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

by

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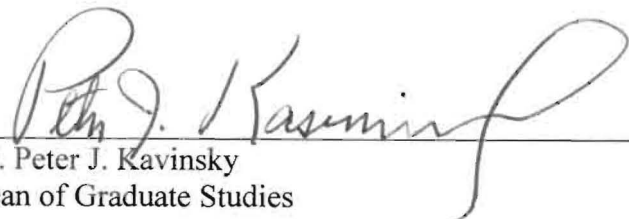Ramnath Kallamadi   Date

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Abstract

The focus of the research involves a convenient method for a synthesis of bis(2,2,2-trifluoroethyl)phosphonoalkynes **43a-d**. The reaction was smooth and achieved good yields (50-60%). The bis(2,2,2-trifluoroethyl)phosphonoalkynes are good dienophiles in cylcoaddition reactions. After successful synthesis of bis(2,2,2-trifluoroethyl)phosphonoalkynes **43a-d**, we synthesized vinyl phosphonates **46a-d**, aryl phosphonates **48a-d** in moderate yields by using Diels-Alder reaction. Cyclopentadiene and 1,3-cyclohexadiene were used as dienes. The products and by-products were purified by vacuum distillation and flash column and characterized by chromatographic (GC) and spectroscopic (NMR, MS) techniques.

Acknowledgement

I would like to express my gratitude to Dr. John A. Jackson for his supervision, guidance, patience and mentorship throughout my thesis evolution. He gave his valuable time and provided the strategic and knowledgeable support which I required to complete this thesis. I would like thank Dr. Peter Norris and Dr. Timothy R. Wagner for being members of my thesis committee.

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List of abbreviations

Abbreviations	Description
AEP	amino ethyl phosphonic acid
APCI	atmospheric pressure chemical ionization
^{13}C	carbon -13
d	doublet
dd	doublet of doublet
dq	doublet of quartet
dt	doublet of triplet
eq	equivalent
EOAc	ethyl acetate
ESI	electro static ionization
g	gram
GC	gas chromatography
^{1}H	hydrogen-1
HMPA	hexamethylphosphoramide
Hz	hertz
J	coupling constant
m	multiplets
mL	milliliter
mmol	millimoles
n-BuLi	butyllithium
NMR	nuclear magnetic resonance

List of abbreviations (continued)

^{31}P	phosphorus-31
PMA	phosphomolybdic acid
ppm	parts per million
s	singlet
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography

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Chapter 1

INTRODUCTION

</div>

A. Organophosphorus compounds

Organophosphorus chemistry is a major branch of organic chemistry. These organic molecules containing phosphorus offer fascinating possibilities for structural, synthetic and mechanistic studies. [1]

Organophosphorus compounds are organic molecules containing carbon and phosphorus as the major elements. The applications of organophosphorus compounds can be summarized as follows. [2]

Medicinal compounds: anti-cancer (cyclophosphamide), antifungal (fosfomycin) antiviral (adfovir) and anitcholenesterase (parathion) drugs.

Agricultural chemicals: herbicide (glyphosate), insecticide (malathion), fungicide (iprobenfos) and plant growth regulator (chlorphonium).

Flame retardents: for fabrics and plastics (tetrakis(hydroxymethyl) phosphonium salts).

Metal extractants: tri-butyl phosphate (TBP) used as extractant of metal ions in uranium (IV) ore.

Plasticizing agents: tricresyl phosphate (TCP) is used as plasticizer in nitrocellulose and PVC.

Antioxidants: Phosphites such as Irgafos® can be used as peroxide decomposers in plastic manufacturing.

Some common typical organophosphorus species include
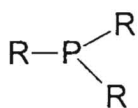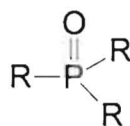
Phosphane ($\sigma^3\lambda^3$)　　　Phosphine Oxide ($\sigma^3\lambda^3$)　　　Phosphonates ($\sigma^4\lambda^5$)
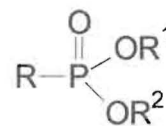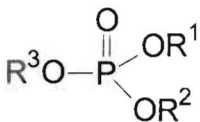
Phosphate esters ($\sigma^4\lambda^5$)　　　Phosphoranes ($\sigma^5\lambda^5$)　　　Phosphaalkenes ($\sigma^2\lambda^3$)
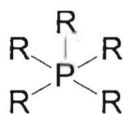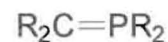
$RC\equiv P$

Phosphaalkynes ($\sigma^1\lambda^3$)

Note: number on σ indicates the number of sigma bonds and number on λ indicates the number of coordination of phosphorus atoms.

B. Phosphonates

Phosphonates are organic compounds containing a stable carbon-phosphorus (C-P) bond. They have many applications in synthetic organic chemistry, biology and biochemistry.

B.1. Stability of Phosphonates

Thermal stability of C-P bond is quite high, its heat of dissociation is about 65 kcal/mol. So phosphonates can be heated upto 150-200 °C or higher in some cases.[2] Phosphoryl (P=O) group is stable to chemical modification and has high heat of dissociation about 128-139 kcal/mol.[3]

B.2.Occurence of Phosphonates in nature

In 1959, Horiguchi and Kandatsu, first observed the natural phosphonate in an amino acid extract from the hydrolysate of rumen protozoal lipid and identified it as 2-aminoethyl phosphonic acid (AEP) [4] **1.**

$$NH_2-CH_2-CH_2-\overset{\overset{\displaystyle O}{\|}}{P}(OH)_2$$
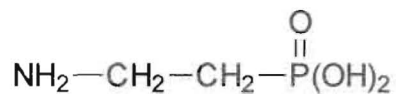
1

Figure 1. AEP

B.3.Distribution in nature

Phosphonates have been found in over 80 species [5a] that are members of 8 phyla in animal kingdom. Some bacteria and plants (such as fungi and dinoflagellates) also contain or produce phosphonates but these represent almost insignificant fractions.

The phosphonate molecule which has been found free and biologically significant is the phosphonate antibiotic, Fosfomycin **2** produced by various species of genus *streptomycetes* which is effective against a number of Gram -tive and –positive microorganisms.

$$CH_3-CH-CH-\overset{\overset{\displaystyle O}{\|}}{P}(OH)_2$$
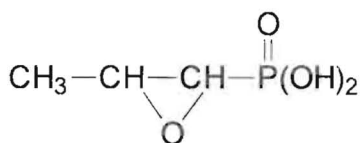
Figure 2: Fosfomycin **2**

In 1969 Merck Sharp & Dohme Research Laboratories, New Jersey synthesized fosfomycin in laboratory. [6]

Glycerophosphonolipids and sphingophosphonolipids contain phosphorus which is mostly in phosphonate form. Linag and Rosenberg identified glycerophosphonolipid,

diacylglyceryl-AEP **3**, the AEP analogue bound to glycerol in lipids extract off the protozoan *Tetrahymena pyriformis.* [7]

$$R-\overset{\displaystyle O}{\overset{\|}{C}}-O-\overset{\displaystyle H_2C-O-\overset{\overset{\displaystyle O}{\|}}{C}-R}{\underset{\displaystyle H_2C-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\displaystyle OH}{P}}-CH_2-CH_2-NH_2}{CH}}$$
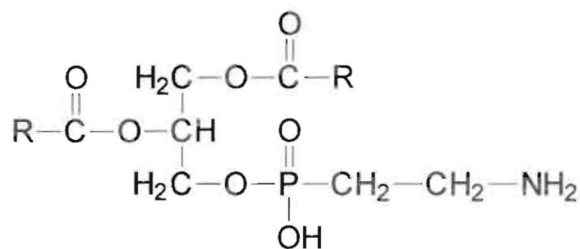
3

Figure 3. Diacylglyceryl-AEP

Rouser et al. [8] identified Ceramide-AEP **4,** the first sphingophosphonolipid which was a component of the lipids of the sea anemone *A.elegantissim*, structure shown that the base to be spingosine with an AEP esterified at the first hydroxyl and an N-acyl group at the second carbon.

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\displaystyle H}{N}-\overset{\displaystyle \overset{\displaystyle OH}{|}}{\underset{\displaystyle H_2C-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\displaystyle OH}{P}}-CH_2-CH_2-NH_2}{\overset{\displaystyle HC-CH=CH-(CH_2)_{12}-CH_3}{C}-H}}$$
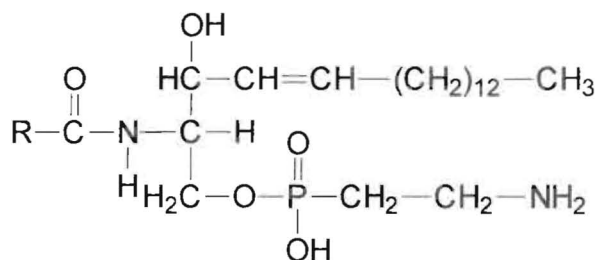
4

Figure 4. Ceramide-AEP

Rosenberg et al. identified that phosphonates were associated with protein in proteinaceous material of sea anemone T. *pyriformis*. Hilderbrand et al.[9] found that a proteinaceous extract from *Metridium dianthus*, following exhaustive lipid extraction, contained 50% of its phosphorus in the phosphonate form.

B.4. Applications of phosphonates

Organic phosphonates offer many applications [5b] as organic phosphates; because of its higher prices when compared to organic phosphates their availability is limited in the market.

Phosphonates have useful synthetic application in Horner-Wardsworth-Emmons (HWE) condensation which is often used to prepare α, β–unsaturated carbonyl compounds [10] **5**.
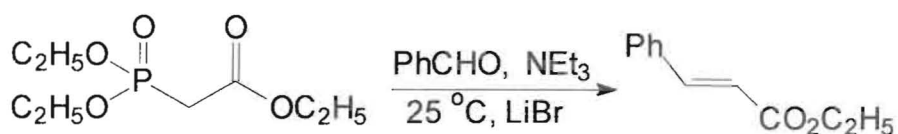
Scheme 1   **5**

Vinyl phosphonates are useful building blocks for synthesis of biologically active compounds. For instance, dialkyl 3-acetoxy-1-alkenyl phosphonates can be used to prepare phosphono amino acids which can be used in the treatment of epilepsy and Parkinson's disease. Vinyl phosphonates are also used to prepare allyl alcohols which are used in synthesis of Antiviral nucleosides.[11, 12]
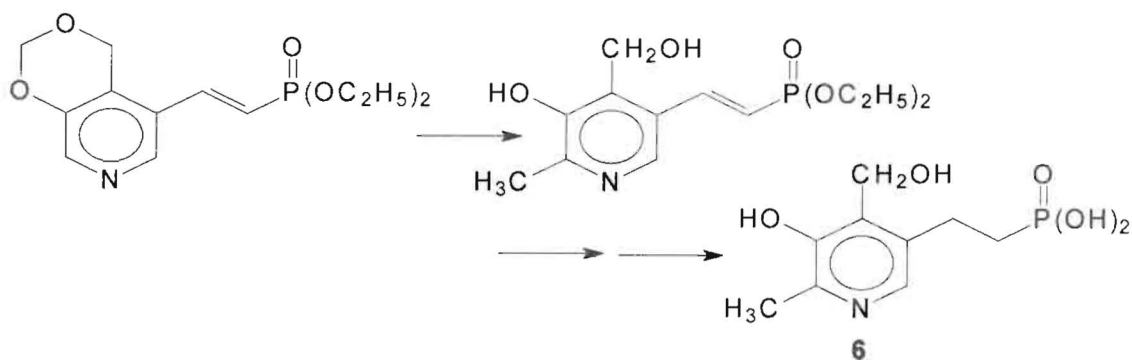
Scheme 2

Vinyl phosphonates used as intermediates [13] to synthesize pyridoxyl phosphonates 6 which in turn inhibit tyrosine decarboxylase enzyme, an enzyme that converts tyrosine into tyramine which is a causative agent for migraine.

The compound bis(2-chloroethyl)vinyl phosphonate is useful in making adhesive compositions.[14a] Vinyl phosphonates can also be used as a catalyst, bis(beta-chloroethyl) vinyl phosphonates reported to be good catalysts for the condensation of isocyanates to carbodiimides. [15]

Phosphonates are also used as anti-inflammatory agents, [13b] anticancer agents [13b] antioxidants, corrosion inhibitors, dentifrice compositions, deodorants, flame retardant polymers, fuel additives, plasticizers, polyurethane additives, sequestering agents, viscosity modifiers, suspending agents and many more in industry. Because of their Acetyl cholinesterase (AChE) inhibition these can be used as insecticide, nerve gas agents in war. It acts as calcium antagonist thereby used as antihypertensive. In plants these are used as herbicides, plant growth regulators.

General methods of synthesis for vinyl phosphonates:

Vinyl phosphonates are a very significant group of compounds with important practical applications, for instance their derivatives are used as copolymers, polymer derivatives, flame retardants, fuel and lubricant additives.

Part C. Synthesis of vinyl phosphonates

1. From alkynyl phosphonates.

Alkynyl phosphonates are very important substrates for the synthesis of vinylphosphonates.

C.1.1. Cycloaddtion reactions

C.1.1.a. [4+2] Cycloadditions

1-Alkynyl phosphonates are potentially useful precursors for introducing organophosphorus substituents into diverse organic structures. So far many alkynyl phosphonates such as ethynyl [15] 2-formylethynyl, [16] sulfonylethynyl, propenyl-1-aldehyde,[16] sulfoxyethynyl [15] and phenylethynyl, haloethynyl derivatives of phosphonates and acetylenebisphosphonates have been utilized as dienophiles and published in different articles. At least one activating group on alkyne is necessary for the cycloaddition to occur. Isoprene, 2,3-dimethyl-1, 3-butadiene, [18] cyclopentadiene, 1,3-cyclohexadiene, anthracene, 9-menthanthracene, 1-phenyl-3,4-dimethylphosphole and alpha –pyrone have been employed as dienes.

Stephane Lelievre and Francois Mercier reported synthesis of phosphanorbornadienephosphonate to synthesize 1-phosphanorbornadiene which are excellent ligands in the rhodium-catalyzed hydrogenation and hydroformylation of alkenes.[17] Thus reaction of phenyl ethynyl phosphonates with 1-phenyl-3,4-dimethylphosphole **7** at 140 °C gave compound **8** in good yield, 80% (Scheme **3**).
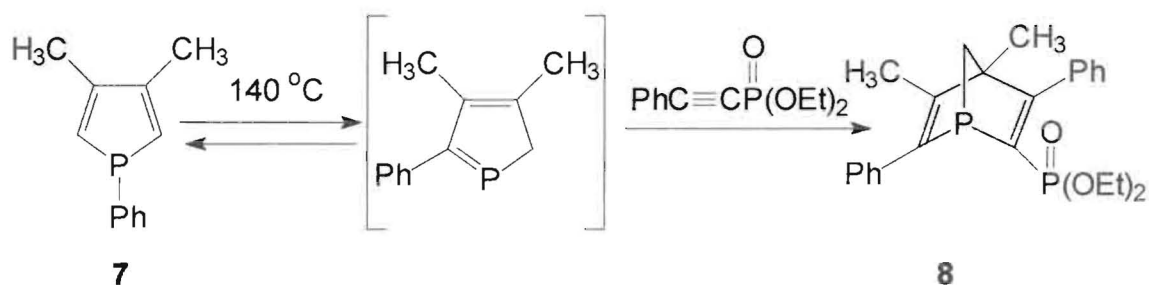
Scheme 3

In 1969 Seyferth reported the synthesis of ortho-phenylene diphosphonate in

93% yield from the reaction of acetylene bisphosphonates **9** with 1,3-cyclohexadiene at 150 °C (Scheme **4**). [20]
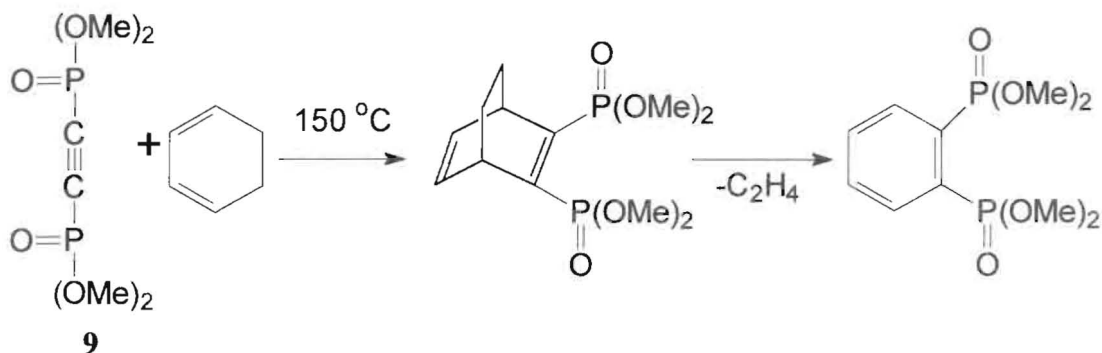
Scheme 4

C.1.1.b. [2+2] Cycloadditions

Functionalized medium sized rings which are useful intermediates in the synthesis of natural products can be synthesized by cycloaddition of enamine with alkynyl phosphonates. Suzanne M. Ruder and Bradley K. Norwood prepared vinyl phosphonates by combining alkynyl phoshonates **10** with freshly distilled enamine **11** and heated to 85-100 °C, the corresponding product **13** was obtained. [21] The hydrolysis of crude reaction mixture when treated with either dilute ethanolic acetic acid or *p*-TsOH/THF/H_2O at room temperature gave **14** (Scheme **5**). They concluded that alkynyl phosphonates are less reactive in cycloaddition reactions with enamines, the reaction temperature required at least 85 °C, at this temperature spontaneous ring opening of thermally unstable butene intermediate **12** affords the compound **13**.

$$n = 1,2$$

| 10 | 11 | 12 | 13 |

13   **14**
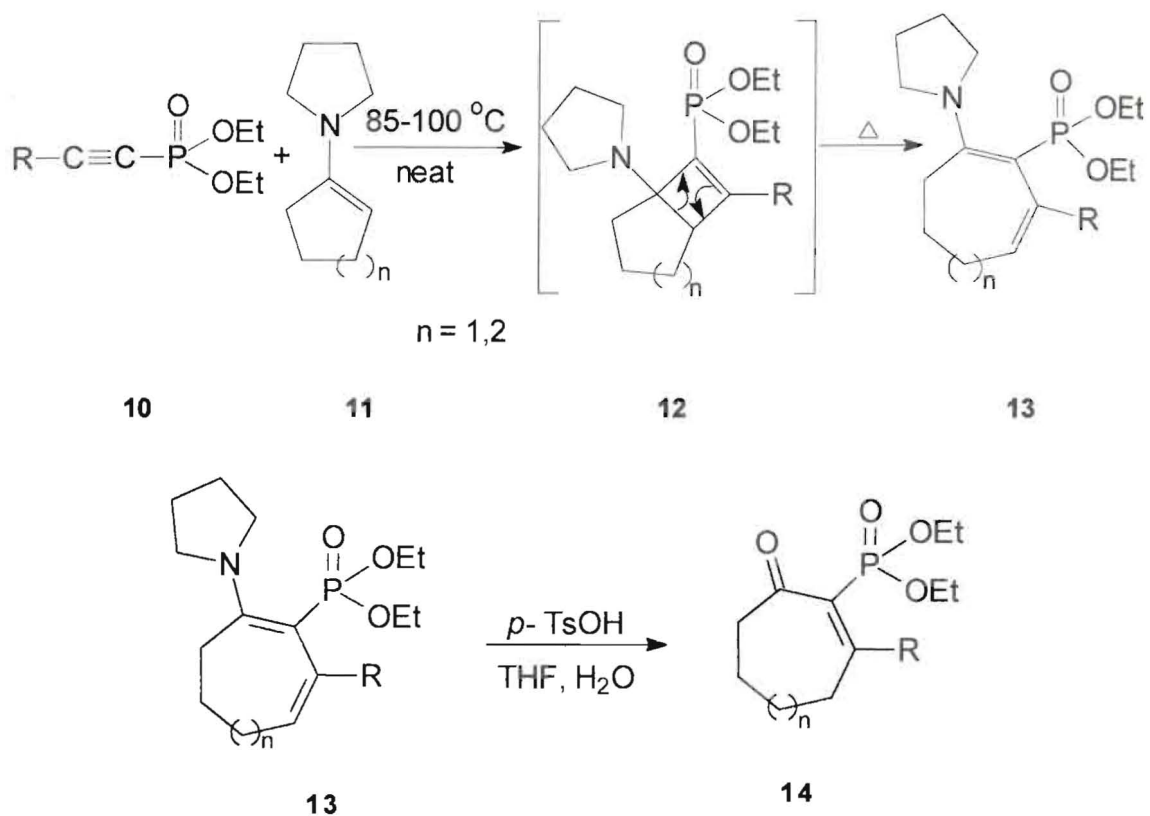
R = H, *n*-Pr, Ph

Scheme 5

C.1.1.c. [3+2] Cycloadditions

5-membered heterocycles such as pyrazoles, triazoles and oxazoles can be easily introduced into the organic structures by synthesizing the heterocyclic substituted vinyl phosphonate intermediates. The vinyl phosphonates, phosphonopyrazoles[22] can be synthesized conveniently by adding diazomethane to ethynylphosphonates, thus diisopropyl ethynyl phosphonate **15** reacts with an excess of diazomethane, yielding the 1-methyl-5-phosphonopyrazole **16** in 28% yield, (Scheme **6**).

15   **16**
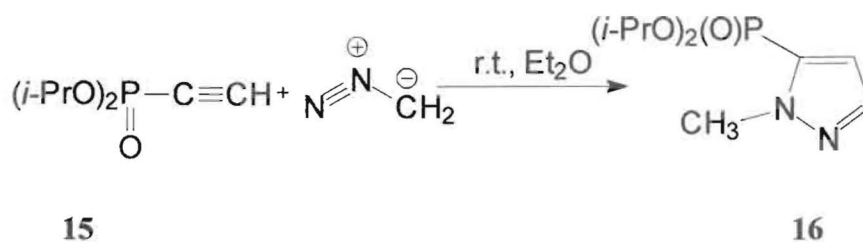
Scheme 6

The tetramethyl acetylenediphosphonate **8** reacts with diazomethane spontaneously in cooled diethyl ether to yield the 4,5-diphosphonopyrazole **17** in 95% yield (Scheme **7**).

9   **17**
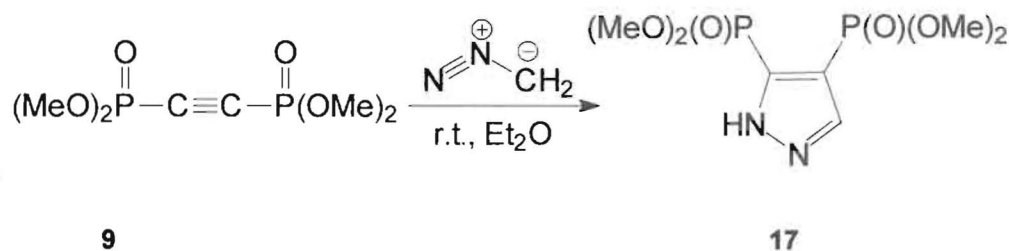
Scheme 7

C.1.2. Via Metal complexes

Amino phosphonates are an important class of organic compounds having significant utilities as antibiotics, [23] enzyme inhibitors, [23a] herbicidal [23b] and antifungals. [23c] Addition of various imines to the 1-alkynyl phosphonate titanium(II)complex **18**, prepared from alkynyl phosphonates **10**, Ti(O-i-Pr)$_4$/i-PrMgCl gave desired 3-amino-1-alkenyl phosphonates **19** in good yields (Scheme **8**). [24]
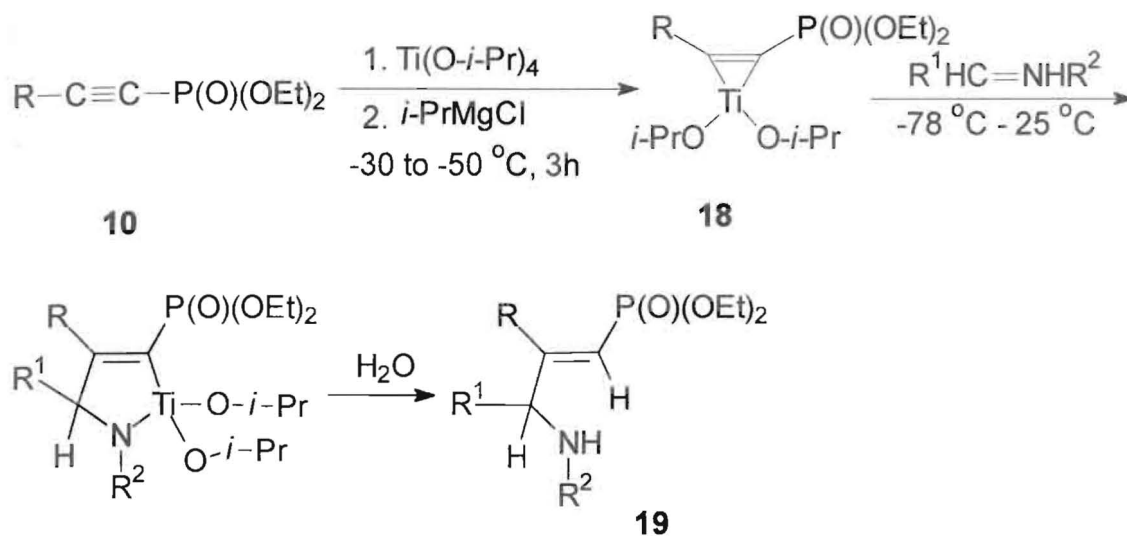
Scheme 8

Zirconation of 1-alkynyl phosphonates called zirconacycles **20** which upon hydrolysis gives vinylphosphonates. Reductive cyclization of alkynyl phosphonates **10** by using Negishi's reagent, $Cp_2ZrCl_2/2$ equiv n-BuLi, afforded 3-membered zirconacycles **20** which were converted to *cis*-vinylphosphonates **21** by simple hydrolysis. [25]
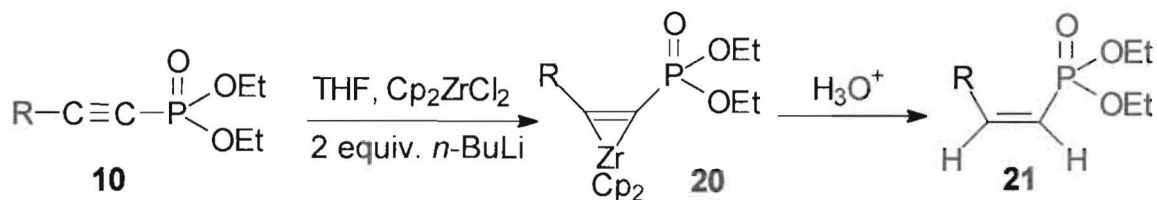
Scheme 9

C.1.3. Carbocupration of 1-alkynyl phosphonates

Regio-, stereo selective 1,2,2-trisubstituted vinylphosphonates can be prepared by carbocupration of 1-alkynyl phosphonates with high yields in one-pot process. 1-Alkynyl

phosphonates **10** were converted into 1-phosphonyl-2,2,-dialkyl vinylcopper (I) intermediates **22** which were subsequently reacted with a variety of electrophiles to give 1,2,2-trisubstituted vinylphosphonates **23** in good to excellent yields (40-97%). [26]
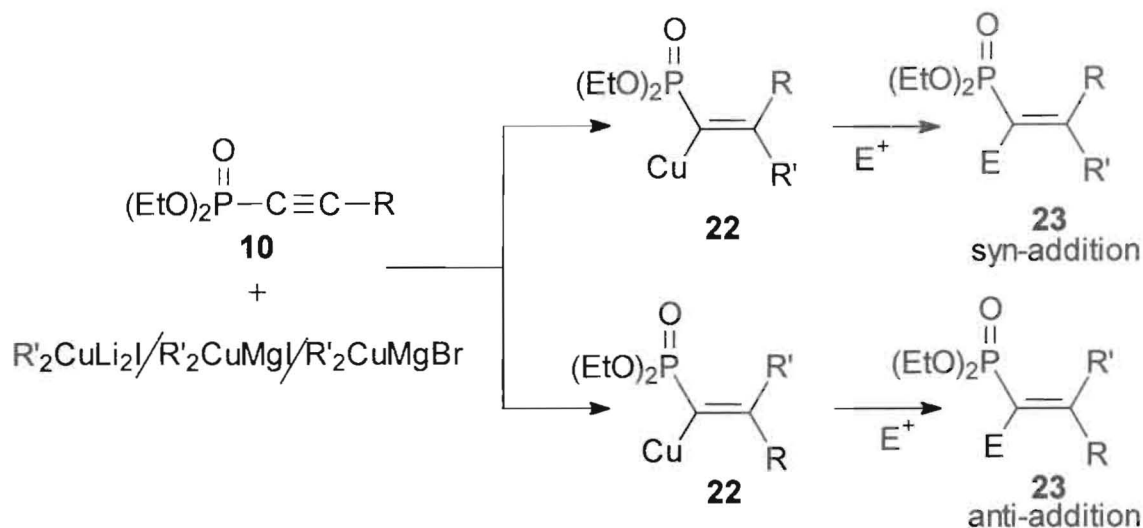
a. R = H   R' = Et   Yield; 85%
b. R = t-Bu R' = Me Yield; 96%
c. R = Ph   R' = n-Bu Yield; 94%
d. R = I   R' = Me Yield; 85%

Scheme 10

It was found that the carbocupration of 1-alkynyl phosphonates **10** with organocopper (I) reagents was only *syn*-addition when R = H, *n*-Bu, *n*-Hex, Ph and *anti*-addition was observed when R = *t*-Bu.

C.1.4. Hydroboration of alkynyl phosphonates

Inna Pergament and Morris Srebnik reported hydroboration of alkynyl phosphonates followed by Suzuki coupling gave region and stereospecific disubstituted 1-alkenylphosphonates.[27] Thus hydroboration of 1-alkynyl phosphonate **10** with pinocolborane (PBH) in CH_2Cl_2 at 25 °C formed unstable vinylphosphonoborane **24** which was immediately Suzuki coupled with aryliodide in presence of palladium-catalyst

gave disubstituted 1-vinyl phosphonates **25**.

R = C$_2$H$_{11}$, Cl(CH$_2$)$_3$, Ph
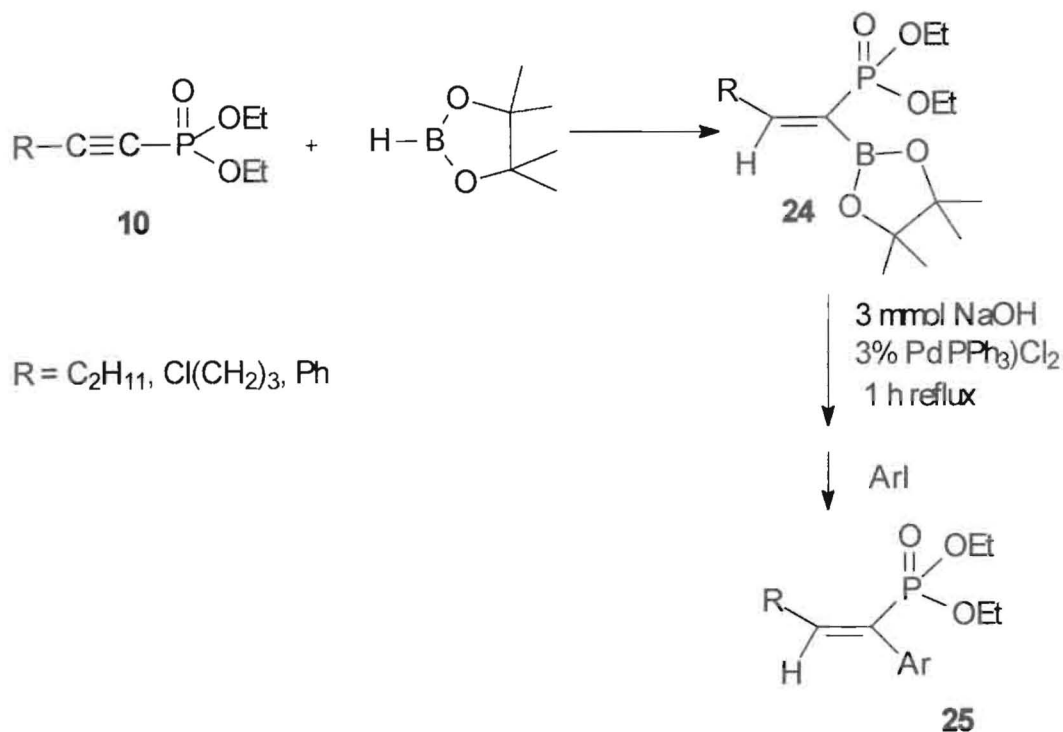
Scheme 11

C.2. Miscellaneous

C.2.1. Hydrophosphorylation of terminal alkynes

Palladium catalysed hydrophosphorylation of terminal alkynes give vinyl phosphonates in excellent yields. [28] A solution of 1-octyne **26** and HP (O) (OR)$_2$ (where R= Me, Et.) in THF was heated to 67 °C in presence of Pd catalyst to furnish alkenyl phosphonates **27** and **28** in good yields. (Scheme **12**). Various alkynes in presence of various Pd catalyst were successful with good yields. The reaction with absence of Pd catalyst gave neither **27** nor **28.**

$$n\text{-}C_6H_{13}\text{—}C\equiv CH + (RO)_2\overset{O}{\overset{||}{P}}H \xrightarrow[\text{THF, 67 °C}]{\text{3 mol \%, Pd(0)}} n\text{-}C_6H_{13}\overset{}{\diagup}P(OR)_2$$

26   **27**

28
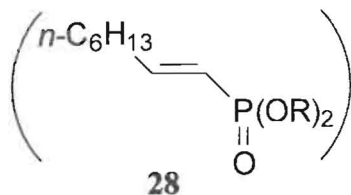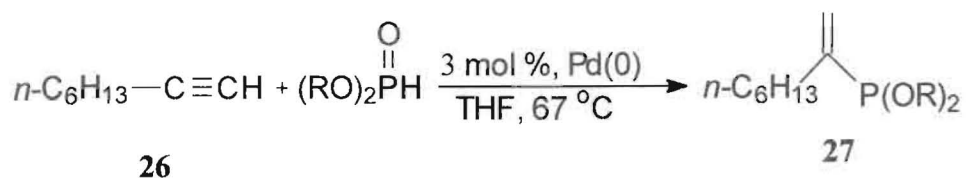
R = Me 91% (**23/24** = 96/4)
R = Et 93% (**23/24** = 90/10)

Scheme 12

C.2.2. Copper promoted synthesis of vinyl phosphonates.

β-bromostyrenes **29** were heated with dialkylphosphonates in presence of a base and copper (I) iodide (Scheme **13**).[29] The reaction afforded good yields in shorter time when hexamethylphosphoric triamide (HMPA) as solvent and KH as base. The reaction is stereospecific and E/Z ratio of the starting bromides were retained in the final products. Besides with alkynyl phosphonates, the reaction is also successful with phenyl phosphonates in good yields.

29   **30**
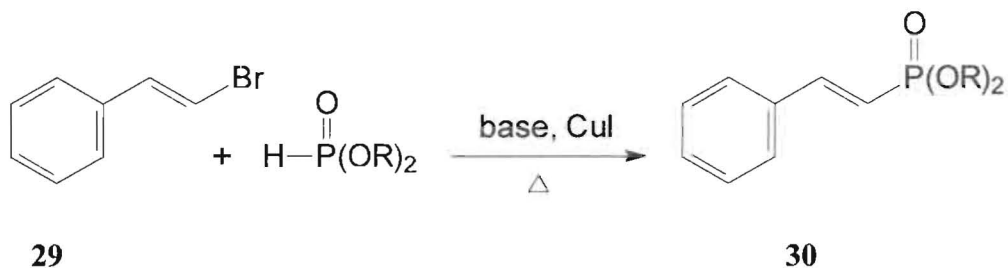
Scheme 13

C.2.3.Michealis-Arbuzov reaction

1 and 2-dialkylaminovinyl phosphonate, 1 and 2-alkoxyvinylphosphonates are

useful compounds as precursors of keto- and aldophosphonates. These compounds were synthesized by using Arbuzov reaction in good yield, cross-coupling reaction of bromo-, chloro- substituted alkenyl-alkyl ethers **31** with triethylphosphite catalyzed by Ni complexes gave alkoxyvinylphosphonates **32** (Scheme **14**).[30] Both bromo-, chloro derivatives **31a-c** proceeds smoothly at temperature 75-120 °C for nickel catalyzed reaction.

Scheme 14

a. R= H, Y = OEt, X = Br c. R= Me, Y = NEt$_2$, X = Cl
b. R= H, Y = OBu, X = Br.

Arbuzov reaction of 2-chlorovinyl ketones with trialkyl phosphates furnished the 3-oxovinylphosphonates **34,** enolphosphonates **35** and 3-oxo-1,1-alkanebisphosphonates **36** (Scheme **15**). [31]

34a R^1 = R^2 = CH$_3$, Yield = 12%
34b R^1 = R^2 = C$_2$H$_5$, Yield = 24%
34c R^1 = CH$_3$, R^2 = C$_2$H$_5$, Yield = 29%
34d R^1 = C$_6$H$_5$, R^2 = CH$_3$, Yield = 40%

Scheme 15

C.2.4. Via carbon radical trapping

Vinyl phosphonates can be easily prepared by reacting carbon radicals with alkyl phosphites via free-radical Arbuzov process. The alkyl phosphite $(MeO)_3P$ fails to react with methyl, primary alkyl radicals to give phosphonates. Xian-Yun Jiao and Wesley G. Bentrude reported the synthesis of vinyl phosphonate dimethyl esters in high yields by trapping alkyl phosphites $(MeO)_3P$ with vinyl radicals. Radical **38** was formed readily by 5-exo-dig-cyclization of the 5-hexynyl radical **37** generated under standard thermal AIBN/Bu$_3$SnH conditions from its precursor bromide. Intermediate **37**, as a primary alkyl radical, will be unreactive toward trimethyl phosphite, $(MeO)_3P$. [32]

37	**38**	**39**
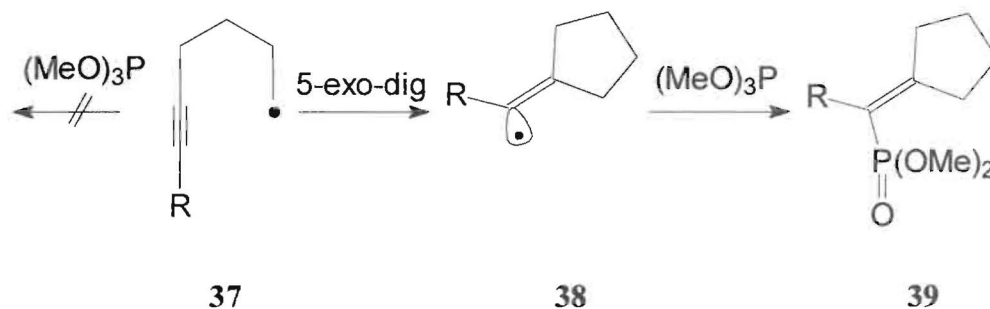
R = H (77%), Me (88%), *i*-Pr (70%), Ph (65%)

Scheme 16

Chapter 2

RESULTS & DISCUSSION

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

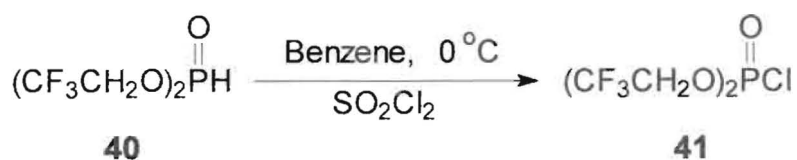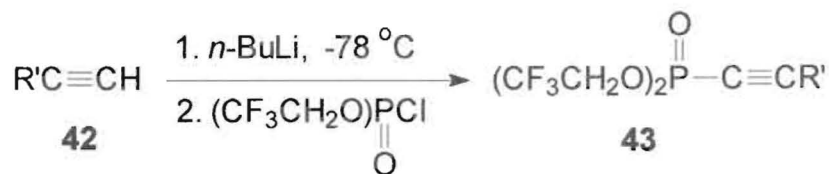This research has focused on synthesis of bis(2,2,2-trifluoroethy)phosphonoalkynes **43a-d** in a clean fashion with about 50-60 % yields. This reaction is bimolecular nucleophilic acyl substitution where lithium acetylide, a nucleophile attacks the phosphorus center in bis(2,2,2-trifluoroethyl)phosphochloridate **(41)**. General synthesis of bis(2,2,2-trifluoroethyl)phosphochloridate **(41)** as follows (Scheme 17).[33]

$$(CF_3CH_2O)_2\overset{\overset{\displaystyle O}{\|}}{P}H \xrightarrow[\text{SO}_2\text{Cl}_2]{\text{Benzene, } 0\,^{\circ}\text{C}} (CF_3CH_2O)_2\overset{\overset{\displaystyle O}{\|}}{P}Cl$$

40　　　　　　　　　　　　　　　　　　　　**41**

Scheme 17

Bis(2,2,2-trifluoroethy)phosphite **(40)** is the starting material which is a commercially available compound, due to its high cost we prepared successfully in laboratory with good yield (80%). The solution of phosphite **(40)** in benzene was treated with sulfuryl chloride at 0 °C, compound **41** was obtained in good yield about 93% with the evolution of hydrogen chloride and sulfur dioxide which are by-products in reaction. The purification was done by vacuum distillation. The compound **41** was obtained at 40 °C/2mm Hg as a dense colorless liquid. The compound **41** was characterized by ^{31}P NMR, a single peak at about +6.5 ppm with no sign of starting material (compound **40**) which shows up as multiplets at 0 ppm in ^{31}P NMR. Proton NMR was also taken to prove

its purity. The appearance of multiplets at 4.55 ppm is indicative of methylene protons in the trifluoro ethoxy group in compound **41** and no other signals were observed.

$$R'C{\equiv}CH \xrightarrow[\text{2. (CF}_3\text{CH}_2\text{O)PCl}]{\text{1. } n\text{-BuLi, -78 }^{\circ}\text{C}} (CF_3CH_2O)_2\overset{\displaystyle O}{\underset{}{P}}{-}C{\equiv}CR'$$

42   **43**

Scheme 18

The bis(2,2,2-trifluoroethyl)phosphonoalkynes **43a-d** were synthesized by metalation of 1-alkynes with *n*-BuLi in 50:50 anhydrous pentane and anhydrous ether at low temperature; the resulting lithium acetylides were treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (**41**).

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

Entry	Alkyne	Phosphonoalkyne	Isolated Yield (%)
(a)	$CH_3(CH_2)_5C{\equiv}CH$ **42a**	$CH_3(CH_2)_5C{\equiv}C{-}\overset{O}{\overset{\|}{P}}(OCH_2CF_3)_2$ **43a**	61
(b)	$CH_3(CH_2)_4C{\equiv}CH$ **42b**	$CH_3(CH_2)_4C{\equiv}C{=}\overset{O}{\overset{\|}{P}}(OCH_2CF_3)_2$ **43b**	45
(c)	$CH_3(CH_2)_3C{\equiv}CH$ **42c**	$CH_3(CH_2)_3C{\equiv}C{-}\overset{O}{\overset{\|}{P}}(OCH_2CF_3)_2$ **43c**	54
(d)	$CH_3(CH_2)_2C{\equiv}CH$ **42d**	$CH_3(CH_2)_2C{\equiv}C{-}\overset{O}{\overset{\|}{P}}(OCH_2CF_3)_2$ **43d**	62

We found that 50:50 anhydrous pentane and anhydrous ether was a good solvent with sufficient polarity, -78 °C, optimum temperature and n-BuLi, a good base. But because of the lower yields of desired monosubstituted phosphonate and higher yield of trisalkynyl phosphine oxide which was a by-product, there was a need to improve the method to get higher yields of desired monosubstituted phosphonate **43a-d**.

The first attempted synthesis was bis(2,2,2-trifluoroethyl)phosphonooctyne (**43a**), 1-octyne was metalated with n-BuLi to produce a highly reactive lithium octylide at -78 °C. At this temperature the reaction mixture was stirred for 1 hour, warmed to 0 °C and stirred continuously for 15 minutes and then the reaction mixture was cooled back to -78 °C. Bis(2,2,2-trifluoroethyl)phosphorochloridate (**41**) was added dropwise and stirred continuously for one more hour, then two hours at room temperature. A good yield about 61% was obtained as a clear liquid at 110 °C/2mm Hg in vacuum distillation. The pure fraction was characterized by ^{31}P NMR. A single peak appeared at -4.77 ppm. We also observed traces of disubstituted phosphonates at about -17 ppm and tris-octynyl phosphine oxide at about -52 ppm in ^{31}P NMR spectrum. It was realized that formation of by-products, disubstituted phosphonate and trisalkynyl phosphine oxide is due to ability of trifluoroethoxy (CF_3CH_2O-) group in compound **41** as leaving group in addition to the chloride anion.

The proton nuclear magnetic resonance (^{1}H NMR) show similar spectral feature for all phosphonoalkynes **43a-d**. The appearance of signals at 0.9, 2.4 and 4.4 ppm are common features for all phosphonoalkynes **43a-d**. The singlet at 0.9 ppm is a triplet which belongs to the methyl protons, the signal at 2.4 ppm are doublet of triplets belongs to propargylic protons which is coupling to adjacent alkyl protons and four bond long

distance coupling to phosphorus. The signal at 4.4 ppm is a doublet of quartet belongs to the CH_2 group of the trifluoroethyl group. This splitting pattern was due to coupling of methylene proton to fluorine and phosphorus. However, the coupling constants between H-F and H-P are close, overlapping in peaks occurs and splitting looks like quintet instead of double of quartets.
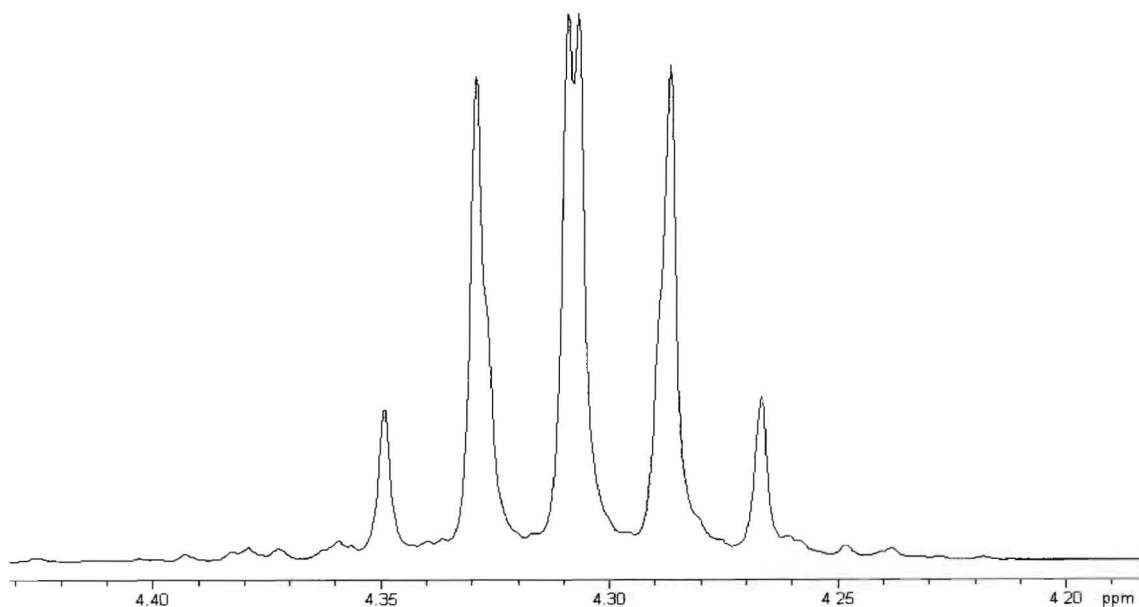

Figure 5. ^{1}H NMR spectrum of methylene protons of CF_3CH_2O group

The ^{13}C NMR spectrum of compound **43c** shows total eight signals, the first four 13.12, 18.79, 21.73, 28.95 ppm are all alkyl carbons. The signals at 67.21 and 107.11 ppm corresponds to α, β sp hybridized carbons of compound **43c**. The α carbon (67.21 ppm) has a very large coupling constant of 328.4 Hz due to its bonding with phosphorus. The β carbon at 107.11 ppm is also doublet, has coupling constant (J) of 58 Hz since it is further away from phosphorus. The signals at 62.59, 122.10 ppm corresponds to CH_2, CF_3 carbons respectively. The splitting patterns of both signals were exhibited as doublets of

quartets. The carbons of CF_3 groups differentiated from the CH_2 by showing a much larger C-F coupling constants about 277 Hz for the CF_3 and 38 Hz for CH_2 group (Figure 6 & 7). The C-P coupling constant between the two groups (CH_2 and CF_3) is very similar (4.2 Hz and 9.85 Hz respectively).
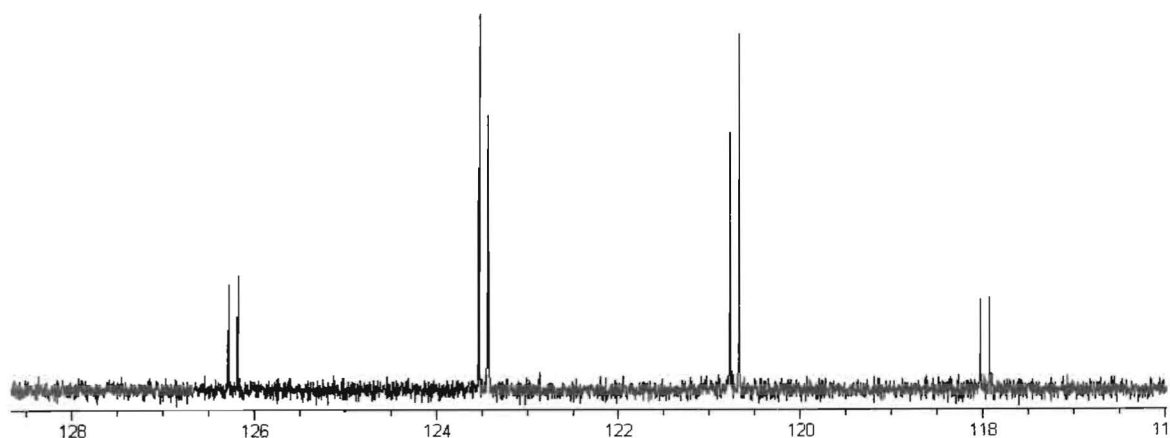

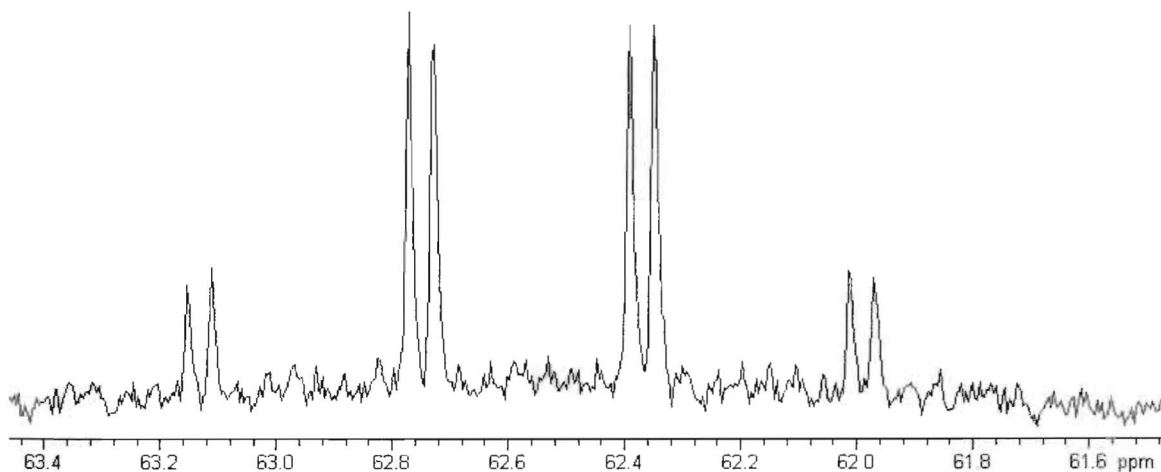**Figure 6.** ^{13}C NMR spectrum of CF_3 in trifluoroethoxy group in compound **43c**

Figure 7. ^{13}C NMR spectrum of CH_2 in trifluoroethoxy group in compound **43c**

An interesting thing to note in the synthesis of phosphonoalkynes was the synthesis of bis(2,2,2-trifluoroethyl)trimethylsilylacetylyl phosphonate (**44**). Here,

trimethylsilyl acetylene was metalated with *n*-BuLi to generate lithium acetylide at -78 °C. The resulting lithium acetylide was treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (**41**) at same temperature. We did not observe bis(2,2,2-trifluoroethyl)trimethylsilylacetylyl phosphonate (**44**) but a major amount of trisethynyl phosphine oxide (**45**) as colorless needle shaped crystals after aqueous workup (Scheme 19).
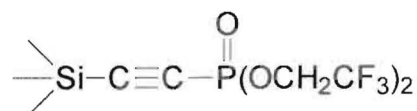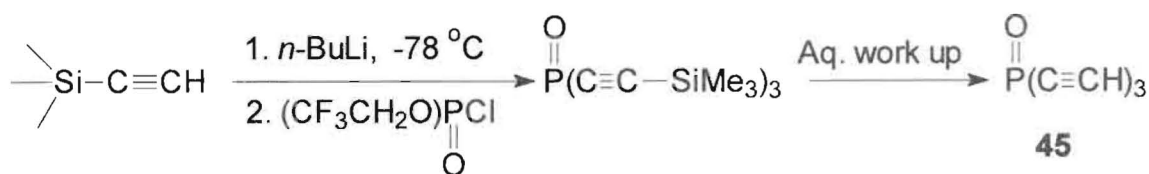
$$\overset{\diagdown}{\underset{\diagup}{}}Si-C\equiv C-\overset{\overset{O}{\|}}{P}(OCH_2CF_3)_2$$

Figure 8. Compound **44**

$$\overset{\diagdown}{\underset{\diagup}{}}Si-C\equiv CH \xrightarrow[\substack{2.\ (CF_3CH_2O)PCl \\ \overset{\|}{O}}]{1.\ n\text{-}BuLi,\ -78\ ^oC} \overset{\overset{O}{\|}}{P}(C\equiv C-SiMe_3)_3 \xrightarrow{Aq.\ work\ up} \overset{\overset{O}{\|}}{P}(C\equiv CH)_3$$

45

Scheme 19

Crystal studies revealed more information in addition to NMR studies. The phosphorus center exhibited a pseudo-tetrahedral geometry with 3 acetylene groups and the double bonded oxygen atom (Figure 9). The packing of crystal was due to hydrogen bonds between the acetylenic hydrogen atoms and the P=O oxygen atom. Three acetylene units are forming strong C—H⋯O hydrogen bonds. Two of the three hydrogen bonds towards each oxygen atom were symmetrical related by the crystallographic mirror plane and were coplanar with each other and the P=O unit. The third C—H⋯O hydrogen bond is at an angle of 67.49 (7) ° to this plane (Figure 10).

The ^{31}P NMR was taken for compound **45**, a single peak was observed at -55 ppm which justifies the literature. The appearance of doublet in proton NMR at 3.3 ppm with

large coupling constant (J) about 12.5 Hz is due to the presence of alkynyl protons which are coupled to phosphorus. In ^{13}C NMR, two signals were observed, one at 77.35 ppm with coupling constant of 233.88 Hz and another at 92.12 ppm with coupling constant of 45.5 Hz. The signal which has larger coupling constant belongs to the α carbon because these are directly attached to phosphorus, other signal belongs to the β carbons which are away from phosphorus resulting in smaller coupling constants.
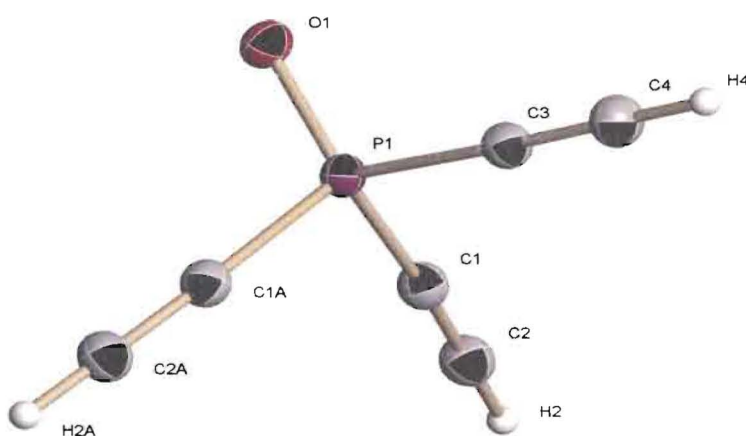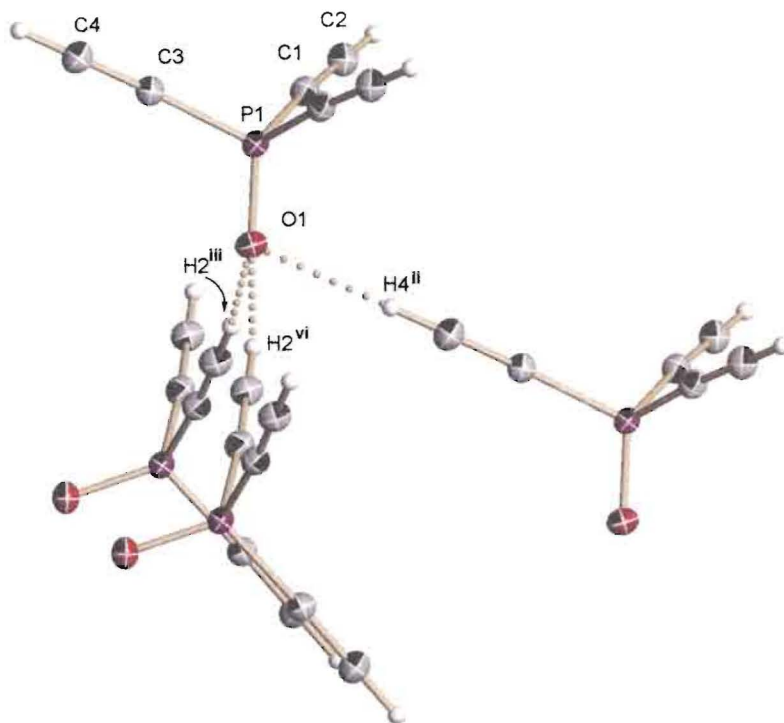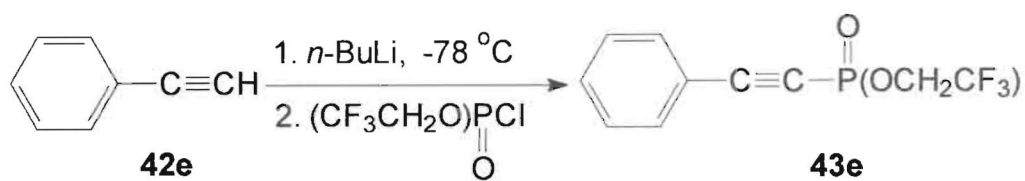

Figure 9. X-ray structure of compound **45**

Figure 10. Hydrogen bonding in compound **45**

Scheme 20

Synthesis of bis(2,2,2-trifluoroethyl)phosphonophenylacetylene (**43e**) was different from other alkynyl phosphonates **43a-d**. We followed the same procedure as we have done for compounds **43a-d**, but the yield was poor. In ^{31}P NMR spectrum of reaction mixture, we observed two major peaks one at -1.9 ppm and other at about -54 ppm. From previous NMR studies of compound **43a-d**, the peak at -52 ppm corresponds to tris(phenylacetyl)phosphine oxide. A small peak was also observed at -4.9 ppm in [31]P

NMR which belongs to the required compound **43e**. The proton NMR also proved the presence of compound **43e.** But we could not isolate the pure product, since it has the same polarity with other by-product which was observed at -1.9 ppm in ^{31}P NMR.
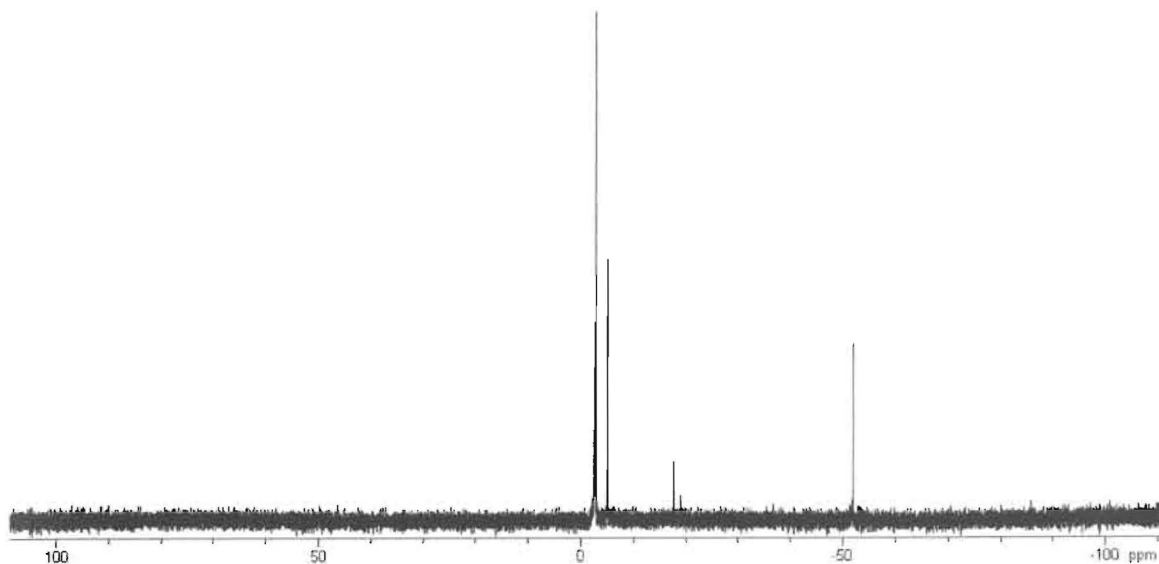

**Figure 11.** ^{31}P NMR spectrum of reaction mixture (Scheme 20)

Diels-Alder Reactions

A) Cycloaddition of bis(2,2,2-trifluoroethyl)phosphonoalkynes with cyclopentadiene

After successful synthesis of bis(2,2,2-trifluoroethyl)phosphonoalkynes, we investigated the Diels-Alder reactions of bis(2,2,2-trifluoroethyl)phosphonoalkynes and achieved moderate yields of bis(2,2,2-trifluoroethyl)vinyl phosphonates.

The first attempted cycloaddition reaction was the synthesis of cycloadduct **46a**, where cyclopentadiene was used as diene. Cyclopentadiene acts as a good diene in Diels-Alder reactions because of its locked *cis*-conformation. Commercially available cyclopentadiene is dicyclopentadiene which is a dimer. We used freshly cracked

cylcopentadiene (monomer) in all cycloaddition reactions. The dimer was cracked and separated into the monomers by distillation (~50 °C) at atmospheric pressure.
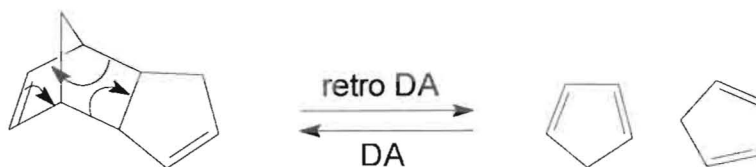
Cracking of dicyclopentadiene

Scheme 21

The procedure began with the addition of one equivalent of cyclopentadiene to 1M concentration of bis(2,2,2-trifluoroethyl)phosphonooctyne **43a** in diglyme and warmed to 40 °C for 24-48 h. There was no reaction except for trace amounts of the product, we believed that cyclopentadiene was not only a diene but also acts as a dienophile so dimerization was predominating the cycloaddition of diene to dienophile.

In attempt to increase the yields of cycloaddition product several variables such as concentration, amount of diene and temperature were explored. We found that 2 equiv. of cyclopentadiene in 0.25M concentration of bis(2,2,2-trifluoroethyl)phosphonooctyne **43a** in diglyme (diethylene glycol dimethyl ether) at 60 °C for 9 h giving better yields (35.2%).

Various literatures [37] showed that cycloaddition reactions give better results when reactions were conducted in sealed tubes. We also adopted this technique for cycloaddtion of bis(2,2,2-trifluoroethyl)phosphonoalkynes **43a-d**. We obtained good yields when solution of 0.25M concentration of bis(2,2,2-trifluoroethyl)phosphonooctyne **43a** in diglyme (diethylene glycol dimethyl ether) was taken with 2 equivalents of

cyclopentadiene were taken in a 10 mL glass tube capped and heated at 110 °C for 6 h in oil bath. Similar yields were obtained as in the reflux method.
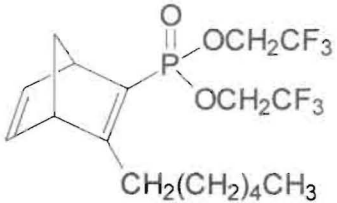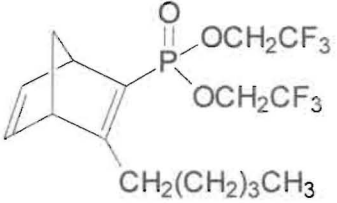
Synthesis of compound **43a**
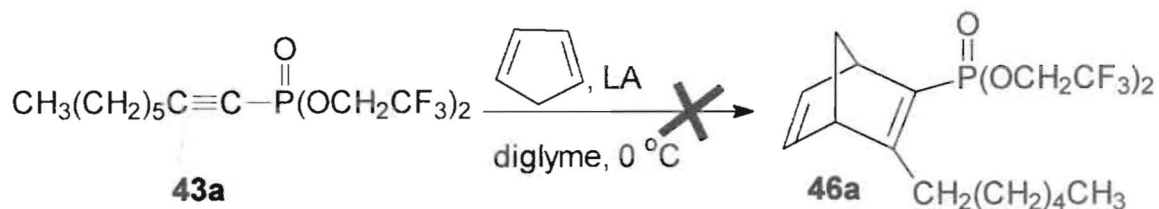
Scheme 22

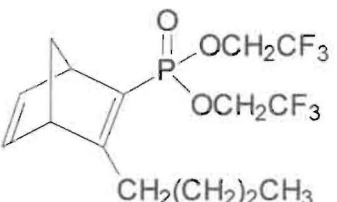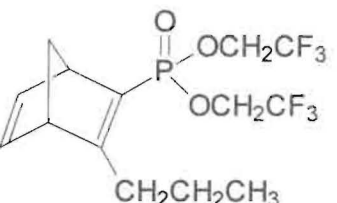LA: Lewis acid

Reaction of alkynyl phosphonate **43a** with cyclopentadiene in presence of $(C_2H_5)_2O$ BF_3, boron trifluoride dietherate at 0 °C afforded no product **46a** (Scheme 22). Samples of reaction mixture was checked TLC periodically for 12 h. We also used titanium tetrachloride, $TiCl_4$ as Lewis acid which resulted no product. The ^{31}P NMR spectrum of reaction mixture after 12 h showed no signals other than starting material.
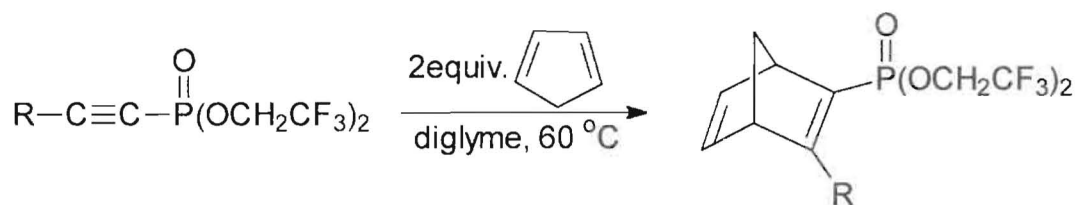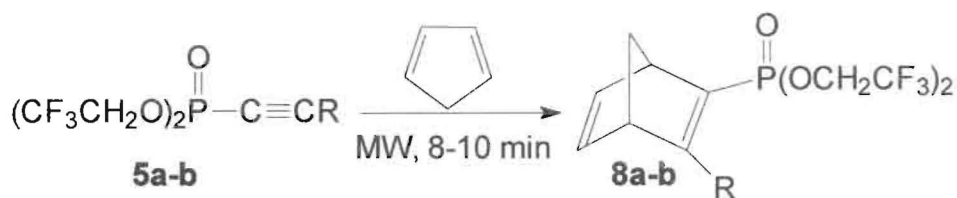

Scheme 23

Table 2. Yields of cycloaddition reaction of bis(2,2,2-trifluoroethyl)phosphonoalkynes with cylcopentadiene

Entry	Phosphonoalkyne	Cycloadducts of Phosphonoalkynes	Isolated Yield (%)
(a)	$CH_3(CH_2)_5C\equiv C-P(OCH_2CF_3)_2$ **43a**	**46a**	35
(b)	$CH_3(CH_2)_4C\equiv C=P(OCH_2CF_3)_2$ **43b**	**46b**	33
(c)	$CH_3(CH_2)_3C\equiv C-P(OCH_2CF_3)_2$ **43c**	**46c**	35.8
(d)	$CH_3(CH_2)_2C\equiv C-P(OCH_2CF_3)_2$ **43d**	**46d**	25

We conducted cycloaddition reactions of compounds **43a-b** under microwave irradiation in solventless conditions.

Scheme 24

The procedure began by transferring alkynyl phosphonate **43a** and one equivalent of cylcopentadiene into a vial, capped and irradiated in domestic microwave for 10 min. Analysis of reaction mixture by GC showed broad peak at 8.1 min retention time (RT) and a small peak at 6.1 min retention time which belongs to starting material. we also observed a peak at 3 min retention time which might be dimmer of cyclopentadine. Though there is no complete conversion of starting material to product, we obtained 55% isolated yield. So the microwave increased the rate of reaction of cycloaddition. The same procedure was followed for compound **43b** to obtain compound **46b**. 50% yield was obtained in 8 minutes.

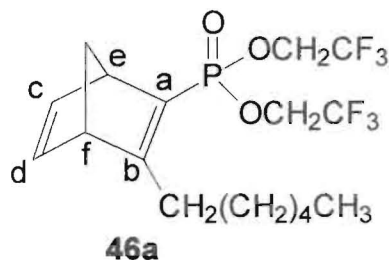The vinyl phosphonates **46a-d** were characterized by ^{1}H, ^{13}C, ^{31}P NMR and MS.

Figure 12. Structure of compound **46a**

The compounds **46a-d** contain two chiral centers which would make the carbons of trifluoroethoxy group non-equivalent, which means that 2 methylene and 2 trifluoro methyl carbons (CF_3) are not equal as they showed up at different but close chemical shifts in the NMR spectrum.
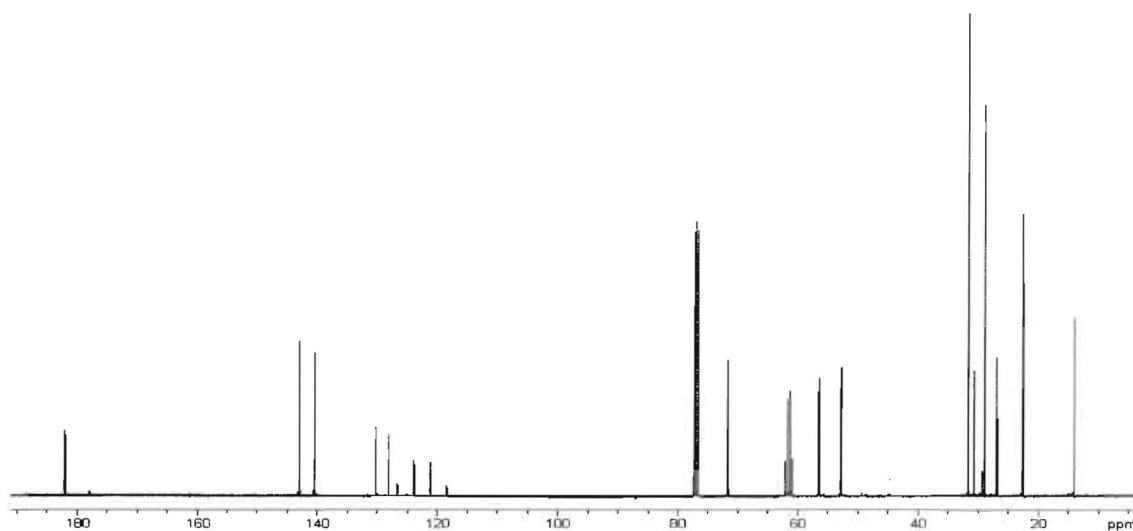
Figure 13. ^{13}C spectrum of compound **46a**

In ^{13}C NMR spectrum of the compound **46a** the CF$_3$ in trifluoroethoxy group does not show up as a doublet of quartets as observed in ^{13}C NMR spectra of phosphonoalkynes **43a-d** but instead are observed as two doublet of quartets, one at 122.46 ppm with coupling constants 9.2 Hz (J$_1$), 277 Hz (J$_2$) and other 122.36 ppm with coupling constants 9.6 Hz (J$_1$), 276.99 Hz (J$_2$) (Figure 13). The splitting pattern of the carbon in CF$_3$ is due to the coupling of carbon to both phosphorus and fluorine.
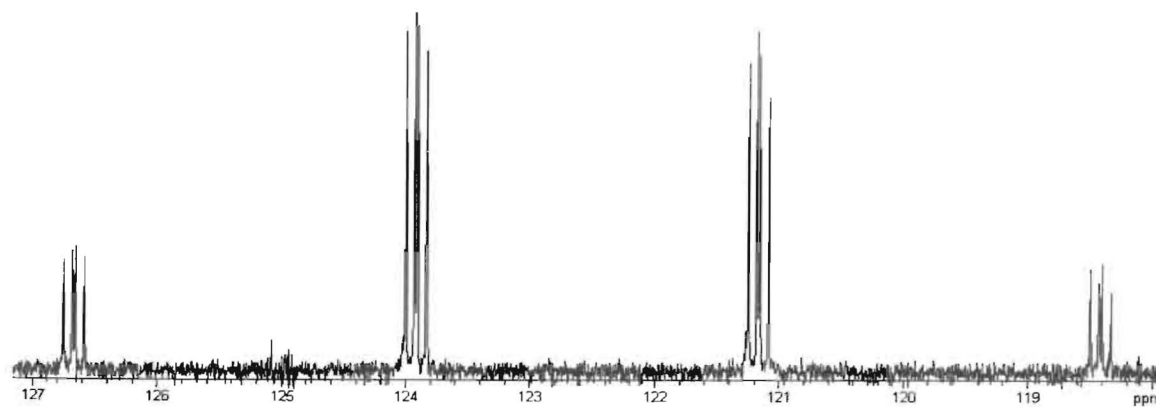

Figure 14. ^{13}C NMR of the CF$_3$ group of the trifluoroethyl groups of compound **46a**

The carbons of CH_2 in trifluoroethoxy group are also non equivalent so they also showed up as two doublets of quartets at two chemical shift one at 61.39 ppm and the other at 61.34 ppm. Due to overlapping they viewed as a quartet of triplets.
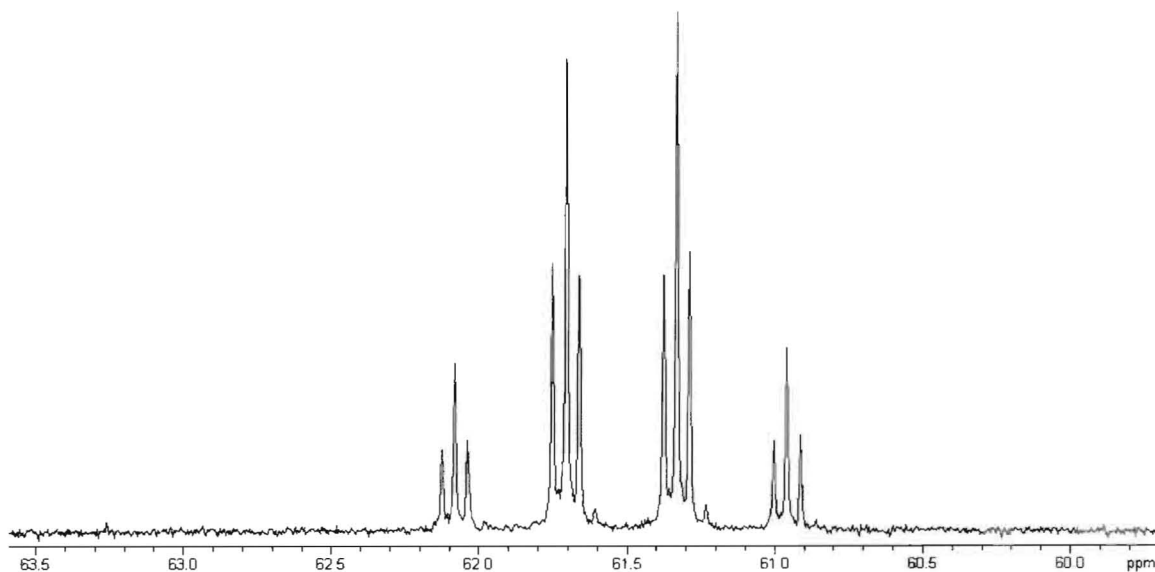

Figure 15. ^{13}NMR of the CH_2 group of the trifluoroethyl groups of compound **46a**

Carbon **a** (compound **46a** in Figure 11) at 129.25 ppm is observed as a doublet because it couples to phosphorus. It has a very large coupling constant 211.09 Hz, which is due to its direct bond to phosphorus as compared to the carbon **b** (compound **46a** in Figure 9) at 181.9 ppm has smaller coupling constant about 19.59 Hz (Figure 17).
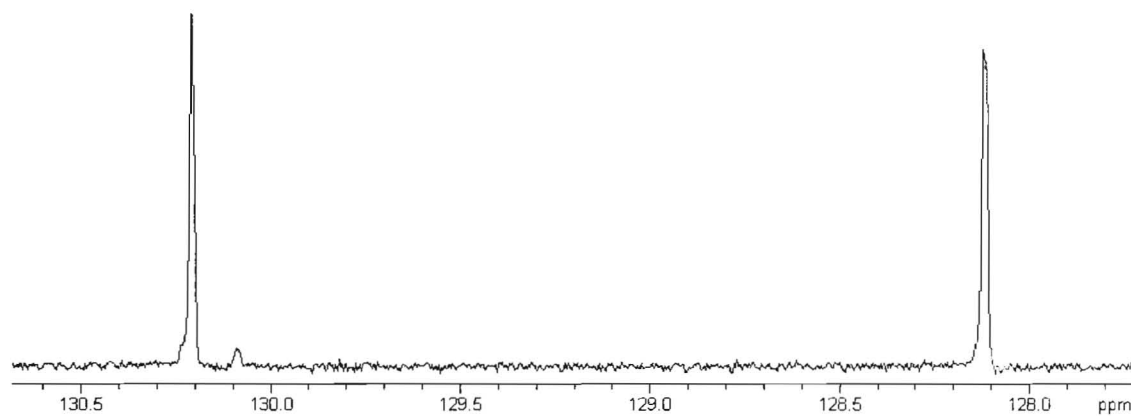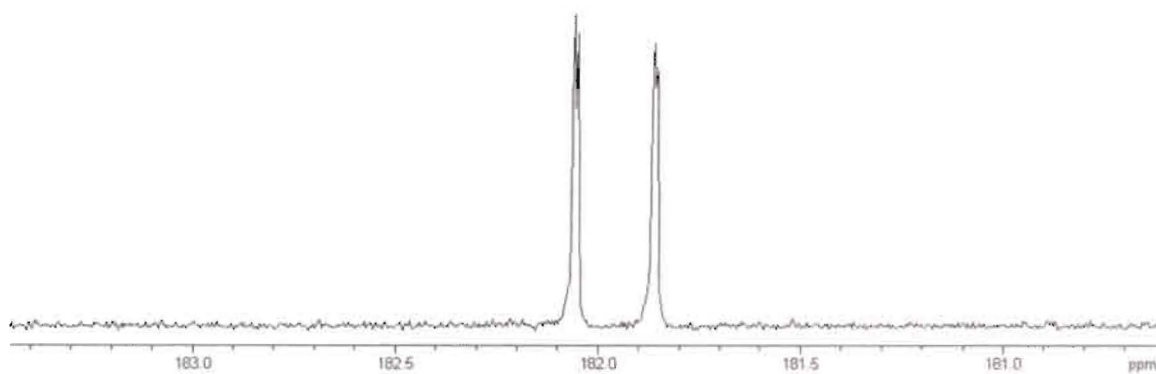
Figure 16. Carbon **a** in compound **46a**

Figure 17. Carbon **b** in compound **46a**

Carbons **c** and **d** of compound **46a** showed up as doublets at 143.55 ppm and other at 143.05 ppm respectively with smaller coupling constants about 2.4 Hz (Figure 18)
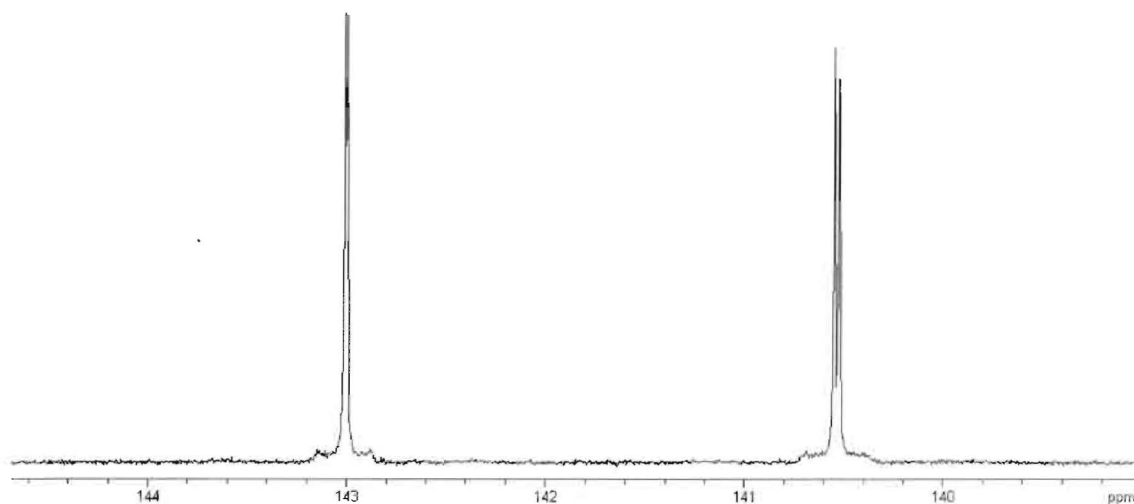
Figure 18. ^{13}C NMR spectrum of carbons **c** and **d** compound **46a**

All alkyl carbons are appearing in the upfield region. Carbons **e** and carbon **f** (Compound **46a** in Figure 13), the 2 chiral centers are observed at 36 ppm and 52 ppm respectively. Carbon **e** has larger C-P coupling constant about 19 Hz comparing to carbon **f** (Figure 12) with smaller coupling constant about 13 Hz. These characteristic splitting patterns are very similar to the rest of the cycloadducts **46b-d** that have been synthesized.

In the mass spectrum of compound **46a**, molecular ion ($M^{+\cdot}$) was found at m/z 420 which is the molecular weight of compound **46a**. The higher abundant fragment peaks were found at 66 and 355 which are retro Diels-Alder fragments cyclopentadiene cation ($C_5H_6{}^+$) and protonated bis(2,2,2,-trifluoroethyl)alkynyl phosphonate cation. The fragment at 401 is due to the elimination of fluorine from parent molecule (Figure 19).
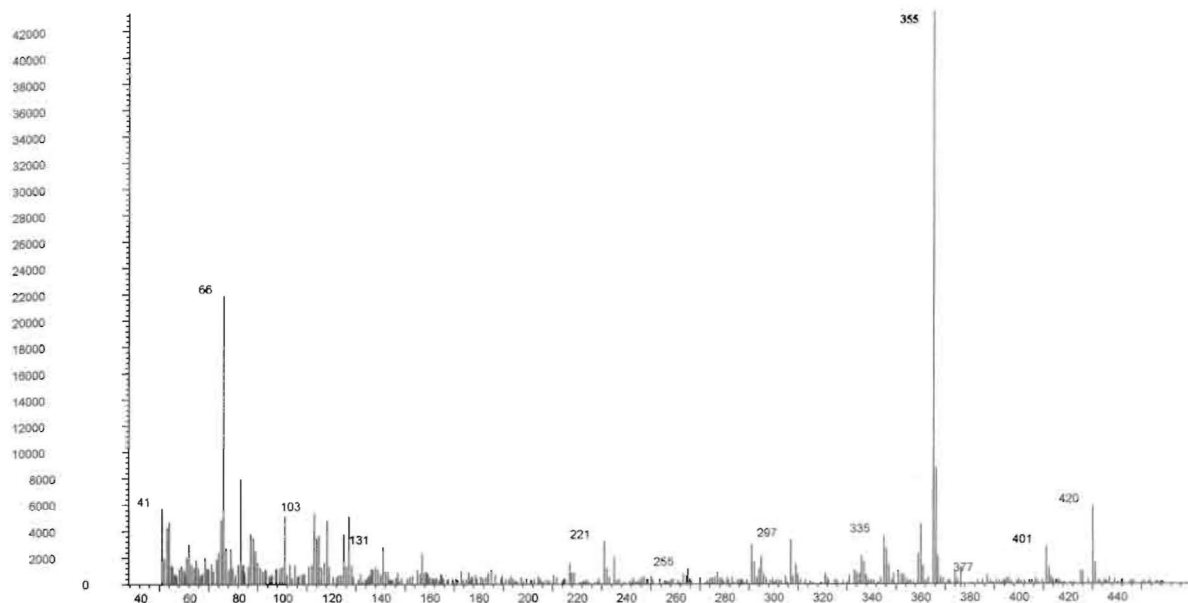
Figure 19. Mass spectrum of compound **46a**

B) Cycloaddition of bis(2,2,2-trifluoroethyl)phosphonoalkynes with
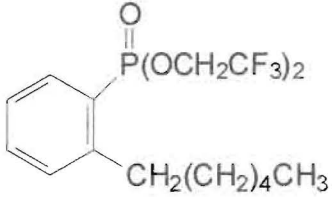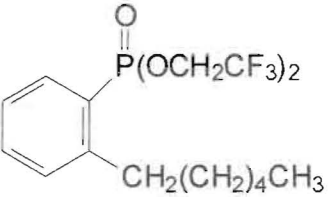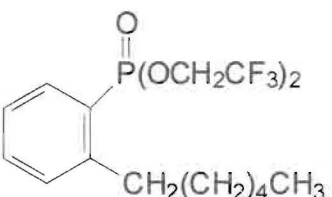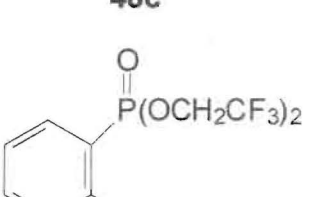
1,3-cyclohexadiene

Initially our intention was to synthesize vinyl phosphonates by cycloaddition of

bis(2,2,2-trifluoroethyl)phosphonoalkynes **43a-d** with 1,3-cyclohexadiene but the

reaction resulted aryl phosphonates at higher temperature. The general reaction as

follows:
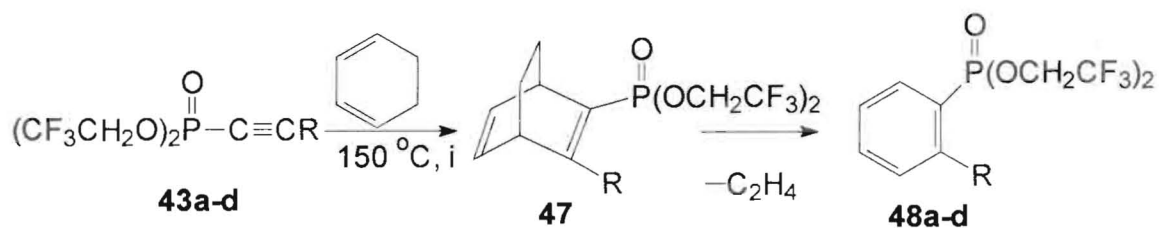
Scheme 24

i = hydroquinone

Table 3. Yields of cycloaddition reaction of bis(2,2,2-trifluoroethyl)phosphono-alkynes with 1,3-cyclohexadiene

Entry	Phosphonoalkyne	Cycloadducts of Phosphonoalkynes	isolated yields (%)
(a)	$CH_3(CH_2)_5C{\equiv}C-P(OCH_2CF_3)_2$ **43a**	**48a**	29%
(b)	$CH_3(CH_2)_4C{\equiv}C-P(OCH_2CF_3)_2$ **43b**	**48b**	25%
(c)	$CH_3(CH_2)_3C{\equiv}C-P(OCH_2CF_3)_2$ **43c**	**48c**	25%
(d)	$CH_3(CH_2)_2C{\equiv}C-P(OCH_2CF_3)_2$ **43d**	**48d**	25%

There was no reaction at low temperatures, the reaction occured at 135 °C where cyclization occured to afford vinyl phosphonate **47a** with resonance signal at +21ppm in ^{31}P NMR, in ^1H NMR spectrum we observed the vinyl protons. We reheated the same reaction mixture at 150 °C for four more hours and a new peak was observed at about +24 ppm in ^{31}P NMR. After isolation, we found that the initial compound at +21 ppm

was vinyl phosphonate, and the compound at +24 ppm was the aryl phosphonate. At higher temperature the vinyl phosphonate aromatized to form more stable aryl phosphonate with elimination of ethylene (C_2H_4).

The synthesis of cycloadducts **48a-d** began by transferring 2 equivalents of 1,3-cyclohexadiene, hydroquinone and bis(2,2,2-trifluoroethyl)phosphonoalkyne **43a-d** to a dried glass tube, flushed with inert gas, capped and heated at 150 °C for 18 h which afforded moderate yields of (~30%) aryl phosphonates **48a-d**.

Hydroquinone is antipolymerizing agent which stops polymerization of 1,3-cyclohexadiene. Addition of hydroquinone improved the yield but not significantly.

The aryl phosphonates were characterized by nuclear magnetic resonance (NMR) spectroscopy, and mass spectroscopy (MS).
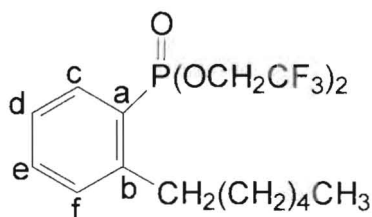
Figure 20. Structure of compound **48c**

The appearance of proton signals at 7.88, 7.54, 7.35 ppm in the ^{1}H NMR spectra are an indication of the protons of phenyl ring (Figure 20). The doublet of doublet of doublets (ddd) signal at 7.88 ppm, which at more downfield is *meta* aromatic proton (**d** in Figure 20) to phosphonate group. This pattern is exhibited because of coupling of the *meta* proton to adjacent *para* and *ortho* aromatic proton and small coupling with phosphorus. Proton signal at 7.54 ppm is *para* aromatic proton which is a doublet of doublet of doublet of doublet (dddd), some peaks are overlapped and appear as a quartet

of triplets. The multiplet at 4.42 ppm belongs to the methylene (CH_2) proton in trifluoroethoxy group, it should show up as doublet of quartets.
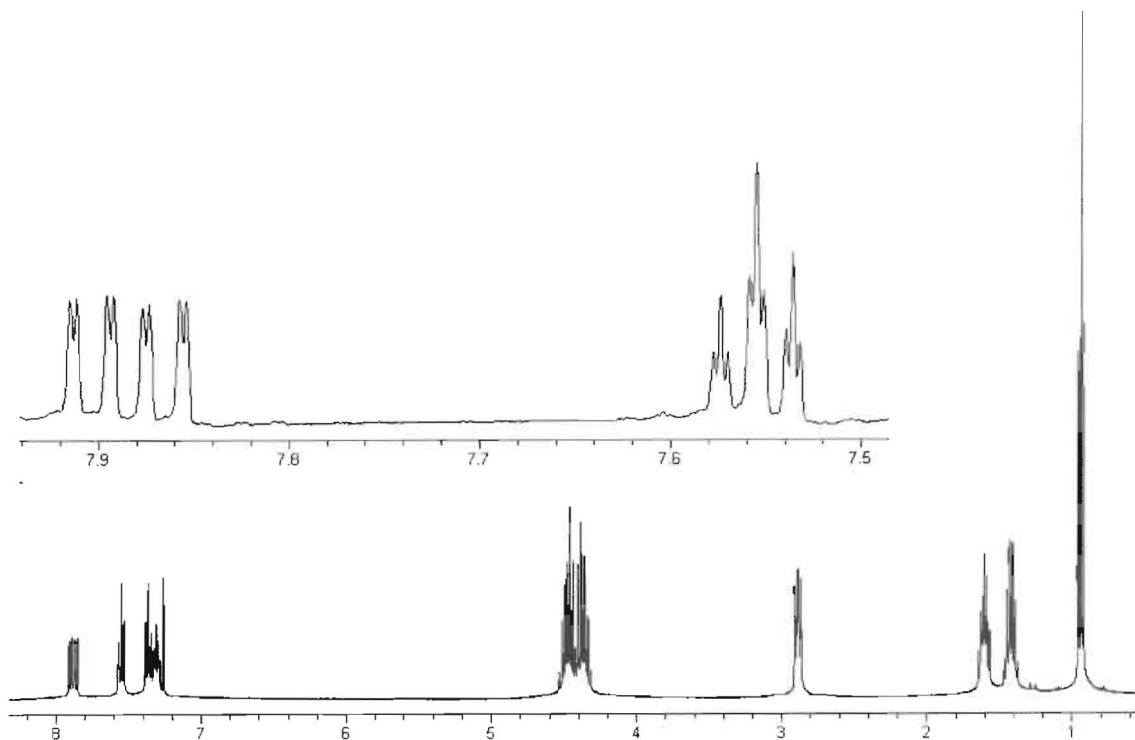
Figure 21. proton NMR spectrum of compound **48c**

The ^{13}C NMR spectra revealed more information, the spectrum of compound **48c** shows both the carbons of the CF_3 group at 122.52 ppm (Figure 24) and CH_2 group at 62.1 ppm as doublets of quartets (Figure 23). The splitting patterns of these two carbons are due to coupling of the carbons to both phosphorus and fluorine. The carbons of CF_3 groups are distinguished from the CH_2 group by a more downfield chemical shift and larger coupling constant (277.06 Hz for the CF_3 and 37.85 Hz for CH_2 group). The carbon-phosphorus coupling constants between the two groups CF_3 and CH_2 very similar (9.2 Hz, 5.1 Hz respectively). These splitting patterns of this compound are similar to other cycloadducts **48a-d**.

Figure 22. ^{13}C NMR spectrum of compound **48c**
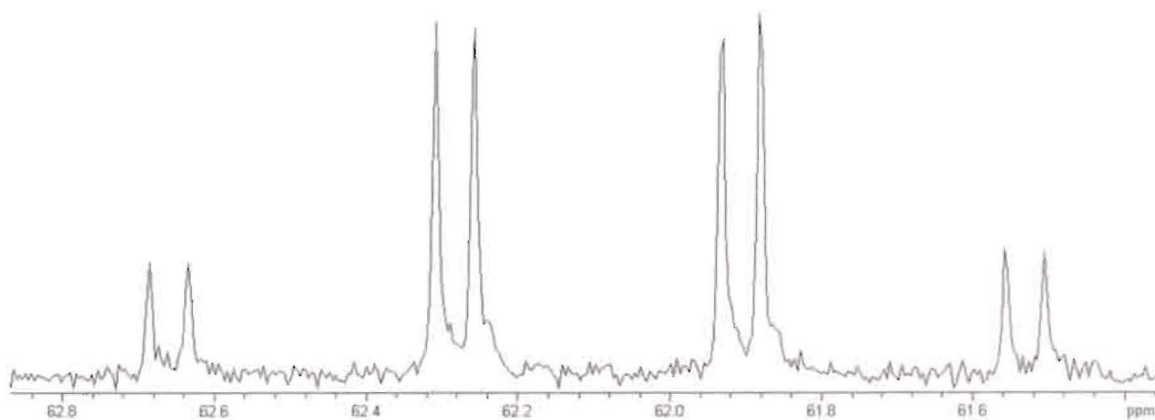
Figure 23. ^{13}C NMR of the CH$_2$ of the trifluoroethoxy groups of compound **48c**

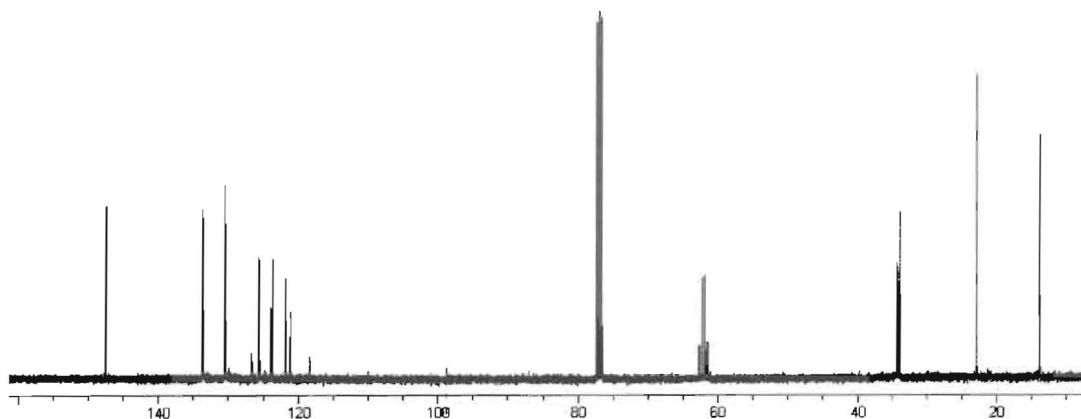Carbon **a** (Figure 20) of an aromatic ring at 122.74 ppm has larger coupling constant about 190.7 Hz comparing to 11.99 Hz carbon **b** (Figure 20) at 147.45 ppm (Figure 22).
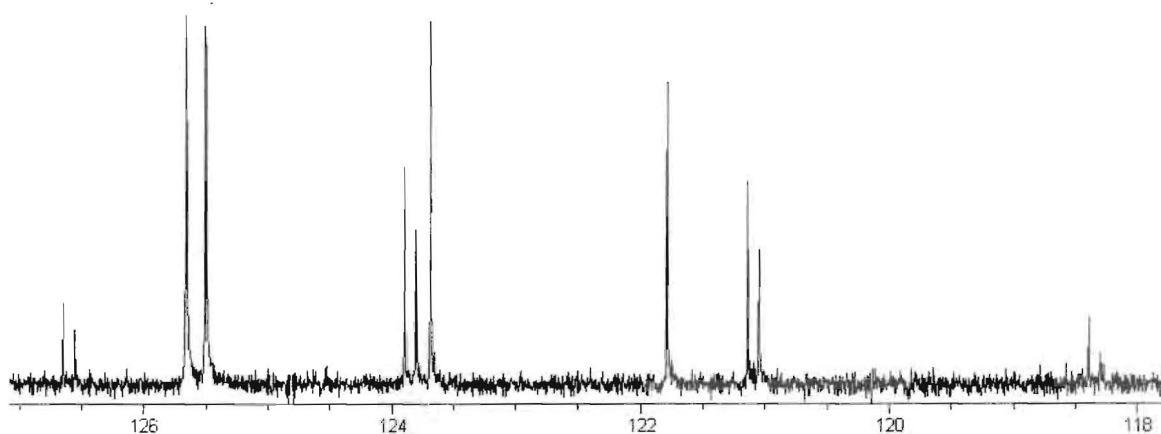
Figure 24. ^{13}C NMR of the CF$_3$ of the trifluoroethoxy groups of compound **48c**

The aromatic carbons **d** and carbon **c** are both doublets with same coupling constants about 16 Hz at 125.6 ppm and 130.5 ppm (Figure 25). The *meta* carbon (carbon **f**) is a doublet with smaller coupling constant about 13.5 Hz and *para* aromatic carbon (carbon **e** in compound **48c**) is singlet at 133.6 ppm.
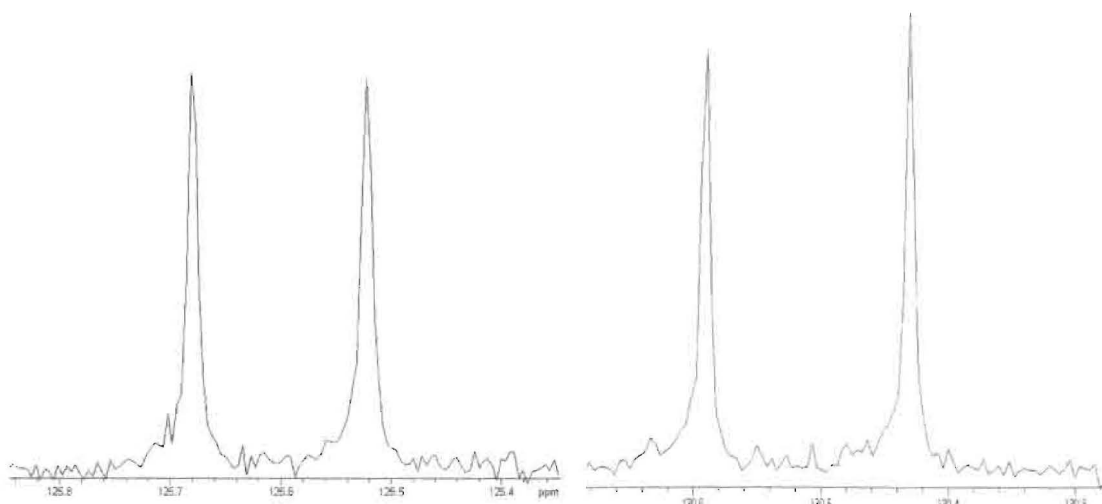
Figure 25. ^{13}C NMR of carbon **d** and carbon **c** compound **48c**

All alkyl carbons are singlets in the up field resonance region but the benzylic carbon which is at 34.22 ppm is a doublet with 4.0 Hz coupling constant.

Conclusion

We have described synthesis of bis(2,2,2-trifluoroethyl)phosphonoalkynes **43a-d** in good isolated yields. The temperature is crucial to the success of reaction. Warming of reaction mixture to 0 ° from -78 °C and recooling to -78 °C before addition of bis(2,2,2-trifluoroethyl)phosphorochloridate (**41**) increasing yield by decreasing the formation of by-products. The use of 1-alkynyl phoshonates in [4+2] cycloaddition reaction for the preparation of vinyl phosphonates **46a-d** and aryl phosphonates **48a-d** also successful with moderate yields. We believe that more yields could be obtained by using microwave irradiation. The cycloaddition of alkynyl phosphonates with 1,3-cycloaddition reaction occur at higher temperature. Our future work includes cycloaddition of bis(2,2,2-trifluoroethyl)phosphonoalkynes with heterocyclic dienes to synthesize heterocyclic phosphonates, which might be useful in various transformations.

Chapter 3

EXPERIMENTAL

General Methods

All reactions were conducted with oven-dried glassware under positive pressure of argon (Ar). Pentane was distilled at 40 °C in calcium hydride (CaH_2). All reactions were distilled at 40 °C in calcium hydride (CaH_2).

Flash Chromatography was performed in glass columns of different sizes packed with Merck grade 200-400 mesh, 60Å silica. Visualization was accomplished with an ultraviolet lamp and stained with 5% phosphomolybdic acid (PMA) in ethanol with heating.

^{1}H NMR spectra were recorded with a Varian Gemini 2000, 400 MHz, and ^{13}C NMR spectra recorded with 100 MHz spectrometer with $CDCl_3$ as a solvent. The ^{1}H NMR chemical shifts were expressed in parts per million (δ) downfield to $(CH_3)_4Si$ (δ = 0), ^{13}C NMR chemical shifts were expressed in parts per million (δ) relative to the central $CDCl_3$ resonance (δ = 77.0) while ^{31}P chemical shifts were reported in parts per million down field from H_3PO_4 (external standard). Coupling constants were reported in Hertz (Hz). Crystal structure determination was performed by :3ruker Smart Apex CCD Diffractometer and structure refinement was done by Shelxtl program.

Bis(2,2,2-trifluroethyl)phosphite (40)

A solution of anhydrous *tert*-butanol (37.0 g, 0.5 mol) in anhydrous dichloromethane (100 mL) was added dropwise to a stirred solution of phosphorus trichloride (43.5 mL, 0.5 mol) in dry dichloromethane (100 mL) over a period of 45 min.

The mixture was maintained for additional 30 min at 0 °C. A solution of anhydrous 2,2,2-trifluoroethanol (100.0 g, 1 mol) in dichloromethane (100 mL) was added to the mixture at 0-5 °C over a period of 30 min. Stirring was continued under a stream of nitrogen at an ambient temperature for 16 h to remove hydrogen chloride. Dichloromethane was removed by distillation at atmospheric pressure. The product was distilled through a Vigreux column.

The product was obtained as a colorless liquid (90.87g, 74%) which was characterized by NMR.

^{1}H NMR (400 MHz, CDCl$_3$) δ 4.45 (dq, J = 8 Hz), 6.82 (d, 1H, J = 760.57 Hz)

Bis(2,2,2-trifluproethyl)phosphorochloridate (41)

To a solution of bis(2,2,2-trifluoroethyl) phosphite (50 g, 203 mmol) in benzene (55 mL), a solution of sulfuryl chloride (20.2 mL, 203 mmol) in benzene (55 mL) was added dropwise at 0 °C over a period of 45 min. After the addition, the mixture was allowed to stir continuously and warmed to room temperature. After 2 h the benzene was removed by rotary evaporation, and the purification was done by vacuum distillation yielding compound 2 (53 g, 93.1%) as a clear liquid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 4.58-4.41 (4H, m).

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

^{31}P NMR δ +6.73

Bis(2,2,2-trifluoroethyl)phosphonooctyne (43a)

A 500 mL, round bottom flask equipped with a magnetic stirring bar, rubber septum and argon inlet was charged with anhydrous pentane (50 mL), anhydrous ether (50 mL) and 1-octyne (7.38 mL, 50 mmol) at -78 °C. To this cooled solution, n-BuLi (1.6 M solution in hexane, 34.4 mL, 55 mmol) was added dropwise and stirred continuously for an hour at the same temperature. After an hour the solution was warmed to 0 °C and stirred for 15 min. The mixture was recooled to -78 °C and bis(2,2,2-trifluoroethyl)phosphorochloridate (9.3 mL, 55 mmol) was added dropwise and stirred overnight. The reaction mixture was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (150 mL). The aqueous layer was washed with ether (3 x 100 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The purification was done by vacuum distillation. The product was obtained as colorless liquid (10.8 g, 61.0%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.899 (t, 3H, J = 6.8 Hz), 1.36 (m, 6H), 1.61 (quintet, 2H, J = 7 Hz), 2.40 (dt, 2H, J$_1$ = 4.6 Hz, J$_2$ = 7 Hz), 4.398 (dq, 4H, J$_1$ = J$_2$ = 8 Hz).

^{13}C NMR δ 13.834, 19.21 (d, J = 4.8 Hz), 22.344, 27.00 (d, J = 4.8 Hz), 28.36, 31.024, 62.54 (dq, J$_1$ = 4.18 Hz, J$_2$ = 37.9 Hz), 67.307 (d, J = 328.8 Hz), 107.213 (d, J = 58.4 Hz), 122.13 (dq, J$_1$ = 10.12, J$_2$ = 275.2 Hz).

^{31}P NMR (162 MHz, CDCl$_3$) δ + 4.71

APCI-MS calculated: 355 (MH$^{+\cdot}$)

Bis(2,2,2-trifluoroethyl)phosphonoheptyne (43b)

A 500 mL, round bottom flask equipped with a magnetic stirring bar, rubber septum and argon inlet was charged with anhydrous pentane (50 mL), anhydrous ether (50 mL) and 1-heptyne (6.58 mL, 50 mmol) at -78 °C. To this cooled solution, n-BuLi (1.6 M solution in hexane, 34.4 mL, 55 mmol) was added dropwise and stirred continuously for an hour at the same temperature. After an hour the solution was warmed to 0 °C and stirred for 15 min. The mixture was recooled to -78 °C and bis(2,2,2-trifluoroethyl)phosphorochloridate (9.3 mL, 55 mmol) was added dropwise and stirred overnight. The reaction mixture was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (150 mL). The aqueous layer was washed with ether (3 x 100 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The purification was done by vacuum distillation. The product was obtained as colorless oily liquid (7.7 g, 45.32%) which was characterized by NMR, MS.

^{1}H NMR (400 MHz, CDCl$_3$) 0.894 (t, 3H, J = 7.2 Hz), 1.34 (m, 4H), 1.60 (q, 2H, J = 7.6 Hz), 2.38 (dt, 2H J = 7.6 Hz), 4.38 (dq, 4H, J$_1$ = J$_2$ = 7.2 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 13.77, 19.25 (d, 4.7 Hz), 22.00, 26.77, 30.85, 62.62 (dq, J$_1$ = 4.1 Hz, J$_2$ = 37.9 Hz), 67.37 (d, J = 329.2 Hz), 107.26 (d, J = 58.3 Hz), 122.14 (dq, J$_1$ = 10.5, J$_2$ = 275 Hz).

^{31}P NMR δ -4.66

ESI-MS calculated (solvents: acetonitrile, H$_2$O): m/z 339.8 (M$^+$)

Bis(2,2,2-trifluoroethyl)phosphonohexyne (43c)

A 500 mL, round bottom flask equipped with a magnetic stirring bar, rubber septum and argon inlet was charged with anhydrous pentane (50 mL), anhydrous ether (50 mL) and 1-hexyne (5.6 mL, 50 mmol) at -78 °C. To this cooled solution n-BuLi (1.6 M solution in hexane, 34.4 mL, 55 mmol) was added dropwise and stirred continuously for an hour at the same temperature. After an hour the solution was warmed to 0 °C and stirred for 15 min. The mixture was recooled to -78 °C and bis(2,2,2-trifluoroethyl)phosphorochloridate (9.3 mL, 55 mmol) was added dropwise and stirred overnight. The reaction mixture was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (150 mL). The aqueous layer was washed with ether (3 x 100 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The purification was done by vacuum distillation. The product was obtained as a clear oily liquid (8.89 g, 54.5 %).

^{1}H NMR(400 MHz, CDCl$_3$) δ 0.84 (t, 3H, J = 7.4 Hz), 1.35 (sextet, 2H, J = 7.2 Hz), 1.52 (quintet, 2H, J = 7.2 Hz), 2.32 (dt, 2H, J$_1$ = 4.8 Hz, J$_2$ = 7.2 Hz), 4.31 (dq, J$_1$ = J$_2$ = 8 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 13.12, 18.79 (d, J = 4.8 Hz), 21.73, 28.95 (d, J = 2.4 Hz), 62.49 (dq, J$_1$ = 4.0 Hz, J$_2$ = 37.9 Hz), 67.21 (d, J = 328.4 Hz), 107.11(d, J = 58 Hz), 122.10 (dq, J = 275 Hz).

^{31}P NMR (162 MHz, CDCl$_3$) δ -4.67

ESI-MS calculated (solvents: acetonitrile, H$_2$O): m/z 325.8 (M$^+$)

Bis(2,2,2-trifluoroethyl)phosphonopentyne (43d)

A 500 mL, round bottom flask equipped with a magnetic stirring bar, rubber septum and argon inlet was charged with anhydrous pentane (50 mL), anhydrous ether (50 mL) and 1-pentyne (4.9 mL, 50 mmol) at -78 °C. To this cooled solution, n-BuLi (1.6 M solution in hexane, 34.4 mL, 55 mmol) was added dropwise and stirred continuously for an hour at the same temperature. After an hour the solution was warmed to 0 °C and stirred for 15 min. The mixture was recooled to -78 °C and bis(2,2,2-trifluoroethyl)phosphorochloridate (9.3 mL, 55 mmol) was added dropwise and stirred overnight. The reaction mixture was then quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (150 mL). The aqueous layer was washed with ether (3 x 100 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The purification was done by vacuum distillation. The product was obtained as a clear liquid (9.8 g, 62.8%) and characterized by NMR, MS.

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.96 (t, 3H, J = 7.4 Hz), 1.59 (sextet, 2H, J = 7.2 Hz), 2.33 (dt, 2H, J$_1$ = 4.8 Hz, J$_2$ = 7 Hz), 4.35 (dq, 4H, J$_1$ = J$_2$ = 8 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 12.73, 20.39, 20.72 (d, J = 4.8 Hz), 62.31 (dq, J$_1$ = 4 Hz, J$_2$ = 38.0), 67 (d, J$_1$ = 329.44 Hz), 106.79 (d, J = 58.37 Hz), 122.04 (dq, J$_1$ = 10.19, J$_2$ = 276.79 Hz).

^{31}P NMR (162 MHz, CDCl$_3$) δ -4.87 ppm

ESI-MS calculated (solvents: acetonitrile, H$_2$O): m/z 311.8 (M$^+$)

Diels-Alder reactions

A) cycloaddition reactions of bis(2,2,2-trifluoroethyl)phosphonoalkynes with cyclopentadiene

Synthesis of compound 46a

A solution of bis(2,2,2-trifluoroethyl)phosphonooctyne (**43a**) (5 mmol, 1.77 g) in diglyme (1.25 mL) and freshly prepared cyclopentadiene (10 mmol, 0.66 g) were transferred to 50 mL capacity round bottom flask. This was heated at 60 °C for 9 h with continuous stirring. The reaction was cooled, quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (25 mL). The combined aqueous layers were washed with ether (3 x 20 mL). The combined organic extracts were washed with saturated sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The reaction mixture was purified by flash column using hexane/ethyl acetate (6:1). The pure product was obtained as a pale yellow liquid (0.736 g, 35 %).

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.867 (t, 3H, J = 7.1Hz), 1.46 (m, 8H), 2.05(m, 2H) 2.56 (m, 2H), 3.61 (m, 1H), 3.82 (m, 1H), 4.25 (m, 4H), 6.69 (dd, 1H, J$_1$ = 2.3 Hz, J$_2$ = 5.04 Hz), 6.82 (dd, J$_1$ = 2.42 Hz, J$_2$ = 5.20 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 13.98, 22.51, 26.85 (d, J = 2.4 Hz), 28.96, 30.66 (d, J = 2.8 Hz), 31.57, 36.49 (d, J = 19.2 Hz), 52.79 (d, J = 13.2 Hz), 61.50 (dq, J$_1$ = 4.4 Hz, J$_2$ = 37.7 Hz), 61.54 (dq, J$_1$ = 4.4 Hz, J$_2$ = 37.7 Hz), 71.70 (d, J = 6.4 Hz), 122.58 (dq, J$_1$ = 9.2 Hz, J$_2$ = 277.06 Hz), 122.51 (dq, J$_1$ = 9.9 Hz, J$_2$ = 276.99 Hz), 129.17 (d, J = 210.3 Hz), 140.54 (d, J= 2.4 Hz), 143.0, 181.96 (d, J = 19.59 Hz).

^{31}P NMR (162 MHz, CDCl$_3$) δ +21.977

EI-MS calculated: m/z 420 (M$^{+\cdot}$), 355 ([M-F]$^{+\cdot}$), 401 ([MH-C$_5$H$_6$]$^{+\cdot}$), 66 ([C$_5$H$_6$]$^{+\cdot}$).

Synthesis of compound 46b

A solution of bis(2,2,2-trifluoroethyl)phosphonoheptyne (**43b**) (5 mmol, 1.7 g) in diglyme and freshly prepared cyclopentadiene (10 mmol, 0.66 g) were transferred to 50 mL capacity round bottom flask, this was heated at 60 $^{\circ}$C for 9 h with continuous stirring. The reaction was cooled, quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and organic layer was washed with ether (3 x 20 mL). The combined aqueous layers were washed with ether. The combined organic extracts were washed with saturated sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The reaction mixuture was purified by flash column using hexane/ethyl acetate (6:1). The pure products was obtained as a pale yellow liquid (0.67 g, 33%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.76 (t, 3H, J = 7.1Hz), 1.35 (m, 6H), 1.85 (m, 2H), 2.5 (m, 2H), 3.69 (m, 1H), 3.49 (m, 1H), 4.2 (m, 4H), 6.62 (dd, 1H, J$_1$ = 2.29 Hz, J$_2$ = 5.04 Hz), 6.69 (dd, J$_1$ = 2.47 Hz, J$_2$ = 5.03 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 13.5, 22.2, 26.33 (d, J = 2.0 Hz), 30.38 (d, J = 2.8 Hz), 31.22, 52.62 (d, J = 13.59 Hz), 56.36 (d, J = 19.19 Hz), 61.34 (dq, J$_1$ = 4.3, J$_2$ = 37.71 Hz), 61.39 (dq, J$_1$ = 4.4 Hz, J$_2$ = 37.77 Hz), 71.48 (d, J = 6.4 Hz), 122.43 (dq, J$_1$ = 9.7 Hz, J$_2$ = 276.93 Hz), 122.46 (dq, J$_1$ = 9.19 Hz, J$_2$ = 276.93 Hz), 128.97 (d, J = 211.1), 140.35 (d, J = 2.4 Hz), 142.78, 181.91 (d, J = 19.59 Hz).

^{31}P NMR (162 MHz, CDCl$_3$) δ +21.87

EI-MS calculated: m/z 406 (M$^+$), 387 ([M-F]$^{+\cdot}$), 341 ([MH-C$_5$H$_6$]$^{+\cdot}$), 66 ([C$_5$H$_6$]$^{+\cdot}$).

Synthesis of compound 46c

A solution of bis(2,2,2-trifluoroethyl)phosphonohexyne (**43c**) (5 mmol, 1.63 g) in diglyme and freshly prepared cyclopentadiene (10 mmol, 0.66 g) were transferred to 50 mL capacity round bottom flask. This was heated at 60 °C for 9 h with continuous stirring. The reaction was cooled, quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (25 mL). The combined aqueous layers were washed with ether (3 x 20 mL). The combined organic extracts were washed with saturated sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The reaction was purified by flash column using hexane/ethyl acetate (6:1). The pure product was obtained as a pale yellow liquid (0.71 g, 35.8 %).

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.894 (t, 3H, J = 7.13 Hz), 1.38 (m, 4H), 3.99 (m, 2H), 2.63 (m, 2H), 3.6 (m, 1H), 3.81 (m, 1H), 4.25 (m, 4H), 6.68 (d, 1H, J$_1$ = 3.0 Hz, J$_2$ = 5.0 Hz), 6.82 (dd, 1H, J$_1$ = 3.0, J$_2$ = 5.0 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 13.89, 29.07 (d, J = 2.4 Hz) 30.47 (d, J = 3.01), 52.85 (d, J = 13.59 Hz), 56.54 (d, J = 19.3 Hz), 61.55 (dq, J$_1$ = 4.7 Hz, J$_2$ = 37.7 Hz), 61.57 (dq, J$_1$ = 5.05 Hz, J$_2$ = 37.72 Hz), 71.77 (d, J = 6.4 Hz), 122.535 (dq, J$_1$ = 10, J$_2$ = 277.06 Hz), 122.62 (dq, J$_1$ = 9.2 Hz, J$_2$ = 277.06 Hz), 129.21 (dq, J = 210.29 Hz), 140.59 (d, J = 2.4 Hz), 143.0, 181.99 (d, J = 19.99 Hz).

^{31}P NMR (400 MHz, CDCl$_3$) δ +21.9

EI-MS calculated: m/z 392 (M$^+$), 373 ([M-F]$^{+\cdot}$), 327 ([MH-C$_5$H$_6$]$^{+\cdot}$), 66 ([C$_5$H$_6$]$^{+\cdot}$).

Synthesis of compound 46d

A solution of bis(2,2,2-trifluoroethyl)phosphonopentyne (**43d**) (5 mmol, 1.63 g) in diglyme and freshly prepared cyclopentadiene (10 mmol, 0.66 g) were transferred to 50 mL capacity round bottom flask. This was heated at 60 $^\circ$ C for 7 h with continuous stirring. The reaction was cooled, quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (25 mL). The combined aqueous layers were washed with ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. After filtration the solvent was removed by rotary evaporation. The reaction was purified by flash column using hexane/ethyl acetate (6:1). The pure product was obtained as pale yellow liquid (0.4751 g, 25.0%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (t, 3H, J = 7.4 Hz), 1.42 (m, 2H), 2.00 (m, 2H), 2.62 (m,2H), 3.38 (m, 1H), 3.82 (m, 1H), 4.25 (m, 4H), 6.68 (dd, 1H, J$_1$ = 3.6 Hz, J$_2$ = 4.9 Hz), 6.82 (dd, 1H, J$_1$ = 3.93 Hz, J$_2$ = 5.2 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 13.76, 20.26 (d, J = 2.4 Hz), 32,52 (d, J = 3.2 Hz), 52.87 (d, J = 13.59 Hz), 56.51 (d, J = 19.2 Hz), 61.56 (dq, J$_1$ = 4.6 Hz, J$_2$ = 37.75 Hz), 61.61 (dq, J$_1$ = 4.6, J$_2$ = 37.75 Hz), 71.82 (d, J = 6.4 Hz), 122.51 (dq, J$_1$ = 9.6 Hz, J$_2$ = 277.06 Hz), 122.57 (dq, J$_1$ = 9.2 Hz, J$_2$ = 277.06 Hz).

^{31}P NMR (162 MHz, CDCl$_3$ δ + 22.00 ppm

EI-MS calculated: m/z 378 (M$^{+\cdot}$), 359 ([M-F]$^{+\cdot}$), 313 ([MH-C$_5$H$_6$]$^{+\cdot}$), 66 ([C$_5$H$_6$]$^{+\cdot}$).

B) B) cycloaddition reactions of bis(2,2,2-trifluoroethyl)phosphonoalkynes with 1,3-Cyclohexadiene

Synthesis of compound 48a

Bis(2,2,2-trifluoroethyl)phosphonooctyne (**43a**) (5 mmol, 1.77 g) 1,3-cyclohexadiene (10 mmol, 0.95 mL) and hydroquinone (140 mg) were transferred to 50 mL capacity glass tube, flushed with argon gas and capped. This tube was heated at 150 °C in oil bath for 18 h. The reaction mixture was cooled and washed with water (3 x 25 mL) to remove hydroquinone. The combined aqueous layers were removed and washed with ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The reaction mixture was purified by flash column using hexane/ethyl acetate (6:1). The pure product was obtained as a pale yellow liquid (0.59 g, 29 %).

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (t, 3H, J = 7.2 Hz) 1.34 (m, 6H) 1.61 (m, 2H) 2.87 (m, 2H) 4.25 (m, 4H) 7.29 (dddd, 1H, J_1 = 7.1, J_2 = 7.1, J_3 = 4.5, J_4 = 1.1 Hz) 7.32 (m, 1H) 7.50 (dddd, 1H, J_1 = 7.62, J_2 = 7.62, J_3 = 1.51, J_4 = 1.51 Hz) 7.88 (ddd, 1H, J_1 = 14.85, J_2 = 7.26, J_3 =1.42 Hz)

^{13}C NMR (100 MHz, CDCl$_3$) δ 14.15 (s) 22.67 (s) 29.5 (s) 31.71 (s) 31.84 (s) 34.53 (d, J = 3.6 Hz) 62.11 (dq, J_1 =6.8, J_2 = 37.91 Hz) 122.48 (dq, J_1 =9.3, J_2 =277.1 Hz) 122.77 (d, J = 190.31 Hz) 124.72 (d, J = 15.99 Hz) 130.51 (d, J = 16. 39 Hz) 133.65 (d, J =11.2 Hz) 133.72 (s) 147.5 (d, J = 11.99 Hz)

^{31}P NMR (162 MHz, CDCl$_3$) δ +22.087

EI-MS calculated: m/z 406 (M$^+$), 387 ([M-F]$^+$), 349 ([M-C$_4$H$_9$]$^+$)

Synthesis of compound 48 b

Bis(2,2,2-trifluoroethyl)phosphonoheptyne (**43b**) (5 mmol, 1.7 g), 1,3-cyclohexadiene (10 mmol, 0.95 mL) and hydroquinone (140 mg) were transferred to 50 mL capacity glass tube, flushed with argon gas and capped tightly. This tube was heated at 150 °C in oil bath for 18 h. The reaction mixture was cooled and washed with water (3 x 25 mL) to remove hydroquinone. The combined aqueous layers were removed and washed with ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The reaction was purified by flash column using hexane/ethyl acetate (6:1). The pure product was obtained as a pale yellow liquid (0.49 g, 25%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.898 (t, 3H, J = 7.05 Hz), 1.36 (m, 2H), 1.63 (m, 2H), 2.90 (m, 2H), 4.42 (m, 4H), 7.3 (dddd, 1H, J$_1$ = 7.12 Hz, J$_2$ = 7.12 Hz, J$_3$ = 4.5 Hz, J$_3$ = 4.5 Hz, J$_4$ = 1.02 Hz), 7.36 (m, 1H), 7.55 (dddd, 1H, J$_1$ = 7.65 Hz, J$_2$ = 7.65 Hz, J$_3$ = 1.56 Hz, J$_4$ = 1.56 Hz), 7.88 (ddd, 1H, J$_1$ = 15.21 Hz, J$_2$ = 7.81 Hz, J$_3$ = 1.40 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 14.15, 22.65, 29.5, 31.77 (d, J = 12.4 Hz), 34.53 (d, J = 3.6 Hz), 62.11 (dq, J$_1$ = 6.8 Hz, J$_2$ = 37.91 Hz), 122.48 (dq, J$_1$ = 9.3 Hz, J$_2$ = 277.1 Hz), 122.77 (d, J = 190.31 Hz), 124.72 (d, J = 15.99 Hz), 130.51 (d, J = 16.39 Hz), 133.65 (d, J = 11.19 Hz), 133.72, 147.5 (d, J = 11.99 Hz).

^{31}P NMR (162 MHz, CDCl$_3$) δ + 22.08

EI-MS calculated: m/z 392 (M$^+$), 373 ([M-F]$^{+\cdot}$), 349 ([M-C$_3$H$_7$]$^{+\cdot}$)

Synthesis of compound 48c

Bis(2,2,2-trifluoroethyl)phosphonohexyne **(43c)** (5 mmol, 1.63 g), 1,3-cyclohexadiene (10 mmol, 0.95 mL) and hydroquinone (140 mg) were transferred to 50 mL capacity glass tube, flushed with argon gas and capped tightly. This tube was heated at 150 °C in oil bath for 18 h. The reaction mixture was cooled and washed with water (3 x 25 mL) to remove hydroquinone. The combined aqueous layers were removed and washed with ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The reaction was purified by flash column using hexane/ethyl acetate (6:1). The pure product was obtained as a pale yellow liquid (0.47 g, 25 %).

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.932 (t, 3H, J = 7.32 Hz), 1.42 (sextet, 2H, J = 7.4 Hz), 1.60 (m, 2H), 2.88 (dt, 2H, J$_1$ = 1.2 Hz, J$_2$ = 8 Hz), 4.42 (m, 4H), 7.3 (dddd, 1H, J$_1$ = 7.6 Hz, J$_2$ =7.6 Hz, J$_3$ = 4.4 Hz, J$_4$ = 1.12 Hz), 7.34 (m, 1H), 7.54 (dddd, 1H, J$_1$ = 7.6 Hz, J$_2$ = 7.6 Hz, J$_3$ =1.47 Hz, J$_4$ =1.47 Hz), 7.88 (ddd, 1H, J$_1$ = 15.2 Hz, J$_2$ = 7.7 Hz, J$_3$ = 1.3 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 13.9, 22.9, 34.23 (d, J = 4.0 Hz), 62.1 (dq, J$_1$ =5.1 Hz, J$_2$ = 37.85 Hz), 122.52 (dq, J$_1$ = 9.2 Hz, J$_2$ = 277.1 Hz), 122.74 (d, J = 190.7), 122.58 (d, J = 16 Hz), 130.52 (d, J = 16 Hz), 133.69, 133.64 (d, J = 13.2 Hz).

^{31}P NMR (162 MHz, CDCl$_3$) δ + 24.086

EI-MS calculated: m/z 378 (M$^+$), 359 ([M-F]$^{+\cdot}$), 349 ([M-C$_2$H$_5$]$^{+\cdot}$).

Synthesis of compound 48d

Bis(2,2,2-trifluoroethyl)phosphonopentyne (**43d**) (5 mmol, 1.56 g), 1,3-cyclohexadiene (10 mmol, 0.95 mL) and hydroquinone (140 mg) were transferred to 50 mL capacity glass tube, flushed with argon gas and capped tightly. This tube was heated at 150 °C in oil bath for 18 h. The reaction mixture was cooled and washed with water (3 x 25 mL) to remove hydroquinone. The combined aqueous layers were removed and washed with ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. After filtration the solvent was removed by rotary evaporation. The reaction mixture was purified by flash column using hexane/ethyl acetate (6:1). The pure product was obtained as pale yellow liquid (0.46 g, 25%). which was characterized by NMR, MS.

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.998 (t, 3H, J = 7.41), 1.66 (sextet, 2H, J = 7.47 Hz), 2.86 (m, 4H), 4.25 (m, 4H), 7.30 (dddd, 1H, J$_1$ = 7.6 Hz, J$_2$ = 7.6 Hz, J$_3$ = 4.3 Hz, J$_4$ = 1.1 Hz) 7.37 (m, H), 7.56 (dddd, 1H, J$_1$ = 7.6 Hz, J$_2$ = 7.6 Hz, J$_3$ = 1.47 Hz, J$_4$ = 1.1 Hz), 7.88 (ddd, 1H, J$_1$ = 15.29 Hz, J$_2$ = 7.78 Hz, J$_3$ = 1.37 Hz).

^{13}C NMR (100 MHz, CDCl$_3$) δ 14.2, 24.93, 36.42 (d, J = 4.0), 62.12 (dq, J$_1$ = 5.1 Hz, J$_2$ = 37.91 Hz), 122.49 (dq, J$_1$ = 9.5 Hz, J$_2$ = 277.06 Hz), 122.86 (d, J = 190.71), 125.66 (d, 15.99), 130.53 (d, J = 15.99 Hz), 133.64 (d, J = 7.6), 133.71, 147.24 (d, J = 11.99 Hz).

^{31}P NMR (162 MHz, CDCl$_3$) δ +24.03 ppm

EI-MS calculated: m/z 364 (M$^+$), 349 ([M-CH$_3$]$^{+\cdot}$).

Synthesis of trisethynyl phosphine oxide (45a)

To a solution of trimethylsilyl acetylene (5mmol, 0.71 mL) in anhydrous ether (5 mL) and anhydrous pentane (7.5 mL), n-BuLi, 1.6 M solution in hexane (6 mmol, 3.8 mL) was added drpwise at -78 °C. The reaction mixture was stirred continuously for 1 hour. After one hour bis(2,2,2-trifluoroethyl)phosphorochloridate (**41**) (6 mmol, 1 mL) was added dopwise at -78 °C. The reaction mixture was stirred overnight.

The reaction mixture was quenched with saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (25 mL). The combined aqueous layer was washed with ether (3 x 20 mL). The combined organic extracts were washed with saturated sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. After filtration solvent was removed by rotary evaporation. The reaction mixture was purified by flash column using hexane/ethyl acetate (6:1). The pure product was obtained as colorless crystals (0.15 g, 24.6 %). which was characterized by NMR and X-ray crystallography.

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.30 (d, 3H, J = 12.45 Hz)

^{13}C NMR (100 MHz, CDCl$_3$) δ 92.12 (d, J = 45.45 Hz), 77.35 (d, J = 233.88 Hz).

^{31}P NMR (162 MHz, CDCl$_3$) δ -55.3

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Appendix A

Figure 26. ^{31}P NMR spectrum of compound **41**
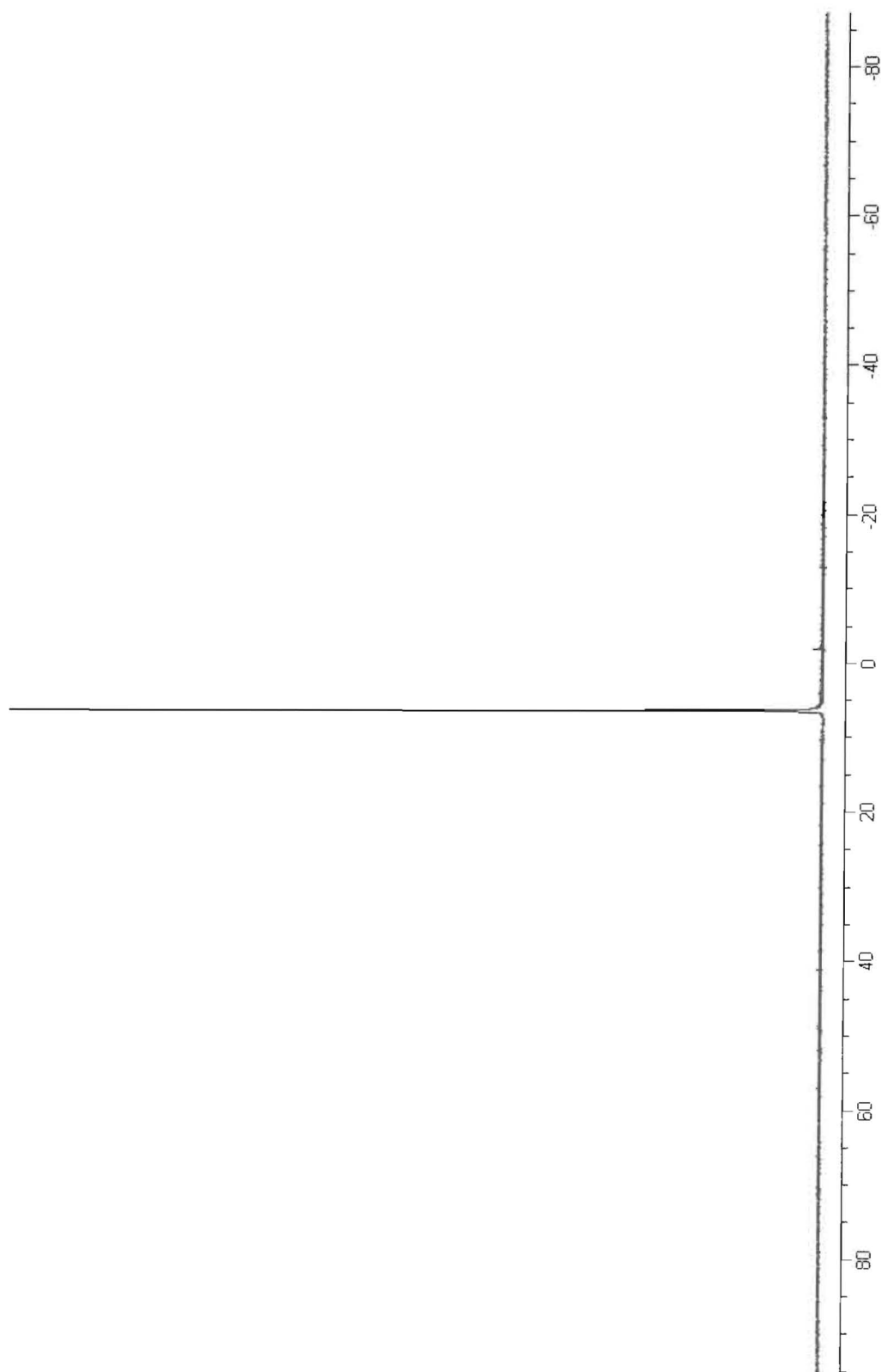
Figure 27. ^{1}H NMR spectrum of compound **41**
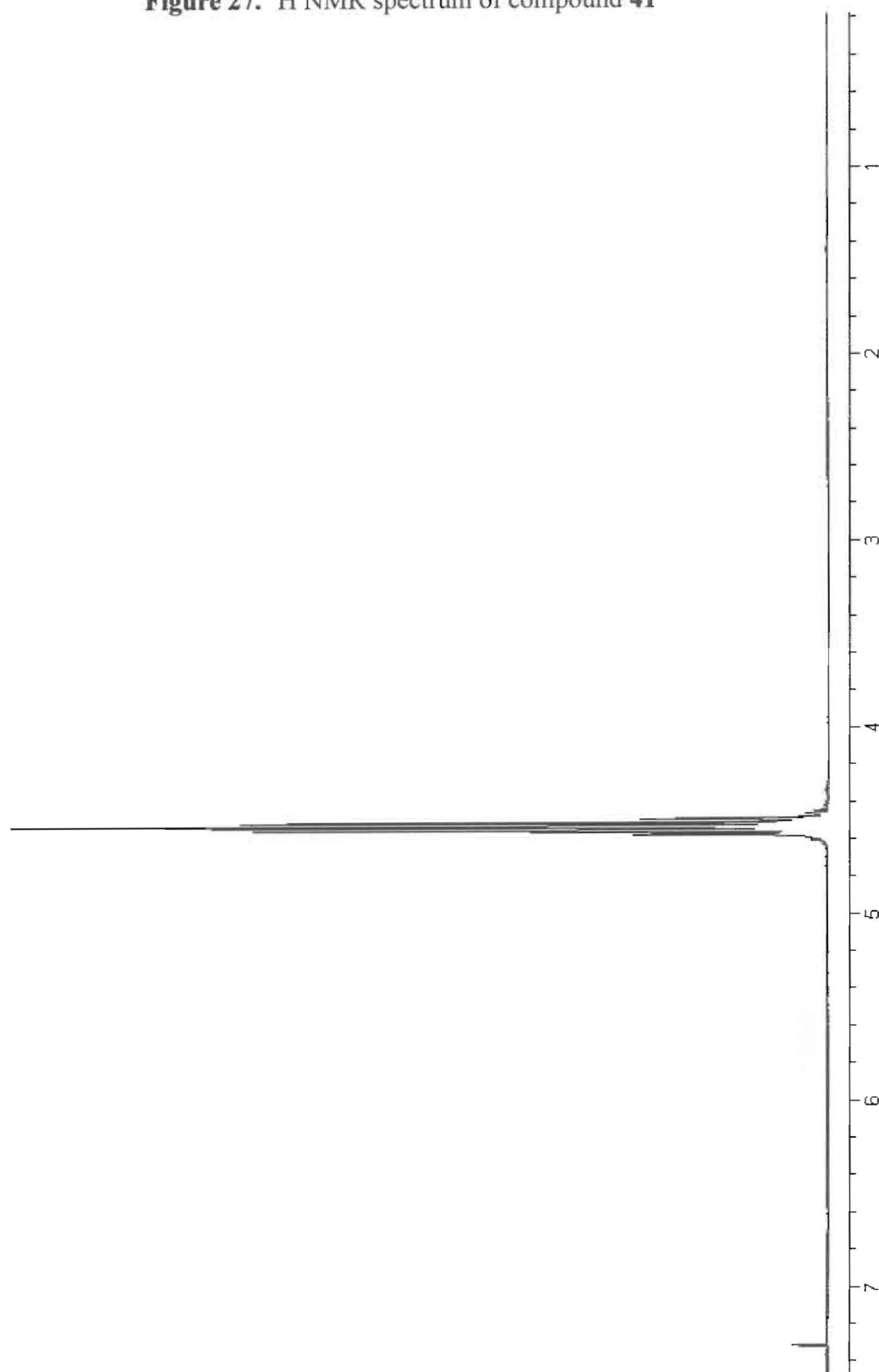
Figure 28. ^{13}C NMR spectrum of compound
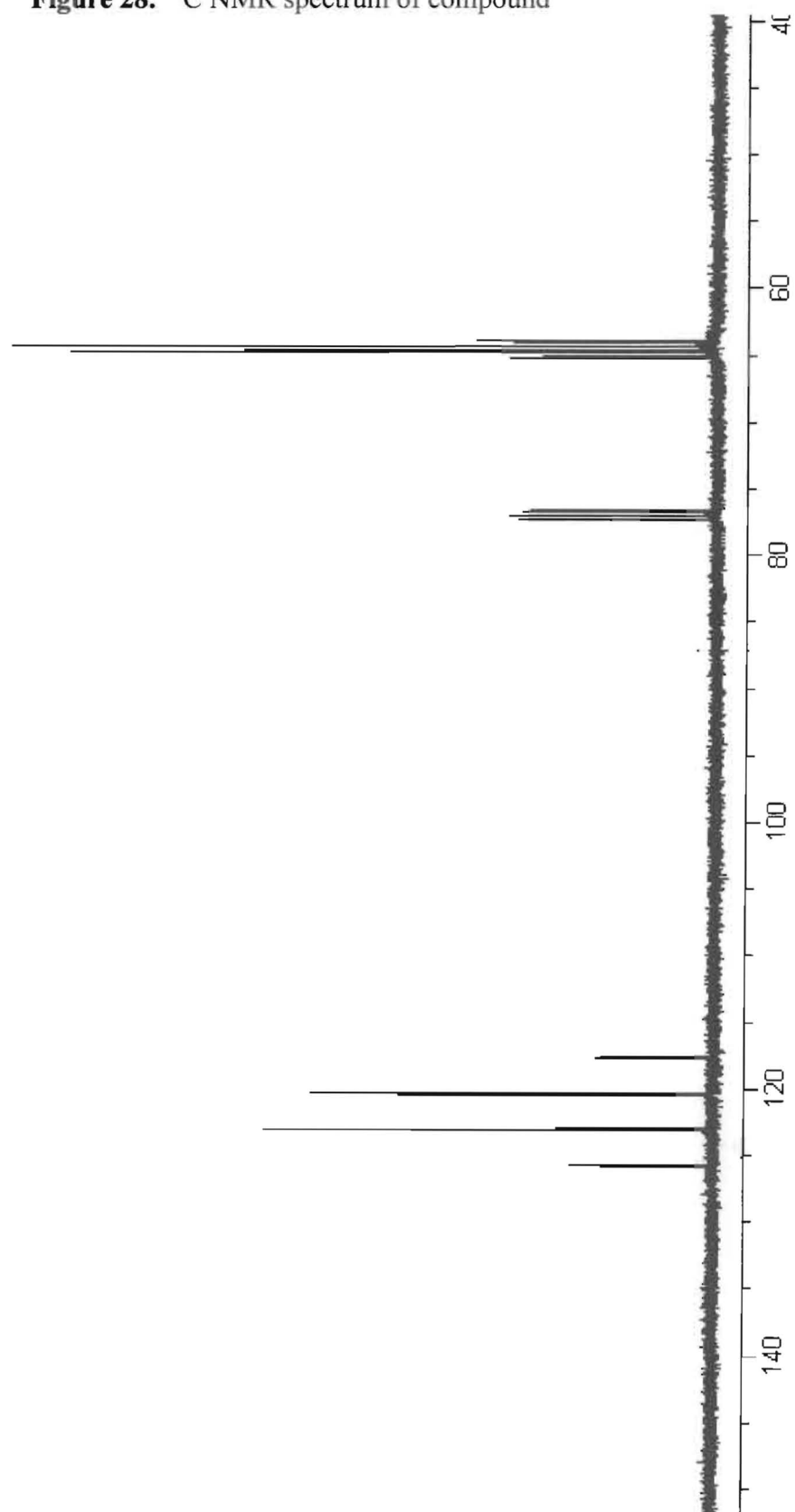
Figure 29. ^{31}P NMR spectrum of compound **43a**
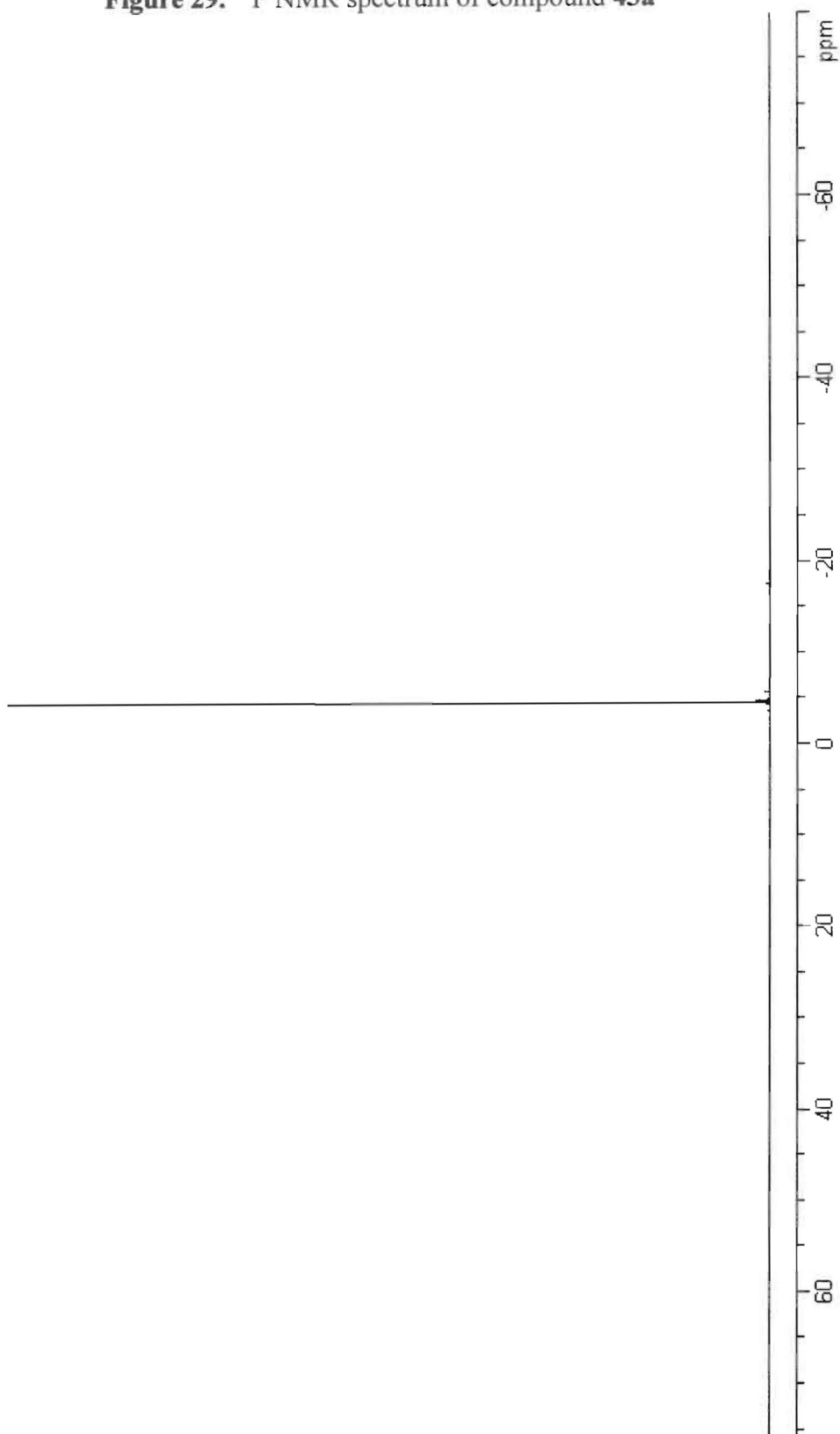
Figure 30. ^{1}H NMR spectrum of compound **43a**
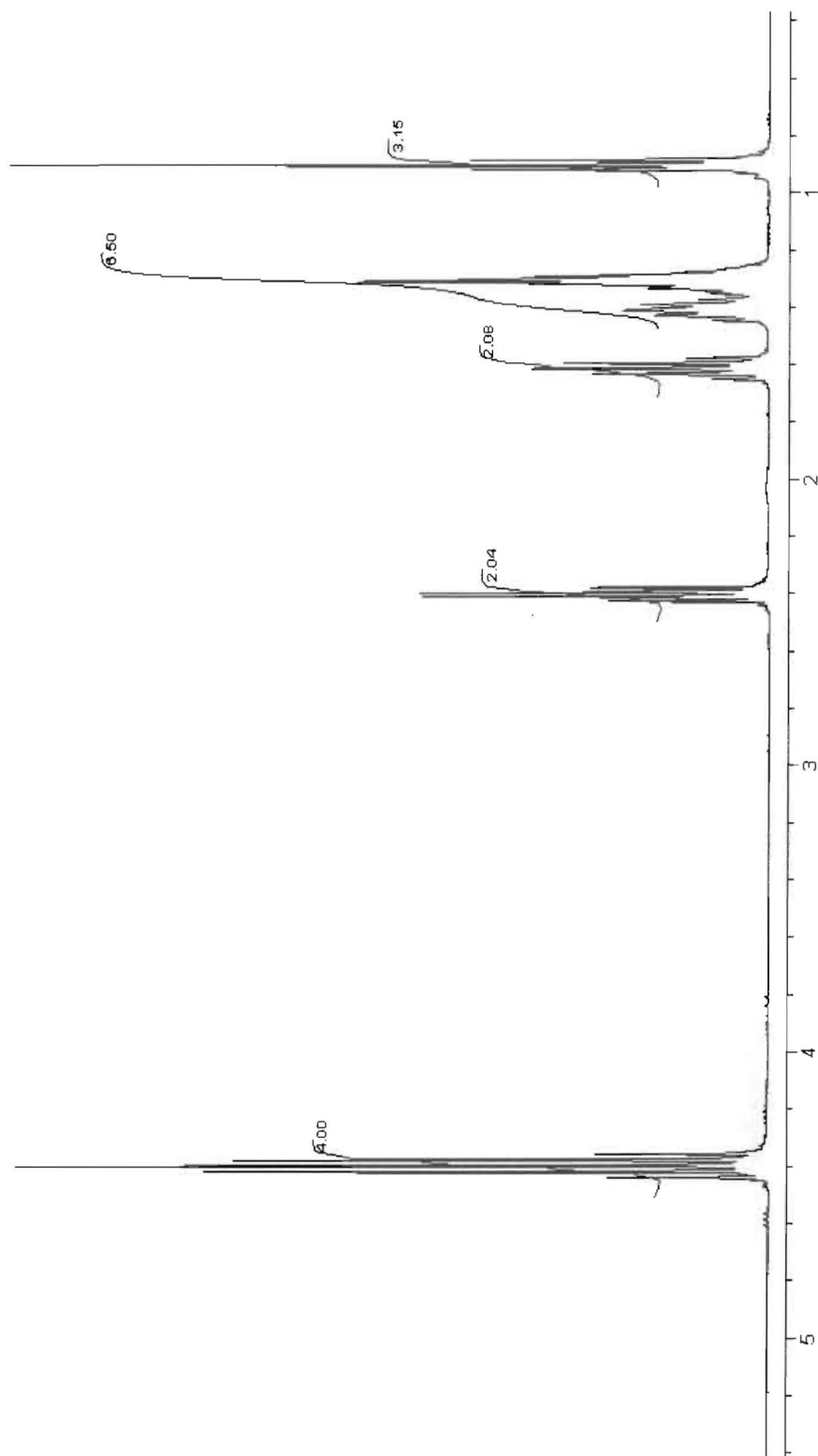
Figure 31. ^{13}C NMR spectrum of compound **43a**
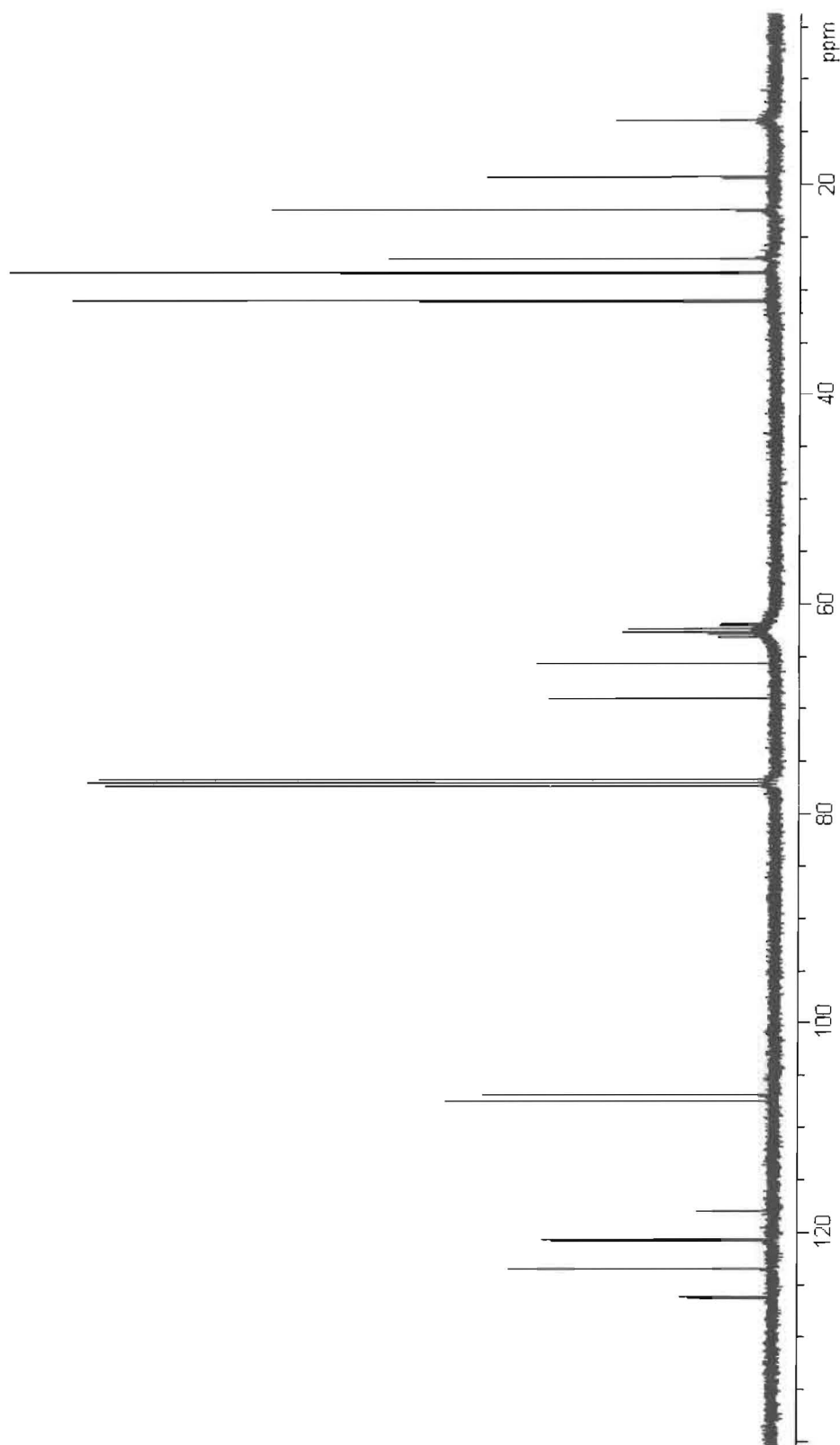
Figure 32. Mass spectrum compound **43a**

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Figure 33. ^{31}P NMR spectrum of compound **43b**
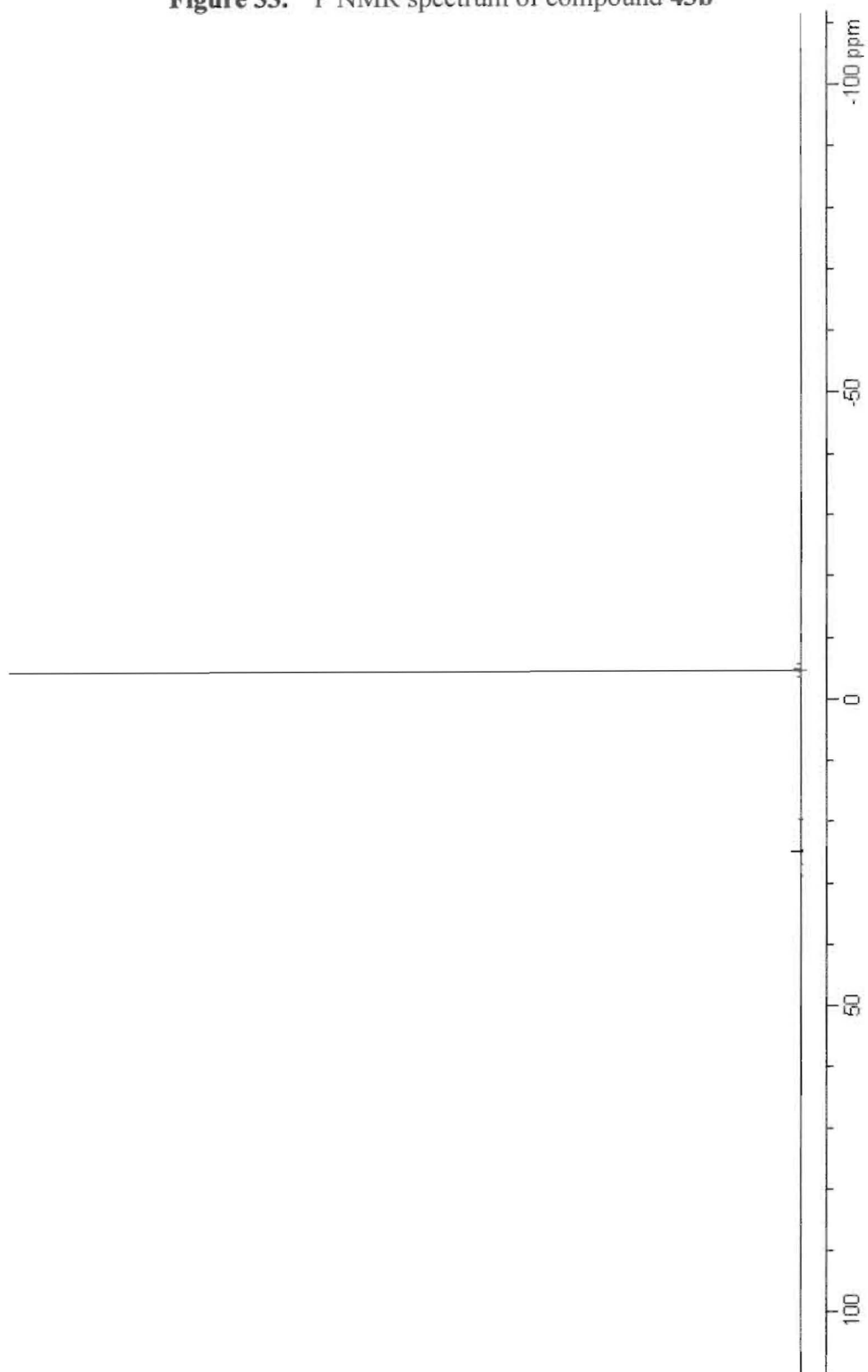
Figure 34. ^{1}H NMR spectrum of compound **43b**
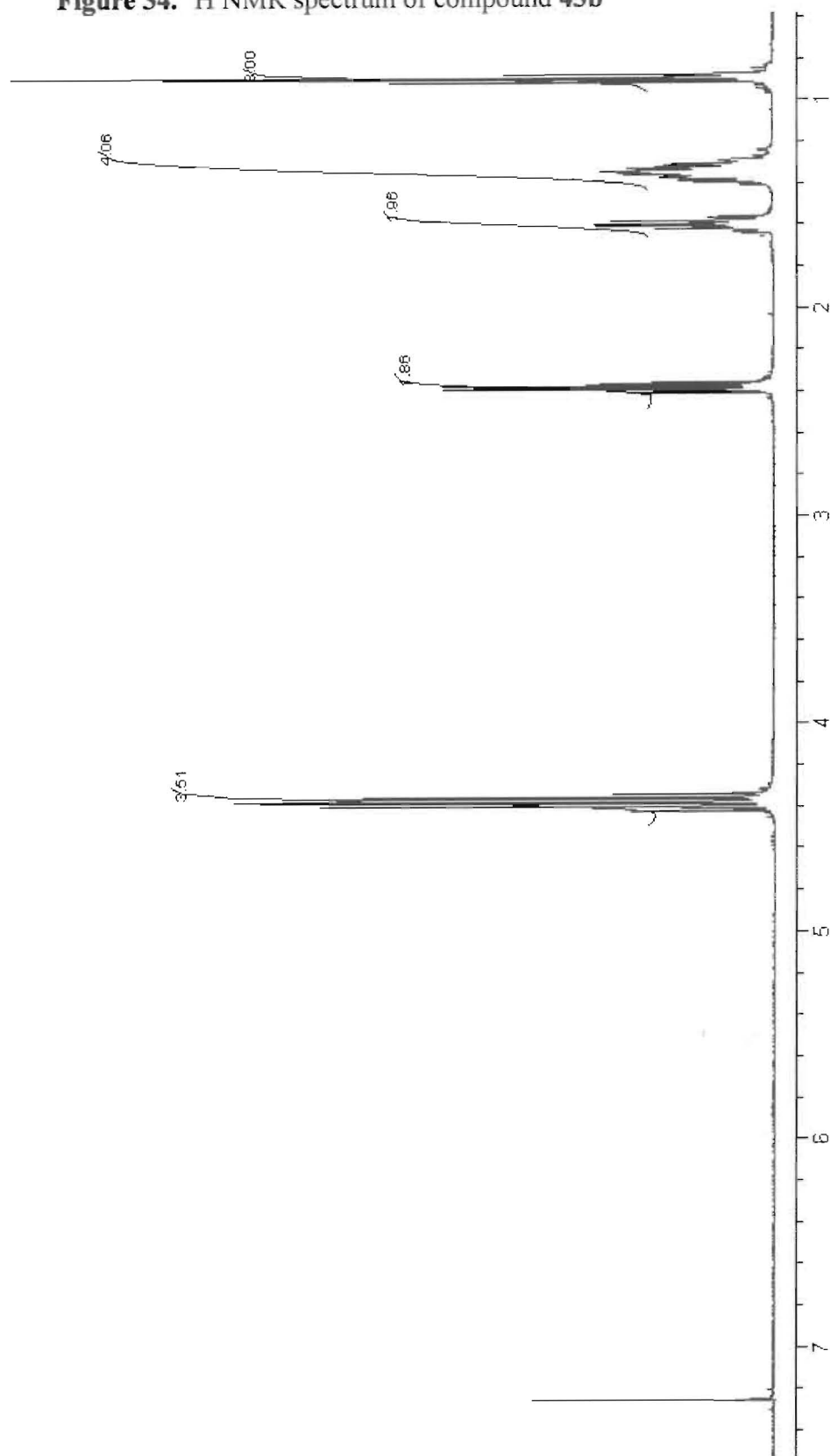
Figure 35. ^{13}C NMR spectrum of compound **43b**
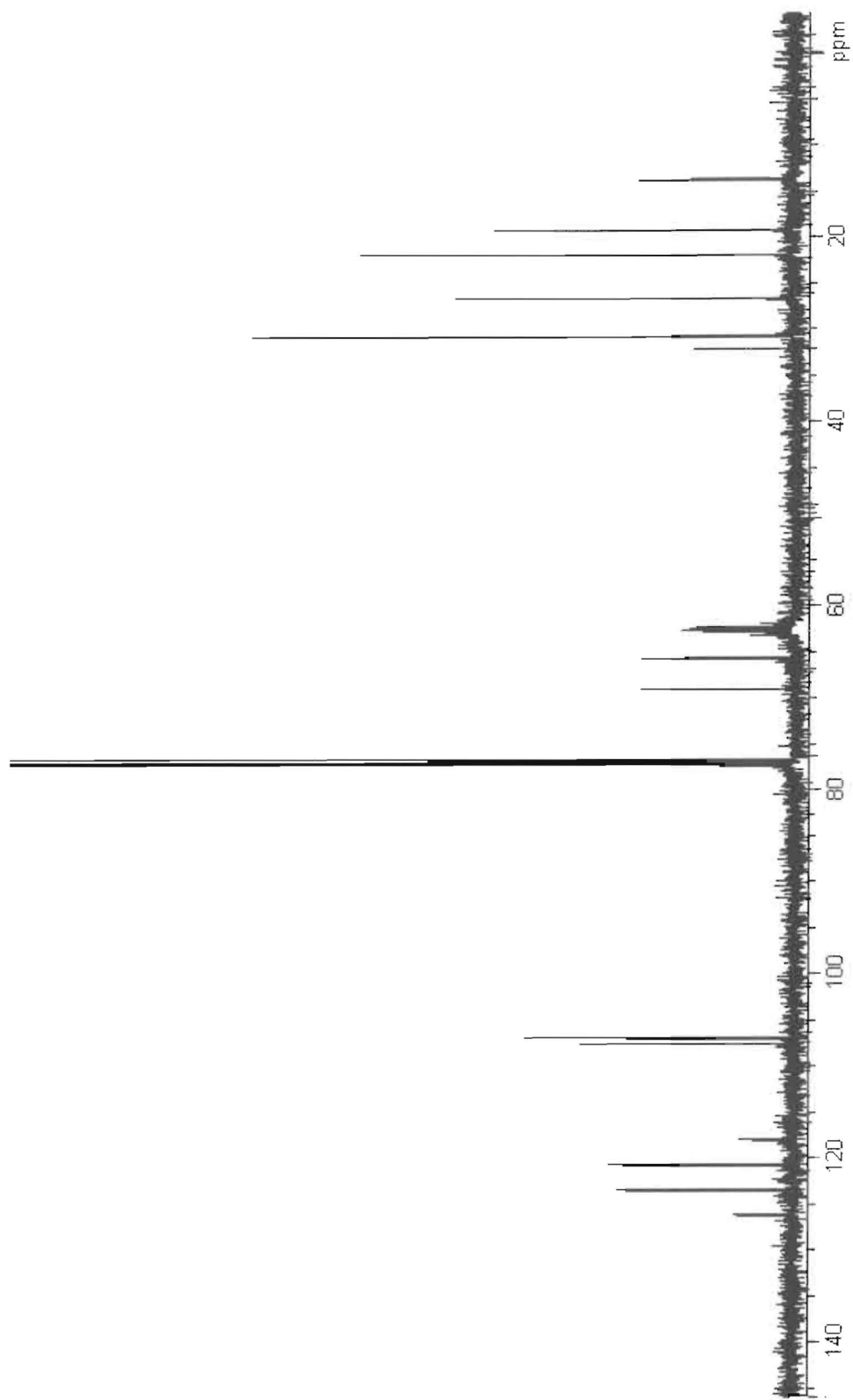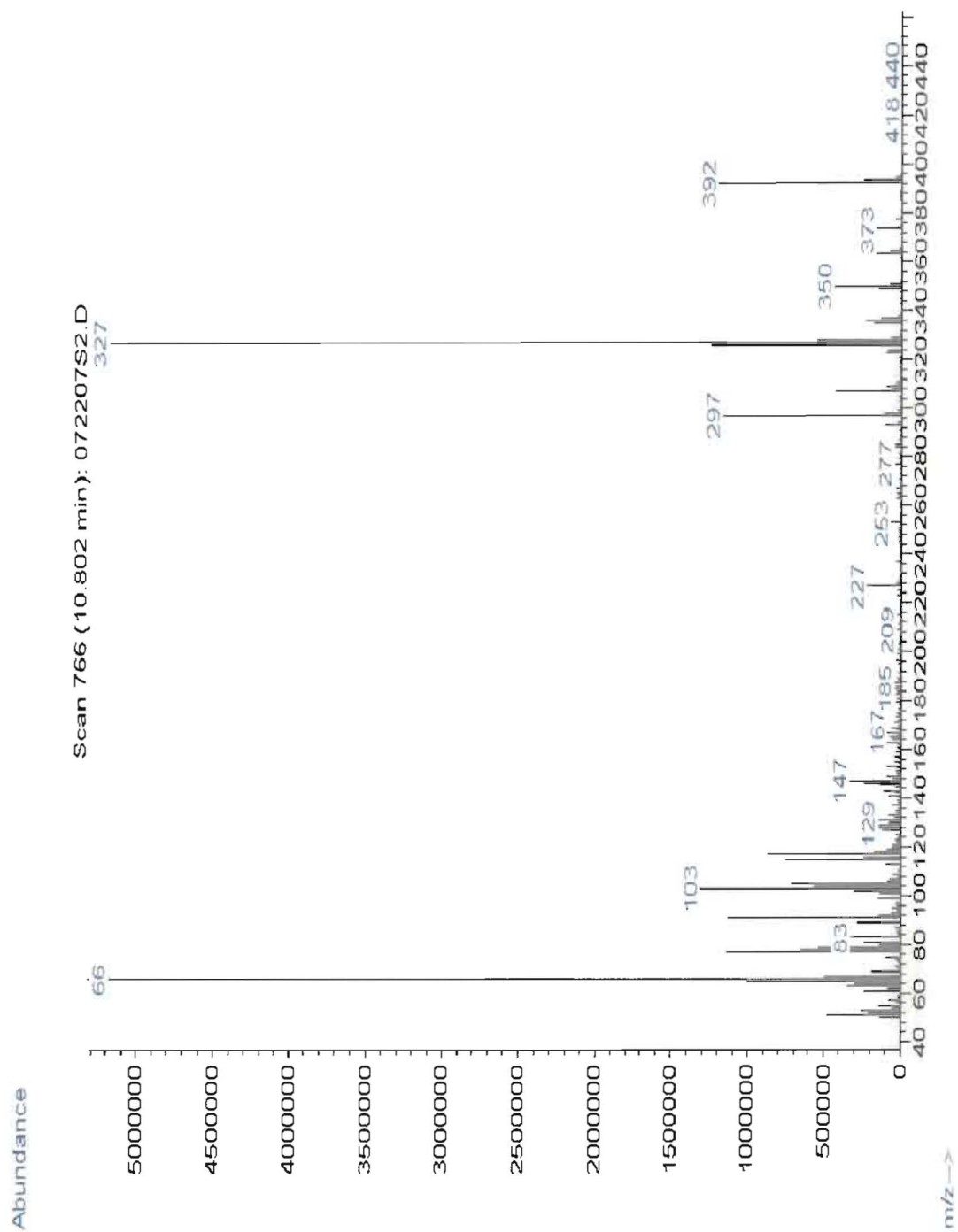
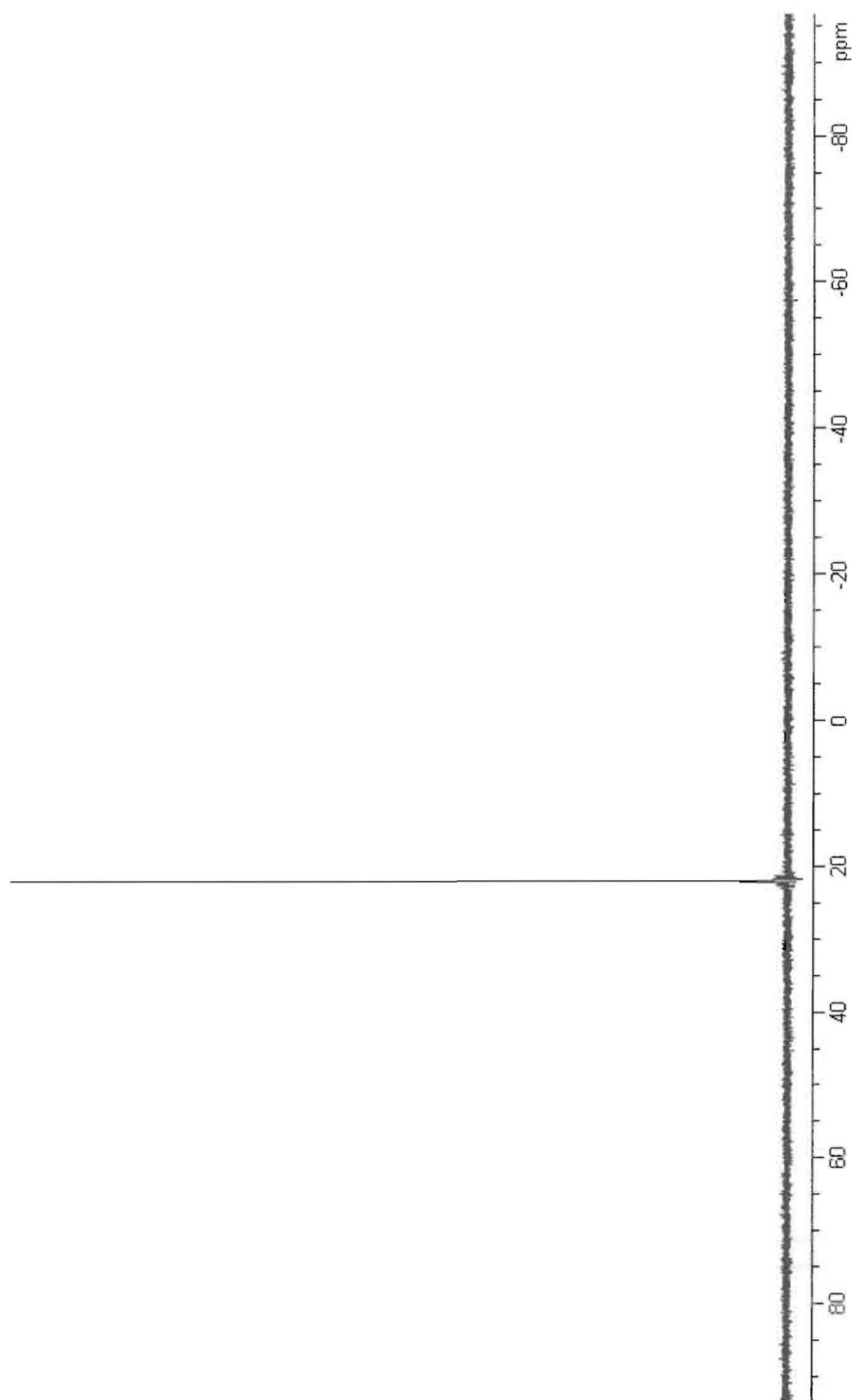**Figure 36**. Mass spectrum compound **43b**
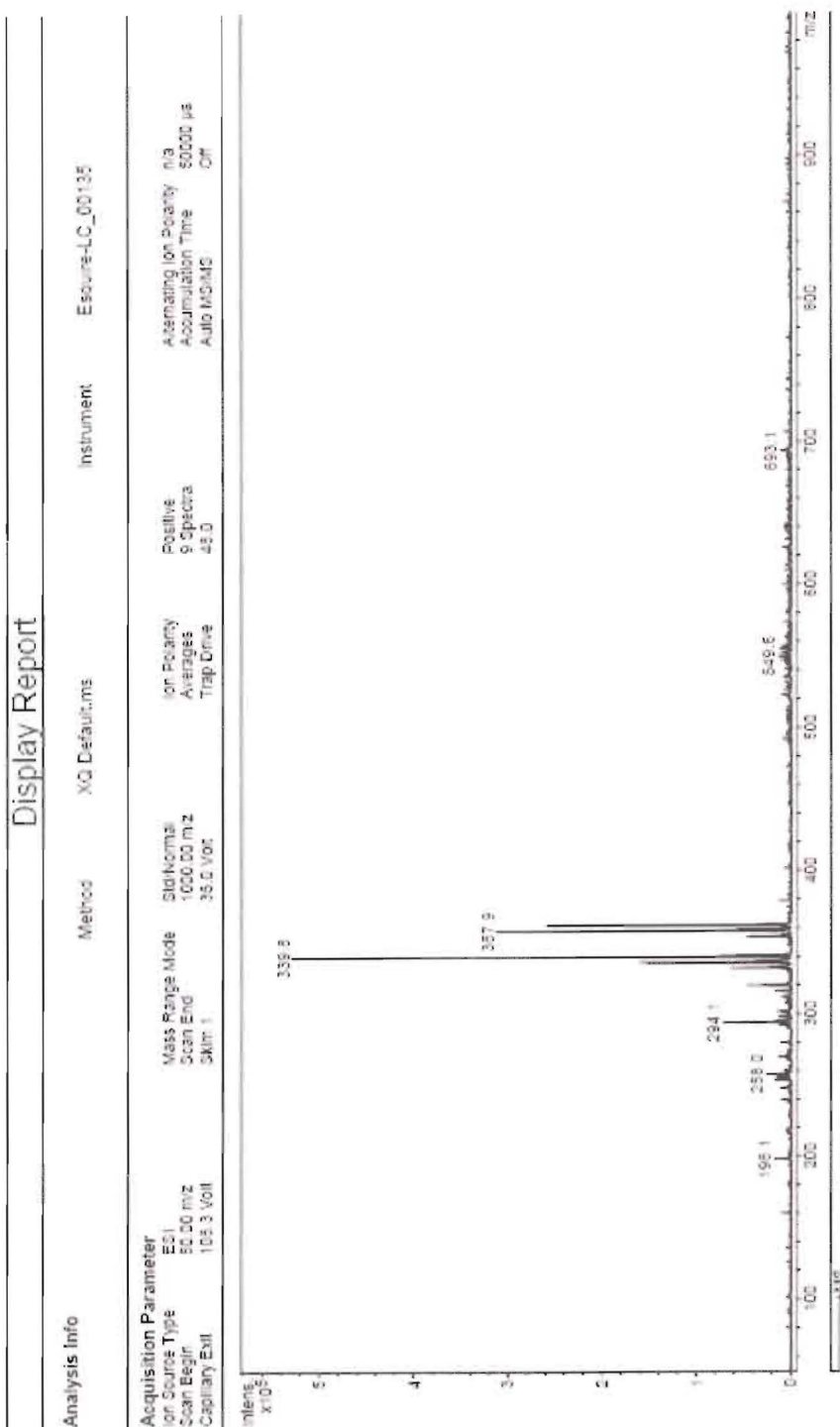
Figure 37. ^{31}P NMR spectrum of compound 43c
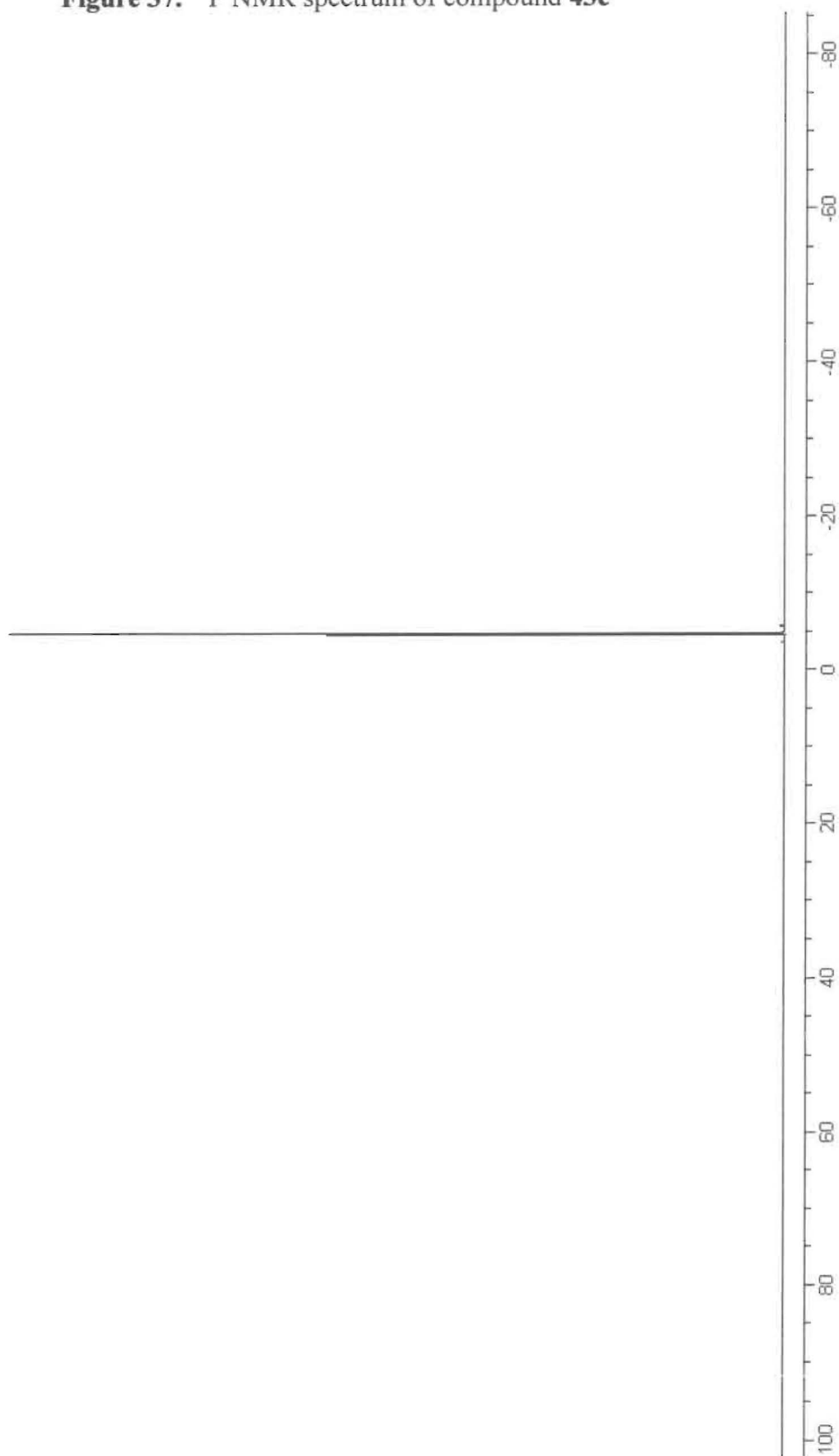
Figure 38. ^{1}H NMR spectrum of compound **43c**
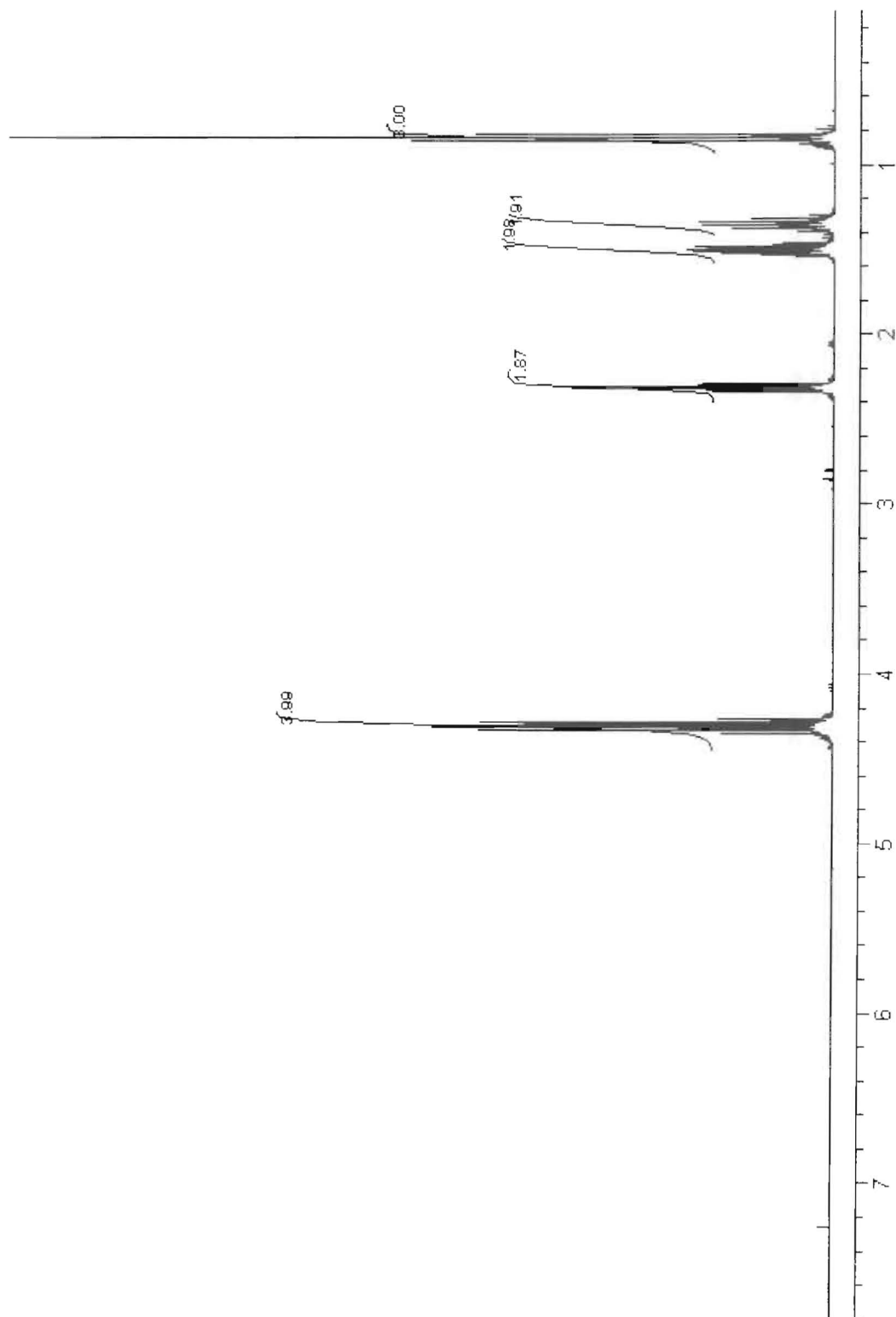
Figure 39. ^{13}C NMR spectrum of compound **43c**
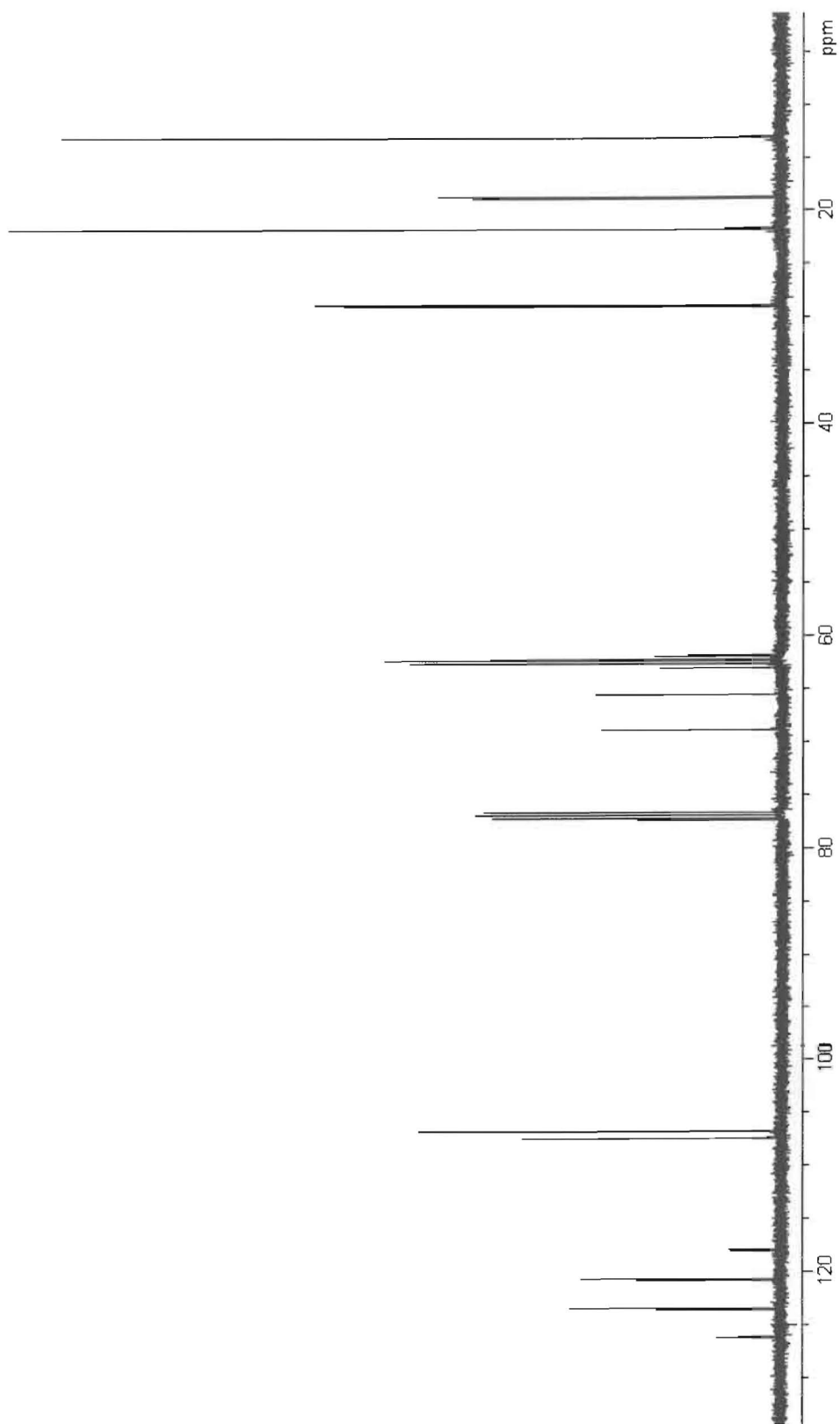
Figure 40. Mass spectrum of compound **43c**
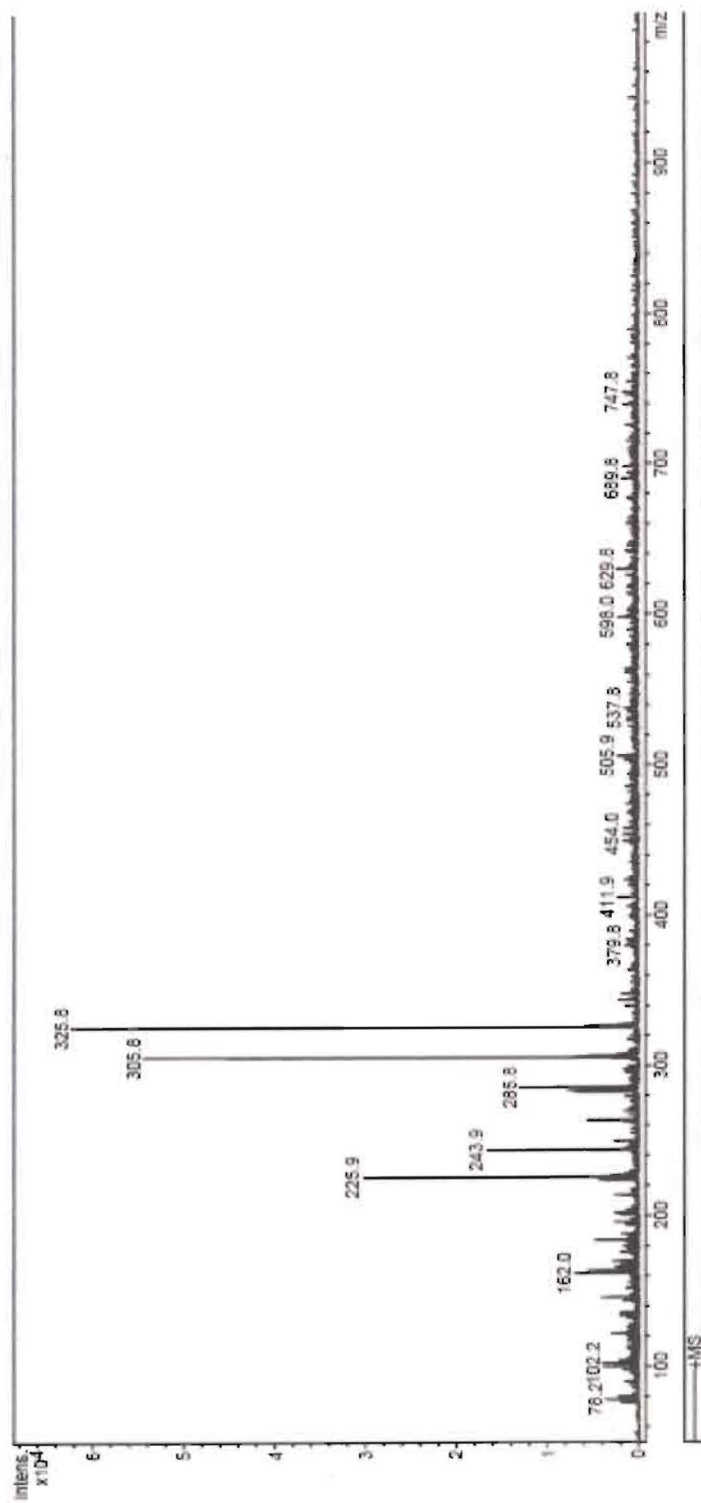
Figure 41. ^{31}P NMR spectrum of compound **43d**
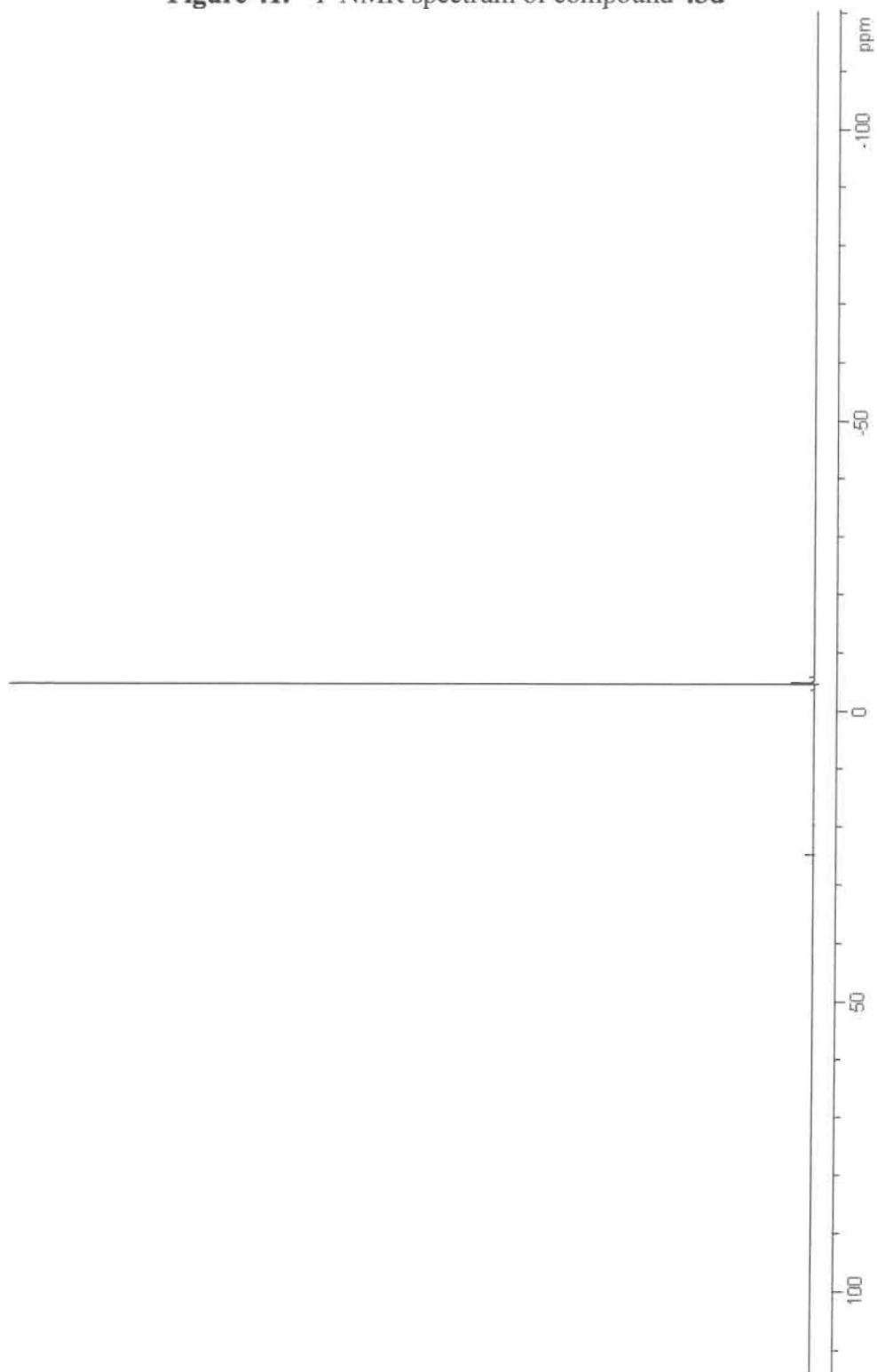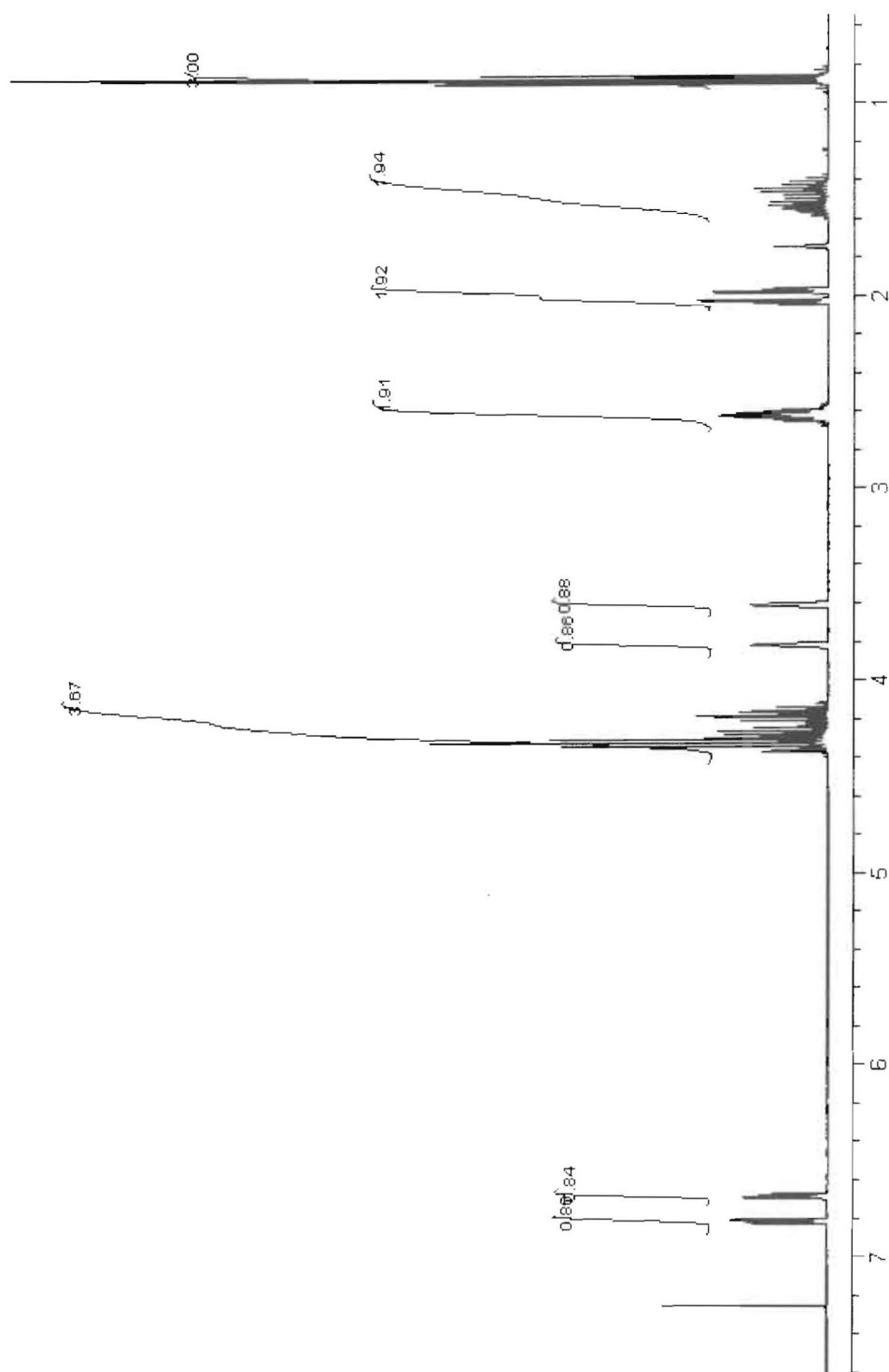
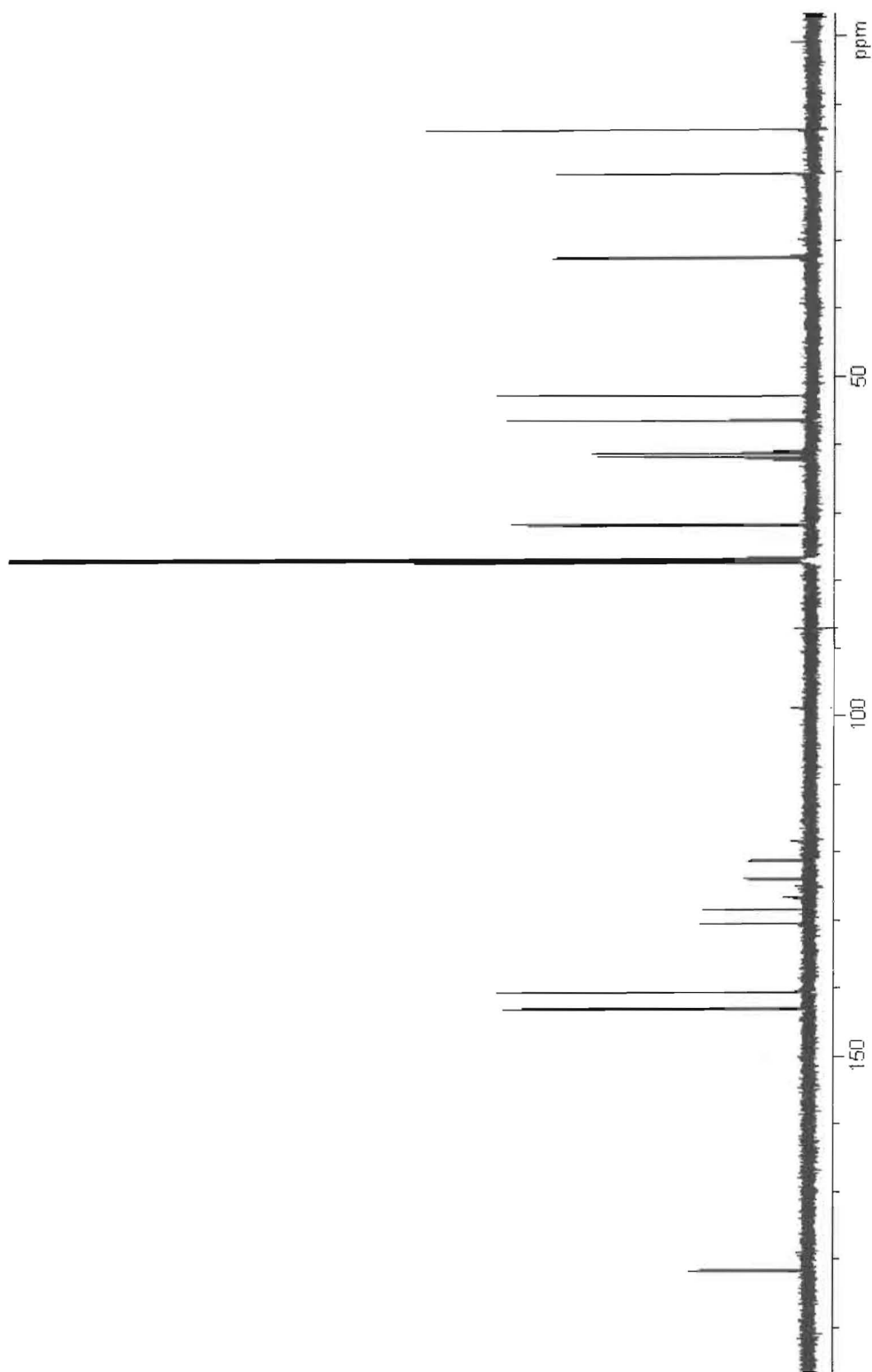**Figure 42.** ¹H NMR spectrum of compound **43d**
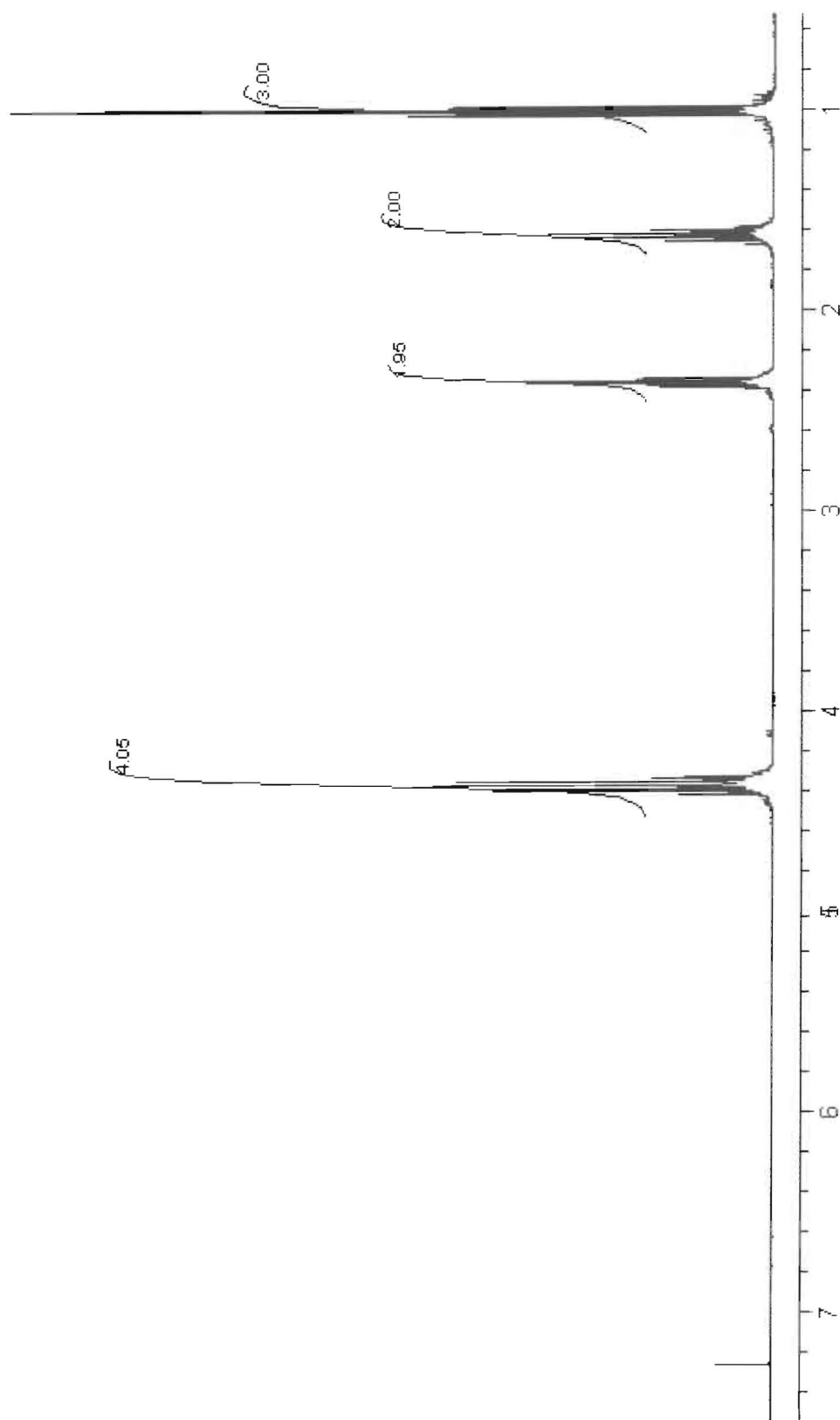
Figure 43. ^{13}C NMR spectrum of compound **43d**
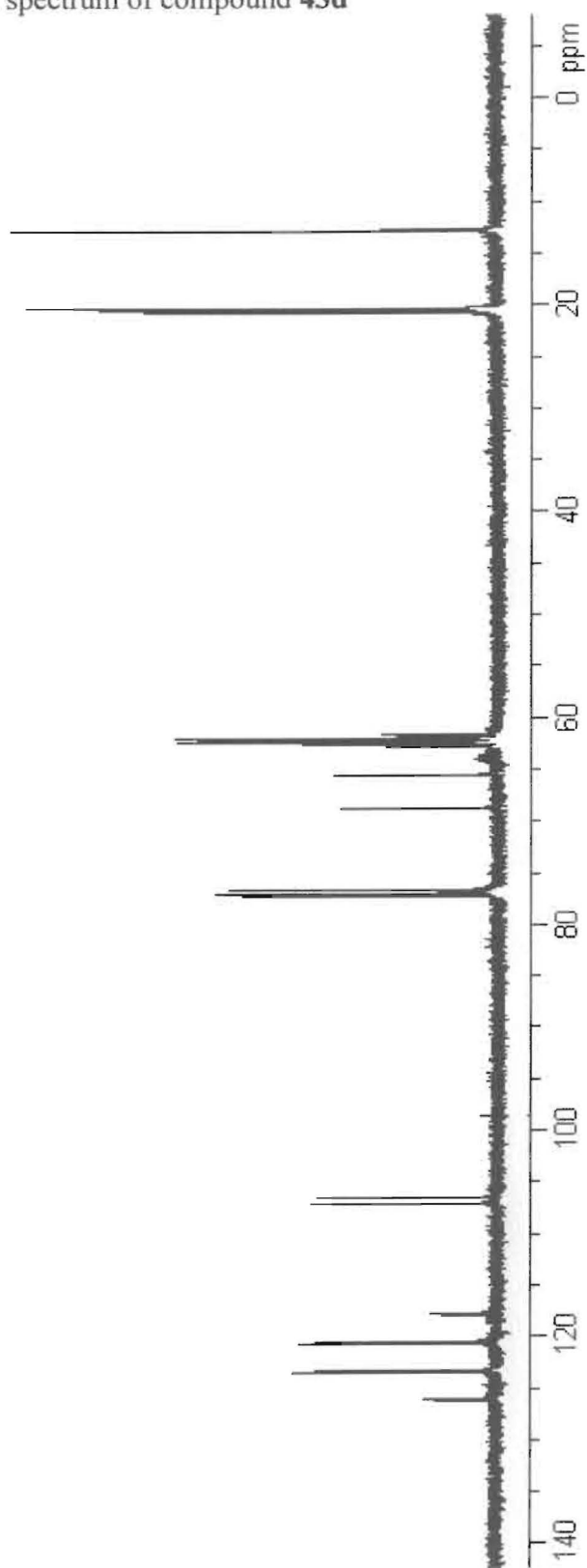
Figure 44. Mass spectrum of compound **43d**
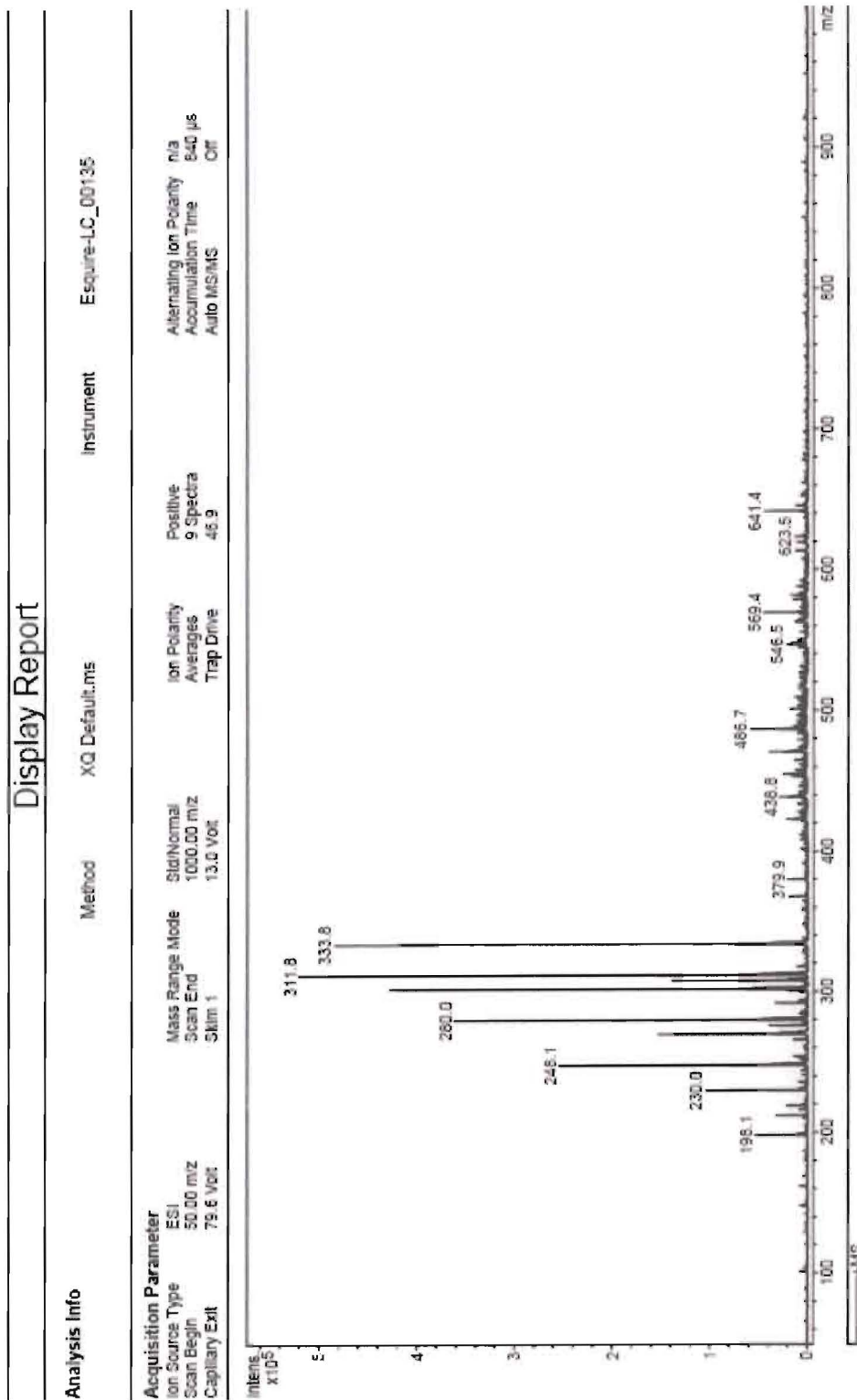
Figure 45. ^{31}P NMR spectrum of compound **46a**
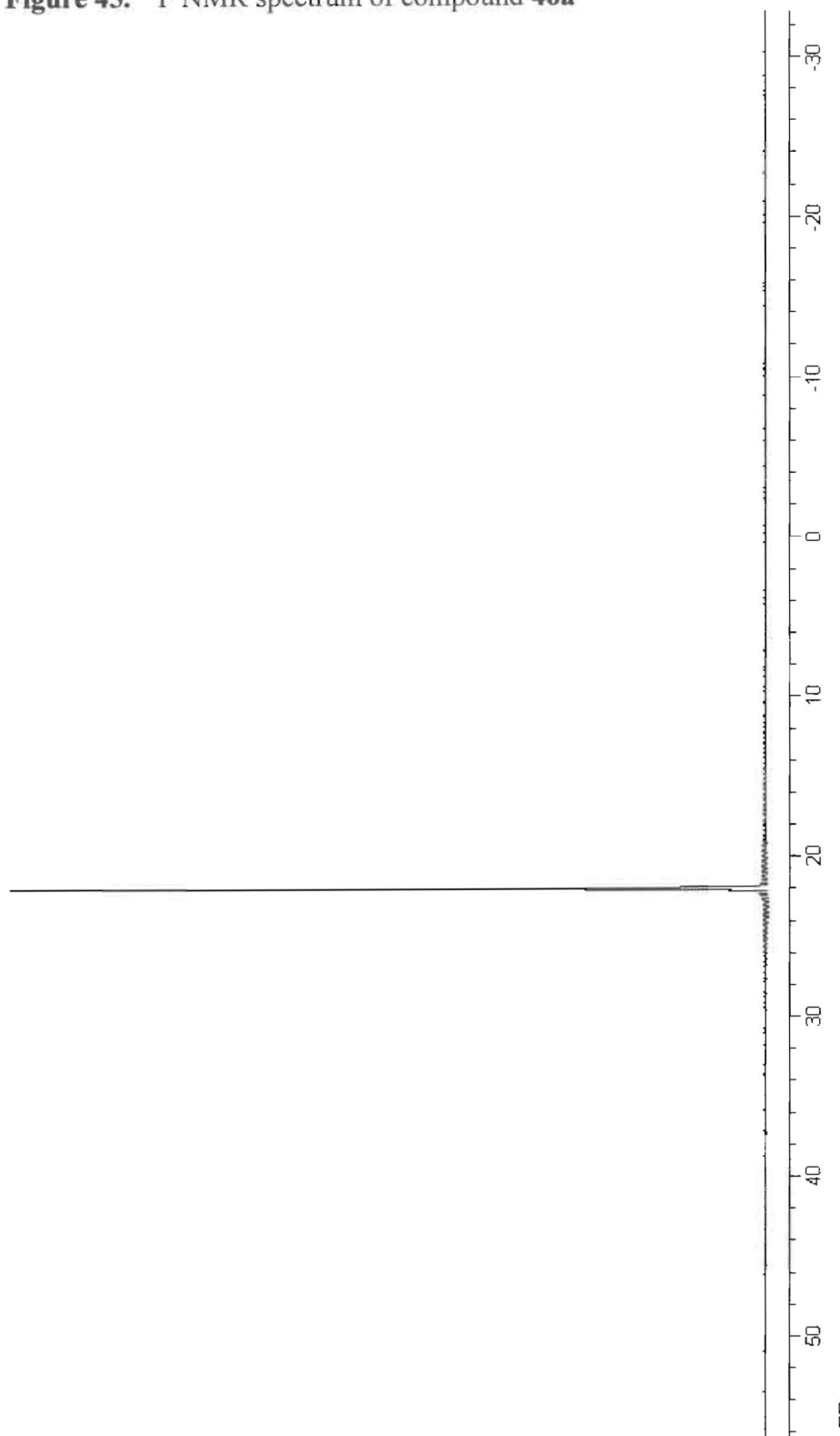
Figure 46. ^{1}H NMR spectrum of compound **46a**
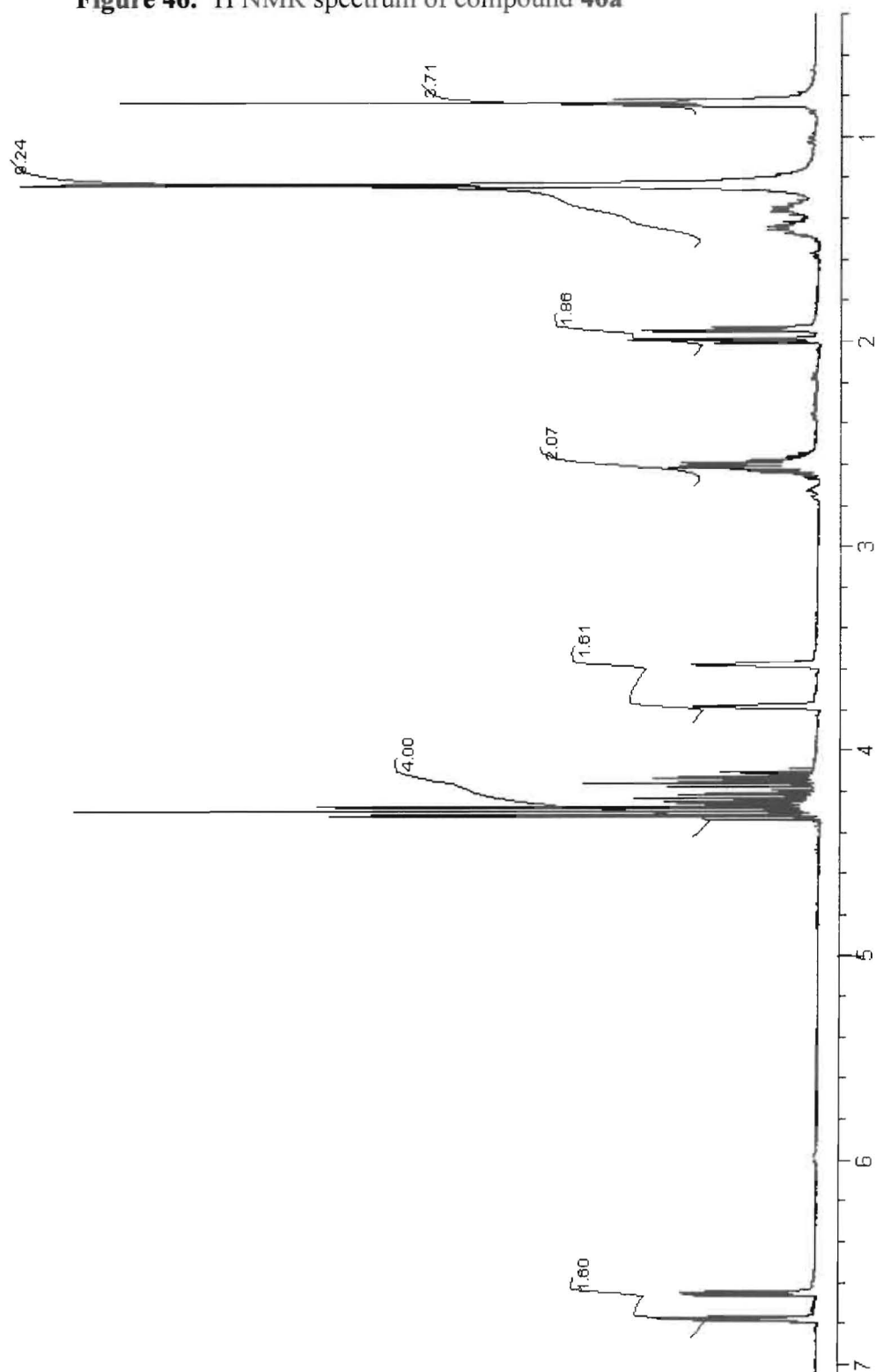
Figure 47. ^{13}C NMR spectrum of compound **46a**
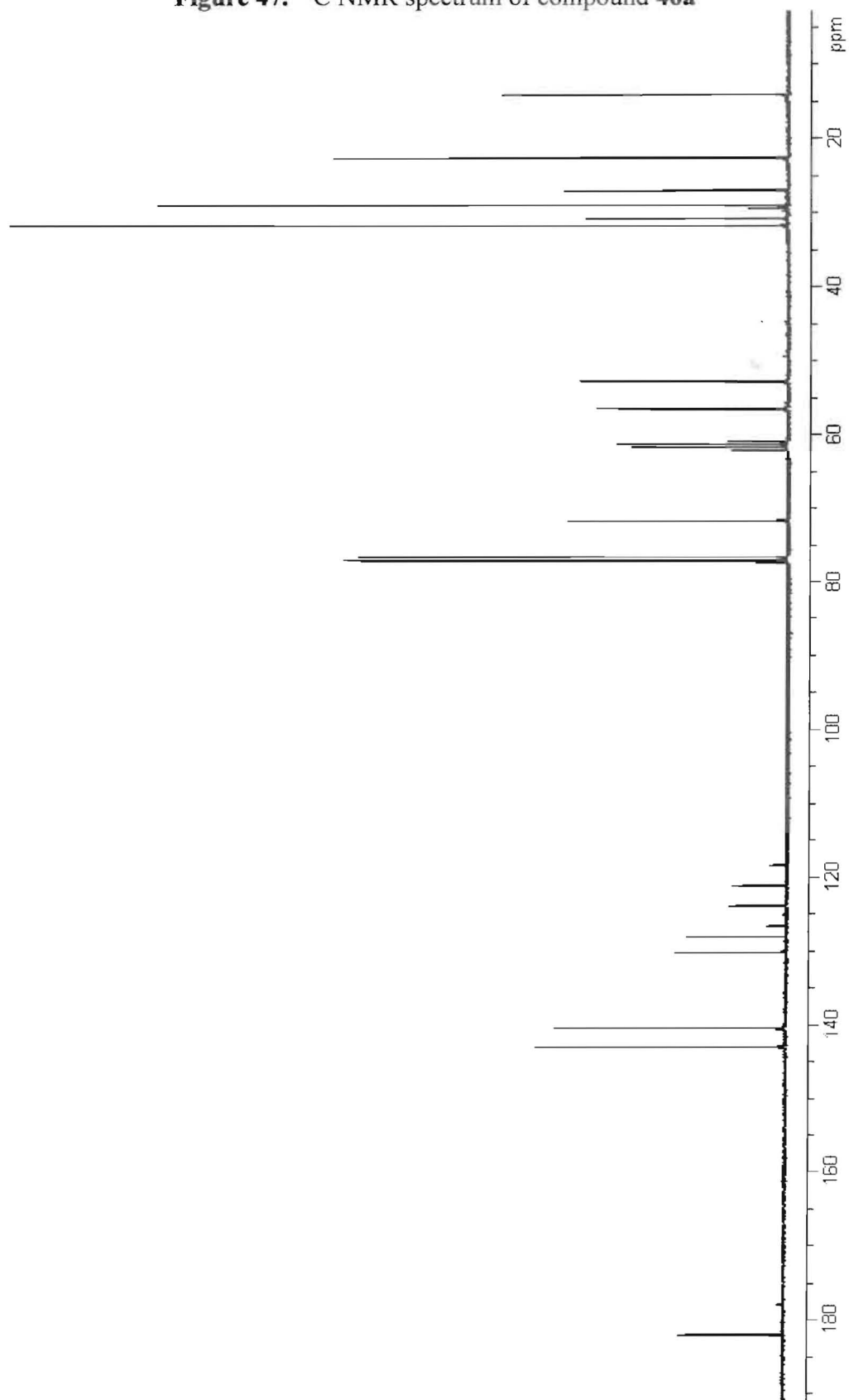
Figure 48. Mass spectrum of compound **46a**
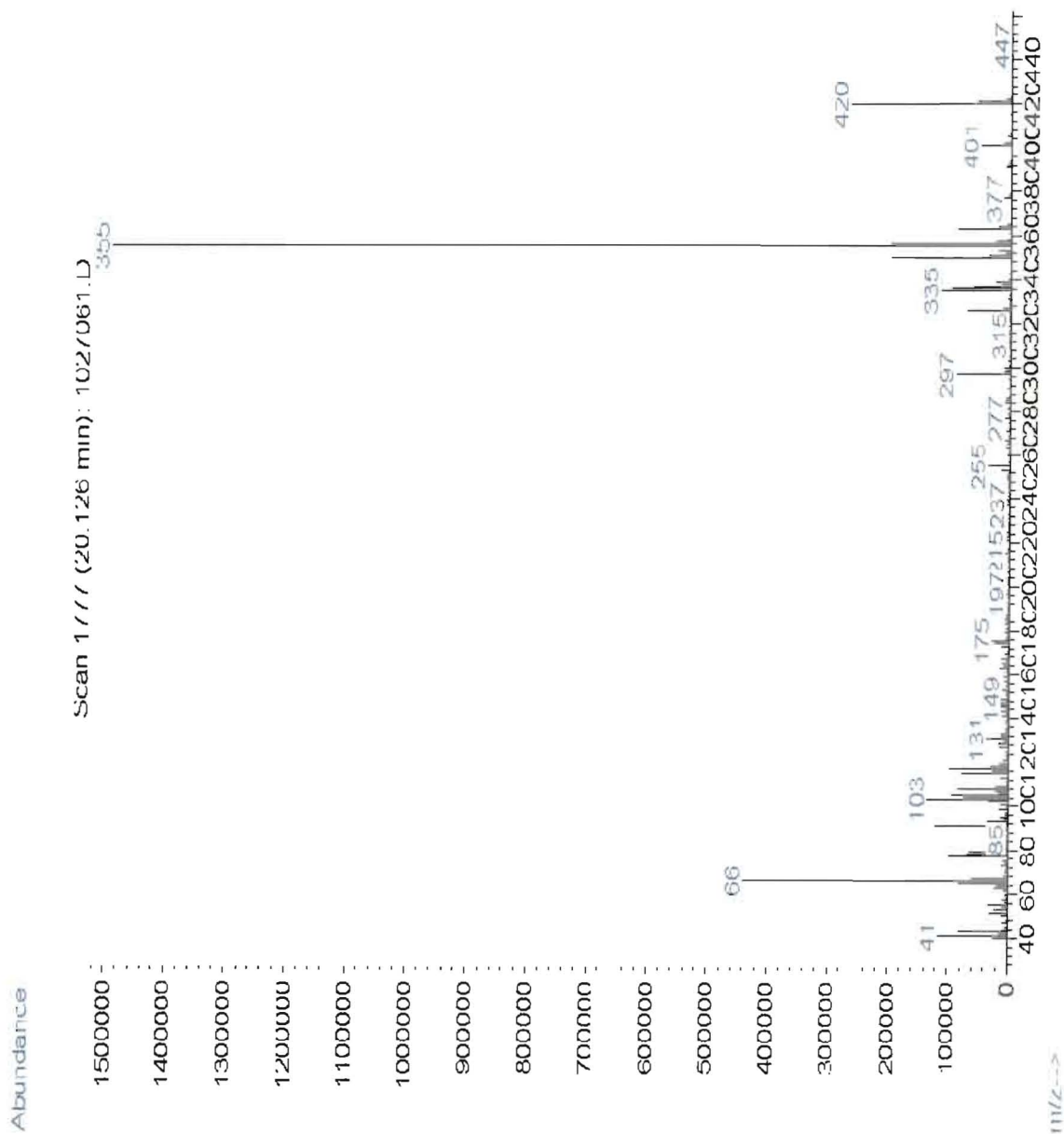
Figure 49. ^{31}P NMR spectrum of compound **46b**
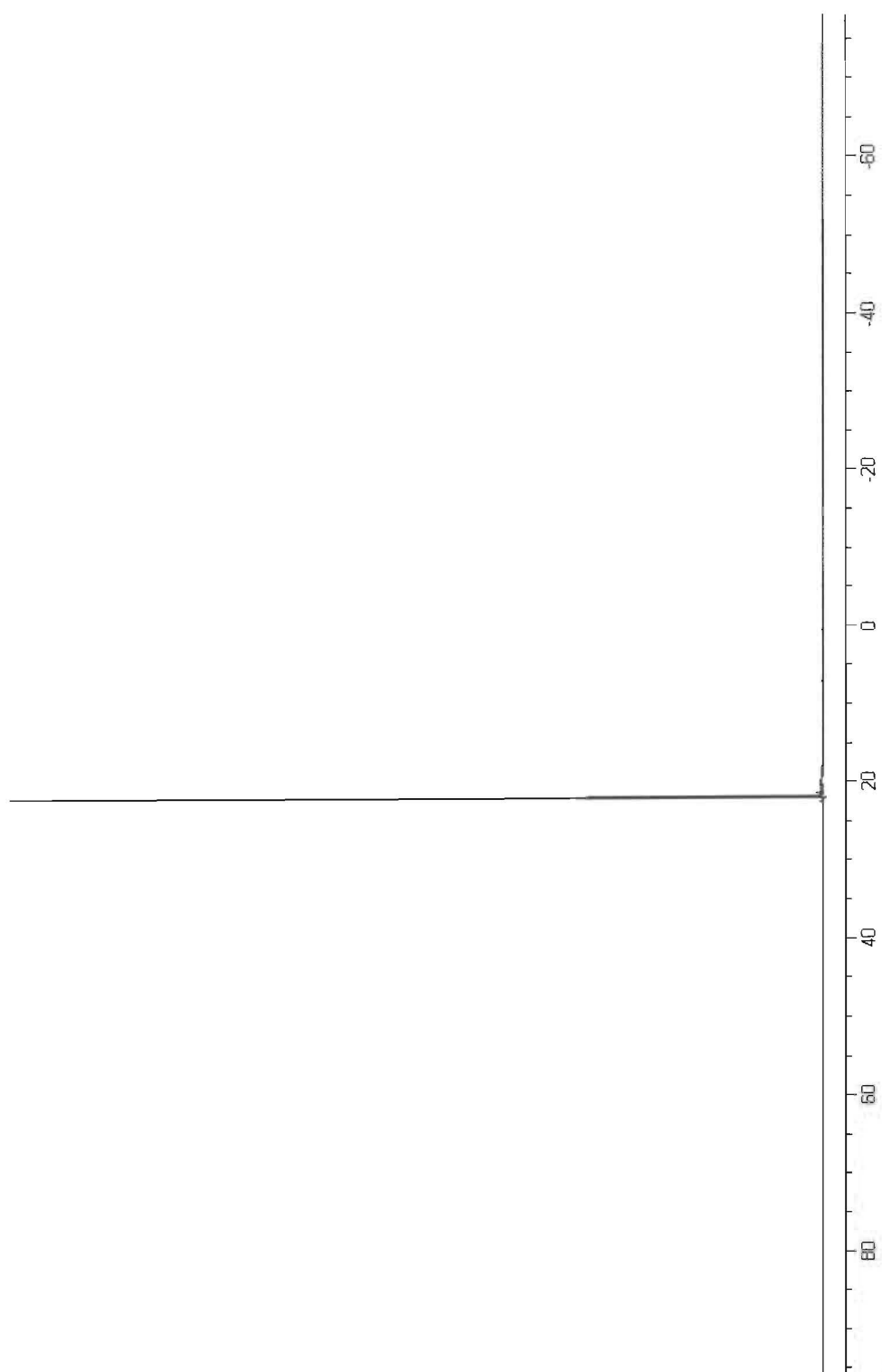
Figure 50. ^{1}H NMR spectrum of compound **46b**
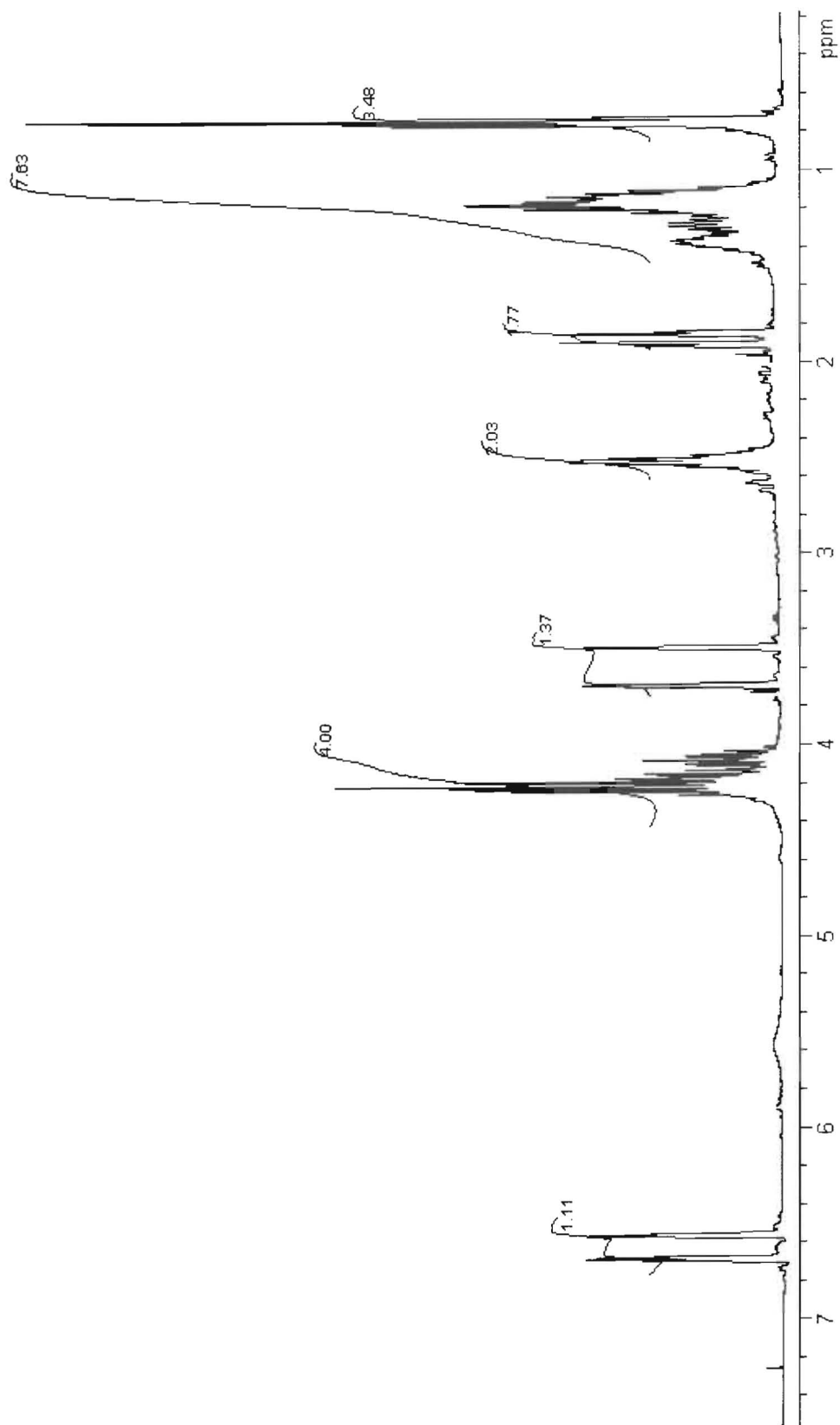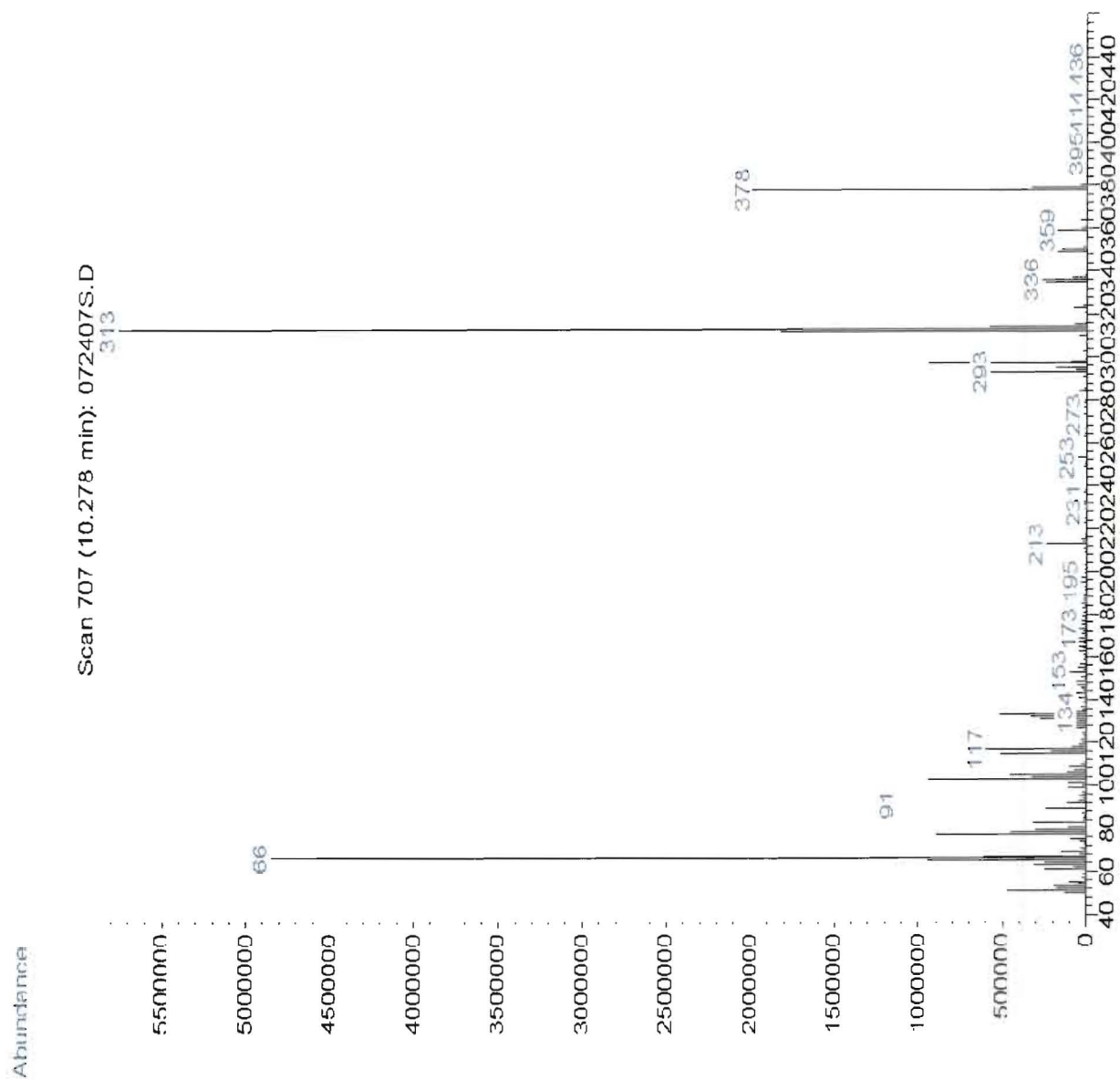
Figure 51. ^{13}C NMR spectrum of compound **46b**
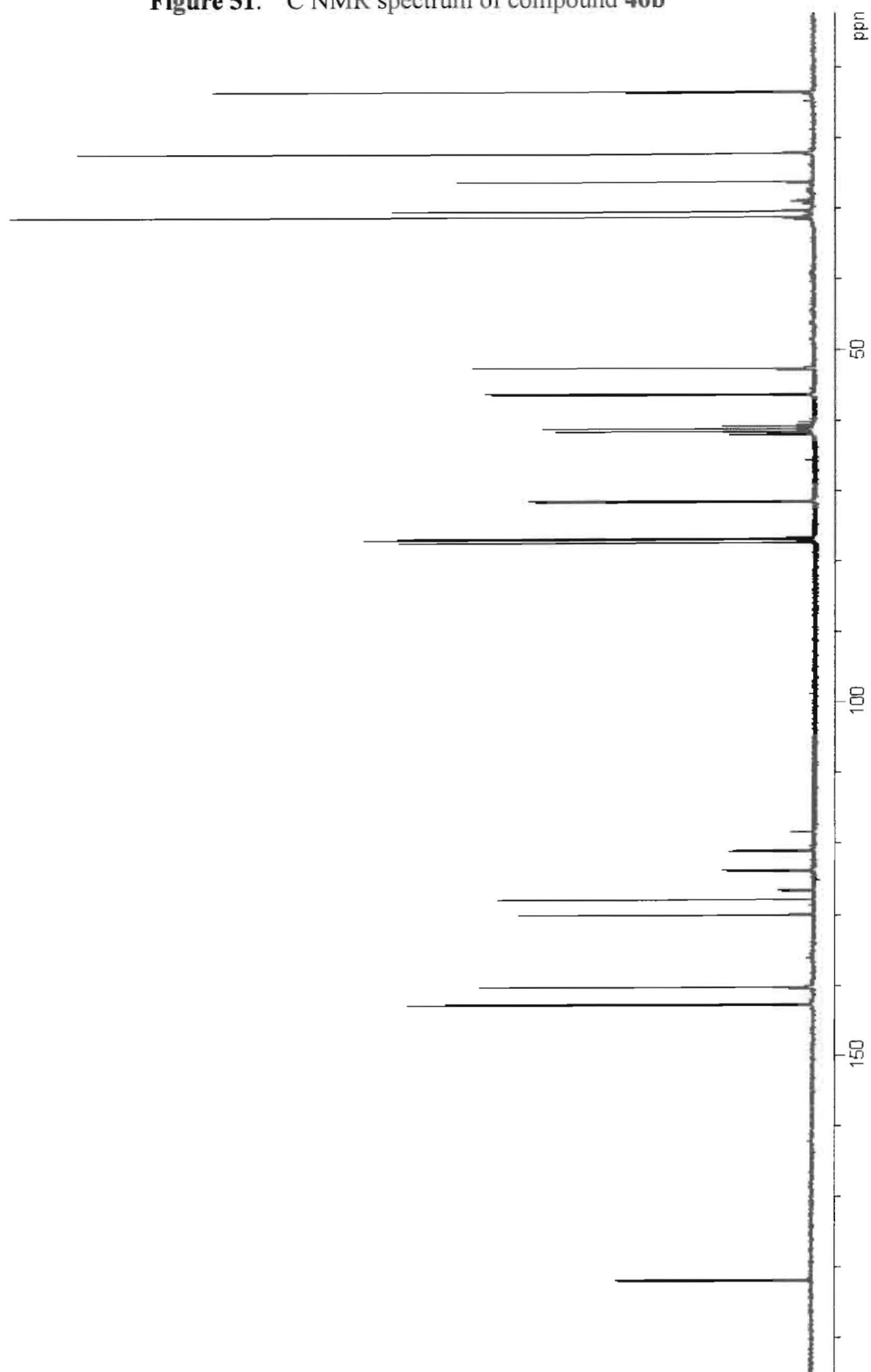
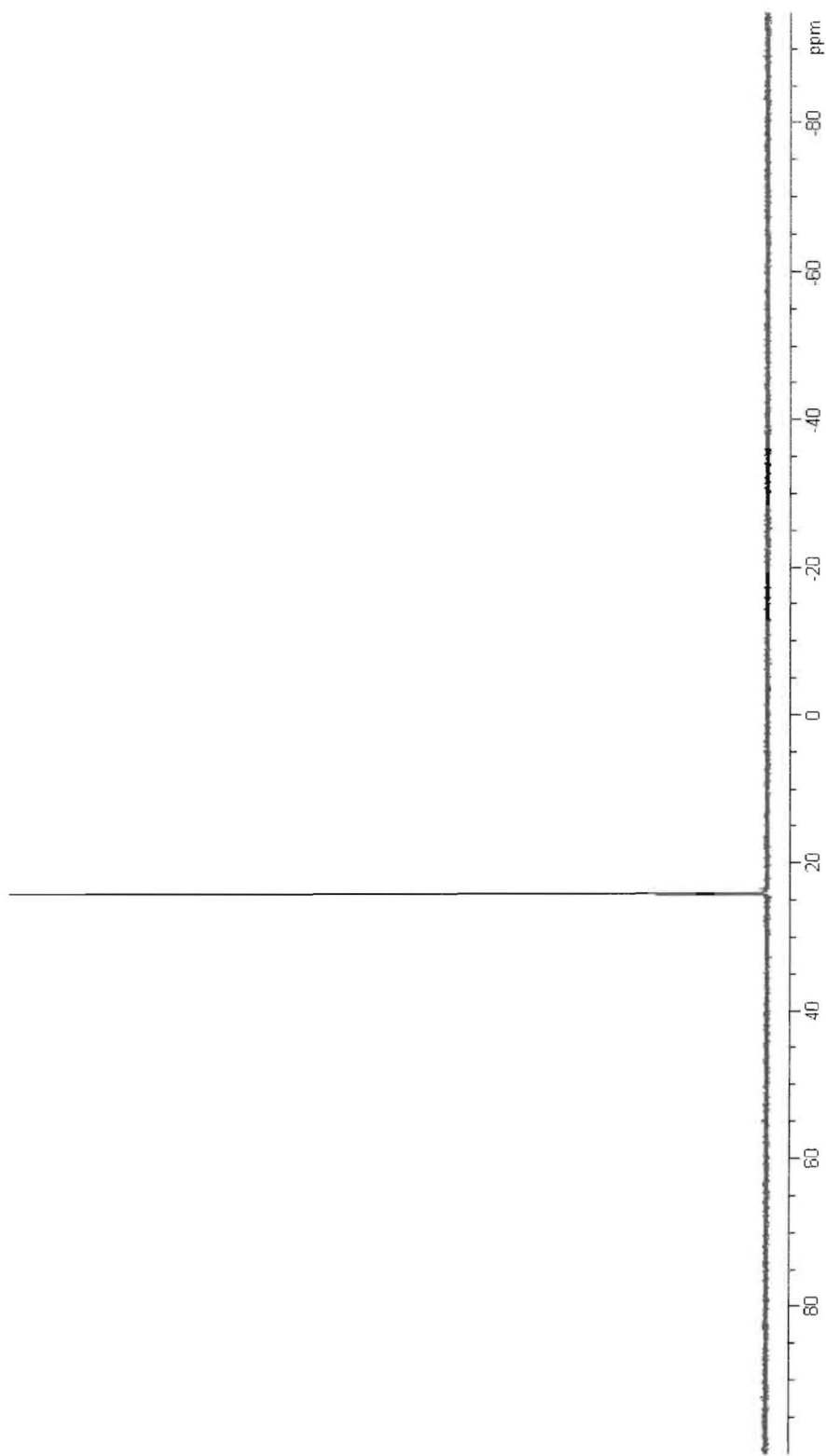**Figure 52.** Mass spectrum of compound **46b**
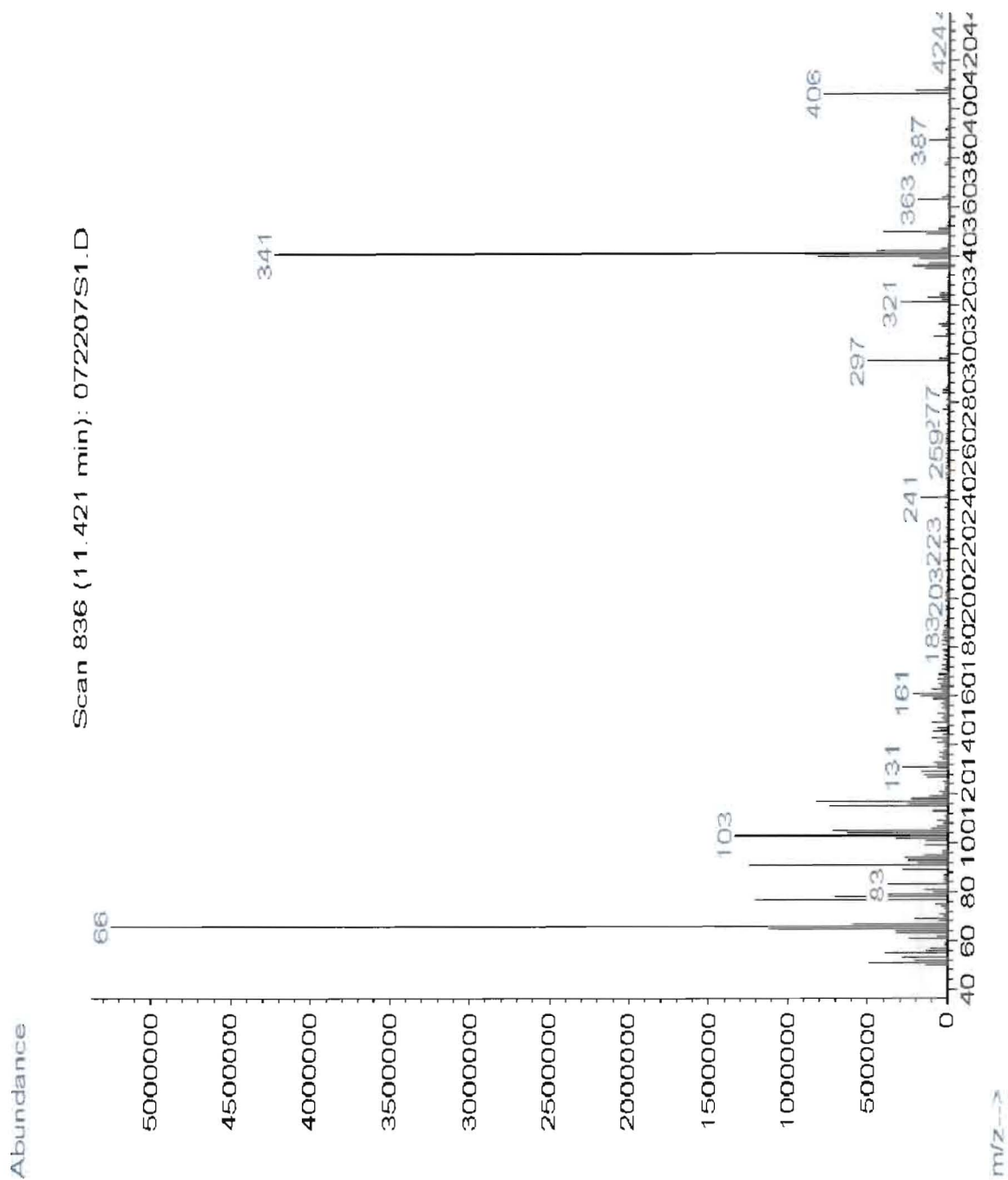
Figure 53. ^{31}P NMR spectrum of compound **46c**
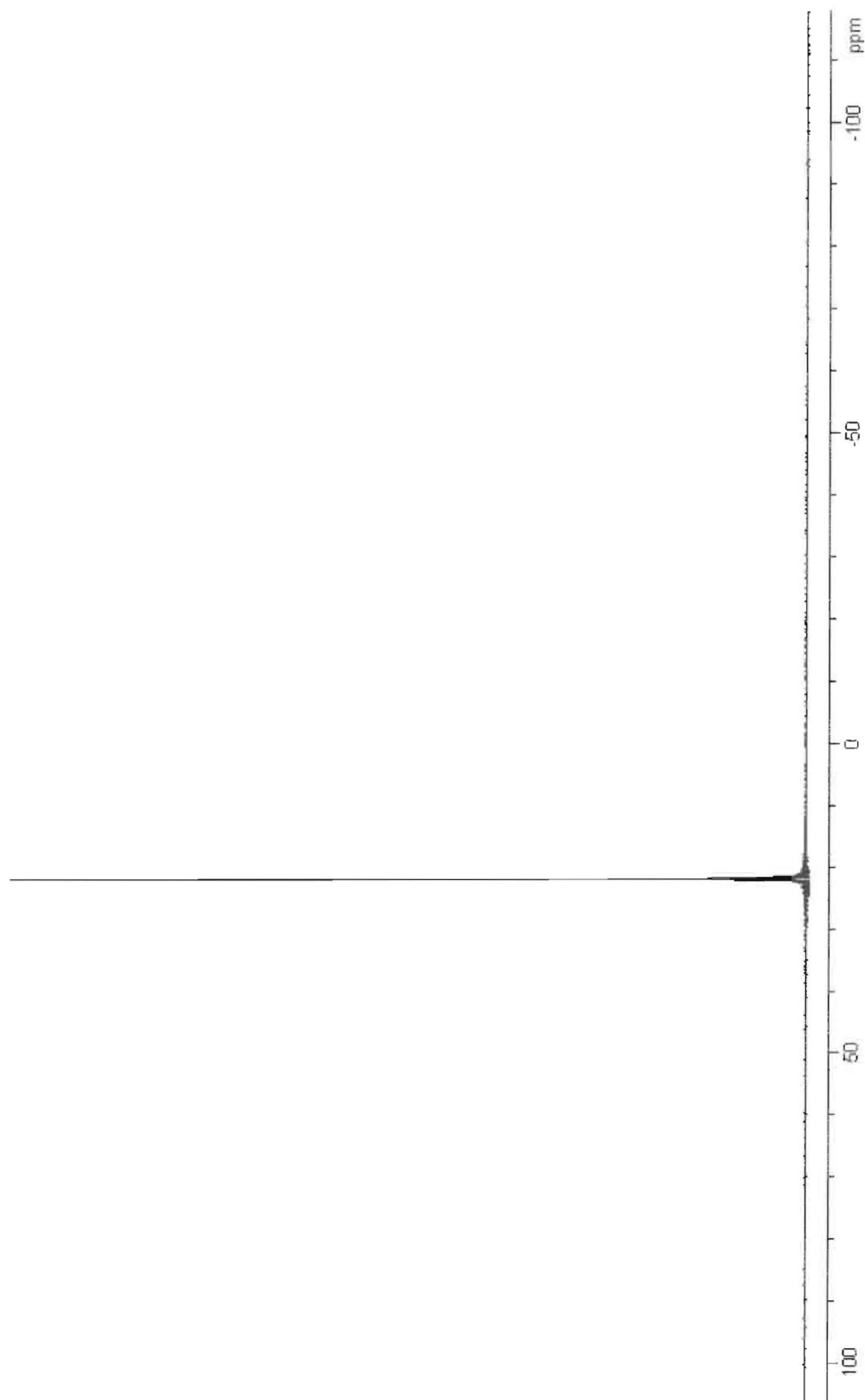
Figure 54. ^{1}H NMR spectrum of compound **46c**
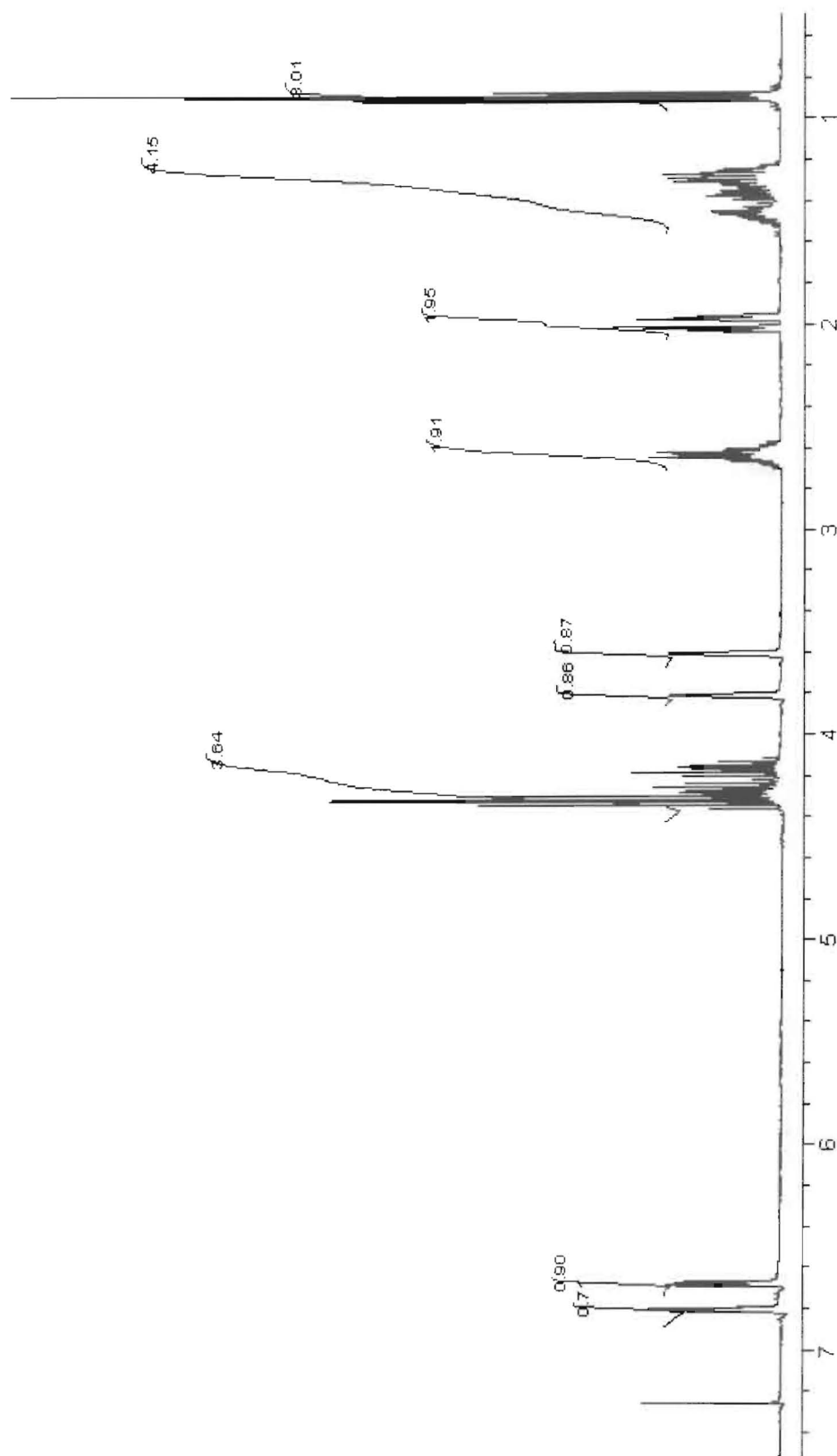
Figure 55. ^{13}C NMR spectrum of compound 46c
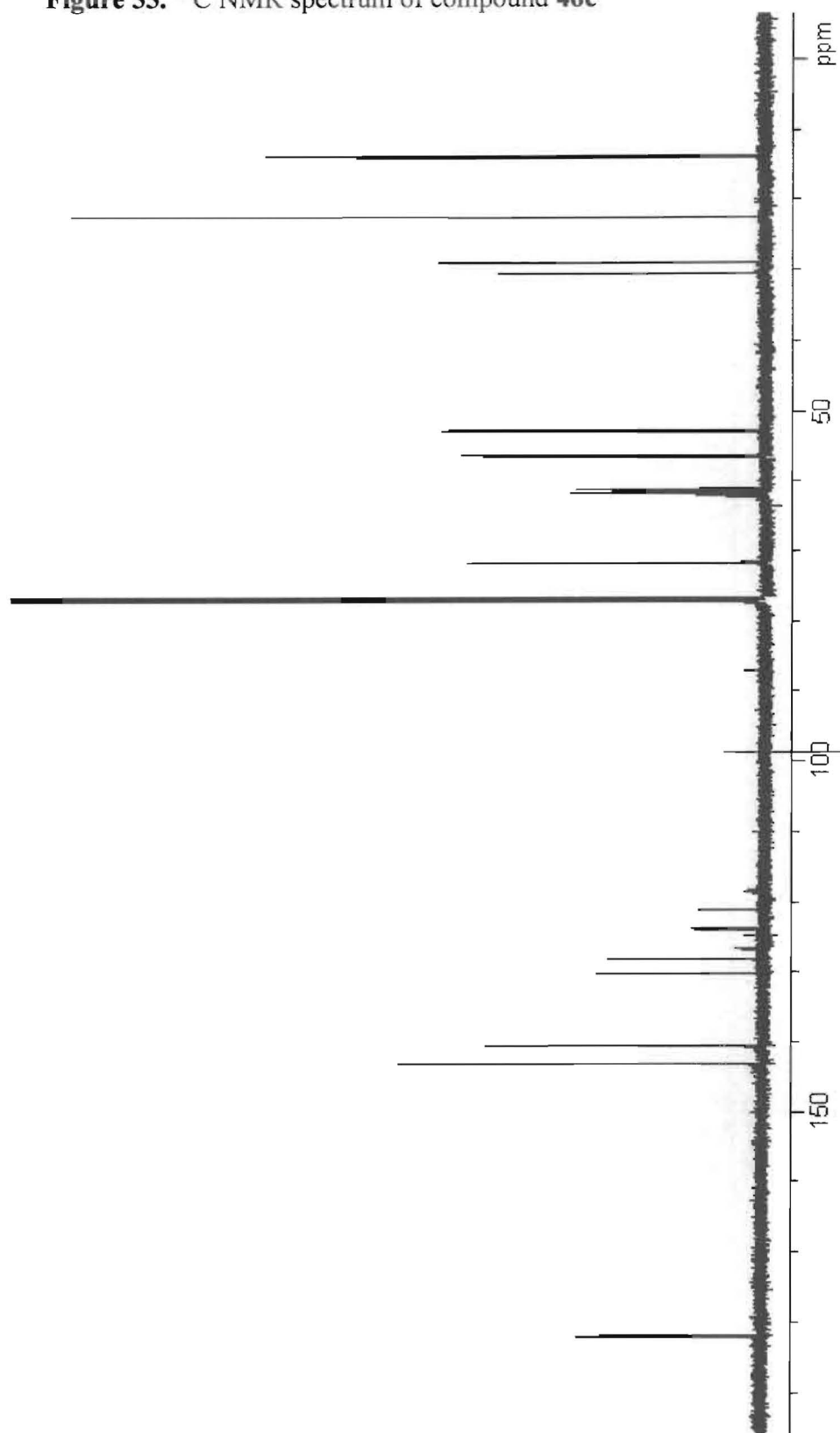
Figure 56. Mass spectrum of compound **46c**
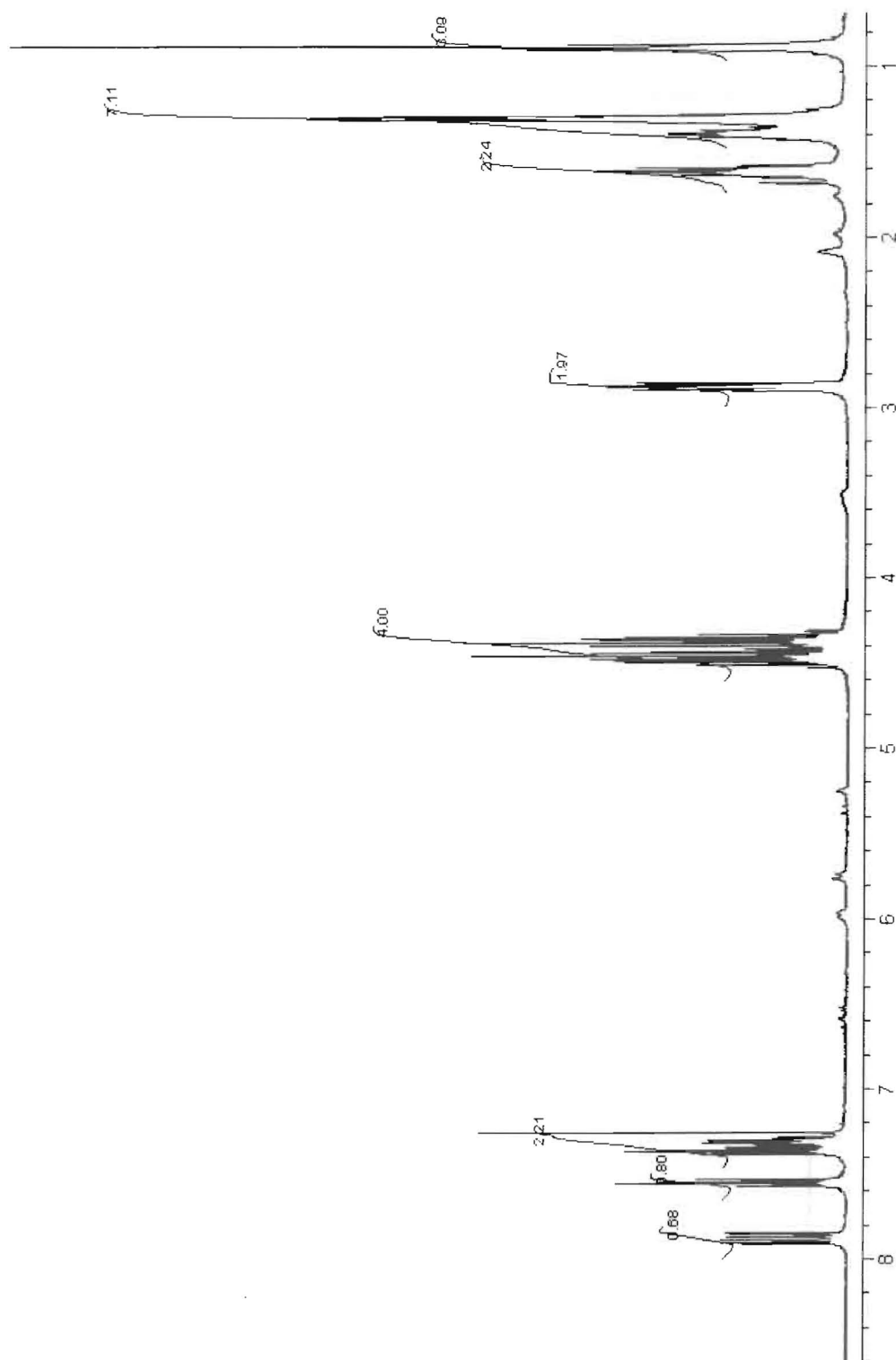
Figure 57. ^{31}P NMR spectrum of compound **46d**

Figure 58. ^{1}H NMR spectrum of compound **46d**

Figure 59. ^{13}C NMR spectrum of compound **46d**

Figure 60. Mass spectrum of compound **46d**

Figure 61. ^{31}P NMR spectrum of compound **48a**
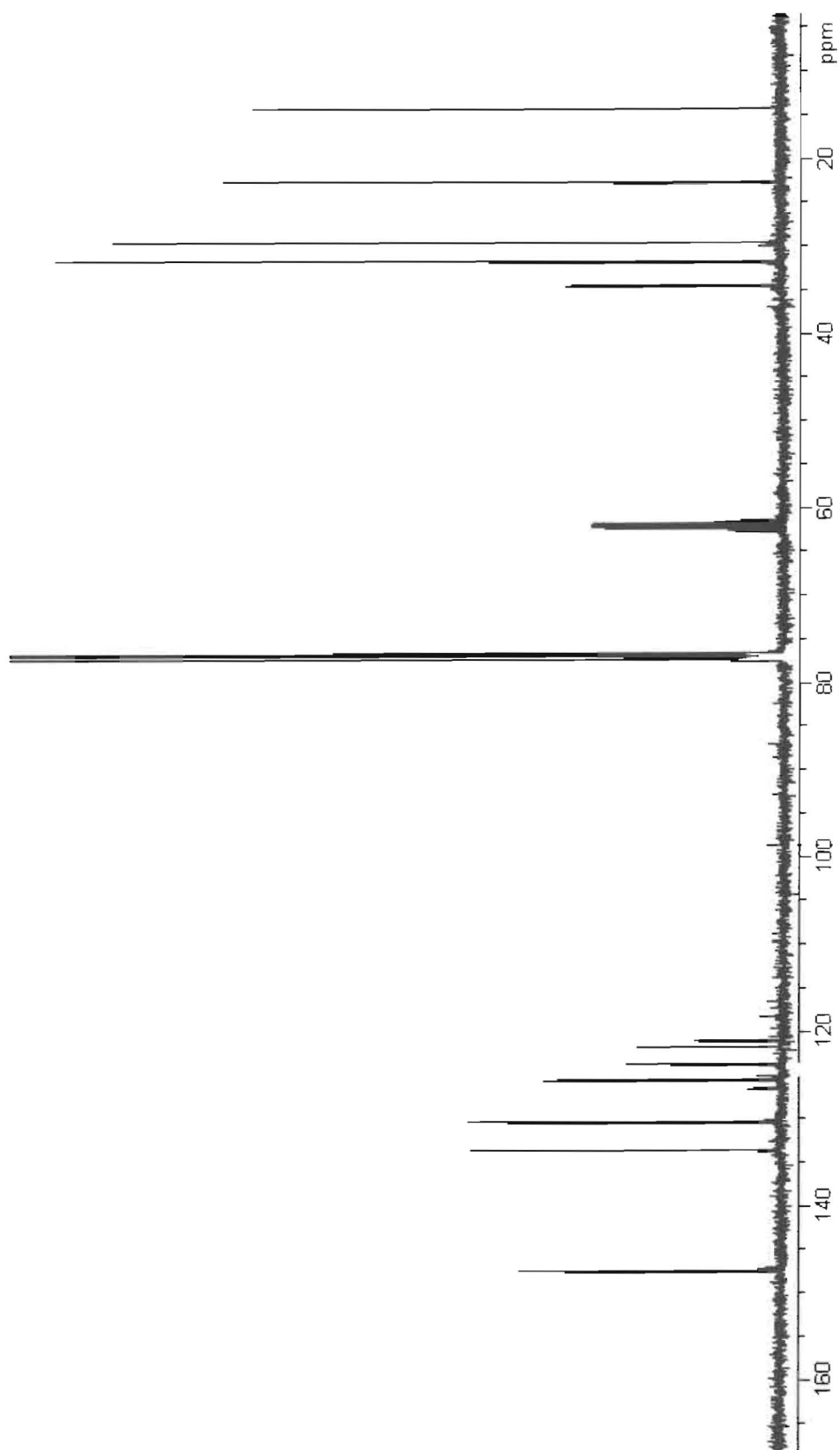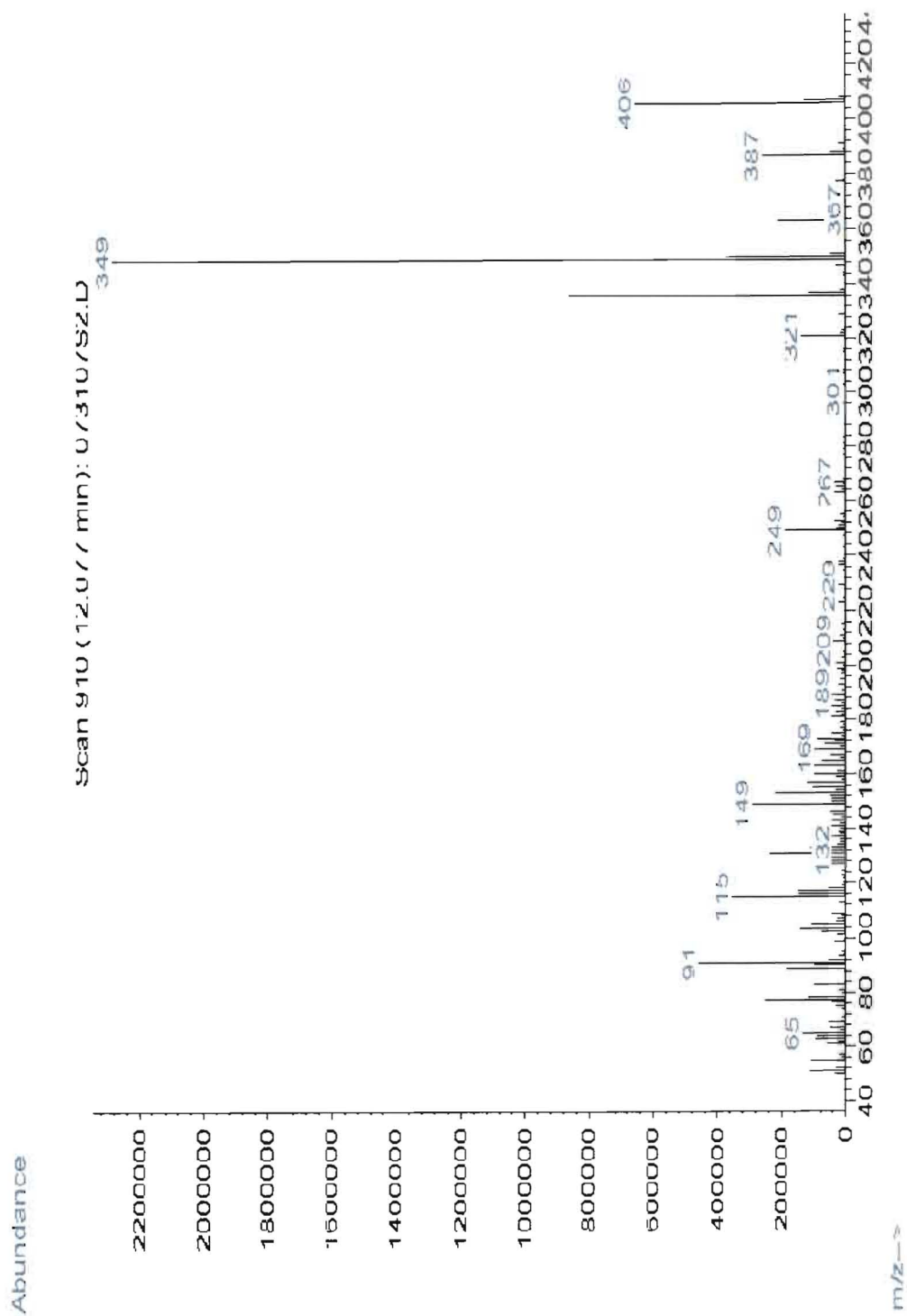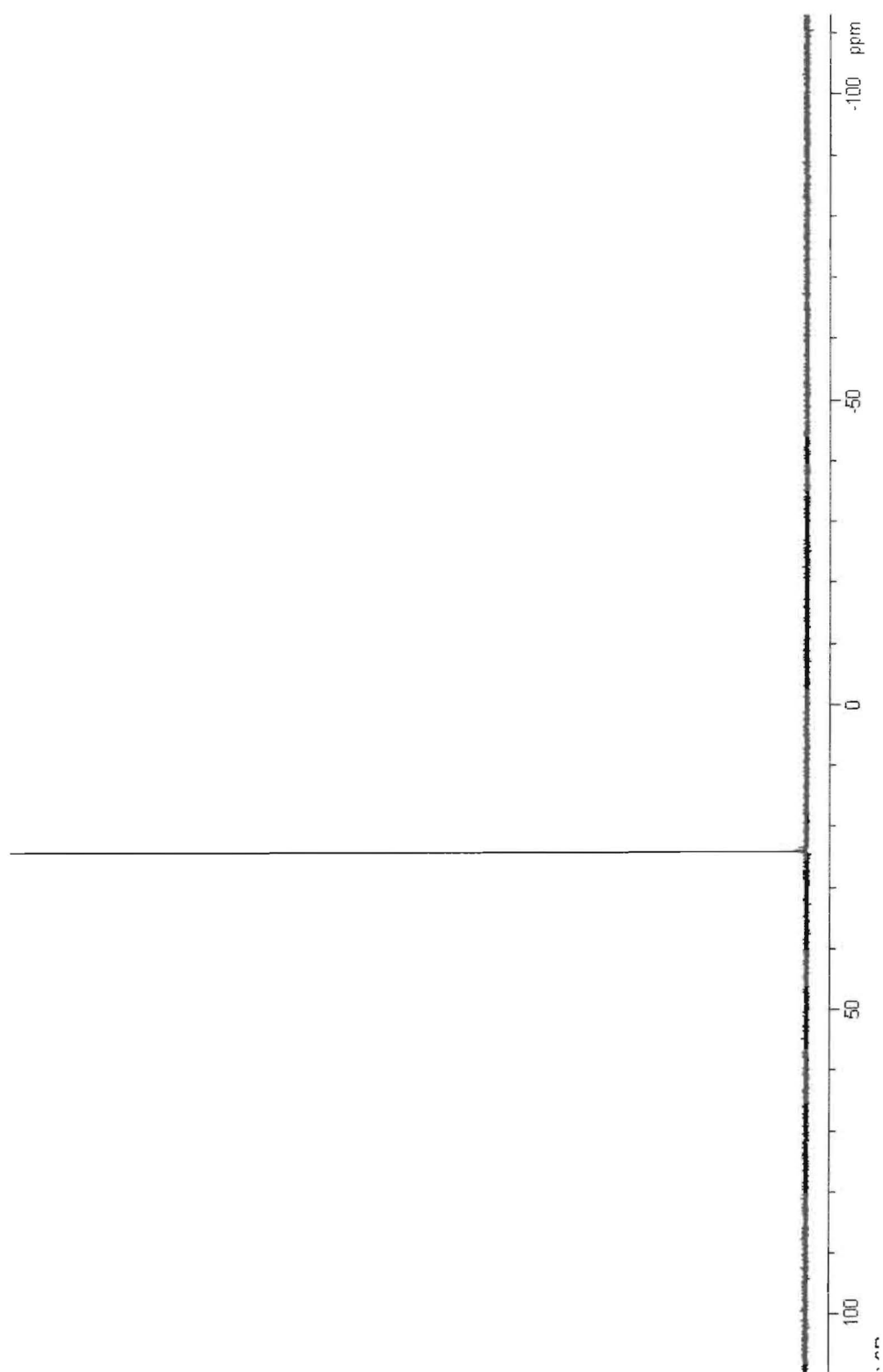
Figure 62. ^{1}H NMR spectrum of compound **48a**

Figure 63. ^{13}C NMR spectrum of compound **48a**

Figure 64. mass spectrum of compound **48a**

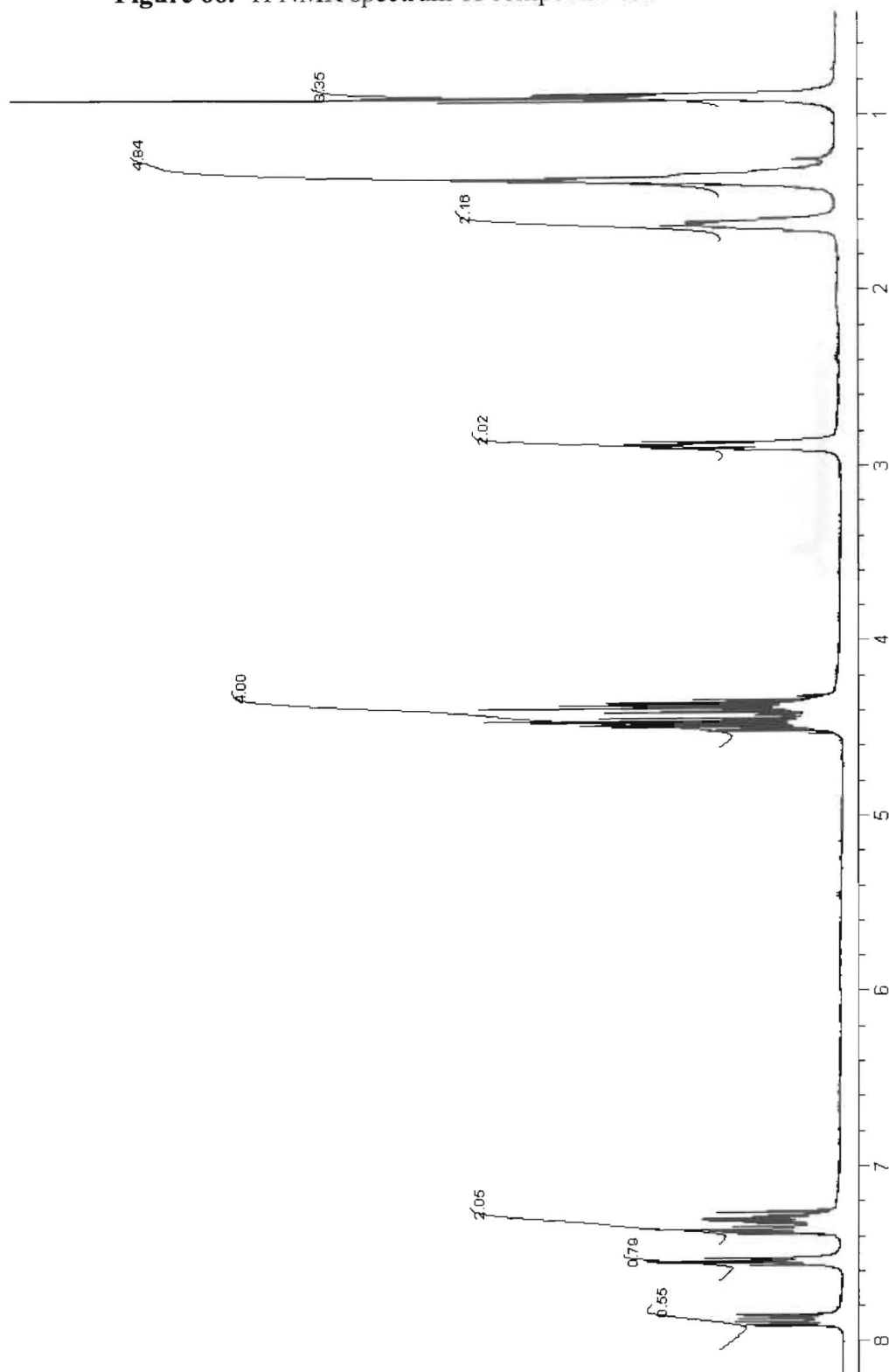**Figure 65.** ^{31}P NMR spectrum of compound **48b**

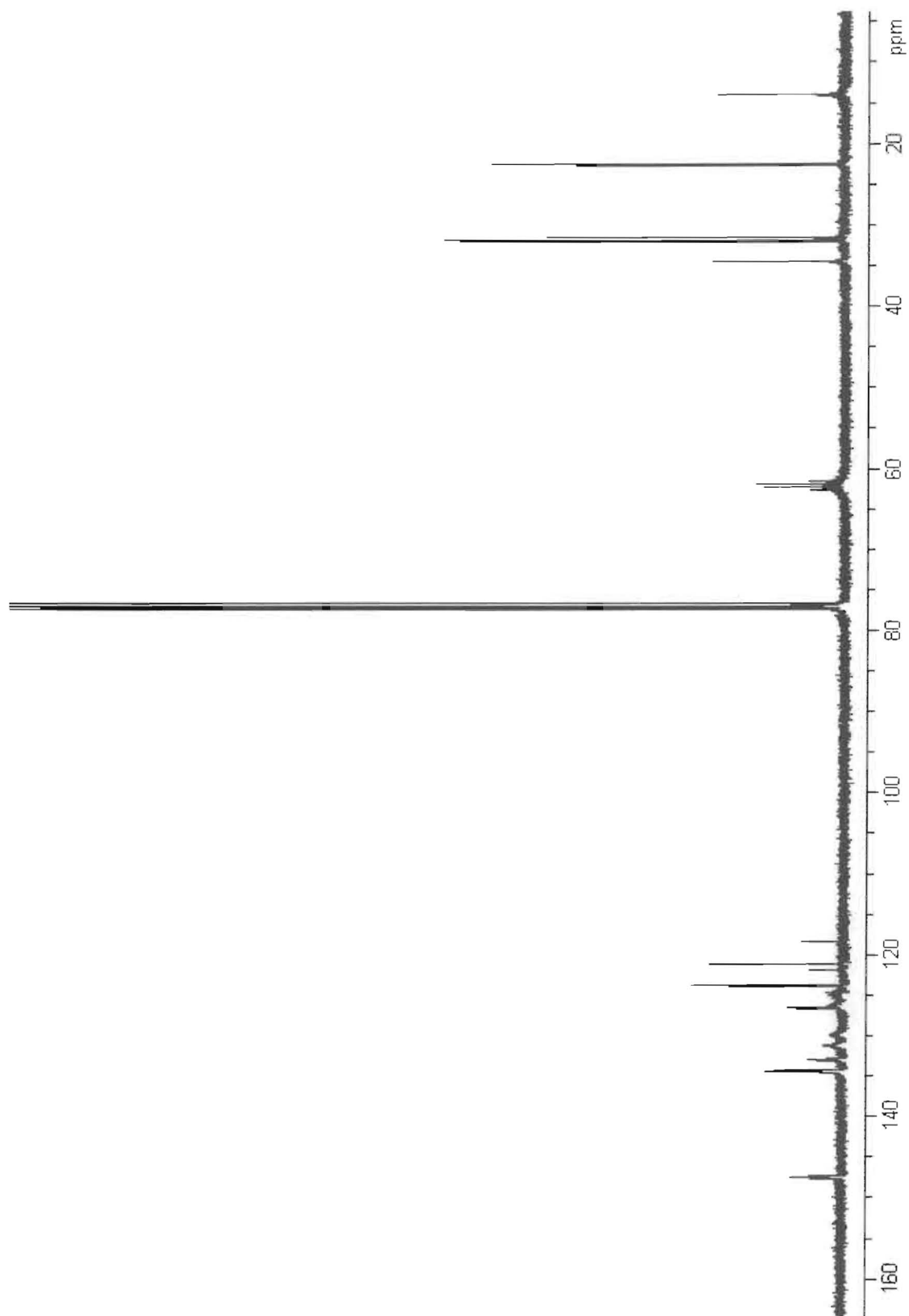**Figure 66.** ^{1}H NMR spectrum of compound **48b**

Figure 67. ^{13}C NMR spectrum of compound **48b**
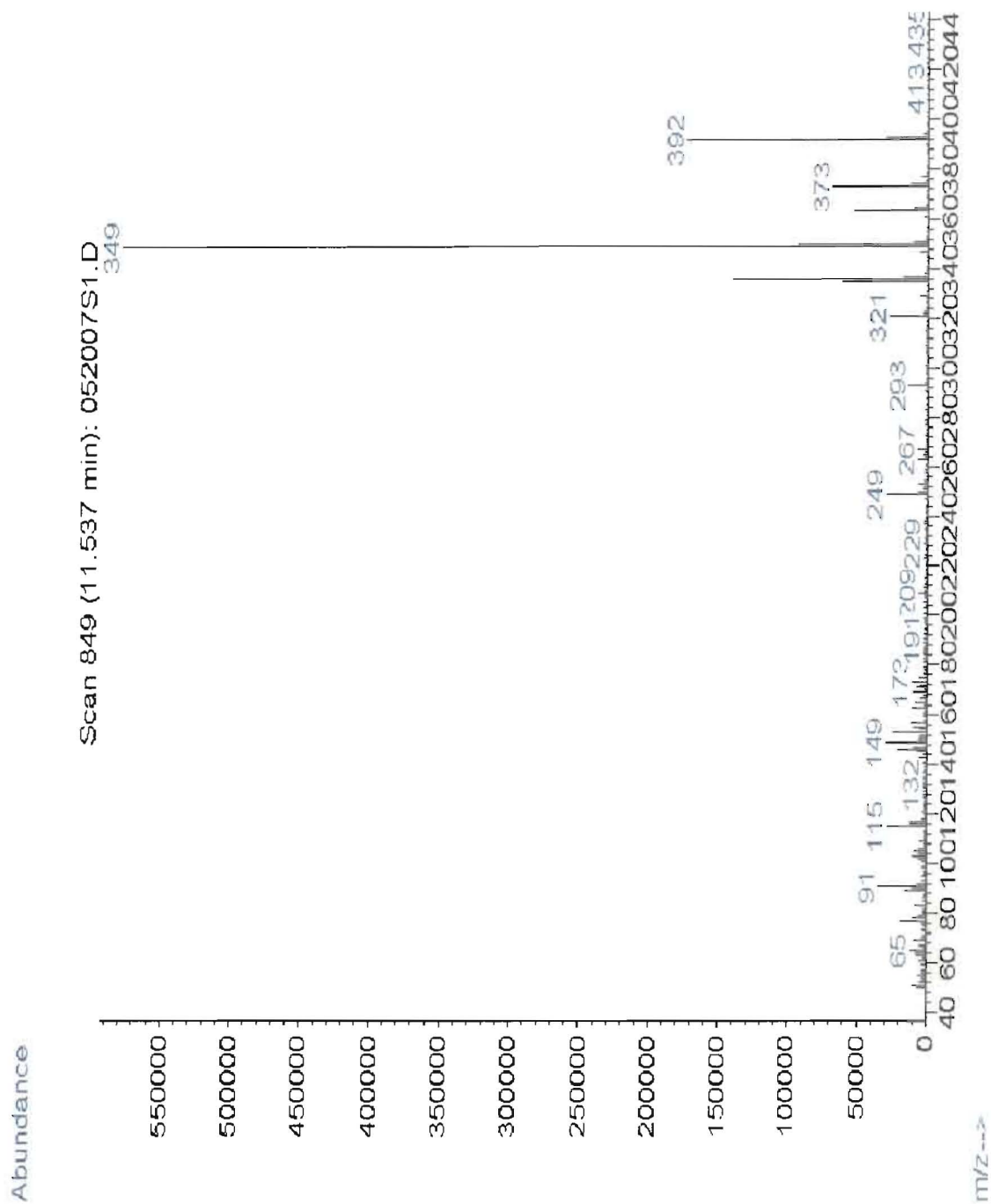
Figure 68. Mass spectrum of compound **48b**

Figure 69. ^{31}P NMR spectrum of compound **48c**

Figure 70. ^{1}H NMR spectrum of compound **48c**

Figure 71. ^{13}C NMR spectrum of compound **48c**
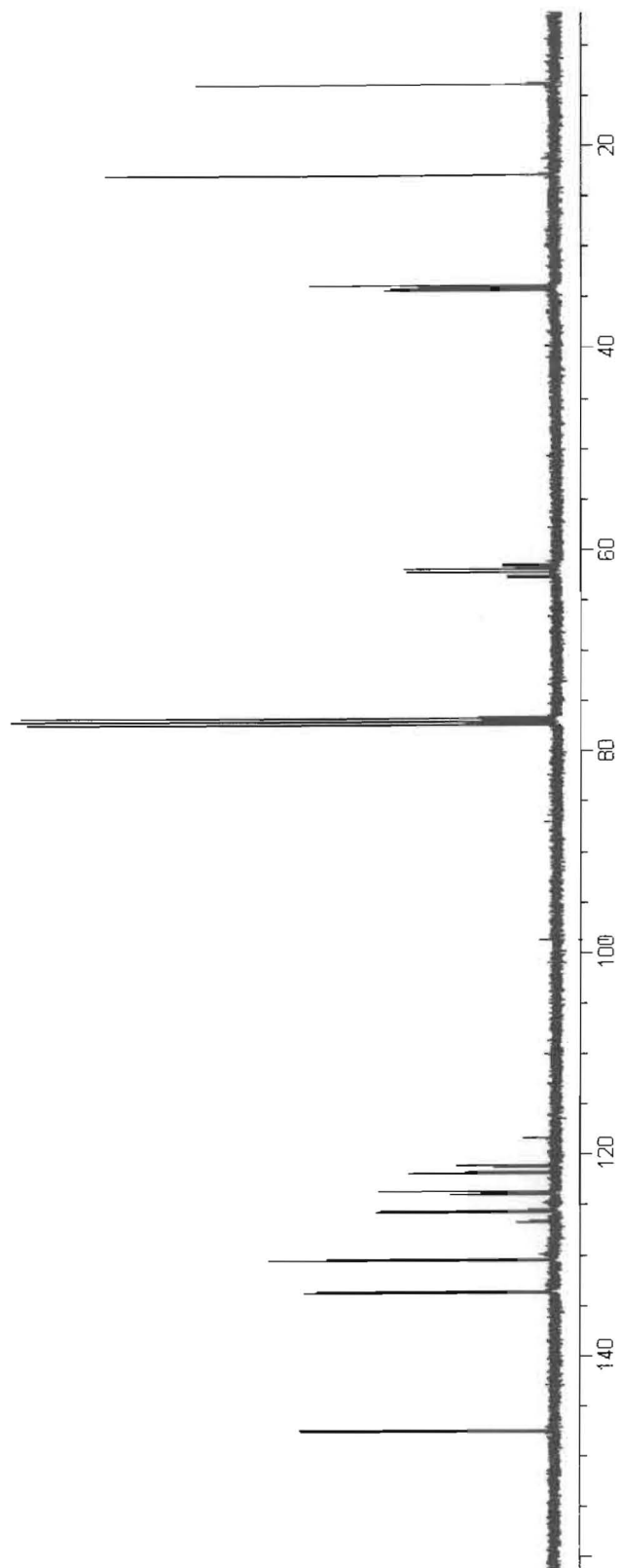
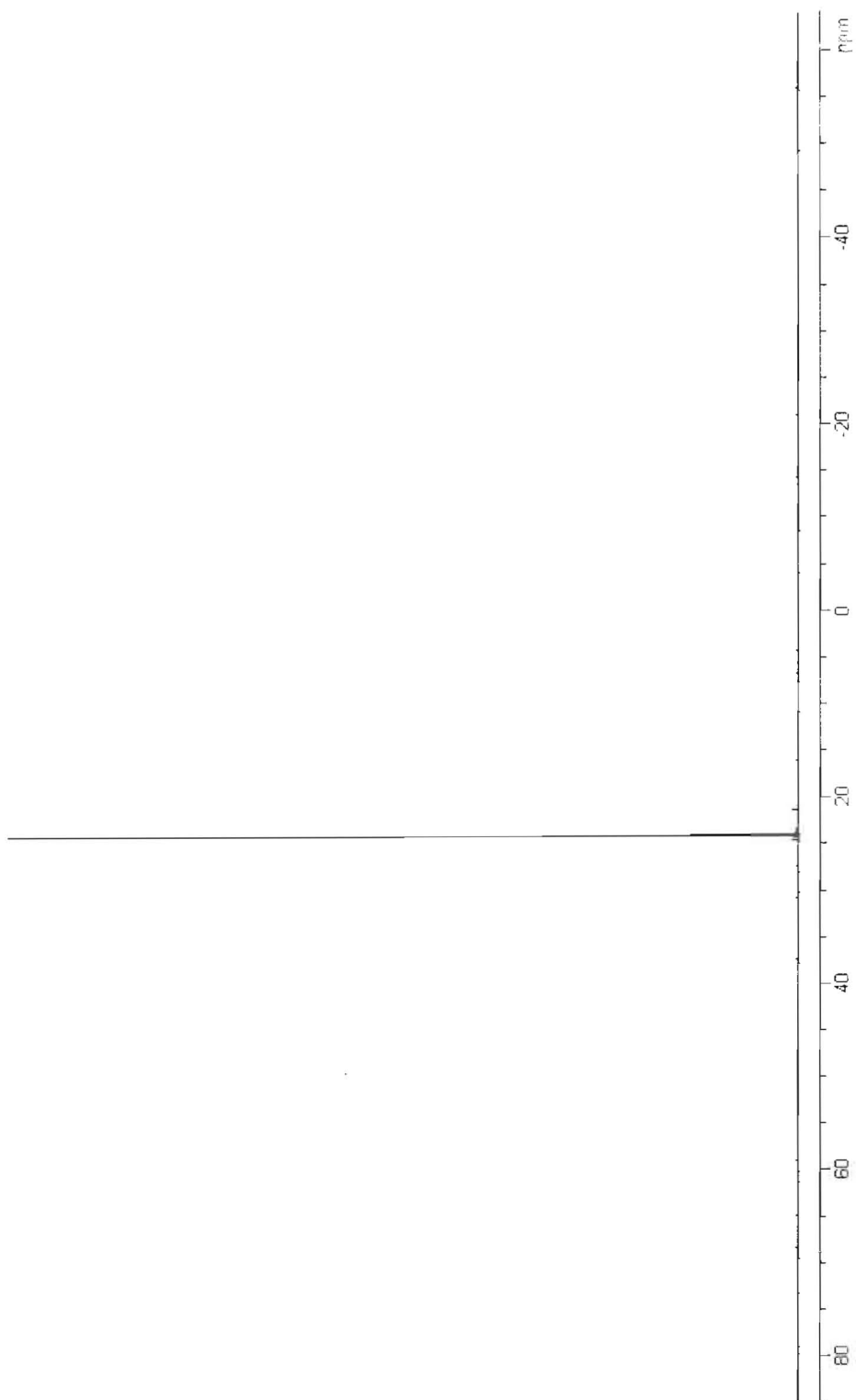**Figure 72.** Mass spectrum of compound **48c**

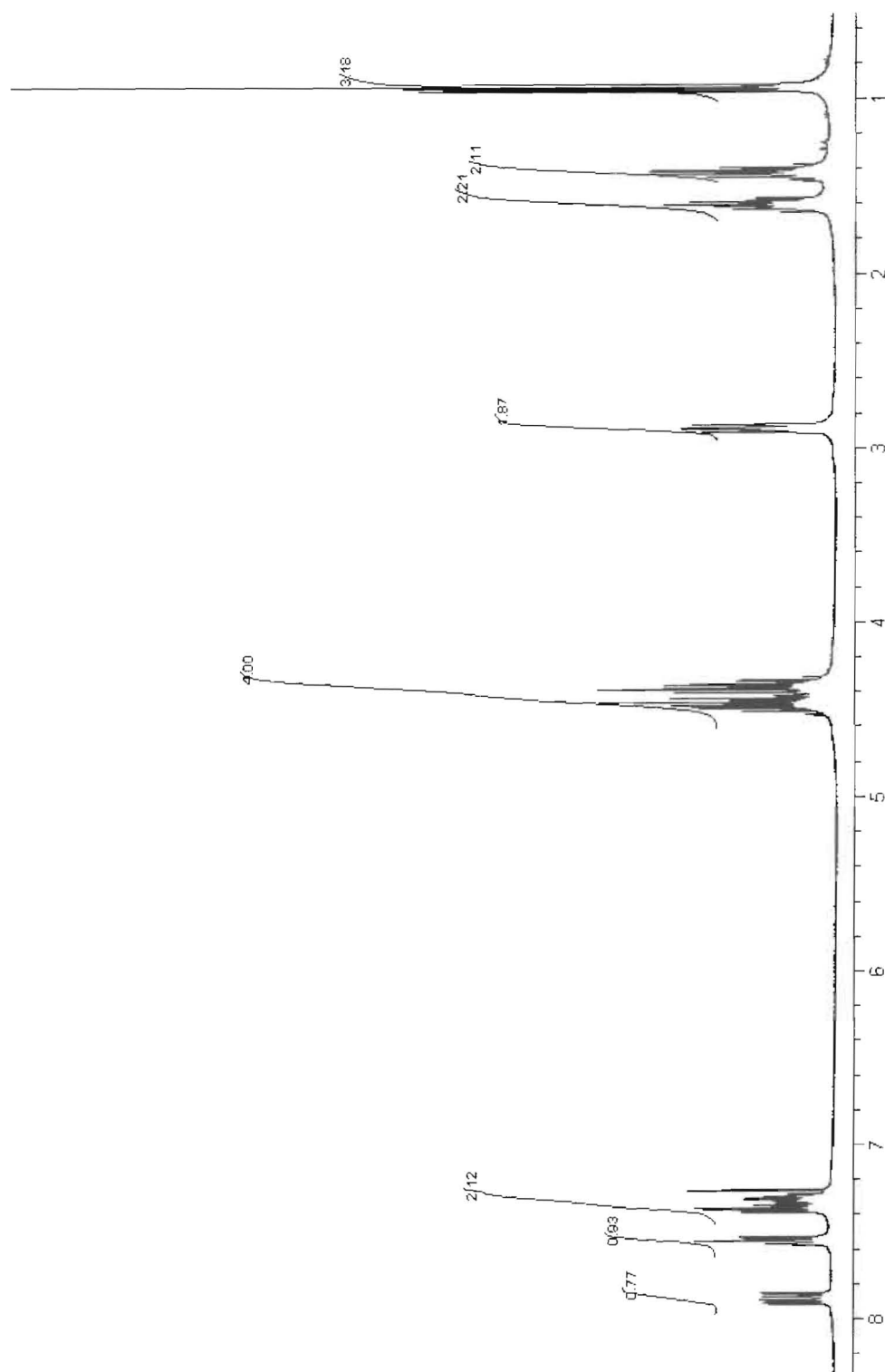**Figure 73.** ^{31}P NMR spectrum of compound **48d**

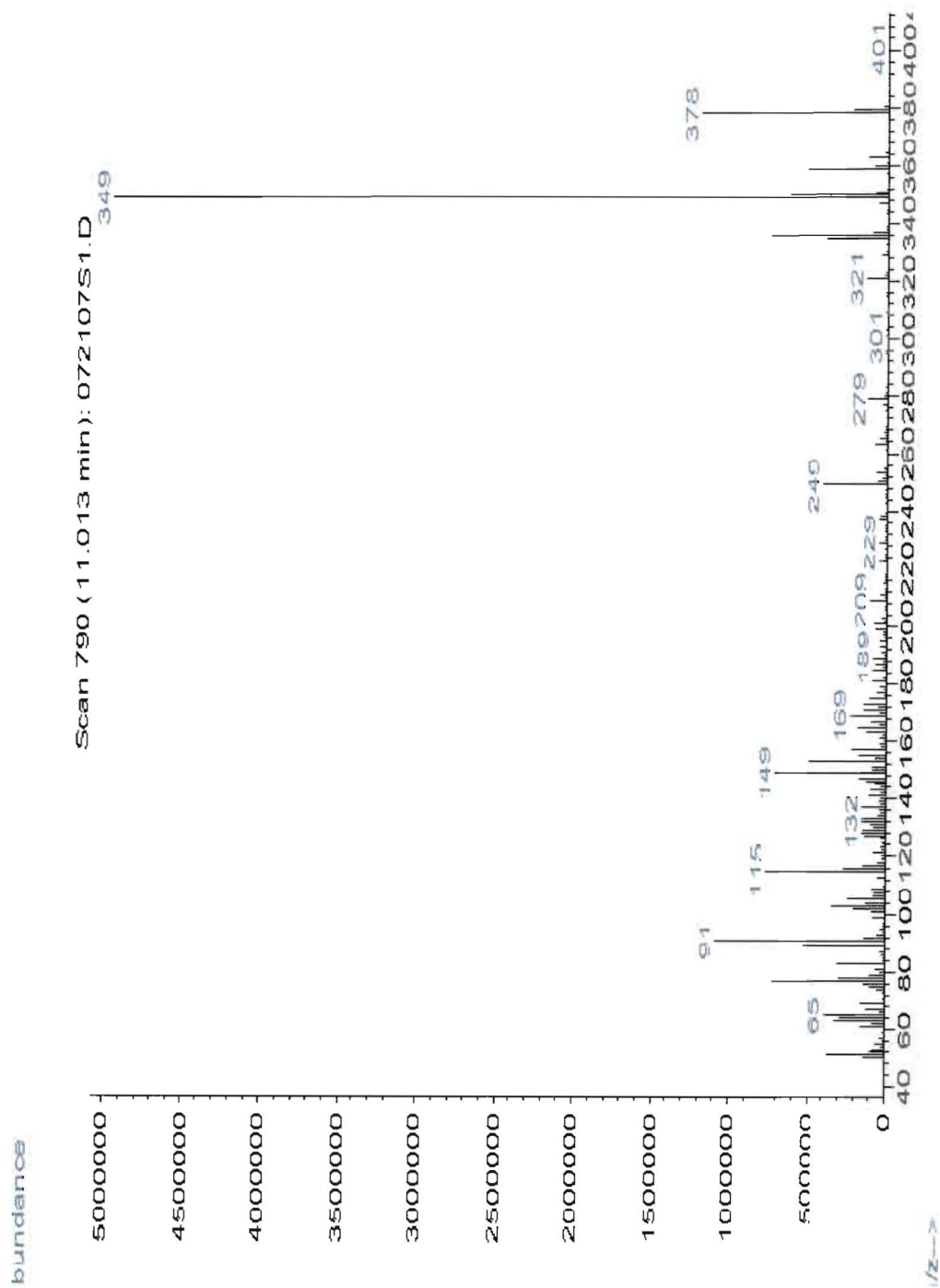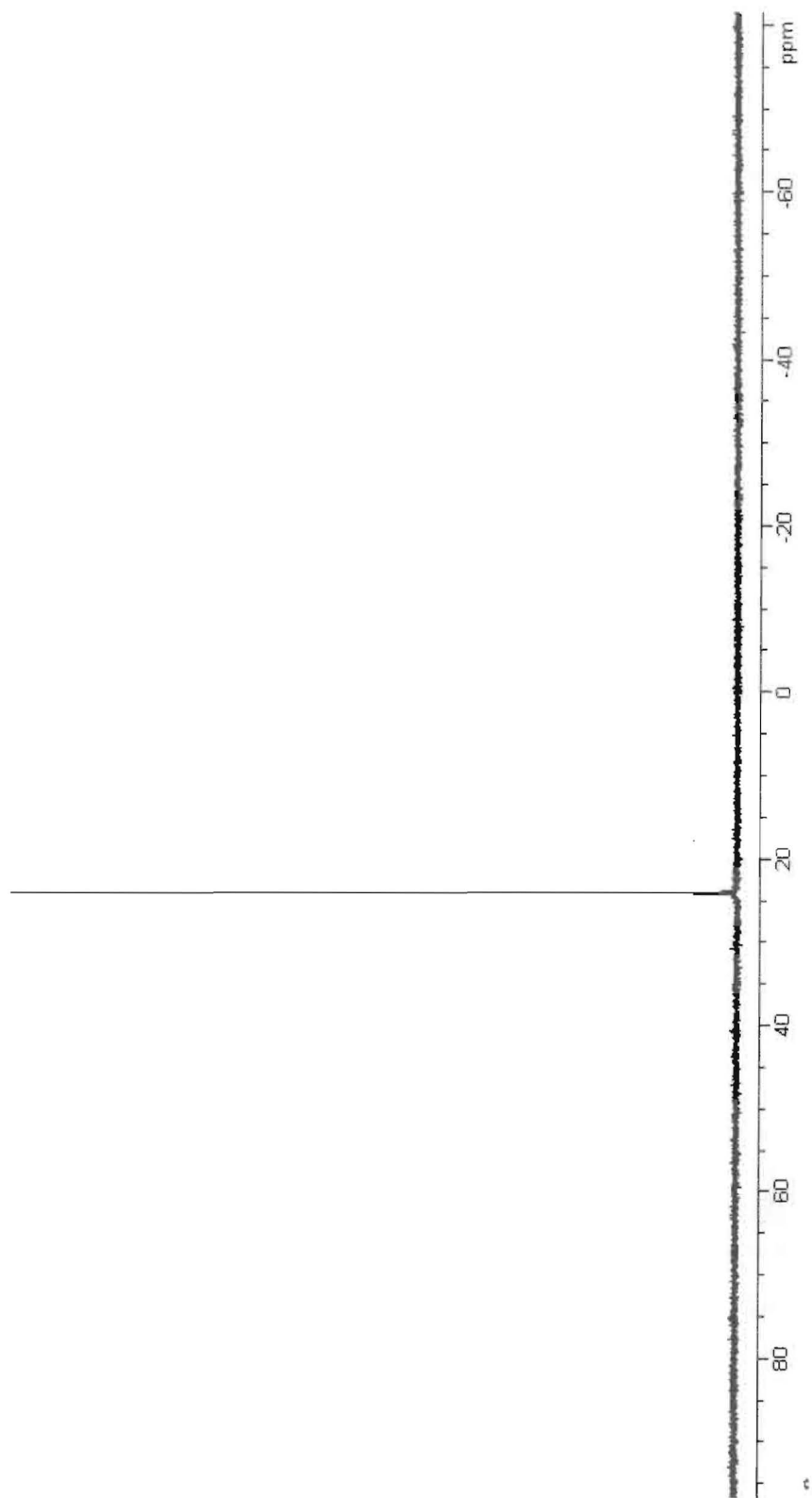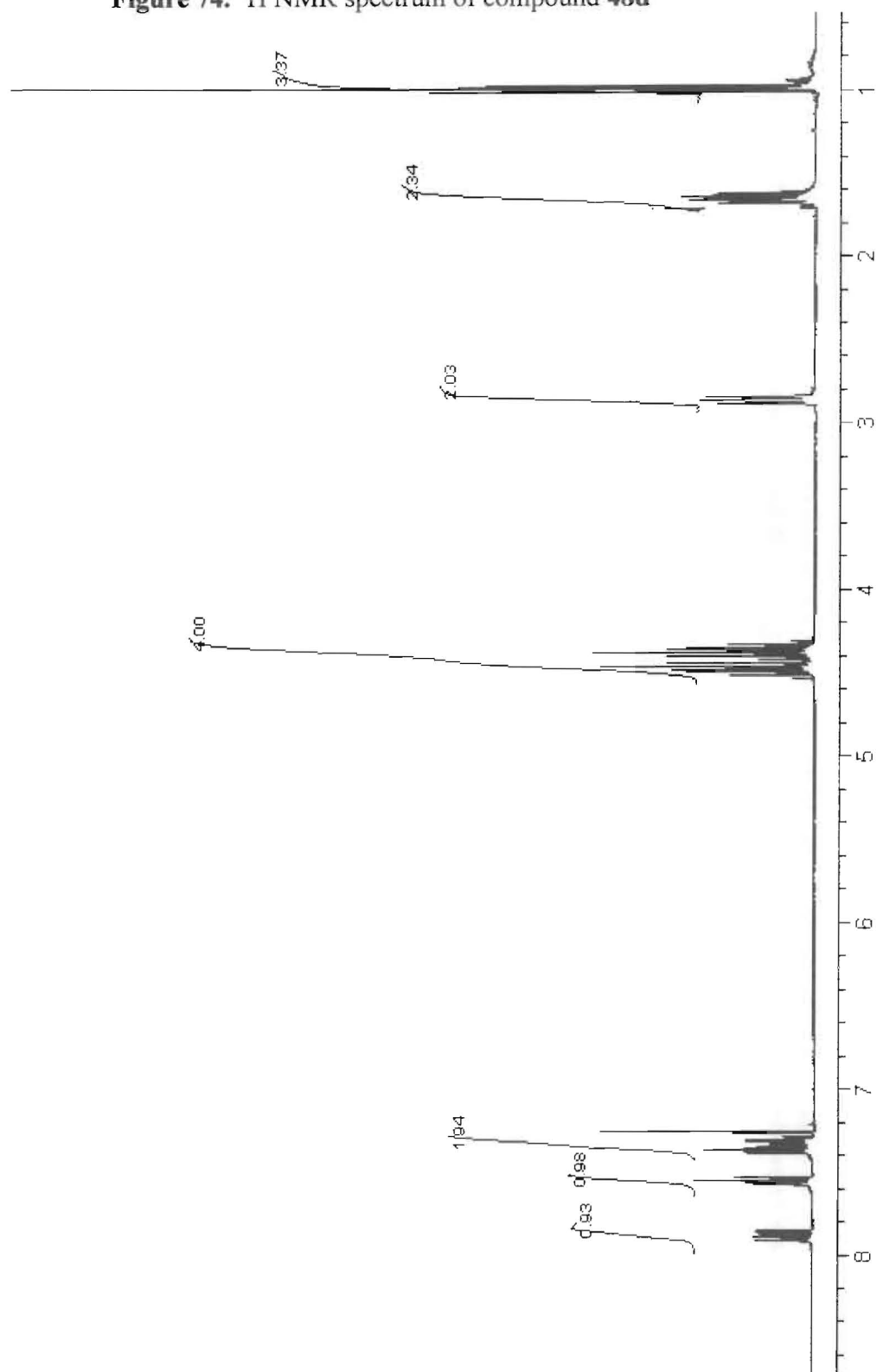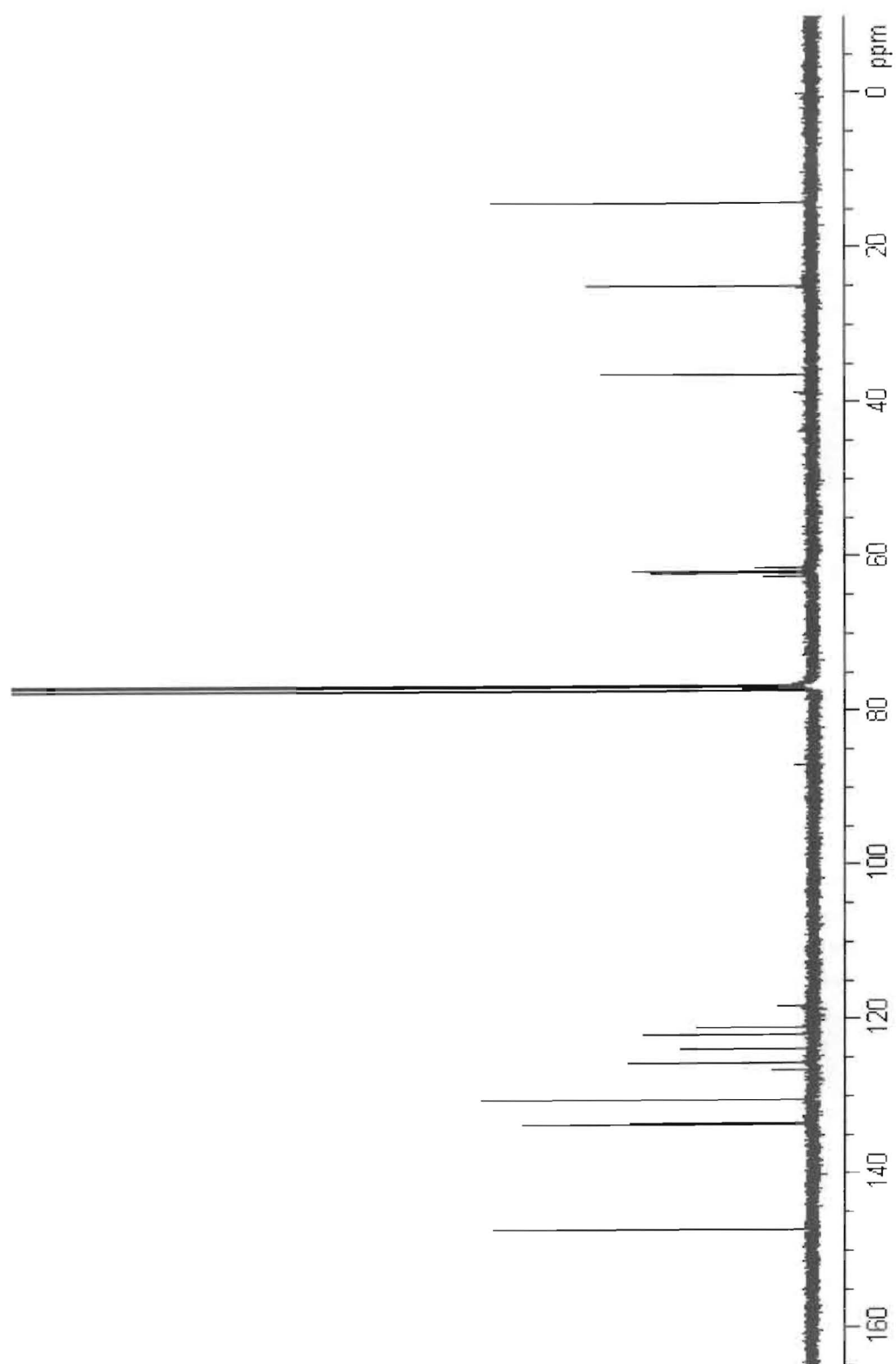**Figure 74.** ^{1}H NMR spectrum of compound **48d**

Figure 75. ^{13}C NMR spectrum of compound **48d**

Figure 76. Mass spectrum of compound **48d**
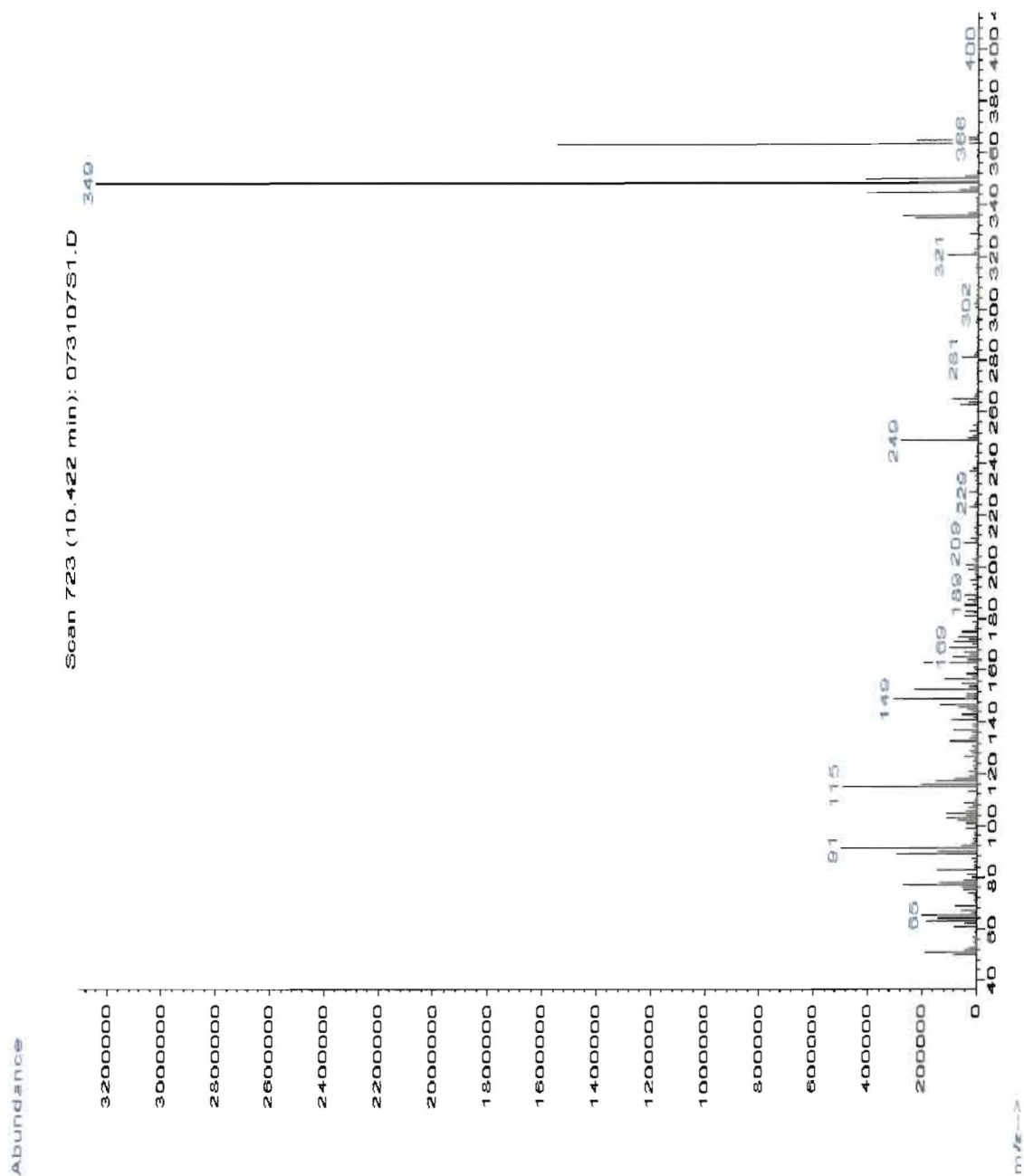
Figure 77. ^{1}H NMR spectrum of compound **45**
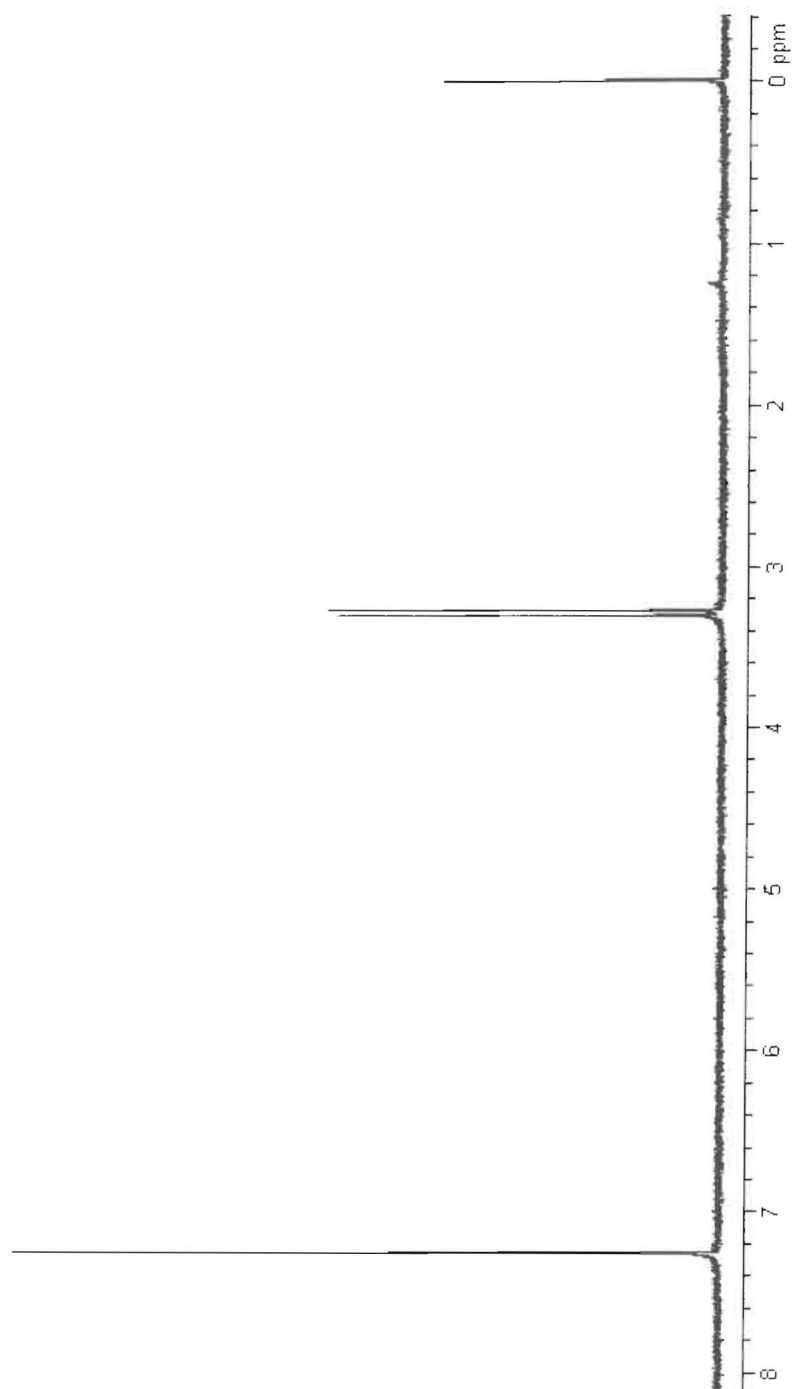
Figure 78. ^{13}C NMR spectrum of compound **45**
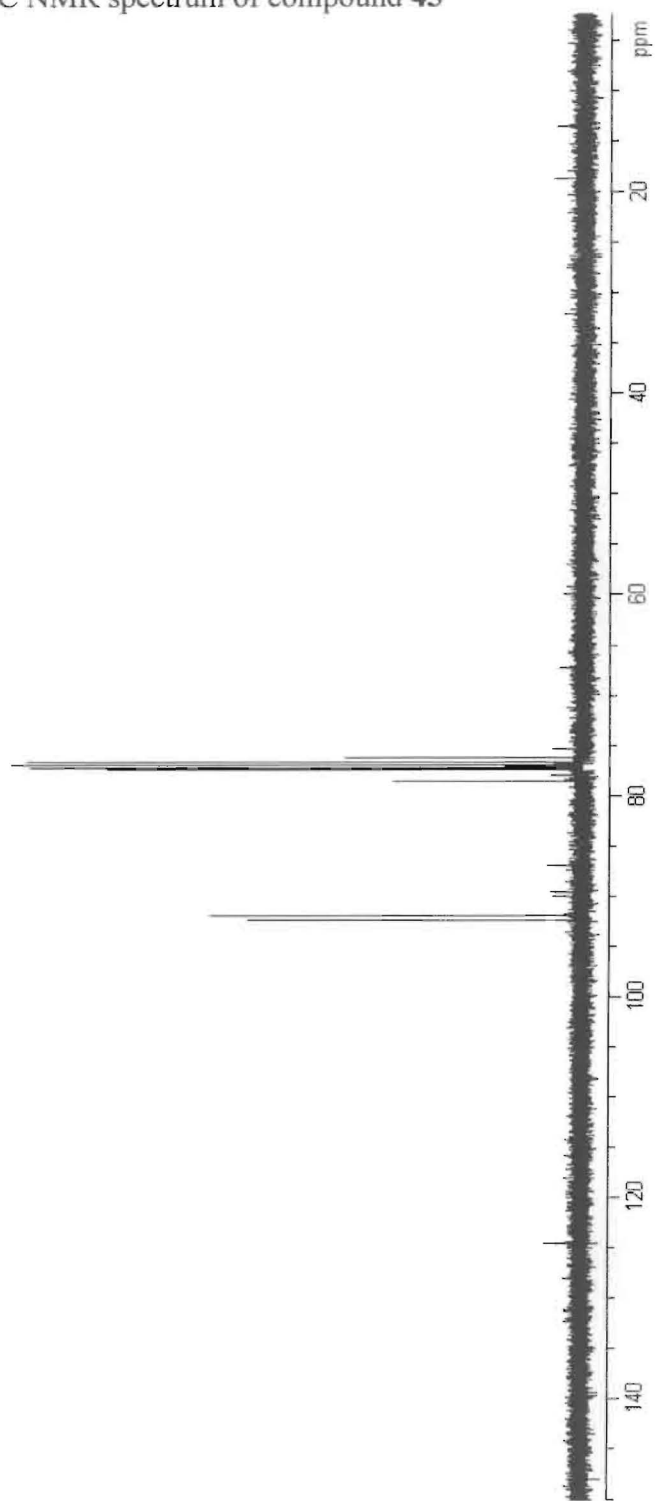
Appendix B

Figure 79. X-ray structure of trisethynyl phosphine oxide **45**
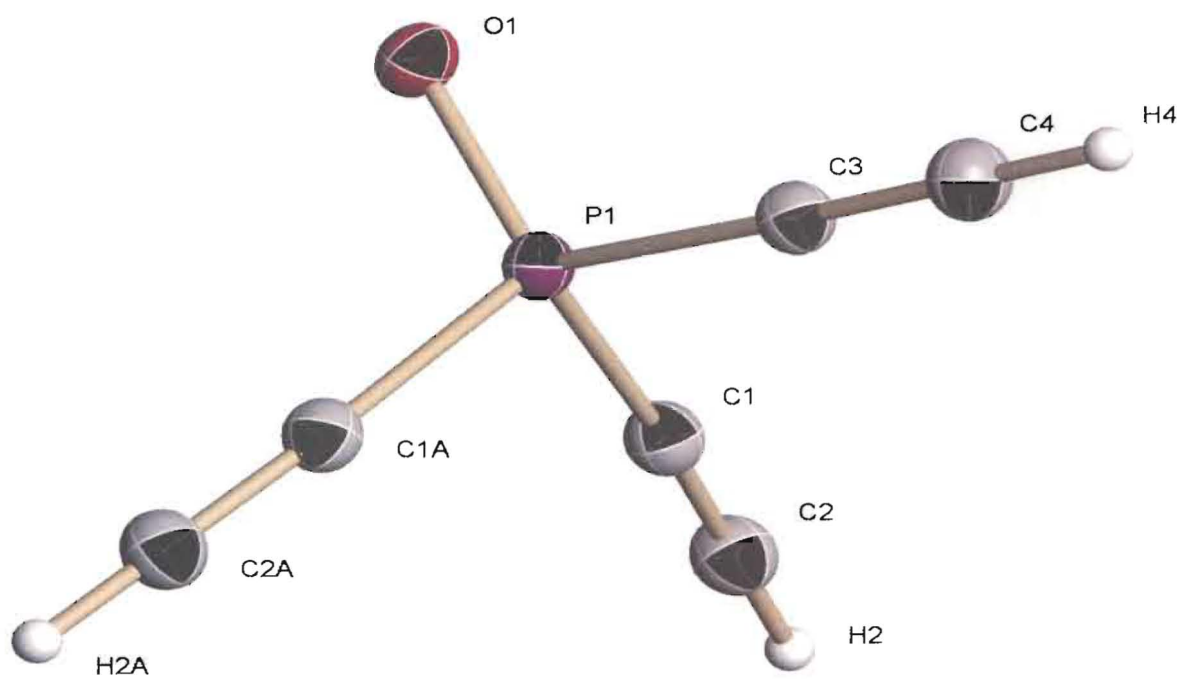
Table 1. Crystal data and structure refinement for 07rk001m:

Identification code	07rk001m
Empirical formula	C6 H3 O P
Formula weight	122.05
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pnma
Unit cell dimensions	
	$a = 6.8646(9)$ Å, $\alpha = 90°$
	$b = 9.7823(13)$ Å, $\beta = 90°$
	$c = 9.3277(12)$ Å, $\gamma = 90°$
Volume, Z	626.37(14) Å^3, 4
Density (calculated)	1.294 Mg/m^3
Absorption coefficient:	0.328 mm^{-1}
$F(000)$	248
Crystal size	0.48 × 0.23 × 0.22 mm
Crystal shape, colour	block, colourless
θ range for data collection	3.02 to 28.28°
Limiting indices	$-9 \leq h \leq 9$, $13 \leq k \leq 13$, $12 \leq$

$$l \leq 12$$

Reflections collected 7459

Independent reflections 821 (R(int) = 0.0177)

Completeness to $\theta = 28.28°$ 100.0 %

Absorption correction multi-scan

Max. and min. transmission 0.930 and 0.708

Refinement method Full-matrix least-squares on F^2

Data / restraints / parameters 821 / 0 / 43

Goodness-of-fit on F^2 1.118

Final R indices [$I>2\sigma(I)$] R1 = 0.0298, wR2 = 0.0838

R indices (all data) R1 = 0.0302, wR2 = 0.0841

Largest diff. peak and hole 0.446 and −0.327 e × $Å^{-3}$

Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors

Treatment of hydrogen atoms:
All hydrogen atoms were placed in calculated positions and were refined with an isotropic displacement parameter 1.2 times that of the adjacent carbon atom.

Table 2. Atomic coordinates [× 10^4] and equivalent isotropic displacement parameters [$\text{Å}^2 \times 10^3$] for 07rk001m. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
P(1)	4205(1)	7500	5343(1)	16(1)
O(1)	2977(2)	7500	4036(1)	21(1)
C(1)	3797(2)	6090(1)	6448(1)	20(1)
C(2)	3387(2)	5144(1)	7194(1)	23(1)
C(3)	6715(3)	7500	5018(2)	19(1)
C(4)	8405(3)	7500	4760(2)	24(1)

All esds (except the esd in the dihedral angle between two l.s. planes)are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate(isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table 3.   Bond lengths [Å] and angles [deg] for 07rk001m.   —

P(1)-O(1)	1.4826(12)
P(1)-C(1)	1.7443(12)
P(1)-C(1)#1	1.7443(12)
P(1)-C(3)	1.7495(18)
C(1)-C(2)	1.1914(17)
C(4)-C(3)	1.185(3)
C(4)-H(4)	0.9500
C(2)-H(2)	0.9500
O(1)-P(1)-C(1)	113.25(5)
C(1)-P(1)-C(1)#1	104.52(8)
O(1)-P(1)-C(3)	114.67(8)
C(1)-P(1)-C(3)	105.09(5)
C(1)#1-P(1)-C(3)	105.09(5)
C(2)-C(1)-P(1)	175.54(11)
C(3)-C(4)-H(4)	180.0
C(4)-C(3)-P(1)	178.24(17)
C(1)-C(2)-H(2)	180.0

Symmetry transformations used to generate equivalent
atoms: #1 x,-y+3/2,z

Table 4.   Anisotropic displacement parameters [Å^2 × 10^3] for
07rk001m.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi2 \ [(h \ a\star)^2 \ U11 + \ ... \ + 2 \ h \ k \ a\star \ b\star \ U12]$$

	U11	U22	U33	U23	U13	U12
P(1)	14(1)	16(1)	18(1)	0	0(1)	0
O(1)	19(1)	22(1)	21(1)	0	-4(1)	0
C(1)	18(1)	20(1)	22(1)	-1(1)	0(1)	0(1)
C(2)	23(1)	22(1)	24(1)	0(1)	2(1)	0(1)
C(3)	19(1)	18(1)	20(1)	0	1(1)	0
C(4)	20(1)	25(1)	26(1)	0	0(1)	0

Table 5. Hydrogen coordinates ($\times$ 10^4) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for 07rk001m.

	x	y	z	U(eq)
H(2)	3060	4390	7788	28
H(4)	9760	7500	4552	28

Table 6. Hydrogen bonds for 07rk001m [Å and deg].

D-H...A	(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(4)...O(1)#2	0.95	2.26	3.210(2)	179.4
C(2)-H(2)...O(1)#3	0.95	2.30	3.2433(14)	173.7

Symmetry transformations used to generate equivalent atoms:

#1 x,-y+3/2,z   #2 x+1,y,z   #3 -x+1/2,-y+1,z+1/2