Nucleophilic Addition of Sugar-Derived Dithiane Nucleophiles to Sugar Lactones: A New Approach to *C*-Disaccharides

by

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Thesis Abstract

Nucleophilic addition of dithiane anions to sugar-derived lactones has been studied as a new route to *C*-disaccharides. Addition of lithium bis(phenylthio)methane to various furanose lactones yields ketoses, which have been reduced to the parent *C*-glycosides. Use of a D-ribofuranose-derived dithiane nucleophile in this chemistry leads to a *C*-disaccharide progenitor, which has been manipulated further to the methylene bridged derivative. The stereochemical course of the addition chemistry, as well as the influence of the sequence of reduction steps will be discussed in detail.

Acknowledgements

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Introduction

During the past 30 years carbohydrate chemistry has become an increasingly important part of chemistry and biology. The surge of interest in carbohydrate synthesis has developed from the discovery of the importance of glycoconjugates, especially glycoproteins and glycolipids, in their ability to control biochemical processes.[1] These advances have made the science of *glycobiology* one of the fastest growing divisions of biochemistry. There have also been discoveries of naturally isolated antibiotics containing unusual saccharide structures, leading to the need for new synthetic methodology for synthesizing these compounds.[2]

Carbohydrate (sugar) containing macromolecules, members of the natural product family, are mainly built from monosaccharides. There are currently over 200 monosaccharides known and each one can be grouped according to the number of carbon atoms contained, the orientation of the attached hydroxyl groups, and whether they are polyhydroxylated aldehydes (aldoses) or polyhydroxylated ketones (ketoses). Combinations of the aforementioned properties give each sugar its own unique characteristics.

Monosaccharides can exist in three distinct forms: a furanose ring (5-membered); a pyranose ring (6-membered); and an acyclic form, also known as the *aldehydo* form (Figure 1-**A**). When aldoses are in either of the closed ring formations they form hemiacetals, which refers to having two oxygen atoms (one O-H and one O-R) attached at C-1, the anomeric carbon. This allows the sugars to be acyclic or cyclic when in solution leading to the different forms of each sugar *via* ring opening and ring closing. This equilibrium in solution has a direct effect on the orientation of the substituent at the anomeric carbon. If the substituent group is above the plane of the ring the monosaccharide is classified as the beta (β) anomer (Figure 1:**C**, **E**), and if the substituent is below the plane it is classified as the alpha (α) anomer (Figure 1:**B**, **D**).

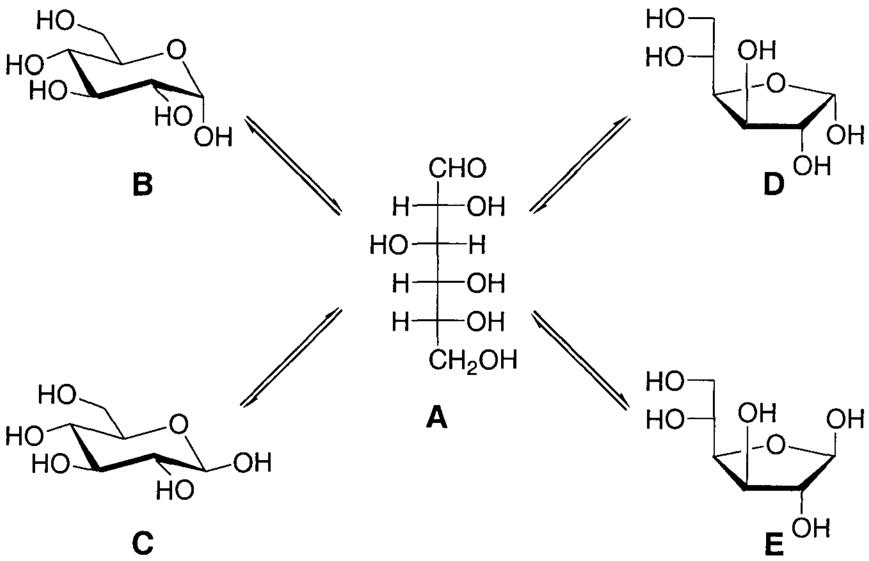


Figure 1. Different forms of D-Glucose

When carbohydrates are in the straight chain form, the classification of either polyhydroxylated ketones or polyhydroxylated aldehydes becomes obvious. Polyhydroxy ketones (ketoses) are sugars which have a ketone functionality in the straight chain form as illustrated with L-fructose (Figure 2), whereas polyhydroxy aldehydes (aldoses) have an aldehyde functionality as illustrated with D-galactose (Figure 2).

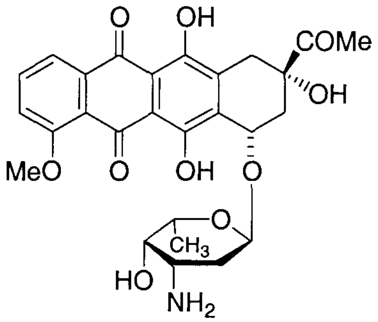
The notations D and L in D-galactose and L-fructose refer to the orientation of the hydroxyl group at the first stereocenter from the bottom in the Fischer projection. In the example of L-fructose the hydroxyl group is positioned to the left side of the main chain and is given the L notation, and with D-galactose it is oriented to the right making it a D-sugar.

L-Fructose **D-Galactose**

Figure 2. Example of an Aldose and a Ketose

Glycosides have become an important class of carbohydrate derivatives, due to their importance in biological systems and drug development. Glycosides are characterized by the replacement of the anomeric hydroxyl with another substituent such as -OR, carbon, or nitrogen. The resulting sugars are given the classifications *O*-glycoside, *C*-glycoside, and *N*-glycoside respectively.

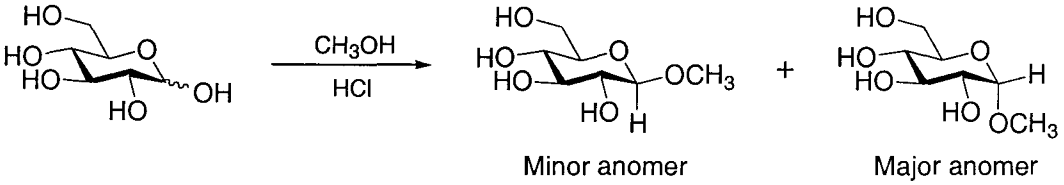
O-Glycosides are present in almost all aspects of nature from plants and animals to microbiological sources. Most antibiotics obtained from microbial sources are derived from carbohydrate precursors, and the need for these compounds has been one of the major stimuli to the pursuit of new glycoside synthetic routes. Daunomycin (Figure 3) is one of many anti-tumor antibiotics in the mycin family of compounds used to fight leukemia and soft-tissue sarcomas and is a good example of why chemists are so interested in developing these new pathways.[3]



Daunomycin

Figure 3. Example of medicinally important *O*-glycoside

When the hydroxyl group at the anomeric carbon is replaced by another electronegative atom in glycoside formation the anomeric effect comes into play, which leads to the stabilization of one anomer over the other. This phenomenon is an electronic interaction in pyranose form sugars between the ring oxygen and the electronegative anomeric substituent group. This interaction stabilizes the α anomer due to the overlap of the back non-bonding orbital of the substituent and one of the lone pairs of the ring oxygen, which is not possible in the β position. This can be observed in the glycosylation of D-glucose to give mainly methyl α-D-glucopyranoside (Equation 1).[4]



Equation 1. Glycosylation of D-Glucose

Carbohydrates are susceptible to biodegradation, limiting their therapeutic potential, which has pushed synthetic chemists to develop more stable analogs with similar medicinal characteristics. Currently a major focus of *glycobiology* is in the formation of *C*-glycosides which, unlike their oxygen-linked counterparts, are not readily hydrolyzable (replacement of the anomeric substituent with –OH) allowing them to withstand degradation in the body. Biologically important glycosides depend on structure recognition between themselves and proteins for their medicinal properties, requiring *C*-glycosides to be isosteric analogs of the naturally occurring *O*-glycosides (Figure 4).

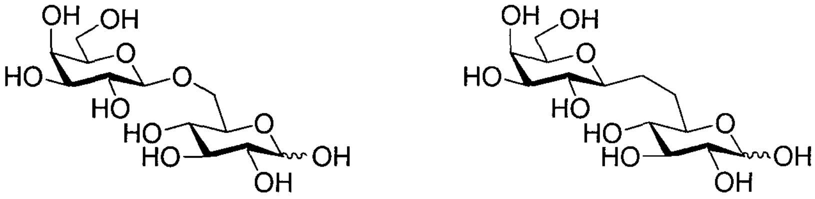


Figure 4. *O*-Lactose and *C*-Lactose

The idea that *C*-glycosides could bind to protein receptors and work as enzyme inhibitors was introduced after naturally occurring analogs were discovered. There are differing opinions as to whether these non-reducible sugars have structure similarity due to the effects of replacing the exocyclic oxygen with a carbon bridge, changing the size and electronics of the molecule.

The conformation of *O*-glycosides around the glycosidic bond is governed by steric effects along with a stereoelectronic effect between the lone pairs of the O-linkage with the σ^*-orbital of the ring C-O bond, known as the "exo-anomeric effect". This stereoelectronic interaction is not present in carbon-bridged derivatives leading many to doubt structure similarity between the two and whether these pseudo-sugars are able to bind to protein receptors.

Experimental evidence, from Espinosa and coworkers, has shown that there are conformational differences between *C*- and *O*-glycosides using *C*- and *O*-lactose as test compounds.[5] Detailed NMR spectroscopy techniques along with molecular mechanics calculations were used to determine that conformational behavior between the two lactoses were similar around the glycosidic bond but not around the glyconic bond. However, NMR studies performed by Kishi and coworkers concluded that α- and β-linked *C*-glycosides adopt the same conformation as the *O*-linked sugars due to steric considerations suggesting that *C*-glycosides will retain biologically active conformations.[6] This was proved with a crystal structure of peanut lectin with four *C*-lactose molecules bound to its active sites (Figure 5).[7]

Figure 5. *C*-lactose bound to peanut lectin

C-Glycosides have numerous biological applications ranging from enzyme inhibitors, anti-viral, anti-microbial agents, and anti-cancer agents to weight management disaccharides. The carbohydrates that these pseudo-sugars mimic are made by enzymes which yield either the α or β anomer exclusively, requiring the need for high yielding, stereoselective syntheses. Synthetic chemists have classically approached the *C*–glycoside problem from three pathways – electrophilic sugars, C-1 nucleophiles, and free radicals.

There are numerous anomeric anionic species that have been employed in the search for *C*-glycoside synthesis, the majority of them being glycosyl lithium species.

These nucleophiles can be used to attack electrophilic carbon species forming the desired carbon-carbon bond. This method of glycosylation has most recently been applied to 1-nitronates, 2-deoxysugars, glycals, and dilithiated sugars (Figure 6) providing more diverse synthetic possibilities.[8]

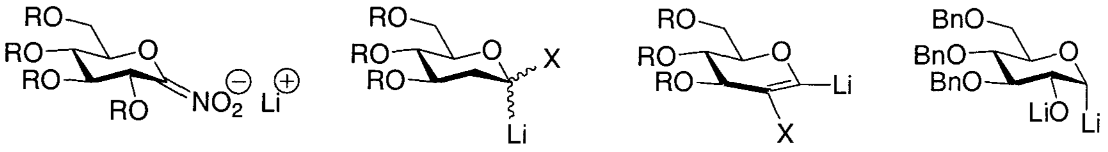
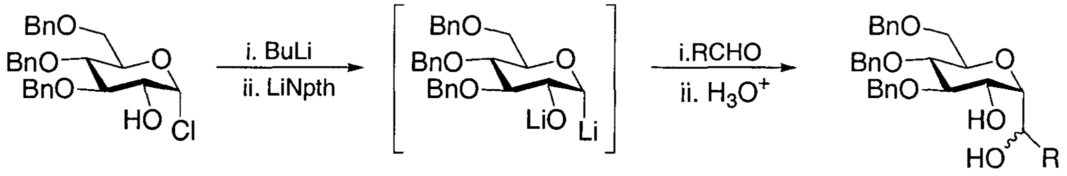


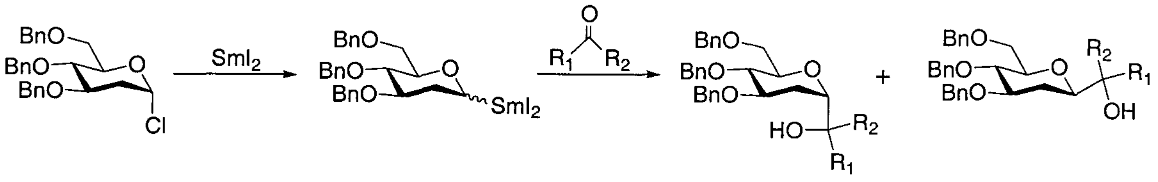
Figure 6. Examples of commonly used C-1 nucleophiles

Kessler provides an example of this method with his reaction of a dilithiated sugar with generic aldehydes to afford the desired *C*-glycosides (Equation 2).[9] The reaction of vicinal halohydrins with *n*-BuLi and lithium naphthalide leads to the formation of the α-dianion which when reacted with aldehydes yields α-*C*-glycosides. Stereoselective formation of the β-anomer can also be achieved through reaction of the β-lithiated species. This technique has been applied to the formation of *C*-disaccharides linking a lithiated sugar with a sugar aldehyde.



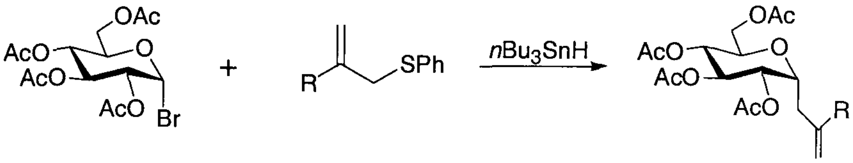
Equation 2. Stereoselective formation of α-*C*-glycoside

Samarium iodide (SmI_2) mediated reactions were recently applied to the field of carbohydrate synthesis through the efforts of Sinaÿ and Beau.[10,11] SmI_2 is believed to form a glycosyl anion intermediate, in a mixture of α and β anomers, which can be used to attack electrophilic species leading to the formation of desired glycosides (Equation 3).



Equation 3. SmI_2 mediated glycosylation to form a mixture of α and β anomers

Another approach to synthesizing sugar analogs has been through the use of intermolecular free radical chemistry. This method has been of importance due to the fact no anion is formed at the anomeric carbon reducing the chance of elimination or ring opening epimerization. Stereoselective glycosylation can be achieved under mild conditions in good yields *via* radical chemistry making this a popular approach for forming *C*-glycosides (e.g. Equation 4).[12]



Equation 4. Formation of α-*C*-glycoside *via* radical glycosylation

Glycosylation reactions using electrophilic sugars have become the most widely used due to the accessibility of these species and the stability of reaction intermediates. There are four main types of anomeric electrophiles commonly used in modern synthesis: glycosyl halides (**A**), sugar lactones (**B**), glycols (**C**), and 1,2-anhydrosugars (**D**) (Figure 7).[ref]

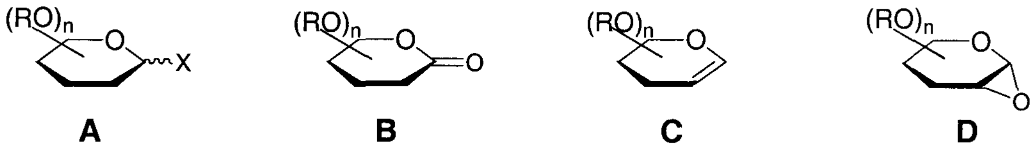
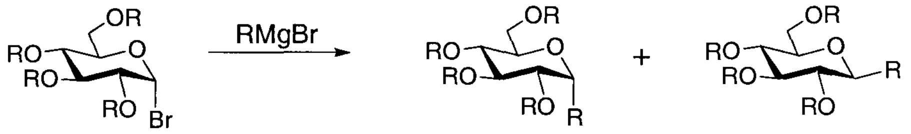
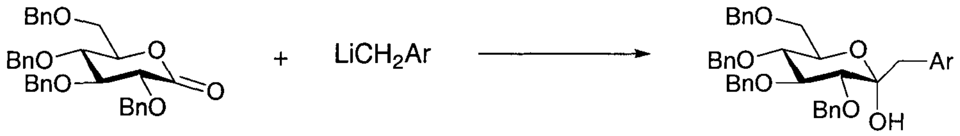


Figure 7. Examples of electrophilic sugars

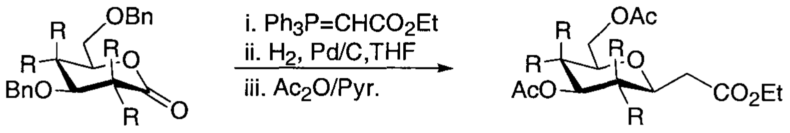
The addition of organometallic nucleophiles including Grignard reagents to glycosyl halides has recently been used to achieve high yielding, stereoselective *C*-glycoside syntheses (Equation 5:**A**).[13] C-1 lactones have also been used in the attempts to find new routes to glycosylation. There are a number of different ways in which lactones have been used ranging from addition of stabilized anions to Wittig olefinations. *C*-Glycoside formation through nucleophilic addition to lactones proceeds through two steps- addition of the anion (Equation 5:**B**) followed by reductive removal of the resulting O-H.[14] Wittig reactions to lactones proceed through formation of *C*-glycosylidenes followed by hydrogenation to the desired *C*-glycosides as seen through the work of Molina and coworkers (Equation 5:**C**).[15] Glycals have classically been used in direct synthesis of *O*-glycosides in high yields with good stereoselectivity, and this chemistry has recently been adapted to *C*-glycosylation by Csuk and coworkers (Equation 5:**D**).[16] 1,2-Anhydrosugars have also been important in the formation of naturally occurring glycosides making them a topic of interest to synthetic carbohydrate chemists. Van Boom and coworkers have shown that *C*-glycosides can be formed stereoselectively by addition of lithiated –yne nucleophiles at C-1 of the epoxide ring (Equation 5:**E**).[17]



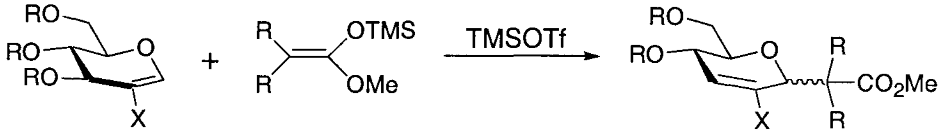
eq 5-A



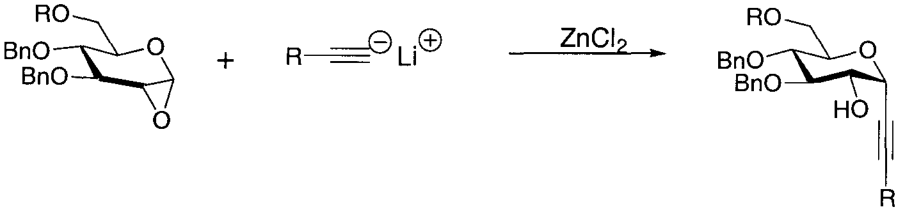
eq 5-B



eq 5-C

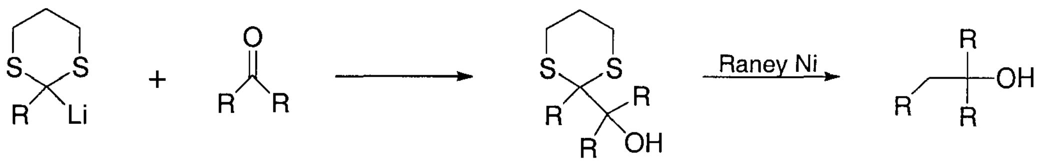


eq 5-D



eq 5-E

Dithioacetals are classified as compounds that have two sulfurs attached to a central carbon. These compounds have been shown in the past to have an acidic proton (pK_a~25) between the two electron withdrawing sulfur groups, which can be removed by treatment with *n*-BuLi. The resulting lithium anion is commonly used in alkylation reactions, followed by reductive removal of the two S-R groups with Raney Ni producing a new carbon-carbon bond (Equation 6).[18] The reactivity of dithioacetals is the basis of the research to be discussed, and the potential for these compounds to form sugar dithianes is investigated. It is reasoned that these sugar dithianes can be added to sugar lactones to form the desired *C*-disaccharide. After reduction of the resulting hydroxyl and removal of the dithiane functionality the resulting product will be the carbon-linked analog of naturally occurring disaccharides.



Equation 6. Reactivity of dithioacetals with electrophiles

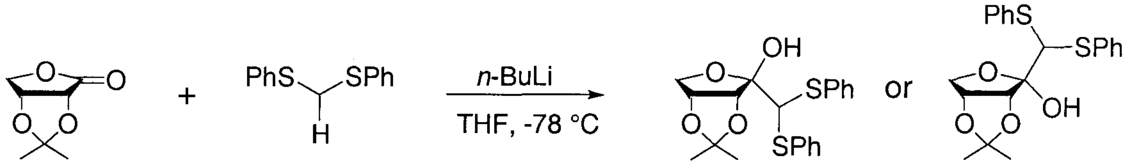
Statement of the Problem

Carbohydrates are susceptible to biodegradation, limiting their therapeutic potential, which has pushed synthetic chemists to develop carbon-linked analogs that are not readily hydrolyzed in the body. The focus of this research is to develop new stereoselective pathways for *C*-disaccharide formation. It was hypothesized that addition of a large diphenyl dithioacetal nucleophile to sugar lactones would effectively yield stereoselective disaccharides. Classic reduction techniques could then be employed to yield the desired *C*-disaccharide.

Results and Discussion

Model study on a simple *C*-glycoside

The goal of the research to be discussed is the development of methodology for the stereoselective synthesis of *C*-disaccharides. Reaction conditions were first tested and optimized on a simple system due to inexpensive starting materials and the simplicity of characterization.



1 **2** **3**

Equation 7.

The system that was chosen for investigation was the addition of the lithium anion of bis(phenylthio)methane (made from compound **2** and *n*-BuLi) to 2,3-*O*-isopropylidene-D-erythronolactone (**1**) (Equation 7). Initial observation of the TLC revealed that a new compound had been formed which had ultra-violet absorbance and an R_f value slightly less than the starting dithioacetal. This can be attributed to the resulting polar hydroxyl formed upon the addition to the lactone. ^{1}H NMR shifts showed a singlet at 3.0 ppm for the resulting O-H, a singlet at 4.9 ppm that is representative of the proton between the two electron withdrawing sulfur groups, and a 10 H multiplet in the aromatic region attributed to the protons on the two benzene rings. Analysis of the ^{13}C NMR spectrum revealed 4 peaks in the range of 65-86 ppm, which are the result of the three ring carbons from the sugar and one carbon from the dithioacetal group. There are also two peaks between 108 and 113 ppm that correspond to the two quaternary carbons, i.e. the center of the isopropylidene protecting group and the newly formed hemiketal at C-2.

Additional indication of reaction comes from the fact that the ^{13}C signal of the carbonyl group of the starting material at around 170 ppm is no longer present in the ^{13}C NMR spectrum of the new material. The mass spectrum of the purified product was also obtained and resulted in a *m/z* of 389.19 in the negative mode which was further proof of the identity of the product.

To determine whether addition of the bis(phenylthio)methane to the sugar lactone was resulting in an α or β *C*-glycoside, energy minimizations for both anomers were performed on PC Spartan Pro. The depictions shown below in Figure 8 represent minimized forms of the α (right) and β (left) *C*-glycoside **3**. Energy calculations predicted the α anomer to be more stable, and this was rationalized by the lowering of electronic interactions between the free hydroxyl and the oxygen atoms of the isopropylidene protecting group. For further discussion purposes only the α form of the *C*-glycosides will be written.

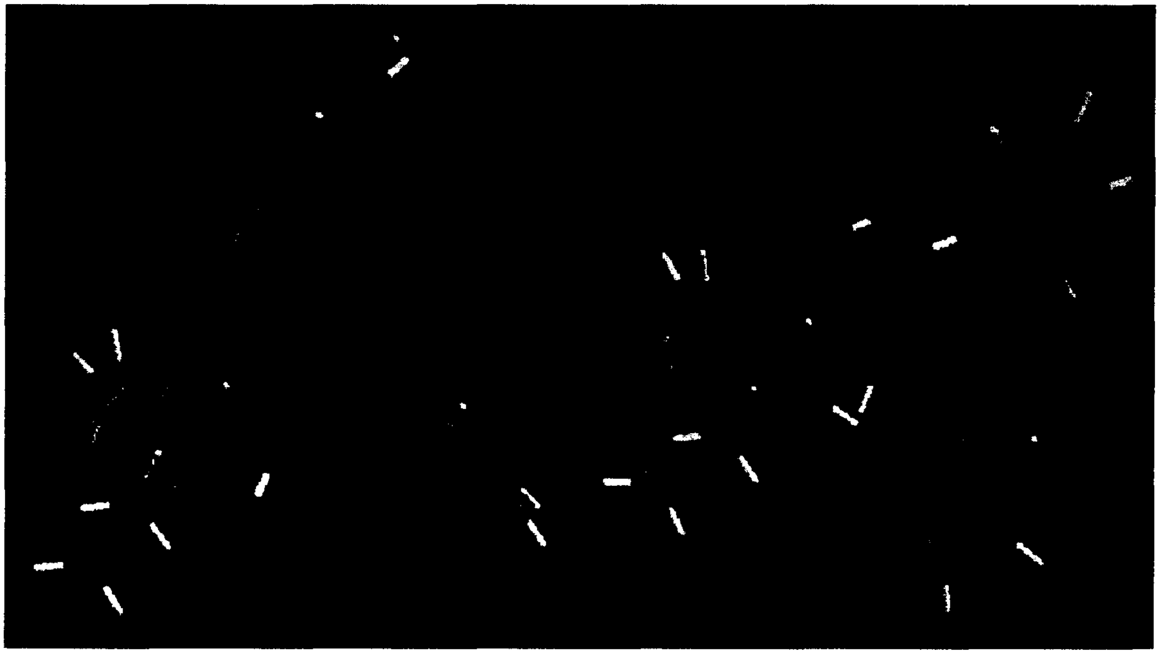
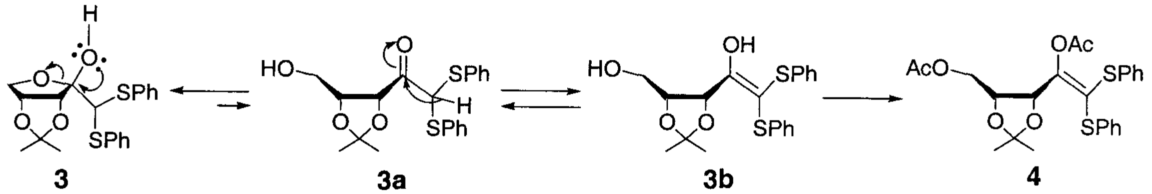


Figure 8. Energy minimizations of **3** with PC Spartan Pro

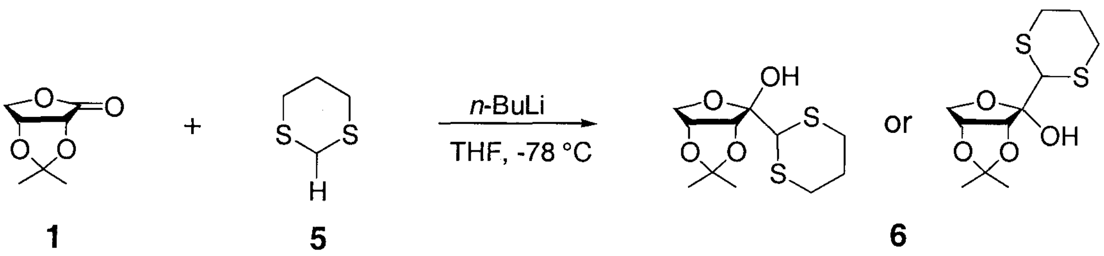
Compound **3** was acetylated in hopes of determining its stereochemical identity. Upon reaction with Ac_2O in pyridine it was determined that **3** had opened to the straight chain form and had been acetylated in two positions *via* the proposed mechanism shown in Equation 8. ^{1}H NMR showed two singlets at 2.0 and 2.3 ppm that correspond to the CH_3 groups of the acetates. There were also only four signals in the range of 4.0 to 6.0 ppm compared to five in the starting sugar. The missing signal is the singlet that was representative of H-1, the proton between the two sulfur groups. The H-3 signal has also been shifted 1.0 ppm downfield because it is now α to a double bond, which is more proof of reaction. Compound **4** revealed three new peaks of interest in the carbon NMR: a peak shifted to 150 ppm for C-2, and two peaks around 170 ppm which relates to the two carbonyls of the acetates. Mass spectrum gave a *m/z* of 475.12 in the positive mode which corresponds with the calculated weight for **4**.



Equation 8.

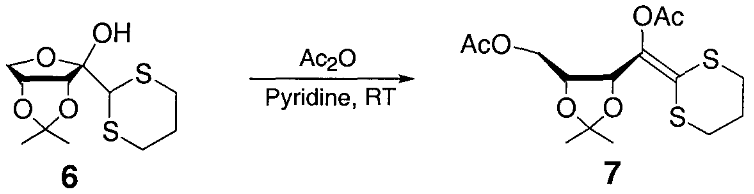
To investigate the possibility of ring opening aided by deprotonation of the hydroxyl at C-2 by pyridine, a simple NMR test was performed with compound **3** and d_5-pyridine in $CDCl_3$. Spectra were taken three times over a period of 24 hours (20 minutes, three hours, and 24 hours) to see if ring opening had occurred. ^{1}H NMR showed that the 3.0 ppm O-H singlet from compound **3** had disappeared as expected but the other peaks remained the same shape and had the same chemical shifts which led to the conclusion that the pyridine was not causing the system to open in solution. Molecular modeling with PC Spartan Pro showed that in a minimized energy conformation of compound **3** the hydroxyl is in a crowded environment, which could be prohibiting the acetylation from taking place in the closed system (Figure 8). The fact that C-2 is a hemiketal allows **3** to exist in the open chain form in small amounts (Equation 8:**3a**). Once the open chain is formed the molecule has the ability to undergo keto-enol tautomerization due to the acidity of the proton between the two sulfur groups (Equation 8:**3b**). It is not quite known as to whether **3a** gets acetylated before enolization or if **3b** is the molecule that gets trapped by acetic anhydride to yield compound **4**.

After characterization of compound **4** was complete it was decided to make another model compound to determine if the initial results could be generalized. The new *C*-glycoside was formed by the addition of lithiated 1,3-dithiane (made from *n*-BuLi and 1,3-dithiane) to the lactone **1** (Equation 9). TLC showed formation of a new compound that was more polar than the starting dithiane, which can be attributed to the polarity of the hydroxyl formed from the addition to the sugar lactone. New peaks at 2.0-3.0 ppm and 4.6 ppm (3 multiplets and a singlet) in the ^{1}H NMR were attributed to the protons on the 1,3-dithiane ring, and the proton between the two sulfurs respectively. ^{13}C NMR revealed five peaks between 26 and 31 ppm, which correspond to the two CH_3 groups from the isopropylidene group on the sugar ring along with three new peaks from the 1,3-dithiane group. Loss of the carbonyl peak at 170 ppm from the starting lactone and the evidence of a new peak at 113.9 ppm for the hemiketal group, along with a *m/z* found of 278.4 was evidence that reaction had occurred.



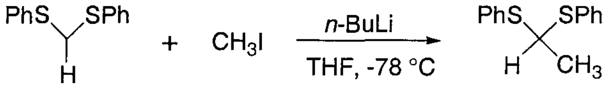
Equation 9.

The next step was to treat compound **6** with Ac_2O in pyridine to determine if the diacetate product would be formed (Equation 10). After 3 hours TLC showed that the starting material had been consumed and that a new less polar product had been formed. Characterization of the product showed that the 1,3-dithiane system formed the diacetate **7**. ^1H NMR was similar to that of the previous *C*-glycoside acetylation with 2 singlets at 2.1 ppm that were representative of the CH_3 groups of the acetates and a doublet for H-5 shifted downfield 1.4 ppm. Likewise, there was a shift of C-4 to 142 ppm and two additional peaks between 168 and 172 ppm that are evidence of the two carbonyl groups of the acetates. Mass spectrum produced a *m/z* of 363.13 which agreed with the expected weight giving more proof of reaction.



Equation 10.

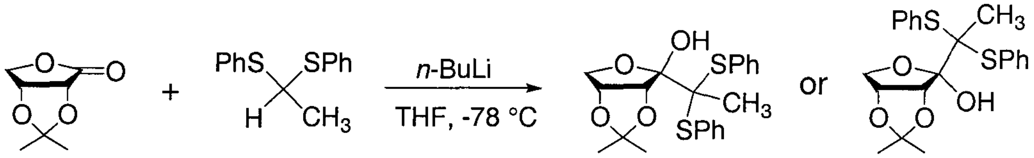
To eliminate problems encountered with enolization in the first two glycoside systems a new nucleophile was synthesized that when added would exist as a quaternary carbon. This was achieved by reacting bis(phenylthio)methane (**2**) with *n*-BuLi and CH_3I (Equation 11) to yield **8**. Addition of the lithium anion of **8** to lactone **1** produced a compound (**9**) that when in the straight chain form was unable to enolize, making the model compound easier to study (Equation 12).



2 **8**

Equation 11.

Formation of the dithioacetal **8** was determined through analysis of the ^{1}H and ^{13}C NMR. Comparison with starting material proton spectra shows loss of a singlet at 4.4 ppm from the CH_2 group and formation of a doublet at 1.6 ppm for the CH_3 group and a quartet at 4.5 for the proton between the two sulfurs. Carbon spectra of the two were similar except for a small shift downfield of the central carbon (going from a 2° to 3° C) and a new peak at 24 ppm for the new CH_3 group.

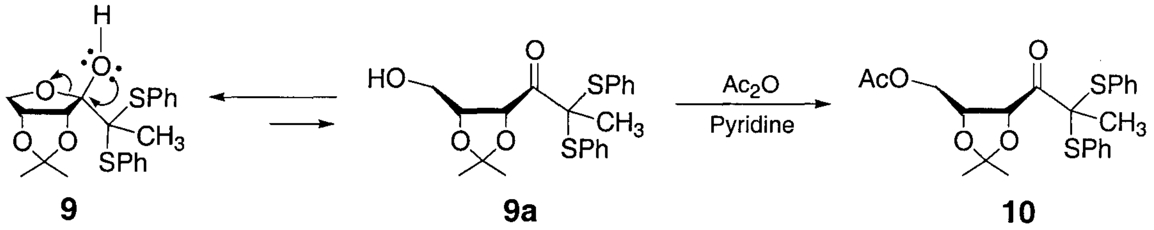


1 **8** **9**

Equation 12.

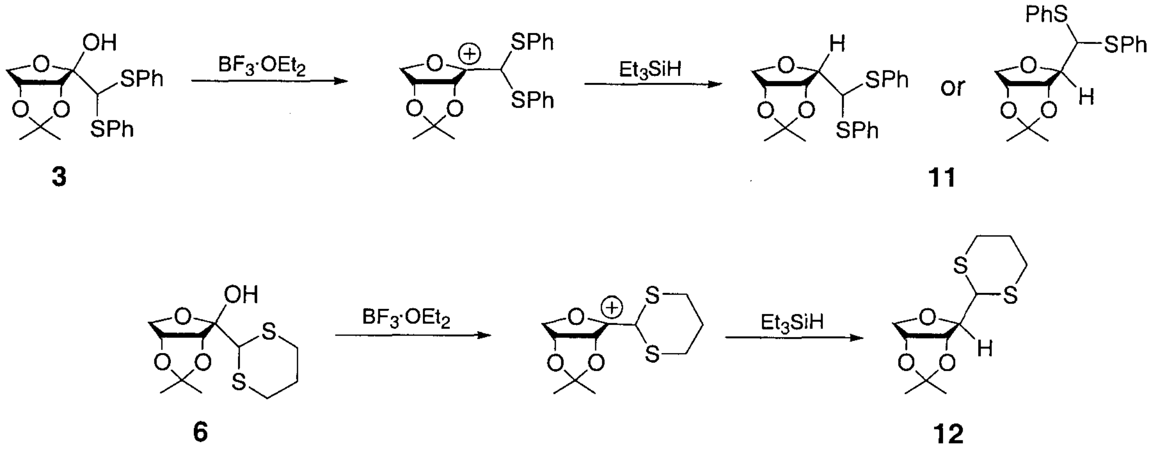
Initial TLC from the addition of lithiated **8** to the lactone **1** revealed formation of a new UV-absorbing spot with a R_f value less than than that of the starting dithiane. Again this can be reasoned because upon addition to the lactone a polar hydroxyl group is formed causing the spot to remain closer to the baseline. ^{1}H and ^{13}C NMR spectra indicate that a new compound **9** was formed and mass spectra confirmed this revealing a *m/z* of 403.12. ^{1}H NMR showed a new peak at 1.5 ppm compared to **6** that is representative of the additional CH_3 as well as a multiplet in the aromatic region that indicates the presence of 10 phenyl protons. The three quartenary C's in the addition product gave three distinct peaks in the range of 107-116 ppm. Evidence of reaction can also be seen by loss of the carbonyl peak at 170 ppm seen in the starting material spectrum.

Acetylation of compound **9** led to formation of the monoacetylated product **10**. As expected the hydroxyl of compound **9** was too hindered in the ring form and acetylated as the open chain form as depicted in Equation 13. Proton NMR showed four singlets (1.3-2.1 ppm) in the region of the four methyl groups of the acetylated product along with the expected chemical shift of H-4 (which is now α to a carbonyl) to 5.7 ppm. New peaks on the carbon spectra at 171 ppm for the ester carbonyl and at 196 ppm for the ketone are evidence of reaction. Further evidence is four signals in the range of 22-29 ppm, which include two from the isopropylidene methyl groups, the methyl between the two sulfurs, and a new methyl group from the acetate. The mass spectrum was also obtained and showed a *m/z* ratio of 464.21 giving more evidence of reaction.



Equation 13.

After the addition reactions were optimized for yield it was decided to attempt reduction reactions to yield the desired *C*-glycoside. The first reaction tested was the reduction of the hydroxyl at C-1 with $BF_3{\cdot}OEt_2$ and Et_3SiH (Equation 14) on compounds **3** and **6**. This particular reaction was chosen because it is usually a stereoselective reduction with the Et_3SiH delivering a hydride *cis* to the protecting group α to the anomeric carbon yielding a β-*C*-glycoside.[19]



Equation 14.

The reduction of compound **6** to give **12** seemed to follow through the desired pathway in a yield of 84%. Extensive studies to determine whether the reduced *C*-glycoside was α or β were not performed, but previous studies suggest structure **12** as correct.[19] Initial TLC of the reduction showed complete consumption of the starting material as well as formation of several new spots. After chromatography, ^{1}H NMR characterization was done and revealed the correct number of proton signals but shape and coupling constants of some of the peaks were somewhat confusing. Ring proton peaks relative to the starting material spectra were shifted upfield, which is evidence of the removal of an electronegative atom at C-4. ^{13}C NMR showed loss of a peak at 107 ppm, which agrees with the reduction of C-4 from a hemiketal to a tertiary carbon.

The reduction of compound **3** with $BF_3{\cdot}OEt_2$ and Et_3SiH showed a loss of starting material and formation of several new spots on the initial TLC. The reaction mixture was worked up and purified *via* flash column chromatography to yield a single spot on TLC. However, when characterization of **11** was done the ^{1}H NMR spectrum pointed to a mixture of two products that were unable to be rationalized. The mass spectrum was obtained and revealed a *m/z* of 373.63 compared to a calculated mass of 374.53 which was evidence of the identity of the product. The proton NMR spectrum appeared to have a set of signals indicating major and minor products, but neither set had the correct number of signals to coincide with the structure the mass spectrum suggested. ^{13}C NMR also seemed to suggest a mixture of two compounds. The major compound seems to agree with the structure of **11** proposed in Equation 14. There are two signals for the major compound in the range of 26-27 ppm, which correspond to the two methyl groups of the isopropylidene protecting group. There are also 5 peaks in the region of 60-85 ppm, which are expected for the 4 ring carbons and the carbon between the two sulfur groups. A signal at 114 ppm for the quartenary carbon of the isopropylidene group and 12 signals in the aromatic region are further proof of the identity of **11**. There are also minor peaks that coincide with the major peaks in the region of 26-27 ppm and three of the major peaks in the range of 60-85 ppm leading to the believe that if the minor product is not the other anomer then it is a compound that is similar.

In past attempts at making *C*-glycosides by way of bis(sulfone) chemistry a crystal structure was obtained for a β-*C*-glycoside (Figure 9) that is the oxidized form of **11**.[20] It was decided to oxidize compound **11** with *m*-CPBA to form **13** (Equation 15) and compare NMR spectra to help determine the stereochemistry of **11**. The oxidation was run for four hours and TLC showed consumption of the starting material and formation of a new compound with a similar R_f value. ^{1}H NMR revealed a mixture of compounds in what seemed to be a 50:50 mixture. When compared with the spectrum of the β-*C*-glycoside they appeared to be a different anomer. The mass spectrum of the chromatographed material gave a *m/z* of 439.29 that confirms the oxidation took place.

This information along with the PC Spartan modeling led to the determination that the reduced product **11** was most likely the α anomer.

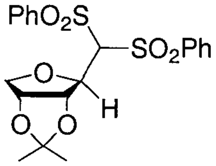
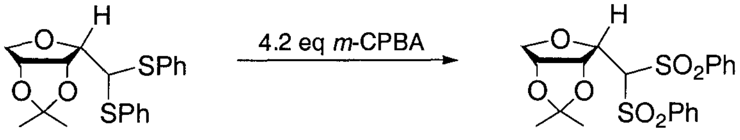


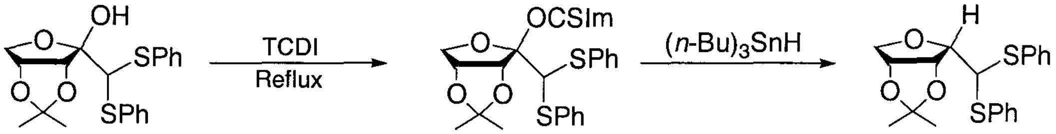
Figure 9. Known β-*C*-glycoside



11 **13**

Equation 15.

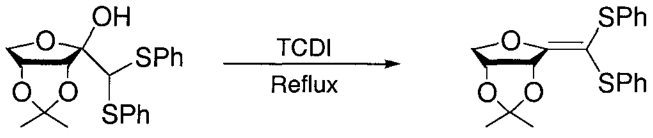
Due to the complications of assigning spectra in the reduction of compound **3** to **11** it was decided to try another reduction which involved addition of thiocarbonyldiimidazole (TCDI) to the hydroxyl of **3** followed by reduction *via* radical chemistry with (n-Bu)$_3$SnH to yield a reduced *C*-glycoside (Scheme 1).[21]



3

Scheme 1.

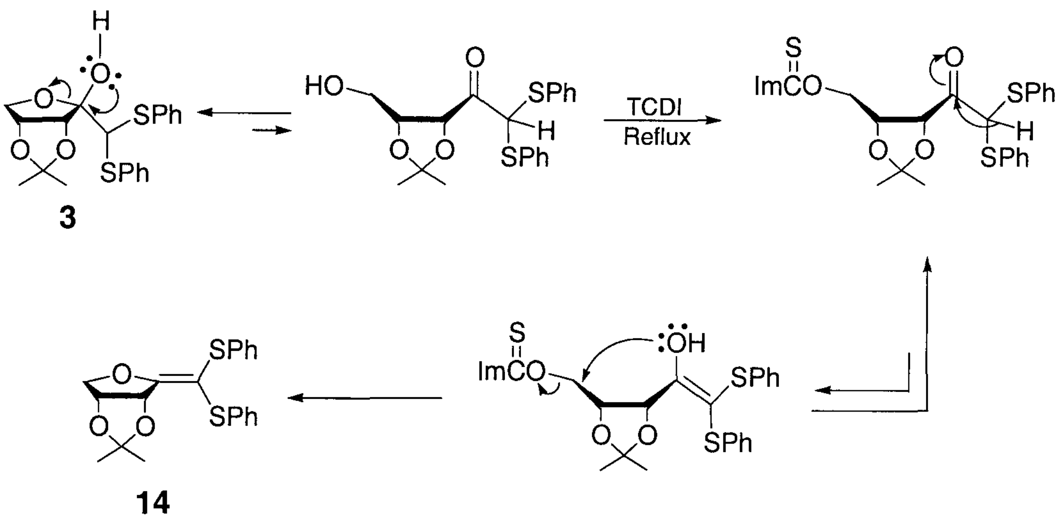
However, upon reaction of **3** with TCDI it was found that an elimination had taken place between C-1 and C-2 to yield compound **14** (Equation 16). Initial TLC revealed a spot that had a similar R_f value as the starting material. Characterization was done on the pure compound, which agreed with the suggested structure of the elimination product. IR spectra showed no peak in the range of O-H stretching (3600-3200 cm^{-1}) and a *m/z* of 373.31 found were evidence for the structure of **14**. ^1H NMR revealed four signals in the range of 4.3-5.5 ppm corresponding to the protons on the sugar ring. Analysis of the signals matched expected shapes: a doublet for H-3, a doublet of doublet of doublets for H-4, and two doublet of doublets for H-5 and H-5'. H-3 also had a chemical shift of 0.7 ppm downfield that agrees with the expected chemical shift. Further evidence came from the ^{13}C NMR, which showed two signals at 27 and 28 ppm for the isopropylidene methyl groups, and three peaks between 77-82 ppm for the sp^3 hybrid carbons of the sugar ring. A signal at 114 ppm for the tertiary carbon of the isopropylidene group, twelve signals in the aromatic region for the phenyl carbons, and two signals at 137 and 168 that correspond to the two sp^2 hybridized carbons were also used to identify the product's structure.



3 **14**

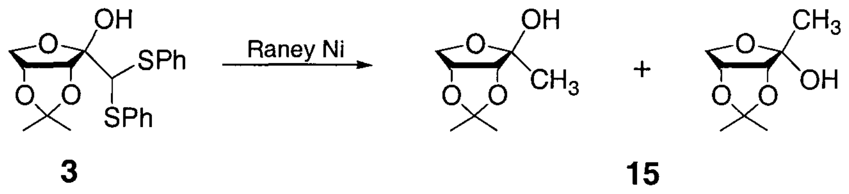
Equation 16.

The mechanism as to how this reaction takes place is not known, but the pathway described in Scheme 1 was abandoned. It was first thought refluxing compound **3** in the presence of the imidazole produced *in situ* was promoting the elimination. However, when compound **3** was refluxed in THF with imidazole overnight no reaction occurred. It was speculated that the elimination proceeds through the proposed mechanism in Scheme 2. Compound **14** could still be useful in the reduction of **3** through hydrogenation but that reaction was not investigated.



Scheme 2.

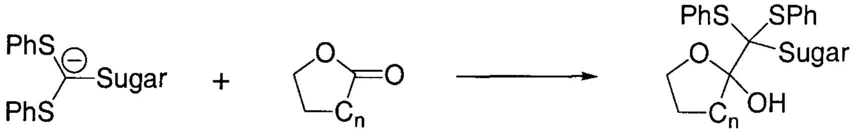
The next step in the investigation of the model compound was to determine if the dithioacetal groups could be reduced leaving a methyl-*C*-glycoside (Equation 17). The reduction reactions were performed by addition of Raney Ni to a stirring solution of **3** in ethanol at room temperature. Initial TLC revealed consumption of the starting material and formation of a new spot that was not UV-absorbing. Spectral data revealed a 5:2 mixture of anomers (*m/z* of 173.13) in an overall yield of 75%. Analysis of the ^{1}H NMR showed five signals in the range of 1.3-1.6 ppm that were representative of 9H (the two methyls of the isopropylidene, and the methyl formed from the reduction). Loss of the phenyl rings was evident by no peaks in the aromatic region of the proton or carbon spectra. There were, however, six peaks between 23 and 28 ppm that were determined to be the methyl groups (α and β anomers) of compound **15**.



Equation 17.

Synthesis of a *C*-disaccharide

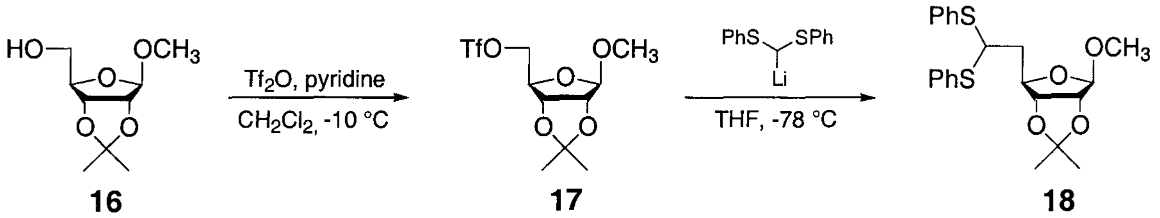
After investigation of the addition of bis(phenylthio)methane to sugar lactones and the ability to efficiently reduce off the dithioacetal functionality along with the resultant hydroxyl group it was decided to use this methodology in the attempt to form a *C*-disaccharide. The first step was to build a sugar-derived dithiane nucleophile that could be added to a sugar lactone yielding a *C*-disaccharide as shown in Scheme 3.



Scheme 3.

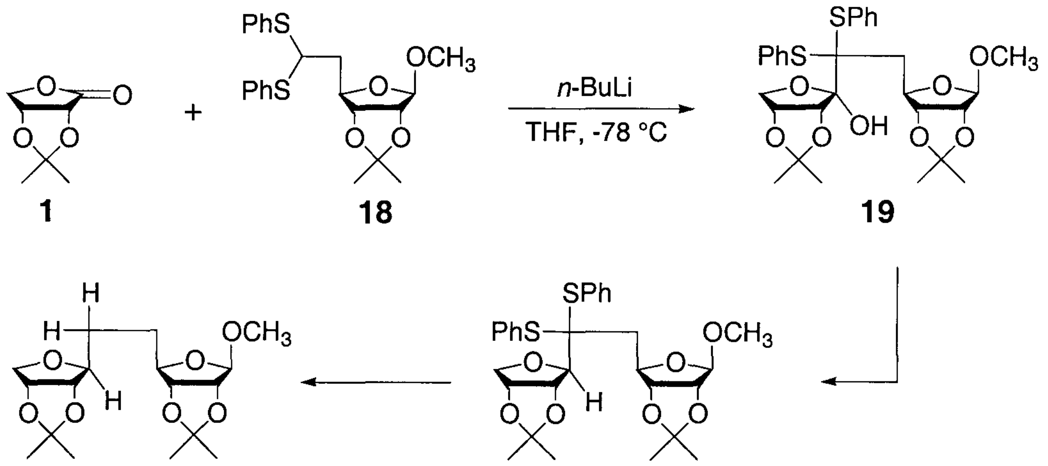
The sugar that was chosen was methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**16**), which is cheap and can be readily made from the protection of D-ribose.[22] This particular sugar was chosen because of the reactivity of the free O-H at C-5. It was thought that if a good leaving group were added to this hydroxyl it could be displaced by a bis(phenylthio)methane nucleophile *via* an S_N2 reaction yielding the desired dithioacetal analog (Equation 18). Formation of a triflate leaving group at C-5 was chosen because it has been shown throughout the literature to be one of the best leaving groups available.[23] This was achieved by adding the protected sugar **16** to a solution of trifluoromethanesulfonic anhydride in pyridine and CH_2Cl_2, which yielded the triflated sugar **17** in a yield of 92%. After three hours TLC showed complete consumption of the starting sugar and formation of a more non-polar compound with a much larger R_f value (due to loss of the free hydroxyl). Protons H-5 and H-5' were shifted downfield 0.9 ppm in the ^1H NMR spectra due to the addition of an electron withdrawing group adjacent to them, and there was a new peak in the carbon spectra at 118 ppm for the CF_3 functionality of the triflate giving evidence of the formation.

Triflate compounds are known to be unstable and will degrade in short periods of time, so the triflated **17** was reacted immediately with the bis(phenylthio)methane anion to give compound **18** in good yields (63%). Formation of this compound was monitored by TLC and revealed a new spot with UV absorbance. Once again the position of protons H-5 and H-5' on the proton spectra were examined to determine if the displacement had taken place. Upon addition of the dithioacetal **2** the protons at C-5 are no longer α to an electronegative atom, which should cause their signals to be shifted upfield as seen in the proton spectrum (H-5 at 1.9 ppm and H-5' at 2.2 ppm). As further evidence there was singlet at 4.9 for the proton between the two sulfurs and enough signals in the aromatic region for the two phenyl rings.



Equation 18.

It has been shown earlier that lithiated dithianes can add to the lactone **1** so it was used in the investigation of the formation of *C*-disaccharides by way of dithiane chemistry (Scheme 4). It was hoped that the isopropylidene protecting groups on the lactone would act to block the α face of the lactone from the large nucleophile giving a stereoselective addition pathway. It was imagined that even if ring opening and closing in solution were to take place the large bis(phenylthio) group would still favor to be in the β position due to the steric hinderance of the methyl groups in the α position. Past studies have shown to favor the α anomer, however steric hindrance is believed to decide stereochemistry with the larger sugar nucleophile. Reduction of the hydroxyl at C-7 before removal of the dithioacetal functionality would cause the disaccharide to retain stereochemistry because there would no longer be a hemiketal in the compound. The last step would require the removal of the two SPh groups to yield the finished *C*-disaccharide.



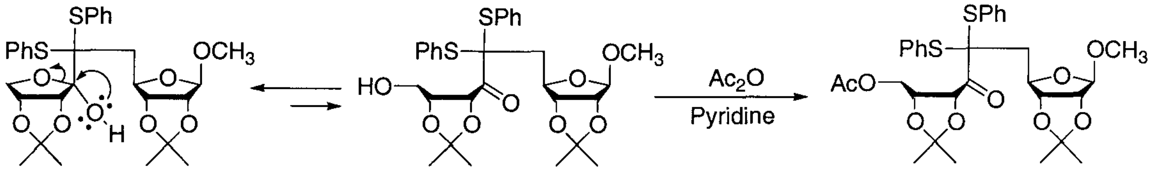
Scheme 4.

The first step was treatment of **18** with *n*-BuLi to form the anion, followed by addition to the lactone **1** to afford the disaccharide **19** in relatively good yields. Reaction conditions for similar systems had already been established making it relatively easy to optimize disaccharide formation. Initial yields for the addition were somewhat low (~ 40%) but it was found that when an excess of the lactone was used the yields improved to around 73% (with respect to **18**) leading us to believe that small amounts of the *n*-BuLi were behaving as nucleophiles and adding to the lactone causing the lower yields. This was justified as a possibility when tests were done that showed the lithium base would add to **1** under similar conditions.

Assignment of proton signals for compound **19** was done by close examination of integration, coupling constants and expected chemical shifts. There were five singlets found in the spectra (1.4, 1.5, 1.6, 1.7, 2.9 ppm) with an integration corresponding to three protons each, which were assigned to the five methyl groups. Signals at 1.4 and 2.0 ppm were found to be protons 5 (J = 7.1, 14.2 Hz) and 5' (J = 9.0, 14.2 Hz) of the methylene bridge and protons 10 (J = 4.0, 10.1 Hz) and 10' (J = 6.0, 10.1 Hz) showed up at 4.0-4.2 ppm. There was a doublet at 4.4 ppm for H-3 (J = 5.9 Hz) that coupled to a doublet at 4.9 ppm for H-2 (J = 6.0 Hz). Two singlets were found at 4.5 and 4.8 ppm that correspond to the hydroxyl proton and the proton at C-1. There were two protons in the range of 5.0 to 5.2 ppm, which correspond to H-9 (J = 4.0, 6.0, 7.3 Hz) and H-4 (J = 7.1, 9.0 Hz) coupling to protons 8, 10, 10' and 5, 5' respectively. The remaining signals on the spectrum, a doublet at 5.4 ppm and a ten proton multiplet between 7.1 and 7.8 ppm were assigned to H-8 (J = 7.3 Hz) and the 10 protons on the phenyl rings.

Formation of compound **19** was confirmed through analysis of the proton NMR but it was still important to determine whether the disaccharide existed in the closed or open chain form. If the hemiketal had opened to the straight chain form then there would be a peak on the ^{13}C NMR spectrum at around 190-200 ppm from the ketone at C-7. The carbon spectrum of the compound **19** showed only a small signal in that region meaning that most of the disaccharide remained in the closed ring form.

As with the previous additions, **19** was acetylated with Ac_2O, to try to better understand stereochemistry, which led to the monoacetylated open chain ketone **20** (Equation 19). As shown before with molecular modeling, the simple *C*-glycosides were too crowded at the hemiketal for acetylation to take place in the closed ring form, so it was reasoned that the more sterically crowded **19** would also be difficult to acetylate unless the ring opened.



19 **19a** **20**

Equation 19.

^{13}C NMR agreed with the proposed structure for the acetylation product **20** showing a signal at 171 ppm for the carbonyl of the acetate and a signal at 196.1, which is relevant to the ketone at C-7. Further evidence comes from a singlet in the ^{1}H NMR spectrum at 2.1 which corresponds to the methyl group on the acetate, and the shift of the proton on C-8 (0.5 ppm downfield), which is α to a ketone in the straight chain form.

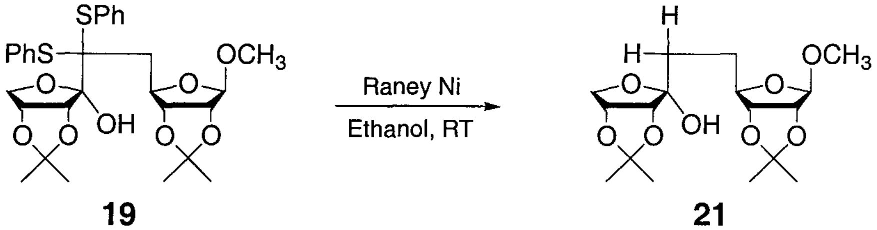
The next step in scheme **3** was to reduce the O-H of the hemiketal **19**. According to the previous test studies this could be achieved by reaction with $BF_3{\cdot}OEt_2$ and Et_3SiH. The reduction was performed under the same conditions as before but TLC showed formation of several new spots. Purification of the reaction mixture was performed by chromatography but yielded nothing identifiable. It was not quite understood what was happening in the reaction but this method was abandoned and other reduction techniques were investigated.

It was decided that a stronger Lewis acid could be employed and have better results in the reduction. Taken from a classical technique, $TiCl_4$ was investigated to see if it could coordinate to and remove the hydroxyl. The resulting carbocation could undergo hydride addition from Ph_3SiH forming the C-7-reduced disaccharide.[24]

However, initial TLC of the reaction also led to formation of several spots, which after chromatography again revealed nothing encouraging.

The literature led to one more reduction technique, which involved the use of trimethylsilyltriflate and Et_3SiH.[25] These reagents had been shown to reduce hydroxyls on quaternary carbons and were expected to work on our system. The reaction was set up and followed by TLC, once again leading to a complex mixture of compounds. Purification of the mixture was not attempted because with so many products formed the reaction was considered useless. Attempts at reducing the hydroxyl were ended at this point but there are still numerous reduction techniques found in the literature that can be tested on **19**.

At this point the reduction of **19** with Raney Ni was attempted to remove the two SPh groups (Equation 20). The *C*-disaccharide **19** was dissolved in ethanol and excess Raney Ni / water slurry was added *via* pipette and reaction was monitored by TLC. Observation of the TLC revealed formation of a new compound (**21**) that was no longer UV-active (as expected with loss of the phenyl groups). The identity of **21** was confirmed with proton NMR, which showed no peaks in the aromatic region verifying loss of the two phenyl rings. There were also four signals between 1.7 and 2.0 ppm that are relevant to the four protons on the methylene bridge after removal of the two SPh groups. ^{13}C NMR showed more evidence of reduction with six signals in the range of 26-33 ppm that are for the four isopropylidene methyl groups and the two CH_2 groups of the sugar linkage.



19 **21**

Equation 20.

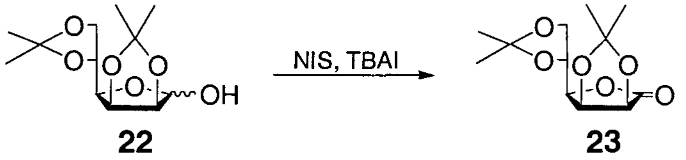
The completely reduced *C*-disaccharide was not achieved at this point but it is predicted that a route for hydroxyl removal can be found in the near future. Before more attempts at reduction were tried the generality of this methodology was tested by formation of different dithioacetal sugars and also synthesis of lactones that are not readily available through commercial companies.

Synthesis of More Lactones and Sugar-Dithianes

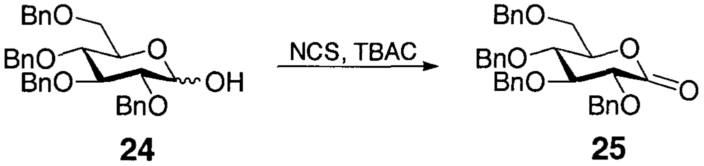
Classically, it has been shown that lactones can be made from oxidizing lactols.[26] This method was employed in this research and involves oxidation of the hemiketal hydroxyl to a carbonyl with *N*-iodosuccinimide (NIS) and tetra-*N*-butylammonium iodide (TBAI) in relatively high yields (~65 % for most compounds). This can also be achieved with the chloro derivatives (NCS and TBAC) but it was found that yields are typically lower. The bromo derivatives were tested but even under refluxing conditions no reaction occurred.

2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose (**22**) was the first sugar to be oxidized because of its commercial availability. Compound **22** was added to a stirring solution of NIS and TBAI and was let react for three hours at room temperature (Equation 21:**a**). TLC showed formation of a more non-polar compound that was believed to be the lactone **23**. The identity of **23** was confirmed by a signal at 174 ppm in the ^{13}C spectrum, which is evidence of the carbonyl formed at C-1. A mass spectrum was done for further evidence yielding a *m/z* of 259.34 compared with the calculated mass of 258.29.

A second lactol, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**24**), was oxidized under similar conditions with NCS and TBAC to yield the lactone **25** (Equation 21:**b**). Verification of reaction was done by TLC and showed formation a more non-polar spot which can be attributed to the oxidation of the polar O-H group at the hemiacetal. ^{13}C NMR confirmed the identity of **25** with a signal at 170 ppm for the carbonyl formed after oxidation.

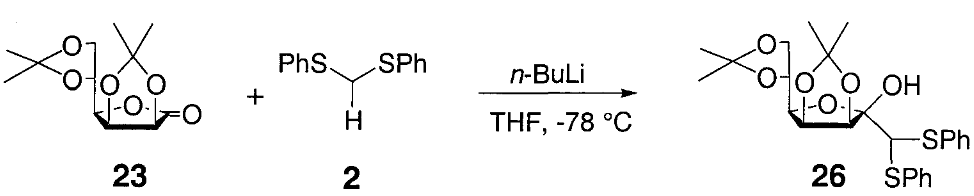


eq 21-a



eq 21-b

After the oxidations were complete and the lactones characterized, the lactone **23** was used to determine if addition of the bis(phenylthio)methane anion was possible. After the lithium anion was formed by treatment of **1** with *n*-BuLi, a solution of the lactone **23** in CH_2Cl_2 was added dropwise and resulted in the addition product **26** (Equation 22). Characterization was done by proton and carbon NMR spectroscopy. Analysis of the proton spectra showed a singlet at 4.8 ppm that is characteristic for the proton between the two sulfur atoms and a ten hydrogen multiplet in the aromatic region for the protons on the phenyl rings. More evidence of reaction can be seen by the presence of three signals in the carbon spectra between 108-114 ppm, which relates to the two quaternary carbons of the isopropylidene groups and the newly formed hemiketal.

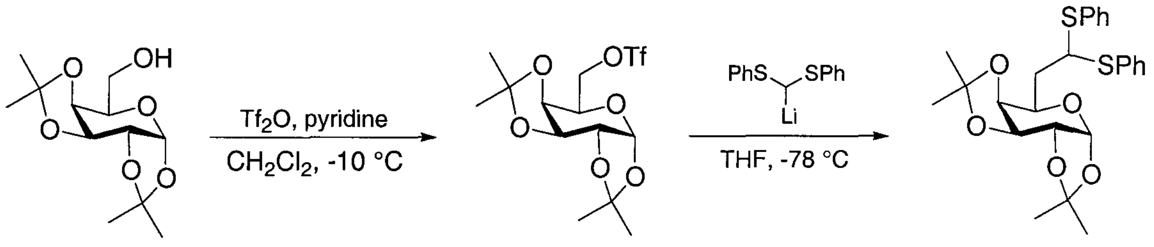


Equation 22.

The final step was to form several dithioacetal sugar analogs from naturally occurring sugars to show the importance and the breadth of *C*-disaccharide formation that could possibly come from this chemistry. The two sugars chosen were protected analogs of D-glucose and D-galactose, both commercially available. The D-galactose derivative, 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**27**), was the first sugar to be tested because hydroxyls at C-1, 2, 3, and 4 were already protected leaving only the reactive free hydroxyl at C-6.

Compound **27** was added to a solution of Tf_2O in CH_2Cl_2 and pyridine to form the triflate leaving group at C-6. After three hours TLC analysis showed consumption of the starting sugar and formation of a new less polar spot, which was concluded to be **28** (Equation 23). There was no spectral data taken since the triflate product was used immediately in the next reaction.

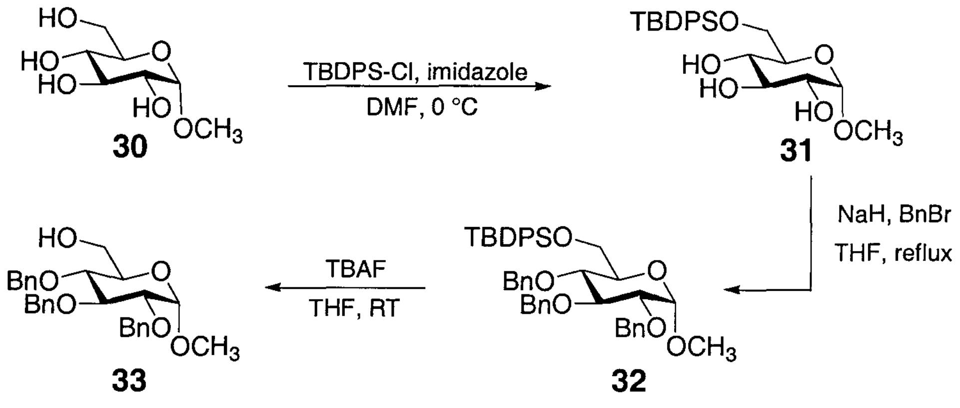
Compound **28** was added to a stirring solution of lithiated bis(phenylthio)-methane and was allowed to mix overnight yielding the dithioacetal sugar **29** (Equation 23). Confirmation of the addition was found in the ^{1}H NMR spectra, which showed a doublet at 5.5 ppm for H-1 coupled to H-2, and a multiplet in the aromatic region for the hydrogens on the phenyl rings. The aromatic carbons of compound **29** also gave distinct signals in the ^{13}C NMR spectrum between 128 and 135 ppm.



27 **28** **29**

Equation 23.

The second dithioacetal to be formed involved a number of protection schemes to yield a free hydroxyl at C-6 of D-glucose. The first step was to selectively protect the primary hydroxyl, which can be achieved with *tert*-butylchlorodiphenylsilane (TBDPS-Cl) at low temperatures. At this point the remaining hydroxyls were protected with base-stable benzyl groups. When this was achieved the silyl protecting group at C-6 was removed with TBAF to yield the reactive primary hydroxyl to be used in formation of the dithioacetal glucose derivative (Scheme 5).



Scheme 5.

Transformation of methyl α-D-glucopyranoside (**30**) into **31** was characterized by ten protons in the aromatic region and a 9H singlet at 1.0 ppm from the proton NMR spectra that is evidence of the phenyl protons and the three methyl groups of *tert*-butyldiphenylsilane (TBDPS). Also present is the singlet at 3.3 ppm for the methoxide group, and signals in the range of 3.5-4.7 ppm for the protons on the sugar ring. ^{13}C NMR confirmed this with signals in the aromatic region and a peak at 100.3 for the quaternary carbon of the TBDPS group.

The protected sugar **31** was then reacted with NaH and $PhCH_2Br$ to give the benzylated sugar derivative **32**. The CH_2 groups from the protection gave distinct signals in the NMR spectra in the range of 4.6-5.0 ppm. Also observed in the ^{1}H spectra was a multiplet, integrated to 25 hydrogens, that agreed with the presence of five phenyl groups in the compound.

Desilylation of **32** with tetra-*N*-butylammonium fluoride yielded compound **33**, which now has a free primary hydroxyl. Analysis of the proton NMR spectra showed loss of the *tert*-butyl group signal at 1.0 ppm and also a multiplet in the aromatic region that corresponded to only 15 hydrogens. The loss of the TBDPS protecting group led to a ^{13}C NMR spectrum that had no signals in the primary or quartenary alkyl range.

Once compound **33** was formed, leaving the primary hydroxyl free it was used in the synthesis of the glucose dithiane derivative. Triflation of compound **33** was achieved under the same conditions used before (Equation 24). The observed change in TLC from starting material to a more non-polar compound was used to determine reaction. When all the starting material had reacted to form **34** it was purified and used in the next reaction.

Conclusions

In conclusion, the formation of *C*-glycosides using dithiane chemistry was studied. This was achieved by adding dithiane nucleophiles to sugar lactones in good yields. The reduction of these *C*-glycosides was also achieved leaving the desired compounds.

This chemistry was also applied to the formation of a *C*-disaccharide using sugar-derived dithioacetals in good yields. Several new sugar-derived dithioacetals were also made but not tested in the formation of disaccharides. Reduction of the SPhs was achieved however numerous attempts at reducing the O-H yielded nothing.

Future work in this field will most probably involve developing chemistry to reduce the resultant hydroxyl. Studies on the other sugar-dithiane nucleophiles to different lactones could also be studied to form a library of *C*-disaccharides.

Experimental

General Procedures

A Varian Gemini 2000 NMR system was used to obtain ^1H and ^{13}C NMR spectra at 400 MHz and 100 MHz respectively, using $CDCl_3$ as solvent. Proton and carbon chemical shifts (δ) are recorded in parts per million (ppm). Multiplicities for NMR spectra are labeled as follows: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), q (quartet), and m (multiplet) with coupling constants (*J*) measured in Hertz. A Bruker Esquire-HP 1100 MS was used to obtain mass spectra. Flash column chromatography was performed with 32-63 μm, 60-Å silica gel.

Formation of the *C*-glycoside 3 from the addition of lithium bis(phenylthio)methane to 2,3-*O*-isopropylidene-D-erythronolactone

In a flame dried 50 mL round bottom flask under nitrogen atmosphere, bis(phenylthio)methane (0.72 g, 3.1 mmol) was dissolved in dry THF (10 mL) and cooled to –78 °C. A solution of 1.6 M *n*-BuLi in hexane (2.3 mL, 3.7 mmol) was added *via* syringe and the mixture was allowed to stir for 20 minutes resulting in a dark yellow solution. At this time a solution of 2,3-*O*-isopropylidene-D-erythronolactone (1.2 g, 7.4 mmol) in dry THF (5 mL) was added dropwise *via* syringe and the resulting mixture was allowed to stir overnight, gradually warming to room temperature. TLC (6:1 hexane:ethyl acetate) showed formation of a new compound with some bis(phenylthio)methane left unreacted. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a syrup. The syrup was purified *via* flash column chromatography (30 g of silica) using a gradient of 10:1 hexane:ethyl acetate to remove the bis(phenylthio)methane and 6:1 hexane:ethyl acetate to afford 1.0 g of **3** as a colorless syrup (83%).

^{1}H NMR: δ 1.4 (s, 3H, CH_3), 1.6 (s, 3H, CH_3), 3.0 (s, 1H, O-H), 3.9 (d, 1H, H-5, *J* = 10.3 Hz), 4.0 (dd, 1H, H-5', *J* = 3.8, 10.4 Hz), 4.76 (d, 1H, H-3, *J* = 5.9 Hz), 4.87 (s, 1H, H-1), 4.9 (dd, 1H, H-4, *J* = 3.7, 5.9 Hz), 7.1-7.5 (m, 10H, Ar-H).

^{13}C NMR: δ 26.4, 27.7, 65.6, 72.7, 81.7, 85.8, 108.6, 113.6, 128.5, 128.8, 129.6 (2 x C), 129.8 (2 x C), 133.5 (2 x C), 133.7 (2 x C), 135.1, 135.7.

m/z calculated: 390.53 *m/z* found (APCI): 389.19

Acetylation of 3 to form the diacetate 4

To a solution of **3** (0.5 g, 1.28 mmol) in anhydrous pyridine (5 mL), at room temperature, was added an excess of acetic anhydride (2 mL) and the solution was allowed to stir for 3 hours. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting dithioacetal and formation of a new compound. The reaction mixture was poured over ice water (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with 5% H_2SO_4 (5 mL), and dried over anhydrous $MgSO_4$. The solution was reduced under vacuum to afford a clear syrup of **4** in an overall yield of 0.52 g (85%).

^{1}H NMR: δ 1.3 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 2.0 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.17 (dd, 1H, H-5, *J* = 5.3, 11.4 Hz), 4.27 (dd, 1H, H-5', *J* = 7.0, 11.4 Hz), 4.5 (ddd, 1H, H-4, *J* = 5.3, 7.1, 7.4 Hz), 5.7 (d, 1H, H-3, *J* = 7.7 Hz), 7.1-7.3 (m, 10H, Ar-H).

^{13}C NMR: δ 20.5, 20.8, 24.5, 26.7, 63.6, 74.5, 75.3, 110.1, 125.0, 126.7, 127.8, 128.4 (2 x C), 128.6 (2 x C), 129.1 (2 x C), 131.8, 132.5, 133.0 (2 x C), 149.7, 167.6, 170.3.

m/z calculated: 474.10 *m/z* found (APCI): 475.12

Test to determine if pyridine had an effect on ring opening of 3

Compound **3** (0.1 g, 0.26 mmol) was dissolved in anhydrous pyridine and allowed to stir at room temperature for 24 hours. TLC (4:1 hexane:ethyl acetate) gave a spot with a similar R_f value as the starting material, so the reaction mixture was concentrated under vacuum and used to determine if **3** had opened to the straight chain form. NMR data showed that compound **3** had remained in the closed chain form.

^{1}H NMR: δ 1.3 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 3.9 (d, 1H, H-5, *J* = 10.3 Hz), 4.1 (dd, 1H, H-5', *J* = 3.8, 10.3 Hz), 4.7 (d, 1H, H-3, *J* = 5.9 Hz), 4.9 (dd, 1H, H-4, *J* = 3.8, 5.5 Hz), 4.9 (s, 1H, H-1), 7.1-7.4 (m, 10H, Ar-H).

^{13}C NMR: δ 26.4, 27.7, 65.9, 72.6, 81.8, 86.1, 108.6, 113.4, 128.1, 128.4, 129.5 (2 x C), 129.7 (2 x C), 133.1 (2 x C), 133.5 (2 x C), 135.5, 136.6.

Formation of *C*-glycoside 6 from the addition of the anion of 1,3-dithiane to 2,3-*O*-isopropylidene-D-erythronolactone

In a flame dried 25 mL round bottom flask under nitrogen atmosphere, 1,3-dithiane (0.14 g, 1.2 mmol) was dissolved in dry THF (5 mL) and the mixture was cooled to –78 °C. A solution of 1.6 M *n*-BuLi in hexane (0.8 mL, 1.3 mmol) was added *via* syringe and allowed to stir for 20 minutes resulting in a dark yellow solution. At this time a solution of 2,3-*O*-isopropylidene-D-erythronolactone (0.2 g, 2.3 mmol) in dry THF (3 mL) was added dropwise *via* syringe and the resulting solution was allowed to stir overnight while warming to room temperature. TLC (4:1 hexane:ethyl acetate) showed formation of a new compound with most of the 1,3-dithiane left unreacted. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a syrup. The syrup was purified *via* flash column chromatography with an eluent of 8:1 hexane:ethyl acetate and 15 g of silica to afford a yellow solid, **6**, in an overall yield of 0.03 g (10%).

^{1}H NMR: δ 1.3 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 1.9 (m, 1H, H-1), 2.1 (m, 1H, H-1'), 2.9 (m, 4H, H-2, H-2', H-2'', H-2'''), 4.0 (m, 2H, H-7, H-7'), 4.6 (d, 1H, H-5, J = 5.9 Hz), 4.6 (s, 1H, H-3), 4.8 (ddd, 1H, H-6, J = 3.9, 5.9, 9.7 Hz).

^{13}C NMR: δ 26.2, 26.7, 27.5, 27.6, 30.5, 51.8, 73.0, 81.2, 85.0, 107.9, 113.9.

m/z calculated: 278.4 *m/z* found (APCI): 277.08

Acetylation of 6 to form the diacetate 7

To a solution of *C*-glycoside **6** (0.12 g, 0.45 mmol) in anhydrous pyridine (5 mL), at room temperature, was added an excess of acetic anhydride (2 mL) and the solution was allowed to stir for 3 hours. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and formation of a new compound. The reaction mixture was poured over ice water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with 5% H_2SO_4 (3 mL), and dried over anhydrous

$MgSO_4$. The solution was evaporated under vacuum to afford a clear syrup of diacetate **7** in an overall yield of 0.16 g (98%).

^{1}H NMR: δ 1.4 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.1 (m, 2H, H-1, H-1'), 2.2 (s, 3H, CH_3), 2.7-3.1 (m, 4H, H-2, H-2', H-2'', H-2'''), 4.0-4.1 (m, 2H, H-7, H-7'), 4.4 (ddd, 1H, H-6, *J* = 4.6, 7.4, 12.1 Hz), 5.5 (d, 1H, H-5, *J* = 7.3 Hz).

^{13}C NMR: δ 21.8, 22.2, 25.8, 25.9, 28.1, 30.2, 30.9, 64.9, 74.5, 76.5, 110.8, 125.1, 141.9, 168.6, 171.6.

m/z calculated: 362.4 *m/z* found (APCI): 363.13

Formation of 1,1-bis(phenylthio)ethane (8) by addition of lithium bis(phenylthio)-methane to CH_3I

In a flame dried 50 mL round bottom flask under nitrogen atmosphere, bis(phenylthio)methane (1.1 g, 4.5 mmol) was dissolved in dry THF (15 mL) and cooled to –78 °C. A solution of 1.6 M *n*-BuLi in hexane (3.1 mL, 5.0 mmol) was added *via* syringe and allowed to stir for 20 minutes resulting in a dark yellow solution. At this time CH_3I (0.4 mL, 6.4 mmol) was added dropwise *via* syringe and the reaction mixture was allowed to stir overnight while warming to room temperature, which resulted in a red solution. TLC (6:1 hexane:ethyl acetate) showed complete consumption of the starting material along with the formation of a new compound. The reaction mixture was quenched with saturated NH_4Cl (15 mL), causing the reaction mixture to turn yellow, and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to afford a yellow oil of **8** in an overall yield of 2.0 g (91%).

^{1}H NMR: δ 1.6 (d, 3H, CH_3, J = 6.9 Hz), 4.5 (q, 1H, H-1, J = 6.9 Hz), 7.2-7.5 (m, 10H, Ar-H).

^{13}C NMR: δ 24.0, 53.3, 128.8 (3 x C), 129.9 (4 x C), 133.9 (4 x C), 135.0.

Formation of *C*-glycoside 9 from the addition of the anion of 8 to 2,3-*O*-isopropylidene-D-erythronolactone

In a flame dried 25 mL round bottom flask under nitrogen atmosphere, 1,1-bis(phenylthio)ethane (0.3 g, 1.3 mmol) was dissolved in dry THF (5 mL) and cooled to – 78 °C. A solution of 1.6 M *n*-BuLi in hexane (0.9 mL, 1.4 mmol) was added *via* syringe and allowed to stir for 20 minutes resulting in a dark yellow solution. At this time a solution of 2,3-*O*-isopropylidene-D-erythronolactone (0.2 g, 1.3 mmol) in dry THF (3 mL) was added dropwise *via* syringe and the solution was allowed to stir overnight while warming to room temperature. TLC (4:1 hexane:ethyl acetate) showed formation of a new compound along with some unreacted 1,1-bis(phenylthio)ethane. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a syrup. The syrup was purified *via* flash column chromatography (15 g of silica) using a gradient of 10:1 hexane:ethyl acetate to remove the 1,1-bis(phenylthio)ethane and 6:1 hexane:ethyl acetate to afford a mixture of **9** as a colorless syrup.

^{1}H NMR: δ 1.2 (s), 1.3 (s), 1.42 (s), 1.45 (s), 1.5 (s), 1.6 (s), 1.7 (s), 3.8 (d), 4.0 (m), 4.2 (dd), 4.4 (d), 4.8 (d), 4.9 (dd), 5.0 (m), 5.2 (d), 7.2-7.7 (m, 10H, Ar-H).

^{13}C NMR: δ 24.0, 25.9, 26.3, 27.2, 27.7, 53.3, 71.6, 72.6, 81.2, 81.3, 82.2, 87.1, 107.8, 108.6, 116.6, 128.8 (2 x C), 129.3, 129.4, 129.9 (3 x C), 133.9 (2 x C), 135.0, 138.7, 138.8.

m/z calculated: 404.53 *m/z* found (APCI): 403.19

Acetylation of 9 to form the monoacetylated ketose 10

To a solution of **9** (0.15 g, 0.37 mmol) in anhydrous pyridine (5 mL), at room temperature, was added an excess of acetic anhydride (2 mL) and the solution was allowed to stir for 3 hours. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and formation of a new compound. The reaction mixture was poured over ice water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with 5% H_2SO_4 (3 mL), and dried over anhydrous $MgSO_4$. The solution was evaporated under vacuum to afford **10** as a clear syrup in an overall yield of 0.16 g (95%).

^{1}H NMR: δ 1.3 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 1.6 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 4.1 (dd, 1H, H-6, *J* = 7.1, 11.5 Hz), 4.2 (dd, 1H, H-6', *J* = 5.3, 11.5 Hz), 4.7 (ddd, 1H, H-5, *J* = 5.0, 6.0, 7.0 Hz), 5.7 (d, 1H, H-4, *J* = 6.4 Hz), 7.2-7.7 (m, 10H, Ar-H).

^{13}C NMR: δ 22.3, 23.6, 27.1, 28.7, 64.4, 68.6, 76.4, 77.1, 111.9, 128.7, 130.0 (2 x C), 130.1, 131.0 (2 x C), 131.2, 131.3, 138.0 (2 x C), 138.7 (2 x C), 171.4, 196.4.

m/z calculated: 446.58 *m/z* found (APCI): 445.12

Reduction of *C*-glycoside 6 with $BF_3 \cdot OEt_2$ and Et_3SiH to form 12

To a solution of **6** (0.12 g, 0.43 mmol) in dry CH_2Cl_2 (5 mL) at –78 °C, $BF_3 \cdot OEt_2$ (0.22 mL, 1.74 mmol) and Et_3SiH (0.28 mL, 1.74 mmol) were added *via* syringe and stirred for 1 hour. At this point the reaction was allowed warm to –10 °C and was stirred for an additional 12 hours in the freezer. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and the formation of a new compound. The reaction mixture was poured over ice water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum and purified *via* flash column chromatography with an eluent of 6:1 hexane:ethyl acetate and 15 g of silica. The pure fractions afforded a clear syrup of **12** in an overall yield of 104 mg (84%).

^1H NMR: δ 1.4 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 1.9 (m, 1H, H-1), 2.1 (m, 1H, H-1'), 2.9 (m, 4H, H-2, H-2', H-2'', H-2'''), 3.5 (dd, 1H, H-7, *J* = 2.9, 10.6 Hz), 3.6 (dd, 1H, H-7', *J* = 3.3, 10.6 Hz), 4.1 (d, 1H, H-4, *J* = 10.5 Hz), 4.4 (d, 1H, H-3, *J* = 10.5 Hz), 4.8 (m, 2H, H-5, H-6).

^{13}C NMR: δ 26.2, 27.0, 27.3, 29.3, 30.0, 44.8, 74.2, 81.2, 81.8, 83.6, 113.5.

Reduction of 3 with $BF_3 \cdot OEt_2$ and Et_3SiH to form 11

To a solution of **3** (0.5 g, 1.3 mmol) in dry CH_2Cl_2 (5 mL) at –78 °C, $BF_3 \cdot OEt_2$ (0.65 mL, 5.16 mmol) and Et_3SiH (0.83 mL, 5.16 mmol) were added *via* syringe and the reaction was stirred for 1 hour. At this point the reaction was allowed to warm to –10 °C and was stirred for an additional 12 hours in the freezer. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and the formation of a new compound. The reaction mixture was poured over ice water (10 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum and purified *via* flash column chromatography with an eluent of 6:1 hexane:ethyl acetate and 20 g of silica. The pure fractions afforded a clear syrup of **11** as a 3:1 mixture of compounds in an overall yield of 0.40 g (82%).

^{1}H NMR: δ 1.3 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 3.3 (d, 1H, H-2), 3.4-3.5 (m, 2H, H-5, H-5' α,β), 4.0-4.1 (2d, 1H, H-3 α,β), 4.7 (2s, 1H, H-1 α,β), 4.7-4.8 (m, 1H, H-4 α,β), 7.2-7.5 (m, 10H, Ar-H).

^{13}C NMR: δ 26.1, 26.2, 27.3, 27.4, 58.6, 74.0, 74.1, 81.5, 81.6, 81.9, 82.1, 84.1, 113.4, 128.9, 129.0, 129.7 (2 x C), 129.8 (2 x C), 130.0, 130.2, 134.6 (2 x C), 134.8 (2 x C).

m/z calculated: 374.53 *m/z* found (APCI): 373.63

Oxidation of 11 to form the sulphone 13

To a solution of **11** (0.11 g, 0.3 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (0.3 g, 1.2 mmol) and the mixture was allowed to stir at room temperature for 4 hours. TLC (3:1 hexane:ethyl acetate) showed complete consumption of starting dithiane and formation of a new compound. The reaction was cooled in an ice bath to precipitate 3-chloro-benzoic acid, which was then removed by vacuum filtration. The remaining filtrate was reduced under vacuum and purified *via* flash column chromatography (8 g of silica) using a gradient of 6:1 hexane:ethyl acetate to remove unwanted products followed by 3:1 hexane:ethyl acetate to afford **13** as a mixture.

^{1}H NMR: δ 1.1 (s), 1.2 (s), 1.3 (s), 1.4 (s), 3.3-3.5 (m), 3.5 (d), 3.6 (d), 3.9 (d), 4.0 (m), 4.1 (dd), 4.6 (dd), 4.8 (m), 5.1 (dd), 5.3 (d), 7.4-8.1 (m, Ar-H).

^{13}C NMR: δ 25.9, 26.3, 26.4, 27.1, 27.2, 28.2, 57.0, 73.7, 74.0, 75.9, 77.0, 77.9, 81.3, 81.7, 82.1, 82.3, 82.9, 83.2, 84.2, 85.7, 86.5, 113.5, 113.7, 114.5, 129.1, 129.3, 129.9, 130.1, 130.3, 130.7, 130.8, 130.9, 134.8, 135.0, 135.5, 135.6, 135.7, 139.5, 139.9, 140.0, 140.9, 141.0.

m/z calculated: 438.53 *m/z* found (APCI): 437.49

Reaction of 3 with thiocarbonyldiimidazole to form 14

In a flame dried round bottom flask, **3** (0.97 g, 2.5 mmol) was dissolved in dry THF (10 mL). Thiocarbonyldiimidazole (1.1 g, 6.2 mmol) was added and the solution was refluxed gently for 6 hours. TLC (2:1 hexane:ethyl acetate) showed formation of a new compound and complete consumption of the starting dithioacetal. The reaction mixture was concentrated under vacuum and purified *via* flash column chromatography using an eluent of 4:1 hexane:ethyl acetate and 30 g of silica. The pure fractions afforded a clear syrup identified as **14** in an overall yield of 0.9 g (98%).

^{1}H NMR: δ 1.4 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 4.3 (dd, 1H, H-5, J = 4.4, 10.6 Hz), 4.5 (dd, 1H, H-5', J = 1.1, 10.8 Hz), 4.9 (ddd, 1H, H-4, J = 1.3, 4.4, 6.0 Hz), 5.5 (d, 1H, H-3, J = 6.2 Hz), 7.1-7.2 (m, 10H, Ar-H).

^{13}C NMR: δ 27.0, 28.2, 77.2, 79.5, 81.4, 114.4, 127.2, 127.3, 129.62 (3 x C), 129.63 (3 x C), 129.67 (2 x C), 130.6, 135.9, 136.7, 168.7.

m/z calculated: 372.53 *m/z* found (APCI): 373.31

Reduction of 3 with Raney Ni to form 15

To a solution of **3** (0.7 g, 1.8 mmol) in 95% EtOH (10 mL) at room temperature was added excess Raney Ni / H_2O slurry and the mixture was allowed to stir overnight. TLC (6:1 hexane:ethyl acetate) showed complete consumption of starting dithioacetal and formation of a new compound. The reaction mixture was vacuum filtered to remove Raney Ni and the EtOH was evaporated under vacuum. The remaining water mixture was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under vacuum to yield **15** as a 5:2 mixture of anomers in an overall yield of 0.23 g (75%).

^{1}H NMR: δ 1.3-1.6 (5s, 9H, 3 x CH_3 α,β), 3.6 (s,1H, O-H), 3.9 (2d, 1H, H-5 α,β, J = 10.4 Hz), 4.0 (2d, 1H, H-5' α,β, J = 3.8 Hz), 4.25-4.4 (2d, 1H, H-3 α,β, J = 6.0 Hz), 4.8-4.9 (2ddd, 1H, H-4 α,β, J = 3.8, 6.0, 9.9 Hz).

^{13}C NMR: δ 23.2, 23.6, 26.1, 26.2, 27.4, 27.6, 71.7, 72.2, 81.2, 82.0, 83.2, 86.1, 104.1, 107.0, 113.4, 114.4.

m/z calculated: 174.53 *m/z* found (ESI): 173.13

Synthesis of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (16) from D-ribose

In a 500 mL round bottom flask a solution of D-ribose (10 g, 65 mmol) in 300 mL of acetone and 100 mL of methanol (saturated with HCl) was stirred overnight at room temperature. Initial TLC showed formation of a spot with the same R_f as authentic **16**. The reaction was evaporated and the resulting brown syrup was partitioned between CH_2Cl_2 and water. The aqueous layer was removed and washed with CH_2Cl_2 (2 x 30 mL). The organic layers were combined and dried over $MgSO_4$ and evaporated to yield a brown oil. The residue was vacuum distilled at 75 °C and at ~1 mm Hg affording the clear oil **16** in a 80 % yield (10.6 g).

^{1}H NMR: δ 1.3 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 3.4 (s, 3H, CH_3), 3.6-3.7 (m, 2H, H-5, H-5'), 4.4 (dd, 1H, H-4, *J* = 2.7, 5.5 Hz), 4.6 (d, 1H, H-3, *J* = 6.0 Hz), 4.8 (d, 1H, H-2, *J* = 6.0 Hz), 5.0 (s, 1H, H-1).

Reaction of 16 with trifluoromethanesulfonic anhydride to form methyl 2,3-*O*-isopropylidene-5-*O*-(trifluoromethylsulfonyl)-β-D-ribofuranoside (17)

To a flame dried 250 mL round bottom flask, under nitrogen atmosphere, was added dry CH_2Cl_2 (120 mL) and anhydrous pyridine (2.7 mL, 33.0 mmol) and the resulting solution was cooled to –10 °C. Triflic anhydride (Tf_2O) (5.2 mL, 30.9 mmol) in CH_2Cl_2 (20 mL) was added dropwise *via* syringe and let stir for 10 minutes resulting in a thick white precipitate. At this point a solution of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside **16** (3.0 g, 14.8 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the reaction mixture was allowed to stir for 1.5 hours. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and formation of a new compound. The reaction was poured over ice water (100 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a brown syrup, which was extracted with hot hexane (3 x 50 mL). The hexane fractions were evaporated to afford **17** in an overall yield of 4.6 g (92%).

^{1}H NMR: δ 1.3 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 3.4 (s, 3H, CH_3), 4.4 (m, 3H, H-4, H-5, H-5'), 4.6 (d, 1H, H-3, *J* = 6.0 Hz), 4.7 (d, 1H, H-2, *J* = 6.0 Hz), 5.0 (s, 1H, H-1).

^{13}C NMR: δ 26.0, 27.5, 56.5, 76.3, 82.0, 84.4, 85.9, 110.7, 114.1, 120.0 (q, *J* = 270 Hz).

Formation of the dithioacetal 18 by addition of lithium bis(phenylthio)methane to 17

In a flame dried 3-neck 250 mL round bottom flask under nitrogen atmosphere, bis(phenylthio)methane (3.2 g, 13.6 mmol) was dissolved in dry THF (40 mL) and cooled to –78 °C. A solution of 1.6 M *n*-BuLi in hexane (9.4 mL, 15.0 mmol) was added *via* syringe and the mixture was allowed to stir for 20 minutes resulting in a dark yellow solution. At this time a solution of **17** (4.6 g, 13.6 mmol) in THF (30 mL) was added dropwise *via* an addition funnel and the reaction was then allowed to stir overnight while warming to room temperature. TLC (4:1 hexane:ethyl acetate) showed the formation of a new compound with some of the dithioacetal left unreacted. The reaction mixture was quenched with saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated down to a yellow syrup. The syrup was purified *via* flash column chromatography (210 g of silica) using an eluent of 10:1 hexane:ethyl acetate to afford 3.6 g of **18** as a yellow syrup (63%).

^{1}H NMR: δ 1.3 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 1.9 (ddd, 1H, H-5, *J* = 4.2, 10.6, 14.4 Hz), 2.2 (ddd, 1H, H-5', *J* = 4.2, 10.6, 14.4 Hz), 3.1 (s, 3H, CH_3), 4.5 (m, 3H, H-2, H-3, H-4), 4.7 (dd, 1H, H-6, *J* = 4.0, 10.6 Hz), 4.9 (s, 1H, H-1), 7.2-7.5 (m, 10H, Ar-H).

^{13}C NMR: δ 26.3, 27.8, 42.4, 56.3, 57.3, 85.3, 85.4, 86.5, 110.9, 129.0, 129.2, 129.9 (3 x C), 130.1, 134.3 (3 x C), 134.4, 134.9 (2 x C).

Formation of *C*-disaccharide 19 from the addition of the lithium anion of 18 to 2,3-*O*-isopropylidene-D-erythronolactone

In a flame dried 50 mL round bottom flask under nitrogen atmosphere, **18** (1.0 g, 2.4 mmol) was dissolved in dry THF (10 mL) and cooled to –78 °C. A solution of 1.6 M *n*-BuLi in hexane (3.0 mL, 4.8 mmol) was added *via* syringe and the mixture was allowed to stir for 20 minutes resulting in a dark yellow solution. At this time a solution of 2,3-*O*-isopropylidene-D-erythronolactone (1.15 g, 7.3 mmol) in dry THF (5 mL) was added dropwise *via* syringe and the resulting mixture was allowed to stir overnight, gradually warming to room temperature. TLC (4:1 hexane:ethyl acetate) showed formation of a new compound with some **18** left unreacted. The reaction mixture was quenched with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a syrup. The syrup was purified *via* flash column chromatography (30 g of silica) with an eluent of 12:1 hexane:ethyl acetate to afford 1.1 g of **19** as a colorless syrup (77%).

^{1}H NMR: δ 1.4 (dd, 1H, H-5, *J* = 7.1 Hz), 1.47 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.0 (dd, 1H, H-5', *J* = 9.0 Hz), 2.9 (s, 3H, CH_3), 4.0 (dd, 1H, H-10, *J* = 4.0, 10.1 Hz), 4.25 (dd, 1H, H-10', *J* = 6.0, 10.1 Hz), 4.4 (d, 1H, H-3, *J* = 5.9 Hz), 4.47 (s, 1H, O-H), 4.8 (s, 1H, H-1), 4.88 (d, 1H, H-2, *J* = 6.0 Hz), 5.0 (ddd, 1H, H-9, *J* = 4.0, 6.0, 7.3 Hz), 5.2 (dd, 1H, H-4, *J* = 7.1, 9.0 Hz), 5.4 (d, 1H, H-8, *J* = 7.3 Hz), 7.1-7.8 (m, 10 H, Ar-H).

^{13}C NMR: δ 26.2, 26.3, 27.6, 27.8, 41.5, 55.4, 72.4, 73.6, 80.7, 83.4, 85.5, 86.0, 86.3, 107.8, 110.3, 112.3, 116.7, 129.2 (2 x C), 129.4 (2 x C), 130.2, 130.6, 131.0, 131.9, 138.8 (2 x C), 140.0 (2 x C).

m/z calculated: 576.62 *m/z* found (APCI): 575.17

Acetylation of the disaccharide 19 to form 20

To a solution of **19** (0.16 g, 0.28 mmol) in anhydrous pyridine (5 mL), at room temperature, was added an excess of acetic anhydride (1 mL) and the solution was allowed to stir for 3 hours. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and formation of a new compound. The reaction mixture was poured over ice water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with 5% H_2SO_4 (3 mL), and dried over anhydrous $MgSO_4$. The solution was evaporated under vacuum to afford a clear syrup of **20** in an overall yield of 0.15 g (87%).

^{1}H NMR: δ 1.2 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 1.6 (s, 3H, CH_3), 1.8 (dd, 1H, H-5, *J* = 1.8, 15.2 Hz), 2.0 (dd, 1H, H-5', *J* = 7.9, 15.6 Hz), 2.1 (s, 3H, CH_3), 3.1 (s, 3H, CH_3), 4.0 (dd, 1H, H-10, *J* = 6.4, 11.5 Hz), 4.2 (dd, 1H, H-10', *J* = 6.2, 11.4 Hz), 4.4 (d, 1H, H-3, *J* = 5.7 Hz), 4.7 (m, 3H, H-2, H-4, H-9), 4.8 (s, 1H, H-1), 5.9 (d, 1H, H-8, *J* = 6.4 Hz), 7.2-7.8 (m, 10H, Ar-H).

^{13}C NMR: δ 25.9, 27.1, 27.5, 28.7, 31.0, 40.0, 55.9, 63.8, 72.1, 76.5, 77.4, 84.7, 86.1, 86.6, 110.5, 111.7, 112.8, 127.2, 129.9 (3 x C), 130.0 (2 x C), 131.3, 131.4, 138.5 (2 x C), 139.3 (2 x C), 171.3, 196.1.

m/z calculated: 618.20 *m/z* found (APCI): 509.20 – (**20** – SPh)

Attempted Reduction of 19 with $BF_3{\cdot}OEt_2$ and Et_3SiH

To a solution of **19** (0.16 g, 0.28 mmol) in dry CH_2Cl_2 (5 mL) at –78 °C, $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) and Et_3SiH (0.15 mL, 0.84 mmol) were added *via* syringe and stirred for 1 hour. At this point the reaction was allowed to warm to –10 °C and was stirred for an additional 12 hours in the freezer. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and the formation of several new compounds. The reaction mixture was poured over ice water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum and a crude ^1H NMR showed a complex mixture of products that was not investigated further.

Attempted Reduction of 19 with $TiCl_4$ and Ph_3SiH

To a solution of **19** (0.17 g, 0.3 mmol) in dry CH_2Cl_2 (5 mL) at room temperature, $TiCl_4$ (0.05 mL, 0.4 mmol) and Ph_3SiH (0.1 g, 0.4 mmol) were added and the mixture was stirred for 8 hours. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and the formation of several new compounds. The reaction mixture was poured over ice water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum and a crude ^1H NMR showed a complex mixture of products that was not investigated further.

Attempted Reduction of 19 with TMS-OTf and Et_3SiH

To a solution of **19** (0.28 g, 0.48 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C Et_3SiH (0.77 mL, 4.8 mmol) was added *via* syringe. At this point TMS-OTf (0.10 mL, 0.48 mmol) was added dropwise and stirred for one hour. TLC (3:1 hexane:ethyl acetate) showed complete consumption of starting material and the formation of several new compounds. Et_3N was added and the solution turned golden yellow. The reaction mixture was poured over ice water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum and a crude ^1H NMR showed a complex mixture of products that was not investigated further.

Reduction of 19 with Raney Ni to form 21

To a solution of **19** (0.5 g, 0.8 mmol) in 95% EtOH (10 mL) at room temperature was added excess Raney Ni / H_2O slurry (2 mL) and the mixture was allowed to stir overnight. TLC (6:1 hexane:ethyl acetate) showed complete consumption of starting material and formation of a new compound. The reaction mixture was vacuum filtered to remove Raney Ni and the EtOH was evaporated under vacuum. The remaining water mixture was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under vacuum to yield **21** in an overall yield of 0.22 g (74%).

^1H NMR: δ 1.3 (s, 6H, 2 x CH_3), 1.45 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.7-2.0 (m, 4H, H-5, H-5', H-6, H-6'), 2.3 (s,1H, O-H), 3.3 (s, 3H, CH_3), 3.9 (d, 1H, H-10, *J* = 11.2 Hz), 4.0 (dd, 1H, H-10', *J* = 3.8, 11.2 Hz), 4.2 (m, 1H, H-4), 4.4 (d, 1H, H-

3, $J = 6.0$ Hz), 4.57 (d, 1H, H-2, $J = 6.0$ Hz), 4.6 (d, 1H, H-8, $J = 5.9$ Hz), 4.8 (dd, 1H, H-9, $J = 3.8, 5.9$ Hz), 4.9 (s, 1H, H-1).

^{13}C NMR: δ 26.1, 26.2, 27.6, 27.7, 30.3, 33.4, 56.4, 72.2, 81.8, 85.2, 85.3, 85.5, 86.6, 88.2, 108.3, 110.7, 113.3.

m/z calculated: 360.63 *m/z* found (APCI): 359.22

Oxidation of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (22) to the lactone 23

To a dark red solution of *N*-iodosuccinimide (4.5 g, 20 mmol) and tetra-*N*-butylammonium iodide (1.5 g, 4 mmol) in dry CH_2Cl_2 (40 mL) was added **22** (1.0 g, 3.9 mmol), and the resulting mixture was allowed to stir at room temperature for 3 hours. TLC (3:1 hexane:ethyl acetate) showed complete consumption of starting material and formation of a new compound. The reaction mixture was quenched with saturated sodium thiosulfate solution (25 mL), resulting in a colorless solution, and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated down to a yellow solid. Lactone **23** was recrystallized from 100% ethanol in an overall yield of 0.65 g (65%).

^{1}H NMR: δ 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.0 (dd, 1H, H-6, $J = 3.7, 9.2$ Hz), 4.1 (dd, 1H, H-6’, $J = 6.0, 9.3$ Hz), 4.3 (dd, 1H, H-4, $J = 3.5, 8.2$ Hz), 4.4 (ddd, 1H, H-5, $J = 3.7, 5.9, 8.2$ Hz), 4.8 (d, 1H, H-2, $J = 5.3$ Hz), 4.9 (dd, 1H, H-3, $J = 3.3, 5.3$ Hz).

^{13}C NMR: δ 26.3, 27.2, 28.0, 28.3, 67.6, 73.7, 77.0, 77.2, 79.3, 111.0, 115.6, 174.4.

m/z calculated: 258.29 *m/z* found (ESI): 259.34

Oxidation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (24) to give the lactone 25

To a solution of *N*-chlorosuccinimide (0.3 g, 2.3 mmol) and tetra-*N*-butylammonium chloride (0.13 g, 0.4 mmol) in dry CH_2Cl_2 (5 mL) was added 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (0.24 g, 0.4 mmol), and the resulting mixture was allowed to stir at room temperature for 3 hours. TLC (3:1 hexane:ethyl acetate) showed complete consumption of starting material and formation of a new compound. The reaction mixture was poured over ice water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated down to a yellow solid. Lactone **25** was recrystallized from 100% ethanol in an overall yield of 0.1 g (42%).

^{1}H NMR: δ 3.6 (dd, 1H, H-6, J = 2.6, 11.0 Hz), 3.7 (dd, 1H, H-6', J = 3.3, 11.1 Hz), 3.9 (m, 2H, H-3, H-5, J = 6.6 Hz), 4.1 (d, 1H, H-4, J = 6.6 Hz), 4.4-4.7 (m, 8H, 4 x CH_2), 5.0 (d, 1H, H-2 J = 11.3 Hz), 7.1-7.4 (m, 20 H, Ar-H).

^{13}C NMR: δ 69.4, 74.7, 74.9 (2 x C), 75.1, 77.2, 78.5, 79.3, 82.1, 128.8 (2 x C), 128.9, 129.0 (3 x C), 129.02 (3 x C), 129.1, 129.3 (2 x C), 129.4 (5 x C), 129.5 (3 x C), 137.9, 138.4, 138.5, 138.6, 170.3.

m/z calculated: 538.66 *m/z* found (APCI): 539.24

Formation of the *C*-glycoside 26 from the addition of the anion of bis(phenylthio)-methane to the lactone 23

In a flame dried 25 mL round bottom flask under nitrogen atmosphere, bis(phenylthio)methane (0.5 g, 2.2 mmol) was dissolved in dry THF (5 mL) and cooled to –78 °C. A solution of 1.6 M *n*-BuLi in hexane (1.2 mL, 1.8 mmol) was added *via* syringe and allowed to stir for 20 minutes resulting in a dark yellow solution. At this time a solution of **23** (0.5 g, 1.8 mmol) in dry THF (3 mL) was added dropwise *via* syringe and the mixture was allowed to stir overnight while warming to room temperature. TLC (4:1 hexane:ethyl acetate) showed formation of a new compound with some of the bis(phenylthio)methane left unreacted. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a syrup, which was purified *via* flash column chromatography (15 g of silica) using an eluent of 6:1 hexane:ethyl acetate to afford 0.34 g of **26** as a colorless syrup (38%).

^{1}H NMR: δ 1.3 (s, 3H, CH_3), 1.4 (s, 6H, 2 x CH_3), 1.4 (s, 3H, CH_3), 3.4 (s, 1H, O-H), 3.5 (dd, 1H, H-7, *J* = 4.4, 8.8 Hz), 3.6 (dd, 1H, H-7', *J* = 6.0, 8.8 Hz), 4.0 (dd, 1H, H-5, *J* = 3.5, 8.1 Hz), 4.1 (ddd, 1H, H-6, *J* = 4.6, 6.2, 8.1 Hz), 4.8 (s, 1H, H-1), 4.8 (d, 1H, H-3, *J* = 5.9 Hz), 4.9 (dd, 1H, H-4, *J* = 3.7, 5.9 Hz), 7.1-7.6 (m,10H, Ar-H).

^{13}C NMR: δ 26.0, 26.5, 27.4, 28.2, 65.3, 67.8, 73.9, 80.7, 81.2, 86.3, 107.9, 110.3, 113.8, 128.4, 129.1, 129.5 (2 x C), 129.9 (2 x C), 132.9 (2 x C), 134.0 (2 x C), 135.0, 136.7.

m/z calculated: 490.66 *m/z* found (APCI): 489.23

Reaction of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (27) with trifluoromethanesulfonic anhydride to form 28

To a flame dried 100 mL round bottom flask, under nitrogen atmosphere, was added CH_2Cl_2 (40 mL) and anhydrous pyridine (1.0 mL, 13.1 mmol) and the resulting solution was cooled to –10 °C. Tf_2O (1.5 mL, 8.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise *via* syringe and let stir for 10 minutes resulting in a thick white precipitate. At this point a solution of **27** (1.1 g, 4.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the reaction mixture was allowed to stir for 1.5 hours. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and formation of a new compound. The reaction was poured over ice water (30 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a brown syrup which was extracted with hot hexane (3 x 15 mL). The hexane fractions were evaporated down to afford **28** in an overall yield of 1.54 g (90%).

^{1}H NMR: δ 1.3 (2s, 6H, 2 x CH_3), 1.4 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 4.1 (ddd, 1H, H-5, J = 2.0, 4.8, 7.0 Hz), 4.2 (dd, 1H, H-4, J = 2.0, 7.9 Hz), 4.3 (dd, 1H, H-2, J = 2.6, 4.9 Hz), 4.5-4.6 (m, 3H, H-3, H-6, H-6'), 5.5 (d, 1H, H-1, J = 4.9 Hz).

^{13}C NMR: δ 24.3, 24.8, 25.7, 25.8, 65.9, 70.0, 70.2, 70.4, 74.5, 95.9, 108.9, 109.8, 119.8 (q, J).

Formation of 29 by addition of lithium bis(phenylthio)methane to 28

In a flame dried 50 mL round bottom flask under nitrogen atmosphere, bis(phenylthio)methane (2.0 g, 8.7 mmol) was dissolved in dry THF (20 mL) and cooled to –78 °C. A solution of 1.6 M *n*-BuLi in hexane (4.0 mL, 6.5 mmol) was added *via* syringe and allowed to stir for 20 minutes resulting in a dark yellow solution. At this time a solution of **28** (1.54 g, 3.9 mmol) in THF (15 mL) was added dropwise *via* a syringe and was allowed to stir overnight while warming to room temperature. TLC (10:1 hexane:ethyl acetate) showed the formation of a new compound with some of the dithioacetal left unreacted. The reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a syrup. The syrup was purified *via* flash column chromatography (45 g of silica) using an eluent of 15:1 hexane:ethyl acetate to afford 1.3 g of **29** as a dark syrup (68%).

^{1}H NMR: δ 1.31 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.6 (s, 3H, CH_3), 1.8 (ddd, 1H, H-6, *J* = 2.9, 10.0, 10.8 Hz), 2.3 (ddd, 1H, H-6', *J* = 3.8, 10.0, 10.9 Hz), 4.1 (dd, 1H, H-4, *J* = 1.8, 7.7 Hz), 4.3 (m, 2H, H-2, H-5, *J* = 2.6, 5.0 Hz), 4.6 (dd, 1H, H-3, *J* = 2.6, 7.9 Hz), 4.7 (dd, 1H, H-7, *J* = 3.7, 10.6 Hz), 5.5 (d, 1H, H-1, *J* = 5.1 Hz), 7.2-7.5 (m, 10H, Ar-H).

^{13}C NMR: δ 25.9, 26.4, 27.2, 27.3, 37.4, 55.7, 66.3, 71.7, 72.2, 74.2, 97.6, 109.9, 110.4, 128.2, 128.8, 129.7 (2 x C), 129.8 (2 x C), 130.0, 133.0 (2 x C), 134.3, 134.5 (2 x C).

Formation of 31 by reaction of *tert*-butylchlorodiphenylsilane (TBDPS-Cl) with methyl α-D-glucopyranoside (30)

To a solution of methyl α-D-glucopyranoside (1.0 g, 5.0 mmol) in DMF (10 mL) was added imidazole (0.7 g, 10 mmol) and the mixture was cooled to 0 °C. TBDPS-Cl (1.0 mL, 4 mmol) was added slowly *via* syringe and the reaction mixture was allowed to stir for 4 hours. TLC (ethyl acetate) showed formation of a new compound and some starting sugar left unreacted. The reaction was poured over water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under vacuum to yield **31** in an overall yield of 1.6 g (99% based on TBDPS-Cl).

^{1}H NMR: δ 1.0 (s, 9H, 3 x CH_3), 3.3 (s, 3H, CH_3), 3.5 (m, 2H, H-6, 6'), 3.6 (m, 1H, H-5, J = 9.2 Hz), 3.7 (t, 1H, H-4, J = 9.2 Hz), 3.8 (dd, 1H, H-3, J = 5.5, 11.0 Hz), 3.9 (dd, 1H, H-2, J = 3.7, 11.0 Hz), 4.7 (d, 1H, H-1, J = 3.7 Hz), 7.2-7.7 (m, 10 H, Ar-H).

^{13}C NMR: δ 20.5, 28.1 (3 x C), 56.2, 65.3, 72.4, 72.5, 73.2, 75.6, 100.3, 128.7 (4 x C), 130.7 (2 x C), 134.2, 134.3, 136.6 (4 x C).

m/z calculated: 432.20 *m/z* found (APCI): 433.08

Benzylation of 31 to form the protected sugar 32

To a solution of **31** (1.7 g, 4.0 mmol) in dry THF (30 mL), under nitrogen atmosphere, was added NaH (0.6 g, 16.0 mmol), and the resulting mixture was allowed to stir at room temperature for 20 minutes. At this time $PhCH_2Br$ (1.9 mL, 16.0 mmol) was added *via* syringe and the reaction mixture was refluxed for 3 hours. TLC (6:1 hexane:ethyl acetate) showed formation of a new compound with some of the $PhCH_2Br$ left unreacted. The reaction mixture was poured over ice water (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a syrup. The syrup was purified *via* flash column chromatography (60 g of silica) using a gradient of hexane to remove unreacted $PhCH_2Br$ followed by ethyl acetate to afford 2.7 g of **32** as a yellow syrup (96%).

^{1}NMR: δ 1.05 (s, 6H, 2 x CH_3), 1.08 (s, 3H, CH_3), 3.3 (s, 3H, CH_3), 3.5 (dd, 1H, H-6, *J* = 3.6, 9.7 Hz), 3.6 (d, 1H, H-6', *J* = 9.7 Hz), 3.7 (dd, 1H, H-5, *J* = 3.4, 6.0 Hz), 3.9 (m, 2H, H-2, H-3), 4.0 (dd, 1H, H-4, *J* =8.9, 9.3 Hz), 4.6 (d, 1H, H-1 *J* = 3.9 Hz), 4.6-5.0 (m, 6H, 3 x CH_2), 7.1-7.7 (m, 25 H, Ar-H).

^{13}C NMR: δ 28.0, 56.0, 64.0, 72.6, 74.5, 76.2, 77.1, 78.9, 81.3, 83.4, 98.9, 128.5 (2 x C), 128.6 (2 x C), 128.9 (2 x C), 129.0 (2 x C), 129.2 (2 x C), 129.4 (2 x C), 129.5 (4 x C), 130.5, 130.6, 136.6 (2 x C), 136.8 (2 x C), 139.2, 139.7.

Desilylation of 32 with tetra-*N*-butylammonium fluoride to give 33

To a solution of **32** (0.8 g, 1.1 mmol) in dry THF (10 mL) was added a solution of 1.0 M tetra-*N*-butylammonium fluoride in THF (1.2 mL, 1.2 mmol) *via* syringe and the resulting mixture was allowed to stir at room temperature for 6 hours. TLC (5:1 hexane:ethyl acetate) showed formation of a new compound with some of **32** left unreacted. The reaction was poured into water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a syrup. The syrup was purified *via* flash column chromatography (20 g of silica) using a gradient of 5:1 hexane:ethyl acetate to remove unreacted **32** and 1:1 hexane:ethyl acetate to afford 0.3 g of the colorless syrup **33** in an overall yield of 64%.

^{1}H NMR: δ 3.3 (s, 3H, CH_3), 3.5 (m, 2H, H-6, H-6'), 3.6-3.7 (m, 3H, H-2, H-3, H-5), 4.0 (dd, 1H, H-4, *J* = 9.2, 9.3 Hz), 4.5 (d, 1H, H-1, *J* = 3.7 Hz), 4.6-5.0 (m, 6H, 3 x CH_2), 7.2-7.4 (m, 15H, Ar-H).

^{13}C NMR: δ 56.4, 62.9, 71.9, 74.6, 76.2, 76.9, 78.5, 81.1, 83.1, 99.3, 128.7, 128.9, 129.0 (2 x C), 129.1 (2 x C), 129.2 (2 x C), 129.4 (2 x C), 129.5 (5 x C), 139.1, 139.2, 139.7.

Reaction of 33 with trifluoromethanesulfonic anhydride to form 34

To a flame dried 100 mL round bottom flask, under nitrogen atmosphere, was added dry CH_2Cl_2 (40 mL) and anhydrous pyridine (0.5 mL, 6.5 mmol) and the resulting solution was cooled to –10 °C. Tf_2O (0.7 mL, 4.3 mmol) in CH_2Cl_2 (5 mL) was added dropwise *via* syringe and let stir for 10 minutes resulting in a thick white precipitate. At this point a solution of **33** (1.0 g, 2.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the reaction mixture was allowed to stir for 1.5 hours. TLC (4:1 hexane:ethyl acetate) showed complete consumption of starting material and formation of a new compound. The reaction was poured over ice water (30 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a brown syrup which was extracted with hot hexane (3 x 15 mL). The hexane fractions were evaporated down to afford **34** in an overall yield of 1.2 g (92%).

Formation of the dithioacetal sugar 35 by addition of the anion of bis(phenylthio)-methane to 34

In a flame dried 50 mL round bottom flask under nitrogen atmosphere, bis(phenylthio)methane (1.0 g, 4.3 mmol) was dissolved in dry THF (15 mL) and cooled to –78 °C. A solution of 1.6 M *n*-BuLi in hexane (2.7 mL, 4.3 mmol) was added *via* syringe and allowed to stir for 20 minutes resulting in a dark yellow solution. At this time a solution of **34** (1.2 g, 2.0 mmol) in THF (10 mL) was added dropwise *via* a syringe and was allowed to stir overnight while warming to room temperature. TLC (10:1 hexane:ethyl acetate) showed the formation of a new compound with some of the dithioacetal left unreacted. The reaction mixture was quenched with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated down to a yellow syrup. The syrup was purified *via* flash column chromatography (30 g of silica) using an eluent of 18:1 hexane:ethyl acetate to afford 0.9 g of **35** as a yellow syrup in a 65% yield.

^{1}H NMR: δ 1.9 (ddd, 1H, H-6, *J* = 3.5, 10.3, 10.8 Hz), 2.2 (ddd, 1H, H-6', *J* = 2.2, 10.4, 10.8 Hz), 3.1 (dd, 1H, H-3, *J* = 9.0, 9.7 Hz), 3.4 (s, 3H, CH_3), 3.5 (dd, 1H, H-2, *J* = 3.5, 9.7 Hz), 4.0 (dd, 1H, H-4, *J* = 9.1, 9.4 Hz), 4.1 (ddd, 1H, H-5, *J* = 2.1, 9.7, 10.4 Hz), 4.5 (d, 1H, H-7, *J* = 10.9 Hz), 4.6 (d, 1H, H-1, *J* = 3.5 Hz), 4.6-5.0 (m, 6H, 3 x CH_2), 7.2-7.5 (m, 25H, Ar-H).

^{13}C NMR: δ 39.3, 54.7, 56.9, 68.5, 74.5, 76.3, 77.0, 81.1, 83.0, 83.1, 99.0, 128.5, 128.7, 128.8, 128.9 (2 x C), 129.0, 129.1 (2 x C), 129.2 (2 x C), 129.41 (2 x C), 129.47 (2 x C), 129.5 (2 x C), 129.6, 129.8 (2 x C), 129.9 (2 x C), 130.1, 133.3 (2 x C), 134.3 (2 x C), 135.2, 139.0, 139.2, 139.7.

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APPENDIX

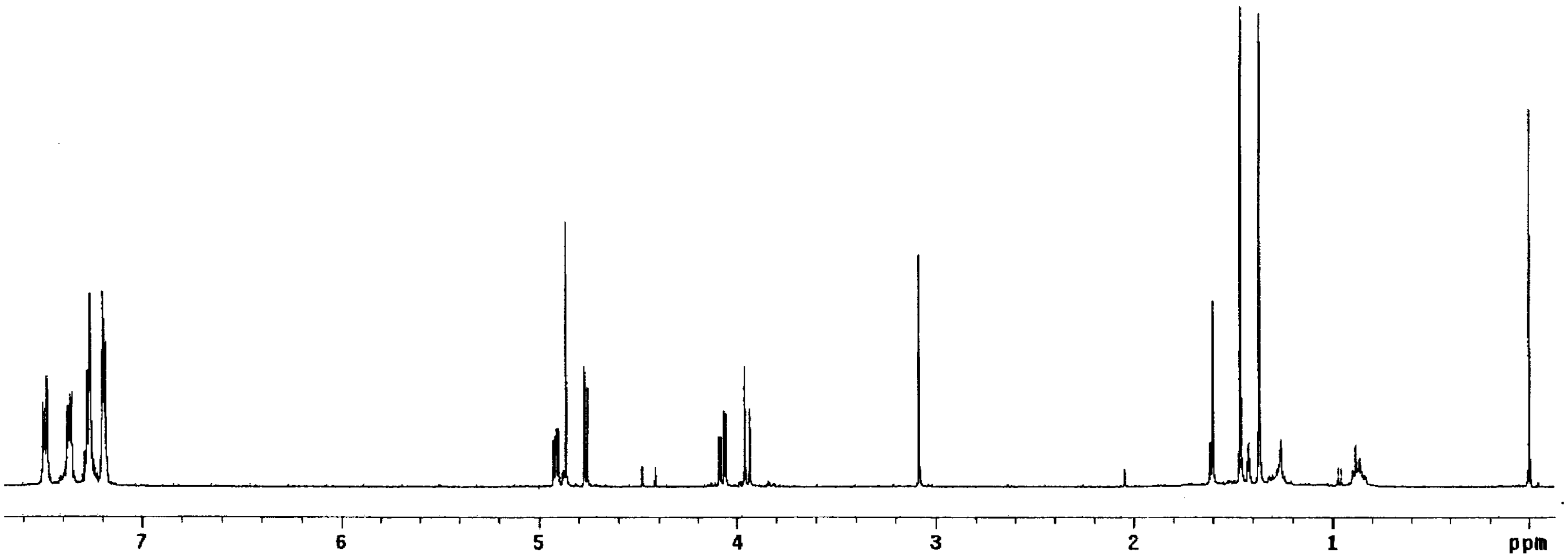


Figure 10. ^{1}H NMR of **3**

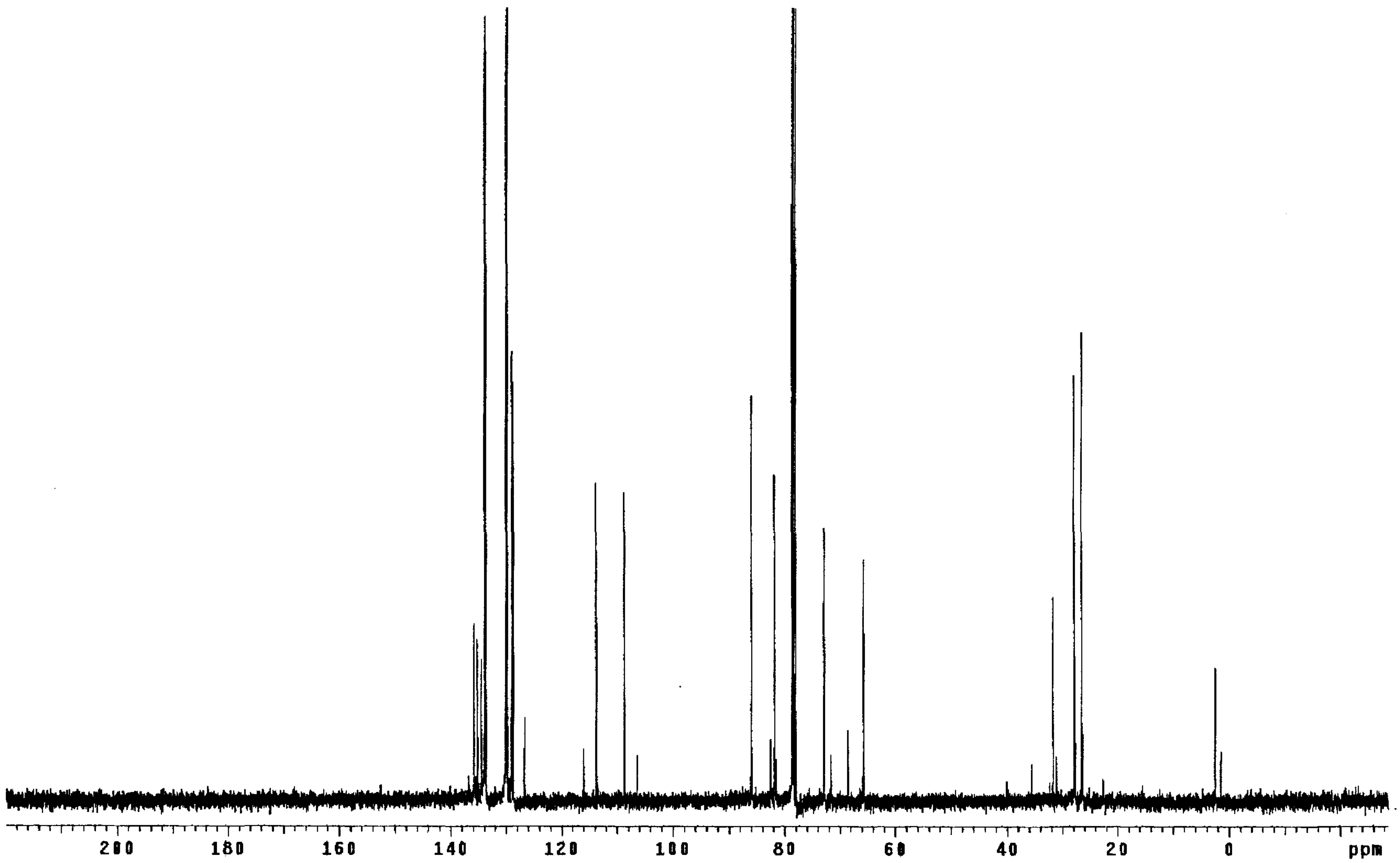
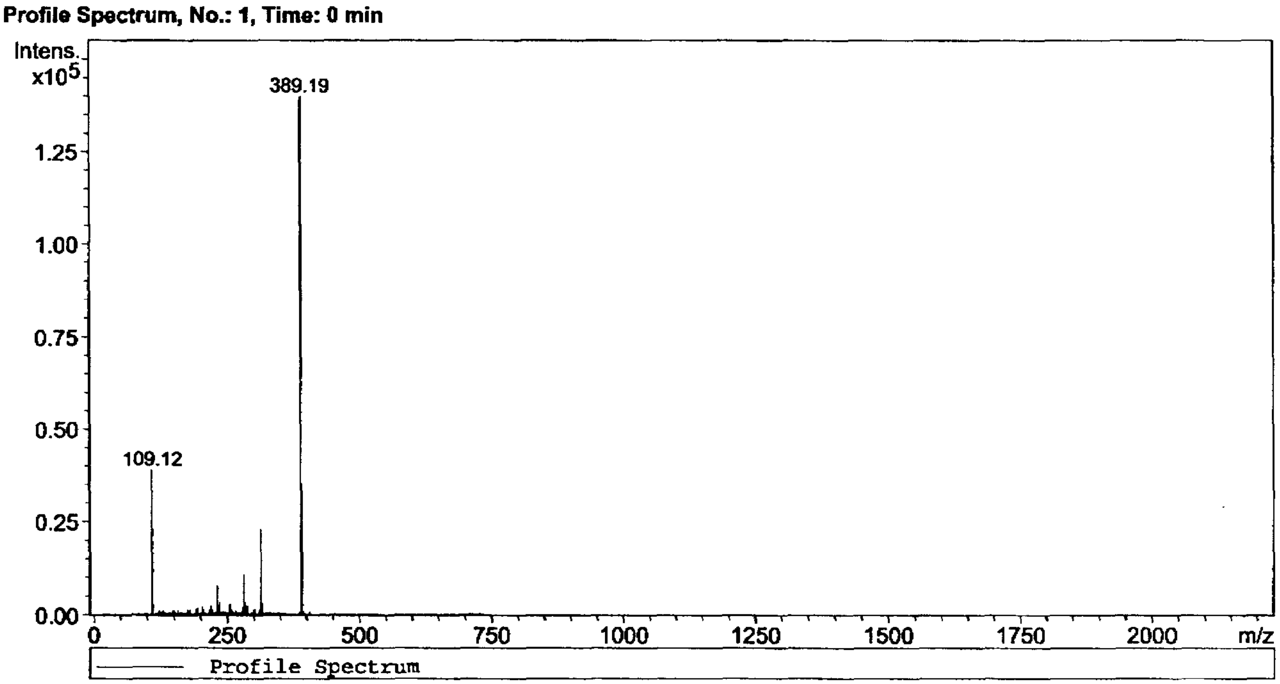


Figure 11. ^{13}C NMR of **3**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
109.12	39065	0.30	219.12	2372	0.40	282.11	2025	0.20
110.07	2526	0.30	221.16	1316	0.40	283.32	3338	0.50
111.09	1266	0.30	231.10	7821	0.40	287.05	2524	0.40
123.17	1086	0.30	232.12	1650	0.40	301.13	1531	0.30
149.10	1322	0.20	233.17	1519	0.30	311.12	1620	0.40
157.10	1275	0.50	235.05	3336	0.30	313.08	23125	0.30
175.15	1467	0.30	241.31	1017	0.20	314.07	5183	0.30
179.10	1336	0.20	255.35	2911	0.50	315.09	2883	0.30
193.16	1925	0.30	259.11	1353	0.20	389.19	140064	0.30
203.17	2109	0.40	265.04	1359	0.20	390.00	35327	0.40
205.20	1387	0.20	279.16	1947	0.40	391.08	16740	0.40
217.21	1181	0.40	281.18	10881	0.40	392.04	4047	0.30

Figure 12. Mass Spectrum of **3**

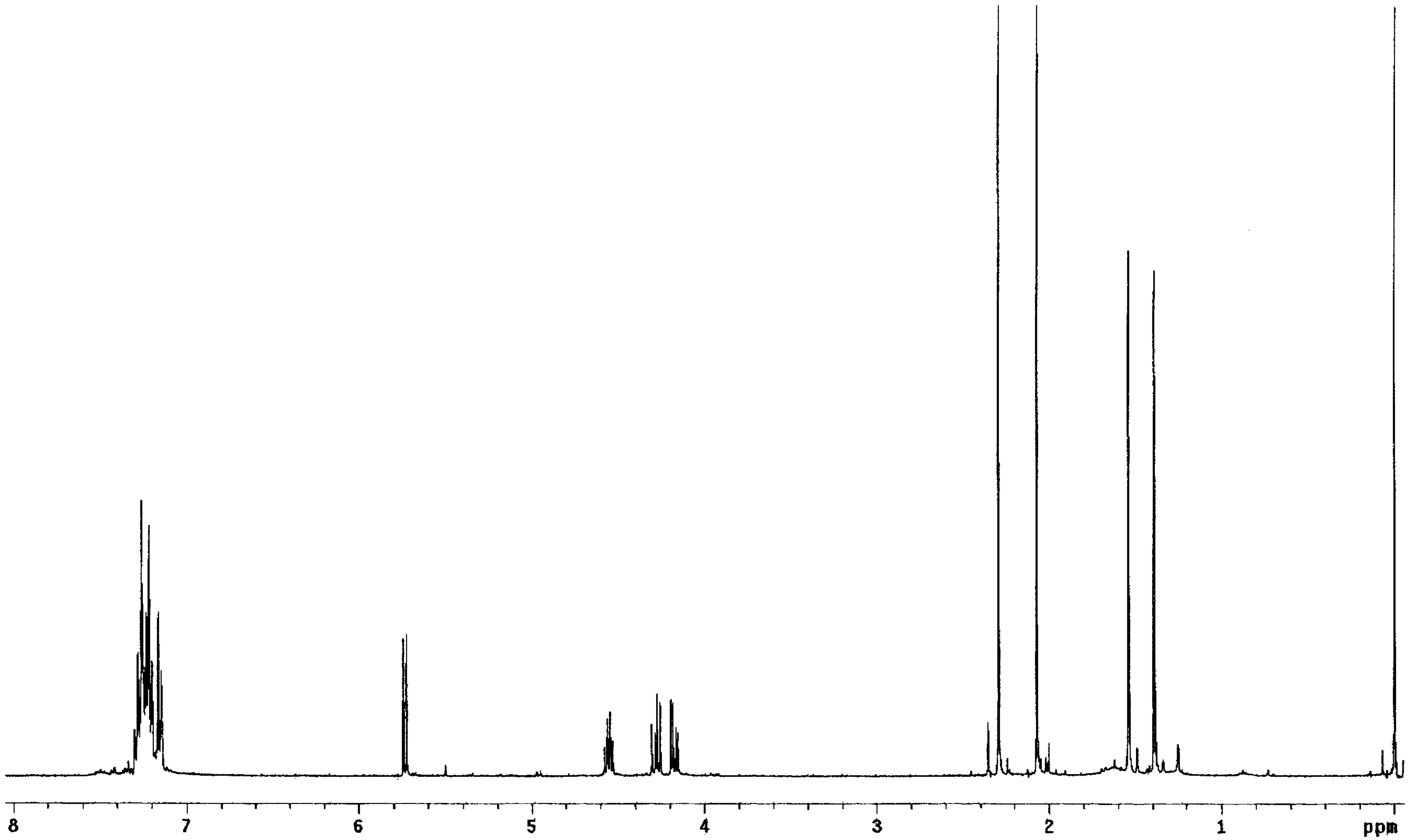


Figure 13. ^{1}H NMR of **4**

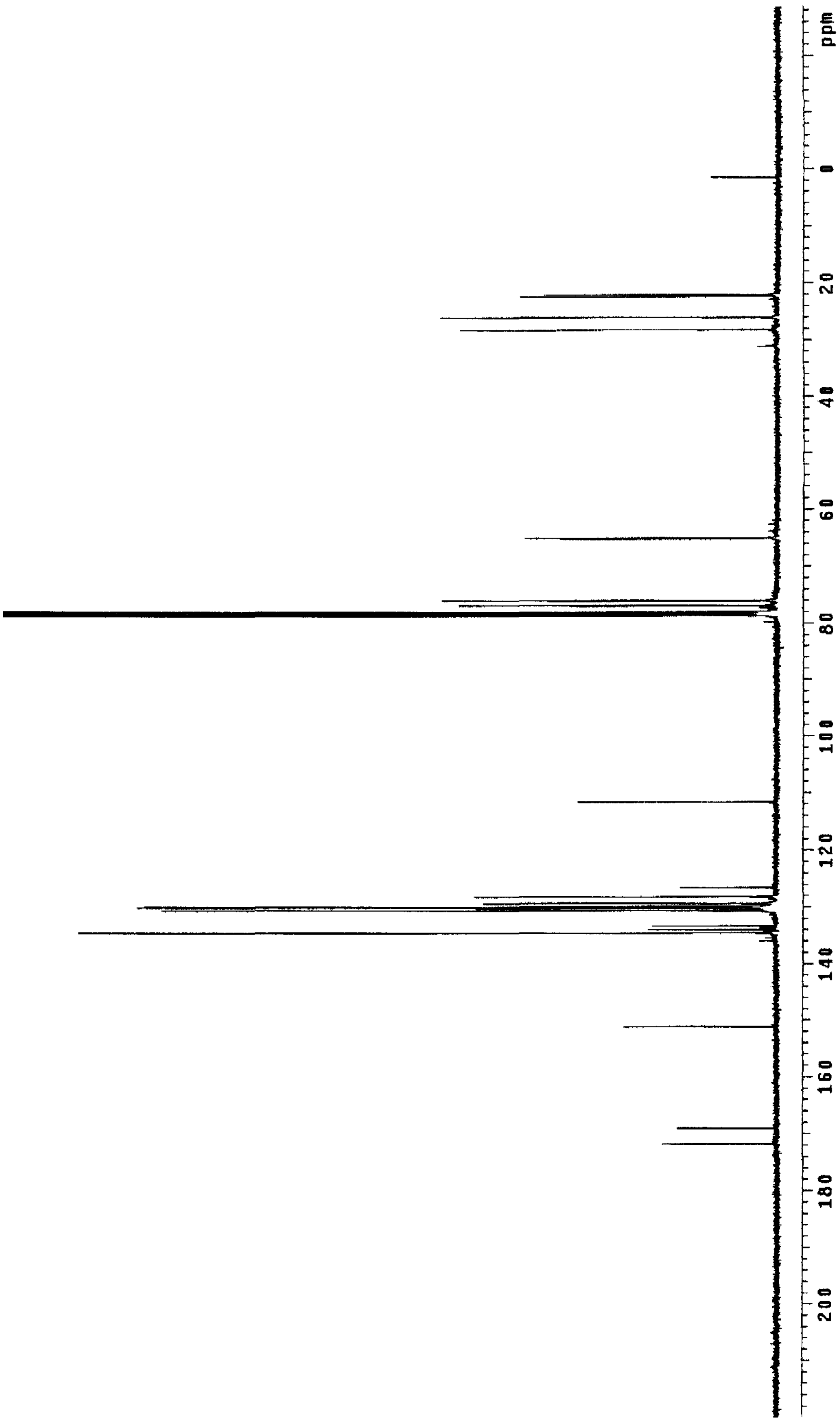
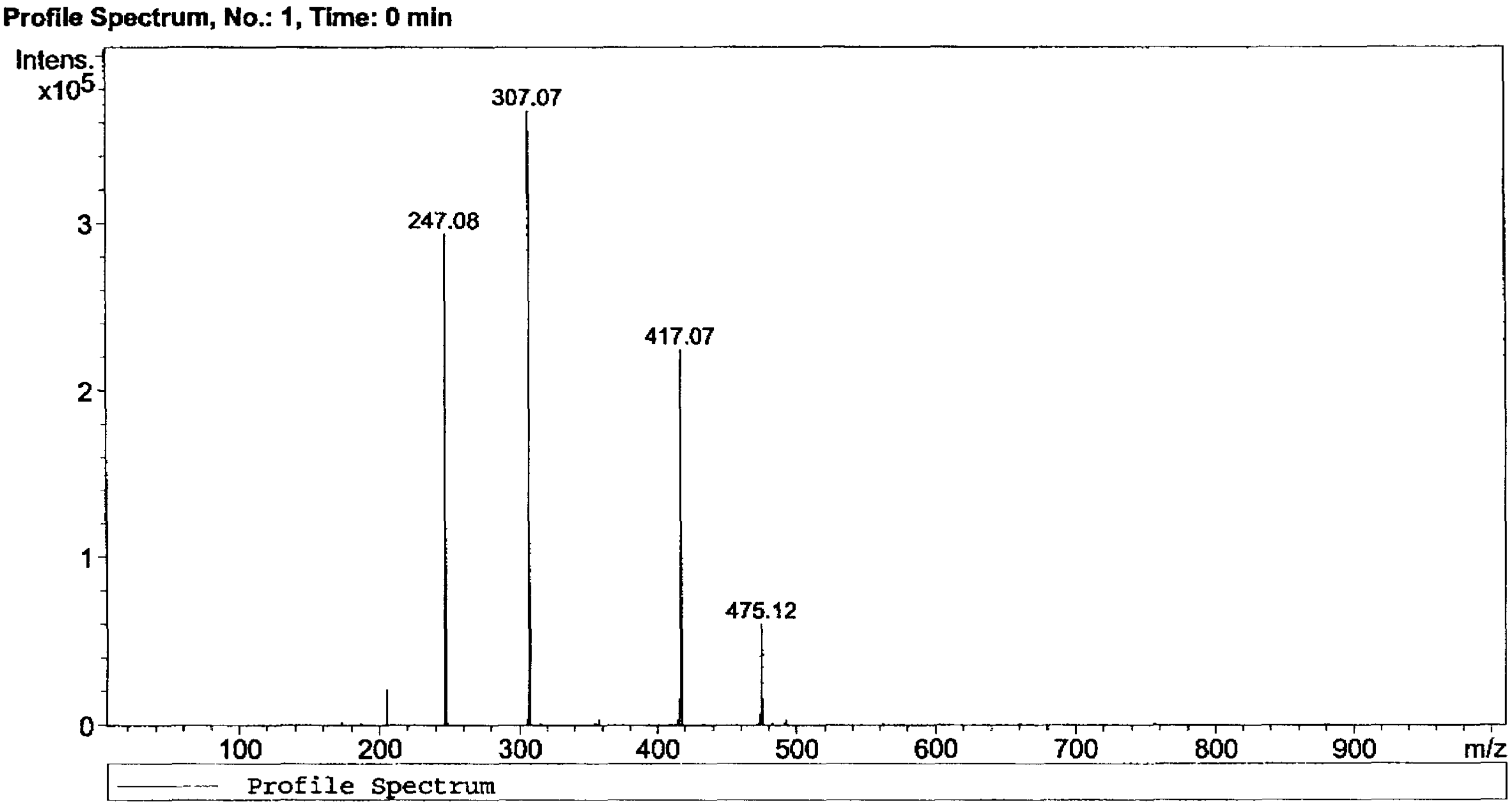


Figure 14. ^{13}C NMR of 4



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
173.15	2053	0.40	307.07	367578	0.30	417.07	224920	0.30
187.15	1095	0.20	315.15	1018	0.30	475.12	60377	0.30
205.12	22237	0.30	354.61	1101	0.20	492.16	3242	0.30
247.08	294006	0.30	355.21	1164	0.40	756.11	1057	0.20
248.05	1780	0.40	357.05	3621	0.20			
305.87	3302	0.20	415.58	15601	0.20			

Figure 15. Mass Spectrum of **4**

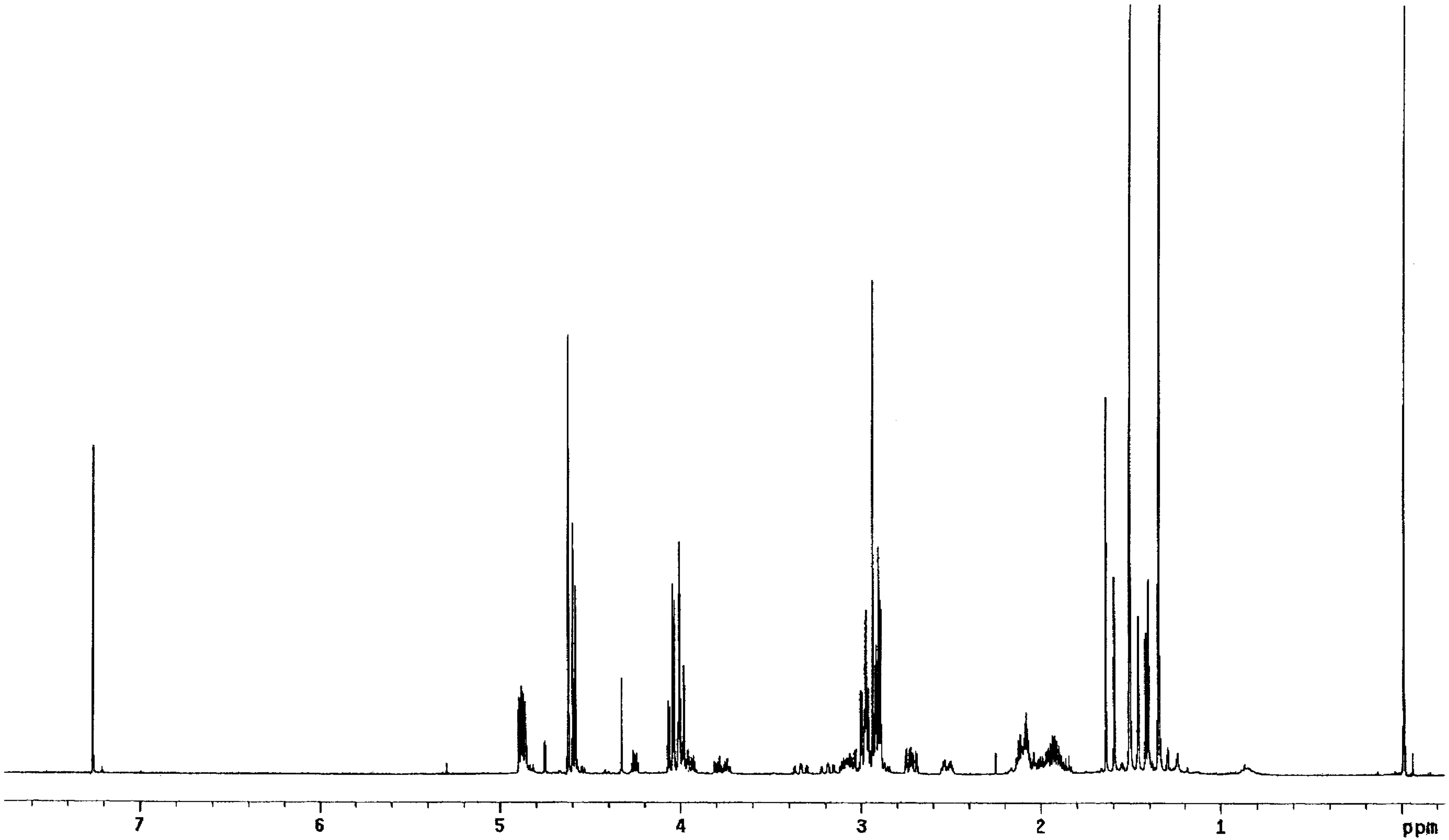


Figure 16. ^{1}H NMR of **6**

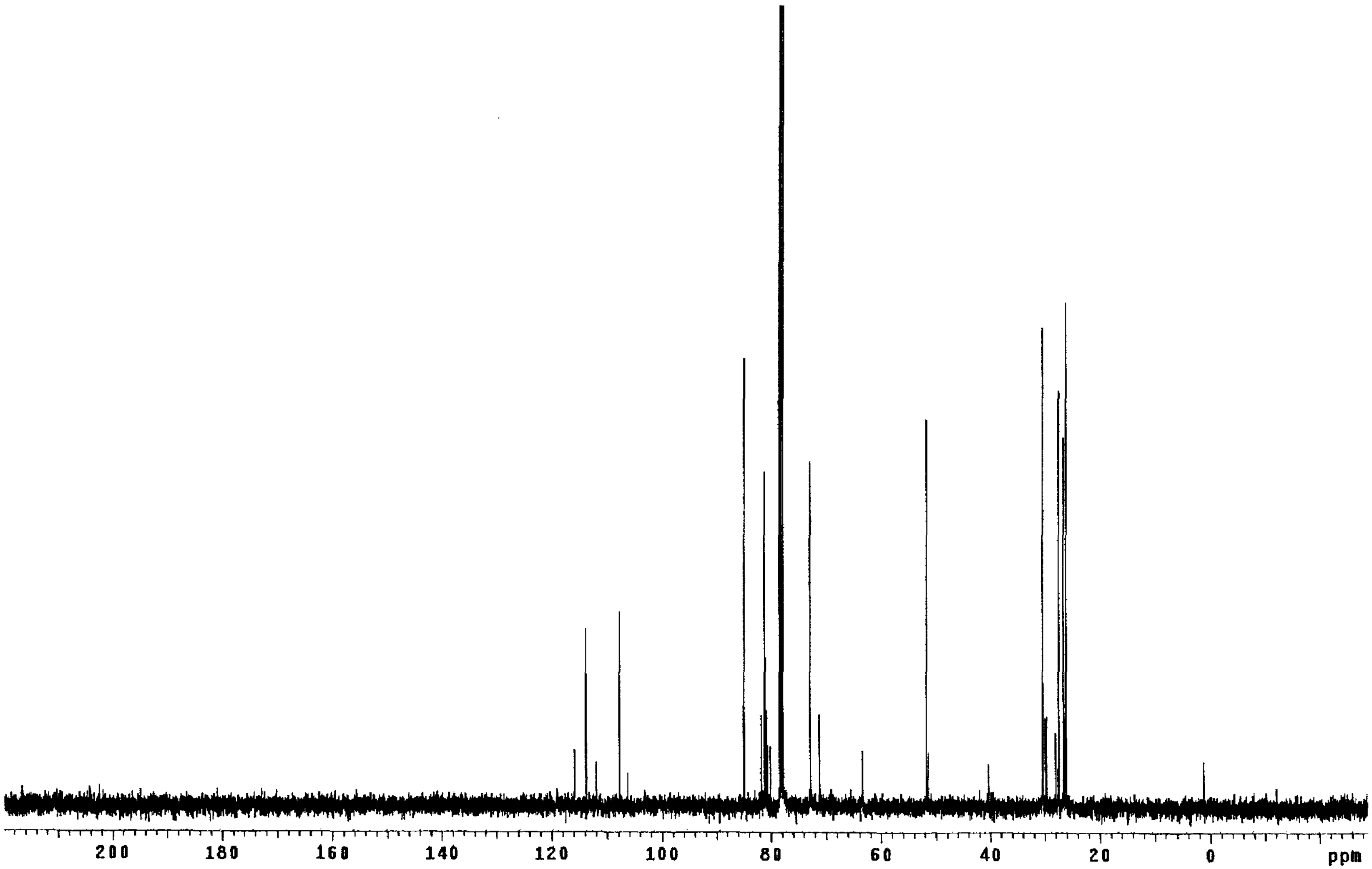
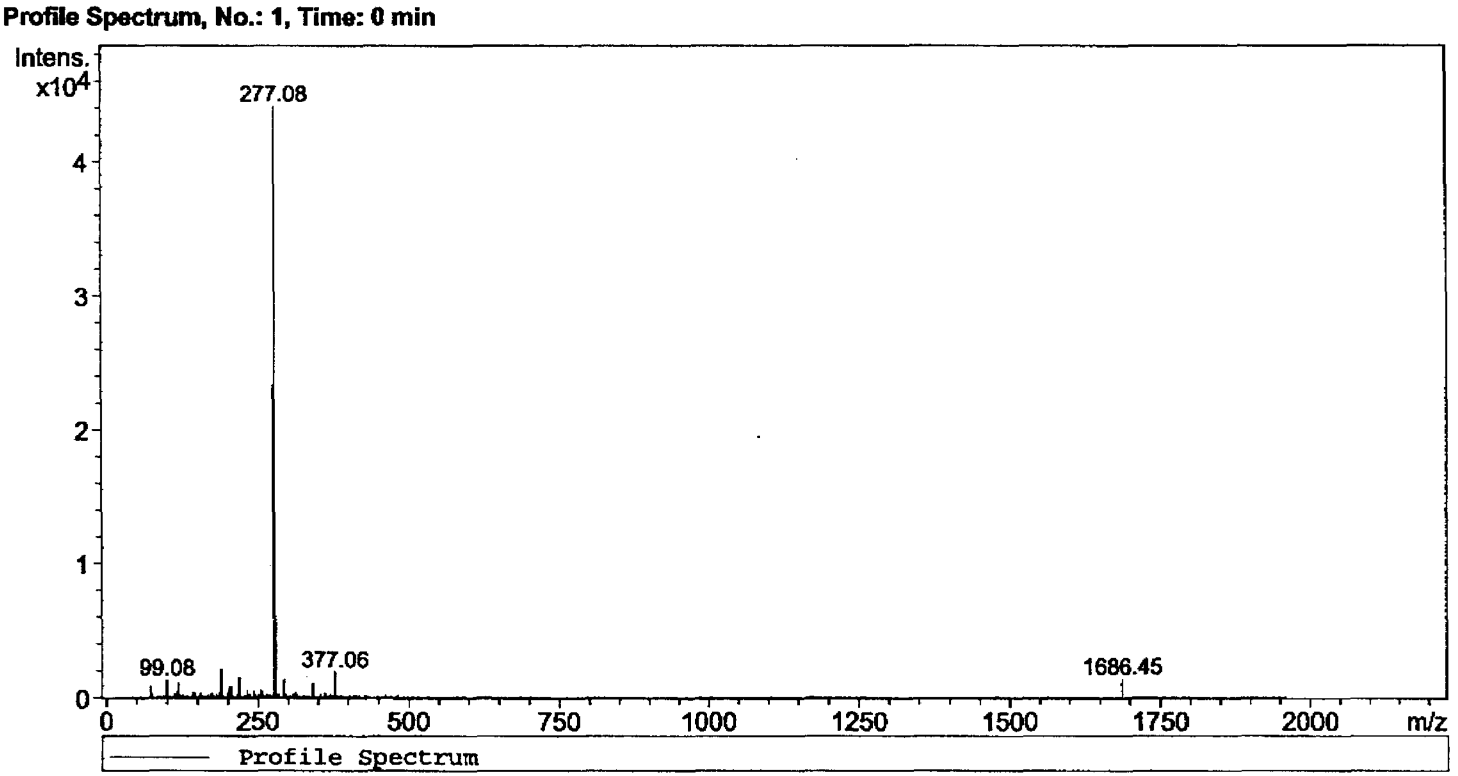


Figure 17. ^{13}C NMR of **6**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
73.07	848	0.40	205.08	871	0.20	279.03	4142	0.30
99.08	1317	0.50	219.05	1533	0.30	280.10	596	0.30
119.03	1140	0.20	231.05	577	0.40	293.04	1356	0.30
189.04	2187	0.30	243.11	553	0.30	341.03	1074	0.20
201.09	845	0.40	255.32	593	0.20	377.06	1944	0.30
203.09	829	0.20	277.08	44149	0.30	378.99	528	0.40
204.12	655	0.40	277.98	6033	0.30	1686.45	1408	0.30

Figure 18. Mass Spectrum of **6**

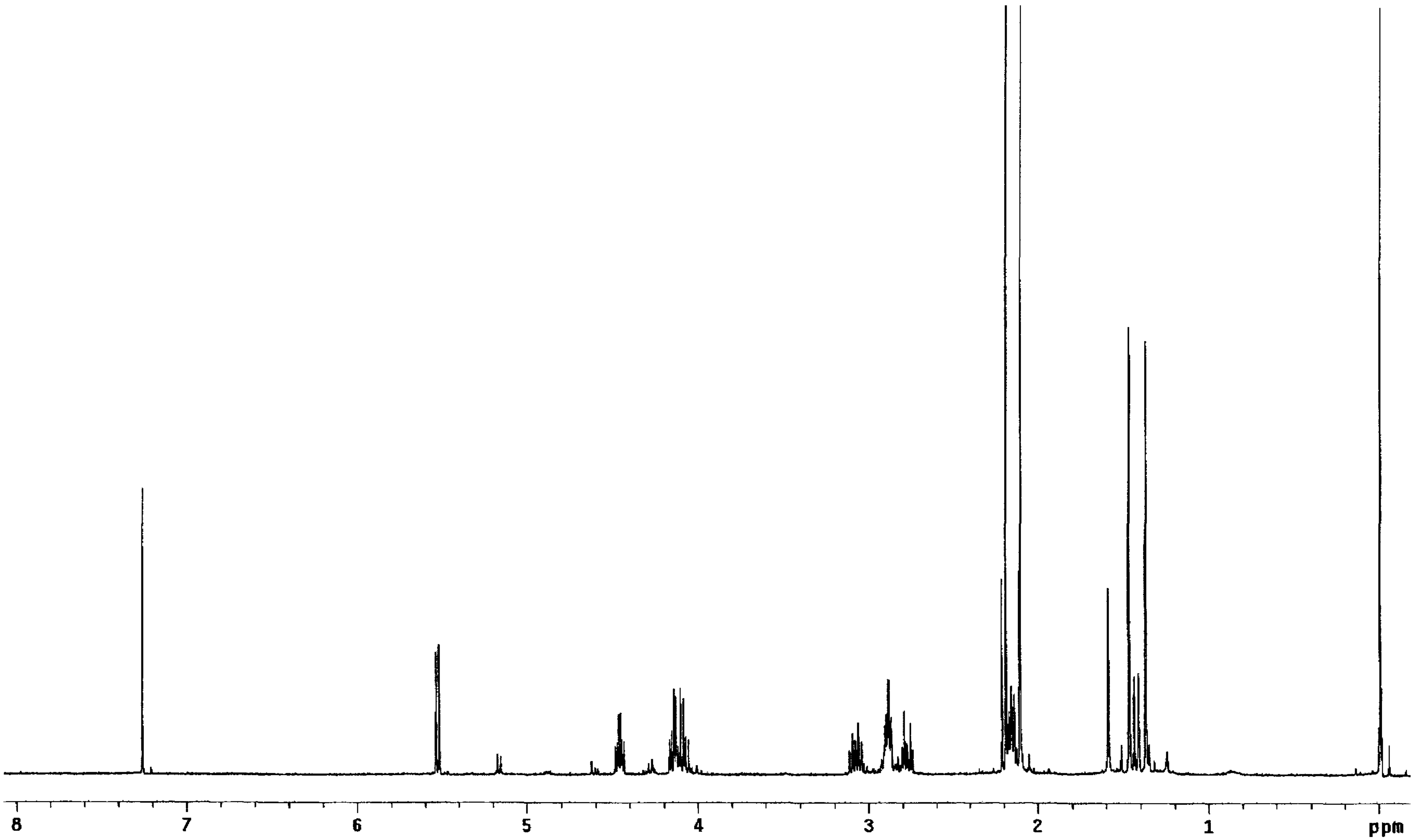


Figure 19. ^{1}H NMR of **7**

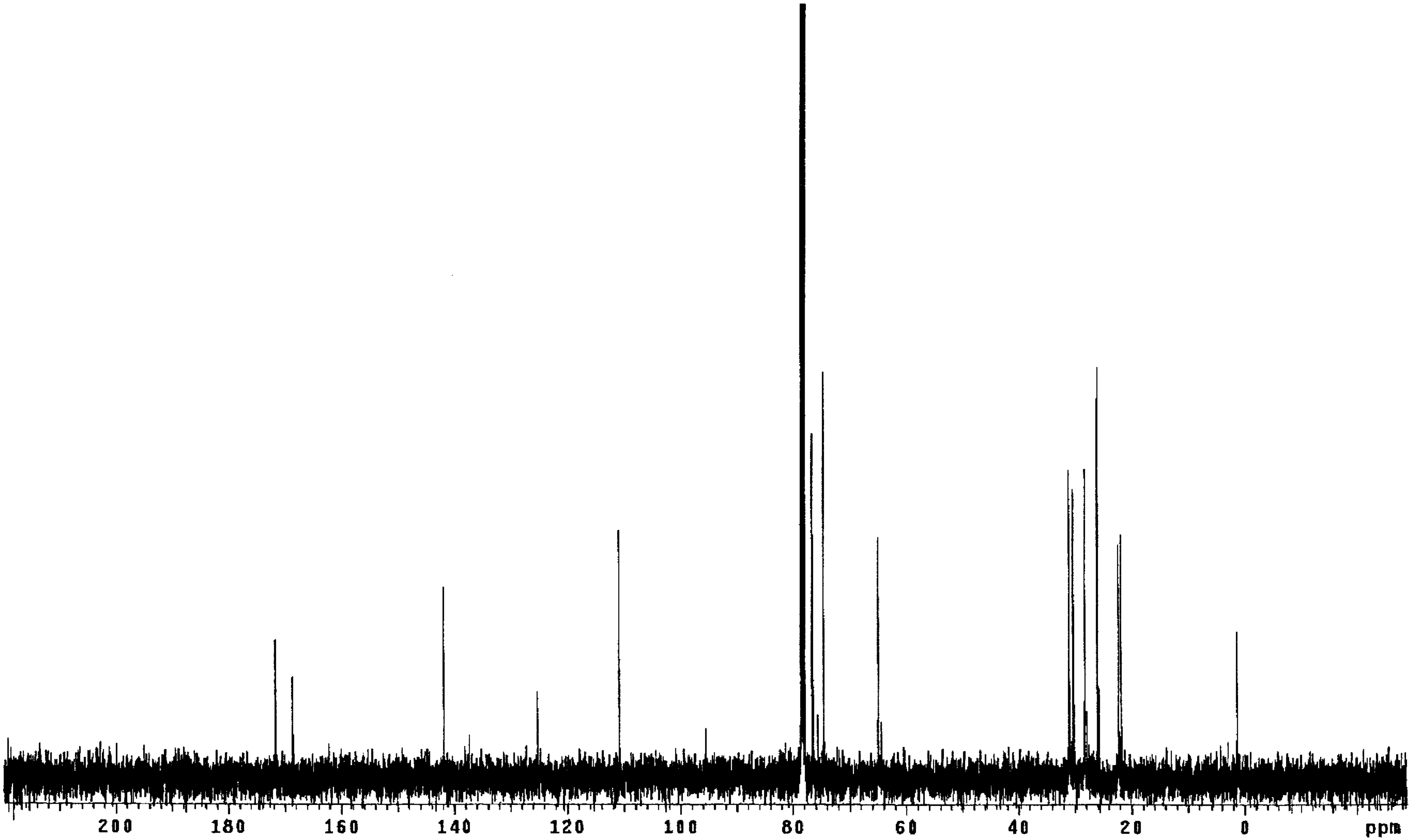
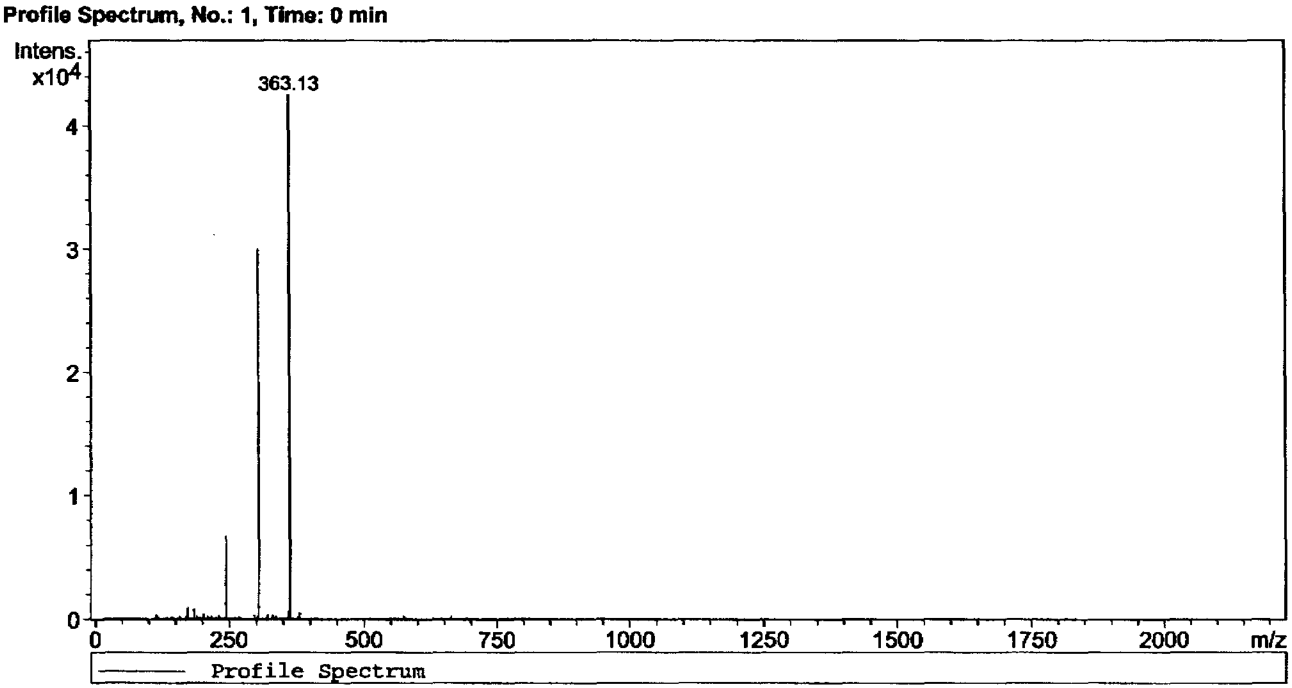


Figure 20. ^{13}C NMR of 7



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
115.06	393	0.30	217.20	254	0.20	337.48	305	0.20
117.09	335	0.40	232.02	310	0.20	361.34	654	0.20
159.04	262	0.40	245.03	6794	0.20	361.53	510	0.40
169.45	204	0.20	269.23	240	0.20	362.18	1196	0.10
171.12	543	0.20	297.22	344	0.20	363.13	42576	0.30
173.09	917	0.20	304.16	815	0.20	379.24	240	0.20
185.04	851	0.20	305.07	30063	0.30	381.37	506	0.20
190.92	321	0.20	319.62	208	0.20	575.02	302	0.20
203.04	449	0.20	322.02	397	0.20	663.95	287	0.20
211.31	214	0.40	331.45	335	0.20			

Figure 21. Mass Spectrum of **7**

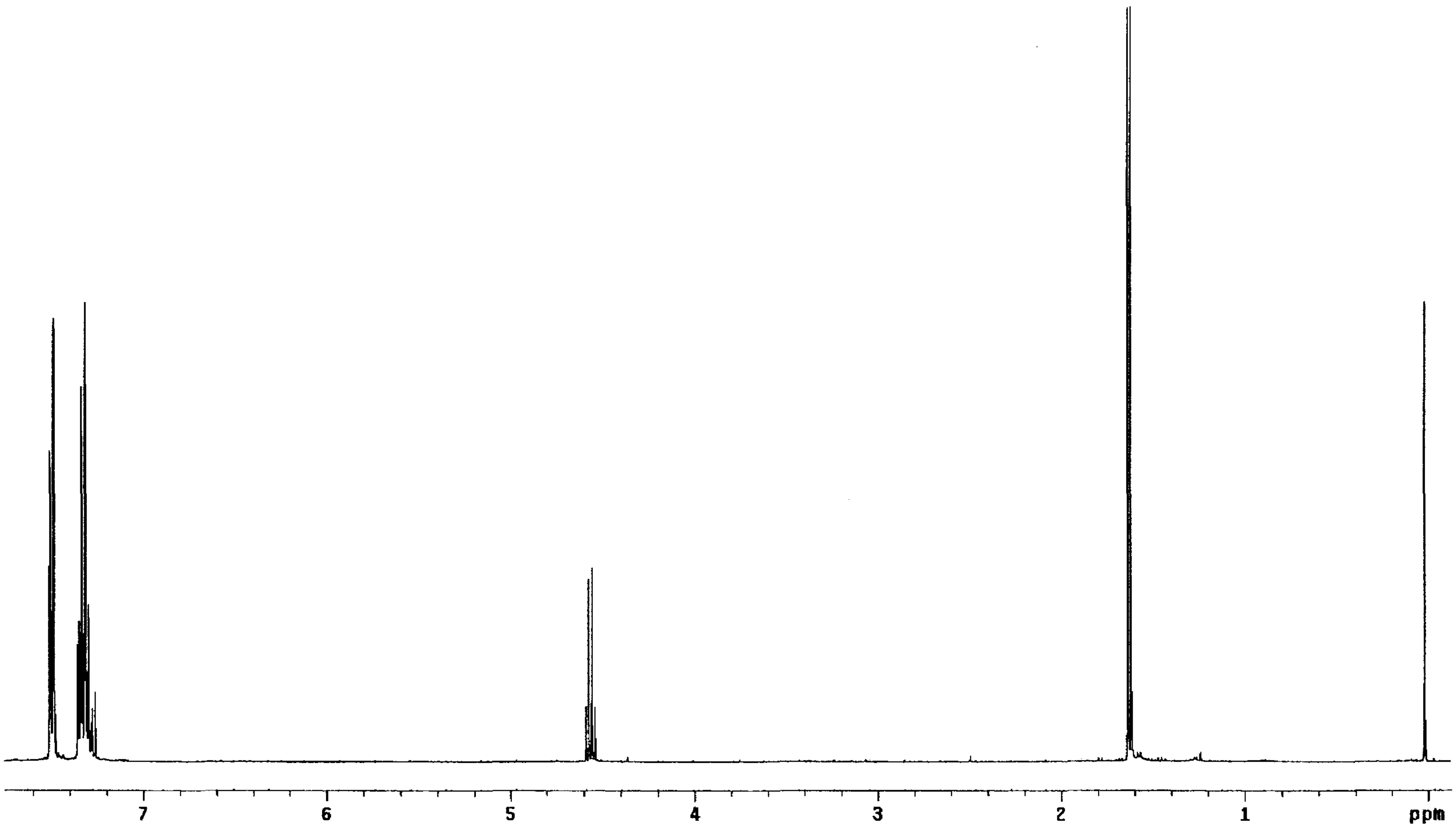


Figure 22. ^{1}H NMR of **8**

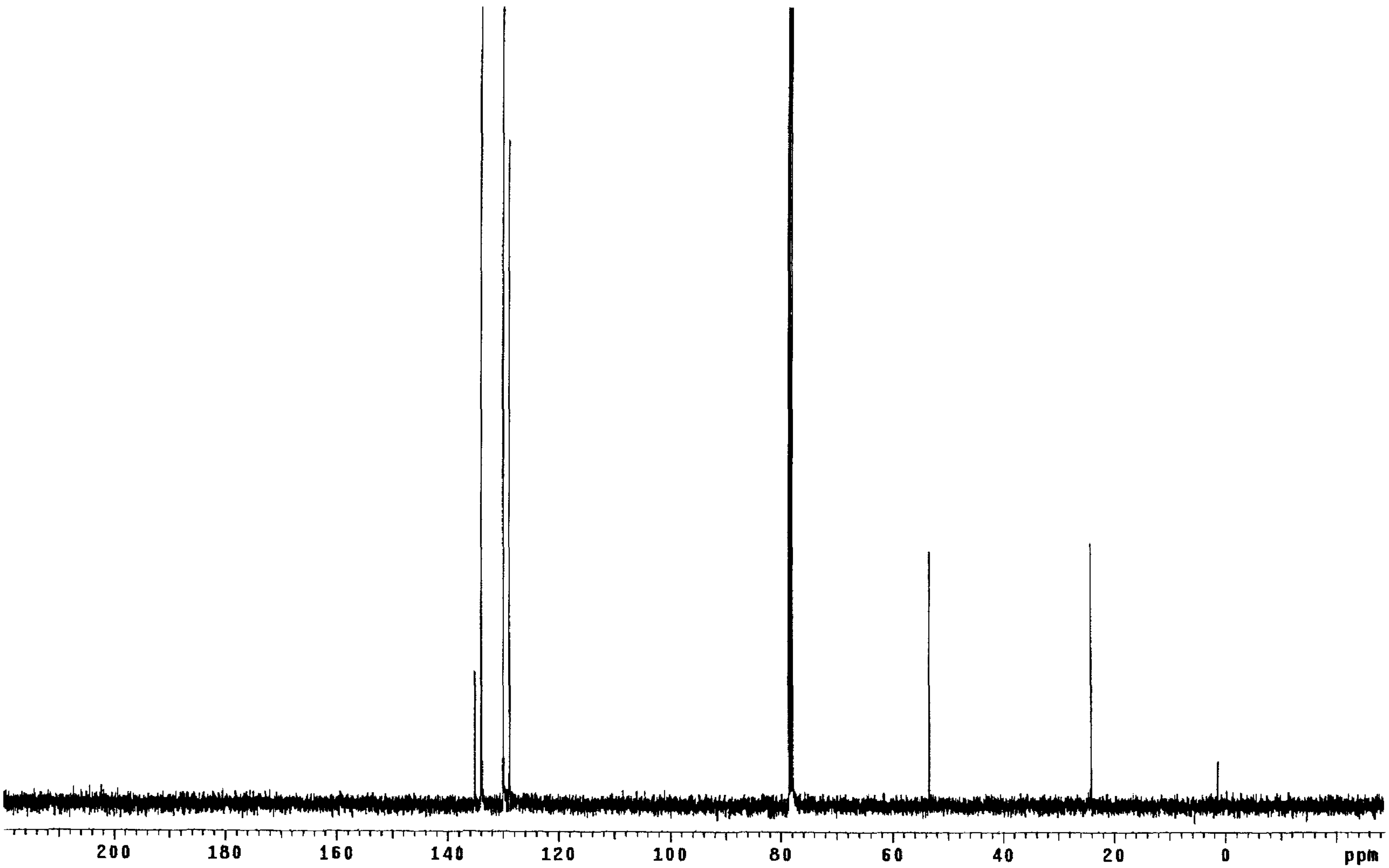


Figure 23. ^{13}C NMR of **8**

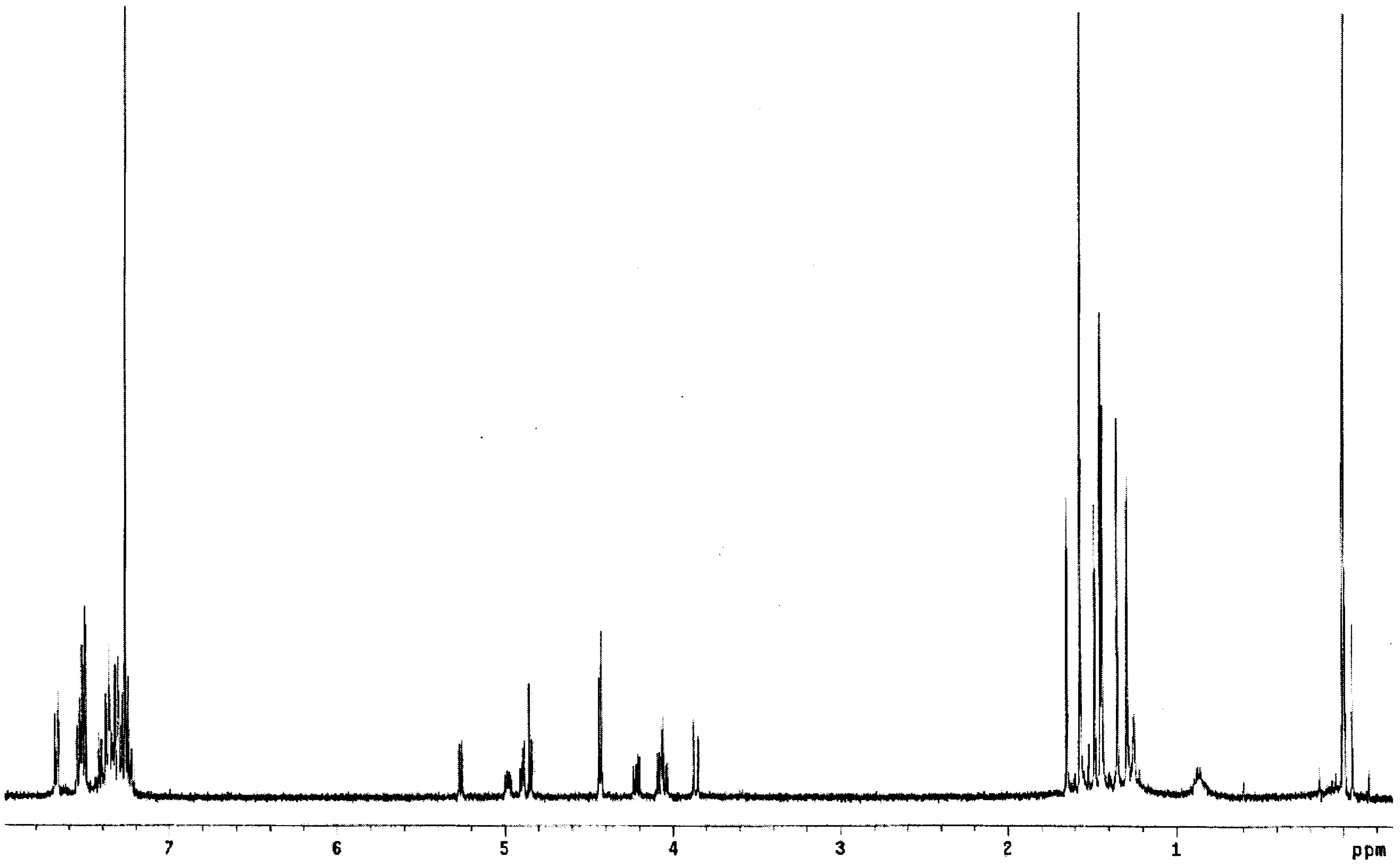


Figure 24. ^{1}H NMR of **9**

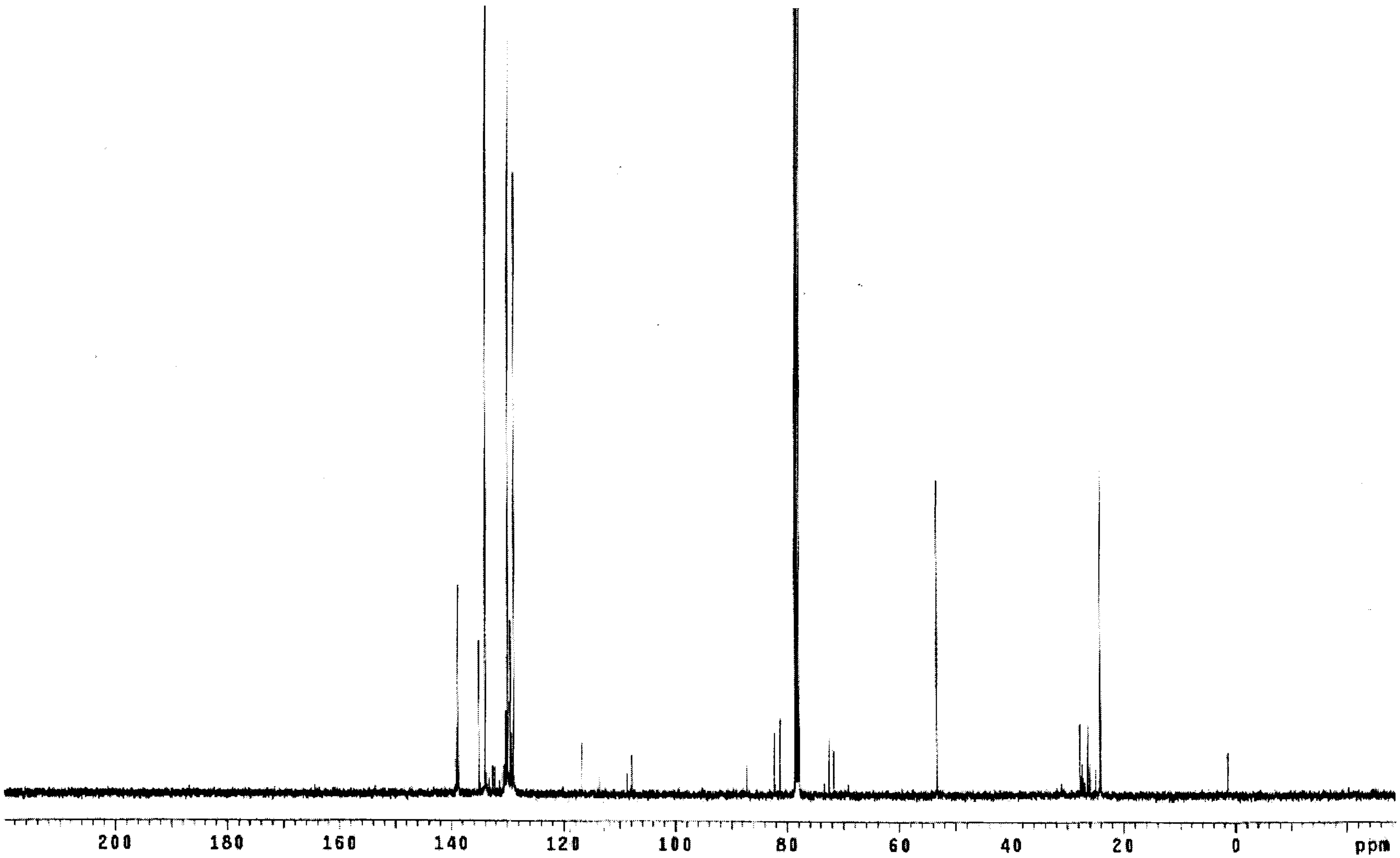
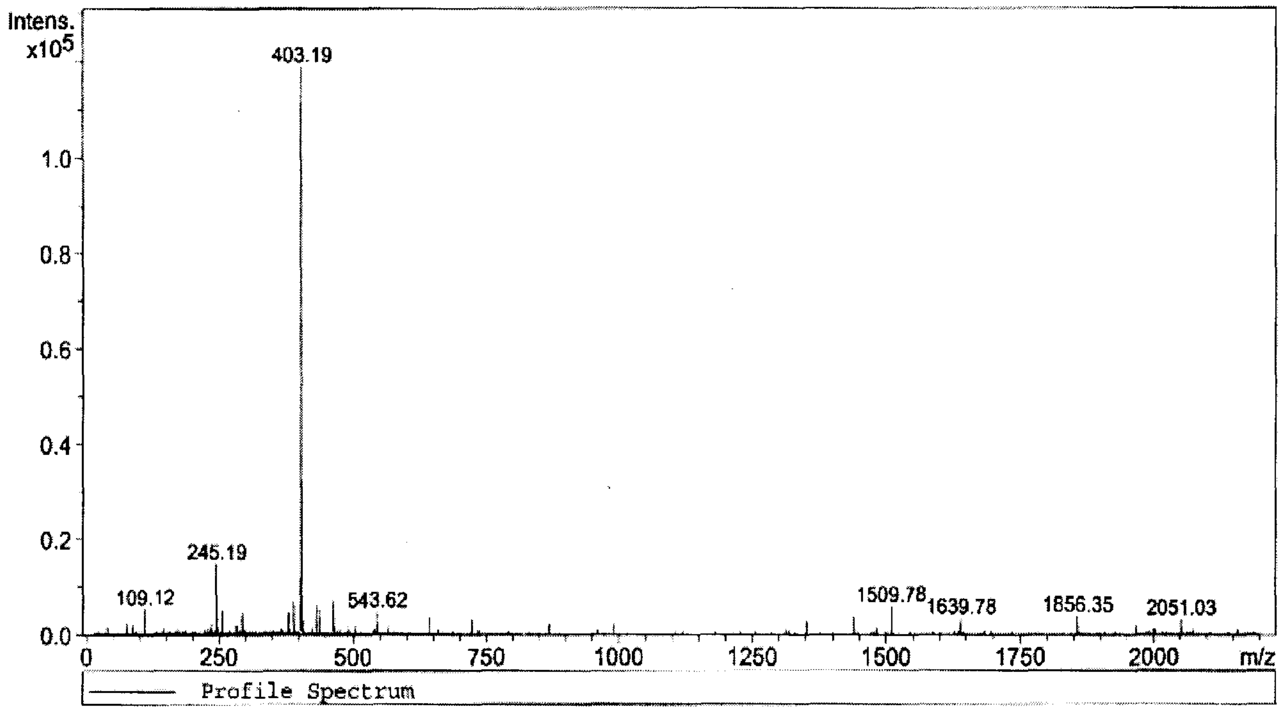


Figure 25. ^{13}C NMR of **9**

Profile Spectrum, No.: 1, Time: 0 min



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
109.12	5276	0.40	403.96	32526	0.30	543.62	4787	0.20
245.19	14795	0.30	405.02	15808	0.40	642.14	3604	0.20
246.17	3262	0.40	406.02	3186	0.40	721.06	3250	0.20
255.42	4938	0.50	431.23	6158	0.30	1439.58	3657	0.20
293.23	4652	0.50	437.09	5195	0.40	1509.78	5870	0.20
379.44	4543	0.20	462.64	5502	0.40	1639.78	3355	0.20
389.18	6986	0.50	463.14	7193	0.40	1856.35	3728	0.20
403.19	119012	0.40	464.01	3353	0.30	2051.03	3147	0.20

Figure 26. Mass Spectrum of **9**

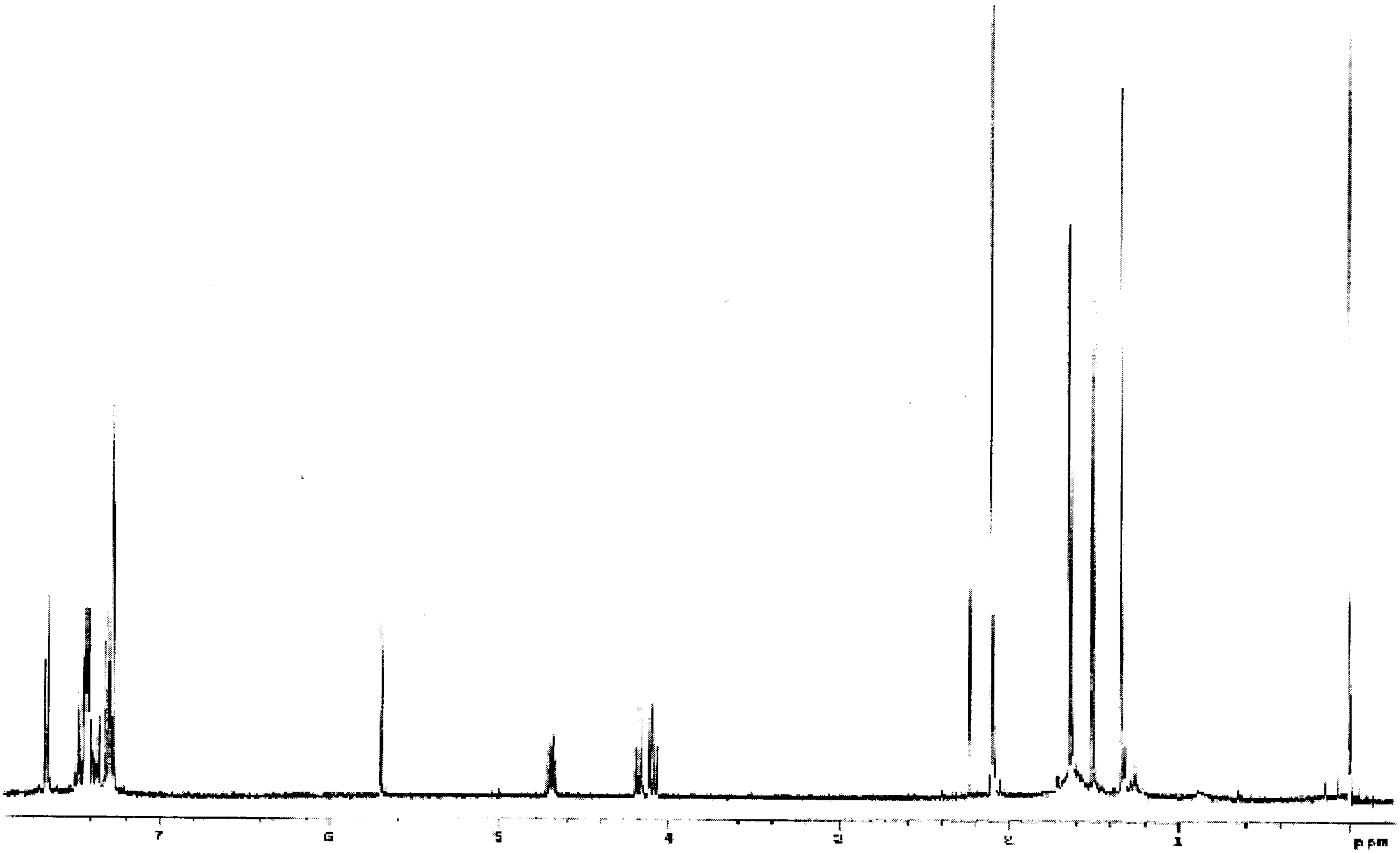


Figure 27. ^{1}H NMR of **10**

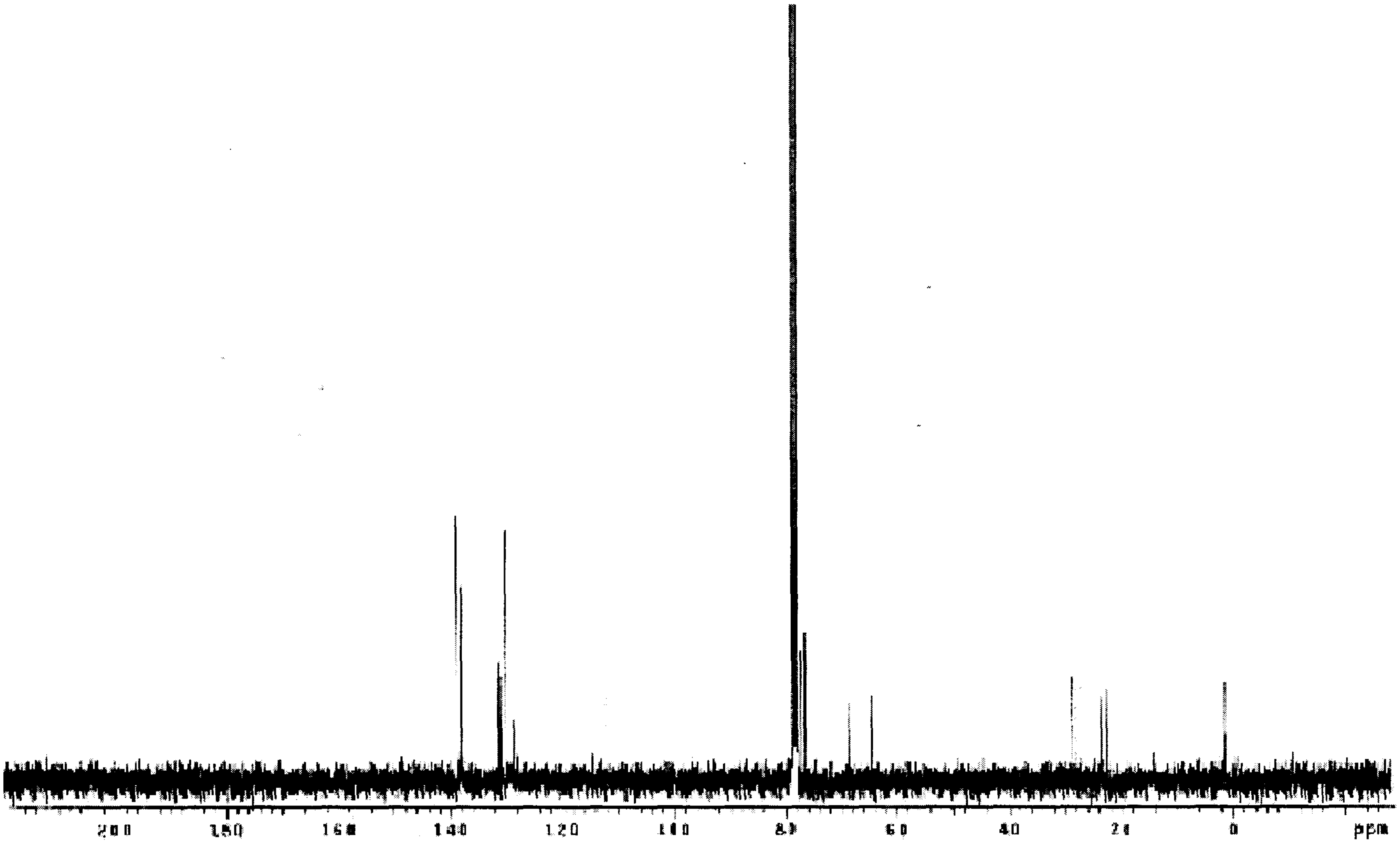
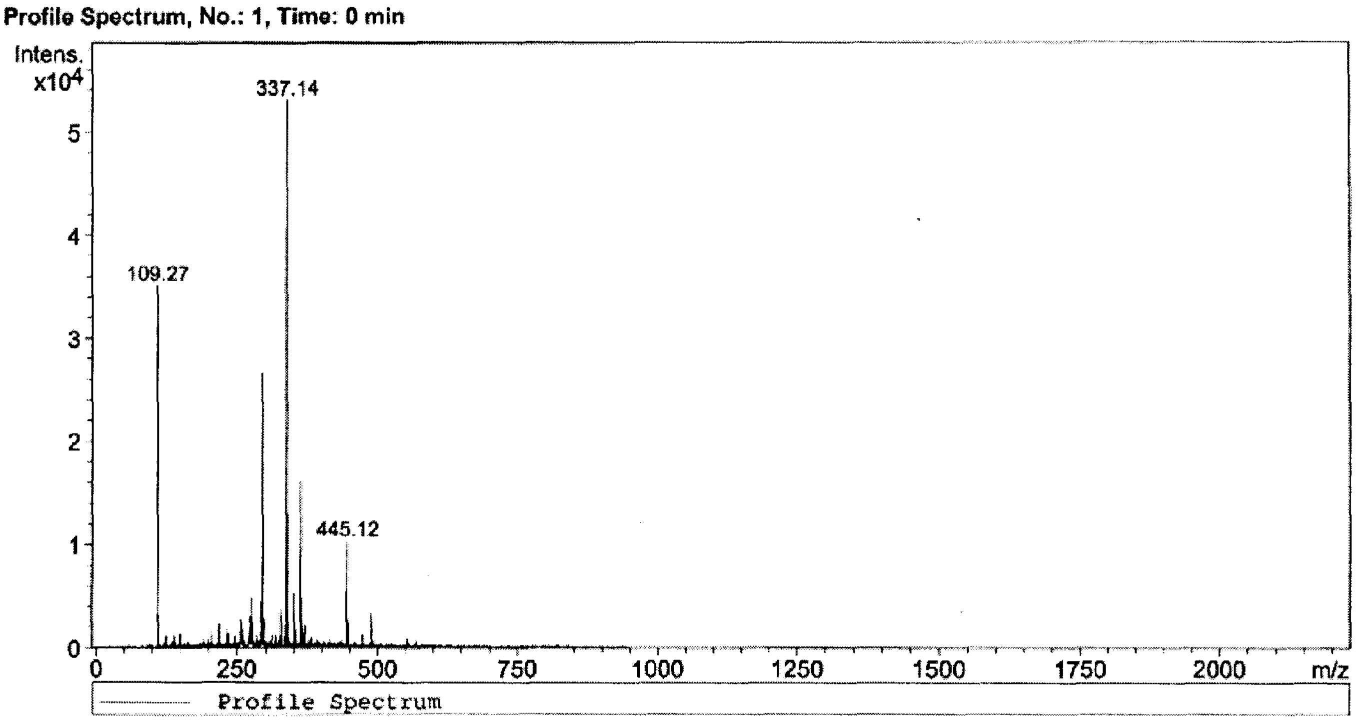


Figure 28. ^{13}C NMR of **10**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
109.27	35151	0.30	295.12	26567	0.30	351.12	5296	0.30
110.11	3143	0.20	296.03	4676	0.30	362.14	16150	0.30
217.43	2270	0.70	297.07	2835	0.50	363.09	4998	0.40
217.61	2019	0.70	327.13	3702	0.40	369.10	2151	0.20
257.33	2706	0.70	335.36	2352	0.40	445.12	10320	0.30
273.18	2948	0.30	336.28	8466	0.40	446.13	2722	0.30
275.27	4726	0.30	337.14	53117	0.30	447.12	2235	0.20
277.29	2864	0.30	338.03	13100	0.30	489.13	3307	0.30

Figure 29. Mass Spectrum of **10**

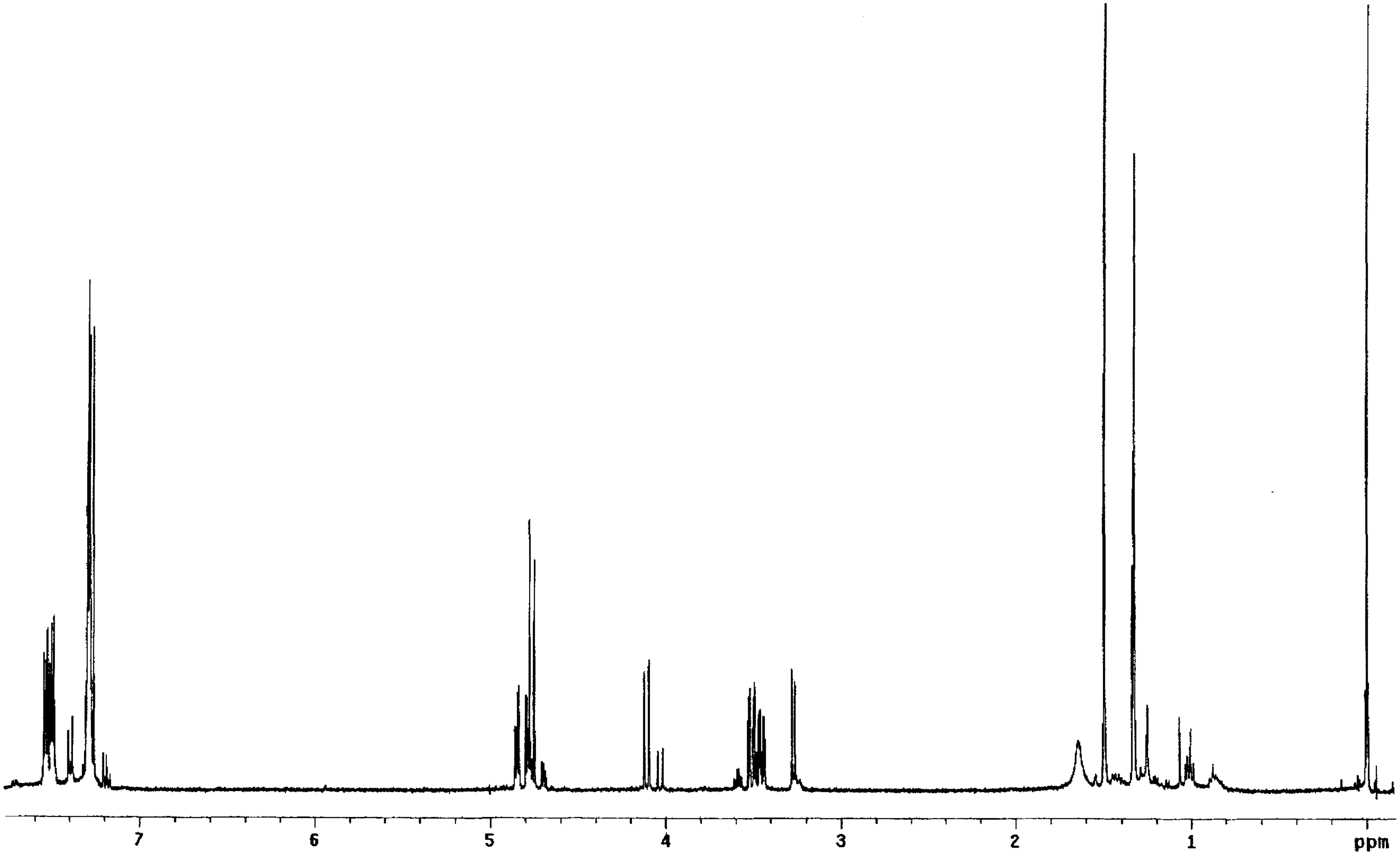


Figure 30. ^{1}H NMR of **11**

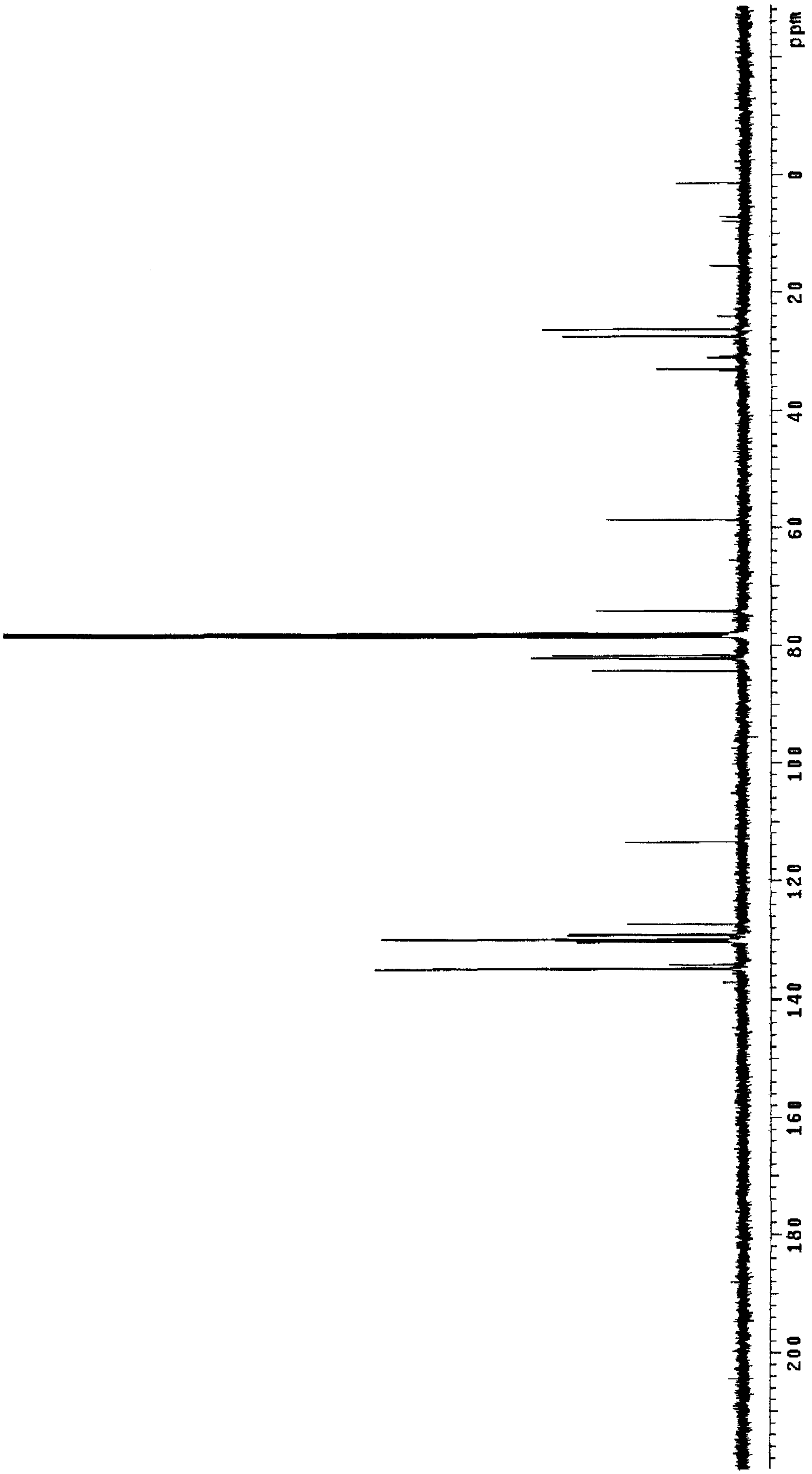
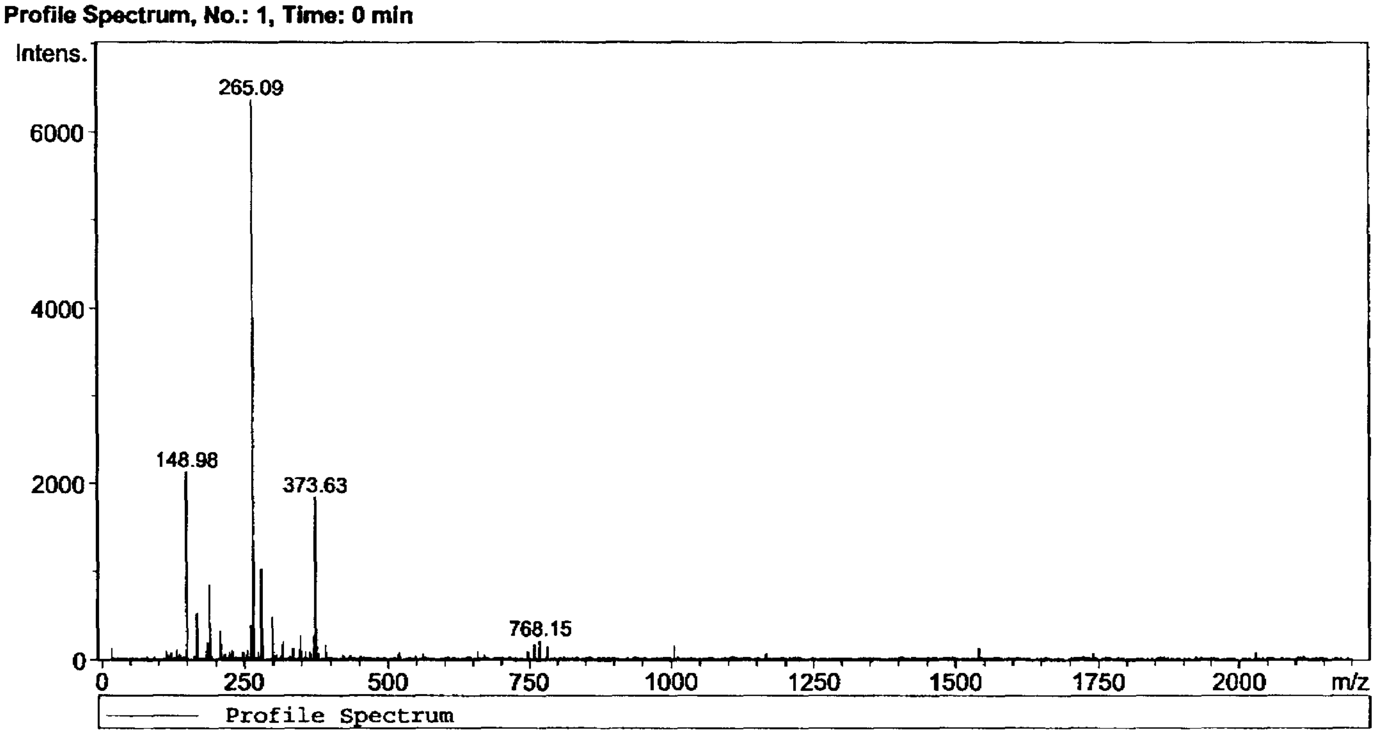


Figure 31. ^{13}C NMR of 11


Profile Spectrum, No.: 1, Time: 0 min

MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
148.98	2142	0.30	262.14	291	0.20	347.25	277	0.20
149.99	576	0.20	263.03	202	0.20	371.07	271	0.20
166.98	531	0.20	265.09	6376	0.20	372.35	240	0.20
185.09	202	0.20	266.11	1242	0.20	373.63	1851	0.30
189.02	854	0.20	279.19	1033	0.20	374.30	597	0.20
190.10	233	0.30	280.08	406	0.20	375.04	1748	0.20
207.13	326	0.30	299.22	491	0.20	375.52	349	0.20
261.15	389	0.30	317.08	217	0.20	768.15	220	0.30

Figure 32. Mass Spectrum of **11**

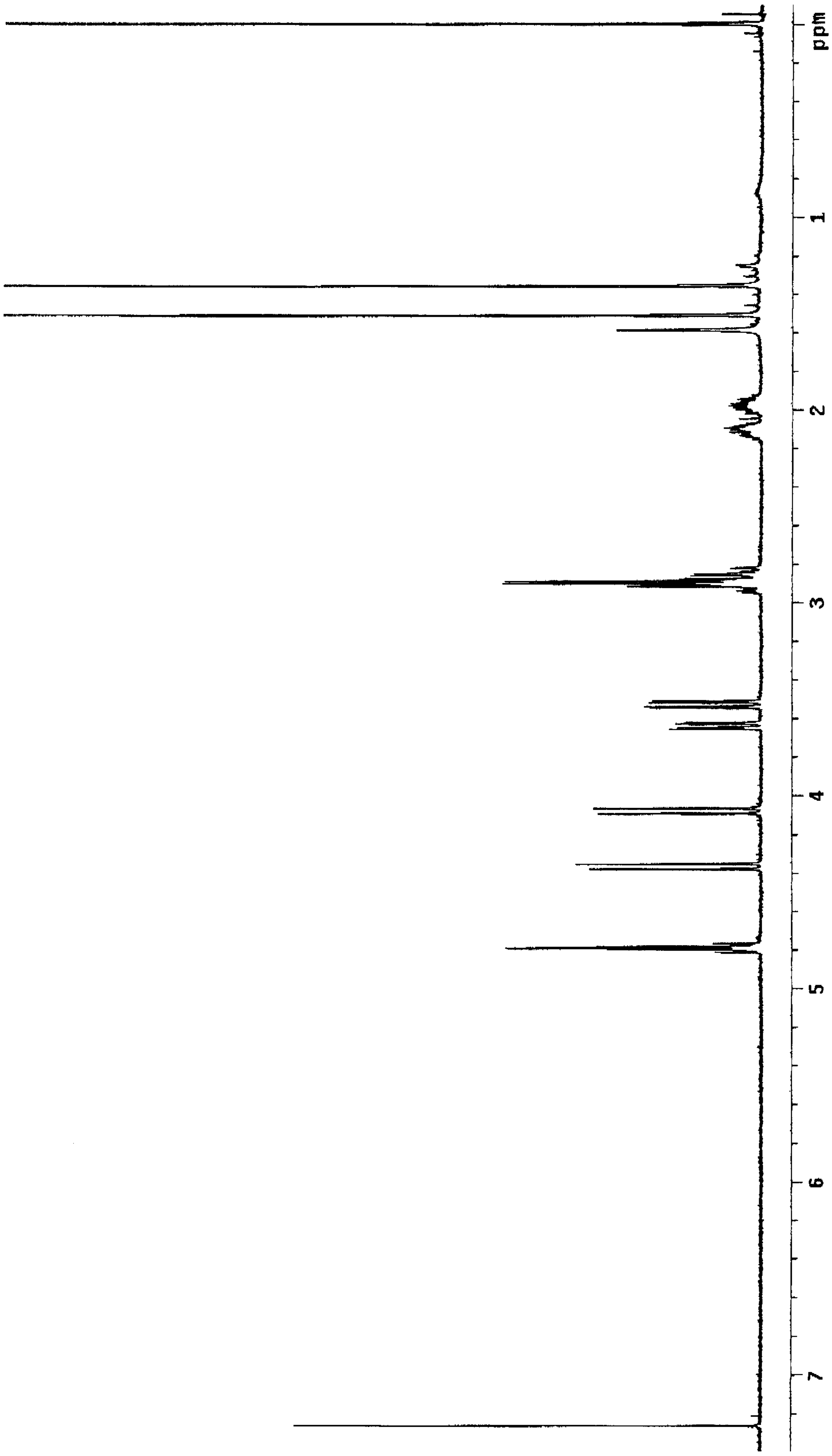


Figure 33. ^{1}H NMR of 12

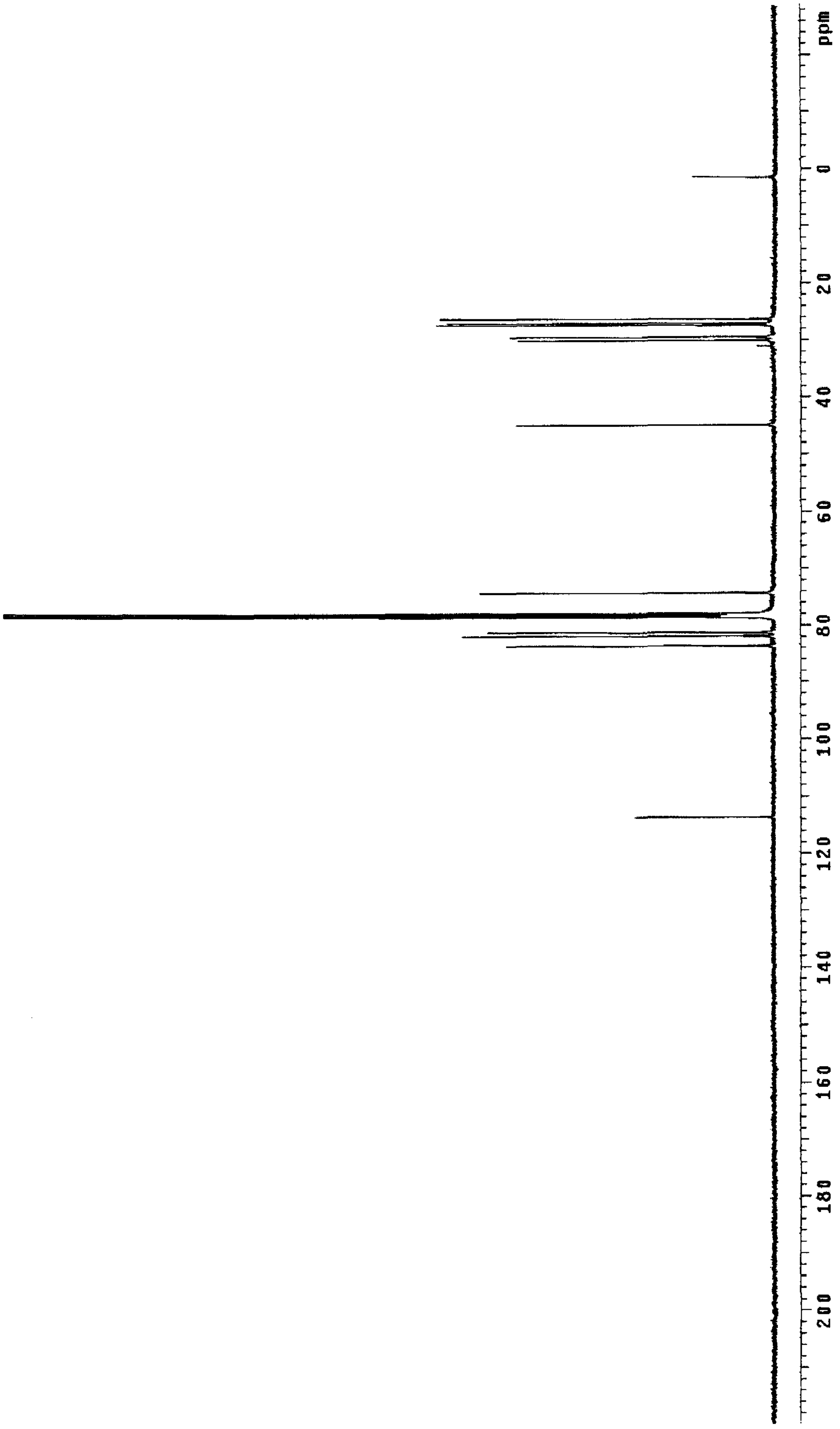


Figure 34. ^{13}C NMR of 12

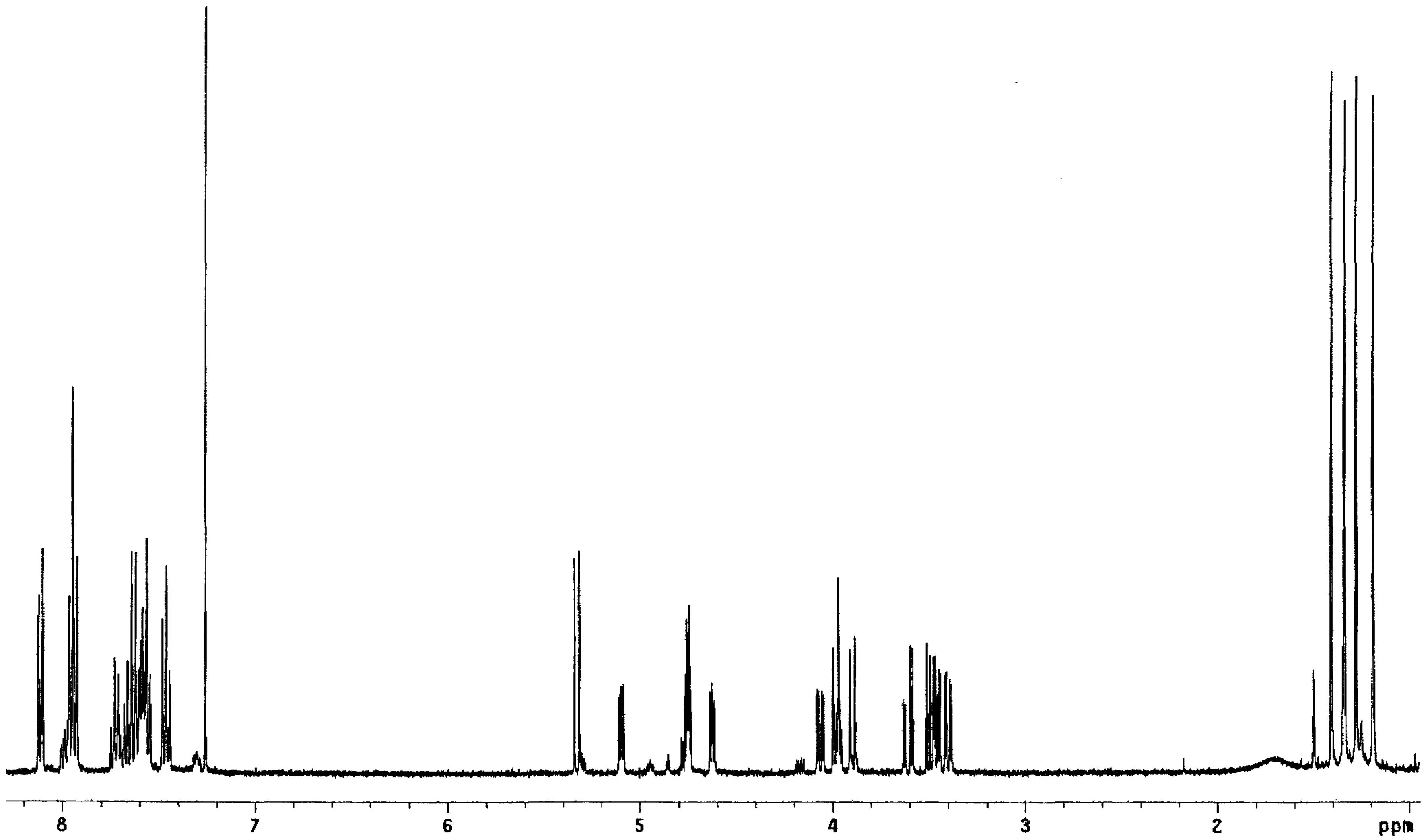


Figure 35. ^{1}H NMR of **13**

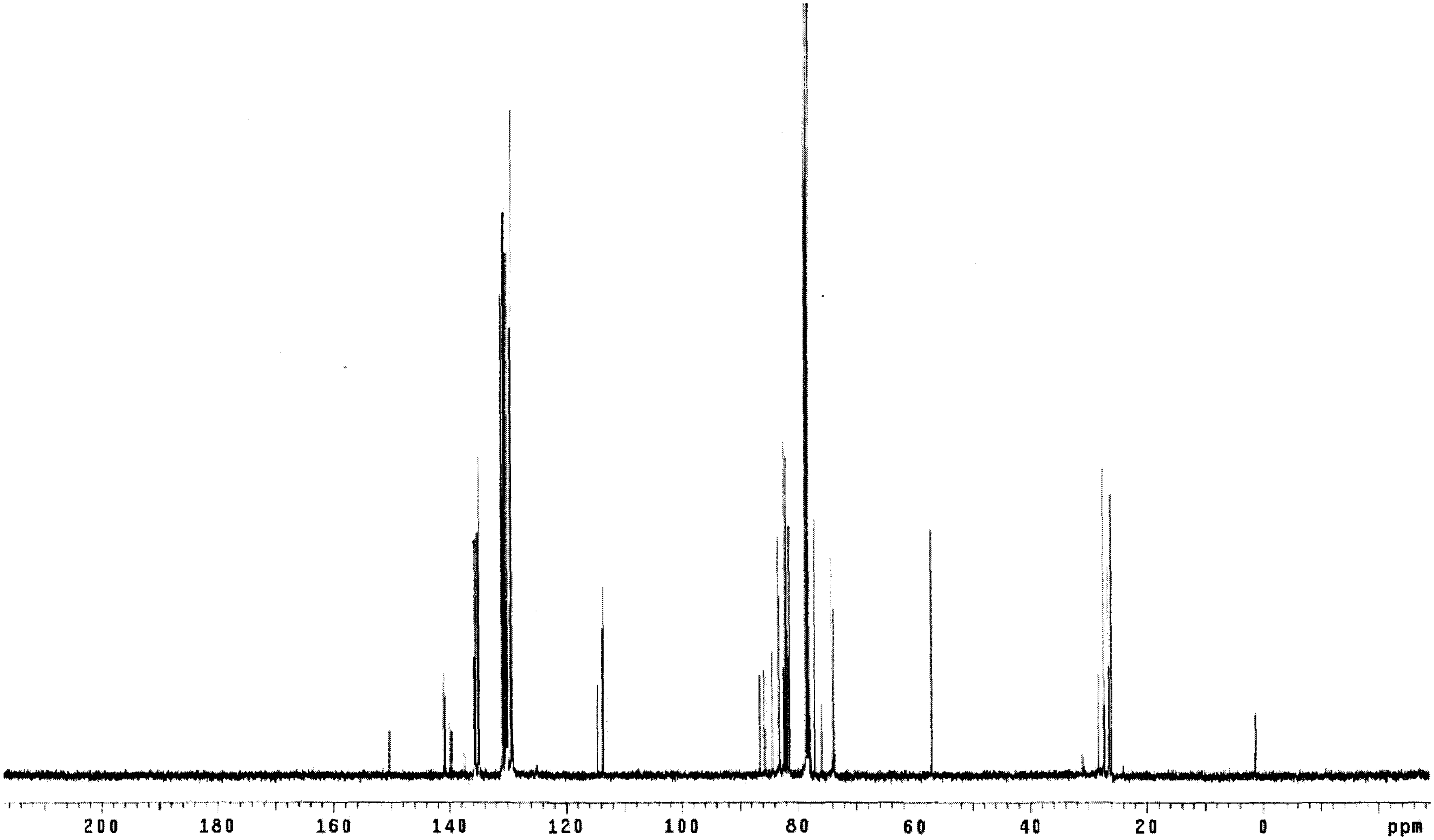
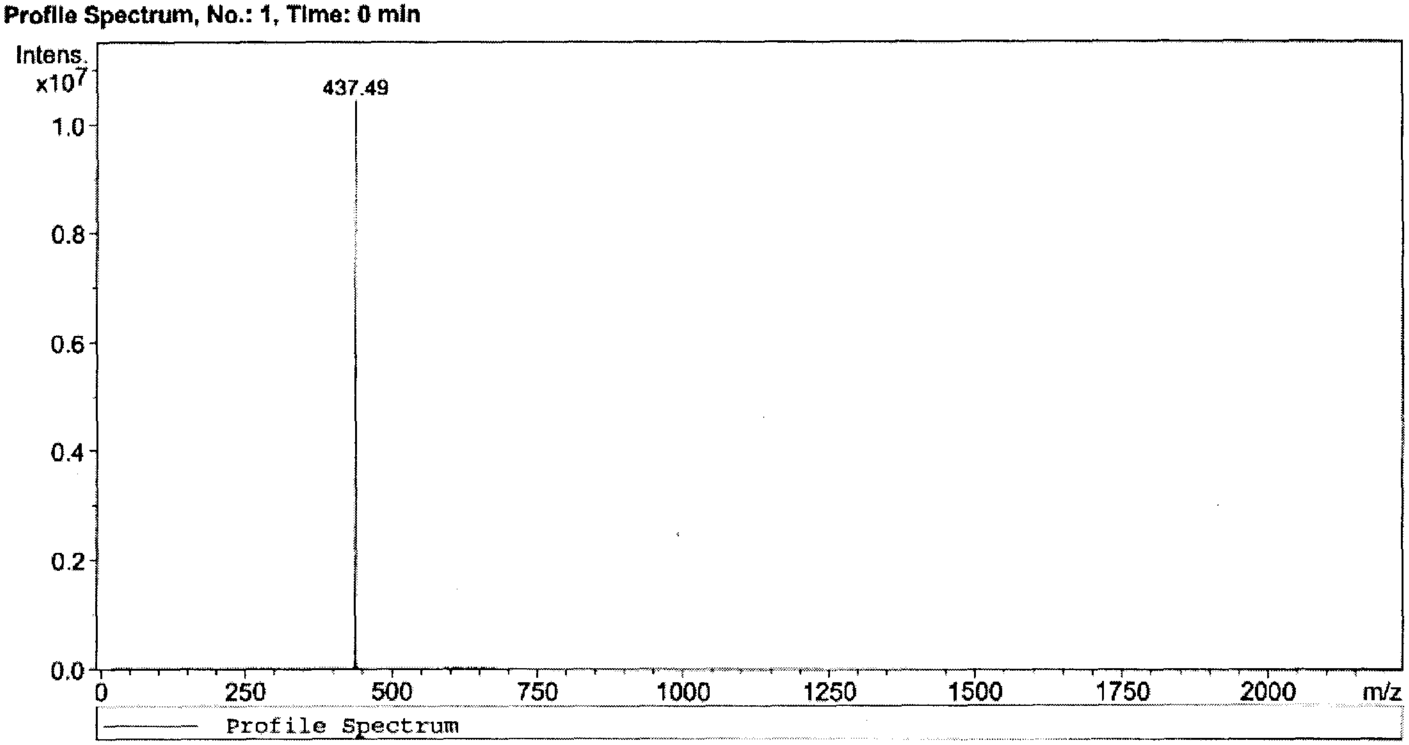


Figure 36. ^{13}C NMR of **13**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
162.82	10038	0.20	342.04	3154	0.40	471.06	5826	0.40
180.41	2559	0.40	437.49	10453221	0.20	472.02	2183	0.20
181.36	10516	0.60	440.85	7614	0.20	473.05	3291	0.20
340.32	2216	0.20	441.17	6484	0.30	489.15	3143	0.30
340.70	2467	0.20	442.56	2816	0.20	501.05	2133	0.30
341.07	3540	0.20	453.14	3856	0.40			
341.55	2392	0.40	455.11	3193	0.40			

Figure 37. Mass Spectrum of **13**

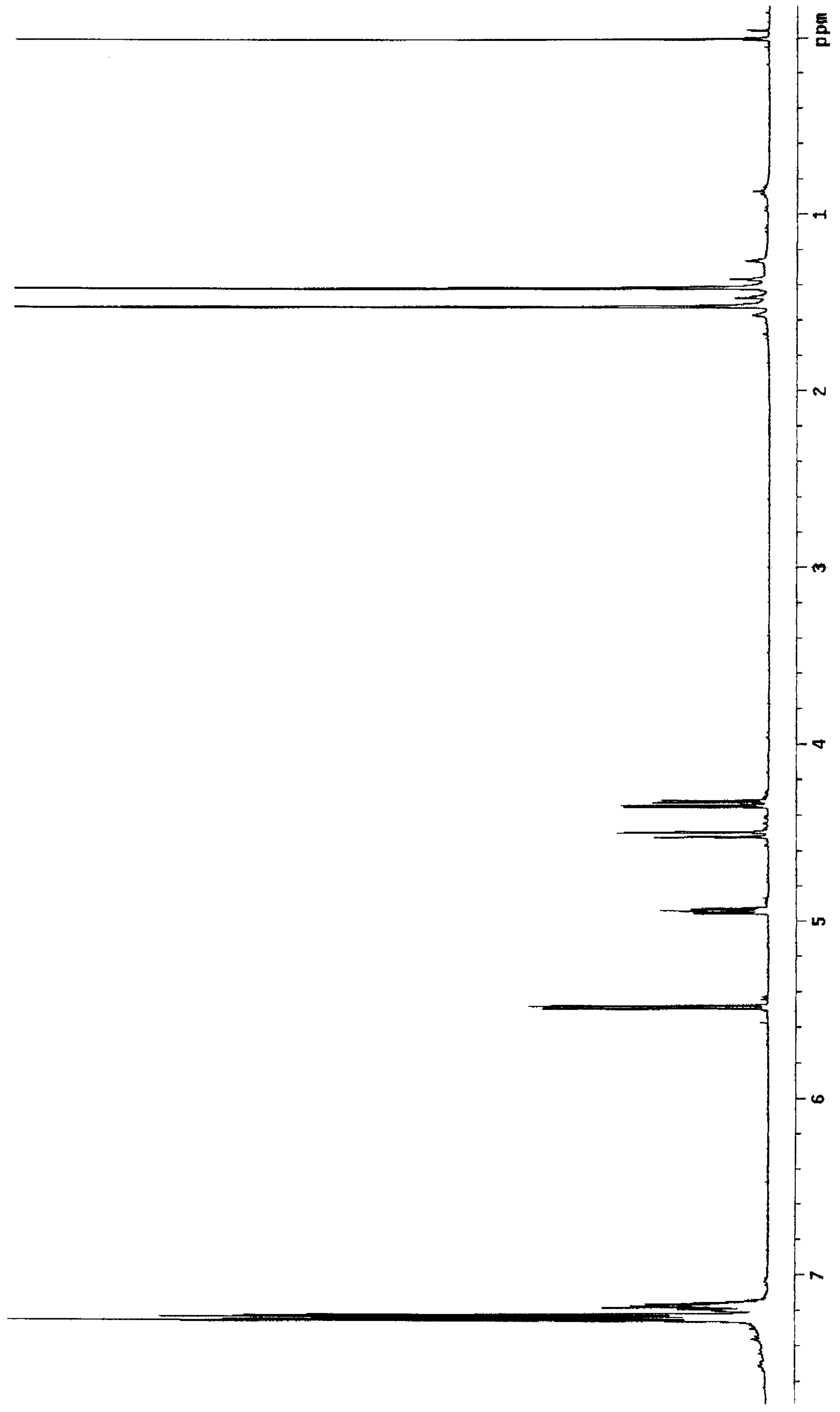


Figure 38. ^{1}H NMR of 14

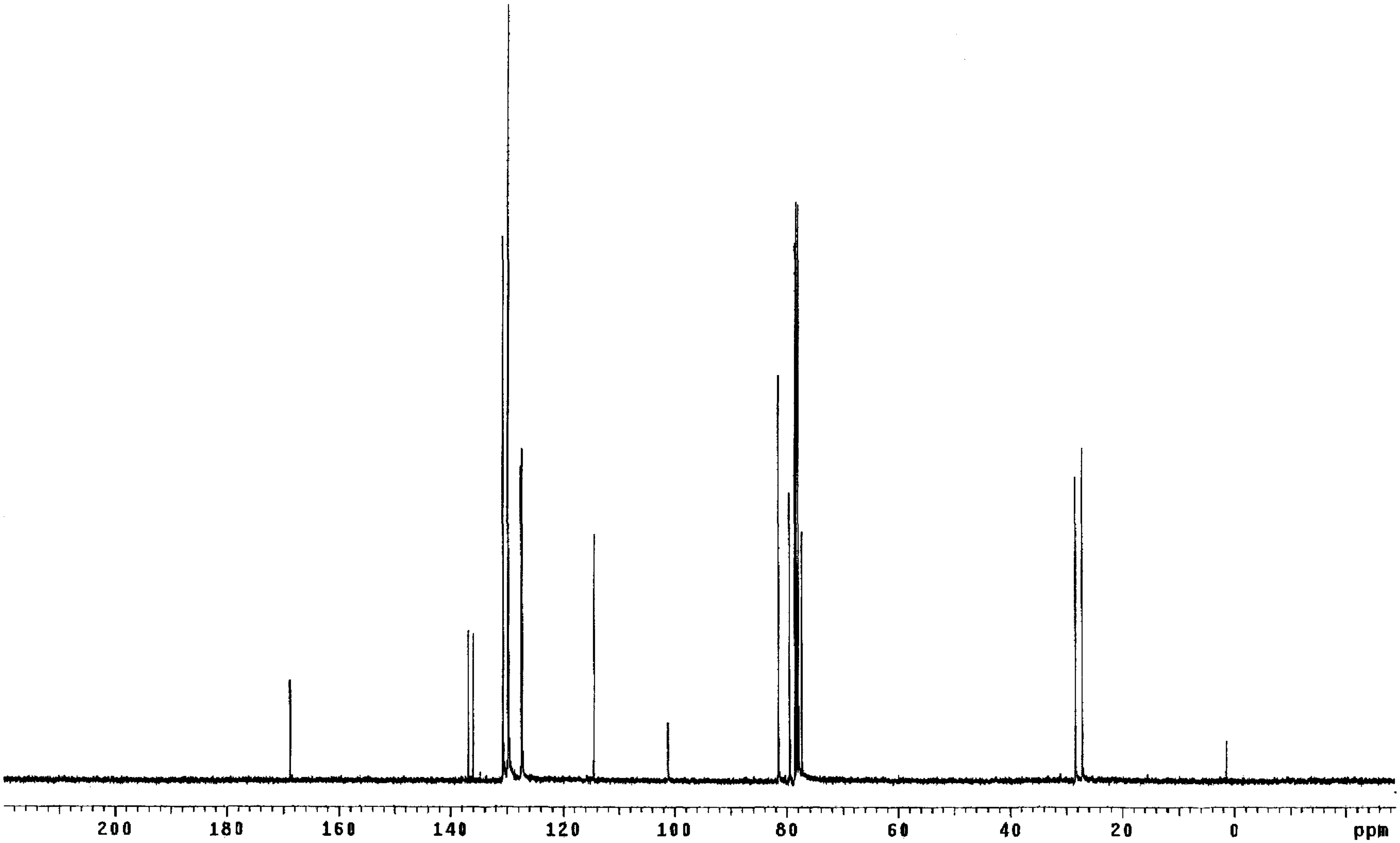
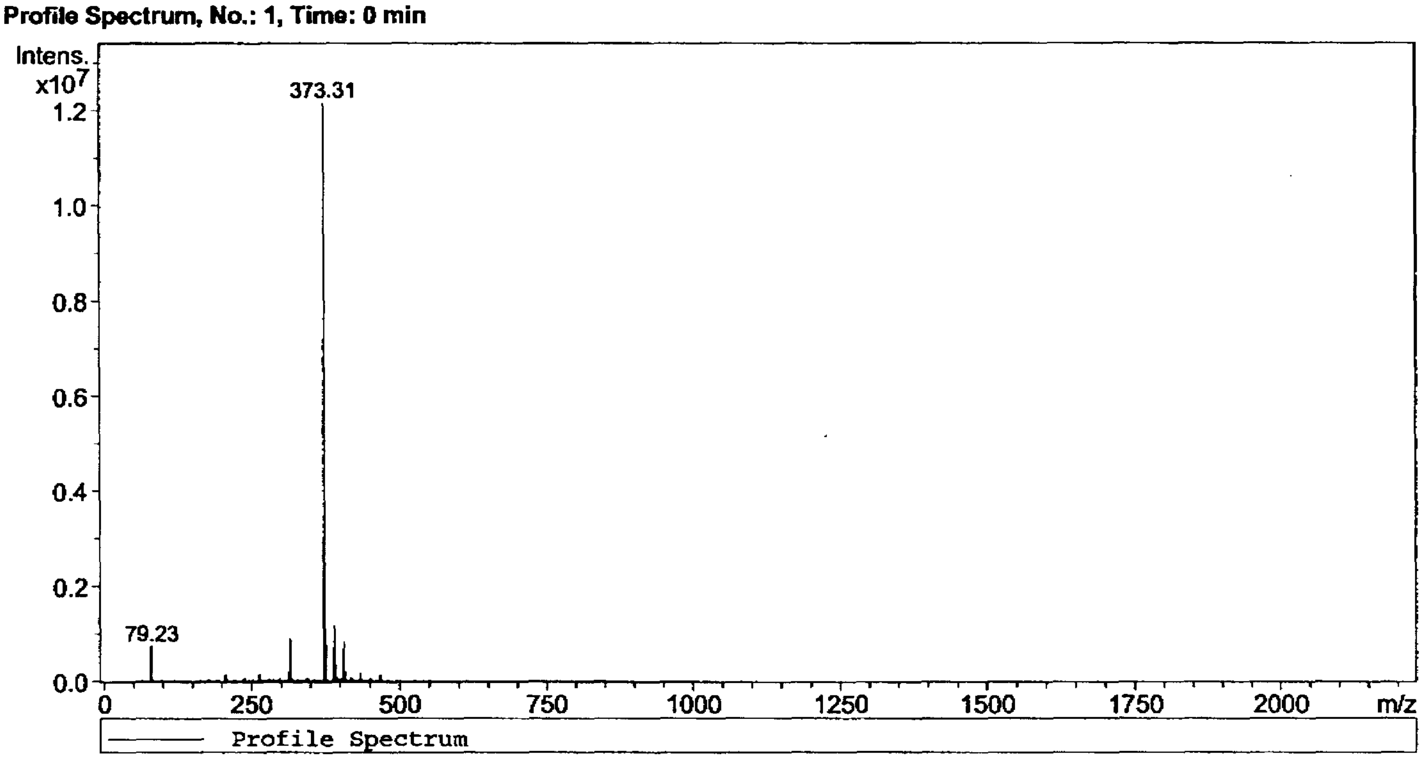


Figure 39. ^{13}C NMR of 14



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
79.23	752636	0.30	373.31	12173808	0.30	392.21	343527	0.40
205.66	127446	0.60	373.96	3003916	0.30	393.07	182179	0.30
263.63	165625	0.70	375.06	1339781	0.30	406.18	837894	0.40
313.71	209708	0.70	376.13	294567	0.30	407.17	209212	0.40
315.51	899496	0.50	389.24	690557	0.40	408.17	129915	0.30
316.31	272366	0.60	390.21	1157889	0.30	434.19	177119	0.20
317.30	135337	0.60	391.19	714157	0.40	467.10	148686	0.30

Figure 40. Mass Spectrum of **14**

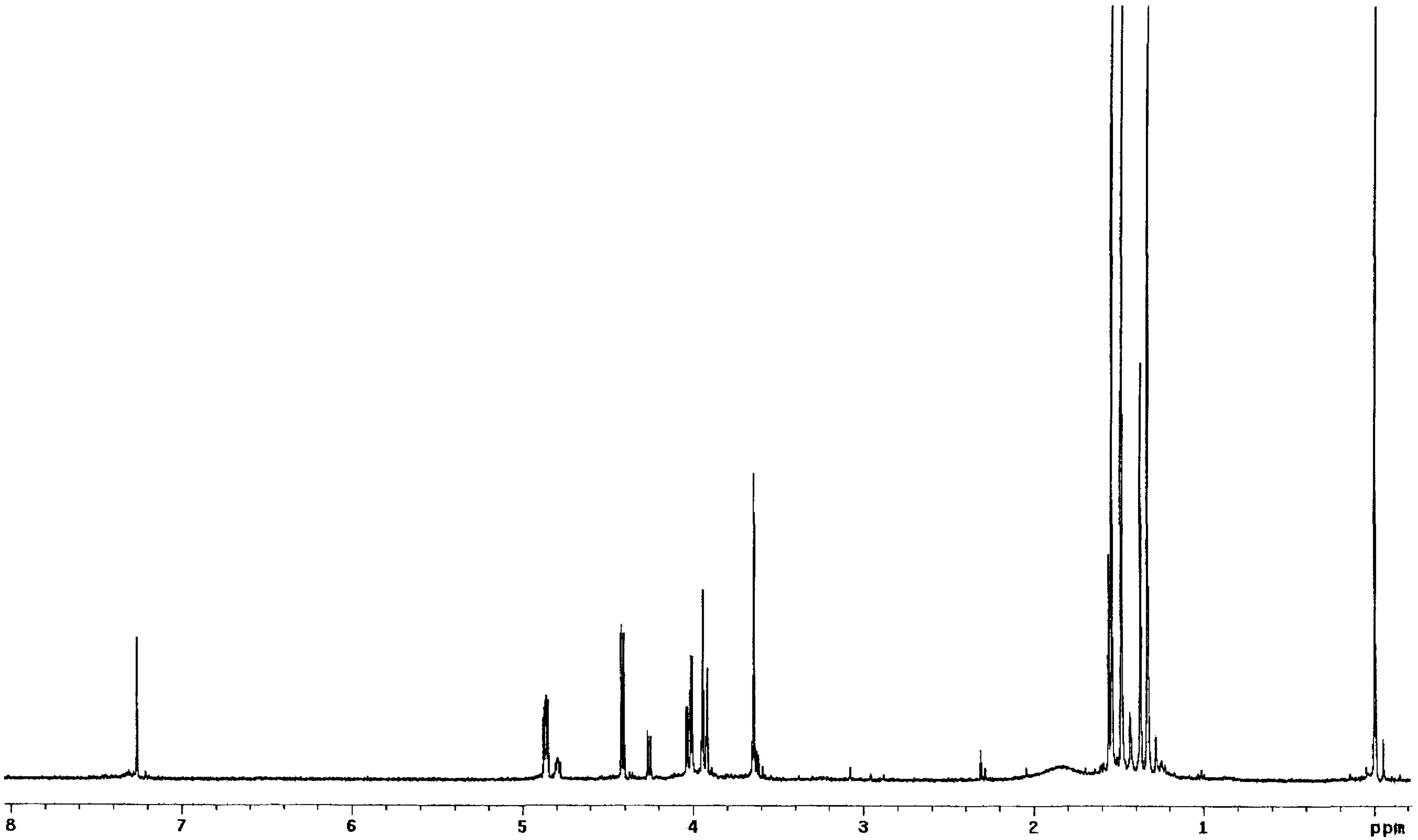


Figure 41. ^{1}H NMR of **15**

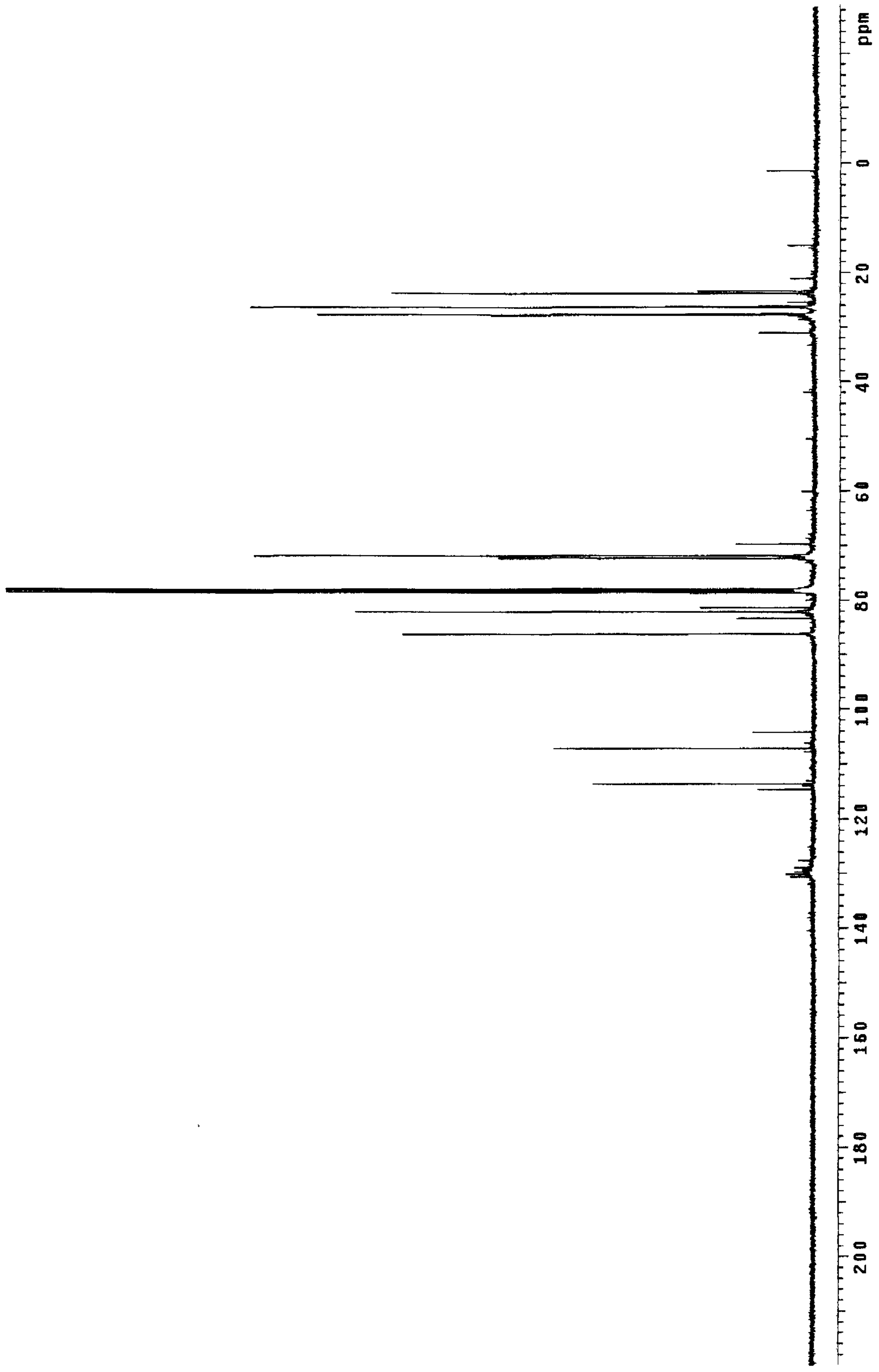
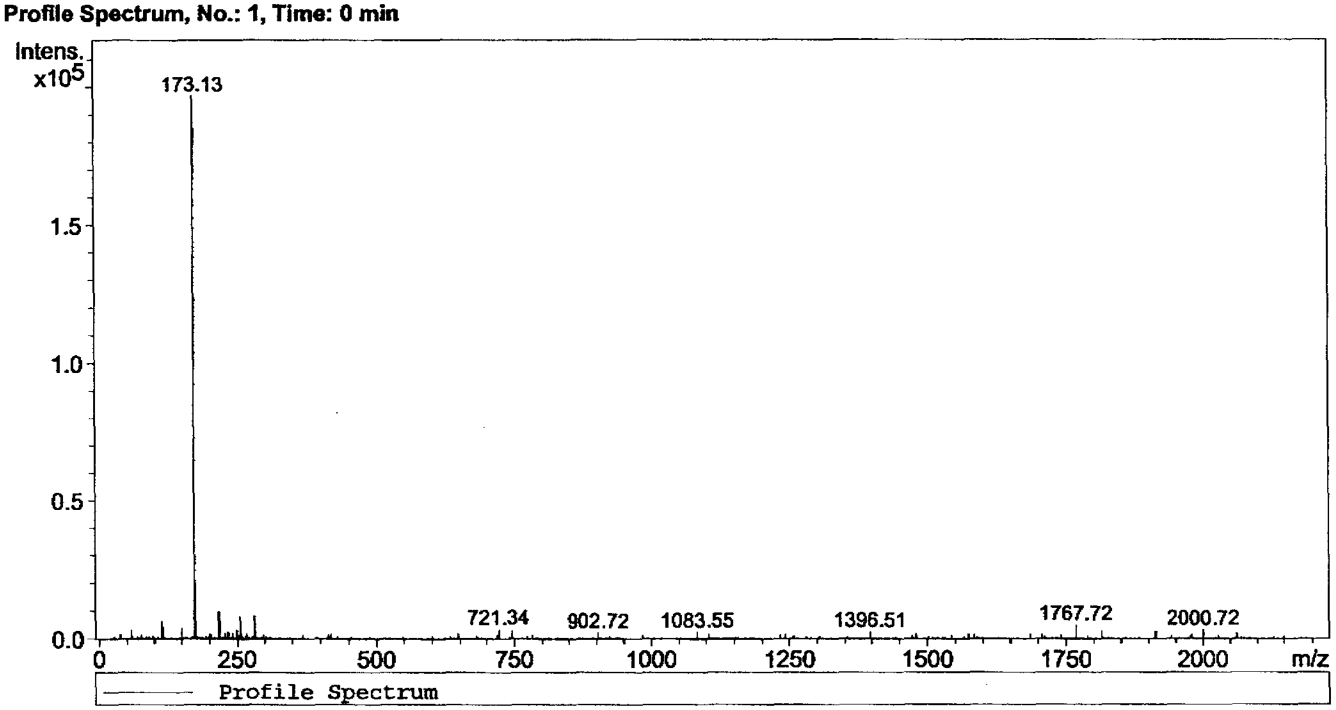


Figure 42. ^{13}C NMR of **15**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
57.40	3192	0.20	233.07	2707	0.30	745.79	2889	0.20
113.13	6697	0.40	241.83	2054	0.20	902.72	2324	0.20
115.21	4409	0.40	249.11	3252	0.30	1083.55	2544	0.20
149.12	4251	0.50	255.28	8197	0.30	1396.51	2653	0.20
173.13	197047	0.30	256.21	2237	0.30	1767.72	5017	0.20
173.98	20393	0.40	266.70	2088	0.20	1815.13	2631	0.20
175.11	8170	0.30	281.14	8410	0.30	1912.42	2751	0.20
199.14	2020	0.40	283.22	2820	0.50	2000.72	3320	0.20
217.12	9987	0.40	647.02	2091	0.20	2061.73	2116	0.20
227.17	2243	0.30	721.34	3597	0.20			

Figure 43. Mass Spectrum of **15**

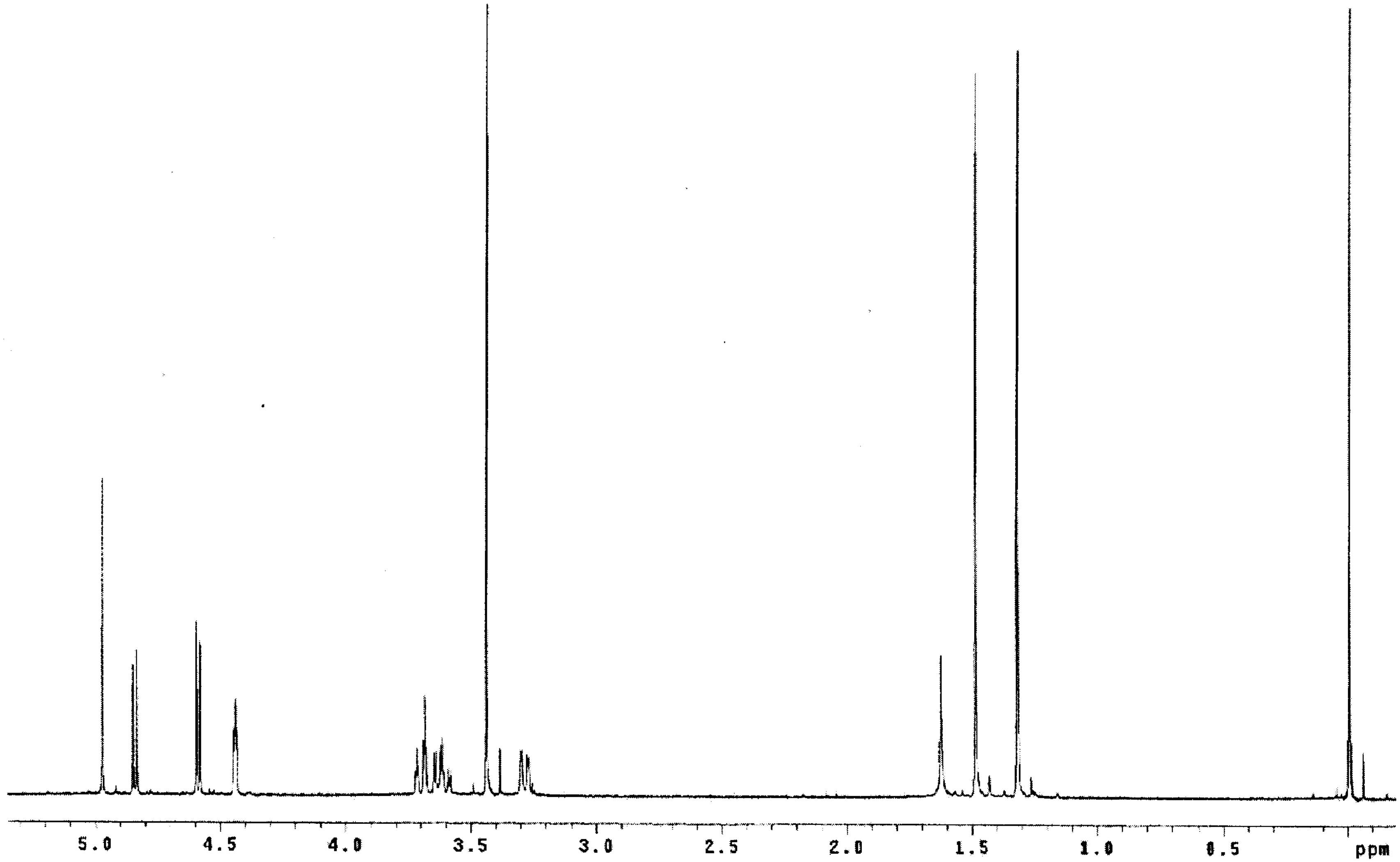


Figure 44. ^{1}H NMR of **16**

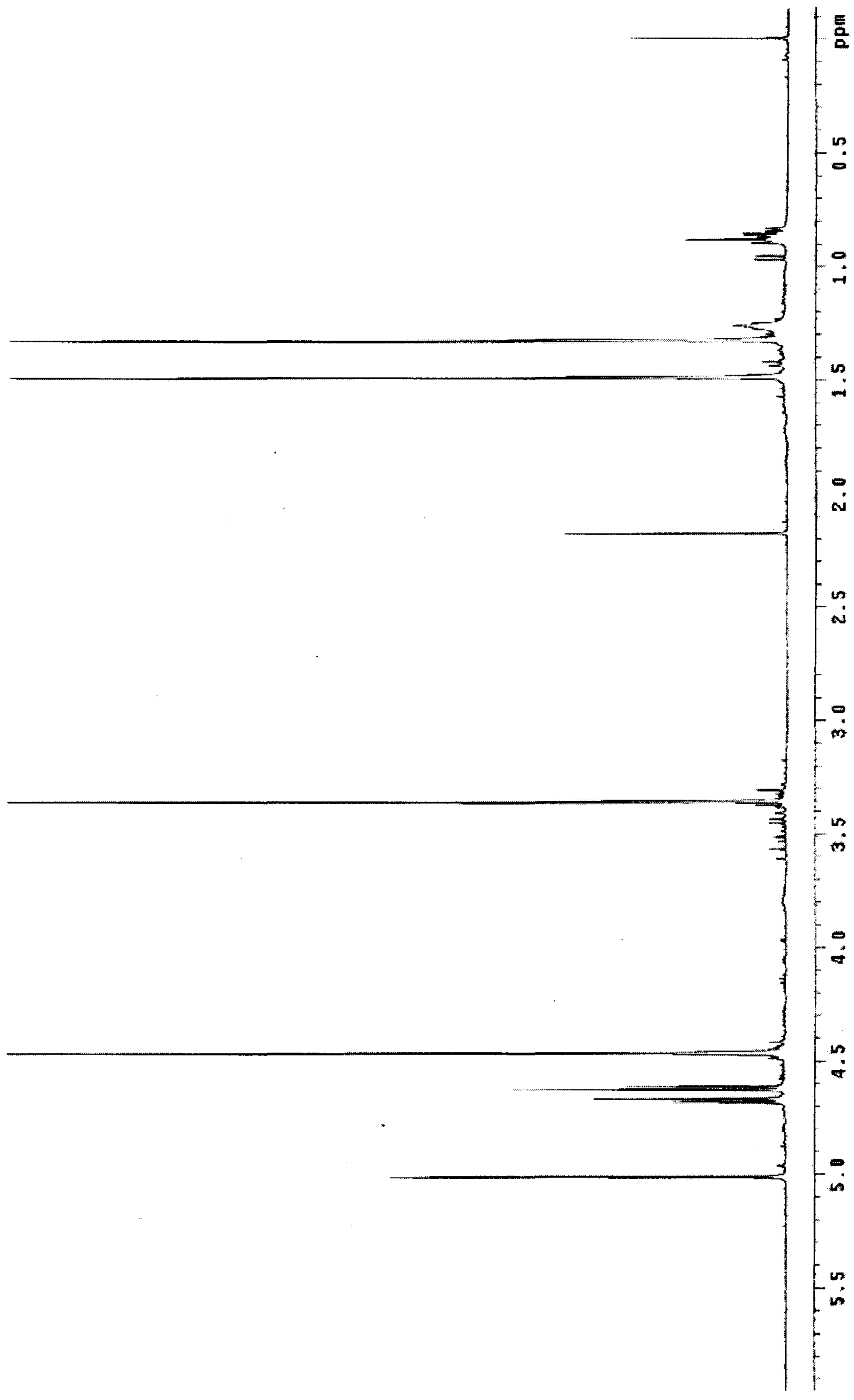


Figure 45. ^{1}H NMR of 17

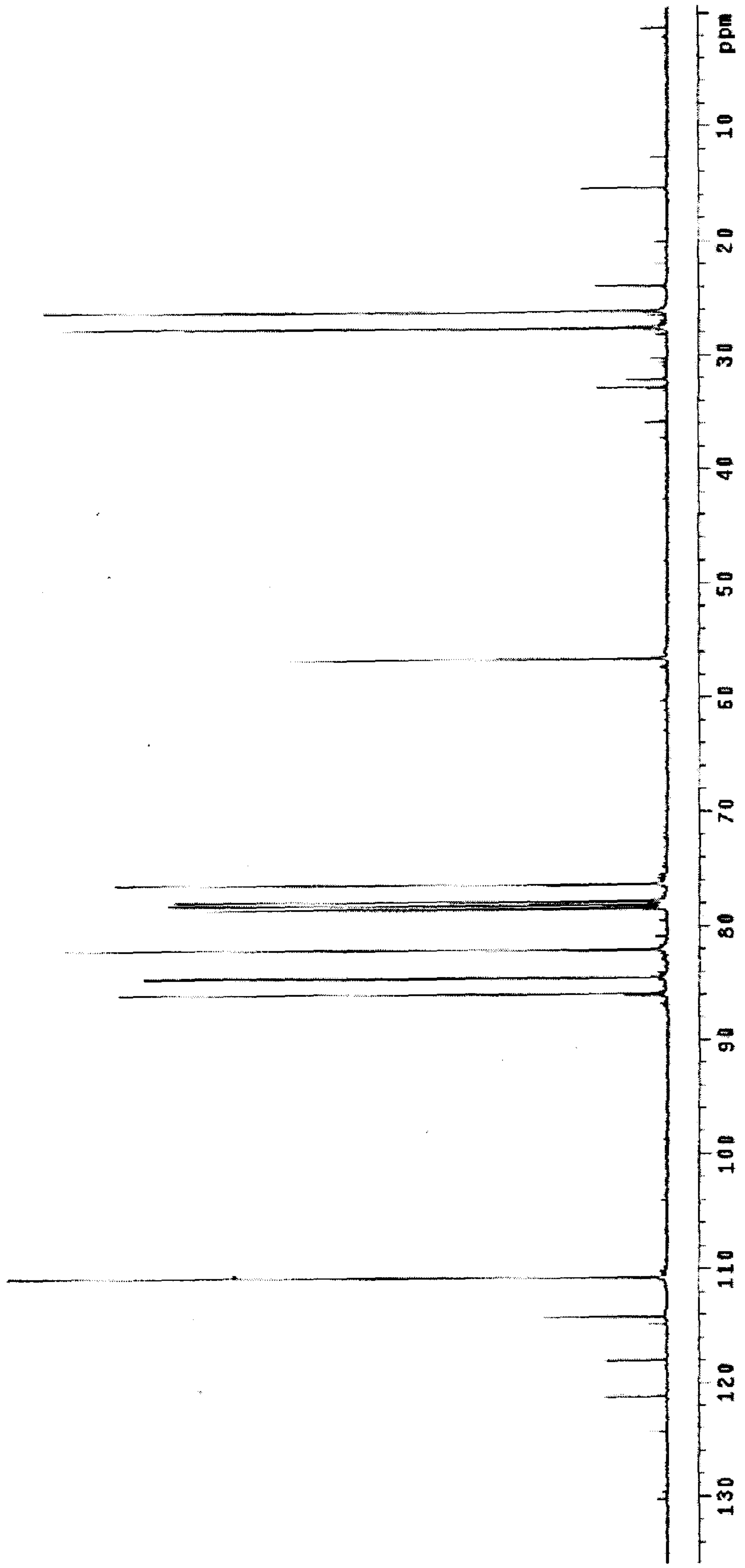


Figure 46. ^{13}C NMR of 17

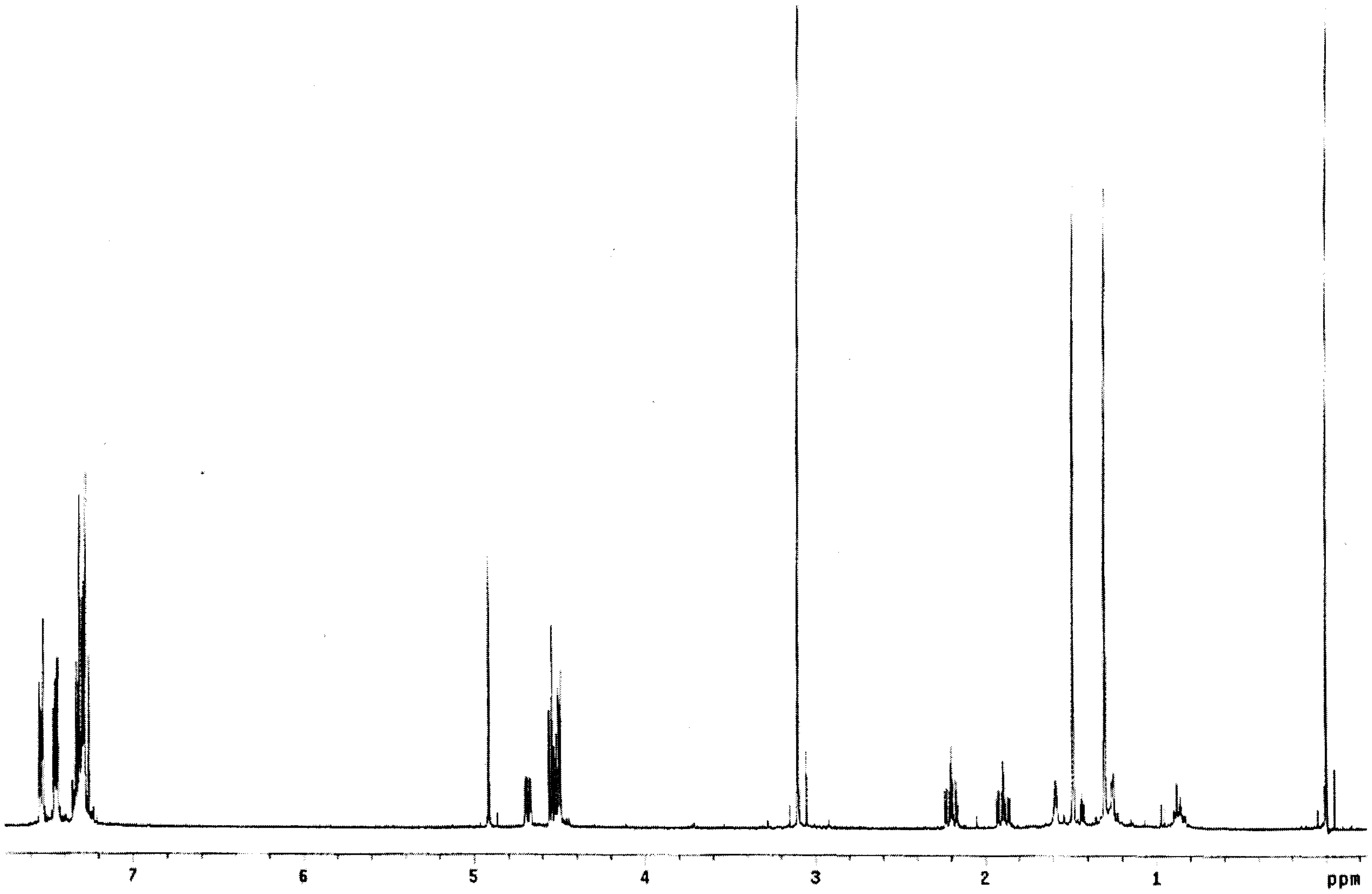


Figure 47. ^{1}H NMR of **18**

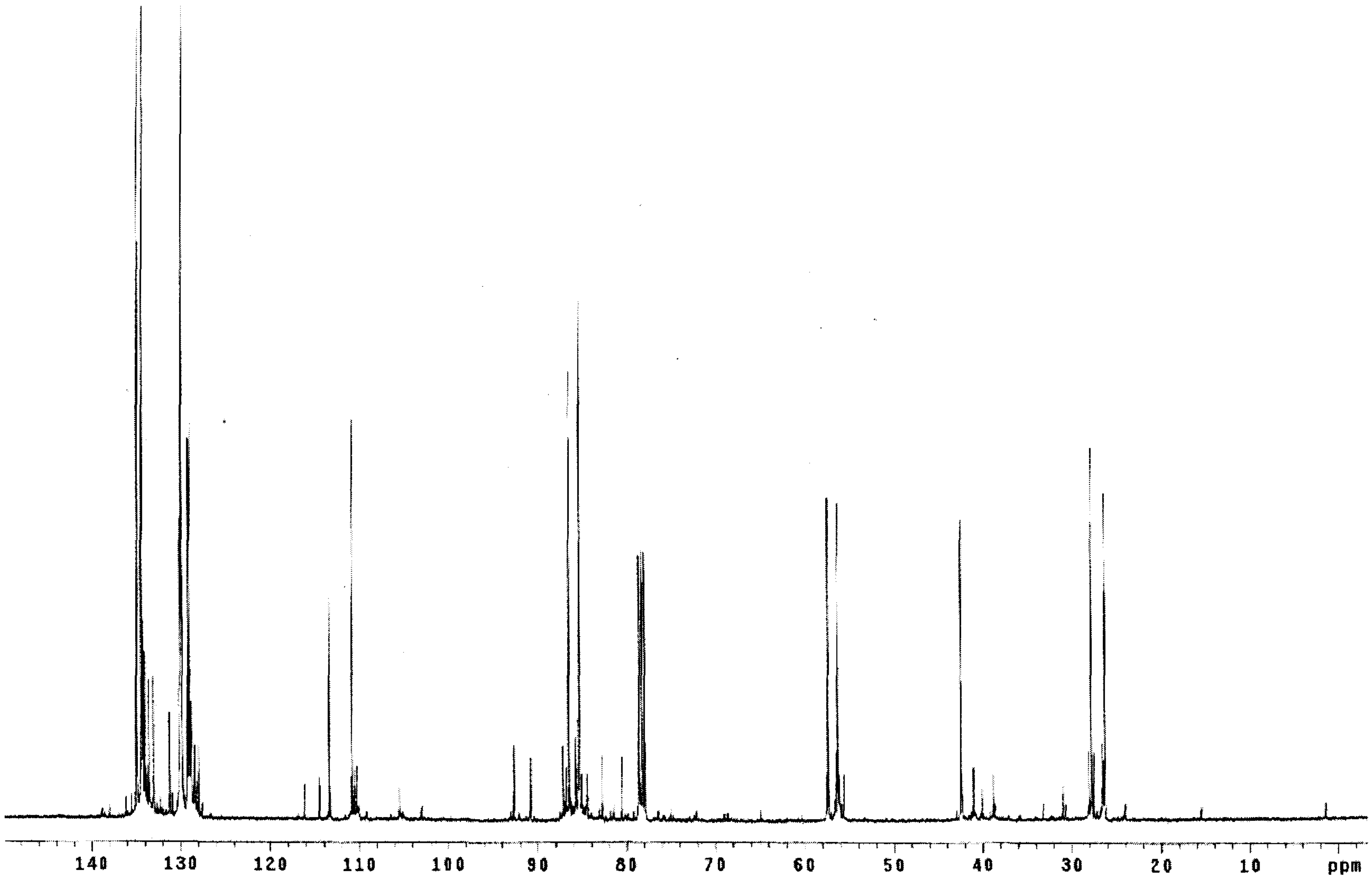


Figure 48. ^{13}C NMR of **18**

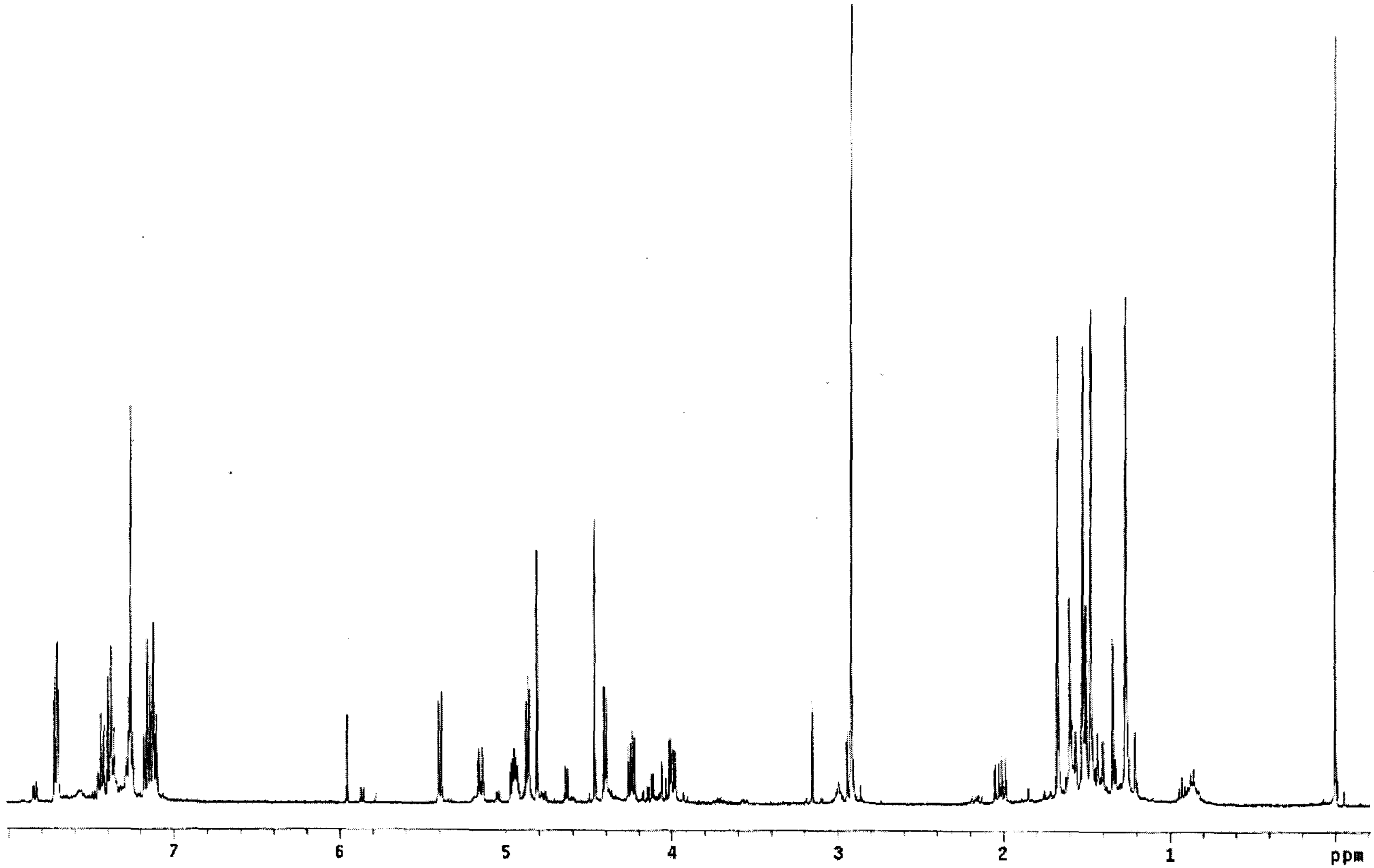


Figure 49. ^{1}H NMR of **19**

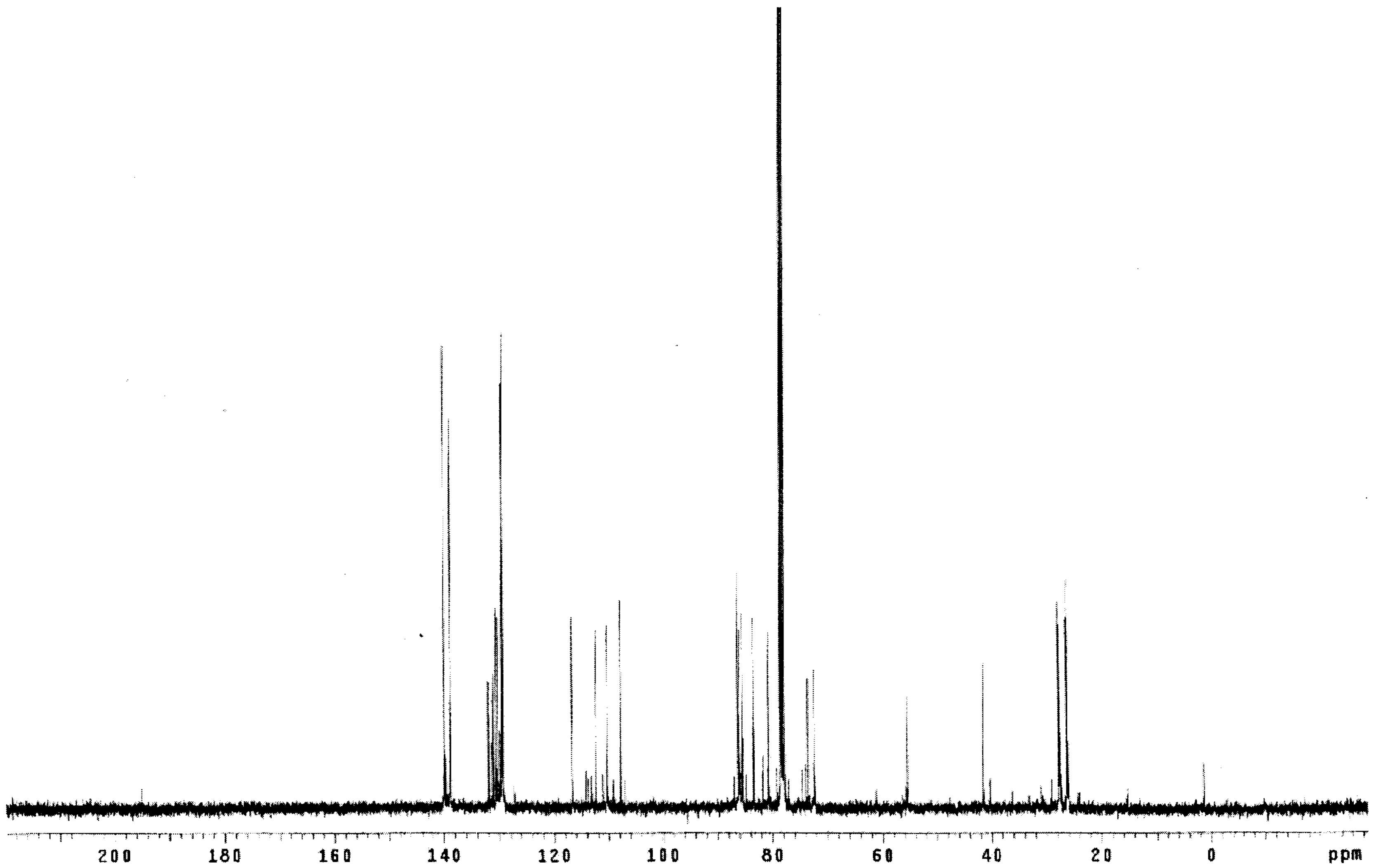
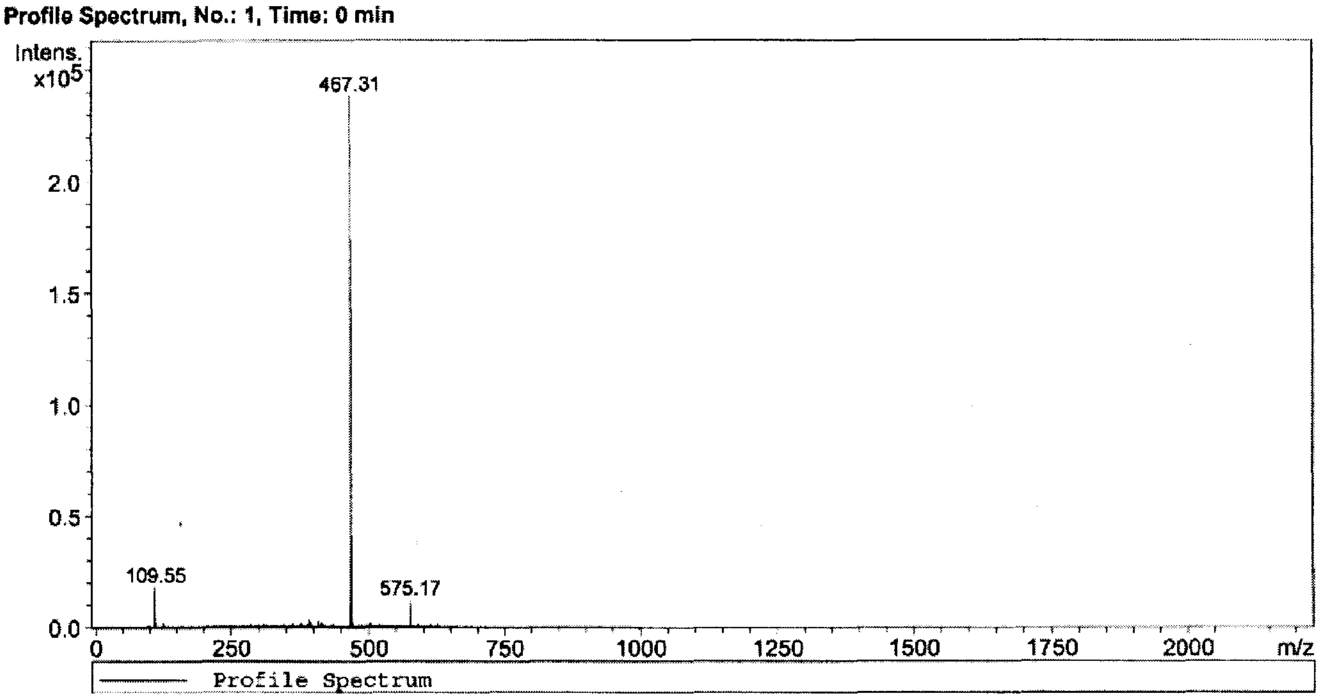


Figure 50. ^{13}C NMR of **19**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
109.55	18487	0.50	393.81	1999	0.20	468.96	22487	0.30
125.79	2162	0.30	407.79	2397	0.40	470.16	4465	0.30
389.90	1822	0.40	408.10	1975	0.20	503.14	1854	0.40
391.59	2630	0.10	413.83	1865	0.40	575.17	12571	0.30
391.95	3172	0.50	466.03	7676	0.60	576.15	4566	0.30
392.12	3132	0.20	467.31	238980	0.30	577.15	2260	0.30
392.63	1964	0.10	467.90	65954	0.30	589.13	1866	0.20

End of report

Figure 51. Mass Spectrum of **19**

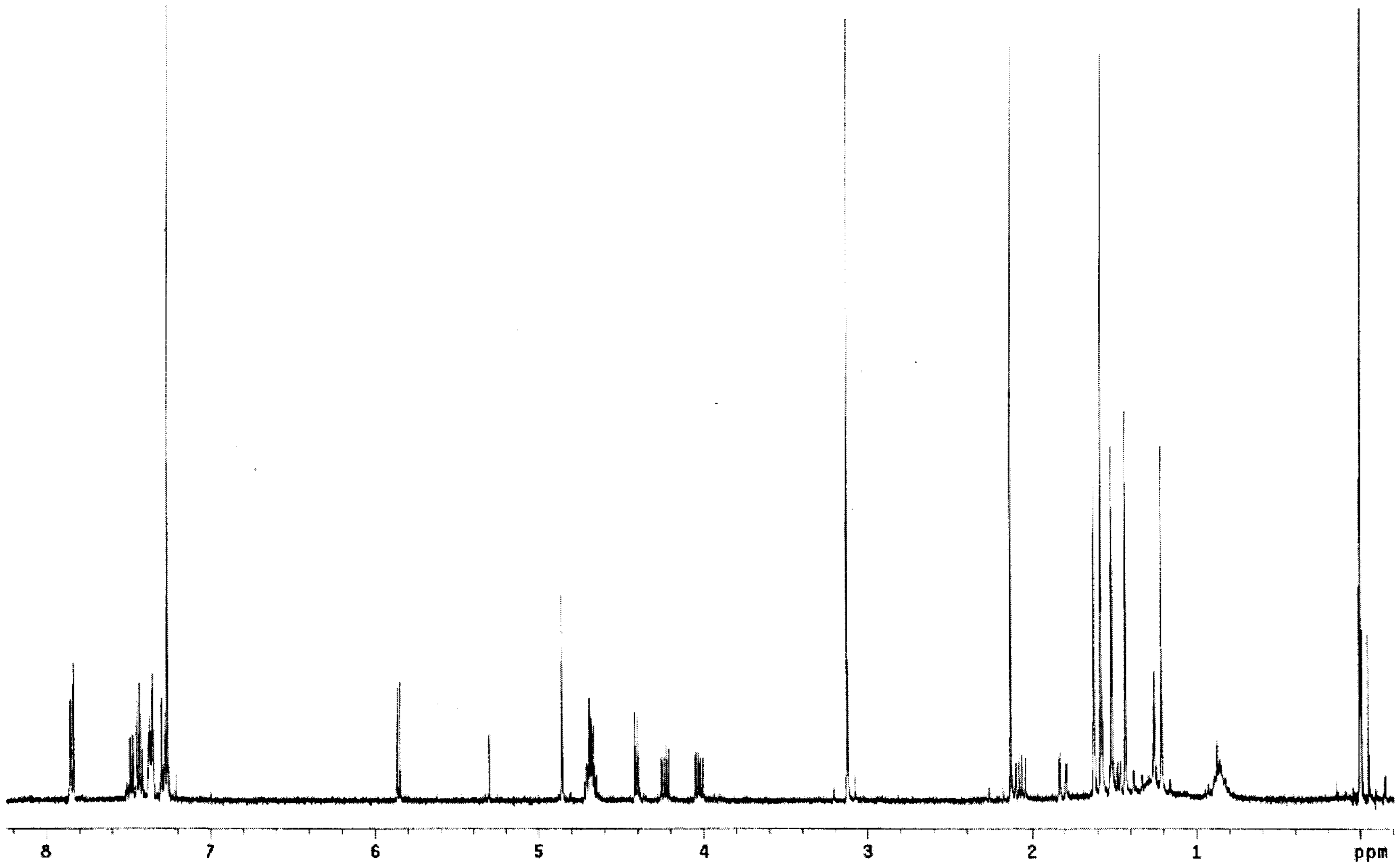


Figure 52. ^{1}H NMR of **20**

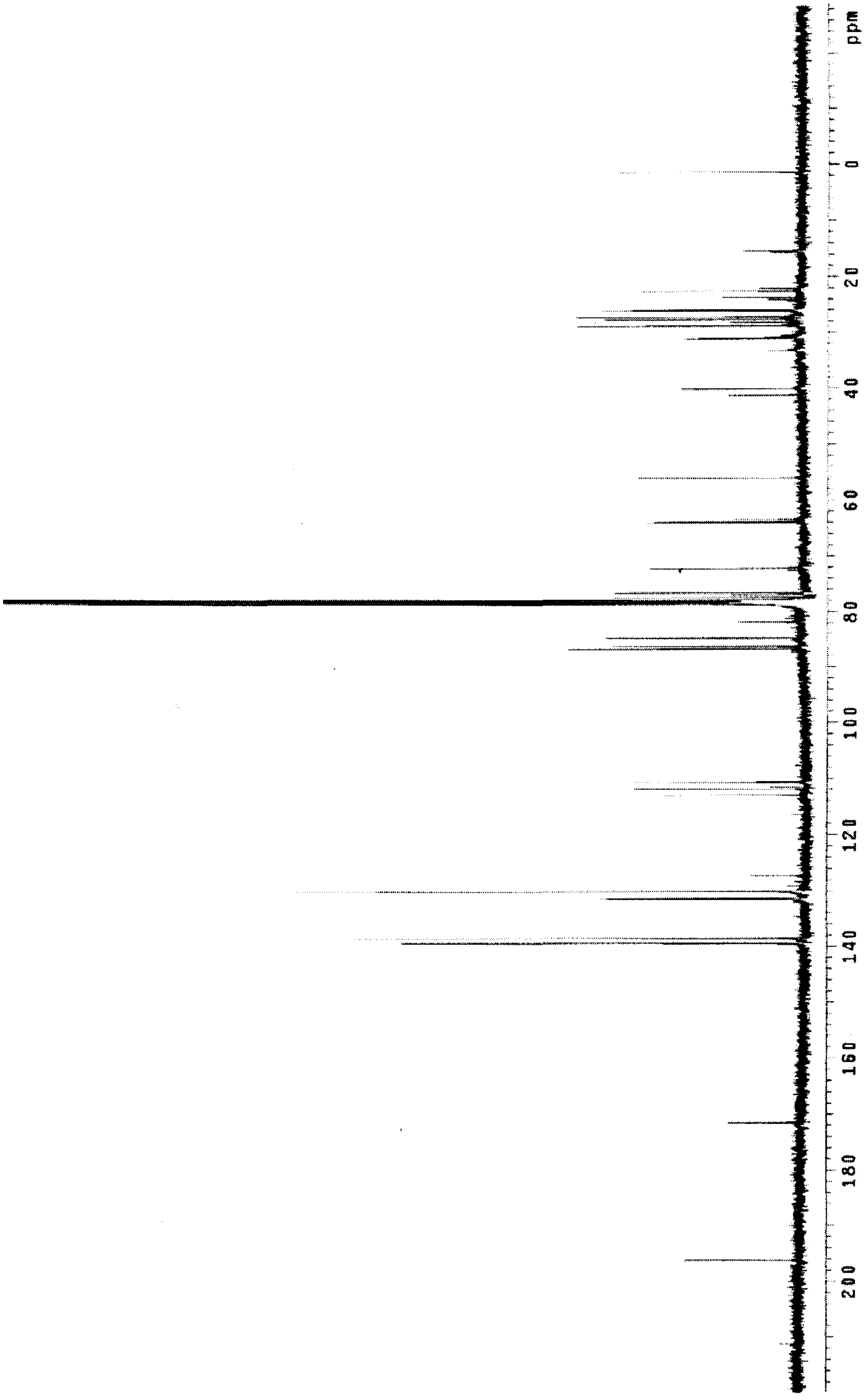
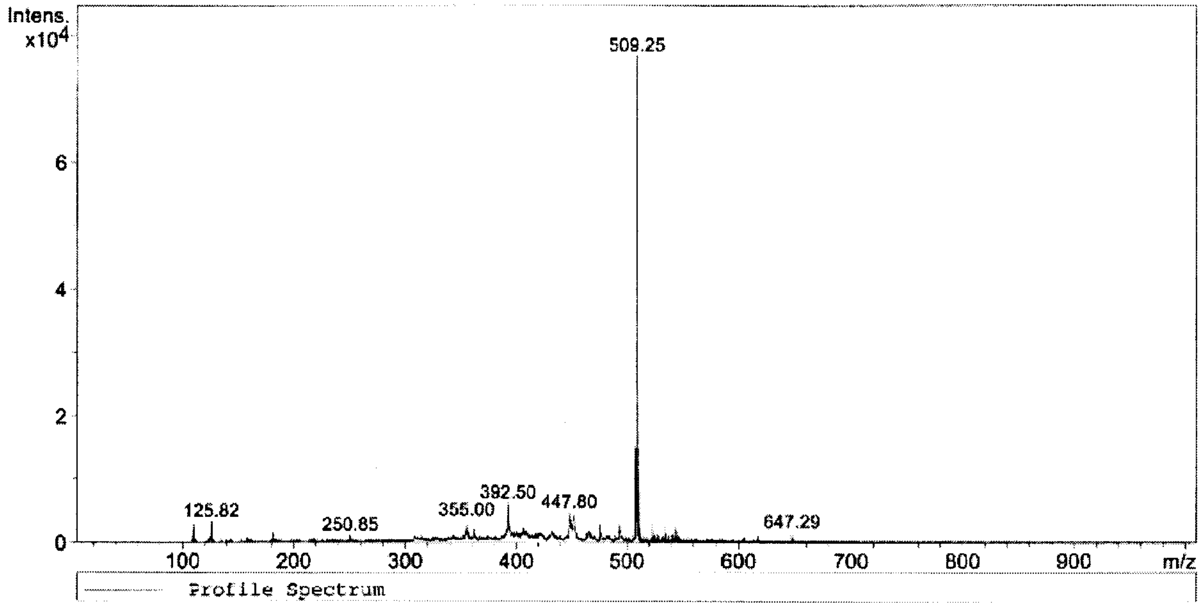


Figure 53. ^{13}C NMR of **20**

Profile Spectrum, No.: 1, Time: 0 min



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
109.84	3134	0.40	447.80	4786	0.50	523.15	2829	0.30
125.82	3351	0.30	448.28	4539	0.20	524.16	1340	0.20
250.85	1184	0.30	449.44	3638	0.30	525.15	1046	0.30
355.00	3531	0.20	450.76	2853	0.20	527.11	1159	0.20
357.05	1501	0.20	467.62	1815	0.30	534.14	3052	0.30
362.11	2002	0.20	475.61	2838	0.60	535.08	1366	0.20
382.26	1090	0.30	493.39	2990	0.30	541.13	1221	0.20
392.50	6302	0.60	507.67	14918	0.50	543.12	2649	0.30
393.50	3310	0.20	508.55	6233	0.40	545.14	2093	0.30
397.45	1596	0.30	509.25	76873	0.30	546.13	1109	0.30
404.00	1592	0.20	509.98	24207	0.30	647.29	1656	0.40
419.67	1408	0.10	511.09	7973	0.40			
429.25	1080	0.10	512.09	2204	0.20			

End of report

Figure 54. Mass Spectrum of **20**

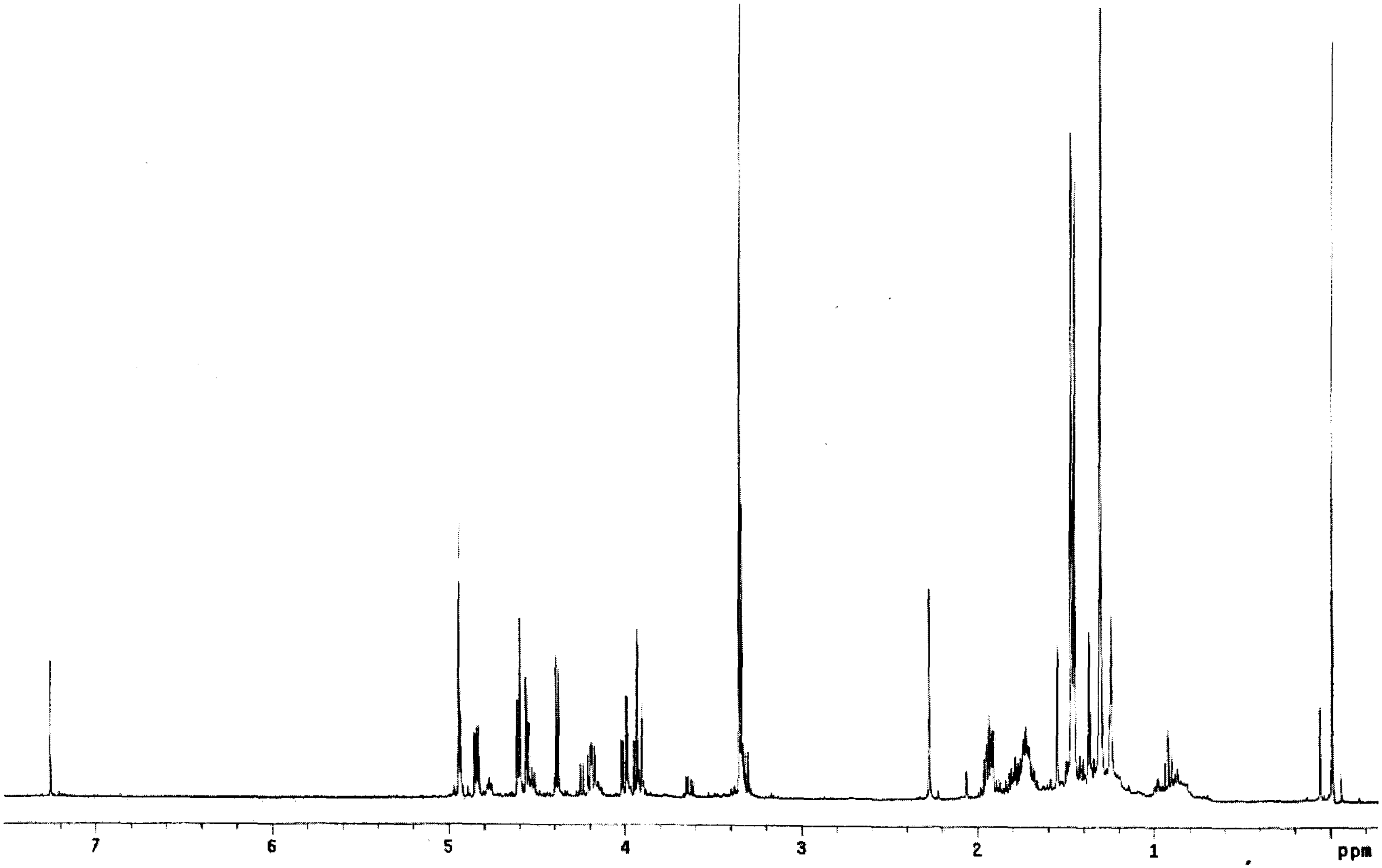


Figure 55. ^{1}H NMR of **21**

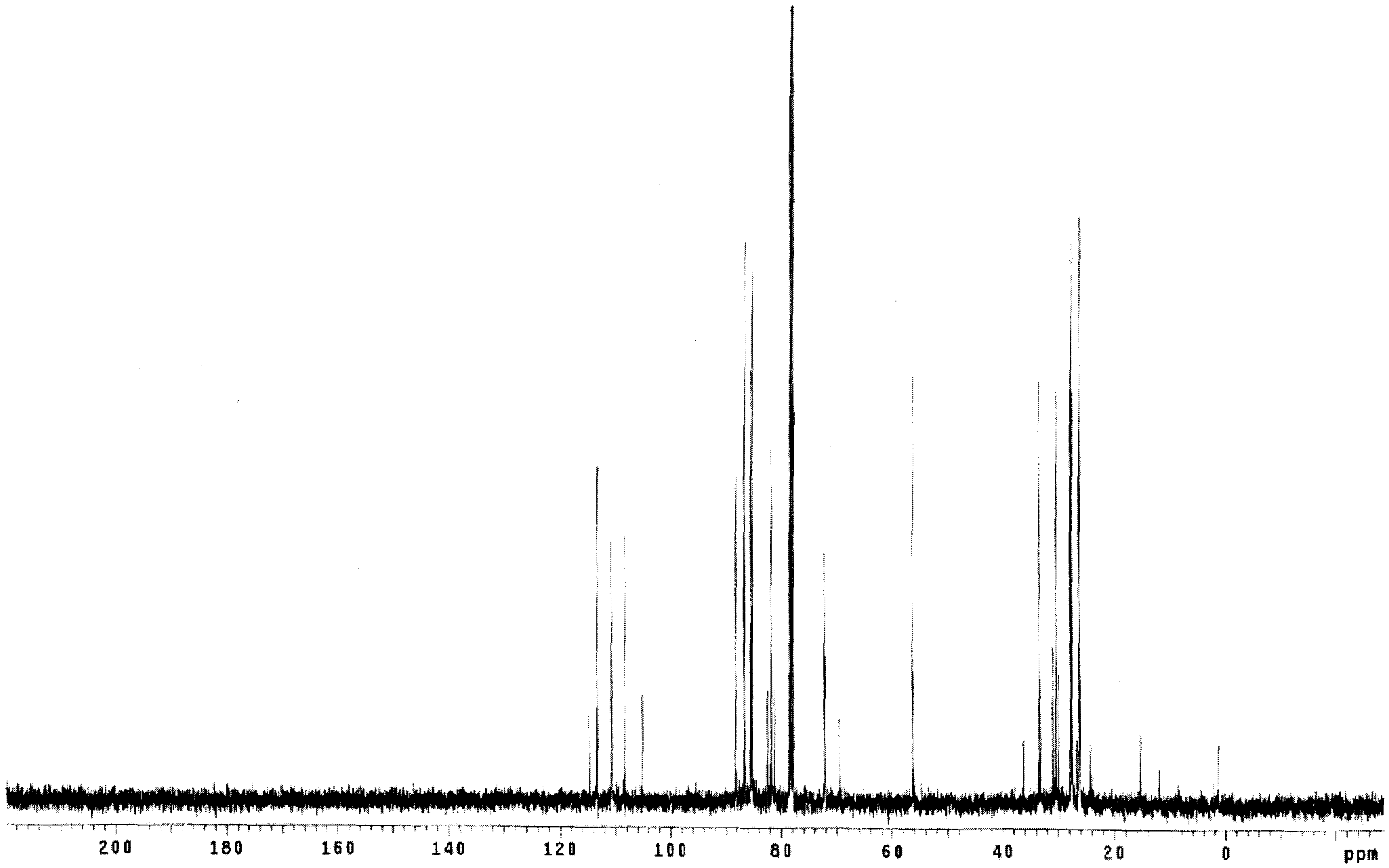
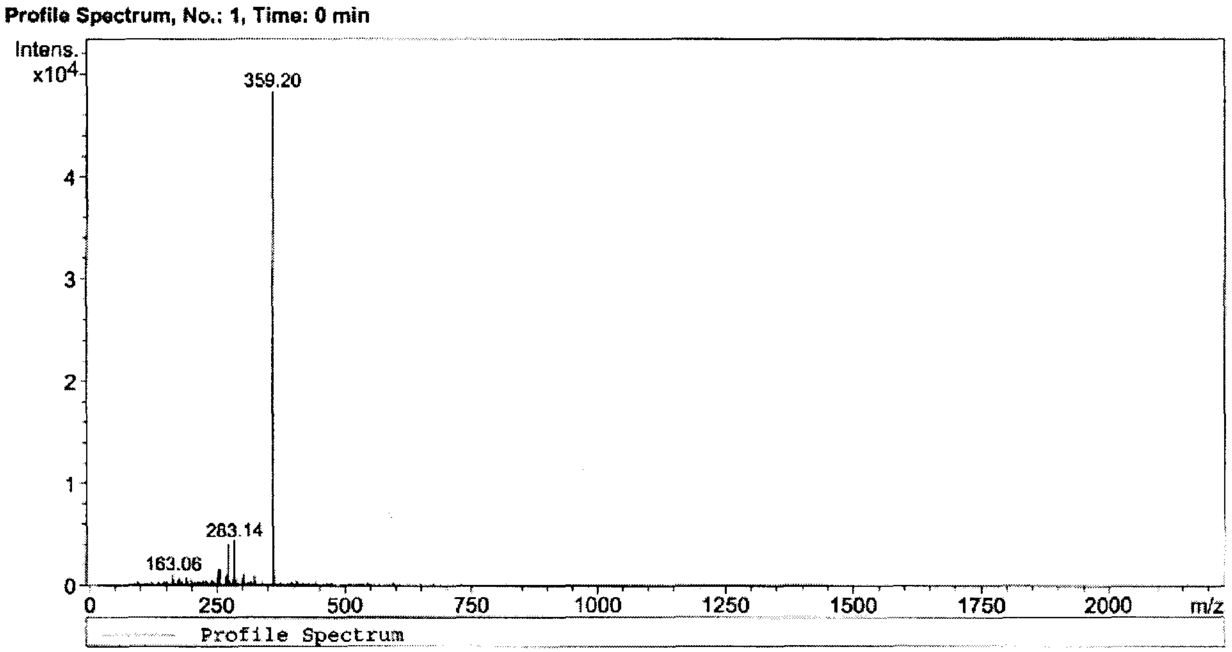


Figure 56. ^{13}C NMR of **21**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
161.07	514	0.20	253.23	1598	0.20	284.15	984	0.30
163.06	1109	0.30	255.23	1598	0.20	285.08	545	0.20
174.03	537	0.30	267.08	897	0.20	287.07	777	0.50
175.05	688	0.40	269.12	1025	0.20	299.12	583	0.20
188.99	560	0.30	270.07	578	0.20	301.09	1195	0.40
189.99	789	0.20	271.11	4088	0.20	323.15	942	0.50
199.08	565	0.40	272.09	847	0.20	359.20	48388	0.40
227.23	541	0.40	274.09	510	0.20	360.14	8276	0.30
239.17	535	0.20	281.22	713	0.40	361.17	2881	0.30
251.11	802	0.30	283.14	4415	0.30	362.19	967	0.20

End of report

Figure 57. Mass Spectrum of **21**

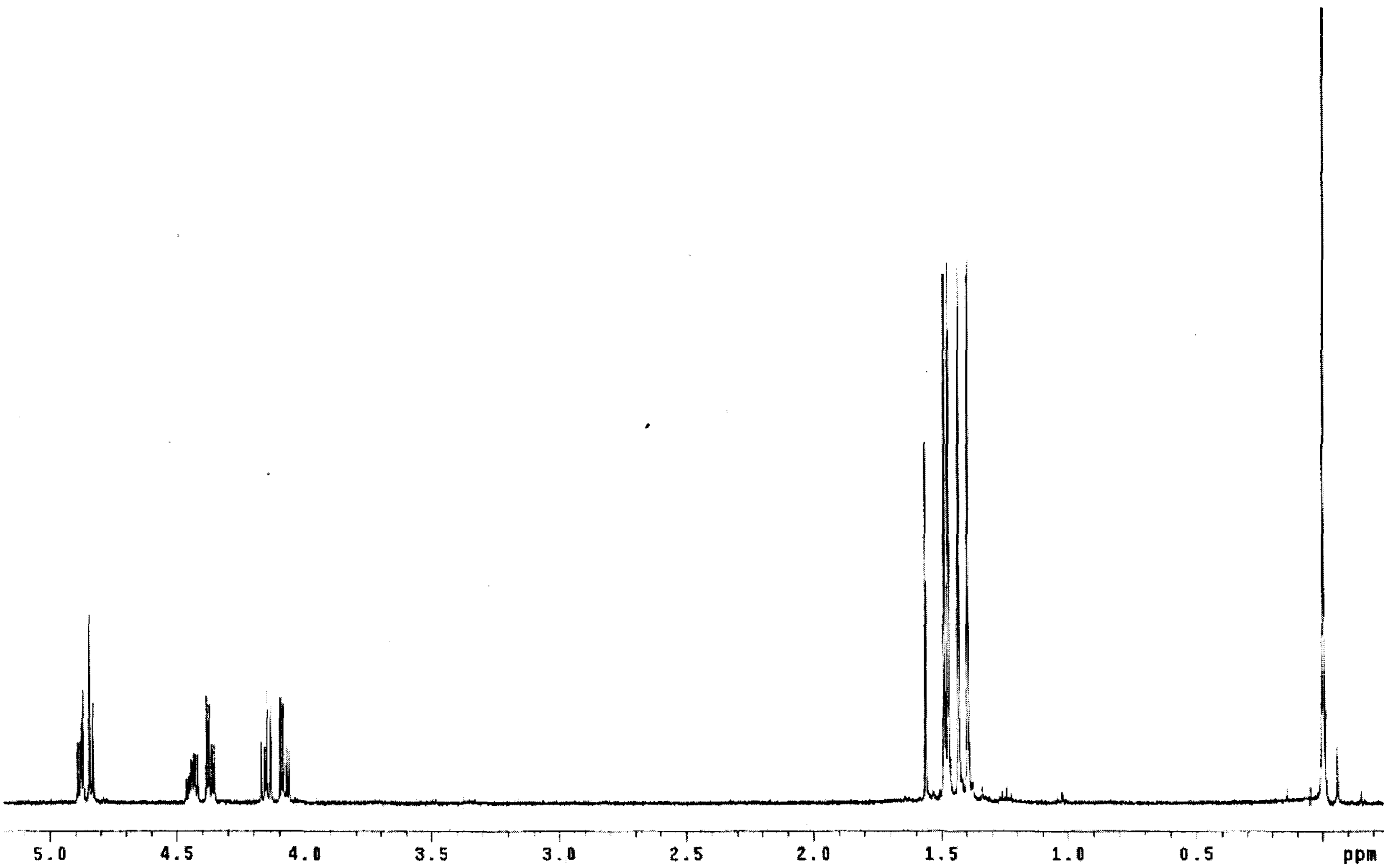


Figure 58. ^{1}H NMR of **23**

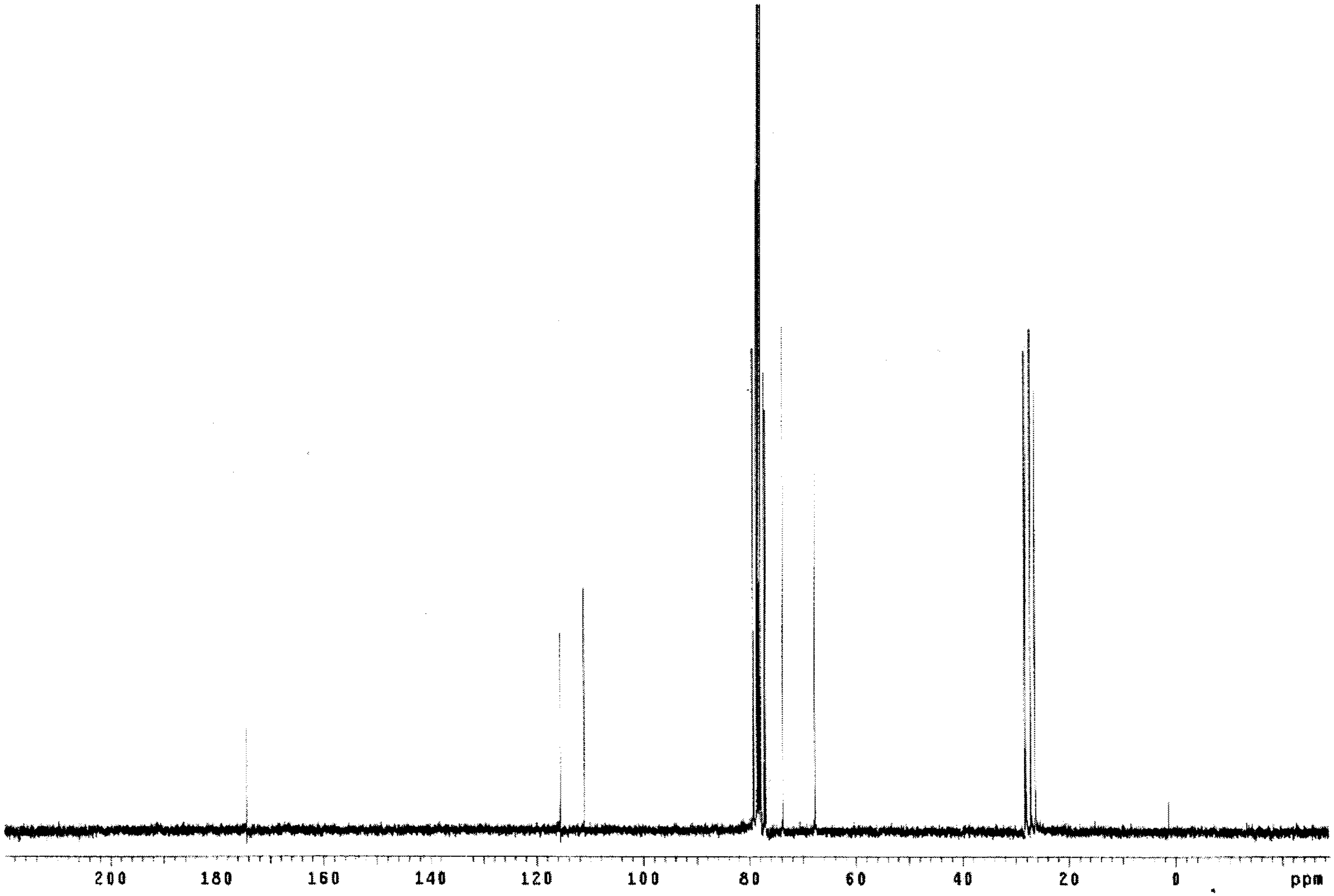
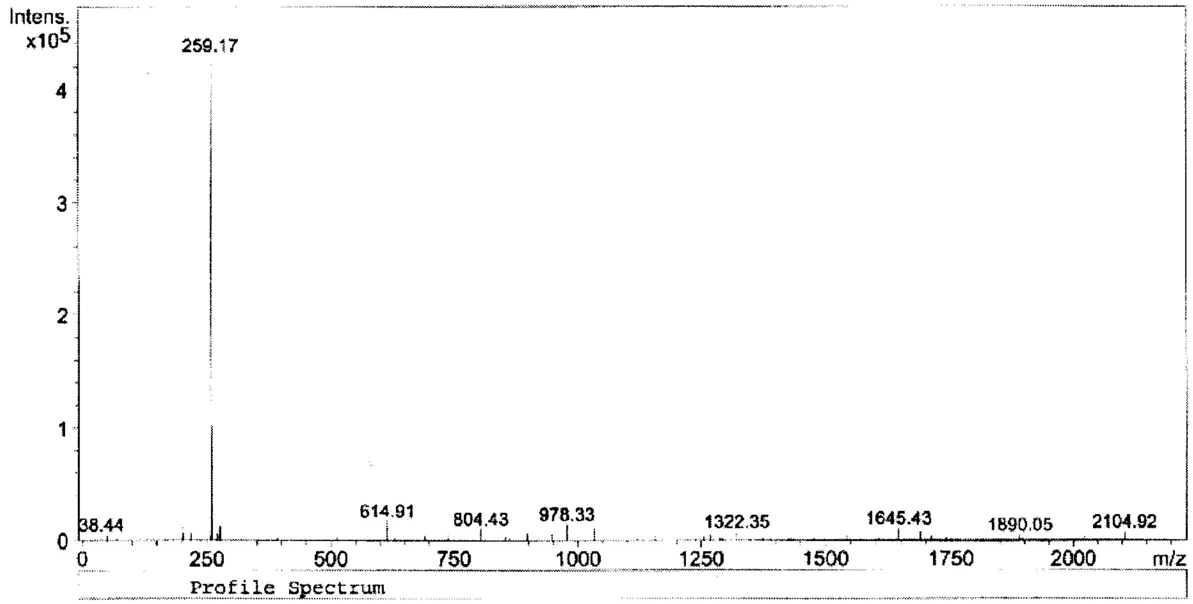


Figure 59. ^{13}C NMR of **23**

Profile Spectrum, No.: 1, Time: 0 min



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
38.44	4852	0.30	614.91	16960	0.20	1322.35	7562	0.20
51.23	4154	0.20	690.54	4081	0.20	1532.32	3210	0.20
187.03	4123	0.20	739.20	4138	0.20	1543.22	4694	0.20
201.21	41559	0.20	804.43	9856	0.20	1645.43	10406	0.20
202.19	5827	0.20	898.01	5893	0.20	1689.16	7330	0.20
218.21	7930	0.40	948.12	5640	0.20	1711.19	3376	0.20
259.17	429849	0.30	978.33	14118	0.20	1890.05	4864	0.20
260.03	99428	0.30	1032.46	12172	0.30	2104.56	4043	0.20
271.36	5980	0.20	1156.20	3448	0.20	2104.92	7688	0.20
276.19	12854	0.30	1255.42	3509	0.30	2105.33	3530	0.20
511.35	4277	0.20	1268.59	4656	0.20			

End of report

Figure 60. Mass Spectrum of **23**

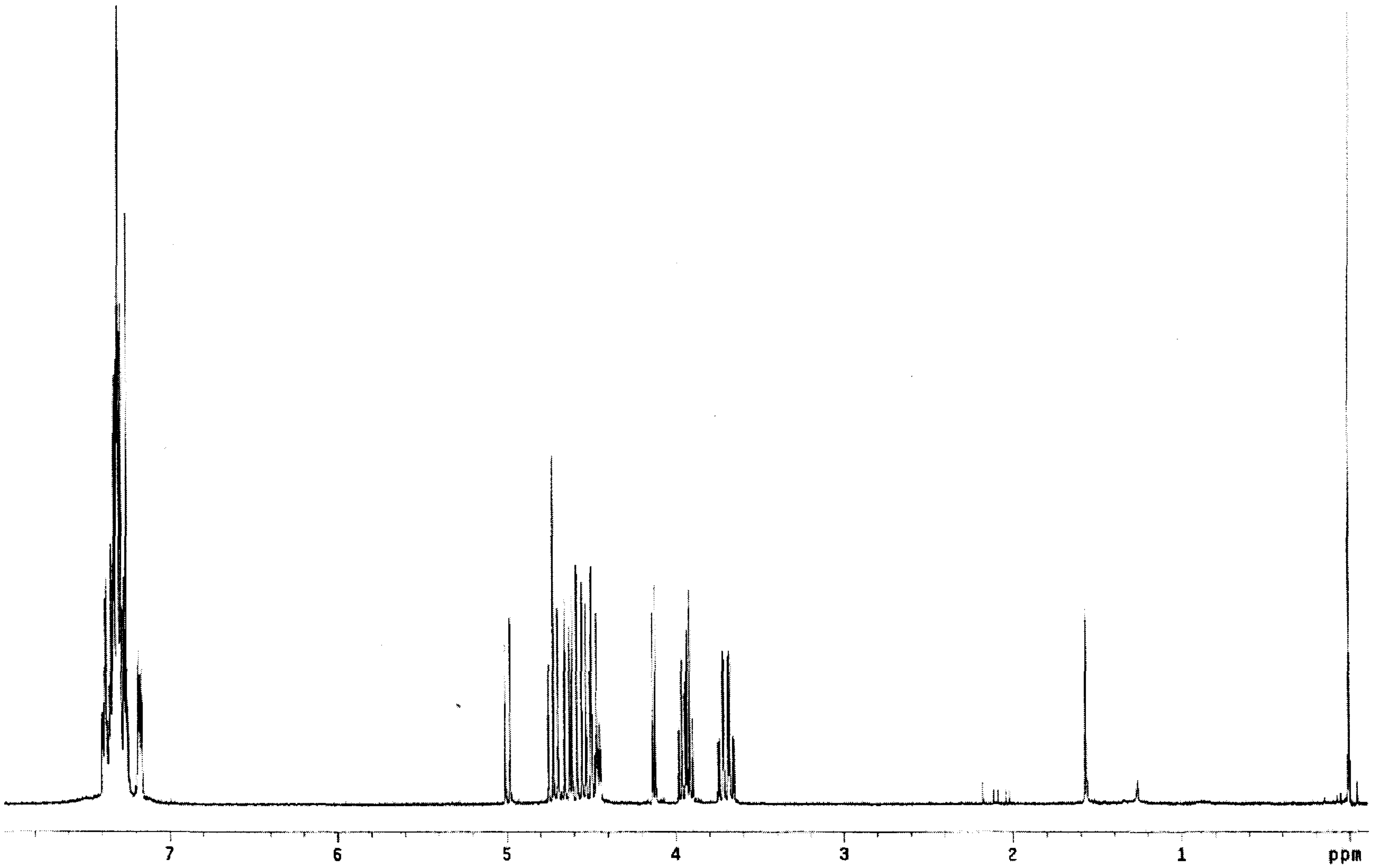


Figure 61. ^{1}H NMR of **25**

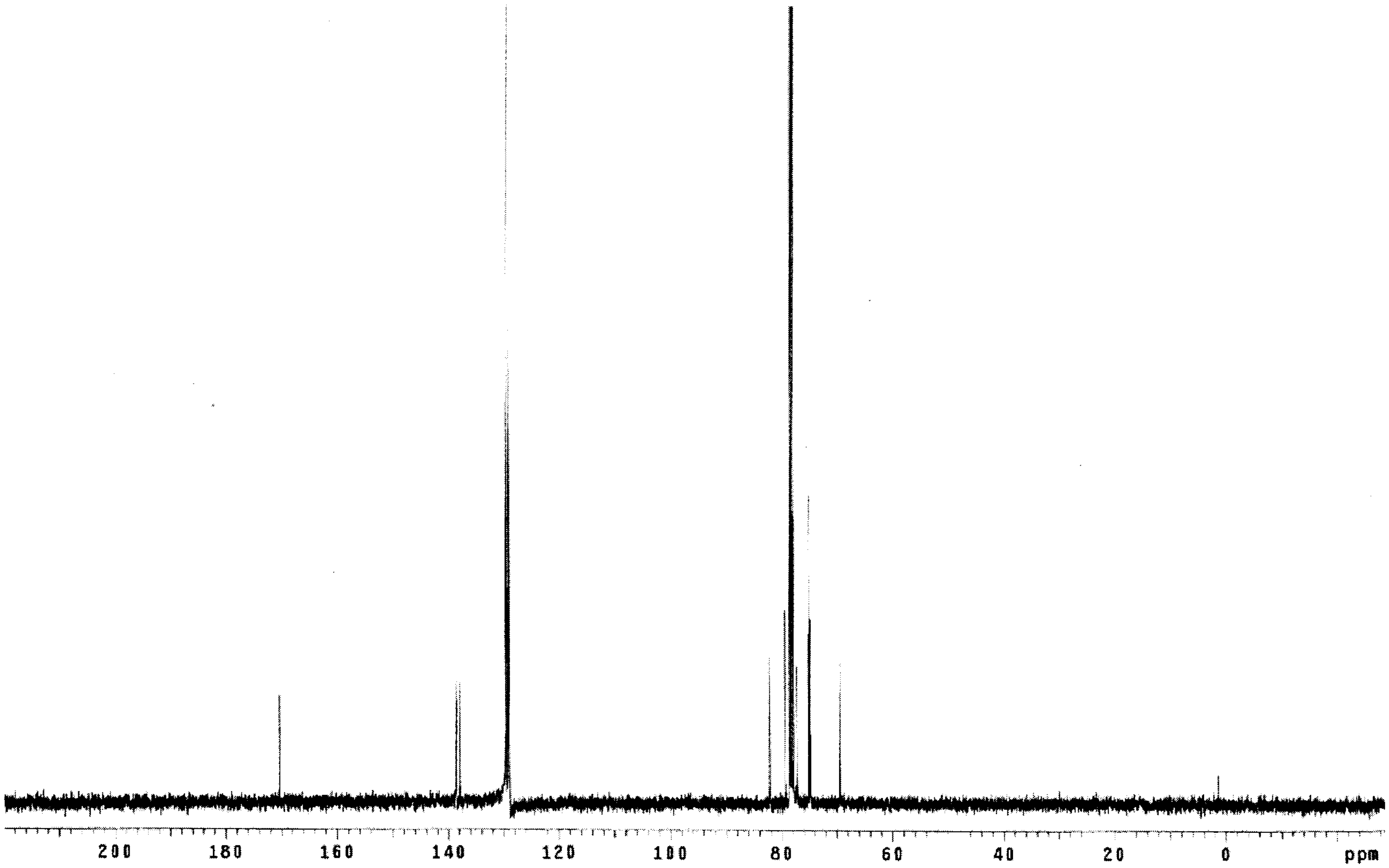
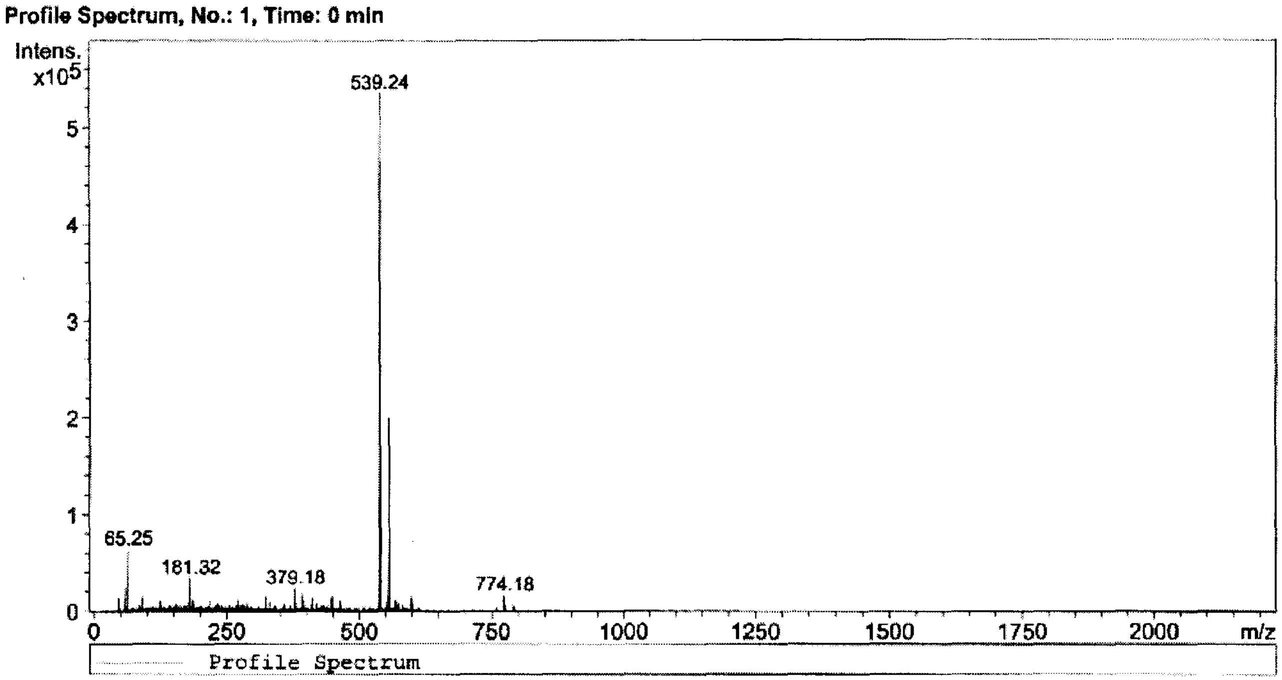


Figure 62. ^{13}C NMR of **25**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
47.31	13614	0.30	379.18	24122	0.50	540.95	34205	0.40
60.26	25101	0.30	391.37	18229	0.50	556.33	200065	0.30
65.25	64582	0.30	396.34	14940	0.50	557.22	84183	0.30
91.26	14132	0.30	411.55	13175	0.30	558.24	19427	0.30
125.29	10047	0.30	447.30	12856	0.30	568.18	11053	0.40
181.32	35240	0.40	448.32	13697	0.20	570.25	10350	0.30
185.28	10832	0.40	449.17	16022	0.40	598.25	15467	0.30
187.25	11521	0.40	463.26	10565	0.30	600.32	12232	0.40
271.31	11634	0.20	539.24	534880	0.30	774.18	17031	0.40
323.24	14529	0.30	539.96	183290	0.30			

End of report

Figure 63. Mass Spectrum of **25**

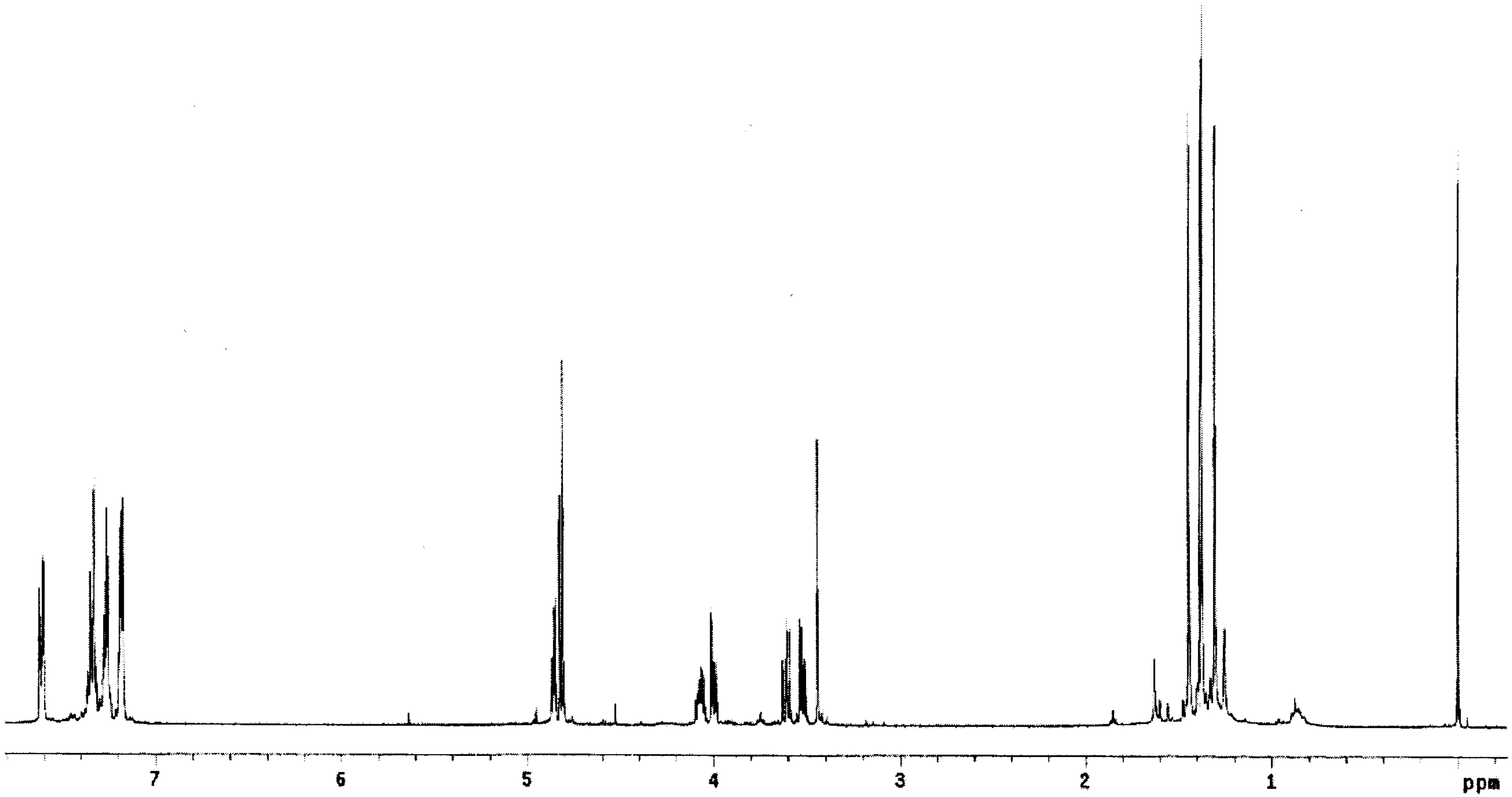


Figure 64. ^{1}H NMR of **26**

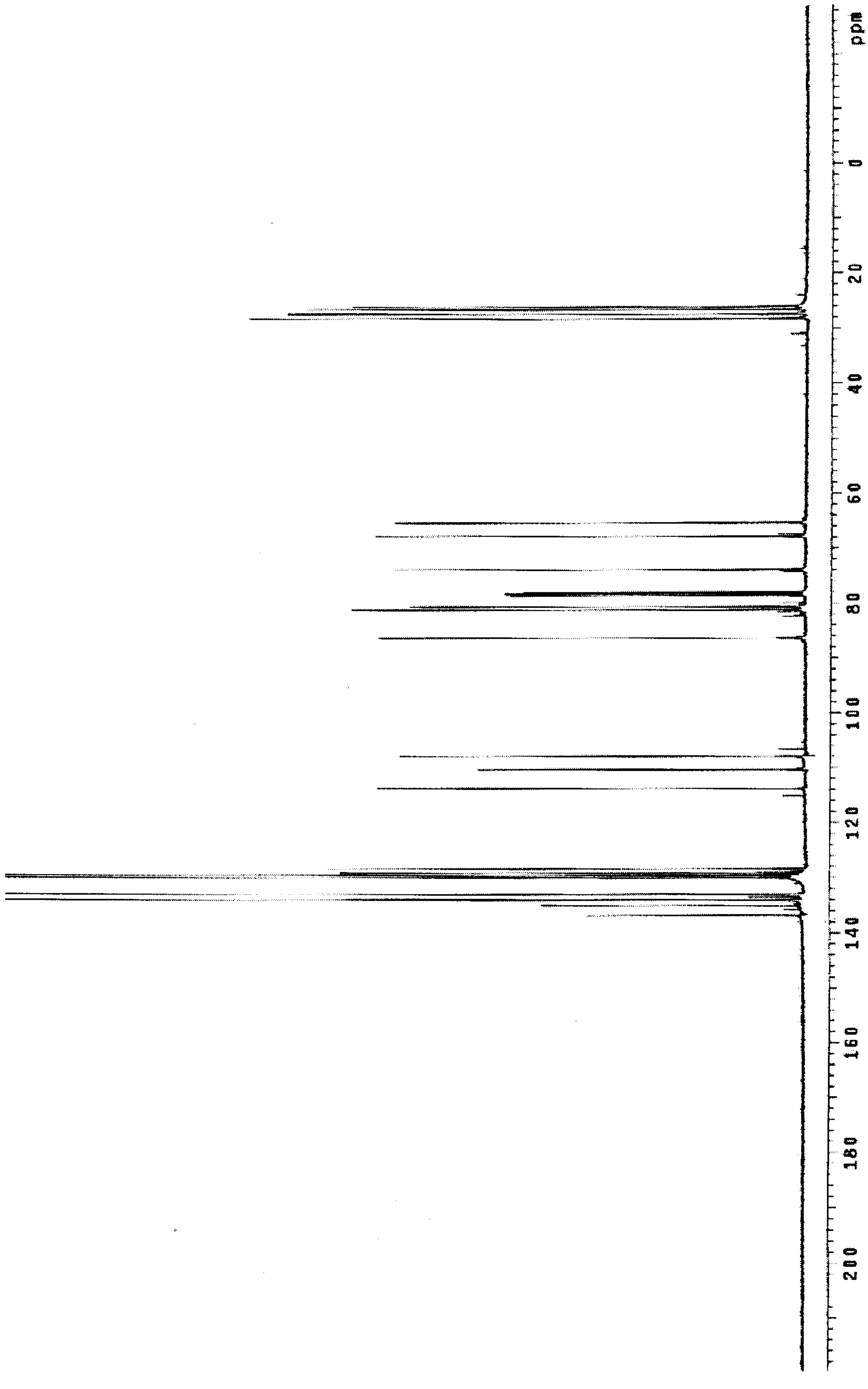
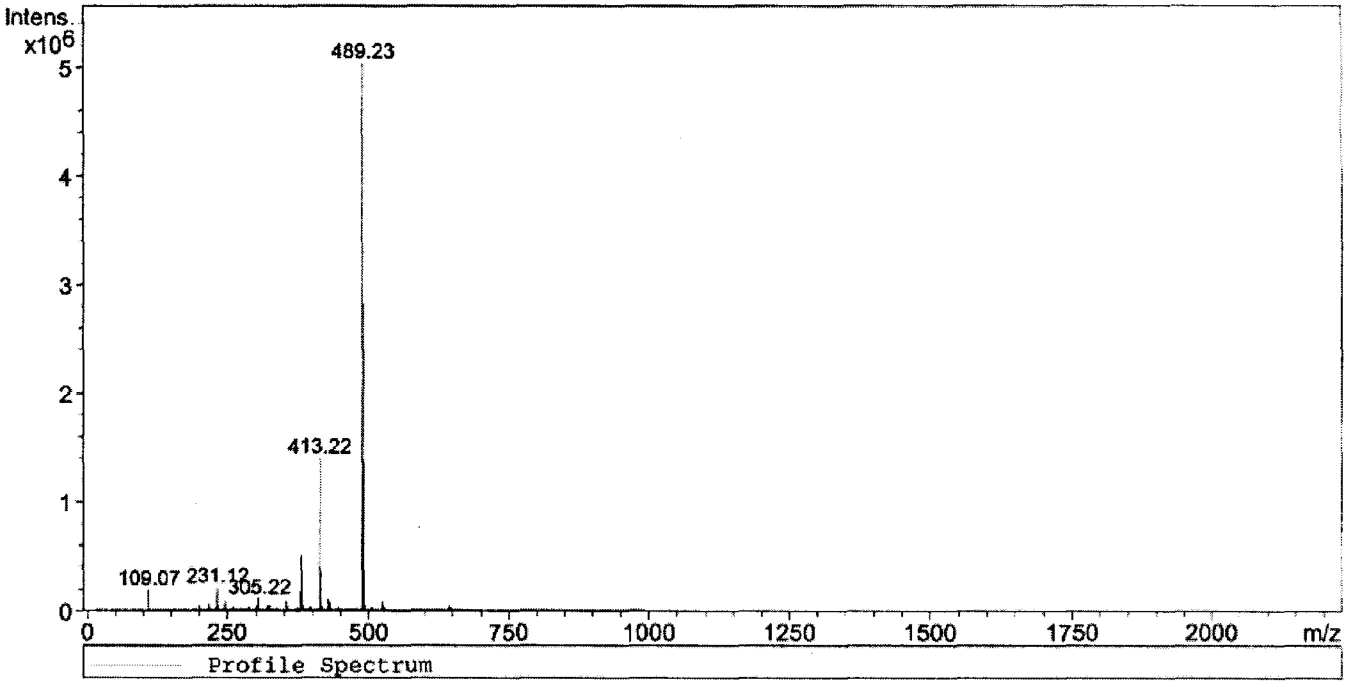


Figure 65. ^{13}C NMR of **26**

Profile Spectrum, No.: 1, Time: 0 min



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
109.07	190657	0.30	381.20	500660	0.40	487.71	54861	0.10
217.15	54614	0.40	382.13	117792	0.30	489.23	5045698	0.30
231.12	212232	0.30	413.22	1404364	0.30	489.95	1646727	0.30
245.10	86773	0.20	414.08	392275	0.30	491.04	741897	0.30
303.15	58405	0.40	415.15	169853	0.30	491.99	191026	0.20
305.22	112204	0.40	429.13	98591	0.30	525.08	84739	0.20
353.18	86691	0.40	431.09	69235	0.40			
379.24	173206	0.30	487.39	69082	0.30			

End of report

Figure 66. Mass Spectrum of **26**

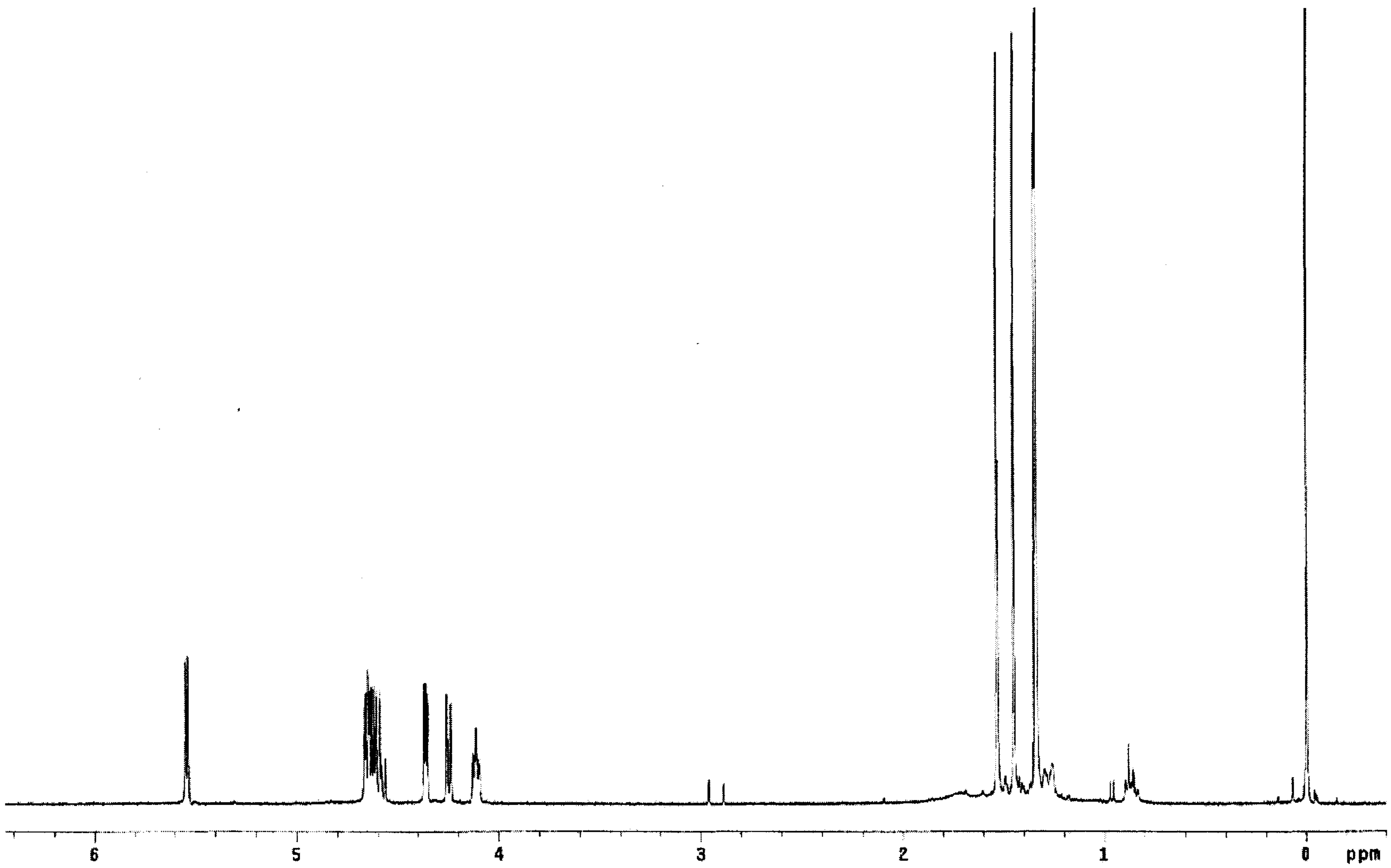


Figure 67. ^{1}H NMR of **28**

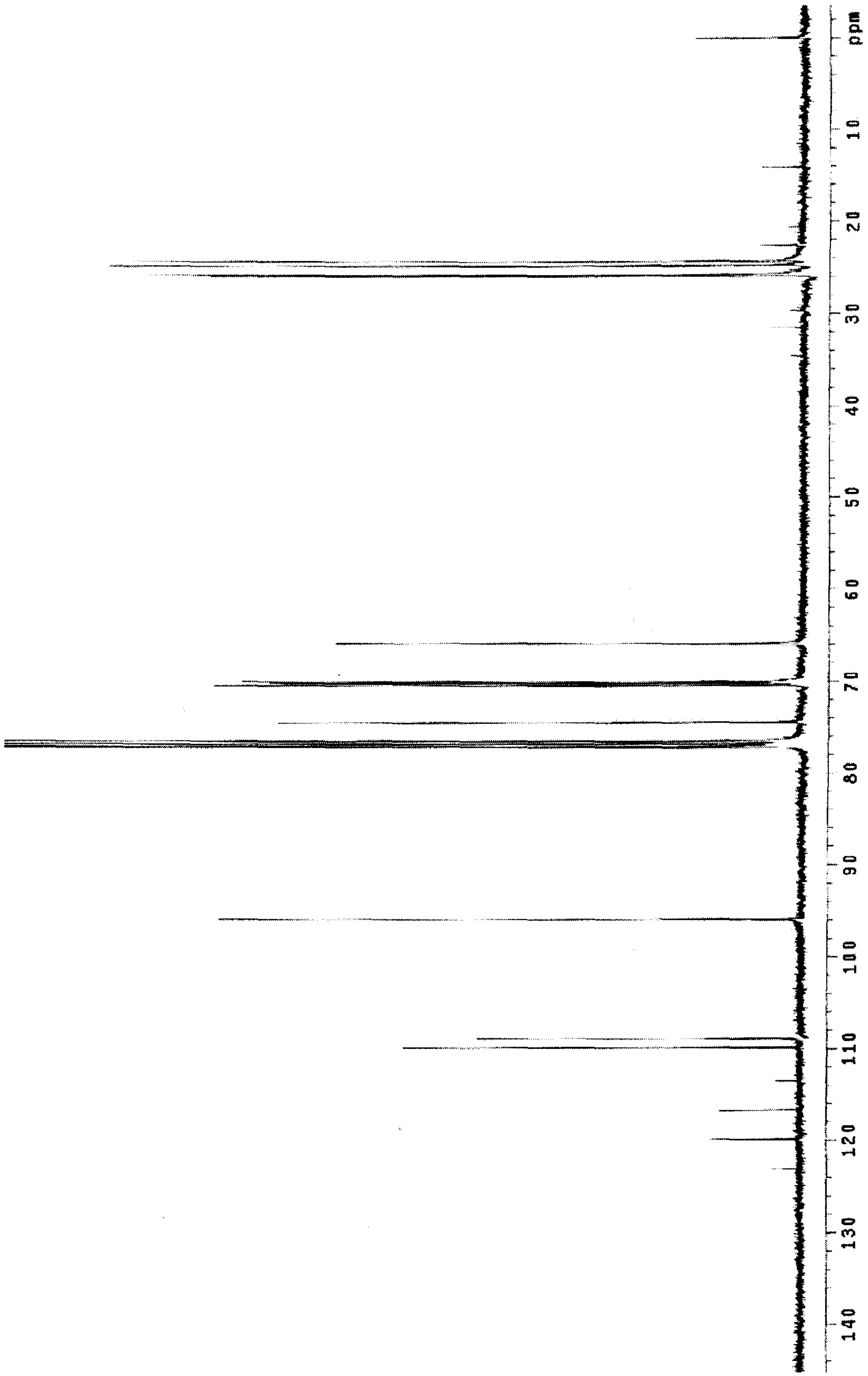


Figure 68. ^{13}C NMR of 28

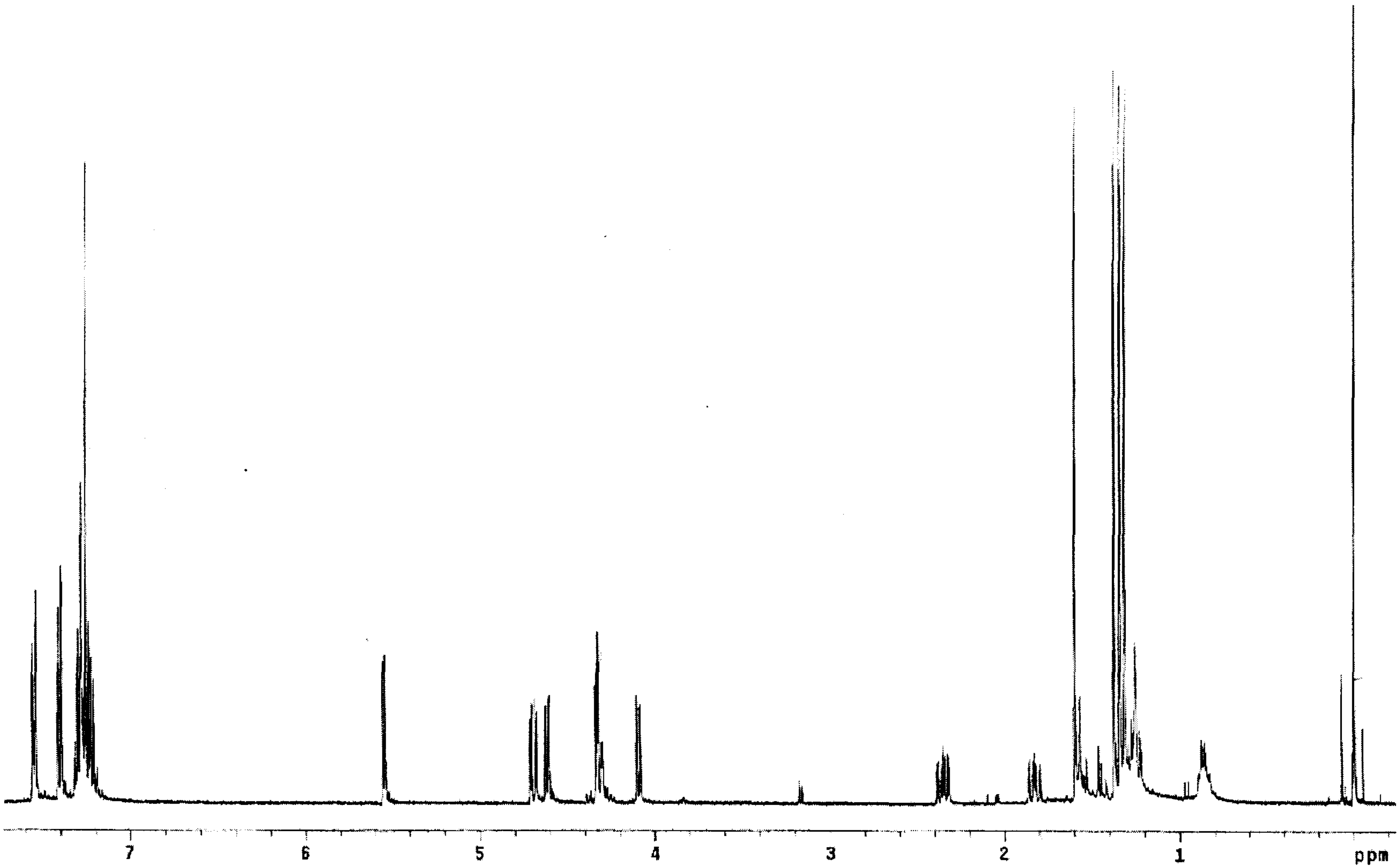


Figure 69. ^{1}H NMR of **29**

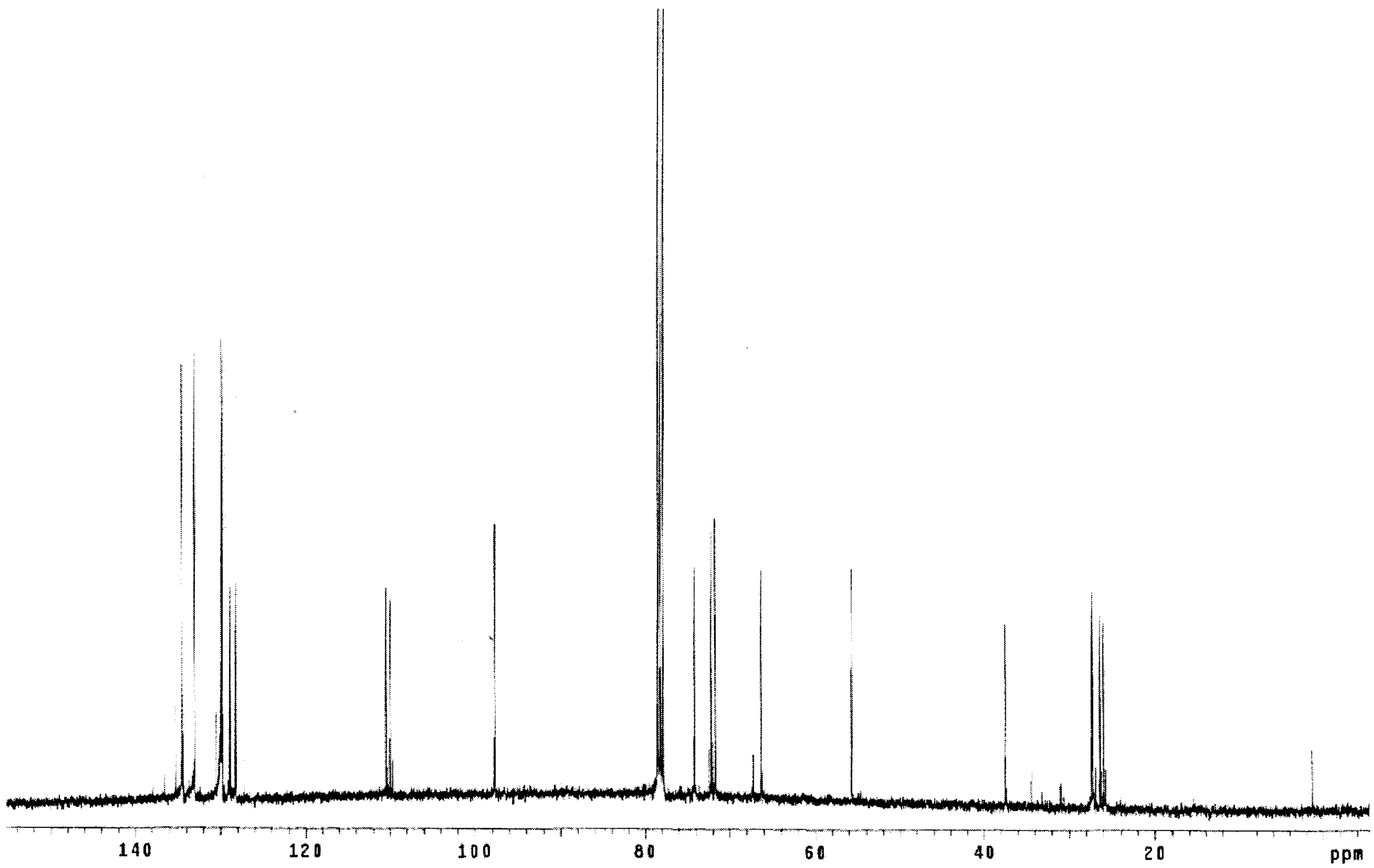


Figure 70. ^{13}C NMR of **29**

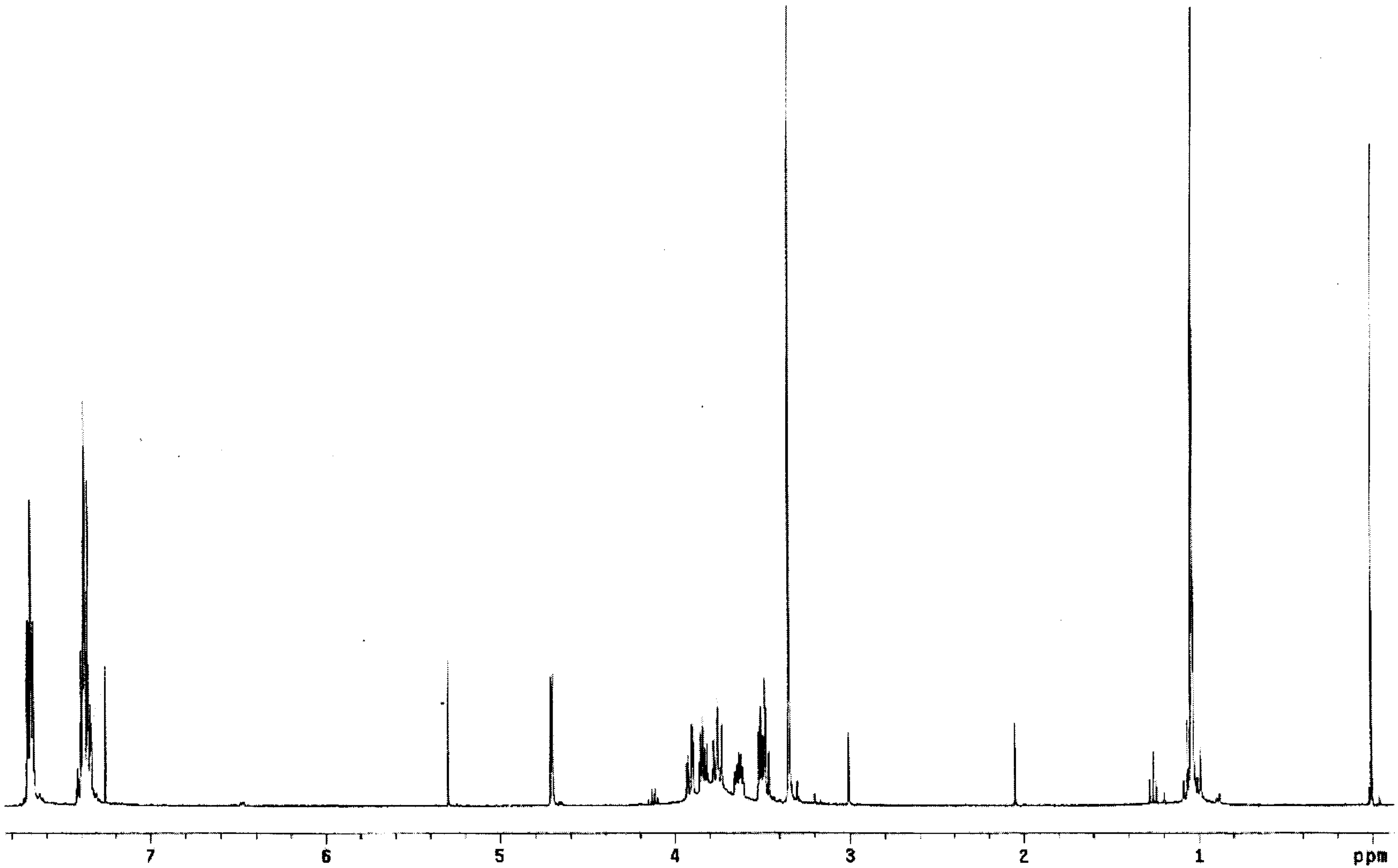


Figure 71. ^{1}H NMR of **31**

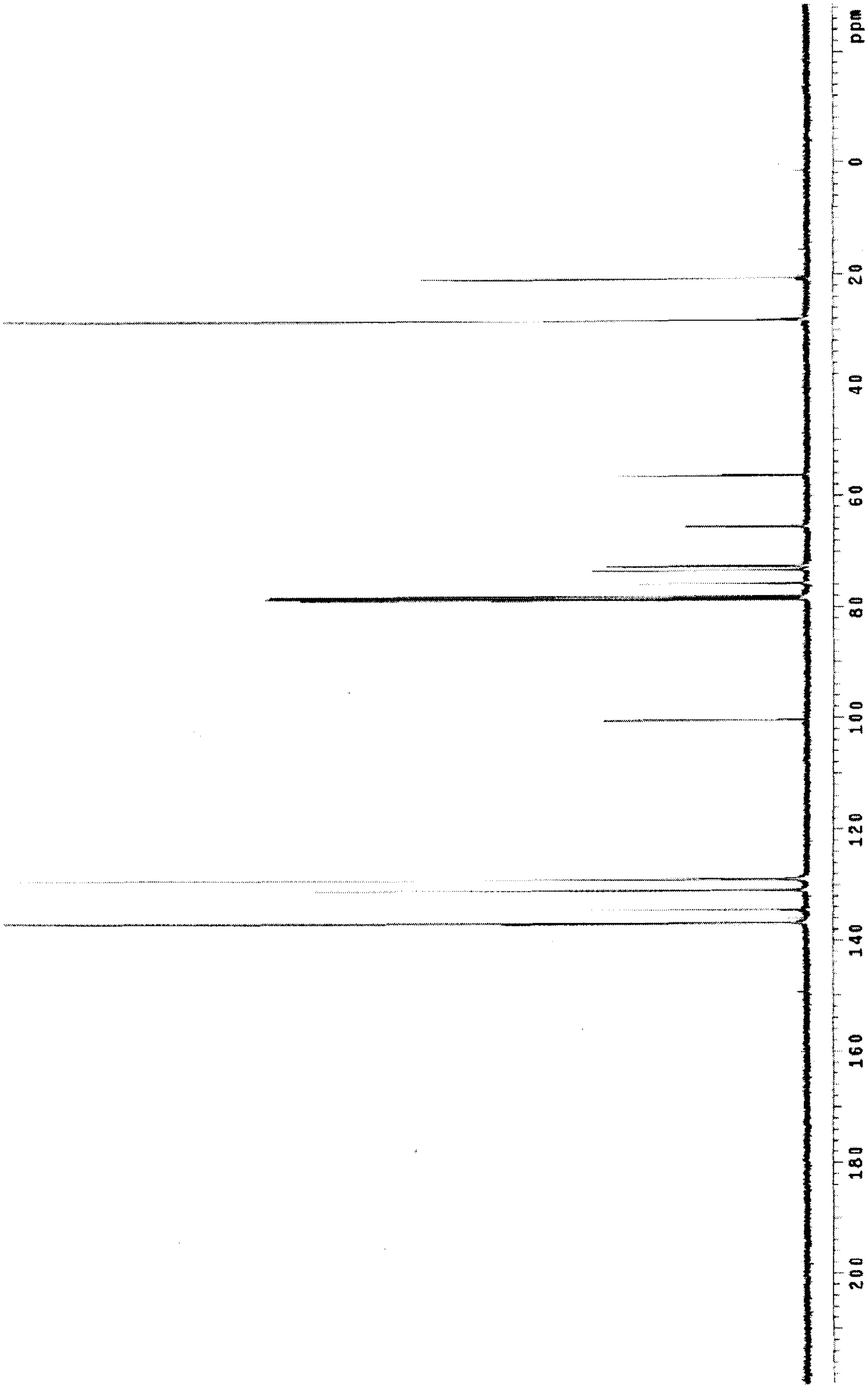
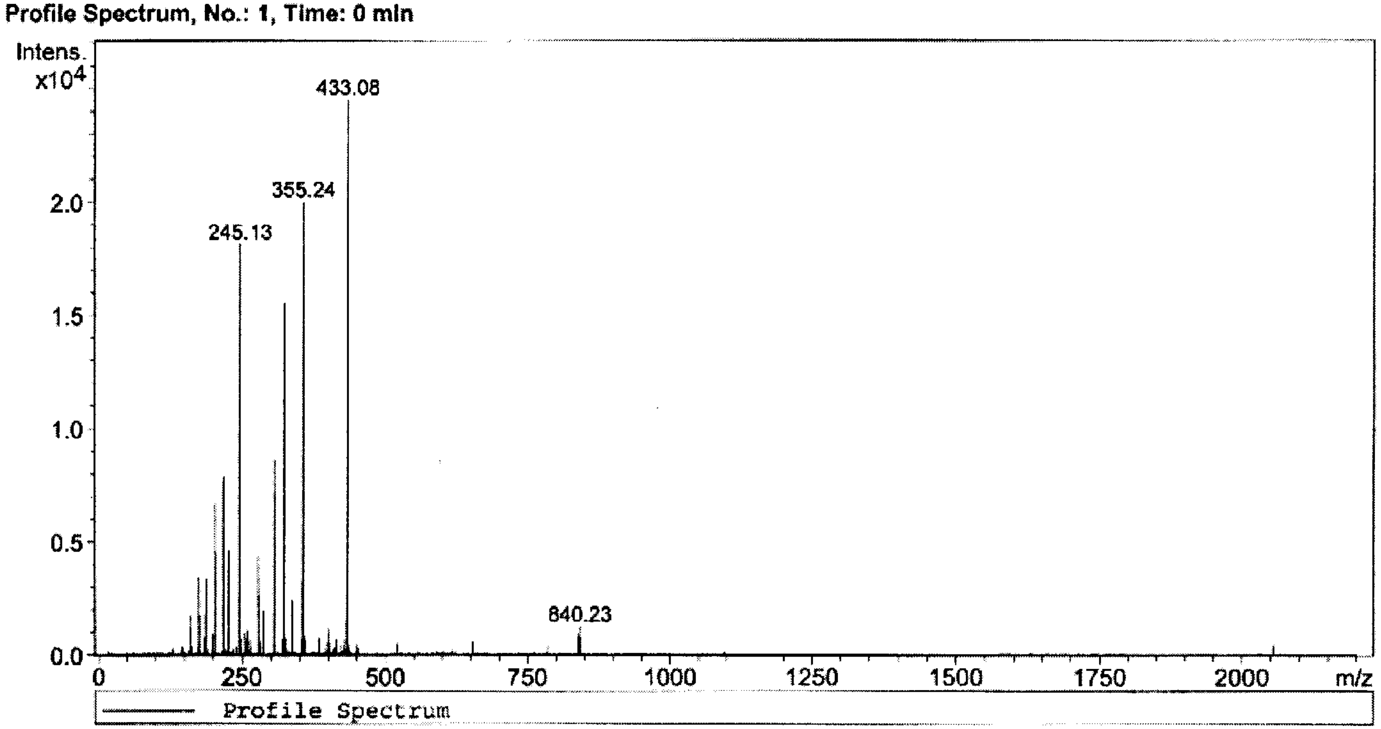


Figure 72. ^{13}C NMR of 31



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
161.08	1754	0.40	277.15	4417	0.30	355.95	2510	0.20
175.13	3419	0.20	287.16	1964	0.30	398.62	1195	0.20
187.08	3348	0.20	305.18	8633	0.20	430.77	1612	0.20
203.14	6708	0.30	323.17	15565	0.30	432.35	13940	0.30
217.15	7891	0.30	337.11	2373	0.40	433.08	24543	0.60
227.06	4607	0.30	354.15	3240	0.20	433.91	1898	0.20
245.13	18185	0.20	354.57	5444	0.10	840.23	1296	0.20
259.10	1079	0.30	355.24	20059	0.30			

End of report

Figure 73. Mass Spectrum of **31**

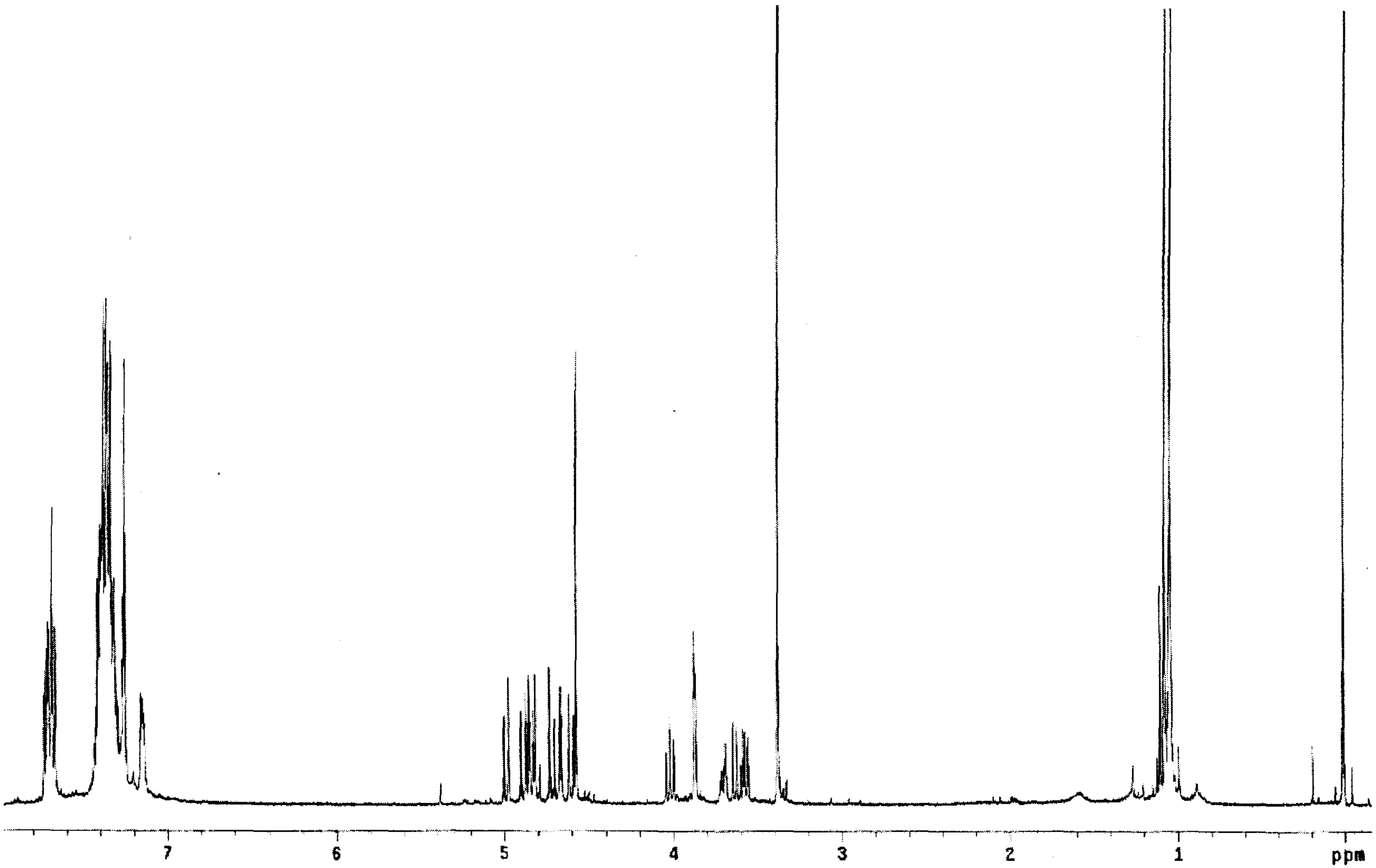


Figure 74. ^{1}H NMR of **32**

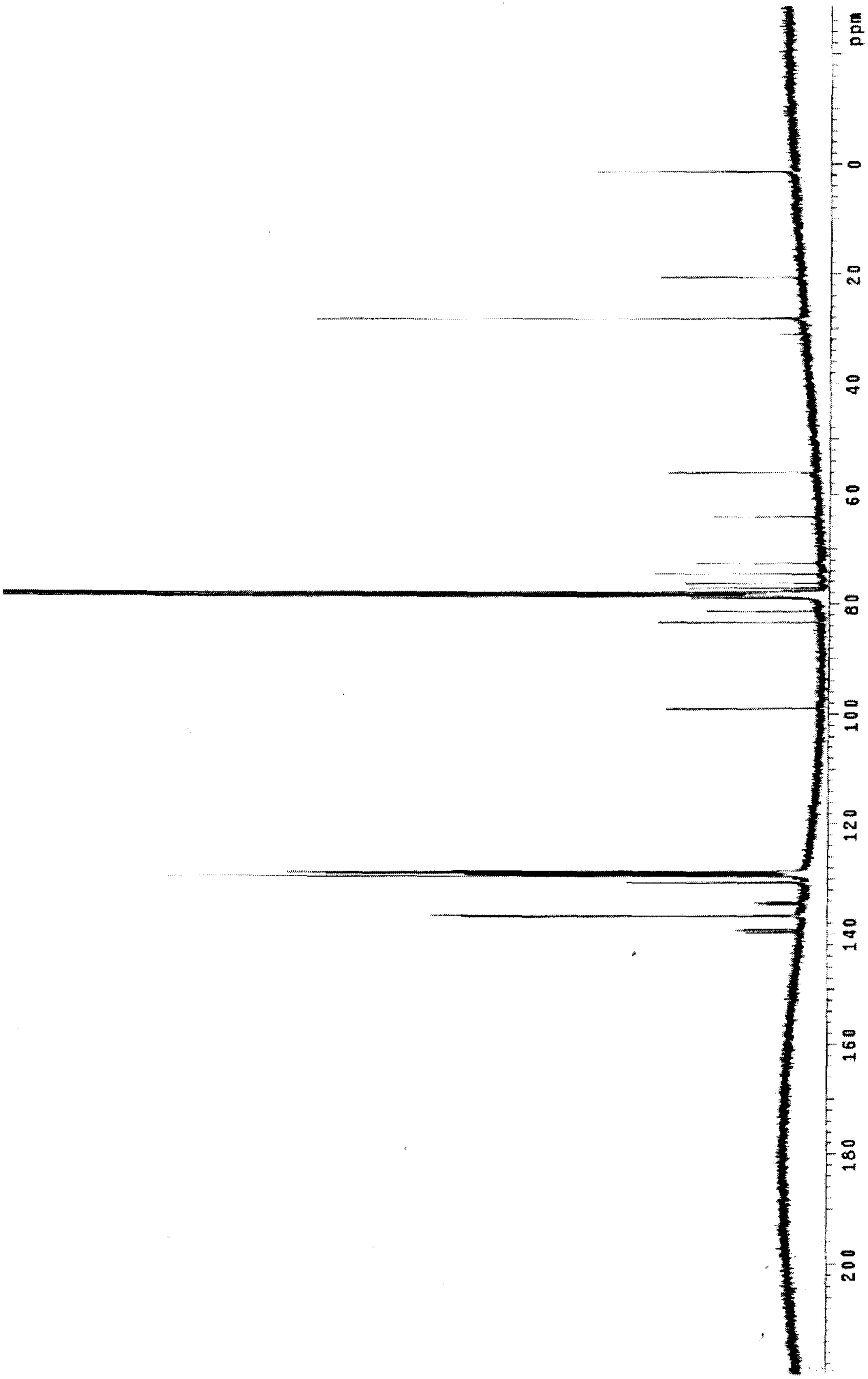


Figure 75. ^{13}C NMR of 32

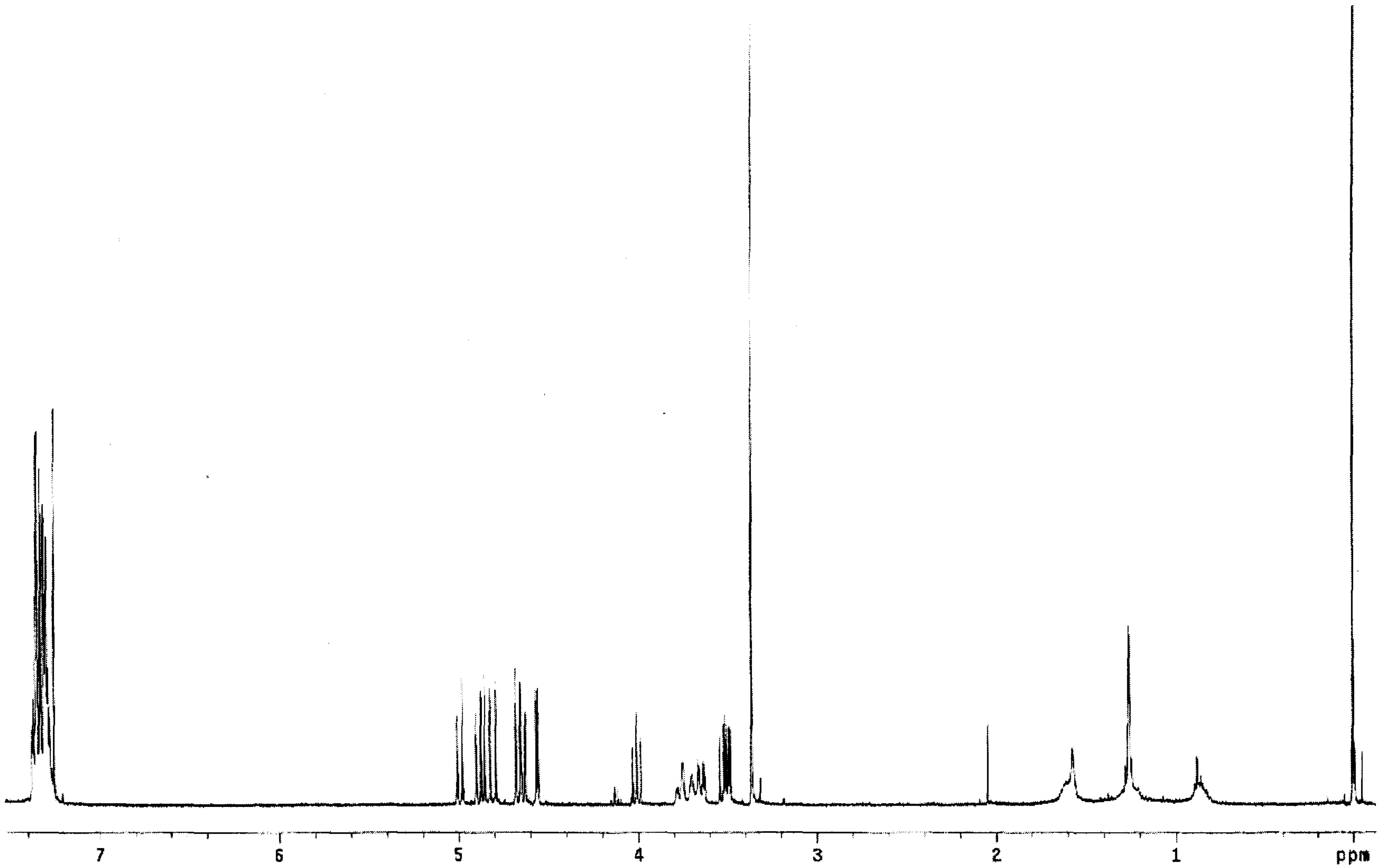


Figure 76. ^{1}H NMR of **33**

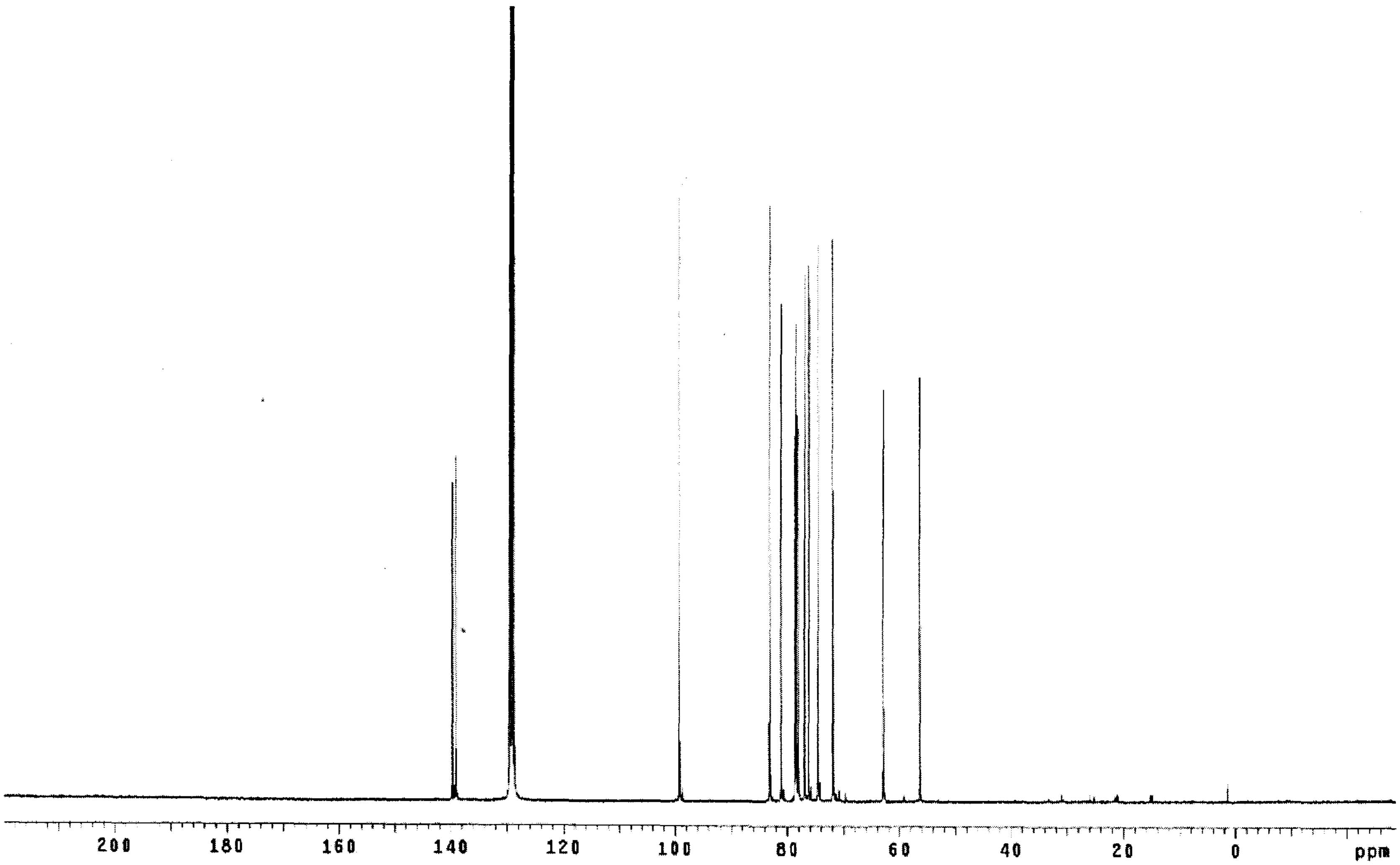


Figure 77. ^{13}C NMR of **33**

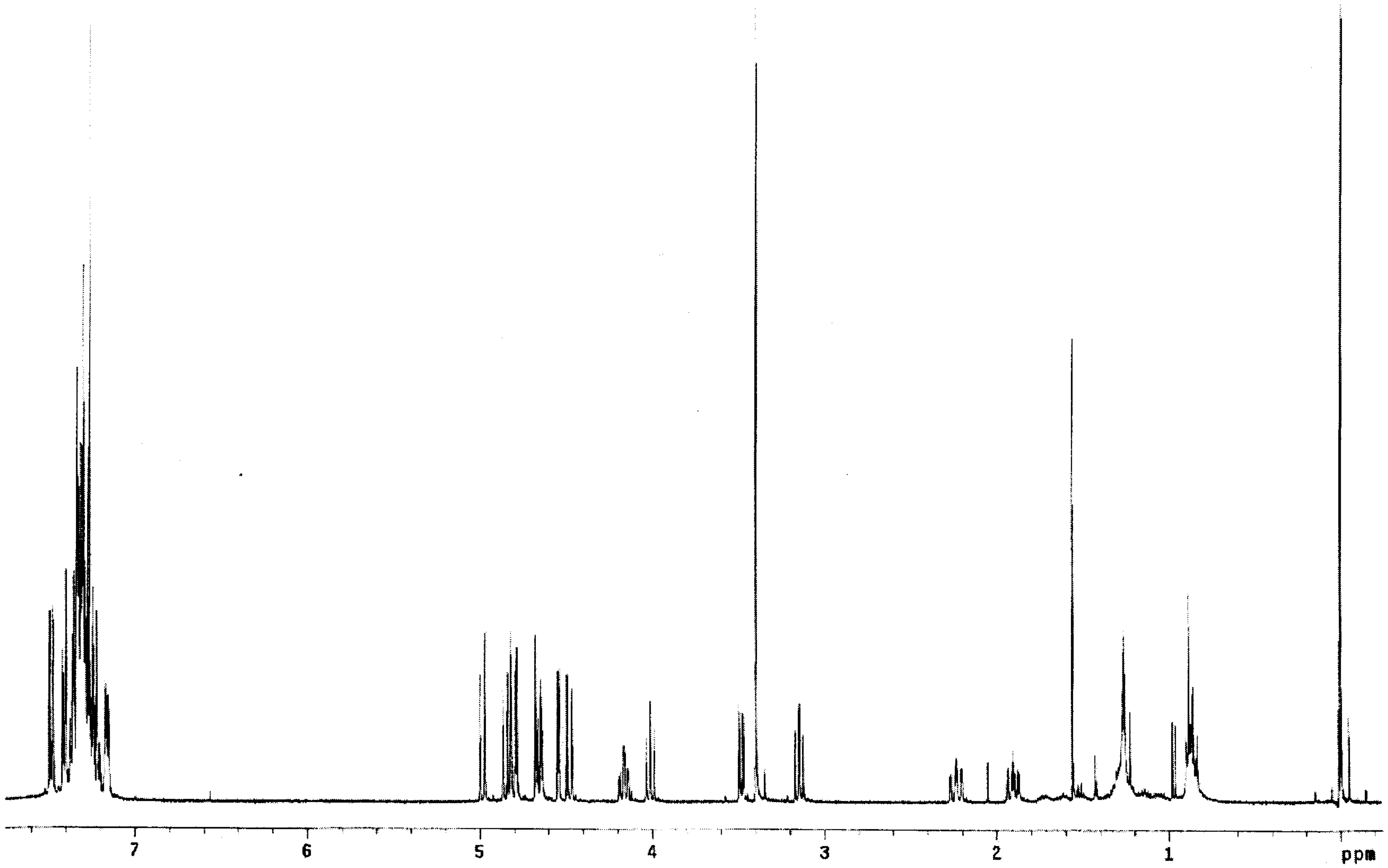


Figure 78. ^{1}H NMR of **35**

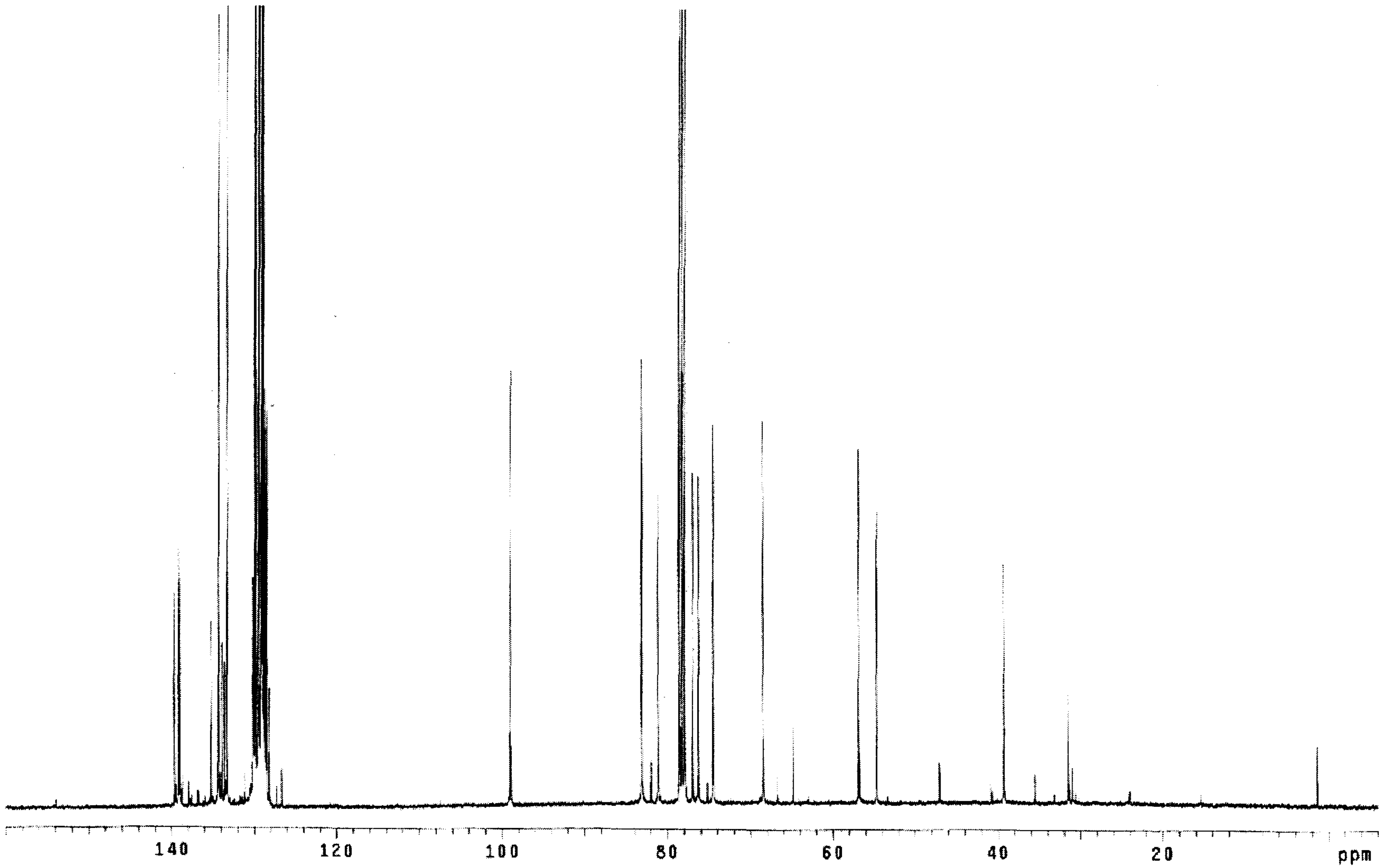


Figure 79. ^{13}C NMR of **35**