Formation of *C*-Glycosides *via* Dithioacetal Chemistry

by

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Introduction

During the later half of the 19th century, Emil Fischer pioneered work with "parent sugars" which were grouped later as "the carbohydrates". Since then, carbohydrates have been found to have importance in areas ranging from food science to medicine.[1] For this reason, organic chemistry has focused on carbohydrates and their derivatives with growing interest. Throughout the subsequent fifty years Haworth and Hudson would build upon the work of Fischer by developing a specialized branch of organic chemistry known as structural carbohydrate chemistry. By the beginning of the 1950's the science of carbohydrates would be changed dramatically with the introduction and development of ^{1}H NMR in the field by Lemieux.[2]

The first carbohydrate to be characterized to a great extent was D-glucose by Fischer in the late 1800's, work that eventually lead to the Nobel Prize in 1902. At the time Fischer was limited to simple chemical and polarimetric techniques in the characterization of D-glucose and its hexose cousins, and his structural elucidation still stands as one of the greatest examples of logic and strategy in organic chemistry.[3]

In general, carbohydrates can have multiple conformations and configurations, and D-glucose can be used as a paradigm to describe the general structure of carbohydrates. Each varies in the number of carbons and in the orientation of the attached hydroxyl groups, with the hydroxyl groups on each carbohydrate existing in various different environments (1°, 2°, and anomeric). The orientation of the hydroxyl groups gives each carbohydrate their own specific characteristics that separate them from all other carbohydrates.

Carbohydrates are classified usually as either aldoses or ketoses, and it is known that carbohydrates, with more than four carbons, can exist in three forms: a furanose ring (five-membered); a pyranose ring (six-membered); and a straight chain (commonly known as the *aldehydo*-form (**A**) shown below in Figure 1).

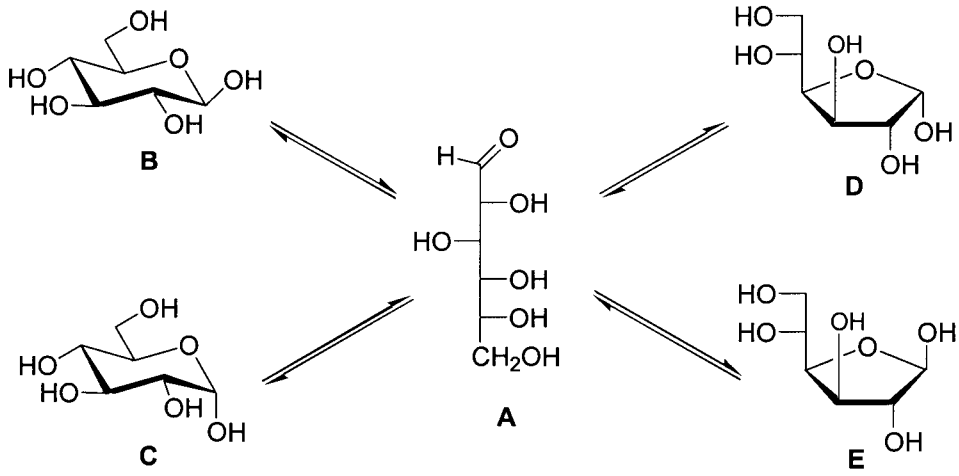
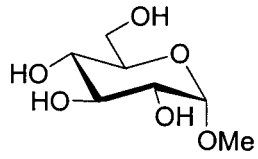


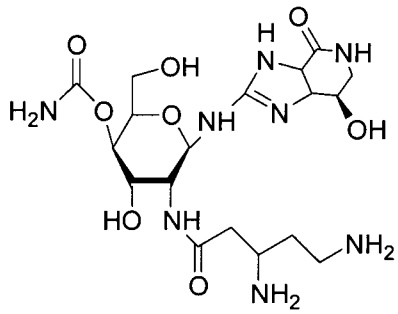
Figure 1. Different forms of D-Glucose

When aldoses are in one of the ring forms they have the characteristic of being hemiacetals, which refers to having two oxygen atoms attached to C-1, the anomeric carbon. The sugars can therefore be acyclic or cyclic in solution, and ring opening and closing has a direct effect on the orientation of the substituent group at the anomeric carbon. If the group is in the equatorial position it is called the beta (β) anomer (**B, E** Figure 1), when the group is in the axial position it is deemed the alpha (α) anomer (**C, D** Figure 1). The label of "D" glucose is derived from the position of the hydroxyl that is directly above the hydroxymethyl group in the Fischer depiction. In the example of D-glucose this particular hydroxyl is pointing to the right; if the substituent were pointing to the left it would be an L-sugar.

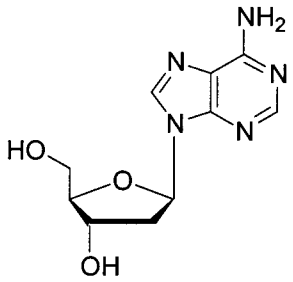
Glycosides have been the focus of research for many years, since it has been shown that various glycosides have different activities in biological systems. The biological relevance is most likely rooted in the fact that glycosides are naturally occurring (e.g. plants, animals, and microbes).[4] The term glycoside in carbohydrate chemistry can describe several different modifications of carbohydrates. These can occur when the exocyclic oxygen at C-1 of the carbohydrate is replaced with an atom such as a nitrogen, carbon, or sulfur. The most basic type of glycoside is an *O*-glycoside where substitution occurs at the anomeric hydroxyl group. This can be synthesized by treating D-glucose with methanol under acidic conditions to yield the methyl α-D-glucopyranoside (Figure 2, **A**). Many other glycosides exist, some of the most recognized glycosides being ones used to combat various bacteria.



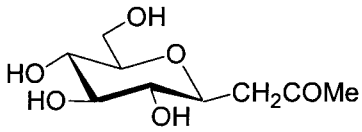
A. *O*-glycoside



B. Streptothricin F



C. Adenine Nucleoside



D. *C*-glycoside

Figure 2. Some forms of Glycosides

Prime examples of sugar-containing antibiotics are Erythromycin A (*O*-glycoside) and Streptothricin F (*N*-glycoside Figure 2, **B**). Some of the most well known glycosides are the *N*-glycosidic nucleosides that make up our genetic material (Figure 2, **C**).[3] There

are also *S*-glycosides, which are uncommon in nature, and the last of the major glycosides are the *C*-glycosides where the anomeric carbon is attached directly to another carbon atom (Figure 2, **D**).

Carbohydrates are especially ubiquitous in the cells of plants, animals, and microbes. They can be found ranging from glycolytic pathway intermediates to major cell wall constituents bound to proteins. For example in *Mycobacterium tuberculosis* and *Staphylococcus aureus*, carbohydrates are brought together to form a major part of the cell walls as polysaccharides and oligosaccharides. In nature, carbohydrates can exist as monosaccharides or can be linked together to form disaccharides, oligosaccharides, and polysaccharides. Sugars, both linked together and as monomers, are involved in many different biological systems, and play key roles as cell energy sources, as well as being major biosynthetic cell wall constituents. The polymeric carbohydrate molecules that are linked together by C-O bonds are referred to as *O*-glycosides. In nature enzymes known as glycohydrolases and glycosyltransferases mediate breakdown and formation of *O*-glycosidic bonds.[5] Metabolic enzymes that are structural architects are constantly acting on carbohydrates in some way or form. It is for this reason that researchers now look to synthesize inhibitors, or sugars that will mimic the naturally occurring carbohydrates. Such compounds are generally termed "carbohydrate mimetics". Nojirimycin (Figure 3) is a prime example of a carbohydrate analogue that acts as an enzyme inhibitor.

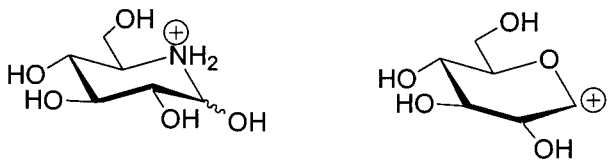
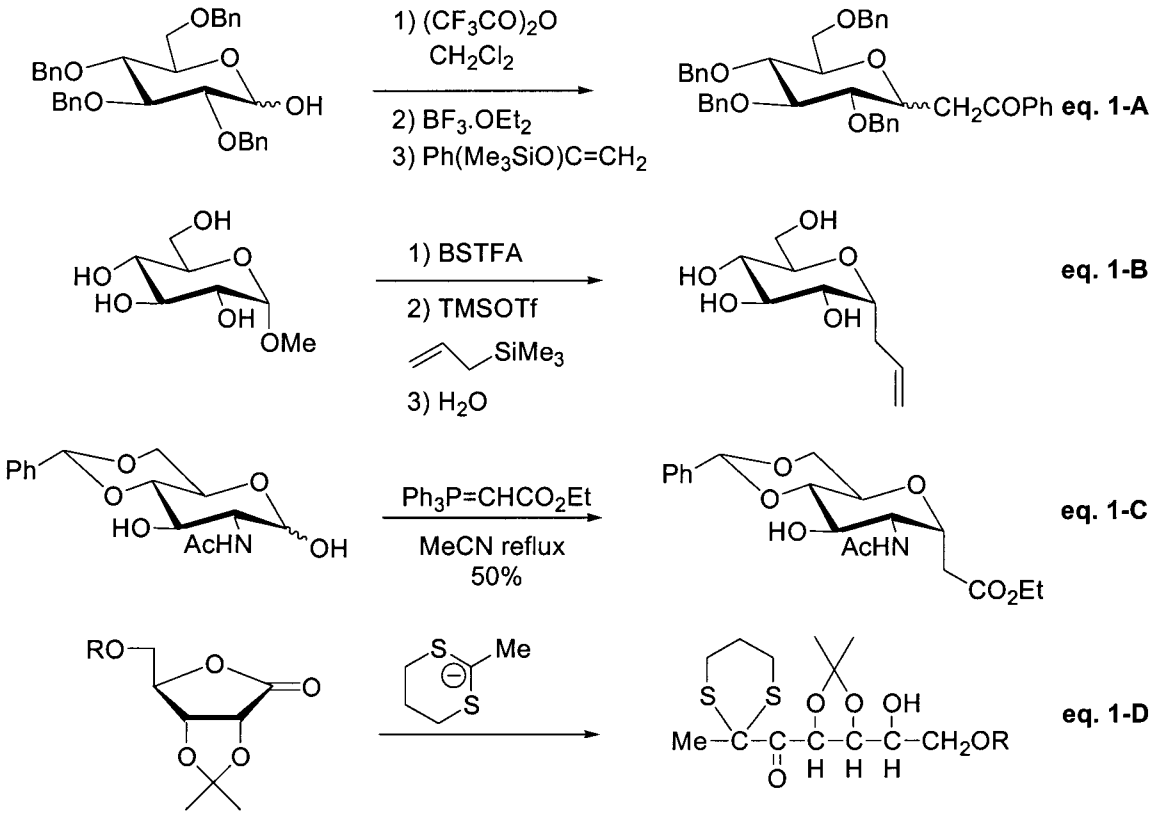


Figure 3. Nojirimycin (left) and the Glycosyl cation it mimics (right)

Nojirimycin specifically is a "transition state analogue" with similar features to the glycosyl cation that is formed enzymatically when an *O*-glycoside is hydrolyzed.[6] This particular compound belongs to a class of molecules known as *iminosugars*. As seen above in Figure 3, the endocyclic oxygen has been replaced with nitrogen and this compound is known to inhibit various glucosidases. Since glycosylhydrolases act on the C-O linkages of *O*-oligosaccharides, by the same theory it is conceivable that a *C*-disaccharide or oligosaccharide could potentially inhibit the action of the same enzyme by binding competitively.[5] Like the class of iminosugars, *C*-glycosides are carbohydrate mimetics, however they differ in that they act as ground state analogues. This potential application demonstrates the importance of *C*-glycosides in bio-organic chemistry.



Many different synthetic strategies have been applied to the production of a variety of *C*-glycosides. For example, Allevi and co-workers demonstrated this in 1987

when they synthesized various *C*-glycosides using trifluoroacetic esters, a Lewis acid, and a carbon nucleophile (equation **1-A**).[7] Bennek and Gray provided another example of *C*-glycoside synthesis by treating methyl glycosides with allyltrimethylsilane (equation **1-B**).[8] Russo, Nicotra and co-workers have taken advantage of a lactol hemiacetal by treatment with a Wittig reagent to yield a 2-deoxy-2-amino sugar (equation **1-C**).[9] More closely related to the work being presented in this thesis is the addition of a methyl-1,3-dithane to 2,3-*O*-isopropylidene-5-*O*-(tetrahydropyran-2-yl)-D-ribono-1,4-lactone which affords an acyclic dithioacetal *C*-glycoside (equation **1-D**).[10]

Current work dealing with *C*-glycoside formation is directed toward the synthesis of enzyme inhibitors. This is a hot topic because of new and emerging pathogens in modern society (e.g. HIV, Hepatitis B, and *M. tuberculosis*), and efficient and mild syntheses of new and improved medicines are a challenge for organic chemists in the pharmaceutical industry.

Many *C*-glycosides have been shown to bind to enzyme active sites, and for this reason it is thought that introducing these molecules into various biological systems might inhibit the enzymes of pathogenic organisms. The feasibility of such interactions has been demonstrated, for example in 1998 by Kishi and co-workers, through an X-ray diffraction study on the binding of *C*-lactose (Figure 4), the *O*-lactose analogue, to peanut agglutinin protein as seen in Figure 5.[11]

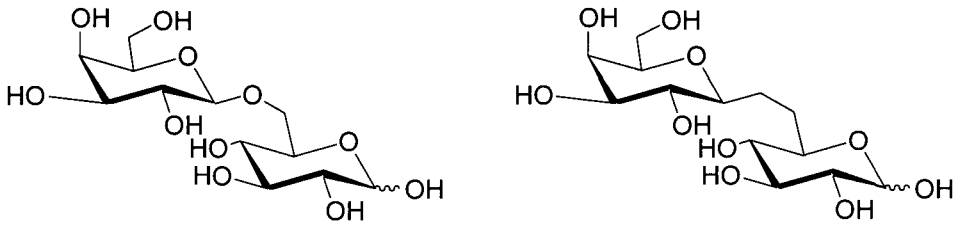


Figure 4. *O*-Lactose and *C*-Lactose

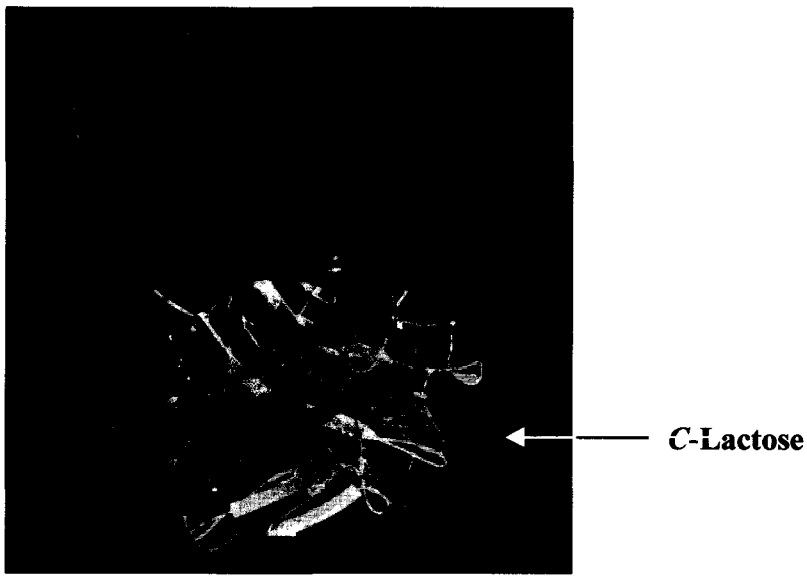


Figure 5

C-glycosides have also been studied in HIV research. HIV is known to invade erythrocytes via attachment mediated by a glycoprotein constructed by enzymes called neuraminidases. Previously, *O*-linked sialic acids were shown to inhibit viral attachment but were not very stable to neuraminidases. Possible medicinal applications arose from work by Nagy and Bednarski where C-O linkages of sialic acid were replaced with C-C linkages. The resulting *C*-linked sialic acid, after attachment to a carbohydrate monomer, was shown to reduce viral plaque formation proportionally as the concentration was increased.[12]

A target for carbohydrate chemists has been the synthesis of novel *C*-glycoside analogues that inhibit various enzymes involved in human disease. This holds true in the area of anti-cancer activity. A particular enzyme known to be involved in cancer metabolic pathways is β-glucuronidase which is known to act on *O*-glucuronide metabolite in retinoic acid. Curley Jr. and co-workers had shown that various *C*-glycoside analogues to *O*-glucuronide metabolites, (see Figure 6), have a noticeable

activity against human mammary tumor cells.[13] It was noted that compounds that have different substituent groups (-OR, Figure 6) at carbon six were shown to have antiproliferative activity but no animal studies have been attempted to date.

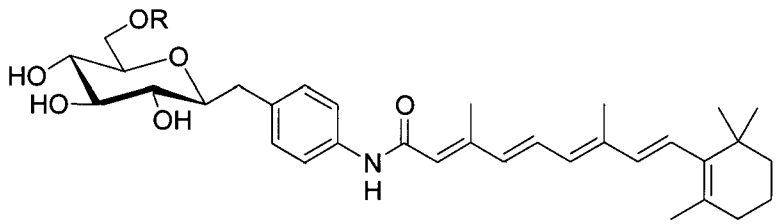


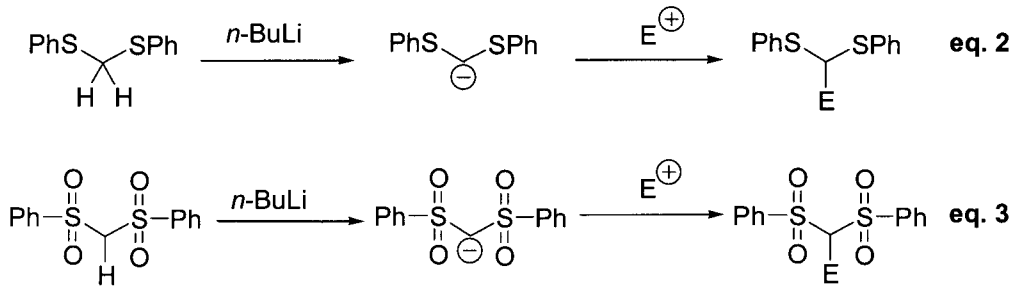
Figure 6. *C*-glucuronide

Dithioacetals

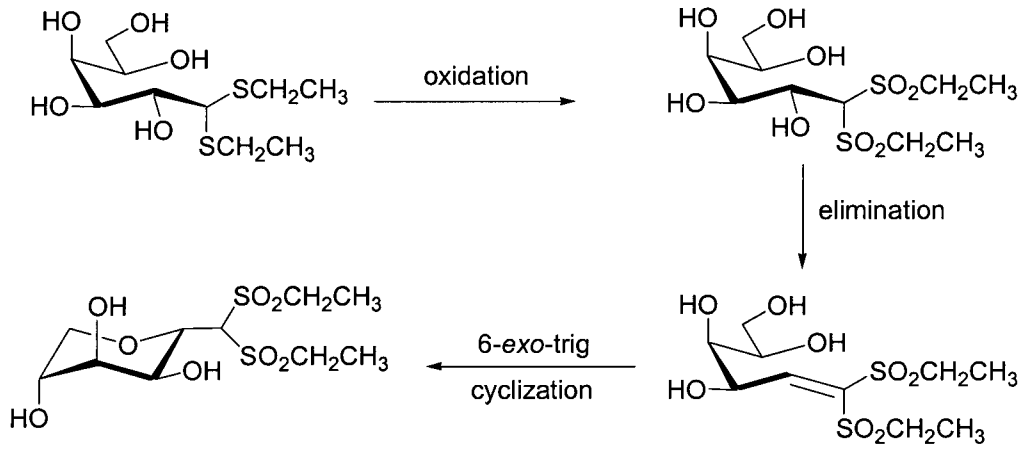
In the interest of exploring new and improved ways of synthesizing *C*-glycosides we have applied the use of dithioacetal chemistry in a variety of ways to carbohydrates. With this in mind it is important to discuss the characteristics of dithioacetals that make them potential synthons for *C*-glycosides and subsequently *C*-disaccharides.

Dithioacetals are 1,3-dithianes, which means there are two sulfur atoms attached to one carbon atom (see equation 2). The sulfurs act as electron withdrawing groups making the protons attached to the central carbon slightly acidic (pK_a~40).[28] The molecule can be treated with a base such as *n*-butyl lithium, which results in anion formation (equation 2). The anion formed can then be used as a nucleophilic species in subsequent reactions.

Several oxidizing agents have been used to form sulfoxides (one oxygen atom bonded to a sulfur atom) species and then sulfones (two oxygen atoms bonded to one sulfur atom) from dithioacetals; some include peroxypropionic acid, 3-chloroperoxybenzoic acid (mCPBA), and magnesium monoperoxyphthalic acid (MMPP).



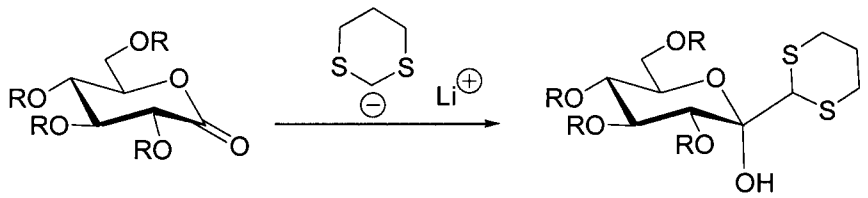
When a 1,3-dithiane is completely oxidized, a geminal bis(sulfone) results. The protons attached to the central carbon atom on a bis(sulfone) become more acidic (pK_a~12) than in dithioacetals and are readily deprotonated due to the added electron withdrawing ability of the oxygen atoms (see equation 3). In the past, reactions of dithioacetals and sulfones have been applied to carbohydrate chemistry, and several attempts at oxidizing carbohydrates containing sulfur have been documented since the 1950's. One example also demonstrates the ability to reform a heterocyclic molecule using sulfone chemistry. Oxidation of D-galactose diethyl dithioacetal results in an acyclic bis(sulfone) which in turn eliminates a molecule of water and cyclizes yielding a pyran carbohydrate derivative (Scheme 1).[14]



Scheme 1. Oxidation, elimination and cyclization of D-galactose diethyl dithioacetal

In earlier studies it had been demonstrated that sulfones are useful in alkylation reactions; for example Kündig, and Cunningham showed that treatment of 1,3-benzodithiole tetroxide with a base, along with various electrophiles, lead to the formation of an alkylated product in good yields.[15]

The potential use for these compounds, and where our interests lie, is in the formation of carbon-carbon bonds on carbohydrates. The area of C-C bond formation using the chemistry of dithioacetals and bis(sulfones) is extensive, and we were interested in new applications in *C*-glycoside synthesis. In an early example of this, Horton and co-workers had shown that the lithium anion of a 1,3-dithiane could be added to a protected D-glucono-1,5-lactone yielding a newly formed *C*-glycoside (see equation 4), specifically a dithianylglucopyranose.[16] By expanding on this earlier work we hoped to apply similar chemistry to the synthesis of *C*-disaccharides.



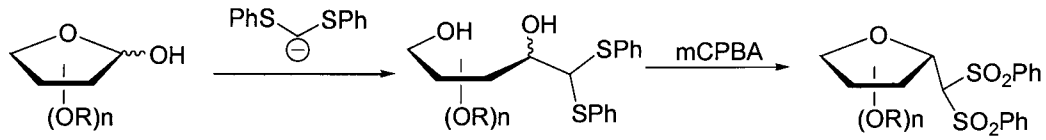
R=SiMe$_3$

eq. 4

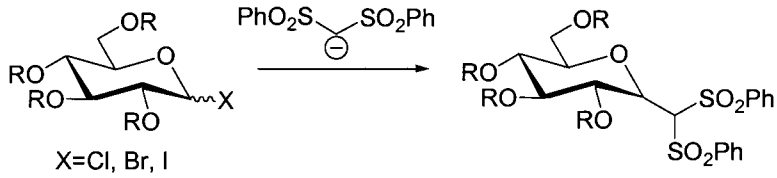
Statement of the Problem

In modern society synthetic organic chemists must take on not only chemical problems but various biological ones also. This especially holds true in the development of new and improved drug syntheses, considering the most pathogenic bacteria are resistant to many of our current antibiotics. Researchers are now focusing on carbohydrate compounds that are involved in the biosynthesis of bacterial components such as cell walls. The enzymes that act on these compounds are therefore prime targets for inhibition.

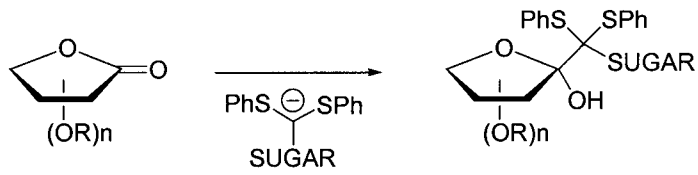
Carbohydrate components such as oligosaccharides and polysaccharides are linked *via* oxygen atoms, and the bacterial enzymes that utilize these carbohydrates often do so by breaking down or by building up these linkages. It could be hypothesized that creating a carbohydrate mimetic with a carbon-carbon bond between two sugars could effectively cause inhibition of the enzymes that act on these compounds. It is through the use of carbohydrate diphenyl dithioacetal derivatives that we hoped to accomplish this. Specifically, we have attempted three different approaches to this problem; the first is the addition of lithium bis(phenylthio)methane to various sugar hemiacetals (equation **5-A**), the second attempt is displacing a leaving group at C-1 of various sugars with the anion of bis(phenylsulfonyl)methane (equation **5-B**), and the third is attack of a carbohydrate-derived dithioacetal anion on a sugar-derived lactone which would yield a *C*-disaccharide (equation **5-C**).



eq. 5-A



eq. 5-B



eq. 5-C

Results and Discussion

1. Formation and Oxidation of Sugar Dithioacetals

The major goal of this project is to create *C*-glycosides that could have biological activity. Different carbohydrates appear in nature that vary greatly by the number of sugar units joined together (oligosaccharides and polysaccharides) down to the number of carbons in the rings and the number of hydroxyls. It is known that various derivatives of five and six carbon sugars play important roles in the biosynthesis of bacterial components. By creating mimics (Figure 7) of these carbohydrates it may be possible to achieve inhibition of key bacterial enzymes.

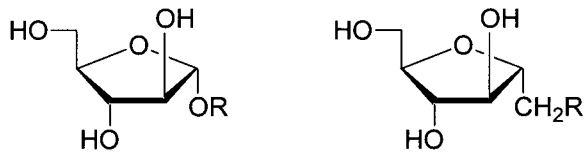
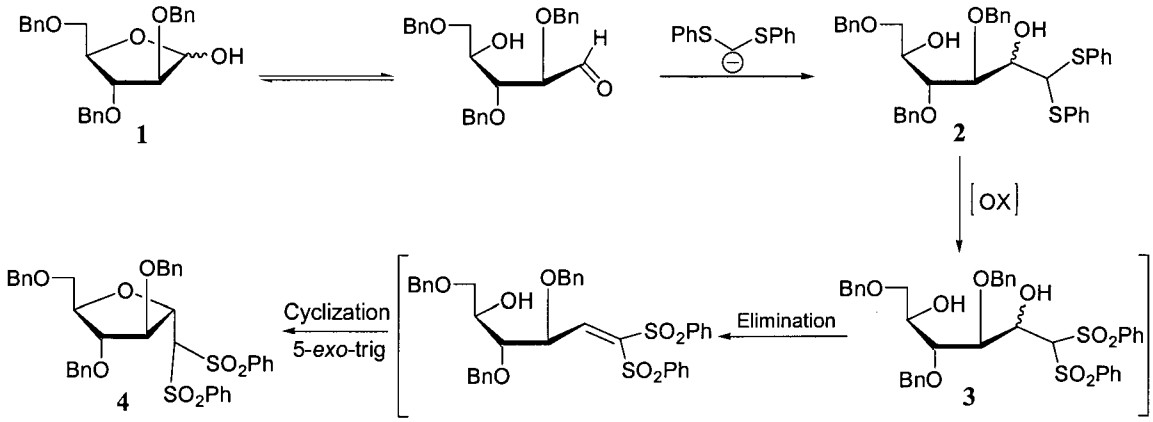


Figure 7. *O*-Glycoside and *C*-Glycoside Mimic

C-Glycoside synthesis therefore began with various attempts at creating arabinofuranoside (5 carbon sugar) derivatives since arabinofuranosides are found in the cell wall of *Mycobacterium tuberculosis*.[17] The initial synthetic route was aimed at creating a new C-C bond at C-1 of 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**1**) using a bis(phenylthio)methane nucleophile. This was accomplished by taking advantage of ring opening at the anomeric carbon in solution which reveals an electrophilic aldehyde to which the bis(phenylthio)methane anion was added (Scheme 2).



Scheme 2. Formation and oxidation of arabinofuranoside dithioacetal

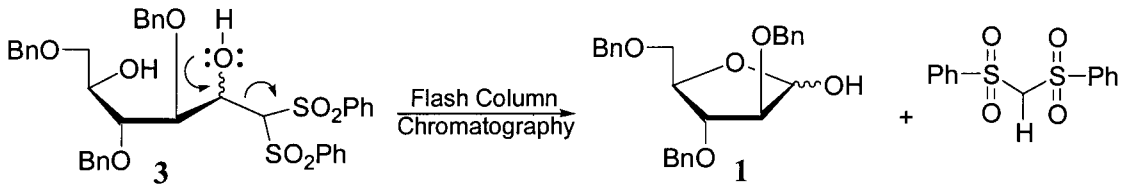
Initial TLC of the reaction mixture revealed multiple compounds and the disappearance of starting material. After aqueous workup, the reaction mixture was purified using column chromatography affording compound **2** in 69% yield. The TLC (3:1 hexane:ethyl acetate) showed that the starting material had an R_f value of 0.22 compared to the less polar products with R_f of 0.32. The lower polarity can be attributed to the non-polar phenyl rings within the dithioacetal. ^{1}H NMR shifts showed a narrow doublet downfield at 4.47 ppm that is representative of the proton between the two sulfurs. A small coupling constant for this doublet of J = 2.75 Hz suggests a dihedral relationship between H-1 and H-2 of ~90°. Carbon NMR also showed peaks between 72 ppm and 78 ppm that represent the original five carbons from the precursor carbohydrate and one carbon from the newly bonded dithioacetal group.

Compound **2** was then treated with 4.2 equivalents of mCPBA in an attempt to oxidize the dithioacetal to its sulfone form where each sulfur atom becomes doubly bonded to two oxygen atoms (Scheme 2). After oxidation, it was theorized that elimination of water would occur between C-1 and C-2 affording a reactive alkene intermediate. Since all the hydroxyls are protected with benzyl groups except the one at

C-5, cyclization might be possible in a 5-*exo*-trig fashion[18] to generate the *C*-glycosidic bis(sulfone) **4** (Scheme 2). TLC (2:1 hexane:ethyl acetate) of the reaction mixture after twelve hours showed no starting material ($R_f = 0.64$) and a newly formed more polar spot ($R_f = 0.32$) that was UV active and charred when burned using a solution of 5% sulfuric acid in ethanol. After a basic workup, ^{1}H NMR demonstrated shifts that are indicative of sulfones. The precursor dithioacetal species phenyl protons show up at approximately 7.2-7.4 ppm as complex multiplets, whereas the same protons are now pulled downfield (7.79-7.84 ppm) due to the four electron withdrawing oxygen atoms attached to the sulfurs. Another major shift is that of H-1 from 4.47 ppm to 5.1 ppm due to the same electron deshielding effect of the oxygen atoms. The shifts in the ^{1}H NMR potentially corresponded to a cyclized molecule but to further verify this, mass spectra were obtained which gave a major peak at formula weight of 716 m/z using electron spray ionization (ESI) and atmospheric pressure chemical ionization (APCI). This data supports the idea that a water molecule did not eliminate, therefore suggesting the reaction stopped at the acyclic bis(sulfone) **3** (Scheme 2). At this point the material was refluxed in solvents such as toluene and dioxane overnight with the hope that introducing heat could promote elimination of a water molecule. After refluxing overnight, TLC and ^{1}H NMR showed that the material remained unchanged under these conditions.

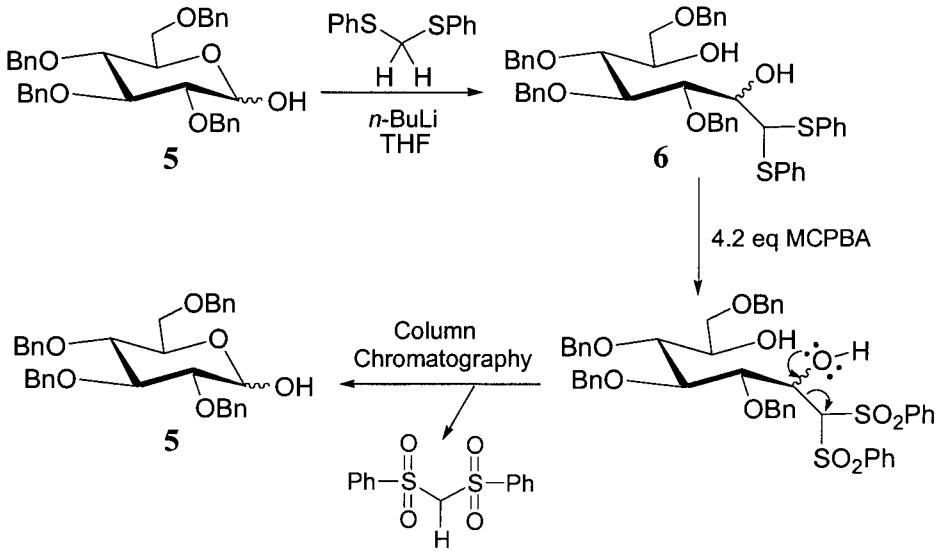
Further purification on the oxidized material was attempted using flash column chromatography. ^{1}H NMR was performed on the material isolated from the column which was determined to be 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**1**) starting material and bis(phenylsulfonyl)methane. Flash column chromatography is by nature somewhat acidic which was thought to contribute to the decomposition of the compound on the

column, but when looking at the acyclic molecule it is feasible to see a retro-aldol reaction occurring (Scheme 3) with the lone-pair of electrons from the hydroxyl at C-2 being used to break the bond from C-1 and C-2. This mechanism is plausible considering the bis(phenylsulfonyl)methane makes a very good leaving group.



Scheme 3. Retro-aldol

In an attempt to extend this methodology to a six carbon sugar a dithioacetal was synthesized by nucleophilic addition of lithium bis(phenylthio)methane to 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**5,** Scheme 4). The nascent dithioacetal was oxidized under the same conditions as the *arabino* derivative (Scheme 4). When the oxidized compound **6** was purified *via* column chromatography the starting material **5** containing a free hydroxl at C-1 was isolated and verified by TLC and ^{1}H NMR. This result supports the idea of degradation of bis(sulfones) through a retro-aldol mechanism.

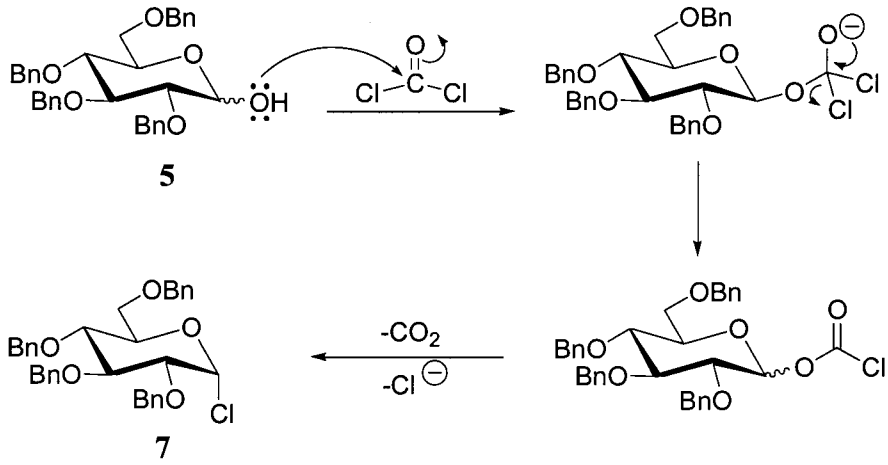


Scheme 4. Addtion and Retro-aldol reaction for the *Gluco* derivative

2. Attempted Displacement of Glycosyl Halides

The next method employed to achieve carbon-carbon bond formation (*C*-glycoside synthesis) at the anomeric position was by synthesizing a carbohydrate derivative with a good leaving group at C-1, such as a chloride, bromide, or iodide. These halides could potentially be displaced by a bis(phenylthio)methane anion.

This project began with the synthesis of a series of glycosyl chlorides (Table 1) with the intent of displacement with the bis(phenylthio)methane anion. The synthetic route chosen was an older procedure but now applied for the first time to sugar hemiacetals.[19] Compounds **8-14** are known in the literature and were verified by ^{1}H NMR (see Experimental section).



Scheme 5. General Chlorination of Hemiacetals using Triphosgene

Treatment of various hemiacetals with triphosgene [$(Cl_3CO)_2CO$] as the chloride source was found to give glycosyl chlorides in good yields. The proposed mechanism for glycosyl chloride formation is an acyl substitution followed by nucleophilic displacement at the anomeric carbon (preliminary evidence indicates S_N1).[19] The first carbohydrate used was 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**5**) with which 0.4 eq of triphosgene

reacted completely. The complete conversion of starting material (R_f = 0.14) to glycosyl chloride (R_f = 0.71) was monitored by TLC and confirmed by ^{1}H NMR.

The glycosyl chloride **7** was recovered in an 84% yield as the α-anomer. The ^{1}H NMR showed a distinct doublet at 6.05 ppm that is representative of H-1, downfield because of its close proximity to the electronegative chloride atom. ^{1}H NMR of the chlorides produced here matches those from other glycosyl chloride syntheses performed by other workers.[20, 21, 22]

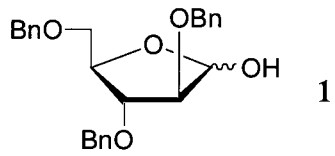
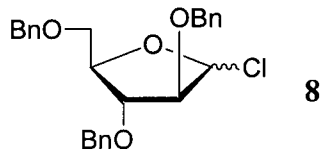
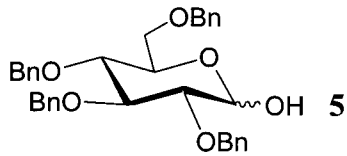
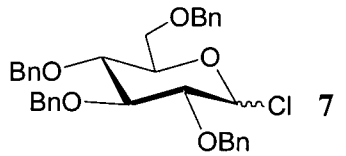
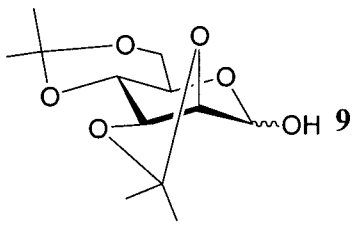
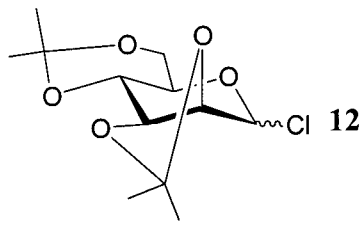
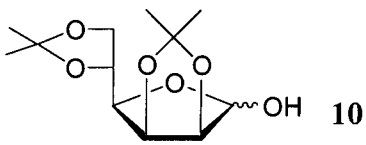
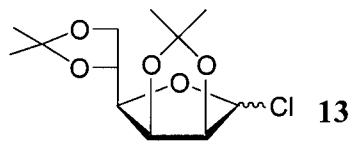
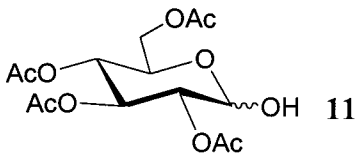
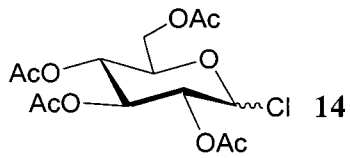
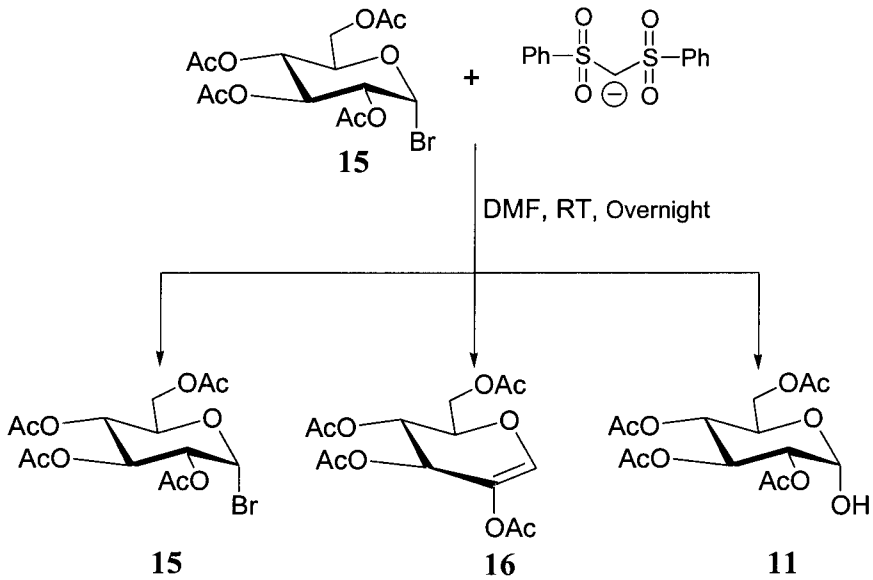
Starting Sugar	Glycosyl Chloride Product
 **1**	 **8**
 **5**	 **7**
 **9**	 **12**
 **10**	 **13**
 **11**	 **14**

Table 1. Glycosyl Chloride Series

The newly formed glycosyl chloride **7** was then treated with the anion of bis(phenylsulfonyl)methane at room temperature overnight. When the reaction mixture was analyzed by TLC, only unreacted chloride and bis(phenylsulfonyl)methane remained indicating no reaction had occurred. Several of the other glycosyl chlorides were also treated with bis(phenylsulfonyl)methane and bis(phenylthio)methane nucleophiles in attempts to displace the halogen. In reactions involving three different glycosyl chlorides no evidence of displacement by the nucleophile was found by TLC and ^{1}H NMR.

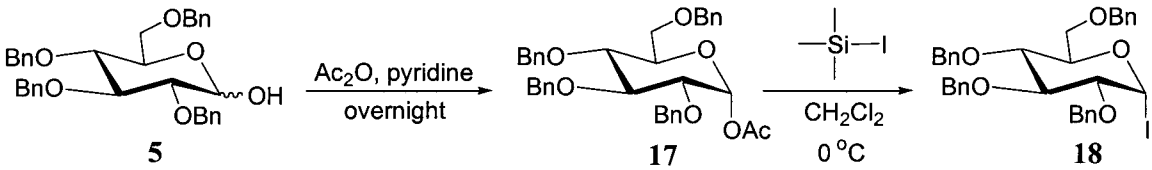
The next halide used for nucleophilic displacement was a commercially available glycosyl bromide. 2,3,4,6-Tetra-*O*-acetyl-1-bromo-α-D-gluco-pyranose (**15**) was reacted with bis(phenylsulfonyl)methane anion. After 20 min. the reaction mixture was analyzed by TLC which showed multiple products that charred in a solution of 5% sulfuric acid in ethanol. The reaction mixture was run overnight and ran the same way on TLC plates.



Scheme 6. Reaction of 2,3,4,6-tetra-*O*-acetyl-1-bromo-α-D-glucopyranose with bis(phenylthio)methane anion

After evaporation the residue was injected onto an MPLC[23] column and the multiple products were isolated. The first compound isolated, by NMR showed peaks for a glucal product **16** (Scheme 6), (doublet of doublets at 5.2 ppm and doublet at 5.44 ppm), which probably resulted from an E-2 elimination between C-1 and C-2 (Scheme 6). The next products isolated from the column were determined to be the bromide starting material **15** and 2,3,4,6-tetra-*O*-acyl-α-D-glucopyranose (**11**). Again, this reaction showed no evidence for nucleophilic displacement of the halide.

A last attempt to displace halogens was attempted with an even better leaving group at C-1, iodide. A convenient method for synthesizing glycosyl iodides was adapted from Gervay *et al* where the precursor to the iodide was a glycosyl acetate.[24] Treating 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**5**) with acetic anhydride and pyridine gave the glycosyl acetate **17** in 84% yield (Scheme 7).



Scheme 7. Formation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl iodide

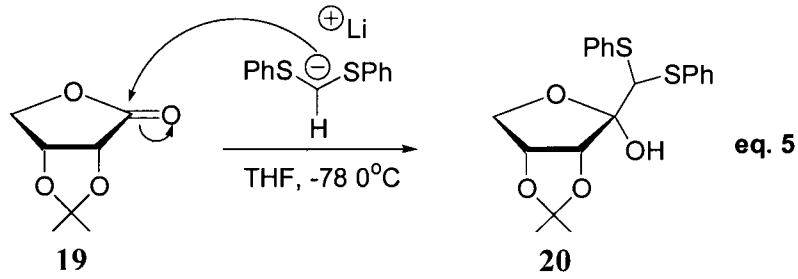
This reaction was confirmed by ^{1}H NMR signals (CH_3 singlet at 2.05) along with one distinct non-polar spot by TLC with an R_f of 0.82 (1:1 hexane:ethyl acetate). The resulting glycosyl acetate (**17**) was then treated with trimethylsilyl iodide in methylene chloride at 0 °C (Scheme 6). The TLC of the reaction mixture showed complete conversion of the acetate to glycosyl iodide **18** within one hour. The formation of the iodide was also verified by comparing NMR spectra from the literature. As soon as the iodide was formed it was treated with bis(phenylsulfonyl)methane anion because of the relative instabilities of these iodides. The reaction mixture was visualized by TLC in

increments of 20 minutes which showed the decomposition back to a free hydroxl at C-1 of the sugar.

3. Addition of Dithianes to an Erythronolactone

The final attempt in forming a *C*-glycosidic bond, and ultimately developing a *C*-disaccharide synthesis, was through nucleophilic addition of dithiane anions to a sugar-derived lactone. The carbohydrate derivatives used in the following syntheses were chosen based on the fact that they were readily synthesized from simple sugars or were commercially available.[25] The first step was to verify that stereoselective nucleophilic addition of bis(phenylthio)methane anion to a lactone was possible. The protecting group on the lactone starting material should direct the bis(phenylthio)methane anion to approach the electrophilic carbon from the β face of the carbonyl.

To do this, lithium bis(phenylthio)methane was treated with 2,3-*O*-iso-propylidene-D-erythronolactone (**19**) in THF at –78 °C. After 24 hours the reaction mixture was analyzed by TLC (UV activity and charring with a solution of 5% phosphomolybdic acid in ethanol) showing the disappearance of starting material. From TLC the lactone starting material could only be observed as a yellow spot with the 5% phosphomolybdic acid solution whereas the newly formed spot charred brown in 5% sulfuric acid in ethanol. The reaction mixture also contained some by-products so column chromatography was unavoidable. After workup and evaporation, the syrup was loaded onto an MPLC column. The major product was isolated from the column and determined to be compound **20** in a 21% yield (equation 5).



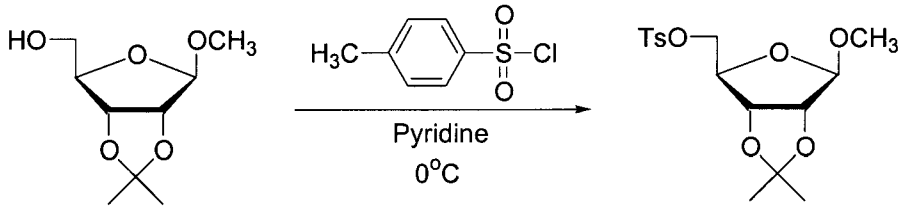
19 **20** **eq. 5**

The ^{1}H NMR spectrum showed a fairly pure compound with distinct signals between 1.36 ppm and 1.46 ppm that represent the isopropylidene protecting group protons. A multiplet between 7.19-7.45 ppm was observed for the phenyl ring protons along with a sharp doublet at 4.76 ppm representing H-1 (J = 6.0 Hz) between the SPh groups. H-3 on the ring is distinct in that it is the only one that is split by three other protons (a multiplet at 4.85 ppm). The yield was low but current attempts are being made to increase amounts obtained after chromatography.

Since the addition of the bis(phenylthio)methane anion to the sugar derived lactone was successful the production of other synthons for a *C*-disaccharide could continue. The next step involved the known protection of D-ribose to give methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**21**).[26] The compound was obtained in a 79% yield and was determined to be pure by ^{1}H NMR and TLC. This compound was of particular interest because of the reactive hydroxy methyl group at C-5. A good leaving group such as a tosylate or a triflate could be added to this primary hydroxyl with the intent of displacement by a bis(phenylthio)methane anion.

The first effort was the formation of a tosylate ester in which *p*-toluenesulfonyl chloride was added to **21** to give methyl 2,3-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-β-D-ribofuranoside (**22**) in 85% yield (Scheme 8). The formation of this compound was

monitored by TLC (2:1 ethyl acetate:hexane) which showed no starting material (R_f = 0.46) and the appearance of a new non-polar spot (R_f = 0.70).

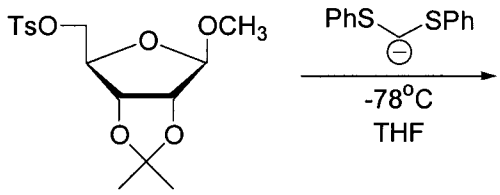


21 **22**

Scheme 8. Tosyl ester formation

A clean ^{1}H NMR confirmed the TLC analysis giving signals for the isopropylidene protons (2 singlets) between 1.28-1.44 ppm. A singlet at 3.23 ppm represented the protons from the methyl ester at C-1. Another specific singlet at 4.9 ppm was assigned to H-1 (which shows no coupling to H-2 because of the 90° angle between the two). The protons from the methyl group on the tosylate showed up at 2.45 ppm and the phenyl ring protons appeared in two distinct areas (7.3 ppm and 7.7 ppm) as doublets due to the sulfonyl moiety at the *ipso* position. H-5 and H-5' were represented by a doublet of doublets at 4.0 ppm which can be attributed to the splitting caused by the interaction with each other and with H-4.

The tosyl ester **22** was added to a stirring solution of lithium bis(phenylthio)methane and was allowed to stir overnight. Initial TLC showed no evidence of reaction with the anion. At this point another 1.2 equivalents of *n*-BuLi was added to be sure there was anion in solution. Even after the addition of more base, TLC continued to show unreacted starting material. After an aqueous workup, ^{1}H NMR signals matched the starting material (equation 6).

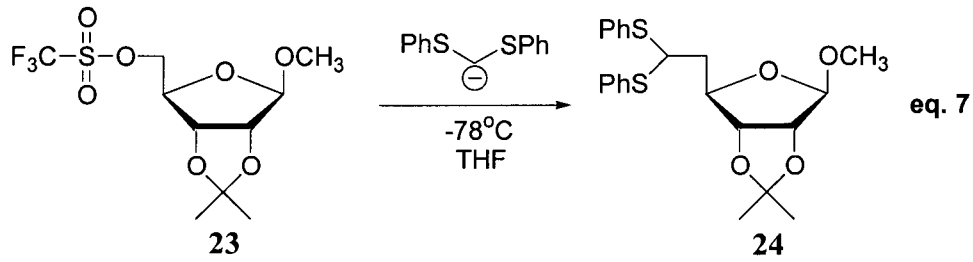


22 **eq. 6**

This result could mean a variety of things, two of which were that either the anion was not being formed in solution or the tosylate group was not a good enough leaving group for this reaction. It has been shown in many cases before in this work that lithium bis(phenylthio)methane was formed in solution. The focus then was directed to the leaving group strategy. It is known that a triflate is a much better leaving group than a tosylate. The next move then was to synthesize a triflate at the same hydroxyl using triflic anhydride.

The reaction is well known in the literature where a mixture of triflic anhydride, pyridine, and methylene chloride as a solvent, is treated with another solution containing the sugar derivative (1° hydroxyl) at –10 °C.[27] The reaction was allowed to stir for 1.5 hours at which time TLC analysis showed complete consumption of starting material that had an R_f of 0.50 and appearance of a more non-polar spot with an R_f of 0.85 (2:1 ethyl acetate:hexane). The synthesis of methyl 2,3-*O*-isopropylidene-5-*O*-(fluoromethyl-sulfonyl)-β-D-ribofuranoside (**23**) was confirmed by data obtained by ^{1}H NMR and ^{13}C NMR. Spectral analysis gave common peaks for the protons from the isopropylidene protecting group (1.25-1.44 ppm), the methyl protons at C-1 (3.35 ppm), and the ring protons between 4.66-5.00 ppm. An extra peak was also observed on the ^{13}C NMR downfield at 110.7 ppm that represents the carbon within the triflate group. The triflate ester was produced in 95% yield with clean NMR spectra.

Immediately after the triflate ester (**23**) was formed it was dissolved in THF and was added dropwise to a prepared solution of lithium bis(phenylthio)methane at –78 °C. After stirring overnight the reaction was checked by TLC that showed the formation of one major product along with other minor ones.



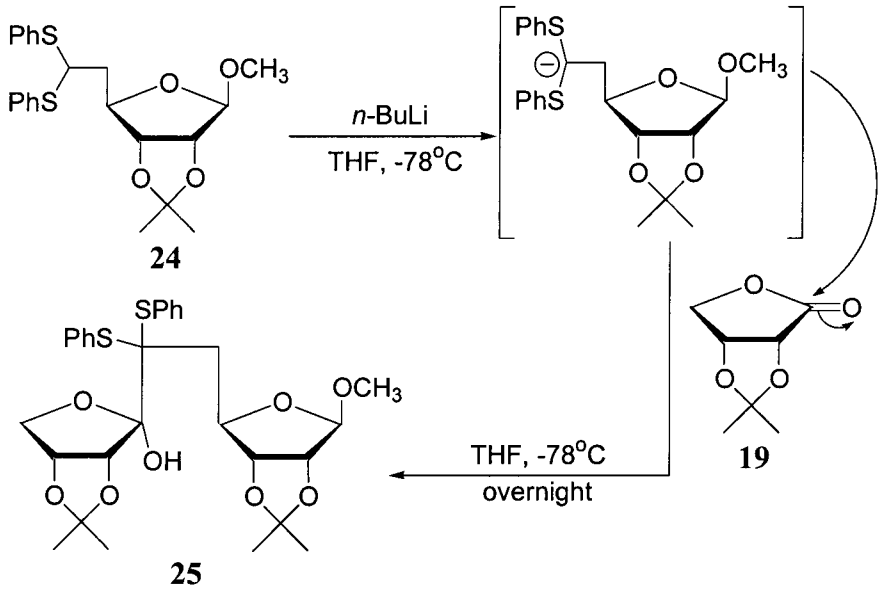
23 **24** **eq. 7**

After acidic workup, the solution was evaporated and the residue was loaded onto a flash column. The major spot (compound **24**) from the TLC was isolated in 38% yield and was determined to be the product from the addition of the bis(phenylthio)methane anion (equation 7). The ^{1}H NMR signals correspond to the correct compound giving signals common to the SPh groups (7.2-7.5 ppm), the acetal protecting group (1.30-1.49 ppm), and the methyl ether protons (3.1 ppm). Some of the more defining signals for H-2, H-3, H-4 are seen as a large multiplet at ~4.5 ppm. The large amount of splitting is due to the adjacent protons on the ring for H-2 and H-3 and the close proximity of H-5 and H-5' to H-4. H-5 and H-5' also have unique new signals (two doublet of doublet of doublets, at 1.86-1.93 ppm and 2.1-2.2 ppm respectively). These protons were next to an oxygen atom in the triflate compound whereas they are now next to a carbon atom and are split by H-4 and H-6 which is between the two electron rich sulfur atoms.

The proton between the two sulfur atoms (H-6) in compound (**24**) could now be deprotonated. The entire sugar-derived dithioactal should now behave as one large

nucleophile that can be added in the same manner as bis(phenylthio)methane was to the sugar derived lactone. By doing so one could create a *C*-glycosidic bond between two sugar derivatives. The reaction should be a stereoselective nucleophilic addition to the β face of the lactone due to the isopropylidene protecting group.

To do so the triflate ester (**23**) was made fresh and the bis(phenylthio)methane was added to it yielding **24** as before. The sugar derived dithiane (**24**) was then dissolved in dry THF and was treated with a solution of 1.6 M *n*-BuLi at –78 °C for 20 minutes. The resulting orange mixture was stirred as a solution of 2,3-*O*-isopropylidene-D-erythrono-lactone (**19**) in dry THF was added dropwise (Scheme 9). The reaction ran overnight and analysis by TLC (6:1 hexane:ethyl acetate) showed the appearance of a new spot ($R_f = 0.20$) more polar than the precursor triflate ($R_f = 0.41$).

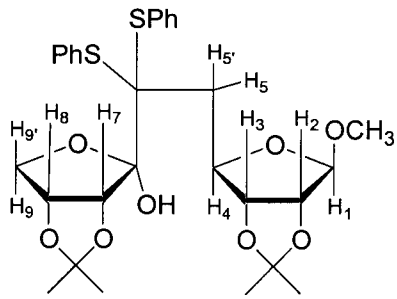


Scheme 9. *C*-Disaccharide formation

One observation was that all of the dithioacetal did not completely react with the lactone even after stirring overnight. The new compound burned brown in the solution of 5% sulfuric acid in ethanol whereas the lactone precursor did not. After aqueous workup

the sample was loaded onto a flash column for further purification. The new compound (**25**) was isolated from the column in a 35% yield (due to the lack of consumption of starting material) and analyzed by ^{1}H NMR and ^{13}C NMR.

In a molecule such as compound **25** it is quite difficult to assign signals from the performed spectra. Figure 8 shows the numbering of the protons around the *C*-glycosidic disaccharide molecule. Some of the more common signals such as the isopropylidene protecting groups were easier to notice showing up between 1.25-1.67 ppm as four singlets. The signals that represent H-5 and H-5' are now compressed into one multiplet (1.9-2.04). At 2.9 ppm there is a singlet that represents the protons from the methyl ether at C-1.



25

Figure 8. Proton Assignment for the *C*-disaccharide

The protons from the phenyl rings are complex multiplets between 7.14-7.70 ppm. The rest of the protons on the two rings and the protons that are outside the rings (H5, H-5', H-9, and H-9') were much harder to differentiate due to complex splitting patterns. To verify which protons they were, a 2-dimensional COSY (correlation spectroscopy) NMR was performed. This type of data analysis allows one to look down upon the ^{1}H NMR spectrum as a second dimension. Protons that couple to each other will show up as joining squares from the first dimension. H-1, as in the starting material,

was a sharp singlet at 4.8 ppm that has no coupling to H-2. The next protons resolved were H-2 and H-3. The signal for H-2 shows up as a doublet (J = 6.0 Hz) that represents the interaction with H-3. The signal for H-3 is also a doublet with a coupling constant of J = 6.0 Hz that dictates coupling to H-2 only. At 5.1 ppm a doublet (J = 6.0 Hz) appears that signifies the splitting for H-4 which is adjacent to H-5 and H-5'. The multiplet at 4.9 ppm represents H-8 which is a neighbor to H-9 and H-9'. H-7 shows up as a distinct doublet with a coupling constant of J = 7.0 Hz describing its interaction with H-8 alone. There are two individual doublet of doublets at 3.9 ppm and 4.2 ppm that describe the splitting of H-9 and H-9' due to the interaction with H-8 and each other. The last unassigned signal was a singlet at 4.47 ppm that could possibly be the proton from the hydroxyl group at C-7.

To support TLC and ^{1}H NMR data, APCI mass spectrometry was performed on **25**. The results showed a molecular ion peak at a formula weight of 467.4 m/z that represents the mass of the entire *C*-disaccharide minus an SPh group. The spectrum also revealed a less intense peak at a formula weight matching that of the *C*-disaccharide (575.2 m/z).

Conclusions

In conclusion, three synthetic routes towards *C*-glycoside synthesis using dithioacetals were studied. Nucleophilic additions to sugar-derived hemiacetals were very successful in good yields but further oxidations seemed to afford only acyclic bis(sulfones) leaving the modified carbohydrate simply extended by one carbon atom. During chromatography the acyclic bis(sulfone) was hypothesized to go through a retro-aldol pathway to give the hemiacetal starting material.

Synthesis of glycosyl chlorides was also successful with the intent of making a good leaving group at C-1. Various nucleophilic displacement reactions of not only the chlorides, but commercial bromides and synthesized iodides did not work under various conditions.

The third attempt at synthesizing *C*-glycosides from sugar-derived dithioacetals was aimed at nucleophilic addition to a sugar lactone. Simple addition of lithium bis(phenylthio)methane to an erythrono lactone was successful. This same chemistry was then applied in the synthesis of a *C*-disaccharide through the addition of a dithiane to a triflate ester. Future work in this area will most likely be directed at increasing the yields of the triflate ester and subsequently the *C*-disaccharide. Once these tasks are accomplished experiments can be attempted to reduce the bis(phenylthio) groups from the *C*-disaccharide leaving only a two carbon bridge between the sugar derivatives.

Experimental

General Procedures

A Varian Gemini 2000 system was used to obtain ^{1}H and ^{13}C NMR spectra at 400 MHz and 100 MHz respectively, using $CDCl_3$ or d_6-DMSO as 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), m (multiplet), with coupling constants (*J*) measured in Hertz. A Bruker Esquire-HP 1100 LC/MS was used to obtain mass spectra. Whatman aluminum-backed flexible plates were used for analytical thin layer chromatography. Flash column chromatography utilized 70-270 mesh 60-Å silica gel. A Perkin Elmer 323 automatic polarimeter was used to collect data on optical rotations.

Synthesis of Dithioacetal 2 from 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (1).

In a flame dried 250 mL three-neck round bottom flask under nitrogen atmosphere, 5 g of bis(phenylthio)methane (21.5 mmol) was dissolved in 100 mL of dry THF. The mixture was stirred and cooled to –78 °C then 13.4 mL of 1.6 M *n*-BuLi (21.5 mmol) was added dropwise and the resultant yellow solution was stirred for 20 min. After this time a 20 mL solution of 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (3.0 g, 7.15 mmol) in dry THF was added dropwise at –78 °C. The reaction mixture was allowed to stir and come to room temperature overnight, after which time TLC (3:1 hexane:ethyl acetate) confirmed completion. The reaction was quenched with saturated NH_4Cl and extracted with 2 x 25 mL portions of ethyl acetate. The organic layers were combined and decolorized with charcoal. After drying ($MgSO_4$) and evaporation the residue was

purified by column chromatography (200 g silica, with a solvent gradient of first 6:1 hexane:ethyl acetate followed by 1:1 hexane:ethyl acetate). After chromatography 3.22 g of a yellowish syrup (**2**) was obtained (69% yield).

^{1}H NMR: δ3.61 (m, 2H, H-6, H-6'), 3.8 (m, 1H, H-2), 4.01 (m, 1H, H-5), 4.1 (m, 1H, H-4), 4.28 (m, 1H, H-3), 4.47 (d, 1H, H-1, *J* 2.75 Hz), 4.5-4.8 (m, 6H, 3 x C$\underline{H_2}$Ph), 7.2-7.4 (m, 25H, Ar-H).

^{13}C NMR: δ 61.8, 65.1, 72.2, 72.4, 74.52, 74.57, 75.1, 78.2, 78.9, 128.5, 128.7, 128.77, 128.8, 128.9, 128.98, 129.1, 129.2, 129.36, 129.39, 129.45, 129.49, 130.0, 130.04, 133.7, 133.8, 134.6, 138.6, 138.7, 139.0.

Synthesis of Dithioacetal 6 from 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (5).

Bis(phenylthio)methane, 3.87 g (16.6 mmol) in 30 mL of dry THF, was added to a 100 mL flame dried three-neck round bottom flask under an atmosphere of nitrogen. The solution was stirrred and was cooled to –78 °C. *n*-BuLi (10.4 mL, 16.6 mmol) was added dropwise resulting in a yellow-orange solution. After stirring for 20 min., 1.5 g (2.7 mmol) of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose in 15 mL of dry THF was added dropwise to the mixture. The reaction mixture was allowed to stir and come to room temperature overnight, after which time TLC (6:1 hexane:ethyl acetate) confirmed consumption of the sugar starting material. The reaction mixture was then quenched with saturated NH_4Cl and extracted with 2 x 25 mL portions of CH_2Cl_2. The organic layers were combined and extracted with 25 mL of H_2O. The organic layer was decolorized with charcoal and filtered, anhydrous $MgSO_4$ was used to dry the organic solution, and the solvent was evaporated to leave an orange syrup. This material was purified by

column chromatography using 150 g of silica with a solvent gradient of 6:1 hexane:ethyl acetate then 1:1 hexane:ethyl acetate. This gave **6** as an orange syrup in an overall yield of 1.55 g (73%).

^{1}H NMR: δ3.6 (m, 2H, H-7, H-7'), 3.67 (m, 1H, H-3), 3.84 (m, 1H, H-4), 4.1 (m, 1H, H-5), 4.4 (m, 1H, H-6), 4.46 (d, 1H, H-1, *J* 2.4 Hz), 4.5-4.9 (m, 8H, 4 x C$\underline{H_2}$Ph), 7.18-7.4 (m, 30H, Ar-H)

^{13}C NMR: δ64.8, 71.6, 72.3, 73.0, 74.3, 74.5, 75.8, 76.0, 78.7, 79.2, 80.6, 128.6, 128.69, 128.74, 128.78, 128.9, 129.0, 129.1, 129.2, 129.3, 129.38, 129.4, 129.44, 129.47, 129.9, 130.0, 131.9, 132.7, 135.2, 133.3, 133.8, 138.8, 138.82, 138.85, 139.2.

Oxidation of Dithioacetal 2 to its sulfone form (3).

In a 100 mL round bottom flask a solution of 0.84 g (1.29 mmol) of **2** in 30 mL CH_2Cl_2 was prepared. To this solution 4.2 equivalents of 70% 3-chloroperoxybenzoic acid (1.33 g, 7.7 mmol) was added. The reaction was allowed to stir overnight at room temperature. The mixture was then tested for completion by TLC in a solvent system of 2:1 hexane:ethyl acetate. The reaction then was poured into a stirring solution of saturated $NaHCO_3$ and allowed to mix for 10 min. The solution was allowed to settle and the organic layer was removed. The aqueous layer was then extracted with 2 x 10 mL portions of CH_2Cl_2 and combined with the original organic layer. The organic solution was then washed with 10 mL of H_2O, dried over $MgSO_4$, and evaporated. The bis(sulfone) **3** was obtained as a yellowish syrup in 66% yield (0.59 g).

^{1}H NMR: δ3.5 (m, 2H, H-6, H-6'), 3.7 (m, 1H, H-2), 3.8 (m, 1H, H-3), 4.66 (m, 1H, H-4), 4.38-4.65 (m, 6H, 3 x C$\underline{H_2}$Ph), 4.7 (1 m, 1H, H-5), 5.1 (d, 1H, H-1, *J* 1.8 Hz), 7.2-7.4 (m, 15H, Ar-H), 7.41-7.3 (m, 4H, Ar-H), 7.55-7.63 (m, 2H, Ar-H), 7.79-7.84 (m, 4H, Ar-H).

^{13}C NMR: δ 71.7, 72.0, 74.5, 74.6, 76.0, 77.6, 77.9, 78.0, 79.8, 128.4, 128.5, 128.7, 128.8, 129.0, 129.2, 129.4, 129.5, 129.6, 129.7, 130.0, 130.4, 130.8, 134.9, 135.5, 138.2, 138.28, 138.7, 138.9, 141.2.

Synthesis of 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride (7) from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (5).

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (0.5046 g, 1 mmol) was dissolved in 5 mL of dry THF in a 25 mL round bottom flask. Triphosgene (120 mg, 0.4 mmol) was added and the mixture was stirred at room temperature. Pyridine (0.1 mL) was added and the mixture was allowed to stir at room temperature for 4 h while being monitored by TLC (3:1 hexane:ethyl acetate). After consumption of the starting material, pyridinium hydrochloride, a white precipitate, was filtered off. The filtrate was evaporated yielding 0.471 g (84%) of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**7**), which was a clear syrup.

^{1}H NMR: δ3.63 (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), 4.11-4.20 (m, 2H, H-5, H-3), 4.44-4.99 (m, 8H, 4 x C$\underline{H_2}$Ph), 6.05 (d, 1H, H-1, *J* 3.7Hz), 7.12-7.38 (m, 20H, Ar-H). NMR data agreed with literature values.[20]

Synthesis of 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride (14) from 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (11).

A 25 mL round bottom flask was charged with 0.449 g (1mmol) of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose and dissolved in 5 mL of dry THF. To this solution 120 mg (0.4 mmol) of triphosgene was added and the mixture was allowed to stir at room temperature. To the solution 0.1 mL pyridine was added dropwise, at which time a white precipitate formed. The reaction was heated at reflux while being monitored by TLC (2:1 hexane:ethyl acetate) until completion (18 h). The white precipitate (pyridinium hydrochloride) was then filtered off and the solvent was removed *en vacuo*, affording 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride (**14**), a clear syrup, in a 50% yield (0.237 g).

^{1}H NMR: δ2.01, 2.03, 2.08, 2.09 (4s, 12H, 4 x $COCH_3$), 4.10-4.33 (m, 3H, H-5, H-6, H-6'), 4.99-5.58 (m, 3H, H-2, H-3, H-4), 6.28 (d, 1H, H-1, *J* 3.8 Hz). NMR data agreed with literature values.[20]

Synthesis of 2,3,5-Tri-*O*-benzyl-α/β-D-arabinofuranosyl chlorides (8) from 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (1).

The experimental procedure describing the syntheses of these chlorides was the same as the *Gluco* derivative (**7**). The α/β mixture (86:14) of **8** was obtained in a 85% yield and the ^{1}H NMR spectrum matched that of literature.[22]

^{1}H NMR: δ3.62 (m, 1H, H-3), 3.96 (m, 1H, H-4), 4.36-4.70 (m, 9H, H-2, H-5, H-5', $C\underline{H_2}Ph$), 6.17 (s, H-1α), 6.21 (d, *J* 4.2 Hz, H-1β), 7.20-7.41 (m, 15H, Ar-H).

Synthesis of 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl chloride (13) from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (10).

2,3:5,6-Di-*O*-isopropylidene-D-mannofuranose (0.2603 g, 1 mmol) was dissolved in 5 mL of dry THF and was allowed to stir at room temperature in a 25 mL round bottom flask. To this solution 120 mg (0.4 mmol) of triphosgene was added and allowed to dissolve, at which point 0.1 mL of pyridine was added dropwise. After 3 hours TLC (2:1 hexane:ethyl acetate) showed complete consumption of starting material. Pyridinium hydrochloride precipitate was filtered off and the solvent was evaporated yielding 0.226 g (81%) of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride as a clear syrup.

^{1}H NMR: δ 1.33 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.46 (s, 6H, 2 x CH_3), 4.01 (dd, 1H, *J* 4.2, 8.8 Hz, H-6), 4.08 (dd, 1H, *J* 6.2, 8.8 Hz, H-6'), 4.19 (dd, 1H, *J* 3.5, 7.7 Hz, H-4), 4.42 (m, 1H, H-5), 4.88 (dd, 1H, *J* 3.5, 5.7, H-3), 4.95 (d, 1H, *J* 5.8, H-2), 6.07 (s, 1H, H-1). NMR data agreed with literature values.[20]

Synthesis of 2,3,4,6-Di-*O*-isopropylidene-D-mannopyranose (9) from D-manno-pyranose. [26]

D-Mannopyranose (5.4 g, 30 mmol) was dissolved in 20 mL of dry DMF in a 100 mL round bottom flask with 1 g of $MgSO_4$ at ~-10 °C. 2-Methoxypropene (5.7 mL, 60 mmol), and *p*-toluenesulfonic acid (20 mg) were added. The solution was stirred for 3.0 hours after which time another 5.7 mL of 2-methoxypropene was added dropwise over 2 hours. The reaction mixture was then tested by TLC (ethyl acetate) showing the disappearance of starting material. The solution was then filtered and the filtrate was

poured over 50 mL of ice water. The resulting mixture was extracted with 4 x 20 mL of CH_2Cl_2, then the organic layers were combined and washed with 4 x 20 mL of H_2O. The organic layers were combined again and dried over $MgSO_4$ and filtered. The mixture was evaporated affording 5.1 g of 2,3,4,6-di-*O*-isopropylidene-D-mannopyranose (64%). The product was isolated in crystalline form after column chromatography (silica gel, hexane/ethyl acetate 1:1 as eluent).

^{1}H NMR: δ 1.3-1.55 (4s, 4 x CH_3), 3.6 (m, 2H, H-6, H-6'), 3.8, 4.0, 4.19, 4.3, 4.7 (m, 1H each, H-1, H-2, H-3, H-4, H-5).

^{13}C NMR: δ 20.05, 27.3, 29.4, 30.2, 62.5, 63.3, 73.9, 75.8, 93.7, 100.7, 110.4, 163.5.

Formation of α,β-2,3,4,6-Di-*O*-isopropylidene-D-mannopyranosyl chlorides (12) from 2,3,4,6-Di-*O*-isopropylidene-D-mannopyranose (9).

A solution of 2,3,4,6-di-*O*-isopropylidene-D-mannopyranose (0.46 g, 1.76 mmol) and triphosgene (0.209 g, 0.4 mmol) in dry THF (5 mL) was allowed to stir at room temperature. Pyridine (0.1 mL) was then added dropwise by syringe giving a white precipitate immediately. The reaction mixture was stirred at room temperature for 3 hours and was monitored by TLC (2:1 hexane:ethylacetate) until the starting material was consumed. The pyridinium hydrochloride precipitate was filtered off and the solvent was removed *en vacuo* giving a clear residue, α,β-2,3,4,6-di-*O*-isopropylidene-D-mannopyranosyl chloride anomers in 67% yield (0.33 g).

^{1}H NMR: δ 1.33-1.55 (8s, 8 x CH_3), 3.68-4.31 (m, 6H, H-2, H-3, H-4, H-5, H-6, H-6'), 6.07 (d, H-1β, *J* 0.6 Hz), 6.26 (s, H-1α). NMR data agreed with literature values.[21]

Attempted reaction of 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl chloride (13) with the anion of bis(phenylsulfonyl)methane.

Bis(phenylsulfonyl) methane (0.296 g, 1 mmol) was dissolved in 10 mL dry DMF to which NaH (0.048 g, 1.2 mmol) was added in a 50 mL round bottom flask. This mixture was stirred at room temperature for 15 min. then 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride (0.226 g, 0.8 mmol) dissolved in 5 mL dry DMF was added dropwise. The reaction mixture was followed by TLC (3:1 hexane:ethyl acetate) which indicated that the chloride was undergoing hydrolysis back to the precursor hemiacetal (2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose). Saturated NH_4Cl was added to the reaction mixture followed by extraction with CH_2Cl_2 (2 x 10 mL). The organic layers were combined then washed with H_2O and dried over $MgSO_4$. The filtrate was then evaporated yielding a yellowish syrup. ^{1}H NMR in $CDCl_3$ and TLC R_f values confirmed the hydrolysis of the chloride to 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose under these reaction conditions. No evidence of chloride displacement by the nucleophile was observed.

Attempted reaction of Lithium bis(phenylthio)methane with 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride (13).

In a flame dried 25 mL three-neck round bottom flask, under nitrogen atmosphere, was dissolved 0.255 g (1.1 mmol) of bis(phenylthio)methane in 5 mL of dry THF. The mixture was stirred and cooled in a dry ice-acetone bath to –78 °C, then *n*-BuLi (0.69 mL, 1.1 mmol) was added dropwise to the mixture resulting in an orange solution. The mixture was stirred at constant temperature (-78 °C) for 20 min. at which time a solution of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride (0.234 g, 0.84 mmol) in 5 mL dry THF was added dropwise by syringe. The reaction mixture was allowed to come to room temperature as it stirred overnight. The reaction was monitored by TLC using 3:1 hexane:ethyl acetate which demonstrated the lack of consumption of the starting material. The mixture was then quenched with NH_4Cl and extracted with CH_2Cl_2 (2 x 10 mL), then the organic layers were combined and extracted with H_2O (2 x 10 mL) and dried over $MgSO_4$. After evaporation the resulting yellow syrup was analyzed by TLC and ^1H NMR that was determined to be unreacted 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride starting material.

Reaction of 2,3,4,6-Tetra-*O*-acetyl-1-bromo-α-D-glucopyranose (15) with the anion of bis(phenylsulfonyl)methane.

Bis(phenylsulfonyl)methane (0.296 g, 1 mmol) was dissolved in 5 mL dry DMF with NaH (0.024 g, 1 mmol) and was allowed to stir at room temperature for 20 min. A solution of 2,3,4,6-tetra-*O*-acetyl-1-bromo-α-D-glucopyranose (0.4112 g, 1 mmol) in 10 mL of dry DMF was then added to the mixture and stirring continued overnight. TLC (2:1 hexane:ethyl acetate) of the reaction mixture indicated multiple products. The mixture was evaporated then dissolved in CH_2Cl_2 (5 mL). Subsequent purification using

MPLC suggested elimination (E2) giving a glucal as one of the major products. The resulting material was analyzed using ^{1}H NMR and TLC which showed no evidence for displacement of bromide by the bis(phenylsulfonyl) anion.

Acetylation of 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (5).

To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1 g, 1.85 mmol) in 10 mL of pyridine was added 5 mL of acetic anhydride. The mixture was allowed to stir overnight at room temperature and completion of reaction was confirmed by the disappearance of starting material on TLC (1:1 hexane:ethyl acetate). The reaction mixture was poured slowly over ice until two layers appeared. A solution of 5% H_2SO_4 was then added to the mixture and was stirred for 10 min. The solution was transferred to a separatory funnel where it was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined and washed with H_2O (10 mL), then dried over $MgSO_4$. The solvent was evaporated affording 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**17**), which was a clear syrup, in 84% yield (0.888 g).

^{1}H NMR: δ 2.05 (s, 3H, CH_3), 3.63 (m, 2H, H-6, H-6'), 3.6, 3.7, 3.8, 3.9 (4m, 1H each, H-1, H-2, H-3, H-4), 4.45 (m, 1H, H-5), 4.6-5.0 (m, 8H, 4 x C$\underline{H_2}$Ph), 7.2-7.4 (m, 20H, Ar-H).

Synthesis of 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl iodide (18) from 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (17). [24]

A solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (0.555 g, 0.0973 mmol) in 15 mL CH_2Cl_2 was cooled to 0 °C. In a dropwise fashion trimethyl silyl

iodide (0.152 mL, 1.1 mmol) was added slowly. The reaction was monitored by TLC (3:1 hexane:ethyl acetate) until consumption of the starting materials 45 min. later. The resulting mixture was evaporated and redissolved in toluene (4 mL) followed by another evaporation. This resulted in a light brown syrup (**18**) in an overall yield of 0.6 g (94%).

^{1}H NMR: δ 2.82 (dd, 1H, H-2, *J* 4.0, 9.0 Hz), 3.67 (d, 1H, H-3, *J* 1.6 Hz), 3.8 (m, 3H, H-4, H-6, H-6'), 3.9 (m, 1H, H-5), 4.4-5.0 (m, 8H, 4 x C$\underline{H_2}$-Ph), 6.87 (d, 1H, H-1, *J* 4.0 Hz), 7.16-7.4 (m, 20H, Ar-H). NMR data agreed with literature values.[24]

Addition of bis(phenylsulfonyl) methane anion to 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl iodide (18).

Bis(phenylsulfonyl) methane (0.2988 g, 1 mmol) was dissolved in 10 mL dry DMF to which NaH (0.04 g, 1.6 mmol) was added. A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl iodide (0.6 g, 0.9 mmol) in 5 mL DMF was then added to the mixture and allowed to stir at room temperature. The reaction was monitored by TLC (1:1 hexane:ethyl acetate) which showed characteristics of the hemiacetal starting material. Excess NaH was quenched with 5% H_2SO_4 (5 mL) and the solution was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined and evaporated yielding a yellowish brown syrup. Analysis of the residue by TLC R_f and ^{1}H NMR showed the hydrolysis back to the free hydroxyl at C-1 with no displacement of the iodide atom with bis(phenylsulfonyl) methane.

Synthesis of Methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (21) from D-ribose. [26]

In a 2000 mL round bottom flask a solution of D-ribose (50 g, 330 mmol) in a 1 L solution of acetone, 100 mL of 2,2-dimethoxypropene, and 200 mL of methanol (20 mL of which was saturated with HCl at 0 °C) was stirred overnight at 25 °C. Pyridine was then added until the mixture was neutral, then evaporated. The resulting residue was dissolved in ether (200 mL) and extracted with H_2O. The aqueous layer was removed and extracted with ether (2 x 200 mL). The organic portions were combined and dried over $MgSO_4$ then evaporated to give a brown oil. The residue was vacuum distilled at ~75 °C and at ~1mm Hg affording a clear oil, methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (**21**), in 79% yield (53.5 g). TLC (4:1 ethyl acetate:hexane) and ^{1}H NMR confirmed the isolation of pure protected glycoside.

^{1}H NMR: δ 1.3 (s, 3H, 1 x CH_3), 1.5 (s, 3H, 1 x CH_3), 3.42 (s, 3H, CH_3), 3.62 (m, 2H, H-5, H-5'), 4.4 (dd, 1H, H-4, *J* 3.0, 3.4 Hz), 3.58 (d, 1H, H-2, *J* 6.0 Hz), 4.8 (d, 1H, H-3, J 6.0 Hz), 4.97 (s, 1H, H-1).

Synthesis of Methyl-2,3-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-β-D-ribofuranoside (22) from methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (21).

To a solution of methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (1.0 g, 5mmol) in 20 mL pyridine was added *p*-toluenesulfonyl chloride (1.4 g, 7.3 mmol) and cooled to 0 °C. The mixture was allowed to stir overnight at which point TLC (2:1 ethyl acetate:hexane) confirmed the consumption of the starting material (a white precipitate formed overnight). The reaction mixture was poured onto 100 g of ice and allowed to dissolve while stirring. As the reaction mixture dissolved a large amount of white

precipitate formed that was vacuum filtered. Filtration gave a white powder (**22**) in an overall yield of 1.5 g (85%).

^{1}H NMR: δ1.28 (s, 3H, 1 x CH_3), 1.44 (s, 3H, 1 x CH_3), 2.45 (s, 3H, CH_3), 3.2 (s, 3H, CH_3), 4.0 (m, 2H, H-5, H-5'), 4.28 (dd, 1H, H-4, *J* 7.0, 15.0 Hz), 4.52 (d, 1H, H-2, *J* 6.0 Hz), 4.58 (d, 1H, H-3, *J* 6.0 Hz), 4.9 (s, 1H, H-1), 7.3 (d, 2H, Ar-H), 7.7 (d, 2H, Ar-H).

Attempted reaction of Methyl-2,3-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-β-D-ribofuranoside (22) with Lithium bis(phenylthio)methane.

In a flame dried 50 mL three-neck round bottom flask under nitrogen atmosphere, bis(phenylthio)methane (0.642 g, 2.7 mmol) was dissolved in 20 mL of dry THF, then 1.6 M *n*-BuLi (1.73 mL) was added dropwise at –78 °C. The solution was stirred for 20 min. before adding a solution of methyl-2,3-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-β-D-ribofuranoside (0.83 g, 2.3 mmol) in 10 mL dry THF. The reaction was allowed to warm to room temperature while stirring overnight. The resulting yellow solution was analyzed by TLC (2:1 ethyl acetate:hexane) which showed unreacted starting material. At this point another 1.2 equivalents of *n*-BuLi was added to the reaction mixture resulting in an orange solution that was stirred overnight. NH_4Cl was added to the reaction mixture, which was then extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with H_2O, dried over $MgSO_4$, and evaporated to give a yellow syrup. ^{1}H NMR and TLC again showed only unreacted starting material and bis(phenylthio)methane, thus indicating no displacement of the tosyl group.

Formation of Methyl-2,3-*O*-isopropylidene-5-*O*-(trifluoromethylsulfonyl)-β-D-ribofuranoside (23) from methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (21).

To a 250 mL flame dried three-neck round bottom flask equipped with two 60 mL addition funnels, under nitrogen atmosphere, was added CH_2Cl_2 (120 mL) and pyridine (2.67 mL). The solution was then cooled to –10 °C. A solution of triflic anhydride (5.15 mL) in 20 mL CH_2Cl_2 was added to one of the addition funnels and a solution of methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (3.0 g, 15 mmol) in 20 mL CH_2Cl_2 was added to the other. The triflic anhydride was added to the reaction flask dropwise which resulted in a thick white precipitate that was stirred for an additional 10 min. At this point the solution containing methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside was added dropwise and allowed to stir for 1.5 hours. The reaction mixture was then poured into 100 mL of ice water, which resulted in the formation of two layers. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL), then all the organic layers were combined, dried with $MgSO_4$, and evaporated. Evaporation gave a light brown syrup that was extracted with hexanes. Evaporation of the hexane yielded 4.7 g (95%) of compound **23**.

^{1}H NMR: δ 1.25 (s, 3H, 1 x CH_3), 1.44 (s, 3H, 1 x CH_3), 3.35 (s, 3H, CH_3), 4.4 (m, 3H, H-4, H-5, H-5'), 4.6 (d, 1H, H-2, *J* 6.0 Hz), 4.66 (d, 1H, H-3, *J* 6.0 Hz), 5.0 (s,1H, H-1).

^{13}C NMR: δ26.0, 27.5, 56.5, 76.3, 82.0, 84.4, 85.9, 110.7, 114.1, 118.0.

Addition of Lithium bis(phenylthio)methane to methyl-2,3-*O*-isopropylidene-5-*O*-(trifluoromethylsulfonyl)-β-D-ribofuranoside (23), formation of dithioacetal 24.

In a 250 mL, flame dried three-neck round bottom flask, bis(phenylthio)methane (3.25 g, 13.9 mmol) was dissolved in dry THF (40 mL) and cooled to –78 °C. *n*-BuLi (8.7 mL, of 1.6 M) was added dropwise resulting in a dark orange solution that was stirred for 20 min. The triflate ester (4.7 g, 13.9 mmol) was dissolved in dry THF (30 mL) and added dropwise to the reaction mixture through an addition funnel. The reaction was allowed to stir overnight and warm to room temperature. TLC (6:1 hexane:ethyl acetate) showed the consumption of starting material but the formation of multiple by-products. NH_4Cl was then added to the solution and allowed to stir for 10 min. at which time the mixture was extracted with CH_2Cl_2 (2 x 25 mL). The extracts were washed with H_2O and subsequently dried with $MgSO_4$. The sample was evaporated onto silica gel (~10 g) and purified on a flash column using 20:1 hexane:ethyl acetate as the eluent. Pure (**24**) was recovered as a yellow syrup in an overall yield of 2.2 g (38 %).

^{1}H NMR: δ1.3 (s, 3H, 1 x CH_3), 1.49 (1s, 3H, 1 x CH_3), 1.86-1.93 (ddd, 1H, H-5, *J* 4.2, 10.6, 14.4 Hz), 2.1-2.2 (ddd, 1H, H-5', *J* 4.2, 10.6, 14.4 Hz), 3.1 (s, 3H, CH_3), 4.5 (m, 3H, H-2, H-3, H-4), 4.67 (dd, 1H, H-6, *J* 4.0, 11.0 Hz), 7.2-7.5 (m, 10H, Ar-H).

^{13}C NMR: δ26.2, 27.7, 42.4, 57.3, 85.2, 85.3, 86.4, 110.8, 113.4, 129.0, 129.1, 129.9, 134.3, 134.9.

Synthesis of *C*-Glycoside 20 from 2,3-*O*-isopropylidene-D-erythronolactone (19).

A solution of bis(phenylthio)methane (1.76 g, 7.6 mmol) in 20 mL dry THF was syringed into a flame-dried 100 mL three-neck round bottom flask under nitrogen atmosphere. After the solution was cooled to –78 °C *n*-BuLi (4.7 mL in 1.6 M hexanes)

was added dropwise and allowed to stir for 20 min. A solution of 2,3-*O*-isopropylidene-D-erythronolactone (1.0 g, 6.3 mmol) in 10 mL dry THF was prepared and added dropwise through an addition funnel. The reaction was run overnight and allowed to warm to room temperature. TLC (2:1 ethyl acetate:hexane) was used to demonstrate the formation of a new major product along with several by-products. The consumption of starting material was indicated by TLC using phosphomolybdic acid for visualization. The reaction was quenched with NH_4Cl and the resulting solution was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined and washed with H_2O, then dried with anhydrous $MgSO_4$. The organic solution was evaporated and dissolved in 5 mL CH_2Cl_2, then purified on an MPLC column in 6:1 hexane:ethyl acetate. A yellow syrup (**20**) was obtained after chromatography in a yield of 0.52 g (21%).

^{1}H NMR: δ 1.36 (s, 3H, 1 x CH_3), 1.46 (s, 3H, 1 x CH_3), 3.9 (d, 1H, H-2, *J* 10.2), 4.1 (m, 1H, H-4, H-4'), 4.76 (d, 1H, H-1, *J* 6.0 Hz), 4.85 (m, 1H, H-3), 7.19-7.45 (m, 20H, Ar-H).

^{13}C NMR: δ 26.3, 27.7, 65.6, 72.7, 81.6, 85.8, 108.5, 113.5, 128.5, 129.6, 129.8, 133.5, 133.7.

Formation of *C*-disaccharide (25) from the addition of the anion of (24) to 2,3-*O*-isopropylidene-D-erythronolactone (19).

In a flame dried 50 mL three-neck round bottom flask under nitrogen atmosphere, **24** (0.5 g, 1.2 mmol) was dissolved in dry THF (10 mL) and was cooled to –78 °C. A solution of 0.82 mL of 1.6 M *n*-BuLi was then added dropwise to the mixture resulting in an dark orange solution that stirred for 20 min. At this time a solution of 2,3-*O*-

isopropylidene-D-erythronolactone (0.19 g, 1.2 mmol) in 5 mL dry THF was added dropwise through an addition funnel and was allowed to mix overnight while warming to room temperature. TLC (6:1 hexane:ethyl acetate) showed the formation of a new compound with some dithioacetal starting material left unreacted. The reaction mixture was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with H_2O (15 mL), and dried over anhydrous $MgSO_4$. The solution was evaporated onto silica (5 g) and purified *via* flash column chromatography using an eluent of 6:1 hexane:ethyl acetate and 40 g of silica. The pure fractions afforded a clear, yellow solution of (**25**) in an overall yield of 0.24 g (35%).

^{1}H NMR: δ 1.21 (s, 3H, 1 x CH_3), 1.24 (s, 3H, 1 x CH_3), 1.45 (s, 3H, 1 x CH_3), 1.67 (s, 3H, 1 x CH_3), 1.9-2.04 (m, 2H, H-5, H-5'), 2.9 (s, 3H, CH_3), 3.9 (dd, 1H, H-9, *J* 4.0, 10.0 Hz), 4.2 (dd, 1H, H-9', *J* 6.0, 10.0 Hz), 4.39 (d, 1H, H-2, *J* 6.0 Hz), 4.47 (s, 1H, OH), 4.8 (s, 1H, H-1), 4.86 (d, 1H, H-3, *J* 6.0 Hz), 4.9 (m, 1H, H-8), 5.1 (d, 1H, H-4, *J* 6.0 Hz), 5.38 (d, 1H, H-7, *J* 7.0 Hz), 7.14-7.7 (m, 10H, Ar-H).

^{13}C NMR: δ 26.2, 26.3, 27.6, 27.7, 41.5, 55.4, 72.3, 80.6, 83.3, 85.4, 85.9, 86.2, 110.2, 112.3, 116.6, 129.2, 129.4, 130.1, 130.5, 138.8, 139.9.

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Appendix

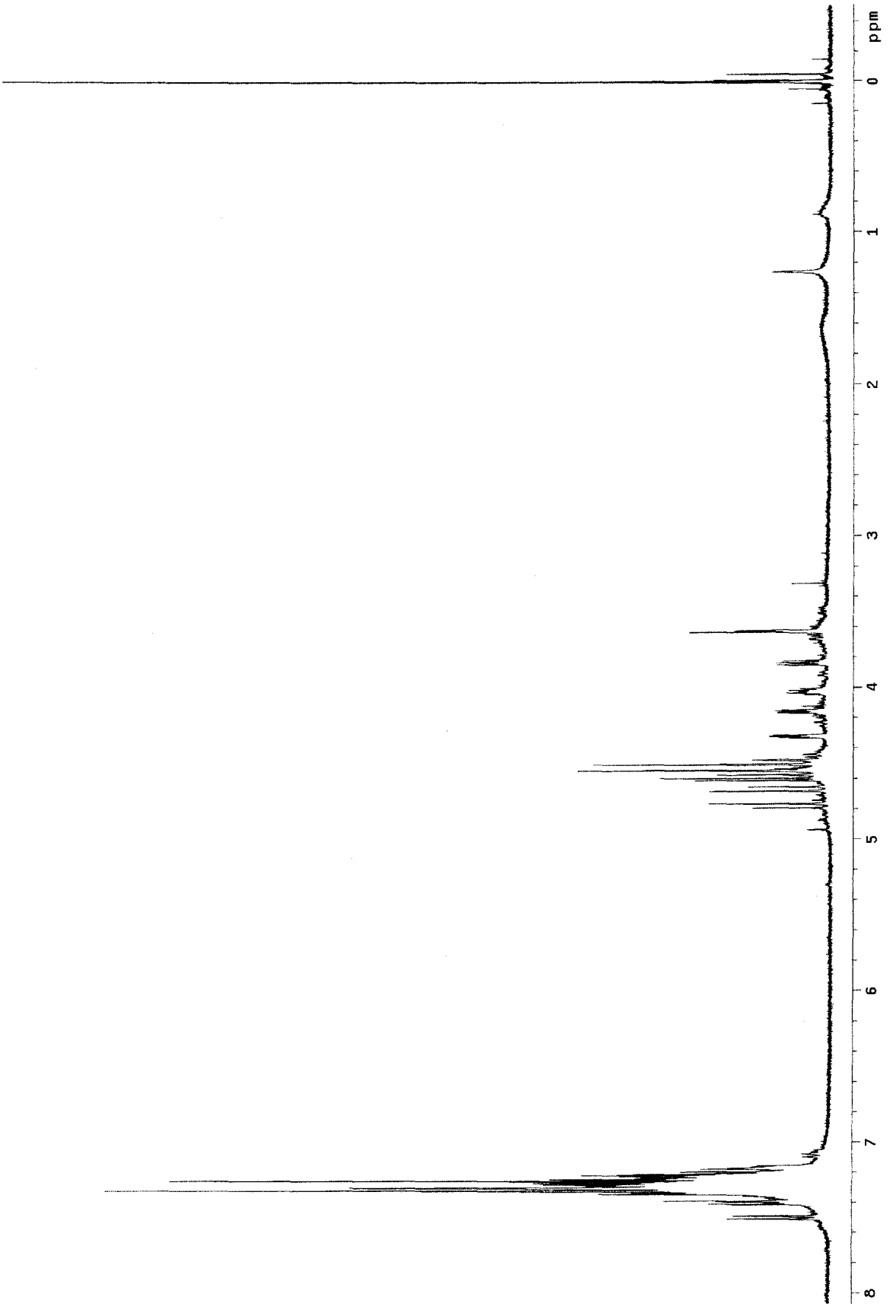

Figure 9. ^{1}H NMR of **2**

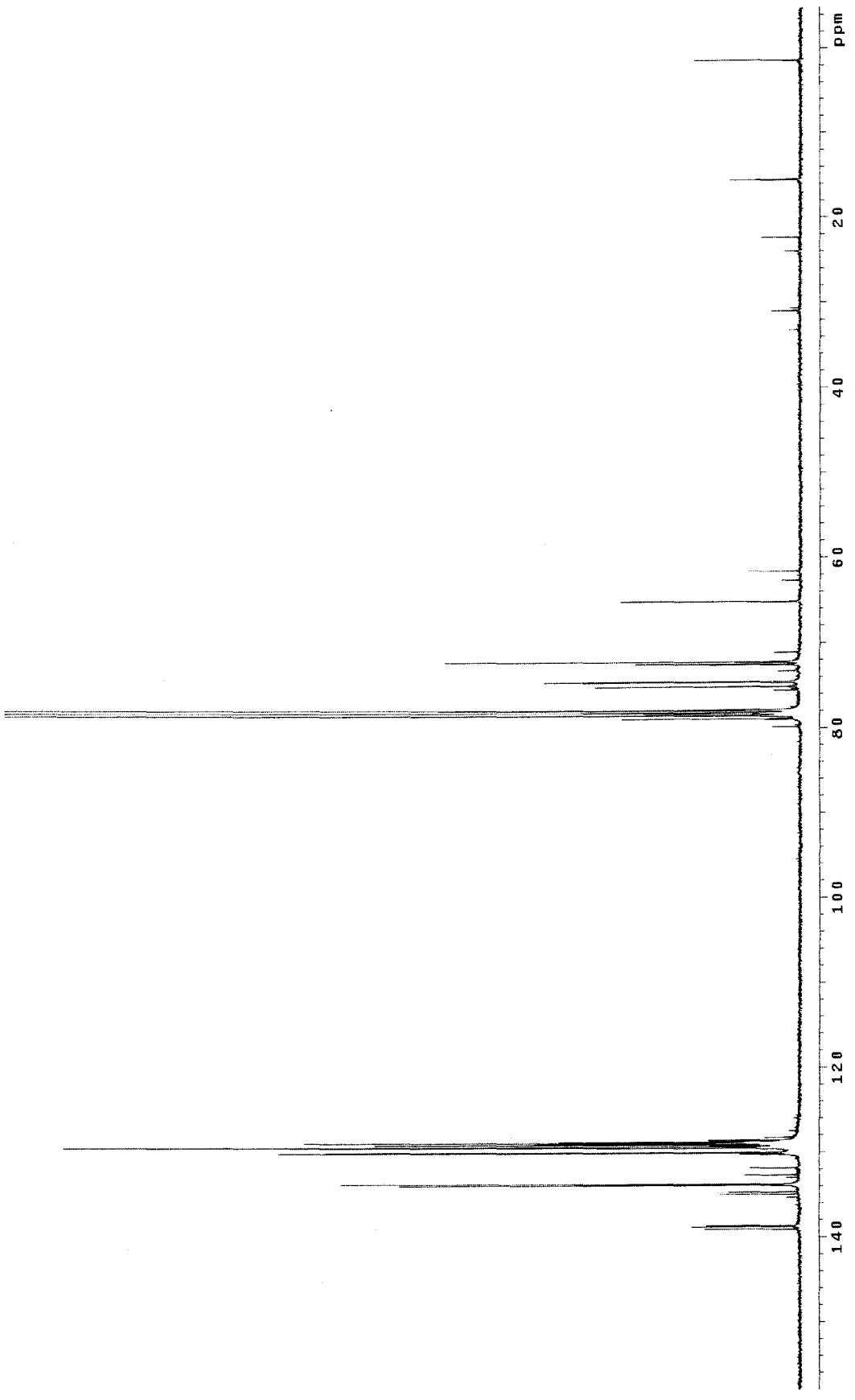

Figure 10. ^{13}C NMR of **2**

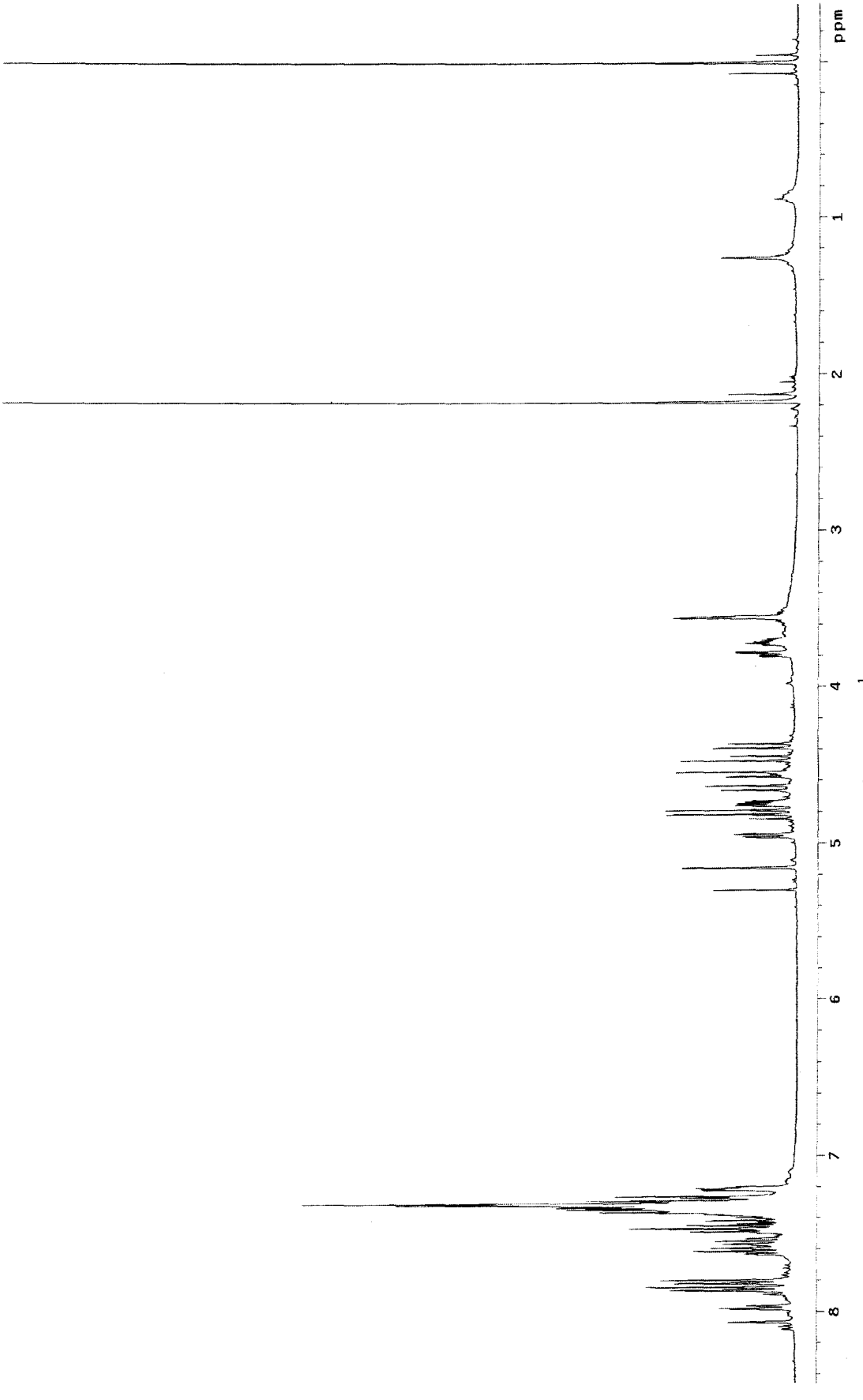

Figure 11. ^{1}H NMR of **3**

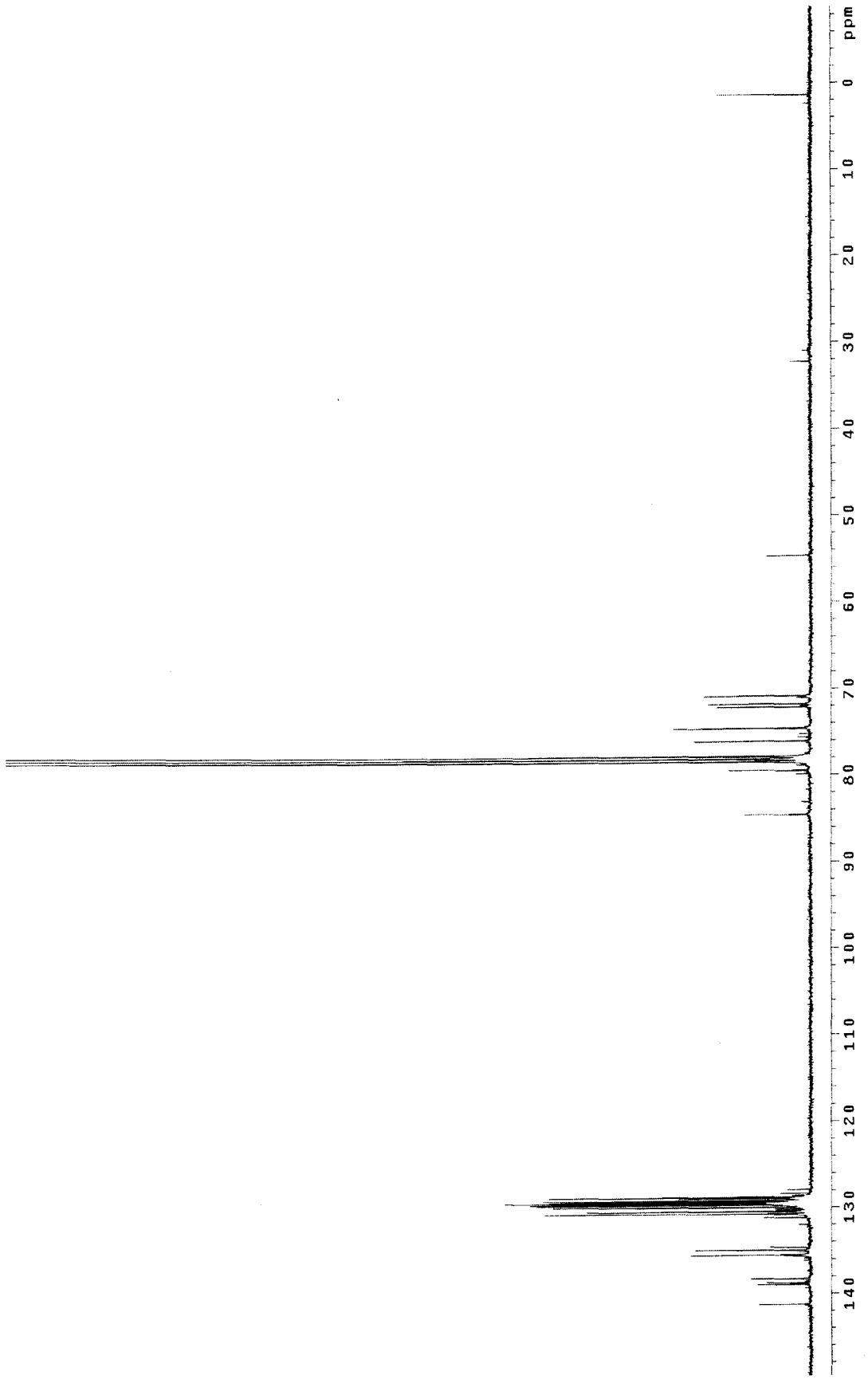

Figure 12. ^{13}C NMR of **3**

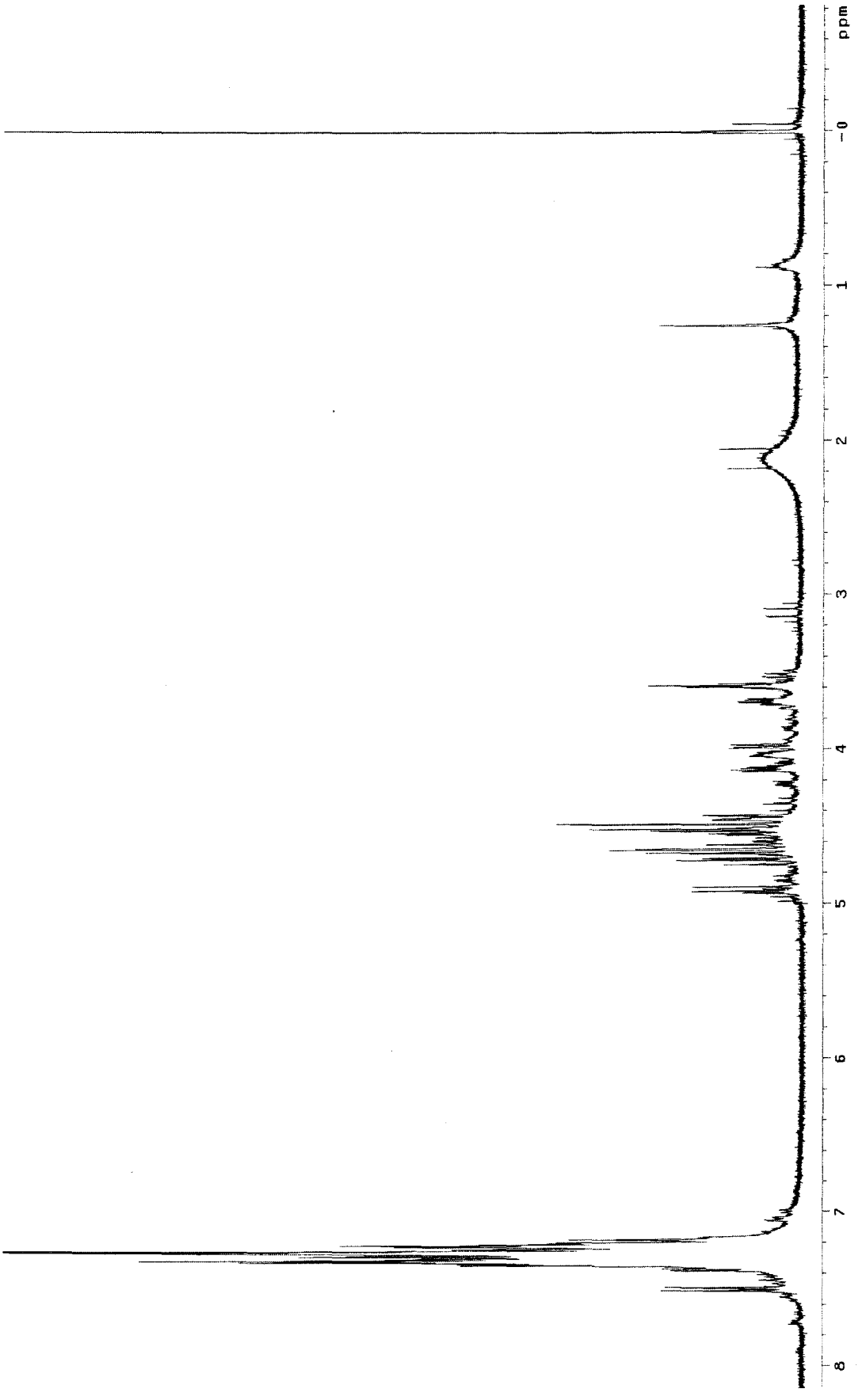

Figure 13. ^{1}H NMR of **6**

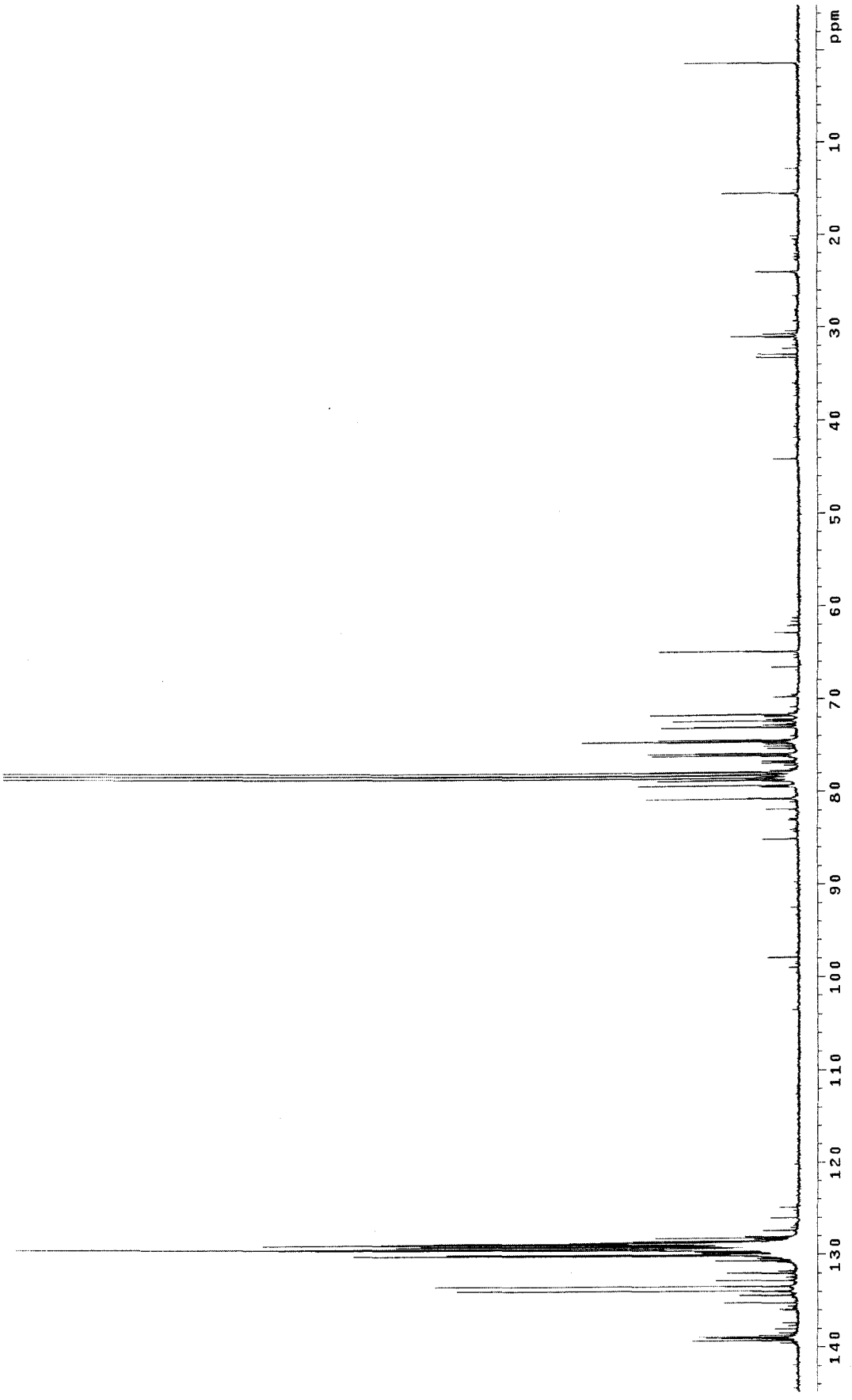

Figure 14. ^{13}C NMR of **6**

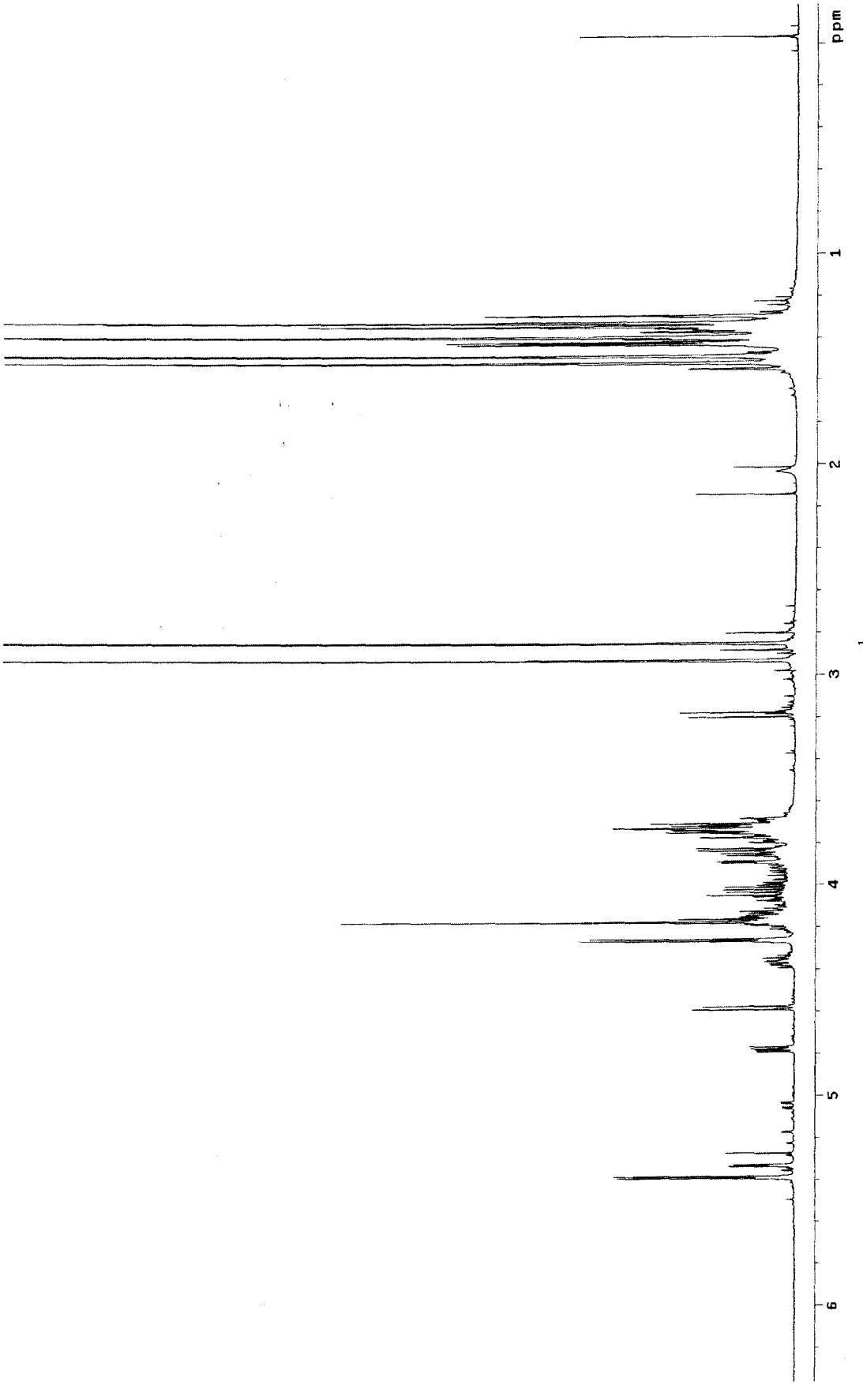

Figure 15. ^{1}H NMR of **9**

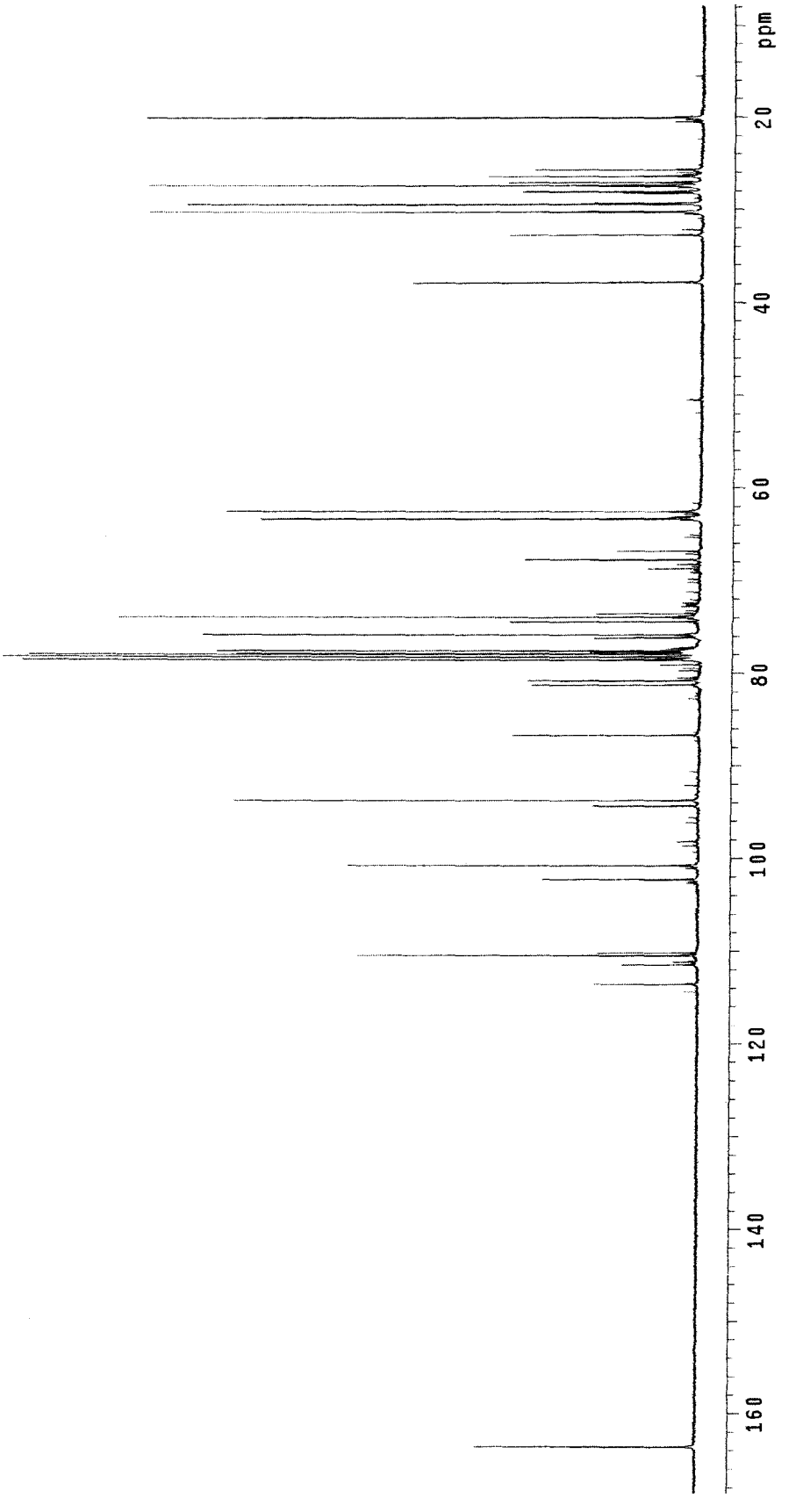

Figure 16. ^{13}C NMR of **9**

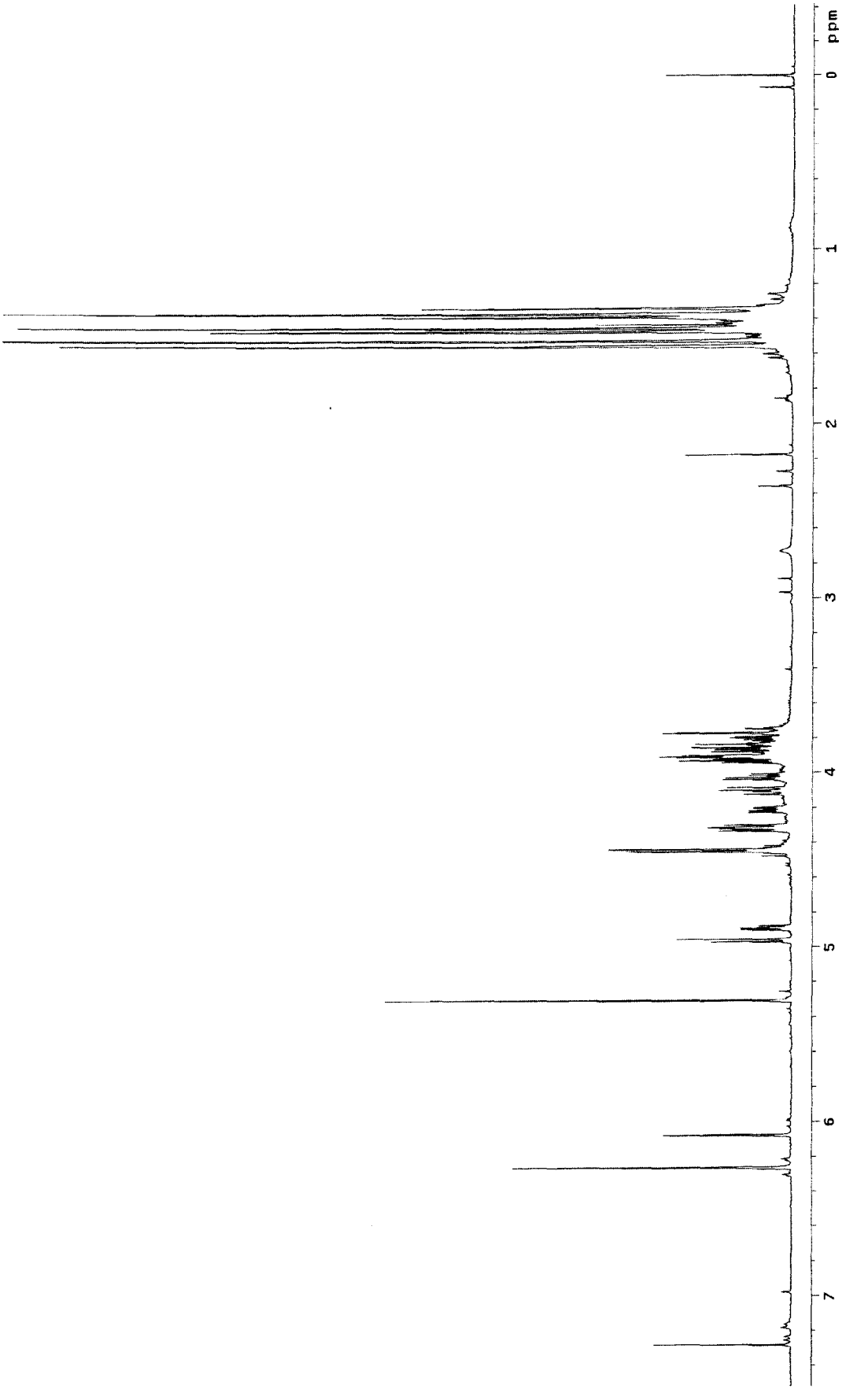

Figure 17. ^{1}H NMR of **12**

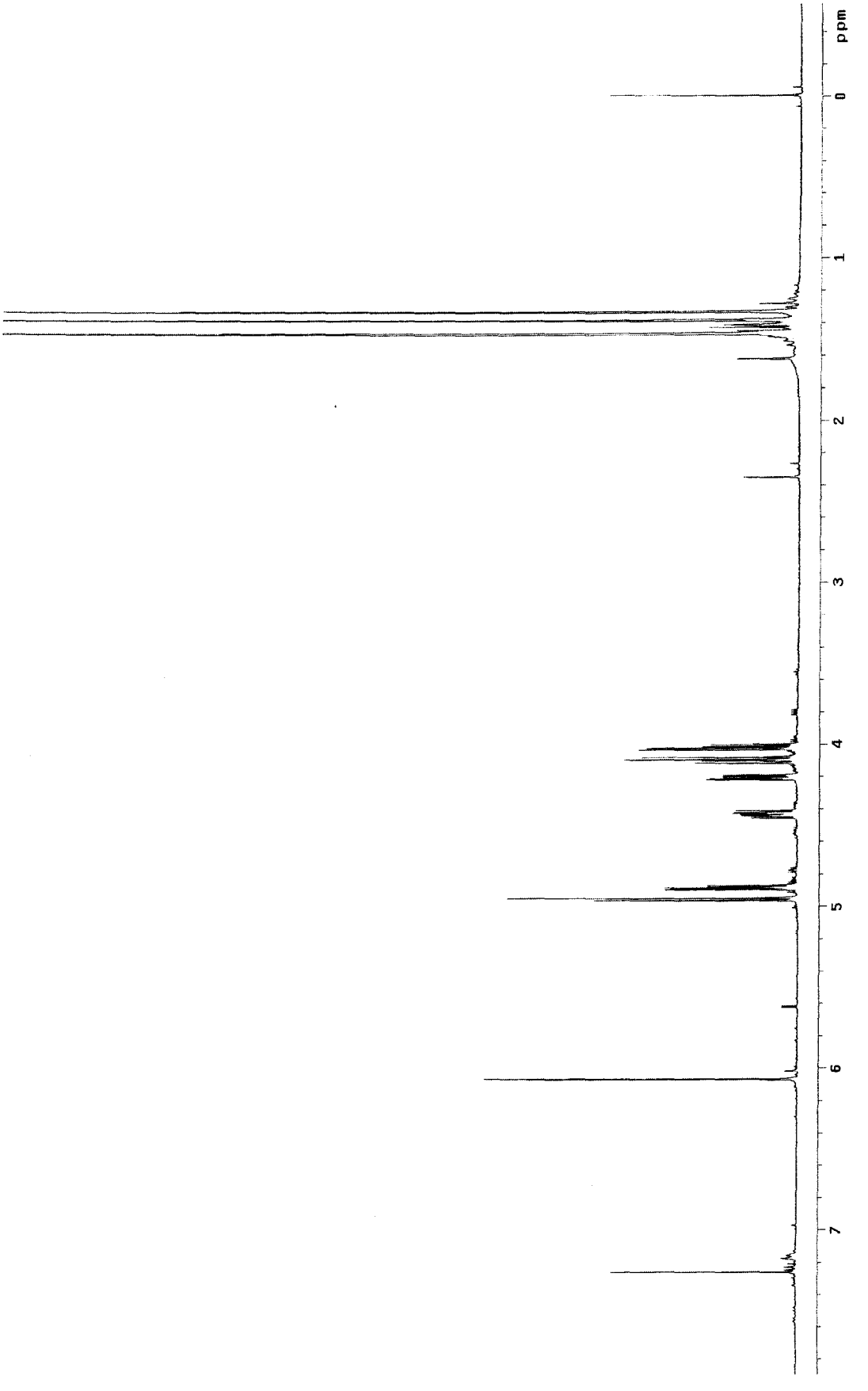

Figure 18. ^{1}H NMR of **13**

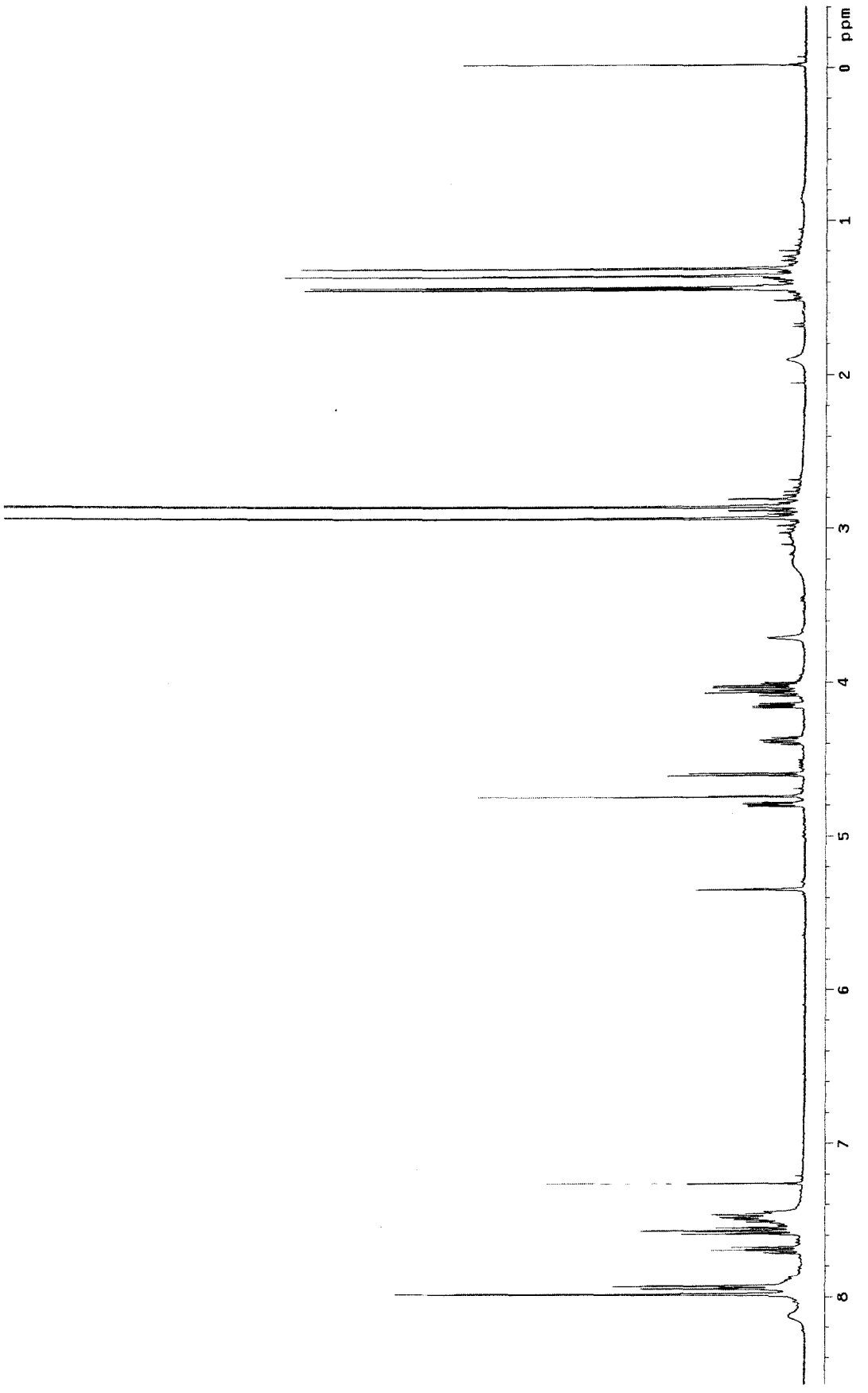

Figure 19. ^{1}H NMR of Addition to **18**

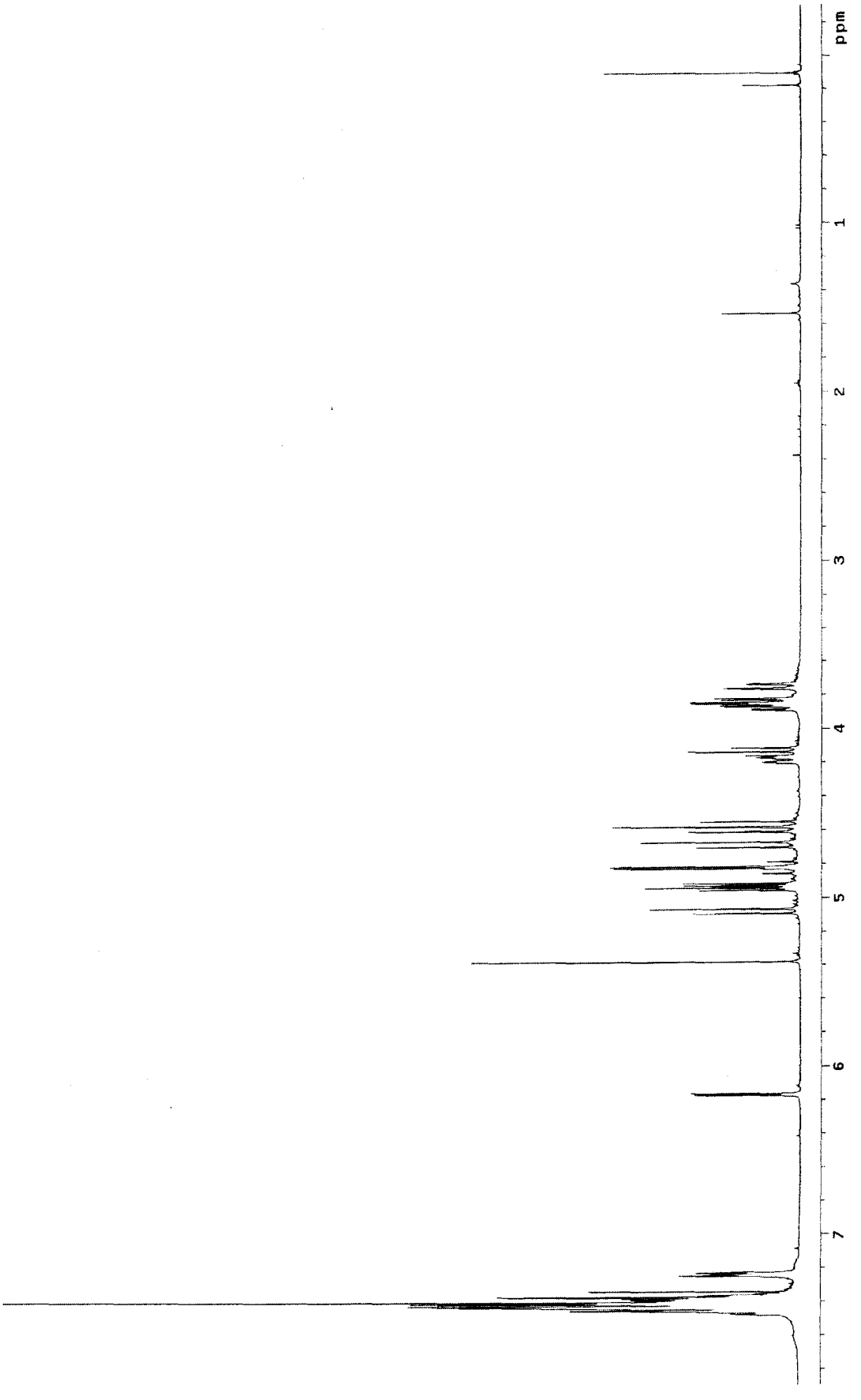

Figure 20. ^{1}H NMR of **7**

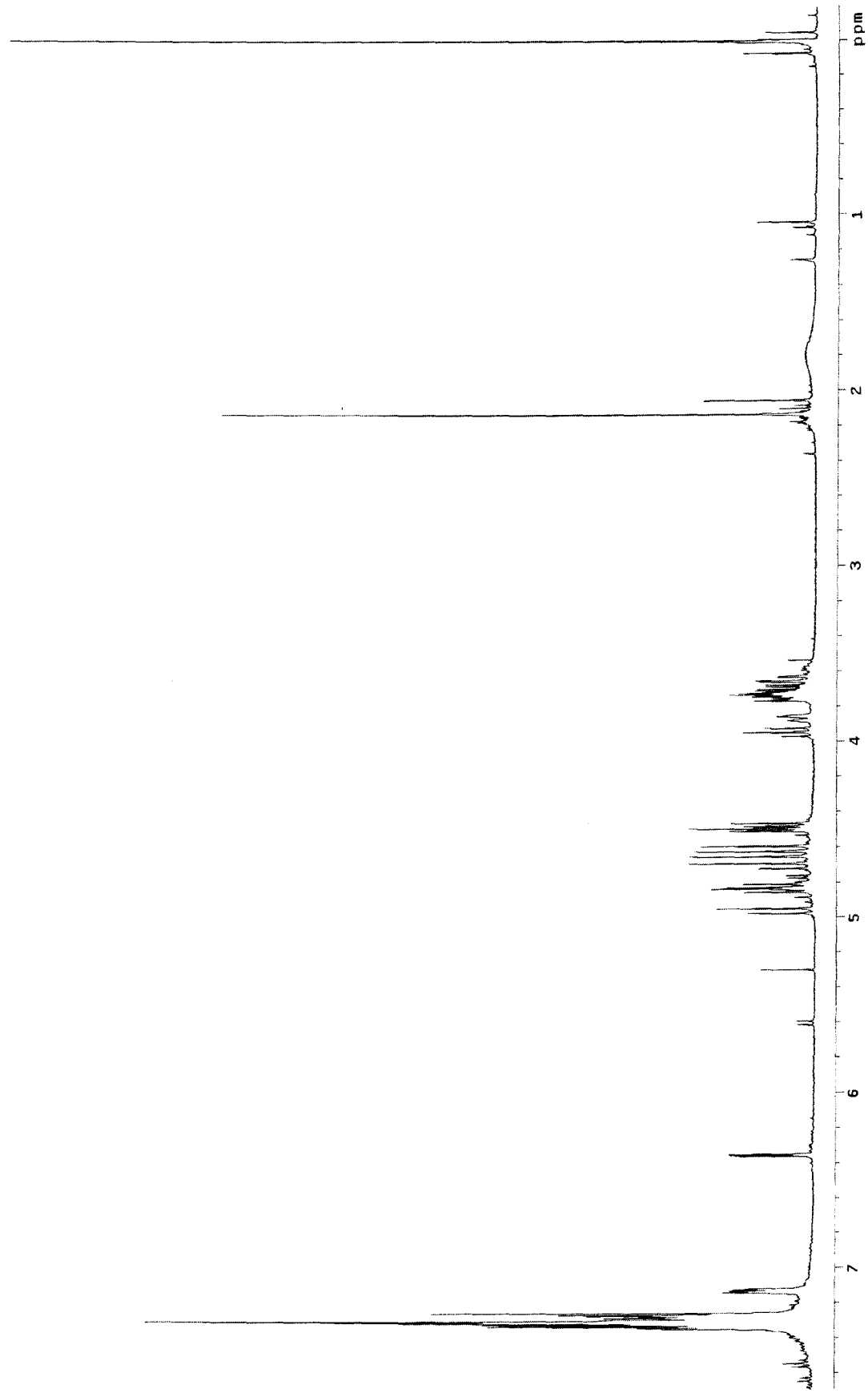

Figure 21. ^{1}H NMR of **17**

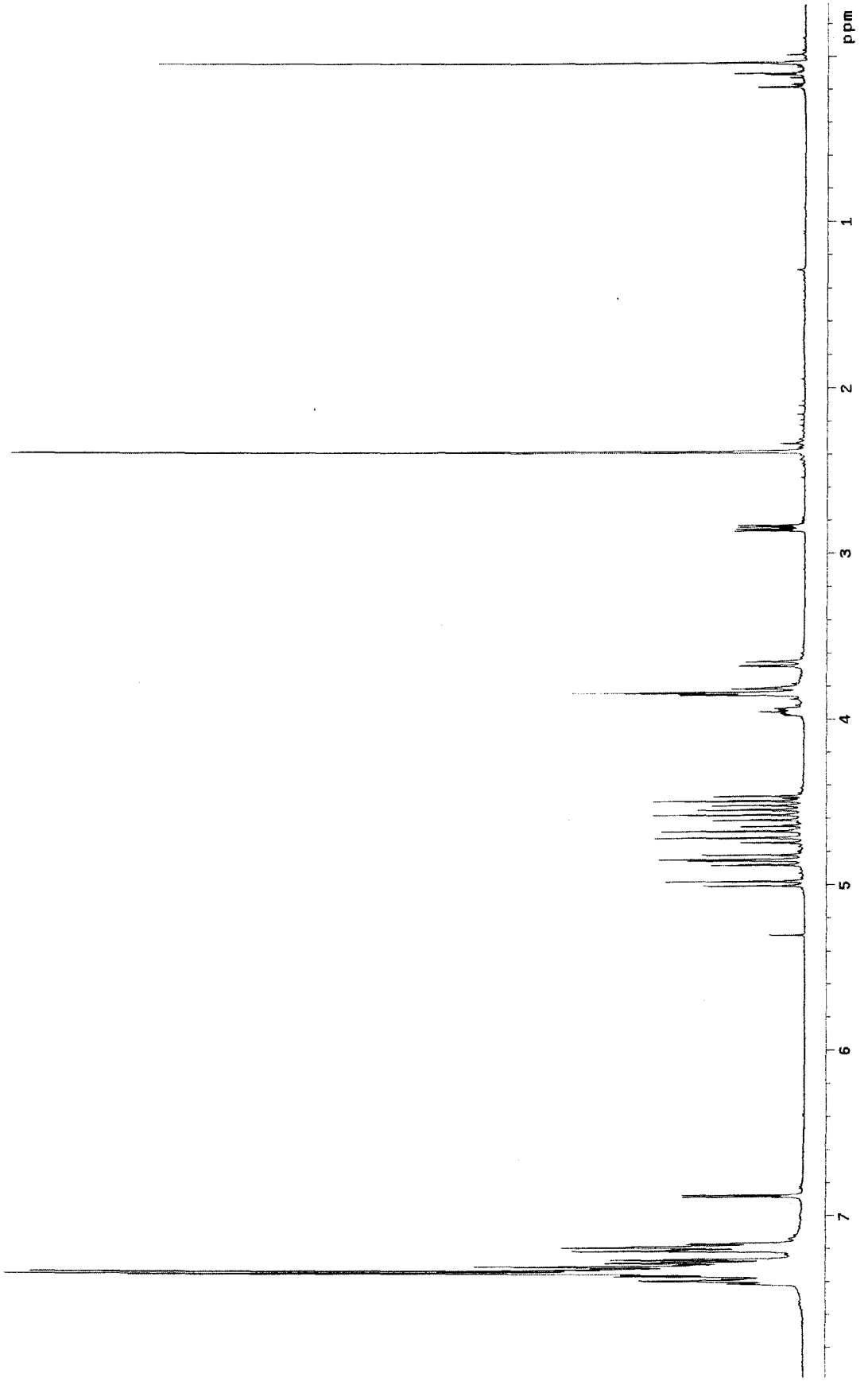

Figure 22. ^{1}H NMR of **18**

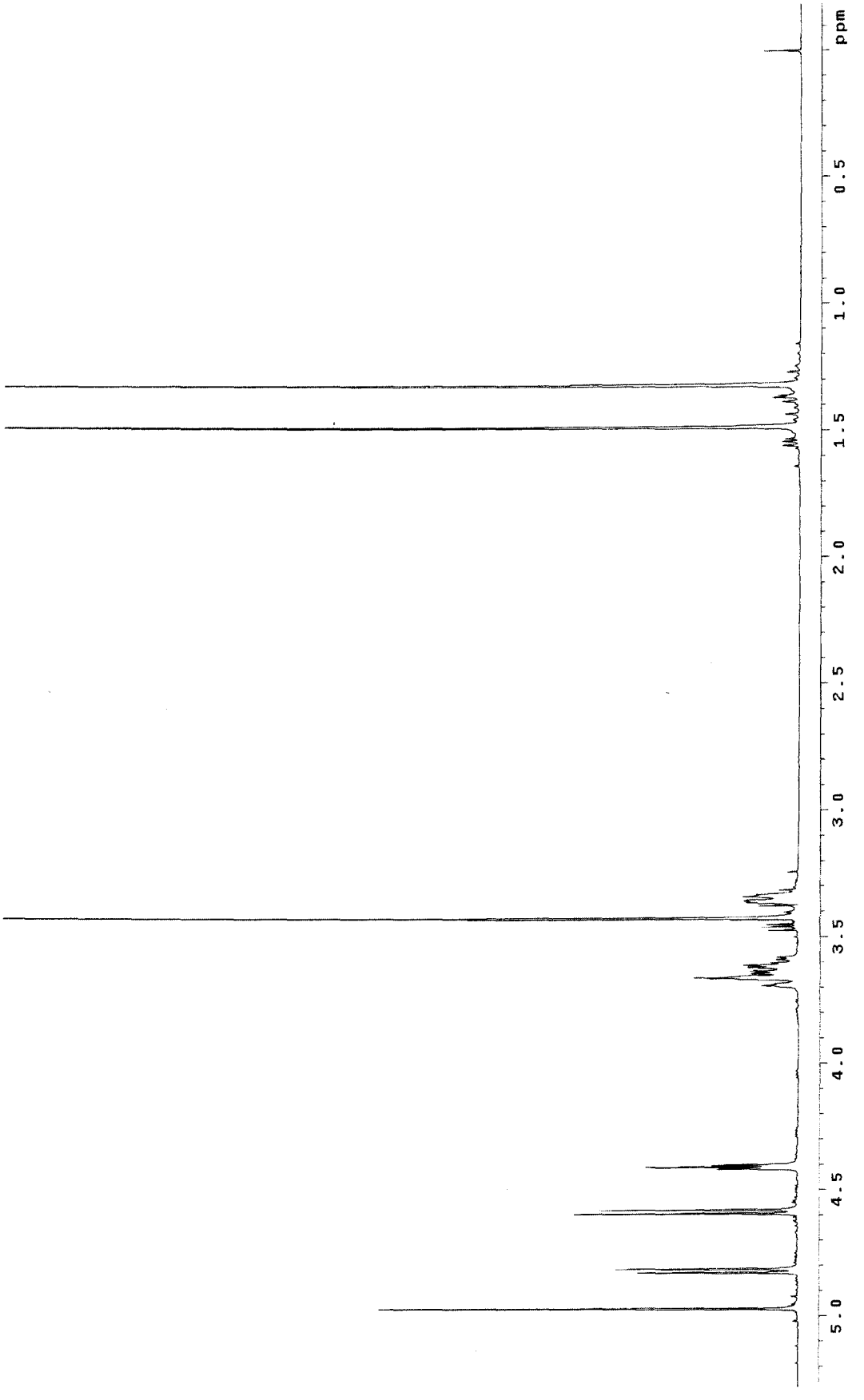

Figure 23. ^{1}H NMR of **21**

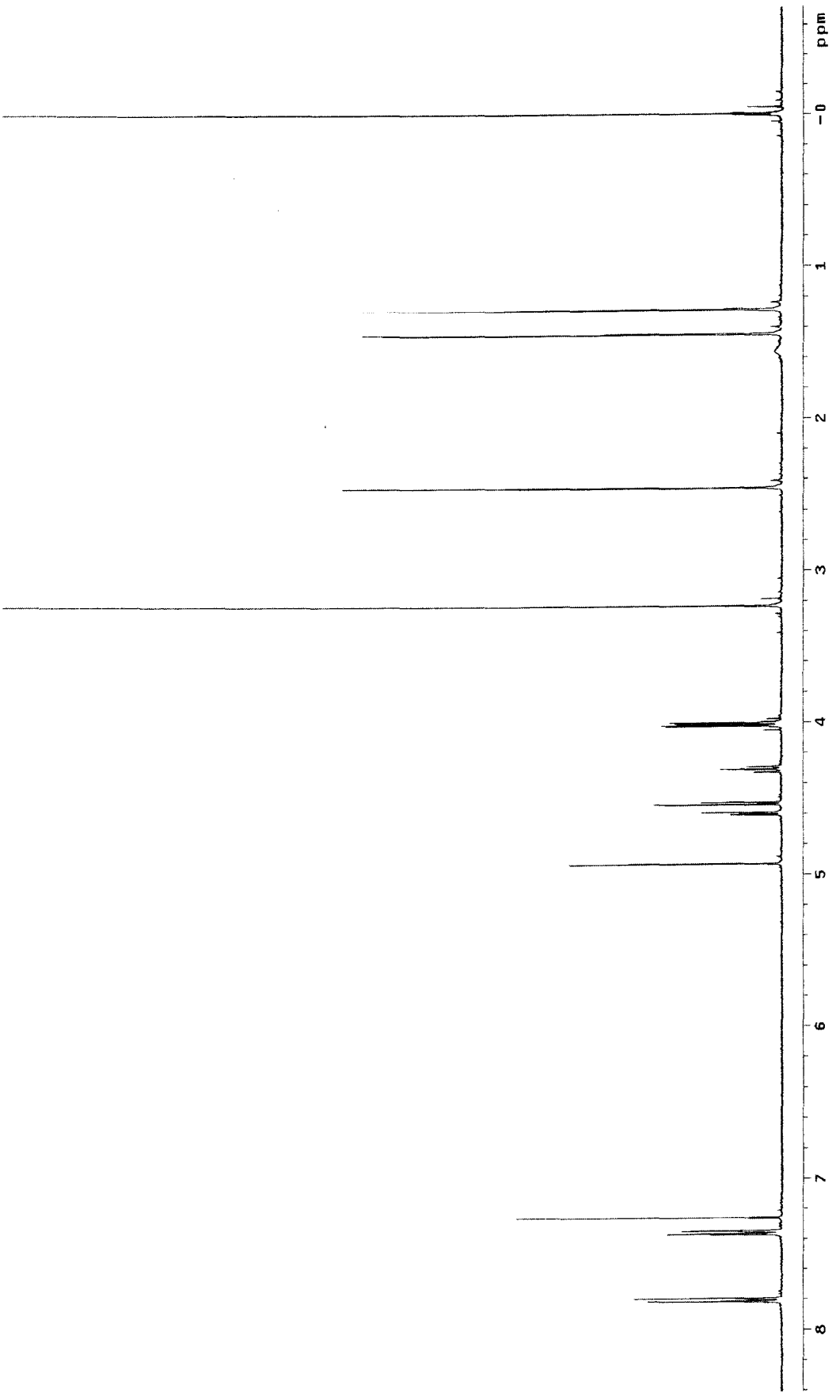

Figure 24. ^{1}H NMR of **22**

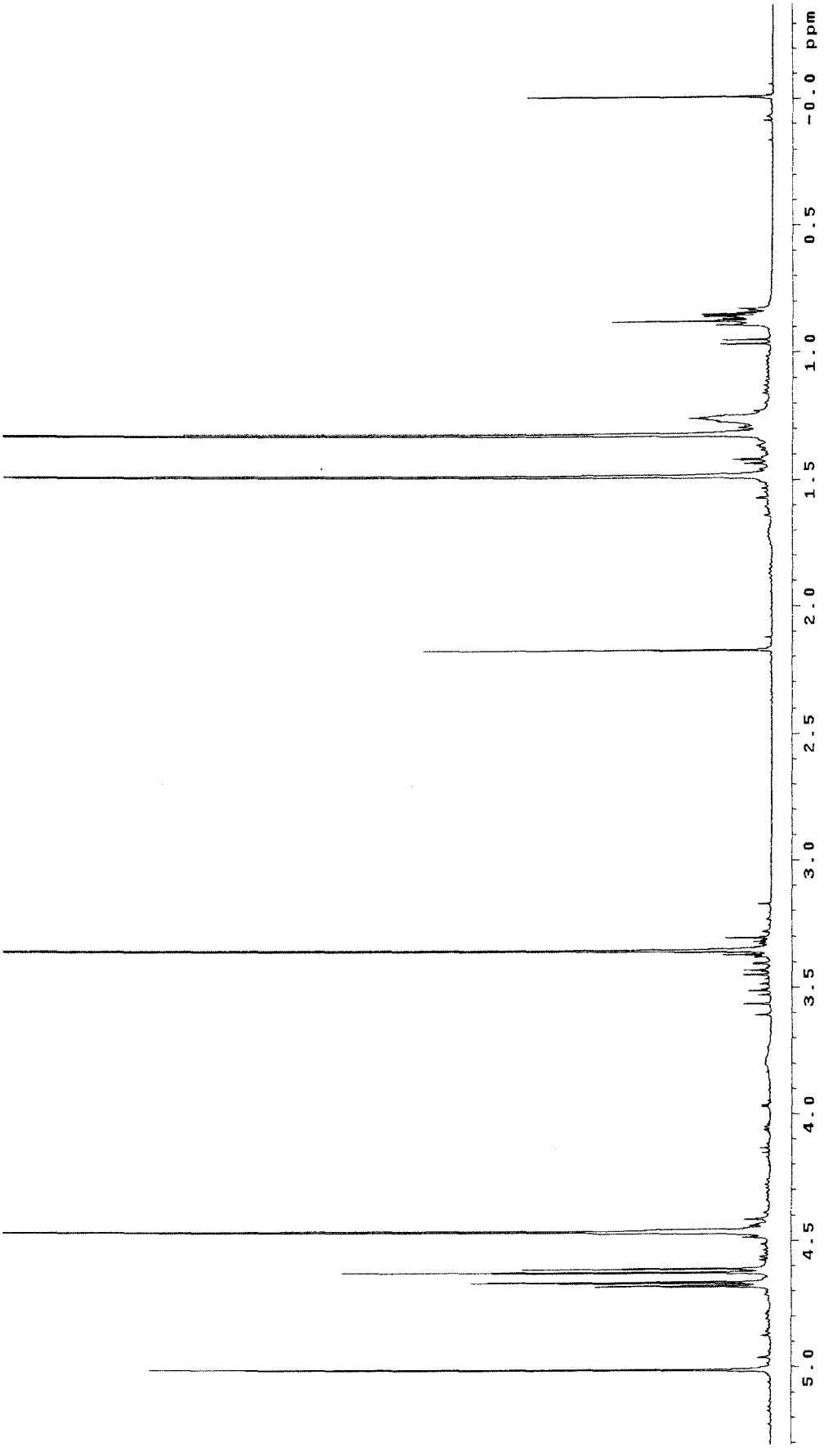

Figure 25. ^{1}H NMR of **23**

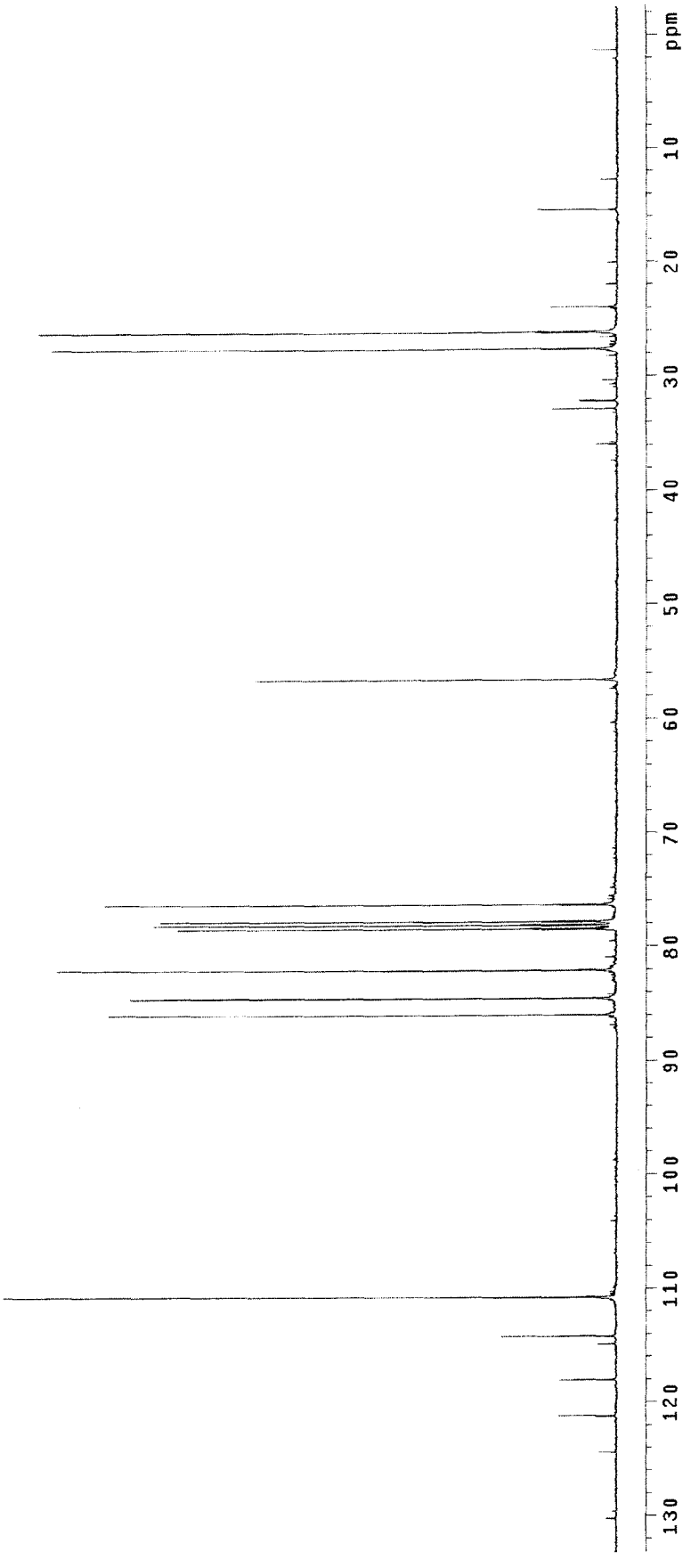

Figure 26. ^{13}C NMR of **23**

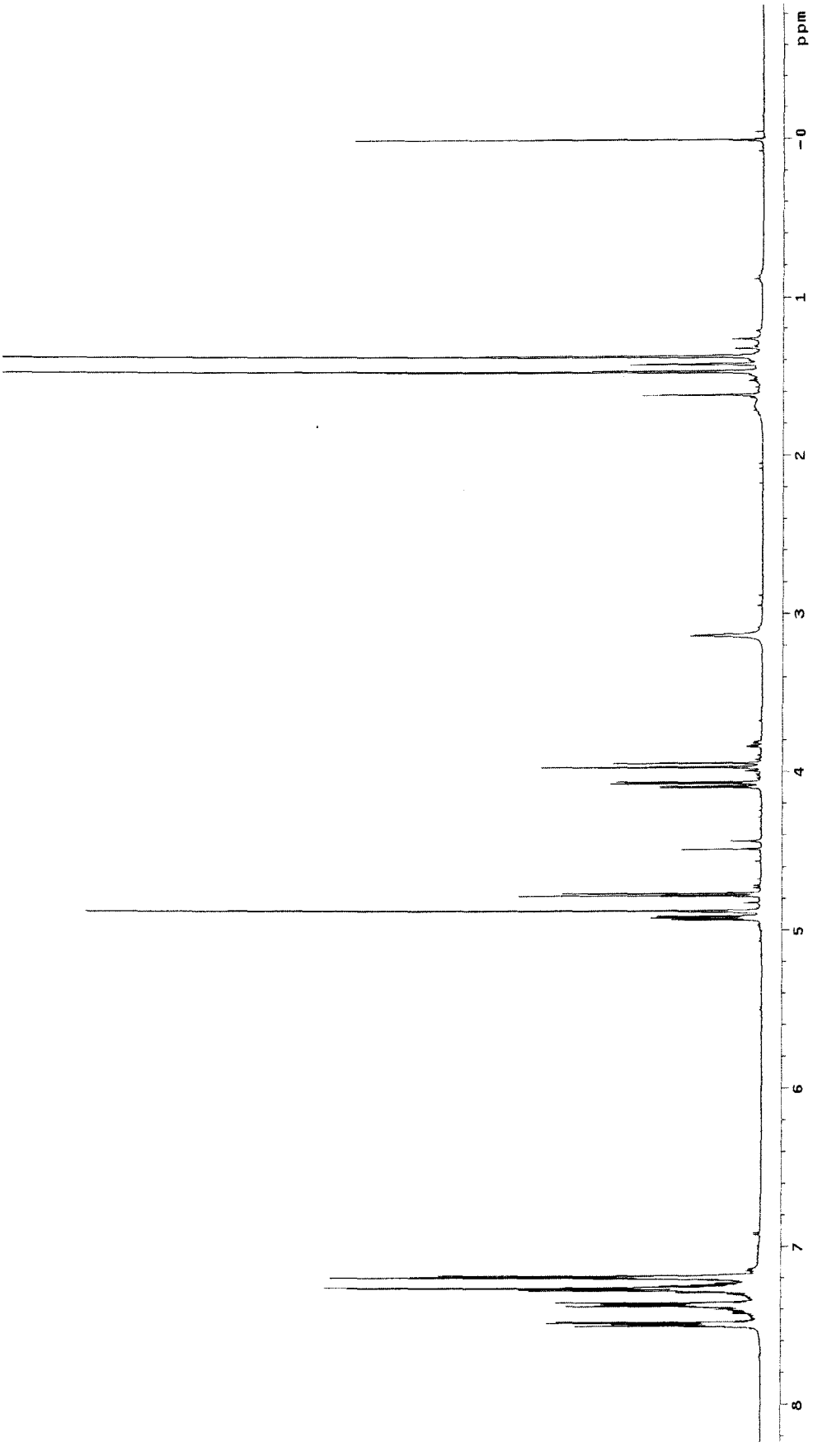

Figure 27. ^{1}H NMR of **20**

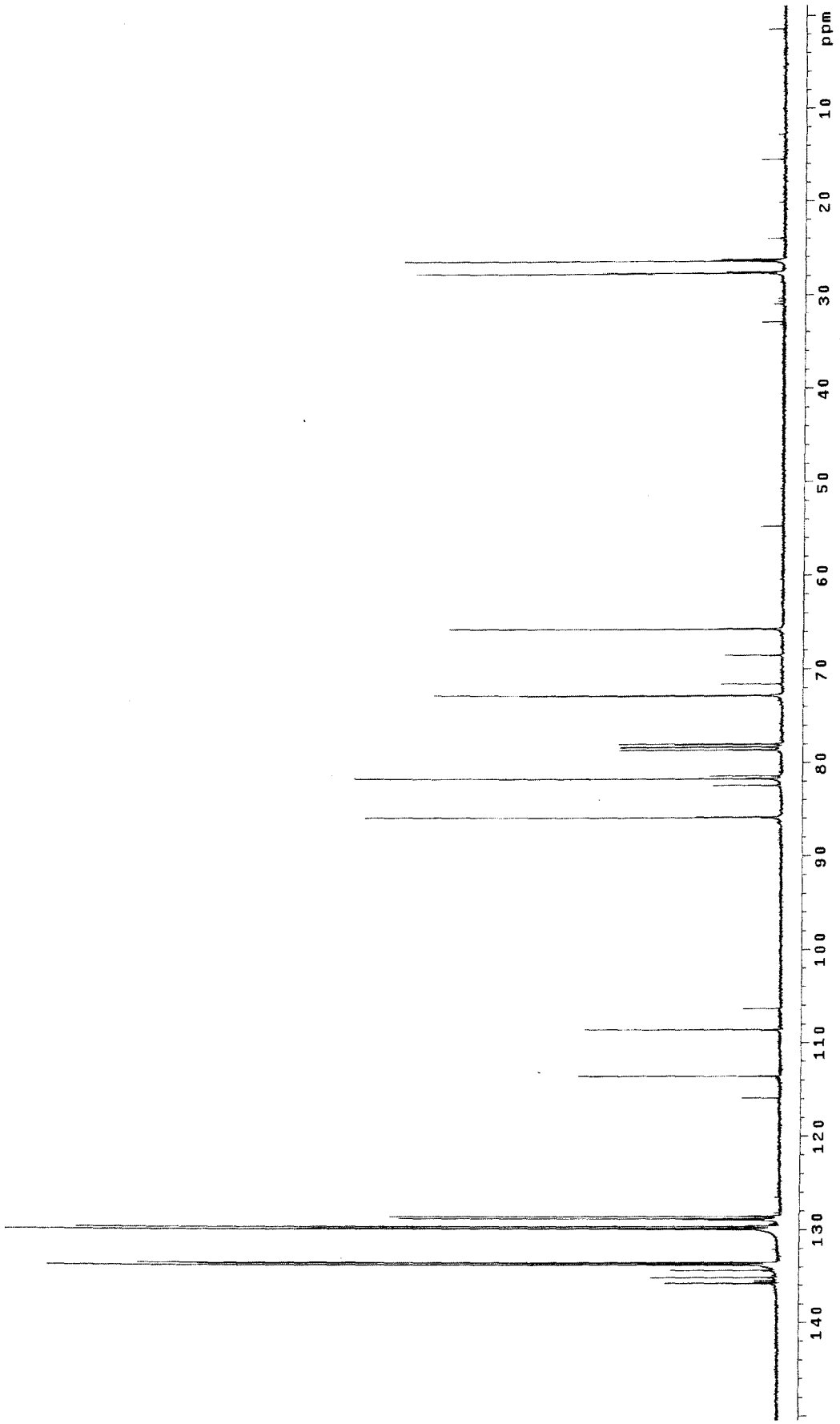

Figure 28. ^{13}C NMR of **20**

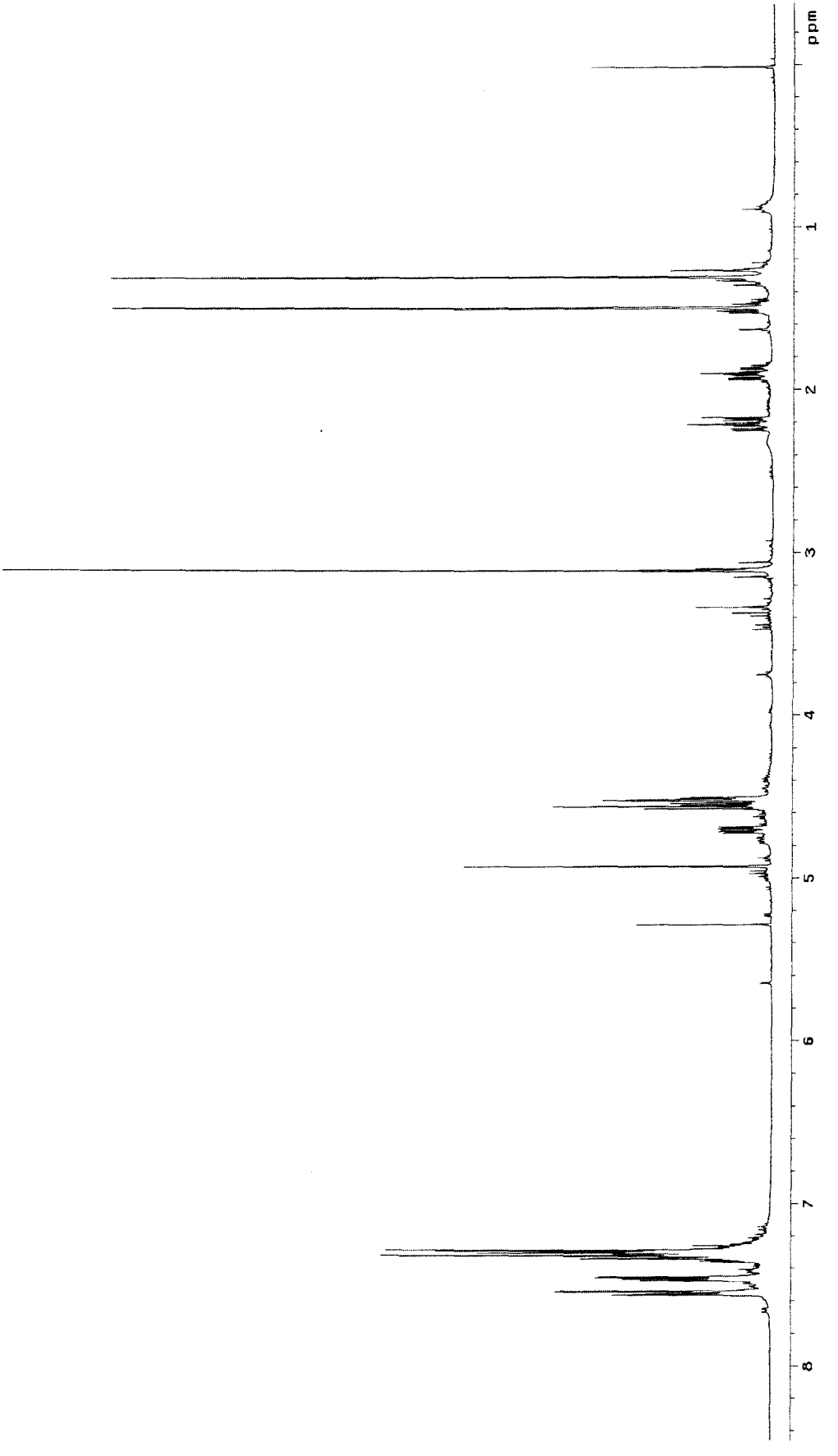

Figure 29. ^{1}H NMR of **24**

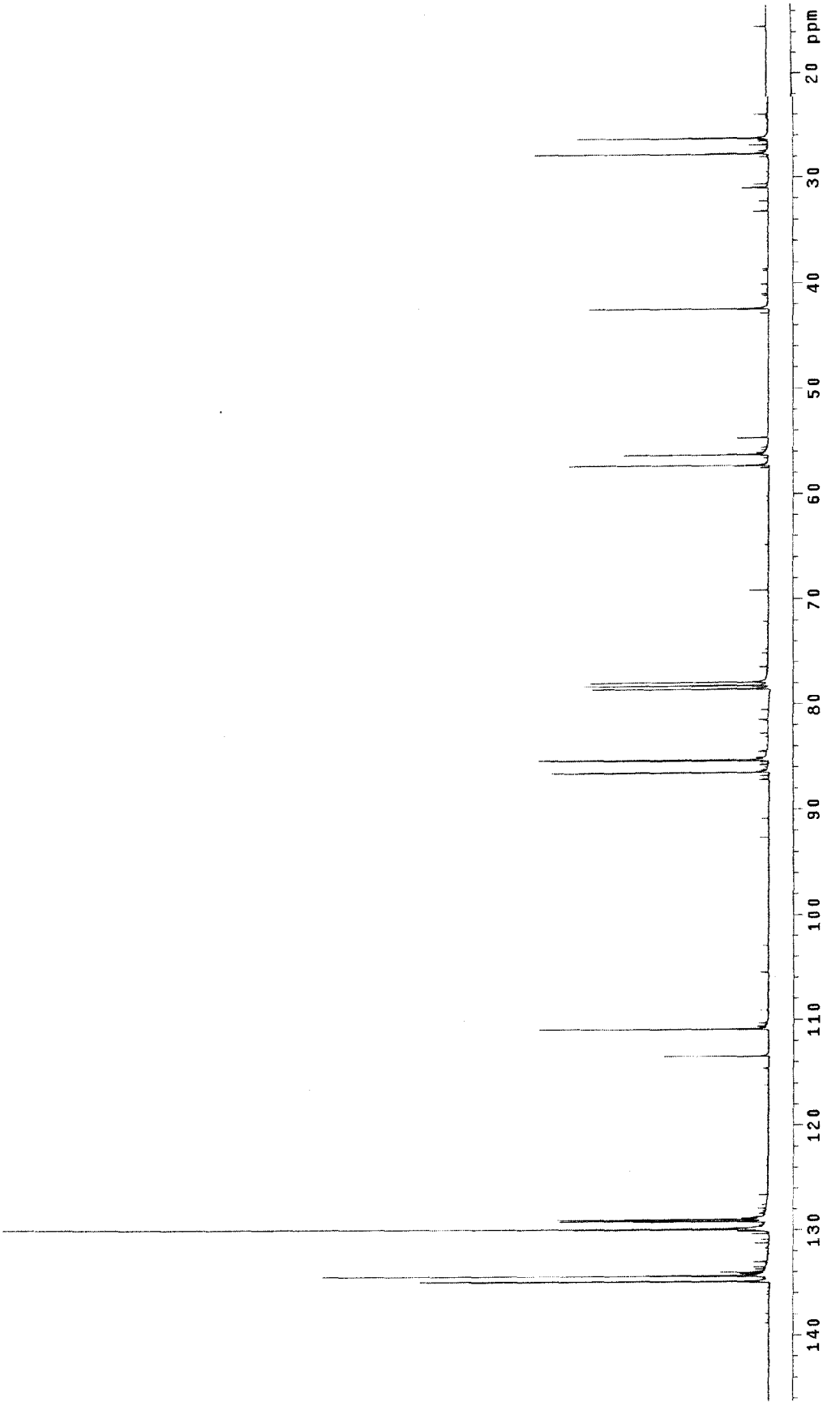

Figure 30. ^{13}C NMR of **24**

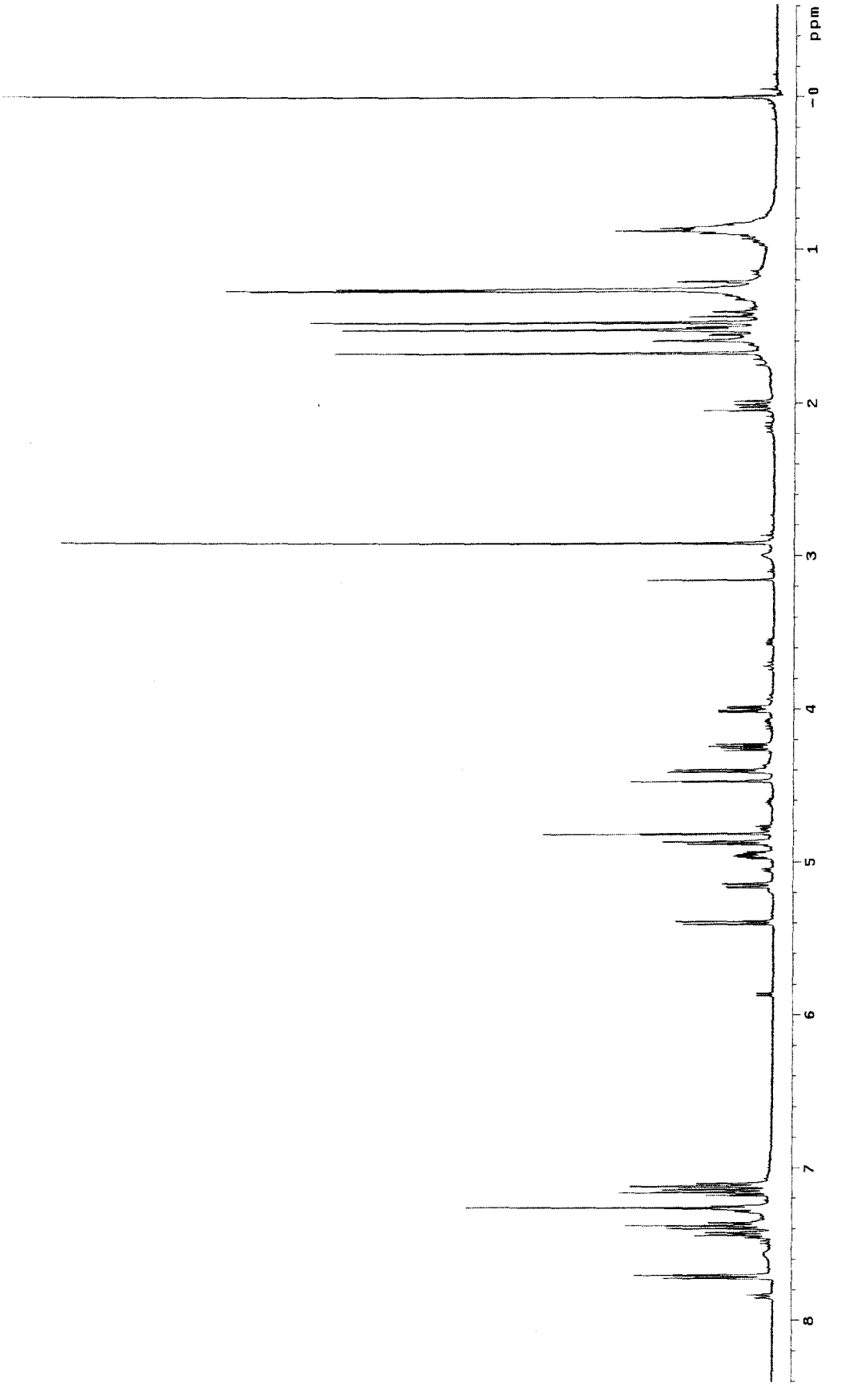

Figure 31. ^{1}H NMR of **25**

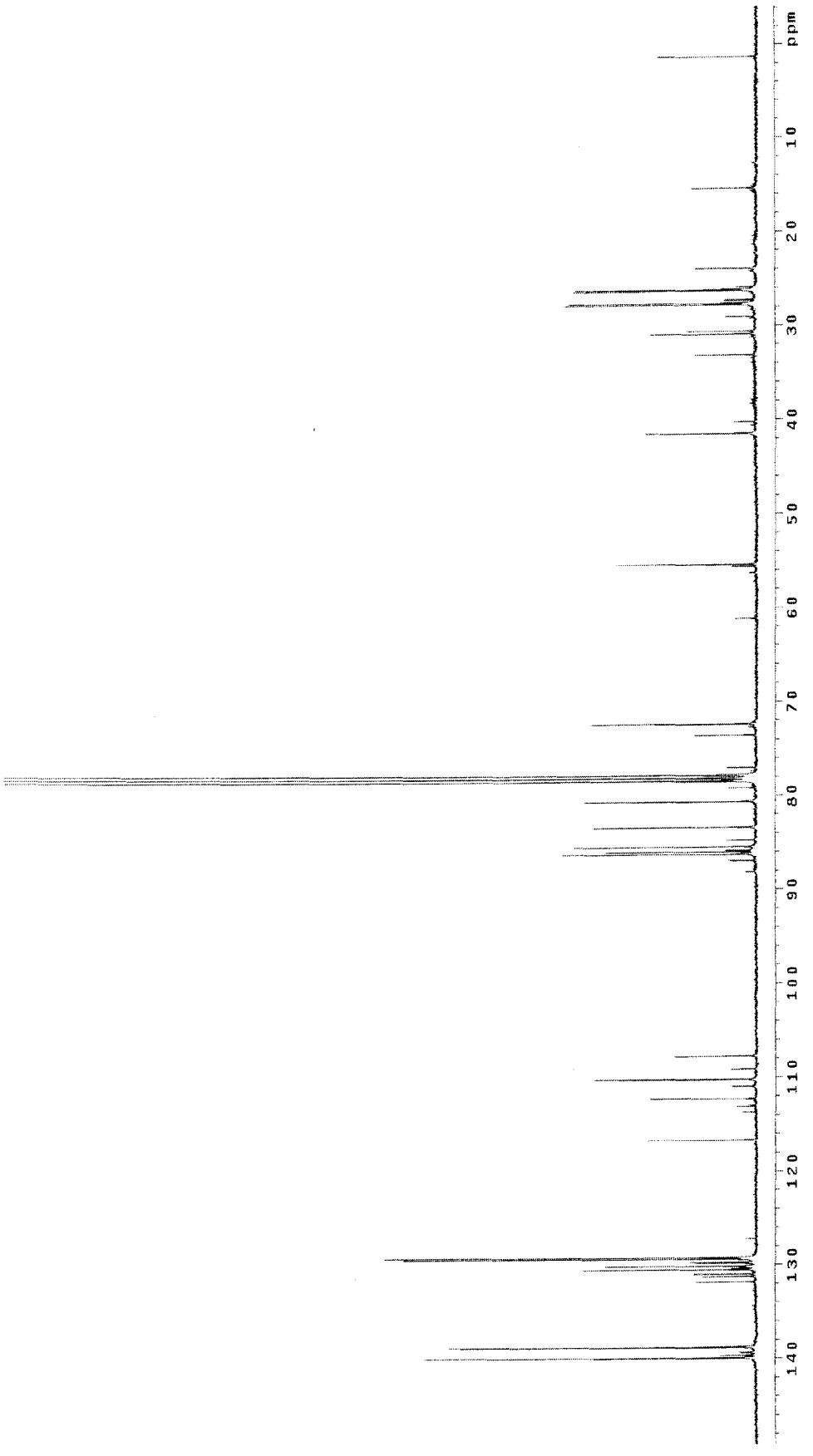

Figure 32. ^{13}C NMR of **25**

Profile MS Report

Analysis Info:

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Date acquired: Wed Jun 21 17:28:53 2000
Instrument: EsquireLC_00135
Task :
Method :

Printed: Wed Jun 21 17:29:59 2000

Operator : Administrator

Sample : ArabinoSulfone(ESI)

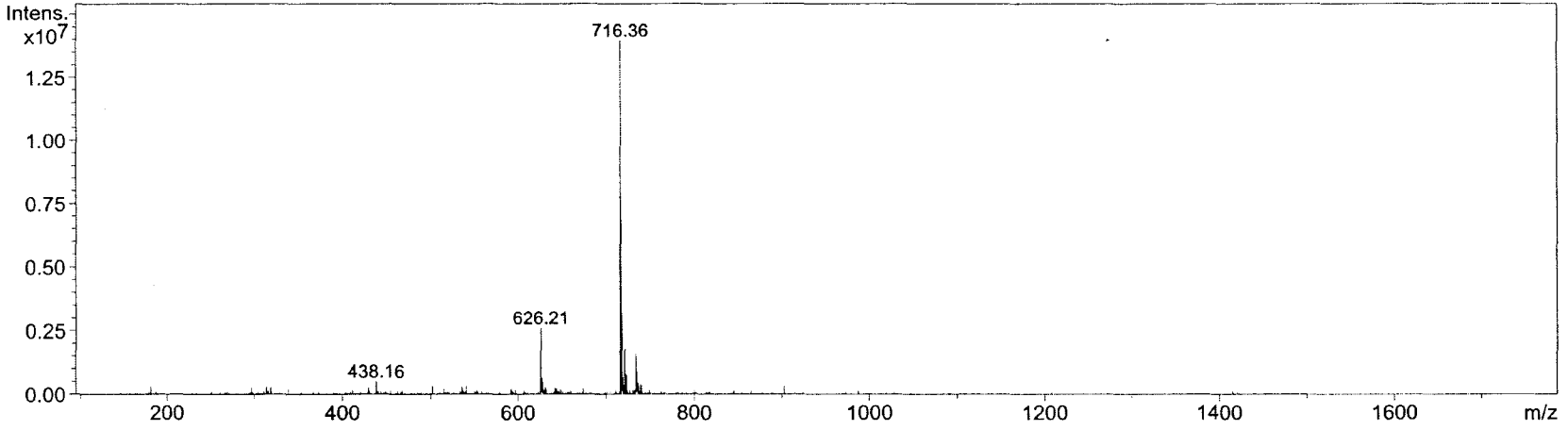
Acquisition Parameter:

Source : ESI
Mode : Std/Normal
CapExit : 81.6 Volt
Scan Range: 15.00 - 1500.00 m/z
Accum.time: 45 μs
MS/MS :

Polarity : Positive

Skim 1 : 14.7 Volt
Trap Drive: 38
Summation : 10 Spectra

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



MS Peak List (Profile Spectrum):

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626.21	2603727	0.20	719.33	692926	0.30	735.89	430397	0.20
627.24	684318	0.40	721.34	1774715	0.30	736.25	452785	0.30
628.20	487471	0.20	722.29	795540	0.20	739.33	401058	0.30
716.36	13965040	0.30	723.29	757935	0.20			
717.33	6838965	0.30	734.29	1565689	0.30			

Figure 33. Mass Spectrum of **3**

Profile MS Report

Analysis Info:

File: D:\DATA\RCIII\CGLYC017.D
Date acquired: Thu Jul 06 13:49:17 2000
Instrument: EsquireLC_00135
Task :
Method :

Printed: Thu Jul 06 13:50:17 2000

Operator : Administrator

Sample : RCIII-30-2

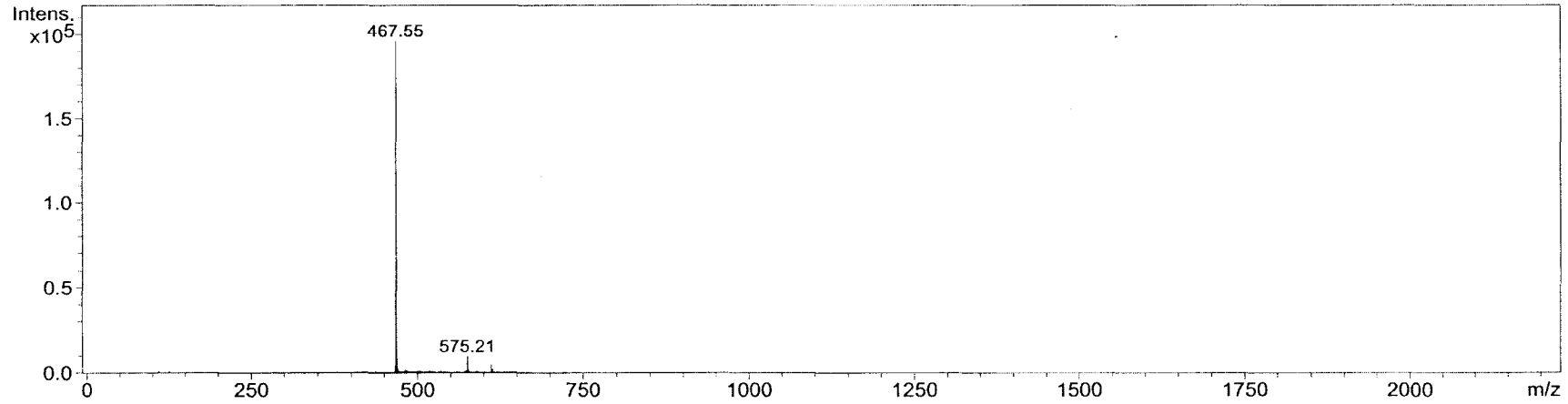
Acquisition Parameter:

Source : APCI
Mode : Std/Normal
CapExit : -105.5 Volt
Scan Range: 15.00 - 2200.00 m/z
Accum.time: 35497 µs
MS/MS :

Polarity : Negative

Skim 1 : -33.0 Volt
Trap Drive: 56
Summation : 10 Spectra

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



MS Peak List (Profile Spectrum):

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467.55	196453	0.30	535.27	1108	0.40	611.21	4863	0.30
470.16	2370	0.60	571.23	1330	0.50	612.14	2142	0.30
481.61	1683	0.70	573.25	1189	0.30	613.09	2164	0.40
482.46	1230	0.30	575.21	9976	0.40			
483.52	1522	0.30	576.09	3958	0.40			

Figure 34. Mass Spectrum of **25**