SYNTHESIS OF BIS(2,2,2-TRIFLUOROETHYL) VINYLPHOSPHATES

by

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Joseph R. Stock

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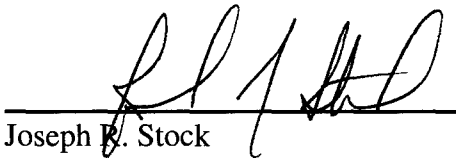

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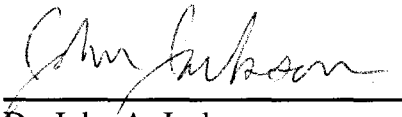

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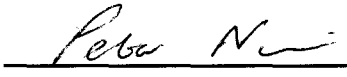

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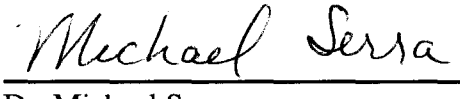

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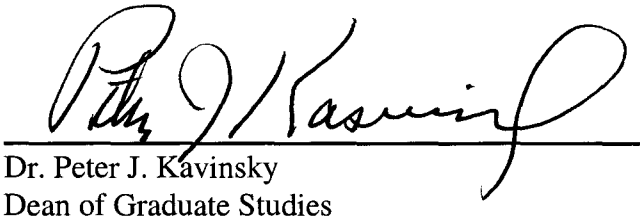

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ABSTRACT

The focus of the research presented here is the synthesis, isolation and characterization of vinyl phosphates containing the bis(2,2,2-trifluoroethyl) group. The first step involved the synthesis of bis(2,2,2-trifluoroethoxy) phosphorochloridate. This reagent was then added to a ketone enolate, formed by the reaction of LDA, prepared *in situ* from diisopropylamine and *n*-butyllithium, and a cyclic ketone to yield the desired vinyl phosphates.

ACKNOWLEDGEMENTS

I would like to thank Dr. John Jackson for his direction and guidance in conducting my research and the writing of this thesis. In addition, I would like to acknowledge and thank Dr. Peter Norris and Dr. Michael Serra for their contributions as members of my thesis committee. I would also like to thank my mother, father and the remainder of my family and friends who encouraged and supported me in the seemingly never-ending pursuit of this degree.

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LIST OF ABBREVIATIONS

Abbreviation	Description
Bn	benzyl
Bu	butyl
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
dq	doublet of quartets
Et	ethyl
g	gram
GC	gas chromatograph
HMPA	hexamethylphosphoramide
Hz	hertz
i-Pr	isopropyl
J	coupling constant (in Hz)
LDA	lithium diisopropylamine
m	multiplet
Me	methyl
mmol	millimole
mL	milliliter
n-Bu	butyl
NMR	nuclear magnetic resonance

n-Pr	propyl
Ph	phenyl
ppm	parts per million
s	singlet
t-Bu	*tert*butyl
TFEOH	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane

Chapter 1: Introduction

Part A: Phosphonates and their uses

Phosphonates have found uses in the fields of synthetic organic chemistry, biology and biochemistry. Phosphonates consist of a pentavalent phosphorus arranged as follows (Fig. 1):

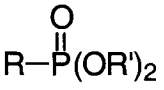
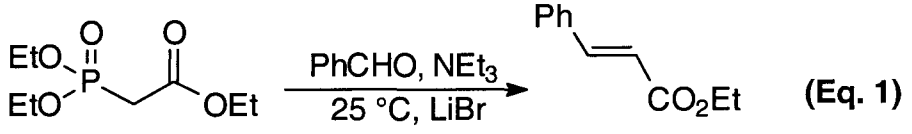
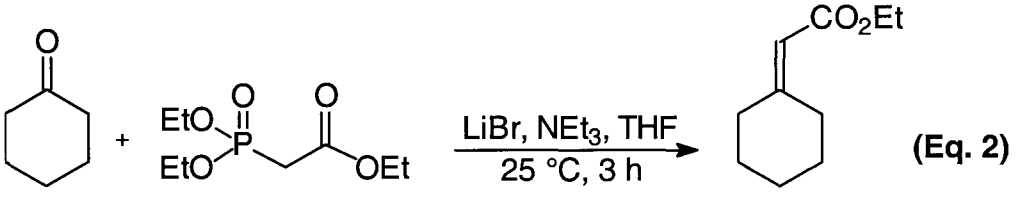


Figure 1: Spatial arrangement of phosphonates

Phosphonates' best known synthetic use is in the Horner-Wadsworth-Emmons (HWE) condensation which is often used to prepare α,β-unsaturated carbonyl compounds from condensations of an aldehyde or ketone with an anion stabilized by both a phosphonate and a second electron withdrawing group.[1] Examples of the HWE condensation are shown below (Eq. 1 and Eq. 2):[2]



(Eq. 1)



(Eq. 2)

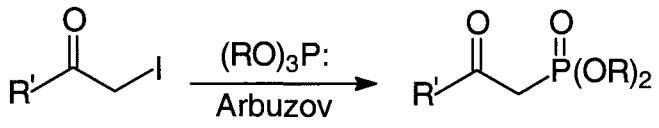
Phosphonates can also be employed to give access to other functional groups, including (but not limited to) nonconjugated olefins and cyclopropanes.[1]

Interest in the biological activity of phosphonates has increased dramatically in the past few years. This is due largely to the fact that phosphonates are close in structure to phosphate esters, which play an important role in metabolism. By replacing the oxygen of a phosphate ester with a methylene group, it not only greatly enhances the metabolic stability of the new compound, it affects the phosphorus acid pK_a's and eliminates the possibility of enzymatic interaction with non-bonded electrons at this site.[1]

A relatively new area of interest in phosphonate chemistry is their use in the preparation of catalytic antibodies. Phosphonates are believed to imitate a high-energy intermediate in acyl transfer reactions when in their monoester, mono-anionic forms. When phosphonates are used to stimulate an immune response they can serve as transition state analogues leading to the formation of antibodies that stabilize reaction intermediates and express catalytic activity.[1]

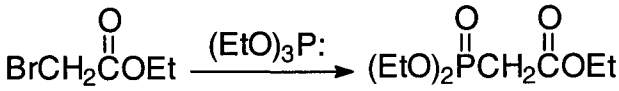
Part B: Phosphonate synthesis with a nucleophilic phosphorus reagent.

Preparative routes for α-, β- and γ-hydroxy phosphonates, α-amino phosphonates and α- and β-keto phosphonates have been studied and discussed in different articles. β-keto phosphonates have been studied extensively due to their usefulness in the HWE condensation. There are two common methods that have been utilized for the synthesis of β-keto phosphonates and α-phosphonoesters, the Arbuzov reaction and the acylation of alkyl phosphonate anions. The Arbuzov reaction involves treating a nucleophilic trialkyl phosphite with an α-halo ester or acyclic α-halo ketones (Eq. 3).[3]



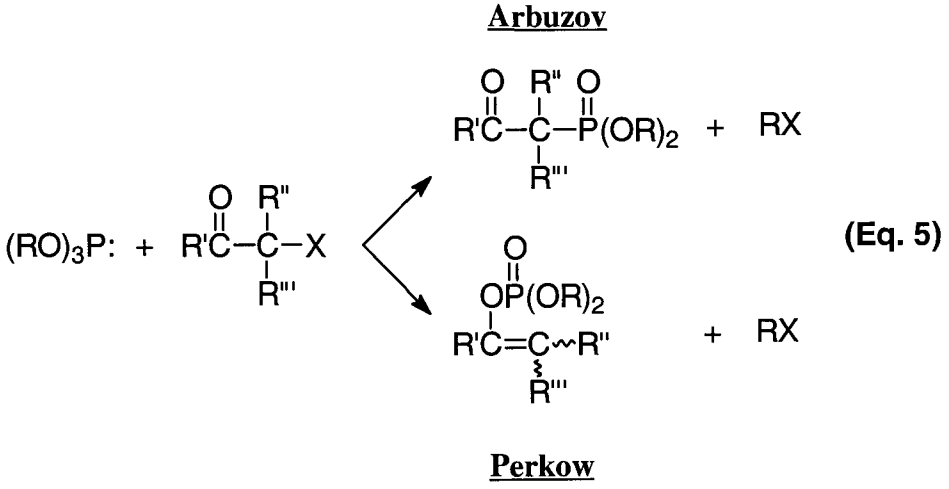
(Eq. 3)

One example of the Arbuzov reaction follows (Eq. 4):



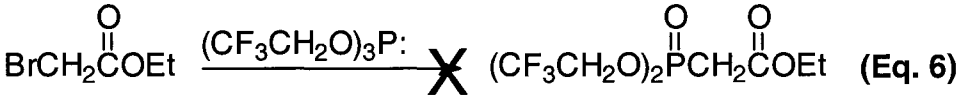
(Eq. 4)

In the synthesis of β-keto phosphonates the Arbuzov reaction works best with nucleophilic phosphites[4] and α-iodo ketones that readily undergo substitution reactions. The limitations of the Arbuzov method are 1) primary α-bromo or α-chloro ketones and cyclic α-halo ketones often undergo a competitive Perkow reaction[5,6,7] (Eq. 5) which affords the isomeric vinyl phosphates and 2) substitution reactions are difficult for secondary halides, thereby limiting the usefulness of this reaction with any secondary α-halo ketones.[5]



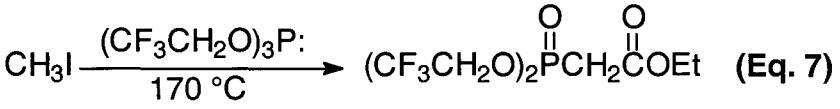
(Eq. 5)

Employing weakly nucleophilic trialkyl phosphites is also problematic and the following reaction fails due to the weakly nucleophilic character of the tris(2,2,2-trifluoroethyl) phosphite (Eq. 6).



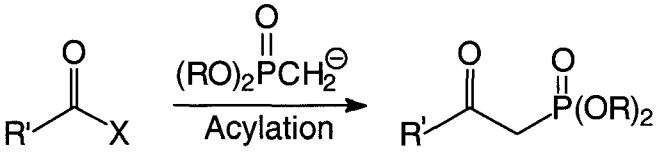
(Eq. 6)

The reaction of methyl iodide with tris(2,2,2-trifluoroethyl) phosphite will proceed but only under the harsh condition of being heated to 170 °C in a sealed tube (Eq. 7).[8]



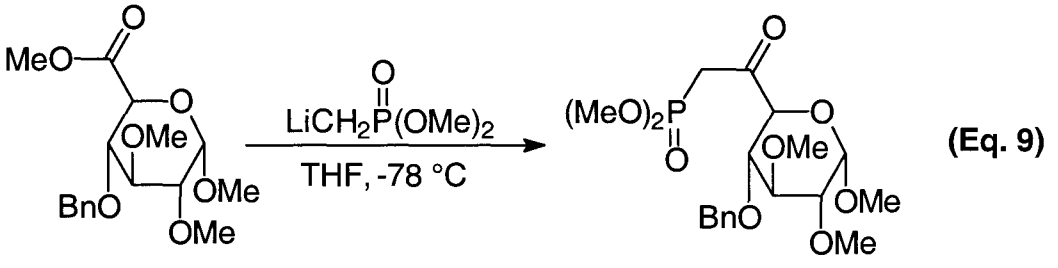
(Eq. 7)

The second method involves the acylation of alkyl phosphonate esters (Eq. 8).[9]



(Eq. 8)

One example of the acylation is (Eq. 9):[2]

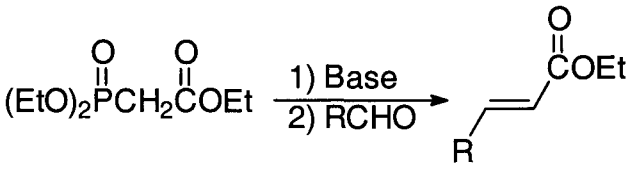


(Eq. 9)

This strategy can be employed to prepare α-substituted phosphono ketones. The acylation reaction is limited by the availability of alkyl phosphonates.

The two methods discussed above, the Arbuzov reaction and the acylation of alkyl phosphonate esters, each have their separate limitations but both share the common limitation of relying upon a nucleophilic phosphorus reagent.

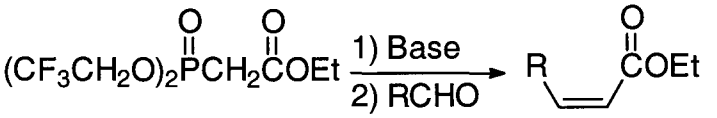
In the HWE reaction treatment of a phosphoryl stabilized anion with an aldehyde shows a preference for the formation of the (*E*)-α,β-unsaturated carbonyl compounds in high yields (Eq. 10).[7,10]



(Eq. 10)

The traditional Arbuzov reaction can be used to synthesize the phosphonate shown above and others like it.

Still has shown that by making the phosphonate ester an electron withdrawing group such as the 2,2,2-trifluoroethyl group the (*Z*)-α,β-unsaturated ester can be obtained in high yields (Eq. 11).[11]

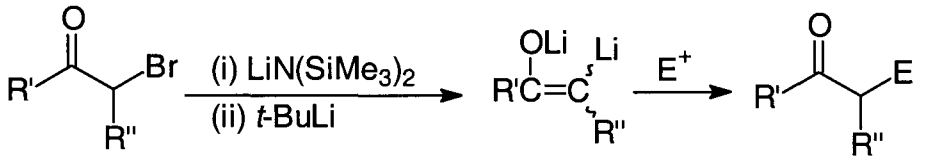


(Eq. 11)

The above phosphonates, however, are not easily synthesized by the Arbuzov reaction and therefore, a new method needed to be developed.

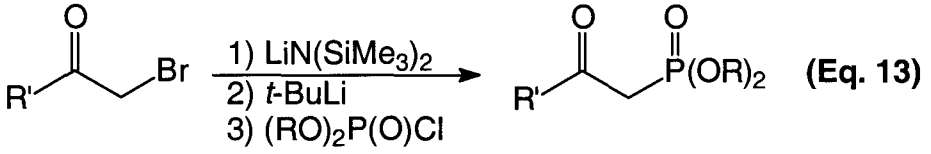
Part C: Phosphonate synthesis with an electrophilic phosphorus reagent.

Since nucleophilic substitution on cyclic systems is difficult and employing weakly nucleophilic trialkyl phosphites in the traditional Arbuzov reaction is also problematic, a better method for these systems was desirable. A newer method, called the dianionic or Umpolung (reverse polarity) approach,[12] relied upon a electrophilic phosphorus reagent (Eq. 12).



(Eq. 12)

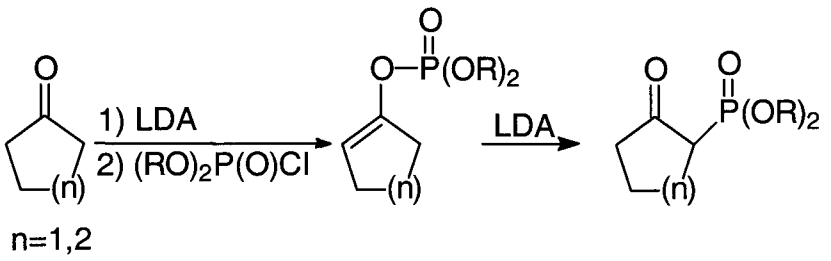
One such reaction involves the use of α-bromo ketones to give β-keto phosphonates (Eq. 13):[5]



(Eq. 13)

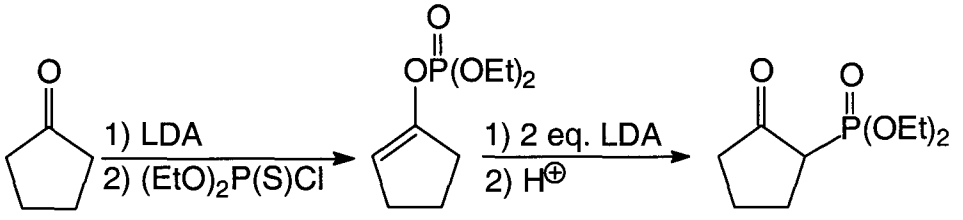
This method allows the use of secondary α-halo ketones and electrophilic phosphorus reagents.

Wiemer has developed new methods for the synthesis of a variety of phosphonates.[1,4,13] By utilizing an electrophilic phosphorous reagent he has arrived at β-keto phosphonates, α-phosphono lactones and esters. The method utilized for synthesizing β-keto phosphonates, from cyclic ketones of 5 or 6 carbons, utilizes a 1,3-phosphorus migration of vinyl phosphonates to produce the β-keto phosphonates (Eq. 14).[13a,b,h,j]



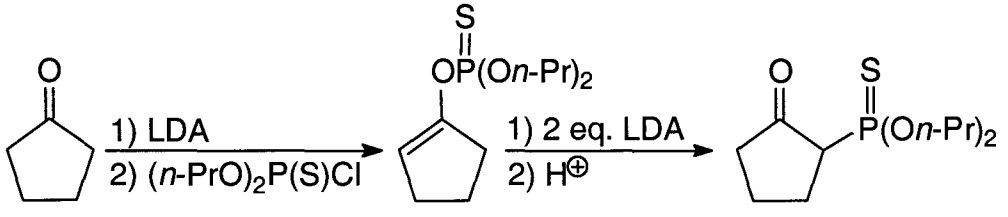
(Eq. 14)

The first step involves the formation of a vinyl phosphate from the reaction of a dialkyl phosphorochloridate with an enolate, formed by the reaction of LDA (lithium diisopropylamide) and a ketone. From here, the phosphorochloridate is treated with 2 equivalents LDA and a 1,3-phosphorus migration occurs giving the β-keto phosphonate. The following is one example(Eq.15):[13a]



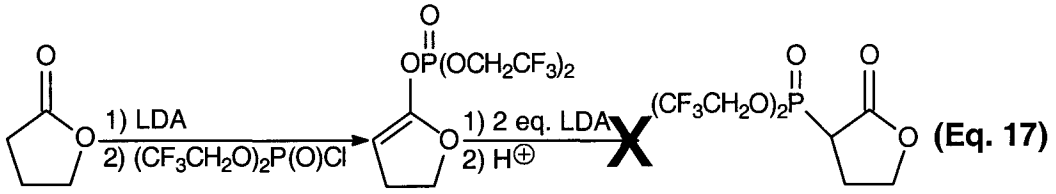
(Eq. 15)

Vinyl thiophosphates undergo a similar rearrangement. However, the reaction is much slower due to the lower electrophilicity of the thiophosphoryl group (Eq. 16).[13c]

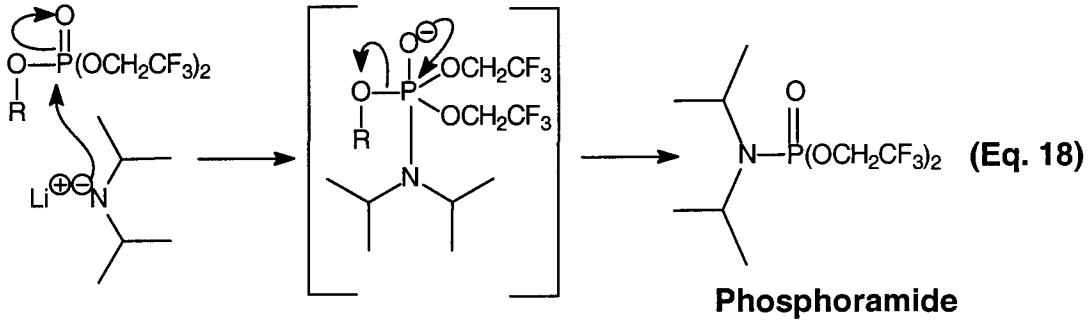


(Eq. 16)

Vinyl phosphates containing the bis(2,2,2-trifluoroethoxy) phosphinyl group do not undergo this rearrangement (Eq. 17). Rather, displacement of the enolate resulting from nucleophilic attack by LDA upon phosphorus produces a phosphoramide byproduct (Eq. 18). The cause of this displacement was determined to be the high electrophilicity at phosphorus.[14]



(Eq. 17)



(Eq. 18)

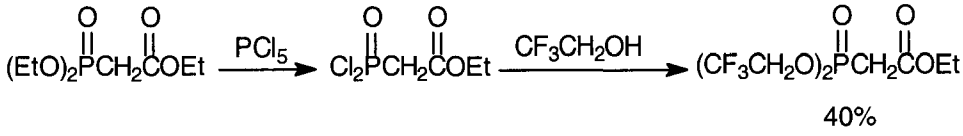
Phosphoramide

Part D: Synthesis of trifluoroethyl phosphonates

There are several other methods utilized for the synthesis of trifluoroethyl phosphonates that do not rely upon a nucleophilic or electrophilic phosphorus reagent.

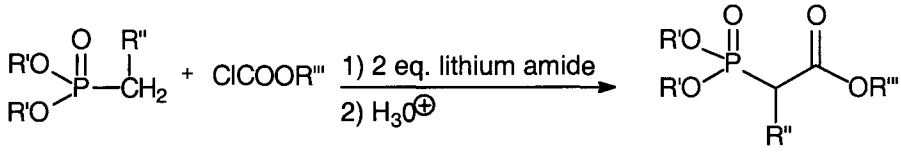
A method utilized by Still,[11] involves treating an α-phosphono ester with phosphorus pentachloride (PCl_5), thus forming the phosphoric dichloride followed by

addition of 2,2,2-trifluoroethanol (Eq. 19). The usefulness of this reaction is limited due to the harsh reaction conditions required for various α-phosphonoesters.[14,15]



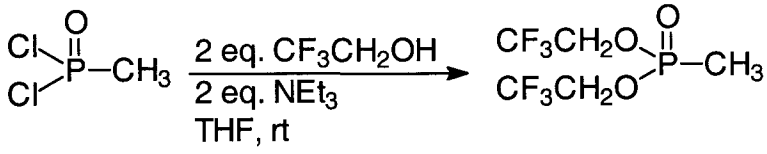
(Eq. 19)

Another method developed by Patois, Savignac, *et al.*, is a general method for the one-pot formation of phosphonocarboxylates and enolates. It involves treating an alkylphosphonate with a chloroformate to give the phosphonocarboxylates and enolates.[16] The general reaction scheme is as follows (Eq. 20):



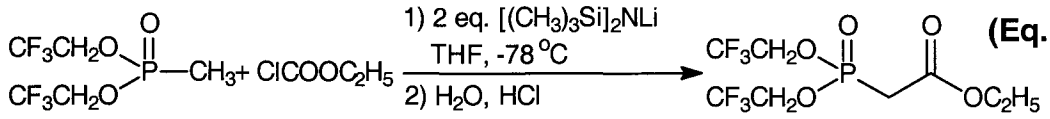
(Eq. 20)

The first step in the synthesis is the preparation of the starting alkyl phosphonate. In the following example a solution of methylphosphonic dichloride in anhydrous THF is reacted with a solution of trifluoroethanol and triethylamine in THF, thus forming the bis(trifluoroethyl) methylphosphonate (Eq. 21).



(Eq. 21)

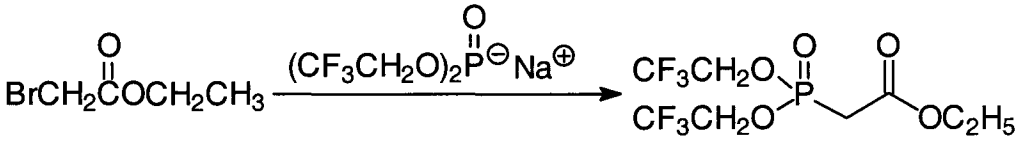
The second step involves taking the alkyl phosphonate from Eq. 21 and reacting it with an enolate (formed from the reaction of ethyl chloroformate and a lithium amide) to give bis(trifluoroethyl) (carboethoxymethyl)phosphonate (Eq. 22).



(Eq. 22)

By varying the choice of starting alkylphosphonate, $(R^1O)_2P(O)CH_2R^2$ where R^2=Me, Et, Pr, etc., the above reaction (Eq. 20) may be extended to α-alkylated phosphonocarboxylates. In conjunction, various carboxylate groups may be obtained by varying the choice of chloroformate ($ClCO_2R^3$; R^3=Me, Et, *i*-Pr, *t*-Bu, etc.).

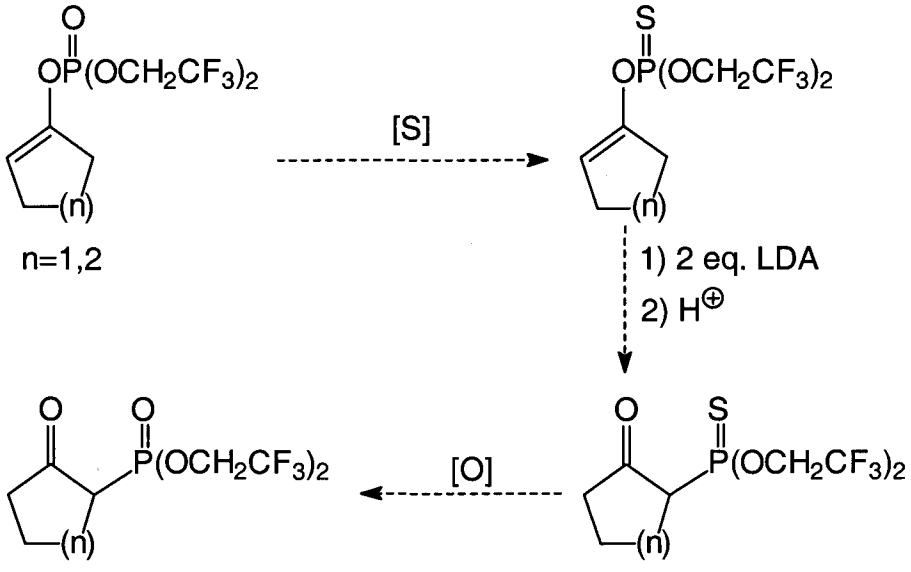
Ciszewski has synthesized trifluoroethyl phosphonates similar to Still and Savignac, but in a cleaner one-step reaction. The compounds are synthesized from the reaction of ethyl bromoacetate and the anion of bis(2,2,2-trifluoroethyl) phosphite to give the bis(trifluoroethyl) phosphonate in approximately 50% yield (Eq. 23).[17]



(Eq. 23)

Part E: Statement of Purpose

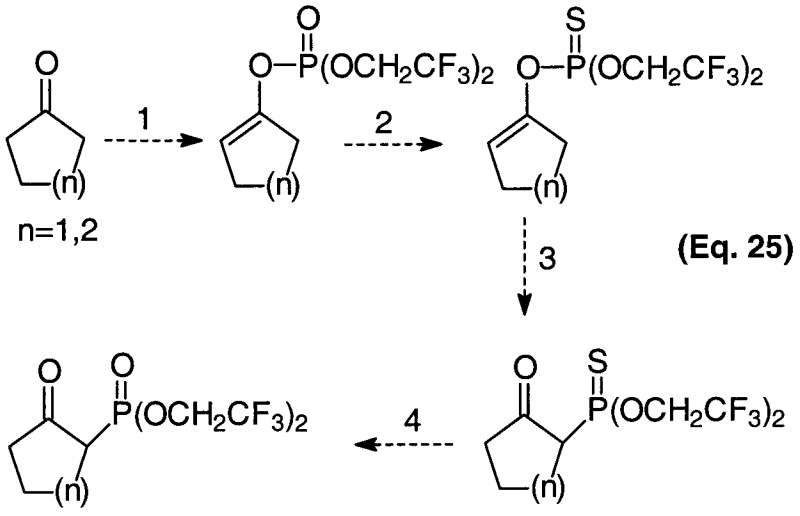
It has been shown that vinyl phosphates and vinyl thiophosphates containing the bis(ethoxy) phosphinyl group will undergo a 1,3-phosphorus migration to form the β-keto phosphonate.[13a,b,h,j] The rearrangement of the vinyl thiophosphate proceeds at a much slower rate due to the lower electrophilicity of phosphorus in the phosphorus-sulfur double bond.[13c] However, vinyl phosphates containing the bis(2,2,2-trifluoroethoxy)phosphinyl group due not undergo this 1,3-migration. Rather, a phosphoramide byproduct is formed do to the displacement of the enolate by LDA, due to the high electrophilicity at phosphorus.[14] By protecting the bis(2,2,2-trifluoroethoxy)phosphinyl group as the vinyl thiophosphate the 1,3-migration should proceed due to the less electrophilic phosphorus. After rearrangement occurs, oxidation of the β-keto thiophosphonate[18] should supply the desired β-keto phosphonate containing the bis(2,2,2-trifluoroethyl) group (Eq. 24).



(Eq. 24)

Chapter 2: Results and Discussion

The initial focus of this research was the synthesis of vinyl phosphonates and β-keto phosphonates, containing the bis(2,2,2-trifluoroethoxy) group, through a four step reaction sequence (Eq. 25).



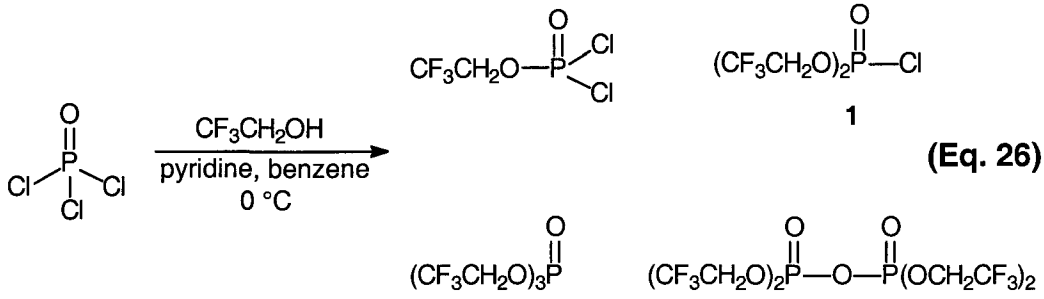
(Eq. 25)

Sequence
1) Synthesis of Vinyl Phosphate
2) Thionation
3) 1,3-Rearrangement
4) Oxidation

Synthesis of bis(2,2,2-trifluoroethoxy) phosphorochloridate (**1**)

Prior to the synthesis of the vinyl phosphate, we needed to synthesize our electrophilic phosphorus reagent: bis(2,2,2-trifluoroethoxy) phosphorochloridate (**1**). The first method attempted was based upon the literature method developed by K. Sellars.[19] The method consisted of a two-step reaction with a fractional vacuum distillation required

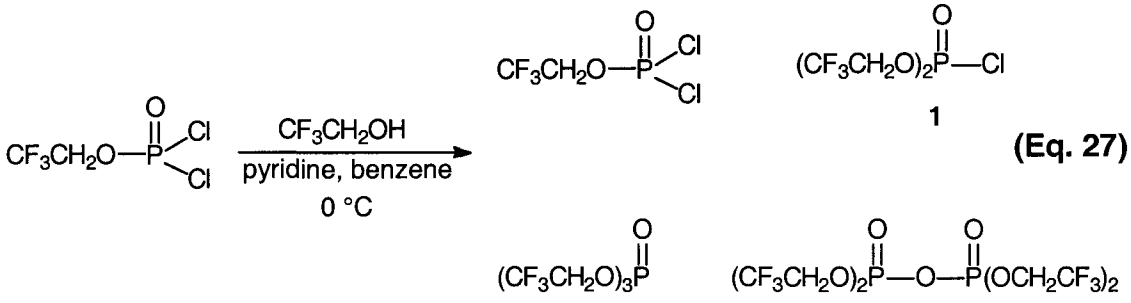
for each step. The first step involved the addition of 2,2,2-trifluoroethanol, pyridine and benzene to phosphorus oxychloride at 0 °C for one hour (Eq. 26).



(Eq. 26)

The possible products were: (2,2,2-trifluoroethoxy) phosphorodichloridate, the desired product of the first reaction, bis(2,2,2-trifluoroethoxy) phosphorochloridate (**1**), the desired final product, along with two byproducts (tris(2,2,2-trifluoroethyl) phosphate and tetrakis(2,2,2-trifluoroethoxy) pyrophosphate) and any other impurities or unreacted starting materials.

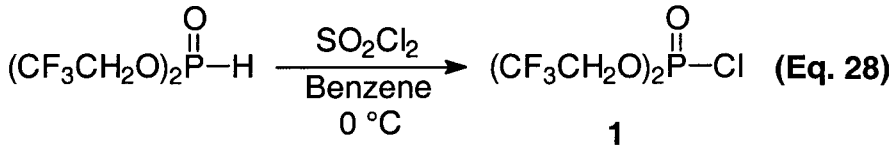
In the second step, 2,2,2-trifluoroethanol, pyridine and benzene were added to the pure (2,2,2-trifluoroethoxy) phosphorodichloridate from step 1 (Eq. 27).



(Eq. 27)

The product was a mixture of bis(2,2,2-trifluoroethoxy) phosphorochloridate (**1**), the two impurities mentioned above, along with any unreacted starting materials. The yields reported by Sellars were unattainable. Neither pure (2,2,2-trifluoroethoxy) phosphorodichloridate or bis(2,2,2-trifluoroethoxy) phosphorochloridate was obtained by this procedure.

Based upon these results, a new method for the synthesis of the bis(2,2,2-trifluoroethoxy) phosphorochloridate needed to be devised. The new synthesis was derived from the Sosnovsky and Zaret general procedure for the preparation of dialkyl chlorophosphates from the corresponding dialkyl phosphites.[20] In this method bis(2,2,2-trifluoroethyl) phosphite in benzene was treated with sulfuryl chloride in benzene at 0 °C (Eq. 28). This reaction afforded quantitative formation of the desired bis(2,2,2-trifluoroethoxy) phosphorochloridate (**1**). Distillation of the product mixture produced compound **1** in 92.7% yield.



(Eq. 28)

The ^{13}C NMR spectra of compound **1** shows the two doublet of quartets (dq) that are expected, based on the carbons of the trifluoroethoxy group coupling to the one phosphorus atom and the three fluorine atoms (Fig. 2).

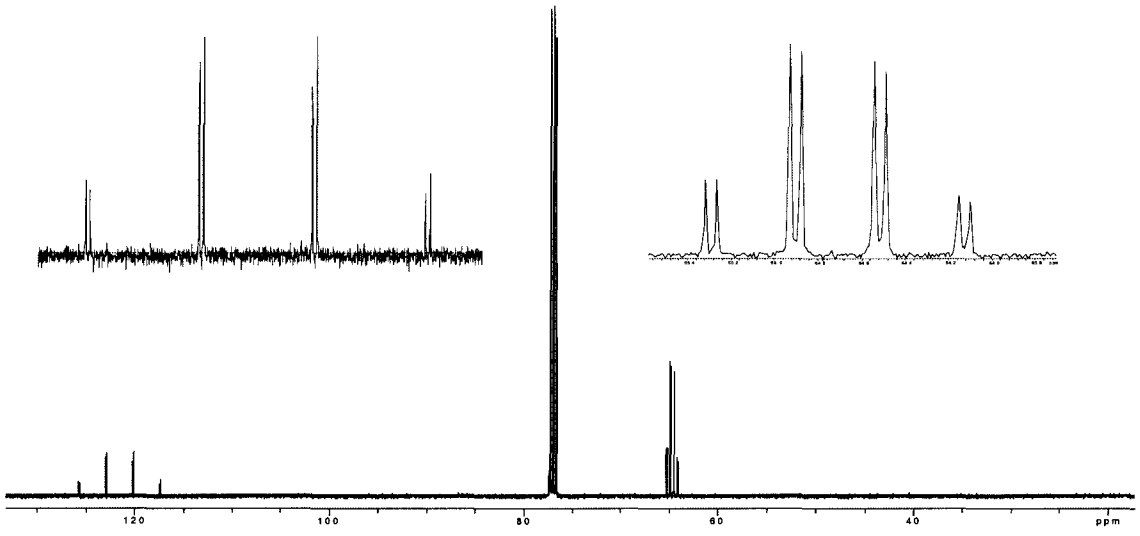


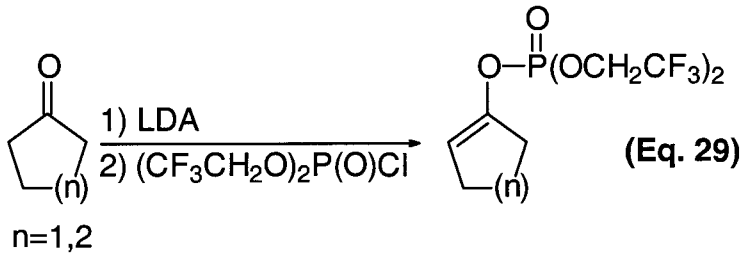
Figure 2: ^{13}C NMR of bis(2,2,2-trifluoroethoxy) phosphorochloridate (**1**)

The first doublet of quartets at 121.58 ppm is the carbon of the CF_3 group and the second doublet of quartets at 64.70 ppm is the carbon of the CH_2. The carbon of the trifluoromethyl group shows a much larger C-F coupling constant (277.0 Hz) as compared to the carbon of the methylene (38.9 Hz) due to its direct bonding to the three fluorine atoms. The C-P coupling constant does not vary as greatly between the CF_3 versus the CH_2 (11.4 Hz vs. 5.3 Hz). These characteristic NMR signals will be prevalent in all the compounds synthesized here and will be an indication of the desired product being formed.

Synthesis of Vinyl Phosphates - **2**, **3** and **6**

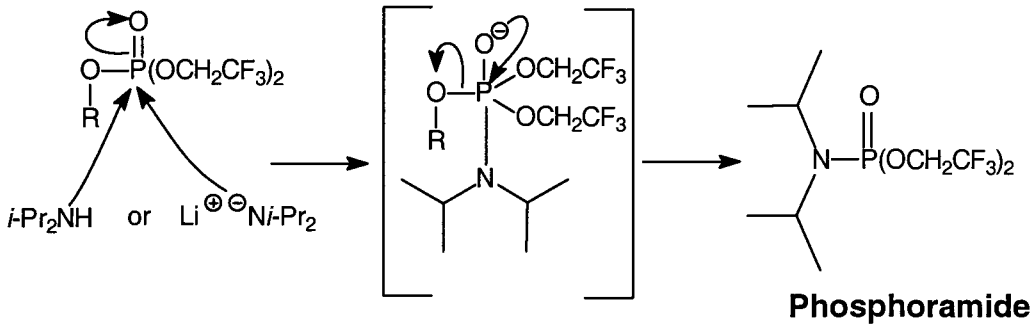
After synthesizing compound **1,** the next step was to form the vinyl phosphate from the reaction of compound **1** and a series of ketone enolates. The general procedure for the synthesis of vinyl phosphates was as follows: To a solution of LDA [6.0 mmol,

prepared *in situ* from diisopropylamine (0.80 mL) and *n*-butyllithium (3.75 mL, 1.6 M in hexane)] in anhydrous THF (15 mL) at -78°C was added dropwise *via* pressure equalizing addition funnel a solution of ketone (*x* mL, 5 mmol) in THF (10 mL). After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The synthesis was initially attempted with cyclopentanone, cyclohexanone and camphor as representative 5 and 6 membered ketones (Eq. 29).



(Eq. 29)

The results for cyclopentanone and cyclohexanone were disappointing in that the crude yield of the vinyl phosphate of cyclopentanone (**2**) by GC was in the 50-60% range, with starting material and phosphoramide byproduct (Eq. 30) in crude yields above 10% each. The cyclohexanone vinyl phosphate (**3**) yield was in the 60-70% range by GC with smaller amounts of starting materials and phosphoramide byproduct.



In an attempt to increase the yields for compounds **2** and **3** a number of steps were taken. The first was to distill both cyclohexanone and cyclopentanone from CaH_2, because water would be detrimental to our reaction due to the fact it would quench LDA, thus preventing formation of the enolate (Eq. 31).

$$Li^{\oplus\ominus}N\textit{i}\text{-}Pr_2 + H_2O \longrightarrow LiOH + \textit{i}\text{-}Pr_2NH \qquad \textbf{(Eq. 31)}$$

Next, two variables within the reaction were changed. The first was to add HMPA as a polar co-solvent and the second was to try an aqueous work up as opposed to the non-aqueous described in the general methods. HMPA is a very polar, aprotic co-solvent and Jackson[14] has shown that by adding 1.1 eq. of HMPA to the reaction mixture, quantitative yields of vinyl phosphates are obtained from the reaction of ester and/or lactone enolates with dialkyl chlorophosphates. Changing only one variable at a time, there was a total of four reactions attempted for both cyclohexanone and cyclopentanone. The crude yields by GC were of no significant difference between the reactions in both

cyclohexanone and cyclopentanone. Though the yields from inclusion of HMPA with an aqueous workup were slightly higher by GC, the crude yield by weight was less than the general procedure, therefore making the difference in yield insignificant. Based on this, the use of HMPA was stopped due to its toxicity, and the non-aqueous workup was utilized since it afforded a slightly better yield. Due to these poor crude yields, and the formation of unwanted byproducts, the yields for compounds **2** and **3** after purification by flash chromatography were 10-15 %.

When the vinyl phosphate synthesis was attempted with camphor, we obtained the vinyl phosphate of camphor (**6**) in 65% yield. The ^{13}C NMR spectra of compound **6** shows the two doublet of quartets that are expected in the vinyl phosphates based on the previous discussion of compound **1**. However, compound **6** contains a chiral center, which would make the carbons of the trifluoroethoxy group non-equivalent. The methylene carbons in this group do not show up as a single doublet of quartets, rather, each shows up as a separate doublet of quartets in close proximity to each other (Fig. 3). The carbons of the trifluoroethyl group, however, show up as a single doublet of quartets (Fig. 4).

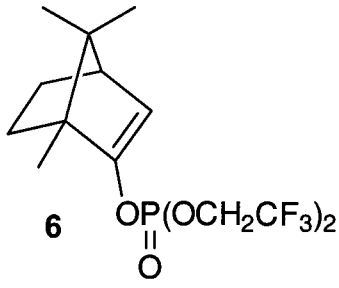


Figure 3: Structure of the vinyl phosphate of camphor (**6**)

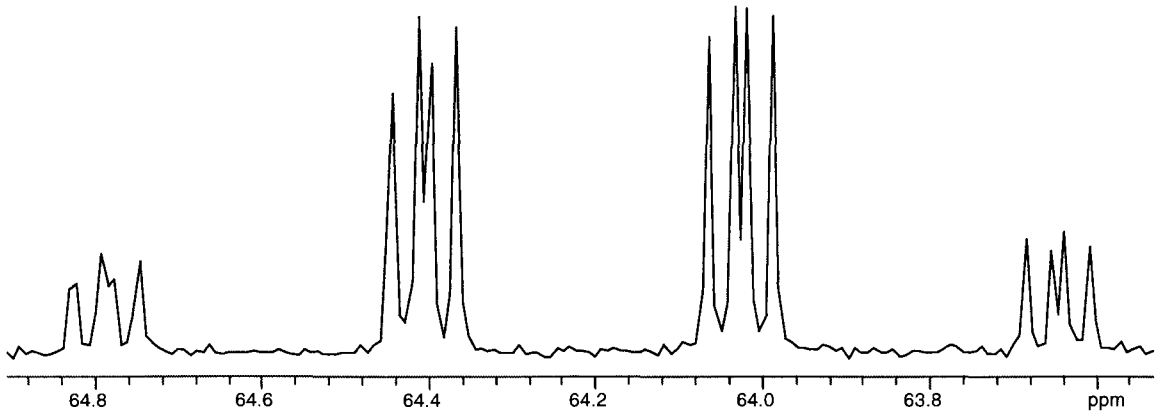


Figure 4: ^{13}C NMR of the CH_2 of the trifluoroethoxy groups of compound **6**

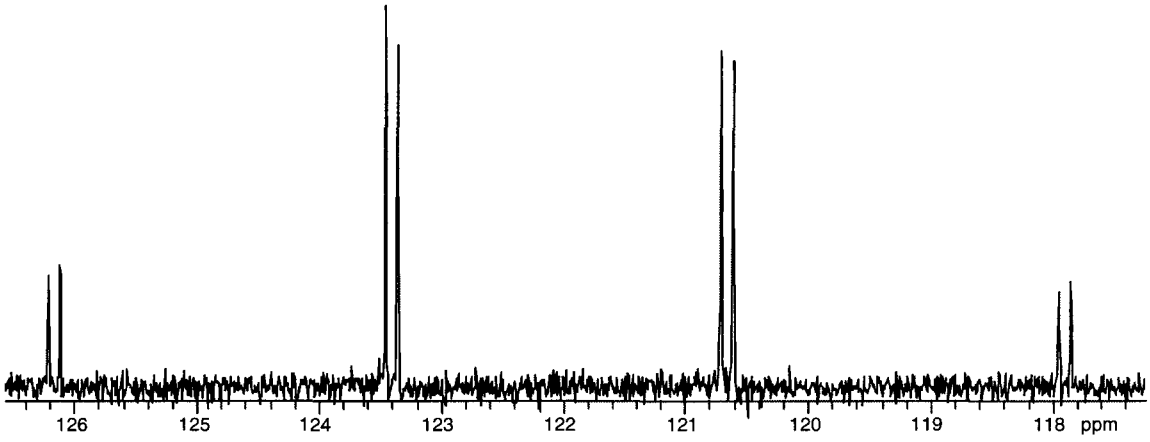


Figure 5: ^{13}C NMR of the CF_3 of the trifluoroethoxy groups of compound **6**

The ^{13}C NMR of the vinyl phosphates show two doublets of quartets for the carbons of the trifluoroethoxy group. The spectra will also show the two vinylic carbons (**a** and **b** from Fig. 5) as doublets (Fig. 6) due to their proximity to the phosphorus atom. Carbon **a** will be located between 155-144 ppm while carbon **b** will be located between 120-110 ppm.

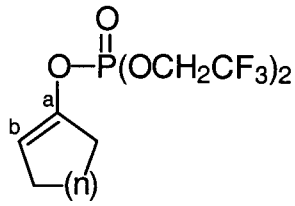


Figure 6: Structural arrangement of vinyl phosphates

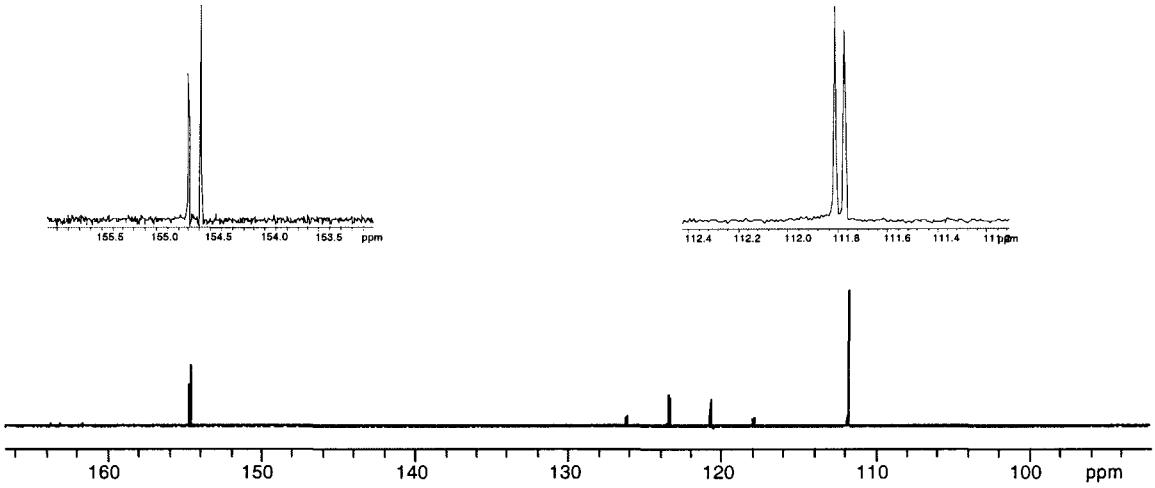


Figure 7: ^{13}C NMR of the vinylic carbons of the camphor vinyl phosphate (**6**)

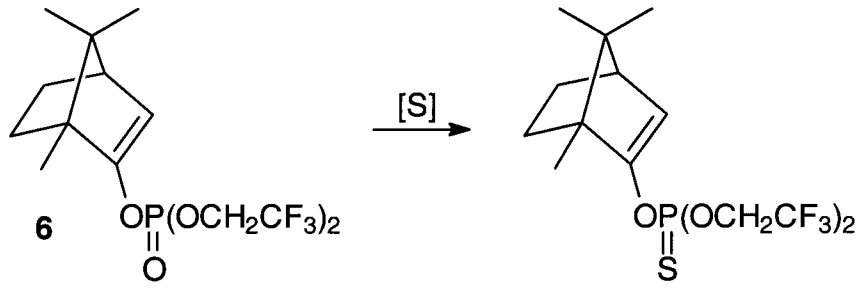
The remainder of the carbons in the vinyl phosphates will show up as singlets or doublets depending upon their proximity to the phosphorus atom.

Synthesis of the Vinyl Thiophosphate

The next step was to take a vinyl phosphate **6** and attempt the thionation reaction. This thionation was attempted based on the fact that the vinyl thiophosphate is less electrophilic at phosphorus than the vinyl phosphate and, therefore, in step 3 of the β-keto

phosphonate synthesis, the LDA should abstract a proton from the ring thus allowing the 1,3 migration of phosphorus from oxygen to carbon to occur.

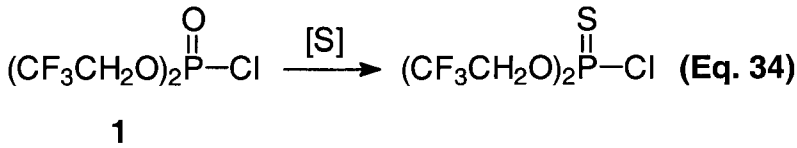
The thionation was attempted utilizing the following thionating reagents: Lawesson's reagent, sulfur, highly purified sulfur and phosphorus pentasulfide. The general procedure for the reaction was to add the thionating reagent (equivalents vary based upon thionating agent utilized) to a 0.25 M solution of vinyl phosphate in toluene and then to reflux this mixture overnight (Eq. 33).



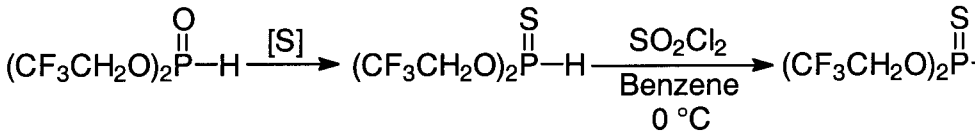
(Eq. 33)

The byproduct of the reaction was to be SO_2 which would be given off as a gas. The toluene would then be removed by rotary evaporation yielding the vinyl thiophosphate. The sulfur and highly purified sulfur returned nearly 100 % starting vinyl phosphate as determined by GC. The Lawesson's reagent and the phosphorus pentasulfide both left large amounts of starting materials as determined by ^{31}P NMR and GC. Reaction conditions were changed by adding excess amounts of the thionating reagent. This did not produce the desired vinyl thiophosphate and large amounts of starting materials remained. One option for the future preparation of the vinyl thiophosphate would be to synthesize the thiophosphorochloridate by thionating

compound **1** (Eq. 34) or thionating the phosphite and then synthesizing the thiophosphorochloridate (Eq. 35).



(Eq. 34)



(Eq. 35)

Synthesis of Vinyl Phosphates - **4**, **5**, **7**, **8**, **9**, and **10**

Since the results of the thionation reaction were less than ideal the decision was made to synthesize other vinyl phosphates. In addition to vinyl phosphates **2**, **3** and **6** that were synthesized earlier three additional ketones (cycloheptanone, cyclododecanone, norcamphor) and three enones (carvone, 2-cyclohexen-1-one, α-tetralone) would be utilized in the vinyl phosphate synthesis. Yields for each reaction can be seen in Table 1.

As discussed earlier, the vinyl phosphates are characterized in ^{13}C NMR by the presence of 2 doublet of quartets for the trifluoroethoxy group and the two doublets for the vinylic carbons. The remainder of the carbons show up as singlets or doublets depending on their proximity to the phosphorus atom. In compound **5** it is interesting to note that due to the large ring structure, the carbons that are furthest from the phosphorus (20-30 ppm) are similar to the point that they overlap. Though the peaks appear to be doublets, they are actually overlapping singlets (Fig. 7).

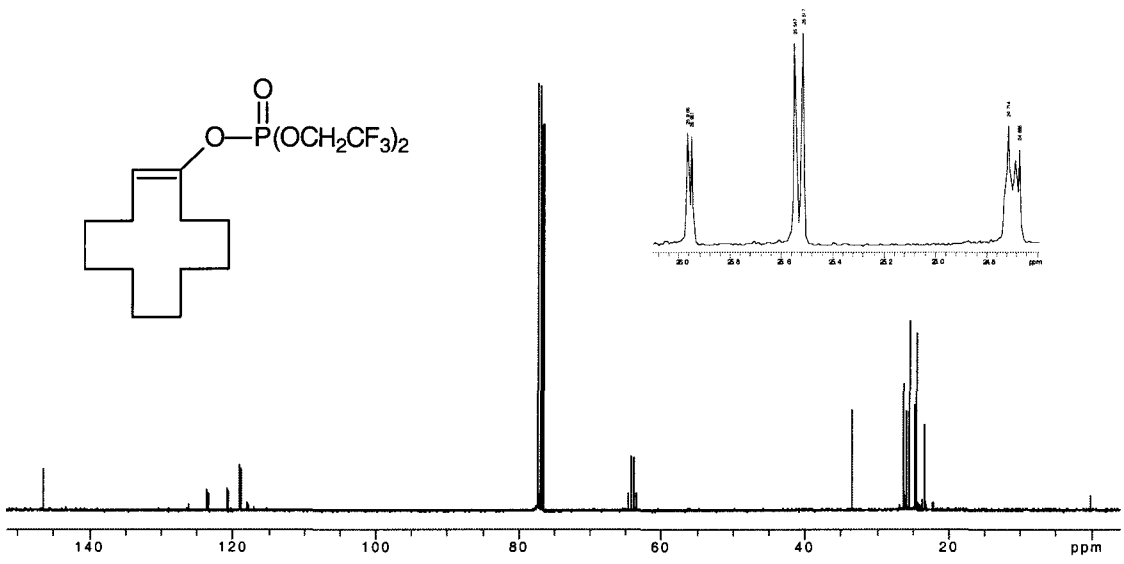
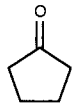
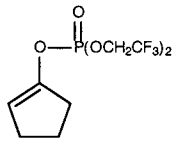
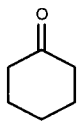
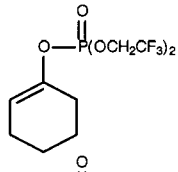
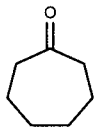
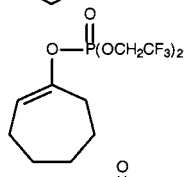
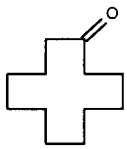
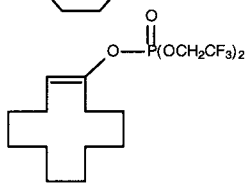
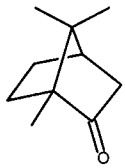
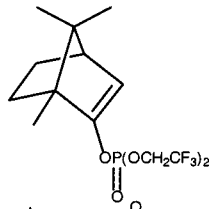
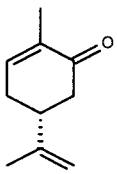
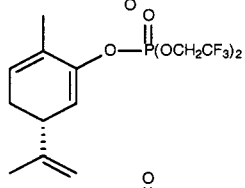
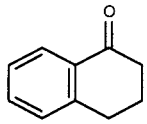
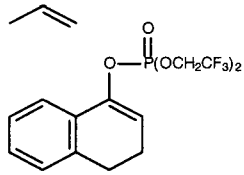
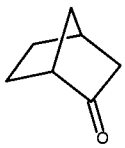
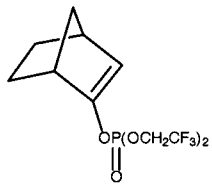
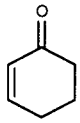
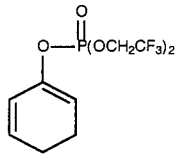
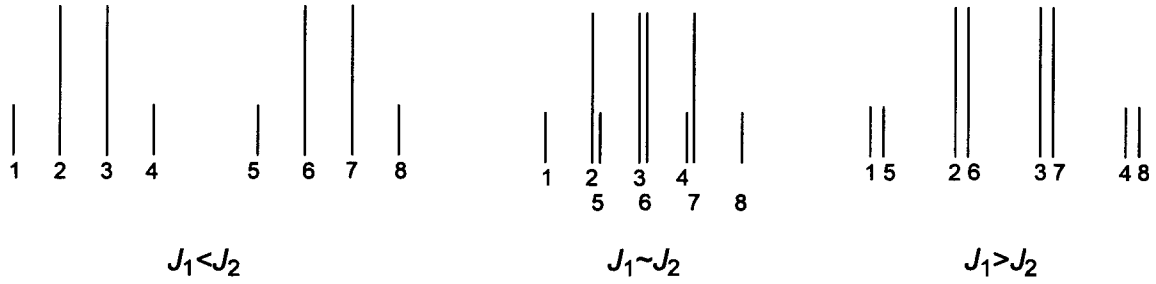


Figure 8: ^{13}C NMR of the vinyl phosphate of cyclododecanone (**5**)

In their ^{1}H NMR spectra, the vinyl phosphate products are characterized by the proton resonances of the CH_2 of the trifluoroethoxy group at around 4.5 to 4.4 ppm. In theory they should show up as doublet of quartets based on their coupling to fluorine and phosphorus, however, they usually show up as multiplets (m). However, in compounds **3** and **4** they do show up as a doublet of quartets (Figs. 8 and 9) but not as eight separate peaks as seen in the ^{13}C NMR. Due to overlapping, the dq shows up as five peaks with peak 2=5, 3=6 and 4=7 (see Fig. 9). Because the C-F and C-P coupling constants are identical (8.1 Hz in both compounds **3** and **4**) the overlap occurs.

Table 1. Yields of Vinyl Phosphates

Ketone	Vinyl Phosphate		Yield
		**2**	12%
		**3**	15%
		**4**	62%
		**5**	67%
		**6**	65%
		**7**	65%
		**8**	81%
		**9**	7% (by GC)
		**10**	68% (by GC)



Three typical splitting patterns for a doublet of quartets are illustrated above. In the first example, J_1 (the coupling constant for each quartet) is much smaller than J_2 (the separation of the two quartets). In the middle example, both J values are about the same, and in the last example J_1 is much greater than J_2.

Figure 9: Typical splitting patterns for a doublet of quartets

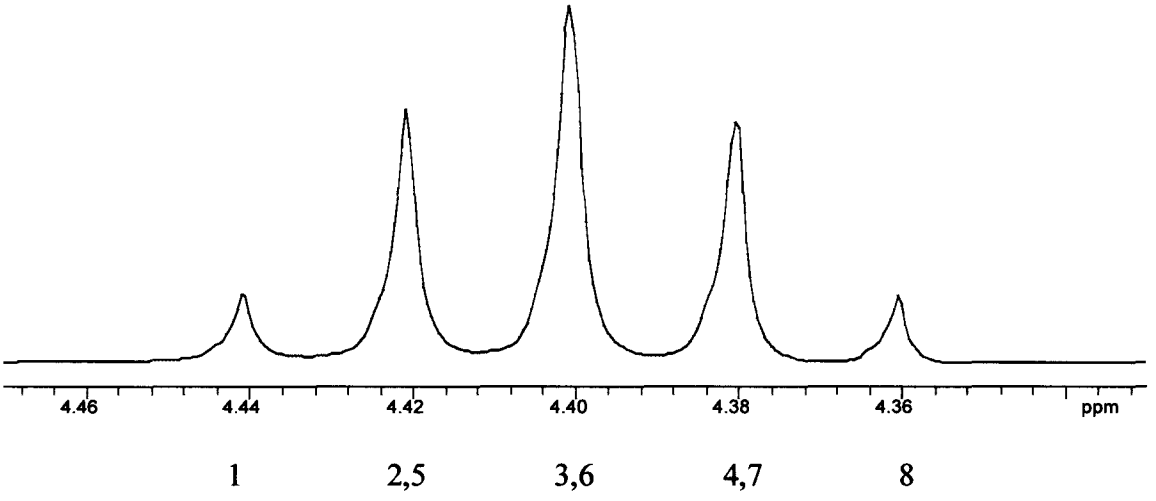


Figure 10: ^{1}H NMR of the overlapping dq of methylene H's from the trifluoroethoxy group of compound **4** (where $J_1 \approx J_2$)

The vinyl phosphate products are characterized by a second proton resonance for the vinylic proton (H_v in Fig. 11) between 6 and 5 ppm.

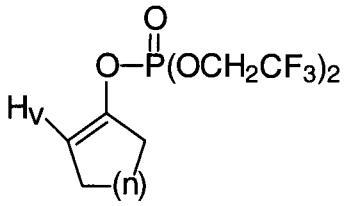


Figure 11: Vinylic proton (H_v) of vinyl phosphates

In theory the proton should show up as a doublet of doublet of doublets (ddd) based on its coupling to phosphorus and the two non equivalent protons in the adjacent allylic position. A doublet of doublet of doublets is characterized by eight separate peaks, provided the three coupling constants (J_1, J_2 and J_3) are significantly different in value (Fig. 12). In the bicyclic compounds, camphor vinyl phosphate (**6**) and norcamphor vinyl phosphate (**9**), we would expect the resonance to appear as a doublet of doublets. This is due to the fact the bridgehead occurs at the adjacent allylic position therefore, only one proton will be found in this position. In the vinyl phosphates synthesized four of seven display the vinylic proton as a multiplet (compounds **3**, **5**, **6** and **7**). However, compounds **2**, **4** (Fig. 13) and **8** (Fig. 14) do display the expected doublet of doublet of doublets. Due to the fact the coupling constants for coupling to the allylic protons are identical (J_1=J_2), the doublet of doublet of doublets does not appear as eight separate peaks, rather, it appears as six peaks (with 3=5 and 2=6).

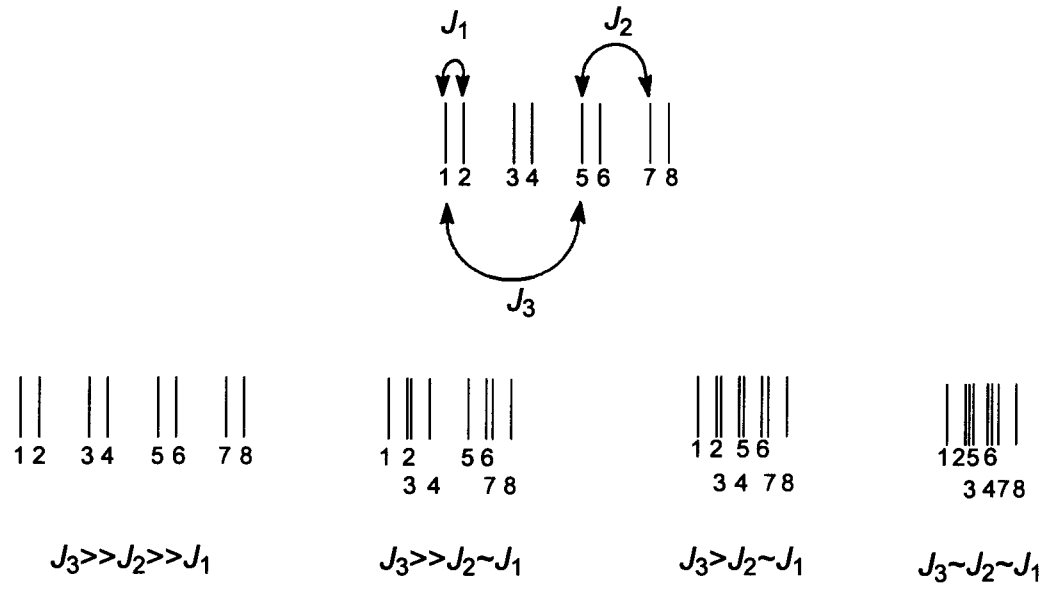


Figure 12: Typical splitting patterns for a doublet of doublet of doublets

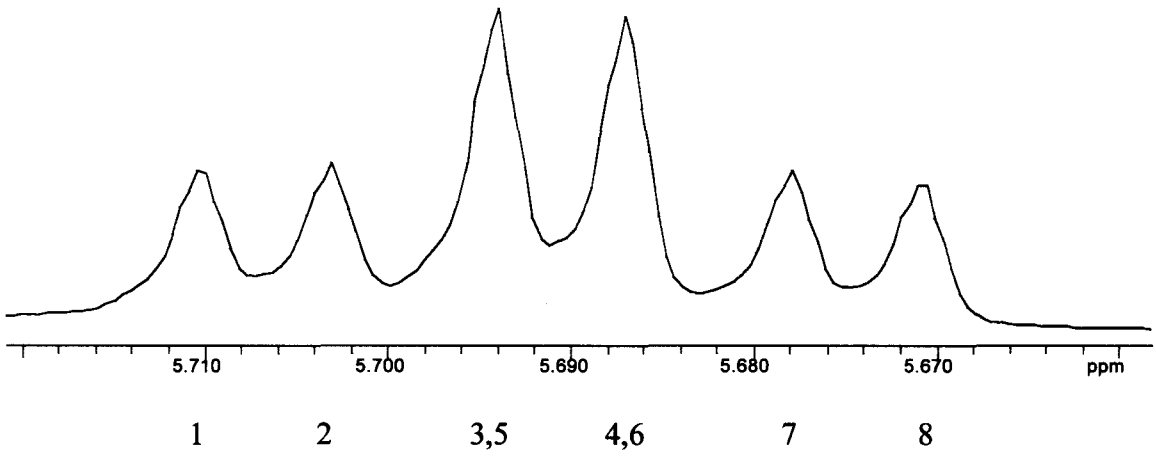


Figure 13: ^{1}H NMR of the ddd of the vinylic proton of compound **4**

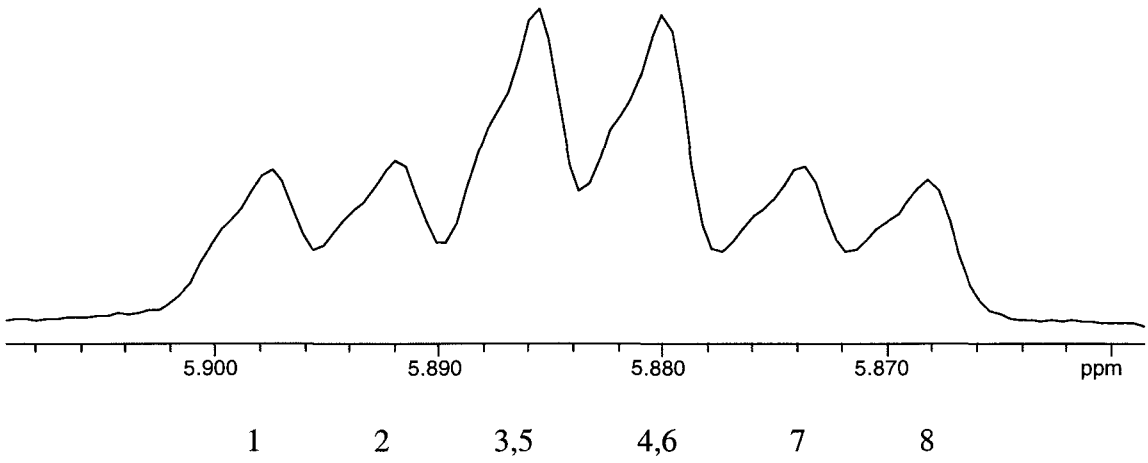


Figure 14: ^{1}H NMR of the ddd of the vinylic proton of compound **8**

The ^{31}P NMR of the vinyl phosphates show only one peak. This is expected due to their having only one phosphorus atom in the structure. The ^{31}P NMR of compound **6** is shown (Fig. 15).

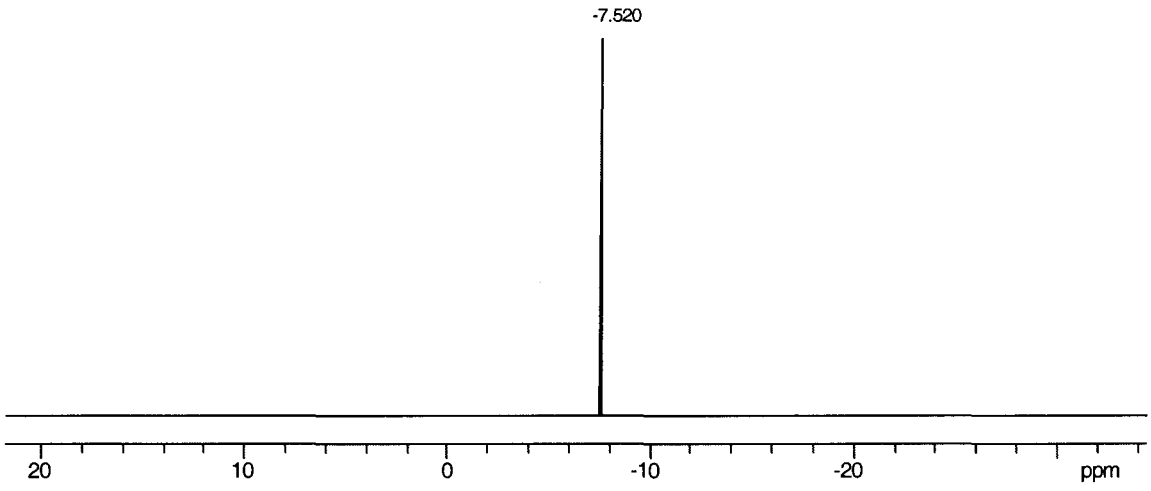


Figure 15: ^{31}P NMR of the vinyl phosphate of camphor (**6**)

Conclusion

The synthesis of compound **1** by the variation to the Sosnovsky and Zaret general procedure for the preparation of dialkyl chlorophosphates from the corresponding dialkyl phosphites[20] afforded excellent yields. The reaction and workup are relatively clean and should be the method utilized in preparing the bis(2,2,2-trifluorethoxy) phosphorochloridate, since it outperforms the Sellars prep.

The vinyl phosphates **4** (vinyl phosphate of cycloheptanone), **5** (vinyl phosphate of cyclododecanone), **6** (vinyl phosphate of camphor) and **7** (vinyl phosphate of carvone) were all obtained in yields above 60%, while compound **8** (vinyl phosphate of α-tetralone) was obtained above 80%. This shows that vinyl phosphates with the trifluoroethoxy group can be synthesized in good yields. Despite repeated distillations and fairly high yields by GC, it appears that the optimal yields for compounds **2** (vinyl phosphate of cyclopentanone) and **3** (vinyl phosphate of cyclohexanone) have not yet been obtained. Also, the poor yield of compound **9** (vinyl phosphate of norcamphor) has no explanation since compound **6** proceeded very well. The reaction should be attempted again. The yield for compound **10** (vinyl phosphate of 2-cyclohexene-1-one) appears to be very similar to compounds **4**, **5**, **6** and **7** and a second purification should yield pure product.

The thionation of compound **6** did not provide the yields that were expected whether pure compound **6** or crude compound **6** was utilized. The next option as discussed earlier would be to actually thionate the bis(2,2,2-trifluorethoxy) phosphorochloridate (**1**).

Chapter 3: Experimental

General Methods. Diisopropylamine, cyclohexanone and cyclopentanone were distilled from CaH_2 prior to use. All other commercial reagents were purchased from Aldrich and used without further purification. All reactions were conducted under a positive pressure of argon. All solvents were dried or distilled by standard techniques. 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, followed by heating.

NMR spectra (^1H, ^{13}C and ^{31}P) were recorded with a Varian Gemini 2000, 400 MHz spectrometer, with $CDCl_3$ as the solvent. The ^1H chemical shifts are reported in parts per million (ppm) downfield from $(CH_3)_4Si$. ^{13}C chemical shifts are reported in parts per million (ppm) downfield from $(CH_3)_4Si$ with $CDCl_3$ as the internal standard (77.0 ppm). ^{31}P chemical shifts are reported in parts per million downfield from H_3PO_4 (external standard). Coupling constants are reported in hertz.

Bis(2,2,2-trifluoroethoxy) phosphorochloridate (1).

A solution of bis(2,2,2-trifluoroethyl) phosphite (50 g, 203 mmol) in benzene (55 mL) was added dropwise to a solution of sulfuryl chloride (20.25 mL, 203 mmol) in benzene (55 mL) at 0 °C for one hour. After the addition, the mixture was allowed to warm to room temperature over two hours. The benzene was removed by rotary evaporation, and

purification by fractional distillation yielded compound **1** (52.76 g, 92.7%) as a clear liquid.

^{1}H NMR δ 4.58-4.41 (4H, m)

^{13}C NMR δ 121.58 (2, dq, *J*=277.0, 11.4 Hz), 64.70 (2, dq, *J*=38.9, 5.3 Hz)

^{31}P NMR δ 6.73

1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy] cyclopentene (2). General procedure for the preparation of bis (2,2,2) trifluoroethyl ketone vinyl phosphates.

Method A.

To a solution of LDA [6.0 mmol, prepared *in situ* from diisopropylamine (0.80 mL) and *n*-BuLi (3.75 mL, 1.6 M in hexane)] in anhydrous THF (15 mL) at -78 °C was added dropwise *via* pressure equalizing addition funnel a solution of cyclopentanone (0.45 mL, 5 mmol) in THF (10 mL). After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was quenched by slow addition of acetic acid in diethyl ether (1 M, 1.2 equivalents) and the resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). After removal of the solvent *en vacuo*, final purification by flash chromatography (silica gel, 85% hexane, 15% EtOAc) produced compound **2** (0.20 g, 12%) as a viscous yellow oil.

^{1}H NMR δ 5.34 (1H, ddd, *J*=4.3, 4.3, 2.1 Hz), 4.46-4.36 (4H, m), 2.49-2.42 (2H, m), 2.37-2.31 (2H, m), 2.01-1.93 (2H, m)

^{13}C NMR δ 148.95 (d, *J*=8.4 Hz), 122.03 (2, dq, *J*=276.8, 9.7 Hz), 111.33 (d, *J*=5.3 Hz), 64.19 (2, dq, *J*=38.4, 4.6 Hz), 31.19 (d, *J*=4.6 Hz), 28.31 (s), 20.94 (s)

^{31}P NMR δ -7.90

Method B.

Cyclopentanone (0.45 mL, 5 mmol) was added dropwise *via* syringe to a solution of LDA (1.1 equivalents) in anhydrous THF (15 mL) at -78 °C. After thirty minutes bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.90 mL, 5.5 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was diluted with 50 mL of ether and quenched by addition of 50 mL of saturated aqueous NH_4Cl. The organic layer was then washed with brine, dried with $MgSO_4$ and filtered. Analysis of the crude product by ^{31}P NMR and GC indicated approximately 73% of compound **2**.

Method C.

Cyclopentanone (0.45 mL, 5 mmol) was added dropwise *via* syringe to a solution of LDA (1.1 equivalents) in anhydrous THF (15 mL) at -78 °C. After thirty minutes, HMPA (0.95 mL, 5.5 mmol) and bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.90 mL, 5.5 mmol) were each added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was diluted with 50 mL of ether and quenched by addition of 50 mL of saturated aqueous NH_4Cl. The organic layer was then washed with brine, dried with $MgSO_4$ and filtered. Analysis of the crude product by ^{31}P NMR and GC indicated approximately 51% of compound **2**.

Method D.

Cyclopentanone (0.45 mL, 5 mmol) was added dropwise *via* syringe to a solution of LDA (1.1 equivalents) in anhydrous THF (15 mL) at -78 °C. After thirty minutes, HMPA (0.95 mL, 5.5 mmol) and bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.90 mL, 5.5 mmol) were each added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was quenched by slow addition of acetic acid in diethyl ether (1 M, 1.1 equivalents). The resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh. Analysis of the crude product by ^{31}P NMR and GC indicated approximately 60% of compound **2**.

1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy] cyclohexene (3).

Method A

To a solution of LDA (1.2 equivalents) in dry THF (15 mL) at -78 °C was added dropwise *via* pressure equalizing addition funnel a solution of cyclohexanone (0.52 mL, 5 mmol) in THF (10 mL). After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was quenched by slow addition of acetic acid in diethyl ether (1 M, 1.2 equivalents) and the resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). After removal of the solvent by rotary evaporation, final purification by flash chromatography (silica gel, 85% hexane, 15% EtOAc) produced compound **3** (0.26 g, 15%) as a viscous yellow oil.

^{1}H NMR δ 5.56-5.53 (1H, m), 4.44 (4H, dq, *J*=8.1, 8.1 Hz), 2.23-2.17 (2H, m), 2.13-2.06 (2H, m), 1.76-1.70 (2H, m), 1.59-1.53 (2H, m)

^{13}C NMR δ 147.22 (d, *J*=9.2 Hz), 122.12 (2, dq, *J*=276.7, 9.9 Hz), 112.39 (d, *J*=6.1 Hz), 64.12 (2, dq, *J*=38.1, 5.3 Hz), 27.44 (d, *J*=3.8 Hz), 23.64 (s), 22.66 (s), 21.43 (s)

^{31}P NMR δ -7.71

Method B.

Cyclohexanone (0.55 mL, 5 mmol) was added dropwise *via* syringe to a solution of LDA (1.1 equivalents) in anhydrous THF (15 mL) at -78 °C. After thirty minutes bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.90 mL, 5.5 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was diluted with 50 mL of ether and quenched by addition of 50 mL of saturated aqueous NH_4Cl. The organic layer was then washed with brine, dried with $MgSO_4$ and filtered. Analysis of the crude product by ^{31}P NMR and GC indicated approximately 68% of compound **3.**

Method C.

Cyclohexanone (0.55 mL, 5 mmol) was added dropwise *via* syringe to a solution of LDA (1.1 equivalents) in anhydrous THF (15 mL) at -78 °C. After thirty minutes, HMPA (0.95 mL, 5.5 mmol) and bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.90 mL, 5.5 mmol) were each added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was diluted with 50 mL of ether and quenched by addition of 50 mL of saturated aqueous NH_4Cl. The organic layer was then washed with brine, dried with $MgSO_4$ and

filtered. Removal of the solvent *en vacuo* produced 1.10 g of crude product. Analysis of the crude product by ^{31}P NMR and GC indicated approximately 88% of compound **3.**

Method D.

Cyclohexanone (0.55 mL, 5 mmol) was added dropwise *via* syringe to a solution of LDA (1.1 equivalents) in anhydrous THF (15 mL) at -78 °C. After thirty minutes, HMPA (0.95 mL, 5.5 mmol) and bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.90 mL, 5.5 mmol) were each added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was quenched by slow addition of acetic acid in diethyl ether (1 M, 1.1 equivalents). The resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). Analysis of the crude product by ^{31}P NMR and GC indicated approximately 71% of compound **3**.

1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy] cycloheptene (4). A solution of cycloheptanone (0.60 mL, 5 mmol) in THF (10 mL) was added dropwise *via* pressure equalizing addition funnel to a solution of LDA (1.2 equivalents) in anhydrous THF (15 mL) at -78 °C. After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was quenched by slow addition of acetic acid in diethyl ether (1 M, 1.2 equivalents) and the resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). After removal of the solvent *en vacuo*, final purification by flash

chromatography (silica gel, 80% hexane, 20% EtOAc) produced compound **4** (1.10 g, 62%) as a viscous yellow oil.

^{1}H NMR δ 5.69 (1H, ddd, *J*=6.5, 6.5, 2.8 Hz), 4.40 (4H, dq, *J*=8.1, 8.1 Hz), 2.43-2.40 (2H, m), 2.12-2.06 (2H, m), 1.73-1.57 (6H, m)

^{13}C NMR δ 151.43 (d, *J*=9.9 Hz), 122.13 (2, dq, *J*=277.0, 9.9 Hz), 117.14 (d, *J*=5.3 Hz), 64.09 (2, dq, *J*=38.0, 5.0 Hz), 33.09 (d, *J*=3.1 Hz), 30.31 (s), 26.79 (d, *J*=1.5 Hz), 24.97 (s), 24.74 (s)

^{31}P NMR δ -7.57

1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy] cyclododecene (5).

To a solution of LDA (1.2 equivalents) in anhydrous THF (15 mL) at -78 °C was added dropwise *via* pressure equalizing addition funnel a solution of cyclododecanone (0.91 g, 5 mmol) in THF (10 mL). After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. Slow addition of acetic acid in diethyl ether (1 M, 1.2 equivalents) quenched the reaction and the resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). After removal of the solvent by rotary evaporation, final purification by flash chromatography (silica gel, 85% hexane, 15% EtOAc) produced compound **5** (1.43 g, 67%) as a viscous yellow oil.

^{1}H NMR δ 5.07-5.03 (1H, m), 4.47-4.36 (4H, m), 2.34-2.31 (2H, m), 2.18-2.14 (2H, m), 1.60-1.47 (4H, m), 1.37-1.30 (12H, m)

^{13}C NMR δ 146.50 (d, *J*=9.2 Hz), 122.12 (2, dq, *J*=276.8, 10.1 Hz), 118.95 (d, *J*=6.9 Hz), 64.11 (2, dq, *J*=38.1, 4.6 Hz), 33.50 (s), 26.26 (s), 25.96 (s), 25.94 (s), 25.54 (s), 25.51 (s), 24.71 (s), 24.68 (s), 24.50 (s), 23.28 (s)

^{31}P NMR δ -7.71

2-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]-1,7,7-trimethylbicyclo[2.2.1]-2-heptene (6).

A solution of (1*R*)(+) camphor (0.76 g, 5 mmol) in THF (10 mL) was added dropwise *via* pressure equalizing addition funnel to a solution of LDA (1.2 equivalents) in dry THF (15 mL) at -78 °C. After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was quenched by slow addition of acetic acid in diethyl ether (1 M, 1.2 equivalents) and the resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). Final purification by flash chromatography (silica gel, 85% hexane, 15% EtOAc), after removal of the solvent *en vacuo*, produced compound **6** (1.29 g, 65%) as a viscous yellow oil.

^{1}H NMR δ 5.40-5.39 (1H, m), 4.48-4.36 (4H, m), 2.38-2.36 (1H, m), 1.93-1.86 (1H, m), 1.61 (1H, ddd, *J*=12.0, 8.6, 3.5 Hz), 1.26 (1H, ddd, *J*=12.2, 9.0, 3.4 Hz), 1.12 (1H, ddd, *J*=12.0, 8.9, 3.3 Hz), 0.99 (3H, s), 0.91 (3H, s), 0.77 (3H, s)

^{13}C NMR δ 154.65 (d, *J*=9.2 Hz), 122.04 (2, dq, *J*=277.0, 9.9 Hz), 111.59 (d, *J*=3.8 Hz), 64.24 (dq, *J*=38.2, 3.1 Hz), 64.19 (dq, *J*=38.1, 2.8 Hz), 56.29 (s), 53.40 (d, *J*=6.1 Hz), 49.77 (s), 31.07 (s), 25.98 (d, *J*=1.5 Hz), 19.83 (s), 19.26 (s), 9.61 (s)

^{31}P NMR δ -7.53

2-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]-3-methyl-6-isopropenyl-1,3-cyclohexadiene (7).

To a solution of LDA (1.2 equivalents) in anhydrous THF (15 mL) at -78 °C was added dropwise *via* pressure equalizing addition funnel a solution of (*R*)(-) carvone (0.78 mL, 5 mmol) in THF (10 mL). After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. Slow addition of acetic acid in diethyl ether (1 M, 1.2 equivalents) quenched the reaction and the resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). After removal of the solvent by rotary evaporation, final purification by flash chromatography (silica gel, 85% hexane, 15% EtOAc) produced compound **7** (1.28 g, 65%) as a viscous yellow oil.

^{1}H NMR δ 5.68-5.65 (1H, m), 5.53-5.51 (1H, m), 4.80-4.77 (2H, m), 4.49-4.39 (4H, m), 3.10 (1H, ddd, *J*=16.2, 8.5, 4.0 Hz), 2.35-2.16 (2H, m), 1.79 (3H, dd, *J*=3.7, 1.8 Hz), 1.75-1.74 (3H, m)

^{13}C NMR δ 146.26 (d, *J*=9.2 Hz), 146.05 (s), 127.90 (d, *J*=6.1 Hz), 125.30 (s), 122.07 (2, dq, *J*=276.6, 9.9 Hz), 112.61 (d, *J*=4.6 Hz), 111.06 (s), 64.26 (2, dq, *J*=38.1, 4.6 Hz), 41.21 (d, *J*=1.5 Hz), 27.92 (s), 20.66 (s), 16.81 (s)

^{31}P NMR δ -7.53

7-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]bicyclo[4.4.0]-1,3,5,7-decatetraene (8).

A solution of α-tetralone (0.67 mL, 5 mmol) in THF (10 mL) was added dropwise *via* pressure equalizing addition funnel to a solution of LDA (1.2 equivalents) in anhydrous THF (15 mL) at -78 °C. After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. The reaction was quenched by slow addition of acetic acid in diethyl ether (1 M, 1.1 equivalents) and the resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). After removal of the solvent *en vacuo*, final purification by flash chromatography (silica gel, 85% hexane, 15% EtOAc) produced compound **8** (1.58 g, 81%) as a white solid.

^{1}H NMR δ 7.36-7.34 (1H, m), 7.25-7.22 (2H, m), 7.17-7.14 (1H, m), 5.89 (1H, ddd, *J*=4.8, 4.8, 2.2 Hz), 4.52-4.40 (4H, m), 2.84-2.80 (2H, m), 2.46-2.40 (2H, m)

^{13}C NMR δ 144.75 (d, *J*=8.4 Hz), 136.39 (s), 129.26 (d, *J*=6.1 Hz), 128.50 (s), 127.41 (s), 126.49 (s), 122.05 (2, dq, *J*=276.9, 9.6 Hz), 121.00 (s), 112.03 (d, *J*=3.8 Hz), 64.33 (2, dq, *J*=38.3, 4.4 Hz), 27.26 (s), 22.07 (s)

^{31}P NMR δ -7.15

2-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]bicyclo[2.2.1]-2-heptene (9).

A solution of norcamphor (0.55 g, 5 mmol) in THF (10 mL) was added dropwise *via* pressure equalizing addition funnel to a solution of LDA (1.2 equivalents) in dry THF (15 mL) at -78 °C. After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was

allowed to warm gradually to room temperature and was then stirred overnight. The reaction was quenched by slow addition of acetic acid in diethyl ether (1 M, 1.2 equivalents) and the resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). Final purification by flash chromatography (silica gel, 85% hexane, 15% EtOAc), after removal of the solvent *en vacuo*, produced a crude mixture (154 mg) which contained 75% of compound **9** as determined by ^{31}P NMR and GC.

2-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]-1,3-cyclohexadiene (10).

To a solution of LDA (1.2 equivalents) in anhydrous THF (15 mL) at -78 °C was added dropwise *via* pressure equalizing addition funnel a solution of 2-cyclohexene-1-one (0.50 mL, 5 mmol) in THF (10 mL). After thirty minutes, bis(2,2,2-trifluoroethoxy) phosphorochloridate (0.95 mL, 6 mmol) was added dropwise *via* syringe to the ketone enolate. The mixture was allowed to warm gradually to room temperature and was then stirred overnight. Slow addition of acetic acid in diethyl ether (1 M, 1.2 equivalents) quenched the reaction and the resulting mixture was filtered through a 1 cm layer of Florisil (60-120 mesh). Final purification by flash chromatography (silica gel, 85% hexane, 15% EtOAc), after removal of the solvent *en vacuo*, produced a crude mixture (1.36 g) which contained 85% of compound **10** as determined by ^{31}P NMR and GC.

Attempted Synthesis of Vinyl Thiophosphate (11) from Vinyl Phosphate (6).

Method A. 0.55 equivalents of Lawessons Reagent (112 mg) was added to a 0.25 M solution of compound **6** (200 mg) in toluene (2 mL) and refluxed for 24 hours. The reaction returned mainly starting materials as determined by TLC, GC and ^{31}P NMR.

Method B. Highly purified sulfur (S_8) (50 mg, 1.5 mmol) was added to a 0.25 M solution of compound **6** (200 mg) in toluene (2 mL) and refluxed for 24 hours. The reaction returned nearly all starting materials as determined by GC.

Method C. Phosphorous pentasulfide (P_4S_{10}) (0.53 g, 1.2 mmol) was added to a 0.25 M solution of compound **6** (200 mg) in toluene (2 mL) and refluxed for 24 hours. The reaction returned mainly starting materials as determined by ^{31}P NMR and GC.

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Figure 16 ^{13}C NMR of Compound **1**

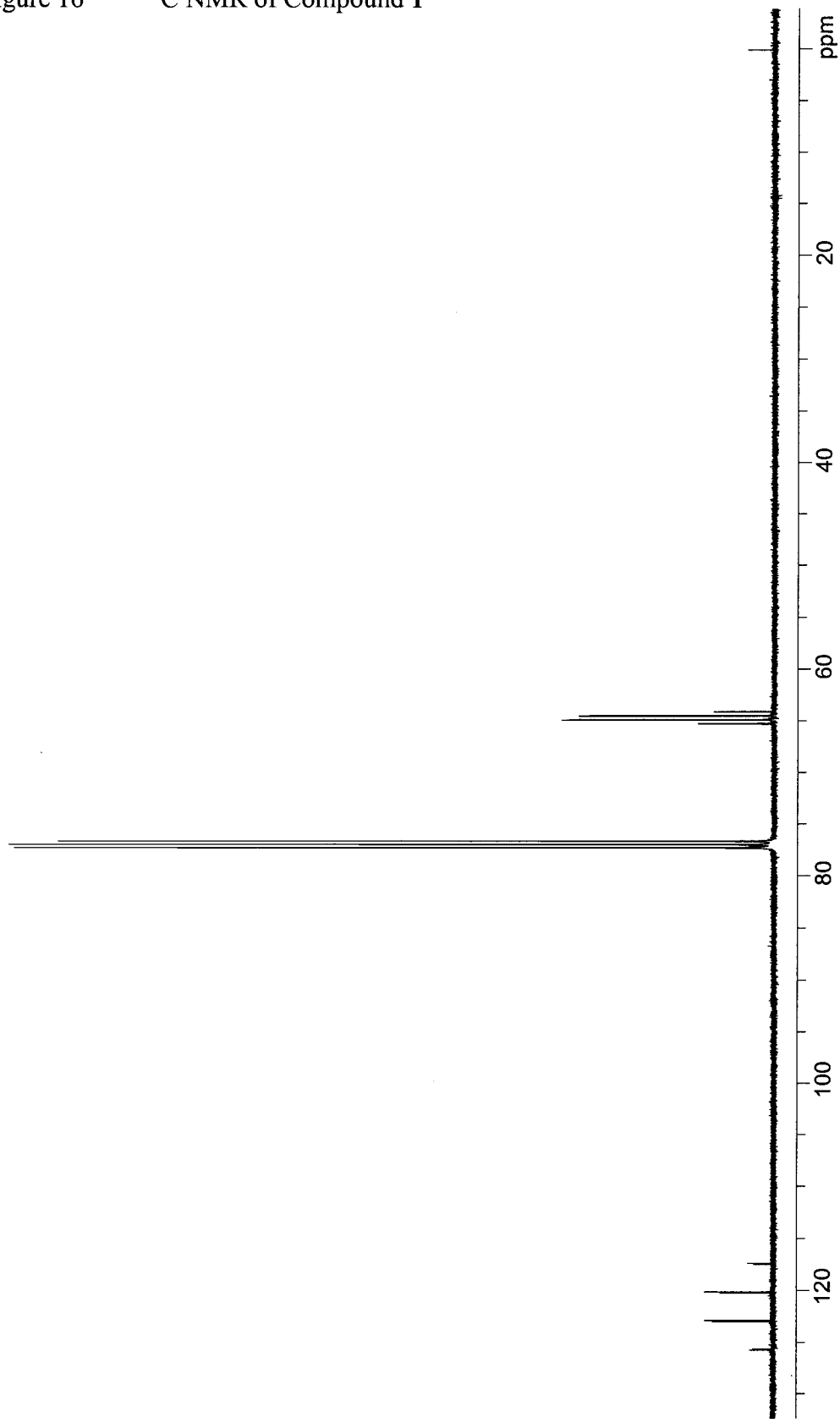

Figure 17 ^{1}H NMR of Compound **1**

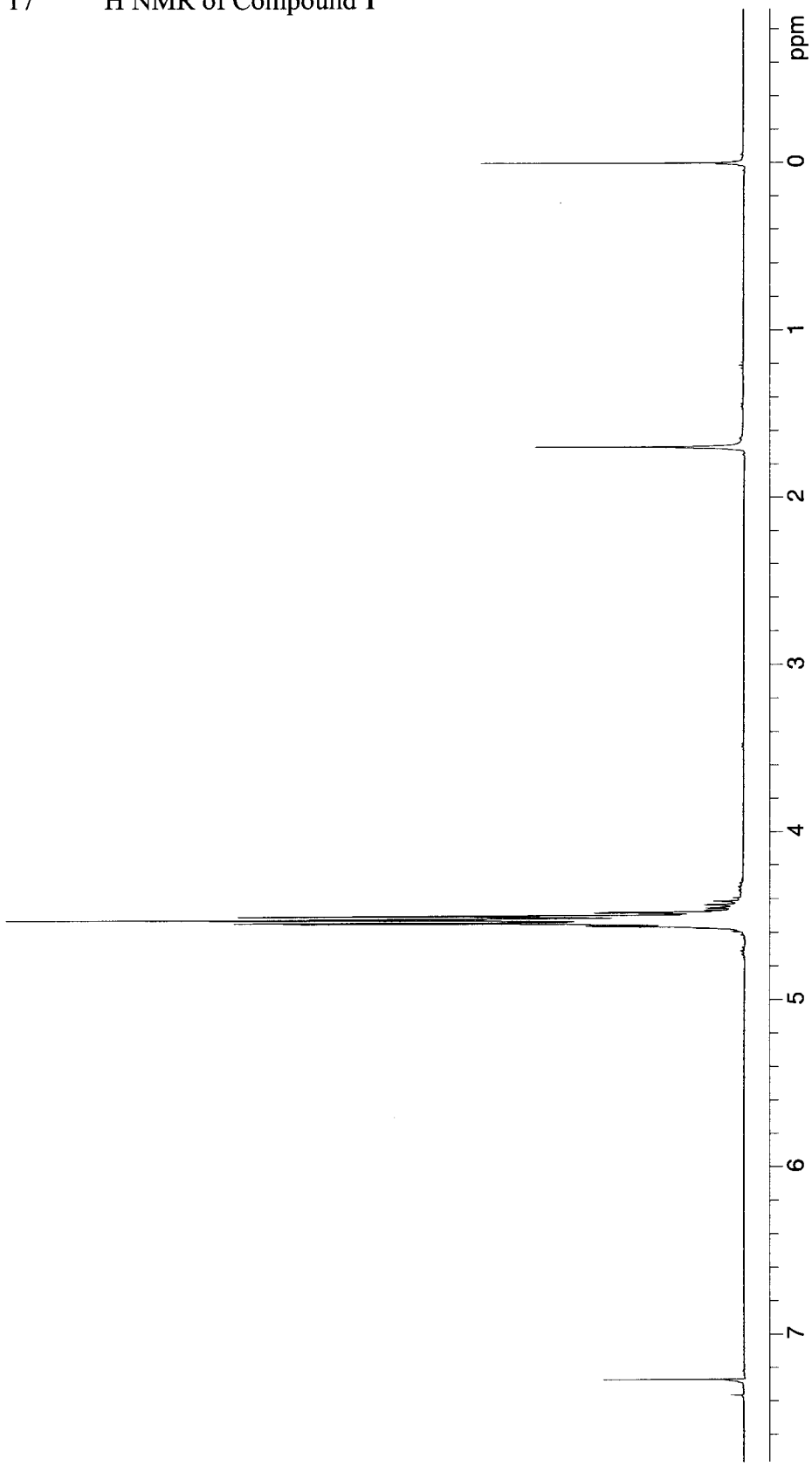

Figure 18 ^{31}P NMR of Compound 1

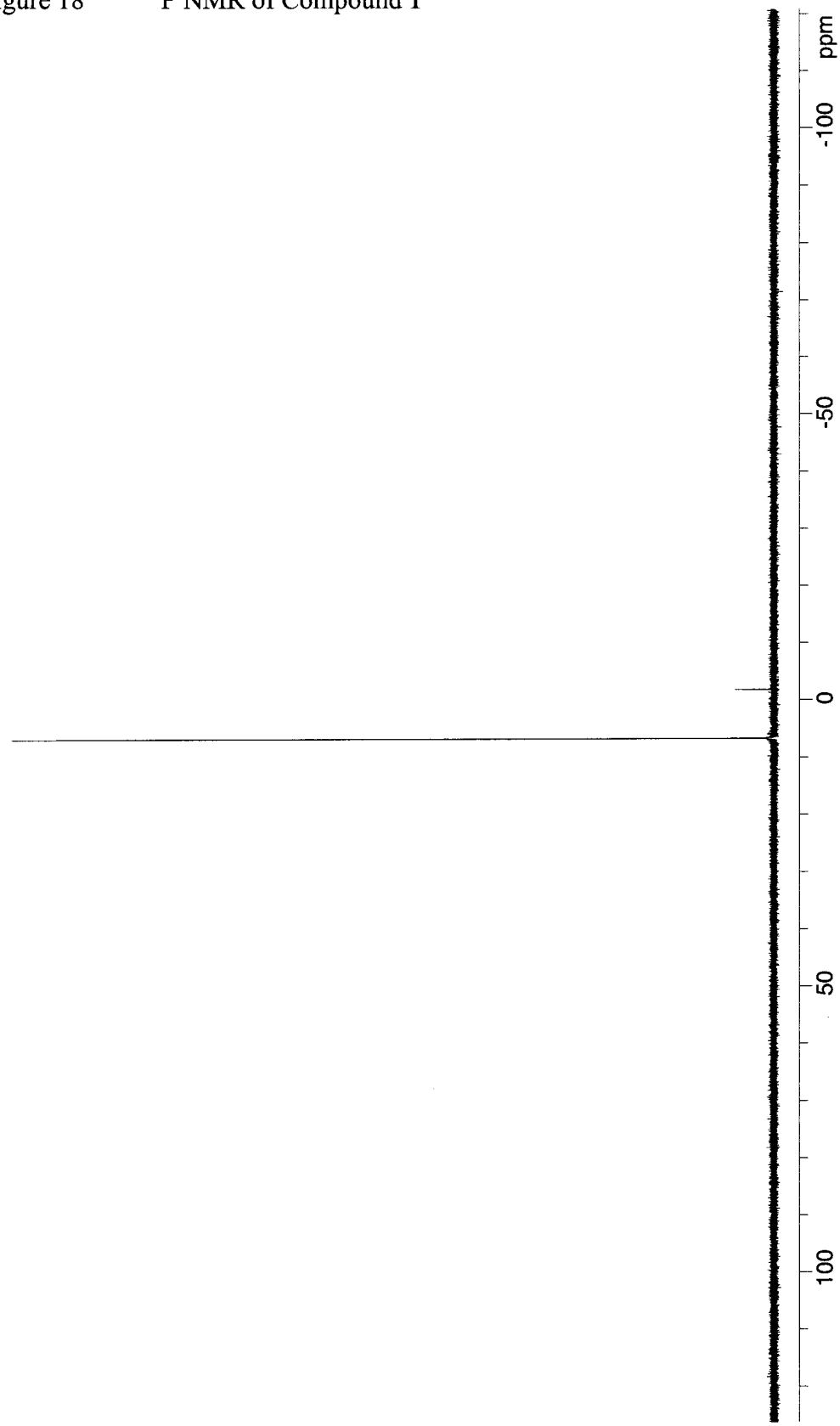

Figure 19 ^{13}C NMR of Compound **2**

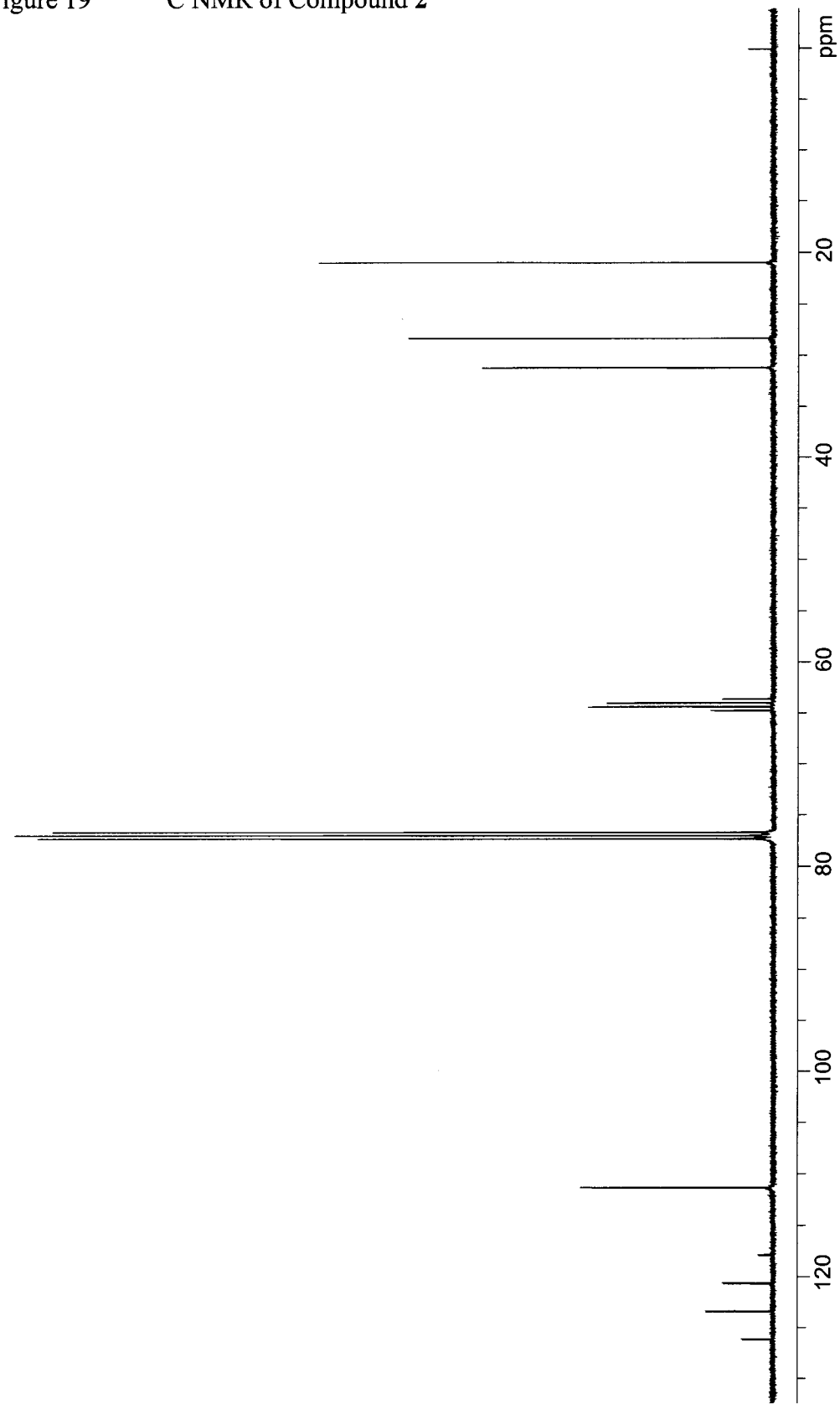

Figure 20 ^{1}H NMR of Compound **2**

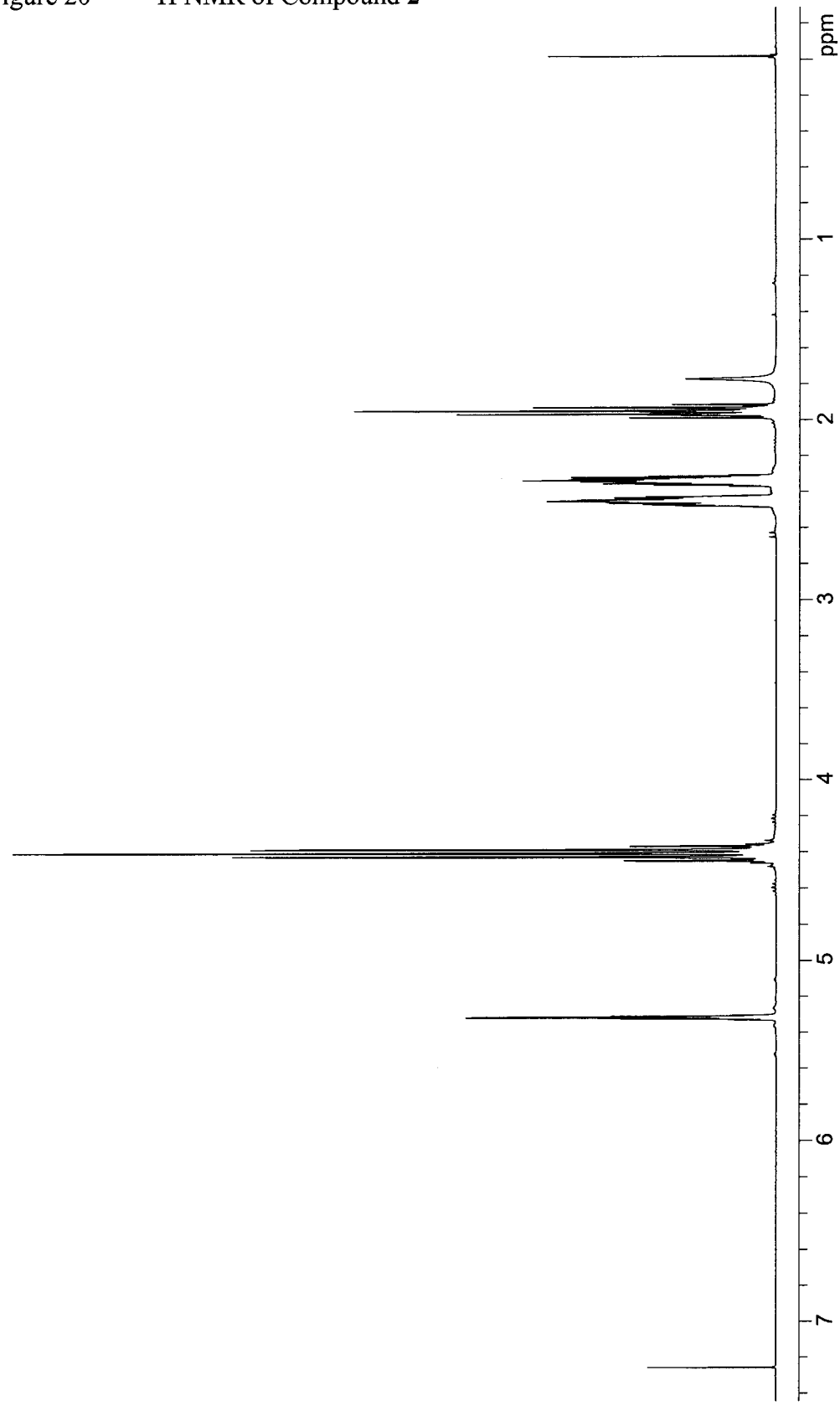

Figure 21 Expanded ^{1}H NMR of Compound **2**

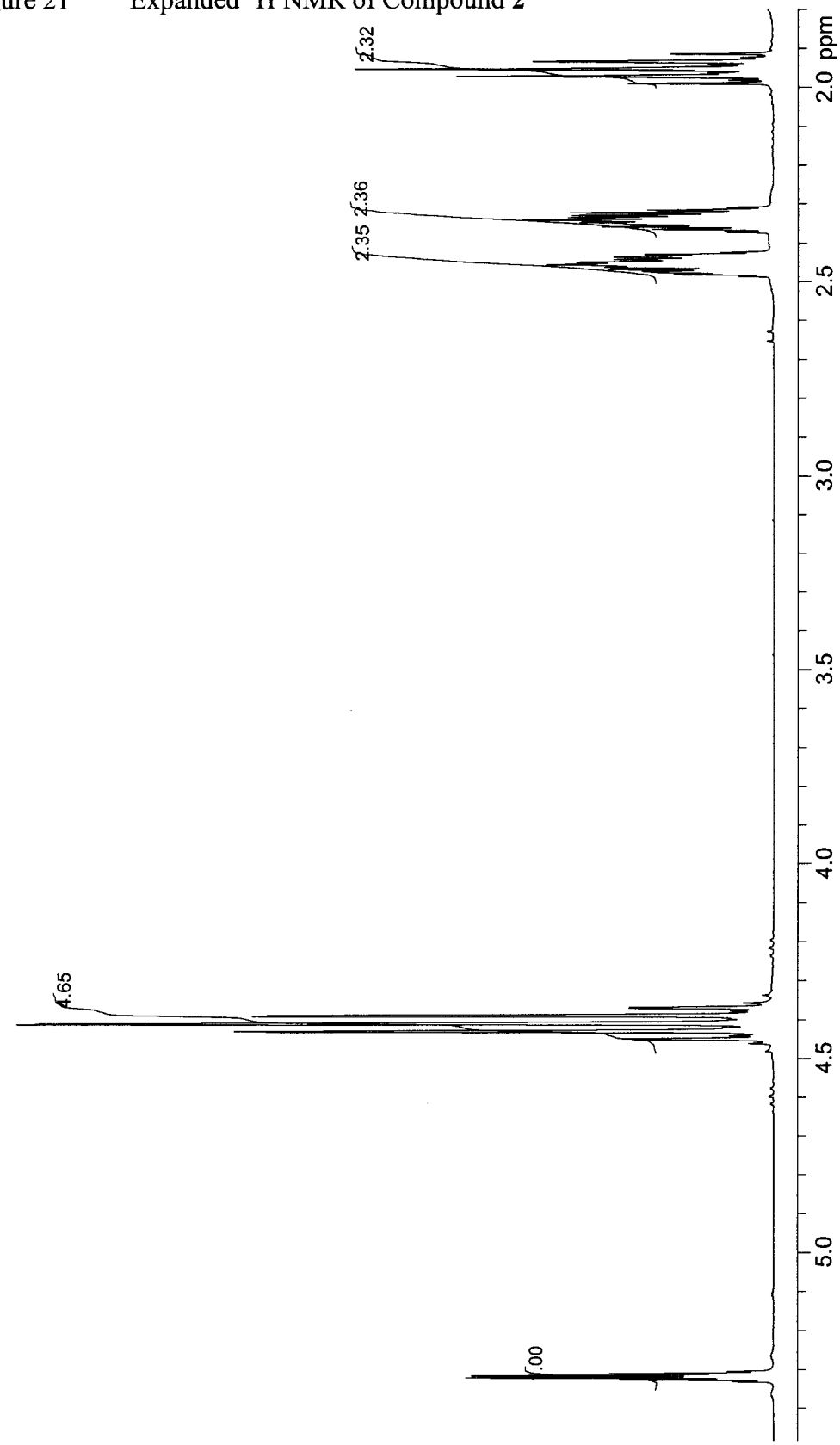

Figure 22 ^{31}P NMR of Compound **2**

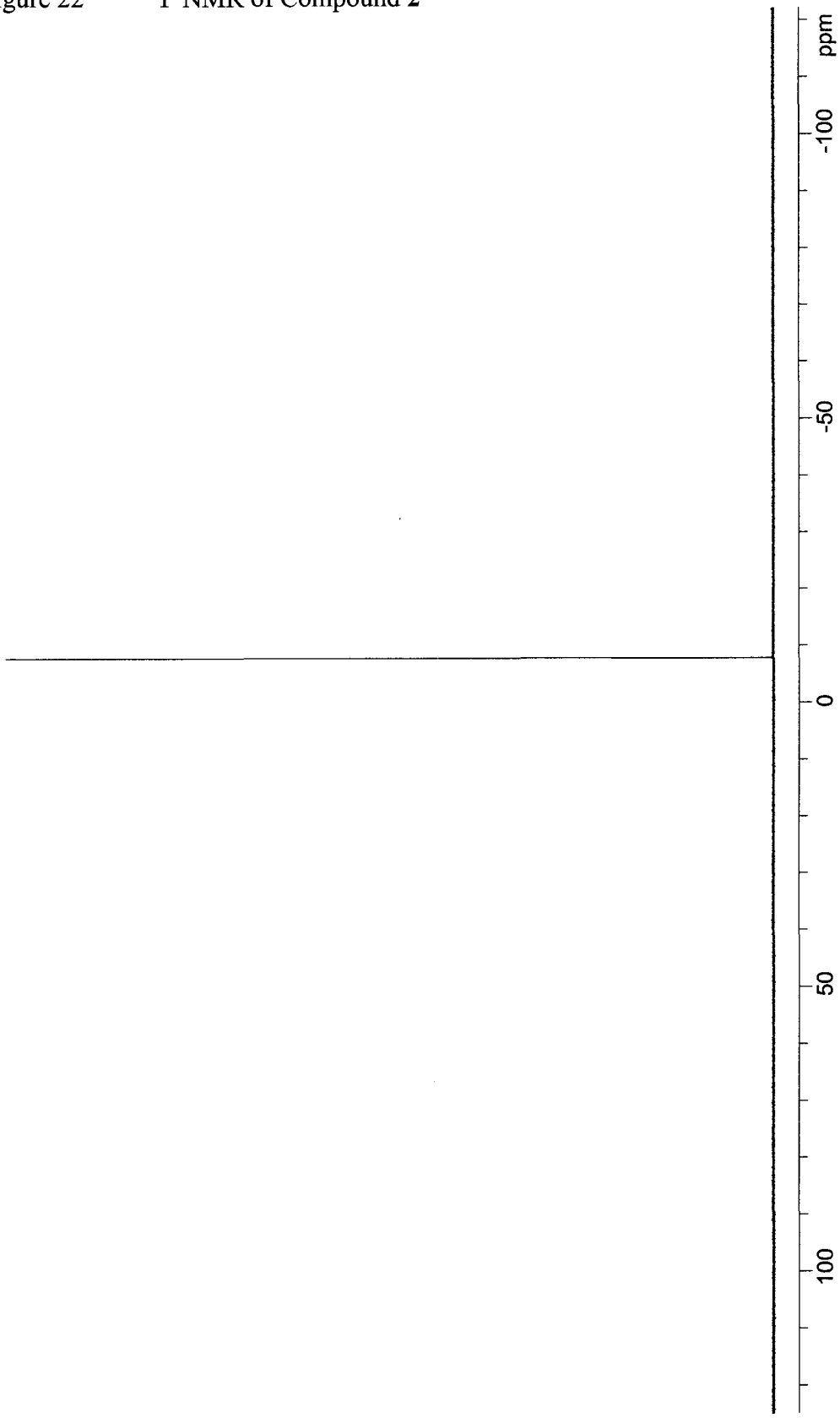

Figure 23 ^{13}C NMR of Compound **3**

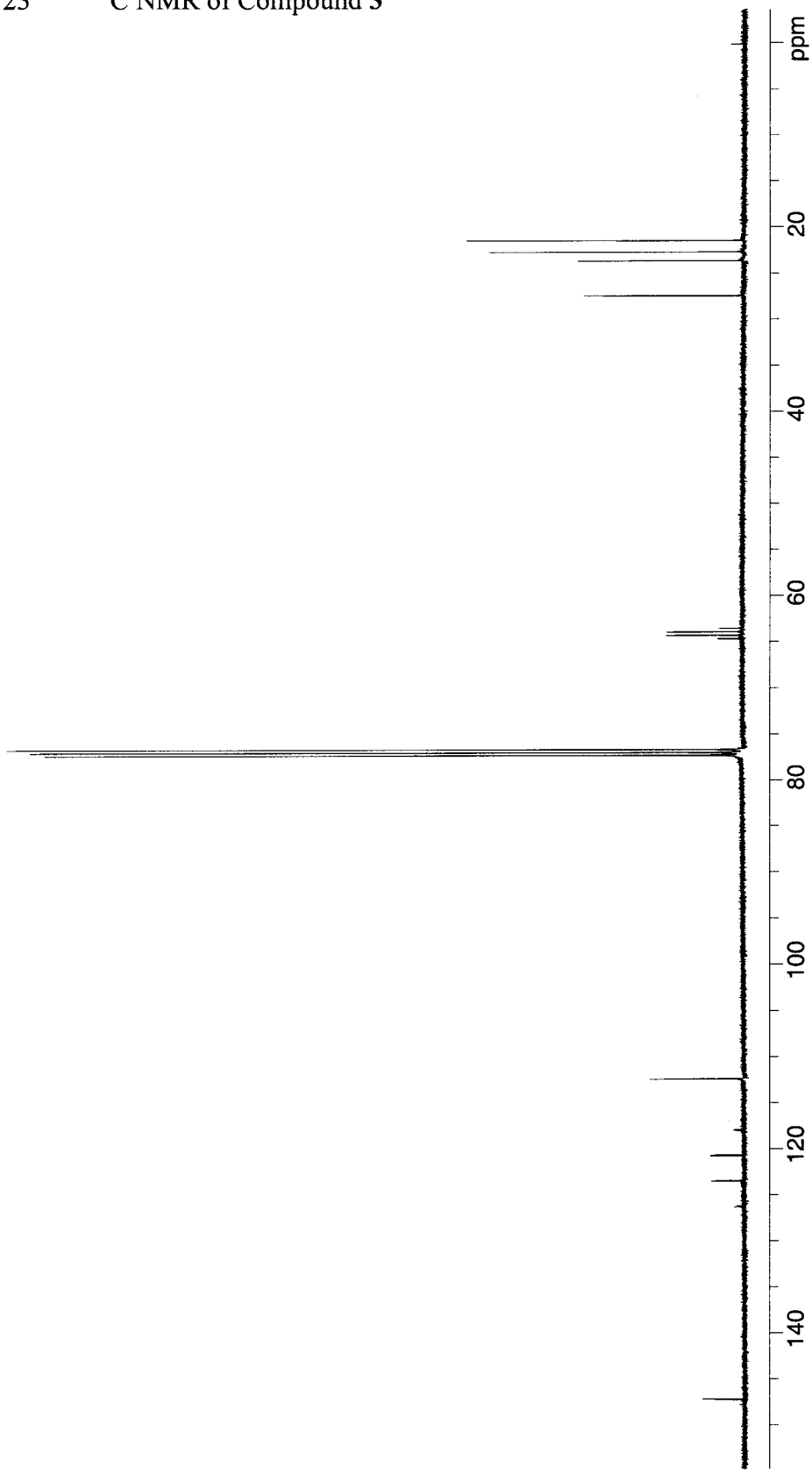

Figure 24 ^{1}H NMR of Compound **3**

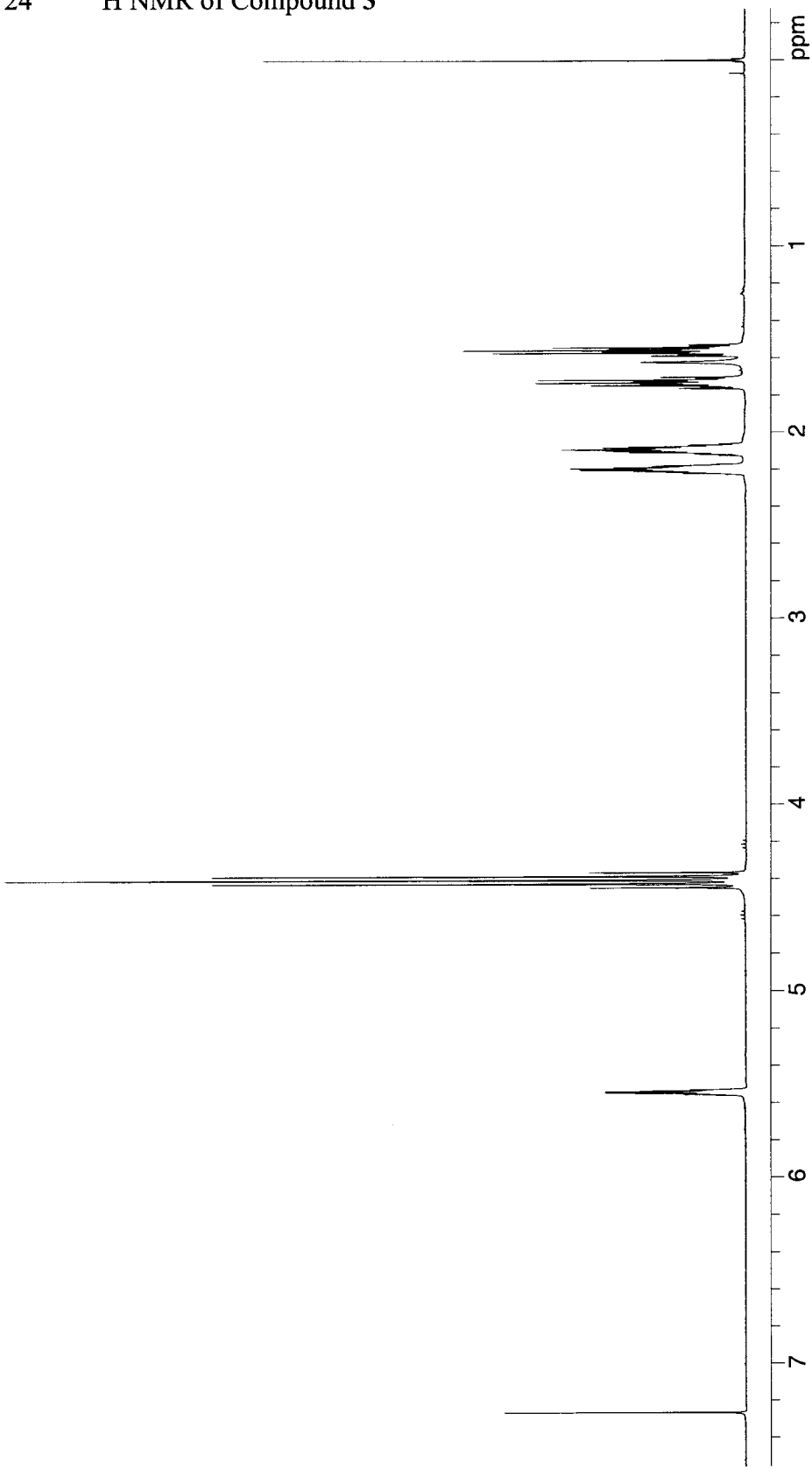

Figure 25 Expanded ^{1}H NMR of Compound **3**

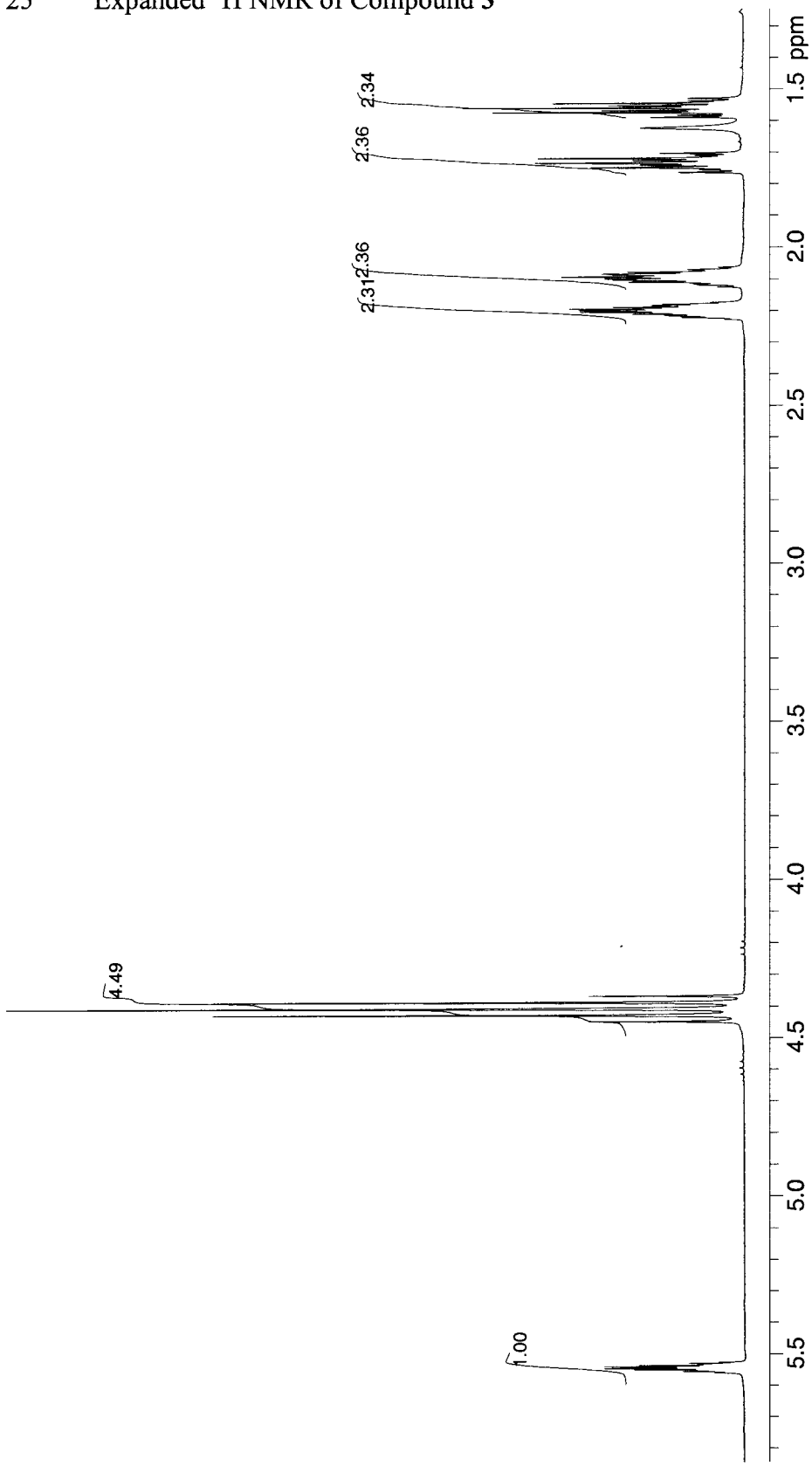

Figure 26 ^{31}P NMR of Compound **3**

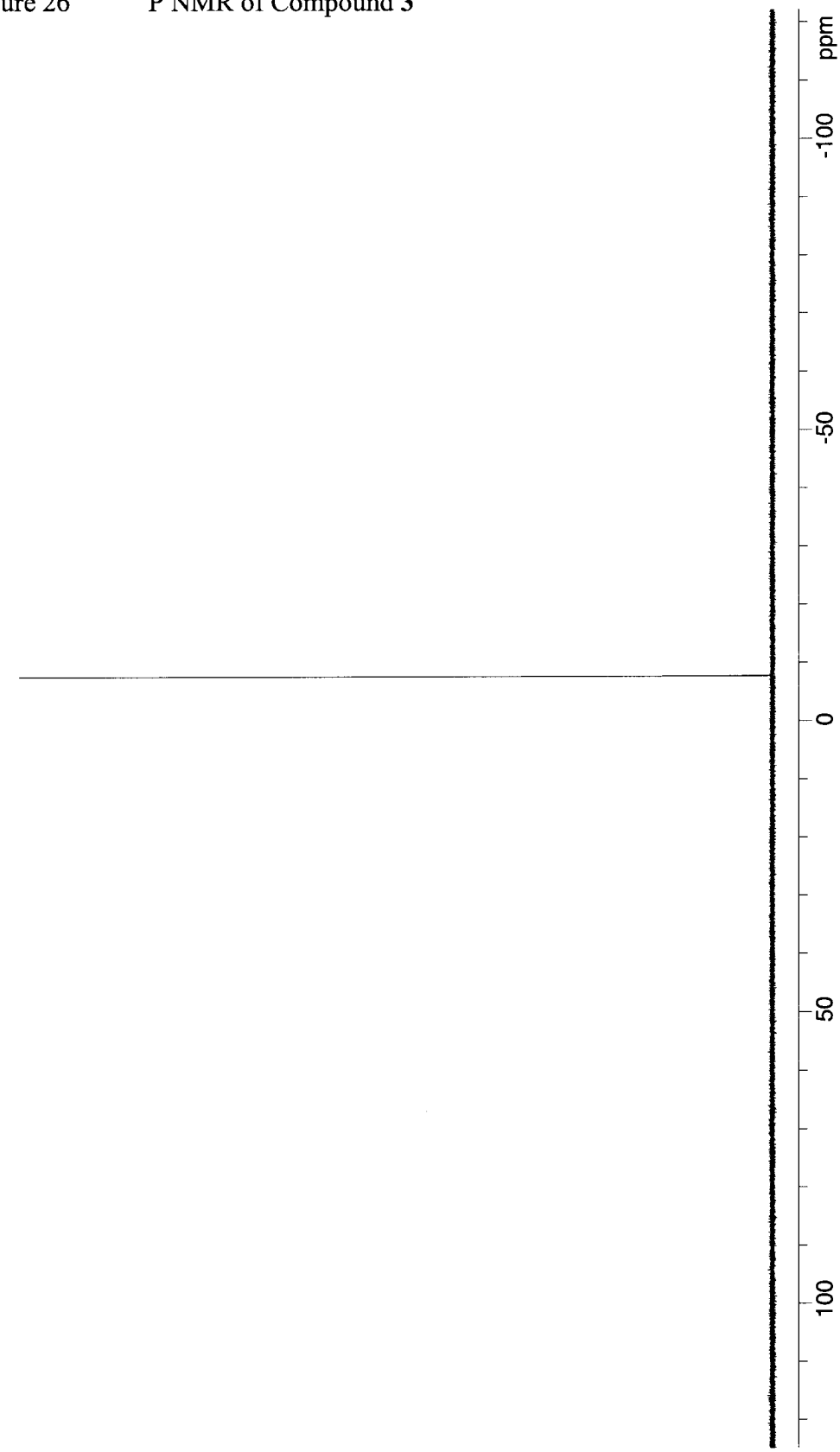

Figure 27 ^{13}C NMR of Compound **4**

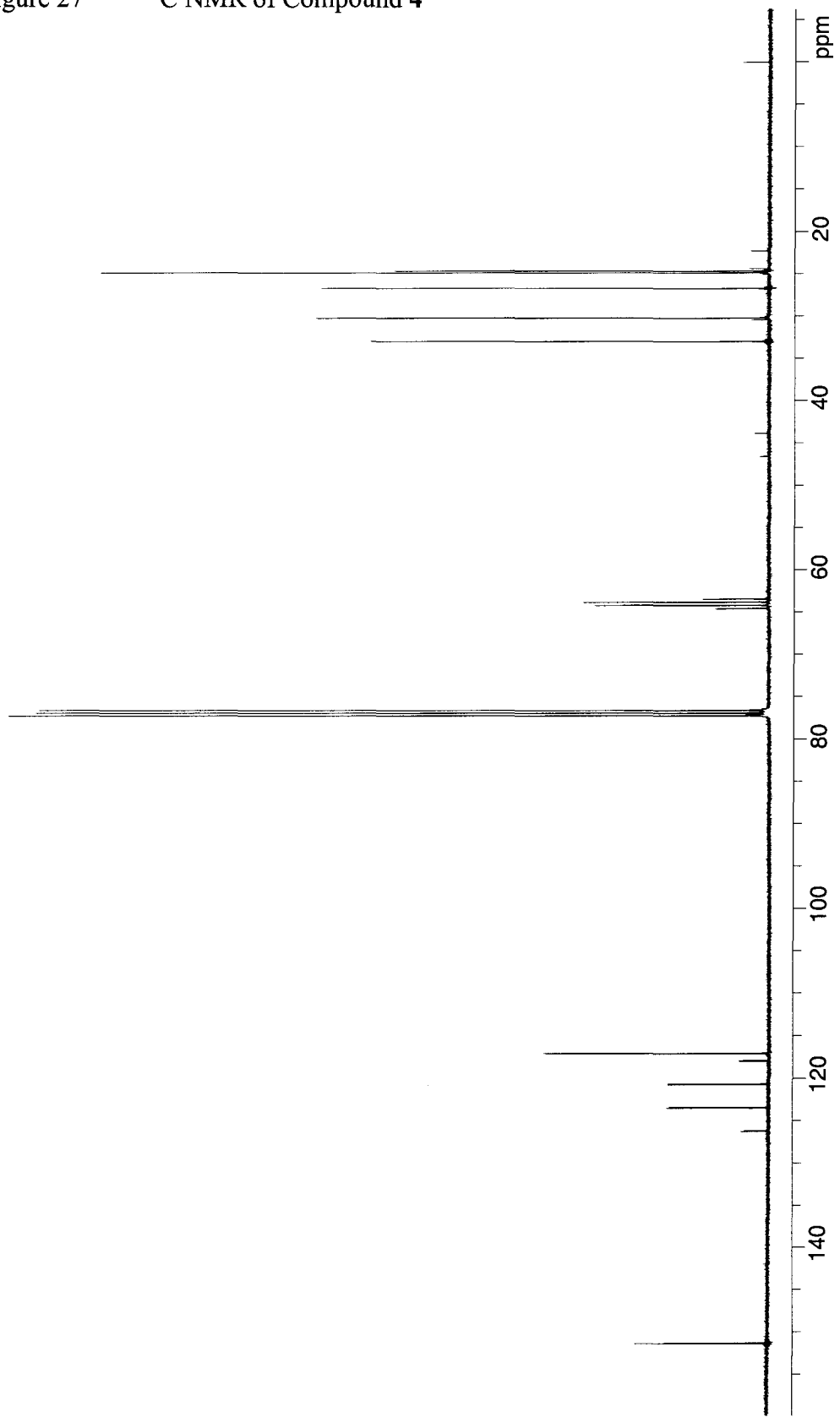

Figure 28 ^{1}H NMR of Compound **4**

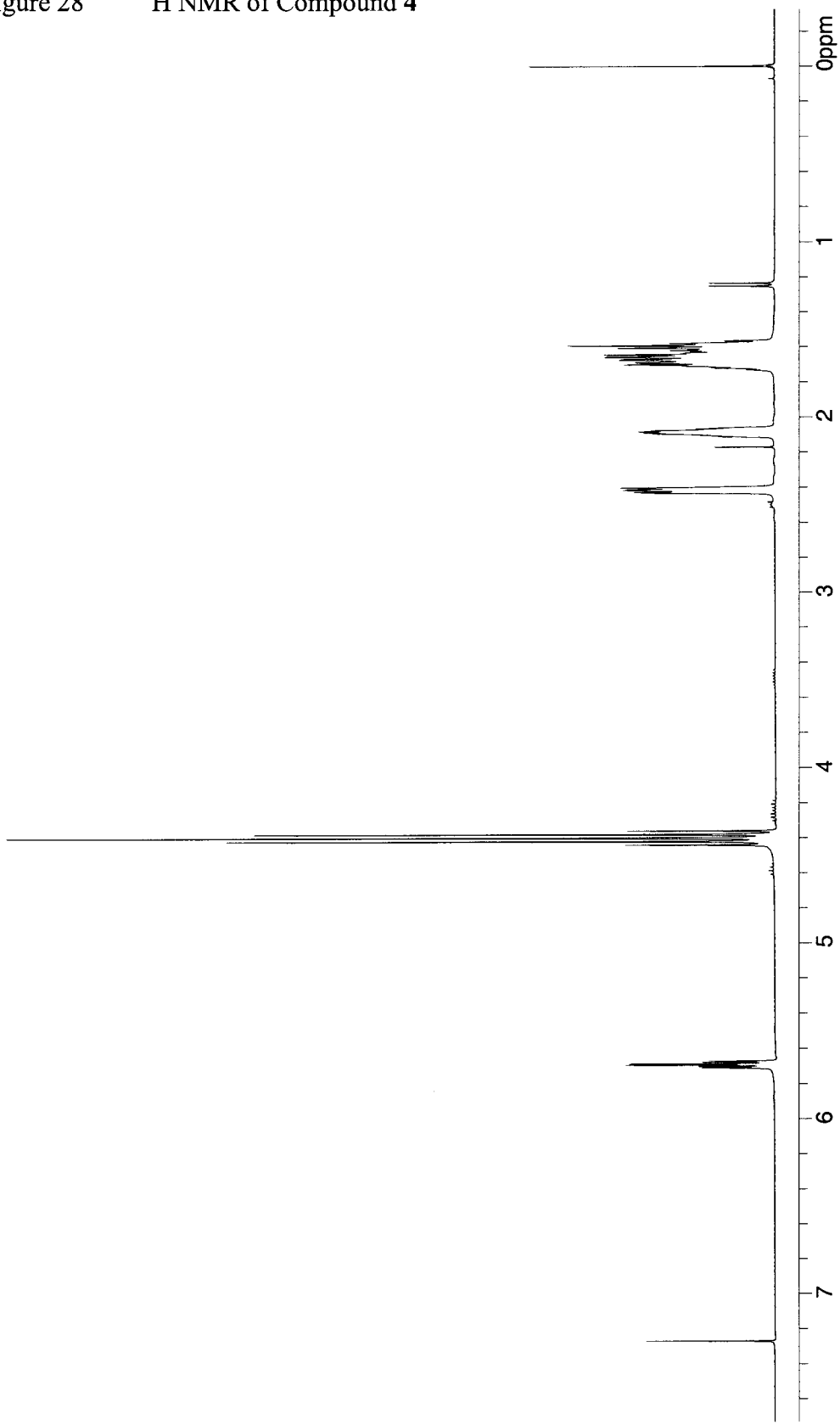

Figure 29 Expanded ^{1}H NMR of Compound **4**

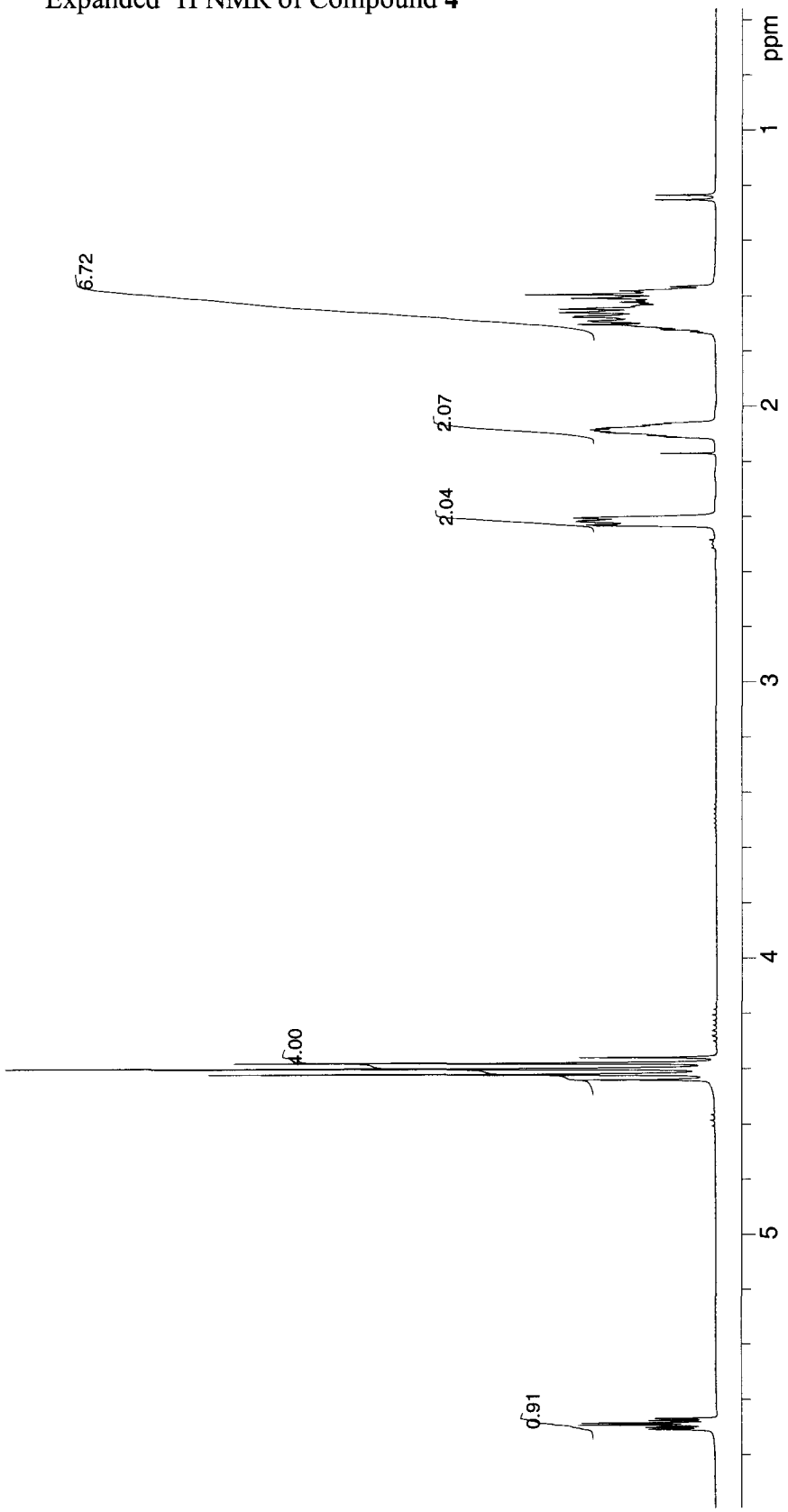

Figure 30 ^{31}P NMR of Compound **4**

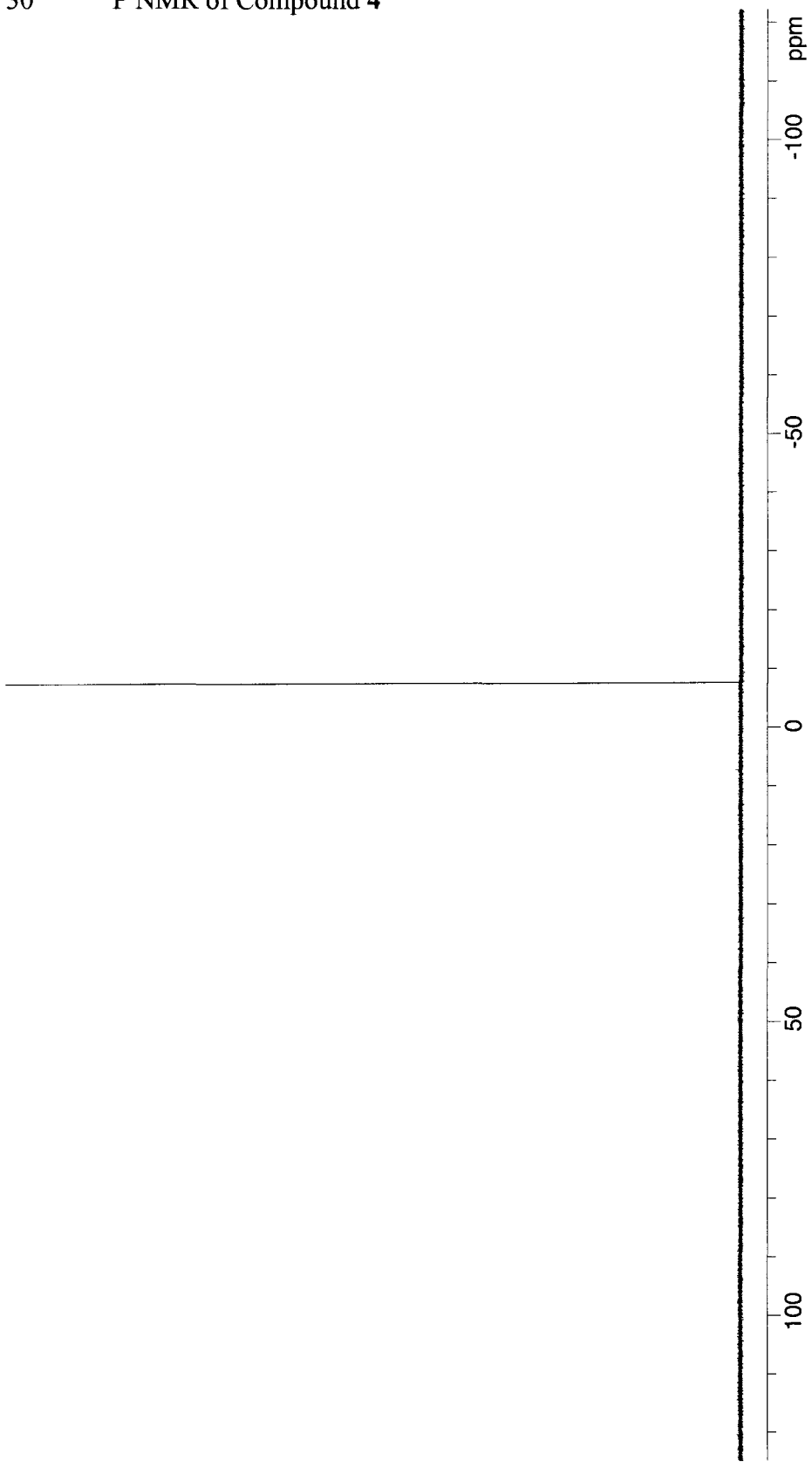

Figure 31 ^{13}C NMR of Compound **5**

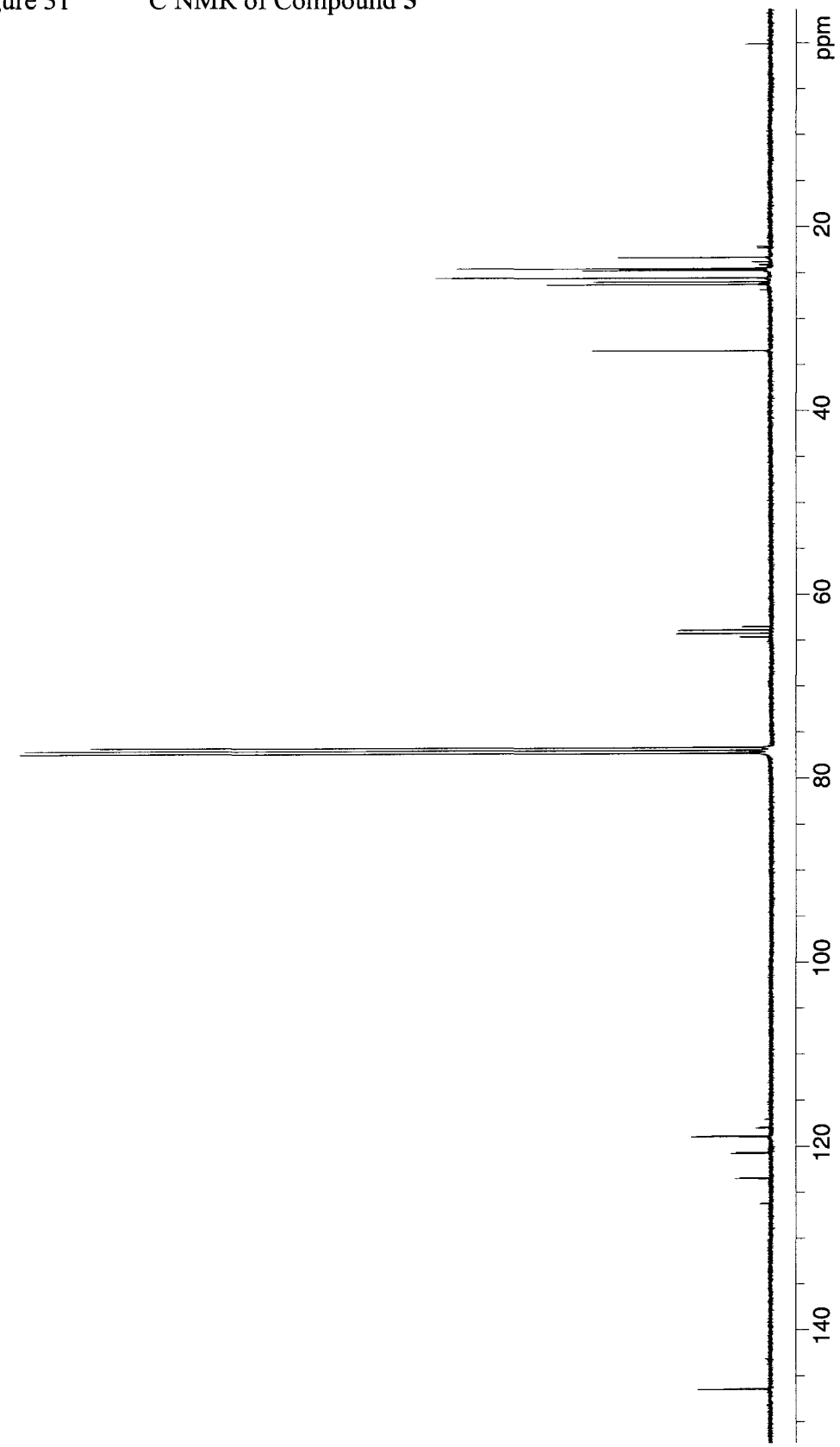

Figure 32 ^{1}H NMR of Compound **5**

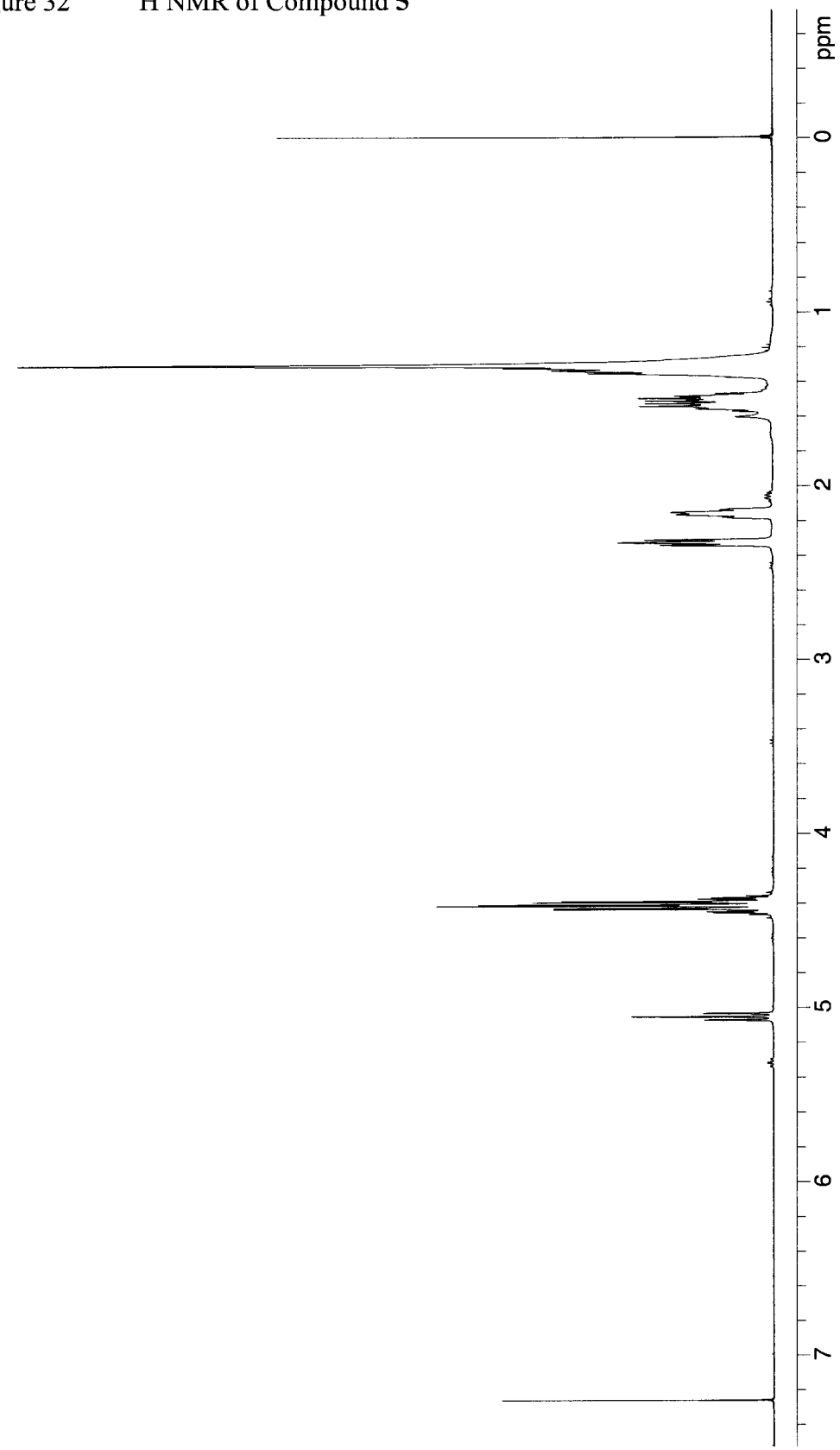

Figure 33 Expanded ^{1}H NMR of Compound **5**

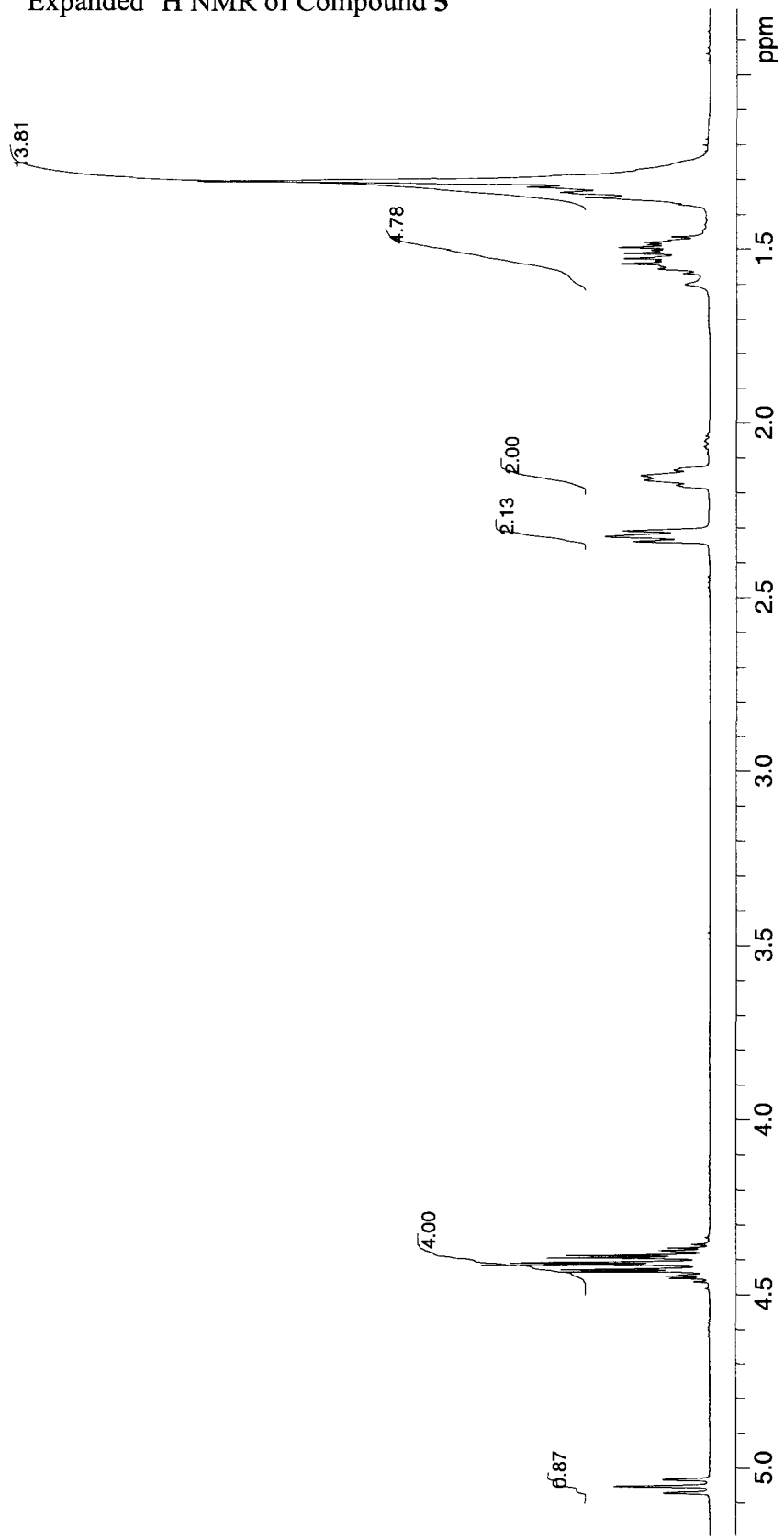

Figure 34 ^{31}P NMR of Compound **5**

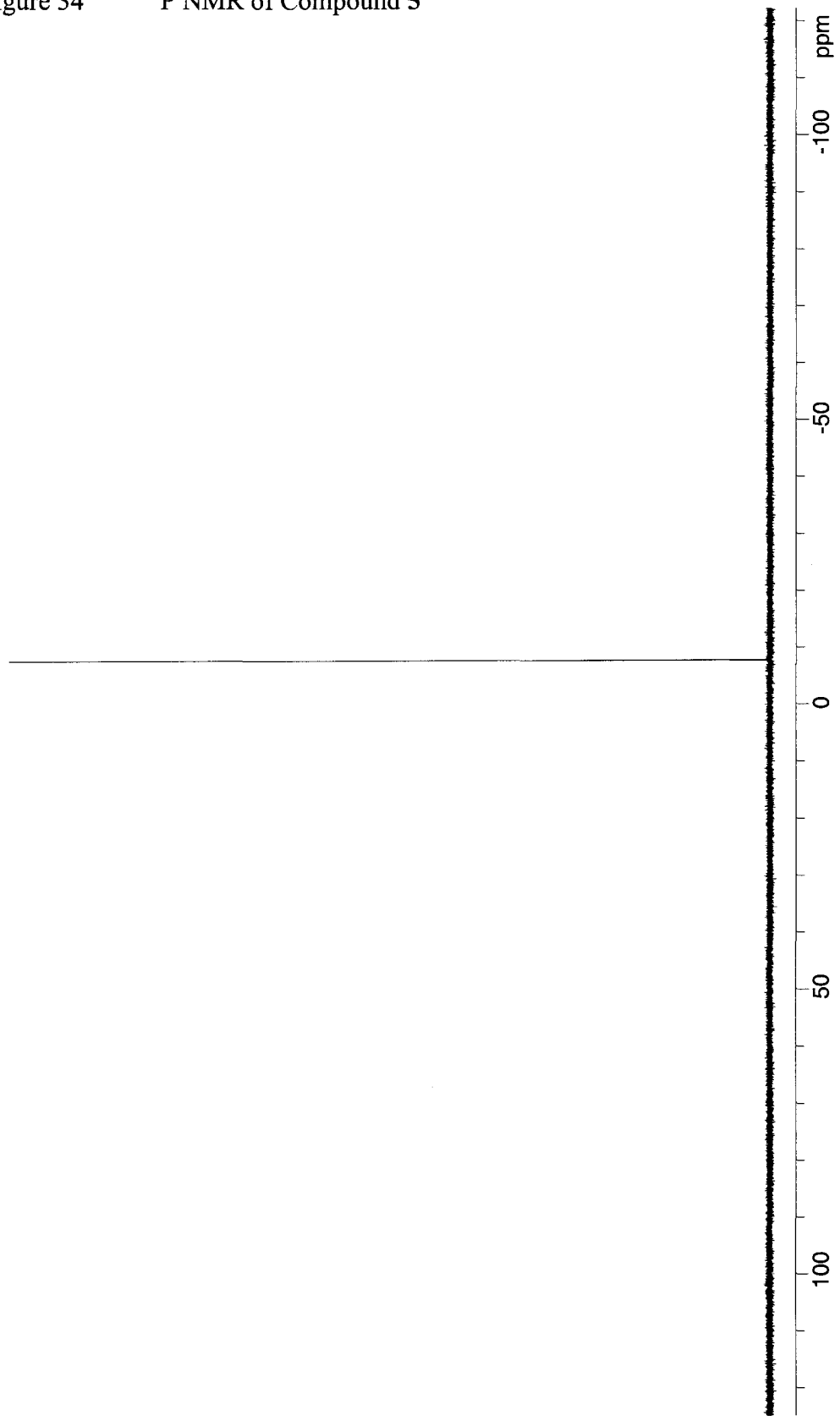

Figure 35 ^{13}C NMR of Compound **6**

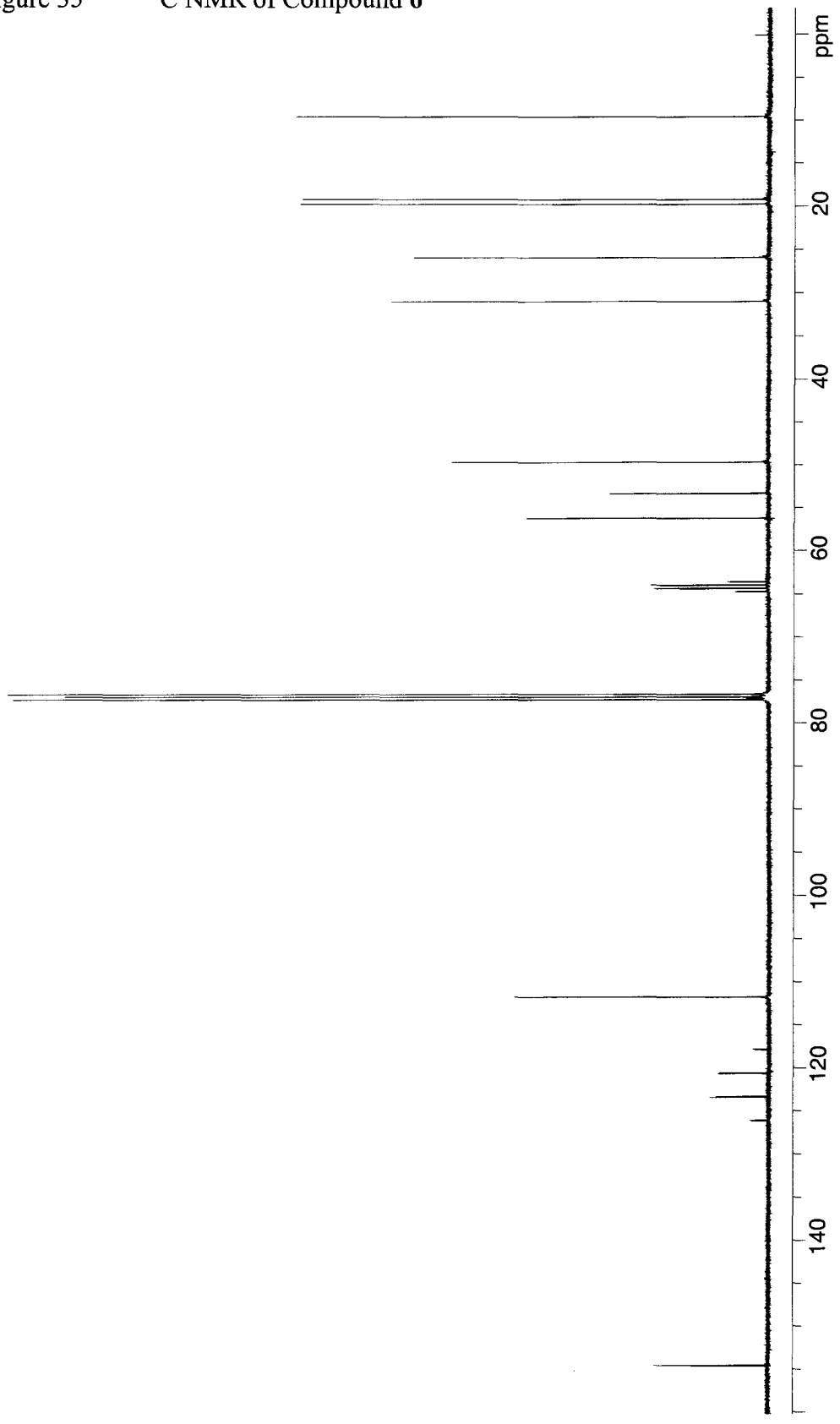

Figure 36 ^{1}H NMR of Compound **6**

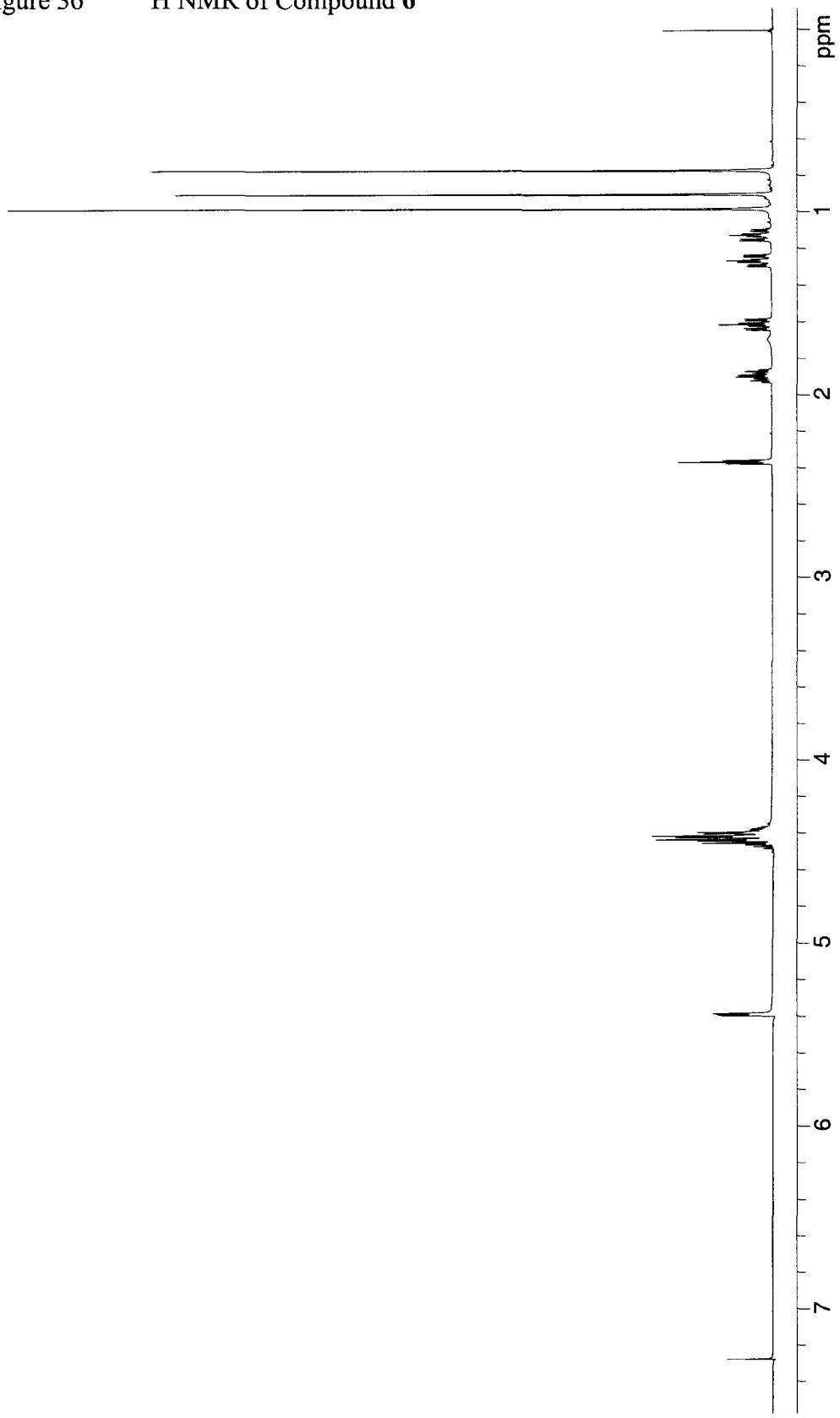

Figure 37 Expanded ^{1}H NMR of Compound **6**

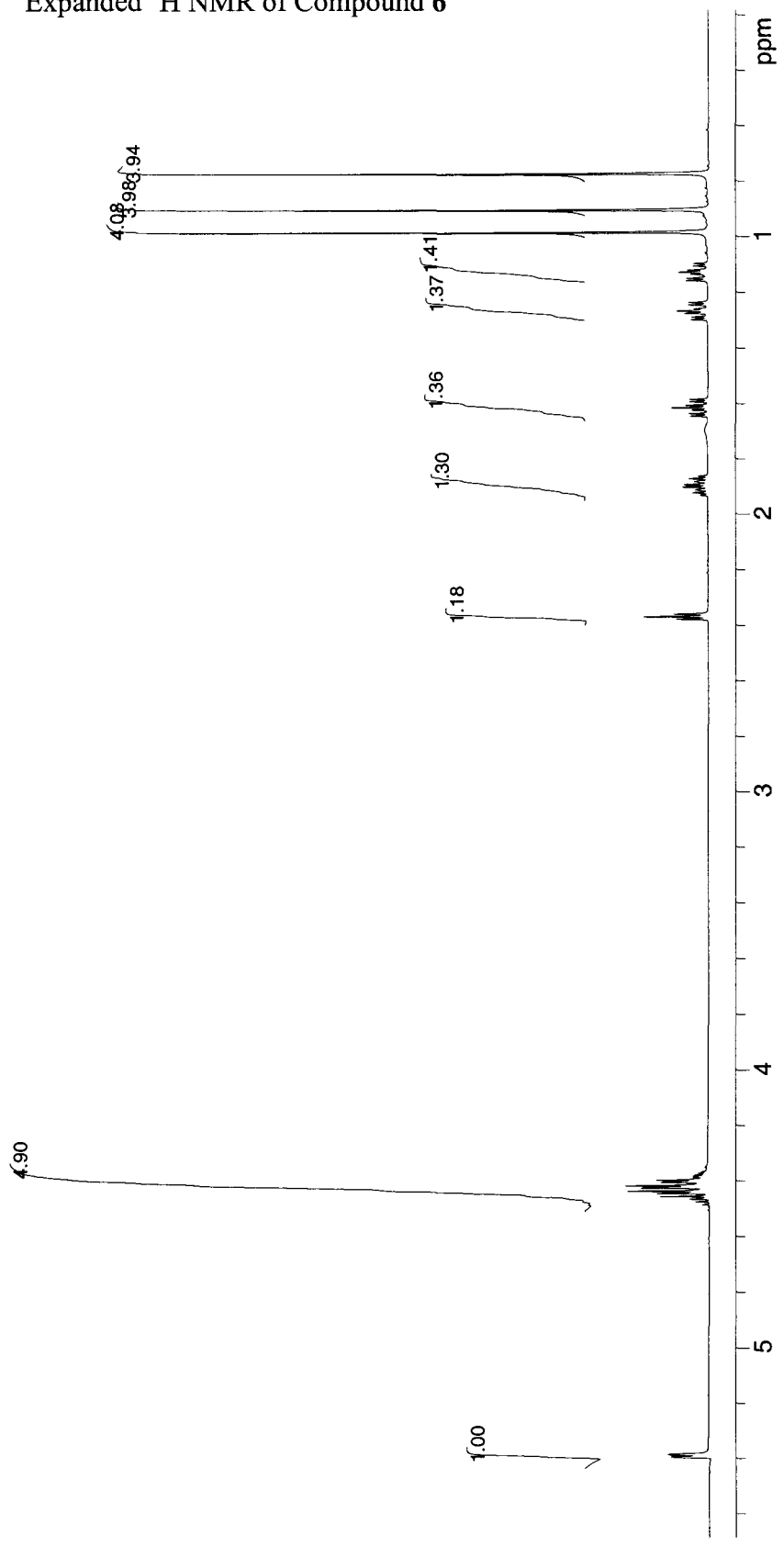

Figure 38 ^{31}P NMR of Compound **6**

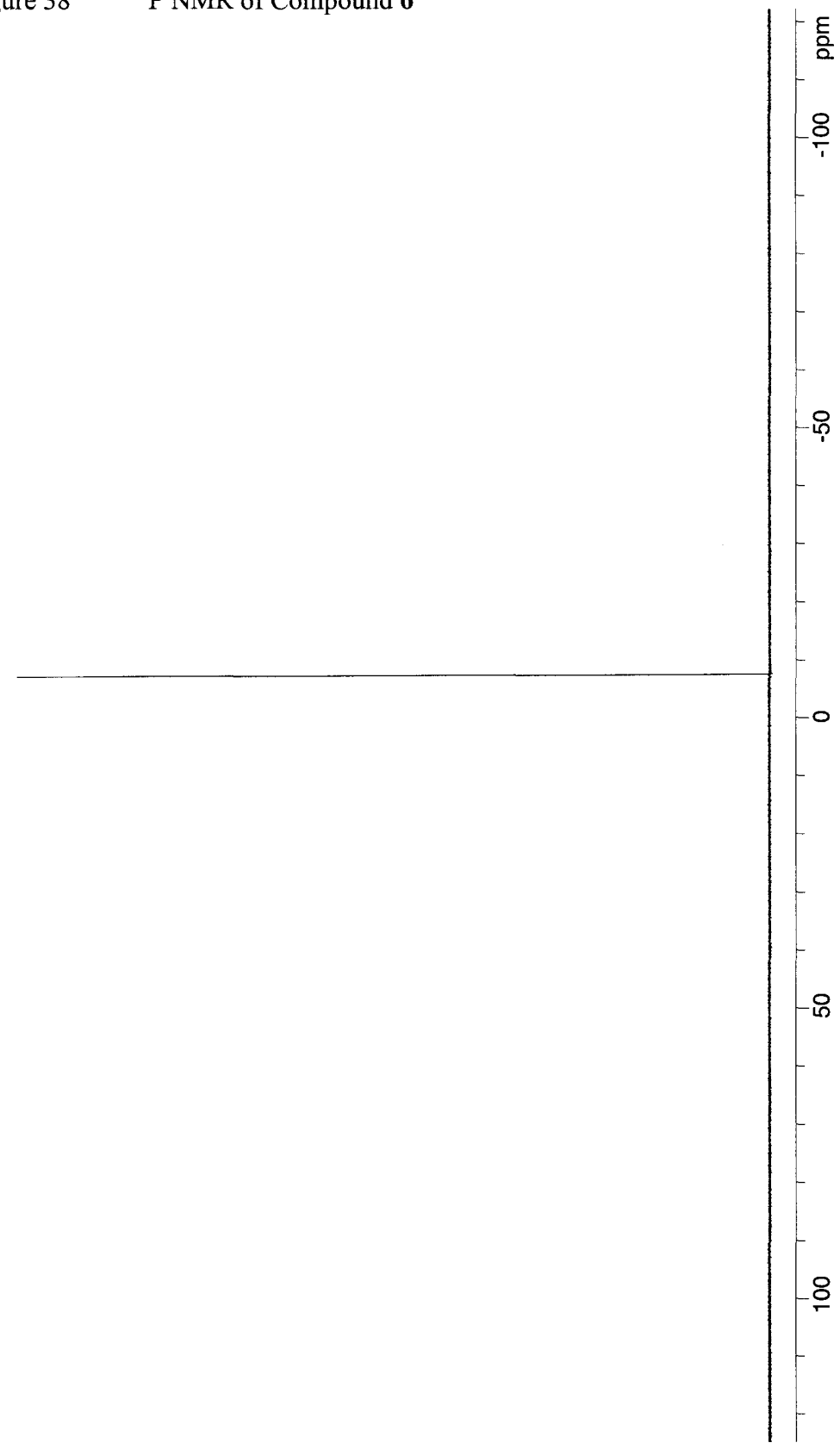

Figure 39 ^{13}C NMR of Compound **7**

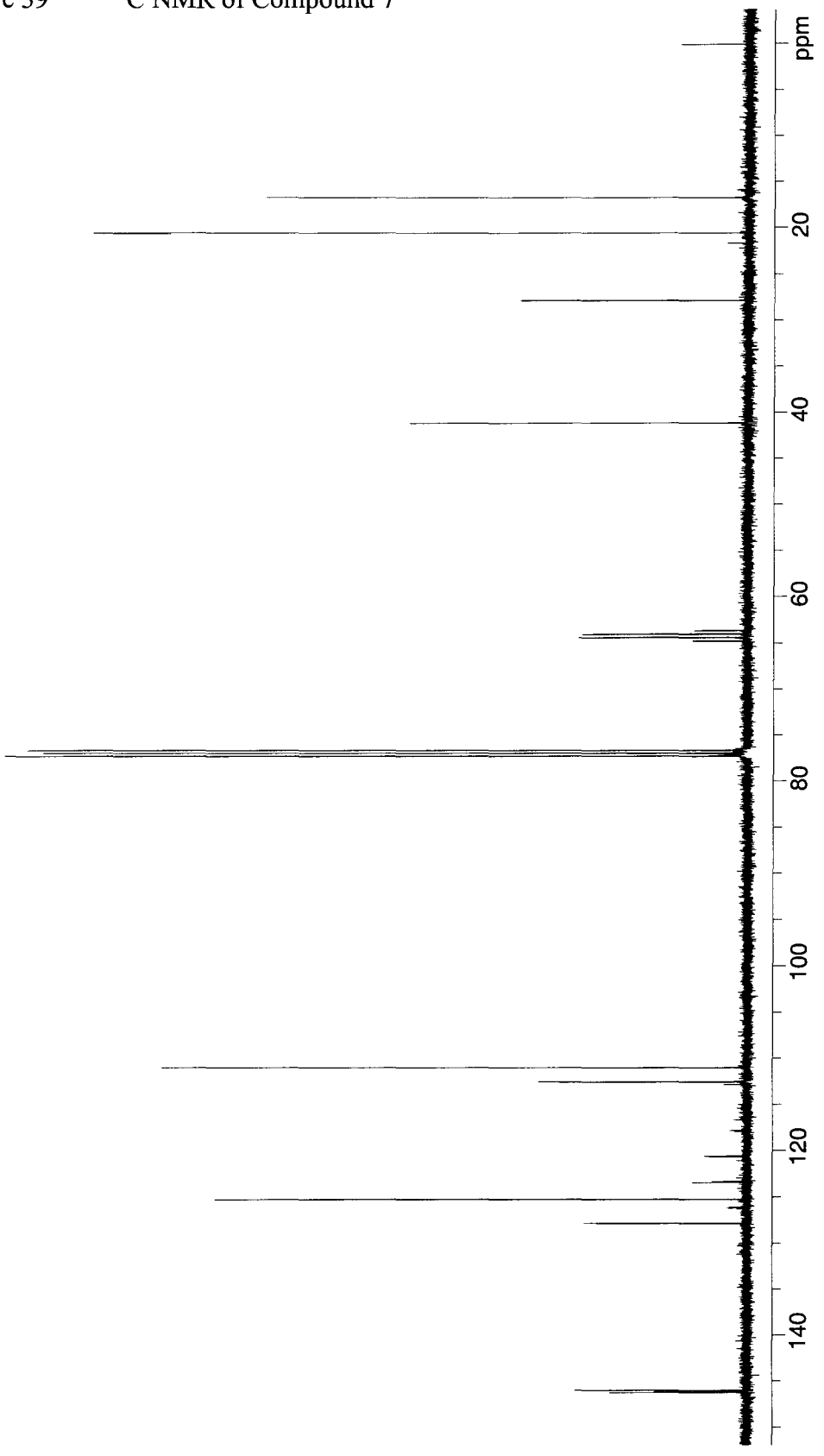

Figure 40 ^{1}H NMR of Compound **7**

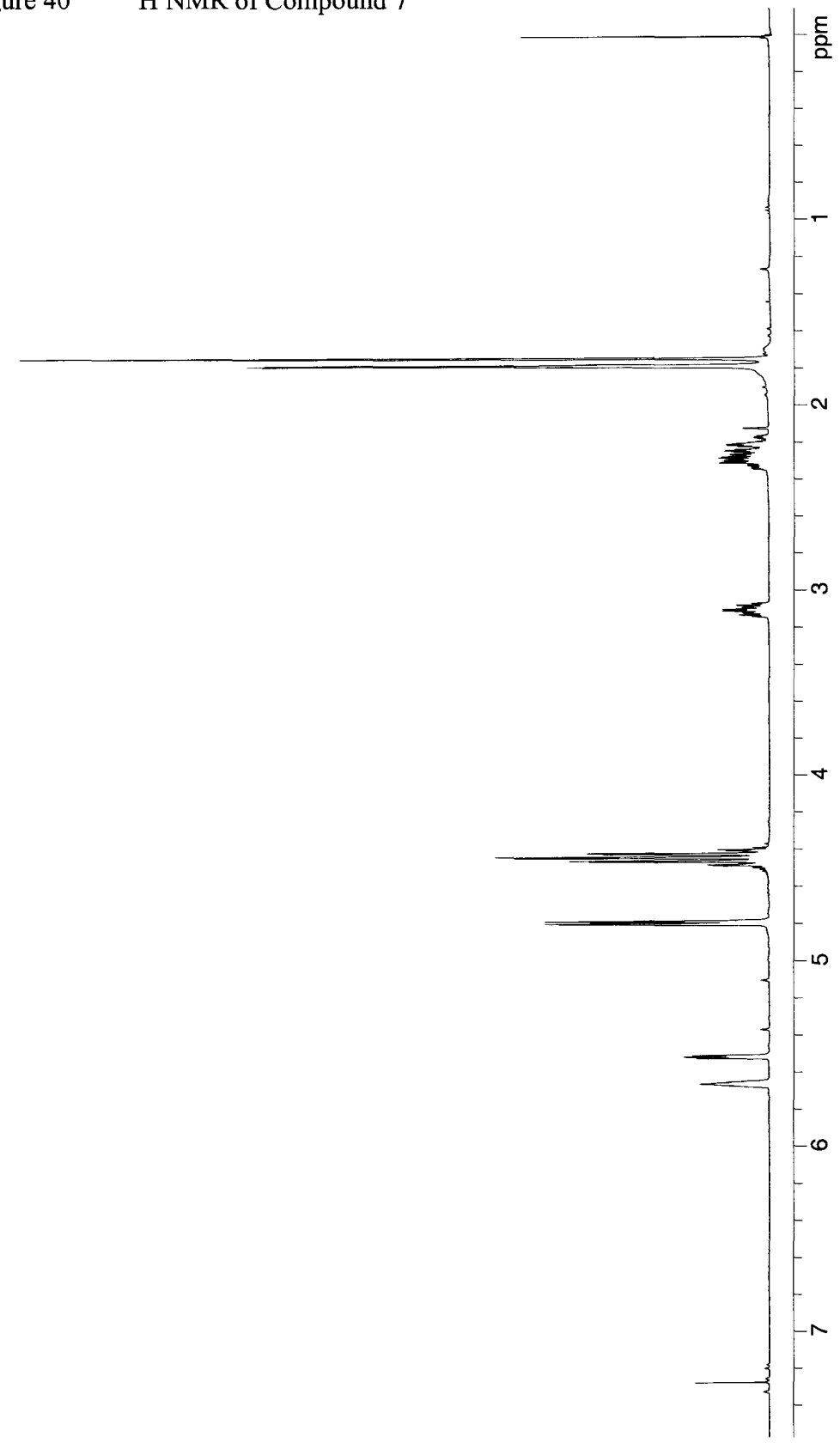

Figure 41 Expanded ^{1}H NMR of Compound **7**

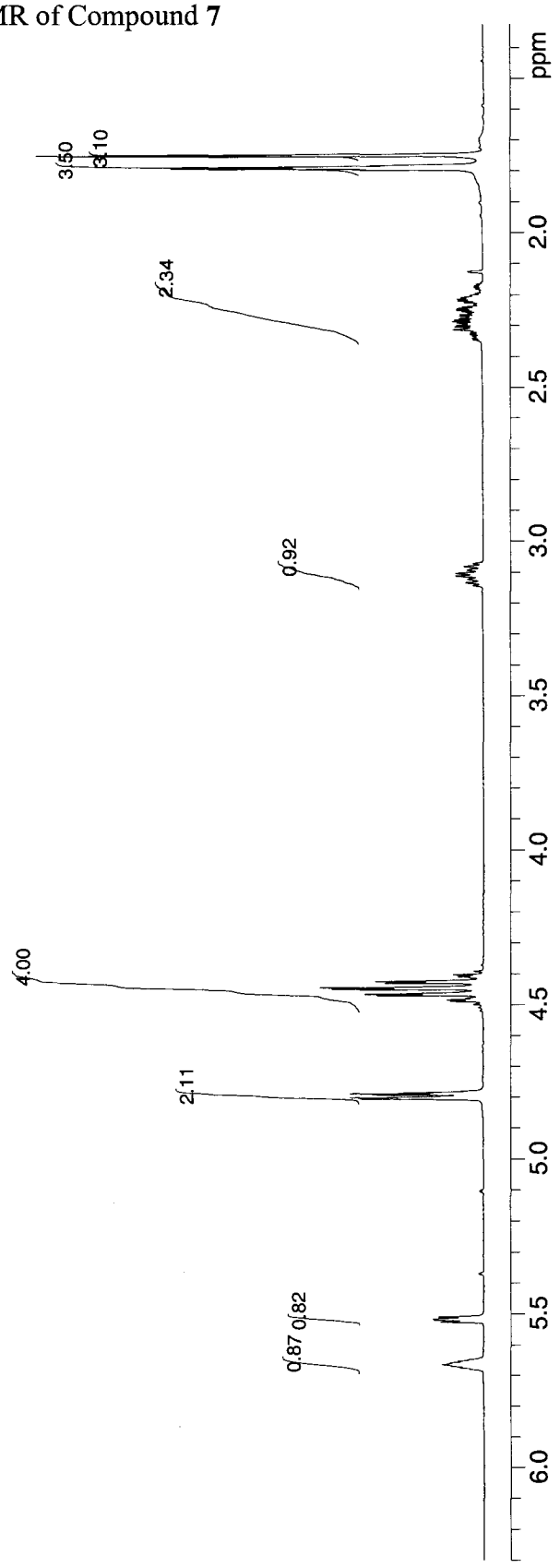

Figure 42 ^{31}P NMR of Compound **7**

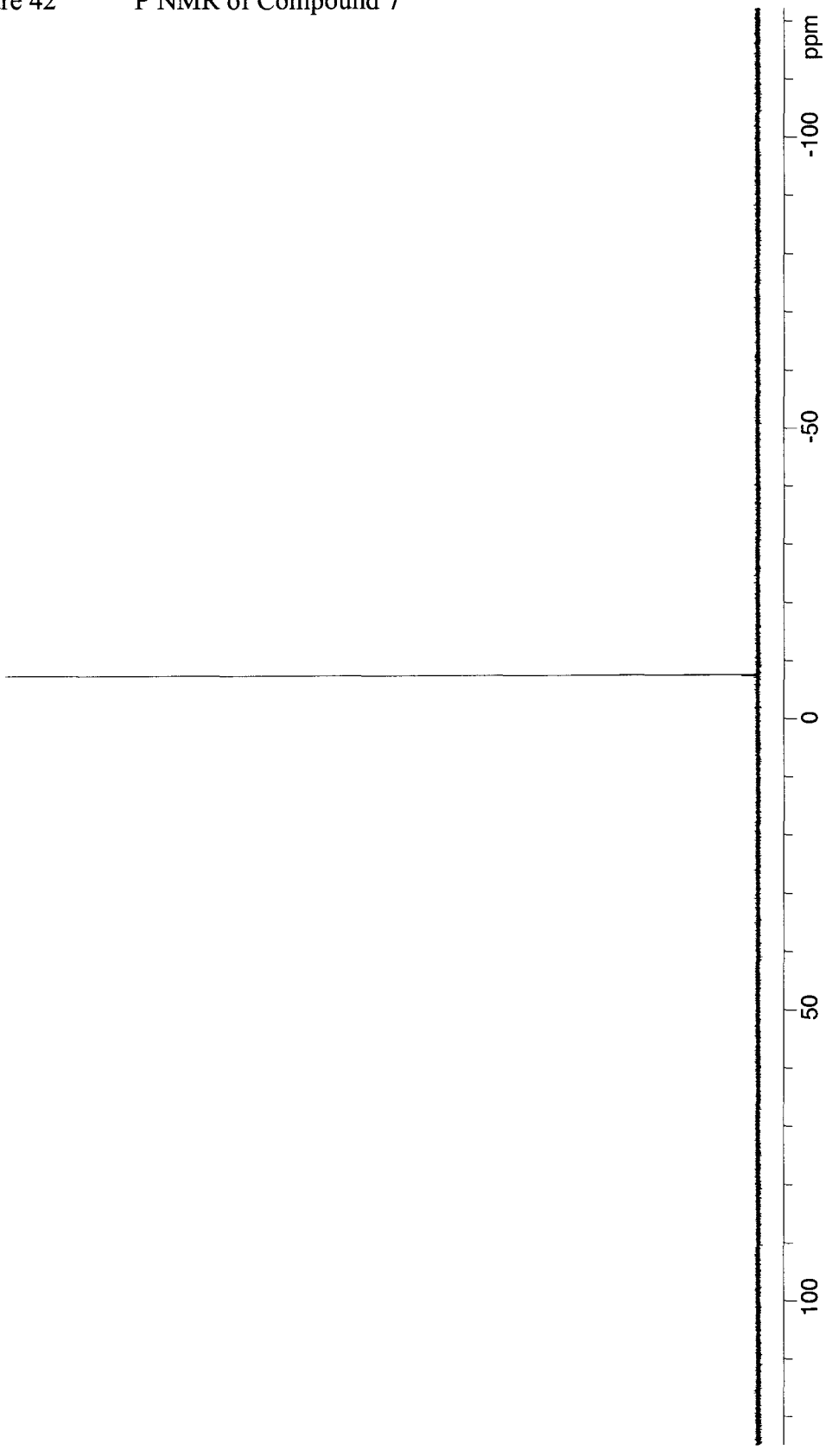

Figure 43 ^{13}C NMR of Compound **8**

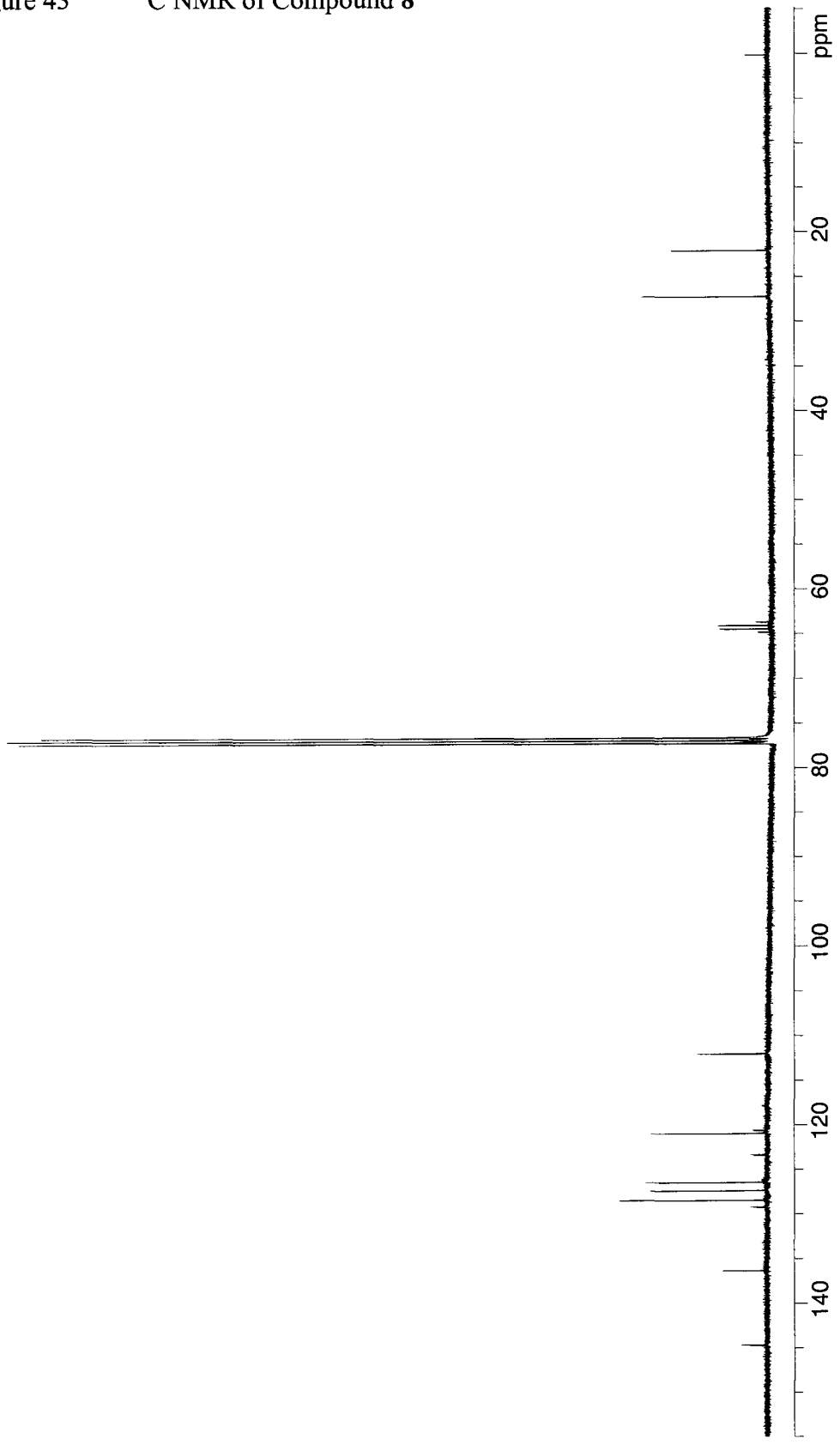

Figure 44 ^{1}H NMR of Compound **8**

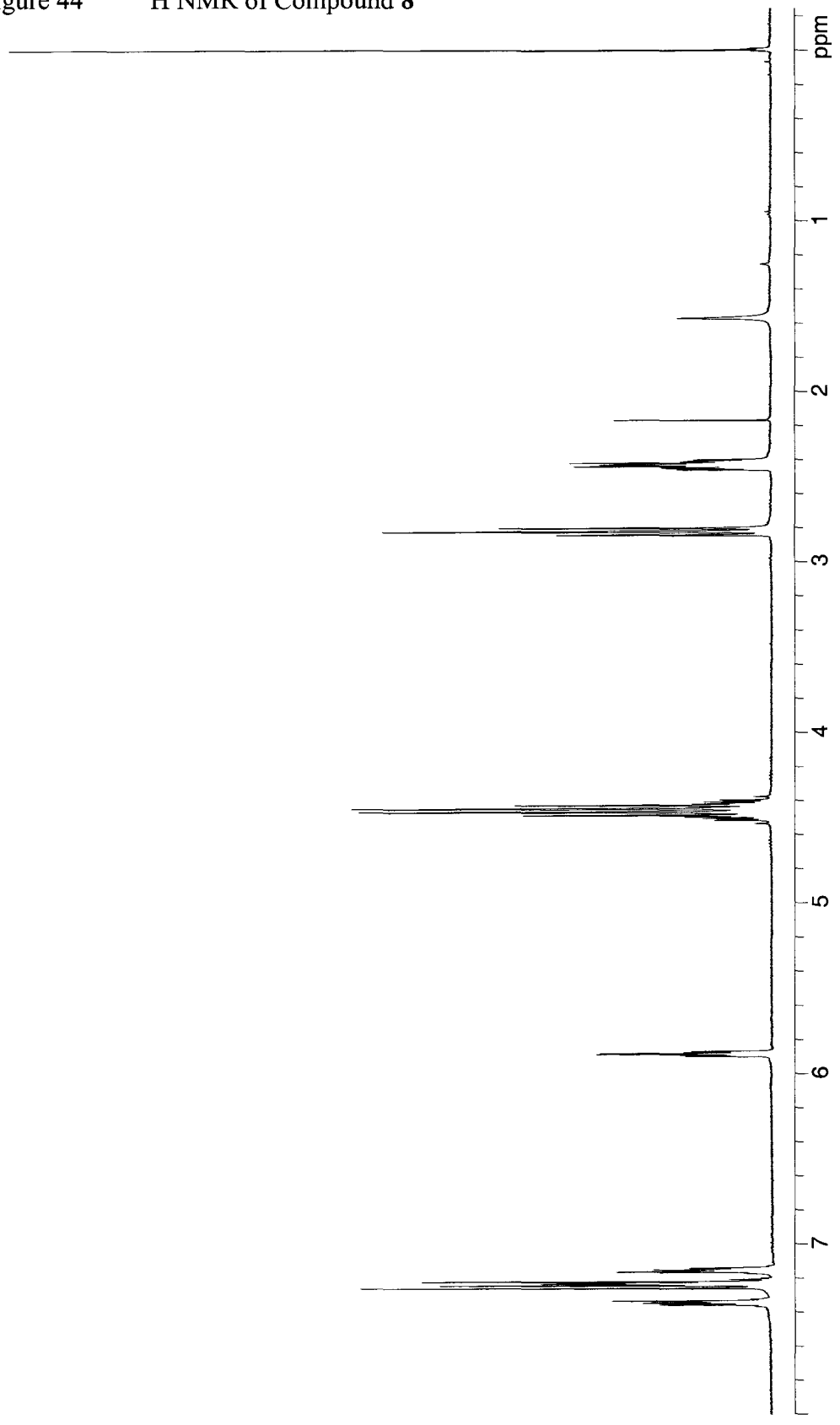

Figure 45 Expanded ^{1}H NMR of Compound **8**

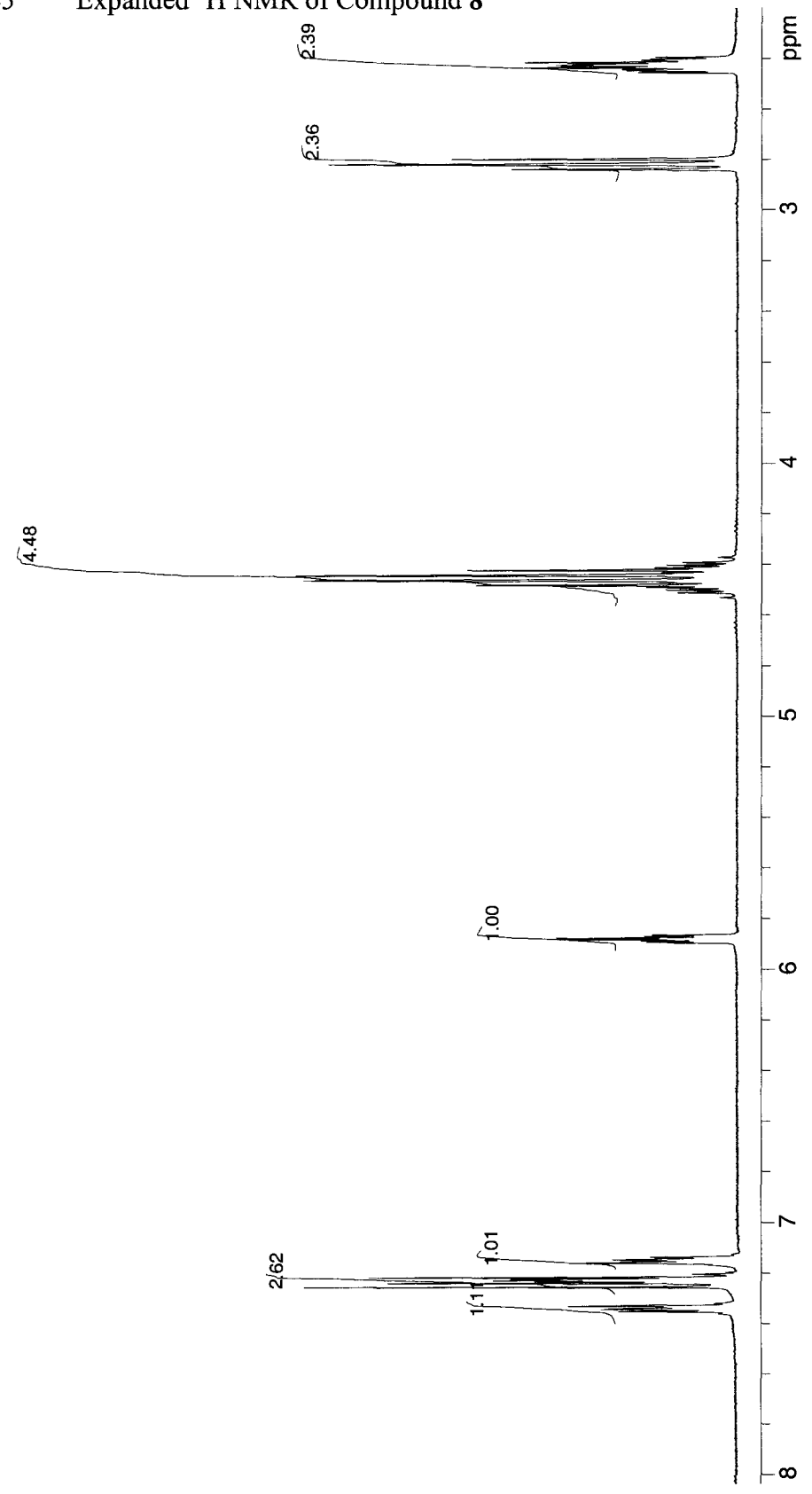

Figure 46 ^{31}P NMR of Compound **8**