STUDIES TOWARDS THE SYNTHESIS OF NEW CARBOHYDRATE-DERIVED HETEROCYCLES

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STUDIES TOWARDS THE SYNTHESIS OF NEW CARBOHYDRATE-DERIVED HETEROCYCLES

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THESIS ABSTRACT

The purpose of this research is to study the synthesis of novel carbohydrate-derived heterocycles by using 1,3-dipole (nitrile oxide), the synthesis of new *C*-glycosides by using sulfonium-ylide and Wittig reagent, and the preparation of carbohydrate-derived azides.

ACKNOWLEDGEMENTS

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INTRODUCTION

This thesis consists of three projects. One is the attempted synthesis of a novel glycosidase inhibitor (natural carbohydrate analog) *via* 1,3-dipolar cycloaddition-sulfoxide elimination reaction on a carbohydrate-derived vinyl sulfoxide compound. The second is the synthesis of *C*-glycosides by using ylide reagents, and the third is the attempted synthesis of carbohydrate-derived acyl azide compound.

1. Biological Significance of the Natural Carbohydrate Analogs and the Synthetic Strategy

It is well known that enzymes catalyze biological reactions selectively. There are many important principles of catalysis in the process of enzymes catalyzing biochemical reactions. One of the important principles is that enzymes facilitate the formation of the transition states of the reactions. The binding forces responsible for stabilization of the transition states are charge-charge interactions, hydrogen bonds, hydrophobic interactions, and van der Waals forces. Because enzymes have three-dimensional structures, the specificity of the substrates is determined by both the chemical properties of the amino acid residues and the shapes of the active sites of the enzymes. So, enzyme inhibitors that mimic the transition states in both shape and chemical property may affect biological reactions and can offer the potential of medicinal treatments for diseases in which that enzymatic process plays a key role. The importance of enzymes in biology, biochemistry, and pharmaceutics extensively encourages the biochemist and organic chemist to devise and synthesize various new enzyme inhibitors.

Carbohydrates are one of the most important classes of organic compounds found in nature. They are specifically biochemically active components of plants, animals and microorganisms. The need to develop new carbohydrate analogs is obvious. It is known that the carbonium ion intermediates, which are stabilized by the enzymes, are critical for glycosidase enzymes to catalyze the cleavage of many glycosides. A variety of carbohydrate-derived heterocyclic compounds have been synthesized and found to act as potent inhibitors of various glycosidases. Figure **1** shows the structures of several known inhibitors.

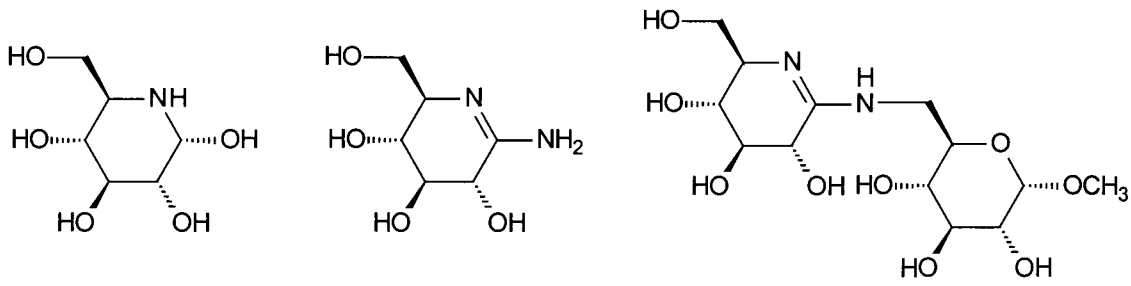
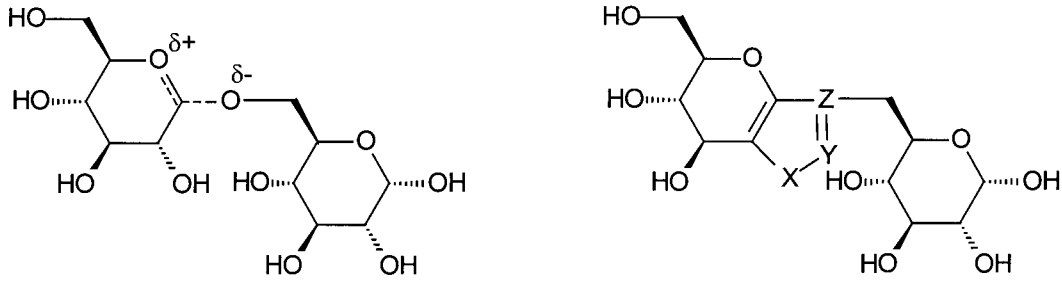


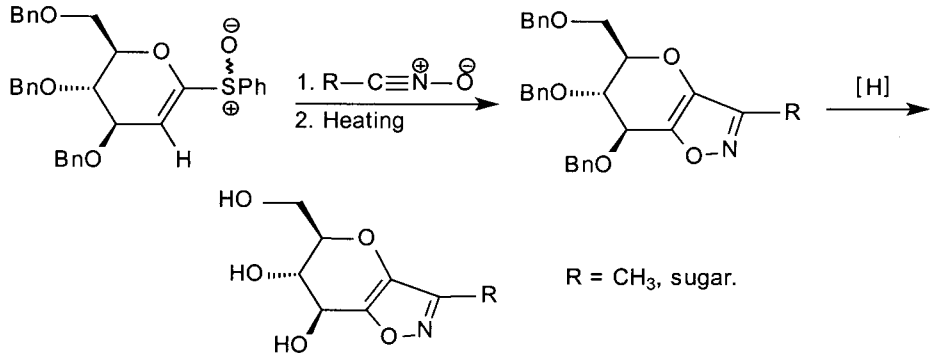
Figure **1**

In our research group, a class of carbohydrate analogs known as pseudodisaccharides (**2**, Figure **2**) in which two sugar units are linked by an aromatic heterocycle at C-1 and C-2 of the "non-reducing" terminus, are being explored *via* 1,3-dipolar cycloaddition reactions. Figure **2** gives the comparison of the theoretical glucose-1,6-glucose cleavage and the potential synthetic disaccharide inhibitor (**2**). The cycloaddition reactions would be expected to be activated by the phenyl sulfoxide group. The loss of the sulfoxide group is expected to occur in the same reaction flask to furnish **2** with the aromatic ring.



1 **2**

Figure **2**. (X, Y, Z are O, N, C depending on the dipole used).



Scheme **1**

This section of the research will focus on the reactions of a sugar-derived vinyl sulfoxide compound with nitrile oxides (Scheme **1**).

The ability of nitrile oxides to react with olefins was first reported by Weygand in 1927 and Huisgen categorized the nitrile oxides as being members of a broader class of 1,3-dipoles that were capable of undergoing [3+2] cycloaddition reaction in 1961.[1] The factors that affect the reactivity of 1,3-dipolar cycloaddition reactions were studied based upon the Frontier Molecular Orbital (FMO) theory.[2,3] For nitrile oxides, they react rapidly with both electron-rich and electron-deficient species.[2] A common method of preparing the reactive nitrile oxides is dehydrohalogenation of hydroxamic acid chlorides which in turn are obtained by chlorination of the corresponding aldoximes with chlorine. This method has disadvantages because of the high reactivity of chlorine towards other functional groups and the difficulty in determining the end point of the chlorination. Improved methods were reported in which *N*-chlorosuccinimide (NCS) replaced chlorine for chlorination of aromatic and aliphatic aldoximes in dimethylformamide.[4]

Larsen and Torssell synthesized a series of 2-isoxazolines with this method.[5] According to their results (Table **1**), we can find that conjugated olefins gave good yields. These results are identical with those predicted by FMO theory. It facilitates the [3+2] cycloaddition reaction because the conjugated olefins have higher HOMO energy and lower LUMO energy.

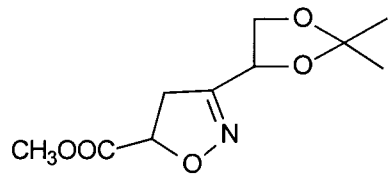
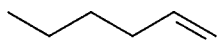
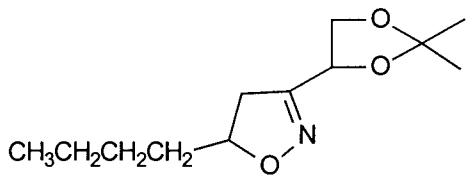
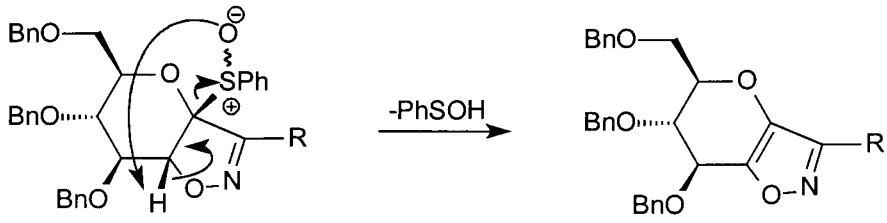
Olefins	2-isoxazoline	Yield
$CH_3OOCCH{=}CH_2$		80%
		61%

Table **1**

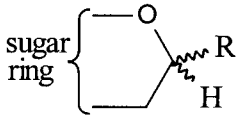
The steric factors should be also considered in the synthesis of **2**. The reaction is expected to be stereospecific.[6] Though nitrile oxide molecules can attack either face of the vinyl molecule, it should favor bottom access to avoid the top hindrance from the C-3 benzyl group. The elimination of the sulfoxide group is likely to be as in the mechanism shown in scheme **2**.



Scheme **2**

2. *C*-Glycoside Chemistry

The anomeric centers within monosaccharide molecules are usually the most reactive sites. They undergo many reactions to achieve different derivatives such as *C*-glycosides, thioglycosides, glycosyl esters and halides (Figure **3**).



C-glycosides: R = -CH_2R'; thioglycosides: R = -SR'; *N*-glycosides: R = $R''NR'$;
glycosyl esters: R = $OCOR'$; glycosyl halides: R = halogens

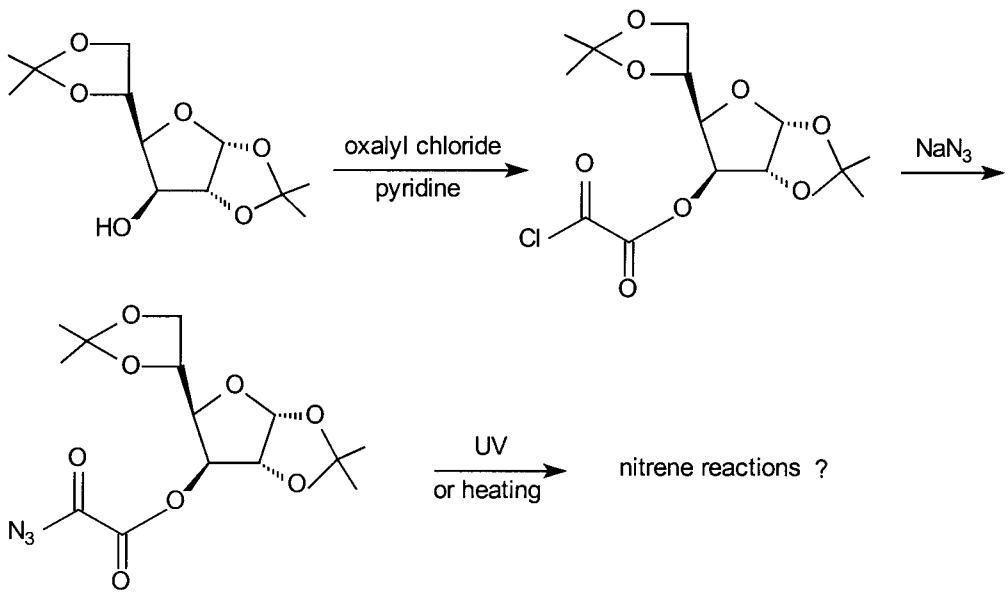
Figure **3**

The reactivity of the anomeric center is due to its hemiacetal character. The carbocations generated by cleaving of the anomeric substitutes are stabilized by mesomeric release of electrons from adjacent oxygen atoms and tend to be attacked by nucleophiles. Also, it is known that free sugars can mutarotate in solution to give, ultimately, equilibrium mixtures of five (or more) modifications: the α- and β- furanoses, the corresponding pyranoses and the aldehyde forms. The aldehyde functional group is one of the most

versatile groups in organic synthesis. It can perform many reactions in which the carbonyl is attacked by nucleophiles and form various derivatives. Based upon the hemiacetal and carbonyl characters of sugars, more and more methodologies of preparing sugar-derivatives have been developed[7] and many *C*-glycosides have been synthesized in the past years.[8] Many of these compounds act as glycosidase inhibitors. Undoubtedly, they have enriched the field of carbohydrate chemistry and show the importance of carbohydrate chemistry as an independent branch in organic chemistry. In this section of the research, reactions of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose with nucleophilic ylides (sulfonium ylide and Wittig reagent) were explored. The *C*-glycoside which is obtained in the Wittig reaction can be a starting material to prepare sugar-derived acyl azide compounds. The detailed reaction mechanisms are given in the Results and Discussion section.

3. Sugar-Derived Acyl Azide Compounds and the Nitrene Chemistry

It is well known that azides are the precursors of nitrenes. Nitrenes can perform many reactions such as dimerization, rearrangement, addition, and insertion. Developing sugar-derived azide compounds and further exploring their nitrene chemistry will achieve many new carbohydrate derivatives. This section of the research is the initial implementation of this idea. Scheme **3** gives the proposed reactions.



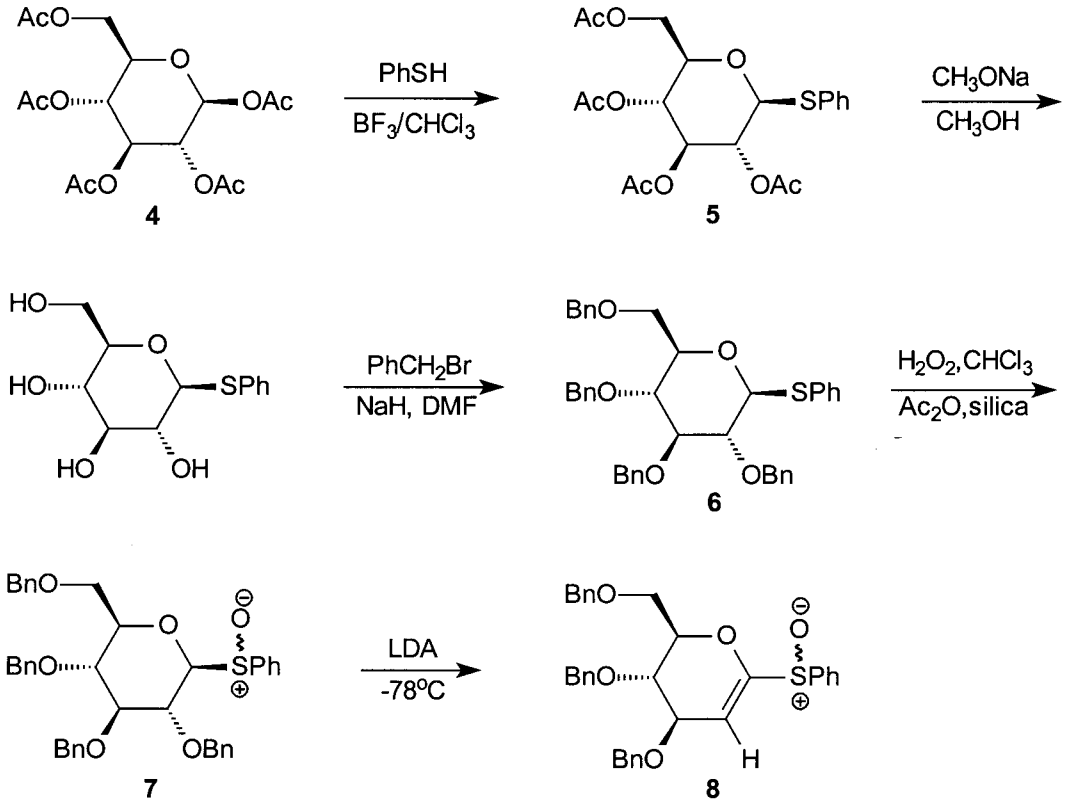
Scheme **3**

STATEMENT OF PROJECTS

By summarizing above introductions, new heterocyclic carbohydrate derivatives could be synthesized by using 1,3-dipolar cycloadditions and the sulfoxide group could activate the reaction and be lost by simply raising the reaction temperature. Sulfonium ylide and Wittig reagents could react with the aldehyde forms of carbohydrates to achieve new *C*-glycosides, which are also heterocyclic compounds (THF derivatives). Sugar-derived acyl azides could be prepared and the nitrene chemistry on carbohydrates could be explored to furnish new heterocyclic carbohydrate compounds for further research. The results of these investigations are given in the next section.

RESULTS AND DISCUSSION

1. The preparation of D-glucose-derived vinyl-sulfoxides and their reactivity in 1,3-dipolar cycloaddition and [4+2] cycloaddition reactions.



Scheme 4

Scheme **4** shows the synthetic route to the sugar-derived vinyl-sulfoxide compounds, which were used to investigate the cycloaddition chemistry. The synthesis began with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucose (**4**), which was treated with thiophenol and boron trifluoride diethyl etherate to form the thioglycoside (**5**). In the preparation of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-gluco-pyranoside (**5**), the α-product was formed inevitably. It was more polar than the β-anomer as seen on the TLC plates. Based on the literature,[9] it can be removed by regular recrystallization. The β-anomer (**5**) was prepared as white crystals in 68.3% yield with m.p 114-116°C (literature melting point 117-118°C, yield, 71%). The ^{1}H NMR (Figure **4**) clearly showed the phenyl signal and there were four singlets at 2.0-2.2 ppm corresponding to the four acetyl protecting groups. This

compound was then deprotected using Na in methanol. The deacetylation reaction occurred smoothly at room temperature. After the starting material had disappeared (shown on TLC), the sodium methoxide was destroyed by adding dry ice and the solvent was evaporated. The resulting white solid was used directly in the next step.[10]

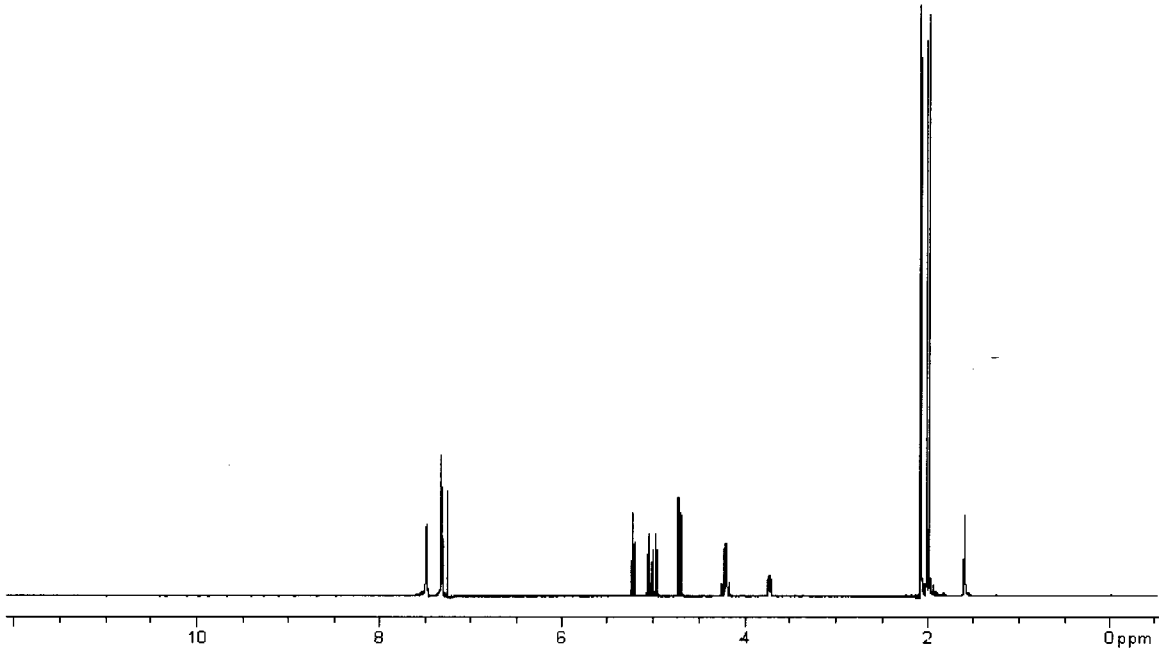


Figure **4**. ^{1}H NMR spectrum of thioglycoside (**5**)

DMF was used as solvent in the Williamson ether synthesis and sodium hydride was used to deprotonate the hydroxyl groups to form the nucleophilic intermediate. It reacted with electrophilic benzyl bromide to form the benzyl-protected glucoside (**6**). **6** was isolated as white crystals with m.p 89-91°C (literature m.p 84-86°C). The ^{1}H NMR (Figure **5**) was also consistent with the structure. The integral showed that the ratio of the aromatic hydrogens to the other hydrogens equaled 1.67 (25/15).

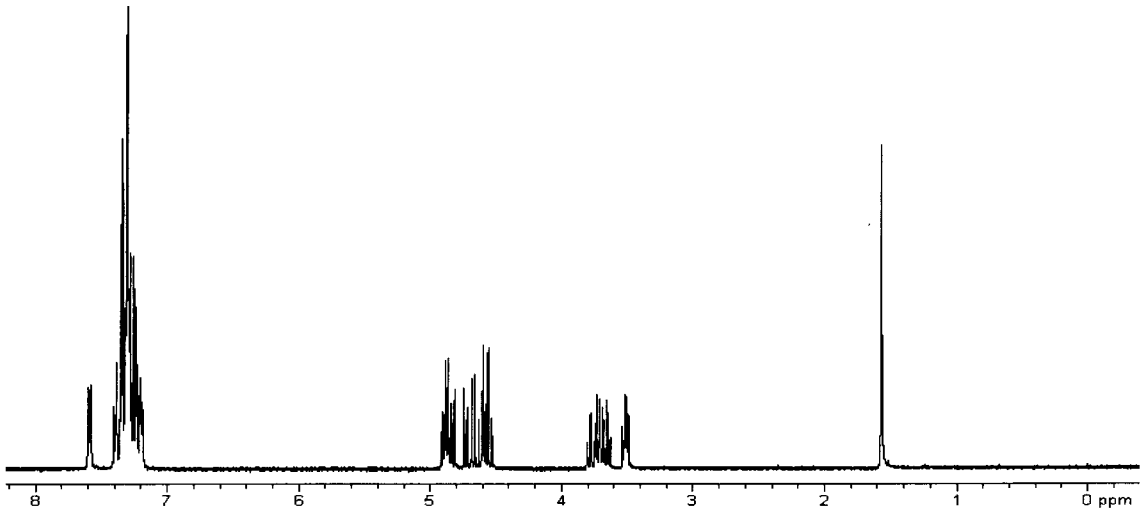


Figure **5**. ^{1}H NMR of benzyl protected derivative **6**

The preparation of **7** is based on the literature method [11] by using hydrogen peroxide instead of *m*-CPBA to avoid the formation of sulfone. Silica was used to increase the yield and reduce the reaction time. It was found that slowly adding oxidant only made the starting material take longer time to disappear.

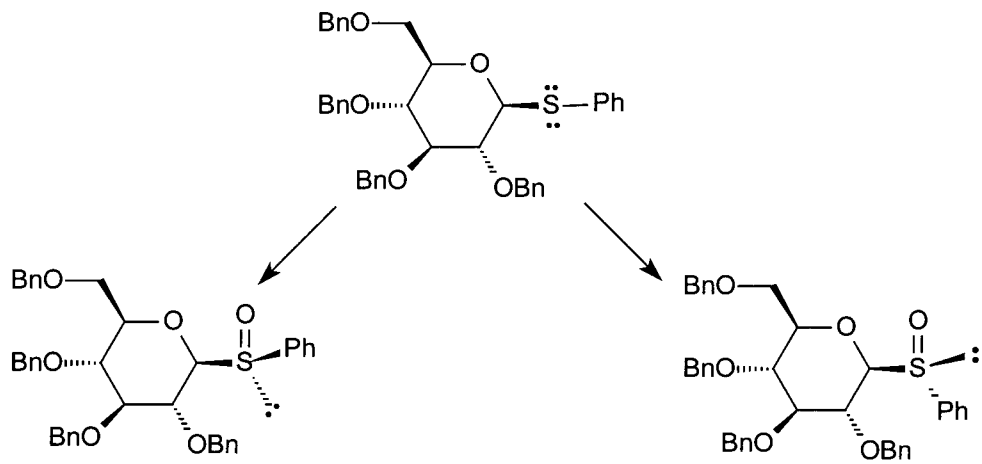


Figure **6.** sulfoxide diastereomers

7 is a mixture of two chiral compounds due to no inversion at the sulfur atom (see Figure **6**). That this is a mixture is reflected by its wide melting range (97-106° C) and the two

spots shown on TLC plates, but the literature did not indicate whether the diastereomers were formed. It was reported that the Rf value (hexane / ethyl acetate, 3:1) of the product was 0.3 and the melting point was 120-122°C. We found that the Rf values of the two products were 0.30 and 0.22 (hexane / ethyl acetate, 3:1). We did not separate the two compounds. The ^{1}H NMR (Figure **7**) showed that the phenyl hydrogen signals of the mixture were split and shifted more downfield (7.59-7.65 ppm) than in the starting material. This is due to the electron withdrawing effect of the sulfoxide group and the existence of the diastereomers.

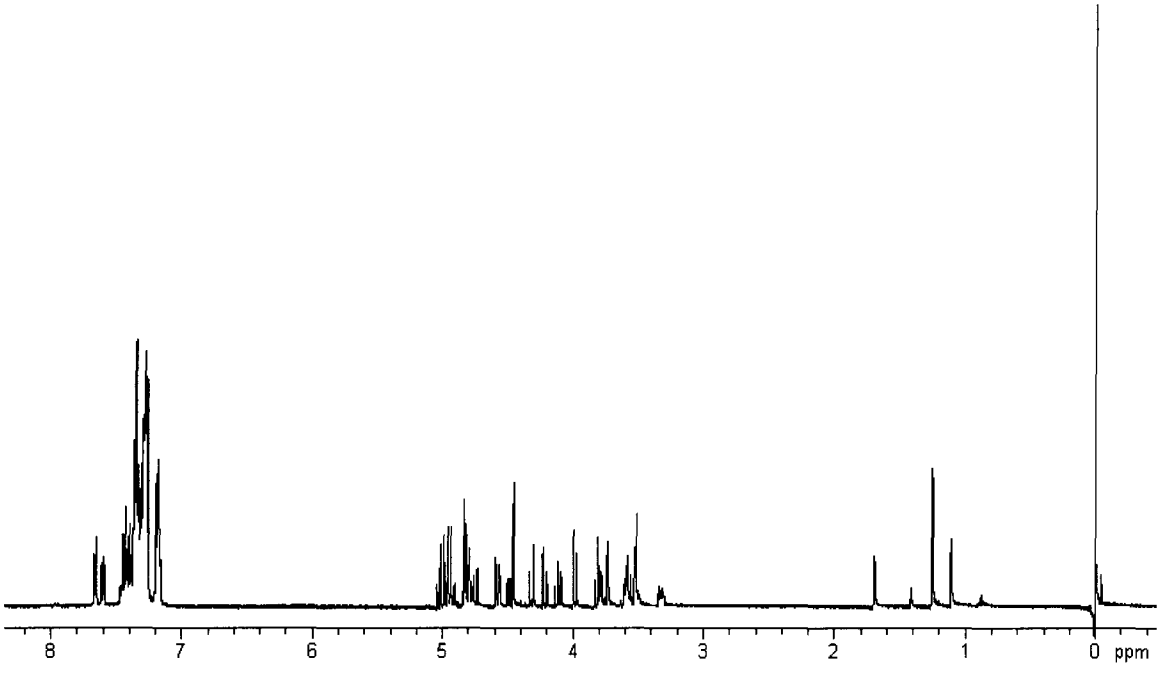


Figure **7**. ^{1}H NMR of sugar-derived-sulfoxides (**7**)

We used this mixture to do an LDA promoted elimination reaction to furnish olefin (**8**) as a major product in 34.5% yield. **8** also showed two spots on the TLC plates (hexane / ethyl acetate, 3:1, Rf 0.22, 0.20). The proton NMR (Figure **8**) gave the signal of the vinyl hydrogen on C-2 atom at 5.9 ppm as two doublets.

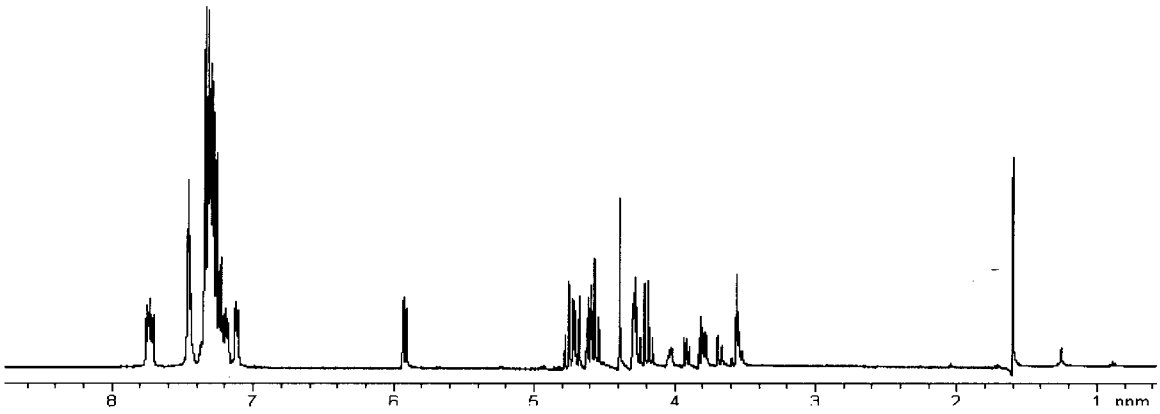


Figure **8**. ^{1}H NMR of sugar-derived-vinyl-sulfoxide (**8**)

The yield is relatively lower. The possible reason is that the reaction was not over at lower temperature, maybe the strong base caused the formation of by-products at room temperature. One of the by-products was separated during the flash chromatography purification (silica, hexane /ethyl acetate, 3:1). Its proton NMR was taken. The chemical shift of the hydrogen on the C-2 atom shifted more down field (6.4 ppm) and the signals were two singlets (Figure **9**). A possible structure is **9** and the possible formation mechanism is indicated in scheme **5**. The conjugated vinyl system would be consistent with the signal of the C-2 hydrogen shift downfield. Also consistent with this structure is the lack of coupling effect due to the loss of the C-3 hydrogen. Scheme **5** also shows a proposed chemical method to identify its structure. If it is **9**, once the benzyl group is reduced, an enol intermediate will be formed and changed to the ketone, which should be seen on the ^{13}C NMR spectrum.

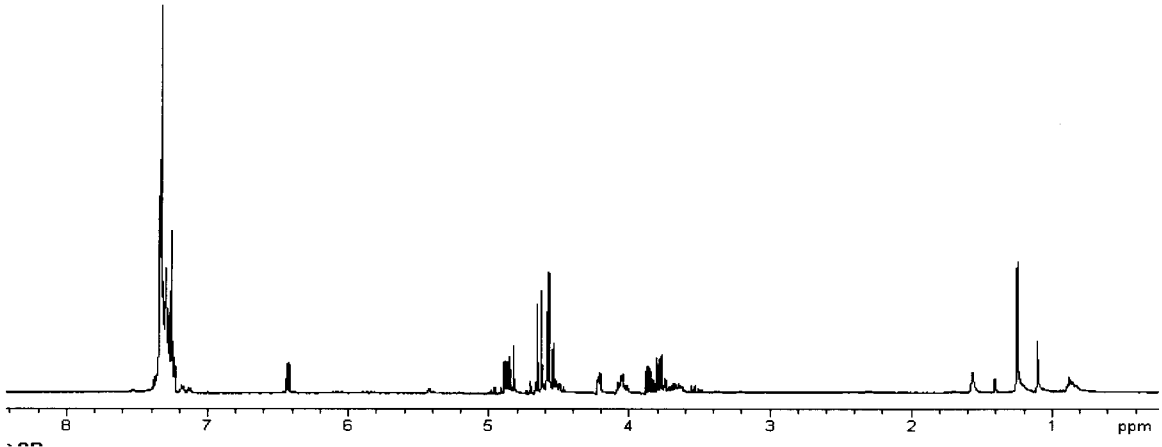
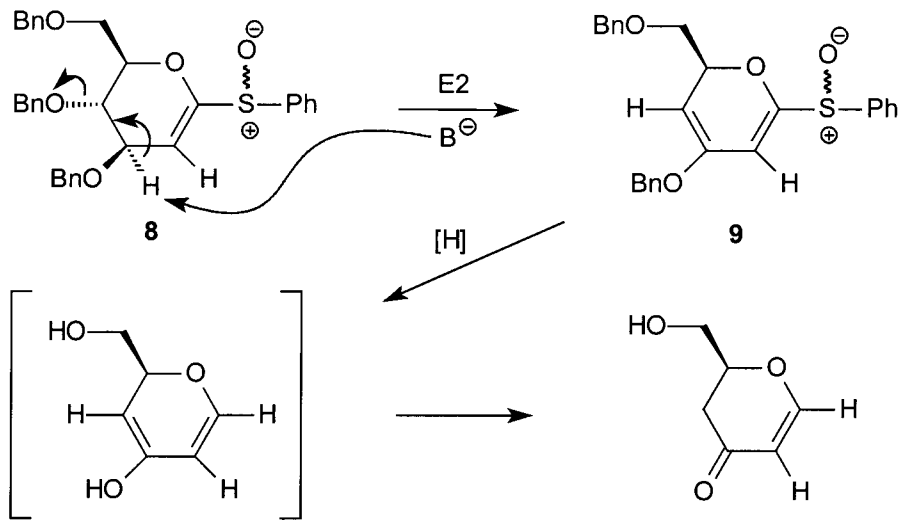


Figure **9**. ^{1}H NMR of the possible by-product



Scheme **5**

Compound **8** was then used in the attempted 1,3-dipolar cycloaddition reaction with $CH_3C{\equiv}N^+{-}O^-$. Because nitrile oxides easily dimerize, the reactions are usually performed *in situ* to avoid the formation of dimers. Reaction started with 0.1 g of **8** and recovered 0.09 g from the column. ^{1}H NMR (Figure **10**) shows that it is the starting material (Scheme **1**).

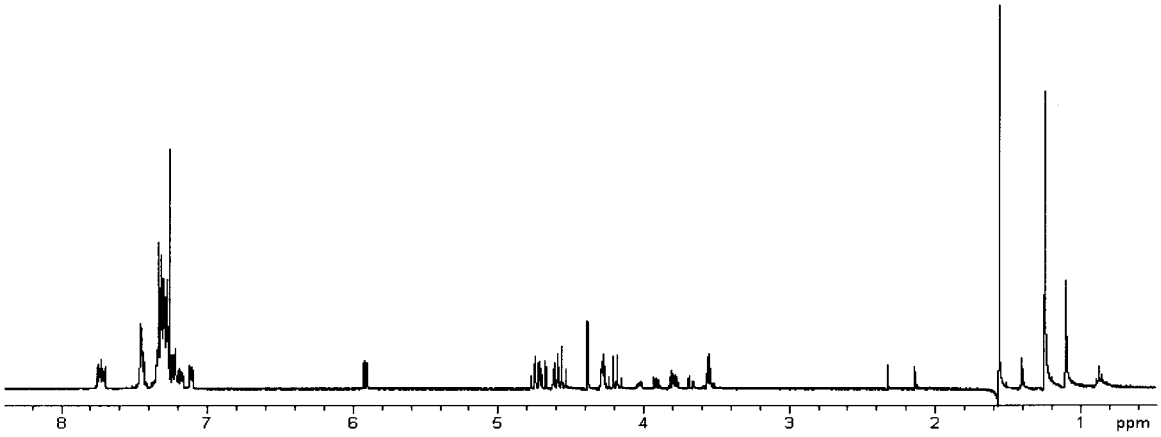
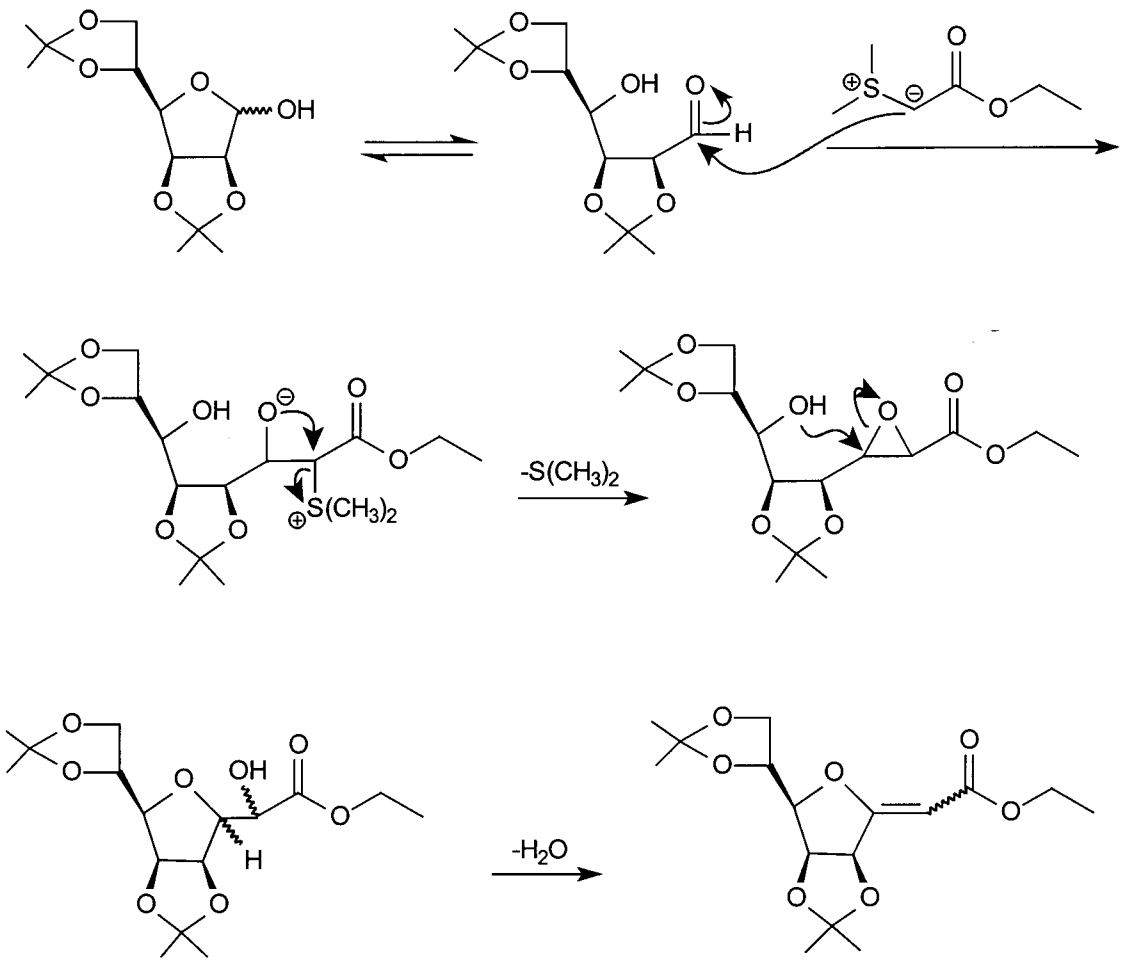


Figure **10**. ^{1}H NMR of the recovered compound

However, the 1,3-dipolar cycloaddition followed by loss of the phenyl sulfoxide group has been observed in our research group in the treatment of 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with phenylvinylsulfoxide in refluxing toluene which resulted in the formation of the aromatic 6-triazole derivative. This result indicates that the reaction could likewise occur on sugar derived vinyl sulfoxide compounds such as **8**. In this experiment, because the dimerization of the nitrile oxide is competitive with the cycloaddition reaction, reactivity of the vinyl compound is more important. A possible reason that no reaction was observed in the case of **8** and $CH_3C{\equiv}N^+{-}O^-$ is the steric hindrance due to the large size of the protecting groups ($-OCH_2Ph$) and the phenyl sulfoxide group. The hindrance possibly made it difficult for the cycloaddition reagent molecules (such as $CH_3C{\equiv}N^+{-}O^-$) to approach either face of the double bond of the sugar-derived vinyl sulfoxide molecule, so, before the nitrile oxide reacted with the vinyl compound, the dimer was formed. In the future, continued work can be done to explore the suitable conditions for this reaction, or to investigate this reaction after removing the protecting groups. In order to explore the reactivity of the vinyl compound **8**, a reaction of **8** with *trans, trans*-1,4-diphenyl-1,3-butadiene was performed. After refluxing for five days in toluene, a black solution was obtained, but pure compounds could not be separated on the column (silica, hexane / ethyl acetate, 5:1). A mixture was recovered and the characterization could not be done.

2. The synthesis of *C*-glycosides by use of ylide reagents

In this section of the research, two kinds of nucleophilic ylide reagents were used to explore the synthesis of new *C*-glycosides. One is ethyl (dimethyl sulfuranylidene) acetate (EDSA) and the other is methyl (triphenylphosphoranylidene) acetate ($Ph_3P{=}CHCO_2CH_3$).



10 **11**

Scheme **6**

EDSA is not stable and should be sealed and stored at -10°C. It was reported that when EDSA was allowed to reflux in benzene (80°C), it decomposed to the extent of 35% in 3 hours.[12] Undoubtedly, the selection of the suitable solvent is important in the reactions involving EDSA. In this project, toluene and acetonitrile were tested and toluene was found to be the relatively more suitable solvent for the explored reactions. Acetonitrile

caused the rapid decomposition of the EDSA at the required reaction temperature possibly due to its high polarity. The EDSA was prepared in high purity by following the literature method.[12] The reaction with 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose gave two products which were thought to be **10** and **11**. Scheme **6** shows the mechanism of this reaction. **10** and **11** were separated by flash chromatography. **10** has a very similar Rf value to the starting material, and **11** is slightly less polar than the starting material (hexane / ethyl acetate, 1:1). The IR and ^{1}H NMR spectra of **10** (Figure **11**) and **11** (Figure **12**) were determined.

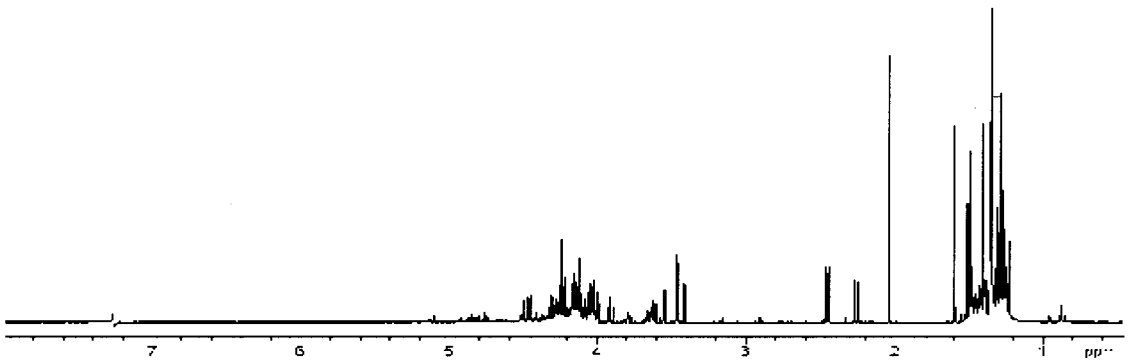


Figure **11**. ^{1}H NMR spectrum of **10**

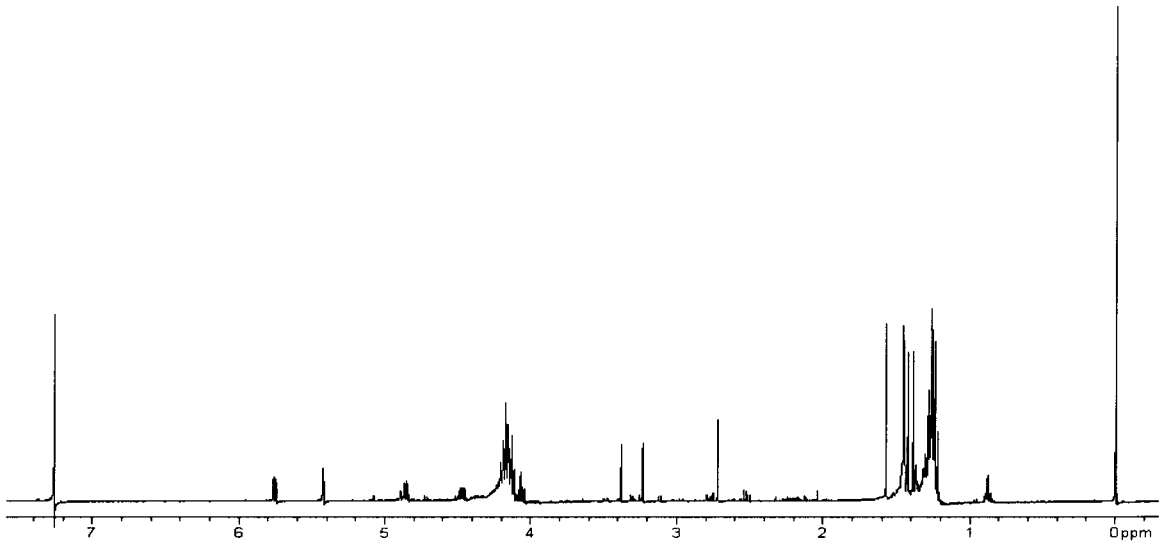


Figure **12**. ^{1}H NMR spectrum of **11**

The IR of **10** shows the O–H stretching at ~3500 cm^{-1} and the carbonyl absorption at 1740 cm^{-1}. The IR of **11** shows no hydroxyl signals but there is carbonyl absorption at ~1740 cm^{-1} and the C=C signal at ~1680 cm^{-1}. Its ^{1}H NMR shows signals at 5.75 ppm which correspond to vinyl hydrogen. Based upon these data and the proposed mechanism, we suggest that the products are **10** and **11**, further characterization work needs to be done to identify that the structures of the products are definitely **10** and **11**. Mass spectrometry using Fast Atom Bombardment (FAB) techniques would be helpful.

Unlike EDSA, $Ph_3P{=}CHCO_2CH_3$ is a stable solid reagent available from commercial sources. The initial purpose of this project was to make **16** by following the synthetic route shown in scheme **7**. Scheme **8** gives the mechanism of the ring closing. In the first reaction, 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose and methyl (triphenylphosphoranylidene) acetate were refluxed in acetonitrile to furnish **12** in 98.3% yield. The reaction did not stop at **17** (Scheme **8**), because intramolecular Michael addition reaction occurred due to the use of polar aprotic solvent (acetonitrile). The hydroxyl group could attack either face of the double bond, so, the products were an anomeric mixture. The ^{13}C NMR (Figure **13**) spectrum showed the carbonyl signals at 171-173 ppm (two peaks because of the anomeric mixture) and no vinyl carbon signals.

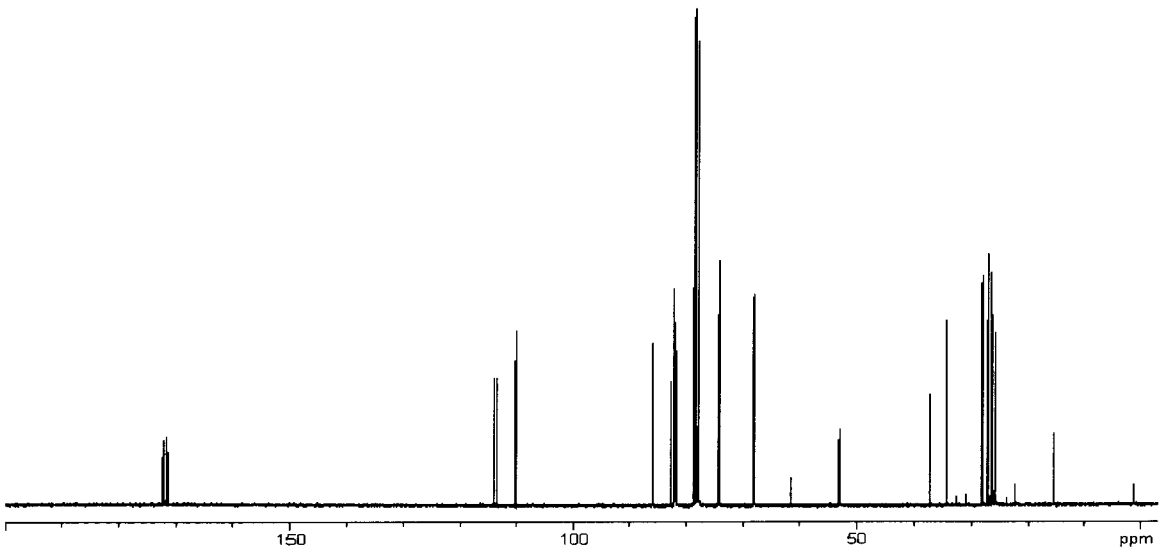
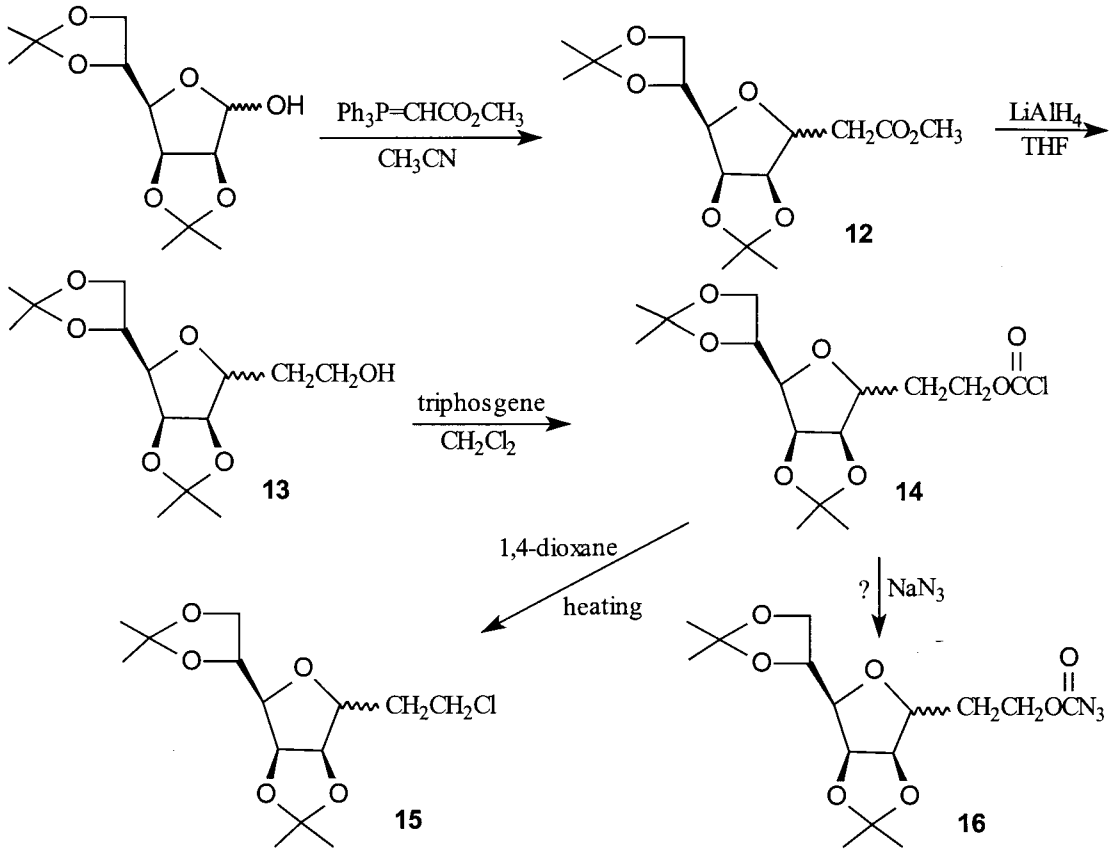
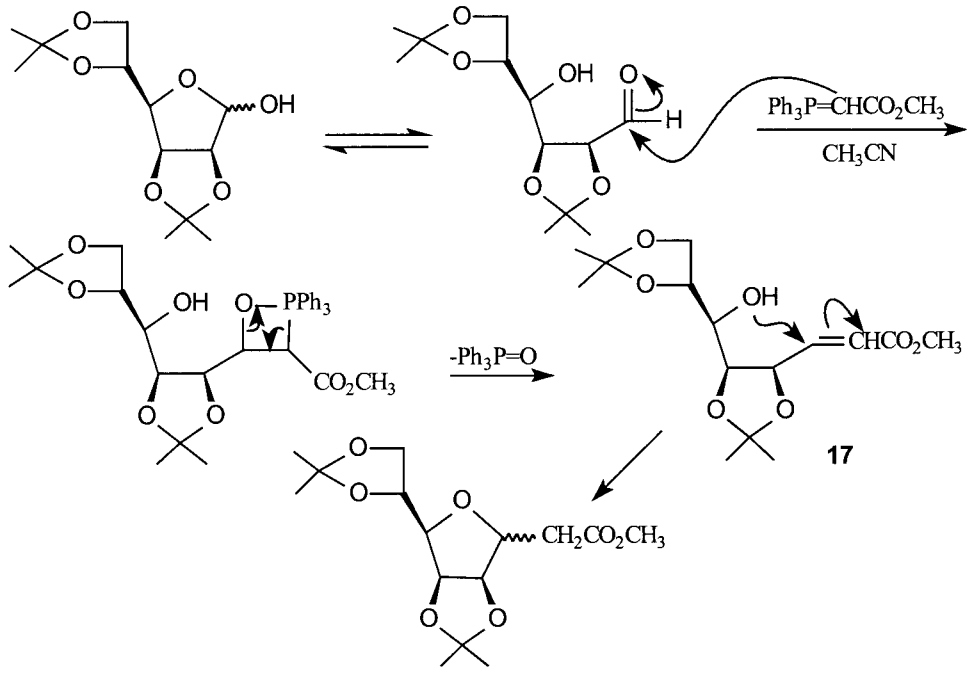


Figure **13**. ^{13}C NMR spectrum of **12**



Scheme 7



Scheme **8**

12 was reduced by $LiAlH_4$ in THF to furnish **13** in 100% yield. Saturated sodium sulfate solution was used to quench the reaction to prevent the formation of the aluminum hydroxyl gel and made the solution easy to suction filter. The ^{13}C NMR (Figure **14**) shows that the carbonyl signals disappeared, also, in the ^{1}H NMR (Figure **15**), the signals of the hydrogen on the carbon which is attached to the ring are observed to be at 1.5-2.1 ppm instead of at 2.4-2.8 ppm on the ^{1}H NMR spectrum (Figure **16**) of **12**.

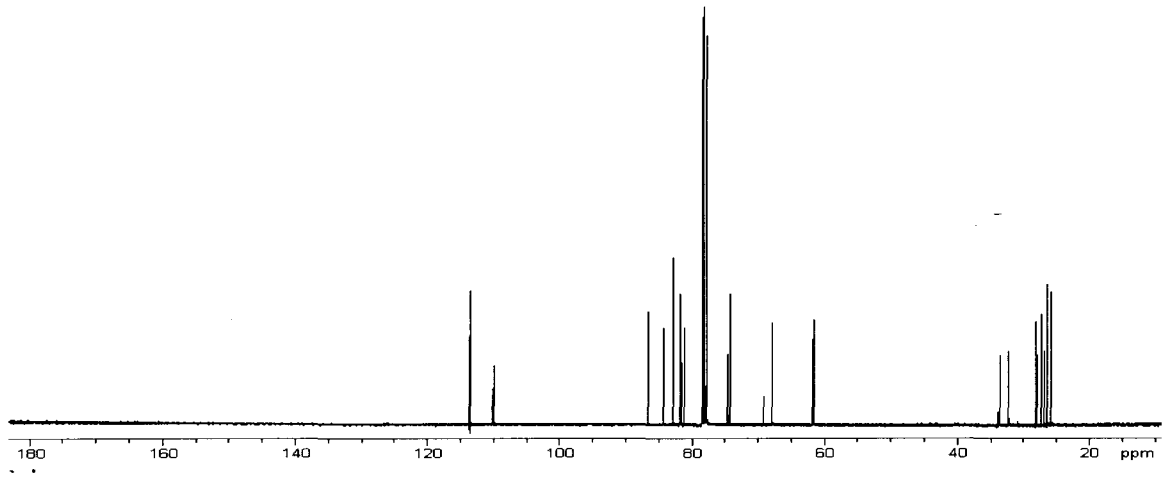


Figure **14**. ^{13}C NMR spectrum of **13**

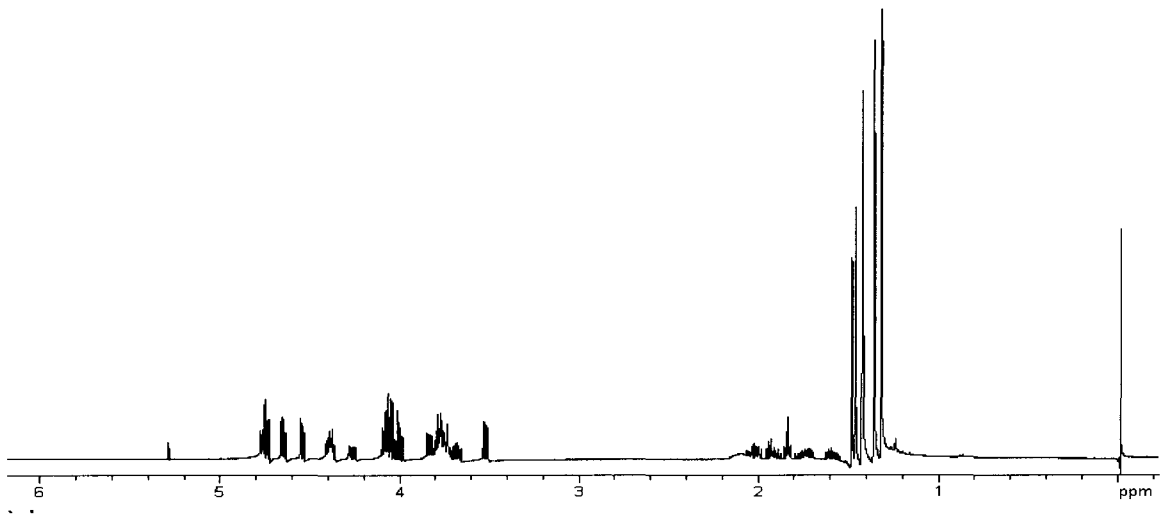


Figure **15**. ^{1}H NMR spectrum of **13**

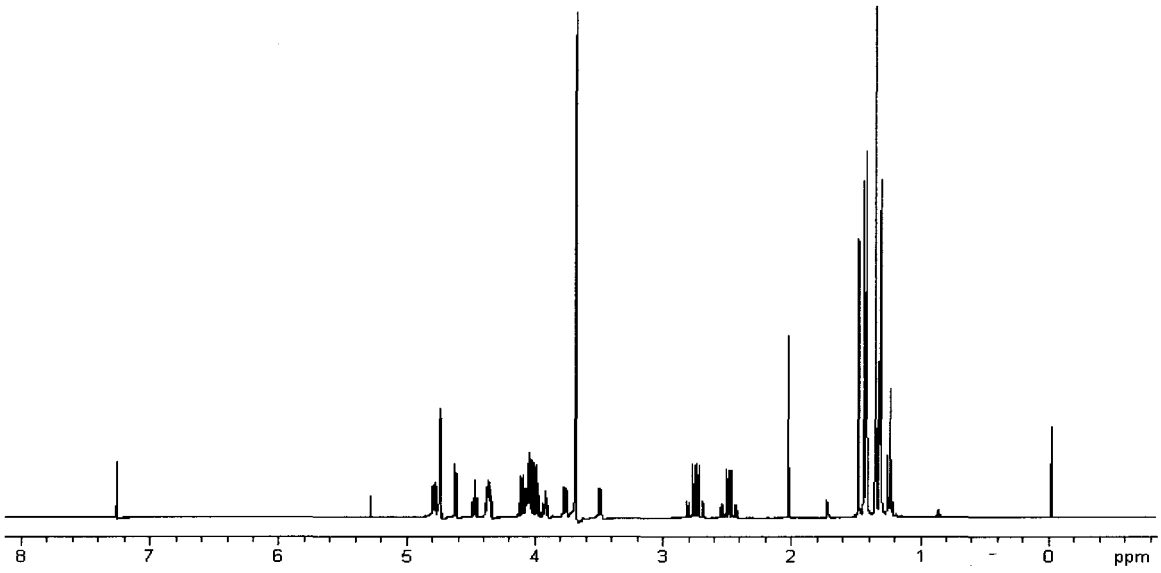
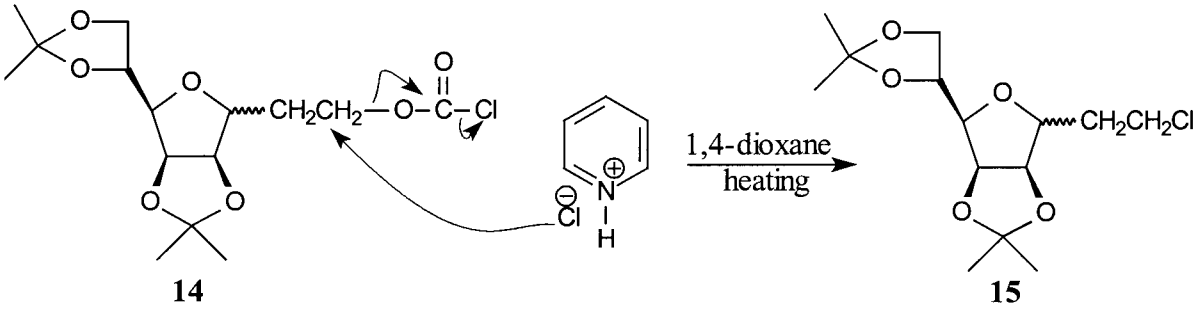


Figure **16**. ^{1}H NMR spectrum of **12**

13 was used to react with triphosgene and sodium azide. A pure colorless syrup was obtained, but the IR and ^{13}C NMR spectra of this compound did not match **16**. There were no carbonyl signals in its ^{13}C NMR spectrum (Figure **17**) and no azide signals (~2200 cm^{-1}) on the IR spectrum.



14 **15**

Scheme **9**

A reaction with no sodium azide added was performed and the same product was recovered. A supposed reaction mechanism shown in scheme **9** shows how the formation of **15** (81.4%) was possible. The IR (C–Cl absorption at ~750 cm^{-1}, no azide and carbonyl signals), ^{1}H NMR (Figure **18**) and ^{13}C NMR (Figure **17**) are also consistent with the structure of **15**. In the ^{13}C NMR, the peaks (62 ppm and 69 ppm) of the carbons which

are attached to the hydroxyl group in **13** are shifted toward upfield (42 ppm and 43 ppm) due to the substitution of the hydroxyl by the chloride atom. Further identification may be done by mass spectrometry. The formation of **15** (anomeric mixture) showed that the intermediate **14** was prepared well though it was not separated during the reaction. In this reaction, primary alcohols tend to be chlorinated faster than secondary and tertiary alcohols. In our research group, the expected acyl azide compound was obtained when diacetone-D-glucose (2° alcohol) reacted with triphosgene and sodium azide under the same conditions. We think that **16** can possibly be formed under mild reaction conditions.

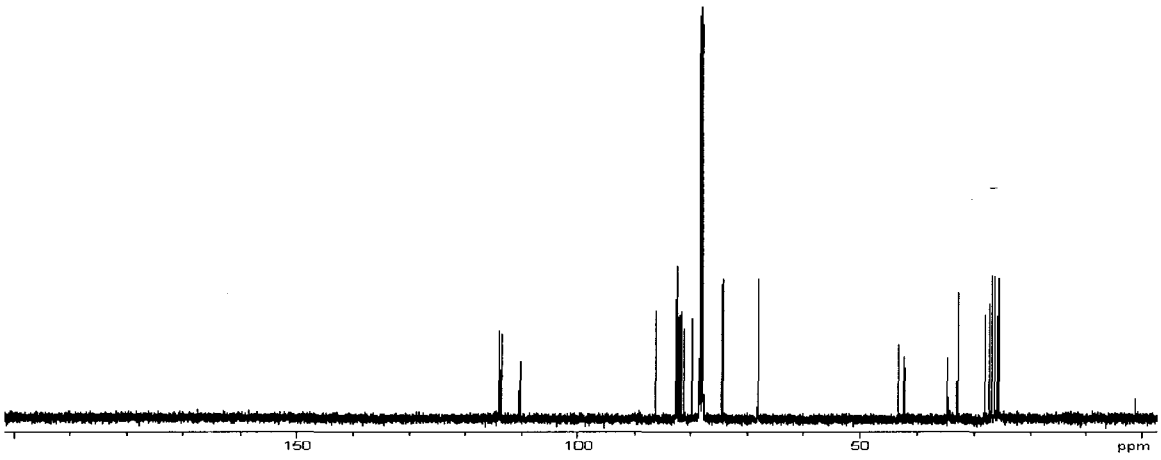


Figure **17**. ^{13}C NMR spectrum of **15**

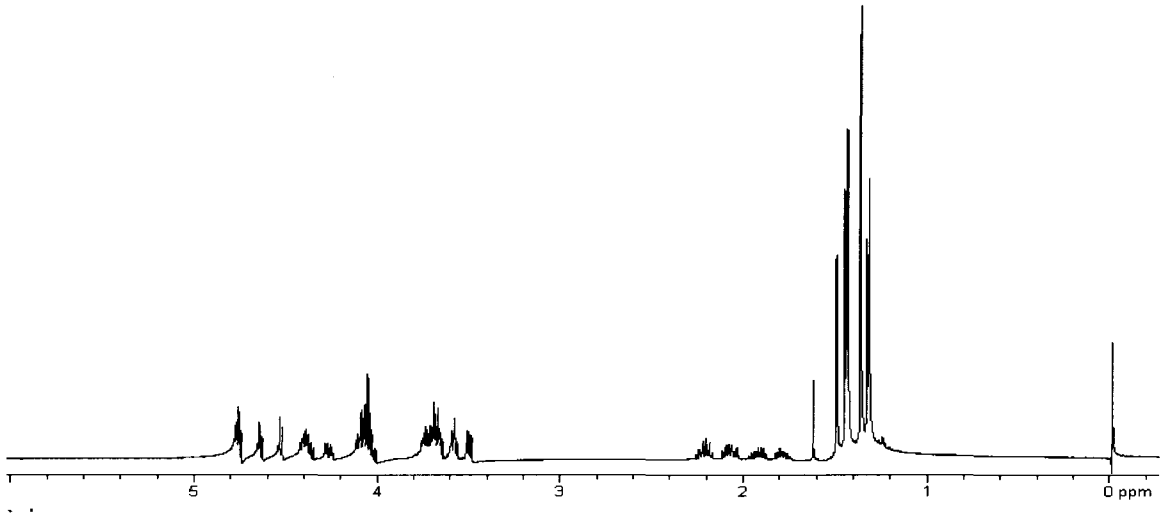


Figure **18**. ^{1}H NMR spectrum of **15**

3. Reaction of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose with oxalyl chloride.

The planned synthesis route to prepare sugar-derived acyl azide (**3**) has been shown in the introduction part (Scheme **3**). The initial thought was that the reaction should run smoothly to give an azide product as in earlier work in our research group. The fact is that the dimer **18** was formed easily as shown in scheme **10**. The ^{13}C NMR (Figure **19**) of the dimer shows one carbonyl signal at 156 ppm due to the symmetry.

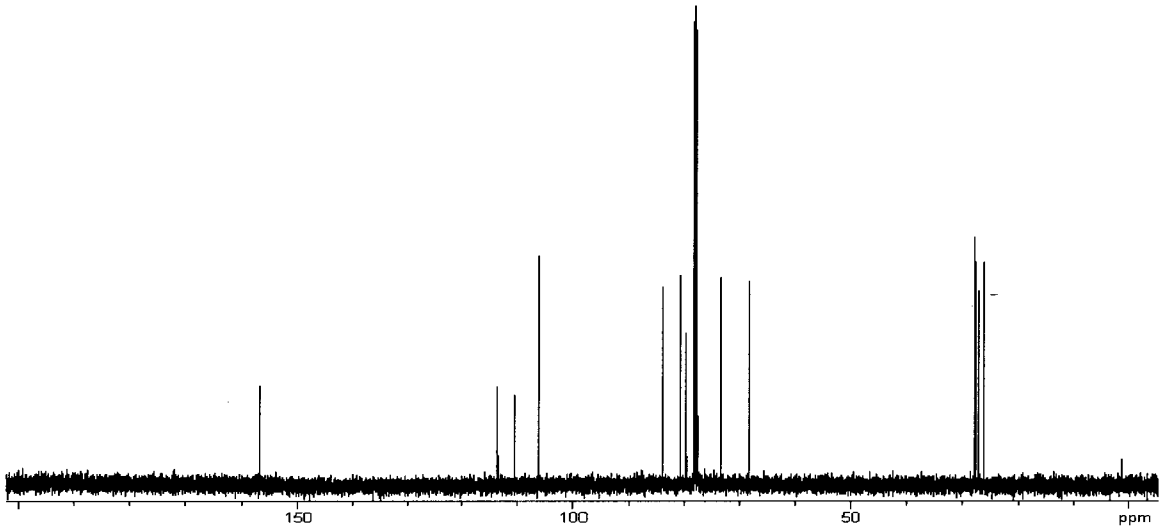
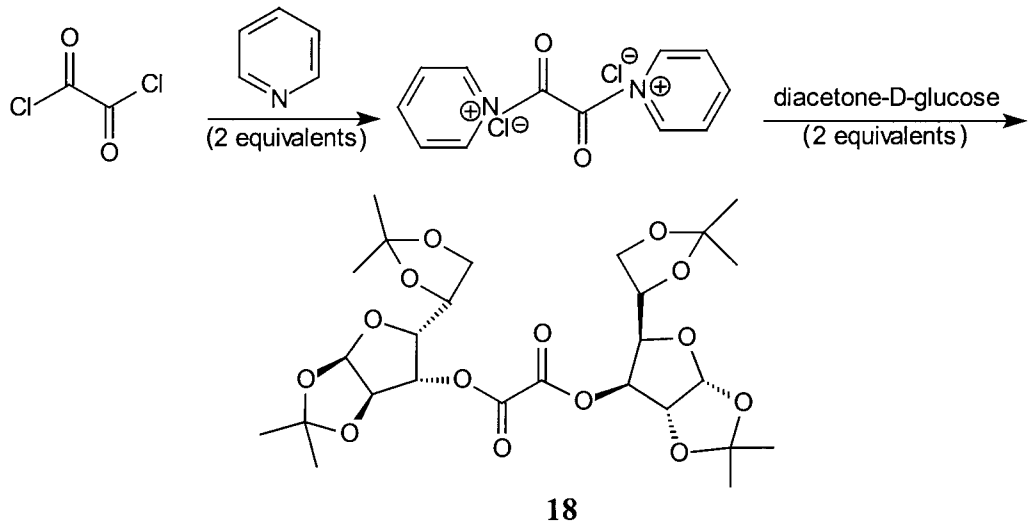


Figure **19**. ^{13}C NMR spectrum of the dimer (**18**)



18

Scheme **10.** The formation of the dimer

In order to possibly decrease the formation of the dimer, CH_2Cl_2 was used as solvent and diacetone D-glucose was added at –10°C (a:b:c = pyridine:oxalyl chloride:diacetone-D-glucose = 1.1:1.1:1) over 1.5 hours. Though TLC showed that the dimer was still formed, the amount was much less than when the sugar was added at room temperature. Continued experiment was performed by using the ratio of a:b:c = 1.1:2.2:1 at lower temperature and no dimer was formed. Adding sodium azide to this material to perform the next reaction gave no azide product. However, when trying to use a:b:c = 4.6:2.2:1, adding sugar at lower temperature, the dimer was formed again. It was confirmed by the result that 0.53 g of pure dimer was recovered as white solid by using 1.04 g (4 mmol) of diacetone-D-glucose, 0.8 ml (8.8 mmol) of oxalyl chloride and 1.51 ml (18.5 mmol) of pyridine. In this experiment, after the sugar disappeared (TLC monitor), the CH_2Cl_2 solution was washed with water (3×20 ml), dried with anhydrous sodium sulfate, evaporated to leave the pure dimer (0.53 g). The deficiency in quantity (1.04 - 0.53 = 0.51) indicated that water-soluble material was probably formed and was washed out by the water. The only possibility was the pyridinium salt of the sugar oxalate. This salt would react with sodium azide to form the expected compound **16**.

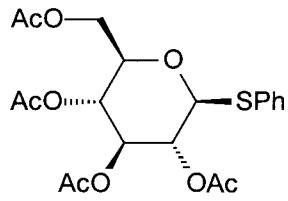
Why though was no dimer formed, and the expected reaction still not occur when little ratio of pyridine was used? Interested by the role of the pyridine in this reaction, an experiment was performed in which diacetone-D-glucose (2 mmol) in 15 ml of dichloromethane was added to the solution of oxalyl chloride (4.4 mmol) in CH_2Cl_2 (20 ml) over 2 hours at room temperature (no pyridine was used). A very polar and UV-active compound was formed and no dimer and starting sugar were observed on the TLC plates. This unidentified compound was also found in the reactions when a small ratio of pyridine was used and was thought to be the pyridinium salt as before. By summarizing the above results, we know the reason that no dimer was formed when using a small amount of pyridine was that most of the diacetone-D-glucose reacted to form this unidentified compound. In our research group, a similar reaction was performed by using the same sugar (diacetone D-glucose) reacted with triphosgene (release $COCl_2$ during the reaction) and no dimer was formed. The reason is that the phosgene molecule is too short to let two large sugar molecules close together. The formation of the dimer in the reaction of diacetone D-glucose with oxalyl chloride is maybe inevitable due to the high reactivity

and longer chain of the oxalyl chloride molecules, and it is not possible to completely avoid the formation of the dimer. Dry-ice acetone bath is also not necessary, but -10°C is preferred. A high ratio of pyridine to oxalyl chloride is necessary for the reaction to avoid the formation of the unidentified compound. Thus, a reaction with a:b:c = 4.6:2.2:1 was performed and the obtained mixture was reacted with sodium azide to furnish a pale brown syrup. TLC showed that it contained two compounds whose Rf values were very close. One is probably the dimer and the other was thought to be the expected product **16**. The IR of this crude product gave the azide absorption at ~2200 cm^{-1}. It is possible however that this signal may come from sodium azide which dissolved in the syrup. It has not been possible to cleanly separate this mixture. So, in the future, more extensive purification work (HPLC for example) should be done to get the pure product to do further characterization work.

EXPERIMENTAL SECTION

All melting points were taken with a Mel-Temp melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra and ^{13}C-NMR were recorded on a Varian Gemini 2000, 400MHz spectrometer. Proton shifts are reported in parts per million (ppm) on the δ scale. Multiplicities are reported as follows: s (singlet), d (doublet), q (quartet), m (multiplet). Carbon chemical shifts are reported in parts per million (ppm). Infrared spectra were taken on a Bio-Rad FTS-40 (FTIR). Solvents and reagents were dried prior to use when deemed necessary. Reactions requiring an inert atmosphere were conducted under a blanket of pre-purified argon. Analytical thin-layer chromatography was carried out on Whatman Flexible Plates. Column chromatography was performed on silica gel (70-270 mesh 60Å).

Preparation of phenyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (5)[9]

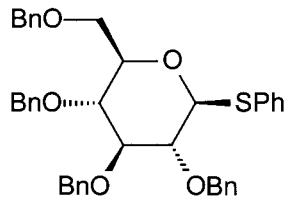


1,2,3,4,6-penta-*O*-acetyl-β-D-glucose (30 g, 0.0769 mol) and thiophenol (10.1 g, 0.0923 mol) were dissolved in chloroform (150 ml). Boron trifluoride diethyl etherate (54.6 g, 0.386 mol) was added. The solution was stirred overnight at room temperature, then washed with saturated sodium bicarbonate solution (2×30 ml) and water (2×30 ml), dried with anhydrous sodium sulfate, and vacuum evaporated to leave a pale yellow solid. Recrystallization with ethyl acetate/hexane furnished white crystals (23.6 g, yield 68.3%) with m.p 114-116°C (literature melting point 117-118°C).

^{1}H NMR: δ 2.00-2.20 (4 s, 12 H, acetyl), 3.70 (m, 1 H), 4.20 (m, 2 H),

4.70 (d, 1 H), 4.95 (t, 1 H), 5.05 (t, 1 H), 7.30-7.50 (m, 5 H).

Preparation of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (6)[10]

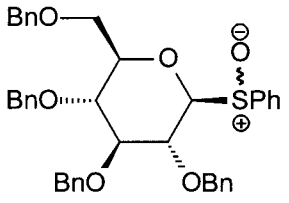


Phenyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (10 g, 0.0227 mol) was dissolved in methanol (300 ml) and a solution of sodium metal (0.6 g, 0.0261 mol) in methanol (50 ml) was added. The solution was stirred for two days at room temperature and the starting material disappeared (TLC). Dry ice was added to destroy the sodium methoxide. Evaporating the solvent left a white solid, which contained phenyl 1-thio-β-D-glucopyranoside (theoretical yield 6.2 g, 0.0227 mol). To a 250 ml round bottomed flask equipped with mechanical stirrer and reflux condenser was added the above white solid and dry N,N-dimethylformamide (75 ml). Sodium hydride (4.7 g, 60%) was added in portions and the mixture was stirred for 15 minutes. Benzyl bromide (14 ml, 0.118 mol) was added and the mixture was held at 120-130°C for 2 hours, then it was poured on to ice (60 g). Ethanol (100 ml) was added while stirring. The precipitate was recrystallized with ethanol to give white crystals (11.2 g, yield 78.3%) with m.p 89-91°C (literature melting point 84-86°C).

^{1}H NMR: δ 3.45-3.55 (t, 2 H), 3.60-3.81 (m, 4 H), 4.56-4.97 (m, 9 H),

7.19-7.41 (m, 23 H), 7.58- 7.62 (m, 2 H).

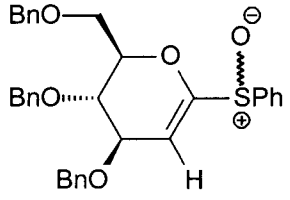
Preparation of phenyl 2,3,4,6-tetra-*O*-benzyl-1-sulfoxide-β-D-glucopyranoside (7)[11]



Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (0.316 g, 0.5 mmol), dichloromethane (2.5 ml), acetic anhydride (0.052 ml) and silica gel (0.1 g, 230-400 mesh) were added to a 25 ml round bottomed flask equipped with magnetic stirrer. Hydrogen peroxide (0.068 ml, 30% water solution) was added in one portion at room temperature while stirring. After starting material had disappeared (TLC, about 4 hours), 10 ml of dichloromethane was added and the mixture was suction filtered to remove the silica. The filtrate was washed with saturated aqueous sodium sulfite (25 ml), saturated sodium bicarbonate (25 ml) and brine (25 ml), and dried with anhydrous sodium sulfate. Evaporation left a syrup and addition ethanol gave a white powder (0.253 g, yield 82%) with m.p 97-106°C (literature melting point 120-122°C).

^{1}H NMR: δ 3.30-3.35 (m), 3.50-3.62 (m), 3.75-3.85 (m), 3.96-4.00 (d), 4.09-4.15 (t), 4.20-4.35 (q), 4.45-4.52 (t), 4.56-4.60 (q), 4.75-4.86 (m), 4.92-5.05 (m), 7.15-7.50 (m, 23 H), 7.60-7.70 (m, 2 H).

Preparation of 1-phenyl sulfinyl glucals (8)[13]

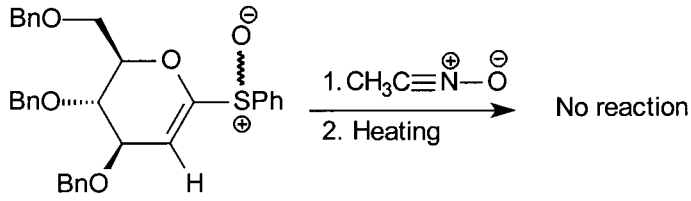


Under an argon atmosphere, a solution of diisopropyl amine (1.12 ml, 8 mmol) in dry tetrahydrofuran (20 ml) was cooled to –78°C by a dry ice-acetone bath. *N*-Butyl lithium was added dropwise *via* syringe to the stirred mixture. The mixture was allowed to stir 15 minutes at about –78°C, then a solution of phenyl 2,3,4,6-tetra-*O*-benzyl-1-sulfoxide-β-D-glucopyranoside (4.0 g, 6.2 mmol, m.p 97-106°C) in dry THF (15 ml) was added *via* syringe. The reaction was stirred overnight at room temperature and was stopped by adding saturated ammonium chloride (20 ml). The solution was extracted with dichloromethane (3×50 ml). The organic extracts were washed with water (1×50 ml), dried with anhydrous sodium sulfate and evaporated to leave a syrup (3.8 g) which was

purified by flash chromatography (silica, hexane / ethyl acetate 3:1) to furnish a pale gray solid (1.14 g, yield 36.4%).

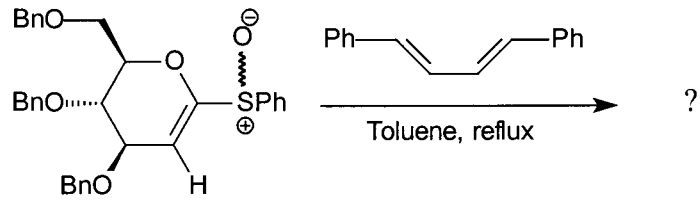
^{1}H NMR: δ 3.50-3.60 (m), 3.62-3.68 (m), 3.75-3.85 (m), 3.90-3.95 (m), 4.15-4.30 (m), 4.55-4.65 (m), 4.70-4.80 (m), 5.90-5.95 (2d, 1 H), 7.10-7.50 (m, 18 H), 7.70-7.80 (m, 2 H).

Attempted reaction of vinyl sulfoxide (8) with nitrile oxide



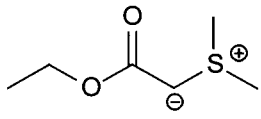
N-Chlorosuccinimide (19.76 mg, 0.148 mmol) and a drop of pyridine were added to a 25 ml round bottomed flask containing dry chloroform (0.5 ml). Acetaldoxime (0.01 ml, 0.148 mmol) was added at 25°C in one portion. Once the NCS disappeared in the solution, the 1-phenyl sulfinyl glucal (**8**) (0.1 g, 0.185 mmol) was added and the temperature was raised to 40-50°C. A solution of triethylamine (0.02 ml, 0.155 mmol) in chloroform (0.03 ml) was added over 30 minutes. The mixture was stirred at 40-50°C for 1 hour. Chloroform (15 ml) was added and the solution was washed with water (2×10 ml), dried with anhydrous Na_2SO_4, and evaporated to leave a syrup (0.11 g). This was purified by flash chromatography (silica, hexane / ethyl acetate 3:1) to furnish a compound (0.09 g) which was identified by ^{1}H NMR as the starting material.

Attempted reaction of phenyl vinyl sulfoxide (8) with *trans, trans*-1,4-diphenyl-1,3-butadiene



0.1 g (0.185 mmol) of 1-phenyl sulfinyl glucal (**8**) and 0.076 g (0.37 mmol) of *trans, trans*-1,4-diphenyl-1,3-butadiene were added in 0.8 ml of toluene and refluxed for five days. A black solution was obtained. The solvent was evaporated and the residue was subjected to flash chromatography (silica, hexane / ethyl acetate 5:1). There was no starting material recovered and no pure compound could be separated.

Preparation of ethyl (dimethyl sulfuranylidene) acetate (EDSA)[12]



A solution of (ethoxycarbonylmethyl)dimethyl sulfonium bromide (2.56 g, 0.0108 mol) in chloroform (10 ml) was cooled to 5-10°C. While stirring vigorously, a mixture of saturated aqueous potassium carbonate (6.5 ml) and sodium hydroxide (12.5N, 0.9 ml) was added in one portion. The reaction mixture was warmed to 15-20°C and stirred for 15 minutes. The salts were removed by suction filter and the filtrate was dried for 2 hours over anhydrous potassium carbonate, and then vacuum evaporated to leave a pale yellow syrup (1.5 g, yield 80%).

^{1}H NMR: δ 1.20 (t, 3 H), 2.70-2.80 (s, 7 H), 3.90 (q, 2 H).

Reaction of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose with EDSA

2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (0.6 g, 0.0023 mol) was dissolved in toluene and the temperature was raised to 65°C. A solution of EDSA (1.16g, 0.0067mol) in toluene (5 ml) was added. The solution was stirred at 80-85°C for three days. Evaporating the solvent left a yellow syrup (1.16 g) which was purified by flash chromatography (silica, hexane / ethyl acetate 3:1) to furnish compound **10** (0.2 g), compound **11** (0.12 g), and a mixture of **10** and **11** (0.28g).

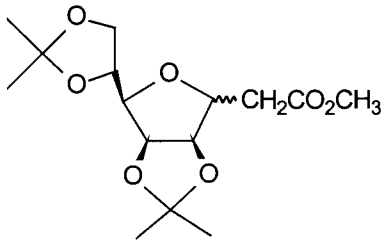
Compound **10**: IR: 3500 cm^{-1} (strong, broad), 1740 cm^{-1} (strong), 1060 cm^{-1} (strong).

^{1}H NMR: δ 1.20-1.60 (m, 15 H), 3.40-3.50 (2 d), 3.54-3.58 (q), 3.60-3.68 (m), 3.76-3.82 (t), 3.90-3.94 (t), 4.00-4.30 (m), 4.44-4.54 (m).

Compound **11**: IR: 1740 cm^{-1} (strong), 1680 cm^{-1}.

^{1}H NMR: δ 1.18-1.54 (m, 15 H), 3.40-3.46 (2 d), 3.52-3.56 (q), 3.60-3.68 (m), 3.76-3.82 (t), 3.90-3.94 (t), 3.98-4.30 (m), 4.42-4.50 (m), 5.40 (s), 5.72-5.78 (q).

Preparation of esters (12)[14]

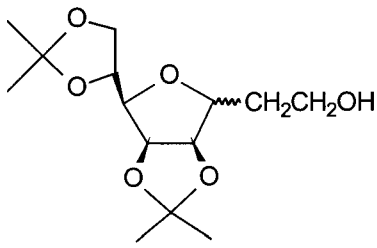


2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (1.15 g, 4.42 mmol), methyl (triphenyl-phosphoranylidene) acetate (3.12 g, 9.14 mmol) and acetonitrile (12 ml) were added to a 25 ml round bottomed flask and refluxed overnight while stirring. Evaporating the solution left a syrup which was combined with the crude product from a previous experiment using 0.26 g of material. Flash chromatography (silica, hexane / ethyl acetate 2:1) furnished the product as a colorless syrup (1.7 g, yield 98.3%).

^{1}H NMR: δ 1.30-1.50 (m, 12 H), 2.42-2.56 (m, 2 H), 2.68-2.84 (m, 2 H), 3.46-3.54 (m), 3.76-3.80 (m), 3.90-3.94 (m), 3.98-4.14 (m), 4.34-4.40 (m), 4.44-4.50 (t), 4.60-4.62 (d), 4.72-4.80 (m).

^{13}C NMR: δ 26.0, 26.5, 27.0, 27.5, 28.5, 32.0, 34.0, 68.0, 74.2, 74.5, 78.0, 78.2, 78.6, 79.0, 82.0, 83.0, 86.0, 110.0, 110.2, 113.5, 114.0, 171.5, 172.2.

Preparation of anomeric alcohols (13)

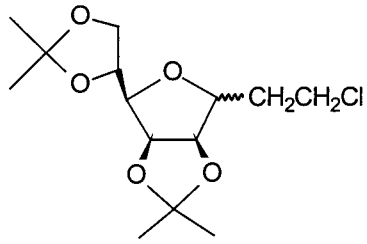


Under an argon atmosphere, **12** (1.65 g, 5.18 mmol) was dissolved in dry THF (8 ml) and cooled with an ice bath. While stirring, $LiAlH_4$ (5.22 ml, 1.0M THF solution) was added dropwise. The mixture was kept stirring at room temperature for 3 hours. Saturated aqueous Na_2SO_4 (0.4 ml) was added dropwise while cooling with an ice bath. The thick mixture was diluted with dichloromethane (30 ml). The salts were easily removed by suction filter and the dichloromethane solution was separated from the filtrate. The aqueous layer was extracted with dichloromethane (2×5 ml). The combined CH_2Cl_2 solution was dried (anhydrous Na_2SO_4) and evaporated to furnish a pure product as colorless syrup (1.5 g, yield 100%).

^{1}H NMR: δ 1.30-1.44 (3 s, 9 H), 1.46-1.50 (d, 3 H), 1.56-1.64 (m), 1.70-1.80 (m), 1.84-2.10 (m), 3.50-3.54 (q, 2 H), 3.66-3.88 (m), 3.98-4.12 (m), 4.26-4.30 (m), 4.36-4.42 (m), 4.54-4.56 (q), 4.64-4.68 (m), 4.74-4.80 (m).

^{13}C NMR: δ 26.0, 27.0, 27.5, 28.5, 32.0, 34.0, 62.0, 68.0, 74.0, 74.5, 78.0, 78.5, 79.0, 81.5, 82.0, 83.0, 84.5, 86.5, 110.0, 113.5, 114.0.

The reaction of 13 with Triphosgene



15

A. Pyridine (3 ml, 37.2 mmol) was added dropwise to a solution of triphosgene (1.84 g, 6.2 mmol) in CH_2Cl_2 (20 ml) while stirring. The mixture was stirred at room temperature for 10 minutes, then cooled with a dry ice-acetone bath. A solution of **13** (0.6 g, 2.07 mmol) in CH_2Cl_2 (10 ml) was added over 2 hours. The mixture was evaporated and the residue was suspended in 1,4-dioxane (20 ml). Sodium azide (1.38 g, 20.7 mmol) was added and the mixture refluxed 3 hours. The mixture was held at 60-65°C overnight, suction filtered to remove the salts and evaporated to leave a syrup. Purification with flash chromatography (silica, hexane / ethyl acetate 3:1) furnished a colorless syrup (**15,** 0.52 g, yield 81.4%).

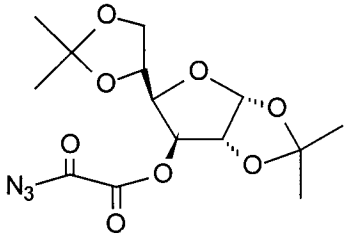
IR: 750 cm^{-1} (strong).

^1H NMR: δ 1.28-1.50 (m, 12 H), 1.74-2.28 (m, 2 H), 3.46-3.54 (m, 2 H), 3.56-3.60 (m), 3.66-3.78 (m), 4.00-4.14 (m), 4.26-4.30 (m), 4.34-4.42 (m), 4.50-4.58 (q), 4.62-4.68 (m), 4.72-4.80 (m).

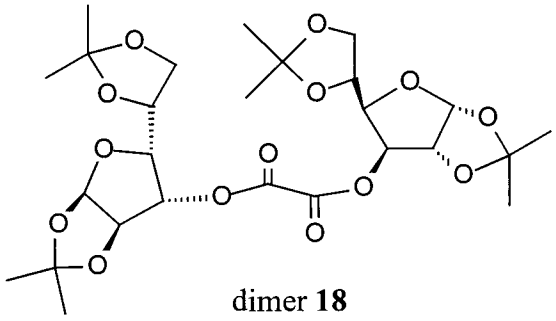
^{13}C NMR: δ 25.9, 26.0, 26.4, 26.5, 27.0, 27.5, 28.5, 33.0, 34.5, 42.0, 43.0, 68.0, 68.2, 74.0, 74.5, 77.5, 78.0, 78.5, 79.5, 81.0, 81.8, 82.0, 82.5, 82.6, 82.8, 86.5, 110.0, 110.5, 113.5, 114.0.

B. Pyridine (1.0 ml, 12.4 mmol) was added to a solution of triphosgene (0.61 g, 2.07 mmol) in CH_2Cl_2 (10 ml) at room temperature while stirring. After 10 minutes, a solution of **13** (0.2 g, 0.69 mmol) in CH_2Cl_2 (10 ml) was added over 40 minutes while cooling with a dry ice-acetone bath. After TLC showed no starting material left, the mixture was evaporated and the residue was suspended in 1,4-dioxane (10 ml) and held at 85-90°C overnight to furnish the same product (**15**) in experiment A.

Attempted preparation of 3, formation of dimer 18



3



dimer **18**

A. Pyridine (0.36 ml, 4.4 mmol) was added to a solution of oxalyl chloride (0.2 ml, 2.2 mmol) in dry 1,4-dioxane (5 ml) and stirred at room temperature for 10 minutes. A solution of diacetone- D-glucose (0.52 g, 2 mmol) in 1,4-dioxane (8 ml) was added dropwise at room temperature. After the starting material disappeared (TLC), sodium azide (0.65 g, 10 mmol) was added and the mixture was stirred for 2 days. The reaction was diluted with water (50 ml) and extracted with CH_2Cl_2 (3×20 ml), dried with anhydrous Na_2SO_4, and evaporated to leave a pale yellow syrup (0.59 g) which was identified as dimer **18**.

^{1}H NMR: δ 1.26-1.56 (4 s, 24 H), 4.00-4.14 (m), 4.22-4.28 (s), 4.56-4.60 (d), 5,40 (s), 5.90 (d).

^{13}C NMR: δ 26.5, 27.5, 28.0, 28.2, 68.5, 73.5, 78.0, 78.2, 78.5, 80.0, 81.0, 84.0, 106.0, 110.5, 114.0, 157.0.

B. To a 50 ml round bottomed flask which contained oxalyl chloride (0.4 ml, 4.4 mmol) and 1,4-dioxane (20 ml) was added a solution of diacetone D-glucose (0.52 g, 2 mmol) over 3 hours at room temperature. A very polar, UV-active compound was formed but which could not be characterized. TLC showed no starting material left and no dimer formed.

C. Pyridine (1.51 ml, 18.5 mmol) was added dropwise to a solution of oxalyl chloride (0.8 ml, 8.8 mmol) in CH_2Cl_2 (40 ml) at room temperature. The mixture was cooled with a dry ice-acetone bath and a solution of diacetone D-glucose (1.04 g, 4 mmol) in CH_2Cl_2 (20 ml) was added over one hour. After the starting material had disappeared (TLC), the solvent was evaporated and the remainder was suspended in 1,4-dioxane (25 ml). The mixture was stirred at 80-85°C overnight, suction filtered to remove the salts, and evaporated to leave a pale brown syrup (1.8 g). IR showed the absorption of azide at 2200cm^{-1}. Isolation of a pure compound was not possible at this point.

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APPENDIX OF NMR SPECTRA

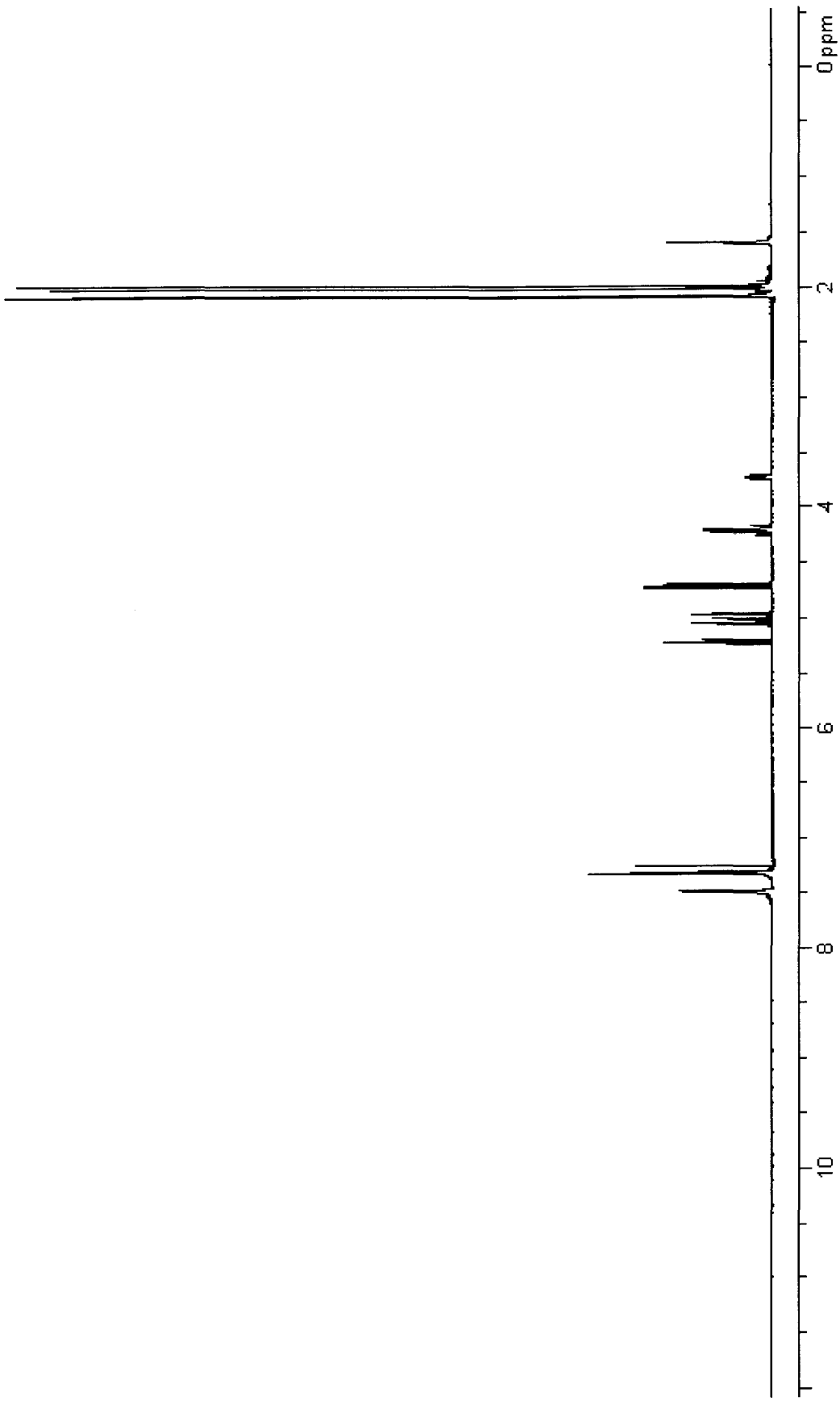

Figure **20**. ^{1}H NMR spectrum of compound **5**

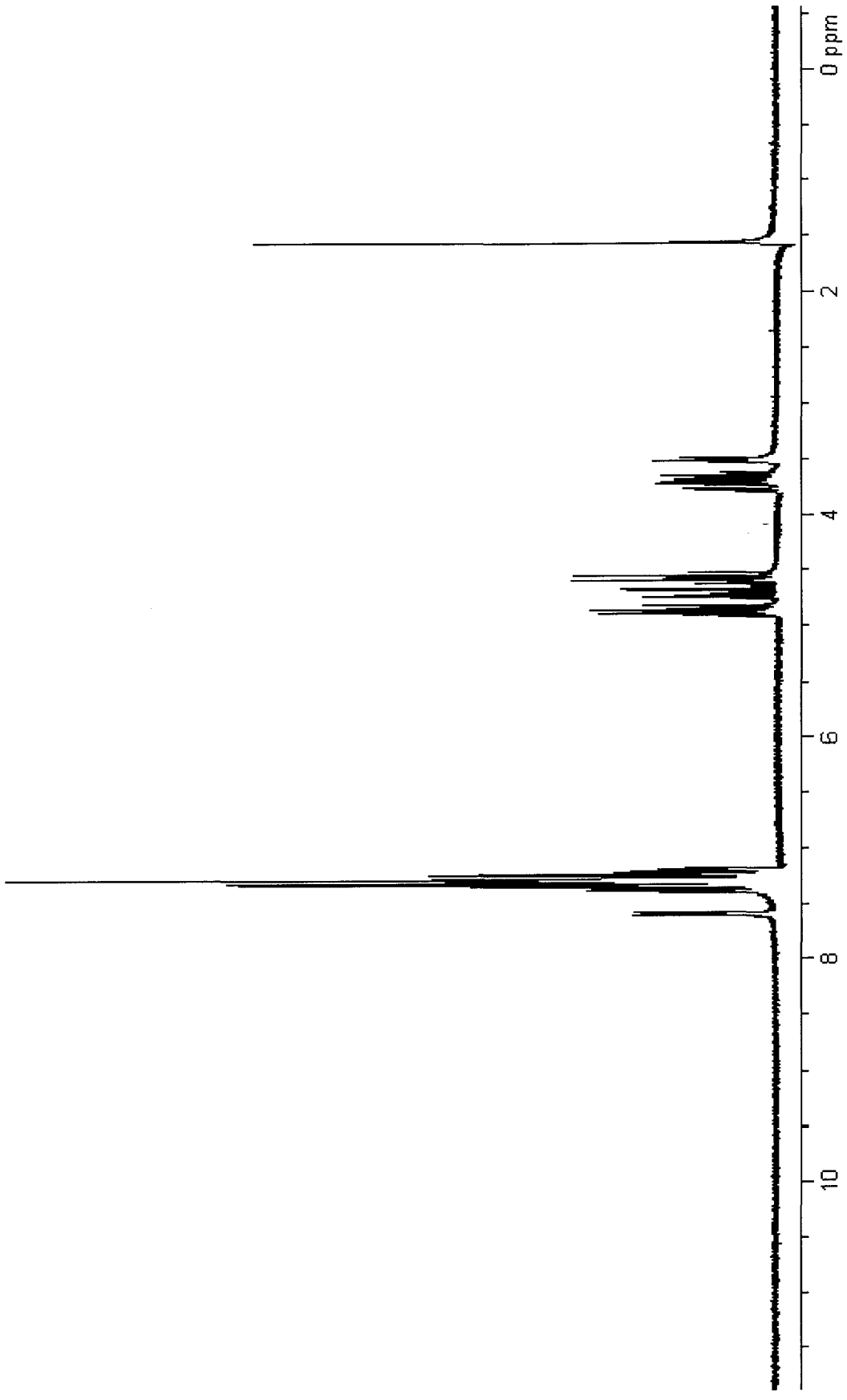

Figure **21**. ^{1}H NMR spectrum of compound **6**

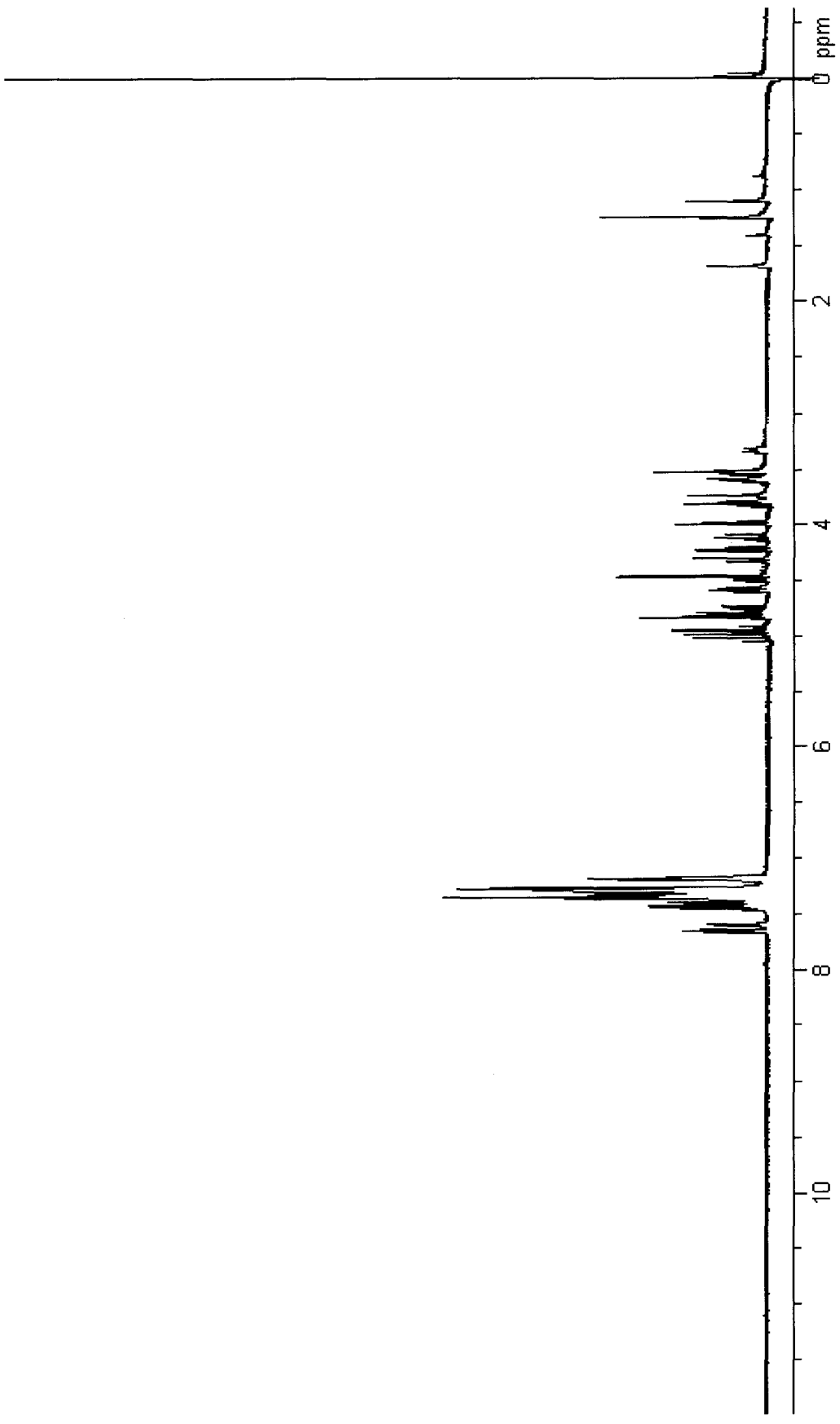

Figure **22**. ^{1}H NMR spectrum of compound **7**

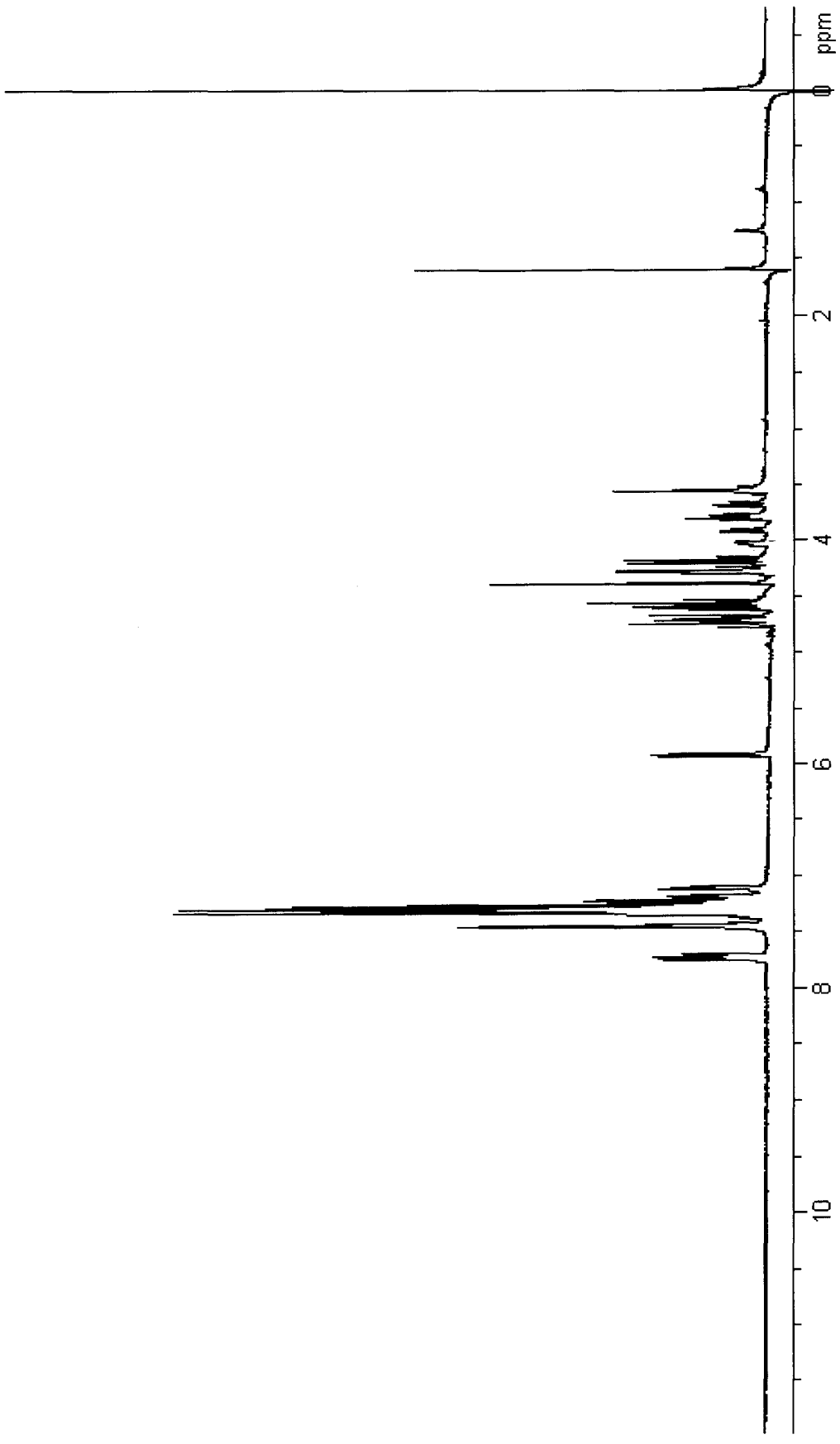

Figure **23**. ^{1}H NMR spectrum of compound **8**

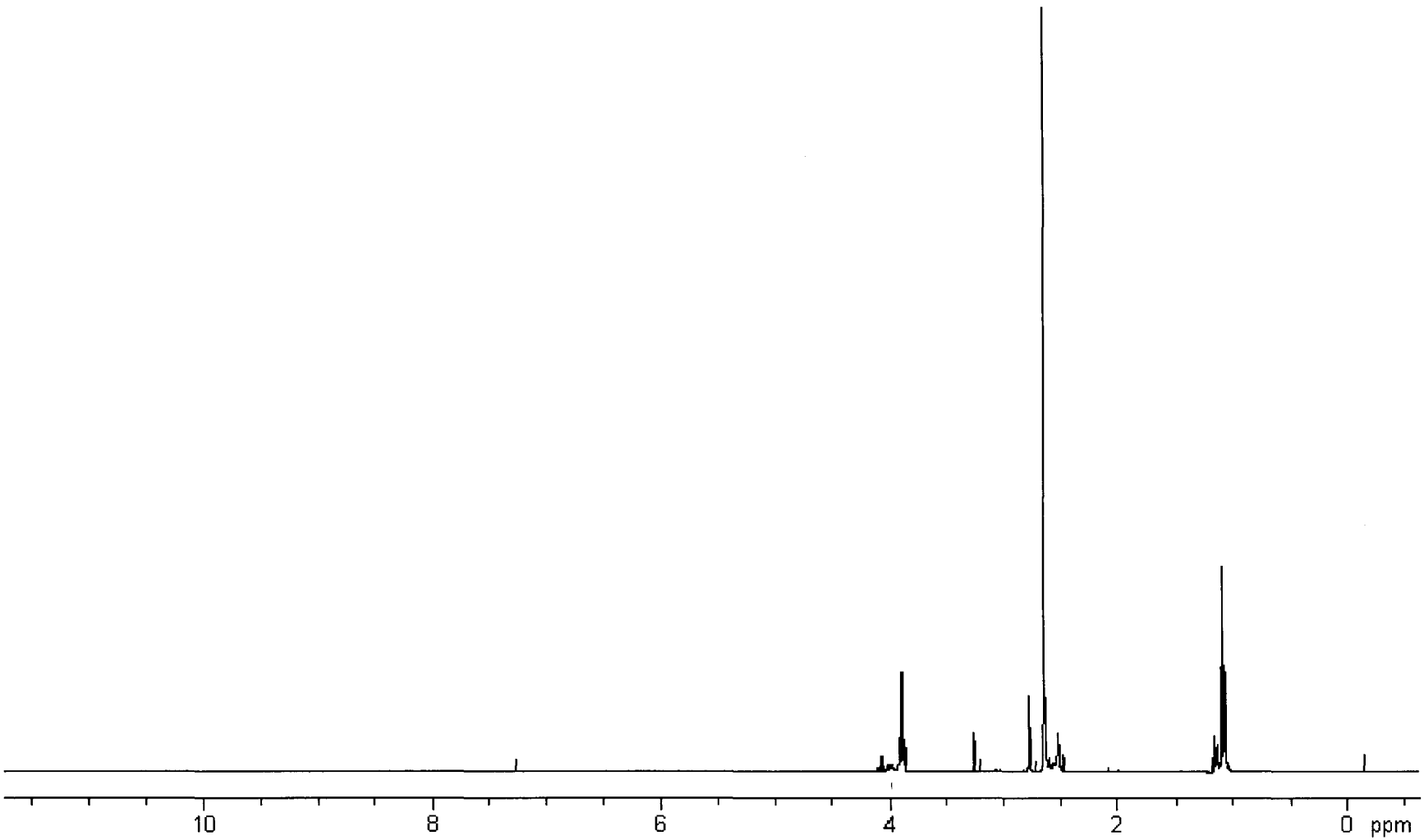

Figure **24**. ^{1}H NMR spectrum of ethyl(dimethyl sulfuranylidene) acetate (EDSA)

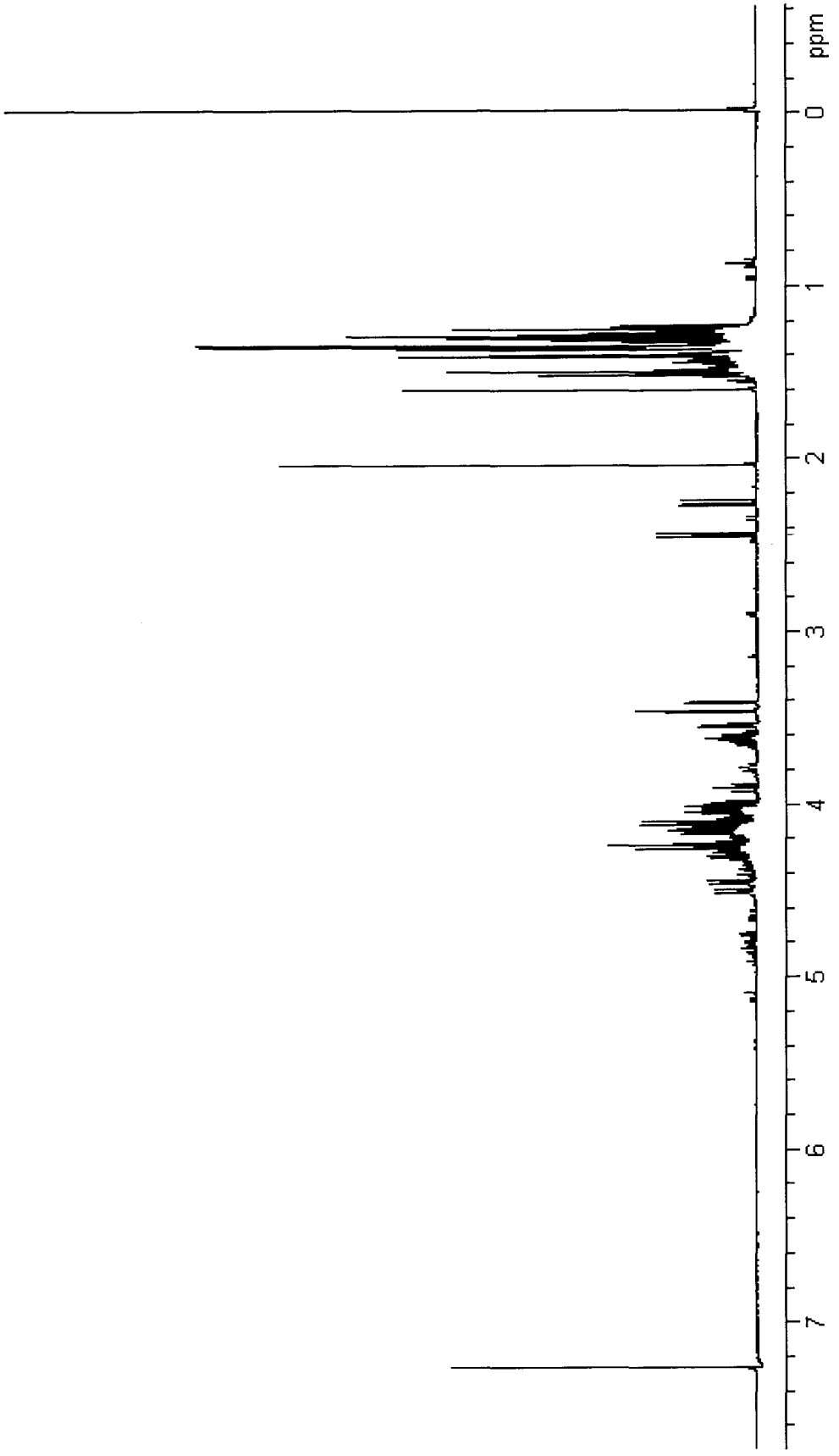

Figure **25**. ^{1}H NMR spectrum of compound **10**

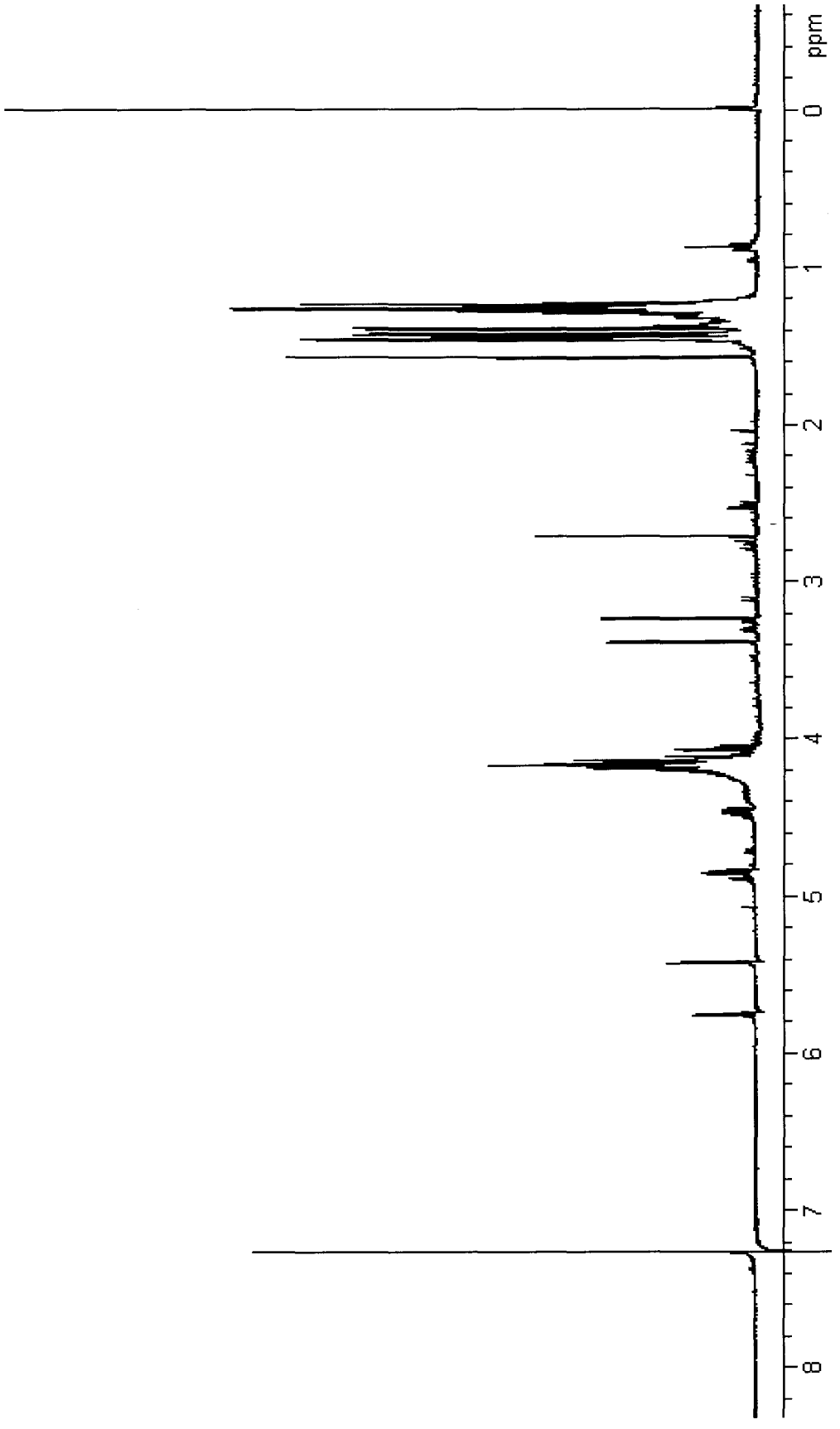

Figure **26**. ^{1}H NMR spectrum of compound **11**

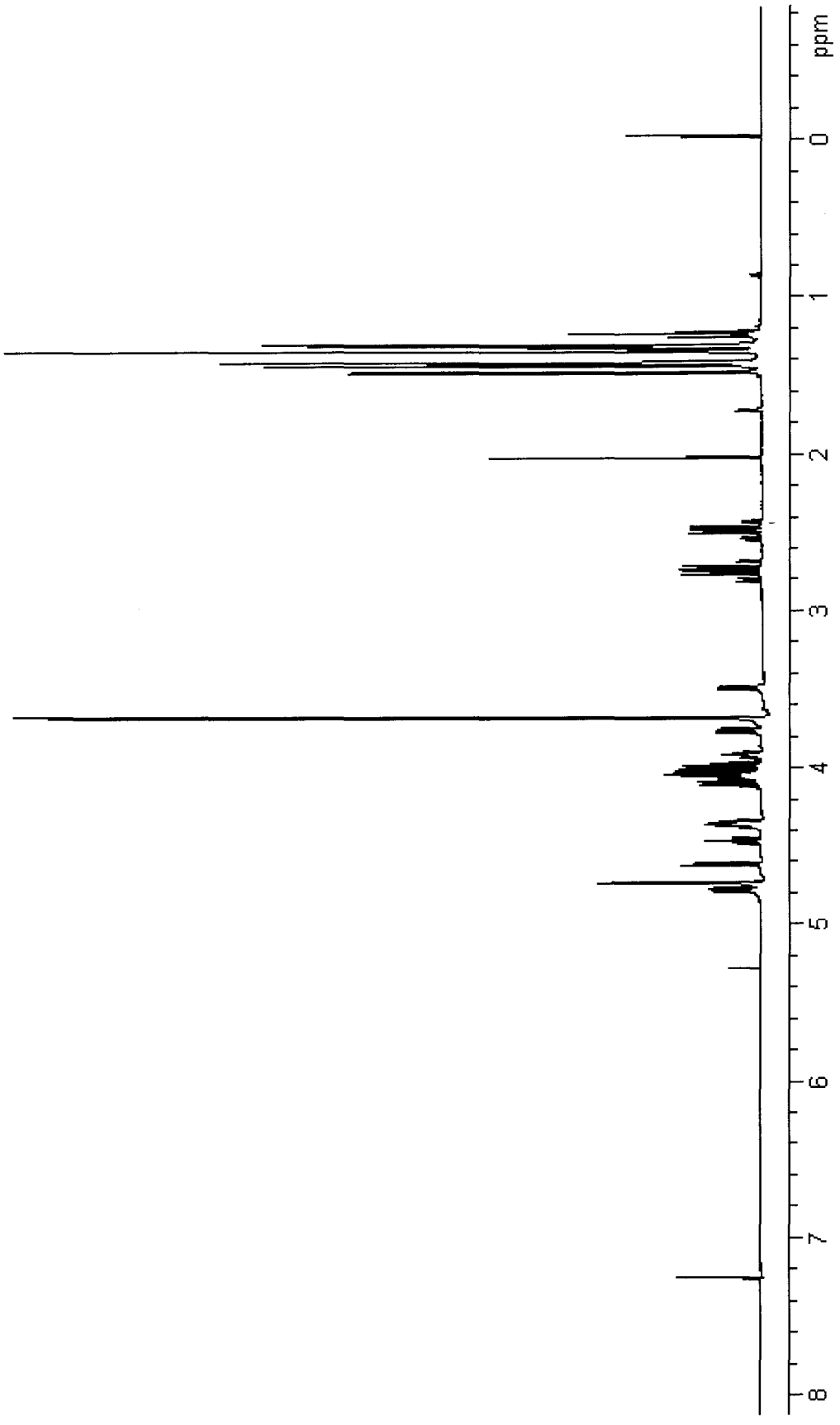

Figure **27**. ^{1}H NMR spectrum of compound**12**

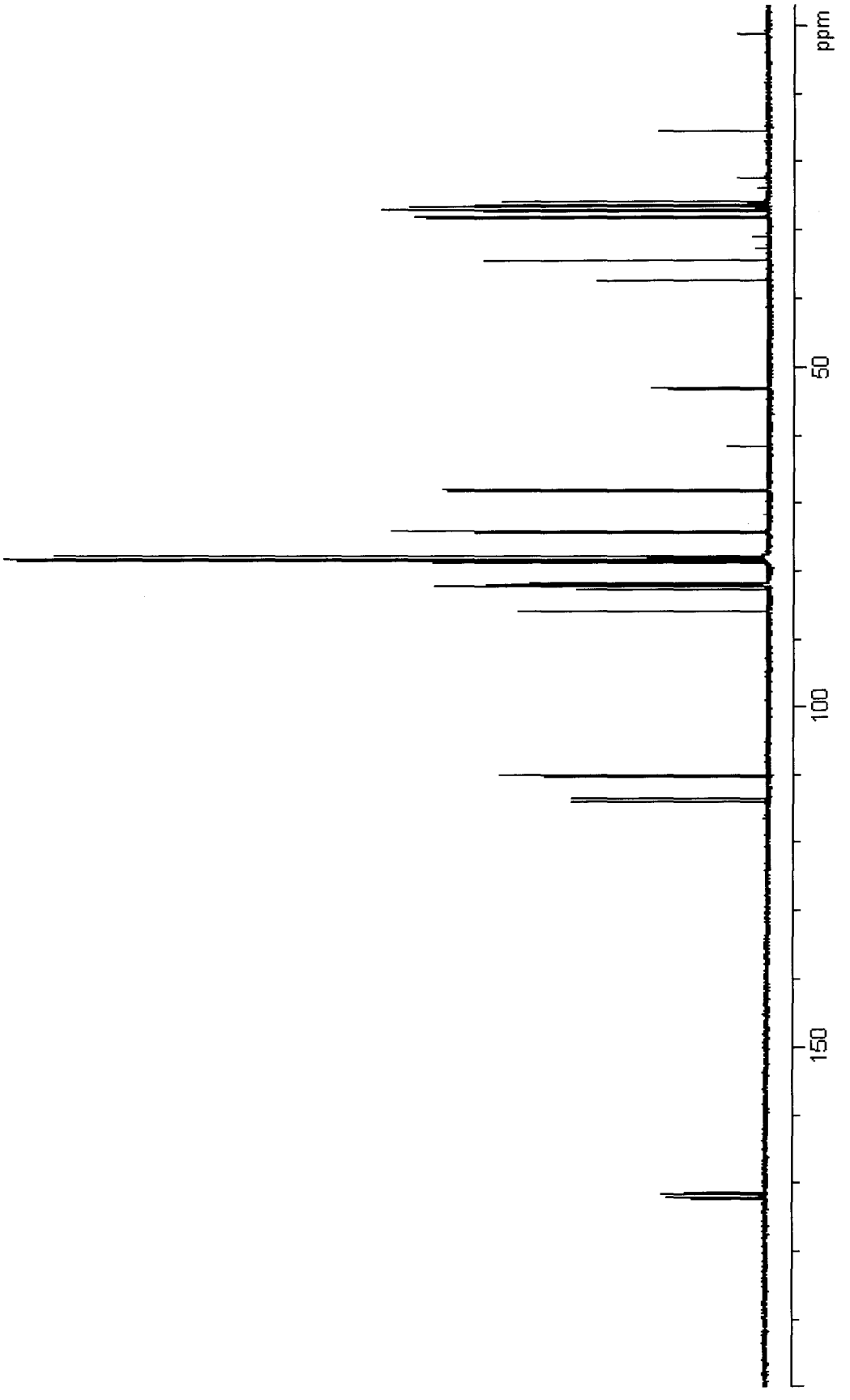

Figure **28**. ^{13}C NMR spectrum of compound **12**

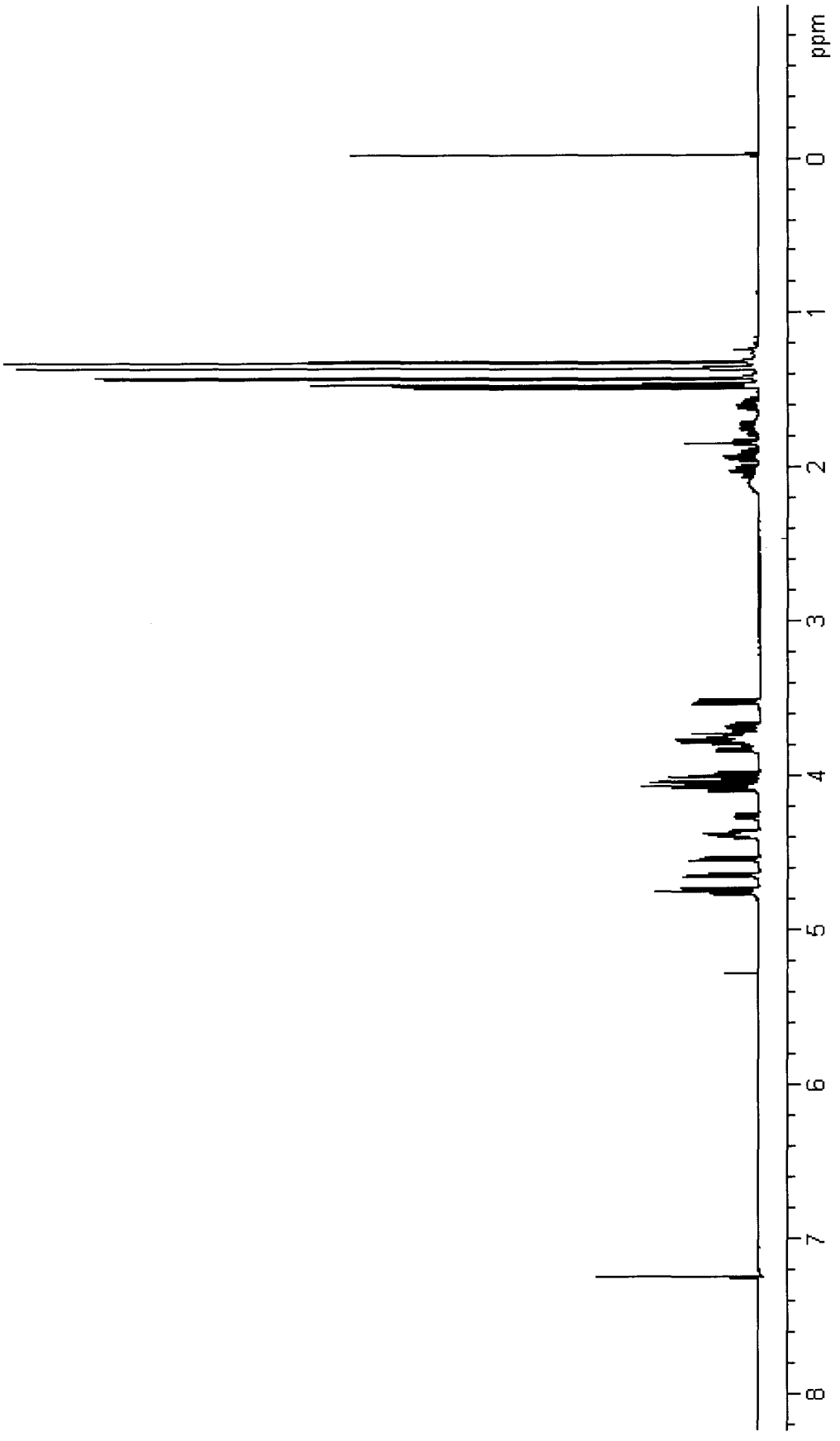

Figure **29**. ^{1}H NMR spectrum of compound **13**

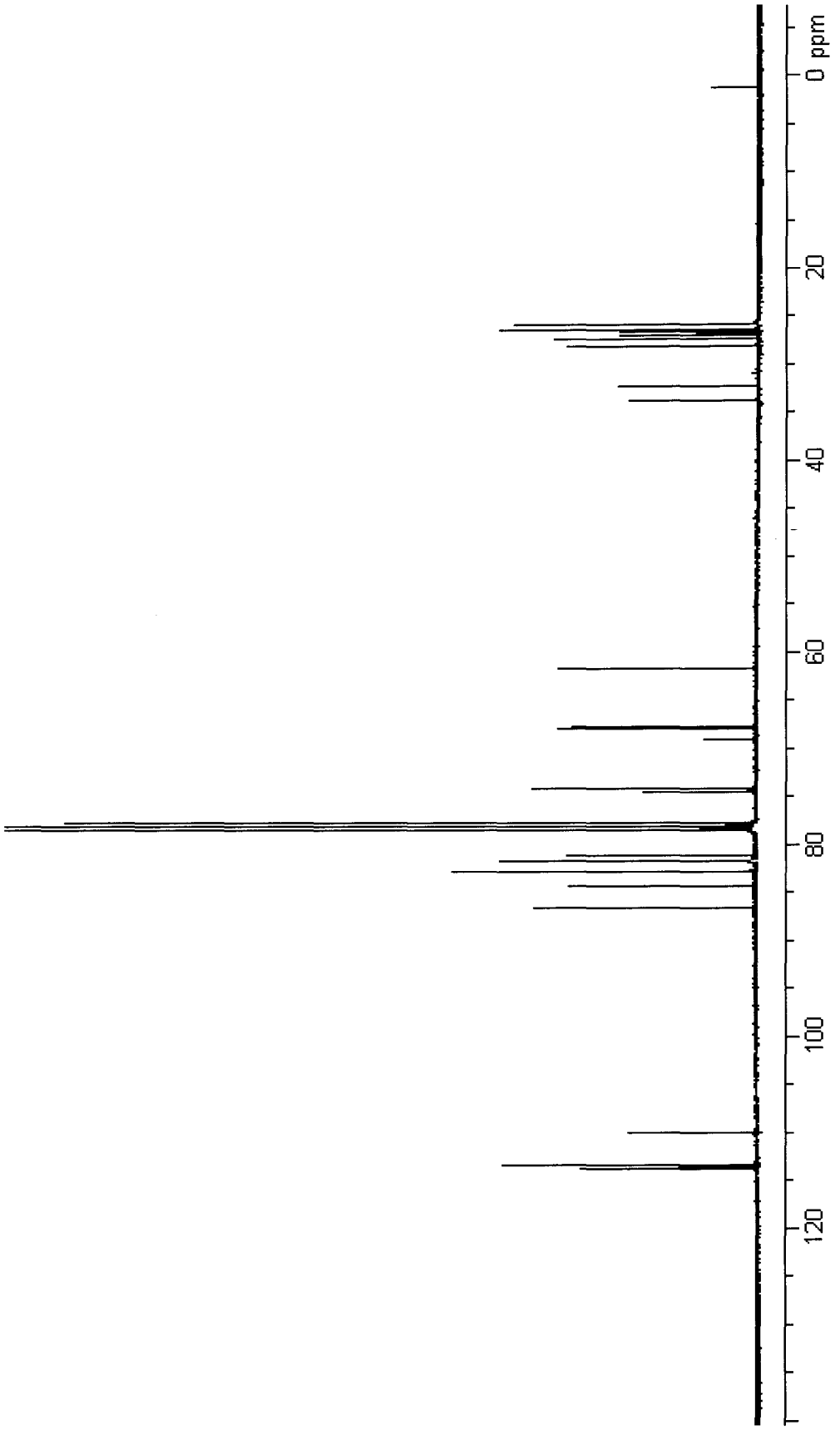

Figure **30**. ^{13}C NMR spectrum of compound **13**

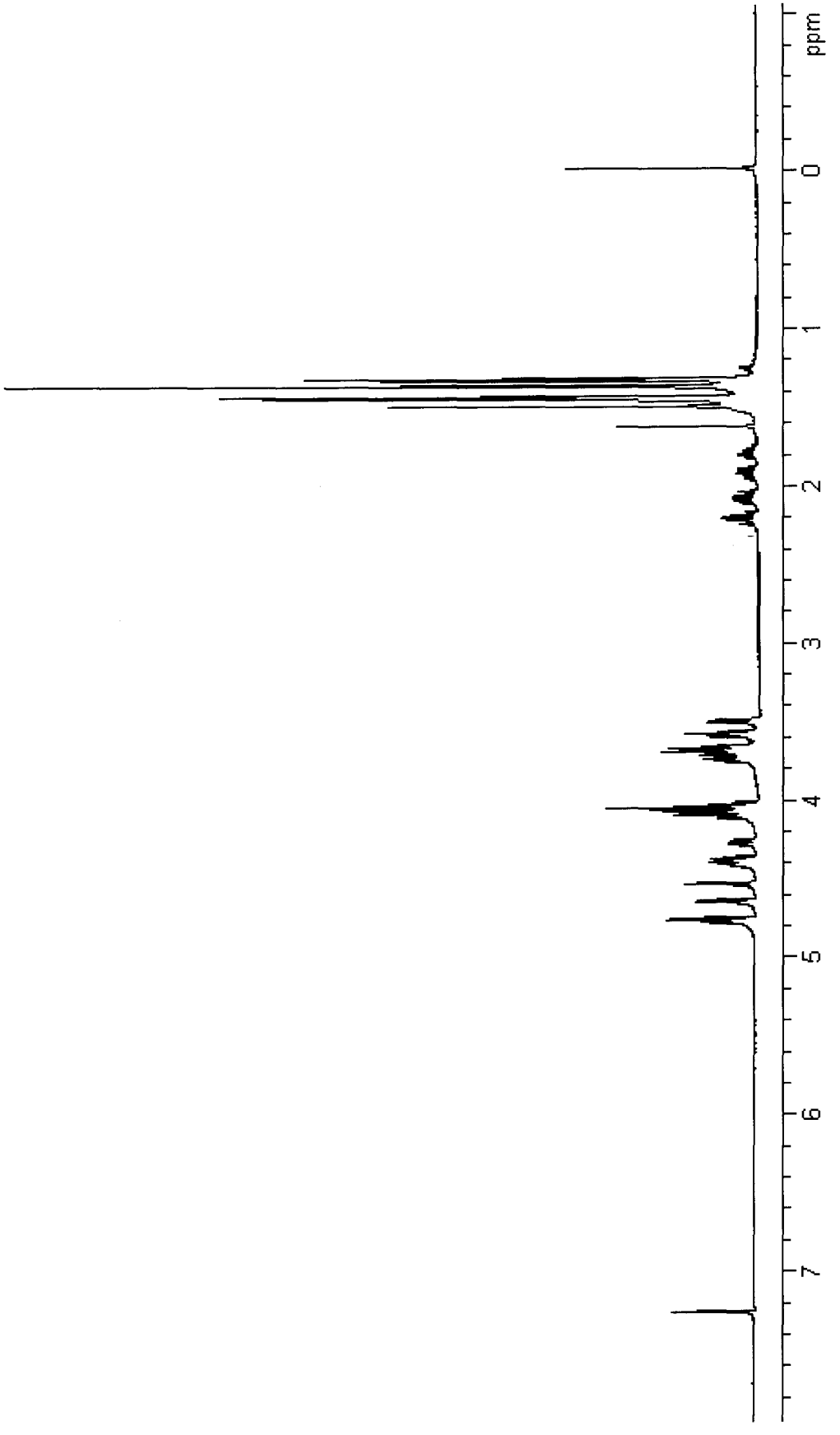

Figure **31**. ^{1}H NMR spectrum of compound **15**

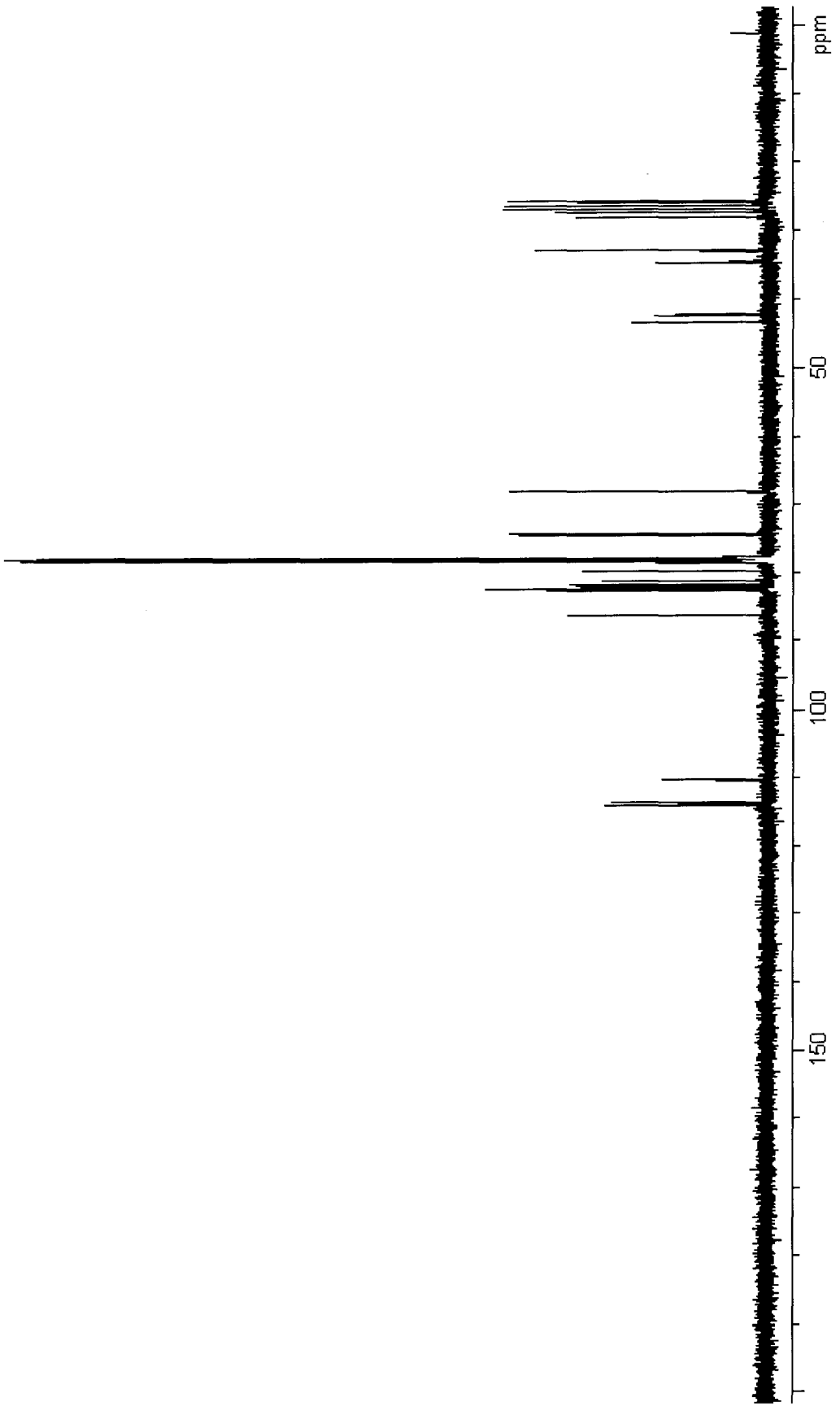

Figure **32**. ^{13}C NMR spectrum of compound **15**

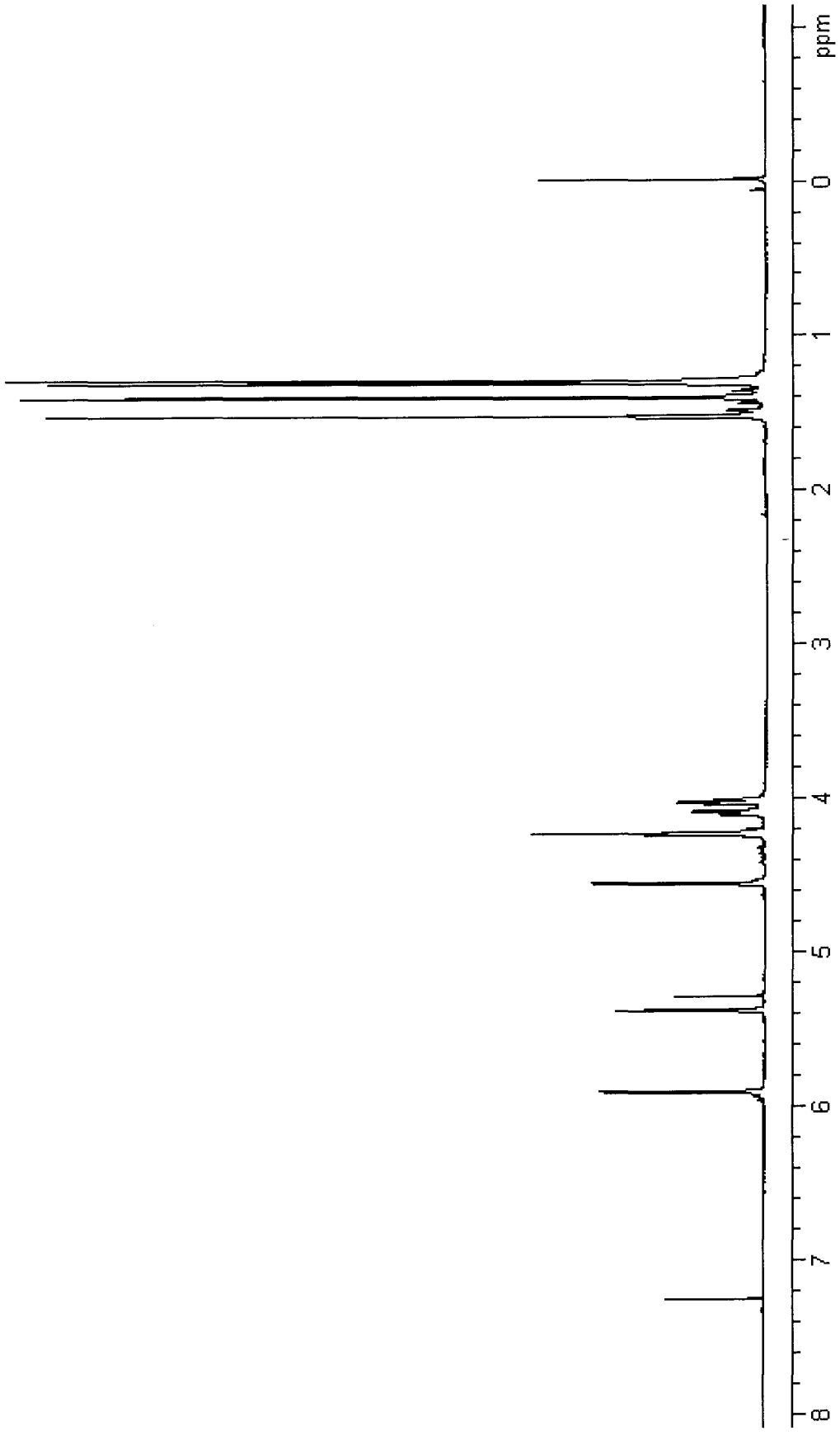

Figure **33**. ^{1}H NMR spectrum of compound **18**

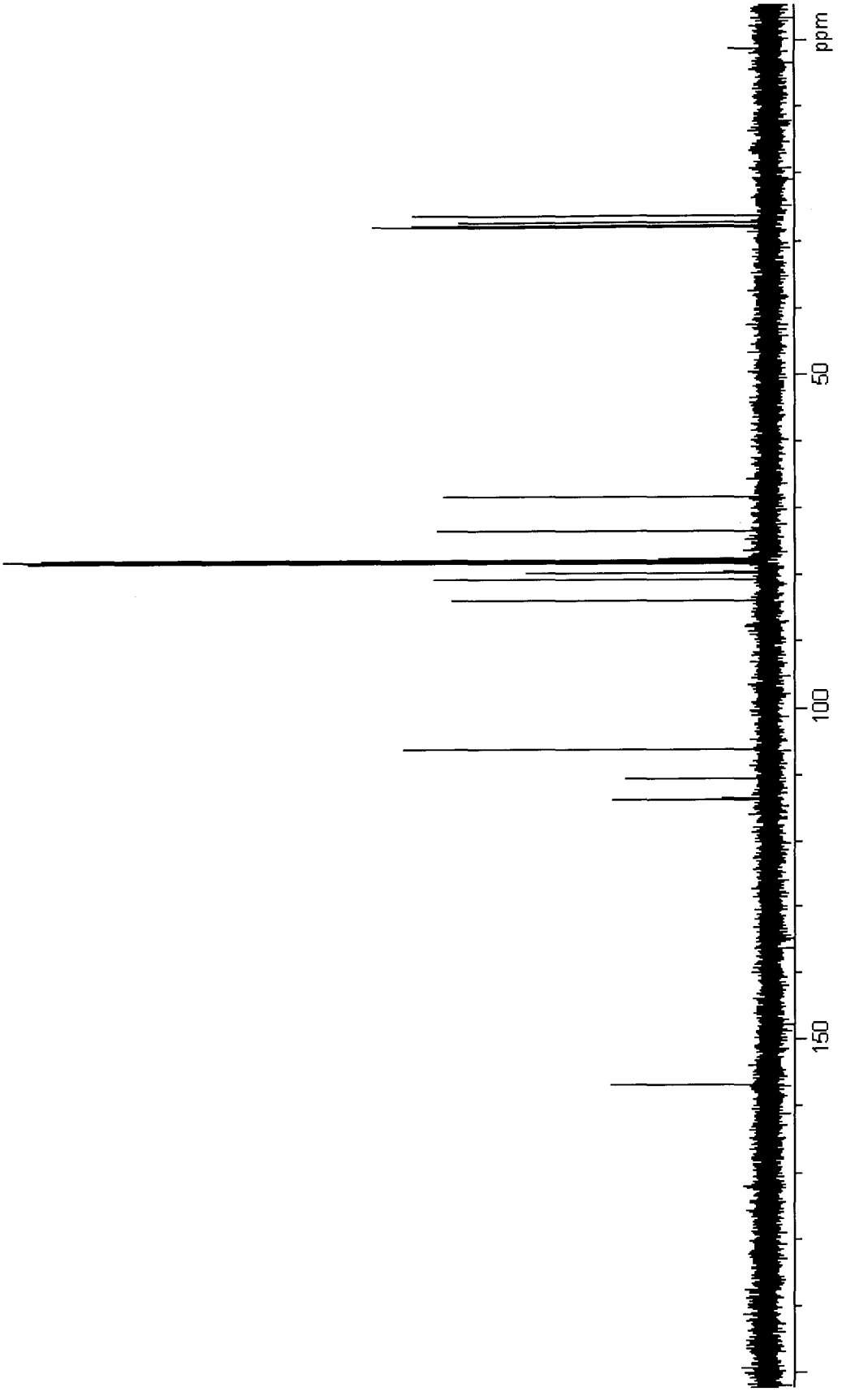

Figure **34**. ^{13}C NMR spectrum of compound **18**