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

by

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

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ABSTRACT

The focus of this research was a nucleophilic substitution of 1-alkynyl anions with bis(2,2,2-trifluoroethyl)phosphorochloridate as the electrophilic center. From this research, we have achieved a greater understanding of the chemistry of nucleophilic carbon on highly electrophilic phosphorus and how the reaction can be performed to favor the monosubstituted bis(2,2,2-trifluoroethyl)phosphonoalkyne product in moderate to good yields.

ACKNOWLEGEMENTS

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LIST OF ABBREVIATIONS

Abbreviation	Description
^{13}C	carbon-13
d	doublet
dd	doublet of doublets
dq	doublets of quartets
equiv.	equivalent
EtOAc	ethyl acetate
g	gram
GC	gas chromatograph
^{1}H	hydrogen-1
HMPA	hexamethylphosphoramide
Hz	hertz
J	coupling constant (in Hz)
LDA	lithium diisopropylamide
m	multiplet
mL	milliliter
mmol	millimole
n-BuLi	butyllithium
NMR	nuclear magnetic resonance
^{31}P	phosphorus-31
ppm	parts per million
s	singlet

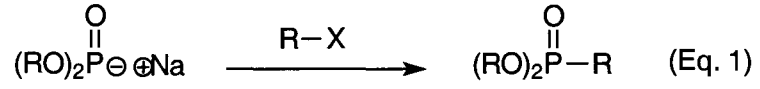
LIST OF ABBREVIATIONS (continued)

t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography

Chapter 1: Introduction

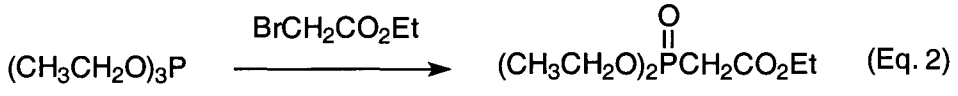
Part A: Carbon-Phosphorus Bond Formation

Historically, the first synthesis of a carbon-phosphorus bond was published in 1897.[1] This reaction, and the many other reactions in this area that followed, can be classified into two main categories. The first category deals with nucleophilic phosphorus reagents while the second category deals with electrophilic phosphorus reagents in carbon-phosphorus bond formation. An example of a nucleophilic phosphorus bond forming reaction, which can be described as a nucleophilic phosphorylation of a saturated carbon by the salts of dialkyl phosphites, is the Michaelis-Becker reaction (Eq. 1).[2]



(Eq. 1)

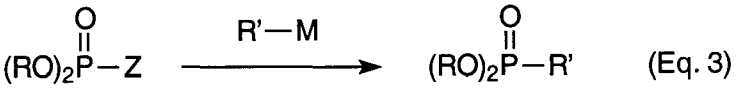
Another reaction involving nucleophilic phosphorus, the Arbuzov reaction, involves treating a trialkylphosphite with an alkyl halide to form a phosphonate (Eq. 2).[3]



(Eq. 2)

While these methods are useful in forming a carbon-phosphorus bond (especially the Arbuzov reaction) a different method involving carbanionic displacement reactions has been employed to form carbon-phosphorus bonds. This method involves nucleophilic attack at a pentavalent phosphorus center with an anionic species. To perform this reaction successfully, a good or moderate leaving group must be attached to

phosphorus. The general scheme of this carbanionic displacement reaction is shown below (Eq. 3).



(Eq. 3)

R = alkyl, aryl
R'= alkyl, alkynyl, aryl, heteroaryl
Z = RO, F, Cl
M= Cu, Li, Mg, Na, Zn

The focus of this research was a nucleophilic substitution of 1-alkynyl anions with bis(2,2,2-trifluoroethyl)phosphorochloridate as the electrophilic center (Fig. 1). From this research, we have achieved a greater understanding of the chemistry of nucleophilic carbon on highly electrophilic phosphorus and how the reaction can be performed to favor the monosubstituted bis(2,2,2-trifluoroethyl)phosphonoalkyne product.

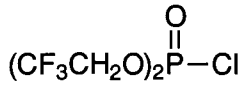


Fig. 1: bis(2,2,2-trifluoroethyl)phosphorochloridate

Part B: Phosphonoalkynes and Their Uses

Phosphonoalkynes consist of a pentavalent phosphorus bonded to one, two, or three sp hybridized carbons as shown below (Fig. 2).

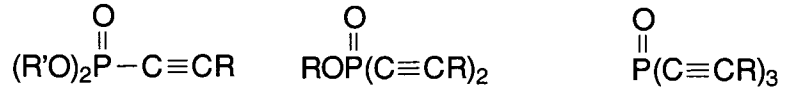
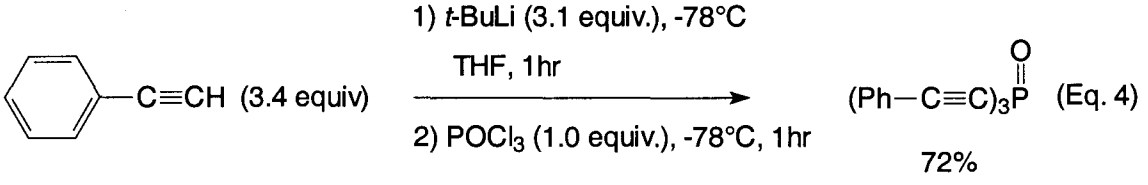


Fig. 2: phosphonoalkynes

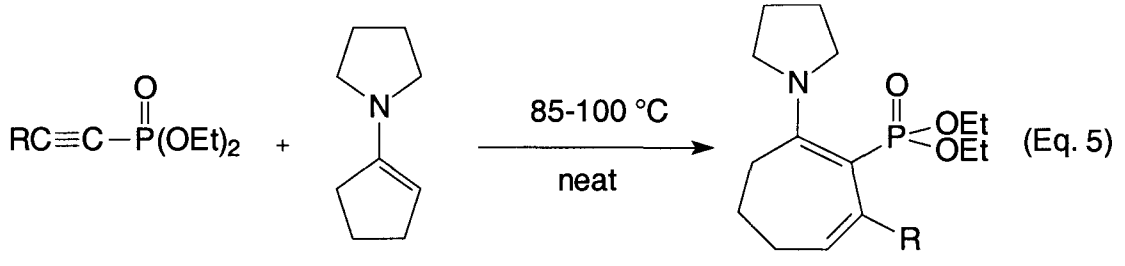
Phosphonoalkynes are useful reagents in synthetic organic chemistry for the formation of large size carbon rings via cycloadditions,[4] and to synthesize vinyl phosphonates.[5-9] They are also precursors to biologically active compounds such as antibiotics, which include the antibiotic Fosfomycin.[10] Phosphonoalkynes can also be used for fire retardant materials in some industrial and consumer applications.[11]

An article by Morgan, which involves the synthesis of "tris" substituted phosphonoalkynes shows that materials containing alkynes and phosphorus have great potential for flame retardant activity.[11] Morgan's synthesis of a "tris" alkynyl phosphonate is shown by the following reaction (Eq. 4).[11]

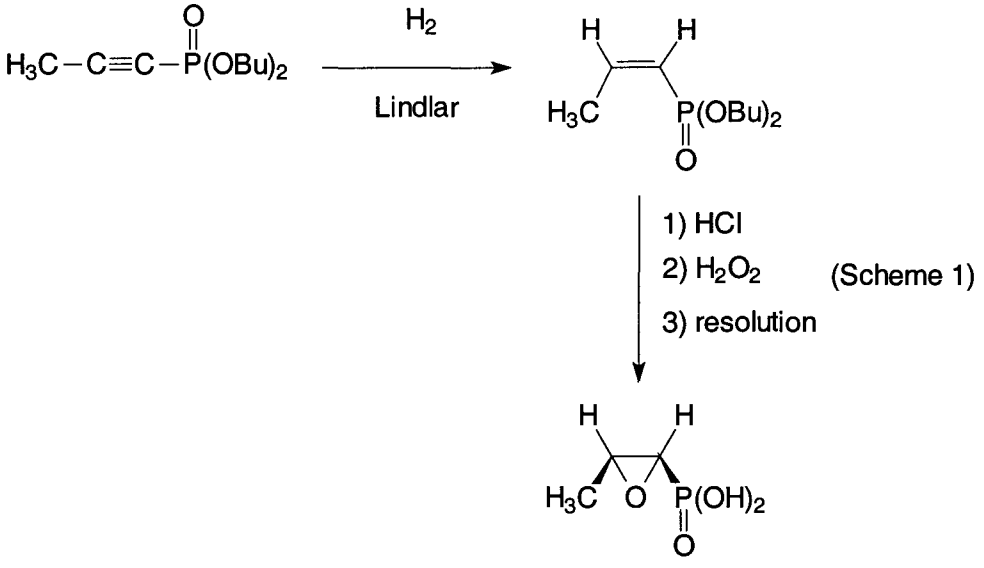


Once the tri(4-phenylethynyl)phosphine oxide had been made, it was then used as a monomer for complex polymers, which have great characteristics of flame resistance, low char formation and a low rate of heat release.[11]

Rudder has used alkynylphosphonates as reagents for cycloadditions in order to obtain ring expansion thus forming 7 and 8-membered rings as found in a variety of natural products (Eq. 5).[4]

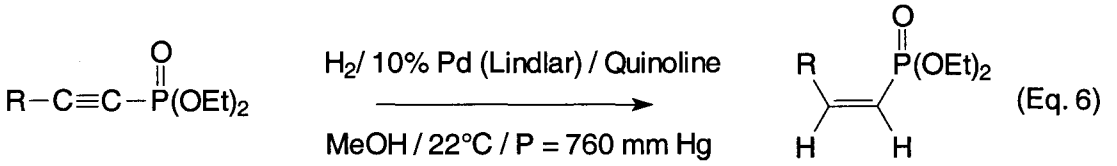


The most interesting use of a phosphonoalkyne that was found was its use as a reagent for a natural product synthesis. This synthesis included a reduction of a 1-propynylphosphonate with H_2 and a Lindlar's catalyst followed by epoxidation of the vinyl phosphonate (Scheme 1).[12] The result of this reaction sequence (Scheme 1) produces Fosfomycin, an antibiotic used in the treatment of bladder infections.[12]



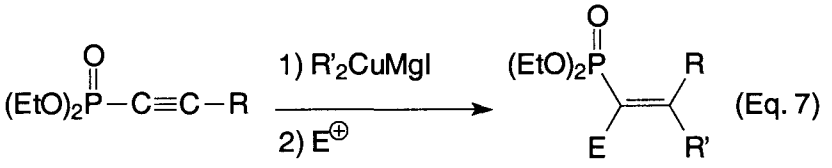
Part C: Use of Alkynylphosphonates in Vinylphosphonate Formation

The previous reaction (Scheme 1) is an example of a reaction where a vinyl phosphonate is made from a phosphonoalkyne in-order to obtain a natural product. Another example of a vinylphosphonate synthesis using phosphosphonoalkynes as a starting material include a synthesis by Cristau, who has developed a catalytic hydrogenation of a phosphonoalkyne to produce predominantly (Z)-vinylphosphonates (Eq. 6).[5] Yields from this synthesis have been reported to be from 77 to 95% depending on the R group on the alkynylphosphonate starting material.



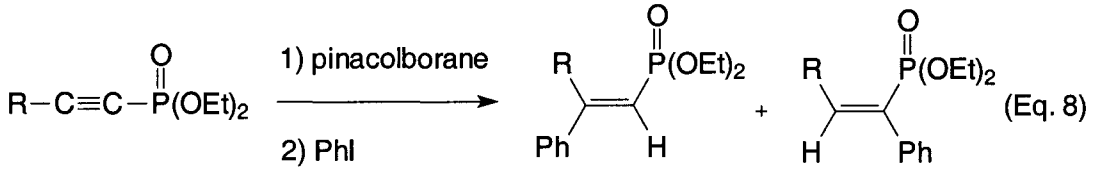
(Eq. 6)

Another reaction by Gil involving a carbocupration of diethyl 1-alkynyl phosphonates has also produced 1,2,2-trisubstituted vinyl phosphonates in high yields (85-97%) with a high degree of stereoselectivity (Eq. 7).[6]



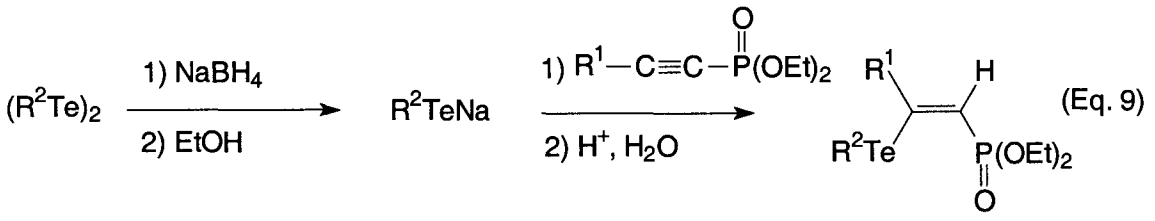
(Eq. 7)

A synthesis by Pergament involved a combination of hydroboration of a phosphonoalkyne and Suzuki coupling of the vinylborane to afford trisubstituted vinylphosphonates (17-48%) (Eq. 8).[7]



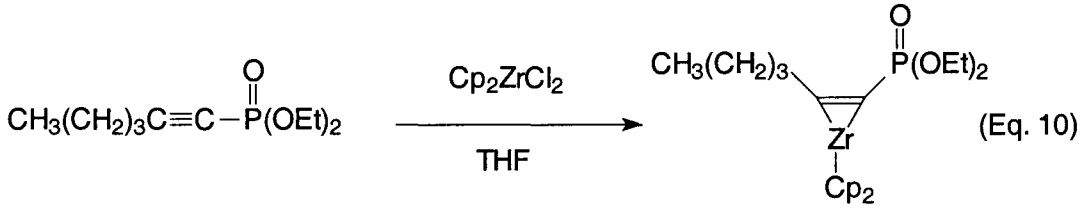
(Eq. 8)

An article by Braga describes the formation of a vinylphosphonate product giving a predominately (*Z*)-stereoisomer product.[8] This reaction involves a reduction of diorganyl ditellurides with sodium borohydride in ethanol at room temperature to form a sodium organyl tellurolate. An alkynylphosphonate was then added to the reaction mixture which was then followed by hydrolysis to form the primarily (*Z*)-substituted alkene (26-70%) (Eq. 9).



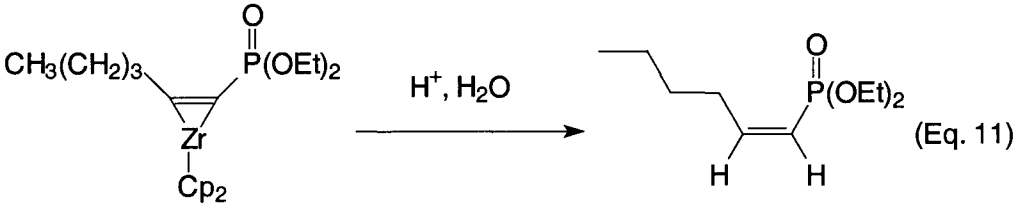
(Eq. 9)

Research by Quntar involving the synthesis (Z)-vinylphosphonates used a zirconocene complex that was added to the alkynylphosphonate, which gave a three-membered zirconacycle (Eq. 10).[9]



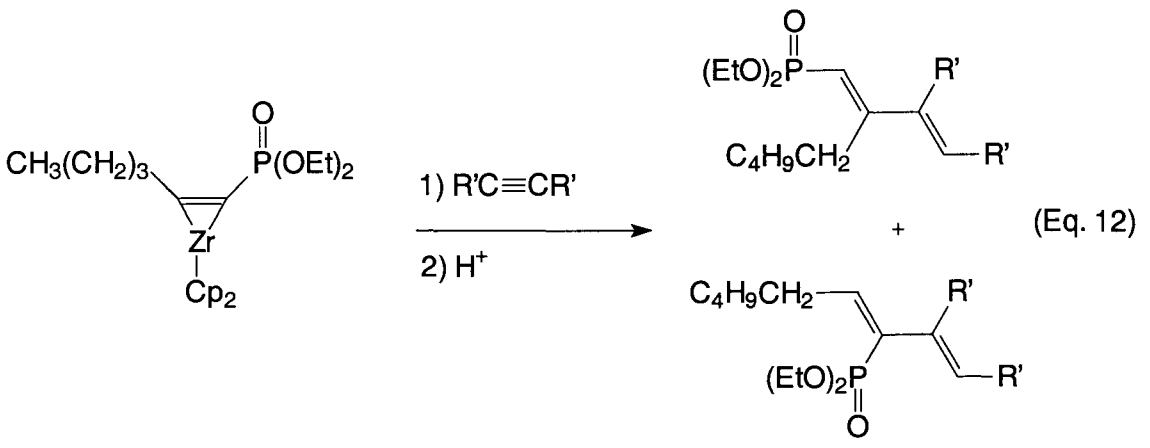
(Eq. 10)

The three-membered zirconacycle was hydrolyzed to give predominately a (Z)-vinyl phosphonate product with yields in the range of 63 to 79% (Eq 11).



(Eq. 11)

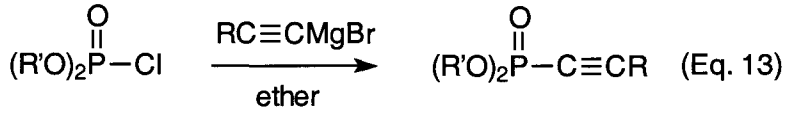
In another reaction, the three-membered zirconacycle was reacted with various alkynes to produce addition products which were then hydrolyzed to give substituted (*Z,E*) and (*E,E*)-1,3-butadienylphosphonates with yields of 57 to 73% (Eq. 12).



(Eq. 12)

Part D: Synthesis of Alkynylphosphonates

Chattha has published one of the first syntheses of an alkynylphosphonate.[12] In this synthesis of alkynylphosphonates, an alkynylmagnesium bromide reacted with diethyl or diphenyl phosphorochloridate to produce the monosubstituted alkynylphosphonate in yields of 51 to 76% (Eq. 13).

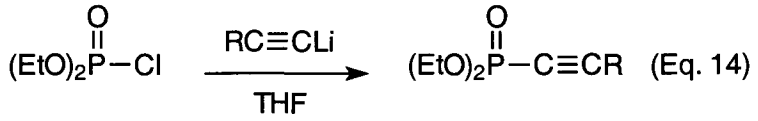


(Eq. 13)

Chatta noted that the success of this reaction is explained by the assumption that the chloride ion is more easily displaced as a leaving group than is the alkoxide and or phenoxide groups.[12]

A more recent paper published on the synthesis of phosphonoalkynes, improves the yields of the monosubstituted phosphonoalkyne product.[13] The main difference of this improved synthesis, when compared to Chatta's paper, is that the acetylenic anion is

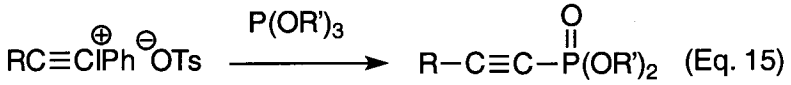
formed by using *n*-BuLi as the base. The first step in this synthetic strategy was to form the anion (using *n*-BuLi) followed by an addition of diethyl phosphorochloridate to form the alkynylphosphonate in yields of 82 to 91% (Eq. 14).



(Eq. 14)

The theory for the increased yields of the alkynylphosphonate (over that of Chatta's reaction) was that the alkynyllithium is actually less nucleophilic than the alkynylmagnesium bromide. By being less nucleophilic, the alkynyllithium was postulated to displace the chloride anion only, which gave higher yields of the monosubstituted product.

Koser, devised a synthesis of dialkyl alkynylphosphonates using a variation of the Arbuzov. This reaction involved using alkynyl(phenyl)iodonium tosylate with trialkyl phosphite to synthesize the desired monosubstituted phosphonoalkyne product (Eq. 15).[14]

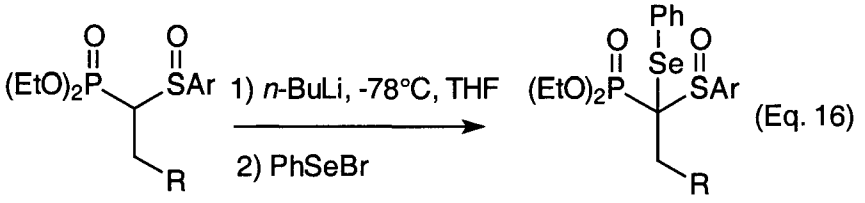


(Eq. 15)

This reaction can be historically categorized as a nucleophilic phosphorylation in the general scheme of carbon-phosphorus bond formation. This synthesis has produced a wide variety of dialkyl alkynylphosphonate products with yields varying from 34 to 90%.[14]

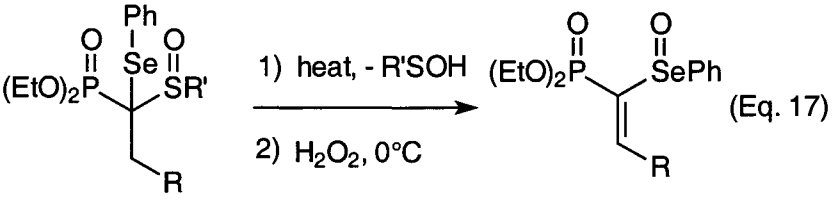
A five step synthesis leading to the monosubstituted alkynyl phosphonate product has been reported by Midura.[15] In this multistep sequence, the anion of an α-

phosphorylvinyl sulfoxide was reacted with phenylseleniumbromide to give a phenylselenide-substituted product (Eq. 16).



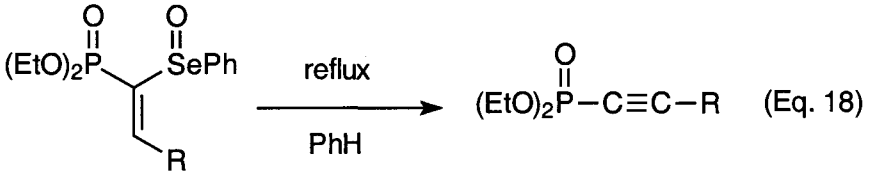
(Eq. 16)

The next step in this synthetic plan was to eliminate an arylsulfenic acid from the phenylselenide-substituted sulfoxide followed by oxidiation with hydrogen peroxide to form an α-phosphorylvinyl selenoxide (Eq. 17).



(Eq. 17)

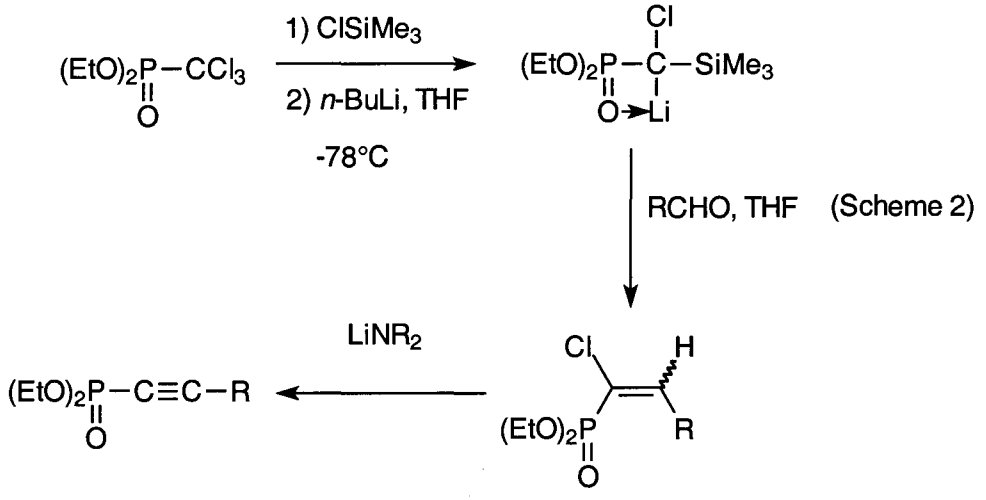
The α-phosphorovinyl selenoxide is the final intermediate to the alkynylphosphonate product, which is formed by refluxing the α-phosphorovinyl selenoxide in benzene (Eq. 18).



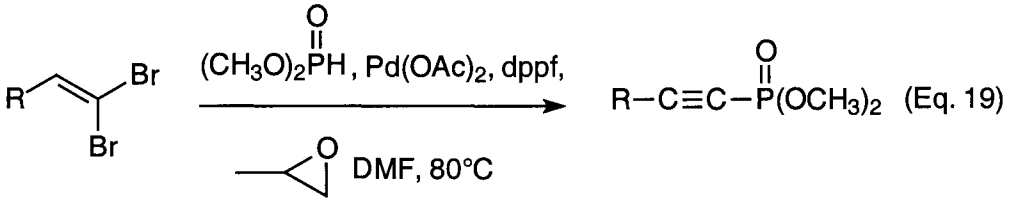
(Eq. 18)

This synthetic scheme requires five steps and gives the monosubstituted alkynylphosphonate in yields of 81 to 95% based on α-phosphorovinyl sulfoxide).

Savignac has developed a synthesis of 1-alkynylphosphonates using $(EtO)_2P(O)CCl_3$ as the main starting material.[16] The first step of the synthesis involves an interesting double chlorine-lithium exchange reaction. The exchange reaction is similar to a Peterson olefination, which was followed by dehydrochlorination with a lithium amide base giving yields of 1-alkynylphosphonates in the 89-96% range (Scheme 2).

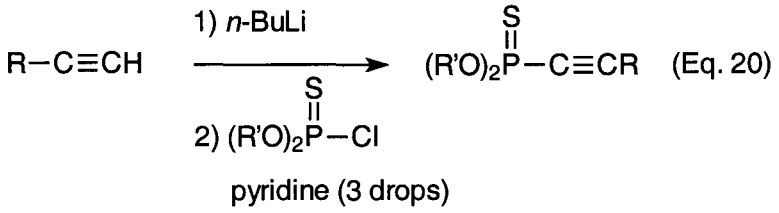


Hayes also developed a one-flask synthesis of alkynylphosphonates using a palladium-catalyzed reaction with 1,1-dibromo-1-alkenes and dimethyl phosphite (Eq. 19).[17] This reaction is similar to the Sonagashira coupling and produces alkynylphosphonates in yields of 16-76%.

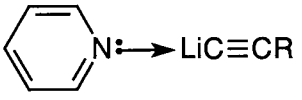


Part E. Synthesis of Alkynyl-1-Thiophosphonates

Aguiar has published a synthesis of dialkyl alkynyl-1-thiophosphonates.[18] In this paper a dialkyl phosphorochloridothionate was used in conjunction with the anions derived from several terminal alkynes to obtain the desired products (Eq. 20).



Due to the fact that alkynyl-1-thiophosphonates are less reactive than their oxygenated counterparts, a small amount of pyridine catalyst was used to increase the reactivity of the acetylenic anion by coordinating to the lithium cation (Fig. 3).



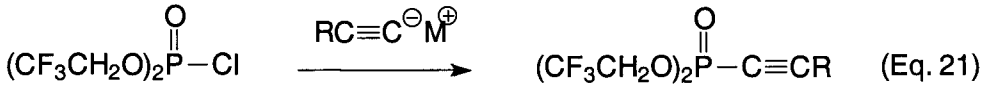
(Fig. 3: pyridine coordinated with Li^+)

Through this coordination effect, the acetylenic anion can perform a nucleophilic attack on phosphorus more efficiently by only displacing the chloride anion. From this reaction (Eq. 20) yields were reported to be from 35 to 79% with various alkynes.

Chapter 2: Results and Discussion

Synthesis of Bis(2,2,2-trifluoroethyl)phosphonoalkynes

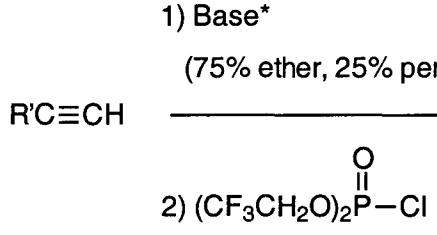
This research has explored the synthesis of bis(2,2,2-trifluoroethyl) phosphonoalkynes through the reaction of bis(2,2,2-trifluoroethyl)-phosphorochloridate with various synthesized acetylenic anions (Eq. 21). Due to the difficulty of this reaction, most of this research has consisted of the use of synthetic methods to find the best conditions that will produce an optimal yield of the monosubstituted bis(2,2,2-trifluoroethyl)phosphonoalkyne product.



(Eq. 21)

The final results of this synthetic problem have been summarized (Table 1).

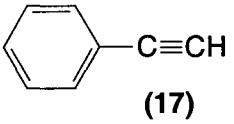
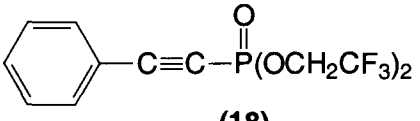
Table 1: Optimized Yields of Bis(2,2,2-trifluoroethyl)phosphonoalkynes



(Eq. 22)

Entry	Alkyne	Phosphonoalkyne	Yield (%)[a,b]
(1)	$HC{\equiv}CNa$ **(1)**	$HC{\equiv}C-\overset{\overset{O}{\|}}{P}(OCH_2CF_3)_2$ **(2)**	0

Table 1: Optimized Yields of Bis(2,2,2-trifluoroethyl)phosphonoalkynes (continued)

Entry	Alkyne	Phosphonoalkyne	Yield (%)[a,b,c]
(2)	$CH_3C{\equiv}CMgBr$ **(3)**	$CH_3C{\equiv}C-\overset{\overset{O}{\|}}{P}(OCH_2CF_3)_2$ **(4)**	38
(3)	$CH_3(CH_2)_2C{\equiv}CH$ **(5)**	$CH_3(CH_2)_2C{\equiv}C-\overset{\overset{O}{\|}}{P}(OCH_2CF_3)_2$ **(6)**	29
(4)	$CH_3(CH_2)_3C{\equiv}CH$ **(7)**	$CH_3(CH_2)_3C{\equiv}C-\overset{\overset{O}{\|}}{P}(OCH_2CF_3)_2$ **(8)**	37
(5)	$CH_3(CH_2)_4C{\equiv}CH$ **(9)**	$CH_3(CH_2)_4C{\equiv}C-\overset{\overset{O}{\|}}{P}(OCH_2CF_3)_2$ **(10)**	37
(6)	$CH_3(CH_2)_5C{\equiv}CH$ **(11)**	$CH_3(CH_2)_5C{\equiv}C-\overset{\overset{O}{\|}}{P}(OCH_2CF_3)_2$ **(12)**	33
(7)	$CH_3(CH_2)_6C{\equiv}CH$ **(13)**	$CH_3(CH_2)_6C{\equiv}C-\overset{\overset{O}{\|}}{P}(OCH_2CF_3)_2$ **(14)**	49
(8)	$CH_3(CH_2)_7C{\equiv}CH$ **(15)**	$CH_3(CH_2)_7C{\equiv}C-\overset{\overset{O}{\|}}{P}(OCH_2CF_3)_2$ **(16)**	56
(9)	 **(17)**	 **(18)**	6

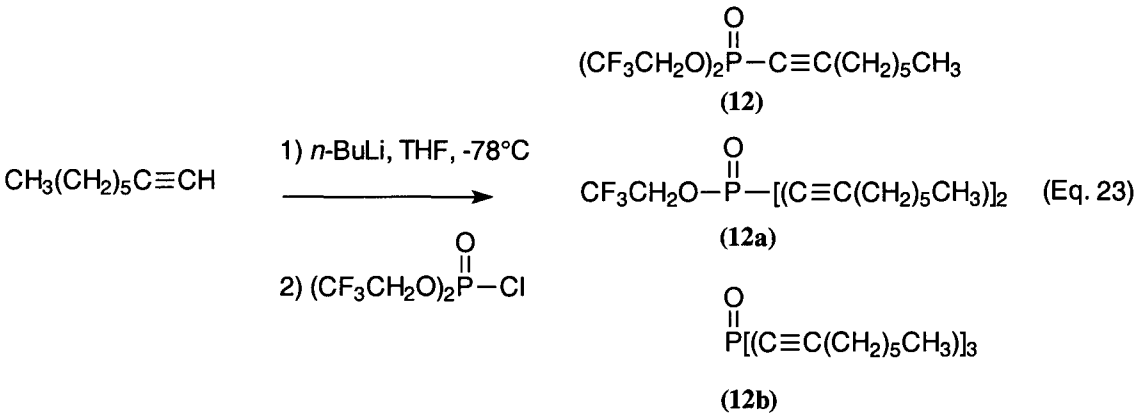
[a]Base used only for deprotonation of terminal alkynes (entries 3-9)
[b]Yield based upon integration of ^{31}P NMR spectrum of reaction mixture (entry 9)
[c]Isolated yield after flash column chromatography (entries 1-8)

From the research done on the synthesis of bis(2,2,2-trifluoroethyl)phosphonoalkynes, several different variables involved in the reaction have been explored. The variables that have been explored in this reaction include reaction temperature, concentration of reagents, base for the terminal alkyne deprotonation, reaction time/order of reagent addition, nucleophilicity of the acetylenic anion, and the solvent polarity.

The first attempted synthesis of a bis(2,2,2-trifluoroethyl)phosphonoalkyne involved reproducing a previously published method of phosphonoalkyne synthesis by Gil using bis(2,2,2-trifluoroethyl)phosphorochloridate instead of diethyl phosphorochloridate as the phosphorus electrophile.[10] This reaction (Eq. 23) involved the addition of *n*-butyllithium to a solution of 1-octyne in THF at –78 °C for one hour. Bis(2,2,2-trifluoroethyl)phosphorochloridate was then added neat and allowed to stir for one hour at –78 °C and then at room temperature for 30 minutes. Upon ^{31}P and ^{1}H NMR analysis of the reaction mixture, it was found to be composed of a complex mixture containing trace amounts of the desired monosubstituted phosphonooctyne **12** along with bis-octynylphosphonate **12a**, with the major reaction product being the tris-octynylphosphonate **12b** with a net yield of 72.6% (Eq. 23).

To account for the high yield of the tris-octynylphosphonate product and the complex product distribution of this reaction, it was realized that the trifluoroethyl groups on bis(2,2,2-trifluoroethyl)phosphorochloridate enhance the electrophilicity of phosphorus when compared to diethyl phosphorochloridate. Also, in addition to the chloride anion being a good leaving group, trifluoroethoxide ($CF_3CH_2O^-$) has the ability to be displaced by the alkynyllithium anion. The following equation represents the three

major products of this reaction (Eq. 23).

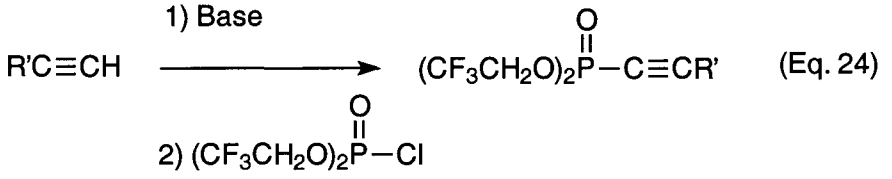


In an attempt to form only the monosubstituted phosphonoalkyne several variables were explored. The first variable of the reaction examined was the reaction temperature. The background literature reports that reaction temperatures used to form the acetylenic anion fall within the range of –78 °C to 0 °C.[12-13] From this information, along with experimentation of different reaction temperatures, it was found that the reaction gives better results at –78 °C.

After the best temperature for the formation of the acetylenic anion was determined, reaction temperatures of –78 °C and 0 °C along with various reaction durations were experimented with in the substitution reaction (Eq. 23). In addition to controlling different reaction temperatures and the time of reaction, different types of bases for anion formation were also explored. Although the majority of the background literature reports the use of *n*-butyllithium, bases such as $NaNH_2$, LDA, and NaH were also used to obtain the acetylenic anion in the reaction (Table 2).[12] Sodium amide has been useful for the deprotonation of 1-alkynes due to the fact that the amide anion is a much stronger base than the desired acetylenic anion.[20] Since the conjugate acid of sodium amide (ammonia) has a pK_a that is ten units above that of the terminal alkyne

proton (pK_a=35 for ammonia vs. pK_a= 25 for 1-alkyne) the formation of the acetylenic anion by the amide base should be very favorable. Sodium hydride is similar to sodium amide in which the pKa of its conjugate acid (hydrogen) is very similar in value (around 35). The reactions involving the use of these bases (NaH, $NaNH_2$, LDA) have produced very poor yields of the desired phosphonoalkyne product.[1] The results of these reactions have been summarized (Table 2).

Table 2: Reaction Temperatures, Base used, and Times of Reaction

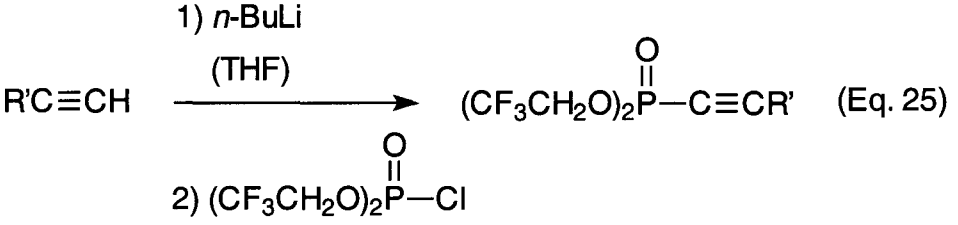


Entry	Alkyne	Base	Temp	Anion formation times	Time of rxn	Phosphono -alkyne	Yield (%)*
1	**(11)**	*n*-BuLi	-78 °C	20 min	12 hrs	**(12)**	1
2	**(11)**	*n*-BuLi	-78 °C	1 hr	1 hr	**(12)**	1
3	**(7)**	*n*-BuLi	-78 °C	1 hr	1 hr	**(8)**	10
4	**(11)**	*n*-BuLi	0 °C	1 hr	1 hr	**(12)**	0
5	**(7)**	*n*-BuLi	-78 °C	30 min	24 hrs	**(8)**	8
6	**(11)**	$NaNH_2$	-78 °C	1 hr	30 min	**(12)**	1
7	**(7)**	LDA	-78 °C	1 hr	24 hrs	**(8)**	1
8	**(17)**	NaH	0 °C	1 hr	2 hrs	**(18)**	1

* Yield based on integration of ^{31}P NMR spectrum of reaction mixture

The next variable of interest that was explored was reagent concentration. Since a large amount of the tris-phosphonooctyne **12b** (as seen by ^{31}P NMR analysis) was being formed using a reaction concentration of 0.200 M we postulated that a decrease in the concentration of reagents might slow the rate of the substitution. Theoretically, by increasing the amount of solvent (thus decreasing the concentration of the reactants) the amount of collisions between the acetylenic anion and bis(2,2,2-trifluoroethyl)phosphorochloridate will decrease favoring the production of the monosubstituted compound.[22] From Table 3 it is evident that some favorable results were seen by decreasing the concentration of reagents from 0.200 M to 0.055 M. This observation lead to the conclusion that the reaction rate was decreased.

Table 3: Effect of Concentration



(Eq. 25)

Entry	Alkyne	Concentration	Product	Yield (%)*
1	**(11)**	0.200 M	**(12)**	9
2	**(3)**	0.200 M	**(4)**	0
3	**(1)**	0.055 M	**(2)**	0
4	**(9)**	0.055 M	**(10)**	1

Table 3: Effect of Concentration (continued)

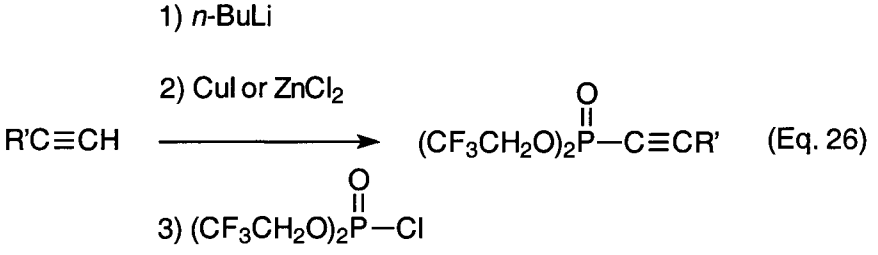
Entry	Alkyne	Concentration	Product	Yield (%)*
5	**(11)**	0.055 M	**(12)**	21

*Yield based on integration of ^{31}P NMR spectrum of reaction mixture

After exploring how the concentration of reagents affects the reaction, the next synthetic variable of interest that was focused upon was to find a way to decrease the nucleophilicity of the acetylenic anion. Theoretically, by decreasing the nucleophilicity of the acetylenic anion, the reaction should favor displacement of only the chloride anion over the trifluoroethyl groups. Various attempts to decrease the nucleophilicity of the acetylenic anion included the use of CuI to form an alkynylcuprate reagent and $ZnCl_2$ to form an alkynylzinc reagent. (Table 4). The attempt to use an alkynylcuprate in place of the alkynyllithium reagent stems from the ability of organocuprate reagents to form ketones from acid chlorides in high yields.[23] The reactivity of the alkynylcuprate reagent should be decreased when compared to the alkynyllithium reagent and, therefore, it should be more selective when compared to the reaction between the alkynyllithium and bis(2,2,2-trifluoroethyl)phosphorochloridate. This decrease in nucleophilicity of the alkynylcuprate has been attributed to the fact that the alkynyl-copper bond has more covalent character than that of the more ionic alkynyl-lithium pair.[24] The results, however, from the reaction of the alkynylcuprate with bis(2,2,2-trifluoroethyl)phosphorochloridate did not improve the yields of the monosubstituted phosphonoalkyne product when compared with the yields of the reaction between the alkynyllithium and bis(2,2,2-trifluoroethyl)phosphorochloridate.

The alkynylzinc reagent should also show a similar decrease in reactivity and, therefore, theoretically have a higher selectivity for the monosubstituted phosphonoalkyne product.[25] The background literature in this area also reports that organozinc reagents add to carbonyl compounds to give carbinols. From this stated fact, it was postulated that an alkynylzinc reagent may have the potential to add an alkyne group more selectively to bis(2,2,2-trifluoroethyl)phosphorochloridate over the reactivity of the copper acetylenic anion.[26] This method involving $ZnCl_2$ has proved to be unsuccessful in the various reactions and the results have been summarized (Table 4).

Table 4: Organometallic Reagents



(Eq. 26)

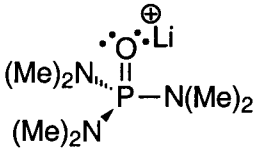
Entry	Alkyne	Metal	Solvent	Phosphono-alkyne	Yield (%)*
1	**(11)**	CuI	THF	**(12)**	18
2	**(9)**	CuI	ether	**(10)**	12
3	**(9)**	CuI	ether	**(10)**	12
4	**(11)**	$ZnCl_2$	THF	**(12)**	1

Table 4: Organometallic Reagents (continued)

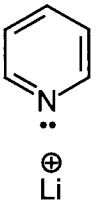
Entry	Alkyne	Metal	Solvent	Phosphono-alkyne	Yield (%)*
5	**(9)**	$ZnCl_2$	ether	**(10)**	1

* Yield based on integration of ^{31}P NMR spectrum of reaction mixture

Another method used to control the nucleophilicity of the anion was done through experimentation of 12-crown-4, HMPA, and pyridine as co-solvents. By using 12-crown-4 in different reactions, the goal was to trap the lithium cation, allowing the acetylide carbanion to react more efficiently with bis(2,2,2-trifluoroethyl)phosphorochloridate. HMPA (Fig. 4) and pyridine (Fig. 5) are postulated to coordinate lithium ions in a similar fashion.[18]



(Fig. 4: HMPA coordinating to Li^+)

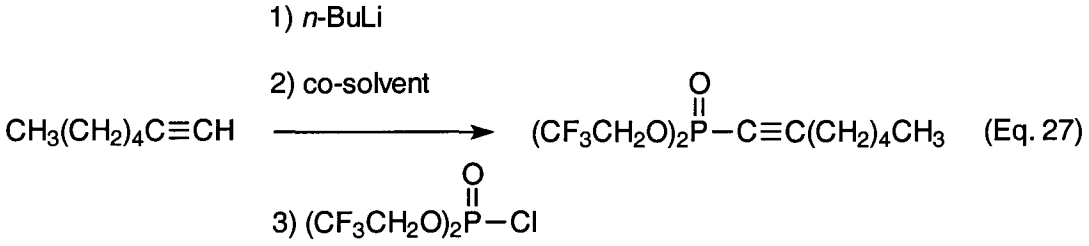


(Fig. 5: pyridine coordinating to Li^+)

From the results listed below (Table 5) it is evident that there was a slight increase in yield for the monosubstituted phosphonoalkyne product with the use of pyridine (as seen in the reaction mixture's ^{31}P NMR spectrum). However, due to the formation of numerous other phosphorus compounds in the reaction (Table 5, Entry 3) using pyridine as a co-solvent, made the purification of the desired product difficult. The use of a 20%

ether-80% THF solvent combination (from the formation of alkynyl-1-thiophosphonates as reported by Aguiar)[18] along with 3 drops of pyridine, was used as an experimental condition to form our target molecule bis(2,2,2-trifluoroethyl)phosphonoheptyne (Table 5, Entry 3). Even though at first pyridine seemed to increase the selectivity of the reaction to favor the desired monosubstituted product, the reaction also formed a large amount of other compounds with very low yields, (in the analysis of the reaction's mixture ^{31}P NMR spectrum), which were difficult to separate from the desired product. From this data, pyridine's use in the reaction was discontinued and solvent polarity was the next focus of the synthetic plan.

Table 5: Co-Solvents and Chelating Reagents



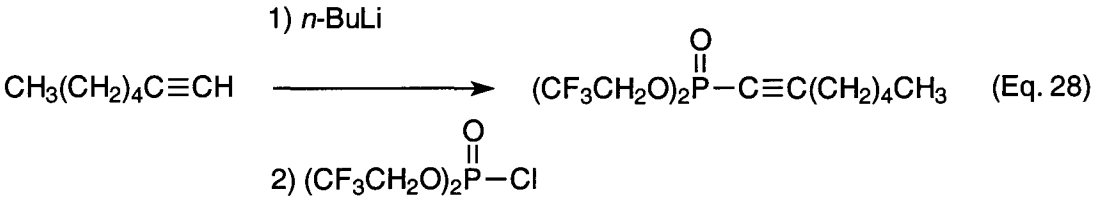
(Eq. 27)

Entry	Solvent	Co-solvent	Yield (%)*
1	THF	12-crown-4	10
2	THF	HMPA	12
3	THF, ether	Pyridine: 3-drops	18
4	THF, ether	Pyridine:1eq	20
5	THF, ether	Pyridine:1.5eq	21

* Yield based on integration of ^{31}P NMR spectrum of reaction mixture

The results from the reactions whose main synthetic aspect was the type of solvent and solvent combination has been summarized (Table 6). From this data (Table 6) we concluded that the reaction gives the highest yields with a non-polar solvent combination of 25% ether, 75% pentane.

Table 6: Solvents Used in the Various Reactions



(Eq. 28)

Entry	Alkyne	Solvent	Phosphono-alkyne	Yield (%)[a]
1	**(11)**	ether	**(12)**	15[a]
2	**(11)**	ether	**(12)**	20[b]
3	**(11)**	pentane	**(12)**	18[a]
4	**(11)**	50% pentane, 50% THF	**(12)**	15[a]
5	**(11)**	90% ether, 10% pentane	**(12)**	11[a]
6	**(11)**	90% pentane, 10% ether	**(12)**	12[a]
7	**(11)**	25% ether, 75% pentane	**(12)**	33[b]

Table 6: Solvents Used in the Various Reactions (continued)

Entry	Alkyne	Solvent	Phosphono-alkyne	Yield (%)
8	**(9)**	THF	**(10)**	1[a]
9	**(9)**	ether	**(10)**	12[a]
10	**(9)**	ether	**(10)**	10[a]
11	**(9)**	25% ether, 75% pentane	**(10)**	37[b]
12	**(7)**	ether	**(8)**	10[a]
13	**(7)**	ether	**(8)**	11[a]
14	**(7)**	90% ether, 10% pentane	**(8)**	1[a]
15	**(7)**	25% ether, 75% pentane	**(8)**	37[b]
16	**(17)**	ether	**(18)**	1[a]
17	**(17)**	25% ether, 75% pentane	**(18)**	6[a]
18	**(3)**	THF	**(4)**	1[a]
19	**(3)**	dioxane	**(4)**	1[a]
20	**(3)**	Ether	**(4)**	1[a]
21	**(3)**	25% ether, 75% pentane	**(4)**	38[b]

Table 6: Solvents Used in the Various Reactions (continued)

Entry	Alkyne	Solvent	Phosphono-alkyne	Yield (%)[a]
22	**(1)**	THF	**(2)**	0[a]
23	**(1)**	dioxane	**(2)**	0[a]
24	**(1)**	ether	**(2)**	0[a]
25	**(1)**	25% ether, 75% pentane	**(2)**	0[a]
26	**(5)**	25% ether, 75% pentane	**(6)**	30[b]
27	**(13)**	25% ether, 75% pentane	**(14)**	49[b]
28	**(15)**	25% ether, 75% pentane	**(16)**	56[a]

[a]Yield based on integration of ^{31}P NMR spectrum of reaction mixture

[b]Isolated yield after flash column chromatography

The ^{31}P NMR spectrum of the reaction mixture, where the main synthetic variable was 25 mL of THF solvent (Fig. 6), shows a 1% yield of the desired monosubstituted phosphonoalkyne product at about -4.90 ppm with the major phosphorus product at –2.16 ppm. A comparison of the ^{31}P NMR spectrum (Fig. 6) of the reaction using THF as a solvent (Table 2, Entry 1) with that of the ^{31}P NMR spectrum (Fig. 7) using ether as a solvent (Table 6, Entry 2) shows an improvement in the yield (18% vs. 1%) of the desired monosubstituted phosphonoalkyne product. This increase in yield of the monosubstituted phosphonoalkyne product has been attributed to the increase in the amount of solvent

used. By determining that the solvent was the main synthetic method of the reaction, it was decided to vary the type and the polarity of the solvent.

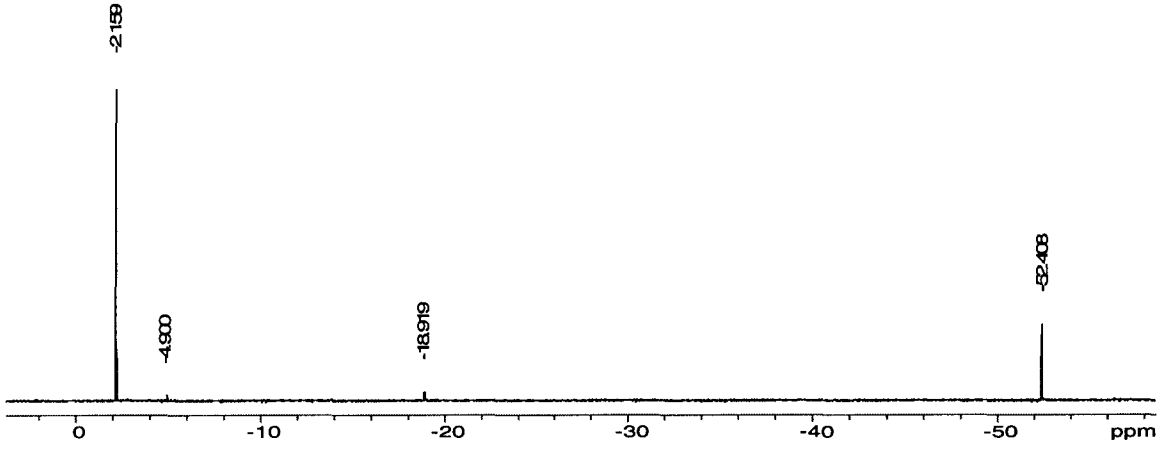


Fig. 6: ^{31}P NMR of reaction mixture Table 1, Entry 1

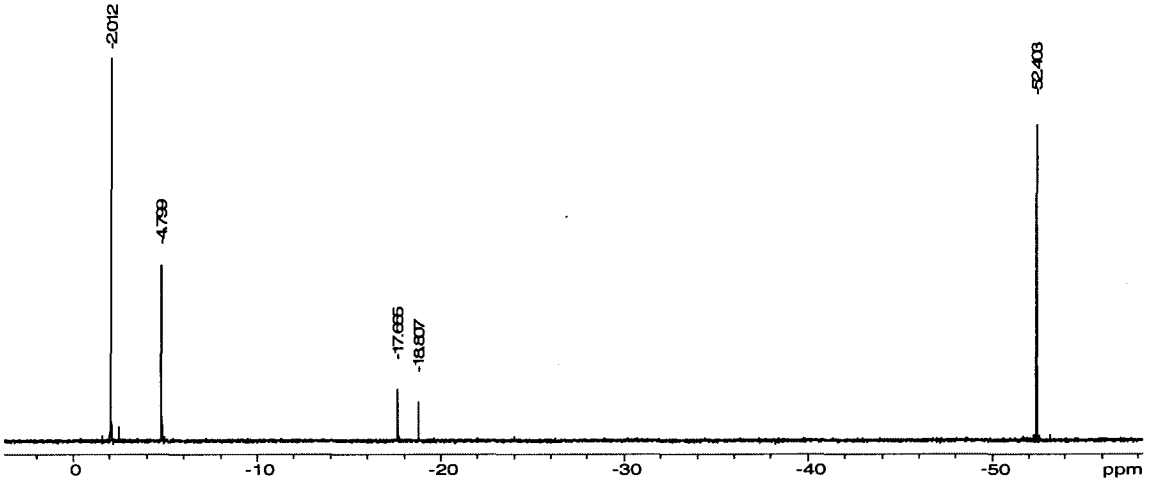


Fig 7: ^{31}P NMR of reaction mixture Table 6, Entry 2

Although there was an increase in the yield of the monosubstituted phosphonoalkyne product, some tris-phosphonoalkyne was still being formed (^{31}P chemical shift of –52 ppm) in the reactions shown above. The decision to focus on the polarity of the solvent was realized after a thorough examination of the results from Table 6 and determining that it was the one variable that had not been tried. Thus the experimentation of solvent polarity in the reaction began by first using 100% pentane then varying the ratio of ether to pentane until the ^{31}P NMR spectrum of the crude reaction mixture showed a relatively clean spectrum with very few byproducts (Fig. 8). After purification of this reaction mixture (Table 6, Entry 4), a ^{13}C NMR spectrum (Fig. 9) of compound **12** was obtained which proves the formation of this product.

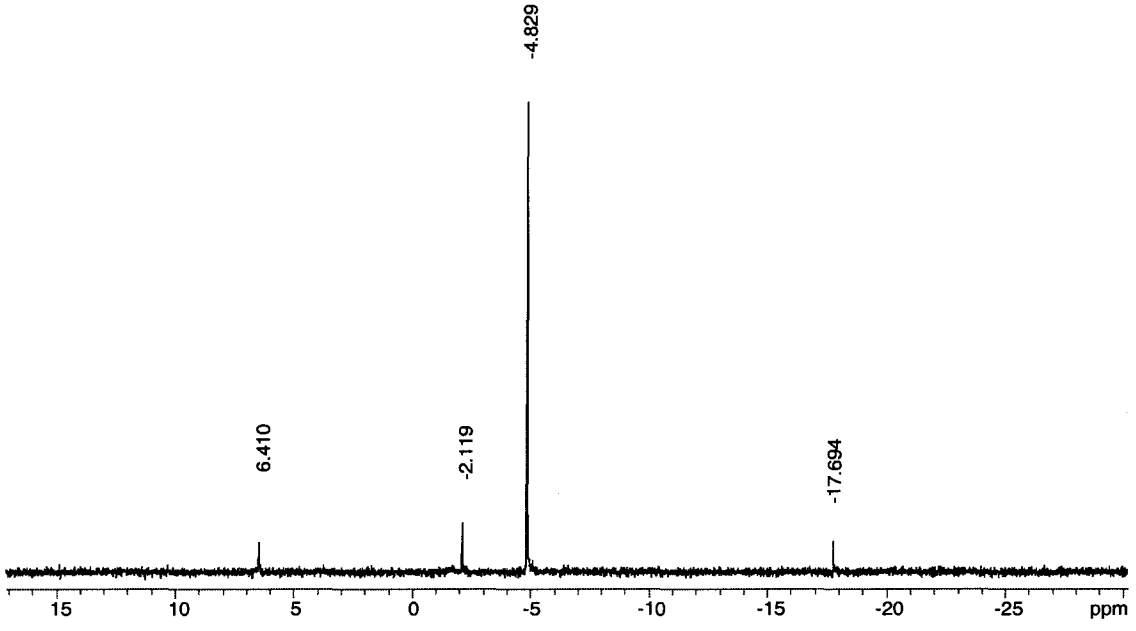


Fig. 8: ^{31}P NMR of reaction Table 6, Entry 4

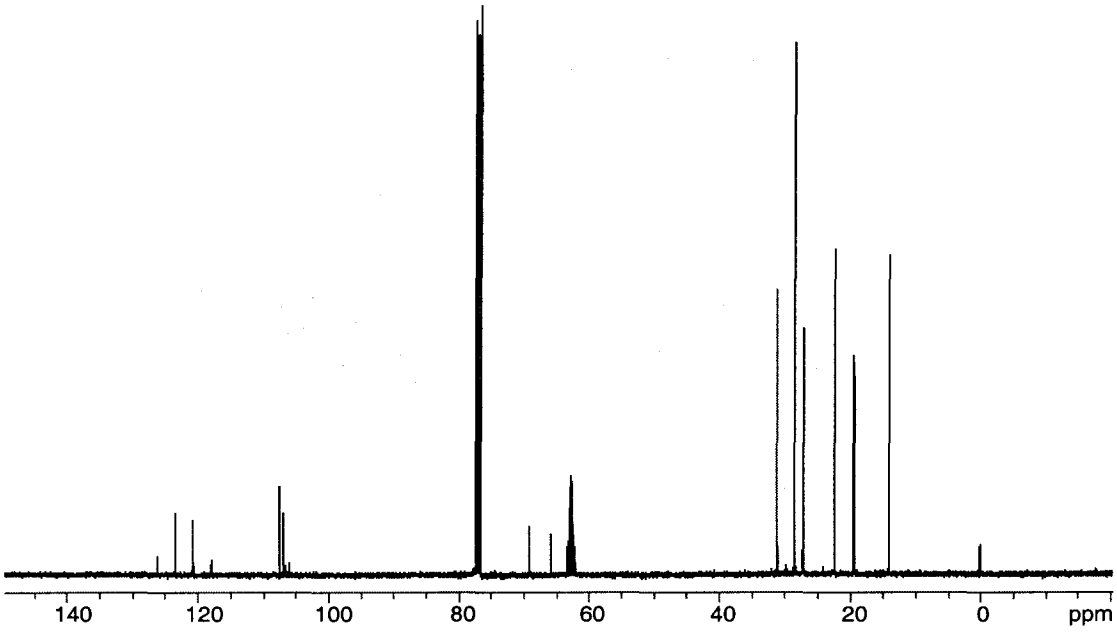


Fig. 9: ^{13}C NMR Spectrum of compound **12**

The ^{13}C NMR spectrum of compound **12** shows both the carbons of the CF_3 group at 122.14 ppm (Fig. 10) and the CH_2 group at 62.71 ppm (Fig. 11) as doublets of quartets. The splitting patterns of these two groups are due to coupling of the carbons to both phosphorus and to fluorine. The carbons of the CF_3 groups are distinguished from the CH_2 group by showing a much larger coupling constant (277.0 Hz for the CF_3 group vs 38.1 Hz for the CH_2 group). The C-P coupling constant between the two groups (CF_3 versus the CH_2) is very similar (9.9 Hz vs 5.3 Hz). These characteristic splitting patterns for this compound will be very similar to the rest of the bis(2,2,2-trifluoroethyl)phosphonoalkynes that have been synthesized.

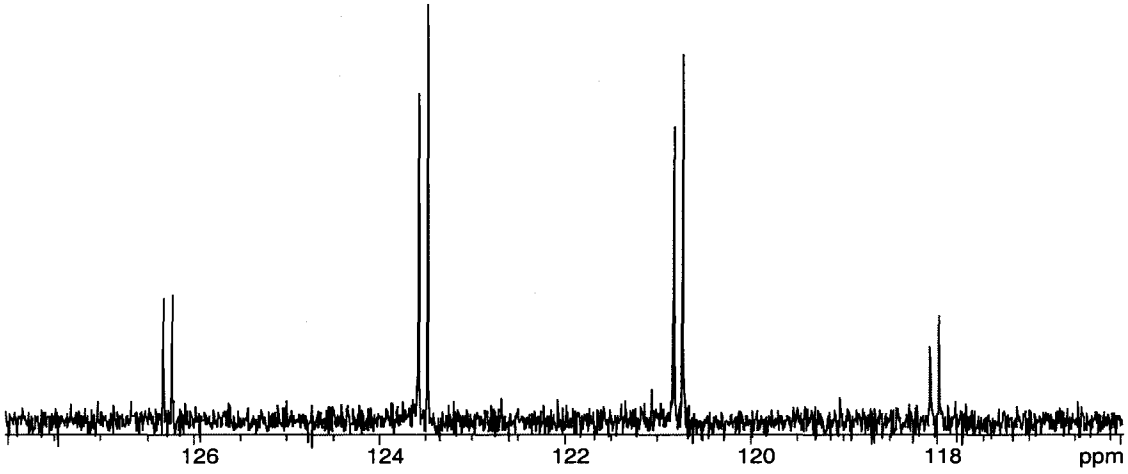


Fig. 10: ^{13}C NMR of the CF_3 groups of the trifluoroethyl groups of compound **12**

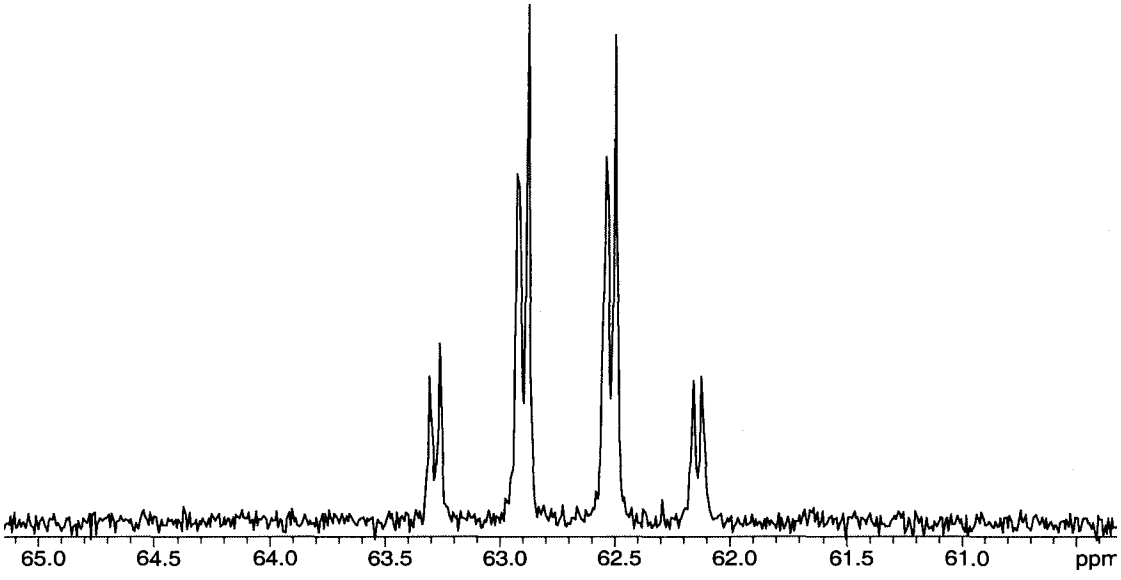


Fig. 11: ^{13}C NMR of the CH_2 groups of the trifluoroethyl groups of compound **12**

The ^{13}C NMR peaks corresponding to the α and β sp hybridized carbons of compound **12** show up as doublets with relatively large coupling constants due to coupling with phosphorus. The α carbon (67.49 ppm) has a very large coupling constant of 331.1 Hz since it is directly bonded to phosphorus (Fig. 12). The β carbon (107.28 ppm) has a smaller *J* value of 59.5 Hz since it is further away from phosphorus (Fig. 13).

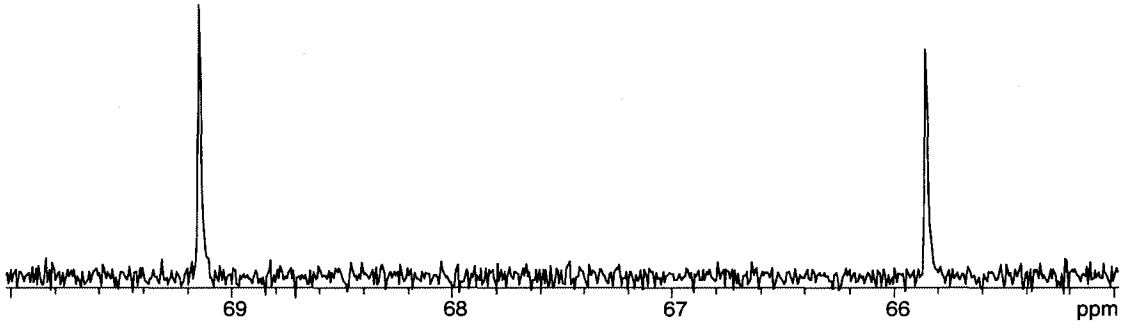


Fig. 12: ^{13}C NMR of the α carbon of compound **12**

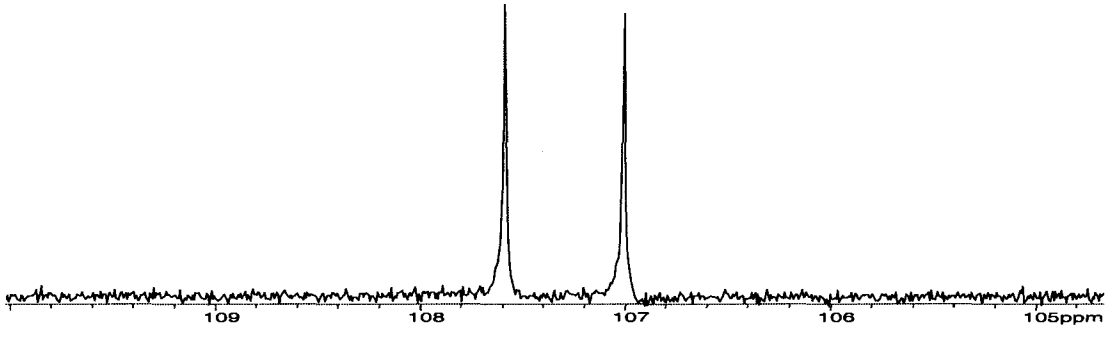


Fig. 13: ^{13}C NMR of the β carbon of compound **12**

In their ^1H NMR spectra, the CH_2 groups of the trifluoroethyl substituents show up as a group of five peaks. The methylene protons of the trifluoroethyl groups should show up as a doublet of quartets. However, because the coupling constants between H-F and H-P are similar, overlapping in the peaks occurs and the peak is viewed as a quintet (Fig. 14).

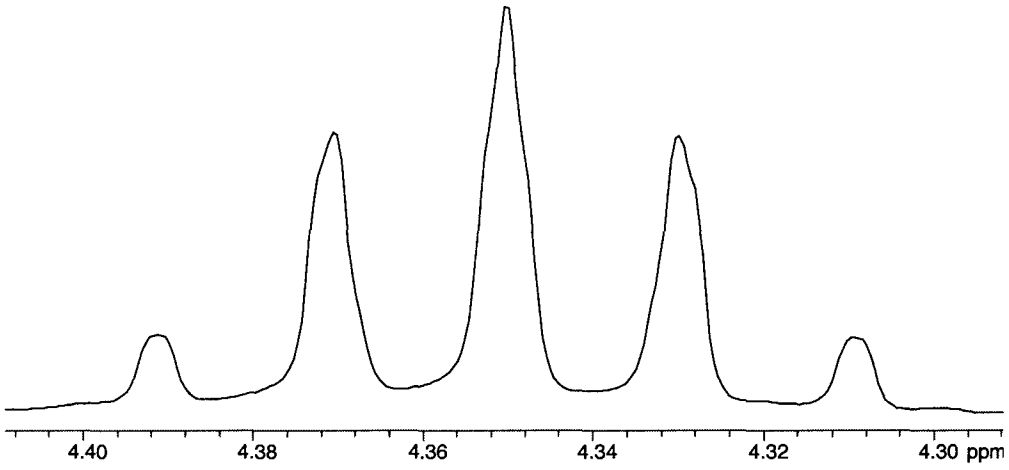


Fig. 14: ^1H NMR of the CH_2 groups of the trifluoroethyl groups of compound **12**

The propargylic protons of compound **12**'s ^1H NMR spectrum show up as a doublet of triplets (Fig. 15). This splitting pattern of the propargylic protons in the ^1H NMR spectrum of bis(2,2,2trifluoroethyl)phosphonooctyne is due to both vicinal coupling of the propargylic protons to the homopropargylic protons of the alkyl chain and also to a four bond long distance coupling to phosphorus. The coupling constant of the proton-proton interaction is calculated to be J = 4.8 Hz while the four bond coupling to phosphorus is calculated to be J = 2.4 Hz (Fig. 15).

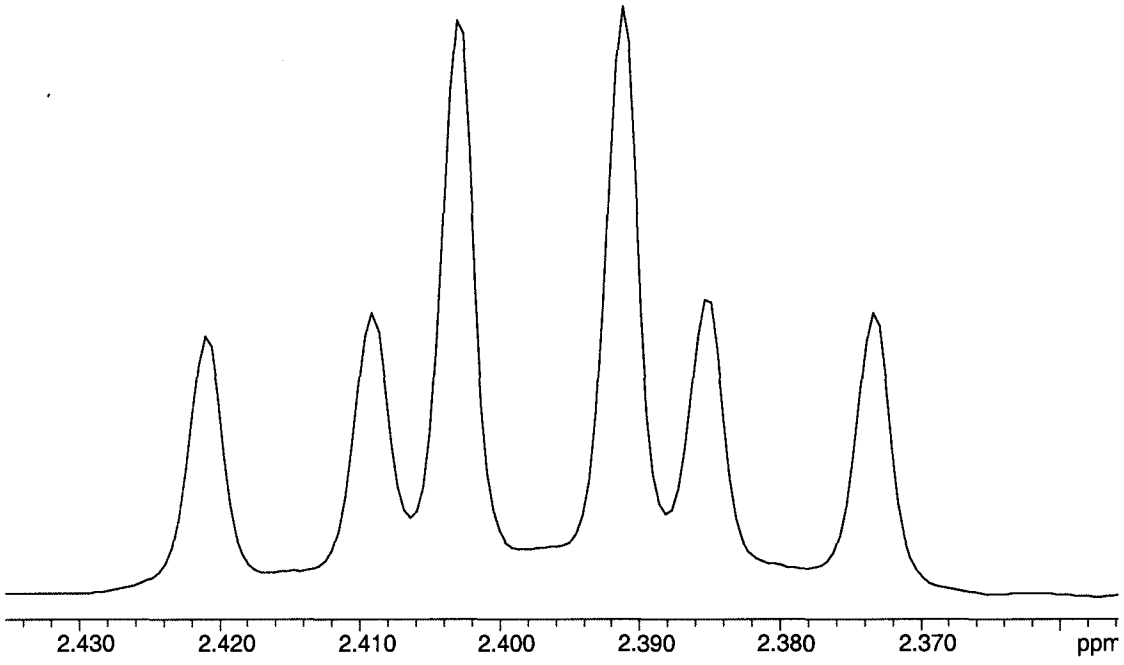
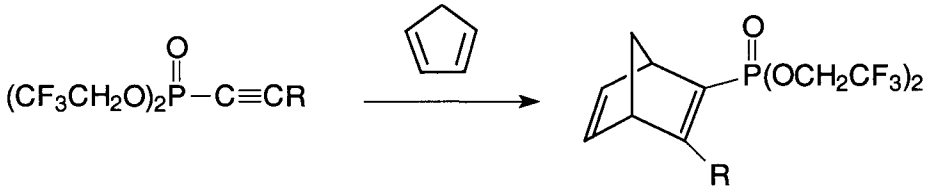


Fig. 15: ^{1}H NMR of the propargylic protons of compound **12**

Conclusion

The synthesis of bis(2,2,2-trifluoroethyl)phosphonoalkynes has proven to be a very challenging project involving the use of a variety of synthetic methods to obtain the product in moderate to good yields. After experimenting with the various combinations of reaction time, temperature, base for anion formation, concentration, solvent polarity and the nucleophilicity of the alkyne anion, the most important factor of the synthesis was found to be solvent polarity. One could postulate that a relatively non-polar solvent system gives a tight ion pair between the lithium cation and the alkyne anion. This tight cation/anion pair slows the reactivity of the alkynyllithium enough so that it would be more efficient in displacing only the chloride anion over the trifluoroethyl groups.

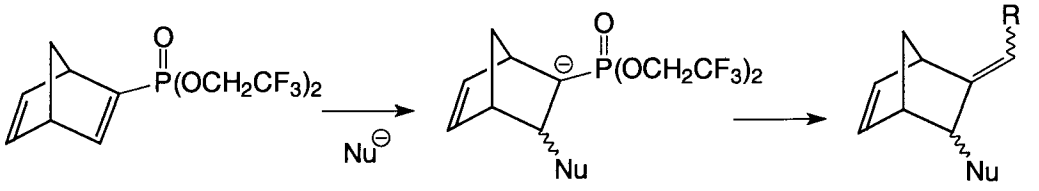
Future research involving the newly synthesized bis(2,2,2-trifluoroethyl)-phosphonoalkynes will explore its reactivity as a dienophile with various dienes to form bis(2,2,2-trifluoroethyl) vinyl phosphonates.



(Eq. 29)

After the vinyl phosphonates have been synthesized they will be used to synthesize olefin products *via* the Horner-Wadsworth-Emmons condensation. In this postulated reaction, an anion must be formed *via* a Michael addition to the vinyl phosphonate. Once the intermediate vinyl phosphonate anion has been formed, the olefin

product can be afforded through the above-mentioned Horner-Wadsworth-Emmons condensation.



(Eq. 30)

This total synthetic plan has the possibility to create four new carbon-carbon bonds through the use of various dienes, nucleophiles, and aldehydes in their corresponding reactions.

Chapter 3: Experimental

General Methods. Dioxane, pentane and diisopropylamine were distilled from CaH_2 prior to use. THF was distilled using sodium-benzophenone ketyl as indicator. All solvents were dried or distilled by standard techniques. All other commercial reagents were purchased from Aldrich and used without further purification. All reactions were conducted under a positive pressure of argon. Flash column 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 and ^{13}C 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-trifluoroethyl)phosphonooctyne (12)

Table 6 , Entry 7

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in pentane (19.5 mL) and ether (6.5 mL) at –78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a

dropwise manner, and the solution was allowed to stir at –78 °C for 60 minutes. Bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) was added dropwise and the solution was allowed to stir for 60 minutes at –78 °C. The reaction was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The combined aqueous extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation, the crude product was purified by flash column chromatography (silica gel, 85% hexane 15% ether) producing compound **12** as a colorless oil (650 mg, 33.3%).

^{1}H NMR δ 4.40 (4H, dq, *J*=8.4 Hz), 2.39 (2H, dt, *J*=4.7, 2.3 Hz), 1.61 (1H, quintet, *J*=7.1), 1.40 (2H, m), 1.29 (5H, m), 0.89 (3H, t, *J*=6.9 Hz).

^{13}C NMR δ 122.14 (dq, *J*=276.9, 9.9 Hz), 107.28 (d, *J*=58.7Hz),

67. 49 (d, *J*=331.1 Hz), 62.70 (dq, *J*=38.1, 3.8), 31.15 (s), 28.50 (s), 27.16 (s), 22.49 (s), 19.45 (s), 14.06 (s).

^{31}P NMR δ -4.84.

ESI-MS calculated: 354.22 found: 355.0 ($M+H^{+}$).

Table 6, Entry 2

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in ether (75 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.7 mL, 5.5 mmol) in a dropwise manner. The solution was allowed to stir for 60 minutes at –78 °C and then bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was added and the solution was

allowed to warm to room temperature overnight. The reaction was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The combined aqueous extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride (3 x 25 mL) and dried over magnesium sulfate. After removing solvent by rotary evaporation the analysis of the reaction mixture by integration of the ^{31}P NMR led to the conclusion that compound **12** was formed in a low yield (~20%).

Table 3, Entry 5

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in THF (30 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner and the solution was stirred for 60 minutes. The alkynyllithium was then added to a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) in THF (70 mL) at –78 °C and the reaction was allowed to warm to room temperature overnight. The reaction was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The combined aqueous extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation the resulting oil was purified by flash column chromatography (silica gel, 85% hexane 15% EtOAc) to produce compound **12** (370 mg, 19%).

Table 4, Entry 1

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in THF (50 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner and the solution was stirred for 30 minutes. CuI (0.525 g, 2.75 mmol) in THF (20 mL) was then added into the –78 °C mixture and the solution was allowed to stir for another 30 minutes. The alkynylcuprate solution was then added to a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) in THF (30 mL) at –78 °C and the reaction was allowed to warm to room temperature overnight. The reaction was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The combined aqueous extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride (3 x 25 mL) and dried over magnesium sulfate. After removing solvent by rotary evaporation, the mixture was purified by flash column chromatography (silica gel, 75% hexane 25% EtOAc) to produce compound **12** (351 mg, 18%).

Table 6, Entry 3

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in pentane (25 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.7 mL, 5.5 mmol) in a dropwise manner. The solution was allowed to stir for 2 hours and then bis(2,2,2-trifluoroethyl)phosphorochloridate (0.92 mL, 5.6 mmol) was added and the solution was allowed stir for 3 hours. The reaction mixture was filtered through celite and the solvent

removed by rotary evaporation. ^{31}P NMR analysis of the crude product suggested that compound **12** was formed in a low yield (~18%).

Table 6, Entry 1

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in ether (25 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.7 mL, 5.5 mmol) in a dropwise manner. The solution was allowed to stir for 60 minutes and then bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride (3 x 25 mL) and dried over anhydrous sodium sulfate. After removing solvent by rotary evaporation the resulting reaction mixture was analyzed by ^{31}P NMR, indicating that compound **12** was formed in a low yield (~15%).

Table 6, Entry 4

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in pentane (14 mL) and THF (14 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.7 mL, 5.5 mmol) in a dropwise manner. The solution was allowed to stir for 2 hours and then bis(2,2,2-trifluoroethyl)phosphorochloridate (0.92 mL, 5.6 mmol) was added and the solution was allowed stir for 2 hours. The crude reaction mixture was then filtered through celite and

the solvent removed by evaporation. ^{31}P NMR analysis of the crude product suggested that compound **12** was formed in a small yield (~15%).

Table 6, Entry 6

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in pentane (2.5 mL) and ether (22.5 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.7 mL, 5.5 mmol) in a dropwise manner. The solution was allowed to stir for 2 hours and then bis(2,2,2-trifluoroethyl)phosphorochloridate (0.92 mL, 5.6 mmol) was added, and the solution was allowed to stir for another 2 hours. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation an analysis of the crude product by ^{1}H and ^{31}P NMR indicated that a small yield of compound **12** was formed (~12%).

Table 6, Entry 5

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in pentane (2.5 mL) and ether (22.5 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.7 mL, 5.5 mmol) in a dropwise fashion. The solution was allowed to stir for 2 hours and then bis(2,2,2-trifluoroethyl)phosphorochloridate (0.92 mL, 5.6 mmol) was added and the solution was allowed to stir for another 2 hours. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation the reaction mixture was analyzed by ^{1}H, ^{31}P, and ^{13}C NMR indicating that compound **12** was formed in a low yield (~11%).

Table 3, Entry 1

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in THF (100 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) using a slow dropwise addition and the solution was stirred for 60 minutes. Bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was added also in a slow dropwise manner into the solution and the mixture was allowed to warm to room temperature overnight. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride (3 x 25 mL) and dried over magnesium sulfate. After removing solvent by rotary evaporation purification of the residue by flash column chromatography (silica gel, 90% hexane 10% EtOAc) gave bis(2,2,2-trifluoroethyl)phosphonooctyne **(12)** (175 mg, 9%).

Table 2, Entry 1

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in THF (25 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a slow dropwise manner and the

solution was allowed to stir for 20 minutes. Bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was then added dropwise into the reaction mixture and the solution was allowed to warm to room temperature overnight. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation an examination of the reaction mixture by ^{1}H and ^{31}P NMR suggested compound **12** was formed in a low yield (~1%).

Table 2, Entry 2

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in THF (30 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) using a dropwise addition method and was stirred for 1 hour. Bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was then added very slowly to the mixture which was allowed to warm to room temperature for over a time period of 60 minutes. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation an examination of the reaction mixture by ^{1}H and ^{31}P NMR suggested compound **12** was formed in a low yield (~1%).

Table 2, Entry 4

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in THF (30 mL) at 0 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a slow dropwise manner, and the mixture was allowed to stir for 1 hour. Bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was then added dropwise into the –78 °C solution and the reaction mixture was allowed to warm to room temperature for 1 hour. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. An analysis of the reaction mixture by ^{31}P NMR led to the conclusion that less than 1% of compound **12** was formed.

Table 2, Entry 6

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in THF (30 mL) at –78 °C was added a solution of $NaNH_2$ (50% wt suspension in xylenes, 0.81 mL, 5.5 mmol) in a dropwise manner. The solution was allowed to warm to room temperature for 1 hour then re-cooled to –78 °C before adding bis(2,2,2-trifluoroethyl)phosphorochloridate (0.81 mL 5.0 mmol). After 30 minutes the reaction 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 extracts were washed with saturated sodium chloride and dried over magnesium sulfate. Analysis of the crude reaction mixture by ^{1}H and ^{31}P NMR showed that only a very small formation of compound **12** was synthesized.

Table 4, Entry 4

To a solution of 1-octyne (0.82 mL, 5.5 mmol) in ether (25 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.7 mL, 5.5 mmol) in a dropwise manner. The solution was allowed to stir for 30 minutes upon the addition of of $ZnCl_2$ [(1.0 M (diethyl ether), 5.5 mL, 5.5 mmol)] *via* an addition funnel at –78 °C. The solution was allowed to stir for another 30 minutes when bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was added and the solution was allowed to warm to room temperature overnight. The work up of the resulting reaction mixture included filtering the product through celite (300 mesh) and washing the product with ether. An analysis of the reaction mixture with ^{31}P NMR gave an indication that only a very small yield of compound **12** was formed.

Bis(2,2,2-trifluoroethyl)phosphonopropyne (4)

Table 6, Entry 21

To a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) in pentane (19.5 mL) and ether (6.5 mL) at -78 °C was added propynyl magnesium bromide (0.5 M solution in THF, 11.0 mL, 5.5 mmol) in a dropwise manner through the use of an addition funnel and the solution was allowed to stir vigorously for 60 min. The reaction 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 extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation the crude product was purified by flash column chromatography

(silica gel, 85% hexane 15% ether) producing compound **4** as light yellow oil (600 mg, 38%).

^{1}H NMR δ 4.40 (4H, dq, *J*=8.2 Hz), 2.09 (3H, d, *J*=5.1 Hz).

^{13}C NMR δ 122.11 (dq, *J*=276.8, 9.9 Hz), 103.03 (d, *J*=58.7 Hz), 67.03 (d, *J*=332.6 Hz), 62.67 (dq, *J*=38.1, 4.6), 4.81 (d, *J*=18.3).

^{31}P NMR δ -5.15.

ESI-MS calculated: 284.09 found: 285.0 ($M+H^+$).

Table 6, Entry 18

To a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) in THF (25 mL) at -78 °C was added propynyl magnesium bromide (0.5 M solution in THF, 11.0 mL, 5.5 mmol) in a slow dropwise addition and the mixture was allowed to stir rapidly for 60 min. The resulting reaction mixture was analyzed by and NMR (^{1}H and ^{31}P) which gave no indication that compound **4** was made.

Table 6, Entry 19

To a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) in dioxane (25 mL) at -78 °C was added propynyl magnesium bromide (0.5 M solution in THF, 11.0 mL, 5.5 mmol) *via* an addition funnel in a dropwise manner and the solution was allowed to stir at a constant rate for 60 min. The resulting reaction mixture was analyzed by NMR (^{1}H and ^{31}P) which led to the conclusion that formation of phosphonoalkyne **4** had occurred.

Table 6, Entry 20

To a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) in ether (25 mL) at -78 °C was added a solution of propynyl magnesium bromide (0.5 M solution in THF, 11.0 mL, 5.5 mmol) in a dropwise manner and the mixture was allowed to stir at a steady pace for 60 min. The resulting reaction mixture was analyzed by NMR (^{1}H and ^{31}P) which gave a product yield of compound 4 that was less than 1%.

Table 3, Entry 2

To a solution of propynyl magnesium bromide (0.5 M solution in THF, 11.0 mL, 5.5 mmol) in THF (100 mL) at –78 °C was added bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) in a very slow dropwise manner and the reaction mixture was allowed to stir while warming to room temperature overnight. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. After removing solvent by rotary evaporation the reaction mixture was purified by flash column chromatography (silica gel, 75% petroleum ether 25% ether) to produce compound **4** (78 mg, 5%).

Bis(2,2,2-trifluoroethyl)phosphonopentyne (6)

Table 6, Entry 26

To a solution of 1-pentyne (0.54 mL, 5.5 mmol) in pentane (19.5 mL) and ether (6.5 mL) at –78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) using a slow dropwise addition technique and the solution was allowed to stir for 60 minutes. After 60 minutes bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) was added dropwise and the solution was allowed to stir for 60 minutes at –78 °C. The reaction 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 extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. After removing the solvent by rotary evaporation the mixture was purified by flash column chromatography (silica gel, 85% hexane 15% ether) producing compound **6** (50 mg, 29%).

^{1}H NMR δ 4.38 (4H, dq, *J*=8.9 Hz), 2.37 (2H, dt, *J*=4.7), 1.64 (2H, quintet, *J*=7.5), 1.02 (3H, t, *J*=7.3).

^{13}C NMR δ 123.28 (dq, *J*=276.9, 9.9 Hz), 108.20 (d, *J*=58.7 Hz), 68.76 (d, *J*=331.12 Hz), 63.84 (dq, *J*=38.1, 3.8 Hz), 22.46 (s), 1.95 (s), 14.65 (s).

^{31}P NMR δ -4.82.

ESI-MS calculated: 312.14 found: 313.00 ($M+H^+$)

Bis(2,2,2-trifluoroethyl)phosphonohexyne (8)

Table 6, Entry 15

To a solution of 1-hexyne (0.63 mL, 5.5 mmol) in pentane (19.5 mL) and ether (6.5 mL) at –78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner and the solution was allowed to stir vigorously for 60 minutes. After 60 minutes bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) was added dropwise and the solution was allowed to stir for 60 minutes at –78 °C. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing the solvent by rotary evaporation the crude product was purified by flash column chromatography (silica gel, 85% hexane 15% ether) producing compound **8** (667 mg, 37%).

^{1}H NMR δ 4.35 (4H, dq, *J*=4.3), 2.36 (2H, *J*=4.8, dt), 1.55 (2H, m), 1.39 (2H, m), 0.89 (3H, t, *J*=7.3).

^{13}C NMR δ 122.12 (dq, *J*=276.8, 10.3 Hz), 107.19 (d, *J*=58.7 Hz), 67.4 (d, *J*=331.1 Hz), 62.65 (dq, *J*=38.2, 3.8 Hz), 29.11 (s), 21.91 (s), 19.05 (s), 13.46 (s).

^{31}P NMR δ -4.86.

ESI-MS calculated: 326.17 found: 327.00 ($M+H^+$)

Table 2, Entry 3

To a solution of 1-hexyne (0.63 mL, 5.5 mmol) in THF (30 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner and the reaction mixture was allowed to stir for 1 hour. Bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was then added slowly in a dropwise addition and the reaction mixture was allowed to slowly warm to room temperature for 60 minutes. The reaction 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 extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. Examination of the reaction mixture by ^{31}P and ^{1}H NMR revealed that only a moderate amount of compound **8** was formed (~10%).

Table 6, Entry 12

To a solution of 1-hexyne (0.63 mL, 5.5 mmol) in ether (25 mL) at –78 °C was added *n*-BuLi (3.7 mL, 5.5 mmol) very slowly in a dropwise manner. The solution was allowed to stir vigorously for 60 minutes and then bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was added and the solution was allowed to warm overnight. The reaction 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 extracts were combined then washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride (3 x 25 mL) and dried over

magnesium sulfate. After removing solvent by rotary evaporation analysis by ^{31}P NMR showed that a moderate amount of compound **8** had been formed (~10%).

Table 2, Entry 5,

To a solution of 1-hexyne (0.63 mL, 5.5 mmol) in THF (25 mL) at 0 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner and the solution was stirred for 30 min. Bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was then added slowly and allowed to stir overnight. The reaction 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 extracts were collected and then washed with ether (3 x 25 mL). The combined organic extracts were then washed with saturated sodium chloride and dried over magnesium sulfate. After removing the solvent by rotary evaporation ^{1}H and ^{31}P NMR analysis of the reaction mixture gave an indication that only a small formation of compound **8** was produced.

Table 2, Entry 7

To a solution of diisopropylamine (0.80mL, 5.5 mmol) in THF (20 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.75 mL, 5.5 mmol) in a dropwise manner while venting under a positive pressure of argon. The mixture was then allowed to warm to 0 °C and then recooled back to –78 °C to ensure the formation of the LDA base. This solution was then used for the following reaction. To a solution of LDA (3.7 mL, 5.5 mmol) in THF (20 mL) was added 1-hexyne (0.63 mL, 5.5 mmol) in a dropwise manner and the solution was allowed to stir vigorously for 1 hour at –78 °C. Bis(2,2,2-

trifluoroethyl)phosphorochloridate was then added in a slow dropwise manner and the solution was allowed to stir rapidly overnight. The reaction was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The combined aqueous extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation an analysis of the crude reaction ^{1}H and ^{31}P NMR showed only a small yield of compound **8** (<1%)

Bis(2,2,2-trifluoroethyl)phosphonoheptyne (10)

Table 6, Entry 11

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in pentane (19.5 mL) and ether (6.5 mL) at –78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a slow dropwise manner and the solution was allowed to stir for 60 minutes. After 60 minutes bis(2,2,2-trifluoroethyl)phosphorochloridate (0.92 mL, 5.6 mmol) was added dropwise into the reaction mixture and the solution was allowed to stir for 60 minutes at –78 °C. The reaction 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 extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation the crude product was purified by flash

column chromatography (silica gel, 85% hexane 15% ether) producing compound **10** (648 mg, 37%).

^{1}H NMR δ 4.37 (4H, quintet, *J*=8.2), 2.38 (2H, dt, *J*=3.8, 7.1), 1.59 (2H, m), 1.33 (4H, m), 0.88 (3H, t, *J*=7.1).

^{13}C NMR δ 122.15 (dq, *J*=276.9, 9.9 Hz), 107.27 (d, *J*=58.8 Hz),

δ 67.43 (d, *J*=331.1), 62.66 (dq, *J*=38.3, 4.4), 30.92 (s), 26.85 (s), 22.08 (s), 19.32 (s), 13.93 (s).

^{31}P NMR δ -4.82.

ESI-MS calculated: 340.20 found: 341.00 ($M+H^{+}$).

Table 5, Entry 5

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in THF (25 mL) and ether (20 mL) was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise addition manner at –78 °C and the solution was allowed to stir for 60 minutes. Pyridine (1.50 mL, 16.5 mmol) and bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) were then added consecutively in a dropwise manner and the solution was allowed to stir for 60 minutes at –78 °C. The reaction 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 extracts were then washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and then dried over magnesium sulfate. After removing solvent by rotary evaporation NMR analysis involving ^{1}H and ^{31}P NMR showed that compound **10** was formed (~21%).

Table 5, Entry 4

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in THF (25 mL) and ether (20 mL) was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner at –78 °C and the solution was allowed to stir for 60 minutes. Pyridine (0.50 mL, 5.5 mmol) and bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) were added consecutively in a dropwise manner and the solution was allowed to stir rapidly for 60 minutes at –78 °C. The reaction 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 extracts were combined and washed with ether (3 x 25 mL). The combined organic extracts were also combined and washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation ^{1}H and ^{31}P NMR analysis of the reaction mixture revealed that compound **10** was formed (~20%).

Table 5, Entry 3

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in THF (25 mL) and ether (20 mL) was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner at –78 °C and the solution was allowed to stir for 60 minutes. Pyridine (3 drops) was added consecutively with bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) in a dropwise manner and the solution was allowed to stir for 60 minutes at –78 °C. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were

collected and washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. After removing solvent by rotary evaporation examination of the reaction mixture by ^{1}H and ^{31}P NMR gave an indication that a moderate amount of compound **10** had been formed (~18%).

Table 4, Entry 2

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in ether (50 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner and the solution was stirred for 30 minutes. CuI (0.53 g, 2.75 mmol) in ether (20 mL) was then added into the –78 °C solution and the mixture was allowed to stir for 30 minutes. The alkynylcuprate mixture was then added to a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) in ether (30 mL) at –78 °C and the reaction was allowed to warm to room temperature overnight. The reaction 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 extracts were combined and then washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation the resulting reaction mixture was purified by flash column chromatography (silica gel, 80% hexane 20% EtOAc) to produce compound **10** (224 mg, 12%).

Table 4, Entry 3

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in THF (50 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in dropwise manner and the solution was allowed to stirred rapidly for 30 minutes. CuI (0.53 g, 2.75 mmol) in THF (20 mL) was then added into the –78 °C solution and the mixture was allowed to stir for another 30 minutes. The alkynylcuprate solution was then added into a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0. 80 mL, 5.0 mmol) in THF (30 mL) at –78 °C. The reaction was then allowed to warm to room temperature overnight. The reaction 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 extracts were collected and washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation the resulting reaction mixture was purified by flash column chromatography (silica gel, 90% hexane 10% ether) to produce compound **10** (224 mg, 12%).

Table 5, Entry 2

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in THF (25 mL) and HMPA (0.96 mL, 5.5 mmol) was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner at –78°C and the reaction was allowed to stir for 60 minutes. After 60 minutes bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) was added neat in a slow dropwise manner and the solution was allowed to stir for 60 minutes at –78 °C. The reaction 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 extracts were washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation ^{1}H and ^{31}P NMR analysis revealed that compound **10** had been formed (~12%).

Table 6, Entry 9

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in ether (25 mL) at –78 °C was added *n*-BuLi (3.7 mL, 5.5 mmol) in a slow dropwise manner. The solution was allowed to stir for 60 minutes and then bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was added slowly and the reaction mixture was allowed to stir while warming to room temperature overnight. The reaction 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 extracts were washed with saturated sodium chloride (3 x 25 mL) and dried over magnesium sulfate. After removing solvent by rotary evaporation an analysis of the resulting reaction mixture by ^{31}P NMR suggested that compound **10** had been formed (~12%).

Table 5, Entry 1

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in THF (25 mL) and 12-crown-4 (0.89 mL, 5.5 mmol) was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a dropwise manner and the solution was allowed to stir vigorously for 60 minutes.

After 60 minutes bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) was added very slowly in a dropwise manner and the solution was allowed to stir for an additional 60 minutes at –78 °C. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were then washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation ^{1}H and ^{31}P NMR analysis revealed that compound **10** had been formed in a moderate amount (~10%).

Table 4, Entry 5

To a solution of 1-heptyne (0.72 mL, 5.5 mmol) in THF (25 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.7 mL, 5.5 mmol) in a dropwise manner. The solution was allowed to stir for 30 minutes upon addition of a solution $ZnCl_2$ (1.0 M solution. in diethyl ether, 5.5 mL, 5.5 mmol) in a dropwise manner *via* an addition funnel at –78 °C. The solution was again allowed to stir for 30 minutes and then added slowly to a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) in THF (25 mL) and the reaction was then allowed to warm to room temperature overnight with rapid agitation. The reaction was then quenched with saturated aqueous ammonium chloride giving a white homogeneous precipitate that was very difficult to separate from the organic and aqueous phases. Once the separation was complete the aqueous layer was removed and the organic layer was washed with water (20 mL). The aqueous extract was washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by

rotary evaporation analysis of the reaction mixture showed that a very low yield of compound **10** had been formed.

Bis(2,2,2-trifluoroethyl)phosphononononyne (14)

Table 6, Entry 27

To a solution of 1-nonyne (0.90 mL, 5.5 mmol) in pentane (19.5 mL) and ether (6.5 mL,) at –78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a slow dropwise manner and the solution was allowed to stir for 60 minutes. After 60 minutes bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) was added in a very slow dropwise manner and the solution was allowed to stir for 60 minutes at –78 °C. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were collected, washed with saturated sodium chloride and dried over magnesium sulfate. After removing solvent by rotary evaporation the resulting reaction residue was purified by flash column chromatography (silica gel, 85% hexane 15% ether) producing compound **14** (980 mg, 49%).

^{1}H NMR δ 4.37 (4H, dq, *J*=8.2), 2.37 (2H, dt, *J*=3.8, 7.3), 1.58 (2H, m), 1.37 (2H, m), 1.27 (6H, m), 0.86 (3H, t, *J*=6.9).

^{13}C NMR δ 122.13 (dq, *J*=276.6, 9.9 Hz), 107.27 (d, *J*=57.9), 67. 41 (d, *J*=331.1), 62.68 (dq, *J*=38.1, 3.8 Hz), δ 31.59 (s), 28.76 (s), 28.64 (s), 27.13 (s), δ 22.62 (s), 19.39 (s), 14.15 (s).

^{31}P NMR δ -4.83.

ESI-MS calculated: 368.25 found: 369.10 ($M+H^+$).

Bis(2,2,2-trifluoroethyl)phosphonodecyne (16)

Table 6, Entry 28

To a solution of 1-decyne (1.0 mL, 5.5 mmol) in pentane (19.5 mL) and ether (6.5 mL) at –78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) *via* a slow dropwise manner and the solution was allowed to stir for 60 minutes. After 60 minutes bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) was added neat in a dropwise manner and the solution was allowed to stir for 60 minutes at –78 °C. The reaction 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 extracts were washed with saturated sodium chloride and dried over magnesium sulfate. After removing the solvent by rotary evaporation compound **16** (1.18 g, 56.2%) was obtained by flash column chromatography (silica gel, 85% hexane 15% ether).

^{1}H NMR δ 4.39 (4H, dq, *J*=7.8 Hz), 2.39 (2H, dt, *J*=6.1, 7.3 Hz), 1.60 (1H, m), 1.39 (1H, 2H, m), 1.27 (8H, m), 0.88 (3H, t, *J*=6.8).

^{13}C NMR δ 122.31 (dq, *J*=276.8, 10.5 Hz), 107.27 (d, *J*=58.7 Hz), 67.45 (d, *J*=331.1 Hz), 62.69 (dq, *J*=38.3, 4.0 Hz), 31.81 (s), 29.09 (s), 28.96 (s), 28.82 (s), 27.18 (s), 22.71 (s), 19.42 (s), 14.23 (s).

^{31}P NMR δ -4.81.

ESI-MS calculated: 382.28, found: 383.10 ($M+H^+$)

1-[Bis(2,2,2-trifluoroethoxy)phosphinyl]-2-phenylethyne (18)

Table 6, Entry 17

To a solution of phenylacetylene (0.604 mL, 5.5 mmol) in pentane (19.5 mL) and ether (6.5 mL) at –78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a slow dropwise manner and the solution was allowed to stir for 60 minutes. After 60 minutes bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) was added in a dropwise manner and the solution was allowed to stir for 60 minutes at –78 °C. The reaction 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 washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. Integration of the ^{31}P NMR spectrum of the corresponding reaction mixture gave an indication that compound **18** was formed (~6%).

Table 3, Entry 4

To a solution of phenylacetylene (0.604 mL, 5.5 mmol) in THF (100 mL) at –78 °C was added *n*-BuLi (1.6 M solution in hexanes, 3.4 mL, 5.5 mmol) in a slow dropwise addition and the solution was stirred for 60 minutes. Bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) was then added dropwise into the solution and the reaction mixture was allowed to warm to room temperature overnight. The reaction 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 extracts were washed with saturated sodium chloride (3 x 25 mL) and dried over magnesium sulfate. Analysis of the resulting reaction mixture by ^{31}P and ^{1}H NMR led to the conclusion that only a small amount of compound **18** was formed.

Table 6, Entry 16

To a solution of phenylacetylene (0.604 mL, 5.5 mmol) in ether (25 mL) at –78 °C was added *n*-BuLi (3.7 mL, 5.5 mmol) in a dropwise manner. The reaction solution was allowed to stir for 60 minutes upon addition of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.80 mL, 5.0 mmol) and the solution was allowed to warm overnight while stirring vigorously. The reaction 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 extracts were washed with saturated sodium chloride (3 x 25 mL) and dried over magnesium sulfate. After removing solvent by rotary evaporation an analysis of the resulting reaction mixture by ^{31}P NMR suggested that compound **18** had been formed.

Attempted Synthesis of Bis(2,2,2-trifluoroethyl)phosphonoethyne (2)

Table 6 Entry 25

To a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) in pentane (19.5 mL) and ether (6.5 mL) at -78 °C was added sodium acetylide [18 wt % slurry in xylene/light mineral oil (1.5 mL, 264 mg, 5.5 mmol in THF)] in a dropwise manner and allowed to stir for 60 min. The brown reaction mixture 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 extracts were collected and washed with ether (3 x 25 mL). The combined organic extracts were also collected and washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. Integration of the ^{31}P and ^{1}H NMR spectra of the corresponding reaction mixture gave no indication that compound **2** was formed.

Table 6, Entry 22

To a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) in THF (25 mL) at -78 °C was added sodium acetylide [18 wt % slurry in xylene/light mineral oil (1.5 mL, 264 mg, 5.5 mmol in THF)] in a very slow dropwise manner and allowed to stir for 60 min. The resulting reaction mixture was analyzed NMR (^{1}H and ^{31}P) which gave no indication that compound **2** was made.

Table 6, Entry 23

To a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) in dioxane (25 mL) at -78 °C was added a solution of sodium acetylide [18 wt % slurry in

xylene/light mineral oil (1.5 mL, 264 mg, 5.5 mmol in THF)] in a dropwise manner and allowed to stir for 60 min. NMR analysis (^{1}H and ^{31}P) of the black reaction mixture gave no indication that compound **2** was made.

Table 6, Entry 24

To a solution of bis(2,2,2-trifluoroethyl)phosphorochloridate (0.93 mL, 5.6 mmol) in ether (25 mL) at -78 °C was added sodium acetylide [18 wt % slurry in xylene/light mineral oil (1.5 mL, 264 mg, 5.5 mmol in THF)] in a dropwise manner and allowed to stir for 60 min. The resulting reaction mixture was analyzed by NMR, (^{1}H and ^{31}P) which gave no evidence for the formation of compound **2**.

References

1. Eymery, F.; Iorga, B.; Savignac, P. *Tetrahedron* **1999**, *55*, 13110.
2. Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.
3. Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.
4. Rudder, S. M.; Norwood, B.K. *Tetrahedron Lett.* **1994**, *35*, 3473.
5. Cristau, H. J.; Mbianda, X. Y.; Beziat, Y.; Gasc, M. B. *J. Organomet. Chem.* **1997**, *529*, 301.
6. Gil, J. M.; Oh, D. Y. *J. Org. Chem.* **1999**, *64*, 2950.
7. Pergament, I.; Srebnik, M. *Org. Lett.* **2001**, *3*, 217.
8. Braga, A. L.; Alves, E. F.; Silveira, C. C.; Andrade, L. H. *Tetrahedron Lett.* **2000**, *41*, 61.
9. Quntar, A. A.; Srebnik, M. *Org. Lett.* **2001**, *3*, 1379.
10. Christensen, B.G.; Leanza,W.J.; Beattie,T.R.; Patchett,A.A.; Arison,B.H.; Ormond,R.E.; Kuehl F.A.; Albers-Schonberg,G.; Jardetzky,O. *Science* **1969**,*166*, 123.
11. Morgan, A.B.; Tour, J.M. *J. Appl. Polym. Sci.* **1999**, *73*, 707.
12. Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1971**, *36*, 2719.
13. Gil, J. M.; Sung, J. W.; Park, C. P.; Oh, D.Y. *Synth. Commun.* **1997**, *27*, 3171.
14. Koser, G. F.; Lodaya, J. S. *J. Org. Chem.* **1990**, *55*, 1513.
15. Midura, W. H.; Mikolajczk, M. *Tetrahedron Lett.* **1995**, *36*, 2871.
16. Savignac, P.; Diziere, R. *Tetrahedron Lett.* **1996**, *37*, 1783.
17. Lera, M.; Hayes, C. J. *Org. Lett.* **2000**, *2*, 3873.
18. Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1971**, *36*, 2720.

19. Bowman, R. S.; Stock, J. R.; Jackson, J. A. *Org. Prep. Proced. Int.* **1999**, *31*, 230.

20. Sittig, M.; Sodium, its Manufacture, Properties, and Uses; 54, Reinhold: New York, **1990**, 1034.

21. Lipshutz, B. H.; Wood, M. R.; Lindsley, C. W. *Tetrahedron Lett.* **1995**, 36, 4385.

22. Fox, M. A.; Whitesell, J. K. *Organic Chemistry*; Jones and Bartlett: England, **1994**, 222.

23. Loudon, G. M. *Organic Chemistry*; 3rd Ed.; Benjamin/Cummings: California, **1995**, 662.

24. Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *11*, 3197.

25. Kitazume, T.; Kasai, K. *Geochim. Cosmochim. Acta.* **2001,** *226*, 51.

26. Carey, F.A.; Sundberg, R. J. *Advanced Organic Chemistry*; 3rd Ed; Plenum: New York, **1990**, 388.

Figure 16: ^{31}P NMR of Compound **4**

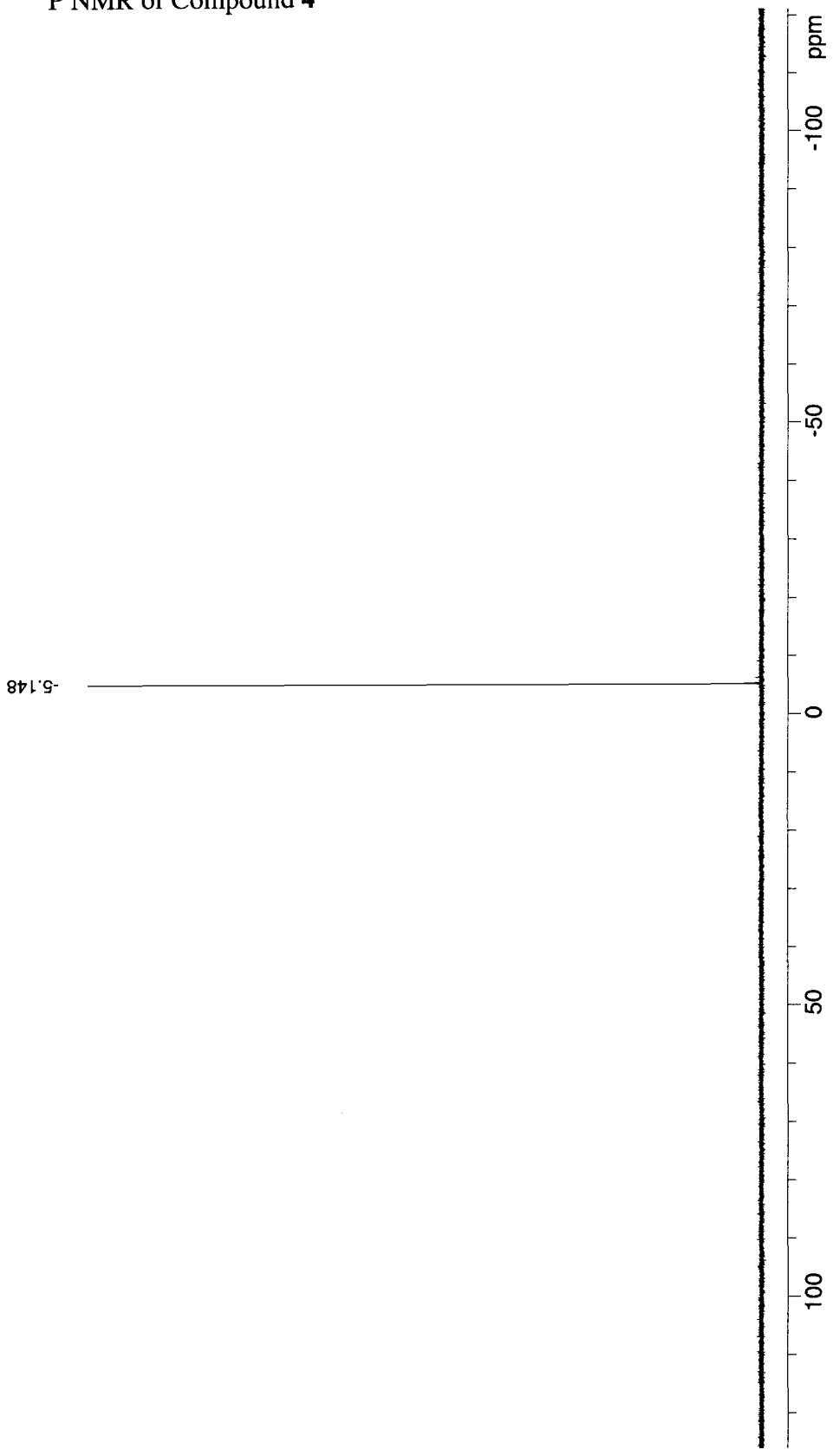


Figure 17: ^{1}H NMR of Compound **4**

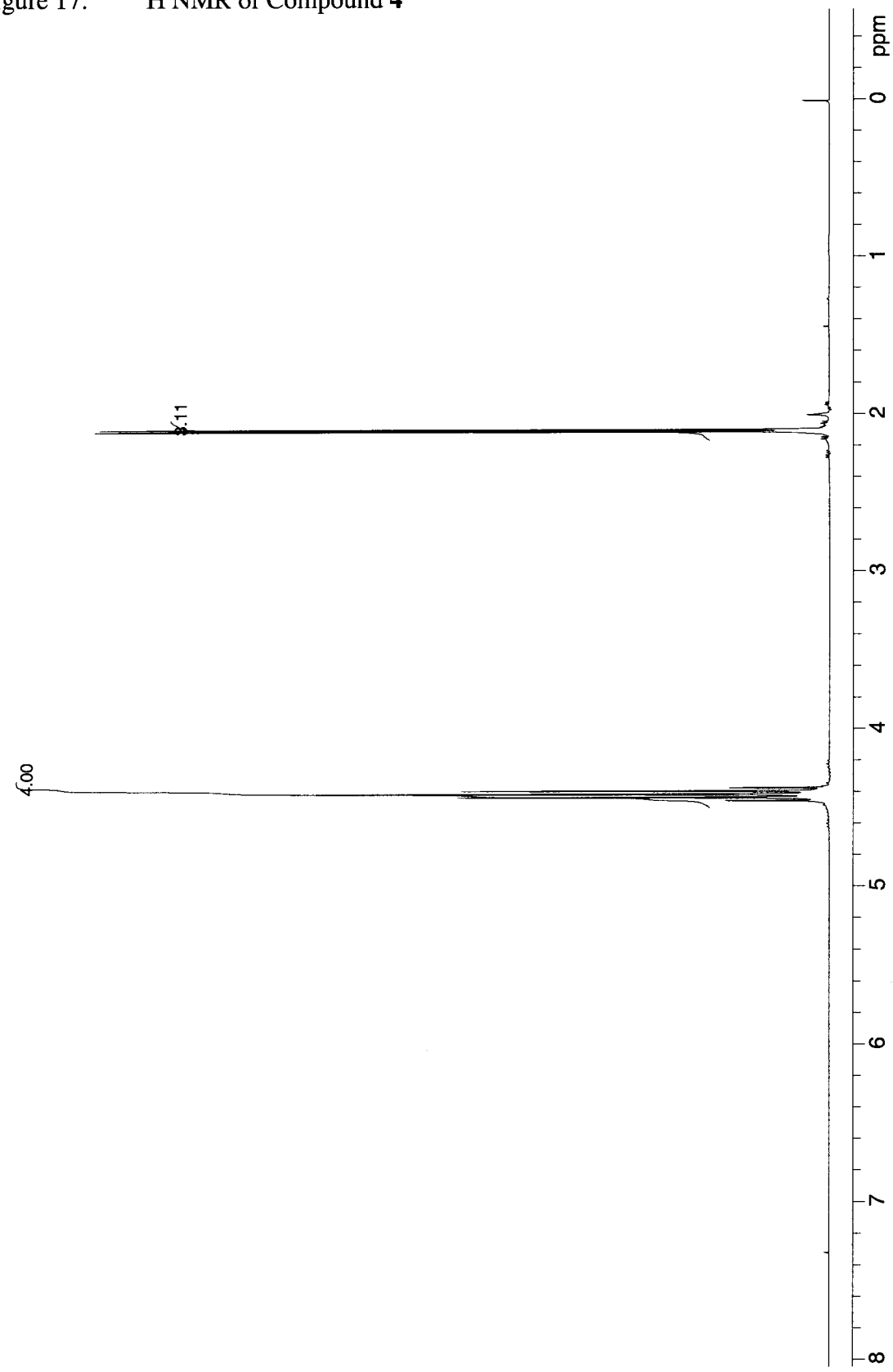


Figure 18: ^{13}C NMR of Compound **4**

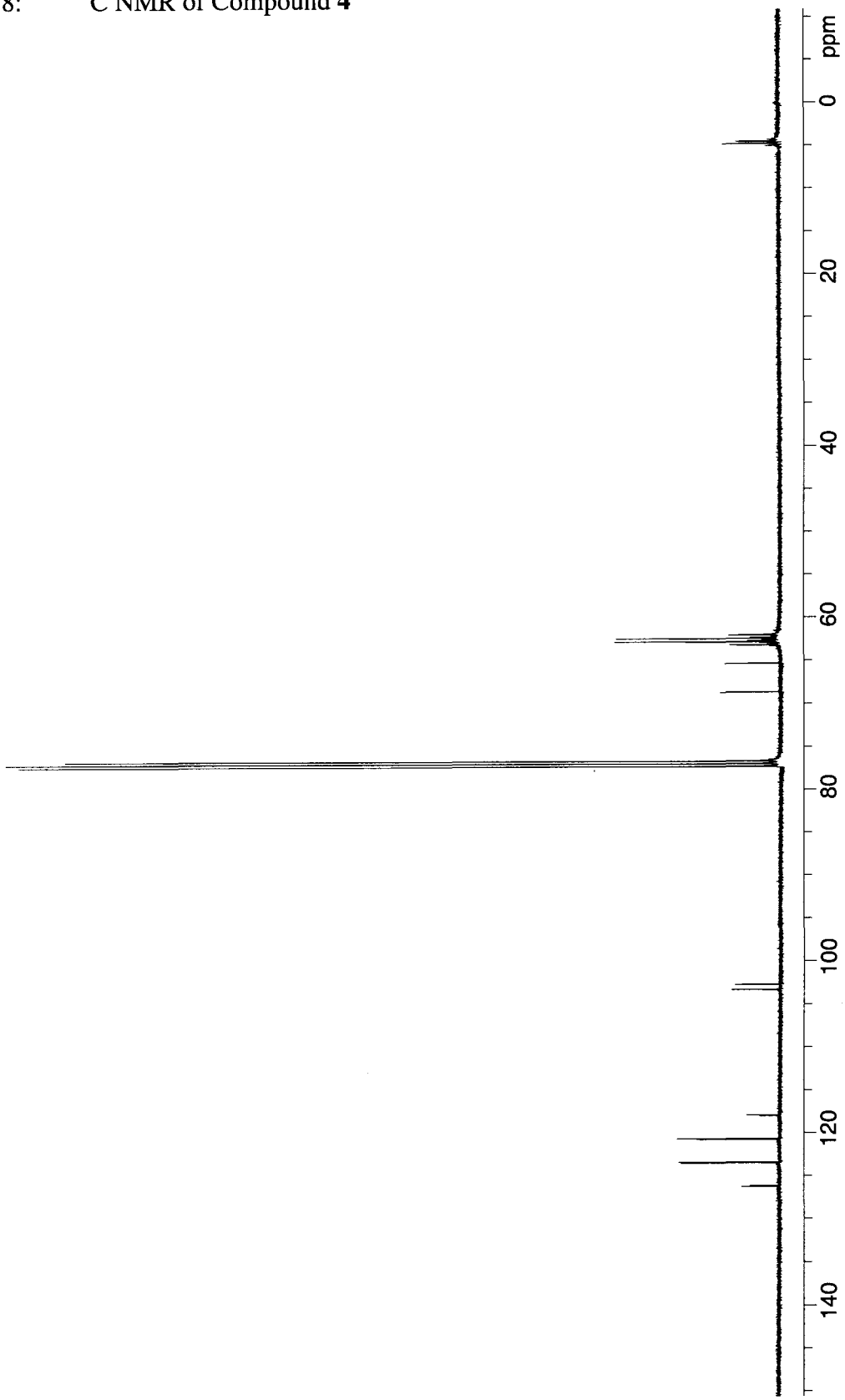


Figure 19: Mass Spectrum of Compound **4**

Acquisition Parameter

Source	:APCI	Polarity	: Positive
Mode	:Standard/Normal	Skim 1	:26.0 volt
CapExit	:77.0 volt	Trap Drive	:35
Scan Range	:15.00 – 2200.00 m/z	Summation	:10 spectra
Accum.time	: 20000 µs		

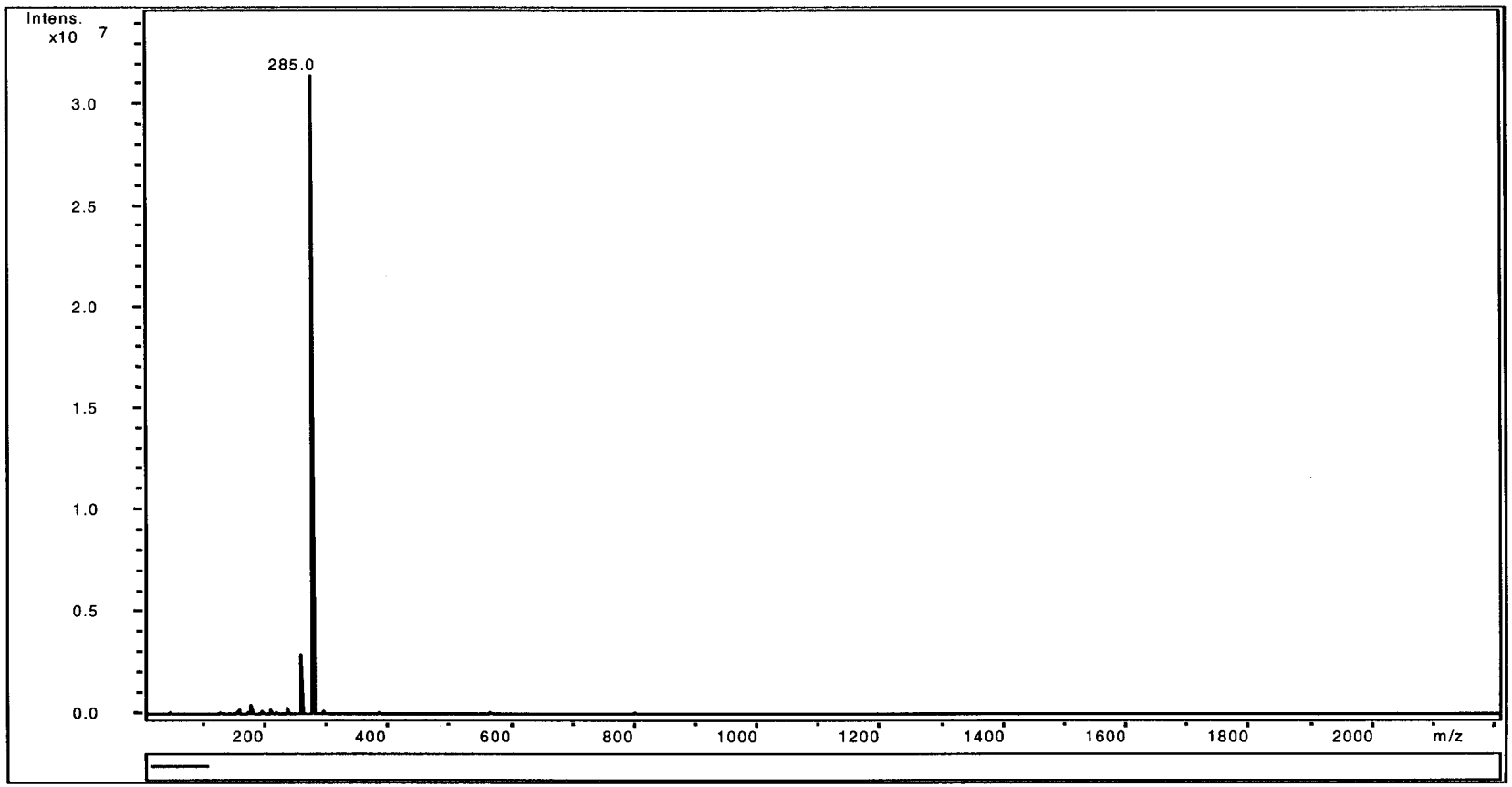


Figure 20: ^{31}P NMR of Compound **6**

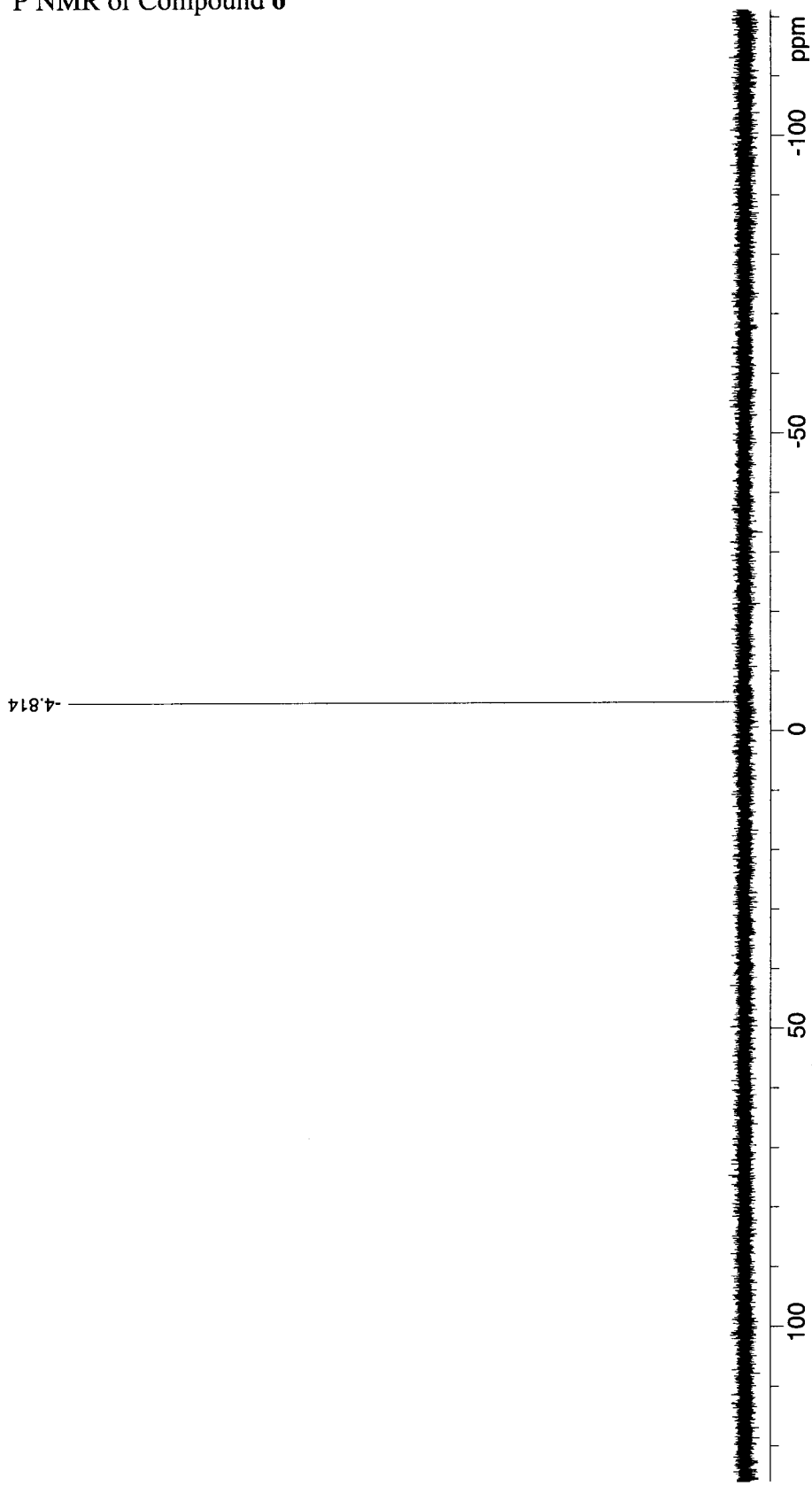


Figure 21: ^{1}H NMR of Compound **6**

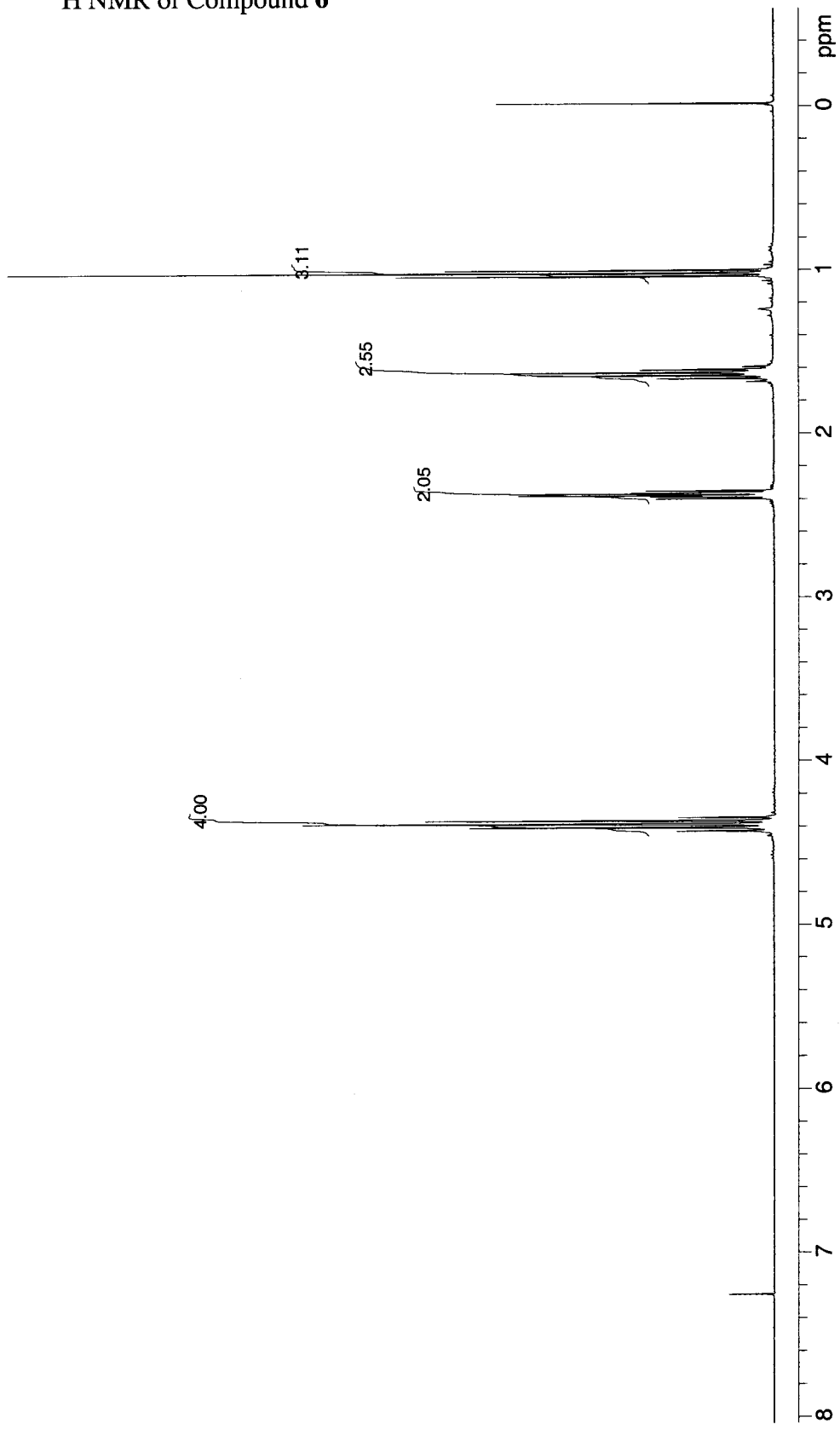


Figure 22: ^{13}C NMR of Compound **6**

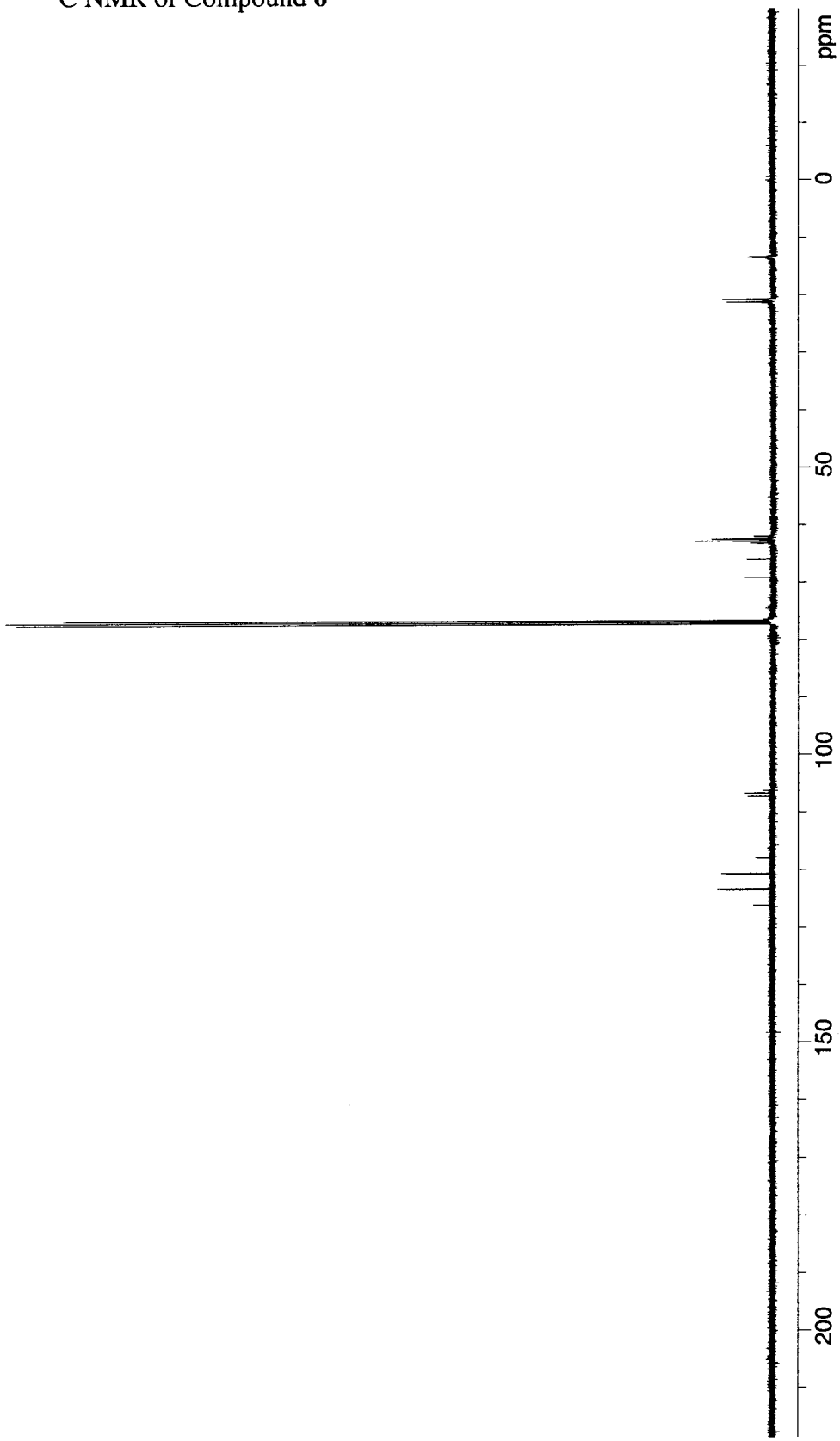


Figure 23: Mass Spectrum of Compound **6**

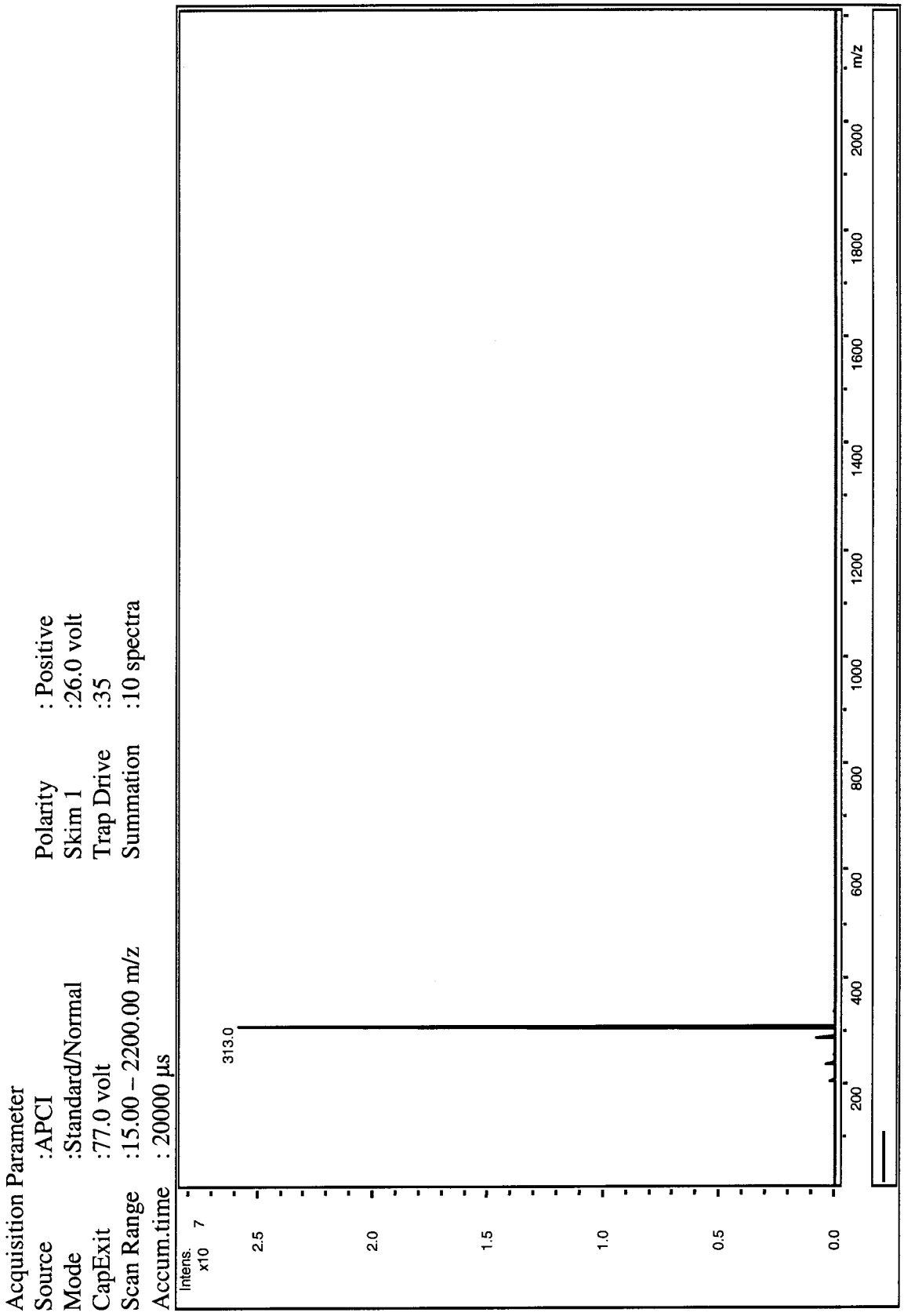


Figure 24: ^{31}P NMR of Compound **8**

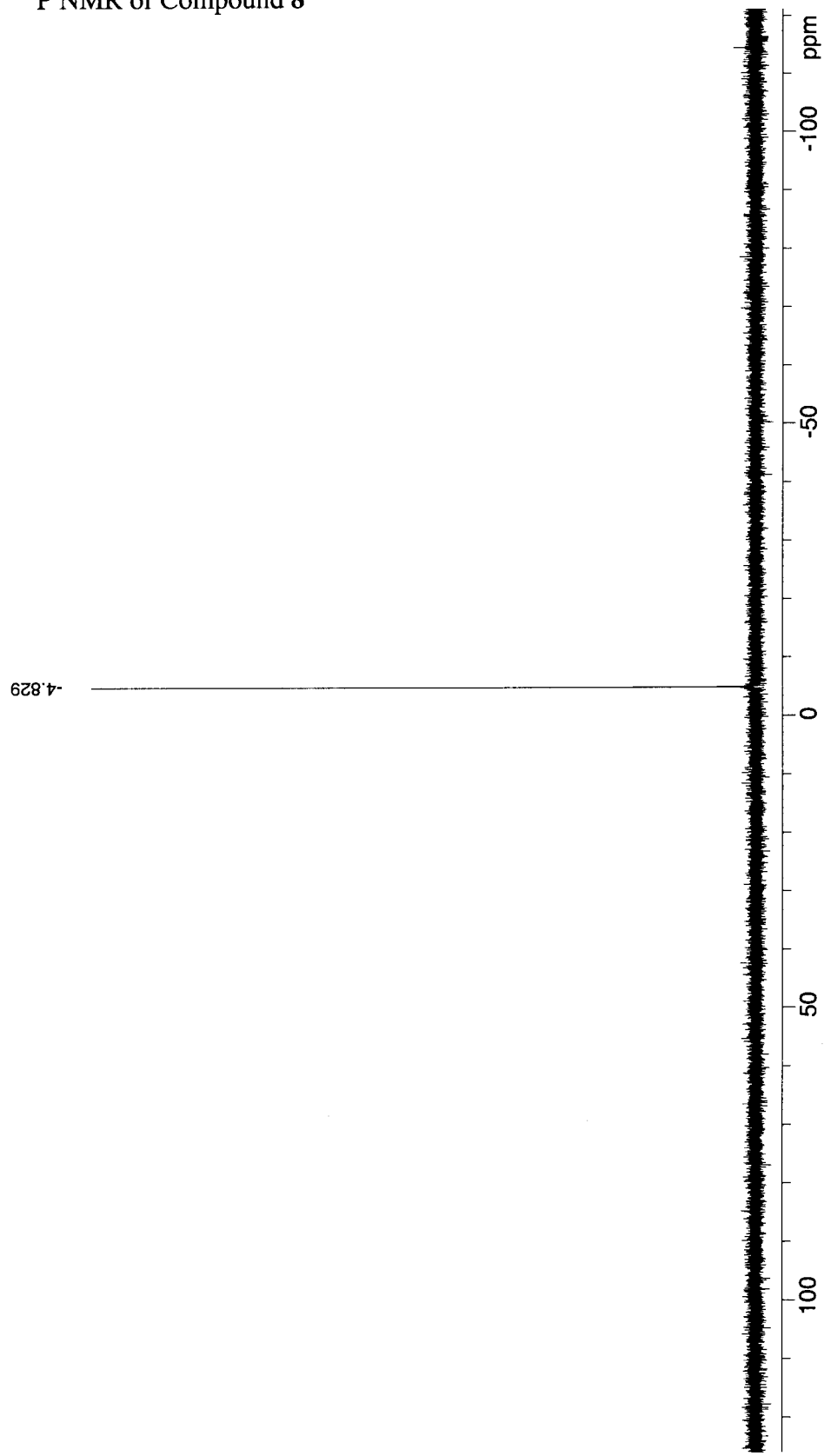


Figure 25: ^{1}H NMR of Compound **8**

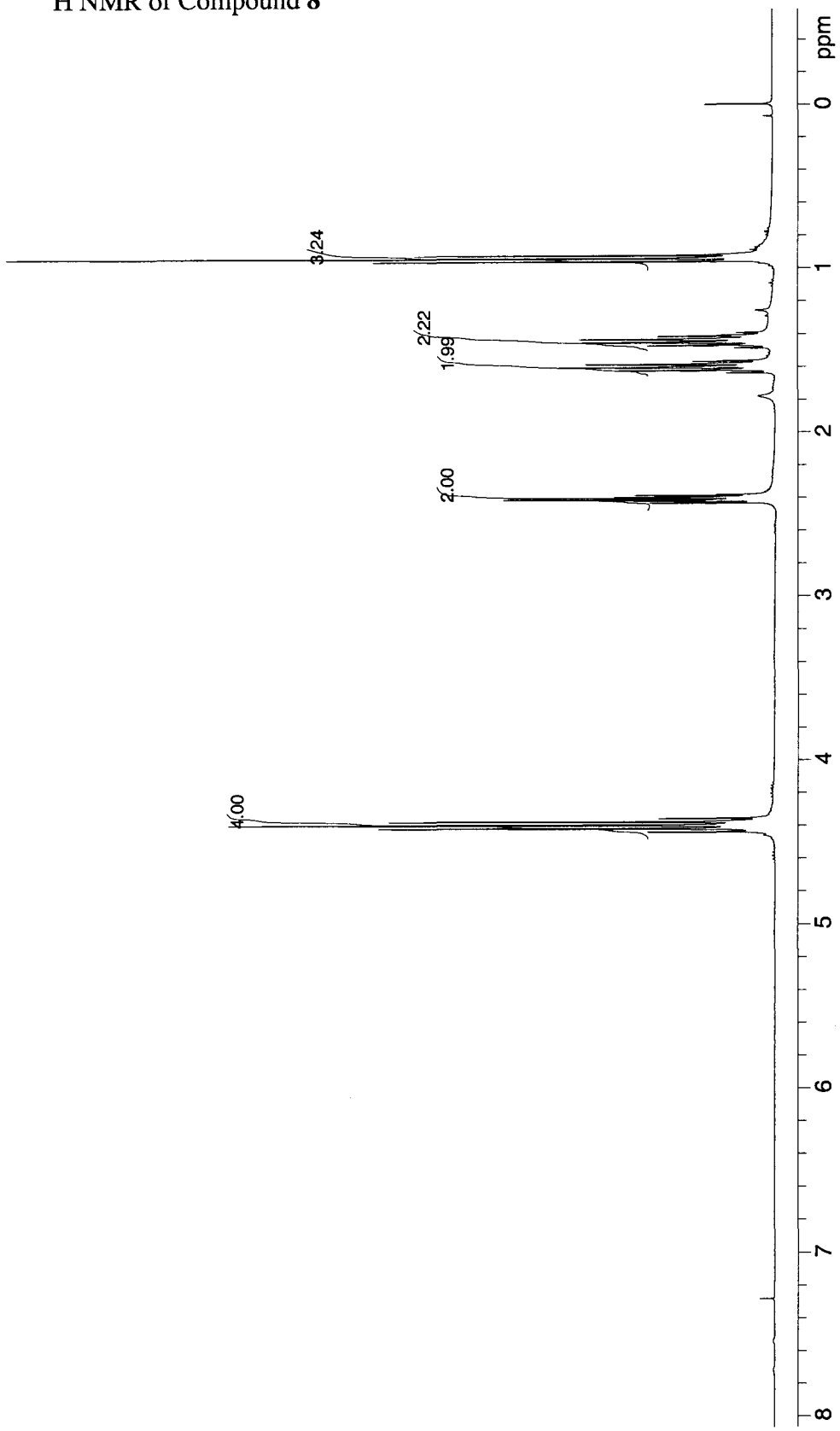


Figure 26: ^{13}C NMR of Compound **8**

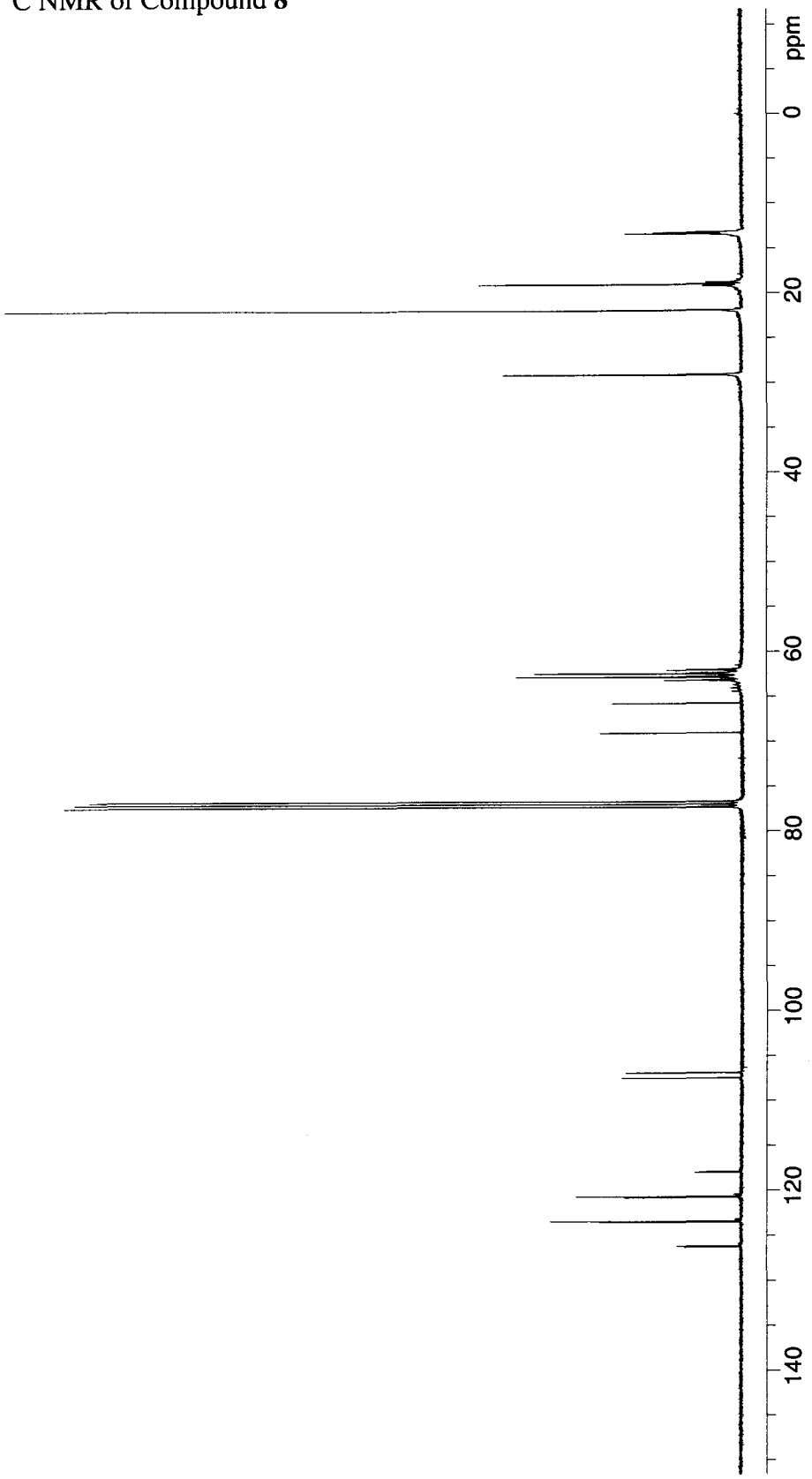


Figure 27: Mass Spectrum of Compound **8**

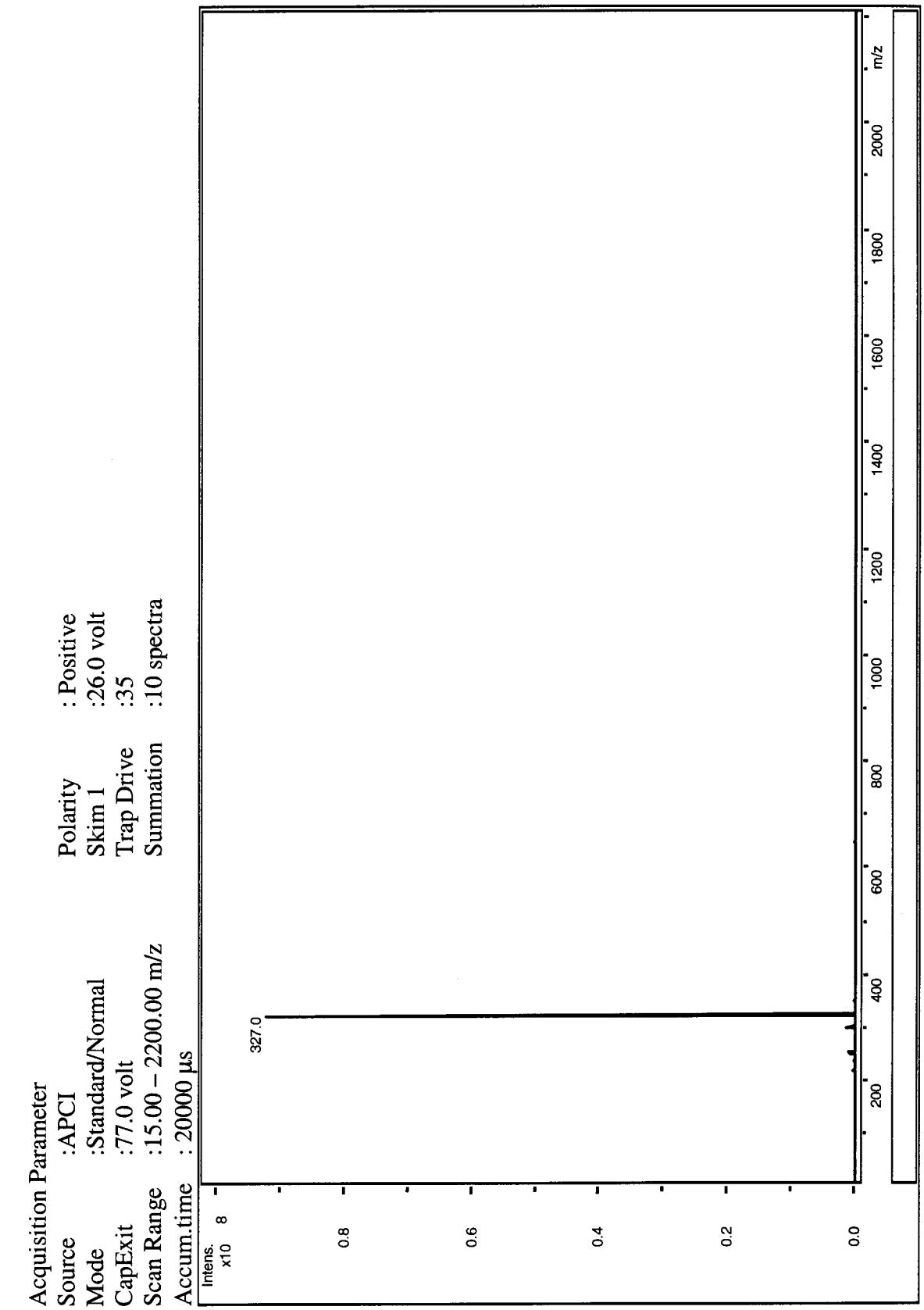


Figure 28: ^{31}P NMR of Compound **10**

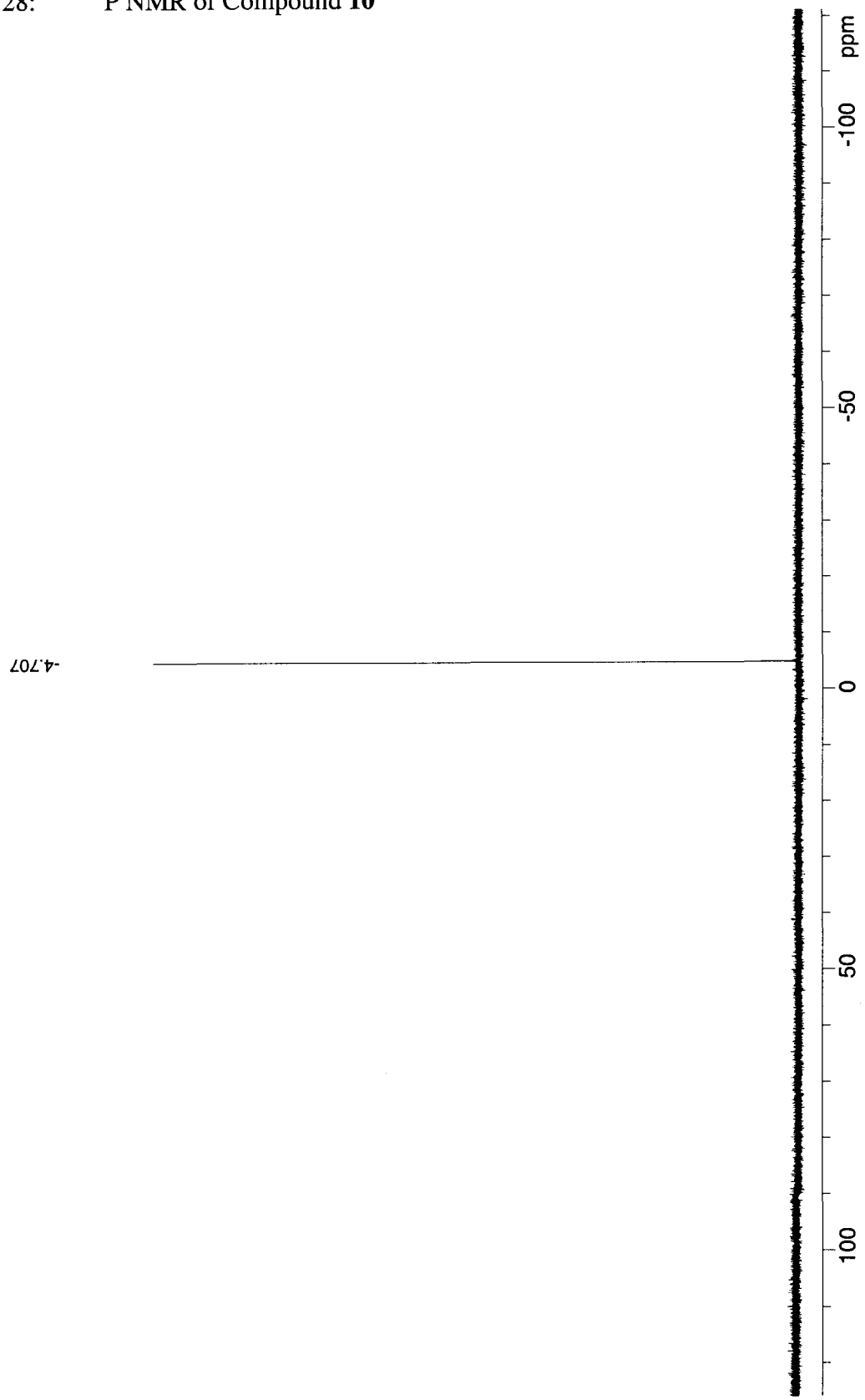


Figure 29: ^{1}H NMR of Compound **10**

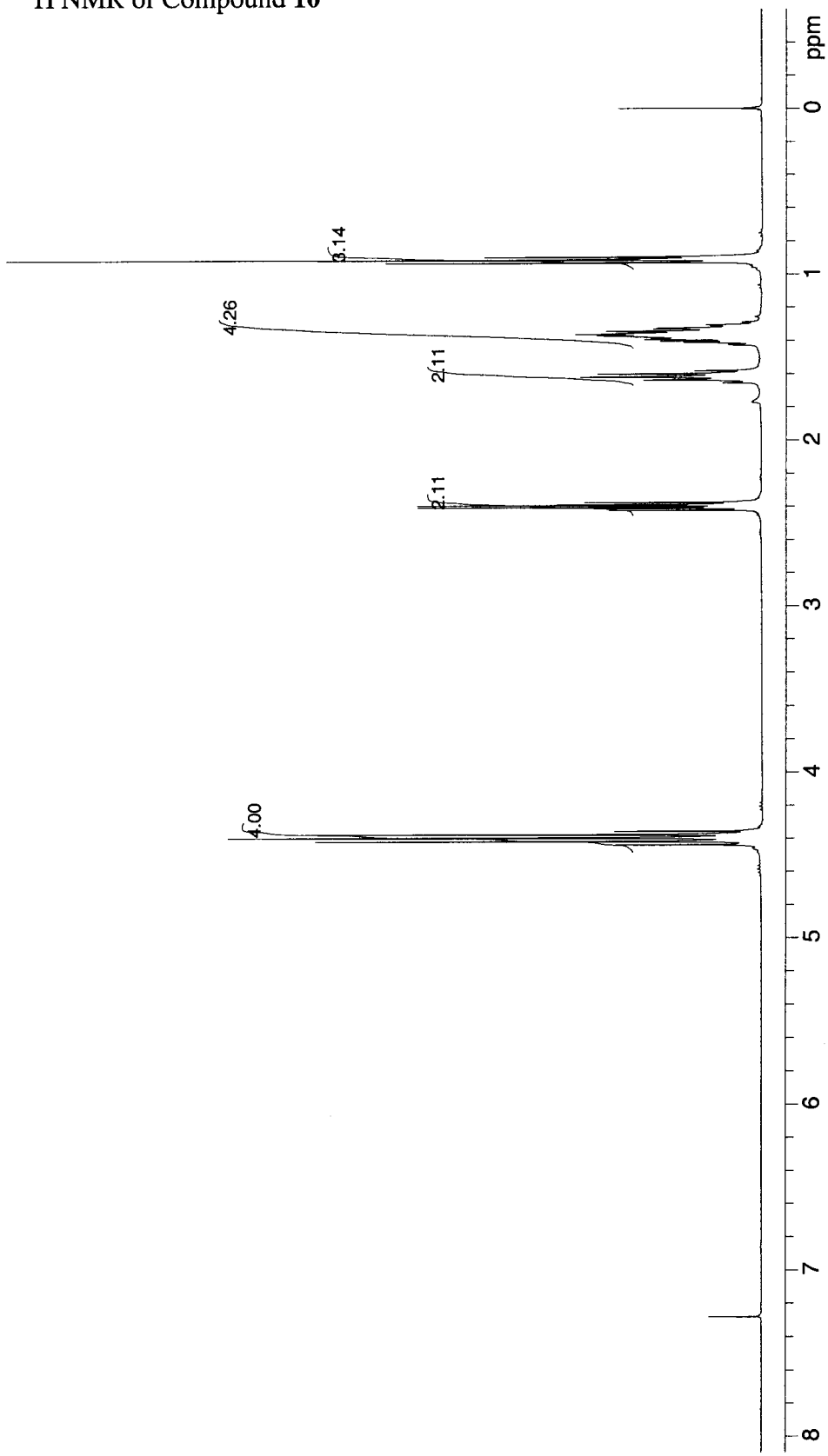


Figure 30: ^{13}C NMR of Compound **10**

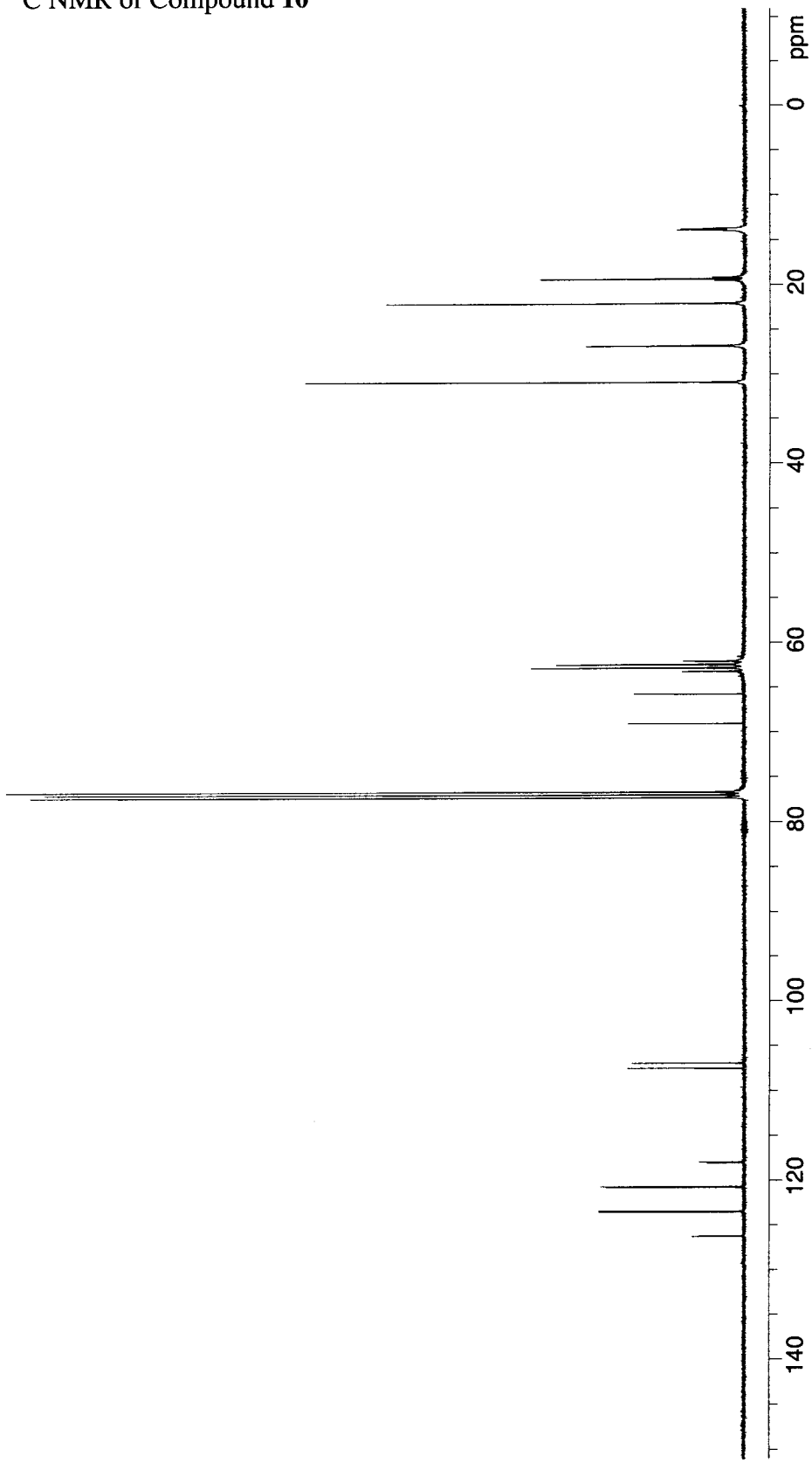


Figure 31: Mass Spectrum of Compound **10**

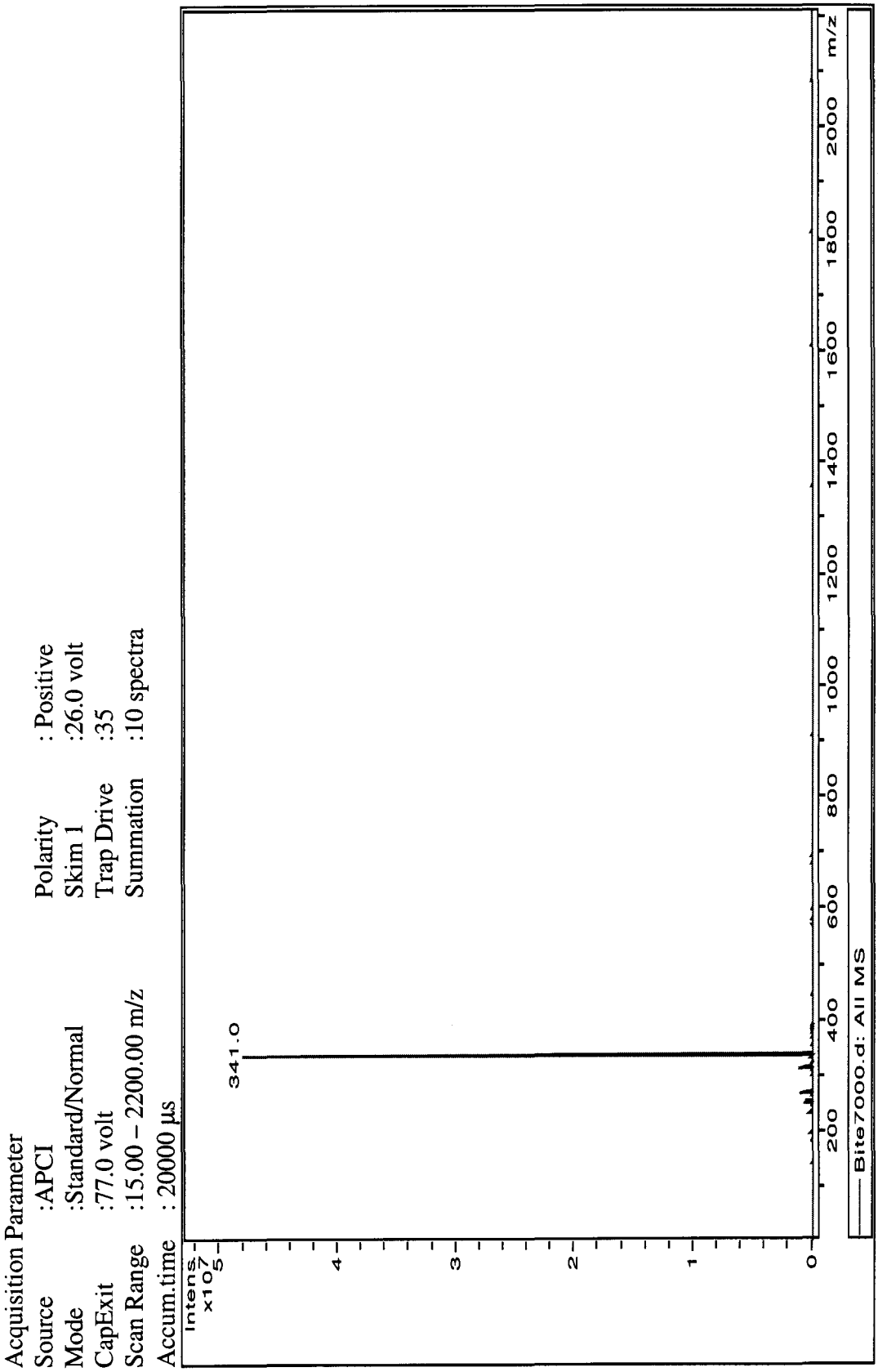


Figure 32: ^{31}P NMR of Compound **12**

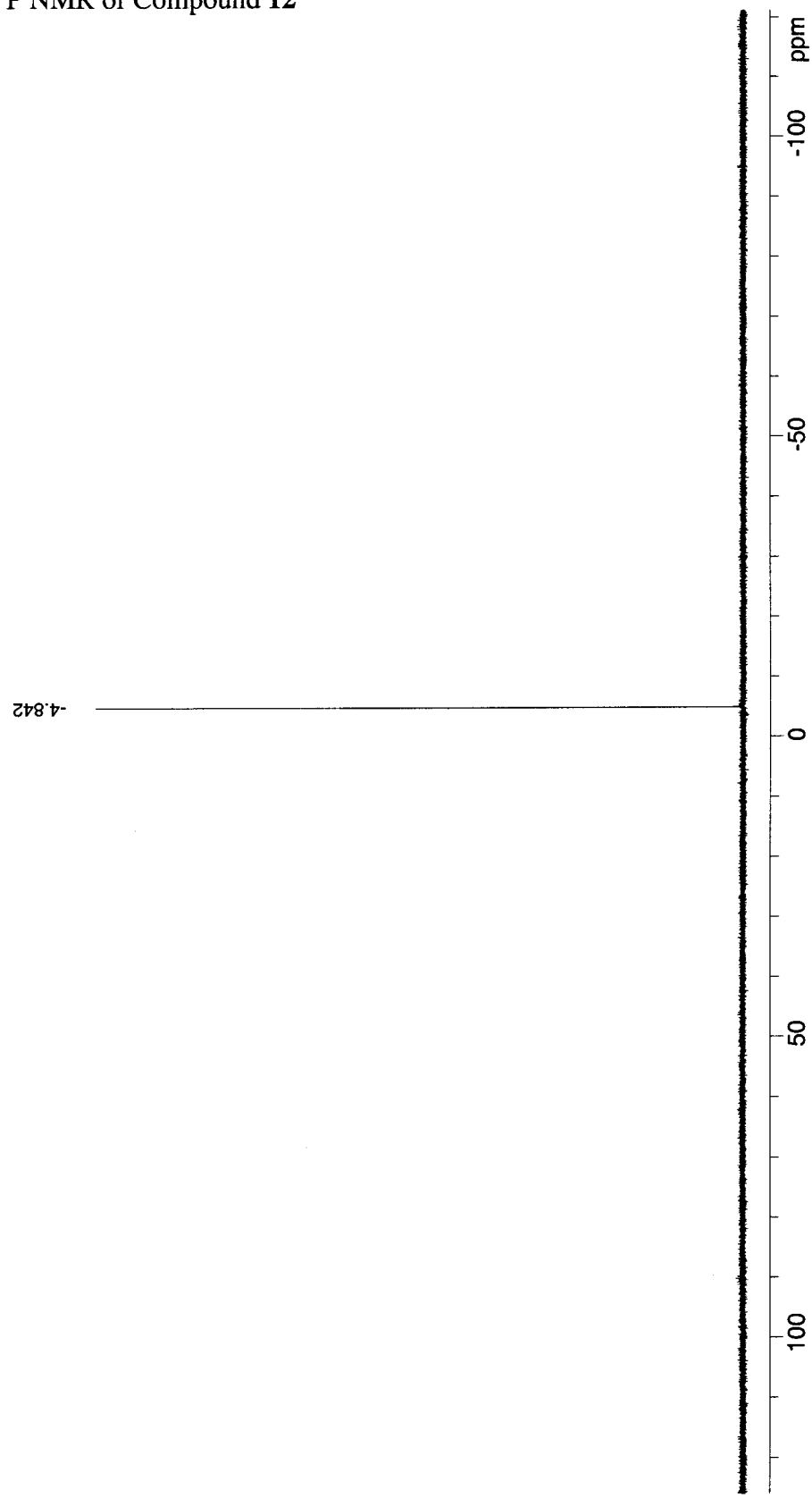


Figure 33: ^{1}H NMR of Compound **12**

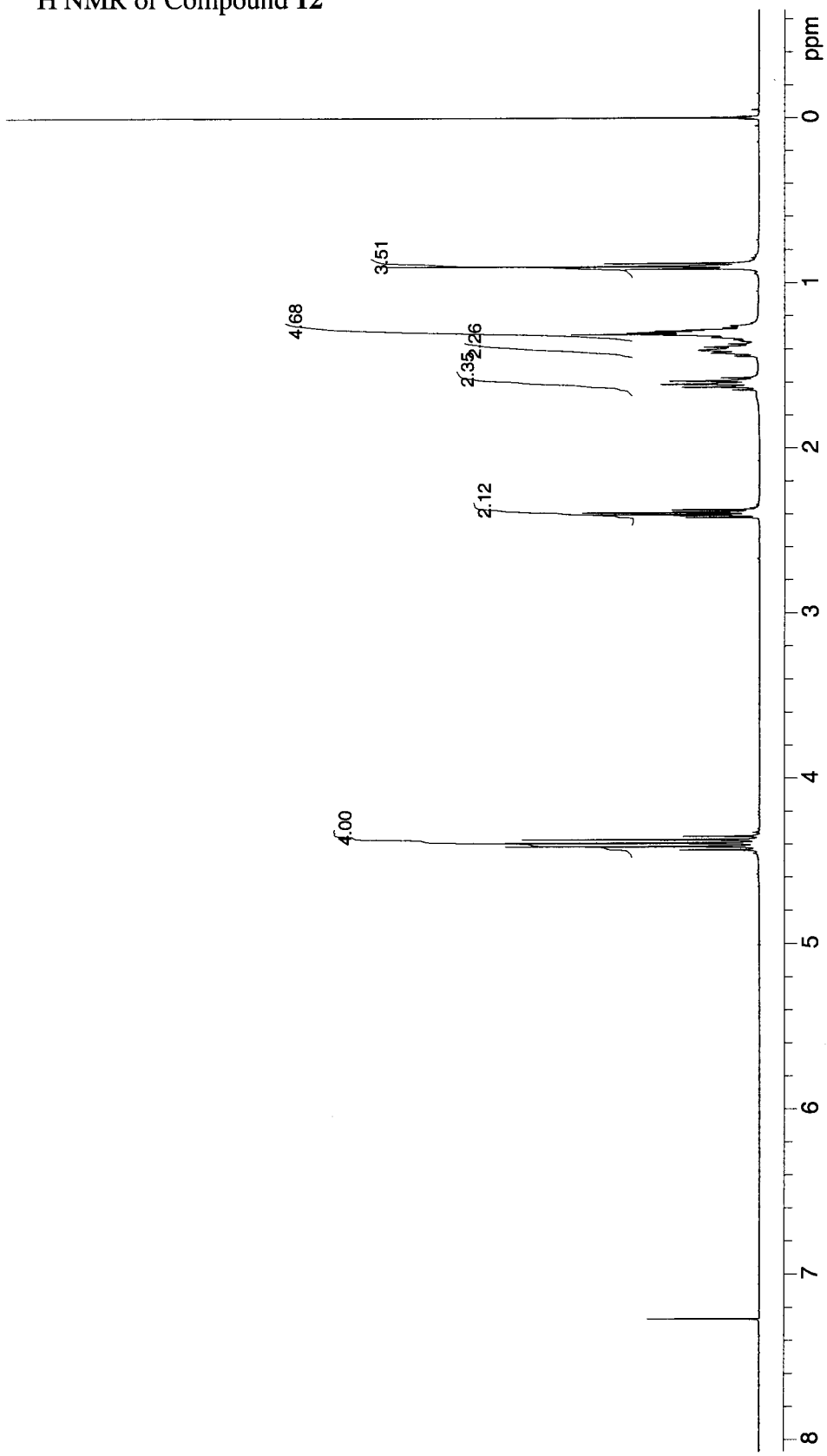


Figure 34: ^{13}C NMR of Compound **12**

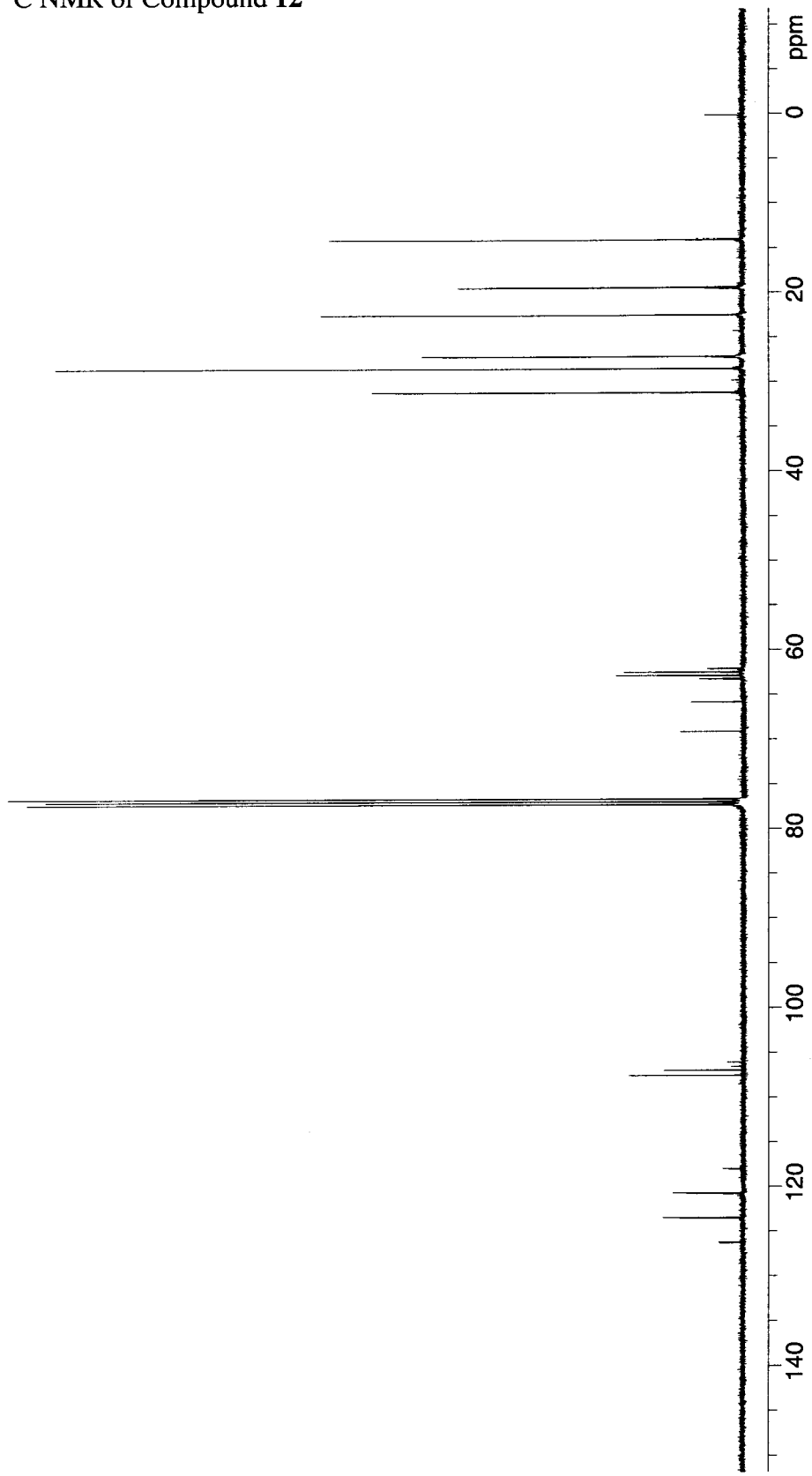


Figure 35: Mass Spectrum of Compound **12**

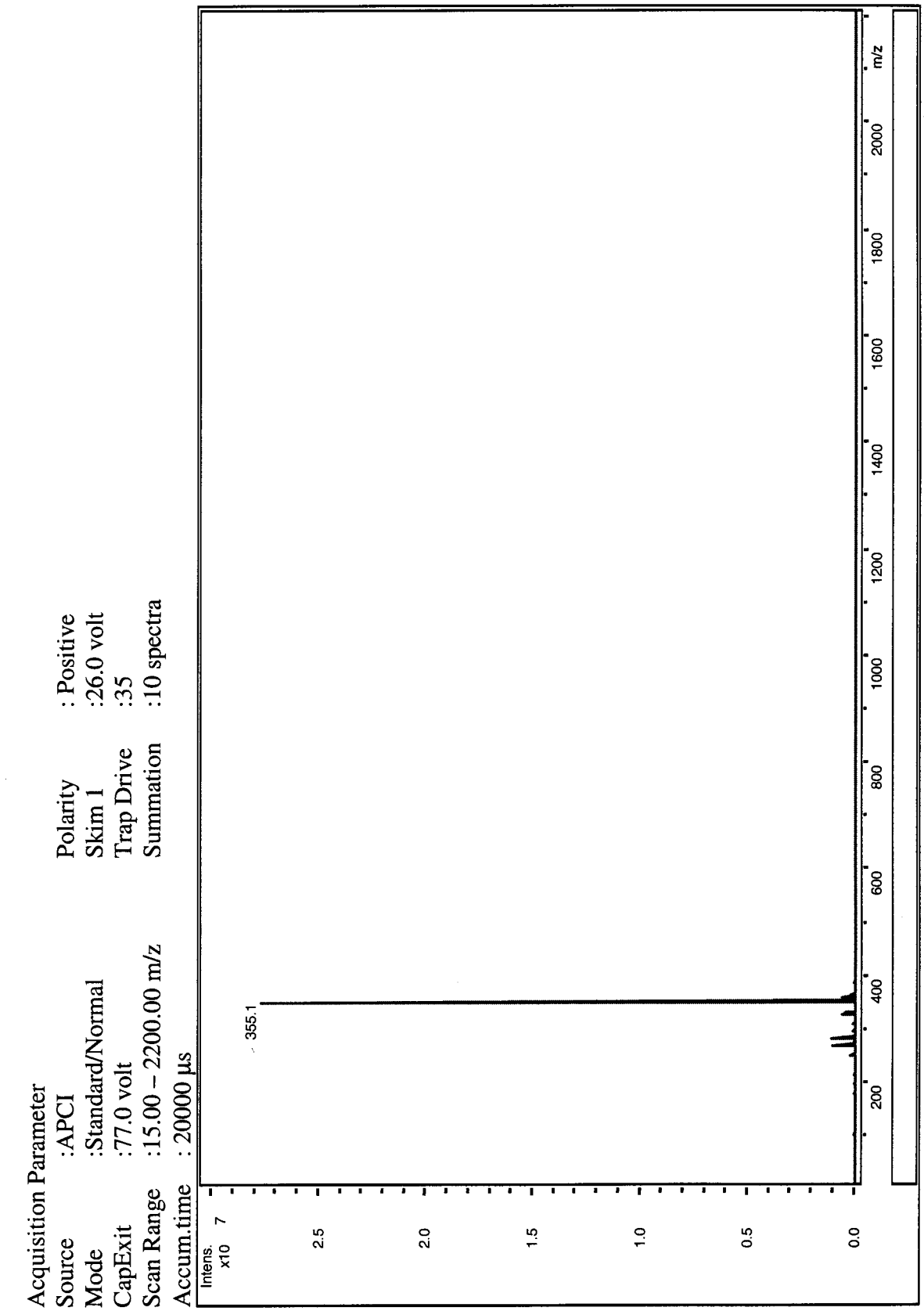


Figure 36: ^{31}P NMR of Compound **14**

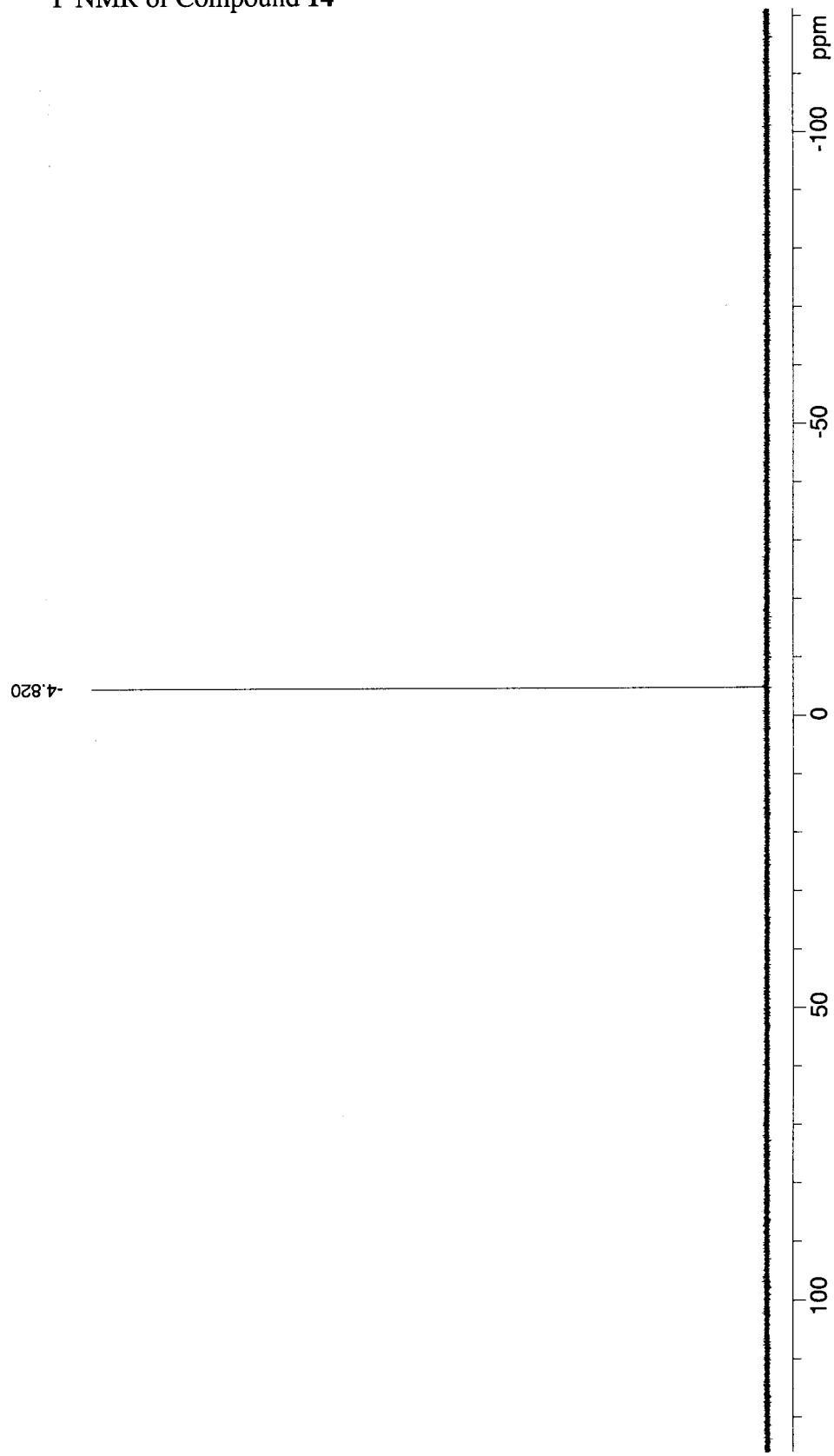


Figure 37: ^{1}H NMR of Compound **14**

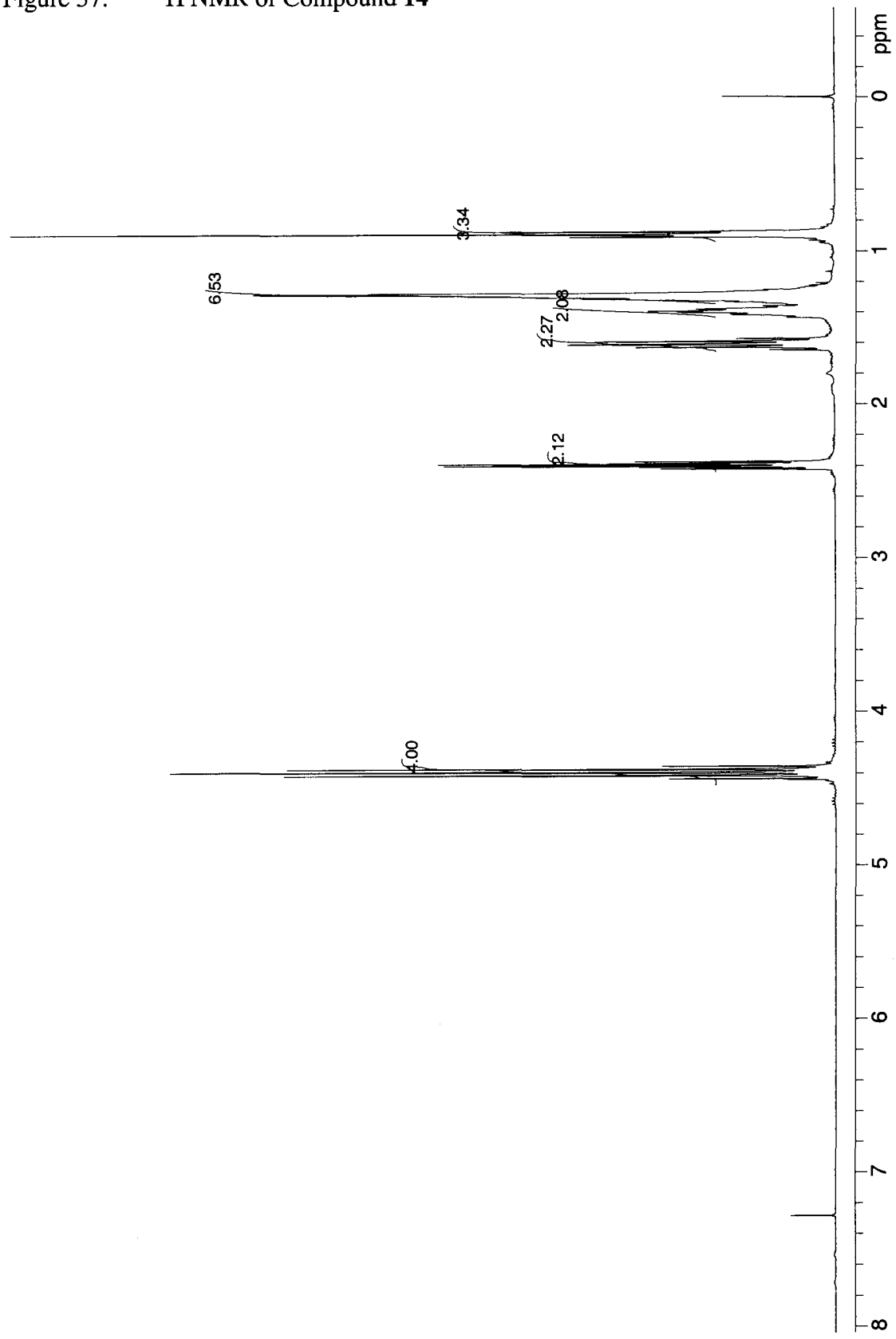


Figure 38: ^{13}C NMR of Compound **14**

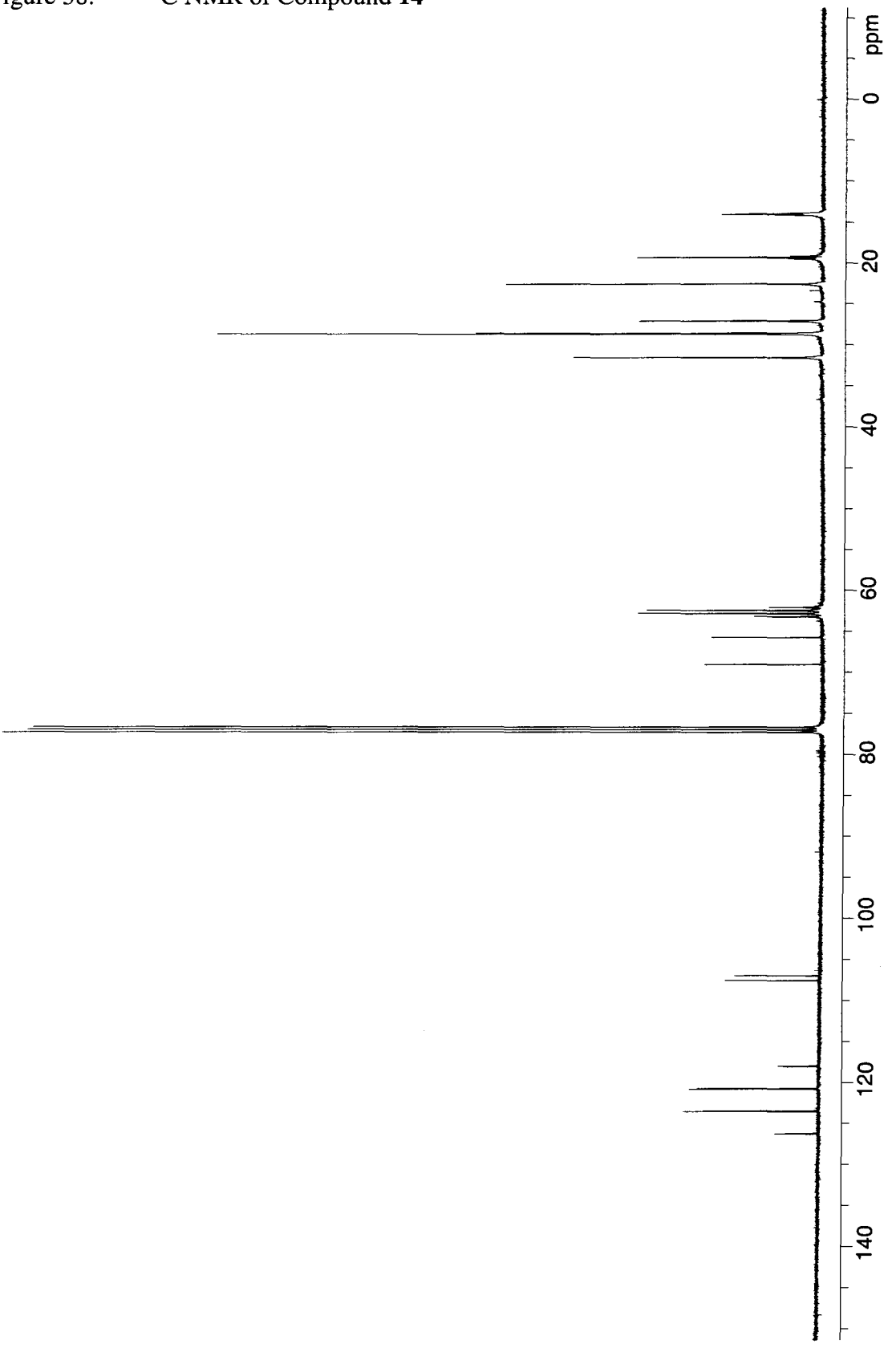


Figure 39: Mass Spectrum of Compound **14**

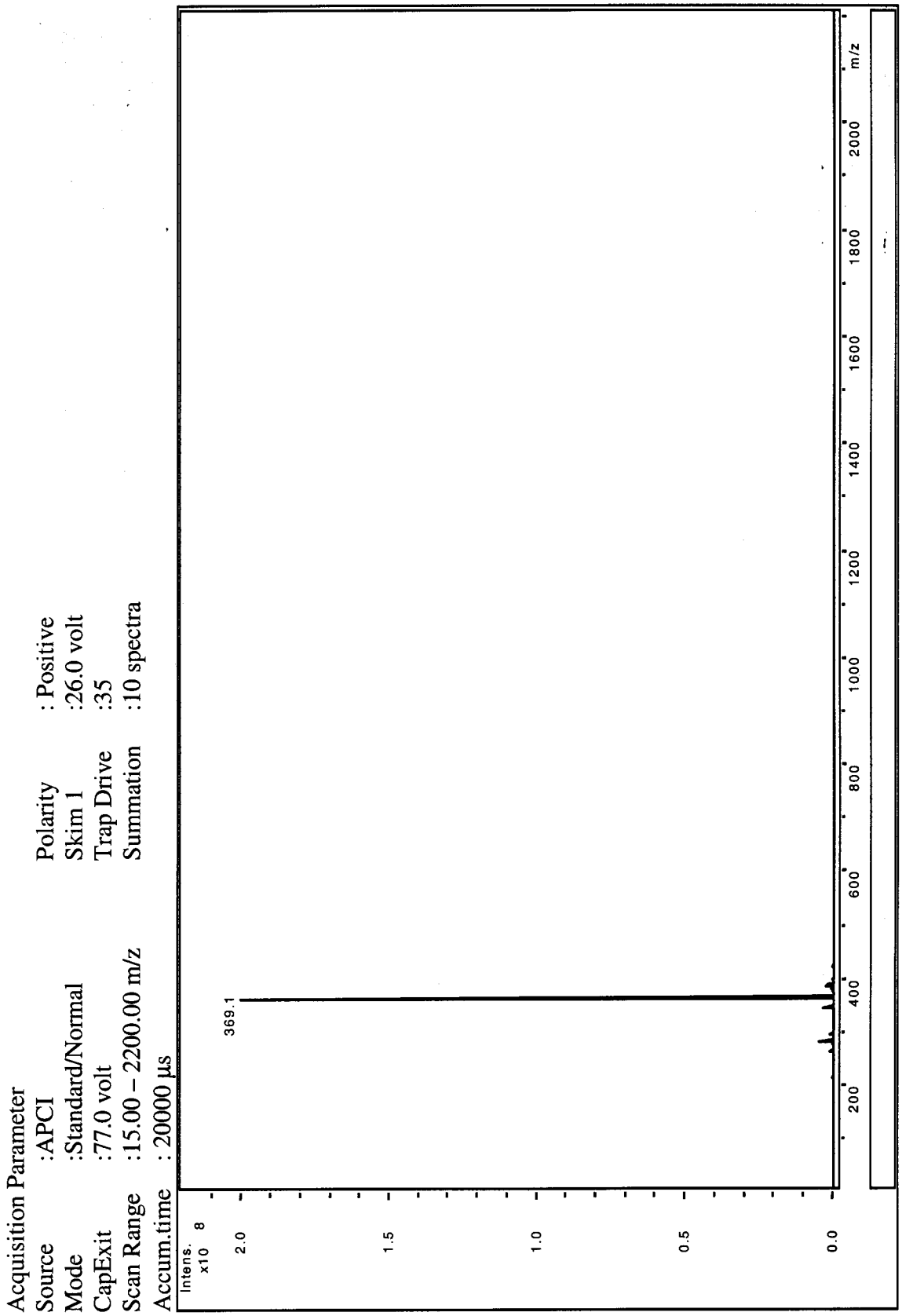


Figure 40: ^{31}P NMR of Compound **16**

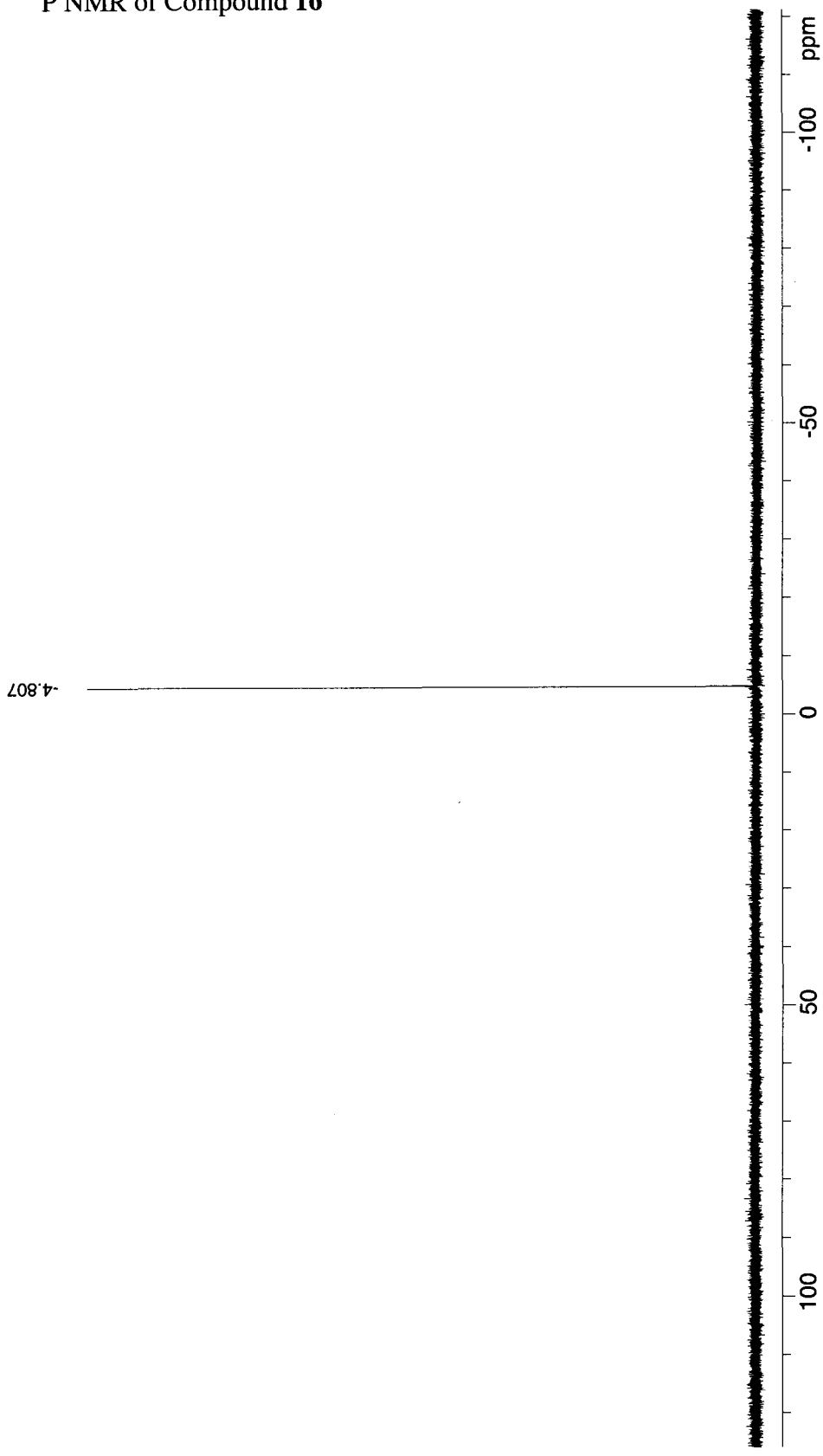


Figure 41: ^{1}H NMR of Compound **16**

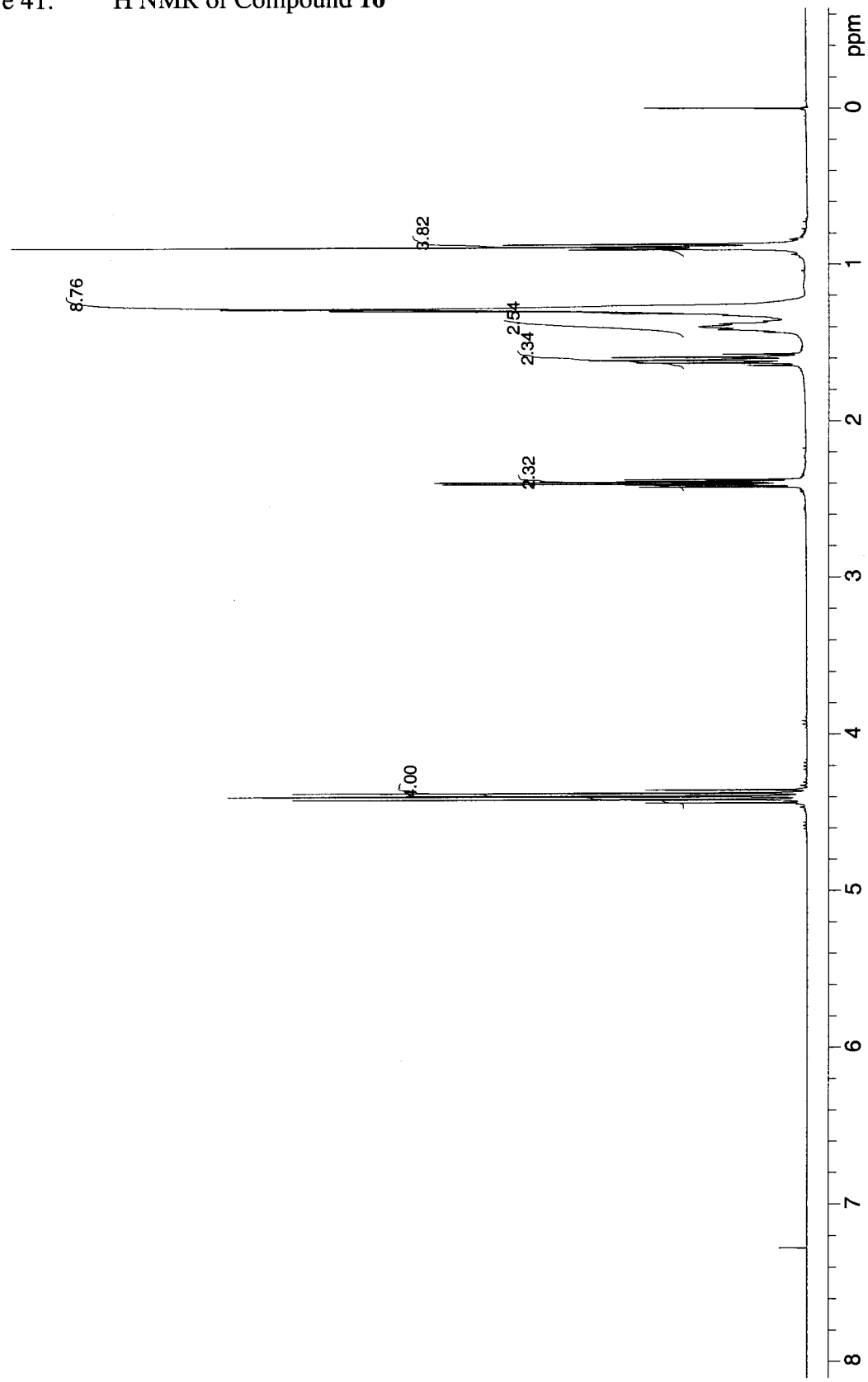


Figure 42: ^{13}C NMR of Compound **16**

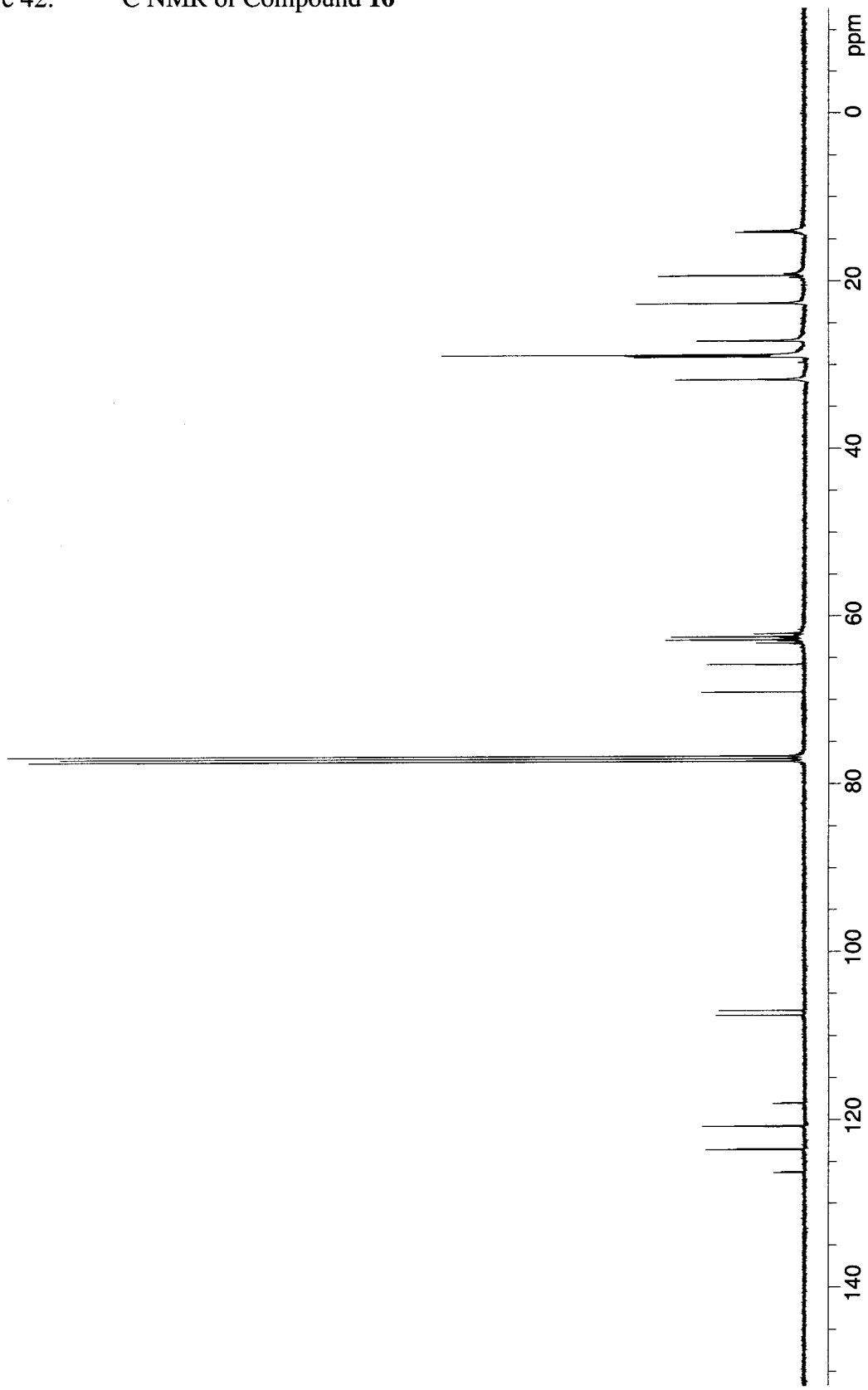


Figure 43: Mass Spectrum of Compound **16**