Synthesis of bis(2,2,2-trifluoroethyl) β-ketophosphonates from bis(2,2,2-trifluoroethyl) 1-alkynylphosphonates via enamine vinyl phosphonates

by

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Synthesis of bis(2,2,2-trifluoroethyl) β-ketophosphonates from bis(2,2,2-trifluoroethyl) 1-alkynylphosphonates via enamine vinyl phosphonates

Ashley DePizzo

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ABSTRACT

A new method for the synthesis of bis(2,2,2-trifluoroethyl) β-ketophosphonates from bis(2,2,2-trifluoroethyl) 1-alkynylphosphonates is described herein. Bis(2,2,2-trifluoroethyl) 1-alkynylphosphonates can be treated with primary and secondary amines to prepare enamine vinyl phosphonates. Bis(2,2,2-trifluoroethyl) β-ketophosphonates are obtained after hydrolysis of the enamine vinyl phosphonate.

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List of Abbreviations

Abbreviation	Description
d	doublet
dt	doublet of triplets
dq	doublet of quartets
Et	ethyl
g	gram
GC	gas chromatography
HMPA	hexamethyl phosphoramide
Hz	Hertz
i-Pr	isopropyl
KHMDS	potassium hexamethyldisilazide
$KN(TMS)_2$	potassium hexamethyldisilazide
LHMDS	lithium hexamethyldisilazide
MHz	megahertz
mL	milliliter
mmol	millimole
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
s	singlet
THF	tetrahydrofuran

TFE	trifluoroethyl
TLC	thin layer chromatography
TMS	tetramethylsilane

Chapter 1: Introduction

Background

Phosphonates have a variety of uses across many science disciplines due to the fact that they are diesters of pentavalent phosphorus and occur in nature. They are characterized by their structural composition shown below (Figure 1):

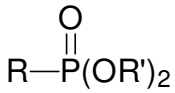


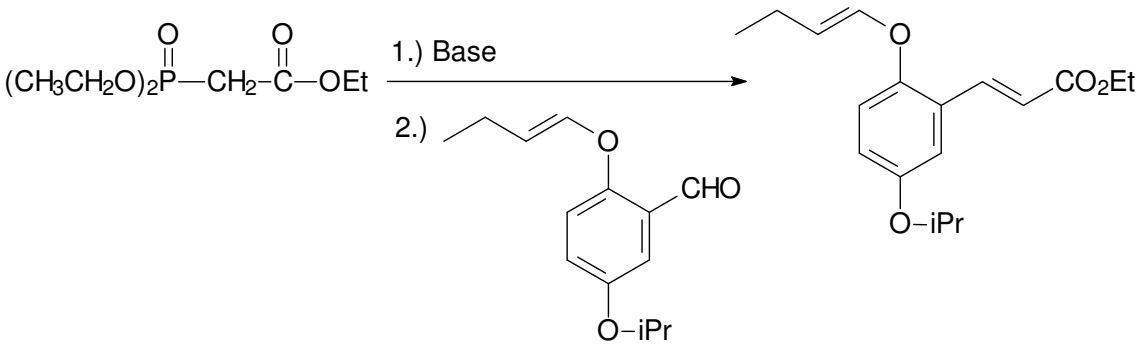
Figure 1: Chemical structure of phosphonates

Phosphonates were first synthesized in 1897 by Von Baeyer and Hoffmann. [1] Phosphonates have been researched aggressively and have been found to be useful in biochemistry and medicinal chemistry. Nucleotide analogues of phosphonates have been shown to be useful antiviral agents[2] and phosphonates may also serve as effective pro-drugs and pharmaceutical agents. [3] Due to phosphonate's ability to inhibit phosphate transport, phosphonates can be used to treat a variety of medical aliments such as chronic renal insufficiency. [4] Perhaps the biggest advantage of phosphonates is their ability to serve as synthetic intermediates because of the reactivity at phosphorus and their diverse chemical structure.

Phosphonates as Synthetic Intermediates

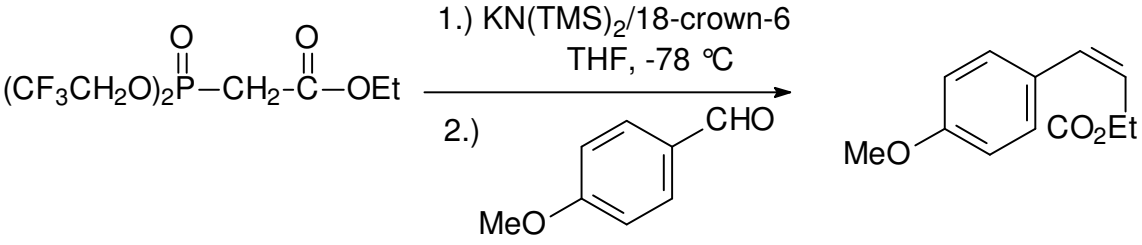
The chemical structure of phosphonates allows for the incorporation of many functional groups. This functional group incorporation and the high reactivity at phosphorus allow phosphonates to undergo many transformations. [5] The most popular reaction that uses phosphonates as a synthetic intermediate is the Horner-Wadsworth-

Emmons reaction (HWE). Through the condensation of the phosphonate with aldehydes, the HWE reaction forms α, β-unsaturated carbonyl compounds. The thermodynamically favored *(E)*-isomer of the corresponding alkene is formed when the ester portions of the phosphonate are simple alkoxy groups. The following is an example (Scheme 1).



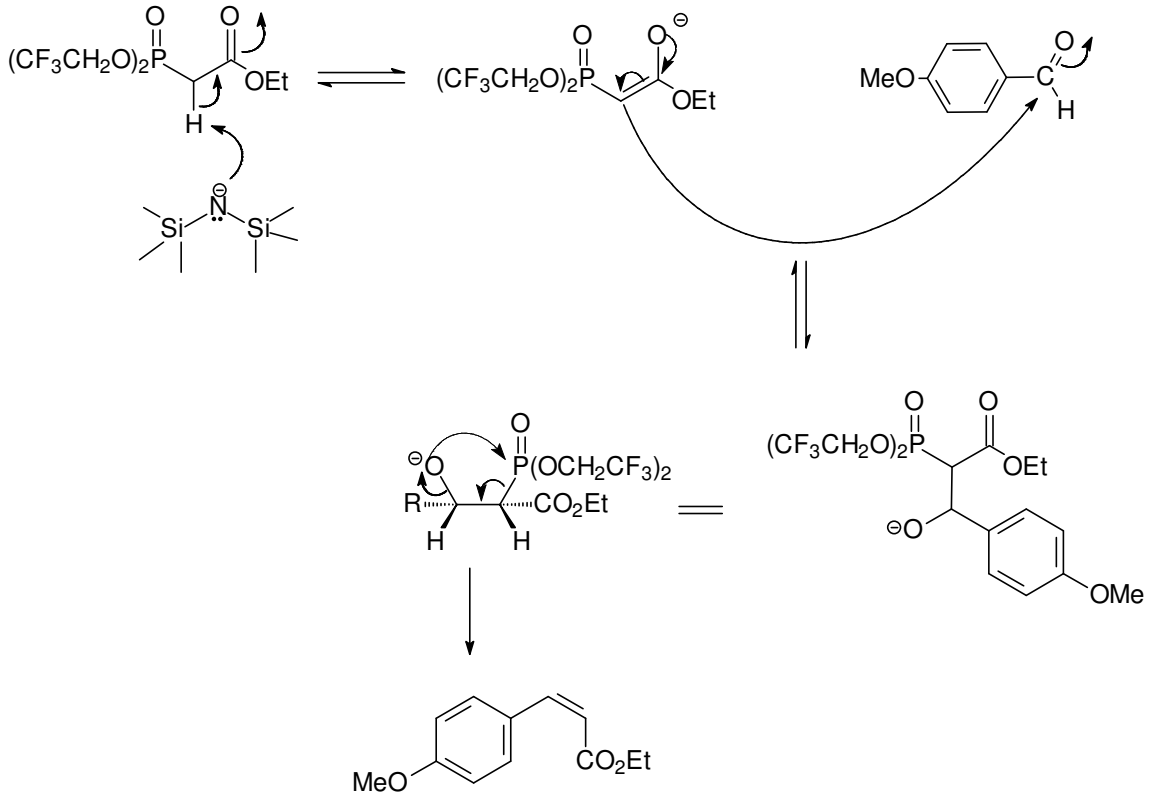
Scheme 1: Example of typical Horner-Wadsworth-Emmons reaction. [6]

A common variation of the HWE reaction is the Still-Gennari HWE olefination which substitutes the simple alkoxy groups with electron withdrawing groups. If the alkoxy group is substituted with bis(2,2,2-trifluoroethyl) the kinetically favored *(Z)*-isomer of the corresponding alkene product predominates. [7, 8] The Still-Gennari HWE olefination typically uses potassium hexamethydisilazide [$KN(TMS)_2$] (also referred to as KHMDS) and 18-crown-6 or another strongly dissociated base system (Scheme 2).



Scheme 2: Still-Gennari HWE olefination. [8]

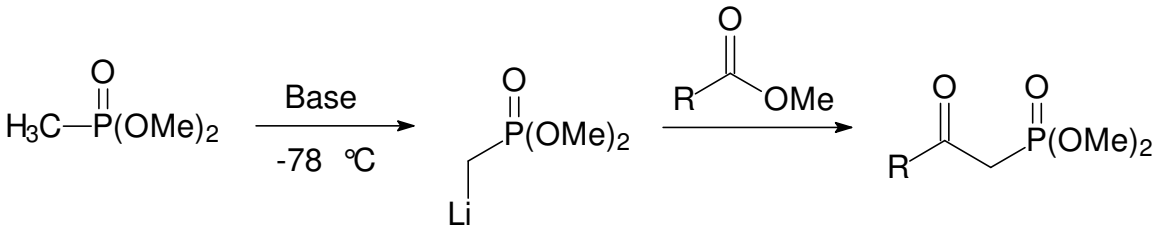
The following scheme illustrates the mechanism of the formation of the kinetic *(Z)*-isomer product (Scheme 3):



Scheme 3: Mechanism for formation of kinetic *(Z)*-isomer.[6]

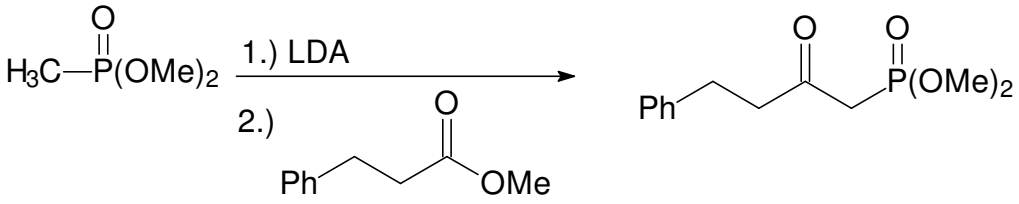
Bis(2,2,2-trifluoroethyl) β-ketophosphonates

While there are several methods for the preparation of β-ketophosphonates, the most common method is a condensation of methyl dialkylphosphonates with esters. This reaction usually involves the deprotonation of dimethyl methylphosphonate with a lithium base at -78 °C and is then followed by the addition of an ester (Scheme 4).



Scheme 4: Preparation of β-ketophosphonate *via* condensation.[9]

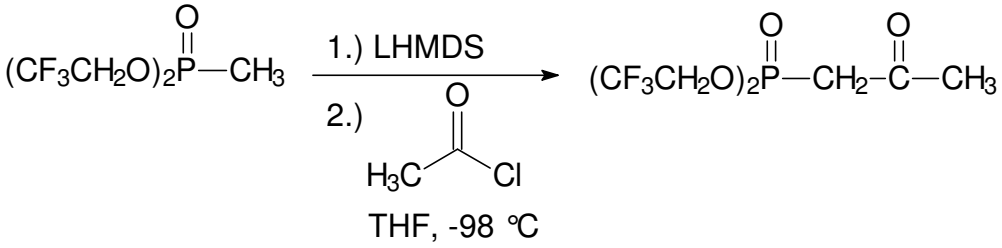
While this condensation method has been used for large-scale synthesis of β-ketophosphonates, there is a problem with the cryogenic conditions and the tendency of the phosphonate anion to decompose at 0 °C or undergo an intermolecular alkyl transfer at -60 °C, therefore, the temperature couldn't rise above -78 °C. A method was then developed to prepare β-ketophosphonates using noncryogenic conditions and to eliminate side reactions. This was achieved by Maloney and Chung when they added LDA to a mixture of dimethyl methylphosphonate and an ester at 0 °C.[9] Only 1 equivalent of phosphonate was needed, therefore, completely suppressing the decomposition of the phosphonate anion. Scheme 5 depicts the LDA-mediated condensation performed by Maloney and Chung.



Scheme 5: LDA-mediated condensation of dimethyl methylphosphonate with an ester.[9]

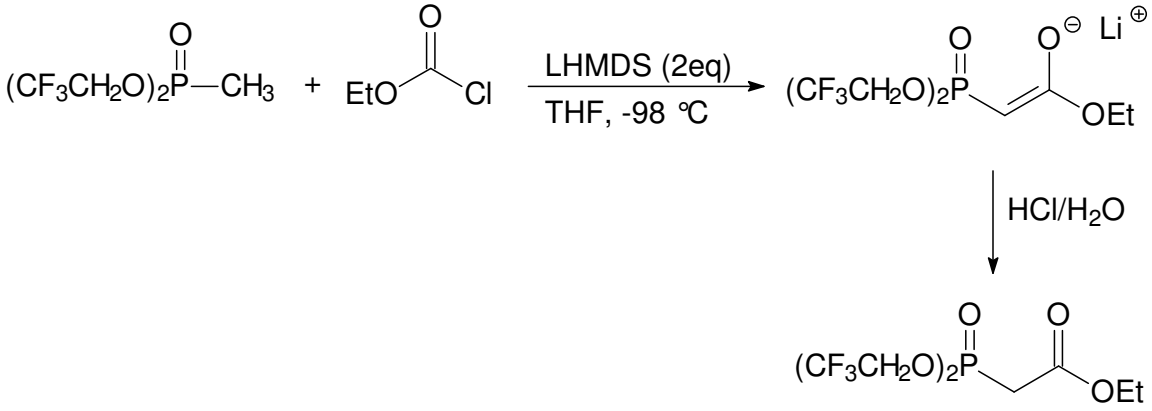
While the LDA-mediated condensation produced high yields of β-ketophosphonates, the conditions were unable to produce β-ketophosphonates with trifluoroethyl esters. It had been noted that minimal research had taken place to prepare or attempt to prepare products containing the fragment $(CF_3CH_2O)_2P(O)CR_2C(O)R$.[10] An *in situ* formation using a lithium-stabilized anion is one of the most common synthetic routes. Bis(2,2,2-trifluoroethyl) methylphosphonate is treated with the strong base lithium hexamethyldisilazide (LHMDS) in THF at -98 °C to form a carbanion nucleophile. The carbanion nucleophile then acts upon an acid chloride to form β-ketophosphonates in good yields.[11-19] It is essential for the reaction to take place at -98 °C

because the phosphonate carbanion decomposes at -78 °C.[7] Illustrated below is a general reaction scheme for the reported synthesis of bis(2,2,2-trifluoroethyl) β-ketophosphonates (Scheme 6).



Scheme 6: Synthesis of bis(2,2,2-trifluoroethyl) β-ketophosphonate.

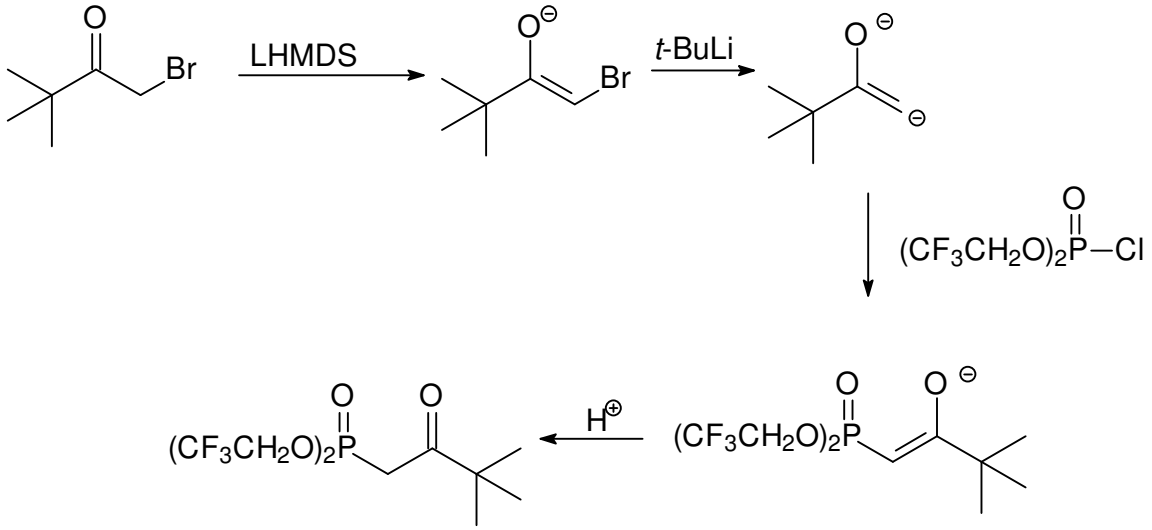
Savignac reported the synthesis of bis-trifluoroethyl phosphonoacetates from bis-trifluoroethyl alkynylphosphonates and alkylchloroformates. In his method he utilized LHMDS and THF[20] as seen in Scheme 7.



Scheme 7: Savignac's synthesis of bis(2,2,2-trifluoroethyl) phosphonoacetates.[20]

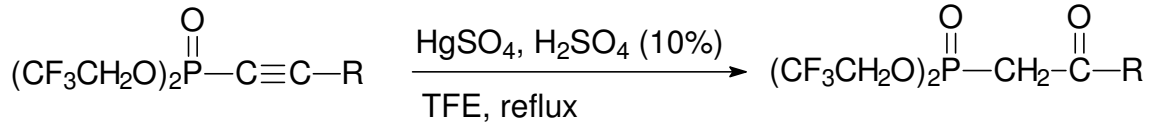
Another method used to obtain bis(2,2,2-trifluoroethyl) β-ketophosphonates was to treat a α-bromo ketone with LHMDS and *tert*-butyllithium. The α-bromo ketone was treated with LHMDS and *tert*-butyllithium at -110 °C to form a dianion. With a bis(2,2,2-trifluoroethyl) phosphorochloridate electrophile available, the dianion can act upon it to obtain bis(2,2,2-trifluoroethyl) β-ketophosphonates in moderate to good

yields[21] (Scheme 8).



Scheme 8: Wiemer synthesis of bis(2,2,2-trifluoroethyl) β-ketophosphonates.[21]

Kevin White, a former member of the Jackson lab group, had reported the formation of bis(2,2,2-trifluoroethyl) β-ketophosphonates by the hydration of a series of straight chain bis(2,2,2-trifluoroethyl) phosphonoalkynes. This hydrolysis method utilized mercury sulfate and 10% aqueous sulfuric acid in 2,2,2-trifluoroethanol.[10] After a gentle reflux, bis(2,2,2-trifluoroethyl) β-ketophosphonates were obtained (Scheme 9).

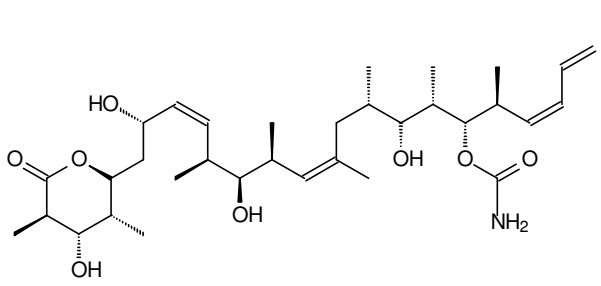


Scheme 9: White's synthesis of bis(2,2,2-trifluoroethyl) β-ketophosphonates.[10]

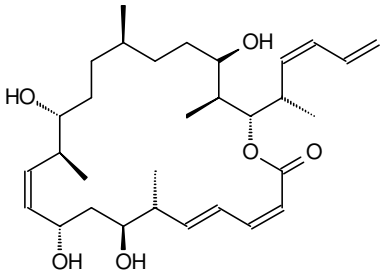
Due to difficulties in obtaining usable quantities of natural products from nature, chemists began a considerable effort directed at the total synthesis of natural products. Some natural products with useful properties are identified and total synthesis is the only way to obtain useful quantities. A class of compounds known as antimitotic agents has

received considerable attention. Specifically, Paclitaxel, also known by the trade name Taxol®, has received much attention. Taxol® was first isolated from the pacific yew tree, native to the Pacific Northwestern United States. Taxol® is currently a prescribed chemotherapeutic agent that is an example of an antimitotic agent.

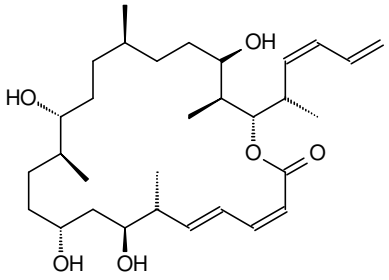
Known members of this class of antimitotic agents include (+)-discodermolide and (-)-dictyostatin. These two compounds were first isolated from deep sea sponge. An antimitotic analogue of dictyostatin is 10, 11-dihydrodictyostatin. Figure 2 depicts the chemical structure of these three compounds.



(+)-Discodermolide



(-)-Dictyostatin

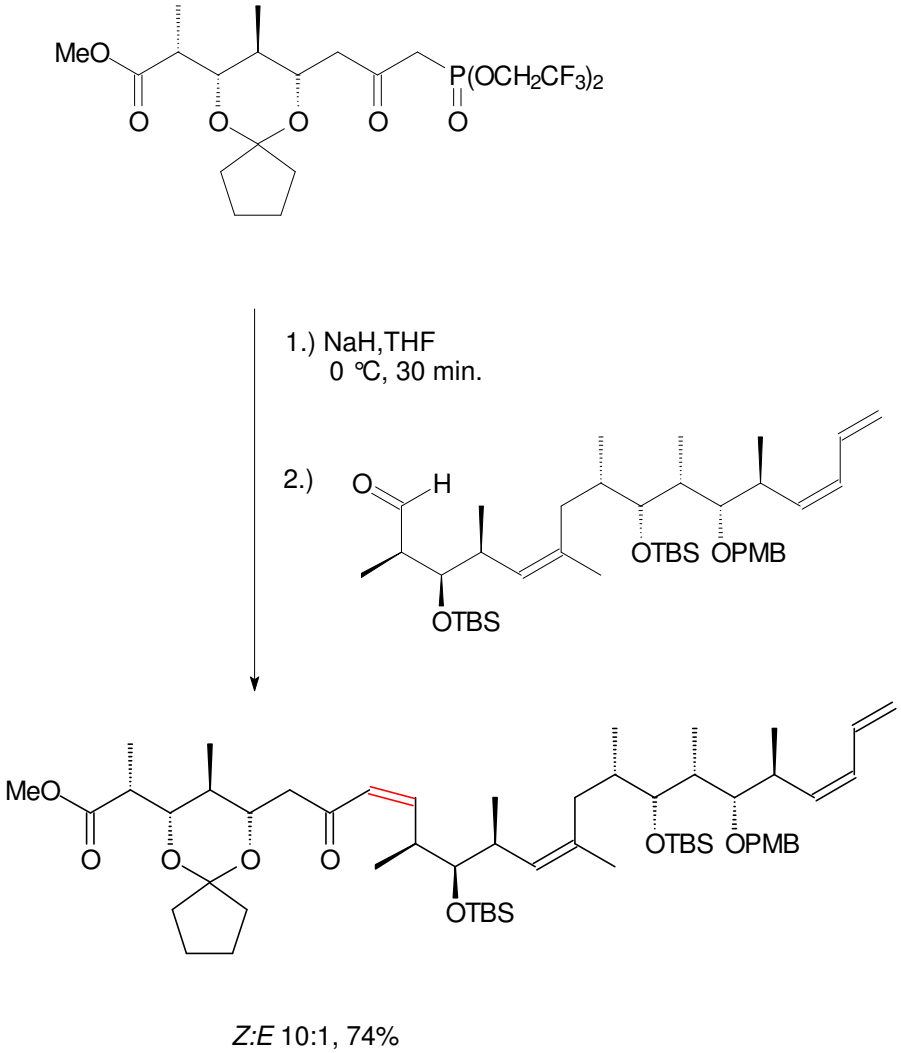


10,11-Dihydrodictyostatin

Figure 2: Chemical structures of antimitotic agents.

Variations of the HWE reaction have been commonly used in natural product syntheses and β-ketophosphonates are frequently employed in the HWE reaction.[11-19] Still-Gennari HWE olefination has been used as key steps in the total synthesis of discodermolide, dictyostatin, and various analogues by Paterson. Paterson has used

advanced bis(2,2,2-trifluoroethyl) β-ketophosphonates in the Still-Gennari HWE olefination to produce these antimitotic agents, therefore demonstrating the utility of the Still-Gennari HWE olefination and the practicality of bis(2,2,2-trifluoroethyl) β-ketophosphonates.[11-18] Scheme 10 shows the key step in a practical synthesis of dicodermolide.

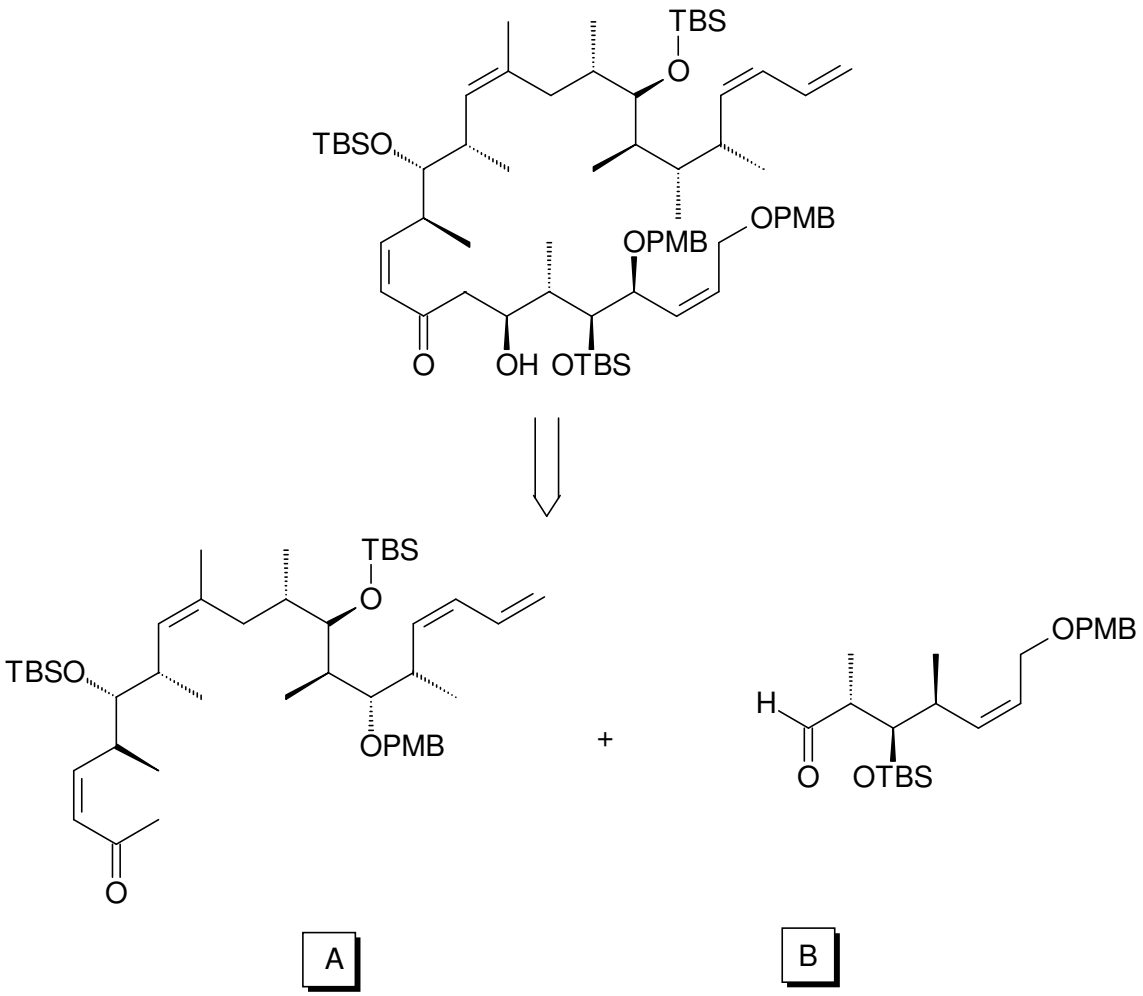


Z:E 10:1, 74%

Scheme10: Key step in Paterson's synthesis of discodermolide.[13]

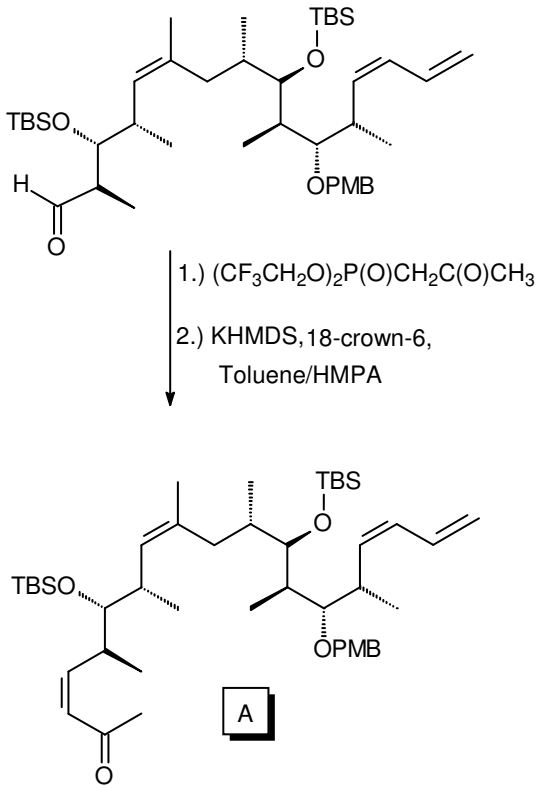
Modern synthetic techniques are then used to obtain a sample identical to the natural product after the skeleton of the molecule has been made.

Paterson also uses the Still-Gennari HWE olefination as a key step in the synthesis of the two fragments (A and B) that make up the skeleton of the hybrid analogue of discodermolide and dictyostatin.[16] The retrosynthetic scheme for the precursor to the target hybrid is shown (Scheme 11).

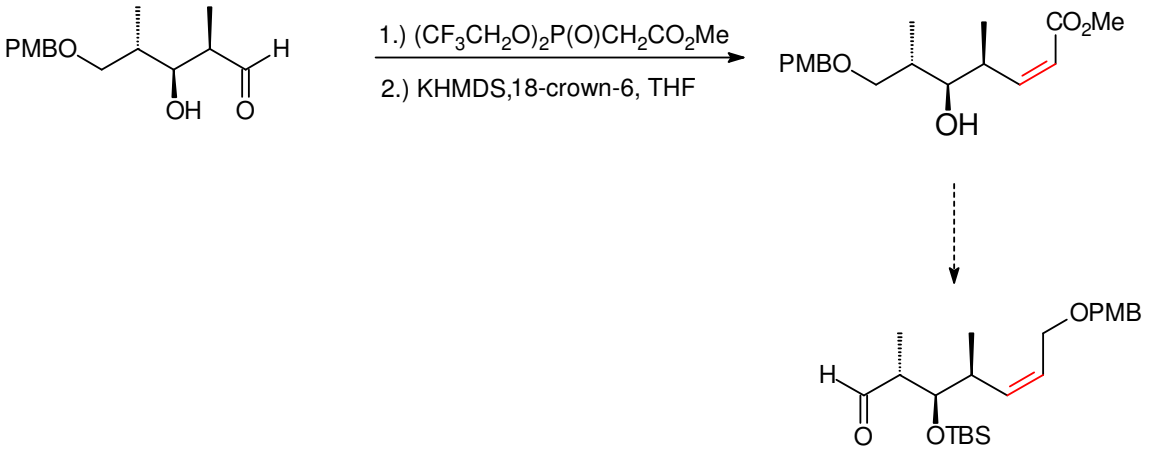


Scheme 11: Retrosynthetic analysis of the hybrid skeleton.[16]

Schemes 12 and 13 show the key steps utilizing the Still-Gennari HWE reaction for the formation of fragments A and B.



Scheme 12: Still-Gennari HWE olefination application for fragment A.

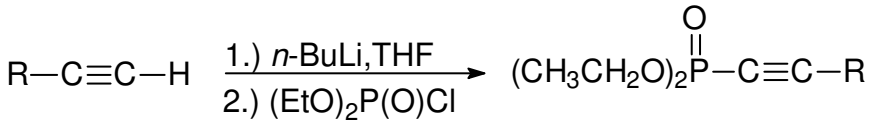


Scheme 13: Still-Gennari HWE olefination application for fragment B.

For fragment B, after the application of the Still-Gennari HWE olefination, it is just a matter of deprotection and reduction to obtain the target compound.

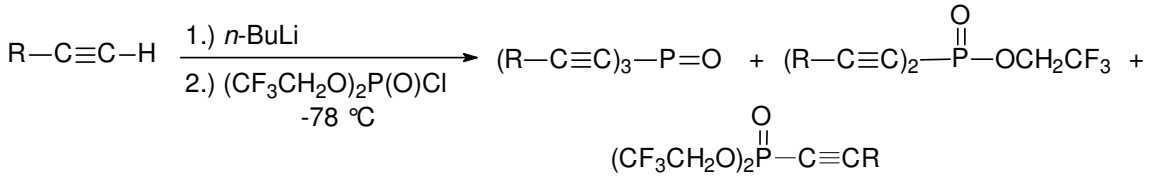
1-Alkynylphosphonates

1-Alkynylphosphonates are versatile synthetic intermediates used in organic syntheses. In 1957 the first 1-alkynylphosphonate was reported[26] and since that time they have been intensely investigated. Terminal alkynes are treated with *n*-butyllithium in tetrahydrofuran (THF) at -78 °C to form the lithium-stabilized nucleophilic carbanion. The carbanion is then allowed to act upon diethyl chlorophosphate to form diethylphosphonoalkynes in yields of 80-90%. This reaction is shown in Scheme 14.[27]



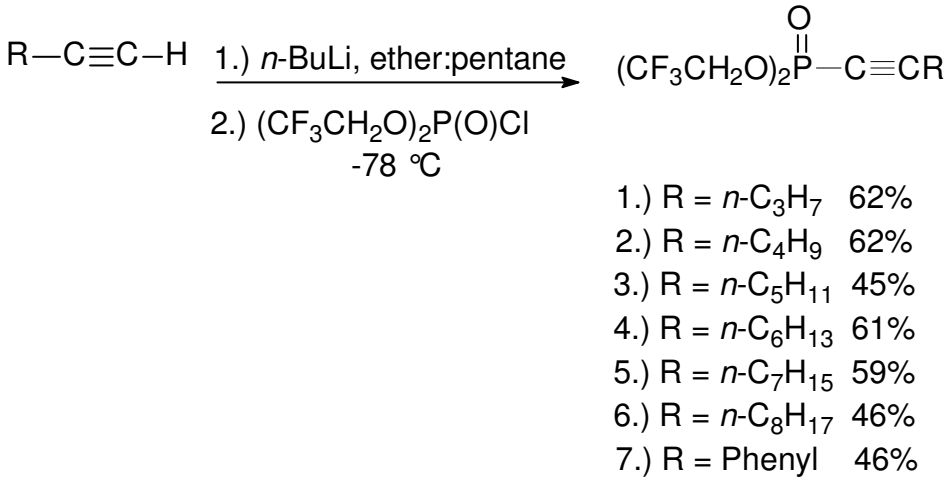
Scheme 14: Synthesis of diethylphosphonoalkynes.

When bis(2,2,2-trifluoroethyl) phosphorochloridate was substituted for diethyl chlorophosphate in the analogous reaction, a complex mixture containing trisalkynylphosphine oxide [$(RCC)_3P{=}O$] was the major product, in addition to trace amounts of the desired alkynyl phosphonate, and bis alkynyl phosphonate (Scheme 15).[25]



Scheme 15: Formation of by-products using bis(2,2,2-trifluoroethyl) phosphorochloridate.

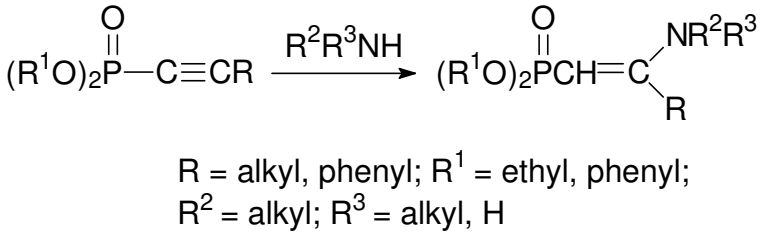
To obtain acceptable yields of bis(2,2,2-trifluoroethyl) phosphonoalkynes, optimized conditions using a 50:50 ether: pentane solvent system were used on large scale (50-100 mmol). Purification of 10-15 gram quantities in 45-62% yields were obtained *via* high vacuum fractional distillation (Scheme 16). [10, 28, 29]



Scheme 16: Synthesis of bis(2,2,2-trifluoroethyl) phosphonoalkynes.

Conjugate Addition of Amines

Primary and secondary aliphatic amines can be added to the triple bond of 1-alkynylphosphonates by way of conjugate addition. The resulting enamine phosphonates are produced in fair to good yields (Scheme 17). [30]



Scheme 17: Addition of aliphatic amines to 1-alkynylphosphonates.[30]

The general procedure used by Chattha and Aguiar consisted of using a 10-12 molar excess of amines and refluxing the reaction for 3-6 days. The remaining amines were then evaporated *in vacuo*. Typically, the resulting enamine phosphonate existed as a *cis-trans* mixture as shown in Figure 3.

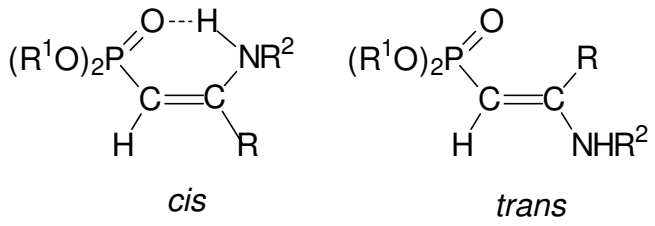
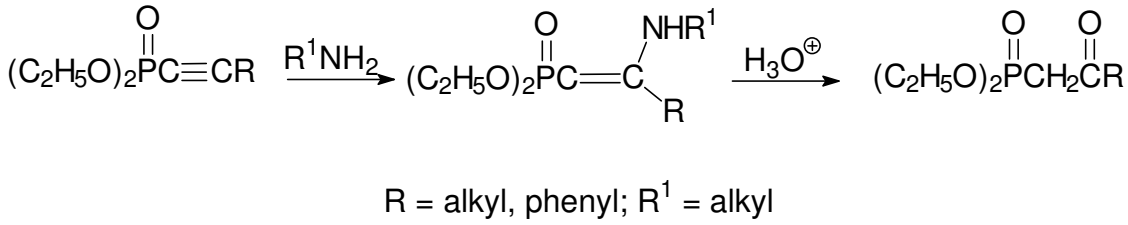


Figure 3: Enamine phosphonates *cis* and *trans* products.[30]

Acid Hydrolysis of Enamine Phosphonates

After an enamine phosphonate is obtained, the resulting adduct can then be dissolved in ether and a 1% aqueous solution of oxalic acid can be added to obtain a two layer system. Chattha and Aguiar then allowed this reaction to stir at room temperature for 7-8 hours before performing a simple aqueous work up. The resulting diethyl β-ketophosphonate was then purified using a short path distillation.[31] This general method is shown in Scheme 18.



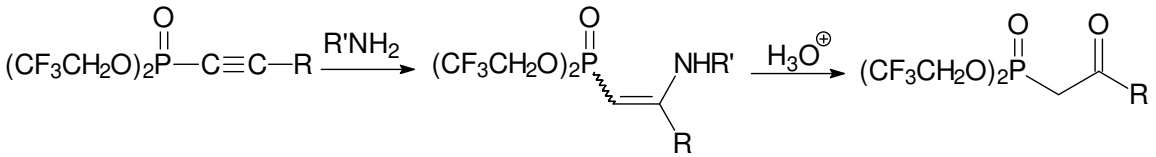
Scheme 18: Preparation of β-ketophosphonate *via* acid hydrolysis of enamine vinyl phosphonates.[31]

Chattha and Aguiar's preparation of β-ketophosphonates uses mild conditions, is straight forward, and produces high yields.

Statement of Purpose

It has been shown that primary and secondary amines can be added to the triple carbon bond of 1-alkynylphosphonates via conjugate addition to obtain enamine phosphonates that can undergo an acid hydrolysis utilizing a 1% oxalic acid solution to synthesize diethyl β-ketophosphonates in high yield. Bis(2,2,2-trifluoroethyl)-β-ketophosphonates have been synthesized utilizing a lithium- stabilized anion of bis(2,2,2-trifluoroethyl) methylphosphonate that acts upon an acid chloride at -98 °C. The other method for synthesizing bis(2,2,2-trifluoroethyl)-β-ketophosphonates involves treating α-halo ketones with two equivalents of a strong base to produce the dianion which then acts upon an electrophilic bis(2,2,2-trifluoroethyl) phosphorochloridate using an extremely low temperature of -110 °C.

The many uses of bis(2,2,2-trifluoroethyl)-β-ketophosphonates and the reactivity of the triple bond of 1-alkynylphosphonates has encouraged us to attempt a conjugate addition of amines to bis(2,2,2-trifluoroethyl) phosphonoalkynes to produce enamine vinyl phosphonates and then carry out an acid hydrolysis on the enamine vinyl phosphonates to obtain bis(2,2,2-trifluoroethyl)-β-ketophosphonates. We have developed a method that is not only complementary to that which is already reported, but we also have developed a quicker method using a 1:1 ratio of starting materials (Scheme 19).



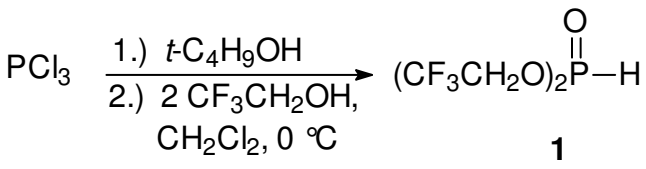
Scheme 19: Proposed synthesis of bis(2,2,2-trifluoroethyl)-β-ketophosphonates.

Chapter 2: Results and Discussion

This research project was focused on finding a new synthetic method for preparing bis(2,2,2-trifluoroethyl)-β-ketophosphonates from bis(2,2,2-trifluoroethyl) alkynylphosphonates.

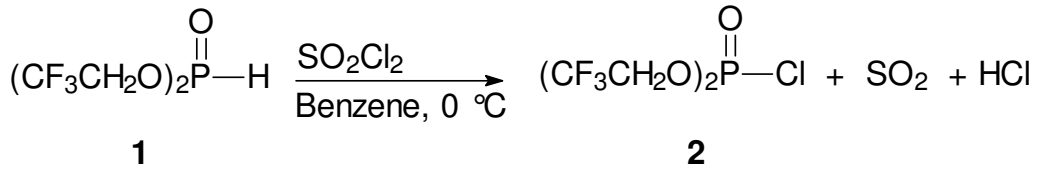
Synthesis of bis(2,2,2-trifluoroethyl) 1-alkynylphosphonates

While bis(2,2,2-trifluoroethyl) phosphite is commercially available, we prepared it following literature procedures. The general procedure utilizes one equivalent of phosphorus trichloride and one equivalent of 2-methyl-2-propanol. Two equivalents of 2,2,2-trifluoroethanol (TFE) in a dichloromethane solvent was then added at 0 °C to obtain satisfactory results.[34] This procedure was able to provide about 100 gram quantities of bis(2,2,2-trifluoroethyl) phosphate **(1)**. Scheme 20 depicts the method.



Scheme 20: Gibbs synthesis of bis(2,2,2-trifluoroethyl) phosphite.[34]

The bis(2,2,2-trifluoroethyl) phosphorochloridate **(2)** used to obtain the bis(2,2,2-trifluoroethyl) alkynylphosphonates was also synthesized. Sulfuryl chloride in benzene was allowed to react with a solution of bis(2,2,2-trifluoroethyl) phosphate **(1)** also in benzene at 0 °C.[32,33] Due to the optimized conditions of this method, bis(2,2,2-trifluoroethyl) phosphorochloridate was obtained in good yield (87%). The synthesis is shown in Scheme 21.



Scheme 21: Synthesis of bis(2,2,2-trifluoroethyl) phosphorochloridate.

Former members of the Jackson lab developed and optimized methods to prepare bis(2,2,2-trifluoroethyl) alkynylphosphonates from commercially available terminal alkynes and bis(2,2,2-trifluoethyl) phosphorochloridate.[25] Terminal alkynes are treated with *n*-butyllithium at -78 °C in 50:50 ether: pentane to form the lithium-stabilized carbanion nucleophile *in situ*. The carbanion nucleophile is then allowed to act upon bis(2,2,2-trifluoroethyl) phosphorochloridate to form the bis(2,2,2-trifluoroethyl) alkynylphosphonates in good to moderate yields.[25]

The bis(2,2,2-trifluoroethyl) alkynylphosphonates that were prepared are summarized (Table 1).

Entry	Alkyne	Alkynylphosphonate	Compound	Yield
(1a)	$CH_3(CH_2)_2C{\equiv}CH$	$(CF_3CH_2O)_2P(O)—C{\equiv}C(CH_2)_2CH_3$	3	46%
(1b)	$CH_3(CH_2)_3C{\equiv}CH$	$(CF_3CH_2O)_2P(O)—C{\equiv}C(CH_2)_3CH_3$	4	47%
(1c)	$CH_3(CH_2)_4C{\equiv}CH$	$(CF_3CH_2O)_2P(O)—C{\equiv}C(CH_2)_4CH_3$	5	41%
(1d)	$CH_3(CH_2)_5C{\equiv}CH$	$(CF_3CH_2O)_2P(O)—C{\equiv}C(CH_2)_5CH_3$	6	35%

Table 1: Yields of bis(2,2,2-trifluoroethyl) alkynylphosphonates.

Synthesis of Enamine Vinyl Phosphonates

Once all the required alkynylphosphonates were synthesized, the conjugate addition of primary and secondary amines was attempted to form the enamine vinyl phosphonates. The first reaction was completed by refluxing bis(2,2,2-trifluoroethyl) hex-1-ynylphosphonate **(4)** with a 10 molar excess of pyrrolidine. The reaction was monitored every thirty minutes via TLC and ^{31}P NMR. After thirty minutes of refluxing, all the hexynyl phosphonate had been consumed and two peaks appeared on the ^{31}P NMR spectrum at 31.26 and 23.63 ppm (Figure 4).

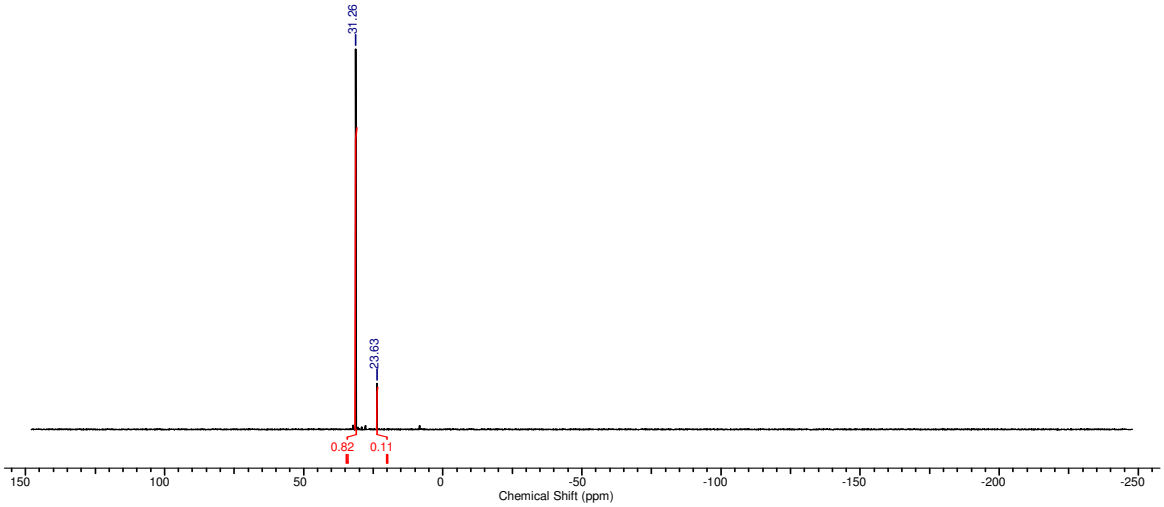
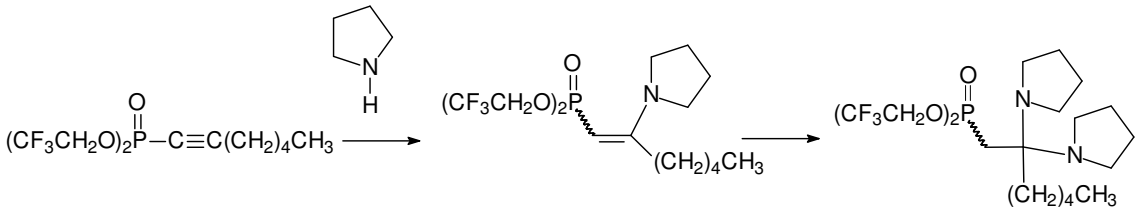


Figure 4: ^{31}P NMR spectrum of enamine vinyl phosphonate **8b** after a thirty-minute reflux.

The peak at 31.26 ppm was determined to be enamine vinyl phosphonate **8b** , while the second peak at 23.63 ppm is due to a second addition of the amine forming compound **11** (Scheme 22).



11

Scheme 22: Formation of by-product during a thirty-minute reflux.

The peak at 23.63 ppm is significantly smaller than the peak appearing at 31.26 ppm, which shows that the second addition is much slower than the first addition. This could be due to the fact the enamine vinyl phosphonate is sterically hindered.

Due to the quickness of the initial reaction, the next reaction was attempted using a 1:1 ratio of hexynyl phosphonate **4** to pyrrolidine. It was determined that since trifluoroethyl is a good electron withdrawing group, our reaction would proceed much quicker with less amine than the reported literature reaction. The reaction was monitored using TLC and ^{31}P NMR. After a thirty minute reflux, the reaction proceeded to form the enamine vinyl phosphonate.

To eliminate the formation of product **11** observed at 23.63 ppm on the ^{31}P NMR, the next reaction using 1:1 hexynyl phosphonate **4**: pyrrolidine was monitored every 10 minutes *via* TLC and ^{31}P NMR. This reaction took about twenty minutes to completely consume the hexynyl phosphonate **4** to form only the enamine vinyl phosphonate **8b**. This is a noteworthy difference because the corresponding *O, O*-diethyl enamine vinyl phosphonates require a 3 – 5 day reflux.[30, 31] This significant difference in time can be attributed to the fact that trifluoroethyl is a good electron withdrawing group. Analysis of

^{31}P NMR spectrum showed the consumption of hexynyl phosphonate **4** and the formation of the enamine vinyl phosphonate **8b** at 30.40 ppm (Figure 5).

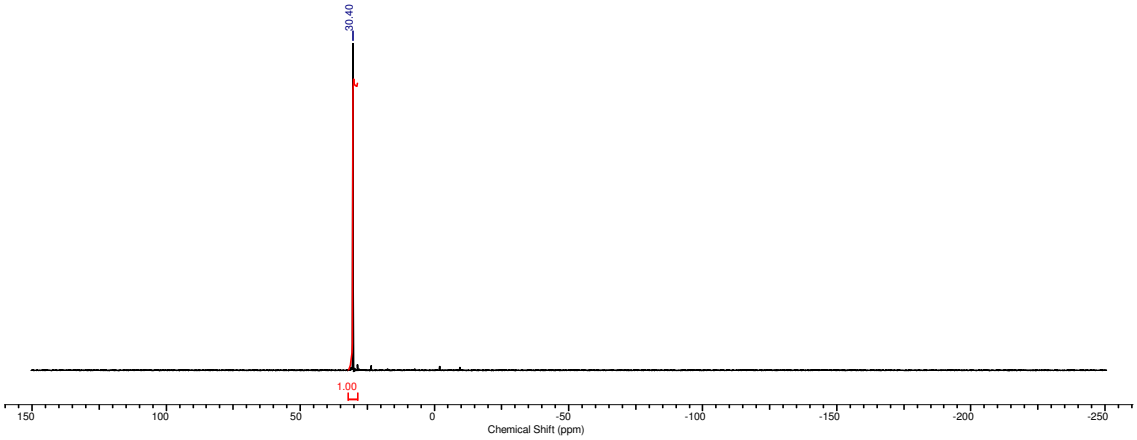
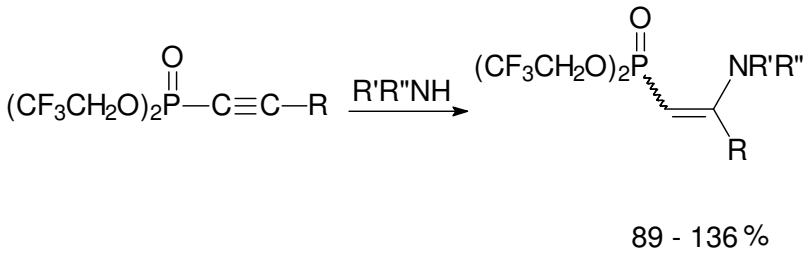


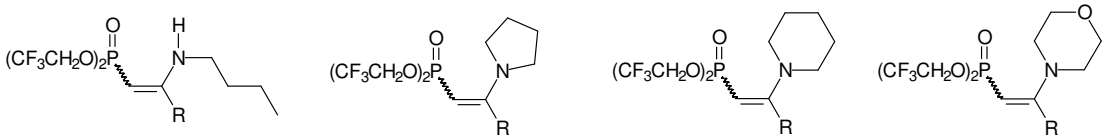
Figure 5: ^{31}P NMR spectrum of enamine vinyl phosphonate **8b**.

After the conditions for the formation of enamine vinyl phosphonate **8b** were optimized, subsequent reactions were performed using piperidine, morpholine, and *n*-butylamine. Each reaction only required twenty minutes to form the enamine vinyl phosphonate. Next, the process was attempted with pentynyl, heptynyl, and octynyl phosphonates and each of the amines, the results were exactly the same in each case. When purification was attempted using flash column chromatography the product decomposed, therefore, no purification was performed on the enamine vinyl phosphonates and only crude yields are reported (Scheme 23).



Scheme 23: Method of the formation of enamine vinyl phosphonates.

A summary of the synthesized enamine vinyl phosphonates and their yields is shown in Table 2.

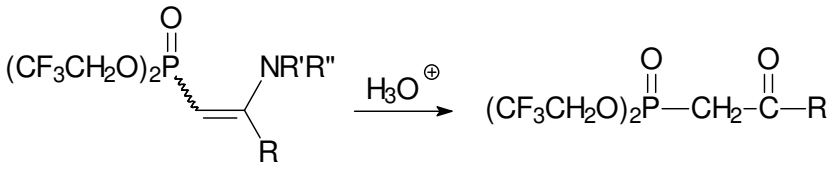


R = n-C_3H_7 (92%) **7a**	R = n-C_3H_7 (101%) **8a**	R = n-C_3H_7 (92%) **9a**	R = n-C_3H_7 (92%) **10a**
R = n-C_4H_9 (136%) **7b**	R = n-C_4H_9 (92%) **8b**	R = n-C_4H_9 (90%) **9b**	R = n-C_4H_9 (90%) **10b**
R = n-C_5H_{11} (108%) **7c**	R = n-C_5H_{11} (91%) **8c**	R = n-C_5H_{11} (99%) **9c**	R = n-C_5H_{11} (99%) **10c**
R = n-C_6H_{13} (94%) **7d**	R = n-C_6H_{13} (99%) **8d**	R = n-C_6H_{13} (101%) **9d**	R = n-C_6H_{13} (101%) **10d**

Table 2: Synthesized enamine vinyl phosphonates and their yields.

Synthesis of bis(2,2,2-trifluoroethyl) β-ketophosphonates

After all of the enamine vinyl phosphonates were prepared, they were then hydrolyzed via a two- phase system using a 1% aqueous oxalic acid solution and diethyl ether to generate the bis(2,2,2-trifluoroethyl) β-ketophosphonates at room temperature. The results were monitored using ^{31}P NMR (Scheme 24).



Scheme 24: Hydrolysis of enamine vinyl phosphonates.

The initial reaction used one equivalent of both enamine vinyl phosphonate and 1% aqueous oxalic acid and was allowed to stir over night at room temperature. After about twenty hours of stirring, a new peak forming at 23.9 ppm was observed *via* ^{31}P NMR. Unfortunately, there was still a peak at 30.4 ppm, therefore all of enamine vinyl phosphonate **8b** had not yet been consumed. The reaction was allowed to stir another twenty-four hours and was checked by ^{31}P NMR again. The starting material was still apparent at 30.4 ppm along with the β-ketophosphonate product at 23.9 ppm.

This reaction was then attempted replacing ether with THF to give a one- phase system. Again a 1:1 ratio of enamine vinyl phosphonate to 1% aqueous oxalic acid was used. After the reaction mixture had stirred overnight for about twenty hours, analysis of the ^{31}P NMR spectrum showed hydrolysis was not complete, as evidenced by the two peaks at 23.9 ppm and 30.4 ppm. The reaction mixture continued to stir for another twenty four hours to yield the same results.

Hydrolysis of the enamine vinyl phosphonate with one equivalent of 1% aqueous oxalic acid solution provided a mixture of β-ketophosphonate and unreacted starting material. Therefore, it was decided to try increasing the amount of 1% aqueous oxalic acid solution. First, a reaction was run with ten equivalents of 1% aqueous oxalic acid solution. After twenty hours of stirring the progress was monitored by ^{31}P NMR and

there was a significant decrease in the enamine vinyl phosphonate **8b** peak at 30.4 ppm and a significant increase in the peak at 23.9 ppm, which corresponds to β-ketophosphonate **13**. The reaction mixture was then allowed to stir for another twenty-four hours and afterwards the progress was monitored again by ^{31}P NMR; only one peak was present at 23.9 ppm. Therefore, it was determined that an increased amount of 1% aqueous oxalic acid solution was needed to form the bis(2,2,2-trifluoroethyl) β-ketophosphonate **13** from the enamine vinyl phosphonate **8b**.

The next reaction was run with only two equivalents of 1% aqueous oxalic acid solution. Again, the progress of the reaction was monitored after twenty hours of stirring *via* ^{31}P NMR. There was again a significant decrease in the peak at 30.4 ppm and a new peak began forming at 23.9 ppm. After another twenty-four hours of stirring all of the enamine vinyl phosphonate **8b** was consumed to obtain the β-ketophosphonate **13**. Therefore, it was determined that only two equivalents of 1% aqueous oxalic acid solution was required to completely form the bis(2,2,2-trifluoroethyl) β-ketophosphonate. It should also be noted that the hydrolysis of our enamine vinyl phosphonates to form β-ketophosphonates took longer than the 7-8 hours reported to form the diethyl β-ketophosphonates.[31]

After the conditions were optimized using the hexynyl phosphonate **4** and pyrrolidine enamine vinyl phosphonate **8b**, the reaction was conducted with all of the enamine vinyl phosphonates to yield the same results. After an aqueous work up was performed the product was purified using flash column chromatography and the

formation of pure bis(2,2,2-trifluoroethyl) β-ketophosphonates was confirmed by ^{31}P, ^{1}H, and ^{13}C NMR.

Figure 6 displays the ^{1}H NMR of bis(2,2,2-trifluoroethyl) 2-oxohexylphosphonate **(13)**.

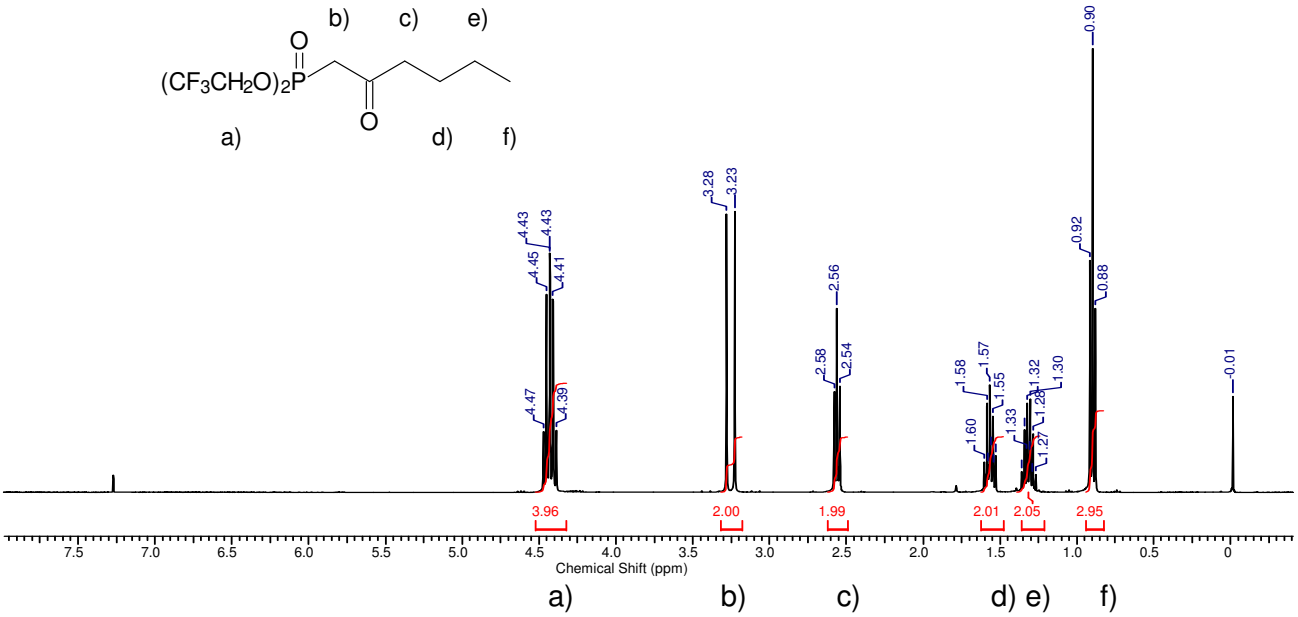


Figure 6: ^{1}H NMR spectrum of bis(2,2,2-trifluoroethyl) 2-oxohexylphosphonate **(13)**.

The methylene groups of the phosphorus ester are observed as a 4H doublet of quartets at 4.47 ppm with coupling constants of 8.2 and 8.0 Hz due to coupling to fluorine and phosphorus. Methylene protons (signal b) are observed as a 2H doublet with a 21.6 Hz coupling constant. This doublet corresponds to the *P*-methylene protons. The triplet that occurs at 2.58 ppm corresponds to the methylene protons that are adjacent to the ketone (signal c) with a coupling constant of 7.3 Hz. Signal d at 1.60 ppm is a 2H quintet with a 7.4 Hz coupling constant. The last methylene protons (signal e) are

observed as a 2H sextet with a coupling constant of 7.4 Hz. Finally, at 0.92 ppm there is a triplet that corresponds to the methyl group (signal f) with a 7.0 Hz coupling constant.

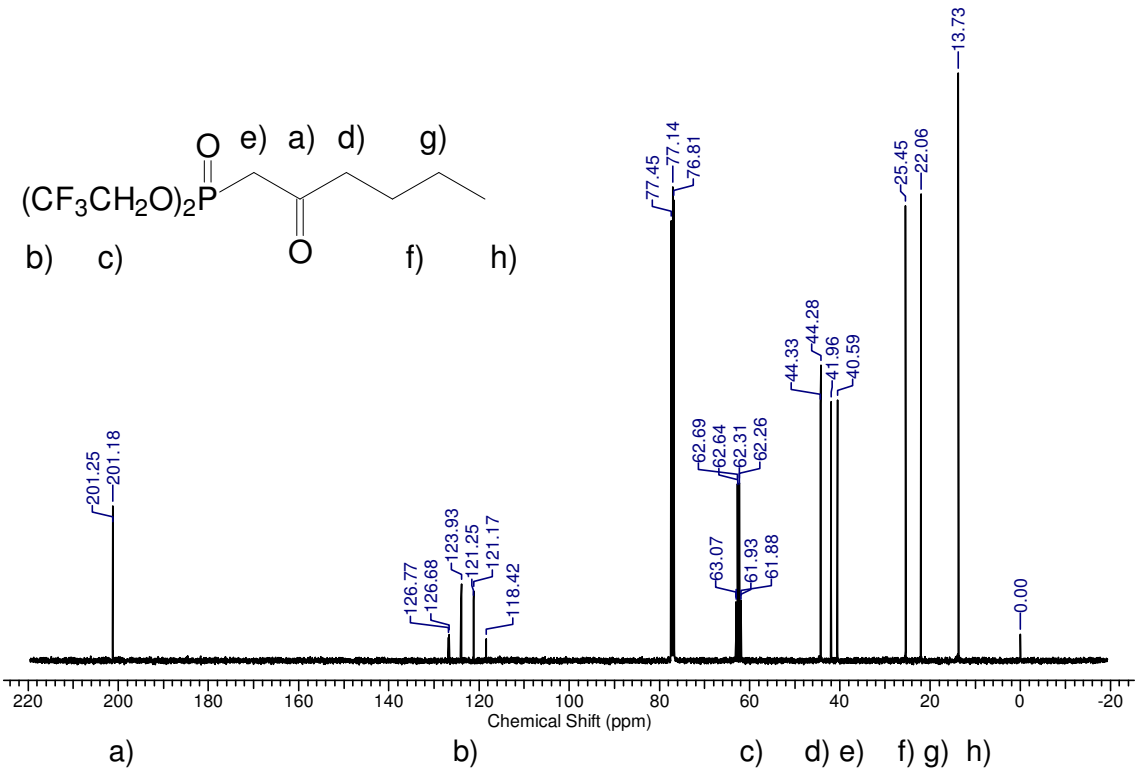
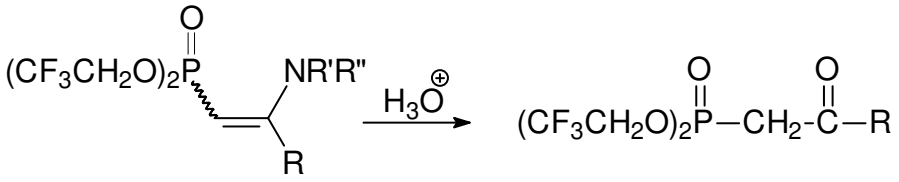


Figure 7: ^{13}C NMR spectrum of bis(2,2,2-trifluoroethyl) 2-oxohexylphosphonate **(13)**.

The ketone carbonyl is observed as a doublet at 201.25 ppm (J = 7.3 Hz) due to two bond carbon phosphorus coupling. The trifluoroethyl groups (signal b) are observed as a doublet of quartets at 126.77 ppm, due to coupling to fluorine (J = 277.3 Hz) and phosphorus (J = 8.5 Hz). The methylenes of the phosphorus ester (signal c) are also observed as a doublet of quartets, however, the carbon-fluorine coupling constant is reduced to 38.2 Hz, due to the fact that it is now a two bond coupling. Signal d at 44.33 ppm there is another doublet that corresponds to the methylene group that is a three bond coupling to phosphorus with a coupling constant of 5.1 Hz. Another doublet occurs at 41.96 ppm (J = 138.0 Hz) that corresponds to the methylene that is adjacent to the ketone

and coupled to phosphorus (signal e). There are singlets at 25.45 ppm and 22.06 ppm corresponding to the remaining methylene carbons. Lastly, there is a singlet at 13.83 ppm that corresponds to the methyl carbon.

The prepared bis(2,2,2-trifluoroethyl) β-ketophosphonates are summarized in Table 3.



R	Enamine Vinyl Phosphonate	β-ketophosphonate	Cmpd.	Yield
n-C_3H_7	**7a**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_2CH_3$	**12**	29%
n-C_3H_7	**8a**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_2CH_3$	**12**	18%
n-C_3H_7	**9a**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_2CH_3$	**12**	19%
n-C_3H_7	**10a**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_2CH_3$	**12**	25%
n-C_4H_9	**7b**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_3CH_3$	**13**	27%
n-C_4H_9	**8b**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_3CH_3$	**13**	35%
n-C_4H_9	**9b**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_3CH_3$	**13**	19%
n-C_4H_9	**10b**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_3CH_3$	**13**	12%
n-C_5H_{11}	**7c**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_4CH_3$	**14**	28%
n-C_5H_{11}	**8c**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_4CH_3$	**14**	44%
n-C_5H_{11}	**9c**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_4CH_3$	**14**	18%
n-C_5H_{11}	**10c**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_4CH_3$	**14**	17%
n-C_6H_{13}	**7d**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_5CH_3$	**15**	40%
n-C_6H_{13}	**8d**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_5CH_3$	**15**	35%
n-C_6H_{13}	**9d**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_5CH_3$	**15**	34%
n-C_6H_{13}	**10d**	$(CF_3CH_2O)_2P(O)-CH_2-C(O)(CH_2)_5CH_3$	**15**	37%

Table 3: Yields of prepared bis(2,2,2-trifluoroethyl) β-ketophosphonates.

Summary and Conclusions

In summary we have shown that bis(2,2,2-trifluoroethyl) β-ketophosphonates can be formed in good yield through the conjugate addition of primary and secondary amines to bis(2,2,2-trifluoroethyl) alkynylphosphonates to form enamine vinyl phosphonates that are then hydrolyzed. Our method is complementary to those previously reported and has been shown to produce respectable yields. Further work can be done with this project to attempt the reaction on a larger scale and increase yields.

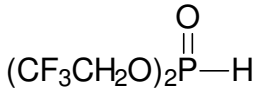
Chapter 3: Experimental

General Methods

Pentane was distilled from CaH_2 prior to use, and THF was distilled from sodium-benzophenone ketyl. All other commercial reagents where purchased from Aldrich or Acros and used without further purification unless otherwise stated. All solvents were dried or distilled by standard techniques. All glassware was previously oven- dried overnight. Flash chromatography was conducted with Merck grade 9385, 230-400 mesh, 60 Å silica. Thin layer chromatography (TLC) was conducted on aluminum- backed silica plates. Visualization was accomplished utilizing an ultraviolet lamp and staining with 5% phosphomolybdic acid (PMA) in ethanol, followed by heating.

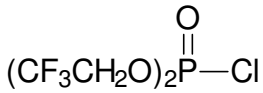
NMR spectra (^{31}P, ^{13}C, and ^{1}H) were recorded with a Bruker Avance AG 400 MHz spectrometer using deuterochloroform as the solvent. The ^{1}H NMR chemical shifts are reported in parts per million (ppm) downfield from internal $(CH_3)_4Si$ (0 ppm). The ^{13}C NMR chemical shifts are reported in parts per million (ppm) downfield from $(CH_3)_4Si$ with $CDCl_3$ as the internal standard (77.0 ppm). ^{31}P NMR chemical shifts are reported in parts per million (ppm) downfield from H_3PO_4 (external standard). Coupling constants are reported in Hertz (Hz).

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



A solution of 2-methyl-2-propanol (37.0 g, 0.5 mol) in dichloromethane (100 mL) was added dropwise to a stirred solution of phosphorus trichloride (43.5 mL, 0.5 mol) in dichloromethane (100 mL) for a period of 45 minutes under an argon atmosphere. After the addition was complete the reaction mixture stirred for 30 minutes at 0-5 ºC, a solution of 2,2,2-trifluoroethanol (100 g, 1 mol) in dichloromethane (100 mL) was then added dropwise for a period of 30 minutes. The temperature was maintained in the range of 0-5 ºC. Stirring was continued under an argon atmosphere for a period of 16 hours to remove excess HCl byproduct. The dichloromethane was removed *via* rotary evaporation and the final product was fractionally distilled under high vacuum to produce bis(2,2,2-trifluoroethyl) phosphite (94 g, 76%) as a clear liquid.

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



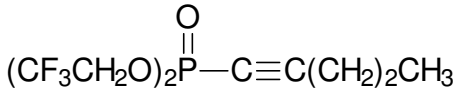
To a 250 mL round bottom flask containing bis(2,2,2-trifluoroethyl) phosphite (25 g, 0.1 mol) in benzene (30 mL) at 0 ºC was added a solution of sulfuryl chloride (10.15 mL, 0.1 mol) in a dropwise manner. The reaction mixture was put under the positive pressure of argon and was allowed to stir overnight. The benzene was removed by rotary evaporation and the product was fractionally distilled to yield bis(2,2,2-trifluoroethyl) phosphorochloridate (49.88 g, 87%) as a clear liquid.

^{31}P NMR ($CDCl_3$) δ 5.71 ppm

^{1}H NMR ($CDCl_3$) δ 4.56-4.48 (m, 4H)

Bis(2,2,2-trifluorethyl) 1-alkynlphosphonates:

Bis(2,2,2-trifluoroethyl) pent-1-ynylphosphonate (3).
General procedure for the formation of bis(2,2,2-trifluoroethyl) 1-alkynlphosphonates.



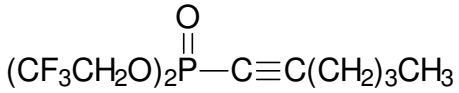
An ampule of 1-pentyne was cooled to -78 ºC due to its volatile nature. 1-Pentyne (4.93, 50 mmol) was then transferred to an argon flushed 500 mL round bottom flask containing a magnetic stir bar and 300 mL of pentane and diethyl ether (50:50). The reaction vessel was then cooled to -78 ºC and put under the positive pressure of argon using a rubber septum and an argon balloon. Stirring was started as *n*-butyllithium (34.4 mL, 50 mmol, 1.6 M in hexanes) was added dropwise *via* syringe over a 30 minute period. After the addition of *n*-butyllithium was complete, the reaction mixture was stirred for 1 hour at -78 ºC, after which the reaction was allowed to warm to room temperature for a period of 1 hour to allow the carbanion to form. After the warming period, the reaction mixture was then cooled down to -78 ºC and allowed to stir for 30 minutes. Finally, bis(2,2,2-trifluoroethyl) phosphorochloridate (9.3 mL, 56 mmol) was added *via* syringe and the reaction mixture was allowed to stir overnight. The reaction mixture was quenched using saturated ammonium chloride (3x50 mL) and washed with water (3x50 mL) to remove excess salts. The product was extracted into ether (3x50 mL), dried over anhydrous magnesium sulfate, and gravity filtered. The solvent was removed by rotary evaporation. The crude product was then fractionally distilled under high vacuum to yield compound **3** (7.23 g, 47%) as clear and colorless viscous oil.

^{31}P NMR ($CDCl_3$) δ -5.62 ppm.

^{1}H NMR ($CDCl_3$) δ 1.05 (t, *J*=7.4 Hz, 3H), 1.69 (sextet, *J*=7.2 Hz, 2H), 2.41 (dt, *J*=7.1, 4.6 Hz, 2H), 4.44 (dq, *J*=9.33, 7.92 Hz, 4H).

^{13}C NMR ($CDCl_3$) δ 13.32 (s), 20.81 (d, *J*=3.0 Hz), 21.28 (d, *J*=5.1 Hz), 63.40 (2, dq, *J*=38.4, 4.2 Hz), 66.16 (s), 107.51 (d, *J*=58.7 Hz), 126.6 (2, dq, *J*=277.6, 10.2 Hz).

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



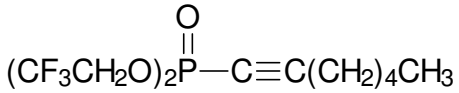
To a solution of 1-hexyne (5.75 mL, 50 mmol) in 300 mL ether: pentane (50:50) was added *n*-butyllithium (34.4 mL, 50 mmol, 1.6 M in hexanes). The resulting carbanion was treated with bis(2,2,2-trifluoroethyl) phosphorochloridate (9.3 mL, 56 mmol) according to the general procedure. Standard work up and purification by high vacuum distillation yielded compound **4** (7.6 g, 47%) as a clear viscous oil.

^{31}P NMR ($CDCl_3$) δ -5.66 ppm.

^{1}H NMR ($CDCl_3$) δ 0.96 (t, *J*=7.4 Hz, 3H), 1.47 (sextet, *J*=7.4 Hz, 2H), 1.64 (quintet, *J*=7.3 Hz, 2H), 2.43 (dt, *J*=7.1, 4.8 Hz, 2H), 4.44 (dq, *J*=8.2, 8.2 Hz, 4H).

^{13}C NMR ($CDCl_3$) δ 13.37 (s), 19.08 (s), 21.96 (s), 28.13 (s), 29.22 (d, *J*=2.2 Hz), 63.44 (2, dq, *J*=38.3, 4.2 Hz), 107.76 (d, *J*=58.0 Hz), 126.66 (2, dq, *J*=277.6, 10.1 Hz).

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



n-butyllithium (34.4 mL, 50 mmol, 1.6 M in hexanes) was added to a solution of 1-heptyne (6.56 mL, 50 mmol) in 300 mL ether: pentane (50:50) and the resulting carbanion was treated with bis(2,2,2-trifluoroethyl) phosphorochloridate (9.3 mL, 56

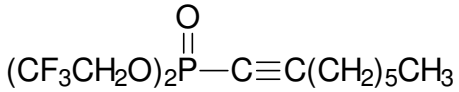
mmol) according to the general procedure. Standard work up and purification by high vacuum fractional distillation produced compound **5** (7.0 g, 41%) as clear and colorless viscous oil.

^{31}P NMR ($CDCl_3$) δ -5.61 ppm.

^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J*=7.1 Hz, 3H), 1.43-1.31 (m, 4H), 1.65 (quintet, *J*=7.3 Hz, 2H), 2.42 (dt, *J*=7.2, 4.8 Hz, 2H), 4.43 (dq, *J*=8.5, 8.0 Hz, 4H).

^{13}C NMR ($CDCl_3$) δ 13.77(s), 19.34 (d, *J*=5.1 Hz), 22.04 (s), 26.83 (s), 30.93 (s), 63.42 (2, dq, *J*=38.4, 3.3 Hz), 69.20 (d, *J*=332.4 Hz), 107.88 (d, *J*=59.4 Hz), 126.57 (2, dq, *J*=277.6, 10.1 Hz).

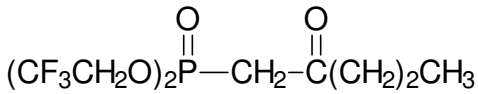
Bis(2,2,2-trifluoroethyl) oct-1-ynylphosphonate (6).



After addition of *n*-butyllithium (34.4 mL, 50 mmol, 1.6 M in hexanes) to a solution of 1-octyne (7.37 mL, 50 mmol) in 300 mL ether: pentane (50:50), the resulting carbanion was treated with bis(2,2,2-trifluoroethyl) phosphorochloridate (9.3 mL, 56 mmol) according to the general procedure. Standard work up and purification by high vacuum fractional distillation gave the desired compound **6** (6.23 g, 35%) as a clear and colorless viscous oil.

Bis(2,2,2-trifluoroethyl) β-ketophosphonates:

Bis(2,2,2-trifluoroethyl) 2-oxopentylphosphonate (12).
General procedure for the formation of bis(2,2,2-trifluoroethyl) β-ketophosphonates.



Bis(2,2,2-trifluoroethyl) pent-1-ynylphosphonate (0.624 g, 2.0 mmol) was added to an argon flushed 100 mL round bottom flask containing a magnetic stir bar. Then, *n*-butylamine (0.2 mL, 2.0 mmol) was added via syringe to the round bottom flask. The reaction mixture was then allowed to reflux for a period of 20 minutes to form enamine vinyl phosphonate **7a**. The remaining amine was removed by rotary evaporation. The resulting product was then dissolved in ether (8 mL), and a 1% aqueous solution of oxalic acid (16 mL) was added. The two-layer reaction mixture was then allowed to stir for 2 days at room temperature to ensure formation of product. The reaction mixture was then transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with ether (2x5 mL) and the combined organic layers were washed with 15 mL of a saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and gravity filtered. The remaining solvent was removed by rotary evaporation. The resulting oil was then purified using flash column chromatography (70:30 hexanes: ethyl acetate, Rf = 0.2) to obtain compound **12** (0.216 g, 29%).

^{31}P NMR ($CDCl_3$) δ 23.95 ppm.

^{1}H NMR ($CDCl_3$) δ 0.95 (t, *J*=7.5 Hz, 3H), 1.68 (sextet, *J*=7.3 Hz, 2H), 2.57 (t, *J*=7.2 Hz, 2H), 3.29 (d, *J*=21.6 Hz, 2H), 4.49 (dq, *J*=8.3, 8.1 Hz, 4H).

^{13}C NMR ($CDCl_3$) δ 13.38 (s), 16.87 (s), 41.97 (d, *J*=137.9 Hz), 46.44 (d, *J*=5.2 Hz), 63.07 (2, dq, *J*=38.0, 5.7 Hz), 126.77 (2, dq, *J*=277.3, 8.0 Hz), 201.16 (d, *J*=6.6 Hz).

Formation of Bis(2,2,2-trifluoroethyl) 2-oxopentylphosphonate (12) with Pyrrolidine.

Pyrrolidine (0.17 mL, 2.0 mmol) was added to bis(2,2,2-trifluoroethyl) pent-1-ynylphosphonate (0.624 g, 2.0 mmol) and the resulting enamine vinyl phosphonate **8a**

was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography produced the desired compound **12** (0.12 g, 18%) as an oily liquid. The NMR data is the same as previously reported.

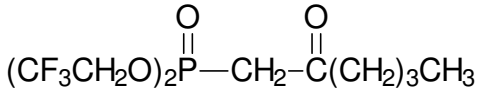
Formation of Bis(2,2,2-trifluoroethyl) 2-oxopentylphosphonate (12) with Piperidine.

To bis(2,2,2-trifluoroethyl) pent-1-ynylphosphonate (0.624 g, 2.0 mmol) was added piperidine (0.2 mL, 2.0 mmol). The resulting enamine vinyl phosphonate **9a** was then treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography yielded compound **12** (0.13 g, 19%). The NMR data is the same as previously reported.

Formation of Bis(2,2,2-trifluoroethyl) 2-oxopentylphosphonate (12) with Morpholine.

After addition of morpholine (0.17 mL, 2.0 mmol) to bis(2,2,2-trifluoroethyl) pent-1-ynylphosphonate (0.624 g, 2.0 mmol), the resulting enamine vinyl phosphonate **10a** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by was flash column chromatography gave the desired product, compound **12** (0.17 g, 25%). The NMR data is the same as previously reported.

Bis(2,2,2-trifluoroethyl) 2-oxohexylphosphonate (13).



To bis(2,2,2-trifluoroethyl) hex-1-ynylphosphonate (0.652 g, 2.0 mmol) was added *n*-butylamine (0.2 mL, 2.0 mmol). The resulting enamine vinyl phosphonate **7b** was

treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography yielded compound **13** (0.18 g, 27%).

^{31}P NMR ($CDCl_3$) δ 23.94 ppm

^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J*=7.4 Hz, 3H), 1.34 (sextet, *J*=7.4 Hz, 2H), 1.60 (quintet, *J*=7.4Hz, 2H), 2.58 (t, *J*=7.3 Hz, 2H), 3.28 (d, *J*=21.6 Hz, 2H), 4.47 (dq, *J*=8.2, 8.1 Hz, 4H).

^{13}C NMR ($CDCl_3$) δ 13.73 (s), 22.06 (s), 25.45 (s), 41.96 (d, *J*=138.6 Hz), 44.33 (d, *J*=5.1 Hz), 63.07 (2, dq, *J*=38.2, 5.2 Hz), 126.77 (2, dq, *J*=277.3, 8.5 Hz), 201.25 (d, *J*=6.6 Hz).

Formation of Bis(2,2,2-trifluoroethyl) 2-oxohexylphosphonate (13) with Pyrrolidine.

Pyrrolidine (0.17 mL, 2.0 mmol) was added to bis(2,2,2-trifluoroethyl) hex-1-ynylphosphonate (0.652 g, 2.0 mmol), and the resulting enamine vinyl phosphonate **8b** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography resulted in the formation of compound **13** (0.31 g, 35%) as an oily liquid. The NMR data is the same as previously reported.

Formation of Bis(2,2,2-trifluoroethyl) 2-oxohexylphosphonate (13) with Piperidine.

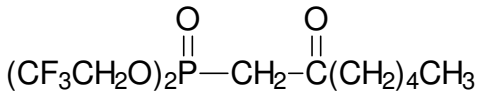
After the addition of piperidine (0.2 mL, 2.0 mmol) to bis(2,2,2-trifluoroethyl) hex-1-ynylphosphonate (0.652 g, 2.0 mmol), the resulting enamine vinyl phosphonate **9b** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography

obtained compound **13** (0.16 g, 19%) as an oily liquid. The NMR data is the same as previously reported.

Formation of Bis(2,2,2-trifluoroethyl) 2-oxohexylphosphonate (13) with Morpholine.

Morpholine (0.17 mL, 2.0 mmol) was added to bis(2,2,2-trifluoroethyl) hex-1-ynylphosphonate (0.652 g, 2.0 mmol), and the resulting enamine vinyl phosphonate **10b** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography resulted in compound **13** (0.105 g, 12%) as an oily liquid. The NMR data is the same as previously reported.

Bis(2,2,2-trifluoroethyl) 2-oxoheptylphosphonate (14).



To bis(2,2,2-trifluoroethyl) hept-1-ynylphosphonate (0.680 g, 2.0 mmol) was added *n*-butylamine (0.2 mL, 2.0 mmol). The resulting enamine vinyl phosphonate **7c** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography yielded compound **14** (0.184 g, 28%) as an oily liquid.

^{31}P NMR ($CDCl_3$) δ 24.06 ppm

^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J*=7.0 Hz, 3H), 1.35-1.25 (m, 4H), 1.63 (quintet, *J*=7.4 Hz, 2H), 2.58 (t, *J*=7.3 Hz, 2H), 3.29 (d, *J*=21.6 Hz, 2H), 4.49 (dq, *J*=8.2, 8.0 Hz, 4H).

^{13}C NMR ($CDCl_3$) δ 13.83 (s), 22.39 (s), 23.06 (s), 31.08 (s), 41.96 (d, *J*=138.0 Hz), 44.59 (d, *J*=5.1 Hz), 63.01 (2, dq, *J*=38.1, 5.2 Hz), 126.75 (2, dq, *J*=277.4, 8.6 Hz), 201.24 (d, *J*=7.3 Hz).

Formation of Bis(2,2,2-trifluoroethyl) 2-oxoheptylphosphonate (14) with Pyrrolidine.

Pyrrolidine (0.17 mL, 2.0 mmol) was added to bis(2,2,2-trifluoroethyl) hept-1-ynylphosphonate (0.680 g, 2.0 mmol) and the resulting enamine vinyl phosphonate **8c** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography resulted in compound **14** (0.32 g, 44%) as an oily liquid. The NMR data is the same as previously reported.

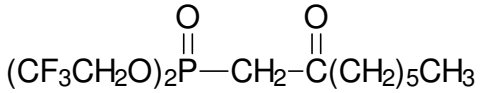
Formation of Bis(2,2,2-trifluoroethyl) 2-oxoheptylphosphonate (14) with Piperidine.

After the addition of piperidine (0.2 mL, 2.0 mmol) to bis(2,2,2-trifluoroethyl) hept-1-ynylphosphonate (0.680 g, 2.0 mmol), the resulting enamine vinyl phosphonate **9c** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography obtained compound **14** (0.12 g, 18%) as an oily liquid. The NMR data is the same as previously reported.

Formation of Bis(2,2,2-trifluoroethyl) 2-oxoheptylphosphonate (14) with Morpholine.

Morpholine (0.17 mL, 2.0 mmol) was added to bis(2,2,2-trifluoroethyl) hept-1-ynylphosphonate (0.680 g, 2.0 mmol), and the resulting enamine vinyl phosphonate **10c** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work and purification by flash column chromatography resulted in compound **(14)** (0.11 g, 17%) as an oily liquid.

Bis(2,2,2-trifluoroethyl) 2-oxooctylphosphonate (15).



To bis(2,2,2-trifluoroethyl) oct-1-ynylphosphonate (0.709 g, 2.0 mmol) was added *n*-butylamine (0.2 mL, 2.0 mmol). The resulting enamine vinyl phosphonate **7d** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography gave the desired product, compound **15** (0.324 g, 40%).

^{31}P NMR ($CDCl_3$) δ 23.97 ppm.

^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 6.8 Hz, 3H), 1.33-1.26 (m, 6H), 1.61-1.55 (m, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 3.29 (d, *J* = 21.9 Hz, 2H), 4.49 (dq, *J* = 8.4 Hz, 8.3 Hz, 4H).

^{13}C NMR ($CDCl_3$) δ 13.84 (s), 22.34 (s), 23.22 (s), 28.47 (s), 31.40 (s), 41.82 (d, *J*=137.9 Hz), 44.50 (d, *J* = 5.1 Hz), 62.94 (2, dq, *J* = 38.0 Hz, 5.7 Hz), 126.63 (2, dq, *J* = 277.4 Hz, 8.5 Hz), 201.14 (d, *J* = 6.6 Hz).

Formation of Bis(2,2,2-trifluoroethyl) 2-oxooctylphosphonate (15) with Pyrrolidine.

Pyrrolidine (0.17 mL, 2.0 mmol) was added to bis(2,2,2-trifluoroethyl) oct-1-ynylphosphonate (0.709 g, 2.0 mmol) and the resulting enamine vinyl phosphonate **8d** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography yielded compound **15** (0.26 g, 35%) as an oily liquid. The NMR data is the same as previously reported.

Formation of Bis(2,2,2-trifluoroethyl) 2-oxooctylphosphonate (15) with Piperidine.

After the addition of piperidine (0.2 mL, 2.0 mmol) to bis(2,2,2-trifluoroethyl) oct-1-ynylphosphonate (0.709 g, 2.0 mmol), the resulting enamine vinyl phosphonate **9d** was treated with ether (8 mL) and 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography obtained compound **15** (0.26 g, 34%) as an oily liquid. The NMR data is the same as previously reported.

Formation of Bis(2,2,2-trifluoroethyl) 2-oxooctylphosphonate (15) with Morpholine.

To bis(2,2,2-trifluoroethyl) oct-1-ynylphosphonate (0.709 g, 2.0 mmol) was added morpholine (0.17 mL, 2.0 mmol). The resulting enamine vinyl phosphonate **10d** was treated with ether (8 mL) and a 1% aqueous oxalic acid solution (16 mL) according to the general procedure. Standard work up and purification by flash column chromatography resulted in compound **15** (0.28 g, 37%) as an oily liquid. The NMR data is the same as previously reported.

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Figure 8 **^{31}P NMR of Compound 2**

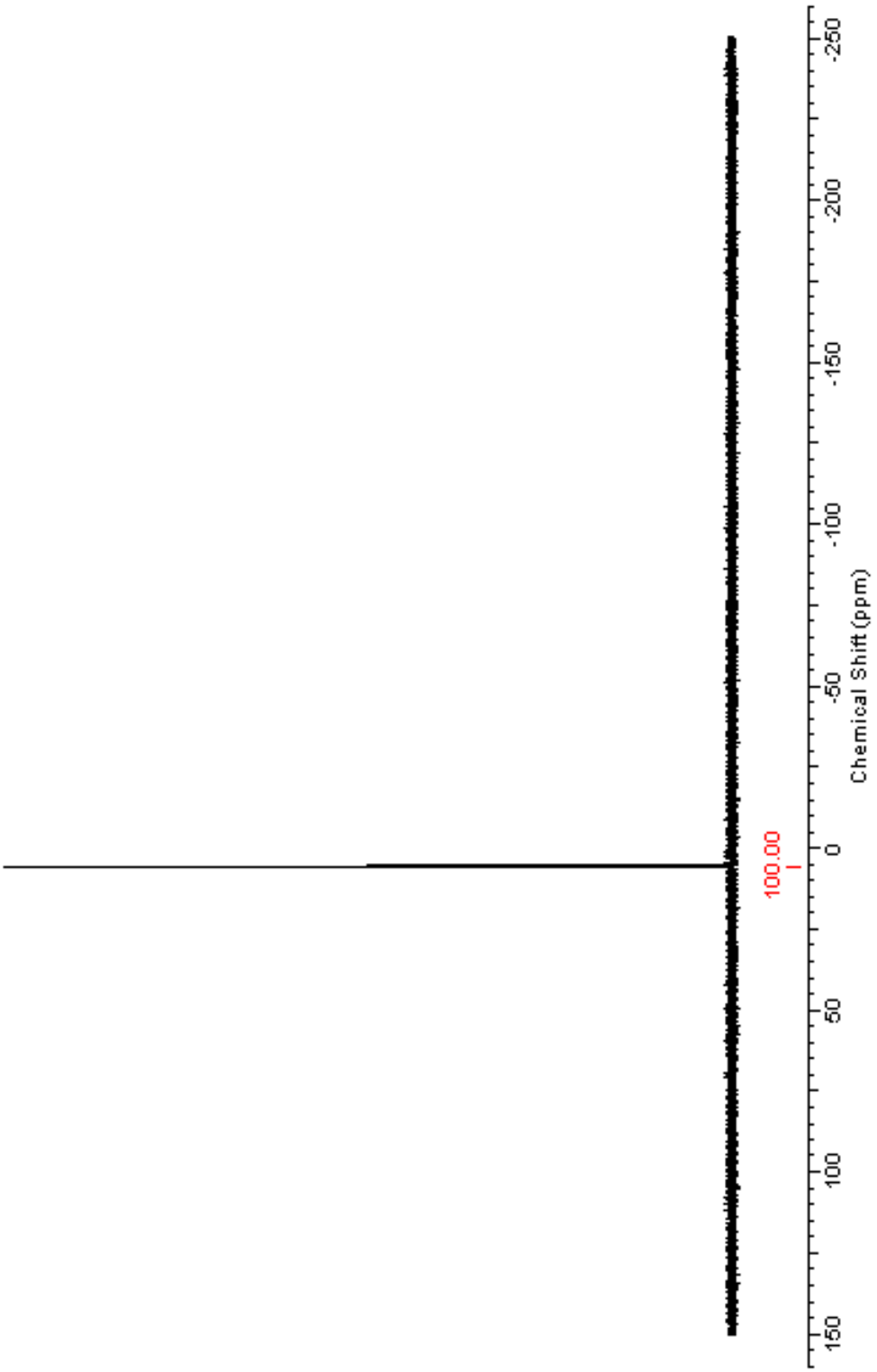

Figure 9 **^{1}H NMR of Compound 2**

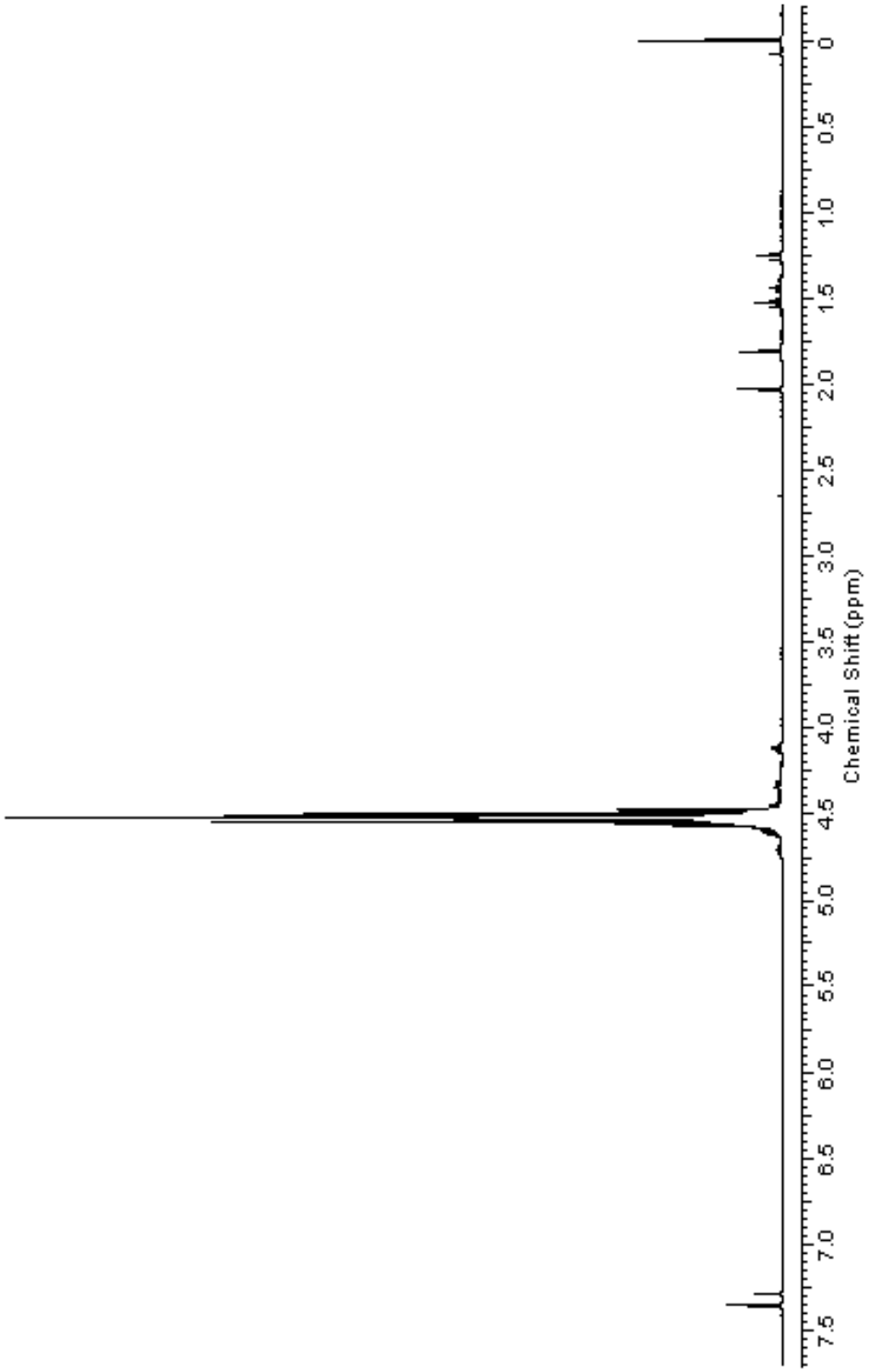

Figure 10 ^{31}**P NMR of Compound 3**

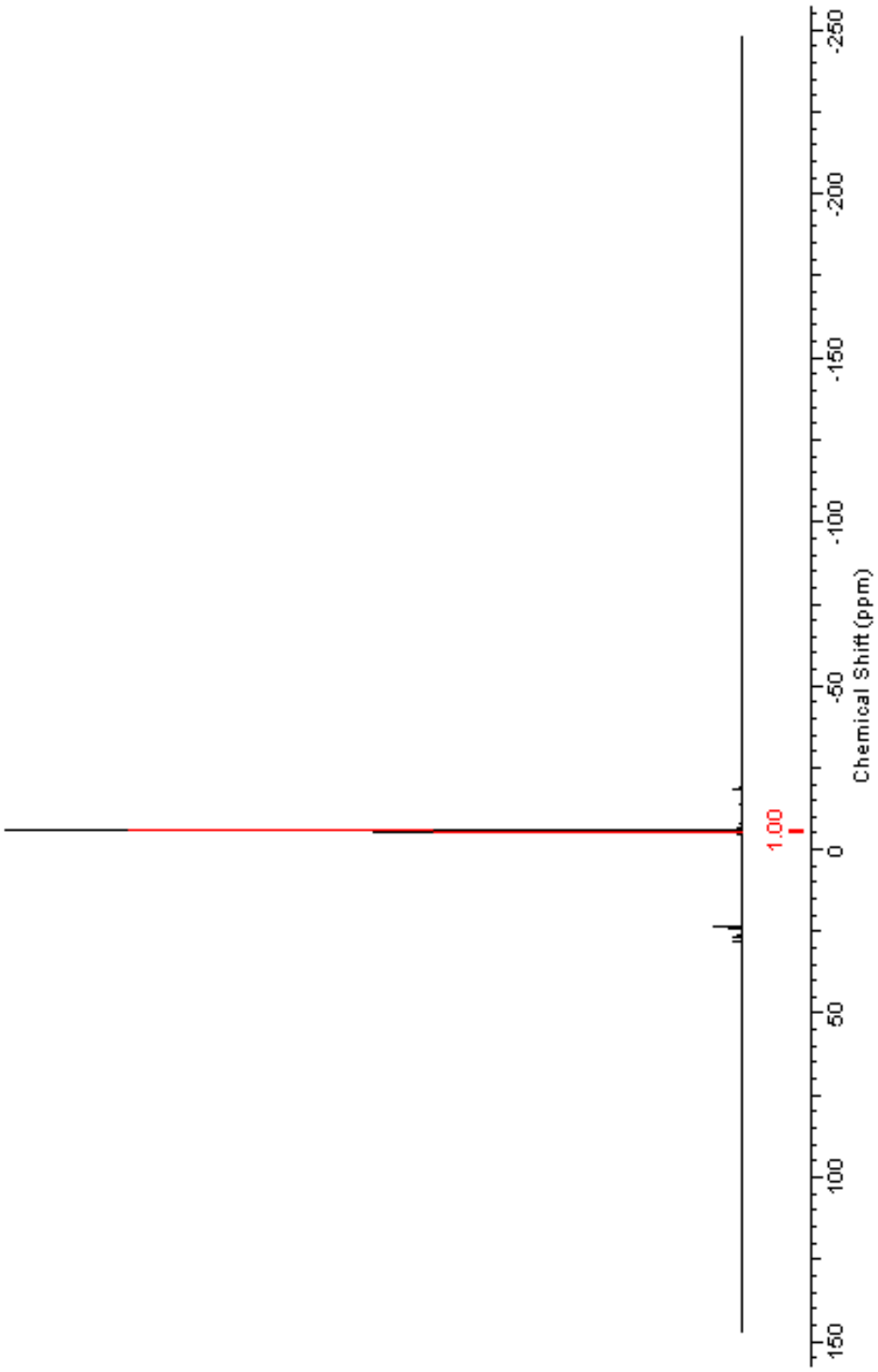

Figure 11 **^{1}H NMR of Compound 3**

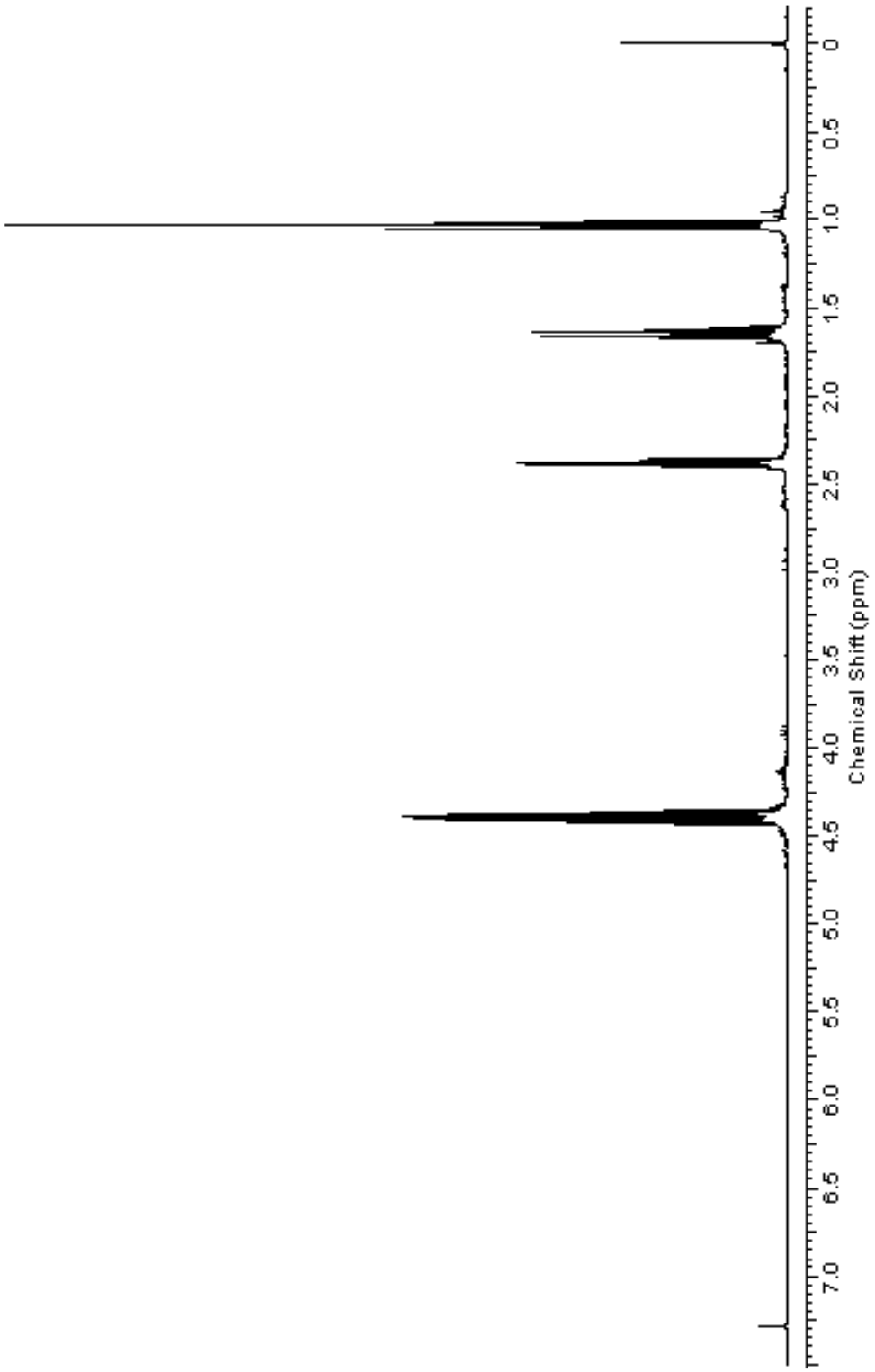

Figure 12 **^{13}C NMR of Compound 3**

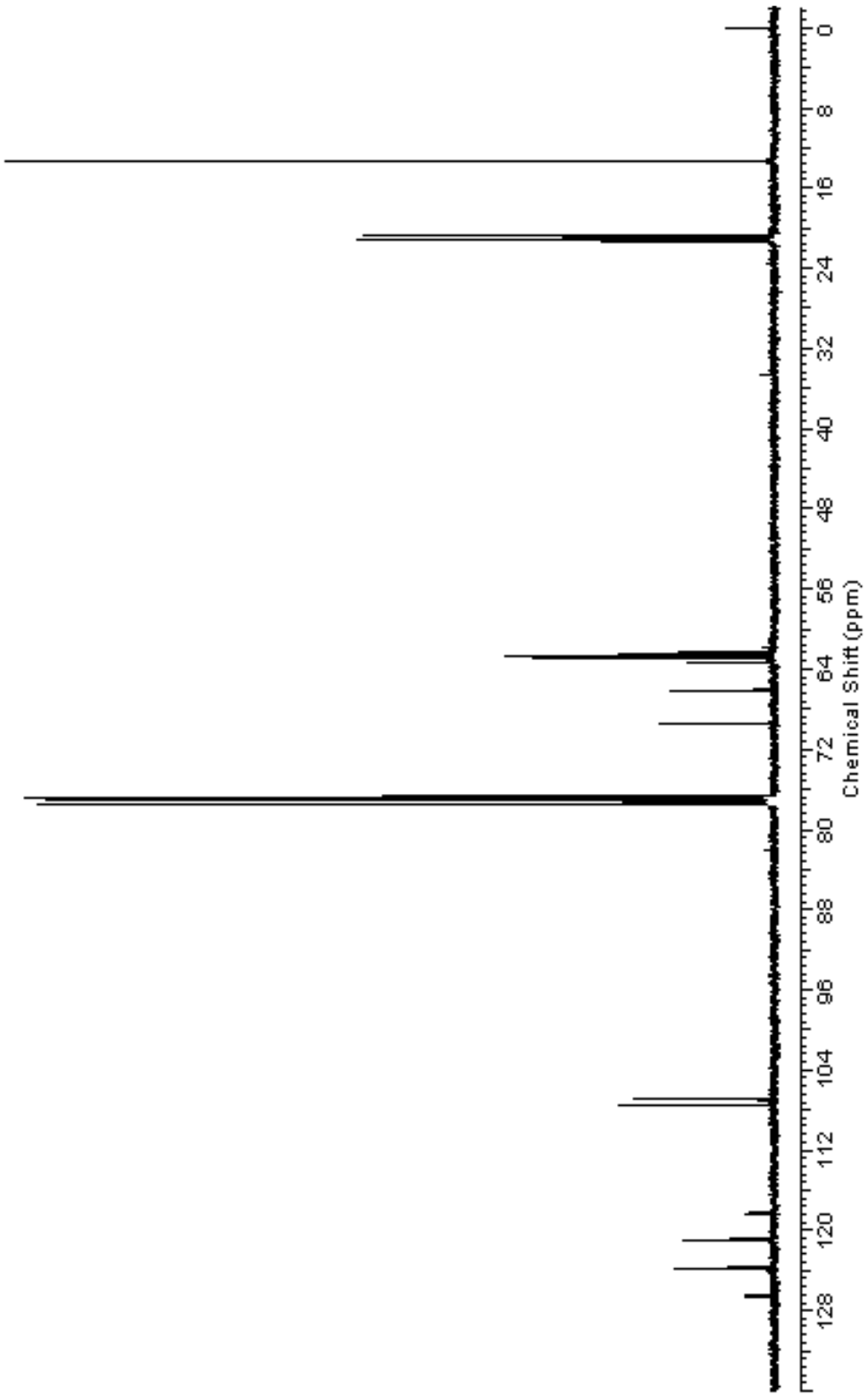

Figure 13 ^{31}**P NMR of Compound 4**

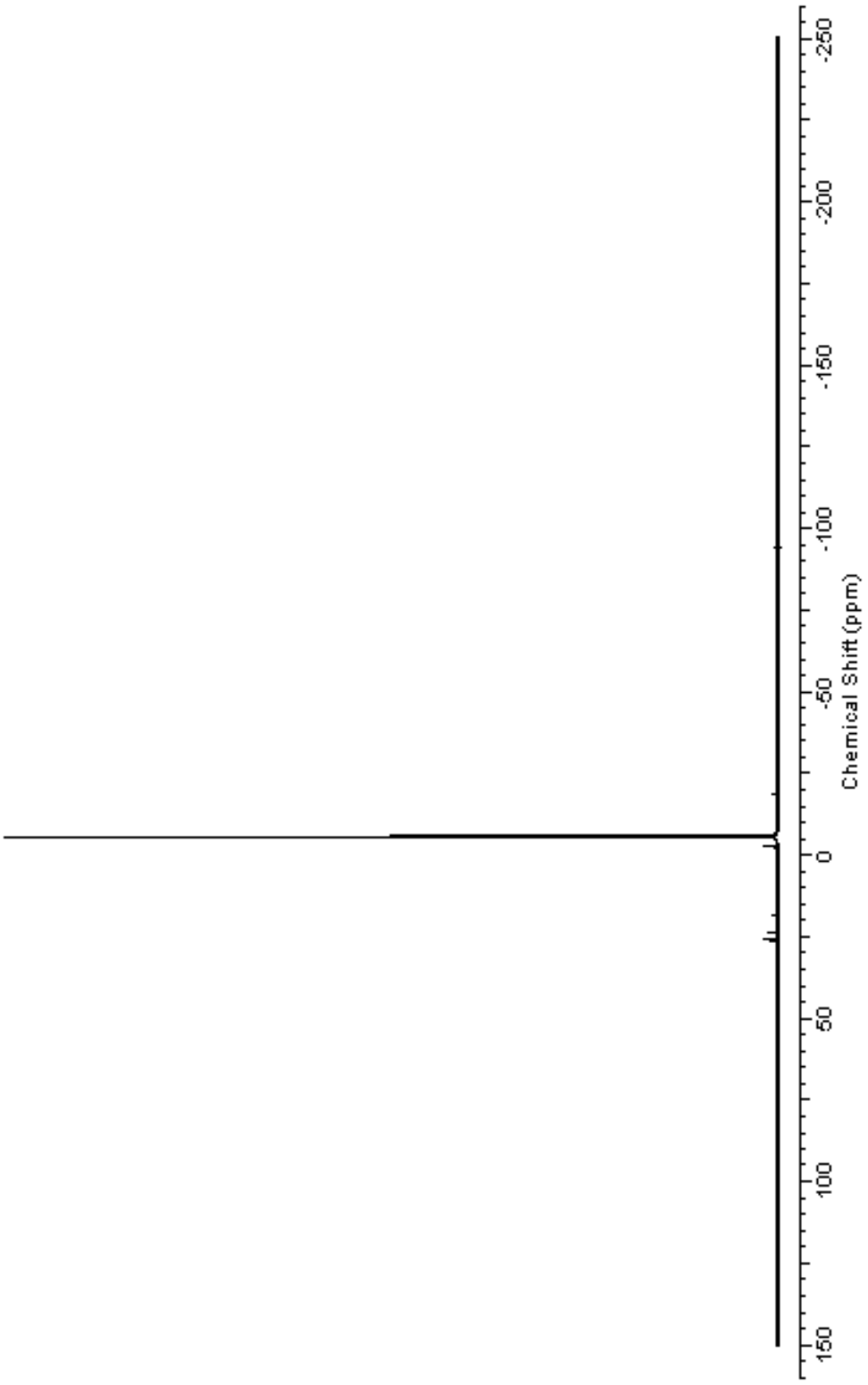

Figure 14 **^{1}H NMR of Compound 4**

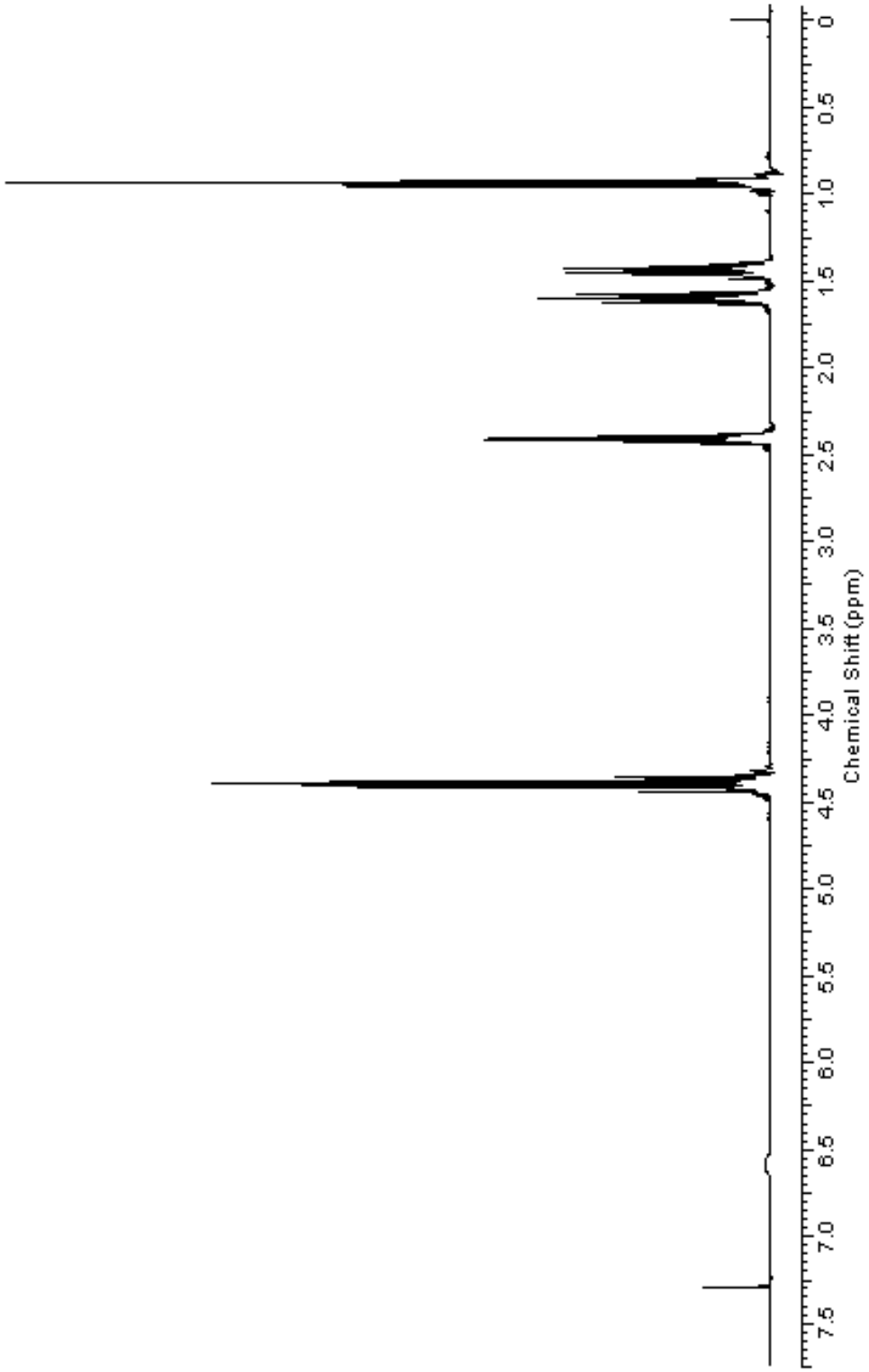

Figure 15 **^{13}C NMR of Compound 4**

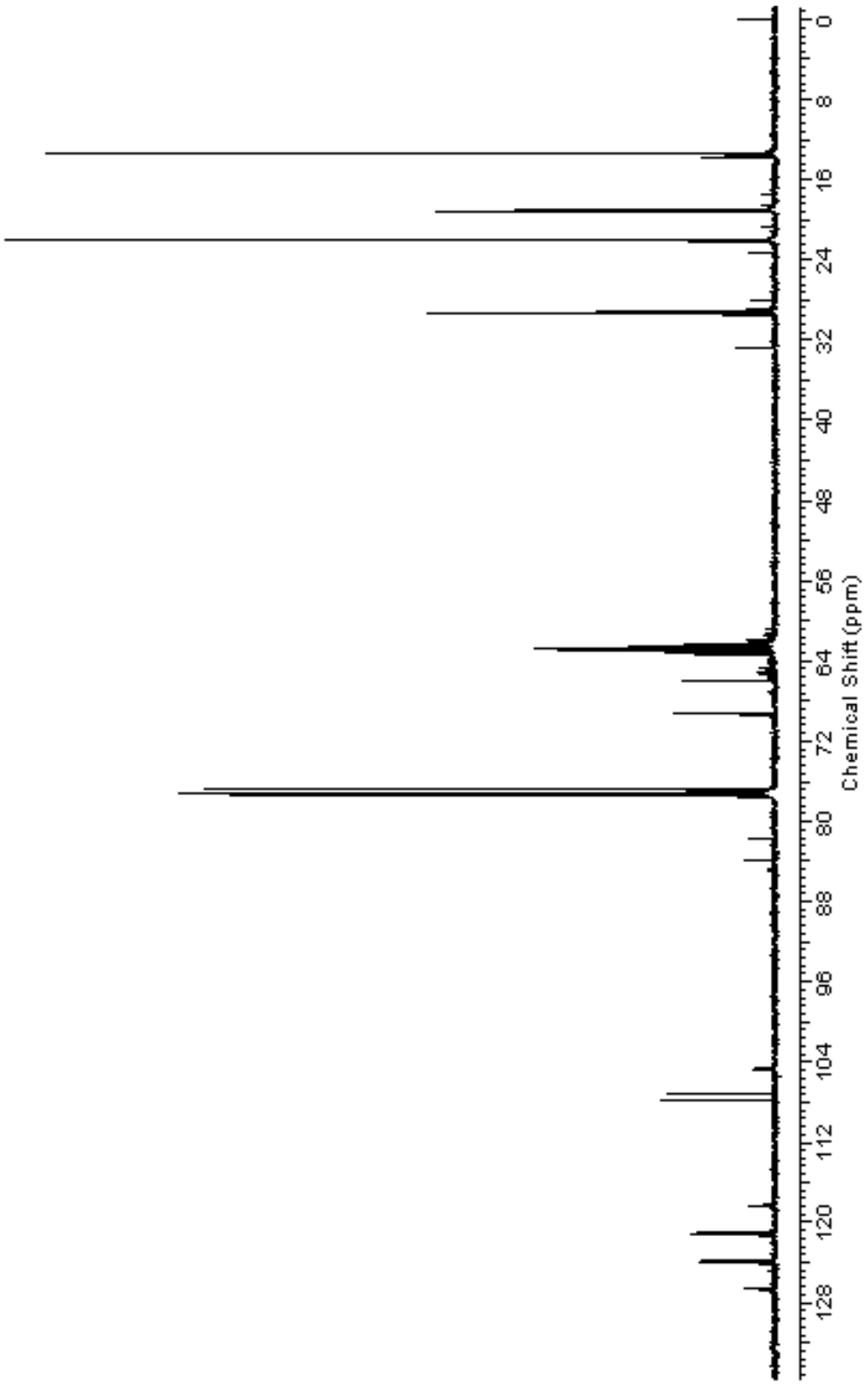

Figure 16 **^{31}P NMR of Compound 5**

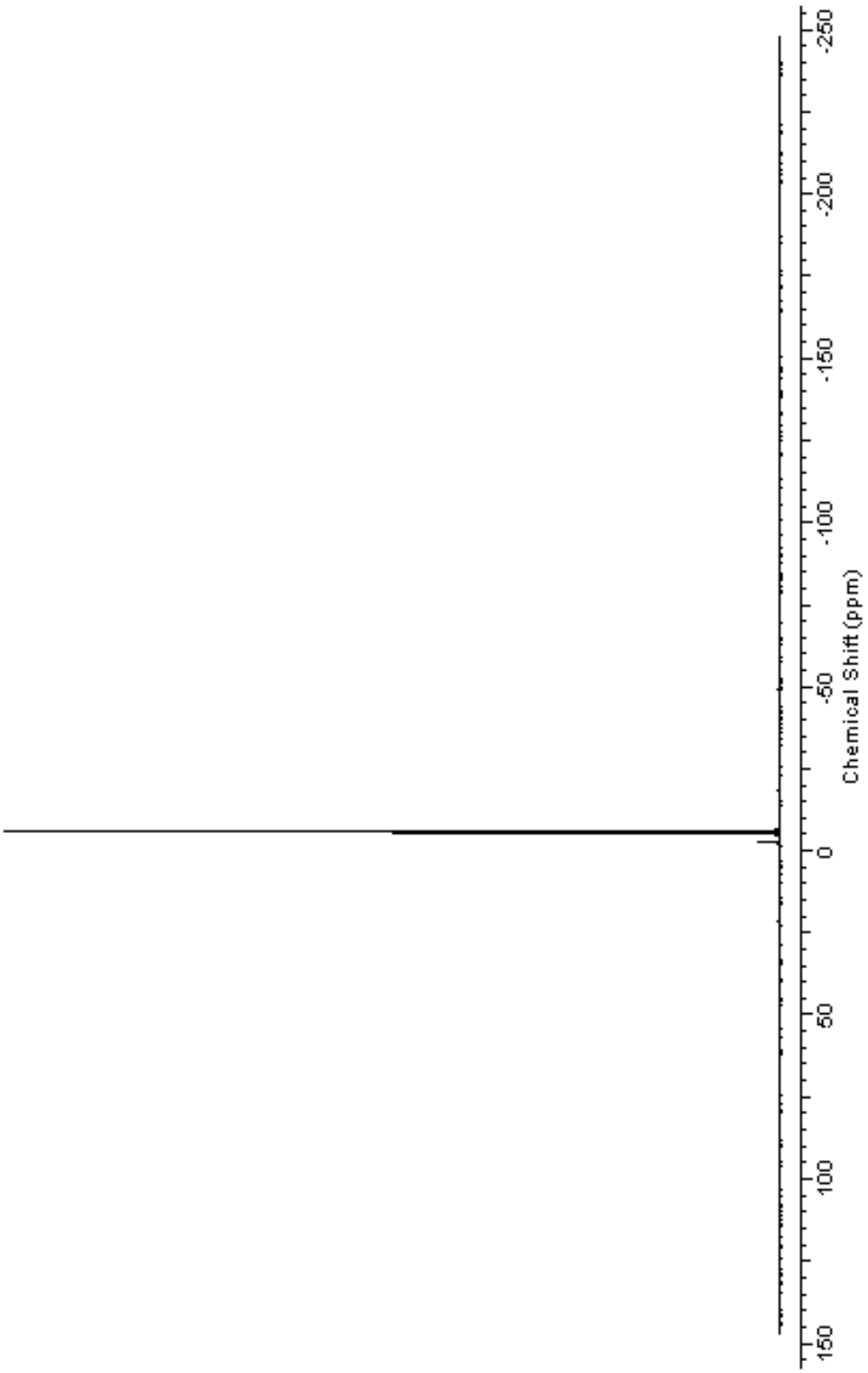

Figure 17 **^{1}H NMR of Compound 5**

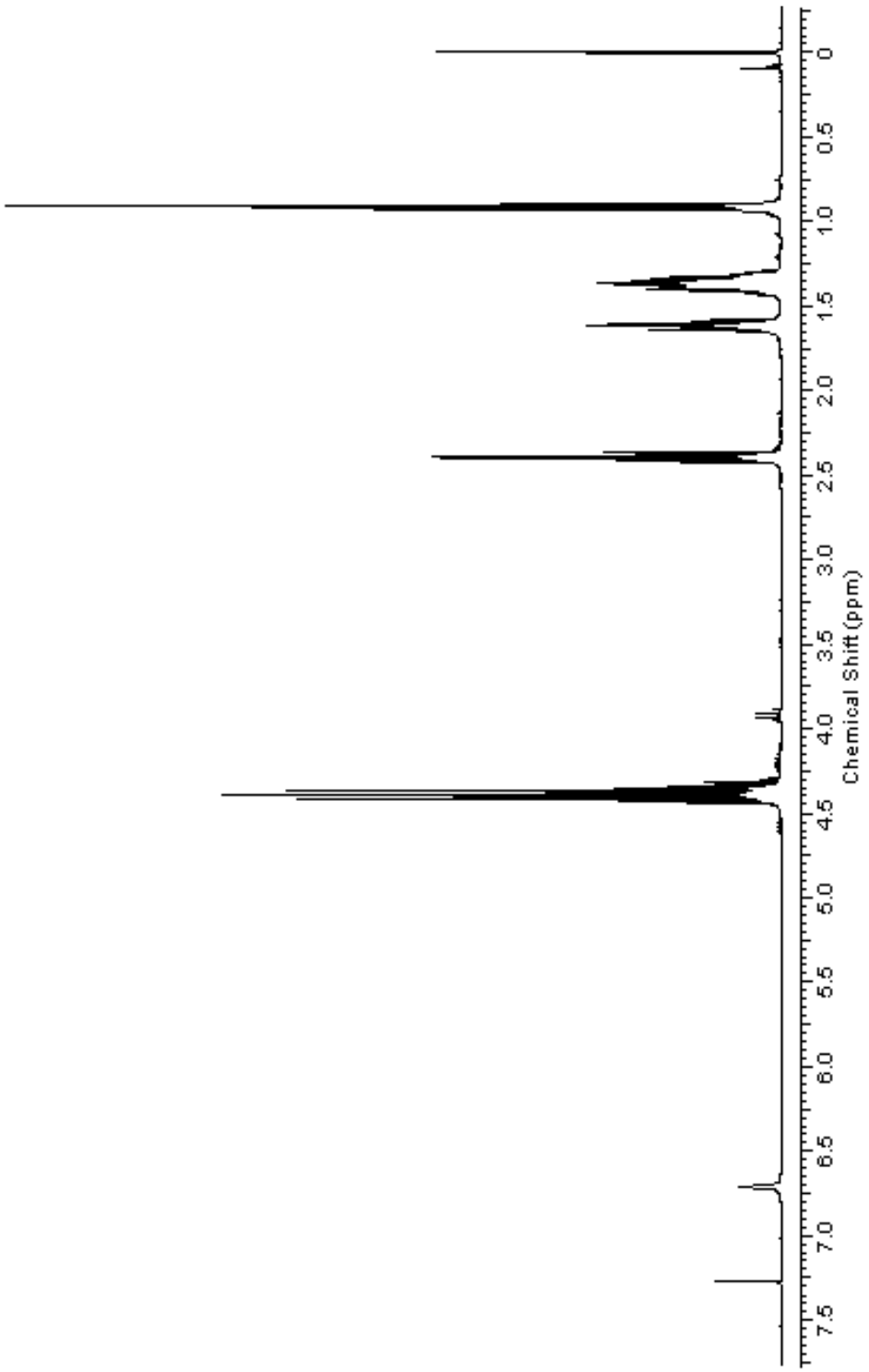

Figure 18 ^{13}C NMR of Compound 5

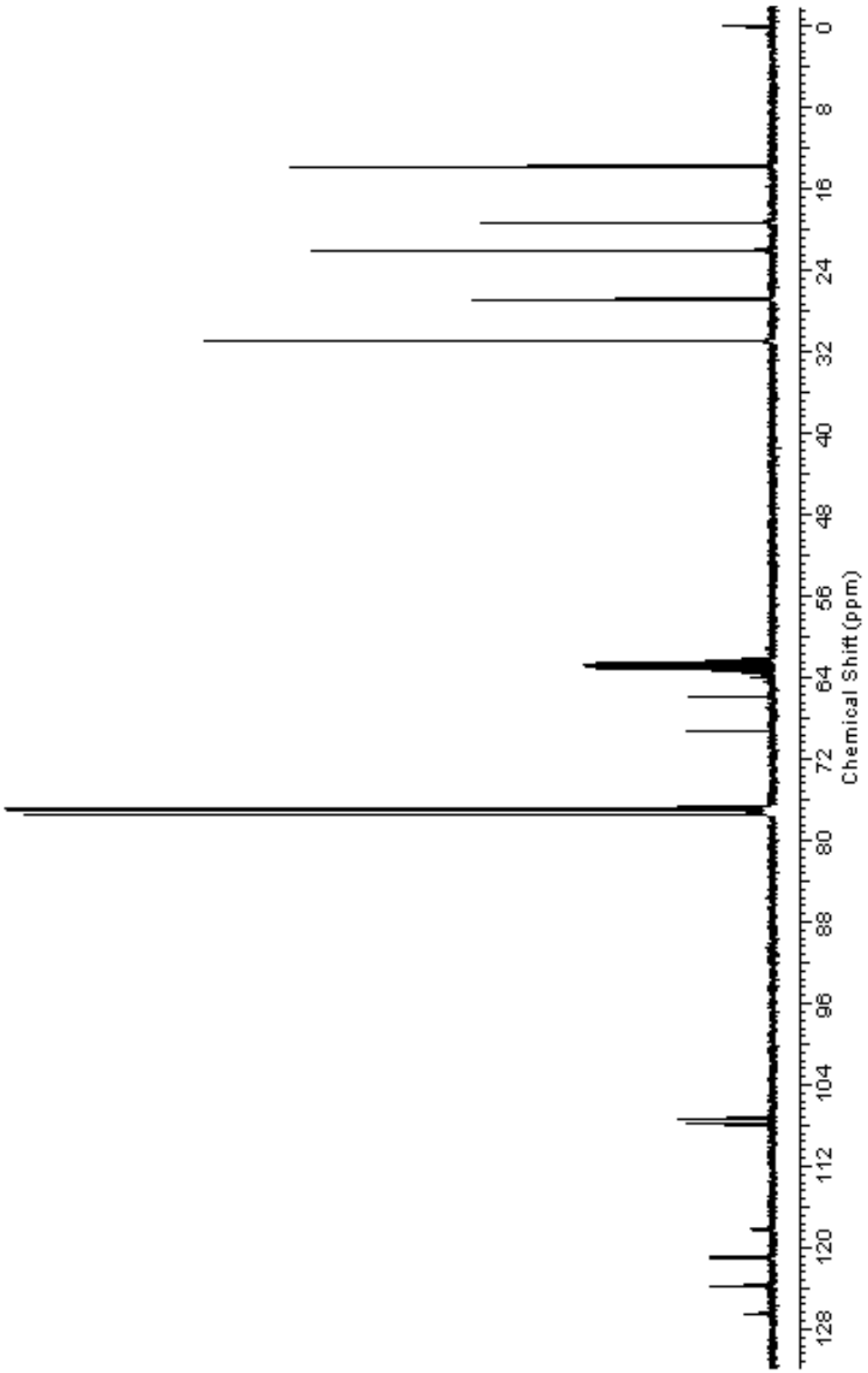

Figure 19 ^{31}**P NMR of Compound 12**

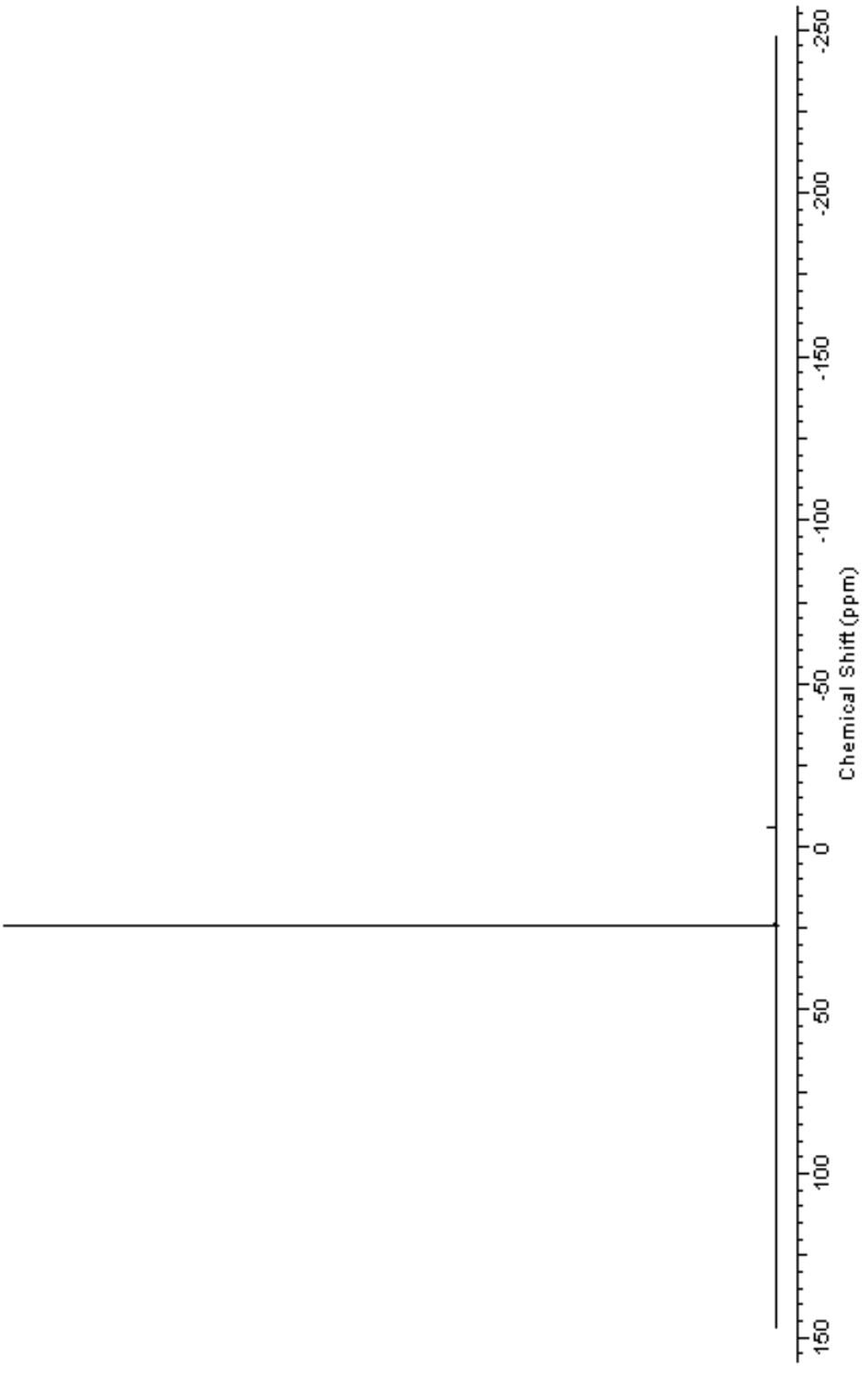

Figure 21 **^{1}H NMR of Compound 12**

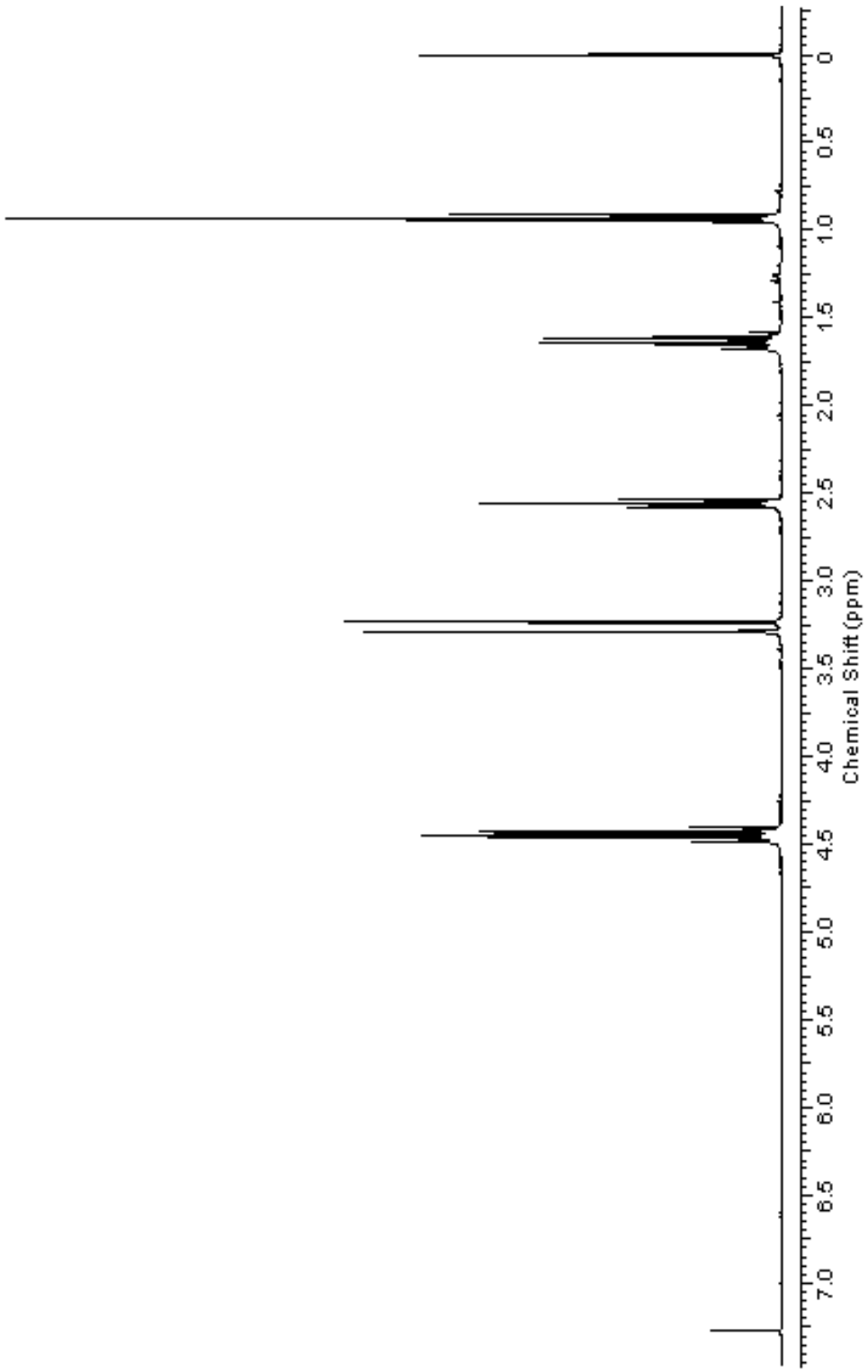

Figure 21 ^{13}**C NMR of Compound 12**

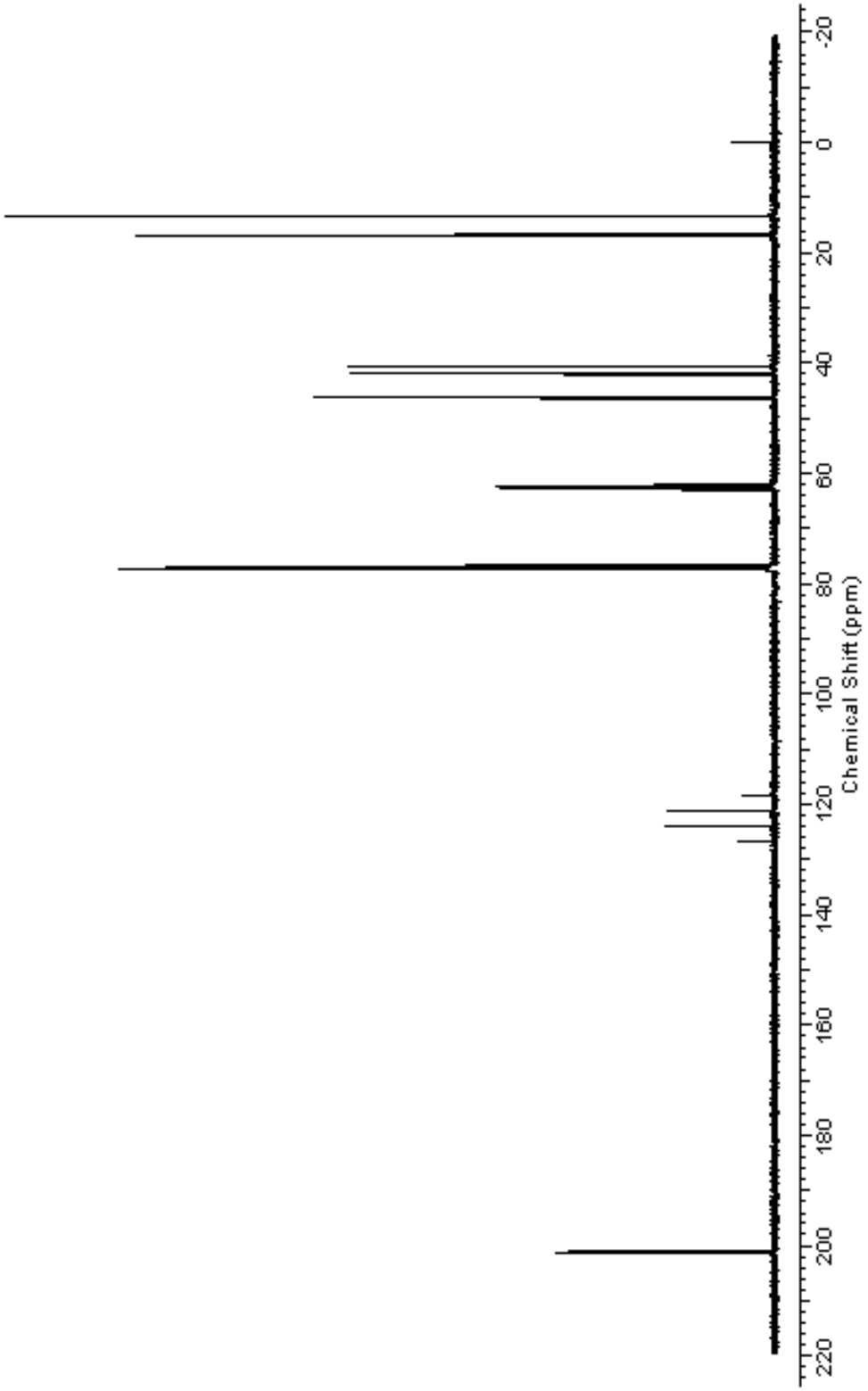

Figure 22 **^{31}P NMR of Compound 13**

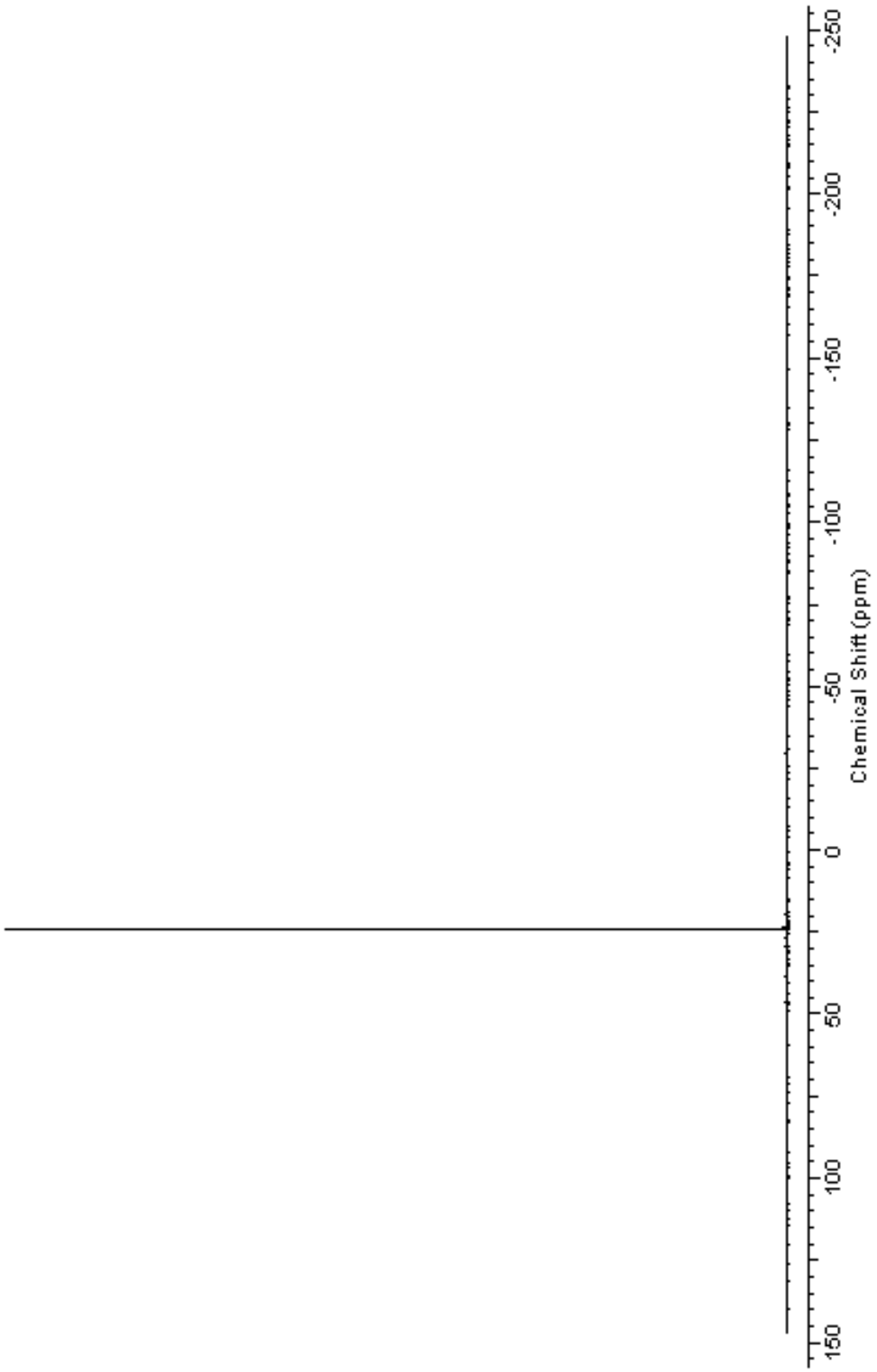

Figure 23 ^{1}**H NMR of Compound 13**

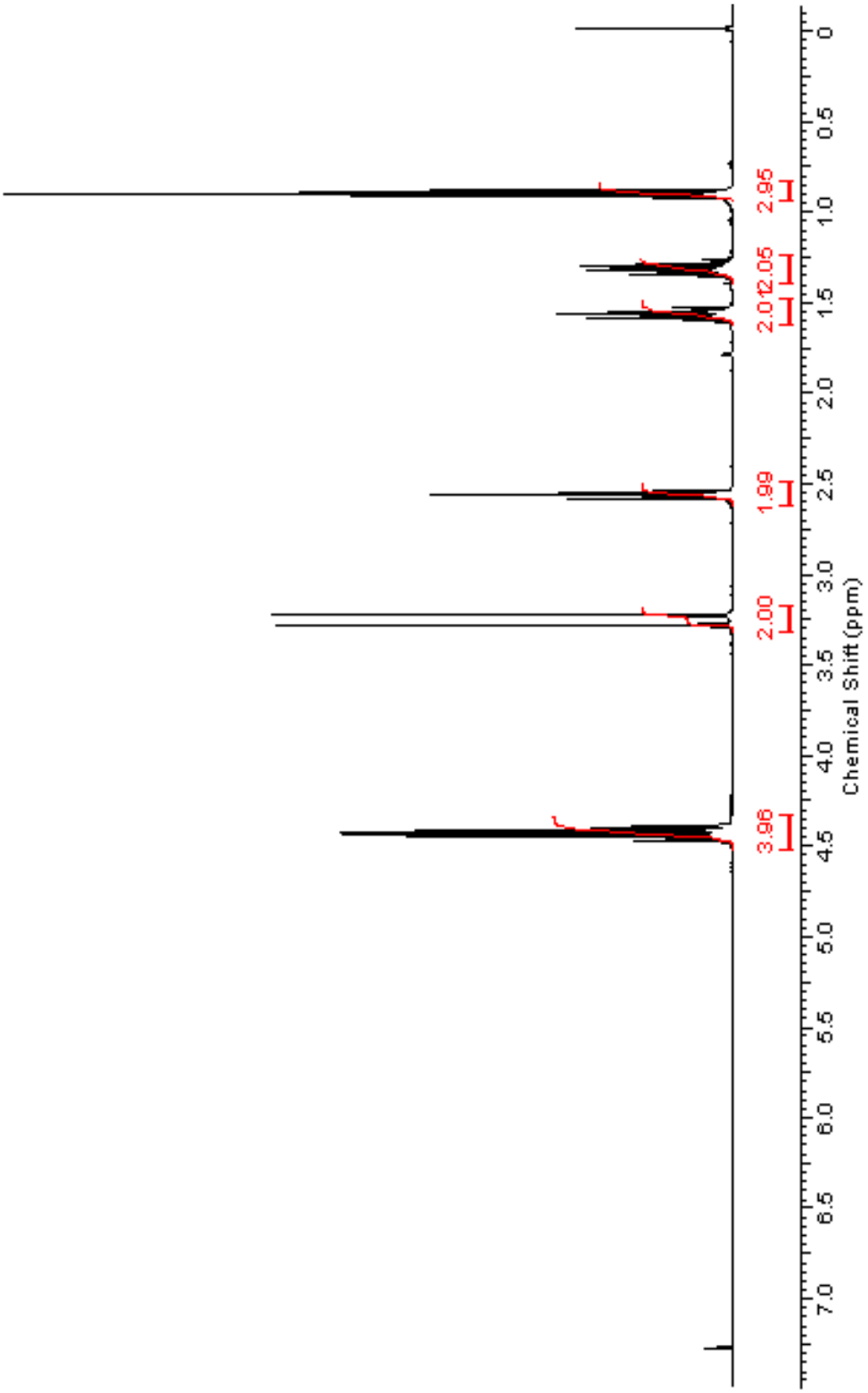

Figure 24 ^{13}C NMR of Compound 13

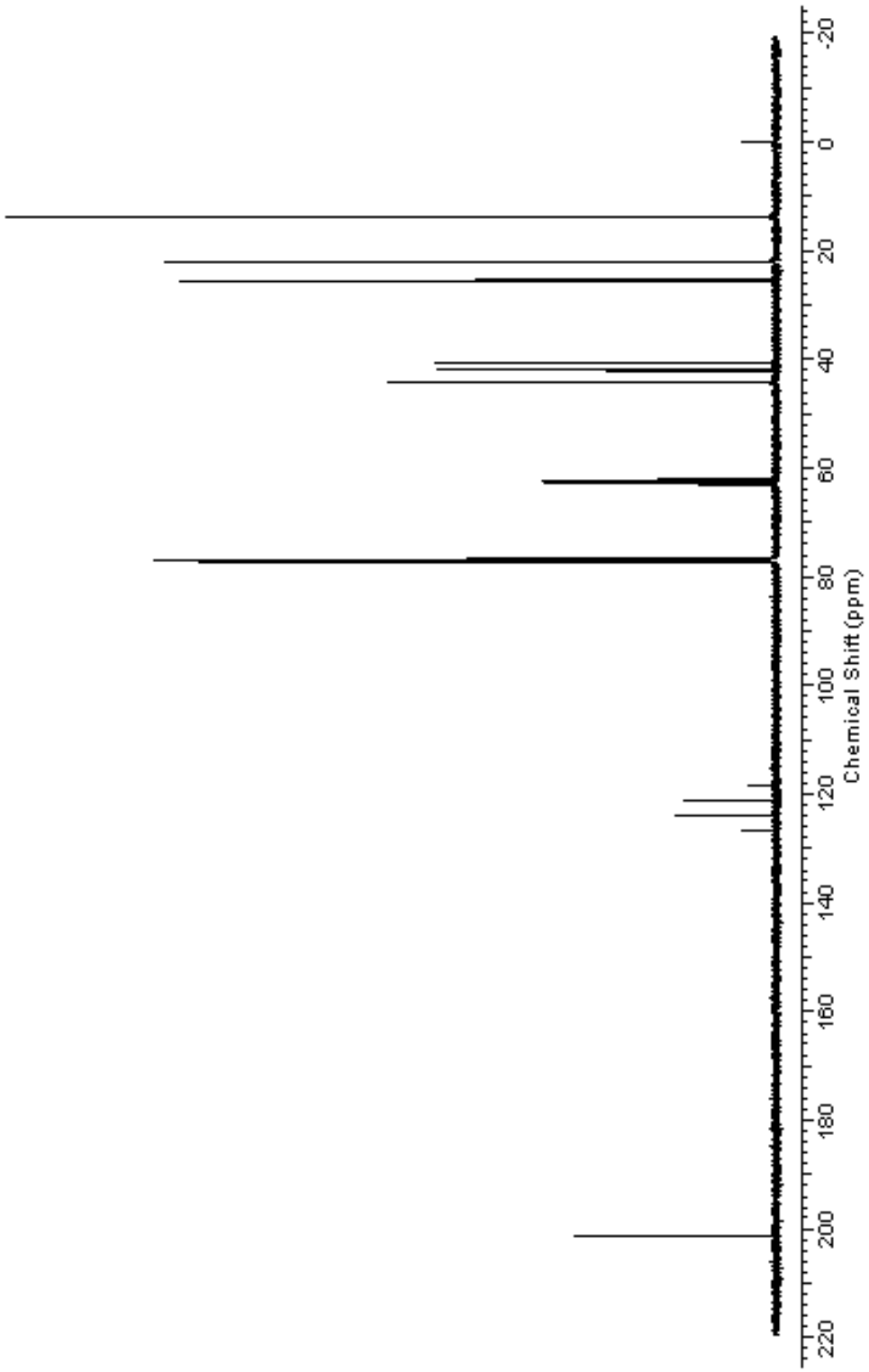

Figure 25 ^{31}**P NMR of Compound 14**

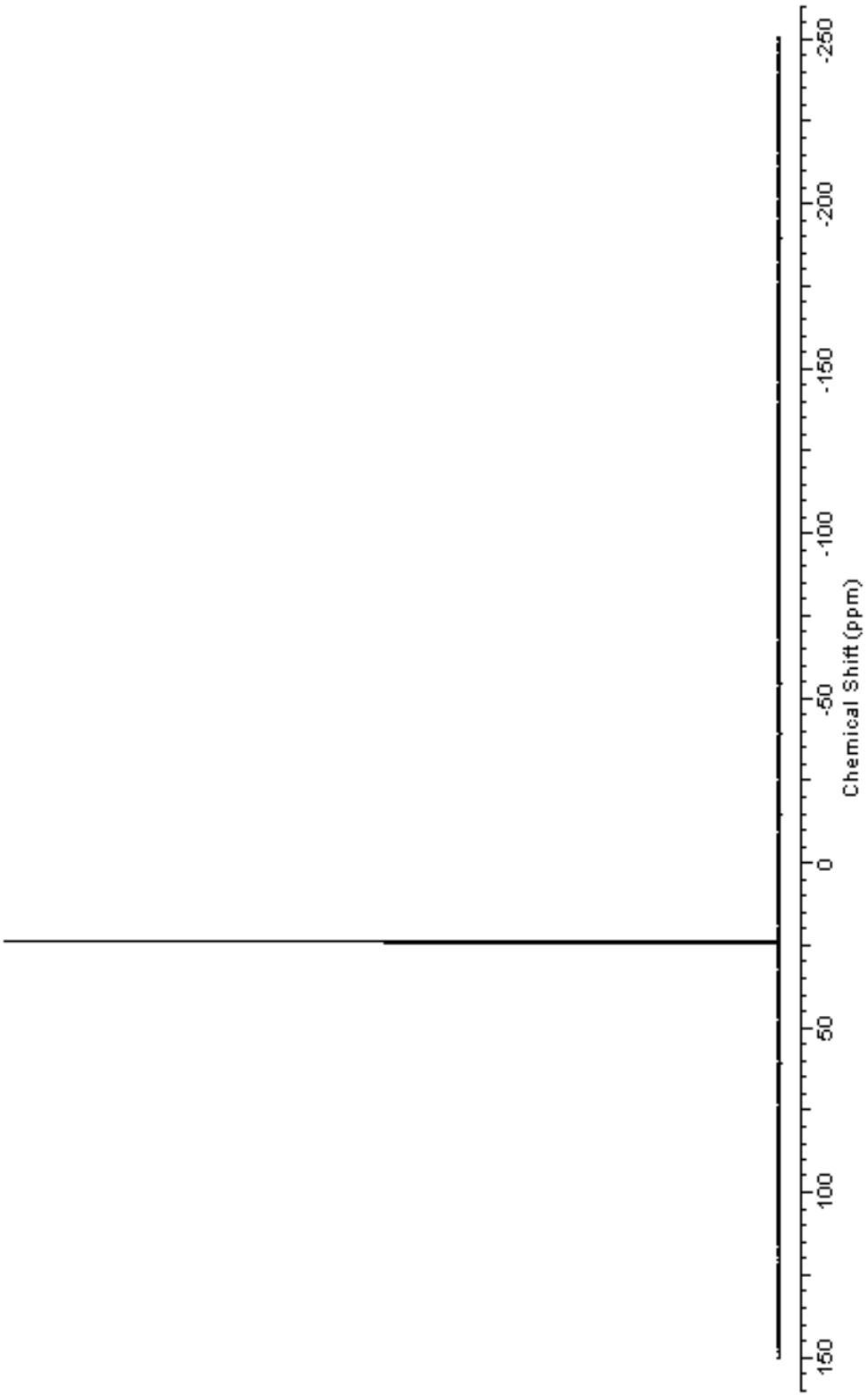

Figure 26 **^{1}H NMR of Compound 14**

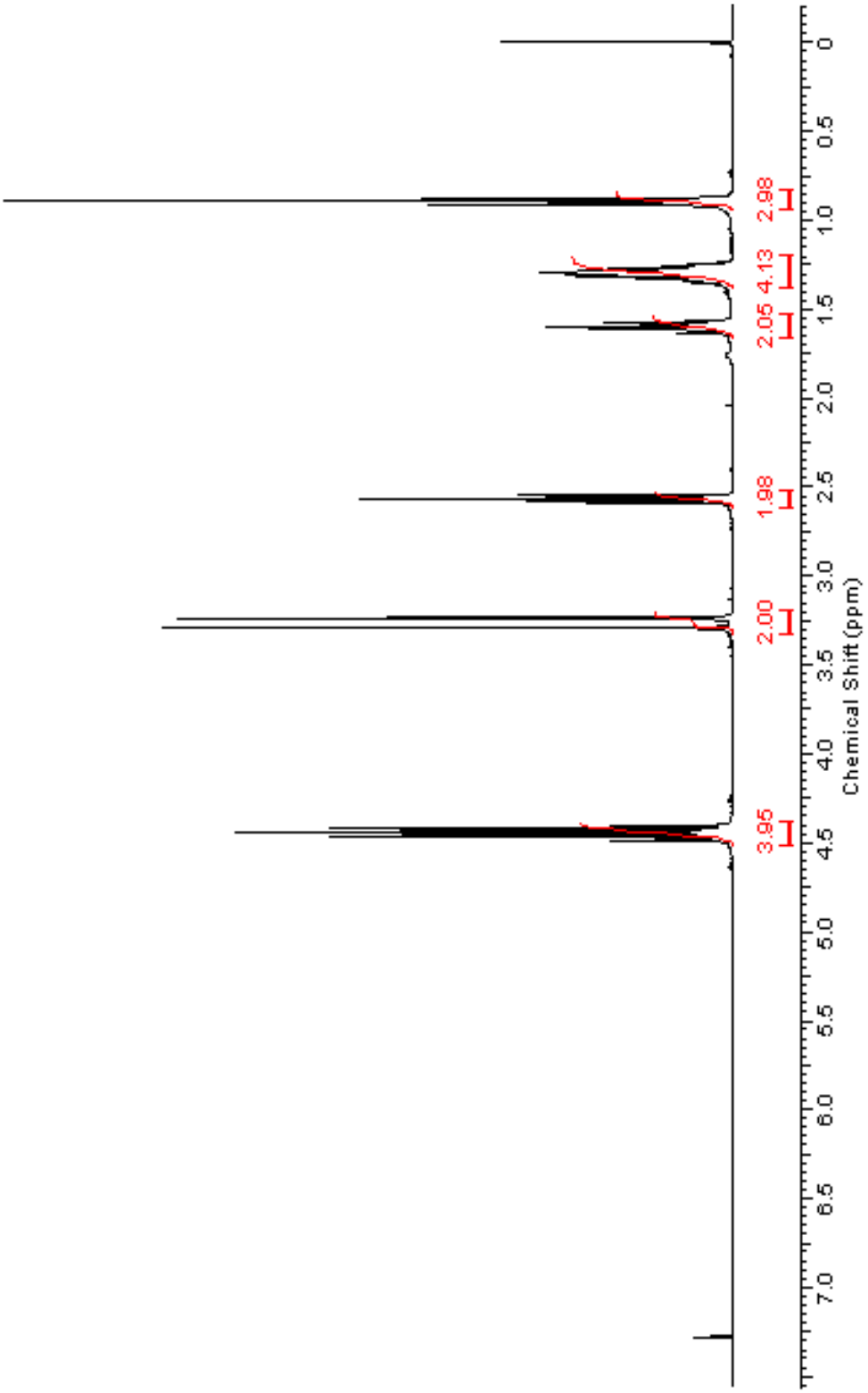

Figure 27 ^{13}**C NMR of Compound 14**

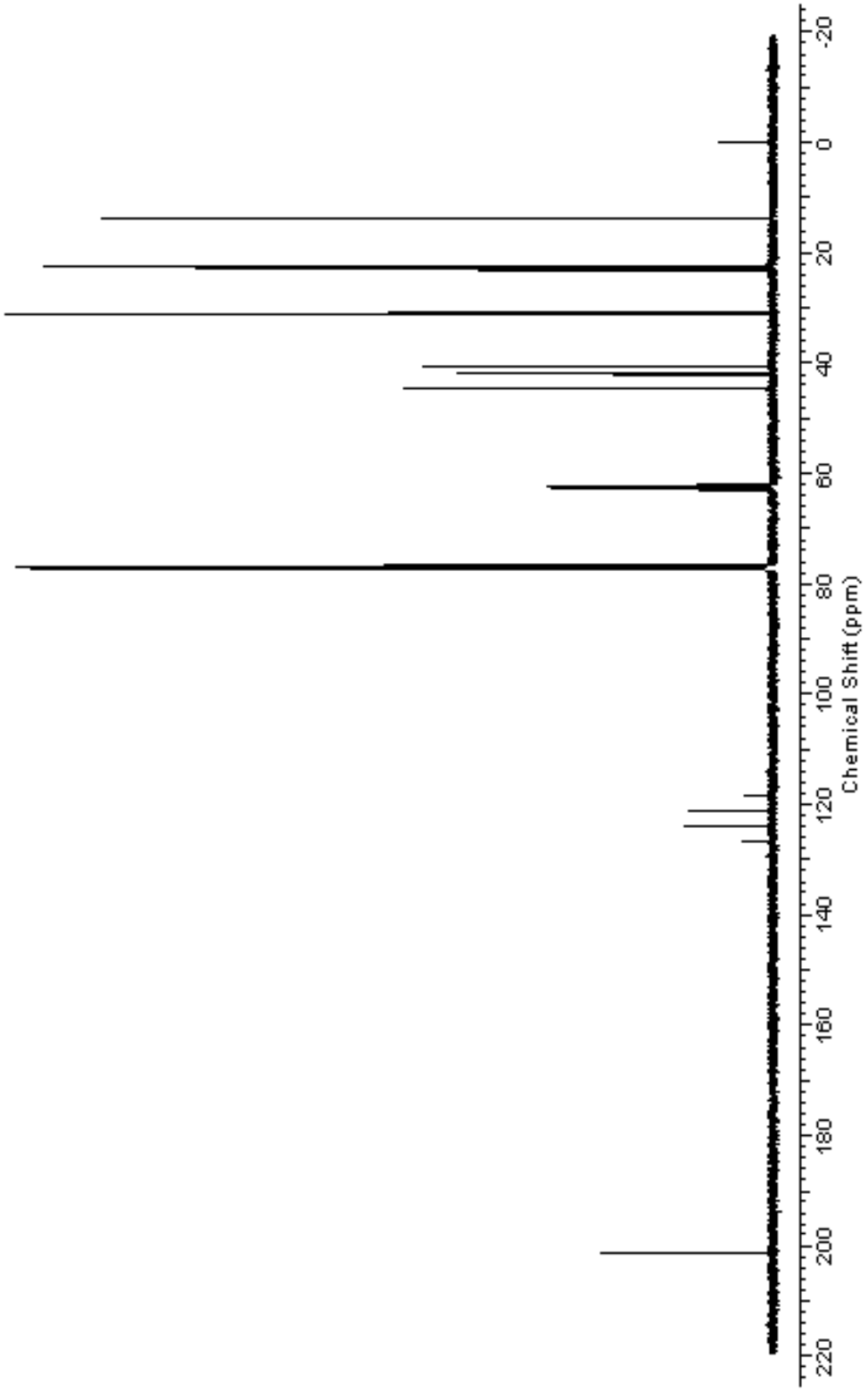

Figure 28 **^{31}P NMR of Compound 15**

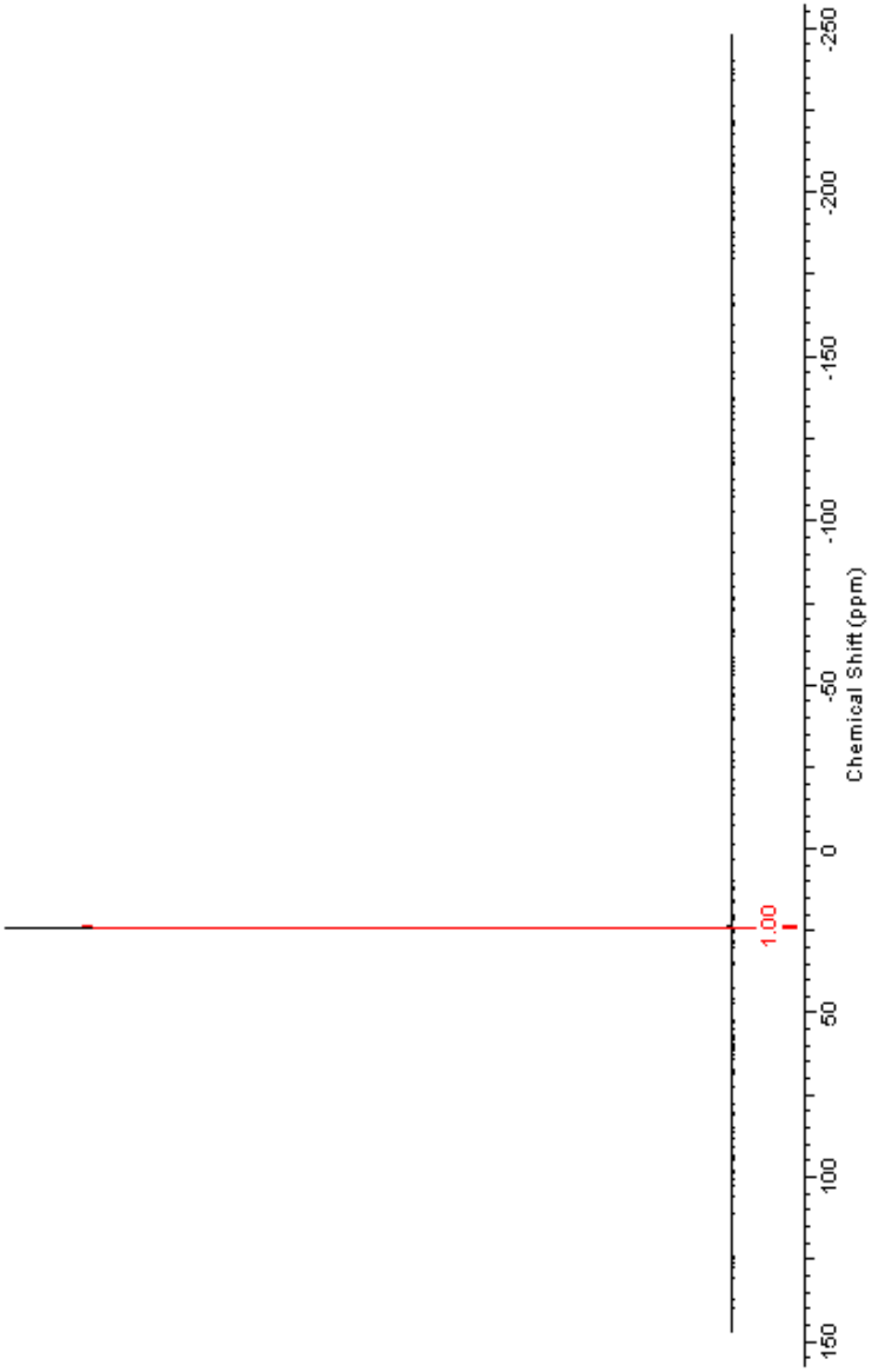

Figure 29 **^{1}H NMR of Compound 15**

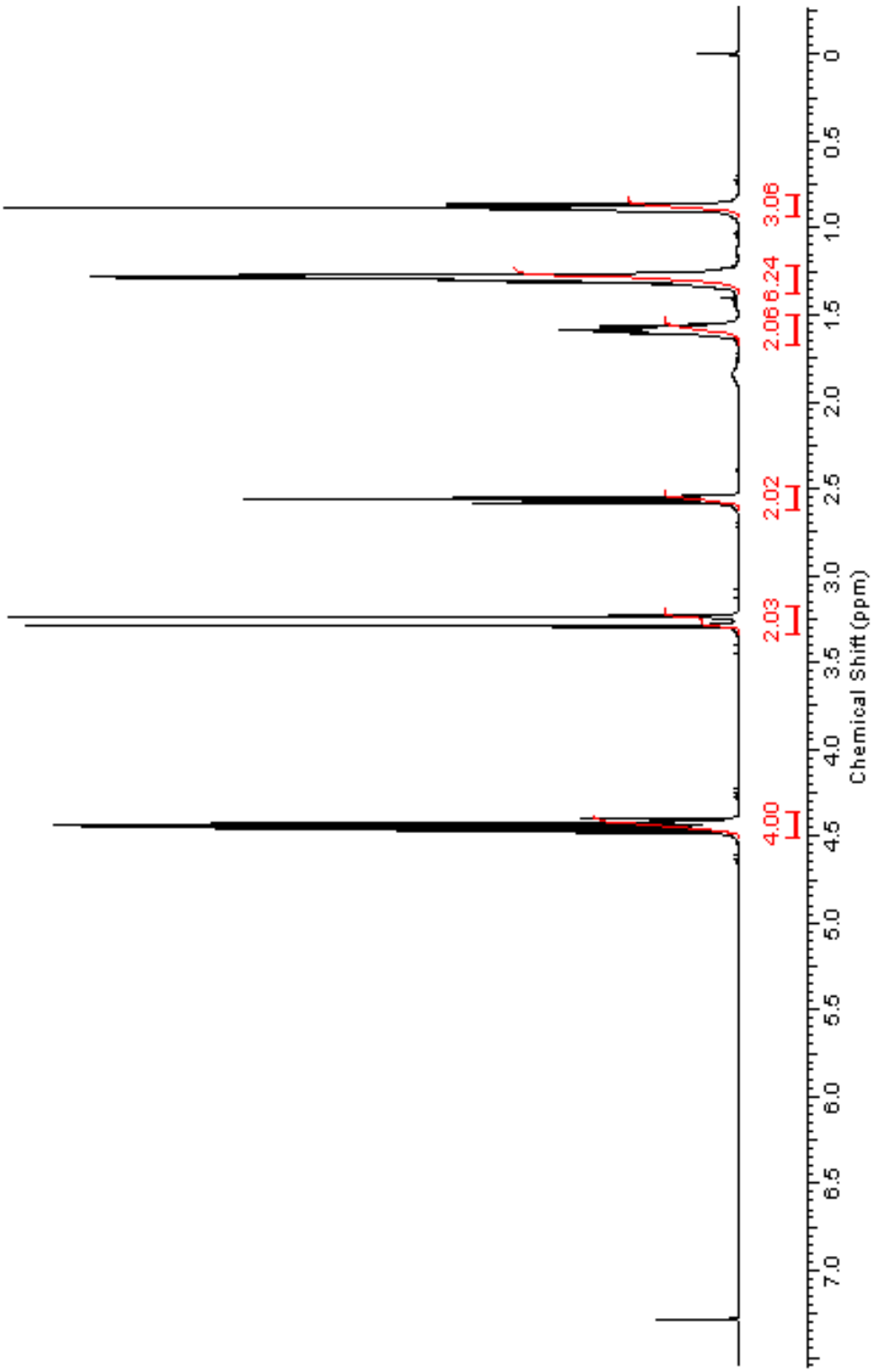

Figure 30 **^{13}C NMR of Compound 15**