New Dipolar Cycloaddition Reactions of a Carbohydrate-Derived Vinyl Sulfoxide Alkyne Equivalent and a Polymer-supported Alkyne with Azides.

By

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Abstract

The attempted synthesis of a class of carbohydrate analogs known as pseudodisaccharides and the study of soluble polymer supports were the focus of this research. The potential of 1,3-dipolar cycloadditions with carbohydrate-derived vinyl sulfoxides and a sulfone with organic azides was investigated to synthesize the pseudodisaccharide. The conditions of the reaction would allow for the cycloaddition followed by the elimination of the sulfur group in a single reaction flask because of the electron withdrawing effects of the sulfur group. The study of soluble polymer supports utilized poly(ethyleneglycol) monomethylether to create soluble polymer-supported carbohydrates. The methodology of dipolar cycloaddition was applied to a polymer-supported alkyne for the synthesis of sugar-derived triazoles.

Acknowledgments

I would like to thank my advisor, Dr. Peter Norris, for all his time and patience with me during the course of my research project and education. I wish him the best of luck in all of his future endeavors.

I would also like to thank the members of my committee, Dr. Smiley and Dr. Jackson, for their time and effort in reviewing my thesis. Also to all the other YSU faculty and staff for their support through the last two years.

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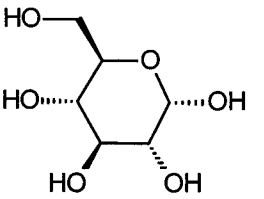
INTRODUCTION

This thesis consists of two projects related by the use of 1,3-dipolar cycloaddition reactions. The first project involved designing a novel route for the synthesis of a glucosidase inhibitor through 1,3-dipolar cycloaddition reactions with vinyl sulfoxides and sulfones. The second project involved the study of soluble polymer supports and dipolar cycloaddition reactions on a soluble polymer-supported dipolarophile.

Biological importance of carbohydrate analogs.

One of the most abundant classes of organic and biological molecules found in nature are carbohydrates, which over the last 30 years have become a growing area in chemical and biochemical research. Carbohydrates store energy and serve as building blocks for nucleic acids and fats in living organisms. The simplest of the carbohydrates are known as monosaccharides, which are synthesized from smaller molecules by either gluconeogenesis or photosynthesis. The most common monosaccharide found in nature is D-glucose (**1**).



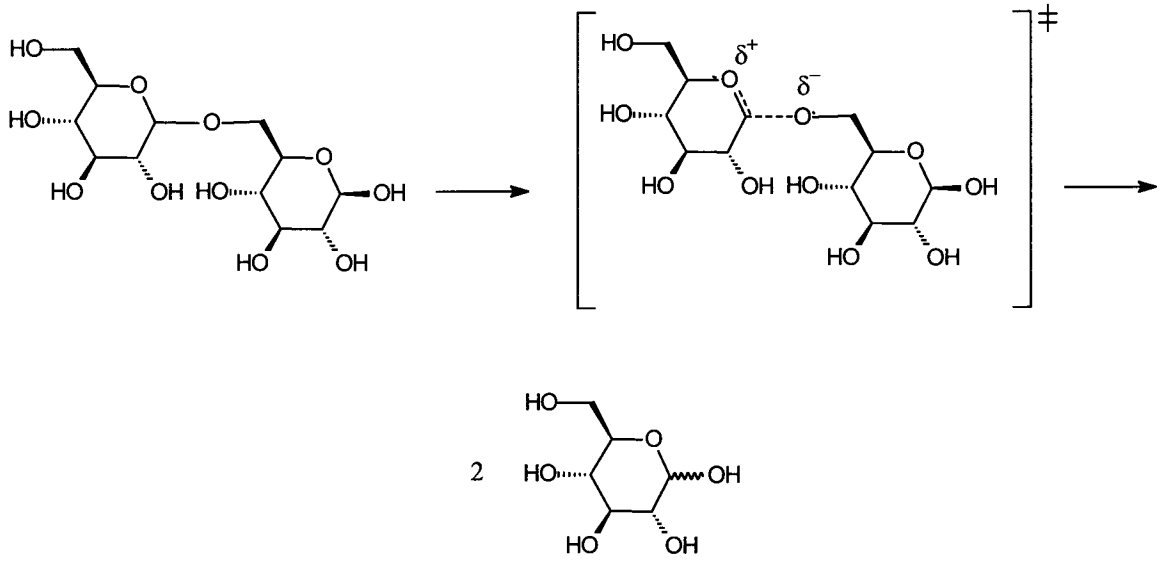
1

Monosaccharides are linked together by glycosidic bonds to form larger molecules such as oligosaccharides and polysaccharides by different metabolic pathways. Enzymes known as glycosidases break down oligosaccharides and polysaccharides in biological systems in various different metabolic pathways.

With increased research in the area of carbohydrates, chemists and biochemists have recognized the importance that they play in biological processes, especially their interaction with enzymes. Enzymes are biological catalysts in biochemical reactions, and it is known that enzymes interact in specific ways with substrates to catalyze these

reactions. The three-dimensional structures of both the enzymes and the substrate play an important role in these reactions and are governed by the following forces: van der Waals, electrostatic, hydrogen bonds, and hydrophobic interactions. In biochemical reactions the same forces mentioned above stabilize transition states within these reactions. This is important because enzymes bind transition states more tightly than the starting substrate.

A class of enzymes of importance in carbohydrate biochemical reactions are the glycosidases. Glycosidases cleave the glycosidic bonds that link sugars together. For example, the accepted glycosidase mechanism for the breakdown of a simple disaccharide into two free sugars is shown in Scheme 1. Stable compounds that have a



Scheme 1

three-dimensional configuration similar to the transition state may be effective inhibitors. Several known carbohydrate-derived heterocycles have been synthesized and found to inhibit glycosidases, based on their three-dimensional configuration and the electronic forces. Figure 1 shows some known inhibitors.

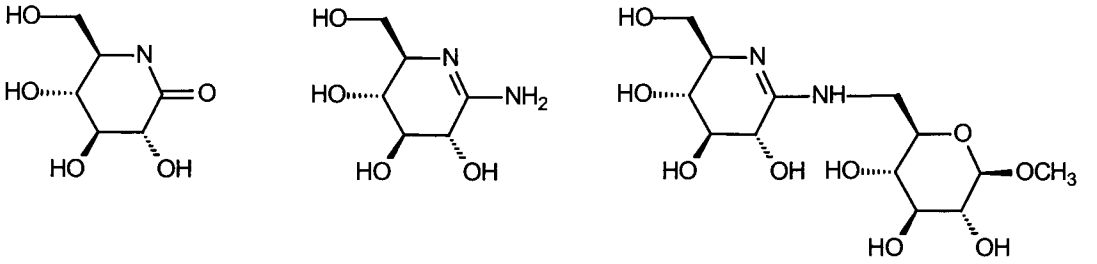
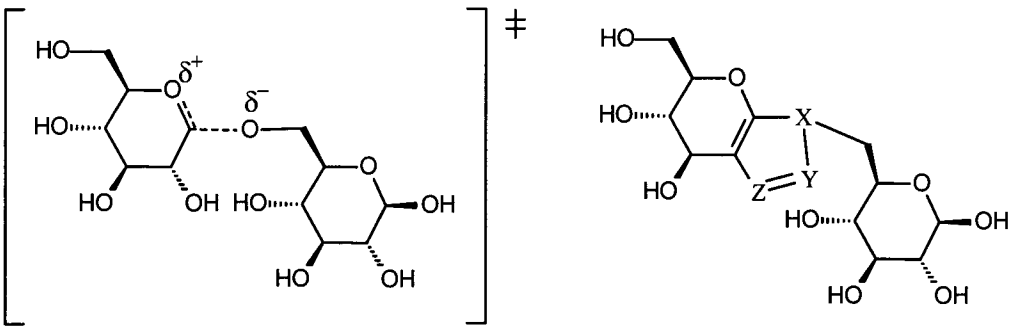


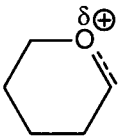
Figure 1. Known glycosidases inhibitors

In this research, the attempted synthesis of a class of carbohydrate analogs known as pseudodisaccharides (**3**) was performed. The pseudodisaccharides were to be composed of two sugar units linked together by an aromatic heterocycle at C-1 and C-2 of the "non-reducing" terminus, which would be formed by a 1,3-dipolar cycloaddition reaction. By using heterocycles to join the two sugar units, the structure of the pseudodisaccharide should have the same geometric or electronic as the transition state (**2**) that occurs during glucosidase action, and may be capable of selectively inhibiting glycosidases, specifically glucosidases.



2 **3**

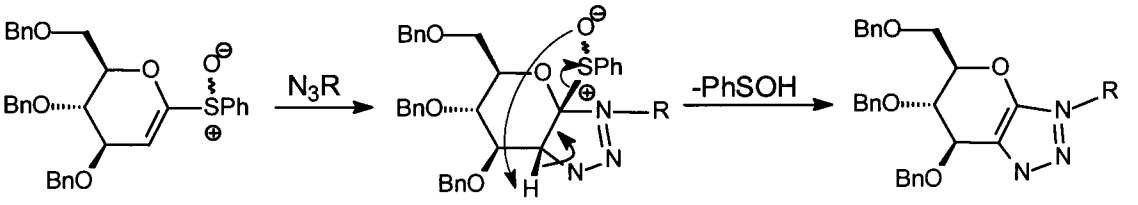
Legler has reviewed mechanistic information on reversible and irreversible inhibitors and describes and illustrates an intermediate, the glycosyl cation (**4**), which plays an important role in glycoside hydrolysis.[1]



4

Legler also discussed those glycosidase inhibitors that have been isolated from natural sources such as iminosugars as shown in figure 1 and many synthetic analogs.[2] Winchester and Fleet studied the biological effects that amino-sugar glycosidase inhibitors have on various metabolic processes. In this study, the compounds studied were iminosugars (figure 1), in which nitrogen replaced the oxygen atom in the ring and were found to inhibit glycosidases.[3] Others, such as Ganem and Wong, have also successfully synthesized and evaluated glycosidase inhibitors that contain imino groups as in figure 1.[4, 5]

Earlier studies of carbon bridged *C*-disaccharides by Schmidt and Preuss gave insight to synthesizing the vinyl sulfoxides and sulfone derivative needed in the present research.[6, 7] The pseudodisaccharide was to be synthesized from these derivatives by 1,3-dipolar cyclocycloaddtions with organic azides. Early studies of cycloaddition reactions with 2,3-unsaturated sugars where reported by Fraser-Reid.[8, 9] The potential of 1,3-dipolar cycloadditions with carbohydrate-derived vinyl sulfoxides and a sulfone with organic azides was investigated. With the electron withdrawing sulfur group, the conditions of the reaction would allow for the cycloaddition followed by elimination of the sulfur group in a single reaction flask (scheme 2). Several of these reactions where attempted in the work decribed here.



Scheme 2

Study of soluble polymer supports.

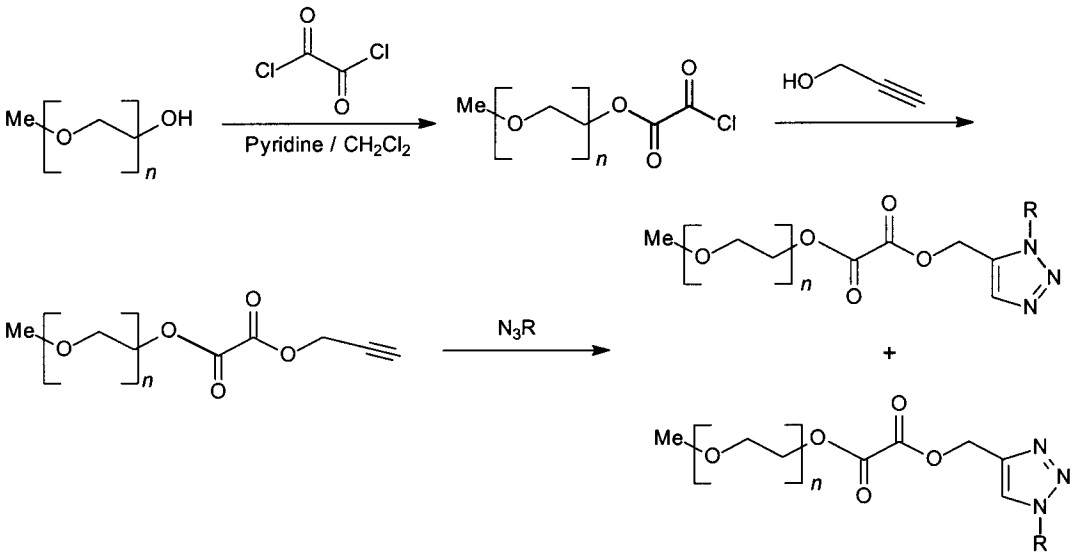
The multistep synthesis of carbohydrate derivatives is difficult and requires many purification steps. The difficulty in synthesizing these derivatives stems from the similar reactivity of the hydroxyl groups and any glycosidic linkages that need to be formed. For these reasons alternative approaches have been sought. One of these approaches has been the use of polymers both in solid-phase and solution-phase to synthesize carbohydrate derivatives. Reactions performed on such polymers should give high yielding reactions and allow for easy clean up. Also, the product formed on the polymer should be able to be removed under mild conditions.

Recent studies by Danishefsky on the use of solid-phase polymer supports to synthesize oligosaccharides have been highly successful.[10] Dipolar cycloaddition methodology has been applied to solid-phase chemistry to synthesize heterocyclic compounds. Solid phase synthesis of isoxazolines by [3+2] cycloaddition has also recently been reported.[11] Using solid-phase polymers, however, has disadvantages in analysis of the products. Analysis of the solid-phase polymer needs to be done by infrared spectroscopy or on the product after removal from the polymer at the end of the reaction.

Work by Krepinsky showed advantages of using a soluble polymer support to synthesize oligosacchaarides. One of the advantages that soluble polymers have over insoluble polymers used in solid-phase reactions is the ability to monitor the reaction by NMR spectroscopy. Krepinsky's studies and his use of poly(ethyleneglycol) mono

methylether in synthesizing oligosaccharrides lead to the use of this polymer in the present research.[12]

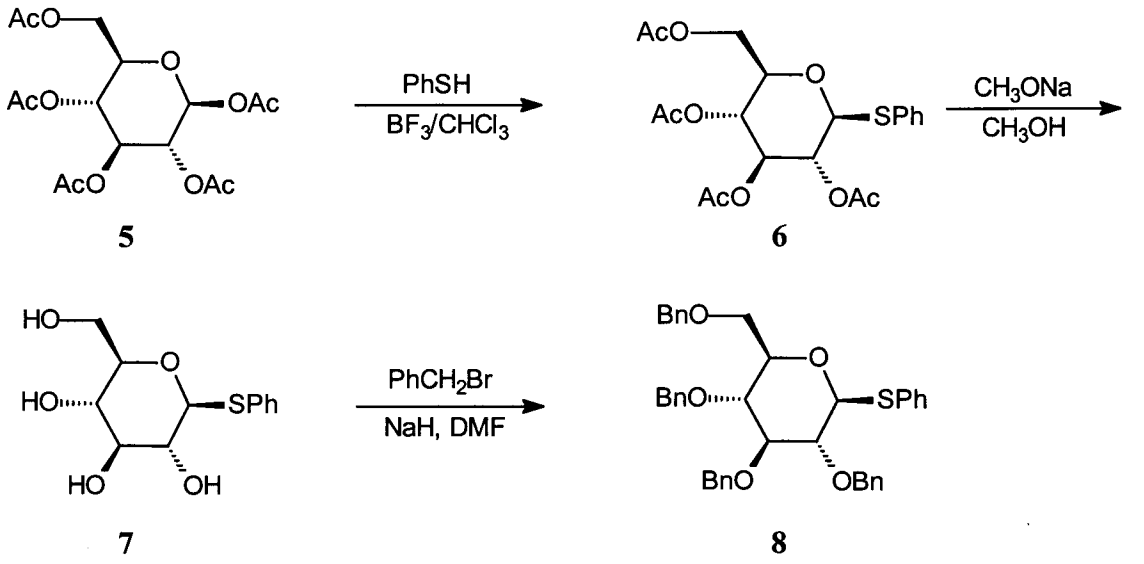
Poly(ethyleneglycol) monomethylether was used in this study to create soluble polymer supported carbohydrates. With the results of these reactions, the methodology of dipolar cycloaddition was applied to a polymer-supported alkyne for the synthesis of triazoles. Scheme 3 shows the proposed reactions.



Scheme 3

RESULTS AND DISCUSSION

1. The preparation of D-glucose-derived vinyl sulfoxides and a vinyl sulfone and their reactivity in 1,3-dipolar cycloaddition reactions.



5 6 7 8

Scheme 4

The vinyl sulfoxides and sulfone needed for cycloaddition studies were prepared by literature methods. Scheme 4 shows the synthetic route to phenyl 2,3,4,6 tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**8**) which was used to develop the vinyl sulfoxides and sulfone needed in this study. 1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (**5**) was converted in a moderate yield (52.1%) to a thioglucoside (**6**) using thiophenol and boron trifluoride. The melting point of this compound was found to be 113-116°C, which compares well to the literature value (117-118 °C). The ^{1}H NMR spectrum of phenyl 2,3,4,6 tetra-*O*-acetyl-1-thio-β-D-glucopyranoside showed a multiplet at 7.30-7.50 ppm that represents the phenyl group (figure 2). These signals are not found in the ^{1}H NMR spectrum of the starting material. At this point, the thioglucoside protection scheme required alteration. Benzyl groups are convenient since they are more stable than the acetyl groups to the basic conditions needed to reach the target glycal, and so the acetyl groups were replaced as follows.

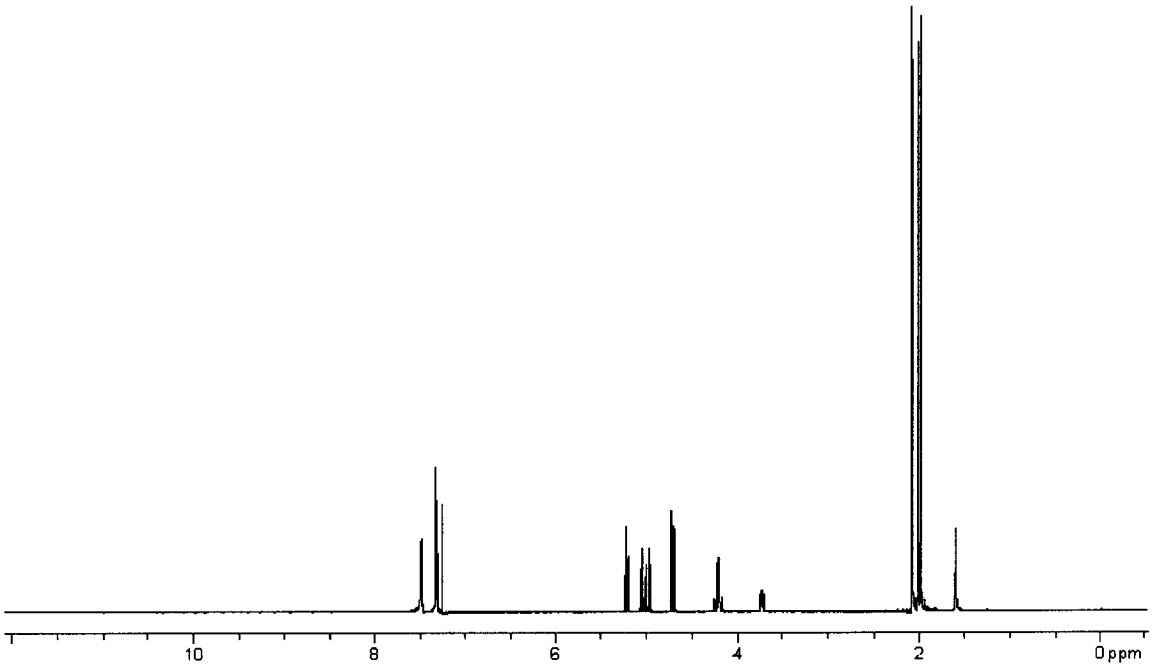


Figure 2. ^{1}H NMR spectrum of thioglucoside **6**

The thioglucoside was deprotected with sodium metal in methanol. The deprotected product, phenyl-1-thio-β-D-glucopyranoside (**7**), was recovered in ~ 100% yield. The melting point of the product was 135-142 °C and the literature reported the melting point at 133-134 °C. The reason for the difference in the ranges of the melting points may be due to remnants of sodium salts left behind from the reaction. The ^{1}H NMR of the product showed the disappearance of the acetyl groups at 2.0-2.1 ppm and the appearance of a multiplet at 3.0-3.6 ppm.

The benzylation of phenyl 1-thio-β-D-glucopyranoside (**7**) with sodium hydride and benzyl bromide gave the tetra-benzylated product (**8**) in a moderate yield (62%) where the literature method reported an 80% yield. The melting point of the product was 87-89 °C, which compares reasonably well to the literature value (84-85 °C). The ^{1}H NMR showed the product to have the same signals as those reported in the literature. The peaks at 7.27-7.39 ppm (aromatic) and 3.55-4.95 (sugar ring) integrate 25/15 respectively. (Figure 3)

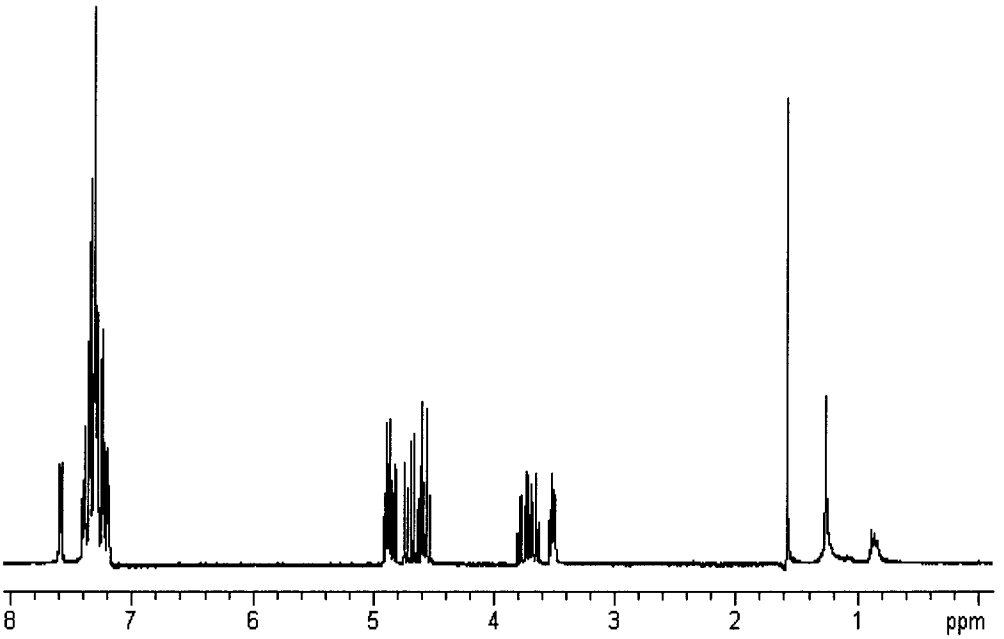
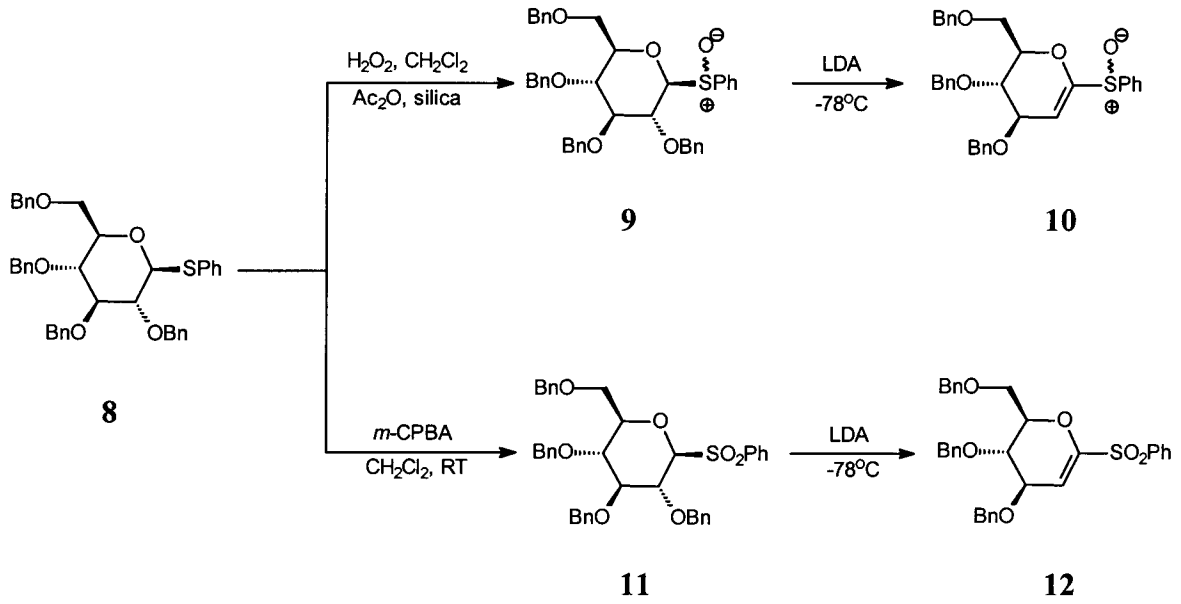


Figure 3. ^{1}H NMR spectrum of benzyl protected derivative **8**

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**8**) was then oxidized to give the sulfoxide and sulfone derivatives shown in scheme 5. First, phenyl 2,3,4,6 tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**8**) was oxidized using silica gel, acetic anhydride and hydrogen peroxide to give the sulfoxide (**9**) in 75 % yield. This method



Scheme 5

was used to minimize the overoxidation of the sulfur atom of compound **8** to form sulfone (**11**), which can happen when *m*-CPBA is used. TLC of compound **9** showed two spots with Rf values, 0.30 and 0.27, which indicated diastereomers, whereas the literature gave only one Rf value at 0.30 and did not mention formation of diastereomers. The diastereomers are due to lack of inversion at the chiral sulfur atom in this compound. The melting point of the product was 98-100 °C, which was lower than the reported literature value of 120-122 °C. The ^{1}H NMR corresponded to that indicated in the literature (Figure 4).

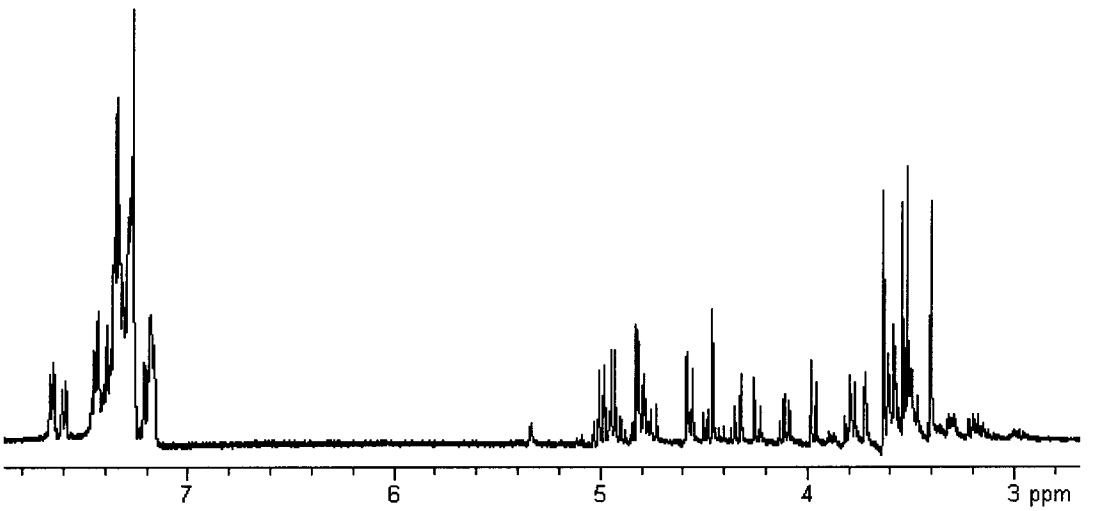


Figure 4. ^{1}H NMR of diasteromeric sugar-derived sulfoxides **9**

Secondly, phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside was oxidized with *m*-CPBA to give the sulfone (**11**) in 100 % yield. The ^{1}H NMR showed a small shift downfield in the aromatic region that differs from the starting material due to the sulfur atom being oxidized (Figure 5).

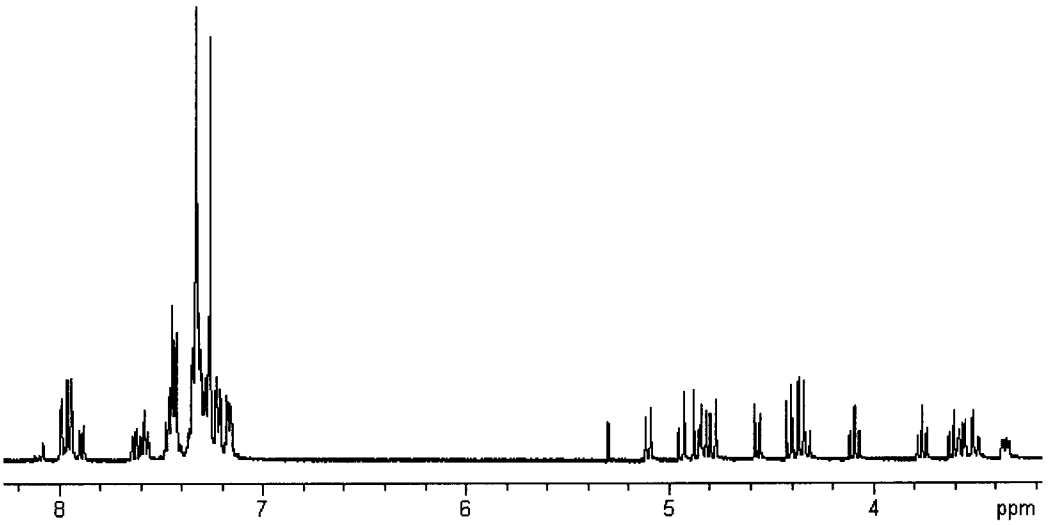


Figure 5. ^{1}H NMR of sugar-derived sulfone **11**

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-sulfoxide-β-D-glucopyranoside (**9**) and the phenyl sulfonyl-β-D-glucopyranoside (**11**) were then deprotonated with lithium diisopropylamine to give, respectively, the vinyl sulfoxide (**10**) and vinyl sulfone (**12**) (scheme 5). In the preparation of the 1-phenyl sulfinyl glucal (**10**), the mixture of diasteromeric sulfoxides was reacted with LDA to give the glucal in 73 % yield. The ^{1}H NMR shows two doublets around 5.9 ppm that represent the proton at C-2 and indicates

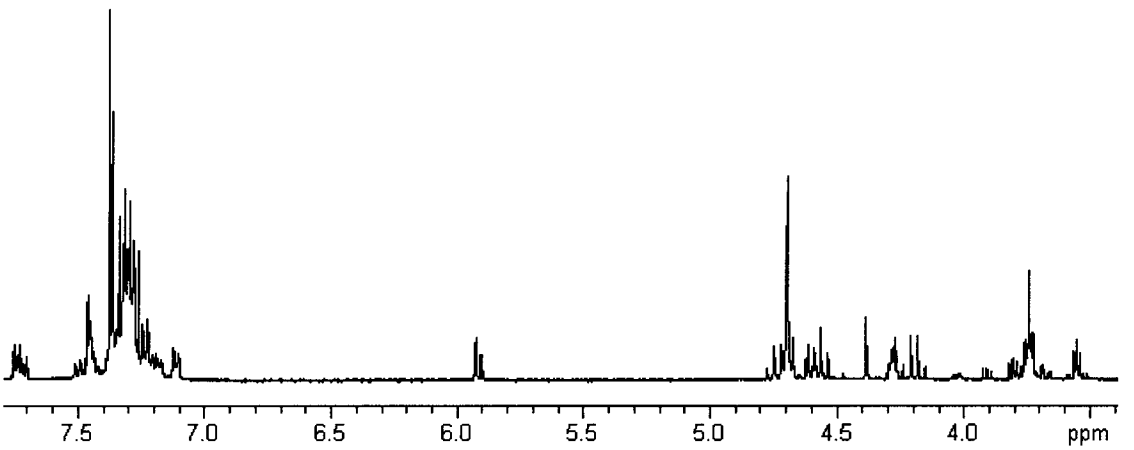


Figure 6. ^{1}H NMR of sugar-derived-vinyl sulfoxide **10**

that the starting vinyl sulfoxide was indeed a mixture of diastereomers (Figure 6). The sulfone reacted using the same procedure as for the sulfoxide. This reaction produced a 62 % yield of the glucal sulfone. The ^{1}H NMR shows a doublet at 6.2 ppm that represents the proton at C-2 (Figure 7).

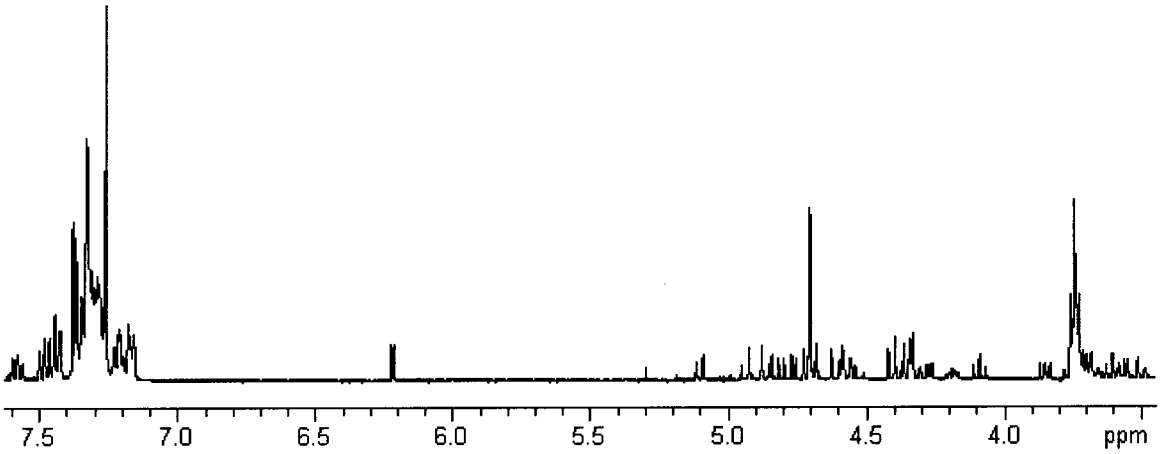


Figure 7. ^{1}H NMR of sugar-derived-vinyl sulfone **12**

The vinyl sulfoxide (**10**) and sulfone (**12**) were then used in attempted 1,3 dipolar cycloadditions and attempted synthesis of branched chain derivatives. The 1,3-dipolar cycloaddition reactions studied involved the reaction of both vinyl compounds with organic azides under different conditions. First, the vinyl sulfoxide (**10**) was treated with tosyl azide in refluxing toluene, which gave only recovered starting material as shown by ^{1}H NMR. In this reaction, the tosyl azide possibly decomposed due to the temperature at which the reaction was performed which led to running a further reaction at room temperature. The reaction at room temperature ran for several days and, unfortunately, only starting material was recovered.

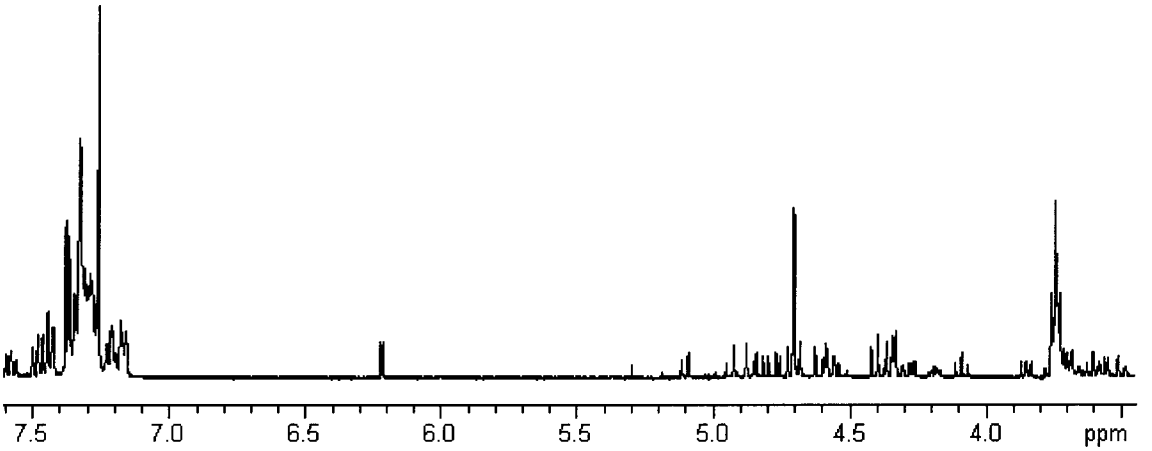


Figure 8. ^{1}H NMR of recovered compound **12**

The vinyl sulfone was also treated with tosyl azide at room temperature to yield only 75 % of the recovered starting material as shown by ^{1}H NMR (Figure 8). After running this reaction, it was thought that the organic azide being used was possibly not a sufficiently reactive dipole. To test if this was so, trimethylsilyl diazomethane was used as a dipole to react with the vinyl sulfoxide. At first, analysis by TLC suggested a possible change, but ^{1}H NMR showed signal at 5.9ppm for the vinyl proton that

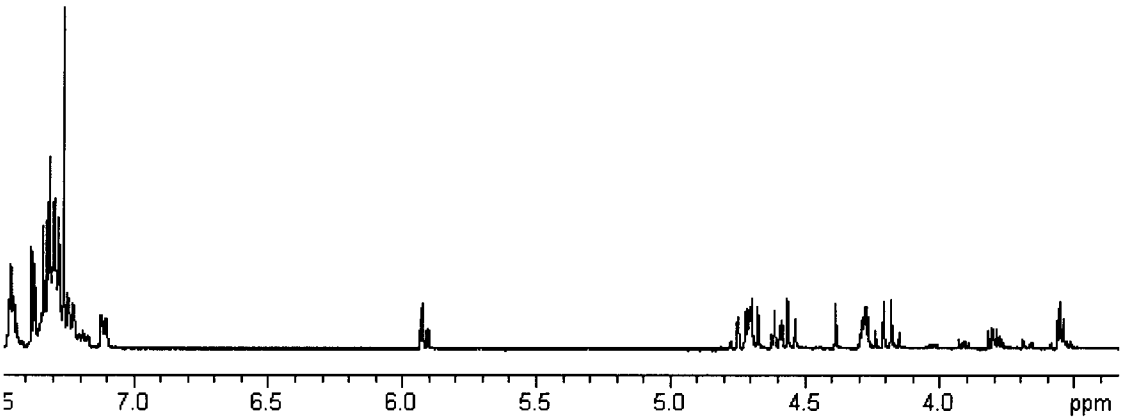


Figure 9. ^{1}H NMR of recovered compound **10**

indicated only starting material was recovered (Figure 9).

Next, a reaction was attempted with a *C*-nucleophile to determine the reactivity of the vinyl sulfone. The vinyl sulfone was reacted with diethyl malonate anion;

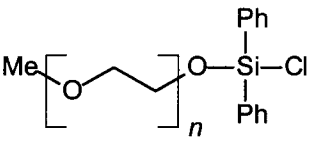
however, again only starting material was recovered as shown by ^{1}H NMR.

The final reaction attempted in this study was a 1,3-dipolar cycloaddition reaction where the vinyl sulfoxides and 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose were heated in refluxing toluene over night. The TLC plates showed no change between the starting material and the product. It is believed that these unsuccessful reactions might be due to steric hindrance about the glucal double bond caused by the large benzyl protecting group at C-3. The hindrance at this position may not allow the dipole to react at either face of the vinyl sulfoxide or sulfone. The position of the (-SOPh) or (-SO_2Ph) at C-1 might also cause steric hindrance depending on its orientation, which is not known. This may be confirmed by a crystal structure of the vinyl sulfoxide.

2. Development of MeO-PEG-Sugar Derivatives

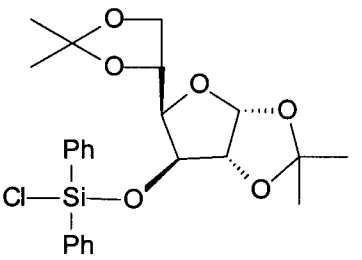
In this section of the research, the potential of working with soluble polymer supports was investigated. The purpose of studying these types of supports is to develop new methods for synthesizing carbohydrate derivatives while reducing the clean-up of the products produced.

The study of soluble polymer supports began with the examination of poly(ethylene glycol) mono-methyl ether and a number of different types of linker with which to attach compounds to the polymer. This was done to determine which linker would be the most useful in further chemistry in terms of stability and reactivity. The first reagent studied was dichlorodiphenylsilane, which gave low yields when linked to either the polymer or to two different carbohydrates. Poly(ethylene glycol) mono methyl ether was reacted with sodium hydride, sodium iodide and dichlorodiphenylsilane to give (MeO-PEG)-chlorodiphenylsilane (**13**) in low yield (32%).



13

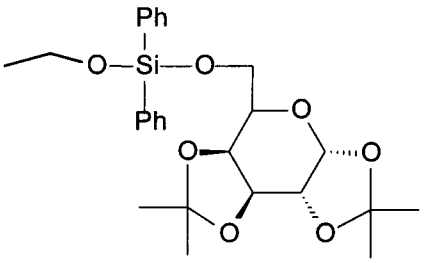
The ^{1}H NMR showed signals at 7.25-7.70 ppm which represent the phenyl groups and at 3.40-3.80 ppm that represent the polymer. Next, 1,2:5,6-di-*O*-isopropylidene-α-D-



14

glucofuranose was reacted with 1,8-diazabicylo[5.4.0]undec-7-ene and dichlorodiphenylsilane to furnish 3-(chlorodiphenylsilyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**14**) in low yield (19 %).

The ^{1}H NMR showed signals for the phenyl groups and the acetyl groups at 7.30-7.72 ppm and at 1.15, 1.28, 1.32, 1.38 ppm respectively. Finally, 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose was reacted with dichlorodiphenylsilane and then ethanol to give 6-(ethoxydiphenylsilyl)-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**15**) in only very low yield (2 %).



15

The ^{1}H NMR showed signals at 7.25-7.75 ppm corresponding to the phenyl groups, at 3.80-386 ppm and 1.17-1.21 ppm to represent the (-CH_2CH_3) and at 1.37–1.59 to correspond to the isopropylidene groups (Figure 10). Though this silyl group is

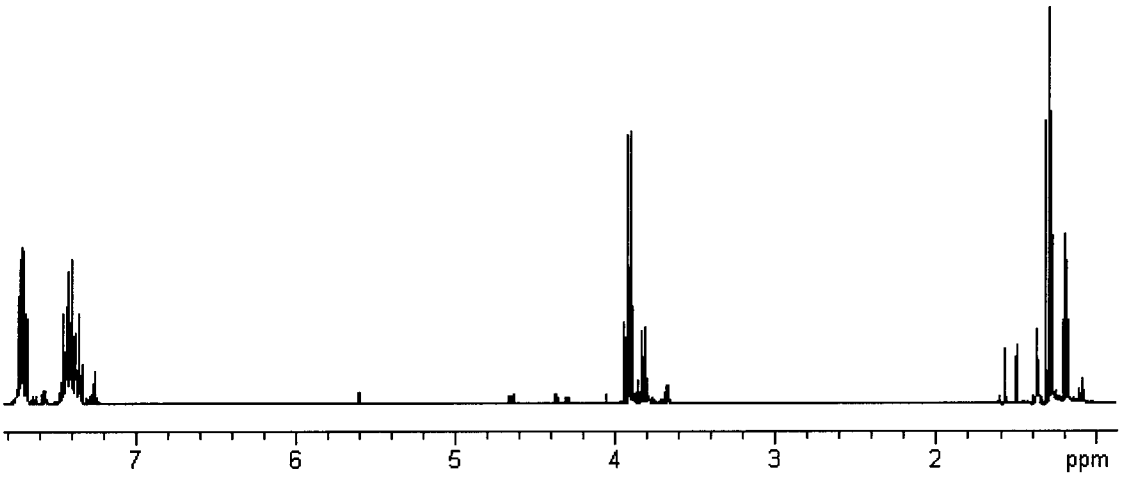
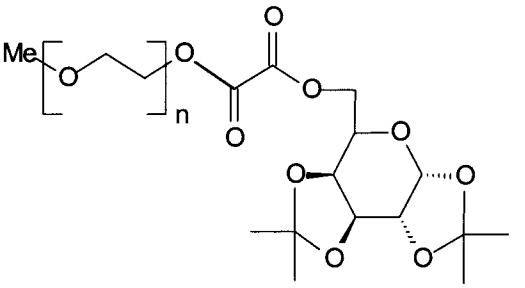


Figure 10. ^{1}H NMR spectrum of **15**

believed to be the most stable of the linkers, the low yields and difficulty in linking to the polymer and the carbohydrates used in this study made it a poor candidate at this time.

The low yields of these compounds may be due to steric hindrance caused by the phenyl groups on silicon.

The second linker studied, oxalate, gave high yields of several polymer-supported derivatives. This linker was initially studied by preparing the ethyl oxalate derivative (**18**), (MeO-PEG)-(1,2,3,4-di-*O*-isopropylidene-D-galactopyranose) oxalate (**16**), and (MeO-PEG)-(1,2:5,6-di-*O*-isopropylidene-D-glucofuranose) oxalate (**17**).



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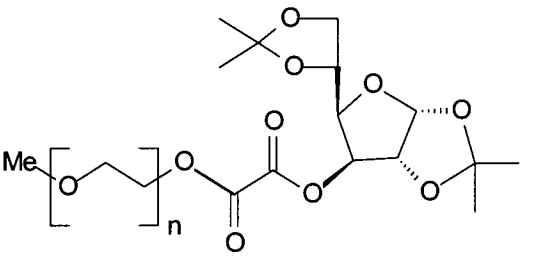

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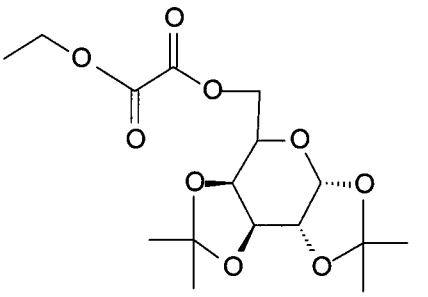

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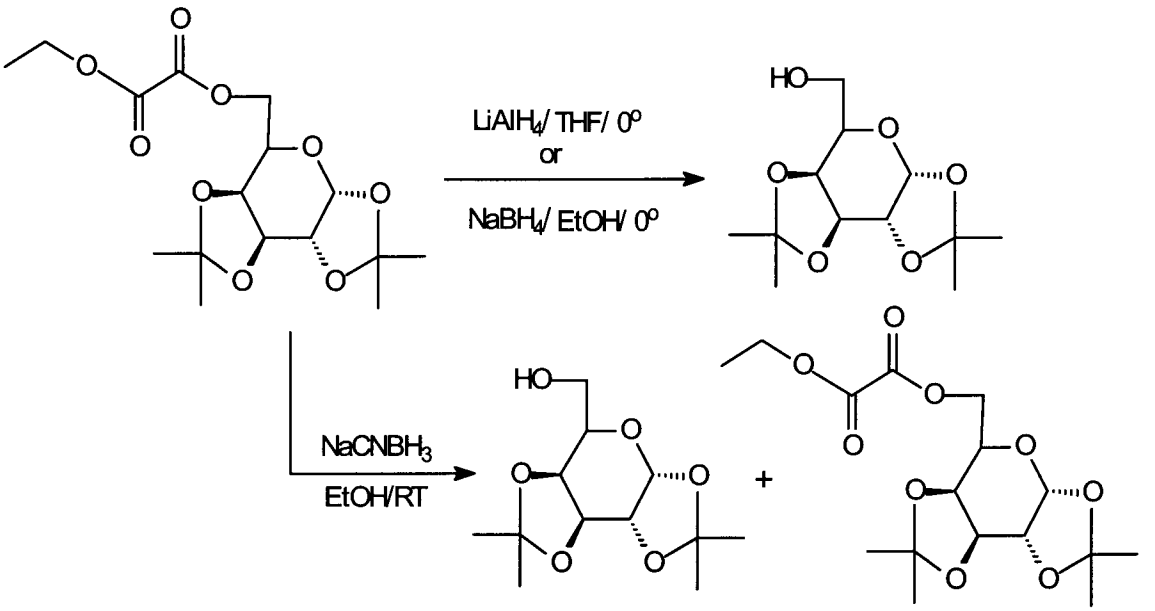
The ethyl oxalate derivative was used to test the stability of the oxalate linker by reducing the derivative with strong to mild reducing agents as seen in Scheme 6. It was found that sodium cyanoborohydride partially cleaved the derivative in ethanol at room temperature and lithium aluminum hydride and sodium borohydride completely reduced the derivative to release the sugar. These conditions would later be applied to the polymer-supported oxalates.

The oxalate linker was then used to attach carbohydrates to the polymer. The carbohydrates that were chosen for this were 1,2,3,4-di-*O*-isopropylidene-D-

galactopyranose and 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose because there was little overlap between their ^{1}H NMR spectra and that of the polymer. The products of



Scheme 6

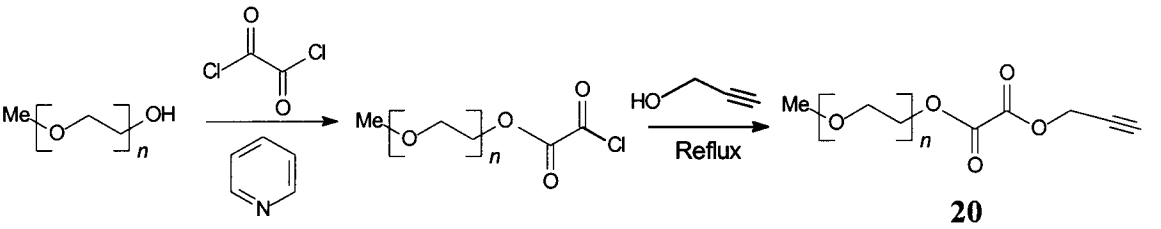
these reactions **16** and **17** gave good yields (70 % and 95 % respectively) and loading (95-100% and 70-75 % respectively).

Monitoring by NMR allows for the calculation of loading since MeO-PEG contains an OCH_3 group that gives a singlet at 3.3 ppm that can be used as an internal standard. The suppression of the glycol peak of MeO-PEG at 3.6 ppm must be done to give good spectra. This method was used for all studies involving polymer reactions.

The last linker studied was succinate, which gave a moderate yield (68 %) in the preparation of (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose)(MeO-PEG) succinate (**19**). The ^{1}H NMR showed signals at 1.25-1.35 ppm and 1.43 ppm for the acetyl groups from the carbohydrate derivative that indicated the successful attachment of the carbohydrate to the linker and polymer. Also the spectrum showed signals at 4.50-4.55 ppm for the methylene group on the polymer next to one of the carbonyl groups, and 5.20 ppm for the proton at C-3 of the sugar. The signals have been shifted downfield due to the carbonyl groups.

3. Dipolar Cycloaddition Reactions on a Soluble Polymer-Supported Dipolarophile.

The preparation of a soluble polymer-supported dipolarophile using an oxalate linker was studied with a view to attempting dipolar cycloaddition reactions. It was decided that propargyl alcohol would be attached to the polymer using oxalate as the



Scheme 7

linker. This dipolarophile was chosen because its ^{1}H NMR signals would occur in areas other than the major signals of the polymer. The reaction produced (propargyl) (MeO-PEG) oxalate (**20**) in high yield (86 %) and with 85 % loading (Scheme 7). The ^{1}H NMR showed signals at 2.56 ppm for the terminal proton from propargyl ester, at 4.82 ppm for the methylene group from propargyl ester of **20** and the signal at 3.60 ppm for the polymer methylene groups (Figure 12).

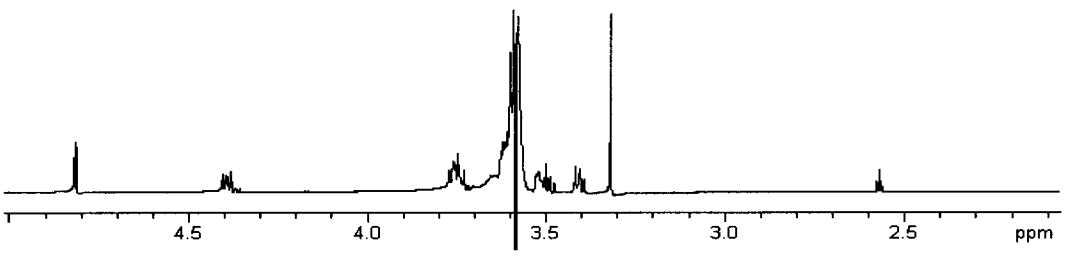
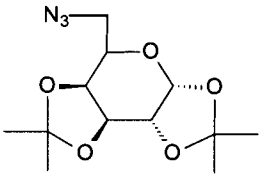
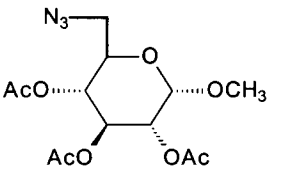


Figure 12. ^{1}H NMR spectrum of **20**

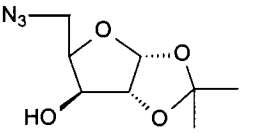
The azide dipoles developed for this study were prepared from commercially available protected carbohydrates. 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**21**), methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside (**22**) and 5-azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (**23**) were prepared to be used as dipoles in cycloaddition reactions with (propargyl) (MeO-PEG) oxalate (**20**).



21



22



23

The preparation of methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside (**22**) from methyl-α-D-glucopyranoside involved a three-step synthesis. Methyl-α-D-glucopyranoside was reacted with *p*-toluene sulfonyl chloride and pyridine to give the 6-*O*-tosylated product in ~30 % yield. The ^{1}H NMR spectrum showed signals

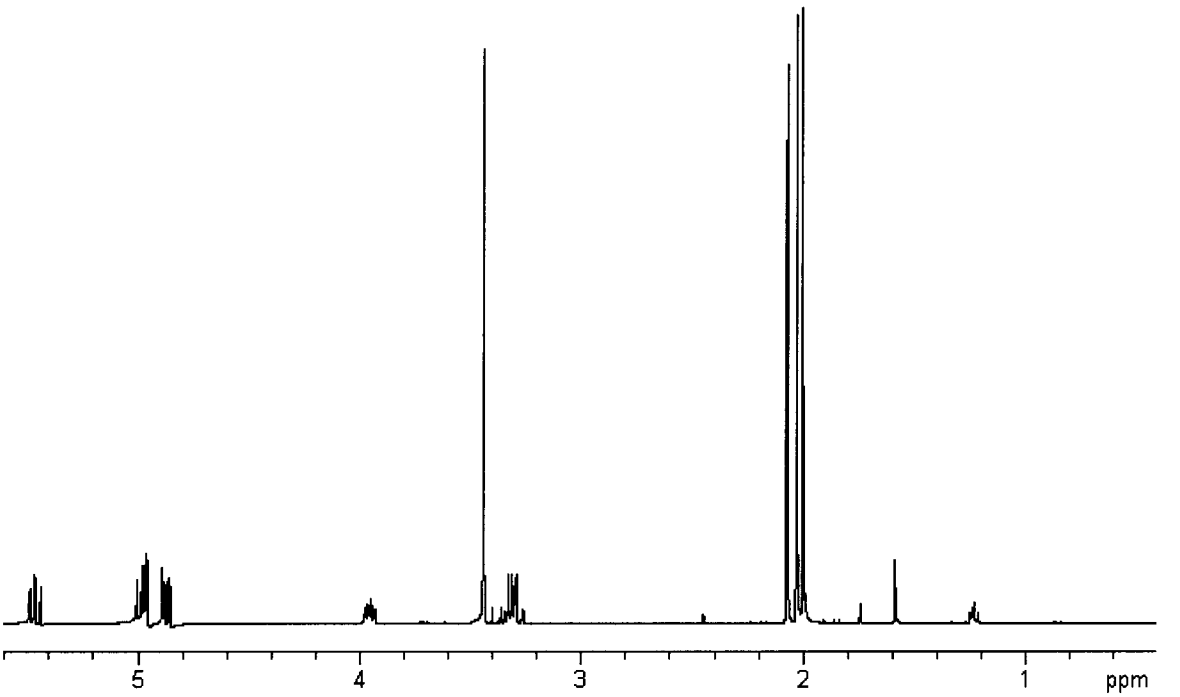


Figure 13. ^{1}H NMR spectrum of **22**

at 7.45-7.77 ppm to indicate the phenyl group of the tosylate at the more accessible 6-position. The tosylated product was then reacted with sodium azide to give methyl 6-azido-6-deoxy-α-D-glucopyranoside with ~100 % yield. The ^{1}H NMR showed the loss of the signals at 7.45-7.77 ppm and the IR showed a strong absorption at ~ 2200 cm^{-1} representing the azide. Methyl 6-azido-6-deoxy-α-D-glucopyranoside was then reacted with acetic anhydride to give methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside in 25% isolated yield. The ^{1}H NMR showed three signals at 2.0-2.1 ppm that represent the acetyl groups at C-2, C-3, and C-4 (Figure 13).

5-Azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (**23**) was prepared in a two step synthesis from 1,2-*O*-isopropylidene-D-xylofuranose. 1,2-*O*-Isopropylidene-D-xylofuranose was reacted with *p*-toluene sulfonyl chloride and pyridine to give the tosylated product in 49 % yield. The ^{1}H NMR spectrum showed signals at 7.25-7.80 ppm indicated the presence of the phenyl group of the tosylate at the 5 position. The tosylated product was then reacted with sodium azide to give 5-azido-5-deoxy-1,2-*O*-

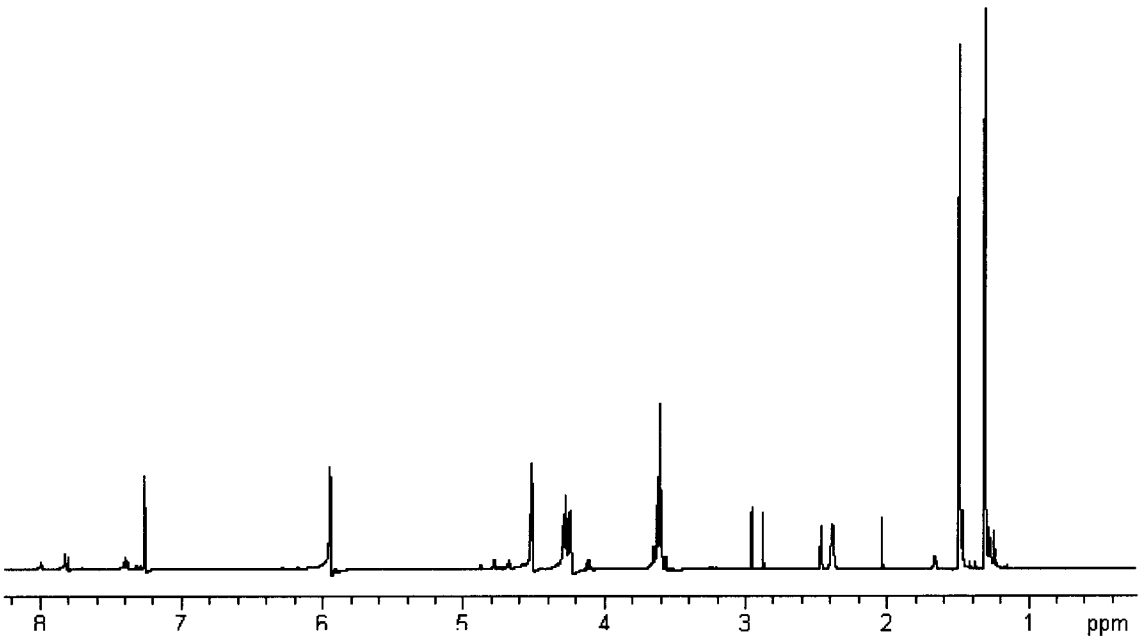
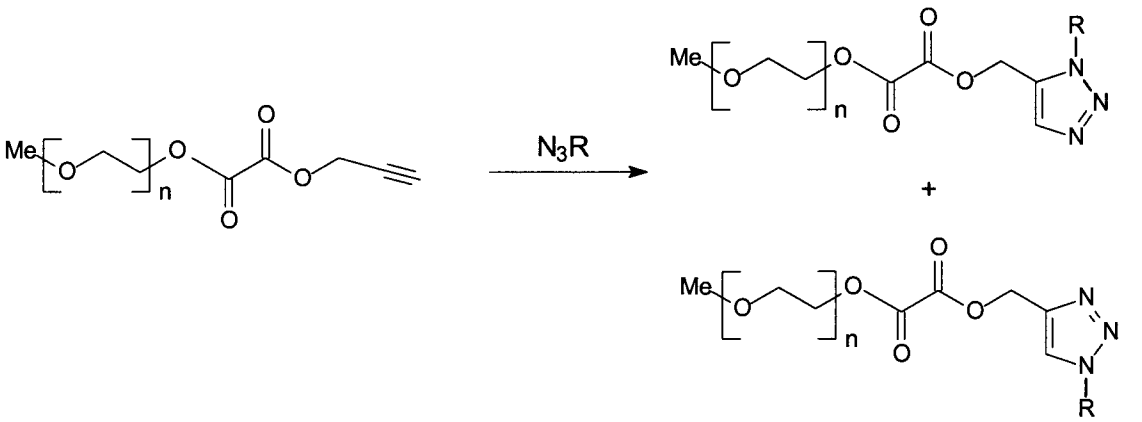


Figure 14. ^{1}H NMR spectrum of **23**

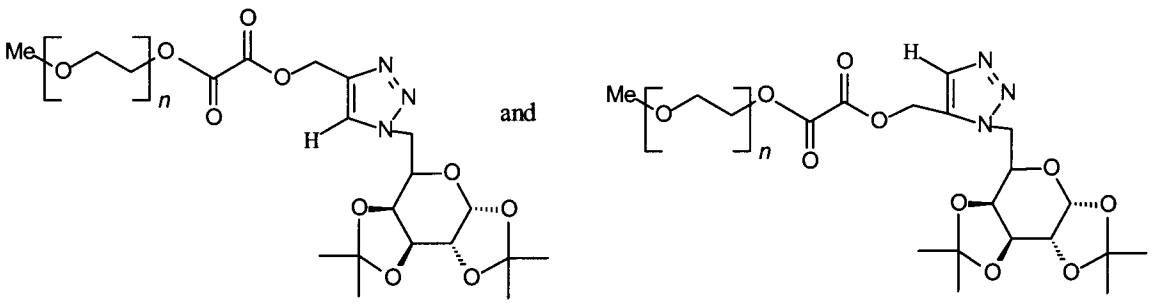
isopropylidene-D-xylofuranose in moderate yield (60 %). The ^{1}H NMR (Figure 14) showed the disappearance of the peaks at 7.25-7.80 to indicate the loss of the tosylate group and IR showed a strong peak at ~ 2200 cm^{-1} indicating the azide. With the synthesis of (propargyl) (MeO-PEG) oxalate and the carbohydrate-derived azides, the

investigation of cycloaddition reactions using the soluble polymer support was performed as seen in Scheme 8.



Scheme 8

(Propargyl) (MeO-PEG) oxalate and 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose were reacted together in refluxing toluene to give D-galactose-derived polymer-supported triazoles (**24**). The product was recovered in high



24a **24b**

yield (85 %) and the cycloaddition step was determined to be 86 % as calculated from the loading percentage of the alkyne on the polymer. Calculation of the cycloaddition was computed by determining the percentage of the loaded alkyne on the polymer and the percent yield from that reaction. These numbers were then factored in to calculate the

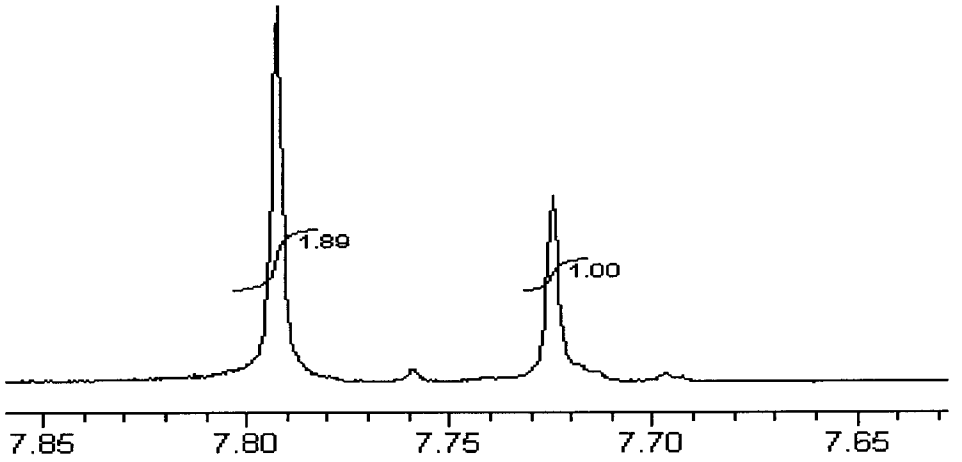


Figure 15. ^{1}H NMR spectrum of **24a/24b**

percentage of the cycloaddition step. The ^{1}H NMR showed signals at 7.25 and 7.79 ppm, which represent the aromatic protons of two regioisomers produced in this reaction (Figure 15). The two regioisomers are formed in a ratio of 1.89:1 and it is believed that the major isomer is orientated head to tail (**24a**).

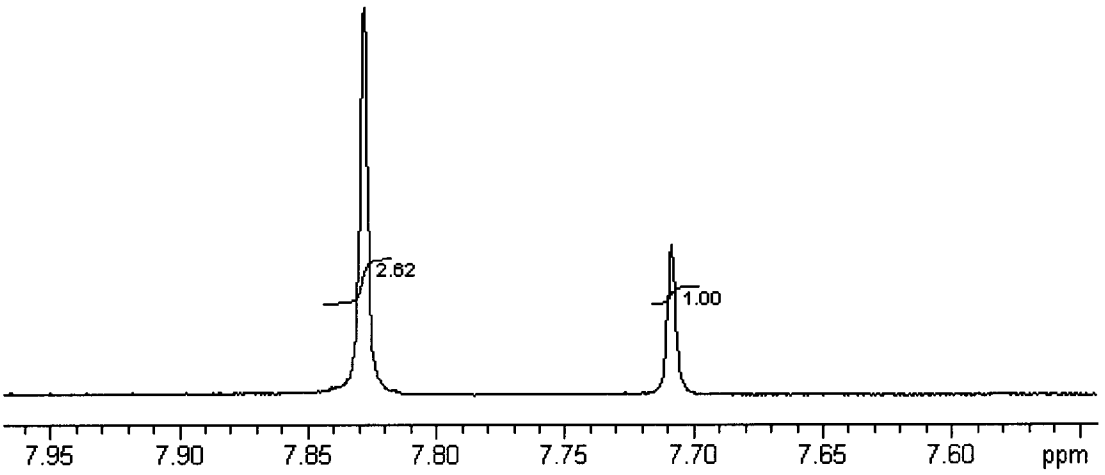
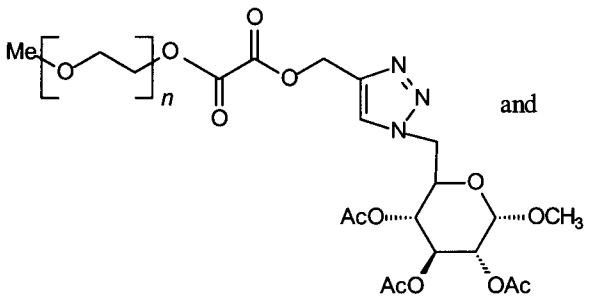
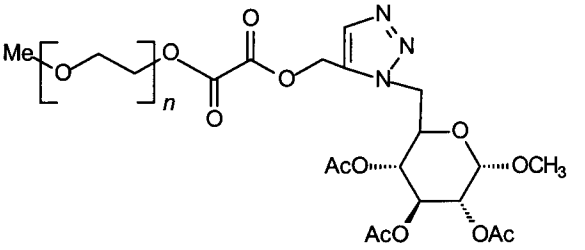


Figure 16. ^{1}H NMR spectrum of **25a/25b**

(Propargyl) (MeO-PEG) oxalate was reacted with methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside in refluxing toluene to give D-glucose-derived polymer-supported triazoles (**25**) in high yield (89 %). The cycloaddition reaction was calculated to be 82 % factoring in the loading percentage of the alkyne. The ^{1}H NMR showed signals at 7.72 and 7.90 ppm that represent the aromatic protons of two regioisomers. The ratio of the two regioisomers in this reaction was 2.62:1 (Figure 16).

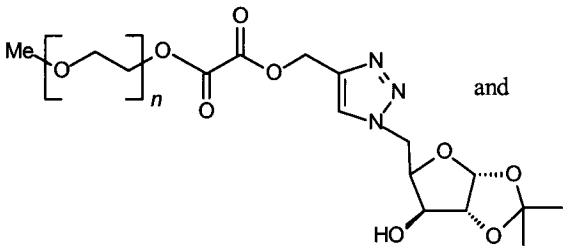


and

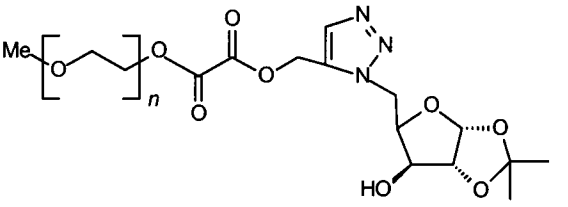


25a **25b**

The reaction between (propargyl) (MeO-PEG) oxalate and 5-azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose in refluxing toluene produced the corresponding D-xylose-derived polymer-supported triazoles (**26**) in high yield (92 %) and a 73 % yield



and



26a **26b**

for the cycloaddition. The ^{1}H NMR showed signals at 7.70 and 7.84 ppm that represent the aromatic protons of two regioisomers and the ratio of the two regioisomers is 2.41:1(Figure 17). Though these reactions produce high yields of recovered material it is believed that the percentage of the cycloadditions are moderate to good. After the

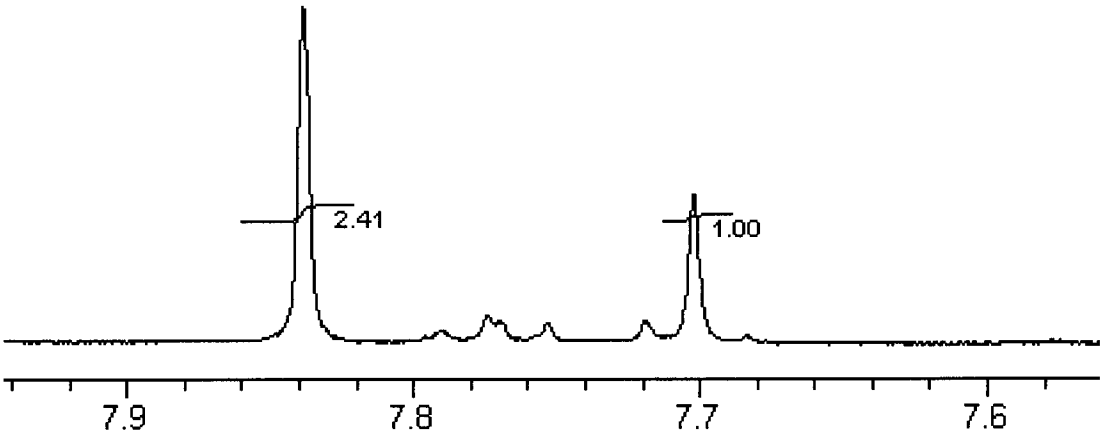


Figure 17. ^{1}H NMR spectrum of **26a/26b**

synthesis of the polymer-supported triazoles, the heterocycles were cleaved from the polymer support using the mild reducing conditions developed earlier.

Thus, the D-xylose-derived polymer-supported triazoles were reduced with sodium borohydride over three hours at room temperature to give the free triazoles (**27**)

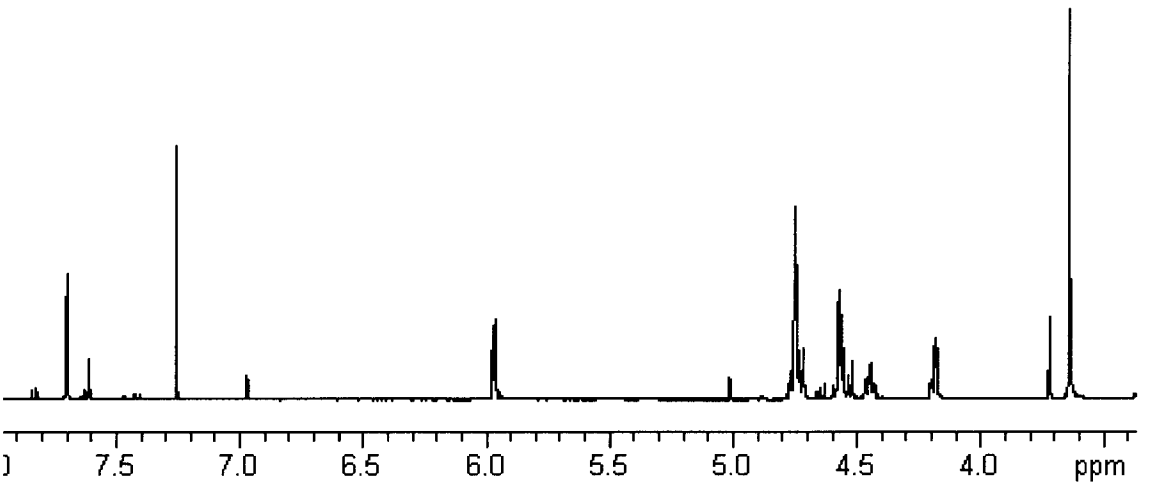
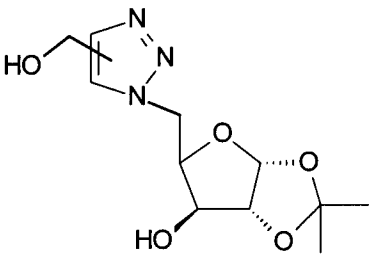


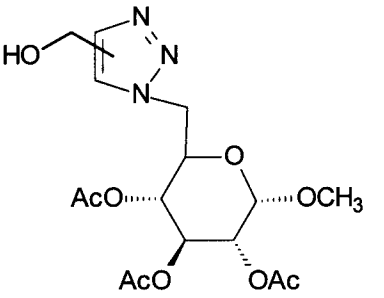
Figure 18. ^{1}H NMR spectrum of **27a/27b**

in good yield (76 %). The ^{1}H NMR showed signals at 7.61 and 7.70 ppm that represent the aromatic protons of the regioisomers and a trace of polymer at 3.6ppm (figure 18). This spectrum matches that of a sample detailed in the literature.[13]

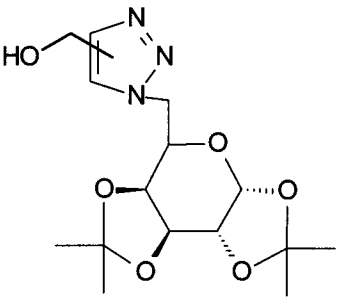
Next, the D-glucose-derived polymer-supported triazoles were reduced with sodium cyanoborohydride to give a moderate yield (70 %) of the triazoles (**28**). The ^{1}H NMR showed a mixture of the product triazoles and the polymer. The final reduction was performed on the D-galactose-derived polymer-supported triazoles to give the triazole (**29**) in only low yield (26 %). The ^{1}H NMR showed signals at 7.65 and 7.70 ppm which represents the aromatic protons of the regioisomers and a peak at 3.6 ppm that is residual polymer (figure 19).



27a/27b



28a/28b



29a/29b

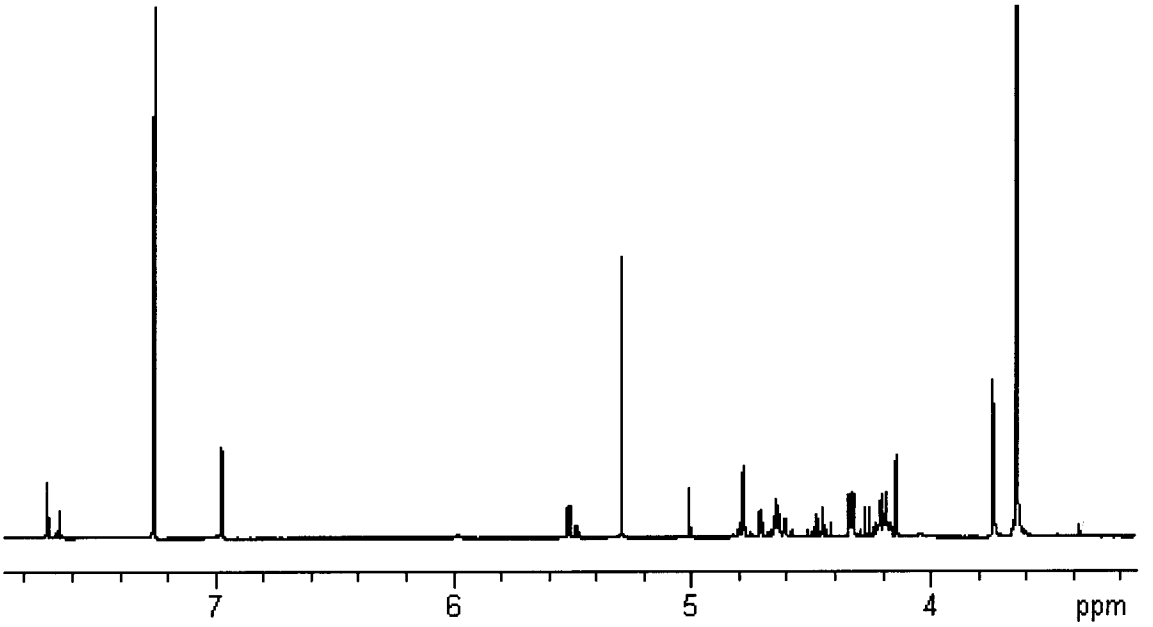


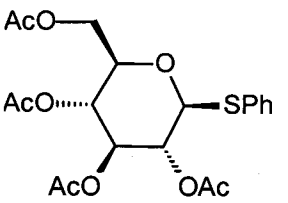
Figure 19. ^{1}H NMR spectrum of **29**

EXPERIMENTAL SECTION

General Methods

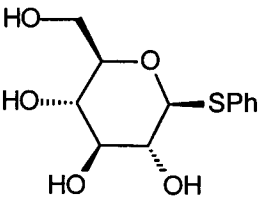
A Melt Temp apparatus was used to take all melting points and these were not corrected. Thin layer chromatography was performed on Whatman 250 μm layer silica gel with aluminum-backed plates. Flash column chromatography was performed on Aldrich silica gel 60 (70-270 mesh). Proton nuclear magnetic resonance spectra were recorded on a Varian Gemini 2000 400 MHz spectrometer. Proton shifts are reported in ppm on the δ scale. The multiplicities are recorded as followed: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). For proton NMR of the polymer supported compounds, the polymer methylene signal at ~3.6 ppm was suppressed to clarify the spectra and the singlet at ~3.3 ppm for the terminal methyl group was used to determine the loading and yields on the polymer.

Preparation of phenyl 2,3,4,6 tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (6).[14]



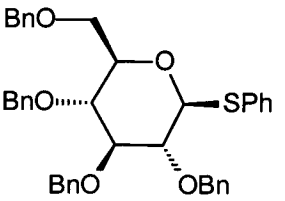
1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (30 g, 0.0769 mol) was dissolved in chloroform (150 ml). Thiophenol (9.51 ml, 0.0923 mol) was added and the mixture was stirred. Boron trifluoride diethyl etherate (48.7 ml, 0.396 mol) was added and the mixture stirred overnight at room temperature. The reaction mixture was washed with saturated aqueous sodium bicarbonate (3 × 30 ml) and water (3 × 30 ml), dried with sodium sulfate (anhydrous), and vacuum evaporated to leave a yellow solid. Recrystallization with ethyl acetate/hexane gave white crystals (17.703 g, 52.1% yield) with a melting point of 113-116 °C. ^{1}H NMR ($CDCl_3$): δ 2.0-2.1 (4 s, 12H); 3.70 (m, 1H); 4.20 (m, 1H); 4.70 (d, 2H, J = 10 Hz), 4.97-5.05 (2 m, 2H), 5.21 (m, 1H), 7.30-7.50 (m, 5H).

Preparation of phenyl-1-thio-β-D-glucopyranoside (7).[15]



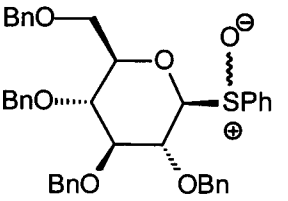
Phenyl 2,3,4,6 tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (5.058 g, 0.011 mol) was dissolved in methanol (100 ml). Sodium metal (0.5 g, 0.022 mol) was added to methanol (20 ml), and this was added to the reaction mixture and stirred for two days. The reaction was quenched with dry ice and vacuum evaporated to leave a white solid (3.00 g, 100 % yield) with a melting point of 135-142°C. ^{1}H NMR (D-$_6$ DMSO): δ 3.0-3.6 (m, 6H); 4.6 (d, 1H, J =); 7.2-7.5 (m, 5H).

Preparation of phenyl 2,3,4,6 tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (8). [16]



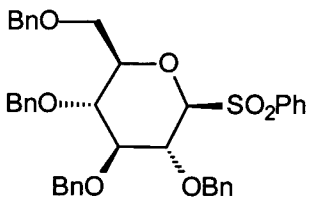
Phenyl 1-thio-β-D-glucopyranoside (1.270 g, 0.0047 mol) was dissolved in *N, N*-dimethylformamide (12 ml) under nitrogen. Sodium hydride (1.076 g, 0.045 mol) was added and reacted for fifteen minutes. Benzyl bromide (2.8 ml, 0.024 mol) was then added, and the reaction mixture was heated to 120 °C for two hours. The reaction mixture was poured over ice (~60 g, 3.3 mol) and ethanol (25 ml) was added with stirring to form a yellow precipitate. The precipitate was filtered and recrystallized from ethanol to give white crystals (1.844g, 62% yield) with a melting point of 87-89°C. ^{1}H NMR ($CDCl_3$): δ 3.55 (m, 1H); 3.66-3.82 (m, 2H); 4.59-4.78 (m, 3H); 4.85-4.95 (m, 1H); 7.27-7.39 (m, 25 H).

Preparation of phenyl 2,3,4,6-tetra-*O*-benzyl-1-sulfoxide-β-D-glucopyranoside (9). [17]



Phenyl 2,3,4,6 tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (6.309 g, 0.01 mol) was dissolved in dichloromethane (50 ml) and silica gel (2.066g) was added to the mixture. Acetic anhydride (1.0 ml, 0.011 mol) and 30% hydrogen peroxide (1.4 ml) were added and stirred at room temperature. After five hours, the reaction mixture was washed with saturated aqueous sodium bisulfite (2 × 100 ml), saturated aqueous sodium bicarbonate (2 × 100 ml), saturated aqueous sodium chloride (2 × 100 ml) and dried over magnesium sulfate (anhydrous). The solvent was vacuum evaporated to give white crystals (4.83 g, 75 % yield) with a melting point of 98-100 °C. ^{1}H NMR ($CDCl_3$): δ 3.51-3.63 (m, 2H); 3.73-3.83 (m, 2H); 3.99-4.15 (m, 1H); 4.25-4.35 (m, 1H); 4.56-5.04 (m, 8H); 7.17-7.67 (m, 25H).

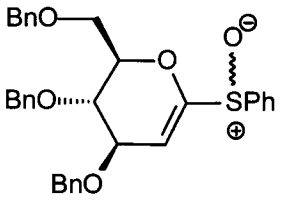
Preparation of phenyl 2,3,4,6-tetra-*O*-benzyl-1-sulfonyl-β-D-glucopyranoside (11). [18]



Phenyl 2,3,4,6 tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (2.022 g, 0.003 mol) and *m*-CPBA (2.600 g, 0.02 mol) were dissolved in CH_2Cl_2 (20 ml) and stirred for three hours at room temperature. The reaction mixture was washed with water (2 x 40 ml), saturated aqueous sodium bicarbonate (2 x 40 ml), and dried with anhydrous sodium sulfate. The solvent was vacuum evaporated to give white crystals (2.04 g, 100 % yield). ^{1}H NMR ($CDCl_3$): δ 3.49-3.61 (m, 1H); 3.74-3.79 (m, 1H); 4.07-4.12 (m, 1H); 4.31-4.43

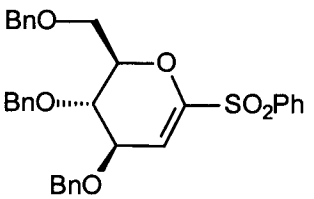
(m, 1H); 4.55 (d, 2H, J = 11.2 Hz), 4.8-4.95 (m, 8H), 5.0 (d, 1H, J = 9.3 Hz) 7.16-8.0 (m, 25H).

Preparation of 1-phenyl sulfinyl glucals (10). [19]



A solution of phenyl 2,3,4,6-tetra-*O*-benzyl-1-sulfoxide-β-D-glucopyranoside (3.225 g, 0.005 mol) in dry THF (25 ml) was added dropwise to a solution of LDA (1.2 equiv, prepared from diisopropylamine [1.0 ml] and n-butyl lithium [3.75 ml]), in THF at –78 °C. The reaction was quenched with saturated aqueous NH_4Cl (20 ml), extracted with ether (40 ml) and dried with magnesium sulfate. The solvent was vacuum evaporated to give a syrup which was purified by flash column chromatography with 3:1 hexane/ethyl acetate to give a pale yellow solid (1.97 g, 73 % yield). ^1H NMR ($CDCl_3$): δ 3.47-3.60 (m, 1H); 3.65-3.81 (m, 1H); 4.19-4.40 (m, 1H); 4.53-4.81 (m, 6H); 5.90-5.93 (2d, 1H); 7.17-7.75 (m, 25H).

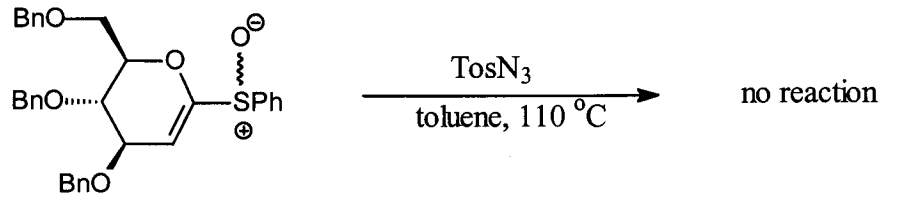
Preparation of vinyl sulfone (12). [20]



A solution of phenyl 2,3,4,6-tetra-*O*-benzyl-1-sulfonyl-β-D-glucopyranoside (2.084 g, 0.003 mol) in dry THF (10 ml) was added to a solution of LDA [1.1 equiv, prepared from diisopropylamine (0.62 ml) and n-butyl lithium (3.15 ml)], in dry THF (10 ml) at –78 °C. After six hours, the reaction was quenched with saturated aqueous NH_4Cl (40 ml), the aqueous layer was extracted with ether (40 ml) and dried with magnesium

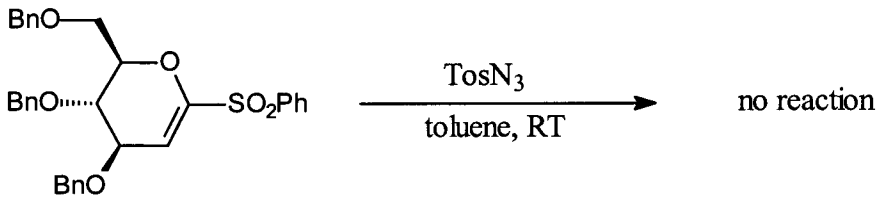
sulfate (anhydrous). The solvent was vacuum evaporated to give white crystals (1.032 g, 62 % yield). ^{1}H NMR ($CDCl_3$): δ 3.50-3.80 (m, 1H); 4.27-4.42 (m, 1H); 4.55-4.27 (m, 1H); 4.68-5.00 (m, 6H); 6.15 (d, 1H, J = 2.9 Hz); 7.16-7.96 (m, 20H).

Attempted reaction of vinyl sulfoxide with tosyl azide.



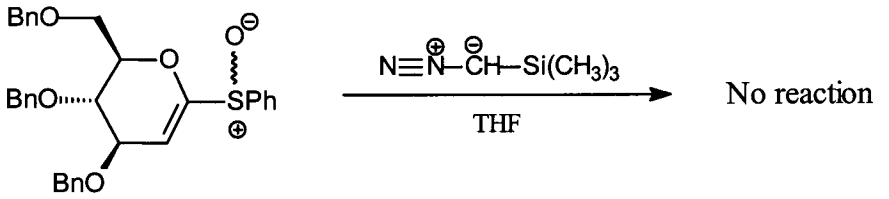
Vinyl sulfoxide (0.102 g, 0.190 mmol) and tosyl azide (0.104 g, 0.570 mmol) were dissolved in toluene (2 ml) and the mixture heated to reflux. The reaction was stirred for seven days at 110 °C then the solvent was vacuum evaporated to give a syrup. Purification by flash chromatography (silica gel, 3:1 hexane/ethyl acetate) and analysis by NMR showed only the starting vinyl sulfoxides.

Attempted reaction of vinyl sulfone with tosyl azide.



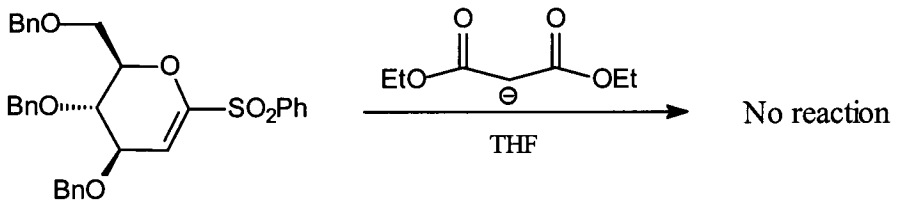
Vinyl sulfone (0.111 g, 0.2 mmol) and tosyl azide (0.310 g, 1.70 mmol) were dissolved in toluene (2 ml) and stirred at room temperature for 24 hours. The solvent was vacuum evaporated and the residue purified by flash chromatography (silica gel, 3:1 hexane/ethyl acetate) to give a syrup. NMR analysis showed only the starting vinyl sulfone.

Attempted reaction of vinyl sulfoxide with trimethylsilyl diazomethane.



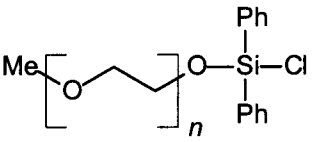
Vinyl sulfoxide (0.109 g, 0.2 mmol) and trimethylsilyl diazomethane (0.2 ml, 0.4 mmol) were dissolved in dry THF (4 ml) and the mixture stirred for three days at room temperature. After the observation of the TLC plate using 2:1 hexane/ethyl acetate indicated only starting sulfoxide, trimethylsilyl diazomethane (0.2 ml, 0.4 mmol) was added and the mixture stirred for 24 hours. The solvent was vacuum evaporated to give a syrup. NMR analysis of the syrup showed only the starting vinyl sulfoxide.

Attempted reaction of vinyl sulfone with diethyl malonate anion.



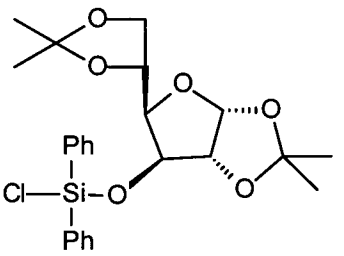
Diethyl malonate (0.028 ml, 0.186 mmol) was dissolved in dry THF (2 ml) and sodium ethoxide (14 mg, 0.20 mmol) was added to generate the diethyl malonate anion. A solution of vinyl sulfone (50 mg, 0.093 mmol) in THF (1 ml) was added to the anion and stirred for five hours. The reaction mixture was then quenched with NH_4Cl and washed with ether (10 ml), separated, dried with sodium sulfate (anhydrous), and filtered. The solvent was vacuum evaporated to give a syrup. NMR analysis of the syrup showed only the starting vinyl sulfone.

Preparation of (MeO-PEG)-Chlorodiphenylsilane. (13)



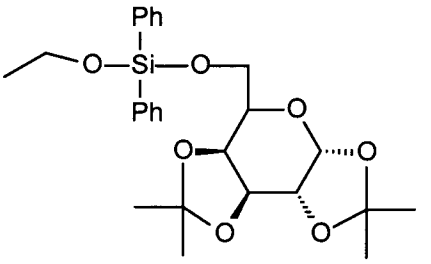
Poly(ethylene glycol) mono methyl ether (5.012 g, 1 mmol) was dissolved in hot dry THF (50 ml) under argon. Sodium hydride (0.131 g, 2.2 mmol) was added and the reaction mixture was stirred for 10 minutes. Sodium iodide (0.177 g, 1.1 mmol) was then added followed by dichlorodiphenylsilane (6.3 ml, 30 mmol). The mixture was stirred at room temperature for one week. The polymer was precipitated with ether at 4 °C, filtered and dried. Recrystallization with ethanol (100 %) gave a yellow solid (1.60 g, 0.32 mmol). ^{1}H NMR ($CDCl_3$): δ 3.33 (s, 3H); 3.40-3.80 (m, polymer), 7.25-7.70 (m, 10H).

Preparation of 3-(chlorodiphenylsilyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. (14)



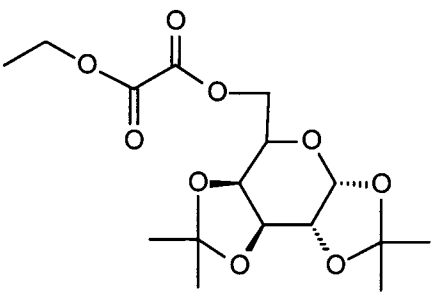
Diacetone-D-glucose (0.268 g, 1 mmol) and 1,8-diazabicylo[5.4.0]undec-7-ene (0.16 ml, 1.1 mmol) were dissolved in CH_2Cl_2 (10 ml) and cooled in an ice-salt bath. A solution of dichlorodiphenylsilane (0.23 ml, 1.1 mmol) in CH_2Cl_2 (5 ml) was added and the mixture was stirred for 3 hours. The reaction was quenched with aqueous NH_4Cl (2 × 20 ml), washed with water (20 ml), and dried with sodium sulfate (anhydrous). The solvent was vacuum evaporated to give a white solid (90 mg, 19 % yield). ^{1}H NMR ($CDCl_3$): δ 1.15 (s, 3H); 1.28 (s, 3H); 1.32 (s, 3H); 1.38 (s, 3H); 4.00-4.19 (m, 2H); 4.24 (d, 1H, J = 3.66 Hz); 4.40-4.48 (m, 1H); 4.90 (d, 2H, J = 3.3 Hz); 5.83 (d, 1H, J = 3.5 Hz); 7.30-7.72 (m, 10H).

Preparation of 6-(ethoxydiphenylsilyl)-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose. (15)



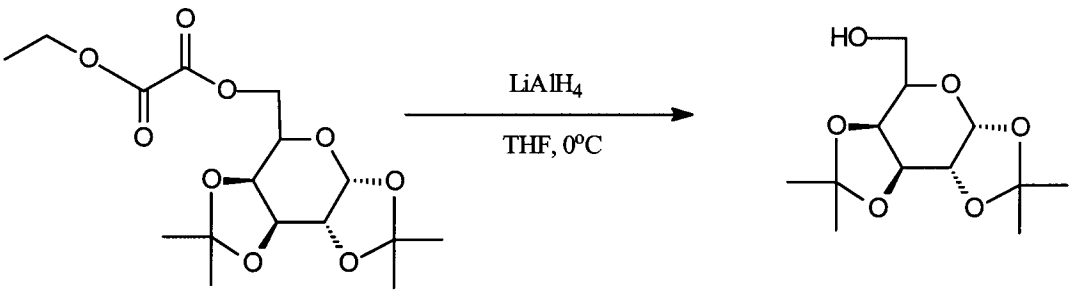
Dichlorodiphenylsilane (0.22 ml, 1 mmol) was dissolved in CH_2Cl_2 (10 ml) and cooled in an ice bath. Pyridine (0.11 ml, 1 mmol) was added dropwise and the mixture was stirred for 15 minutes. A solution of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (0.395 g, 1.5 mmol) in CH_2Cl_2 (10 ml) was added and the mixture stirred for 3 hours. An additional amount of dichlorodiphenylsilane (0.05 ml, 0.2mmol) was added and the mixture was stirred for 30 minutes. Ethanol (5 ml, 100 %) was added and the mixture was stirred overnight. The solvent was vacuum evaporated and the residue was purified by flash chromatography (silica gel, 1:1 hexane/ethyl acetate) to give a solid (8 mg, 2% yield). ^{1}H NMR ($CDCl_3$): δ 1.17-1.21 (t, 3H); 1.37 (s, 6H); 1.50 (s, 3H); 1.59 (s, 3H); 3.80-3.86 (q, 2H); 4.28-4.39 (m, 5H), 4.63 (d, 1H, J = 5.5 Hz), 5.60 (d, 1H, J = 5.5 Hz), 7.25-7.75 (m, 10H).

Preparation of the ethyl oxalate derivative of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose. (18)



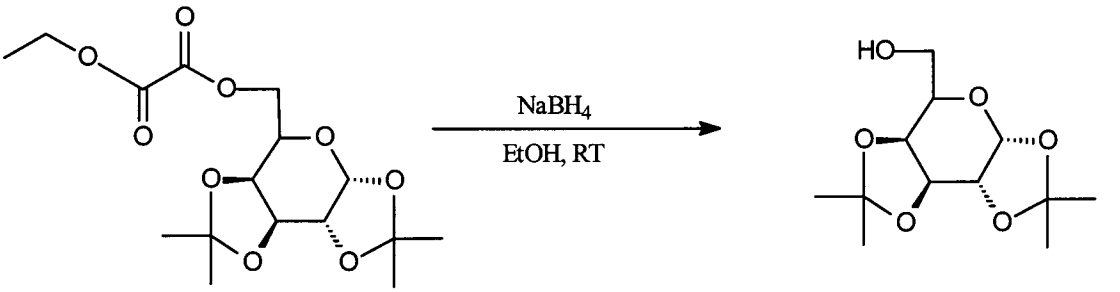
Oxalyl chloride (1 ml, 10 mmol) was dissolved in dry dichloromethane (30 ml) and cooled to 0 °C with an ice bath. Pyridine (1 ml, 11 mmol) was added dropwise and the mixture stirred for 15 minutes. A solution of 1,2:3,4 di- *O*-isopropylidene-D-galactopyranose (2.6 g, 10 mmol) in dry dichloromethane (50 ml) was added and the mixture stirred for 2 hours. Ethanol (100 %, 50 ml) was added and stirred for one hour. The reaction was extracted with water (50 ml) and the organic layer was dried with sodium sulfate (anhydrous). The solvent was vacuum evaporated to give a syrup that was purified by flash chromatography (silica gel, 1:1 hexane/ethyl acetate) to give white crystals (1.70 g, 50% yield). ^{1}H NMR ($CDCl_3$): δ 1.28-1.30 (m, 9H); 1.40 (s, 3H); 1.47 (s, 3H), 4.09 (m, 1H); 4.21 (m, 1H); 4.29-4.36 (m, 3H); 4.38 (d, 1H, J = 6 Hz); 4.58-4.605 (m, 1H); 5.47 (d, 1H, J = 4.9 Hz).

Reduction of the ethyl oxalate derivative of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose with Lithium Aluminum Hydride.



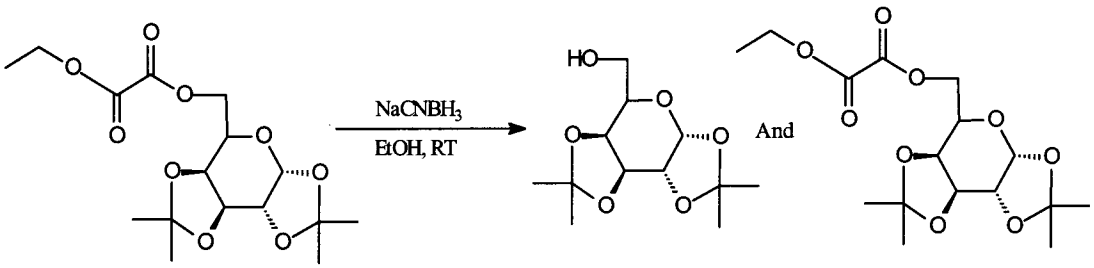
The ethyl oxalate derivative of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (0.359 g, 1 mmol) was dissolved in THF (10 ml) under argon and cooled to 0 °C with an ice bath. $LiAlH_4$ (1.0 ml of a 1.0M in THF, 1 mmol) was added and the mixture stirred for 1 hour. The reaction was quenched with water (1 ml), aqueous sodium hydroxide (15 % solution, 1 ml), and water (3 ml). The solution was then filtered and the filtrate was vacuum evaporated to give a syrup. NMR analysis showed the major product to be 1,2: 3,4-di-*O*-isopropylidene-D-galactopyranose.

Reduction of the ethyl oxalate derivative of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose with Sodium Borohydride.



The ethyl oxalate derivative of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (0.375 g, 1.05 mmol) was dissolved in ethanol (10 ml, 95 %). $NaBH_4$ (46 mg, 1.1 mmol) was added at room temperature and the mixture stirred for 3 hours. The reaction was quenched with water (10 ml), the aqueous layer was extracted with CH_2Cl_2, and dried with sodium sulfate (anhydrous). The solvent was vacuum evaporated to give a syrup (130 mg, 50 % yield). NMR analysis showed this material to be 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose.

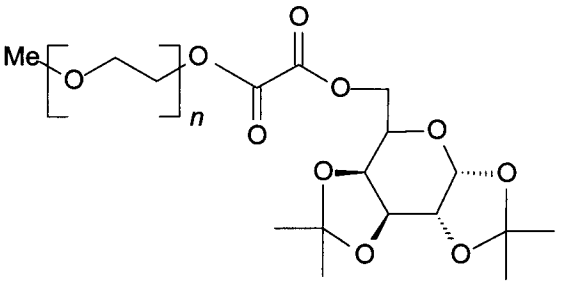
Reduction of the ethyl oxalate derivative of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose with Sodium Cyanoborohydride.



Ethyl oxalyl derived 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (0.210 g, 0.6 mmol) was dissolved in ethanol (10 ml, 95 %). $NaCNBH_3$ (42 mg, 0.7 mmol) was added and the mixture stirred overnight. The reaction was quenched with water (10 ml), the aqueous layer was extracted with CH_2Cl_2, which was then dried with anhydrous sodium sulfate. The solvent was vacuum evaporated to give a syrup (120 mg, 77% yield). NMR

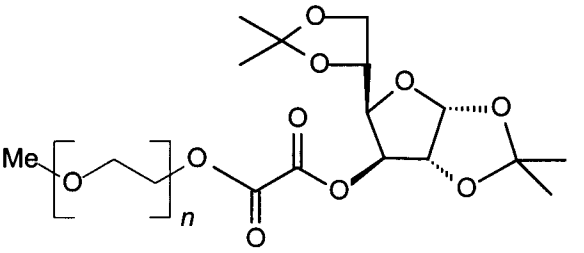
analysis showed starting material and 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose in the product.

Preparation of (MeO-PEG)-(1,2,5,6-Di-*O*-isopropylidene-D-galactopyranose)oxalate. (16)



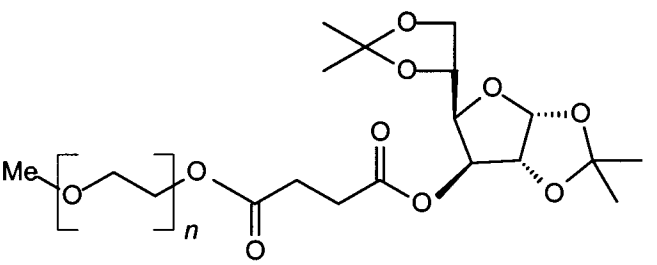
Oxalyl chloride (0.1 ml, 1 mmol) was dissolved in dry dichloromethane (10 ml) and cooled to 0 °C with an ice bath. Pyridine (0.11 ml, 1.1 mmol) was added dropwise and the mixture was stirred for 15 minutes. A solution of poly(ethylene glycol) mono methyl ether (5.014 g, 1 mmol) in dry dichloromethane (50 ml) was added dropwise to the reaction over several minutes and the mixture stirred for two hours. A solution of 1,2: 3,4-di-*O*-isopropylidene-D-galactopyranose (0.848 g, 3.3 mmol) in dry dichloromethane (5 ml) was added dropwise to the reaction mixture which was then heated to reflux for 72 hours. The reaction was cooled in ice to 4 °C and the product was precipitated with ether (250 ml) and filtered. Recrystallization from 100% ethanol gave a white solid (3.530g, 70% yield, 95-100% loading by ^{1}H NMR). ^{1}H NMR ($CDCl_3$): δ 1.28-1.35 (2s, 6H); 1.40 (s, 3H); 1.45 (s, 3H); 3.35 (s, 3H); 3.40-3.80 (m, polymer); 4.05 (m, 2H); 4.25 (m, 2H); 4.30 (m, 1H); 4.35 (m, 1H); 4.60 (m, 2H), 5.50 (d, 1H, J = 5 Hz).

Preparation of (MeO-PEG)-(1,2:5,6-Di-*O*-isopropylidene-D-glucofuranose)oxalate. (17)



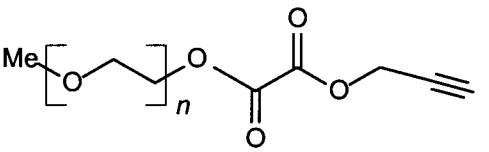
Oxalyl chloride (0.1 ml, 1 mmol) was dissolved in dry dichloromethane (10 ml) and cooled to 0 °C with an ice bath. Pyridine (0.11 ml, 1.1 mmol) was added dropwise and the mixture was stirred for 15 minutes. A solution of poly(ethylene glycol) mono methyl ether (5.019 g, 1 mmol) in dry dichloromethane (50 ml) was added dropwise to the reaction over several minutes and the mixture stirred for two hours. A solution of diacetone-D-glucose (1.373 g, 5 mmol) in dry dichloromethane (10 ml) was added and the mixture heated to reflux for 72 hours. The reaction was cooled to 4 °C in an ice bath and the product was precipitated with ether (250 ml) and filtered. Recrystallization from 100 % ethanol gave a white solid (4.727 g, 95 % yield, 70-75 % loading by ^{1}H NMR). ^{1}H NMR ($CDCl_3$): δ 1.3 (s, 3H); 1.35 (s, 3H); 1.45 (s, 3H); 1.50 (s, 3H); 3.35 (s, 3H, polymer); 3.40-3.80 (m, polymer); 4.25 (m, 2H, polymer); 4.30-4.48 (m, 3H); 4.55 (m, 2H); 5.90-5.95 (2 d, 1H).

Preparation of (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose)(MeO-PEG) succinate (19).



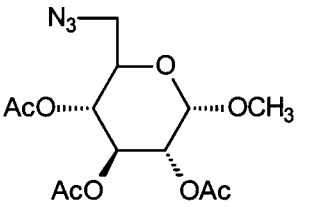
Succinyl chloride (0.1 ml, 1 mmol) was dissolved in dry dichloromethane (10 ml) and cooled to 0 °C with an ice bath. Pyridine (0.11 ml, 1.1 mmol) was added dropwise and the solution was stirred for 15 minutes. A solution of poly(ethylene glycol) mono methyl ether (5.007 g, 1 mmol) in dry dichloromethane (50 ml) was added dropwise to the reaction over several minutes and the mixture was stirred for two hours. A solution of diacetone-D-glucose (1.340 g, 5 mmol) in dry dichloromethane (10 ml) was added to the reaction mixture which was then refluxed over night. The reaction was cooled in ice to 4 °C and the product was precipitated with ether and filtered. Recrystallization from 100 % ethanol gave a gray solid (3.335 g, 68 % yield, 50 % loading). ^{1}H NMR ($CDCl_3$): δ 1.25-135 (m), 1.43 (d), 2.6 (m), 3.32 (3H, s), 3.40-3.80 (polymer, m), 4.20 (2H, m), 4.50-4.55 (m), 5.20 (d), 5.80 (d), 5.97 (d).

Preparation of (propargyl)(MeO-PEG)oxalate. (20)



Oxalyl chloride (1.0 ml, 10 mmol) was dissolved in dry dichloromethane (100 ml) and cooled to 0 °C with an ice bath. Pyridine (1.2 ml, 11 mmol) was added dropwise and the mixture was stirred for 15 minutes. A solution of poly(ethylene glycol) mono methyl ether (50 g, 10 mmol) in dry dichloromethane (500 ml) was added dropwise to the reaction over several minutes and stirred for two hours. A solution of propargyl alcohol (3.00 ml, 50 mmol) in dry dichloromethane (10 ml) was then added and the solution was refluxed over night. The reaction was cooled to 4 °C in an ice bath and the product was precipitated with ether and filtered. Recrystallization with 100% ethanol gave a white solid (42.855 g, 86 % yield, 85 % loading by ^{1}H NMR). ^{1}H NMR ($CDCl_3$): δ 2.56 (m, 1H); 3.32 (s, 3H, polymer); 3.58-3.60 (m, polymer); 4.35-4.45 (m, 2H, polymer); 4.82 (d, 1H, J = 2.3 Hz).

Preparation of methyl 2,3,4,-tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside (22).[20]



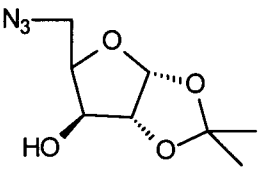
Methyl-α-D-glucopyranoside (5.010 g, 26 mmol) was dissolved in pyridine (100 ml) and cooled in an ice bath. A solution of *p*-toluene sulfonyl chloride (5.354 g, 28 mmol) in pyridine (25 ml) was added and the reaction mixture was stirred over night at room temperature. The reaction mixture was washed with water (500 ml), the aqueous layer was extracted with CH_2Cl_2 (100 ml) and dried with sodium sulfate (anhydrous). The solvent was vacuum evaporated to give a colorless syrup (2.57 g, 30 % yield). ^1H NMR (D_6-DMSO): δ 3.19 (s, 3H); 4.0-4.2 (m, 1H); 4.41-4.56 (m, 2H); 4.78 (d, 1H, J = 7 Hz); 4.86 (d, 1H, J = 5 Hz); 5.14 (d, 1H, J = 6 Hz); 7.45-7.77 (m, 5H).

Methyl 6-*p*-tolylsulfonyl-α-D-glucopyranoside from the previous reaction (2.57 g, 7.4 mmol) was dissolved in acetone (40 ml). A solution of sodium azide (2.055 g, 32 mmol) in water (15 ml) was added and the reaction mixture was stirred at reflux for 3 days. The solvent was vacuum evaporated to give a colorless syrup (1.79 g, 100 % yield). ^1H NMR (D_6-DMSO): δ 3.27 (s, 3H); 3.40-3.55 (m, 2H); 4.54 (d, 1H, J = 4 Hz); 4.82 (d, 1H, J = 7 Hz); 4.87 (d, 1H, J = 4 Hz); 5.14 (d, 1H, J = 6 Hz).

Methyl 6-azido-6-deoxy-α-D-glucopyranoside from the previous experiment (1.79 g, 10 mmol) was dissolved in pyridine (20 ml) and cooled in an ice bath. Acetic anhydride (10 ml, .10 mol) was added and the reaction mixture was stirred for 3 hours. The reaction mixture was pour over ice (~ 50 g) then the aqueous mixture was extracted with CH_2Cl_2 (3 x 25 ml), washed with H_2SO_4 (5 %, 3 x 15 ml) and dried with sodium sulfate (anhydrous). The solvent was vacuum evaporated and the residue crystallized

from ethanol to give pale yellow crystals (0.801 g, 25 % yield). ^{1}H NMR ($CDCl_3$): δ 2.0-2.1 (3s, 9H); 3.2 (m, 2H); 3.4 (s, 3H); 4.0 (m, 2H); 4.8-5.0 (m, 2H); 5.4 (t, 1H).

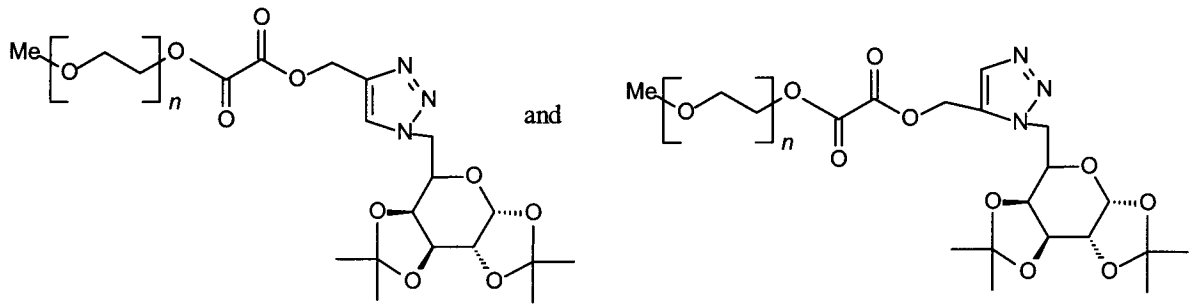
Preparation of 5-azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (23). [21]



1,2-*O*-Isopropylidene-D-xylofuranose (3.356 g, 18 mmol) was dissolved in pyridine (15 ml) and cooled in an ice bath. A solution of *p*-toluene sulfonyl chloride (3.676 g, 19 mmol) in $CHCl_3$ (6 ml) was added and the reaction stirred over night. Water (0.5 ml) was added and the reaction stirred for 30 minutes. The reaction was quenched with water (100 ml) and then washed with $CHCl_3$ (3 × 10 ml), H_2SO_4 (5 %, 3 × 15 ml), water (1 × 50 ml) and dried with sodium sulfate (anhydrous). The solvent was vacuum evaporated to give (3.05 g of product, 49 % yield). ^{1}H NMR ($CDCl_3$): δ 1.2 (s, 3H); 1.4 (s, 3H); 4.14 (m, 1H); 4.29-4.35 (m, 2H); 4.5 (d, 2H, J = 9 Hz); 5.86 (d, 1H, J = 8 Hz); 7.25-7.80 (m, 5H).

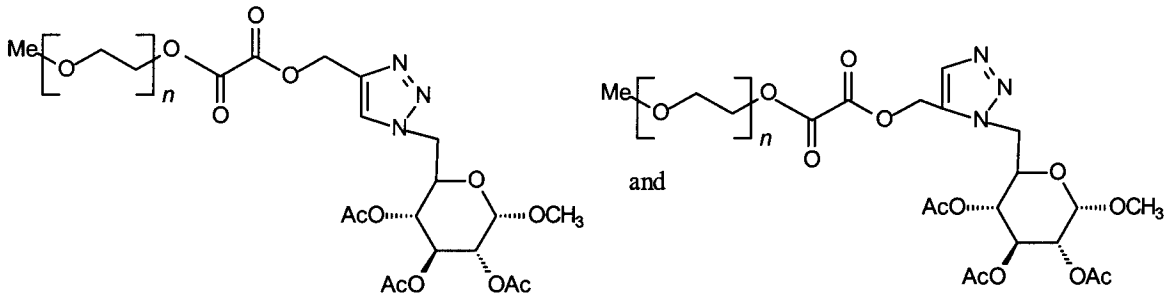
5-*p*-Tolylsulfonyl-1,2-*O*-Isopropylidene-D-xylofuranose (2.642 g, 7.7 mmol) was dissolved in *N,N*-dimethylformamide (30 ml). Sodium azide (0.610 g, 9 mmol), water (1.5 ml), and urea (14 mg) were added and the reaction mixture was stirred and heated to 110 °C under nitrogen over night. The reaction mixture was then poured over ice (~50 g) and the organic layer was extracted with ethyl acetate (3 × 25 ml), washed with water (25 ml), saturated sodium bicarbonate (2 × 20 ml), water (25 ml), and dried with sodium sulfate (anhydrous). The solvent was vacuum evaporated to give white crystals (1.06 g, 60 % yield). ^{1}H NMR ($CDCl_3$): δ 1.2 (s, 3H); 1.4 (s, 3H); 3.6 (m, 1H); 4.2-4.3 (m, 2H); 4.5 (d, 2H, J = 9 Hz); 5.95 (d, 1H, J = 9 Hz).

Preparation of D-Galactose-derived polymer-supported triazoles. (24a and 24b)



(Propargyl) (MeO-PEG) oxalate (5.007 g, 1 mmol) was dissolved in toluene (30 ml) with heating and then cooled. 6-Azido-6-deoxy-1,2:3,4-di- *O*-isopropylidene-D-galactopyranose (0.464 g, 2 mmol) was added and the solution refluxed over night. The product was precipitated with ether at 4 °C for one hour then filtered and air dried for one hour. Recrystallization with ethanol (100 %) gave a white solid (4.433 g, 85 % yield, 86 % for cycloaddition step). ^{1}H NMR ($CDCl_3$): δ 1.33-1.50 (m, 12H); 3.32 (s, 3H); 3.40-3.80 (m, polymer); 4.35-4.45 (m, 2H), 4.8 (d, 1H, J = 2.7 Hz); 7.65 (s, 1H); 7.92 (s, 1H).

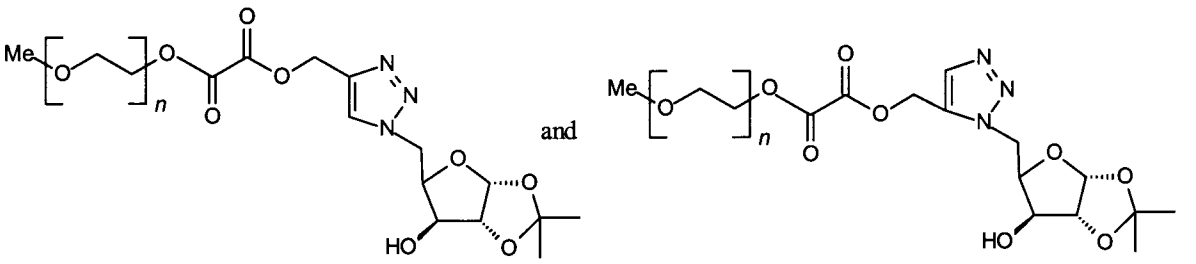
Preparation of D-Glucose-derived polymer-supported triazoles. (25a and 25b)



Propargyl) (MeO-PEG) oxalate (5.017 g, 1 mmol) was dissolved in toluene (30 ml) with heat and then cooled. Methyl 6-azido-6-deoxy-2,3,4,-tri-*O*-acetyl-α-D-glucopyranoside (0.721 g, 2 mmol) was added and the mixture refluxed over night. The product was precipitated with ether at 4 °C for one hour then filtered and air dried for one hour. Recrystallization with ethanol (100 %) gave a white solid (4.290 g, 89 % yield, 82

% for cycloaddition step). ^{1}H NMR ($CDCl_3$): δ 1.96 (s, 3H); 2.02 (s, 3H); 2.07 (s, 3H); 3.07 (s, 3H); 3.33 (s, 3H); 3.40-3.80 (m, polymer); 4.37-4.42 (m, 2H); 4.77-4.87 (m, 2H); 7.72 (s, 1H); 7.90 (s, 1H).

Preparation of D-Xylose-derived polymer-supported triazoles. (26a and 26b)



(Propargyl) (MeO-PEG) oxalate (5.010 g, 1 mmol) was dissolved in toluene (30 ml) with heat and then cooled. 5-Azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (0.701 g, 2 mmol) was added and the solution refluxed over night. The product was precipitated with ether at 4 °C then filtered and air dried for one hour. Recrystallization with ethanol (100%) to give a white solid (4.832 g, 92 % yield, 73 % for cycloaddition step). ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 3H); 1.41 (s, 3H); 3.32 (s, 3H); 3.40-3.80 (m, polymer); 4.05-4.20 (m, 2H); 4.38-4.60 (m, 2H); 5.90 (m, 1H); 7.65 (s, 1H); 7.92 (s, 1H).

Reduction of D-Galactose-derived polymer-supported triazole. Synthesis of (29a and 29b)

The polymer-supported triazole (**24a** and **24b**) (1.00 g, 0.2 mmol) was dissolved in ethanol (30 ml, 100 %) with heat and then cooled. $NaBH_4$ (25 mg, 0.4 mmol) was added and the reaction stirred at room temperature for 5 hours. The reaction mixture was treated with ether (150 ml), filtered, and then the filtrate was vacuum evaporated to give a colorless syrup (15 mg, 26 % yield) that was mainly triazoles **29a** and **29b**. ^{1}H NMR ($CDCl_3$): δ 1.25-1.60 (8 s, 12H); 3.6 (residual polymer); 4.15-4.80 (m, 5H); 5.5 (d, 1H, J = 6 Hz); 7.65 and 7.70 (2s, 1H).

Reduction of D-Glucose-derived polymer-supported triazole. Synthesis of (28a and 28b)

The polymer-supported triazole (**25a** and **25b**) (1.00 g, 0.2 mmol) was dissolved in ethanol (100 ml). $NaCNBH_3$ (17 mg, 0.2 mmol) was added and the mixture stirred at room temperature over night. The reaction mixture was treated with ether (150 ml) and filtered then the filtrate was vacuum evaporated to give a colorless syrup (38 mg, 70 % yield). NMR analysis showed possible reduction and polymer starting marterial that was not clearly defined.

Reduction of D-Xylose-derived polymer-supported triazole. Synthesis of (27a and 27b)

The polymer-supported triazole (**26a** and **26b**) (1.00 g, 0.2 mmol) was dissolved in ethanol (30 ml, 100 %) with heat and then cooled. $NaBH_4$ (25 mg, 0.4 mmol) was added and the mixture stirred at room temperature for 3 hours. The reaction mixture was treated with ether (150 ml), filtered, and then the filtrate was vacuum evaporated to give a colorless syrup (30 mg, 76 % yield). ^1H NMR ($CDCl_3$): δ 1.3 (s, 3H); 1.4 (s, 3H), 4.2-4.8 (m, 7H), 5.96 (d, 1H, $J = 9$ Hz), 7.61 and 7.7 (2s, 1H).

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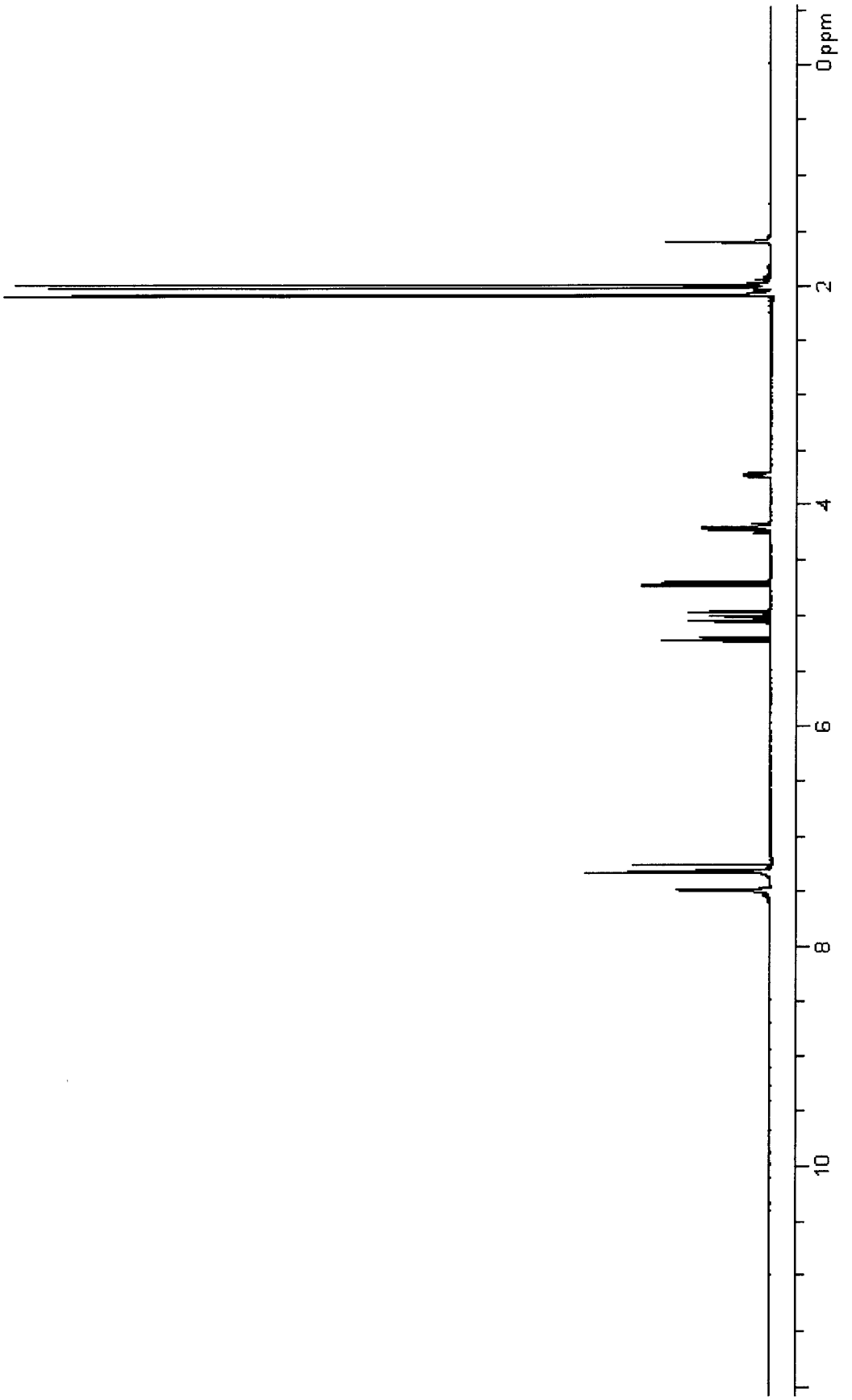

Figure 20. ^{1}H NMR spectrum of thioglucside **6**

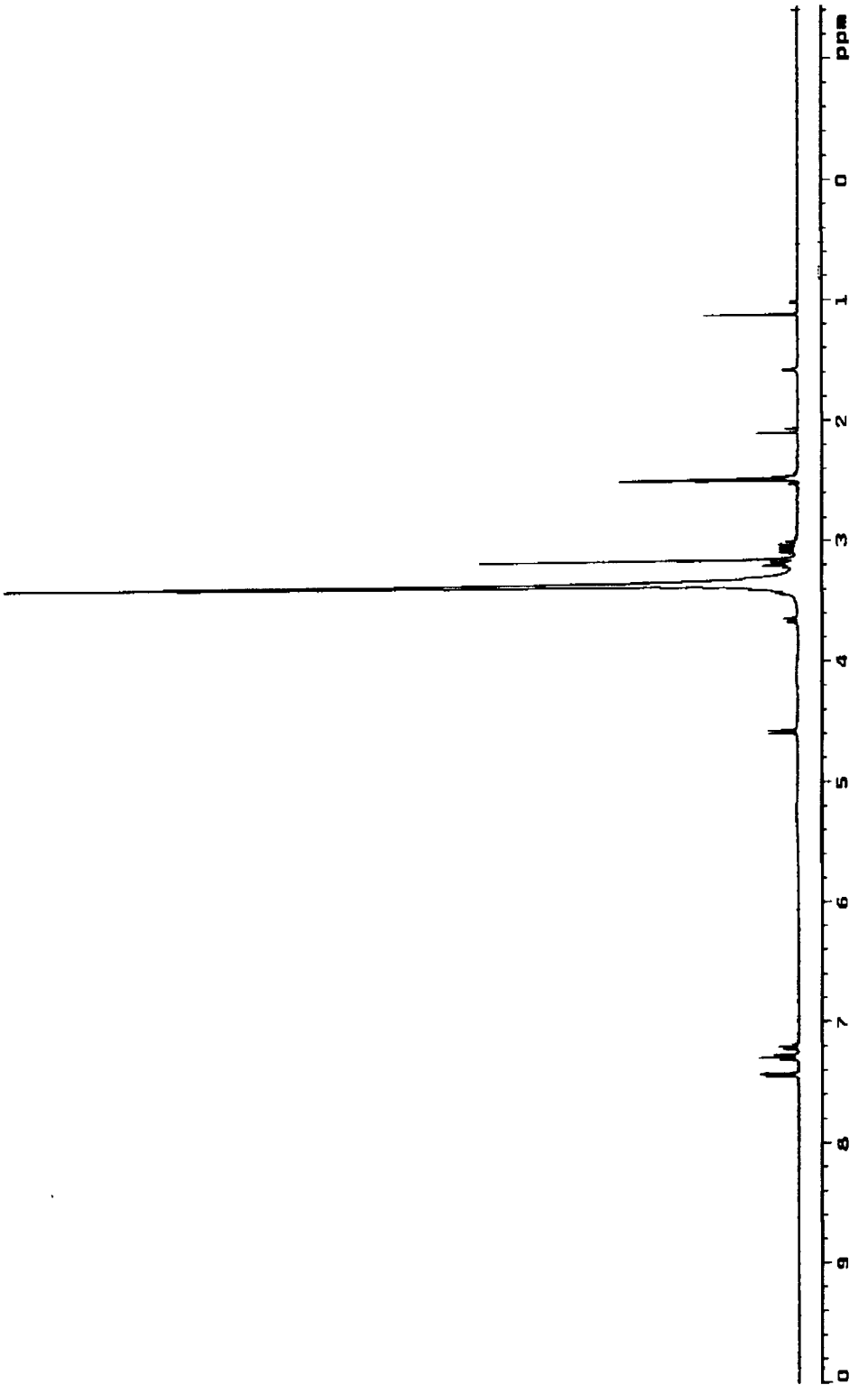

Figure 21. ^{1}H NMR spectrum of compound **7**

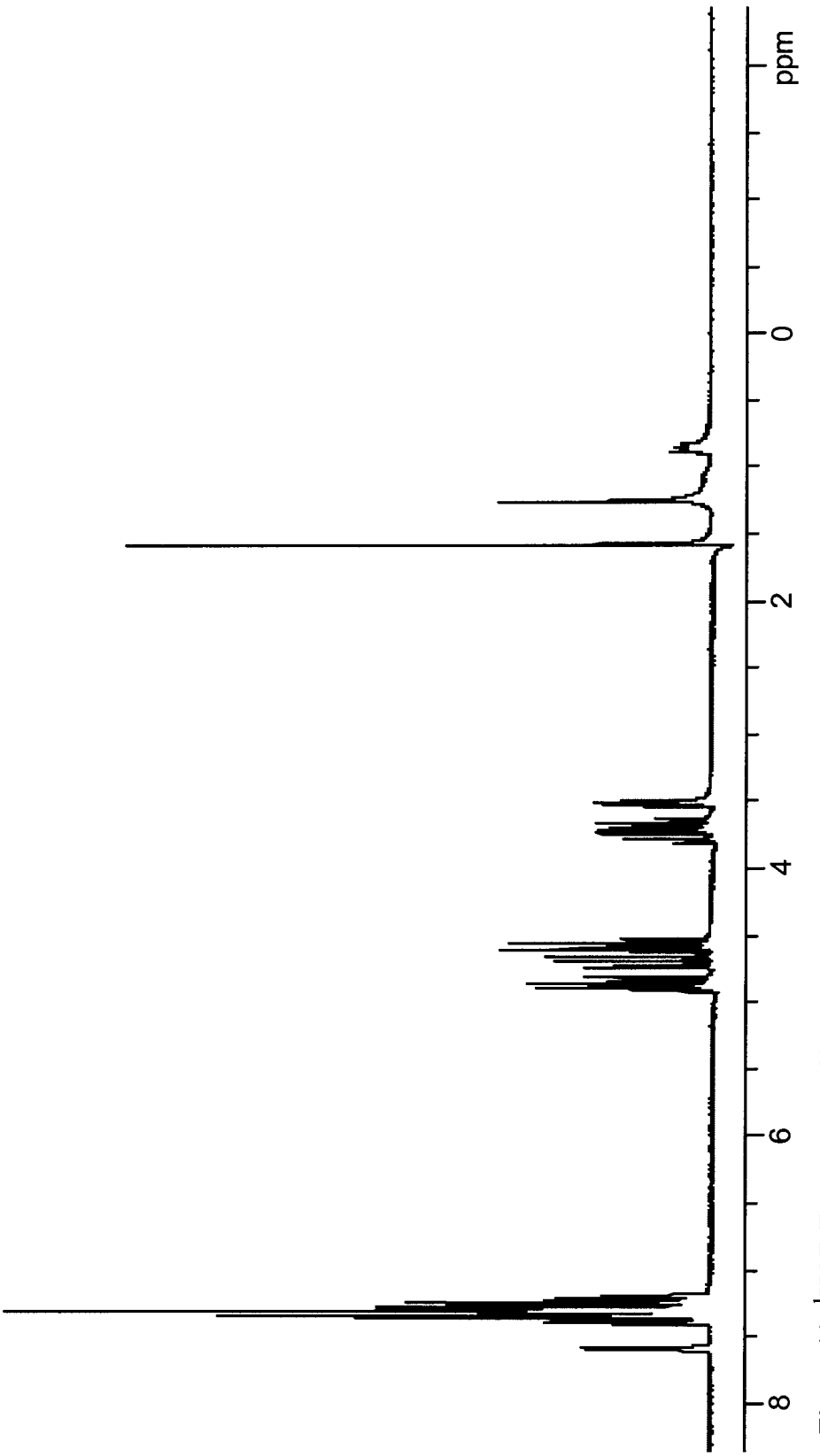

Figure 22. ^{1}H NMR spectrum of benzyl protected derivative **8**

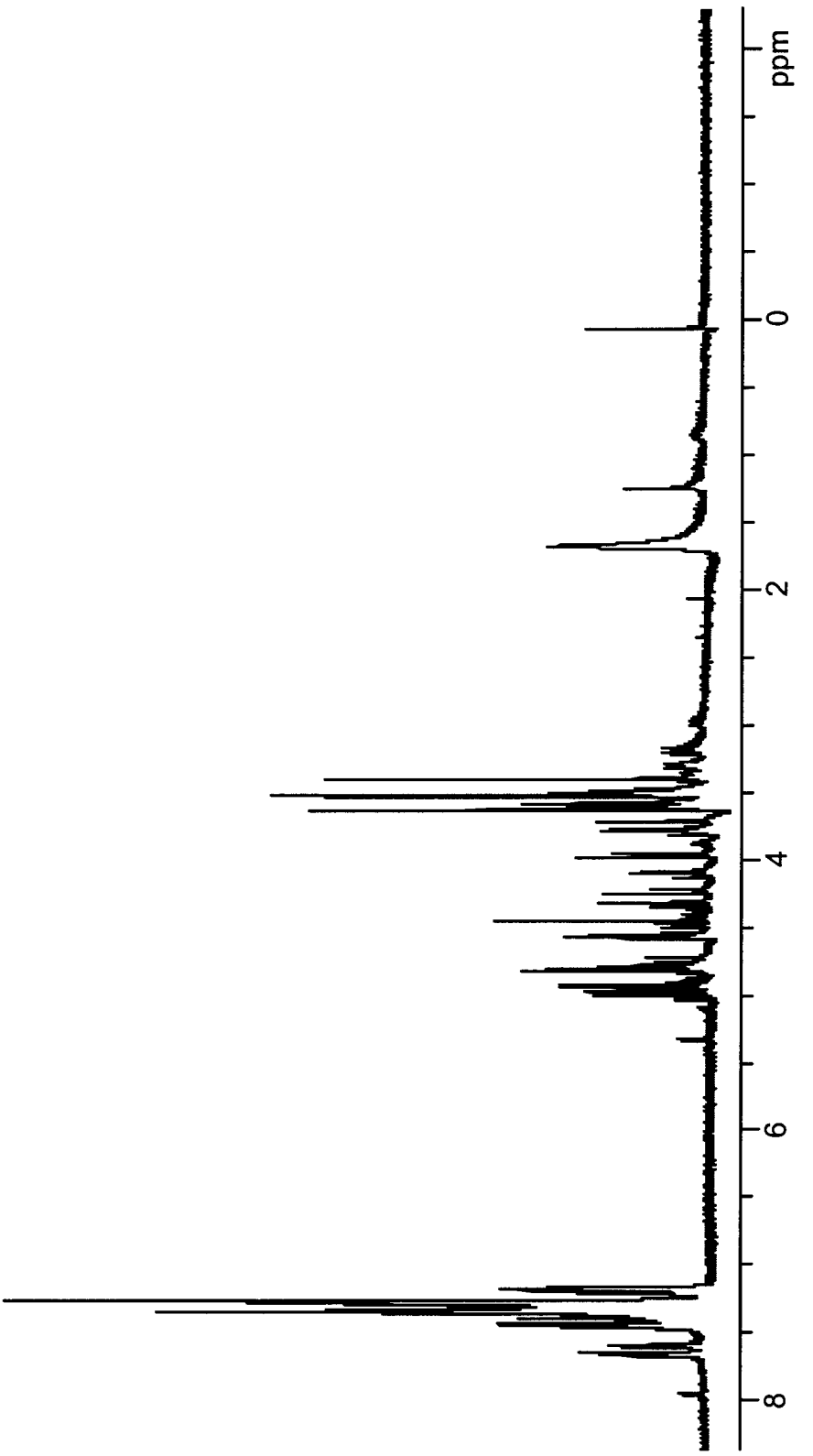

Figure 23. ^{1}H NMR of sugar-derived sulfoxides **9**

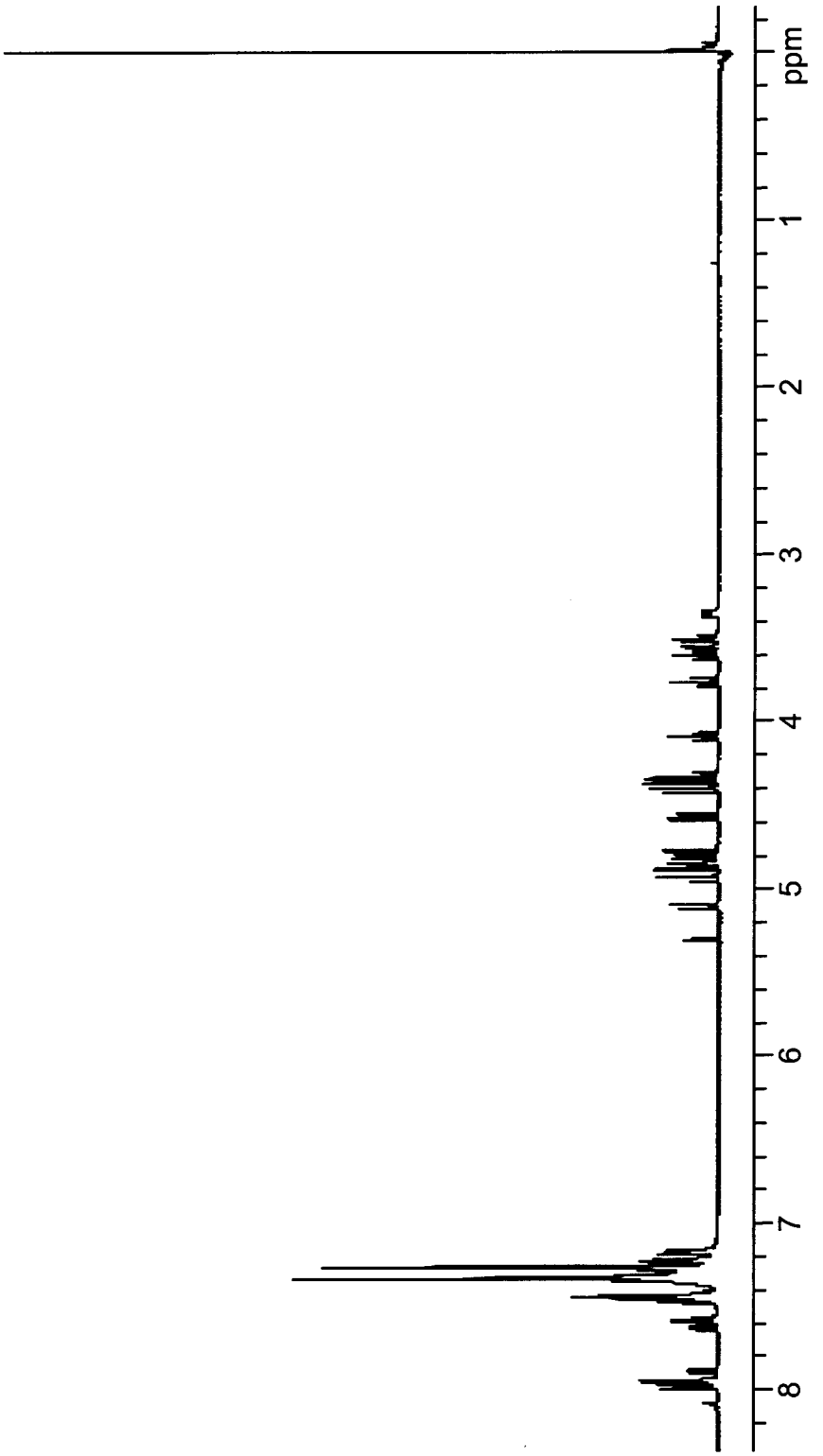

Figure 24. ^{1}H NMR of sugar-derived sulfone **11**

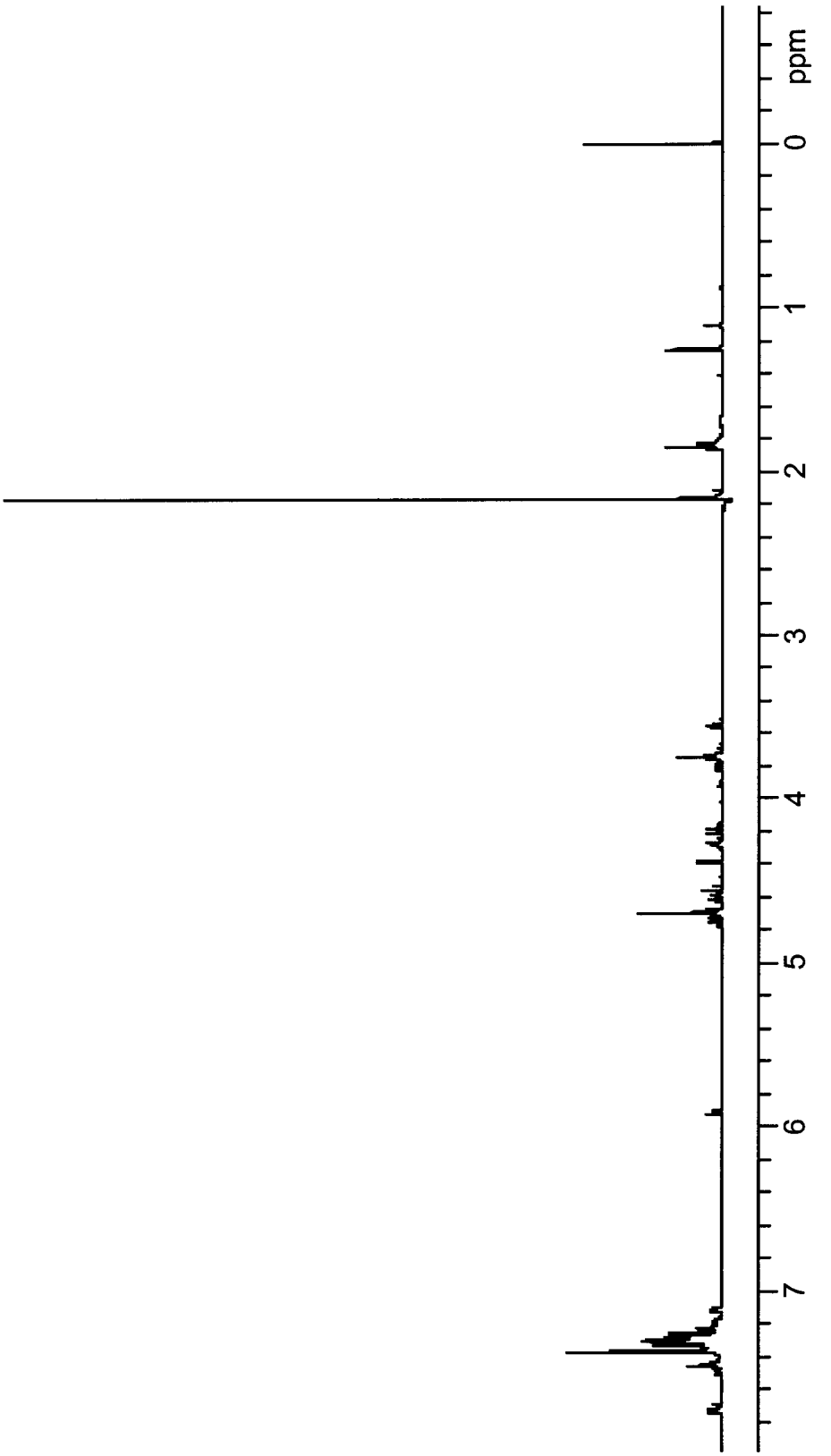

Figure 25. ^{1}H NMR of sugar-derived-vinyl sulfoxide **10**

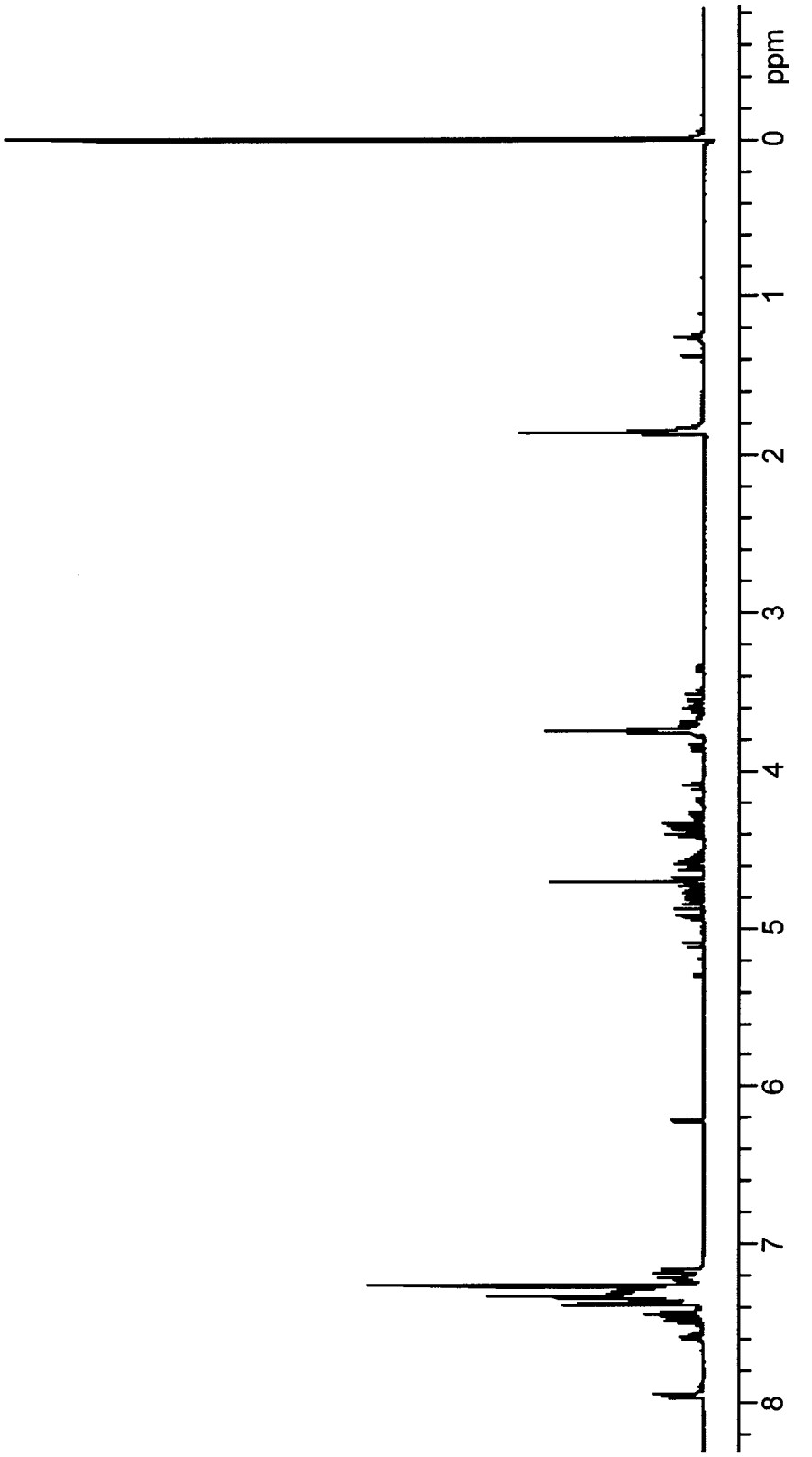

Figure 26. ^{1}H NMR of sugar-derived-vinyl sulfone **12**

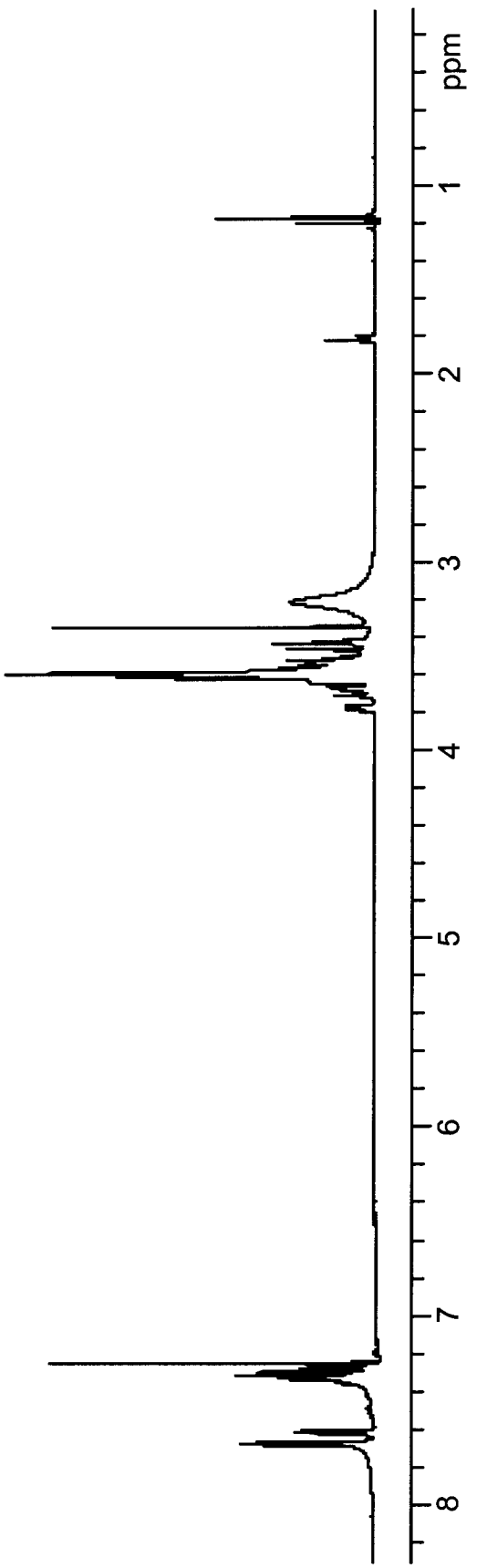

Figure 27. ^{1}H NMR spectrum of compound **13**

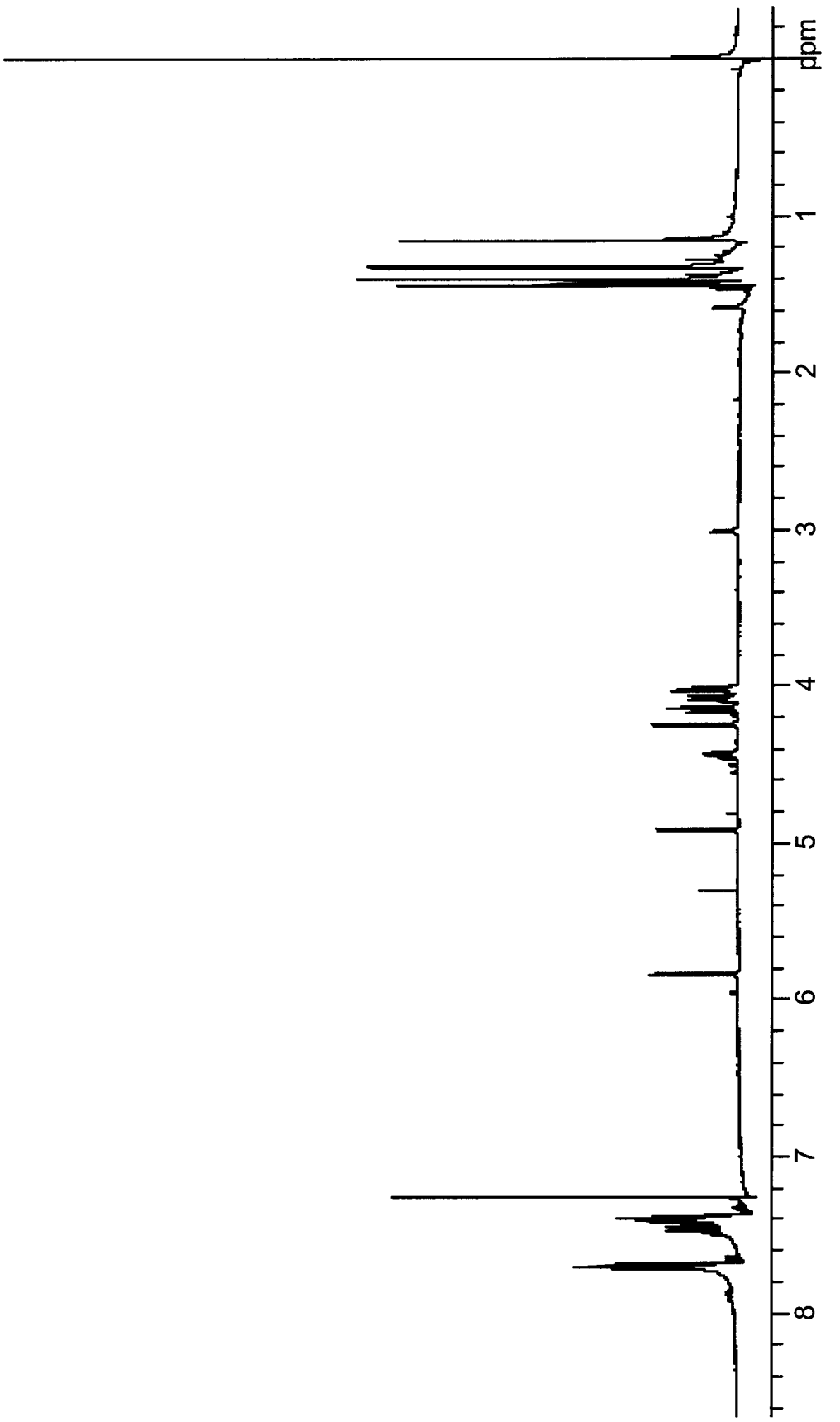

Figure 28. ^{1}H NMR spectrum of compound **14**

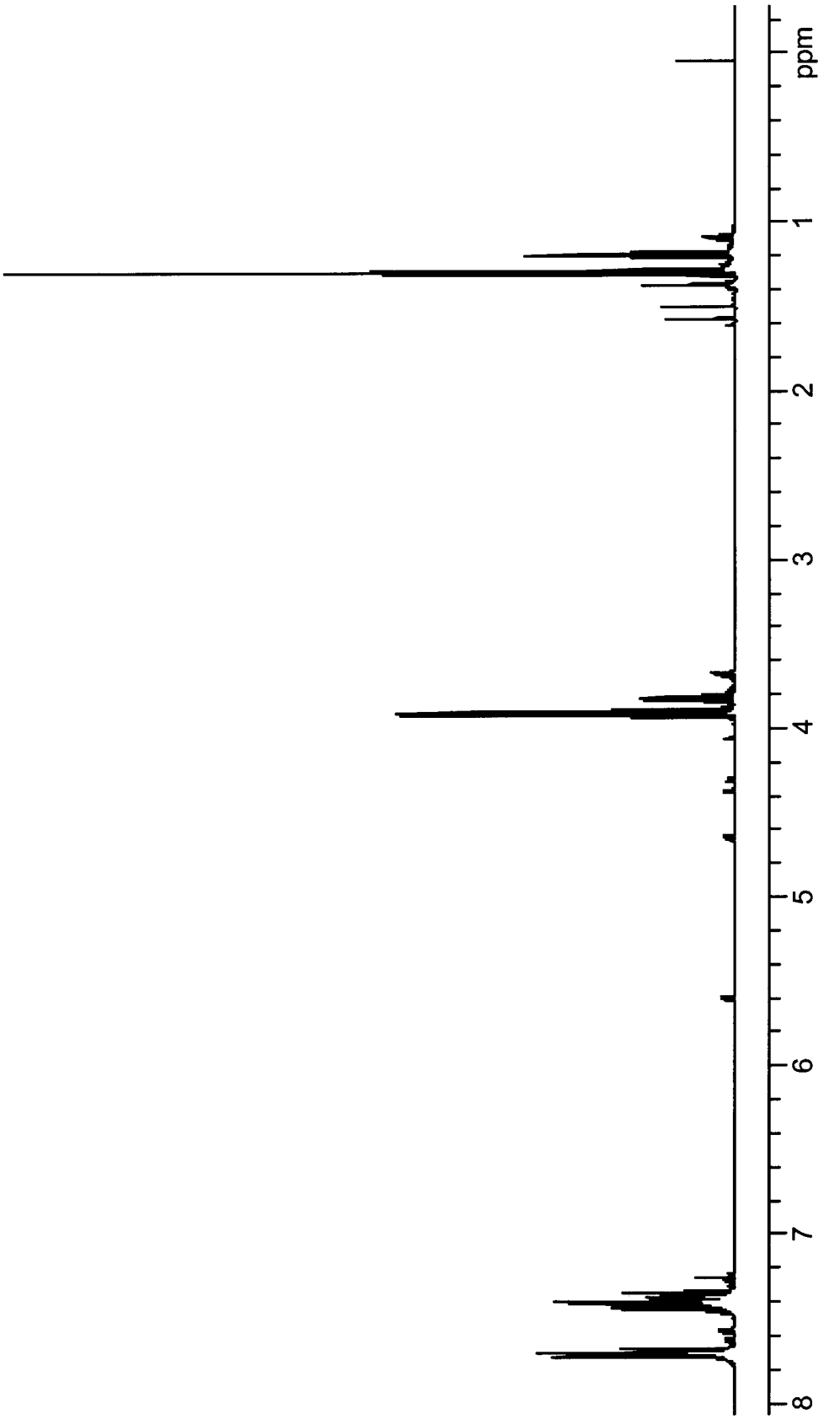

Figure 29. ^{1}H NMR spectrum of compound **15**

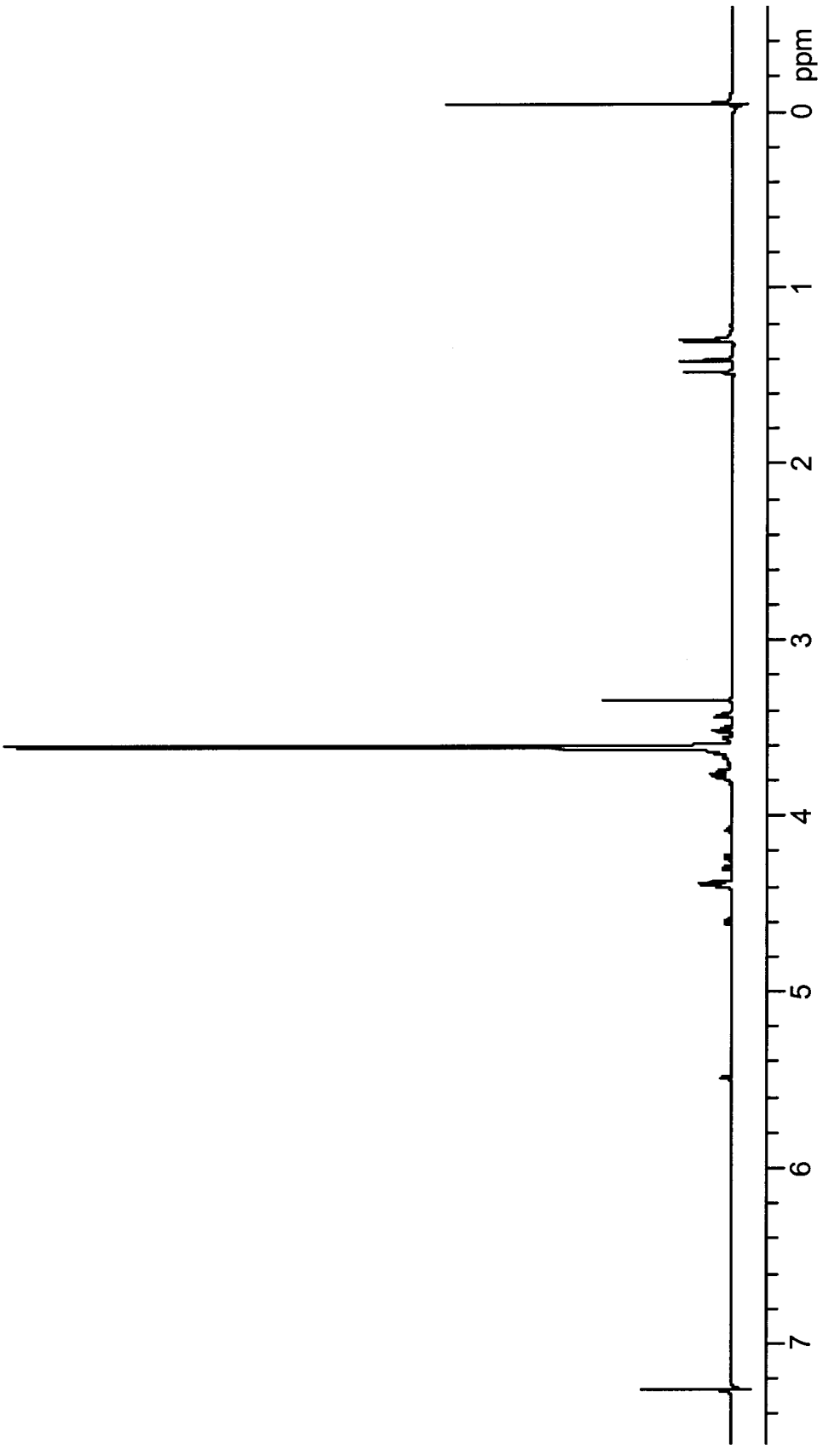

Figure 30. ^{1}H NMR spectrum of compound **16**

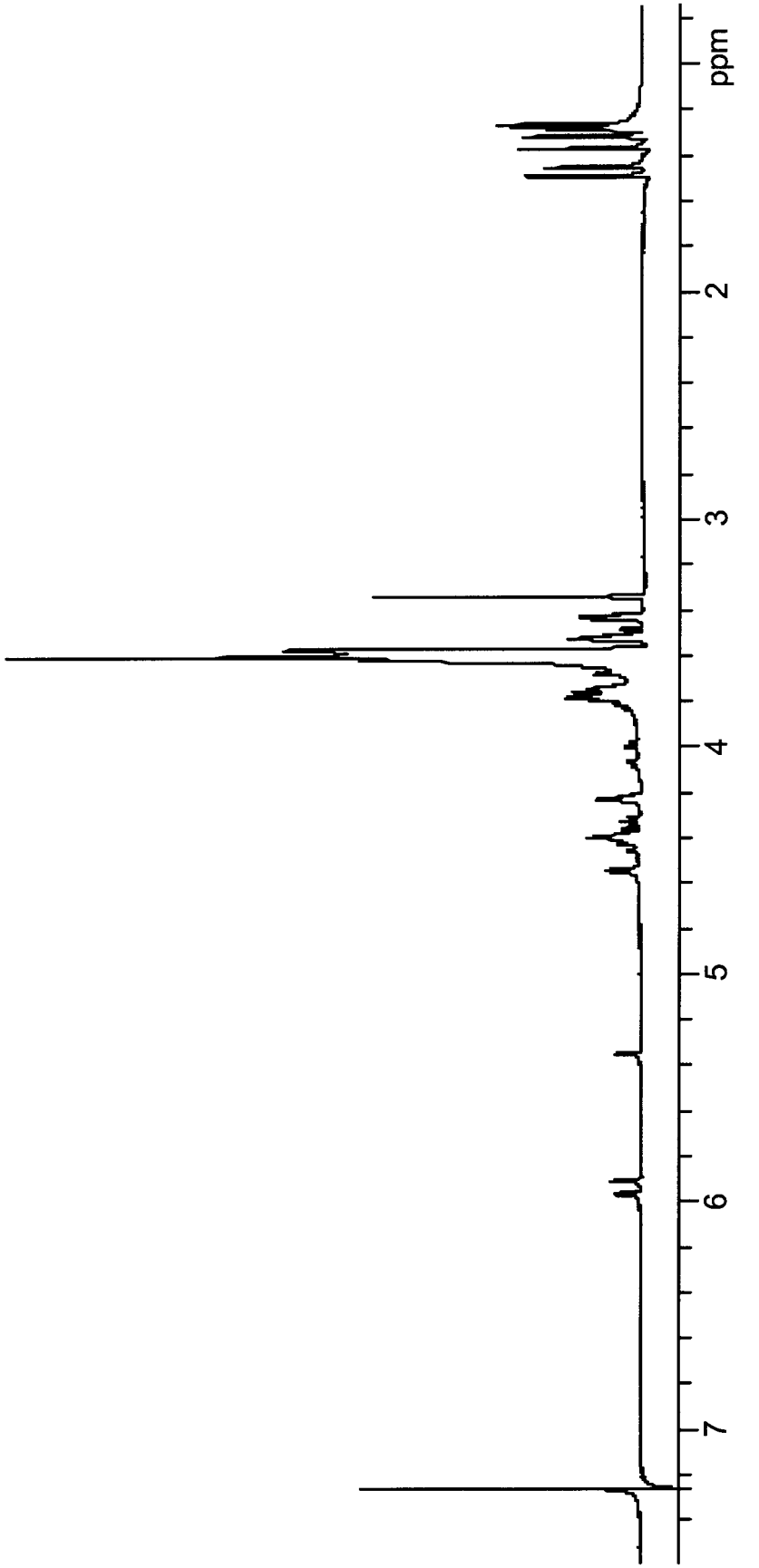

Figure 31. ^{1}H NMR spectrum of compound **17**

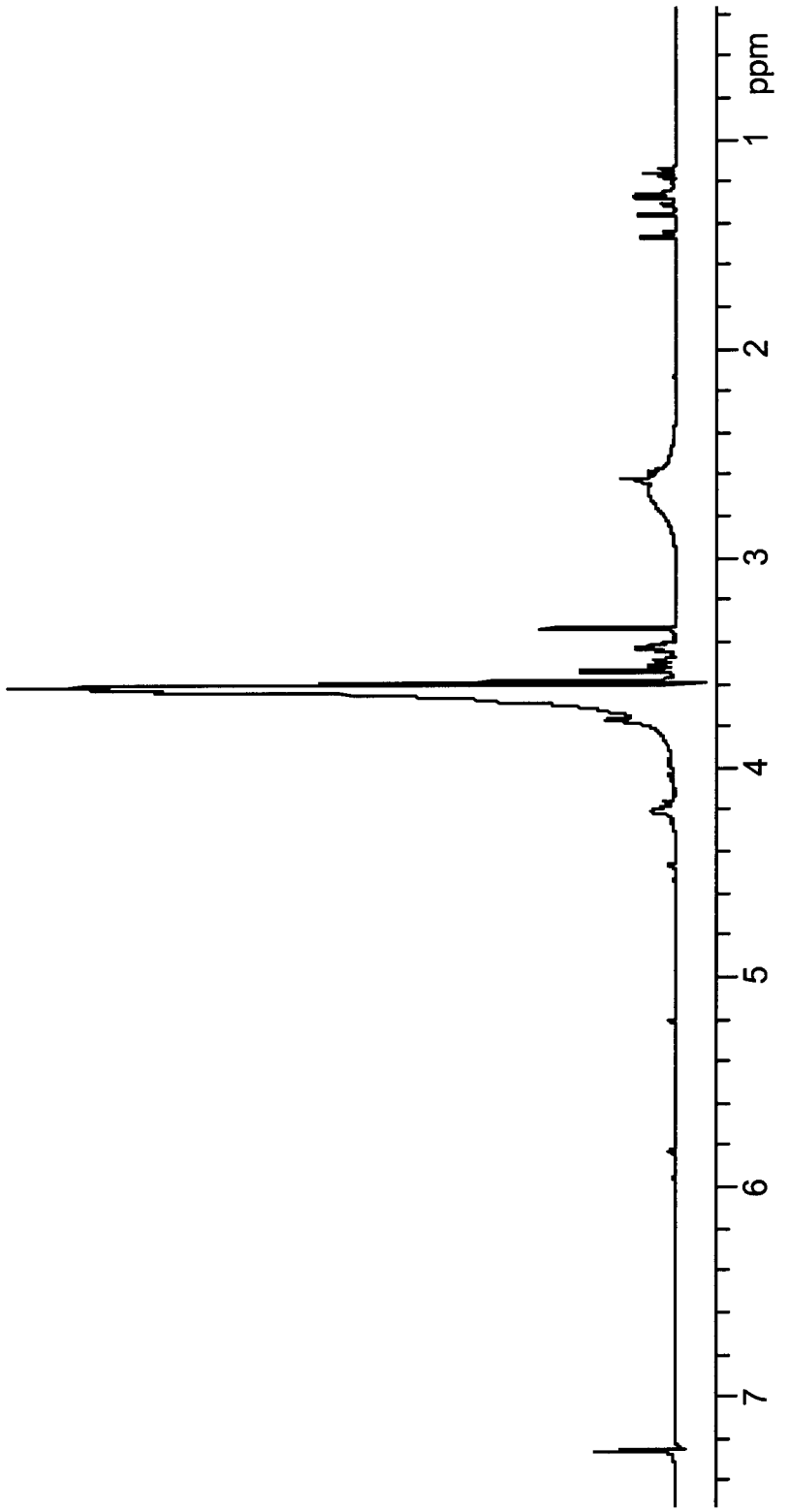

Figure 32. ^{1}H NMR spectrum of **19**

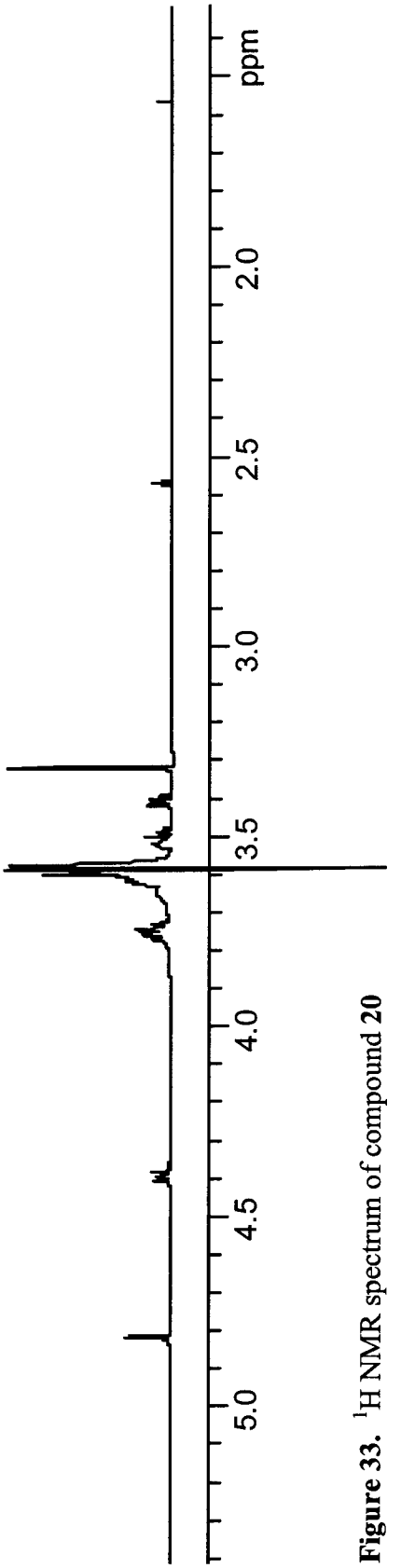

Figure 33. ^{1}H NMR spectrum of compound **20**

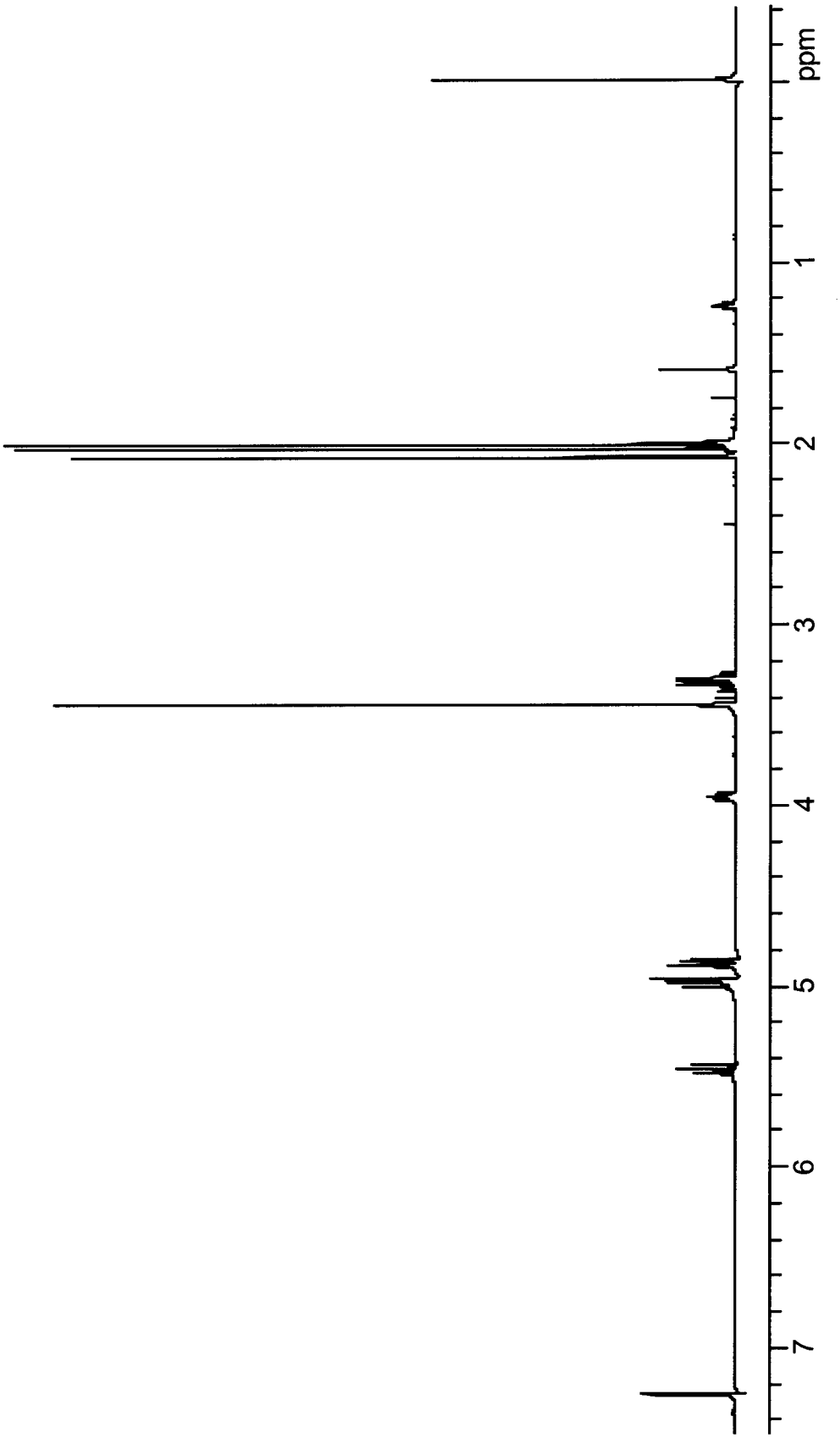

Figure 34. ^{1}H NMR spectrum of compound **22**

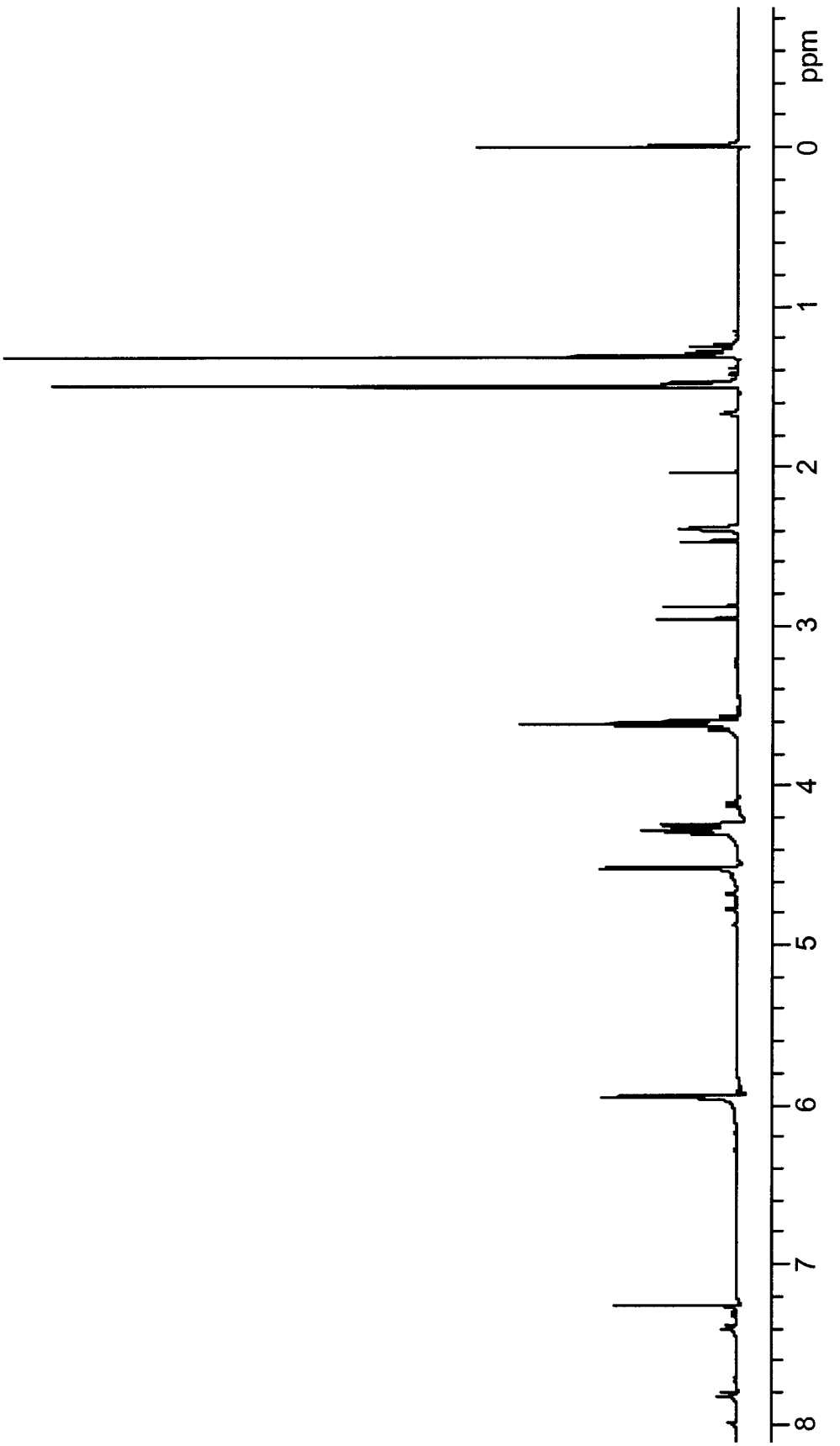

Figure 35. ^{1}H NMR spectrum of compound **23**

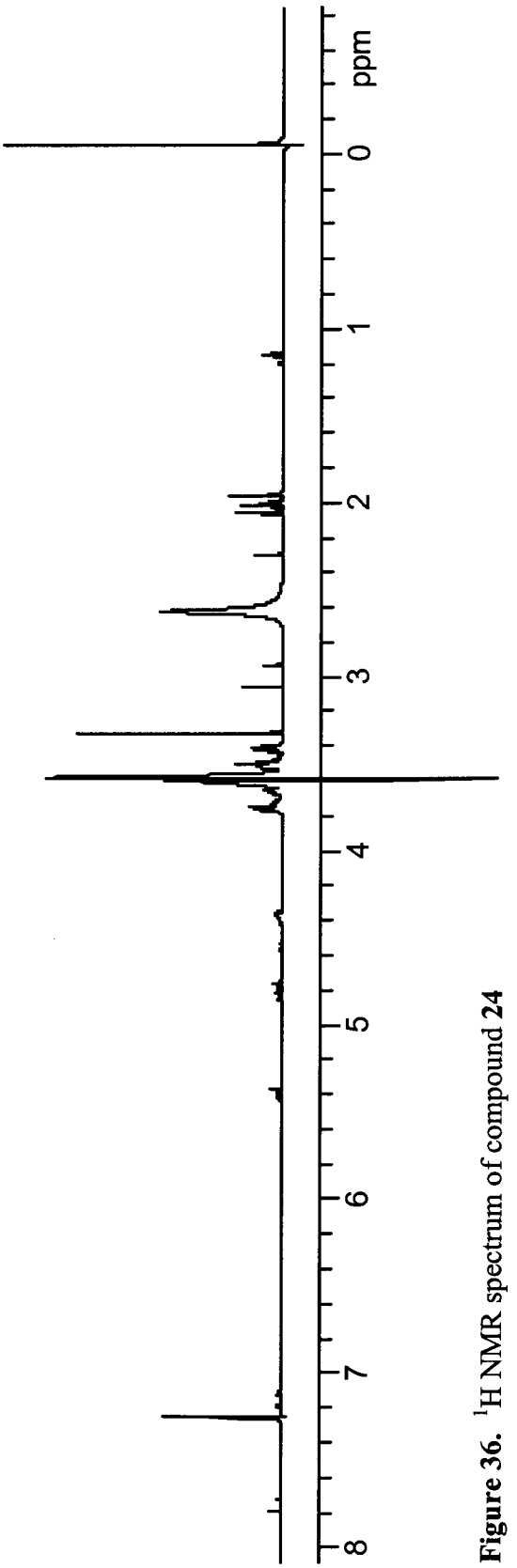

Figure 36. ^{1}H NMR spectrum of compound **24**

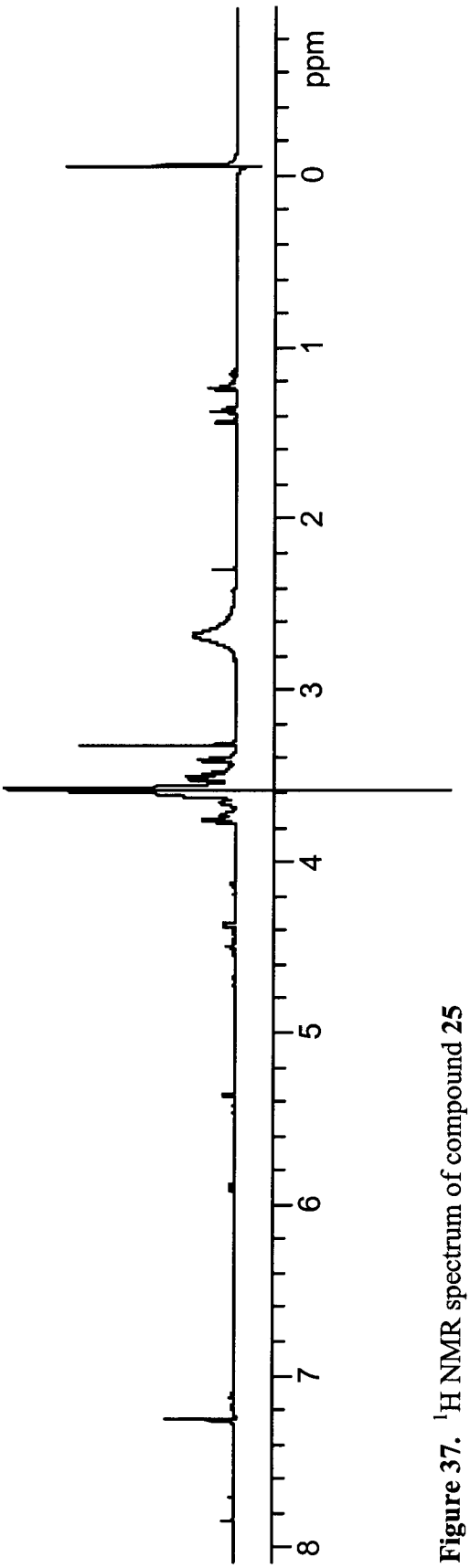

Figure 37. ^{1}H NMR spectrum of compound **25**

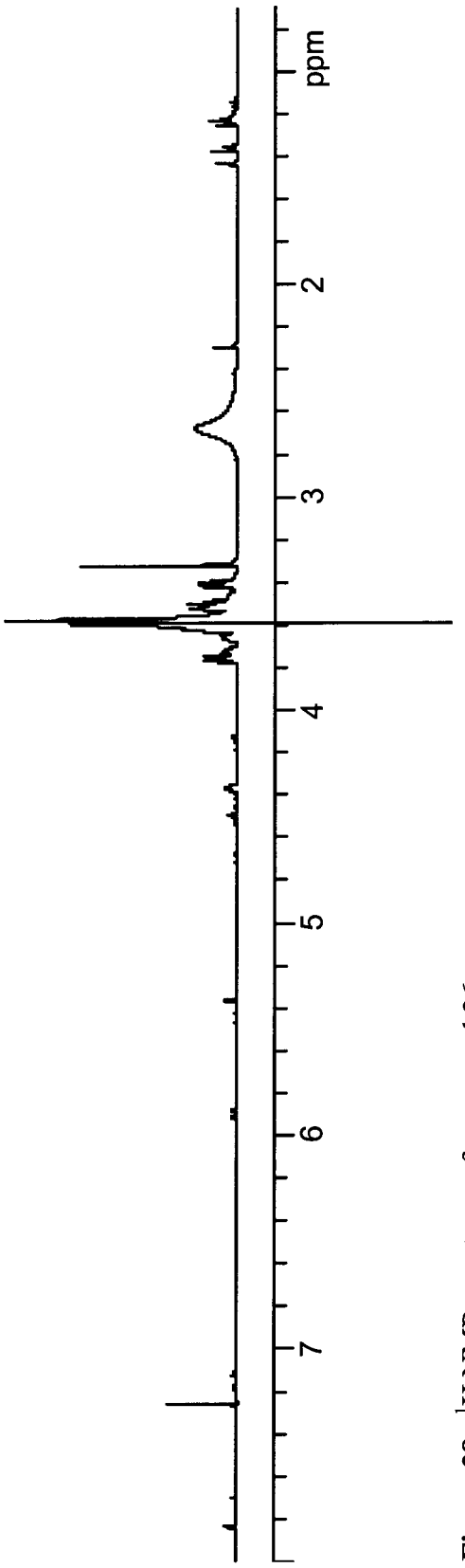

Figure 38. ^{1}H NMR spectrum of compound **26**

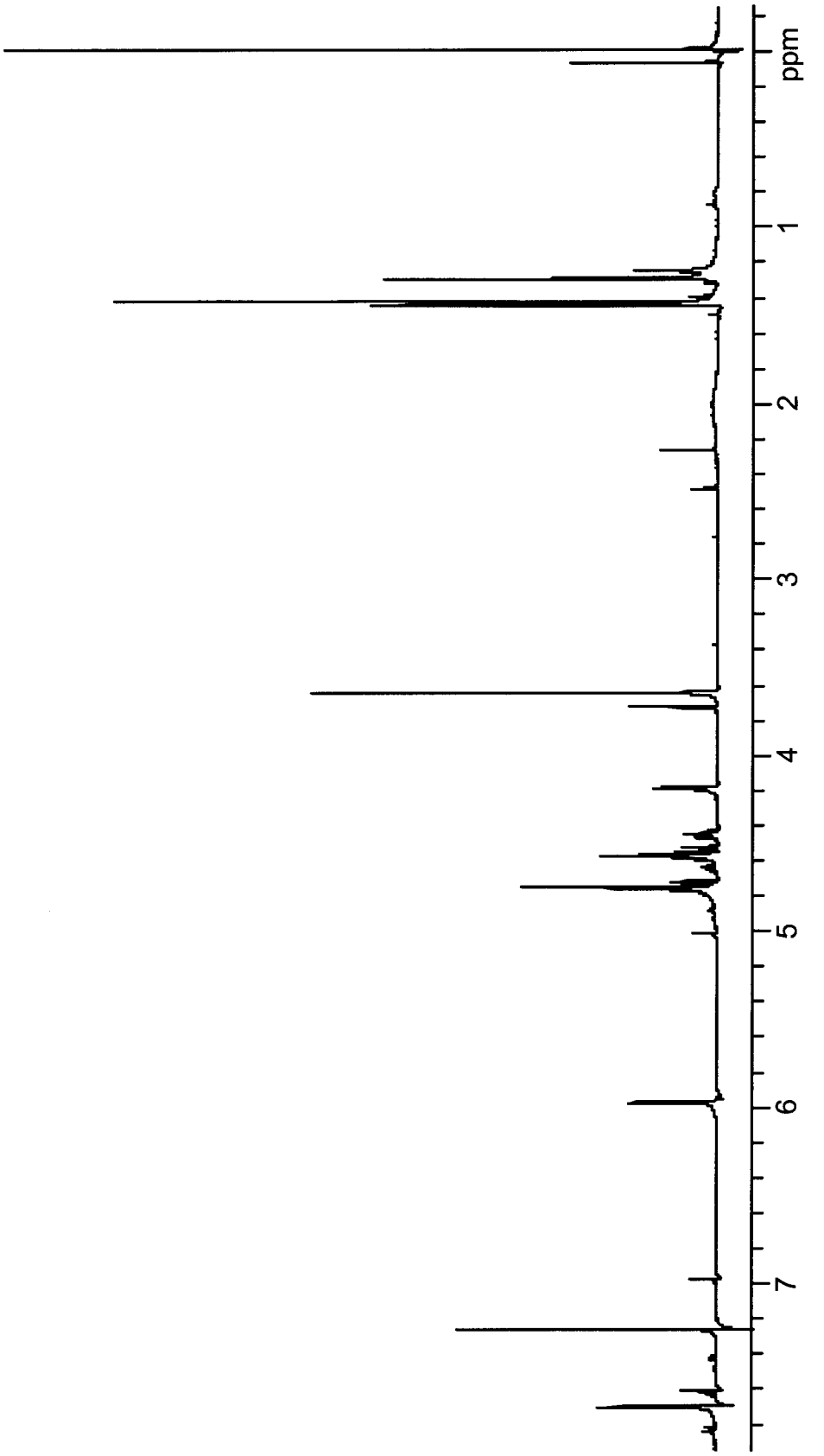

Figure 39. ^{1}H NMR spectrum of compound **27**

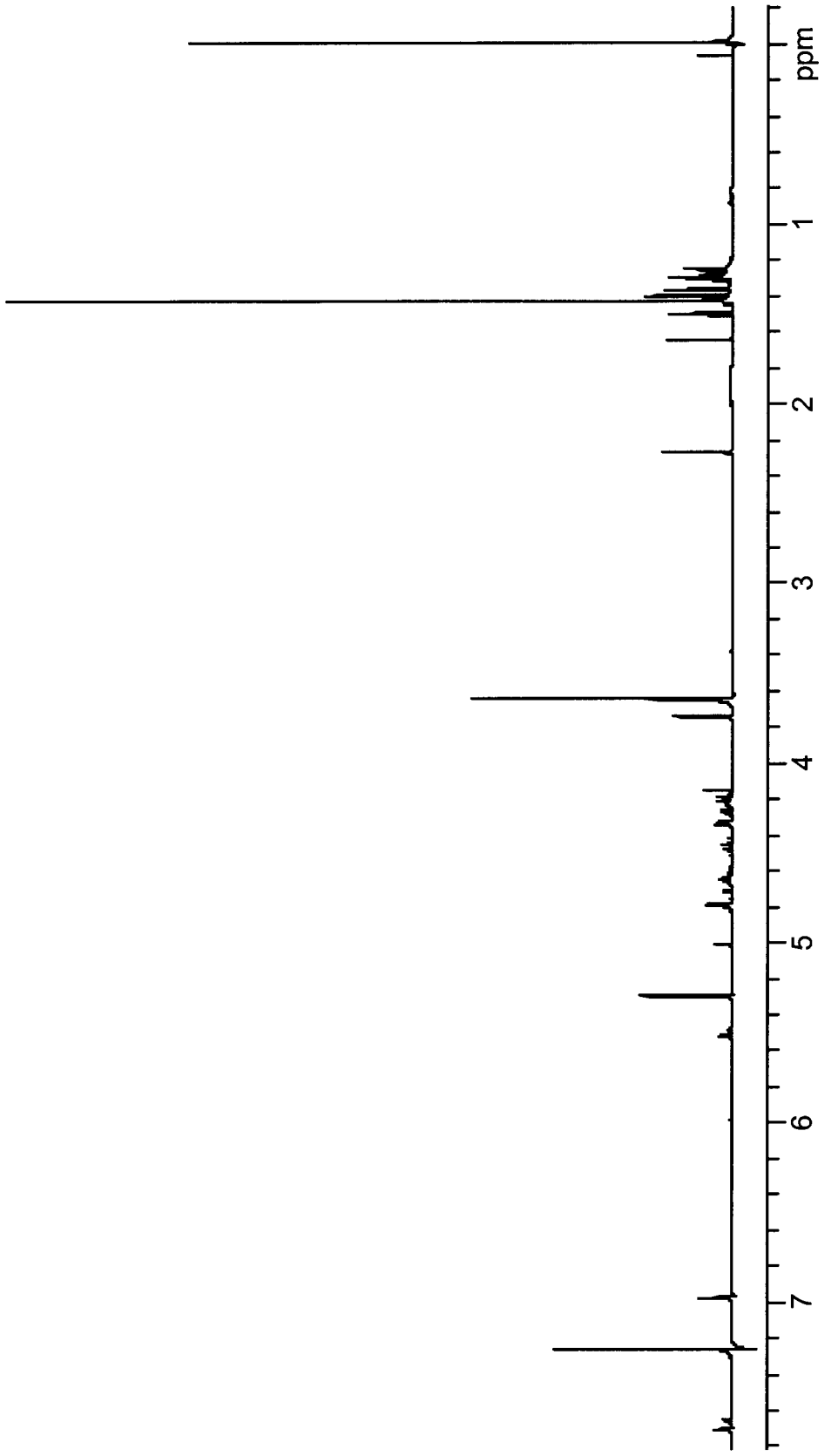

Figure 40. ^{1}H NMR spectrum of compound **29**