka and Co-Workers.



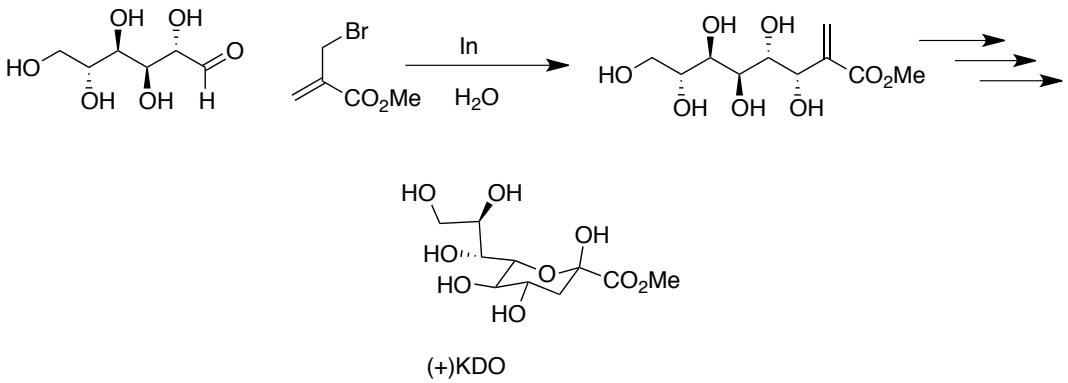
Scheme 1-2 Dihalogenation of Aryl Aldehydes.

The new reactions were developed after discovering that boron trichloride reacts with aromatic aldehydes to form dichloromethanes (**Scheme 1-2**).[15] A NMR study revealed that the reaction proceeds through a benzyloxyboron dichloride intermediate after boron coordinates with the carbonyl group. Other reactions were developed when this intermediate was modified using various boron chloride derivatives including alkyl,[19] alkenyl,[12] alkynyl,[13] allyl, aryl,[18d] and halo derivatives.[12] The general mechanism was found to involve a 1,2 Grignard-like addition to the carbonyl group followed by C-O bond cleavage and subsequent migration of a substituent from boron to carbon. Alkoxides could also be used to provide mono-substituted products.[12-13] The new organoboron methodology offers several synthetic advantages including mild reaction conditions, ease of preparation, atom economy, regioselectivity, and a tolerance of important functional groups. Later in this thesis, use of alcohols as an alternative to preparing the alkoxides is discussed. Alcohols can be directly alkenylated, allylated, alkynylated, or reduced to provide a wide variety of functionalized products. A brief review of other methods of accomplishing these transformations is presented in this chapter. Most require protection or deprotonating of the alcohol prior to substitution,[13] a significant limitation when compared to organoboron chloride based methodology.

1.1.3 Reactions of Indium in Organic Chemistry

In addition to Lewis acidity, metals find synthetic use in organic chemistry due to their ability to perform single-electron transfers. Edward Frankland discovered this significant property in 1849 when he first synthesized diethyl zinc using iodoethane and zinc metal.[20] Many organometallic reactions soon followed with the successes of Reformatsky,[21] Barbier,[22] Grignard,[23] and Gilman.[24] While each serves as a milestone in organometallic chemistry, when a carbonyl compound is used as an electrophile, the transformations are now frequently referred to as Barbier-Grignard type reactions.[25] The number of syntheses using this type of reaction is enormous, but a major requisite restricts their use: the strict exclusion of moisture and acidic hydrogens.

Presumably, due to its low abundance, indium has been neglected in chemical synthesis compared to other metals. Prior to 1990, there are only a few scattered examples of its use in Reformatsky type reactions performed by Rieke[26] and Butsugan.[27] The use of indium in organic chemistry did not become of interest until Chan and co-workers demonstrated indium allylation using water as a solvent (**Scheme 1-3**).[28] At the time, methodology that employed zinc and tin were consider too harsh to be of use in the synthesis of sialic acid derivatives. A more reactive metal was required. After examining the first ionization potentials of different metals, Chan et al. deduced that indium was most suitable.[29] Since then, indium has been used to mediate a range of reactions including allylation reactions, propargylation reactions,[30] Reformatsky reactions,[31] and Aldol reactions.[32]



(+)KDO

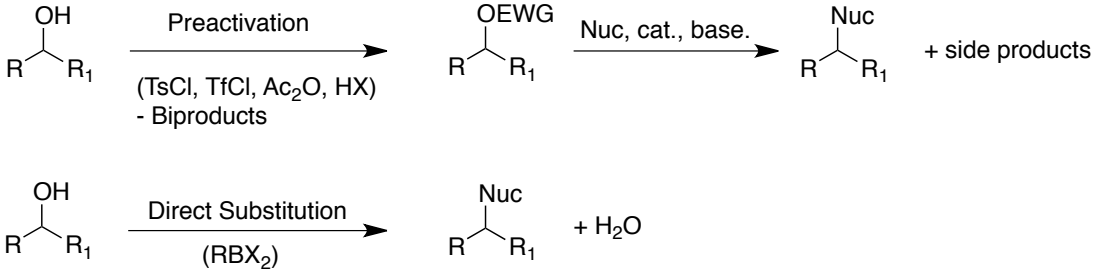
Scheme 1-3 Aqueous Indium Mediated Allylation Synthesis of (+)KDO by Chan et al. (1995).

Indium is quickly becoming more widely used in organic synthesis due to its chemical properties:

1. Indium metal does not readily oxidize in air or oxygen at ambient temperature.
2. Moisture has no affect on its reactivity, unlike other metals.
3. The first ionization potential of indium is on par with alkali metals giving it exceptional reactivity.
4. Indium exhibits low heterophilicity in organic reactions. This makes it ideal for mediating C-C bond forming reactions because it can tolerate a wide variety of functional groups.
5. Transformations are usually diastereoselective; and ligands can be used to increase enantioselectivity.
6. Toxicity is low compared to lead and tin, which are highly and moderately toxic, respectively.

1.2 Alcohol Functional Group Conversion

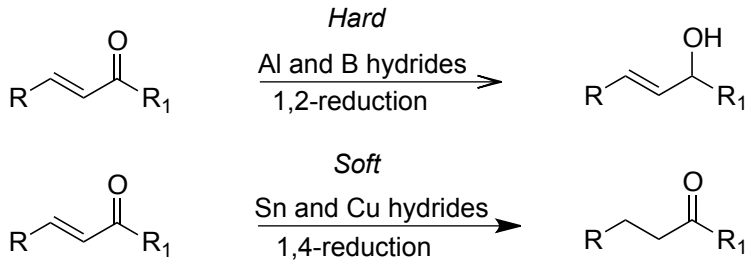
Alcohols are ideal starting materials in organic synthesis due to their ease of production, availability, and their ability to function as precursors to other functionalized compounds such as carbonyls, ethers, and alkenes. Unfortunately, hydroxyl groups possess an acidic hydrogen, which makes them poor leaving groups. Typically alcohols are converted into a better leaving groups (OTs, OTf, X, OAc) prior to direct substitution (**Scheme 1-4**). This requires additional steps, results in the formation of large amounts of byproduct, and increases the possibility of side reactions. In terms of efficiency, atom economy, and environmental concerns, the direct substitution of the hydroxyl group is highly desirable because water is the generated as the only by product. Direct carbon bond substitution of the hydroxyl group remains a challenging goal. Chapters 2 and 3 focus on the use of boron chlorides to achieve direct C-C and C-H bond formation from unaltered alcohols.



Scheme 1-4 Pre-activation/Substitution vs. Direct Substitution of Alcohols.

1.3 Reductions in Organic Chemistry

Commonly referred to as "Redox" reactions, reduction-oxidation reactions change the oxidation state of a molecule with either the loss or gain of electrons; termed oxidation and reduction respectively. The oxidation state of many organic functional groups can be changed by removing (oxidation) or adding (reduction) hydrogen atoms.[33] Reductions in organic chemistry typically use a hydride source ($NaBH_4$, $LiAlH_4$, NaH) to transfer hydrogen via nucleophilic substitution. While hydrides are extremely effective at reduction, they are also strong bases and can destroy sensitive functional groups. Many are pyrophoric and react violently with water.[34] Direct use of hydrogen gas is possible when a heterogeneous metal catalyst is employed.[33] However, hydrogen gas is flammable and some reactions required high pressure, which can be dangerous. Due to the large difference in electronegativity in a Si-H bond, silanes can function as reducing agents.[35] In particular, triethylsilane is commonly used as a stoichiometric reductant. Polymethylhydrosiloxane (PMHS) is a less expensive and milder reducing agent that can transfers hydrides easily to metal centers.[36] The common reducing agents $LiAlH_4$ and $NaBH_4$ direct 1,2-reduction of the carbonyl due to the HSAB theory discussed in **1.1.4**.



Scheme 1-5 Reductions of Unsaturated Carbonyl Compounds.

1.4 Alkenylation, Alkynylation, and Allylation of Carbonyl Groups

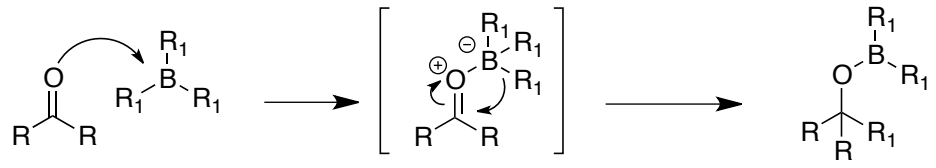
1.4.1 Carbonyl Chemistry

In addition to alcohols, molecules containing carbonyl groups are ideal starting materials in synthesis due to the highly polarizable C-O double bond. The increased reactivity causes carbon to become electrophilic and thus, more reactive toward nucleophilic addition. The lone pairs on oxygen are reactive and form bonds with protons and Lewis acids, which can further increase the electrophilicity of carbon. Additional reactivity occurs at the alpha carbon adjacent to the carbonyl group. The electron withdrawing effect of oxygen and subsequent stabilized resonance structure significantly increase the acidity of the neighboring alpha hydrogens.[37] Under acid and basic conditions, carbonyls tautomerize to their respective enols and enolates; both of which are nucleophiles capable of forming C-C bonds.

Organometallic reagents containing Mg,[38] Zn,[31] Li,[39] Na,[40] or K,[40] all readily add to the carbonyl (1,2-addition) in aldehydes and ketones. Nucleophilic addition to the higher oxidized carbonyls (ester, amide, carboxylic acid) is slower but in general, the reaction rate increases if more reactive reagents are used. Due to the increased electronegativity of copper, organocuprates are often less nucleophilic than the analogous magnesium or zinc reagents.[41]

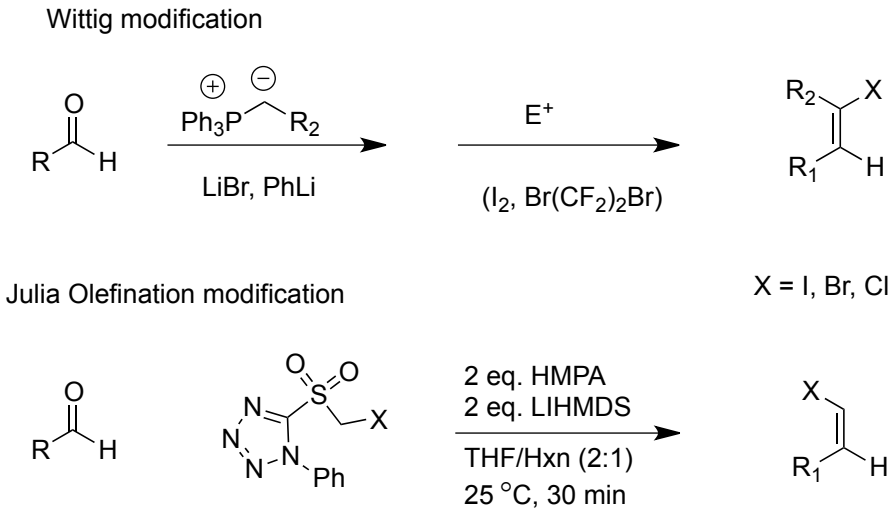
1.4.2 Alkenylation

Organoboranes are also capable of 1,2-additions to carbonyl compounds. The resulting products are analogous to ones prepared using Grignard reagents, though they do not react in the same manner. Grignard reagents are nucleophilic and thought to add to carbonyl groups by a single electron transfer mechanism.[38] Organoboranes on the other hand, are electrophilic and readily accept the lone pairs on oxygen. The resulting negatively charged tetrahedral intermediate is nucleophilic toward many electrophiles. This results in a transfer of a nucleophilic group from boron to the electrophilic center (**Scheme 1-6**).[7d] The propensity of an organic group to migrate depends on its ability to stabilize a negative charge: alkynyl > aryl = alkenyl > primary alkyl > secondary alkyl > tertiary alkyl.[42] The migration is stereoselective and results in retention of configuration at the carbon-based electrophiles.[43] This type of mechanism allows for the transfer of stereodefined alkenes from preformed alkenylboranes. Synthetically useful alkenyl halides can be transferred using haloalkenylboron chlorides,[12] which are easily prepared by the haloboration of an alkyne. The added alkenyl halide can then be transformed into a number of functional groups using transition-metal catalyzed cross coupling reactions or ozonolysis.



Scheme 1-6 Prevailing Mechanism of Carbonyl Additions via Organoboranes.

Recent advances in organophosphorus chemistry now allow for the preparation of alkenyl halides using Wittig reagents.[44] A halogen source can be added following the addition of the phosphonium ylide reagent to provide *E*-bromo and *E*-iodo substituted alkenes from aldehydes (**Scheme 1-7**). A modification of the Julia olefination reaction uses α-halomethyl sulfones to synthesize alkenyl halides with high *E*/*Z* stereoselectivity.[45] Recently our group reported that alkenyl halides are accessible via haloallylation of aryl aldehydes using 2-bromoallyltrimethylsilane and boron trichloride.[14]



Scheme 1-7 Alternative Methods for Preparing Alkenyl Halides Using Modified Wittig and Julia Olefination Reactions.

1.4.3 Alkynylation

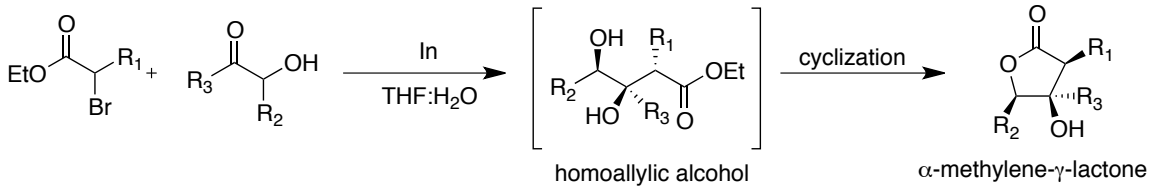
Alkynes have a rich history and are commonly used in synthetic organic chemistry to make C-C bonds. Terminal alkynes are synthetically useful due to their acidic hydrogen. Removal of the terminal hydrogen with a base creates a nucleophilic carbanion that is capable of adding to carbon-based electrophiles. Alkynes have been historically prepared by the addition of bromine to an alkene, followed by a double elimination with a base.[46] Once formed, the alkyne is a reactive functional group that can participate in many organic transformations. In organoboron chemistry, alkenes,[12] as well as alkynes,[13] can be transferred to electrophilic centers. Reacting boron trichloride with an acetylide generates alkynylboron chlorides easily *in situ*. This method offers an electrophilic alternative to carbanion-based methods that may destroy unprotected base sensitive functional groups.

1.4.4 Allylation

The Lewis acid mediated allylation of a carbonyl compound produces homoallylic alcohols, a structurally important functional group in organic synthesis.[47] In general, an allylic leaving group (halo-, silyl-, boro-) donates its electrons to form a new bond with the carbonyl carbon using a metal or Lewis acid. Asymmetric syntheses of homoallylic alcohols have been accomplished using chiral ligands and various metals including Li, In[25], Pd, Mg, Cu, Rh, Ti[48], Zn, Ru, Au, Sn, and more. Due to boron's Lewis acidic nature, it has seen considerable use in the synthesis of homoallylic alcohols; progress has been made by Brown,[49] Roush,[50] Corey,[51] Hafmer,[52] Soderquist,[53] and our own research

group,[54] among many others. Other methods of homoallylic alcohol preparation include Alder-Ene reaction,[55] Hosomi-Sakurai reaction,[56] Nozaki-Hiyama coupling,[57] [2,3]-Wittig rearrangement,[58] and Baylis-Hillman type chemistry.[59]

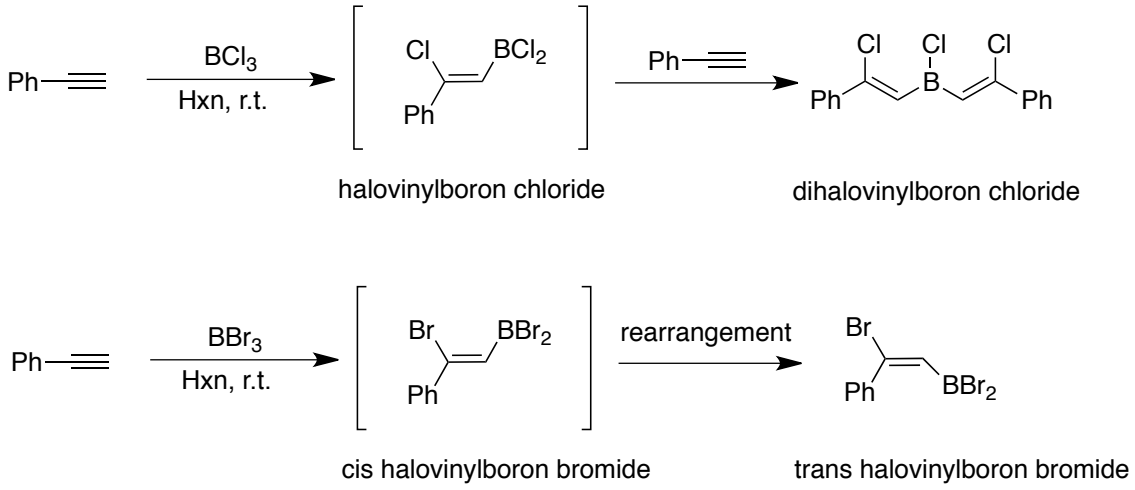
The numerous synthetic routes that have been published document the fact that homoallylic alcohols are exceptionally useful, especially for synthesizing lactones (**Scheme 1-8**).[60] Allylation with α, β -unsaturated esters yields straight-chain homoallylic alcohols that can be cyclized under acidic conditions, basic conditions, or using a coupling reagent such as dicyclohexylcarbodiimide (DCC).[61] This method has proven useful for preparing α-methylenebis-γ-lactones, a common structure in many natural products.[60]



Scheme 1-8 Indium Mediated Allylation and Subsequent Cyclization of Homoallylic Alcohols by Baba (2006)

1.5 Haloboration of Alkynes

The haloboration of terminal alkynes using boron trihalides generates halovinylboron halides with high regio- and stereoselectivity.[7b] Additions are controlled by stoichiometric equivalency; that is two equivalent of alkyne will provide the disubstituted dihalovinylboron chlorides.[62] When boron trichloride is used to haloborate alkynes, the *Z* isomer forms exclusively.[63] However, when boron tribromide is used, a *syn* addition still occurs, but the *cis* isomer spontaneously isomerizes to the *trans* isomer[64] (**Scheme 1-9**). Like many other organometallic reagents, halovinylboron chlorides are air and water sensitive. These shortcomings can be overlooked when considering their synthetic versatility resulting from the presence of a Lewis Acid, transferable alkene, and vinyl halide, all within one reagent.



Scheme 1-9 Haloboration of Phenylacetylene Using Boron Halides.

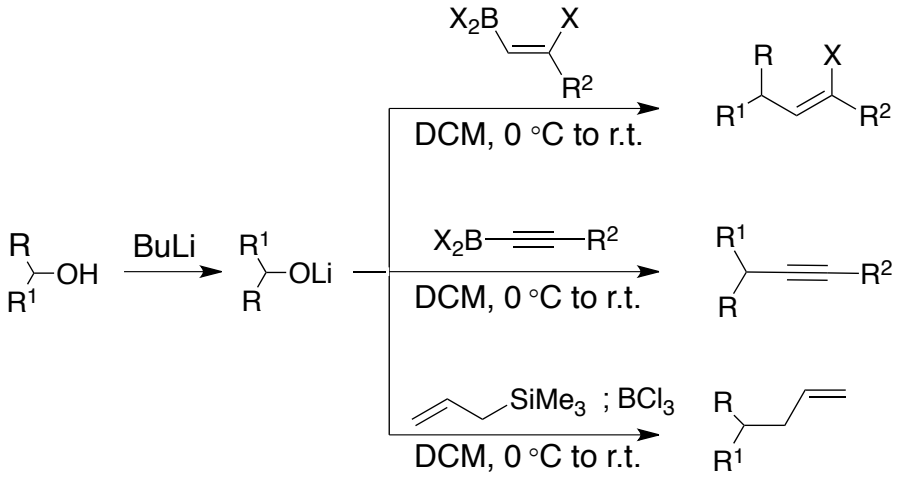
1.6 Statement of Problem

Lewis acids, copper hydrides, boranes and indium can all mediate the formation of new C-C and C-H bonds. This research was focused on a study of reactions of these reagents with alcohols and carbonyl compounds. Novel reduction chemistry was developed using chloroboranes while investigating the feasibility of a H-migration reaction. Alkenylation reactions were reinvestigated to eliminate the use of butyllithium, which allows for direct C-C bond formation from an unprotected alcohol. Alkynylation was achieved using dialkynylboron chlorides and alcohols. Investigation of use with aldehydes resulted in the dialkynylation of aryl aldehydes. Methodology developed in this research was applied in an attempt to synthesize α-methylenebis-γ-lactones. Our group was able to use indium to allylate aldehydes and cyclize the resulting homo allylic alcohol. This methodology was applied to the synthesis of bislactones and serves as an example of the importance of stereochemistry in the preparation of homoallylic alcohols as well as the electronic effects of withdrawing groups on indium mediated allylation reactions.

CHAPTER 2 – DEOXYGENATION OF BENZYLIC ALCOHOLS USING BORON DIHALIDES

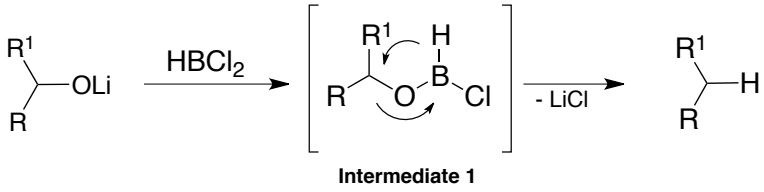
2.1 Introduction

Our research group has focused on the chemistry of organoboron halide derivatives for many years. Recently, we discovered the transition-metal-free coupling of alkoxides with halovinylboron dihalides[12] and alkynylboron dichlorides[13] under mild reaction conditions. These reactions provide unprecedented routes for replacing hydroxyl groups with stereodefined halovinyl- and alkynyl- groups (**Scheme 2-1**). In all these reactions, migration of either a vinyl or an alkynyl group from a boron center atom to a carbon center is involved. Notably, the heightened Lewis acidity of the boron center in alkoxyboron halide intermediates permits the migration to proceed smoothly without the addition of additional Lewis acids. A recent mechanistic investigation[62] revealed that this pathway likely involves a carbocation intermediate.



Scheme 2-1 Coupling of Alkoxides with Various Boron Halides.

Encouraged by these results, we postulated that a hydrogen migration in an intermediate such as **1** (generated by mixing an alkoxide with dichloroborane) should be feasible (**Scheme 2-2**). In this case, dichloroborane would act as both Lewis acid and hydride source. The method would provide a new route to diarylmethane derivatives,[65] which are important in pharmaceutical,[66] dye,[67] and materials chemistry.[68]

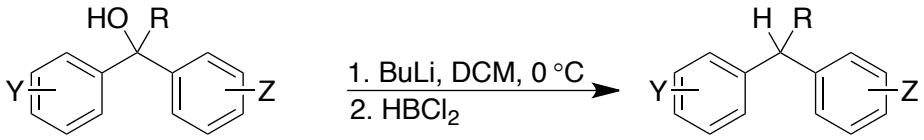


Scheme 2-2 Deoxygenation of Alkoxides Using Dichloroborane.

2.2 Results and Discussion

As shown in **Table 2-1**, the deoxygenation reaction proceeds efficiently at room temperature to offer products in moderate to high yields. Ether and halo groups survive the Lewis acidic conditions although, in a few cases, chlorinated by-products may form. In previously reported methods for deoxygenation of secondary alcohols (including lithium-ammonia,[69] sodium borohydride-trifluoroacetic acid,[70] zinc iodide-sodium cyanoborohydride,[71] indium trichloride-chlorodiphenylsilane,[72] hypophosphourus-iodine,[73] and $Mo(CO)_6$ –Lawesson's reagent[74]), ether cleavage and hydrogenolysis are common side reactions due to either high acidity or the use of strongly reducing conditions.

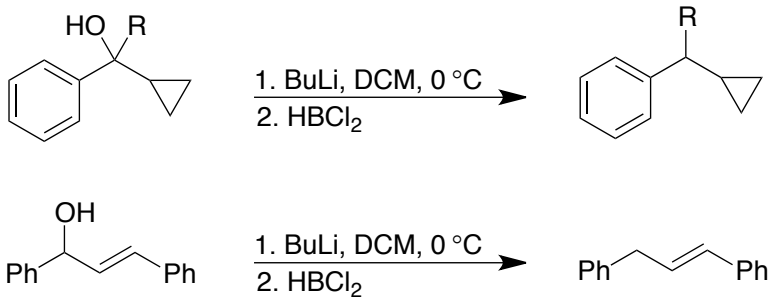
Table 2-1 Deoxygenation Reactions Using $HBCl_2$



Entry	R	Y	Z	Product	Yield (%)[b]
1	H	H	H	**201**	63
2	H	4-Cl	H	**202**	67
3	H	4-F	4-F	**203**	70
4	H	4-Me	H	**204**	82
5	H	2-MeO	H	**205**	84
6	H	4-MeO	4-MeO	**206**	72 (95)[c]
7	H	H	4-NO_2	**207**	58
8	H	H	4-OBn	**208**	65[d] (78)[c]
9	H	H	4-OMOM	**209**	76[e]
10	Ph	H	H	**210**	96
11	Me	H	H	**211**	94
12	H	-[f]	-[f]	**212**	56[g]

[a] All reactions were carried out on a 1.5 mmol scale.
[b] Isolated yield.
[c] H_2BCl was used in place of $HBCl_2$.
[d] A 12% yield of diarylchloromethane was isolated.
[e] The MOM group was cleaved during reduction.
[f] 9-Hydroxyfluorene was used as starting material.
[g] A 21% yield of 9-chloro-9H-flourene was isolated.

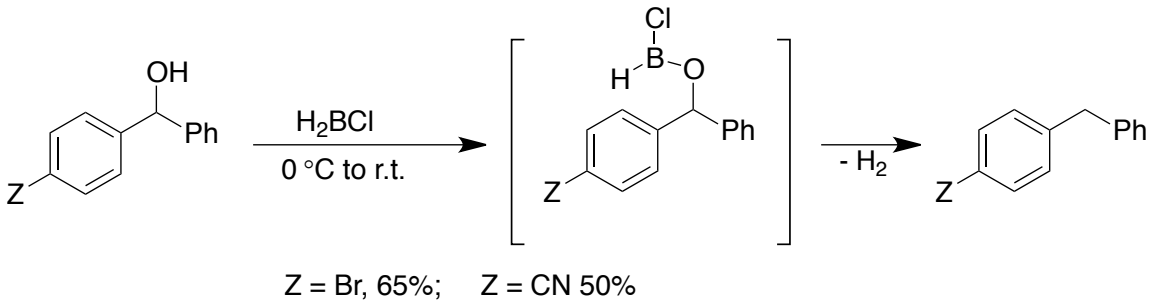
The new deoxygenation reaction also works well for benzylic alcohols bearing a cyclopropyl group (**Scheme 2-3**). The tolerance of the cyclopropyl group indicates that the reaction most likely proceeds through a concerted reaction mechanism rather than through a carbocation intermediate. In previous boron alkenylation experiments, the cyclopropyl group was lost, due to ring opening reactions. In addition, vinyl groups are stable under the reaction conditions. This is intriguing because no haloborated product was detected.



Scheme 2-3 Deoxygenation of Alkoxides with Cyclopropyl- and Vinyl groups.

As noted in entries 9 and 13 (**Table 2-1**), the deoxygenation reaction can lead to undesired chlorinated by-products, which can then lead to difficulties during purification. Therefore, we examined the possibility of using H_2BCl in place of $HBCl_2$, which would result in the formation of an alkoxide bearing only hydrogen atoms on the boron attached to the oxygen (**Scheme 2-4**). This modification successfully inhibited the formation of the chlorinated by-product (entry 9, **Table 2-1**). Little improvement was noted in the reaction using 9-hydroxyfluorene. However, the deoxygenation of the primary alcohols using H_2BCl is remarkable, though the reaction produced only moderate yields.

We also examined the possibility of generating intermediate **1** by mixing benzylic alcohols with monochloroborane (**Scheme 2-3**). The liberation of hydrogen instead of precipitating LiCl, would obviate the use of butyllithium. This would be beneficial when certain base sensitive functional groups (-Br and –CN) are present. The direct reaction produces products in moderate yields.



Z = Br, 65%; Z = CN 50%

Scheme 2-4 Deoxygenation of Alcohols Using Monochloroborane.

2.3 Conclusion

In conclusion, new boron-based deoxygenation methods for converting benzylic alcohols to diarylmethanes are reported. The deoxygenation of alkoxides using dichloroborane not only expands our knowledge of organoboron dihalide chemistry but also provides evidence helpful in understanding the importance of Lewis acidity in previously reported deoxyenation methods. The results of these studies were summarized in the following publication: Deoxygenation of Benzylic Alcohols using Chloroboranes. *Tetrahedron Letters* **2010,** *51,* 853-855.

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

2.4.2 Typical Reaction Procedure

Benzhydrol (276 mg, 1.50 mmol) and dry hexane (10 mL) were placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a stirring bar. The solution was cooled using an ice bath, and *n*-butyllithium (1.6 mmol, 1.0 mL of a 1.6 mmol hexane solution) was added via syringe. The ice bath was removed, and the solution stirred for 20 minutes at room temperature. The solution was then cooled using an ice bath, and boron trichloride (1.5 mmol, 1.5 mL of a 1.0 *M* hexane solution) was added via syringe. The ice bath was removed, and the solution was allowed to stir for two hours at room temperature. The resulting mixture was hydrolyzed with water (20 mL) and extracted with hexanes (3 x 20 mL). The organic layers were combined and dried using anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the product purified by silica gel column chromatography using hexanes as an eluent.

2.4.3 Characterization of Compound 201-212

Diphenylmethane (**201**)[75]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23-7.09(m, 10H), 3.86 (S, 2H. ^{13}C NMR ($CDCl_3$): δ 141.1, 128.7, 128.4, 126.9, 41.7.

(4-Chlorophenyl)phenylmethane (**202**)[76]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.27 (m, 3H), 7.25-7.16 (m, 4H), 7.15-7.11 (m, 2H), 3.96 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 140.5, 139.6, 131.9, 130.2, 128.8, 128.5, 126.3, 41.2.

4,4'-Difluorodiphenylmethane (**203**)[77]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 2H), 6.93 (dd, J = 8.4, 9.2 Hz, 4H), 7.07 (dd, 3J = 8.4 Hz, 5.2 Hz, 4 H). ^{13}C NMR ($CDCl_3$): δ 40.3, 115.4, 130.3, 136.8, 161.7.

(4-Methylphenyl)phenylmethane (**204**)[78]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (m, 2H), 7.33 (m, 2H), 7.24 (s, 4H), 4.09 (s, 2H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 141.6, 138.2, 135.6, 129.3, 129.0, 128.96, 128.6, 126.1, 41.7, 21.1.

2-Methoxydiphenylmethane (**205**)[79]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.23 (m, 6H), 7.12 (m, 1H), 6.93 (m, 2H), 4.04 (s, 2H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 157.4, 141.1, 130.4, 129.7, 129.06,128.35,127.5, 125.8, 120.5, 110.4, 55.4, 35.9.

Bis(4-methoxyphenyl)methane (**206**)[80]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 6H), 3.86 (s, 2 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 7.10 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 40.2, 55.3, 114.0, 129.8, 133.8, 158.0.

1-Benzyl-4-nitrobenzene (**207**)[81]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.35-7.30 (m, 4H), 7.25 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.19-7.16 (m, 2H), 4.08 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 148.8, 146.5, 139.2, 129.6, 128.9, 128.8, 126.7, 123.7, 41.7.

1-Benzyl-4-(benzyloxy)benzene (**208**)[82]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-6.85 (m, 14H), 4.99 (s, 2H), 3.90 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 157.1, 141.5, 137.1, 133.5, 129.8, 128.8, 128.5, 128.4, 127.9, 127.4, 125.9, 114.8, 69.9, 41.0.

4-Benzylphenol (**209**)[79]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 7.07-7.03 (m, 2H), 6.77-6.73 (m, 2H), 3.91 (s, 2H). ^{13}C NMR (75 MHz $CDCl_3$): δ 153.9, 141.5, 133.3, 130.0, 128.8, 128.4, 125.9, 115.3, 40.9.

1,1,1-Triphenylmethane (**210**)[83]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.55 (s, 1H), 7.10-7.12 (m, 6H), 7.20-7.22 (m, 3H), 7.25-7.29 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 56.8, 126.3, 128.3, 129.4, 143.9.

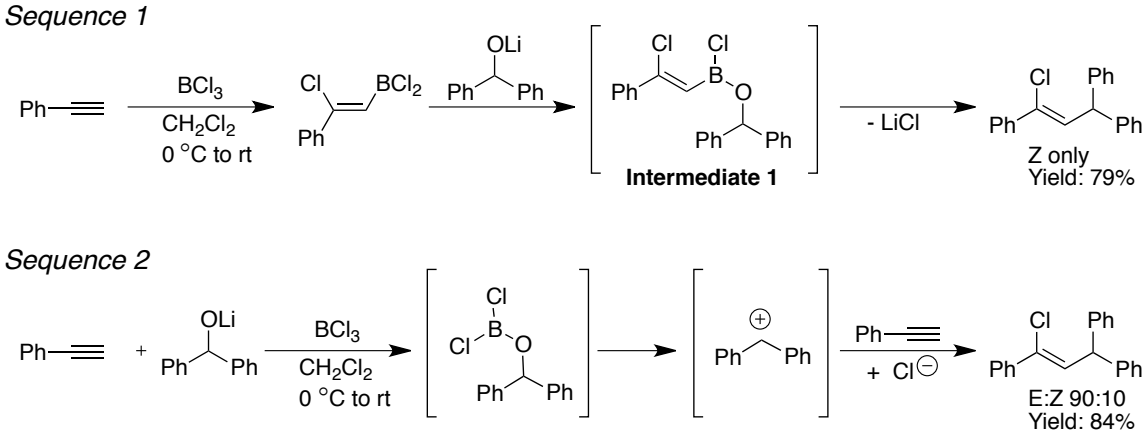
1,1-Diphenylethane (**211**)[84]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.26 (m, 10H), 4.24 (quin, *J* = 7.3 Hz, 1H), 1.74 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 146.3, 128.3, 127.6, 126.0, 44.8, 21.8.

CHAPTER 3 – ALKENYLATION OF BENZYLIC ALCOHOLS WITH BORON TRIHALIDES

3.1 Introduction

Direct carbon bond-forming reactions are essential in organic synthesis. New methods are constantly being developed to assemble the carbon framework in organic molecules. Alkenyl halides, in particular, are versatile substrates as they can be easily converted into other valuable compounds;[86,87] however, the availability of alkenyl halides is low and they are often costly to produce.[88] Due to their diversity, availability, and low cost, benzylic alcohols are attractive starting materials in the synthesis of alkenyl halides.[88] Several research groups, including our own, have developed new routes to haloalkenes using BCl_3,[89] $TiCl_4$,[69] $FeCl_3$,[69] $ZnCl_2$,[90] and Ru.[91] Very few of these methods for producing alkenyl halides are useful due to significant practical drawbacks including: drastic reaction conditions, solvent compatibility, expensive reagents, incompatibility with functional groups, long reaction times, the use of toxic chemicals, and the production of large amounts of waste limit their application in industrial processes.[92] Development of simple methods for producing alkenyl halides is therefor attractive for large-scale syntheses.

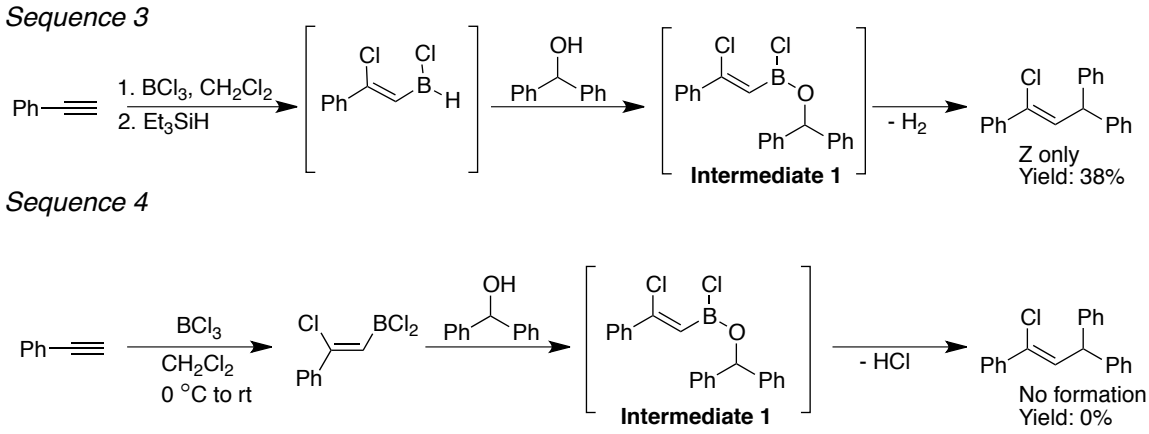
In 2005, our research group reported the alkenylation of various allylic,[93] propargylic,[13] and benzylic alkoxides[12] using boron trihalides. In these reactions, alkenylation involves C-O bond cleavage of an alkoxides followed by nucleophilic addition of (*Z*)-halovinylboron dihalide (Sequence 1, **Scheme 3-1**). In all cases, the *Z* stereoisomer obtained was found to be dependent upon the preformation of a (*Z*)-halovinylboron halide prior to the addition of alkoxides.[12] It was later realized that



Scheme 3-1 Stereochemical Modification via Modification of Reagent Addition Sequences.

addition of boron trihalides to a mixture of alkoxide and alkyne results in (*E*)-alkenes as the major product (Sequence 2, **Scheme 3-1**). In all cases, the reaction proceeds smoothly at room temperature within a few hours. The biggest limitation in these reactions is the use of butyllithium, a strong base that requires proper handling and can hinder the use of base sensitive functional groups in the starting materials. If butyllithium could be omitted, these boron alkenylation reactions would be more attractive to industries that prefer not to use dangerous amounts of butyllithium in large-scale reactions. It would

also allow base sensitive functional groups to be used as starting materials. In the previous chapter, dehydroxylation occurred using H_2BCl with benzylic alcohol. By liberating hydrogen in place of precipitating LiCl, the necessary intermediate was formed. We decided to determine if the same strategies could be applied to alkenylation reactions (**Scheme 3-2**).



Scheme 3-2 Modifications of Alkenylation to Eliminate Butyllithium.

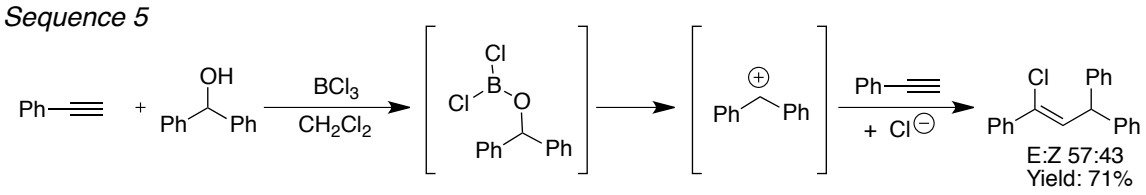
3.2 Results and Discussion

Initially, we thought intermediate **1** (**Scheme 3-2**) could be prepared using triethylsilane to convert (*Z*)-halovinylboron dihalides to (*Z*)-halovinychloroboranes. Triethylsilane is known to replace hydrogen for chlorine in boron halides by generating chlorotriethylsilane[94]. The addition of an alcohol to a halovinylchloroborane should liberate hydrogen gas to generate intermediate **1** (Sequence 3, **Scheme 3-2**). By analogy to our previous work, this would generate intermediate **1** required for alkenylation (Sequence 1, **Scheme 3-1**). The reaction did form *Z* alkenes but in low yields due to the

formation of chlorodiphenylmethane and diphenylmethane as by-products. The observed yields can be explained in a variety of ways. Stoichiometric control of the reagents is difficult because of the reactivity of BCl_3 with moisture and air. Boron trichloride can also react with the triethylsilane and equilibrate to produce a mixture of chloroboranes and dichloroboranes, both reagents were used successfully in the previous chapter to deoxygenate benzylic alcohols.

Due to low yields using halovinylchloroboranes, our attention was turned toward alternative pathways to intermediate **1**. The halovinylchloroboranes were chosen to facilitate the formation and liberation of hydrogen gas, but the same intermediate **1** could be reached by a reaction involving halovinylboron dihalide and elimination of HCl (Sequence 4, **Scheme 3-2**). This method was examined under various conditions, solvents and temperatures. Surprisingly, no alkene product was formed and only chlorobenzhydrol was recovered. This seemed to indicate the alkenyl species was not migrating as expected. Likely, complete removal of HCl was not possible and its presence could significantly reduce the nucleophilicity of the alkenylboron chloride reagent.

Rather than preforming the halovinylboron dichloride reagent, boron trichloride was added to a mixture of benzhydrol and phenylacetylene (Sequence 5, **Scheme 3-3**). At room temperature, this method yielded the desired alkene (71%) as a 57:43 mixture of *E* and *Z* isomers (**Figure 3-1**). Solvent and temperature play important roles in the stereochemical outcome. The same reaction at -78 °C produces the alkenes (74%) with a 94:6 *E*:*Z* ratio (**Table 3-1**).



Scheme 3-3 Boron Trichloride Addition to a Mixture of Benzhydrol and Phenylacetylene.

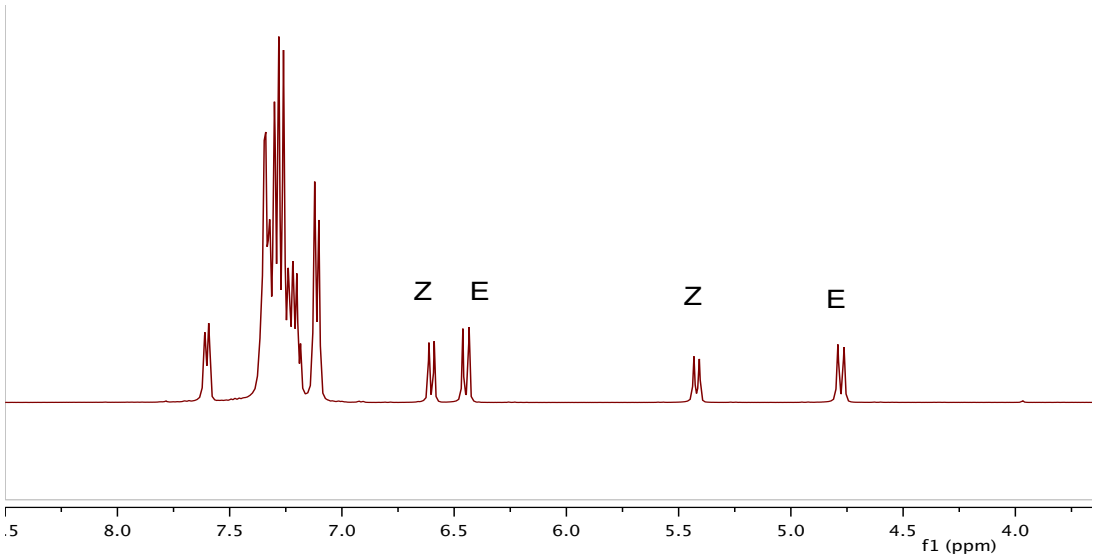
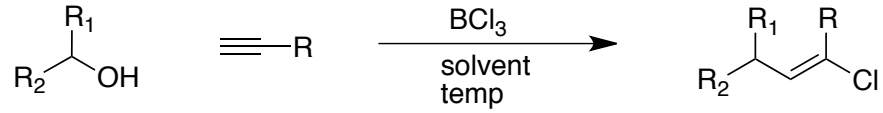


Figure 3-1 ^{1}H NMR of compound **301** and **302** showing a mixture of E and Z isomers

Table 3-1 Boron Trichloride Mediated Coupling of Benzylic Alcohols with Alkynes.[a]



Entry	R_1	R_2	R	Solvent	Temp.[b]	Prod.	*E*:*Z*[c]	Yield (%)[d]
1	Ph	Ph	Ph	DCM	-78	**301**	94:6	74
2	Ph	Ph	Ph	DCM	rt	**301**	57:43	71
3	Ph	Ph	Ph	DCM	reflux	**301**	36:64	76
4	Ph	Ph	Ph	Hxn	rt	**301**	5:95	55
5	Ph	Ph	Ph	Hxn	reflux	**301**	5:95	74
6	4-Cl	Ph	Ph	DCM	-78	**302**	65:35	49
7	4-Cl	Ph	Ph	DCM	rt	**302**	18:82	50
8	4-Cl	Ph	Ph	DCM	reflux	**302**	5:95	88
9	4-Cl	Ph	Ph	Hxn	rt	**302**	12:88	10
10	4-$OMeC_6H_4$	4-$OMeC_6H_4$	Ph	DCM	-78	**303**	82:18	10
11	4-$OMeC_6H_4$	4-$OMeC_6H_4$	Ph	DCM	rt	**303**	74:26	24
12	4-$OMeC_6H_4$	4-$OMeC_6H_4$	Ph	DCM	reflux	**303**	82:18	78
13	4-$OMeC_6H_4$	4-$OMeC_6H_4$	Ph	Hxn	reflux	**303**	78:22	34
15	4-MeC_6H_4	Ph	Ph	DCM	reflux	**304**	65:35	76
16	4-BrC_6H_4	Ph	Ph	DCM	reflux	**305**	13:87	86
17	4-$NO_2C_6H_4$	Ph	Ph	DCM	reflux	-	-	0[e]
18	4-$CF_3C_6H_4$	Ph	Ph	DCM	reflux	-	-	0[e]

[a]Reactions carried out in the solvent and at the temperature indicated in the table using 1.1 equivalents of phenylacetylene and 1.1 BCl_3 (see experimental section for details).
[b]Room temperature is considered 25 °C. Dichloromethane refluxes at 40 °C. Hexane refluxes at 69 °C.
[c]*E*:*Z* ratio determined by NMR.
[d]Isolated yield based on alcohol.
[e]Chlorodiphenylmethane was isolated

At dichloromethane reflux temperatures (40 °C), the *Z* isomer was favored (76%; 36:64 *E*:*Z*). When the solvent was changed to hexane and refluxed, the *Z* isomer was more favored, (74%, 5:95 *E*:*Z*). However, when the reaction was carried out in hexane at room temperature, the yield fell from 74% to 55%. This is likely due to the low solubility of benzhydrols in hexane.

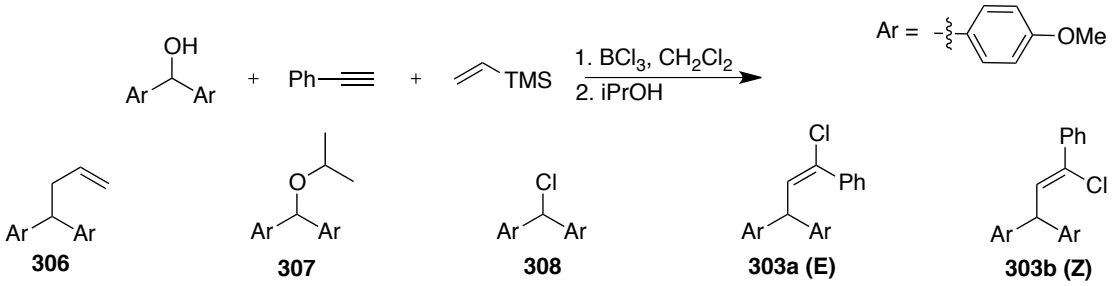
This new method was applied to several substituted benzhydrols to test its scope and limitations. Electron-donating groups such as alkyl-, halo-, and methoxy- ethers are well tolerated and lead to good yields. This is beneficial because it is known that BCl_3 can be used to deprotect methyl ethers.[7d] Unfortunately, electron-withdrawing groups, such as nitro- and trifluoromethyl, led to poor yields of alkene and high yields of chlorobenzhydrol.[92] This is likely due to the electron-withdrawing groups ability to destabilize carbocations. Stereochemical outcome of the alkene is unique to the benzhydrol and can be altered to some degree with temperature and solvent.

3.3 Mechanistic Study

Failure of benzhydrols containing electron-withdrawing groups to react was expected and supports a cationic mechanism;[92] however, failure of the dimethoxybenzhdroyl was puzzling as it should produce a more stable carbocation, that should lead to the desired product. Instead of alkenylation, dimethoxyisopropylbenzhydrol was found to be the major product. The isopropyl substitution occurred unexpectedly during the quench with 2-propanol, which was chosen over the water to prevent freezing at low temperatures.

To help delineate the mechanism, a study was devised using allyltrimethylsilane, a useful a carbocation scavenger. A competition experiment was designed by placing benzhydrol, phenylacetylene, and allyltrimethylsilane together in dichloromethane.[62] After the temperature was adjusted accordingly, boron trichloride solution in hexane (1.0 *M*) was added slowly. After 5 hours, a mixture of products was detected by NMR. Allyl substitution was the major product followed by isopropyl substitution. The desired alkene, both *E* and *Z*, were formed in trace amounts at -78 °C. The formation of the *Z* isomer is intriguing because the reaction was run below the temperature needed for chloroboration to occur. This evidence supports the postulation that the *Z* isomer was formed via a carbocation mechanism and not chloroboraton of phenylacetylene followed by alkenyl migration.[62] Likely, low yields are a consequence of a stable carbocation generated from dimethoxybenzhydrol not being sufficiently reactive toward a weak nucleophile like phenylacetylene at low temperatures. When a stronger nucleophile such as allyltrimethylsilane or isopropanol is added, the reaction proceeds smoothly and generates higher yields (**Table 3-2**).

Table 3-2 Relative Ratios of Products from the Competitive Reaction with Allyltrimethylsilane.[a,b]

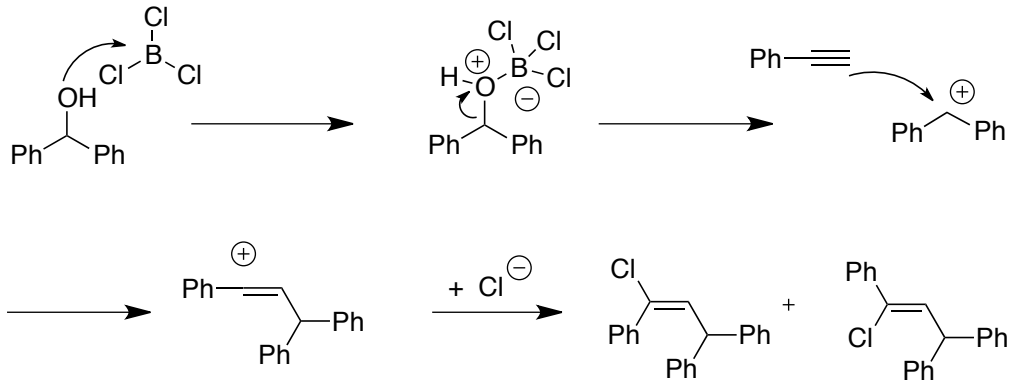


Entry	Temp. (°C)	**306** (%)	**307** (%)	**308** (%)	**303a** (%)	**303b** (%)
1	-78	-[c]	54	30	13	3
2	-40	-[c]	64	30	5	1
3	0	-[c]	67	18	10	5
4	-78	56	30	8	5	1
5	0	95	1	0	3	1

[a]Reactions carried out on 1.0 mmol scale using 1.1 equivalents of BCl_3 and allowed to stir at the indicated temperature for a minimum of 5 hours (See Experimental Details).
[b]Relative ratios determined by ^1H NMR.
[c]Allytrimethylsilane was omitted.

3.4 Conclusion

In summary, a method for preparing trisubstituted alkenyl halide derivatives without the use of butyllithium has been developed. This reaction appears tunable as stereoselectivity modifications can be achieved by changes in temperature and solvent. The mechanistic study supports a carbocation mechanism (**Scheme 3-4**) and confirms that the presence of Brønsted acid reduces the nucleophilicity of preformed halovinylboron dichlorides. These findings add to our knowledge of carbocation chemistry and should help facilitate the discovery of new boron transformation reactions.



Scheme 3-4 Proposed Mechanism of Boron Trichloride Mediated Direct Alcohol-Alkyne Coupling.

3.5 Experimental Details

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

3.4.2 Typical Reaction Procedure

Phenylacetylene (153mg, 1.50 mmol), benzhydrol (276 mg, 1.50 mmol), and dry dichloromethane (10 mL) were placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a stirring bar. The solution was adjusted to the desired temperature and boron trichloride (1.5 mmol, 1.5 mL of 1.0 *M* hexane solution) was added via syringe. The solution was allowed to stir 5 hours at the appropriate temperature before lowering it to room temperature. The resulting mixture was concentrated in vacuo and the product was purified by silica gel column chromatography using dichloromethane and hexane (1:10) as eluent.

3.4.3 Characterization of Compound 301-308

(*Z*)-1-Chloro-1,3,3-triphenyl-1-propene (301a)[17]: ^{1}H NMR (300MHz, $CDCl_3$): δ 7.56–7.59 (m, 2H), 7.17– 7.30 (m, 13H), 6.59 (d, *J* = 9.47 Hz, 1H), 5.42 (d, *J* = 9.47 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 142.9,137.8, 133.4, 129.5, 128.6, 128.3, 126.6, 50.8.

(*E*)-1-Chloro-1,3,3-triphenylprop-1-ene (301b)[17]: ^{1}H NMR (300MHz, $CDCl_3$): δ 7.08-7.36 (m, 15H), 6.45 (d, 1H, *J* = 11.0 Hz), 4.78 (d, 1H, *J* = 11.0 Hz). ^{13}C NMR ($CDCl_3$): δ 143.3, 136.9, 131.5, 131.4, 128.9, 128.6, 128.3, 128.1, 126.6, 50.7.

(*E*)-1-Chloro-1,3-diphenyl-3-(4-chloro)phenyl-1-propene (302a)[12]: ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.96-7.34 (m, 14H), 6.38 (d, 1H, *J* = 11.0 Hz), 4.74 (d, 1H, *J* = 11.0 Hz). ^{13}C NMR ($CDCl_3$): δ 142.7, 141.8, 136.7, 131.9, 130.8, 129.4, 128.9, 128.7, 128.5, 128.4, 127.9, 126.8, 50.1. Anal. calcd. for $C_{21}H_{16}Cl_2$: C, 74.35; H, 4.75. Found: C, 74.49; H, 4.70.

(*Z*)-1-Chloro-1,3-diphenyl-3-(4-chloro)phenyl-1-propene (302b)[12]: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.56–7.60 (m, 2H), 7.13–7.35 (m, 12H), 6.53 (d, *J* = 9.40 Hz, 1H), 5.36 (d, *J* = 9.40 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 142.5, 141.4, 137.7, 133.9, 132.4, 129.6, 128.9, 129.8, 128.7, 128.3, 128.2, 126.8, 126.6, 50.2. Anal. calcd. for $C_{21}H_{16}Cl_2$: C, 74.35; H, 4.75. Found: C, 74.39; H, 4.87.

(*E*)-1-Chloro-1-phenyl-3,3-di(4-methoxyphenyl)prop-1-ene (303a)[17]: ^{1}H 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.

(*Z*)-1-Chloro-1-phenyl-3,3-di-(4-methoxy)phenyl-1-propene (303b)[17]: ^{1}H NMR: δ 7.59– 7.62 (m, 2H), 7.31–7.35 (m, 3H), 7.17 (d, J = 8.61 Hz, 4H), 6.85 (d, J = 8.61 Hz, 4H), 6.54 (d, J = 9.58 Hz, 1H), 5.31 (d, J = 9.58 Hz, 1H), 3.78 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 158.2, 137.9, 135.4, 130.1, 129.2, 128.6, 128.3, 126.6, 113.4, 55.2, 49.1. Anal. calcd. for $C_{23}H_{21}ClO_2$: C, 75.71; H, 5.80. Found: C, 75.47; H, 5.96.

(*E*)-1-Chloro-3-*p*-tolylprop-1-ene-1,3-diyl)dibenzene (304a): ^{1}H NMR: (250 MHz, $CDCl_3$): δ 6.97-7.37 (m, 14H), 6.44 (d, 1H, J = 11.0 Hz), 4.74 (d, 1H, J = 11.0 Hz), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 143.5, 140.3, 136.9, 136.1, 131.6, 131.2, 129.3, 128.8, 128.6, 128.3, 128.0, 127.9, 126.5, 50.3, 20.9. Anal. calcd. for $C_{22}H_{19}Cl$: C, 82.87; H, 6.01. Found: C, 83.87; H, 6.22.

(*Z*)-1-Chloro-3-*p*-tolylprop-1-ene-1,3-diyl)dibenzene (304b): ^{1}H NMR: (250 MHz, $CDCl_3$): δ 6.97-7.11 (m, 14H); 6.37 (d, 1H, J = 9.5 Hz), 4.72 (d, 1H, J = 9.5 Hz), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 143.5, 140.3, 136.9, 136.1, 131.6, 131.2, 129.3, 128.8, 128.6, 128.3, 128.0, 127.9, 126.5, 50.3, 20.9. Anal. calcd. for $C_{22}H_{19}Cl$: C, 82.87; H, 6.01. Found: C, 83.87; H, 6.22.

(*E*)-1-Chloro-1,3-diphenyl-3-(4-bromo)phenyl-1-propene (305a): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4-6.97 (m, 14H); 6.38 (d, 1H, *J* = 11.1 Hz); 4.74 (d, 1H, *J* = 11.1 Hz). ^{13}C NMR ($CDCl_3$): δ 142.7, 141.9, 136.6, 131.9, 130.8, 129.4, 128.9, 128.7, 128.5, 128.4, 127.9, 126.8, 50.1. HRMS calcd. for $C_{21}H_{16}BrCl$ 382.0124, found 382.0186.

(*Z*)-1-Chloro-1,3-diphenyl-3-(4-bromo)phenyl-1-propene (305b): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.11 (m, 14H); 6.52 (d, 1H, *J* = 9.5 Hz); 4.74 (d, 1H, *J* = 9.5 Hz). ^{13}C NMR ($CDCl_3$): δ 142.4, 142.0, 137.7, 133.9, 131.7, 129.4, 128.7, 128.3, 128.2, 126.8, 126.6, 120.5, 50.2. HRMS calcd. for $C_{21}H_{16}BrCl$ 382.0124, found 382.0186.

4,4-Di-(4-methoxyphenyl)-1-butene (306)[95]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.8 Hz, 4H), 7.06 (d, J = 7.8 Hz, 4H), 6.08–5.92 (m, 1H), 5.35–5.16 (m, 2H), 4.18 (t, J = 7.8 Hz, 1H), 3.97 (s, 6H), 3.01 (t, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 136.9, 128.6, 116.0, 113.6, 54.9, 49.4, 40.2; EIMS m/z 268 (M^+), HRMS calcd. for $C_{18}H_{20}O_2$ 268.1463, found 268.1465.

1,1'-[(1-Methyethoxy)methylene]bis[4-methoxy-benzene] (307)[96]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, J = 8.76 Hz, 2H), 6.98 (d, J = 8.76 Hz, 2 H), 5.57 (s, 1 H), 3.84 (s, 6 H), 3.73-3.83 (m, 1 H), 1.36 (d, J = 6.11 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 135.8, 128.6, 114.0, 79.9, 69.0, 55.4, 22.6.

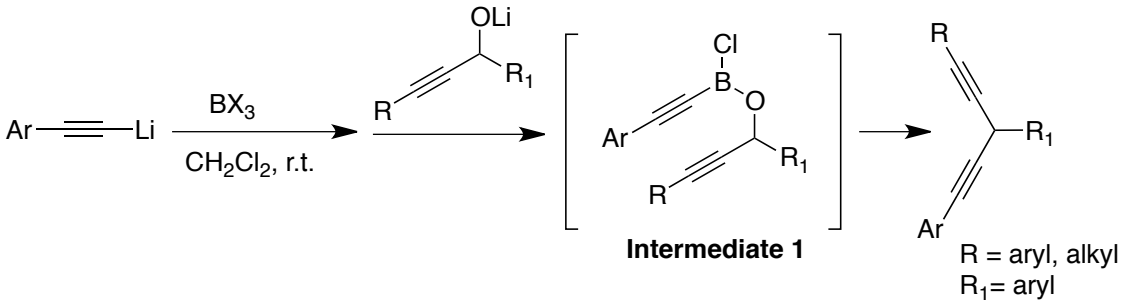
1,1'-(Chloromethylene)bis(4-methoxybenzene) (308)[97]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82–7.26 (m, 8H), 6.26 (s, 1H), 3.78 and 3.89 (2s, 6H). MS (m/z %): 264, 262, 227(100), 197(14), 153(12), 77(16).

CHAPTER 4 – DIALKYNYNLATION OF ARYL ALDEHYDES USING DIALKYNYLBORON CHLORIDE

4.1 Introduction

1,4-Diynes are valuable monomers for the construction of carbon networks due to their high carbon content.[98] In addition, 1,4-diynes are useful intermediates in the preparation of pyrroles[99] and furans[100] as well as skipped dienes.[101] As an example, a large number of polyunsaturated fatty acids were synthesized by using 1,4-diynes as intermediates followed by a catalytic Lindlar partial reduction reaction.[102] The principal approach to 1,4-diynes[103] involves cross-coupling of propargylic electrophiles with copper-acetylides.[104,105] The requisite acetylenic copper species are usually generated *in situ* from combinative systems, such as alkynylmetals /copper (I) salts,[106] terminal acetylene/base/copper (I) salts,[101a, 107-108] and TMS-protected acetylene/fluoride source/ copper (I) salts.[109] Although widely employed, the copper-mediated cross-coupling approach has several limitations. First, the required basic conditions can induce isomerization of the product 1,4-diyne to the inseparable alkynylallenes.[110] Second, functional group incompatibility caused by the highly nucleophilic alkynyl metals restrict their applications in the synthesis of complex organic molecules. Finally, the reaction work-up can be tedious if a stoichiometric amount of copper salt is used. In addition to the copper-mediated cross-coupling reactions, scattered examples of Lewis acid-mediated coupling of soft nucleophiles (alkynylalane[111,112] and alkynylsilane[112,113]) with propargylic electrophiles have been reported.

In 2006, we discovered a novel route to 1,4-diynes via the coupling of propargyl alkoxides with alkynylboron dichlorides.[89,93] In this reaction, alkynylboron dichloride acts as both a Lewis acid and reactant (**Scheme 4-1**). The acidic reaction conditions successfully circumvent the isomerization problem that prevailed the in earlier reported methods. The reaction of lithium propargyl alkoxide with alkynylboron dichloride generates the unstable boron complex intermediate **1**. The subsequent rearrangement then produces 1,4-diynes. The advantage of this method is the ability to perform tandem reaction, using propargyl alkoxides generated *in situ* from the reaction of aldehydes with alkynylmetal reagents. However, the use of alkynylmetal reagents required for the preparation of the starting propargyl alkoxides limits the use of the reaction when certain functional groups are present. The use of butyllithium in this reaction restricts use on a large scale.



Scheme 4-1 Previously Reported Alkynylation of Propargylic Alkoxides.

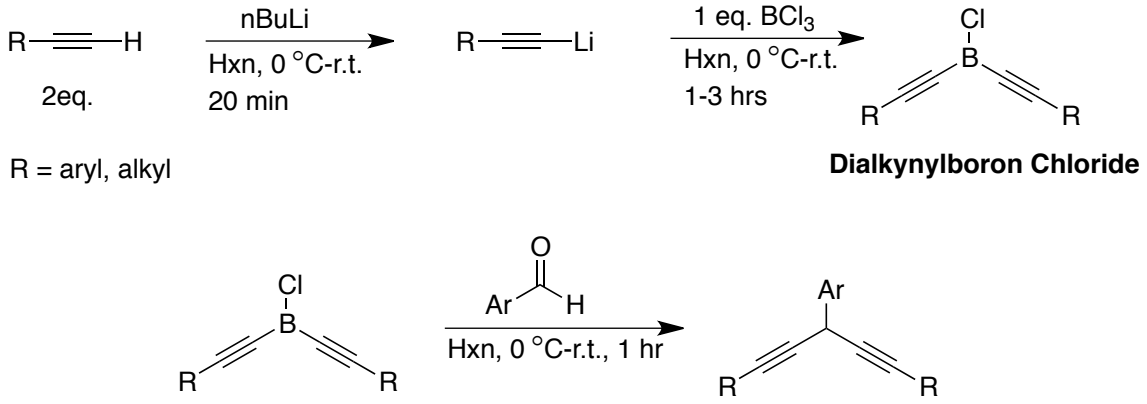
Encouraged by these results, we investigated the feasibility of carrying out a double alkynylation through a similar dialkynylboron chloride intermediate. Herein, we report a novel route to 1,4-diynes via dialkynylation of aryl aldehydes using dialkynylboron chlorides. The transition-metal-free nature of the reaction makes it quite attractive.

4.2 Results and Discussion

Alkynylboranes are known to add to non conjugated aldehydes and more slowly to ketones, to give the corresponding propargyl alcohols.[114,115] However, to the best of our knowledge, the reaction of alkynylboron halides with aldehydes has never been explored. Encouraged by our previous studies, especially the dialkenylation of aldehydes using dialkenylboron halides,[62] we felt that aldehydes would react with dialkynylboron chlorides to form dialkynylated products and provide an efficient route to 1,4-diynes. The reaction begins with a Grignard-like addition of dialkynylboron chloride to the aldehyde to generate propargyloxoboron intermediate **1**, followed by a rearrangement to afford the product 1,4-diyne (**Scheme 4-2**). Since organoboron derivatives exhibit little reactivity toward a variety of functional groups, this novel method provides a route to 1,4-diynes otherwise not attainable using reported methods.

The required dialkynylboron chloride is readily synthesized by first deprotonating a terminal alkyne (2.0 eq.) with butyllithium followed by addition of one equivalent of BCl_3 (**Table 4-1**). The resulting dialkynylboron chloride is used directly without further purification. The results indicate that the reaction of dialkynylboron chlorides with aldehydes proceeds smoothly at room temperature to generate the desired 1,4-diynes in good to excellent yields. Functional groups such as, –Br, -Cl, -OMe, and $–NO_2$ are unaffected under the reaction conditions. The lower yields when using 4-nitrobenzaldehyde supports the involvement of a carbocation (entry 10, **Table 4-1**). This method is notable for its simplicity and mildness.

Table 4-1 Dialkynylation of Aryl Aldehydes Using Dialkynylboron Chloride.[a]

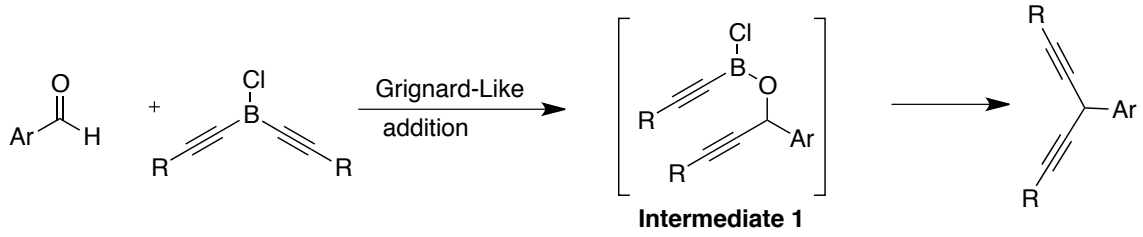


Entry	Ar	R	Product	Yield (%)[b]
1	Ph	Ph	**401**	76
2	4-MePh	Ph	**402**	87
3	4-BrPh	Ph	**403**	67
4	4-ClPh	Ph	**404**	85
5	2-FPh	Ph	**405**	82
6	4-FPh	Ph	**406**	90
7	2-MePh	Ph	**407**	75
8	3,4-(OCH_2O)Ph	Ph	**408**	63
9	3-MeOPh	Ph	**409**	53
10	4-NO_2Ph	Ph	**410**	42
11	2-Naphthyl	Ph	**411**	50
12	4-ClPh	*n*-C_4H_9	**412**	25

[a]Reactions carried out on 1 mmol scale using 2 equivalents of phenylacetylene and allowed to react until complete (1-3 hrs). See Experimental Details.
[b]Isolated yield based upon aldehyde.

4.3 Conclusion

In summary, a novel dialkynylation reaction of aryl aldehydes in the absence of transition metal catalysts has been developed using easily prepared dialkynylboron chlorides. The new method provides an efficient route to symmetric 1,4-diynes. Though a thorough mechanistic study was not conducted, the dialkynylation presumably proceeds via Grignard like addition to the carbonyl followed by a cationic rearrangement of intermediate **1** to afford the 1,4-diyne (**Scheme 4-2**). This study also extends the knowledge base related to carbonyl addition chemistry and complements the well documented 1,2-addition reactions of aldehydes with organometallic reagents (RMgX, RZnX, and 9-BBN derivatives). The results of these studies were summarized in the following publication: Dialkynylation of aryl aldehydes using dialkynylboron chlorides: Transition-metal-free route to 1,4-diynes. *J. Organomet. Chem*., **2012**, *722*, 164-166.



Scheme 4-2 Dialkynylation of Aryl Aldehydes Using Dialkynylboron Chloride.

4.4 Experimental Details

4.4.1 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). ^{1}H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, respectively. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents.

4.4.2 Typical Reaction Procedure

Phenylacetylene (306 mg, 3.00 mmol) and 10 mL of dry hexanes were placed in a dry argon-flushed 50 mL round-bottomed flask equipped with a stirring bar. The solution was cooled using an ice bath, and *n*-butyllithium (1.6 mmol, 1 mL of 1.6 *M* hexane solution) was added via syringe. The ice bath was removed, and the solution was allowed to stir for 20 minutes at room temperature. The solution was then cooled using an ice bath, and boron trichloride (1.5 mmol, 1.5 mL of a 1.0 *M* hexane solution) was added via syringe. The ice bath was removed and the solution stirred for 20 minutes at room temperature. The solution was cooled again using an ice bath, and benzaldehyde (159 mg, 1.5 mmol) was added as a solution in 2 mL of dry hexane. The ice bath was removed, and the solution allowed to stir for 1 hour at room temperature or to completion as indicated by TLC. The resulting mixture was concentrated *in vacuo*, and the product isolated using silica gel column chromatography with hexanes as an eluent.

4.4.3 Characterization of Compound 401-412

1,3,5-Triphenyl-1,4-pentadiyne (401)[116]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.20 (s, 1H), 7.26-7.32 (m, 6H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.42-7.52 (m, 4H), 7.67 (d, *J* = 7.7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 22.64, 82.79, 86.58, 122.95, 127.29, 127.51, 128.19, 128.71, 131.78, 137.95.

1-(4-Methylphenyl)-3,3-diphenyl-1-propyne (402)[89]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07–7.45 (m, 14H), 5.19 (s, 1H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 142.2, 141.9, 138.0, 131.5, 128.9, 128.6, 128.4, 128.0, 127.2, 126.8, 89.4, 80.0, 43.7, 21.3.

1,5-Diphenyl-3-(4-bromophenyl)-1,4-pentadiyne (403)[117]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (s, 1H), 7.29-7.35 (m, 6H), 7.48-7.51 (m, 4H), 7.52-7.59 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 29.66, 83.16, 85.92, 121.51, 122.70, 128.26, 128.40, 129.08, 131.78 , 137.09.

(3-(4-Chlorophenyl)penta-1,4-diyne-1,5-diyl)dibenzene (404)[116]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (s, 1 H), 7.30-7.33 (m, 6 H), 7.36-7.38 (m, 2 H), 7.46-7.49 (m, 4 H), 760-7.62 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 29.8, 83.3, 86.2, 122.9, 128.5, 128.6, 128.9, 129.1, 132.0, 133.6, 136.6.

1,5-Diphenyl-3-(2-fluorophenyl)-1,4-pentadiyne (405)[89]: ^{1}HNMR (250 MHz, $CDCl_3$): δ 7.07-7.82 (m, 14 H), 5.42 (s, 1H) , 7.09-7.49 (m, 12 H), 6.80 (d, J = 8.0 Hz, 1 H), 5.94 (s, 2H), 5.10 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 161.8, 157.9, 131.8, 129.7, 129.5, 129.3, 129.2, 128.3, 128.2, 127.3, 126.6, 126.4, 125.6, 125.4, 125.4, 124.5, 122.8, 119.0, 115.7, 115.4, 85.5, 82.3, 23.9. HRMS for $C_{23}H_{15}F$: 310.1158. Found: 310.1166.

3-(4-Fluorophenyl)penta-1,4-diyne-1,5-diyl)dibenzene (406)[116]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.18 (s, 1 H), 7.05-7.09 (m, 2 H), 7.30-7.32 (m, 6 H), 7.47-7.49 (m, 4 H), 7.63-7.65 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 29.6, 83.2, 86.5, 115.8, 123.0, 128.5, 128.6, 129.15, 132.0, 133.9, 162.4.

1,5-Diphenyl-3-(2-methylphenyl)-1,4-pentadiyne (407)[116]: ^{1}H NMR (300 MHz, $CDCl_3$): 2.56 (s, 3H), 5.23 (s, 1H), 7.20-7.32 (m, 9H), 7.40-7.48 (m, 4H), 7.78 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 19.31, 28.22, 82.45, 86.30, 123.02, 126.46, 127.64, 127.69, 128.17, 130.79, 131.75, 135.86, 136.11.

1,5-Diphenyl-3-(benzo[d][3,4]dioxole)-1,4-pentadiyne (408): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09-7.49 (m, 12 H), 6.80 (d, J = 8.0 Hz, 1 H), 5.94 (s, 2 H), 5.10 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 147.9, 147.0, 131.8, 128.2, 122.9, 120.5, 108.2, 108.0, 101.2, 86.6, 82.7, 29.8. HRMS for $C_{24}H_{16}O_2$: 336.1150. Found: 336.1162.

1,5-Diphenyl-3-(3-methoxyphenyl)-1,4-pentadiyne (409): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 7.7 Hz, 1 H), 7.44-7.46 (m, 4 H), 7.22-7.32 (m, 7 H), 6.39-7.02 (m, 2 H), 5.51 (s, 1 H), 3.89 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 156.1, 131.8, 128.8, 128.6, 128.0, 123.2, 120.9, 110.9, 87.2, 81.3, 55.8, 24.0. HRMS for $C_{24}H_{18}O$: 322.1358. Found: 322.1369.

1,5-Diphenyl-3-(4-nitro)-1,4-pentadiyne (410): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, J = 8.6, 2 H), 7.52-7.28 (m, 12 H), 4.74 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 148.1 145.2, 131.9, 129.4, 128.5, 124.1, 123.99, 89.9, 84.9, 30.1. HRMS for $C_{23}H_{15}NO_2$: 337.1103. Found: 337.1198.

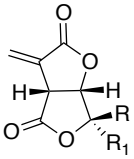
1,5-Diphenyl-3-(2-naphthyl)-1,4-pentadiyne (**411**)[117]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.35 (s, 1H), 7.28-7.33 (m, 6H), 7.46-7.53 (m, 7H), 7.77 (dd, *J* = 8.7 Hz, *J* = 1.8 Hz, 1H), 7.83-7.90 (m, 2 H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 30.33, 83.07, 86.54, 122.96, 125.61, 125.81, 126.06, 126.30, 127.66, 128.02, 128.23, 128.25, 128.59, 131.84, 132.79, 133.41, 135.33.

1,5-Di(*n*-butyl)-3-(4-chlorophenyl)-1,4-pentadiyne (**412**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.32 (m, 4 H), 6.37 (s, 1H), 5.10 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 147.9, 147.0, 131.8, 128.2, 122.9, 120.5, 108.2, 108.0, 101.2, 86.6, 82.7, 29.8. HRMS for $C_{19}H_{23}Cl$: 286.1488. Found: 286.1503.

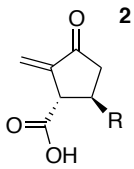
CHAPTER 5 – TOWARD THE SYNTHESIS OF NATURALLY OCCURING LACTONES

5.1 Introduction

Naturally occurring α-methylenebis-γ-lactones represent the biologically active component of many fungal strains including *Xylaria obovata* (**1b**),[118] *Penicillium canadense* (**1d**, **1i**),[119] *Sporothrix sp* (**1g**),[120] and *Aspergillus avenaceus* (**1h**)[121] (**Figure 5-1**). Many more natural products contain similar structures such as a saturated version in (+)-dihydrocanadensolide[122] or α-methylene-γ-lactone acids (**2**), which feature a single lactone.[123,124] Recently, α-methylene-γ-lactone derivatives have received attention due to their biological activity.[125] In particular sporothriolide **1g**, has shown antibacterial, antifungal, and phytotoxic proprieties.[120] The biological activity is likely a result of a key structural feature, a Michael-acceptor.[125a] The olefin adjacent to the carbonyl group has a propensity for Michael-type addition reactions. Due to their unique stereochemistry, with an *exo*-methylene group, three contiguous stereogenic centers, and interesting biological activity, many research groups (including our own) have directed attention toward their synthesis (**Figure 5-2**).



1 a. R = R_1 = H
b. R = H, R_1 = Ethyl ; **xylobovide**
c. R = Ethyl, R_1 = H
d. R = H, R_1 = Butyl ; **canadensolide**
e. R = Butyl, R_1 = H ; **nor-canadensolide**
f. R = Hexyl, R_1 = H ; **sporothriolide**
g. R = H, R_1 = Hexyl
h. R = Octyl, R_1 = H ; **avenociolide**
i. R = H, R_1 = Octyl ; **isoavenociolide**



2 a. R = Pentyl
b. R = Undecyl ; **nephrosterinic acid**
c. R = Tridecyl ; **protolichesterinic acid**

Figure 5-1 Natural Products Containing α-Methylene-γ-lactones

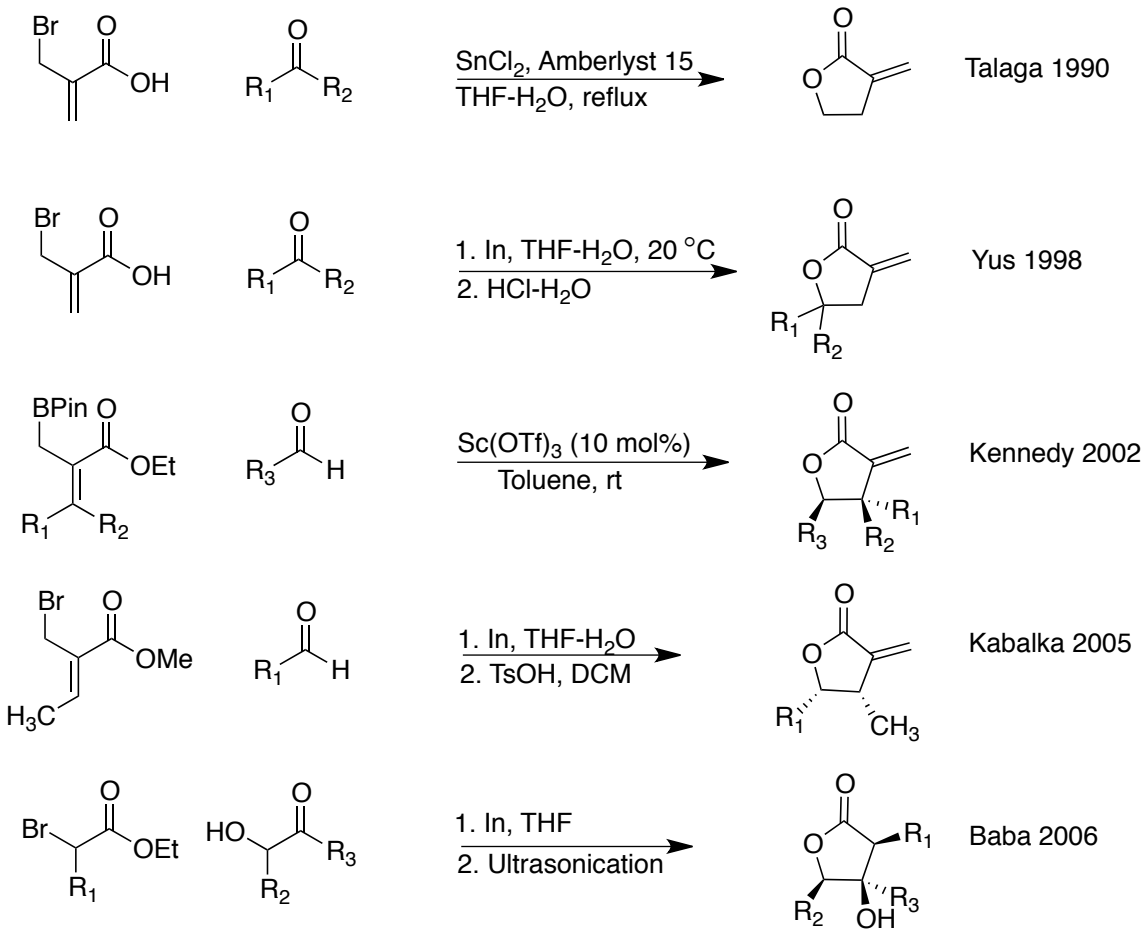


Figure 5-2 Methodologies for the Synthesis of α-Methylenebis-γ-Lactones.

A variety of synthetic methodologies for preparing α-methylene-γ-lactones have been developed; the most common method involves the reaction of allylic derivatives with various carbonyl compounds and a metal (**Figure 5-2**).[125a] Successful techniques have employed zinc,[126,127] tin,[128-130] lithium,[131] indium,[132] and allylborates,[61] for the synthesis of α-methylene-γ-lactones. However, far fewer methods have been developed for the installation of the second lactone to form the α-methylenebis-γ-lactone. The few total syntheses of natural *bis*-lactones utilize tungsten complexes,[133] radical couplings,[134] cyclopropanation of glycals,[135] and a Johnson-Claisen rearrangement[136] (**Figure 5-3**).

While all of these syntheses are good examples of methodology implication, they are lengthy or use exotic expensive reagents. Recent success in the synthesis of the α-methylene-γ-lactone eupomatilone 5 inspired us to investigate chloroborane chemistry and a bislactonization to form the natural product sporothriolide **1g**.[60]

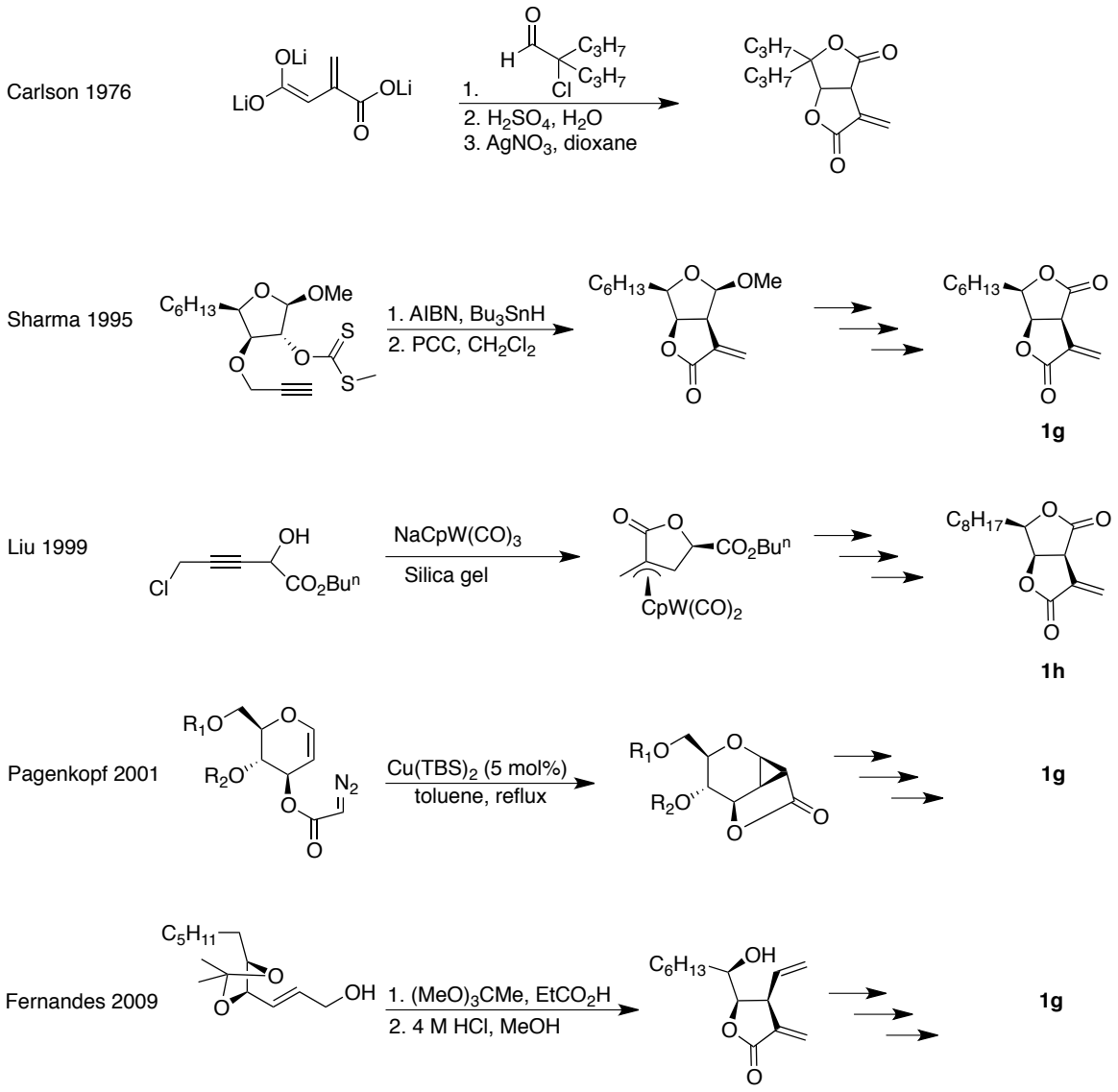
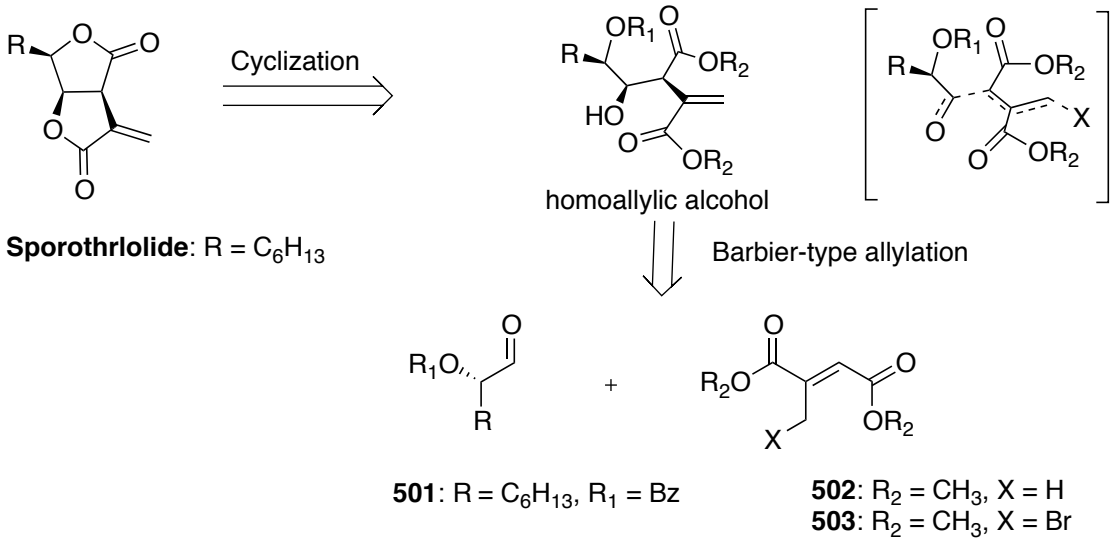


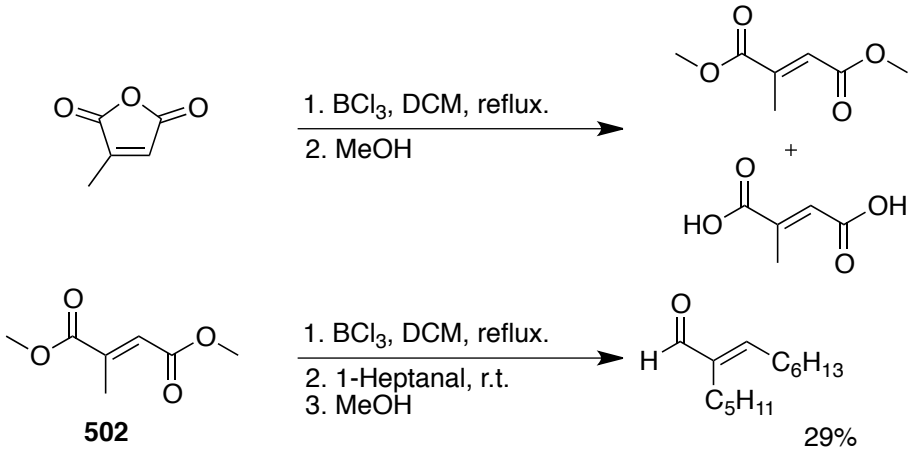
Figure 5-3 Selected Total Syntheses of α-Methylenebis-γ-lactones.

5.2 Results and discussion

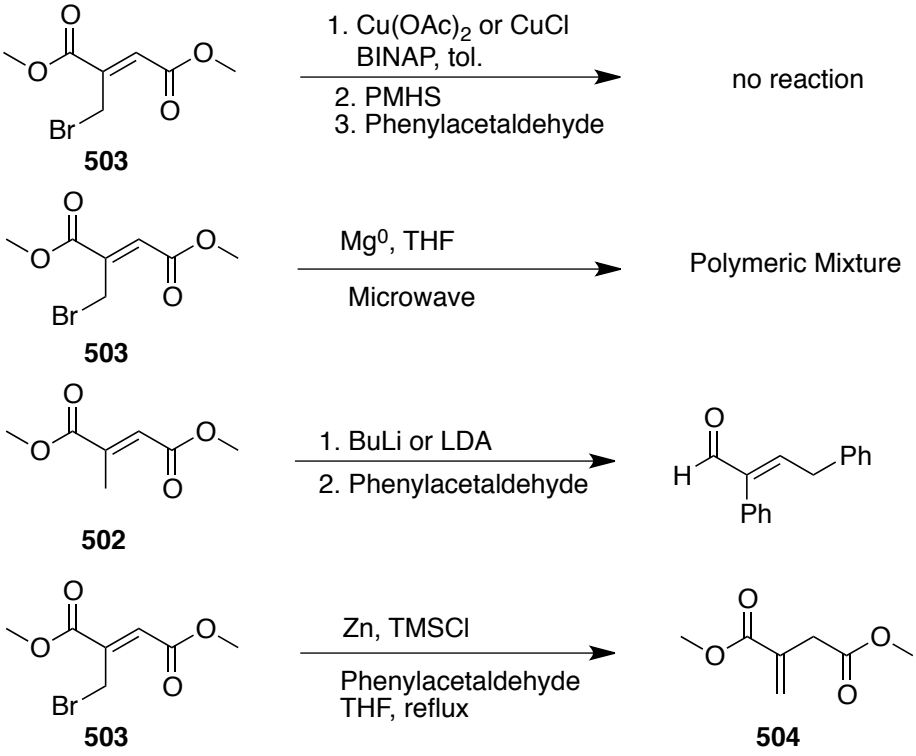


Scheme 5-1 Retrosynthetic Analysis of Sporothriolide.

A retrosynthetic analysis revealed that a bislactone could theoretically be prepared from protected α-hydroxyaldehyde **501** and a mesaconic derivative **502** (**Scheme 5-1**). Our initial studies focused on implementing the new methodology outlined in the previous chapters to close the lactone ring. We felt that the prerequisite β-hydroxyester could be prepared via chloroboration followed by coupling methyl mesaconate **502** with an alkyl aldehyde (heptanal or phenylacetaldehyde). In trial reactions, heptanal was used, but we switched to phenylacetaldehyde to aid in locating products using UV light. Our group has used this methodology to prepare homoallylic alcohols in the past.[54] Unfortunately, the addition of BCl_3 to methyl mesaconate **502** resulted in hydrolysis of the ester to form mesaconic acid and none of the chloroborated product was detected (**Scheme 5-2**). Efforts were then directed toward employing a tandem 1,4 reduction of methyl bromomesaconate **503** and phenylacetaldehyde. Both Cu(I) and Cu(II) reactions failed and starting material was recovered (**Scheme 5-3**).



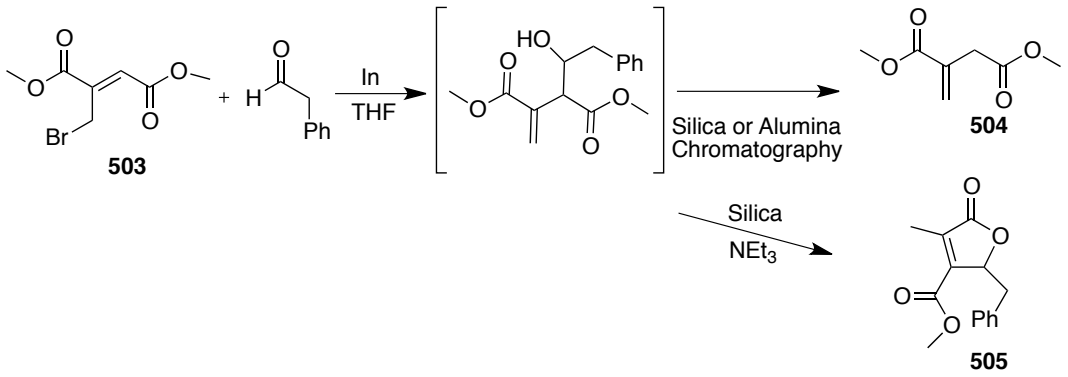
Scheme 5-2 Attempted Chloroboration of Citraconic Anhydride and Dimethyl Mesaconate.



Scheme 5-3 Attempted Metal Mediated Aldehyde Coupling Reaction with Dimethyl Bromomesaconate

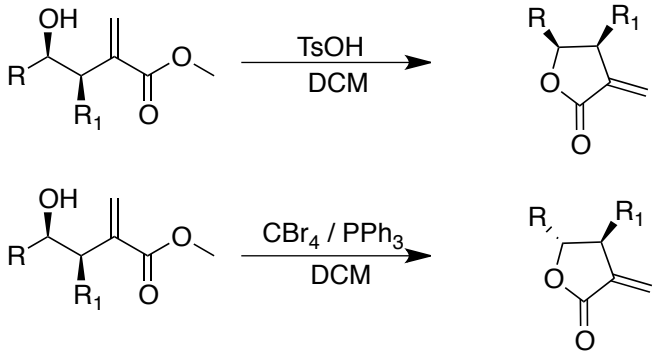
A Grignard reaction using magnesium metal in THF also failed to initiate under normal conditions. Applying heat or microwave irradiation formed the Grignard reagent, but an inseparable mixture resulted (**Scheme 5-3**). The lithium enolate of **502** could be formed using either butyllithium or LDA. Adding an aldehyde to the lithium enolate did not form the desired homoallylic alcohol. Instead, the aldol product recovered indicated a reaction occurred between two molecules of aldehyde instead of the desired reaction (**Scheme 5-3**). A Reformatsky reaction using zinc showed promise when dimethyl itaconate **504** was recovered (**Scheme 5-3**). This product indicated the zinc inserted but the intermediate did not couple to provide the desired compound. Several attempts were made to optimize the Reformatsky reaction using various methods for activating the zinc including, I_2, TMSCl, and copper amalgams. These experiments revealed that the desired alcohol was forming but that it decomposed to dimethyl itaconate **504** during to purification.

Attention was then turned toward using an indium Barbier type reaction, which had been successfully used to form eupomatilone 5.[60] A crude ^{1}H NMR of the unpurified products showed the alcohol formed nicely at room temperature-using THF as a solvent. Unfortunately, all attempts to purify the alcohol via silica or alumina chromatography resulted in decomposition to dimethyl itaconate **504** (**Scheme 5-4**). Basifying the silica gel prior to separation with triethylamine showed promise by TLC analysis. However, an NMR of the separated product revealed the double bond had shifted inside of the ring providing lactone **505** (**Scheme 5-4)**. Presumably, triethylamine is basic enough to allow a rearrangement to the more stable internal double bond. Since purification was ineffective it seemed direct formation of the lactone was a logical option.



Scheme 5-2 Indium Barbier Reaction with Dimethyl Bromomesaconate and Phenylacetaldehyde.

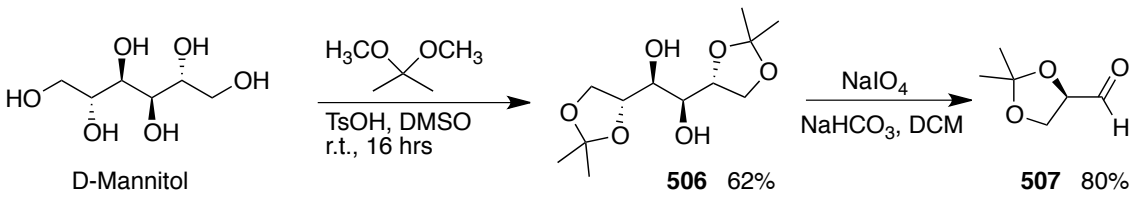
Several literature methods exist for closing α-methylene-γ-lactones (**Scheme 5-5**). Typically, the homoallylic alcohol is acidified using concentrated HCl or TsOH in DCM.[61,132a] Attempts were made to cyclize the alcohol using acid, reflux, and sonication as reported by Baba et al.[132b] In each case, the dimethyl itaconate **504** was recovered as well as small amounts of the rearranged lactone **505**. Encouraged by signs of lactone formation, we attempted to optimize the indium reaction using various solvents, toluene, hexane, THF:H_2O, THF:HCl (0.1% aq.), DCM, and DMF. Reactions in nonpolar solvents failed and polar solvents resulted in inseparable mixtures of lactone, alcohol, and starting



Scheme 5-3 Stereospecific Cyclization of Homoallylic Alcohols.

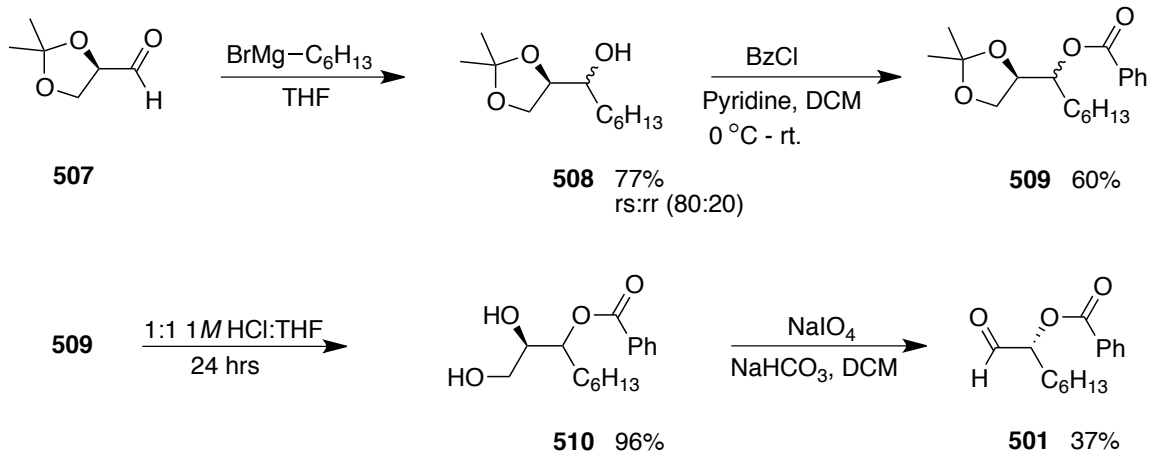
material. THF proved to be the best solvent followed by acidic lactonization using TsOH and DCM. The natural product sporothriolide is reported to exist as a transparent solid. With chromatography resulting in decomposition, it was hoped the final product could be recrystallized and we moved forward with our synthesis of sporothriolide.

Synthesis of the necessary protected α-hydroxyaldehydes began by diol protection of D-mannitol using dimethoxypropane and TsOH in DMSO (**Scheme 5-6**). A 62% yield of the protected diol **506** was isolated. A periodate oxidation of the diol **506** gave D-glyceraldehyde **507** in 80% yield. A Grignard reaction using bromohexane and D-



Scheme 5-4 Synthesis of D-Glyceraldehyde.

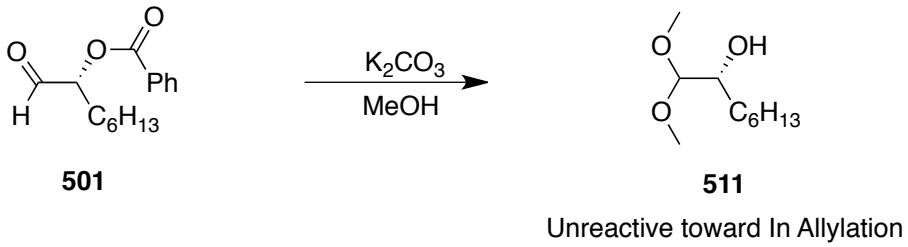
glyceraldehyde provided a 70% yield of inseparable diastereomers **508** (80:20) (**Scheme 5-7**). The diastereomers were carried through and protected using benzoyl chloride to provide 60% of **509**. Aqueous deprotection was ineffective using acetic acid, but proceeded cleanly using 1 *M* HCl:THF (1:1) to afford the diol **510**. The unmasked diols provide enough polarity so that the diastereomers could be separated by column chromatography using ethyl acetate:hexane (1:2) as the eluent. The major isomer gave an optical rotation of -25.8° in $CHCl_3$. Periodate oxidation of the diol **510** furnished the necessary protected α-hydroxyaldehyde **501** in 37% yield.



Scheme 5-5 Synthesis of 2-Benzoyloxyoctanal.

It was not apparent as to whether the protected α-hydroxyaldehydes **501** should be used directly or the benzoyl group removed to provide the α-hydroxyaldehyde for the indium reaction. Baba et al showed the free α-hydroxy group could provide a chelation-controlled nucleophilic addition resulting in high diastereoselectivity.[132b] However, unprotected α-hydroxyaldehydes are known to undergo *alpha*-keto rearrangements to provide internal ketones.[137,137b] Because the ketone would be less reactive toward indium than the aldehyde, we decided to remove the benzoyl group using K_2CO_3 in methanol (**Scheme 5-8**). After 1 hr, the mixture was filtered and the methanol was removed. A rapid ^{1}H NMR analysis was carried out prior to the indium reaction with dimethyl bromomesaconate. Unfortunately, the indium reaction failed. It was later determined, while the deprotection of **501** did occur. However, the aldehyde was transformed into the dimethoxyacetal **511,** which would not react with the bromoester **503** in THF. More of the protected α-hydroxyaldehydes **501** was synthesized and the indium reaction was attempted with the benzoyl-protected α-hydroxyaldehydes **501**. The crude mixture was subjected to acid catalyzed cyclization using TsOH in DCM. TLC indicated a mixture of

products and the NMR showed the starting material aldehyde had reformed as well as methyl itaconate **504**.

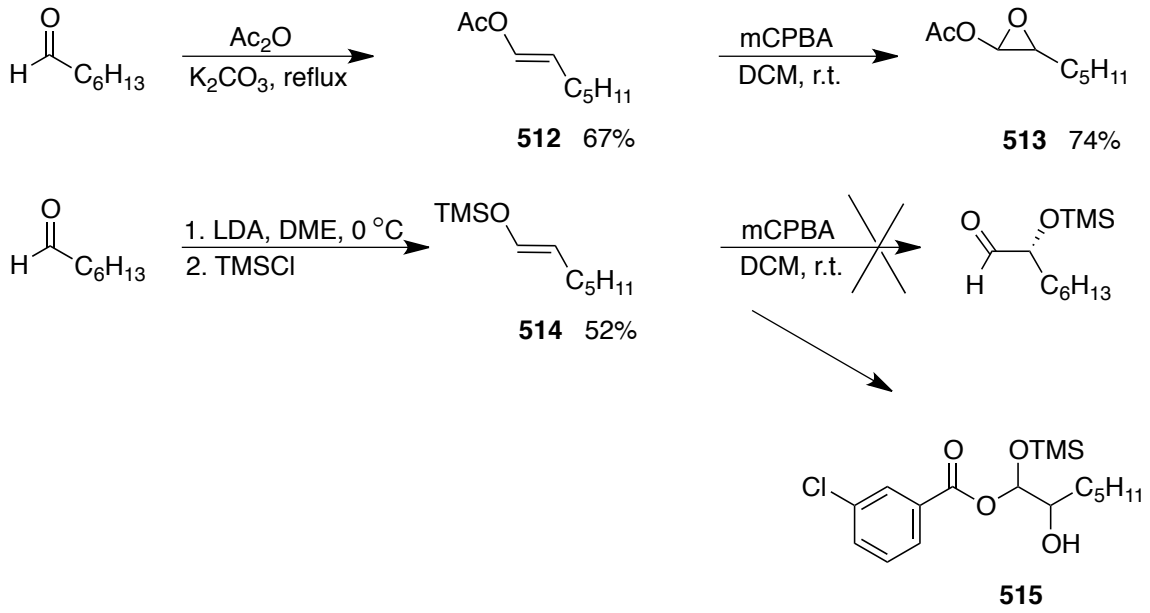


501 **511**

Unreactive toward In Allylation

Scheme 5-6 Deprotection of 2-Benzoyloxyoctanal.

At this point, it was determined the indium reaction should be optimized with the protected aldehyde. Rather than using our chiral product, we attempted to synthesize a large amount of a racemic protected α-hydroxyaldehyde. The acyl-protected enol **512** was prepared in 67% yield using heptanal and acetic anhydride (**Scheme 5-9**). Epoxidation using MCPBA provided a 74% of **513**. The acyl epoxide **514** was subjected to the protonolysis using the literature method[138] with TsOH and heat, however a polymeric mixture resulted and no purification was performed. It was thought the epoxide **514** could be used directly in the indium reaction, but NMR analysis did not reveal formation of the desired product. Attempts were made to prepare the TMS protected α-hydroxyaldehyde **515** using *m*CPBA,[139] but it was determined *m*-chlorobenzoic acid impurity added to the epoxide to form **516**.



Scheme 5-7 Alternate Synthetic Strategies to form protected 2-Hydroxyaldehydes

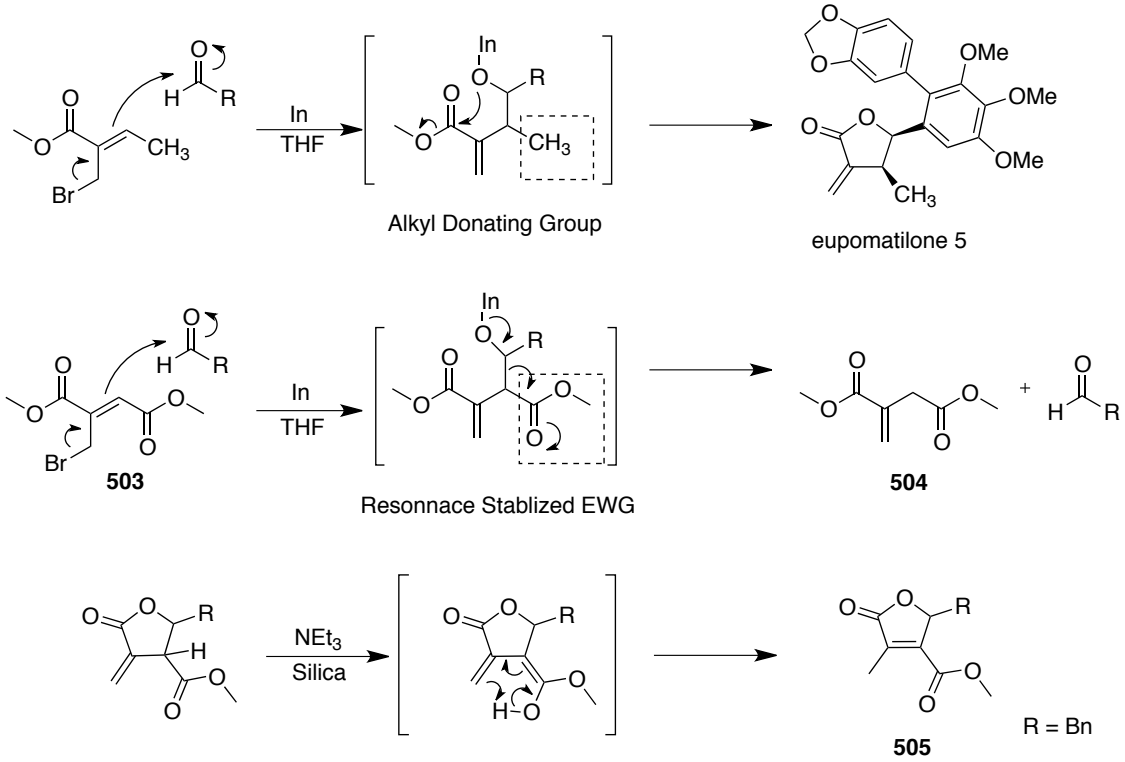
5.3 Conclusion

The desired coupling reaction to form α-methylene-γ-lactones was attempted with methodology developed in previous chapters as well as other previously reported methods. All reaction failed to produce the desired product. The indium reaction between dimethyl bromomesaconate and phenylacetaldehyde produced a rearranged lactone in low yields. Attempts to optimize this reaction by varying temperatures and solvents failed. Originally, it was thought the degradation was occurring during purification, we commenced with the synthesis of sporothriolide in hope of purification by recrystallization. Unfortunately, all attempts using the indium reaction failed.

Two scenarios are possible: the coupling reaction occurs and the alcohol/lactone product readily decomposes, or no coupling occurs. The formation of the lactone **7** led us

to believe the desired coupling was occurring. An exhaustive literature search revealed dimethyl bromomesaconate might be unstable. Laursen et al report that the *cis* carboxylic acid isomer can ready isomerize to the *trans* isomer, and Campbell et al have shown that the bromo *trans* isomer can undergo substitution and then cyclized in warm water.[131, 140, 146] Carlson and Oyler noted stable lithium anions could not be generated from dimethyl itaconate even at reduced temperatures.[141] They also found the hydrolysis of methyl itaconate led to the isomerization to the butenolide **504**.[141]

Our synthesis of eupomatilone 5 in 2005 came from methyl 2-(bromomethyl)but-2-enoate, which bears a methyl group at the key carbon in the transition state (**Scheme 5-10**).[60] In dimethyl bromomesaconate **503**, the donating methyl group is replaced by an electron withdrawing ester. The electronic effect likely aids in degradation of the β -hydroxyester under acidic or basic conditions. When triethylamine was added to the



Scheme 5-8 Possible Pathways for the Formation of Lactone **505**.

eluent it facilitated isomerization to the lactone **505.**

Indium reactions are known to occur in high diastereoselectivity but if the wrong isomer formed, the alcohol may not cyclize. Chen et al. did in fact, have a problem with cyclizing the wrong isomer in their synthesis of isoavenociolide.[133] Our previous work revealed that the *cis* homoallylic alcohol isomer forms during the synthesis of eupomatilone 5.[60] In 2008, Baba et al, found that α-hydroxyketones furnished lactones diastereoselectivity in high yield, however α-alkoxyketones proceed through a boat-type transition state, to provide the *trans* isomers.[132b] Our aldehyde moiety **501** possesses a benzoyl group, which may disrupt chelation resulting in the incorrect stereochemistry, inhibiting cyclization. This was the ultimate reasoning for removing the benzoyl group during our first attempt.

The main problems are cyclization of the alcohol and purification. It may be possible to overcome both obstacles by using bromomesaconic acid in place of the dimethyl ester **503**. The carboxylic acid derivatives cyclize easier and are solids, which allows for purification by acid/base extractions and recrystallization.[142,132a] This may circumvent the problems occurring during chromatography. If the resulting alcohol is not the desired one, methodology developed by our group using CBr_4/PPh_3 could be used to correct the stereochemistry and cyclize the alcohol to provide the α-methylene-γ-lactone (**Scheme 5-3**).[61] Unfortunately, our entire synthesis relies on the use of a mesaconic derivate. If the presence of the additional ester is ultimately affecting the outcome, a new route to sporothriolide may need to be investigated.

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

5.4.2 Typical Reaction Procedure:

Dimethyl bromomesaconate (474 mg, 2.00 mmol) and the aldehyde (1.00 mmol) were dissolved in THF or another solvent (2 mL). Powdered indium (136 mg, 1.20 mmol) was added and the reaction mixture stirred at room temperature overnight. After completion of the reaction, the mixture was filtered through Celite and the solvent was removed. The residue was purified by column chromatography using hexanes and ethyl acetate (5:1) as an eluent. For lactone **505**, triethylamine (3% by volume) was added to the eluent.

Dimethyl itaconate (**504**)[143]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.31 (s, 1H), 5.70 (s, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 166.5, 133.5, 128.5, 52.09, 52.01, 37.4.

Lactone (**505**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.11 (m, 5Hs), 5.31 (td, J = 3.9, 2.0 Hz, 1H), 3.87 (s, 3H), 3.37 (dd, J = 14.4, 3.7 Hz, 1H), 3.02 (dd, J = 14.3, 6.2 Hz, 1 H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 162.6, 146.5, 138.4, 134.8, 129.6, 128.4, 127.1, 81.0, 52.4, 38.6, 10.7. HRMS for $C_{14}H_{14}O_4$: 246.2586. Found: 246.8678

5.4.3 Synthesis of Dimethyl Bromomesaconate (503):

Dimethyl mesaconate (5.0 g, 31 mmol), NBS (11 g, 62 mmol), and AIBN (500 mg, 3 mmol) were dissolved in CCl_4 and refluxed overnight. The reaction was allowed to cool and the mixture was placed in the refrigerator to facilitate precipitation of the salt byproduct. Reaction mixture was then filtered through Celite and washed with CH_2Cl_2. The organic filtrate was washed with H_2O (3 x 20 mL), brine (1 x 20 mL) and dried over anhydrous Na_2SO_4. Solvent was removed and the residue was purified by column chromatography using ethyl acetate and hexanes as an eluent (1:10). Yield 74%.

Dimethyl bromomesaconate (**503**)[143]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 1 H), 4.70 (s, 2 H), 3.85 (s, 3H), 3.8 (s, 3H). ^{13}C NMR (60 MHz, $CDCl_3$): δ 165.2, 165.0, 142.7, 128.3, 53.0, 22.4.

5.4.4 Synthesis of Diacetonide (506):

A mixture of powdered D-mannitol (10 g, 55 mmol), *p*-toluenesulfonic acid (53 mg, 2.0 mmol), and 2,2-dimethoxypropane (14.3 g**,** 137 mmol) in dry DMSO (20 mL) was placed in a 100 mL rounded-bottomed flask and the mixture stirred at room temperature under argon. Within 1 hour, the suspended solids had dissolved. After 16 hours, the reaction solution was poured into 3% aqueous $NaHCO_3$, (30 mL). The mixture

was extracted with ethyl acetate (4 x 50mL), and the extracts were washed with brine (20 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was heated to reflux to redissolve the solids, and then the solution was diluted with hot hexane (80 mL). The mixture was allowed to cool slowly overnight, and the resulting crystalline material was collected by filtration and then washed with Et_2O-hexane (1:3) and dried over anhydrous Na_2SO_4 to give 6 g (41%) of the diacetonide **506**.

1,2:5,6-Diisopropylidene-D-mannitol (**506**)[144]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22–4.10 (m, 4 H), 3.98 (dd, J = 8.4 Hz, J = 5.4 Hz, 2 H), 3.75 (br t, J = 6.2 Hz, 2 H), 2.70 (d, J = 6.7 Hz, 2 H), 1.42 (s, 6 H), 1.36 (s, 6 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 109.4, 76.2, 71.2, 66.7, 26.7, 25.2.

5.4.5 Synthesis of 2,3-O-(Isopropylidene)-D-glyceraldehyde (507):

To a vessel equipped with a thermometer was added diacetonide **506** (33 g, 0.13 mol) in CH_2Cl_2 (350 mL). Saturated aqueous $NaHCO_3$ (11.9 mL) was then added to the flask while maintaining the temperature at or below 25 °C. Solid KIO_4 (57.5 g, 0.25 mol) was then added over 20 minutes with vigorous stirring, and the reaction allowed to proceed for 2 hours, while the temperature was maintained below 30 °C. The solids, which were found to be the desired product, were removed by filtration and used without further purification.

2,3-O-(Isopropylidene)-D-glyceraldehyde (**507**)[144]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55 (d, J =1.8 Hz, 1 H), 4.25 (m, 1 H), 4.04–3.93 (m, 2 H), 1.42 (s, 3 H), 1.36 (s, 3 H). ^{13}C NMR (60 MHz, $CDCl_3$): δ 201.4, 110.8, 79.5, 65.1, 25.8, 24.7.

5.4.6 Synthesis of Alcohol (508):

Magnesium turnings (365 mg, 15.0 mmol) were placed in an oven-dried 50 mL rounded-bottomed flask. 1-Bromohexane (2.47 g, 15.0 mmol) in 5 ml THF was added via syringe. A crystal of iodine was added, and the mixture was heated to 40 °C and allowed to stir until all the magnesium was consumed. The mixture was cooled using an ice bath, and D-glyceraldehyde (1.3g, 10mmol) was added as a solution in 3 mL of THF via syringe. Once the addition was complete, the ice bath was removed, and the solution was allowed to stir at room temperature for 1 hour. The reaction was quenched using 5 mL of a sat. NH_4Cl solution and then transferred to a separatory funnel. The mixture was extracted with 20 mL of ethyl acetate (x3), washed with 20 mL of H_20 and dried over Na_2SO_4. The organic layer was concentrated *in vacuo* to give 1.67 g, an 80% yield of clear oil, which was used directly without further purification.

1-[2,2-Dimethyl-(4*S*)-1,3-dioxolan-4-yl]-(1*S*)-heptan- 1-ol (**508**)[145]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 4.76 Hz), 1.26–1.32 (m, 8H), 1.34 (s, 3H), 1.39 (s, 3H), 1.42–1.46 (m, 2H), 2.05 (br s, 1H), 3.45–3.49 (m, 1H), 3.71 (dd, 1H, J = 7.20, 6.70 Hz), 3.91–4.02 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 108.9, 78.7, 70.7, 64.5, 32.6, 31.7, 29.3, 25.8, 22.6, 14.1.

5.4.7 Synthesis of Benzoyl Ester (509):

The alcohol **508** (2.34 g, 11.0 mmol) and pyridine (1.74 g, 22.0 mmol) were placed in a 100 mL oven-dried rounded-bottomed flask along with 25 mL of dry dichloromethane and the mixture was cooled using an ice bath. Benzyl chloride (1.74 g, 22.0 mmol) was added as a solution in 10 mL of dry dichloromethane via syringe. The

ice bath was removed and the mixture stirred at room temperature overnight. The reaction was quenched using 25 mL of H_2O and 50 mL of dichloromethane. The organic layer was subsequently washed twice with H_2O and $NaHCO_3$, once with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 4.9 g (77%, yield) of yellow oil, which was used directly without further purification.

4-[1-Benzyloxy-(1*S*)-heptyl]-2,2-dimethyl-(4*S*)-1,3- dioxolane (**509**)[145]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 4.76 Hz), 1.26–1.32 (m, 10H), 1.38 (s, 3H), 1.42 (s, 3H), 3.39 (m, 1H), 3.62 (dd, 1H, J = 7.20, 6.70 Hz), 3.96 (dd, 1H, J = 7.20, 6.70 Hz), 4.18 (dd, 1H, J = 6.71, 4.32 Hz), 4.61 (d, 1H, J = 11.7 Hz), 4.76 (d, 1H, J = 11.7 Hz), 7.22– 7.38 (m, 5H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.9, 132.9, 130.3, 129.5, 128.3, 109.5, 74.1, 66.0, 31.6, 31.6, 30.9, 29.1, 25.2, 22.5, 13.9.

5.4.8 Synthesis of Diol (510):

The crude ester **509** (4.86 g, 15.0 mmol) was placed in a 100 mL rounded-bottomed flask along with 50 mL of a 1:1 THF:H_2O solution. Concentrated HCl (2 mL) was added, and the mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with 20 mL of H_20 and 30 mL of ethyl acetate. Then transferred to a separatory funnel. The H_2O layer was extracted three times with 20 mL of ethyl acetate. The combined organic layer were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 3.95 g (96% yield) of clear oil. The oil was purified by silica gel column chromatography using ethyl acetate and hexane (1:2) as eluent.

3-Benzyloxy-(2*S*,3*S*)-nonane-1,2-diol (**510**)[145]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 4.76 Hz), 1.26–1.38 (m, 10H), 3.39 (m, 1H), 3.62 (dd, 1H, J = 7.10, 6.70 Hz), 3.82–3.89 (m, 2H), 4.72 (s, 2H), 7.22–7.38 (m, 5H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.9, 133.2, 129.9, 129.7, 128.4, 75.1, 73.2, 62.9, 31.7, 30.6, 29.2, 25.4, 22.6, 14.0.

5.4.9 Synthesis of Aldehyde (501):

The diol **510** (560 mg, 2.0 mmol) was placed in a 50 mL rounded-bottomed flask along with dichloromethane (5mL) and saturated aqueous $NaHCO_3$ (0.5 mL). $NaIO_4$ (730 mg, 4.0 mmol) was added in small portions over 20 minutes. Once the reaction was complete as indicated as indicated by TLC, 25 mL of dichloromethane was added and filtered through Celite. The filtrate was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 420 mg (85% yield) of clear oil. Purification was done using silica gel column chromatography using a 1:5 ethyl acetate:hexanes mixture as eluent to provide the aldehyde in 37% yield overall.

2-(Benzoyloxy)octanal (**501**)[146]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1 H), 8.2-7.2 (m, 5 H), 5.15 (t, J= 6 Hz, 1 H), 2.4-1.0 (m, 10 H), 0.88 (br t, J = 6 Hz, 3 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 198.4, 166.1, 133.5, 129.8, 129.3, 128.5, 78.8, 31.5, 28.9, 24.9, 22.5, 13.9.

5.4.10 Synthesis of Acetal (511):

The ester (162 mg, 0.65 mmol) was placed in a 25 mL rounded-bottomed flask along with 2 mL of MeOH and cooled using an ice bath. K_2CO_3 (207 mg, 1.50 mmol) was added and the ice bath removed. The mixture was allowed to stir at room temperature for 1 hour and then filtered through Celite. The filtrate was dried using

anhydrous Na_2SO_4 and concentrated *in vacuo* to give 250 mg of yellow oil, which contained the crude acetal and used directly without further purification.

1,1-dimethoxyoctan-2-ol (**511**)[147]: ^{1}H NMR (60 MHz, CCl_4): δ 4.0 (d, J = 6 Hz, 1 H), 3.60-3.30 (m, 1 H), 3.37 (s, 3 H), 3.30, (s, 3 H), 2.08 (br s, 1 H), 1.08-1.07 (m, 10 H), 0.90 (t, J = 6 Hz, 3 H).

5.5 Failed Reactions Experimental

5.5.1 Hydroboration of Citraconic Anhydride:

Citraconic anhydride (112 mg, 1.00 mmol) and dry DCM (10 mL) were placed in a rounded-bottomed flask under argon and cooled to using a dry ice/acetone bath. Boron trichloride (1.1 mL, 1.1 mmol, 1 *M* in DCM) was added via syringe and the mixture stirred for 2 hours at -78 °C. After the solution was allowed to warm to room temperature, methanol (3 mL) was added and the solvent was removed under reduced pressure to give clear oil. NMR analysis revealed the mixture was composed of citraconic anhydride, dimethyl itaconate, and small amounts of carboxylic acid. No product was obtained.

5.5.2 Hydroboration of Dimethyl Citraconate:

Dimethyl mesaconate (233 mg, 1.50 mmol) and dry DCM (10 mL) were placed in a rounded-bottomed flask underneath argon. Boron trichloride (2.0 mL, 2.0 mmol, 1 *M* in DCM) was added via syringe and the mixture stirred at room temperature for 2 hours. Methanol (3 mL) was added and the solvent was removed under reduced pressure to give amber colored oil. NMR analysis revealed the mixture was composed of dimethyl itaconate. No yield.

5.5.3 Aldehyde Coupling with Boron Trichloride:

Dimethyl mesaconate (316 mg, 2.0 mmol) and dry DCM (10 mL) were placed in a rounded-bottomed flask underneath argon. Boron trichloride (2.0 mL, 2.0 mmol, 1 *M* in DCM) was added via syringe and the mixture was refluxed for 1.5 hrs. After cooling to room temperature, 1-heptanal (251 mg, 2.20 mmol) was added as a solution in 3 mL of DCM. After 1 hr, the solution had turned red and allowed to cool to room temperature. Water (25 mL) was added slowly and the resulting mixture was extracted with DCM (20 mL), dried with anhydrous Na_2SO_4, and concentrated i*n vacuo* to provide a red oil (286mg). Column chromatography was performed using silica and eluted using ethyl acetate and hexanes solution (1:9). The major product (62 mg) was the aldol product (*E*)-2-pentylnon-2-enal, a 29% yield.

Dimethyl mesaconate (316 mg, 2.0 mmol) and dry DCM (10 mL) were placed in a rounded-bottomed flask. Boron trichloride (2.2 mL, 2.2 mmol, 1 *M* in DCM) was added via syringe, and the mixture was refluxed for 1.5 hours. The reaction was allowed to reach room temperature and then cooled using a dry ice/acetone bath. 1-heptanal (251 mg, 2.20 mmol) was added as a solution in 3 mL of DCM dropwise over 5 minutes and allowed to stir for 10 minutes. The cooling bath was removed and the solution was allowed to warm to ambient temperature. After stirring overnight, the reaction was quenched with 25 mL H_2O and extracted with DCM. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and then concentrated. A TLC analysis revealed a complex mixture of mostly dimethyl itaconate and heptanal.

Dimethyl mesaconate (474 mg, 3.00 mmol), phenylacetaldehyde (360 mg, 3.00 mmol), and dry DCM (15 mL) were placed in a 50 mL rounded-bottomed flask. Boron trichloride (2.2 mL, 2.2 mmol, 1 *M* in DCM) was added via syringe and the mixture was allowed to stir overnight. A TLC analysis revealed a mixture of starting material.

5.5.4 Grignard Reactions:

Dimethyl bromomesaconate (360 mg, 1.50 mmol), magnesium turnings (36 mg, 1.50 mmol), and dry diethyl ether (6 mL) were placed in an oven-dried 50ml rounded-bottomed flask under argon. After several hours, none of the magnesium had been consumed, indicating no reaction. No product could be isolated from the mixture.

Dimethyl bromomesaconate (948 mg, 4.00 mmol), magnesium turnings (95 mg, 3.90 mmol), and dry THF (20 mL) were placed in an oven-dried 50ml rounded-bottomed flask under argon. The mixture was subjected to microwave irradiation for 1 hour. The resulting solution had a large amount of white precipitate, presumably polymeric, and unreacted magnesium metal. No product could be isolated from the complex mixture.

5.5.5 Copper Reactions:

$Cu(OAc)_2 \cdot H_2O$ (10 mg, 0.05 mmol), (*S*)-BINAP (31 mg, 0.05 mmol), and toluene (4.0 mL) were added into an oven-dried 50 mL rounded-bottom flask. The resulting mixture was stirred at room temperature for 30 minutes. Then, PMHS (0.24 mL, 4.0 mmol) was added to the reaction mixture, which was stirred for 30 minutes. A solution dimethyl bromomesaconate (237 mg, 1.00 mL) and phenylacetaldehyde in toluene (2.0 mL) was added and the reaction vessel was sealed, and the mixture stirred for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution,

and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The product was purified by chromatography on silica gel. The major product (158 mg) was dimethyl bromoitaconate starting material.

Copper(I) bromide (205 mg, 1.00 mmol) and THF (10 mL) were placed in an oven-dried 50 mL rounded bottomed flask under argon. Dimethly bromomesaconate (284 mg, 1.20 mmol) and phenylacetaldehyde (120 mg, 1.00 mmol) were added as a solution in 2 mL of THF. The reaction was stirred overnight. A TLC analysis showed only starting material. No product could be isolated from the mixture.

5.5.6 Zinc Reactions:

Powdered zinc metal (261 mg, 4.00 mmol) was place in a 50 mL rounded-bottomed flask and covered with 5 mL of diethyl ether. A single crystal of elemental iodine was added and the mixture stirred for 20 minutes. Dimethyl bromomesaconate (237 mg, 1.00 mmol) and phenylacetaldehyde (120 mg, 1.00 mmol) were added together as a solution in 2 mL of Et_2O. Once the iodine color disappeared, the reaction was refluxed for 1 hour and then cool to ambient temperature. The mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL). Additional diethyl ether was added and the mixture was washed with ammonium chloride, water, and then dried over anhydrous sodium sulfate. The crude mixture was subjected to NMR analysis revealed only starting material.

Copper acetate (784 mg, 4.00 mmol) and 5 mL of acetic acid were placed in a 50 mL rounded-bottomed flask. Powdered zinc metal (261 mg, 4.00 mmol) was added, and the resulting precipitate was washed with 5 mL of Et_2O. A single crystal of elemental iodine was added and the mixture stirred for 20 minutes. Dimethyl bromomesaconate (237 mg, 1.00 mmol) and phenylacetaldehyde (120 mg, 1.0 mmol) were added as a solution in 2 mL of Et_2O. Then reaction was refluxed overnight and then cooled to ambient temperature. The mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL). Diethyl ether was added and the mixture was washed with NH_4Cl, water, and then dried over anhydrous sodium sulfate. The crude mixture was subjected to silica gel column chromatography using 8% ethyl acetate in hexanes as an eluent. The starting materials, dimethyl mesaconate and dimethyl itaconate, were recovered.

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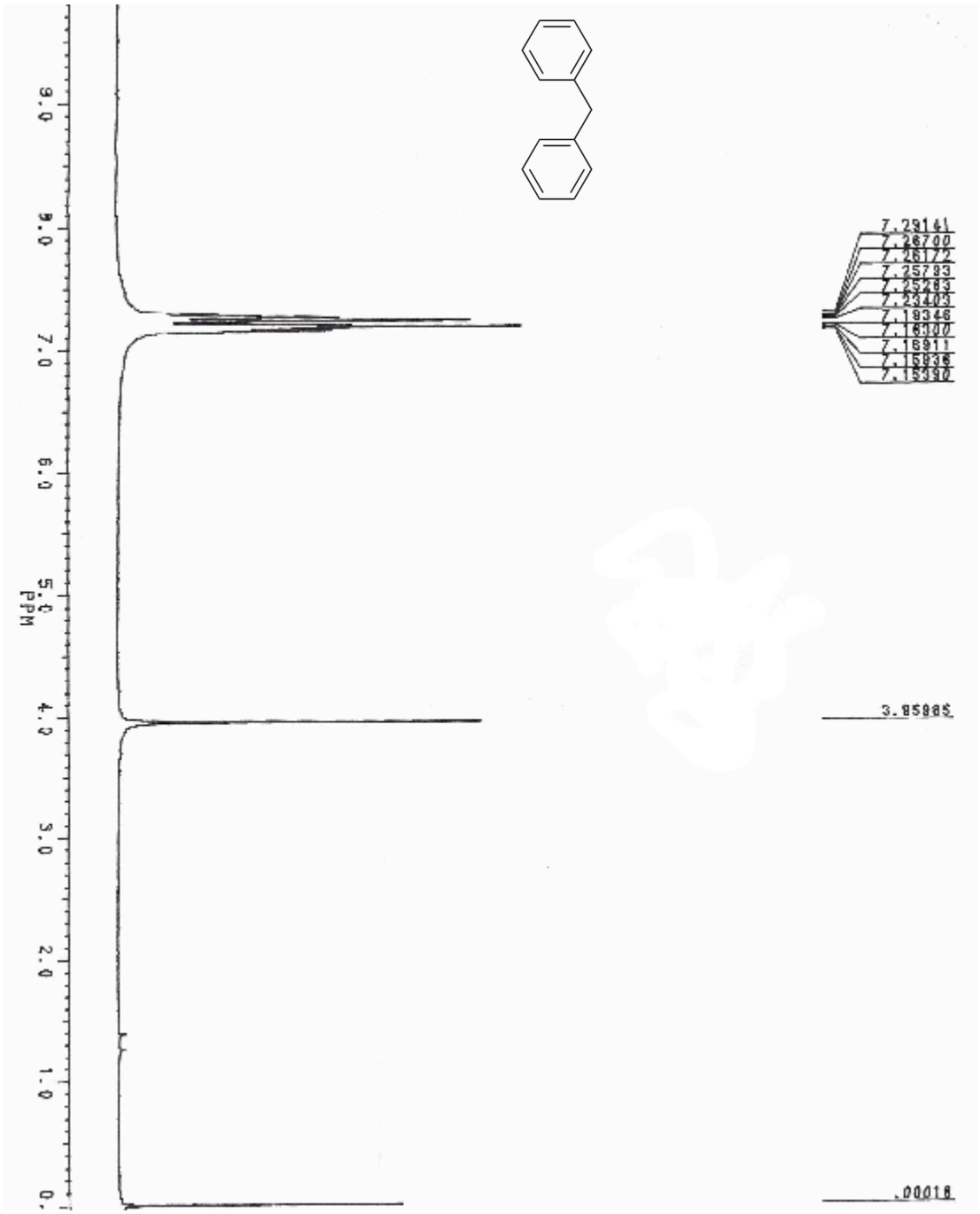
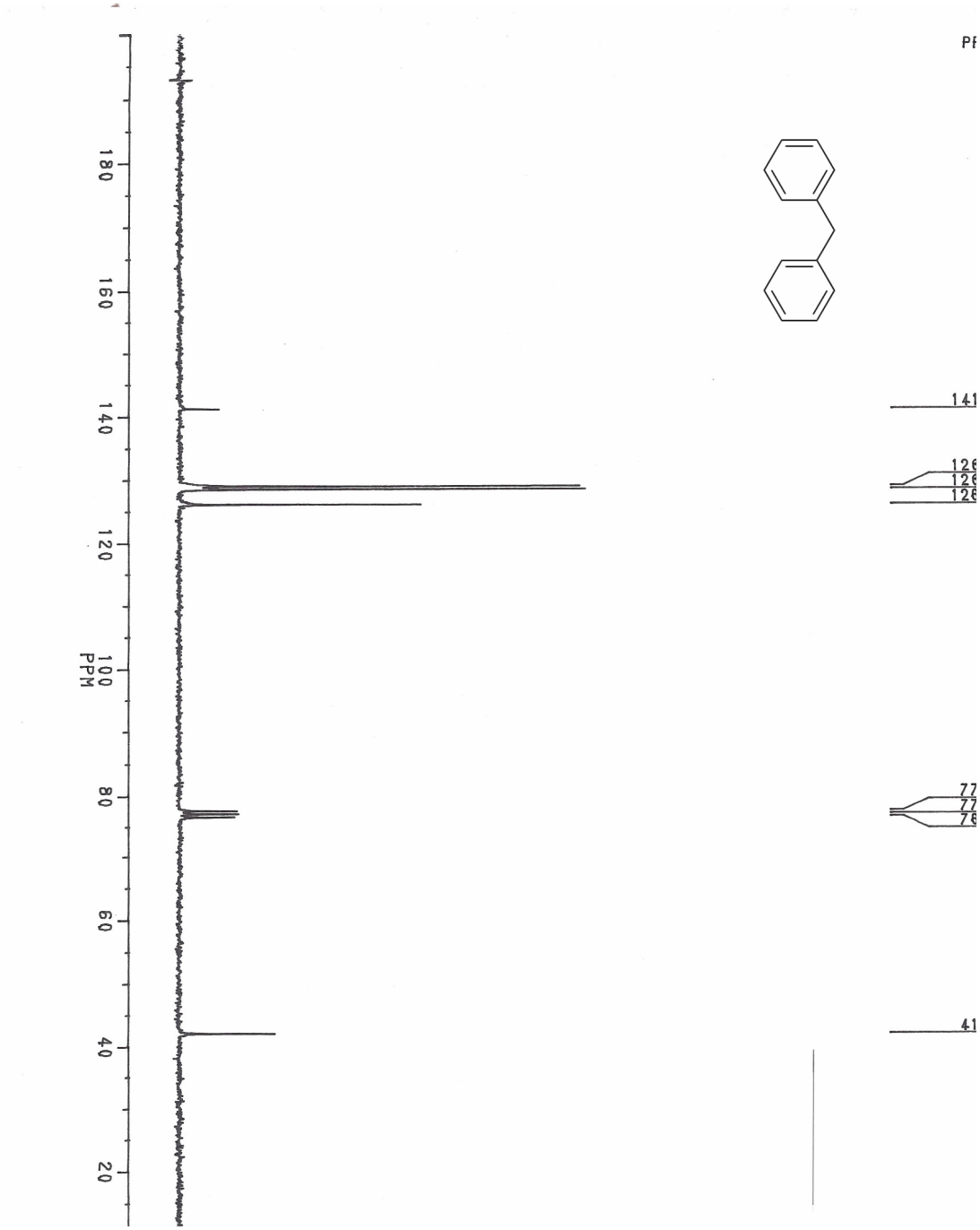
APPENDICES

Appendix A: Representative NMR Spectra From Chapter 2

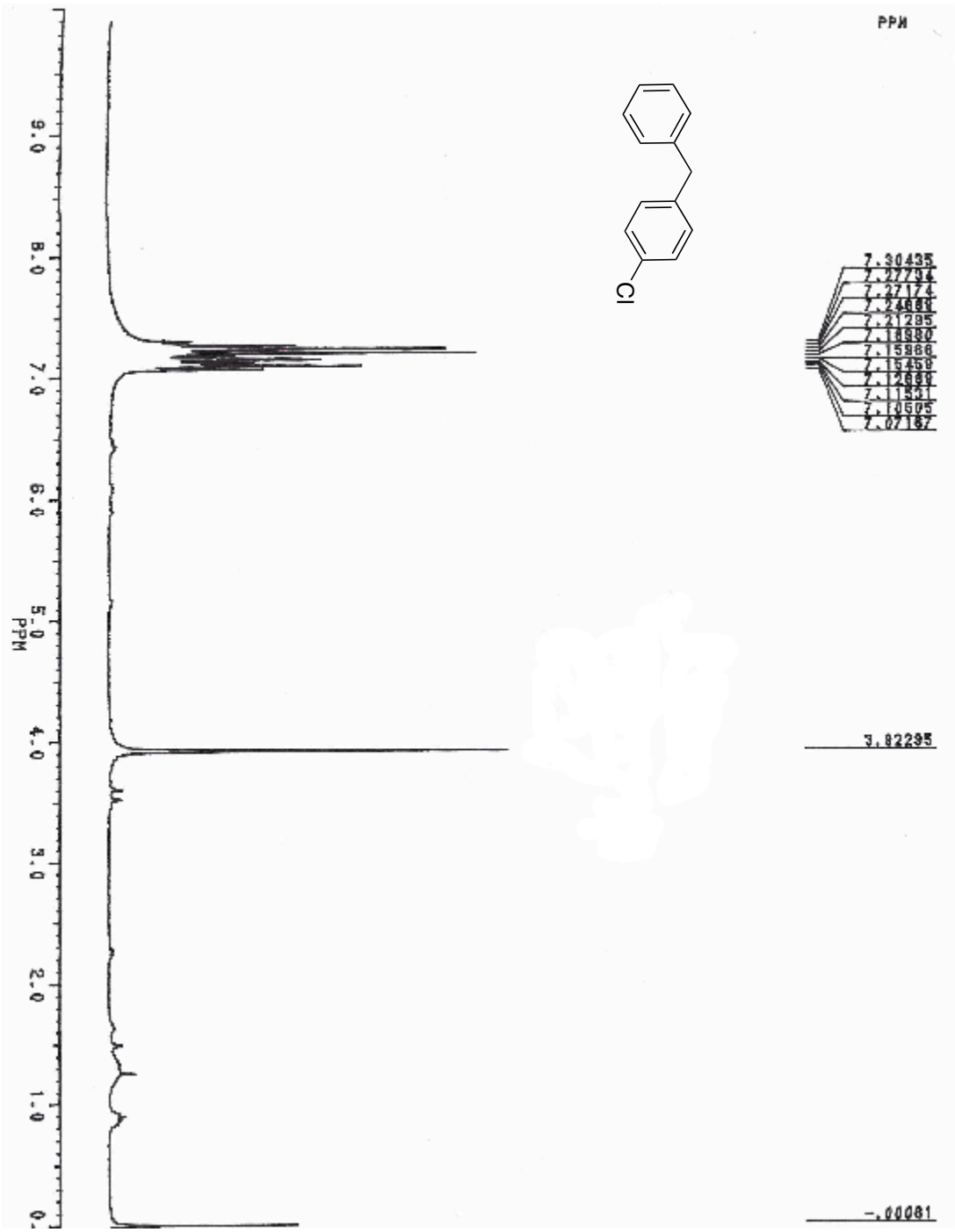
^{1}H NMR spectrum of compound 201



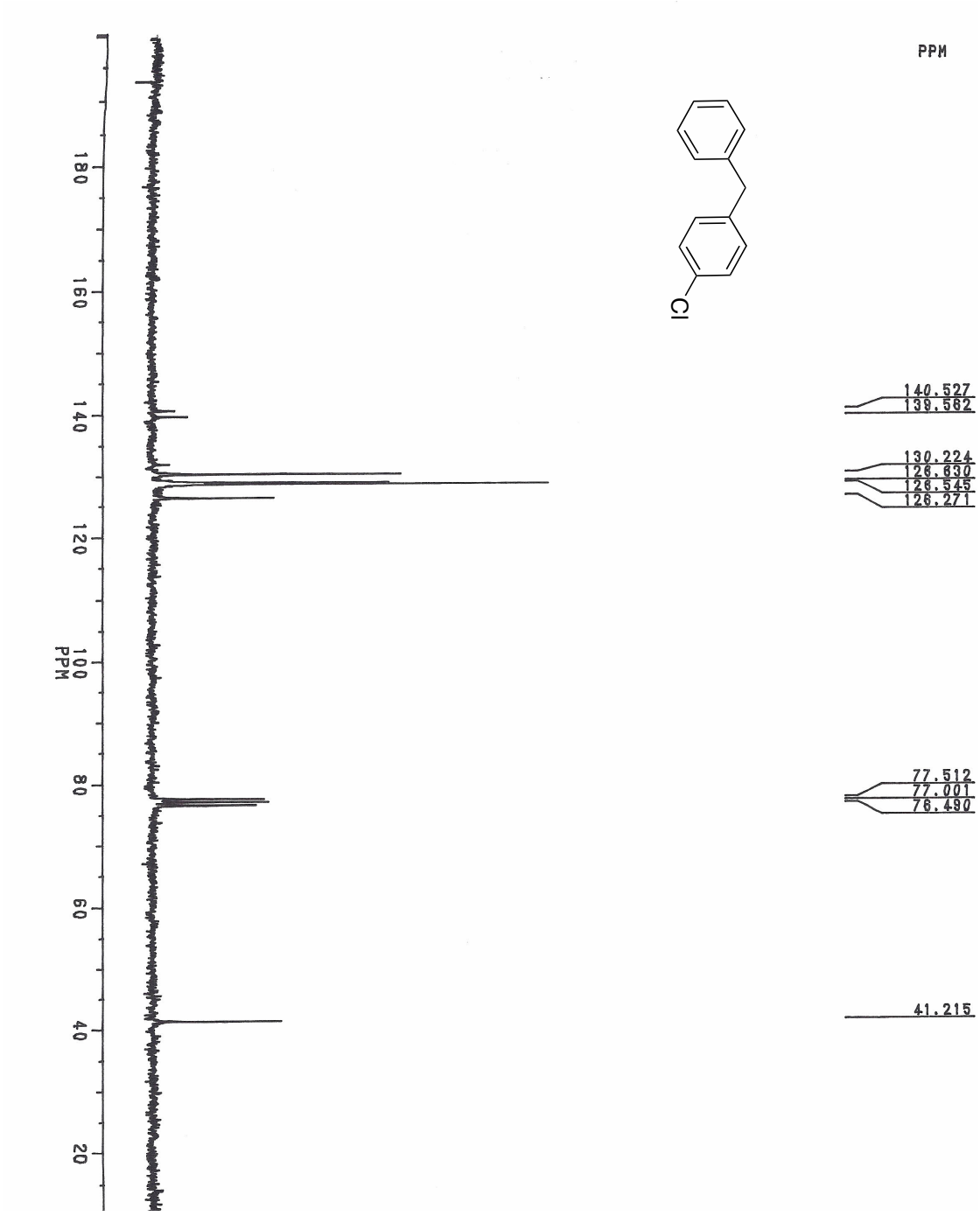
^{13}C NMR spectrum of compound 201



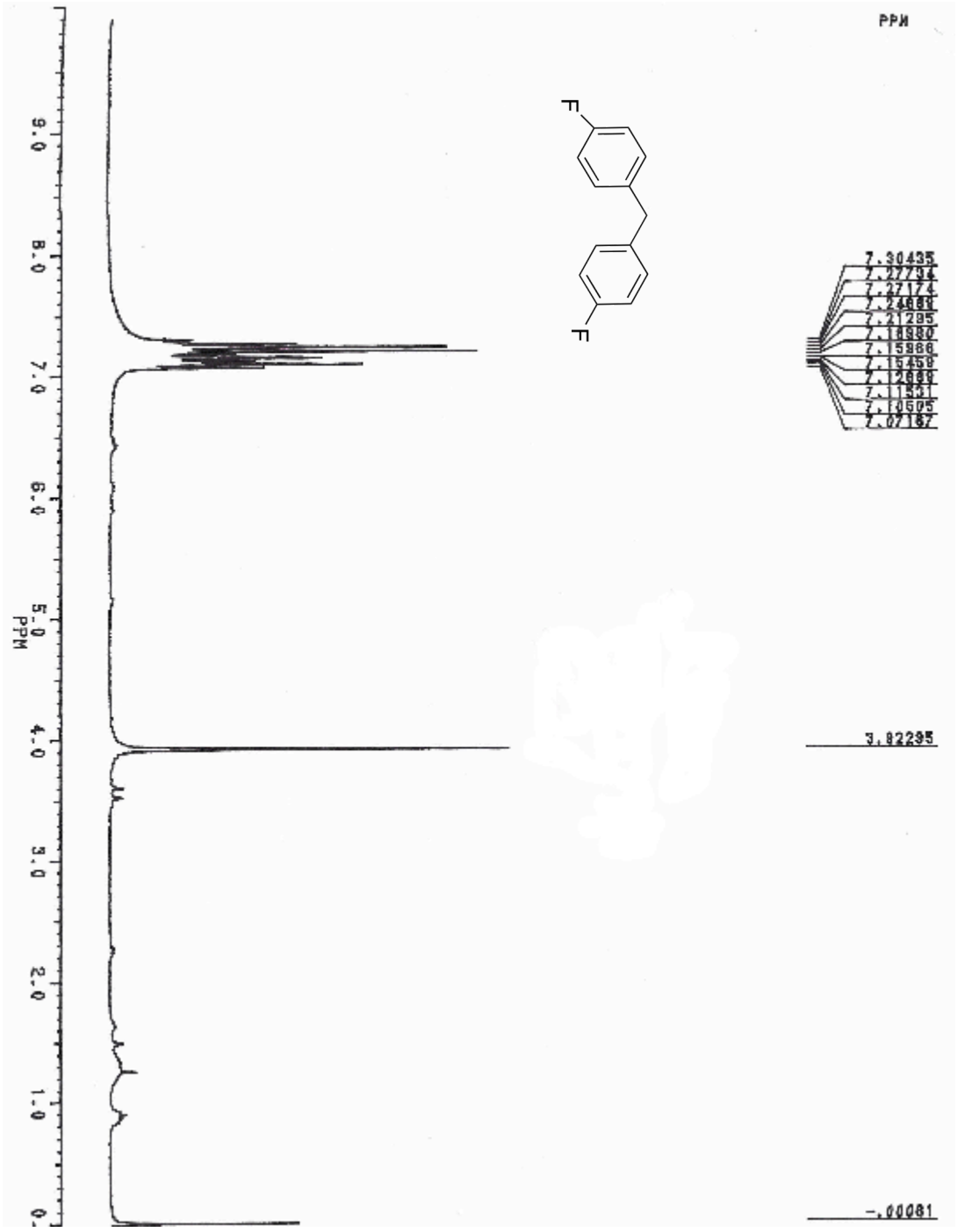
^{1}H NMR spectrum of compound 202



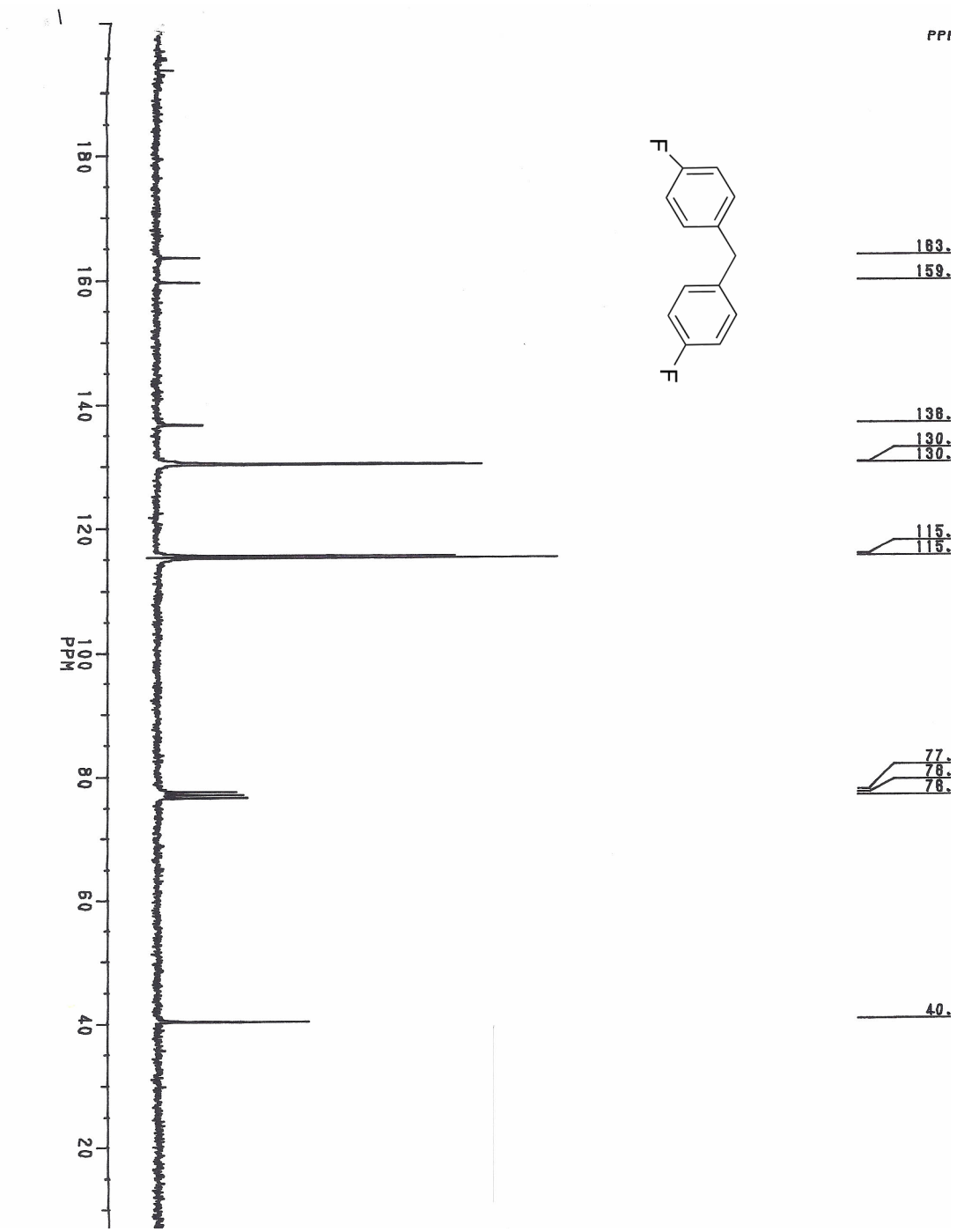
^{13}C NMR spectrum of compound 202



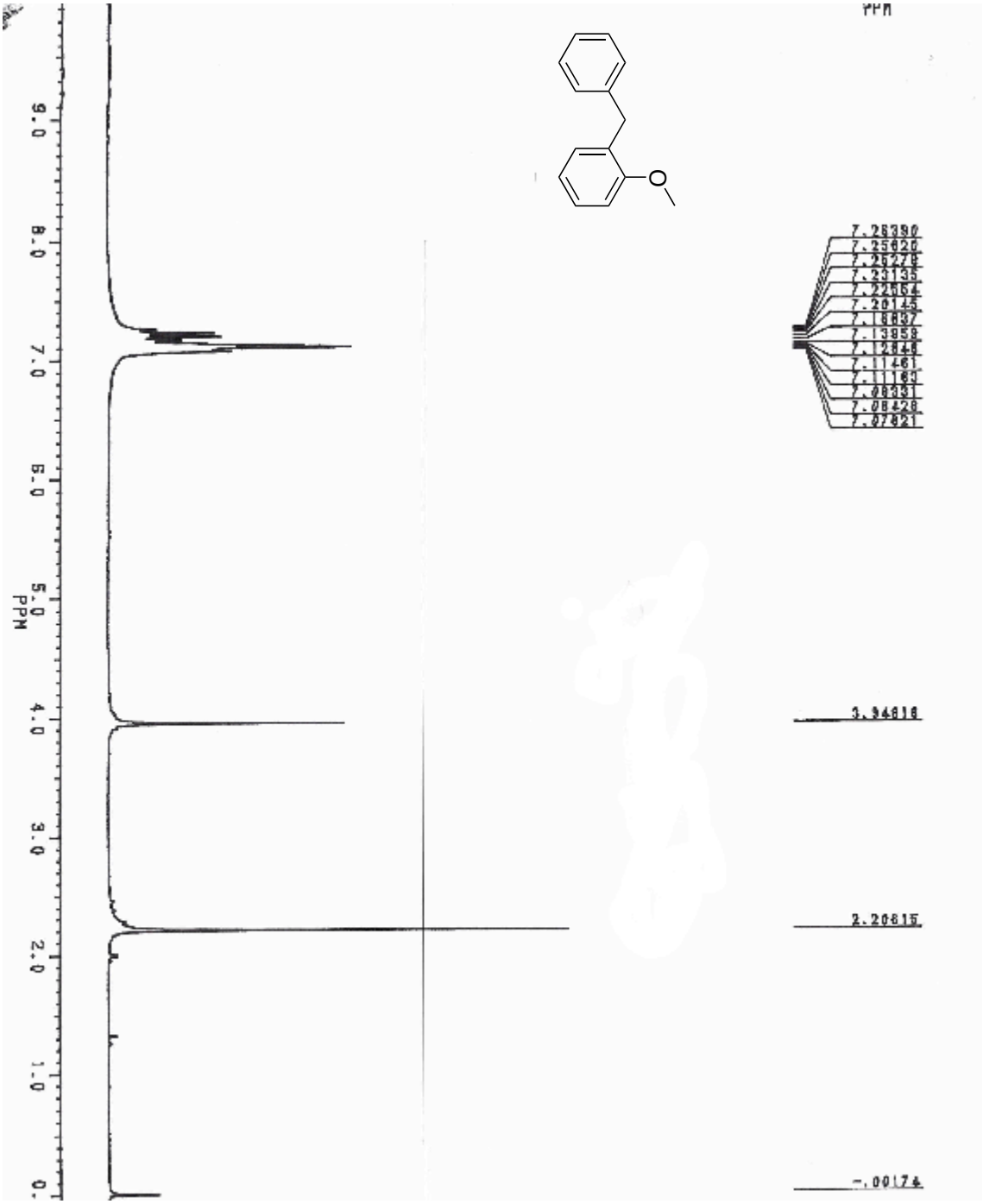
^{1}H NMR spectrum of compound 203



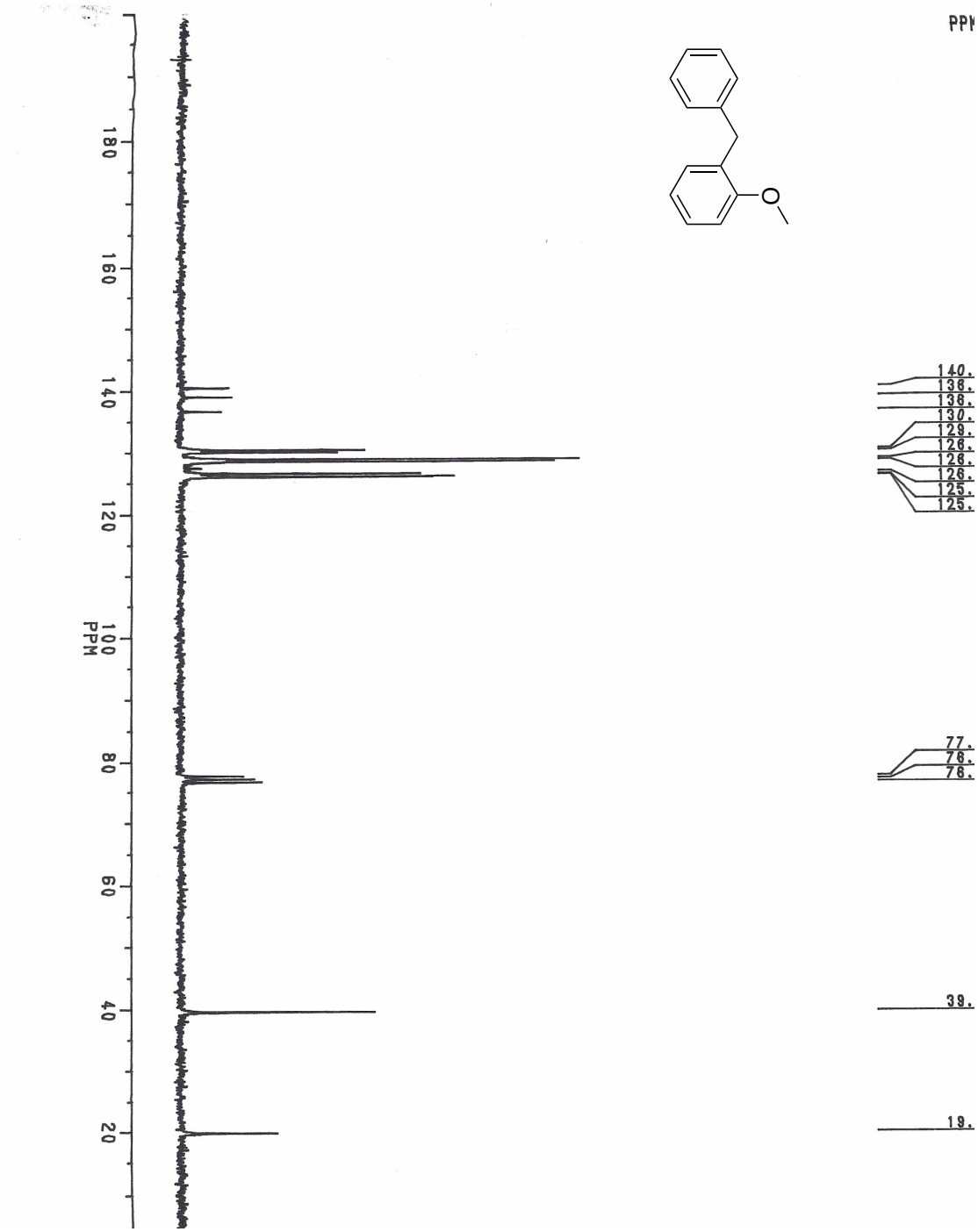
^{13}C NMR spectrum of compound 203



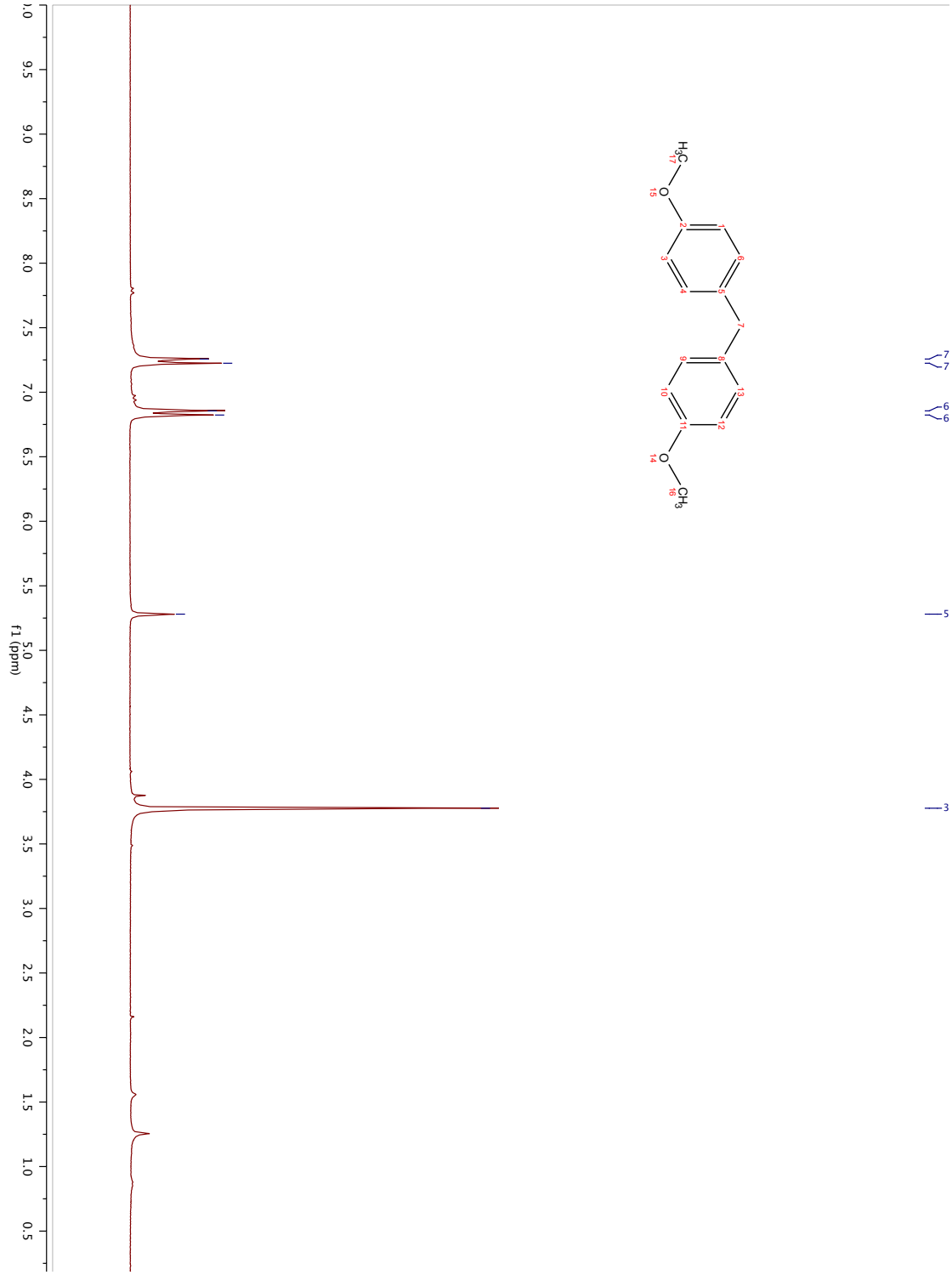
^{1}H NMR spectrum of compound 205



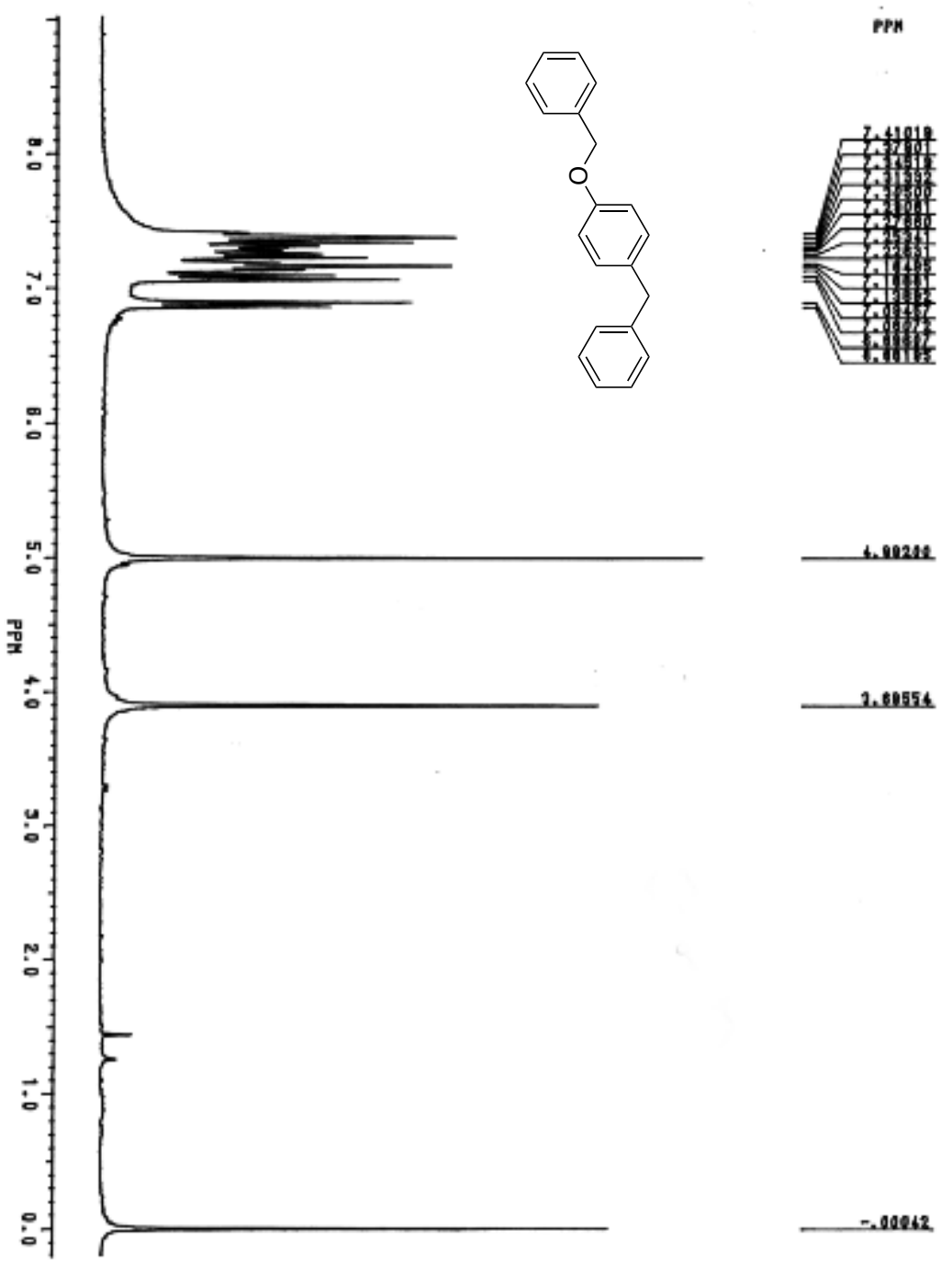
^{13}C NMR spectrum of compound 205



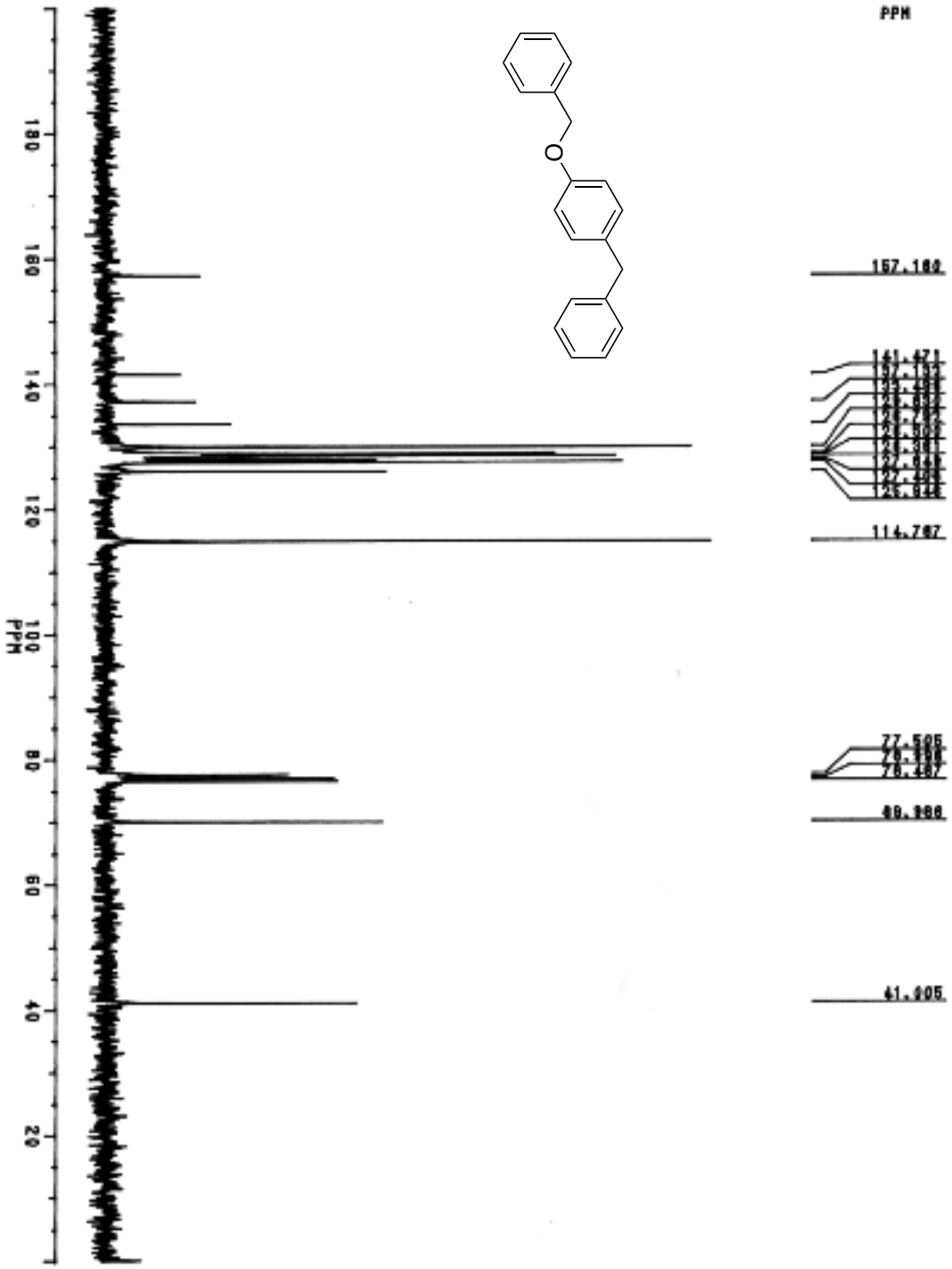
^{1}H NMR spectrum of compound 206



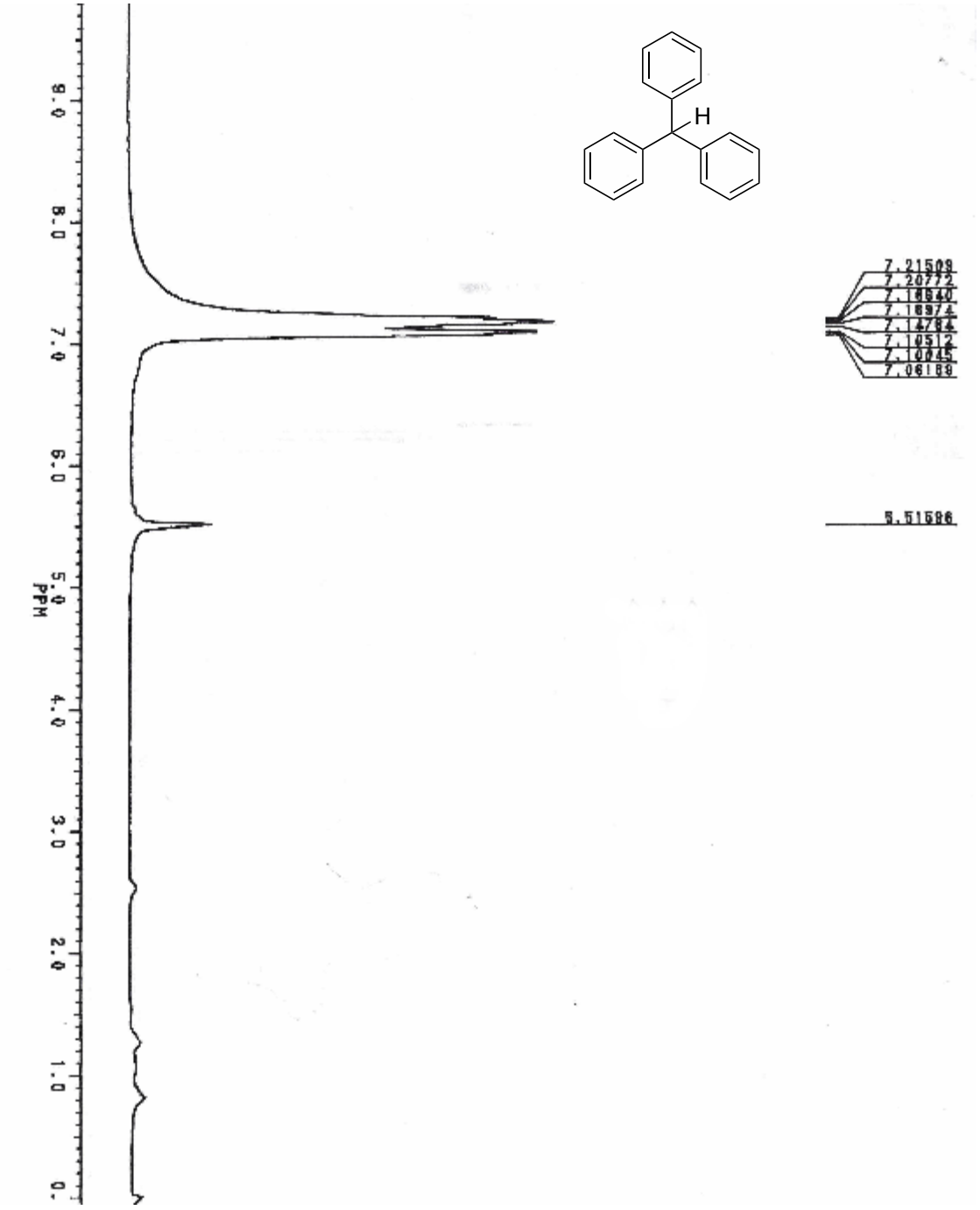
^{1}H NMR spectrum of compound 208



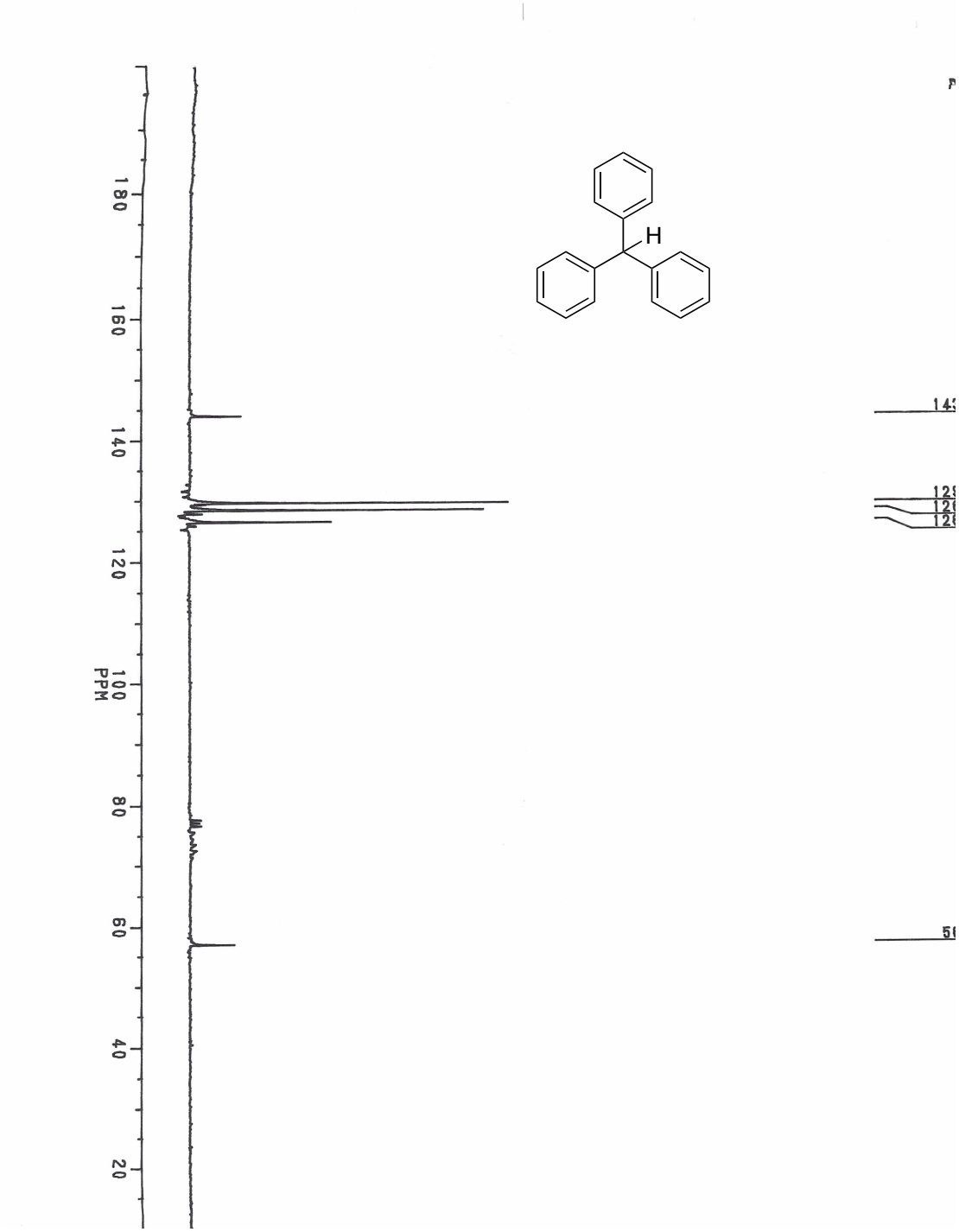
^{13}C NMR spectrum of compound 208



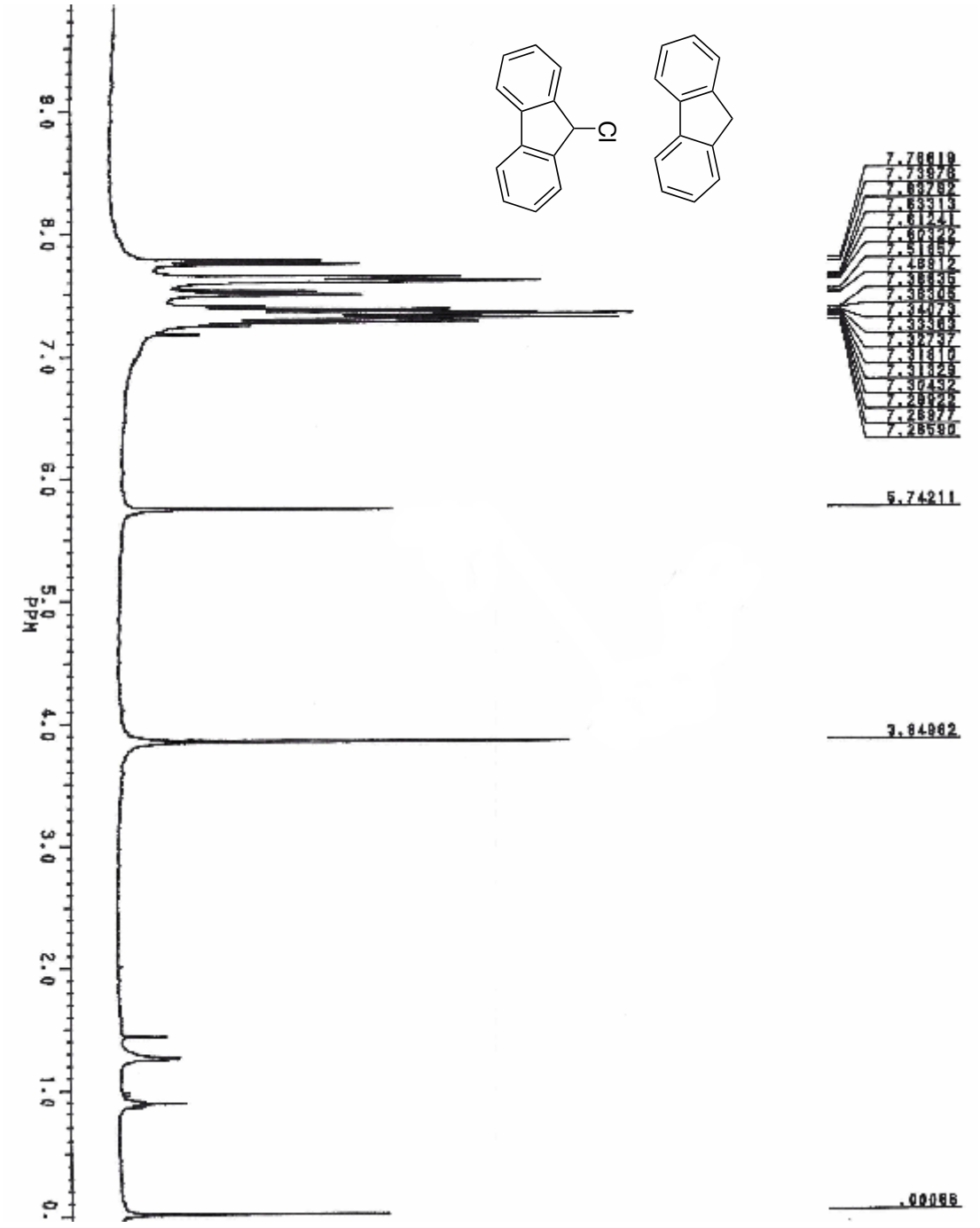
^{1}H NMR spectrum of compound 210



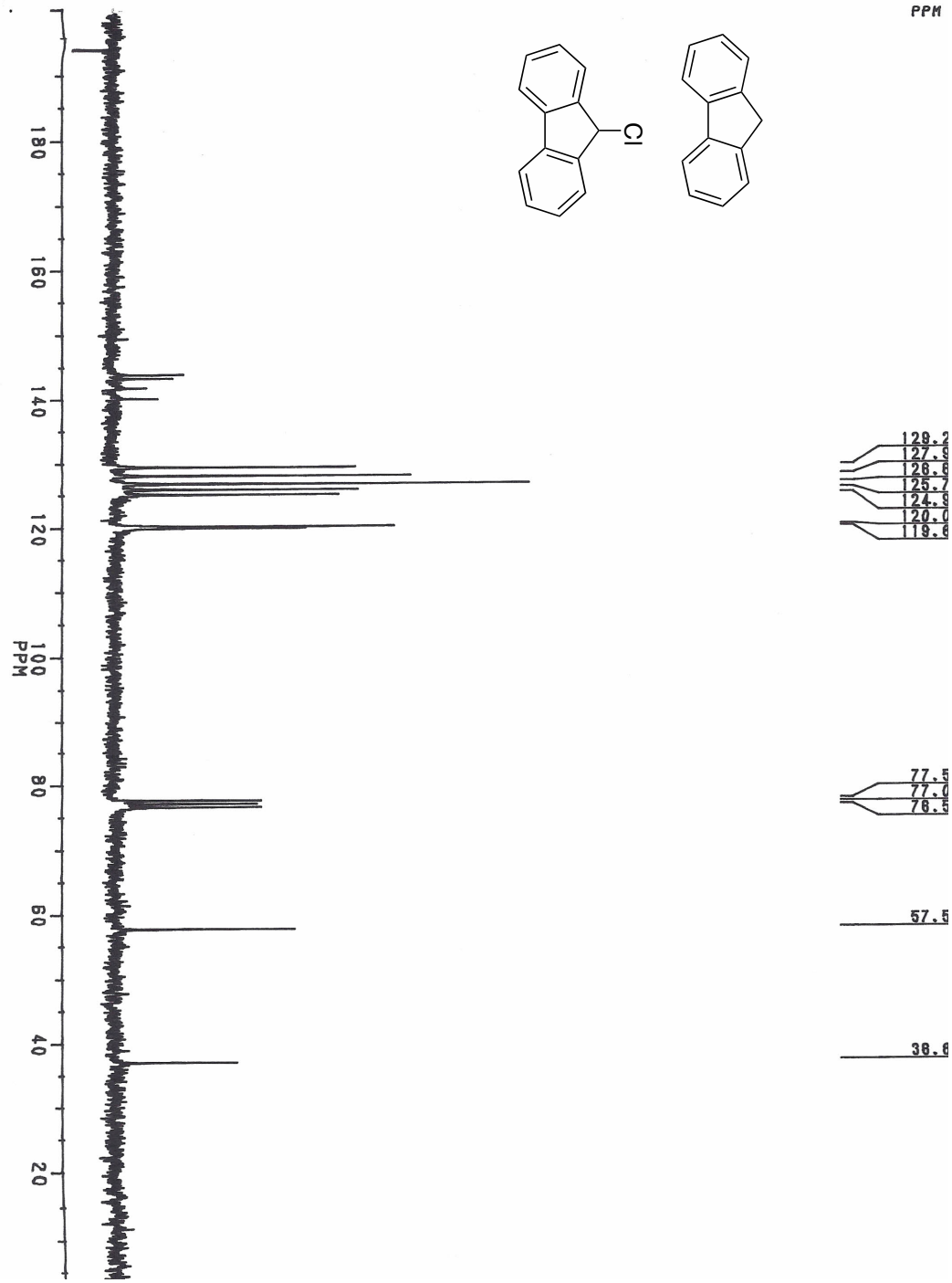
^{13}C NMR spectrum of compound 210



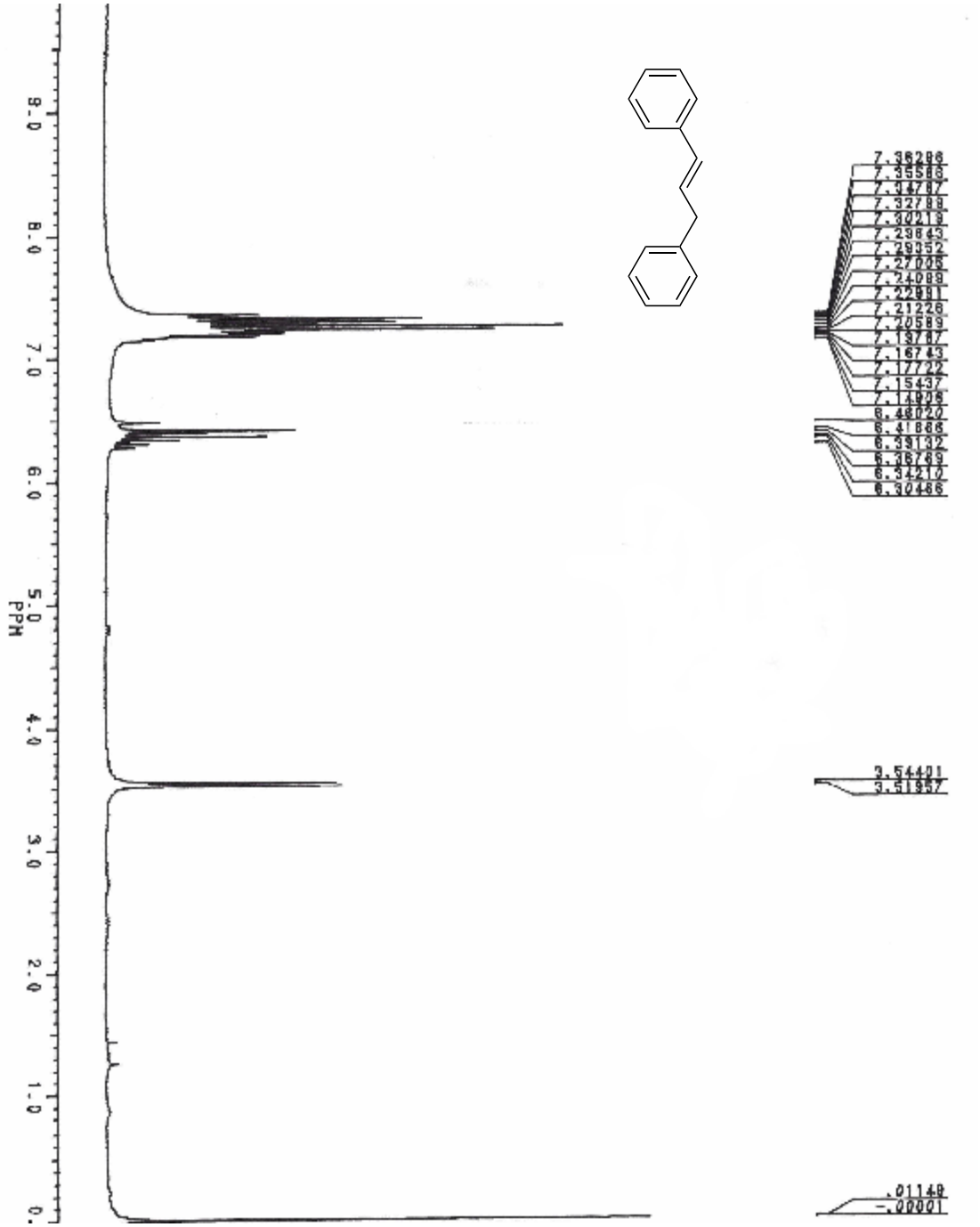
^{1}H NMR spectrum of compound 212



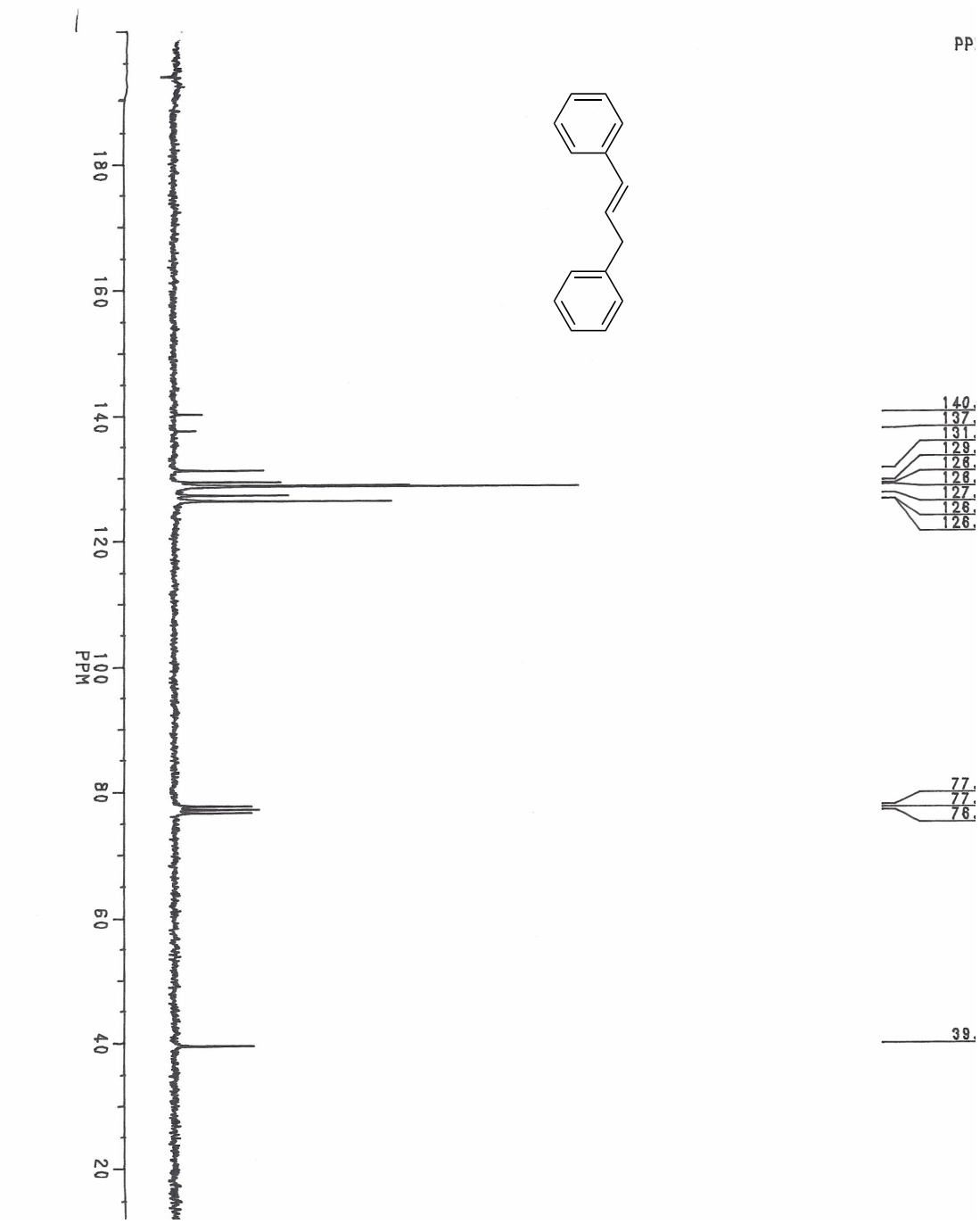
^{13}C NMR spectrum of compound 212



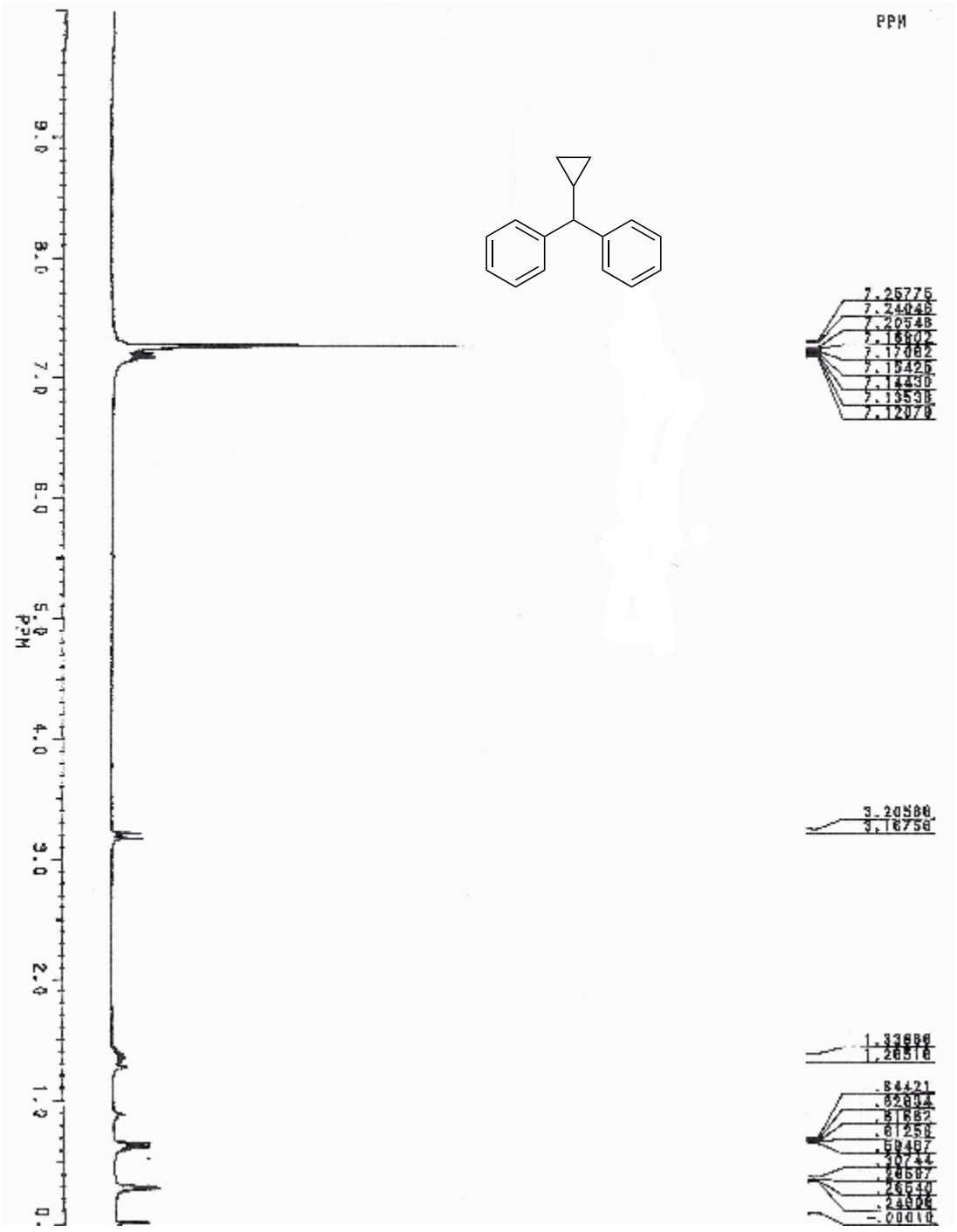
^{1}H NMR spectrum of compound 213



^{13}C NMR spectrum of compound 213



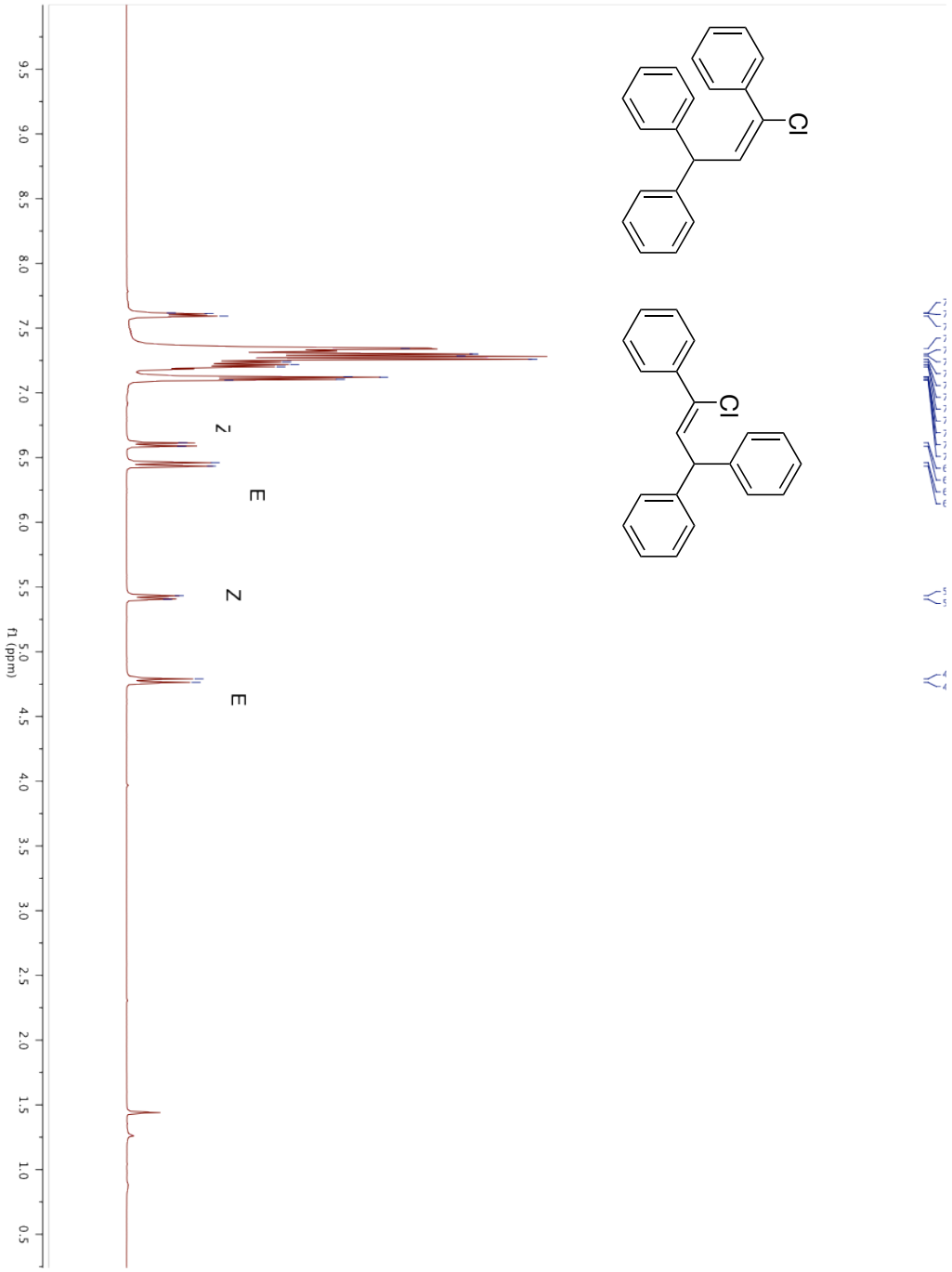
^{1}H NMR spectrum of compound 214



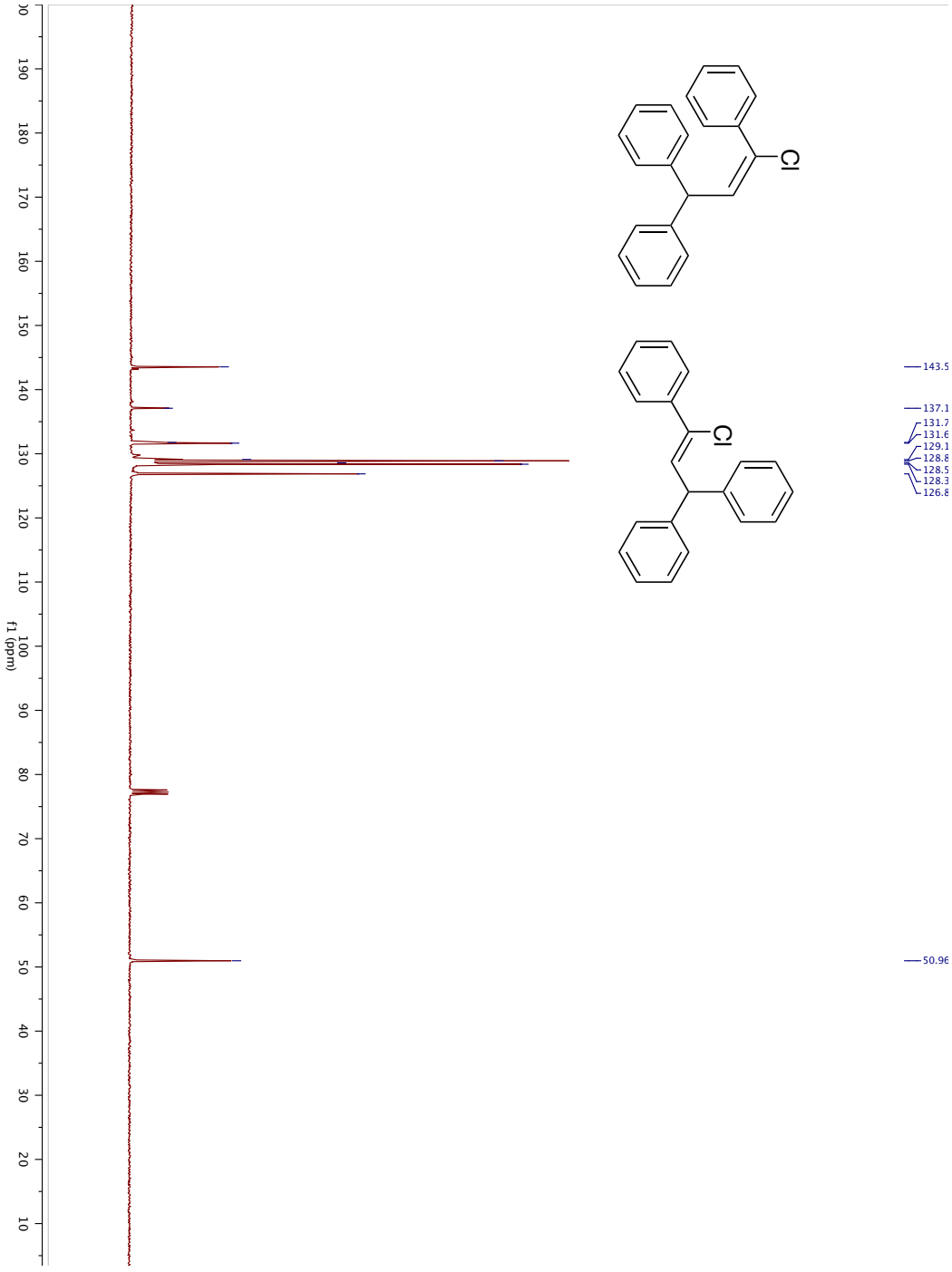
^{13}C NMR spectrum of compound 214

Appendix B: Representative NMR Spectra From Chapter 3

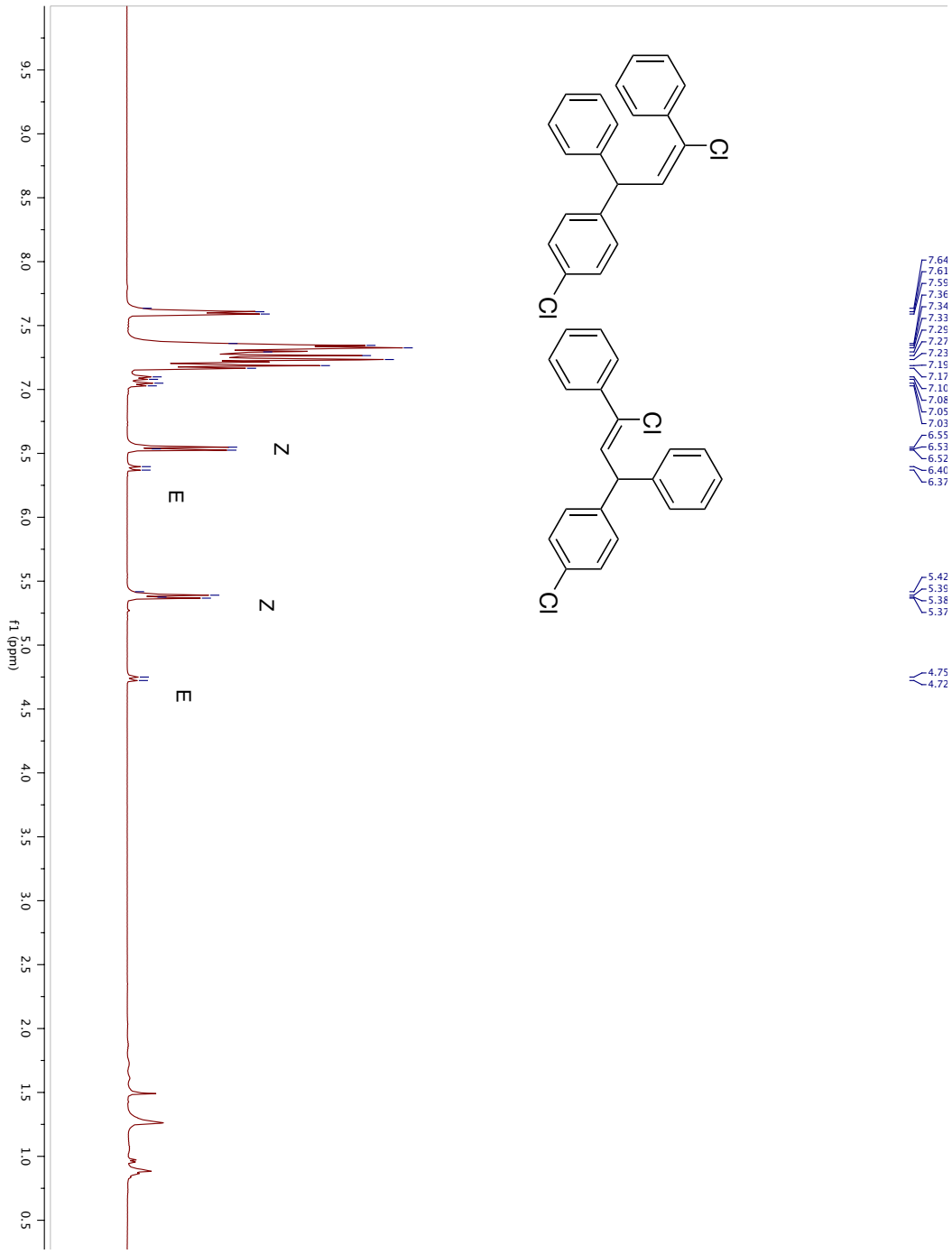
^{1}H NMR spectrum of 301a and 301b



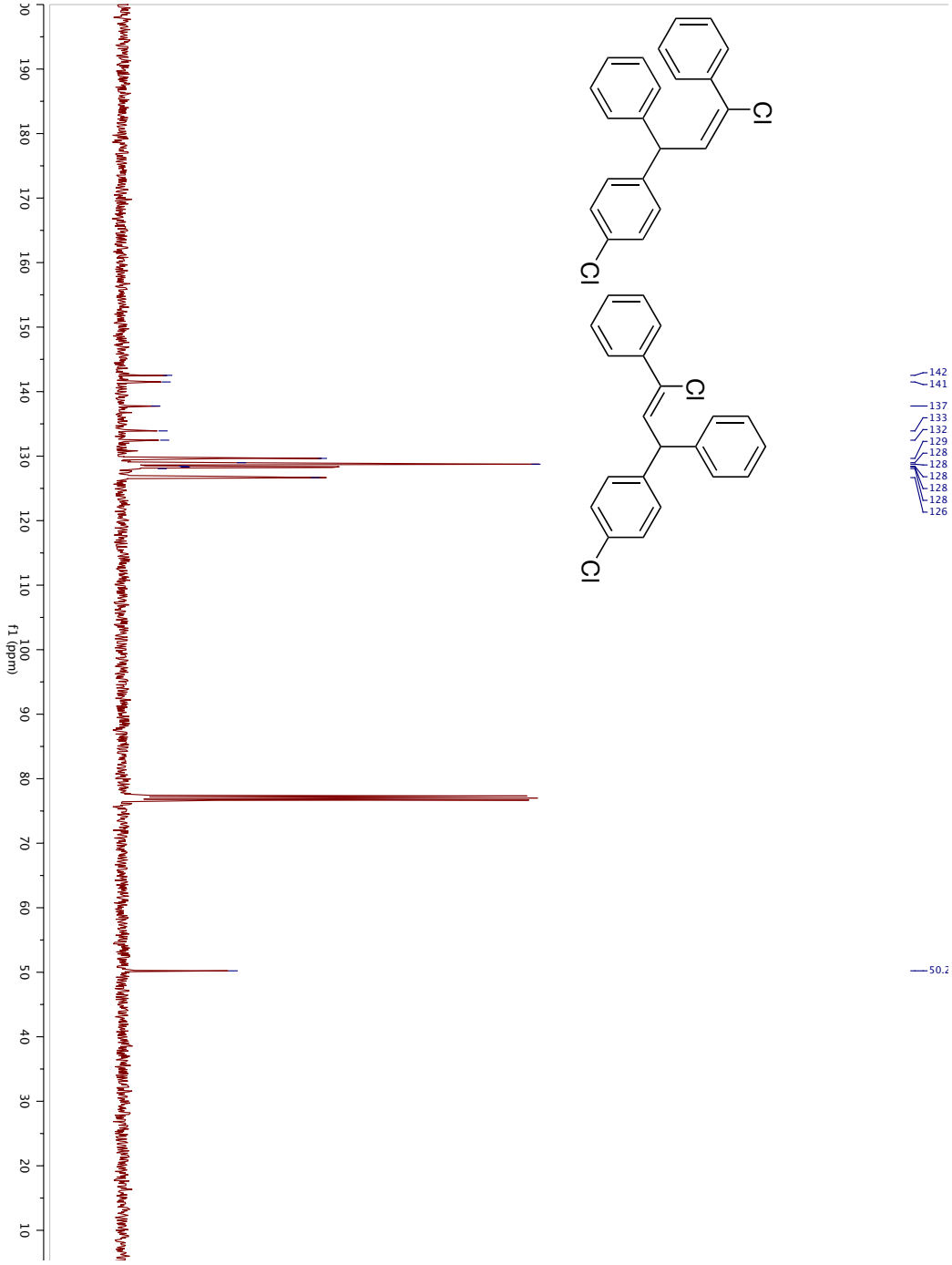
^{13}C NMR spectrum of compound 301a and 301b



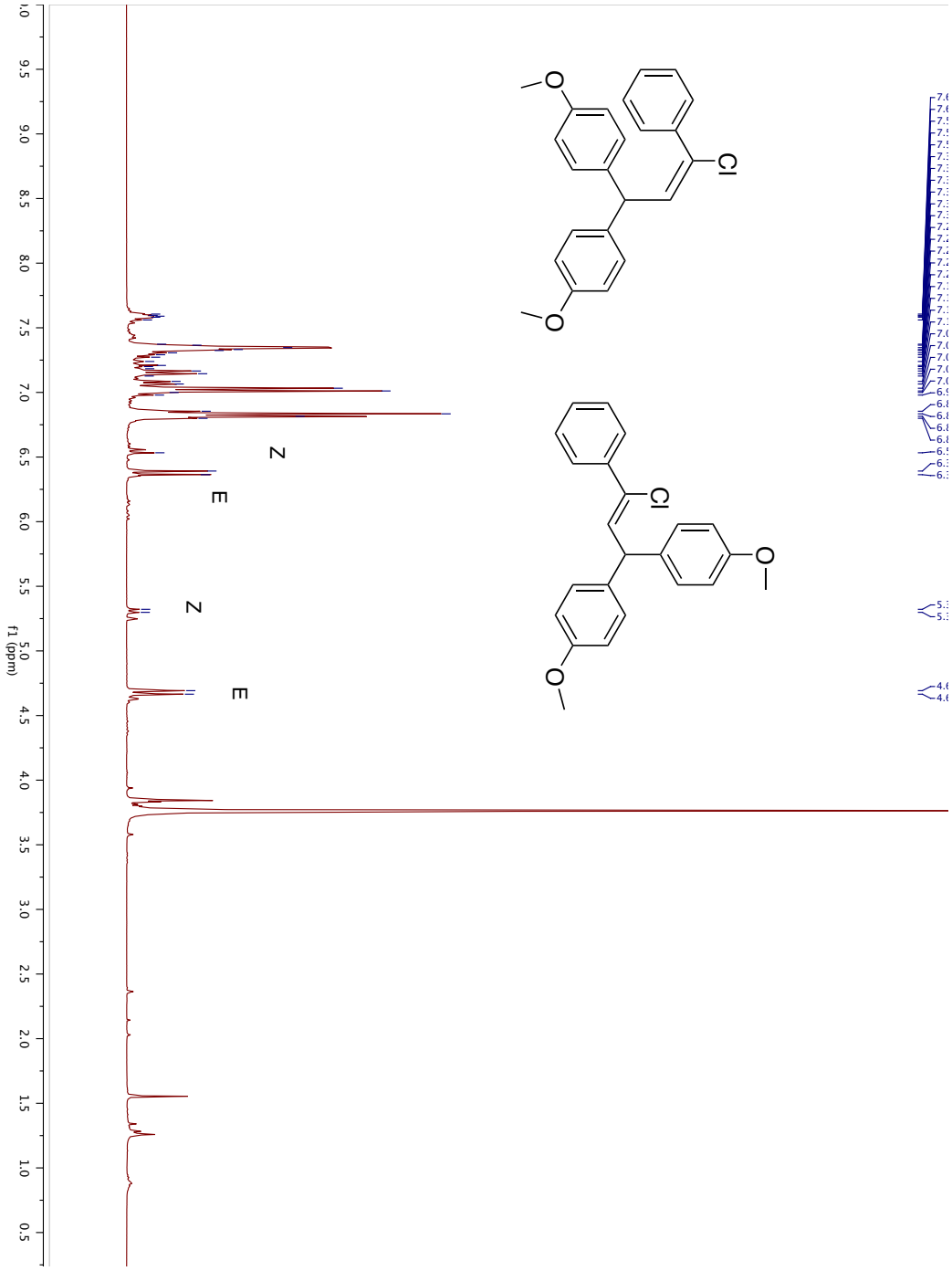
^{1}H NMR spectrum of 302a and 302b



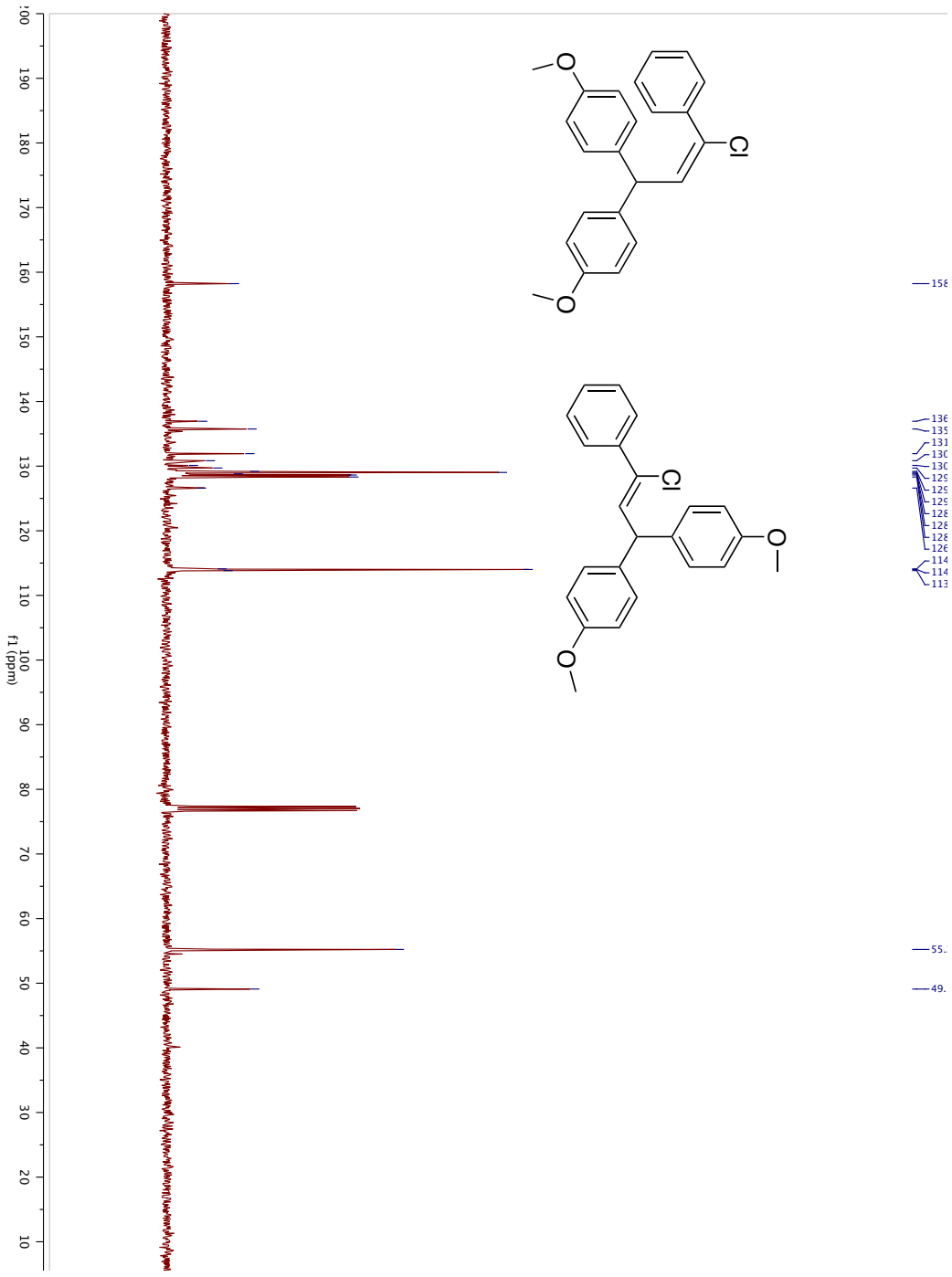
^{13}C NMR spectrum of 302a and 302b



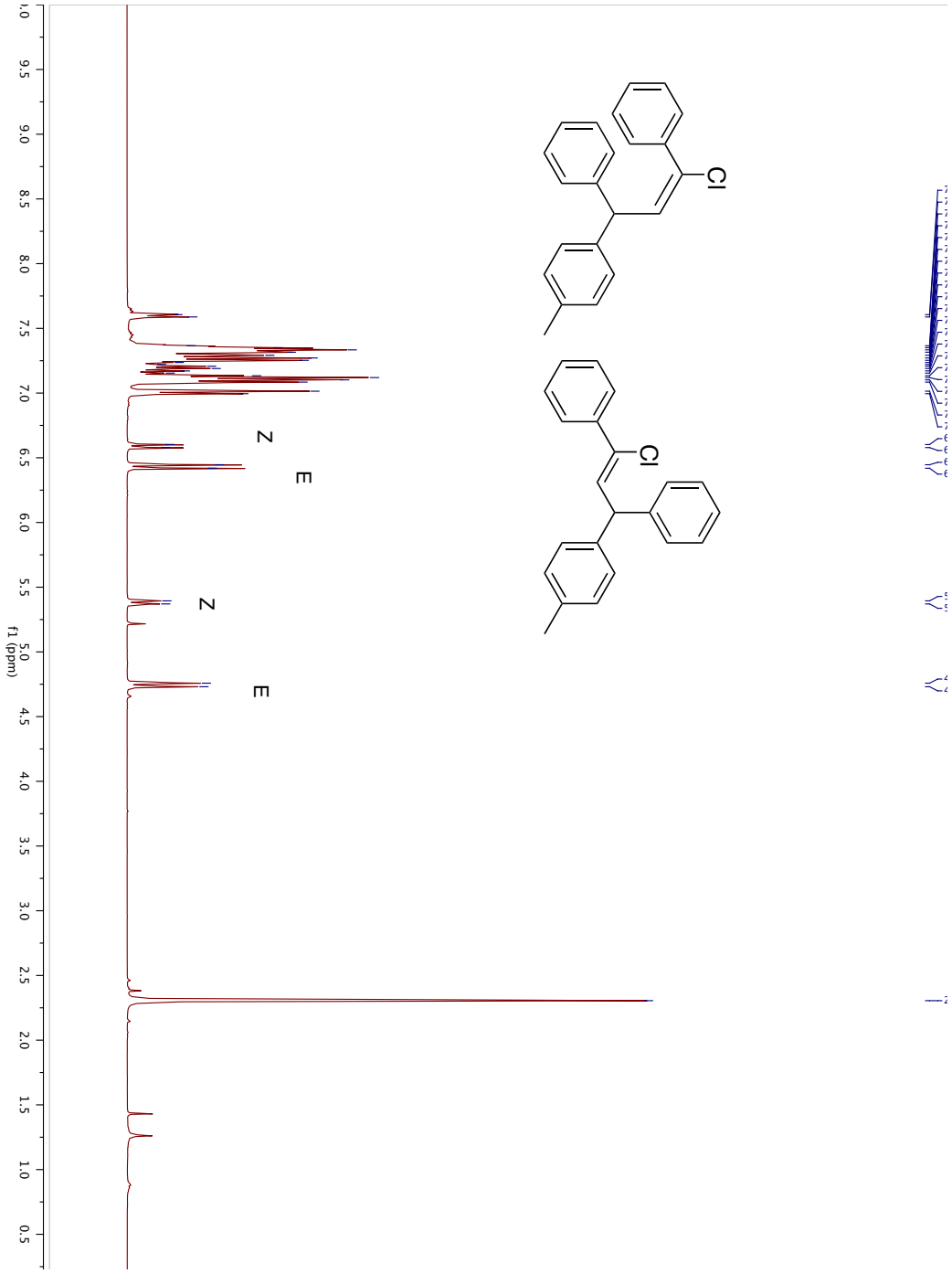
^{1}H NMR spectrum of 303a and 303b



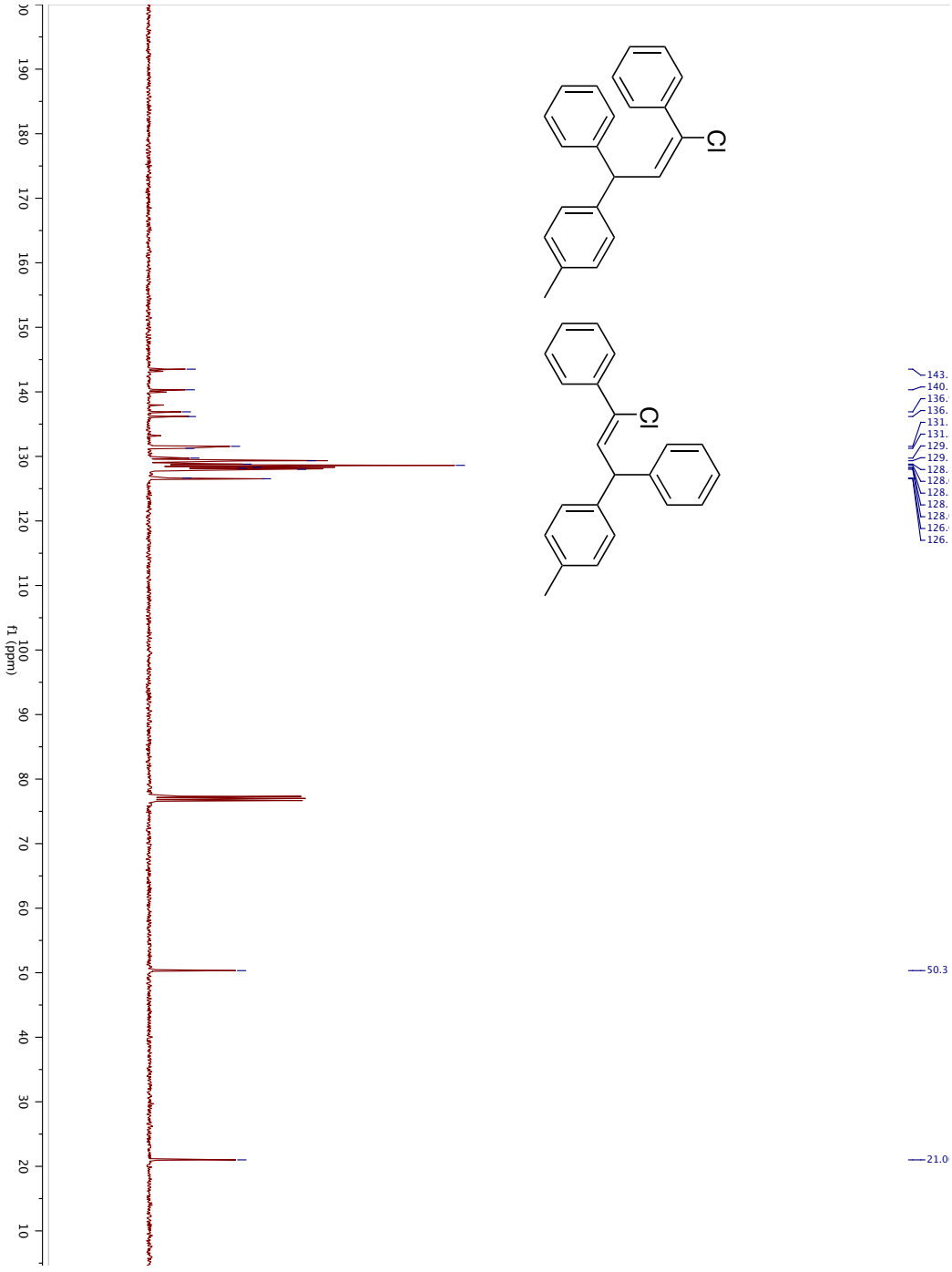
^{13}C NMR spectrum of 303a and 303b



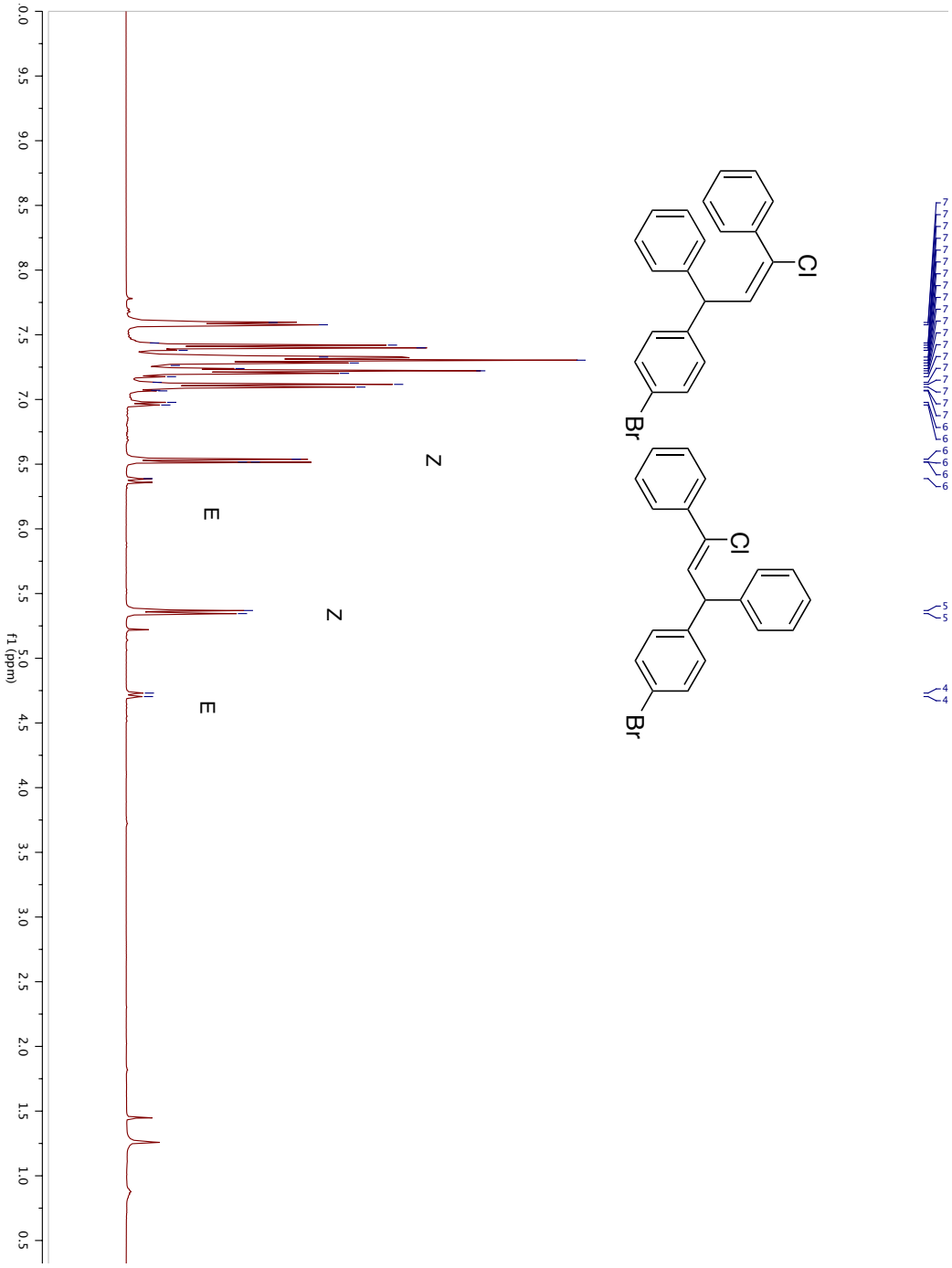
^{1}H NMR spectrum of 304a and 304b



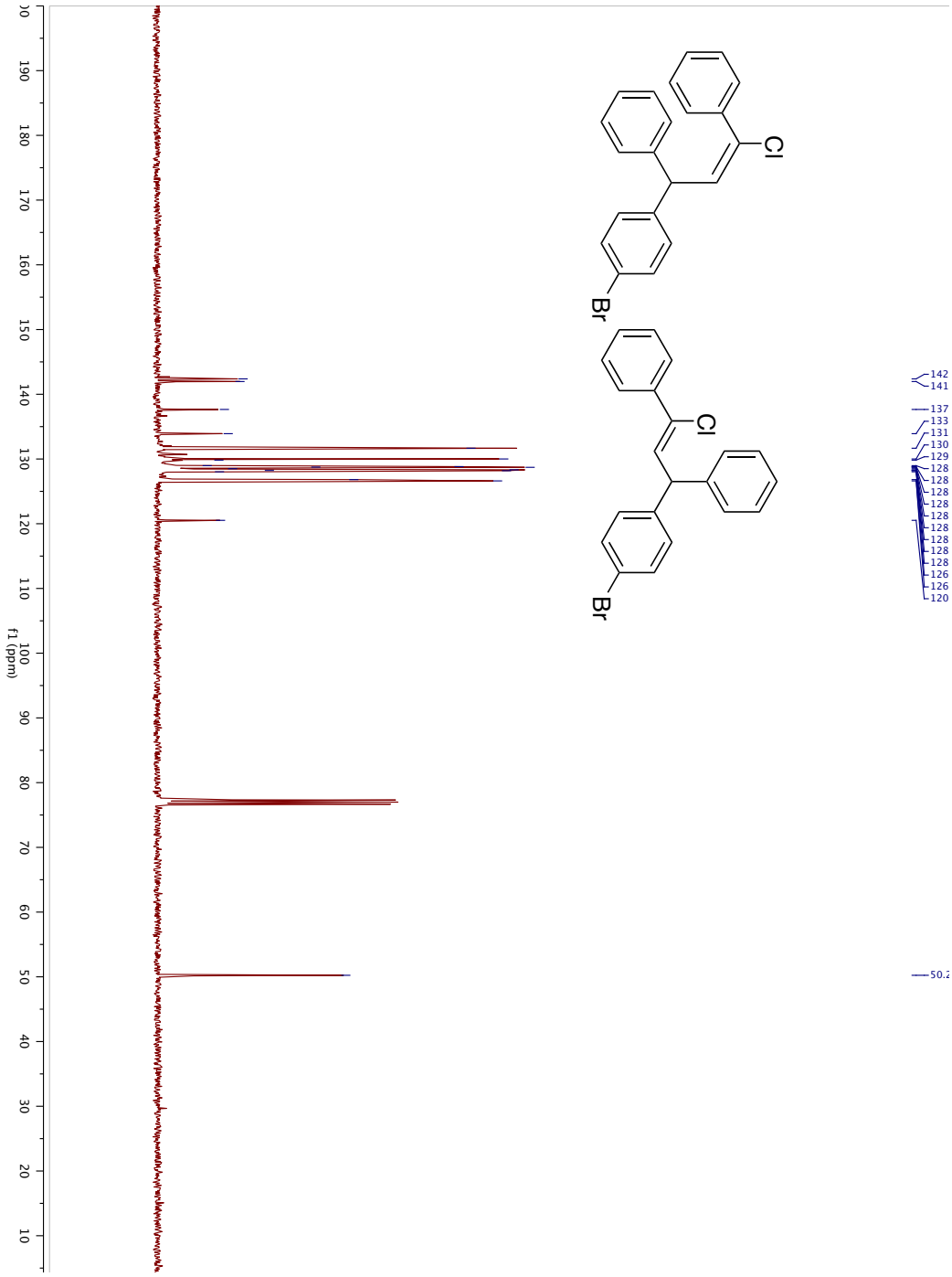
^{13}C NMR spectrum of 304a and 304b



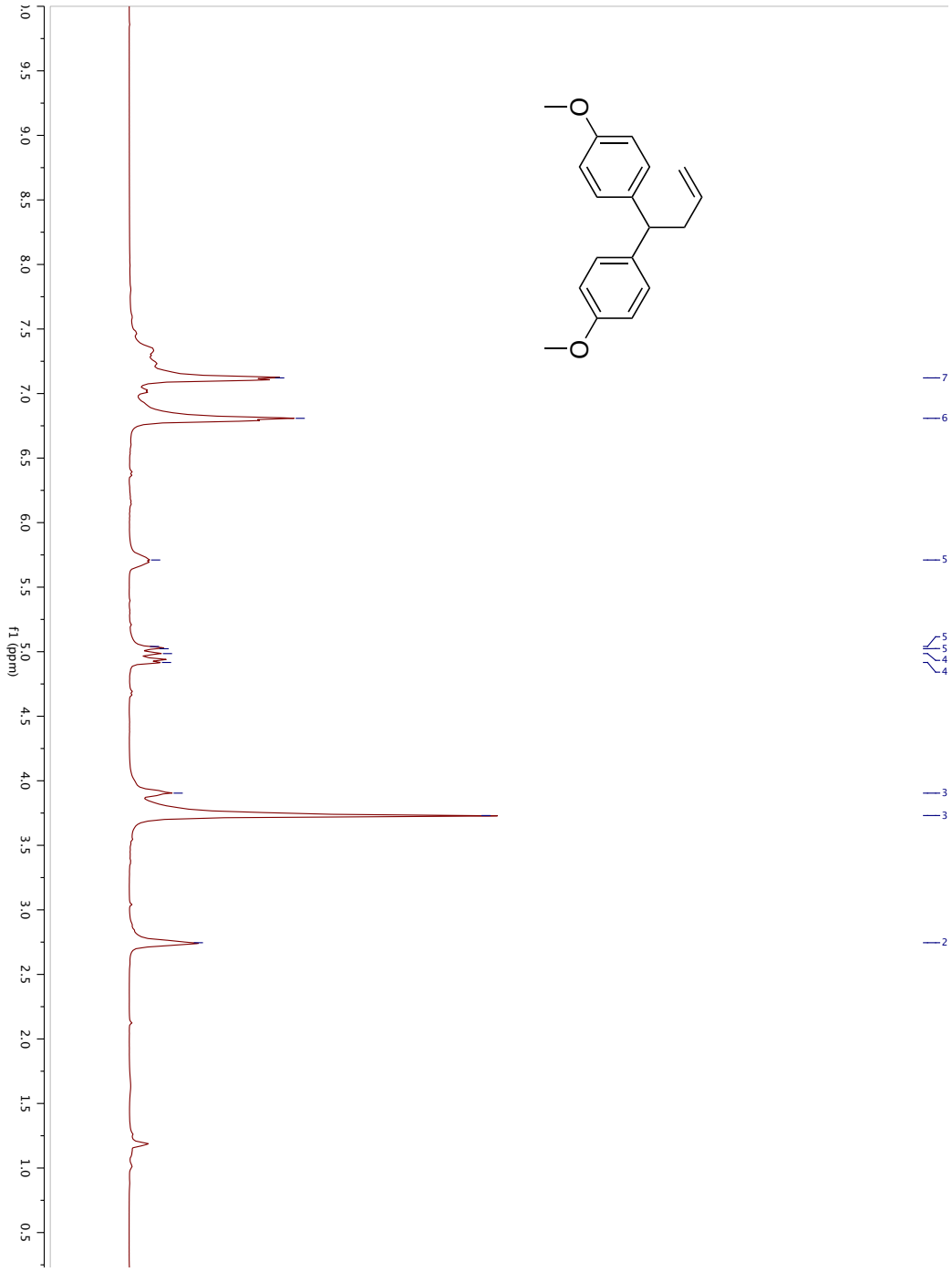
^{1}H NMR spectrum of 305a and 305b



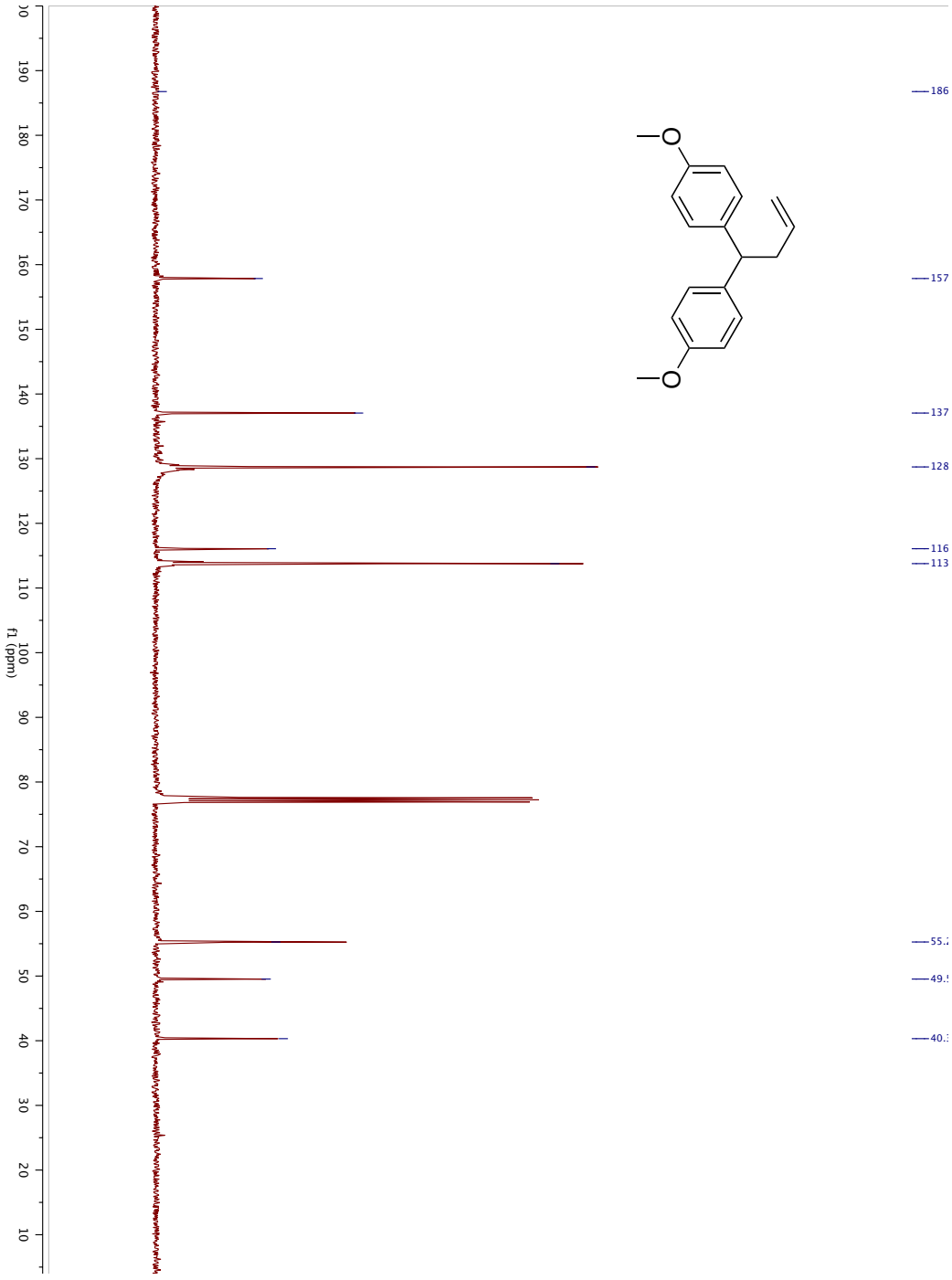
^{13}C NMR spectrum of 305a and 305b



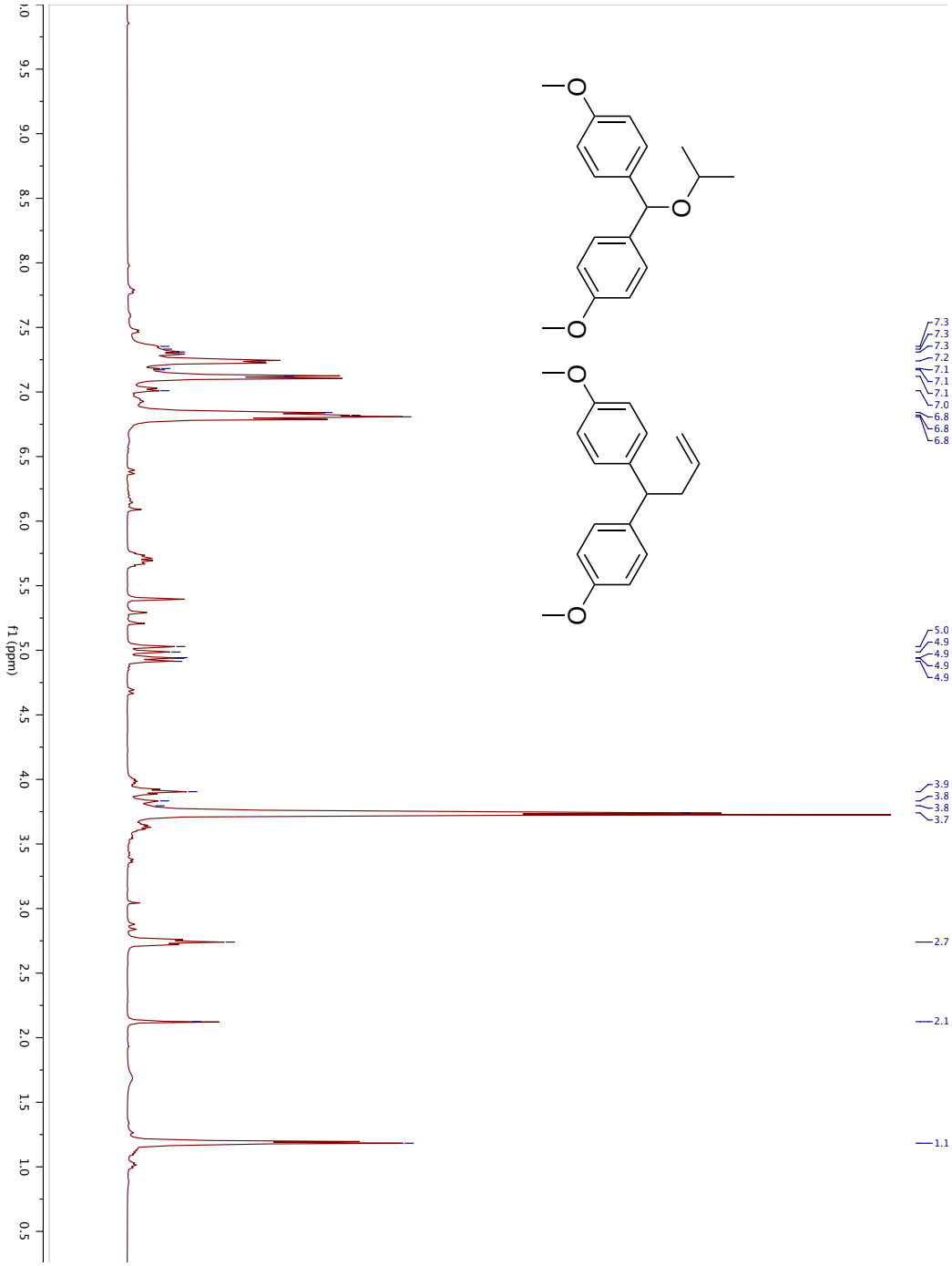
^{1}H NMR spectrum of 306



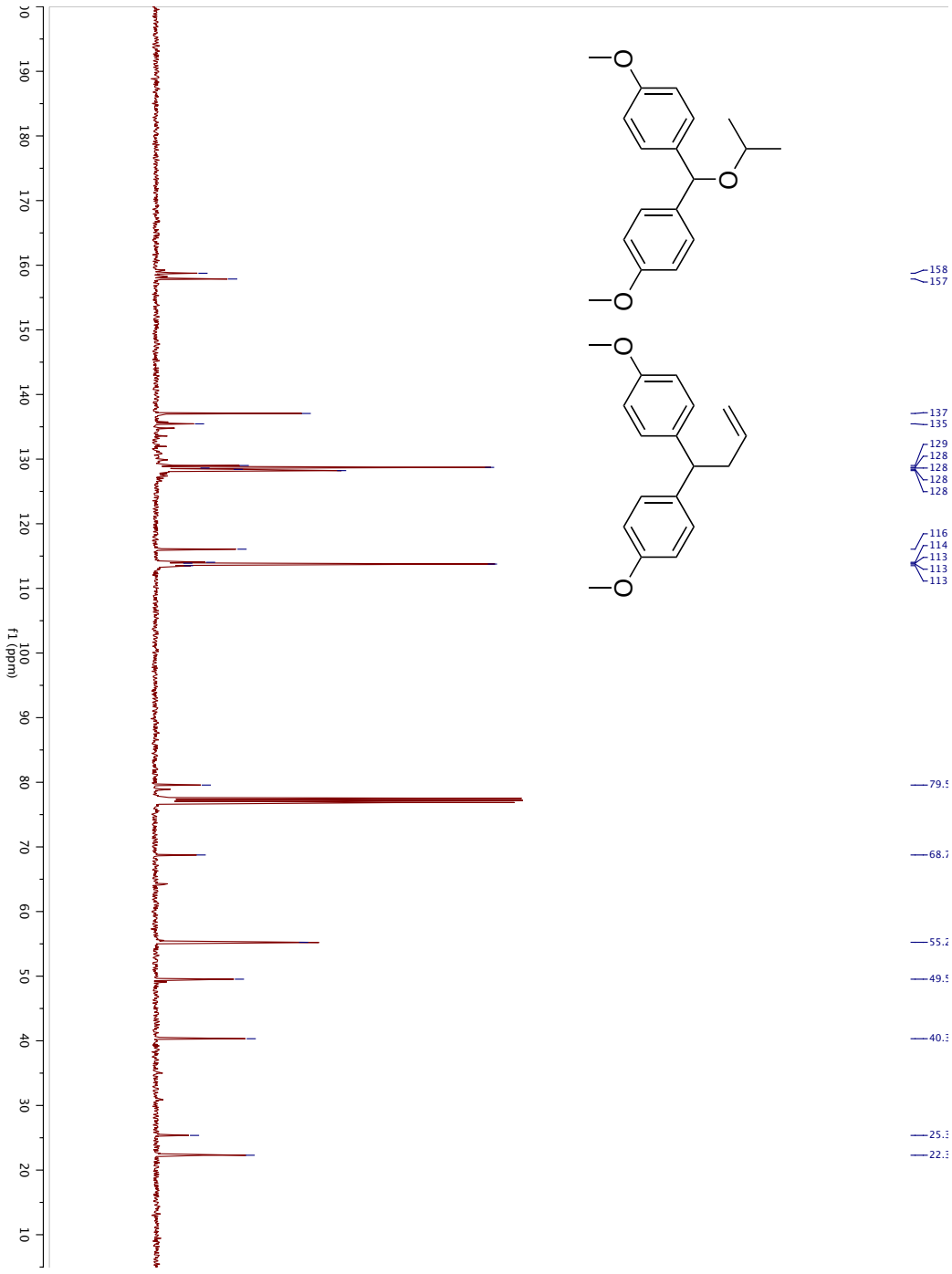
^{13}C NMR spectrum of 306



^{1}H NMR spectrum of 307 and 306

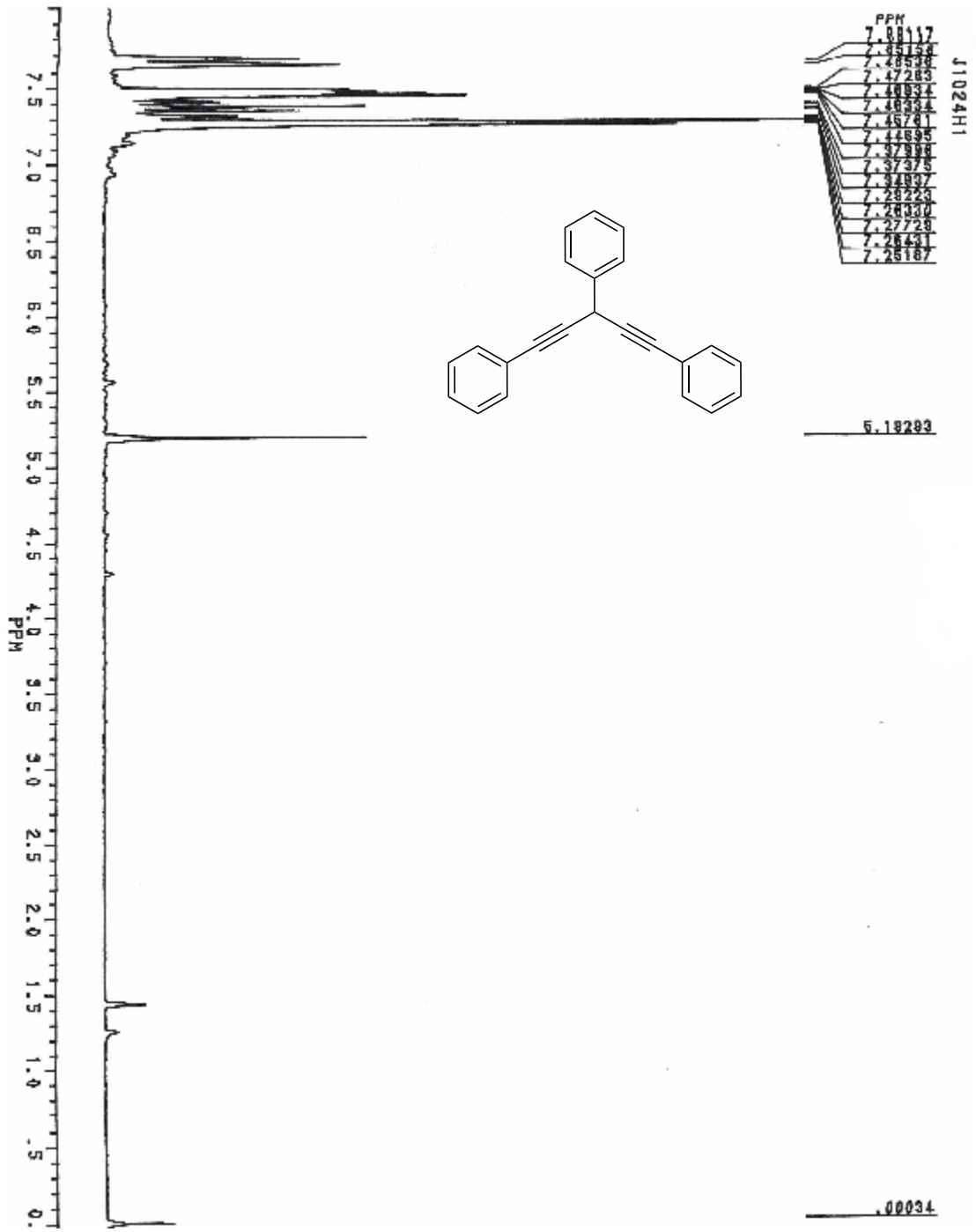


^{13}C NMR spectrum of 307 and 306

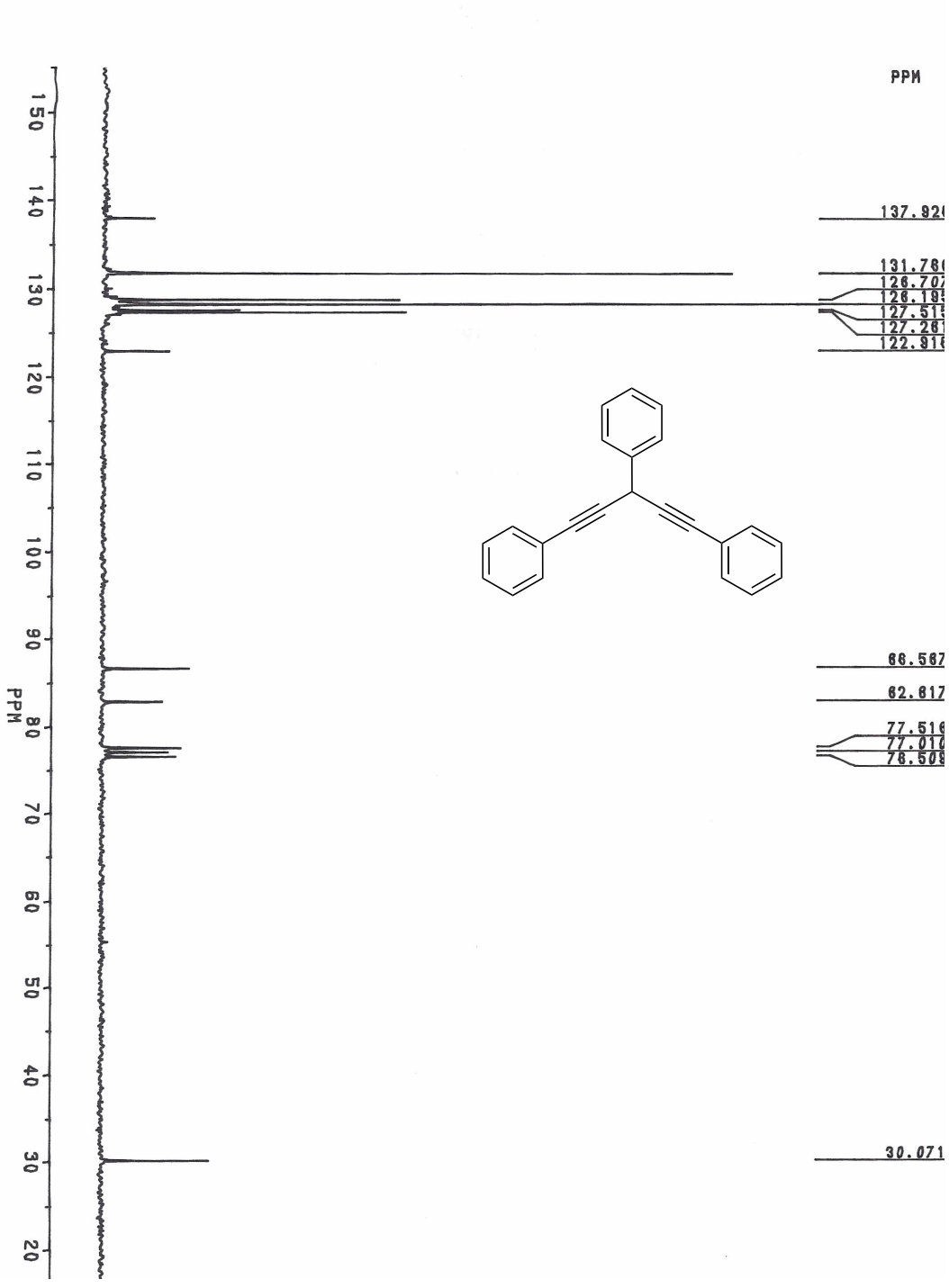


Appendix C: Representative NMR Spectra From Chapter 4

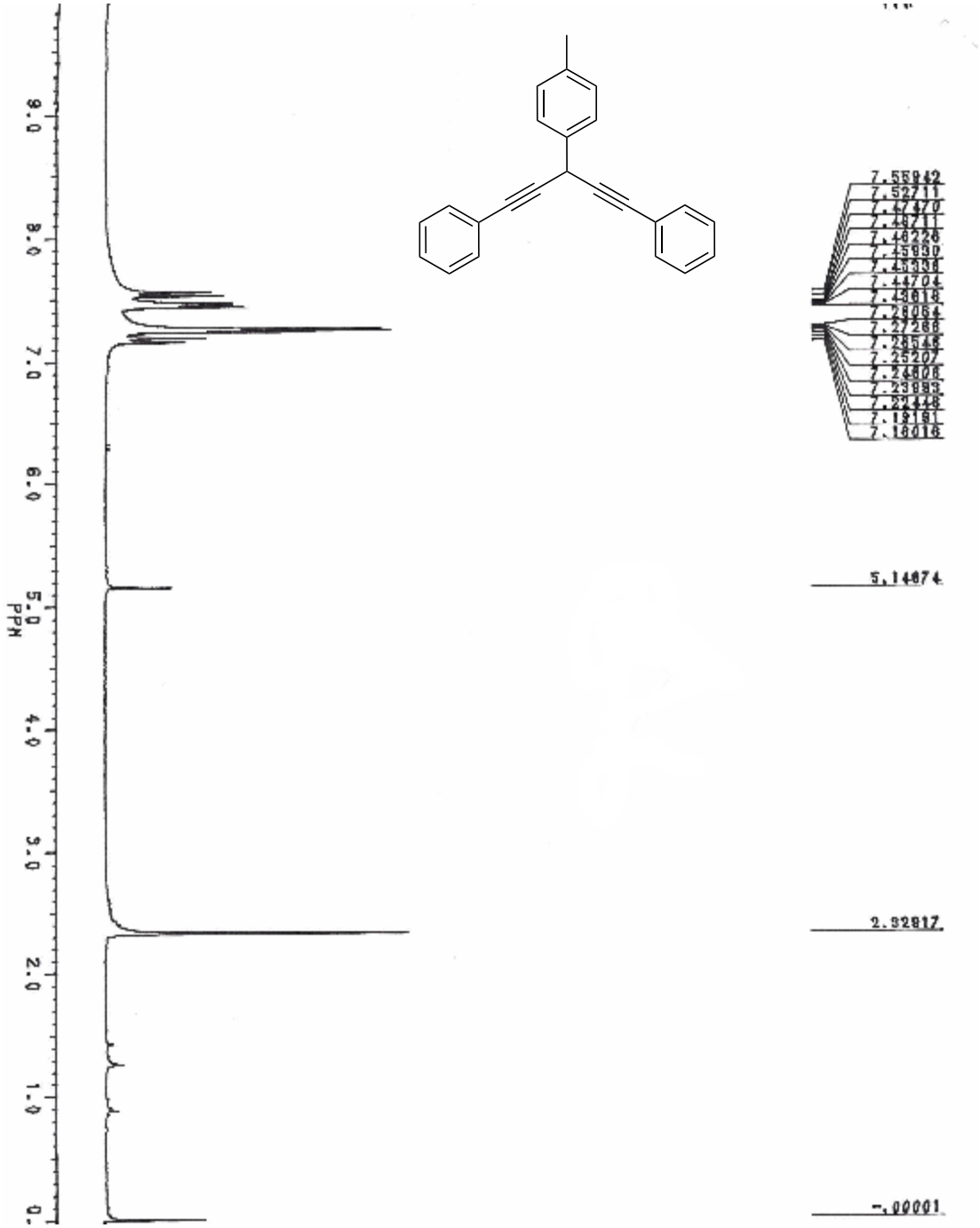
^{1}H NMR spectrum of 401



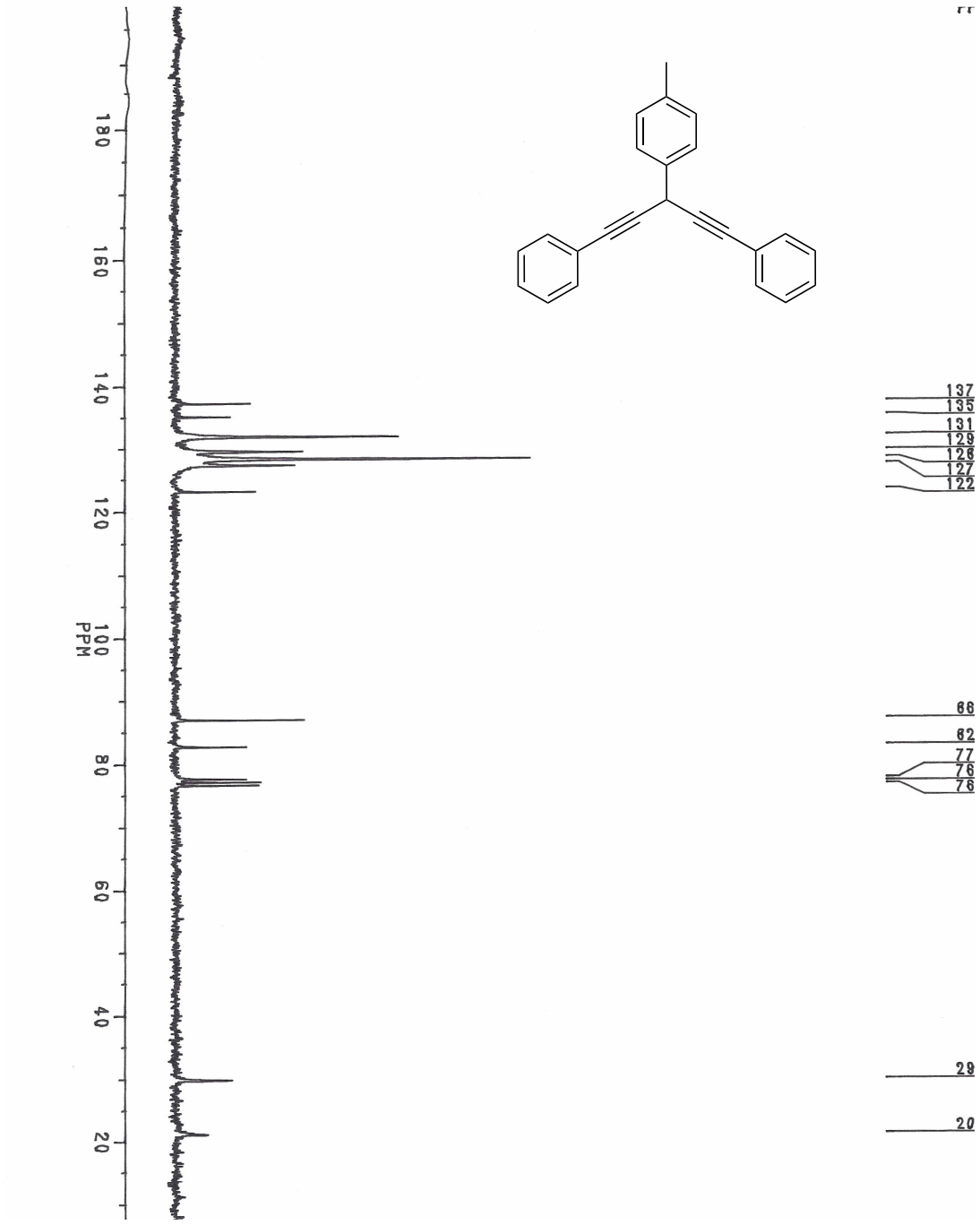
^{13}C NMR spectrum of 401



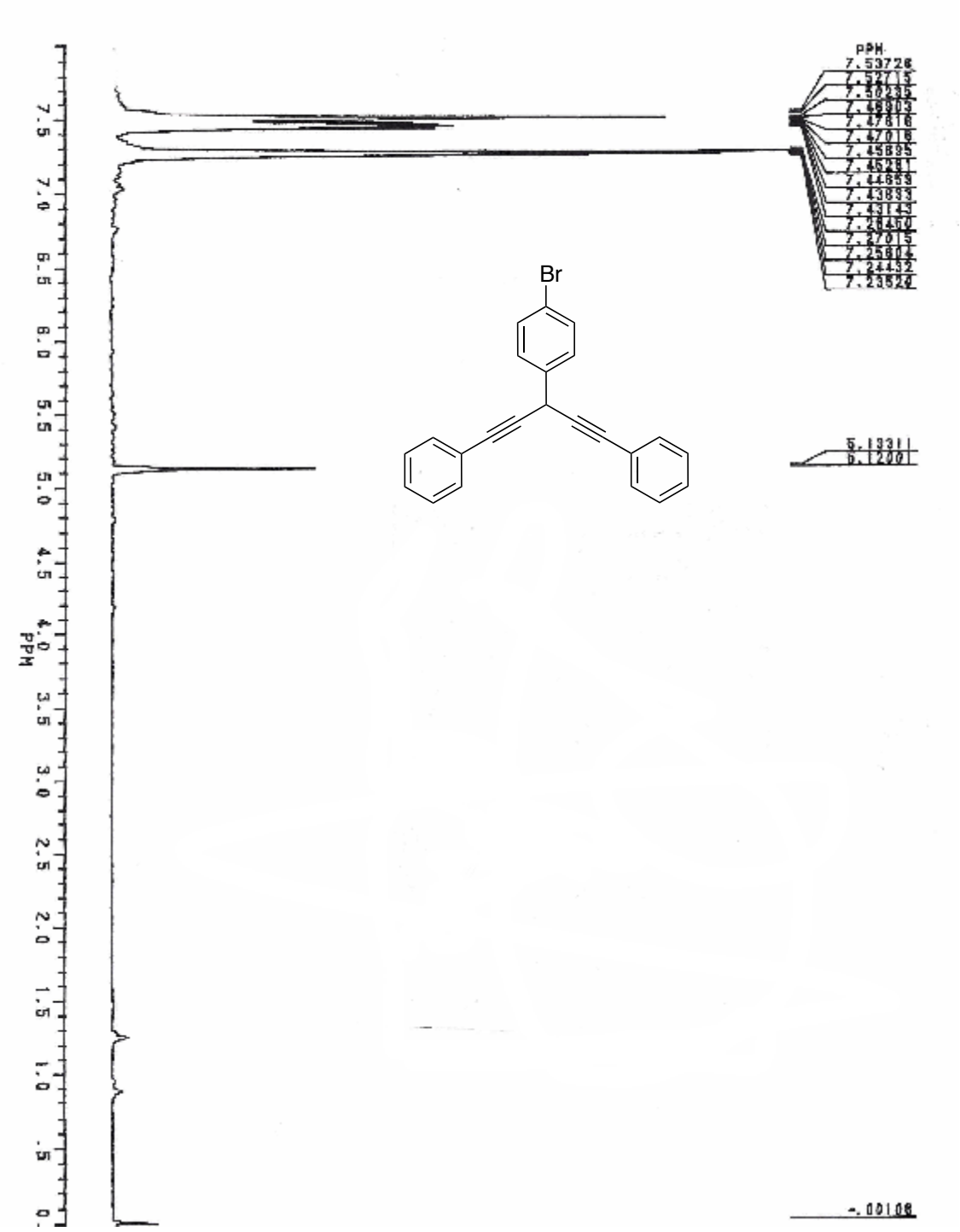
^{1}H NMR spectrum of 402



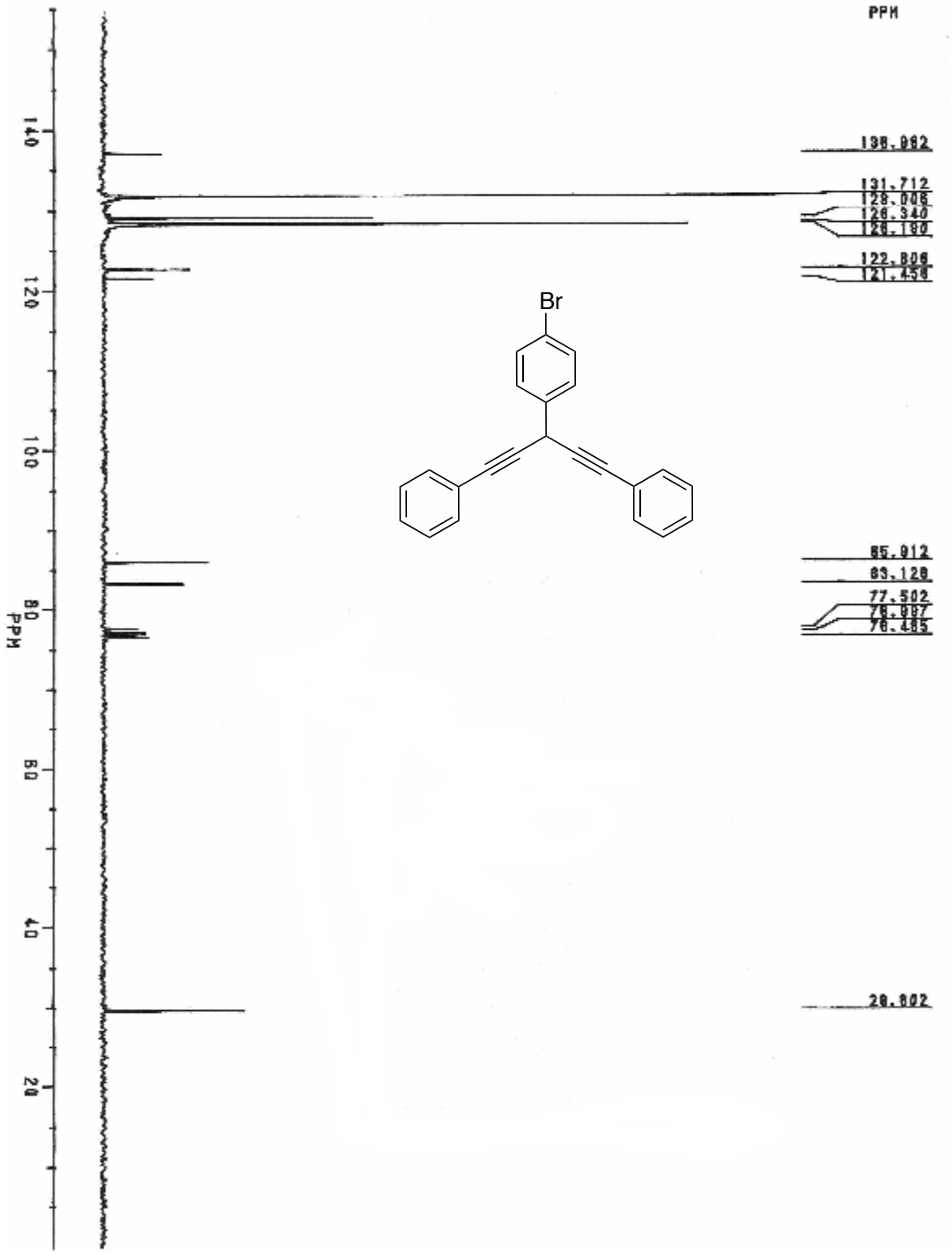
^{13}C NMR spectrum of 402



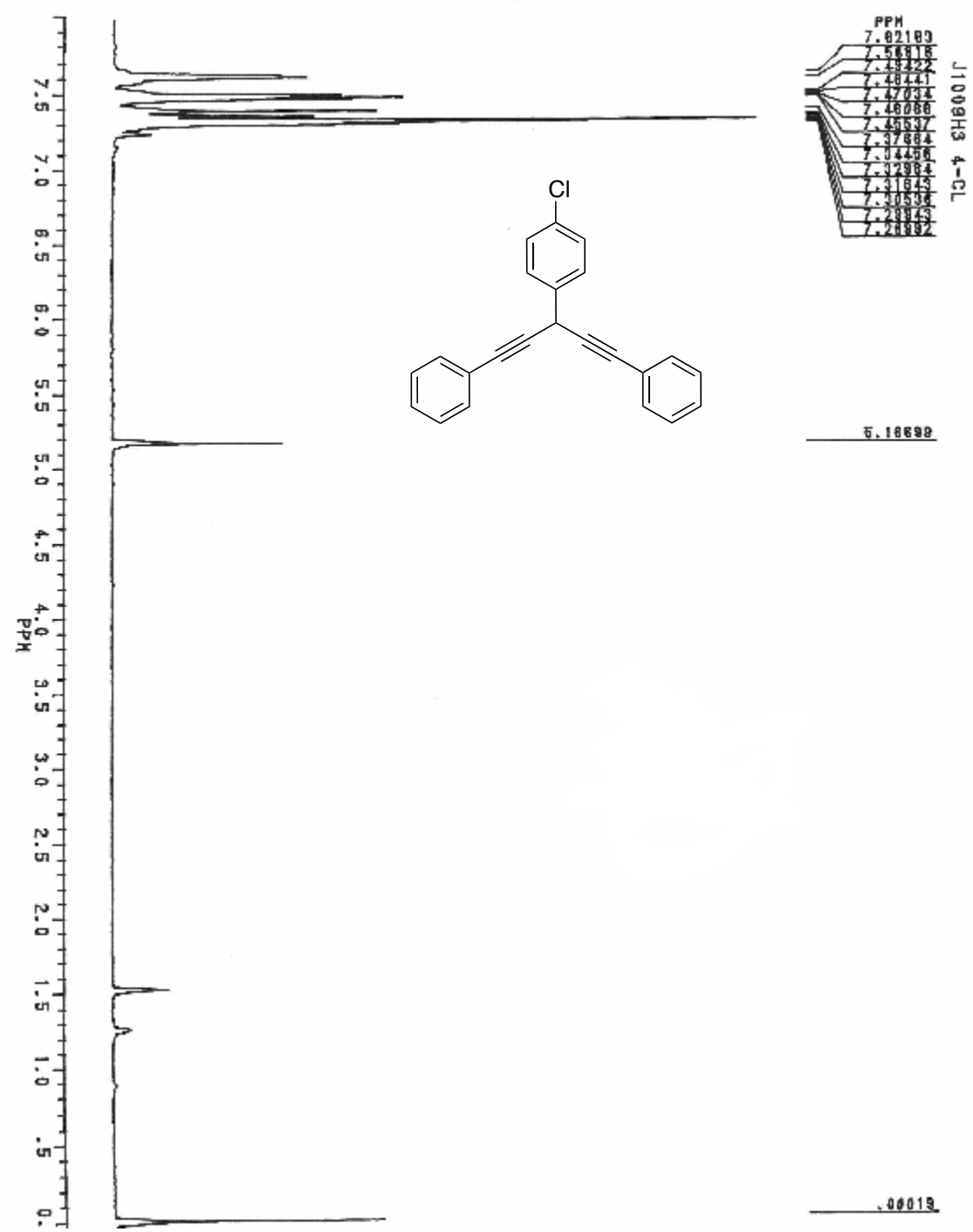
^{1}H NMR spectrum of 403



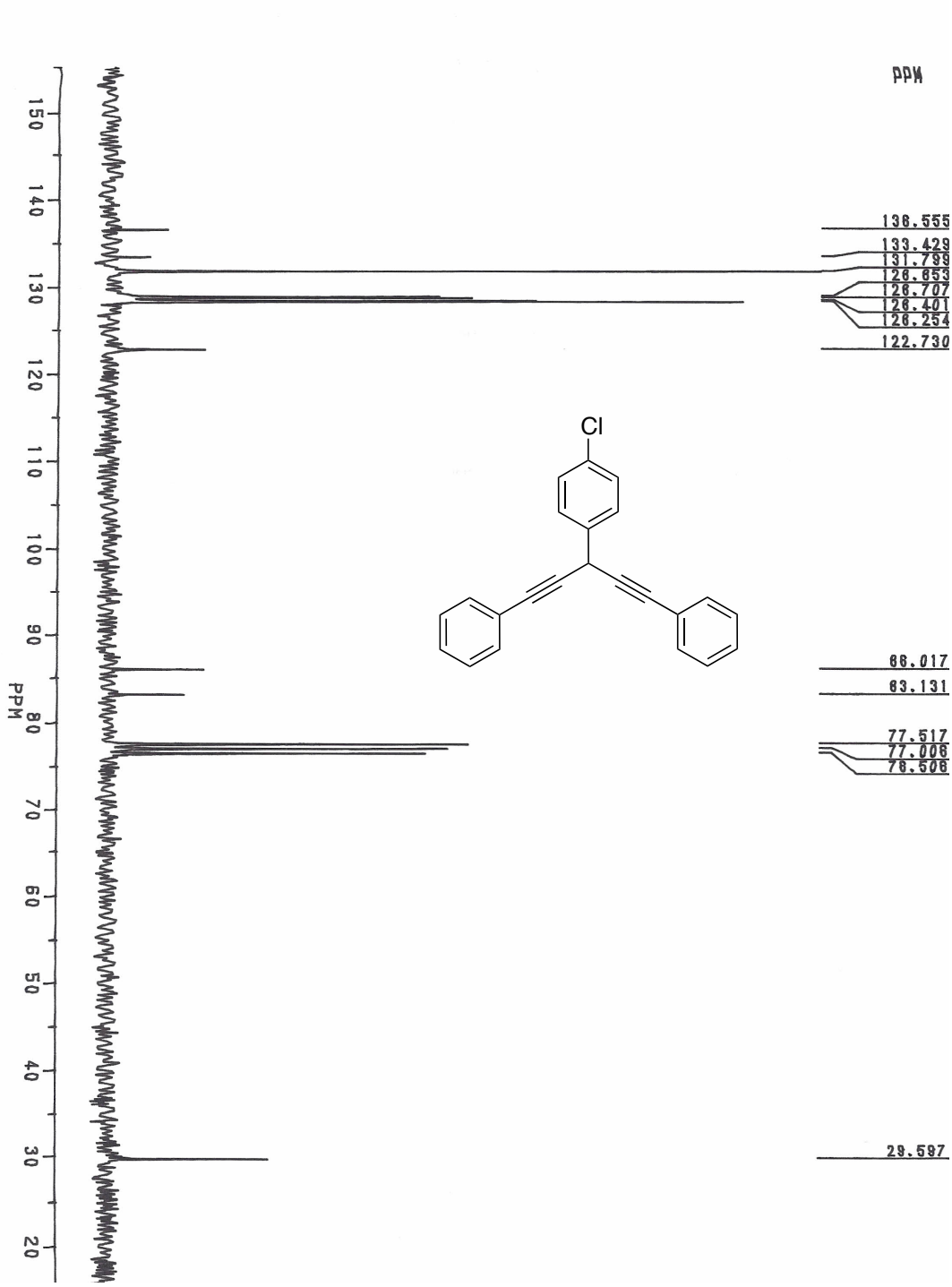
^{13}C NMR spectrum of 403



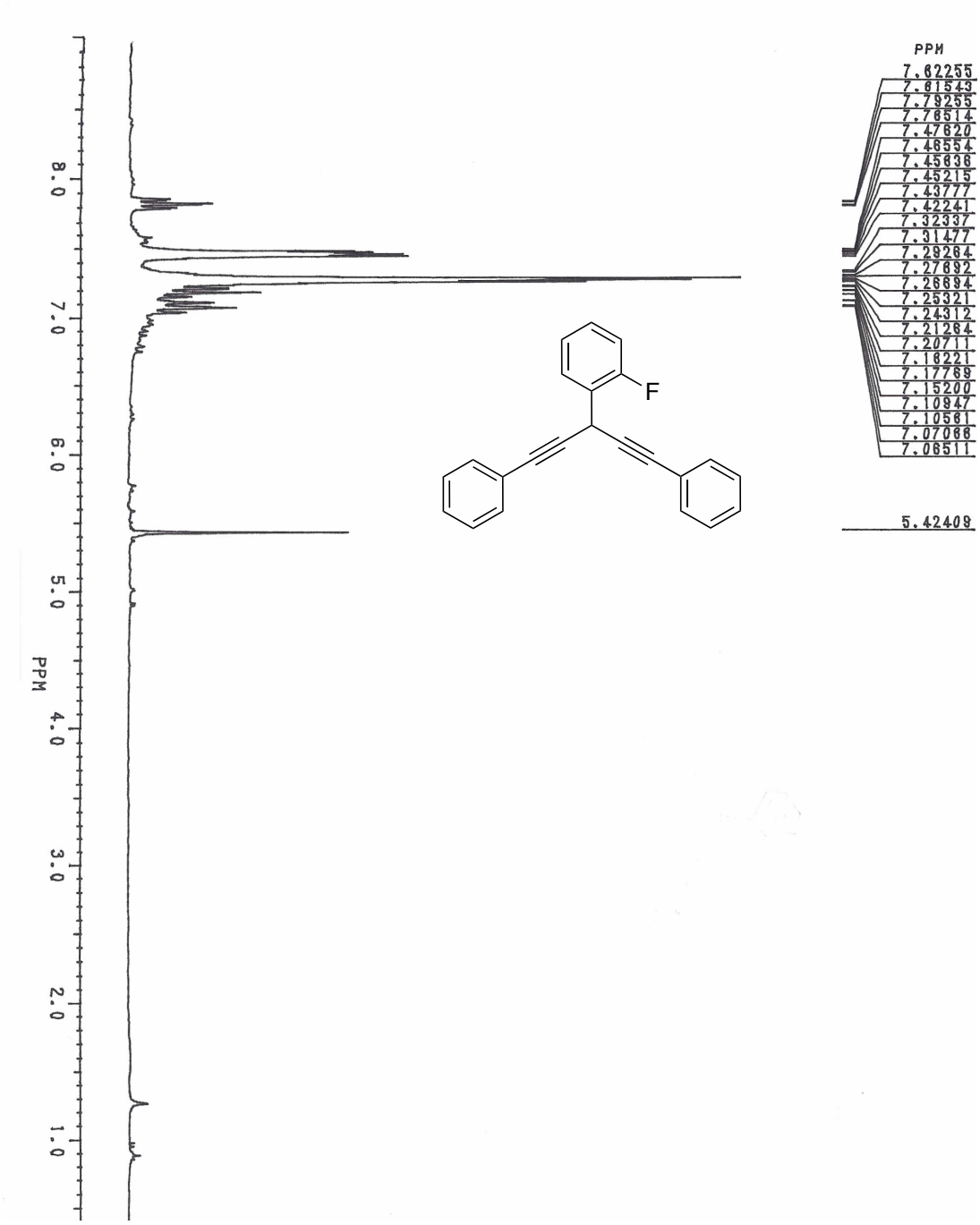
^{1}H NMR of compound 404



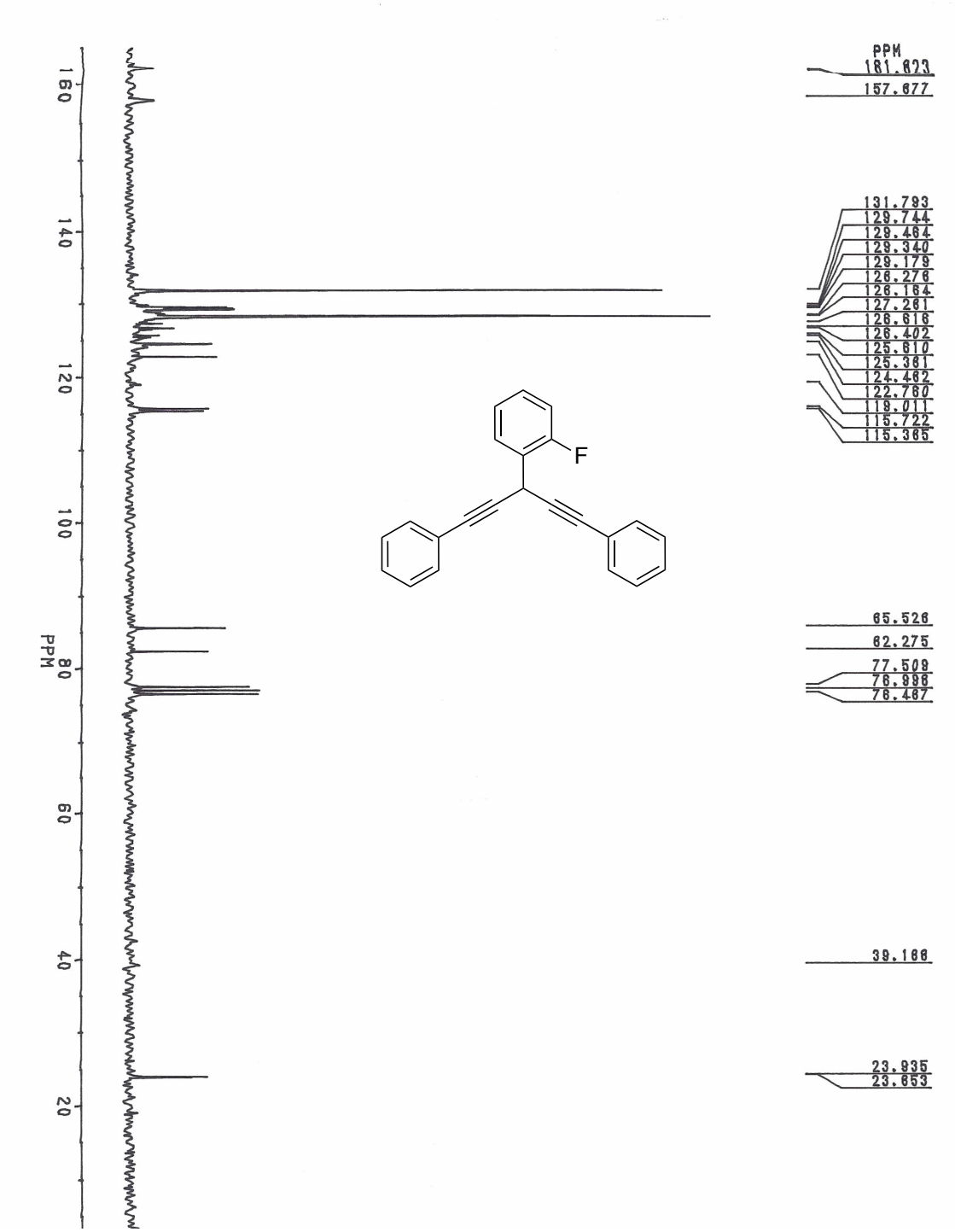
^{13}C NMR of compound 404



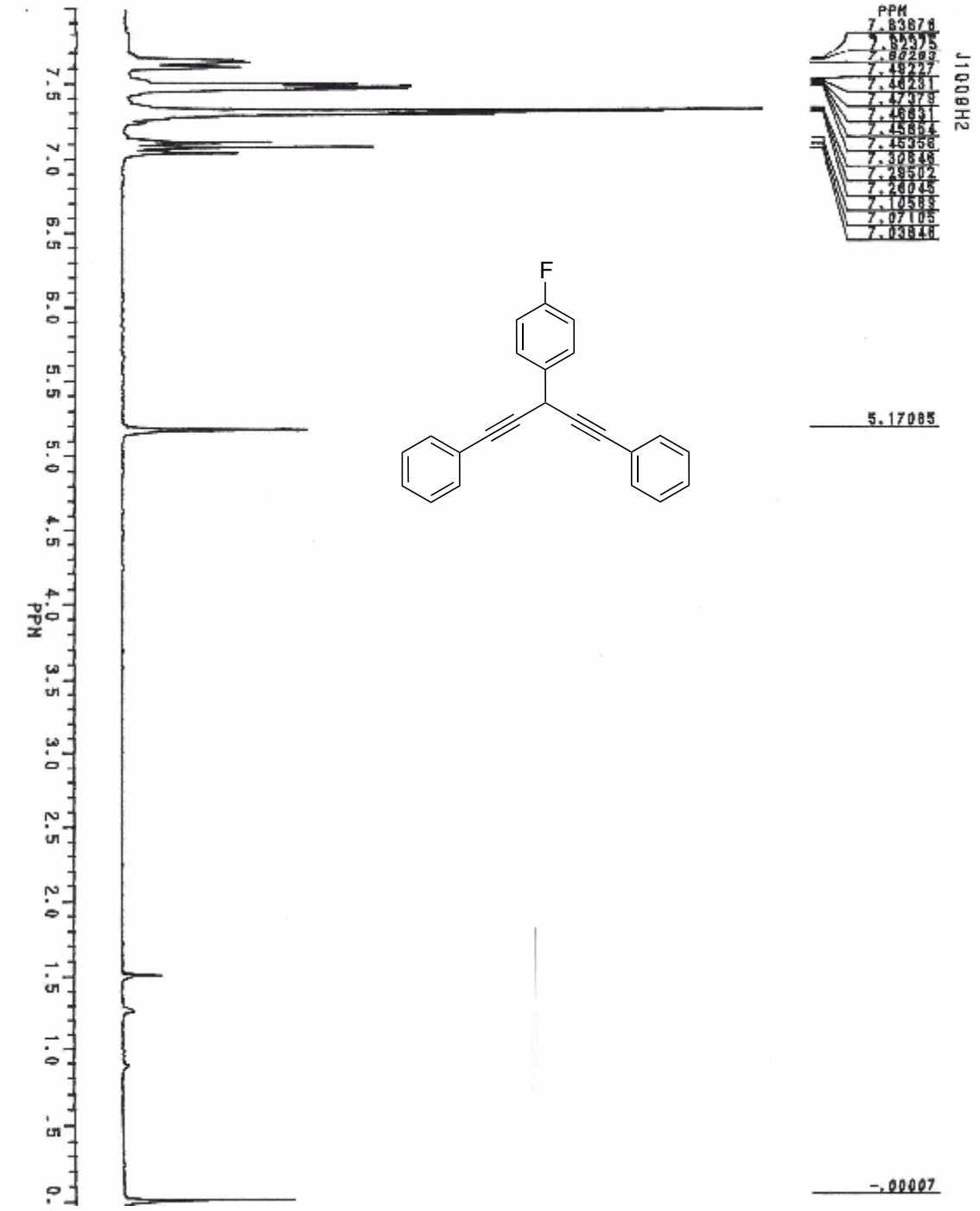
^{1}H NMR of compound 405



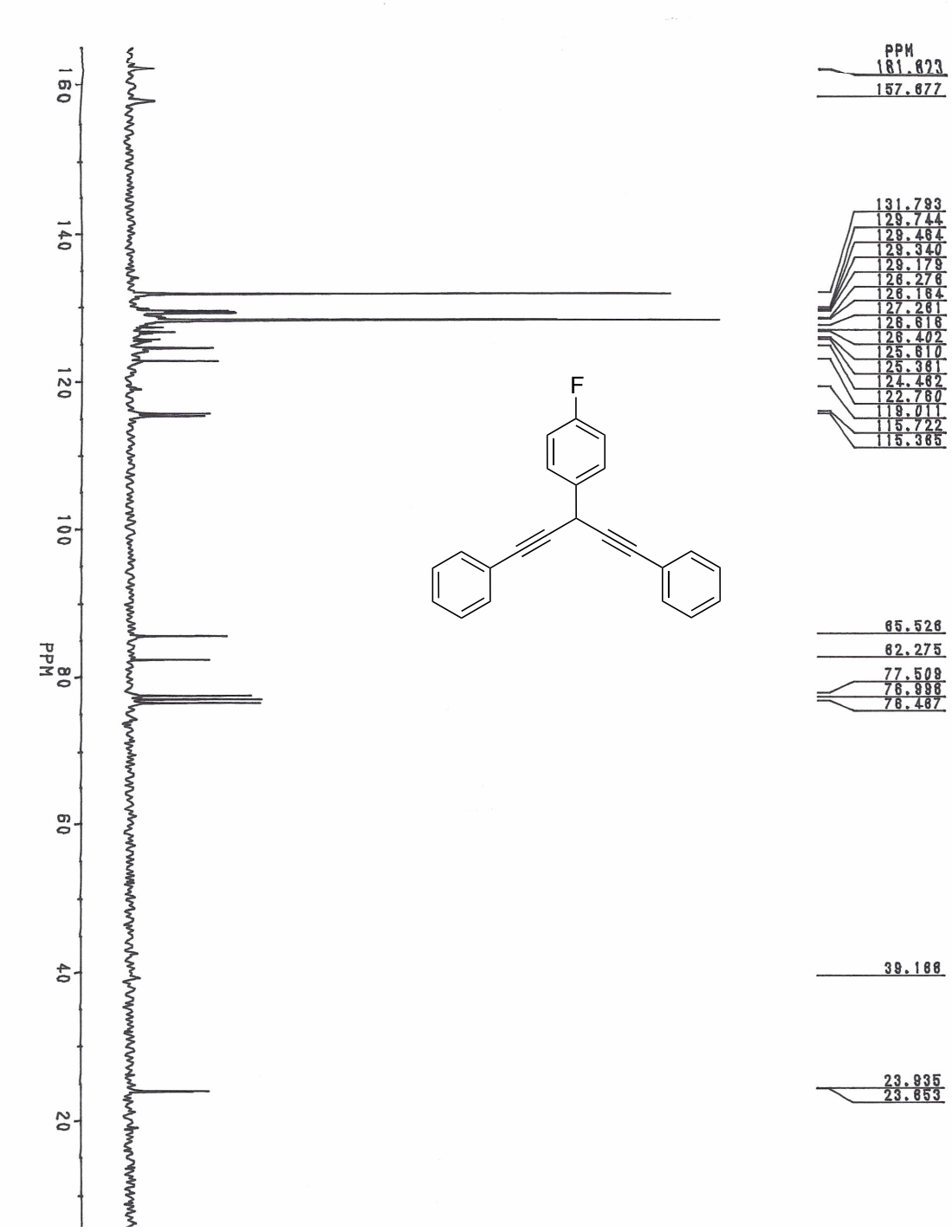
^{13}C NMR of compound 405



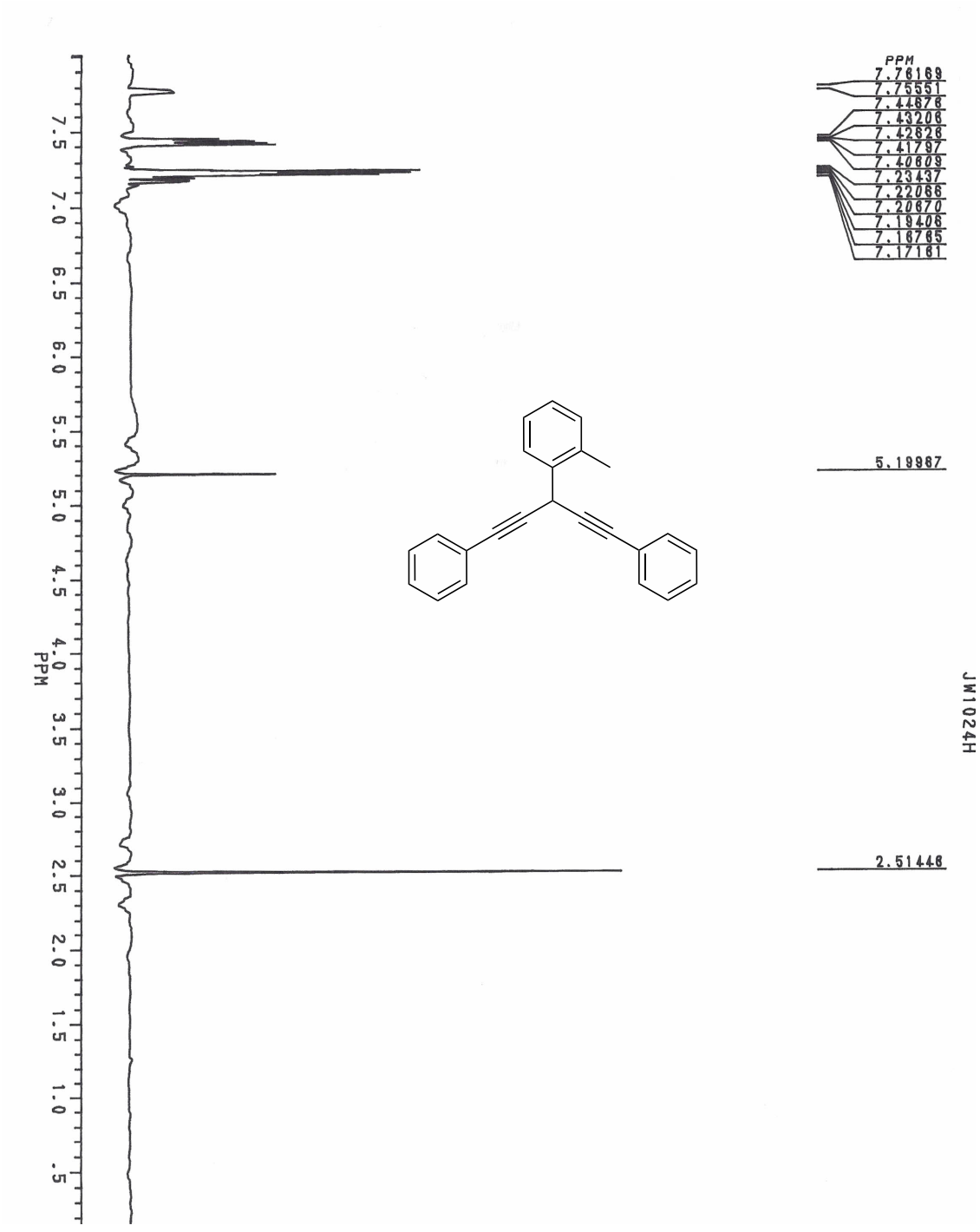
^{1}H NMR of compound 406



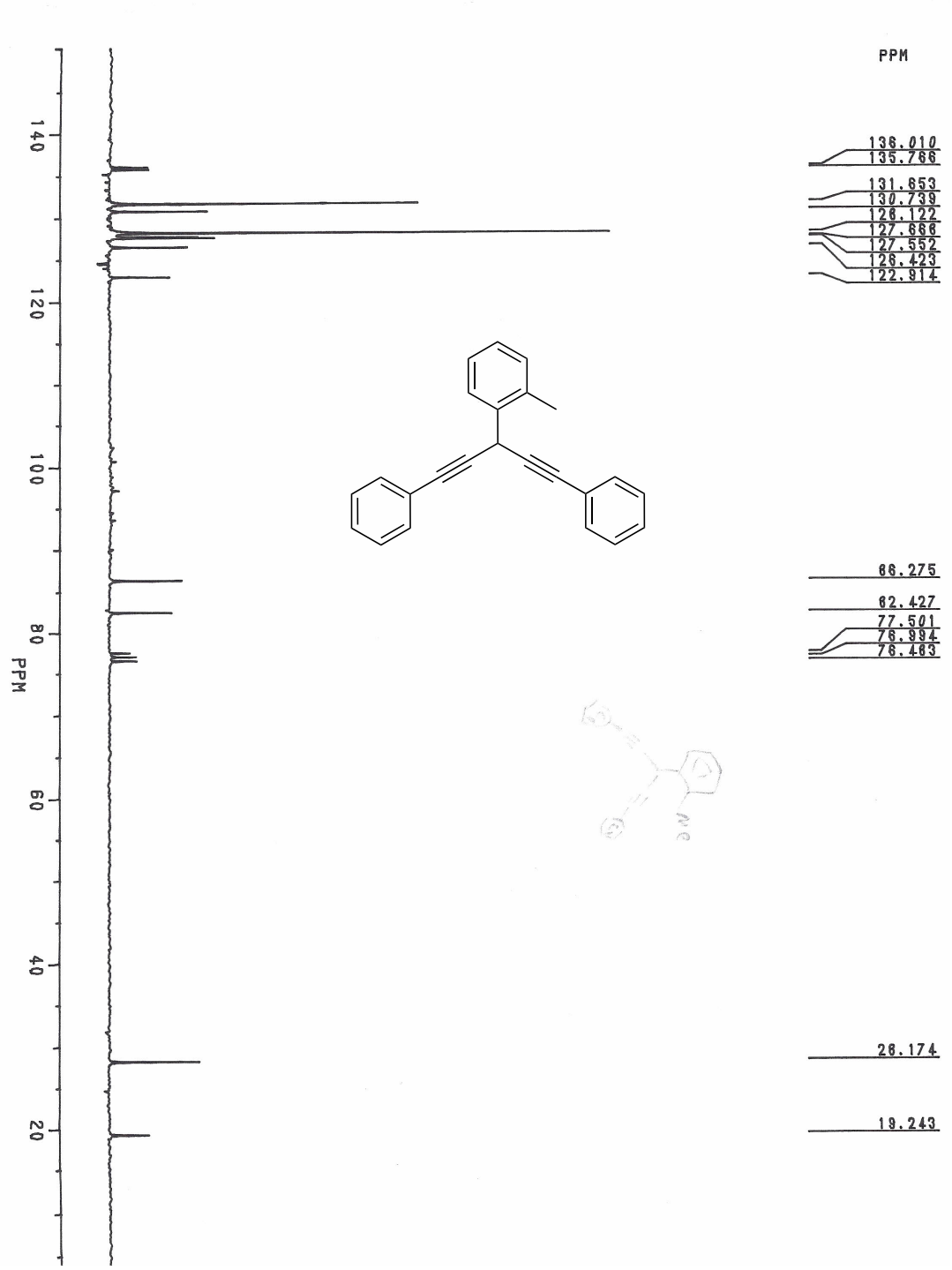
^{13}C NMR of compound 406



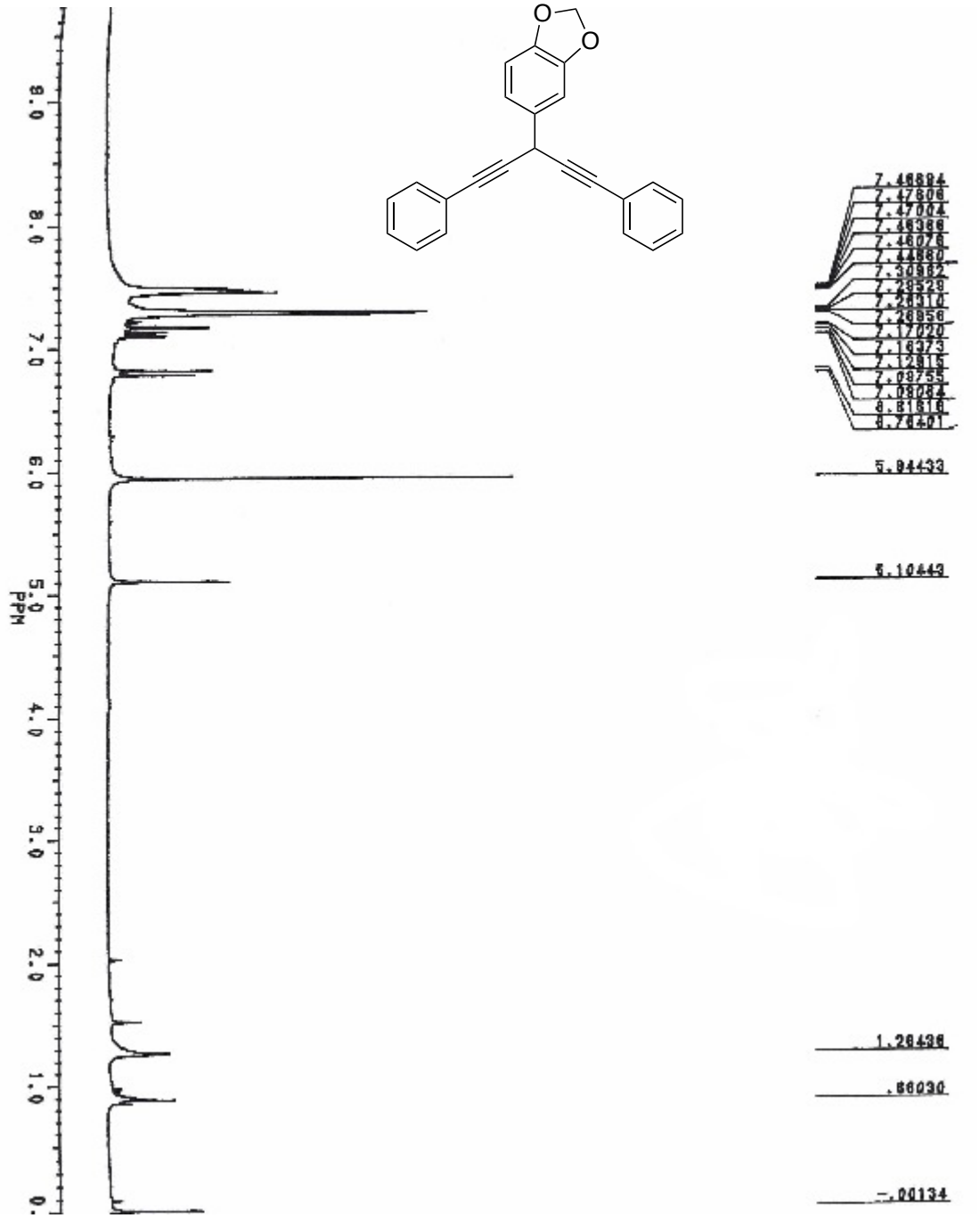
^{1}H NMR of compound 407



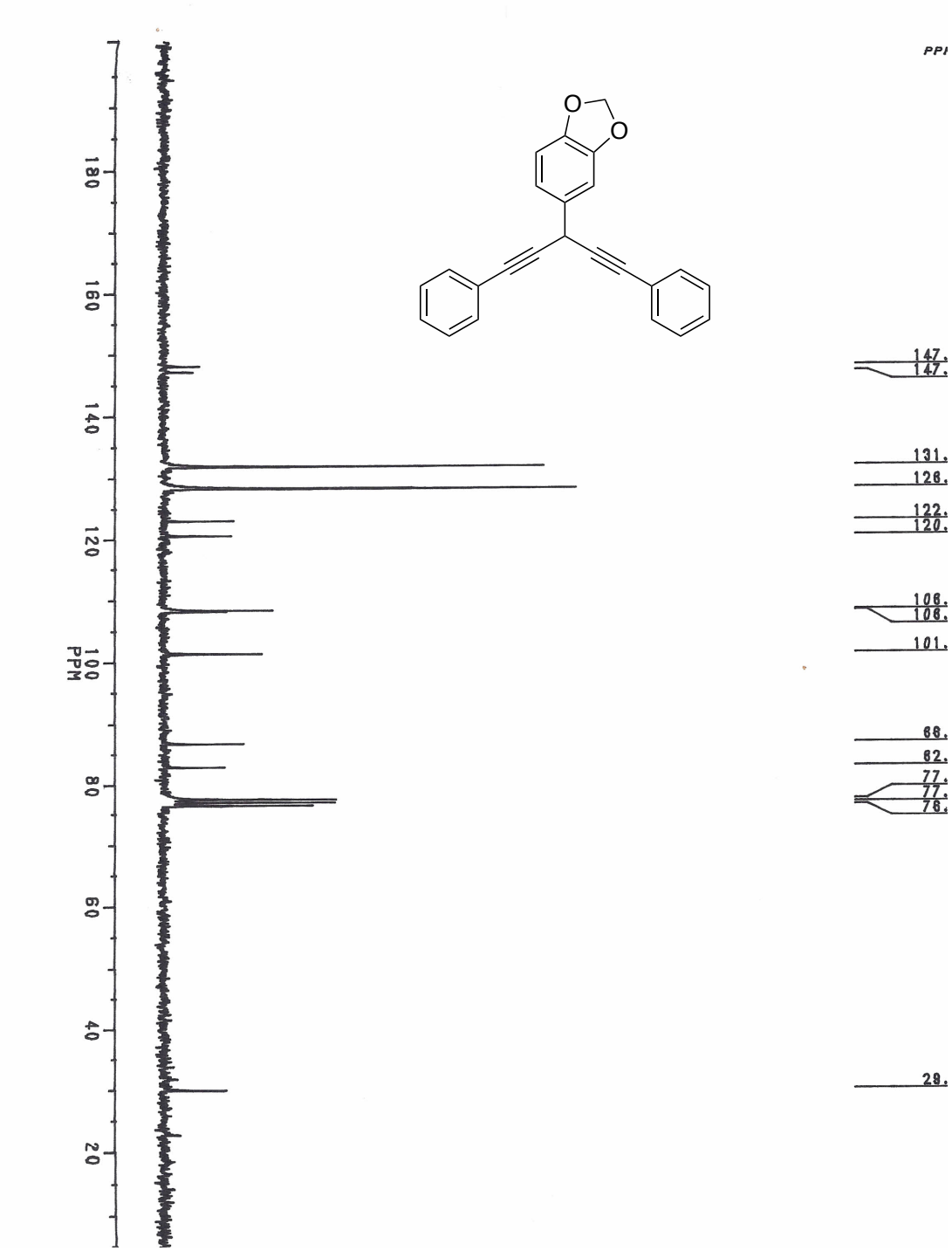
^{13}C NMR of compound 407



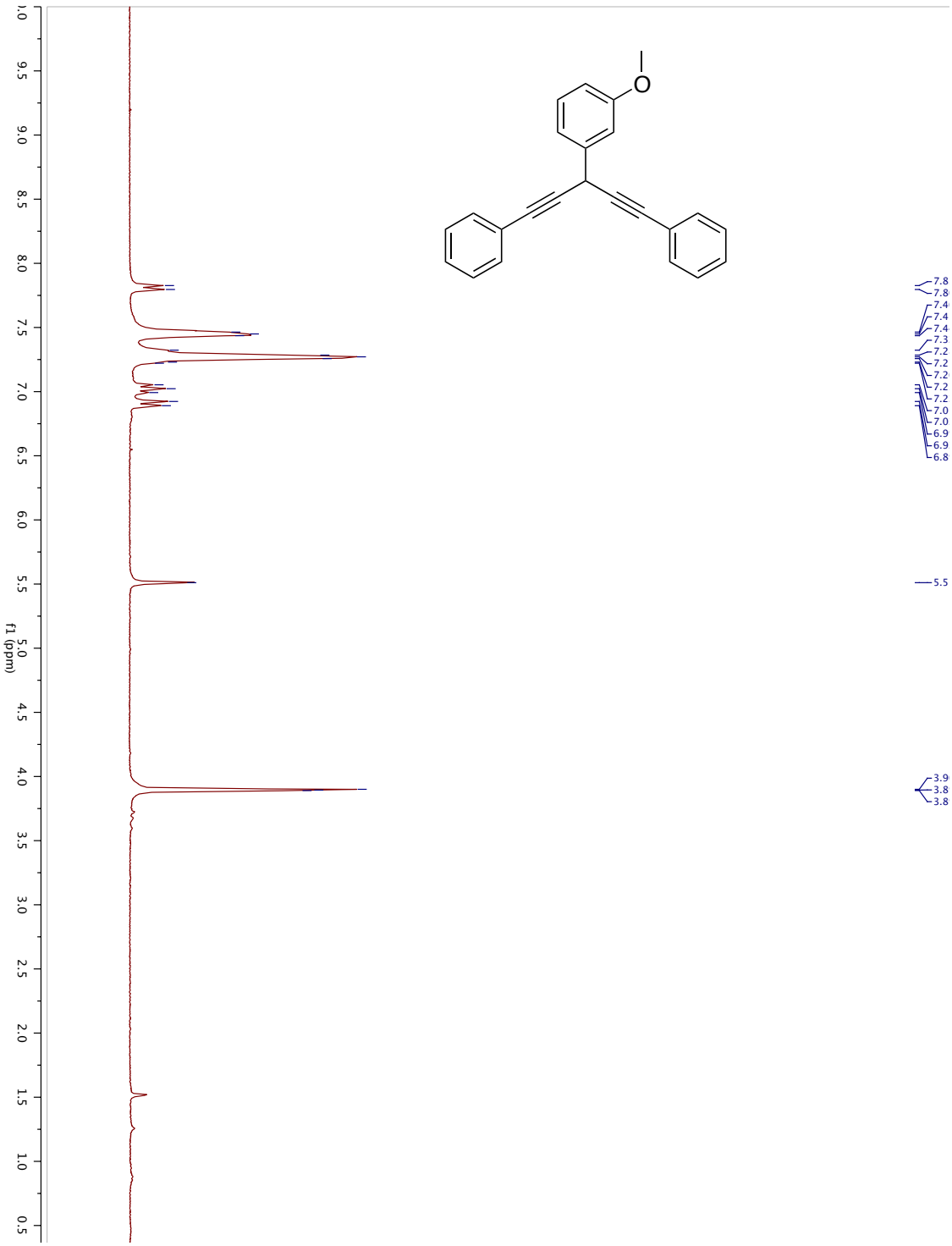
^{1}H NMR of compound 408



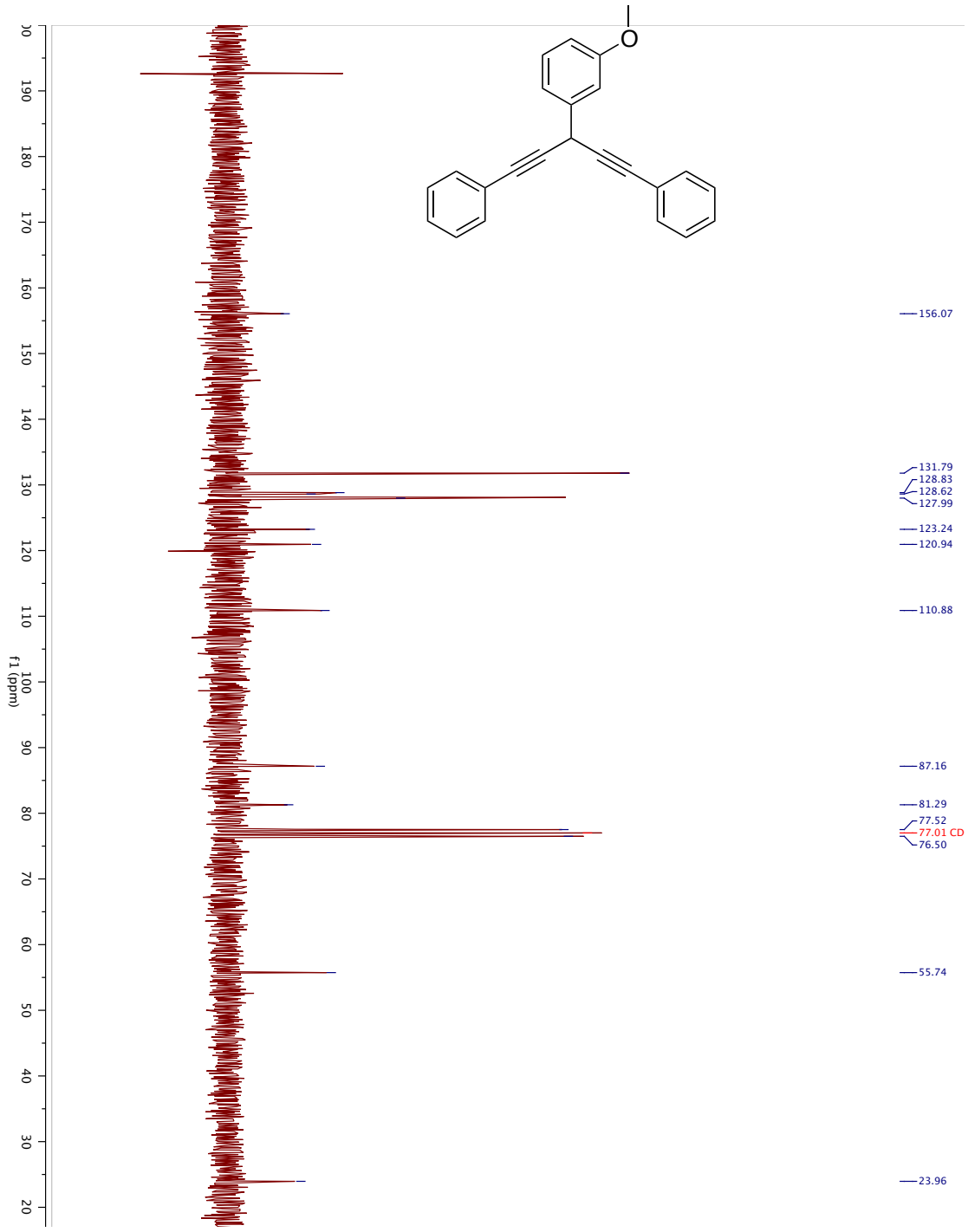
^{13}C NMR of compound 408



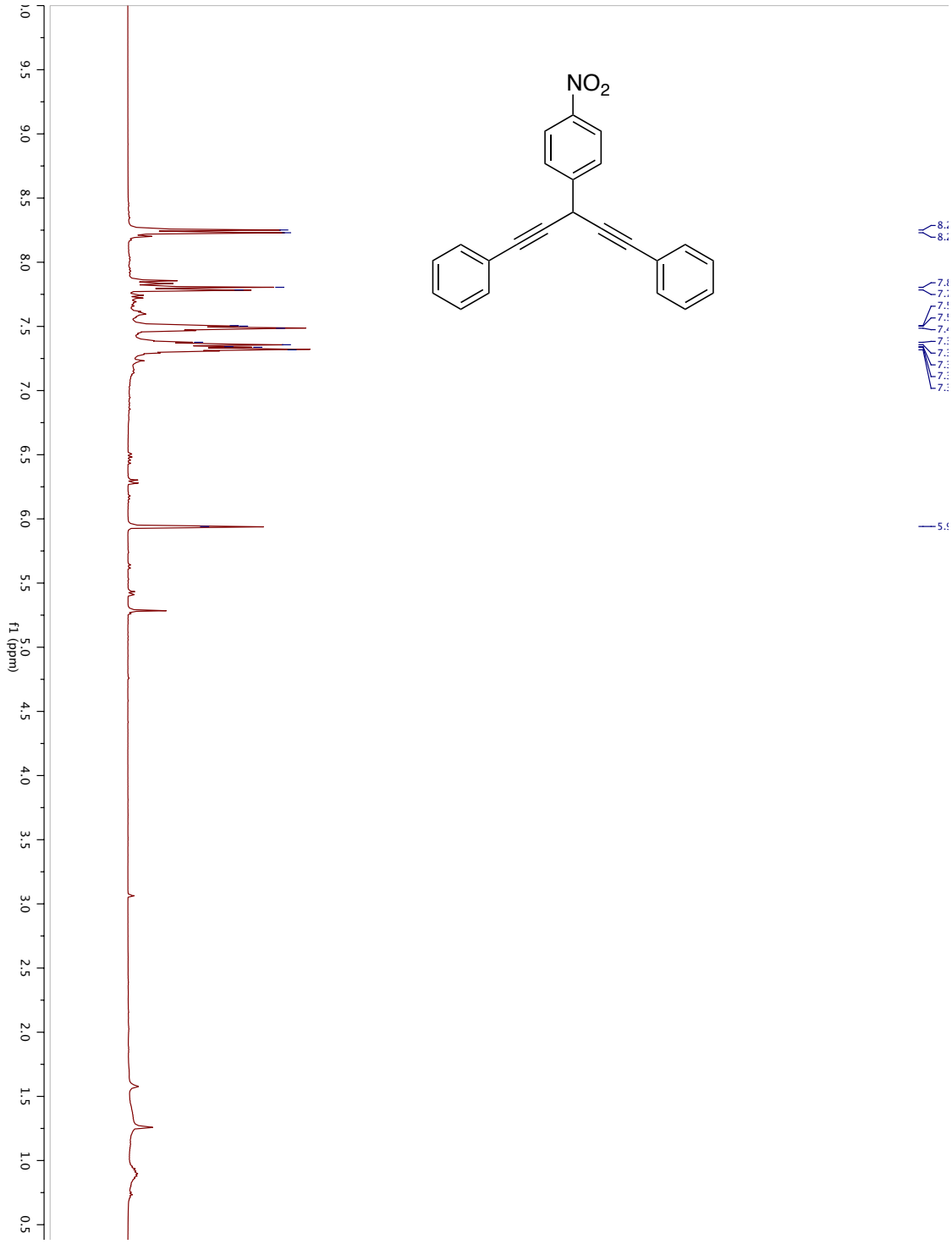
^{1}H NMR of compound 409



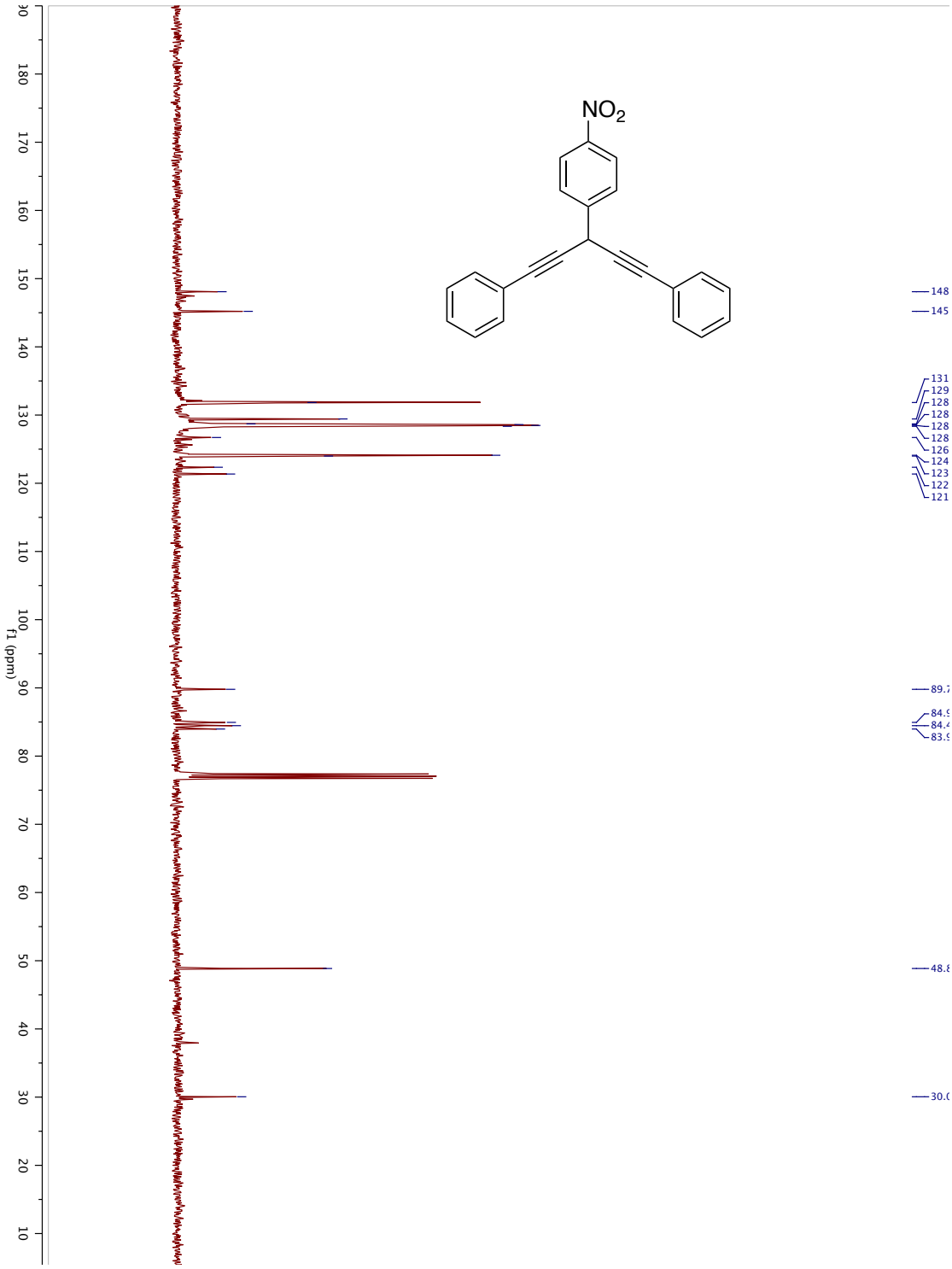
^{13}C NMR of compound 409



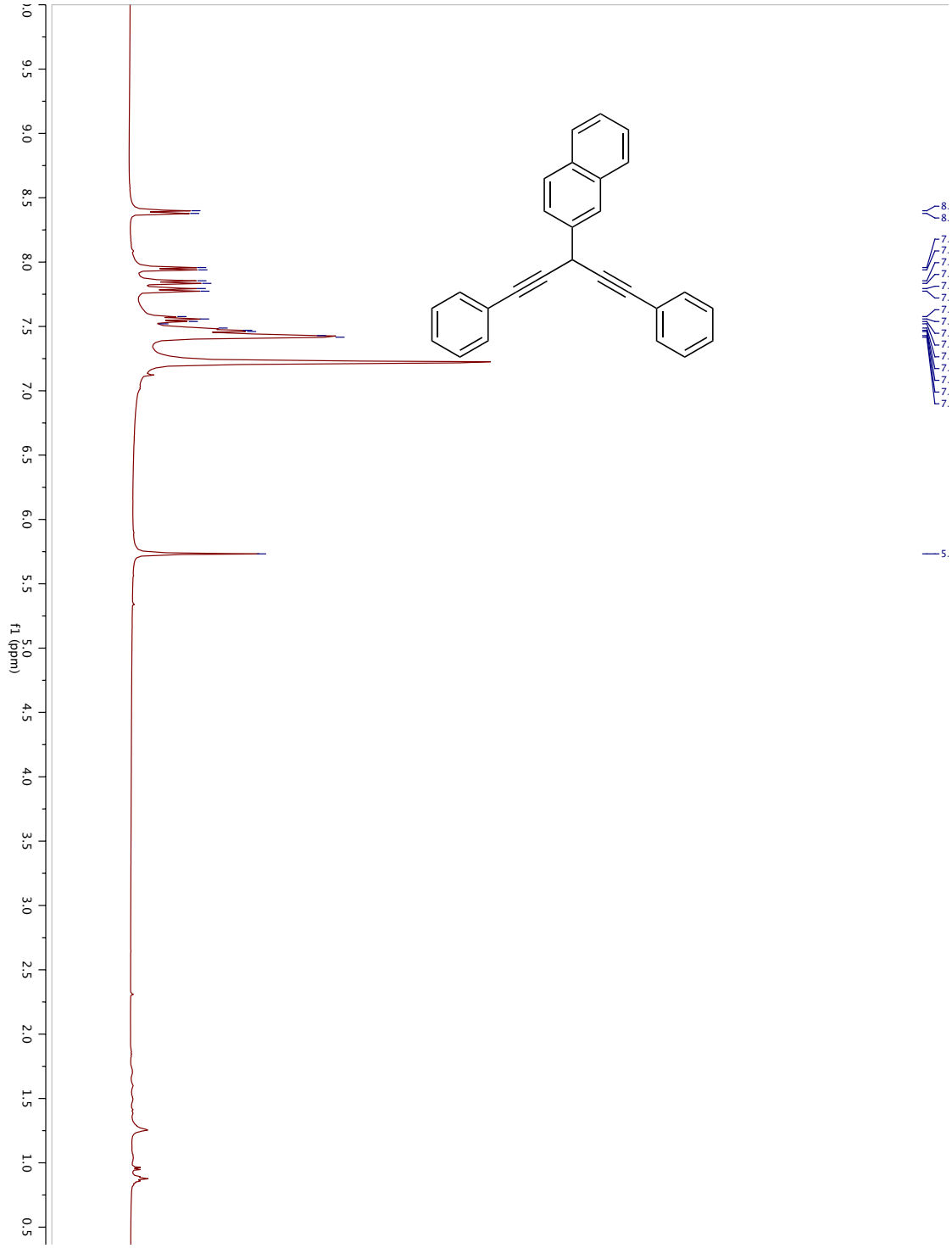
^{1}H NMR of compound 410



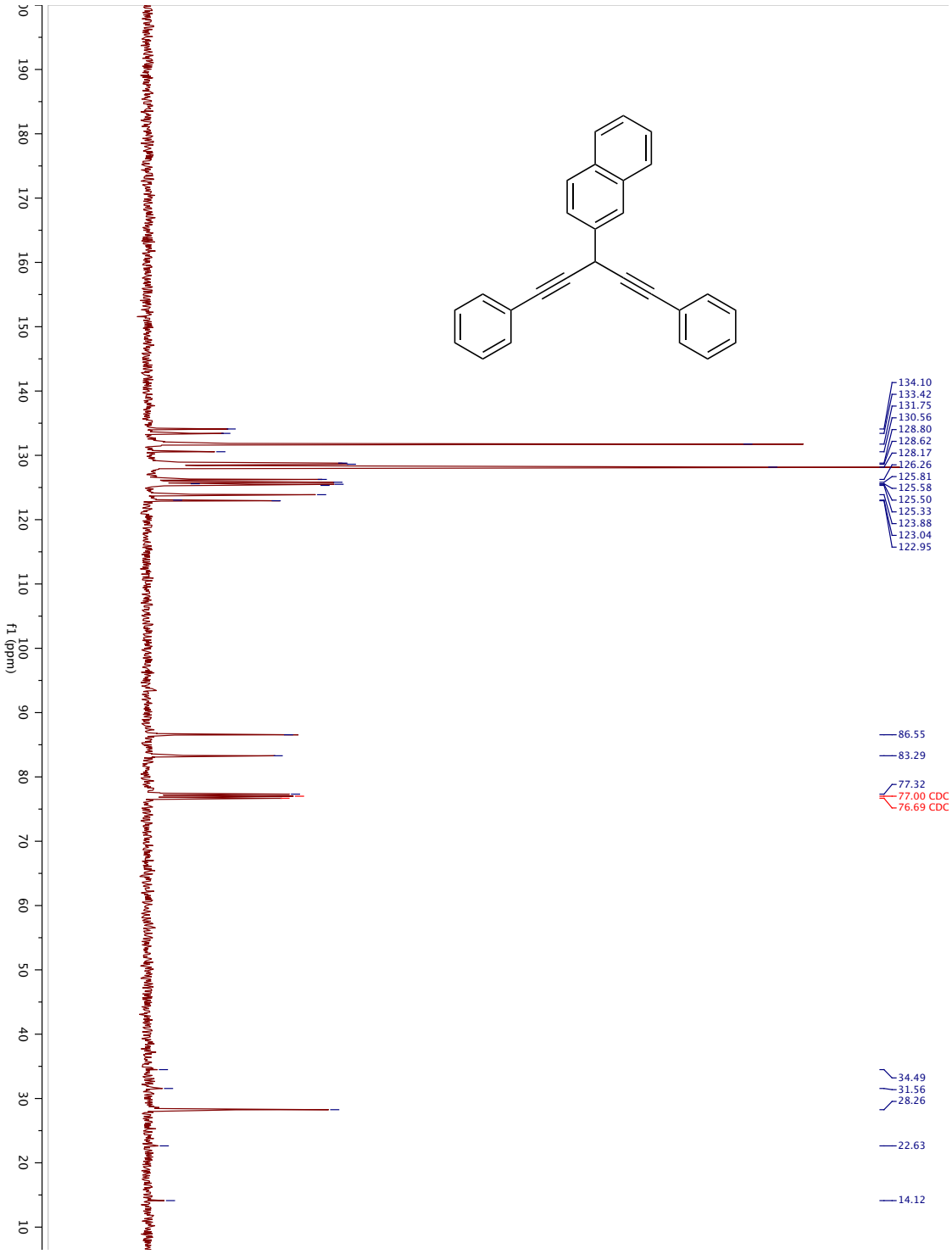
^{13}C NMR of compound 410



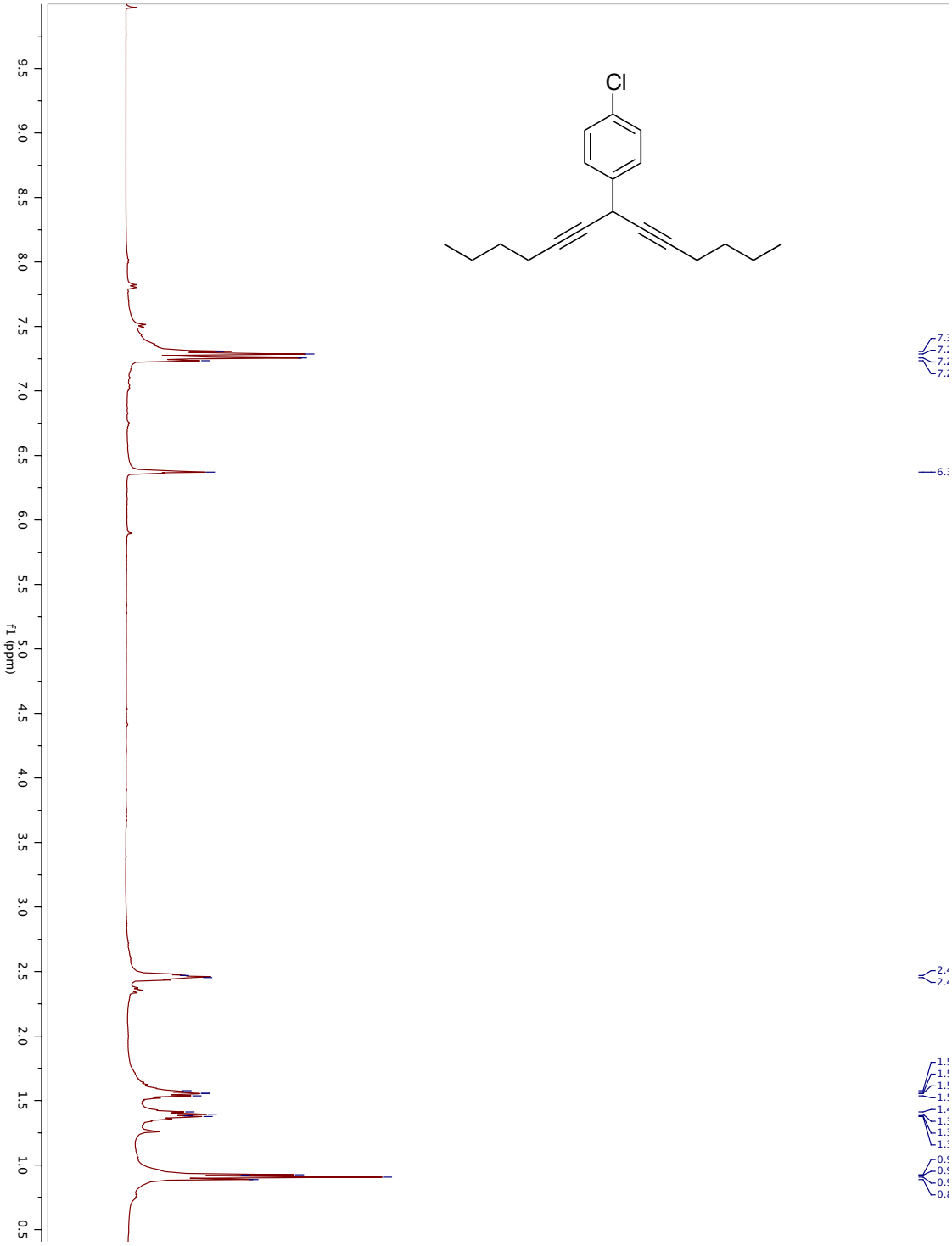
^{1}H NMR of compound 411



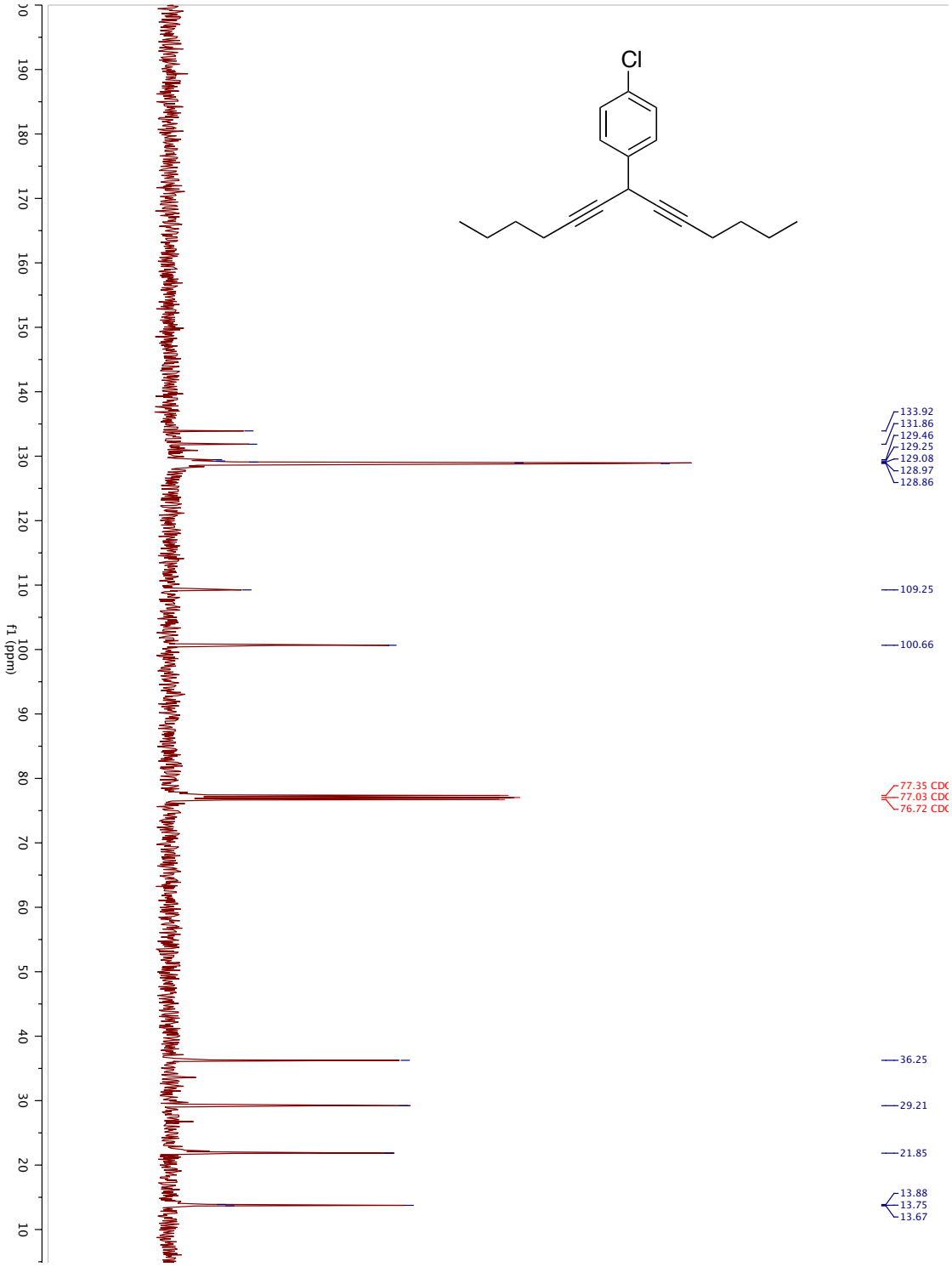
^{13}C NMR of compound 411



^{1}H NMR of compound 412

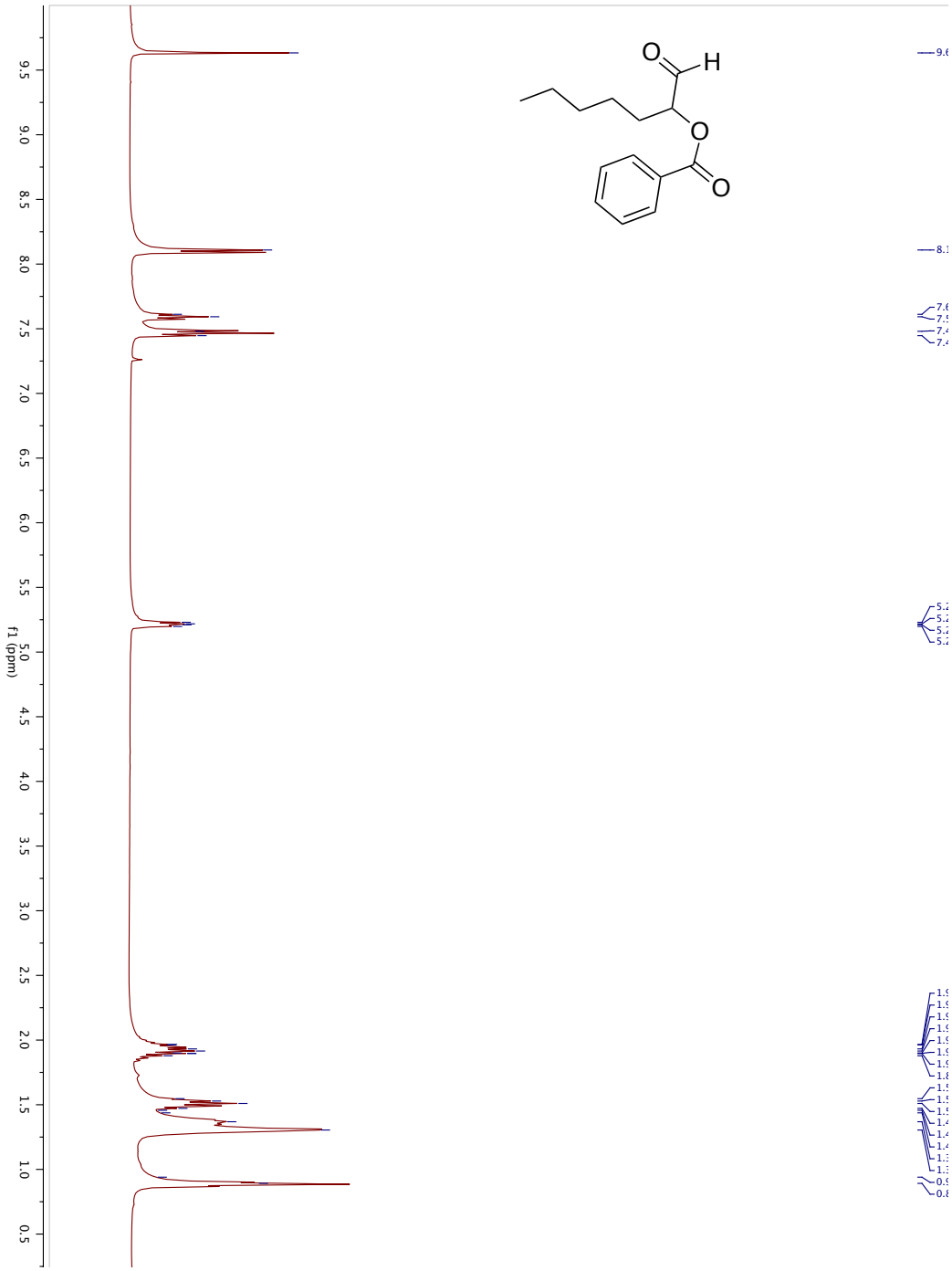


^{13}C NMR of compound 412

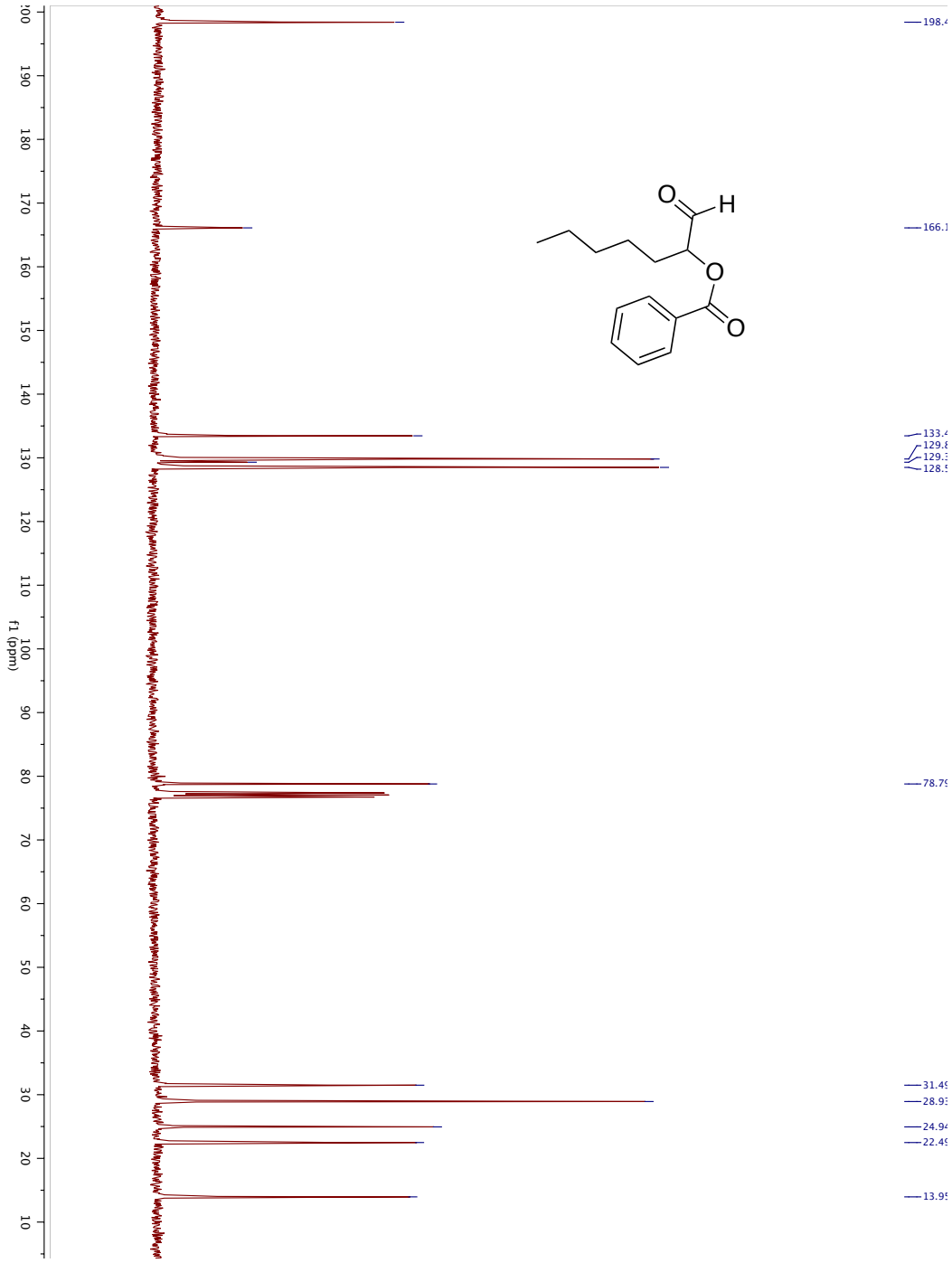


Appendix D: Representative NMR Spectra From Chapter 5

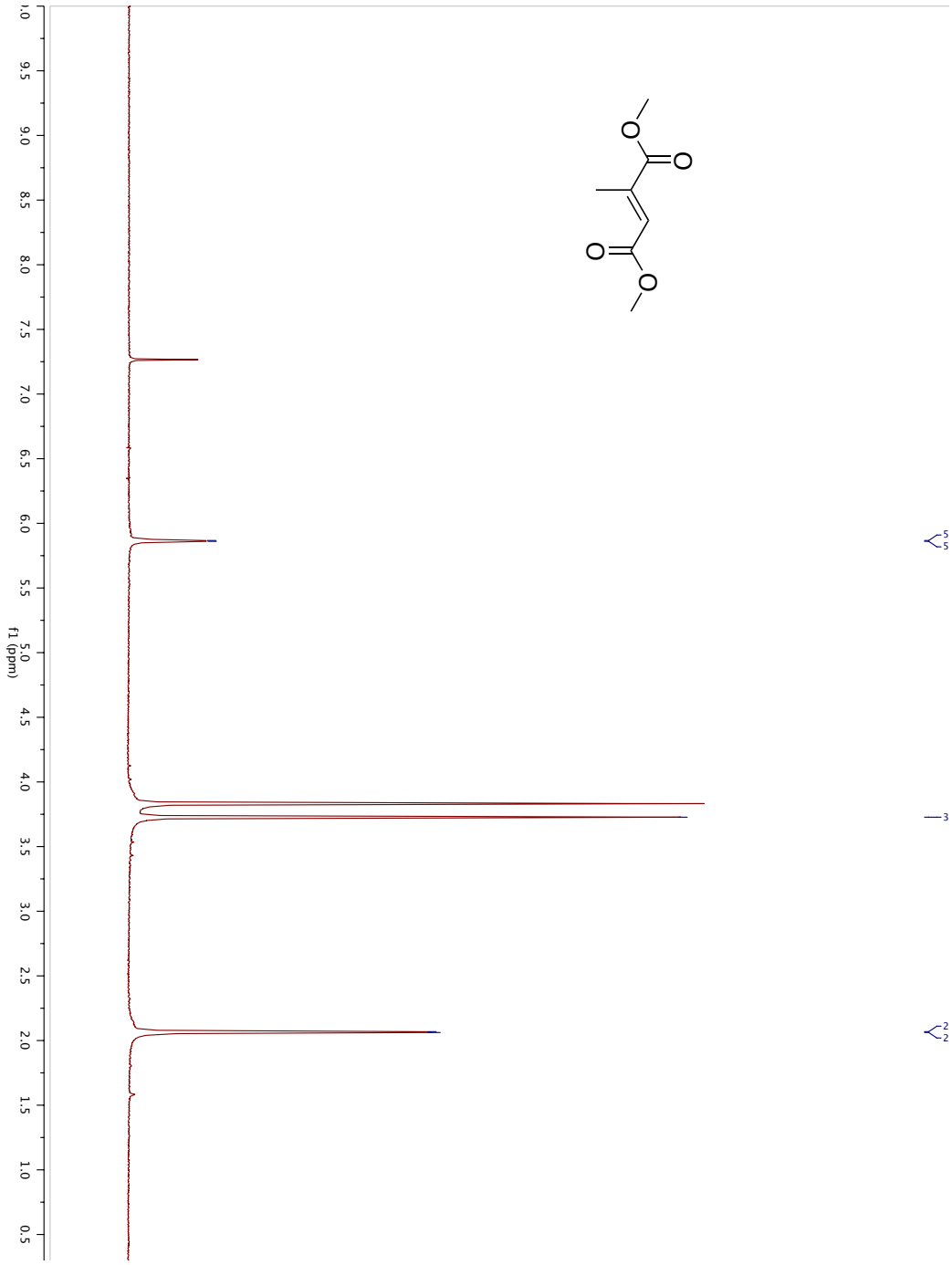
^{1}H NMR spectrum of 501



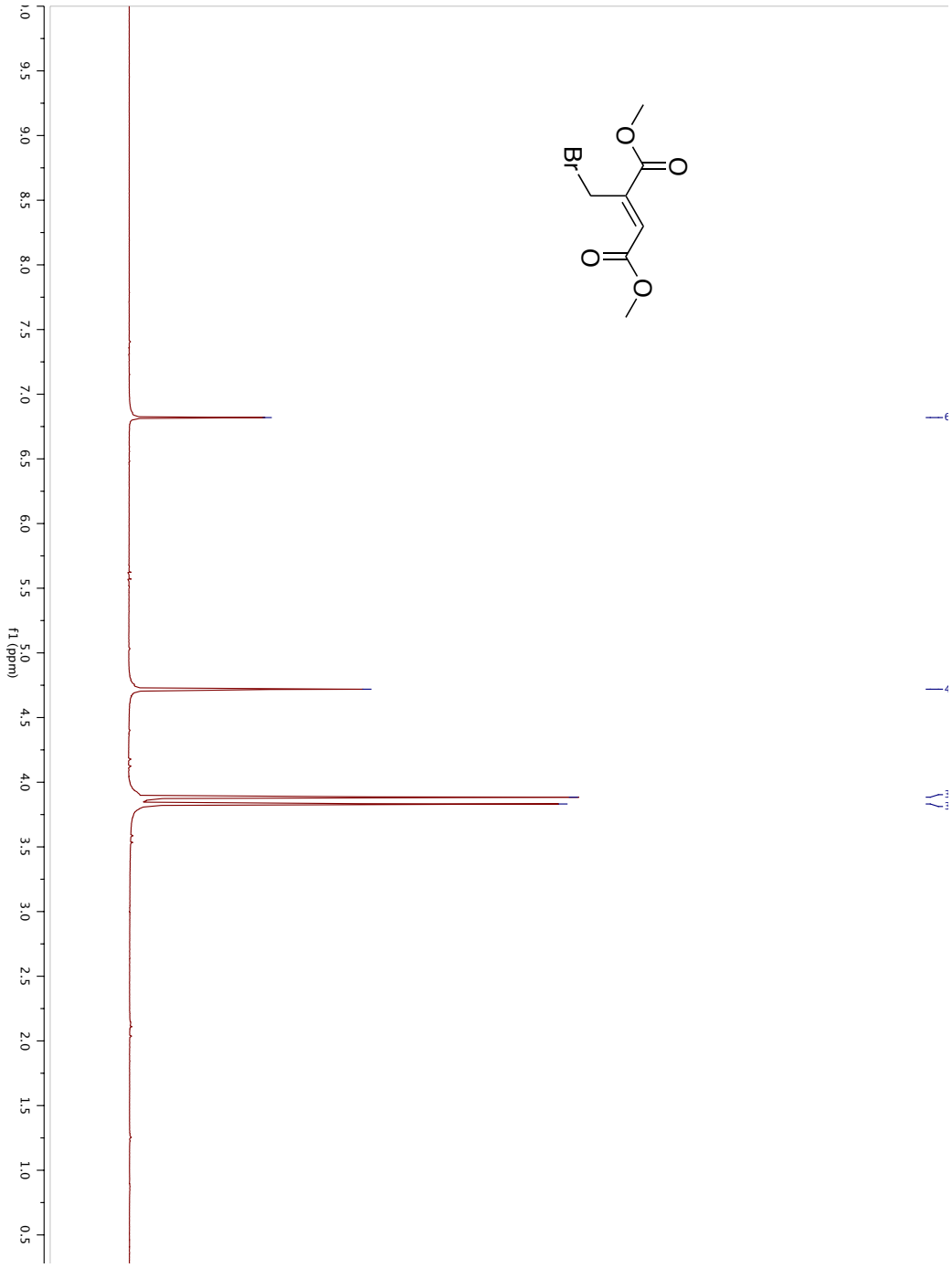
^{13}C NMR spectrum of 501



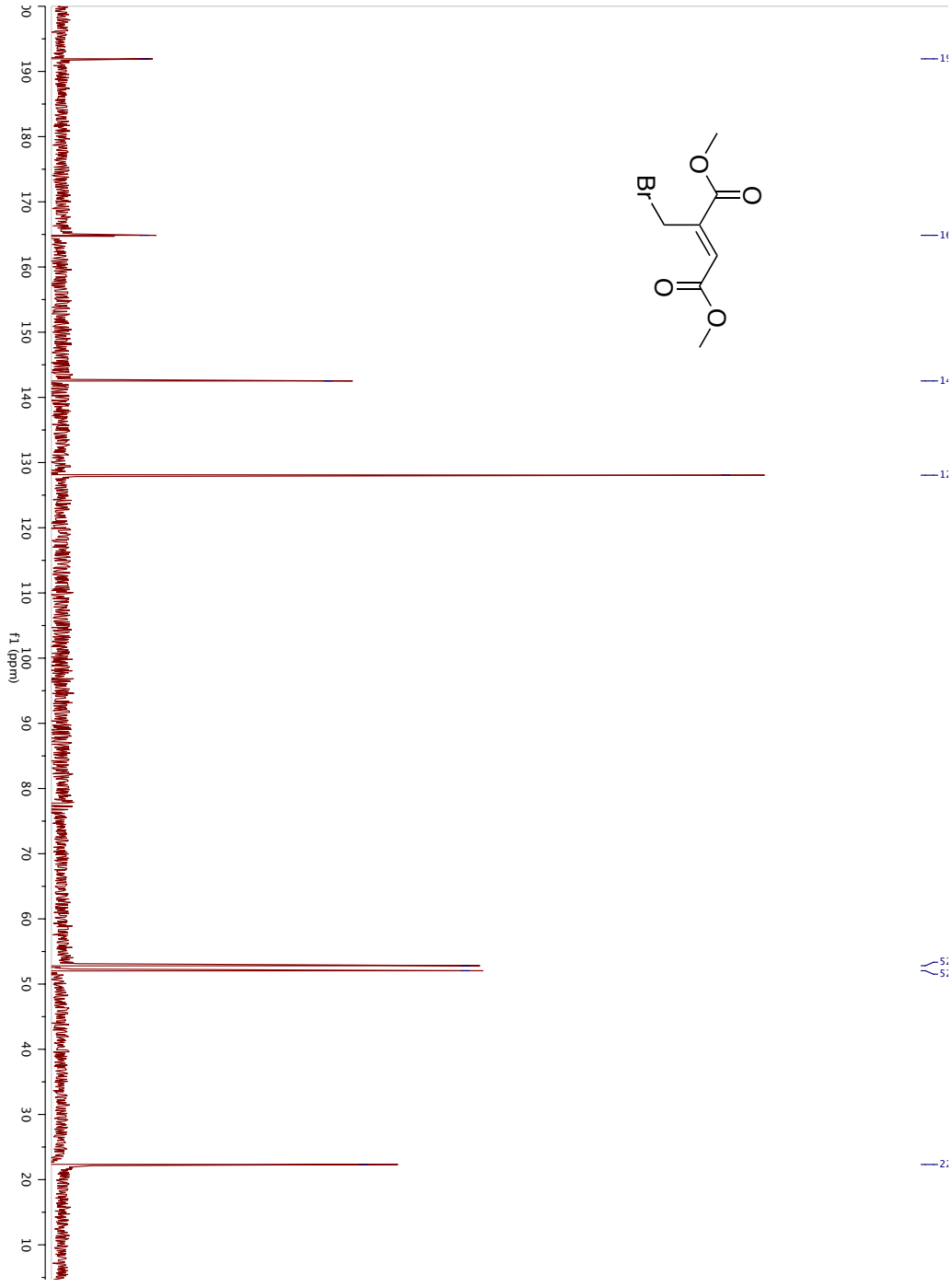
^{1}H NMR spectrum of 502



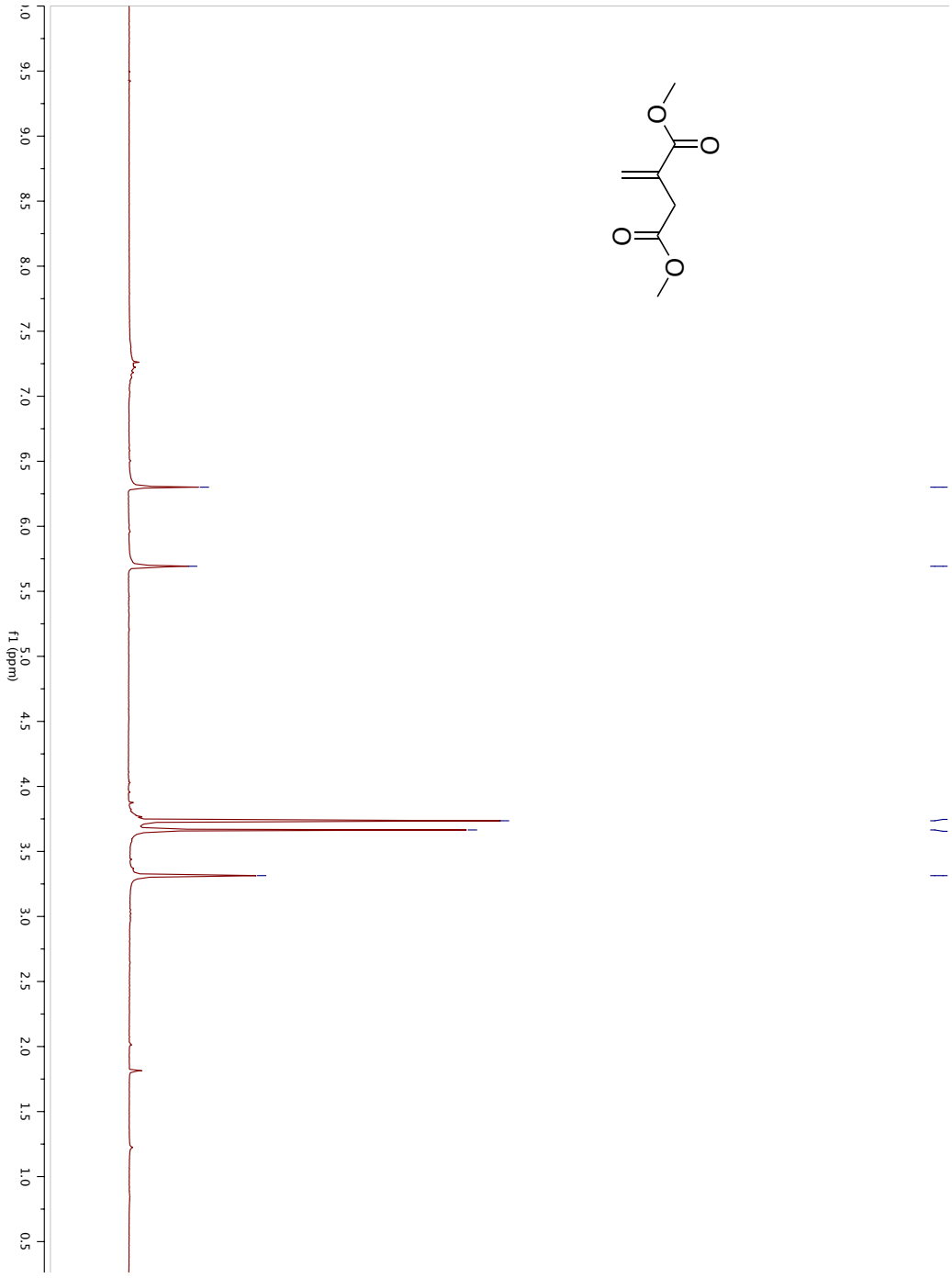
^{1}H NMR spectrum of 503



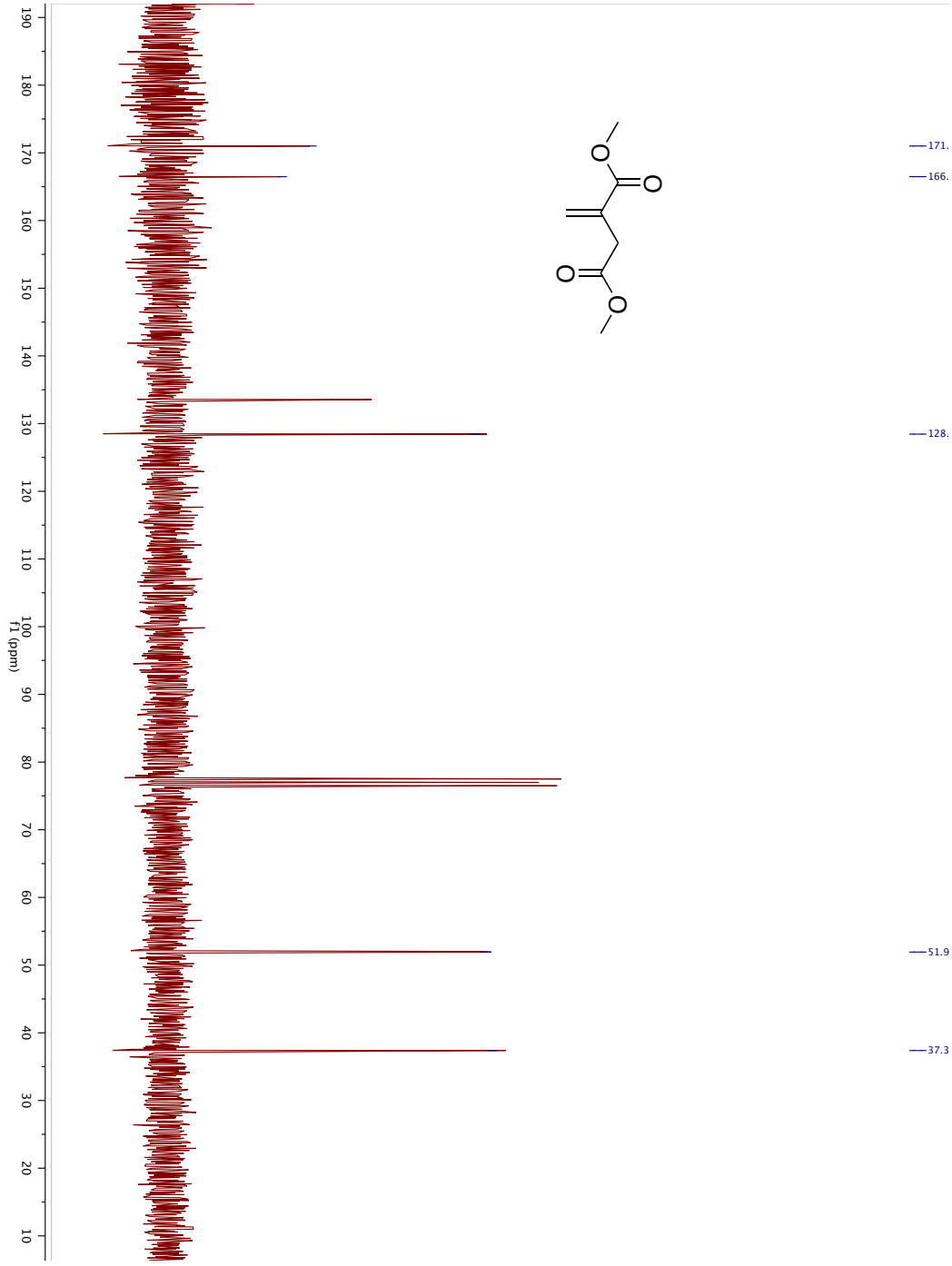
^{13}C NMR spectrum of 503



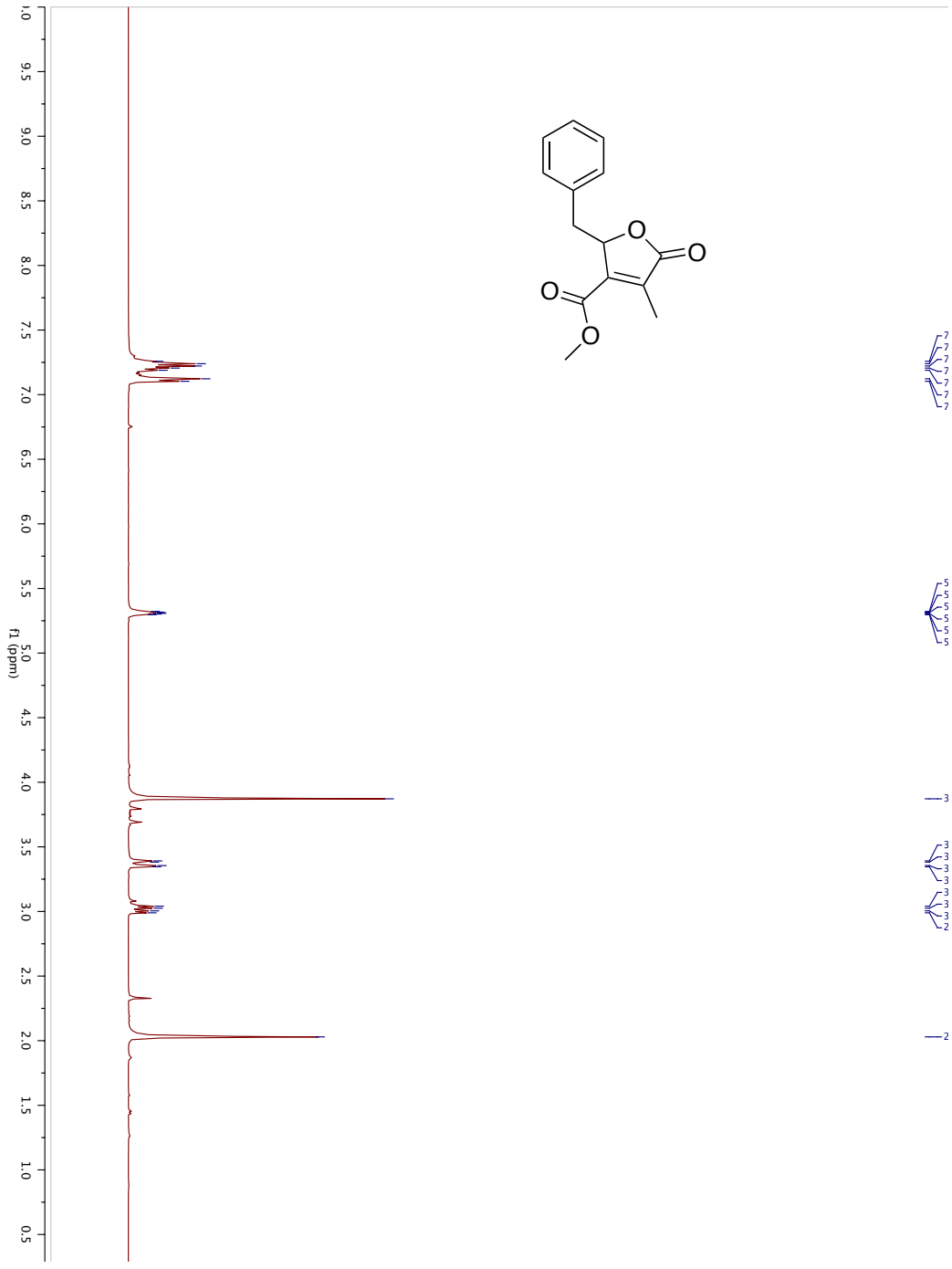
^{1}H NMR spectrum of 504



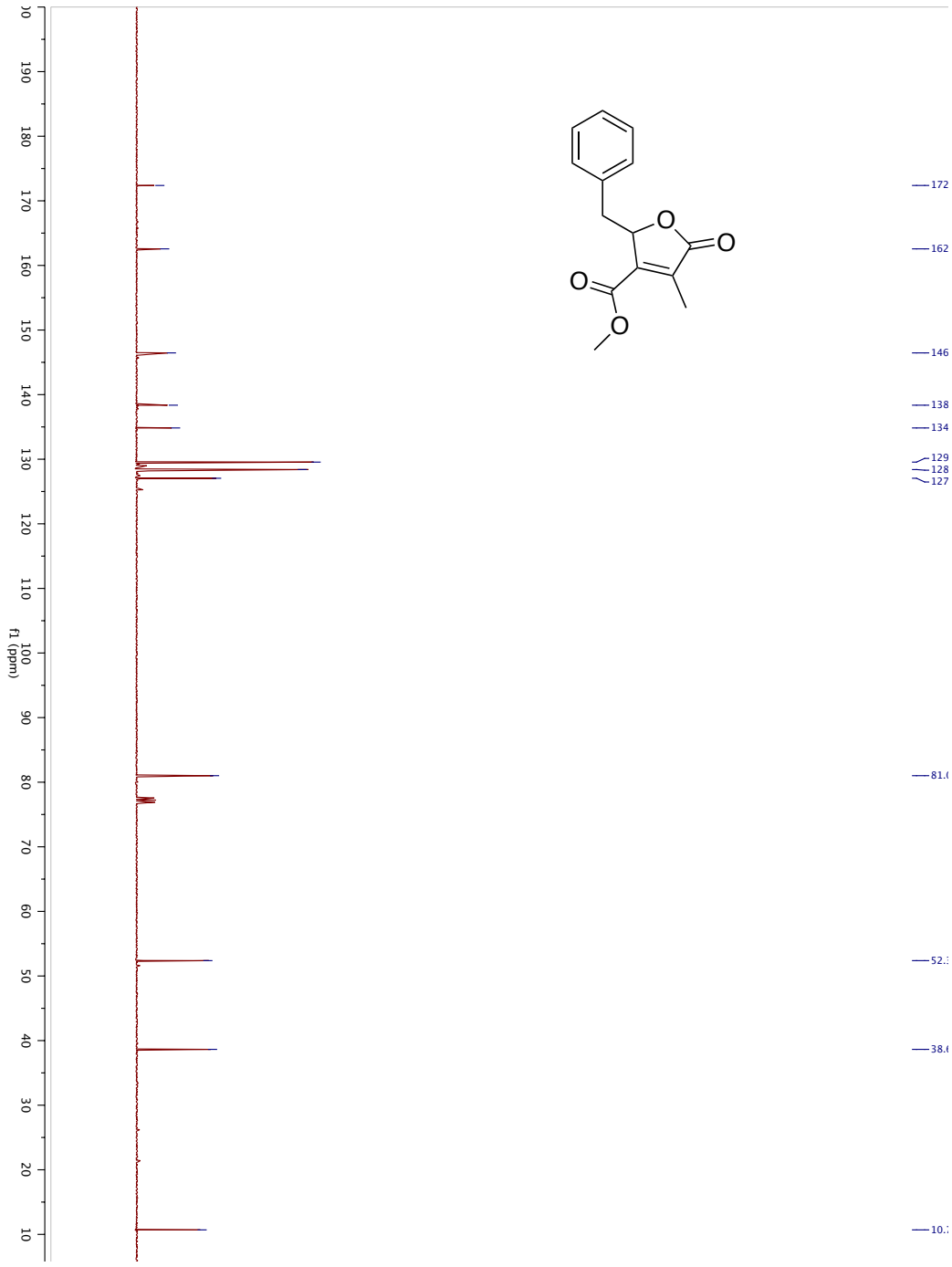
^{13}C NMR spectrum of 504



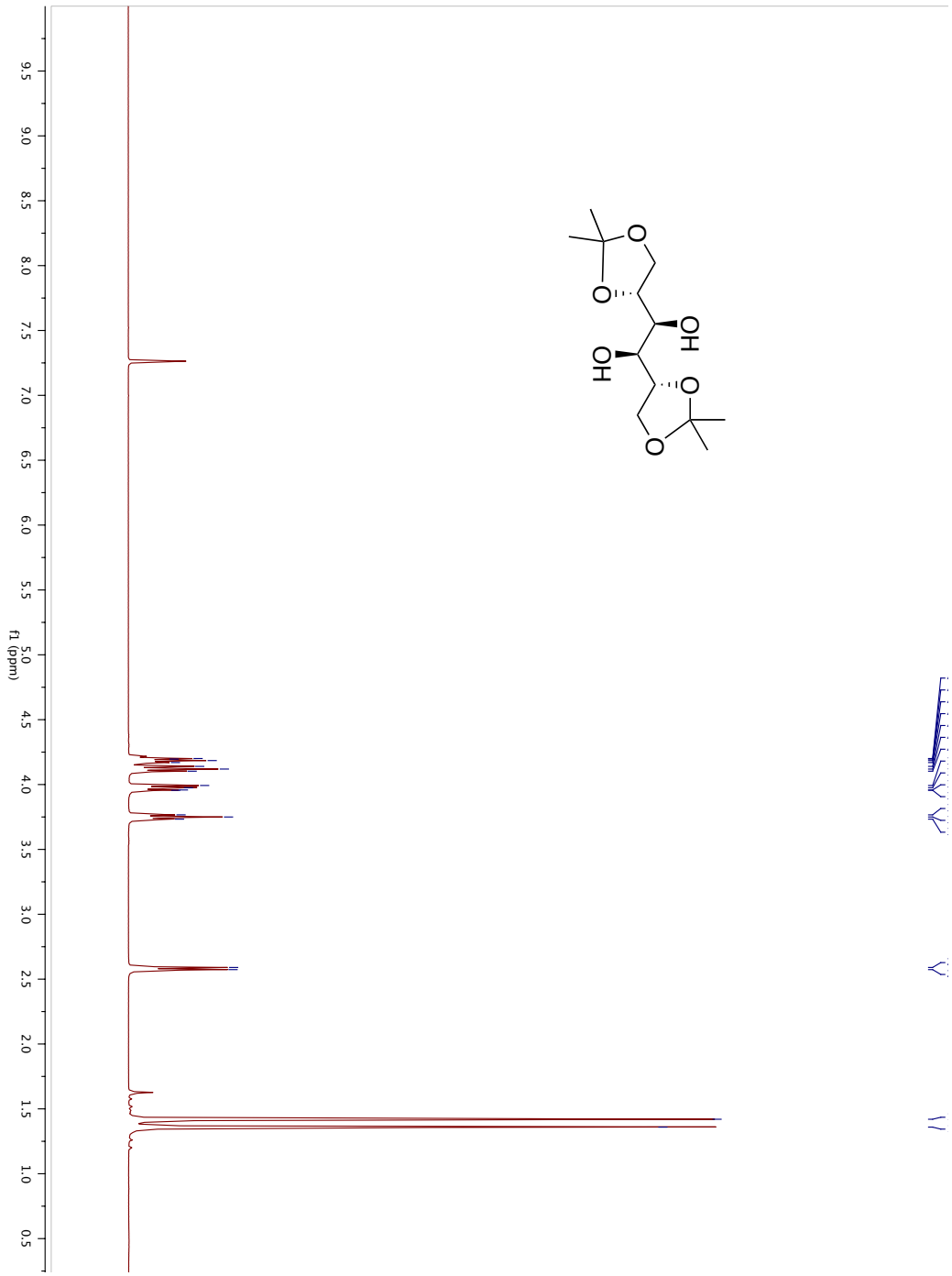
^{1}H NMR spectrum of 505



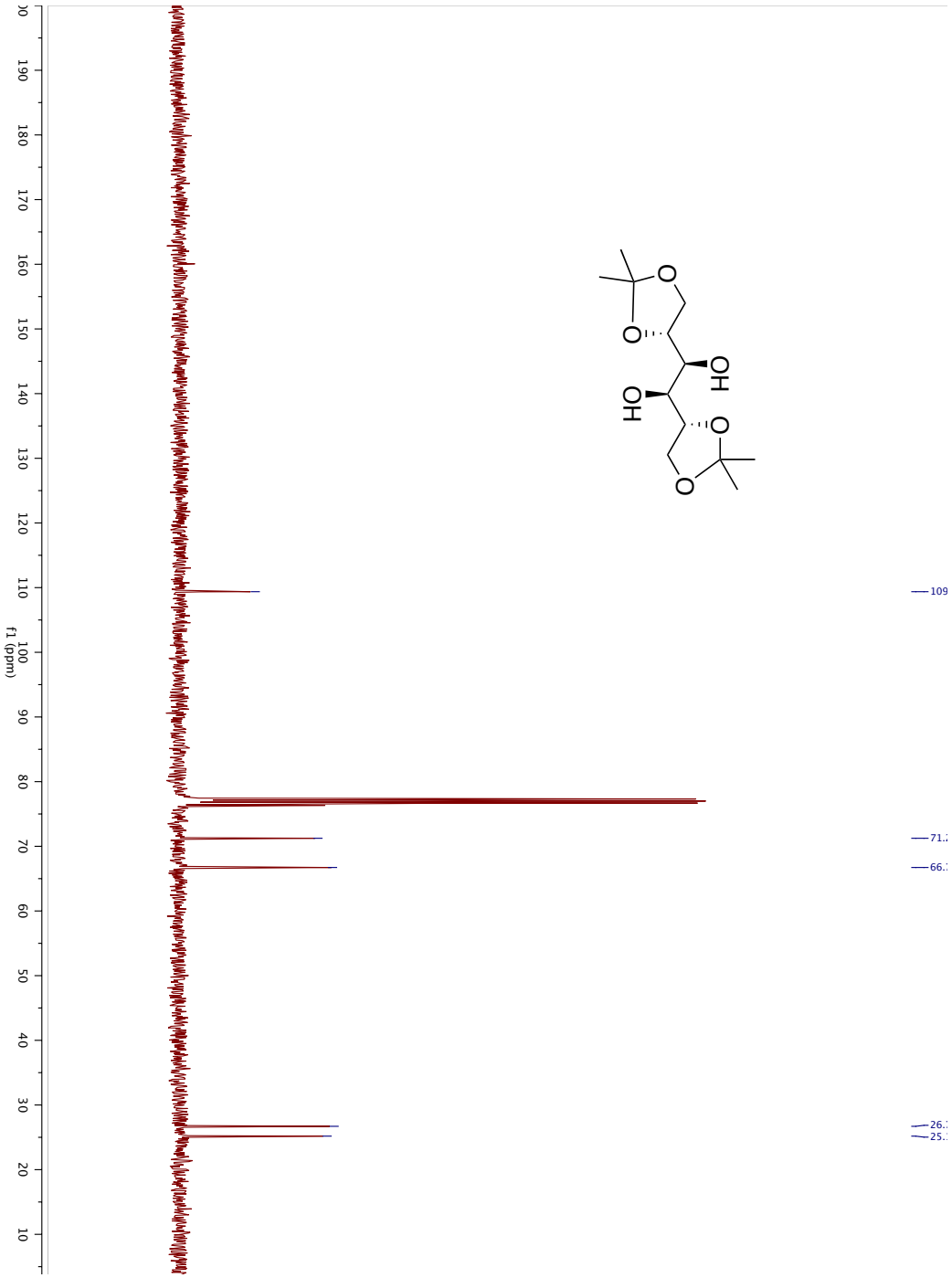
^{13}C NMR spectrum of 505



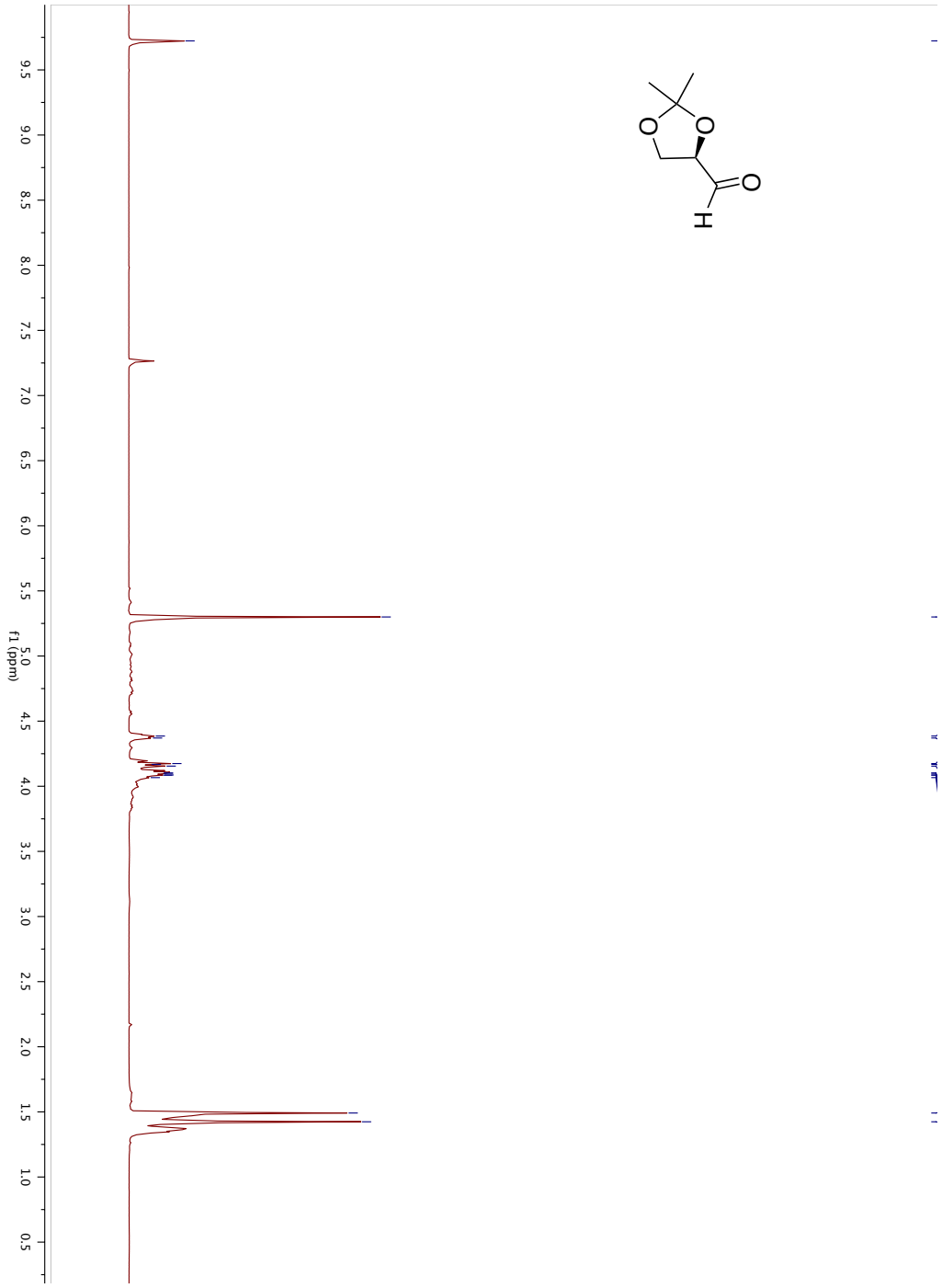
^{1}H NMR spectrum of 506



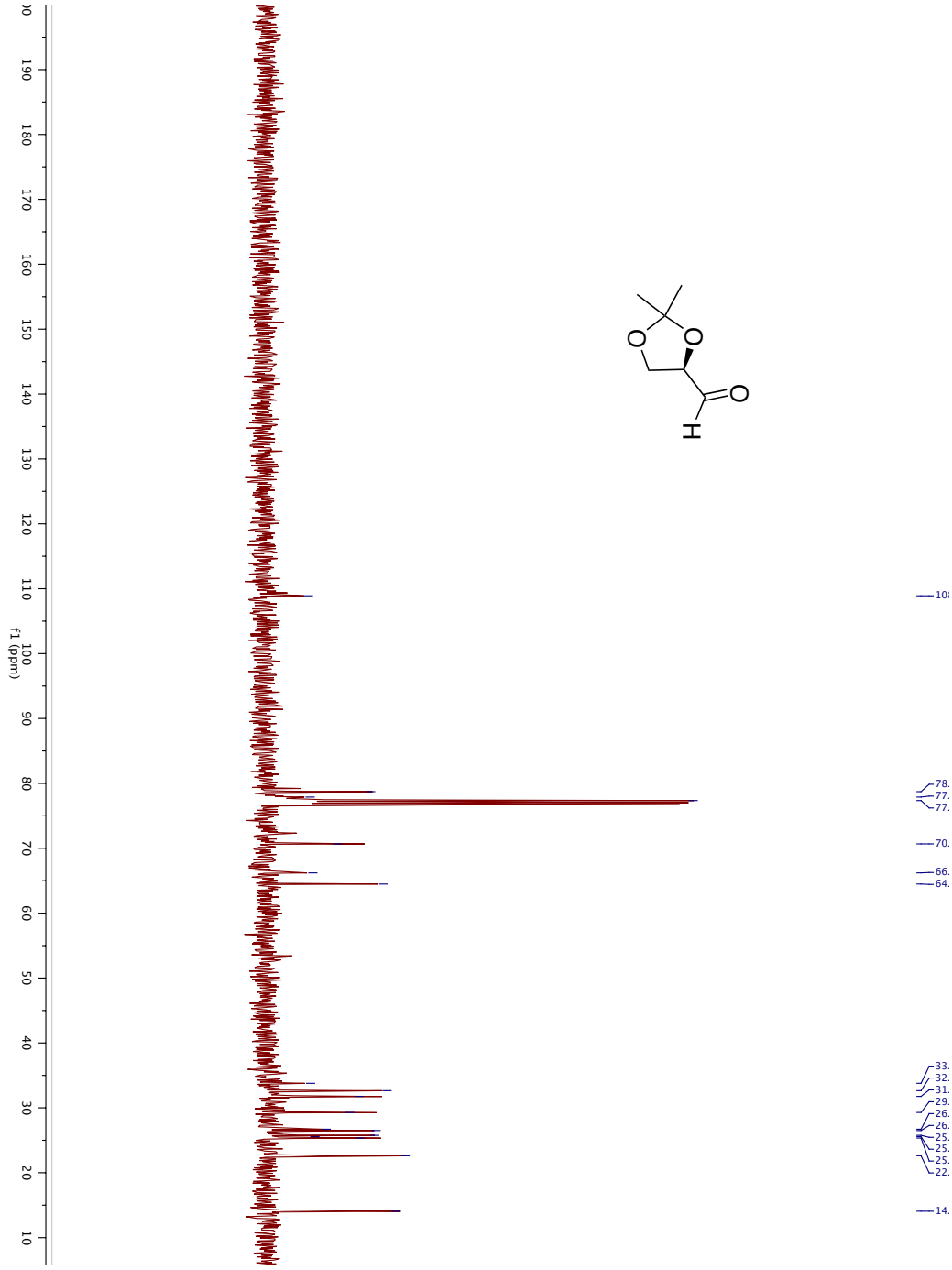
^{13}C NMR spectrum of 506



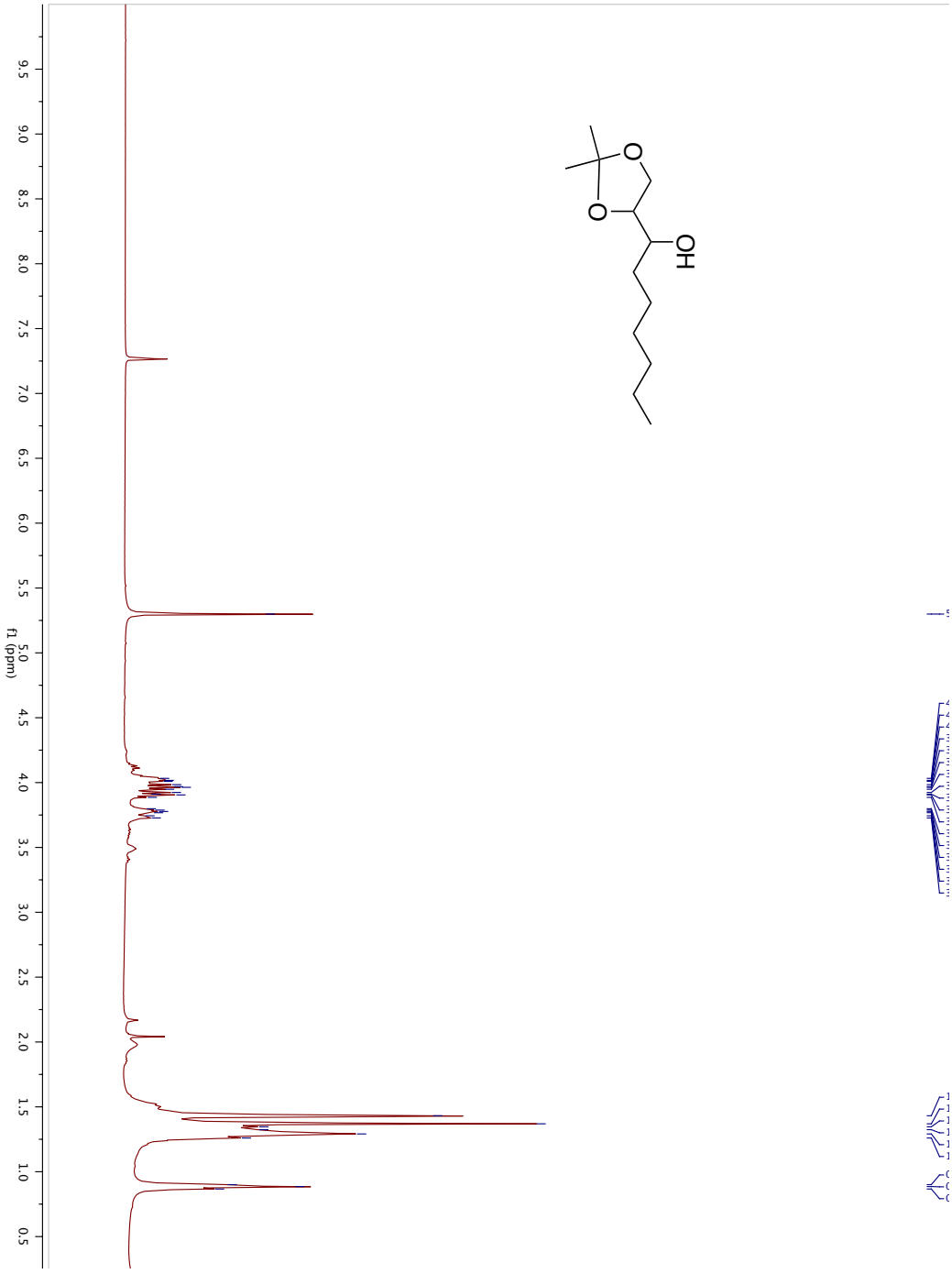
^{1}H NMR spectrum of 507



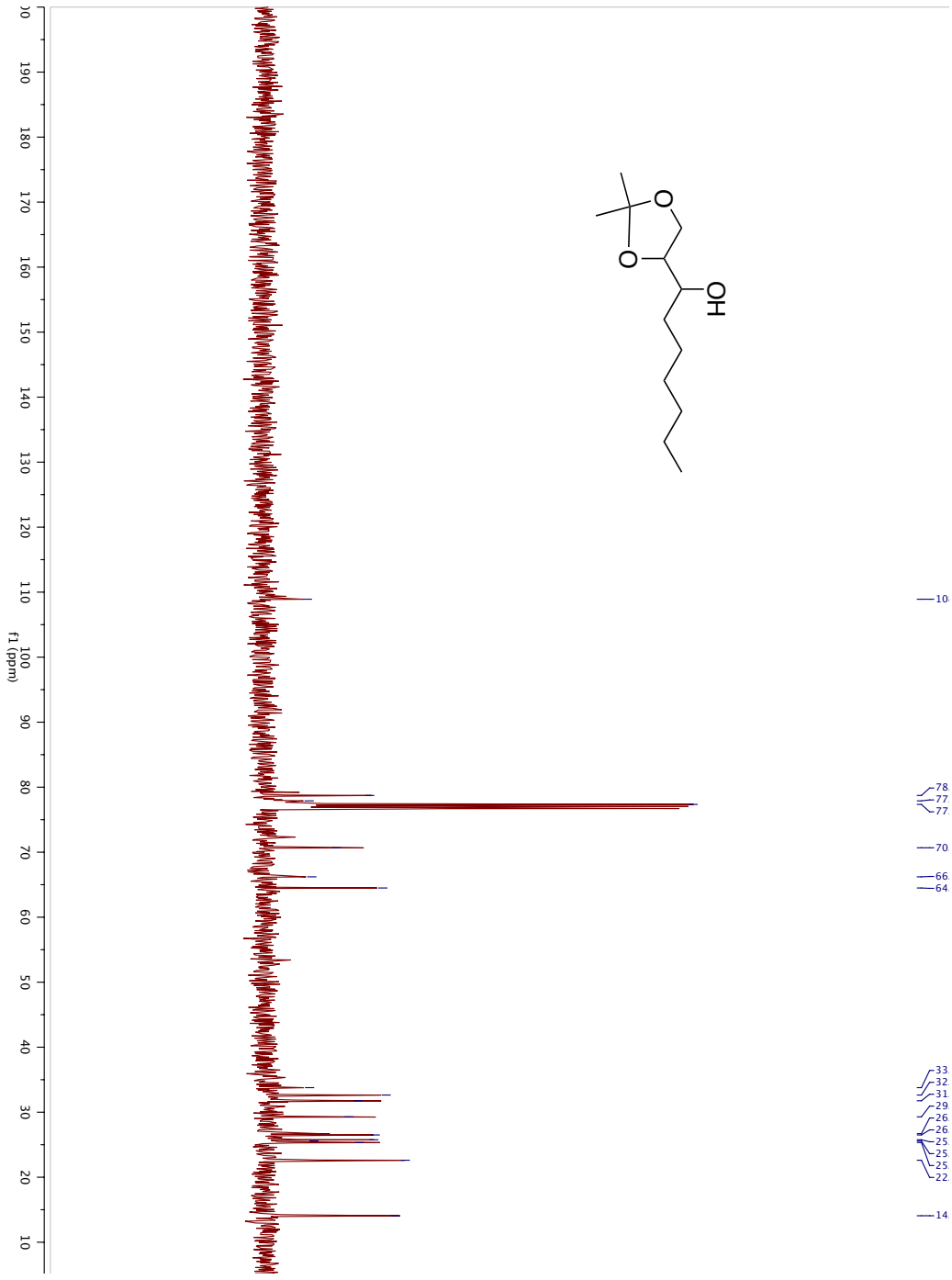
^{13}C NMR spectrum of 507



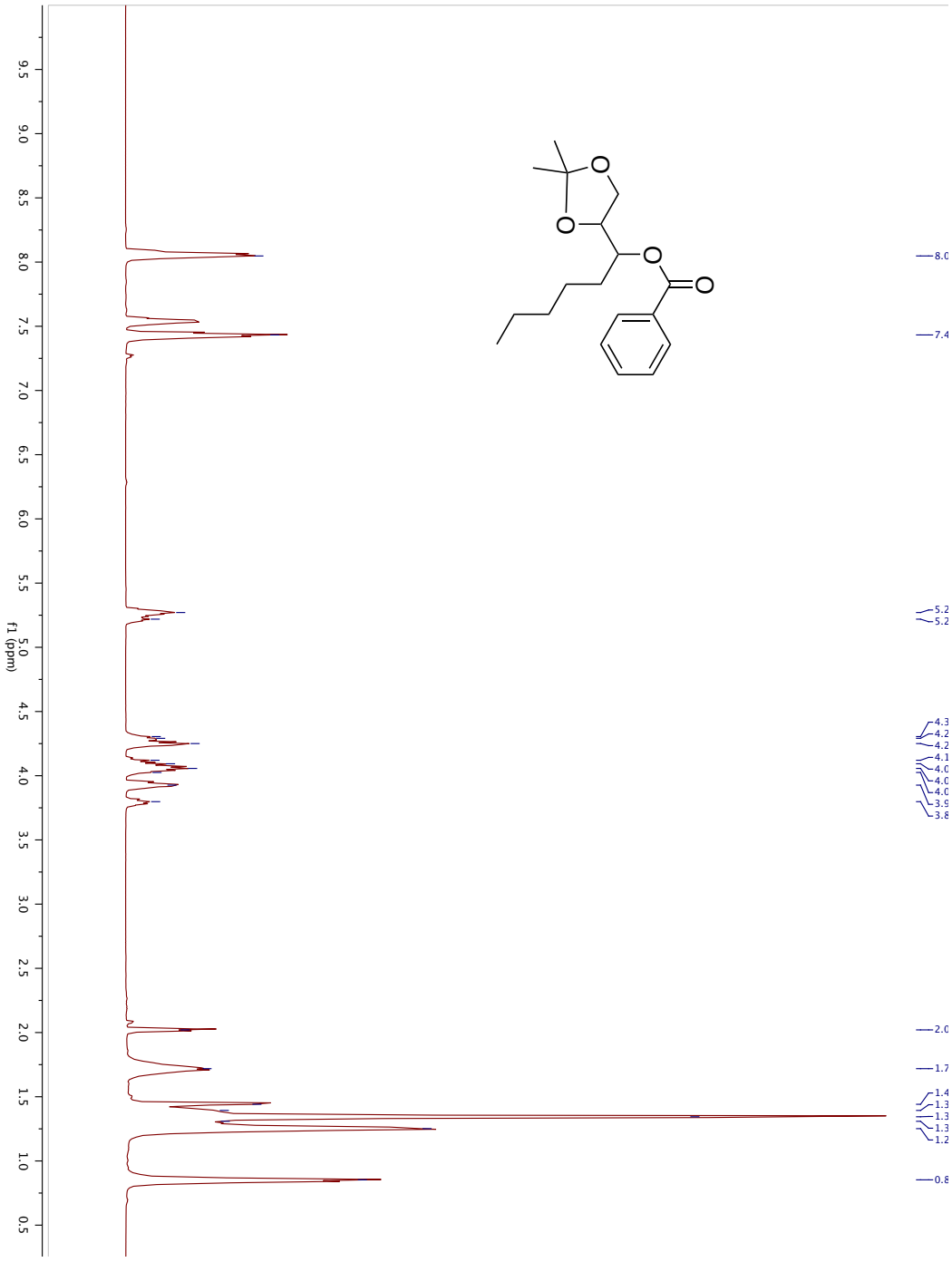
^{1}H NMR spectrum of 508



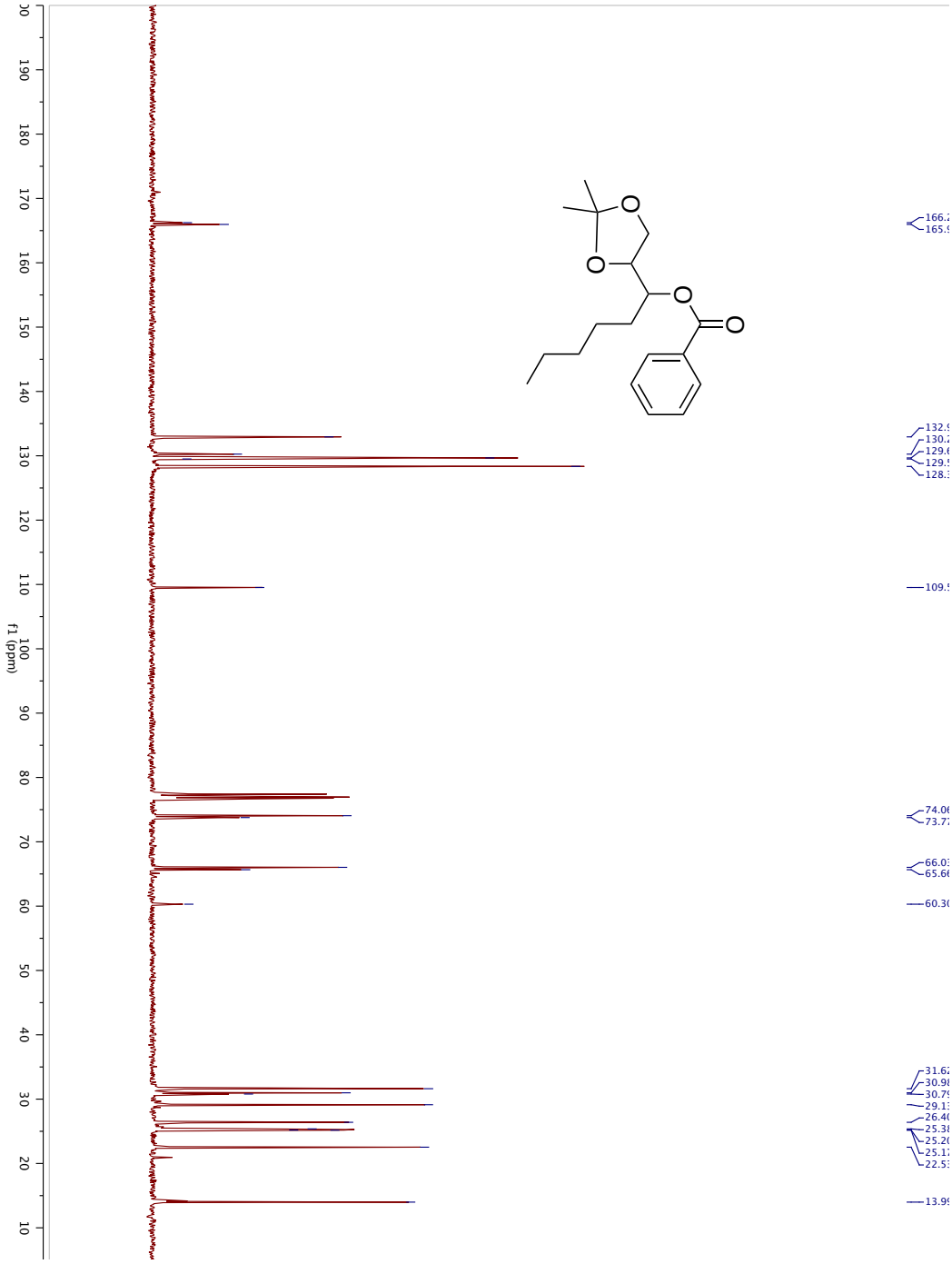
^{13}C NMR spectrum of 508



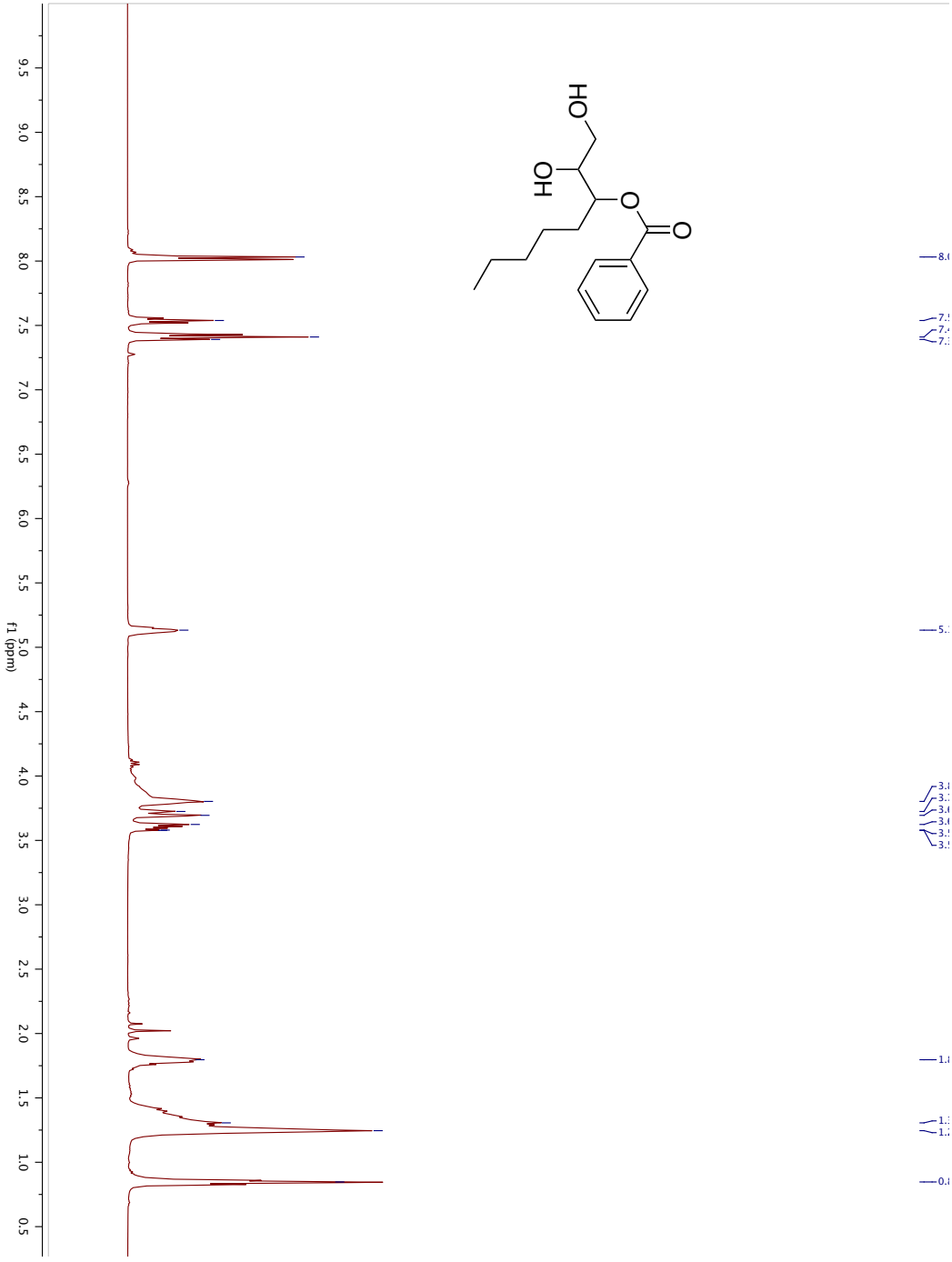
^{1}H NMR spectrum of 509



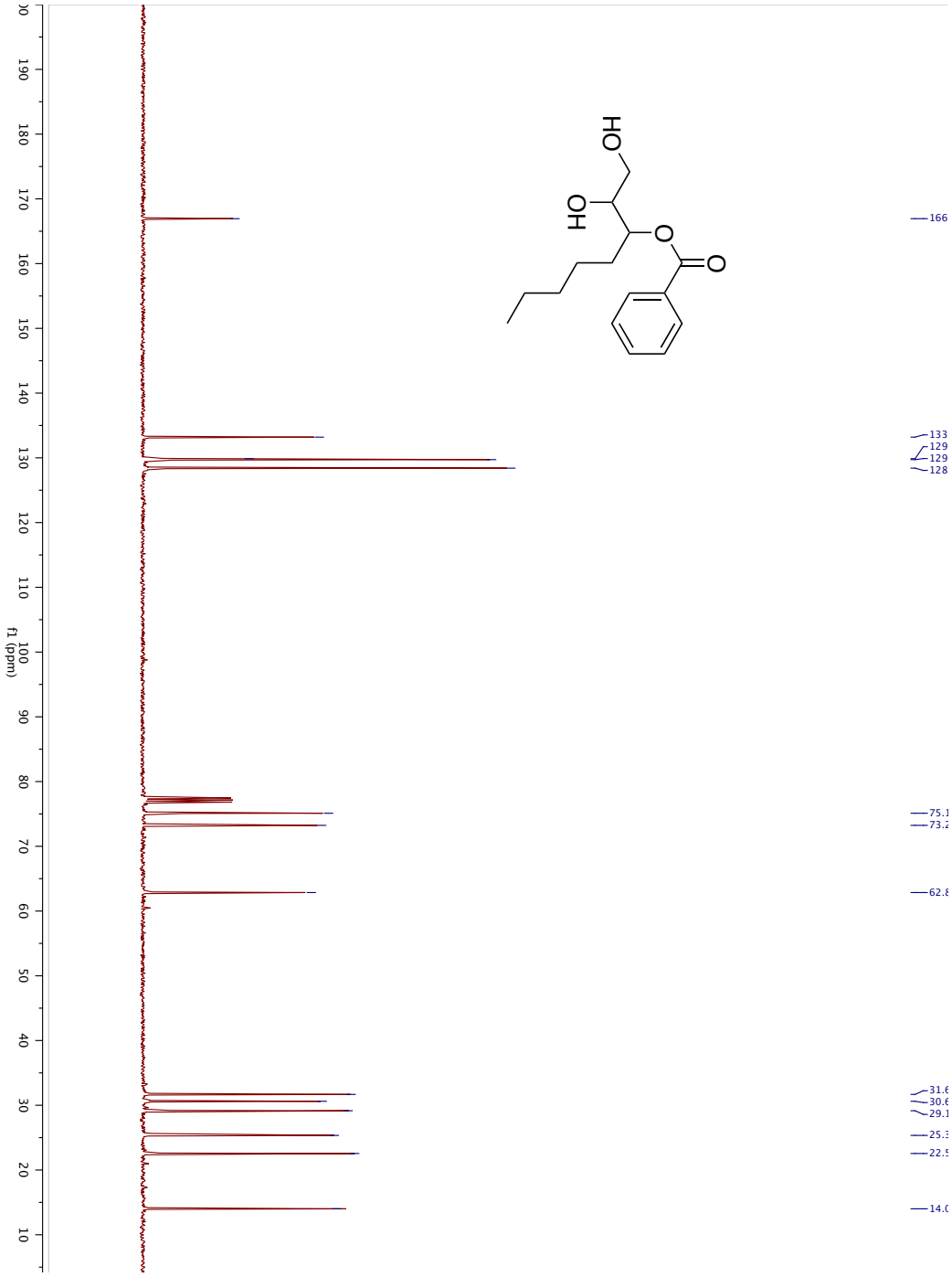
^{13}C NMR spectrum of 509



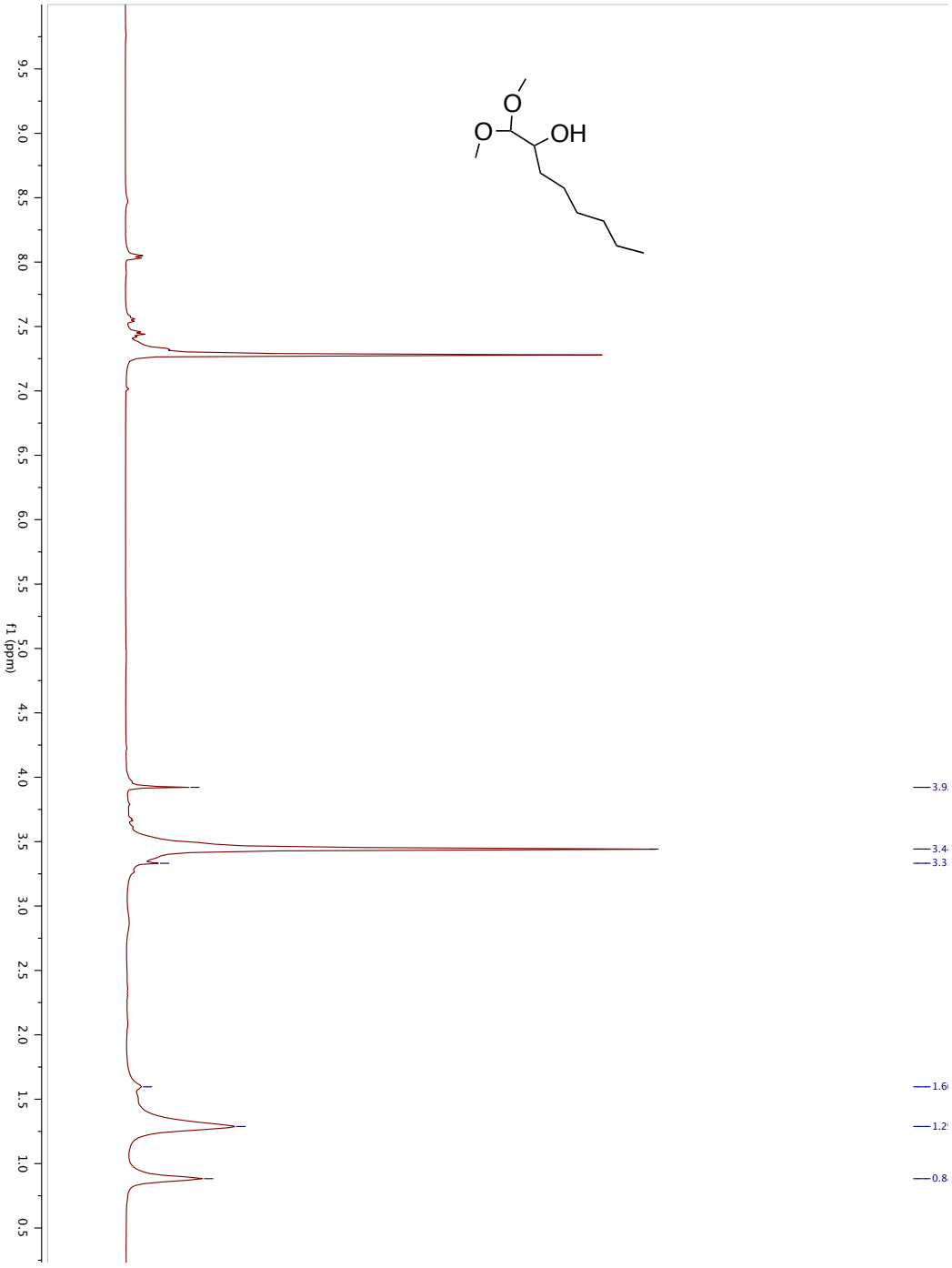
^{1}H NMR spectrum of 510



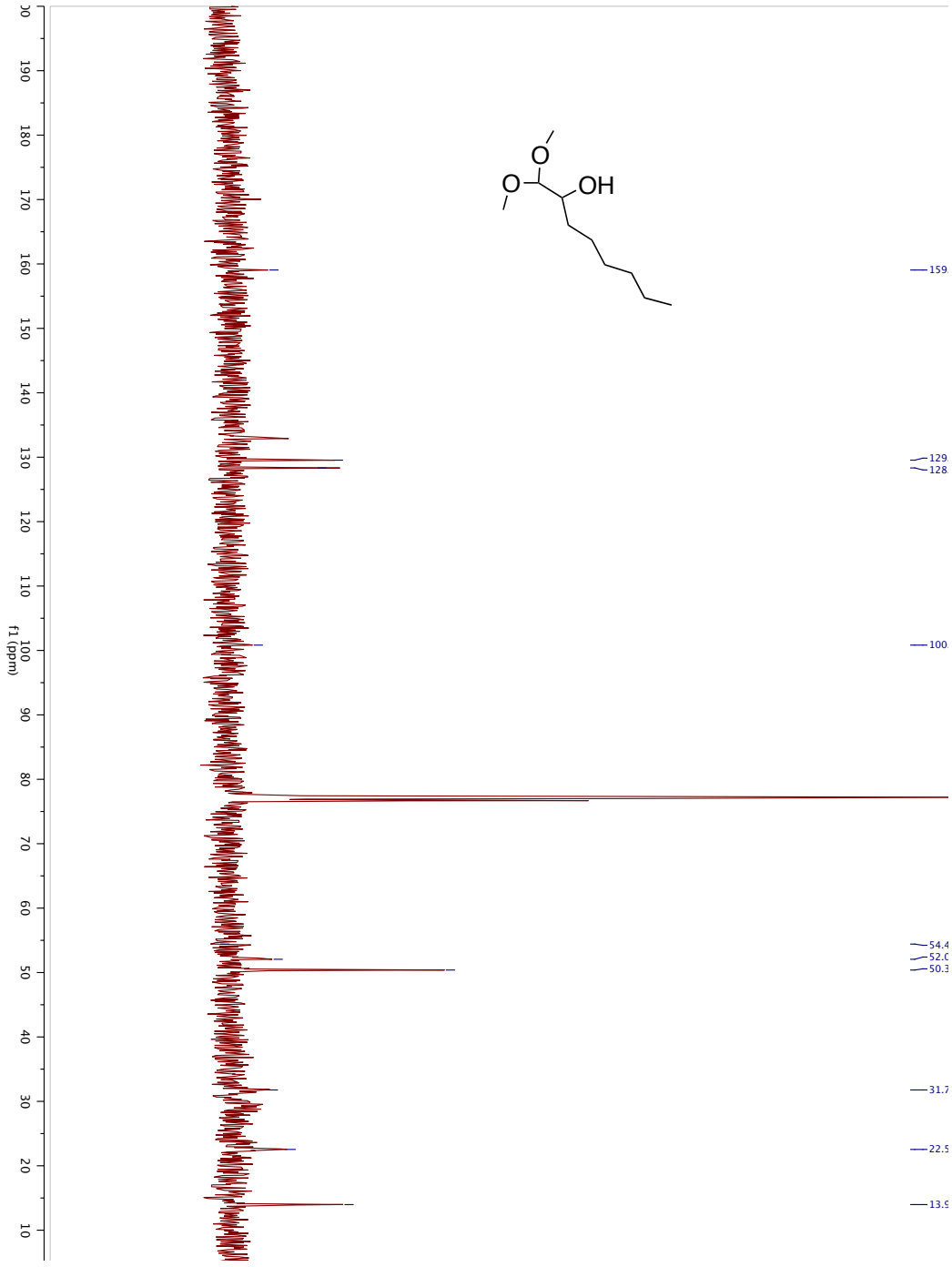
^{13}C NMR spectrum of 510



^{1}H NMR spectrum of 511



^{13}C NMR spectrum of 511



VITA

Adam Barret Pippin, son of Dr. William Pippin and Dr. Cheryl Pippin, brother of Zachary Pippin, and husband of Stacey Hall Pippin, was born on May 10th, 1985 in Huntington, West Virginia. In 1988, his family moved to Columbus, Ohio, where he grew up and attended grade school at Chapman Elementary and Davis Middle School. Though his parents divorced, he stayed in Columbus to attend high school at Dublin Scioto. In the fall of 2003, he was accepted to Ohio University where he had the best time of his life until graduating in June of 2007. After graduating with his Bachelor of Science in Chemistry, he moved to Knoxville, Tennessee in pursuit of his Ph.D. in organic chemistry. In the spring of 2008, he joined the research group of Dr. George Kabalka, and focused on developing novel chemistry methodology using boron trihalides. In July of 2008, his high school sweetheart, Stacey Hall, moved to Knoxville to accompany him and to purse her advanced nurse practitioner degree from the University of Tennessee. After a 10-year relationship, Adam Pippin and Stacey Hall were married on August 25th, 2012, in their hometown, Columbus, Ohio. Shortly after, in December of 2012, Adam received his Doctor of Philosophy in Chemistry.