Novel Approaches Toward the Synthesis of Bis(2,2,2-trifluroethoxy) Phosphono Esters

by

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Abstract

The synthesis of several phosphonate esters via reaction of the salt of bis(2,2,2-trifluroethyl) phosphite and a given alpha halo carbonyl compound in a Michaelis-Becker reaction scheme. As an alternative to the use of strong base, we employed cesium carbonate as a mild reagent in hopes of successfully synthesizing our target compounds in high yields.

Acknowledgments

I would like to thank Dr. John Jackson for providing me with this project. I would like to thank Mr. Calvin Austin for his assistance and expertise in obtaining mass spectral data. I would also like to thank my committee members for dedicating portions of their time toward the revision of my thesis. Lastly, I would like to thank my mother and my wife for their encouragement during my academic endeavors.

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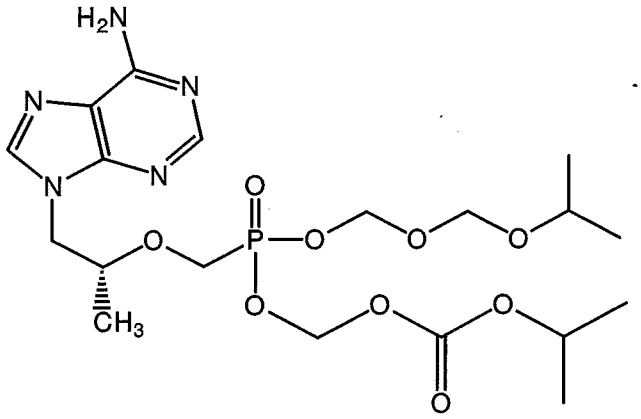
List of Abbreviations

Abbrev./Acronym	Description
^{13}C	carbon-13
DMF	N,N-dimethylformamide
THF	tetrahydrofuran
DMSO	dimethyl sulfoxide
g	gram
TLC	thin layer chromatography
^{1}H	hydrogen-1
NMR	nuclear magnetic resonance
^{31}P	phosphorus-31
Hz	Hertz
J	coupling constant (in Hz)
ppm	parts per million
PTC	phase transfer catalyst (catalysis)

Chapter 1: Introduction

Phosphonates are compounds that serve a variety of application in the field of organic chemistry. These compounds are world renowned in the formation of carbon-carbon double bonds in the Horner-Wadsworth-Emmons (HWE) condensation. Recently, these organophosphorus compounds have rose to fame in the world of medicinal chemistry. They appear to display biologically important properties serving as phosphonopeptides, amino acid analogues, natural products and pro-drugs.[1] Later still, phosphonates have been demonstrated as potent antiviral nucleoside phosphonate analogs. The structure shown, Viread, is a nucleoside phosphonate that displays anti-HIV properties.

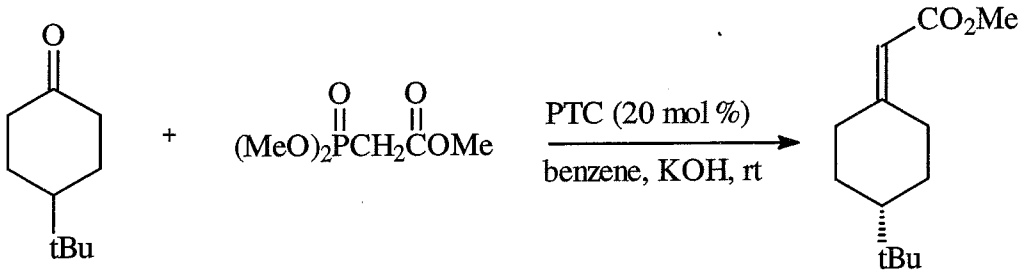


VIREAD (Tenovir Diisoproxil Fumarate)

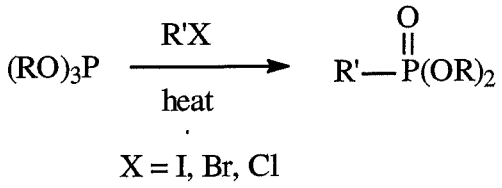
As aformentioned phosphonates are used as reagents in the HWE condensation. These compounds have emerged as valuable synthetic intermediates in the preparation of alkenes, dienes, polyenes and α, β-unsaturated esters.[2, 3]

Illustrated below, a phosphonate compound is used in a modern HWE reaction to yield a (Z) alkene.[4] This type of "clever" chemistry not only produced the desired olefin,

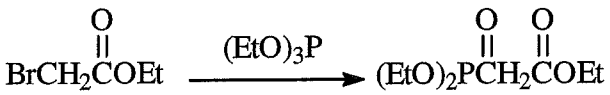
but, it also induced two different stereochemical conformations within the desired compound.



Phosphonate compounds can be prepared through the reaction of a dialkyl phosphite salt and an alkyl halide. This method is not without a couple of key disadvantages. This reaction pathway generally involves the use of strong, anhydrous base, extreme temperatures and long reaction times. Furthermore, the reaction results in poor yields and complicated reaction mixtures. To aid in the circumvention of problems with reaction yields, the Michaelis-Arbusov reaction was discovered. As noted in below, a trialkyl phosphite is treated with an alkyl halide to generate a dialkyl phosphonate compound.

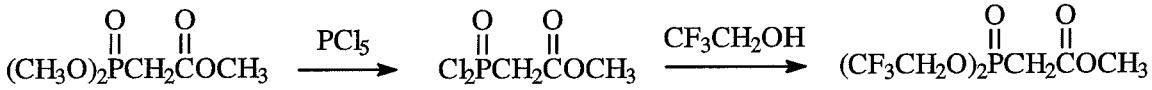


The Michaelis-Arbusov reaction can be extended to form alpha phosphonoesters. In this reaction, a trialkyl phosphite is reacted with a α-halo ester to generate the desired product.[5]

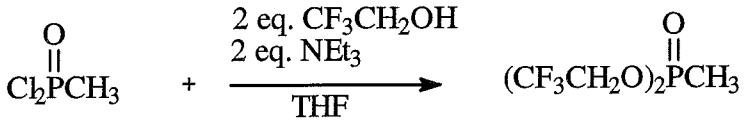


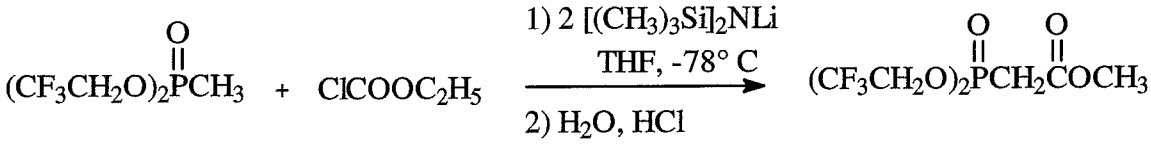
Unfortunately, this synthetic methodology is not applicable to dialkyl phosphites in which the trifluroethyl group is present. The electron withdrawing capabilities of the trifluroethyl groups decrease the nucleophilicity of the phosphite, leaving it too unreactive for an S_N2 reaction with an alkyl halide.

W.C. Still discovered a method in which the ethoxy groups on a preformed phosphonate were converted to trifluroethyl groups in a two step reaction sequence.[4] The first step involved the use of phosphorus pentachloride with methyl 2-dimethoxyyphosphoryl) acetate, followed by addition of trifluroethanol in a second step to yield methyl 2-bis (2,2,2-trifluroethoxyphosphoryl) acetate in 40% yield.[3]

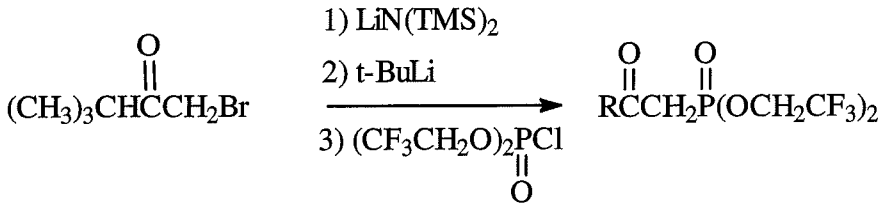


In an attempt to resolve the issues of low yields with these particular compounds, P. Savinac used the strong, non-nucleophilic base lithium bis-trimethylsilyl amide followed by a treatment with ethyl chloroformate to also yield bis (2,2,2-trifluroethoxyphosphoryl) acetate, but in a greater yield.[6] The overall reaction scheme is shown below.[2,3]

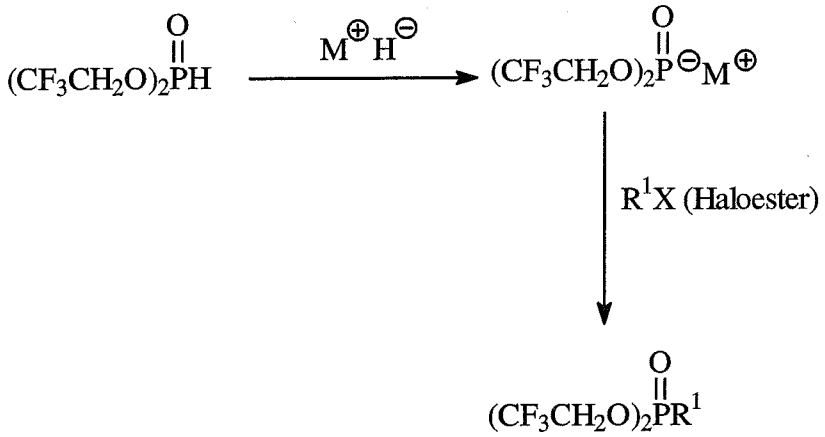




Wiemer synthesized bis (2,2,2-trifluroethyl) β-keto phosphonates from α-bromo ketones as shown below.[7] The best yields were observed when the substituent R, was a bulky phenyl group or a *tert*-butyl group. Unfortunately, due to the use of highly reactive tert-butyllithium, this reaction scheme is not very useful when highly functionalized compounds are desired from a synthetic procedure.[7]

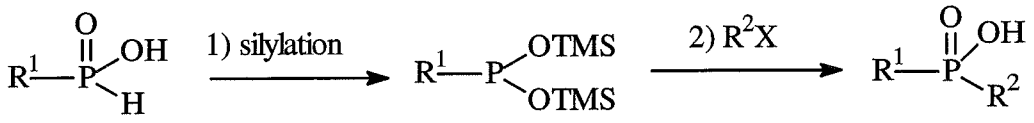


Gregory Ciszewski provided a Michaelis-Becker approach to phosphonate synthesis in which bis (2,2,2 trifluoroethyl) phosphite was deprotonated using a metal hydride base to form the corresponding phosphite salt. The phosphite salt was then reacted with various haloesters to give moderate to good yields.[12]



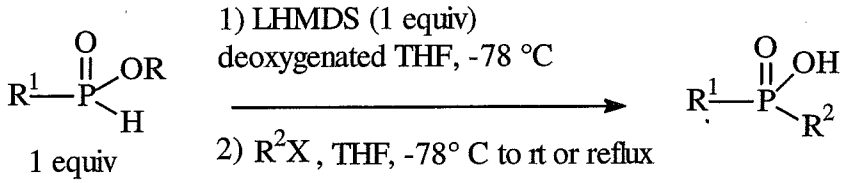
Some disadvantages of this method include long reaction times and the use of metal hydride base. These disadvantages tend to make this particular approach impractical.

Another approach to the synthesis of phosphonates involves the silyation of H-phosphinic acids. Once two silyl groups are attached, the intermediate in this process encounters an alkyl halide in an Arbusov-type reaction. The limitation of this method is that it often requires esterification of the dialkylphosphinic acid products if further manipulations are desired.[13]

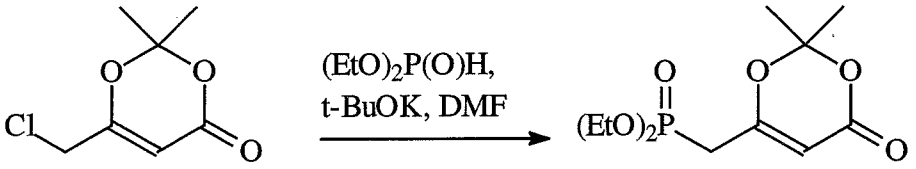


A relatively new approach to phosphonate synthesis involves the use of lithium hexamethyl disilyazide (LHMDS) as a base. Montchamp displays a technique in which a typical H-phosphinate ester reacts with an alkyl halide in a Michaelis-Becker type

reaction to yield the desired phosphonate. Unfortunately, this reaction fails when excess base and heating are used. It was also proven unsuccessful with bromoacetates.



Lastly, a method described by Boekman uses the base potassium tert-butoxide to deprotonate diethyl phosphite. The potassium salt of this phosphite is then further reacted with the alkyl halide 6-chloromethyl-2,2-dimethyl-1,3-dioxen-4-one to yield the desired phosphonate compound in 48-50% yield.[14]



Phase Transfer Catalysis

Many desirable reactions cannot occur because the reactants are not equally soluble in a given reaction solvent. For anionic bases and nucleophiles, phase transfer catalysis (PTC) is an often used solution to this problem. It uses catalytic amounts of phase transfer agents which facilitate interphase transfer of species, making reactions between reagents in two immiscible phases possible.[8] This synthetic method is used to accomplish a variety of reactions that include but are not limited to alkylations, Wittig and Horner reactions, oxidations, reductions, addition reactions and polymerizations.

Phase transfer catalysis has made possible the use of cheaper and more easily available alternative raw materials like potassium carbonate and sodium hydroxide as bases, and the use of aqueous solutions, thereby negating the need for severe anhydrous conditions and dangerous bases such as metal hydrides, or expensive organometallic reagents.[8]

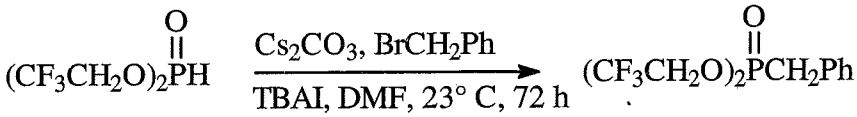
The most common agents used as phase transfer catalysts are ammonium and phosphonium salts, crown ethers, cryptands and open chain polyethers. Both types of phase transfer catalysts, the "onium" salts and the cation chelating variants, are based on the same principle, and there are two basic requirements in choosing a phase transfer catalyst. The reagent must be a salt (such as the "onium" types), or it must form a salt under the reaction conditions (such as the cryptant type by chelating an inorganic cation), and the cation of this salt has to possess an organic structure that allows it to be easily soluble in the organic phase and thus to carry over the nucleophile or base over along with the cation.[10] The second requirement is that the orbital overlap between the cation and the anion should be loose to avoid the formation of unreactive ion pairs and thus creating a basically unsolvated highly reactive anion in the organic phase. Of all of the aforementioned, phase transfer catalysts, quaternary "onium" salts are most commonly utilized.[5] Some examples of these reagents are tetrabutylammonium bromide (TBAB), and tetrabutylammonium iodide (TBAI). These "onium" compounds are favored over crown ethers and cryptands because they are environmentally safe and cost effective. There are two basic requirements in choosing a phase transfer catalyst. The reagent must be cationic and possess an organic structure that allows it to partition the nucleophile or

base into the organic phase.[8] Lastly, the orbital overlap between the cation and the anion should be loose enable maximal anionic reactivity.

There are two main types of phase transfer reactions. These two types of reactions are liquid-liquid phase transfer catalysis (LLPTC) and solid-liquid phase transfer catalysis (SLPTC). In a LLPTC, the nucleophile or base is dissolved in an aqueous phase. Conversely, in SLPTC, the nucleophile or base behaves as a suspended solid in an organic phase. Although PTC enjoys many advantages, it has the disadvantage in that these reagents are either difficult to recover or separate from the reaction mixture. The use of these compounds is being vastly explored in an effort to support the idea of "green chemistry".

Phase Transfer Catalysis and Phosphonate Synthesis

In the realm of phophonate synthesis, phase transfer catalysis can potentially eliminate of harsh reaction conditions and low yields that result from the use of traditional Michaelis Becker reaction conditions.[9] Salvatore describes a method shown below in which he used cesium carbonate and the onium PTC, tetrabutylammonium iodide in the synthesis of various phosphonate compounds. The scheme below illustrates one phosphonate in particular in which the starting compound was the bis (2,2,2) trifluroethyl phosphite. In this reaction, the mild base cesium carbonate is used to deprotonate the phosphite. Since cesium carbonate is insoluble in DMF, it is thought that a phase transfer catalysts was employed to aid in solvating the carbonate anions in a solid-liquid PTC mechanism. The phosphite salt was then allowed to encounter a highly activated electrophile which resulted in the desired compound in 64% yield.[1]



Clearly, this novel result is a catalyst that sparks a scientific curiosity that may indeed lead to the development of more modern synthetic approaches for trifluroethyl phosphonate compounds.

Statement of the Problem

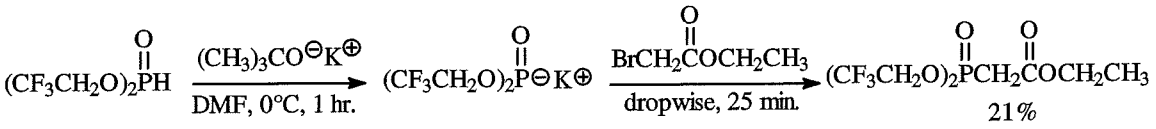
Phosphonates are an important class of compounds that have either proven useful by themselves or in secondary reactions leading to the synthesis of natural products. The Michaelis-Becker synthesis of phosphonates is a well-known pathway leading toward the formation of the desired product in moderate to good yields. Extensive research has been conducted using the phosphite salts of phosphite compounds other than bis(2,2,2-trifluoroethyl)phosphite. An ongoing research interest is the development of better methods to increase the yields and minimize the common side reactions that characterize the Michaelis-Becker reaction. The goal of this research project is to develop better synthetic methods leading to the formation of bis(2,2,2-trifluoroethoxy) phosphono esters.

The following work describes new approaches toward the synthesis of the aforementioned class of phosphonate compounds. The first approach uses cesium carbonate as a base and tetrabutylammonium idodide as a phase transfer catalyst to allow for increased solubility of the inorganic base in a given polar aprotic solvent. This is followed by subsequent deprotonation of the phosphite compound to form the nucleeophile. The second approach details a similar approach in which potassium tert-butoxide is used as a base to form the nucleophilic phosphite salt.

Chapter 2: Results and Discussion

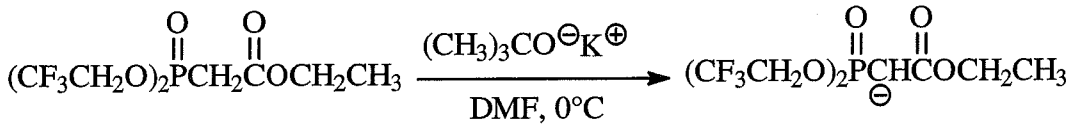
This project entailed an attempt to discover new synthetic strategies that would allow for the synthesis of bis (2,2,2 trifluroethyl) phosphonates in higher yields and a more tolerable set of reaction conditions. While these compounds are well documented in chemical literature, there remains a desire to improve the efficiency of these reactions as they relate directly to the possibility of a more widespread use of trifluroethyl phosphite in synthetic organic chemistry.[12] The synthetic pathway described in this thesis use a general Michaelis-Becker reaction scheme in which the anion of bis (2,2,2-trifluroethyl) phosphite is reacted with a series of haloesters to generate the desired phosphonate product.

The first reaction to be discussed is the synthesis of ethyl [bis (2,2,2 trifluroethoxy) phosphinyl] acetate with potassium *tert*-butoxide as a base, which served as a template for the use of other haloesters in similar reactions. The phosphite salt of bis (2,2,2 trifluroethyl) phosphite was reacted with ethyl bromoacetate in DMF. Under these conditions, the desired compound was obtained in an isolated yield of 21%.



It was found that the amount of base used was a crucial step in this synthesis. A 1:1 ratio of base to phosphite proved to be the best ratio here. If an excess of base was used, then lingering amounts of base not consumed in the acid-base step would move forward to easily deprotonate ethyl [bis (2,2,2 trifluroethoxy) phosphinyl] acetate.

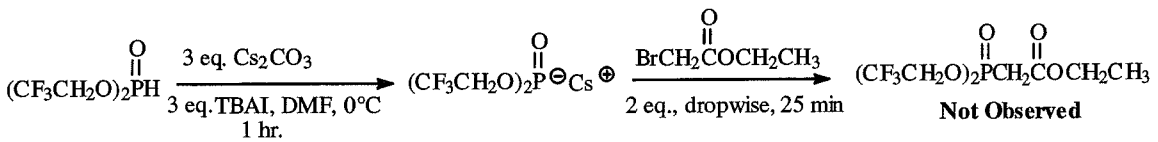
Fortunately though, this resonance stabilized anion did not appear to participate in secondary alkylation reactions and is considered rather stable.



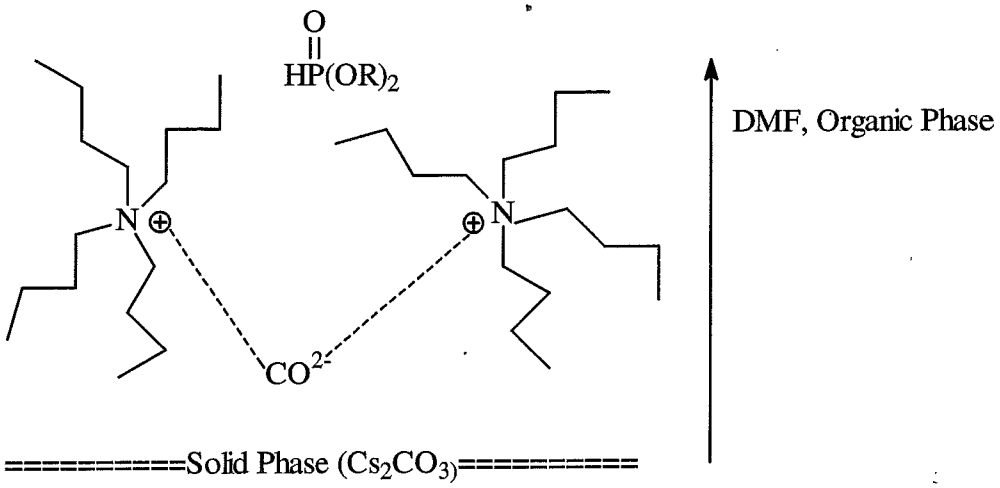
Another factor that appeared to be critical was reaction time. Over time, byproducts tend to accumulate with a decrease in the intensity of the phosphonate ^{31}PNMR peak at 24.27. Thus, the reaction was not allowed to commence any further than the allotted period of 1.5 hours.

By ^{31}PNMR, it was also concluded that this reaction works best at a temperature around 0 °C. At this temperature, any side reactions that may otherwise be more favorable at higher temperatures seem to be sufficiently minimized. Thus, throughout the entire course of the reaction, this optimum temperature was maintained.

Based on the experience with using potassium *tert*-butoxide, the reaction was also attempted using the milder base cesium carbonate. Previous experimentation lead to the hypothesis that the base ratios used by Salvatore were not compatible with our synthetic goals.[1] Thus, a trial reaction was needed to test this assumption.



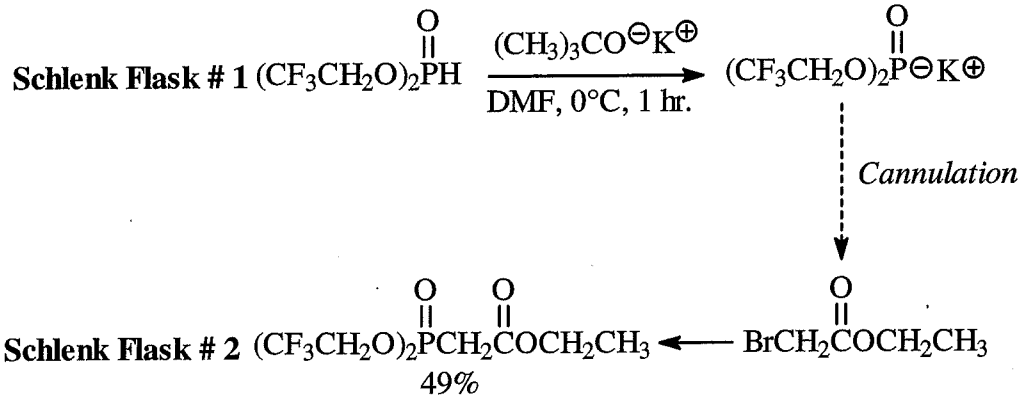
In an attempt to prove this rationale, bis (2,2,2 trifluroethyl) phosphite, 3 equivalents of cesium carbonate and 3 equivalents of TBAI were added. After an hour of stirring at room temperature to allow for deprotonation of the phosphite, ethyl bromoacetate was added immediately and stirred for 48 hours at room temperature. An analysis of the ^{31}PNMR spectrum did not reveal the presence of the desired product. While the result was not surprising, a change in the ratios of reagents in the reaction mixture proved to be most successful. As a first modification of the previous procedure, only one equivalent of cesium base was used. The phase transfer catalyst TBAI functions as an "anion shuttle" and two equivalents the ammonium salt should be adequate to sufficiently increase the solubility of the base in the organic phase.



Theoretical TBAI "Anion Shuttle" Mechanism
R = $(OCH_2CF_3)_2$

The reaction was conducted at 0 °C and the haloester was added dropwise, resulting in an isolated yield of 14%.

In an attempt to improve the yield and minimize byproduct formation, both steps of the reaction were conducted apart from each other in reverse. Instead of dropwise addition of the haloester to the phosphite salt, the salt was added to a solution of the haloester via cannulation. In theory, this would minimize side reactions involving the base and the desired product.



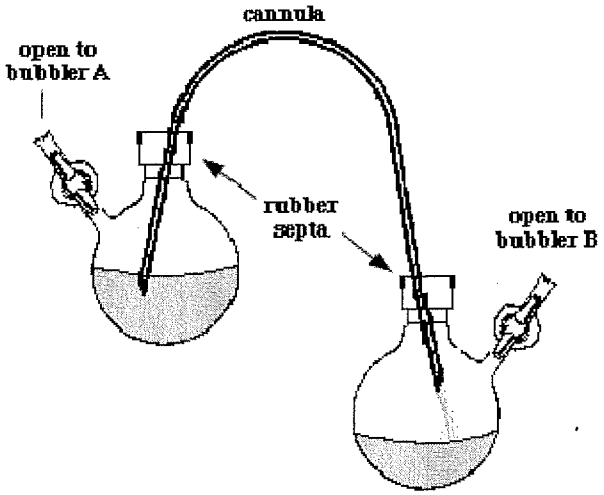


Table 1: Synthesis of ethyl [bis (2,2,2 trifluroethoxy) phosphinyl] acetate

Procedure	Base Used	Solvent	Temperature	Addition Time	% Yield
I	potassium *tert*-butoxide	DMF	0°C	Dropwise (20 min)	21%
II	cesium carbonate	DMF	0°C	Dropwise (20 min)	14%
III	cesium carbonate	DMF	25°C	Dropwise (20 min)	0%
V	potassium *tert*-butoxide	THF	0°C	Immediate (addition of phosphite salt)*	49%
VI	potassium *tert*-butoxide	THF	25°C	Immediate (addition of phosphite salt)	48%

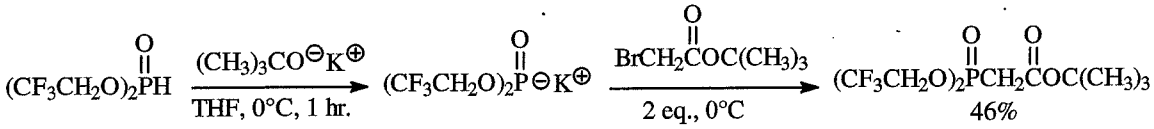
The second compound of interest that was synthesized was tert-butyl [bis(2,2,2 trifluoroethyl)phosphinyl] acetate. A different synthetic approach was utilized in the synthesis of this phosphonate compound. As mentioned about, a one hour period was allotted to ensure complete deprotonation of the phosphite to form the nucleophilic potassium phosphite salt. Once the formation of this species was complete, *t*-butyl bromoacetate was immediately added to the stirring solution and allowed to react for 30 minutes at 0 °C to minimize any unfavorable side reactions. This method yielded the desired product in 28%.

Table 2: Yields of trifluoroethyl phosphonates

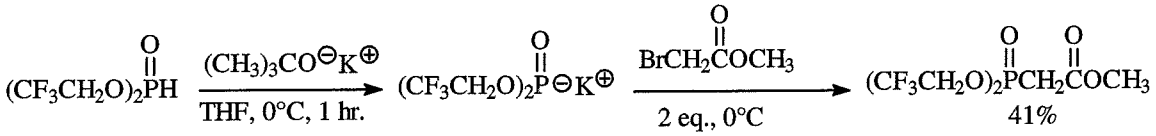
α-halo compound	Base Used	Solvent	Temperature	Addition	%Yield
tert-butyl bromoacetate	potassium *tert*-butoxide	THF	0 °C	Immediate	28%
methyl bromoacetate	potassium *tert*-butoxide	THF	0 °C	Immediate	41%
methyl chloroacetate	potassium *tert*-butoxide	THF	0 °C	Immediate	37%
isopropyl bromoacetate	potassium *tert*-butoxide	THF	0 °C	Immediate	36%
propyl chloroacetate	potassium *tert*-butoxide	THF	0 °C	Immediate	10%
1-chloropinacolone	potassium *tert*-butoxide	THF	0 °C	Immediate	11%
α-bromo-γ-butrolactone	potassium *tert*-butoxide	THF	0 °C	Immediate	0%
3-chloro-2-butanone	potassium *tert*-butoxide	THF	0 °C	Immediate	0%
vinyl chloroacetate	potassium *tert*-butoxide	THF	0 °C	Immediate	0%
trimethyl silyl bromoacetate	potassium *tert*-butoxide	THF	25 °C	Immediate	0%
ethyl chloroacetate	potassium *tert*-butoxide	THF	0 °C	Immediate	34%

The synthesis of the compounds shown in table **2** above employed the same procedure used in the synthesis of *tert*-butyl [bis (2,2,2 trifluroethoxy) phosphinyl] acetate. It should also be noted that the use of chlorinated electrophiles showed a some effect in terms of overall reactivity. As the experimental data shows, the overall yield decreases when the chlorine atom was substituted for bromine as a leaving group. This particular result is not shocking as bromine manifests as a better leaving group than chlorine in nucleophilic substitution reactions. Though, in this particular case, it is improper to solely consider leaving group ability since the nucleophile can be considered fairly docile.

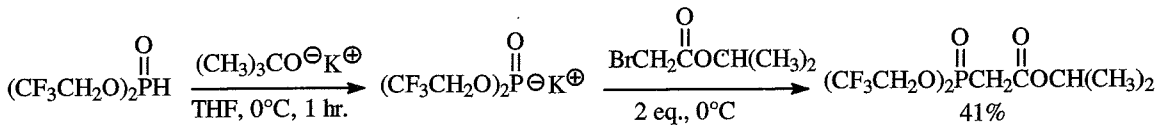
Scheme 1: Synthesis of *tert*-butyl [bis (2,2,2 trifluroethoxy) phosphinyl] acetate



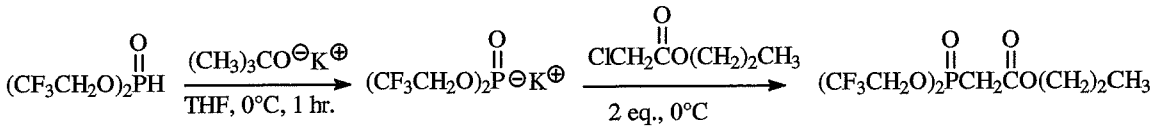
Scheme 2: Synthesis of methyl [bis (2,2,2 trifluroethoxy) phosphinyl] acetate



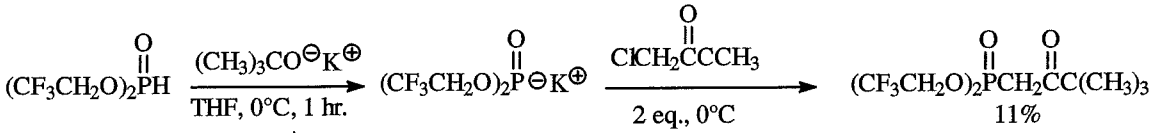
Scheme 3: Synthesis of isopropyl [bis (2,2,2-trifluroethoxy)phosphinyl] acetate



Scheme 4: Synthesis of propyl [bis (2,2,2-trifluroethoxy)phosphinyl] acetate

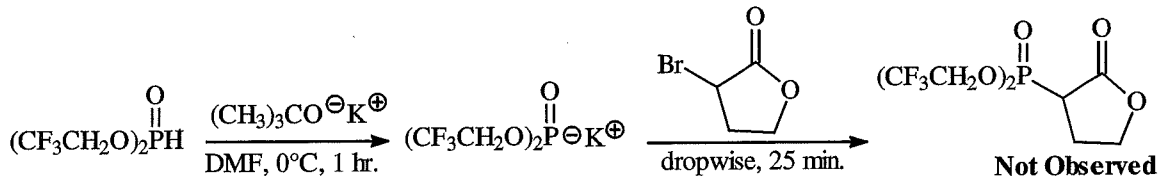


Scheme 5: Synthesis of [bis (2,2,2-trifluroethoxy)phosphinyl] pinacolone



An attempted synthesis of α-[bis(2,2,2-trifluoroethoxy)phosphinyl]-γ-butyrolactone was embarked upon (see scheme below). Using potassium *tert*-butoxide, the phosphite was deprotonated over a period of an hour. As in past synthetic methods, the halo-lactone was added slowly over twenty minutes and allowed to react for an additional 15 minutes after the dropwise addition at 0 °C. This reaction proved unsuccessful in that ^{1}H NMR and ^{31}P NMR displayed unreacted starting material and byproducts.

Scheme 6: Synthesis of α-[bis(2,2,2-trifluoroethoxy)phosphinyl]-γ-butyrolactone



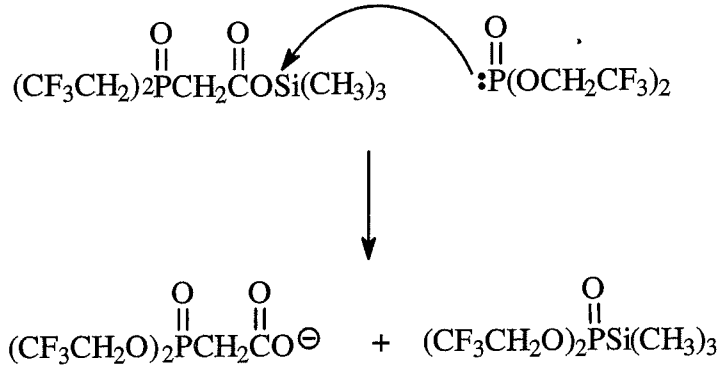
Unfortunately, this particular compound did not yield the phosphonate product that we anticipated. Lactones are under ring strain, even despite the documented stability of five membered ring systems. But, since neither a strong acid nor a strong nucleophile is not present, steric hinderance can be considered an issue here.

In the attempted synthesis of bis (2,2,2-trifluroethoxy)phosphinyl acetophenone, once more, our results differed from chemical intuition. According to Savingnac, the nucleophile preferentially attacks the carbonyl carbon.[15] Upon formation of the alkoxide anion, attack on the alpha carbon ensues which results in a different class of phosphonates termed epoxyphosphonates. Although an epoxyphosphonate compound was not isolated due to other general reaction complications which will be discussed further, formation of epoxyphosphonate compounds under these reaction conditions have been reported in the literature.[15]

With regards to the synthesis of bis (2,2,2-trifluroethoxy)phosphinyl butanone, to our surprise, this subtrate proved to be one that underwent yet another reaction pathway that we were not fully cognizant of. In any case, the desired product was not formed.

The synthesis of vinyl [bis (2,2,2-trifluroethoxy)phosphinyl] acetate presented an interesting problem. It was hypothesized that this reaction would proceed smoothly to product due to the fact that other halo-acetates in this study did not behave unexpectedly as electrophiles. A definite reason as to why this reaction was unsuccessful is unknown.

Lastly, a reaction must be discussed in which the starting material appears to possess two reactive sites which potentially lead to the destruction of the desired product. The starting material, trimethyl silyl bromoacetate, features an oxygen silicon bond which has one crucial implication. That oxygen silicon bond can be easily cleaved by a nucleophile from either the starting compound or the corresponding phosphonate. The mechanism shown below is based on the assumption that the only nucleophilic species present is the phosphite anion. There may potentially be unreacted base in solution to perform the same action. This mechanistic detail is based upon the findings of Dr. Janusz Rachon at Gdansk University of Technology. The research presented in this article entails the synthesis of potassium monoalkyl phosphonates using potassium trimethylsilanolate, the silicon equivalent to the strong base potassium tert butoxide. Silicon is directly under carbon in column 4A of the periodic table of elements. Thus, without regard to atomic size and orbital overlap, it can be assumed that carbon and silicon share the same behavior in terms of reactivity. The silicon oxygen bond can be considered more "loose" than that of the carbon oxygen bond. This chemical perspective can be disregarded in terms of overall base character of the two compounds. Unfortunately, there is no spectroscopic evidence to support this claim.



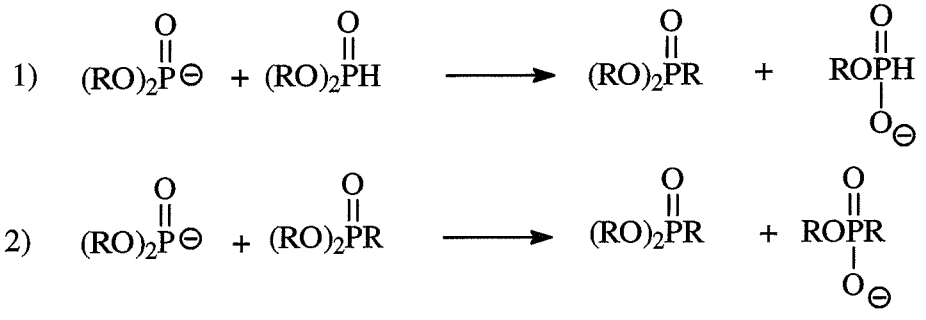
In the mechanism noted above, unreacted phosphite anion commences nucleophilic attack on the silicon atom, subsequently cleaving the silicon oxygen bond. In another proposed reaction, the phosphite anion attacks the phosphoryl group of a protonated phosphite molecule in a nucleophilic substitution reaction in which one trifluroethoxy group is displaced. In a seemingly unlikely event, the trifluroethoxy anion which is now in solution, encounters a molecule of newly formed trimethyl silyl [bis (2,2,2-trifluroethoxy)phosphinyl] acetate. The silicon atom undergoes nucleophilic attack, similar to the event described above, which results in the destruction of the desired compound. This event appears to be unlikely due to the stabilization of the negative charge on the oxygen atom in the trifluoroethoxy anion through inductive effects. The same principle applies to the nucleophilic capabilities of the phosphite anion. Unfortunately, there is no spectroscopic evidence to support this claim.

In respect to other undesirable side reactions, one must first consider the chemical structure of bis (2,2,2 trifluroethyl) phosphite. The molecule possesses two trifluoroethyl groups. This molecule also possesses a phosphoryl group. This particular functional group coupled with the trifluoroethyl groups all function as excellent electron withdrawing groups. This three fold electron withdrawing character that is exhibited on the phosphorus atom makes it a good electrophile. This phenomenon was first noticed when several similar reactions yielded two of the same byproducts by TLC analysis. It was initially hypothesized that these byproducts were the result of subsequent alkylation reactions due to the removal of the alpha hydrogen (pka 11.89)

on the desired phopshonate and subsequent reaction with unreacted haloester. This preconceived notion proved to be erroneous.

The phosphite was placed in base laden THF and allowed to react for 30 minutes with monitoring by TLC every three minutes. After a reaction time of just two minutes, the same troublesome spots appeared which were characteristic of every potential phosphonate yielding reaction. Our conclusion was that these stubborn byproducts were indeed phosphorus based and not the result of over alkylation. The solvent was then evaporated from the reaction mixture and the two byproducts were extracted from the syrupy reaction mixture using chloroform. A micro flash column was constructed using a pipette and silica gel and one of the byproducts was isolated for potential mass analysis by mass spectrometry. The molecular ion(s) from the mass spectrometer could then be used to predict a working structure for the particular byproduct.

A few possible mechanisms are reported by Dr. Kenneth Kem, who studied phase transfer catalyzed Michealis-Becker reactions at the Occidental Research Corporation. The mechanistic details displayed in the journal article are noted below.[9]



The various byproducts that result from the Michaelis-Becker synthesis of phosphonates have not only presented a mechanistic problem, but they have major

synthetic implications. The various side reactions that clearly involve the nucleophile directly greatly reduce the availability of reactive nucleophile to form the desired phosphonate which limits reaction yield. The phosphonate itself is a reactive entity that could go on to participate in a number of side reactions which further limits the yield from this synthetic method. The nucleophile itself can be considered fairly weak. The negative charge that exists on the phosphorus atom in the phosphite salt is stabilized by the electron withdrawing effects of the trifluroethyl groups through inductive effects. This then, makes it imperative to use two times the amount of electrophiles which are generally considered potent lachrymators which cause some biological and environmental concerns. Thus, another pitfall in this reaction method is that it would not prove practical on the large scale. Lastly, the aforementioned byproducts not only diminish the yields severely, but, they also pose serious chromatographic separation issues. Moreover, the desired product(s) usually have R_f differences relative to impurities of 0.10 or less. Therefore, purification is a cumbersome task According to Savinac, the Michealis-Becker route in synthesis to phosphonates is rarely considered to date.

This is mostly due to reaction inefficiency due to poor reaction yield and complicated reaction mixtures of which present separation issues. These key pitfalls have been noted throughout the course of this project.

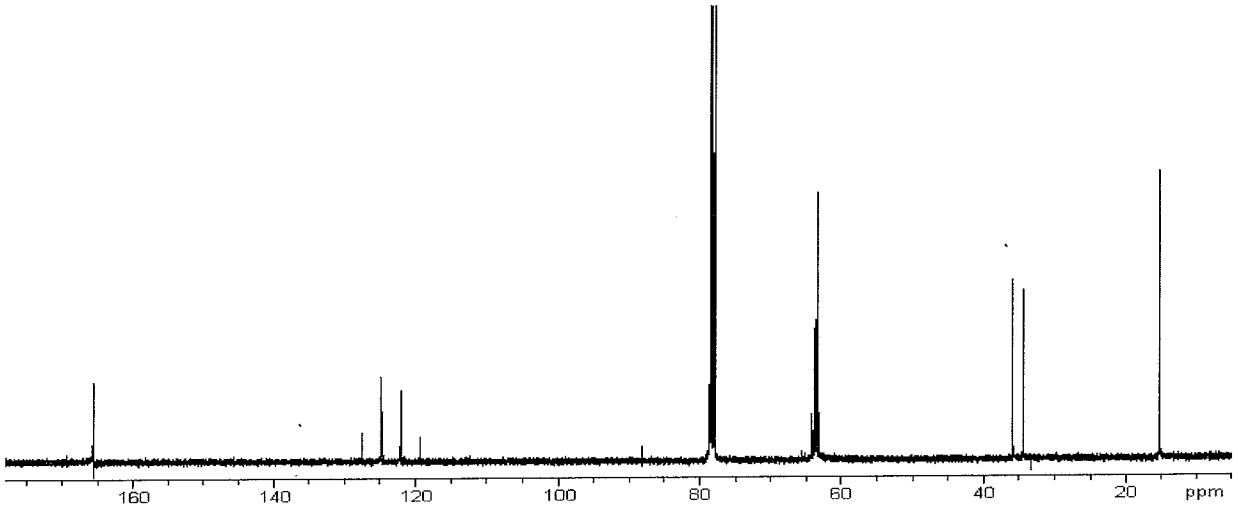
The goal of this project was to develop a mild and efficient manner in which to synthesize trifluroethyl phosphonate compounds through the use of a soft base. A deeper understanding of this reaction was gained through the initial use of a stronger

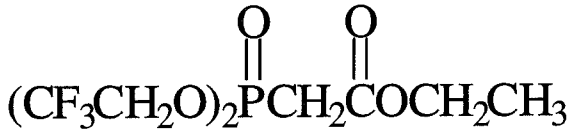
base. It was through the use of this technique and a thorough analysis of the reaction mechanism that enabled a stable set of reaction conditions and reagent ratios to be set. In comparison between the use of a strong base and a weak base for phosphonate synthesis, it can be stated that better results were achieved through the use of the stronger base in terms of overall product yield.

While the use of cesium carbonate and a phase transfer catalyst did not provide higher yields as anticipated although it provided a remedy for the complicated reaction mixtures that result from the use of stronger bases. This result was expected since cesium carbonate tends to deprotonate the phosphite to a lesser extent and the solubility of the base in solution is directly proportional to the amount of phase transfer catalyst available. This advantage is also a notable disadvantage throughout the course of the reaction. It is somewhat cumbersome to ascertain with any degree of certainty as to the molar amounts of base that are "truly" solvated in a given reaction mixture. Thus, over time, undissolved base may become solvated at improper intervals of the reaction and lead to base catalyzed destruction of the desired product through cascade-like side reactions.

In a standard ^{13}CNMR spectrum, the observed peaks appear as singlets when the protons attached are decoupled. The organophosphorus compounds being presented contain ^{31}P and ^{19}F, both of which are characterized by nuclei with ½ spin close to 100% natural abundance. As a result of these phenomena, complex splitting typically results.

Figure 1: ^{13}C NMR spectrum of ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (**1**)



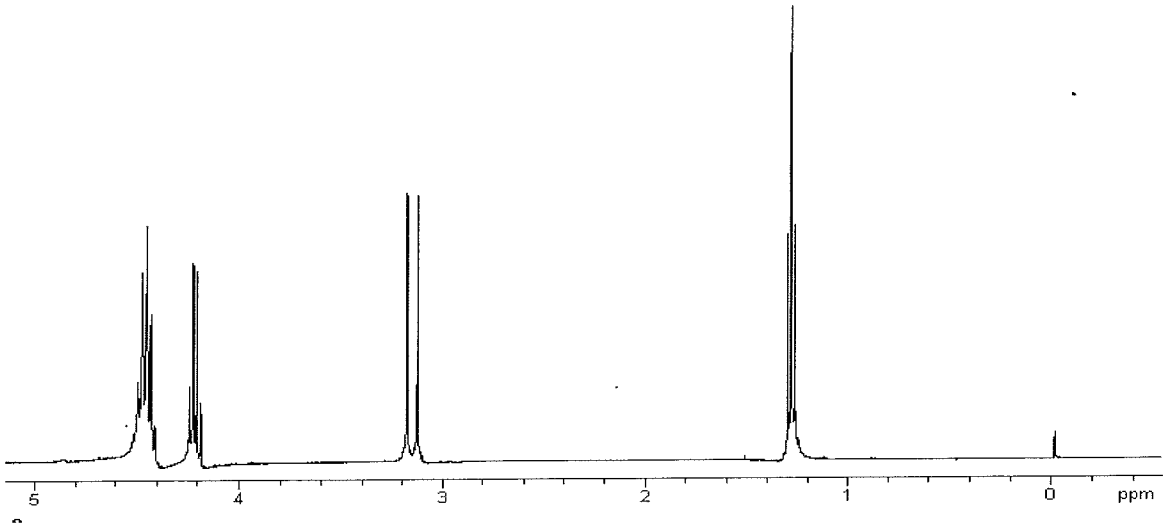


(b) (c) (e) (a) (d) (f)

Signal **a** corresponds to the carbonyl carbon atom and is displayed as a doublet (J= 4.0 Hz) at 165.6 ppm. This splitting pattern results from phosphorus coupling. The signal denoted as **e** is representative of the CH_2 between the phosphorus and carbon atoms. This signal was observed as a doublet (*J*=144 Hz) at 34.4 ppm. The large *J* value results from direct linkage of the carbon atom to phosphorus. The signals representative of **d** and **f** are

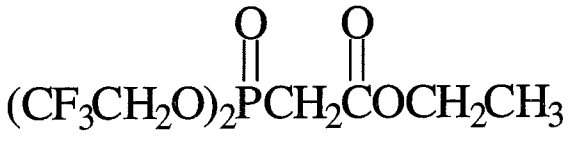
observed at 63 and 15.1 ppm respectively. These signals correspond to the carboethoxy group within this particular compound.

Figure 2: ^{1}H NMR of ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (**1**)



a b c d

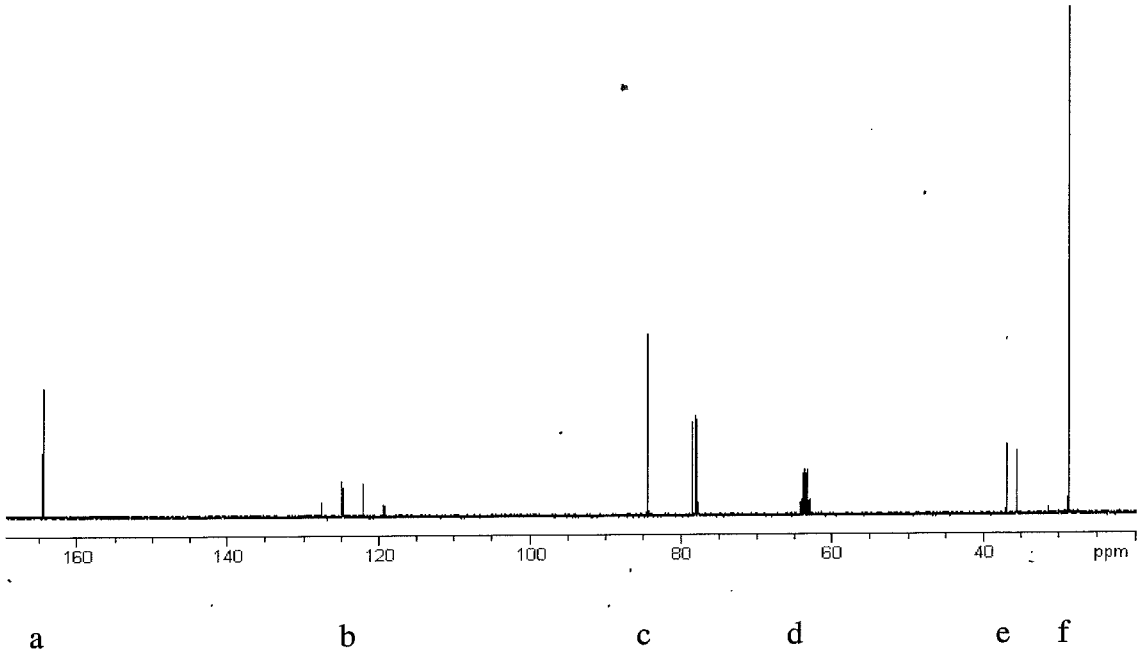
In the analysis of the ^{1}HNMR spectrum of compound **1**, the signal designated as **a** corresponds to the two methylene groups that are a part of the trifluroethyl group appears as a multiplet between the ranges of 4.47-4.43 ppm. Signal **b** appears as a quartet within the limits of 4.24-4.19 ppm (J=7.2 Hz). Upon integration, it was found that this signal

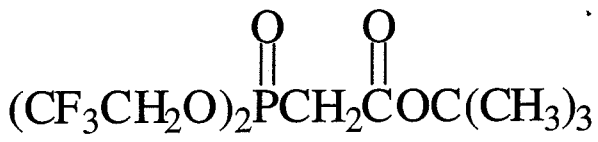


(a) (c) (b) (d)

corresponded to two hydrogen atoms which are a part of the carboethoxy group in the molecule. The doublet at 3.12 ppm (J=21.1 Hz) corresponds to the methylene group between the phosphoryl and carbonyl groups. It should be noted that the large value for J results from the coupling of the two protons to phosphorus. Lastly, the triplet at 1.27 ppm (J=7.1 Hz) denoted as **d** in the spectrum, corresponds to the methyl group of the carboethoxy group.

Figure 3: ^{13}C NMR spectrum of *tert*-butyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate **2**

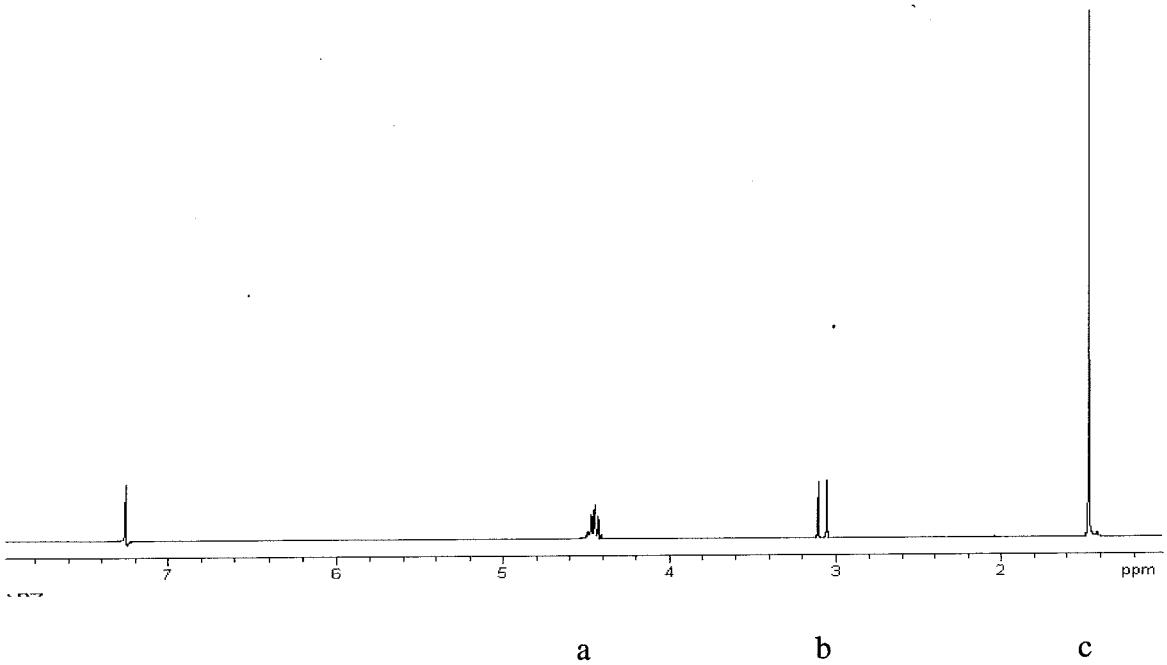




(b) (d) (e) (a) (c) (f)

In the analysis of the ^{13}C NMR spectrum of compound **2**, a doublet at 164.5 ppm (**signal a**) corresponds to the carbonyl carbon atom. This signal has a coupling constant value of 4.0 Hz as a result of coupling to phosphorus. The doublet of quartets at 124 ppm (**signal b**) with coupling constants of 277, 8.5 Hz corresponds to the two carbon atoms that are part of the trifluroethyl groups. The singlet at 84.5 ppm (**signal c**) directly relates to the 4° carbon of the *tert*-butyl group. The doublet of quartets at 63.5 ppm (**signal d**) with coupling constants of 39.2, 5.6 Hz, corresponds to the two methylene carbon atoms of the trifluroethyl group. The doublet at 36.5 ppm (**signal e**) correlates to the methylene group in between the phosphoryl and carbonyl groups in the molecule. This peak has a coupling constant of approximately 144 Hz as a result of coupling to the phosphorus atom. Lastly, the singlet at 28.79 ppm (**signal f**) corresponds to the three methyl groups that comprise the *tert*-butyl group.

Figure 4: ^{1}HNMR of *tert*-butyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (**2**)



With regards to the ^{1}H NMR spectrum of this compound, the singlet at 1.62 ppm (**signal c**) corresponds to nine protons that comprise the *tert*-butyl group. The multiplet at 4.45 ppm (**signal a**) corresponds to the four protons of the methylene groups that comprise the trifluroethyl groups. Lastly, a doublet at 3.08 ppm (**signal b**) corresponds to two alpha protons in this molecule. This signal also possesses a coupling constant of 21.1 Hz as a result of coupling to the phosphorus atom.

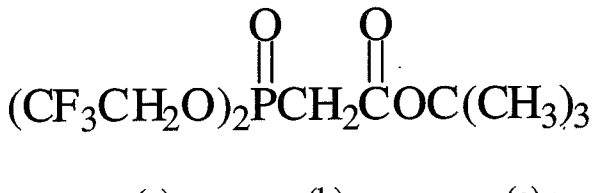
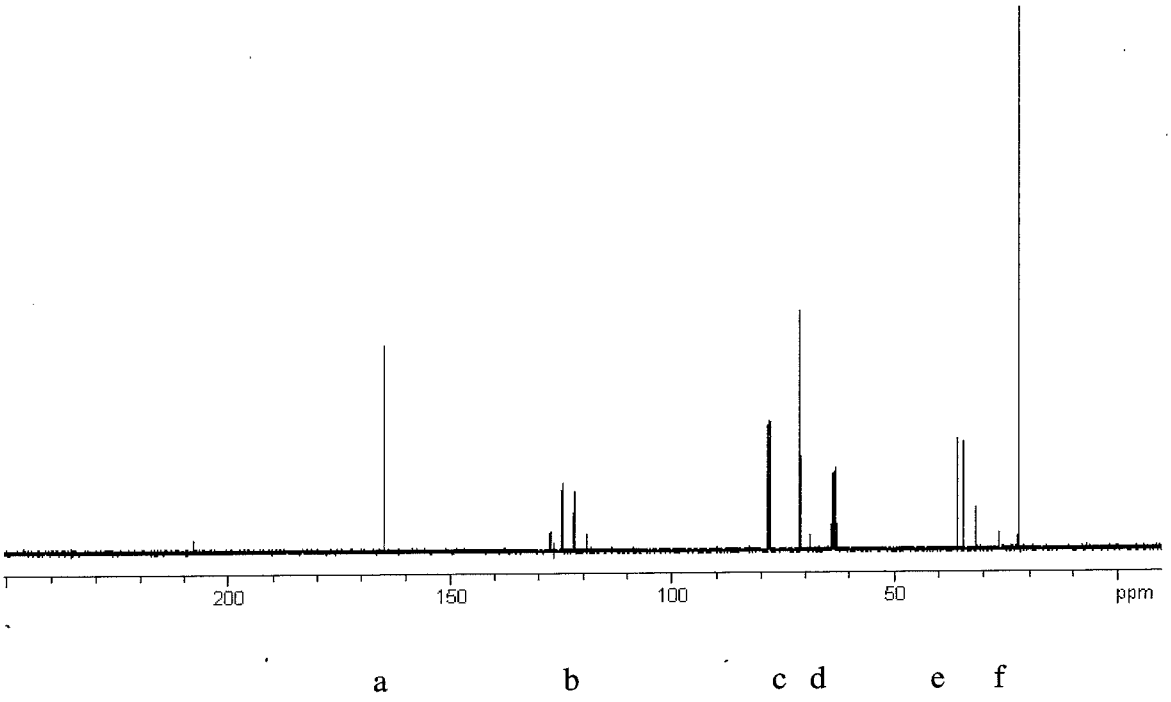
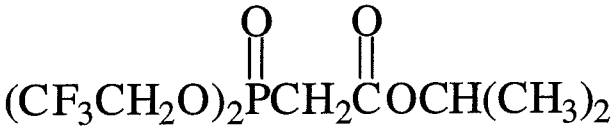


Figure 5: ^{13}C NMR spectrum of isopropyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate **3**

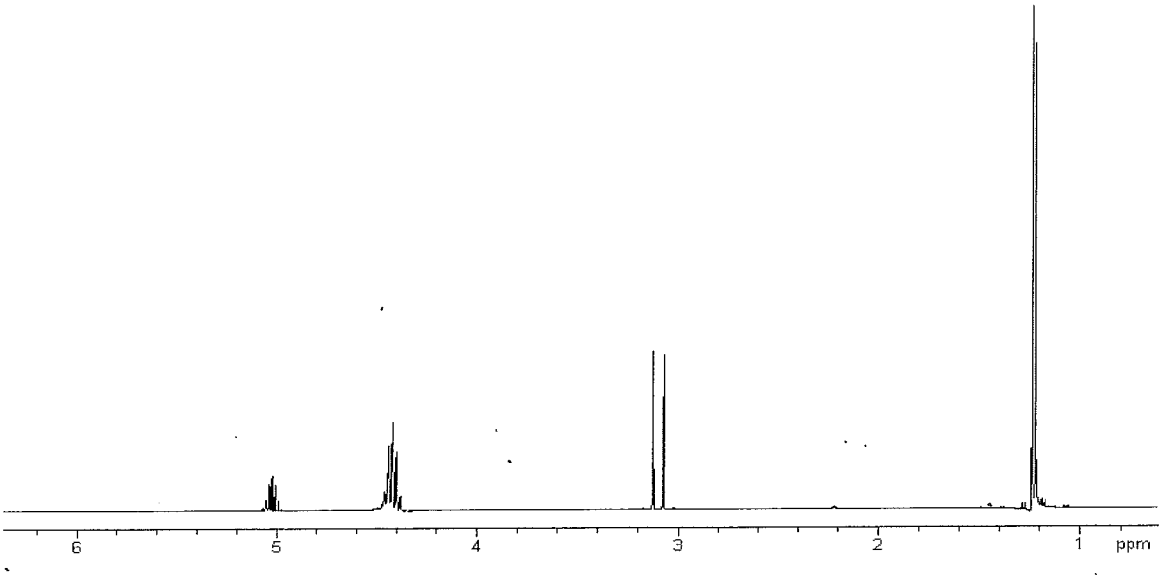


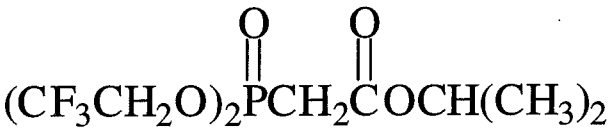
In reference to the ^{13}C NMR spectrum of this particular compound, the doublet at 165 ppm (**signal a**) with a coupling constant of 4.4 Hz corresponded to the carbon group. The doublet of quartets at 124 ppm (**signal b**) with coupling constants of 276.5 and 8.4 Hz correspond to the CF_3 groups of the trifluroethyl groups in this molecule. The singlet at 71.25 ppm (**signal c**) corresponds to the central carbon of the isopropyl group. The doublet of quartets at 63.55 ppm (**signal d**) with coupling constants of 39.2 and 5.6 Hz corresponds to the two methylene groups of the trifluroethyl groups. The signal at 35.28 (**signal e**) corresponds to the alpha carbon. As a result of splitting from phosphorus, this signal has a coupling constant of 143.1 Hz. Lastly, the signal at 21 ppm (**signal f**) corresponds to the two methyl groups of the isopropyl group.



(b) (d) (e) (a) (c) (f)

Figure 6: ^{1}H NMR of isopropyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate **3**



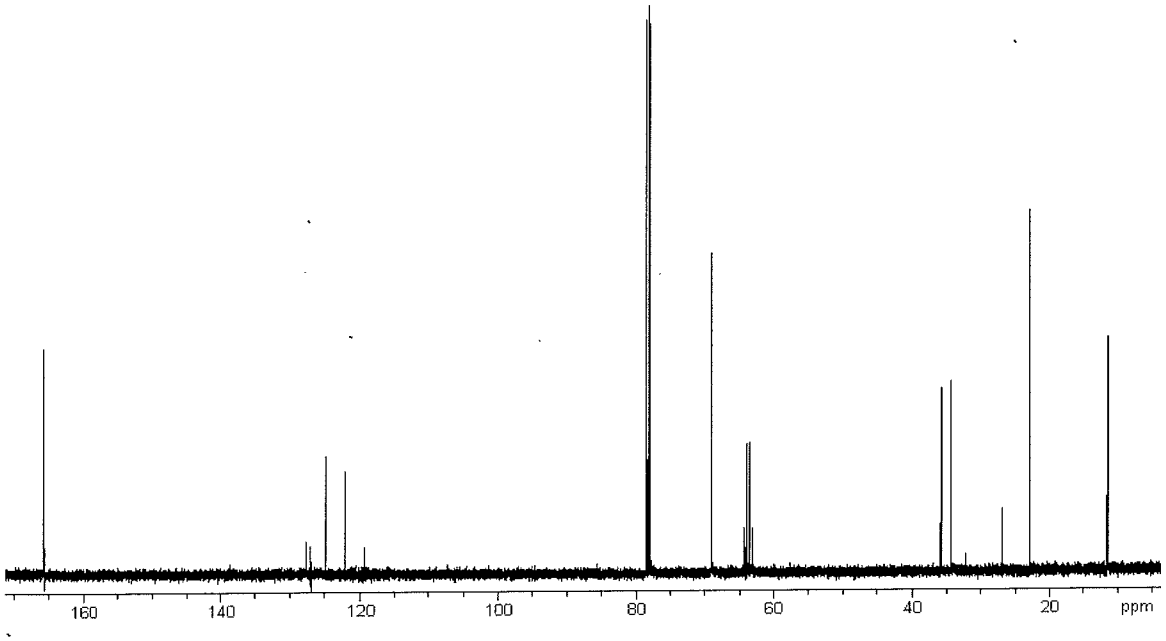


(b) (c) (a) (d)

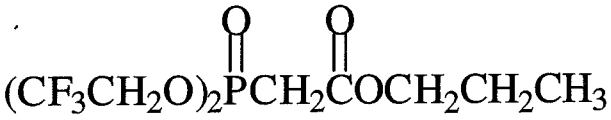
The ^{1}HNMR of isopropyl reveals some key characteristic signals. A doublet at 1.23 ppm (**signal d**) corresponds to the six methyl protons of the isopropyl group. The doublet at 3.09 ppm (**signal c**) with a coupling constant of 21 Hz corresponds to the two alpha protons of the methylene group in between the phosphoryl and carbonyl groups. The multiplet at 4.42 ppm (**signal b**) directly relates to the four protons of the methylene groups of the trifluroethoxy groups. Lastly, the septet at 5.10 ppm (**signal a**) corresponded to the proton attached to the central carbon of the isopropyl group. This

signal is shifted significantly relative to a normal alkyl proton due to the electronic effects of the neighboring electronegative oxygen atom which deshields it.

Figure 7: ^{13}C NMR spectrum of propyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate **4**



a b c d e f g



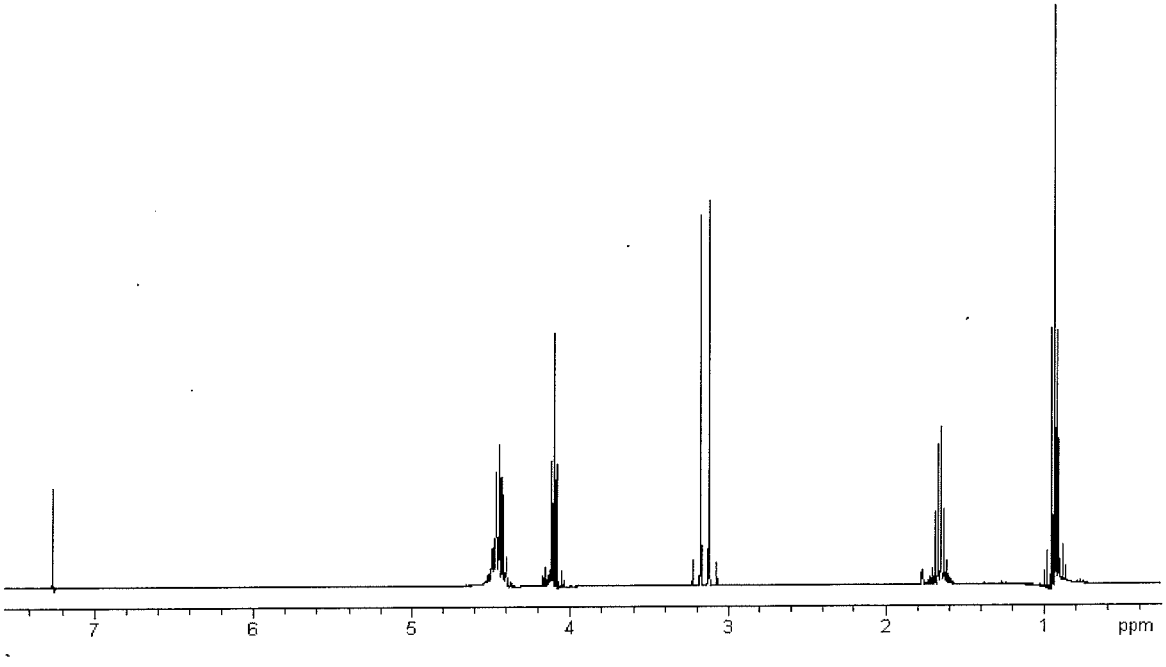
(b) (d) (e) (a) (c) (f) (g)

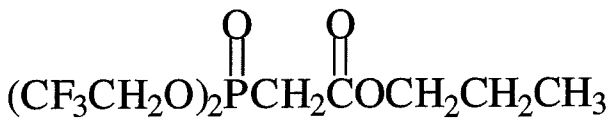
The doublet at 166 ppm (**signal a**) with a coupling constant of 4.0 Hz corresponds to the carbonyl carbon. The doublet of quartets at 124 ppm (**signal b**) corresponds to the two CF_3 groups of the trifluroethyl groups. This signal shows splitting by phosphorus with coupling constant values of 276.5 and 8.4 Hz. The singlet at 68.9 ppm (**signal c**) is resultant of the methylene carbon of the propyl group directly attached to the oxygen

atom. The doublet of quartets at 63.55 ppm (**signal d**) with coupling constants of 39.2 and 5.6 Hz correspond to the two methylene groups of the trifluroethyl groups.

The doublet at 35.10 ppm (**signal e**) corresponds to the signal for the alpha carbon. This signal is split by phosphorus, thus, it possesses a coupling constant value of 144.3 Hz. Lastly, the singlets at 22.93 and 11.36 ppm (**signals f and g respectively**) corresponds to the terminal methylene and methyl groups of the propyl group respectively.

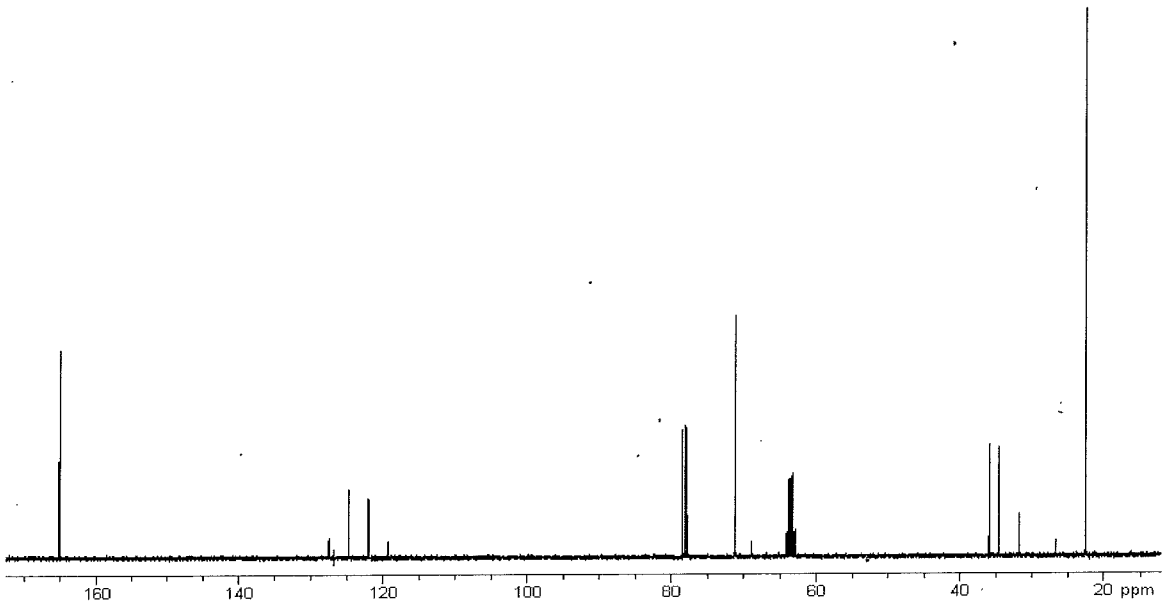
Figure 8: ^{1}H NMR of propyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (**5**)

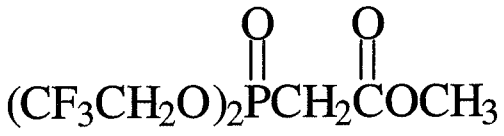




In the ^{1}HNMR of this compound, the triplet at 0.93 ppm (**signal e**) corresponds to the methyl group of the terminal end of the propyl group. The sextet at 1.66 ppm (**signal d**) results from the methylene group that is neighbored to the right by a methyl group and to the left by another methylene group. The triplet at 4.10 ppm (**signal b**) corresponds to the methylene group of the propyl group that is directly attached to oxygen. The doublet at 3.15 ppm (**signal c**) with a coupling constant of 21.5 Hz results from the alpha protons directly attached to the alpha carbon. Lastly, the multiplet at 4.44 Hz (**signal a**) corresponds to the two methylene groups of the trifluroethyl groups directly attached to the phosphorus atom.

Figure 9: ^{13}C NMR spectrum of methyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate

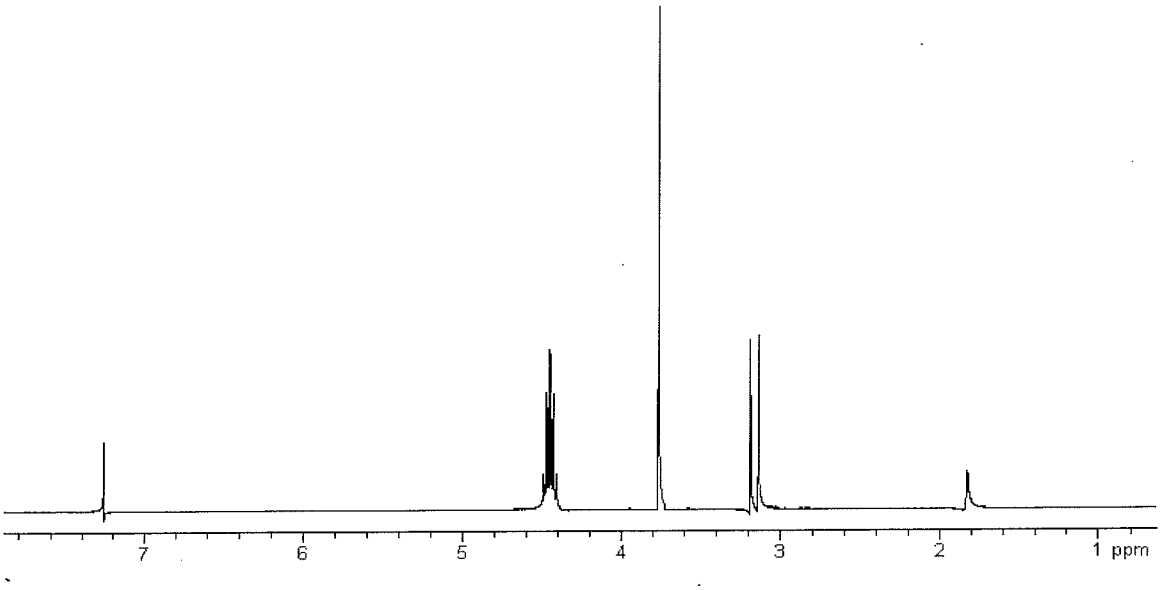


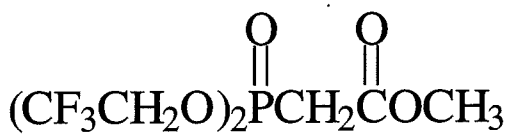


(b) (d) (e) (a) (f)

In the ^{13}C NMR spectrum of this phosphonate compound, the doublet at 161.91 ppm (**signal a**) with a coupling constant of 4.4 Hz corresponds to the carbonyl carbon in this molecule. The doublet of quartets at 122.25 ppm (**signal b**) with *J* values of 275.6, 8.4 Hz directly relates to the two CF_3 groups of the trifluroethyl group. The doublet of quartets at 62.76 ppm (**signal d**) with *J* values of 39.2, 5.6 Hz corresponds to the methylene carbon of the trifluroethyl groups. The singlet at 22 ppm (**signal f**) represents the methyl group of the methoxy group in this molecule. Lastly, the doublet at 33.68 ppm (**signal e**) with a coupling constant value of 144.7 Hz is the signal that represents the alpha carbon.

Figure 10: ^{1}H NMR of methyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (**6**)

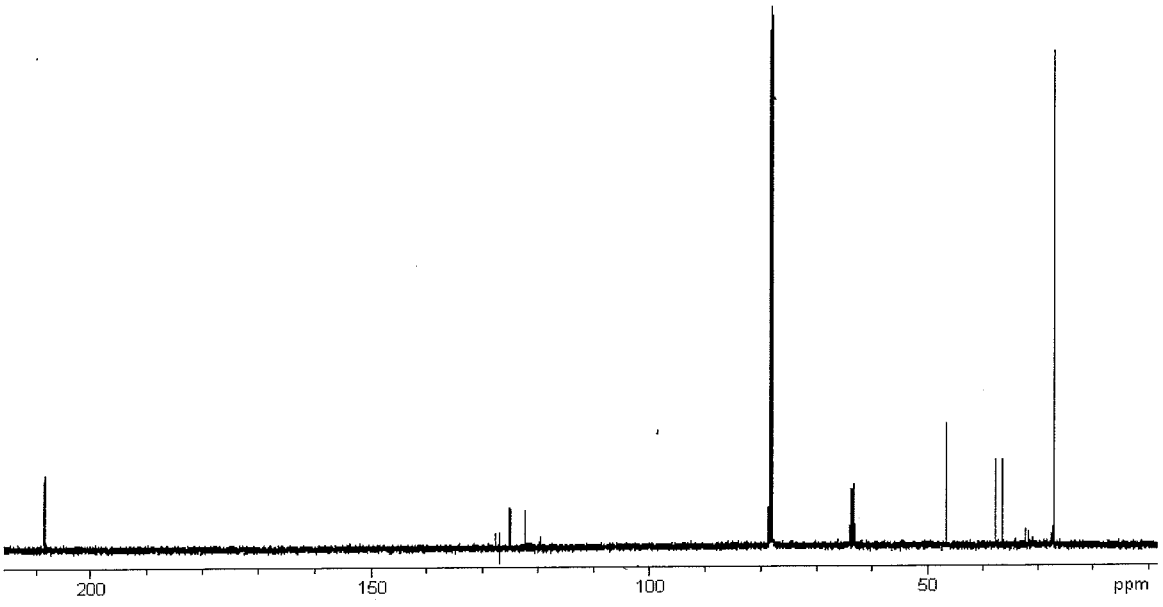




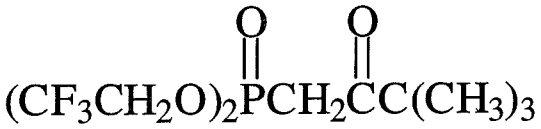
(a) (c) (b)

Pertaining to the ^{1}H NMR spectrum, the singlet at 3.7 ppm (**signal b**), is representative of the three protons that comprise the methyl group of the terminal methoxy group. Secondly, the doublet at 3.16 ppm (**signal c**) with a *J* value of 21.1 Hz is representative of the two alpha protons attached to the alpha carbon. This signal has a coupling constant of 21.1 Hz as a result of coupling to phosphorus. Lastly, the multiplet at 4.45 ppm (**signal a**) corresponds to the protons from the two methylene groups of the two trifluroethyl groups attached to phosphorus.

Figure 11: ^{13}C NMR spectrum of [bis(2,2,2-trifluoroethoxy)phosphinyl] pinacolone **7**



a b c d e f

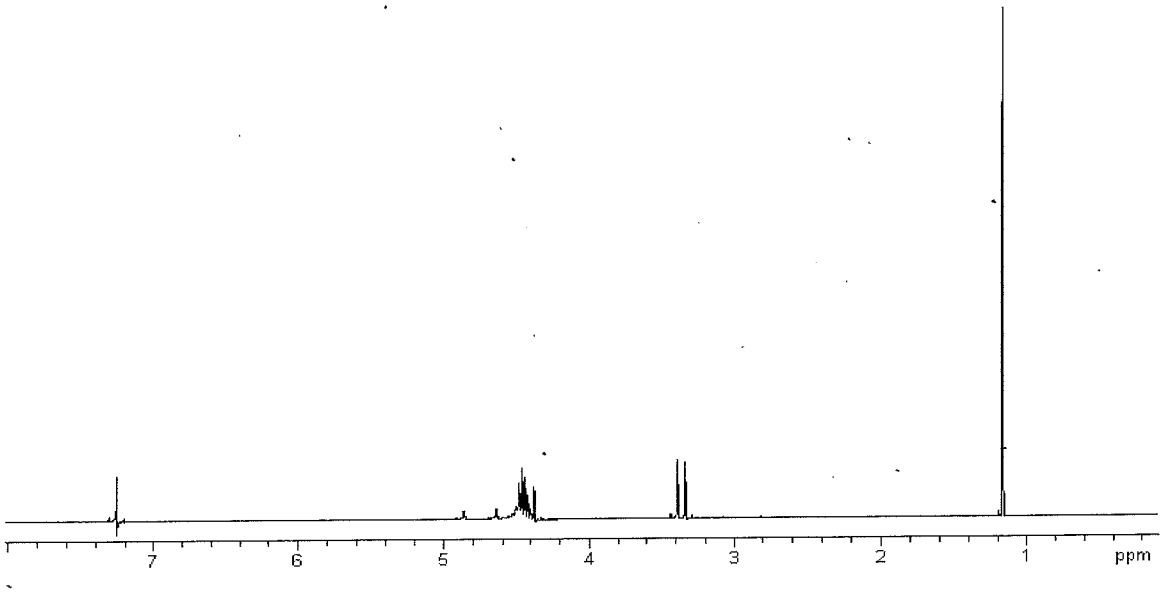


(b) (c) (e) (a)(d) (f)

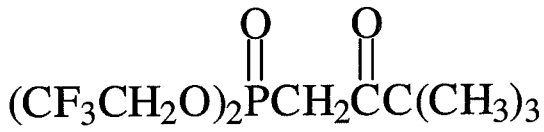
In the ^{13}C NMR, the doublet at 228 ppm (**signal a**) with a coupling constant of 4.4 Hz corresponds to the carbonyl carbon atom. The doublet of quartets at 124 ppm (**signal b**) with coupling constants of 276.9 and 3.1 Hz corresponds to the two CF_3 groups of the two trifluroethyl groups attached to phosphorus. The doublet of quartets at 64.00 ppm (**signal c**) with *J* values of 39.2 and 5.6 Hz is representative of the two methylene groups of the two trifluroethyl groups. The doublet at 46.50 ppm (**signal d**) corresponds to the central carbon of the *tert*-butyl group. The doublet at 36.87 (**signal e**) with a value for the

coupling constant at 144 Hz is representative of the alpha carbon in this molecule. Lastly, the singlet at 27.07 ppm (**signal f**) is produced by the three methyl carbon atoms of the *tert*-butyl group.

Figure 12: ^{1}H NMR of [bis(2,2,2-trifluoroethoxy)phosphinyl] pinacolone (**8**)



a b c



(a) (b) (c)

In the ^{1}HNMR, the singlet at 1.16 ppm (**signal c**) represents the nine protons of the three methyl groups that comprise the *tert*-butyl group. The doublet at 3.35 ppm (**signal b**) corresponds to the two alpha protons attached to the alpha carbon. The

coupling constant for this signal is 21.1 Hz as a result of splitting due to phosphorus. Lastly, the multiplet at 4.45 ppm (**signal a**) represents the protons comprising the two methylene groups of the two trifluroethyl groups attached to the phosphorus atom.

Conclusions and Future Work

Through experimentation with several electrophiles it was determined that this synthetic method compares well to the two common methods described by Still and Savignac. It also provided insight into the synthesis of a different class of phosphonate compounds termed epoxyphosphonates. The isolated phosphonates in this experiment display some interesting fragmentation properties in the gas phase through mass spectral analysis. Thus, future work could attempt to diagram gas phase reaction mechanisms of these compounds. Lastly, definite structures for the byproducts obtained through the reaction of the phopshite salt with the phosphite starting material were not able to be obtained due to technical difficulties. Determinations of these structures by mass spectral analysis and NMR techniques could provide further insight as to the prevention of these key side reactions which proved to reduce the availability of the nucleophile and subsequent yield reduction.

Chapter 3: Experimental

General methods. All reactions were conducted under inert argon atmosphere. All commercial reagents were used without further purification. Flash chromatography was performed using Merk grade 9385, 230-400 mesh silica. Thin Layer Chromatography (TLC) was conducted on silica plates. The results were visualized using an iodine chamber, ultraviolet lamp or by staining using a solution of potassium permanganate. NMR spectra (^{1}H, ^{13}C, ^{31}P) were measured using a Varian Gemini 2000 400 MHz spectrometer with $CDCl_3$ as the solvent. The ^{1}H and ^{13}C chemical shifts are reported in parts per million downfield relative to $(CH_3)_4Si$. ^{31}P NMR chemical shifts are reported in parts per million downfield relative to phosphoric acid (external standard). Coupling constants are reported in Hertz.

The Synthesis of Bis[2,2,2-trifluroethyl] phosphite (1).[17]

A solution of anhydrous 2-methyl-2-propanol (37.0 g, 0.5 mol) in dry dichloromethane (100 ml) was added dropwise to a stirred solution of phosphorus trichloride (43.5 mL, 0.5 mol) in dichloromethane (100 ml) over a period of 45 minutes. The reaction mixture was maintained at 0 °C using an ice bath under an inert argon atmosphere. After the addition of phosphorus trichloride was completed, stirring was continued for an additional 30 minutes at 0 °C. A solution of anhydrous 2,2,2-trifluoroethanol (100.0 g, 1 mol) in dichloromethane (100 mL was added to the mixture over a period of 30 minutes. After the addition, stirring was continued under the inert atmosphere of argon at 25 °C for 16 hours to liberate hydrogen chloride. Dichloromethane was removed using a rotary

evaporator. The product was obtained by fractional distillation. (93 g, 75.6%) b.p. 43-44°C/2 torr .

^{1}H NMR ($CDCl_3$): δ (ppm): 7.04 (m, 1H, *J*=756.7 Hz,), 4.43 (m, 4H)

^{31}P NMR ($CDCl_3$): δ (ppm): 8.71

Ethyl [bis(2,2,2-trifluroethoxy)phosphinyl] acetate (2).

Procedure I. To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous DMF (23 mL) at 0 °C, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was stirred for one hour while maintaining a steady temperature of 0 °C using an ice bath. Ethyl bromoacetate (1.44 mL, 63 mmol) was added dropwise over twenty minutes by syringe. After the addition was complete, the reaction mixture was allowed to stir for an additional fifteen minutes at 0 °C. The reaction was then quenched with a saturated solution of aqueous ammonium chloride (20 mL), the organics were extracted using diethyl ether (3 x 20 mL) and the combined extracts were washed with a saturated solution of sodium chloride (1 x 20 mL) and water (1 x 20 mL). Subsequently, the organic extracts were dried using anhydrous magnesium sulfate. After the removal of solvent by rotary evaporation, the crude material was further concentrated using an oil pump vacuum and purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) yielding compound **1** (250 mg, 37%).

^{1}H NMR ($CDCl_3$): δ (ppm) 4.45 (m, 4H), 4.22 (q, 2H, *J*=7.2 Hz), 3.12 (d, 2H, *J*=21.1 Hz), 1.27 (t, 3H, *J*=7.1 Hz)

^{13}C NMR ($CDCl_3$): δ (ppm) 165.6 (d, *J*=4.0 Hz), 122.0 (2, dq, *J*=276.6, 8.4 Hz), 63.5 (2, dq, *J*=39.2, 5.6 Hz), 63.0 (s), 34.4 (d, *J*=144 Hz), 15.1 (s).

^{31}P NMR ($CDCl_3$): δ (ppm) 24.24

Procedure II. To a solution of cesium carbonate (2.05 g, 6.333 mmol) and tetrabutylammonium iodide (6.96 g, 19 mmol) at 0 °C, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was then allowed to stir rapidly for one hour. After this time interval, ethyl bromoacetate (1.44 mL, 6.33 mmol, 10 drops/min) was added dropwise over twenty minutes. After the completion of addition, the reaction was allowed to stir for an additional fifteen minutes. Thereafter, the reaction was quenched with aqueous ammonium chloride (20 mL). The organics were extracted using 3 x 20 mL aliquots of diethyl ether. The combined organic phases were washed with 1 x 20 mL saturated sodium chloride and water 1x 20 mL, and dried using anhydrous magnesium sulfate. The solvent was removed through the use of a rotary evaporator, and the crude product was further dried using a vacuum pump. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) yielding compound **1** (160 mg, 14%).

Procedure III. A solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in 23 ml of anhydrous THF was stirred and cooled to 0 °C in a Schlenk flask using an ice bath. Bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added to this solution by syringe under inert gas and stirred for one hour. In another Schlenk flask, a solution of ethyl bromoacetate (1.44 mL, 6.33 mmol) and 10 ml of THF was prepared and also stirred at 0 °C. After 1 h, the phosphite salt formed in Schlenk flask was quickly transferred to the second flask by cannula transfer. After this addition, the reaction was allowed to stir for an additional fifteen minutes at 0 °C. After this time, the reaction was quenched using a saturated ammonium chloride solution. The organic portions were extracted using diethyl ether (3 x 20 mL). The combined organic extracts were washed

with saturated sodium chloride (1 x 20 mL) and water (1 x 20 ml). The resultant solution was dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and subsequent use of a vacuum pump. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) producing compound **1** (580 mg, 49%).

Procedure IV. To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF at 0 °C in a Schlenk flask, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was allowed to stir for one hour. In another Schlenk flask, 2.44 mL of ethyl bromoacetate was stirred and cooled to 0 °C. After one hour, the solution from the first flask was transferred to the second using a cannula. This solution was monitored by TLC and allowed to stir for one hour. After this time, the reaction was quenched using a saturated ammonium chloride solution. The organic portions were extracted using diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated sodium chloride (1 x 20 mL) and water (1 x 20 mL). The resultant solution was dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and subsequent use of a vacuum pump. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) producing compound **1** (568 mg, 48%).

Procedure V. To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF at 0 °C in a Schlenk flask, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was allowed to stir for one hour. In another Schlenk flask, 1.34 mL of ethyl iodoacetate was stirred and cooled to 0 °C. After one hour, the solution from the first flask was transferred to the second using a cannula. This solution was monitored

by TLC and allowed to stir for 15 minutes. After this time, the reaction was quenched using a saturated ammonium chloride solution. The organic portions were extracted using diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL) and saturated sodium chloride (1 x 20 mL). The resultant solution was dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and subsequent use of a vacuum pump. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) producing compound **1** (539 mg, 45%)

Procedure VI: To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF at 0 °C in a round bottomed flask, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was allowed to stir for one hour at 0 °C. After one hr, ethyl chloroacetate (2.96 mL, 12.6 mmol) was added to the stirring solution via syringe. This solution was allowed to stir for 30 minutes. After this time, the reaction was quenched using a saturated ammonium chloride solution. The organic portions were extracted using diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL) and saturated sodium chloride (1 x 20 mL). The resultant solution was dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and subsequent use of a vacuum pump. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) producing compound **1** (409 mg, 34%).

***Tert*-butyl [bis(2,2,2-trifluroethoxy)phosphinyl] acetate (3).**

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF (23 mL) at 0 °C, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. After

this period, *tert*-butyl bromoacetate (3.25 mL, 12.66 mmol) was added by syringe. Once the addition was complete, the reaction was allowed to proceed for one hour with monitoring by TLC. The reaction was then quenched with. The reaction was then quenched with a saturated solution of aqueous ammonium chloride (20 mL). The organics were extracted with diethyl ether (3 x 20 mL). The combined extracts were washed water (3 x 20 mL) and a saturated sodium chloride solution (1 x 20 mL). After the removal of solvent by rotary evaporation, the crude material was further concentrated under oil pump vacuum. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) yielding compound **6** (541 mg, 28%).

^{1}HNMR ($CDCl_3$): δ (ppm): 1.62 (s, 9H), 3.08 (d, 2H, *J*=21.1 Hz), 4.45 (m, 4H).

^{31}PNMR ($CDCl_3$): δ (ppm): 24.87.

^{13}CNMR ($CDCl_3$): δ (ppm): 164.5 (d, *J*=4.0 Hz), 124 (dq, *J*=277, 8.5 Hz), 84.37 (s), 63.51 (dq, *J*=39.2, 5.6 Hz), 36.29 (d, *J*=144.0 Hz), 28.79 (s).

M.S: Calculated: 360 amu; Observed: 359 m/z (M^+-1)

Methyl [bis (2,2,2-trifluroethoxy)phosphinyl] acetate (4).

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF (23 mL) at 0 °C, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. After this period, methyl bromoacetate (1.72 mL, 12.66 mmol) was added by syringe. Once the addition was complete, the reaction was allowed to proceed for one hour with monitoring by TLC. The reaction was then quenched with. The reaction was then quenched with a saturated solution of aqueous ammonium chloride (20 mL). The organics were extracted with diethyl ether (3 x 20 mL). The combined extracts were washed water (3 x 20 mL) and a saturated sodium chloride solution (1 x 20 mL). After the removal of solvent by

rotary evaporation, the crude material was further concentrated under oil pump vacuum. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) yielding compound **7** (482 mg, 41%)

^{1}HNMR ($CDCl_3$): δ (ppm): 1.84 (s, 3H), 3.16 (d, 2H, *J*=21.1 Hz), 4.45 (m, 4H).

^{31}PNMR ($CDCl_3$): δ (ppm): 24.05.

^{13}CNMR ($CDCl_3$): δ (ppm): 164.91 (d, *J*= 4.4 hz), 122.25 (dq, *J*=275.6, 8.4 Hz), 62.76 (dq, *J*=39.2, 5.6 Hz), 53.0 (s), 33.68 (d, *J*=144.7 Hz).

M.S: Calculated: 318 amu; Observed: 316.9 m/z (M^+-1)

Procedure II:

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF (23 mL) at 0 °C, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. After this period, methyl chloroacetate (0.91 mL, 12.66 mmol) was added by syringe. Once the addition was complete, the reaction was allowed to proceed for one hour with monitoring by TLC. The reaction was then quenched with a saturated solution of aqueous ammonium chloride (20 mL). The organics were extracted with diethyl ether (3 x 20 mL). The combined extracts were washed water (3 x 20 mL) and a saturated sodium chloride solution (1 x 20 mL). After the removal of solvent by rotary evaporation, the crude material was further concentrated under oil pump vacuum. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) yielding compound **7** (433 mg, 37%).

Isopropyl [bis (2,2,2-trifluroethoxy)phosphinyl] acetate (5).

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF (23 mL) at 0 °C, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. After this period, isopropyl bromoacetate (0.61 mL, 12.66 mmol) was added by syringe. Once the addition was complete, the reaction was allowed to proceed for one hour with monitoring by TLC. The reaction was then quenched with. The reaction was then quenched with a saturated solution of aqueous ammonium chloride (20 mL). The organics were extracted with diethyl ether (3 x 20 mL). The combined extracts were washed water (3 x 20 mL) and a saturated sodium chloride solution (1 x 20 mL). After the removal of solvent by rotary evaporation, the crude material was further concentrated under oil pump vacuum. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) yielding compound **8** (431 mg, 36%).

^{1}HNMR ($CDCl_3$): δ (ppm): 1.23 (d, 6H, *J*=8.24), 3.09 (d, 2H, *J*=21.1 Hz), 4.42 (m, 4H), 5.10 (septet, 1H, *J*=6.63).

^{31}PNMR ($CDCl_3$): δ (ppm): 24.41.

^{13}CNMR ($CDCl_3$): δ (ppm): 165 (d, *J*=4.4 Hz), 124 (dq, *J*=276.5, 8.4 Hz), 71.25 (s), 63.55 (dq, *J*=39.2, 5.6 Hz), 35.28 (d, *J*=143.1).

Propyl [bis (2,2,2-trifluroethoxy)phosphinyl] acetate (6).

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF (23 mL) at 0 °C, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. After this period, Propyl chloroacetate (1.20 mL, 12.66 mmol) was added by syringe. Once the addition was complete, the reaction was allowed to proceed for one hour with monitoring by TLC. The reaction was then quenched with. The reaction was then quenched with a

saturated solution of aqueous ammonium chloride (20 mL). The organics were extracted with diethyl ether (3 x 20 mL). The combined extracts were washed water (3 x 20 mL) and a saturated sodium chloride solution (1 x 20 mL). After the removal of solvent by rotary evaporation, the crude material was further concentrated under oil pump vacuum. The final product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate) yielding compound **10** (80 mg, 10%).

^{1}HNMR ($CDCl_3$): δ (ppm): 0.93 (t, 3H, *J*=7.51 Hz), 1.66 (m, 2H, *J*=6.77, 7.32 Hz), 4.10 (t, 2H, *J*=6.77 Hz), 3.15 (d, 2H, *J*=21.0 Hz), 4.44 (m, 4H).

^{31}PNMR ($CDCl_3$): δ (ppm): 24.31.

^{13}CNMR ($CDCl_3$): δ (ppm): 166 (d, *J*= 4.0 Hz), 124 (dq, *J*=276.5, 8.4 Hz), 68.9 (s), 35.10 (d, *J*=144.3 Hz), 22.93 (s), 11.36 (s).

[bis (2,2,2-trifluroethoxy)phosphinyl] pinacolone (7)

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF at 0 °C in a round bottomed flask, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was allowed to stir for one hour at 0 °C. After one hr, 1-chloropinacolone (0. 906 mL, 12.66 mmol) was added to the stirring solution via syringe. This solution was allowed to stir for 30 minutes. After this time, the reaction was quenched using a saturated ammonium chloride solution. The organic portions were extracted using diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL) and saturated sodium chloride (1 x 20 mL). The resultant solution was dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and subsequent use of a vacuum pump. The desired compound was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate). (114 mg, 12%).

^{1}HNMR ($CDCl_3$): δ (ppm): 1.16 (s, 9H), 3.35 (d, 2H, *J*=21.1 Hz), 4.45 (m, 4H).

^{31}PNMR ($CDCl_3$): δ (ppm): 26.445.

^{13}CNMR ($CDCl_3$): δ (ppm): 228 (d, *J*=4.4 Hz), 124 (dq, *J*=276.9, 3.1 Hz), 64.00 (dq, *J*=39.2, 5.6 Hz), 46.50 (d, *J*=6.0 Hz), 36.87 (d, *J*=144 Hz), 27.075 (s).

Attempted synthesis of vinyl [bis (2,2,2-trifluroethoxy)phosphinyl] acetate (8)

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF at 0 °C in a round bottomed flask, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was allowed to stir for one hour at 0 °C. After one hr, vinyl chloroacetate (0.789 ml, 12.6 mmol) was added to the stirring solution via syringe. This solution was allowed to stir for 30 minutes. After this time, the reaction was quenched using a saturated ammonium chloride solution. The organic portions were extracted using diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 ml) and saturated sodium chloride (1 x 20 mL). The resultant solution was dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and subsequent use of a vacuum pump. The desired compound was not formed by NMR analysis.

Attempted synthesis of bis (2,2,2-trifluroethoxy)phosphinyl acetophenone (9)

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF at 0 °C in a round bottomed flask, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was allowed to stir for one hour at 0 °C. After one hr, 2-chloroacetophenone (0.974 mL, 12.6 mmol) was added to the stirring solution via syringe. This solution was allowed to stir for 30 minutes. After this time, the reaction

was quenched using a saturated ammonium chloride solution. The organic portions were extracted using diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL) and saturated sodium chloride (1 x 20 mL). The resultant solution was dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and subsequent use of a vacuum pump. The desired compound was not observed by NMR analysis.

Attempted synthesis of bis (2,2,2-trifluroethoxy)phosphinyl butanone (10)

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF at 0 °C in a round bottomed flask, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was allowed to stir for one hour at 0 °C. After one hour, 3-chloro-2-butanone (0.781 mL, 12.6 mmol) was added to the stirring solution via syringe. This solution was allowed to stir for 30 minutes. After this time, the reaction was quenched using a saturated ammonium chloride solution. The organic portions were extracted using diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 ml) and saturated sodium chloride (1 x 20 mL). The resultant solution was dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and subsequent use of a vacuum pump. The desired compound was not formed by NMR or TLC analysis.

Attempted synthesis of trimethyl silyl [bis (2,2,2-trifluroethoxy)phosphinyl] acetate (11)

To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous THF at 0 °C in a round bottomed flask, bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol) was added. This solution was allowed to stir for one hour at 0 °C. After one hr, trimethyl silyl bromoacetate (2.94 mL, 12.6 mmol) was added to the stirring solution via syringe. This solution was allowed to stir for 30 minutes. After this time, the reaction was quenched using a saturated ammonium chloride solution. The organic portions were extracted using diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL) and saturated sodium chloride (1 x 20 mL). The resultant solution was dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and subsequent use of a vacuum pump. The desired compound was not formed by NMR.

Attempted synthesis of α-[bis(2,2,2-trifluoroethoxy)phosphinyl]-γ-butyrolactone (12)

Procedure I. To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous DMF (23 mL) at 25 °C was added bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol). This solution was stirred for one hour at room temperature. After one hour, the solution was cooled down to 0 °C over fifteen minutes followed by the dropwise addition of α-bromo-γ-butyrolactone (0.583 mL, 6.33 mmol) over twenty minutes by syringe. After the addition was complete, the reaction mixture was allowed to stir for an additional fifteen minutes at 0 °C. The reaction was then quenched with a saturated solution of aqueous ammonium chloride (20 mL). The organics were extracted with diethyl ether (3 x 20 mL). The combined extracts were washed using a saturated solution of sodium chloride (1 x 20 mL) and water (1 x 20 mL). Subsequently, these extracts were

dried using anhydrous magnesium sulfate. The solvent was removed by rotary evaporation. Analysis of the crude reaction mixture by ^{31}P and ^{1}H NMR did not indicate that the desired product was formed.

Procedure II. To a solution of potassium *tert*-butoxide (705 mg, 6.33 mmol) in anhydrous DMF (23 mL) at 25 °C was added bis (2,2,2-trifluroethyl) phosphite (1.00 mL, 6.33 mmol). This solution was stirred for one hour at room temperature followed by the dropwise addition of α-bromo-γ-butyrolactone (0.583 mL, 6.33 mmol) at room temperature over twenty minutes by syringe. After the addition was complete, the reaction mixture was allowed to stir for an additional fifteen minutes. The reaction was then quenched with a saturated solution of aqueous ammonium chloride (20 mL). The organics were extracted using diethyl ether (3 x 20 mL). The combined extracts were washed with a saturated solution of sodium chloride (1 x 20 mL) and water (1 x 20 mL). and dried using anhydrous magnesium sulfate. The solvent was removed by rotary evaporation. Analysis of the crude reaction mixture by ^{31}P and ^{1}H NMR did not indicate that the desired product was formed.

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Appendix

NMR and Mass Spectra

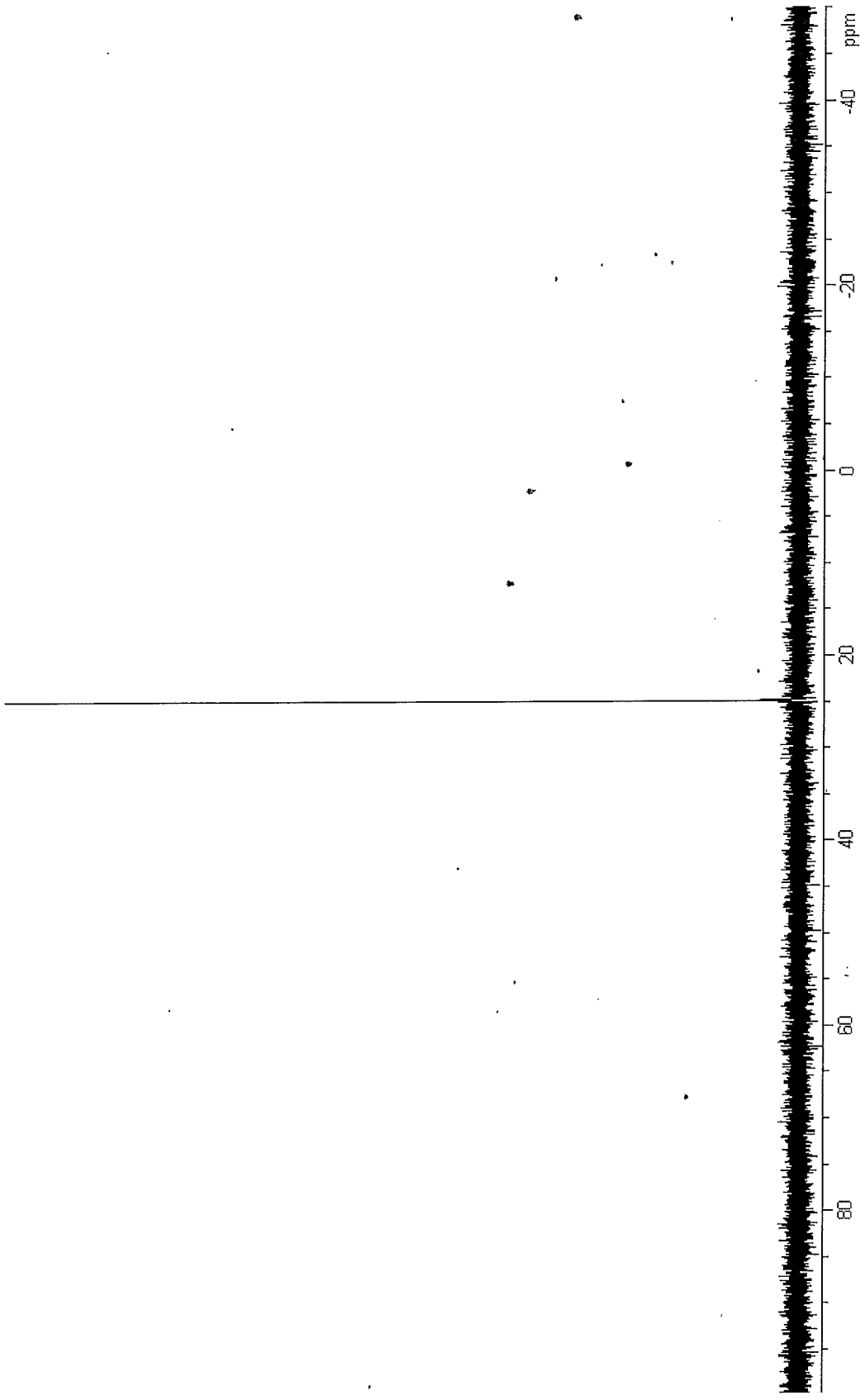

Figure 13: ^{31}PNMR of *tert*-butyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (2)

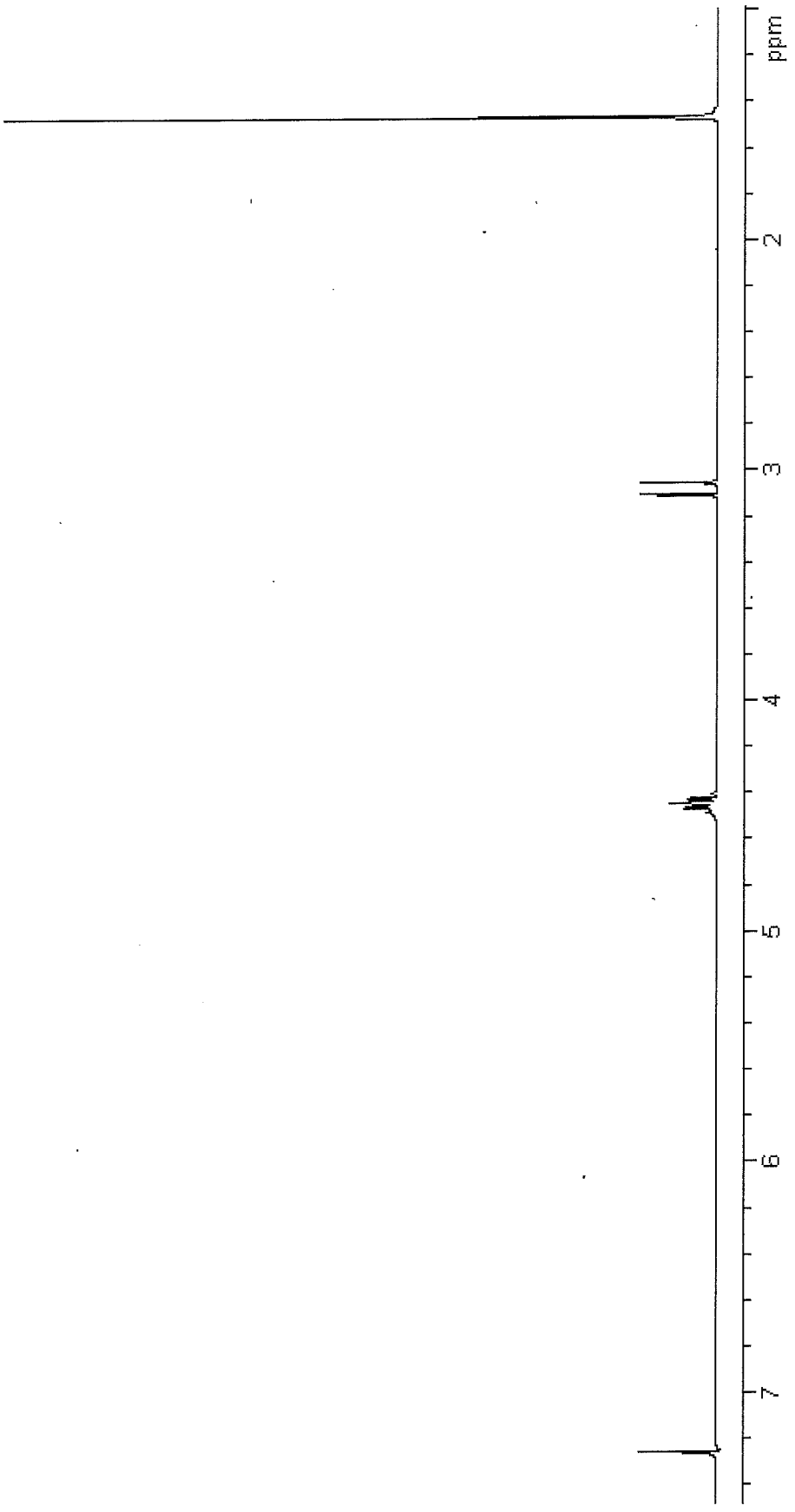

Figure 14: ^{1}HNMR of *tert*-butyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (2)

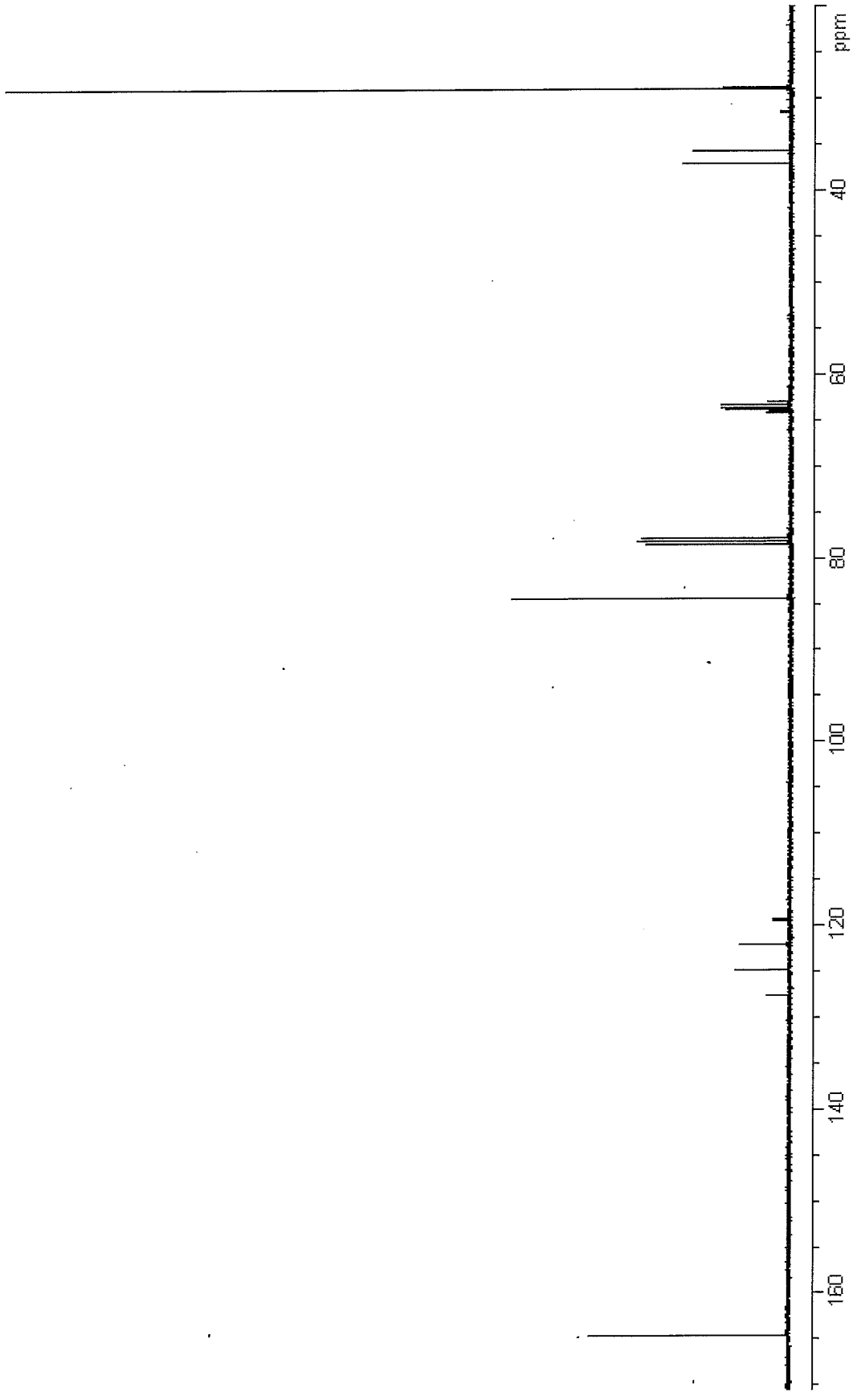

Figure 15: ^{13}CNMR of tert-butyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (2)

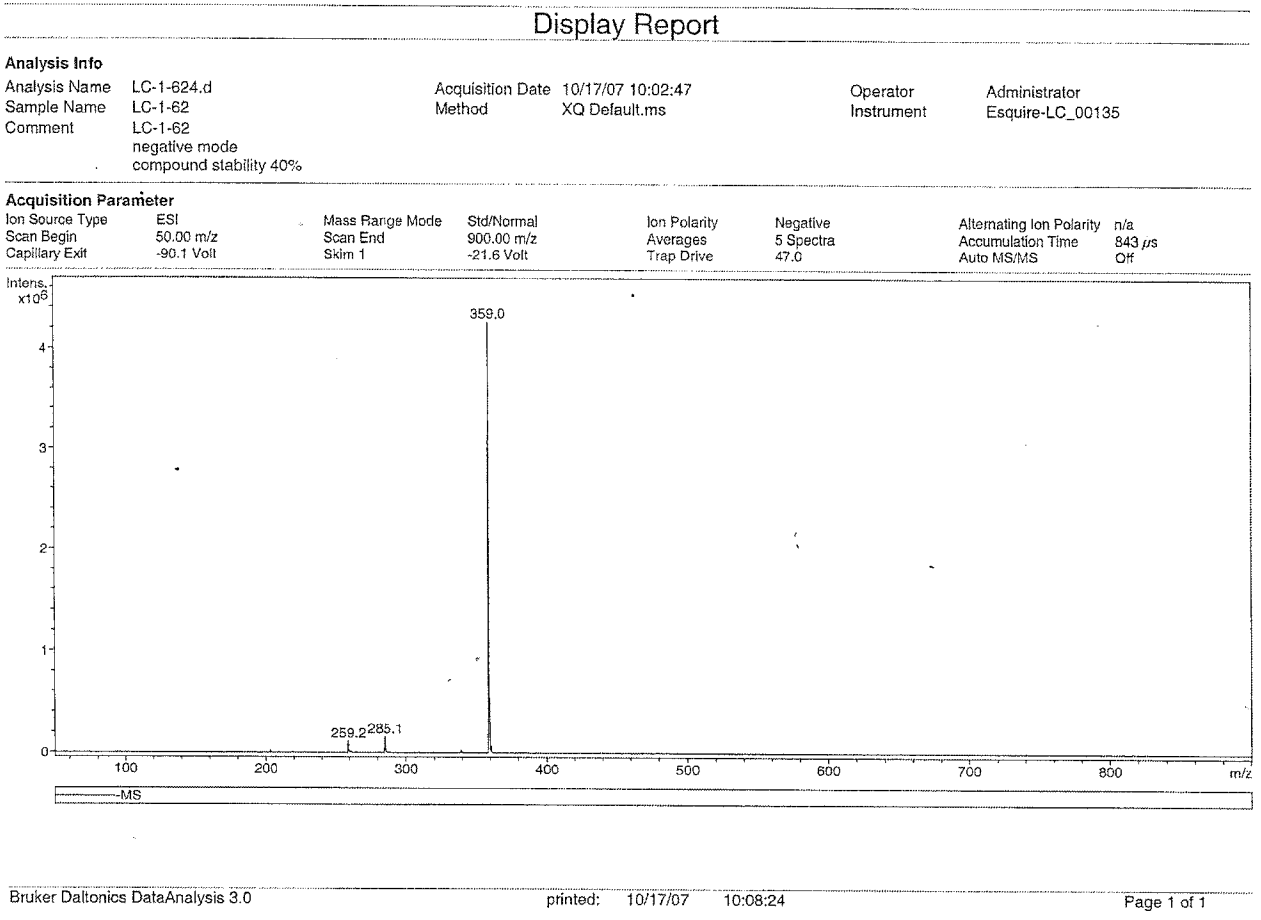

Figure 16: ESI mass spectrum of *tert*-butyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (2)

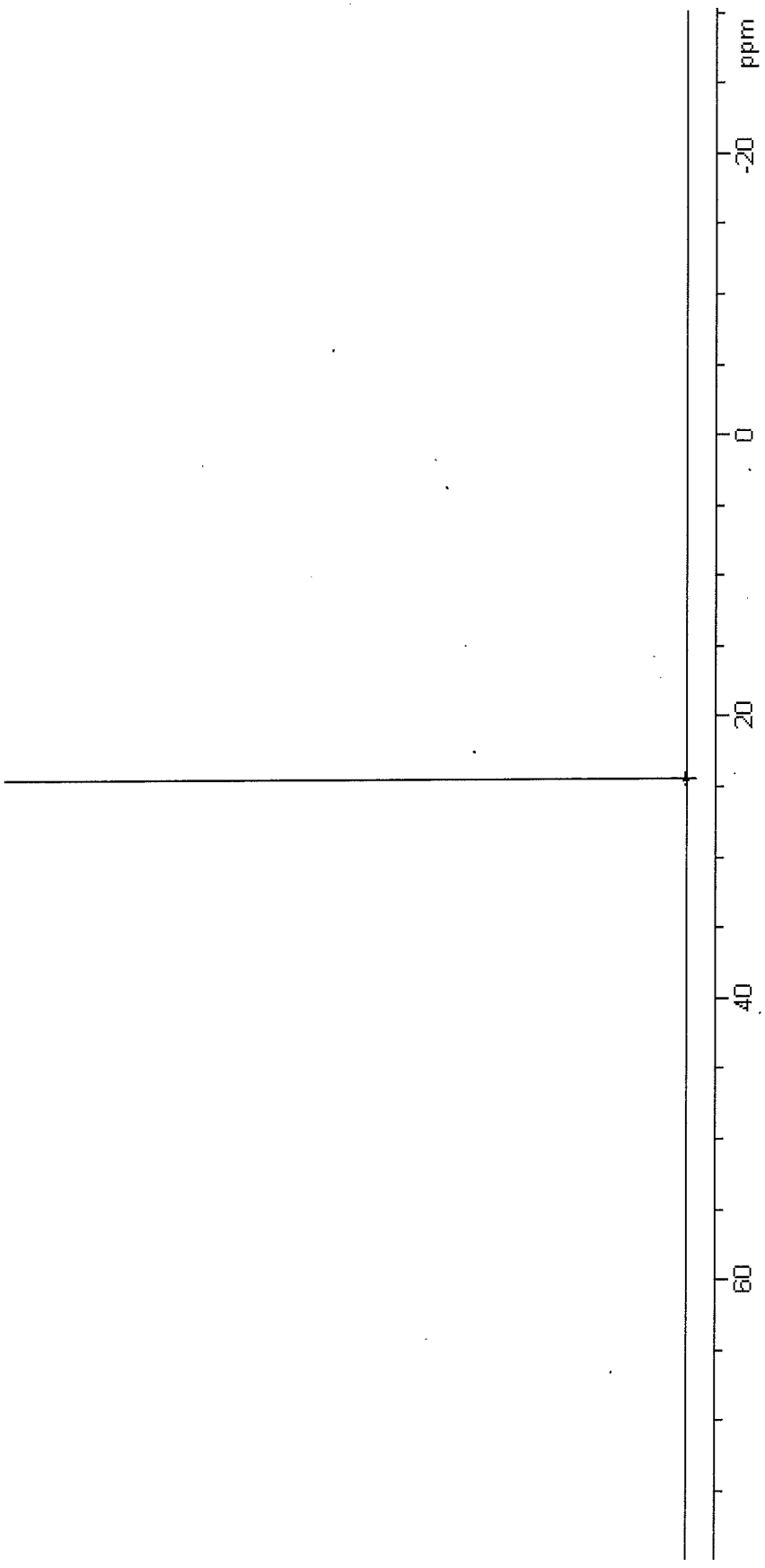

Figure 17: ^{31}PNMR of isopropyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (3)

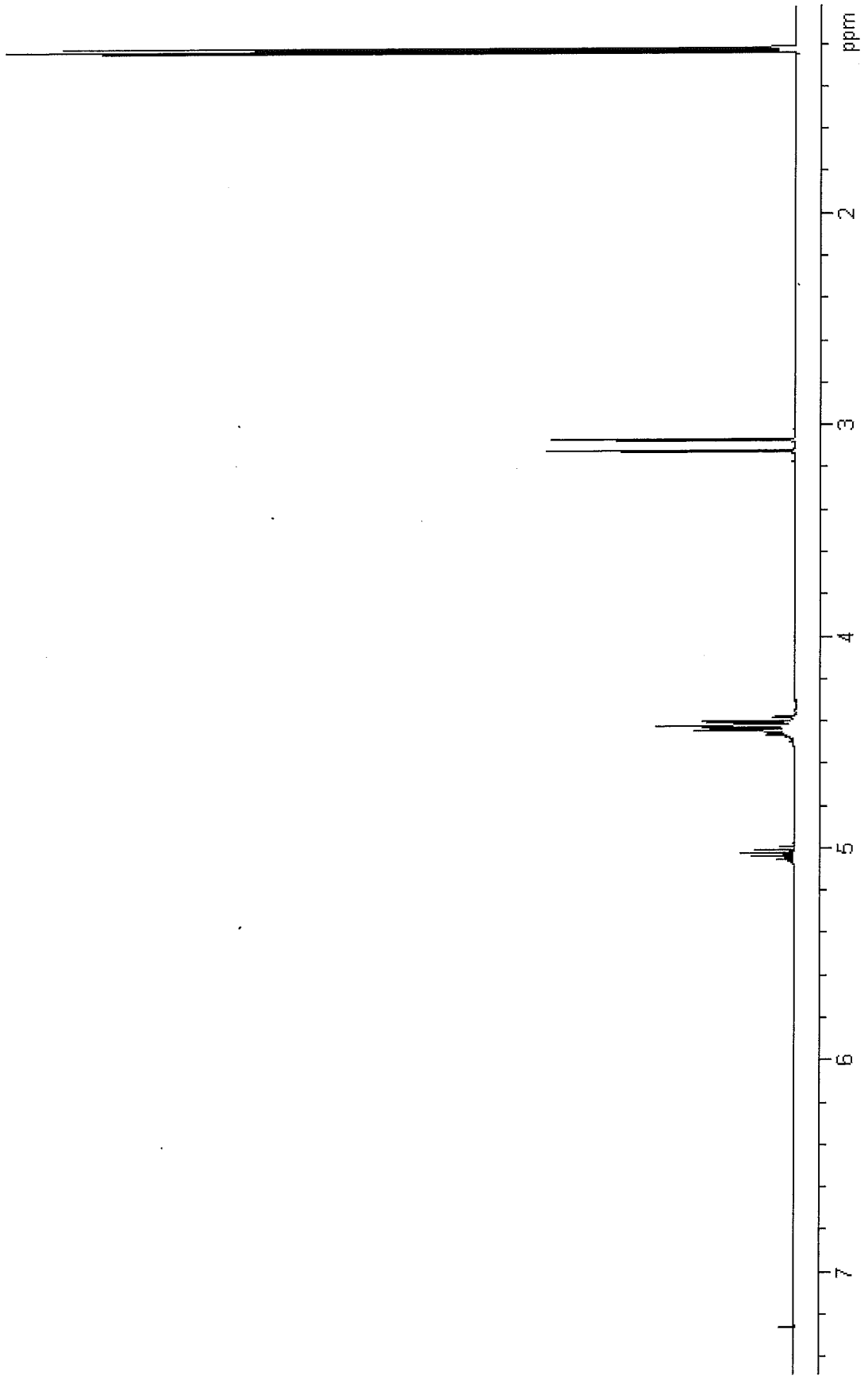

Figure 18: ^{1}HNMR of isopropyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (3)

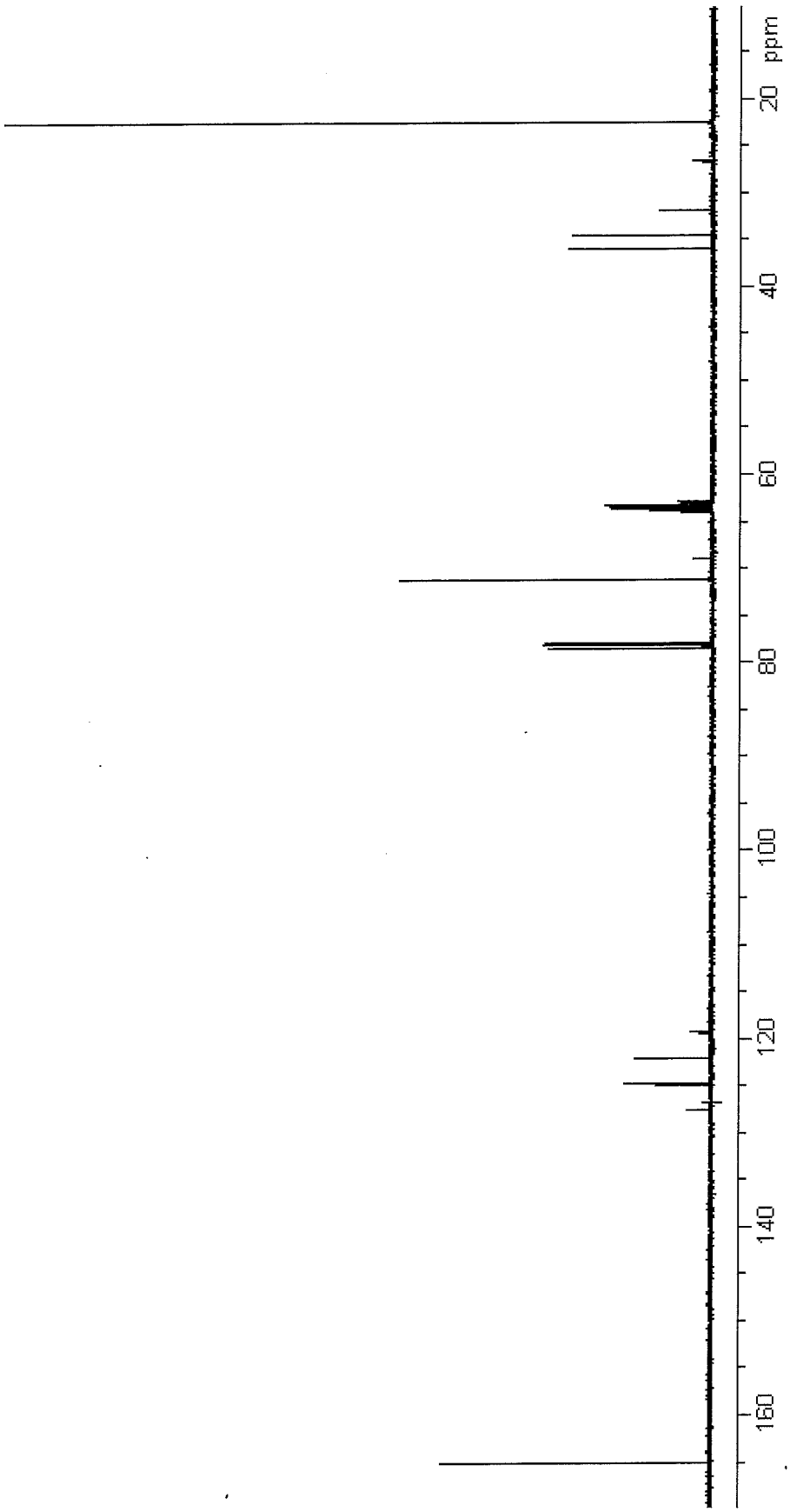

Figure 19: ^{13}CNMR of isopropyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (3)

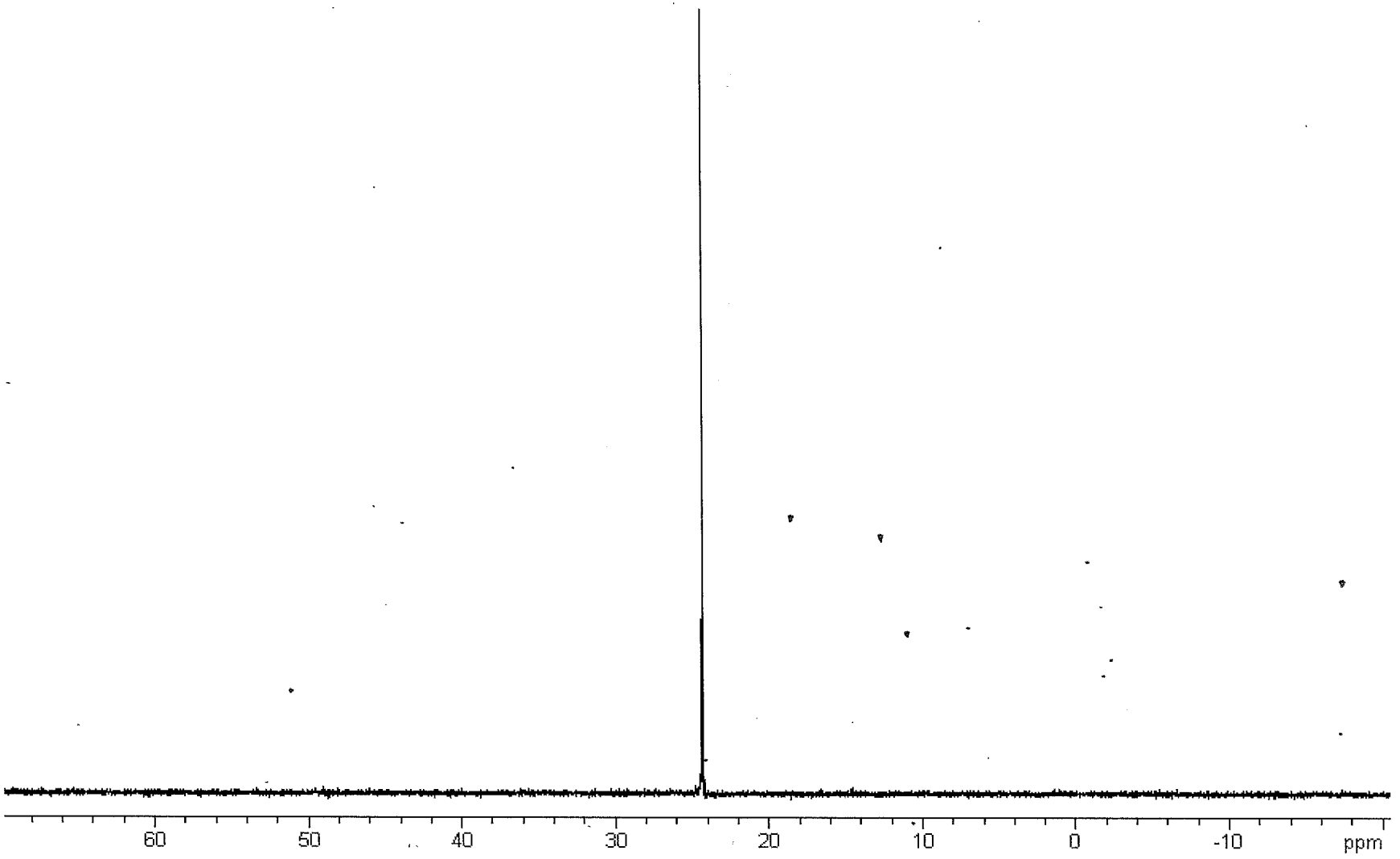

Figure 20: ^{31}PNMR of propyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (4)

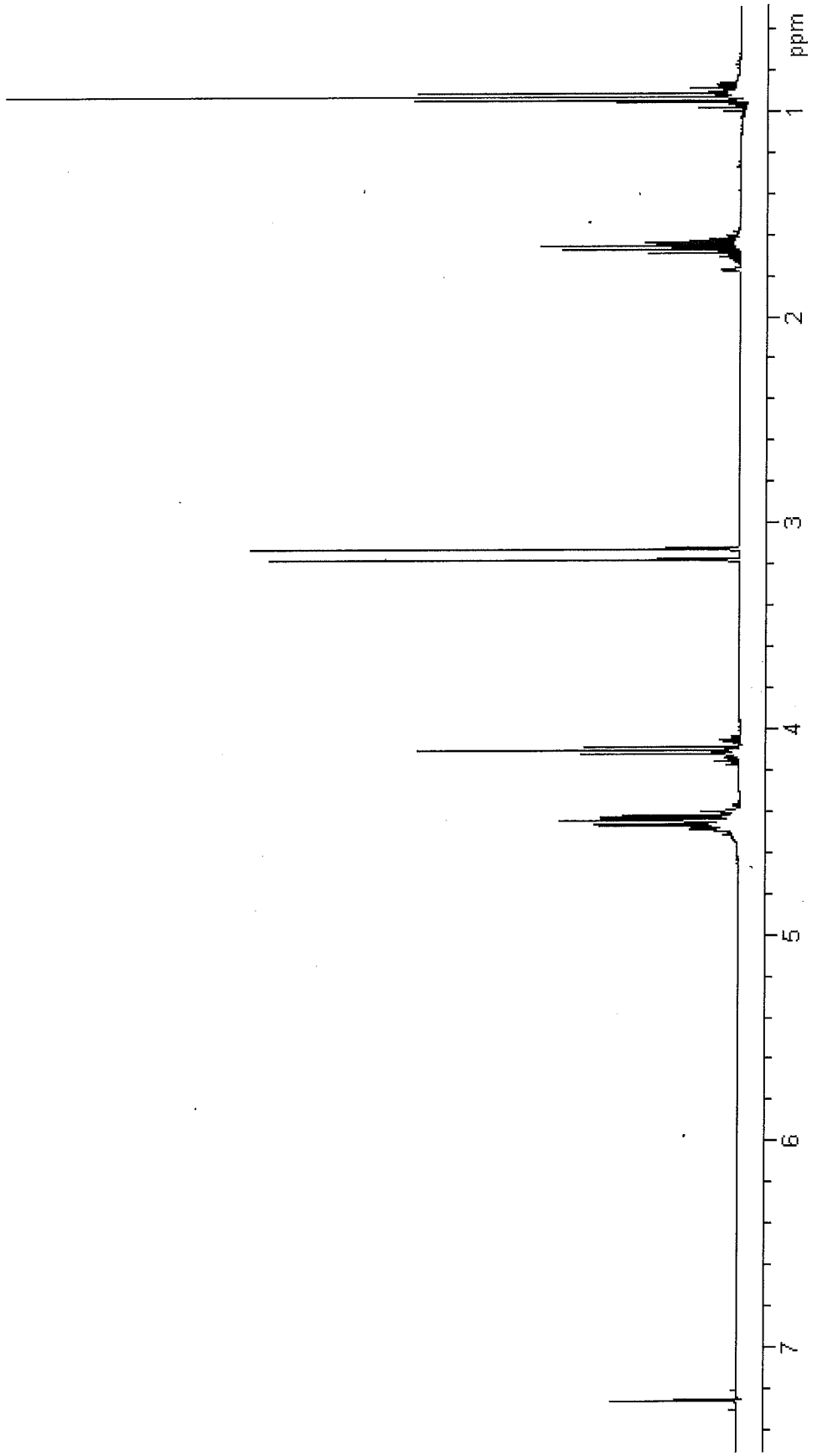

Figure 21: ^{1}HNMR of propyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (4)

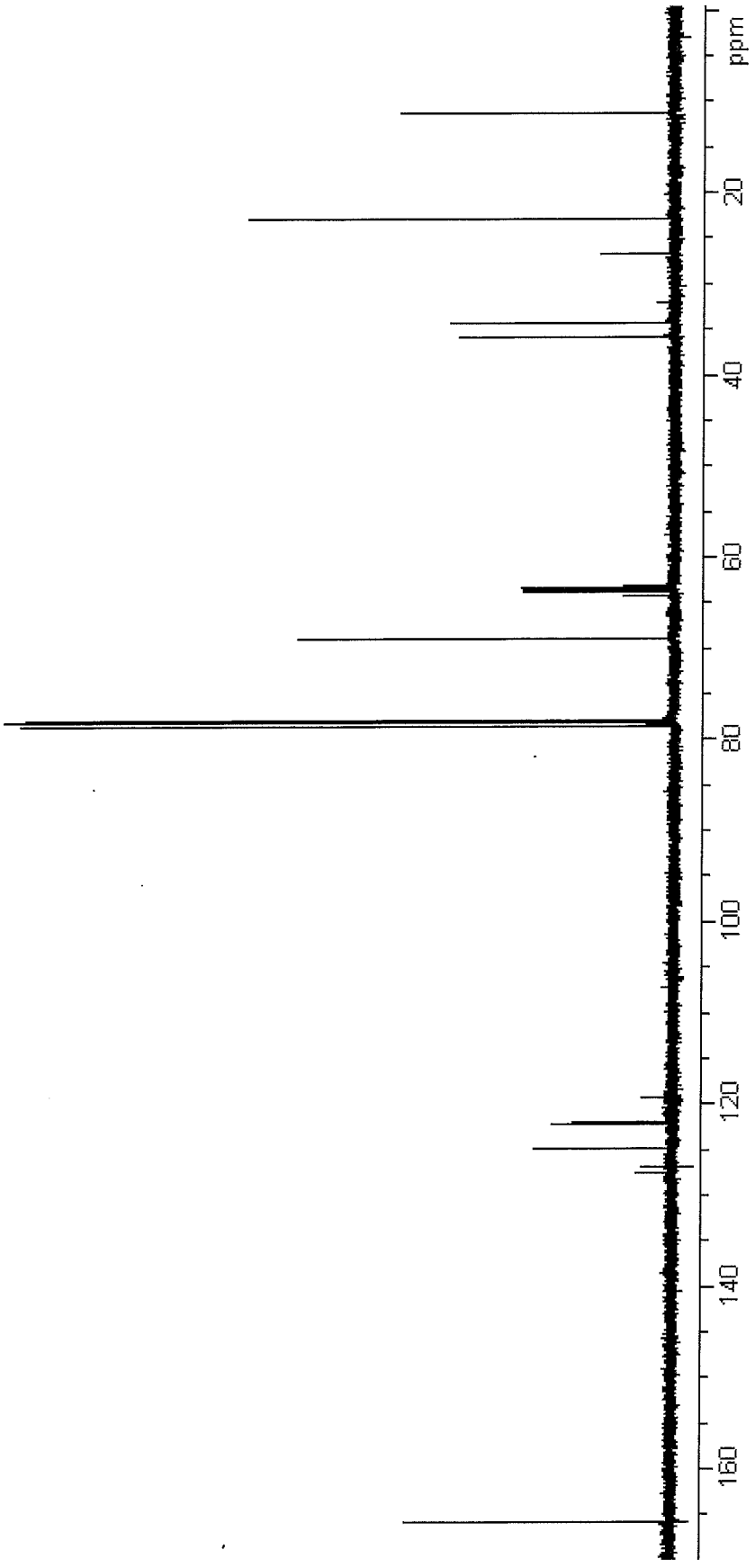

Figure 22: ^{13}CNMR of propyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (4)

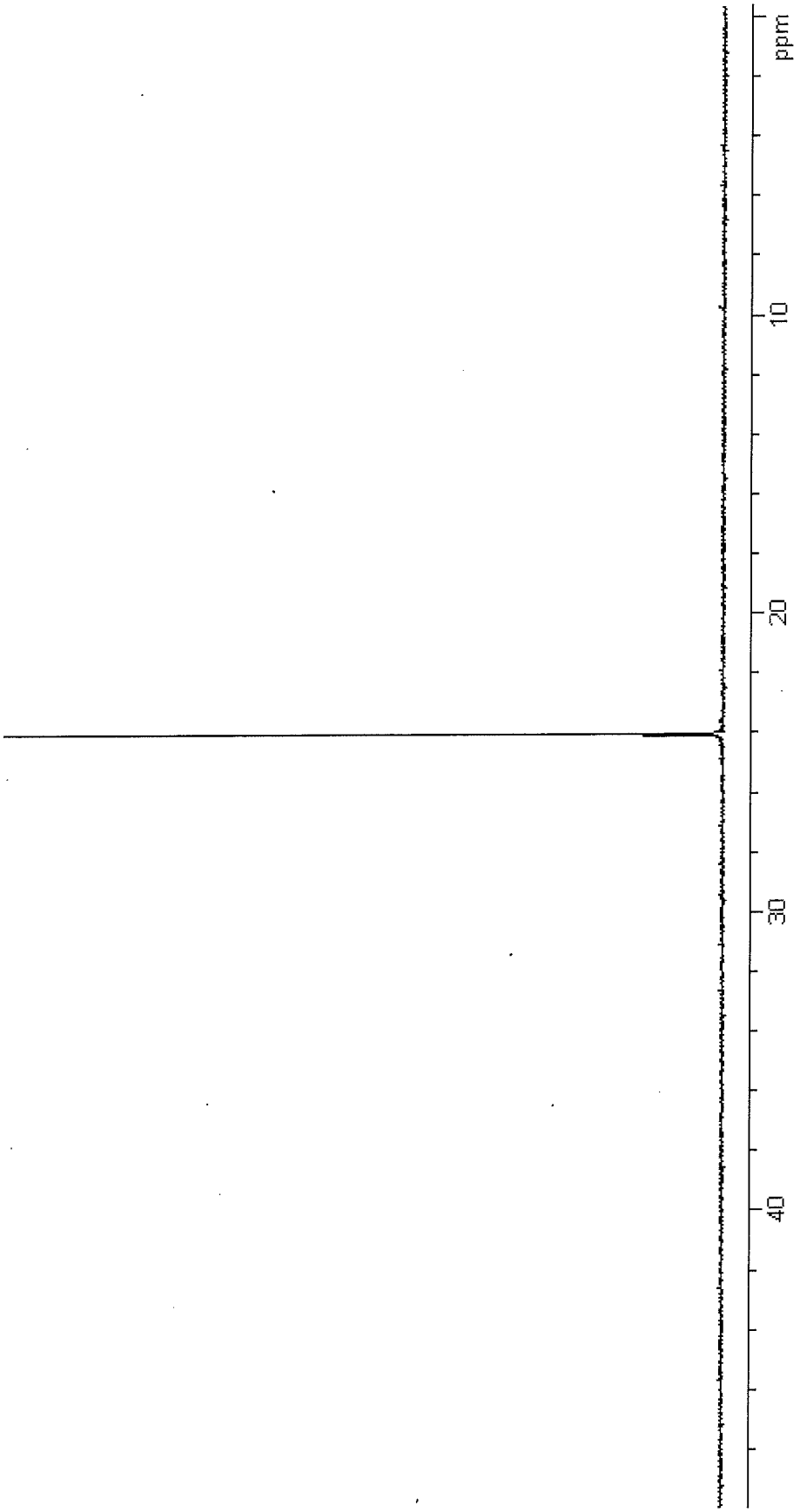

Figure 23: ^{31}PNMR of methyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (5)

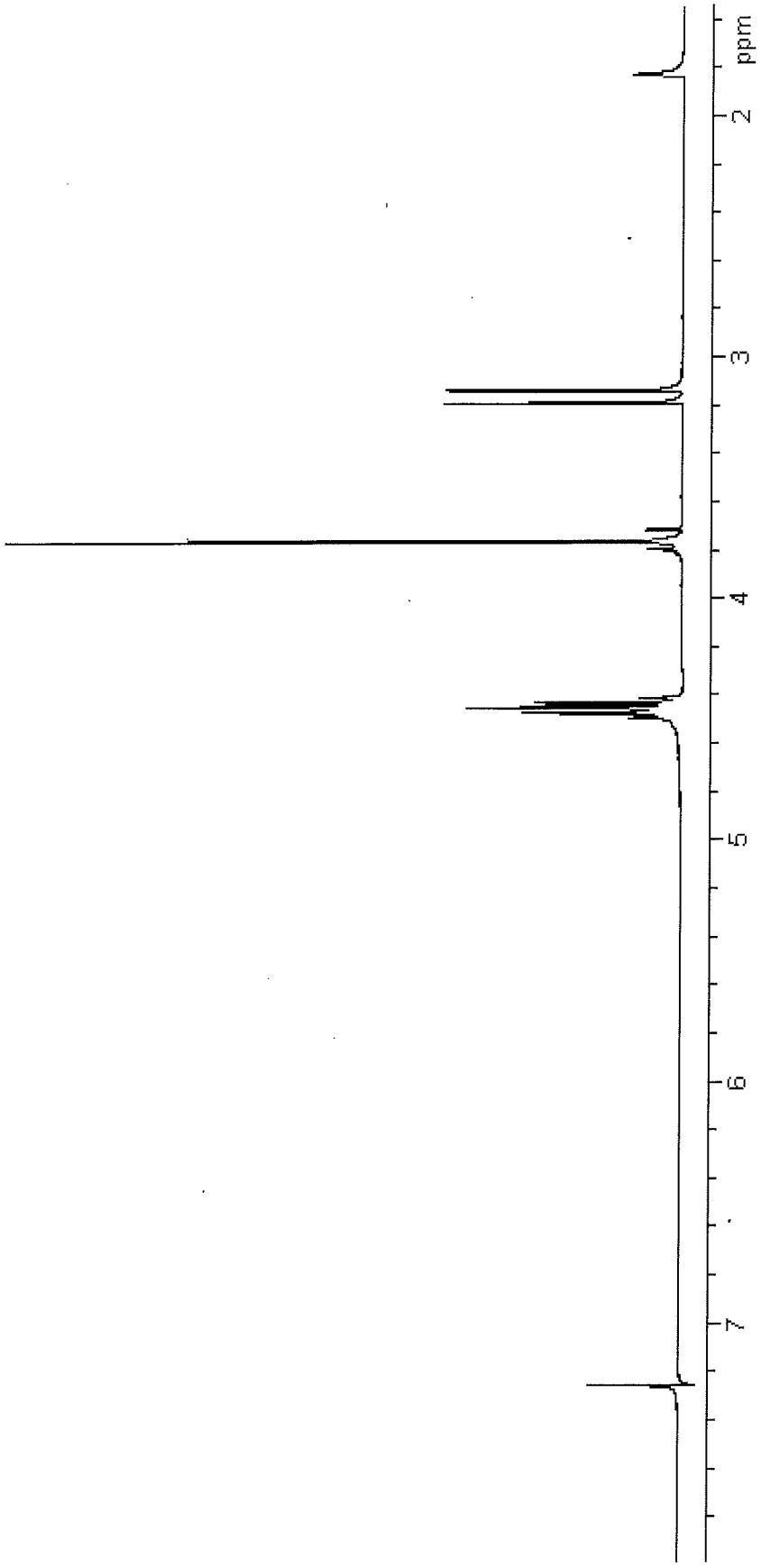

Figure 24: ^{1}HNMR of methyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (5)

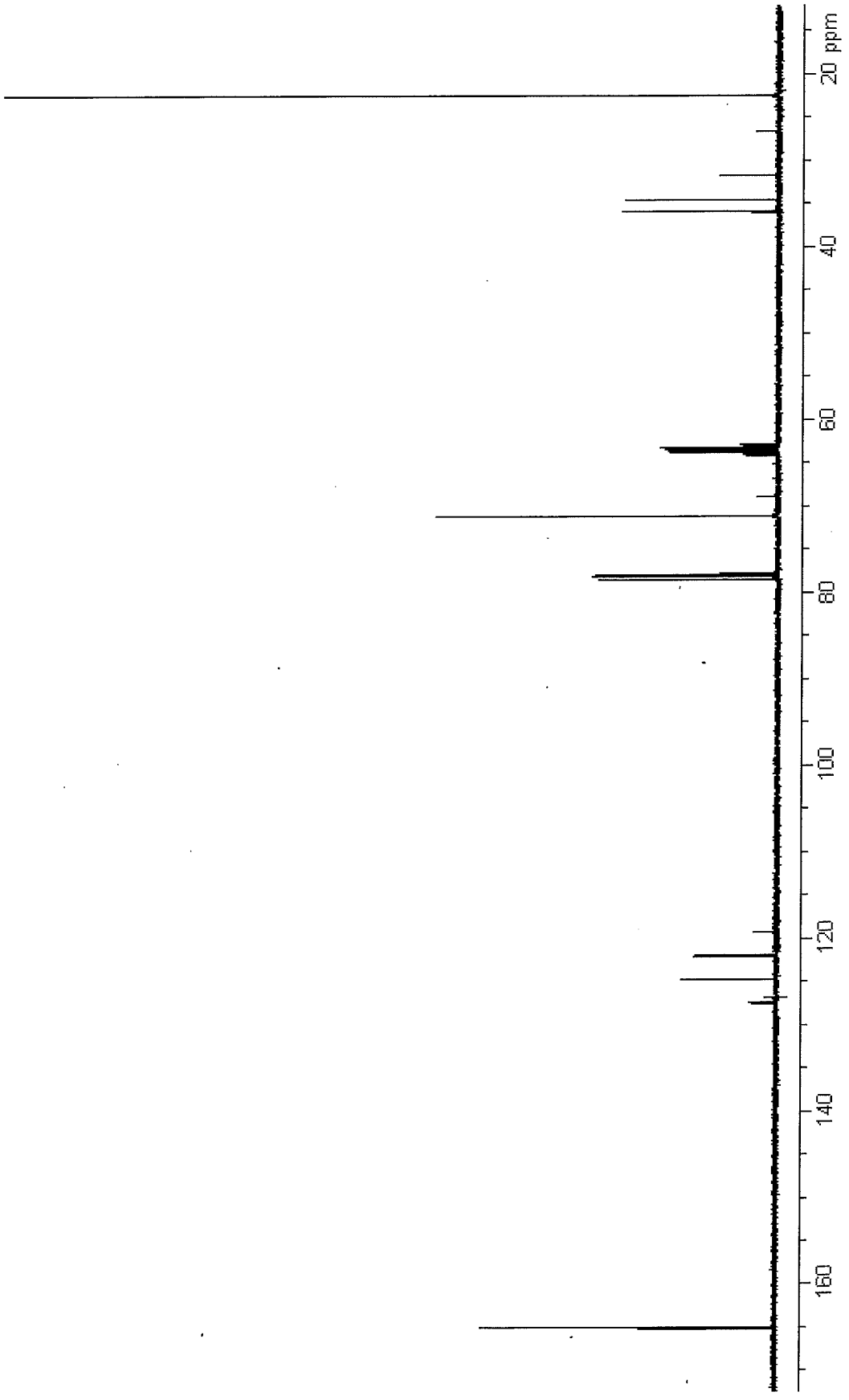

Figure 25: ^{13}CNMR of methyl[bis(2,2,2-trifluroethoxy)phosphinyl]acetate (5)

Display Report

Analysis Info

Analysis Name	LC-2-634.d	Acquisition Date	10/17/07 10:42:11	Operator	Administrator
Sample Name	LC-2-63	Method	XQ Default.ms	Instrument	Esquire-LC_00135
Comment	LC-2-63 negative mode compound stability 30%				

Acquisition Parameter

Ion Source Type	ESI	Mass Range Mode	Std/Normal	Ion Polarity	Negative	Alternating Ion Polarity	n/a
Scan Begin	50.00 m/z	Scan End	900.00 m/z	Averages	5 Spectra	Accumulation Time	3098 µs
Capillary Exit	-84.3 Volt	Skim 1	-16.9 Volt	Trap Drive	45.3	Auto MS/MS	Off

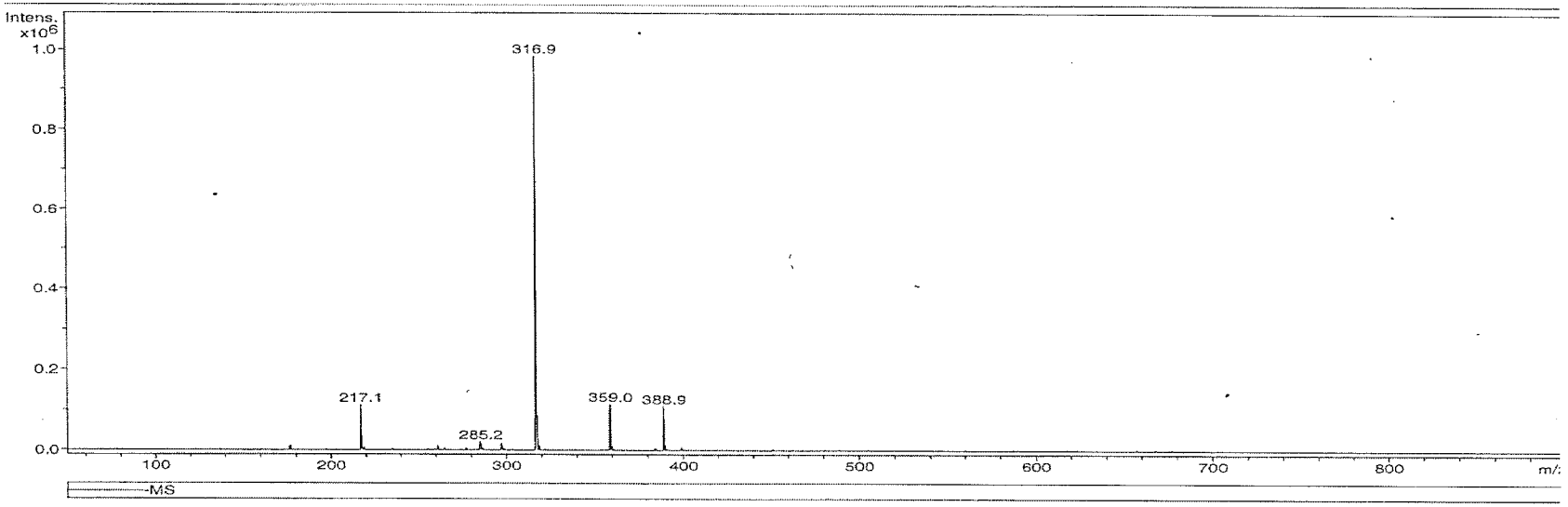

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Figure 26: ESI mass spectrum of methyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (5)

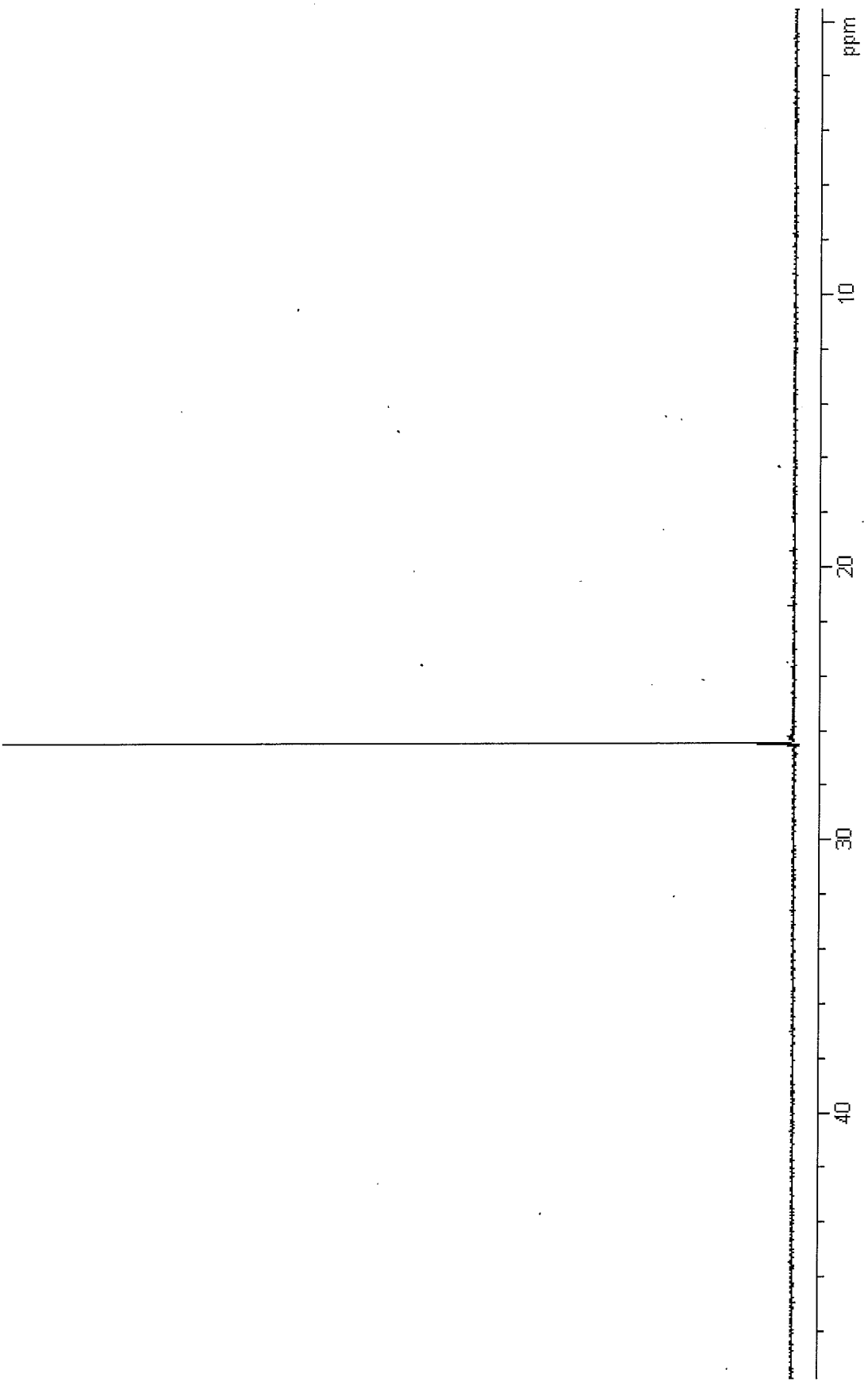

Figure 27: ^{31}PNMR of bis(2,2,2-trifluoroethoxy)phosphinyl pinacolone (6)

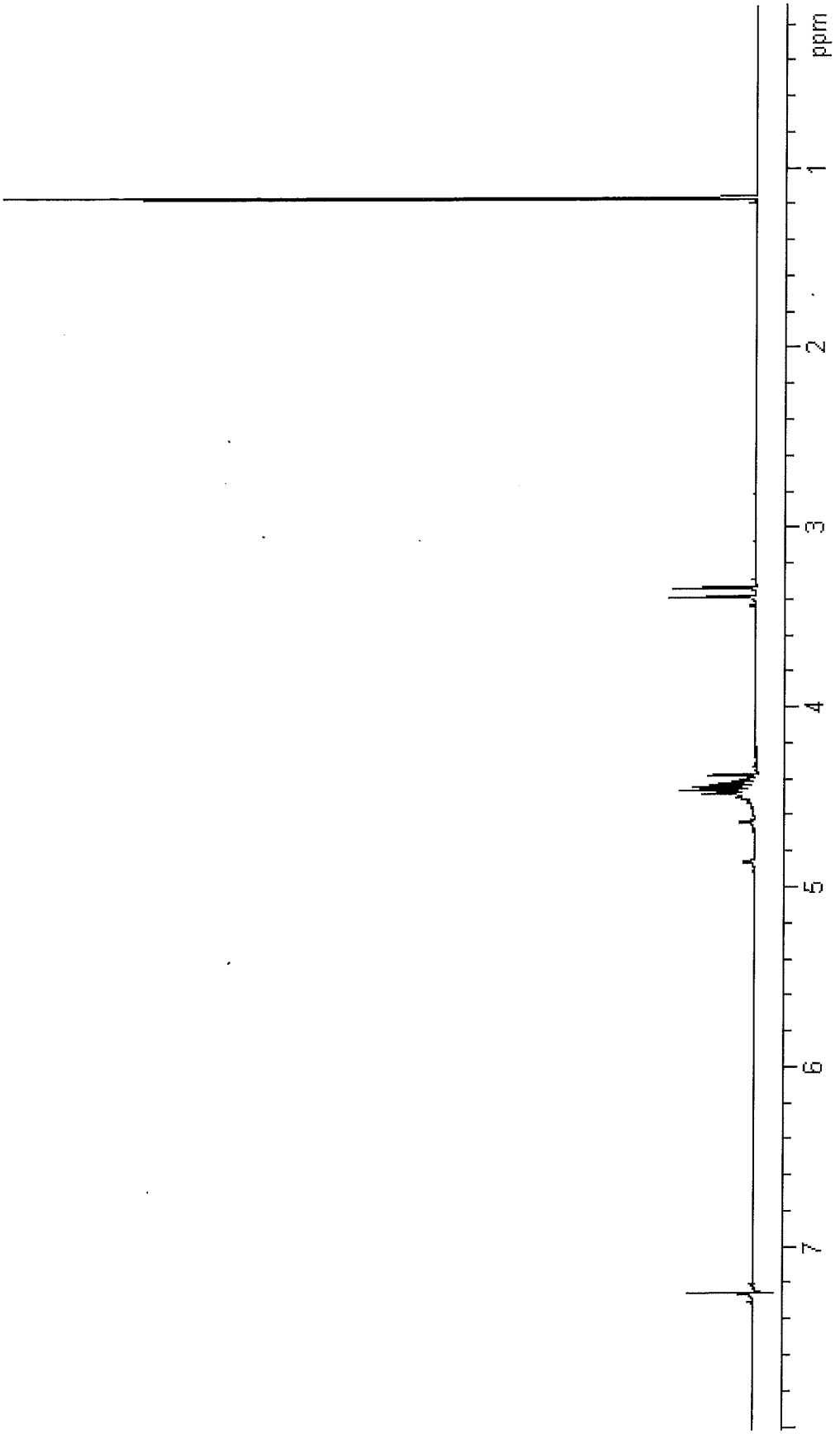

Figure 28: ^{1}HNMR of bis(2,2,2-trifluoroethoxy)phosphinyl pinacolone (6)

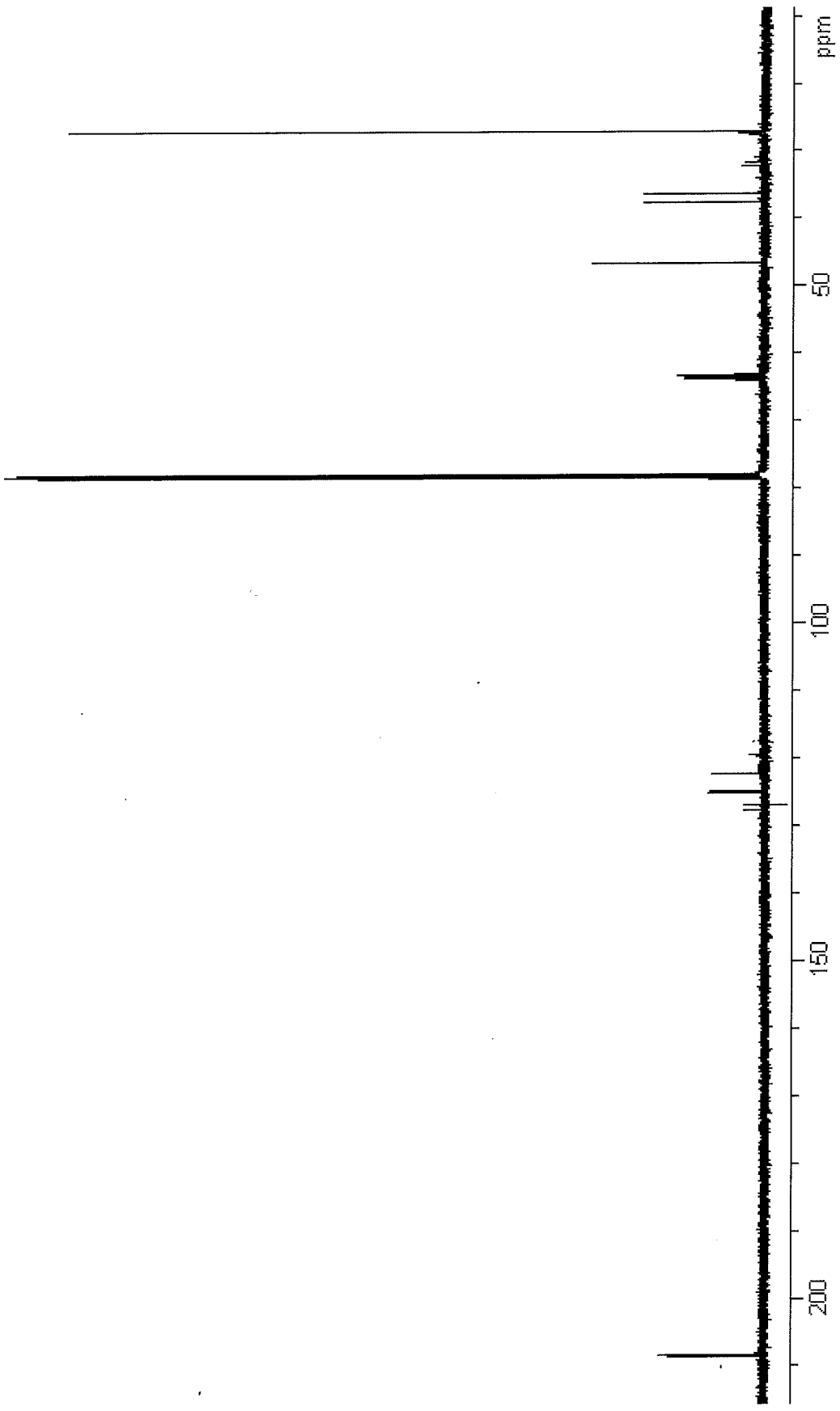

Figure 29: ^{13}CNMR of bis(2,2,2-trifluoroethoxy)phosphinyl pinacolone (6)

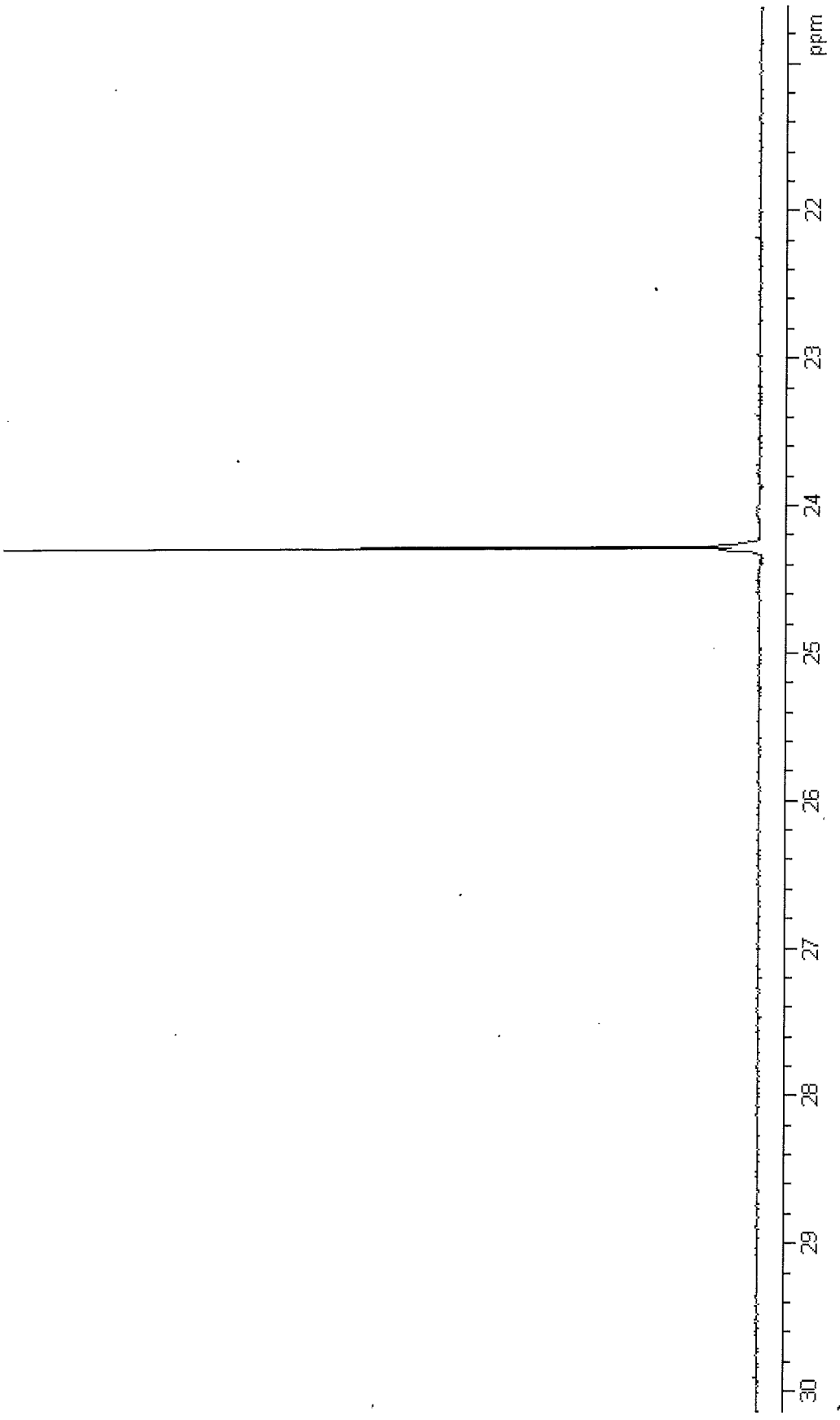

Figure 30: ^{31}PNMR of ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (1)

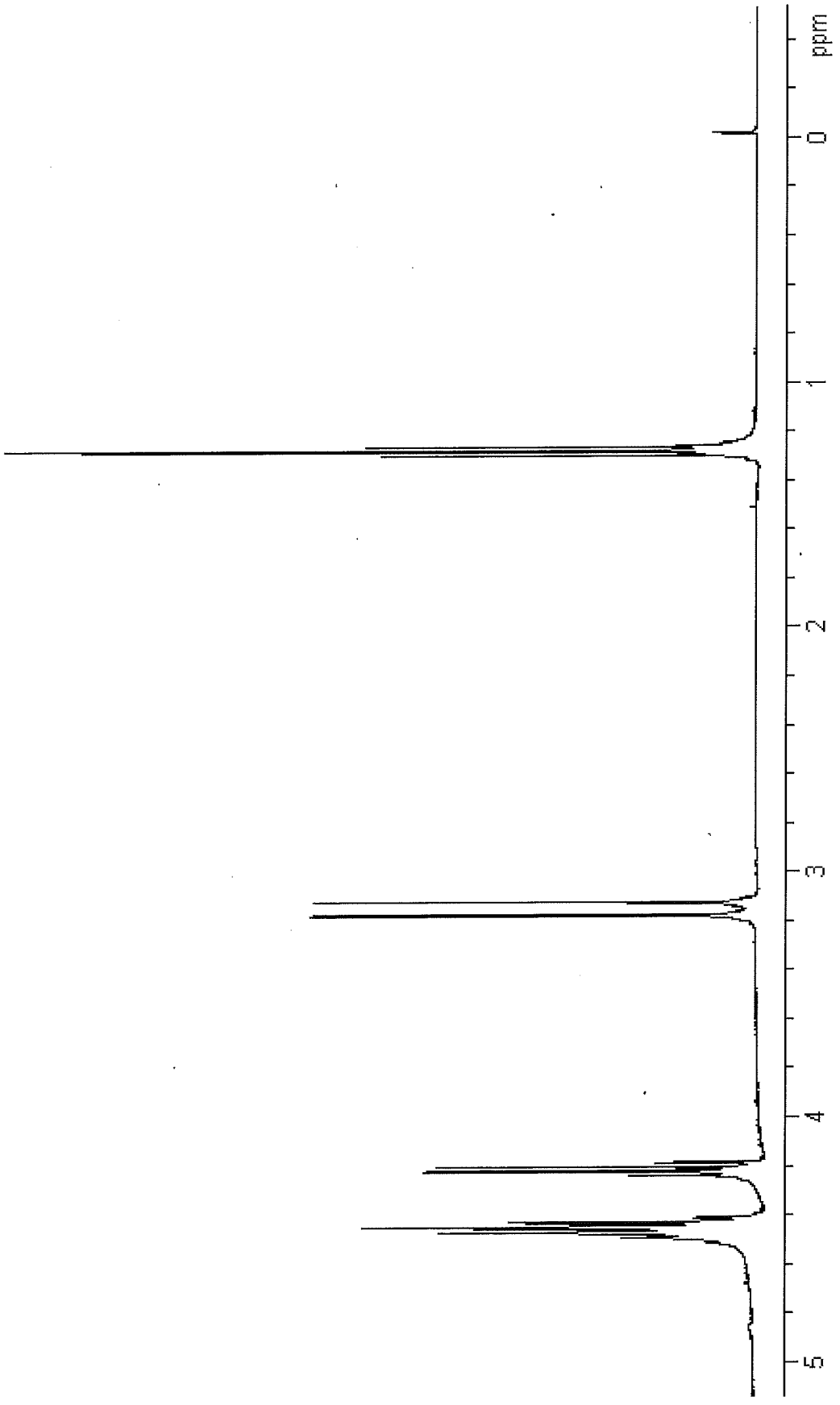

Figure 31: ^{1}HNMR of ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (1)

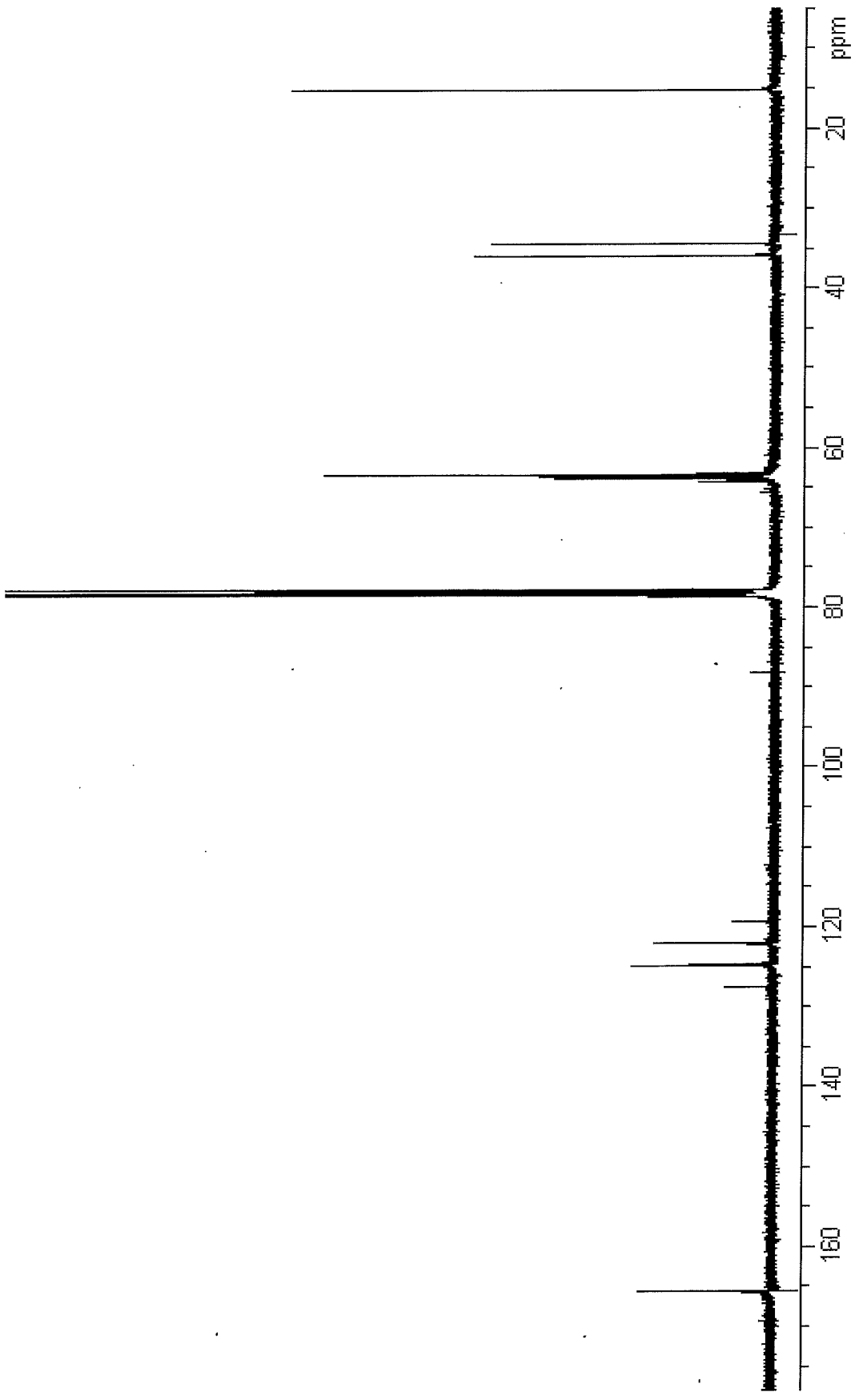

Figure 32: ^{13}CNMR of ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (1)