Chemical Synthesis of Terpenoid *O*-Glycosides

by

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Thesis Abstract

The following work describes new synthetic routes toward terpenoid-*O*-glycosides. Two different approaches have been studied to add terpene functionality to the anomeric position of a D-Glucose. Firstly, a variety of glycosyl halides were investigated as intermediates to produce the C-O bond at the anomeric position. The second approach incorporated the classic Fischer glycosylation with protected and unprotected sugars reacting with terpene alcohols.

Acknowledgements

I would like to dedicate this to my daughter Devin who has given me inspiration and joy for the last two and half years, I thank you. I would like to thank the Department of Chemistry and the School of graduate studies for allowing me the chance to pursue this degree. For the many questions I asked and for being a part of my thesis committee, I thank Dr. Smiley and Dr. Jackson. I would also like to thank Dr. Levinson for the time he spent on obtaining mass spectra.

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Table of Contents

Title Page..i

Signature Page..ii

Abstract..iii

Acknowledgements..iv

Table of Contents..v

List of Figures..vi

Introduction..1

Statement of Problem..10

Results and Discussion..11

1. Formation of Glycosyl Halides..11
2. *O*-Glycosylations with Simple Alcohols..17
3. *O*-Glycosylations with Terpene Alcohols..21
4. Fischer *O*-Glycosylations with Terpene Alcohols..24

Conclusions..29

Experimental..30

References..45

Appendix..47

List of Figures

Figure 1 Different forms of D-Glucose........2

Figure 2 Fischer Glycosylation........3

Figure 3 Lemieux's Method of Glycosyl Halide Formation........4

Figure 4 Nucleophilic Attack........4

Figure 5 Synthesis of *O*-Glycosides........5

Figure 6 Amygdalin........5

Figure 7 Isoprene Units........6

Figure 8 Classifications of Monoterpenes........7

Figure 9 Protected Terpene-*O*-glycoside........8

Figure 10 Unprotected Terpene-*O*-glycoside........9

Figure 11 ^{1}H NMR Spectrum of Compound **2**........48

Figure 12 ^{13}C NMR Spectrum of Compound **2**........49

Figure 13 ^{1}H NMR Spectrum of Compound **4**........50

Figure 14 ^{13}C NMR Spectrum of Compound **4**........51

Figure 15 ^{1}H NMR Spectrum of Compound **5**........52

Figure 16 ^{13}C NMR Spectrum of Compound **5**........53

Figure 17 ^{1}H NMR Spectrum of Compound **6**........54

Figure 18 ^{1}H NMR Spectrum of Compound **7**........55

Figure 19 ^{1}H NMR Spectrum of Compound **9**........56

Figure 20 ^{13}C NMR Spectrum of Compound **9**........57

Figure 21 Mass Spectrum of Compound **9**........58

Figure 22 ^{1}H NMR Spectrum of Compound **10**........59

Figure 23 ^{13}C NMR Spectrum of Compound **10**..60

Figure 24 Mass Spectrum of Compound **10**..61

Figure 25 ^{1}H NMR Spectrum of Compound **11**..62

Figure 26 ^{1}H NMR Spectrum of Compound **12** from Compound **4**..................63

Figure 27 ^{13}C NMR Spectrum of Compound **12** from Compound **4**..................64

Figure 28 Mass Spectrum of Compound **12** from Compound **4**........................65

Figure 29 ^{1}H NMR Spectrum of Compound **12** from Compound **13**..................66

Figure 30 ^{13}C NMR Spectrum of Compound **12** from Compound **13**..................67

Figure 31 Mass Spectrum of Compound **12** from Compound **13**........................68

Figure 32 ^{1}H NMR Spectrum of Compound **17**..69

Figure 33 ^{13}C NMR Spectrum of Compound **17**..70

Figure 34 Mass Spectrum of Compound **17**..71

Figure 35 Mass Spectrum of Compound **17**..72

Figure 36 ^{1}H NMR Spectrum of Compound **18**..73

Figure 37 ^{13}C NMR Spectrum of Compound **18**..74

Figure 38 Mass Spectrum of Compound **18**..75

Figure 39 ^{1}H NMR Spectrum of Compound **19**..76

Figure 40 ^{13}C NMR Spectrum of Compound **19**..77

Figure 41 Mass Spectrum of Compound **19**..78

Figure 42 ^{1}H NMR Spectrum of Compound **20**..79

Figure 43 ^{13}C NMR Spectrum of Compound **20**..80

Figure 44 Mass Spectrum of Compound **20**..81

Figure 45 ^{1}H NMR Spectrum of Compound **21**..82

Figure 46 ^{13}C NMR Spectrum of Compound **21**..83
Figure 47 Mass Spectrum of Compound **21**.. 84
Figure 48 ^{13}C NMR Spectrum of Compound **22**..85
Figure 49 Mass Spectrum of Compound **22**..86
Figure 50 ^{1}H NMR Spectrum of Compound **23**..87
Figure 51 Mass Spectrum of Compound **23**...88
Figure 52 ^{1}H NMR Spectrum of Compound **25** from Compound **24**....................89
Figure 53 Mass Spectrum of Compound **25** from Compound **24**..........................90
Figure 54 ^{1}H NMR Spectrum of Compound **18** from Compound **24**....................91
Figure 55 ^{13}C NMR Spectrum of Compound **18** from Compound **24**....................92

Introduction

In the past few decades a subdivision of organic chemistry involving the carbohydrates has seen an increase in importance from a chemical and biological point of view. It has been understood that these molecules play vital roles in the food, agrochemical and medicinal fields. They were first categorized in detail by Emil Fischer in the late 1800's but since the 1970's the development of carbohydrate chemistry has been phenomenal due in part to advances in spectroscopy.[1] Other reasons for the growth in interest include the concept that carbohydrates can be used as synthons for the synthesis of new chiral compounds that are significant in the bioorganic field. Synthetic organic chemists find it useful to use carbohydrates as inexpensive, readily available, optically pure starting materials.[2]

The pharmaceutical industry is extremely interested in ways to develop enantioselective syntheses of a potential drug. Racemic drugs are on the decline because they are found in two different forms in the biological system, one of which may have the desired properties and the other that is potentially hazardous. One way to achieve an enantioselective reaction is to use a chiral starting material, the least expensive of which is sucrose. Sucrose is a carbohydrate but hasn't yet proved to be valuable in this respect. However, organic chemists value glucose as well as other inexpensive sugars for their use as building blocks for many important carbohydrate and non-carbohydrate chiral products.[3]

D-Glucose belongs to the family of monosaccharides, which mainly consists of five- and six-carbon compounds with a certain number of hydroxyl groups attached. Organic chemists find it very useful to incorporate these simple sugars into their

chemistry because monosaccharides in solution can interconvert between three different forms (Figure1). The central molecule (Figure 1-**A**) is in the *aldehydo* form. If the *aldehydo* form cyclizes from nucleophilic attack from the –OH group at carbon five, a six-membered ring results to give the pyranose form (Figure 1:**B**,**C**). However, if the *aldehydo* form undergoes nucleophilic attack from the –OH group at carbon four, the sugar cyclizes to a five-membered ring to give the furanose form (Figure 1:**D**,**E**). Configurations of the hydroxyl groups play important roles in the type of chemistry the sugar undergoes. Alpha (α) configurations are given to the sugars (Figure 1:**B**,**D**) when the hydroxyl group at the anomeric position is in the axial position, while beta (β) configurations are given to sugars (Figure 1:**C**,**E**) when the anomeric hydroxyl is equatorial.[4] Interconversion between these anomers (mutarotation) is very rapid in the presence of either an acid or a base.

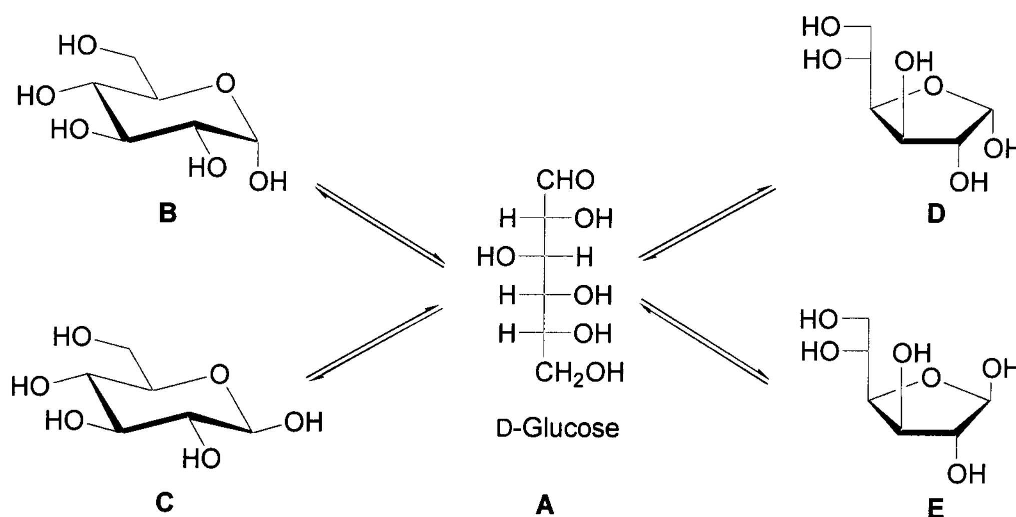


Figure 1

C-1 of the sugar molecule, the anomeric position, is particularly reactive and a glycoside is formed when something other than a hydroxyl is attached to the anomeric

carbon. When free hydroxyl sugars are treated with an alcohol in the presence of an acid, an *O*-glycoside is formed. This is known as the Fischer glycosylation, which is one of the simplest ways to prepare these types of glycosides. Mechanistically the *aldehydo* form reacts with the alcohol to give a hemiacetal, then eventually a full acetal.[5] The resulting *O*-glycosides are in the α (Figure 2-**A**) and the β (Figure 2-**B**) forms with respect to the anomeric position. The major anomer that results is determined by steric hindrance, the chemical nature of the "R" groups and a phenomenon known as the anomeric effect.[6] This phenomenon occurs when the lone pair of electrons on the ring oxygen interacts with the σ* orbitals of the C-1-*O* bond to favor the α configuration in most cases (Figure 2-**A**).[7]

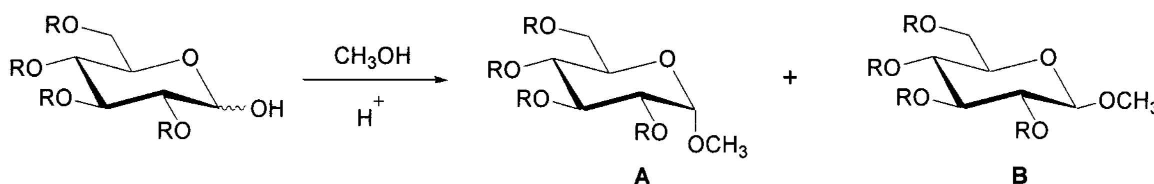


Figure 2

To introduce functionality at the anomeric position, glycosyl halides are readily prepared as intermediates, and in the presence of a metal promoter, further functionality can be introduced.[8] Usually glycosyl halides are activated as glycosyl donors by metal chelation and the stereochemical outcome is dictated by the anomeric effect or the nature of the protecting group at C-2. A less common displacement occurs when the halide undergoes S_N2 reaction by an incoming nucleophile.[9]

From a historical point of view, glycosyl halides were first observed through synthesis by Reiche and Gross in 1959. This involved the treatment of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose with dichloromethyl methyl ether (DCMME) to give tetra-*O*-

acetyl-α-D-glucopyranosyl chloride.[10] A more useful synthesis of this glycosyl halide was achieved in 1963 by R. U. Lemieux, which involved reacting β-D-glucopyranose pentaacetate (Figure 3-**A**) with titanium tetrachloride to yield crystalline tetra-*O*-acetyl-α-D-glucopyranosyl chloride (Figure 3-**B**).[11]

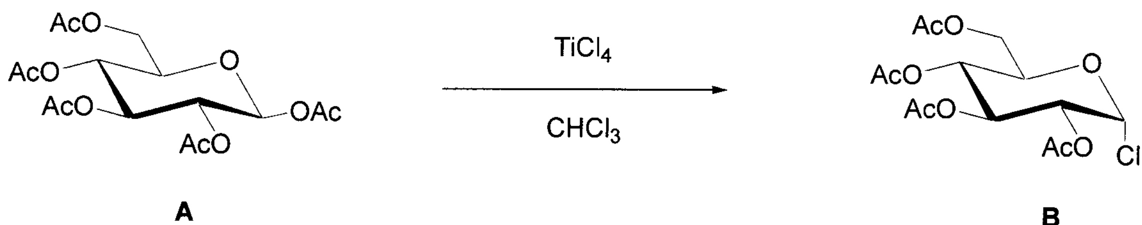


Figure 3

The protecting group at C-2 plays a vital role in which orientation results for the substituent at C-1 if the reaction involves a carbocation at the anomeric carbon. If the protecting group at C-2 of a *gluco* starting material is an ester group then an incoming nucleophile usually enters from the equatorial position resulting in a beta product (Figure 4). This is due to a lone pair of electrons on the ester group at C-2 stabilizing the carbocation, hence blocking the nucleophile's approach from the axial position. Protecting groups like benzyl groups at C-2 that do not help stabilize the carbocation intermediate may result in both alpha and beta product orientations.[12]

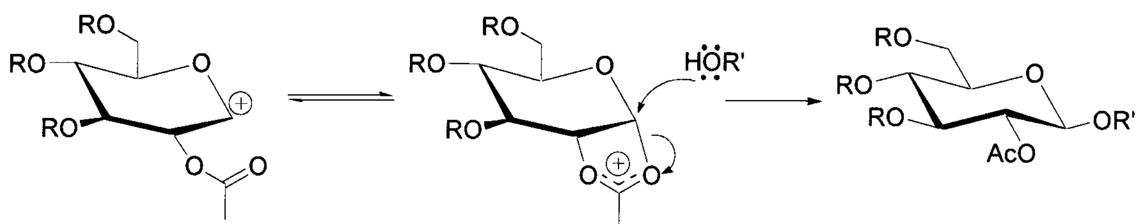


Figure 4

In 1901 the Koenigs-Knorr method was introduced as a way to exchange the anomeric hydroxyl group with bromine or chlorine in the first step of preparing an *O*-glycoside. The second step reacted the glycosyl halide in the presence of a metal promoter such as a silver salt and an alcohol to give the desired product (Figure 5).[13]

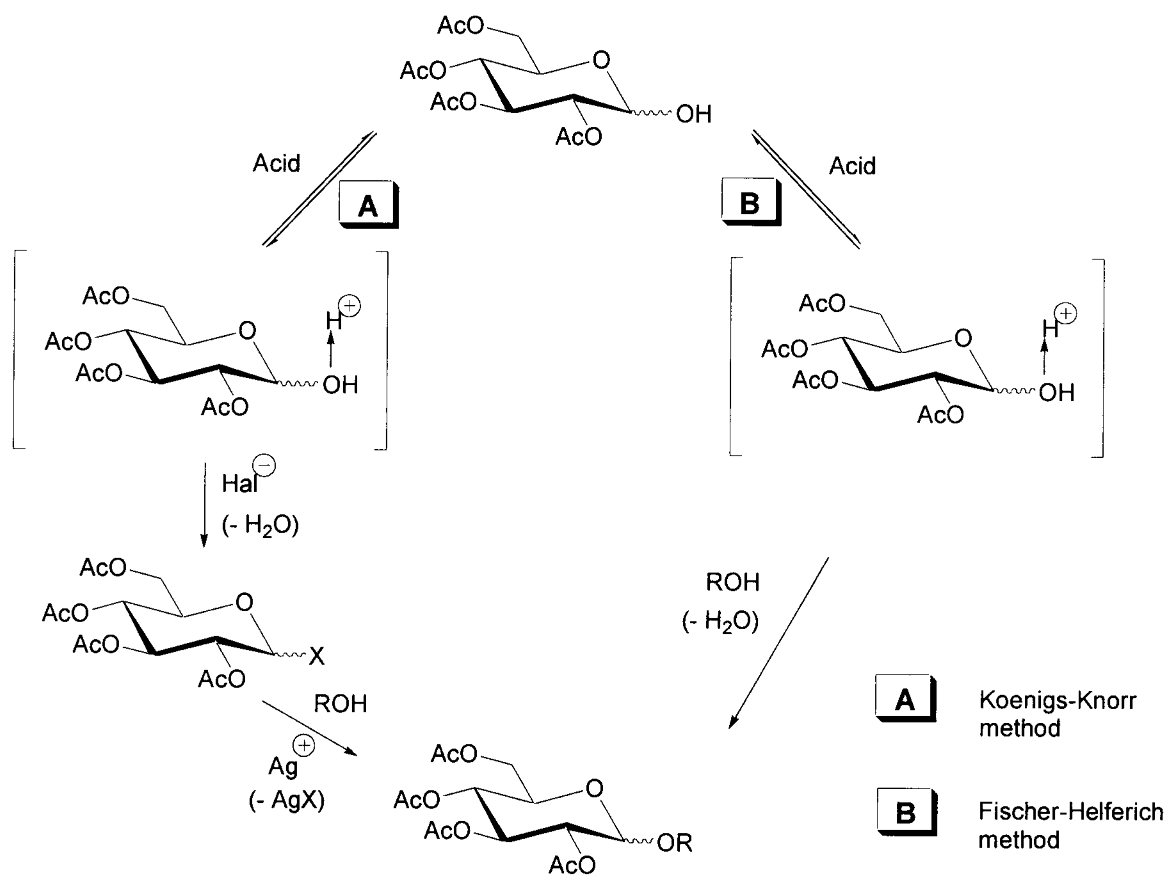


Figure 5 Synthesis of *O*-glycosides

O-Glycosides primarily evolved in nature from plants. Even though these sugars can be bound to other carbohydrates or even proteins and lipids, *O*-glycosides can also be found glycosidically attached to a broad range of other substances. This results in distinct roles that the sugar can perform in nature. For example amygdalin (Figure 6) is an important cyanogenic glycoside because it has gained prominence as a cancer

chemotherapeutic agent. Hydrogen cyanide is spontaneously released upon enzymatic hydrolysis resulting in the desired biochemical consequence that it has on cancer cells. However it has not yet been approved by the FDA for drug use.[14]

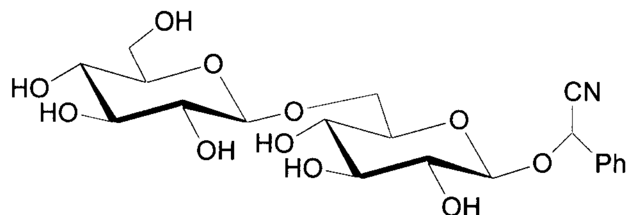


Figure 6 Amygdalin

Terpenes are primarily plant products, which are involved in a broad range of areas. They are commonly found in the perfume and food industries due to their pleasant odors and distinct flavors. Terpenes are the precursors to steroids and terpeniods and more importantly they are found to be primary regulators of cellular processes. On the inter-organismic level, terpenoid compounds (e.g. Vitamins A and E) play essential roles in maintaining a species' very existence.[15] Terpenes are molecules that consist of C-5 isoprene units (Figure 7), and the number of isoprene units dictates the class to which the terpene belongs.

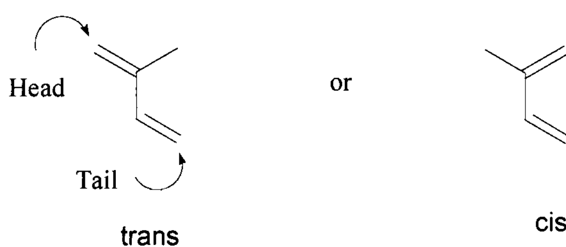


Figure 7 Isoprene units

Monoterpenes are the simplest form of terpenes. They consist of two isoprene units joined together directly or indirectly *via* a self condensation thus making the molecule ten carbons in length. These are the terpenes responsible for the pleasant odors

found in many plant secretions. Monoterpenes are categorized as 'acyclic' (Figure 8-**A**), 'monocyclic' (Figure 8-**B**), 'bicyclic' (Figure 8-**C**) and 'irregular' (Figure 8-**D**). Terpenes are synthesized in nature by the plant and animal kingdoms. The discovery of mevalonic acid (MVA) as a precursor to the steroid and terpenoid families brought great insight into the synthesis of monoterpenes. This approach was then applied to the synthesis of more complex terpenes such as diterpenes (twenty carbons, four isoprene units), triterpenes (thirty carbons, six isoprene units), and tetraterpenes (forty carbons, eight isoprene units). When MVA reacts with ATP the most important precursors to terpene synthesis results, which are isopentyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). When IPP and DMAPP come in contact with a base, a nucleophilic substitution reaction takes place to give geranyl pyrophosphate,[16] which is the major precursor to all acyclic, monocyclic, and bicyclic monoterpenes.[17]

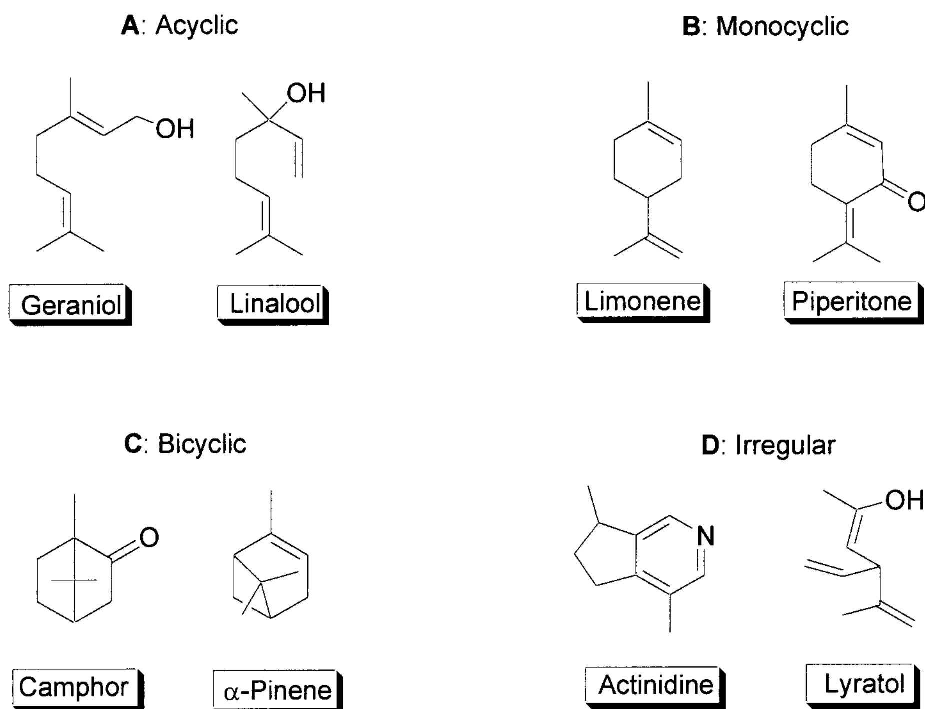


Figure 8 Classifications of Monoterpenes

Another class of plant sugars that occur in nature are compounds known as terpene-*O*-glycosides. These types of compounds are known to have certain biochemical and flavor properties and, from a pharmaceutical point of view, terpene-*O*-glycosides have been found to be enzyme inhibitors. A key enzyme in diabetic complications such as cataract formation is known to be aldose reductase and the acetylated forms (Figure 9) of certain terpene-*O*-glycosides have been shown to inhibit this enzyme.[18]

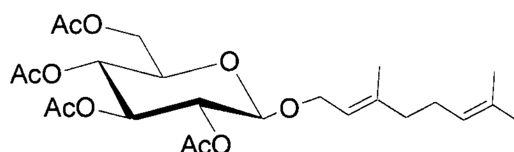


Figure 9 Protected Terpene-*O*-glycoside

Terpene glycosides are important contributors to the flavor of many classes of wines. Although many forms of terpene glycosides can exist, the most abundant are the β-D-glucopyranosides of geraniol, nerol and linalool.[19] Three categories of monoterpene alcohols exist in grapes: the free aroma, the polyhydroxylated form and the glycosidically conjugated form. The free aromas include such terpenes as nerol, geraniol, and linalool. The polyhydroxylated form is known to be odorless until it breaks down to the oxide and diol form. The glycosidically conjugated form of the monoterpenes is the most abundant in the wine, however they do not contribute to the aroma of the wine as much as the free aroma form does. It has been shown that the flavor threshold of nerol is three to four times higher than that of linalool.[20]

Terpene glycosides can break down to form the free aroma terpene alcohols that are responsible for taste and aroma through different pathways. One such way is through

acid-catalyzed hydrolysis at a specific temperature and pH. At a typical wine pH (3.0) and at room temperature, geranyl glucopyranoside (Figure 10) undergoes hydrolysis that results in fourteen different compounds, some of which are the free aroma terpene alcohols.[21]

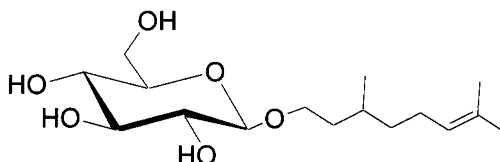


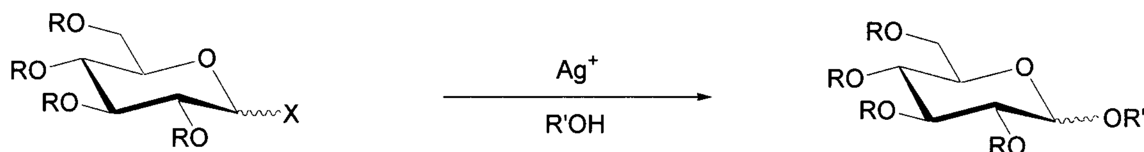
Figure 10

The use of enzymes such as β-glycosidases also plays a role in liberating the terpene alcohol from the sugar. The four main yeasts that contain β-glycosidases are *Kloeckera apiculata, Metshnikowia pulcherrima, Saccharomyces cereviae, and Piichia anomala.* However, the only yeasts that participate in the liberation of the terpene alcohol are the non-*Saccharomyces* yeasts. Each of these three yeasts also play a role in the specific characteristics the wine has. Certain yeasts will liberate certain alcohols at certain concentration thus giving the wine a different flavor and odor.[22]

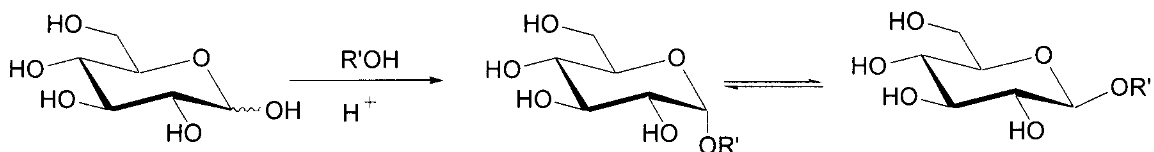
Statement of the Problem

Since discovering which yeasts yield the best flavor in wines, it can be hypothesized that by manipulating the terpene-*O*-glycosides, these wines will take on different properties in aroma and taste. Biochemists have successfully isolated these terpene glycosides and have also prepared them through enzymatic synthesis. However, few preparations have been attempted from a synthetic organic point of view.

We have selected two different approaches towards synthesizing these terpene glycosides from both monosaccharides and disaccharides. Firstly, we utilized the Koenigs-Knorr method of displacing a glycosyl halide in the presence of a metal promoter. Since the halide is a good leaving group at C-1, the carbocation intermediate that results can then trap the terpene alcohol, producing the *O*-glycoside (Equation 1). The second approach we attempted involved the classic Fischer glycosylation, which reacts the *aldehydo* form of the sugar with a terpene alcohol to produce the desired *O*-glycoside (Equation 2).



Equation 1



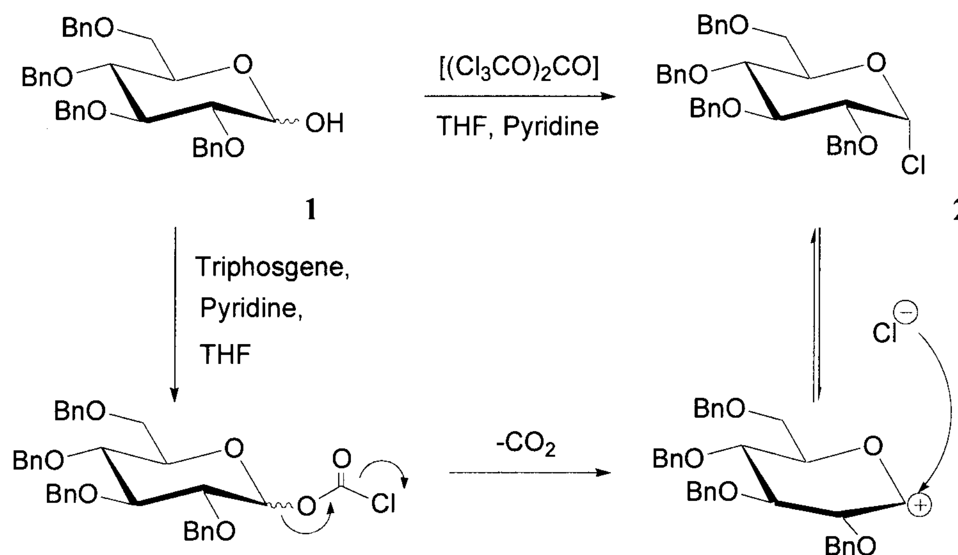
Equation 2

Results and Discussion

1. Formation of Glycosyl Halides

The major objective of this research was to synthesize *O*-glycosides *via* glycosyl halide intermediates. Several different synthetic pathways have been investigated to synthesize glycosyl halides since halides are known to be good leaving groups. This approach has been chosen to introduce further functionality at the anomeric position, specifically an oxygen-carbon bond.

This project began with converting 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) into 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**2**) through a stereospecific S_N1 reaction pathway (Scheme 1).

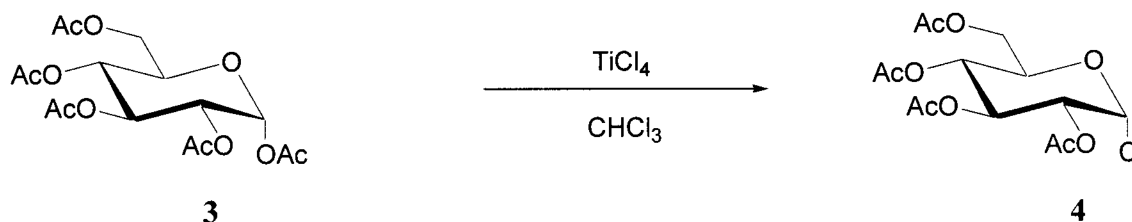


Scheme 1 Chlorination of **1** using Triphosgene

By utilizing triphosgene [$(Cl_3CO)_2CO$] as the chlorine source, an acyl substitution followed by a nucleophilic displacement reaction occurs at the anomeric position. This reaction was followed by TLC to ensure the consumption of the starting material (**1**, R_f = 0.21 in 3:1 hexane:ethyl acetate) and the formation of the desired product (**2**, R_f = 0.64 in

3:1 hexane:ethyl acetate). A doublet at 6.05 ppm with a J value of 3.9 Hz is seen in the ^{1}H NMR spectrum of **2**, which indicates that the anomeric proton, H-1, is further downfield than the H-1 of the starting material **1**. A J value of 3.9 Hz indicates that the dihedral angle between H-1 and H-2 is small thus implying that the chlorine atom occupies the axial position at C-1 of **2**.

In attempts to produce several glycosyl halides that might be used as intermediates, a different pathway was considered. Lemieux's method (Equation 3) was chosen in which β-D-glucopyranose pentaacetate (**3**) reacts with titanium tetrachloride to yield the acetate-protected glycosyl halide **4** when refluxed in chloroform.

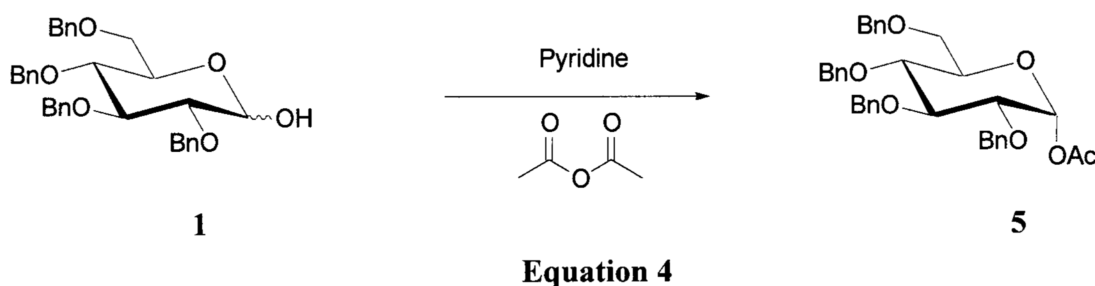


Equation 3

The reaction was monitored by TLC to ensure completeness and consumption of **3** (R_f = 0.48 in 1:1 hexane:ethyl acetate). This method afforded **4** in an overall yield of 63% (R_f = 0.58 in 1:1 hexane:ethyl acetate) in an alpha configuration due to the anomeric effect. ^{1}H NMR indicated a doublet downfield at 6.28 ppm for H-1 because of its close proximity to a chlorine atom. It also showed the loss of an acetate signal at 2.06 ppm in the ^{1}H NMR spectrum and the loss of the corresponding C=O signal at 170.8 ppm in the ^{13}C NMR spectrum.

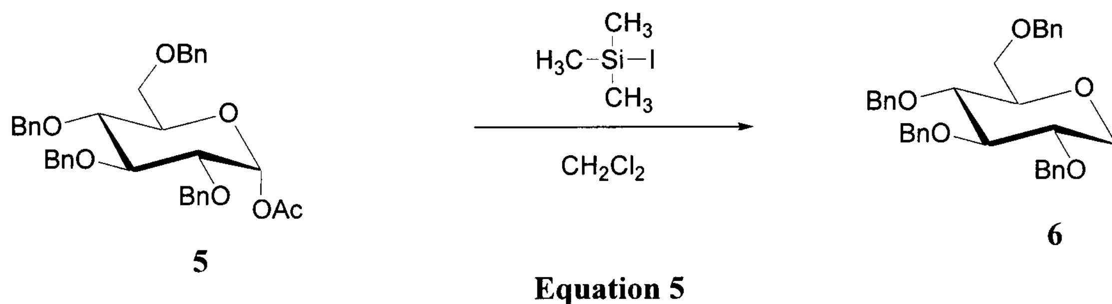
The third approach to synthesizing a glycosyl halide utilized Gervay's method, which involved the use of a glycosyl acetate as a precursor to the formation of a glycosyl iodide at C-1 (Equation 5).[23] The synthesis of the glycosyl acetate **5** began with reacting

1 with pyridine and acetic anhydride overnight at room temperature (Equation 4). The reaction was monitored by TLC which showed a less polar spot (**5**, Rf = 0.51 in 2:1 hexane:ethyl acetate) when compared to **1**. This is due to the replacement of the –OH at C-1 with an acetate group. Characterization of the compound by ^{1}H NMR showed the addition of a $-OCOCH_3$ group at 2.1 ppm in the α configuration and the addition of a peak at 170.4 ppm in the ^{13}C NMR spectrum. The *J* value for the coupling between H-1 and H-2 (the anomeric proton, which is located as a doublet at 6.41 ppm) is 3.7 Hz, which indicates a small dihedral angle between the H-1 and H-2.



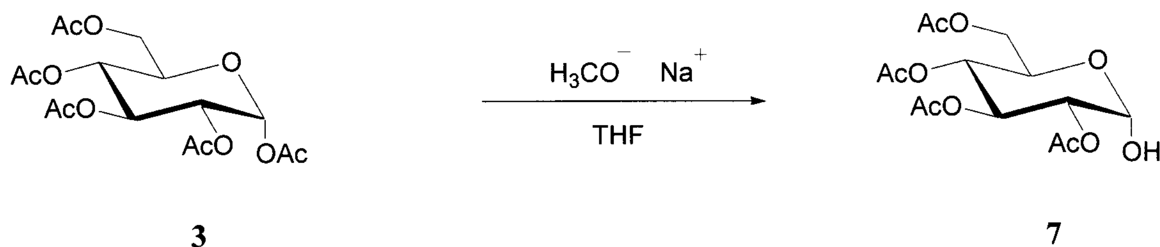
Equation 4

The newly formed glycosyl acetate **5** was then treated with trimethylsilyl iodide in methylene chloride at 0 °C (Equation 5) to produce the glycosyl halide **6**. The reaction mixture was followed by TLC until compound **6** (R_f = 0.55 in 3:1 hexane:ethyl acetate) was fully formed from the starting material. After the workup on the reaction mixture, ^{1}H NMR showed a doublet at 6.87 ppm and a *J* value for H-1 of 4.0 Hz. This indicates that the iodide on compound **6** is in the axial position. Later attempts at displacing these iodides proved to be ineffective due to the instabilities of the glycosyl iodides.



Equation 5

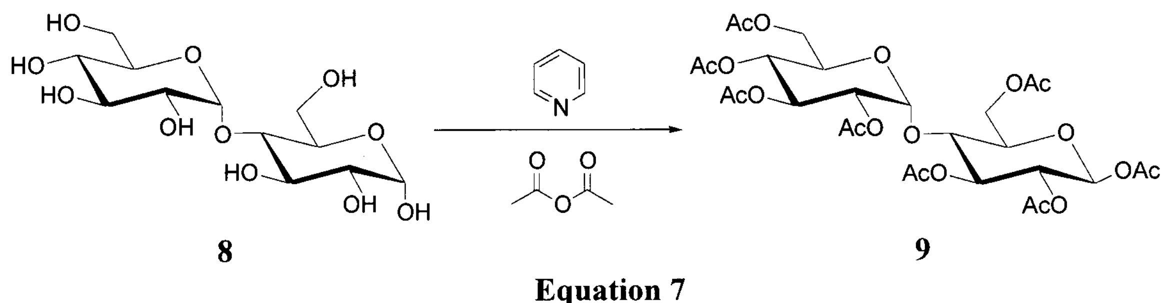
Glycosyl halide formation was also investigated on disaccharides. Maltose (**8**) is a readily available unprotected disaccharide that was considered to be a precursor to a disaccharide glycosyl halide. It was necessary to remove the protecting group at the anomeric position of the reducing end of a maltose precursor, however this deprotection was first practiced on a cheap monosaccharide (Equation 6). Deprotection at the anomeric position was accomplished by reacting β-D-glucose pentaacetate (**3**) with sodium methoxide and THF at –5 °C in an ice/salt/water bath to yield compound **7**. TLC (in 100% ethyl acetate) revealed one spot that was significantly more polar than that of compound **3**, the structure of which was confirmed with the disappearance of a CH_3 group at 2.10 ppm in the ^{1}H NMR spectrum.



Equation 6

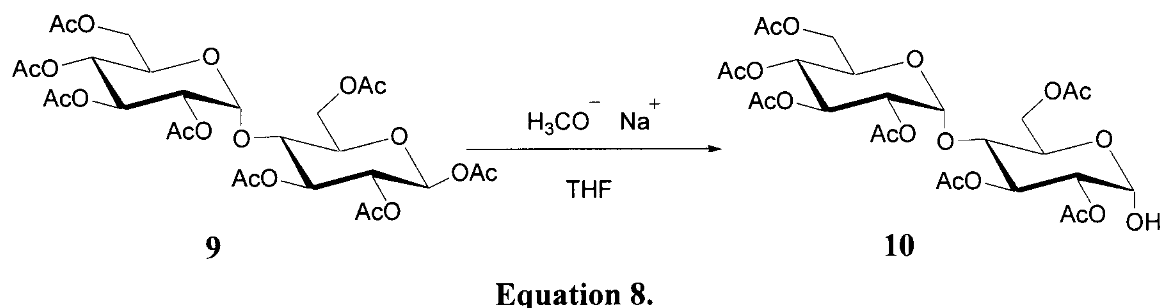
After the selective deacetylation was complete on compound **3**, it was necessary to use this chemistry on maltose (**8**) so that it could be used to make a glycosyl halide. Firstly, a nucleophilic acyl substitution reaction took place between the free hydroxyls of maltose and acetic anhydride in the presence of pyridine (Equation 7). The reaction mixture was followed by TLC for 1.5 days until all the starting material was consumed to afford compound **9** (R_f = 0.57 in 100% ethyl acetate). Integration of the ^{1}H NMR spectrum revealed the correct number of acetates that were added to compound **3**, and the ^{13}C NMR revealed eight carbonyl peaks around 170 ppm. ^{1}H NMR indicated that the

acetate at the anomeric carbon was in the equatorial position because the dihedral angle between H-1 and H-2 was large with a *J* value of 8.0 Hz. The mass spectrum in APCI (Atmospheric Pressure Chemical Ionization) mode was obtained for compound **9** for further proof of structure, which resulted in a *m/z* of 696.30 for $C_{28}H_{38}O_{19}$ ($M^{\oplus}$ + H_2O).



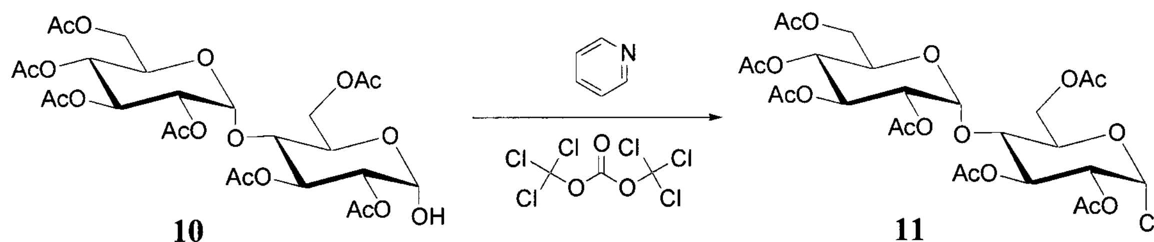
Equation 7

The next step in this synthesis was to selectively deacetylate compound **9** to yield a free hydroxyl at the anomeric position (Equation 8). Deprotection at the anomeric position was accomplished by reacting maltose octaacetate (**9**) with sodium methoxide and THF at –5 °C in an ice/salt/water bath to afford compound **10** with a yield of 86%. TLC (in 100% ethyl acetate) revealed one spot that was significantly more polar then that of **9**, the structure of which was confirmed with the disappearance of protons from the CH_3 group on the acetate at 2.10 ppm in the ^1H NMR spectrum and the loss of a C=O at 170 ppm in the ^{13}C NMR spectrum. The *J* value for the coupling between H-1 and H-2 for compound **10** is 3.8 Hz, which suggests that the H-1 proton lies in the equatorial position thus providing more proof to the structure given in equation 8. ESI-MS was also obtained on compound **10**, which gave a *m/z* of 654 ($M^{\oplus}$ + H_2O).



Equation 8.

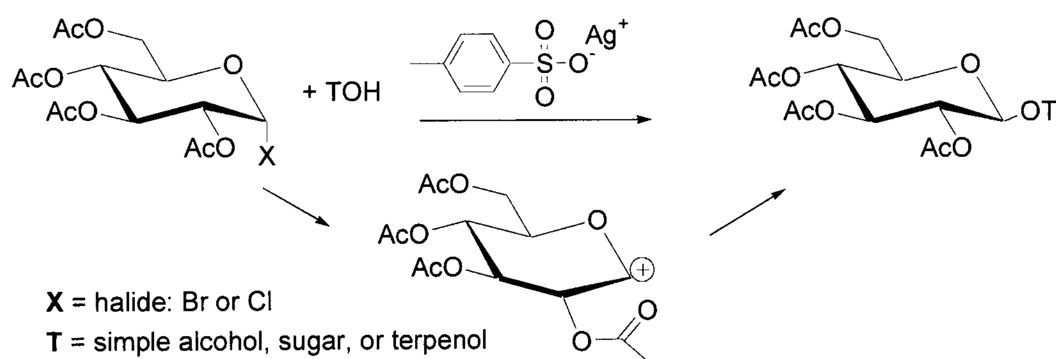
The final step was to apply the triphosgene method to compound **10** to make a glycosyl halide (Equation 9). An acyl substitution followed by a nucleophilic displacement reaction took place at the anomeric free hydroxyl in compound **10**. The reaction mixture was refluxed and monitored by TLC for 36 hours until the starting material was fully consumed to afford compound **11** (R_f = 0.33 in 1:1 hexane:ethyl acetate). The newly formed glycosyl halide **11** has a chlorine atom in the axial position due to the anomeric effect. Support for this comes from a small dihedral angle for H-1 and H-2 with a *J* value of 3.0 Hz. ^{1}H NMR characterization shows the correct number of acetyl groups along with a doublet further downfield (6.3 ppm) for the anomeric proton because of its close proximity to the electronegative chlorine atom. A crude yield of 56% was obtained on compound **11** in Equation 9, however only a trace amount of pure **11** was recovered from flash chromatography for use in NMR analysis. It was concluded that compounde **11** decomposed on the silica gel and later attempts in displacing the halide proved to be ineffective. This chlorination method on this particular disaccharide was difficult to achieve, due in part to the acetyl protecting groups on the sugar. The carbocation intermediate that is formed is stabilized by the lone pair of electrons on the acetyl group on C-2, thus making it difficult for the carbocation to trap the chlorine atom.



Equation 9

2. *O*-Glycosylations with Simple Alcohols

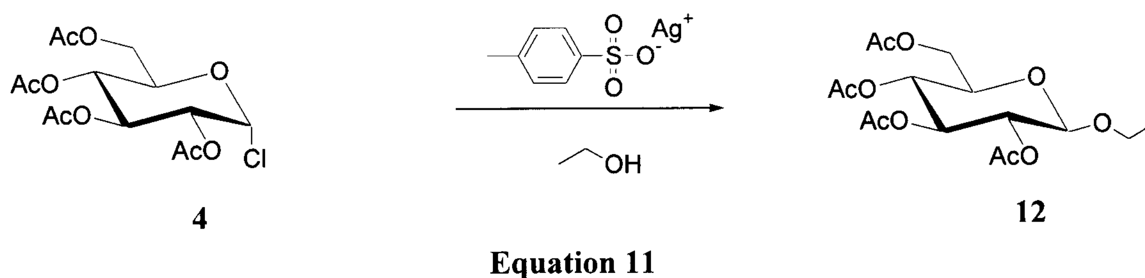
Once a variety of glycosyl halides had been successfully synthesized, it was desired to use these compounds as a way to introduce functionality at the anomeric position. The halide at C-1 could now be removed by a metal promoter, which would result in a carbocation at the anomeric position. This could then trap a nucleophile such as a simple alcohol, a free hydroxyl group on a sugar, or a terpene alcohol (Equation 10).



Equation 10

This type of glycosylation was practiced on simple alcohols before it was investigated on more complex alcohols like terpenols. Ethanol was chosen as the simple alcohol to react with the glycosyl halide in the presence of silver *p*-toluenesulfonate (Equation 11). Since silver *p*-toluenesulfonate is sensitive to light, this reaction was performed in the dark and under an inert atmosphere. Molecular sieves were added to eliminate H_2O because of the tendency of the carbocation intermediate to trap moisture instead of the desired alcohol. This reaction had to be refluxed for two days and monitored by TLC to afford the desired product **12** (R_f = 0.36 in 1:1 hexane:ethyl acetate). The ^{1}H NMR spectrum indicated a shift of the doublet at 6.28 ppm to an upfield

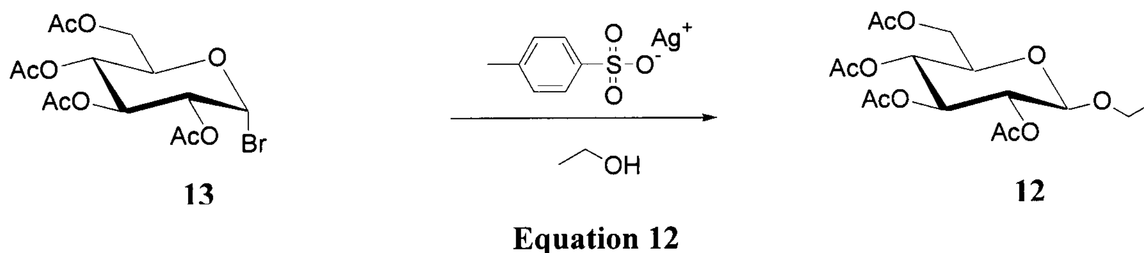
position of 4.5 ppm, which was indicative of the expected loss of the halide. It also showed the correct integration for the number of protons in the four acetate peaks along with the addition of a triplet at 1.17 ppm for the CH_3 group and a set of multiplets at 3.9 and 3.5 ppm for the CH_2 group. It was concluded that the CH_2 group showed two different multiplet signals instead of one because the protons are diastereotopic.



Equation 11

Acetobromo-α-D-glucose (**13**) was selected to be the glycosyl halide for the following reactions because of the bromine being a better leaving group than chlorine. Compound **13** is readily available from Aldrich and was found to be more convenient than synthesizing the glycosyl halides mentioned previously. Again, ethanol was chosen to be reacted with a glycosyl halide. The same reaction set up was employed as in Equation 11 however the system did not have to be refluxed. The reaction was monitored by TLC until all of the glycosyl halide **13** was consumed, which resulted in one spot more polar than that of the starting material. When the solvent was evaporated, the newly formed *O*-glycoside (R_f = 0.38 in 1:1 hexane:ethyl acetate) crystallized into a white solid after an aqueous extraction. The ^{1}H NMR and ^{13}C NMR spectra of the product was expected to be the same as that of compound **12**, since it is the same molecule but made from a different starting material. Again the ^{1}H NMR showed a set of

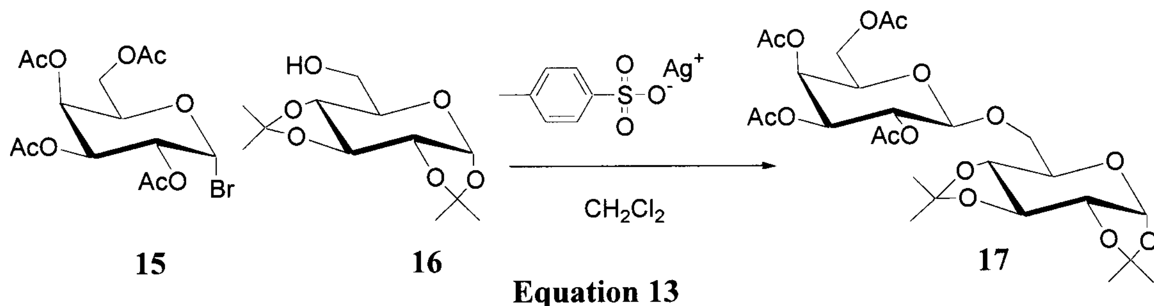
multiplets around 3.0 and 3.5 for the diastereotopic protons for the CH_2 group and another set of diastereotopic protons (4.1 and 4.2 ppm) for the hydrogens on C-6 of the sugar. APCI mass spectrometry in the negative ion mode was performed on compound **12** to help prove the structure, which resulted in a *m/z* of 375.15.



Equation 12

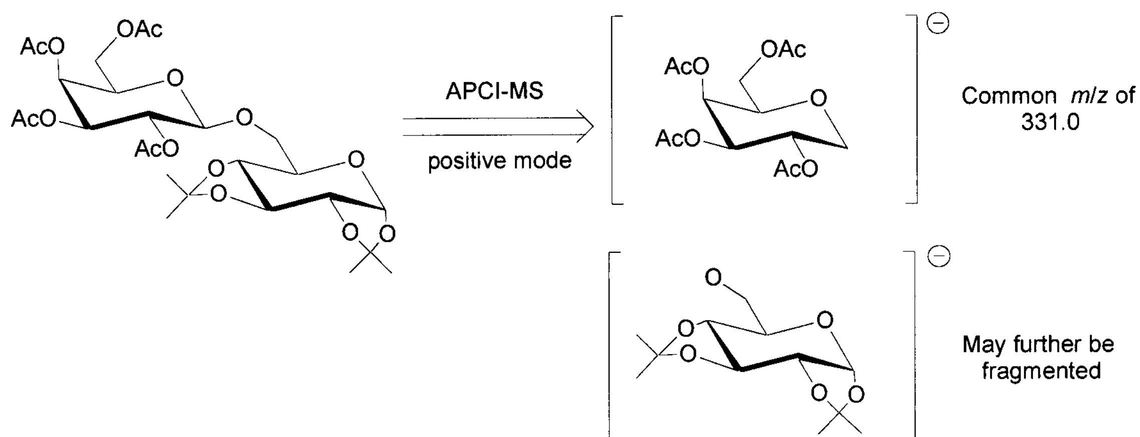
After confirming that this type of reaction scheme (Equation 10) could work on simple alcohols, it was desired to use this approach to trap a free hydroxyl of a protected sugar (Equation 13). The reaction was set up under an inert atmosphere with foil wrapped around the round-bottom flask to omit light and molecular sieves were added to consume excessive moisture. The sugars of choice for this method were acetobromo-α-D-galactose (**15**, for the displacement of the halide) and an excess of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**16**, for use of the free hydroxyl at C-6). The sugars were dissolved in methylene chloride, then silver *p*-toluenesulfonate was added and the reaction was let to stir overnight. TLC indicated the consumption of compound **15** and a new spot more polar than **15** and less polar than that of **16**. Flash chromatography was used to isolate the desired product **17** with $R_f = 0.46$ in 2:1 hexane:ethyl acetate with a yield of 12%. The ^{1}H NMR spectrum indicated a doublet at 5.38 ppm for the proton attached to C-1 (anomeric carbon) with a *J* value of 4.9 Hz and a doublet at 5.38 ppm for the proton attached to C-1' with a *J* value of 2.4 Hz, which indicated that the anomeric

proton was in the equatorial position and the C-1' proton was in the alpha position. It also indicated four singlet peaks around 2.0 ppm for the protons attached to the acetate groups and four singlets around 1.5 ppm for the protons attached to the isopropylidene groups.



Equation 13

APCI mass spectra in both positive and negative modes were obtained on compound **17**, which resulted in a *m/z* of 608.25 (M + H_2O) and a *m/z* of 589.16 respectively for each mode. This type of mass spectrometry technique also includes other masses shown in the data spectrum due to fragmentation of the desired compound into other smaller species. As a result a *m/z* of 331.14 is also shown in the mass spectrum of compound **17**. A possible fragmentation example is given below to show that the bond between the oxygen and the anomeric carbon was cleaved (Equation 14). It has been concluded that many of the previous and future examples (*vide supra*) of *O*-glycosides behave in the same way when being analyzed by APCI mass spectrometry in the positive mode. A common place for fragmentation is at the anomeric carbon in both *O*-glycosides with simple alcohols and with terpenes.



Equation 14

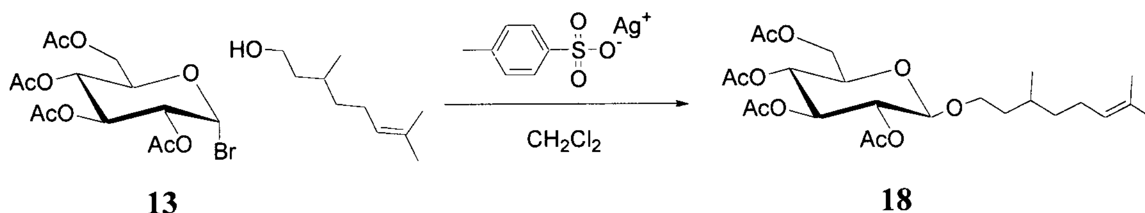
3. *O*-Glycosylations with Terpene Alcohols

The use of more complex alcohols such as terpenols was investigated to see if they too could add more functionality to the anomeric position of a protected carbohydrate. Acyclic monoterpenes such as nerol, geraniol and citronellol were chosen to be nucleophiles in the following reactions. Linalool was also chosen, however, it proved to be ineffective as a nucleophile due to it being a 3° alcohol.

This part of the project began by selecting the readily available protected carbohydrate **13**, and reacting it with citronellol in the presence of a metal promoter (Equation 15). A round bottom flask was prepared like before with foil wrapped around the sides of it and molecular sieves were introduced to consume excess moisture. Citronellol and compound **13**, dissolved in methylene chloride, were added to the round bottom flask through an addition funnel. After the silver *p*-toluenesulfonate was added to the reaction, the mixture was analyzed by TLC until all of the starting material was consumed. TLC indicated three new spots, two of which were identified after flash

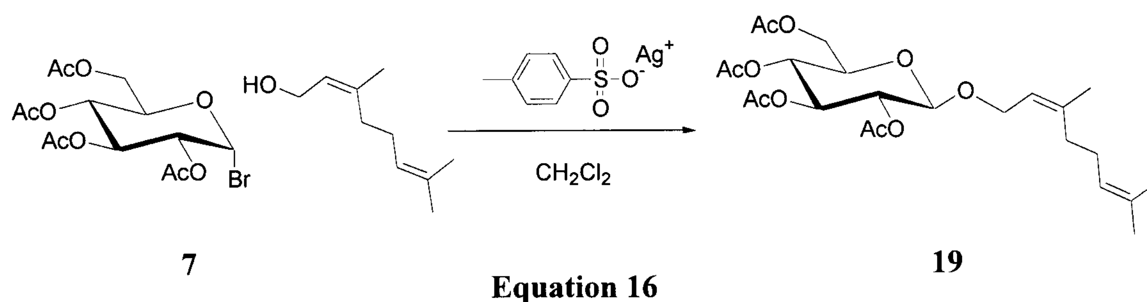
chromatography. The reaction mixture was then worked up with water to remove excess silver *p*-toluenesulfonate. One of the new spots was identified as the desired product **18** (R_f = 0.36 in 2:1 hexane:ethyl acetate) after characterization of NMR spectra with a yield of 33%. The other spot was significantly more polar then that of compounds **18** and **13** and was identified as compound **7** (R_f = 0.07 in 2:1 hexane:ethyl acetate). It was concluded that the carbocation intermediate trapped a water molecule instead of trapping the desired terpene alcohol, thus giving a free hydroxyl at the anomeric position. The ^{1}H NMR spectrum of compound **18** gave the correct signals for the sugar and for the addition of the terpene alcohol. There were two singlets at 1.6 and 1.7 ppm for the two methyl groups at the terminal end of the terpene and a doublet at 0.87 ppm with a J value of 6.6 Hz for the methyl attached to the chiral carbon of the terpene portion of the molecule. The spectrum also showed four singlets for the protons on the acetate groups on compound **18** and the correct number of protons for the rest of the sugar. The signal for the anomeric proton had moved up field because it was not next to an electronegative halide and was axial. It now appeared as a doublet at 4.48 ppm with a J value of 7.9 Hz. This indicates that the alcohol had to add from the equatorial position since the dihedral angle between H-1 and H-2 is large. This can be accounted for by the stabilization of the carbocation intermediate by the acetate group on C-2. As shown in Figure 4, page 4, the lone pair of electrons on the oxygen stabilizes the carbocation, hence blocking attack from the axial position. A doublet was also observed at 0.84 ppm for the methyl group attached to the aglycon with a J value of 6.6 Hz. Since the citronellol used in the sythesis was racemic, compound **18** was synthesized as a diastereomeric mixture. The ^{1}H NMR indicated this with an overlapping of signals. For example, the spectrum also showed

another doublet for the anomeric proton at 4.47 ppm with a *J* value of 7.9 Hz and a doublet at 0.85 ppm with a *J* value of 6.6 Hz for the methyl group attached to the aglycon. For further proof of structure APCI-MS in the negative ion mode gave a *m/z* 485.25 which corresponds to the correct mass of product **18**.



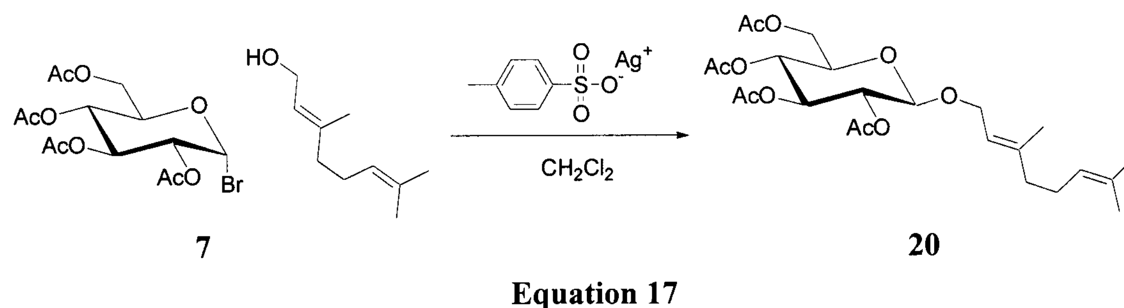
Equation 15

The reaction setup for the following two examples employed the use of foil and molecular sieves as previously stated in the last example. Nerol (Equation 16) and geraniol (Equation 17) were the next two terpene alcohols selected to react with a protected glycosyl halide. After workup, compound **19** was isolated with a R_f value of 0.29 in 4:1 hexane:ethyl acetate and characterized by NMR. The ^{1}H NMR spectrum indicated three singlets at approximately 1.6 ppm for the methyl groups attached to the terpene portion of the glycoside. Four singlets for the protons on the acetate groups were also shown around 2.0 ppm. The anomeric proton had been shifted more upfield and was calculated to have a bigger dihedral angle then that of the starting material. It lies at 4.45 ppm with a *J* value of 8.1 Hz. This also implies that the nucleophile had to attack the carbocation from the equatorial position, which results in the anomeric proton adjusting to the axial orientation. To help further the proof of the structure, APCI-MS in the negative ion mode was taken on compound **19**, which resulted in the expected *m/z* of 483.30.



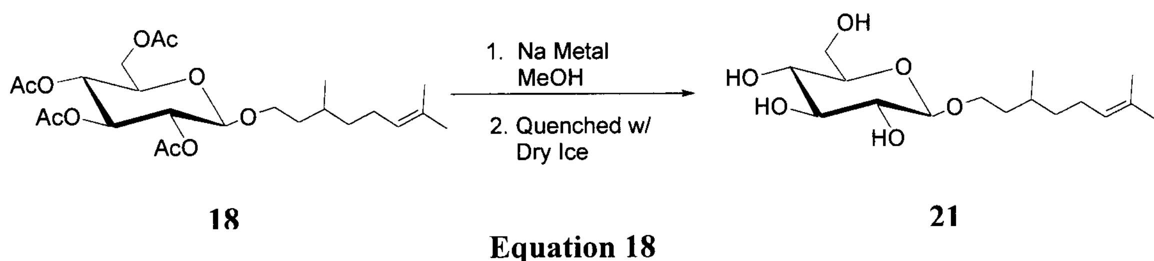
Equation 16

The final terpene alcohol chosen to displace a glycosyl halide was geraniol (Equation 17). Once again the same reaction conditions were used as in the previous examples. After consumption of the starting material and isolation of the desired product **20** through flash chromatography, TLC showed $R_f = 0.29$ in 2:1 hexane:ethyl acetate. The ^{1}H NMR spectrum showed three singlets around 1.6 ppm, which pertain to the methyl groups on the terpene part of the molecule. It also showed the correct number of acetate protons when integrated and the correct number of peaks in the ^{1}H and ^{13}C NMR spectra (four peaks in each, approximately 2.0 ppm for the ^{1}H and 171.0 ppm for the ^{13}C NMR spectra). The anomeric proton signal appeared as a doublet at 4.45 ppm with a J value of 8.1 Hz. APCI-MS in the negative ion mode was also obtained which resulted in a m/z of 483.25.



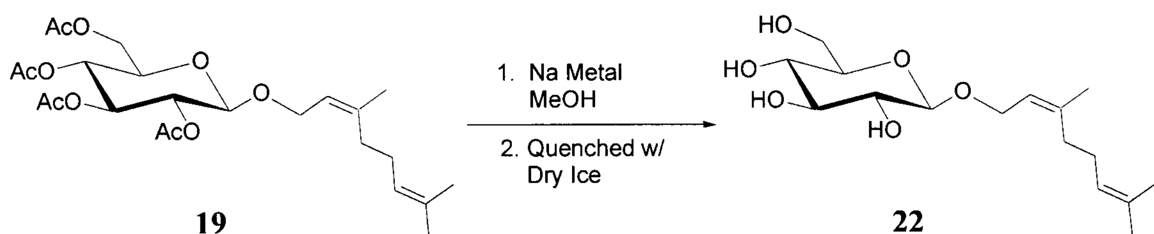
Equation 17

The next step after successfully synthesizing compounds **18** and **19** was to deprotect the carbohydrate, by removing the acetates (Equation 18 and 19 respectively). This involved a nucleophilic acyl substitution reaction with sodium methoxide. A round bottom flask was prepared under an inert atmosphere and the sugar was added after it was dissolved in methanol. A catalytic amount of sodium metal was added and the mixture was followed by TLC until all the starting material was consumed. Then the reaction was quenched with dry ice. The desired product **21** was a great deal more polar ($R_f = 0.1$ in 100% ethyl acetate) than that of **18**. Flash chromatography yielded 73.3% of the new terpene-*O*-glycoside **21**. The ^{1}H NMR spectrum indicated the loss of proton signals for the acetates. However it still included the protons for the rest of sugar. Two singlets at 1.6 ppm pertain to the methyl groups at the terminal end of the terpene while a doublet at 0.9 ppm signifies the methyl at the chiral portion of the terpene. The ^{13}C NMR spectrum also showed the loss of four acetate signals, which should have been around 170 ppm. Mass spectrum was obtained on compound **21** for further proof of structure. Because sugars with free hydroxyls are susceptible to caramelization during the course of certain mass spectrum methods, a technique known as Electrospray Ionization Mass Spectrum (ESI-MS) in the negative mode was employed to obtain the mass of **21**. It revealed a *m/z* of 317.47, which corresponds to the correct mass.



Equation 18

The next step was to deacetylate compound **19** into the free hydroxyl form. The same reaction conditions were employed as the previous example and the result was the desired product **22** in a yield of 88% (R_f = 0.12 in 100 % ethyl acetate). It was discovered that compound **22** crystallized when mixed with ethyl acetate and hexane. There was no need for chromatography because TLC and NMR spectra showed the compound to be pure. The ^{1}H and ^{13}C NMR spectrum showed the loss of acetate peaks around 2.0 ppm and 170 ppm respectively. ESI-MS was obtained in the negative mode for compound **22**, which resulted in a *m/z* of 315.29.

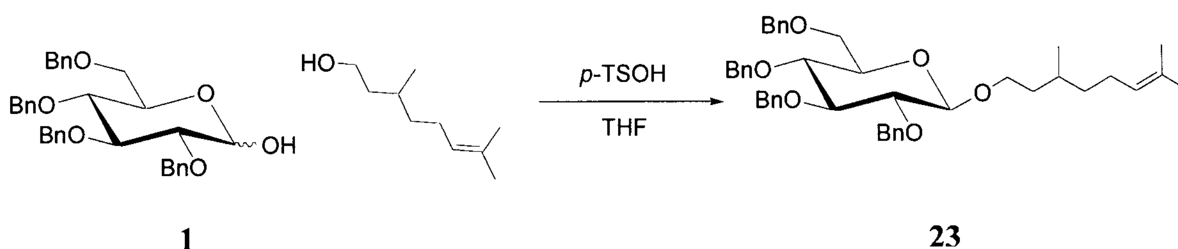


Equation 19

4. Fischer *O*-Glycosylations with Terpene Alcohols

This segment of the research dealt with the investigation of Fischer glycosylations to protected and unprotected carbohydrates with terpene alcohols. As explained in Figure 2, it may be possible to add functionality to the anomeric carbon of a carbohydrate when the sugar is in the *aldehydo* form. After reaction occurs in the presence of an alcohol and an acid, the ring reforms to produce an *O*-glycoside (Equation 20). Citronellol was chosen as the nucleophilic alcohol to 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose in the presence of *p*-toluenesulfonic acid monohydrate. The reaction mixture was refluxed for 30 hours and monitored by TLC until the starting material was completely consumed to

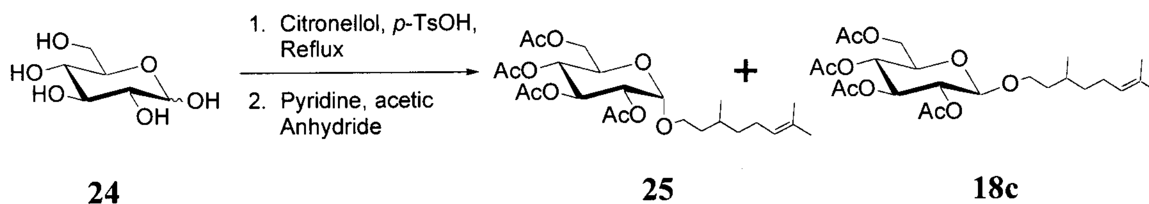
give the desired product **23** with a 30% yield ($R_f = 0.63$ in 6:1 hexane:ethyl acetate). The ^{1}H NMR spectrum showed a doublet at 4.41 ppm with a *J* value of 7.87 Hz for H-1 and H-2, which indicated that the H-1 proton was in the axial position. The spectrum also showed the correct peaks for the addition of the terpene, specifically two singlets at 1.61 and 1.70 ppm and a doublet at 0.9 ppm. APCI-MS in the positive ion mode was obtained on compound **23**, which gave the expected mass value of 696.49 ($M+H_2O$). The mass spectrum also showed fragmentations of compound **23**, specifically a *m/z* of 523.22, which is the expected mass of the carbohydrate after cleavage of the C-O bond at the anomeric position.



Equation 20

It was then necessary to apply this reaction scheme to an unprotected carbohydrate like glucose (Equation 21). D-Glucose (**24**), citronellol, and *p*-toluenesulfonic acid monohydrate were dissolved in THF. The reaction mixture was refluxed and followed by TLC for 36 hours until most of the starting material was consumed. Then the reaction mixture was gravity filtered to remove excess D-glucose. Due to the complexity of the crude ^{1}H NMR spectrum, it was decided to acetylate the free hydroxyls of the sugar. Acetylation was achieved by reacting this unprotected terpene-*O*-glycoside with pyridine and acetic anhydride. The reaction mixture was refluxed and followed by TLC for 24 hours. It was then worked up by adding ice and 5%

sulfuric acid and then extracted with water. Flash chromatography yielded two forms of the protected terpene-*O*-glycoside, one of which was α (**25**) and the other β (**18**). Since citronellol is a chiral molecule, **25** and **18** were synthesized as a diastereomeric mixture. This is shown with an overlapping of signals. For example, the ^{1}H NMR spectra for compound **25** has a doublet for the anomeric proton at 4.34 ppm with and a doublet at 4.37 ppm with a J value for both signals of 2.2 Hz. Likewise, the ^{1}H NMR spectrum for compound **18** has a doublet for the anomeric proton at 4.4 ppm and 4.5 ppm with a J value for both signals of 8.1 Hz. The ^{13}C spectrum also shows that all the hydroxyl were acetylated with four signals for the C=O groups at around 170 ppm. APCI-MS in the negative ion mode showed the correct mass with a *m/z* of 485.23.



Equation 21

Conclusion

In conclusion, the formation of terpene-*O*-glycosides using both glycosyl halides and the Fischer glycosylation method were successful. The displacement of the halide atom at the anomeric position of a protected carbohydrate proved to be successful in trapping a terpene alcohol, and this resulted in an acetylated terpene-*O*-glycoside that was eventually deprotected to afford good yields of the desired natural product.

The Fischer method also proved to be successful in affording terpene-*O*-glycosides of protected and unprotected sugars. It was difficult to find solvents that were compatible to the physical properties of the unprotected sugars. This was concluded to be the reason of the low yields for this type of glycosylation.

Experimental

General Procedures

A Varian Gemini 2000 NMR system was used to obtain ^{1}H and ^{13}C NMR spectra at 400 MHz and 100 MHz respectively, using $CDCl_3$ as the solvent. Proton and carbon 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 doublets of doublets), t (triplet), q (quartet), and m (multiplet) with coupling constants (*J*) measured in Hertz. H-1 and C-1 are protons and carbons assigned to the sugar, whereas H'-1 and C'-1 are protons and carbons assigned to the aglycon. A Bruker Esquire-HP 1100 LC/MS was used to obtain mass spectra. Aluminum-backed flexible plates were used for thin layer chromatography. Flash column chromatography was performed with 32-63 μm, 60-Å silica gel.

Synthesis of 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl Chloride (2) from 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose (1).

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose (0.5406 g, 1 mmol) was added to a flame-dried 25 mL round bottom flask containing triphosgene (0.120 g, 0.4 mmol). THF (5 mL) was added to the mixture and the solution was allowed to stir at room temperature. Pyridine (0.1 mL) was then added to the solution and the reaction was allowed to stir for 4 hours. The reaction was followed by TLC (3:1 hexane:ethyl acetate) to ensure completeness. A white precipitate, pyridinium hydrochloride, was gravity filtered off. The filtrate was then evaporated to yield a clear syrup of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**2**) 0.519 g (93%).

^{1}H NMR: δ 3.63 (dd, 1H, H-6, J 2.0,11.0 Hz), 3.82 (m, 2H, H-2, H-4), 3.86 (dd, 1H, H-6', J 2.7, 11.0 Hz), 4.11-4.20 (m, 2H, H-5, H-3), 4.44-4.99 (m, 8H, 4 x C<u>H</u>$_2$Ph), 6.05 (d, 1H, H-1, J 3.9 Hz), 7.12-7.38 (m 20 H, Ar-H).

^{13}C NMR: δ 67.8, 72.94, 73.38, 73.49, 75.17, 75.79, 77.31, 79.81, 81.35, 92.44, 127.53, 127.62, 127.70, 127.78, 127.88, 127.81, 127.94, 128.25, 128.31, 128.40, 130.01, 137.28, 137.50, 137.62, 137.85, 138.33.

NMR data agreed with literature values.[8]

Synthesis of Tetra-*O*-acetyl-α-D-glucopyranosyl Chloride (4)

To a flame-dried 250 mL three neck round bottom flask was added a solution of β-D-glucopyranose pentaacetate (20 g, 0.0513 mol) dissolved in 100 mL of pure dry chloroform. A solution of 5.8 mL of titanium tetrachloride in 35 mL of chloroform was added through an addition funnel. After the yellow precipitate dissolved, the reaction mixture was refluxed for 3 hours. The reaction was monitored by TLC (1:1 hexane:ethyl acetate) to ensure completeness. After consumption of the starting material, the reaction mixture was treated with calcium chloride. The calcium chloride was gravity filtered off and the filtrate was evaporated to yield a colorless syrup. The syrup was crystallized using anhydrous ether and petroleum ether. White crystals of **4** resulted in a yield of 11.42 g (63%). A melting point of 71 °C was taken of the product which agreed with the literature value of 73 °C.[11]

^{1}H NMR: δ 2.03, 2.04, 2.10, 2.11 (4s, 12H, 4 x $COCH_3$), 4.09 (dd, 1H, H-5, J 3.7, 14.1 Hz), 4.29-4.32 (m, 2H, H-6, H-6'), 4.99 (dd, 1H, H-2, J 4.0, 10.1 Hz), 5.1

(dd, 1H, H-4, *J* 9.88, 9.88 Hz), 5.5 (dd, 1H, H-3, *J* 9.7 Hz), 6.28 (d, 1H, H-1, *J* 4.0 Hz).

^{13}C NMR: δ 21.85, 21.89, 21.92, 21.97, 62.24, 68.51, 70.52, 71.48, 71.84, 91.14, 170.39, 170.80, 170.82, 171.47.

NMR data were not given in original reference.[11]

Acetylation of 2,3,4,6-Tetra-*O*-Benzyl-α-D-Glucopyranose

To a flame dried 25 mL round bottom flask, under nitrogen atmosphere, was added compound **1** (1 g, 1.85 mmol). Pyridine (10 mL) was added to the round bottom flask to dissolve **1**. Acetic anhydride was syringed into the solution and the reaction mixture was stirred overnight. The reaction was followed by TLC (2:1 hexane:ethyl acetate). Upon completion, the solution was poured over ice and quenched with 10 mL of 5% H_2SO_4. The solution was transferred to a separatory funnel and extracted with 2 x 15 mL of CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the filtrate was evaporated to a clear syrup that yielded 0.87 g (83%) of compound **5**.

^{1}H NMR: δ 2.2 (s, 3H, 1 x $COCH_3$), 3.7-3.8 (m, 3H, H-2, H-4, H-6), 4.0 (dd, 1H, H-6', *J* 9.3, 9.3 Hz), 4.5-4.6 (m, 2H, H-5, H-3), 4.7-5.0 (m, 8H, 4 x $C\underline{H}_2Ph$), 6.41 (d, 1H, H-1, *J* 3.7 Hz), 7.17-7.40 (m 20 H, Ar-H).

^{13}C NMR: δ 22.41, 22.55, 69.21, 74.48, 74.67, 74.73, 74.78, 76.91, 91.23, 128.75, 128.79, 128.85, 128.91, 129.06, 129.17, 129.21, 129.25, 129.30, 123.45, 129.50, 129.55, 138.59, 138.78, 138.99, 139.63, 170.42.

NMR data agreed with literature values.[9]

Synthesis of 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl Iodide (6) from 5

To a flame dried, two neck 50 mL round bottom flask, was added 0.53 g of compound **5** dissolved in 15 mL of dry CH_2Cl_2. Trimethylsilyl iodide (0.152 mL) was added *via* syringe into the reaction mixture and stirred for 45 minutes. The reaction was followed by TLC (3:1 hexane:ethyl acetate). Upon completion, the solution was evaporated to produce a residue, which was then redissolved in toluene and evaporated again to produce 0.107 g (17 %) of the desired compound **6**.

^{1}H NMR: δ 2.64 (dd, 1H, H-2, J 4.0, 9.0 Hz), 3.65 (d, 1H, H-3, J 1.6 Hz), 3.75 (m, 3H, H-4, H-6, H-6'), 3.9 (m, 1H, H-5), 4.4-5.1 (m, 8H, 4 x C$\underline{H}_2$-Ph), 6.87 (d, 1H, H-1, J 4.0 Hz), 7.2-7.4 (m, 20 H, Ar-H).

NMR data agreed with literature values.[9]

Selective 1-*O*-Deacetylation of β-D-Glucopyranose Pentaacetate

Sodium methoxide (60.8 mg) was suspended in 5 mL dry THF and cooled to -5° C in an ice/salt/water bath. The acetylated sugar (**3**) (0.250 g, 0.6408 mmol) was then added in one portion and allowed to stir vigorously. The reaction was monitored by TLC (100% ethyl acetate). After consumption of the starting material, glacial acetic acid (0.1 mL) was added to quench the reaction, and the mixture was stirred for 10 minutes and then evaporated. The residue was dissolved in 15 mL of chloroform and extracted with 3 x 10 mL portions of water. The organic layer was dried over $MgSO_4$, the solution was gravity filtered and the filtrate was evaporated to a white syrup, to give 0.120 g (53.8%) of compound **7**.

^{1}H NMR: δ 1.98, 1.99, 2.06, 2.07 (4s, 12H, 4 x $COCH_3$), 4.07-4.25 (m, 3H, H-5, H-6, H-6'), 4.84 (d, 1H, H-1, J 3.7 Hz), 5.03 (dd, 1H, H-2, J 9.2, 9.2 Hz), 5.2 (dd, 1H, H-4, J 9.5 Hz), 5.47 (dd, 1H, H-3, J 9.8 Hz).

NMR data agreed with literature values.[9]

Synthesis of Maltose Octacetate

In a 100 mL three neck round bottom flask was dissolved of 5 g (14.6 mmol) of maltose (**8**) in 25 mL of pyridine. The apparatus was placed in an ice bath and stirred until the solution reached 0 °C, whereupon 10 mL of acetic anhydride was slowly added. The reaction mixture was heated to 60 °C and stirred for 1.5 days. The reaction was followed by TLC (100% ethyl acetate) to ensure that all hydroxyls were acetylated. The reaction was poured over 50 g of ice and quenched with 5% sulfuric acid. It was then transferred to a separatory funnel and washed with 2 x 20 mL of ethyl acetate and 2 x 20 ml of water. The organic layer was dried over $MgSO_4$, and the filtrate was evaporated to yield 8.53g (86%) of a white residue **9**.

^{1}H NMR: δ 1.92, 1.92, 1.93, 1.94, 1.95, 1.98, 2.0, 2.01, 2.04 (8s, 3H each, 8 x $COCH_3$), 3.92 (m, 1H, H-5), 3.96 (m, 1H, H'-5), 4.0-4.3 (m, 4H, H-6, H-6', H'-6, H'-6'), 4.74 (dd, 1H, H-2, J 4.02, 10.6 Hz), 4.86 (dd, 1H, H'-2, J 8.6 Hz), 4.94 (dd, 1H, H'-3, J 9.8 Hz), 5.1-5.2 (m, 3H, H-3, H-4, H'-4), 5.3 (d, 1H, H-1, J 4.0 Hz), 5.6 (d, 1H, H'-1, J 8.1 Hz).

^{13}C NMR: δ 21.66, 21.70, 21.79, 21.83, 21.91, 21.99, 22.05, 22.11, 61.44, 62.47, 63.56, 69.52, 69.71, 70.98, 71.11, 71.87, 72.04, 73.49, 73.88, 74.04, 169.60, 170.24, 170.39, 170.67, 170.88, 171.22, 171.29, 171.35.

Selective 1-*O*-Deacetylation of Maltose Octaacetate

Sodium methoxide (0.216 g, 4 mmol) was suspended in 15 mL of dry THF and cooled to –5 °C in a salt/ice/water bath. Maltose octaacetate (**9**) (1.35 g, 2 mmol) was added and allowed to stir vigorously overnight. The reaction was monitored by TLC (1:1 hexane:ethyl acetate) to ensure the consumption of the starting material. Acetic acid (0.25 mL) was added to quench the reaction. The mixture was stirred for 10 minutes and was then evaporated. The residue was dissolved in 25 mL of chloroform and extracted with 3 x 10 mL portions of water. The organic layer was dried over $MgSO_4$, the solution was gravity filtered and the filtrate was evaporated to give a white residue of compound **10** (0.94 g, 75%).

^{1}H NMR: δ 1.93, 1.94, 1.95, 1.97, 1.98, 2.07, 2.07 (7s, 3H each, 7 x $COCH_3$), 3.89-4.1 (m, 2H, H-5, H'-5), 4.19-4.2 (m, 2H, H-6, H'-6), 4.4-4.45 (m, 2H, H-6', H'-6'), 4.6-79 (m, 2H, H-2, H'-2), 4.9 (d, 1H, H'-1, *J* 3.1 Hz), 5.0-5.2 (m, 2H, H-3, H'-3), 5.3 (m, 1H, H-4), 5.39 (d, 1H, H-1, *J* 4.1 Hz), 5.5 (dd, 1H, H'-4, *J* 9.7, 9.7 Hz).

^{13}C NMR: δ 21.85, 21.89, 21.98, 22.07, 22.13, 22.16, 22.25, 63.92, 69.34, 69.52, 71.02, 71.15, 72.69, 72.79, 73.24, 73.37, 73.49, 73.57, 73.73, 170.89, 171.08, 171.26, 171.35, 171.47, 171.57, 171.59.

Chlorination of 2,3,6,2',3',4',6'-septa-*O*-Acetyl-D-maltose

To a 25 mL round bottom flask containing 0.0991 g (0.334 mmol) of triphosgene was added 0.425g (0.66803 mmol) of compound **10**. The system was purged with nitrogen and 5 mL of dry THF was added. Pyridine was added in 3 portions of 0.03 mL

producing a white precipitate. The reaction was stirred for 30 hours and followed by TLC (2:1 hexane:ethyl acetate). The pyridinium hydrochloride was gravity filtered off and the filtrate was evaporated to produce a yellow syrup. Flash chromatography was performed (3:1 hexane:ethy acetate) to produce a trace amount of compound **11**.

^{1}H NMR: δ 2.00, 2.02, 2.03, 2.06, 2.07, 2.10, 2.15 (7s, 3H each, 7 x $COCH_3$), 3.59 (m, 1H, H-5), 4.02-4.11 (m, 2H, H'-5, H-6), 4.22-4.35 (m, 2H, H-6, H'-6), 4.50-4.62 (m, 1H, H'-6'), 4.80-4.92 (m, 3H, H'-3, H-2, H'-2), 5.05 (dd, 1H, H'-4, *J* 10.0, 10.0 Hz), 5.35 (dd, 1H, H-3, *J* 9.5, 9.5 Hz), 5.4 (d, 1H, H-1, *J* 4.0 Hz), 5.6 (dd, 1H, H-4, *J* 9.3, 9.3 Hz), 6.2 (d, 1H, H'-1, *J* 3.8 Hz).

O-Glycosylation of Tetra-*O*-Acetyl-α-D-Glucopyranosyl Chloride with Ethanol

A 25 mL two neck round bottom flask was prepared by flame drying under a nitrogen atmosphere. Foil was wrapped around the flask to omit light from the reaction mixture and molecular sieves (0.2 g) were added to eliminate excess moisture. A solution containing **4** (0.1 g, 0.273 mmol) dissolved in 10 mL of absolute ethanol was syringed into the round bottom flask. Silver *p*-toluenesulfonate (0.0759 g, 0.273 mmol) was carefully added and the reaction mixture was refluxed overnight. The reaction was followed by TLC (1:1 hexane:ethyl acetate). Flash chromatography (4:1 hexane:ethyl acetate) resulted in 0.0747 g (73%) of compound **12** as a white residue.

^{1}H NMR: δ 1.17 (t, 3H, 1 x CH_3, *J* 5.1 Hz), 1.94 (s, 12H, 4 x $COCH_3$), 3.55 (m, 1H, H'-7), 3.66 (m, 1H, H-5), 3.88 (m, 1H, H'-1'), 4.1 (dd, 1H, H-6, *J* 12.26, 2.4 Hz), 4.2 (dd, 1H, H-6', *J* 12.45, 4.9 Hz), 4.5 (d, 1H, H-1, *J* 8.1 Hz), 4.94 (dd, 1H, H-2, *J* 8.1, 9.52 Hz), 5.06 (dd, 1H, H-3, *J* 9.7 Hz), 5.18 (dd, 1H, H-4, *J* 9.52 Hz).

^{13}C NMR: δ 21.8, 21.9, 21.99, 22.0, 22.2, 63.1, 66.7, 72.8, 72.9, 101.6, 129.2, 130.0, 170.3, 170.33, 171.3, 171.7.

NMR data agreed with literature values.[23]

O-Glycosylation of Acetobromo-α-D-Glucose with Ethanol

A 25 mL two neck round bottom flask was prepared by flame drying under a nitrogen atmosphere. Foil was wrapped around the round bottom flask to omit light from the reaction mixture and molecular sieves (0.2 g) were added to eliminate excess moisture. A solution containing **13** (1 g, 2.43 mmol) dissolved in 10 mL of 200 proof ethanol was added via syringd into the round bottom flask. Silver *p*-toluenesulfonate (0.679 g, 2.43 mmol) was carefully added and the reaction mixture was stirred at room temperature for three hours. The reaction mixture was followed by TLC (1:1 hexane:ethyl acetate). The solution was gravity filtered to remove the silver bromide and the filtrate was evaporated to a white residue. Flash chromatography (4:1 hexane:ethyl acetate) provided a white residue with a yield of 0.85 g (93%) of compound **12**.

^{1}H NMR: δ 1.18 (t, 3H, 1 x CH_3, J 7.14 Hz), 2.0 (s, 12H, 4 x $COCH_3$), 3.53-3.59 (m, 1H, H'-7), 3.66-3.71 (m, 1H, H-5), 3.87-3.92 (m, 1H, H'-1'), 4.1 (dd, 1H, H-6, J 12.26, 2.2 Hz), 4.3 (dd, 1H, H-6', J 12.45, 4.9 Hz), 4.5 (d, 1H, H-1, J 8.1 Hz), 4.94 (dd, 1H, H-2, J 9.52, 9.52 Hz), 5.06 (dd, 1H, H-3, J 9.7, 9.7 Hz), 5.18 (dd, 1H, H-4, J 9.52, 9.52 Hz).

^{13}C NMR spectrum is identical to compound **12** on page 36.

NMR data agreed with literature values.[23]

O-Glycosylation of Acetobromo-α-D-Galactose (15) with 1,2:3,4-Di-O-Isopropylidene-D-Galactopyranose (16)

A 25 mL two neck round bottom flask was prepared by flame drying under a nitrogen atmosphere. Foil was wrapped around the flask to omit light from the reaction mixture and molecular sieves (0.2 g) were added to eliminate excess moisture. A combination of 0.411 g (1 mmol) of compound **15** and 0.2603 g (1 mmol) of **16** in 25 mL of CH_2Cl_2 were added to the round bottom flask. Silver *p*-toluenesulfonate was carefully added to the reaction mixture, which was then allowed to stir overnight at room temperature. Upon completion, confirmed by TLC (2:1 hexane:ethyl acetate), the reaction mixture was diluted with 50 mL of CH_2Cl_2 and filtered through a frit using vacuum to remove AgBr. The filtrate was evaporated and flash chromatography (3:1 hexane:ethyl acetate) was used to isolate 0.0710 g (12%) of the desired product as a clear syrup **17**.

^{1}H NMR: δ 1.24 (s 3H, 1 x CH_3), 1.31 (s 3H, 1 x CH_3), 1.44 (s 3H, 1 x CH_3), 1.50 (s 3H, 1 x CH_3), 1.97, 2.04, 2.08, 2.13 (s, 12H, 4 x $COCH_3$), 3.6 (dd, 1H, H'-4, J 7.68, 11.53 Hz), 3.88 (m, 3H, H'-5, H'-6, H'-6'), 4.02 (dd, 1H, H-2, J 3.29, 11.53 Hz), 4.11 (m, 3H, H-5, H-6, H-6'), 4.19 (dd, 1H, H'-2, J 2.57, 4.95 Hz), 5.57 (dd, 1H, H'-3, J 2.92, 7.87 Hz), 5.0 (dd, 1H, H-3, J 3.47, 10.62 Hz), 5.2 (dd, 1H, H-4, J 7.87, 10.43 Hz), 5.39 (d, 1H, H-1, J 2.4 Hz), 5.4 (d, 1H, H'-1, J 4.9 Hz).

^{13}C NMR: δ 21.8, 21.9, 22.0, 22.1, 22.2, 25.5, 26.3, 27.2, 27.3, 62.4, 68.01, 68.12, 70.81, 71.53, 71.64, 71.84, 97.20, 97.41, 103.01, 103.12, 109.72, 110.51, 170.68, 171.11, 171.21, 171.39.

NMR data agreed with literature values.[24]

O-Glycosylation of Acetobromo-α-D-glucose with Nerol

A 25 mL two neck round bottom flask was prepared by flame drying under a nitrogen atmosphere. Foil was wrapped around the round bottom flask to omit light from the reaction mixture and molecular sieves (0.2 g) were added to eliminate excess moisture. Acetobromo-α-D-glucose (0.250 g, 0.6079 mmol) was dissolved in 10 mL of methylene chloride in a separate vial. It was then added *via* syringe into the round bottom flask along with 0.5 ml of nerol. Silver *p*-toluenesulfonate (0.5 g) was carefully and quickly added and the reaction mixture was stirred for 1.5 hours. After the consumption of the starting material, followed by TLC (2:1 hexane:ethyl acetate), the methylene chloride was evaporated from the reaction mixture to leave a green residue. Flash chromatography was immediately performed (4:1 hexane:ethyl acetate) to yield 0.100 g (34%) of a clear syrup **19**.

^{1}H NMR: δ 1.5, 1.6 1.7 (s, 9H, 3 x CH_3), 1.91-2.02 (m, 4H, H'-3, H'-3', H'-4, H'-4'), 1.97, 1.98, 2.0, 2.05 (s, 12H, 4 x $COCH_3$), 3.64-3.65 (m, 1H, H-5), 4.09-4.29 (m, 4H, H-6, H-6', H'-1, H'-1'), 4.5 (d, 1H, H-1, J 8.0 Hz), 4.9 (dd, 1H, H-2, J 8.05, 8.05 Hz), 5.0 (m, 2H, H-3, H'-5), 5.18 (dd, 1H, H-4, J 8.6, 8.6 Hz), 5.2 (t, 1H, H'-2, J 1.69 Hz).

^{13}C NMR: δ 18.9. 21.86, 21.89, 21.95, 21.97, 24.82, 26.94, 27.91, 33.31, 63.14, 66.25, 69.52, 72.39, 72.83, 74.05, 99.89, 121.18, 124.51, 133.19, 143.09, 170.25, 170.29, 171.23, 171.59.

NMR data were not given in original reference.[18]

***O*-Glycosylation of Acetobromo-α-D-glucose with Citronellol**

A 25 mL two neck round bottom flask attached to an addition funnel was prepared by flame drying under a nitrogen atmosphere. Foil was wrapped around the flask to omit light from the reaction mixture and molecular sieves (0.2 g) were added to eliminate excess moisture. Silver *p*-toluenesulfonate (4.0 g) and a stir bar were then added. Acetobromo-α-D-glucose (3 g, 7.29 mmol) dissolved in 3 mL of citronellol and 5 mL of methylene chloride was added to the round bottom flask through the addition funnel. The reaction was stirred for 3 hours and followed by TLC (2:1 hexane:ethyl acetate) to ensure consumption of the starting material. The reaction mixture was evaporated to yield a gray residue. Flash chromatography (6:1 hexane:ethyl acetate) produced 1.2 g of compound **18** as a mixture of diastereoisomers with a yield of 33%.

^{1}H NMR: δ 0.853 (d, 3H, 1 x CH_3 (S or R), J 4.0 Hz), 0.86 (d, 3H, 1 x CH_3 (R or S), J 3.9 Hz), 1.2-1.4 (m, 5H, H'-2, H'-2', H'-3, H'-3', H'-4), 1.5, 1.7 (s, 6H, 2 x CH_3), 2.0-2.1 (s, 12H, 4 x $COCH_3$), 3.5 (m, 1H, H'-1), 3.66 (m, 1H, H-5), 3.8 (m, 1H, H'-1'), 4.1 (dd, 1H, H-6, J 2.2, 12.26 Hz), 4.2 (dd, 1H, H-6', J 4.5, 12,26 Hz), 4.47 (d, 1H, H-1 (S or R), J 7.9 Hz), 4.48 (d, 1H, H-1 (R or S), J 7.9 Hz), 4.9 (dd, 1H, H-3, J 8.05, 9.52 Hz), 5.06 (m, 2H, H-2, H'-4), 5.19 (dd, 1H, H-4, J 9.52, 9.52).

^{13}C NMR: δ 19.01, 21.90, 21.92, 22.04, 26.63, 26.98, 37.44, 37.42, 38.39, 69.56, 69.64, 69.68, 71.99, 72.43, 72.84, 73.98, 74.01, 101.75, 102.01, 125.61, 170.33, 171.24, 171.27, 171.66.

NMR data were not given in original reference.[18]

O-Glycosylation of Acetobromo-α-D-glucose with Geraniol

A 25 mL two neck round bottom flask attached to an addition funnel was prepared by flame drying under a nitrogen atmosphere. Foil was wrapped around the flask to omit light from the reaction mixture and molecular sieves (0.2 g) were added to eliminate excess moisture. Silver *p*-toluenesulfonate (4.0 g) and a stir bar were added to the round bottom flask. Acetobromo-α-D-glucose (3 g, 7.29 mmol) dissolved in 3 mL of geraniol and 5 mL of methylene chloride was added to the round bottom flask through the addition funnel. The reaction was allowed to stir for 3 hours and followed by TLC (2:1 hexane:ethyl acetate) to ensure consumption of the starting material. The reaction mixture was evaporated to a gray residue. Flash chromatography (6:1 hexane:ethyl acetate) produced 1.7 g of compound **20** in a yield of 42%.

^{1}H NMR: δ 1.53, 1.58 1.59 (s, 9H, 3 x CH_3), 1.9-2.1 (m, 4H, H'-3, H'-3', H'-4, H'-4'), 1.93, 1.95, 1.96, 2.01 (s, 12H, 4 x $COCH_3$), 3.57-3.59 (m, 1H, H-5), 4.05-4.2 (m, 4H, H-6, H-6', H'-1, H'-1'), 4.45 (d, 1H, H-1, J 8.1 Hz), 4.89 (dd, 1H, H-2, J 8.05, 8.05 Hz), 4.98-5.0 (m, 2H, H-3, H'-5), 5.1 (dd, 1H, H-4, J 8.6, 8.6 Hz), 5.17 (t, 1H, H'-2, J 6.42).

^{13}C NMR: δ 18.9. 21.86, 21.89, 21.95, 21.97, 24.82, 26.94, 27.91, 33.31, 63.14, 66.25, 69.52, 72.39, 72.83, 74.05, 99.89, 121.18, 124.51, 133.19, 143.09, 170.25, 170.29, 171.23, 171.59.

NMR data were not given in original reference.[18]

Deacetylation of compound 18

A 25 mL round bottom flask was prepared under nitrogen atmosphere with a stir bar. Compound **18** (0.5 g, 1.02 mmol) was dissolved in 20 mL of methanol and syringed into the round bottom flask. A catalytic amount of sodium metal was added and the reaction mixture was left to stir for 6 hours. Upon consumption of the starting material, followed by TLC (100% ethyl acetate), the reaction mixture was quenched with 1 g of dry ice. The excess methanol was evaporated to produce a white residue. A flash column in 100 % ethyl acetate gave 0.24 g (73.3%) of compound **21**.

^{13}C NMR: δ 18.95, 20.77, 26.69, 26.99, 30.79, 30.81, 30.95, 37.71, 37.76, 38.45, 70.08, 70.29, 74.37, 76.63, 125.64, 132.25.

NMR data were not given in original reference.[21,3]

Deacetylation of compound 19

A 25 mL round bottom flask was prepared under nitrogen atmosphere with a stir bar. Compound **19** (0.5 g, 1 mmol) was dissolved in 20 mL of methanol and syringed into the round bottom flask. A catalytic amount of sodium metal was added and the reaction mixture was let to stir for 6 hours. Upon consumption of the starting material, followed by TLC (100% ethyl acetate), the reaction mixture was quenched with 1 g of dry ice. The excess methanol was evaporated to produce a white solid with a yield 0.29 g (88%) of compound **22**.

^{13}CNMR: δ 20.01, 24.88, 27.19, 27.24, 27.84, 33.28, 40.27, 41.69, 71.55, 74.49, 78.28, 78.36, 125.16, 125.38, 132.56, 140.42.

NMR data were not given in original reference.[21,3]

Synthesis of Compound 23

A flame-dried 50 mL round bottom flask was equipped with a stir bar and 20 ml of THF. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose (0.5406 g, 1 mmol) and 1.8 mL of citronellol were added to the round bottom flask. In a separate vial, *p*-toluenesulfonic acid monohydrate was dissolved in THF and then syringed into the reaction mixture. The reaction was let to reflux for 30 hours and followed by TLC (2:1 hexane:ethyl acetate) until consumption of the starting material. Flash chromatography (6:1 hexane:ethyl acetate) immediately followed to isolate a colorless syrup in a 30% yield (0.20g).

^{1}H NMR: δ 0.809 (d, 3H, 1 x CH_3 (S or R), *J* 4.0 Hz), 0.91 (d, 3H, 1 x CH_3 (R or S), *J* 3.9 Hz), 1.1-2.0 (m, 5H, H'-2, H'-2', H'-3, H'-3', H'-4), 1.62, 1.71 (s, 6H, 2 x CH_3), 3.63-3.70 (m, 2H, H-6, H-6'), 3.6-3.95 (m, 3H, H-5, H'-1, H'-1'), 4.0-4.2 (m, 8H, 4 x C$\underline{H_2}$Ph), 4.41 (d, 1H, H-1 (S or R), *J* 7.87 Hz), 4.47 (d, 1H, H-1 (R or S), *J* 7.81 Hz), 4.5-5.2 (m, 4H, H-2, H-3, H-4, H'-4), 7.15-7.4 (m 20 H, Ar-H).

Synthesis of compounds 25 and 18

A 50 mL round bottom flask was equipped with a stir bar and molecular sieves. D-Glucose and 15 mL of THF were added and refluxed until the sugar started to dissolve. Citronellol and *p*-toluenesulfonic acid monohydrate were then added and the reaction mixture was let to reflux. It was monitored by TLC in 4:1 toluene:methanol for 36 hours until no more starting material reacted. The solution was gravity filtered to remove unreacted D-glucose and the filtrate was evaporated to a yellow syrup. It was then added to a 100mL three neck round bottom flask equipped with a stir bar and molecular sieves.

20 mL of pyridine were then added to dissolve the sugar and the reaction mixture was let to stir for ten minutes. Acetic anhydride (10 mL) was then added and the reaction mixture was heated at 60 °C over night. TLC (2:1 hexane:ethyl acetate) indicated the consumption of the starting material and the reaction mixture was then quenched with 100 g of ice and 5% sulfuric acid. Flash chromatography in 6:1 hexane:ethyl acetate isolated a 41% yield of compound **25** and 37% yield of compound **18** both being a clear syrup.

^{1}H NMR (**25**): δ ^{1}H NMR: δ 0.853 (d, 3H, 1 x CH_3 (S), J 4.0 Hz), 0.86 (d, 3H, 1 x CH_3 (R), J 3.9 Hz), 1.2-1.4 (m, 5H, H'-2, H'-2', H'-3, H'-3', H'-4), 1.5, 1.7 (s, 6H, 2 x CH_3), 2.0-2.1 (s, 12H, 4 x $COCH_3$), 3.48 (m, 1H, H'-1), 3.66 (m, 1H, H-5), 3.7 (m, 1H, H'-1'), 4.1 (dd, 1H, H-6, J 2.2, 12.26 Hz), 4.24 (dd, 1H, H-6', J 4.5, 12.26 Hz), 4.46 (d, 1H, H-1 (S), J 2.2 Hz), 4.48 (d, 1H, H-1 (R), J 2.2 Hz), 4.95 (dd, 1H, H-3, J 8.05, 9.52 Hz), 5.05 (m, 2H, H-2, H'-4), 5.19 (dd, 1H, H-4, J 9.52, 9.52).

^{13}C NMR: δ 21.80, 21.82, 22.0, 26.53, 26.78, 37.34, 37.42, 38.29, 69.16, 69.44, 69.68, 72.23, 72.84, 73.98, 74.11, 80.01, 101.85, 102.01, 125.61, 131.2, 170.33, 171.24, 171.27, 171.66.

^{1}H NMR (**18**): δ ^{1}H NMR: δ 0.84 (d, 3H, 1 x CH_3 (S), J 4.0 Hz), 0.86 (d, 3H, 1 x CH_3 (R), J 3.9 Hz), 1.08-1.4 (m, 5H, H'-2, H'-2', H'-3, H'-3', H'-4), 1.59, 1.67 (s, 6H, 2 x CH_3), 2.0-2.1 (s, 12H, 4 x $COCH_3$), 3.5 (m, 1H, H'-1), 3.66 (m, 1H, H-5), 3.8 (m, 1H, H'-1'), 4.1 (dd, 1H, H-6, J 2.2, 12.26 Hz), 4.2 (dd, 1H, H-6', J 4.5, 12.26 Hz), 4.34 (d, 1H, H-1 (S), J 8.1 Hz), 4.35 (d, 1H, H-1 (R), J 8.1 Hz), 4.9

(dd, 1H, H-3, *J* 8.05, 9.52 Hz), 5.06 (m, 2H, H-2, H'-4), 5.5 (dd, 1H, H-4, *J* 9.52, 9.52).

NMR data were not given in original reference.[18]

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APPENDIX

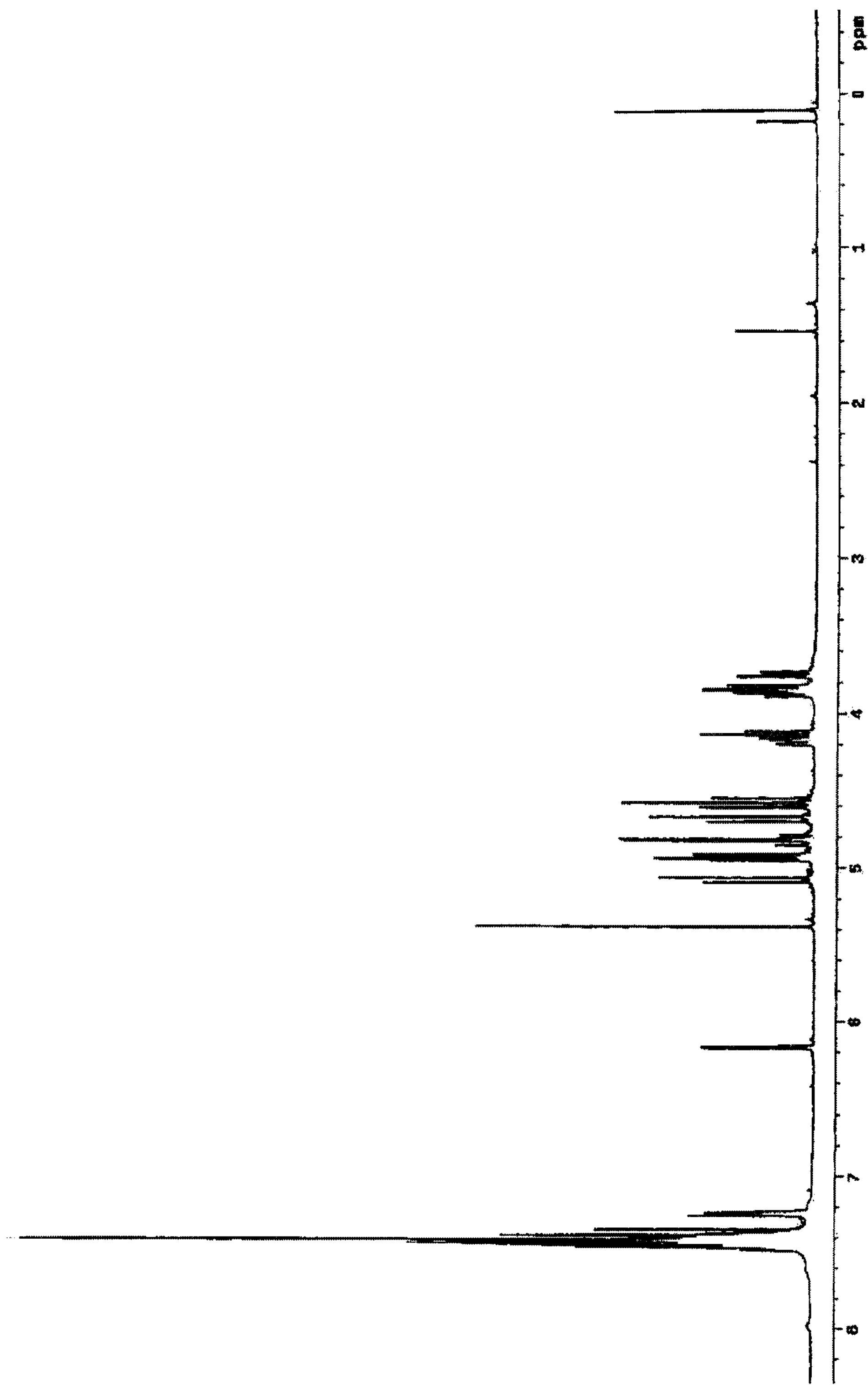


Figure 11: ^{1}H NMR of **2**

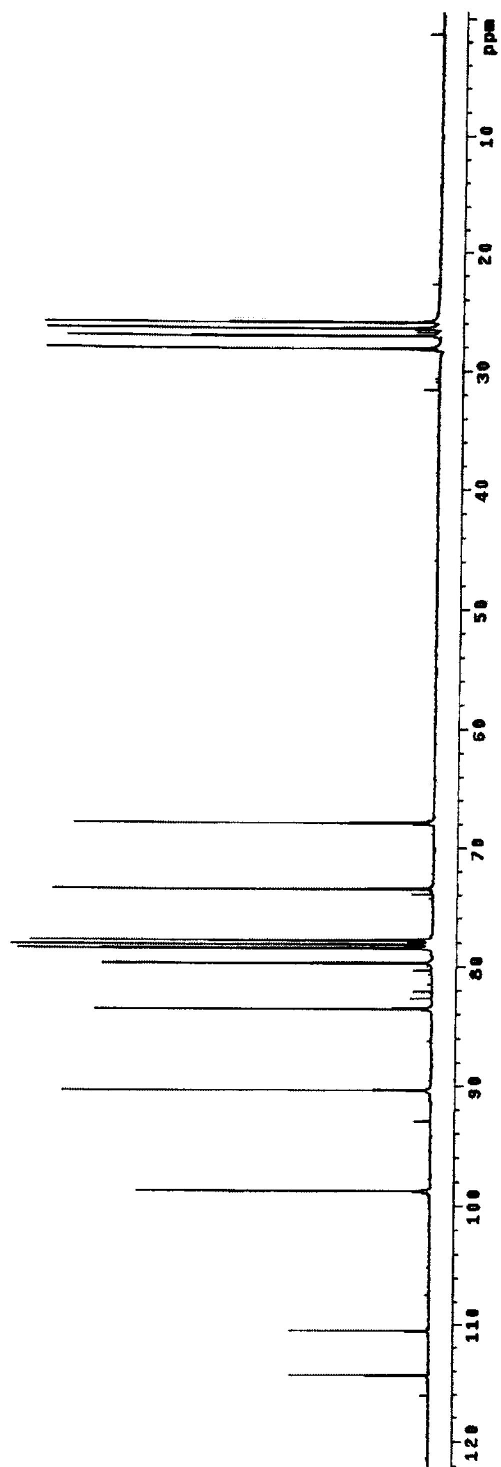


Figure 12: ^{13}C NMR of **2**

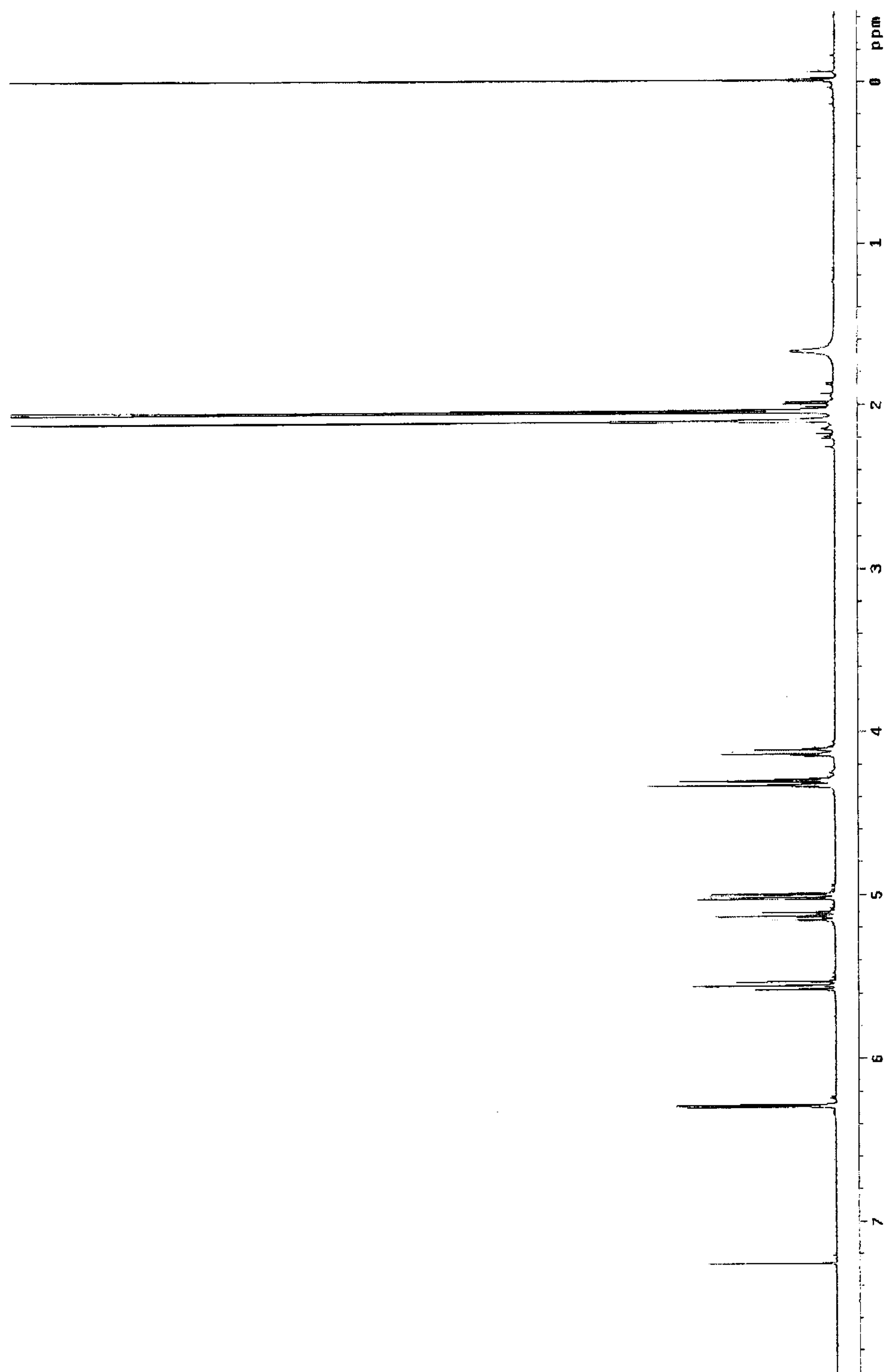


Figure 13: ^{1}H NMR of **4**

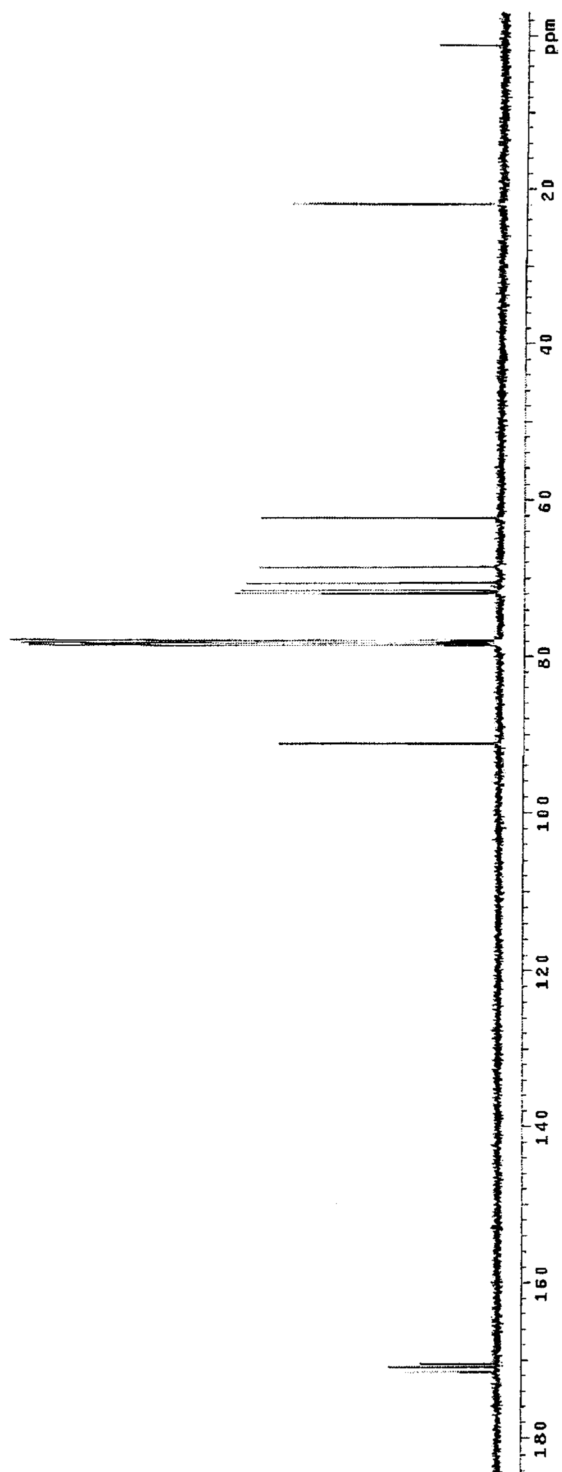


Figure 14: ^{13}C NMR of **4**

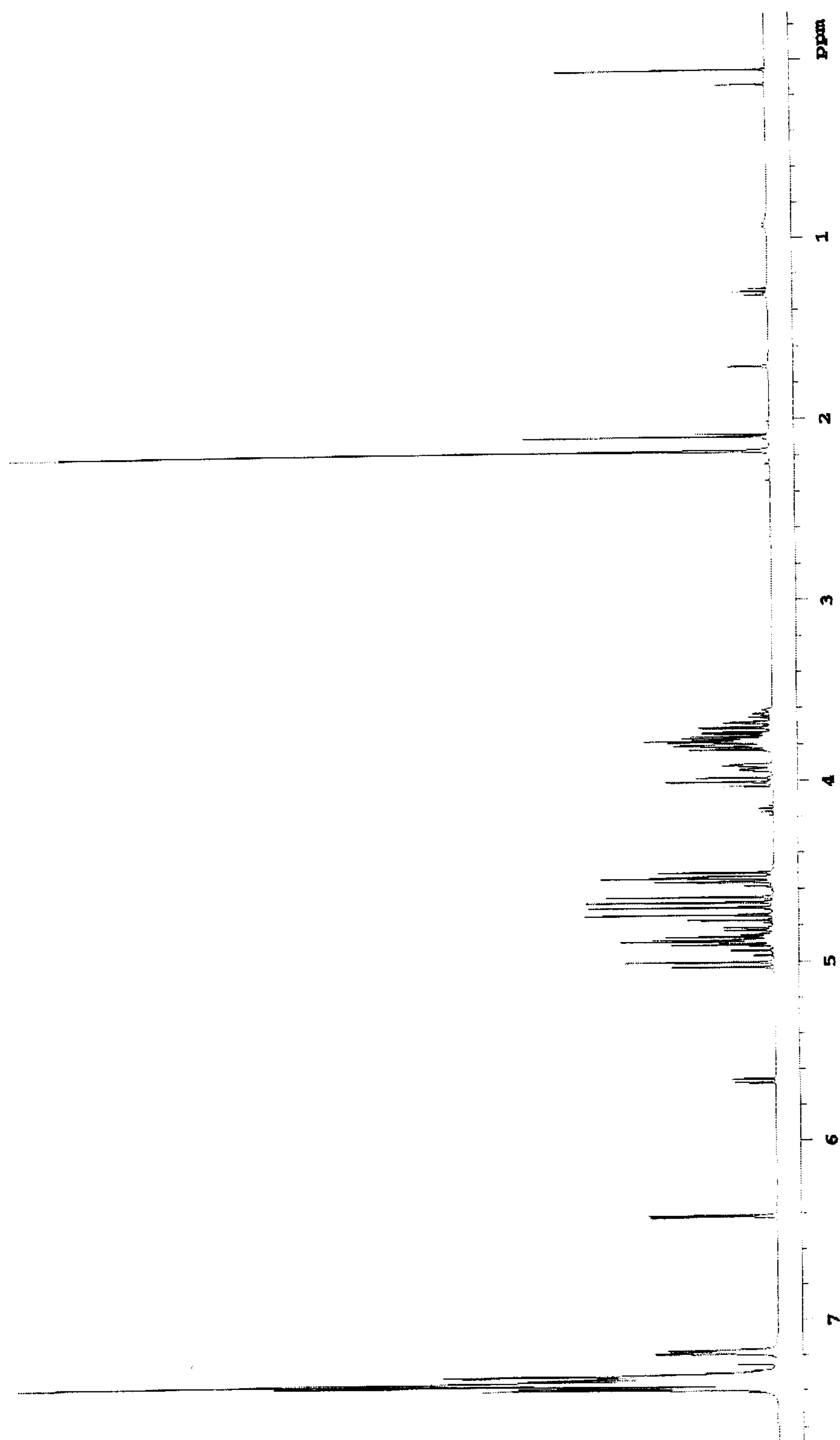


Figure 15: ^{1}H NMR of **5**

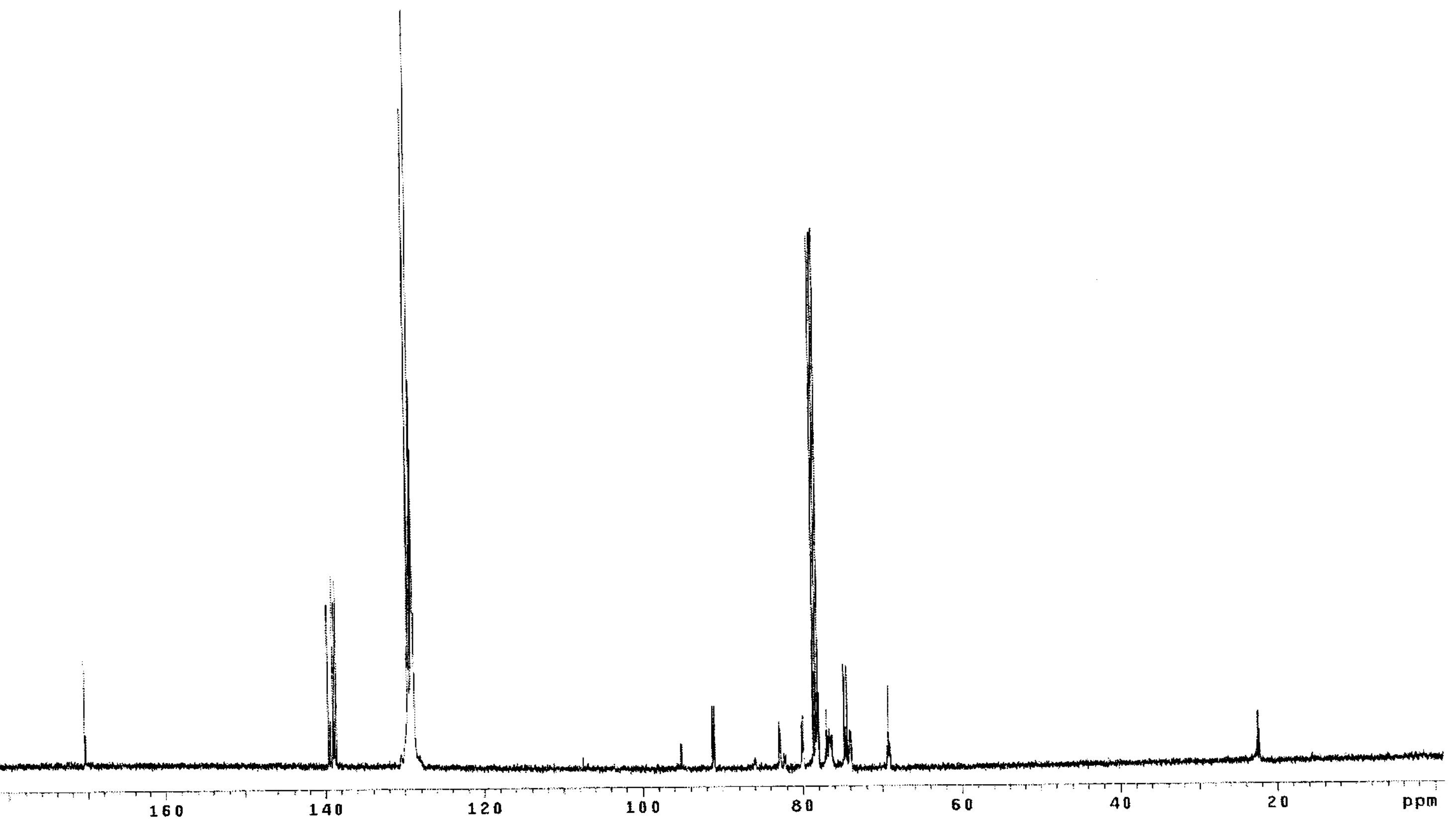


Figure 16: ^{13}C NMR of **5**

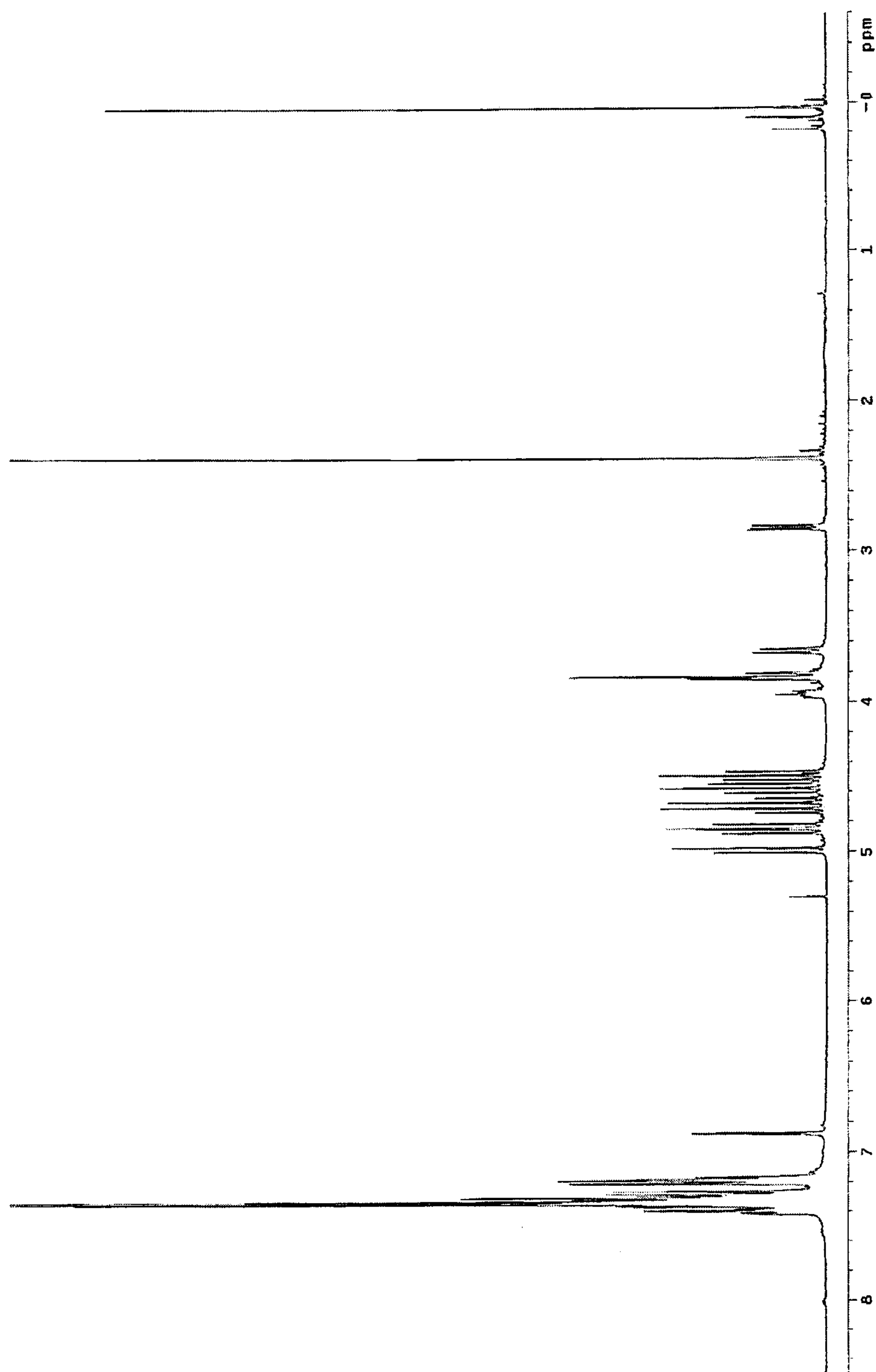


Figure 17: ^{1}H NMR of **6**

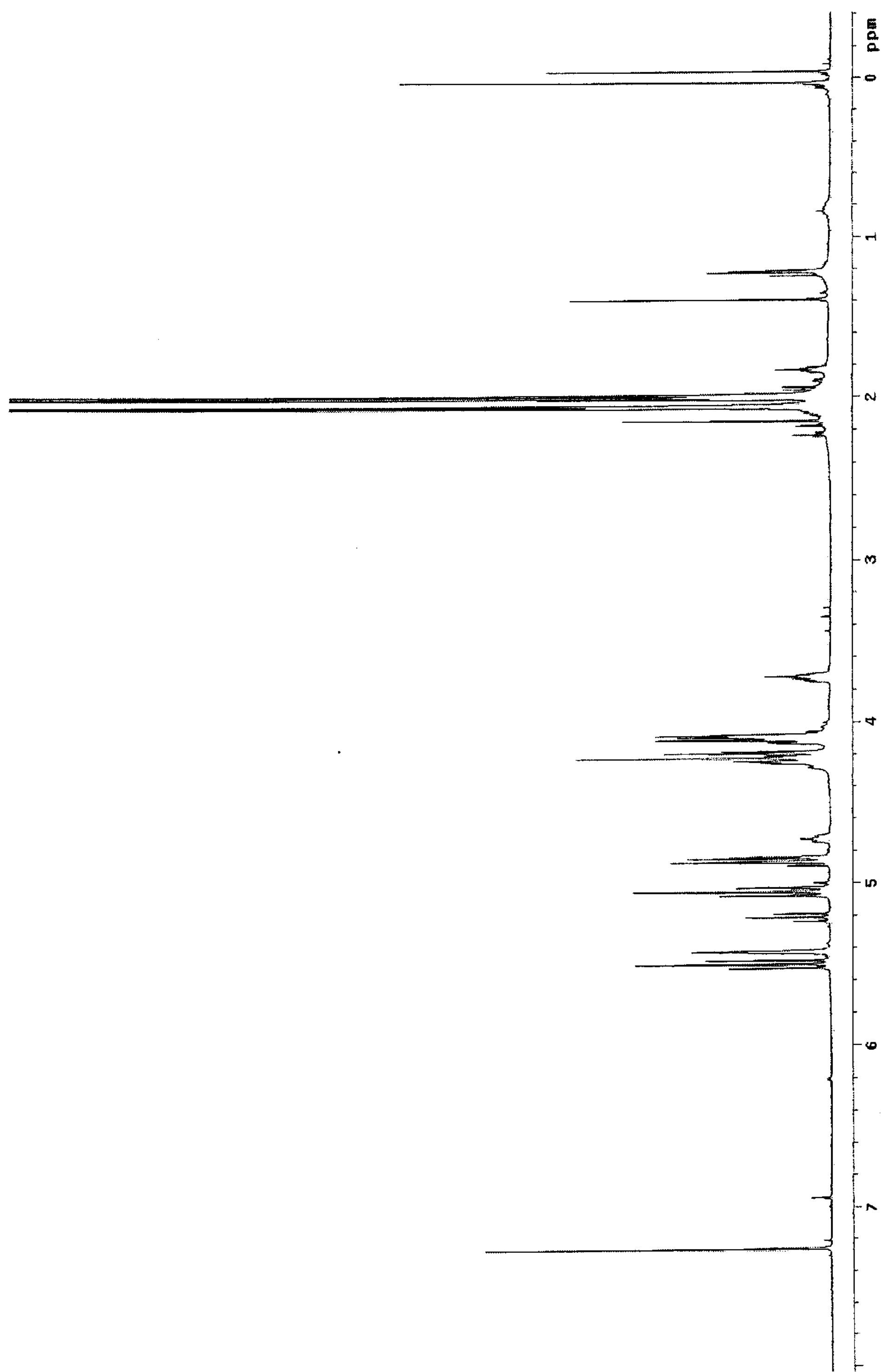


Figure 18: ^{1}H NMR of 7

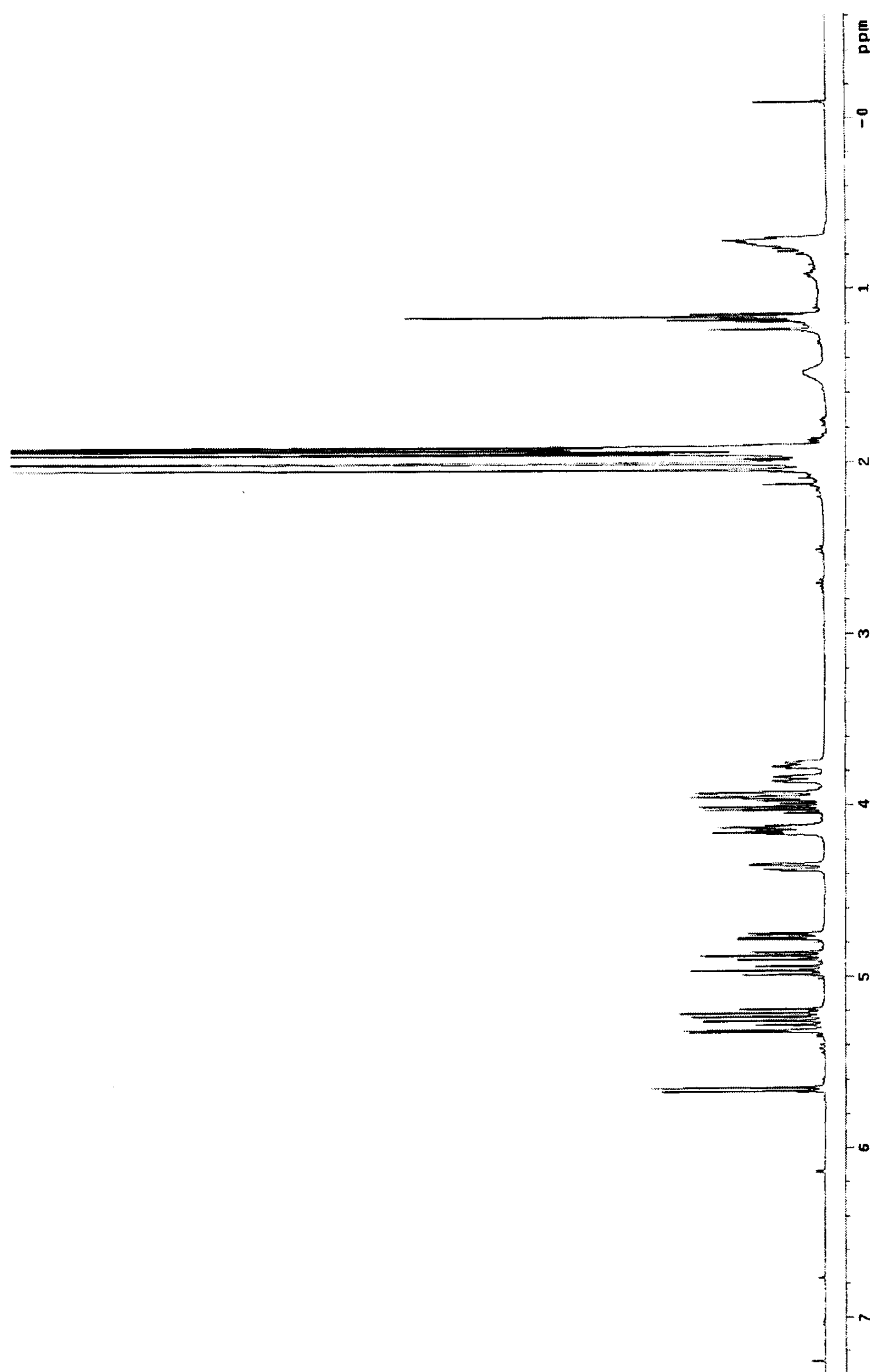


Figure 19: ^{1}H NMR of **9**

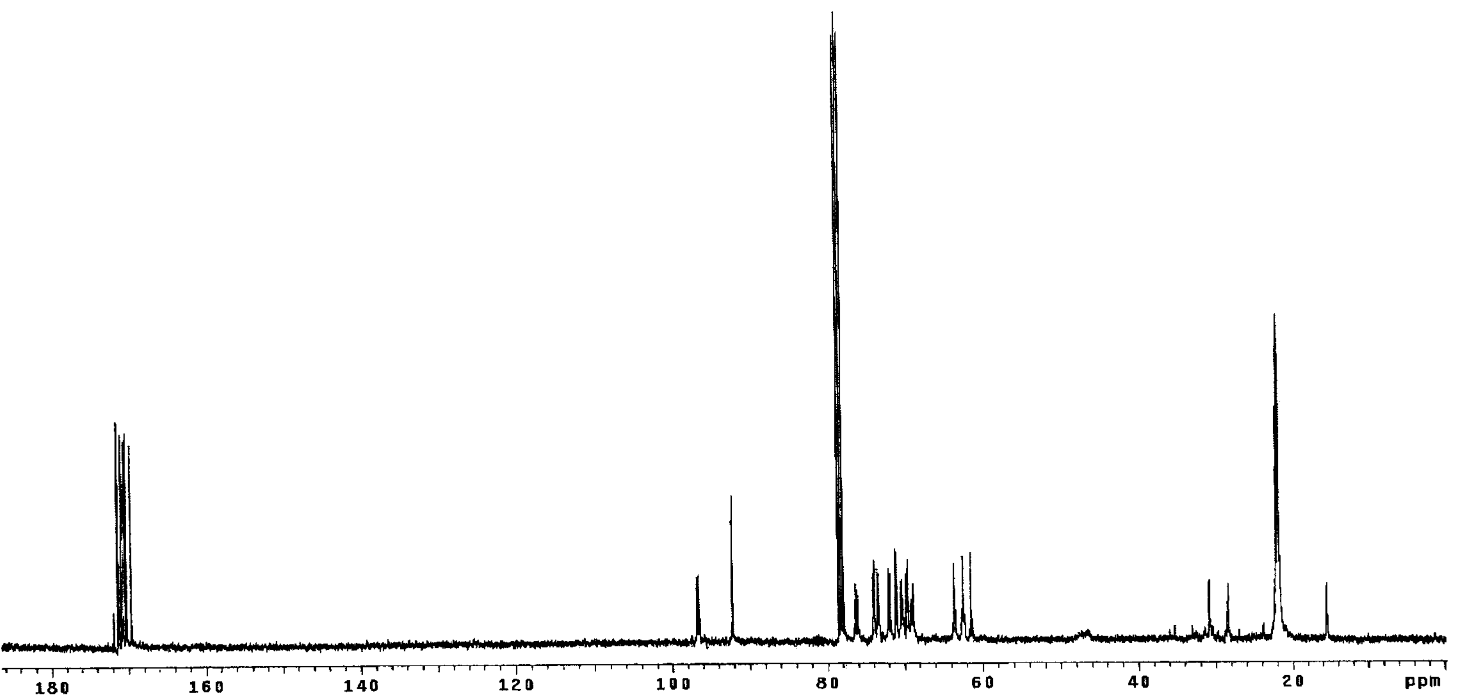
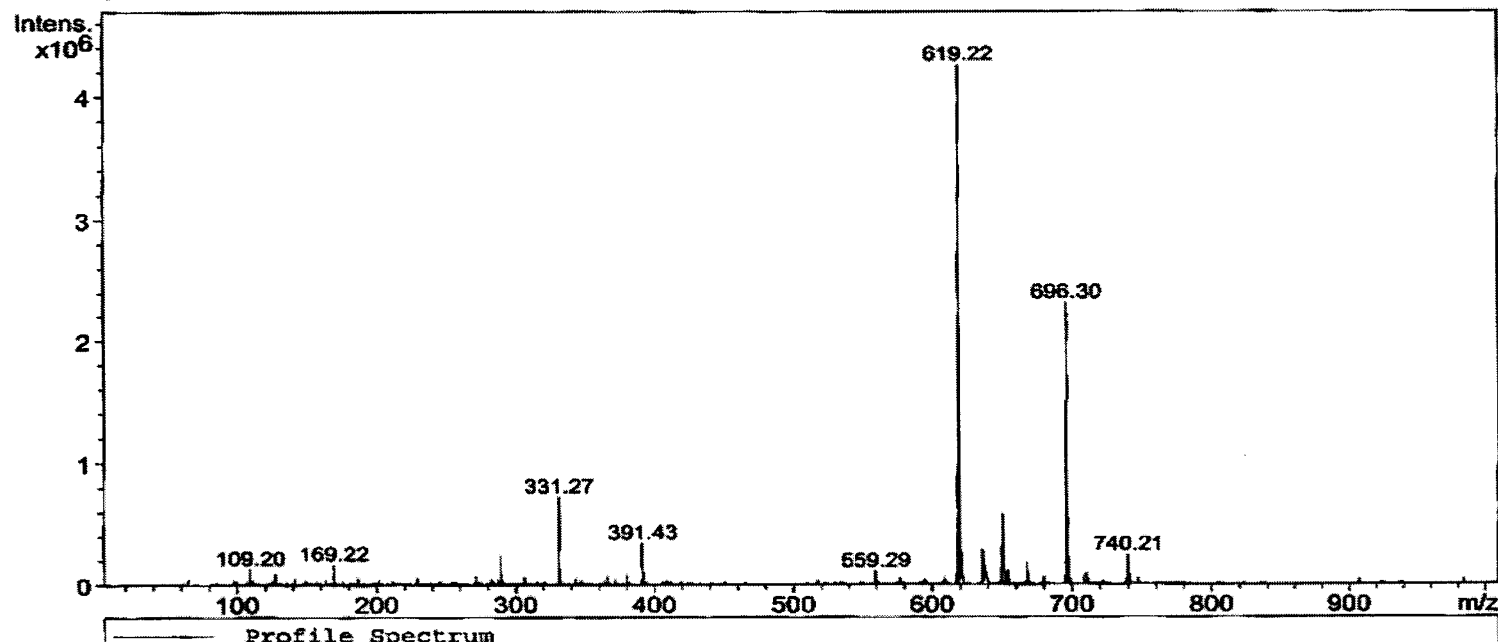


Figure 20: ^{13}C NMR of **9**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
109.20	134310	0.20	619.22	4263444	0.30	668.22	176711	0.30
169.22	170802	0.30	619.85	1219348	0.20	696.30	2312433	0.40
289.30	243982	0.40	620.86	280227	0.40	697.10	724374	0.30
331.27	720825	0.40	636.30	288103	0.30	698.17	219823	0.30
332.25	128826	0.30	637.15	231102	0.30	739.23	107949	0.30
391.43	342531	0.50	638.21	121201	0.20	740.21	243644	0.40
392.45	110139	0.40	650.48	576151	0.50			
559.29	111878	0.40	654.13	116608	0.40			

Figure 21: Mass Spectrum of **9**

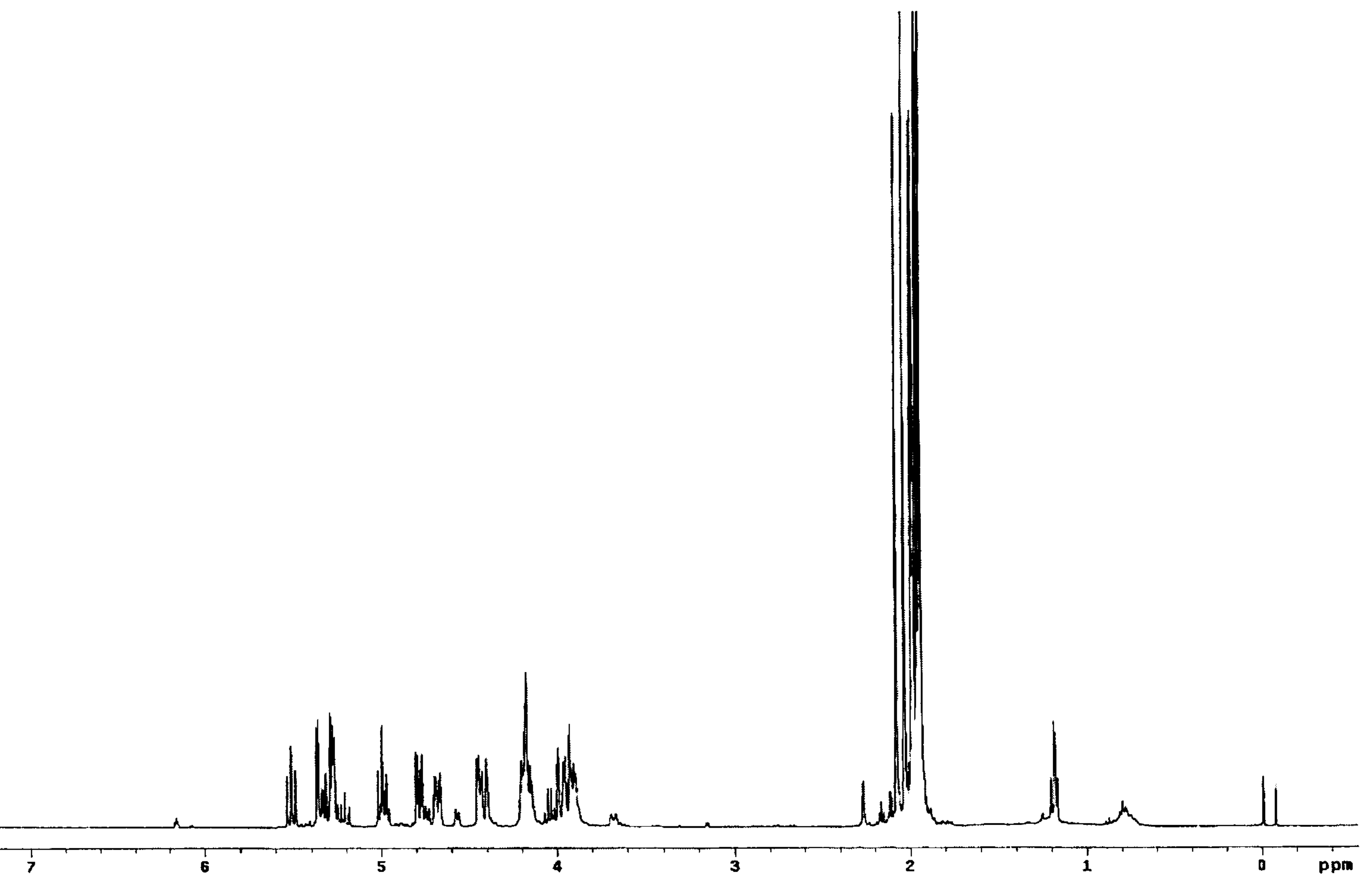


Figure 22: ^{1}H NMR of **10**

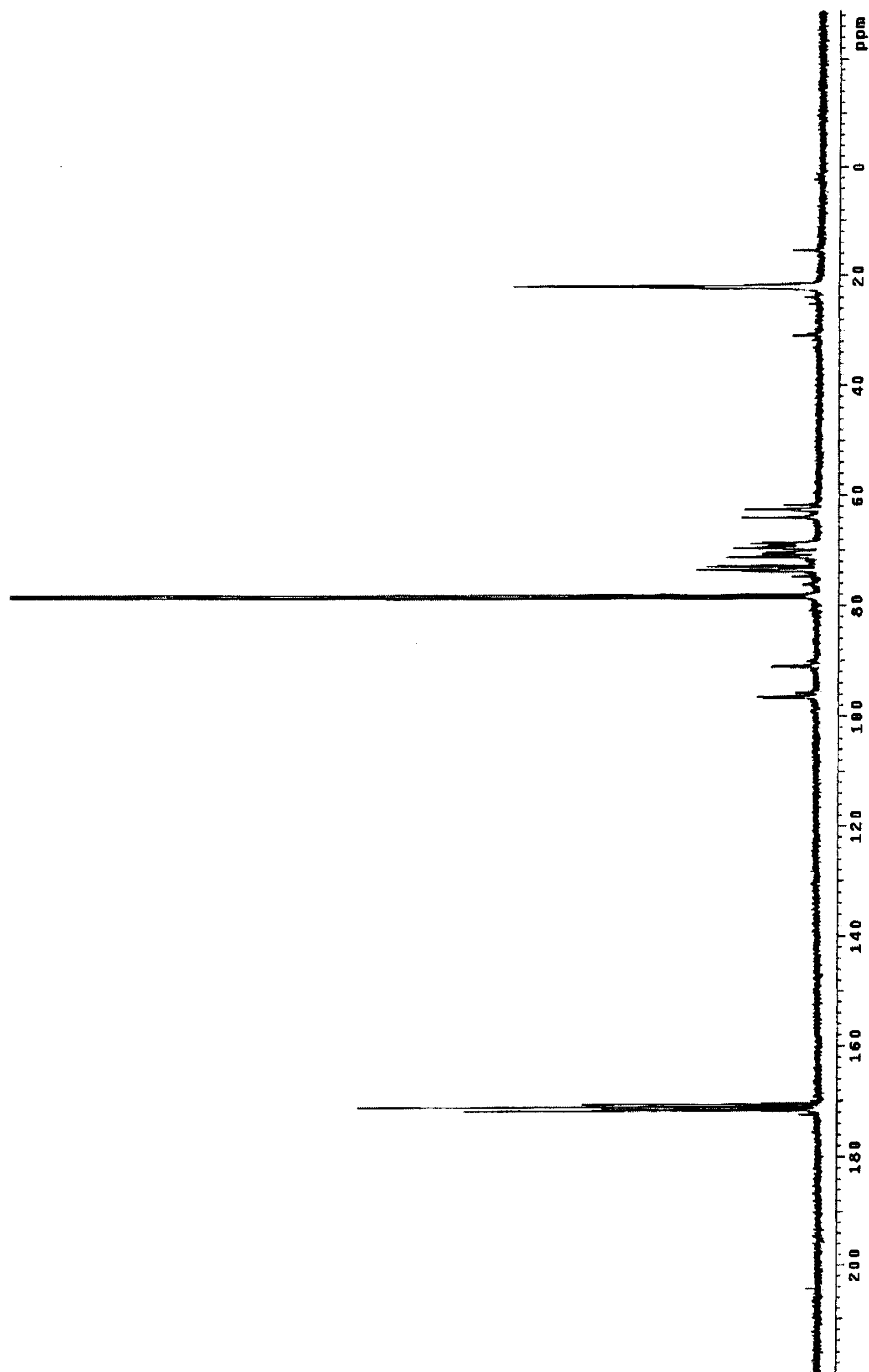


Figure 23: ^{13}C NMR of **10**

Acquisition Parameter

Ion Source Type	ESI	Ion Polarity	Positive		
Mass Range Mode	Std/Normal	Scan Begin	15.00 m/z	Scan End	2200.00 m/z
Skim 1	44.3 Volt	Cap Exit Offset	82.9 Volt	Trap Drive	53.7
Accumulation Time	4928 µs	Averages	10 Spectra		

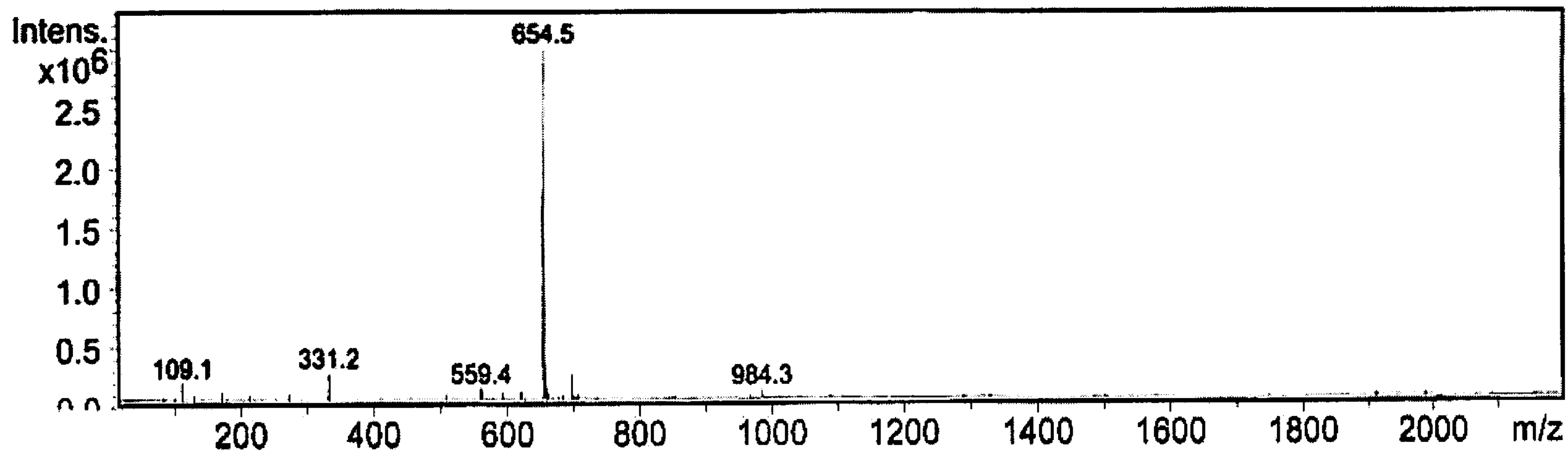


Figure 24: Mass spectrum of **10**

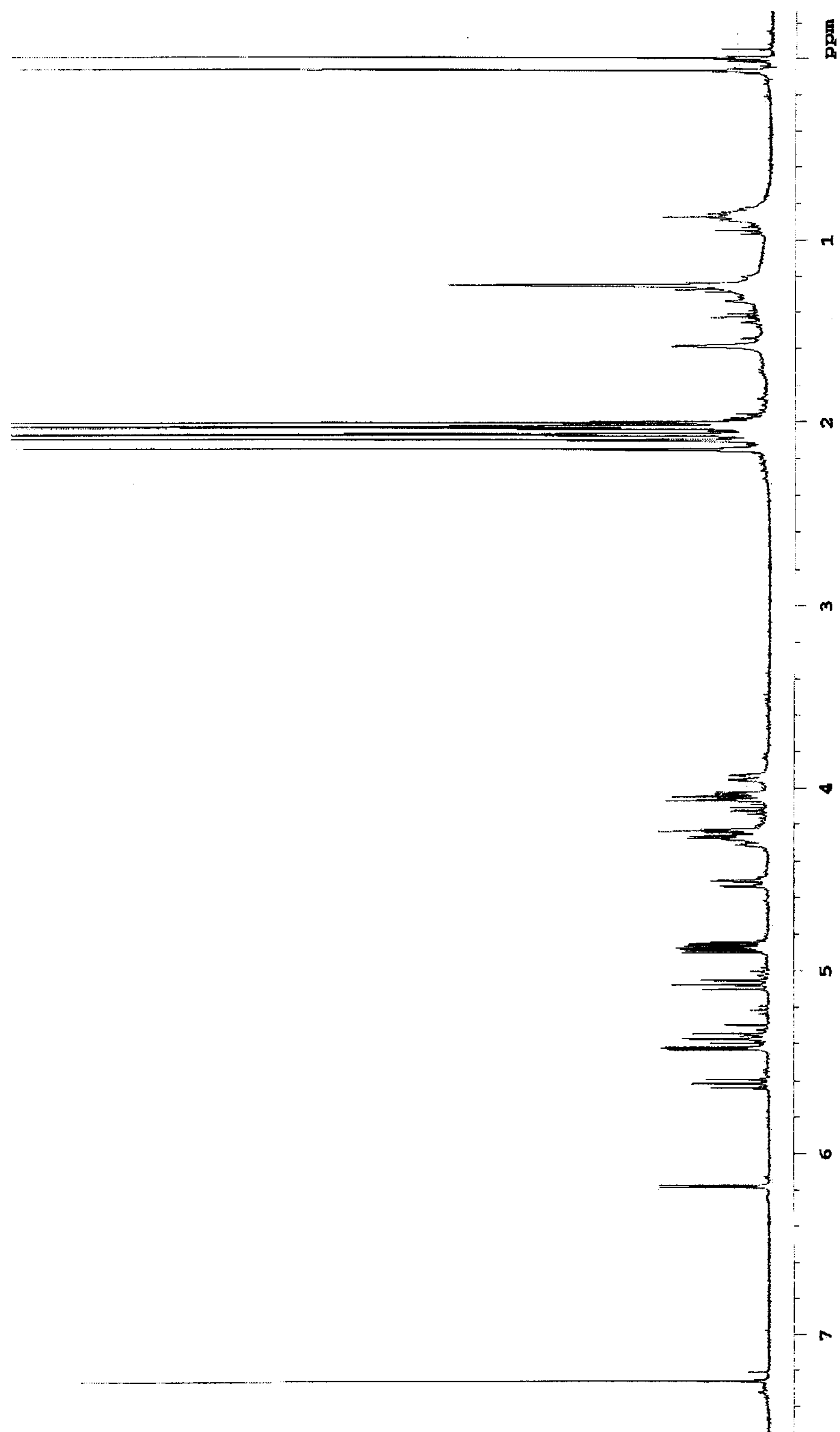


Figure 25: ^{1}H NMR of **11**

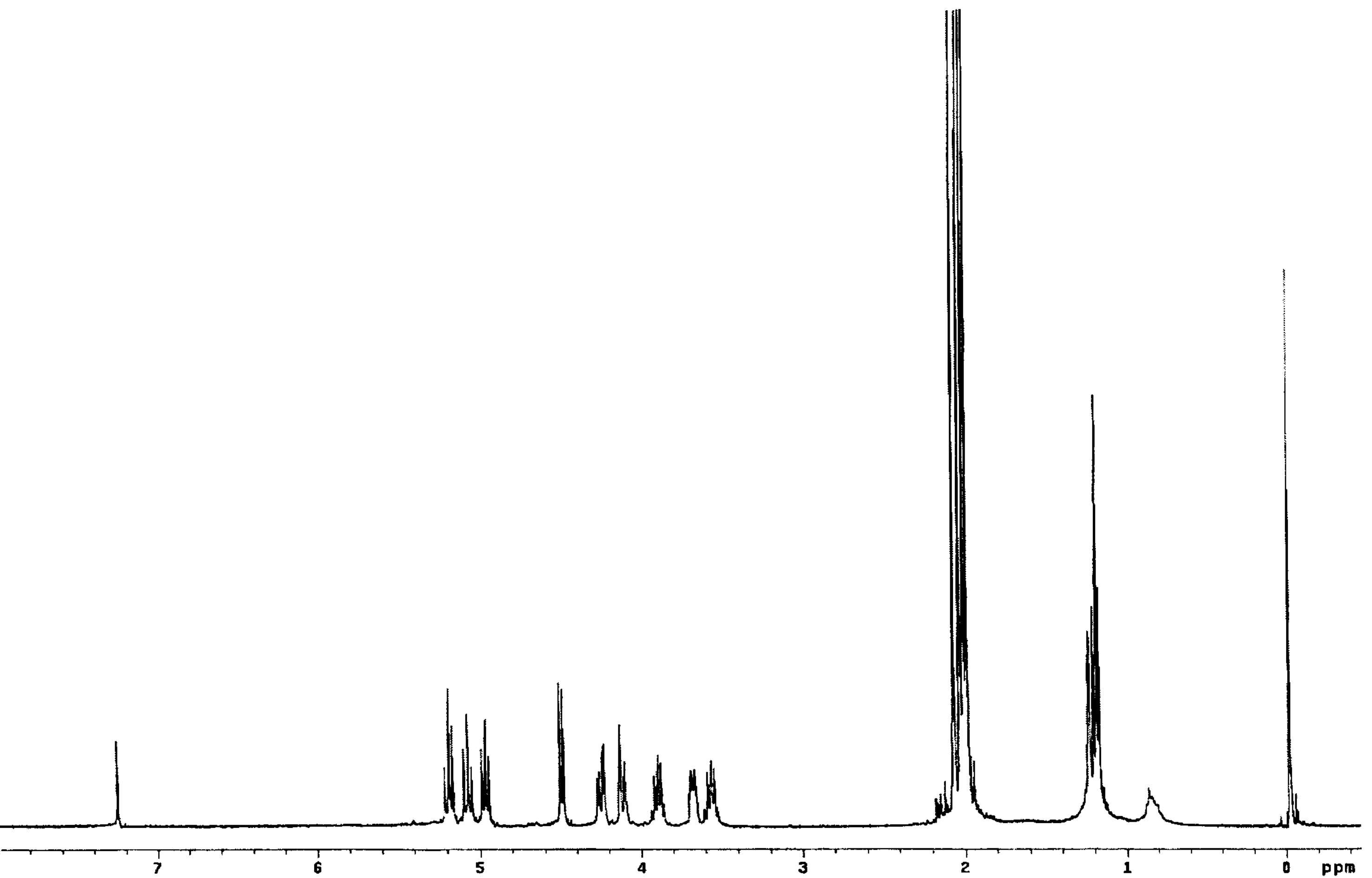


Figure 26: ^{1}H NMR of **12** from compound **4**

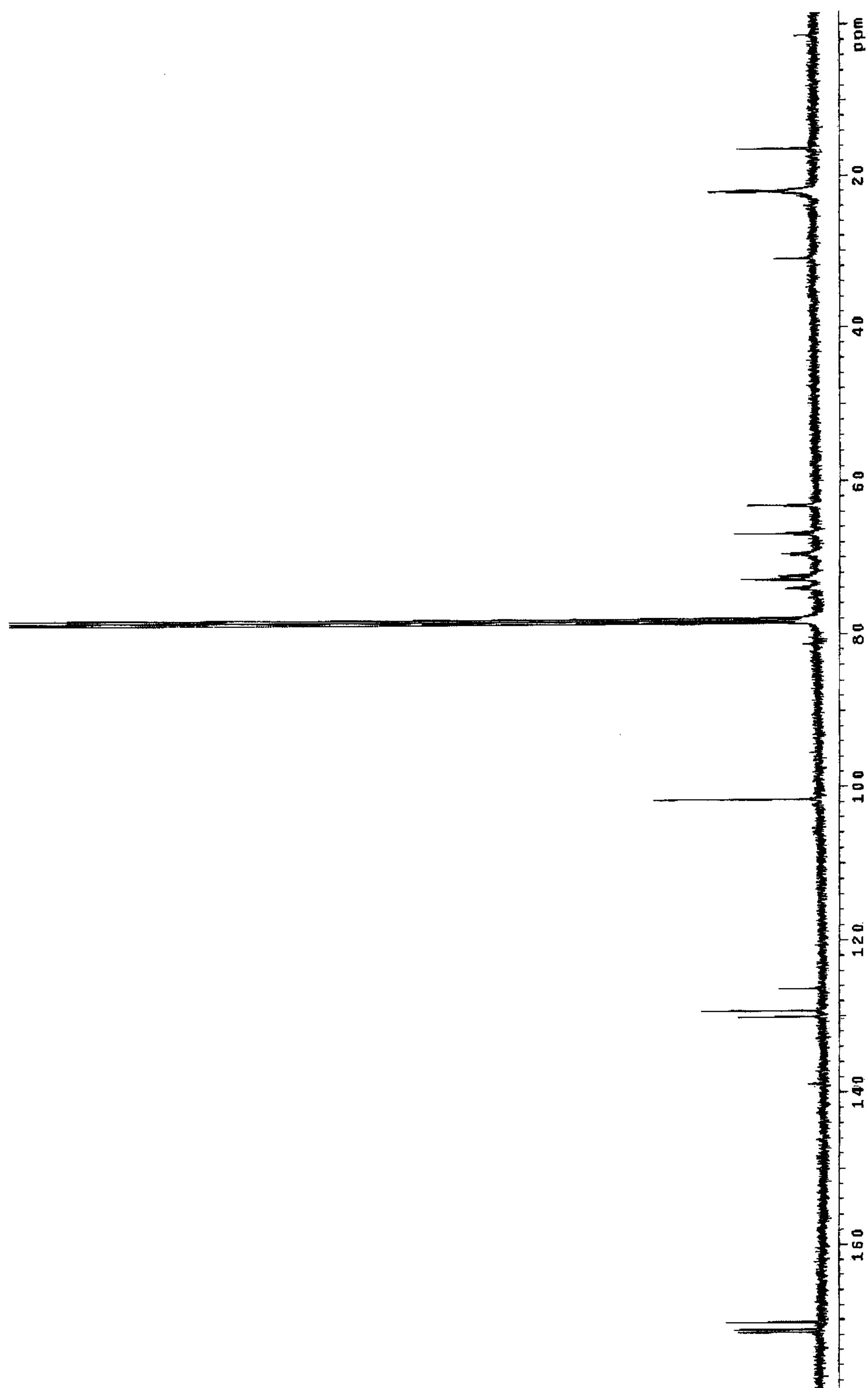
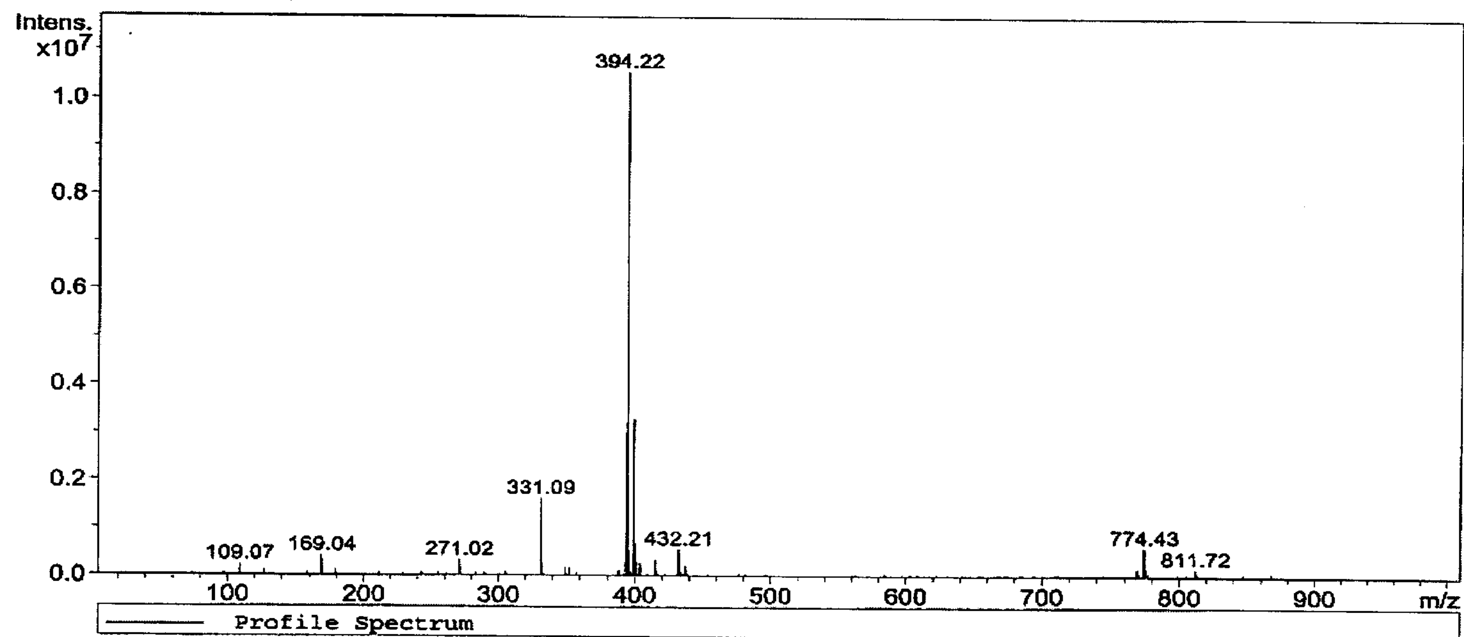


Figure 27: ^{13}C NMR of **12** from compound **4**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
109.07	229905	0.30	388.63	102120	0.20	415.14	326432	0.30
169.04	420085	0.30	394.22	10566889	0.30	432.21	560175	0.30
179.29	129541	0.20	395.18	2096379	0.30	437.23	216691	0.30
271.02	331843	0.20	396.19	531008	0.30	769.29	165717	0.20
331.09	1621956	0.30	399.17	3278039	0.30	769.54	143294	0.20
332.08	251787	0.40	400.18	676887	0.20	774.43	611518	0.50
349.23	165047	0.30	401.15	123938	0.30	775.19	328901	0.30
352.18	165067	0.40	401.52	289024	0.20	776.20	128950	0.20
388.22	114979	0.20	403.96	267182	0.20	811.72	166907	0.20

Figure 28: Mass Spectrum of **12** from compound **4**

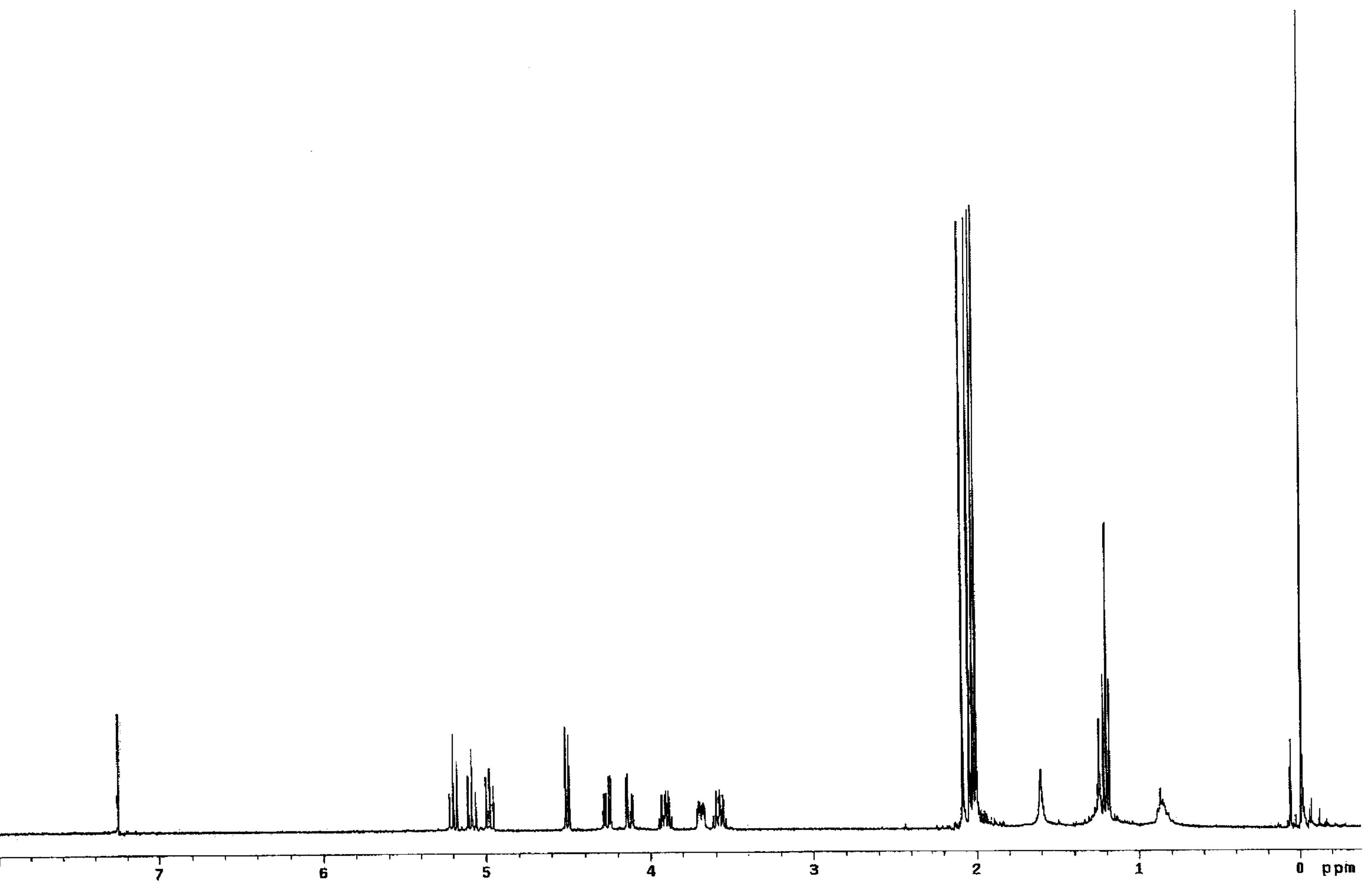


Figure 29: ^{1}H NMR of **12** from compound **13**

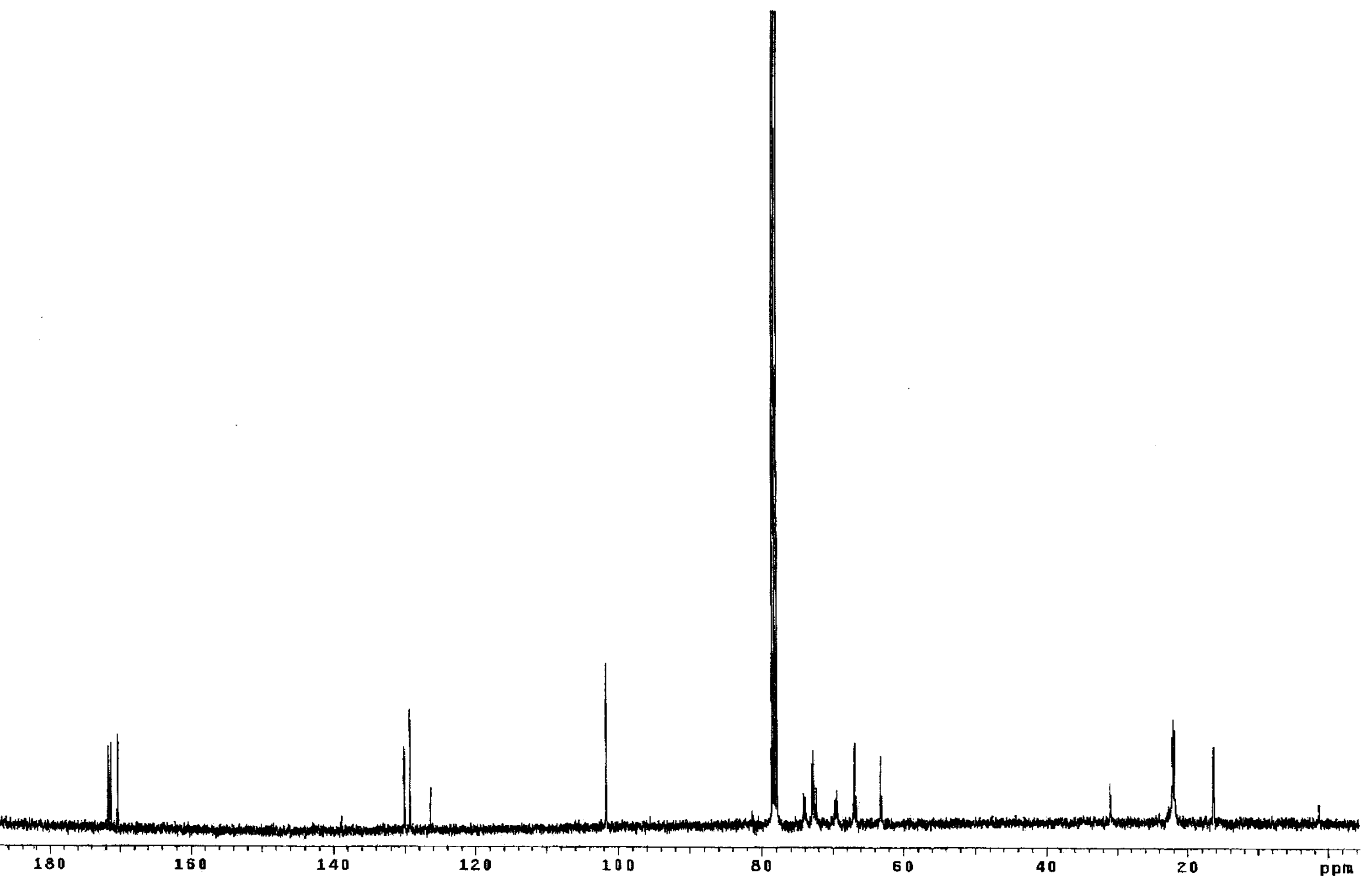
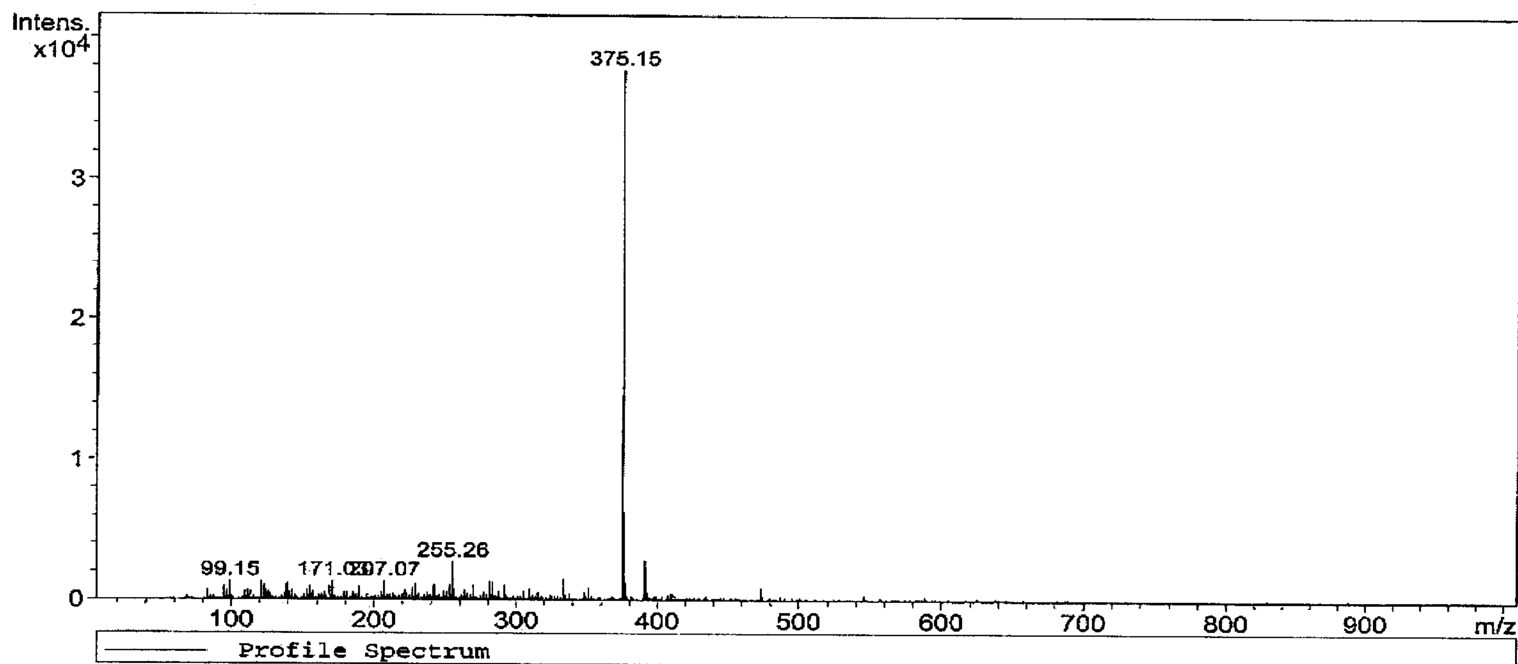


Figure 30: ^{13}C NMR of **12** from compound **13**



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
95.06	1005	0.30	207.07	1392	0.30	283.26	1307	0.40
99.15	1372	0.30	229.02	1156	0.30	291.16	1145	0.20
121.04	1331	0.30	242.08	1151	0.30	333.15	1581	0.30
123.06	1073	0.30	253.25	1160	0.40	375.15	37805	0.30
139.01	1314	0.20	255.26	2766	0.40	376.06	6260	0.30
171.03	1394	0.30	269.22	1149	0.40	377.05	1426	0.30
189.09	1021	0.20	281.25	1358	0.30	391.16	2895	0.30

Figure 31: Mass Spectrum of **12** from compound **13**

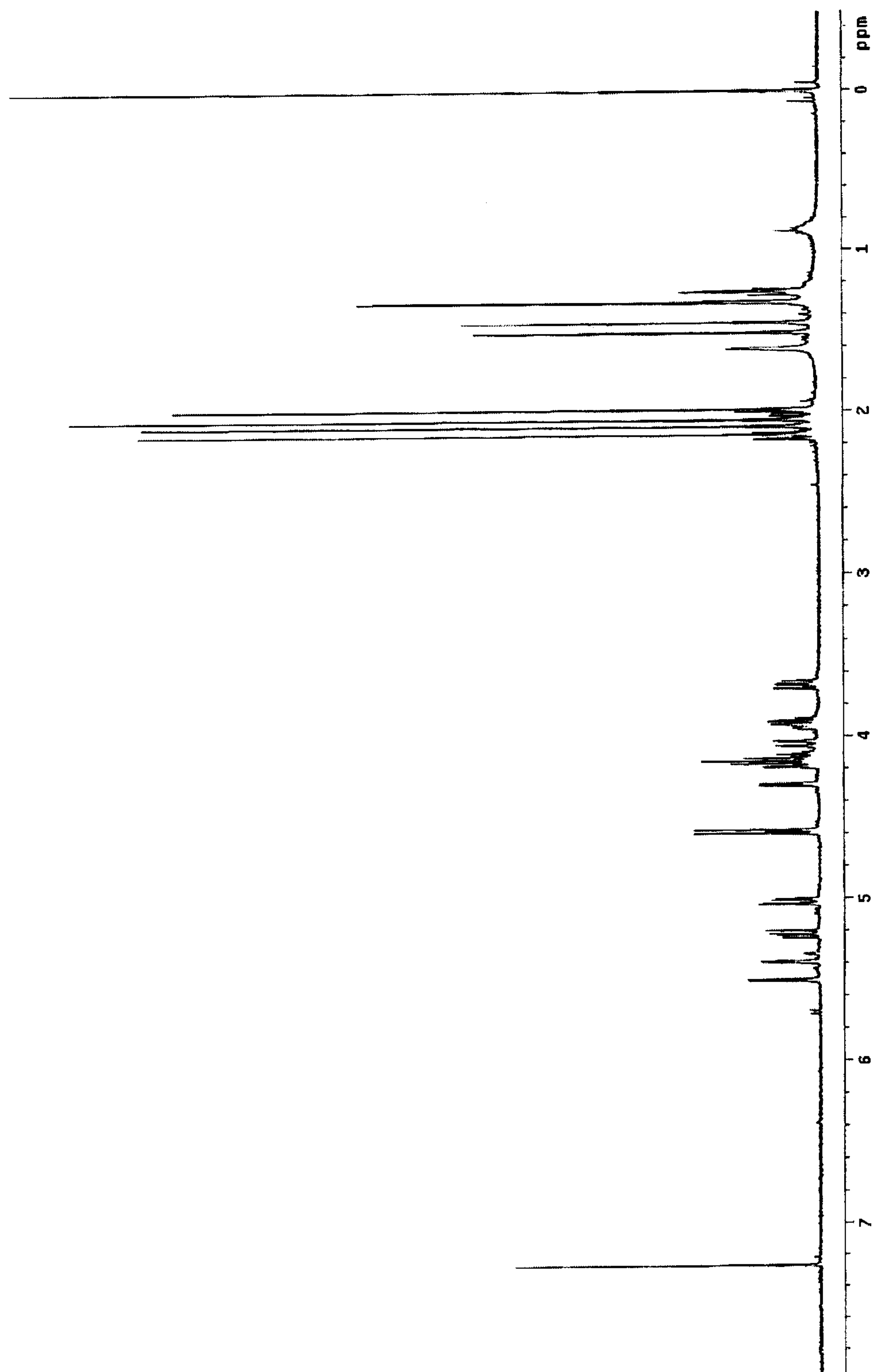


Figure 32: ^{1}H NMR of 17

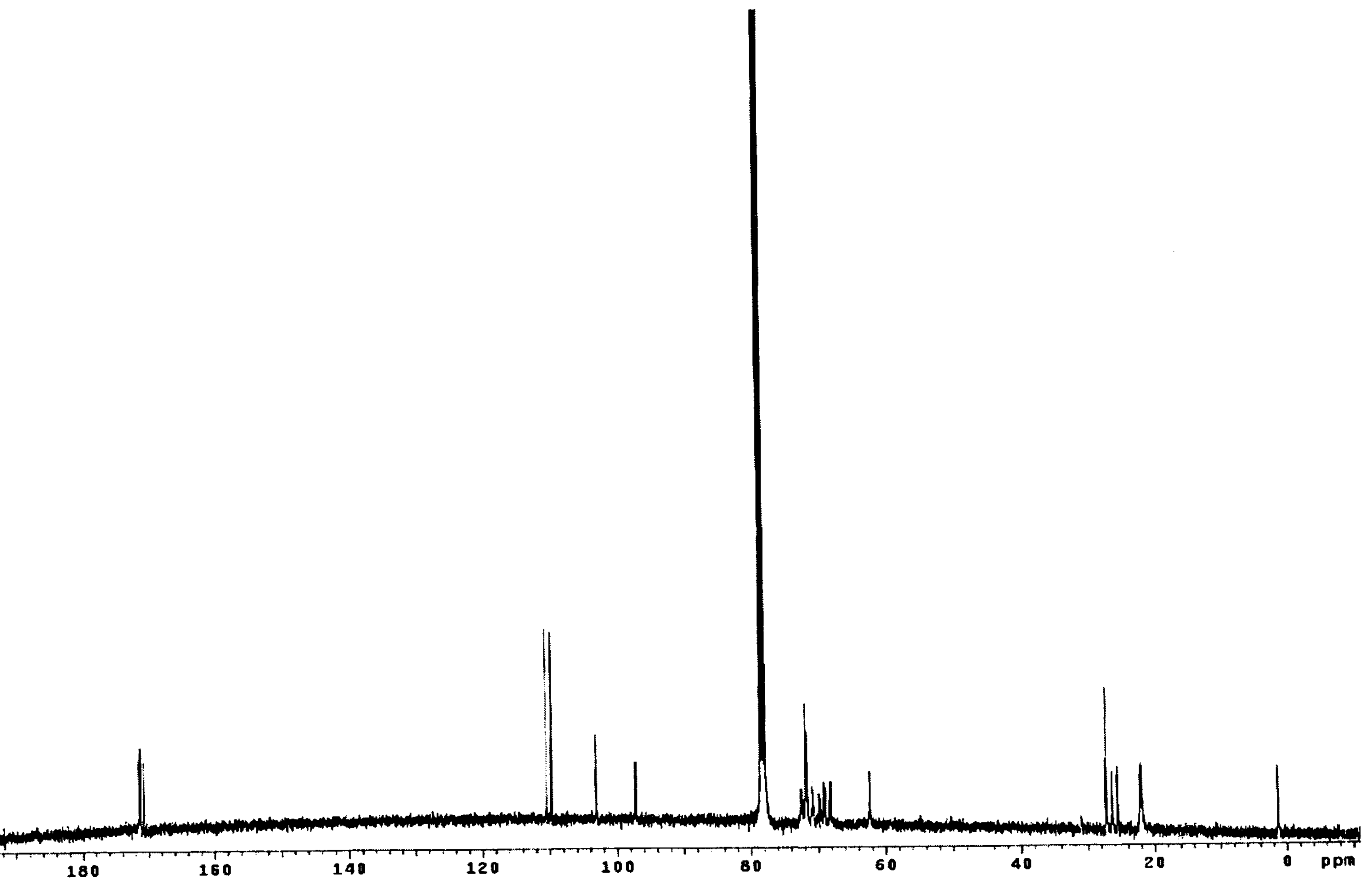
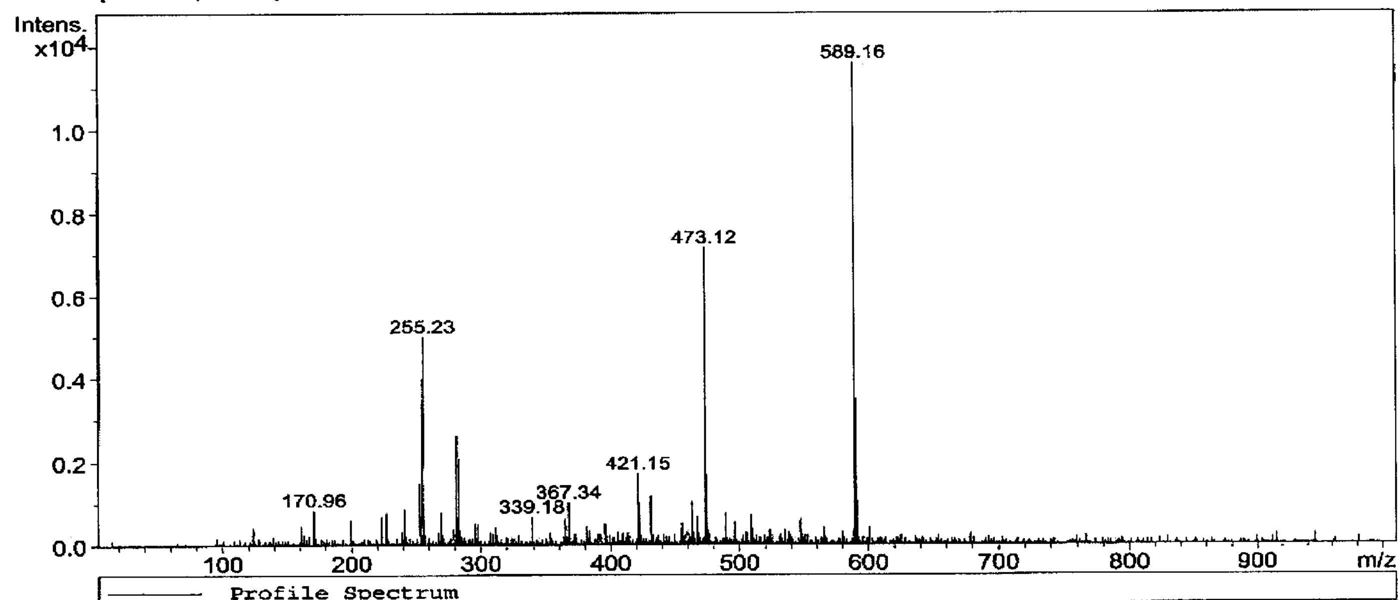


Figure 33: ^{13}C NMR of **17**

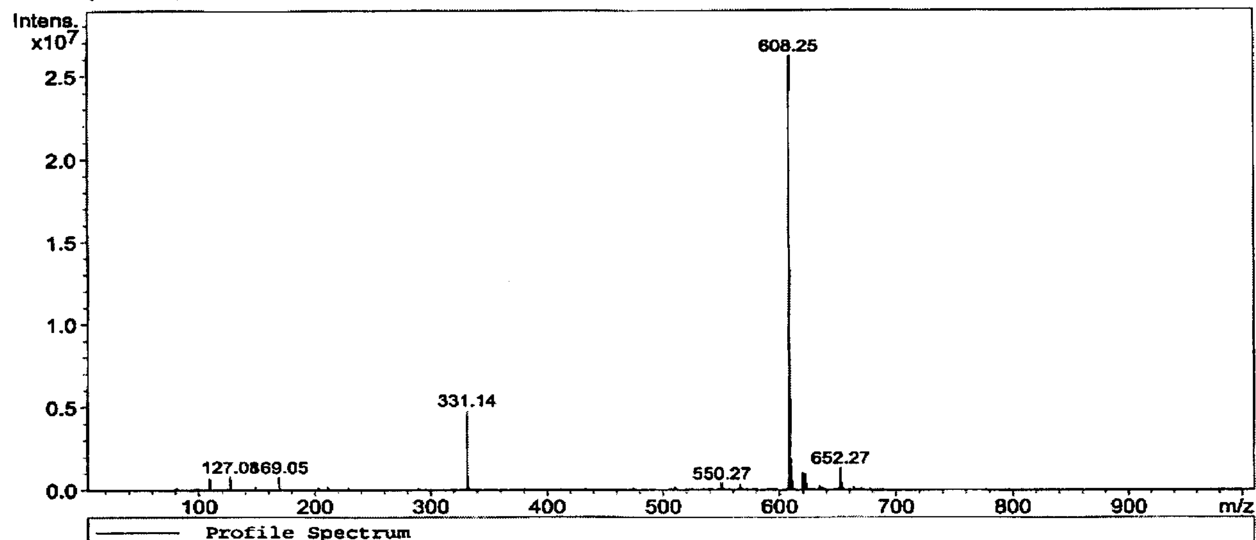


MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
170.96	845	0.30	283.25	2075	0.30	467.18	685	0.30
199.18	609	0.30	295.18	521	0.30	473.12	7165	0.40
223.22	675	0.20	339.18	678	0.30	474.09	1707	0.40
227.24	798	0.50	365.02	658	0.30	489.14	758	0.20
241.16	879	0.20	367.34	1023	0.30	496.13	540	0.40
253.21	1490	0.20	395.45	514	0.40	509.15	706	0.30
255.23	5007	0.30	421.15	1709	0.30	547.18	616	0.30
256.24	970	0.30	422.20	1036	0.20	589.16	11611	0.30
269.22	794	0.30	431.12	1188	0.30	590.16	3512	0.30
281.26	2641	0.30	455.13	539	0.20	591.17	1395	0.30
282.23	648	0.20	463.17	1024	0.20			

Figure 34: Mass Spectrum (-) of **17**

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



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
80.14	104386	0.20	411.52	114110	0.20	634.23	282540	0.40
81.21	126529	0.50	432.42	134233	0.20	635.38	170633	0.60
97.14	127381	0.20	474.11	168929	0.20	636.25	156440	0.30
109.08	721082	0.30	510.20	222679	0.20	637.48	110255	0.40
127.08	827242	0.20	550.27	423773	0.40	638.29	106941	0.40
148.98	212927	0.20	551.24	145997	0.20	650.47	131858	0.20
169.05	813398	0.30	566.25	318343	0.80	651.31	105253	0.20
203.14	189233	0.20	608.25	26233410	0.30	652.27	1359621	0.40
211.06	229610	0.30	609.20	8359742	0.30	653.34	476561	0.40
229.13	155496	0.20	610.24	1799297	0.30	654.41	142288	0.20
289.12	122253	0.20	611.18	433915	0.20	663.46	239736	0.30
331.14	4835067	0.30	620.20	1100236	0.20	664.28	172228	0.20
332.14	772773	0.30	621.24	245463	0.70	669.78	131580	0.20
333.14	125513	0.30	622.30	990729	0.40	670.22	141952	0.20
364.18	106209	0.20	623.27	400641	0.30	677.93	162847	0.20
380.17	142736	0.20	633.76	123356	0.20			

Figure 35; Mass Spectrum (+) of **17**

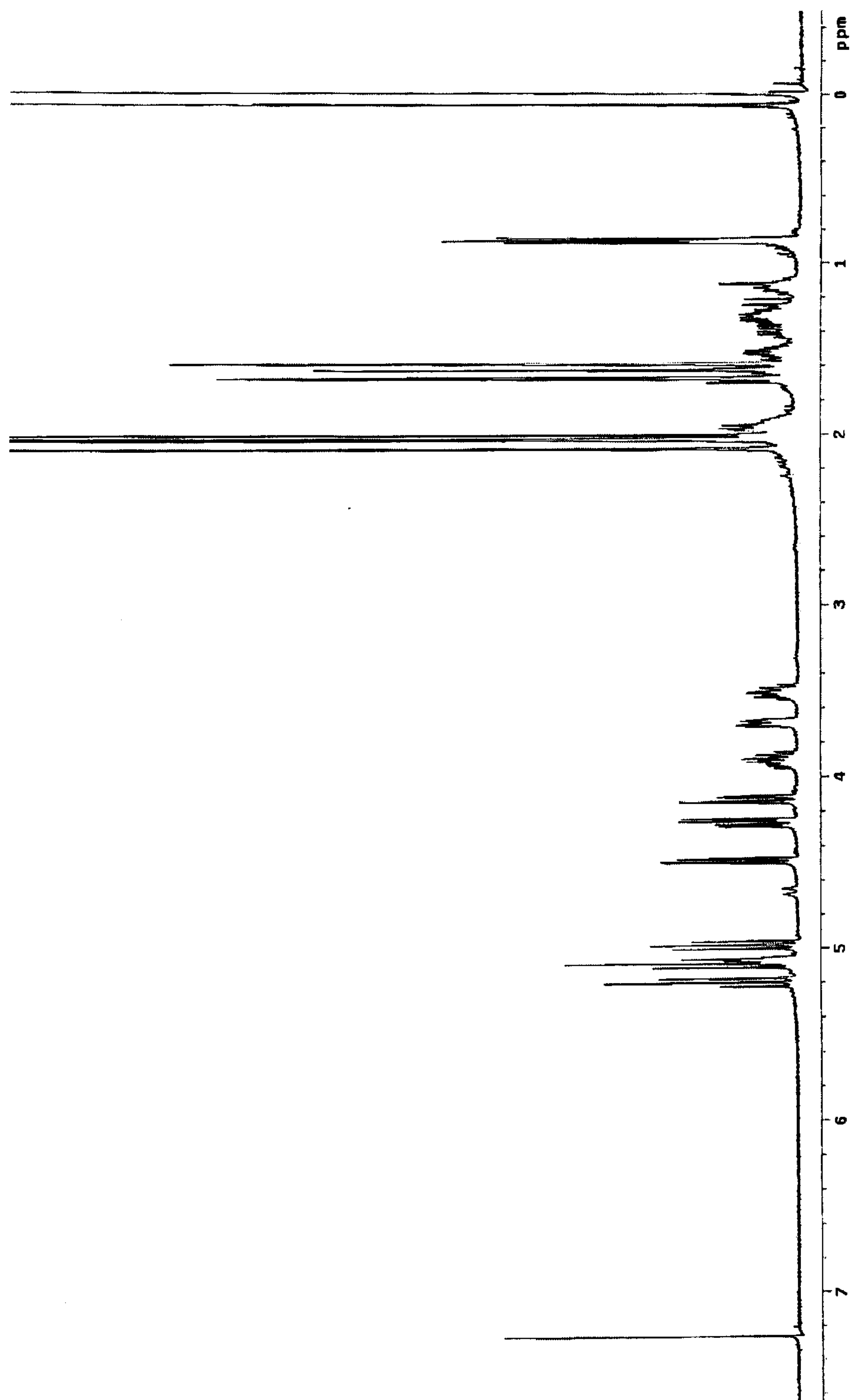


Figure 36: ^{1}H NMR of **18**

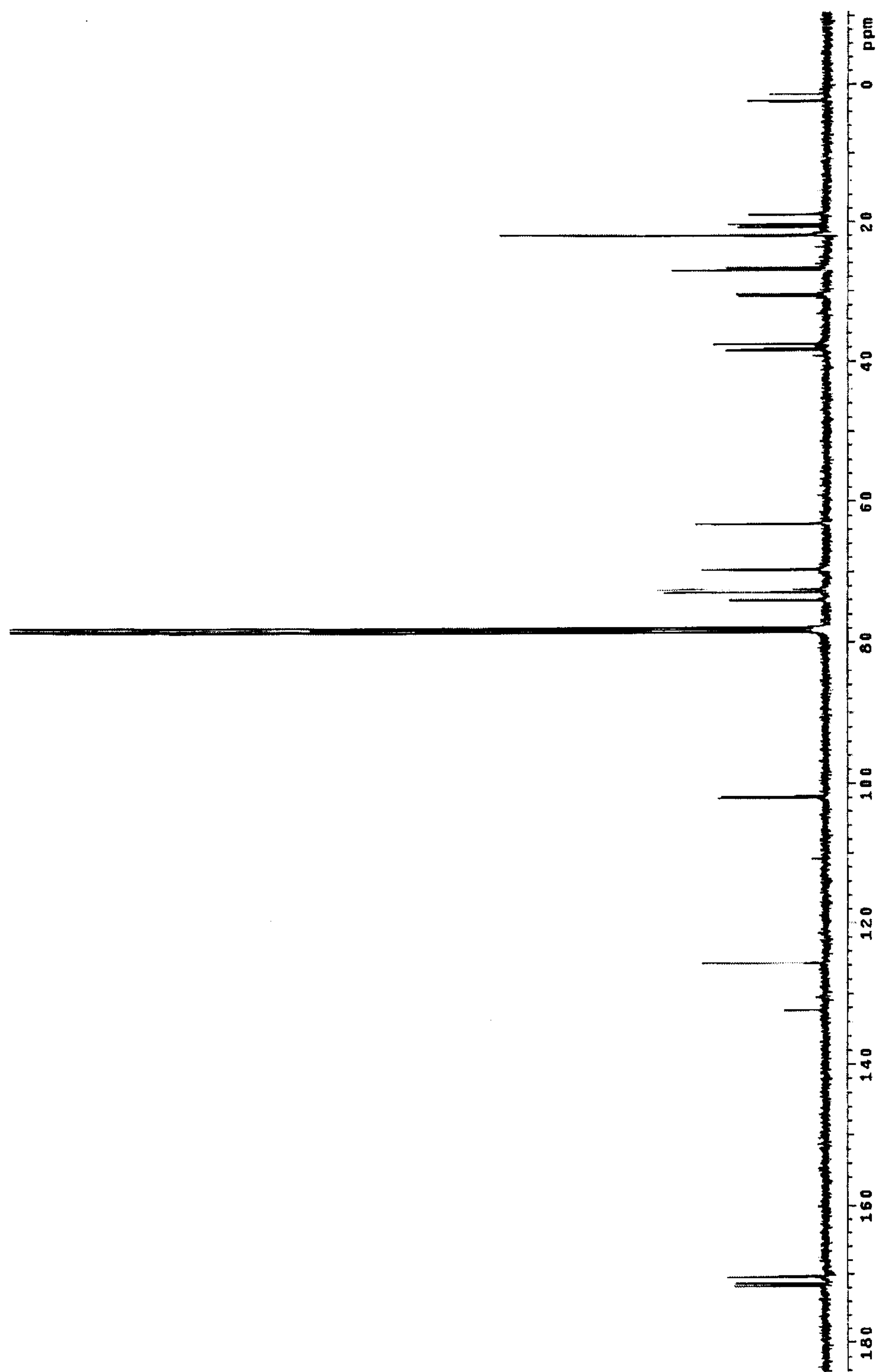
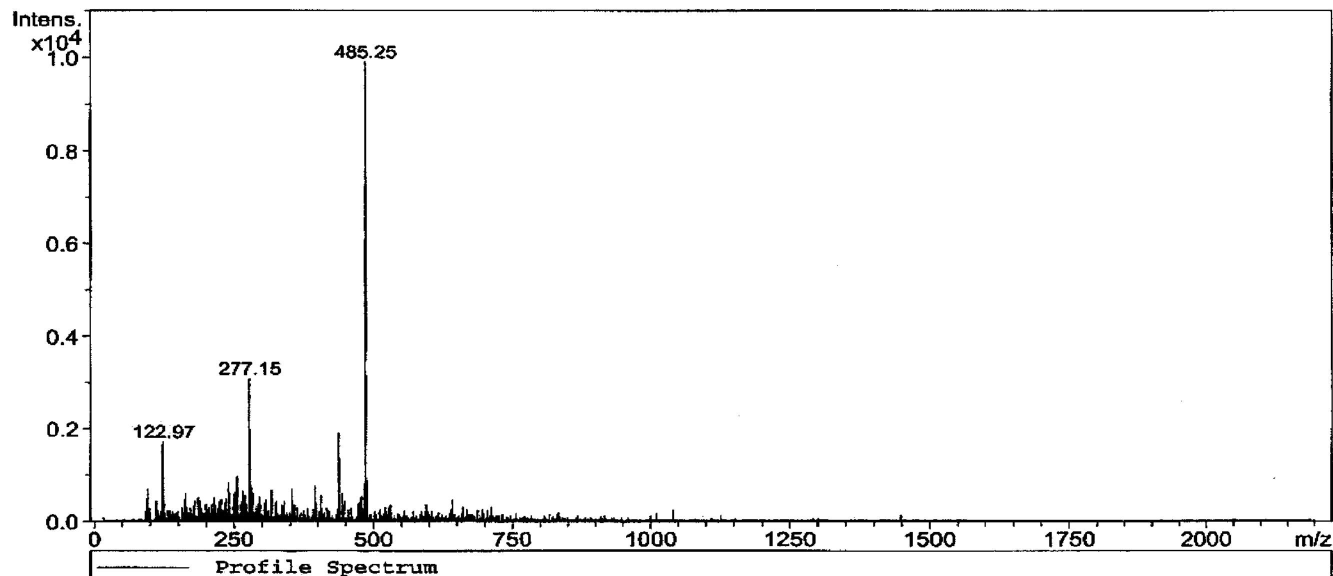


Figure 37: ^{13}C NMR of **18**

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



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
95.05	699	0.30	254.08	555	0.20	395.18	770	0.30
121.01	1663	0.20	255.21	965	0.20	405.29	558	0.20
122.97	1717	0.30	264.95	645	0.20	437.24	1900	0.30
124.00	959	0.20	267.13	559	0.40	439.25	561	0.30
163.07	592	0.20	269.08	560	0.40	443.31	605	0.20
185.05	509	0.30	277.15	3092	0.30	475.16	505	0.40
213.13	510	0.30	278.16	638	0.50	476.19	508	0.20
239.09	827	0.20	279.22	870	0.20	479.24	546	0.30
241.14	602	0.40	281.22	727	0.40	483.28	825	0.20
249.15	516	0.40	283.19	615	0.20	485.25	9912	0.30
250.16	621	0.30	295.10	519	0.40	486.25	3163	0.30
251.13	504	0.20	317.16	679	0.40	487.25	886	0.30
253.12	943	0.20	353.14	696	0.20			

Figure 38: Mass Spectrum of **18**

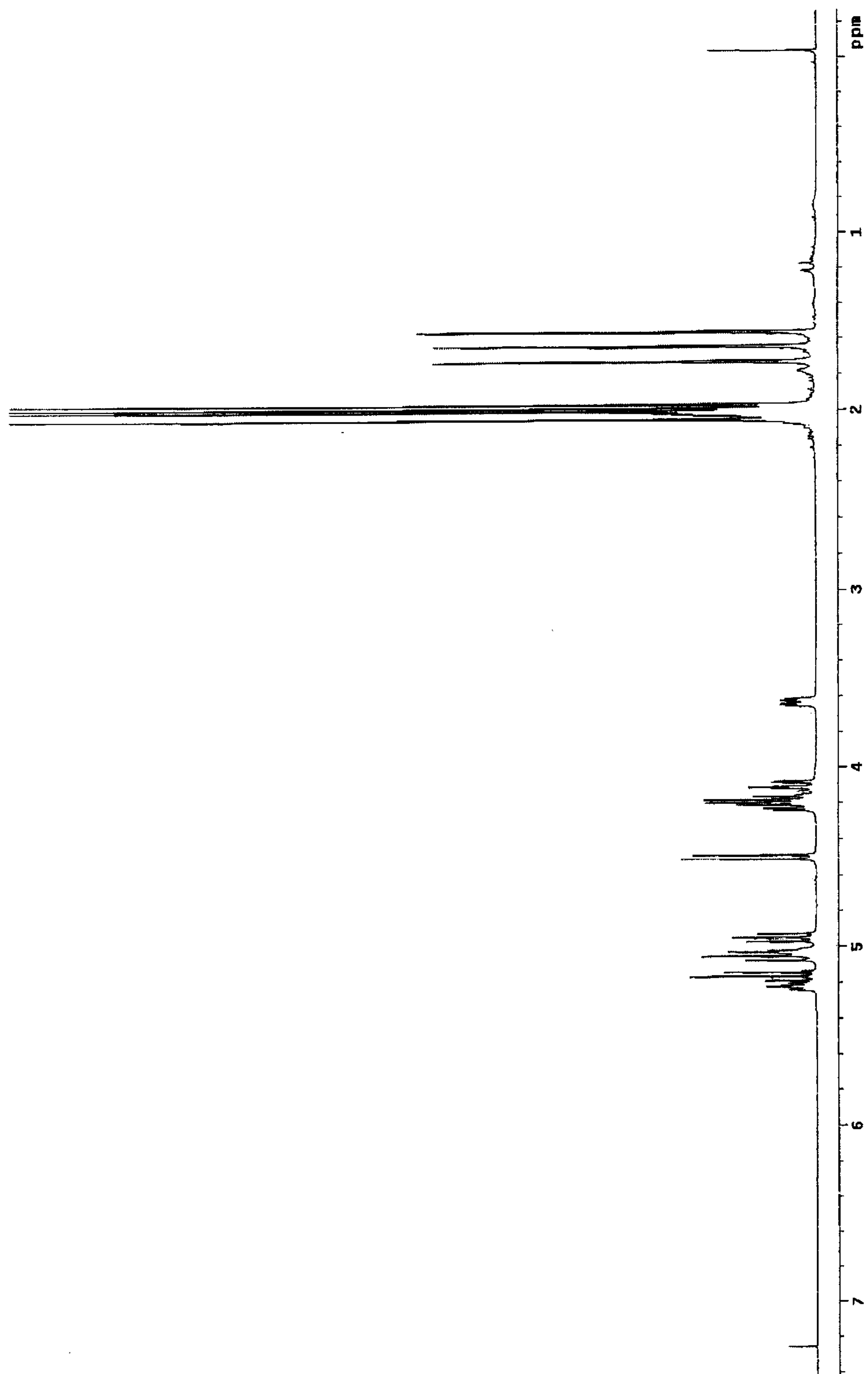


Figure 39: ^{1}H NMR of **19**

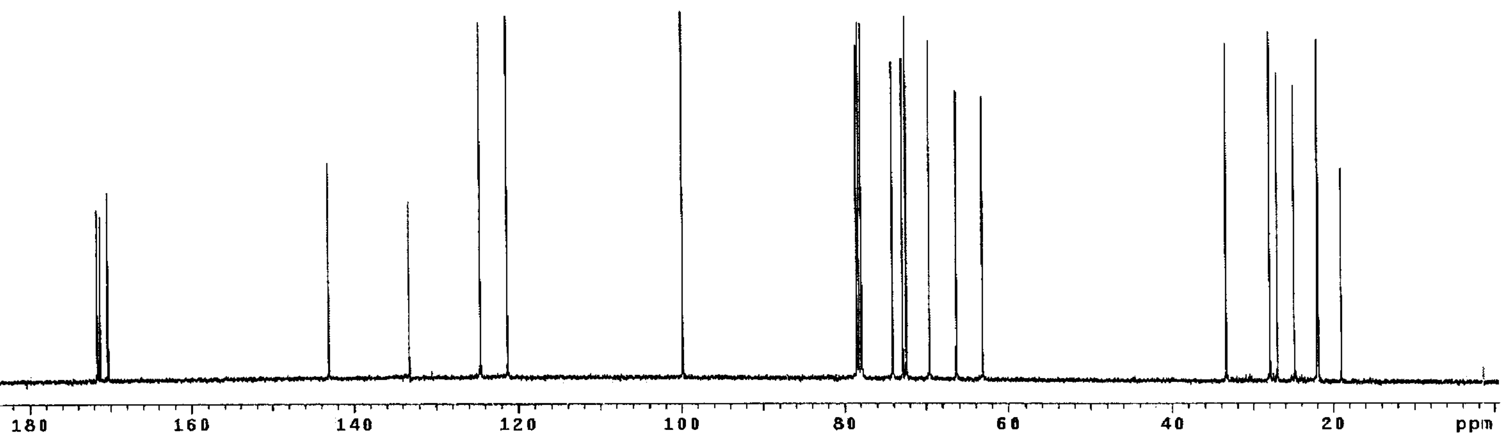
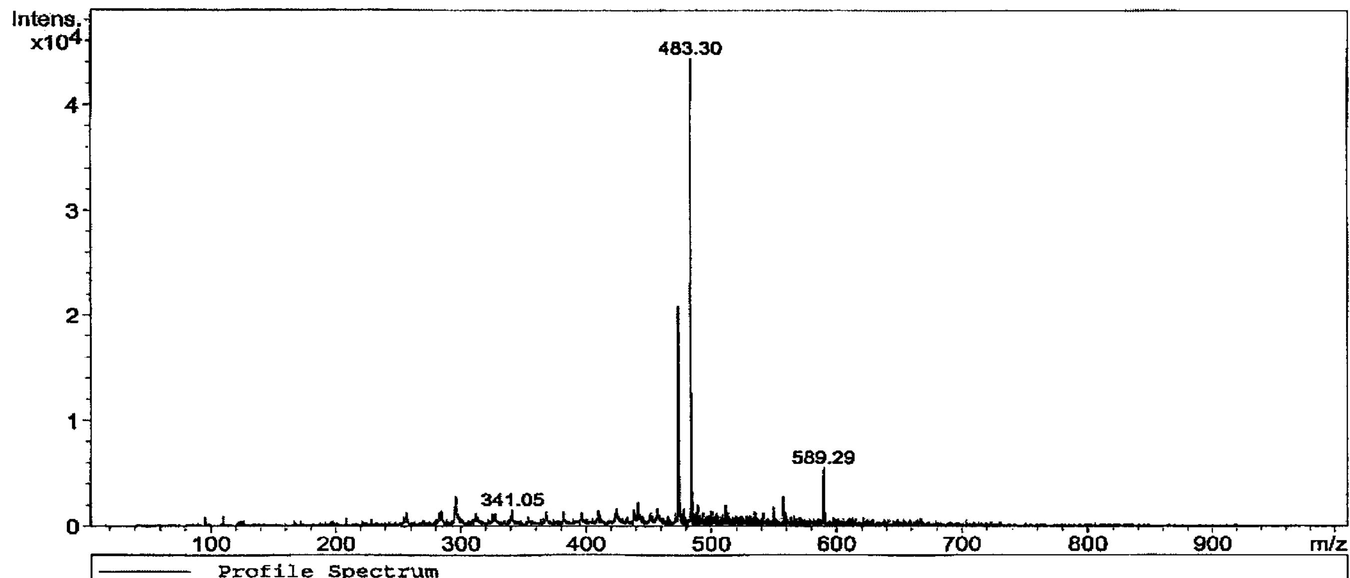


Figure 40: ^{13}C NMR of **19**

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



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
341.05	1586	0.30	485.19	3323	0.40	535.39	1293	0.20
409.76	1548	0.30	487.36	1399	0.40	541.32	1356	0.20
437.55	1596	0.30	488.29	1451	0.50	549.40	1931	0.40
438.48	1637	0.50	489.28	2071	0.30	550.42	1398	0.30
441.34	2311	0.20	497.33	1040	0.30	557.32	2885	0.30
473.46	20930	0.50	499.27	1540	0.30	558.31	1471	0.20
474.32	9562	0.30	504.38	1319	0.30	559.30	1367	0.40
475.30	2181	0.40	511.24	2035	0.40	560.36	959	0.20
476.39	1119	0.20	512.23	1336	0.20	563.35	873	0.30
477.33	1743	0.40	523.27	1055	0.20	589.29	5580	0.20
478.42	1507	0.20	524.38	914	0.20	590.30	1679	0.20
483.30	44397	0.20	531.34	1007	0.40	591.24	1229	0.20
484.12	12806	0.30	534.39	1421	0.40			

Figure 41: Mass Spectrum of **19**

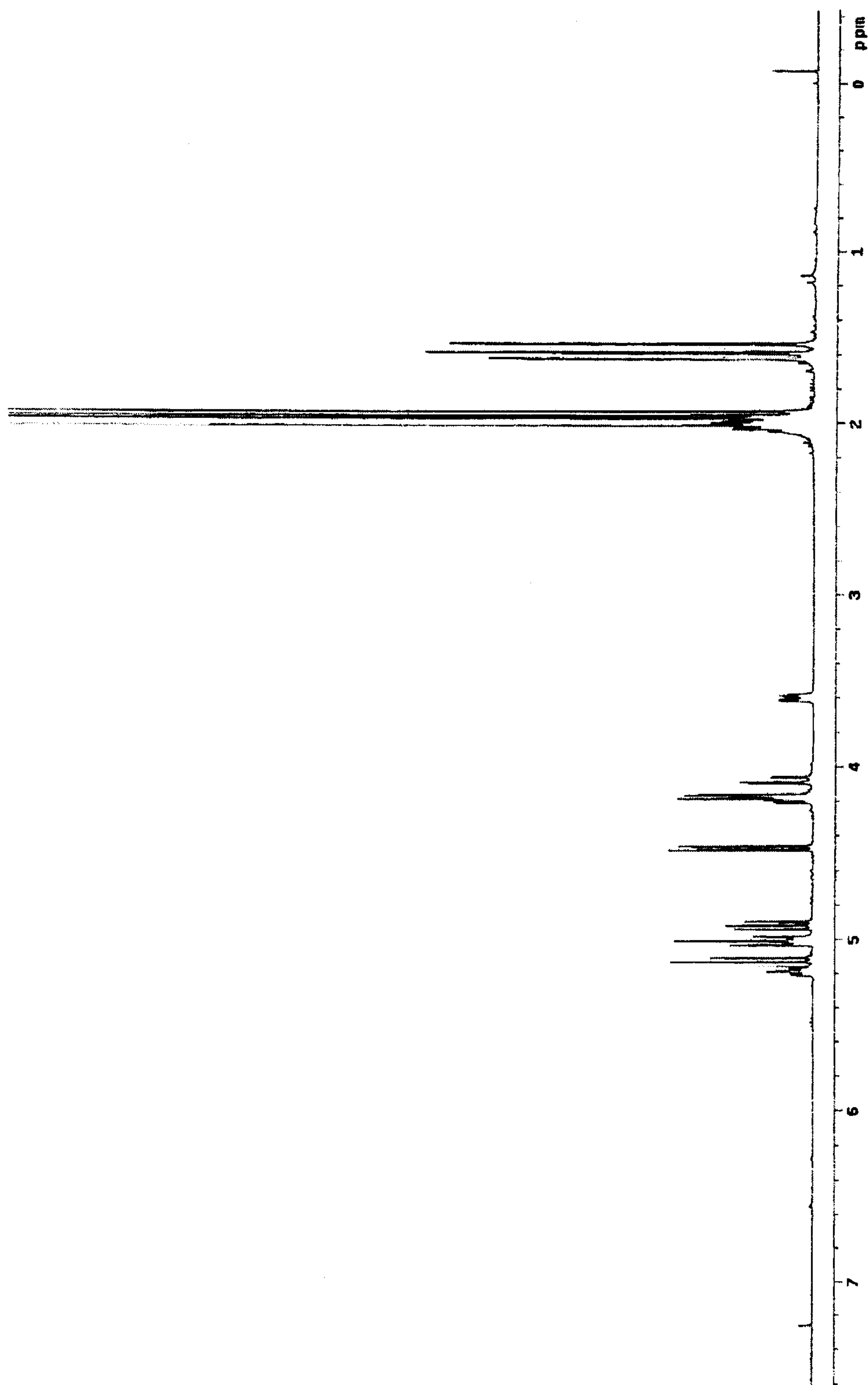


Figure 42: ^{1}H NMR of **20**

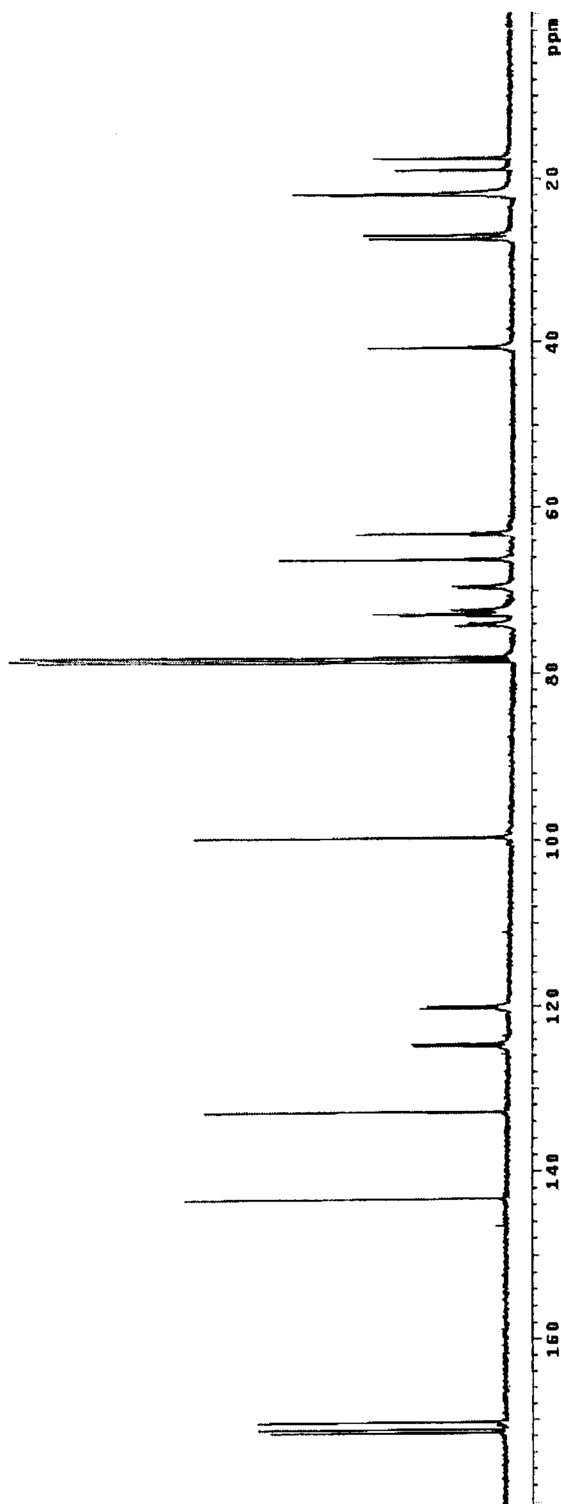
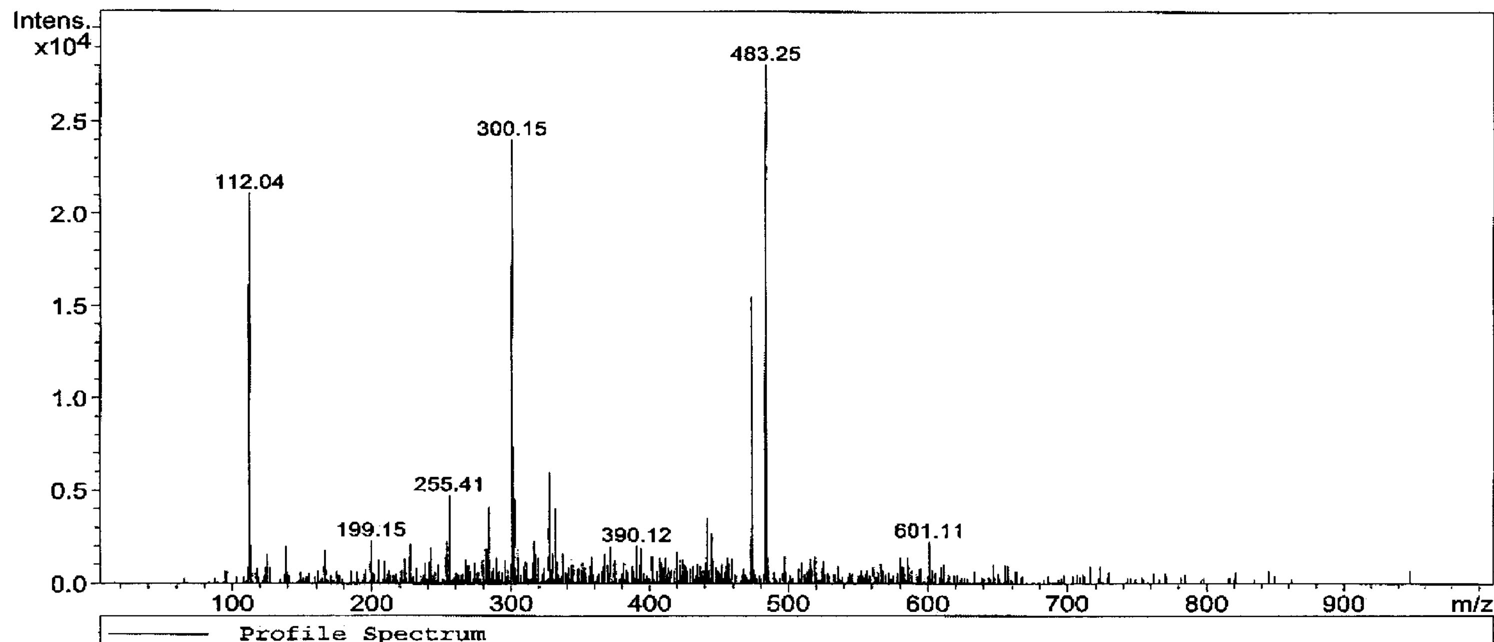


Figure 43: ^{13}C NMR of **20**

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



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
112.04	21125	0.30	301.12	7410	0.20	445.05	2726	0.20
113.18	2109	0.40	302.10	4524	0.40	473.27	15500	0.40
199.15	2309	0.20	316.16	2266	0.30	474.19	4881	0.20
227.11	2138	0.20	327.23	5977	0.30	483.25	28075	0.30
253.29	2268	0.20	328.07	2295	0.40	484.17	8409	0.30
255.41	4754	0.40	332.15	4027	0.20	601.11	2283	0.40
283.42	4100	0.20	390.12	2035	0.20			
300.15	24042	0.30	441.26	3577	0.30			

Figure 44: Mass Spectrum of **20**

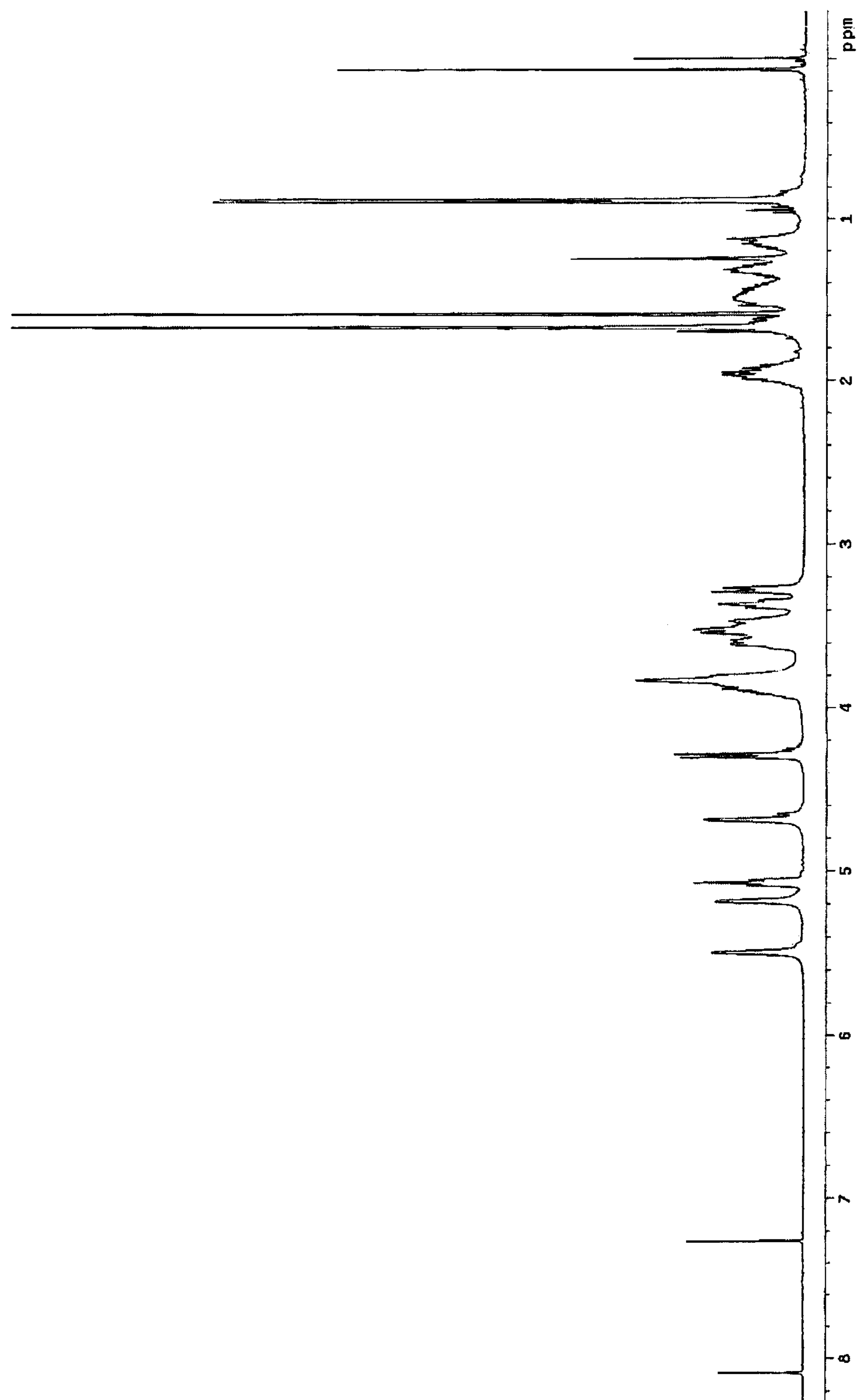


Figure 45: ^{1}H NMR of **21**

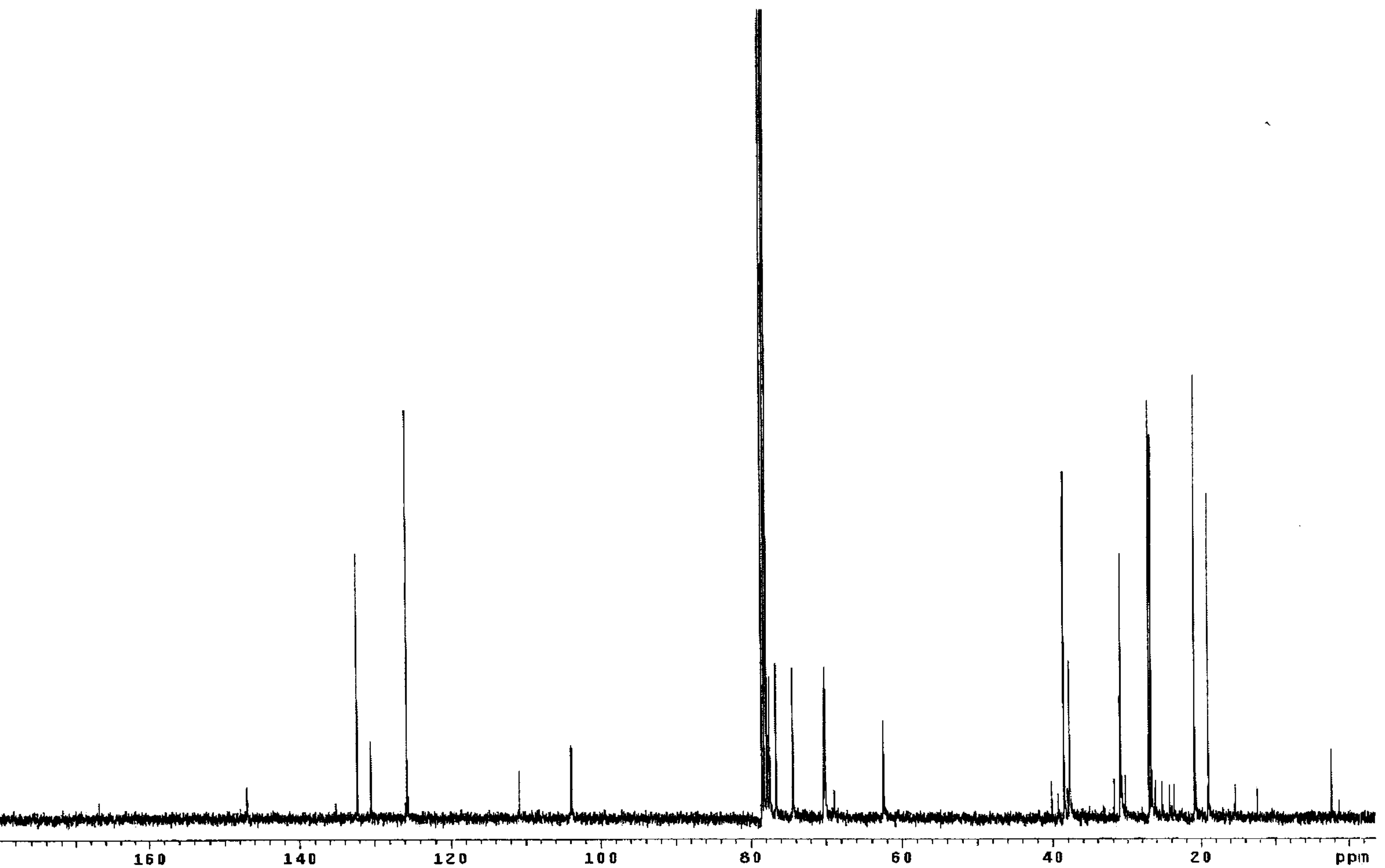
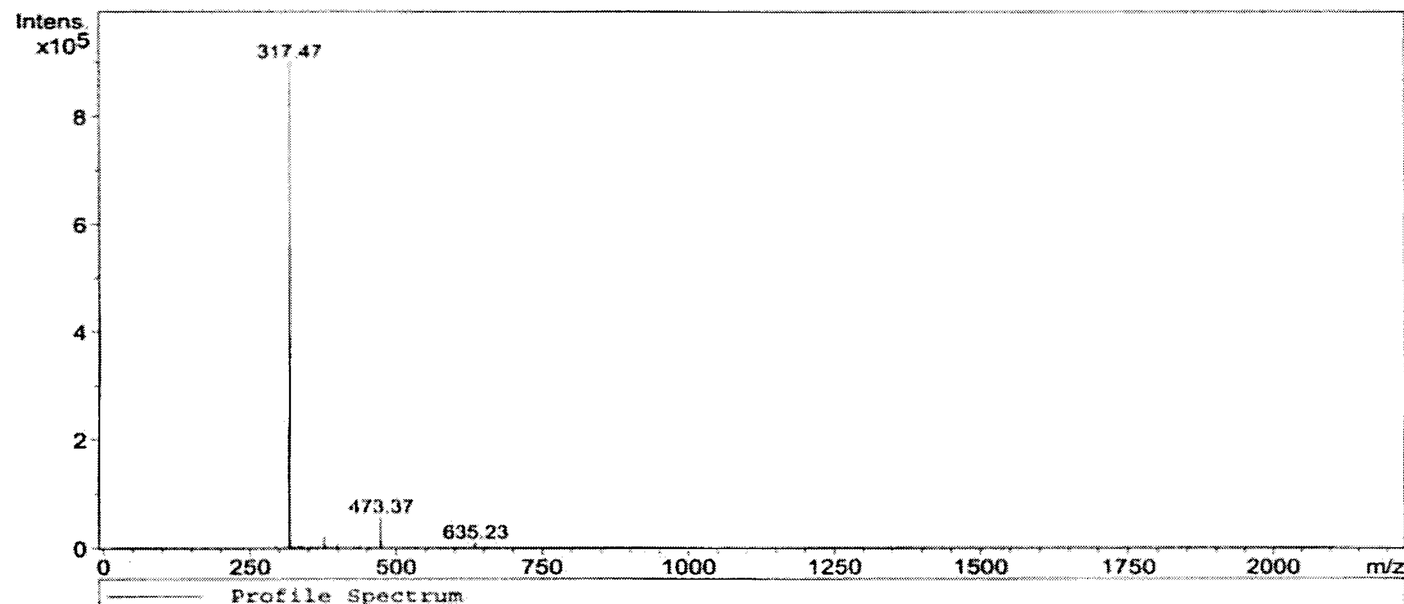


Figure 46: ^{13}CNMR of **21**

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



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
101.67	1742	0.30	349.24	1732	0.30	473.37	57346	0.30
294.98	1898	0.50	353.33	2128	0.40	474.25	16806	0.30
317.47	900320	0.20	355.34	1655	0.30	475.33	3755	0.30
318.70	13395	0.30	375.30	2389	0.40	533.32	3222	0.20
320.44	1660	0.50	377.24	22866	0.30	635.23	10464	0.40
325.30	2809	0.50	378.15	5252	0.30	636.24	3289	0.40
325.42	3115	0.50	399.25	7667	0.30	657.41	2421	0.40
333.33	5679	0.30	400.24	1723	0.30	704.62	1584	0.20
335.34	1648	0.30	437.15	3370	0.30	791.49	1681	0.30
337.35	3033	0.40	450.16	2994	0.20	817.72	1585	0.20
339.29	3195	0.20	453.28	3399	0.30			

Figure 47: Mass Spectrum of **21**

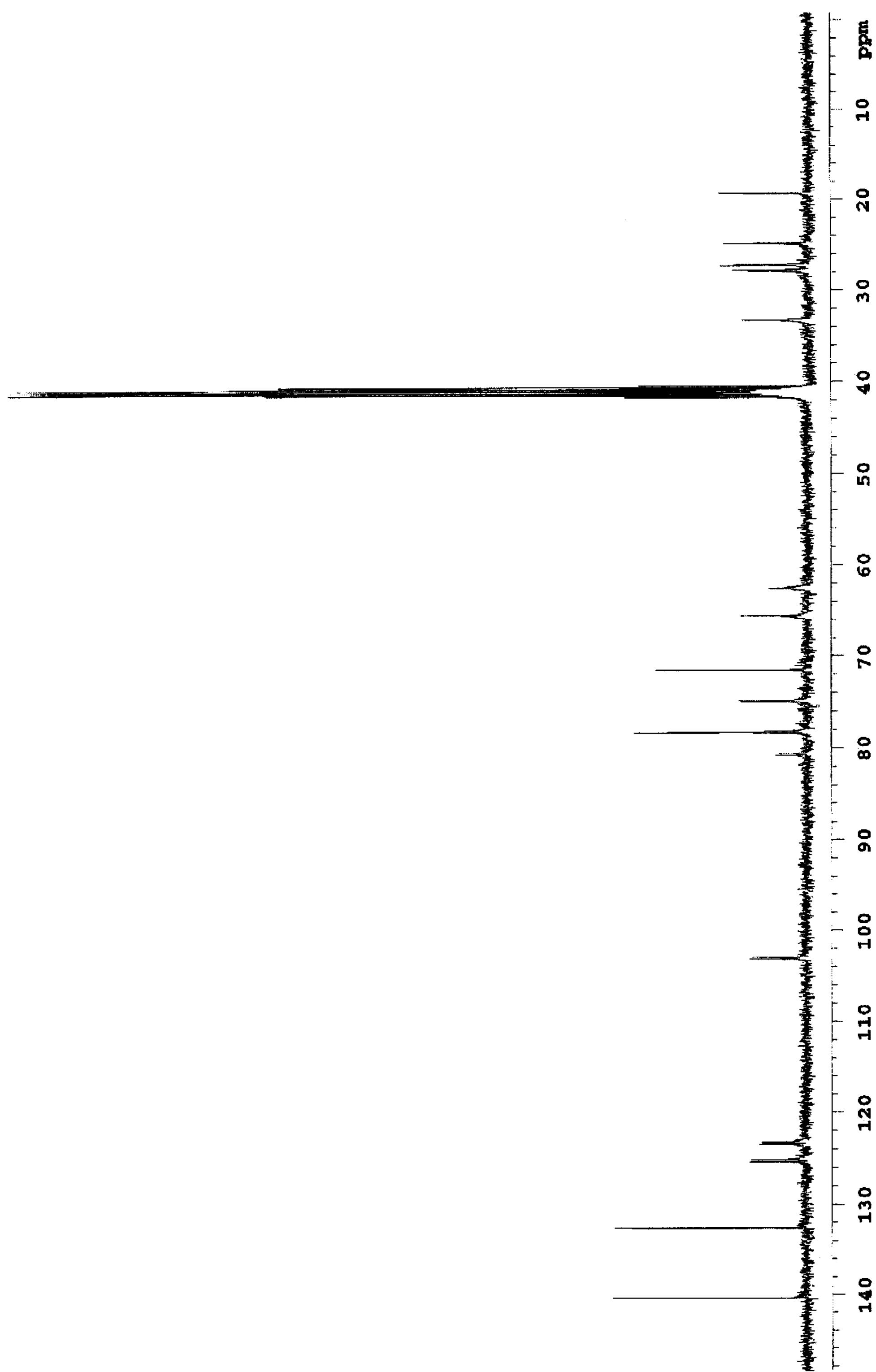
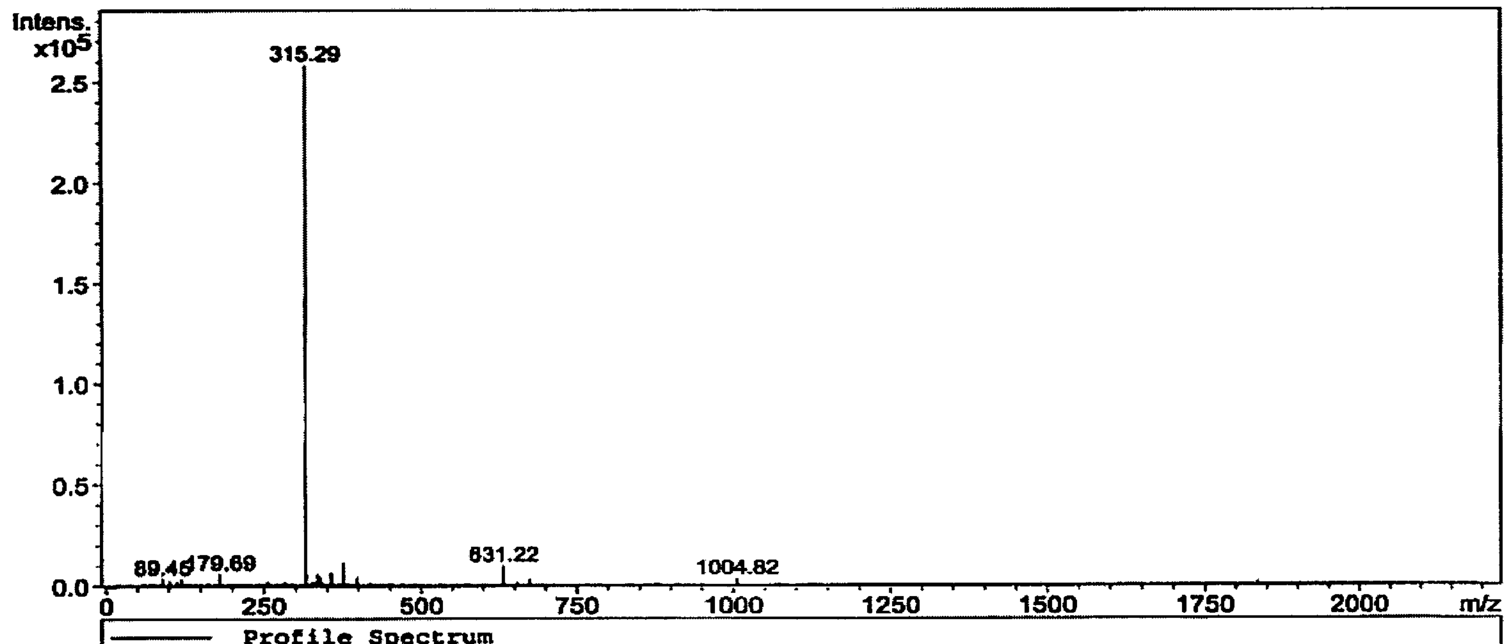


Figure 48; ^{13}C NMR of **22**

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



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
89.45	3556	0.40	325.24	2539	0.40	376.20	2197	0.20
101.44	2357	0.50	334.22	4420	0.20	397.23	4332	0.40
119.56	3371	0.50	335.22	5791	0.40	631.22	10052	0.50
179.69	6015	0.60	339.25	4100	0.30	632.20	3458	0.50
256.02	2192	1.10	355.38	6412	0.30	672.95	2227	0.20
315.29	258662	0.20	356.43	2003	0.20	673.25	2675	0.20
315.81	50844	0.30	357.21	5944	0.40	1004.82	3476	0.20
317.07	5941	0.40	375.19	11377	0.30	1834.62	2155	0.20

Figure 49: Mass Spectrum of **22**

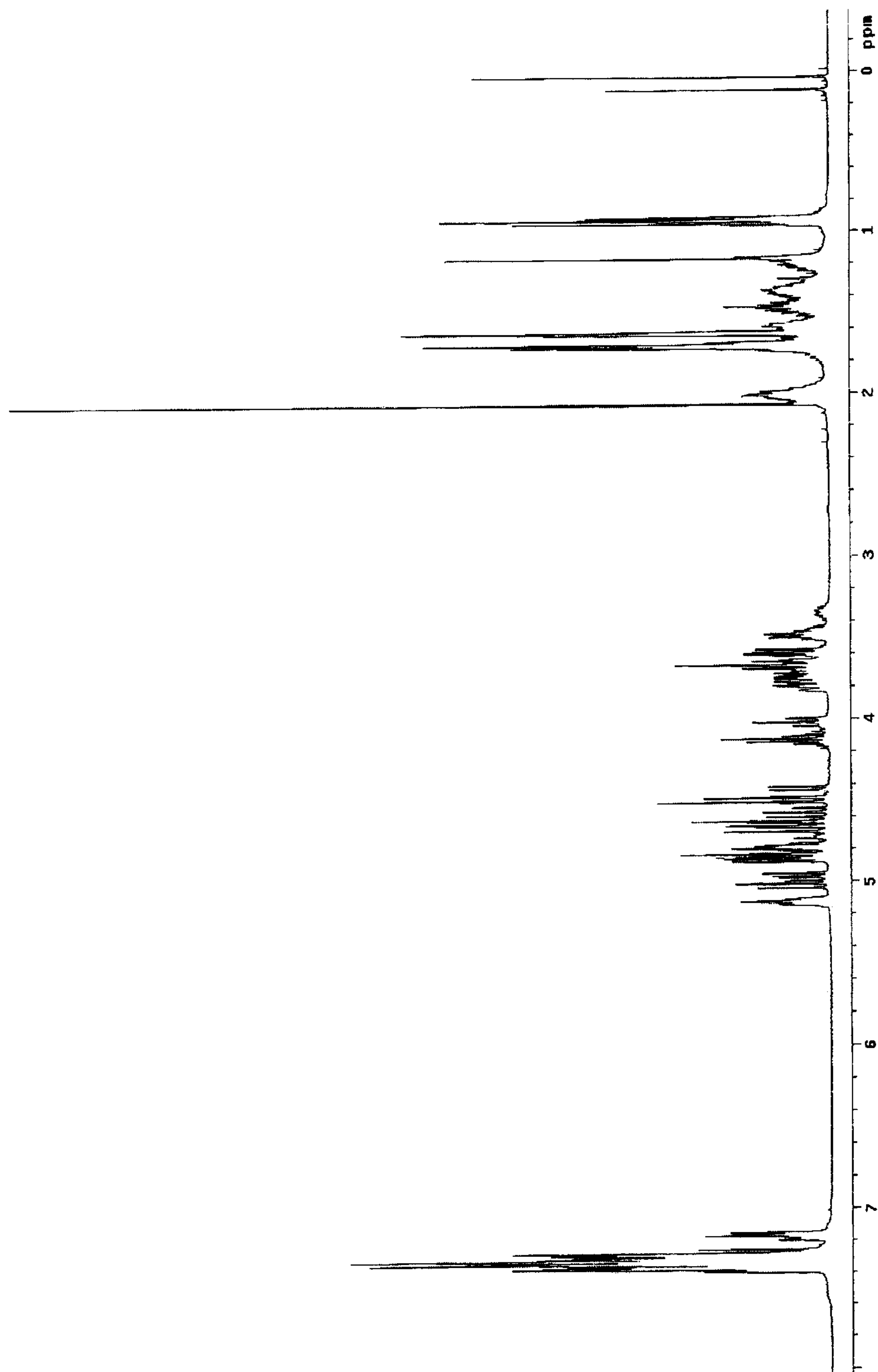
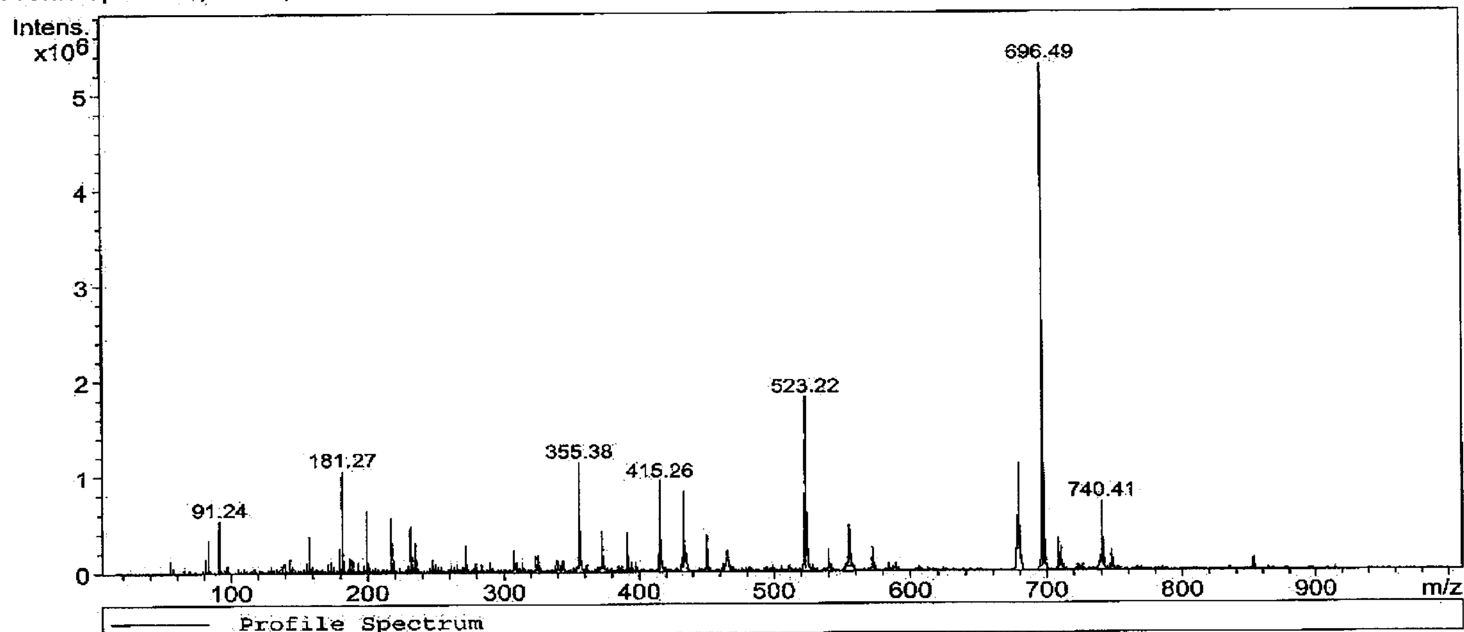


Figure 50: ^{1}H NMR of **23**

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



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
83.27	340393	0.30	356.34	426841	0.30	555.21	481620	0.60
91.24	541971	0.30	372.45	418380	0.40	679.29	1118349	0.30
157.32	374844	0.40	391.37	408625	0.40	680.17	459697	0.40
181.27	1061321	0.30	415.26	937494	0.30	696.49	5297629	0.40
199.34	636105	0.30	416.21	330857	0.40	697.31	2589605	0.30
217.25	570954	0.30	433.22	833515	0.40	698.31	658642	0.40
231.28	476342	0.30	450.29	378410	0.30	708.41	334876	0.30
235.22	304313	0.20	523.22	1815664	0.30	740.41	718795	0.30
355.38	1141111	0.40	524.08	655767	0.50	741.35	335829	0.40

Figure 51: Mass Spectrum of **23**

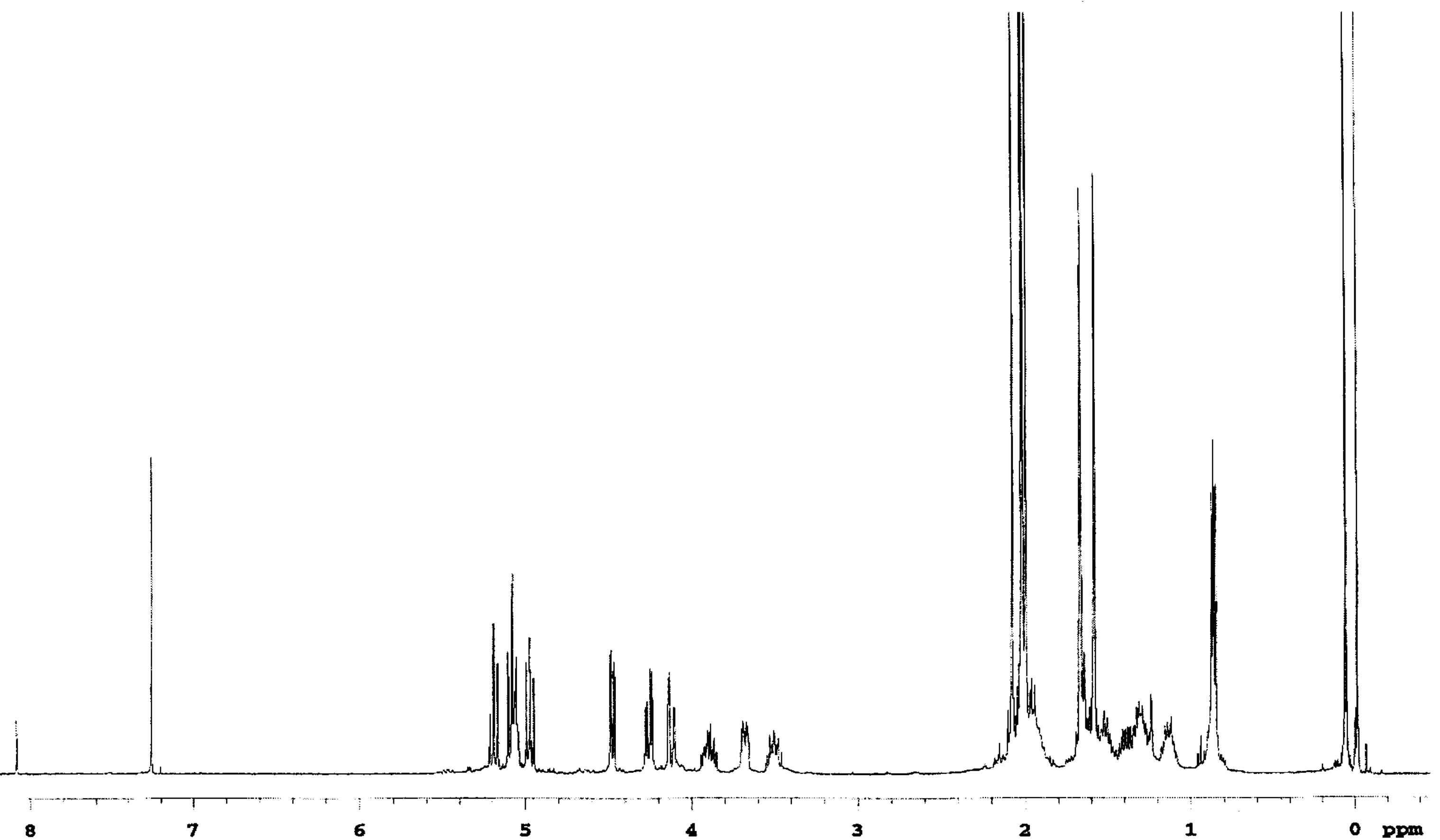
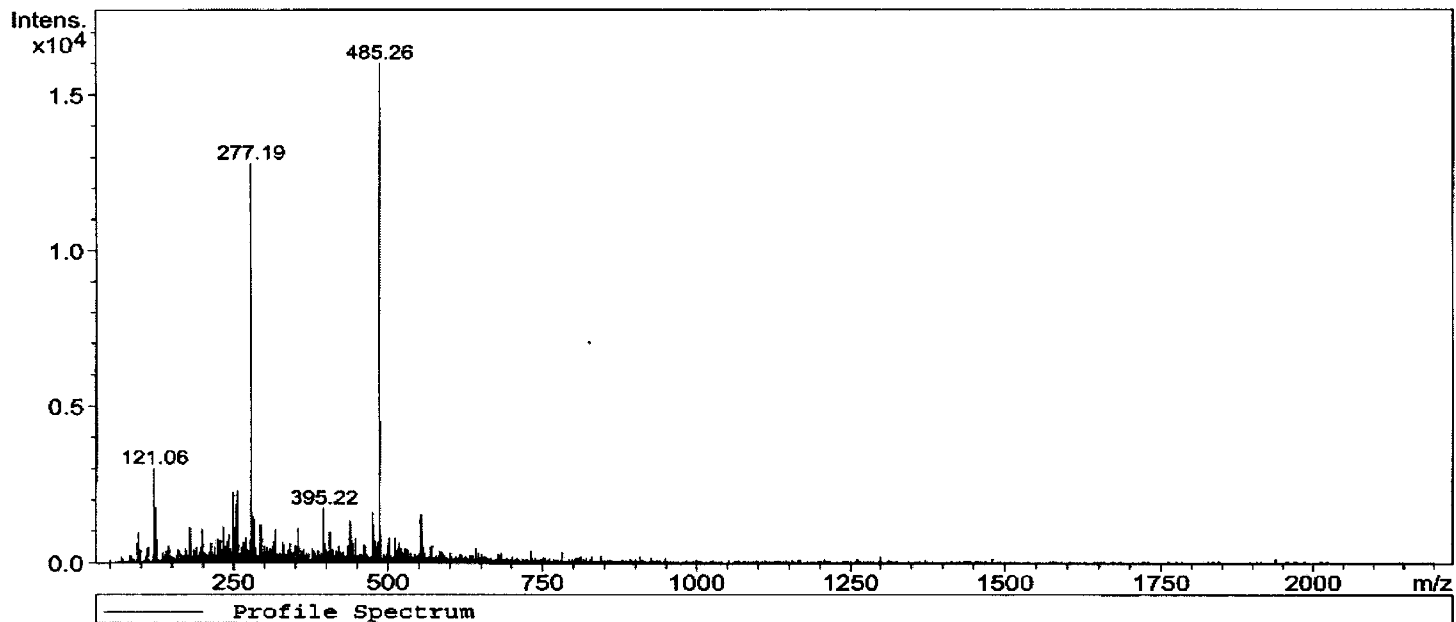


Figure 52: ^{1}H NMR of **25** from compound **24**

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



MS Peak List (Profile Spectrum):

Mass	Intensity	Width	Mass	Intensity	Width	Mass	Intensity	Width
121.06	3031	0.30	277.19	12819	0.20	395.22	1742	0.20
123.06	1772	0.30	278.15	2645	0.30	405.24	1001	0.30
179.11	1138	0.20	279.21	1452	0.30	437.24	1336	0.30
199.11	1077	0.30	281.28	1458	0.30	439.20	1224	0.20
233.09	1151	0.20	283.33	1394	0.30	475.24	1609	0.50
249.23	2255	0.30	293.19	1237	0.20	485.26	16024	0.30
250.19	1127	0.40	317.22	1061	0.20	486.24	4510	0.40
253.24	1852	0.30	353.25	1073	0.30	553.25	1550	0.40
255.25	2285	0.30	354.25	1097	0.30			

Figure 53: Mass Spectrum of **25** from compound **24**

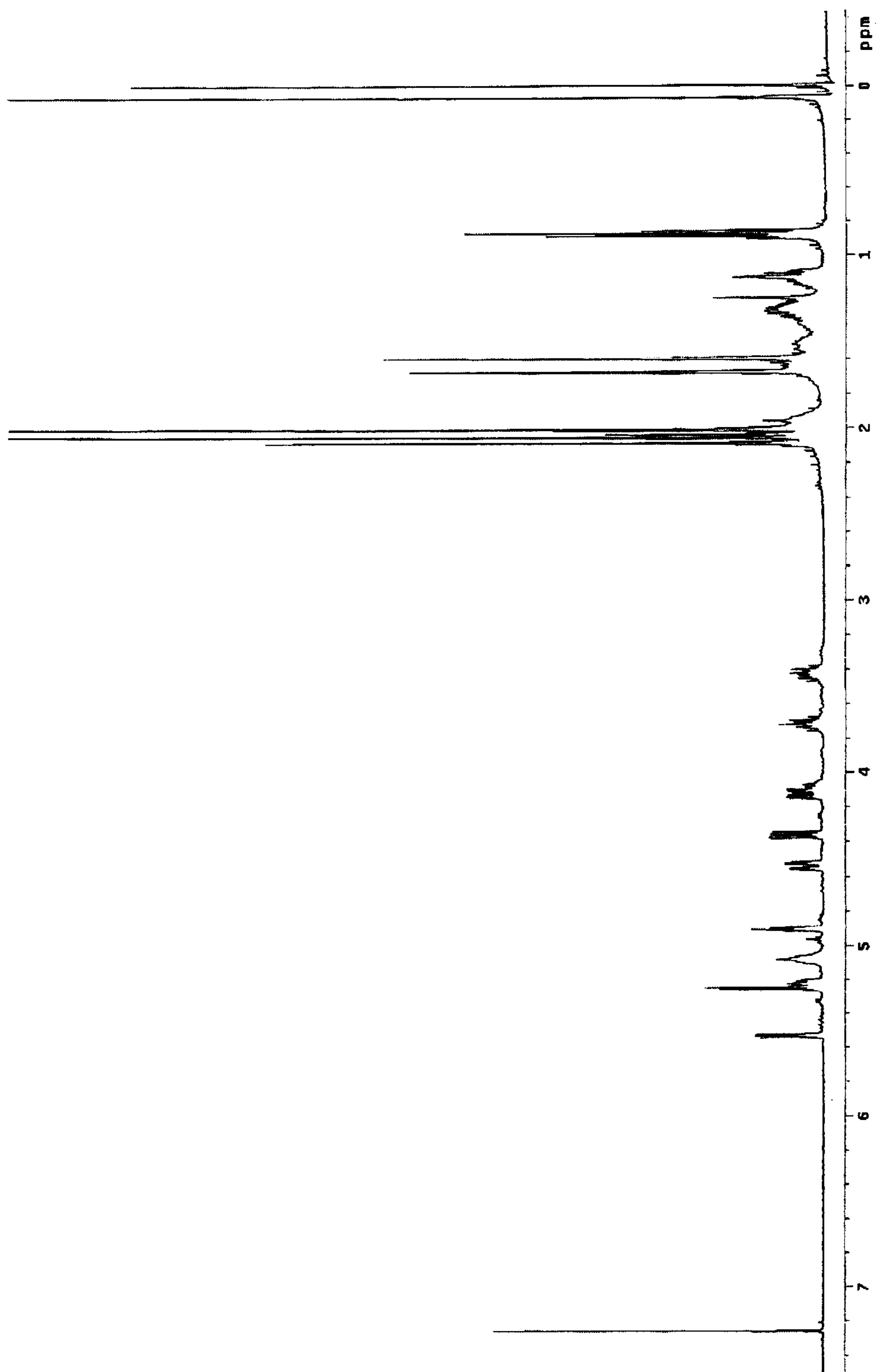


Figure 54: ^{1}H NMR of **18** from **24**

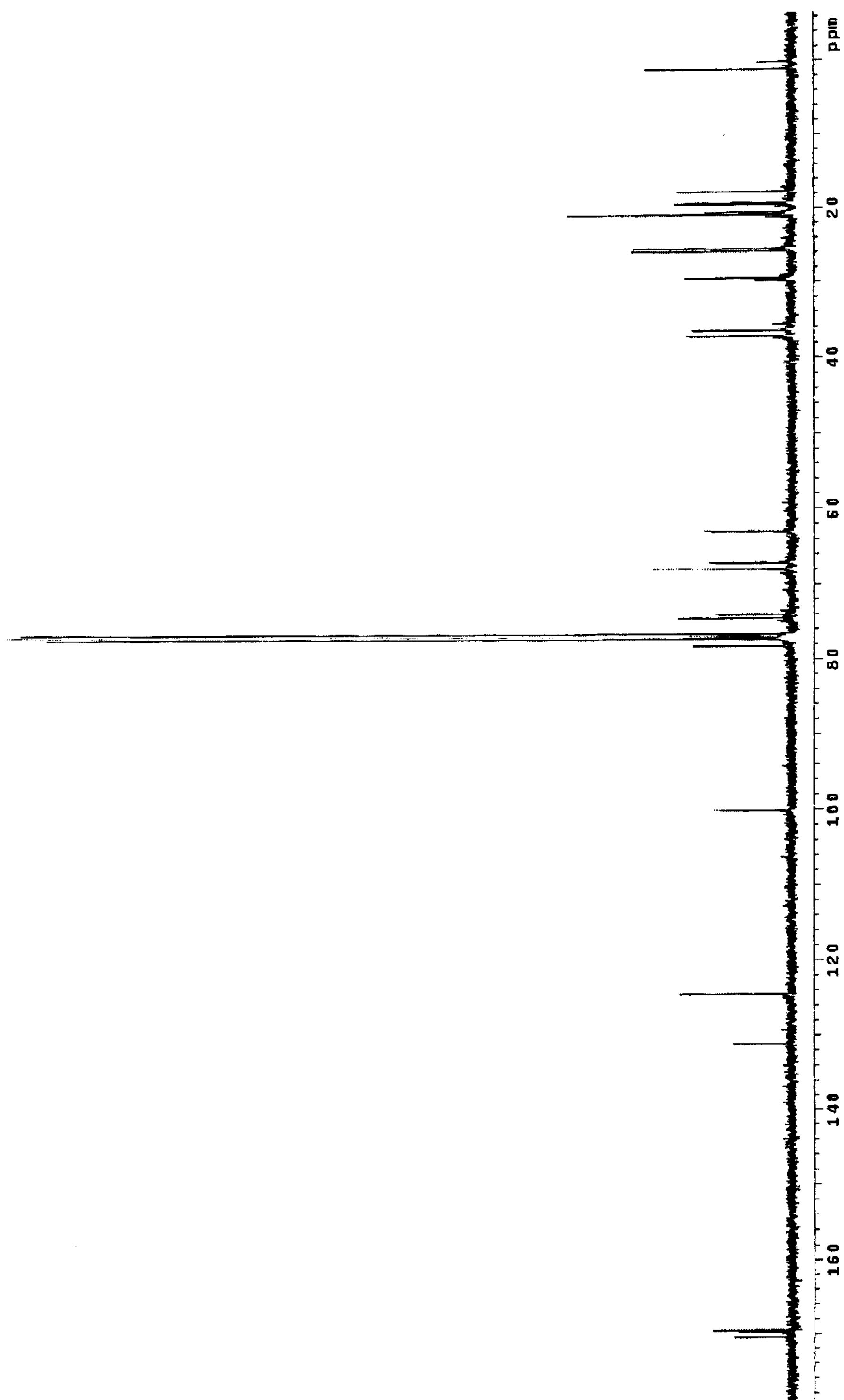


Figure 55: ^{13}C NMR of **18** from compound **24**