

Microwave-Enhanced Chemistry of Organotrifluoroborates

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Abstract

This dissertation contains a summary of the research efforts focused on the utilization of microwave technology in organoborate chemistry. More specifically, the central topic is focused on the chemistry of potassium organotrifluoroborate compounds that have recently attracted a lot of attention as useful reagents for diverse transformations in organic synthesis such as, cross-coupling, homocoupling, as well as 1,2- and 1,4-addition reactions. The use of microwave radiation in these and other reactions is particularly appealing for improving and facilitating synthetic procedures by reducing reaction times, minimizing by-product formation, and increasing reaction yields. In this dissertation, we combine microwave technology and organotrifluoroborate chemistry to develop novel methodologies in organic synthesis. As an example, we developed microwave-assisted hydrolysis of organotrifluoroborates under mild conditions using aluminum oxide as a fluorophile and water as a solvent. The procedure was then applied to a variety of organotrifluoroborates, demonstrating the generality of the approach. The advantage of this method is that it offers fast, clean, and environmentally friendly conversion of organotrifluoroborates to the corresponding boronic acids. We also investigated and improved the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of alkynyltrifluoroborates. Our method provides a copper-free alternative to the Sonogoshira coupling reaction with the benefit of very low catalyst loading and a short reaction time. Work on symmetrical biaryls, widely encountered in natural products and medicinal chemistry, led to the development

of an efficient method for the synthesis of these compounds through homocoupling reactions of potassium organotrifluoroborates. Here, the use of microwave radiation and ligandless palladium catalysts provides a rapid and effective access to a variety of symmetrical biaryl compounds. Finally, we describe our efforts in surveying new applications of organoborates as alternatives to organoboranes compounds for C-C bond formation. The former are more stable than organoboranes and could display interesting chemical features under microwave activation.

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List of Symbols and Abbreviations

Symbol	Description
°C	Degree Celsius
γ	Gamma
Abbreviation	Description
3D	Three dimension
BX ₃	Boron trihalides
BF ₃ K	Potassium trifluoroborate
n-BuLi	n-Butyllithium
cm	Centimeter
CDCl ₃	Chloroform-d
CP	Cyclopentadiene
DCM	Dichloromethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMM	Dimethyl maleate
eq	Equivalent
g	Grams
GC	Gas Chromatography
GHz	Gigahertz
h	Hours

Hz	Hertz
HOMO	Highest occupied molecular orbital
IP	Isoprene
IR	Infrared
J	Proton-proton coupling constant
KHF ₂	Potassium hydrogen difluoride
L.A	Lewis acid
LUMO	Lowest occupied molecular orbital
m	Meter
MA	Methyl acrylate
MHz	Hertz
mL	Milliliter
min	Minute
mmol	Millimoles
NMR	Nuclear magnetic resonance
¹ H NMR	Proton nuclear magnetic resonance
¹³ C NMR	Carbon nuclear magnetic resonance
¹¹ B NMR	Boron nuclear magnetic resonance
mol	Moles
M	Molarity (mols/L)
MS	Mass Spectroscopy
MW	Microwave
pKa	The negative logarithm of the acid dissociation constant
PdCl ₂	Palladium chloride
PdCl ₂ (dppf)CH ₂ Cl ₂	[1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with dichloromethane

Pd(OAc) ₂	Palladium acetate
sec	Second
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
W	Watt

Chapter 1

Microwave Chemistry

1.1 History of Microwave Chemistry

Microwaves were first discovered in the 1940's by Percy Spencer. Despite their quick adoption for use in radar technology and in the food industry [1], their application in organic chemistry began only 40 years later. The long delay in the implementation of microwaves in organic synthesis was related to the inability of microwave devices to fulfill the requirements necessary for controlled chemical reactions. Non-uniform heating, inefficient or absent stirring and temperature control were the main obstacles to applying microwave radiation as a source of heat for organic reactions [2]. The solution to the above mentioned difficulties came with the invention of safer, better, and more accurate instruments that allowed chemists to control important parameters such as temperature, stirring, and pressure. One of the earliest articles describing the use of microwave irradiation in organic chemical transformations appeared in 1986, published by the Gedye group, who presented four types of reactions: hydrolysis of benzamide, permanganate oxidation of toluene, esterification of benzoic acid, and a $\text{S}_{\text{N}}2$ reaction between sodium 4-cyanophenoxide and benzyl chloride [3]. Since that time, a large number of scientific papers in the field on microwave chemistry

has been published, demonstrating not only the efficiency of microwave technology but also its advantages over conventional methods [4–7]. For instance, microwave heating techniques have been shown to exhibit dramatic reductions in reaction times and in unwanted side-reactions combined with a considerable increase in the yields and purity of products [8]. Taken together, these advantages led to the diverse application of microwaves in broad scientific areas including total syntheses of natural products, medicinal chemistry [9], nanotechnology [10], polymer synthesis [11], and material science [12]. Every year the number of scientific publication describing the application and use of microwave technology is growing, leading to the worldwide application of this technique as a replacement for conventional heating technology.

1.2 Microwave Radiation and its Role in Chemical Reactions

By definition, microwave radiation corresponds to the part of the electromagnetic spectrum that lies between radio and infrared waves possessing characteristics wavelengths between 1 mm (0.3 GHz) and 1 m (300 GHz) (Fig. 1.1). Microwave frequencies find broad applications in telecommunication, domestic “kitchen” devices, and chemical reactors. The latter application of microwave radiation is of particular interest to us and is the major topic of this dissertation.

The standard frequency of operation for microwave chemical reactors is 2.45 GHz. This frequency is chosen specifically to prevent interference with other wireless communication technologies. In addition, 2.45 GHz is found to be the optimal frequency for alignment of matter with the applied field (as discussed later). Depending on the nature of the matter, microwaves can be absorbed, transmitted, or reflected. The energy of microwave radiation generated at a frequency of 2.45 GHz (0.0016 eV) is

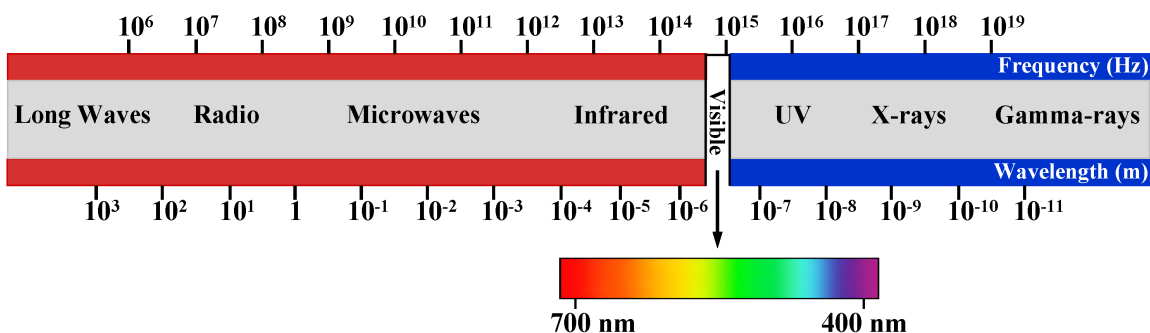


Figure 1.1: Schematic diagram of electromagnetic spectrum.

very low, and as seen from the Table 1.1, its energy is much weaker than a hydrogen bond (0.04-0.44 eV) and even Brownian motion which suggests that microwaves cannot induce chemical reactions by direct interaction of electromagnetic energy with a substance.

It is now widely accepted that microwave chemistry is based on efficient heating of materials by a “dielectric heating” mechanism [13]. This mechanism can be explained by the ability of polar materials to produce heat by absorption of microwave energy. Microwaves contain both electric and magnetic field components (Fig. 1.2). For most practical uses related to microwave synthesis, it is the electric component

Table 1.1: General types of radiation, corresponding energies and comparison to chemical bonds.

Radiation Type	Frequency (MHz)	Quantum Energy (eV)	Bond Type	Bond Energy (eV)
Gamma rays	$3.0 \cdot 10^{14}$	$1.24 \cdot 10^6$	C-C	3.61
X-rays	$3.0 \cdot 10^{13}$	$1.24 \cdot 10^5$	C=C	6.35
Ultraviolet	$1.0 \cdot 10^9$	4.1	C-O	3.74
Visible light	$6.0 \cdot 10^8$	2.5	C=O	7.71
Infrared light	$3.0 \cdot 10^6$	0.012	C-H	4.28
Microwaves	2450	0.0016	O-H	4.80
Radiofrequencies	1	$4.0 \cdot 10^{-9}$	hydrogen bond	0.04-0.44

Adapted from reference [14].

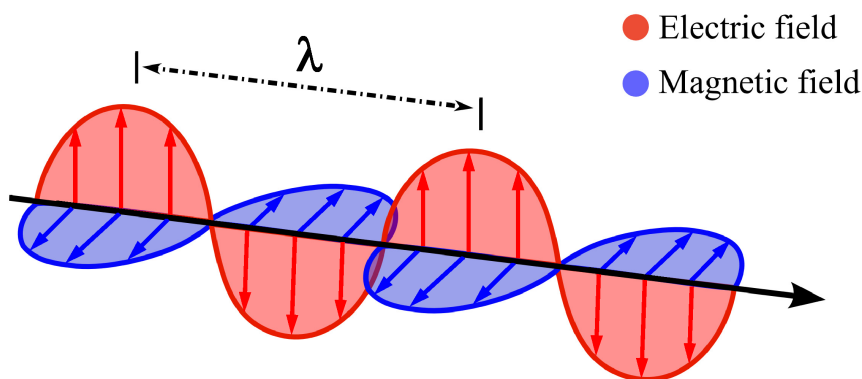


Figure 1.2: Electromagnetic wave showing electric and magnetic field components.

that is of importance for wave-material interactions. The electric field will interact with any polar or ionic molecule. Dipole polarization and ionic conduction are thus the two main mechanisms that explain how the matrix can absorb microwaves and generate heat [15,16]. The presence of a dipole moment in the molecule is the main condition for the dipole polarization mechanism to occur. When polar molecules are subjected to microwave radiation, they orient themselves such that their dipole moments will try to align with the electric field. Dipoles of the matrix are constantly realigned by the oscillating microwave (electric) field which leads to heat formation through molecular rotations, collisions, and dielectric loss [2]. Depending on how well the matrix can adjust itself to the electric field, the amount of heat produced may vary. The faster the process of realignment, the greater amount of energy that is released. As noted above, the frequency of microwave irradiation at 2.45 GHz results in highly efficient energy absorption by matter and optimal alignment of molecules with field. If the dipole is exposed to a high frequency electromagnetic field, it has no time to realign and no heat is produced; if instead a low frequency field is applied, the dipole reorients itself too fast resulting in no heating as well. Lying between these two extremes, radiation at 2.45 GHz allows molecules to generate a phase difference between the orientation of the field and that of the dipoles, and as a result,

heating occurs through molecular rotations and dielectric loss. The loss tangent is a parameter that describes dielectric properties of the compound and dictates how efficient the microwaves can be absorbed by the medium and converted into heat [17]. Ionic conduction is the second mechanism by which dielectric heating operates. It is a stronger mechanism than dipole polarization but can only be applied to reaction systems containing ions. When charged particles are exposed to microwaves, they oscillate back and forth and generate heat by collisions with neighboring ions or molecules.

1.3 Comparison of Microwave and Conventional Thermal Heating Techniques

Oil baths, sand baths, and electric heating mantles are traditionally used by chemists as a source of heat to carry out chemical reactions [18]. The main drawback of conventional heating is that energy transfer from the heat source to the reaction mixture is slow and inefficient because it depends on thermal conductivity and convection currents in various materials. Heat is transferred to the reactants by passing through the walls of the vessel; and as a result, the temperature of the vessel is generally higher than that of the reaction mixture. Moreover, there is a possibility of formation of a temperature gradient inside of the reaction mixture, which leads to local overheating, and as a result, decomposition of reaction components takes place. The effect of microwave irradiation on materials is totally different when compared to thermal heating [19]. Microwaves heat the matter through direct absorption of radiation by polar molecules such as the solvent, catalyst, or reagent and raise the temperature within the whole volume simultaneously and uniformly. In comparison, in a traditionally heated vessel, the reaction mixture touching the vessel wall is heated first.

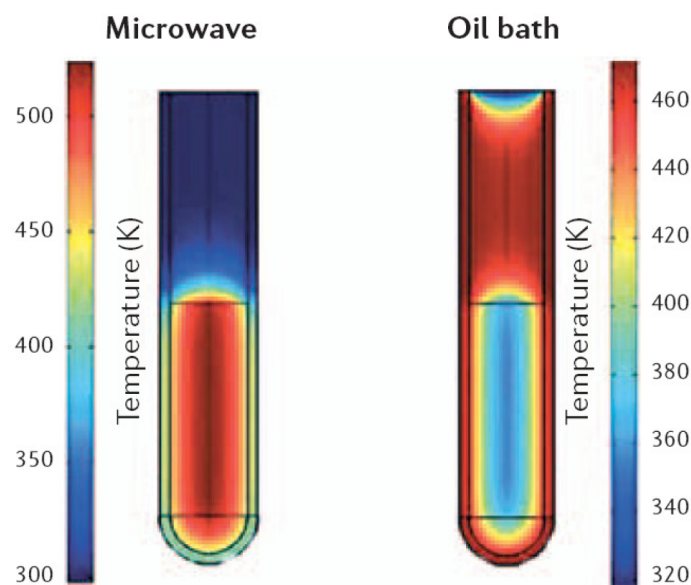


Figure 1.3: Comparison of microwave and conventional heating effects. Reprinted with permission from Ref. [20] [Kappe C.O.; Dallinger, D. *Nat. Rev. Drug Discov.* **2006**, *5*, 51-63].

Borosilicate glass, Teflon, and quartz are the most common materials employed in fabrication of microwave chemistry vessels due to their transparency to microwave radiation. Because of that, when exposed to microwaves the vessel's walls are not heated leading to a formation of an inverted temperature gradient and a very efficient internal heat transfer (no hot wall surface) (Fig.1.3) [20].

1.4 Effect of Microwaves on Chemical Reactions

Despite the fact that microwave technology has become a more wide spread and accepted tool among organic chemists, there are still things that remain unexplored [21]. For instance, the exact mechanism relating to how and why microwaves enhance chemical reactions is still under debate. Almost all scientific papers published to date describe faster reactions and improved yields of products using microwave assistance in comparison to reactions carried out in an oil-bath at the same temperature.

This observation has led to the hypothesis of a non-thermal or specific microwave effect [22, 23]. Many scientists agree and conclude that the phenomenon is a result of a thermal/kinetic effect; in other words, a consequence of a high reaction temperature being achieved by absorption of microwave energy by polar material (reaction mixture) under closed vessel conditions. For example, methanol ($\tan \delta = 0.659$) exposed to microwave radiation in a sealed vessel can be heated to a temperature much higher (above 100°C) than its boiling point in a very short period of time. Ionic liquids show similar effects reaching temperatures above 200°C in just few seconds. These temperature profiles are very difficult to achieve and reproduce under conventional heating.

1.5 Effects of Solvent

Solvent plays an important role in the successful outcome of a chemical reaction. In most cases, solvents used in microwave-assisted organic reactions are those used in conventional methods. However, the most important criteria for choosing a solvent suitable for microwave synthesis is not the boiling point of the solvent but its dielectric properties, particularly the $\tan \delta$ value (Table 1.2). Solvents that possess higher $\tan \delta$ values absorb microwave radiation more strongly and convert that energy into heat more efficiently than solvents with low $\tan \delta$ values. In other words, the more polar the solvent, the faster the increase in the temperature of a reaction mixture. In some reactions, where the use of a non-polar solvent is required (for example, toluene or DCM) temperature increase can be achieved by absorption of radiation by polar components of the mixture which then transfer the heat to the nonpolar solvent molecules. Another way to achieve a high temperature with non-polar solvents is to dope them with polar additives such as ionic liquids. In some cases, even a solvent-free reaction can be performed under microwave conditions [24]. Generally,

Table 1.2: Boiling points, $\tan \delta$ and efficiency of microwave absorbance for some common solvents. The $\tan \delta$ is the phase difference between the electric field and the polarization of the material.

Solvent	bp ($^{\circ}\text{C}$)	$\tan \delta$	Microwave absorbance
Ethylene glycol	197	1.350	very good
Dimethylsulfoxide	189	0.825	good
Ethanol	78	0.941	good
Methanol	65	0.659	good
Water	100	0.123	medium
1-Methyl-2-pyrrolidone	204	0.275	medium
N,N-dimethylformamide	153	0.161	medium
1,2-Diclorobenzene	180	0.280	medium
Acetonitrile	81	0.062	medium
Dicloromethane	40	0.042	low
Tetrahydrofuran	66	0.047	low
Toluene	110	0.040	very low

Adapted from reference [17].

these types of reactions are cost effective, environmentally friendly, clean, and safe.

1.6 Microwave Devices

One of the earliest examples of microwave assisted organic reactions was reported in the 1980's by Gedye and coworkers [3]. At that time, microwave reactions were performed in domestic microwave ovens. Despite a good chemical outcome, there were control and safety problems that needed to be addressed. These included the absence of a stirring function, no pressure control devices, no temperature control, nonuniform heating, and a high risk of solvent explosion. Nevertheless, kitchen microwaves are still widely used to perform solvent-free or "dry-media" chemistry [25].

The existing drawbacks of domestic microwave ovens were overcome in the 1990's

by the development of industrial microwave chemical reactors. All current industrial microwave units have build-in magnetic stirring options, temperature monitors (either infrared sensor or fiber optic probes), pressure control devices, and variable power output. These parameters are controlled by software and can be easily adjusted before and during the reaction. Today, there are two main types of microwave instruments used for chemical applications: monomode and multimode (Fig. 1.4) reactors.

Multimode microwaves operate very similarly to kitchen microwave appliances. After a magnetron generates microwaves, they enter the large cavity and are reflected by the internal walls until fully absorbed by a reaction medium. Monomode microwaves have a smaller cavity that allows the generated radiation to be directly focused on the reaction vessel [26]. Both types of instruments possess some advantages and disadvantages. Multimode reactors, due to their large volume, are capable of performing large-scale reactions but the microwave field does not spread uniformly, leading to localized overheating and reproducibility problems. Monomode reactors heat the sample very fast and efficiently, but because of the small size of the cavity, the volume of the vessel is limited. In both types, a chemical reaction can be performed in a closed vessel mode (sealed vessel under pressure) or in an open vessel mode (under atmospheric pressure). Furthermore, both reactors allow reactions to occur under an inert atmosphere.

1.7 Microwave-Assisted Organic Reactions

Microwave radiation enhances many different types of organic reactions but the most important and well studied are the transition-metal-catalyzed reactions. These reactions provide a straightforward method for carbon-carbon bond formation, but a major drawback in their application is the long reaction time using conventional

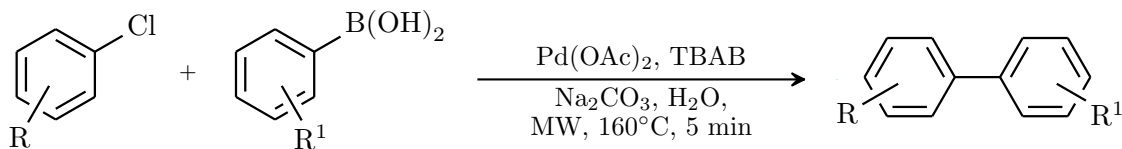


Figure 1.4: (a) Multimode and (b) monomode microwave reactors.

heating techniques. The use of microwave radiation for the enhancement of metal-catalyzed reactions becomes very useful due to the dramatic reduction of the reaction time from several hours (or days) to minutes. In addition, an increase in the product yield and a significant decrease in catalyst loading are also reported [27]. Some of the most common transition-metal-catalyzed reactions are the Suzuki-Miyaura, Mizoroki-Heck, Stille, and Sonogashira coupling reactions that are discussed in more detail below.

1.7.1 Suzuki-Miyaura Cross-Coupling Reaction

The Suzuki-Miyaura reaction is one the most versatile chemical reaction for carbon-carbon bond formation and is widely accepted by scientists in both academia and industry [28, 29]. One of the advantages of the Suzuki reactions is that they often can be carried out in aqueous solutions making them highly attractive from the perspective of “green” chemistry (i.e environmentally friendly processes). Moreover, a wide variety of organoboron reagents can be used in these type of transformations. Organoboron reagents are easy to prepare, stable, nontoxic, and commercially available. In addition, the availability of different palladium catalysts, ligands, and bases (organic, and inorganic) make the Suzuki coupling reaction a popular choice among synthetic organic chemists [30–35]. A classical example is the cross coupling reaction of an organoboron reagent with an aryl halide in the presence of a palladium catalyst and a base [36] (Scheme 1.1).



Scheme 1.1: Microwave assisted Suzuki-Miyaura coupling [36].

The mechanism involves the oxidative addition of the palladium to the aryl halide to form an organopalladium intermediate. The boronate complex is formed by addition of the base to the organoboron reagent, which then transmetallates with organopalladium species. Reductive elimination results in formation of the product and regeneration of the palladium catalyst (Fig. 1.5).

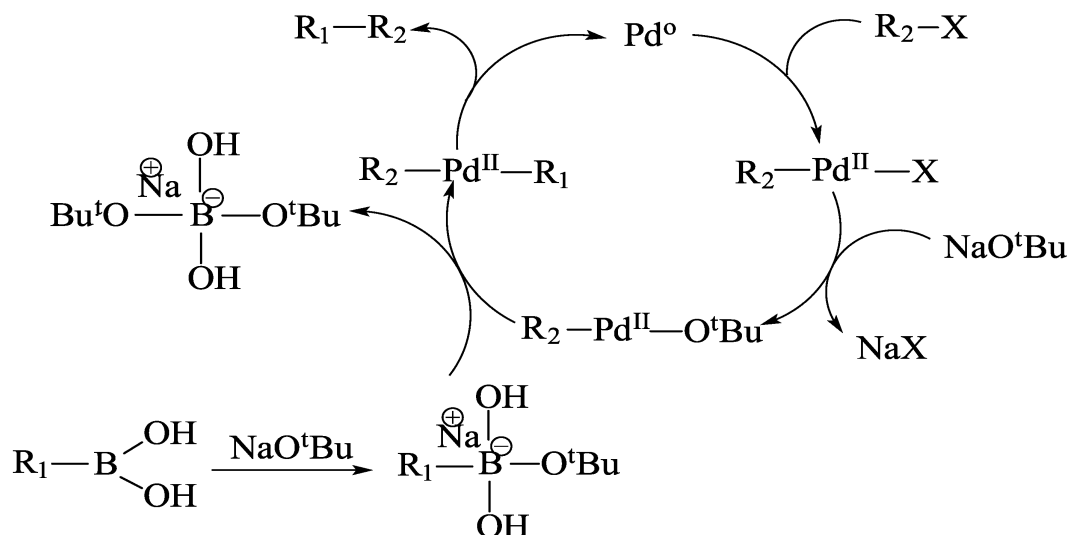
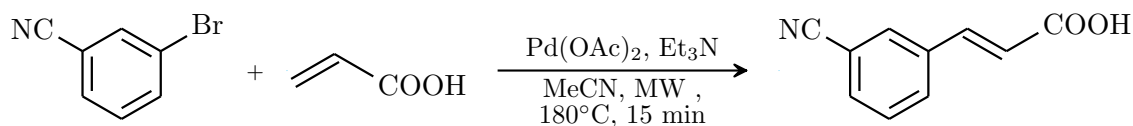


Figure 1.5: The palladium catalytic cycle. Adapted from reference [37].

1.7.2 Heck Reaction

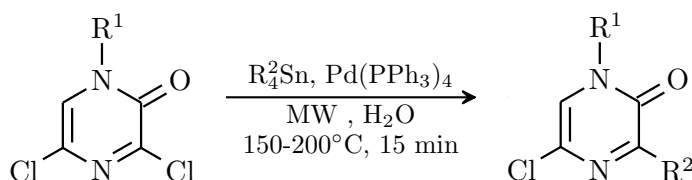
The Heck reaction is an elegant metal-catalyzed chemical transformation for creating carbon-carbon bonds [38]. This reaction involves a vinylic substitution between an alkene and organohalide or triflate. The first microwave-assisted Heck coupling was reported in 1996 [39]. The reaction mechanism is similar to the Suzuki-Miyaura coupling reaction, and an example of the Heck reaction is depicted in Scheme 1.2 where an aryl bromide reacts with acrylic acid to form a cinnamic acid [40].



Scheme 1.2: Formation of cinnamic acid using the Heck reaction [40].

1.7.3 Stille Coupling Reaction

Microwave-assisted Stille coupling reactions were reported in the early 2000's by Larhed *et al.* [41]. This type of transformation provides a straightforward route to carbon-carbon bond formation involving an organotin compound and an organic halide (or pseudohalide) catalyzed by palladium (Scheme 1.3). The advantage of this reaction include the stability of organostannanes and the ability to synthesize a wide variety of functionally substituted organic compounds. The main drawback of this method is that organostannanes compounds are toxic and very non-polar which limits the use of water as a solvent and often leads to separation problems. In addition, boronic acids and their derivatives undergo similar chemistry and achieve the same results without the drawbacks noted above.

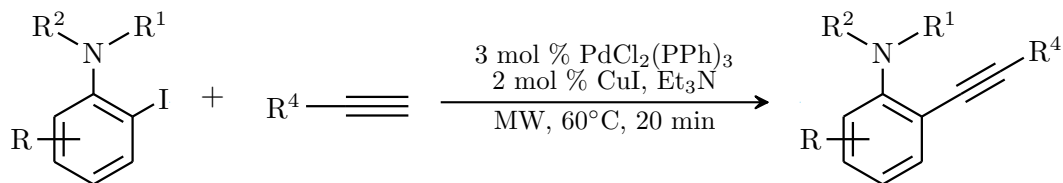


Scheme 1.3: Microwave assisted Stille coupling reaction [42].

1.7.4 Sonogashira Reaction

The Sonogashira reaction involves the coupling of terminal alkynes and organic halides in the presence of a palladium catalyst, a copper salt as a co-catalyst, and a base [43]. Erdmlyi and Gogoll reported a microwave-assisted Sonogashira coupling in

2001 [44] (Scheme 1.4). The reaction mechanism parallels that of the Suzuki coupling but with addition of a copper cycle. In some cases, the outcome of the Sonogashira transformation may also be achieved by Suzuki coupling without using copper as co-catalyst.

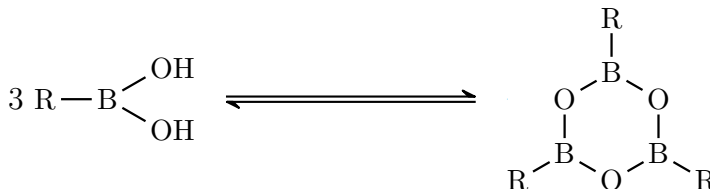


Scheme 1.4: Microwave assisted Sonogashira coupling reaction [45].

1.7.5 Organotrifluoroborates

Organometallic reagents, in particular organolithium and organomagnesium compounds, play an important role in organic chemistry by providing access to the essential molecules used in medicinal chemistry, agriculture, and the pharmaceutical industries [46, 47]. Despite their usefulness in organic synthesis, organolithium and organomagnesium compounds possess significant disadvantages due to their high nucleophilicity and basicity, which limit their application when sensitive functional groups are present in the reaction mixture. As an alternative to lithium and magnesium based reagents, Zn, Si, B, and Sn based materials have attracted attention as promising candidates for metal-catalyzed reactions because of their tolerance to various functional groups [47]. Among these reagents, organoboranes and organostannanes have become the most commonly used compounds in various transition-metal-catalyzed reactions [48]. The toxicity of the organostannanes and the difficulties associated with final product purification are the two main disadvantages associated with their use. Organoboranes, on the other hand, became the most frequently used reagents after the discovery of the Suzuki-Miyaura reaction [49] that offers

a straightforward method for carbon-carbon bond formation. Many organoboron reagents are commercially available or can be readily prepared via transmetallation or hydroboration reactions [50]. The main advantage of organoboron reagents is their lack of toxicity [51], making them environmentally friendly when compared to other organometallic reagents. However, most trivalent organoboranes also have limitations. For instance, the precursors for the Suzuki reaction are often prepared from catecholborane or 9-BBN that lack atom economy. Many boronic acids form reactive anhydrides on standing, and their purification can be problematic because they are often waxy solids. Since boronic acids can contain anhydrides and boroxines, this leads to problems in determining reaction stoichiometry (Scheme 1.5).



Scheme 1.5: Formation of boroxines.

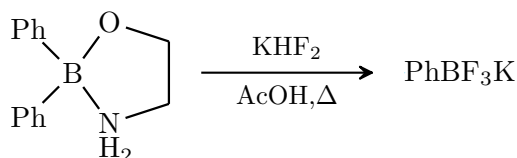
Boronate esters are more stable than organoboronic acids, but their sensitivity to water impacts their reactivity. In addition, boronated esters are more expensive because of the high cost of the alcohols and diols used in their preparation.

The most important disadvantage of all trivalent boron compound is their instability under atmospheric conditions due to the vacant *p* orbital on the boron atom. The presence of an empty orbital makes these compound very reactive toward moisture, nucleophiles, bases, and oxidizing agents [52].

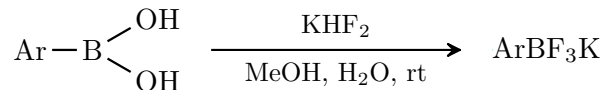
The discovery of potassium organotrifluoroborates in the late 1960's was a significant breakthrough in the field of organoborane chemistry [53] (Scheme 1.6). In contrast to trivalent organoboranes, these reagents show exceptional stability toward

nucleophiles as well as both air and moisture. The vast majority can be stored at room temperature without any precaution; but at the same time, they are highly reactive in a large variety of reactions, particularly palladium catalyzed cross-coupling reactions.

A very efficient method for preparing potassium organotrifluoroborates was described by Vedejs *et al.* in 1995 [54]. This synthesis allows the conversion of arylboronic acids or esters to potassium aryltrifluoroborates in quantitative yields upon treatment with KHF_2 in aqueous methanol (Scheme 1.7).

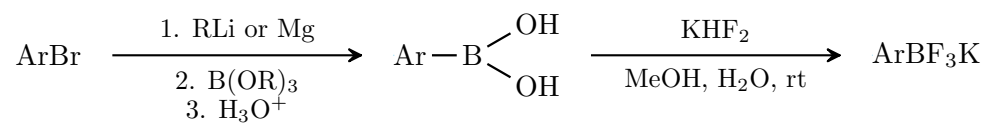


Scheme 1.6: Preparation of potassium organotrifluoroborates [53].



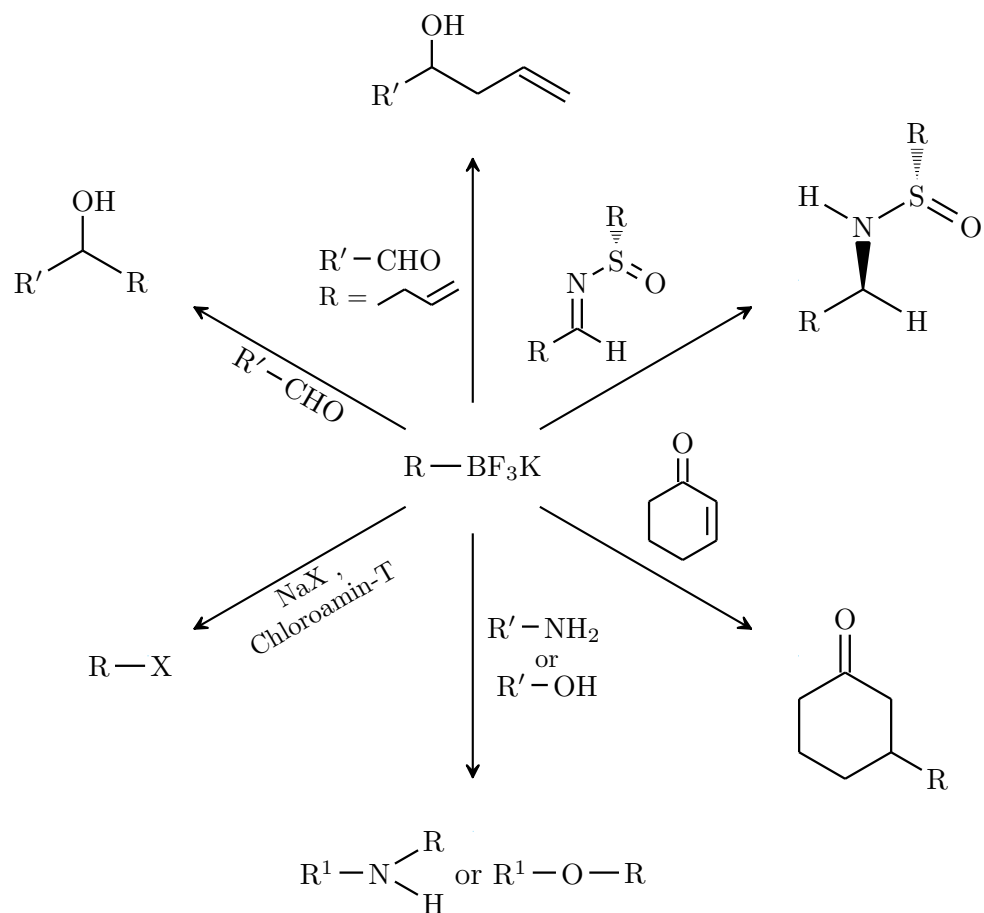
Scheme 1.7: Synthesis of organotrifluoroborates from boronic acids [54].

A variety of potassium aryltrifluoroborates can be prepared by straightforward procedures using classical methods of organoboron synthesis. For example, lithium-halogen exchange or magnesium insertion, followed by boronation and hydrolysis, furnish crude boronic acids, which on treatment with KHF_2 give aryltrifluoroborates in high yields [55] (Scheme 1.8). The benefit of this procedure is that there is no need to isolate the intermediate arylboronic acid. Another advantage of organotrifluoroborates is that they are versatile reagents not only for metal-catalyzed coupling reactions but are also useful participants in diverse chemical transformations such as C-O and C-N bond formation, halogenation, allylation, and 1,2- and 1,4-addition reactions [56–61] (Scheme 1.9).



Scheme 1.8: Synthesis of organotrifluoroborates from aryl halides.

To conclude, potassium organotrifluoroborates have become very promising alternatives to organoboronic acids and esters mainly due to the exceptional stability of these compounds not only toward moisture and oxygen but also nucleophiles. The ease of preparation and purification, multifunctionality, and often superior reactivity compared to organoboron derivatives, make these boronate complexes valuable in a variety of organic reactions.



Scheme 1.9: Organotrifluoroborates as versatile reagents in organic synthesis. Adapted from reference [62].

Chapter 2

Thermal and Microwave

Hydrolysis of

Organotrifluoroborates Mediated

by Alumina

Chapter 2 is an adaptation of the research article by Kabalka, G. W.; Coltuclu, V. *Tetrahedron Lett.* **2009**, *50*, 6271-6272.

2.1 Introduction

Organoboronic acids have become fundamental building blocks in synthetic organic chemistry with the advent of the Suzuki-Miyaura coupling reaction [63]. The fact that ester derivatives of organoborates and organotrifluoroborate salts also undergo a wide variety of metal-catalyzed coupling reactions has only served to enhance the importance of the organoboronic acids [64]. The facile conversion of organoboronic acids to organotrifluoroborate and ester derivatives has permitted researchers to uti-

lize whichever organoboron derivative that reacts most effectively [54]. However, the hydrolysis of organotrifluoroborates to the corresponding organo boronic acids can be problematic [65].

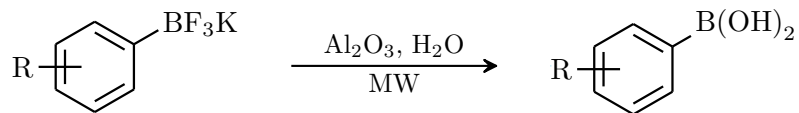
2.2 Results and Discussion

We have had a continued interest in organic reactions carried out in the presence of alumina [66]. We have also explored the use of microwave irradiation for enhancing organic reactions [67] including those involving organotrifluoroborate reagents [68]. Intrigued by the idea of combining both research areas, we investigated the potential use of microwave irradiation in the hydrolysis of organotrifluoroborate derivatives. Since earlier studies made it clear that the hydrolysis reaction proceeds more rapidly in the presence of a base, we initiated the studies under basic conditions [65]. We found that the hydrolysis of organotrifluoroborates proceeds far more rapidly upon microwave irradiation than under thermal conditions (reaction times decrease from 24 h to a matter of minutes). As was noted in the earlier report [69], aryl trifluoroborates containing electron-donating groups hydrolyze more rapidly than those containing electron-withdrawing groups under either thermal or microwave conditions.

In our hands, bases such as Na_2CO_3 and NaHCO_3 were effective for hydrolyzing aryltrifluoroborates containing electron-donating groups in microwave reactions. However, we found that hydrolysis products from aryltrifluoroborates derivatives containing electron-withdrawing groups often contained significant amounts of the protonolysis byproducts. Protonolysis also occurred when an organic base such as Hunigs base was utilized in the microwave-induced hydrolysis reactions. It should be noted that hydrolysis reactions of the organotrifluoroborates can be readily monitored by ^{11}B NMR (the organotrifluoroborates exhibit resonances near 7 ppm, boric

acid resonates near 20 ppm, and the organoboronic acids resonate near 30 ppm in the ^{11}B NMR spectrum).

We then explored the hydrolysis reactions in the presence of alumina using microwave irradiation carried out in a commercial monomode reactor (Scheme 2.1).



Scheme 2.1: Hydrolysis of organotrifluoroborates.

The hydrolysis reaction proceeded rapidly and in a very high yield for all aryltrifluoroborates investigated. Significantly, no organotrifluoroborate starting material remained after hydrolysis and protonolysis was not observed for any of the materials examined, Table 2.1. The reactions were quite straightforward in that the product arylboronic acids were recovered by simple extraction (ethyl acetate) followed by evaporation of the solvent.

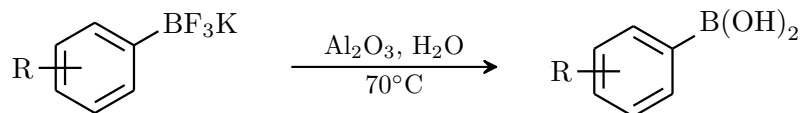
Table 2.1: Hydrolysis of organotrifluoroborates.

$$\text{R-C}_6\text{H}_4\text{-BF}_3\text{K} \xrightarrow[70^\circ\text{C}]{\text{Al}_2\text{O}_3, \text{H}_2\text{O}} \text{R-C}_6\text{H}_4\text{-B(OH)}_2$$

Entry	R	MW Yield (%)	Thermal yield (%)
1	4-CH ₃	90	88
2	4-F	94	90
3	4-OCH ₃	93	92
4	2-OCH ₃ , 6-OCH ₃	87	84
5	4-CHO	92	89
6	4-CH ₃ CO	95	91
7	4-CF ₃	85	82

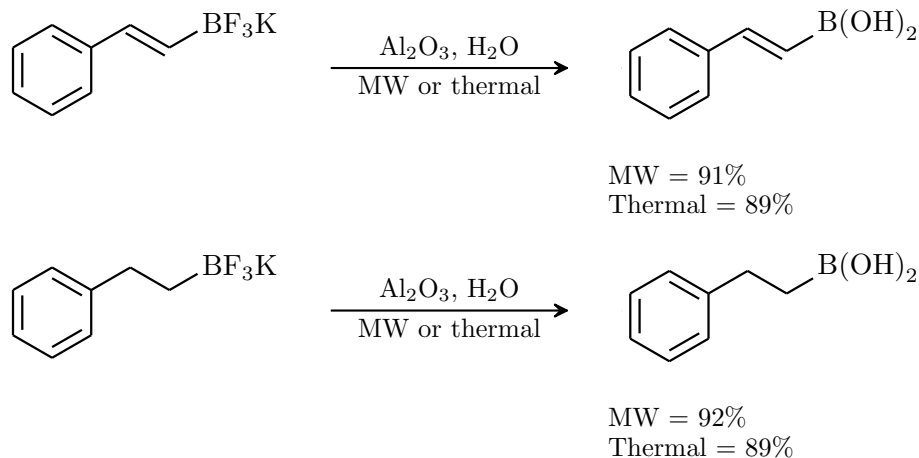
Isolated yields of pure products. Reactions were carried out at 70 °C for 15 min.

As a next step, we examined the hydrolysis reaction under thermal conditions. At ambient temperatures, the reactions proceeded at a relatively low rate (reaction times ranged from 12 to 24 h). However, hydrolysis proceeded quite readily at 70 °C. The synthetic procedure parallels that used in the microwave reactions (Scheme 2.2).



Scheme 2.2: Hydrolysis under thermal conditions.

We also examined the hydrolysis of a vinyltrifluoroborate and an alkyltrifluoroborate derivatives (Scheme 2.3). The reactions proceeded in excellent yields with no evidence of protonolysis. In each case, the isolated yields of pure products were excellent.



Scheme 2.3: Hydrolysis of an alkenyl- and alkyl-trifluoroborates.

Although a detailed mechanistic study has not been carried out, the efficacy of alumina in the hydrolysis reactions may be due in part to the large enthalpy of the aluminum fluoride bond and the fact that the resultant product is insoluble in the reaction mixture. In contrast to previously reported organotrifluoroborate

hydrolysis reactions, protodeboronation is not observed. A parallel hypothesis has been put forth to explain the efficiency of lithium hydroxide in hydrolysis reactions of organotrifluoroborates under solution conditions [65].

2.3 Conclusions

We have developed a straightforward procedure for hydrolyzing organotrifluoroborates to the corresponding boronic acids in excellent yields under very mild conditions. We have demonstrated the efficiency of this newly developed method through hydrolysis of ten organoboronic acids. We conclude that this procedure can be generalized to a broad class of organotrifluoroborates. Aluminum oxide was found to be a good fluorophile that induced no protodeboronation and the use of water as solvent makes this methodology environmentally friendly.

2.4 Experimental

2.4.1 General Information

The potassium organotrifluoroborate reagents were supplied by Frontier Scientific Inc. (Logan, UT, USA) and were used as received. Aluminum oxide was purchased from Sigma-Aldrich (St. Louis, MO, USA). Column chromatography was performed using silica gel (60 Å, 230-400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical thin-layer chromatography was performed using 250 μ m silica plates (Analtech, Inc., Newark, DE, USA). ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, on a Bruker Avance 400 instrument. Chemical shifts are measured with respect to the residual protons in the deuterated solvents.

2.4.2 Typical Reaction Procedure

To a solution of potassium 4-formylphenyltrifluoroborate (212 mg, 1.00 mmol) in 10 mL of water was added 0.2 g of Al_2O_3 contained in a 25 mL round-bottomed flask. The resulting suspension was inserted into a CEM Discover microwave unit and stirred for 15 min at 70 °C. The mixture was extracted with ethyl acetate (3×10 mL), the extracts combined, dried over anhydrous sodium sulfate, filtered, and the solvent evaporated to yield 4-formylphenylboronic acid as a white solid (134 mg, 92%).

2.4.3 Characterization of Compounds

4-Methylphenylboronic acid (1): ^1H NMR ($\text{DMSO-}d_6$): δ 7.69 (d, $J = 7.5$ Hz, 2H), 7.13 (d, $J = 7.6$ Hz, 2H), 2.29 (s, 3H). ^{13}C NMR ($\text{DMSO-}d_6$): δ 139.4, 134.2, 128.1, 21.2.

4-Fluorophenylboronic acid (2): ^1H NMR ($\text{DMSO-}d_6$): δ 7.97–7.88 (m, 2H), 7.18 (t, $J = 8.9$ Hz, 3H). ^{13}C NMR ($\text{DMSO-}d_6$): δ 164.8, 162.4, 135.7, 114.5, 114.3.

4-Methoxyphenylboronic acid (3): ^1H NMR ($\text{DMSO-}d_6$): δ 7.75 (d, $J = 8.5$ Hz, 2H), 6.89 (d, $J = 8.5$ Hz, 2H), 3.75 (s, 3H). ^{13}C NMR ($\text{DMSO-}d_6$): δ 161.0, 135.9, 113.0, 54.9.

2,5-Dimethoxyphenylboronic acid (4): ^1H NMR ($\text{DMSO-}d_6$): δ 7.82 (s, 2H), 7.21 (t, $J = 8.2$ Hz, 1H), 6.55 (d, $J = 8.2$ Hz, 2H), 3.69 (s, 6H). ^{13}C NMR ($\text{DMSO-}d_6$): δ 161.9, 130.0, 103.6, 55.3.

4-Formylphenylboronic acid (5): ^1H NMR ($\text{DMSO-}d_6$): δ 10.01 (s, 1H), 8.00 (d, $J = 7.6$ Hz, 2H), 7.86 (d, $J = 7.6$ Hz, 2H). ^{13}C NMR ($\text{DMSO-}d_6$): δ 193.6, 141.5, 137.3, 134.7, 128.4.

4-Acetylphenylboronic acid (6): ^1H NMR ($\text{DMSO-}d_6$): δ 7.97–7.87 (m, 4H), 2.57 (s, 3H). ^{13}C NMR ($\text{DMSO-}d_6$): δ 198.3, 137.9, 134.4, 127.1, 26.9.

4-Trifluoromethylphenylboronic acid (7): ^1H NMR (DMSO- d_6): δ 8.00 (d, J = 7.7 Hz, 2H), 7.66 (d, J = 7.8 Hz, 2H). ^{13}C NMR (DMSO- d_6): δ 139.2, 134.7, 125.8, 123.9.

(*E*)-Styrylboronic acid: ^1H NMR (DMSO- d_6): δ 7.78 (s, 1H), 7.47 (d, J = 7.3 Hz, 2H), 7.40–7.21 (m, 3H), 6.12 (d, J = 18.4 Hz, 1H). ^{13}C NMR (DMSO- d_6): δ 145.8, 137.6, 128.7, 126.6, 123.3.

Chapter 3

Microwave-Enhanced Cross-Coupling Reactions Involving Alkynyltrifluoroborates with Aryl Bromides

Chapter 3 is an adaptation of the research article by Coltuclu, V.; Dadush, E.; Naravane, A.; Kabalka, G. W. *Molecules* **2013**, *18*, 1755-1761.

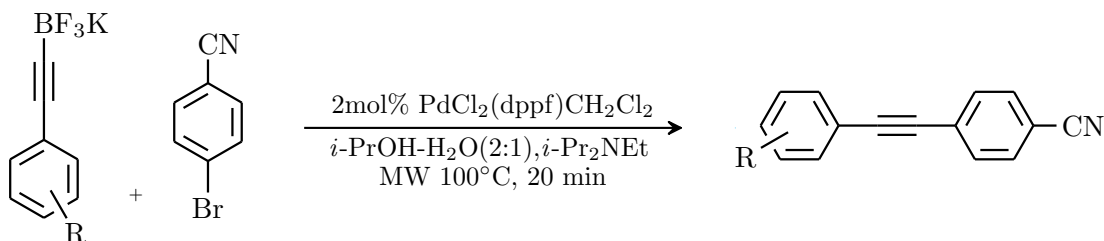
3.1 Introduction

The palladium-catalyzed alkynylation of aromatic rings has emerged as one of the most reliable methods for the synthesis of arylalkynes [70]. Classic methods for preparing aryl alkynes include the copper-promoted Castro-Stephens reaction [71] and the Sonogoshira reaction [43]. Of these, the Sonogoshira reaction is generally considered to be the most versatile and is used widely in natural product synthesis as well as in materials science [72,73]. Negishi also developed an effective palladium-

catalyzed alkynylation reaction utilizing alkynylzinc reagents [74, 75] and 1-halo-1-alkynes [76]. In spite of these advances, there are instances in which the alkynyl coupling reactions fail to provide acceptable yields. The availability of new catalysts and more stable organoborane reagents such as the potassium organotrifluoroborates has broadened the possible applications of alkynyl coupling reactions. Organoboron compounds offer several advantages over other organometallic reagents in that they are generally less toxic and possess remarkable stability when compared to zinc and magnesium reagents [77–79]. Furthermore, the ease of preparation, stability, and commercial availability of a variety of boron reagents enhance their synthetic utility. At the same time, the stability of many of the new organoboron reagents does not diminish their reactivity in a large variety of reactions [80, 81]. We have been exploring the use of microwave irradiation in cross-coupling reactions between potassium organotrifluoroborates and organic halides [82]. Microwaves have become increasingly important in organic syntheses in that minimal amounts of solvent are required and reactions often proceed under catalyst-free conditions. We recently reported the use of microwaves for cross-coupling reactions involving both alkynyltrifluoroborates and vinyltrifluoroborates [83]. In that study, moderate yields of the desired coupled products were obtained when aryl iodides were coupled with alkynyltrifluoroborates. In a continuation of those studies, we have discovered that the reactions are much more efficient when aryl bromides are utilized as the coupling partners. A study focused on the cross-coupling reactions of various potassium alkynyltrifluoroborates with aryl bromide reagents using microwave irradiation is summarized in this chapter.

3.2 Results and Discussion

Molander and co-workers reported the successful coupling of aryl bromides with alkynyltrifluoroborates under thermal conditions [84]. Their syntheses generally requires long reaction times (12 h) and relatively high catalyst loadings (9 mol%). Using microwave irradiation, we have found that the coupling reactions can be carried out in 20 min in the presence of less catalyst. Typical reaction conditions involve a catalyst loading of 2 mol% $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ while providing yields comparable to the thermal reactions (Scheme 3.1).



Scheme 3.1: Cross-coupling reaction of alkynyltrifluoroborates.

We initiated the current study by coupling a variety of substituted aryl bromides with potassium 1-octynyltrifluoroborate (Table 3.1). The presence of an electron-withdrawing group on the aryl bromide slightly enhances the yield of the desired coupling reaction (i.e., a cyano group). The presence of an additional halide (for example, chlorine in 4-bromochlorobenzene) does not affect the reaction yield but demonstrates that bromine is more reactive than chlorine in the coupling reaction. The presence of an electron-donating substituent, such as a methyl or methoxy group, leads to lower yields. Increasing the reaction time also results in lower yields due to decomposition reactions. 4-Bromobenzonitrile was then coupled with various potassium alkynyltrifluoroborates (Table 3.2). The reaction works well with essentially all of the alkynyltrifluoroborate reagents investigated. However, the presence of a free

Table 3.1: Cross-coupling of aryl bromides with potassium octynyltrifluoroborate.

Entry	RBF ₃ K	Ar-Br	R-R	Yield (%)
1				75
2				65
3				60
4				54
5				40

All reactions carried out at 100 °C; Yields of pure products isolated by silica gel chromatography.

hydroxyl group is detrimental to the coupling reaction; since the starting 6-hydroxy-1-hexynyltrifluoroborate is consumed in the reaction, it is possible that protonolysis of the carbon-boron bond is occurring. The somewhat lower yield obtained when using the 2-(4-cyanophenyl)ethynyltrifluoroborate (Entry 9, Table 3.2) is also puzzling since the corresponding 4-methoxy derivative gives a good yield of the desired product.

3.3 Conclusions

An efficient method for coupling alkynyltrifluoroborates with various aryl bromides in the presence of a palladium catalyst has been developed using microwave irradiation.

Table 3.2: Cross-coupling reactions of alkynyltrifluoroborates with 4-bromobenzonitrile.

Entry	RBF ₃ K	Ar-Br	R-R	Yield (%)
1				84
2				87
3				87
4				54
5				80
6				76
7				70
8				78
9				45
10			NR	

All reactions were carried out at 100 °C; Yields of pure products isolated by silica gel chromatography.

The reaction is straightforward and rapid, producing the coupled products in good yields. Short reaction time and low catalyst loading make this methodology very effective for synthesis of variety of alkynes.

3.4 Experimental

3.4.1 General Information

The palladium catalyst, $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ and most of the potassium trifluoroborate reagents were supplied by Frontier Scientific Inc. (Logan, UT, USA) and were used as received. Potassium(2-methyl-1-buten-3-yn-4-yl)trifluoroborate, potassium (1-octyn-1-yl)trifluoroborate, potassium [1-(3,3-dimethyl)-butyn-1-yl]trifluoroborate, and potassium (4-methoxyphenylethynyl)trifluoroborate were prepared according to published procedures [84–86]. N,N-Diisopropylethylamine and the aryl bromides were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. 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, USA). ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, on a Bruker Avance 400 instrument. Chemical shifts are referenced to TMS and measured with respect to the residual protons in the deuterated solvents.

3.4.2 General Procedure

The potassium organotrifluoroborate (0.50 mmol) and $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ (0.01 mmol) were placed in a dry Pyrex tube containing a magnetic stir bar. The tube was then capped with an airtight rubber cap and flushed with argon to maintain a moisture and oxygen free environment. The aryl bromide (0.50 mmol) and Hünig's base

(N,N-Diisopropylethylamine)(265 μ L) were then added via syringe (in our hands, Hünig's base provided more consistent results than carbonate salts). A mixture of 2-propanol/water (2:1, 5.0 mL) was added to the tube, followed by an argon purge. The resulting mixture was placed in a CEM microwave unit in the closed vessel mode and allowed to react at 100 °C for 20 min. The reaction mixture was then transferred to a separatory funnel and diluted with diethyl ether (20 mL). The mixture was washed with water (3 x 20 mL) to remove byproducts. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, concentrated, and the product isolated by silica gel chromatography using hexane/ethyl acetate (100/1) as eluent. The solvents were removed using a rotary evaporator to yield pure product. NMR spectra were compared to the previously reported data.

3.4.3 Characterization of Compounds from Table 3.1

4-(1-Octynyl)benzonitrile (1): ^1H NMR (CDCl_3): δ 7.56 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 1.67 (t, J = 7.4 Hz, 2H), 1.51-1.42 (m, 2H), 1.40-1.27 (m, 4H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (CDCl_3): δ 132.4, 132.2, 129.5, 118.9, 111.2, 96.0, 79.8, 31.7, 28.9, 28.8, 22.9, 19.9, 14.4.

1-(4-Chlorophenyl)-1-octyne (2): ^1H NMR (CDCl_3): δ 7.31 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 2.38 (t, J = 7.1 Hz, 2H), 1.63-1.55 (m, 2H), 1.48-1.40 (m, 2H), 1.35-1.30 (m, 4H), 0.90 (t, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl_3): δ 133.8, 133.2, 128.9, 123.1, 92.0, 80.0, 31.8, 29.1, 29.1, 23.0, 19.9, 14.5.

1-(4-Methoxyphenyl)-1-octyne (3): ^1H NMR (CDCl_3): δ 7.32 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.78 (s, 3H), 2.38 (t, J = 7.2 Hz, 2H), 1.62-1.54 (m, 2H), 1.50-1.44 (m, 2H), 1.34-1.32 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR (CDCl_3): δ 159.5, 133.3, 116.8, 114.3, 89.3, 80.7, 55.7, 31.9, 29.3, 29.0, 23.0, 19.9, 14.5.

1-(3-Methoxyphenyl)-1-octyne (4): ^1H NMR (CDCl_3): δ 7.32 (d, $J = 8.6$ Hz, 2H), 6.80 (d, $J = 8.6$ Hz, 2H), 3.78 (s, 3H), 2.38 (t, $J = 7.2$ Hz, 2H), 1.62-1.54 (m, 2H), 1.50-1.44 (m, 2H), 1.34-1.32 (m, 4H), 0.90 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (CDCl_3): δ 159.5, 133.3, 116.8, 114.3, 89.3, 80.7, 55.7, 31.9, 29.3, 29.0, 23.0, 19.9, 14.5.

1-(4-Methylphenyl)-1-octyne (5): ^1H NMR (CDCl_3): δ 7.30 (d, $J = 7.9$ Hz, 2H), 7.10 (d, $J = 7.9$ Hz, 2H), 2.38 (t, $J = 7.0$ Hz, 2H), 2.31 (s, 3H), 1.66-1.51 (m, 2H), 1.52-1.43 (m, 2H), 1.38-1.25 (m, 4H), 0.90 (s, $J = 6.7$ Hz, 3H). ^{13}C NMR (CDCl_3): δ 137.9, 132.1, 129.5, 121.9, 90.3, 80.9, 31.8, 29.4, 28.8, 22.8, 21.6, 19.6, 14.9.

3.4.4 Characterization of Compounds from Table 3.2

4-(6-Chlorohex-1-yn-1-yl)benzonitrile (1): ^1H NMR (CDCl_3): δ 7.57 (d, $J = 8.3$ Hz, 2H), 7.45 (d, $J = 8.3$ Hz, 2H), 3.60 (t, $J = 6.5$ Hz, 2H), 2.49 (t, $J = 6.9$ Hz, 2H), 1.95 (p, $J = 6.7$ Hz, 2H), 1.78 (p, $J = 7.1$ Hz, 2H). ^{13}C NMR (CDCl_3): δ 132.5, 132.3, 129.2, 118.9, 111.4, 94.8, 80.4, 44.8, 32.0, 26.0, 19.2.

4-(3-Methylbut-3-en-1-yn-1-yl)benzonitrile (2): ^1H NMR (CDCl_3): δ 7.65 (dd, $J = 6.8, 1.9$ Hz, 2H), 7.51 (dd, $J = 6.6, 1.7$ Hz, 2H), 5.39 (t, $J = 0.8$ Hz, 1H), 5.30 (m, 1H), 1.90 (s, 3H). ^{13}C NMR (CDCl_3): δ 131.3, 131.1, 128.0, 126.3, 123.1, 119.2, 111.9, 95.1, 86.5, 23.1.

4-(4-tert-Butyldimethylsiloxy-1-butyn-1-yl)benzonitrile (3): ^1H NMR (CDCl_3): δ 5.5 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.5$ Hz, 2H), 3.81 (t, $J = 6.8$ Hz, 2H), 2.64 (t, $J = 6.8$ Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (CDCl_3): δ 132.5, 132.3, 129.3, 119.0, 111.5, 93.0, 80.7, 61.9, 26.3, 24.4, 18.7, -4.8.

4-(1-Octynyl)benzonitrile (4): ^1H NMR (CDCl_3): δ 7.56 (d, $J = 8.4$ Hz, 2H), 7.45 (d, $J = 8.6$ Hz, 2H), 2.42 (t, $J = 7.2$ Hz, 2H), 1.67 (t, $J = 7.4$ Hz,

2H), 1.51-1.42 (m, 2H), 1.40-1.27 (m, 4H), 0.92 1456 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (CDCl_3): δ 132.4, 132.2, 129.5, 118.9, 111.2, 96.0, 79.8, 31.7, 28.9, 1457 28.8, 22.9, 19.9, 14.4.

4-(3,3-Dimethylbut-1-ynyl)-benzonitrile (5): ^1H NMR (CDCl_3): δ 8.48 (d, $J = 8$ Hz, 2H), 7.42 (d, $J = 8$ Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (CDCl_3): δ 132.7, 132.5, 129.7, 120.0, 111.2, 103.9, 78.8, 31.3, 28.6.

4-((Trimethylsilyl)ethynyl)benzonitrile (6): ^1H NMR (CDCl_3): δ 7.56 (d, $J = 8.5$ Hz, 2H), 7.50 (d, $J = 8.5$ Hz, 2H), 0.27 (s, 9H). ^{13}C NMR (CDCl_3): δ 133.1, 132.2, 127.9, 118.5, 112.0, 103.1, 100.0, -0.5.

4-Phenylethynylbenzonitrile (7): ^1H NMR (CDCl_3): δ 7.62 (m, 4H), 7.55 (m, 2H), 7.36 (m, 3H). ^{13}C NMR (CDCl_3): δ 132.3, 132.1, 131.7, 129.2, 128.5, 128.3, 122.3, 118.6, 111.6, 93.9, 87.8.

4-((4-Methoxyphenyl)ethynyl)benzonitrile (8): ^1H NMR (CDCl_3): δ 7.59 (q, $J = 8.5$ Hz, 4H), 7.48 (d, $J = 8.8$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (CDCl_3): δ 160.8, 133.8, 132.5, 132.3, 129.1, 119.1, 114.8, 114.7, 111.5, 94.6, 87.2, 55.8.

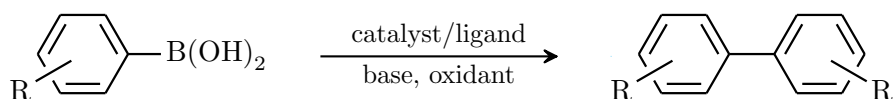
4,4'-Dicyanophenylethynylene (9): ^1H NMR (CDCl_3): δ 7.66 (4H, d, $J = 8.2$ Hz), 7.64 (4H, d, $J = 8.2$ Hz). ^{13}C NMR (CDCl_3): δ 132.3, 132.2, 127.1, 118.5, 112.6, 91.9.

Chapter 4

Microwave-Enhanced Homocoupling of Organotrifluoroborates

4.1 Introduction

Unsymmetrical and symmetrical biaryls have received significant attention due to their wide application as building blocks in the synthesis of natural products [87] and organometallic catalysts [88]. There has been a large number of methods reported in the literature on the synthesis of unsymmetrical biaryls [89–91]. Among them, the most widely accepted method presently used in both academia and industry, is the palladium-catalyzed coupling of aryl boronic acids with organic halides, known as the Suzuki-Miyara reaction [92]. The synthesis of symmetrical biaryls is also of current interest and one of the most studied methods for symmetrical biaryl preparation are the oxidative homocoupling reactions of arylboronic acids involving palladium salts as catalysts [93–96] (Scheme 4.1).



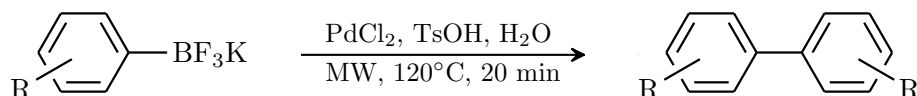
Scheme 4.1: Homo-coupling reaction of arylboronic acid.

As an example, in 1987 Suzuki and coworkers described the homocoupling reaction of arylboronic acids using Pd(OAc)_2 and PPh_3 [93]. Later, Jackson's group found that self-coupling of arylboronic acids proceeds in the presence of oxygen and Pd(OAc)_2 , but the reaction is slow [94]. A different approach was taken by Kabalka *et al.* in 2002 by using a ligandless palladium chloride-catalyzed homocoupling reaction in aqueous media in the presence of Na_2CO_3 and p-toluenesulfonyl chloride [95]. Moreover, in 2006 Yoshihiko *et al.* demonstrated that palladium-catalyzed homocoupling of arylboronic acids proceeds under base and ligand-free aerobic conditions [96]. All of these reported methods employ organoboronic acids as the homocoupling reagent. It should be noted however, that boronic acids are not stable for a long period under atmospheric conditions and often form boroxines which in turn leads to uncertain stoichiometry and unexpected side reactions.

Organotrifluoroborates, often called protected organoboronic acids, have gained popularity as a substitute for organoboronic acids in the Suzuki-Miyaura reaction. Being stable in air, the stoichiometry is easier to control when compared to organoboronic acids. Surprisingly, not many studies exploring organotrifluoroborates as homocoupling reagents for preparation of symmetrical biaryls have been carried out. In 2006, Sakurai *et al.* reported oxidative homocoupling of potassium organotrifluoroborates catalyzed by gold nanoclusters under aerobic conditions [97]. Another method was put forward by Oliveira *et al.*, in which the homocoupling of organotrifluoroborates in the presence of Pd(OAc)_2 and K_2CO_3 in aqueous media was attempted [98]. In either methods however, the reaction is slow and takes about 24-48 hours.

4.2 Results and Discussion

As noted in the previous chapters, microwave radiation has several advantages over conventional heating techniques. As a result, microwave technology has become a preferred source of energy in a variety of chemical reactions. With this consideration in mind and also with our successful application of microwaves in Suzuki-Miyaura coupling reaction (Chapter 3), we developed a simple palladium-catalyzed homocoupling reaction using potassium organotrifluoroborates and microwave radiation (Scheme 4.2).



Scheme 4.2: Homo-coupling reaction of organotrifluoroborates.

We began our studies by determining the most efficient conditions. For this purpose we used potassium phenyltrifluoroborate as a standard reagent. As can be seen from the data in Table 4.1, 5 mol% of PdCl_2 gave the best yield; however, a similar result, with only slightly lower yield, was obtained with 2 mol% loading of PdCl_2 . We also found that palladium(II) acetate (5 mol%) gave almost identical results to palladium chloride. Copper(II) chloride and copper(II) acetate were also active in homocoupling reactions but gave much lower yields (17% and 13%, respectively).

In our attempts to explore the use of organic and inorganic bases, such as Na_2CO_3 , K_2CO_3 , and DIPEA, we found them to be ineffective giving only low yields of the homocoupled products. This is presumably due to protonolysis of the organotrifluoroborates under aqueous microwave conditions. *p*-Toluenesulfonyl chloride was also ineffective for this reaction because, in addition to very low yields of the desired product, it produced a great number of by-products. On the other hand, *p*-tolylsulfonic acid gave better results and became our reagent of choice.

Table 4.1: Optimization of reaction conditions.

$$\text{C}_6\text{H}_5\text{BF}_3\text{K} \xrightarrow[\text{MW, 120}^\circ\text{C, 20 min}]{\text{catalyst, TsOH}} \text{C}_6\text{H}_5\text{C}_6\text{H}_5$$

Entry	Catalyst	(mol%)	Solvent	Yield(%)
1	Pd(OAc) ₂	(5)	H ₂ O	81
2	PdCl ₂	(5)	H ₂ O	85
3	PdCl ₂	(2)	H ₂ O	83
4	Cu(OAc) ₂	(5)	H ₂ O	13
5	CuCl ₂	(5)	H ₂ O	17

We used water as solvent for our reactions because it is cheap, safe, dissolves organotrifluoroborates quite well, and is suitable for microwave reactions. The only case where a mixture of water : THF (4v:1v) was used was with naphthyltrifluoroborate due to its low solubility in water.

We found that the optimal conditions for microwave-enhanced self-coupling of potassium trifluoroborates are: 0.5 mmol of RBF₃K, 2 mol% of PdCl₂, 0.25 mmol of TsOH, 5 ml of H₂O, reaction temperature of 120 °C, and the reaction time of 20 min. Having determined the optimal conditions, we extended our research of homocoupling reactions to a variety of organotrifluoroborates. Our results are summarized in Table 4.2. One of the important observations from our studies is that the homocoupling reaction is mainly influenced by two effects: electronic and steric. Potassium organotrifluoroborates bearing electron-donating groups gave higher yields than substrates with electron-withdrawing groups. In the case of Entry 8 (Table 4.2), where a *ortho*-substituted aryl trifluoroborate was used, the yield is low, indicating that the homocoupling is sensitive to steric hindrance in the substrate. Binaphthyls and polythiophenes are well known to be useful components in the synthesis of natural products [99] and organic semiconductors [100]. In this context, we synthesized

Table 4.2: Homocoupling reaction of trifluoroborates.

Entry	RBF ₃ K	R-R	Yield(%)
1			83
2			85
3			87
4			69
5			79
6			75
7			77
8			45
9			80

1,1'-binaphthalene and 2,2'-bithiophene in good yields.

4.3 Conclusions

We have developed a simple, rapid procedure for preparing biaryls from potassium organotrifluoroborates. Here we demonstrated the applicability of this procedure to a total of nine different organotrifluoroborates. More generally, low catalyst loading, the use of water as a “green” solvent, and short reaction times make this method useful for synthesis of a variety of biaryl compounds.

4.4 Experimental

4.4.1 General Information

The potassium organotrifluoroborate reagents were supplied by Frontier Scientific Inc. (Logan, UT, USA) and were used as received. Palladium chloride was purchased from Sigma-Aldrich (St. Louis, MO, USA). 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, USA). ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, on a Bruker Avance 400 instrument. Chemical shifts are measured with respect to the residual protons in the deuterated solvents.

4.4.2 General Procedure

The potassium organotrifluoroborate (0.50 mmol), *p*-toluenesulfonic acid (0.25 mmol), and PdCl_2 (2 mol%) were placed in a dry Pyrex tube containing a magnetic stir bar. Water (5.0 mL) was added to the tube. The resulting mixture was placed in a CEM microwave unit in the closed vessel mode and allowed to react at 120 °C for 20 min.

The reaction mixture was then transferred to a separatory funnel and diluted with diethyl ether (20 mL). The mixture was washed with water (3 x 20 mL) to remove byproducts. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, concentrated, and the product isolated by silica gel chromatography using hexane/ethyl acetate (100/1) as eluent. The solvents were removed using a rotary evaporator to yield pure product.

4.4.3 Characterization of Compounds from Table 4.2

1,1'-biphenyl (1): ^1H NMR (CDCl_3): δ 7.68 (d, $J = 7.3$ Hz, 4H), 7.52 (t, $J = 7.6$ Hz, 4H), 7.42 (t, $J = 7.4$ Hz, 2H). ^{13}C NMR (CDCl_3): δ 141.7, 129.2, 127.7, 127.6.

4,4'-dimethyl-1,1'-biphenyl (2): ^1H NMR (CDCl_3): δ 7.56 (d, $J = 8.1$ Hz, 2H), 7.31 (d, $J = 7.8$ Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (CDCl_3): δ 138.7, 137.1, 129.9, 127.3, 21.5.

4,4'-dimethoxy-1,1'-biphenyl (3): ^1H NMR (CDCl_3): δ 7.50 (d, $J = 8.7$ Hz, 4H), 6.98 (d, $J = 8.7$ Hz, 4H), 3.86 (s, 6H). ^{13}C NMR (CDCl_3): δ 159.1, 133.9, 128.2, 114.6, 55.8.

2,2'-binaphthalene (4): ^1H NMR (CDCl_3): δ 8.19 (s, 2H), 8.01–7.87 (m, 10H), 7.53 (d, $J = 5.8$ Hz, 2H). ^{13}C -NMR (CDCl_3): δ 138.9, 134.2, 128.9, 128.7, 128.2, 126.8, 126.6, 126.5, 126.2.

4,4'-difluoro-1,1'-biphenyl (5): ^1H NMR (CDCl_3): δ 7.48 (dd, $J = 8.5, 5.3$ Hz, 4H), 7.12 (t, $J = 8.7$ Hz, 4H). ^{13}C -NMR (CDCl_3): δ 164.1, 161.7, 136.8, 129.0, 128.9, 116.2.

4,4'-bis(trifluoromethyl)-1,1'-biphenyl (6): ^1H NMR (CDCl_3): δ 7.73 (q, $J = 8.3, 7.9$ Hz, 8H). ^{13}C NMR (CDCl_3): δ 143.7, 128.1, 126.4, 126.4.

4,4'-bisacetylbiphenyl (7): ^1H -NMR (CDCl_3): δ 8.06 (d, $J = 8.0$ Hz, 4H), 7.73 (d, $J = 7.9$ Hz, 4H), 2.65 (s, 6H). ^{13}C -NMR (CDCl_3): δ 197.9, 144.7, 136.9, 129.4,

127.8, 27.1.

2,2'-dimethylbiphenyl (8): $^1\text{H-NMR}$ (CDCl_3): δ 7.21-7.26 (m, 6H), 7.09-7.11 (m, 2H), 2.05 (s, 6 H). $^{13}\text{C-NMR}$ (CDCl_3): δ 142.1, 136.2, 130.3, 129.7, 127.6, 125.9, 20.3.

2,2'-bisthiophen (9): $^1\text{H-NMR}$ (CDCl_3): δ 7.19 (ddd, $J = 12.4, 4.4, 1.3$ Hz, 4H), 7.02 (dt, $J = 5.1, 3.3$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ 128.3, 128.2, 124.8, 124.2.

Chapter 5

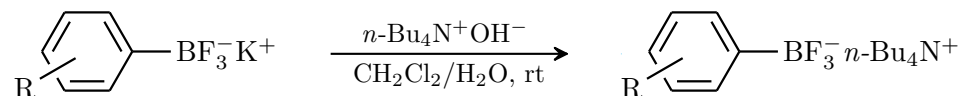
Exploration of Borate Chemistry

5.1 Synthesis of Tetrabutylammonium Organotrifluoroborates

5.1.1 Introduction

Organotrifluoroborates are commonly used reagents for Suzuki coupling reactions due to their high reactivity and their stability under atmospheric conditions. Despite their synthetic usefulness, they have a significant drawback - low solubility in many organic solvents. Essentially all borate salts will dissolve in water, methanol, acetonitrile, THF, and mixture of these solvents. However, they are not particularly soluble in other organic solvents, for example chloroform, dichloromethane, diethyl ether, ethyl acetate, and ethanol. This lack of solubility limits applications of organotrifluoroborates in various organic solvents. One solution to this problem is to perform counterion exchange reactions that result in formation of more soluble organotrifluoroborates. This section is focused on the development of a new methodology based on exchange of the potassium cation with the tetraalkylammonium cation and comparison of the reactivities of the two salts.

To date, there has been a paucity of scientific literature describing counterion exchange reactions related to potassium organotrifluoroborates. In 1999, Vedejs *et al.* published one example, describing the reactions of tetraalkylammonium trifluoroborate reagents, but reactions were very slow, requiring time from 18 h [101] to several weeks [102]. An improved method for counterion exchange was proposed by Batey and Quanch, who obtained tetraalkylammonium organoborate salts by treatment of potassium organotrifluoroborates with an aqueous solution of tetrabutylammonium hydroxide in a DCM/H₂O solvent system at room temperature (Scheme 5.1) [103].

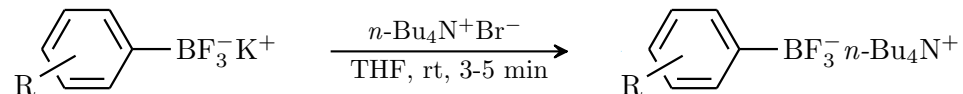


Scheme 5.1: Counterion exchange reaction.

Taken together, the counterion exchange reactions provide an access to a new type of organotrifluoroborates. High solubility of tetraalkylammonium trifluoroborates in nonpolar solvents make them intriguing reagents for organic synthesis, and thereby we propose a new method for achieving a cation exchange reaction.

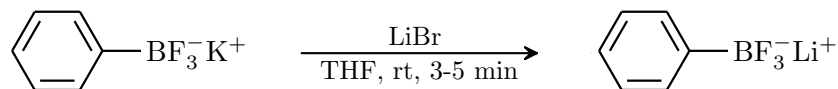
5.1.2 Results and Discussion

The method we developed for preparing tetraalkylammonium trifluoroborates is based on the low solubility of potassium bromide in THF during the reaction of a potassium organotrifluoroborate with tetrabutylammonium bromide in THF at room temperature (Scheme 5.2)



Scheme 5.2: Synthesis of a tetrabutylammonium trifluoroborate.

The reaction proceeds very quickly, and more importantly, provides high yields of the desired products. Generally, it takes 3-5 minutes for reactions to go to completion during which time potassium bromide precipitates and is separated from the reaction media by simple filtration. Subsequent evaporation of the THF gives a pure salt that displays good solubility in many nonpolar organic solvents. This protocol was extended to the preparation of other potassium organotrifluoroborate salts. The results are summarized in Table 5.1. It is interesting to note, that lithium organotrifluoroborates can also be easily obtained using the same methodology. An example of the reaction is outlined in Scheme 5.3.

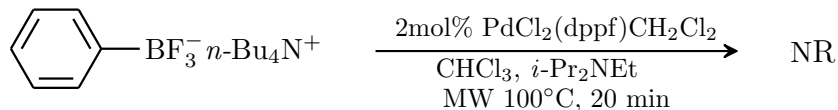


Scheme 5.3: Formation of a lithium organotrifluoroborate.

Table 5.1: Formation of tetrabutylammonium trifluoroborates.

Entry	RBF_3^-K^+	$\text{RBF}_3^-n\text{-Bu}_4\text{N}^+$	Yield(%)
1			97
2			95
3			97
4			96
5			94

Having tetraalkylammonium salts in hand, we initiated an investigation that implemented the use of these compounds in Suzuki coupling reactions using anhydrous chloroform or isopropanol as a solvent (Scheme 5.4). Unfortunately, all attempts



Scheme 5.4: Suzuki coupling reaction of tetraalkylammonium borate.

to isolate the desired product under anhydrous conditions and microwave radiation were unsuccessful. The investigation, however, leads to an important conclusion that the presence of water as a co-solvent is essential for the reaction to occur. Despite good solubility in nonpolar organic solvents, without water tetraalkylammonium organotrifluoroborates behave in the same manner as potassium organotrifluoroborates leading to the conclusion that the nature of the cation has no influence on the Suzuki coupling reaction in the absence of water.

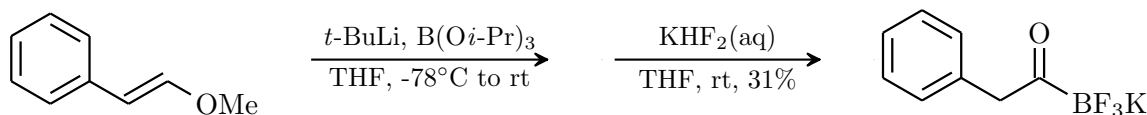
5.1.3 Conclusions

We have developed a fast and straightforward methodology for the synthesis of tetrabutylammonium organotrifluoroborates from the corresponding potassium organotrifluoroborates. In addition, this protocol can also be applied for counterion exchange with other inorganic cations. Despite good solubility in nonpolar organic solvents, tetrabutylammonium organotrifluoroborates do not undergo Suzuki coupling and do not show an improved reactivity under anhydrous condition.

5.2 Towards Preparation of Acyltrifluoroborates

5.2.1 Introduction

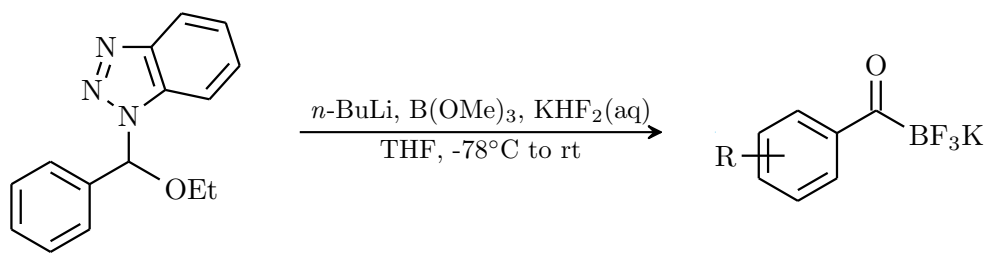
Organoboronic acids and their derivatives (esters and trifluoroborates) have attracted attention in the scientific community not only as good substrates for the Suzuki-Miaura coupling reactions but also as versatile reagents which are tolerant to many functional groups and stable towards a variety of reaction conditions. As a result, a large number of boronic acids have become commercially available [104]. Lately, in addition to commonly used aryl and alkenylboronic acids, the commercial availability of these acids has been expanded to boronic acids and their derivatives containing alkynyl [105], heteroaryl [106], α -alkoxy, and other functional groups [107]. Despite the large library of boronic acids available today, the acylboronic acids are considered to be rare compounds due their difficult preparation. At present, only five acylboronic acids have been synthesized [108]. In 2010, Molander and coworkers reported the preparation of a single acyltrifluoroborate involving an α -borylvinyl ether as an intermediate [109]. The reaction is depicted in Scheme 5.5.



Scheme 5.5: Synthesis of an acyltrifluoroborate by Molander *et al.* [109].

Recently, Bode's group described the synthesis of a series of acyltrifluoroborates that employed benzotriazole-ethoxy N,O-acetals (Scheme 5.6) [110]. The yields of the final products ranged from 28% to 45%.

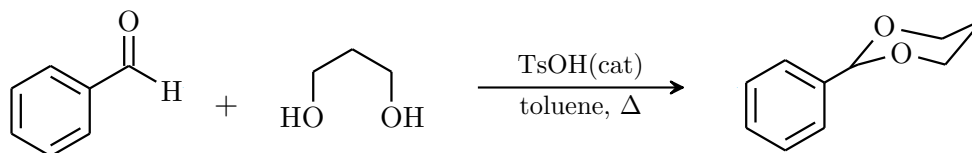
The availability of only a few methodologies and the low reported yields of acyltrifluoroborates inspired us to explore deeper this area of research.



Scheme 5.6: Synthesis of an acyltrifluoroborates by Bode *et al.* [110].

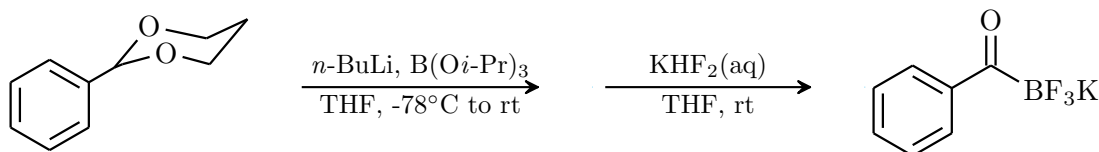
5.2.2 Results and Discussion

To simplify a previously reported procedure focused on the synthesis of acyltrifluoroborates [110], we used an acetal prepared from benzaldehyde and 1,3-propanediol (Scheme 5.7).



Scheme 5.7: Formation of an acetal.

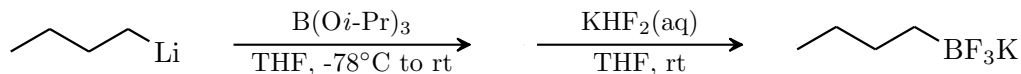
After this step we followed the reported procedure which involves deprotonation with *n*-butyllithium followed by treatment with triisopropylborate. Next, the reaction mixture was quenched with a saturated aqueous solution of potassium hydrogen difluoride (Scheme 5.8).



Scheme 5.8: Formation of an acyltrifluoroborate.

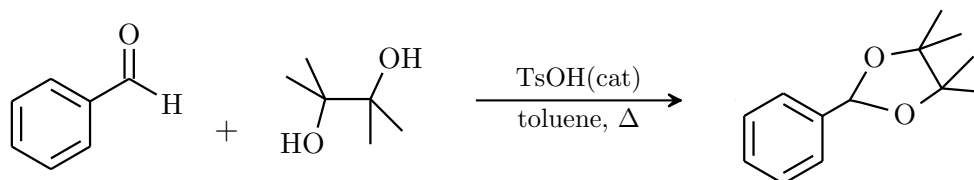
^{11}B NMR and ^1H NMR were obtained after isolation and purification of the product. ^{11}B NMR data confirmed the formation of an organotrifluoroborate, but the

^1H NMR spectrum showed that the product was butyltrifluoroborate (BuBF_3K) and not the desired acyltrifluoroborate. After repetition of the experiment at different temperatures, the same results were obtained. Presumably, the lithium cation coordinates to the acetal oxygens and doesn't allow *n*-butyllithium to react as a base. Instead, it reacts with triisopropylborate as a nucleophile which in turn, leads to formation of BuBF_3K (Scheme 5.9).



Scheme 5.9: Formation of potassium butyltrifluoroborate.

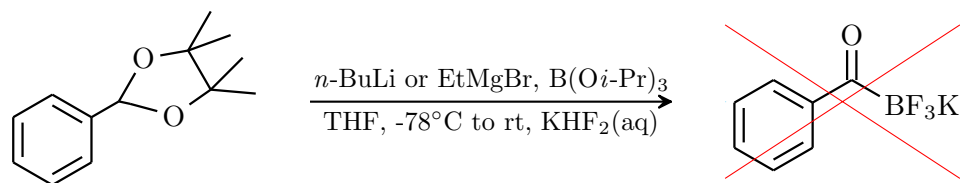
In an attempt to overcome the formation of butyltrifluoroborate, we prepared the initial acetal using pinacol (2,3-dimethyl-2,3-butanediol) instead of 1,3-propanediol since the former has a shorter carbon chain and is a more hindered substrate (Scheme 5.10). Unfortunately, the reaction was unsuccessful, giving BuBF_3K once again as the final product.



Scheme 5.10: Formation of an acetal using pinacol.

We then replaced *n*-butyllithium with a Grignard reagent - ethylmagnesium bromide. Our hypothesis was that the larger size of the magnesium would prevent coordination with the oxygens. However, the same results were obtained (Scheme 5.11).

Finally, we used sodium hydride as a base. However, the desired product was not formed. Presumably deprotonation did not occur. Despite all the modifications attempted in the synthesis of acyltrifluoroborates, the desired products were not



Scheme 5.11: Attempt to make acyltrifluoroborate.

formed.

5.2.3 Conclusions

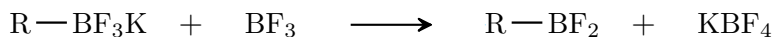
We have explored a new method for synthesizing of acyltrifluoroborates. During the investigation, we established that *n*-butyllithium behaves as a nucleophile rather than a strong base, preventing formation of acyltrifluoroborate. In an attempt to generate the desired product, we performed experiments using a variety of bases and diols, and also different temperatures. The result of our efforts was formation of BuBF_3K salt as the final product. To conclude, the synthesis of acyltrifluoroborates remains a challenging task in the field of organoboron chemistry.

5.3 Cross-Coupling Reaction of Organotrifluoroborates and Acetals

5.3.1 Introduction

Potassium organotrifluoroborates are widely accepted by the scientific community in academia and industry as substrates for palladium-catalyzed Suzuki-Miyaura coupling reaction. In comparison with organoboronic acids and esters, these compounds are stable under atmospheric conditions and provide excellent atom economy. However, despite the huge success of the Suzuki coupling reactions in organic synthesis

and drug discovery, they are often criticized for their use of toxic and expensive palladium catalysts [111]. Therefore, the development of new cross-coupling methods for C-C bond formation that do not employ palladium catalysts is of great interest. One such area involves potassium organotrifluoroborates for use in $\text{BF}_3 \cdot \text{OEt}_2$ -promoted, palladium-free cross-coupling reactions. In 2009, Bertolini and Woodward reported the rapid 1,4-alkynylation of acyclic enones using alkynyltrifluoroborates [112]. The authors outlined a method that improved the previously reported procedure by Suzuki [113]. The key step involves $\text{BF}_3 \cdot \text{OEt}_2$ -promoted formation of organodifluoroborane (Scheme 5.12).



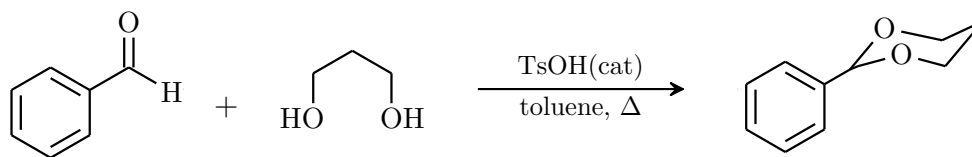
Scheme 5.12: Formation of organodifluoroborane.

Later, Bode *et al.* published an extensive study focused on ether-forming cross-coupling reactions of organotrifluoroborates and acetals [114]. Using the same key intermediate, organodifluoroborane, they synthesized a library of ether compounds. Inspired by the chemistry reported by Bode group, we initiated a study focused on the reaction of organotrifluoroborates with acetals for preparing secondary alcohols.

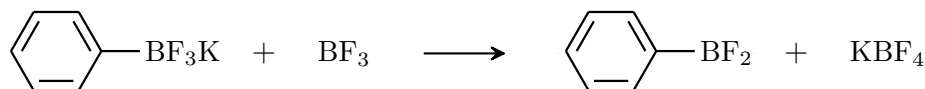
5.3.2 Results and Discussion

The first step involves the synthesis of an acetal using benzaldehyde and 1,3-propanediol as starting materials in the presence of catalytic amounts of *p*-tolylsulfonic acid (Scheme 5.13). Then, formation of the key intermediate takes place by reacting potassium phenyltrifluoroborate with $\text{BF}_3 \cdot \text{OEt}_2$ in DCM at 0 °C (Scheme 5.14).

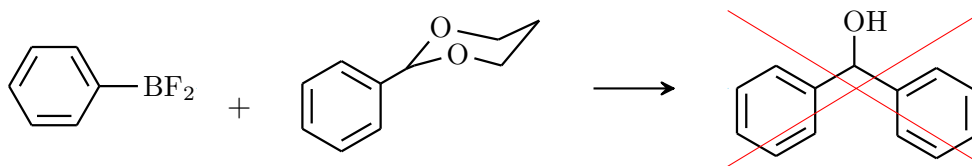
Finally, the acetal was slowly added to the intermediate at 0 °C, and then the reaction was allowed to stir for 2 hours at room temperature. Quenching of the reaction mixture with saturated solution of sodium bicarbonate gave none of the



Scheme 5.13: Formation of an acetal.



Scheme 5.14: Formation of phenyldifluoroborane.



Scheme 5.15: An attempt to make a secondary alcohol.

desired products (Scheme 5.15).

GS/MS data showed that the acetal was deprotected and formed benzaldehyde. We therefore, changed the order of addition of the components, but that however, did not lead to product formation. Varying the temperature profile also was unsuccessful. Presumably, organodifluoroborane coordinates equally to both oxygens of the acetal, which delocalizes the electron density and stops the reaction. We then changed the structure of the acetal by using pinacol. The latter is still symmetrical but is more sterically hindered, which might minimize delocalization of the electron density and initiate the reaction. Unfortunately, this approach was also not ineffective and benzaldehyde was recovered after quenching the reaction mixture.

5.3.3 Conclusions

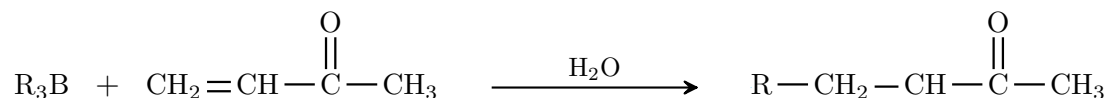
We attempted to synthesize secondary alcohols using $\text{BF}_3 \cdot \text{OEt}_2$ -promoted cross-coupling reactions of organotrifluoroborates and acetals. During the investigation we established that the key intermediate, organodifluoroborane, was successfully formed, but the migration of the phenyl group did not occur. Modifying the structure of the acetal and varying the reaction temperature were also unsuccessful. Implementation of organodifluoroboranes in the development of new methodologies in organic synthesis remains a challenging task.

5.4 Chemistry Involving Boronoate Esters

5.4.1 Reactions with α, β -Unsaturated Carbonyl Compounds

5.4.1.1 Introduction

Alkylation of α, β -unsaturated carbonyl compounds represent one of the most useful and atom-economical methods for the formation of C-C bonds. Despite the existence of many synthetic approaches to perform 1,4-addition reactions, this section will focus on reactions that involve organoboron compounds. One of the earliest reports regarding the reaction between organoboranes and α, β -unsaturated carbonyl compounds, involved methyl vinyl ketone and was reported by Suzuki *et al.* in 1967 [115]. The reaction was found to proceed rapidly and produced saturated methyl ketones in high yields (Scheme 5.16).



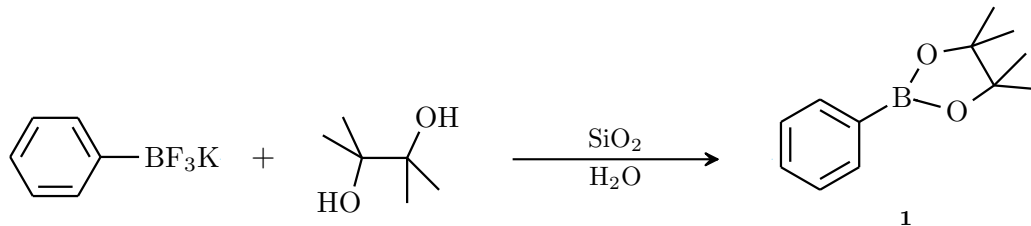
Scheme 5.16: Synthesis of methyl ketones.

Later, the Brown group reported that the organoboranes react with acrolein un-

der the same conditions and produced the corresponding saturated aldehydes in high yields [116]. Thus, alkylation of α, β -unsaturated carbonyl compounds with organoboranes provides a rapid method for C-C bond formation. However, the drawback of this methodology is the use of organoboranes, which are not stable under atmospheric conditions. Finding more stable boron containing compound that undergo the same chemistry would significantly improve the methodology.

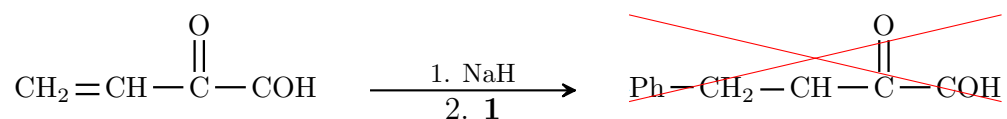
5.4.1.2 Results and Discussion

Candidates that are more stable than organoboranes and have an empty p orbital on the boron atom are boronate esters. The latter can be easily prepared by Molander's procedure from a potassium organotrifluoroborate and pinacol in the presence of silica gel and water (Scheme 5.17) [117].



Scheme 5.17: Synthesis of phenylboronic acid pinacol ester.

The 1,4-addition reaction starts with deprotonation of acrylic acid by sodium hydride to make the oxygen more nucleophilic. Then, the phenylboronic acid pinacol ester is slowly added to the reaction mixture, and the reaction is allowed to stir for 30 minutes under microwave irradiation (Scheme 5.18). A possible mechanism is depicted in Fig. 5.1. After that, the mixture is quenched and the product is purified and analyzed as a white solid. ^{11}B NMR and ^1H NMR demonstrated that the isolated compound is phenylboronic acid pinacol ester. This result indicate that coordination of the oxygen with boron did not take place. To verify this, we repeated the experiment but before quenching the reaction mixture, an aliquot of the solution



Scheme 5.18: An attempt to perform 1,4-addition.

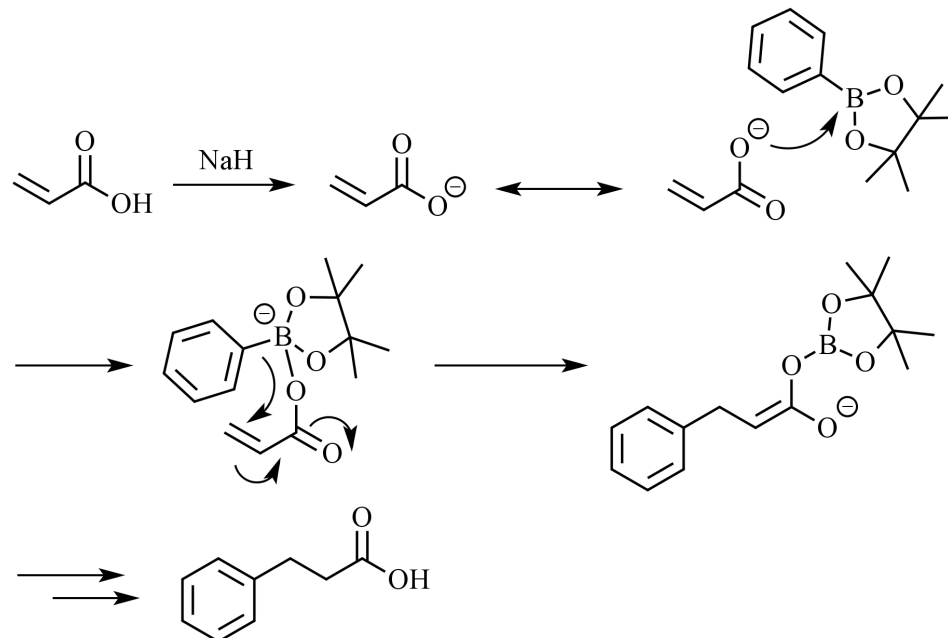


Figure 5.1: Possible mechanism of 1,4-addition.

was analyzed by ^{11}B NMR. The spectra revealed that coordination did not occur. In order to initiate coordination of the oxygen with boron we increased the reaction temperature and also used phenylboronate ester with different electron withdrawing groups (-F, -NO₂, -CF₃). Unfortunately, formation of the desired product did not take place.

5.4.2 α -Alkylation of Carbonyl Compounds

5.4.2.1 Introduction

We decided to extend our research related to boronate esters as possible alkylating agents by investigating carbanion chemistry. It is well-known, that trialkylboranes

react with carbanions derived from α -halocarbonyl compounds to give organoborate intermediates that, after rearrangement, form α -alkylated products (Scheme 5.19) [51].

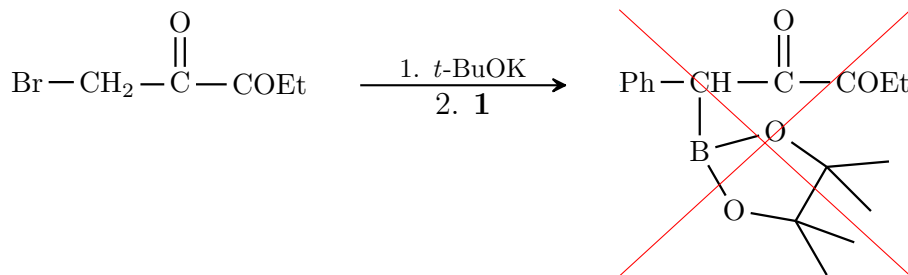


Scheme 5.19: α -Alkylation of carbonyl compounds.

The use of *B*-alkyl-9-BBN derivatives in place of trialkylboranes provides better utilization of the alkyl group, and these molecules react with α -halocarbonyl to give the desired products in good yields. However, the main drawbacks of 9-BBN derivatives are their air sensitivity and lack of atom economy. So, utilization of boronate esters might solve these problems.

5.4.2.2 Results and Discussion

The first step of the alkylation reaction starts with generation of a carbanion from the α -halocarbonyl compound. In our case it was ethyl bromoacetate, and *t*-BuOK served as a base. When formation of the carbanion was complete, slow addition of phenylboronic acid pinacol ester followed. The reaction mixture was then subjected to microwave irradiation for 30 minutes (Scheme 5.20).



Scheme 5.20: An attempt to perform α -alkylation.

After work-up and isolation of the product, ^{11}B NMR and ^1H NMR spectra were taken. Unfortunately, the spectra showed none of the desired product, and starting boronate ester remained in the reaction mixture. This indicates that the formation of C-B bond did not occur. A wide set of temperature and various electron withdrawing groups on the boronate ester did not lead us to the desired product.

5.4.2.3 Conclusions

Organoboranes are good alkylating reagents for α, β -unsaturated and α -halocarbonyl compounds. However, their instability under atmospheric conditions initiated our interest in evaluating boronate esters as alkylating reagents. The study shows that, being weak Lewis acids, boronate esters do not coordinate to the oxygen of a carbonyl group, and, as a result, formation of the desired product does not occur. Applying conditions that might have increased Lewis acidity also did not lead to the desired products. Alkylation of α, β -unsaturated and α -halocarbonyl compounds involving boronate esters is still an area of research interest.

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Appendix

Appendix A

Representative NMR Spectra of compounds from Chapter 2

Below, we show ^1H and ^{13}C NMR spectra for the compounds listed in Table 2.1. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, on a Bruker Avance 400 instrument. Chemical shifts are measured with respect to the residual protons in the deuterated solvents.

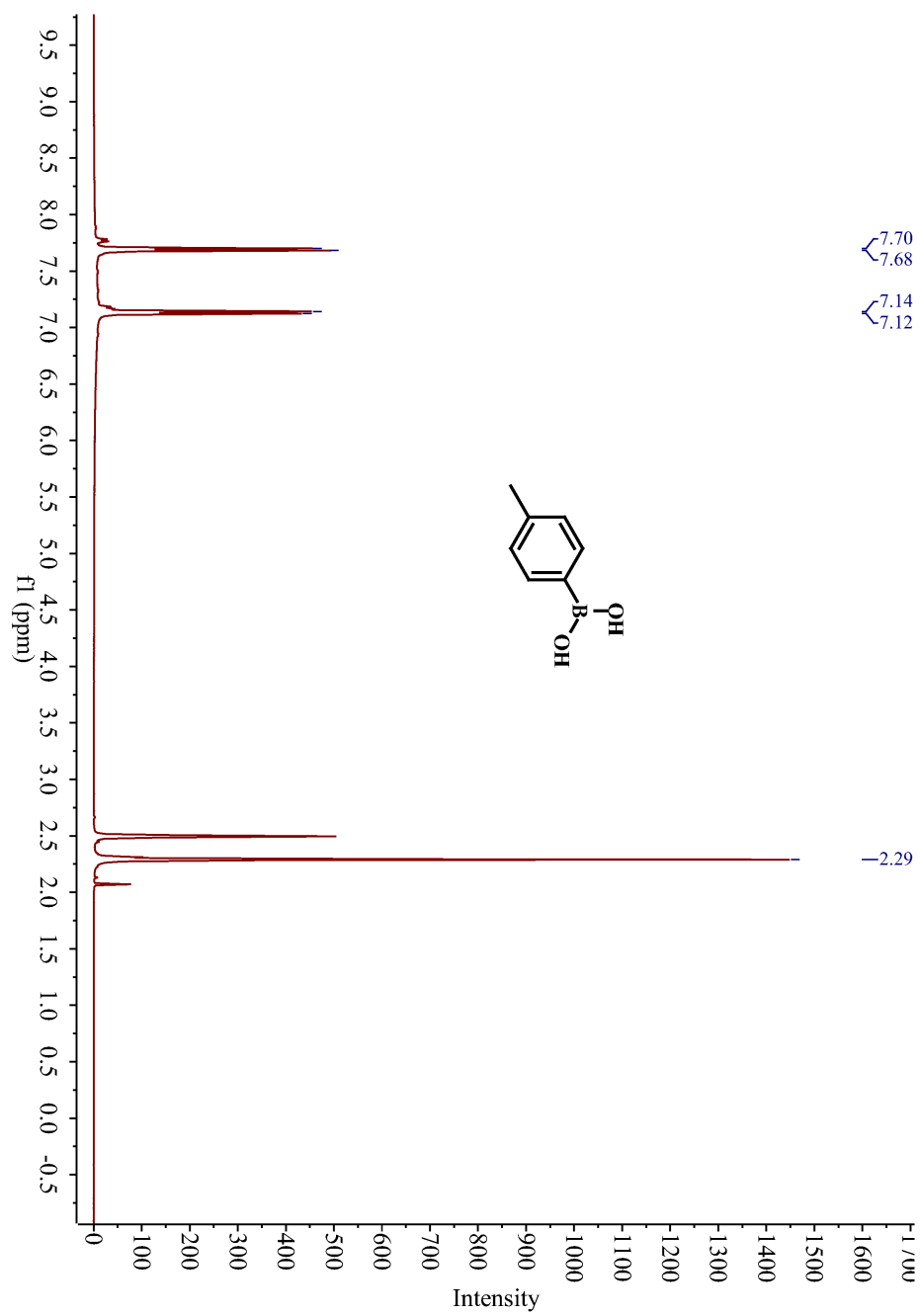


Figure A.0.1: ^1H spectrum of 1.

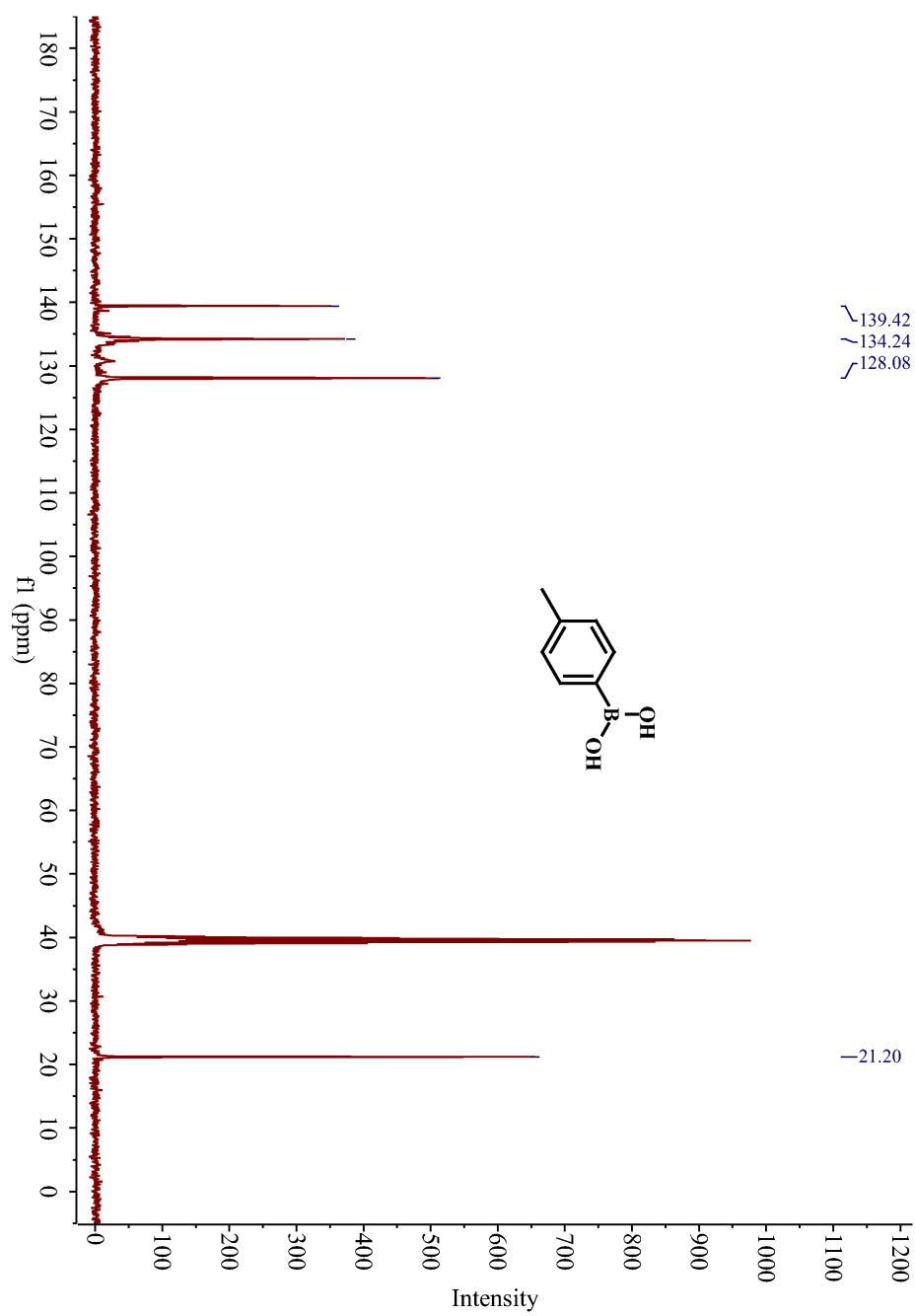


Figure A.0.2: ^{13}C spectrum of 1.

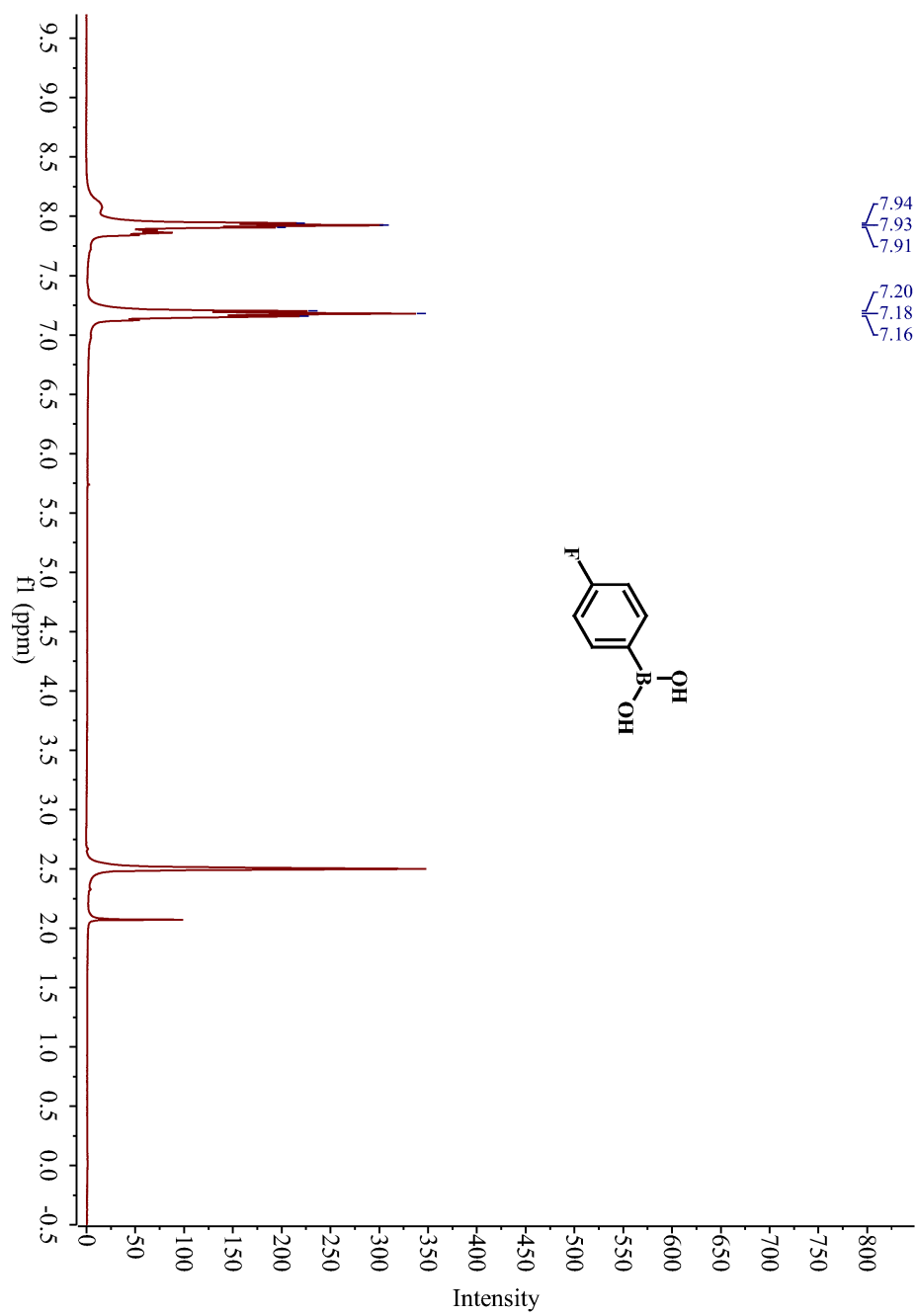


Figure A.0.3: ^1H spectrum of 2.

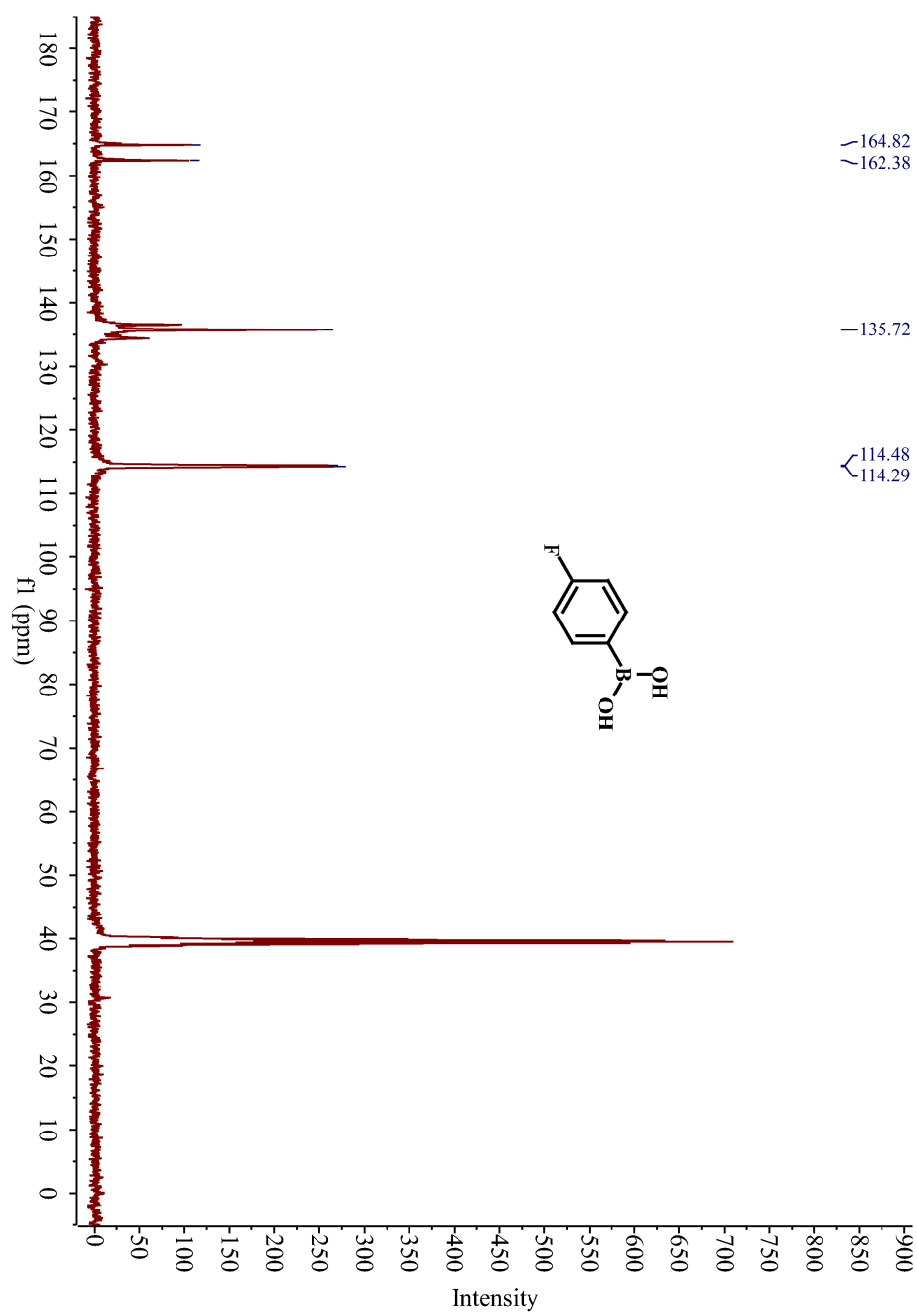


Figure A.0.4: ^{13}C spectrum of 2.

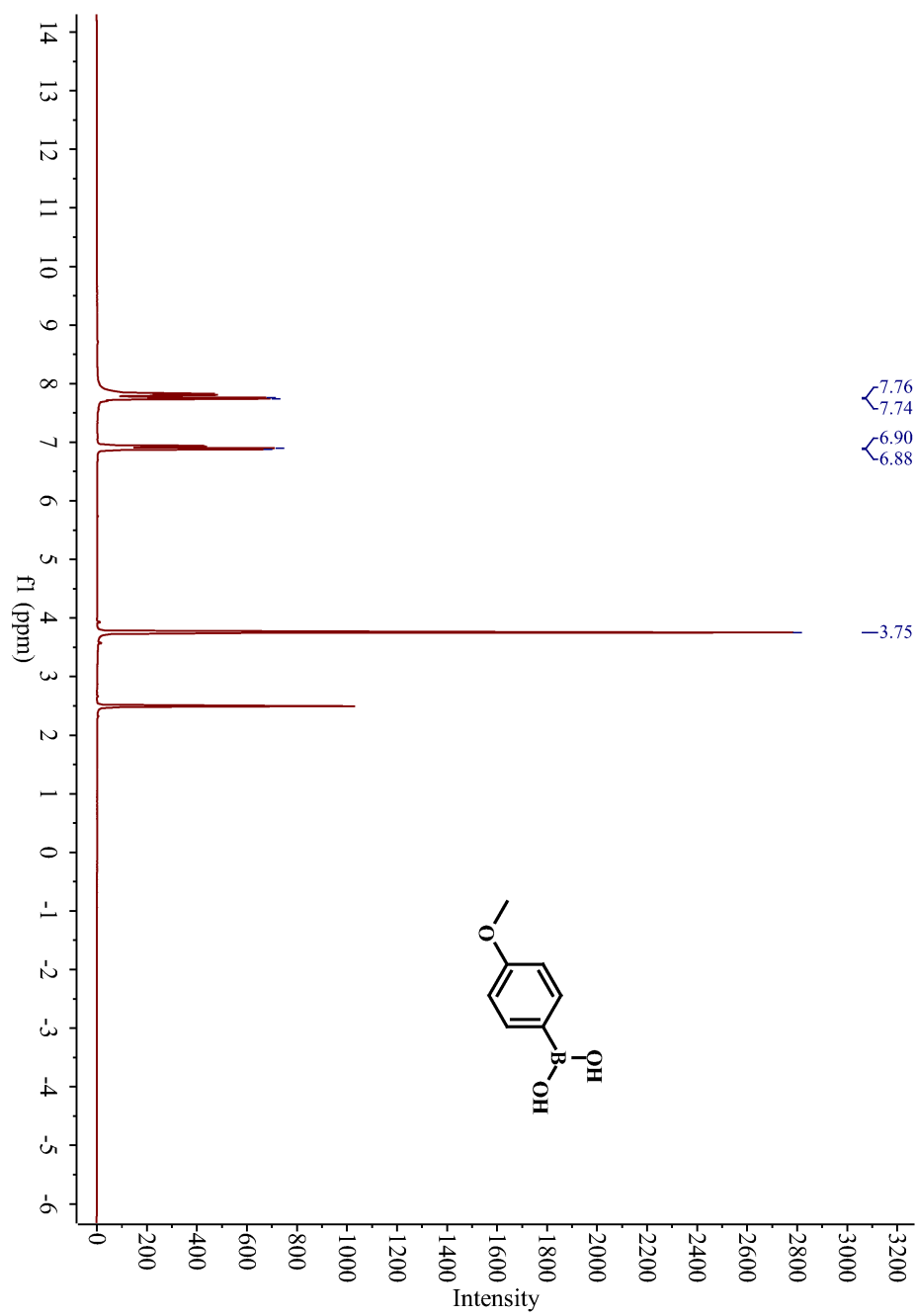


Figure A.0.5: ^1H spectrum of 3.

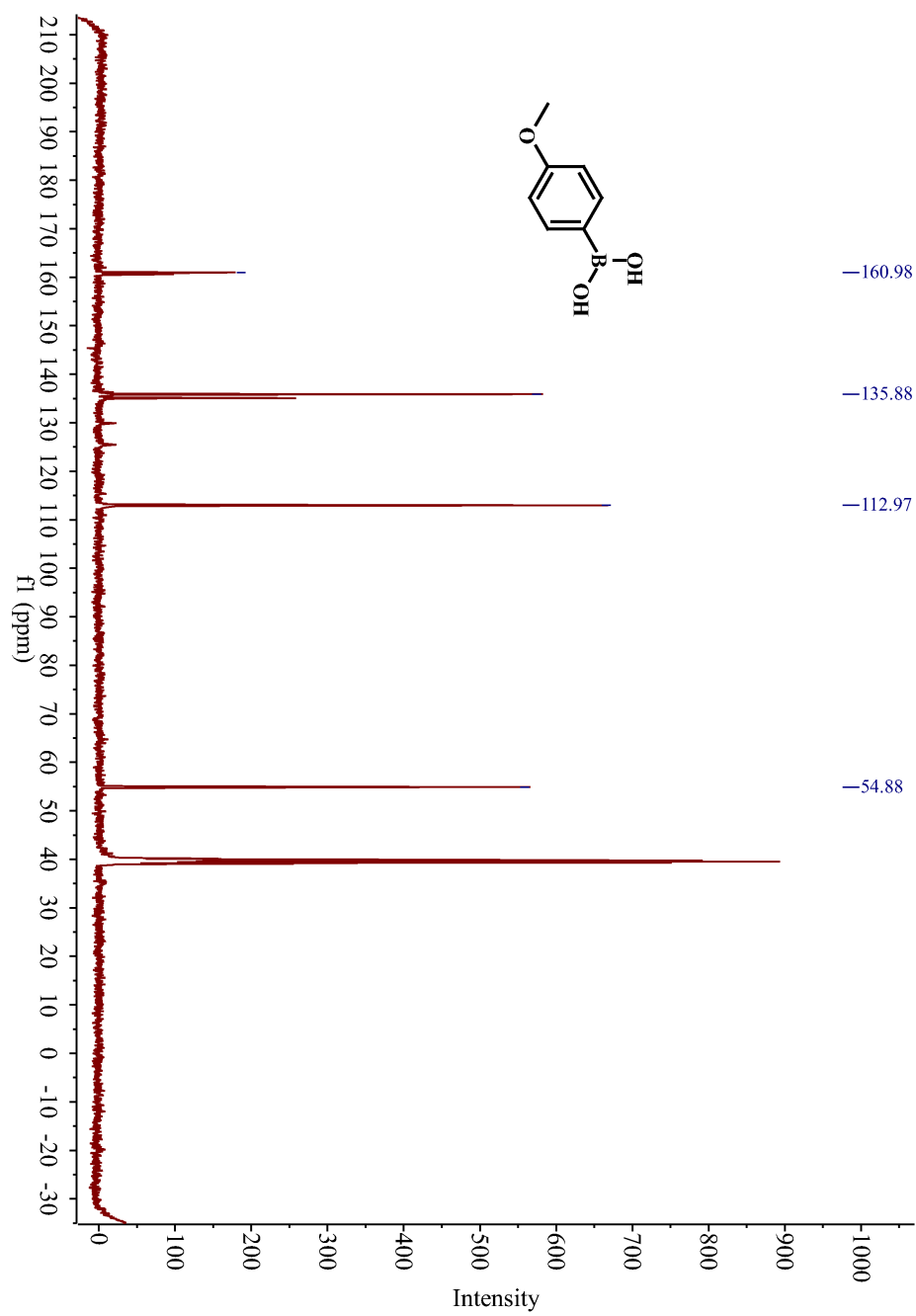


Figure A.0.6: ^{13}C spectrum of 3.

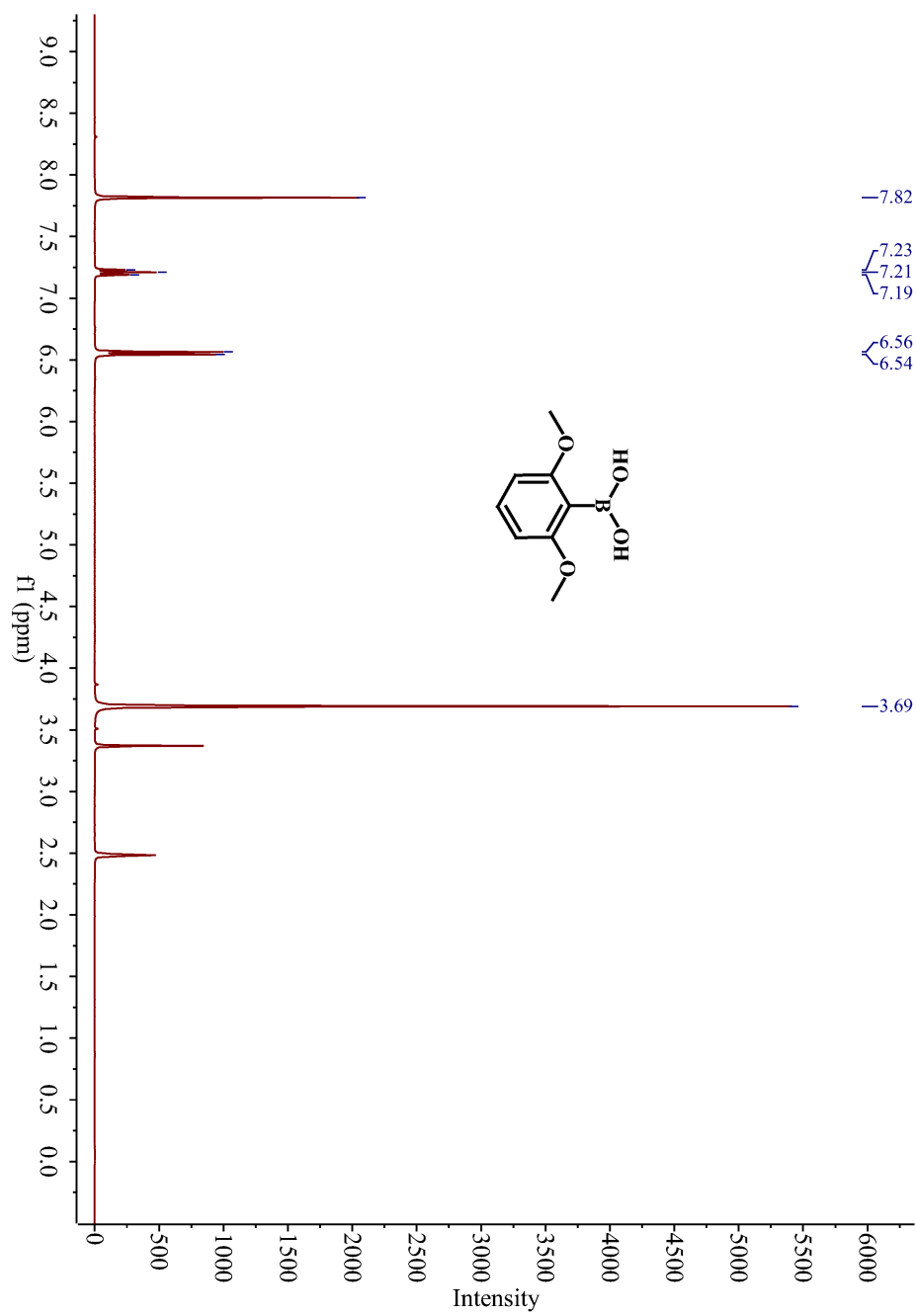


Figure A.0.7: ^1H spectrum of 4.

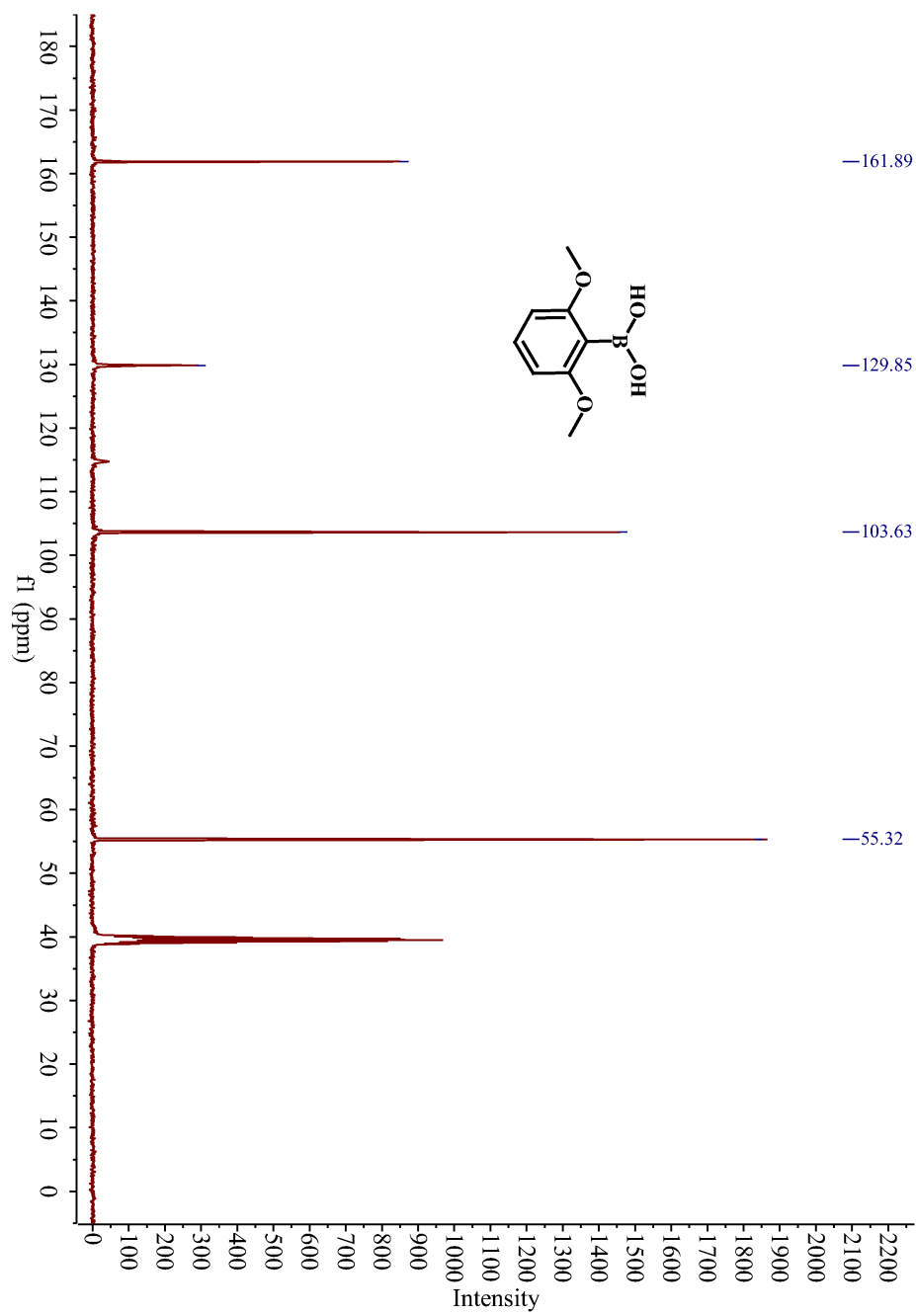


Figure A.0.8: ^{13}C spectrum of 4.

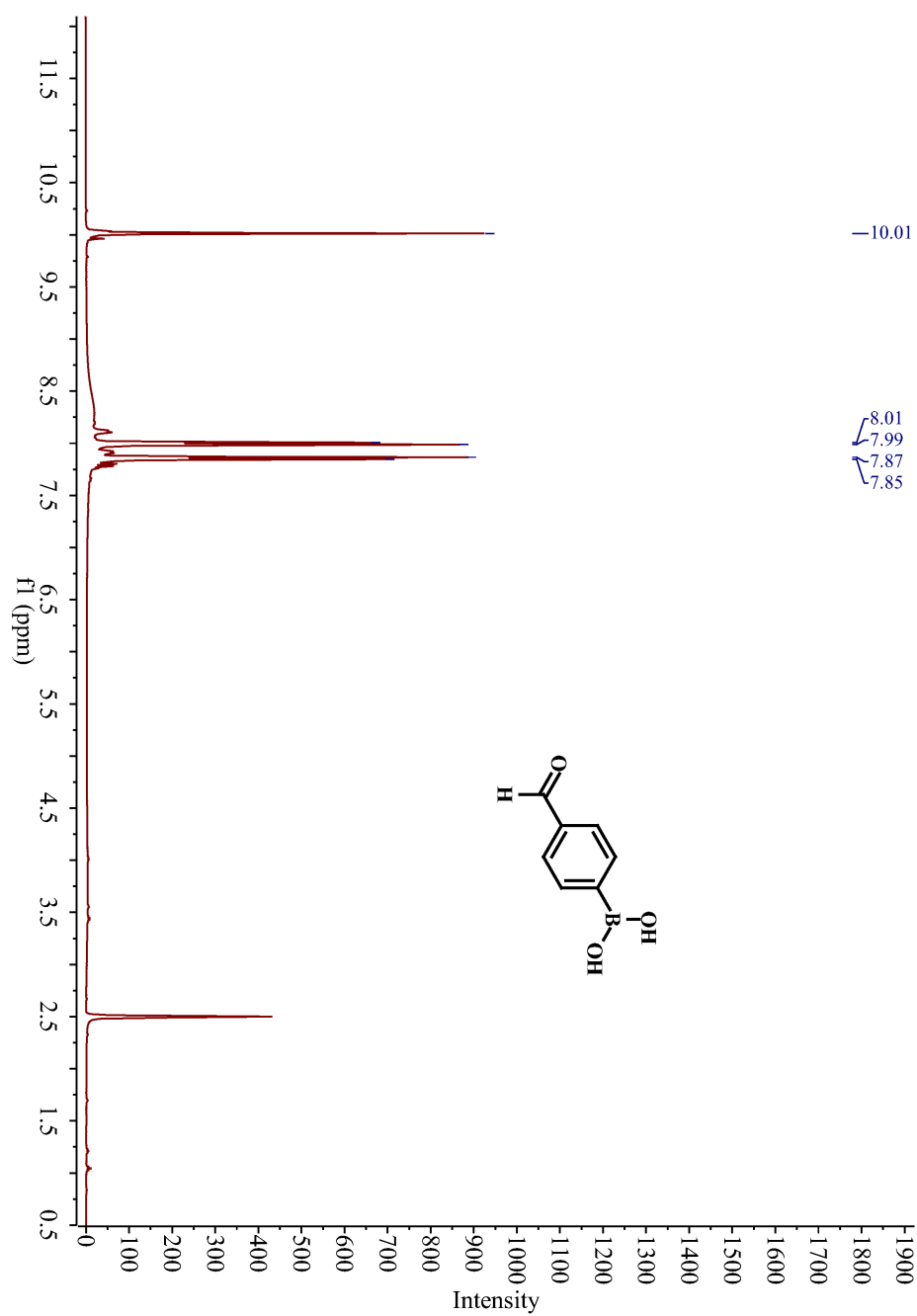


Figure A.0.9: ^1H spectrum of 5.

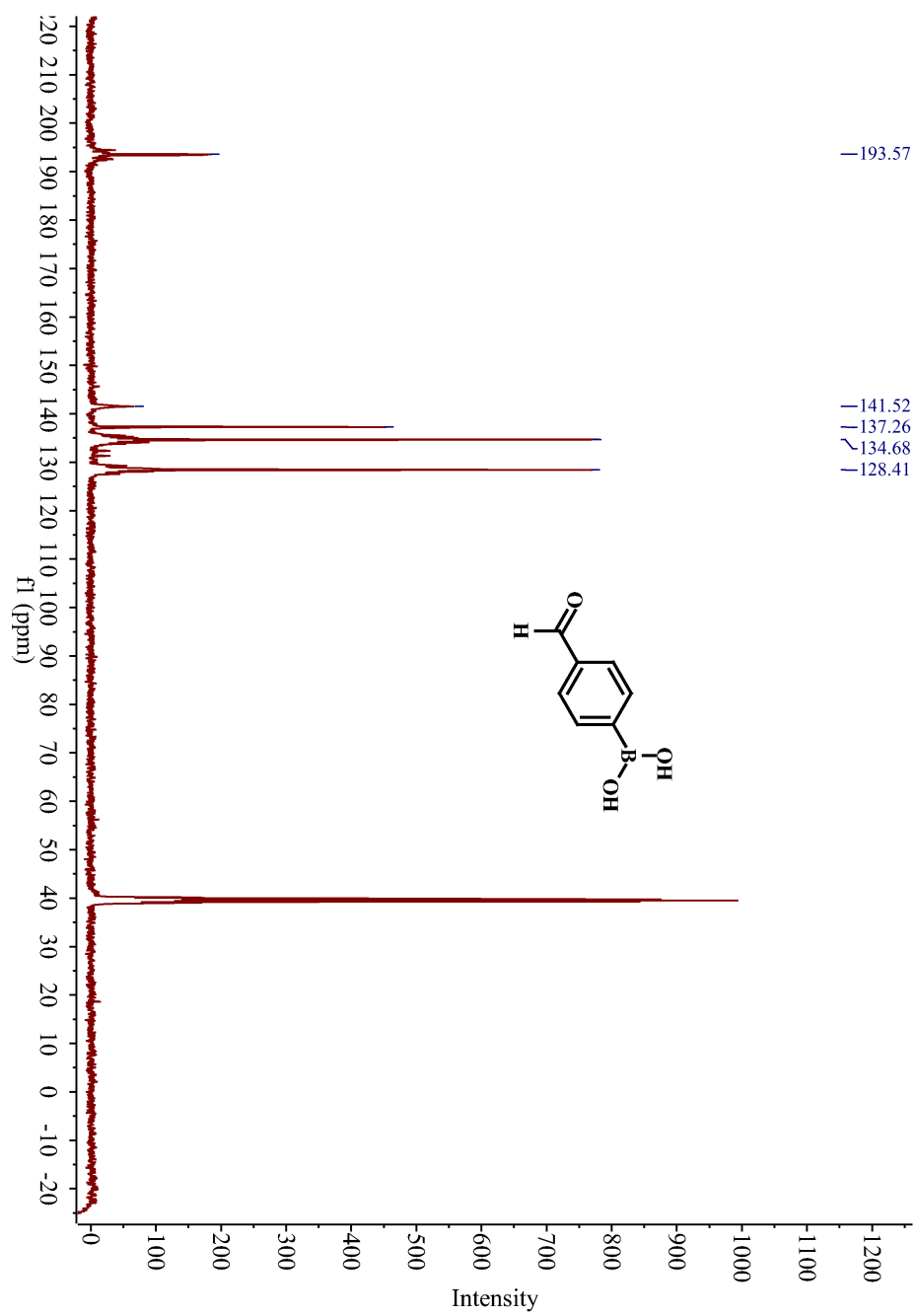


Figure A.0.10: ^{13}C spectrum of 5.

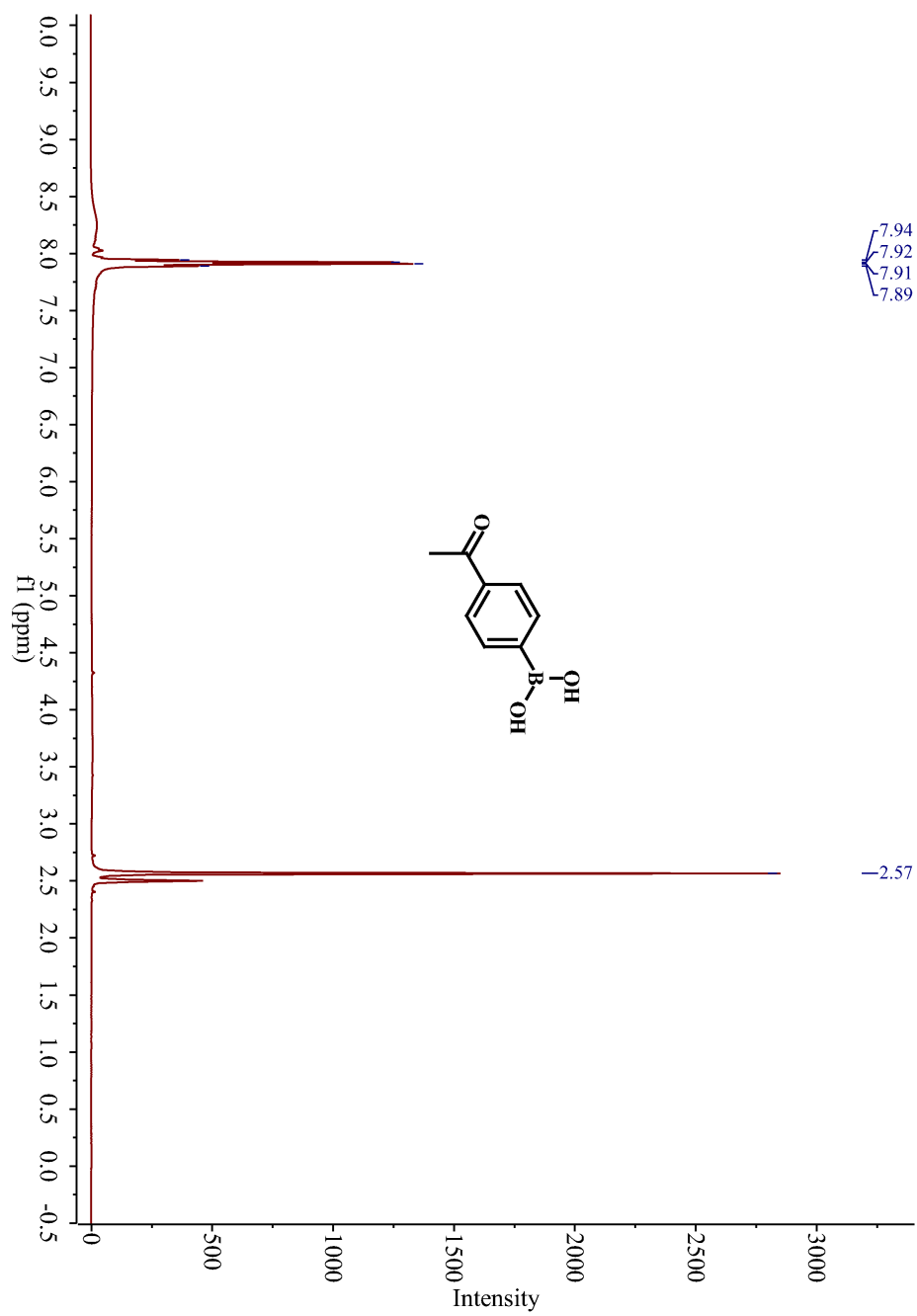


Figure A.0.11: ^1H spectrum of 6.

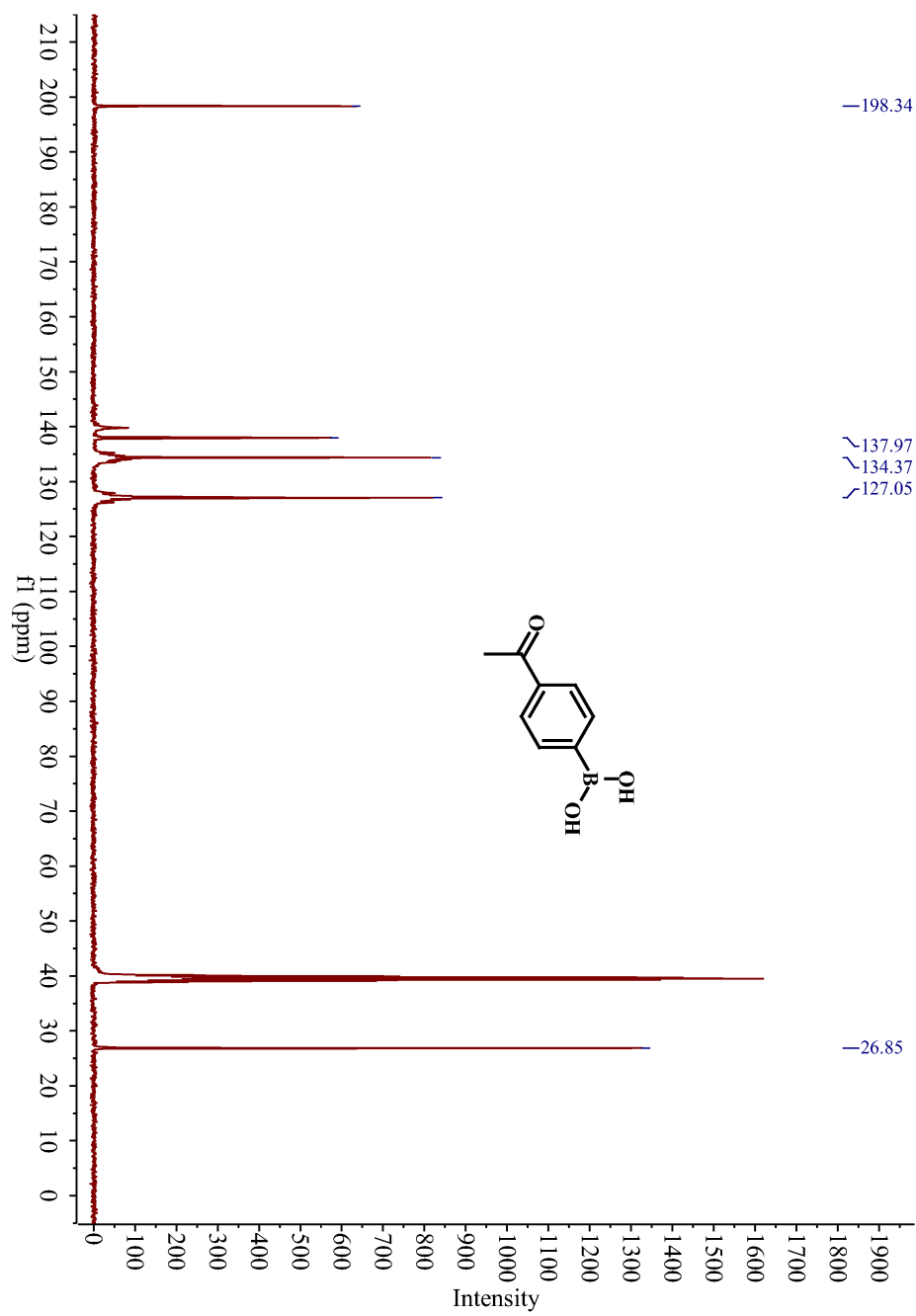


Figure A.0.12: ^{13}C spectrum of 6.

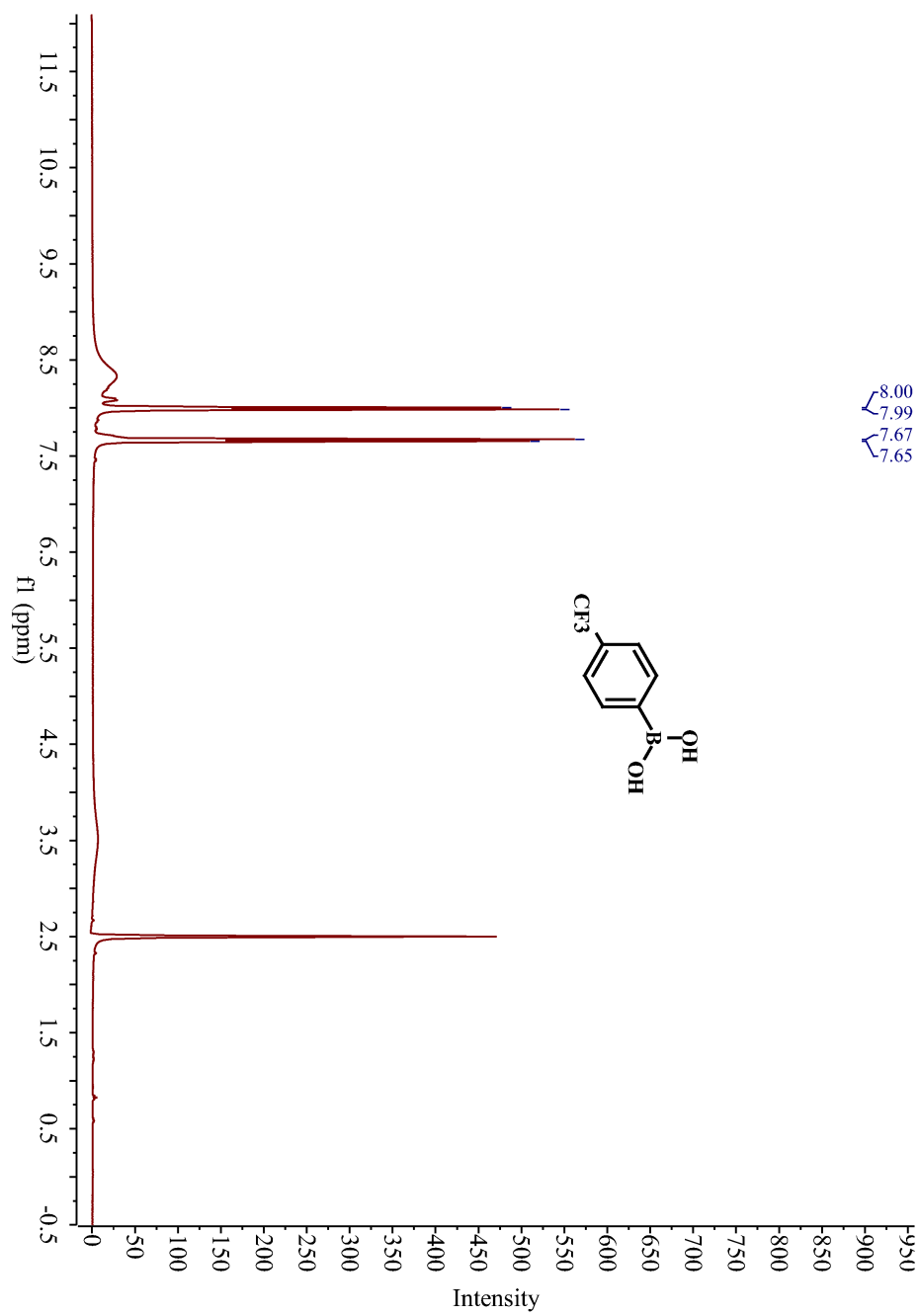


Figure A.0.13: ^1H spectrum of 7.

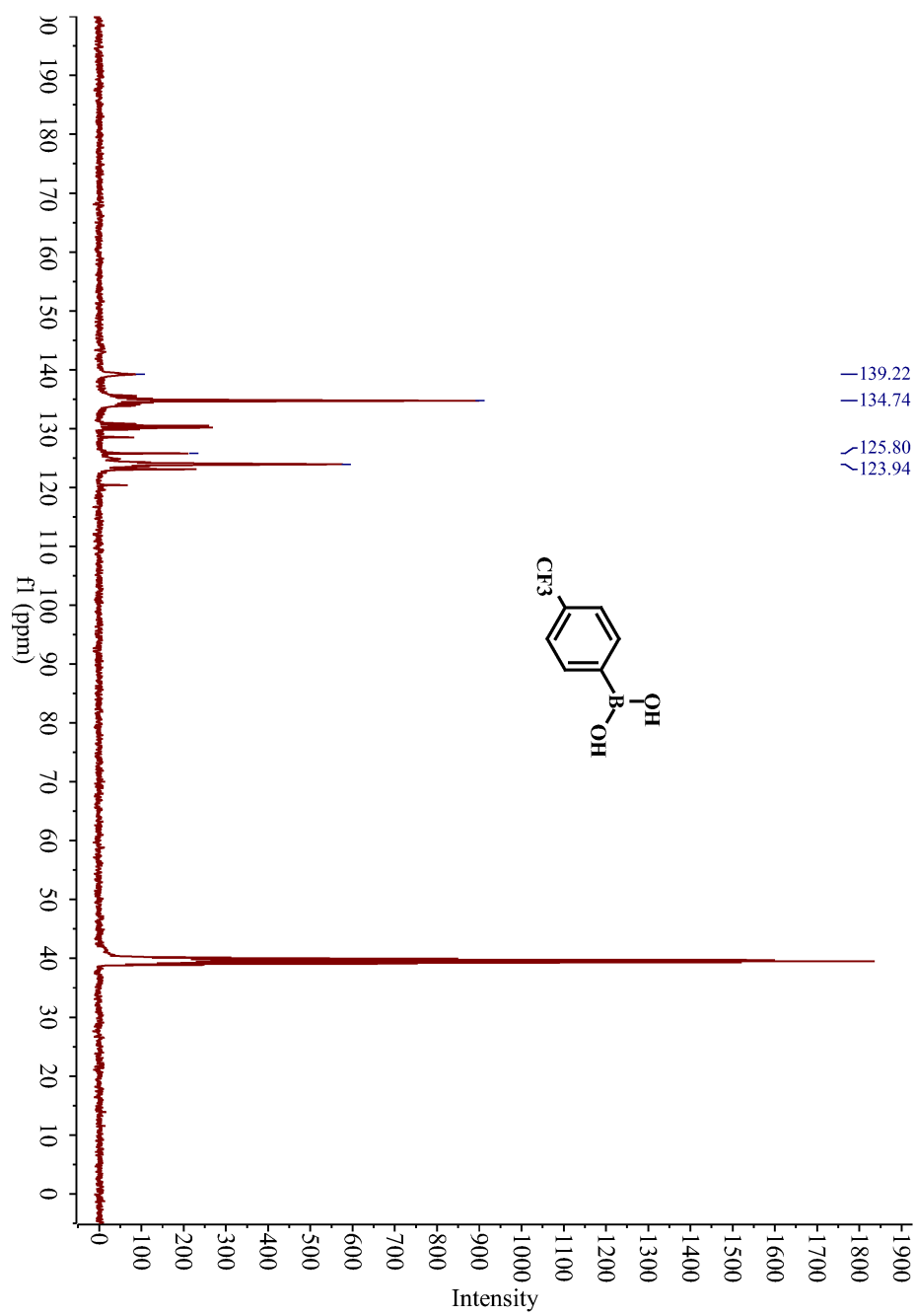


Figure A.0.14: ^{13}C spectrum of 7.

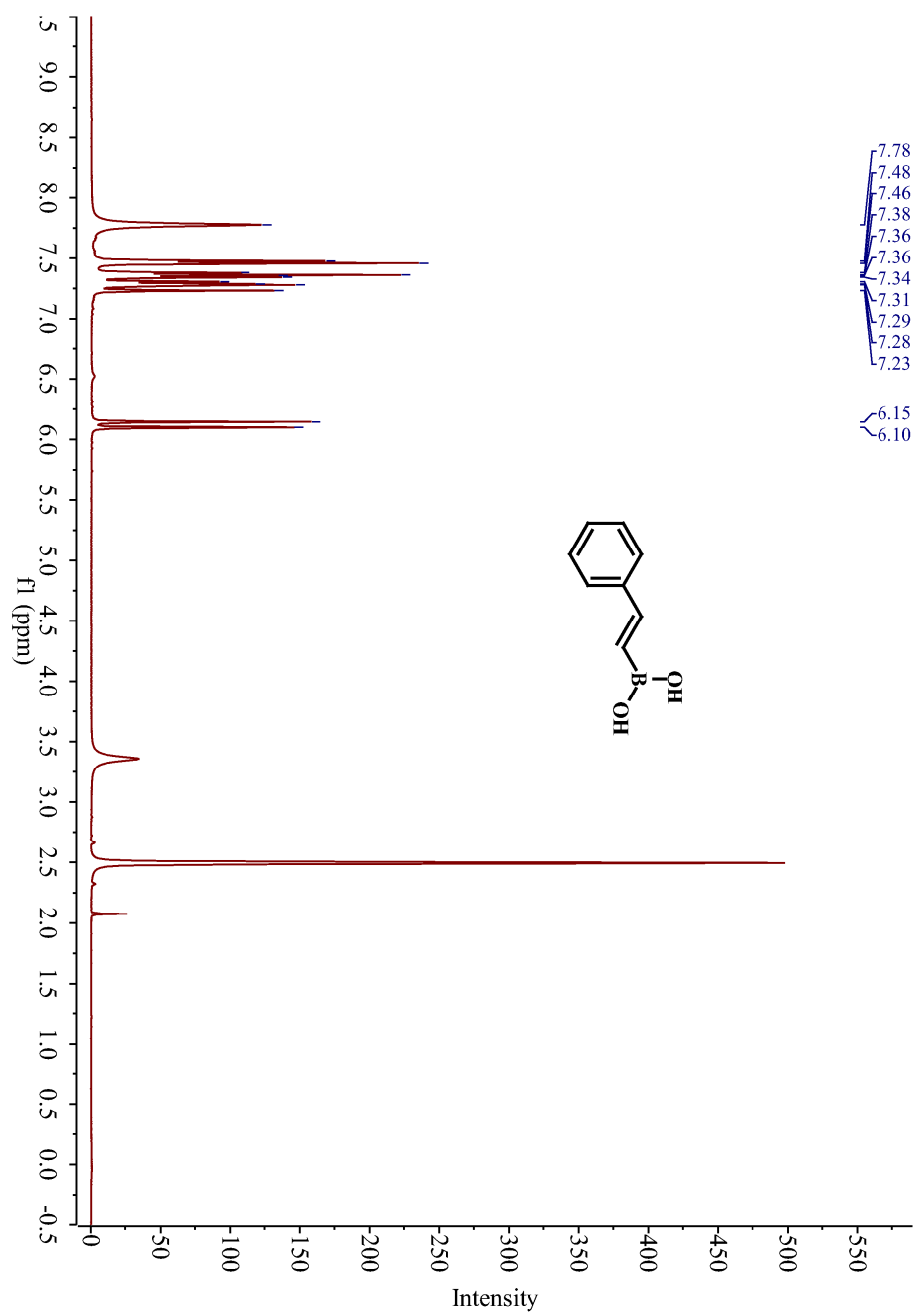


Figure A.0.15: ¹H spectrum of 8.

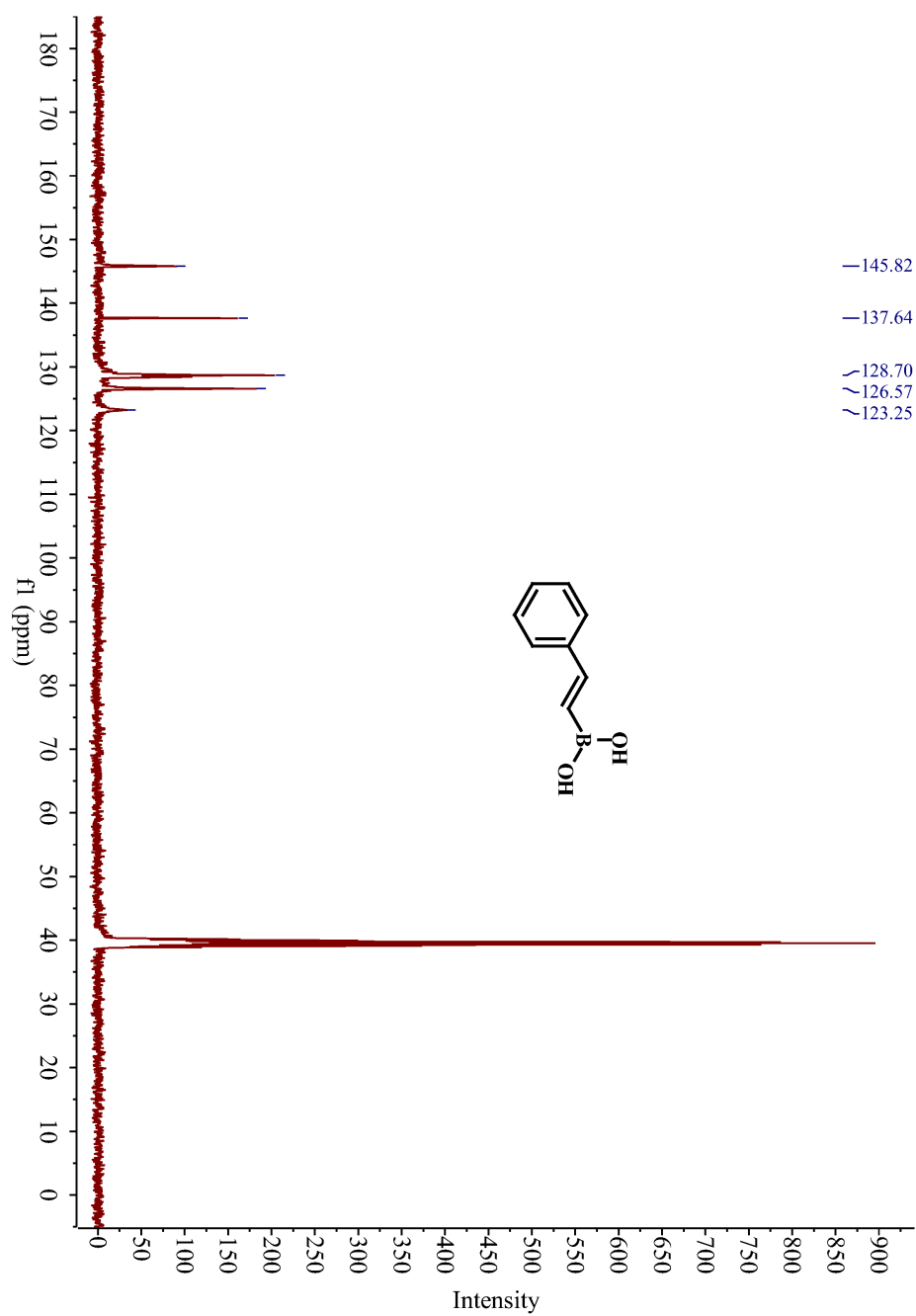


Figure A.0.16: ^{13}C spectrum of 8.

Appendix B

Representative NMR Spectra of compounds from Chapter 3

B.1 Compounds from Table 3.1

Below, we show ^1H and ^{13}C NMR spectra for the compounds listed in Table 3.1. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, on a Bruker Avance 400 instrument. Chemical shifts are measured with respect to the residual protons in the deuterated solvents.

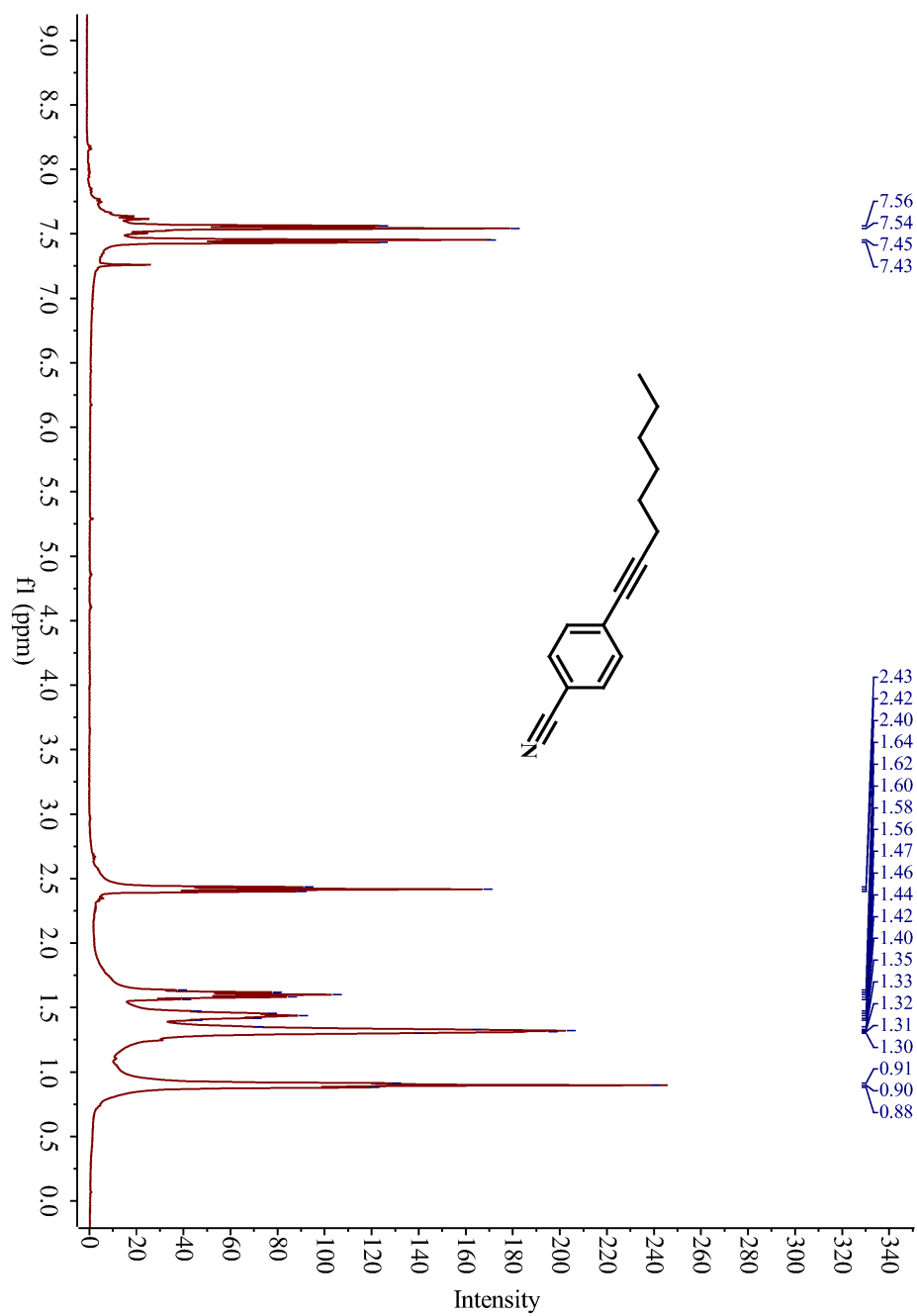


Figure B.1.1: ¹H spectrum of 1.

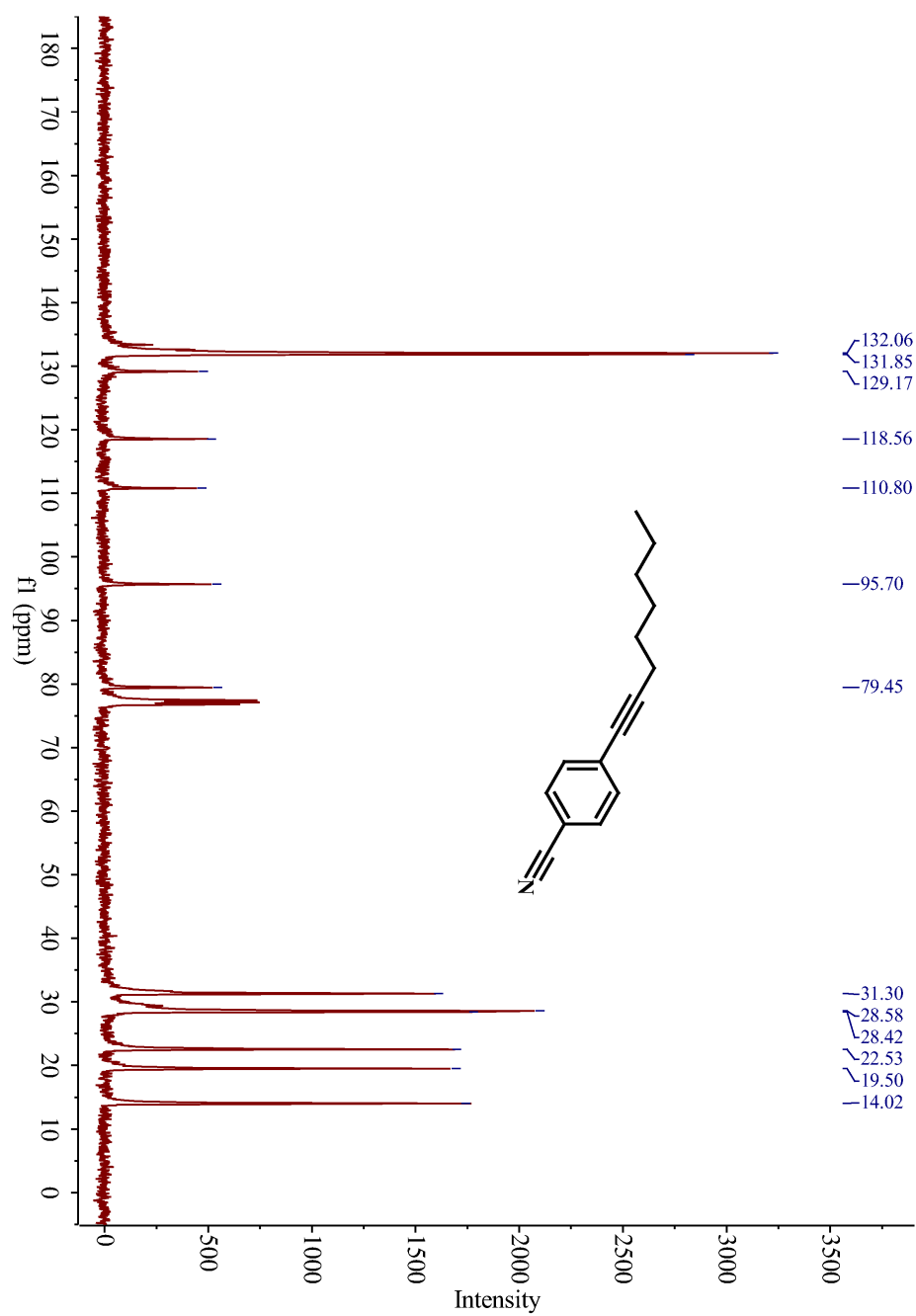


Figure B.1.2: ^{13}C spectrum of 1.

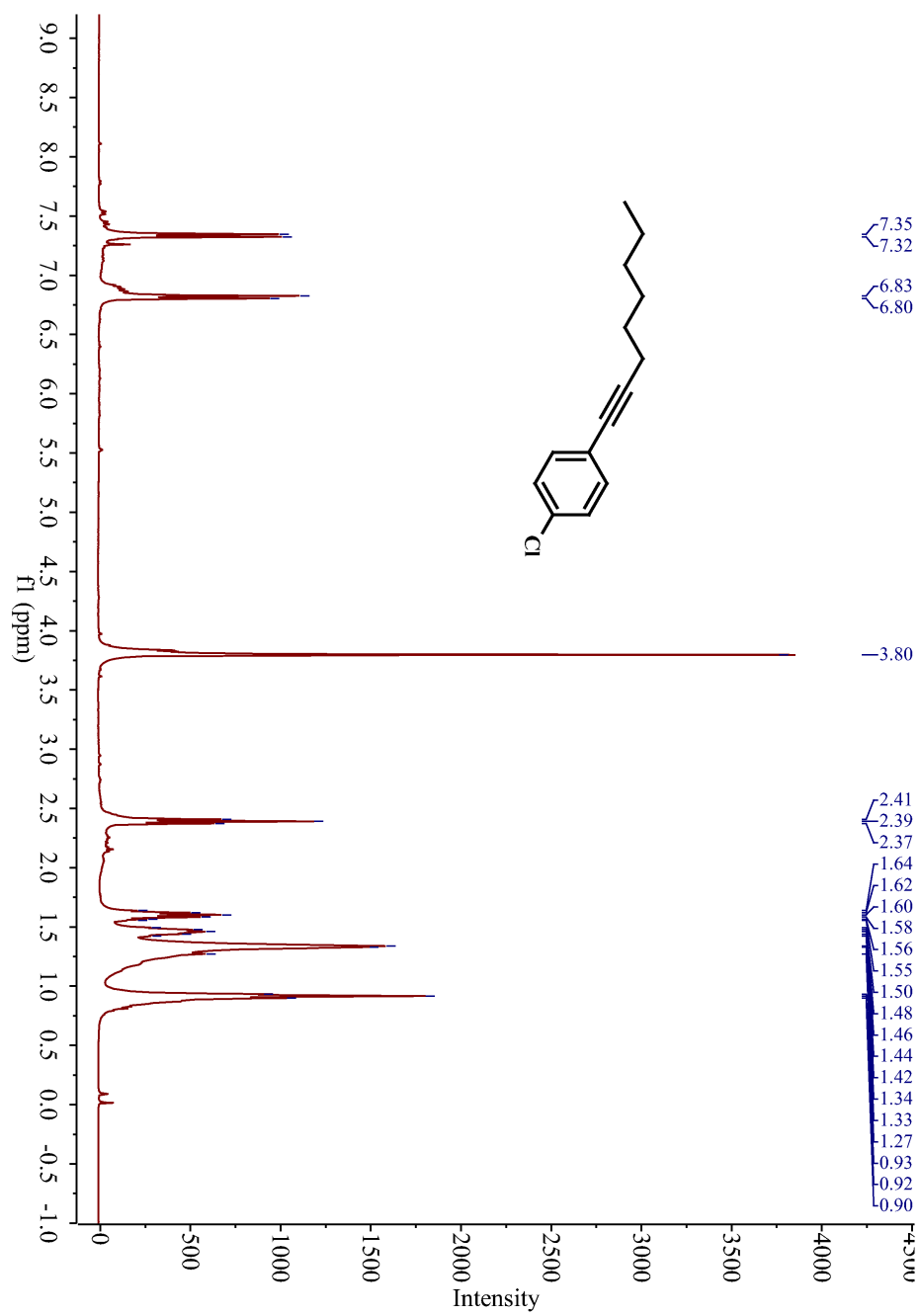


Figure B.1.3: ^1H spectrum of 2.

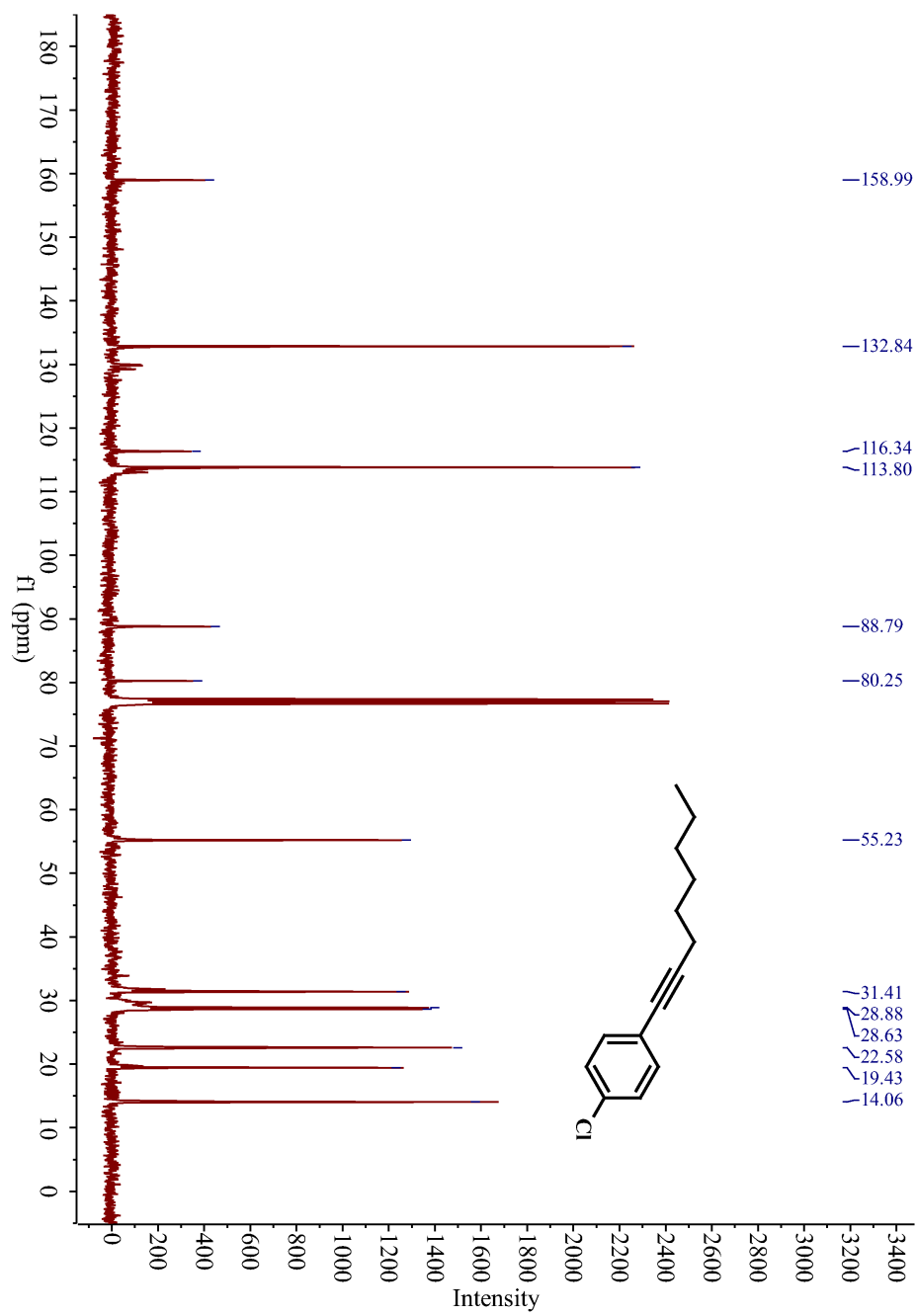


Figure B.1.4: ^{13}C spectrum of 2.

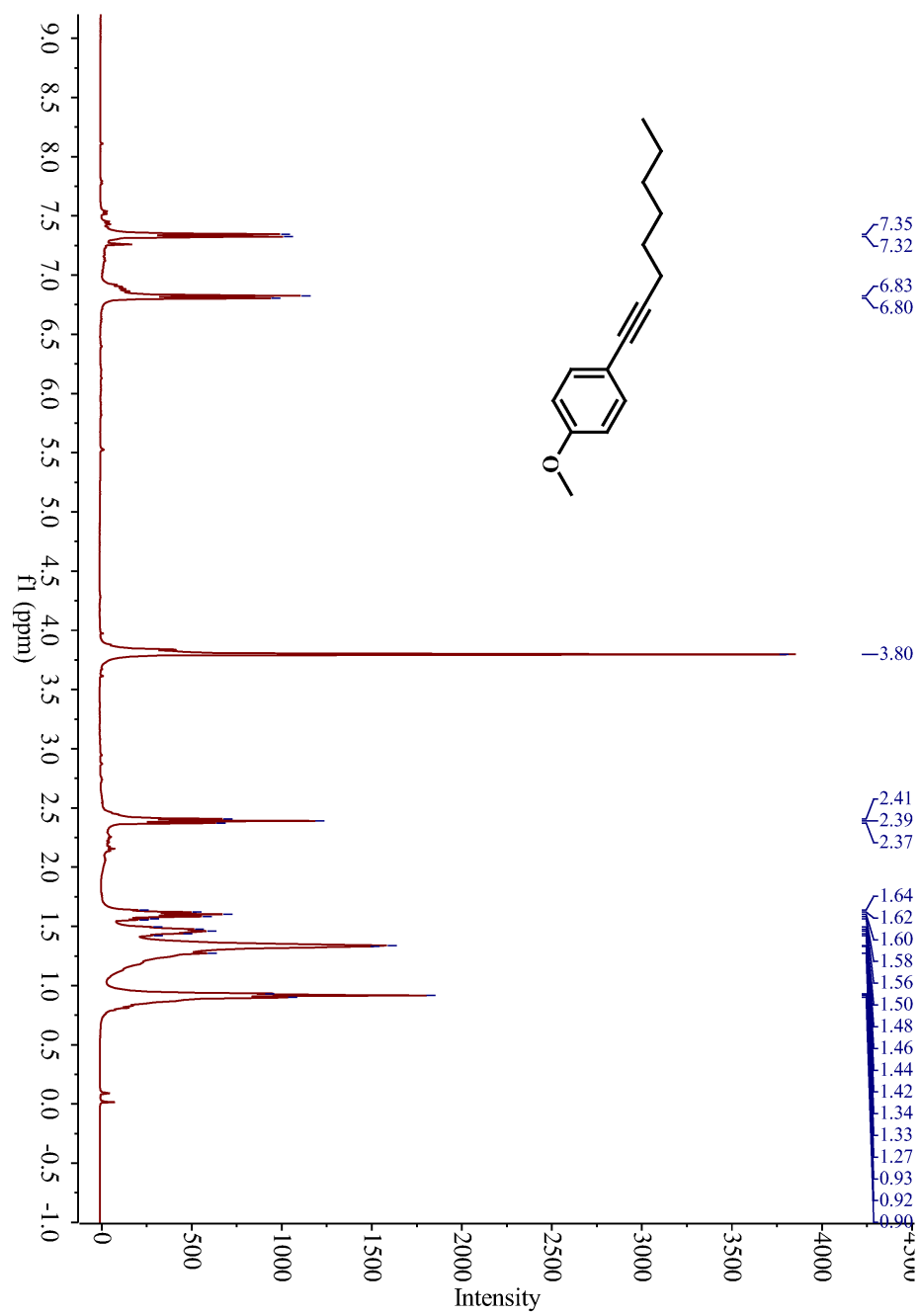


Figure B.1.5: ¹H spectrum of 3.

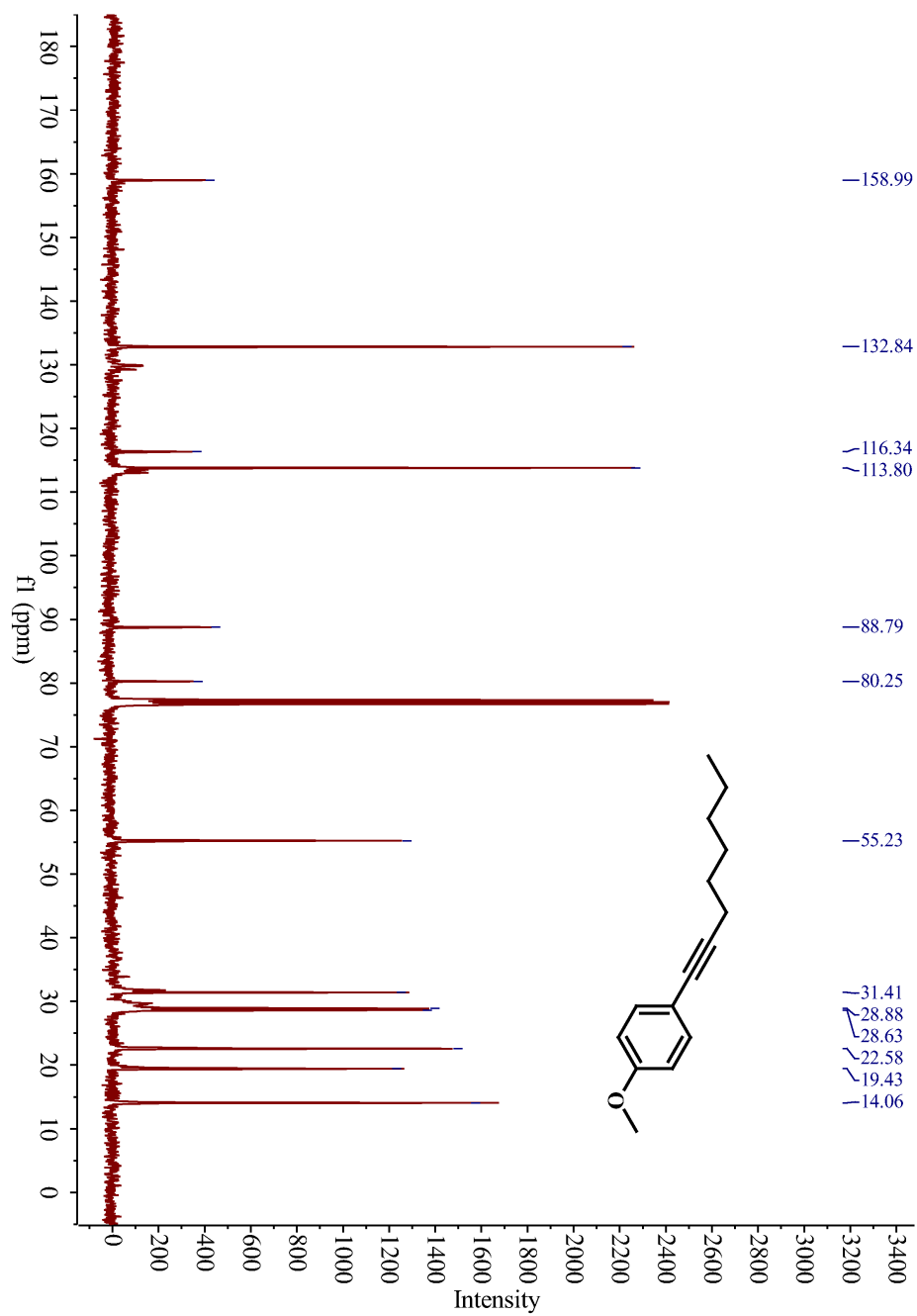


Figure B.1.6: ^{13}C spectrum of 3.

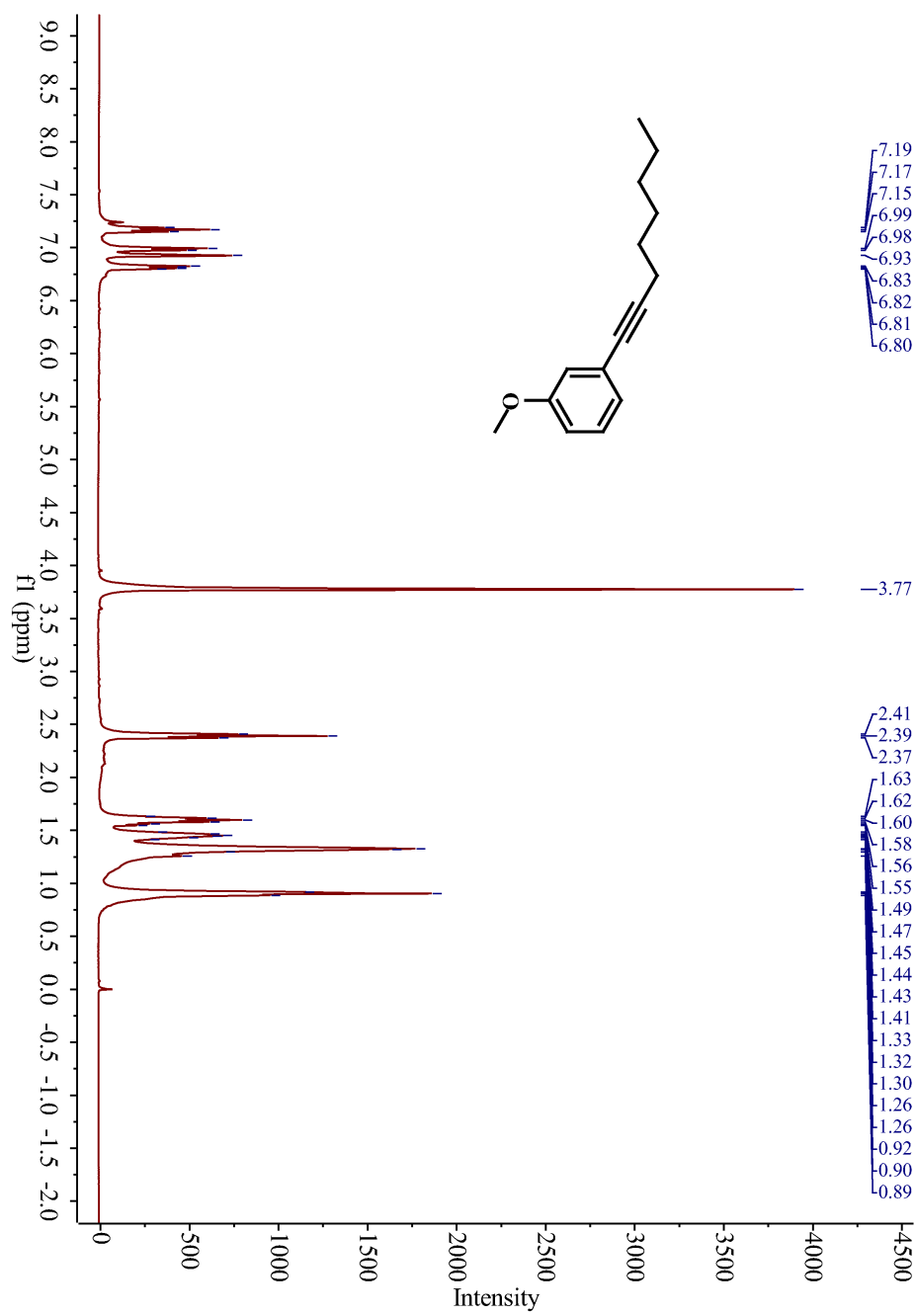


Figure B.1.7: ¹H spectrum of 4.

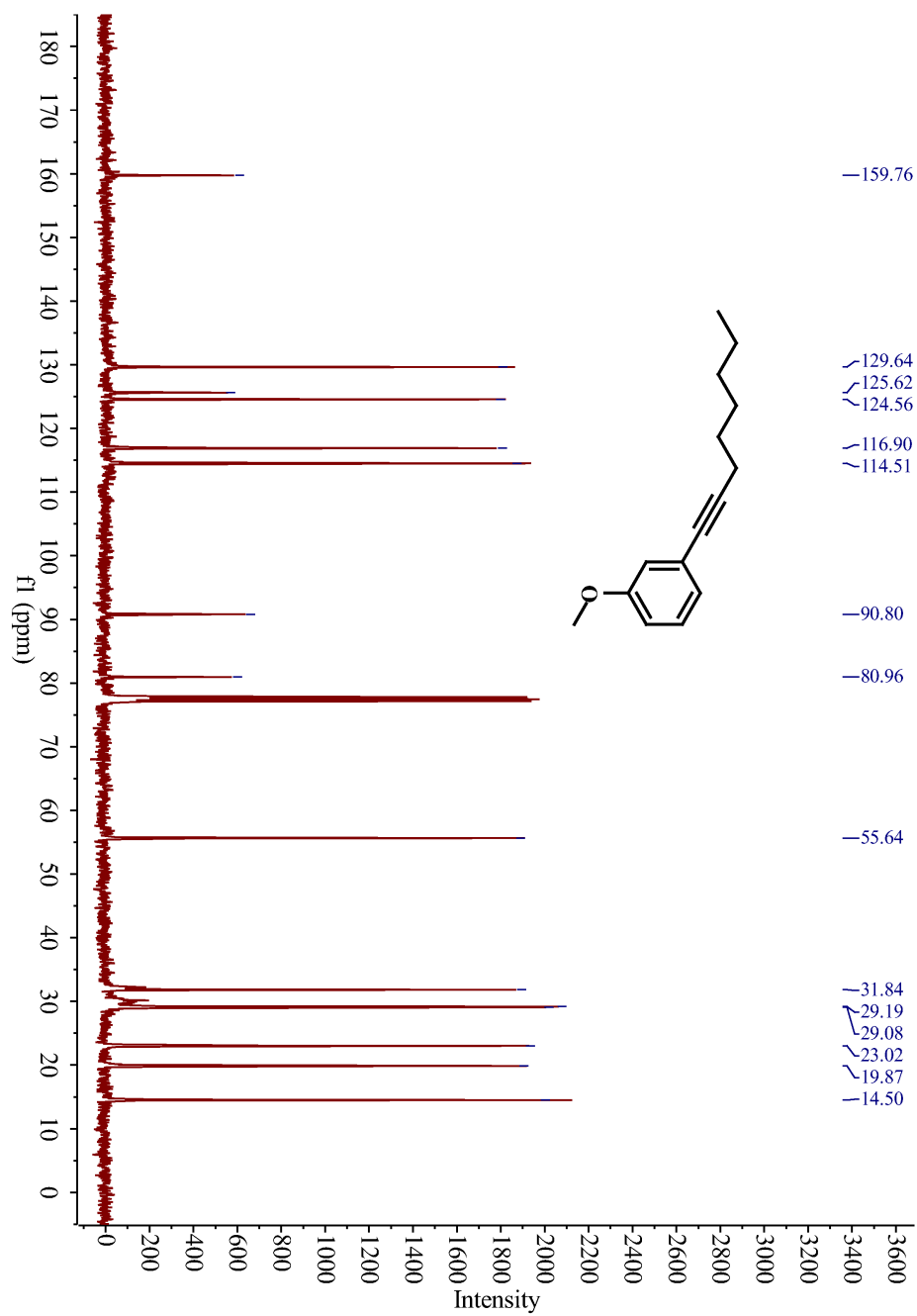


Figure B.1.8: ^{13}C spectrum of 4.

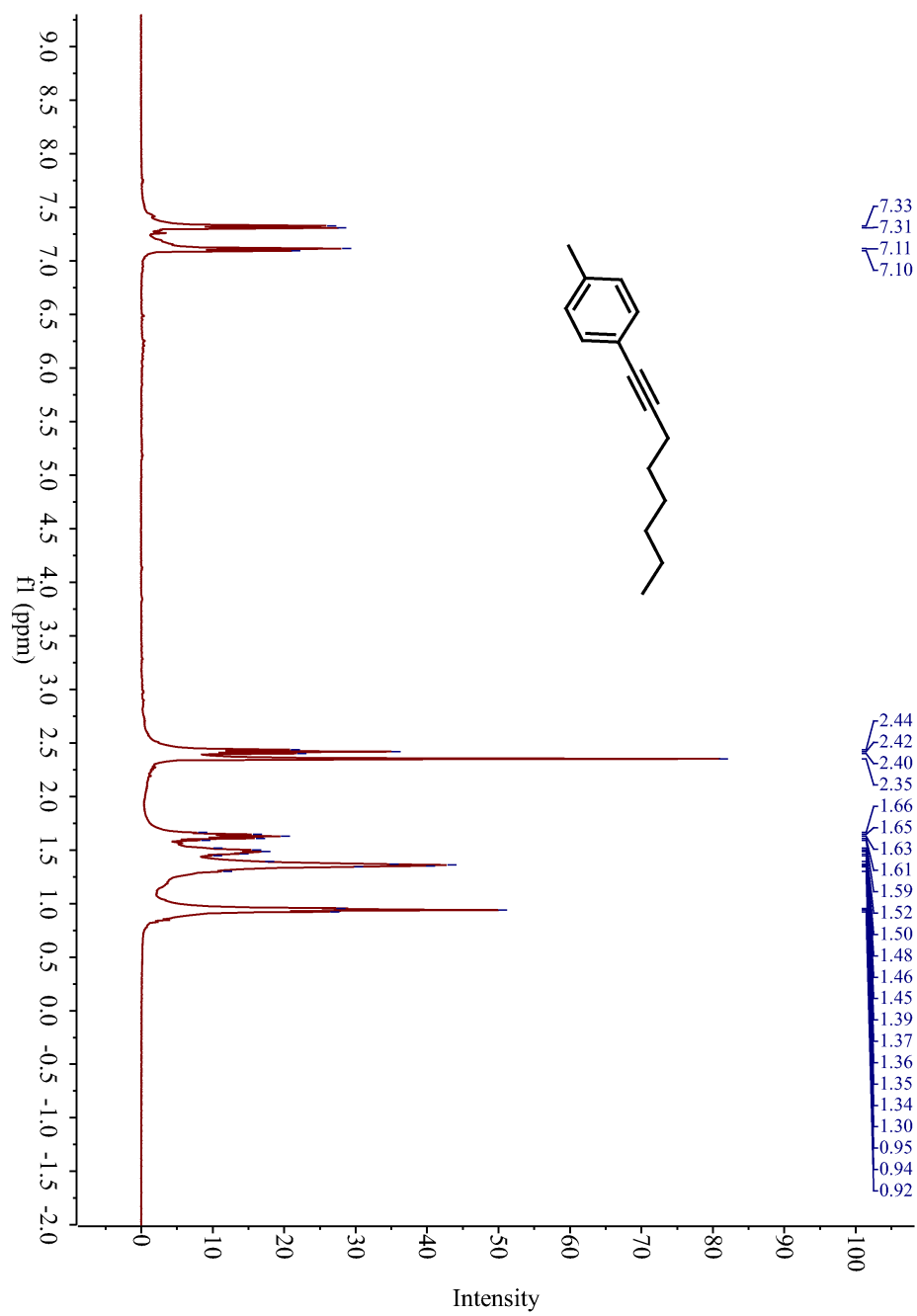


Figure B.1.9: ^1H spectrum of 2.

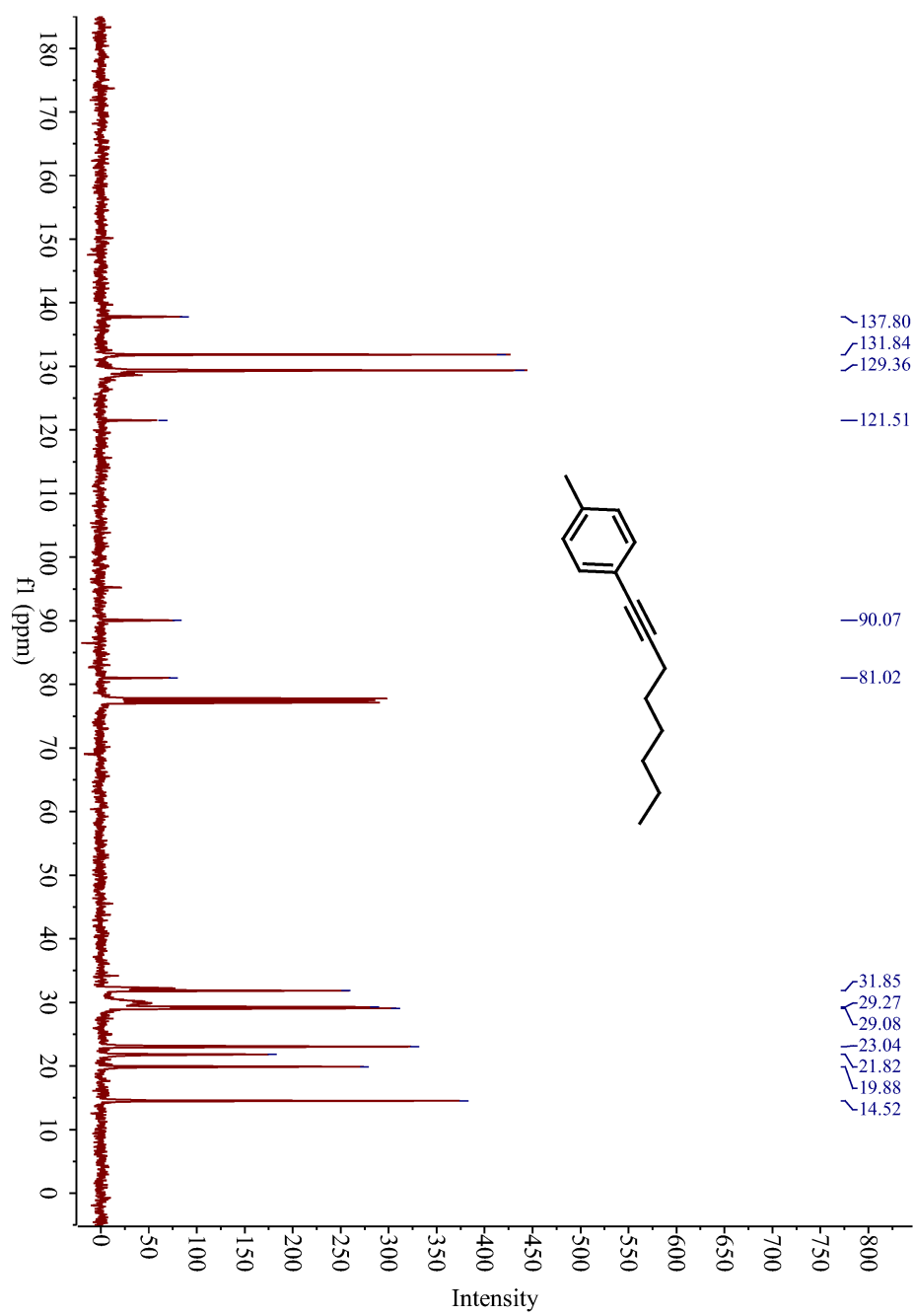


Figure B.1.10: ^{13}C spectrum of 2.

B.2 Compounds from Table 3.2

Below, we show ^1H and ^{13}C NMR spectra for the compounds listed in Table 3.2. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, on a Bruker Avance 400 instrument. Chemical shifts are measured with respect to the residual protons in the deuterated solvents.

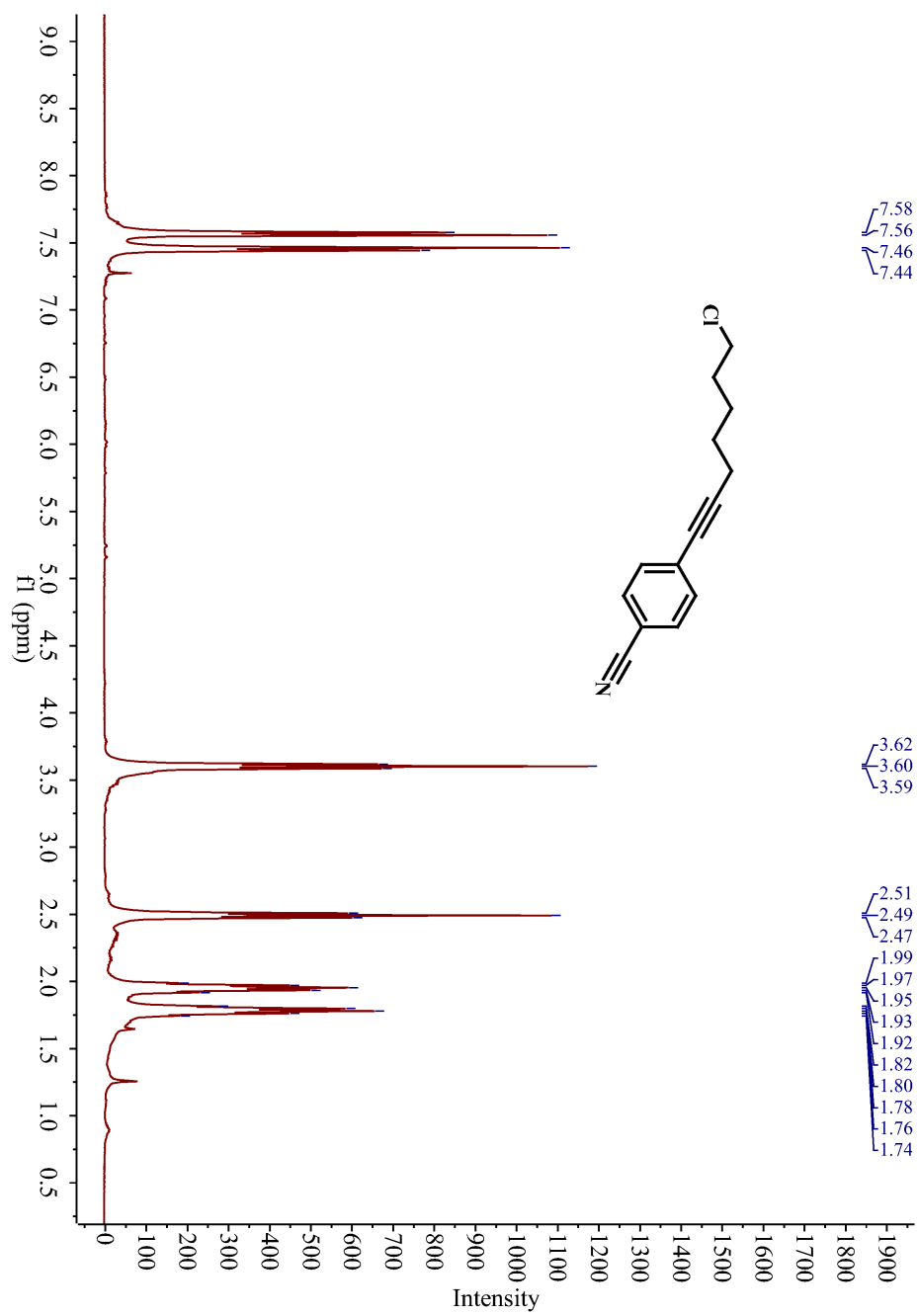


Figure B.2.1: ^1H spectrum of 1.

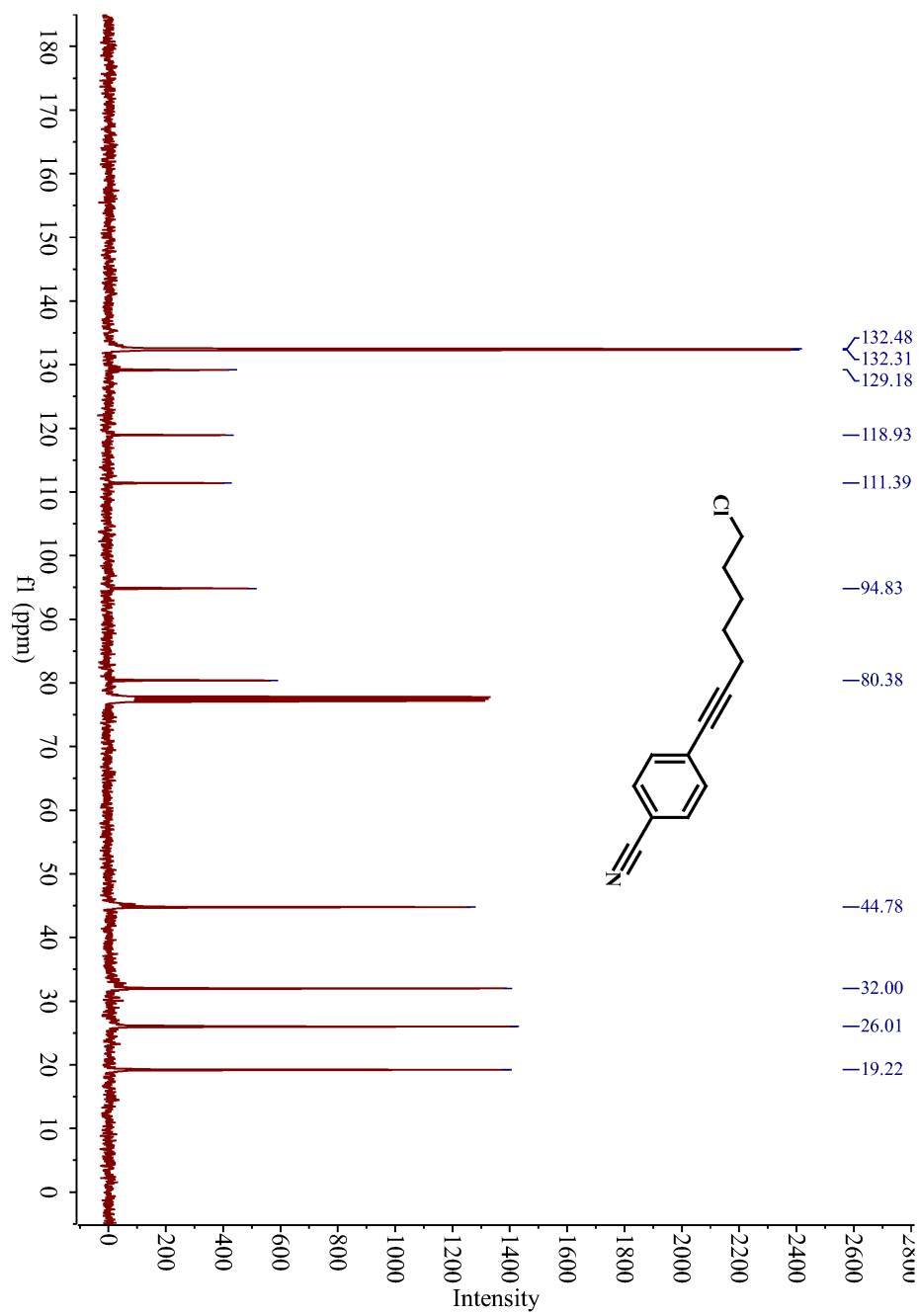


Figure B.2.2: ^{13}C spectrum of 1.

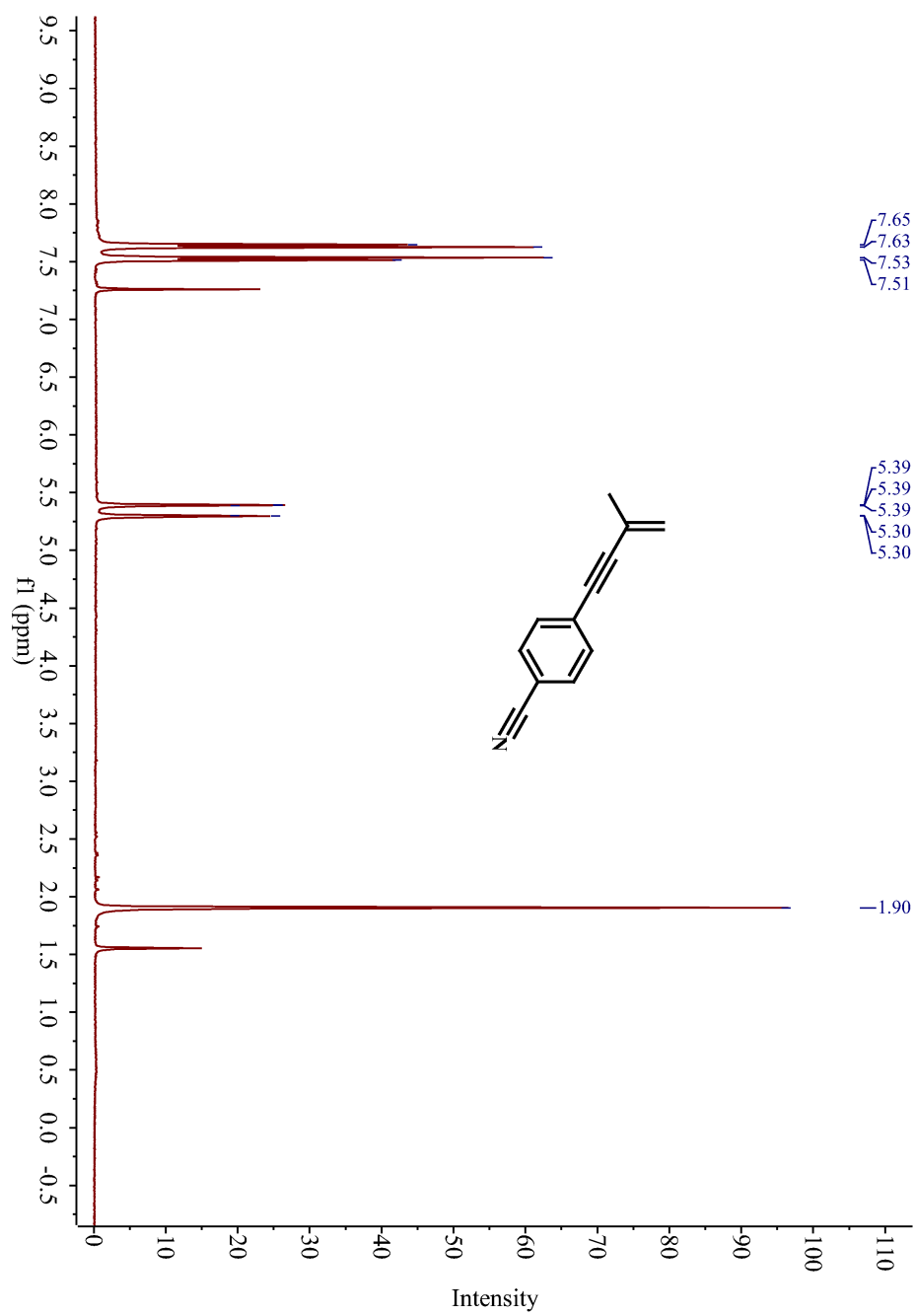


Figure B.2.3: ^1H spectrum of 2.

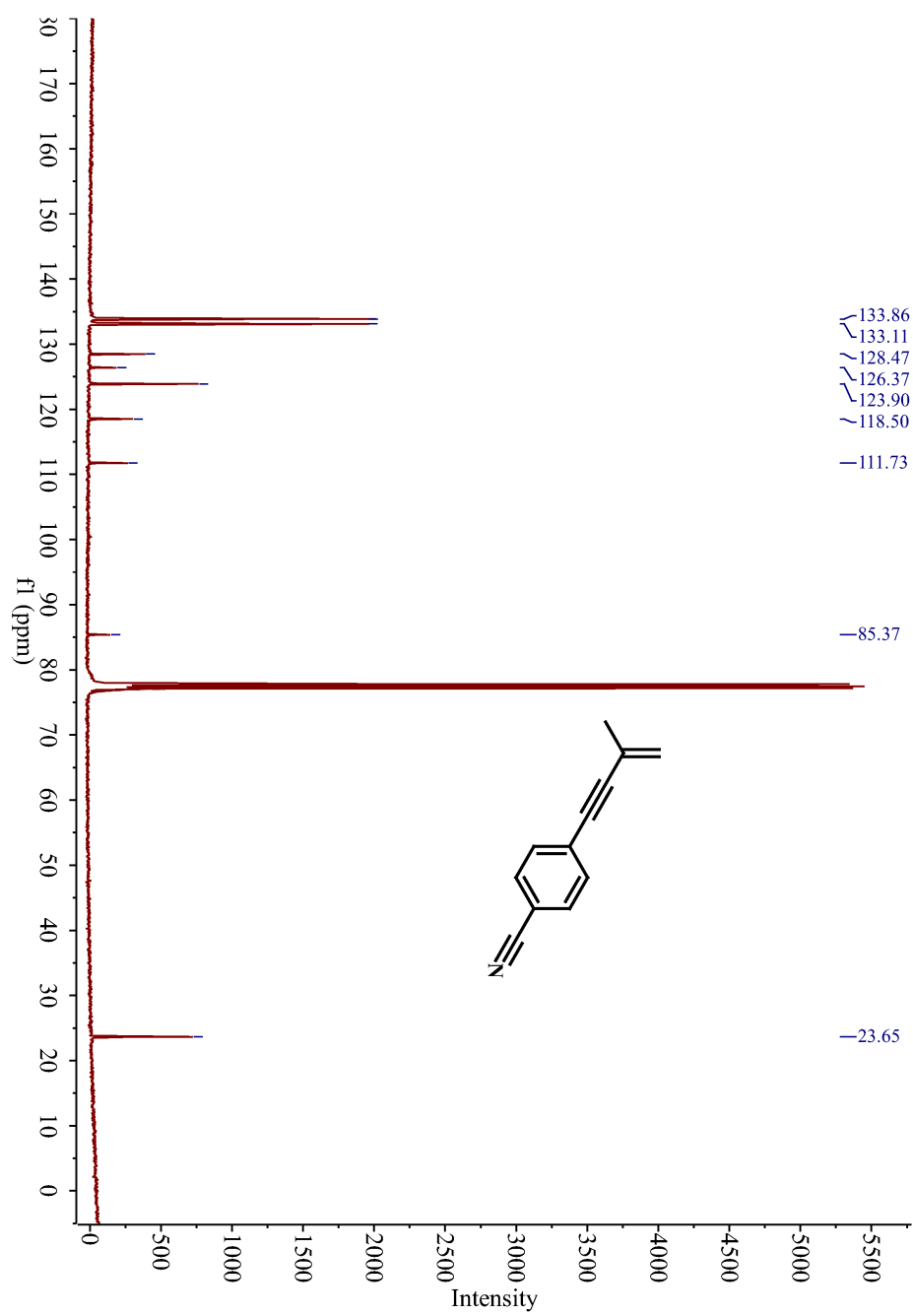


Figure B.2.4: ^{13}C spectrum of 2.

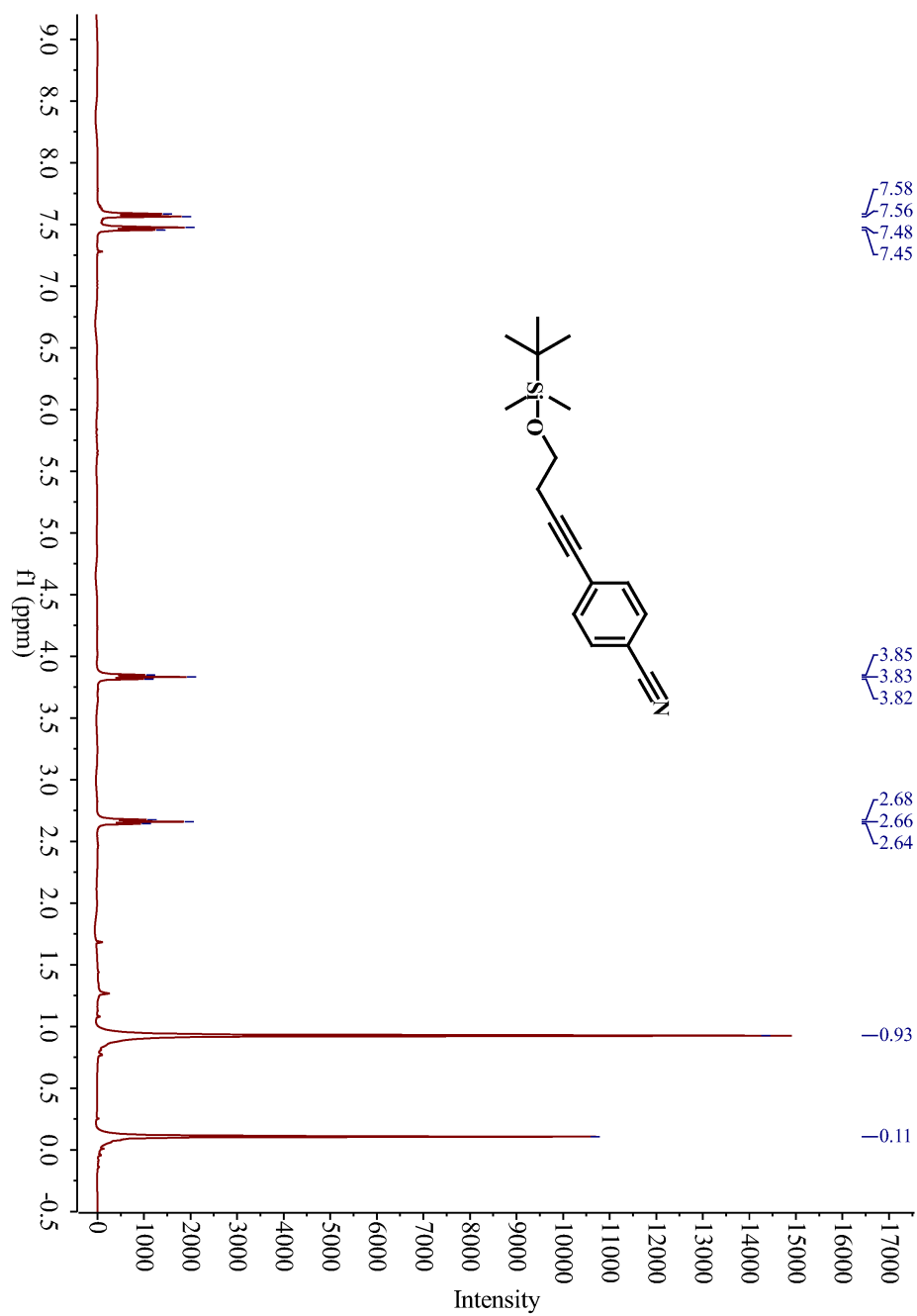


Figure B.2.5: ^1H spectrum of 3.

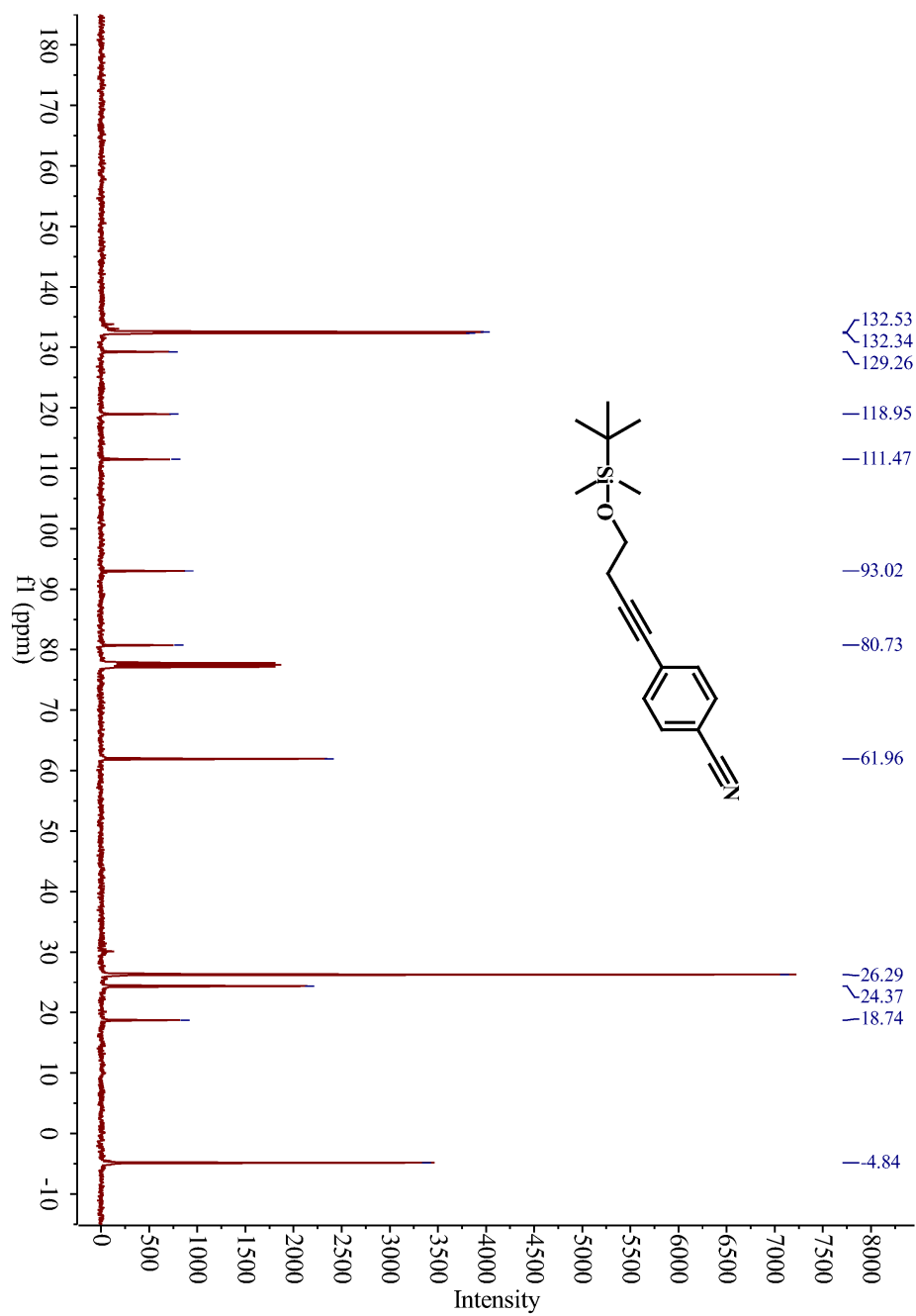


Figure B.2.6: ^{13}C spectrum of 3.

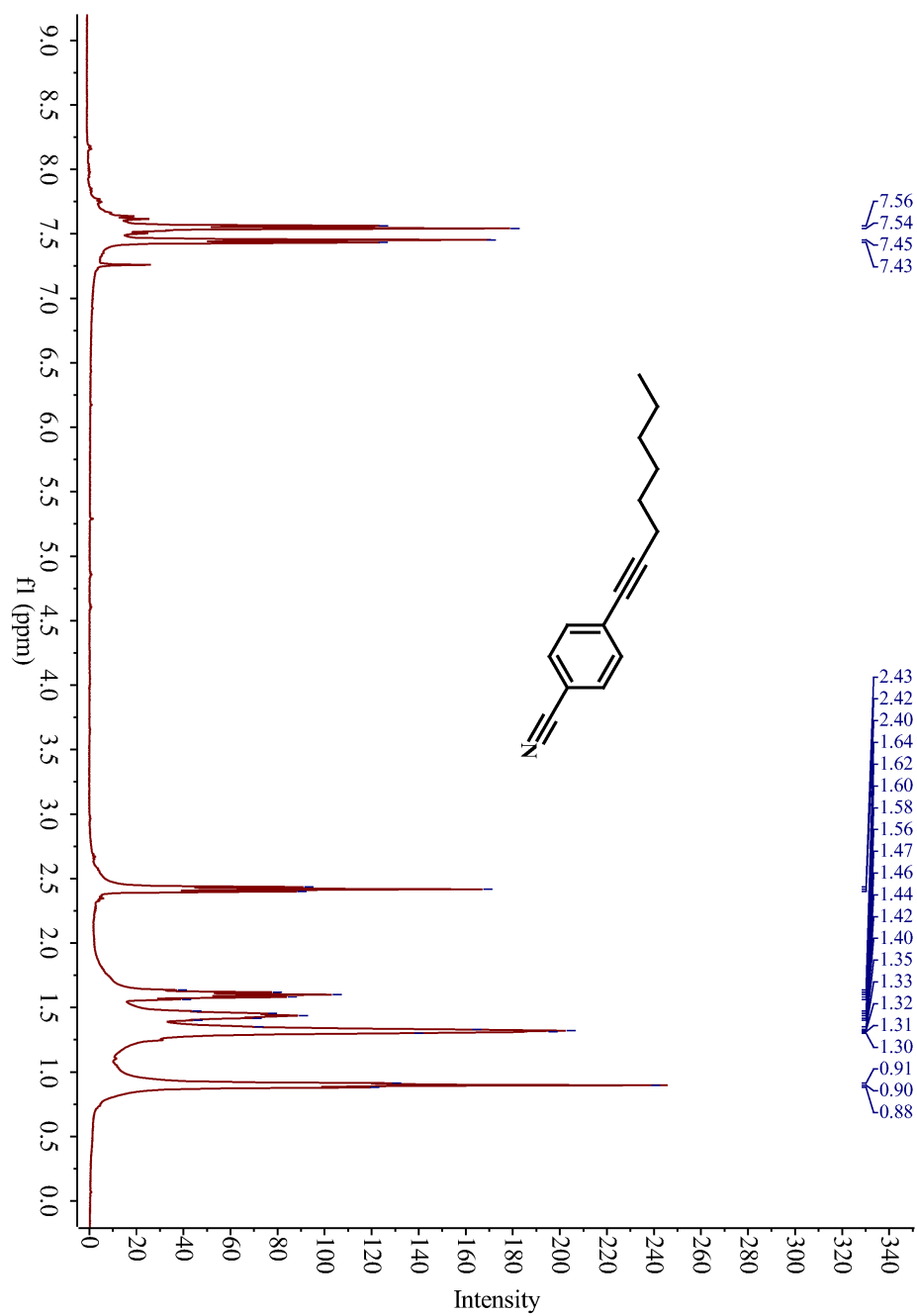


Figure B.2.7: ^1H spectrum of 4.

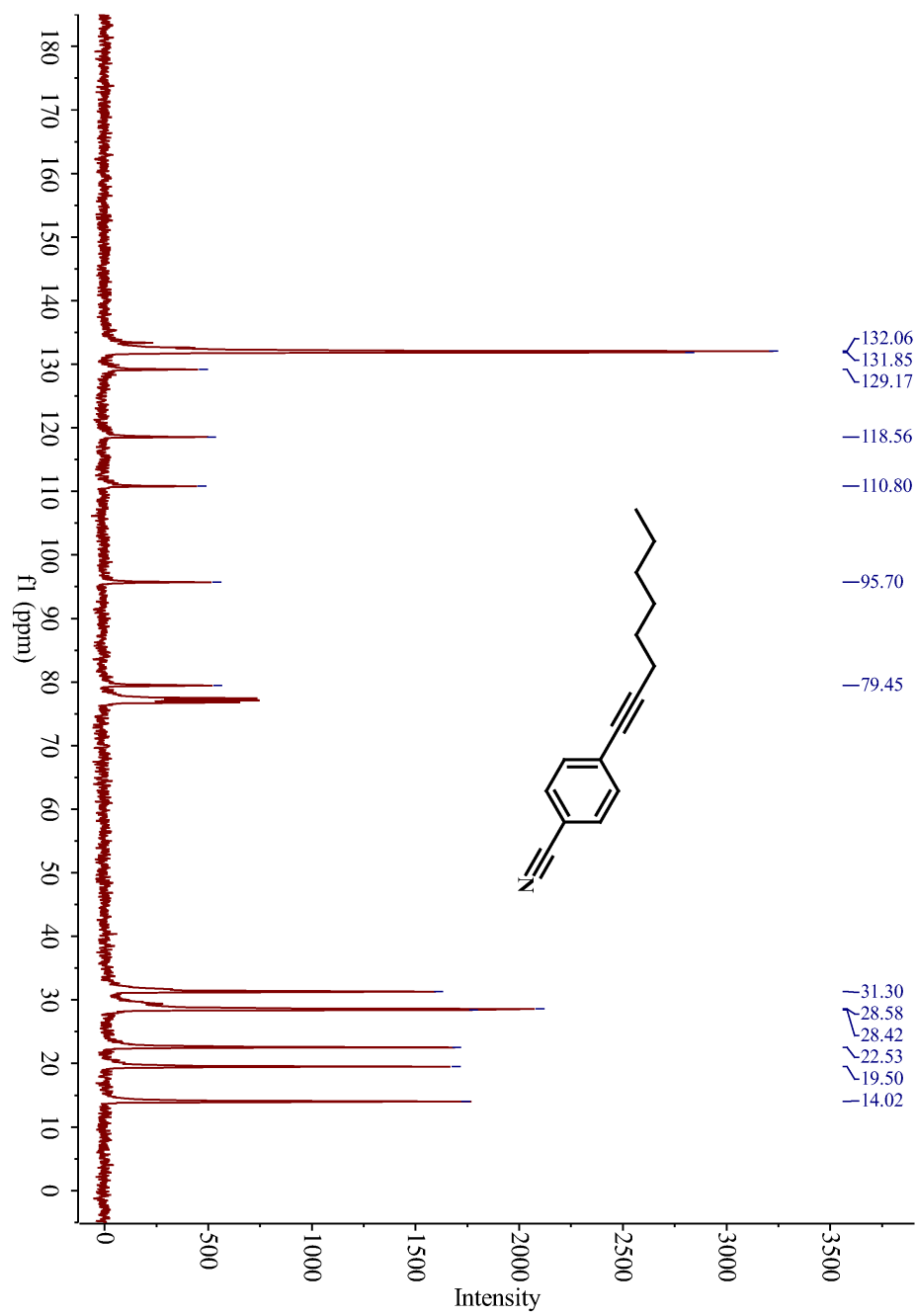


Figure B.2.8: ^{13}C spectrum of 4.

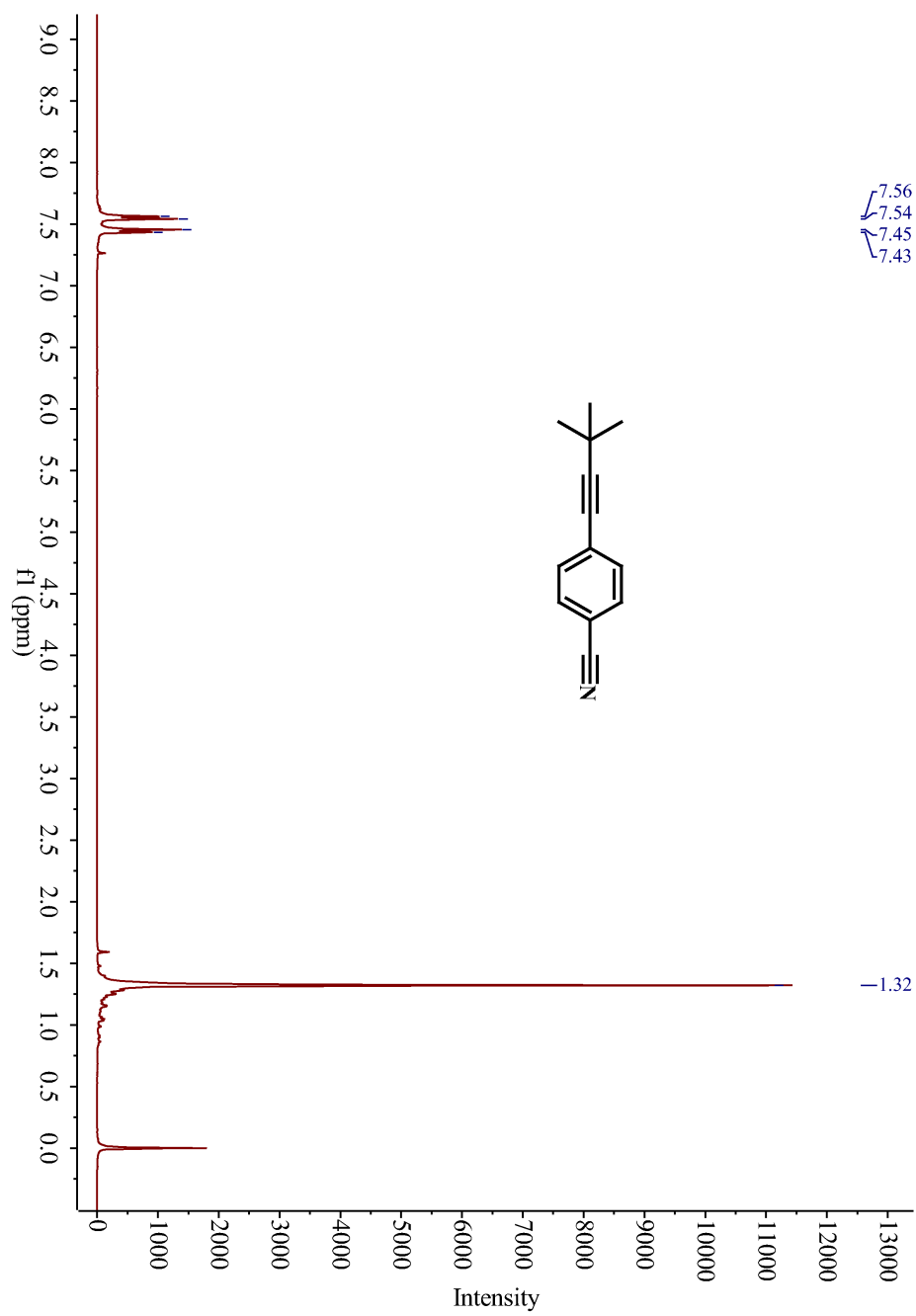


Figure B.2.9: ^1H spectrum of 5.

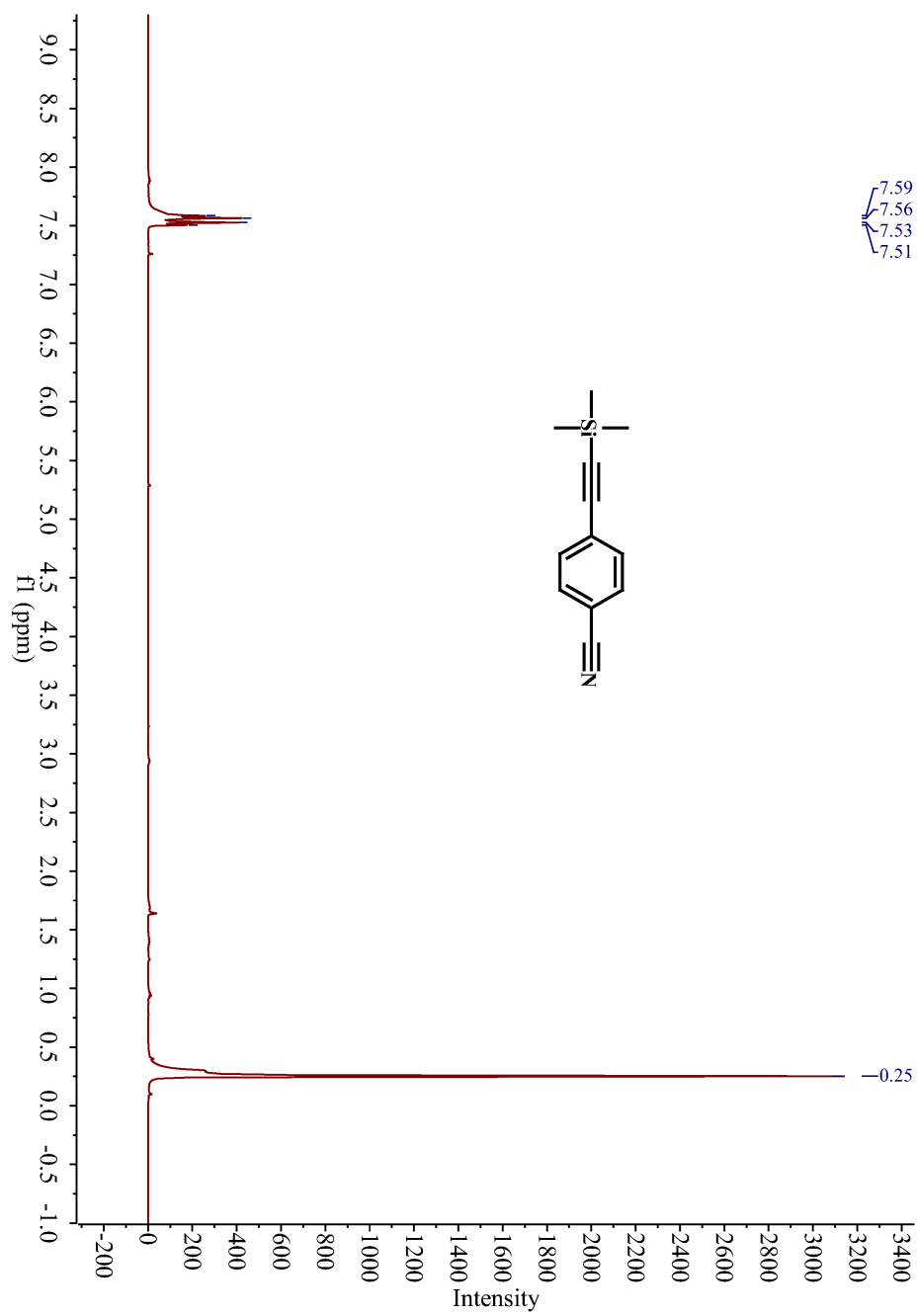


Figure B.2.10: ^1H spectrum of 6.

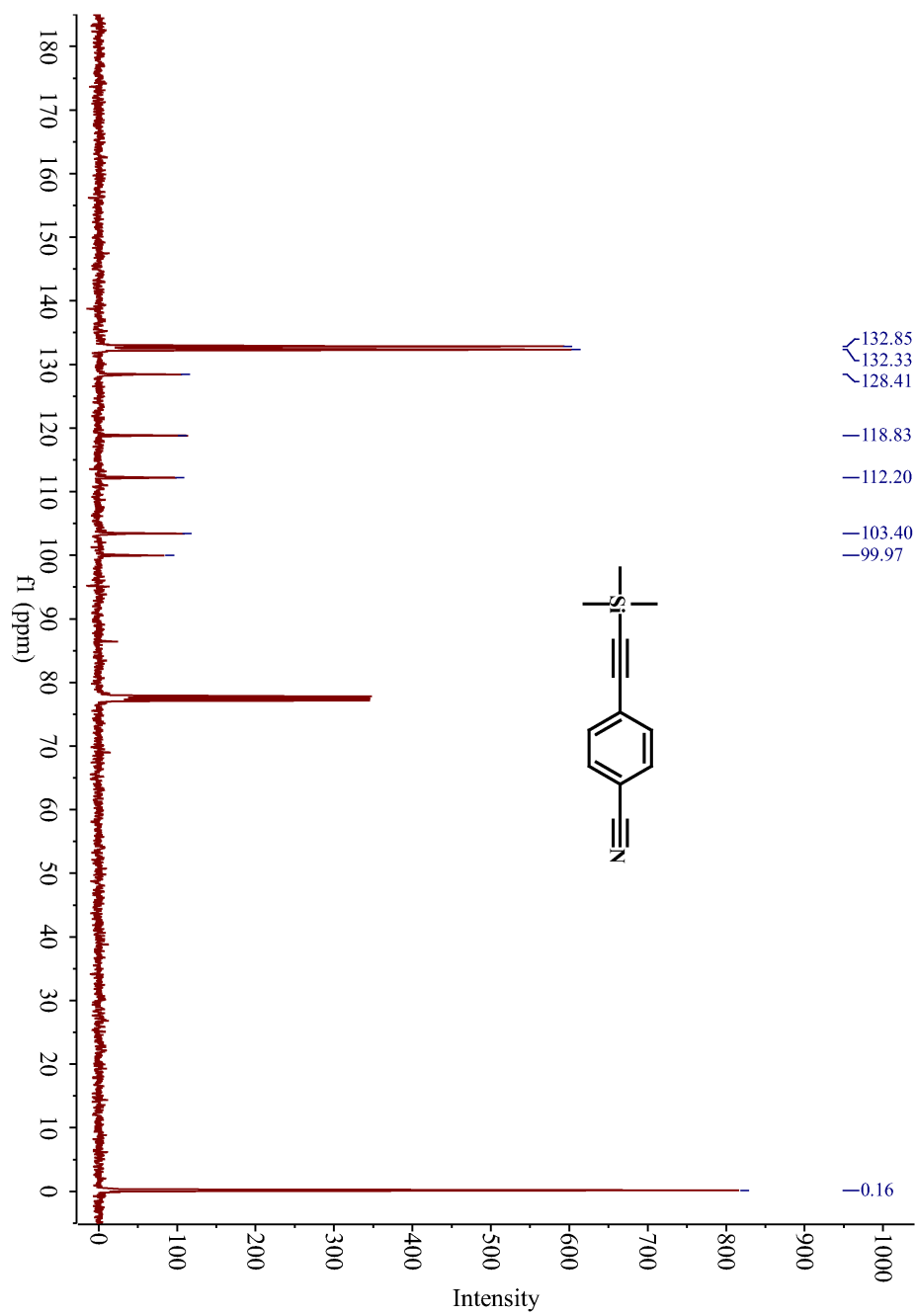


Figure B.2.11: ^{13}C spectrum of 6.

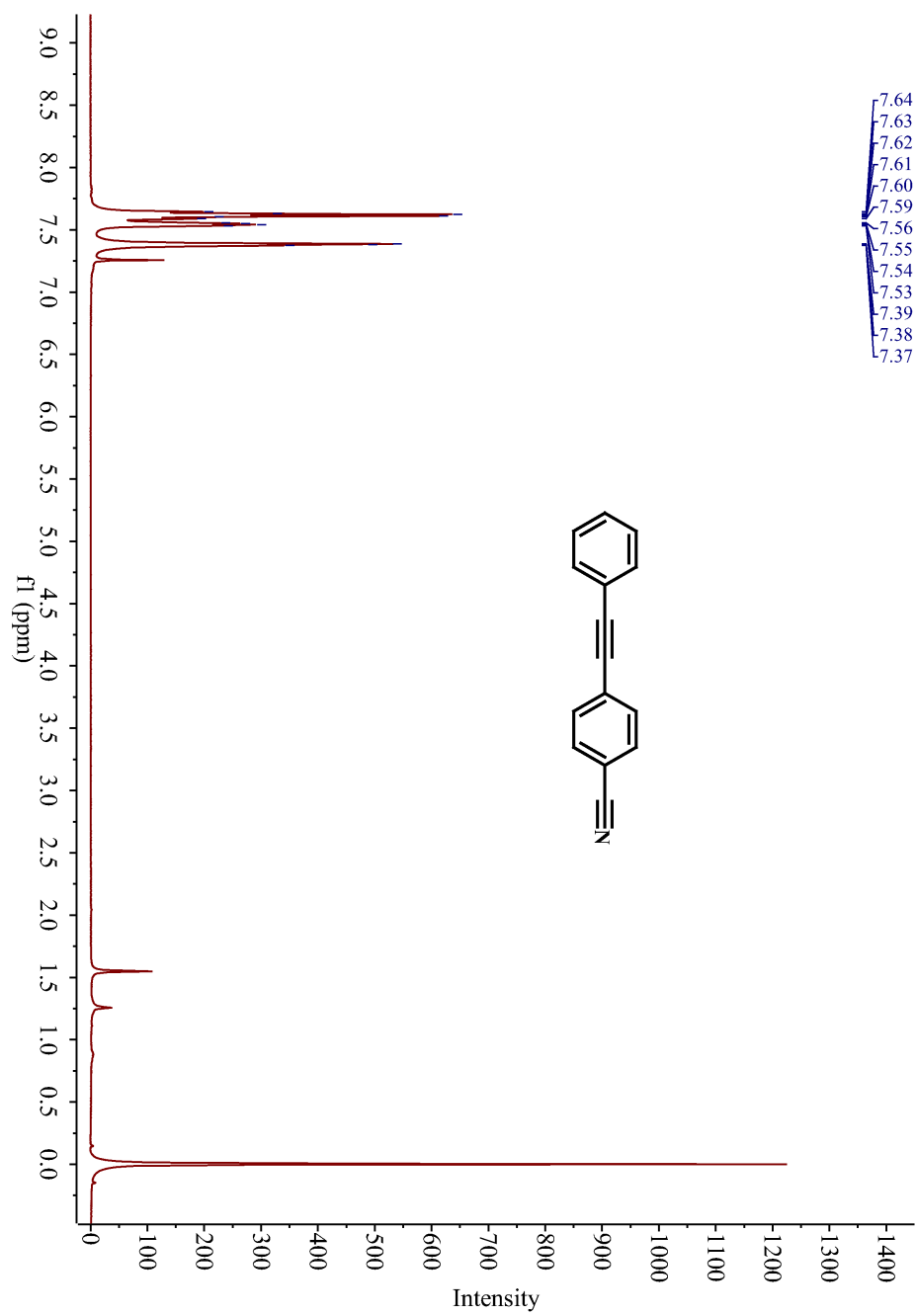


Figure B.2.12: ^1H spectrum of 7.

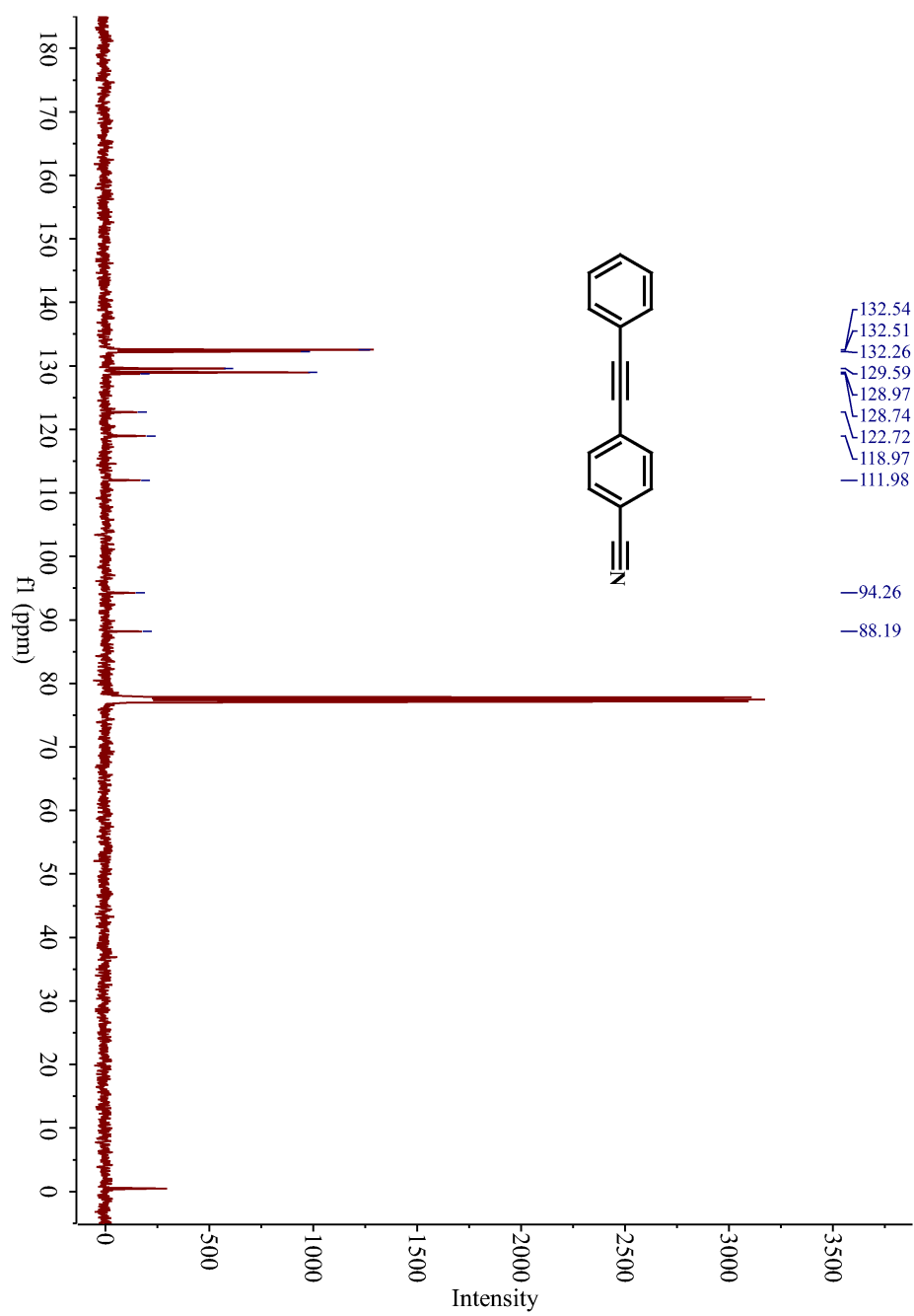


Figure B.2.13: ^{13}C spectrum of 7.

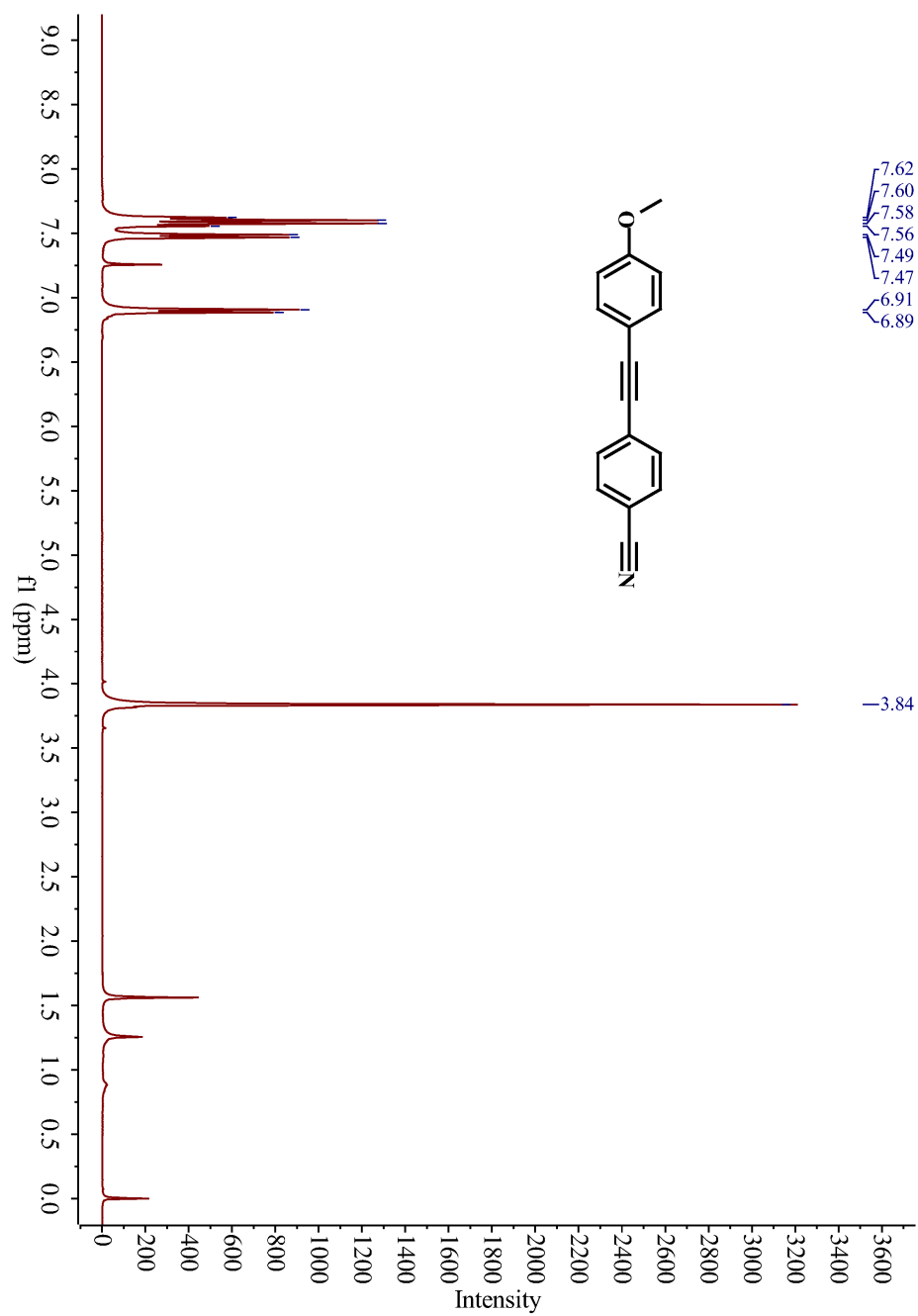


Figure B.2.14: ^1H spectrum of 8.

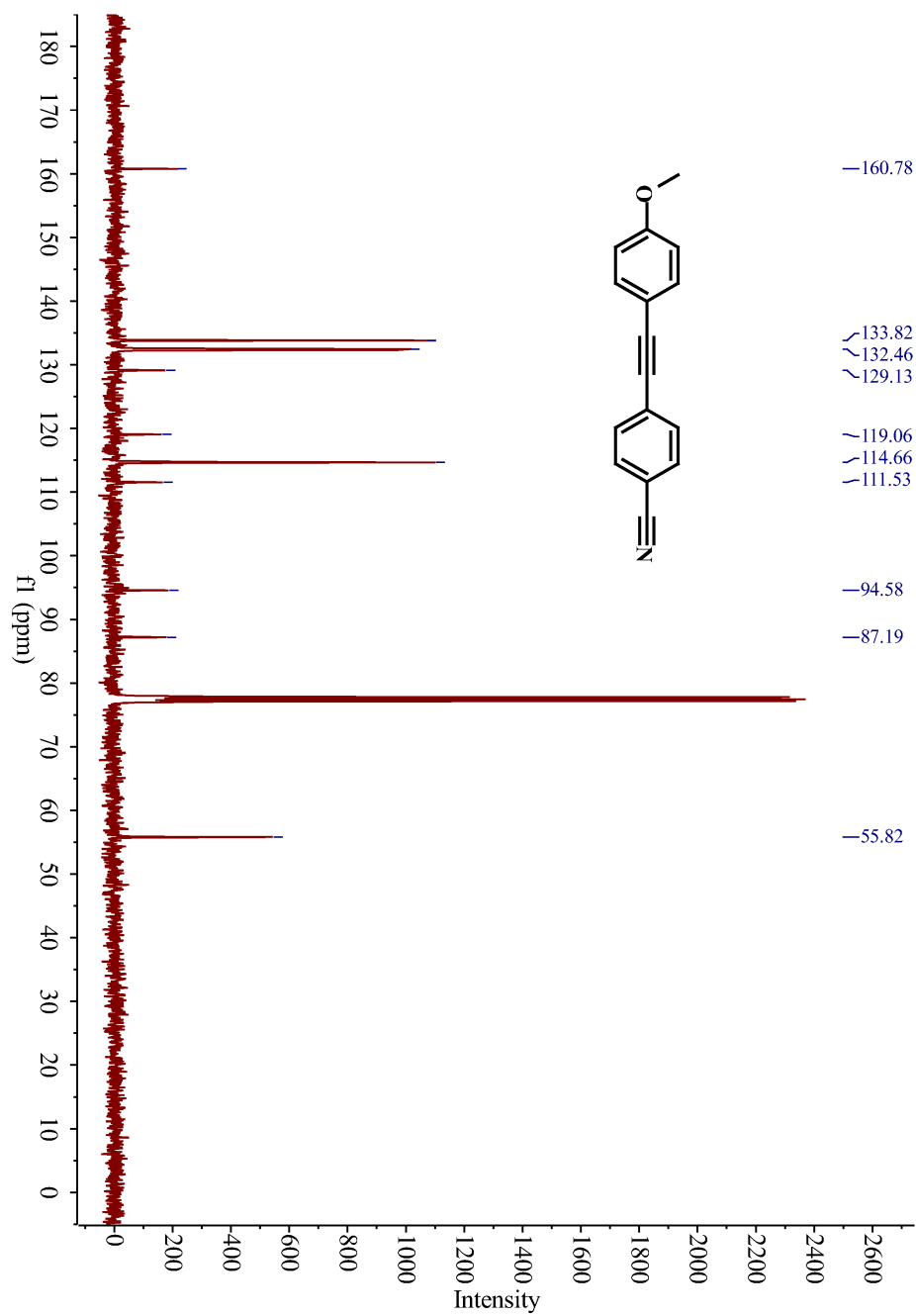


Figure B.2.15: ^{13}C spectrum of 8.

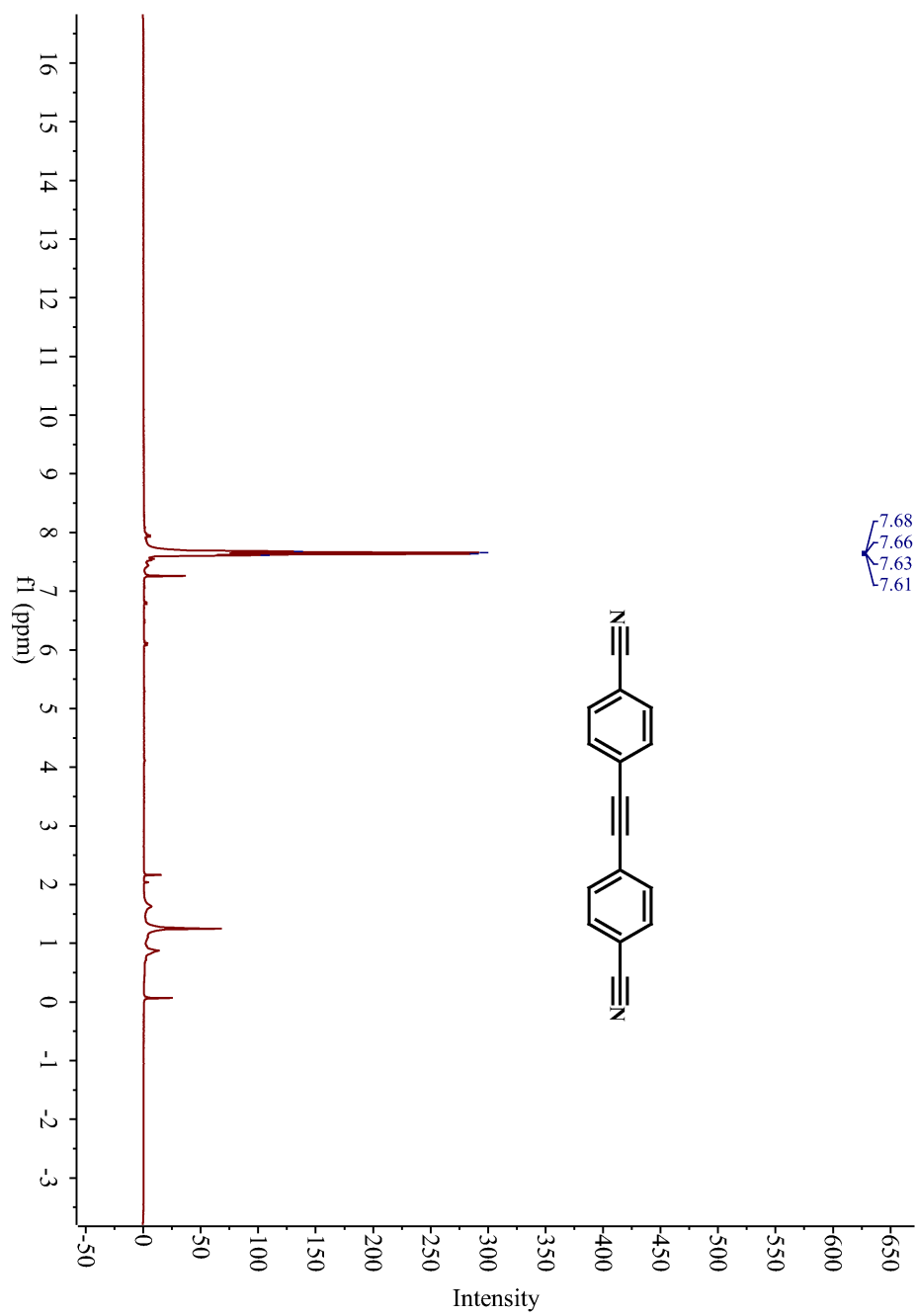


Figure B.2.16: ^1H spectrum of 9.

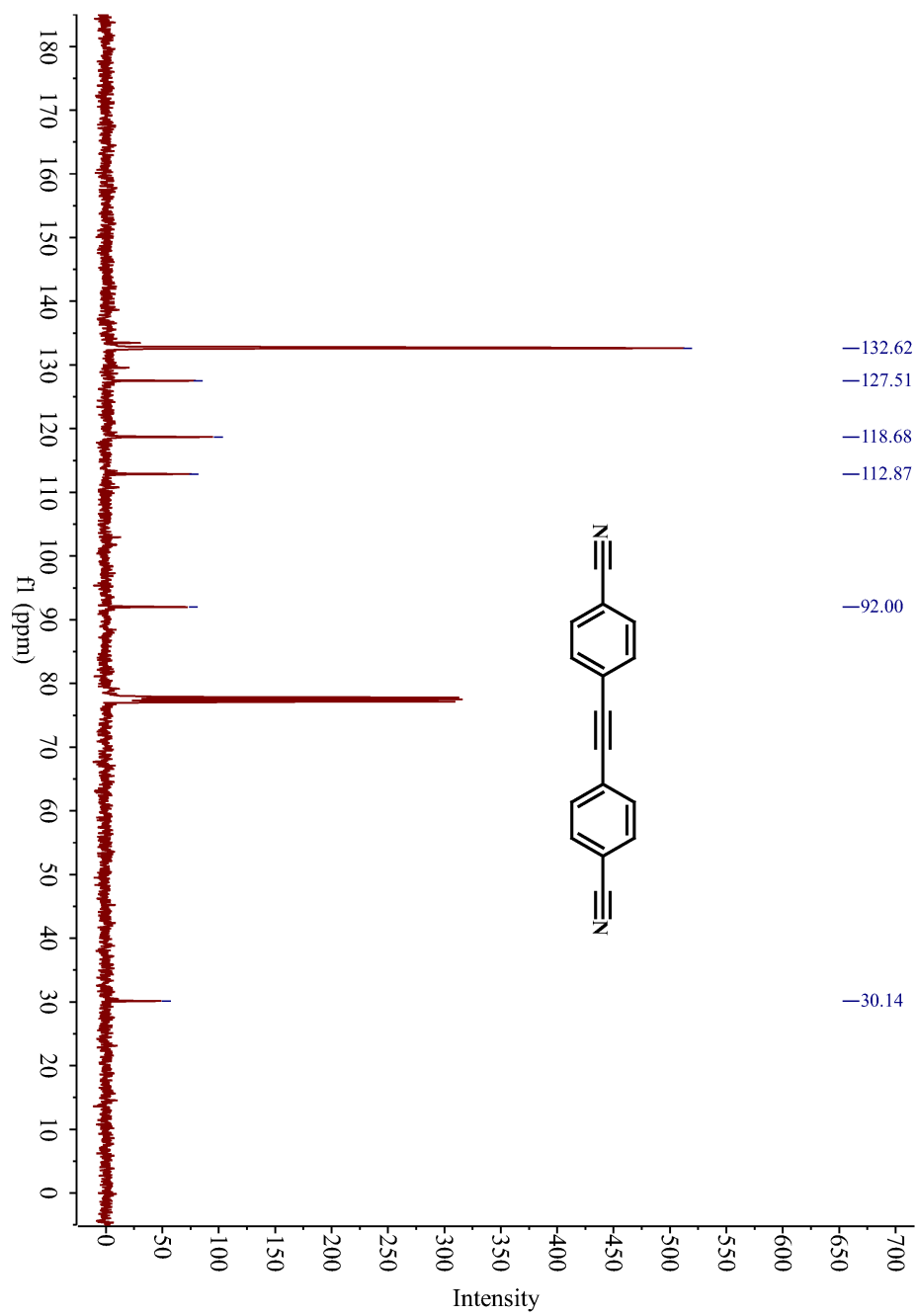


Figure B.2.17: ^{13}C spectrum of 9.

Appendix C

Representative NMR Spectra of compounds from Chapter 4

Below, we show ^1H and ^{13}C NMR spectra for the compounds listed in Table 4.2. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, on a Bruker Avance 400 instrument. Chemical shifts are measured with respect to the residual protons in the deuterated solvents.

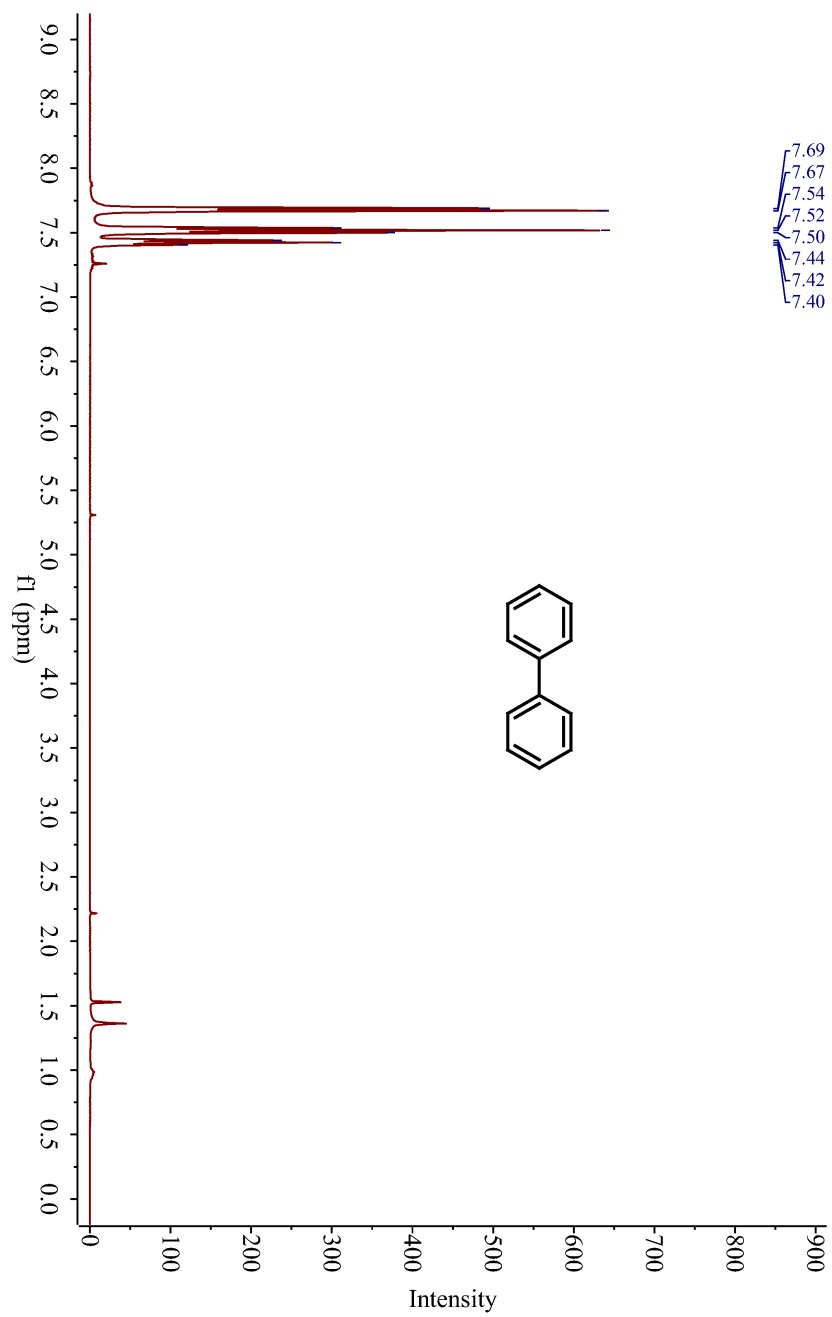


Figure C.0.1: ^1H spectrum of 1.

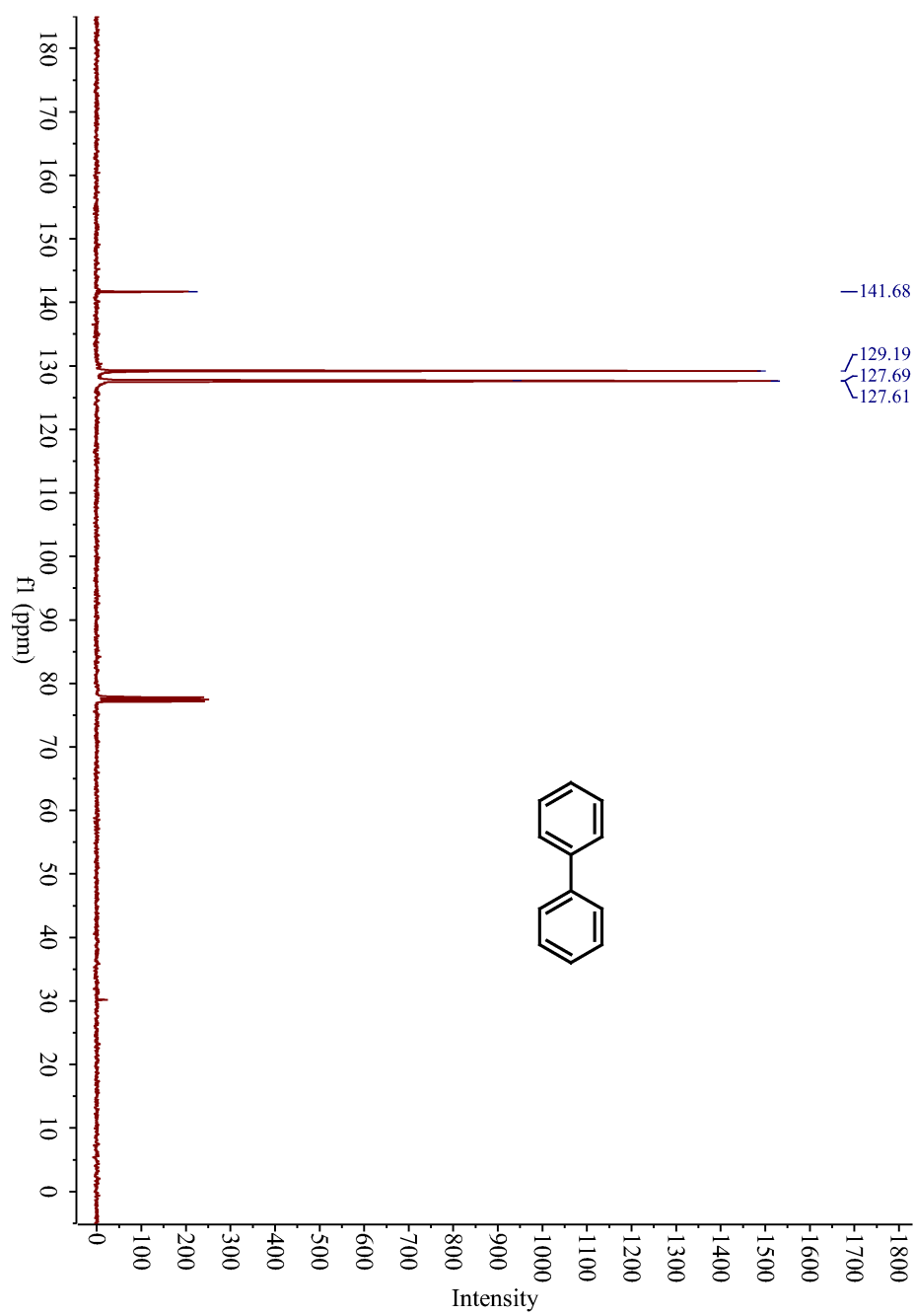


Figure C.0.2: ^{13}C spectrum of 1.

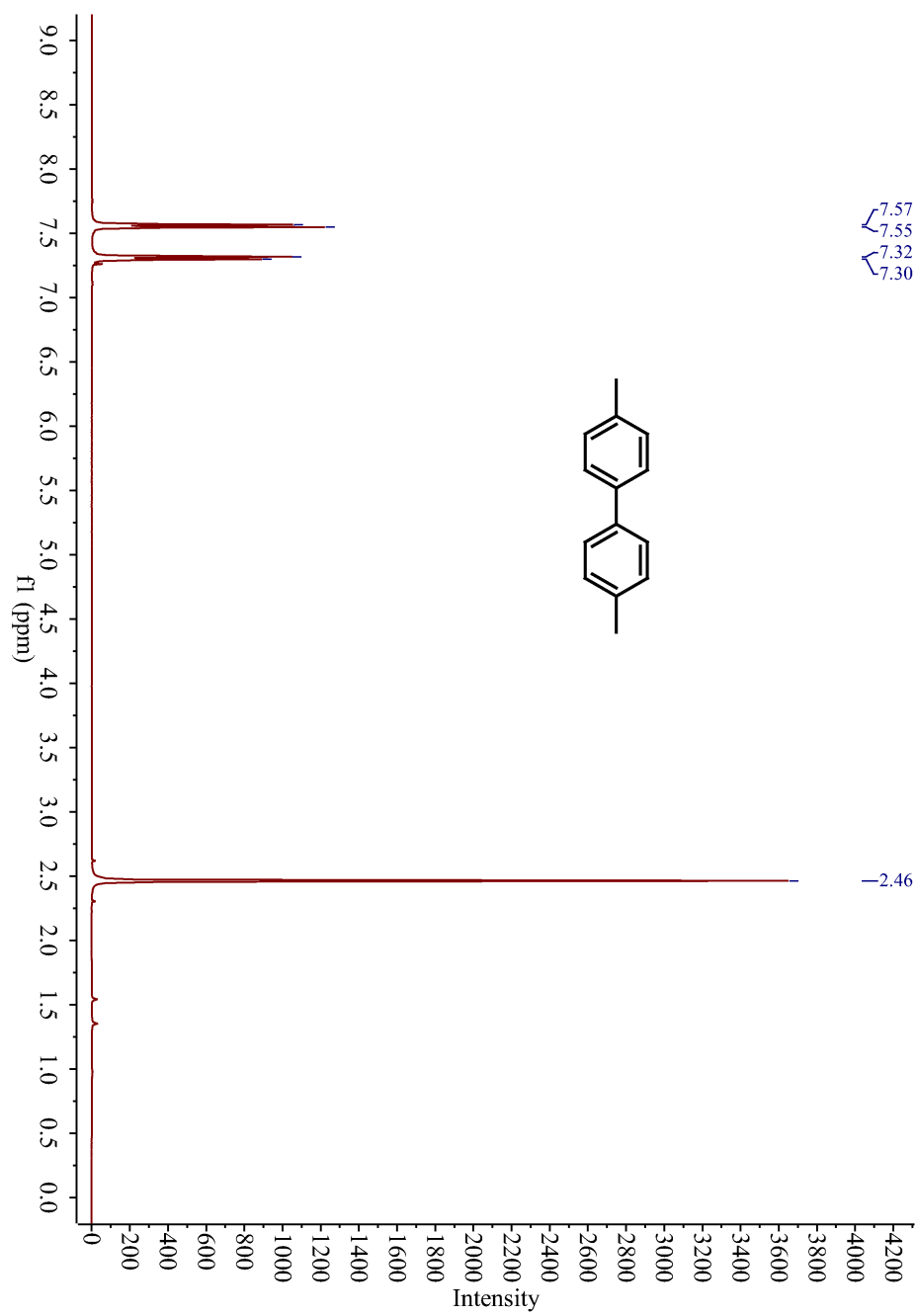


Figure C.0.3: ^1H spectrum of 2.

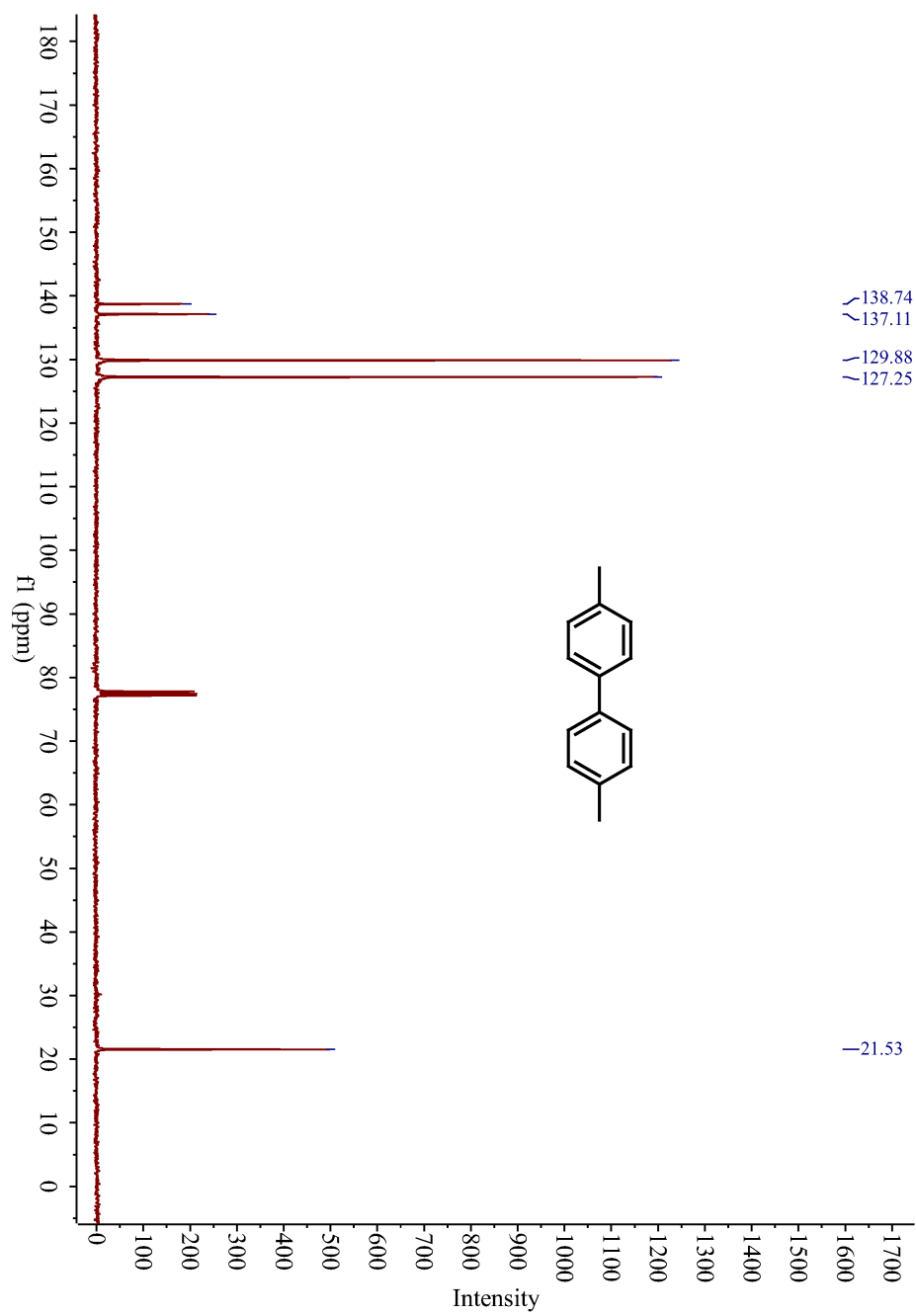


Figure C.0.4: ^{13}C spectrum of 2.

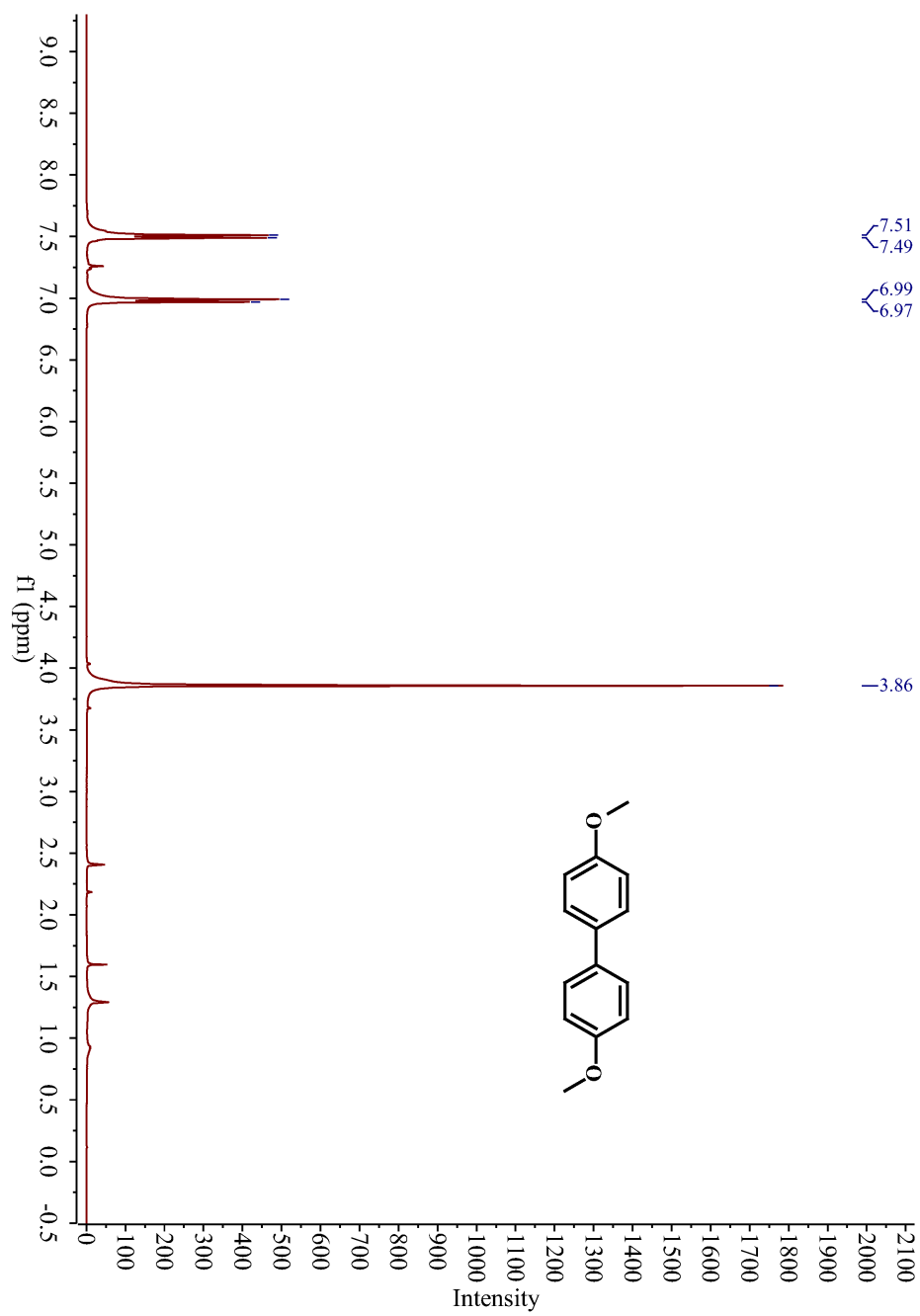


Figure C.0.5: ^1H spectrum of 3.

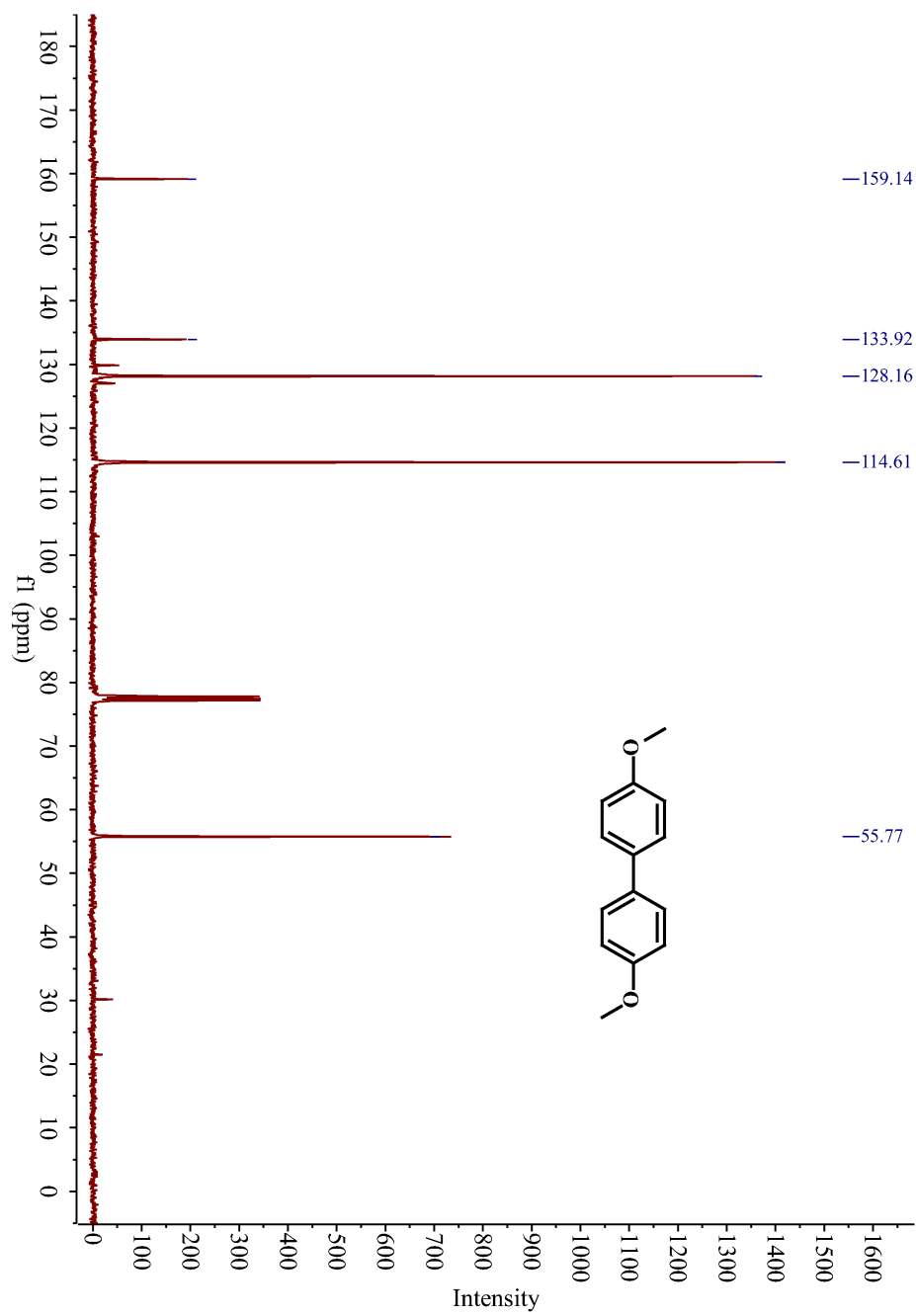


Figure C.0.6: ^{13}C spectrum of 3.

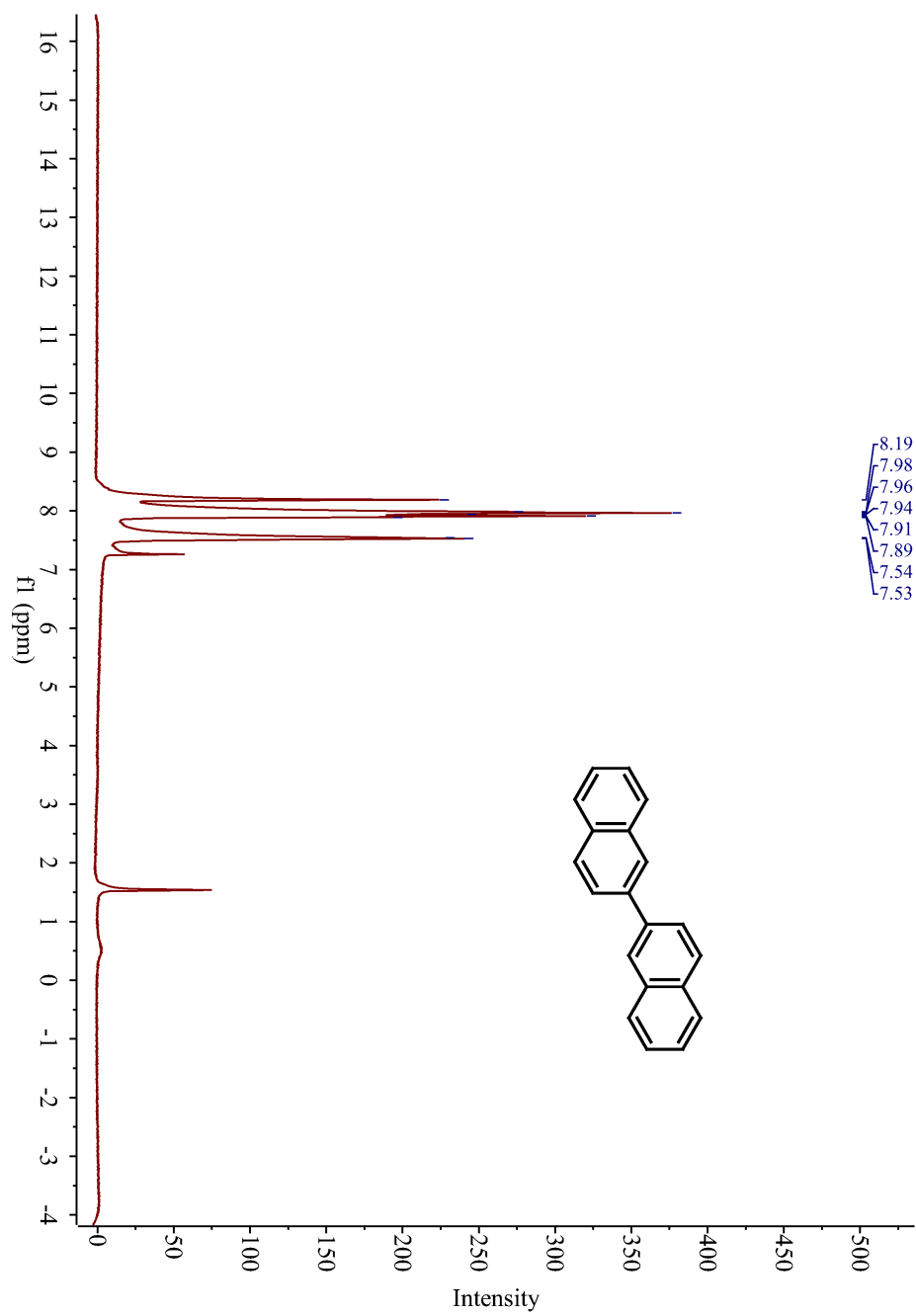


Figure C.0.7: ^1H spectrum of 4.

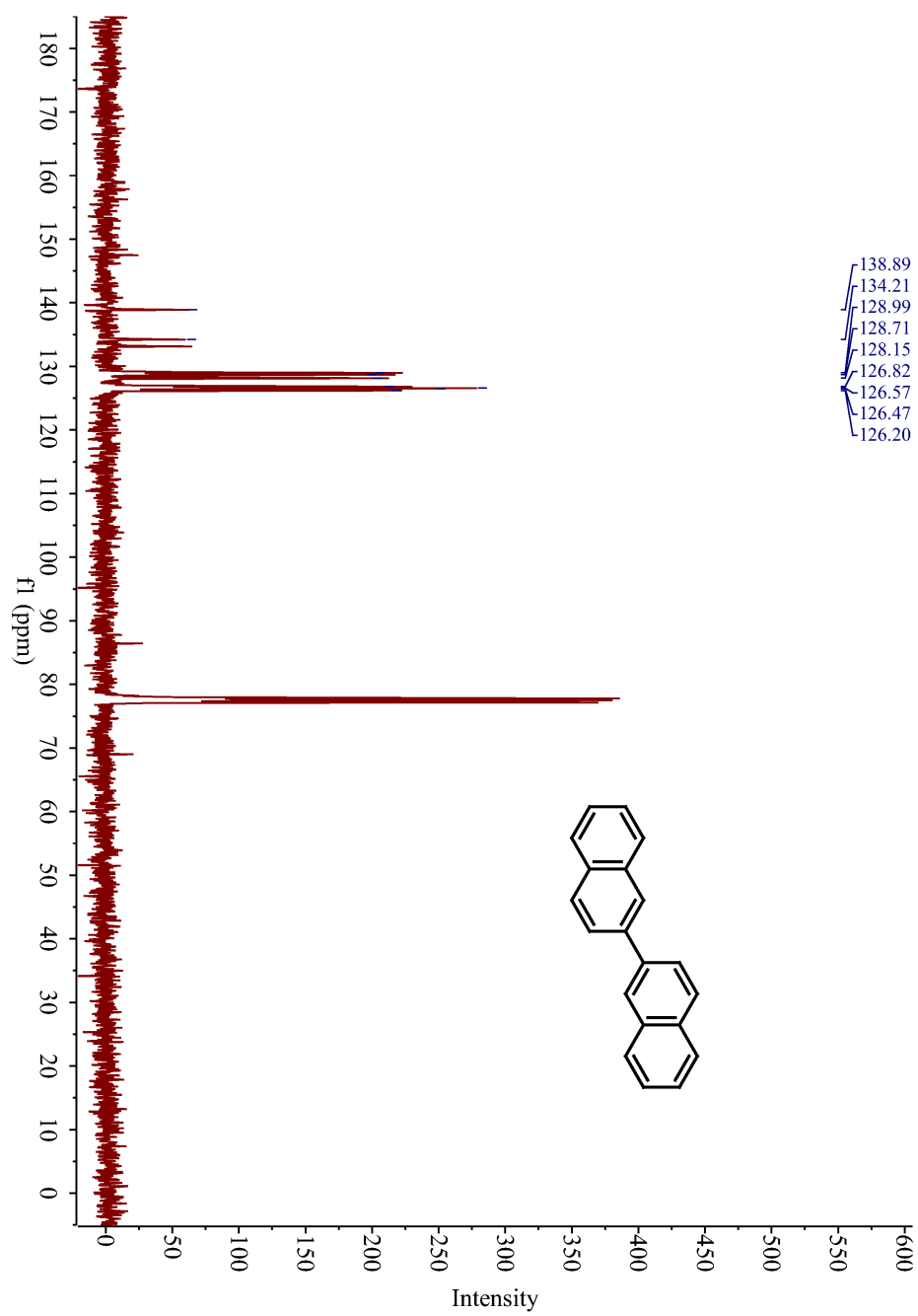


Figure C.0.8: ^{13}C spectrum of 4.

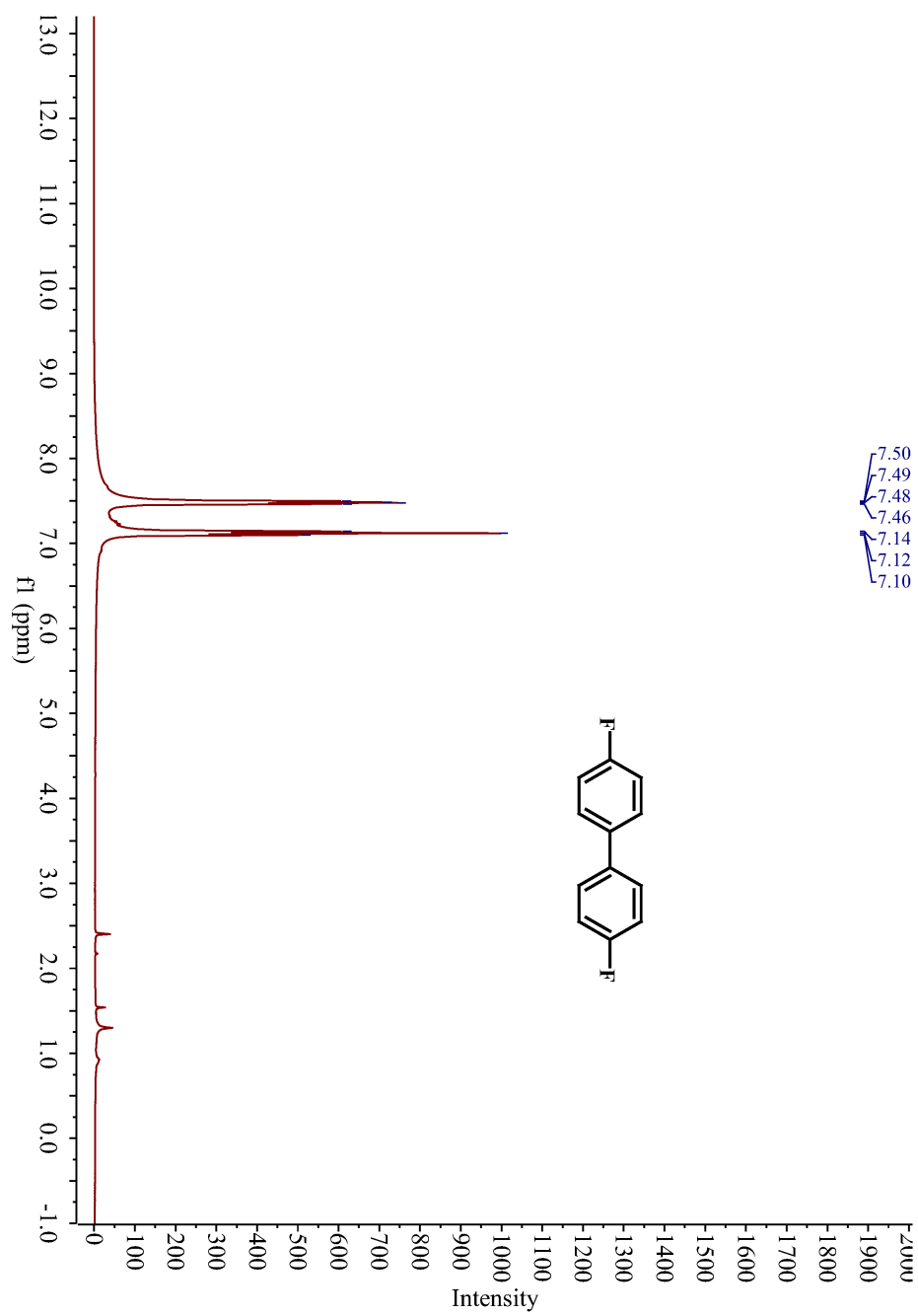


Figure C.0.9: ^1H spectrum of 5.

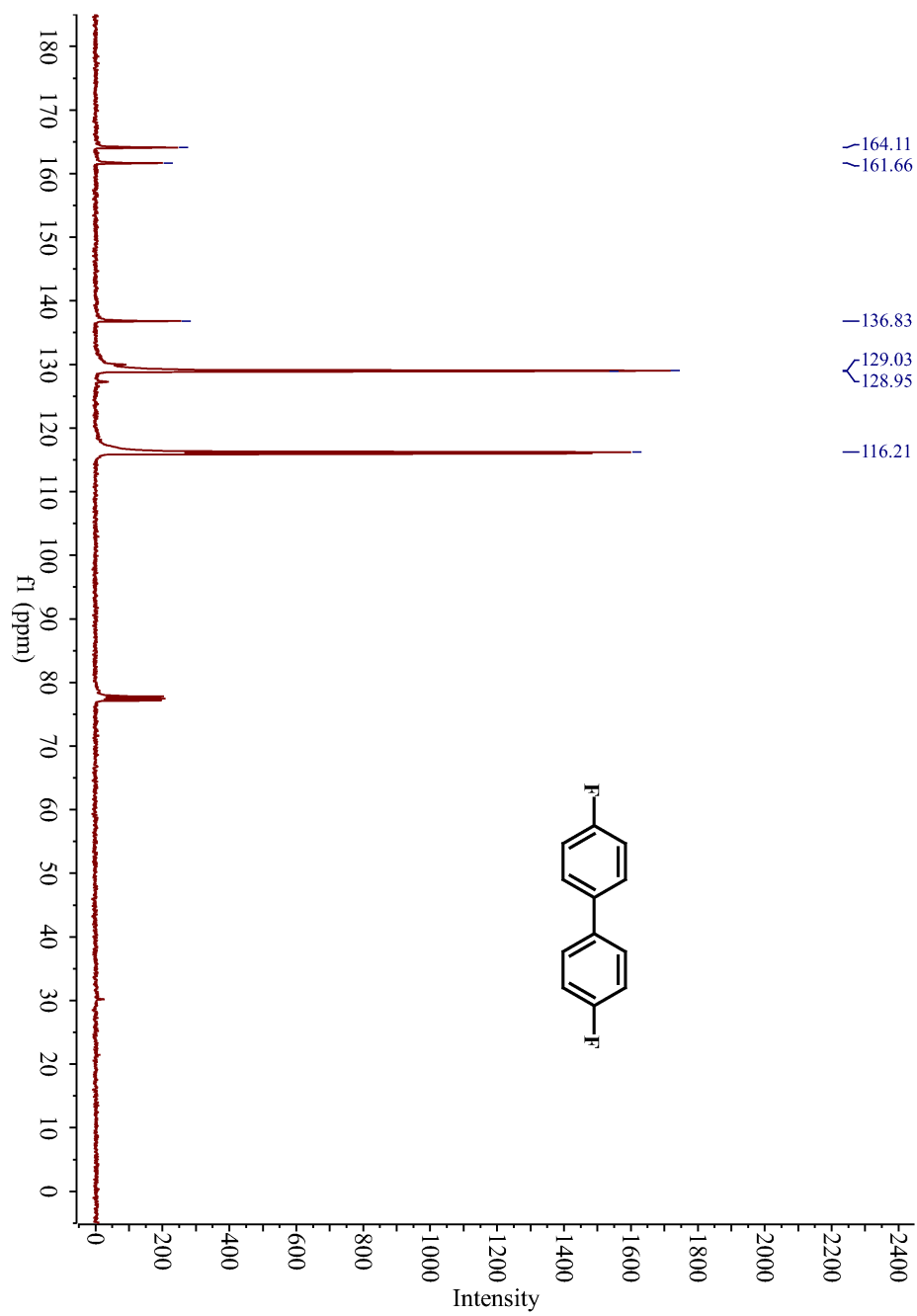


Figure C.0.10: ^{13}C spectrum of 5.

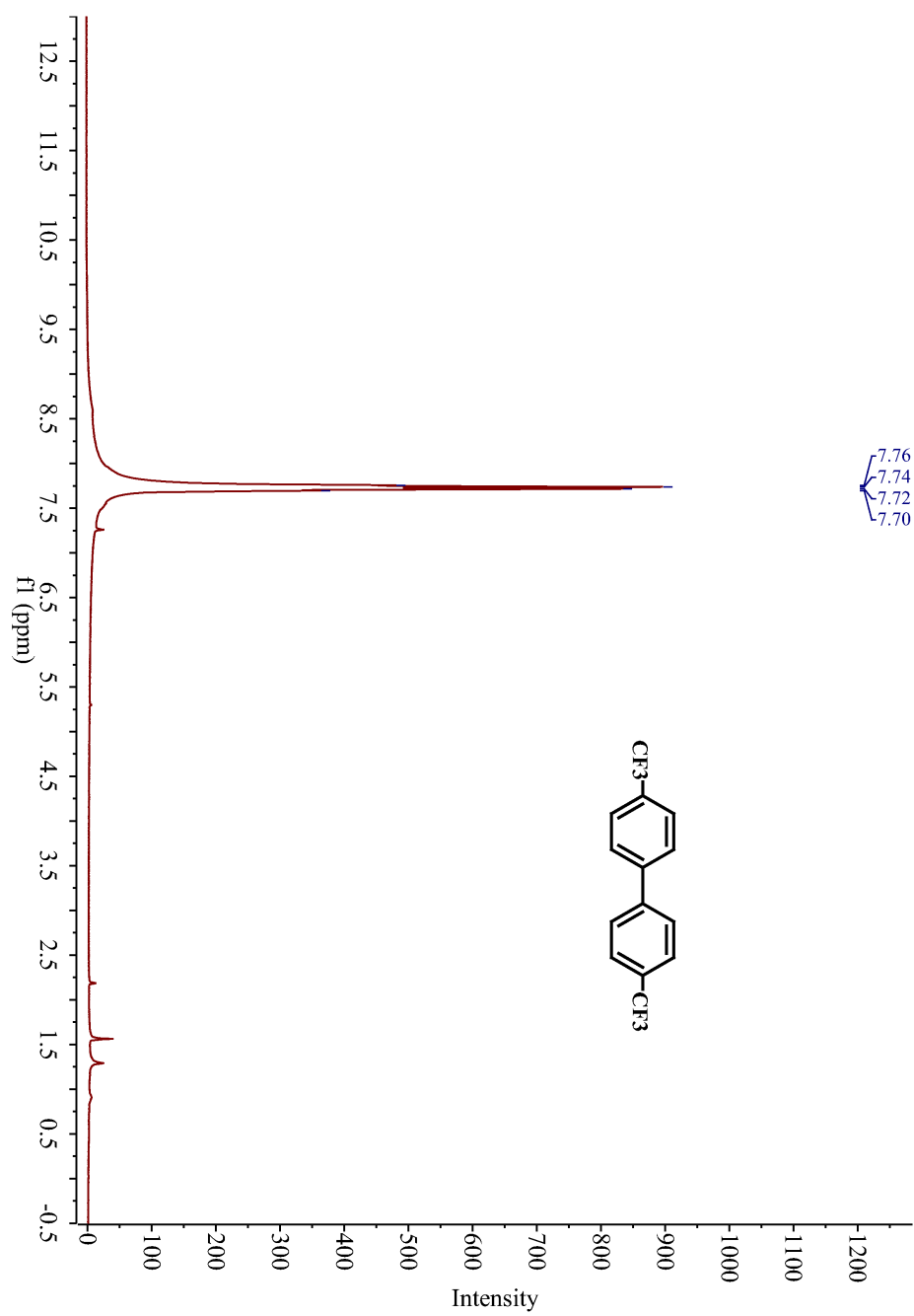


Figure C.0.11: ^1H spectrum of 6.

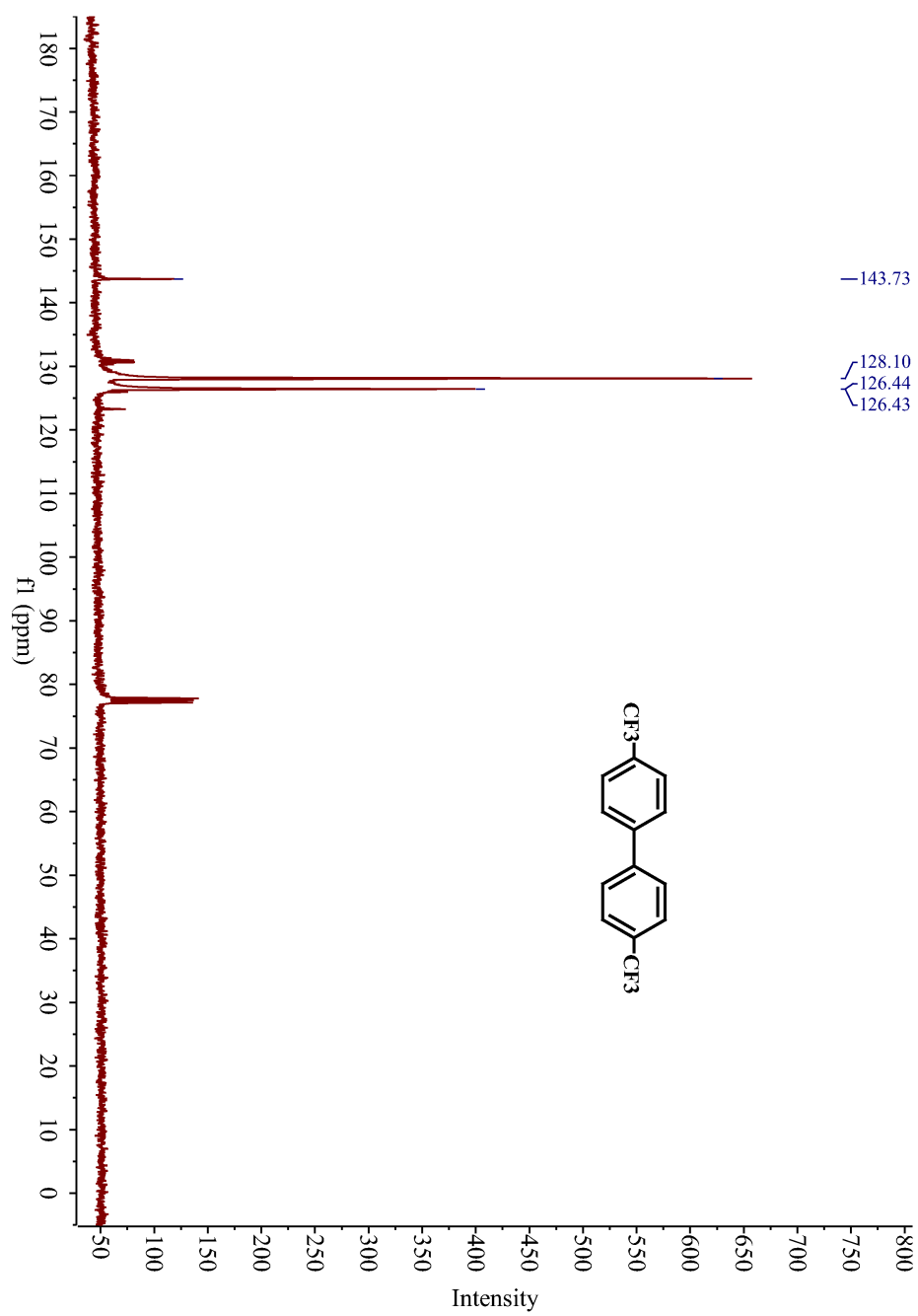


Figure C.0.12: ^{13}C spectrum of 6.

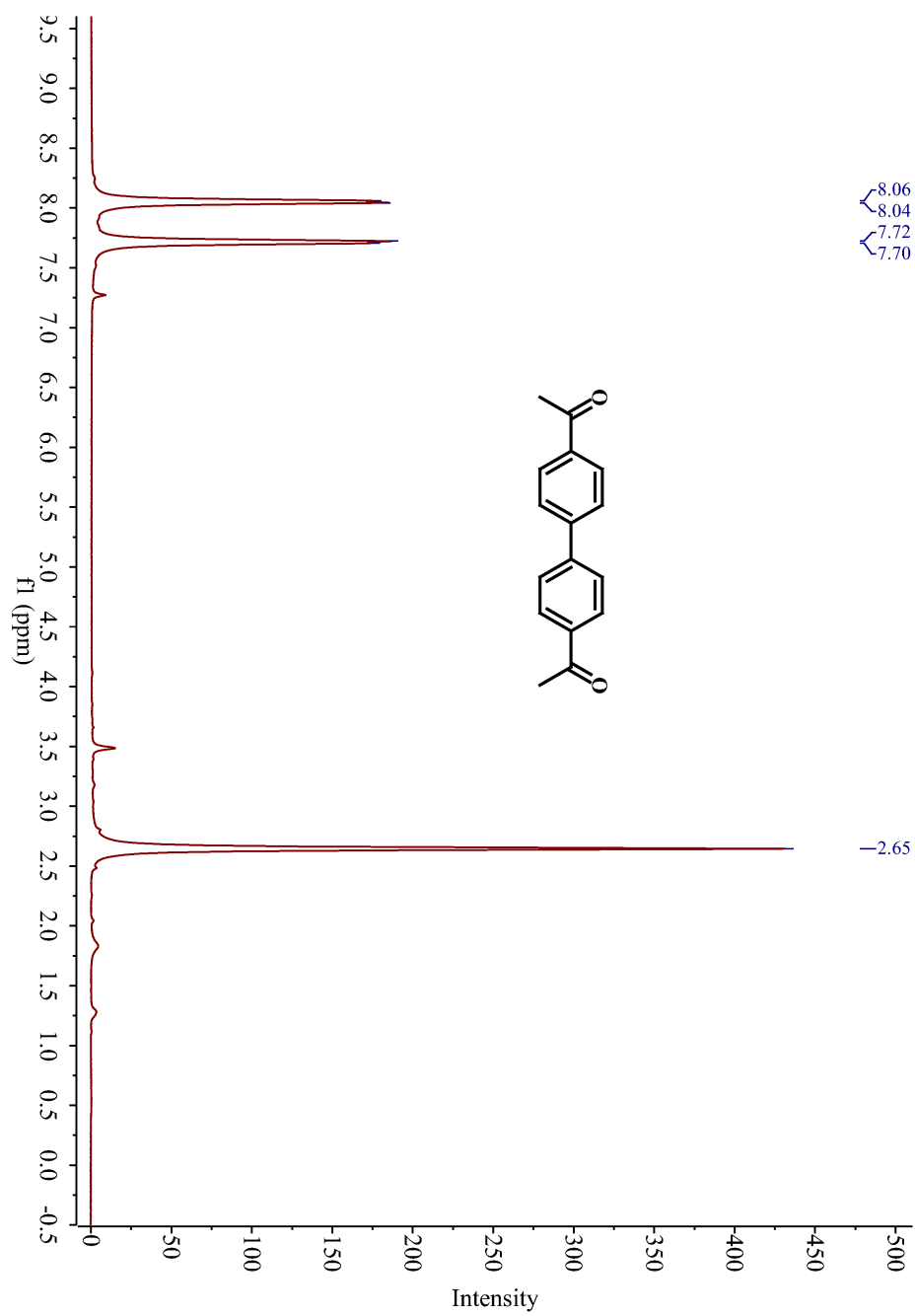


Figure C.0.13: ^1H spectrum of 7.

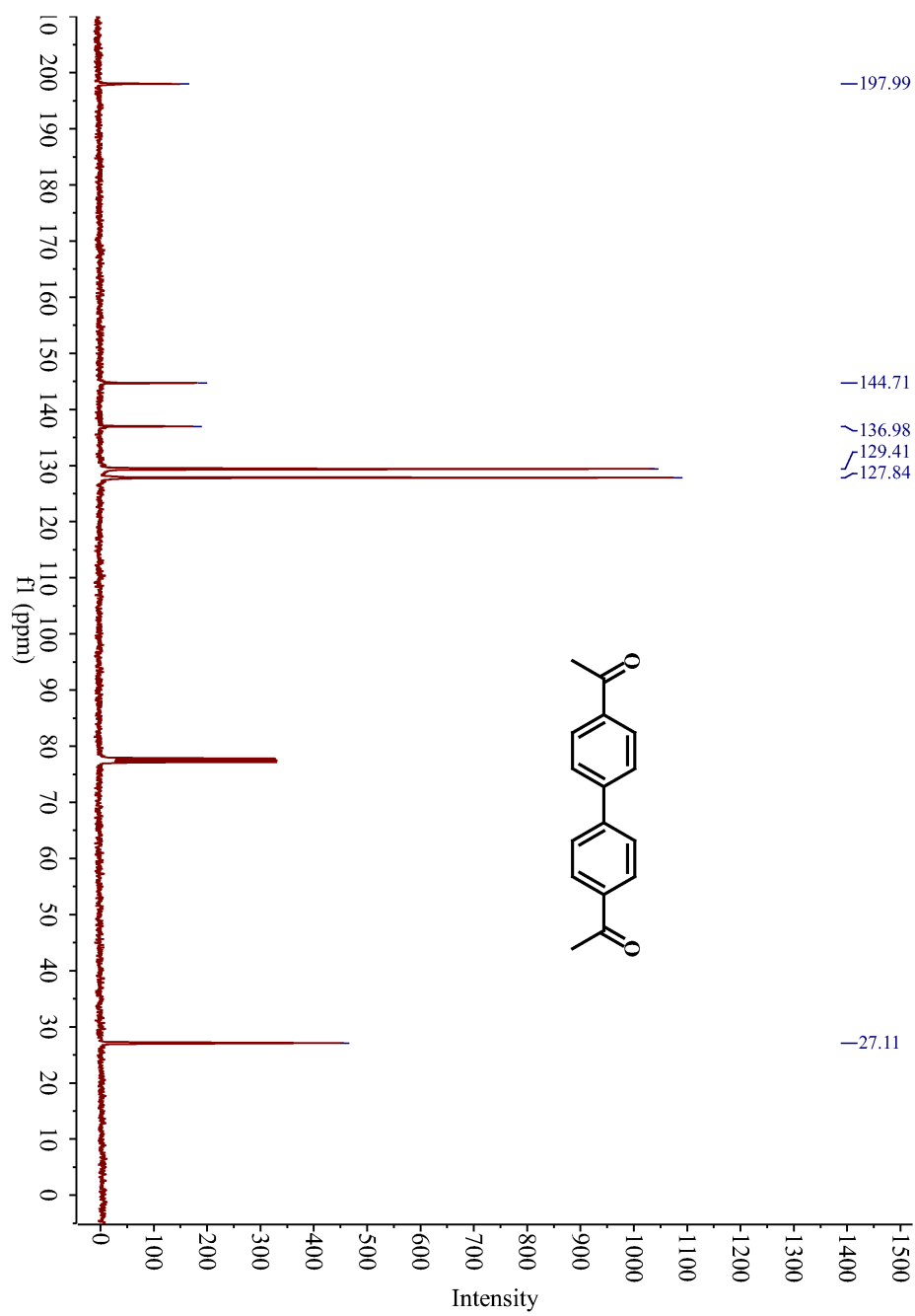


Figure C.0.14: ^{13}C spectrum of 7.

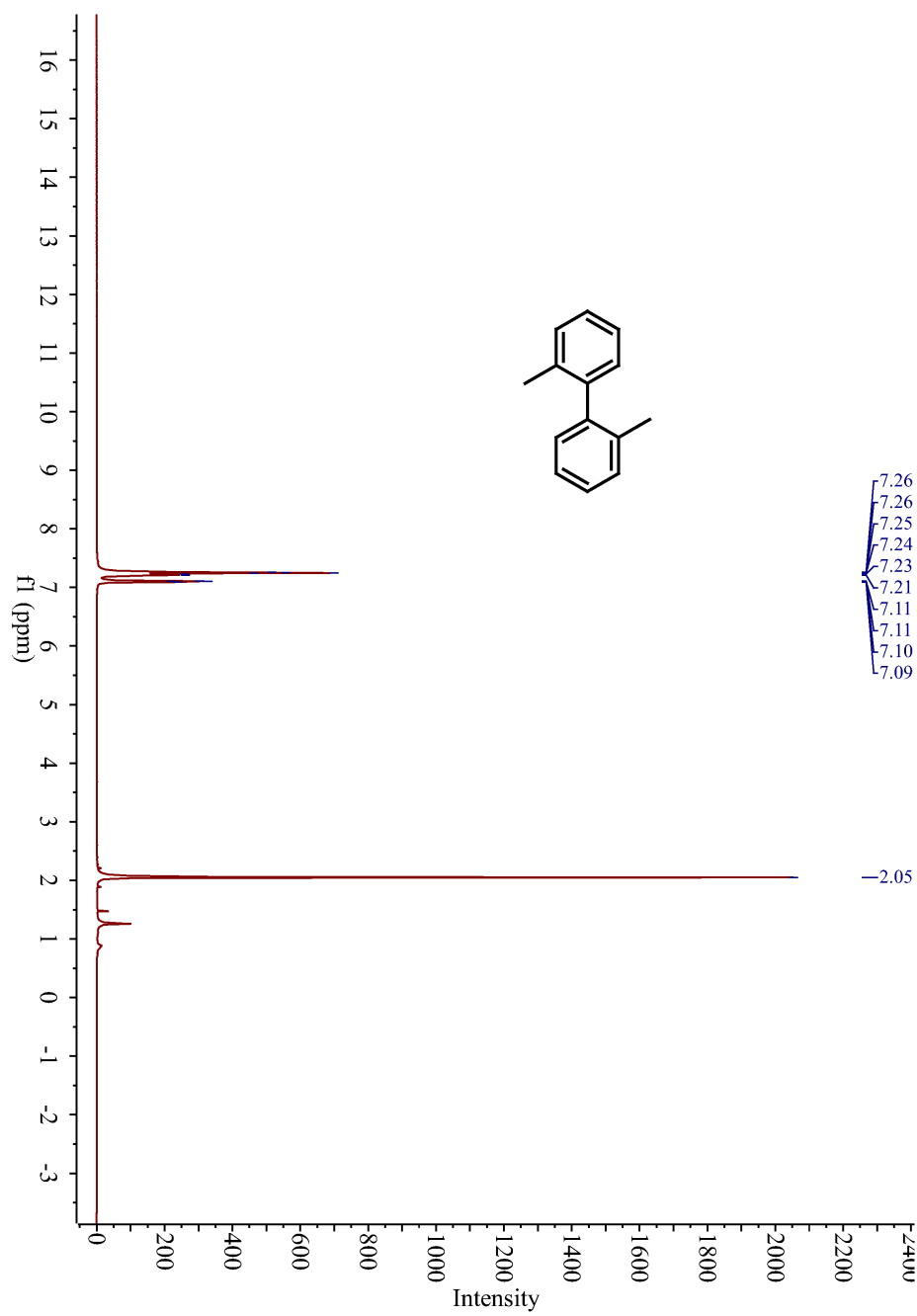


Figure C.0.15: ^1H spectrum of 8.

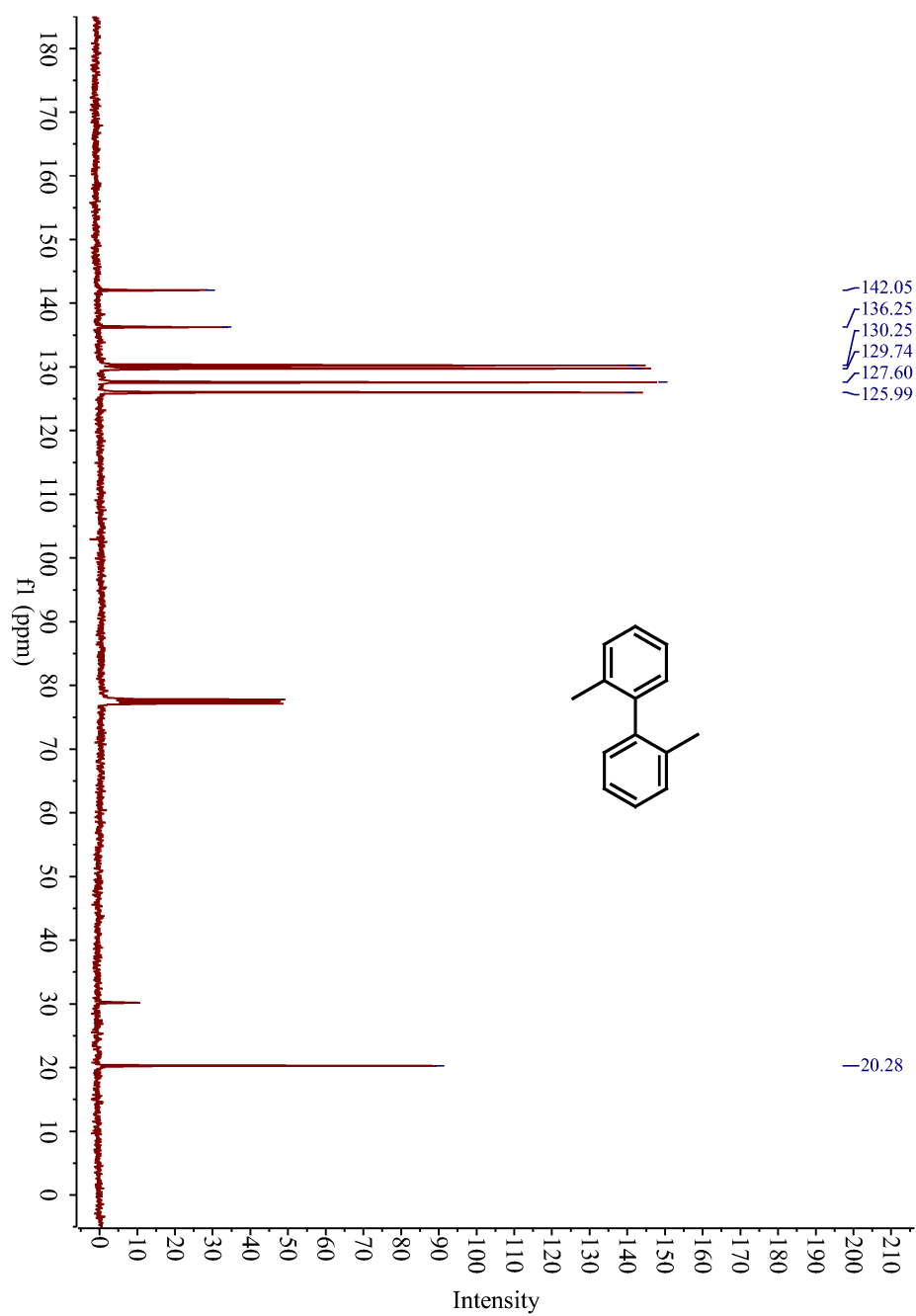


Figure C.0.16: ^{13}C spectrum of 8.

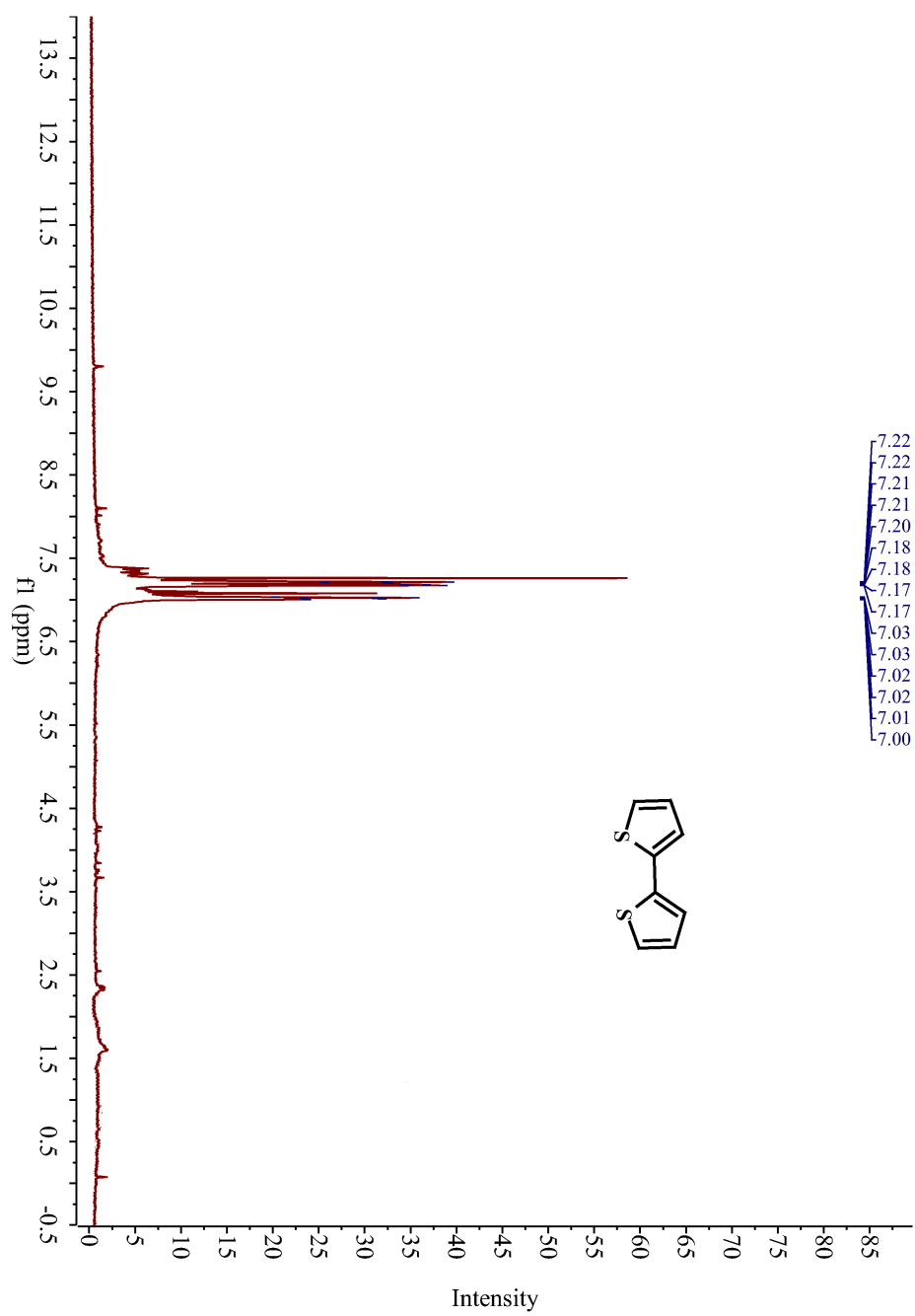


Figure C.0.17: ^1H spectrum of 9.

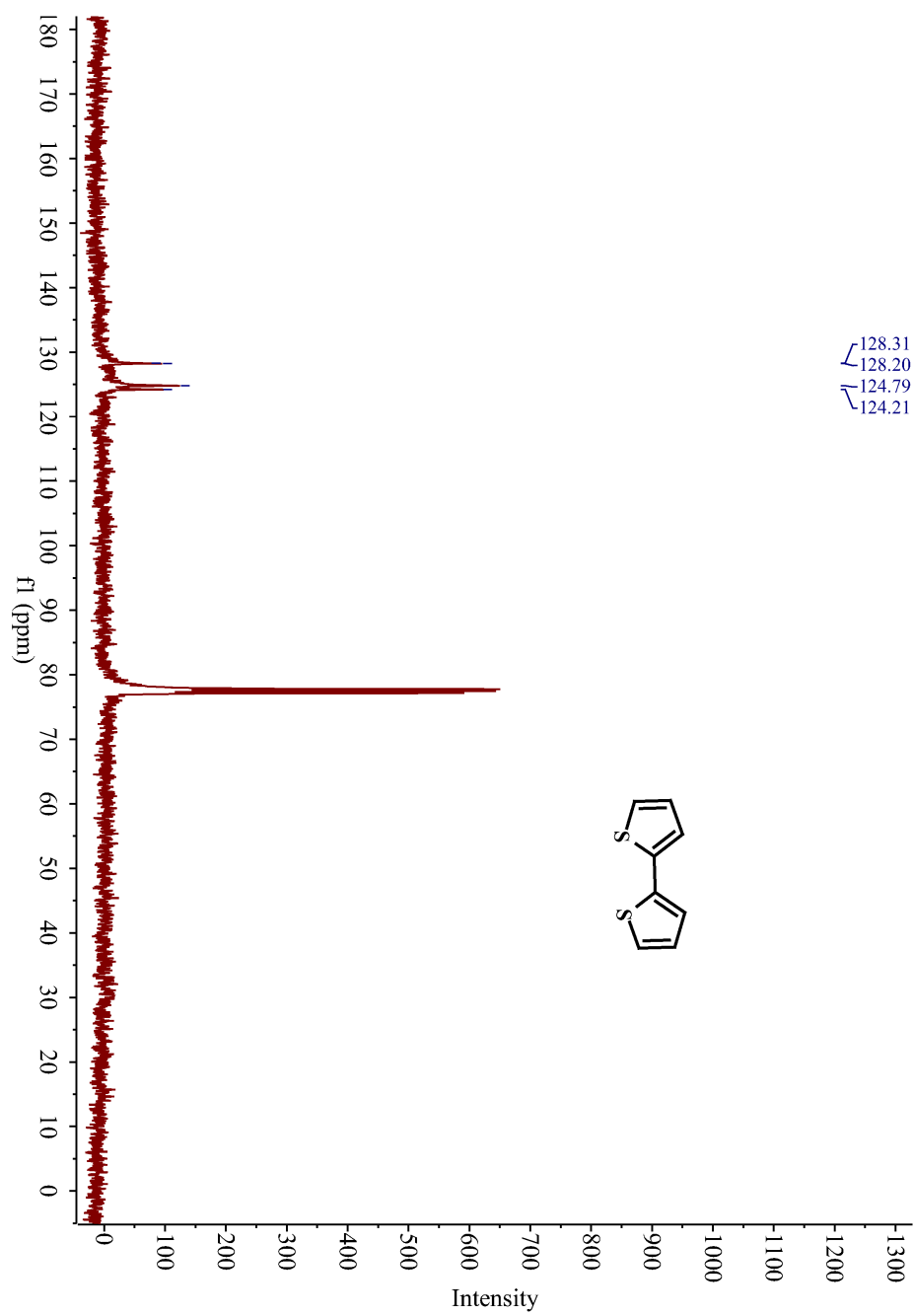


Figure C.0.18: ^{13}C spectrum of 9.

Appendix D

Representative NMR Spectra of compounds from Chapter 5

Below, we show ^1H and ^{13}C NMR spectra for the compounds listed in Table 5.1. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, on a Bruker Avance 400 instrument. Chemical shifts are measured with respect to the residual protons in the deuterated solvents.

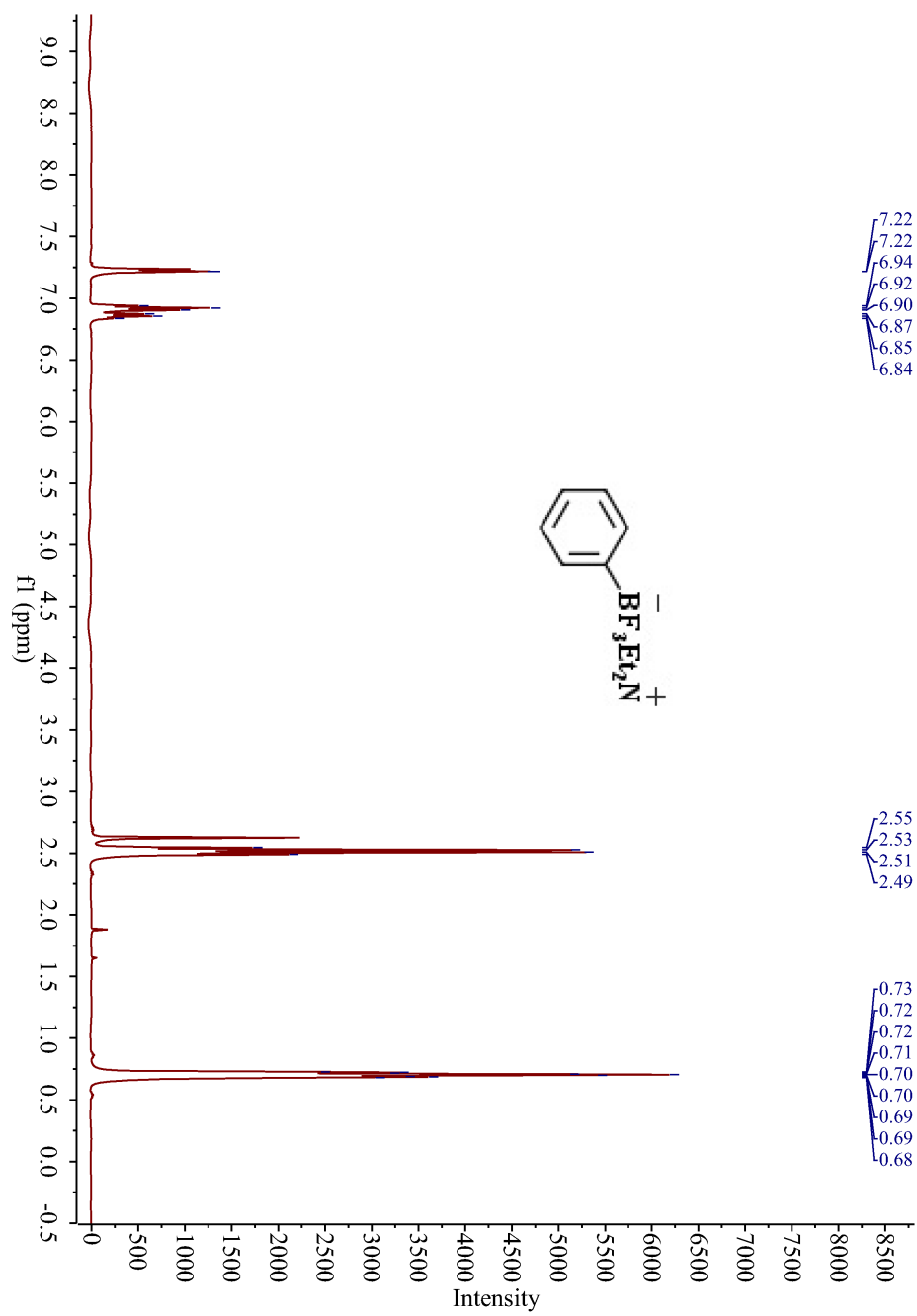


Figure D.0.1: ^1H spectrum of 1.

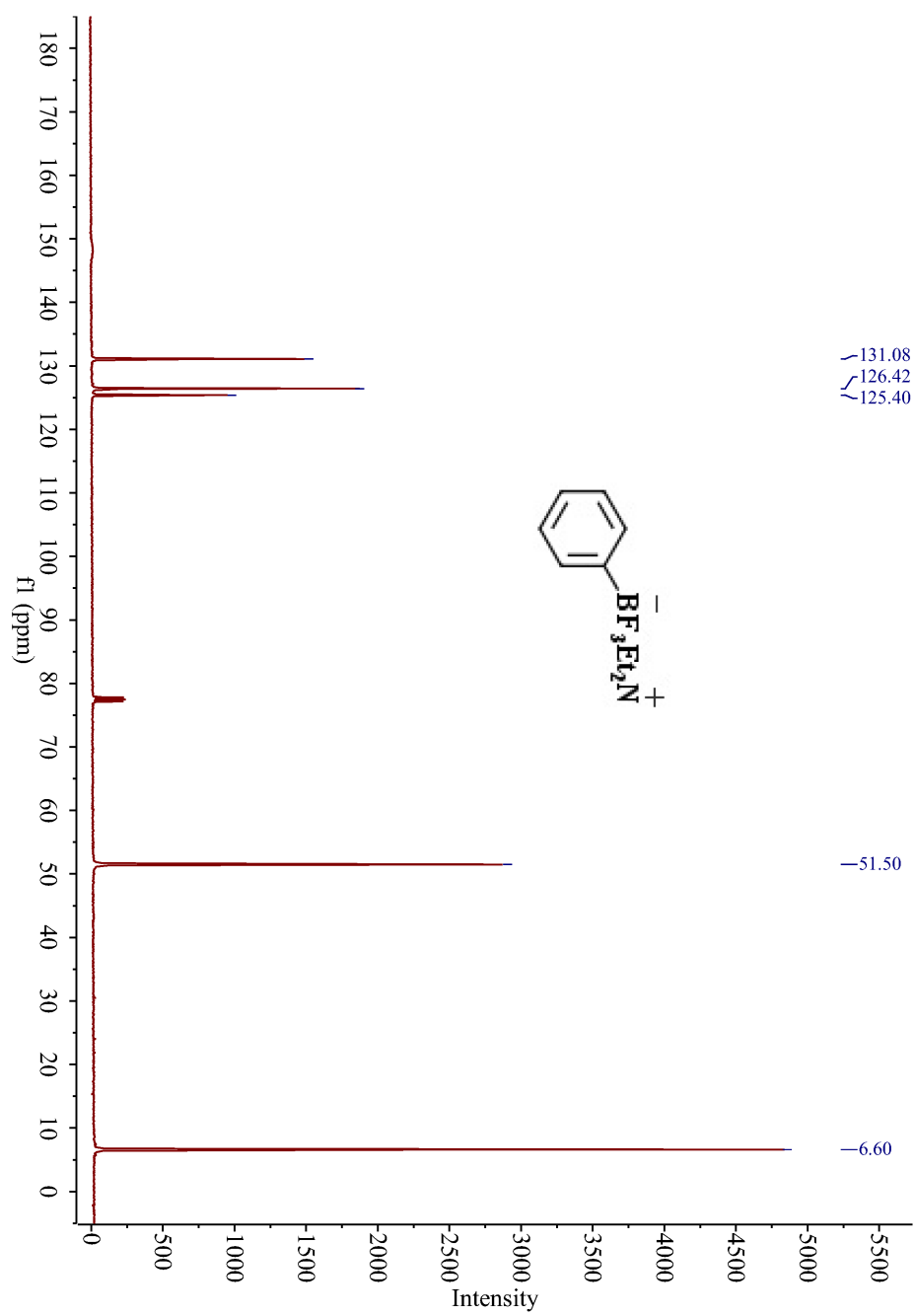


Figure D.0.2: ^{13}C spectrum of 1.

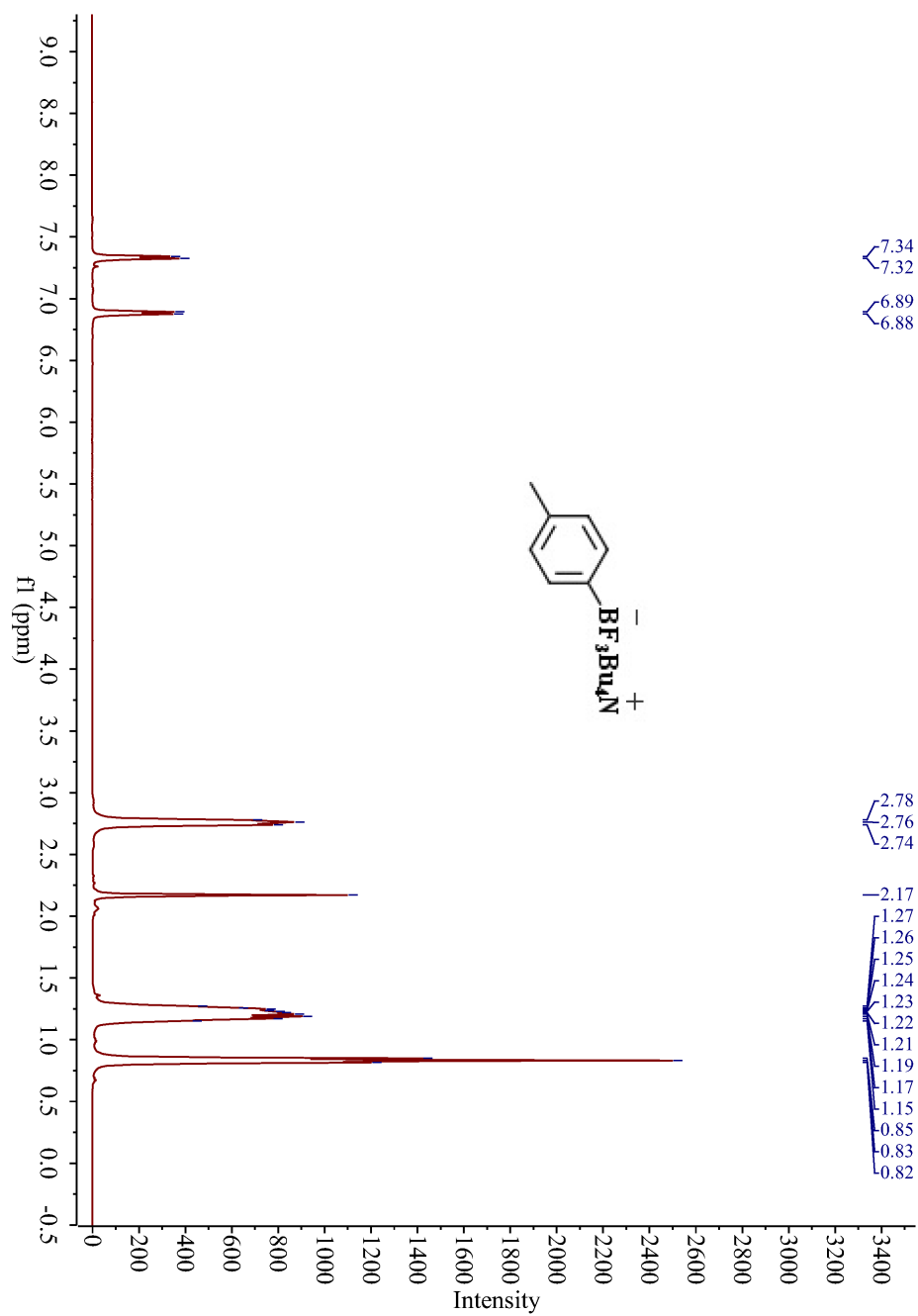


Figure D.0.3: ^1H spectrum of 2.

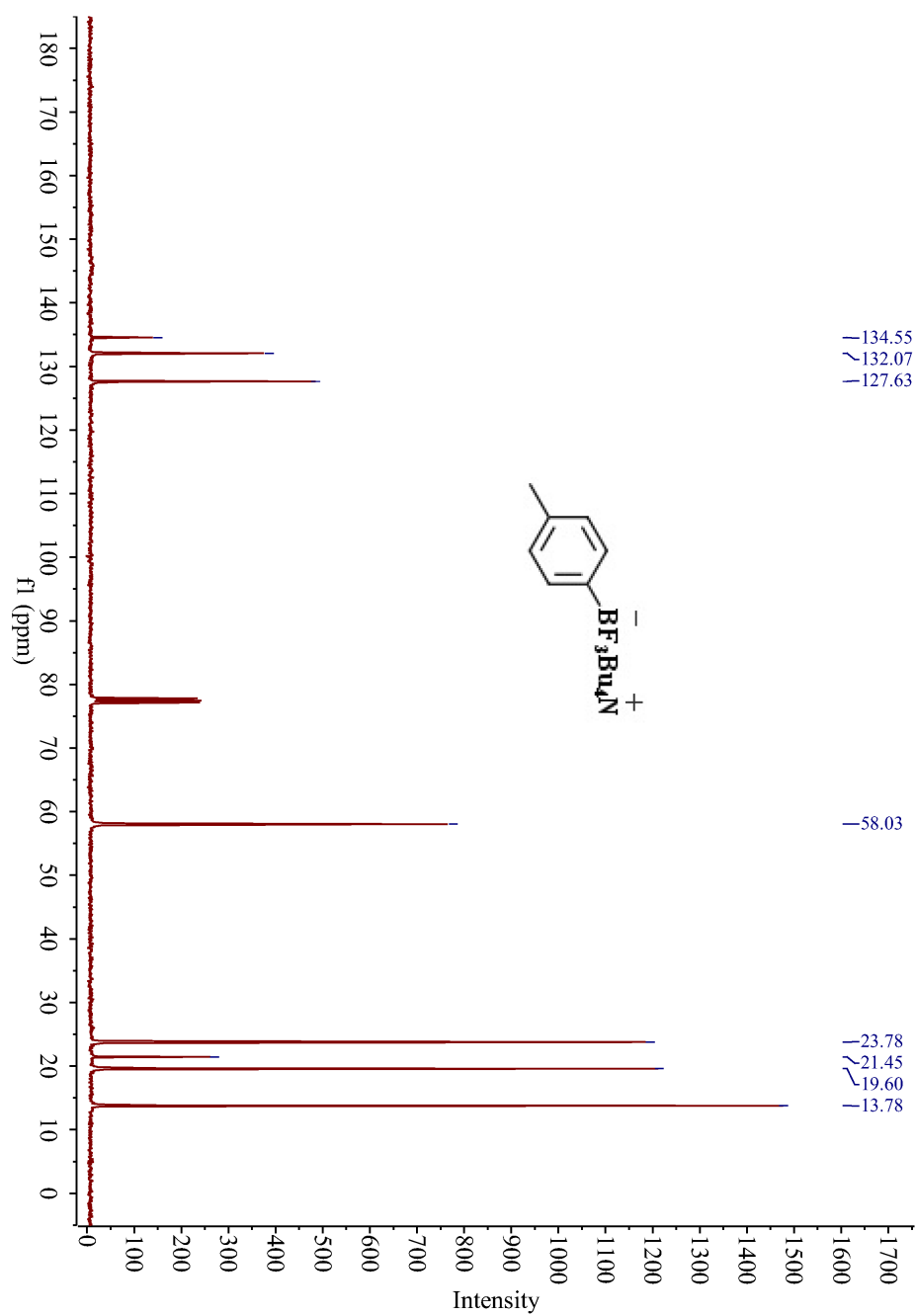


Figure D.0.4: ^{13}C spectrum of 2.

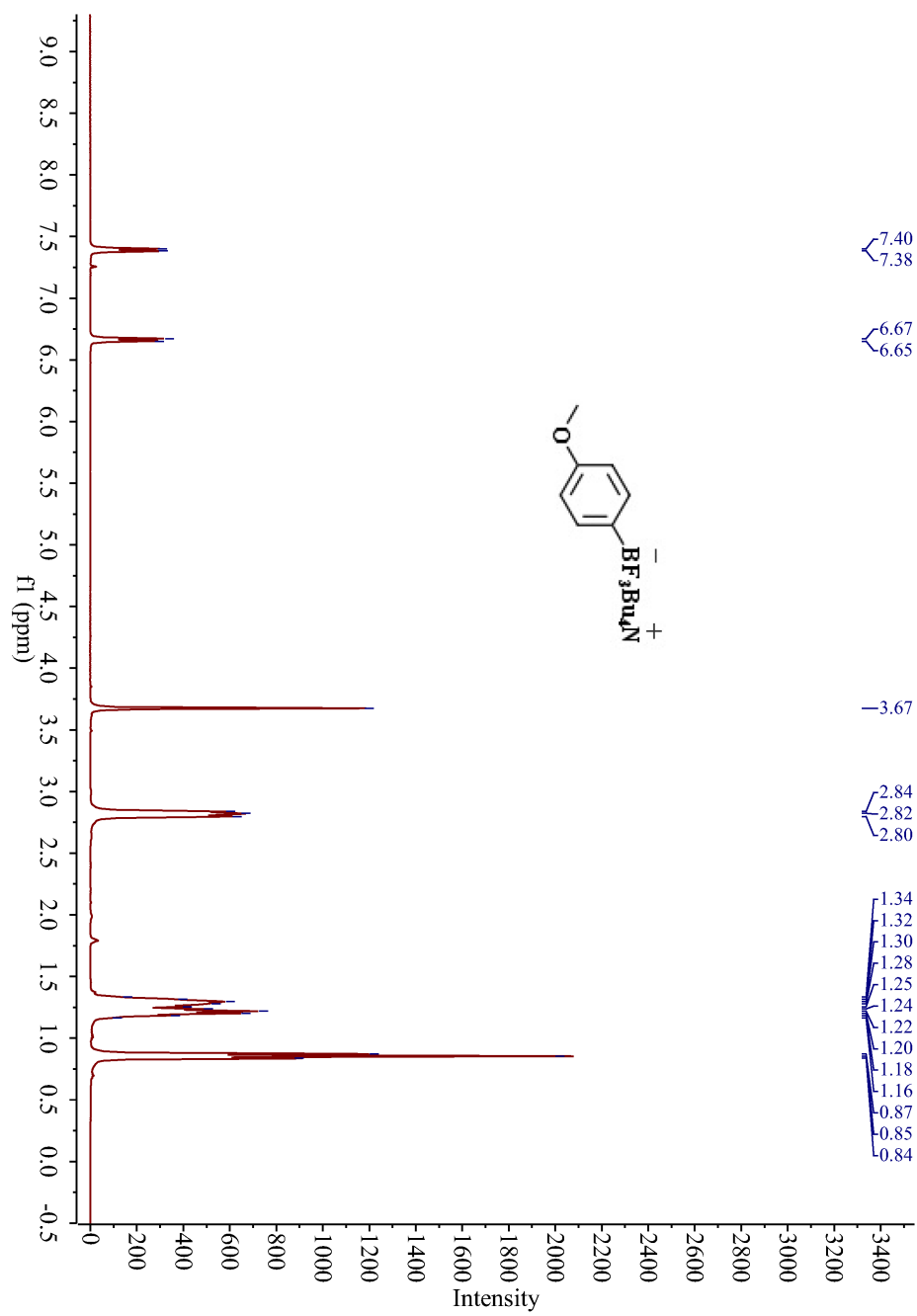


Figure D.0.5: ¹H spectrum of 3.

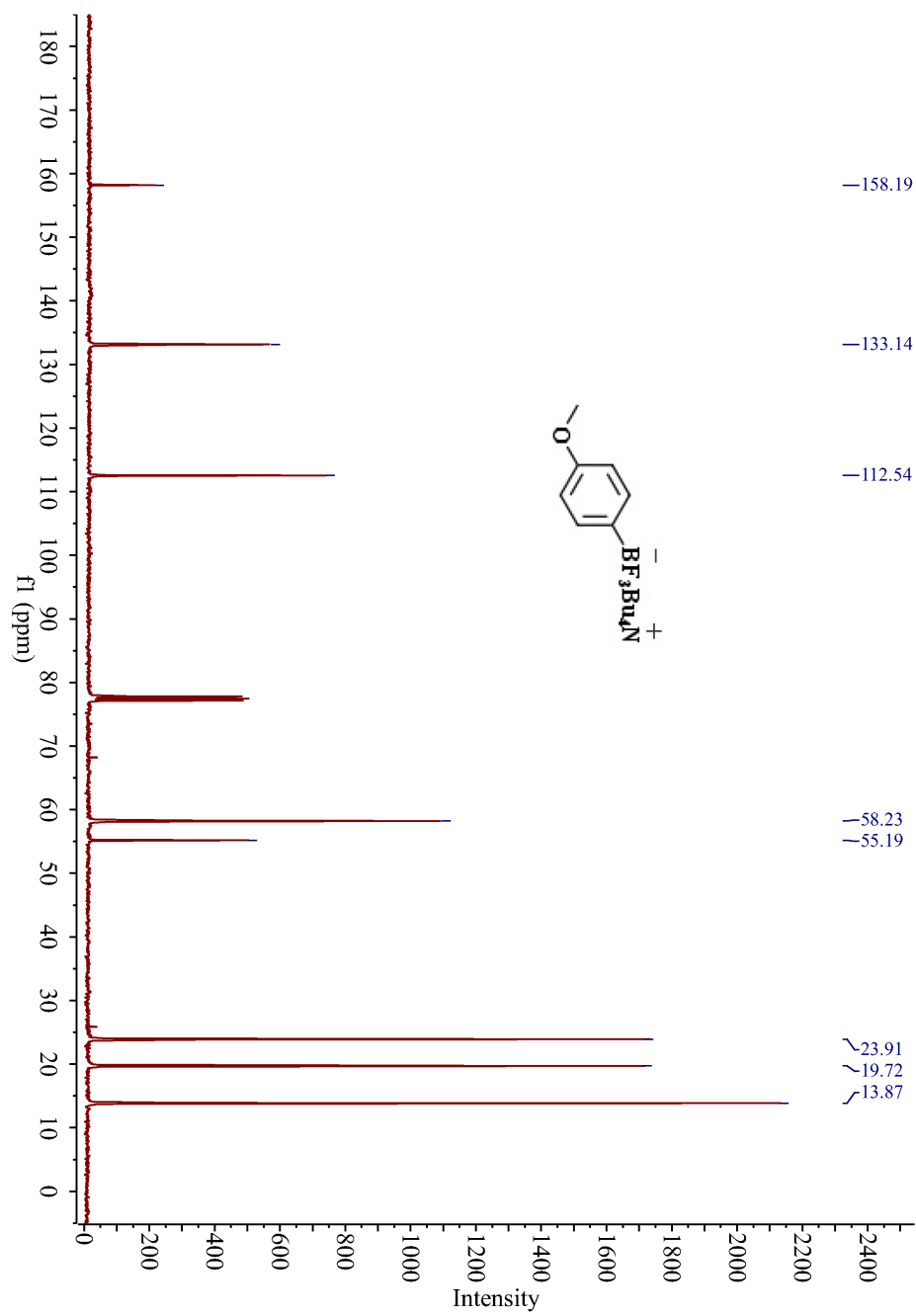


Figure D.0.6: ^{13}C spectrum of 3.

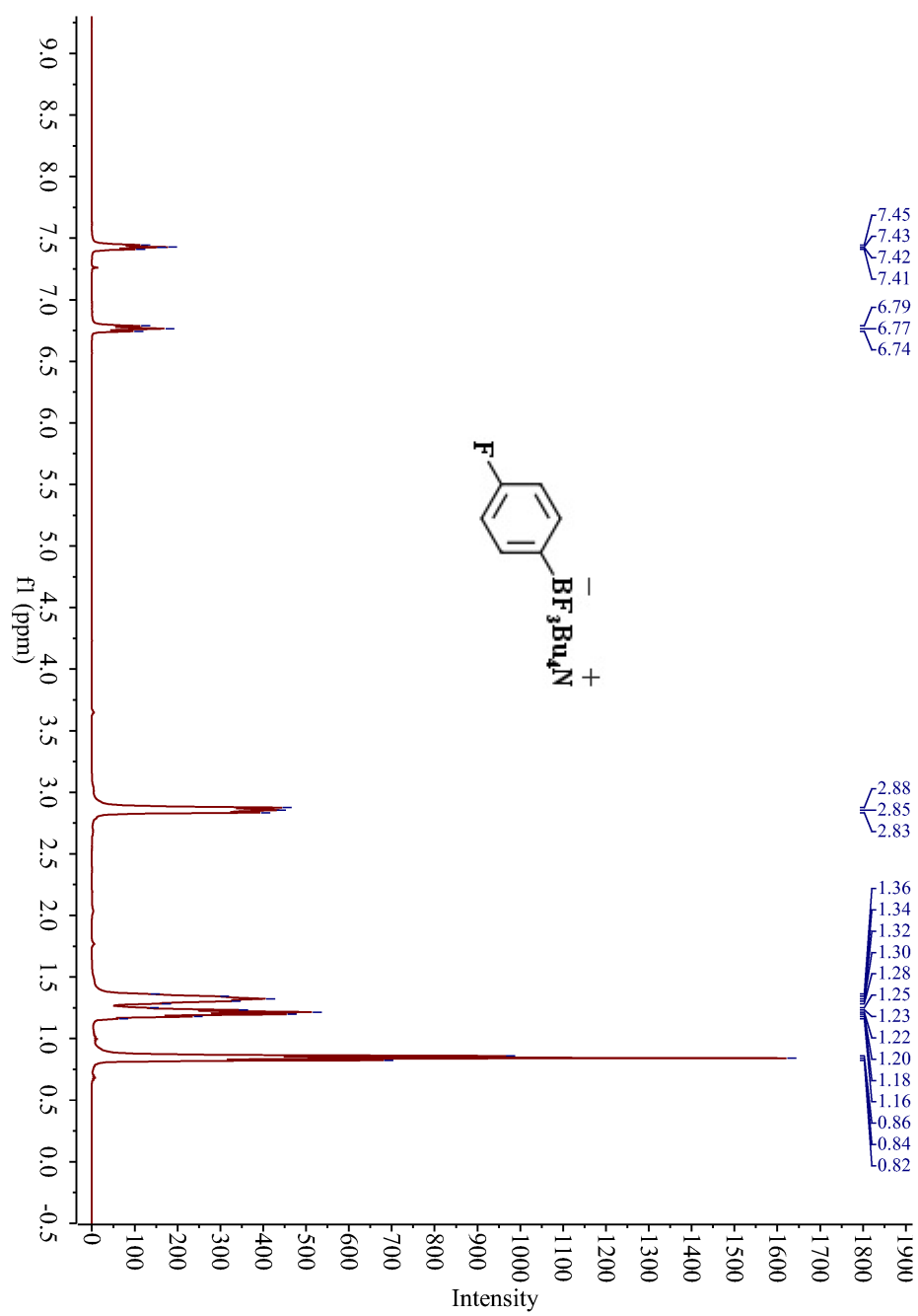


Figure D.0.7: ¹H spectrum of 4.

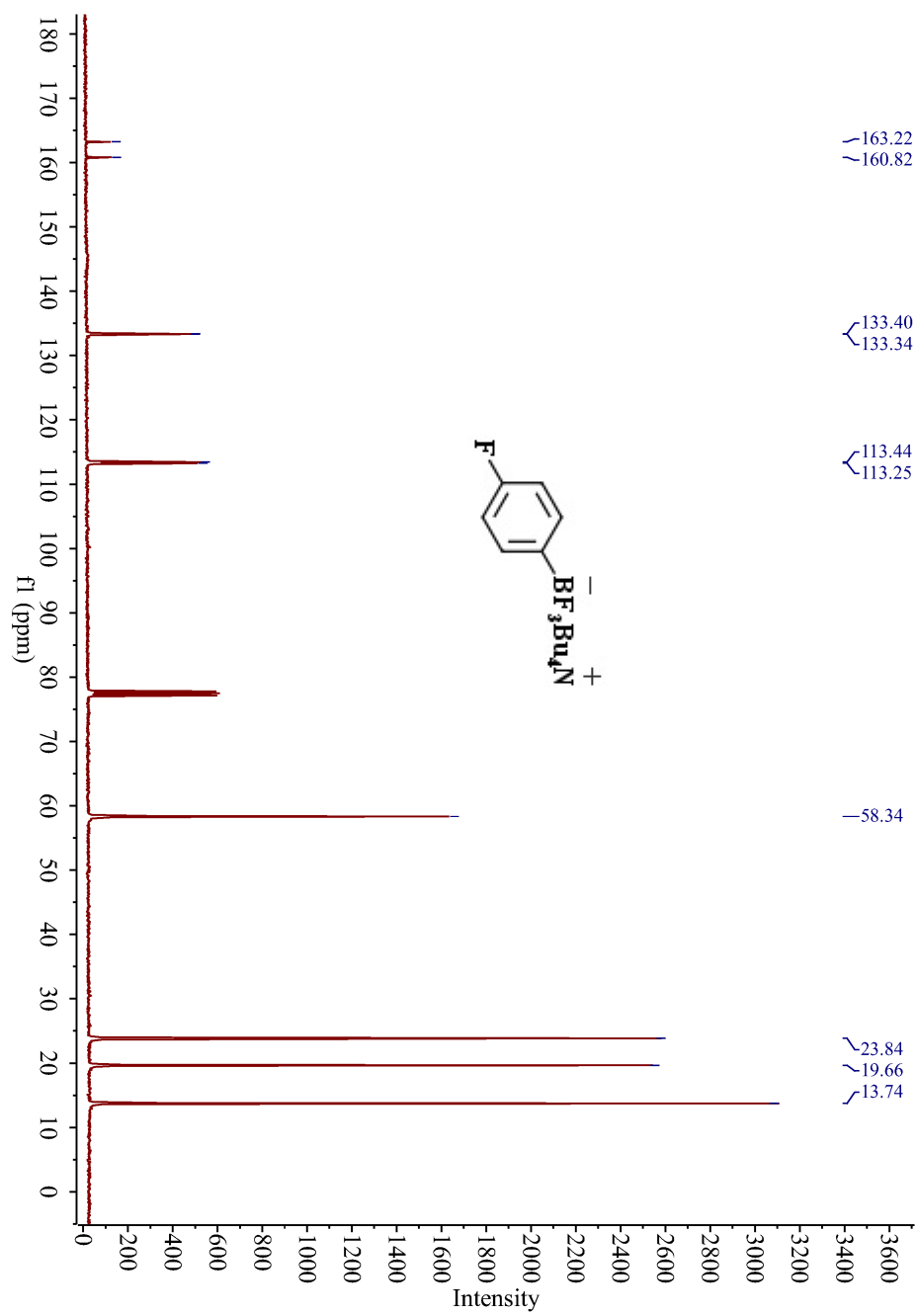


Figure D.0.8: ^{13}C spectrum of 4.

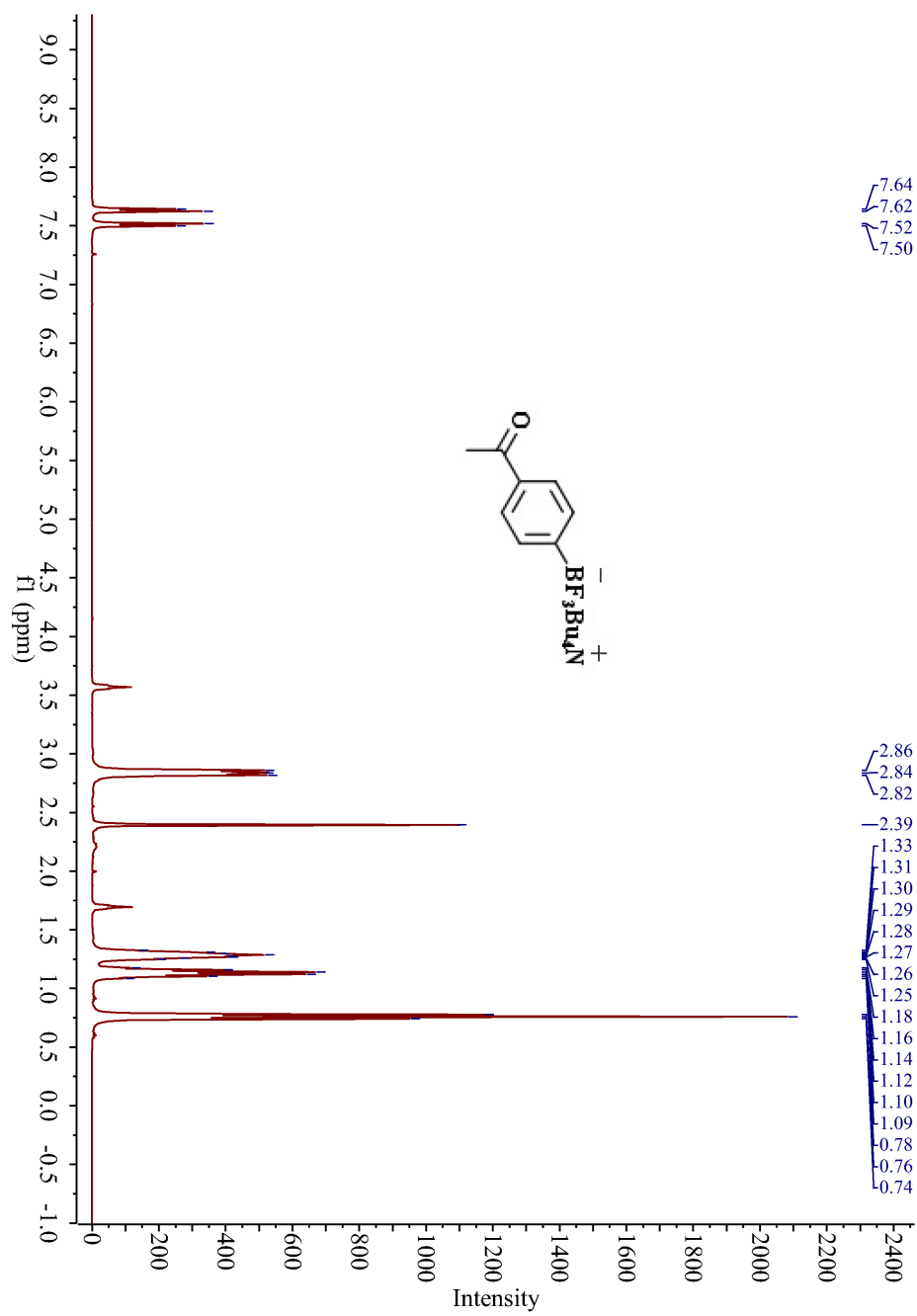


Figure D.0.9: ^1H spectrum of 5.

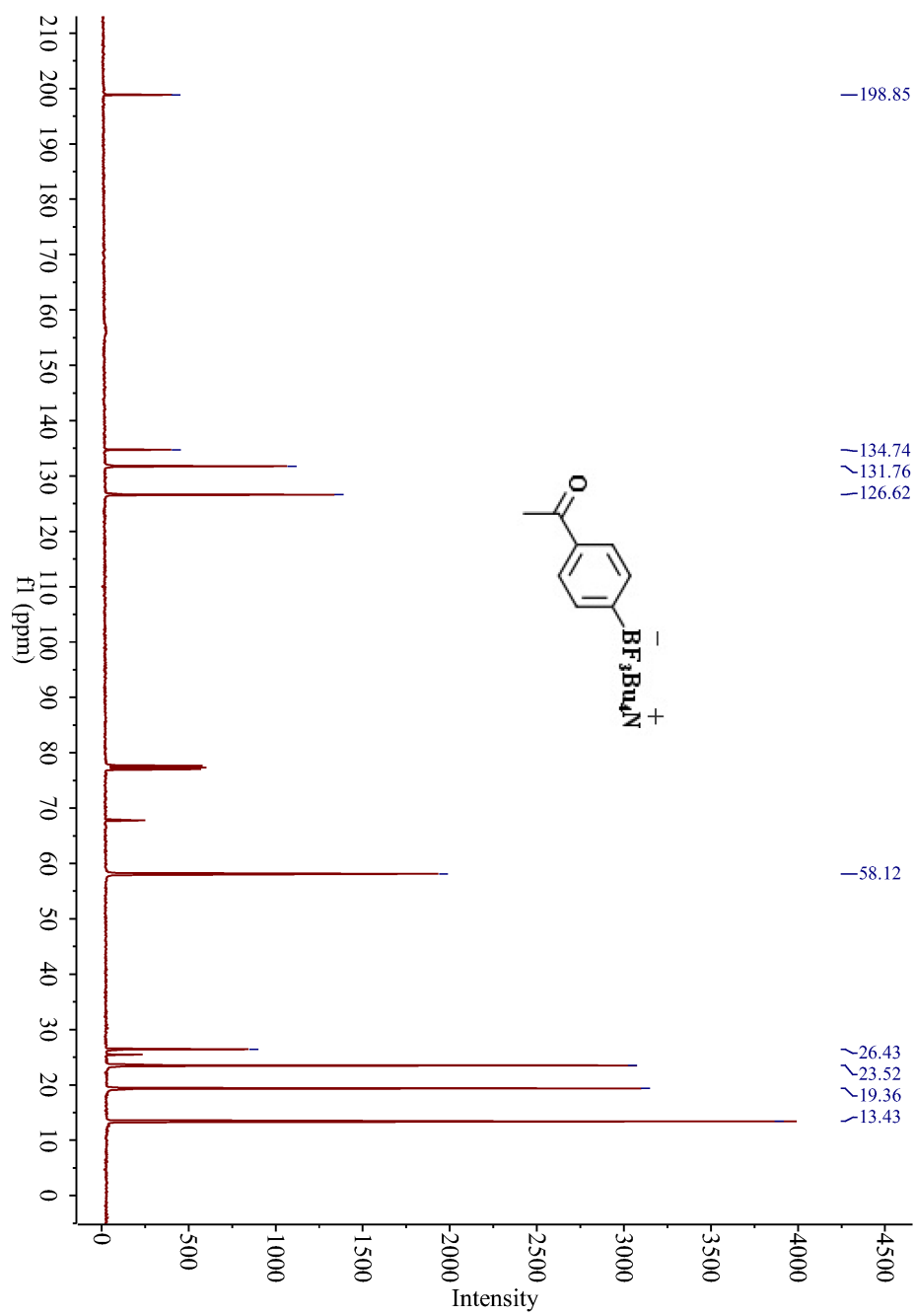


Figure D.0.10: ^{13}C spectrum of 5.

Vita

Vitali Coltuclu was born in Ceadir-Lunga, Moldova. He attended Moldova State University between 2001 and 2006, where he received Licentiate (B.S.) and M.S degrees in Chemistry. In Spring 2008, he entered the graduate program at the Department of Chemistry, University of Tennessee, Knoxville. He joined Dr. George Kabalka's group to begin research in the field of organoboron chemistry. Vitali Coltuclu received a Doctor of Philosophy Degree in Chemistry from the University of Tennessee in Summer 2013.