

Synthesis of Bis(2,2,2-Trifluoroethyl) (*Z*)-Vinylphosphonates

by

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Synthesis of Bis(2,2,2-trifluoroethyl) (*Z*)-vinylphosphonates

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## **ABSTRACT**

A new method for the synthesis of bis (2,2,2- trifluoroethyl) (*Z*)-vinyl phosphonates from bis (2,2,2-trifluoroethyl) 1-alkynyl phosphonates is described. 1-Alkynyl phosphonates, in the presence of Lindlar's catalyst, trifluoroethanol and H<sub>2</sub> (g), are used to prepare the corresponding vinylphosphonates via a semireductive synthetic approach. With the starting materials in hand, specifically the 1-alkynylphosphonates, which were synthesized using bis(2,2,2-trifluoroethyl)phosphorochloridate and the commercially available 1-alkynes, the obtaining of the desired target was accomplished. The semireduction of the triple bond was successful using Lindlar's catalyst in the presence of quinoline with 2,2,2-trifluoroethanol as reaction solvent. Additionally, a modified approach to this synthesis is explored such that only the kinetic (*Z*) isomer is formed.

## **ACKNOWLEDGEMENTS**

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**LIST OF ABBREVIATIONS**

<b><u>Abbreviation</u></b>	<b><u>Description</u></b>
AIDS	Acquired Immunodeficiency Syndrome
$\beta$	beta
$^{\circ}\text{C}$	degrees, Celsius
$^{13}\text{C}$	carbon-13
$\text{CDCl}_3$	deuteriochloroform
d	doublet
DMI	dimethylimidazolidinone
dd	doublet of doublets
ddt	doublet of doublet of triplets
dq	doublet of quartets
Eq	equivalent
EA	ethyl acetate
EtOH	ethanol
g	gram
GC	gas chromatograph
$^1\text{H}$	hydrogen-1
HIV	human immunodeficiency virus
$\text{H}_3\text{PO}_4$	phosphoric acid
Hz	hertz
<i>i</i> -Pr	isopropyl
<i>J</i>	coupling constant (in Hz)
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
m	multiplet
mL	milliliter

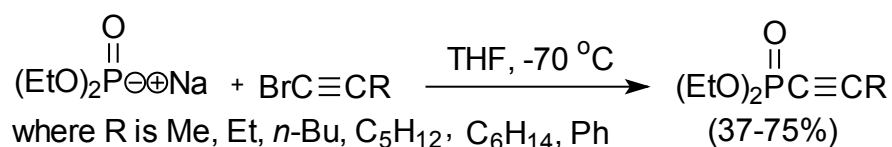
**LIST OF ABBREVIATIONS (continued)**

<b><u>Abbreviation</u></b>	<b><u>Description</u></b>
mmol	millimole
<i>n</i> -BuLi	butyllithium
NMR	nuclear magnetic resonance
<sup>31</sup> P	phosphorus-31
PMA	phosphomolybdic acid
ppm	parts per million
s	singlet
t	triplet
TFE	trifluoroethyl
TFEOH	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane

## Chapter 1: Introduction

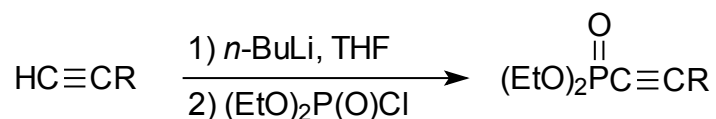
### Background

Since their discovery in 1957,<sup>1</sup> alkynylphosphonates have proven to be an important class of compounds. Early on, however, the transformation of alkynes to alkynylphosphonates proved difficult because the resulting reaction mixtures contained many by-products which were difficult to remove. But as researchers attempted to create novel reagents, new synthetic routes were found which produced a fair yield of product (Scheme 1). Currently, producing alkynylphosphonates from alkynes is reliable. High yields with few by-products, in a relatively short time, under mild conditions are some of the improvements made as a result of the studies of these compounds.<sup>2</sup>



### Scheme 1: The Michaelis-Becker reaction.

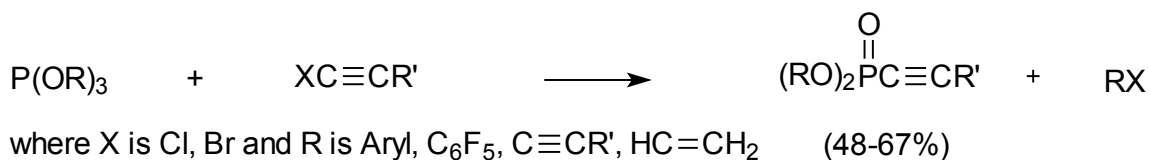
Gil and associates work showed that terminal alkynes can be treated sequentially with *n*-butyllithium and diethyl chlorophosphate to produce the corresponding 1-alkynylphosphonates in good yield (80-90%)<sup>3</sup> (Scheme 2).



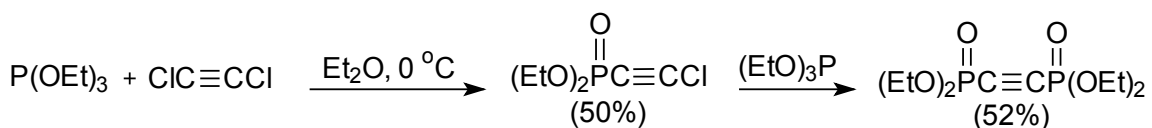
### Scheme 2: Gil's synthesis of alkynylphosphonates.

The Michaelis-Arbuzov reaction, a nucleophilic displacement reaction, was reported to produce fair to good yields when 1-bromoalkynes were adjacent to either

vinyl or aryl groups (Scheme 3).<sup>2</sup>

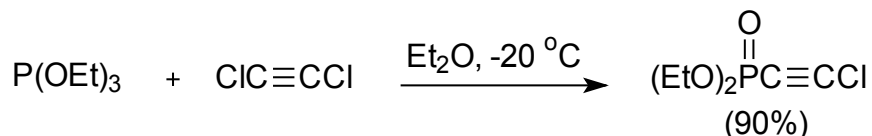


**Scheme 3:** Synthesis of alkynylphosphonates via the Michaelis-Arbuzov reaction.



**Scheme 4:** Synthesis of alkynylphosphonates via the Michaelis-Arbuzov reaction.

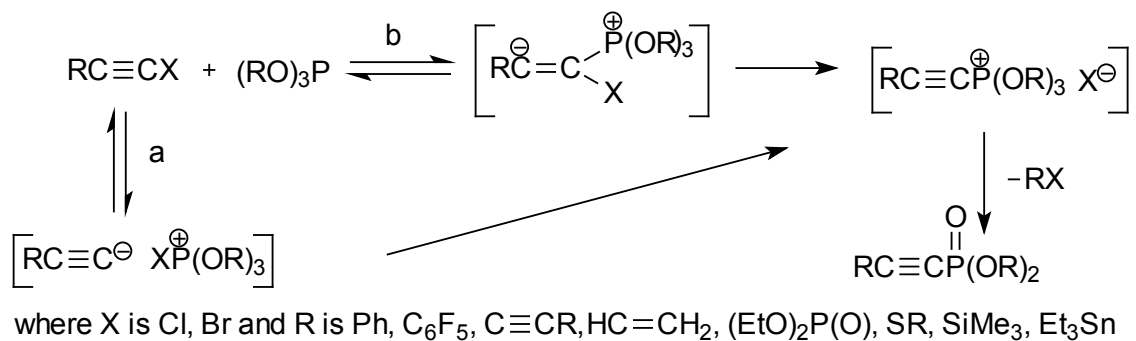
Later, improved yields<sup>4</sup> of diethyl 2-chloroethynylphosphonate, the product of the first step (above, Scheme 4), were reported by Kyba, when the reaction was run at -20 °C (90%) (Scheme 5).



**Scheme 5:** Kyba's synthesis of diethyl 2-chloroethynylphosphonate.

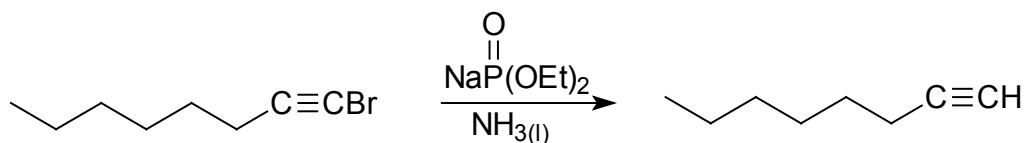
Studies of haloalkyne reactivity to produce dialkyl 1-alkynylphosphonates suggest two pathways: one that involves positive halogen abstraction (a) or an addition/elimination

(b), as shown below (Scheme 6).



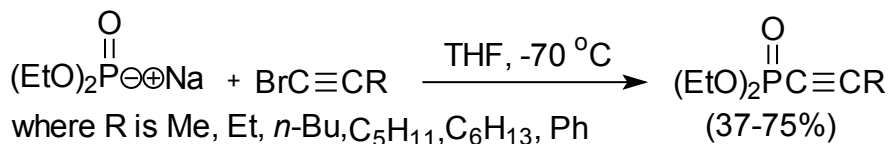
**Scheme 6:** Reactivity study deduced two possible pathways.

The Michaelis-Becker approach, as described in 1965, attempted to prepare 1-alkynylphosphonates by combining 1-bromo-1-octyne with sodium diethyl phosphite in liquid ammonia but only 1-octyne was produced (Scheme 7).<sup>5</sup>



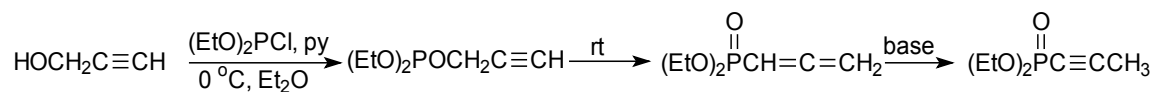
**Scheme 7:** Halogen-metal exchange caused undesired by-products.

The reduction of 1-bromo-1-octyne was speculated to occur as a halogen-metal exchange followed by the conversion of diethyl bromophosphate to the diethyl phosphoramidate in the presence of liquid ammonia. This reaction was problematic as it formed undesirable side-products. However, performing the reaction at -70 °C in THF and adding the bromoalkyne slowly gave better results (37-75% yield) (Scheme 8).



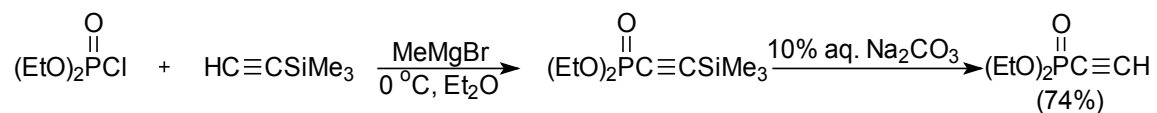
**Scheme 8:** Improved Michaelis-Becker approach for synthesis of alkynylphosphonates.

The next class of reactions, the phosphite-allenylphosphonate rearrangement was reported by both US and Russian (USSR) chemists in 1962.<sup>6,7</sup> The reaction of diethyl chlorophosphite with propargyl alcohol in ether and pyridine (or triethylamine) at 0 °C formed diethyl 2-alkynylphosphate. Upon standing at room temperature, a rearrangement occurred producing a diethyl allenylphosphonate. Then, with the addition of base, excellent yields of 1-alkynylphosphonate were achieved (92%) (Scheme 9).



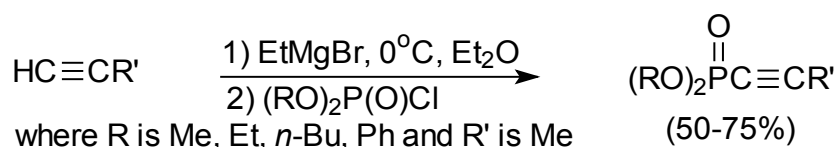
**Scheme 9:** The phosphite-allenylphosphonate rearrangement.

The third important reaction category is the carbanionic displacement. This approach reacts diethyl chlorophosphate with an alkynyl Grignard reagent in THF to produce yields of 12-25%. However, more recently, Acheson used a protection approach, which reacted trimethylsilylethyne with diethyl chlorophosphate, methylmagnesium bromide at 0 °C in diethyl ether followed by hydrolysis using a 10% sodium carbonate solution. 1-Diethyl alkylphosphonates were produced in good yield (scheme 10).<sup>8</sup>



**Scheme 10:** Acheson's synthesis utilizing a protection group approach.

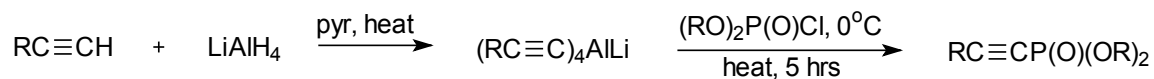
Later, Chattha discovered a preparation for alkynylphosphonates which became widely used by chemists in this particular area of research. It involved reacting an alkynyl phosphonate with a Grignard reagent in diethyl ether in the first step followed by treatment with a dialkyl phosphorochloridate to give the corresponding alkynylphosphonate in good yield (Scheme 11).<sup>9</sup>



**Scheme 11:** Chattha's method for synthesizing alkynylphosphonates.

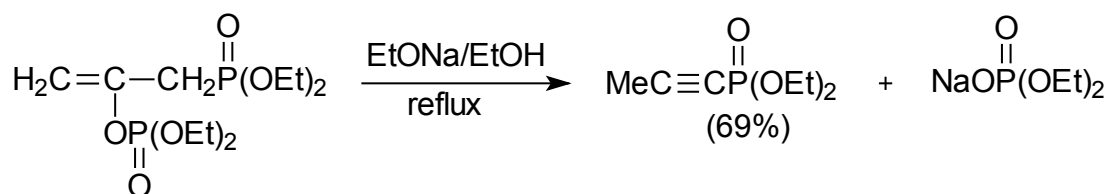
This reaction gave the highest yields when the alkyne salt was added to the chlorophosphate. On the other hand, alkynyllithiums, being more reactive than the corresponding alkynyl Grignards, appear to be well suited for reacting at low temperatures (-70 °C) with diethyl phosphorochloridate.<sup>3</sup>

This favorable temperature match reportedly minimizes side reactions and, in turn, gave good yields with good reproducibility. In general, this route was far superior for producing a crude mixture that was easily purified (via distillation) and gave good yield (70-80%), whereas the Michaelis-Abruzov/Michaelis-Becker method generally afforded yields of 30-40%. An alternate approach exists which reacts lithium tetraorganoaluminates with dialkyl phosphorochloridates in the presence of pyridine to produce good yields of dialkyl-1-alkynylphosphonates (60-80%). However, they are slow to react, often taking five hours, and require higher temperatures upward of 105 °C (Scheme 12).<sup>10</sup>



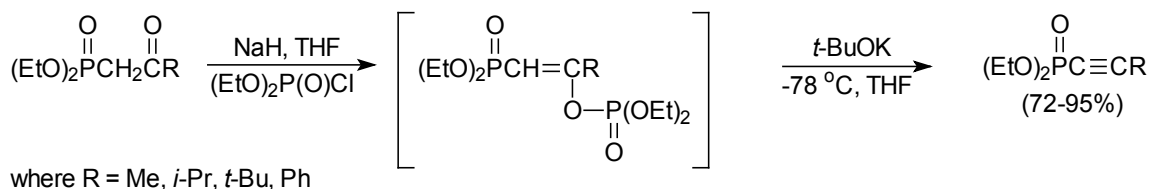
**Scheme 12:** Yagudeev's synthesis via a lithium tetraorgano-aluminate reagent.

Alkynylphosphonates can be synthesized via an elimination reaction. The first recorded elimination reaction appeared in 1957, when Jacobson reacted sodium ethoxide with diethyl-3-diethyl phosphonoisoprenyl phosphate in refluxing ethanol to form diethyl 1-propynylphosphonate (69%) (Scheme 13).<sup>1</sup>



**Scheme 13:** Jacobson's elimination reaction for producing alkynylphosphonates.

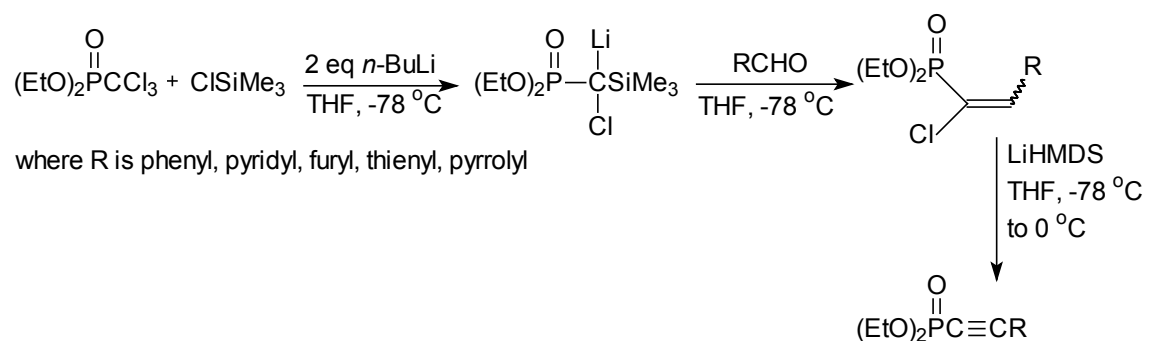
More recently, Hong's reaction of diethyl 2-oxoalkylphosphonate to yield 1-alkynylphosphonates (72-95%) was carried out using sodium hydride base and THF in the presence of diethyl chlorophosphate. In a subsequent step using potassium *tert*-butoxide in THF at low temperature, the alkynylphosphonate was realized as shown below (Scheme 14).<sup>11</sup>



**Scheme 14:** Hong's synthesis via an enol phosphate intermediate.



The final noteworthy reaction of the  $\beta$ -elimination type is shown below. When both (*E*) and (*Z*) isomers of an alkenylphosphonate are formed and subsequently treated with lithium hexamethyl disilazide (LiHMDS) in THF solvent at low temperature, alkynylphosphonates were produced in high yield (87-96%)(Scheme 15).<sup>12</sup>



**Scheme 15:** An alternative synthesis of alkynylphosphonates.

### Application of Vinyl Phosphonates and General Preparation

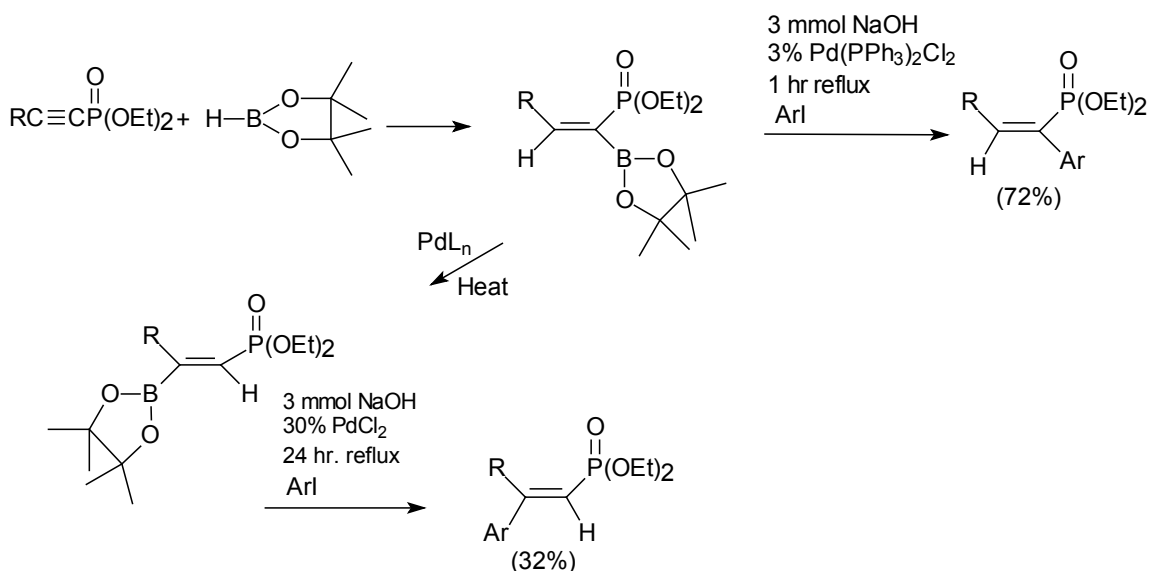
Alkynylphosphonates are readily reduced to vinyl phosphonates. Therefore, synthesis of the vinyl phosphonate is the next logical step for creating new synthetic routes using alkynylphosphonates as the starting material. Vinyl phosphonates have a variety of uses as polymer additives, in flame retardant products, agrochemicals and intermediates for drug synthesis as well as precursors to other important syntheses, including antiviral agents for treating HIV and AIDS.<sup>13</sup> Vinyl phosphonates are most easily made via hydrogenation of an alkynylphosphonate.

### Possible Routes for Achieving Vinylphosphonates

One of the goals of the current research is to find the best pathway for the synthesis of vinyl phosphonates from alkynylphosphonates. An important consideration for choosing the appropriate conditions is the regioselectivity of the reaction. Reagents

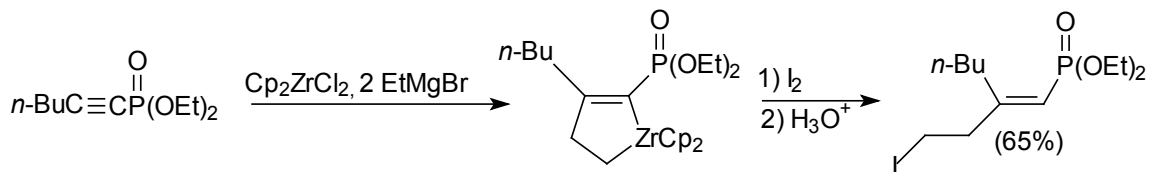
that are bulky, such as disiamylborane, would provide the conditions necessary to achieve a specific regioselectivity. Several interesting routes have been proposed and most have been very successful.

Srebnik reports that using hydroboration is successful in generating 1-alkenylphosphonates and that under controlled conditions, boron can be placed at C1, in the formation of the kinetic product, or on C2 the thermodynamic product by using larger amounts of catalyst or by heating. In a subsequent step utilizing the Suzuki reaction with aryl iodides the regioselective products can be obtained (Scheme16).<sup>14</sup>



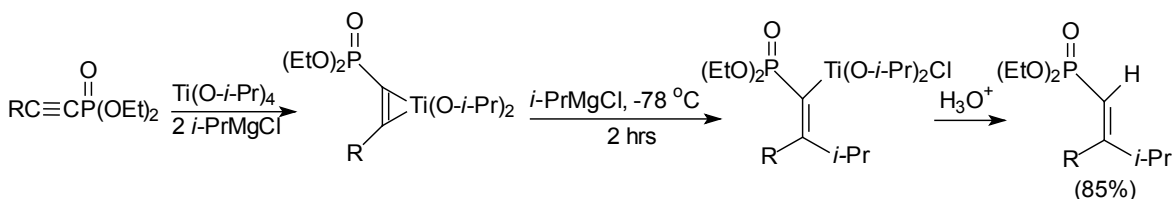
**Scheme 16:** Srebnik's synthesis using a hydroboration-coupling approach.

Ben-Valid et al. performed a reaction using a zirconium reagent with an alkenyl phosphonate and 2 equivalents of ethyl magnesium bromide to form the zircon substituted cyclic vinylphosphonate. Subsequent addition of iodine under acidic conditions gave the iodine substituted vinyl phosphonate in good yield (65%),<sup>15</sup> as shown (Scheme 17).



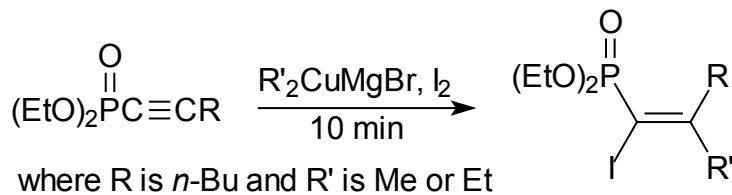
**Scheme 17:** Vinyl phosphonate synthesized through a zirconium reagent.

Al-Quntar synthesized vinyl phosphonates by reacting 1-alkynylphosphonates with various group (V) metals.<sup>16</sup> Like Ben-Valid, Al-Quntar used a group (V) metal. He reacted titanium tetrakisopropyl oxide with a 1-alkynylphosphonate, 2 equivalents of isopropyl magnesium chloride (at low temperature) forming a three membered titanacycle intermediate. In a subsequent step, 2 equivalents of isopropyl magnesium chloride were added and allowed to react for 2 hours. Finally, treatment with acid afforded good yield of disubstituted vinyl phosphonates (85%) (Scheme 18).



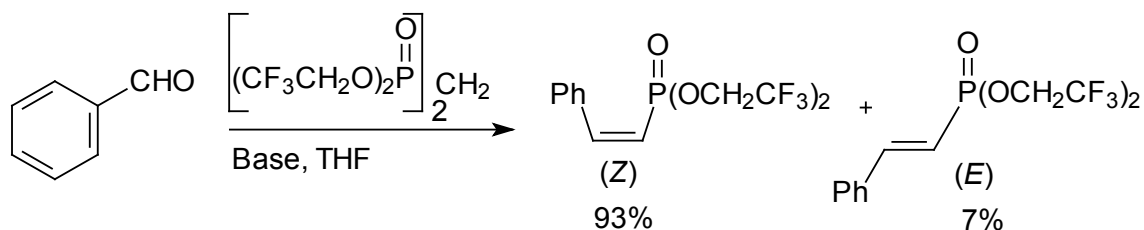
**Scheme 18:** Al-Quntar's synthesis of vinyl phosphonates.

Carbocupration is another metal catalyzed scheme for synthesizing vinylphosphonates. Gil used copper reagents and reacted them with a 1-hexynylphosphonate to synthesize trisubstituted vinyl phosphonates. When allowed to react for 10 hours with iodine, the highest yields obtained were from dimethyl and diethyl copper magnesium bromide giving nearly quantitative yield, 97 and 98%, respectively (Scheme 19).<sup>17</sup>



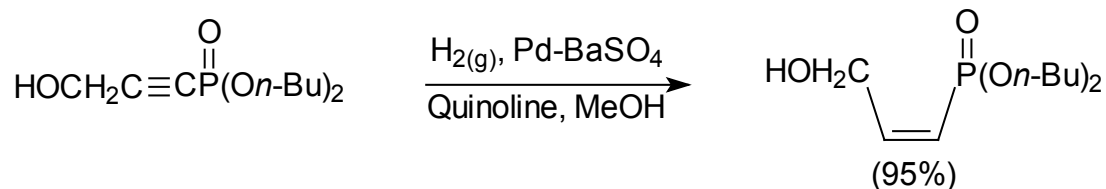
**Scheme 19:** Gil's carbocupration reaction.

As reported in 1998, Kiddle synthesized a new reagent, tetrakis(2,2,2-trifluoroethyl) methylene bisphosphonate, to accomplish the synthesis of (*E*) and (*Z*)-isomers of vinylphosphonates. Through a Wadsworth-Emmons reaction between benzaldehyde and a bisphosphonate in THF, the isomeric mixture was realized. The (*Z*)-isomer was dominant in a ratio of 93 to 7 with nearly quantitative yields (99%) in the presence of KHMDS and 18-crown-6 at -78 °C (Scheme 20).<sup>18</sup>



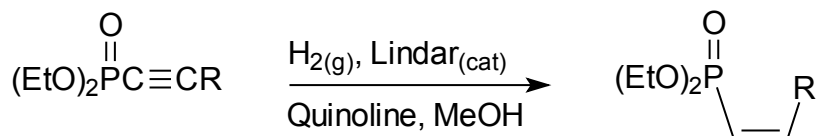
**Scheme 20:** Kiddle's synthesis of (*Z*)-alkenylphosphonates.

Machida described the first  $\gamma$ -hydroxy- $\alpha,\beta$ -unsaturated phosphonic acid derivative which was, in later steps, cyclized to what he referred to as a 1,2-oxaphosphol-3-ene system, as shown (Scheme 21).<sup>19</sup>



**Scheme 21:** Machida's synthesis of vinyl phosphonates.

Catalytic semi-reduction, one of the easiest and most reliable methods for reducing the triple bond, can be used for synthesizing vinyl phosphonates. By reacting a 1-alkynylphosphonate with hydrogen gas, Lindlar catalyst and quinoline, the corresponding vinyl phosphonate is realized as shown below (Scheme 22).<sup>20</sup>

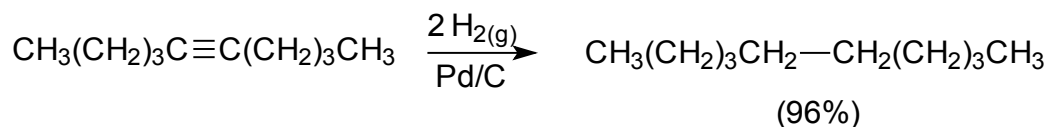


**Scheme 22:** Cristau's synthesis of diethyl hex-1-(*Z*)-enylphosphonate.

Since both the (*E*) and (*Z*)-isomers are produced the crude mixture must be purified via flash column chromatography. Although yields are expected to be nearly quantitative, when the reaction is run at -10 to -30 °C, only the (*Z*)-isomer is produced.<sup>21</sup>

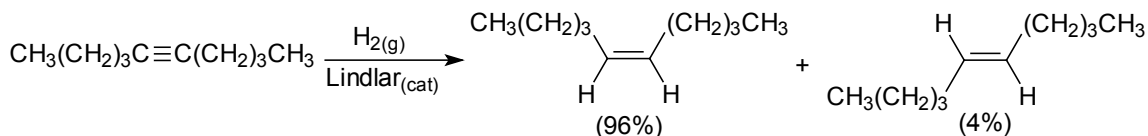
### Alkynes and Catalysis: An Important Pair

Unsaturated compounds, specifically alkynes, are readily transformed into saturated compounds via many methods. The most intriguing alkyne transformation is the catalytic hydrogenation reaction. This reaction uses a platinum or palladium catalyst on carbon (or Raney nickel) in the presence of hydrogen gas when the fully hydrogenated alkane is desired (Scheme 23).<sup>22</sup>



**Scheme 23:** Catalytic Hydrogenation of an internal alkyne.

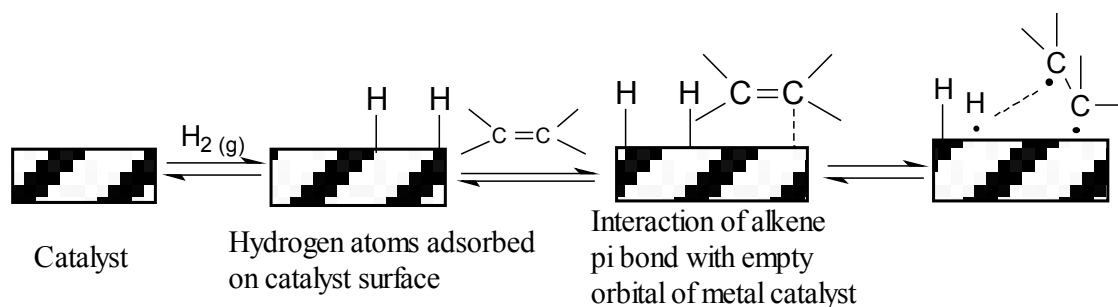
When the same reaction is performed using Lindlar catalyst, a mixture of products is realized with the *cis* isomer being the major product (Scheme 24).<sup>22</sup>



**Scheme 24:** Lindlar catalyst hydrogenation stops the reaction at the alkene.

Lindlar catalyst is a finely divided palladium metal that has been precipitated onto a calcium carbonate support and is subsequently modified, or poisoned, with lead acetate. The catalyst, when paired with quinolone, is further deactivated. J. A. Bennett, et al. account for the superior selectivity of the catalytic hydrogenation to be a result of several factors. The major factors are metal catalyst topography (terraces and corners or edges, called defects), alkyne and alkene selectivity for catalyst topographies and poisoning with select metal ions. The effects of catalyst poisoning using lead (Pb) and bismuth (Bi) have been studied and reported.<sup>23</sup> Lead acetate, a common reagent for this application, interferes with terrace topography. The interference that lead creates is a type of promotion of the terrace topography, which plays a significant role in alkyne hydrogenation. Whereas, selective poisoning with Bi blocks edge sites thereby making terraces more available upon which alkyne hydrogenation can occur. And since alkenes are further hydrogenated on edge sites, the reaction stops at the alkene.

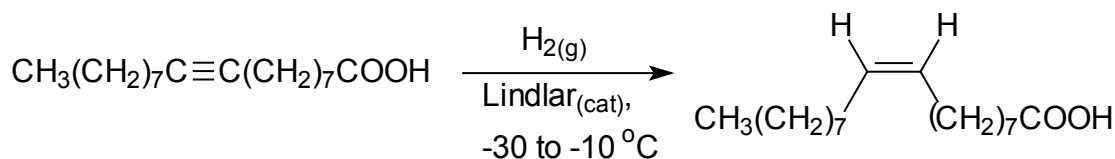
Lindlar catalyst is intentionally less active than Pd/C thereby preventing over reduction of the alkyne to the alkane. The predominant *cis* alkene isomer is produced with Lindlar catalyst through a syn addition. The syn stereochemistry is a consequence of the molecule-catalyst interaction whose mechanism is represented below (Figure 1).<sup>24</sup>



**Figure 1:** A general mechanism for catalytic hydrogenation.

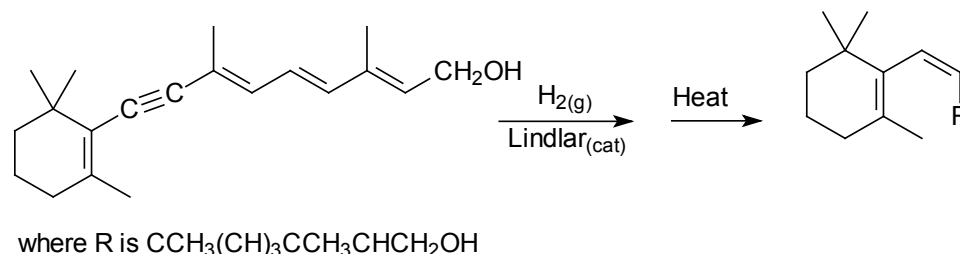
Two types of hydrogenation mechanisms through hydrometallation have been postulated by Yu and Spencer.<sup>25</sup> Their studies involving isotopic labeling have demonstrated that two possible electronic modes are responsible,  $M^{\delta+} - H^{\delta-}$  or  $M^{\delta-} - H^{\delta+}$ . The former appears to be the mode exclusively responsible for hydrometallation when electron withdrawing groups are conjugated with the reactive site. Through resonance, it becomes apparent that the  $\beta$ -C is electron deficient thereby allowing the best conditions for deuterium substitution to occur. This modification is said to be responsible for the mode enhancing activity which leads to superior selectivity.

At room temperature, the hydrogenation of an alkyne to produce a cis alkene causes a 1-3% impurity with trans isomer. However, when performed at reduced temperature, very little isomerization occurs.<sup>21</sup>



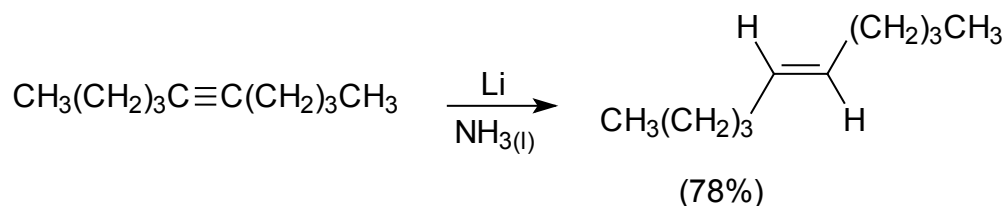
**Scheme 25:** The hydrogenation reaction executed at reduced temperature.

Catalytic hydrogenation is used in industry. A pharmaceutical company that synthesizes Vitamin A does so by transforming the cis isomer to the desired trans isomer by heating.<sup>22</sup>



**Scheme 26:** Synthesis of 7-*cis*-Retinol

Reaction of 5-decyne with lithium metal in liquid ammonia yields *trans*-5-decene.<sup>22</sup>



**Scheme 27:** Traditional method for the synthesis of a trans isomer.

Because vinyl phosphonates have a variety of uses, including the synthesis of antiviral agents, and alkynylphosphonates are readily reducible, the next logical step for creating new compounds lies with the syntheses of vinyl phosphonates, which is the scope of this work.

**Statement of Purpose**

Since triple bonds of 1-alkynylphosphonates lend themselves well to selective hydrogenation, it was thought that a convenient method for generating (*Z*)-bis(2,2,2-

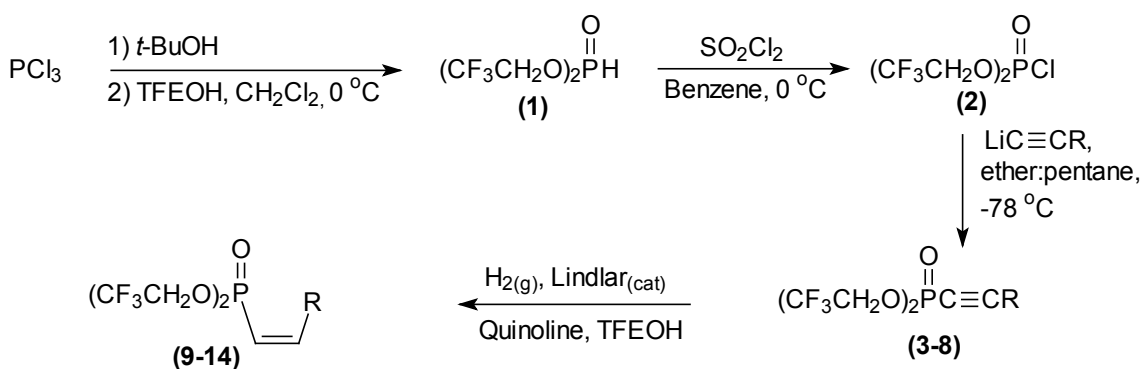


trifluoroethyl)alkenylphosphonates would be realized and then easily purified via flash column chromatography.

This work explores a selective synthesis for generating (*Z*)-vinyl phosphonates that are complementary to those already reported in the literature but using readily available or easily obtainable starting materials, relatively mild reaction conditions and no special apparatus. If successful, we will have found a convenient method for the synthesis of (*Z*)-bis(2,2,2-trifluoroethyl)alkenylphosphonates.

## Chapter 2: Results and Discussion

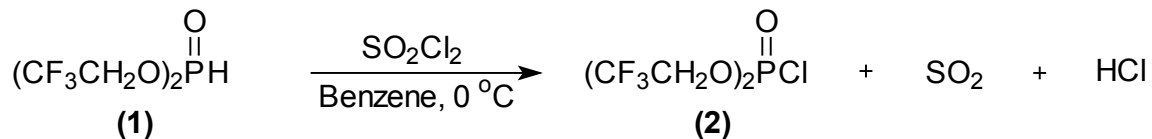
The research executed herein is concerned with finding the optimal conditions for the syntheses of (*Z*)-alkenylphosphonates from 1-alkynylphosphonates using Lindlar's catalyst, quinoline and hydrogen gas under mild conditions with readily available reagents and supplies. The stereochemistry about the double bond is also examined. The proposed strategies are described in greater detail below (Scheme 28).



**Scheme 28:** Strategy for preparing bis(2,2,2-trifluoroethyl)alkenyl phosphonates.

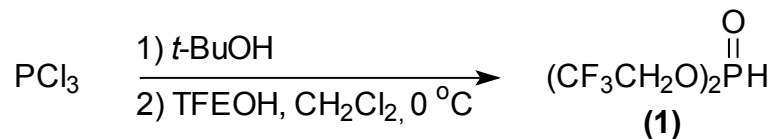
### Synthesis of bis(2,2,2-trifluoroethyl) alkynylphosphonates

In order to obtain these commercially unavailable alkynylphosphonate compounds, one must first synthesize the starting materials bis(2,2,2-trifluoroethyl) phosphite, (**1**), and bis(2,2,2-trifluoroethyl) phosphorochloridate, (**2**), both of which are easily and economically made, and can be isolated in good yield. Bis(2,2,2-trifluoroethyl) phosphite is available commercially in technical grade and is very expensive but bis(2,2,2-trifluoroethyl) phosphorochloridate is not available commercially. Synthesis of bis(2,2,2-trifluoroethyl) phosphorochloridate, in recent years, has been optimized to 93% yields<sup>26</sup> (Scheme 29).



**Scheme 29:** Synthesis of bis(2,2,2-trifluoroethyl) phosphorochloridate, (2).

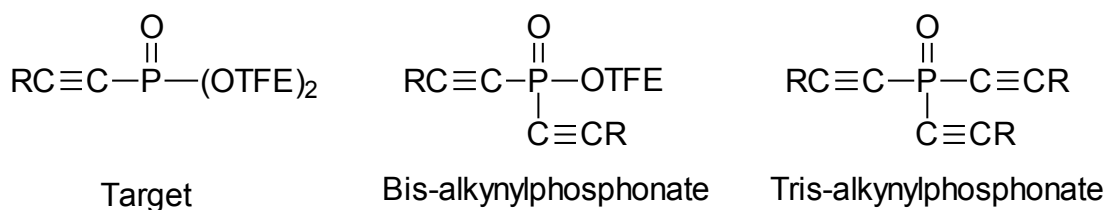
Bis(2,2,2-trifluoroethyl) phosphite (1) was synthesized in our lab because it was economically feasible. The synthesis involves mixing phosphorous trichloride with *tert*-butanol in the initial step, followed by adding a mixture of two equivalents of 2,2,2-trifluoroethanol in dichloromethane and allowing it to react at 0 °C (Scheme 30).



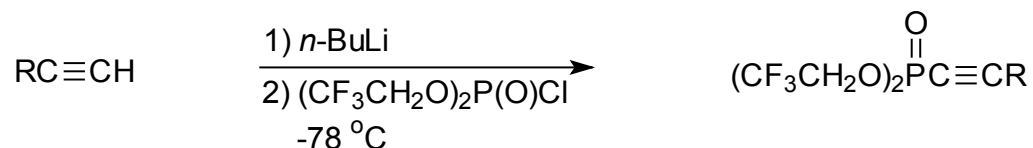
**Scheme 30:** Gibb's synthesis of bis(2,2,2-trifluoroethyl) phosphite, (1).<sup>27</sup>

Former Jackson lab members have successfully optimized the syntheses of 1-alkynylphosphonates. The optimization approach included using terminal alkynes in a 1:1 pentane : ether solvent system. By reacting 1-alkynes at -78 °C with an excess of *n*-butyllithium to form the acetylide ion (a good nucleophile) and then introducing bis(2,2,2-trifluoroethyl) phosphorochloridate, 1-alkynylphosphonates were realized.

Slight modifications were made to this synthesis. Troublesome by-products (Figure 2) are formed making the purification of alkynylphosphonates challenging.



**Figure 2:** By-products formed during 1-alkynylphosphonate synthesis.<sup>28</sup>

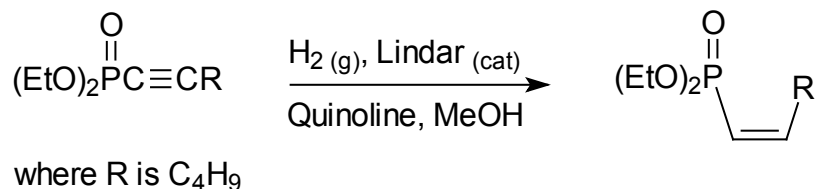


**Scheme 31:** General synthesis of alkynylphosphonates.

<u>Entry</u>	<u>Alkyne</u>	<u>Alkynylphosphonate</u>	<u>Yield</u>
(1a)	$\text{CH}_3(\text{CH}_2)_2\text{C}\equiv\text{CH}$	$(\text{CF}_3\text{CH}_2\text{O})_2\overset{\text{O}}{\parallel}{\text{P}}\text{C}\equiv\text{C}(\text{CH}_2)_2\text{CH}_3$ (3)	57%
(1b)	$\text{CH}_3(\text{CH}_2)_3\text{C}\equiv\text{CH}$	$(\text{CF}_3\text{CH}_2\text{O})_2\overset{\text{O}}{\parallel}{\text{P}}\text{C}\equiv\text{C}(\text{CH}_2)_3\text{CH}_3$ (4)	53%
(1c)	$\text{CH}_3(\text{CH}_2)_4\text{C}\equiv\text{CH}$	$(\text{CF}_3\text{CH}_2\text{O})_2\overset{\text{O}}{\parallel}{\text{P}}\text{C}\equiv\text{C}(\text{CH}_2)_4\text{CH}_3$ (5)	14%
(1d)	$\text{CH}_3(\text{CH}_2)_5\text{C}\equiv\text{CH}$	$(\text{CF}_3\text{CH}_2\text{O})_2\overset{\text{O}}{\parallel}{\text{P}}\text{C}\equiv\text{C}(\text{CH}_2)_5\text{CH}_3$ (6)	63%
(1e)	$\text{CH}_3(\text{CH}_2)_6\text{C}\equiv\text{CH}$	$(\text{CF}_3\text{CH}_2\text{O})_2\overset{\text{O}}{\parallel}{\text{P}}\text{C}\equiv\text{C}(\text{CH}_2)_6\text{CH}_3$ (7)	49%
(1f)	$\text{CH}_3(\text{CH}_2)_7\text{C}\equiv\text{CH}$	$(\text{CF}_3\text{CH}_2\text{O})_2\overset{\text{O}}{\parallel}{\text{P}}\text{C}\equiv\text{C}(\text{CH}_2)_7\text{CH}_3$ (8)	15%

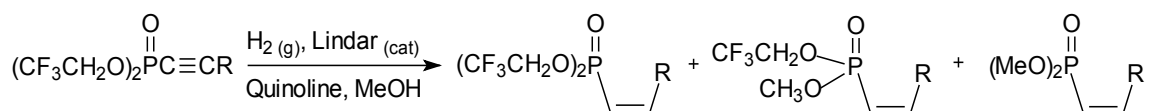
**Table 1:** Bis(2,2,2-trifluoroethyl) alkynylphosphonate yields.

**Synthesis of bis(2,2,2-trifluoroethyl) (Z)-alkenylphosphonates**



**Scheme 32:** Cristau's Synthesis of diethyl hex-1-(Z)-enylphosphonate.<sup>20</sup>

Our initial synthesis employed much of the same approach as Cristau but without any special apparatus for the administration of the gas. Bis(2,2,2-trifluoroethyl) oct-1-ynyl phosphonate, Lindlar's catalyst and quinoline in methanol were added to a flask and then fitted with a septum. Hydrogen gas was allowed to flow into the reaction vessel. The reaction was allowed to proceed for two hours and then analyzed by <sup>31</sup>P NMR which showed approximately one percent conversion to product as evident by the growth of the product peak at 20.0 ppm. It was decided that a longer reaction time was needed. Subsequent trials were performed in which the reaction mixture was allowed to stir for 24 hours and one trial going for 8 days hours without full conversion to product. Additionally, it was thought that transesterified products were being formed (Figure 3).



**Figure 3:** Transesterified products.

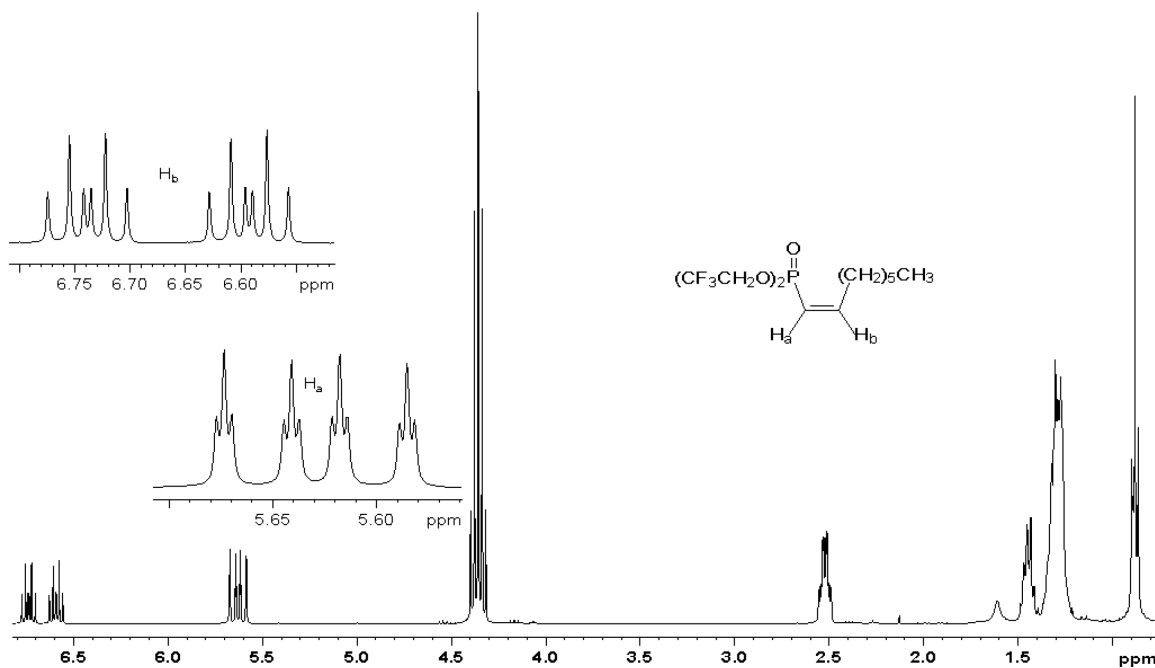
Since transesterified products were undesirable, a change in reaction solvent from methanol to 2,2,2-trifluoroethanol was made. Additional benefits were gained by this solvent change. The switch to 2,2,2-trifluoroethanol significantly reduced the reaction time to less than four hours, in most trials, and offered complete conversion to product.

<u>Entry</u>	<u>Alkenylphosphonate</u>	<u>Compound</u>	<u>Solvent</u>	<u>Duration</u>
(2b)		(10)	TFEOH	4.75 hrs.
(2b)		(10)	MeOH	8 days
(2d)		(12)	TFEOH	3.50 hrs.
(2d)		(12)	MeOH	24 hrs.

**Table 2:** Reaction duration of select (*Z*)-Bis(2,2,2-trifluoroethyl) alkenylphosphonates.

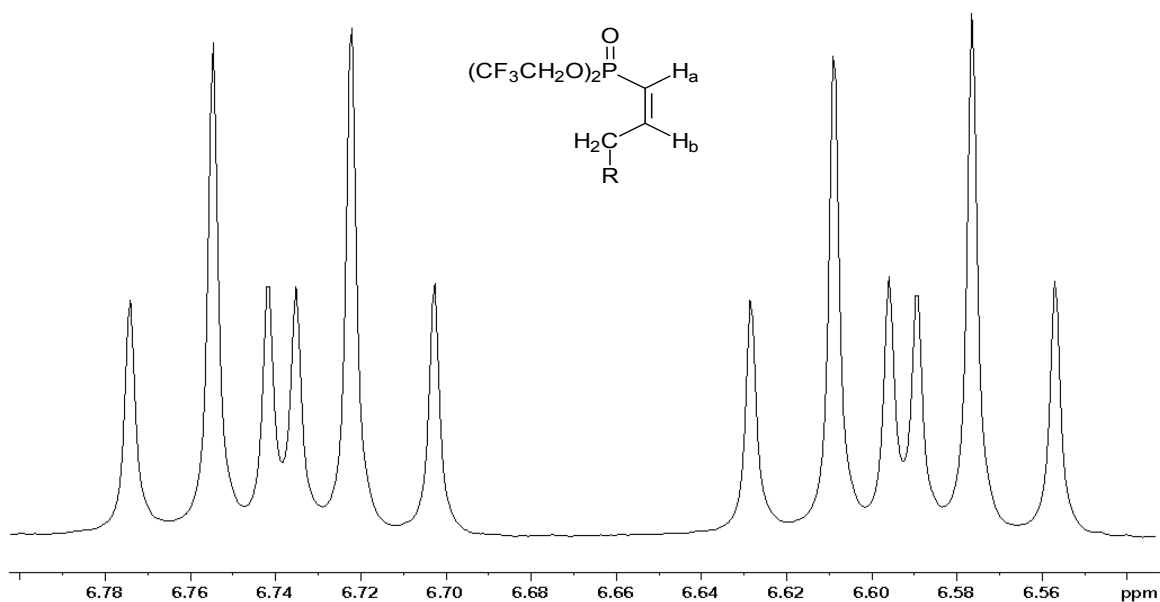
Several factors influencing the rate of a chemical reaction are temperature (thermodynamic versus kinetic product), concentration, physical state of the reactants and the presence of a catalyst. Another important consideration is reaction solvent. As illustrated in Table 2, reaction durations were upwards of 8 days when methanol was used. Solubility issues between polar methanol solvent and nonpolar alkenylphosphonate molecules would result in fewer interactions with the solid catalyst thereby causing the reaction to fail to go to completion. On the other hand, when 2,2,2-trifluoroethanol was the solvent of choice, reaction durations were shortened considerably. This may be due to the non-nucleophilic nature of 2,2,2-trifluoroethanol. 2,2,2-Trifluoroethanol is more acidic than methanol due to the electron withdrawing fluorine groups. 2,2,2-Trifluoroethanol has a  $pK_a$  of 12.5 while methanol has a  $pK_a$  of 15.5.

Of special interest were the coupling constants of the olefinic protons in following spectra of (*Z*)-alkenylphosphonates (Figure 4).



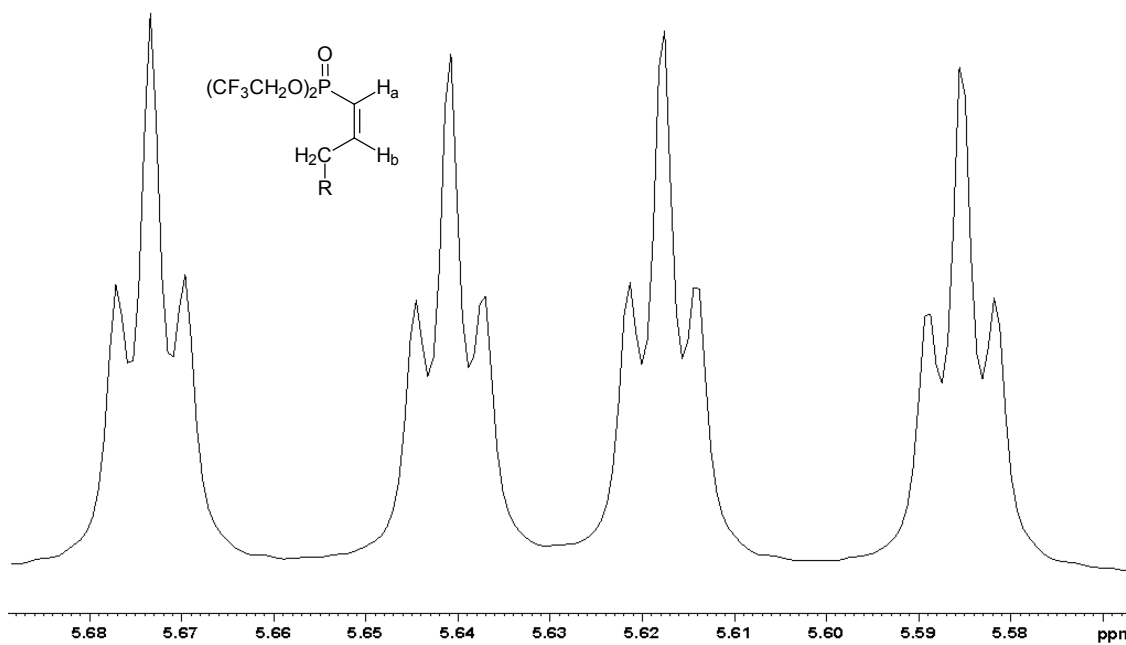
**Figure 4:**  $^1\text{H}$  NMR of bis(2,2,2-trifluoroethyl) oct-1-(*Z*)-enyl phosphonate (**12**).

In the proton spectrum of compound (**12**),  $\text{H}_b$  is a doublet of doublet of triplets (ddt) due to coupling with phosphorous (58.2 Hz), *cis* coupling to  $\text{H}_a$  (13.1 Hz) and vicinal coupling to the allylic protons (7.8 Hz).



**Figure 5:**  $^1\text{H}$  NMR of bis(2,2,2-trifluoroethyl) oct-1-(*Z*)-enyl phosphonate (**12**).

$H_a$  is a doublet of doublet of triplets (ddt) due to coupling with phosphorous (22.2 Hz), *cis* coupling to  $H_b$  (13.0 Hz) and allylic coupling to the allylic protons (1.5 Hz).



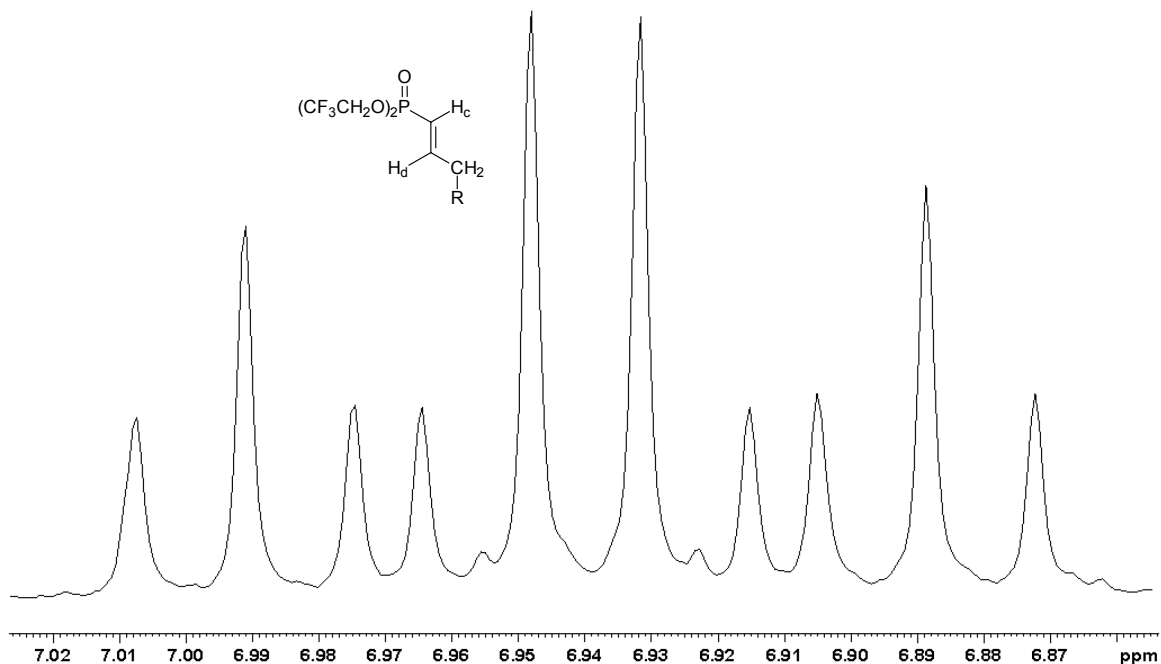
**Figure 6:**  $^1\text{H}$  NMR of bis(2,2,2-trifluoroethyl) oct-1-(*Z*)-enyl phosphonate (**12**).

The most noticeable difference between the signals of both  $H_b$  (Figure 5) and  $H_a$  (Figure 6) is the peak appearance. The coupling constant for each triplet is smaller for  $H_a$  than for  $H_b$  while the separation between each triplet is larger for  $H_a$  than  $H_b$ .

From the detailed spectrum, the hydrogen to phosphorus coupling ( $J_{H_a-P}$ ) is observed at 22.2 Hz while the phosphorus to  $H_b$  coupling was observed at 58.4 Hz.  $H_a$  is coupled differently to phosphorus than  $H_b$ . The *cis* coupling for  $H_a$  is 13.0 Hz, which is roughly equal to  $H_b$  at 13.1 Hz. As one might expect,  $H_a$  and  $H_b$  are coupled similarly to each other.

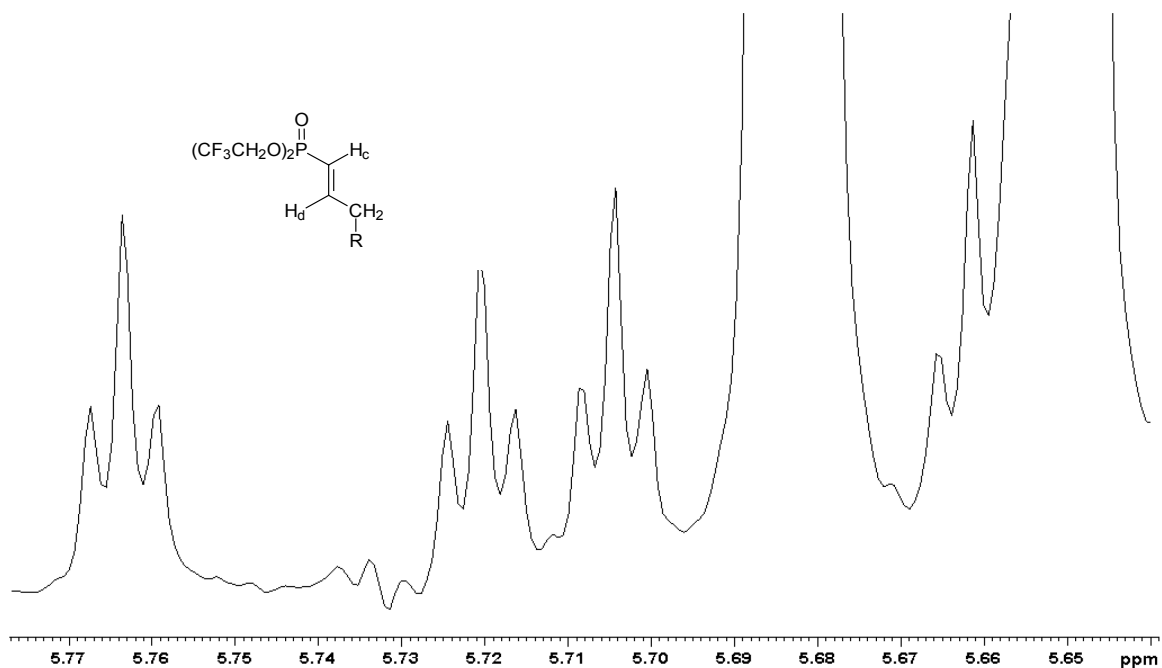


The coupling constant of phosphorous to hydrogen ( $J_{\text{Hb-P}}$ ) of the (*E*)-isomer is 23.8 Hz. The phosphorous to hydrogen coupling of the (*Z*)-isomer is 58.4 Hz. The overlapping signals are, indeed, a doublet of doublet of triplets.<sup>23</sup>



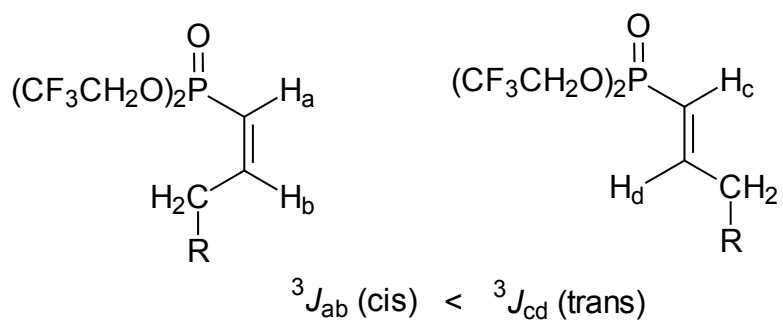
**Figure 7:** <sup>1</sup>H NMR of bis(2,2,2-trifluoroethyl) hept-1-(*E*)-enyl phosphonate (11).

The  $J_{\text{Ha-P}}$  coupling constant of the (*E*) and (*Z*)-isomers are reported as follows, 23.6 and 22.2 Hz respectively. Because the focus of this research was the synthesis of the (*Z*)-isomer, the (*E*)-isomer was not isolated in pure form. Therefore, the spectrum (Figure 8) is a crude mixture in which one of the peaks is obscured by the peak set corresponding to the more abundant and desired (*Z*)-isomer.



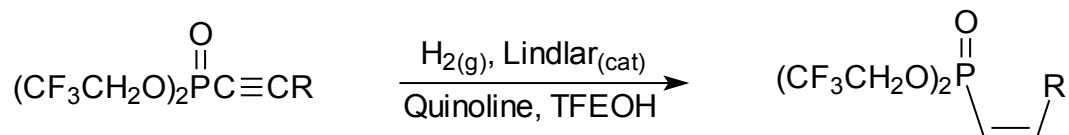
**Figure 8:**  $^1\text{H}$  NMR of bis(2,2,2-trifluoroethyl) hept-1-(*E*)-enyl phosphonate (**11**).

The vicinal coupling of  $\text{H}_b$  to the allylic protons on the adjacent carbon of the (*E*) isomer was observed at 6.6 Hz.



**Figure 9:** Diagram of the proton coupling of the (*Z*) and (*E*)-isomers.

The observed coupling constants were consistent with the literature values.<sup>18</sup>



**Scheme 34:** Hydrogenation of alkynylphosphonates to yield (Z)-alkenylphosphonates.

<b>Entry</b>	<b>Alkynylphosphonate</b>	<b>Alkenylphosphonate</b>	<b>Z:E (Yield)</b>
(3a)	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{C}\equiv\text{C}(\text{CH}_2)_2\text{CH}_3$	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{CH}=\text{C}(\text{CH}_2)_2\text{CH}_3$ ( <b>9</b> )	97:3 (65%)
(3b)	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{C}\equiv\text{C}(\text{CH}_2)_3\text{CH}_3$	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{CH}=\text{C}(\text{CH}_2)_3\text{CH}_3$ ( <b>10</b> )	96:4 (68%)
(3c)	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{C}\equiv\text{C}(\text{CH}_2)_4\text{CH}_3$	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{CH}=\text{C}(\text{CH}_2)_4\text{CH}_3$ ( <b>11</b> )	93:7 (43%)
(3d)	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{C}\equiv\text{C}(\text{CH}_2)_5\text{CH}_3$	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{CH}=\text{C}(\text{CH}_2)_5\text{CH}_3$ ( <b>12</b> )	99:1 (19%)
(3e)	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{C}\equiv\text{C}(\text{CH}_2)_6\text{CH}_3$	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{CH}=\text{C}(\text{CH}_2)_6\text{CH}_3$ ( <b>13</b> )	99:1 (42%)
(3f)	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{C}\equiv\text{C}(\text{CH}_2)_7\text{CH}_3$	$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{CH}=\text{C}(\text{CH}_2)_7\text{CH}_3$ ( <b>14</b> )	94:6 (14%)

**Table 3:** Yield of (Z) Bis(2,2,2-trifluoroethyl) alkenylphosphonates.

The hydrogenation reaction typically affords quantitative yields. Unfortunately, the data obtained does not reflect the expected outcome. Losses could have been attributed to the filtration and extraction steps. Once the reaction is deemed complete, which is evident by  $^{31}\text{P}$  NMR analysis as the disappearance of the starting material peak at -5.6 ppm, the mixture is filtered through Celite to remove the catalyst. If the Celite is not rinsed thoroughly enough with solvent or not allowed to filter under house vac long enough then losses can occur. Losses could also be attributed to the extraction step. After the excess solvent was evaporated and 10% HCl was added to the reaction mixture, it was allowed to stir for 15 minutes and was followed by extraction with ether. Additionally, the undesired (*E*)-isomer and other minor by-products (such as the overly hydrogenated product) were being formed in addition to the target.

Interestingly, when the hydrogenation reaction is run at reduced temperature, from -30 to -10 °C, the (*Z*)-isomer is said to be produced exclusively.<sup>21</sup> A single attempt was made to synthesize the (*Z*)-isomer of bis(2,2,2-trifluoroethyl)hept-1-enyl phosphonate exclusively. The usual reagents were used and added to the flask in the usual manner, but the reaction temperature was somewhat difficult to maintain. An ice water and calcium chloride bath was used to obtain the low temperature needed. It was monitored and maintained at temperatures between -5 to 0 °C.  $^{31}\text{P}$  NMR analysis taken at hour two showed the disappearance of the starting material peak at -5.5 ppm, two minor impurities at 24 and 28 ppm and the growing target molecule peak at 19.5 ppm but no (*E*)-isomer. However, the  $^{31}\text{P}$  NMR sample taken at the third hour shows the first appearance of the (*E*)-isomer peak at 22 ppm. In the hours following, the (*E*)-isomer peak height remains the same or even diminishes. The mixture was allowed to react for a total

of seven hours.  $^{31}\text{P}$  NMR analysis showed the (*Z*) and (*E*)-isomers, starting materials (less than 1%) and trace amounts of starting material impurities.

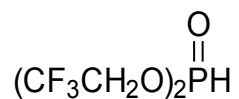
### **Summary and Conclusions**

In summary, the syntheses of (*Z*)-alkenylphosphonates have been successful with fair yields in most trials. Initially the reactions were run in methanol which resulted in long reaction times and very little conversion to product. Successful trials were realized once the switch to 2,2,2-trifluoroethanol reaction solvent was made. The reaction itself was carried out with relative ease using Lindlar's catalyst, quinoline and hydrogen gas to hydrogenate the triple bond of a variety of 1-alkynylphosphonates. However, the purification of the target molecule had been problematic using flash column chromatography. For example, a 60:40 hexane:ethyl acetate eluant on a 50 g silica gel column was successful in purifying bis(2,2,2-trifluoroethyl) hept-1-enylphosphonate but was unsuccessful, after several attempts, on related alkenylphosphonates. At that point, the research focus shifted toward finding, what appeared to be, the compound-specific eluant systems for the remaining six compounds. Bis(2,2,2-trifluoroethyl) non-1-enylphosphonate was successfully purified using a 90:10 hexanes:ethyl acetate and a 100 g silica gel column. Ideally, if the perfect reaction conditions existed, the necessity for further purification steps would be eliminated. Therefore, several trials of the hydrogenation at reduced temperature are needed so its practical aspects could be ascertained. Additionally, future research in a related area could include the syntheses of alkenylphosphonates from more complex alkynylphosphonates while an inquiry into the kinetics of this important reaction could also be a worthwhile endeavor.

## **Chapter 3: Experimental**

### **General Methods**

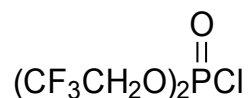
For all syntheses described herein, the glassware used was allowed to dry overnight in a drying oven. Where applicable, reduced temperatures of  $-78\text{ }^{\circ}\text{C}$  were achieved using a bath mixture of dry ice and acetone. Reactions requiring  $0\text{ }^{\circ}\text{C}$  and  $-10$  to  $0\text{ }^{\circ}\text{C}$  were accomplished using ice-water and ice-water calcium chloride baths, respectively. All reactions pertaining to starting material syntheses were carried out under an inert atmosphere of argon gas. Pentane was distilled from calcium hydride. Starting materials were purified using fractional vacuum distillation on a Vigreux column (300 mm). Thin layer chromatography (TLC) was performed on aluminum backed silica gel plates, visualized with a portable UV lamp, developed with a solution of 5% phosphomolybdic acid (PMA) in ethanol and subsequently heated with a heat gun. Purification by flash column chromatography was performed with silica gel (230-400 mesh,  $60\text{ }\text{\AA}$ ).  $^{31}\text{P}$  NMR,  $^{13}\text{C}$  NMR, and  $^1\text{H}$  NMR were performed on the Bruker Avance III AG 400 MHz (Oxford magnet, 2 channel, with indirect broadband probe) or the Avance III Ultrashield (magnet, 3 channel with broadband probe and autosampler) using deuteriochloroform ( $\text{CDCl}_3$ ) solvent. Phosphoric acid ( $\text{H}_3\text{PO}_4$ ) was the external standard used for  $^{31}\text{P}$  NMR analyses while the internal standards used for  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR analyses were tetramethylsilane, TMS (0 ppm) and  $\text{CDCl}_3$  (77.0 ppm) respectively. All coupling constants were calculated in Hertz (Hz).

**Bis(2,2,2-trifluoroethyl) phosphite (1).**

To a 1 L oven dried round bottom flask was added phosphorus trichloride (44.50 mL, 0.51 mol) in dry dichloromethane (100 mL). A pressure equalizing funnel containing anhydrous 2-methyl-2-propanol (37.00 g, 0.50 mmol) dissolved in dry dichloromethane (100 mL) delivered dropwise the mixture which was then cooled to 0 °C. The reaction mixture was allowed to stir for 75 minutes under an argon atmosphere. To the mixture was added 2,2,2-trifluoroethanol (100 g, 1 mol) dissolved in dry dichloromethane (100 mL) over a 30 minute period. The solution was allowed to stir 16 hours. Excess solvent was evaporated to concentrate the product. Distillation afforded pure compound **(1)** (103.05 g, 83.93%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.97

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.41-4.50 (m, 4H), 7.06 (d,  $J = 755.4$  Hz, 1H).

**Bis(2,2,2-trifluoroethyl) phosphorochloridate (2).**

To a 250 mL round bottom flask was added bis(2,2,2-trifluoroethyl) phosphite (30.14 g, 122 mmol) in benzene (38 mL). The mixture was cooled to 0 °C and sulfuryl chloride (14 mL, 23.34 g, 172.9 mmol) in benzene (38 mL) was added dropwise from a pressure equalizing addition funnel. While stirring, the contents were then allowed to warm to room temperature. The excess solvent was removed via rotary evaporation and

the crude material was distilled under vacuum to yield pure compound **(2)** (28.74 g, 83.60%).

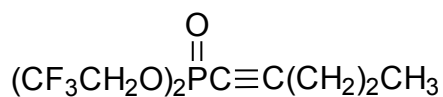
$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.68.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.48-4.57 (m, 4H).

### **Bis(2,2,2-trifluoroethyl) phosphonoalkynes**

**General procedure for the formation of bis(2,2,2-trifluoroethyl)-1-alkynylphosphonates.**

**Bis(2,2,2-trifluoroethyl) pent-1-ynylphosphonate (3).**



To an argon purged 1 L round bottom flask, a 1:1 pentane:ether (500 mL) solution was added via syringe. 1-Pentyne (10 mL, 100 mmol) was added, and the mixture was cooled to  $-78^\circ\text{C}$ . Once cool, *n*-butyllithium (60 mL, 96 mmol, 1.6 M in hexanes) was added dropwise over thirty minutes. The mixture was allowed to stir an additional hour. After which, the dry ice-acetone bath was removed and the reaction mixture was allowed to warm to room temperature. Once again the mixture was cooled back down to  $-78^\circ\text{C}$  and let stir for one hour. At that point, bis(2,2,2-trifluoroethyl) phosphorochloridate (14 mL, 81.1 mmol) was added slowly and the reaction mixture was allowed to stir overnight. The reaction mixture was carefully transferred to a separatory funnel and then quenched with a saturated solution of ammonium chloride (3 x 60 mL). The organic layers were combined and then rinsed with water (3 x 60 mL) to remove excess salts. The combined aqueous layers were subsequently extracted with ether (3 x 60 mL). All



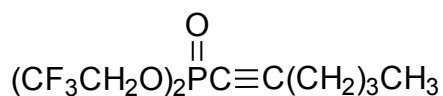
organic extracts were washed with Brine (3 x 60 mL) and then dried over anhydrous magnesium sulfate. The organic liquid was filtered then evaporated by rotary evaporation to concentrate the product. Purification by fractional distillation yielded compound **(3)** (18.06 g, 57%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -5.57

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.03 (t,  $J$  = 7.4 Hz, 3H), 1.62-1.68 (m, 2H), 2.39 (dt,  $J$  = 3.8, 7.1 Hz, 2H), 4.40 (dq,  $J$  = 6.6, 12.5 Hz, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.22, 20.66 (d,  $J$  = 2.4 Hz), 21.14, 62.68 (2, dq,  $J$  = 4.3, 35.7 Hz), 67.54 (d,  $J$  = 331.9 Hz), 107.21 (d,  $J$  = 58.9 Hz), 122.26 (2, dq,  $J$  = 10.1, 277.6 Hz).

**Bis(2,2,2-trifluoroethyl) hex-1-ynylphosphonate (4).**



To a solution of pentane and anhydrous ether (1:1, 500 mL) was added 1-hexyne (11.9 mL, 102.5 mmol). The solution was cooled to  $-78$  °C under argon atmosphere. *n*-Butyllithium (60.9 mL, 97.4 mmol, 1.6 M in hexanes) was added dropwise to the cooled solution while stirring over a one half hour period. The mixture was allowed to stir an additional hour under the same conditions. The reaction mixture was then allowed to warm to room temperature. The temperature was decreased to  $-78$  °C and bis(2,2,2-trifluoroethyl) phosphorochloridate (23.9 mL, 102.48 mmol) was added dropwise via syringe over a fifteen to thirty minute period. After stirring overnight, the reaction mixture was carefully transferred to a separatory funnel and then quenched with a saturated solution of ammonium chloride (3 x 30 mL). The organic layers were combined

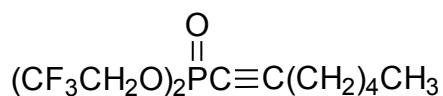
and then rinsed with water (3 x 30 mL) to remove excess salts. The combined aqueous layers were subsequently extracted with ether (3 x 30 mL). All organic extracts were washed with Brine (3 x 30 mL) and then dried over anhydrous magnesium sulfate. The organic liquid was filtered then evaporated by rotary evaporation to concentrate the product. The crude material was distilled under vacuum to afford pure compound (**4**) (17.23 g, 53%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  - 5.56.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.94 (t,  $J$  = 7.3 Hz, 3H), 1.44 (sextet,  $J$  = 7.4 Hz, 2H), 1.60 (quintet,  $J$  = 7.4, 2H), 2.41(dt,  $J$  = 3.8, 7.1 Hz, 2H), 4.40 (dq,  $J$  = 8.0, 8.0 Hz, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  12.99, 18.70 (d,  $J$  = 4.8 Hz), 21.66, 28.90 (d,  $J$  = 2.2 Hz), 62.53 (2, dq,  $J$  = 4.2, 38.3 Hz), 65.54 (d,  $J$  = 332.4 Hz), 107.60 (d,  $J$  = 59.1 Hz), 122.24 (2, dq,  $J$  = 10.2, 277.3 Hz).

**Bis(2,2,2-trifluoroethyl) hept-1-ynylphosphonate (5).**



To a 500 mL round bottom flask fitted with a septum was added pentane and anhydrous ether (250 mL) via syringe. 1-Heptyne (6.6 mL, 50 mmol) was added via syringe under argon atmosphere. While stirring, the reaction was cooled to -78 °C. Then *n*-butyllithium (29 mL, 46.4 mmol, 1.6 M in hexanes) was added slowly over a period of thirty minutes. The reaction mixture was allowed to stir an additional hour, after which, the bath was removed and the reaction mixture was allowed to warm to room temperature. The temperature was reduced to -78 °C and while stirring, bis(2,2,2-

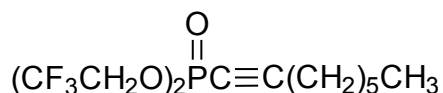
trifluoroethyl) phosphorochloridate (8.4 mL, 50 mmol) was added slowly, over a twenty minute period. The mixture was stirred overnight. The opaque reaction mixture was carefully transferred to a separatory funnel and then quenched with a saturated solution of ammonium chloride (3 x 40 mL). The organic layers were combined and then rinsed with water (3 x 40 mL) to remove excess salts. The combined aqueous layers were subsequently extracted with ether (3 x 40 mL). All organic extracts were washed with Brine (3 x 40 mL) and then dried over anhydrous magnesium sulfate. The organic liquid was filtered then evaporated by rotary evaporation to concentrate the product. Fractional distillation afforded pure compound **(5)** (2.356 g, 14%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -5.64

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.91 (t,  $J$  = 7.1 Hz, 3H), 1.30-1.50 (m, 4H), 1.62 (quintet,  $J$  = 7.3 Hz, 2H), 2.40 (dt,  $J$  = 3.8, 7.2 Hz, 2H), 4.39 (dq,  $J$  = 8.0, 8.2 Hz, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.57, 19.13 (d,  $J$  = 4.7 Hz), 21.88, 26.70 (d,  $J$  = 2.21 Hz), 30.78, 62.64 (2, dq,  $J$  = 4.2, 38.5 Hz), 67.46 (d,  $J$  = 331.2 Hz), 107.32 (d,  $J$  = 58.5 Hz), 122.27 (2, dq,  $J$  = 10.2, 277.4 Hz).

**Bis(2,2,2-trifluoroethyl) oct-1-ynylphosphonate (6).**



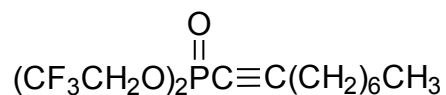
To a 500 mL round bottom flask, a 1:1 pentane:ether solution (250 mL) was added. 1-Octyne (7.2 mL, 50 mmol) was introduced via syringe and subsequently the temperature was reduced to  $-78$  °C. The reaction mixture was allowed to stir forty minutes. While stirring vigorously, *n*-butyllithium (34.4 mL, 55.0 mmol, 1.6 M in

hexanes) was added dropwise over thirty minutes. The reaction mixture was then allowed to stir an additional thirty minutes. The mixture equilibrated to room temperature and was again reduced to  $-78\text{ }^{\circ}\text{C}$ . Added slowly, over fifteen minutes, was bis(2,2,2-trifluoroethyl) phosphorochloridate (8.3 mL, 56 mmol). The mixture was stirred overnight. The reaction mixture was carefully transferred to a separatory funnel and then quenched with a saturated solution of ammonium chloride (3 x 30 mL). The organic layers were combined and then rinsed with water (3 x 30 mL) to remove excess salts. The combined aqueous layers were subsequently extracted with anhydrous ether (3 x 30 mL). All organic extracts were washed with Brine (3 x 30 mL) and then dried over anhydrous magnesium sulfate for 15-20 minutes. The organic liquid was filtered then concentrated en vacuo. The product was purified by fractional distillation which afforded pure compound **(6)** (10.96 g, 63%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -5.60.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.80 (t,  $J$  = 6.9 Hz, 3H), 1.17-1.26 (m, 4H), 1.28-1.36 (m, 2H), 1.52 (quintet,  $J$  = 7.4 Hz, 2H), 2.30 (dt,  $J$  = 3.8, 7.2 Hz, 2H), 4.30 (dq,  $J$  = 8.0, 8.3, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.95, 19.31 (d,  $J$  = 4.5 Hz), 22.39, 27.08 (d,  $J$  = 9.7 Hz), 28.41, 31.07, 62.72 (2, dq,  $J$  = 3.7, 38.4 Hz), 67.41 (d,  $J$  = 332.6 Hz), 107.50 (d,  $J$  = 58.9 Hz), 122.27 (2, dq,  $J$  = 10.1, 277.6 Hz).

**Bis(2,2,2-trifluoroethyl) non-1-ynylphosphonate (7).**

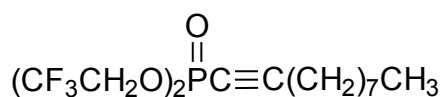
A 500 mL round bottom flask was purged with argon gas, then pentane-ether (1:1, 250 mL) was added via syringe as was 1-nonyne (8.2 mL, 50 mmol). The mixture was cooled to  $-78\text{ }^\circ\text{C}$ , while stirring. Over a thirty minute time period, *n*-butyllithium (30 mL, 48 mmol, 1.6 M in hexanes) was added dropwise and the reaction mixture allowed to stir an additional hour. Afterward, the reaction mixture was allowed to equilibrate to approximately  $0\text{ }^\circ\text{C}$ . The temperature was reduced to  $-78\text{ }^\circ\text{C}$  and bis(2,2,2-trifluoroethyl) phosphorochloridate (9.1 mL, 56 mmol) was added slowly. The mixture was allowed to stir overnight. The reaction mixture was carefully transferred to a separatory funnel and then quenched with a saturated solution of ammonium chloride (3 x 60 mL). The organic layers were combined and then rinsed with water (3 x 60 mL) to remove excess salts. The combined aqueous layers were subsequently extracted with ether (3 x 60 mL). All organic extracts were washed with Brine (3 x 60 mL) and then dried over anhydrous magnesium sulfate. The organic liquid was filtered then evaporated by rotary evaporation to concentrate the product. Vacuum distillation of the crude material afforded pure compound **(7)** (8.96 g, 49%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -5.60.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.89 (t,  $J = 6.9$  Hz, 3H), 1.21-1.29 (m, 6H), 1.30-1.32 (m, 2H), 1.61 (quintet,  $J = 7.3$  Hz, 2H), 2.38 (dt,  $J = 3.8, 7.1$  Hz, 2H), 4.39 (dq,  $J = 8.0, 8.0$  Hz, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.02, 19.22, 22.57, 27.21, 28.62, 28.74, 31.56, 62.56 (2, dq,  $J = 3.8, 38.0$  Hz), 69.06 (d,  $J = 330.0$  Hz), 105.2 (d,  $J = 59.3$  Hz), 122.5 (2, dq,  $J = 11.4, 277.7$  Hz).

**Bis(2,2,2-trifluoroethyl) dec-1-ynylphosphonate (8).**



A 500 mL round bottom flask was purged with argon gas, then the pentane-ether (1:1, 250 mL) solvent was added via syringe as was the 1-decyne (9.0 mL, 50 mmol). The mixture was cooled to  $-78$  °C, while stirring. Added dropwise over a 30 minute time period was *n*-butyllithium (29.0 mL, 46.4mmol, 1.6 M in hexanes). The mixture was allowed to stir an additional hour. Afterwards, it was allowed to equilibrate to approximately 0 °C. The temperature was then reduced to  $-78$  °C and bis(2,2,2-trifluoroethyl) phosphorochloridate (56 mmol, 9.3 mL) was added slowly over a 20 minute interval. The mixture was allowed to stir overnight. The reaction mixture was carefully transferred to a separatory funnel and then quenched with a saturated solution of ammonium chloride (3 x 40 mL). The organic layers were combined and then rinsed with water (3 x 40 mL) to remove excess salts. The combined aqueous layers were subsequently extracted with ether (3 x 40 mL). All organic extracts were washed with Brine (3 x 40 mL) and then dried over anhydrous magnesium sulfate. The organic liquid was filtered to remove the drying agent then evaporated by rotary evaporation to concentrate the product.. Vacuum distillation of the crude material afforded compound **(8)** (2.779 g, 15%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -5.61.

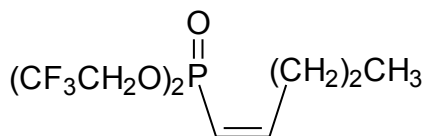
$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.89 (t,  $J = 6.9$  Hz, 3H), 1.28-1.32 (m, 8H), 1.38-1.42 (m, 2H), 1.61 (quintet,  $J = 7.4$  Hz, 2H), 2.40 (dt,  $J = 3.8, 7.1$ , 2H), 4.40 (dq,  $J = 8.2, 8.3$  Hz, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.74, 19.04 (d,  $J = 4.7$  Hz), 22.45, 26.95 (d,  $J = 8.1$  Hz), 28.59, 28.74, 28.88, 31.60, 62.54 (2, dq,  $J = 4.3, 38.3$  Hz), 67.25 (d,  $J = 331.5$  Hz), 107.38 (d,  $J = 58.8$  Hz), 122.25 (2, dq,  $J = 10.2, 277.4$  Hz).

**Bis(2,2,2-trifluoroethyl) phosphonoalkenes**

**General procedure for the formation of bis(2,2,2-trifluoroethyl)-1-alkenylphosphonates.**

**Bis(2,2,2-trifluoroethyl) pent-1-enylphosphonate (9).**



To a 50 mL two necked flask was added Lindlar catalyst (0.107 g) and quinoline (0.15 mL, 1.2 mmol). The flask was purged with hydrogen gas prior to the addition, via syringe, of 2,2,2-trifluoroethanol (16.0 mL, 222 mmol) and bis(2,2,2-trifluoroethyl)1-pentynyl phosphonate (1.55 g, 3.84 mmol). Hydrogen gas was added to the flask while stirring vigorously and the reaction was monitored until it was complete, 4.5 hours. The mixture was filtered through a three centimeter layer of Celite. The filtrate was concentrated by rotary evaporation then HCl (10%, 16 mL) was added and the mixture was allowed to stir 15 minutes. The reaction mixture was added to a separatory funnel and diethyl ether (3 x 20 mL) was added, shaken and allowed to set for 10 minutes. The organic layers were combined and dried over magnesium sulfate, then filtered and finally concentrated en vacuo. Purification by flash column chromatography (50 g silica, 90:10 hexane:ethyl acetate) yielded compound **(9)** (0.644 g, 65%).

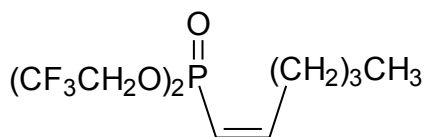
$^{31}\text{P}$  ( $\text{CDCl}_3$ )  $\delta$  19.97

$^1\text{H}$  ( $\text{CDCl}_3$ )  $\delta$  0.96 (t,  $J = 7.41$  Hz, 3H), 1.50 (sextet  $J = 7.39$  Hz, 2H), 2.42-2.55 (m, 2H), 4.37 (dq,  $J = 8.1, 8.2$  Hz, 4H), 5.56 (ddt,  $J = 1.49, 12.99, 22.48$  Hz, 1H), 6.68 (ddt,  $J = 6.48, 14.76, 58.45$  Hz, 1H).



$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.48, 21.86, 32.99 (d,  $J = 8.74$  Hz), 61.71 (2, dq,  $J = 4.99$ , 37.93 Hz), 113.33 (d,  $J = 190.1$  Hz), 122.60 (2, dq,  $J = 8.96$ , 277.54 Hz), 157.89 (d,  $J = 5.30$  Hz).

**Bis(2,2,2-trifluoroethyl) hex-1-enylphosphonate (10).**



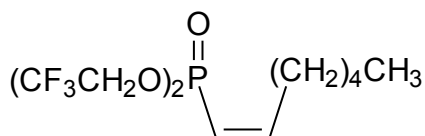
To a 50 mL two necked round bottom flask was added Lindlar catalyst (0.165 g) and quinoline (0.2 mL, 1.7 mmol). After the flask was purged with hydrogen gas, 2,2,2-trifluoroethanol (20.0 mL, 278 mmol) was added through a syringe followed by bis(2,2,2-trifluoroethyl)1-hexynyl phosphonate (2.03 g, 5.18 mmol). While the mixture was stirring vigorously, hydrogen gas was introduced.  $^{31}\text{P}$  NMR analysis showed the reaction was complete in 2.5 hours. The mixture was filtered through Celite and excess solvent was subsequently evaporated using the rotary evaporator. HCl (10%, 18 mL) was added and the mixture was allowed to stir fifteen minutes. The mixture was carefully transferred to a separatory funnel. Anhydrous diethyl ether (3 x 30 mL) was added, shaken and allowed to set for the standard time period (10 – 15 minutes). The organic layers were combined and were dried over magnesium sulfate, filtered then concentrated en vacuo. The crude product was purified by flash column chromatography (50 g silica, 85:15 hexane:ethyl acetate) to yield pure compound **(10)** (1.06 g, 68%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.88

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.92 (t,  $J = 7.2$  Hz, 3H), 1.33-1.50 (m, 4H), 2.50-2.60 (m, 2H), 4.37 (dq,  $J = 8.0, 8.1$ , 4H), 5.64, (ddt,  $J = 1.5, 12.9, 22.3$  Hz, 1H), 6.68 (ddt,  $J = 6.5, 14.8, 58.3$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.52, 22.08, 30.64, 30.83, 61.58 (2, dq,  $J = 5.0, 38.0$  Hz), 112.99 (d,  $J = 190.1$  Hz), 122.56 (2, dq,  $J = 8.9, 277.4$  Hz), 157.93 (d,  $J = 5.6$  Hz).

**Bis(2,2,2-trifluoroethyl) hept-1-enylphosphonate (11).**



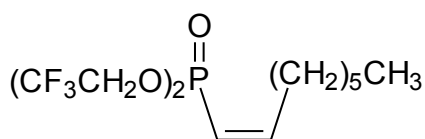
A 50 mL two necked round bottom flask was charged with quinoline (0.2 mL, 1.7 mmol) and Lindlar catalyst (0.147 g) then purged with hydrogen gas. Using a syringe, 2,2,2-trifluoroethanol (20.0 mL, 278 mmol) and bis(2,2,2-trifluoroethyl) 1-heptynyl phosphonate (2.02 g, 4.59 mmol) were introduced to the flask. The reaction stirred vigorously as the gas was added through the gas adapter.  $^{31}\text{P}$  NMR monitoring of the reaction showed complete transformation of starting materials to product after 24 hours. The mixture was then filtered through Celite and subsequently rotary evaporated to remove excess solvent. Added to the flask was HCl (10%, 18 mL). The mixture was allowed to stir for fifteen minutes which was followed by extraction with anhydrous diethyl ether (3 x 30 mL). The organic layers were combined, dried over magnesium sulfate, then filtered and concentrated en vacuo. Purification via flash column chromatography (100 g silica gel, 60:40 hexane: ethyl acetate,  $R_f = 0.58$ ) yielded pure compound (**11**) (0.674 g, 43%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.01.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.89 (t,  $J = 4.64$  Hz, 3H), 1.30-1.34 (m, 4H), 1.42-1.49 (m, 2H), 2.49-2.56 (m, 2H), 4.37 (dq,  $J = 8.1$  8.2 Hz, 4H), 5.64 (ddt,  $J = 1.46, 12.96, 22.31$  Hz, 1H), 6.68 (ddt,  $J = 6.50, 14.77, 58.37$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.87, 22.38, 28.30 (d,  $J = 2.0$  Hz), 31.14 (d,  $J = 8.77$  Hz), 31.26, 61.69 (2, dq,  $J = 4.98, 37.97$  Hz), 113.08 (d,  $J = 189.9$  Hz), 122.60 (2, dq,  $J = 8.99, 277.60$  Hz), 158.14 (d,  $J = 5.3$  Hz).

**Bis(2,2,2-trifluoroethyl) oct-1-enylphosphonate (12).**



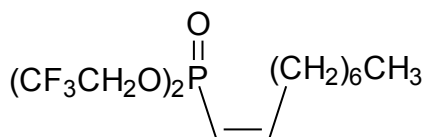
Lindlar catalyst (0.130 g) and quinoline (0.2 mL, 1.7 mmol) were added to a 50 mL round bottom flask which was then purged with hydrogen gas. 2,2,2-Trifluoroethanol (20.0 mL, 278 mmol) was added via syringe immediately preceding the addition of bis(2,2,2-trifluoroethyl)1-octynyl phosphonate (1.86 g, 4.07 mmol). Hydrogen gas was introduced while the reaction mixture stirred vigorously. Upon  $^{31}\text{P}$  NMR confirmation that the reaction was complete, the mixture was subsequently filtered, excess solvent was evaporated via rotary evaporator. Hydrochloric acid (10%, 18 mL) was added and was allowed to stir vigorously for 15 minutes. The mixture was then carefully poured into a separatory funnel. Added to the funnel was anhydrous diethyl ether (3 x 30 mL). The funnel was shaken and allowed to set. The layers were separated. The organic layers were combined then dried over magnesium sulfate, filtered, then removed under vacuum to concentrate the crude product. Flash column chromatography (100 g silica gel, 60:40 hexane:ethyl acetate) yielded compound **(12)** (0.33g, 19%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.9

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.9$  Hz, 3H), 1.2-1.4 (m, 6H), 1.4-1.5 (m, 2H) 2.48-2.56 (m, 2H), 4.36 (dq,  $J = 8.1, 8.2$ , 4H), 5.63 (ddt,  $J = 1.5, 13.0, 22.2$  Hz, 1H), 6.67 (ddt,  $J = 7.8, 13.0, 58.3$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.05, 22.59, 28.66, 29.06 (d,  $J = 6.7$  Hz), 31.21 (d,  $J = 8.8$  Hz), 31.69, 61.71 (2, dq,  $J = 4.9, 37.9$  Hz), 113.1 (d,  $J = 190.1$  Hz), 122.60 (2, dq,  $J = 9.6, 277.5$  Hz), 158.18 (d,  $J = 5.3$  Hz).

**Bis(2,2,2-trifluoroethyl) non-1-enylphosphonate (13).**



A 50 mL two necked round bottom flask was charged with Lindlar catalyst (0.169 g) and quinoline (0.2 mL, 1.7 mmol). After the flask was purged with hydrogen gas, 2,2,2-trifluoroethanol (20.0 mL, 278 mmol) and bis(2,2,2-trifluoroethyl) 1-nonyl phosphonate (2.34 g, 5.29 mmol) were added via syringe. While stirring vigorously, the hydrogen gas was introduced. The reaction was monitored at 1.5 hours initially, then every half hour until complete consumption of starting material was achieved, which occurred after 3.25 hours. The mixture was filtered through Celite then excess solvent was removed by rotary evaporation. HCl (10%, 21.0 mL) was added and the solution was allowed to stir vigorously for 15 minutes. The reaction mixture was transferred to a separatory funnel. Extraction with ether (3 x 30mL) was executed. The combined organic layers were dried over magnesium sulfate, filtered then concentrated en vacuo.

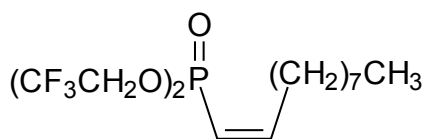
Purification by flash column chromatography (100 g silica gel, 85:15 hexane:ethyl acetate, 100% ethyl acetate) produced compound **(13)** (0.767 g, 42%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.01.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 7.0$  Hz, 3H), 1.30-1.39 (m, 8H) 1.40-1.42 (m, 2H), 2.51-2.53 (m, 2H), 4.34 (dq,  $J = 8.1, 8.2$ , 4H), 5.64, (ddt,  $J = 1.5, 13.0, 22.3$  Hz, 1H), 6.67 (ddt,  $J = 6.5, 14.8, 58.4$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.06, 22.59, 28.67 (d,  $J = 2.1$  Hz), 29.03, 29.10, 31.21 (d,  $J = 8.8$  Hz), 31.70, 61.72 (2, dq,  $J = 5.1, 37.9$  Hz), 113.08 (d,  $J = 190.0$  Hz), 122.60 (2, dq,  $J = 8.9, 277.6$  Hz), 158.2 (d,  $J = 6.0$  Hz).

**Bis(2,2,2-trifluoroethyl) dec-1-enylphosphonate (14).**



To a 50 mL two necked flask was added bis(2,2,2-trifluoroethyl)1-decynyl phosphonate (2.223g, 6.1 mmol), Lindlar catalyst (0.143 g) and quinoline (0.20 mL, 1.7 mmol). 2,2,2-Trifluoroethanol (20 mL, 278 mmol) was added via syringe. Hydrogen was added to the flask while stirring vigorously and the reaction was monitored at hour two. The mixture was filtered through a 3 cm layer of Celite. The excess solvent was evaporated then HCl (10%, 20 mL) was added. The mixture stirred fifteen minutes. Then the liquid was poured carefully into a separatory funnel. Anhydrous diethyl ether (3 x 20 mL) was added to the funnel and then shaken. The liquid was allowed to set for the usual duration. Two layers were evident and subsequently separated. The organic layers

were combined and dried over magnesium sulfate, filtered and concentrated en vacuo.

Purification by flash column chromatography (50 g silica gel, 90:10 hexane:ethyl acetate) yielded the target (*Z*) isomer, compound (**14**) (0.311 g, 14%).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.04.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.9$  Hz, 3H), 1.30-1.39 (m, 10H) 1.40-1.49 (m, 2H), 2.45-2.55 (m, 2H), 4.36 (dq,  $J = 8.1, 8.2$ , 4H), 5.64, (ddt,  $J = 1.4, 12.9, 22.4$  Hz, 1H), 6.67 (ddt,  $J = 6.5, 14.8, 58.4$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.99, 22.61, 28.63 ( $J = 2.1$  Hz), 29.12, 29.24, 29.30, 31.16 (d,  $J = 8.8$  Hz), 31.77, 61.67 (2, dq,  $J = 4.9, 37.9$  Hz), 113.04 (d, 190.1 Hz), 122.6 (2, dq,  $J = 9.0, 277.6$  Hz), 158.13 (d,  $J = 5.5$  Hz).

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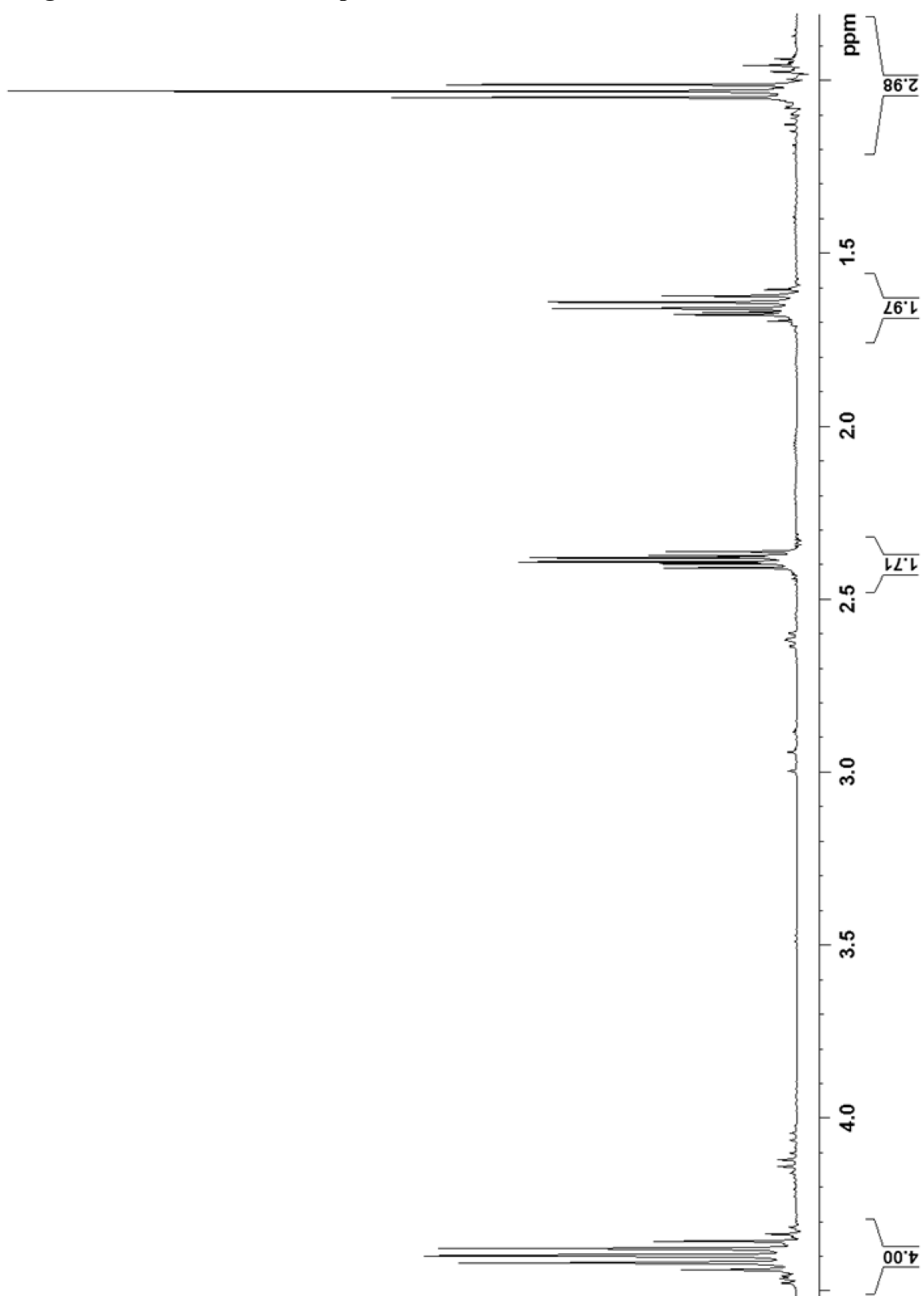
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**Figure 10**  $^1\text{H}$  NMR of Compound 3

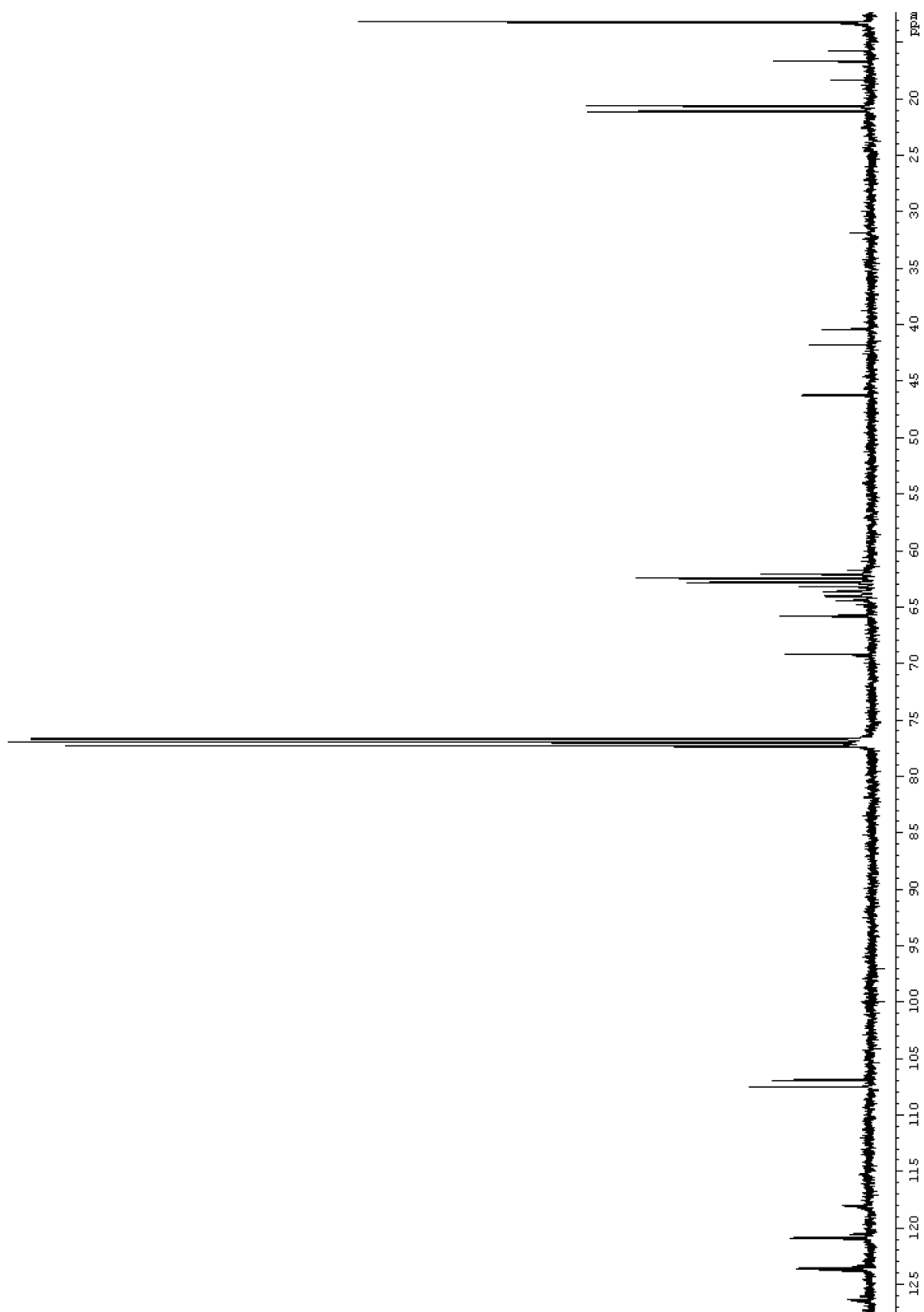
**Figure 11**  $^{13}\text{C}$  NMR of Compound 3

Figure 12  $^{31}\text{P}$  NMR of Compound 3

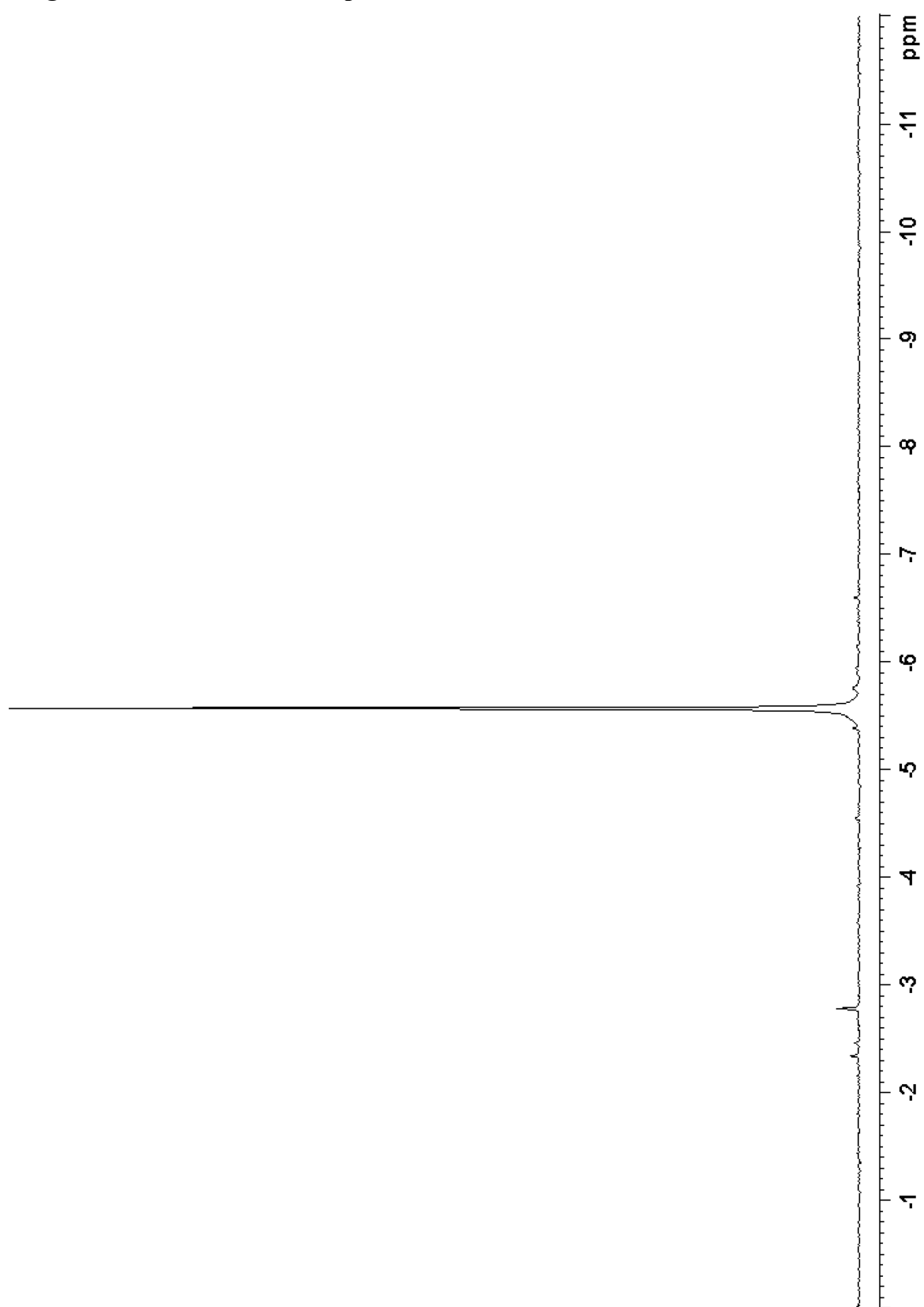
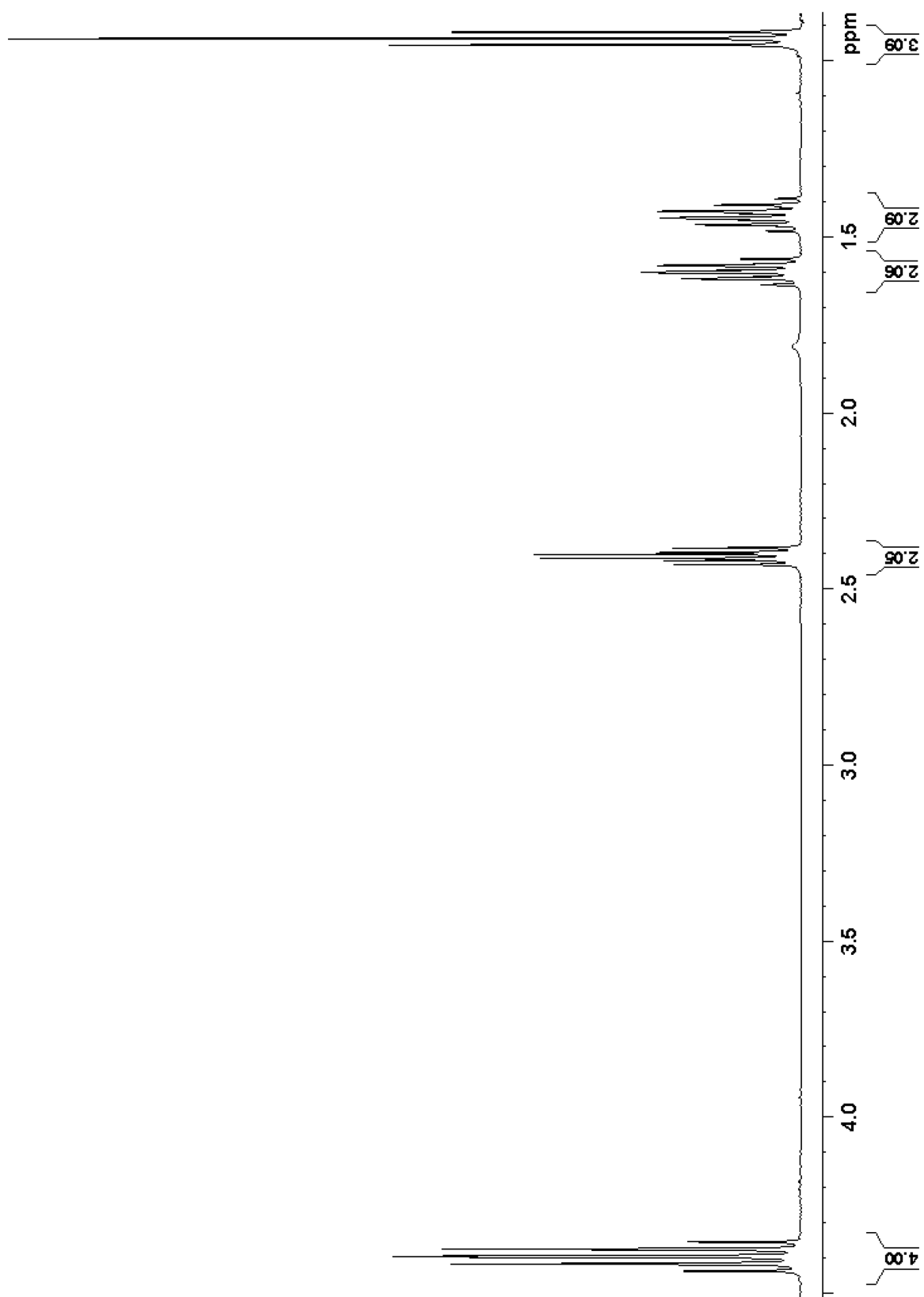


Figure 13  $^1\text{H}$  NMR of Compound 4

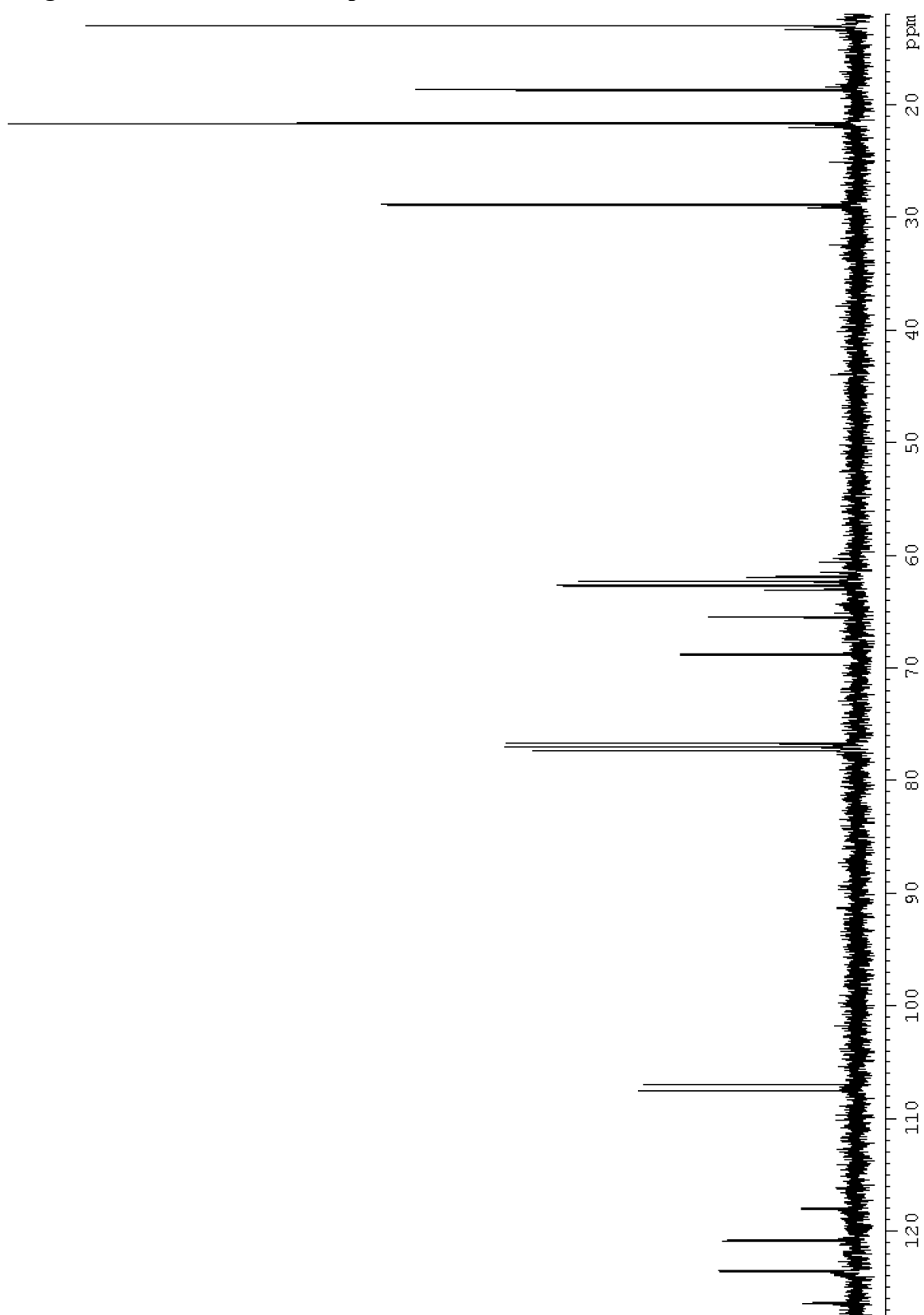
**Figure 14**  $^{13}\text{C}$  NMR of Compound 4

Figure 15  $^{31}\text{P}$  NMR of Compound 4

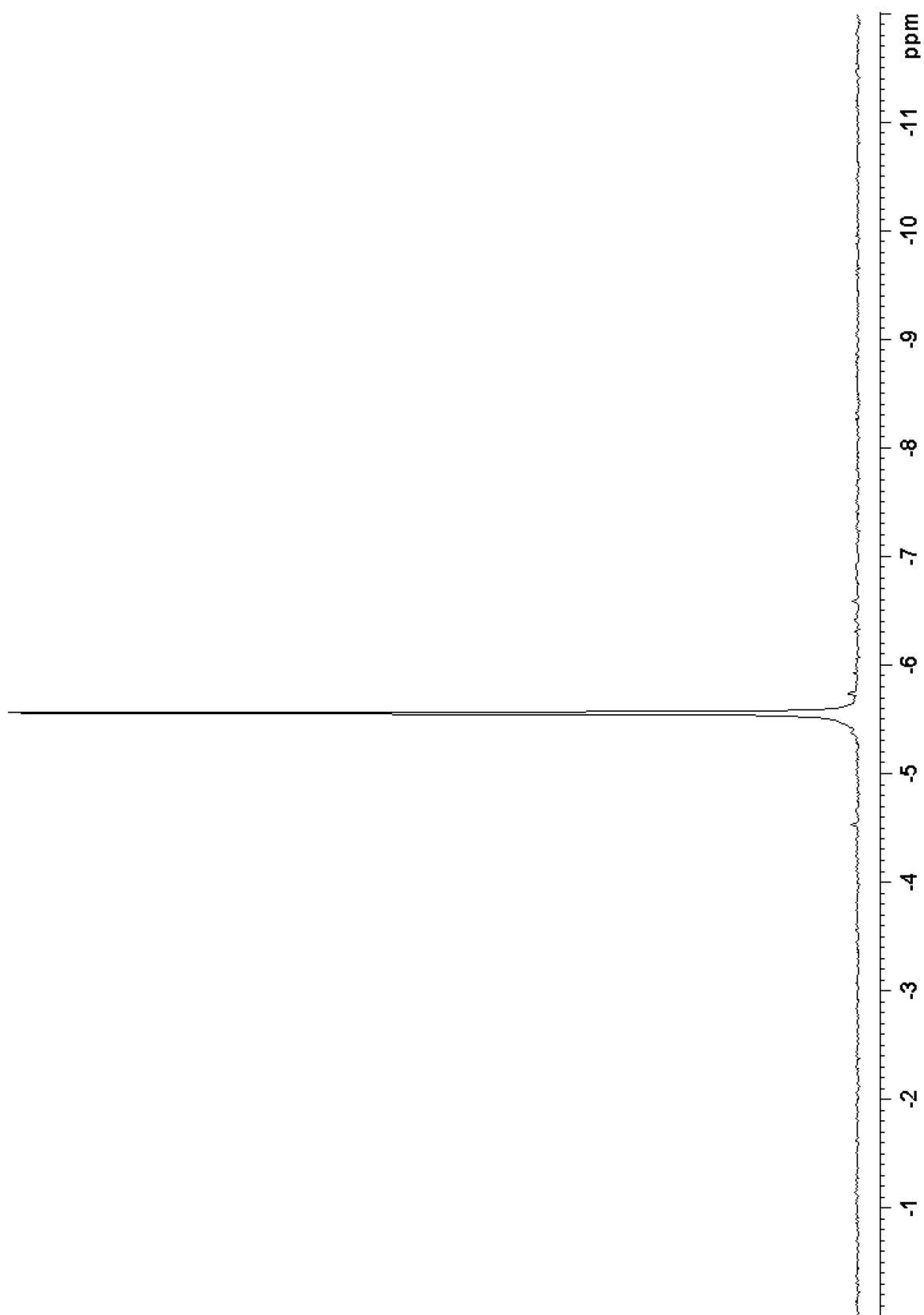
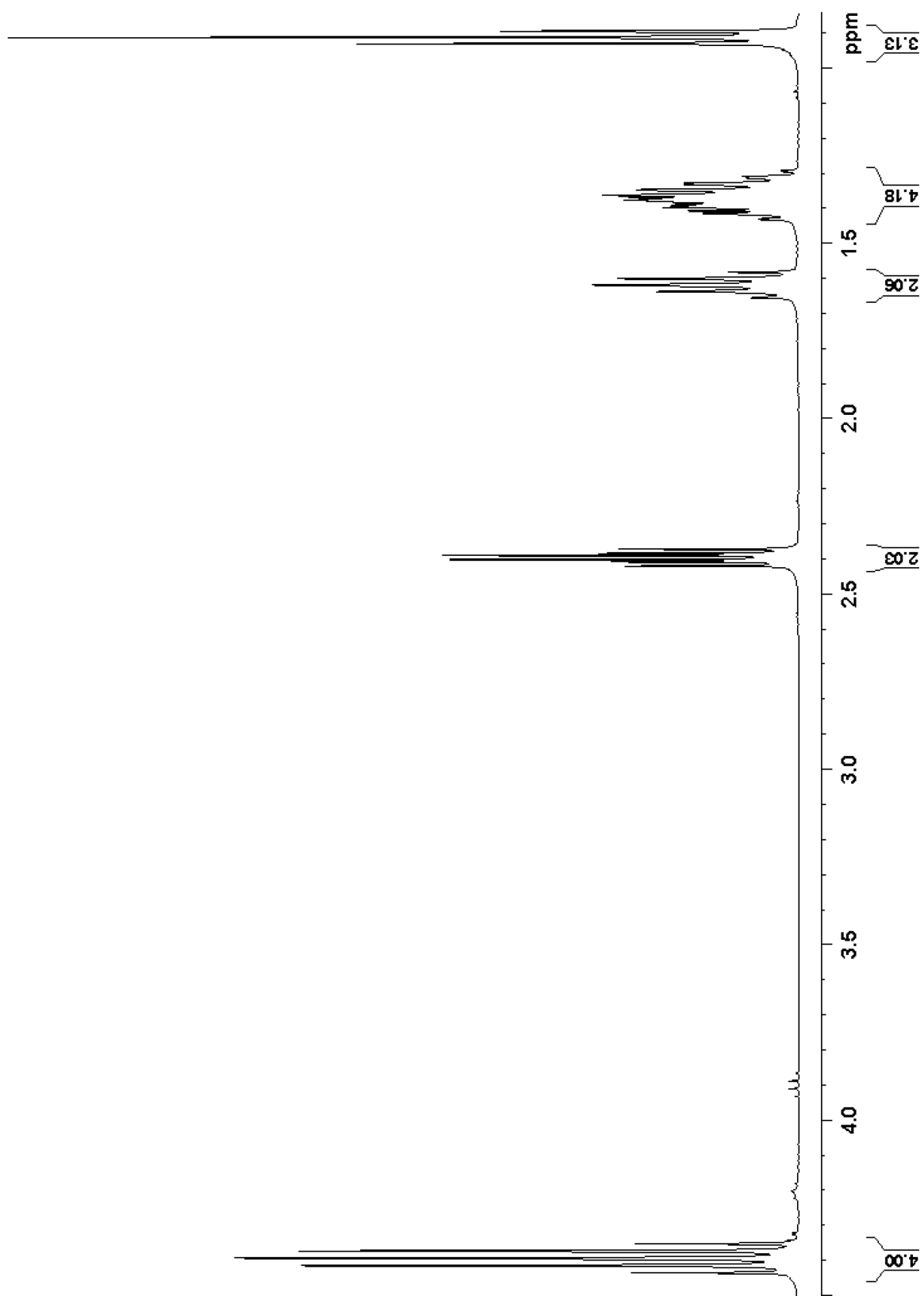
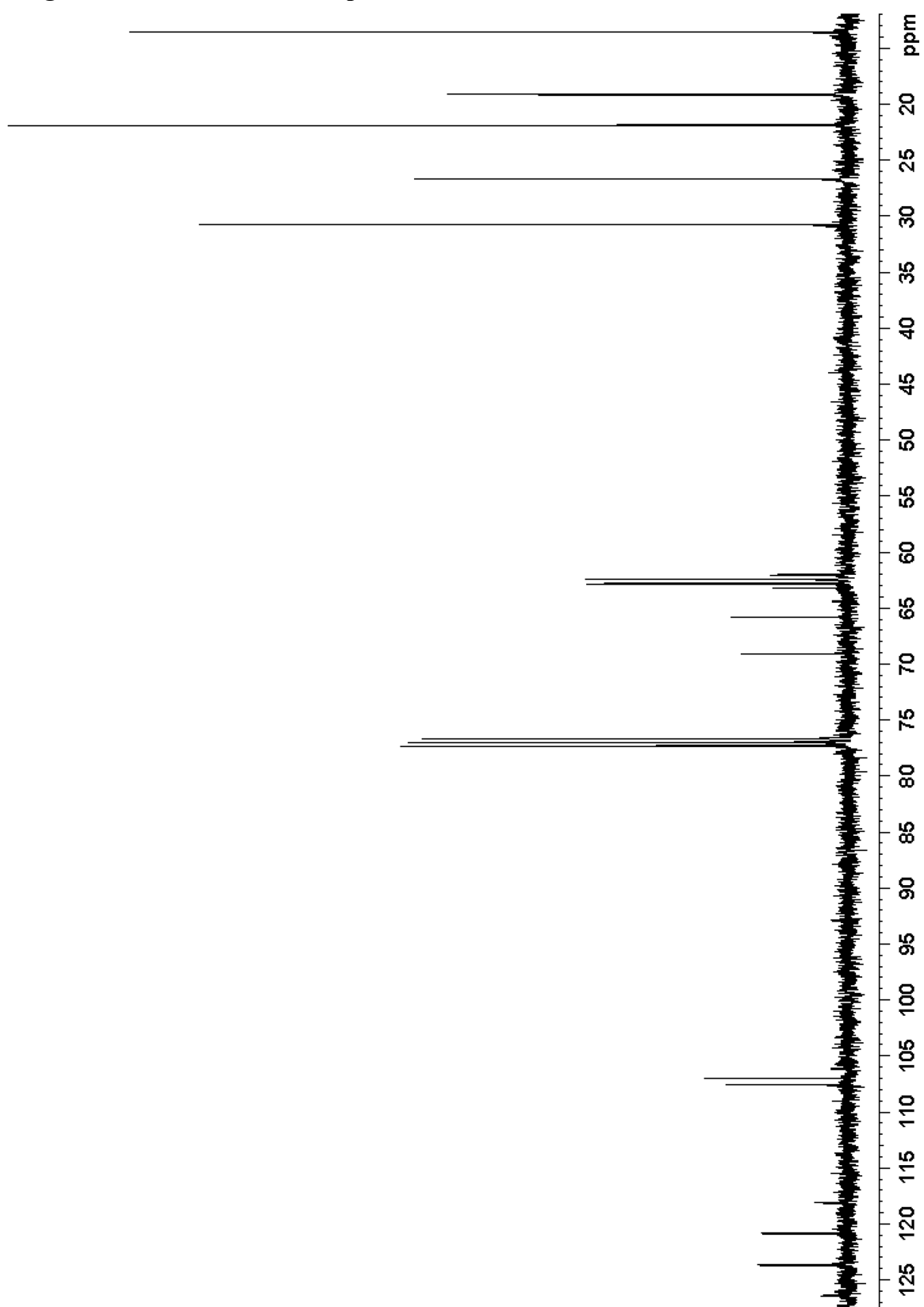


Figure 16  $^1\text{H}$  NMR of Compound 5



**Figure 17**  $^{13}\text{C}$  NMR of Compound 5

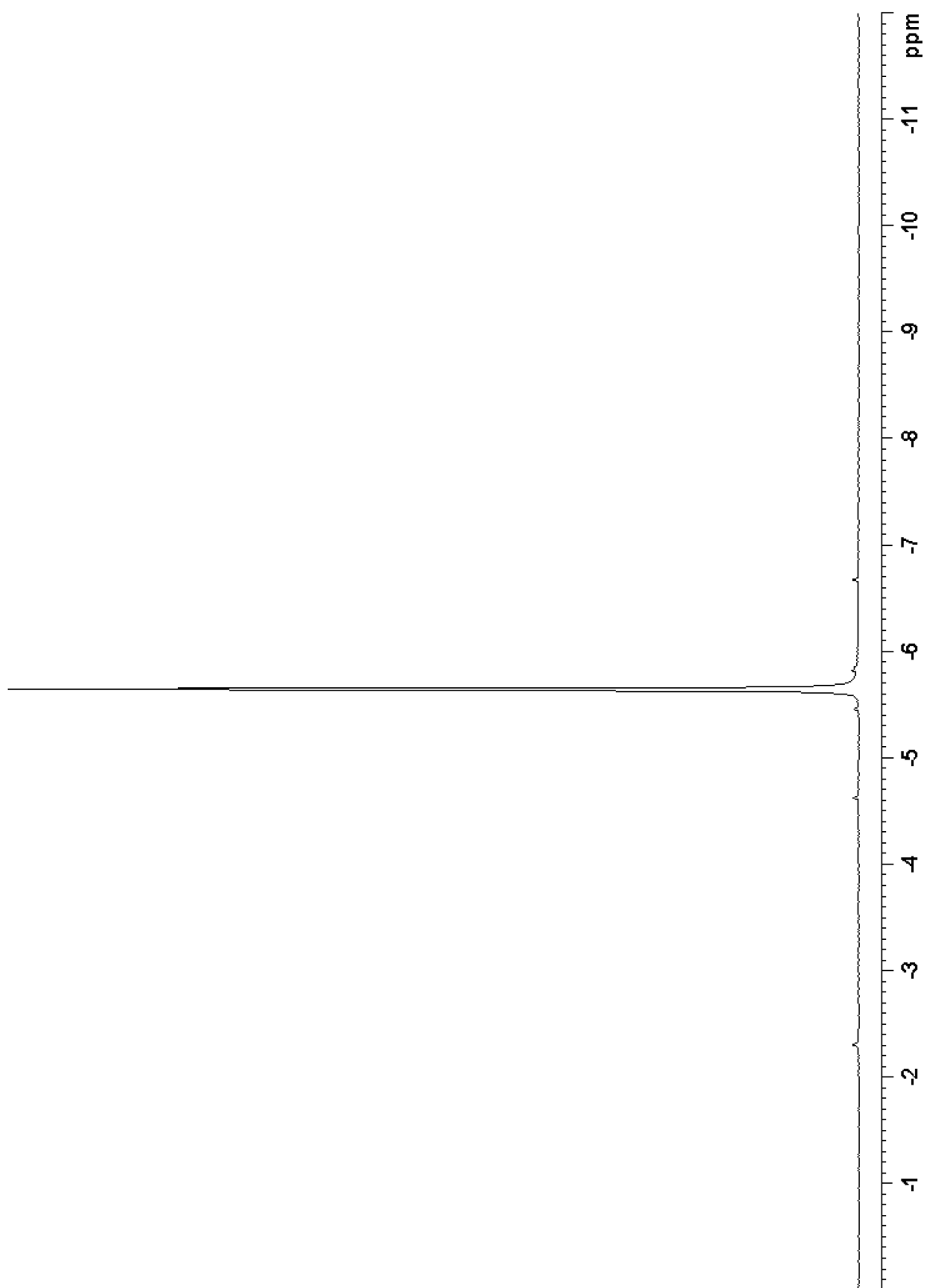
**Figure 18**  $^{31}\text{P}$  NMR of Compound 5

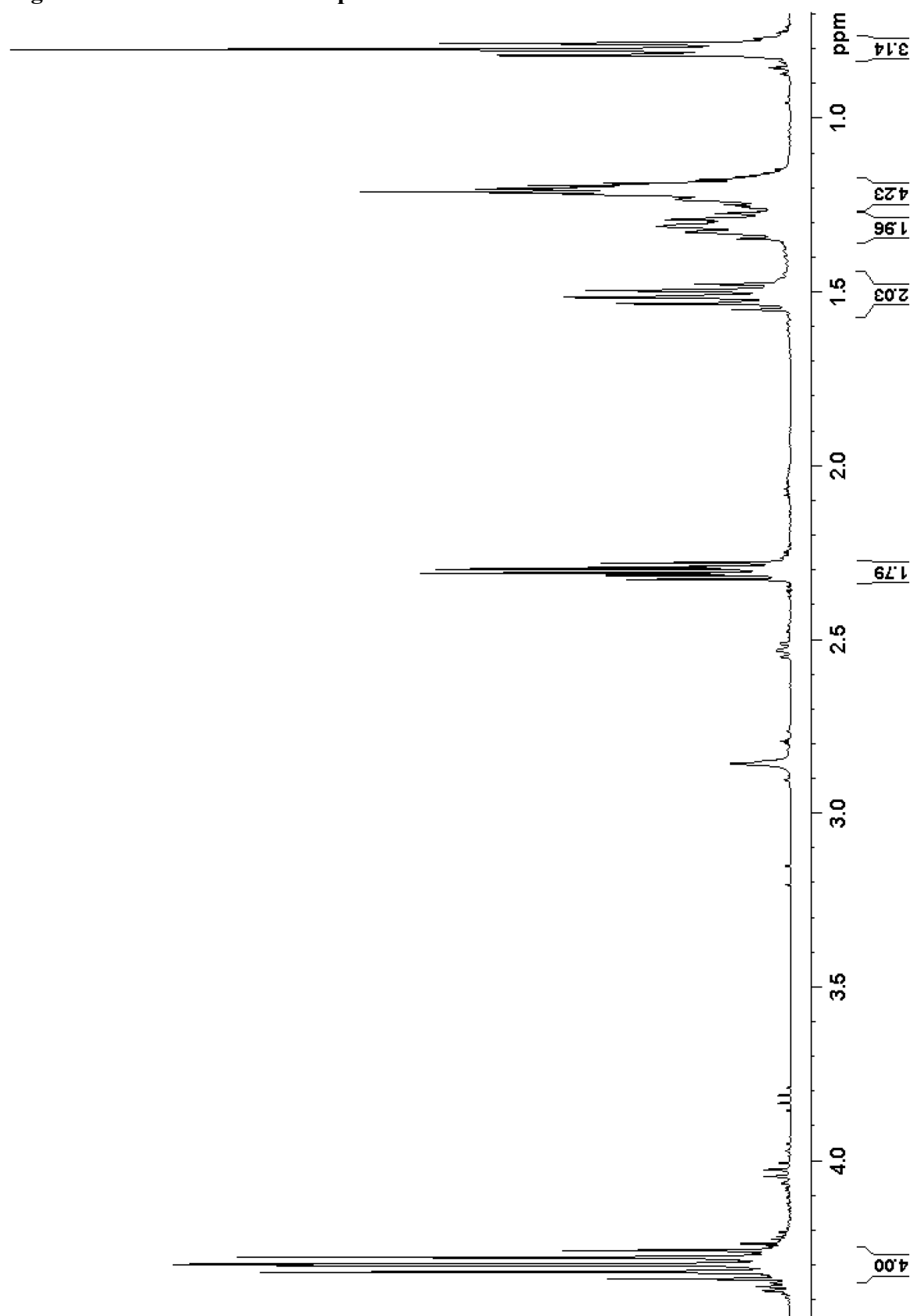
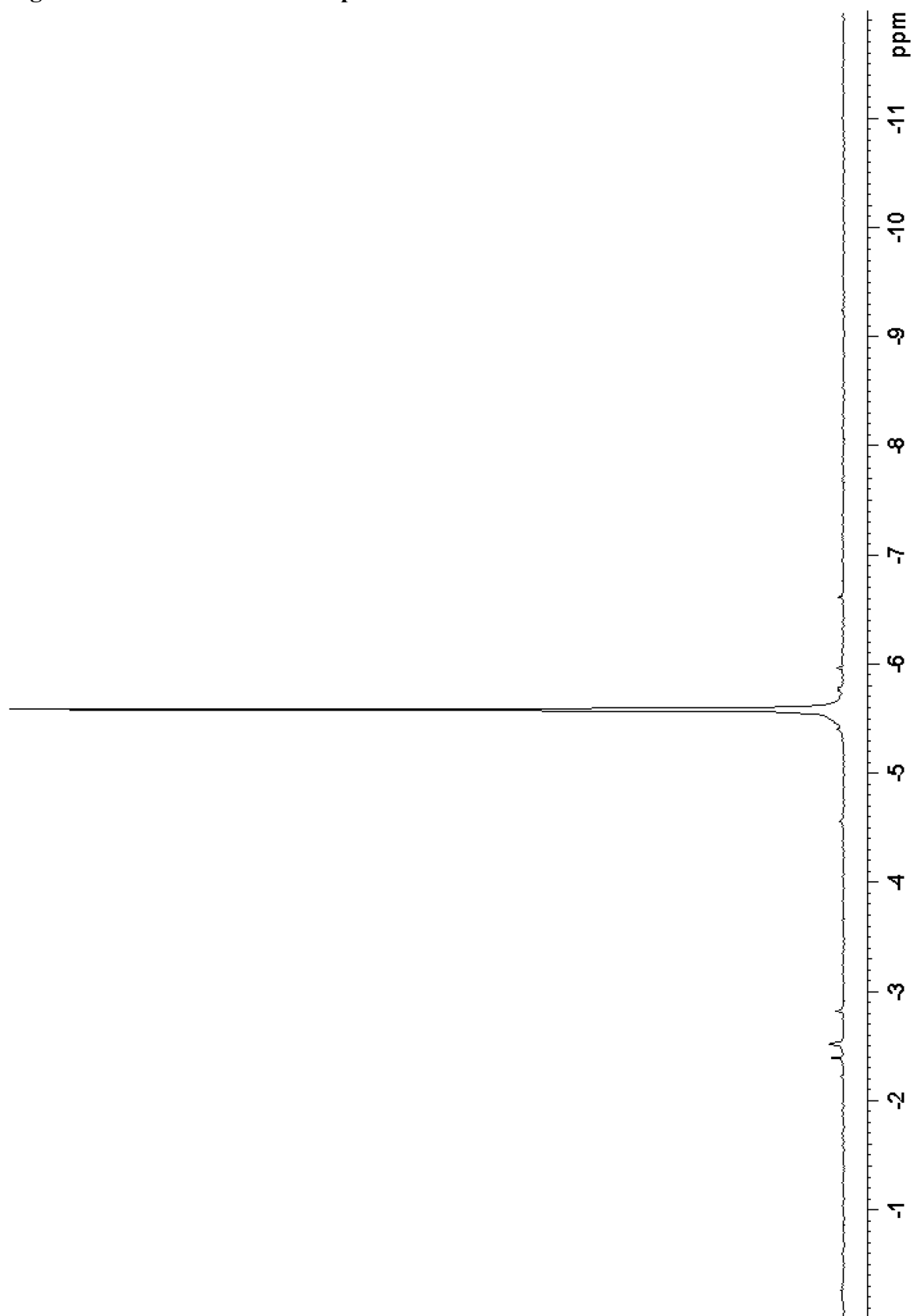
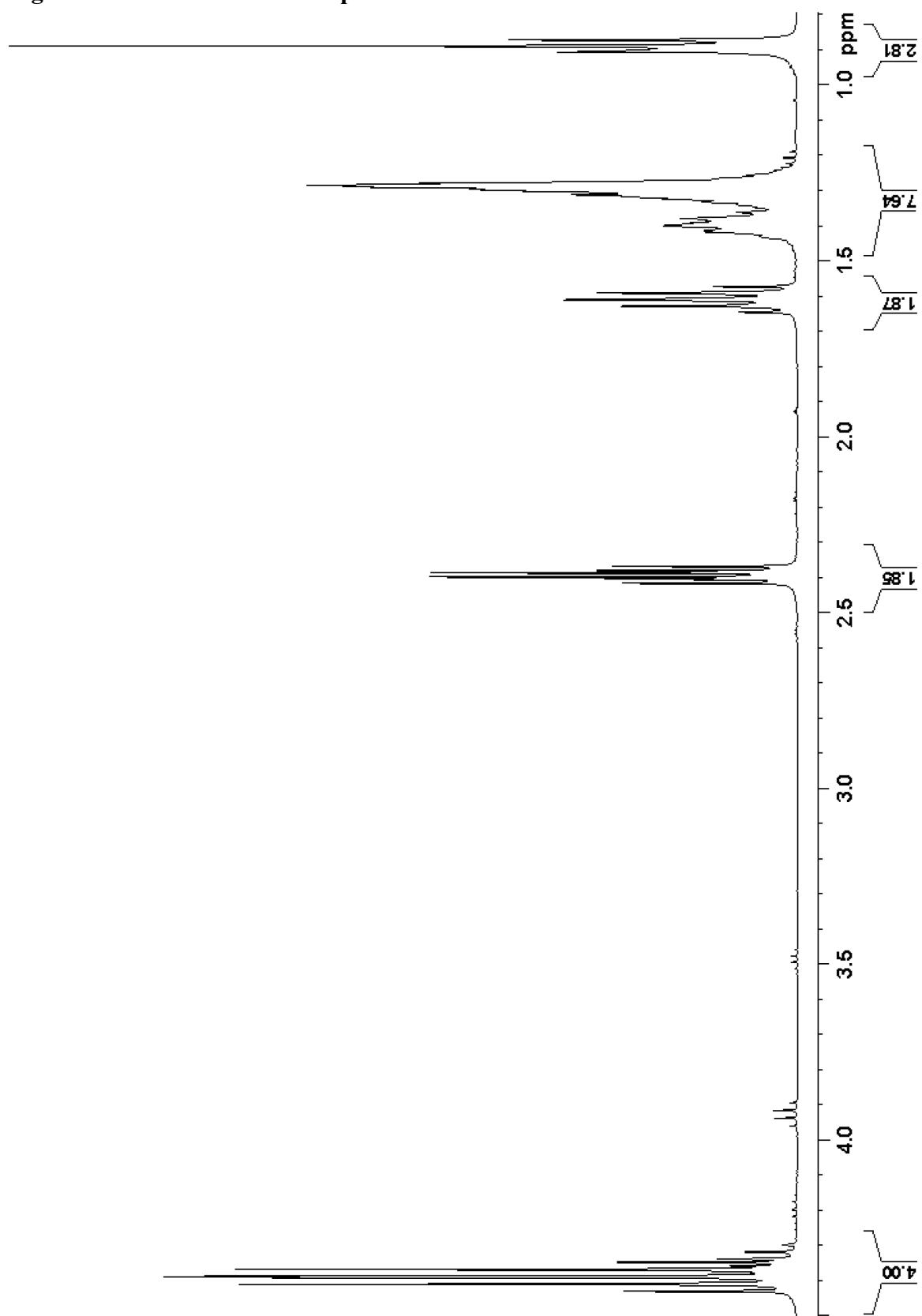
Figure 19  $^1\text{H}$  NMR of Compound 6



Figure 21  $^{31}\text{P}$  NMR of Compound 6



**Figure 22**  $^1\text{H}$  NMR of Compound 7

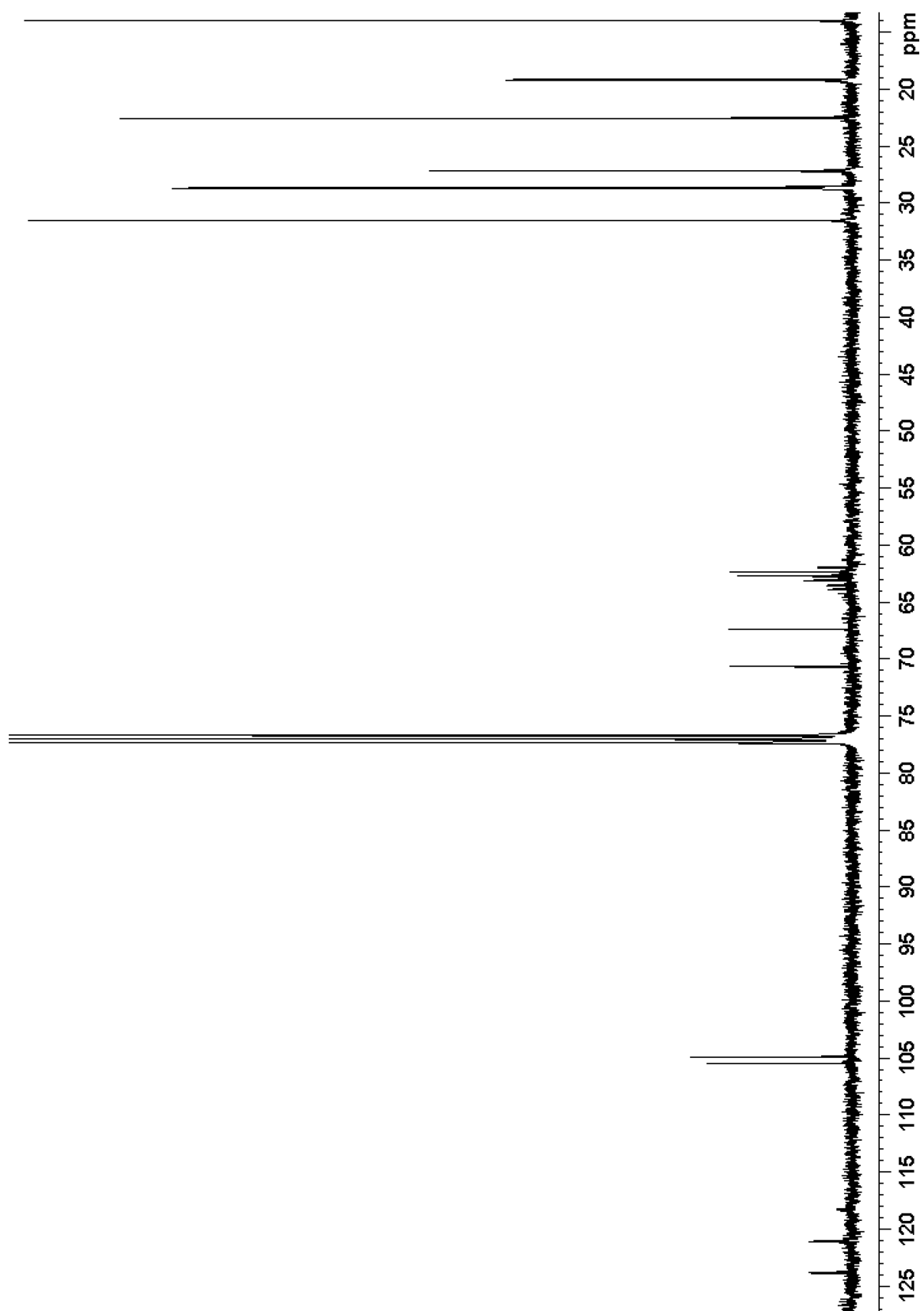
**Figure 23**  $^{13}\text{C}$  NMR of Compound 7

Figure 24  $^{31}\text{P}$  NMR of Compound 7

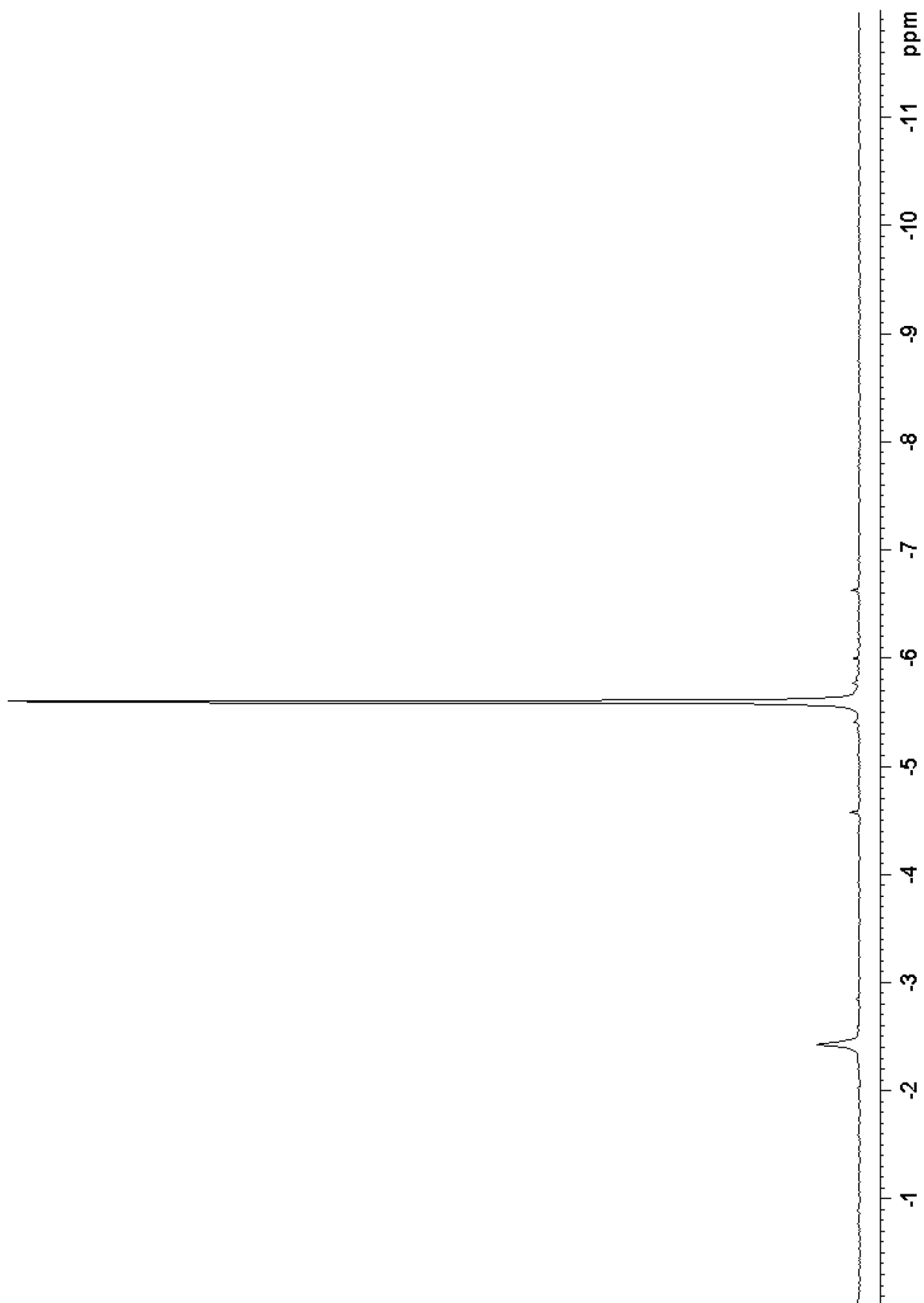
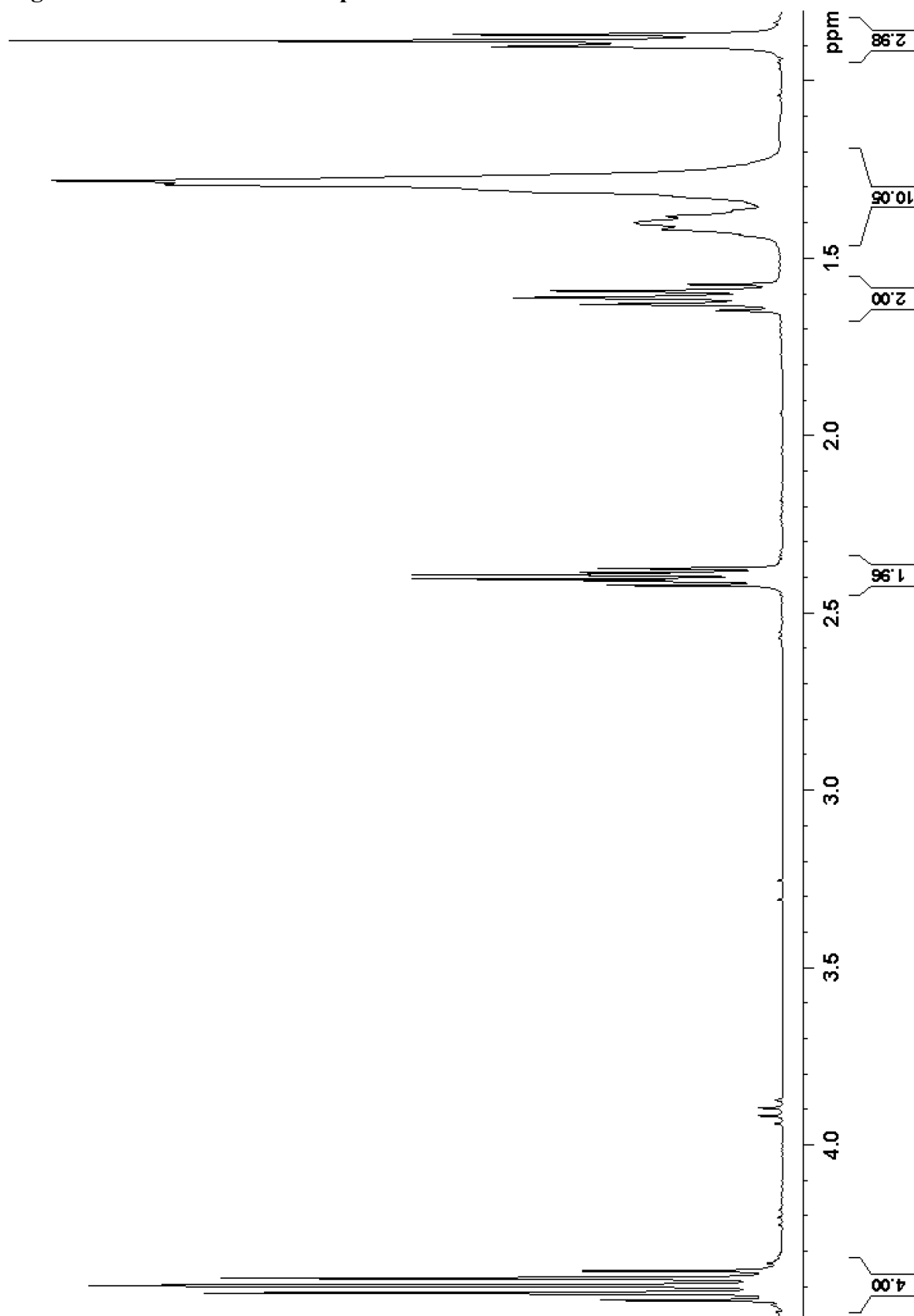




Figure 25  $^1\text{H}$  NMR of Compound 8

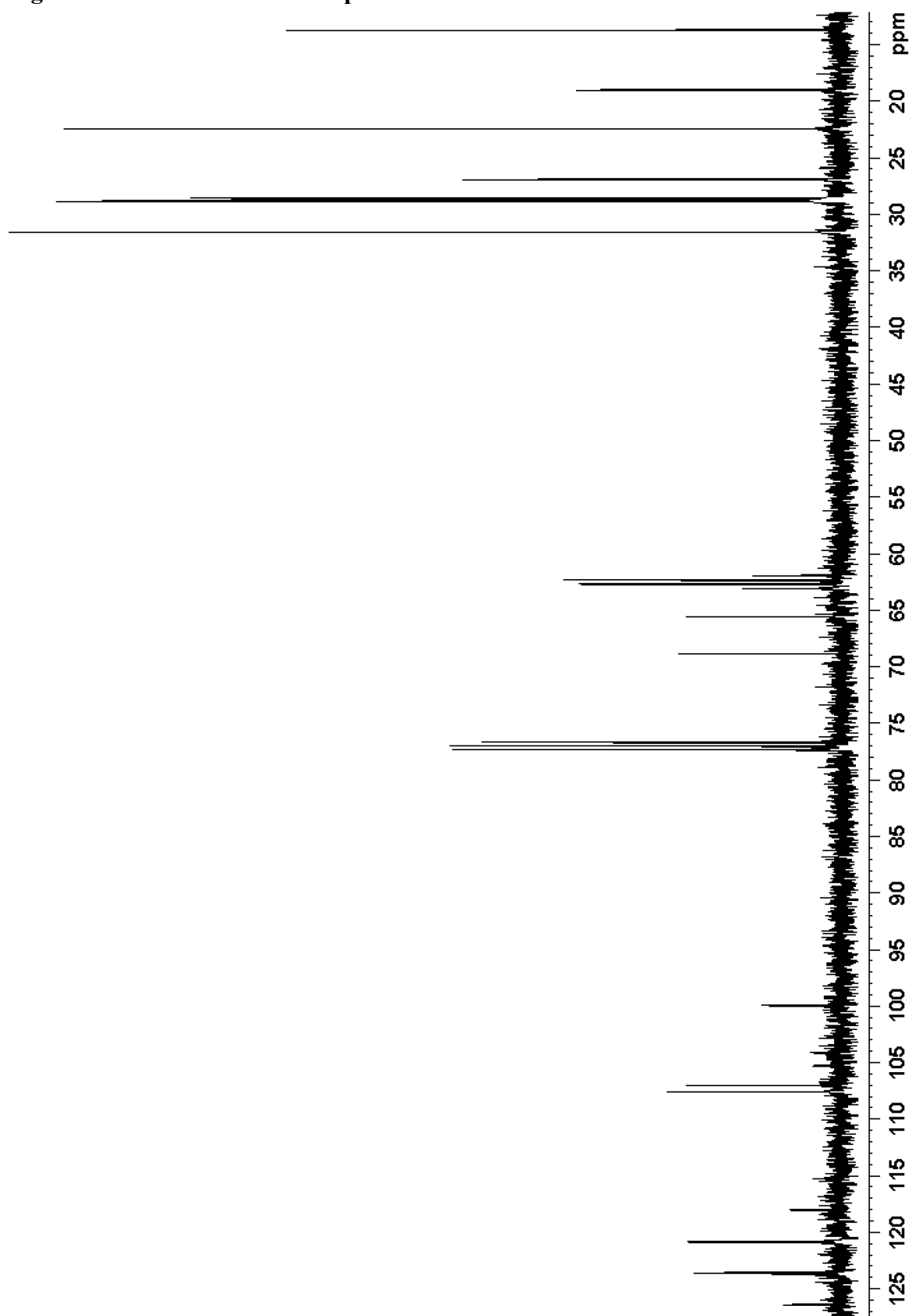
**Figure 26**  $^{13}\text{C}$  NMR of Compound 8

Figure 27  $^{31}\text{P}$  NMR of Compound 8

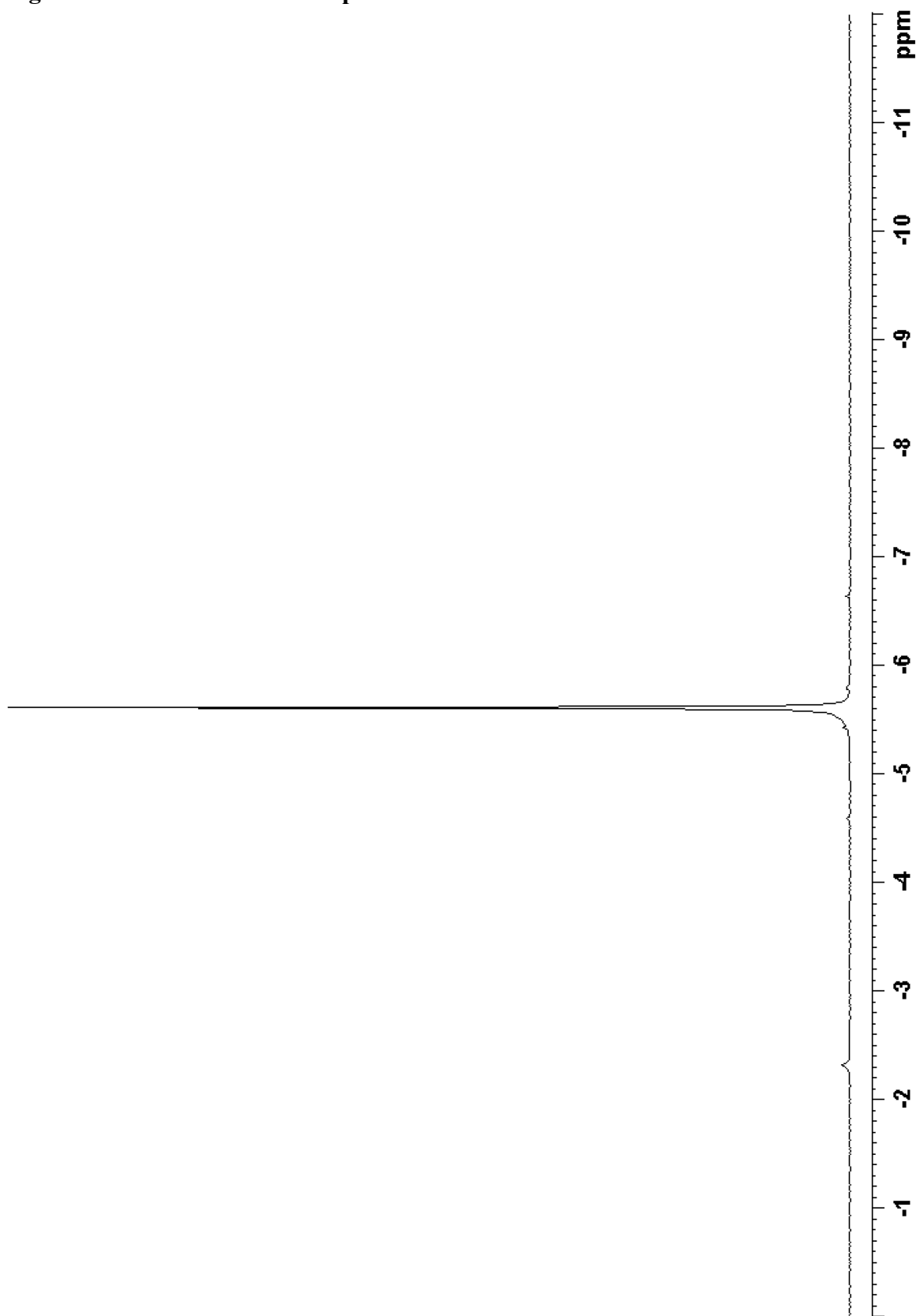
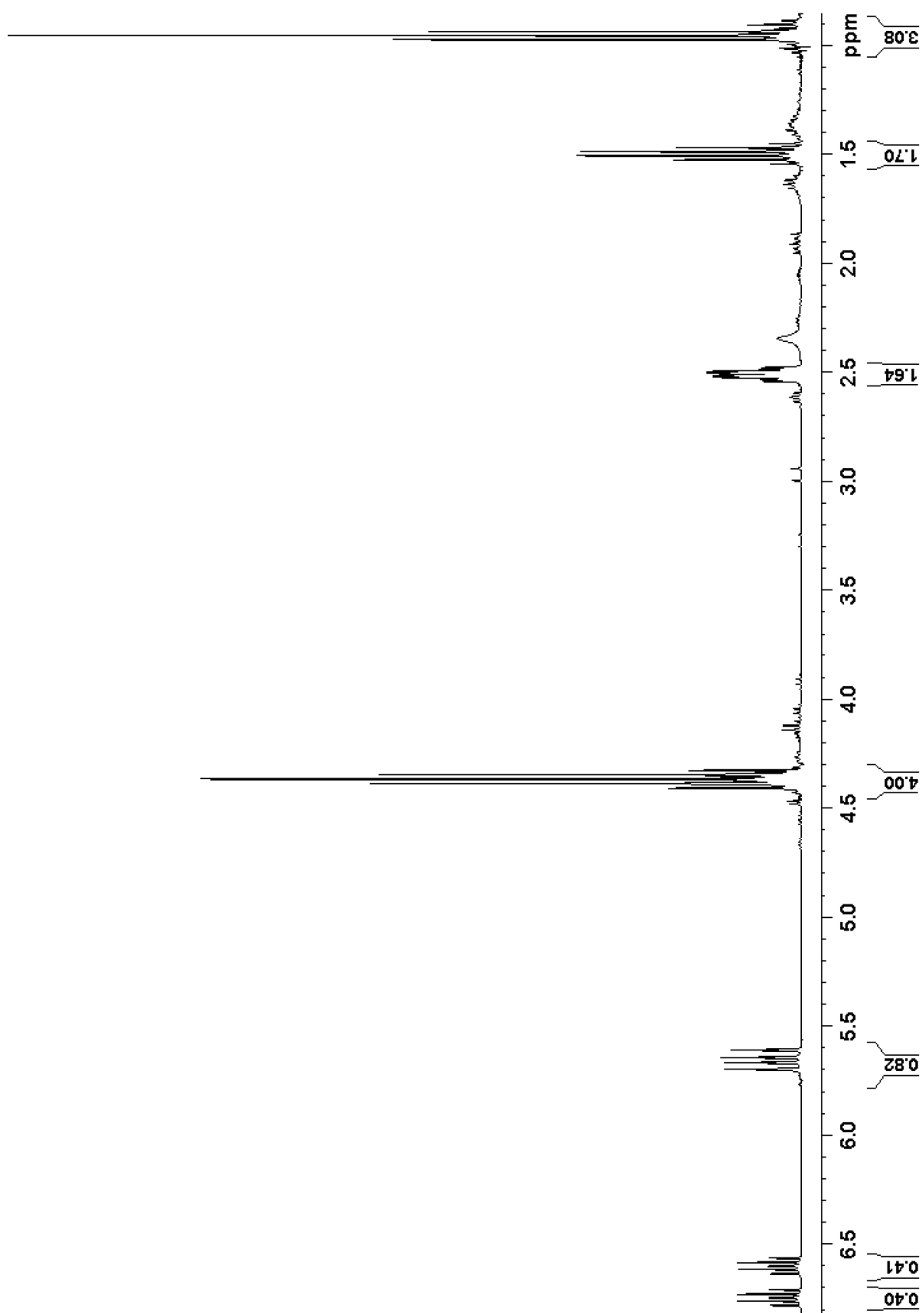


Figure 28  $^1\text{H}$  NMR of Compound 9

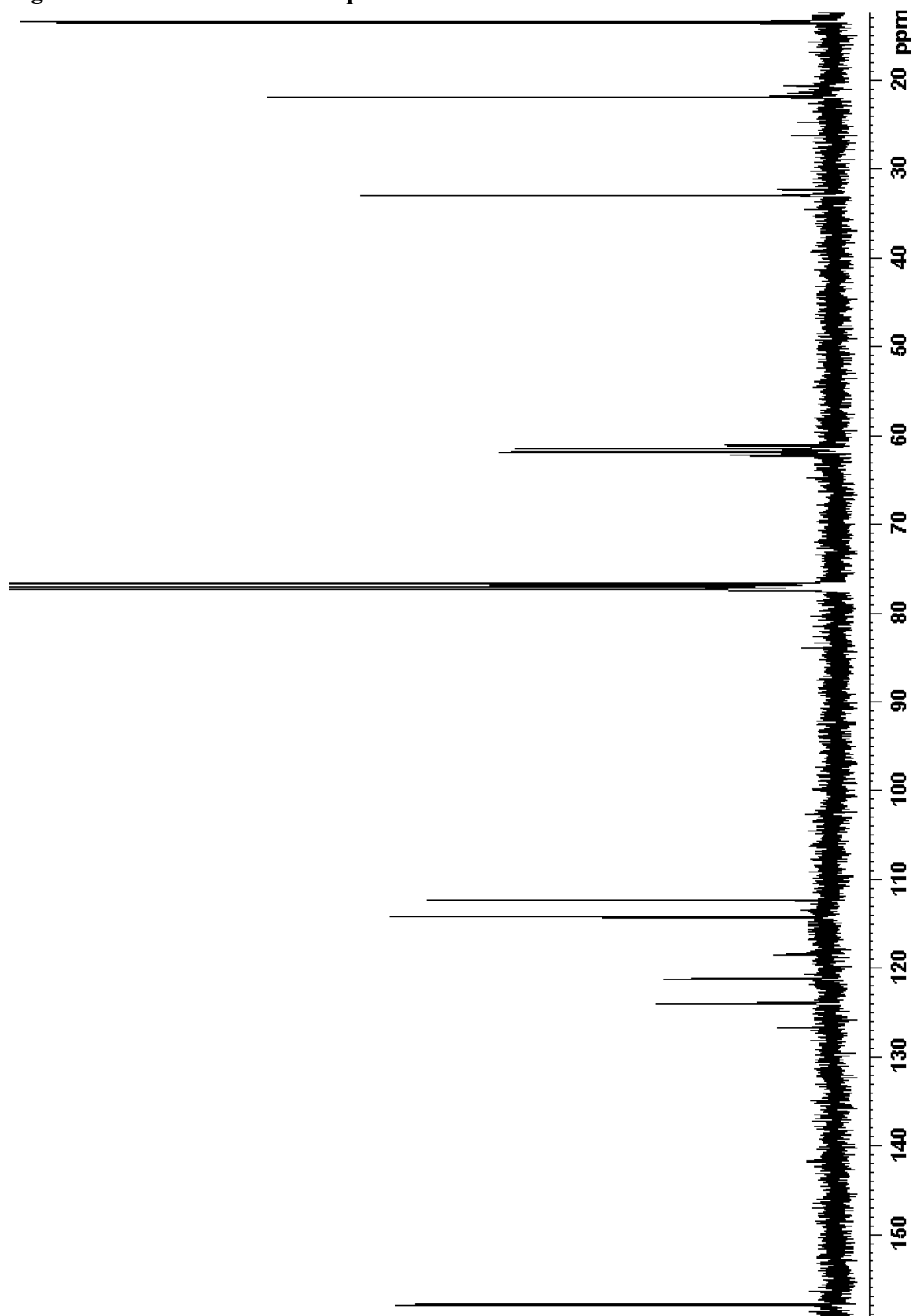
**Figure 29**  $^{13}\text{C}$  NMR of Compound 9

Figure 30  $^{31}\text{P}$  NMR of Compound 9

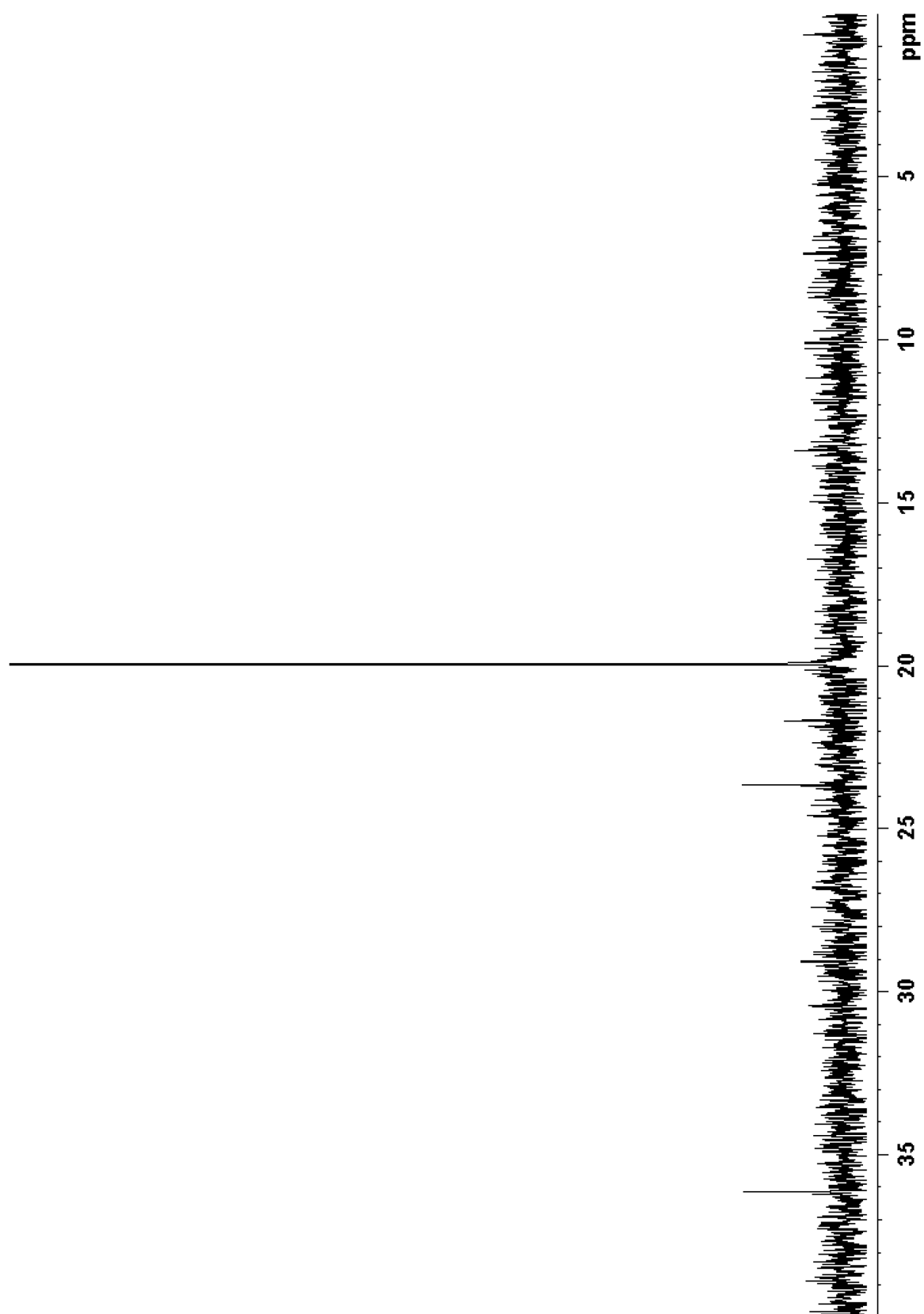
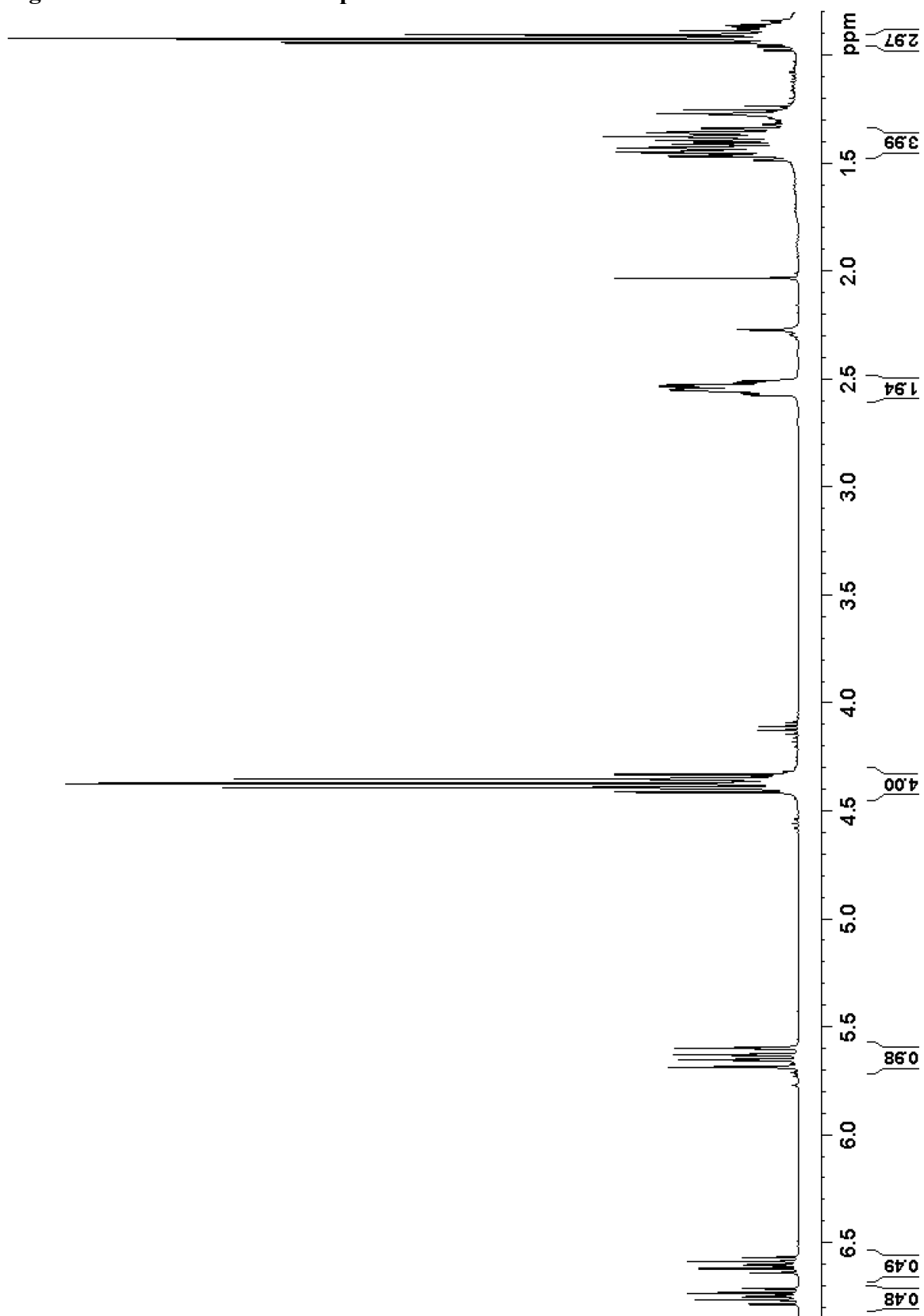
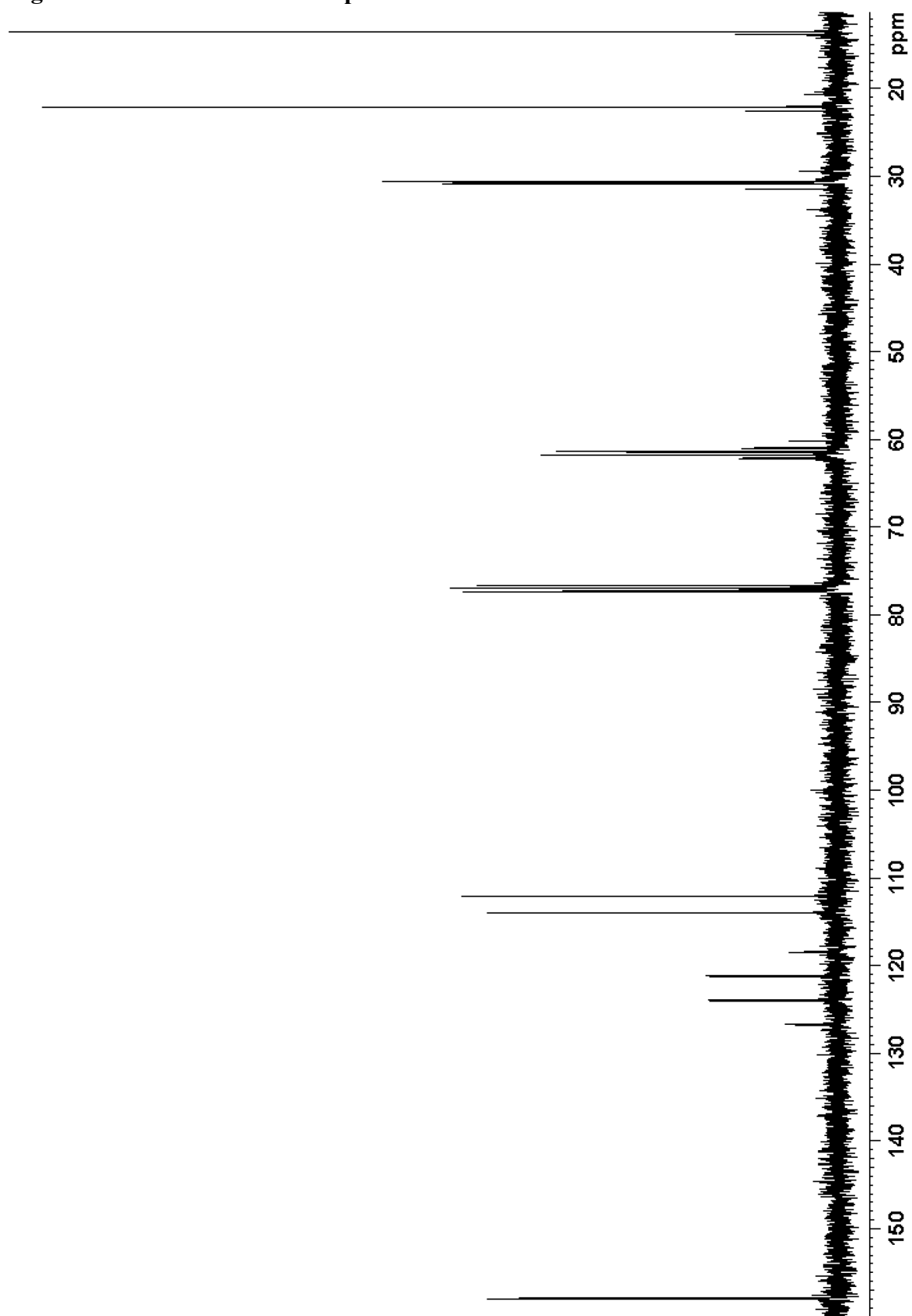


Figure 31  $^1\text{H}$  NMR of Compound 10

**Figure 32**  $^{13}\text{C}$  NMR of Compound 10



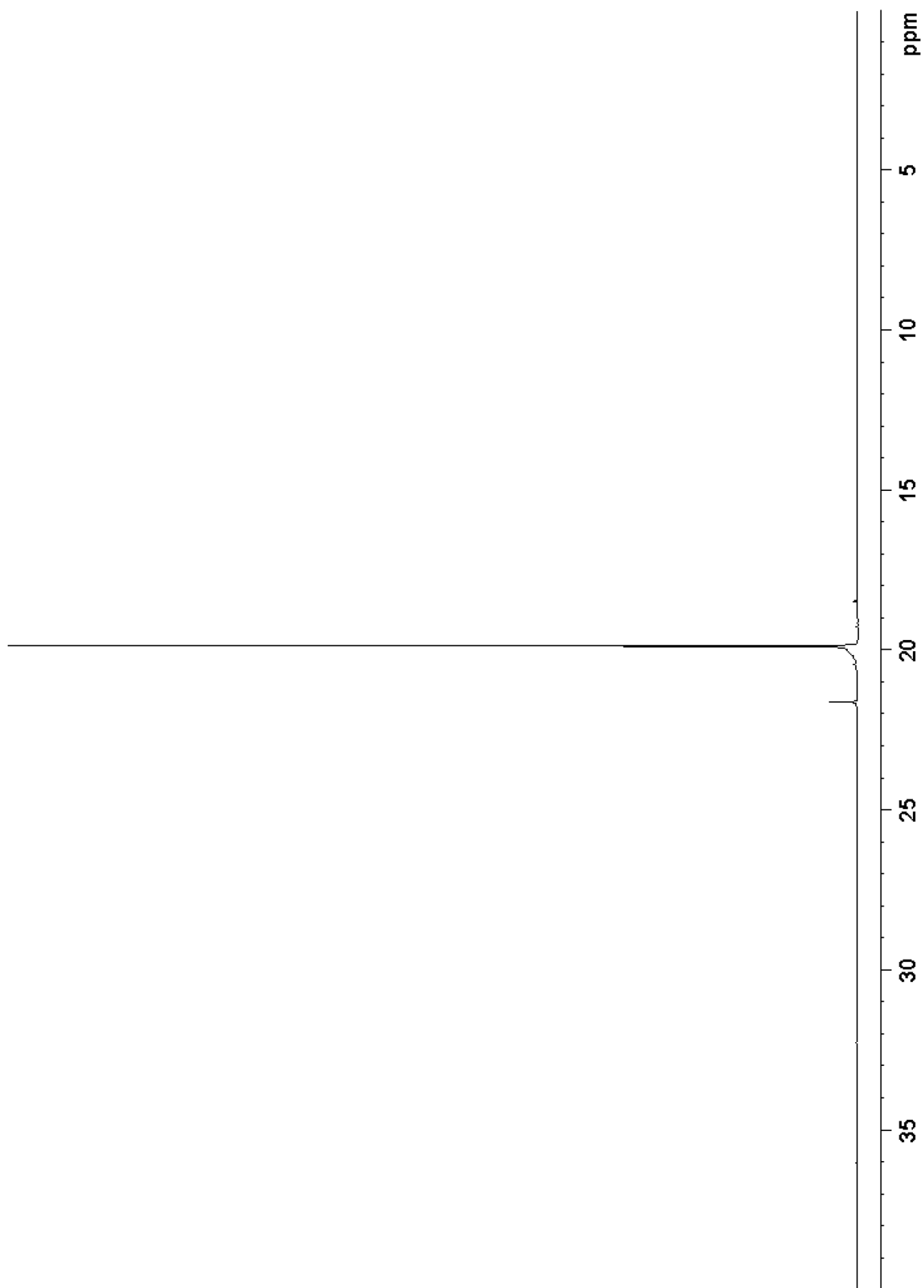
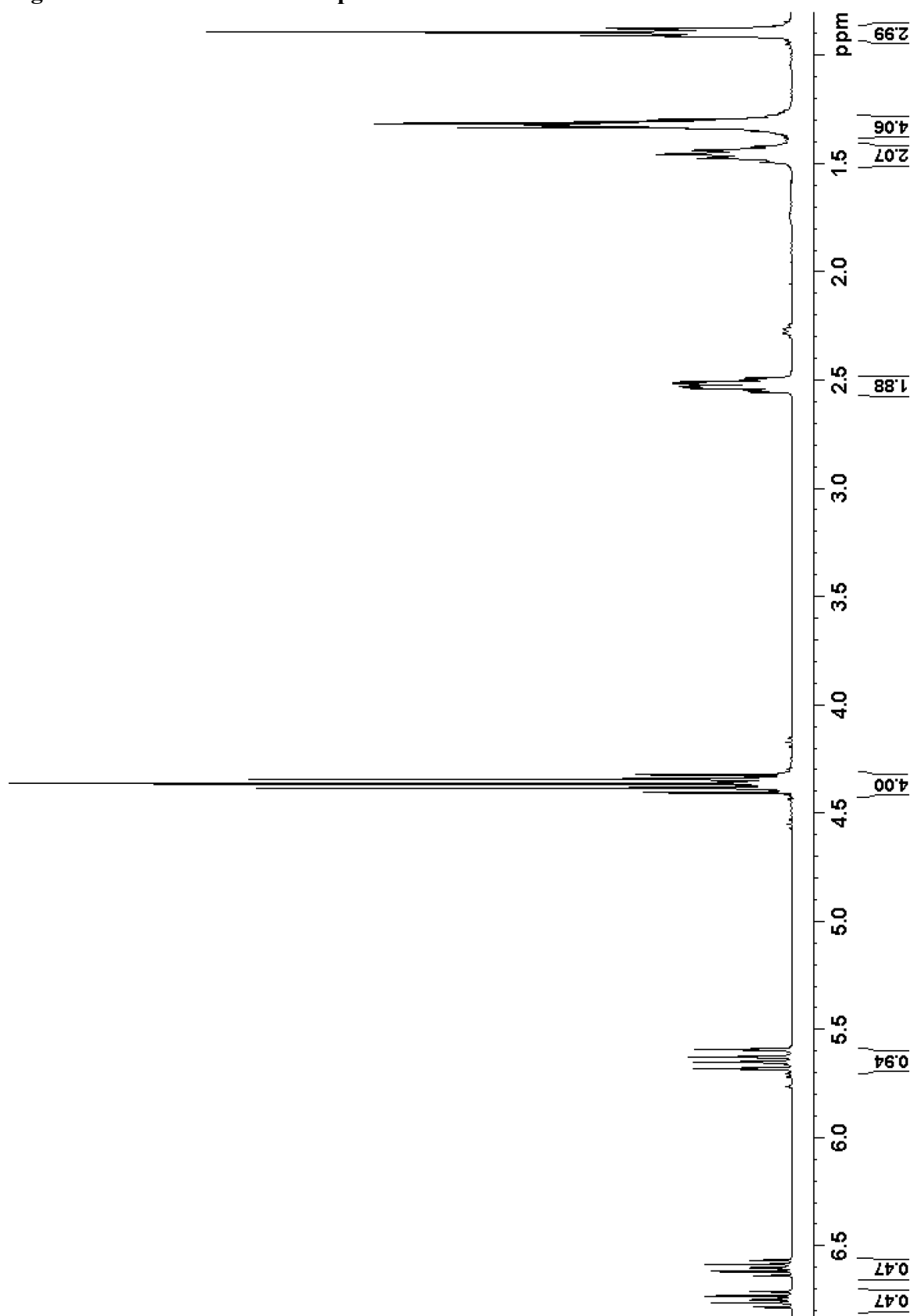
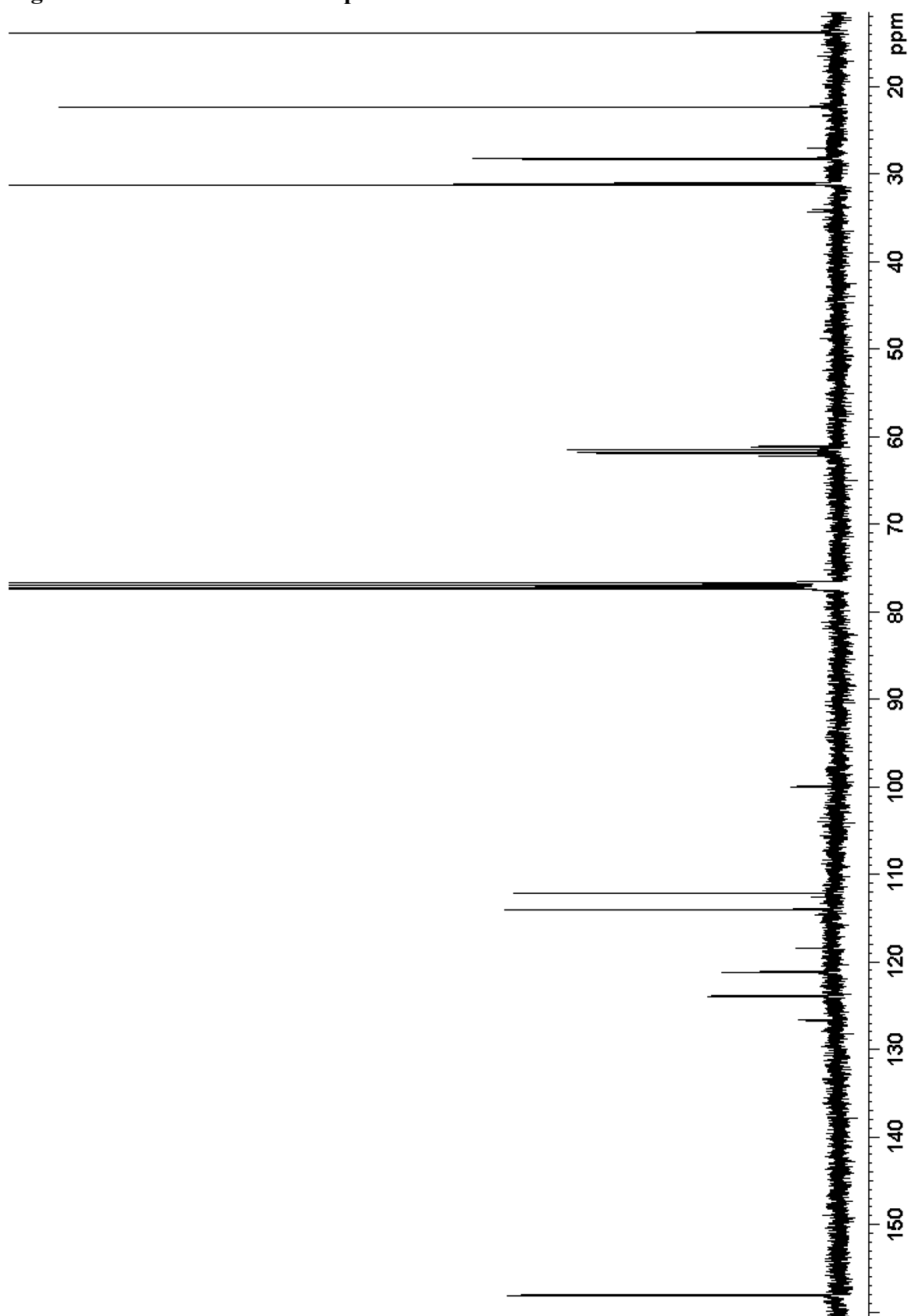
**Figure 33**  $^{31}\text{P}$  NMR of Compound 10

Figure 34  $^1\text{H}$  NMR of Compound 11

**Figure 35**  $^{13}\text{C}$  NMR of Compound 11

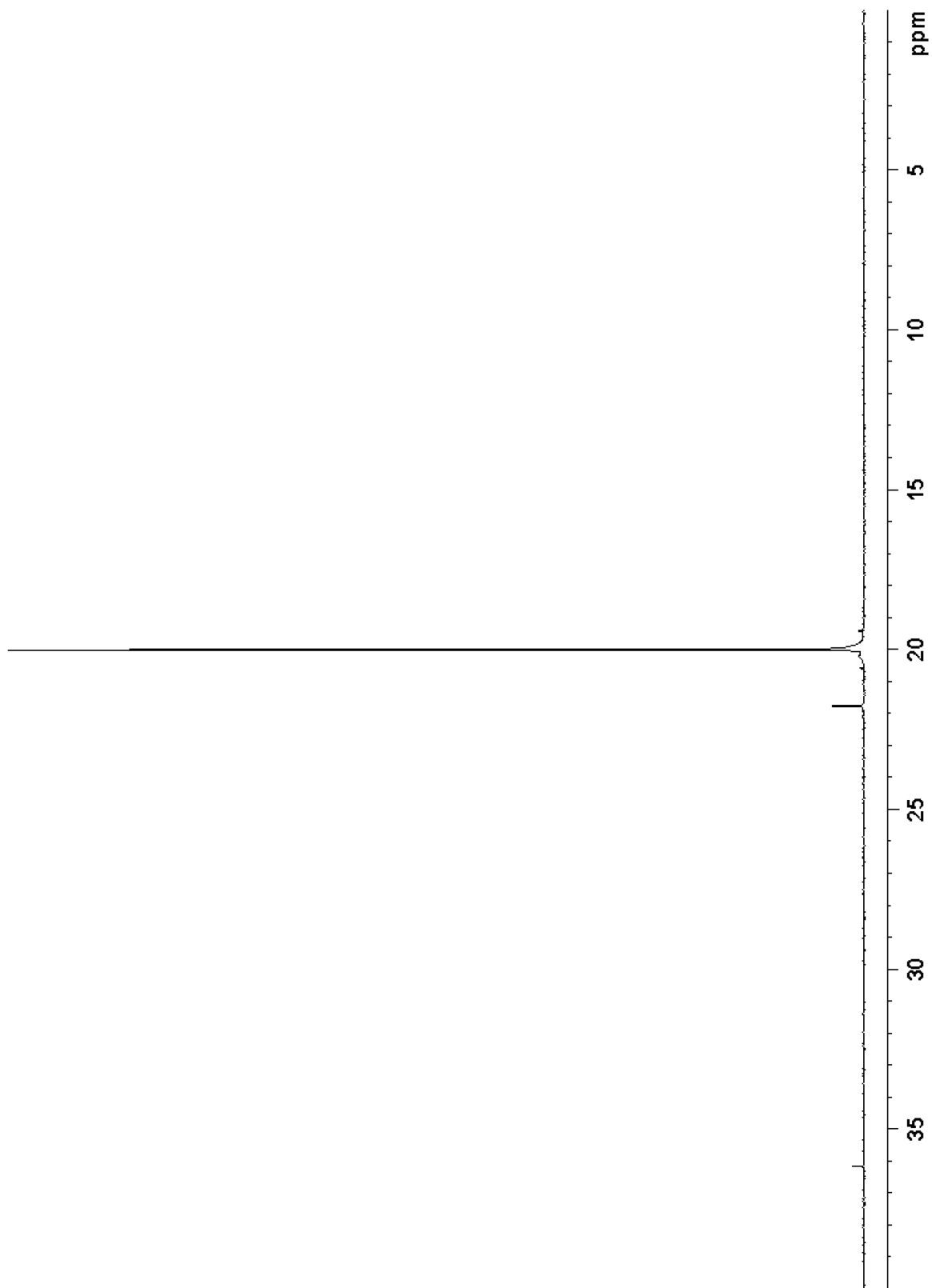
**Figure 36**  $^{31}\text{P}$  NMR of Compound 11

Figure 37  $^1\text{H}$  NMR of Compound 12

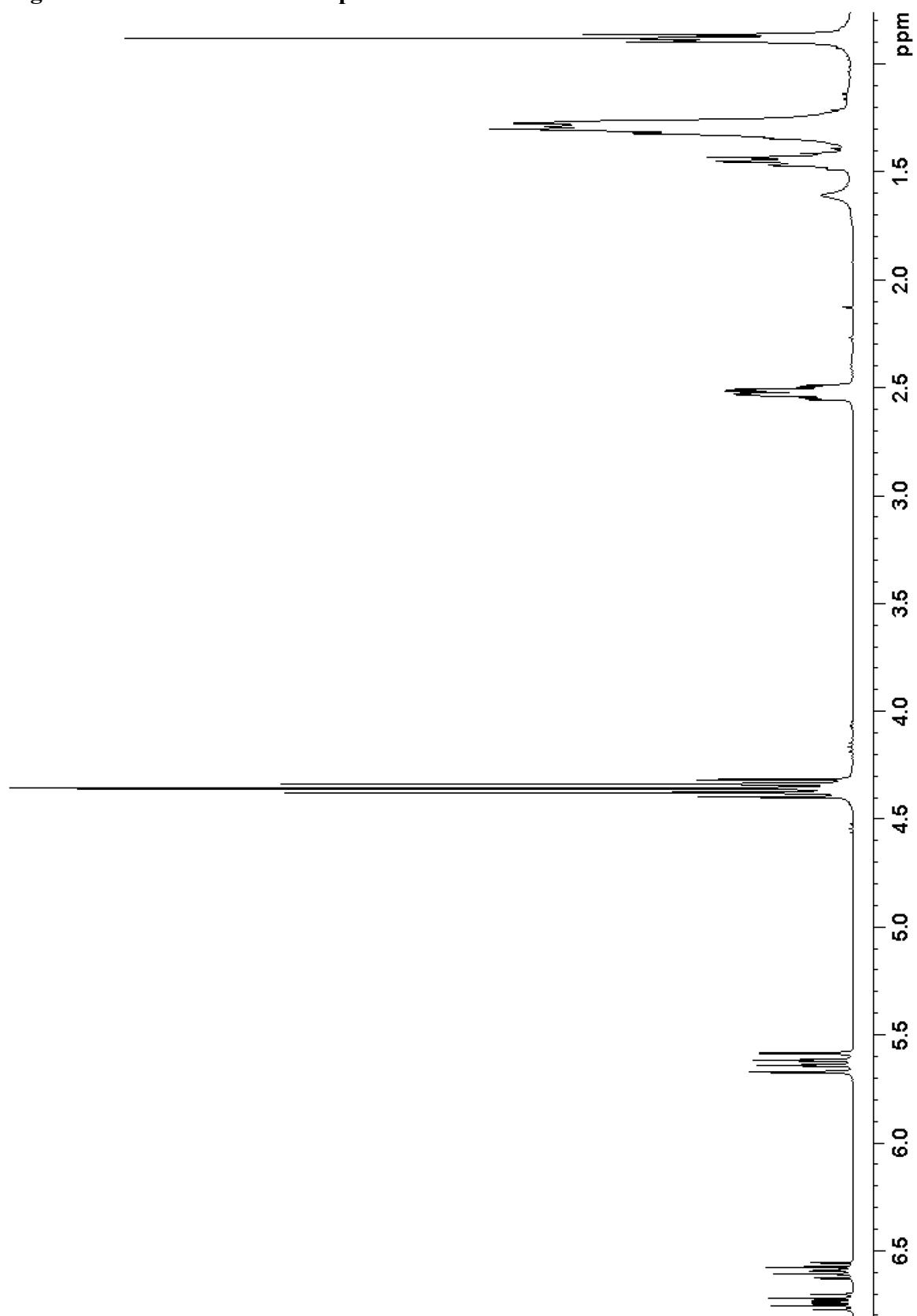


Figure 38  $^{13}\text{C}$  NMR of Compound 12

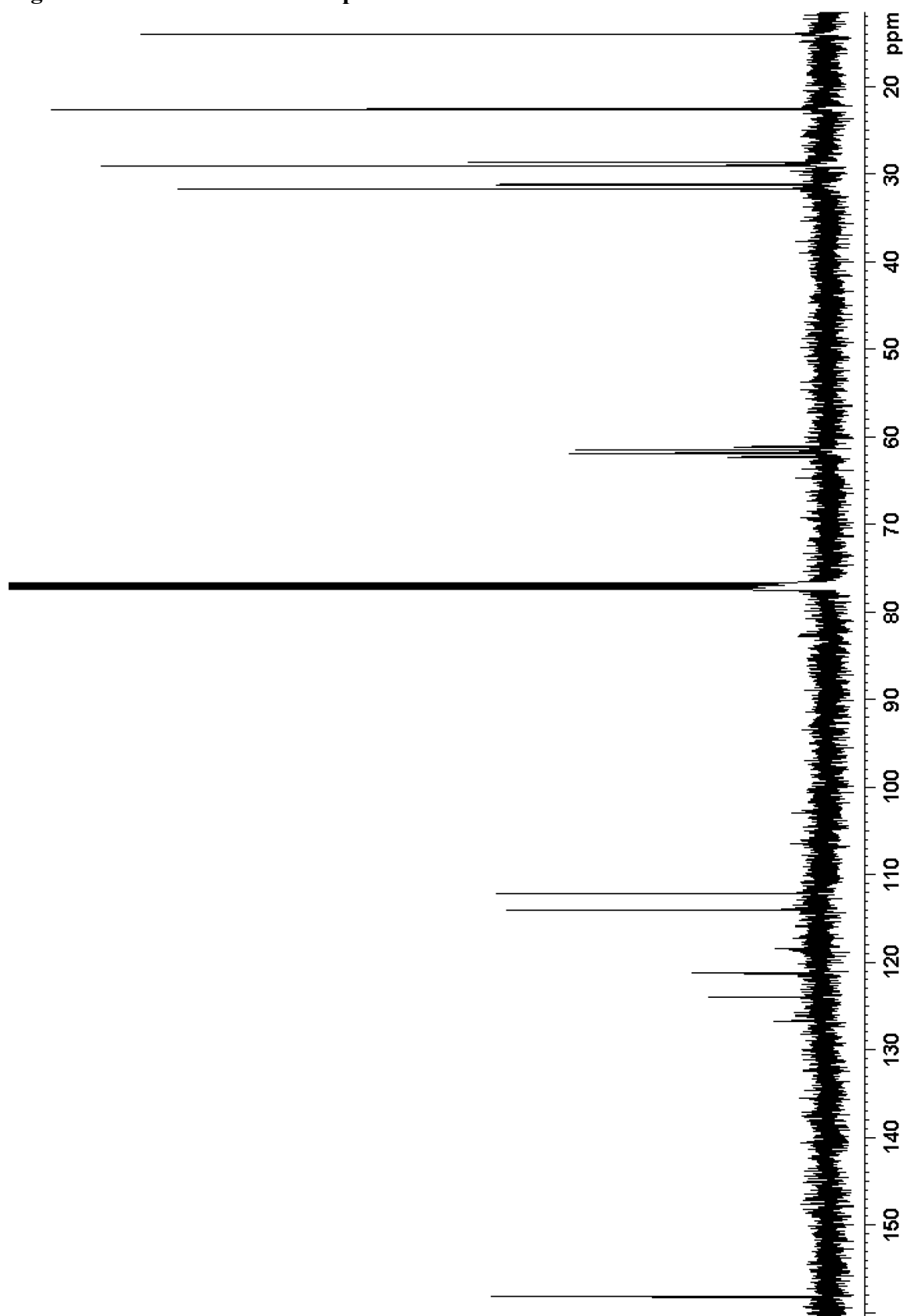


Figure 39  $^{31}\text{P}$  NMR of Compound 12

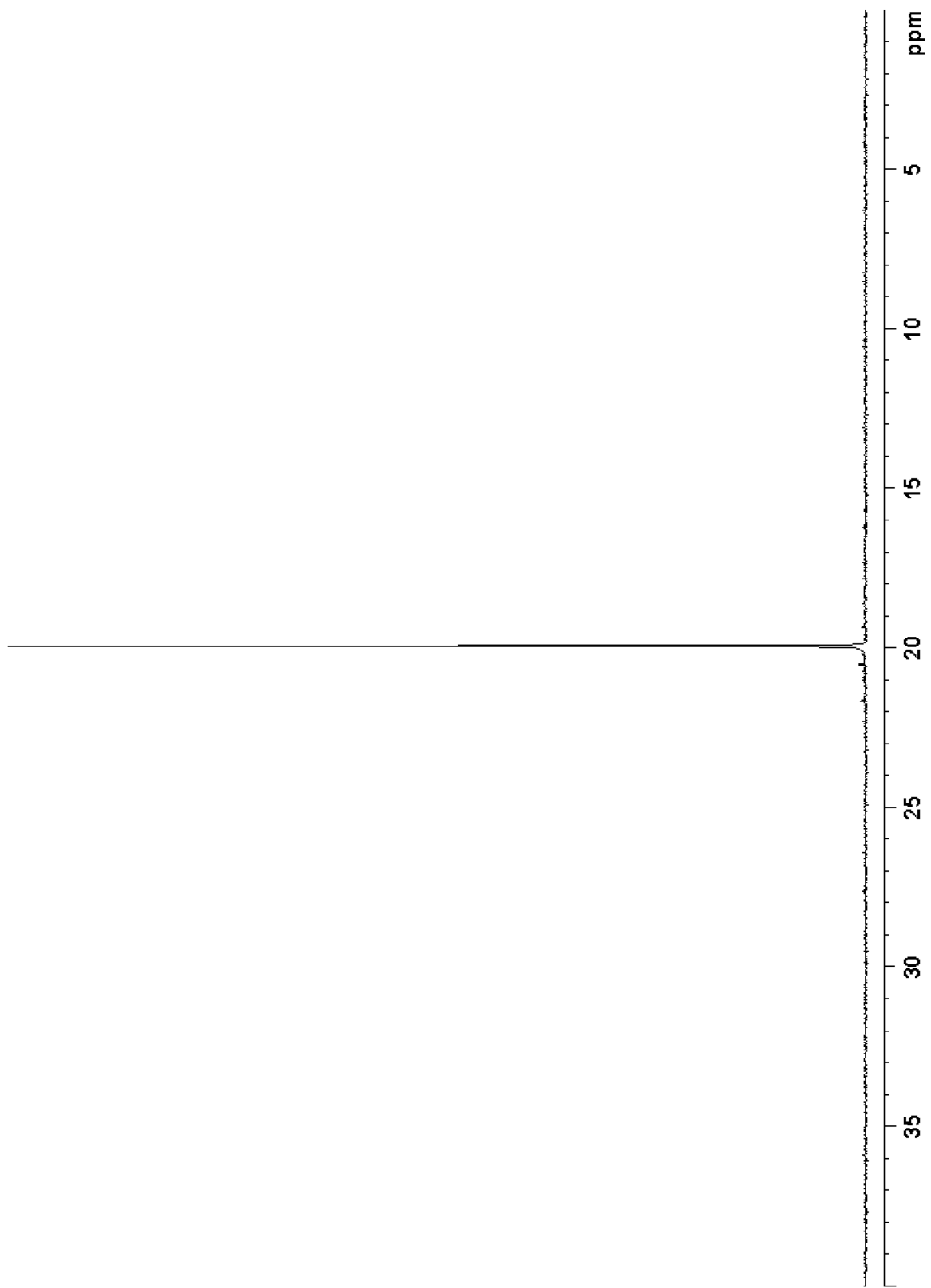
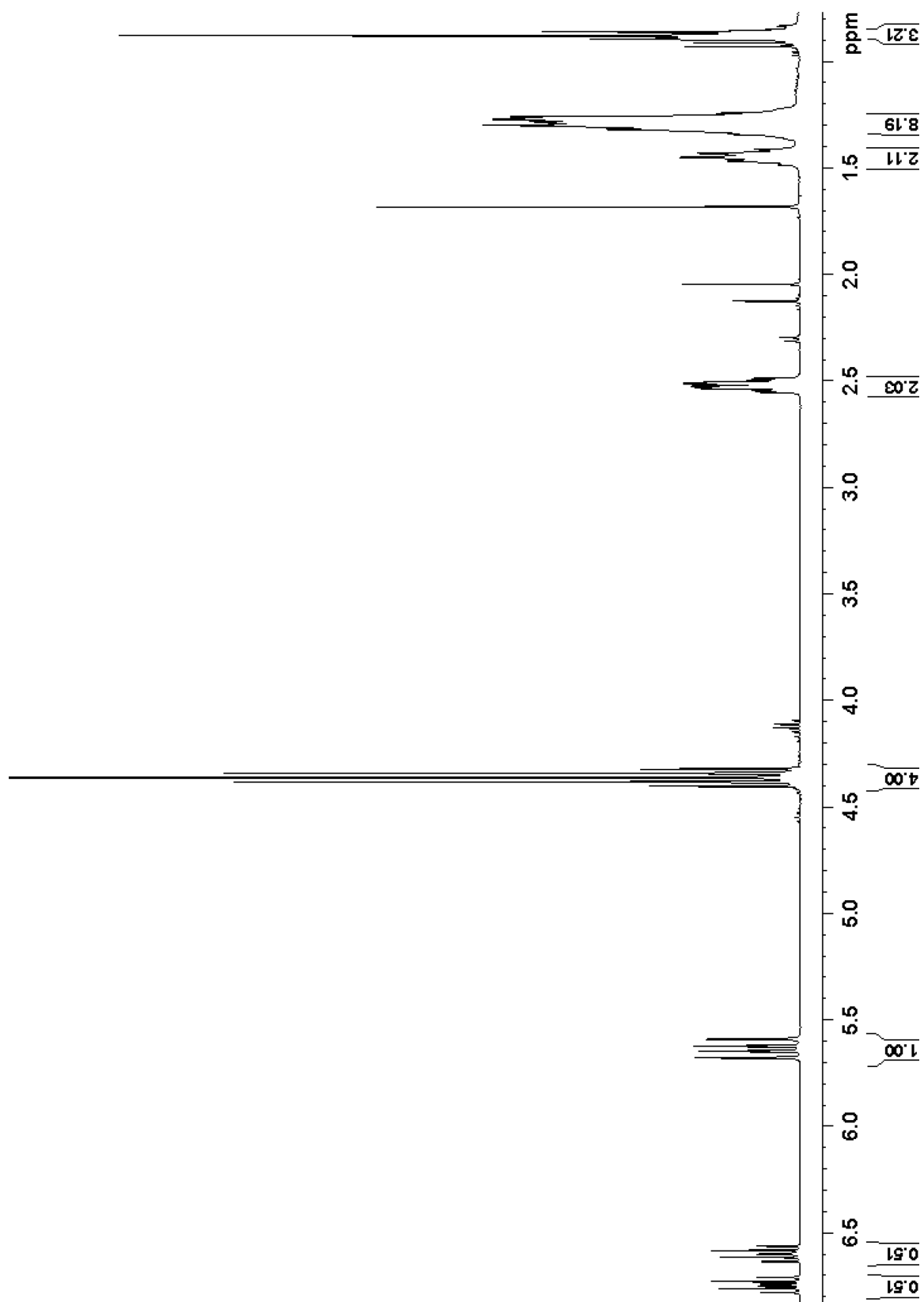
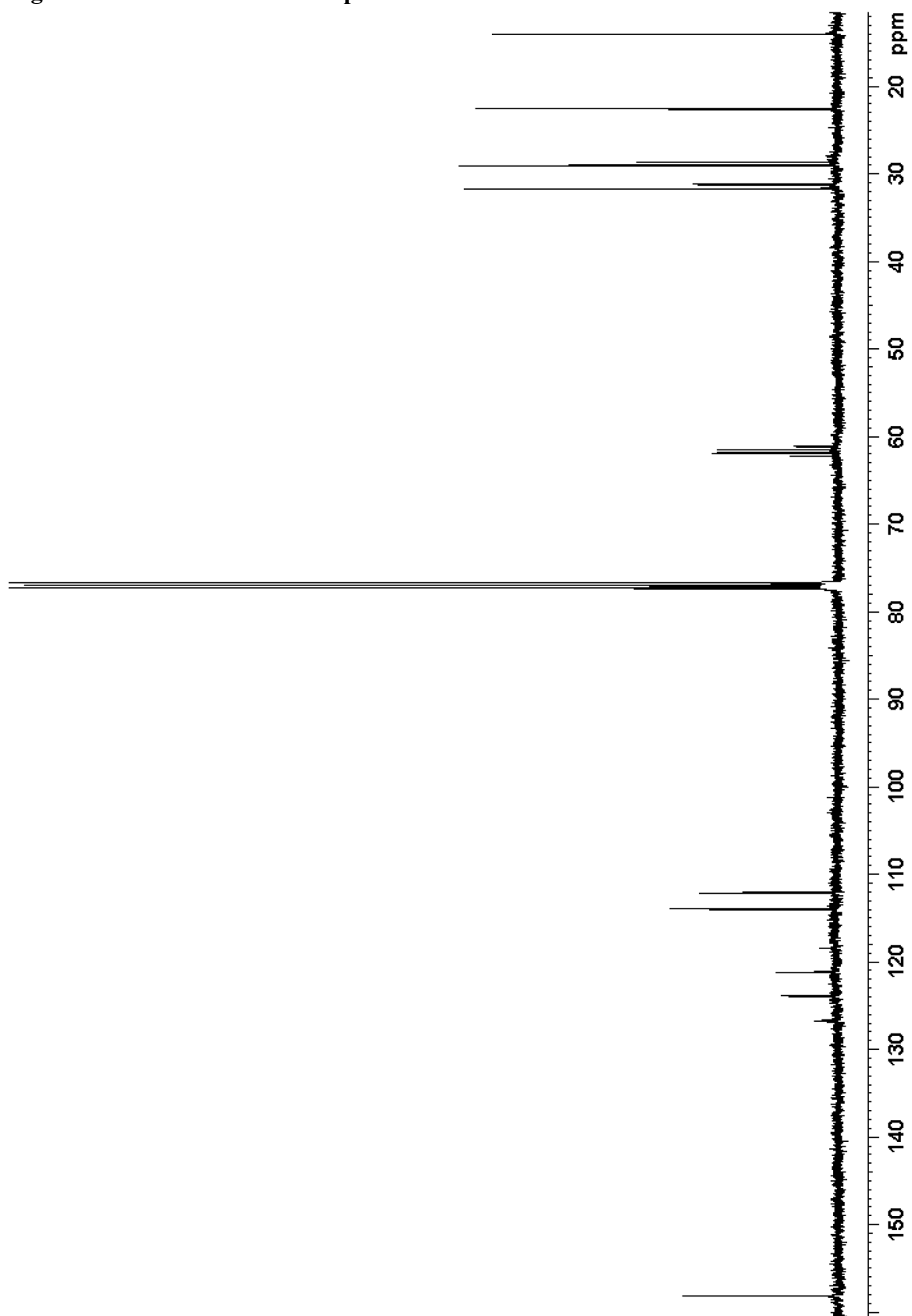


Figure 40  $^1\text{H}$  NMR of Compound 13



**Figure 41**  $^{13}\text{C}$  NMR of Compound 13

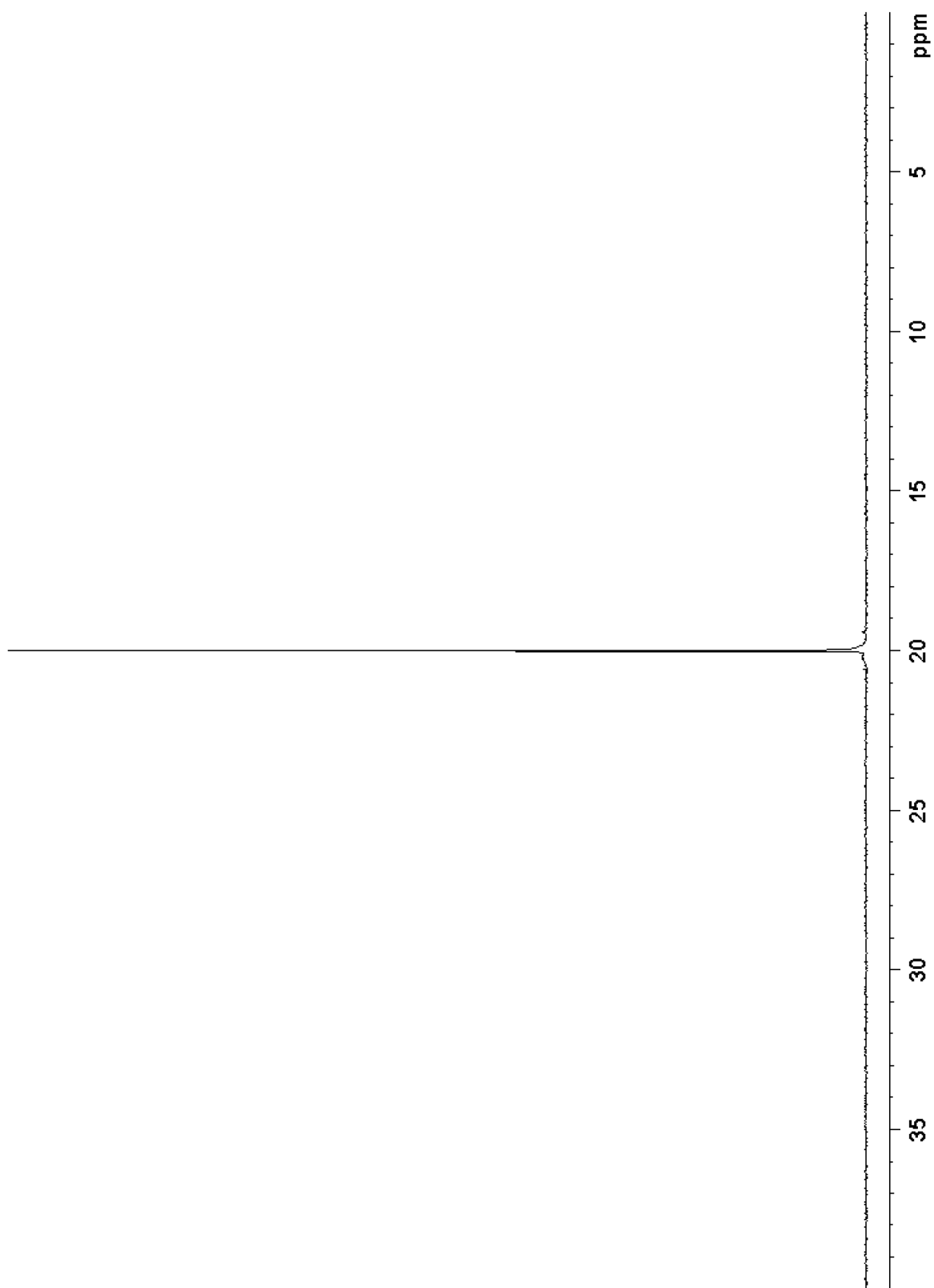
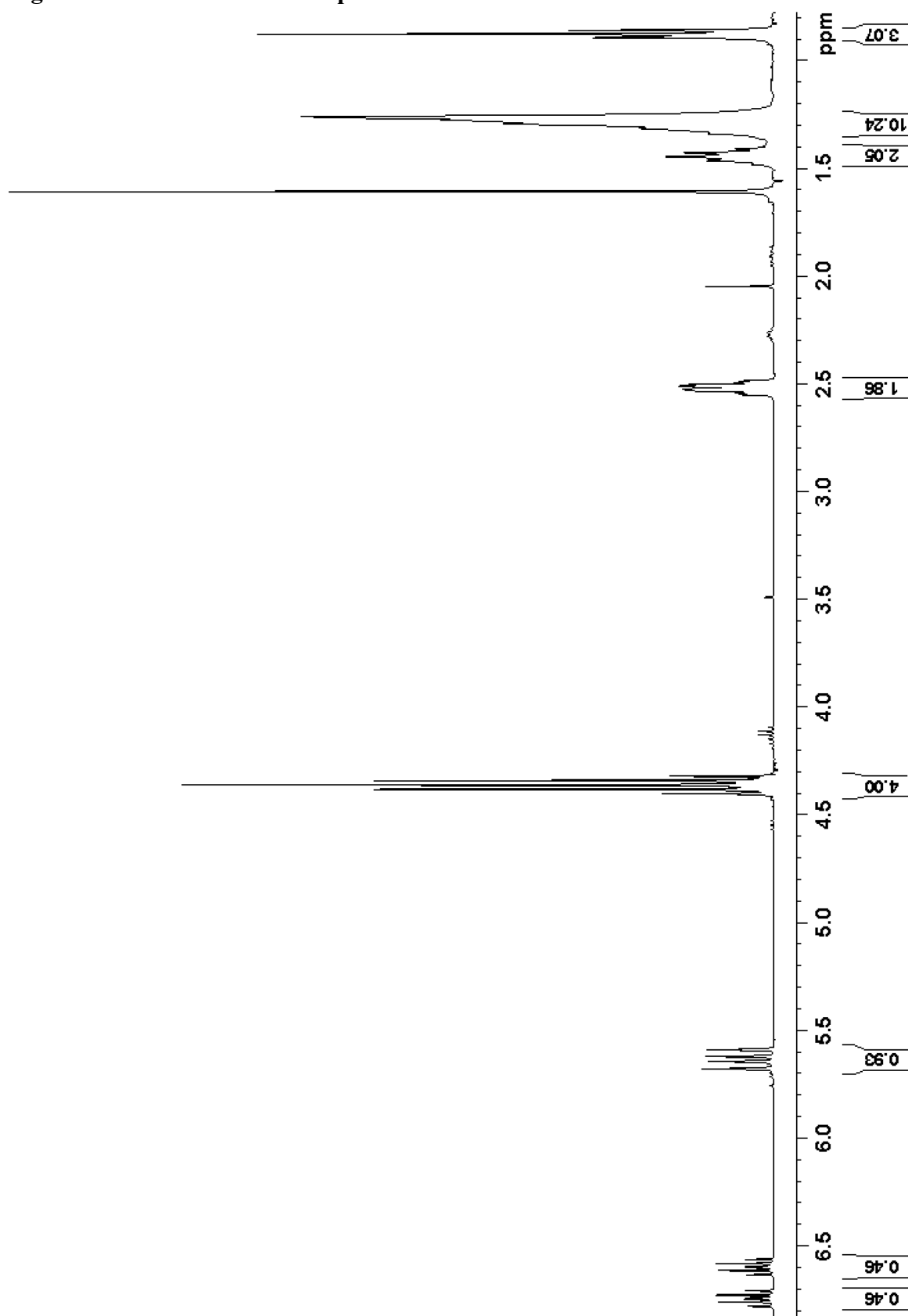
**Figure 42**  $^{31}\text{P}$  NMR of Compound 13

Figure 43  $^1\text{H}$  NMR of Compound 14

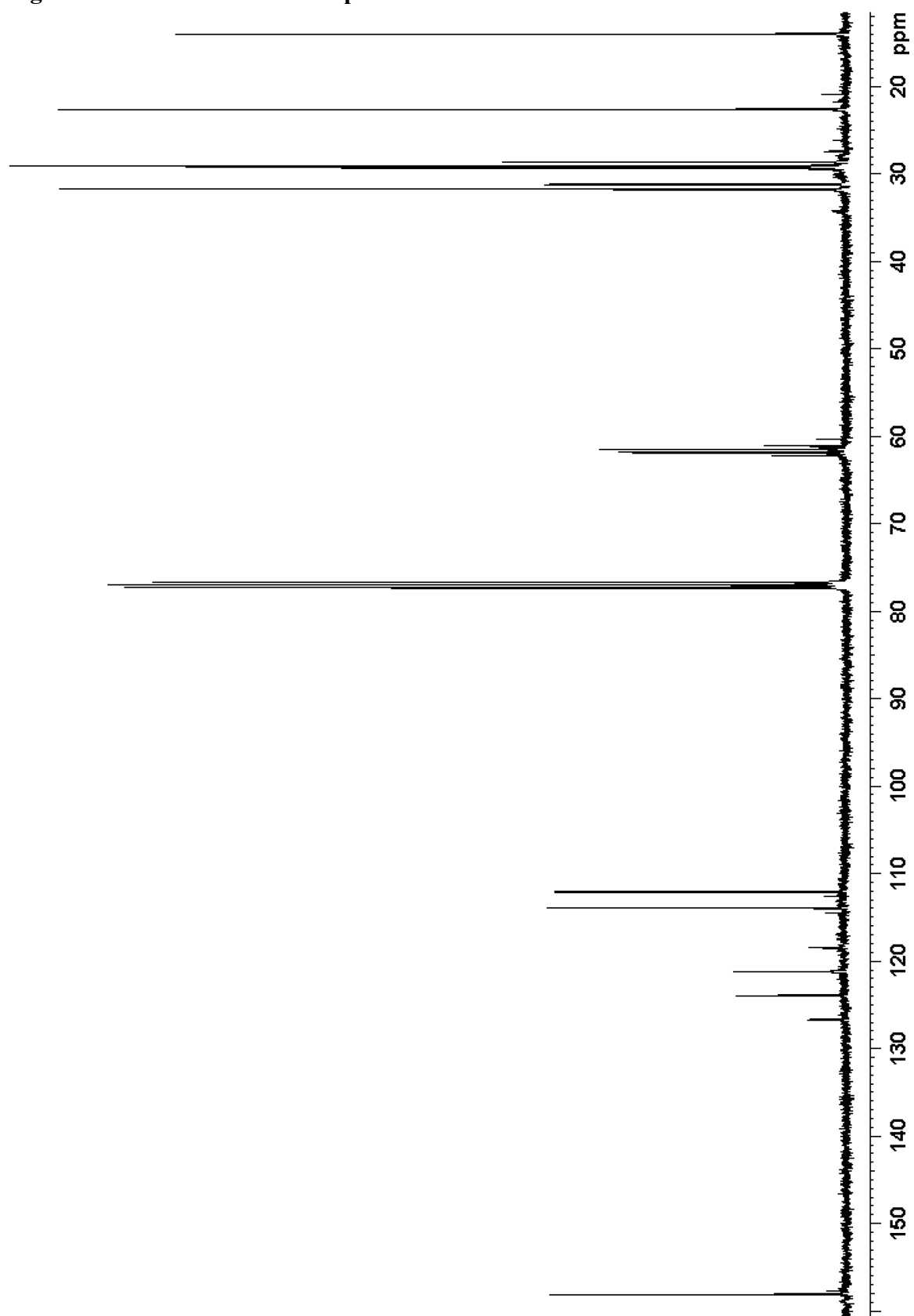
**Figure 44**  $^{13}\text{C}$  NMR of Compound 14

Figure 45  $^{31}\text{P}$  NMR of Compound 14

