# Synthesis of Bis(2,2,2-trifluoroethyl) Phosphonates

A New Method

for the

Synthesis

of

Phosphonates

by

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Synthesis of

Bis(2,2,2-trifluoroethyl) Phosphonates

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## Abstract

The Michaelis-Becker reaction was extended to the synthesis of bis(2,2,2-trifluoroethyl) phosphonates. Reaction of the anion of bis(2,2,2-trifluoroethyl) phosphite with a series of α-halo esters produced the corresponding phosphonates in good to moderate yield.

## Acknowledgements

I would like to thank Dr. Jackson for his generous help and guidance that he has provided during this research project. I would also like to thank my committee members, Dr. Norris and Dr. Smiley, for their time and effort in revising my thesis. Lastly, I would like to thank my parents for their support and understanding along with all of my fellow graduate students.

## Table of Contents

## List of Tables

## List of Figures

## List of Abbreviations

| Abbreviation | Description |
|---|---|
| $^{13}C$ | carbon-13 |
| DMF | *N,N*-dimethylformamide |
| g | gram |
| GC | gas chromatograph |
| $^{1}H$ | hydrogen-1 |
| HMPA | Hexamethylphosphoramide |
| Hz | Hertz |
| *J* | coupling constant (in Hz) |
| NaH | sodium hydride |
| NMR | nuclear magnetic resonance |
| $^{31}P$ | phorosphorus-31 |
| ppm | parts per million |
| THF | tetrahydrofuran |

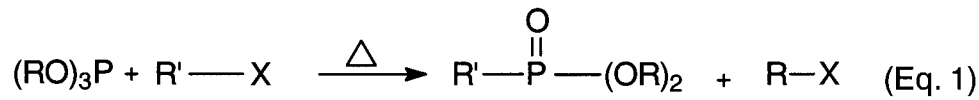
# Chapter 1: Introduction

In the past several years, many syntheses and uses of phosphonic acids and their derivatives have been studied. They have been used in organic chemistry in the synthetic preparation of carbon-carbon double bonds.[1,2] Additionally, these compounds are also used in the preparation of catalytic antibodies for a variety of reactions.[1]

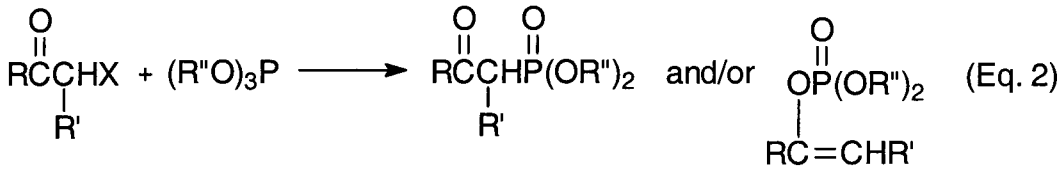
Phosphonates are best known for their use in the Horner-Wadsworth-Emmons (HWE) condensation.[3] They are typically used to synthesize α, β-unsaturated carbonyl compounds *via* condensation of an aldehyde or ketone with a phosphonyl stabilized anion. Phosphonates have recently drawn interest in the preparation of chiral compounds, which has lead to the development of nonracemic phosphonates. In addition, phosphonates can be used in the preparation of nonconjugated olefins and cyclopropanes.[1]

## Synthesis of Phosphonates

Phosphonates can be synthesized several different ways. The reaction of dialkyl phosphite salts with alkyl halides was discovered by Michaelis and Becker. This reaction was limited by low yields of product. In order to increase yields, a better synthetic process was developed. One of the most commonly used methods is the Arbuzov reaction.[3] The general form of the Arbuzov reaction is the treatment of an alkyl halide with a trialkyl phosphite yielding a dialkylphosphonate (Eq 1).



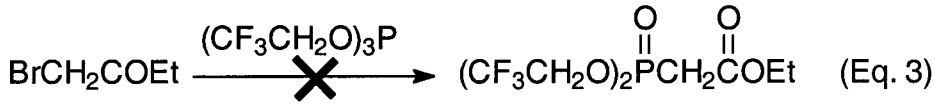
In this reaction the R group can be an alkyl group, R' can be an alkyl or acyl group and the X group can be chlorine, bromine, or iodine.[3] The Arbuzov reaction is also used to prepare β-keto phosphonates. This reaction (Eq. 2) involves the addition of a trialkylphosphite to an α–halo ketone. The best results were obtained by using a nucleophilic phosphite and an α–iodo ketone. The reaction of α-chloro or α-bromo ketones with the trialkyl phosphites often produces isomeric vinyl phosphates through the Perkow reaction.[1]



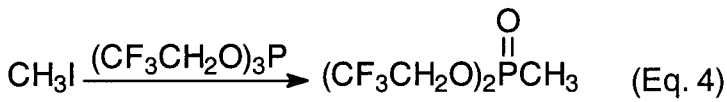

Arbuzov product

Perkow product

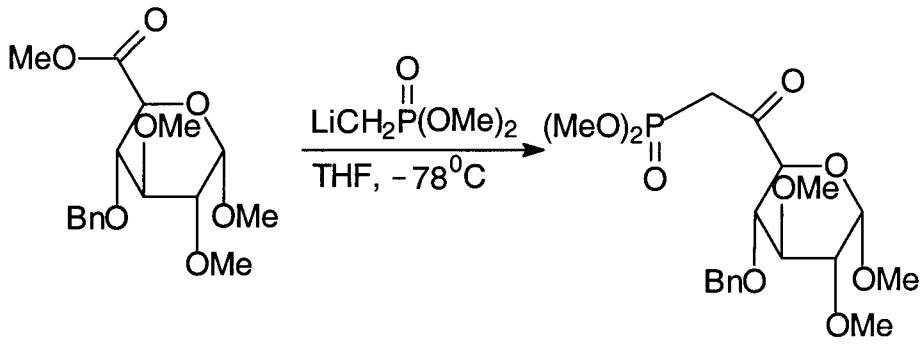
The Arbuzov Reaction also generally fails in the synthesis of bis(2,2,2-trifluoroethyl) phosphonates (Eq. 3). This is due mainly to the weakly nucleophilic character of tris(2,2,2-trifluoroethyl) phosphite as shown in equation 3.[4]




Indeed, tris(2,2,2-trifluoroethyl) phosphite undergoes reaction with methyl iodide only when heated in a sealed tube at 170 °C (Eq. 4).[5]



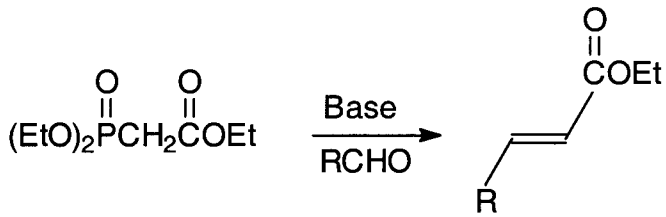
Another common synthetic method for the preparation of phosphonates is the acylation of alkylphosphonate anions [6] (Eq. 5). The acylation is limited by availability of the corresponding alkyl phosphonate starting materials.




(Eq. 5)

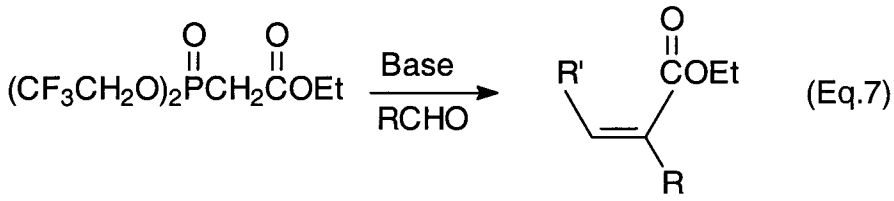
**Reactions of Phosphonates**

In the HWE reaction, treatment of a phosphonyl stabilized anion with an aldehyde generally produces high yields of (*E*)-α,β-unsaturated carbonyl compounds (Eq. 6).[7,8]




(Eq. 6)

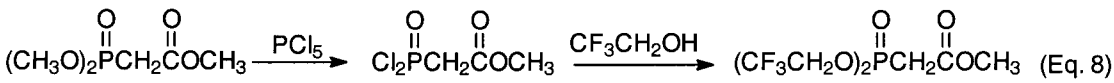
Still has shown that changing the phosphonate ester to the electron-withdrawing 2,2,2-trifluoroethyl group affords high yields of the (Z) α,β-unsaturated carbonyl compounds (Eq. 7)[8] in the HWE condensation. The best yields were obtained by Still using a base of $KN(TMS)_2$ in 18-crown-6/THF while the R group was a methyl or hydrogen.



(Eq.7)

**Synthesis of bis(2,2,2-trifluoroethyl) phosphonates**

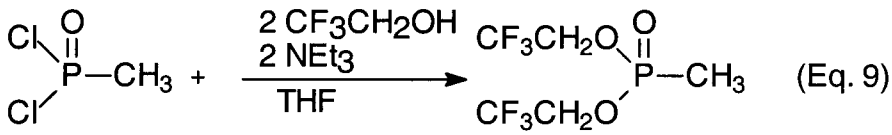
The new phosphonate shown used in equation 8 was not synthesized by the Arbuzov reaction. Still prepared the new phosphonate by treating the α phosphono ester with phosporus pentachloride to form a phosphoric dichloride. In turn, the phosphoric dichloride was treated with trifluoroethanol as shown in equation 8, which formed the phosphonate in 40% yield overall.[8]



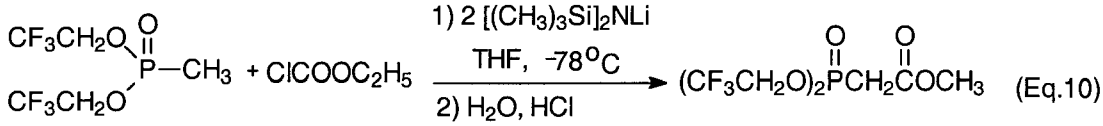
(Eq. 8)

Unfortunately, the Still method requires harsh reaction conditions, which create limitations and the method is useful only in the synthesis of a small number of phosphonates.

A general method for a one-pot synthesis of bis(2,2,2-trifluoroethyl) methylphosphonate was later developed by Savignac (Eq. 9).[6] Methylphosphonic dichloride was reacted with trifluoroethanol in a mixture of triethylamine and THF. This produced bis(2,2,2-trifluoroethyl) methylphosphonate, which was then reacted with ethyl chloroformate to produce bis(2,2,2-trifluoroethyl) (carboethoxymethyl) phosphonate (Eq. 10).[9, 10]

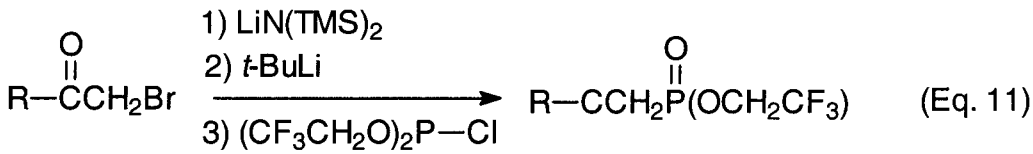



(Eq. 9)




(Eq.10)

Wiemer also synthesized bis(2,2,2-trifluoroethyl) phosphonates from α-bromo ketones as shown in equation 11. The best yields were obtained when the R group was either Ph (32% yield) or *t*-Bu (56% yield). However, the use of the reaction in the synthesis of more functionalized compounds is limited by the use of *tert*-butyllithium.[11]

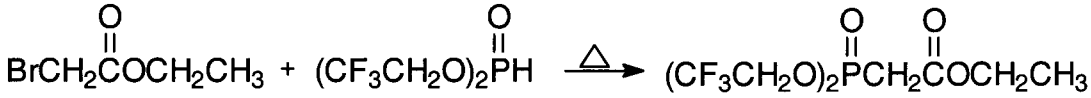



(Eq. 11)

Currently, there are a limited number of trifluoroethyl phosphonate compounds available. Approaches to new synthetic methods should be explored.

## Chapter 2: Results and Discussion

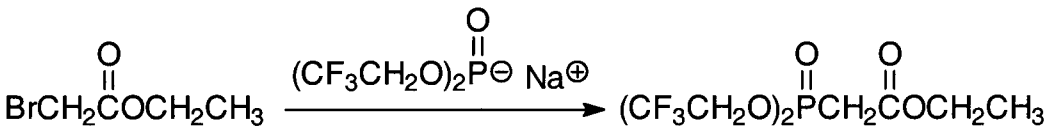
The purpose of this project was to explore the viability of the Michaelis-Becker reaction in the synthesis of bis(2,2,2-trifluoroethyl) phosphonates. This was to be done by treating the anion derived from bis(2,2,2-trifluoroethyl) phosphite with several different α-halo esters to produce bis(2,2,2-trifluoroethyl) phosphonates. The first synthesis involved the reaction of ethyl bromoacetate with the bis(2,2,2-trifluororethyl) phosphite.



**1**

The first synthesis involved heating a neat mixture of bis(2,2,2-trifluoroethyl) phosphite and ethyl bromoacetate. Remarkably, ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (**1**) was formed in about 10 % yield. This result was surprising due to the electron withdrawing ability of the trifluoroethyl groups, which makes the phosphite relatively nonnucleophlic.

Encouraged by this unexpected result, we examined reactions of the more nucleophilic phosphite anion with a series of α-halo esters. In this project, we varied base, temperature, solvent, and concentrations, as well as sequence of addition in order to optimize yields. The first series of reactions were conducted by forming the phosphite anion with sodium hydride in THF.



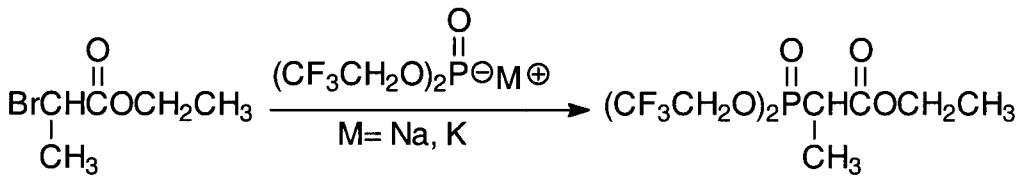
1

The addition time of ethyl bromoacetate also had dramatic consequences upon the reaction along with reaction temperature. If the ethyl bromoacetate was not added immediately, little or no reaction took place. When ethyl bromoacetate was added 30 minutes after the phosphite anion formed, no detectable reaction took place. This was also verified by little or no variation in peaks obtained on gas chromatography and $^{31}P$ NMR. The best time to add the ethyl bromoacetate was immediately after the formation of the phosphite anion. This produced bubbling in the reaction along with a color change from grayish to creamy white. The GC trace also showed a new product peak with a retention time of 4.8 minutes, which was also observed by $^{31}P$ NMR at 23.17 ppm.

The yield of product **1** was greatly dependent upon reaction temperature. The addition of the phosphite to a solution of sodium hydride in THF gave a vigorous reaction at room temperature. Ethyl bromoacetate was immediately added to the solution which was refluxed to produce only 5% of compound **1** (Method C). The reaction was then run at –78 °C (dry ice, acetone) and allowed to warm to room temperature over a 24 hour period, which yielded 49% of compound **1** (Method B, as noted in table 1). The best results were obtained when the reaction was cooled to –42 °C (dry ice, acetonitrile), with immediate addition of ethyl bromoacetate to the phosphite anion (Method A). Compound **1** was produced in 59% yield. It was also noted that over an extended period of time the desired product decreased while the byproducts increased.

**Table 1:** Synthesis of Compound **1**

| Method | Base | Solvent | Temperature | Time of Addition | % Yield |
|---|---|---|---|---|---|
| A | NaH | THF | –42 °C | Immediate | 59 |
| B | NaH | THF | –78 °C | Immediate | 49 |
| C | None | Neat | Reflux | Immediate | 10 |
| D | NaH | THF | Room Temp | Immediate | 5 |




**2**

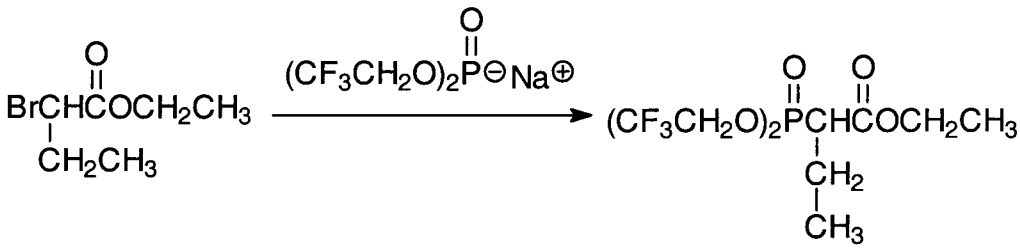
The next compound synthesized was ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]propionate (**2**). The reaction was first attempted under the optimal conditions used in of synthesis of compound **1** (Method A). Bis(2,2,2-trifluoroethyl) phosphite was added immediately to the a solution of sodium hydride and THF at –42 °C, followed by the immediate addition of ethyl 2-bromopropionate. After the additions were made, the reaction was allowed to warm to room temperature over a 24 hour period. The reaction changed from a grayish color to a creamy white color. After purification, compound **2** was produced in 11% yield.

This reaction was also run with potassium *tert*-butoxide as the base in THF at –78 °C (dry ice, acetone) and allowed to warm to room temperature over 24 hours (Method F). This reaction yielded ~ 10% of compound **2** as referred to in Table 2. The synthesis of compound **2** was also attempted in a solvent mixture of with *N, N*-dimethylformamide (DMF) and THF with a base of NaH (Method G). This resulted in a yield of 12% compound **2**.

The optimal yield of phosphonate **2** (34%) was obtained by using hexamethylphosphoramide (HMPA) in the reaction with NaH as base at a temperature of 10 °C (Method E). The reaction was maintained at 10 °C for 4.5 hours to prevent byproducts from forming.

**Table 2:** Synthesis of compound **2**

| Method | Base | Solvent | Temperature | Time of Addition | % Yield |
|---|---|---|---|---|---|
| E | NaH | THF/HMPA | 10 °C | Immediate | 34 |
| F | KOtBu | THF | –78 °C | Immediate | 10 |
| G | NaH | THF/DMF | –78 °C | Immediate | 12 |
| A | NaH | THF | –42 °C | Immediate | 11 |

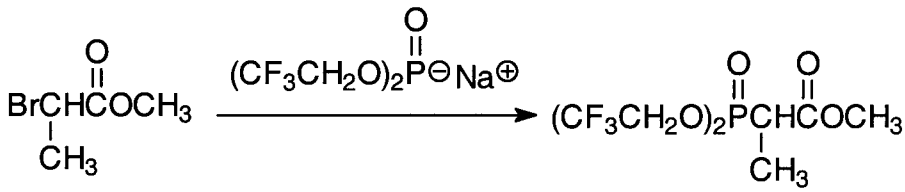


**3**

The optimal synthesis of ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]butyrate (**3**) was obtained in a solvent mixture of THF and HMPA with sodium hydride as the base (Method E). The reaction was run at 10 °C for 9 hours affording 37% of compound **3**. Here, HMPA improved the reactivity of the halo ester with the phosphite anion. The reaction was also run at –42 °C with sodium hydride and THF producing **3** in a yield of 12% (Method A).

**Table 3**: Synthesis of compound **3**

| Method | Base | Solvent | Temperature | Time of Addition | % Yield |
|---|---|---|---|---|---|
| E | NaH | THF/HMPA | 10 °C | Immediate | 34 |
| A | NaH | THF | –42 °C | Immediate | 12 |



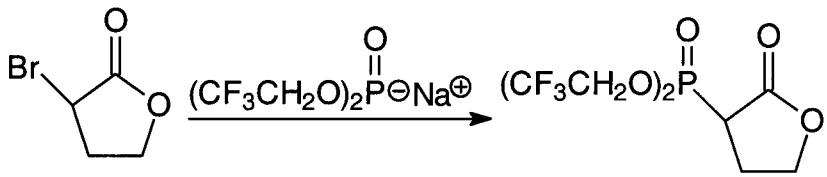
**4**

Methyl [bis(2,2,2-trifluoroethoxy)phosphinyl]propionate (**4**) was formed in 34% isolated yield when methyl 2-bromopropionate was added to a solution of bis(2,2,2-trifluoroethyl) phosphite and sodium hydride in THF at –42 °C (Method A). Lower yields were produced at reaction temperatures of 0 °C and 10 °C as noted in Table 4. The addition of HMPA into the reaction mixture did not give an increase in the yield.

The yields of compounds **3** and **4** did not differ significantly from compound **2**. This may be attributed to the fact that all three compounds are 2° halides. This may hinder the ability of the phosphite anion to displace the halide in a $S_n2$ reaction.

**Table 4**: Synthesis of compound **4**

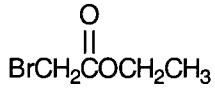
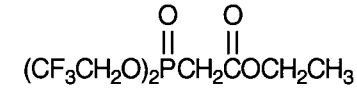
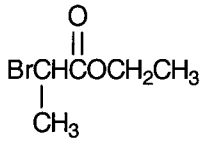
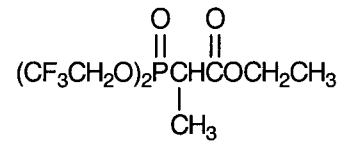
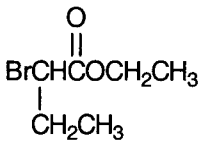
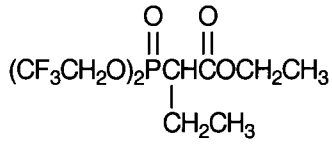
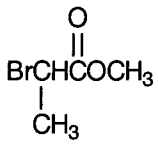
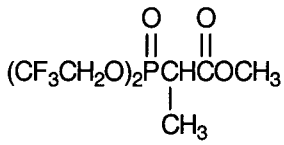
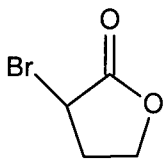
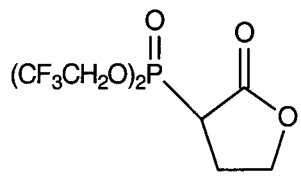
| Method | Base | Solvent | Temperature | Time of Addition | % Yield |
|---|---|---|---|---|---|
| A | NaH | THF | –42 °C | Immediate | 34 |
| G | NaH | THF | 0 °C | Immediate | 7 |
| E | NaH | THF/HMPA | 10 °C | Immediate | 15 |




**5**

The synthesis of α-[bis(2,2,2-trifluoroethoxy)phosphinyl]-γ-butyrolactone was unsuccessful. Bis(2,2,2-trifluoroethyl)phosphite was added to a solution of α-bromo-γ-butyrolactone and sodium hydride in THF at 0 °C. The reaction was then allowed to warm to room temperature over a 24 hour period producing 0% of compound **5**.

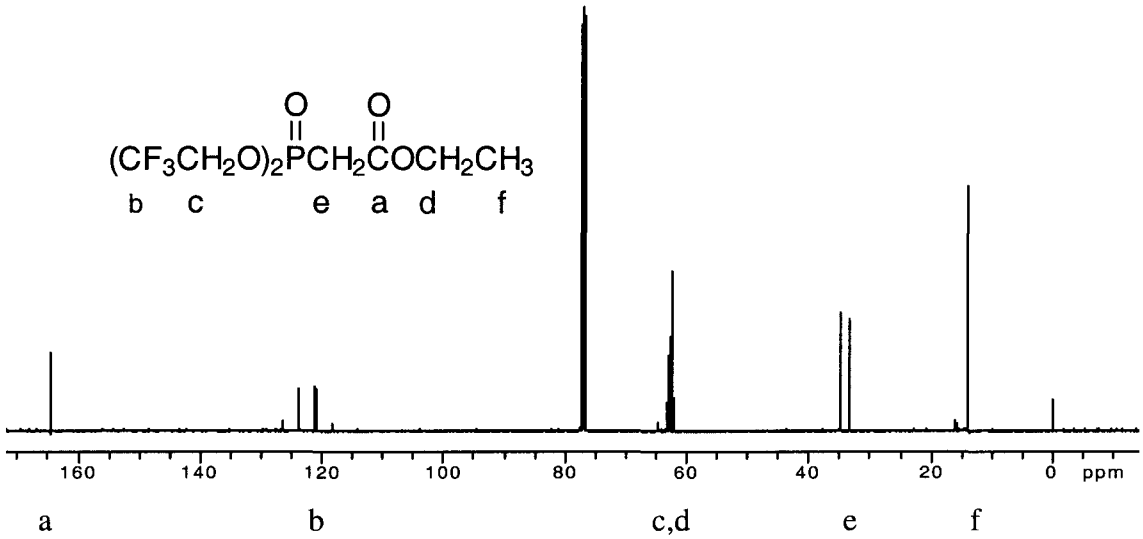
**Table 5:** Optimal yields of trifluoroethyl phosphonates.

| Starting Material | Product | Yield | Method |
|---|---|---|---|
|  |  | 59 | A |
|  |  | 34 | E |
|  |  | 38 | E |
|  |  | 34 | A |
|  |  | 0 | C |

In a typical $^{13}C$ NMR spectrum of an organic compound, all of the peaks are singlets if the attached protons are decoupled. However, compounds **1, 2, 3,** and **4** contain $^{31}P$ and $^{19}F$, both spin ½ nuclei with close to 100% natural abundance. This will cause extensive splitting. For example, the trifluoroethyl groups of the phosphorus ester of compound **1** have two signals (**b** and **c**, Fig. 1). Due to the presence of phosphorus and fluorine, both of these signals are observed as a doublet of quartets (dq). The $CF_3$ group (signal **b**, Fig. 2) has a chemical shift of 123.4 ppm, and a carbon-fluorine coupling constant (*J*) of 277.3 Hz, and a carbon- phosphorus coupling constant of 8.2 Hz. The $CH_2$

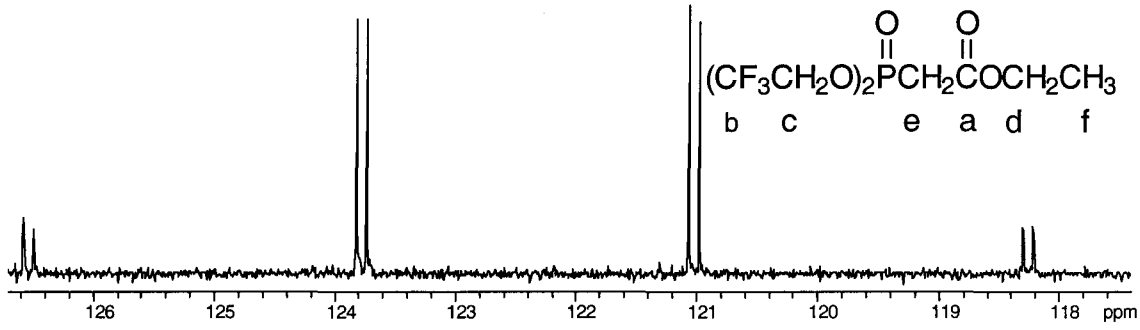
group of the phosphorus ester (signal **c**) has a chemical shift of 62.6 ppm, and a carbon-fluorine coupling of 38.1 Hz and a carbon-phosphorus coupling constant of 5.3 Hz.

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



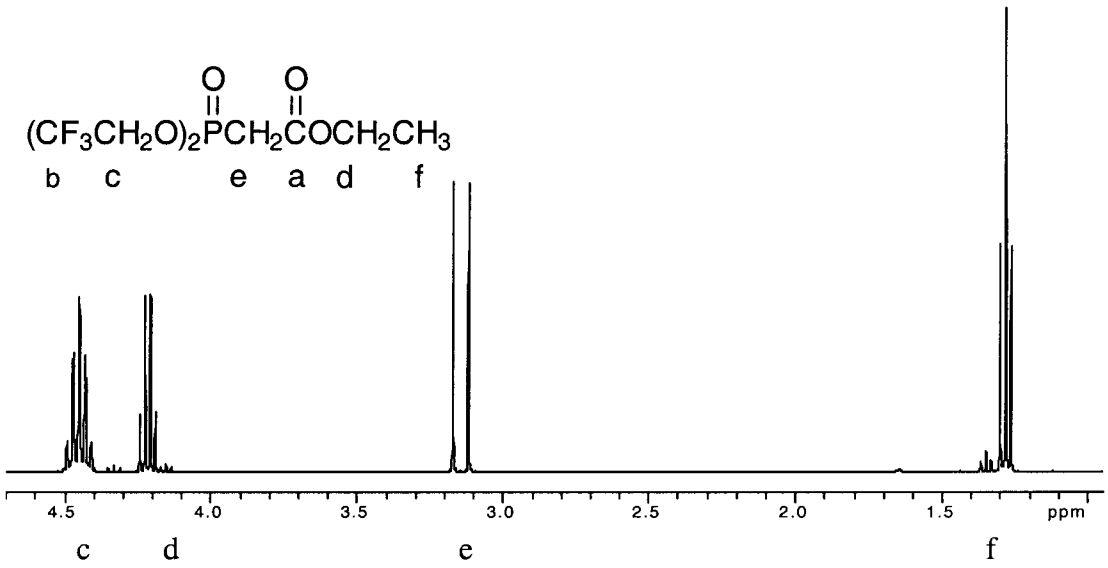

The $CH_2$ group (signal **e**) was observed as a doublet at 34.0 ppm, with a very large coupling constant of 145.0 Hz, a result of being directly bonded to the phosphorus. The carbonyl group (signal **a**) was observed as a doublet ($J$=4.6 Hz) at a chemical shift of 164.6 ppm, the splitting resulting from the phosphorus coupling. The $CH_2$ and the $CH_3$ groups of the carboethoxy group were observed at 62.3 and 13.9 ppm respectively. Neither of these (signals **d** and **f**) showed any coupling to the phosphorus.

**Figure 2:** $^{13}C$ NMR of Signal b.



In the $^{1}H$ NMR spectrum of compound **1**, the $CH_2$ group of the phosphorus ester (signal **c**, Fig. 3) was observed as a multiplet with a chemical shift of 4.49-4.40 ppm. The methylene of the carboethoxy group (signal **d**) was observed as a quartet (q, $J$=7.1 Hz) at 4.22 ppm. The last $CH_2$ group (signal **e**) was found as a doublet ($J$=21.2 Hz) at a chemical shift of 3.14 ppm. The large splitting was a result of a two bond coupling of being directly bonded to the phosphorus. The $CH_3$ group of the carboethoxy group (signal **f**) was found as a triplet at a chemical shift of 1.28 ppm.

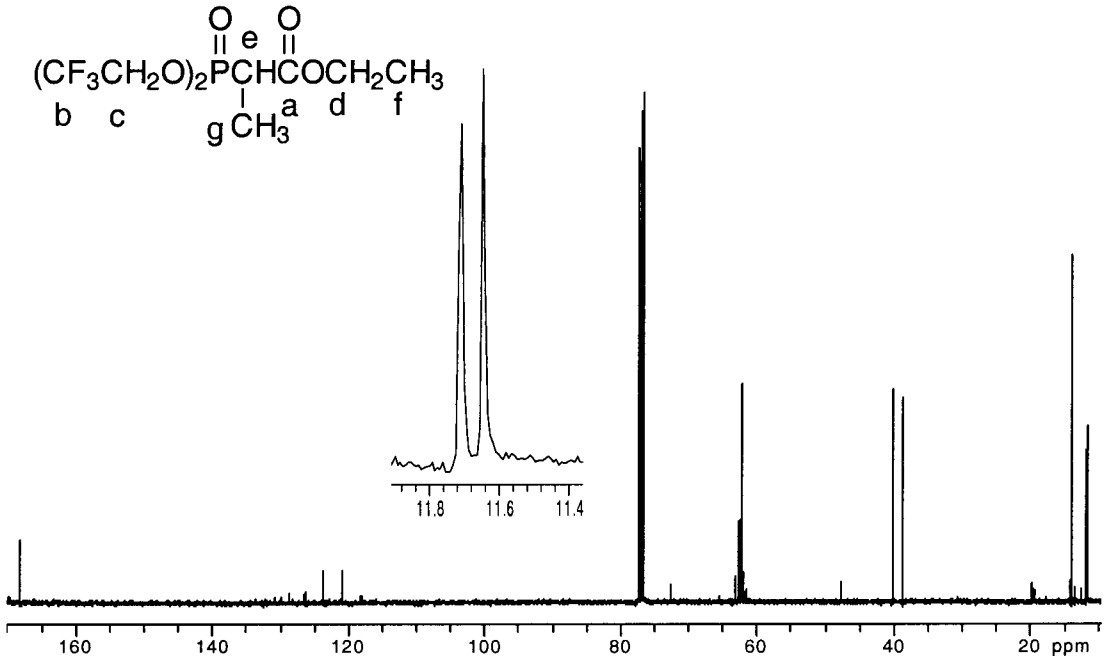
**Figure 3**: $^{1}H$ NMR of Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (**1**).




In the $^{13}C$ NMR of compound **2** (Fig. 4), the doublet at a chemical shift of 168.1 ppm ($J$=3.1 Hz) was the result of the carbonyl group (signal **a**) being coupled to phosphorus. The $CF_3$ groups of the phosphorus ester (signal **b**) were observed as two doublets of quartets at 123.5 ($J$=277.0, 3.1 Hz) and 123.4 ppm (277.0, 3.1 Hz). This was the result of the two $CF_3$ groups being nonequivalent. The lack of impurities in the sample of compound **2** was verified by the observation of only one peak (26.66 ppm) in the $^{31}P$ NMR. The $CH_2$ group of the phosphorus ester (signal **c**) was also noted as a doublet of

quartets at 62.6 (J=38.2, 5.3 Hz) ppm. The carboethoxy group of $CH_2$ and $CH_3$ (signals **d**, **f**) were observed as singlets at 62.2 and 14.0 ppm, respectively. Signal **e**, the $CH_2$ group bonded to the phosphorus, was observed as a doublet at 40.5 ppm with a large coupling constant of 140.4 Hz. The methyl group (signal **g**) was observed as a doublet at 11.7 ppm (3.1 Hz) which was the result of coupling to the phosphorus.

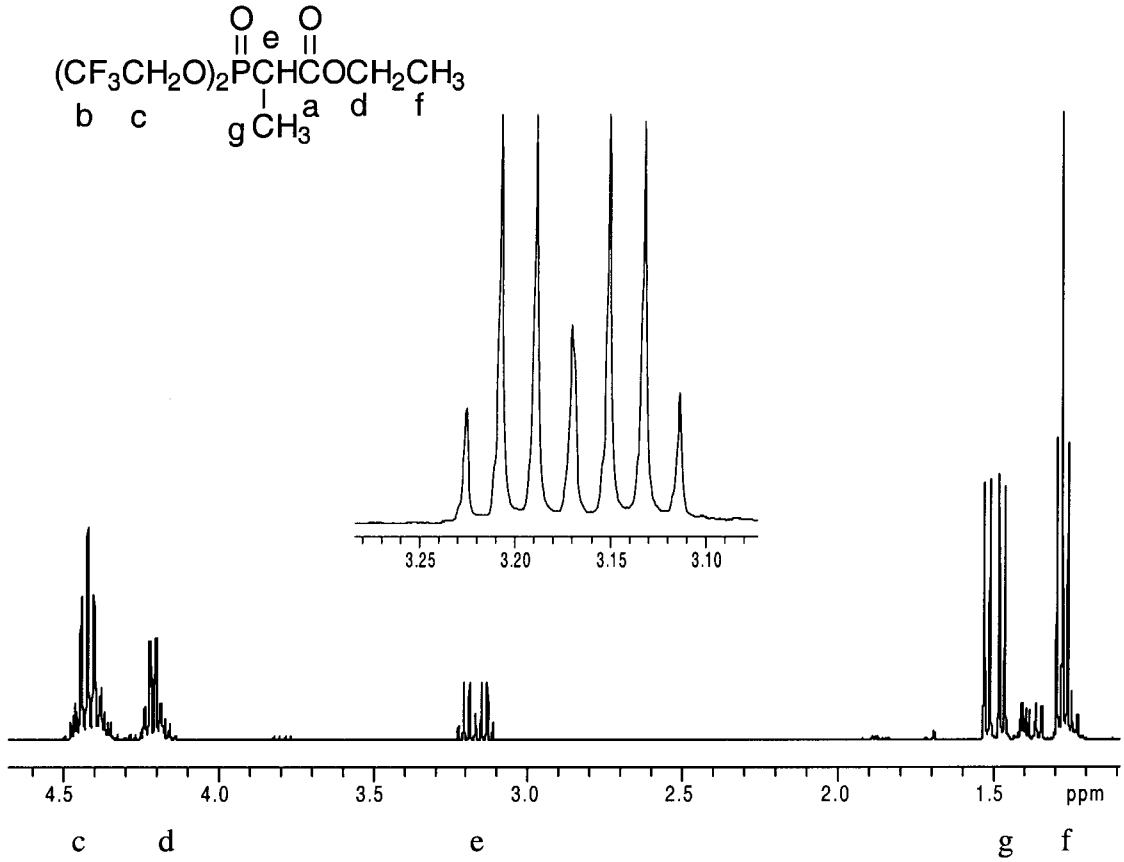
**Figure 4:** $^{13}C$ NMR of Ethyl [bis(2,2,2- trifluoroethoxy)phosphinyl]propionate (**2**)




a b c,d e g,f

In the $^1H$ NMR of compound **2** (Fig. 5), the CH group (signal **e**) was observed as a doublet of quartets at a chemical shift of 3.17 ppm (*J*=22.6, 7.5 Hz). The $CH_2$ group of the phosphorus ester (signal **c**) was observed as a multiplet at a chemical shift of 4.54 ppm. The $CH_3$ group (signal **g**) was observed as a doublet of doublets at 1.55 ppm (*J*=19.3, 7.4 Hz). The $CH_2$ group of the carboethoxy group (signal **d**) was observed as a quartet at 4.2 ppm (*J*=7.1 Hz). The $CH_3$ group of the carboethoxy group (signal **f**) resulted in a triplet at 1.27 ppm.

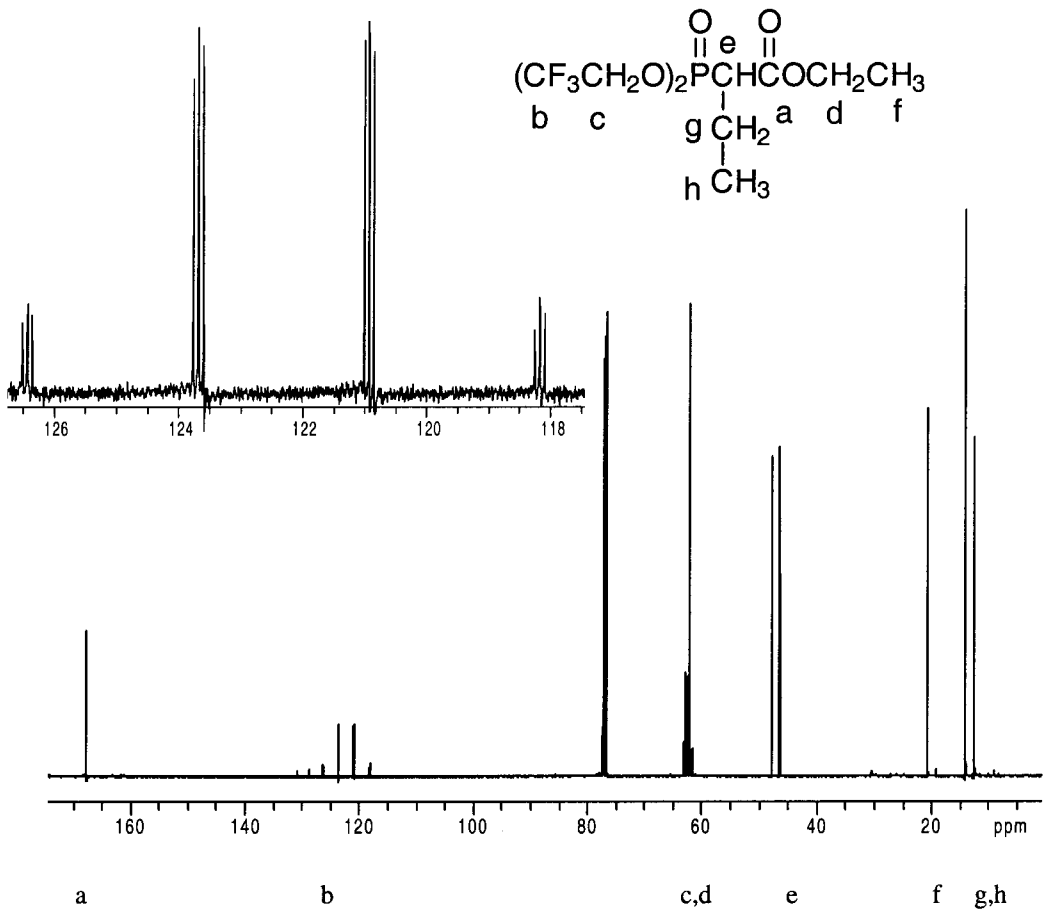
**Figure 5**: $^{1}$H NMR of Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]propionate (**2**)




In the $^{13}$C NMR of compound **3** (Fig. 6), the carbonyl group (signal **a**) was split by the phosphorus resulting in a doublet at 167.7 ppm ($J$=3.1 Hz). The $CF_3$ groups of the phosphorus ester were observed as a set of doublets of quartets at 122.3 ($J$=276.7, 8.0 Hz) and 122.3 ($J$=276.8, 7.8 Hz) ppm. This was the result of the two $CF_3$ groups being nonequivalent, due to the presence of a chiral center in the racemic product. The two doublets of quartets observed at 62.7 ($J$=38.0, 5.9 Hz) and 62.4 ($J$=38.2, 6.1 Hz) ppm can be assigned to the two nonequivalent $CH_2$ (signal **c**), of the phosphorus ester. The $CH_2$ and $CH_3$ of the carboethoxy group showed no coupling with phosphorus. These signals (**d** and

**f**) were singlets at 62.1 and 14.1 ppm. The $CH_2$ group (signal **g**) had coupling with phosphorus which resulted in doublet of at 20.8 ppm ($J$=5.4 Hz) whereas the methyl group (signal **h**) had no coupling to phosphorus. The CH group (signal **e**) was observed as a doublet at 47.1 ppm ($J$=136.6 Hz) a direct result of the carbon being directly bonded to phosphorus.

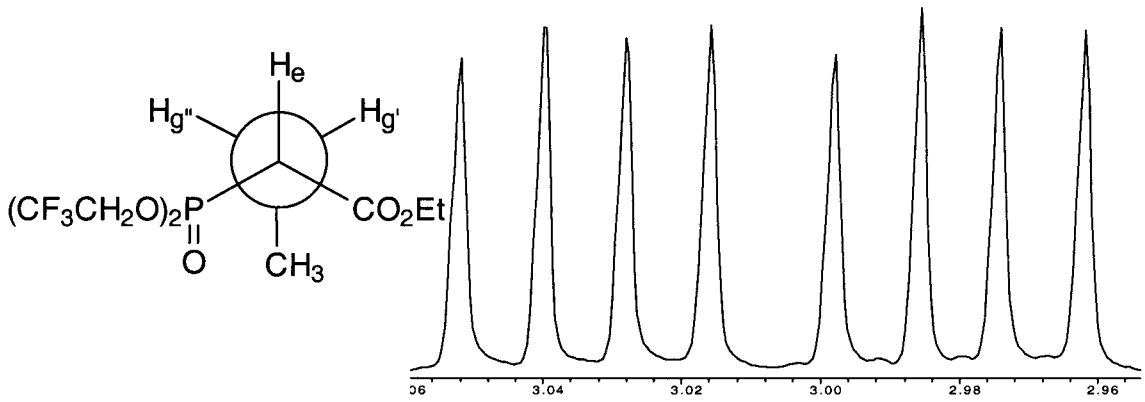
**Figure 6:** $^{13}C$ NMR of Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]butyrate (**3**)




In the $^1H$ NMR of compound **3** (Fig. 7) a doublet of doublets of doublets (ddd) was observed for the proton label $H_e$ at a chemical shift of 3.2 ppm. The signal is the result of coupling of $H_e$ to the two diastereotopic protons ($H_{g'}$, $H_{g''}$) and phosphorus. The two $CH_2$ groups of the phosphono ester (signal **c**) were observed as a multiplet with a chemical

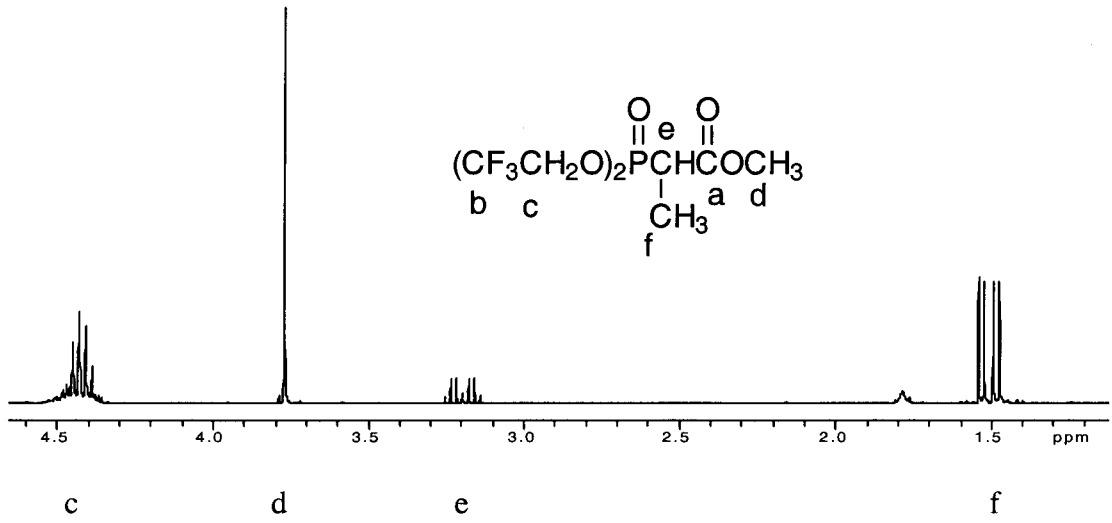
shift of 4.45-4.32 ppm. The $CH_2$ group of the carboethoxy group (signal **d**) was found as a quartet at 4.22 ppm. The two $CH_3$ groups (signals **f** and **h**) were observed as triplets at 1.24 and 1.01 ppm, respectively.

**Figure 7:** $^1$H NMR of $H_e$ of Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]butyrate (**3**)




In the $^1$H NMR of compound **4**, the signal for the $CH_2$ group of the phosphorus (signal **c**) was observed as a mutiplet at a chemical shift of 4.35-4.25 ppm. The CH group (signal **e**) was observed as a doublet of quartets at a chemical shift of 3.2 ppm. The $CH_3$ group (signal **f**) was observed as a doublet of doublets at 1.5 ($J$=19.3 Hz) ppm.

**Figure 8:** $^1$H NMR of Methyl [bis(2,2,2- trifluoroethoxy)phosphinyl]propionate (**4**)



The syntheses of compounds **1, 2, 3,** and **4** were attempted under a variety of different reaction conditions. The synthesis of compounds **1** and **4** gave optimal yields by method A. (Method A: NaH, THF, –42 °C) While the preparation of compounds **2** and **3** had optimal yields with method E. (Method E: NaH, THF, HMPA, 10 °C)

Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (**1**) gave the best yield of 59% of all the compounds. This yield compares very favorably to Stills method in which the reported literature value (40%) is lower for the same compound synthesized.

Future work could involve further variation of conditions, in order to obtain higher yields. These changes may include different bases (*n*-butyllithium, triethylamine, etc.), different polar aprotic solvents (DMSO, ether, DME, etc), and changes in temperature. The reaction of the anion of bis(2,2,2-trifluoroethyl) phosphite with other substrates such as α-haloketones, or other substrates could also be attempted.

## Chapter 3: Experimental

**General methods**. All reactions were conducted under a positive pressure of argon. All solvents were dried by standard techniques. All commercial reagents were used without further purification. Flash chromatography was conducted with Merck grade 9385, 230-400 mesh silica. Analytical thin layer chromatography (TLC) was conducted on aluminum backed silica plates. Visualization was accomplished with an ultraviolet lamp and staining with 5% phosphomolybdic acid (PMA) in ethanol with heating. NMR spectra ($^{1}H$, $^{13}C$, and $^{31}P$) were recorded with 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 from $(CH_3)_4Si$, while $^{31}P$ chemical shifts are reported in parts per million downfield from $H_3PO_4$ (external standard). Coupling constants are reported in Hertz.

**Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (1).**

Method A. Bis(2,2,2-trifluoroethyl) phosphite (5.0 mmol, 0.80 mL) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil, 0.400g, 0.016 mol) in anhydrous THF (22 mL) at –42 °C (dry ice, acetonitrile) followed by the immediate addition of ethyl bromoacetate (4.0 mmol, 0.44 mL). The reaction was allowed to warm to 15 °C over a 5 hour period and it was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The aqueous extract was then washed with ether (3 x 25 mL). The combined organic extract was washed with saturated sodium chloride and dried over

magnesium sulfate. After removing solvent by rotary evaporation, the residuefinal product was purified by column chromatography (silica gel, 80% hexane, 20% ethyl acetate) producing compound **1** (0.40g, 59%).

$^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 4.49-4.40 (m, 4H), 4.22 (q, 2H, *J*=7.1 Hz), 3.14 (d, 2H, *J*=21.2 Hz), 1.28 (t, 3H, *J*=7.1 Hz).

$^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 164.6 (d, *J*=4.6 Hz), 122.4 (2, dq, *J*=277.3, 8.2 Hz), 62.6 (2, dq, *J*=38.1, 5.3 Hz), 62.3 (s), 34.00 (d, *J*=145.0 Hz), 13.9 (s).

$^{31}$P NMR ($CDCl_3$): $\delta$ (ppm) 23.17

Method B. To a solution of sodium hydride (0.624 g, 0.026 mol) in THF (25 mL) at −78 °C was added in a dropwise manner bis(2,2,2-trifluoroethyl) phosphite (5.0 mmol, 0.80 mL). Immediately after addition, ethyl bromoacetate (5.0 mmol, 0.55 mL) was added dropwise. The reaction was allowed to warm to room temperature over a 20 hour period. The reaction was then quenched with a solution of acetic acid in diethyl ether and the resulting mixture was filtered through a 2 cm layer of Florisil (60-120 mesh). After removal of solvent by rotary evarporation, the product was purified by column chromatography (silica gel, 80% hexane, 20% ethyl acetate) producing compound **1** (0.37 g, 49%).

Method C. Bis(2,2,2-trifluoroethyl) phosphite (5.0 mmol, 0.80 mL) and ethyl bromoacetate (5.0 mmol, 0.55 mL) were combined in a neat mixture at 0 °C. After 2 hours, the reaction was allowed to warm to room temperature for 24 hours. The reaction was then refluxed for 3 hours. The product was purified by column chromatography (silica gel, 80% hexane, 20% ethyl acetate affording 1 (0.07 g, 10%).

Method D. Bis(2,2,2-trifluoroethyl) phosphite (5.0 mmol, 0.80 mL) was added, (*via* syringe) to a solution of sodium hydride (0.429 g 0.017 mol) in THF (20 mL) at room temperature. After 3 minutes, ethyl bromoacetate (5.0 mmol, 0.55 mL) was added to the mixture by syringe. The reaction was then refluxed for 24 hours and quenched with a solution of acetic acid in diethyl ether. The resulting mixture was filtered through a 2 cm layer of Florisil (60-120 mesh). After removal of solvent, the product was purified by column chromatography (silica gel, 50% hexane, 50% ethyl acetate) yielding compound **1** (0.04 g, 5%).

**Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]propionate (2)**

Method E. Bis(2,2,2 trifluoroethyl) phosphite (5.0 mmol, 0.79 mL) was added to a solution of sodium hydride (0.420 g, 0.018 mol) and HMPA (8.6 mmol, 1.5 mL) at 10 °C in THF (20 mL). Immediately after addition, ethyl 2-bromopropionate (3.9 mmol, 0.50 mL) was added dropwise. The reaction temperature was maintained 10 °C for 4.5 hours. The reaction was then quenched with saturated aqueous ammonium chloride (2mL) and standard aqueous work-up was performed. Final purification by flash column chromatography (silica gel, 80% hexane, 20% ethyl acetate) produced compound **2** (0.24 g, 34%).

$^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 4.44-4.02 (m, 4H), 4.21 (q, 2H, *J*=7.11, 1.88 Hz), 3.17 (dq, 1H, *J*=22.61, 7.51 Hz), 1.79 (dd, 3H, *J*=19.32, 7.42 Hz), 1.27 (t, 3H, *J*=7.14 Hz)

$^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 168.1 (d, *J*=3.1 Hz), 123.5 (dq, *J*=277.0, 3.1 Hz), 123.4 (dq, *J*=277.0, 3.1 Hz), 62.6 (dq, *J*=38.2, 5,3 Hz), 62.5 (dq, *J*=38.1, 6.1 Hz), 62.2 (s), 40.5 (d, *J*=140.4 Hz), 14.0 (s), 11.8 (d, *J*=3.1 Hz).

$^{31}$P NMR ($CDCl_3$): $\delta$ (ppm) 26.66.

Method E. To a solution of potassium *tert*-butoxide (0.01 mmol, 1.356 g) in THF (22 mL) at –78 °C was added dropwise bis(2,2,2-trifluoroethyl) phosphite (4.70 mmol, 0.75 mL). After 30 minutes, ethyl 2-bromopropionate (3.3 mmol, 0.59 mL) was added in a dropwise manner. The reaction was warmed to room temperature over a 24 hour period before being quenched with saturated ammonium chloride. Standard aqueous workup was then performed. After removing the solvent by rotary evaporation, the product was purified by column chromatography (silica gel, 80% hexane, 20% ethyl acetate) yeilding compound **2** (0.08 g, 10%).

Method G. Bis(2,2,2-trifluoroethyl) phosphite (5.0 mmol, 0.80 mL) was added to a solution of sodium hydride (0.567 g, 0.024 mmol) and DMF (3.0 mL, 0.038 mmol) at 10 °C in THF (25 mL). Immediately after addition, ethyl 2-bromopropionate (3.7 mmol, 0.48 mL) was added dropwise. The reaction was then maintained at 10 °C for 2.5 hours before being quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The aqueous layer was then washed with ether (3 x 25 mL). The organic extract was washed with saturated sodium chloride and dried over magnesium sulfate. After removing the solvent by rotary evaporation, final product was purified by column chromatography (silica gel, 80% hexane, 20% ethyl acetate) producing compound **2** (0.08 g, 12%).

Method A. To a solution of sodium hydride (0.406 g, 0.16 mol) in THF (23 mL) at –42 °C was added bis(2,2,2-trifluoroethyl) phosphite (5.0 mmol, 0.80 mL) *via* a dropping funnel. Ethyl 2-bromopropionate (4.0 mmol, 0.52 mL) was added immediately after the last addition of the phosphite. The reaction was allowed to warm to room temperature

over 24 hour period. It was then quenched with saturated ammonium chloride. Standard aqueous workup was done before purifying by column chromatrography (silica gel, 80% hexane, 20% ethyl acetate) which afforded compound **2** (0.82 g, 11%).

**Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]butyrate (3).**

Method E. To a solution of sodium hydride (0.393 g, 0.016 mol) in THF (21 mL) and HMPA (8.6 mmol, 1.5 ml) at 10 °C was added dropwise bis(2,2,2-trifluoroethyl) phosphite (5.0 mmol, 0.79 mL). Immediately after addition, ethyl 2-bromobutyrate (3.4 mmol, 0.50 mL) was added in a dropwise manner. After 9 hours at −10 °C, the reaction was quenched by addition of saturated aqueous ammoium chloride which was added *via* dropping funnel. The aqueous layer was removed and the organic layer was washed with water (20 mL). The aqueous solution was then washed with ether (3 x 25 mL). The organic extract was washed with saturated sodium chloride and dried over magnesium sulfate. After removing the solvent by rotary evaporation, the product was purified by column chromatography (silica gel, 80% hexane, 20% ethyl acetate) producing compound **3** (0.25g, 37.8%)

$^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 4.45-4.32 (m, 4H), 4.22 (q, 2H, $J$=7.1 Hz), 3.00 (ddd, 1H, $J$=21.6, 9.5, 5.0 Hz), 1.90-2.04 (m, 2H), 1.24 (t, 3H, $J$=7.1 Hz), 1.01 (t, 3H, $J$=7.4 Hz).

$^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 167.7 (d, $J$=3.1 Hz), 122.3 (dq, $J$=276.7, 8.0 Hz), 122.3 (dq, $J$=276.8, 7.8 Hz) 62.7 (dq, $J$=38.0, 5.9 Hz), 62.4 (dq, $J$=38.2, 6.1 Hz), 62.1 (s), 47.14 (d, $J$=136.6 Hz), 20.8 (d, $J$=5.4 Hz), 14.1 (s), 12.6 (s).

$^{31}$P NMR ($CDCl_3$): $\delta$ (ppm) 25.82.

Method A. Bis(2,2,2-trifluoroethyl) phosphite (5.0 mmol, 0.80 mL) was added in a dropwise manner to a solution of sodium hydride (0.438 g, 0.018 mmol) in THF (20 mL) at a temperature of –42 °C. Ethyl 2-bromobutyrate (4.0 mmol, 0.59 mL) was added via dropping funnel to the reaction. The reaction was allowed to warm to room temperature over a 12 hour period before being quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with 25 mL of water. The aqueous portion was then washed with ether (3 X 25 mL). The combined organic extract was washed with saturated sodium chloride and dried over magnesium sulfate. After removal of the solvent, *en vacuo,* product was purified by flash chromatography (silica gel, 80% hexane, 20% ethyl acetate) yielding **2** (0.59g, 10%).

**Methyl [bis(2,2,2-trifluoroethoxy)phosphinyl]propionate (4)**

Method A. Bis(2,2,2 trifluoroethyl) phosphite (4.7 mmol, 0.75 mL) was added dropwise to a mixture of THF (28 mL) and sodium hydride (0.415g, 0.017 mol) at –42 °C. Methyl 2 bromopropionate (3.4 mmol, 0.375 mL) was added immediately to the solution *via* addition funnel. The reaction was allowed to warm to room temperature over a 24 hour period. The reaction was then quenched with acetic acid in diethyl ether and the resulting mixture was filtered through a 2 cm layer of Florisil (60-120 mesh). After removal of solvent, the product was purified by column chromatography (silica gel, 80% hexane, 20% ethyl acetate) producing compound **4** (0.191 g, 34%).

$^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 4.25-4.35 (m, 4H) 3.77 (s), 3.19 (dq, 1H, $J$=22.7, 7.5 Hz), 1.51 (dd, 3H, $J$=19.32, 7.42 Hz).

$^{31}$P NMR ($CDCl_3$): $\delta$ (ppm) 26.66

Method F. To a solution of sodium hydride (0.482 g, 0.02 mol) in THF (22 mL) at 0 °C was added, *via* a dropping funnel, bis(2,2,2-trifluoroethyl) phosphite (4.7 mmol, 0.75 mL). Methyl 2-bromopropionate (4.50 mmol, 0.50 mL) was promptly added to the reaction. The reaction was allowed to stir for 5 hours before being quenched with saturated ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The aqueous was then washed with ether (3 x 25 mL). The organic extract was washed with saturated sodium chloride and dried over magnesium sulfate. Solvent was removed by rotary evaporation and purified by column chromatography affording compound **4** (0.05 g, 6.7%).

Method E Bis(2,2,2-trifluoroethyl) phosphite (4.7 mmol, 0.75 mL) was added to a solution of sodium hydride (0.462 g, 0.019 mol) and HMPA (8.6 mmol, 1.5 mL) at 10°C in THF (20 mL). Methyl 2-bromopropionate (4.5 mmol, 0.50 mL) was added immediately after the phosphite. Reaction was maintained at 10 °C for 5 hours before being quenched with saturated ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (25 mL). The aqueous was then washed with ether (3 x 30 mL). The organic extract was washed with saturated sodium chloride and dried over magnesium sulfate. Solvent was removed by rotary evaporation and the product was purified by column chromatography (silica gel, 80% hexane, 20% ethyl acetate) which gave compound **4** (0.11 g, 15%).

**Attempted synthesis of α-[bis(2,2,2-trifluoroethoxy)phosphinyl]-γ-butyrolactone (5).**

Method E Bis(2,2,2-trifluoroethyl) phosphite (4.5 mmol, 0.73 mL) was added dropwise to a solution of sodium hydride (0.638 g, 0.026 mol) in THF (24 ml) at 0 °C followed by

the immediate addition of α-bromo-γ-butyrolactone (4.2 mmol, 0.35 mL). The reaction was allowed to warm to room temperature over a 24 hour period when it was quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The aqueous extract was then washed with ether (3 x 25 mL). The combined organic extract was washed with saturated sodium chloride and dried over magnesium sulfate. Removal of the solvent by rotary evaporation produced a dark brown oil (0.52 g). Analysis of the product mixture by $^{31}P$ NMR indicated that phosphonate **5** was not formed.

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Figure **9**: $^{31}P$ NMR of Ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate

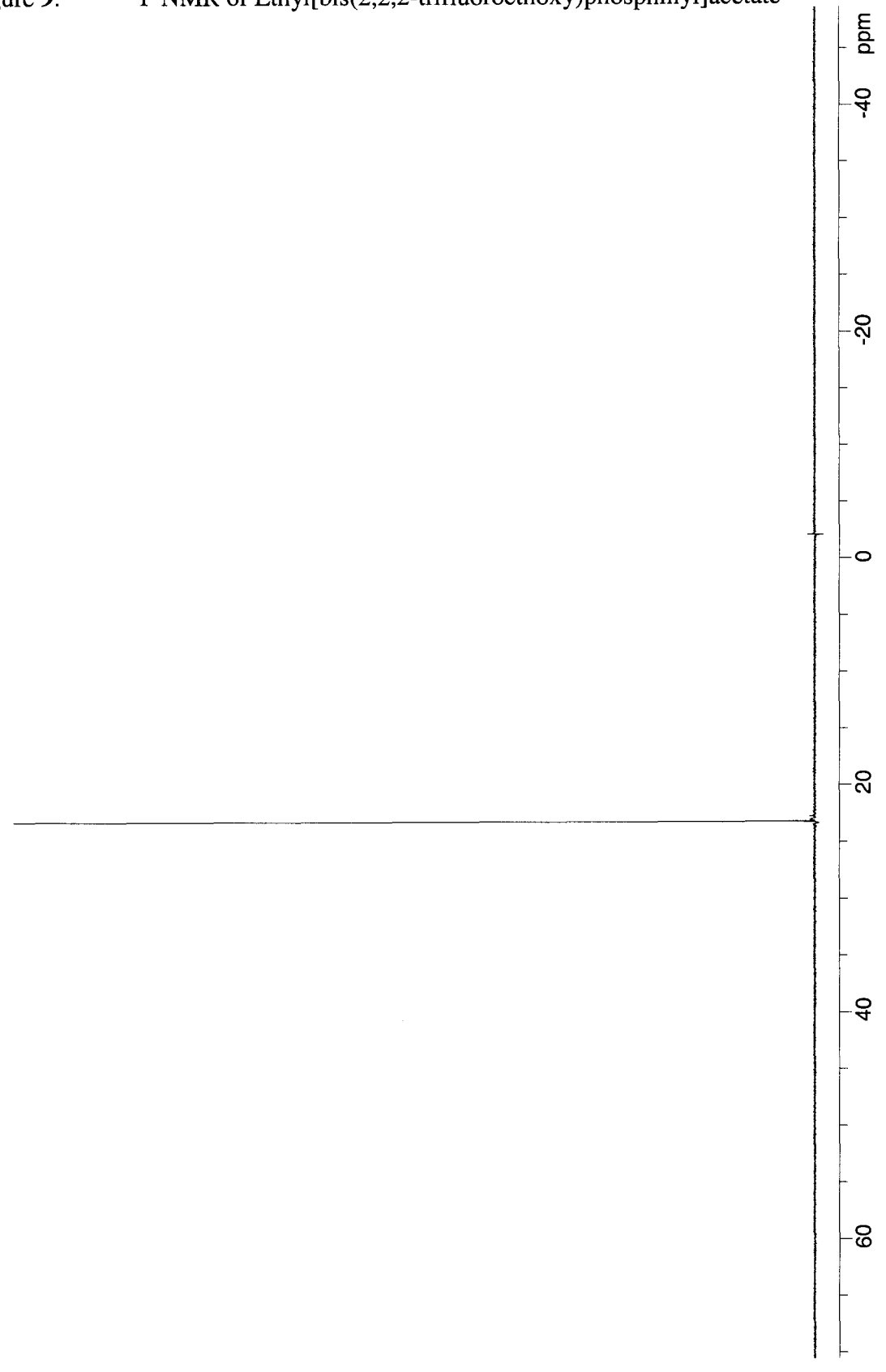

Figure **10**: $^{1}H$ NMR of Ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate

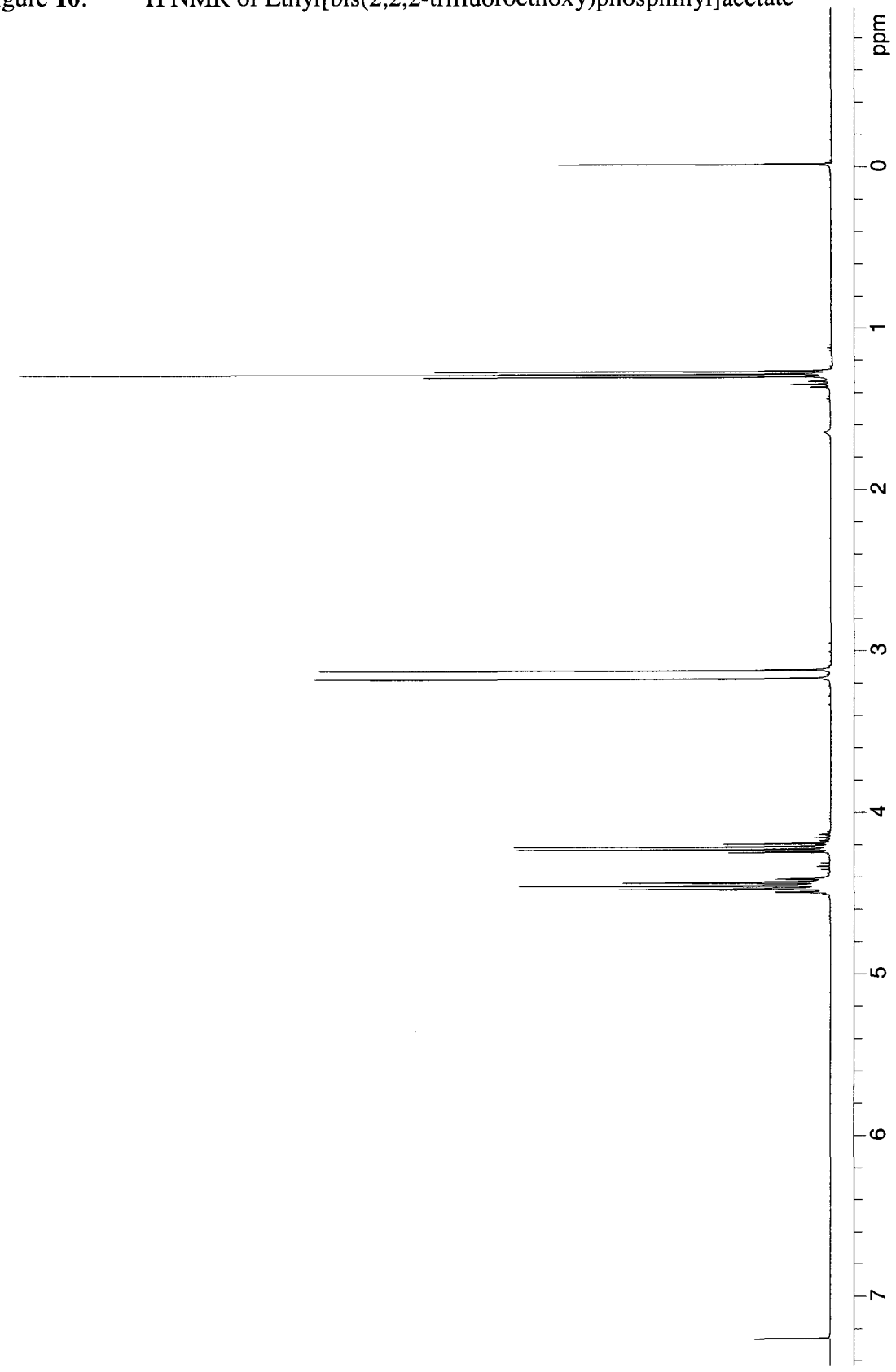

Figure **11**: $^{13}C$ NMR of Ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]acetate

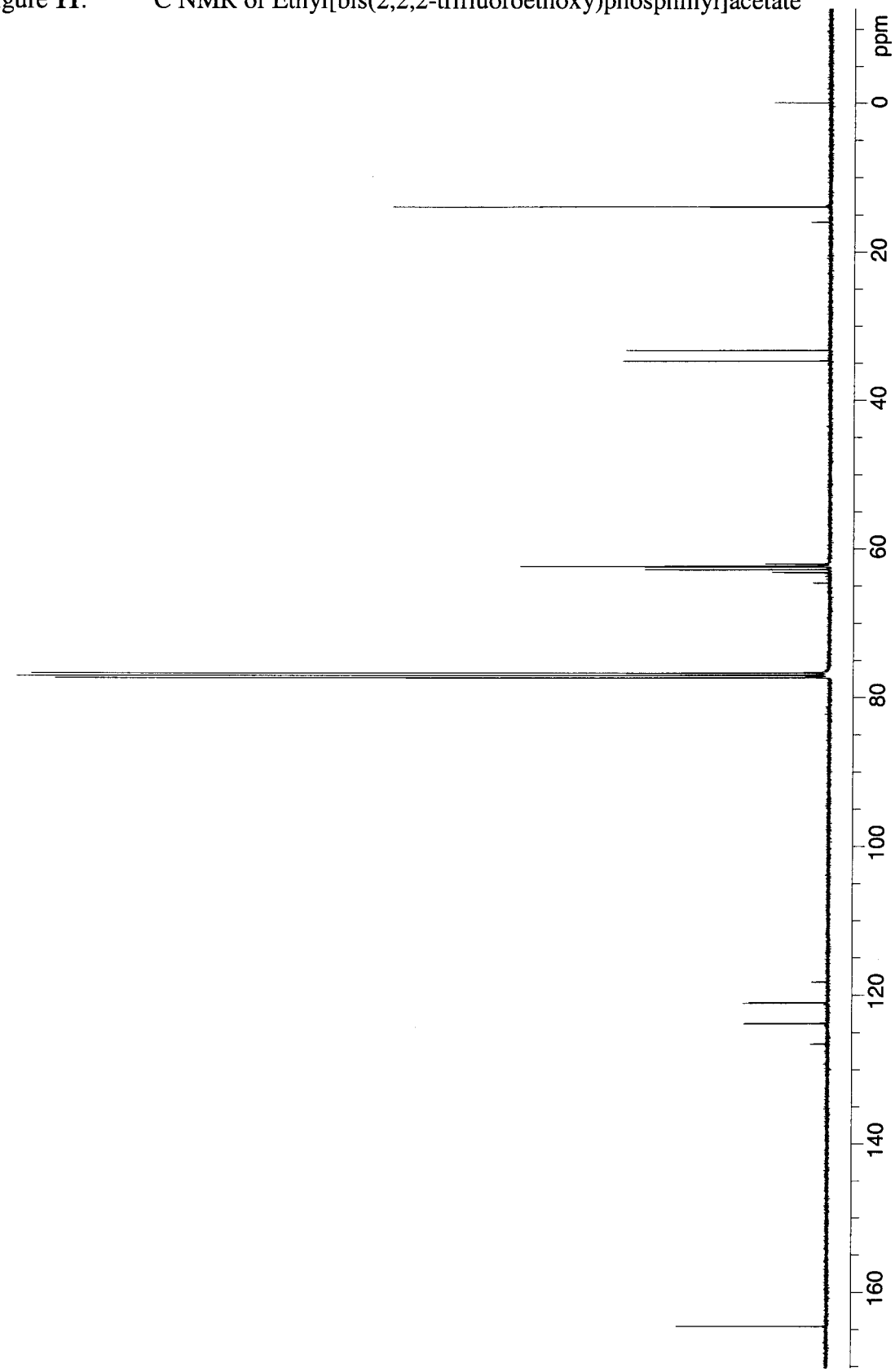

Figure **12**: $^{31}P$ NMR of Ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]propionate

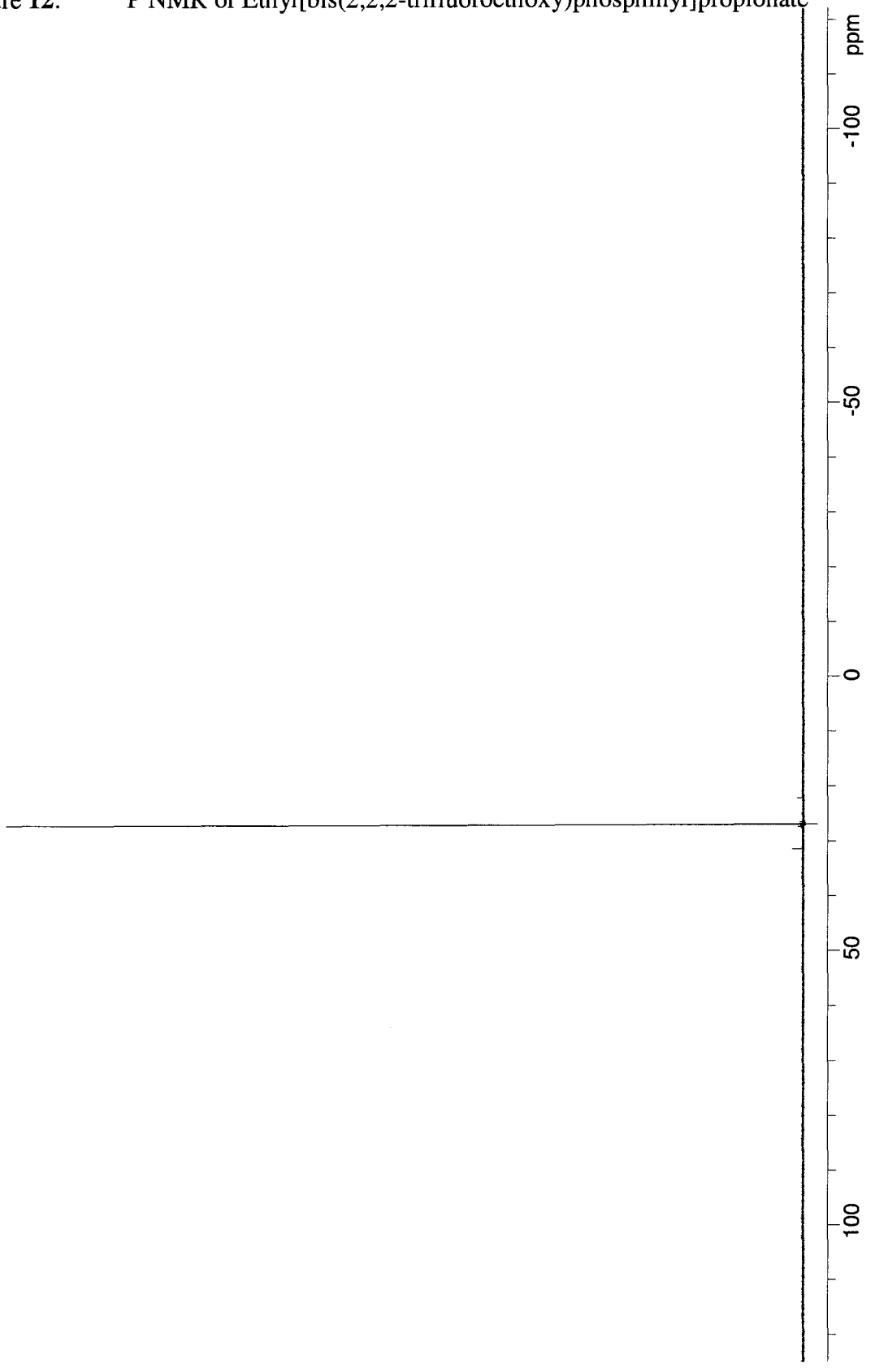

Figure **13**: $^{1}H$ NMR of Ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]propionate

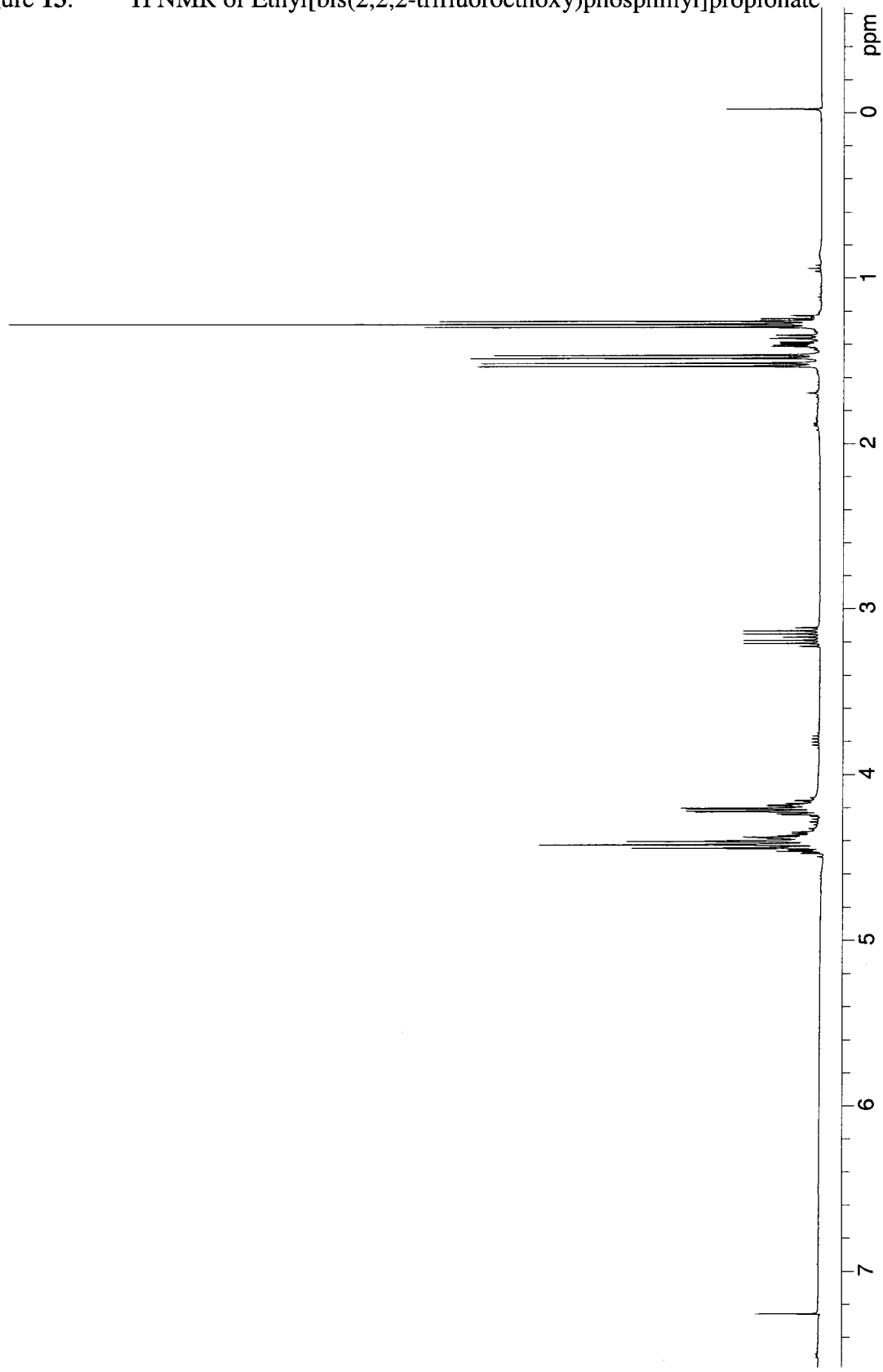

Figure **14**: $^{13}C$ NMR of Ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]propionate

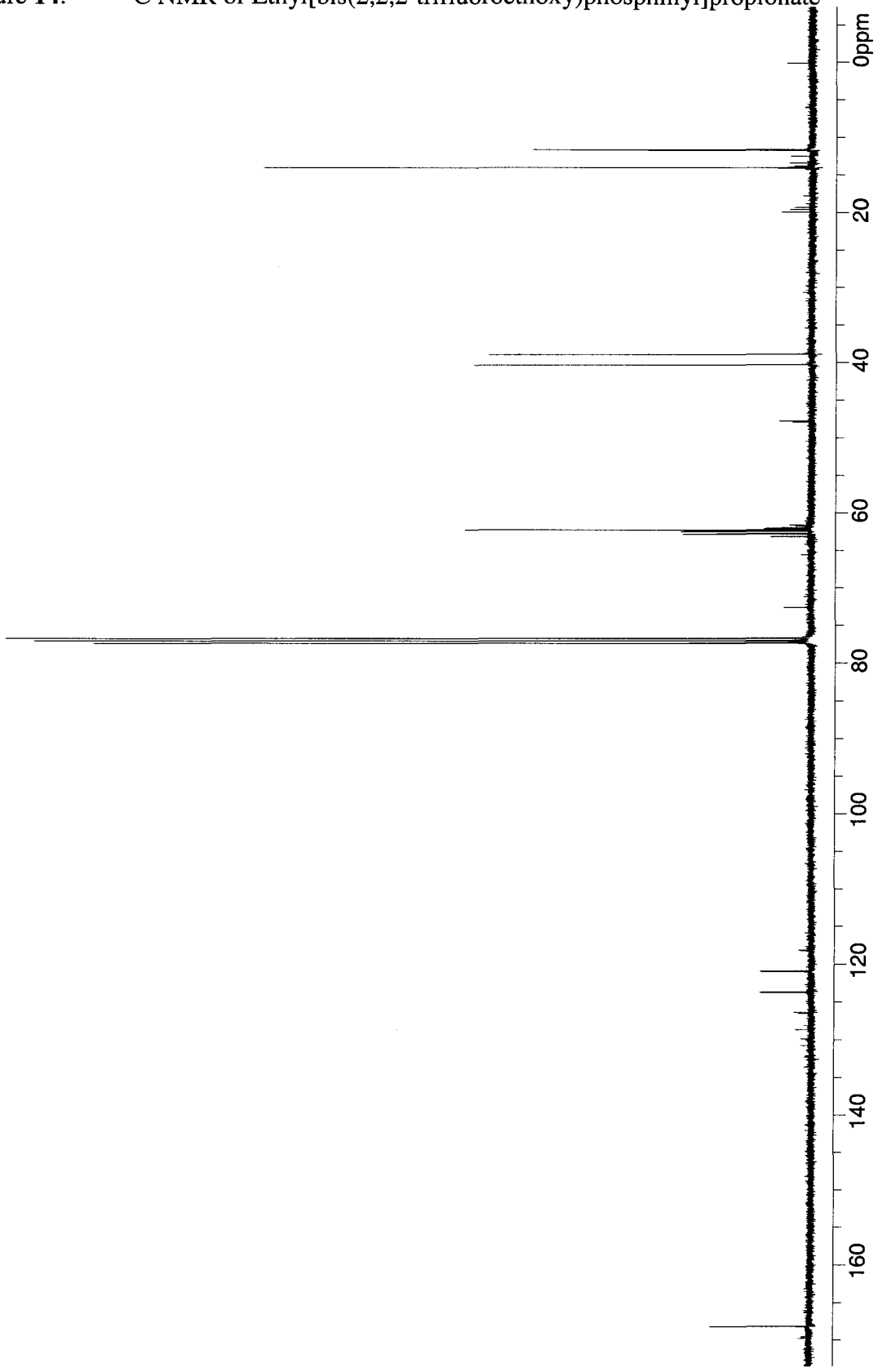

Figure **15:** $^{31}P$ NMR of Ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]butyrate

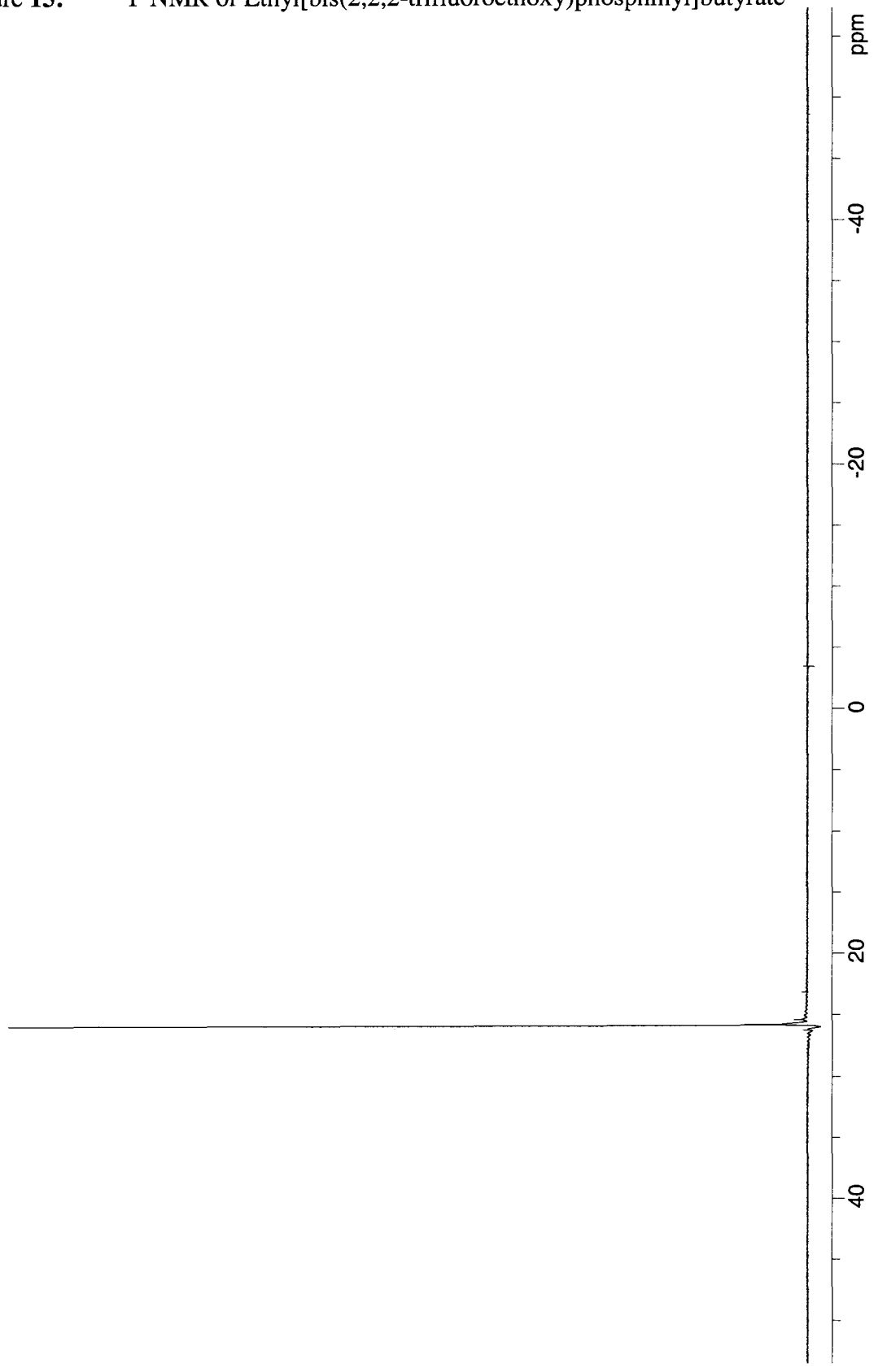

Figure **16**: $^{1}H$ NMR of Ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]butyrate

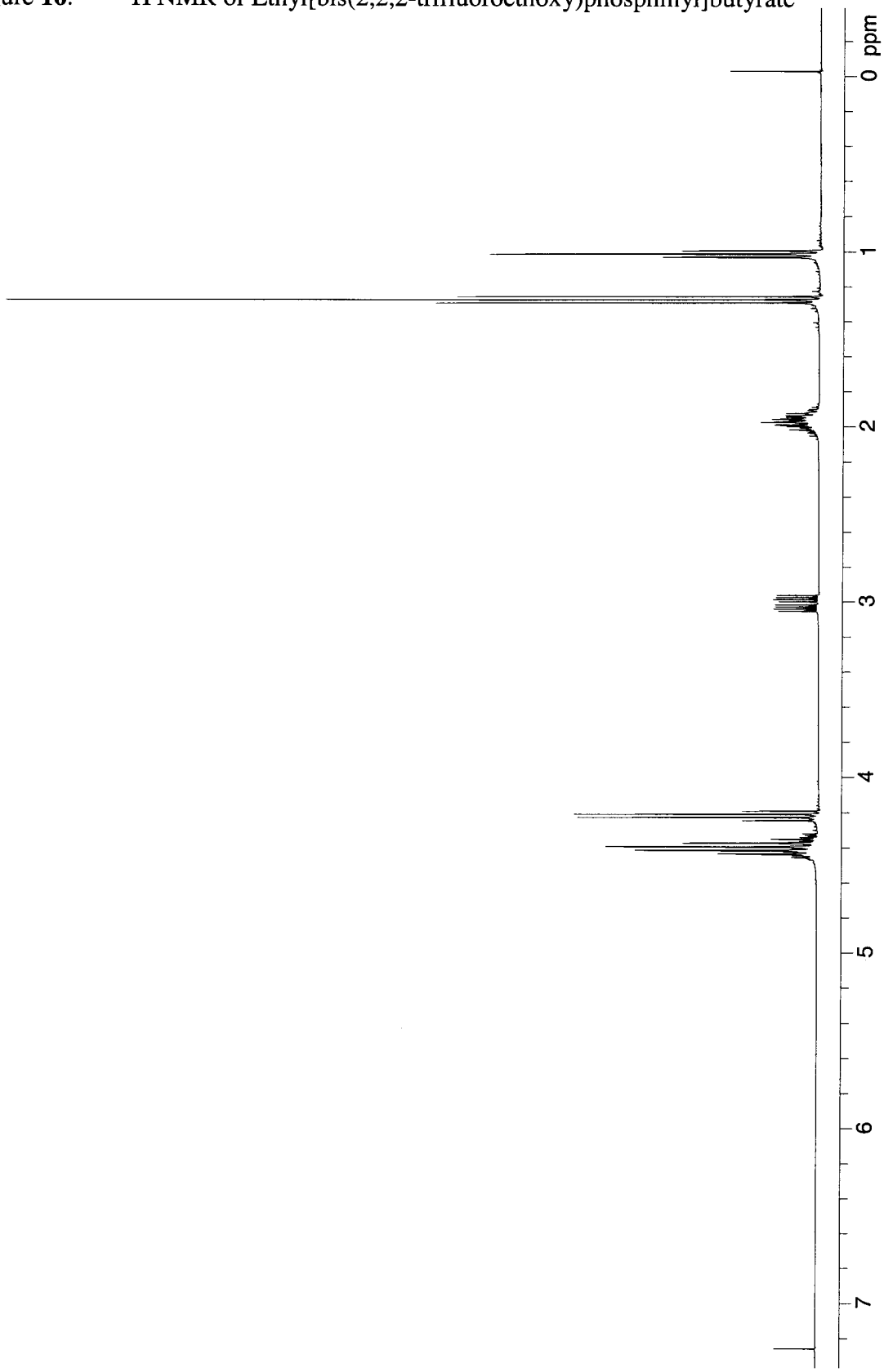

Figure **17**: $^{13}C$ NMR of Ethyl[bis(2,2,2-trifluoroethoxy)phosphinyl]butyrate

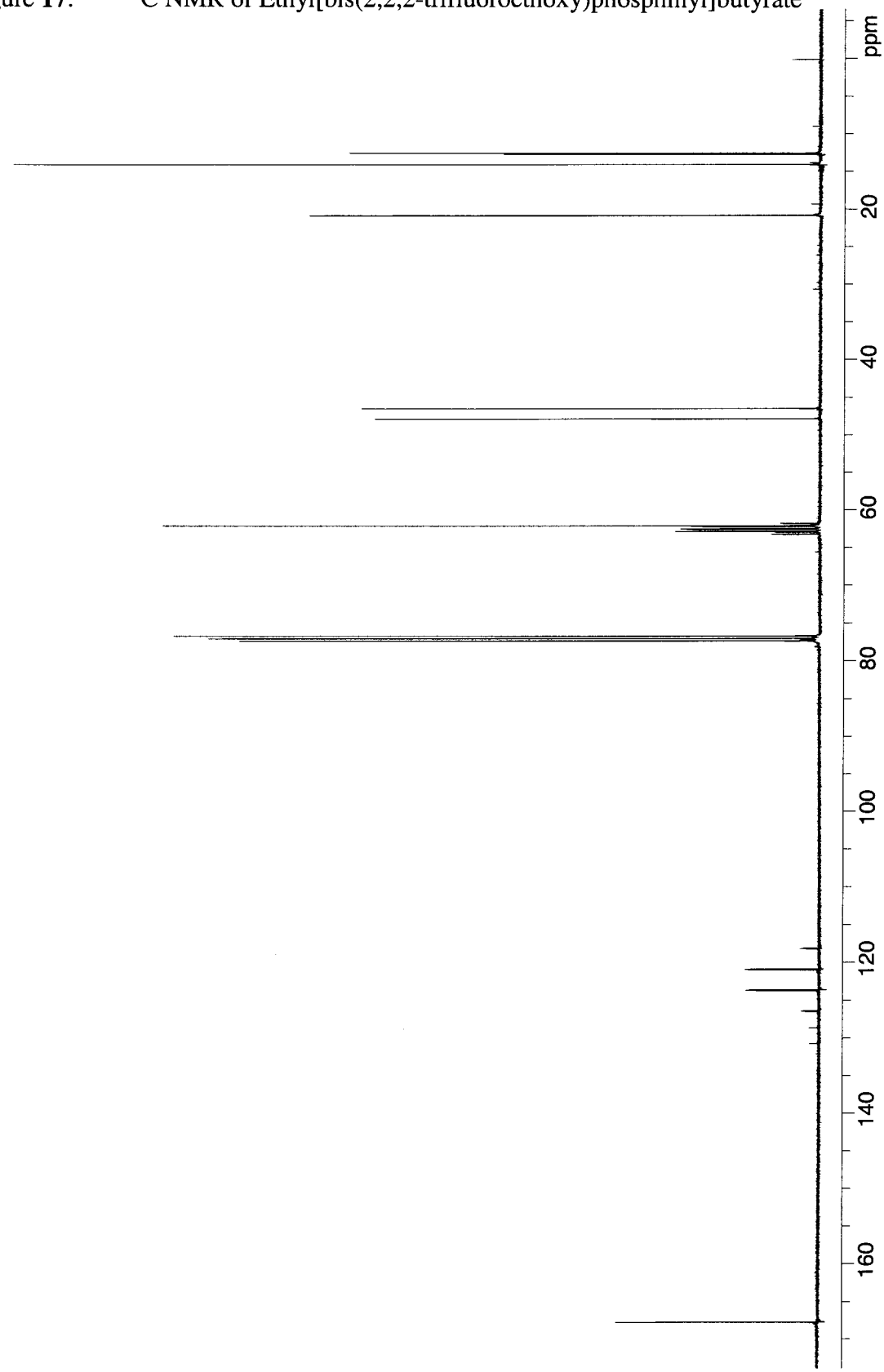

Figure **18**: $^{31}P$ NMR of Methyl[bis(2,2,2-trifluoroethoxy)phosphinyl]propionate

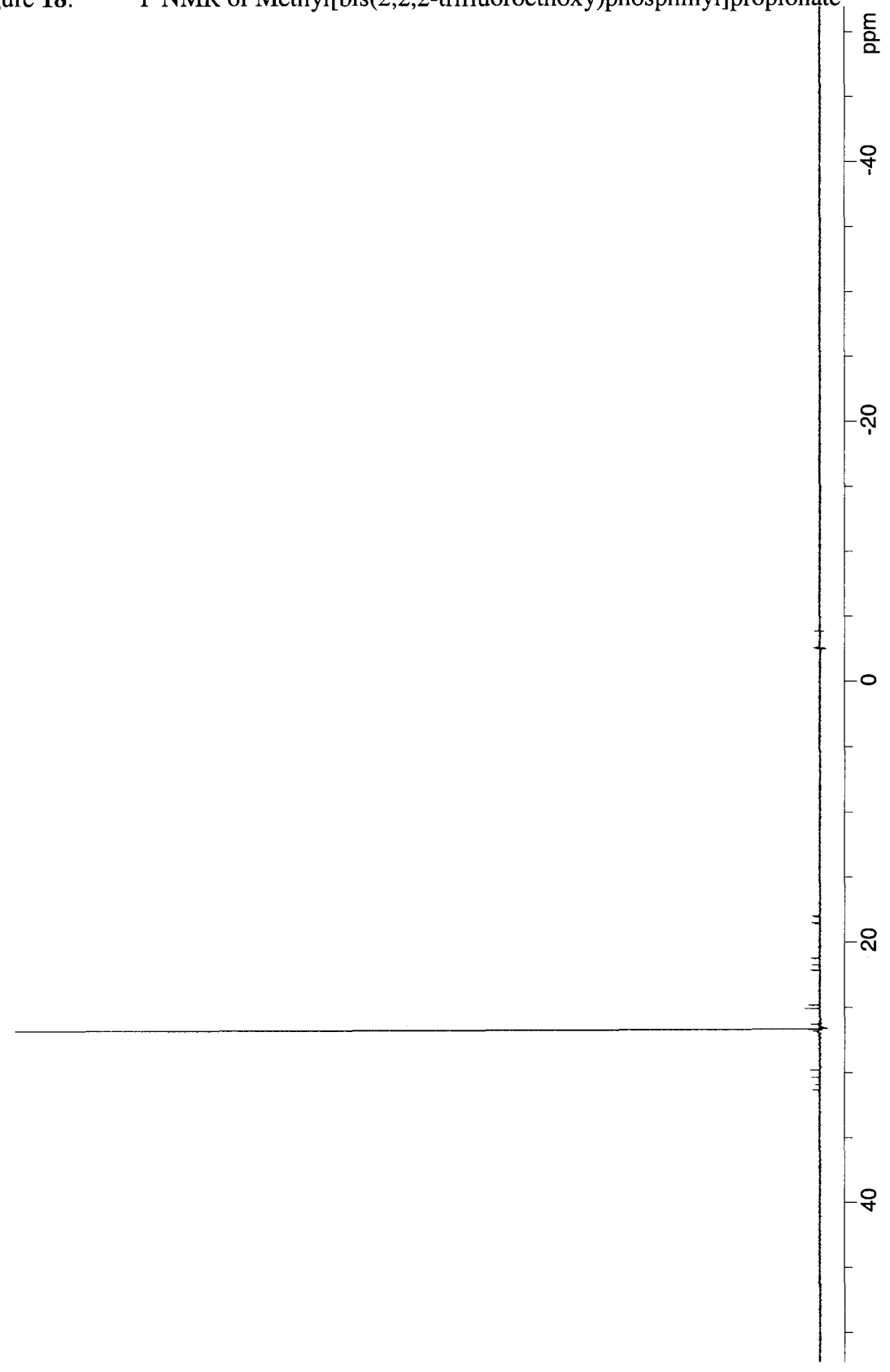

Figure **19**: $^{1}H$ NMR of Methyl[bis(2,2,2-trifluoroethoxy)phosphinyl]propionate