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DEVELOPMENT OF A NEW GLYCOSIDATION METHOD TO OBTAIN 2-DEOXY-beta-GLYCOSIDES

AND

STUDY OF SYNTHESES OF THE TRISACCHARIDE CHAIN IN THE AUREOLIC ACID

by

M. ANGELES DIOS

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New york

1999

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

December 16 1998
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THE CITY UNIVERSITY OF NEW YORK

Abstract

DEVELOPMENT OF A NEW GLYCOSIDATION METHOD TO OBTAIN 2-DEOXY-beta-GLYCOSIDES

AND

STUDY OF SYNTHESES OF THE TRISACCHARIDE CHAIN IN THE AUREOLIC ACID

by

M. Angeles Dios

Advisor: Professor Richard W. Franck

Part 1:

An innovative method for the syntheses of 2-Deoxy-β-glycosides was developed. A bicyclic glycosyl donor was formed through a hetero Diels-Alder reaction. This 1,4 oxathiin system formed in the Diels-Alder reaction was used to obtain a disaccharide through conventional activation in the presence of a suitable acceptor. Reduction of the sulfur at C2 of the donor unit in the disaccharide by treatment with Ra-Ni produced 2-deoxy-glycosides in good yield. Studies on the novel stereoelectronic behavior of the bicyclic glycosyl donors were conducted.

Part 2:

The glycosidation method developed in part 1 was applied to a study of the syntheses of the trisaccharide unit present in the aureolic acid. Several cycloadducts were synthesized and the stereoselectivity of hetero Diels-Alder reactions was studied.

This work is dedicated to

my parents, Manuel Dios and Josefa Lema

and my brother Santiago for their

tremendous support and encouragement

Acknowledgments

I wish to express my gratitude to my parents and brother for their love, help and patience without which this work would have never been completed. I also wish to thank Dr. Samuel H. Wilen whose memory will always be an inspiration to me, as well as Dr. Neil McKelvie and Dr. Klaus Grohmann for their guidance and encouragement. I thank Dr. David R. Mootoo and Dr. A. David Baker for their numerous suggestions, which have improved this work significantly. Finally, I thank my mentor Dr. Richard Franck for his teachings, patience and support throughout my research.

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PART 1

DEVELOPMENT OF A NEW GLYCOSIDATION METHOD TO OBTAIN 2-DEOXY-β-GLYCOSIDES

Introduction

Photosynthesis is one of the most important of all life processes. It provides nature with the means to transform inorganic carbon into carbon dioxide and then into carbohydrates which are further transformed in plants into structural and food storage materials used later by animals as sources of energy. Together, all photosynthetic organisms on earth produce about 14×10^{10} tons of organic matter every year[1] according to the process shown below.

$$CO_2 + H_2O \xrightarrow[\text{photosynthetic organisms}]{h\upsilon} \text{Carbohydrates} + O_2$$

Because they are intermediates in the biosynthesis of all organic compounds, carbohydrates are the most abundant class of organic compounds in nature. Many natural carbohydrates can be considered to be primary metabolites, because they are present in, and essential for, most life-forms.

Carbohydrates rival proteins in being one of the most functionally versatile natural products[2]. They range from structural materials as mentioned above, to biochemically active components of plants, animals and micro-organisms. Many other biological roles are performed by carbohydrate materials:

glycopeptides and glycoproteins are involved in biological recognition, and nucleic acids contain monomeric carbohydrates as part of their structure. Aside from their biological importance, carbohydrates are extremely versatile compounds that can be chemically manipulated in a multitude of ways. Many polymeric, oligomeric and monomeric products in the food, clothing, pharmaceutical and agrochemical industry are derived from them. In the synthetic arena, carbohydrates are useful chiral starting materials for a large number of organic compounds and as chiral auxiliaries.

A central reaction in carbohydrate chemistry is glycosidation. Glycosidation involves reaction at the anomeric carbon of a sugar. Often the reaction is with the hydroxyl group of another sugar. Most complex saccharides in nature are linked through glycosidic bonds, and that fact makes the ability to control the yield and stereochemistry of this reaction of extreme importance.

The stereochemistry of glycosidation is controlled by a phenomenon called the anomeric effect. This effect is defined as the preference of an electronegative substituent at the anomeric center of pyranoses for the axial orientation[3]. In D sugars, this axial stereochemistry of an electronegative group (frequently oxygen), is known as an α substituent, and the equatorial isomer is called β substituent. A monosaccharide can then be the α or β anomer (figure 1).

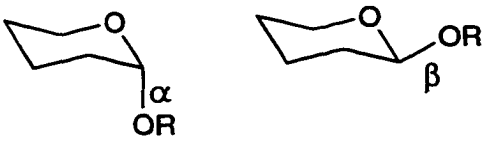


Fig. 1

Simple considerations of steric interactions suggest that the equatorial conformer would be more stable than the axial one. The reasons for the observed preference for the axial position have been debated. Two theories, possibly complementary have been advanced.

The first claims that since the anomeric effect decreases with the polarity of the solvent and increases with the electronegativity of the substituent X at the anomeric center, the effect is caused mainly by electrostatic effects, which result from repulsions between unshared electrons in the oxygen in the ring and the substituent X in the β-anomer, and unfavorable destabilization of the molecule due to a large net dipole[4].

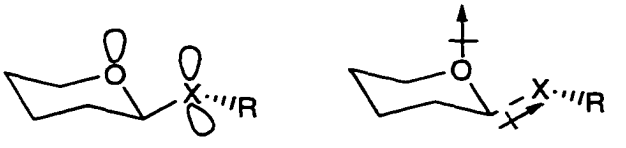


Fig. 2

The second theory claims that a bonding n-σ* interaction between a non-bonding electron-pair on oxygen and the low-energy antibonding orbital of a C-X bond exists in the α anomer. The evidence for this interaction is the systematic

variation in the pattern of bond lengths at the anomeric center when the electronegativity of the group X is changed[5]. The geometrical requirement for optimum overlap in the α isomer is that the orbital should be antiperiplanar[6] as shown below.

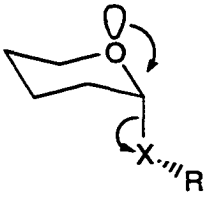


Fig. 3

The anomeric effect has a direct effect in glycoside hydrolysis at the anomeric center. This is of special importance in glycosidation reactions, as the first step in them is cleavage of a C-X bond at the anomeric center of the donor sugar. It is experimentally well known that the rate of hydrolysis of β-glycopyranosides (equatorial anomer) is faster than that of α-glycopyranosides (axial anomer) of the same sugar[7]. One of the most interesting theoretical explanations of this has been advanced by Fraser-Reid[8], based on *ab initio* studies of proton induced cleavage of α and β glycopyranosides.

The main points of his theory are shown in figure 4.

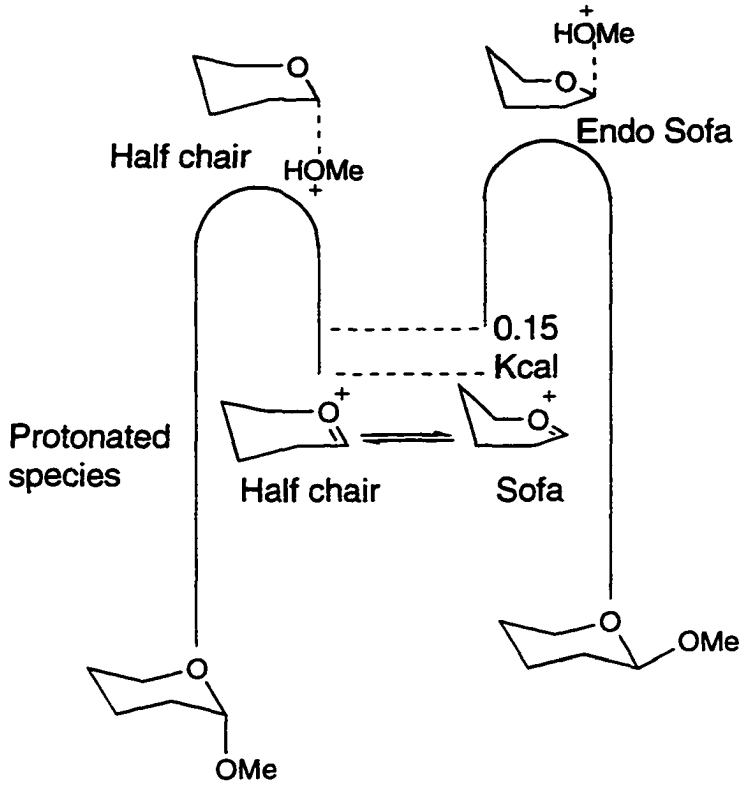


Fig. 4

The anomers cleave by going through transition states of different energies. The β anomer flattens out into a sofa conformation of higher energy, and the α one flattens out into a half-chair. Fraser-Reid also finds that the observed correlations in the calculations between the O_5-C_1 and C_1-O_1 in α and β anomers indicate that n-σ* interactions are present in the transition state. This means that the energy of both the axial anomer in the ground state and the equatorial anomer in the transition state is lowered by the anomeric effect. Therefore, the relative stabilization of axial and equatorial anomers in both the ground and excited state have to be compared in order to understand which anomer will hydrolyze faster.

Glycosidation methodology is concerned with control of the stereochemistry of the formation of the glycoside bond and the theoretical considerations are of fundamental importance.

Synthesis of β glycosides is specially difficult, since formation of the α anomer is favored due to the anomeric effect. Traditional methods to obtain a glycoside linkage are based on glycosidation via electrophilic activation of the anomeric center followed by nucleophilic substitution. From this main idea two different types of methodologies have been developed: The one we will call type A is based on the production of electrophilic transfer species by conversion of the anomeric functionality to a good leaving group as in the Koenigs-Knorr method[9] in which bromides are complexed with heavy metal salts; or the Schmidt method[10], in which the anomeric hydroxy is transformed into a trichloroacetimidate which are activated with a Lewis acid. Other methods include the use of sulfones with strong acids, or pentenyl glycosides with a positive halogen and a strong acid[11]. The main problem with this approach is the fact that the stereochemistry at the anomeric center is controlled through neighboring group participation (or lack thereof) by functional groups at C-2 of the sugar.

Type A

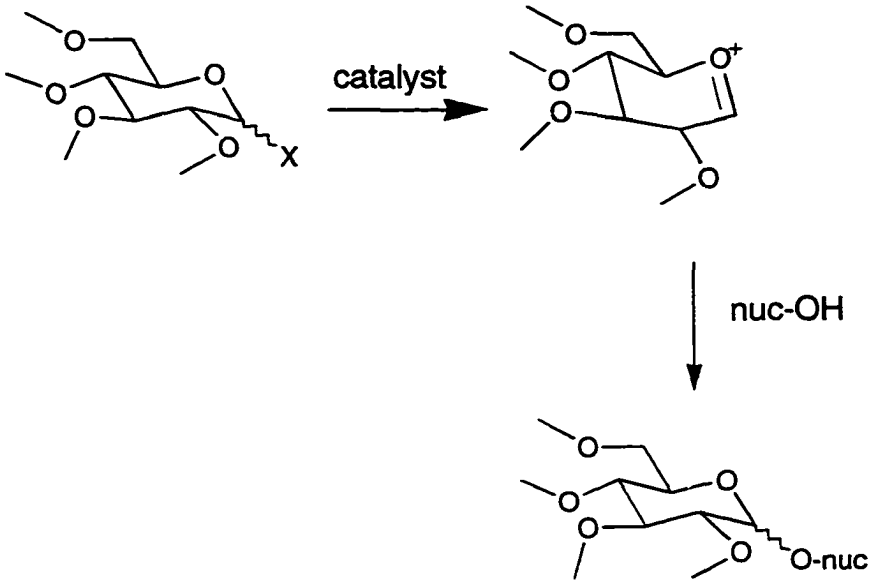
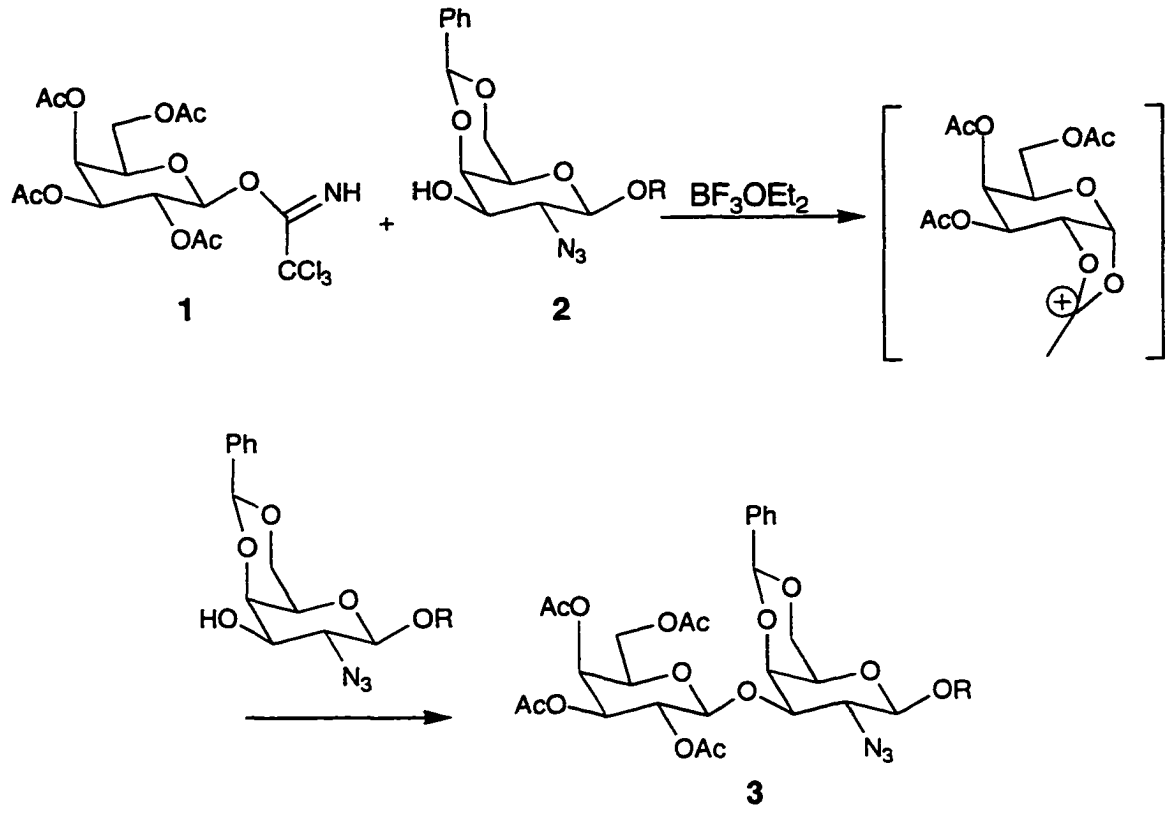


Fig 5.

In order to obtain a β anomer, a C-2 protecting group such as an ester which can undergo neighboring group participation with the oxocarbocation as intermediate must be used. This directs the attack of the acceptor at the equatorial position as show in Scheme 1. This is called neighboring group participation. To form an α anomer, a non participating protecting group must be used. The need for all of these modifications to the anomeric center, and the use of different protecting groups to control the stereoselectivity, lowers significantly the final yield of glycosidation.



Scheme 1. Neigboring group participation.

The second methodology that we will call type B and is based on the activation of a glycal by electrophilic attack[12] by a positive oxygen, sulfur, selenium, halogen, proton, mercury or nitrogen. In these cases the final stereochemistry depends on the preferred facial attack of the electrophile. A 2-deoxy-sugar can easily be obtained in many of these methods by reducing the heteroatom left at C-2 if it is sulfur selenium or a halogen.

Type B

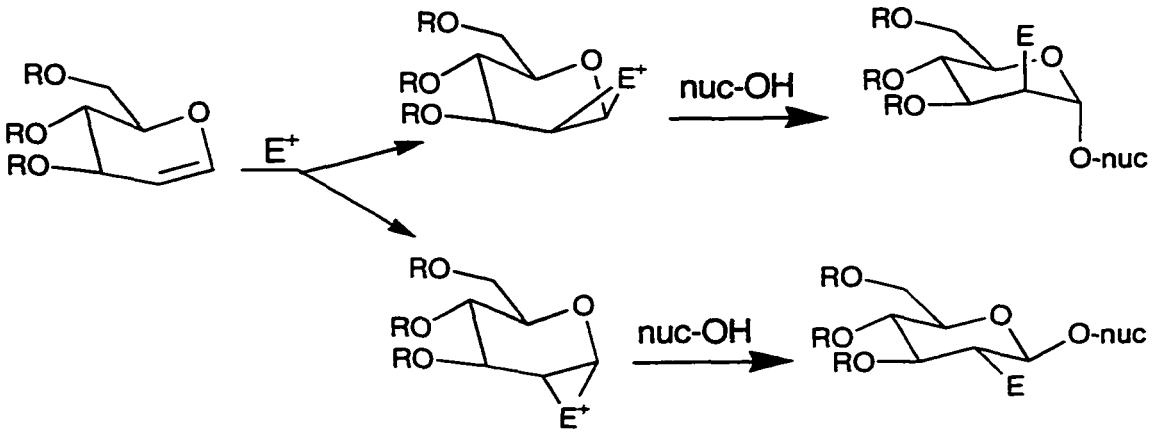
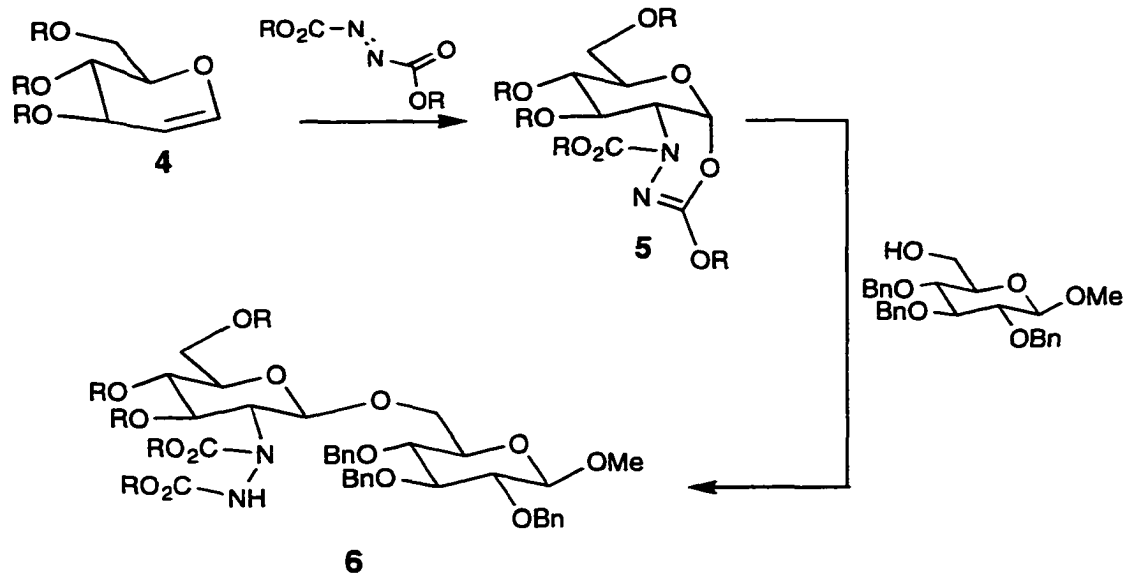


Fig 6.

Both types of methods lack adequate stereochemical control of the final products, and for this reason most type B methods are not completely successful in yielding 2-deoxy-β-glycosides, which was the focus of our project.

The new glycosidation method to be described here is a method based on glycosyl transfer via cycloaddition chemistry. It involves the formation of a cycloadduct derivative of a glycal through a heterocycloaddition, which will later form the disaccharide through conventional activation in the presence of a suitable acceptor. A precedent for this type of reaction was reported by Leblanc[13] in which azodicarboxylate derivatives of glycals were formed and then reacted with a primary alcohol in the presence of BF_3 as shown in scheme 2.



Scheme 2. Leblanc's method

Because we wished to synthesize 2-deoxy-β-glycosides, we needed to form a derivative of glycal with a heteroatom at C-2 that was easily removable. Since sulfur can be removed through Ra-Ni reduction, it was decided to use a thiono-oxo system to obtain a derivative **8** that could then be activated to react with sugar acceptors to produce β disaccharides **9**. Treatment of **9** with Ra-Ni to produce the 2-deoxy- glycosides **10**.

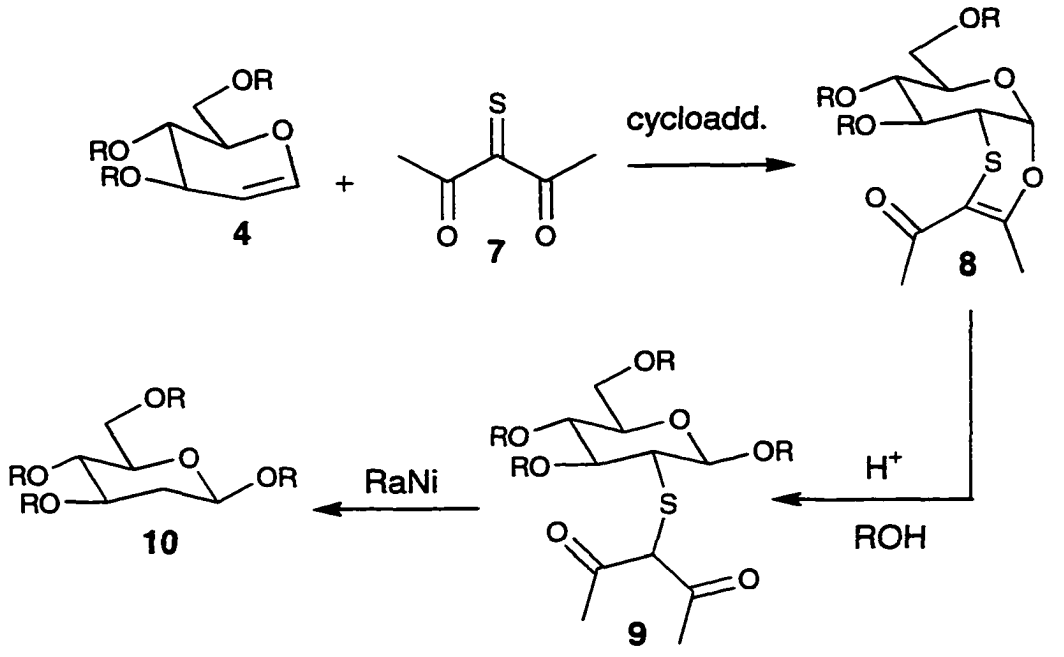
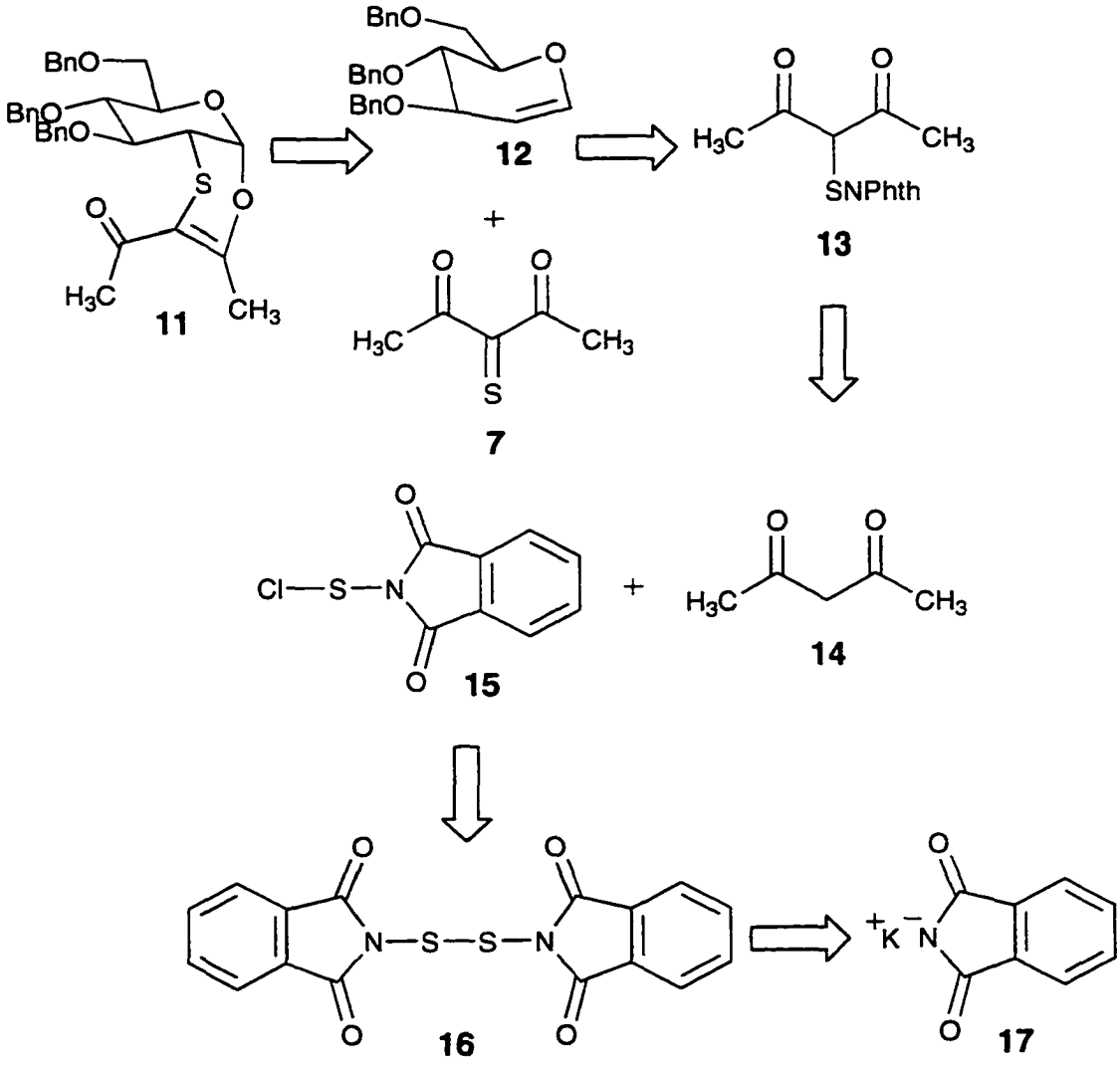


Fig 7. Initial idea

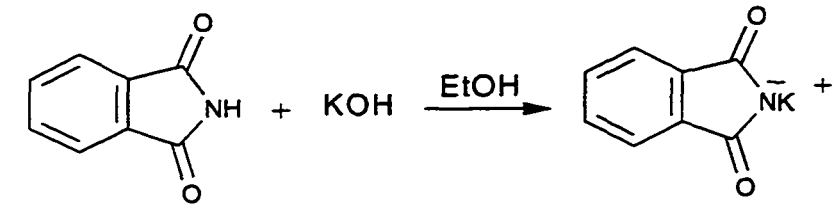
The glycal adduct shown in figure 7 can be modified in several different ways depending on the particular disaccharide one is attempting to synthesize. One of the strengths of this system is its versatility. We studied several modifications of the original idea in the course of this research.

Results and Discussions

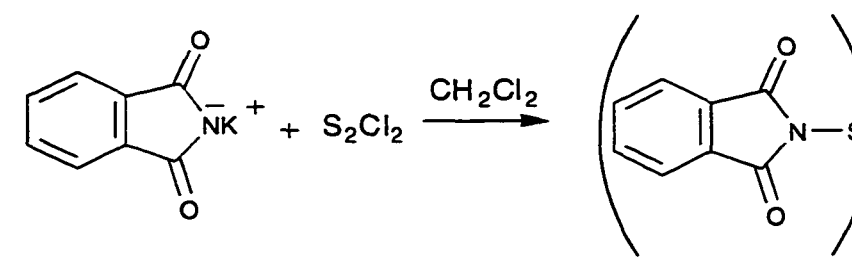
The reaction used to obtain the glycal cycloadduct (1-O,2-S-(2-Acetyl-1-methyl-1,2-ethenediyl)-3,4,6-tris-O-(phenyl- methyl)-2-thio-α-D-glucopyranose) used as starting material in the glycosidation was first developed by Capozzi[14] who discovered a thione-oxo heterodiene **7**, which was observed to undergo cycloaddition to electron-rich dienophiles. Subsequently, the reaction was applied to 3, 4, 6 tri-O-benzyl-glucal. The retrosynthesis is shown below.



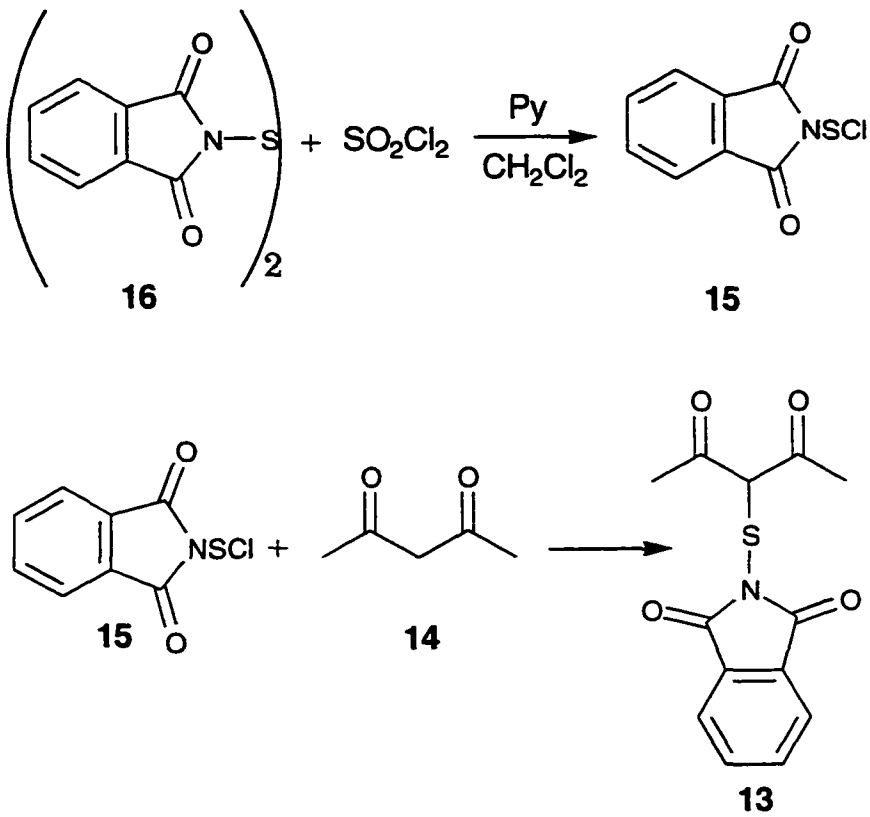
The 3, 4, 6 tri-O-benzyl-D-glucal was obtained by deacetylation followed by benzylation of 3, 4, 6 tri-O-acetyl-D-glucal, which is commercially available. The 3-phthalimidethio-2, 4-pentanedione **13**, however, had to be synthesized in the laboratory from phthalimide, which was transformed into potassium phthalimide and then phthalimide-N-sulphenyl chloride. This was in turn made to react with 2,4 pentenedione to give the final product[15]. The diene **7** is a postulated intermediate in the reaction, but was never actually isolated. The sequence of these reactions is shown in scheme 2. It was perfected in our laboratory by Magdalena Tamarez and Dr. War War Win.



18 **17**



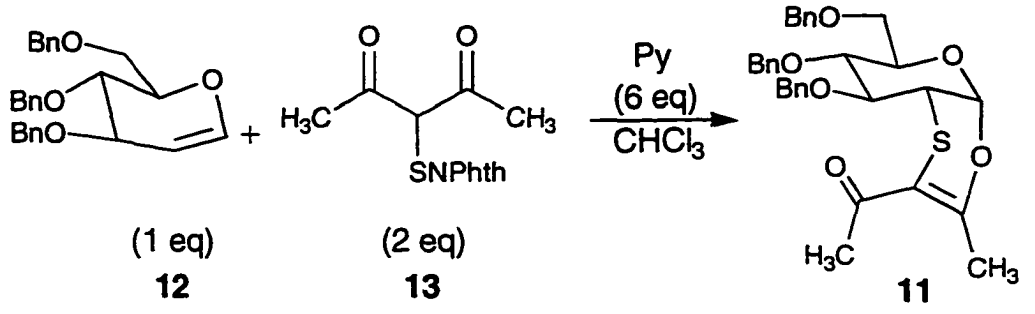
17 **16**



Scheme 3.

The cycloaddition reaction was first tried in Florence, but the yield achieved was extremely disappointing. Even though an 80% yield based on recovered starting material **3**, was reported after seven days, when the reaction was repeated at Hunter College, only a 29% conversion of adduct **4** was ever obtained. The reaction seemed to be an inverse electron demand hetero Diels-Alder, that went very slowly at room temperature. The reaction was monitored both by TLC, using a $PdCl_2$ spotting reagent that gives a characteristic yellow hue when the compound has sulfur present in the molecule, and by ^{1}HNMR, looking at the anomeric peak of the new adduct (5.6 ppm). The original reaction was run in chloroform, with six equivalents of pyridine to abstract the acidic

proton in **13**, and form the diene required by the Diels-Alder reaction *in situ*.



(1 eq) **12** (2 eq) **13** **11**

However, this yield was not satisfactory if we were going to use **11** as a starting material. The low yield and the fact that a large amount of glucal was recovered forced us to search for a change in the conditions. From the beginning we thought that the nature of the base and amount used could be a major factor in the results obtained, so a wide range of possibilities was tried. First we considered the possibility that more base than the six equivalents was needed. However, when the pyridine was used as a solvent, the results were poor. Activation of the reaction through heat was tried next, but even though the reaction was faster, the yield was even worse than with the original reaction conditions. The next stratagem was the use of a more hindered base because we thought that some of the pyridine was really acting as a nucleophile and displacing the phthalimide off instead of extracting the acidic proton of the diene precursor **13**. Changing the base to a more hindered 2, 6 lutidine increased the rate of the reaction, but the yield was not significantly improved. Finally, when the amount of equivalents of base was diminished to one

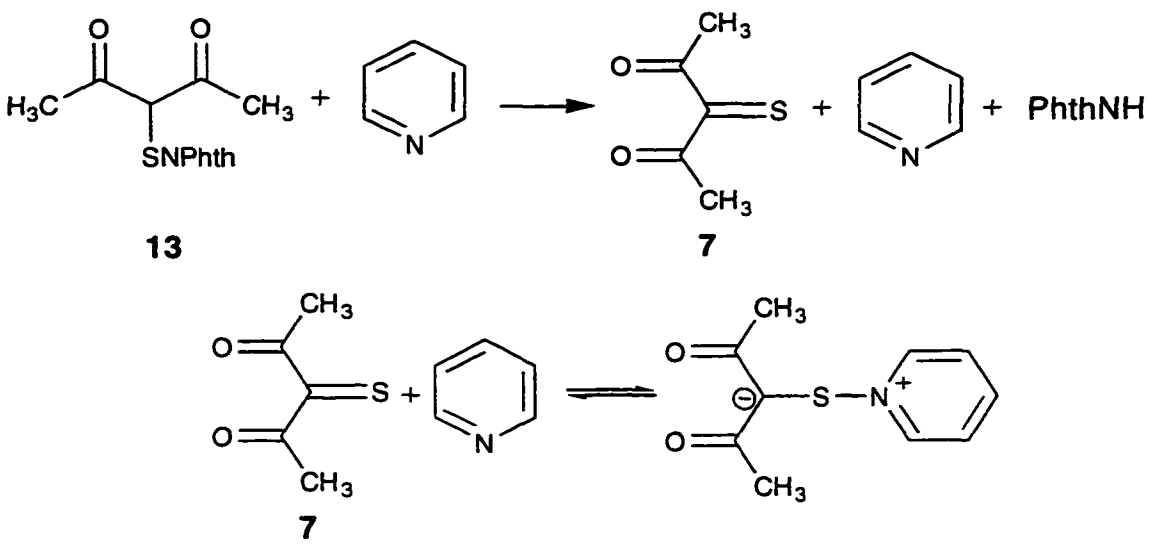
equivalent, the reaction's yield increased dramatically, to give an acceptable yield. Further diminishing the amount of base though, increased the time of reaction to unacceptable lengths.

Table 1.

BASE	EQUIVALENTS	TIME	YIELD	GLUCAL RECOV.
Pyridine	6 eq.	8 days	30%	80%
Pyridine	solvent	7 days	none	none
Pyridine	6 eq, refluxing	1 day	3.1%	1.5%
2, 6 Lutidine	6 eq.	8 days	40%	not isolated
2, 6 Lutidine	1 eq.	3 days	81%	15.4%
2, 6 Lutidine	1/4 eq	10 days	70.5%	8%

An explanation of this phenomenon of increasing yields with decreasing amount of base, can be found if the possibility of an equilibrium between the pyridine and the intermediate shown in scheme 4 is considered. It is then clear that the larger the amount of base present, the lower the yield would be, since the concentration of reactive diene would be proportionally reduced.

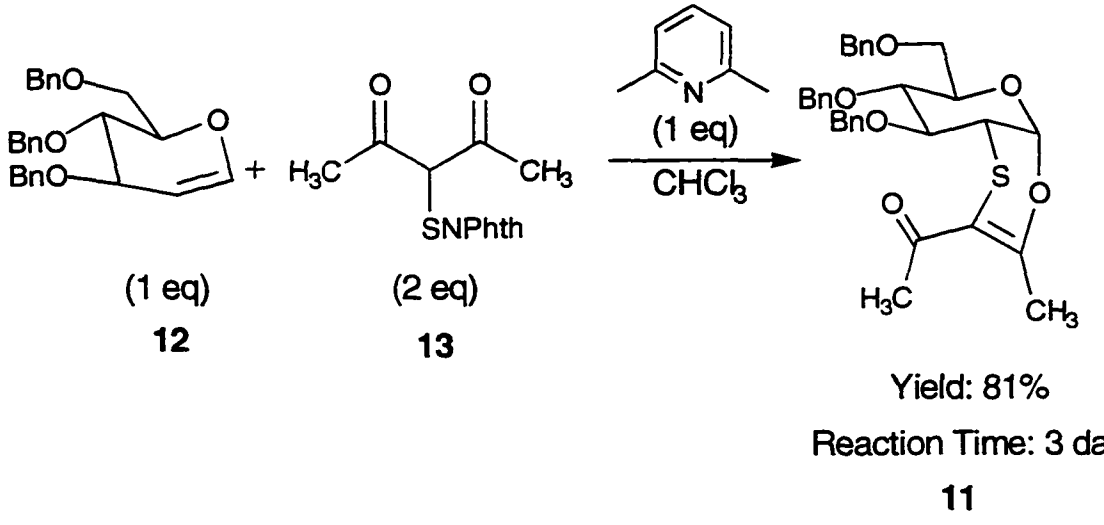
We also hypothesize that using 2, 6 lutidine instead of pyridine increases the speed of the reaction because the higher steric hindrance makes the undesired equilibrium less favorable which will increase the concentration of diene.



Scheme 4.

It could be possible then, that the base is only acting as an acid scavenger and not directly participating in the reaction. To test this theory, a ^{1}HNMR experiment was run in which the reaction was run without any base for seven days in $CDCl_3$. After this time, a minor amount of cycloadduct was found, but the major products seemed to be due to some secondary reactions, probably acid catalyzed. When the same experiment was repeated using 1, 1, 3, 3 tetramethyl urea as a non basic acid scavenger, the amount of peaks due to side products diminished considerably, although they did not disappear, and the quantity of side products was still larger from peak integration of the ^{1}HNMR than the amount of product. The same experiment, run with 1, 1, 3, 3 tetramethyl urea in acetonitrile gave equal quantities of product **11** and side products according

to integration of the ^{1}HNMR, and almost total consumption of **12**. This suggests that the base in our reaction is only acting as an acid scavenger to prevent the side products from acid catalysis. The final recipe for our reaction is shown in scheme 5.

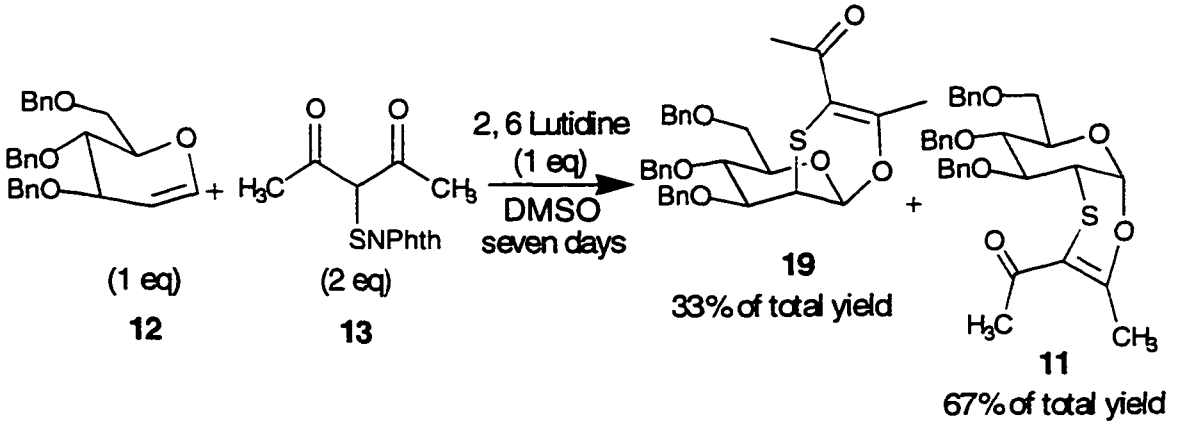


Scheme 5.

The ^{1}HNMR of the crude from this reaction showed a small doublet at 5.2 ppm that we thought could be due to the anomeric proton due to the formation of the top face diastereomer of **11**, since the anomeric peak of the bottom face adduct **11** is a doublet at 5.6 ppm. The yield of the reaction for the top diastereomer was approximately 1% according to integration of the ^{1}HNMR peak at 5.2 ppm, which was not practical to isolate. Related investigations on the formation of other cycloadducts derived from different glycals and thiono-oxo systems had shown that the top face cycloadduct exhibited a peculiar solvent effect in other

systems, where running the reaction in DMSO increased the yield for the top face diastereomer significantly[16]. Cycloaddition experiments monitored by ^{1}HNMR and run in DMSO and acetonitrile in the standard system showed the peak characteristic of the top face cycloadduct at 5.2 ppm in large ratio, so we decided to carry out the experiment on a preparative scale in DMSO which gave the best ratio of top face diastereomer according to peak integration .

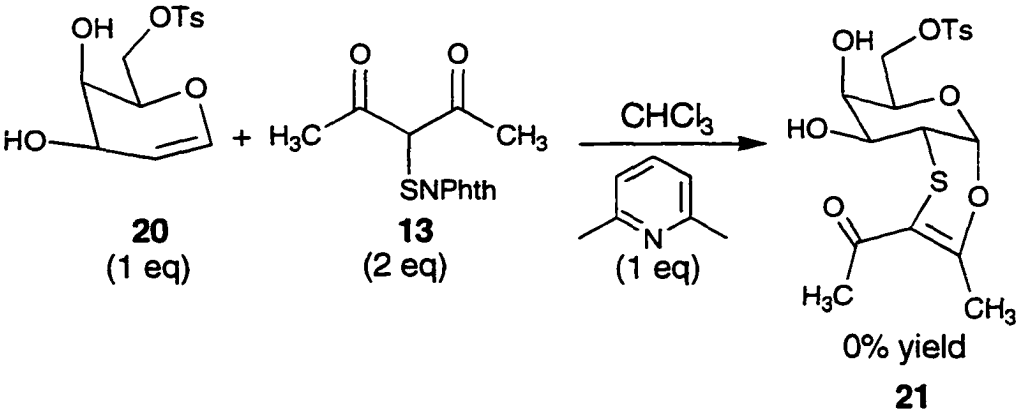
When the reaction shown in scheme 6 was run using DMSO as solvent, the total yield dropped to 59%. Of this total amount of product, only 33% was top face adduct **19**, 67% bottom face adduct **11**, and 25% of the initial amount of 3, 4, 6, tri-O-benzyl-glucal **12** was recovered.



Scheme 6.

As in all Diels-Alder reactions, the interaction of the HOMO of one component with the LUMO of the other is of pivotal importance. Our system is one of inverse-electron demand where the gap between the HOMO of the dienophile

and the LUMO of the diene determines the reactivity of the system. It is possible to calculate this energy gap and predict fairly accurately whether systems related to the one studied would react or not[17]. When in the standard reaction shown in scheme 5, the benzyl protecting groups are substituted by electron withdrawing acetates, no cycloaddition takes place due to the increase on the HOMO-LUMO gap between diene and dienophile. Even when only one strongly deactivating group is introduced in the glycal like the tosyl group in compound **20**, the energy gap might increase enough to prevent the reaction from going forth.



20 (1 eq) **13** (2 eq) (1 eq)

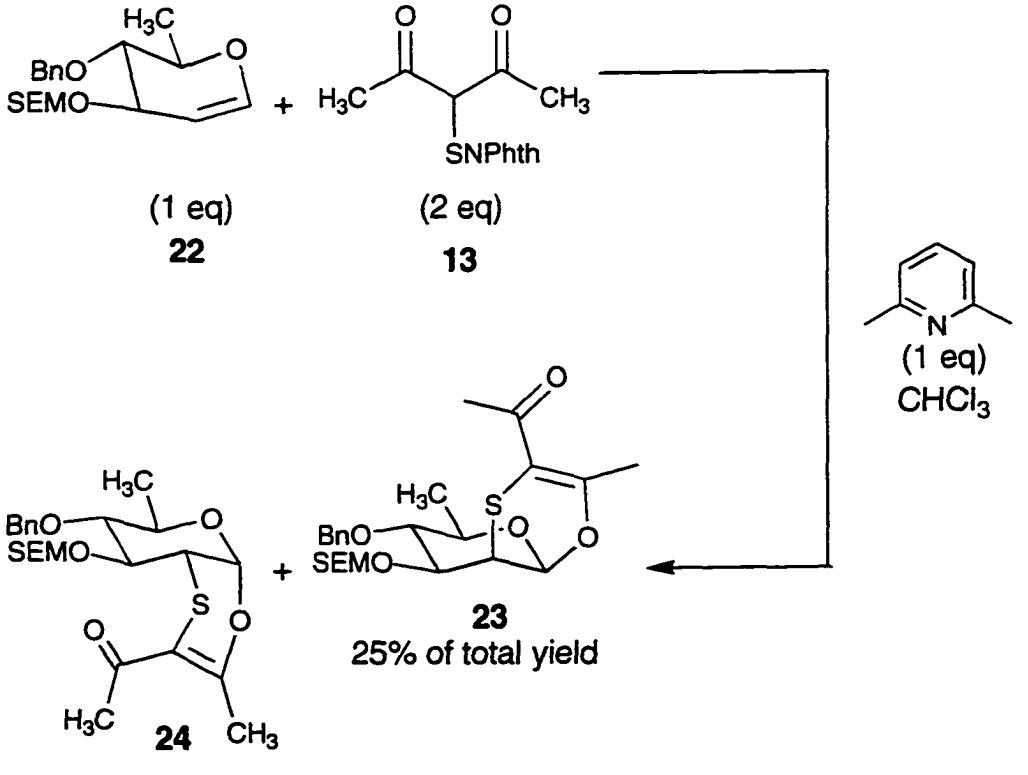
0% yield

21

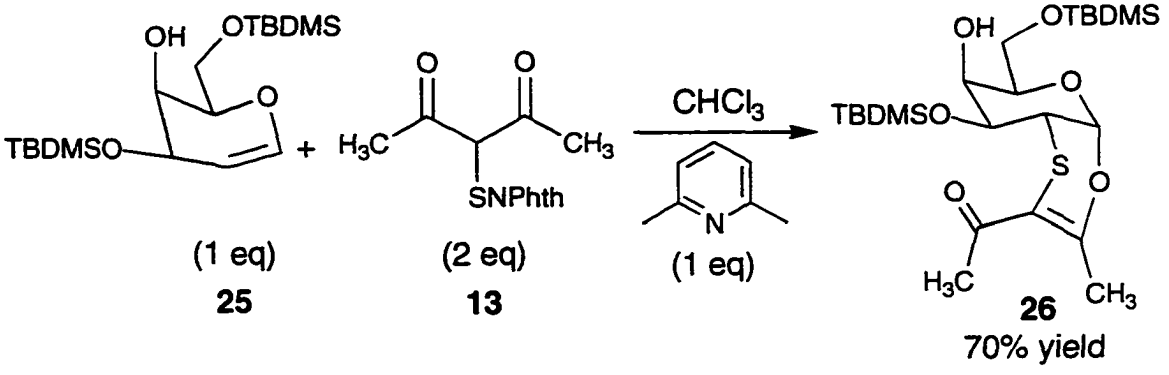
Scheme 7.

Another property of Diels-Alder reactions is the effect that solvents and substituents of both diene and dienophile have in the rate and the stereocontrol of the reaction. It has been documented how changing the number and nature

of the substituents on a dienophile or diene can change the reaction mechanism[18]. In the case of glycals acting as dienophiles, the C-3 substituent of six-member ring glycals exerts stereocontrol on hetero Diels-Alder reactions[19]. This same property of the C-3 substituent has been observed in our particular system[20], just as the effect of steric hindrance and different substituents in the glycal in this same system has been shown to have an important effect in the percentage of top face adduct present in the reaction. In the reaction below, we see the consequences of both changing the protecting group at C-3 and dehydroxylating C-6 in the glucal. We believe that dehydroxylation of C-6 promotes the formation of top face adduct by diminishing the steric hindrance between the glucal and the diene in the transition state leading to formation of the top face diastereomer.



Another example of the effect of substituent groups, and of stereochemistry of the glycal is the one with the galactal **25**; where steric hindrance due to the silyl groups, and interaction with the axial hydroxy group makes impossible the presence of a top face diastereomer.

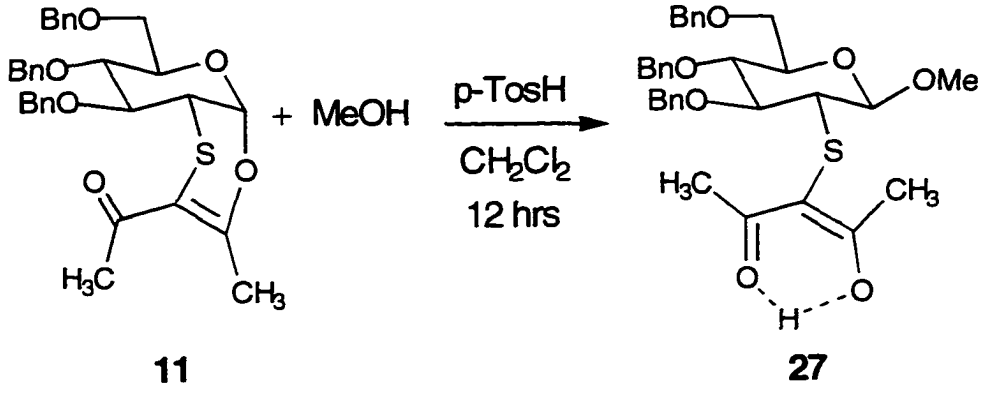


Scheme 8.

The solvent dependency of the stereoselectivity of top versus bottom adduct observed in schemes 5 and 6, is difficult to explain. No obvious correlation has been found with other solvents, and the only studied examples in the literature show influence of solvents in rate reactions[21], and in endo/exo and regioselectivity, but no example of diastereofacial selectivity was found.

A. Glycosidation Methods. Preliminary Research

The first glycosidation reaction in this project was initially done by Dr. Neelu Kaila and Ms. Maria Tamarez. This first experiment is shown in scheme 9:



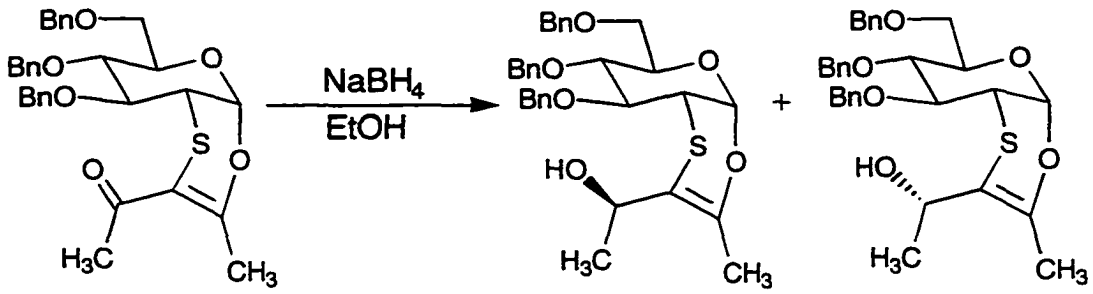
11 27

Scheme 9.

The problem with the reaction above, however was that it would not go with nucleophiles other than methanol were ineffective. The reason was attributed to the diminished nucleophilicity of primary alcohols in comparison with methanol. Therefore, we tried to devise methods by which both the reactivity and rate of the reaction increased significantly. Our first choice was to reduce the carbonyl group present in **11** to an alcohol with the hope that elimination of water would help drive the reaction towards completion.

This reduction was achieved by using sodium borohydride in ethanol, giving a mixture of two diastereomers **28** that could be separated by flash chromatography. Initially, cerium trichloride was used in the reaction to

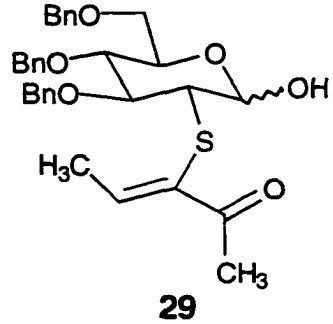
prevent 1, 4 addition to the conjugated ketone, but it was later seen that no protection was necessary.



11 28

Scheme 10.

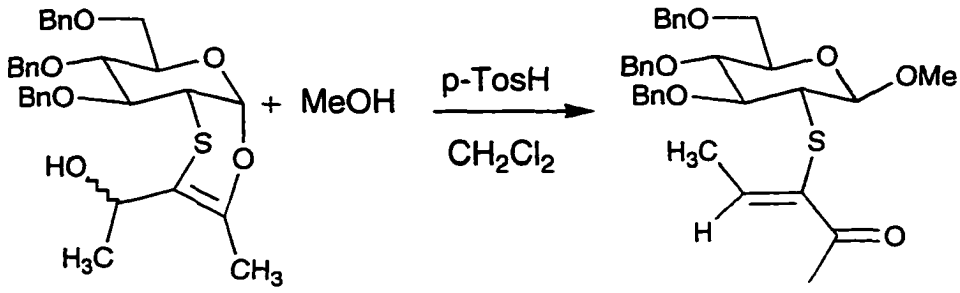
When the major diastereomer from mixture **28** which we will call **28a** was made to react with methanol under the same conditions used with the adduct **11**, the reaction took only 7 hrs., and gave a yield of 41% of **30** and 57% of pyranose **29** the latter is presumably formed by competing attack by water.



29

In that reaction, shown in scheme 11, two different isomers were possible depending on the orientation of the methyl group attached to the newly formed

double bond. Only one of those isomers is formed according to spectroscopic data, the chemical shift of the proton from the double bond in the ^{1}HNMR agrees with the one calculated for the molecule with the methyl orientation of **30**.

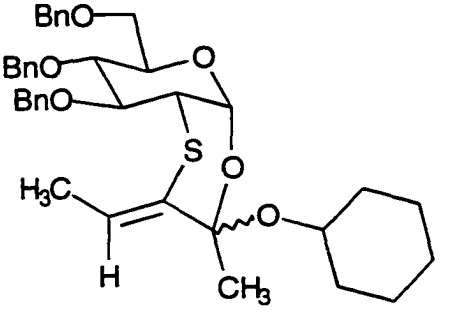


28a **30**

Scheme 11.

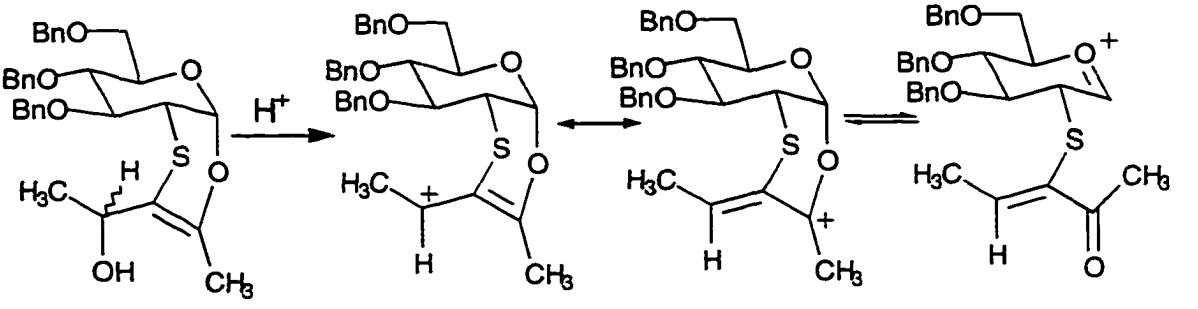
Cyclohexanol, a less nucleophilic secondary alcohol was then used in the same reaction, and under the same conditions that were successful with methanol. The signal for the methyl group attached to the double bond was split into a doublet as for **30**. The signal for the proton in the double bond was also split into a quartet as expected, but with a chemical shift of about 6 ppm, compared to 7.1 ppm in compound **30**. Also, the splitting pattern of the proton at C-2 indicated an α type substitution at the glycosidation center. At the beginning we thought that the change in acceptor had caused a change in the chemical shift, but when an IR was taken of the crude and no peak for a conjugated ketone was observed, we concluded that the ring had never been opened and no

glycosidation had taken place. Instead, our alcohol had added to the double bond in the major diastereomer of the reduced ketone **28a**, and water had been eliminated, but the reaction had proceeded no further.



31

In theory, there are two likely pathways for the reaction depending on which one of the species in scheme 12 is trapped, but we have never found a case where the pathway due to formation of the oxonium ion **34** and opening of the ring prevailed over the attack on the allylic species **32**, **33**, even though different solvents, acids and conditions were tried to promote the formation of the oxonium ion.

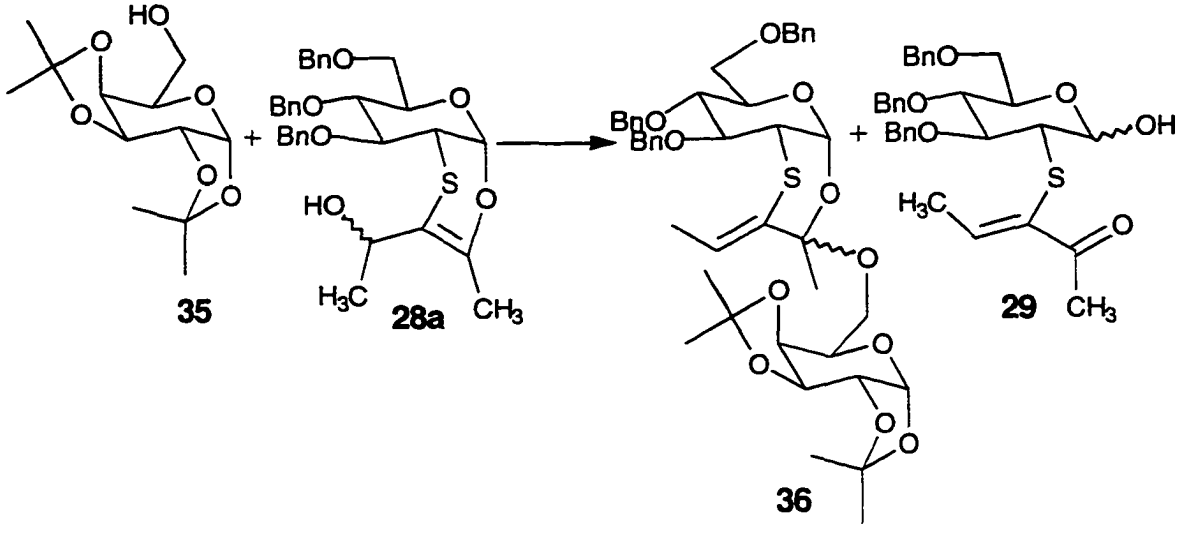


28a **32** **33** **34**

Scheme 12.

Because cyclohexanol was extremely difficult to separate from the crude by flash chromatography, all of the attempts to promote glycosidation were done using 1, 2: 3, 4 Di-O-Isopropylidene-α-D-galactopyranose, which is a clear sticky syrup and also commercially available.

Table 2:



Entry	28a[a]	13	Catalyst	Solvent	36	29
1	1eq	2 eq	p-TosH, (0.2)eq	CH_2Cl_2	none	72%
2	1eq	2 eq	$(CF_3CO_2)_2IPh$, (0.1)eq	CH_2Cl_2	50%	none
3	1eq	4eq	p-TosH, (0.1)eq	Toluene	25%[b]	50%[b]
4	1eq	3.5eq	$(CF_3CO_2)_2IPh$, (0.11)eq	Toluene	67%[b]	none
5	1eq	4eq	CF_3COOH, (0.11)eq	Toluene	42%	none
6	1eq	4eq	$CF_3SO_3Si(CH_3)_3$, (0.1)eq	Toluene	67%[b,c]	none
7	1eq	2eq	CF_3COOH, (0.12)eq	CH_3CN	38%[c]	none

a: in all reactions we used the major diastereomer in the mixture **28** obtained from reduction of **11**.
b: yield derived from integration of peaks on ^{1}HNMR, not yield form isolated product.
c: only one of the possible diastereomers of **36** observed in the ^{1}HNMR

In all reactions shown, a tentative assignment is that the mixture of isomers obtained as **36** are those due to different face of attack by the alcohol on the double bond. The difference in chemical shift between the two quartets at around 6 ppm is small and is not consistent with E, Z double bond isomers.

In a whole set of reactions we used CH_2Cl_2 as the solvent. When we used p-TosH as a catalist, using 0.1eq, after 1 hr. we saw mainly an α / β mixture of pyranoses (due to H_2O attack) of the starting material. Next we used the catalyst [Bis(trifluoroacetoxy)iodo] benzene, and the mixture of intermediates **36** was obtained in 50% after 2 hrs.

With toluene as solvent and p-TosH as catalyst, **29** was the main product in 5 min. reaction time. When we tried [Bis (trifluoro acetoxy) iodo] benzene in the same solvent **36** was also formed in five minutes. We had hoped that [Bis (trifluoro acetoxy) iodo]benzene would catalyze the reaction by reacting with the sulfur and giving it a positive charge[22]. This would promote opening of the ring by attack of a nucleophile, instead of by forming the allylic species shown in scheme 12, but $(CF_3CO_2)_2IPh$ did not work as expected. Instead, we found that trifluoroacetic acid present in the catalyst as an impurity was the driving force behind our results. By comparing the ^{1}HNMR of both crudes in table entries 4 and 5 we realized that both sets of NMR's are identical. It is then to be expected that the mechanism of reaction is the same. The reaction with TFA also took only 5 min. A longer time of reaction, 1.5 hrs. was needed when TMSF was used as a catalyst, and only one diastereomer of the two possible for **36** was

observed in the ^{1}HNMR of the crude.

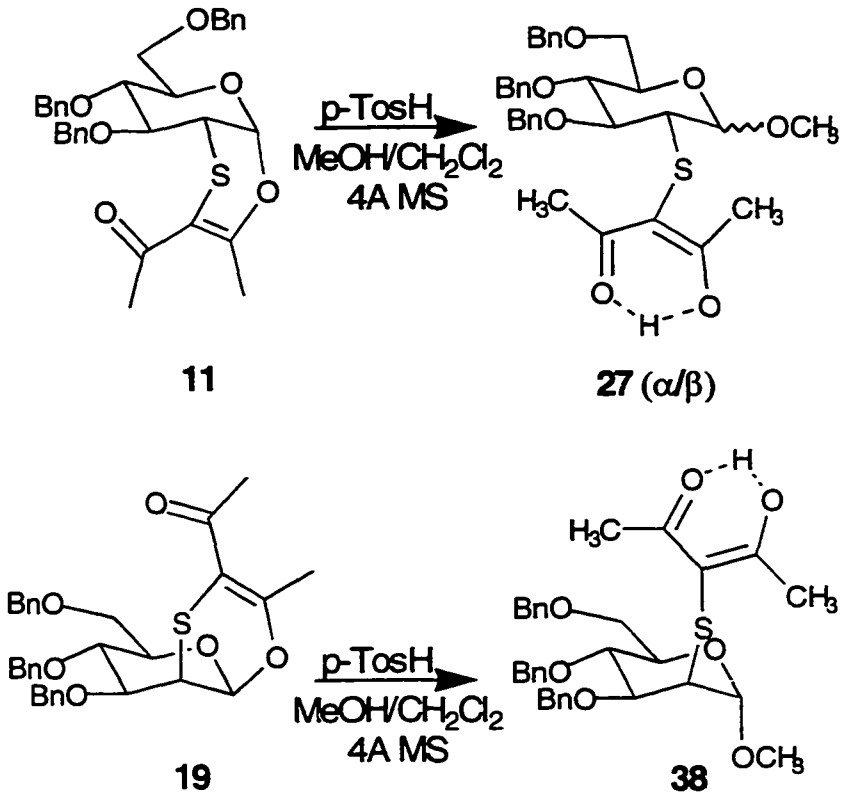
A major change seemed to happen when acetonitrile was used as solvent and TFA as catalyst. The reaction took 3 hrs., and even then did not go to completion. Also, only one of the two possible diastereomers of **36** was isolated in 37% yield.

At this point it was already obvious that addition to the double bond as the only product was occurring in all cases, no matter what conditions were used. The idea of optimizing reaction conditions to form the glycoside was abandoned. Instead, we decided to determine whether the intermediate could be forced to react by simply adding more equivalents of sugar acceptor and some extra catalyst. This will be discussed later in the thesis. Before that, a deeper analysis of the reasons for the failure of the first glycosidation reaction tried, the one using **11** as donor and methanol as acceptor is in order.

B. Kinetic Studies of Nucleophilic Methanol Attack.

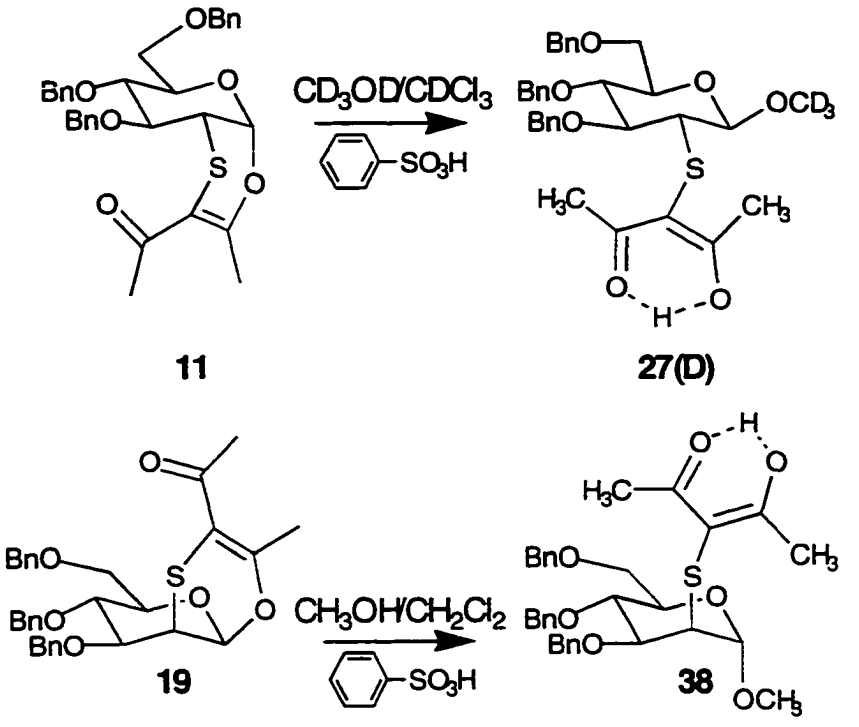
A variation in the experiment of addition of methanol to **11** was due to the fact that once we had synthesized the top face diastereomer **19**, we could devise an experiment to measure the relative speeds of methanol glycosidation in top and bottom diastereomers. This experiment would in fact be measuring the consequences of anomeric effect on sugar glycosidation. The experiment was tried as shown in scheme 13 and followed by TLC. Unfortunately, no conclusive evidence was obtained because **11** and **27** (methanol-β-glycoside) co-spot in TLC, so the reaction was left overnight when it was actually over in a few hours, and

an α/β mixture of **27** was obtained instead. The reaction which gave **38** went to completion in 5 hrs.



Scheme 13.

This same experiment was then repeated using benzenesulfonic acid hydrate as catalyst and followed by ^{1}HNMR as shown in scheme 14.



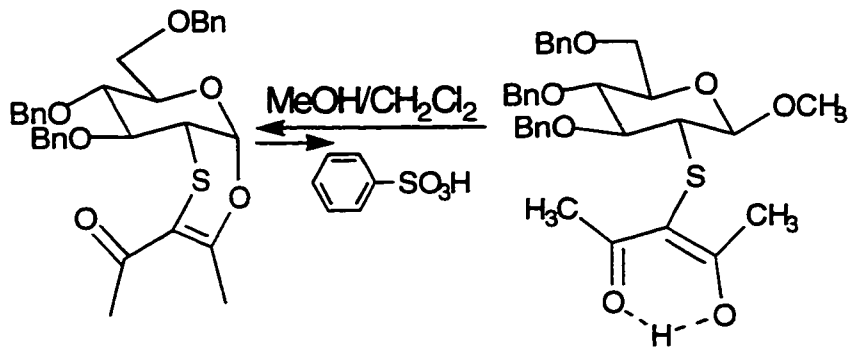
Scheme 14.

The reason for the change in acid is that the reaction was monitored through the integration curves of the new methyl peaks due to the formation of **27(D)** and **38** and the methyl peak in p-toluensulfonic acid made this way of monitoring the reaction impossible. There was a problem in that even after using two equivalents of the acid, the attack on **11** was so slow that after eighteen hours the reaction was still not complete. Since the pH of p-toluensulfonic and benzenesulfonic acid are quite similar, we assumed it might be that the molecular sieves present in the reaction were absorbing the acid, therefore significantly diminishing the acidity of the medium. In order to solve that problem, it was necessary to dry the benzenesulfonic acid hydrate by

making it react with triflic anhydride and then distill the mixture under vacuum to give a yellow-greenish solid as a residue. One equivalent of this acid was used in the experiment as shown in scheme 14. It was necessary to use deuterated methanol and $CDCl_3$ as cosolvents for the reaction on adduct **11** and to set up the reaction in an NMR tube, instead of simply following a reaction run in non deuterated solvents by NMR as in the case of the opening of **19**. When no molecular sieves were used, the rate of both reactions speeded up greatly.

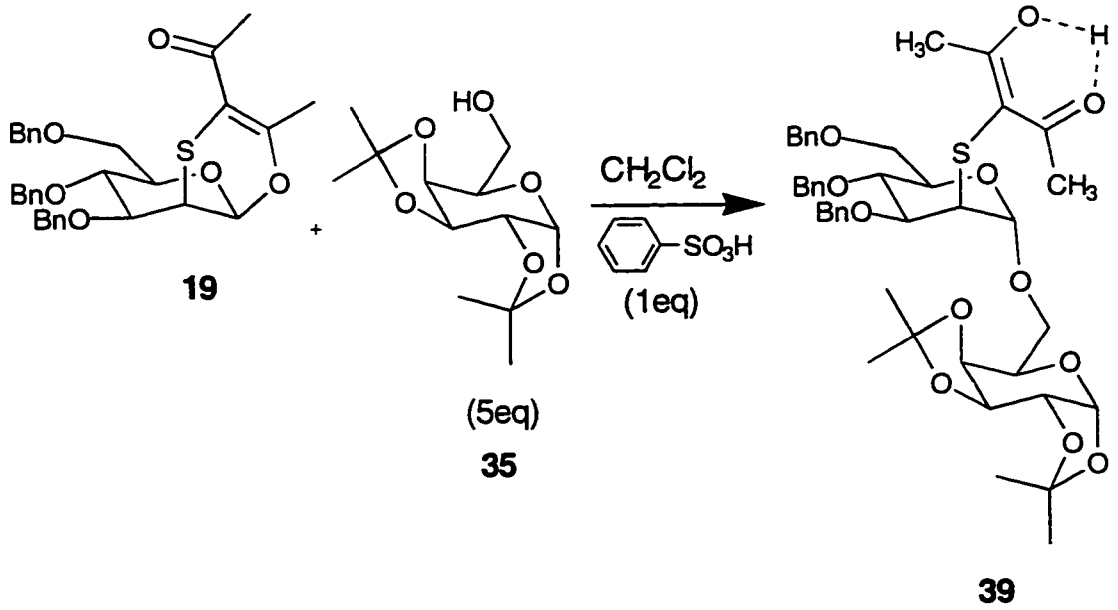
The data in tables 3 and 4 and graphs 1 and 2 is due to the integration curves of methyl peaks of product formed versus starting material in both reactions shown in scheme 14. In the first reaction in scheme14, the opening of the bottom face diastereomer, the two methyl peaks of the starting material **11** show in the ^{1}HNMR as two singlets at 2.308 ppm and 2.314 ppm and the two methyl groups of **27(D)** give a singlet at 2.467ppm. In the second reaction, the opening of the top face adduct **19**, the methyl peaks of the starting material show also as two singlets at 2.302 ppm and 2.372 ppm and the methyl peaks of product **38** as a singlet at 2.429 ppm. This data shows that the nucleophilic attack on **19** was a pseudo first order reaction which was almost completed in three hours, but the reaction in the case of **11** is a more complicated situation. The reaction on **11** started off in the first half an hour followed by a stagnant period before increasing again slowly, and this suggests that this reaction is not a straightforward nucleophilic attack by the methanol on the protonated adduct, but that an equilibrium might be occurring where the product is reversibly going

back to the starting material in the acidic medium.



11 27

Another fact that suggests this reversibility is that when we attempted to obtain an α glycoside **39** through the same methodology that gave **38** for the top face adduct, we did obtain an α glycoside **39** in 73% yield instead of just the starting material back.



Scheme 15.

This theory was confirmed when we took **27** and dissolved it in CH_2Cl_2 together with one equivalent of benzenesulfonic acid. After only about half an hour, the ^{1}HNMR showed starting material **11** forming. When **38** was left overnight under the same conditions, however, no starting material was formed at all, and only decomposition products appeared eventually.

Table 3: Glycosidation reaction of adduct **19** and Methanol

Entry	Time (min.)	st/(st+prod)	Ln[st/(st+prod)]
1	4	0.65	-0.44
2	34	0.53	-0.63
3	94	0.16	-1.8
4	124	0.077	-2.6

Graph 1: time vs Ln[st/(st+prod)] for reaction of adduct **13** and Methanol

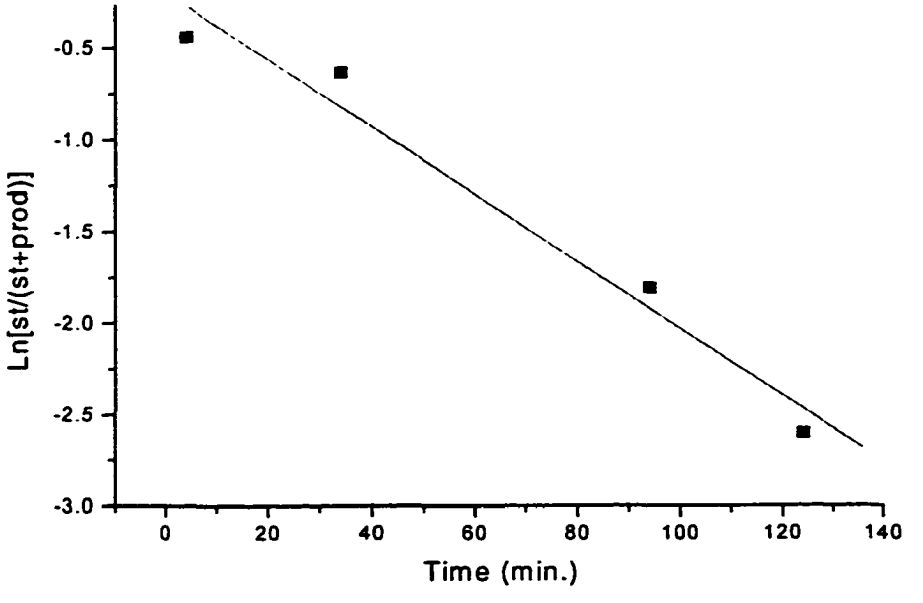
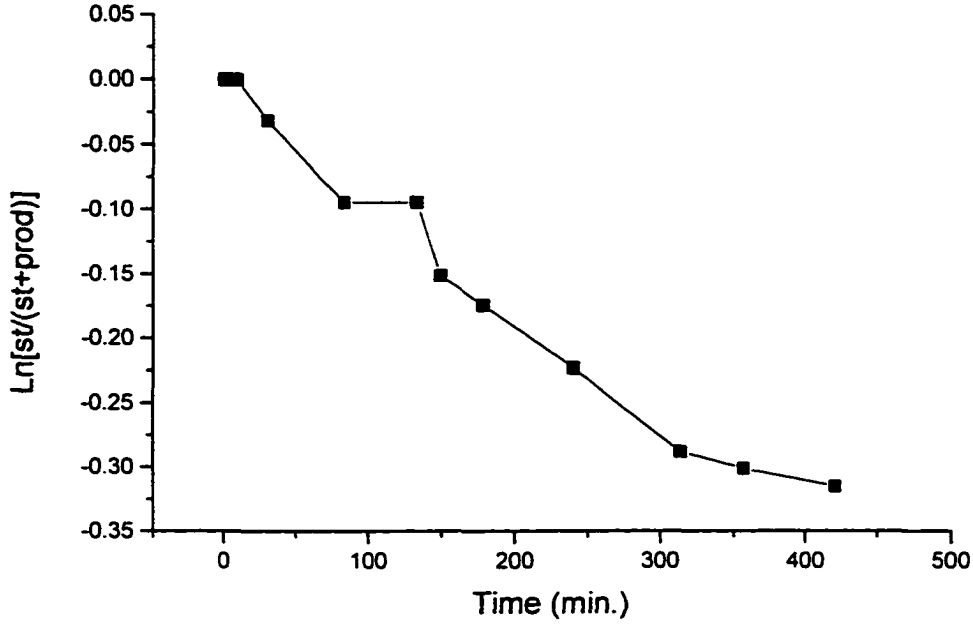


Table 4: Glycosidation reaction of adduct 11 and CD_3OD.

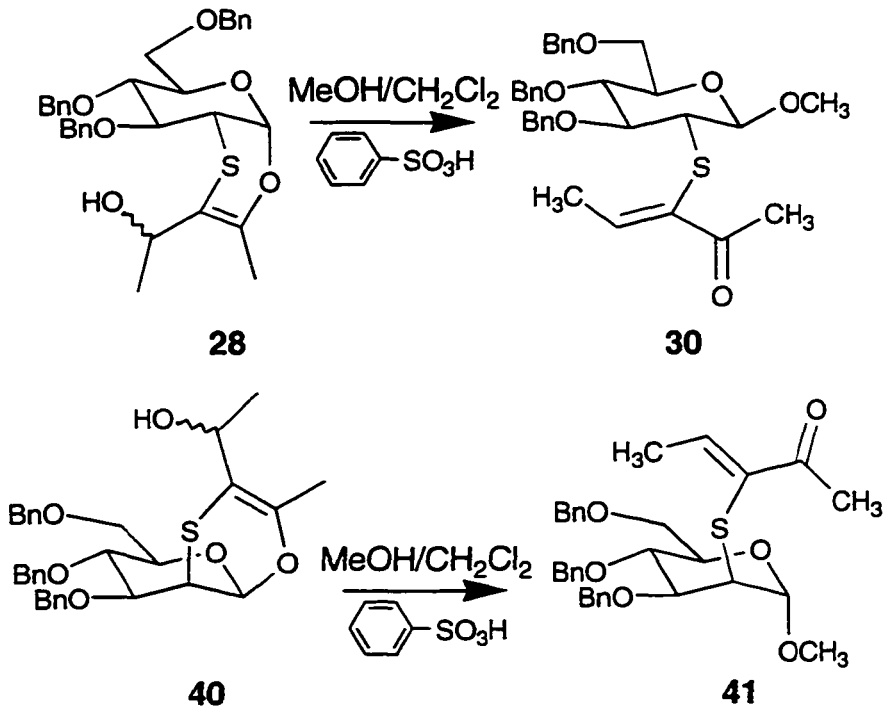
Entry	Time (min.)	st/(st+prod)	Ln[st/(st+prod)]
1	0	1	0
2	9	1	0
3	30	0.97	-0.031
4	83	0.91	-0.094
5	133	0.91	-0.094
6	149	0.86	-0.151
7	178	0.84	-0.174
8	240	0.80	-0.223
9	314	0.75	-0.288
10	357	0.74	-0.301
11	421	0.73	-0.315

Graph 2: time vs Ln[st/(st+prod)] for reaction of adduct **11** and CD_3OD.



The next logical step was to try the same study in a case where reversibility was not possible, to see if the relative rates of reaction were maintained. However, when this reaction was tried separately on all four possible diastereomers due to the reduction of the ketone on both **11** and **19**, it was impossible to compare the reactions through ^{1}HNMR integrations of methyl peaks of the products versus the integration of methyl peaks from the starting materials. Both diastereomers from the reduction of **19** reacted so fast that within ten minutes the reaction was done as followed both by ^{1}HNMR and by TLC. In the case of the diastereomers obtained from the reduction of **11** the reactions were slower. There was however, a difference between the two possible diastereomers of the

mixture **28**, **28a** and **28b**. The diastereomer that is least abundant, and whose methyl singlet appears at 1.9 ppm, **28b** reacted completely in one hour and a half, while the other diastereomer **28a**, which is the major product of reduction of **11** and the one used in the glycosidation experiments in this investigation took two hours to go to completion. Scheme 16 shows the two reactions.



Scheme 16.

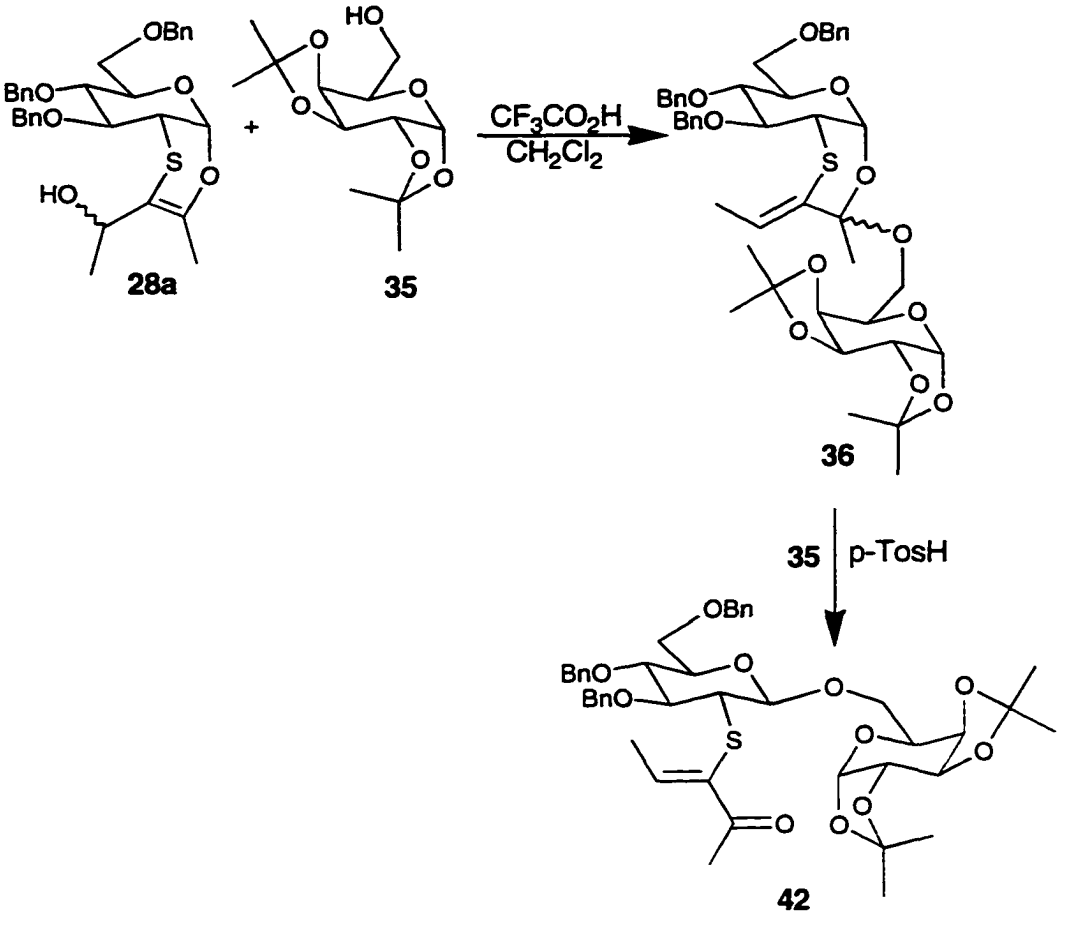
This second set of experiments apparently shows that the slower rate of glycosidation of **11** compared to **19** is not only due to reversibility of the glycosidation reaction in the former case. We believe the reason for these

results is the fact that the stabilization due to the anomeric effect present when we have a bottom face diastereomer lowers the ground state energy of the starting material and therefore makes hydrolysis of the C1-O bond slower, which will slow down the glycosidation rate. In the case of **11** this explains why the reaction is reversible. When we take away the possibility of a reversible reaction, it forces the nucleophile to add to an allylic species **33** (shown in scheme 12), which preserves the axial bond at C-1 before a second molecule of methanol can force the ring to open. We know this because intermediate species due to addition of MeOH to **33** have been isolated. The fact that in the last case, if the reaction was left long enough it is the glycoside **30** we obtained, clearly indicated that if we took any of the intermediates we had obtained when we reacted 1, 2: 3, 4 Di-O-Isopropylidene-α-D-Galactopyranose with **28a**, we would obtain a β glycoside, and this might very well be an excellent glycosidation method. Another possibility is the fact that if we could prevent the reaction of the bottom face adduct in scheme 13 from reversing, the initial cycloadducts could be used directly as glycosyl donors, without the need for reduction to the alcohol.

C. Glycosidation Methods.

As mentioned previously, we decided to try to force glycosidation from the point of addition to the double bond. All of the glycosidation products obtained in the experiments shown in Table 2 were dissolved in methylene chloride and 1, 2: 3, 4 Di-O-Isopropylidene-α-D-Galactopyranose and PTSA were added. After 2 hours, we obtained some β glycoside as later confirmed by spectroscopy, especially the IR spectra which showed the signal due to the conjugated ketone present in the glycoside but absent in **36**, and elemental analysis. The yield, however, could not be calculated, since much of the intermediate we used was not isolated, but used as a crude containing a lot of excess 1, 2: 3, 4 Di-O-Isopropylidene-α-D-Galactopyranose from the original reactions.

The reaction was repeated using TFA as the initial catalyst, as can be seen in scheme 17. Initially, the total yield of the glycosidation was rather disappointing, but after improving the drying techniques of the starting material **35**, we were able to dramatically increase our overall yields from **28a** to 80% in the the case of the intermediate adduct at 53% for the final glycoside.



Scheme 17.

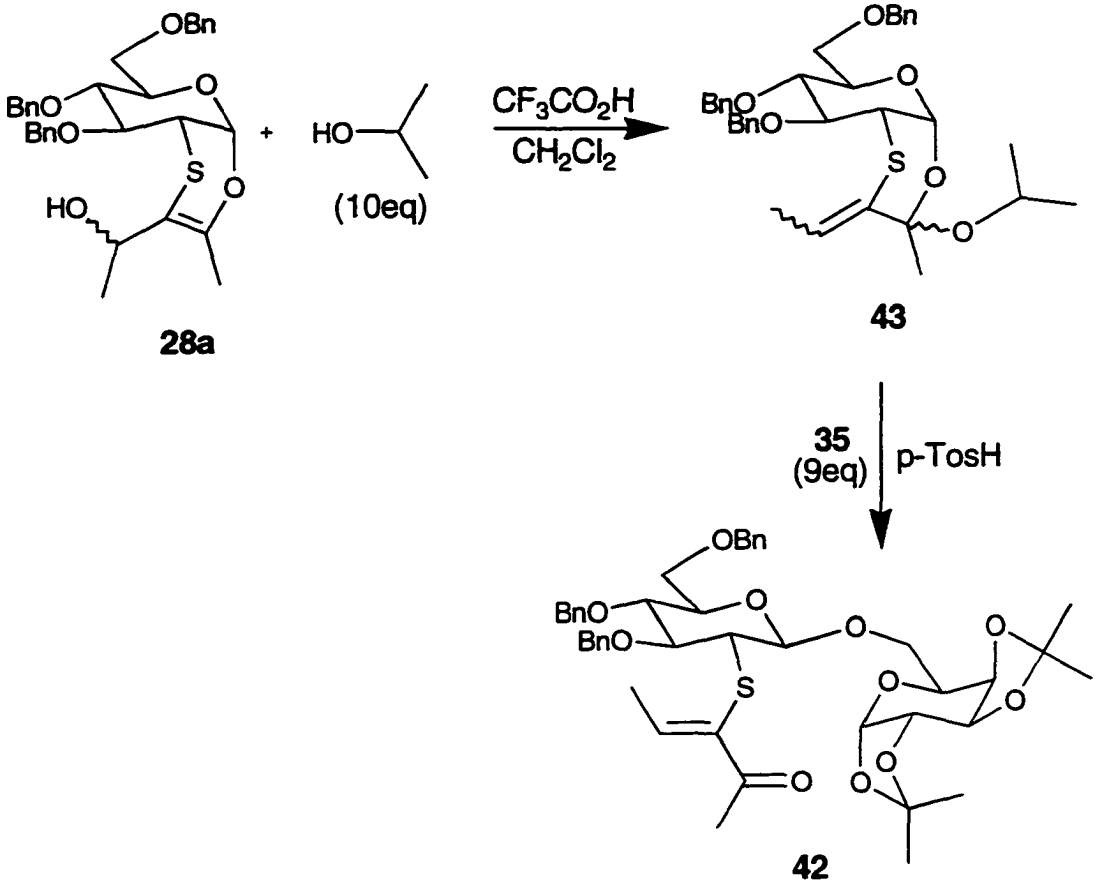
It is particularly interesting that we ended up with only one diastereomer of the two possible for the disaccharide **42** as shown in scheme 17, which is in agreement with our previous assumption that the two diastereomers in the intermediate adduct are not due to isomerism at the methyl group in the double bond, but in the carbon next to the oxygen in the six member ring.

It is also important to notice an imperfection of the method consisting in the fact that it is necessary to workup the reaction after the initial addition of the primary alcohol **35** to the double bond of the donor takes place even though it

is not necessary to purify the intermediate. If the workup is not done at this intermediate stage, the reaction gives only unreacted intermediate and the mixture of products of pyranoses due to addition of water.

It was also a concern that too many equivalents of the acceptor sugar were necessary to obtain the product. Even though the excess acceptor was recovered from the column and could therefore be recycled, it would simplify matters if that were not necessary. Would the method work however if a sacrificial alcohol was used in the first step of a reaction? To find this out a new experiment was set up.

The diastereomer **28a** was made to react with 2-propanol in CH_2Cl_2 using TFA as the catalyst (1/3eq), and after the product of this reaction was formed, the reaction was worked up and **35** was made to react with the intermediate in CH_2Cl_2 using p-TosH (1eq) as catalyst. The large amount of primary alcohol used was probably not necessary for the success of this reaction, but this experiment was done simply to prove the point that this idea of using a sacrificial alcohol in the reaction was feasible.



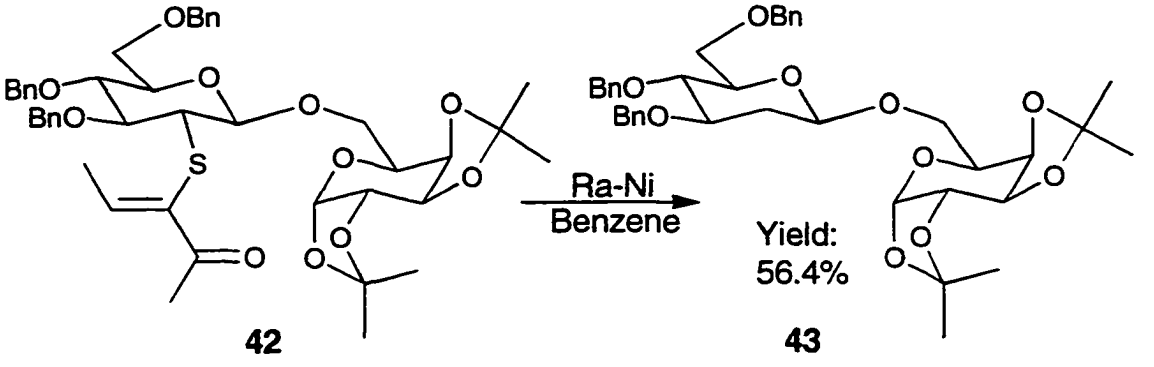
Scheme 18.

The total yield of **42** was 42% calculated from the amount of starting material **28a**. The difference in yield with the previous reaction to obtain **42** might be due to any number of experimental factors, including the fact that activated 4A molecular sieves were used instead of 3A as in the original experiment, and different amounts of catalysts and reaction times were required.

Once the glycosidation reaction had been successful, it was still left to prove that a 2-deoxy-disaccharide could be obtained through this method by breaking the C-S bond. If this was not achieved, the whole exercise would be of little use,

since it is the 2-deoxy compounds that are present in a large number of natural products, and the ones that are usually exceedingly hard to synthesize in an easy manner and with a reasonable yield.

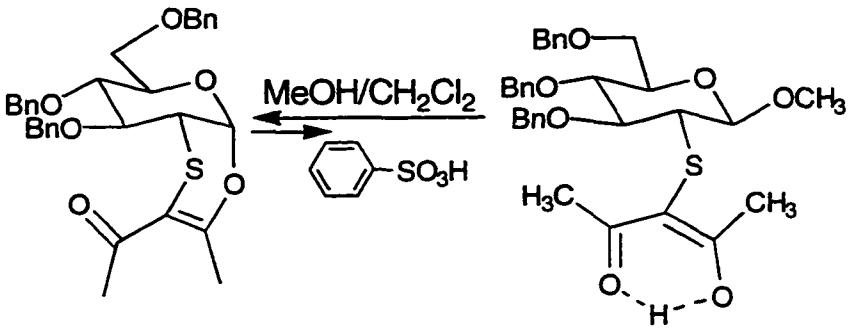
The bond to sulfur, however was easily broken using activated Raney-nickel catalyst in a reaction developed in our laboratories by Ms. Maria Tamarez as part of her thesis research.



Scheme 19.

The identification of the 2-deoxy-compound **43** was done by spectroscopic data and elemental analysis.

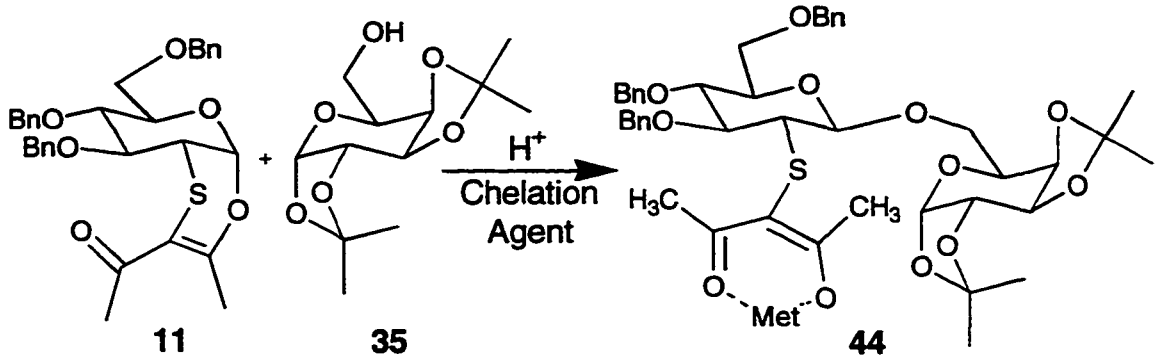
The cycloadduct could also be used as a glycosyl donor if we figured out a way to stop the equilibrium shown below from happening.



11 **27**

We thought that a good way to shift the equilibrium to the right was to somehow either form a derivative of **27** immediately after formation of the glycoside or precipitating this glycoside right after it was formed. One way to achieve this would be to form a β-diketone metal chelate with the β-diketone present when the adduct is open through acid catalyst as in the case above. Formation of this type of chelates is known in the literature[23], but we could not find an instance where they had been applied as a synthetic method in an organic reaction in order to precipitate a final product out of solution or force an equilibrium towards the formation of a product.

We first decided to try and use as chelating agents Mg or Cu because they would not interfere in the ^{1}HNMR of the crude and they were metals known to form β-diketone metal chelates in the literature and these chelates showed great stability in thermodynamic studies[23a]. The new reaction is shown in scheme 20.



Scheme 20.

The first problem appeared when we tried to perform a reaction with magnesium trifluoromethane sulfonate in THF/acetone, one equivalent of benzenesulfonic acid as acid catalyst and 2.4 equivalents of **35**. The magnesium triflate did not dissolve in solution, and as a consequence the reaction did not go for about six hours at room temperature (we had first tried to run the reaction at -30°C and then 0°C but not product was formed at all under those conditions) and it was left to run overnight. Both the ^{1}HNMR and mass spectra run suggest the presence of glycoside, but the ^{1}HNMR showed peaks that if they belong to a glycoside of **11** and **35** could only be due to the α glycoside, and the reaction did not go to completion. In fact, about half of the starting material did not react according to TLC and ^{1}HNMR. The question was then whether the formation of this α isomer was due to the length of reaction time necessary because of poor solubility of the chelating agent, or whether it was due to the chelating agent opening the ring before the acceptor primary alcohol had attacked the adduct and formed a β glycosidic bond. In the first case a β

disaccharide would be formed first and then it isomerized giving a thermodynamic mixture of α and β glycosides. In the second case the axial position would be open to attack, and therefore the axial anomeric isomer would be formed.

The first chelate reagent, magnesium trifluoromethane sulfonate was used again to try and repeat the reaction using as solvent a mixture of THF/DMF, but even though we used sonication to try and induce the solid to dissolve, it took such large amount of solvent to get the magnesium trifluoromethane sulfonate that the reaction did not go because of the excessive dilution of the mixture.

This last experiment convinced us it was time to change the metal chelate to a more soluble compound and so $MgBr_2$ was tried next. Two experiments were run in basically the same conditions as before, but using a THF/ether mixture as solvent. In one case benzenesulfonic acid was used as the catalyst, and in the other triflic acid was used. Initially, one equivalent of the acid was used in both experiments, but two hours before quenching the reactions, one equivalent of the corresponding acid was added followed by one equivalent of the metal chelating reagent in hopes to increase the amount of product obtained. It is also important to note that in the reaction catalyzed with triflic acid no product was obtained until the temperature had risen from -30°C to 0°C. The reaction catalyzed by sulfonic acid took 6hrs. and 30 min. and starting material remained, even though not in large amounts and β glycosides seem to be

present in the crude. The reaction catalyzed by triflic acid took 4 hrs. and 30min. at 0^0C. When a column was run a glycosidic mixture of β/α mixture was found and its mass spectra confirmed they were the disaccharides sought. Even though the β glycoside was the major component of the mixture, the yield was low (30% yield). The issue of improving the stereospecificity of the reaction and the question of why it was lost are still questions that need to be answered. It is also necessary to find the changes necessary to increase the yield of the reaction to an acceptable level. Continuing with the development of this methodology, however is out of the scope of this study and will have to be taken up in a future occasion.

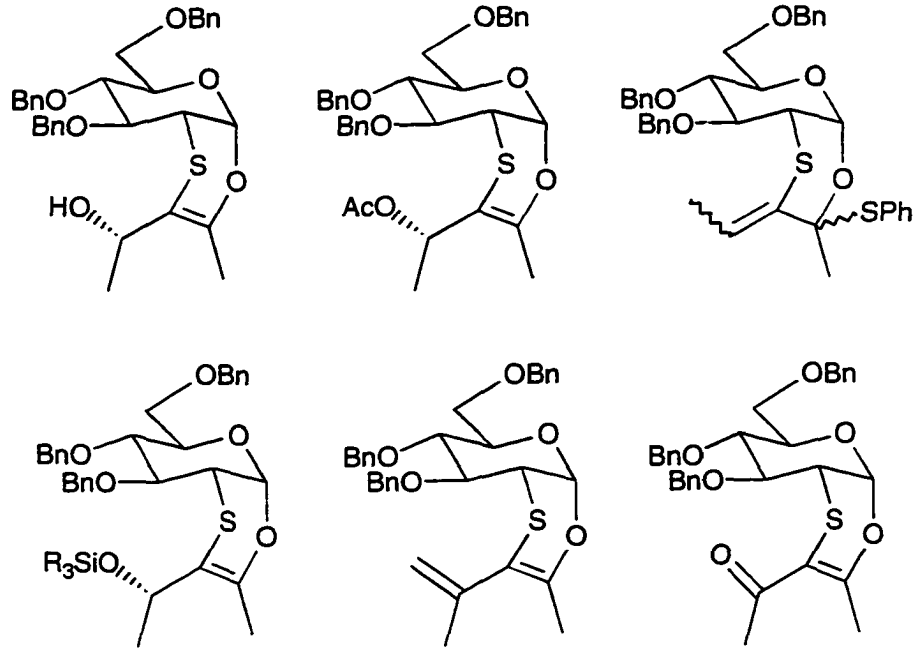
Conclusion

We have developed and optimized a glycosidation method based on glycosyl transfer via cycloaddition chemistry for 2-deoxy-β-glycosides.

An extremely useful Diels-Alder type reaction has been developed and optimized to give useful amounts of different types of adducts. A very interesting solvent effect on the cycloaddition face selectivity on our particular system was also observed and warrants further study to seek total control of the stereoselectivity. If we are able to find the way to control the stereoselectivity, a new method to obtain 2-deoxy-α-glycosides with great ease and in high yield will be available.

The comparison in the rate of formation of β-glycosides and α-glycosides led us to observe novel stereoelectronic behavior of the original bicyclic glycosyl donors. The differences in rates of glycosyl transfer, including hydrolysis, have been investigated for decades. The challenging question is whether the difference in ground state energy are large enough to offset the difference in the energy of activation, so that the rate for axial bond cleavage and subsequent glycosyl transfer is faster or slower than equatorial bond cleavage, where the anomeric effect can not be important. In the case of our bicyclic donors it is apparent that the anomeric effect in the ground state is large enough to guarantee a larger stability of the axial anomeric bond in the adduct **11**, and as a consequence the faster formation of the α-glycosides from addduct **19**. This is significant because both adducts **11** and **19** have similar structures but the

anomeric effect is only present in the bottom face adduct **11**, and therefore the difference in hydrolysis rates seems to be connected with the anomeric effect. Finally, it is important to mention that the major advantage of this type of bicyclic glycal donors is their versatility. By only slightly modifying some fraction of the system studied here several collaborators[24] have optimized new and effective glycosidation methods, and many more can be developed from the same parent molecule. Some of the derivatives both we and other people have worked on are shown below.



The application of this concept to the Aureolic acid family of antibiotics will be discussed in part two of this thesis.

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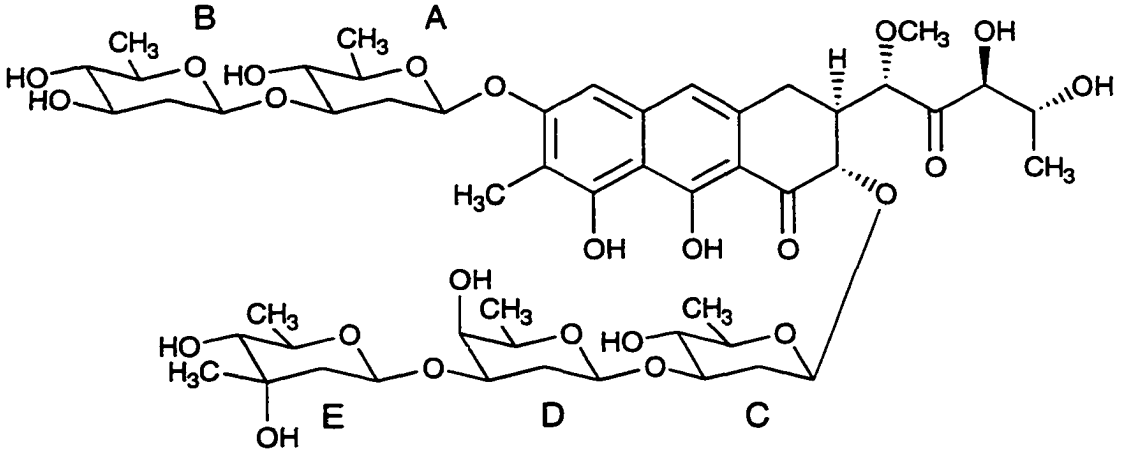
PART 2

STUDY OF SYNTHESES OF THE TRISACCHARIDE CHAIN IN THE AUREOLIC ACID

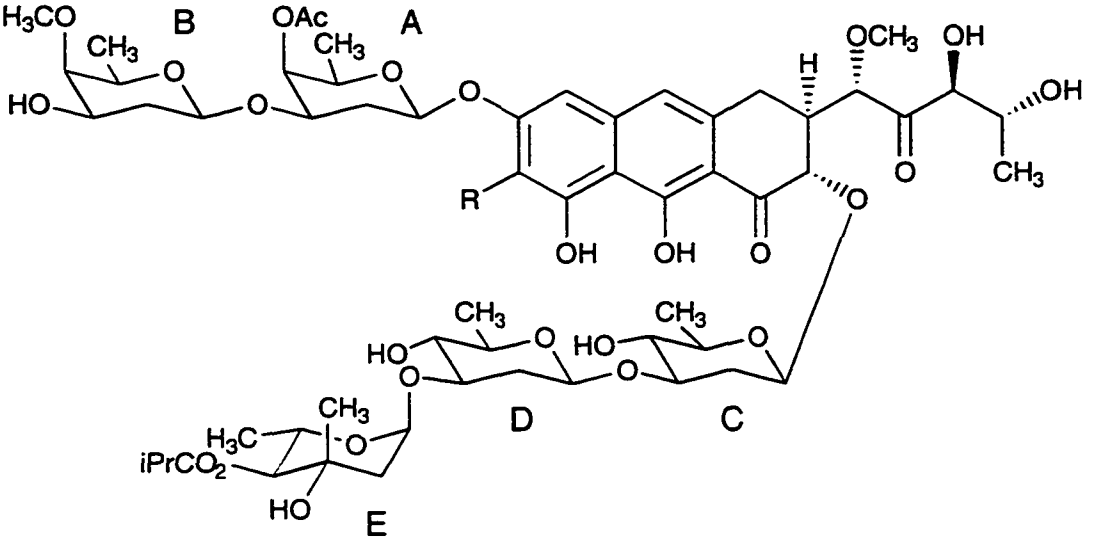
Introduction

The aureolic acids are a well known family of antibiotics[1] with significant antitumor properties, but also high toxicity. They work as antitumor agents because they are inhibitors of DNA-dependent RNA polymerase and they bind as 2:1 antibiotic Mg^{+2} complexes in the DNA minor groove[2], but are not commonly used because of their high toxicity. Activity studies have shown that the two intact oligosaccharide chains are essential for DNA binding and biological activity[2]. The family includes aureolic acid, the chromomycins, the olivomycins and other related compounds.



AUREOLIC ACID

Aureolic acid was first isolated by Grundy and coworkers[3] at Abbot laboratories in 1953. The main structural differences between aureolic acid, chromomycins and Olivomycins is in the structure of the oligosaccharide chains and in the case of the Olivomycins in the change of the methyl group at the C-7 in the aglycon by a hydrogen.



R=Me Chromomycins
R=H Olivomycins

Our interest in aureolic acid is due both to the fact that this compound is linked at the 2- and 6- position of the aglycon to chains of two and three units of 2-deoxy sugars, and that until very recently the hydroxy group at C-4 in ring D was thought to be in the equatorial position instead of axial and so previous syntheses[4] of this trisaccharide did not match that of the natural product.

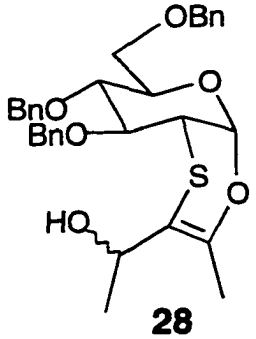
Synthesis of both carbohydrate chains of the aureolic acid have been many, but none of the glycosidation methods to obtain the β-linkage of the 2-deoxy components of the chains has been completely satisfactory, so we decided to apply the methods and system developed in part 1 of this thesis to the synthesis of the trisaccharide present in aureolic acid.

The gist of our strategy in this synthesis will be to achieve 2-deoxy-β-glycosides through glycosyl transfer via cycloaddition chemistry, specifically Diels-Alder type reactions already described in part 1.

Two possible retrosynthetic schemes were considered:

The one in scheme 1, where all of the three components of the trisaccharide were obtained through a Diels-Alder reaction and then joined together by acid catalyst.

The one in scheme 2, where the precursor to ring C is a glycal compound instead of a cycloadduct, which had the advantage that it gave a lot more flexibility to hook the carbohydrate unit to the aglycone portion of the aureolic acid.



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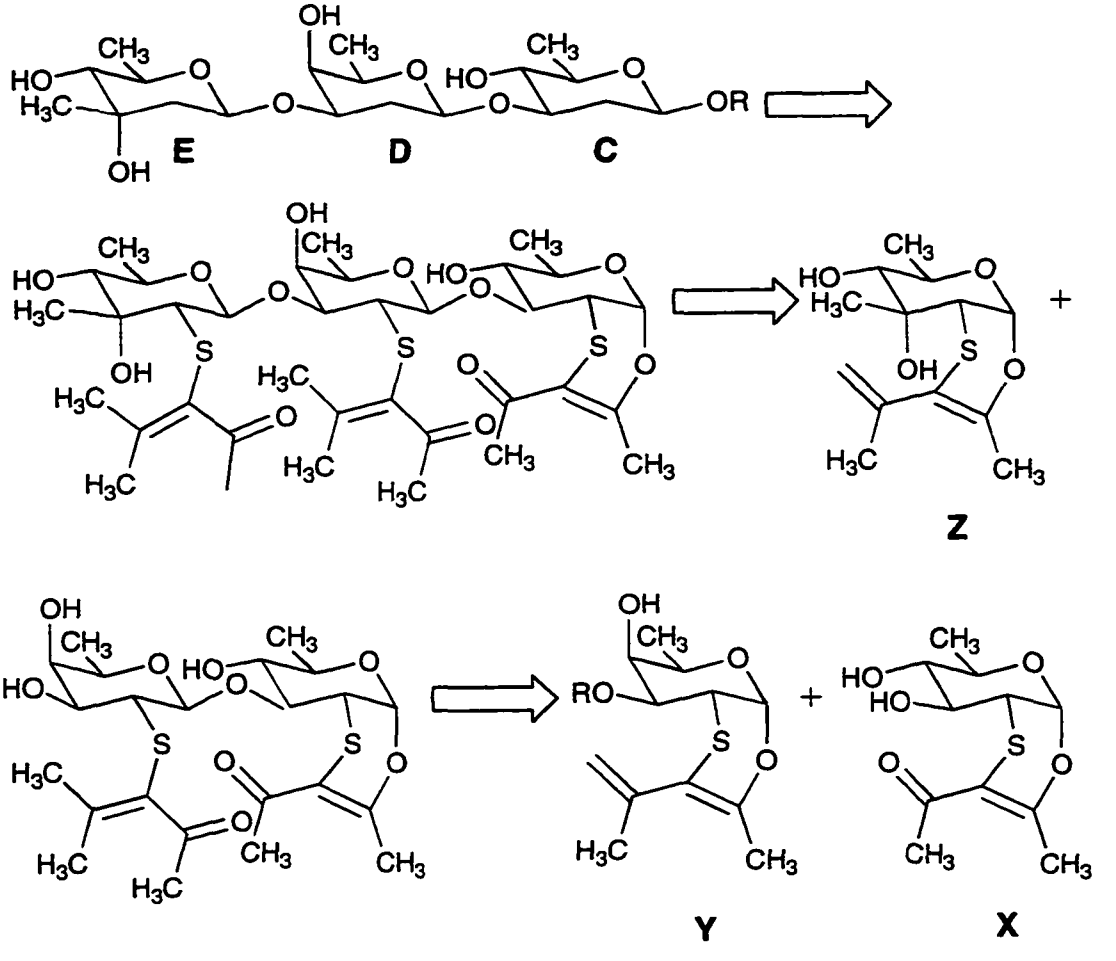
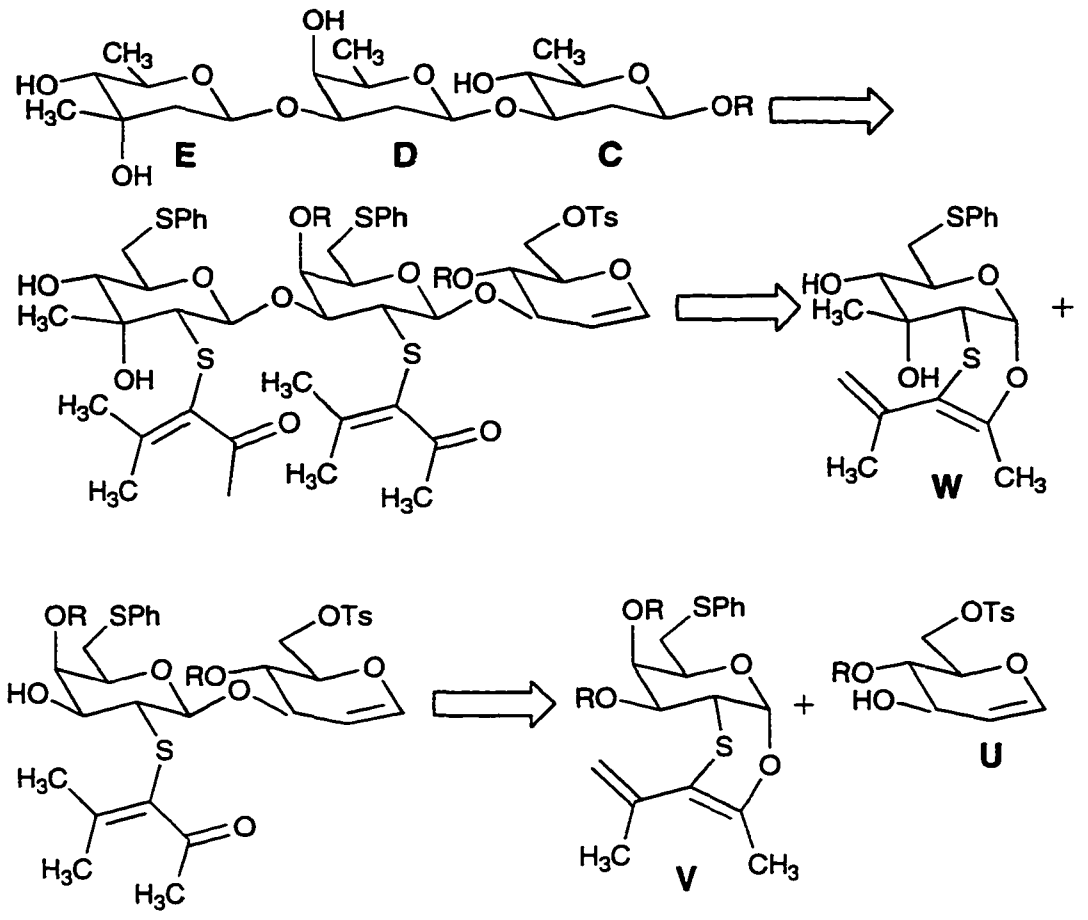
In these two proposed strategies, the cycloadduct unit used to promote glycosidation is not the same adduct **28** that was studied in part 1, because the use of this new type of adducts such as **Y** and **Z**, had been proven[5] to give better yield in glycosidations of primary and secondary alcohols than the ones developed in part 1.



Scheme 1.

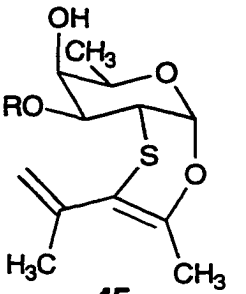
The cycloadduct **X** would be linked to **Y** through acid catalysis, the fact that a conjugated ketone instead of a diene was present in **X** was to prevent the formation of dimers and assure that **X** would act as the acceptor, while the conjugated diene **Y** was the donor. In all of the reactions of this type, the conjugated diene would act as the donor while the conjugated ketone would deactivate the reaction and make the cycloadducts act as the acceptor. Once the glycoside **Y-X** was formed, it would be linked to **Z** through acid catalysis to form a trisaccharide. Once the aglycone portion of the molecule was added, Ra-Ni was to be used to break off the sulfur chains and give a β-2-deoxy trisaccharide chain.

As pointed out previously, a second retrosynthetic plan shown is scheme 2 was thought out afterwards, in order to give more versatility in the joining of the oligosaccharide chain to the aglycone portion of the aureolic acid molecule. The thiophenols seen on the C-6 of the cycloadducts were added to ensure their stability, which diminishes when the hydroxy group at C-6 is substituted by a hydrogen, like in scheme 1. The tosyl group at C-6 in the glucal in scheme 2 was meant to deactivate the double bond and thus make it more stable and specially protect it during the acid catalysis. These thiophenol groups would come off at the same time as the sulfur chains at C-2 reduced with Ra-Ni.



Scheme 2.

The fundamental mechanism of the glycosidation reaction proposed for the method used in both of these synthesis was similar to the one proposed in the method where the adduct obtained through reduction of the ketone to an alcohol **28** was used as a donor, which was explored before. The difference is that in this case, a tertiary carbocation due to addition of a proton to the terminal double bond of the diene is formed, instead of a secondary one due to loss of water.



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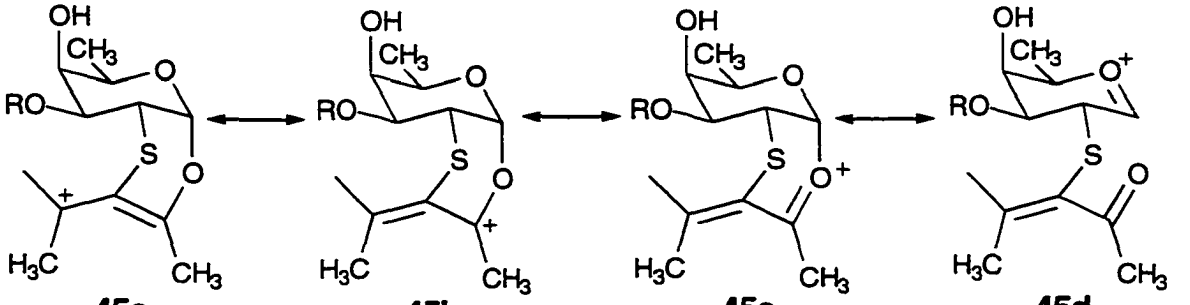
If for example we were to add an acid catalyst to compound **45**, the tertiary carbocation formed and its possible resonance forms are shown in scheme 3. And attack of an alcohol or any other type of nucleophile would give a β glycoside, because **45c** and **45d** are the two resonance forms that contribute the most to the resonance hybrid, and are thus the most stable ones, so the nucleophile is more likely to attack at the anomeric carbon of our cycloadduct.



Scheme 3.

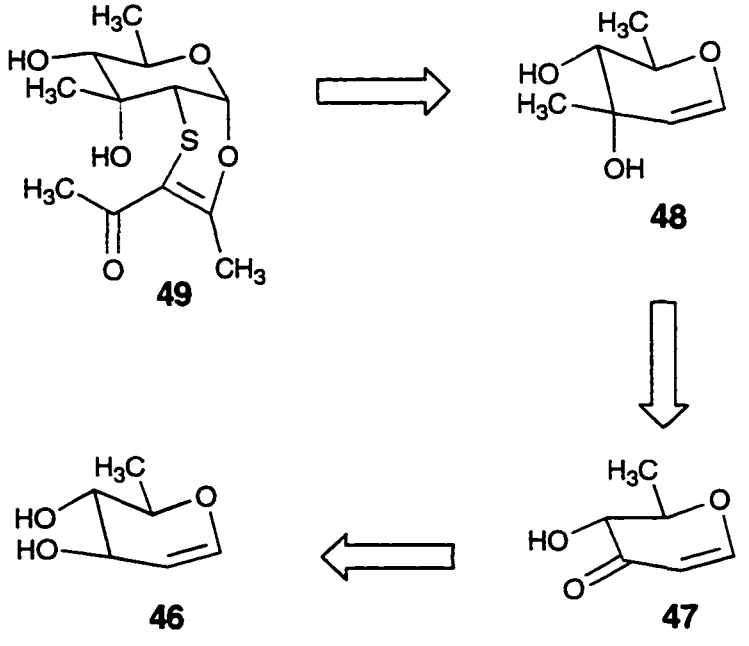
The synthetic scheme followed was really the second one, even though synthesis of the precursor of **Y** in scheme 1 had already been obtained by the time we decided to follow scheme 2. The synthesis of the precursor **Y** will be described, as well as the synthesis of the adducts shown in scheme 2, and the attempts at joining together those adducts. We were not successful in those attempts, and although good strides were made towards solving the problems inherent to obtaining these glycosides, eventually trying to use different glycosidation methods, which would involve following different synthetic schemes, we had to conclude this investigation before a breakthrough was achieved. The main problem faced by all systems was the extremely labile nature of the glucal present in scheme 2, and the low nucleophilicity of the adducts as acceptors.

Results and Discussion

Each of the cycloadducts synthesized to put together the trisaccharide chain in the aureolic acid, required its own independent synthesis and each one presented a different challenge. They will therefore be dealt with in separate sections, with the last one dedicated to the glycosidation reactions run to connect all three precursors of our trisaccharide

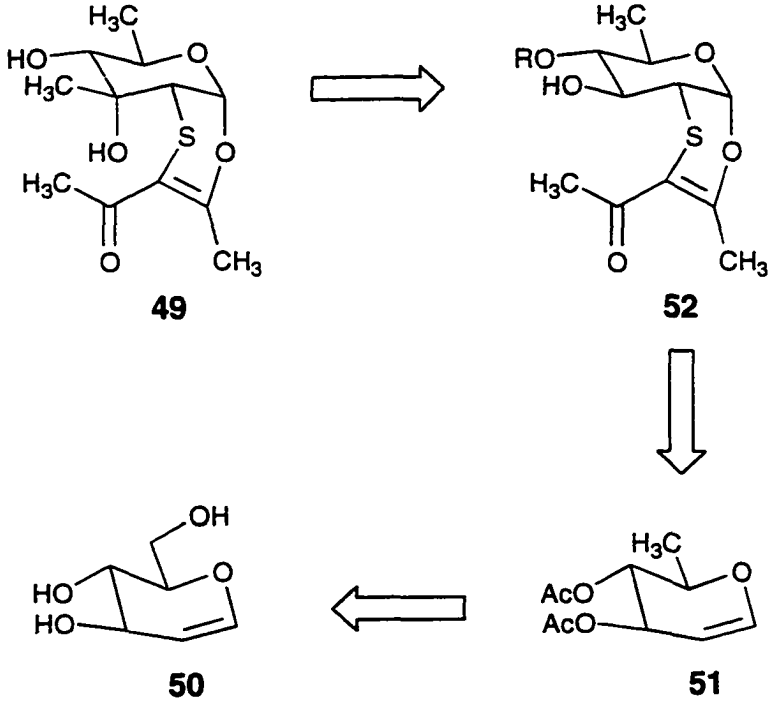
A. Synthesis of a Cycloadduct Precursor of Ring E

We first considered the route shown in scheme 4 in order to synthesize ring E, but this strategy has three serious problems, which is why it was not chosen.



Scheme 4.

The first problem is that two diastereomers resulting from the attack of methyl lithium on **47** are always obtained: **48** and the corresponding one with an equatorial hydroxy. Diastereomer **48** is the major one according to the literature[6]. The second problem is that **48** and the corresponding diastereomer are not stable and form a furan derivative when contacted by silica gel, and the third is that the presence of the axial hydroxy group probably changes the diastereomeric control in the cycloaddition reaction so that the top face adduct forms as the major product in the cycloaddition instead of **49**. Because of these problems, it was decided that the another retrosynthetic route shown in scheme 5 was more desirable than the previous one and it was followed instead.



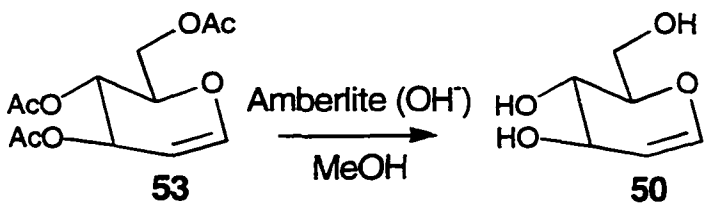
49 **52** **50** **51**

Scheme 5.

In principle, cycloadduct **49** would be obtained through the synthesis of 3,4,-Di-O-acetyl-1, 5-anhydro-2, 6-dideoxy-D-arabino-hex-1-enitol (D-rhamnal diacetate) followed by its cycloaddition and further modifications to introduce the equatorial methyl group at C-3. Even though we finally settled in the retrosynthetic route shown in scheme 5, the equatorial methyl group at C-3 posed the question of whether to introduce this group before the cycloaddition to the glucal as is shown in the literature[6], or after the cycloaddition to the glucal.

The synthesis from tri-hydroxy glucal to D-rhamnal diacetate was obtained from a reference by Fraser-Reid[7]. Two routes are possible to obtain the final product, and both were attempted.

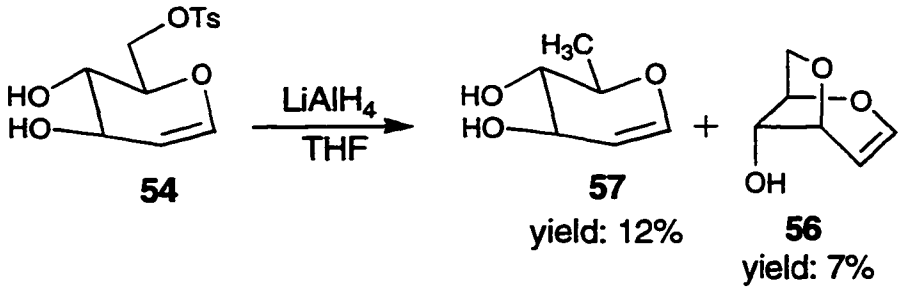
We used triacetyl glucal as our starting material. It was bought from Aldrich and deprotected quantitatively using an ion exchange resin, Amberlite IRA-400 (OH), in dry methanol.



53 **50**

The glucal **50** was then dissolved in pyridine, and freshly recrystallized p-toluensulfonyl chloride and DMAP were added at 0°C. The reaction mixture was stirred overnight and then worked to yield 60% of **54**. The tosylate **54**

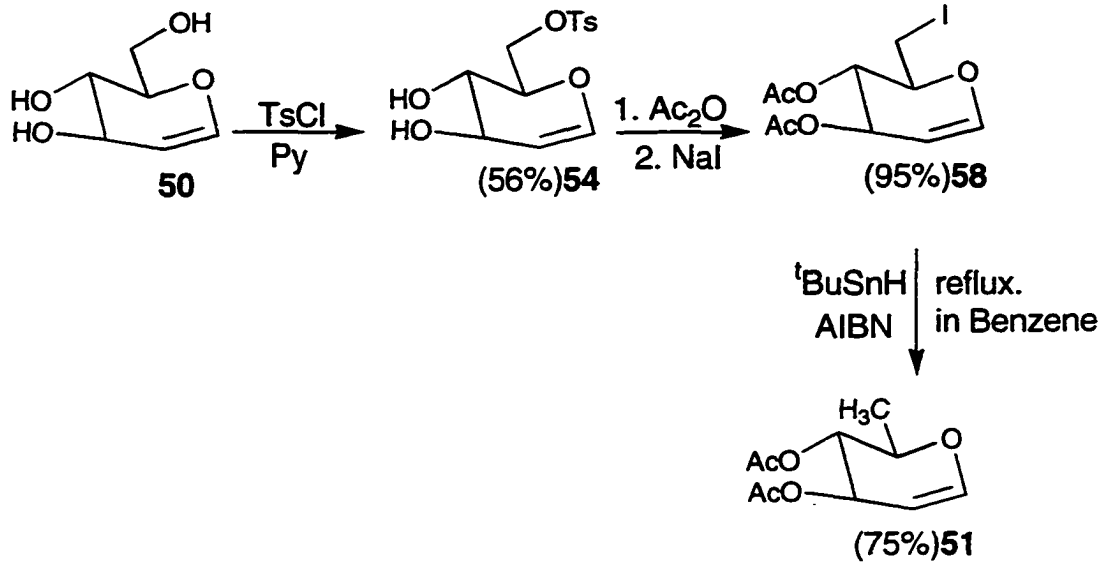
was made to reflux[8] in THF with $LiALH_4$ for eight hours to give only 12% yield of **51** and 7% of **56**. The yield for **51** as reported by Fraser-Reid was 40%, the same as for **56**.



54 **57** yield: 12% **56** yield: 7%

Scheme 6.

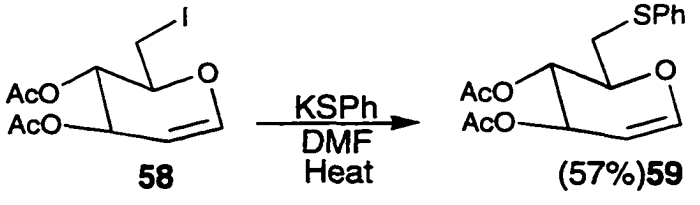
The alternative route to **57** is shown in scheme 7 and consists of a nucleophilic substitution of the tosyl group in C-6 by iodine after a quantitative acetylation of the two hydroxy groups in **54** using acetic anhydride, pyridine and DMAP as catalyst. The iodination was done by refluxing sodium iodide with tetrabutyl amonium iodide in 4 methyl-2-pentanone at 100°C overnight followed by reduction of **58** by a radical reduction with tributyl tin hydride in refluxing benzene for 3hrs. and 30 min. The reduction was difficult, because the freshness of the AIBN used, dryness of the components and dilution of the mixture greatly influenced the final yield. Also, a large excess of the tin reagent is necessary to achieve acceptable yields.



Scheme 7.

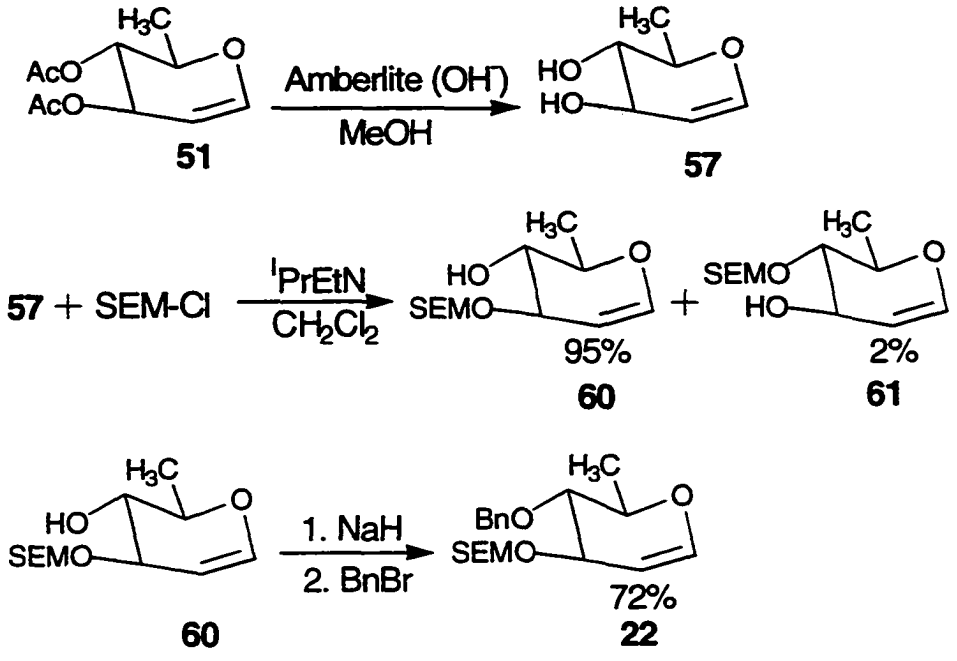
Because of the complications with the tin hydride reduction we tried to use tris (trimethylsilyl) silane[9] as a reducing agent on **58**. However, no reduced product was obtained using TTMSS.

We also experimented with obtaining compound **59** because of reports of the lack of stability in 6-Deoxy-glycals. Subsequently it was noted that **51** was stable enough for our purposes, and subsequently abandoned the syntheses of compound **59**.



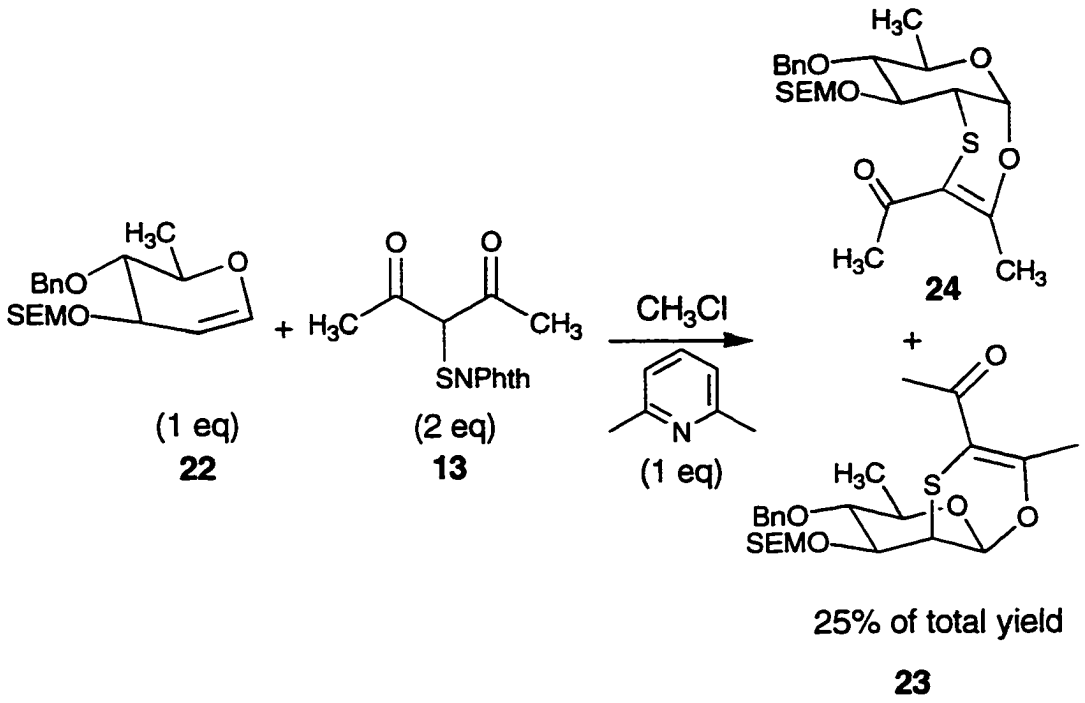
Scheme 8.

The cycloaddition of a glycal protected with electron withdrawing groups like acetates such as **51** and 3-phthalimidethio-2,4-pentenedione is not possible due to the large HOMO-LUMO gap between diene and dienophile. The cycloaddition of **54** is also not possible because of the electron withdrawing effect of the tosyl group. When the cycloaddition of **54** under standard contitions was tried, only starting material was recovered. It was also shown that attempting the cycloaddition of **57** with the precursor 3-phthalimidethio-2,4-pentenedione resulted only in decomposition of the D-rhamnal sugar, the reaction conditions being too drastic for this labile molecule. Because of this sensitivity, we decided to deprotect the hydroxy groups at carbons 3 and 4 of **51**, and then protect them again with two different protecting groups that allowed for the cycloaddition to take place, and that at the same time made selective deprotection of a particular hydroxy group possible at a later stage of the synthesis. This series of reactions are shown in scheme 9. The fact that **60** is the major diastereomer in the silylation reaction could not be verified easily with spectroscopic data, so it was proven by oxidizing the minor component of the mixture with MnO_2. Since this oxidizing agent is specific to allylic alcohols, It is clear that **61** is in fact the minor component in the diastereomeric mixture resulting from the silylation reaction.



Scheme 9.

After compound **22** was synthesized, the cycloaddition in scheme 10 was carried out. The reaction yield was 75%. The ratio of top/bottom cycloadduct was 1/2. Therefore cycloaddition of **22** produced a significant amount of top face diastereomer unlike the tribenzyl glucal, cycloaddition previously seen. This might be because of the lower steric interaction of C-6 compared to tribenzyl glucal. It might also be due to stereoelectronic effects of the different substituents in the sugar on the hetero Diels-Alder reaction, as has been shown in the literature[10]. Related data from our group[11] about the cycloaddition of 3-hydroxy 4, 6 dibenzyl glucal produced a significant amount of top face cycloadduct, which gives more support to the stereoelectronic effect theory.



Scheme 10.

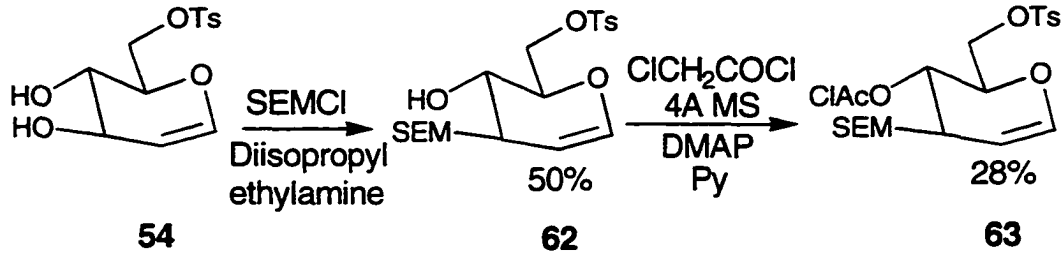
We have thus succeeded in synthesizing a cycloadduct **24** which is stable and only two steps away from the precursor **49** that we need in our synthesis. It was now time to tackle the synthesis of the precursors of the other units in the trisaccharide chain.

B. Synthesis of a Glucal Precursor of Ring C

We synthesized the protected tosyl glucal by using a silyl group[12] as protecting group at C-3 and chloroacetyl group at C-4. The chloroacetyl group, because of its electron withdrawing nature, was intended to ensure the integrity of the double bond in the glucal during the glycosyl transfer step, much like the tosyl group at C-6. However, we had difficulties both in the protection and deprotection steps.

We first tried to protect C-3 with a SEM group using N, N-diisopropyl ethylamine as base in methylene chloride overnight. Even though in previous cases the silylation reaction went in quantitative yield, in this case only 43% yield was obtained, due to the deactivating nature of the tosyl group, which lowers the nucleophilicity of the allylic alcohol. This deactivation factor of the tosyl group was operative at every point in the synthesis of compounds in this series. Next, the secondary alcohol was protected using chloroacetyl chloride (2eq) with pyridine in methylene chloride as solvent. The reaction was run at low temperature, the mixture was cooled to -60°C before adding the chloroacetyl chloride, and the reaction was left to stir at low temperature for about 9 hrs. 4-dimethylaminopyridine (DMAP) was added in small amount (1/3 eq) to catalyze the reaction. The final yield was quite low, as shown in scheme 11, probably due to the deactivation effect of the tosyl group. Also, since the rate of reaction was slow for the acetylation of the secondary hydroxy group, the tendency of the chloroacetyl chloride to easily

undergo hydrolysis, would make a lot less of the reactant available for protection of the hydroxy group. Activated molecular sieves were used in this reaction precisely to limit the amount of hydrolysis the acid chloride underwent due to presence of water.

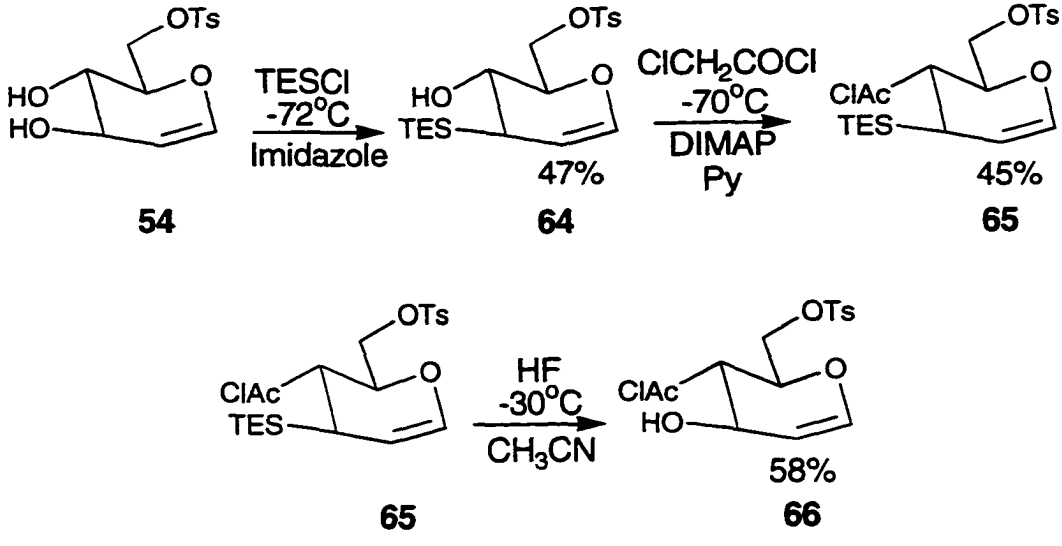


54 62 63

Scheme 11.

There were some difficulties in deprotecting the SEM group without also cleaving the labile chloroacetyl group at C-4. Therefore **63** was put aside as the precursor to the ring C that would be used as glycosidic acceptor. Instead, TES was used as protecting group, since it is easier to deprotect in a selective manner in the presence of chloroacetate without producing **54** as the final product. The yield of silylation was still low, but in this case the main side product was the one with two TES groups protecting both hydroxy groups in **54** even though the reaction was run at low temperature, as can be seen in scheme 12. The yield of the chloroacetylation of C-4 improved for this case after the temperature was lowered, the amount of chloroacetyl chloride increased to 3 eq., and we used 1eq of DMAP instead of a catalytic amount.

The amount of starting material recovered was 50% of the initial amount, which makes it possible to increase the yield of this reaction just by recycling the starting material left over from each acetylating reaction.

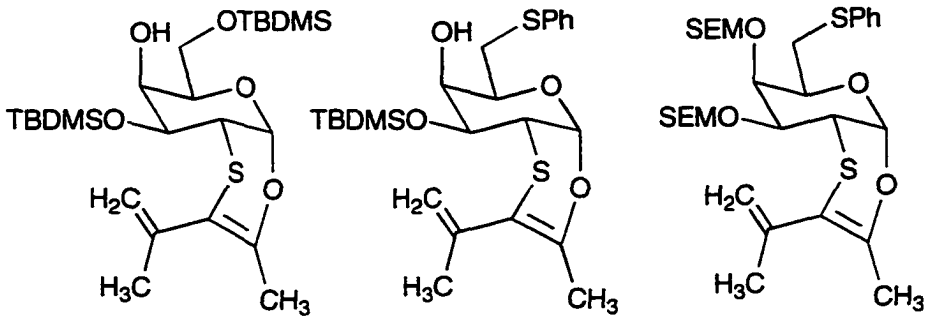


Scheme 12.

When the desilylation of **65** with hydrofluoric acid to give **66** takes place, it is especially important to keep the temperature low and quench the reaction inmediately after 26 minutes or the ClAc group is taken off as well. Intact **65** is recovered in 20% yield, so recycling is also possible for this reaction. Compound **66** is unstable, and has a lifetime of about two months in the freezer and three weeks in the refrigerator.

C. Synthesis of a Cycloadduct Precursor of Ring D.

Three different derivatives of galactose, **67**, **68**, and **69** were synthesized as potential precursors to ring D. Glycosidation experiments were later run with all three. A major effort went into developing the techniques for the synthesis of these materials, most of which involves the nuisances of protecting and deprotecting chemistry of silyl compounds[12].



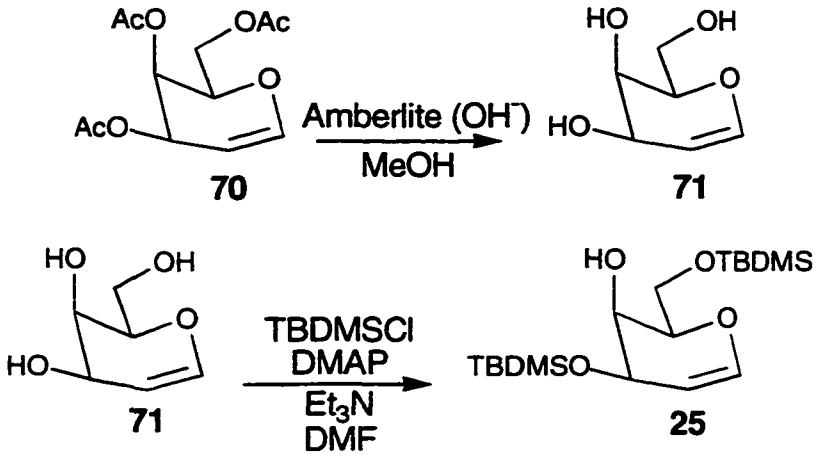
67 **68** **69**

Scheme 13.

The precursor to the conjuated dienes[13] **67-69** is ketone **26** whose synthesis begins with galactal.

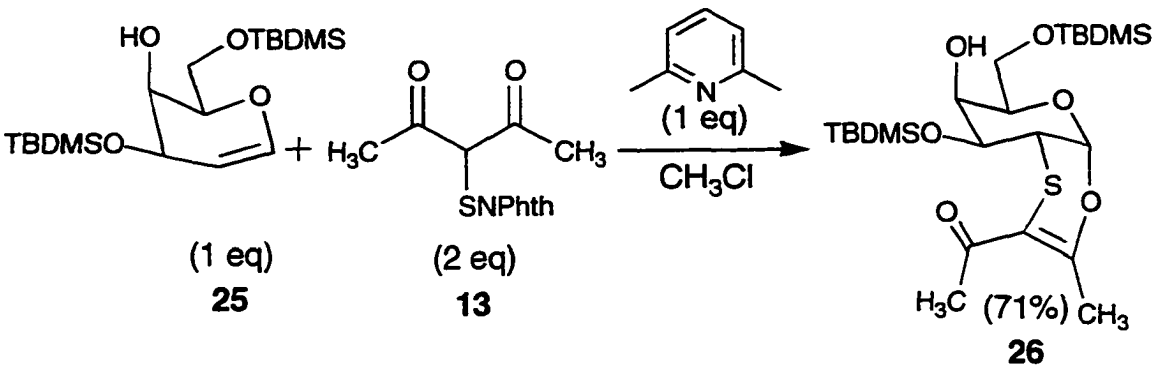
The first step in obtaining **26** is the preparation of tri-acetyl-galactal following a literature procedure[14]. After deacetylation of the galactal, silylation of two of the three hydroxy groups present in the molecule using t-butyldimethylsilyl chloride as reagent. A quantitative yield for the disilylation of two of the hydroxy groups was obtained, even though an excess of silylating reagent was used with the intent of total silylation of the

molecule. Even though longer reaction times and larger amounts of reactants were tried, it turns out that steric interactions of the axial OH in the galactal prevent its reaction with a group as large as the TBDMS.



Scheme 14.

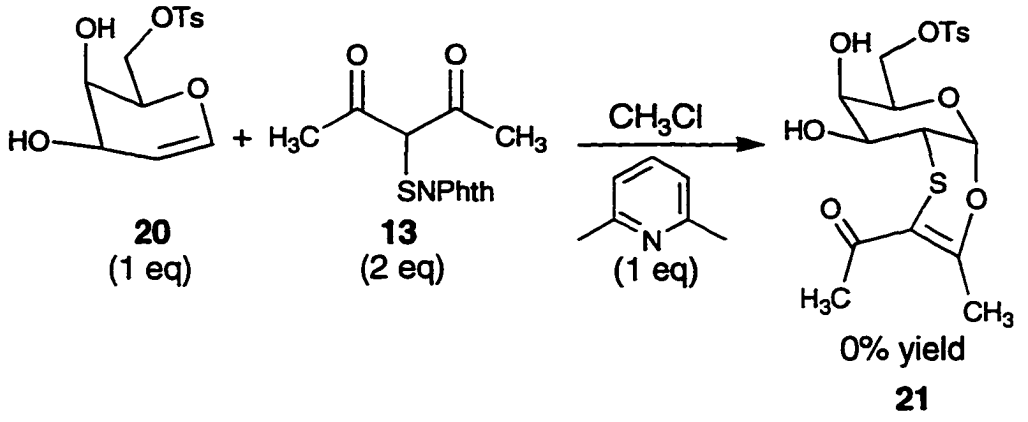
The cycloaddition of **25** was done following the usual procedure and gave a yield only slightly lower than the tribenzylated adduct we used as model to develop the reaction. However, the reaction was much faster, since it goes to completion overnight instead of in three days. It is also interesting that no top face diastereomer was detected. We believe this is due to steric factors. Even in other cases no top face adduct has ever been identified in a cycloaddition reaction with a galactal sugar, due to the steric effect of the axial hydroxy group that controls the diastereoselectivity in this instance. Adduct **67** was then obtained from **26** using Wittig chemistry.



Scheme 15.

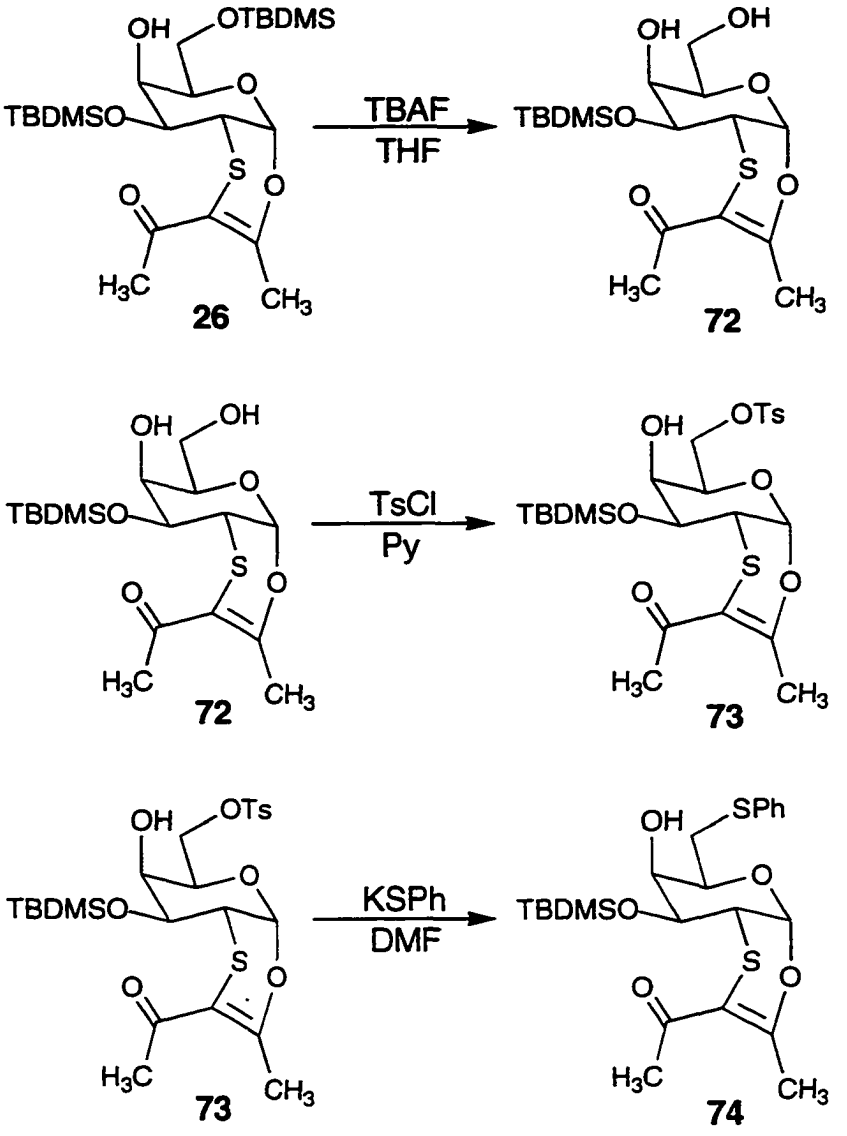
The other donors **68** and **69** were both synthesized from adduct **26**. The main reason was that cycloadduct **26** was less sensitive than galactal to the protection/deprotection manipulations required to produce introduce the 6-thiophenol. Also, the cycloaddition in scheme 16 failed because of the deactivating nature of the tosyl group. Decomposition of the carbohydrate took place before any cycloaddition. The main product was **20** which was recovered from the reaction mixture in large amounts.

This is a case where the stereoelectronic effects prevent the reaction from happening due to the deactivation of the double bond by the tosyl group which probably increases the HOMO-LUMO gap to a value just too high for the reaction to occur, just as it happens with the acetyl groups in triacetyl glucal.



Scheme 16.

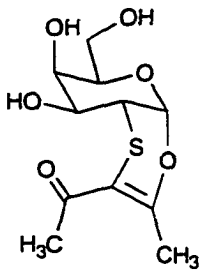
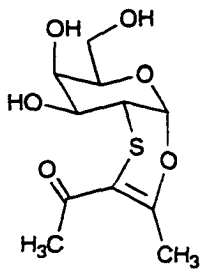
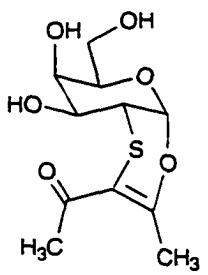
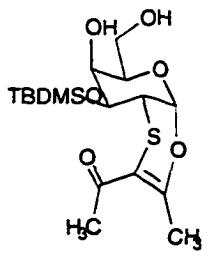
The main problem in the synthesis of **68** is to obtain selective deprotection of the silyl groups in the primary hydroxy group versus the secondary one. Attempts to synthesize **74** from **26** by deprotecting the silyl group at C-6 and then obtaining a thiophenol adduct directly through a Mitsunobu[15] reaction failed. This failure required the formation of the tosyl adduct **73** by standard tosylation of the primary hydroxy formed by selective deprotection of **26**. Elimination of the tosyl leaving group using potassium thiophenoxide as nucleophile made the synthesis of the thiophenol **74** possible.



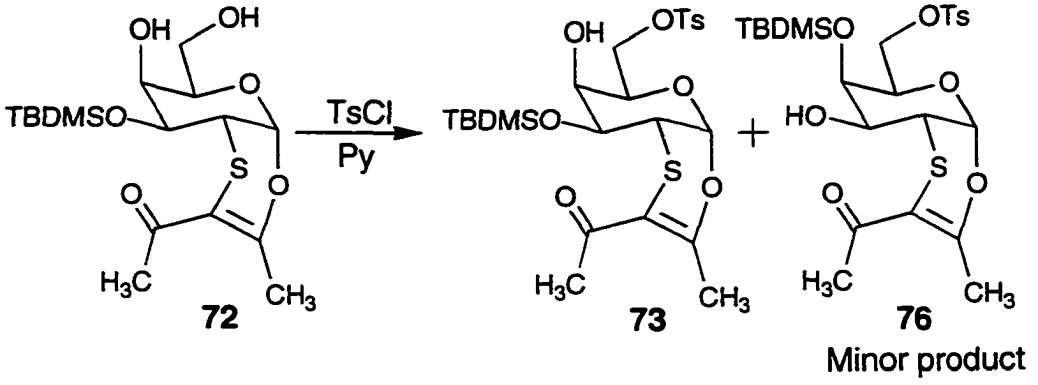
Scheme 17.

The selective deprotection of **26** to give a monosilylated adduct was not a straightforward issue. Many reactions were tried using different reagents and reaction conditions in order to avoid total deprotection of the adduct. Finally, conditions and reagents were refined to give the reaction in the last entry of the table 1.

Table 1.

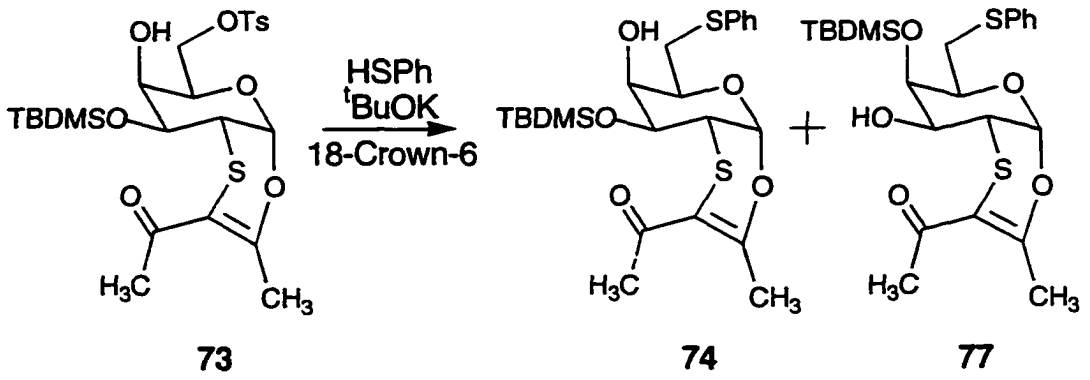
REAGENT	SOLVENT	TIME	PRODUCT	YIELD
KF, 18-Crown Ether-6	CH_3CN Room Temp.	Overnight	 **75**	27%
KF 18-Crown Ether-6	CH_3CN Refluxing	1 hr. 40 min.	 **75**	41.2%
CsF 18-Crown Ether-6	THF Refluxing	3hr.	 **75**	47%
TBAF	THF -21°C	8 min.	 **72**	62%

Tosylation of **72** to give **73** was done using the same conditions as in the case of the glycals, and the yield was the same, 60% not counting the minor side product **76** due to migration of the silyl group[16] in basic medium.



Scheme 18.

The formation of the thiophenol adduct[17] adduct also involved a series of trial reactions where reaction conditions were fine tuned to maximize the yield. The first set of reactions were developed using **73**, 1.5-2 eq. of thiophenol, 0.2 eq. of potassium t-butoxide in 1M solution in THF and 1.5-2 eq. of 18-crown-6 and changing the solvents, the reaction temperatures and the time of reaction. We finally settled on DMF as the best solvent, and at least twelve hours at room temperature as best reaction time and temperature, but still the results did not improve until we began changing the amount of base and thiophenol used in the reaction to find the optimum quantities of both reagents.



73 74 77

Scheme 19.

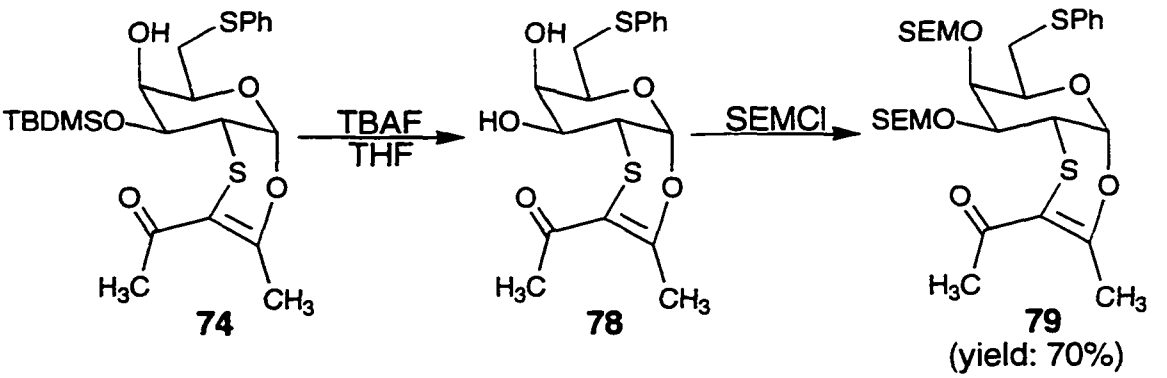
We finally found that the best conditions for the reaction in scheme 19 were an initial 2 eq. of thiophenol, and 0.4 eq. of base followed after 12-14 hrs. by 9-10 eq. of thiophenol and another 24 hrs of stirring under nitrogen before workup. All of the conditions tried in this reaction are shown in table 2.

Table 2.

REAGENTS	SOLVENT	TIME	YIELD
1.5eq HSPh, 0.2eq ^{t}BuOK 18-Crown Ether-6	DMF Refluxing	1hr., 40 min.	18%
1.5eq HSPh, 0.2eq ^{t}BuOK 18-Crown Ether-6	DMF Room Temp.	7hrs.	19%
1.5eq HSPh, 0.2eq ^{t}BuOK 18-Crown Ether-6	MeOH Refluxing	5hrs., 30 min.	19.4%
1.5eq HSPh, 0.2eq ^{t}BuOK 18-Crown Ether-6	DMSO Room Temp.	5hrs., 30 min.	11%
1.5eq HSPh, 0.2eq ^{t}BuOK 18-Crown Ether-6	DMF Room Temp, Refluxing	12 hrs., 1hr. (Ref.*)	33%
1.5eq HSPh, 0.2eq ^{t}BuOK 18-Crown Ether-6	DMF-THF Refluxing	1 hr.	-----
1.5eq HSPh, 0.2eq ^{t}BuOK 18-Crown Ether-6	EtOH Refluxing	6 hrs.	17%
1.5eq HSPh, 0.2eq ^{t}BuOK 18-Crown Ether-6	Benzene Refluxing	6 hrs.	18%
2eq HSPh, 0.4eq ^{t}BuOK 18-Crown Ether-6	DMF Room Temp.	48 hrs.	44%
5.3eq HSPh, 0.3eq ^{t}BuOK 18-Crown Ether-6	DMF Room Temp.	12 hrs.	30%
11eq HSPh, 0.4eq ^{t}BuOK 18-Crown Ether-6	DMF Room Temp.	48 hrs.	59%

*** Refluxing for 1hr. after stirring overnight at room temperature**

The major inconvenience in this reaction is that migration of the silyl groups is more prevalent than in the tosylation reaction and so the product is a mixture. In the context of our synthetic effort, it does not make a difference which diastereomer we use, but the fact that there is a mixture promotes further problems in the area of isolation and purification. Also, there is the issue that during the glycosidation reaction migration might occur, further complicating an already complex NMR with an undesirable mixture. This is what ultimately prompted us to synthesize **79**, where both hydroxy groups are protected and so there is no possibility of migration. This synthesis involves two reactions, one in which we deprotect the hydroxy group at C-3 and a second one in which we protect both hydroxy groups in the molecule using SEMCl. Compound **78** was never purified, the silylation reaction was run directly on a crude.



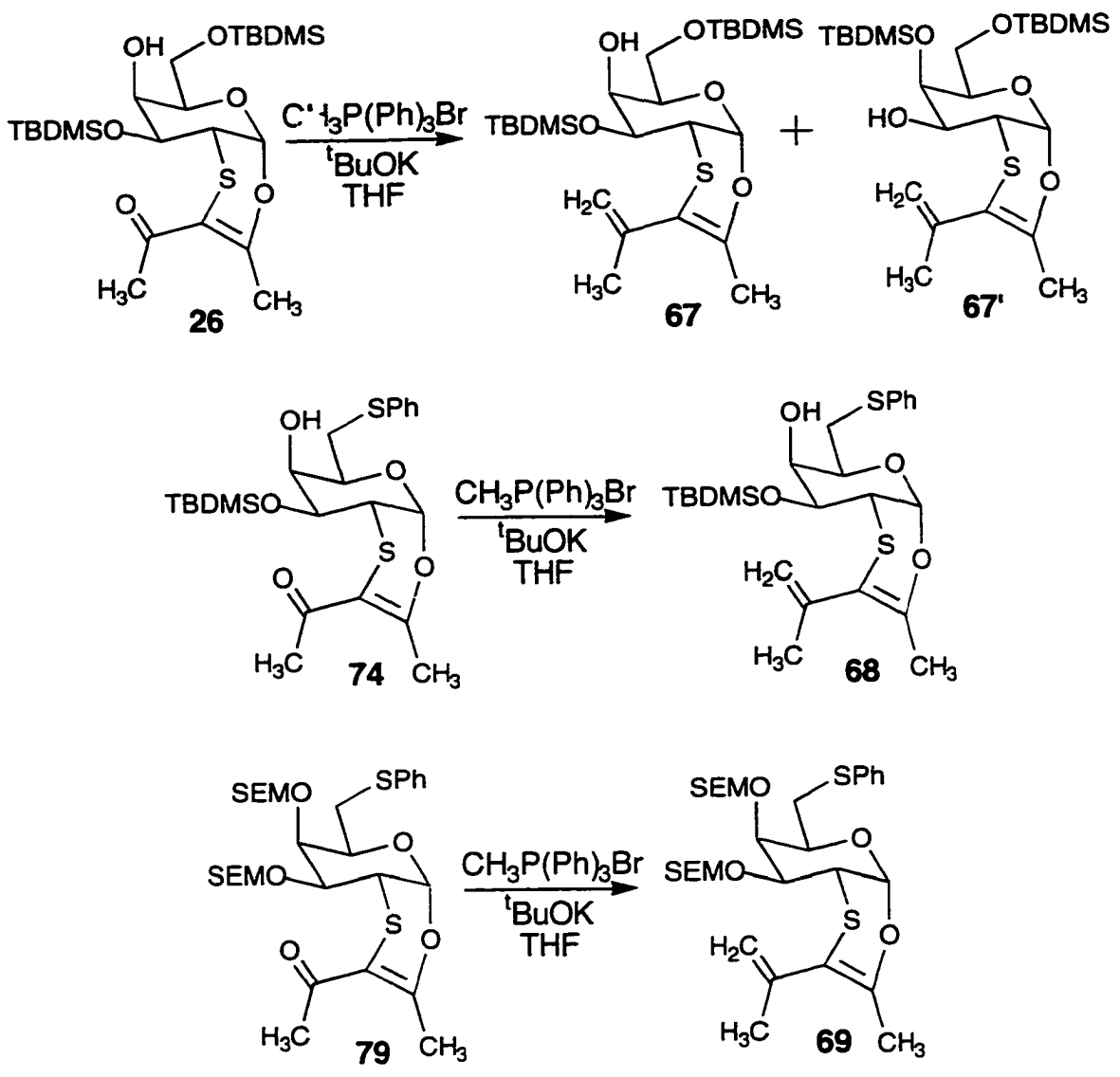
Scheme 20.

This reaction could also be run with the diastereomer **77** to give the same final product **79**.

Once the conjugated ketones **26**, **74**, and **79** were obtained, we needed to find a way to transform them into their conjugated diene counterparts. Wittig chemistry was used in all cases to obtain the methylene in the adducts, the only difference with standard reaction is the use of crown ether to improve the yield of the reaction and allow us to use "salt free" conditions, this is not having to use lithium bases like n-butyl lithium. Instead, we used ^{t}BuOK in 1M solution of THF. An additional advantage of this reaction is the ease of workup, where the triphenylphosphine oxide residue is eliminated by filtering through a pad of silica gel. However, further research indicated the presence of the crown ether was not necessary and so it was eliminated from the prep.

As it can be seen in scheme 21, the continuing problem with silyl migration is still present in this case. The yield of the reaction is 64%.

The same reaction on **74** did not give a good yield (15%), and the reaction on **79** went on to give a 60% yield.

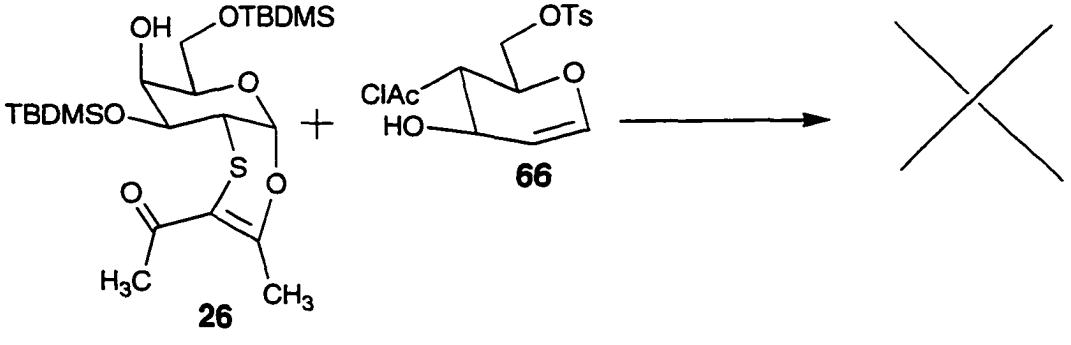


Scheme 21.

D. Glycosidation Reactions

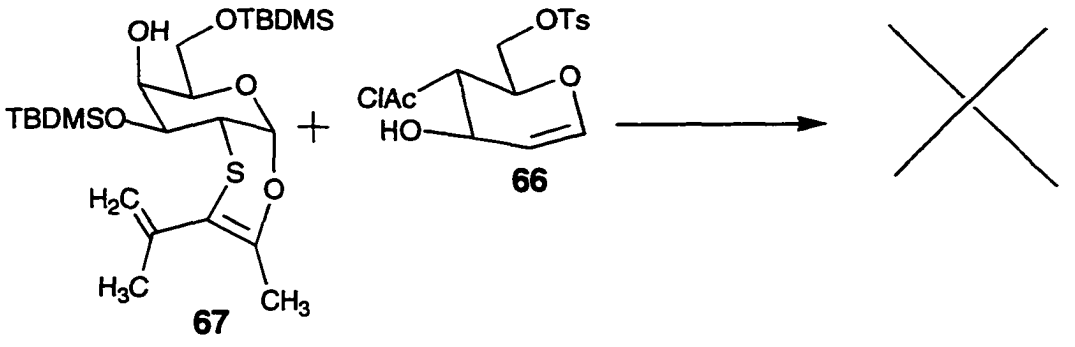
There are several possible[18] catalysts and conditions that can be used to promote glycosidation under acidic conditions, some of them already explored in this system[5]. Molecular sieves were used in all glycosidation attempts, and all reactions were monitored by TLC and left to continue until no starting material was left. The amount of catalyst used was generally one equivalent. A glycosidation attempt was made with ketone adduct **26** as a blank for the study. The results of this trial are shown in table 3. The first attempts of glycosidation using a conjugated diene were on the totally silylated adduct **67** and are shown in table 4.

Table 3.



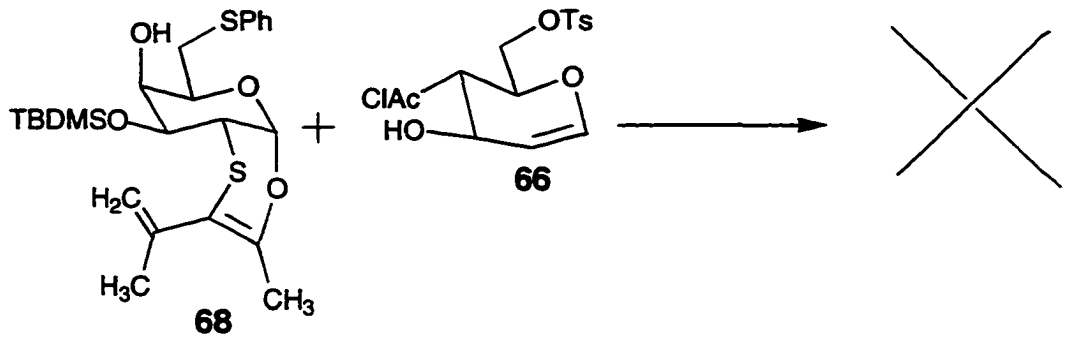
DONOR	ACCEPTOR	SOLVENT	TEMP.	CATALYST
26 (1eq)	**66** (2eq)	CH_2Cl_2	Room Temp.	$(Ph)_3PBrH$
26 (1eq)	**66** (2eq)	CH_2Cl_2	Room Temp.	Triflic ac.

Table 4.



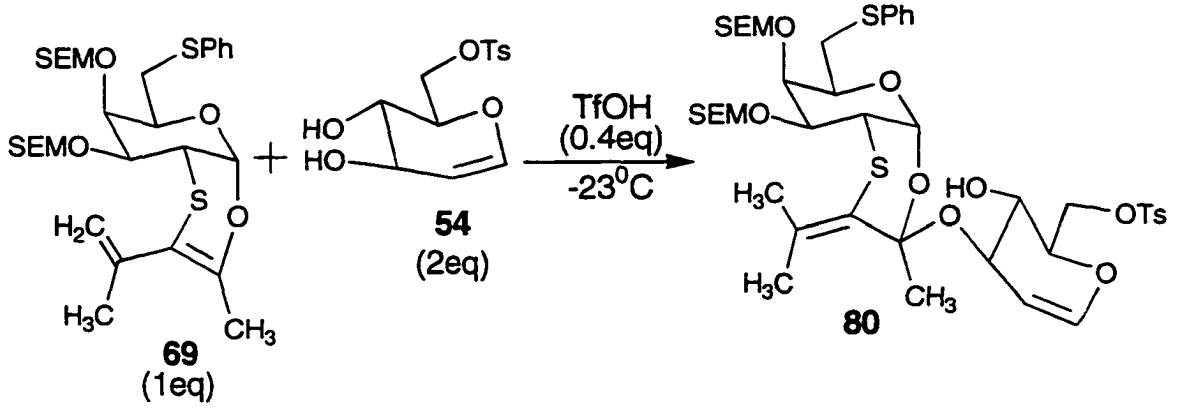
DONOR	ACCEPTOR	SOLVENT	TEMP.	CATALYST
67 (1eq)	**66** (2eq)	CH_2Cl_2	-20°C	Triflic ac.
67 (1eq)	**66** (2eq)	CH_2Cl_2	-18°C	Triflic ac.
67 (1eq)	**66** (2eq)	CH_2Cl_2	-78°C	Triflic ac.

As previously said, the glycosidation reaction using **68** as donor was only tried once because the complications observed with the mixtures due to silyl group migration convinced us to try another set of protecting groups. The reaction was run in CH_2Cl_2 using $(Ph)_3PBrH$ (triphenyl phosphine hydrobromide) as catalyst at room temperature. The logic behind the use of this particular catalyst is the fact that it is a very soft catalyst which would prevent in theory decomposition of our starting materials. This however, was not the case.



Scheme 22.

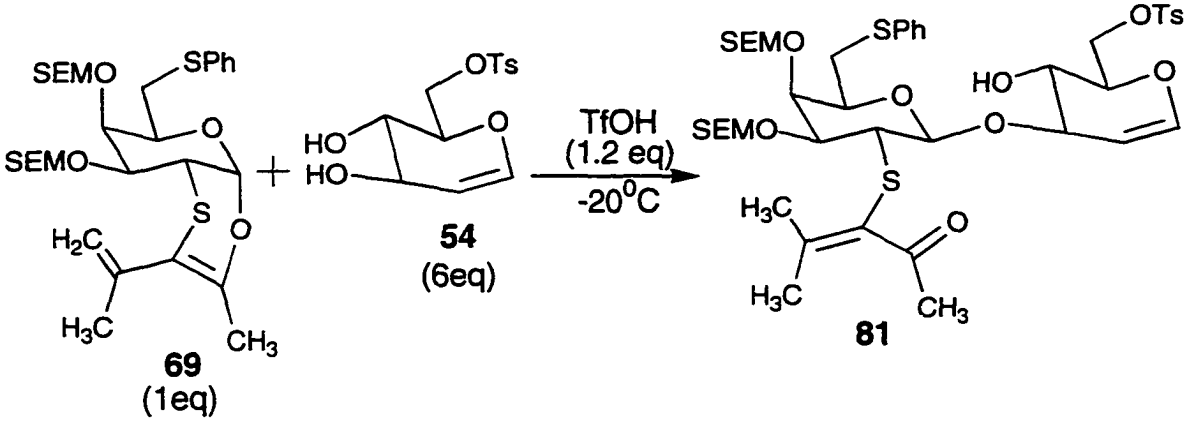
We first began seeing some results when using adduct **69** we did the reaction shown in scheme 23 using CH_2Cl_2 as solvent.



Scheme 23.

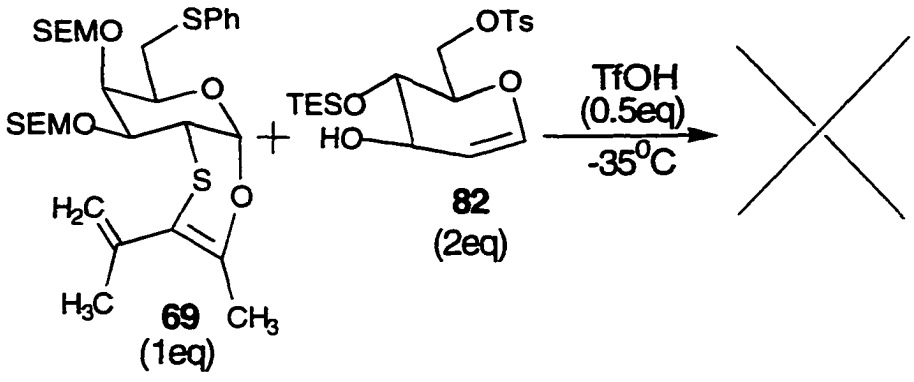
When we tried to force **80** to rearrange to the β-glycoside by reacting it again with more of **54** and using the same acid as catalyst, it did not rearrange. Rather, it gave decomposition of **54**, and unwanted side reactions.

When the reaction was repeated though using 1.2 eq. of TfOH at -20°C and 6 eq of **54** as shown in scheme 24, we finally obtained our glycoside, although it took extensive purification using prep plates to separate our compound from the large amount of decomposition material from **54**. When the same reaction was repeated using 1eq of Benzenesulfonic acid as catalyst and only 2.6 eq. of **54** a similar result was obtained.



Scheme 24.

Finally, the reaction in scheme 25 was done in hopes that **82** would be less labile. Unfortunately, only side products and decomposition material was obtained. The synthesis of **82** is trivial, and involves protection of both hydroxyl groups using TESCl and then selective deprotection of the allylic hydroxy group using HF in acetonitrile at low temperature (-25°C).



Scheme 25.

As it has been shown, only one set of conditions was successful in the glycosidation scheme, and even in this one case the yield was extremely disappointing. The apparent reason for this lack of success in our systems is both the fact that our glucal acceptor is not nucleophilic enough to react with our diene before secondary reactions take place, and the extreme labile nature of the glucal derivatives we used. Even when the protecting groups in the glucal were changed to TES at C-4, a sturdier protecting group, decomposition set in before nucleophilic attack on the diene adduct. The case where no protecting group was used in the acceptor has difficulties because the dihydroxy glucal decomposes in the presence of acid to a green goo even at relative low temperatures in slightly acidic conditions. Part of the overall problem is the fact that the galactal diene is less reactive than the glucal one that was used to develop the system, which combines with the factors already mentioned to work against us.

Conclusion

The bicyclic system **69** (and similar bicyclics) have been shown in our group to be useful glycosyl donors to alcohol acceptors that are not acid sensitive. In this chapter we have shown that this approach is limited when the acceptor is itself acid sensitive. What is required is a non-acidic catalyst to promote the ring-opening of bicyclics such as **69**. This search for a new type of catalyst will be a future project for our group.

EXPERIMENTAL

General Experimental: NMR spectra were recorded on GE QE 300, JEOL FX 400 instruments with $CDCl_3$ as solvent. Elemental analyses were performed by Robertson Microlit Laboratories Inc, Madison, NJ. Melting points were determined on a Fisher- Johns melting point apparatus. Optical rotations were determined using a Rudolph Research Autopol III automatic polarimeter. Thin-layer chromatograms were done on pre coated TLC sheets of silica gel 60 F_{254} (E. Merck), and short-long wave ultraviolet light was used to visualize the spots. Chromatotron plates (radial chromatography) were prepared by using Kieselgel 60 PF_{254} gipshaltig (E. Merck). Flash chromatography was performed with silica gel (230-400 mesh). The molecular sieves were bought from Aldrich Chemical Co. and activated by heating them in an oven at about 100°C for 24 hrs. Another method used was heating them up with a bunsen burner under high vaccum. Dry THF was obtained by refluxing over sodium metal with benzenophenone as indicator, and dry methylene chloride was obtained by refluxing over P_2O_5. All other solvents were distilled or bought dry from Aldrich Chemical Co.

General Deacetylation Method.

The acetyl glycal is dissolved in dry methanol and stirred under N_2 atmosphere with Amberlite IRA-400 (OH) ion exchange resin from Aldrich in amount at least 1.2 times the weight of the acetyl glycal used. The time of reaction varies from 1 hour to four depending on the nature of the glycal and is followed by

TLC. The only workup necessary is the filtration of the resin while washing the material with small amounts of methanol, and evaporation of the anhydrous methanol. Pure compound is obtained without the need for further purification.

General Tosylation Method.

The sugar compound with a hydroxy group to be tosylated is dissolved in Pyridine and cooled down to 0°C. Next, 1-2 eq. of DMPA and 2 eq. of p-toluensulfonyl chloride freshly recrystallized are added and the reaction is left to warm up to room temperature. After 7-12 hours of stirring under N_2, a small amount of de-ionized water is added followed after five to ten minutes of stirring by more water roughly about the same volume as the pyridine used in the reaction. A mixture of CH_2Cl_2/EtOAc is added and the mixture is transferred to a separatory funnel were the organic phase is separated and then washed twice with a $NaCO_3H$(aq) saturated solution, twice with a NH_4Cl(aq) saturated solution and at least once with brine. Drying over $MgSO_4$ and evaporation of the crude followed by chromatographic purification leads to the desired tosylated carbohydrate.

General Wittig Reaction.

In the reaction vessel, 3 eq. of dry (methyl)-triphenylphosphonium bromide are dissolved in a small aliquot of THF, followed by 3 eq. of the base potassium tert-butoxide, to form the phosphonium ion. After the solution turns bright yellow indicating the formation of the ion, the ketone adduct is syringed in dissolved in THF and the reaction is allowed to stir until no starting material

is left according to TLC. After rotary-evaporation of the solvent in the reaction mixture, the crude is dissolved in a mixture of EtOAC-P.E. and filtrated through silica gel. The resulting crude is then purified by flash chromatography.

Preparation of 1-O, 2-S-(2-Acetyl-1-methyl-1,2-ethenediyl)-3,4,6-tris-O-(phenyl- methyl)-2-thio-α-D-glucopyranoside (11).

3-Phthalimidosulfenyl-2,4-pentanedione (1.32 g, 4.80 mmol) was dissolved in 10 mL of dry $CHCl_3$ under N_2 atmosphere with powdered 3 A molecular sieves (activated, 0.5 g). To the solution was added tri-O-benzyl-D-glucal (1.01 g, 2.4 mmol) followed by dry 2,6-lutidine (0.28 mL, 2.4 mmol) by syringe. The reaction mixture turned brown immediately, and over a 4 d period, it acquired a deep red color. At this time, the reaction had proceeded completely as monitored by ^1H NMR analysis. The mixture was quenched with a saturated solution of $NH_4Cl_{(aq)}$. The aqueous fraction was then washed three times with CH_2Cl_2. The organic fractions were combined and dried with anhydrous Na_2SO_4 and concentrated. The resulting crude was subjected to flash chromatography on silica gel (EtOAc: P.E., 1:4) to give starting material (0.156 g, 15%) and compound **11** (1.10 g, 83%), mp 114-116 °C.

^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 6H), 3.23 (dd, J=3.1 and 10.5 Hz, 1H), 3.59-3.97 (m, 5H), 4.51-4.92 (3 AB quartets, 6H), 5.62 (d, J=3 Hz, 1H), 7.10-7.40 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.6, 30.2, 41.8, 68.2, 73.1, 73.7, 75.3, 77.8, 78.4, 96.1, 102.0, 127.8-128.5 (15 C), 137.8-138.0 (3 C), 159.6, 195.3; IR (neat, cm^{-1}) 3029, 1676, 1562, 1132, 1043, 929, 737, 697.

Preparation of 1-O,2-S-(2-Acetyl-1-methyl-1,2-ethenediyl)-3,4,6-tris-O-(phenyl- methyl)-2-thio-β-D-mannopyranoside (19).

3-Phthalimidosulfenyl-2,4-pentanedione (2.02 g; 5.3 mmol; 2.0 eq) and tri-O-benzyl-D-glucal (1.11 g; 2.7 mmol; 1eq) were dissolved in 15 mL of dry DMSO under N_2 atmosphere with powdered 3A molecular sieves in a dry 50-mL flask. Dry 2,6 lutidine (0.32 mL; 2.7 mmol; 1eq) was added by syringe, and the reaction mixture turned golden-red immediately. After 7 days, the reaction mixture had turned black in color. The starting material was completely consumed with formation of α and β cycloadduct judging from the ^1H NMR analysis of a reaction aliquot. The mixture was poured into a separatory funnel and 70 mL of CH_2Cl_2 were added to it, followed by a saturated solution of $NH_4Cl_{(aq)}$. The organic fraction was separated out and then washed with water eight times to get rid of the DMSO, dried with Na_2SO_4 and concentrated. The resulting crude was put through a flash silica gel column (EtOAc: P. E., 1:4) which afforded a total yield including top and bottom cycloadduct of 1.126 g (59%). The fraction eluting first gave 0.377g (33% of total adduct obtained) was 1-O,2-S-(2-Acetyl-1-methyl-1,2-ethenediyl)-3,4,6-tris-O-(phenyl- methyl)-2-thio-β-D-mannopyranose, a white powder of mp=116-118^{0}C, and the fraction after that gave 0.749 g (67% of total amount of adduct) was 1-O,2-S-(2-Acetyl-1-methyl-1,2-ethenediyl)-3,4,6-tris-O-(phenyl- methyl)-2-thio-α-D-glucopyranose. The amount of starting material (tri-benzyl-D-glucal) recovered was 0.2786 g (25% of total yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.30 (s, 3H), 3.56 (m, J=9.3, 3, 1H), 3.65 (dd, J=1.3, 4.2, 1H), 3.68 (m, J=2.4, 1.8, 4.2, 2H), 3.89 (dd, J=4.5, 8.4, 1H), 3.96 (dd, J=9, 8.7, 1H), 4.40-4.90 (3 AB quartets, 6H), 5.10 (d, J=0.9, 1H), 7.10-7.40 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.4, 29.3, 41.2, 68.9, 71.0, 73.5, 73.7, 75.2, 80.2, 92.3, 105.6, 127.5-128.5 (15C), 137.2-138.2 (3C), 155.6, 195.5; IR (neat, cm^{-1}) 3030, 1679, 1573, 1453, 1356, 1261, 1094, 738, 699; EIMS [m/z (% relative intensity)] 564 (M^++NH_4, 6), 168 (18.6), 118 (100), 101 (33.2).

Preparation of 1-O,2-S-(2-(1-Hydroxy ethyl)-1-methyl-1,2-ethenediyl)-3,4,6-tris-O-(phenyl-methyl)-2-thio-α-D-glucopyranoside (28).

To a stirred solution of the cycloadduct **11** (0.313 g; 0.57 mmol; 1eq) in absolute ethanol (80 mL), $NaBH_4$ (0.108 g; 2.8 mmol; 5 eq) was added slowly, and the reaction was followed by TLC. After 1hr, the reaction mixture became a clear solution. The mixture was poured into a 125 mL separatory funnel and diluted with 60 mL of water. The product was extracted with three portions of CH_2Cl_2 (55 mL). The organic washings were combined, dried with $NaSO_4$, concentrated, and the crude was purified using a 2 mm chromatotron plate. [(1) EtOAc-P.E. (10:90) (2) EtOAc-P.E. (15:85) (3) EtOAc-P.E. (20:80)]. The separation afforded two major fractions, first a major diastereomer, (0.150 g, 48%) followed by a second diastereomer (0.073 g, 24%).

Major component in the mixture **28a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, J=4.5, 3H), 1.5 (d, 1H), 1.97 (s, 3H), 3.21 (dd, J=3, 10, 1H), 3.67-4.01 (m, 5H), 4.40-5.10 (m, 8H), 5.52 (d, J=3, 1H), 7.10-7.50 (m, 15H); ^{13}C NMR (300 MHz,

$CDCl_3$) δ 18.3, 22.5, 43.0, 67.0, 69.5, 73.2, 74.5, 77.0, 79.0, 80.0, 96.0, 103.8, 128-130 (15C), 138.7, 139.2, 145.4; IR (neat, cm^{-1}) 3453 (broad), 3030, 1645, 1496, 1453, 1359, 1222, 738, 698.

Minor component in the mixture **28b**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, J=6.3, 3H), 1.63 (d, 1H), 1.90 (s, 3H), 3.20 (dd, J=3, 10, 1H), 3.60-4.10 (m, 6H), 4.40-5.00 (m, 8H), 5.52 (d, J=3, 1H), 7.10-7.50 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.6, 22.9, 42.1, 67.6,68.7, 73, 73.8, 75.5, 79.09, 79.3, 95.0, 103.6, 127.9-128 (15C), 138.4, 138.6; IR (neat, cm^{-1}) 3445 (broad), 3030, 1649, 1496, 1453, 1359, 1225, 738, 697.

Preparation of 1-O,2-S-(2-(1-Hydroxy ethyl)-1-methyl-1,2-ethenediyl)-3,4,6-tris-O-(phenyl-methyl)-2-thio-β-D-mannopyranoside (40).

To a stirred solution of **19** (0.312 g; 0.57 mmol; 1eq) in absolute ethanol, (35 mL) $NaBH_4$ (0.164 g; 4.3 mmol; 7.6 eq) was added and the reaction was followed by TLC. After 4 hrs, the reaction mixture became a clear solution. The mixture was quenched with water. The product was extracted with three portions of CH_2Cl_2. All of the organic washings were combined, dried with $NaSO_4$, concentrated, and the crude was purified using a 2 mm chromatotron plate (EtOAc:P.E., 25:75). The separation afforded two major fractions, first a minor diastereomer, (0.067g, 21%) followed by a second diastereomer (0.1817 g, 57%).

Minor diastereomer **40a**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J=6.3, 3H), 1.896 (s, 3H), 2.03 (s, 1H), 3.57-3.61 (m, 1H), 3.66 (dd, J=4.5, 0.9), 3.74 (d, J=3.3, 2H),

3.93 (dd, J=4.5, 8.7, 1H), 4.06 (dd, J=8.7, 9.2), 4.45-4.90 (3AB quartet, 6H), 5.07 (d, J=1.2, 1H), 7.10-7.60 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.8, 22.2, 40.9, 67.3, 69.0, 70.8, 73.5, 73.9, 75.3, 80.9, 92.1, 107.1, 127.6-128.6 (15C), 137.8, 138.4, 139.1; IR (neat, cm^{-1}) 3445, 3030, 1656, 1603, 1497, 1454, 1362, 1235, 1911, 873, 736, 698.

Major diastereomer **40b**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J=6.6, 3H), 1.99 (s, 3H), 3.55-3.60 (m, 1H), 3.65-3.90 (m, 5H), 3.94 (dd, J=4.5, 8.7, 1H), 4.10 (dd, J=9, 9, 1H), 4.40-4.90 (3AB quartet, 6H), 5.08 (d, J=1.2, 1H), 7.10-7.60 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.9, 21.8, 66.9, 68.8, 70.9, 73.5, 73.9, 75.4, 80.6, 92.2, 105.9, 127.6-128.6 (15C), 137.6, 138.4, 138.5; IR (neat, cm^{-1}) 3441, 3030, 1667, 1602, 1497, 1454, 1362, 1236, 911, 874, 735, 698.

Preparation of Methyl 3, 4, 6-Tri-O-benzyl-2-deoxy-2-S-(-3-thio-2, 4-pentadienone)-β-D-glucopyranoside (27β).

To a solution of **11** (0.1026 g; 0.20 mmol; 1 eq), in 0.5 mL of CH_2Cl_2, and 0.5 mL of CH_3OH, benzenesulfonic acid, dried by vacuum distillation after reaction with triflic anhydride, was added (0.0347 g; 0.22 mmol; 1 eq). The reaction was followed for 18 hrs. The reaction was then quenched with a saturated solution of $NaHCO_{3(aq)}$. The aqueous fraction was then washed three times with CH_2Cl_2. The organic fractions were mixed and dried with anhydrous Na_2SO_4 and concentrated. The resulting crude was purified through flash chromatograpy using silica gel (EtOAc: Hexanes, 1:3) and a white solid (0.055 g; 53%) was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 6H), 2.73 (dd, J=8.4, 11, 1H), 3.36-3.34 (m, 1H), 3.43 (s, 3H), 3.44-3.49 (m, 1H), 3.64 (dd, J=8,8 1H), 3.72 (d, J=3, 1H), 4.33 (d, J=8.4, 1H), 4.50-5.00 (m, 7H), 7.10-7.60 (m, 15H), 17.05 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.8, 56.5, 57.0, 69.0, 73.7, 75.1, 75.2, 79.7, 82.8, 104.4, 105.5, 128.0-128.7 (15C), 138.2, 138.3, 138.4, 197.6; EIMS [m/z (% relative intensity)] 596 ($M^{\cdot}+NH_4$, 71), 466 ($C_{28}H_{30}O_5^{\cdot\cdot}+NH_4$, 56), 434 ($C_{27}H_{38}O_4^{\cdot\cdot}+NH_4$, 21), 168 (100), 150 ($C_5H_9O_2S^{\cdot\cdot}+NH_4$, 35), 118 (74).

Kinetic Study of the Formation of Methyl 3, 4, 6-Tri-O-benzyl-2-deoxy-2-S-(-3-thio-2, 4-pentadienone)-β-D-glucopyranoside (27β(D)).

In order to study the kinetics of the reaction of formation of Methyl 3, 4, 6-Tri-O-benzyl-2-deoxy-2-S-(-3-thio-2, 4-pentadienone)-β-D-glucopyranoside, **27β** a ^{1}HNMR experiment was devised:

Cycloadduct **11** (0.0155 g; 0.028 mmol; 1 eq) was dissolved in 0.3 ml of CD_3OD and 0.3 ml of deuterated chloroform. The solution was transferred to an NMR tube and dry benzenosulfonic acid (0.0065 g; 0.043 mmol; 1.5 eq) was added to the mixture. The NMR tube was kept inside the spectrometer for seven hours at a temperature of 29.1 °C and a ^{1}H NMR was taken at regular intervals during this time. The integration curves in each spectra of the two singlets at 2.30 and 2.31 ppm belonging to the starting material **11** were normalized and graphed against the reaction time in minutes.

Preparation of Methyl 3, 4, 6-Tri-O-benzyl-2-deoxy-2-S-(-3-thio-2, 4-pentadienone)-α-D-mannopyranoside (38).

To a solution of **19** (0.0457 g; 0.084 mmol; 1 eq) in 0.4 mL of dry CH_2Cl_2, and 0.4 mL of dry CH_3OH, benzenesulfonic acid, dried by vacuum distillation after reaction with triflic anhydride, was added (0.0167 g; 0.086 mmol; 1 eq) and the reaction was left to stir under N_2 for five and a half hours. The mixture was quenched with a saturated solution of $NaHCO_{3(aq)}$. The aqueous fraction was then washed three times with CH_2Cl_2 (60 mL). The organic fractions were mixed and dried with anhydrous $MgSO_4$ and evaporated to dryness. The residue was purified by flash chromatography (EtOAc: P.E., 1:4) to give pure product (0.0206 g; 43%).

^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 6H), 3.29 (dd, J=1.2, 4.5, 1H), 3.31 (s, 3H), 3.60-3.80 (m, 3H), 4.00 (dd, J=4.5, 9, 1H), 4.18 (dd, J=4.5, 9, 1H), 4.50-4.90 (3AB quartet, 6H), 4.66 (d, J=1.2, 1H), 7.10-7.44 (m, 15H), 17.18 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 25.0, 52.1, 69.4, 72.1, 72.2, 73.5, 74.9, 75.3, 79.5, 100.2, 103.1, 127.6-128.6 (15C), 138.1, 138.6, 138.6, 198.3; Anal. Calcd. for $C_{33}H_{38}O_7S$: C, 68.5; H, 6.6; S, 5.5. Found: C, 68.8; H, 6.5; S, 5.7.

Kinetic Study of the Formation of Methyl 3, 4, 6-Tri-O-benzyl-2-deoxy-2-S-(-3-thio-2, 4-pentadienone)-α-D-mannopyranoside (38).

The reaction of formation of **38** was repeated as previously described and aliquotes of the reaction mixture were taken at regular intervals, dried under high vacuum and ^1H NMR was done of each sample using deuterated chloroform

as solvent. The integration curves in each spectra of the two singlets at 2.30 and 2.37 ppm belonging to the starting material **19** were normalized and graphed against the reaction time in minutes.

Preparation of Preparation of Methyl 3, 4, 6-Tri-O-benzyl-2-deoxy-2-S-(-3-thiopent-3-en-2-one)-β-D-glucopyranoside (30).

To a solution of **28** (either one of the diastereomers), (0.103 g; 0.19 mmol; 1 eq) and trimethyl orthoformate (0.031mL, 0.28 mmol, 1eq), in dry CH_2Cl_2 (0.5 mL), and dry CH_3OH (0.5 mL), benzenosulfonic acid dried by vacuum distillation after reaction with triflic anhydride (0.0295 g; 0.19 mmol; 1 eq) was added, and the reaction was left to stir under N_2 for one and a half hours, when the reaction was quenched using $NaHCO_{3(aq)}$. The aqueous fraction was then washed four times with CH_2Cl_2. The organic fractions were combined, dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude was purified by flash chromatography (EtOAc:P.E., 1:4) to give pure product (0.072g; 68 %).

^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (d, J=6.9, 3H), 2.34 (s, 3H), 3.09 (dd, J=8.7, 10.8, 1H), 3.38 (s, 3H), 3.39-3.9 (m, 5H), 4.25 (d, J=8.7, 1H), 4.50-5.00 (3 AB quartet, 6H), 8.04(q, J=6.9, 1H), 7.10-7.60 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.9, 27.1, 54.0, 56.8, 69.1, 73.7, 75.1, 75.9, 79.3, 83.2, 105.6, 128.0-128.6 (15C), 138.2, 138.2, 138.4, 144.3, 197.1; IR (neat, cm^{-1}) 3030, 1684, 1601, 1496, 1453, 1355, 1238, 736, 698; EPIMS [m/z (% relative intensity)] 580 (M^++NH_4, 38); Anal. Calcd. for $C_{33}H_{38}O_6S$: C, 70.44; H, 6.81; S, 5.70. Found: C, 70.66; H, 6.86; S, 6.12.

Preparation of Methyl 3, 4, 6-Tri-O-benzyl-2-deoxy-2-S-(-3-thiopent-3-en-2-one)-α-D-mannopyranoside (41).

To a solution of **40** (either one of the diastereomers), (0.1058 g; 0.19 mmol; 1 eq) and trimethyl orthoformate (0.0311mL, 0.28 mmol, 1eq), in dry CH_2Cl_2 (0.5 mL), and dry CH_3OH (0.5 mL), benzenosulfonic acid dried by vacuum distillation after reaction with triflic anhydride (0.0325 g; 0.21 mmol; 1.1 eq) was added, and the reaction was left to stir under N_2 for one and a half hours, when the reaction was quenched using $NaHCO_{3(aq)}$. The aqueous fraction was then washed four times with CH_2Cl_2. The organic fractions were combined, dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude was purified by flash chromatography (EtOAc:P.E., 1:4) to give pure product (0.0958 g; 89 %).

^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (d, J=6.9, 3H), 2.36 (s, 3H), 3.31 (s, 3H), 3.60-3.80 (m, 4H), 3.97 (dd, J=9.9,1H) 4.15 (dd, J=4.5, 8.7, 1H), 4.47-4.95 (m, 7H), 7.15 (q, J=6.9, 1H), 7.17-7.60 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.5, 27.1, 49.5 , 55.1, 69.5, 71.4, 72.0, 73.5, 74.9, 75.2, 79.0, 101.0, 127.5-128.5 (15C), 137.5, 138.5, 138.7, 148.0, 197.0; IR (neat, cm^{-1}) 3030, 1674, 1601, 1496, 1453, 1361, 1236, 738, 699; EPIMS [m/z (% relative intensity)] 580 (M^++NH_4, 39); Anal. Calcd. for $C_{33}H_{38}O_6S$: C, 70.44; H, 6.81; S, 5.70. Found: C, 70.11; H, 6.65; S, 5.70.

Preparation of 1-O,2-S-(2-Acetyl-1-methyl-1-(1,2:3,4 Di-O-Isopropylidene-α-D-galactopyranose)1,2-ethenadiyl)-3,4,6-tris-O-(phenyl-methyl)-2-thio-α-D-glucopyranoside (36).

To a solution of 1,2:3,4 Di-O-Isopropylidene-α-D-galactopyranose (0.221 g; 0.85 mmol; 3.7 eq) with powdered 4A molecular sieves (0.1 g) in dry CH_2Cl_2 (1 mL) the major diastereomer from the reduction of **11** (0.126 g; 0.23 mmol; 1eq) was added, followed by trifluoroacetic acid (0.0018 mL; 0.023mmol; 1/10 eq). The reaction mixture sea stirred at 25°C for 5hrs. and 30 min., then quenched with $NaHCO_{3(aq)}$, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography over silica gel (EtOAc:P.E., 1:3) and the product (0.146 g; 80.4%) was obtained as a clear gel.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24, 1.25, 1.36, 1.45 (all s, 12H), 1.51 (s, 3H), 1.76 (d, J=6.6, 3H), 2.80 (dd, J=10.4, 2.7, 1H), 3.50-489 (m, 18H), 5.43 (d, J=5.1, 1H), 5.51 (d, J=3, 1H), 6.03 (q, J=6.6, 1H), 7.12-7.36 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 15.0, 18.0, 23.0, 24.0, 24.4, 25.0, 25.9, 26.0, 26.1, 42.0, 46.0, 61.0, 62.0, 67.0, 68.0, 68.2, 68.4, 70.6, 70.7, 70.8, 71.6, 72.7, 73.0, 75.0, 75.2, 76.2, 76.3, 78.2, 78.6, 81.0, 92.0, 95.0, 96.0, 97.0, 103.0, 108.5, 108.6, 109.0, 109.4, 112.0, 127.5-130 (15C), 138.0, 138.0, 138.2, 138.5, 147; Anal. Calcd. for $C_{44}H_{54}O_{11}S$: C, 66.80; H, 6.90; S, 4.10. Found: C, 66.91; H, 6.90; S, 3.88.

Preparation of 1, 2:3, 4 Diisopropylidene-6-O-{3, 4, 6-Tri-O-benzyl-2-deoxy-2-S-(-3-thiopent-3-en-2-one)-β-D-glucopyranosyl}-α-D-galactopyranoside (42).

To a solution of 1,2:3,4 Di-O-Isopropylidene-α-D-galactopyranose (0.428 g; 1.64 mmol; 4.2 eq) with powdered 4A molecular sieves (0.390 g) in dry CH_2Cl_2 (2mL) the major diastereomer from the reduction of **11** (0.211 g; 0.39 mmol; 1eq) was added, followed by trifluoroacetic acid (0.005 mL; 0.065mmol; 1/6 eq). The reaction mixture was stirred at 25°C for 5hrs. and 30 min., then quenched with $NaHCO_{3(aq)}$, dried over $MgSO_4$ and evaporated in vacuo. The residue obtained was dissolved in dry CH_2Cl_2 (3.5mL) with powdered 4A molecular sieves (0.411 g) and para-toluensulfonic acid was added (0.017 g; 0.089mmol; 1/4.5 eq). The mixture was stirred at 25°C for 6 hrs. another fraction of PTSA (0.038 g; 0.1mmol; 1/2 eq) was then added, and after stirring for 1 hr. and 30 min. the reaction was quenched with $NaHCO_{3(aq)}$, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by column chromatography over silica gel (EtOAc:CH_2Cl_2, 1:2.5), and the product (0.160 g; 52.6%) was obtained as a white foamy gel.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.25 (s, 3H), 1.34 (s, 3H), 1.46 (s, 3H), 2.00 (d, J=6.9, 3H), 2.28 (s, 3H), 3.21 (dd, J-8.4, 10.5, 1H), 3.3-4.78 (m, 18H), 4.85 (d, J=10.8, 1H), 5.42 (d, J=4.8, 1H), 7.00 (q, J=6.9, 1H), 7.10-7.50 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.9, 24.5, 24.9, 26.0, 26.1, 27.0, 52.4, 67.1, 68.8, 70.4, 70.6, 71.4. 73.5, 74.8, 77.4, 78.6, 83.0, 96.2, 104.5, 108.5, 109.2, 127.5, 127.6,

127.7, 127.8, 127.9, 128.2, 138.1, 138.1, 138.4, 144.1, 196.7; IR (neat, cm^{-1}) 3030, 1681, 1604, 1454, 1375, 1211, 899, 804, 736, 698; Anal. Calcd. for $C_{44}H_{54}O_{11}S \times 3H_2O$: C, 62.54; H, 6.44; S, 3.80. Found: C, 62.74; H, 6.49; S, 4.12.

Preparation of 1, 2:3, 4 Diisopropylidene-6-O-{3, 4, 6-Tri-O-benzyl-2-deoxy-2-S-(-3-thio-2,4pentenedione)-α-D-mannopyranosyl}-α-D-galactopyranoside (39).

To a solution of 1,2:3,4 Di-O-Isopropylidene-α-D-galactopyranose (0.158 g; 0.61 mmol; 3 eq), and **19** (0.112 g; 0.21 mmol; 1 eq) in 3 mL of dry CH_2Cl_2, dry benzene- sulfonic acid was added (0.0423 g; 0.27 mmol; 1.3 eq) and the reaction was left stirring under N_2. After the acid was added, the reaction mixture's color changed from clear to yellow and then to gray after about twenty minutes. When no starting material could be observed by TLC, fifty minutes after the benzenesulfonic acid had been added, the reaction was quenched using $NaHCO_{3(aq)}$. The organic fractions were dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by column chromatography over silica gel (EtOAc:P.E., 1:3), and the product (0.1214 g; 73%) was obtained as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 6H), 1.41 (s, 3H), 1.50 (s, 3H), 2.41 (s, 6H), 3.27 (dd, J= 1.5, 4.4, 1H) 3.60-3.98 (m, 7H), 4.06 (dd, J=9.3, 9, 1H), 4.14 (dd, J=1.5, 5.9, 1H) 4.21 (dd, J=3.3, 6.9, 1H), 4.32 (dd, J= 1.9, 3.9, 1H), 4.40-4.70 (m, 6H), 4.86 (d, J=5.5, 1H), 4.88 (d, J=1.9, 1H), 5.50 (d, J=3.8, 1H), 7.10-7.40 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.8, 25.0, 25.1, 26.2, 26.3, 52.5, 65.8, 66.1, 69.1, 70.7, 70.8, 71.2, 72.4, 73.4, 74.9, 75.3, 79.4, 96.5, 99.3, 103.3, 108.7, 109.6,

128.2-128.5 (15C), 138.1, 138.6, 138.7, 198.1; IR (neat, cm^{-1}) 3030, 1585, 1497, 1454, 1382, 1256, 1211, 917, 735, 698; EPIMS [m/z (% relative intensity)] 829 (M^{+}+Na, 100), 439 (12); Anal. Calcd. for $C_{44}H_{54}O_{12}S$: C, 65.49; H, 6.74; S, 3.97. Found: C, 65.63; H, 6.55; S, 4.10.

Preparation of 1, 2:3, 4 Diisopropylidene-6-O-{3, 4, 6-Tri-O-benzyl-2-deoxy-β-D-glucopyranosyl}-α-D-galactopyranoside (43).

To three an a half tea spoons of Raney-Nickel (about 0.05 g) made in the lab and washed with absolute ethanol until pH=7 was achieved and then once with benzene, a solution of **42** (0.0645 g; 0.082 mmol) in benzene (2 mL) was added and the mixture was stirred for half and hour. The Raney-Nickel was filtered out through a pad of elite and the solvent of the solution was evaporated. The residue was filtered through a pad of celite and purified by column chromatography (EtOAc:P.E., 1:6) to give the product (0.0313 g; 56.4%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.32 (s, 3H), 1.44 (s, 3H), 1.54 (s, 3H), 2.45 (dd, J=4.9, 12.5, 1H), 3.35-3.42 (m, 5H), 3.53 (dd, J=9,9, 1H), 4.01 (dd, J=1.8, 7.8, 1H), 4.08 (dd, J=3.3, 10.8, 1H), 4.21 (dd, J=1.8, 8.1, 1H), 4.35 (dd, J=2.4, 5.1, 1H), 4.47-4.70 (m, 9H), 4.95 (d, J=10.8, 1H), 5.55 (d, J=4.8, 1H), 7.10-7.45 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.4, 25.0, 26.0, 26.1, 36.6, 67.9, 69.4, 70.5, 70.8, 71.3, 73.5, 74.8, 75.3, 78.2, 79.5, 96.4, 100.4, 108.6, 109.3, 127.5-128.4 (15C), 138.4-138.6 (3C); IR (neat, cm^{-1}) 3030, 1497, 1454, 1381, 1211, 900, 737, 698; EIMS [m/z (% relative intensity)] 694 (M^{+}+NH_4, 0.4), 278 (100), 203 (89), 91 (54); Anal. Calcd. for $C_{39}H_{48}O_{10}$: C, 69.2; H, 7.1. Found: C, 69.04; H, 7.03.

Preparation of 3, 4 di-O-acetyl 6-thiophenyl-D-glucal (59).

In a solution of DMF (6 ml) potassium thiophenoxide was formed in situ by adding potassium t-butoxide dissolved in a 1M solution in THF (4.6 mL; 4.6 mmol; 1 eq.) and thiophenol (3.6 mL; 35 mmol; 8 eq.). After stirring for 10 minutes, a solution of 3, 4 di-O-acetyl 6-iodo-D-glucal **58** (1.53 g; 4.5 mmol; 1 eq.) in DMF (10 mL) was added and the reaction was then refluxed under N_2 at 85°C for 2 hrs. and 30 min. The reaction was then allowed to cool down to room temperature, diluted with de-ionized water and extracted with two fractions of ether (50 mL each). All of the organic washings were combined, dried with $NaSO_4$, concentrated. The resulting crude was put through a flash silica gel column [(1) EtOAc-P.E. (5:95) (2) EtOAc-P.E. (10:90) (3) EtOAc-P.E. (20:80)] which afforded 0.722 g (57%) of product.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.06 (s, 3H), 3.24 (m, J=6.8, 9, 10.5 Hz, 2H), 4.23 (dd, J-1.2,6.0 Hz, 1H), 4.86 (dd, J=3.6, 6.3 Hz, 1H), 5.25 (dd, J=3.6, 4.5 Hz, 1H), 5.33 (dd, J=4.8, 5.4 Hz, 1H), 6.46 (dd, J=6.2, 1.2 Hz, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.9, 21.5, 34.4, 66.4, 69.2, 74.4, 98.5(2 C), 126-145 (5 C), 135, 169, 170.

Cycloaddition of 4-O-Benzyl-3-O-β-(trimethylsilyl)ethoxymethyl-D-rhamnal (22) with 3-phthalimidethio-2, 4-pentanedione (13).

3-phthalimidosulfenyl-2, 4-pentanedione (0.3928 g; 0.88 mmol; 2.0 eq.) was dissolved in 2.2 mL of dry Chloroform under N_2 atmosphere with powdered 4A molecular sieves (activated; 0.144 g) in a dry 25-mL flask. To the solution, the

D-rhamnal **22** obtained according to the literature[19] was added (0.1516 g; 0.43 mmol; 1 eq.) followed by dry 2, 6 lutidine (0.05 mL; 0.43 mmol; 1 eq.) added by syringe. The reaction mixture turned brown with in 15 minutes, and over a 24 hour period, it acquired a deep red color. After 4 hrs. the reaction had proceeded to a yield of about 100% judging from the ^{1}H NMR analysis of a reaction aliquot. The reaction mixture was poured into a separatory funnel and was quenched with a saturated solution of NH_4Cl(aq) and washed with CH_2Cl_2 three times. The combined organic fractions were dried with $NaSO_4$ and concentrated. The resulting crude was put through a flash silica gel column,[(1) EtOAc-P.E. (5:95) (2) EtOAc-P.E. (10:90) (3) EtOAc-P.E. (25:75)] which afforded 0.1531 g (75% yield) of a mixture of 0.1092 g of 1-O-, 2-S-(2-Acetyl-1-methyl-1, 2-ethenediyl)-6-deoxy-4-O-Benzyl-3-O-β-(trimethylsilyl) ethoxymethyl-2thio-α-D-glucopyranose **24** and 0.043 g of 1-O-, 2-S-(2-Acetyl-1-methyl-1, 2-ethenediyl)-6-deoxy-4-O-Benzyl-3-O-b-(trimethylsilyl) ethoxymethyl-2thio-β-D-mannopyranose **23**.

Third fraction, **24** (bottom face diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.92 (dd, J=8.4, 8.7 Hz, 2H), 1.34 (d, J=6.3, 3H), 2.32 (s, 3H), 2.35 (s, 3H), 3.14 (dd, J=3, 10.5 Hz, 1H), 3.23 (dd, J=9.3, 8.1 Hz, 1H), 3.65 (dd, J=10.8, 10.5 Hz, 1H), 3.66-3.80 (m, 3H), 3.95 (dd, J=6.3, 6 Hz, 1H), 4.69-4.90 (AB quartet, J=11 Hz, 2H), 4.97 (s, 2H), 5.57 (dd, J=3.3 Hz, 1H), 7.30-7.40 (m, 5H); ^{13}CNMR (300 MHz, $CDCl_3$) δ -1.2, 0.2, 18.1, 18.2, 21.8, 30.4, 42.3, 66.8, 69.7, 75.2, 75.6, 76.6, 77.95, 84.5, 96.0, 96.6, 97.2 (machine artifact), 109.5, 128.0, 128.2, 128.7, 138, 159.7, 195.4; IR (neat, cm^{-1}) 3036, 2966, 2907, 1666, 1555,

1355, 1249, 1132, 1055, 932, 826, 749, 691; M/S positive chemical ionization (m/z %) 498 (M^++NH_4, 100), 481 (24.1), 405 (44.3), 363 (64.8), 220 (67.6), 203 (43.6), 118 (13.7), 90 (19.9); $\alpha]_D$=+120.2; Anal. calc. for $C_{24}H_{36}O_6SSi$: C, 60.0; H, 7.50; S, 6.70. Found: C, 59.32; H, 7.59; S, 6.43.

Fourth fraction, **23** (top face diastereomer): ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.00-0.04 (m, 9H), 0.96 (m, 2H), 1.40 (d, J=6 Hz, 3H), 2.33 (s, 3H), 2.35 (s, 3H), 3.50-4.00 (m, 4H), 4.1 (dd, J=4.5, 4.5 Hz, 1H), 4.64-4.90 (AB quartet, J=10.8 Hz, 2H), 4.85 (m, 2H), 5.25 (dd, J=1.2 Hz, 1H), 5.57 (dd, J=3.3 Hz, 1H), 7.30-7.40 (m, 5H).

Preparation of 3, 6-di-O-tert-butyldimethylsilyl-D-galactal (25).

Tri-O-hydroxy-D-Galactal **71** (1.36 g; 9.3 mmol; 1 eq.) was dissolved in 6 mL of DMF to which Et_3N (13 mL; 93 mmol; 10 eq.) was added under N_2 atmosphere followed by the catalyst DMAP (0.43 g; 3.5 mmol; 0.38 eq.) and the silylating reagent tert-butyldimethylsilyl chloride (7.3 g; 48.4 mmol; 5.2 eq.). After 2 hrs., monitoring by TLC showed no starting material remaining, so the reaction mixture was transferred to a separatory funnel and was quenched with a saturated solution of $NaCO_3H$(aq) and washed with hexanes three times. The combined organic fractions were dried with $MgSO_4$ and concentrated to dryness. The white semi-solid compound obtained is pure **25**, 3.5 g (100% yield), so no further purification is needed.

^{1}HNMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.07 (s, 6H), 0.86 (s, 12H), 0.87 (s, 6H), 2.66 (s, 1H), 3.81-3.90 (m, 4H), 4.40 (dd, 1H), 4.77 (dd, J=6.3 Hz, 1H), 6.30 (dd, J=6.0 Hz, 1H); ^{13}CNMR (300 MHz, $CDCl_3$) δ -5.4, -5.5, -4.9, -4.7, 8.6, 18.0, 18.1,

25.7, 25.8, 45.8, 61.9, 64.8, 65.0, 102.2, 144.1; M/S positive chemical ionization (m/z %) 392 (M^++NH_4, 16.5), 260 ($C_{12}H_{24}O_4Si^{\bullet+}$, 43.6), 242 (83.7), 225 (100), 192 (65.1).

Cycloaddition of 3, 6-di-O-tert-butyldimethylsilyl-D-galactal (25) with 3-phthalimidethio-2, 4-pentanedione (13).

3, 5-di-O-tert-butyldimethylsilyl-D-galactal (1.02 g; 2.7 mmol; 1 eq.) and 3-phthalimidosulfenyl-2, 4-pentanedione (1.12 g; 4.0 mmol 1.5 eq.) were dissolved with powdered 4A molecular sieves and under N_2 in a dry 50 mL round bottom flask, using 10 ml of CH_2Cl_2. Dry 2, 6 lutidine (0.25 mL; 2.2 mmol; 1 eq.) was syringed in, and the reaction turned brown inmediately. After stirring overnight, ^{1}HNMR showed that no galactal was left in the reaction mixture, so the mixture was pured into a separatory funnel, 20 mL of CH_2Cl_2 were added, followed by 60 mL of NH_4Cl(aq). The organic fraction was separated out and the aqueous was washed four more times with CH_2Cl_2. All of the organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo.

The crude was put through a flash silica gel column (EtOAc-P.E. (10:90)) which gave 1.02 g (68% yield) of pure 1-O, 2-S-(2-Acetyl-1-methyl-1, 2-ethenediyl)-3, 6-di-O-tert-butyldimethylsilyl-2-thio-α-D-galactopyranose **26**.

^{1}HNMR (300 MHz, $CDCl_3$) δ= 0.07 (s, 3H), 0.10 (s, 6H), 0.15 (s, 3H), 0.90 (s, 12H), 0.93 (s, 6H), 2.30 (s, 3H), 2.31 (s, 3H), 2.68 (s, 1H), 3.41 (dd, J=3, 10.4 Hz, 1H), 3.70 (dd, J=3, 10.3 Hz, 1H), 3.82 (dd. J=8.4, 12.6 Hz, 1H), 3.95 (d, 3H), 5.6 (d, J=3 Hz, 1H); ^{13}CNMR (300 MHz, $CDCl_3$) δ= -5.5, -5.3, -4.7, -4.5, 18.1, 18.3,

21.6, 25.7, 25.8, 29.7, 39.2, 61.9, 67.7, 68.9, 72.0, 96.3, 101.9, 159.3, 195.1; IR (neat, cm^{-1}) 3567, 2937, 1674, 1559, 1461, 1359, 1249, 1140, 934, 891, 777; M/S positive chemical ionization (m/z, %) 522 (M^++NH_4, 28), 505 (M^++H), 392 (46), 260 ($C_{12}H_{24}O_4Si^{\bullet+}$, 100), 243 (77), 225 (67), 192 (77).

Preparation of 1-O, 2-S-(2-Acetyl-1-methyl-1, 2-ethenediyl)-3-O-tert-butyldimethylsilyl-6-thiophenyl-2-thio-α-D-galactopyranose (74).

In a solution of DMF (2mL) potassium thiophenoxide was formed in situ by adding potassium t-butoxide dissolved in a 1M solution in THF (0.65 mL; 0.65 mmol; 0.4 eq.) and thiophenol (0.33 mL; 3.2 mmol; 2 eq.) together with 18-crown-6 ether (0.64 g; 2.4 mmol; 1.5 eq.). After stirring for 10 minutes, a solution of 1-O, 2-S-(2-Acetyl-1-methyl-1, 2-ethenediyl)-3-O-tert-butyldimethylsilyl-6-O-tosyl-2-thio-α-D-galactopyranose **73** (0.88 g; 1.6 mmol; 1 eq.) in DMF (7 mL) was added and the reaction was left to stir under N_2 overnight. 1-O, 2-S-(2-Acetyl-1-methyl-1, 2-ethenediyl)-3-O-tert-butyldimethylsilyl-6-O-tosyl-2-thio-α-D-galactopyranose **73** was obtained through standard tosylation of the primary alcohol in the adduct **72** obtained through desilylation of the 6-O-tert-butyldimethylsilyl group in the totally protected ketone adduct **26**. After 12 hrs., thiophenol was added in large excess (0.6 mL; 5.9 mmol; 7.4 eq.) and the reaction went on for another 36 hrs. The reaction mixture was the cooled down to 0°C with an ice bath and about 1 mL of a 20% (W/V) of a NaOH/H_2O solution was added to the stirring reaction. The crude was then transferred to a separatory funnel where it was extracted three

times with three aliquots of EtOAc. The combined organic layers were washed once with brine and dried over $MgSO_4$ and evaporated to dryness. The crude was purified using flash chromatography, [(1) EtOAc-P.E. (15:85) (2) EtOAc-P.E. (20:80) (3) EtOAc-P.E. (25:75)] which afforded two different diastereomers due to the migration of the silyl group at C-3 to C-4 in the minor product of the reaction. The total amount of product obtained from the reaction was 0.459 g (59% yield) of which 0.297 g (38%), are 1-O,2-S-(2-Acetyl-1-methyl-1,2-ethenediyl)-3-O-tert-butyldimethylsilyl-6-thiophenyl-2-thio-α-D-galactopyranose, **74** and 0.162g (21%) are 1-O, 2-S-(2-Acetyl-1-methyl-1, 2-ethenediyl)-4-O-tert-butyldimethylsilyl-6-thiophenyl-2-thio-α-D-galactopyranose, **77**. The starting material was recuperated in 14.5%

Tosyl adduct **73**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.14 (s, 3H), 0.91 (s, 9H), 2.30 (s, 6H), 2.50 (s, 3H), 3.28 (dd, J=3.0, 10.2 Hz, 1H), 3.66 (dd, J=3.3, 9.3 Hz, 1H), 3.77 (s, 1H), 4.09-4.36 (m, 3H), 5.56 (d, J=2.7 Hz, 1H) 7.35 (AB quartet, J=8.4 Hz, 2H), 7. 82 (AB quartet, J=8.4 Hz, 2H).

Thiophenyl adduct **74**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H) 0.12 (s, 3H), 0.89 (s, 9H), 2.24 (s, 3H), 2.28 (s, 3H), 3.21-3.31 (m, J=9.9, 8.7 Hz, 2H), 3.33 (dd, J=2.2, 7.7 Hz, 1H), 3.62 (dd, J=2.5, 7.7 Hz, 1H), 3.86 (d, J=2.5 Hz, 1H), 3.99 (dd, J=5.2, 5.2 Hz, 1H), 5.63 (d, J=2.2 Hz, 1H), 7.10-7.42 (m, 5H); ^{13}CNMR (300 MHz, $CDCl_3$) δ -4.5, -4.3, 18.3, 21.8, 25.8, 26.0, 26.1, 30.0, 33.9, 39.1, 67.7, 69.4, 70.9, 96.3, 102.1, 126.8, 129.3, 130.1, 135.6, 159.5, 195.4; IR (neat, cm^{-1}) 3558 (br), 3036, 2953, 1676, 1556, 1251, 1147, 1033, 940, 836, 777; M/S positive chemical

ionization (m/z, %) 500 (M^++NH_4, 9), 483 (M^++H, 83), 390 (92), 373 (60), 260 (100), 241(57).

Thiophenyl adduct **77**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.17 (s, 3H), 0.94 (s, 9H), 2.20 (s, 3H), 2.27 (d, J=3.6 Hz, 1H), 2.31 (s, 3H), 3.04-3.25 (m, 2H), 3.42 (dd, J=3.0, 10.5 Hz, 1H), 3.51-3.60 (m, J=2.7 Hz, 1H), 3.91 (dd, J=7.2, 7.0 Hz, 1H), 4.21 (d, J=2.1 Hz, 1H), 5.65 (d, J=3.0 Hz, 1H), 7.18-7.40 (m, 5H); M/S positive chemical ionization (m/z, %) 500 (M^++NH_4, 24), 483 (M^++H, 100).

Preparation of 1-O, 2-S-(2-Acetyl-1-methyl-1, 2-ethenediyl)-3, 4-O-β-(trimethylsilyl)ethoxymethyl-6-thiophenyl-2-thio-α-D-galactopyranose (79).

Thiophenol adduct **74** (0.250 g; 0.52 mmol; 1 eq.), was dissolved in 7 mL of THF and the solution was cooled to -20 °C using a ethylene glycol-dry ice bath under N_2 atmosphere. TFAB (1.3 mL; 1.3 mmol; 2.5 eq.) dried over activated 4A molecular sieves was injected into the stirring solution and the reaction was allowed to run for 1/2 hr. The reaction was quenched by adding a saturated solution of $NH_4Cl_{(aq)}$ and letting it warm up to room temperature. The crude was then transferred to a separatory funnel where it was extracted three times with three aliquots of EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The unpurified crude was then dissolved in CH_2Cl_2 (2.8 mL) and N, N diisopropylamine was added (0.44 mL; 2.5 mmol; 5 eq.) followed by 2-β-(trimethylsilyl) ethoxymethyl chloride (0.9 mL; 5.1 mmol; 9.8 eq.). The reaction was left to stir overnight and the next day more 2-β-

(trimethylsilyl) ethoxymethyl chloride was added (0.9 mL; 5.1 mmol; 9.8 eq.) followed by tetrabutyl amonium iodide (0.184 g; 0.5 mmol; 1 eq.) as a catalyst. The reaction was again left overnight and the next day more of the base N, N diisopropylamine was added (0.4 mL; 2.3 mmol; 4.4 eq.) and after 3 hrs. the reaction was finally quenched by adding de-ionized water to the mixture and extracting it three times with CH_2Cl_2 the combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The crude was put through a flash silica gel column (EtOAc-P.E. (10:90)) which gave 0.194 g (60% yield) of pure **79**. ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.03 (s, 18H), 0.87-0.92 (m, 4H), 2.20 (s, 3H), 2.27 (s, 3H), 3.10-3.23 (m, J=4.4, 6.0, 10.3, 10.3 Hz, 2H), 3.53-3.80 (m, 6H), 3.98 (dd, J=5.2, 5.1 Hz, 1H), 4.14 (d, J=1.4 Hz, 1H), 4.72 (AB quartet, J=5.2 Hz, 1H), 4.82 (dd, J=1.7, 5.2 Hz, 2H), 4.94 (AB quartet, J=5.2Hz, 1H), 5.65 (d, J=2.2 Hz, 1H), 7.21-7.40 (m, 5H); ^{13}CNMR (300 MHz, $CDCl_3$) δ -1.2, 18.2, 18.4, 21.8, 30.3, 34.1, 38.1, 66.3, 66.5, 71.6, 71.8, 73.3, 94.9, 96.3, 96.5, 102.4, 126.9, 129.3, 130.0, 135.4, 159.4, 195.2; IR (neat, cm^{-1}) 3058, 2952, 1674, 1245, 1011, 933, 856, 832; M/S positive chemical ionization (m/z, %) 646 (M^++NH_4, 100), 629 (M^++H, 98), 516 (36), 386 (54), 180 (99), 118 (38), 90 (55).Anal. Calcd. for $C_{29}H_{48}O_7S_2Si_2$: C, 55.38; H, 7.69; S, 10.20. Found: C, 55.05; H, 7.38.

Preparation of 1-O, 2-S-(2-(2-propanoloxy)-1-methyl-1, 2-ethenediyl)-3, 6-di-O-tert-butyldimethylsilyl-2-thio-α-D-galactopyranose (67).

In a 25 mL round bottom flask, 3 eq. of (methyl)-triphenyl phosphonium anion were created in the standard manner by mixing dry (methyl)-triphenyl

phosphonium bromide (0.2196 g; 0.602 mmol; 3 eq.) in 1mL of THF with a 1M solution of ^{t}BuOK in THF (0.6 mL; 0.6 mmol; 3 eq.) under N_2 atmosphere. After the solution turned bright yellow, we added **26** (0.1047 g; 0.21 mmol; 1 eq.) dissolved in 1.8 mL of THF. The reaction mixture turned orange inmediately and was left to stir for 1 hr. and 30 min. The reaction was worked up by evaporating the reaction mixture to dryness and filter the crude through a silica gel pad after dissolving it with a EtOAc-P.E. mixture. The evaporated crude was actually a mixture of the two possible diastereomers of pure product due to migration of the silyl group, so no chromatography was necessary.

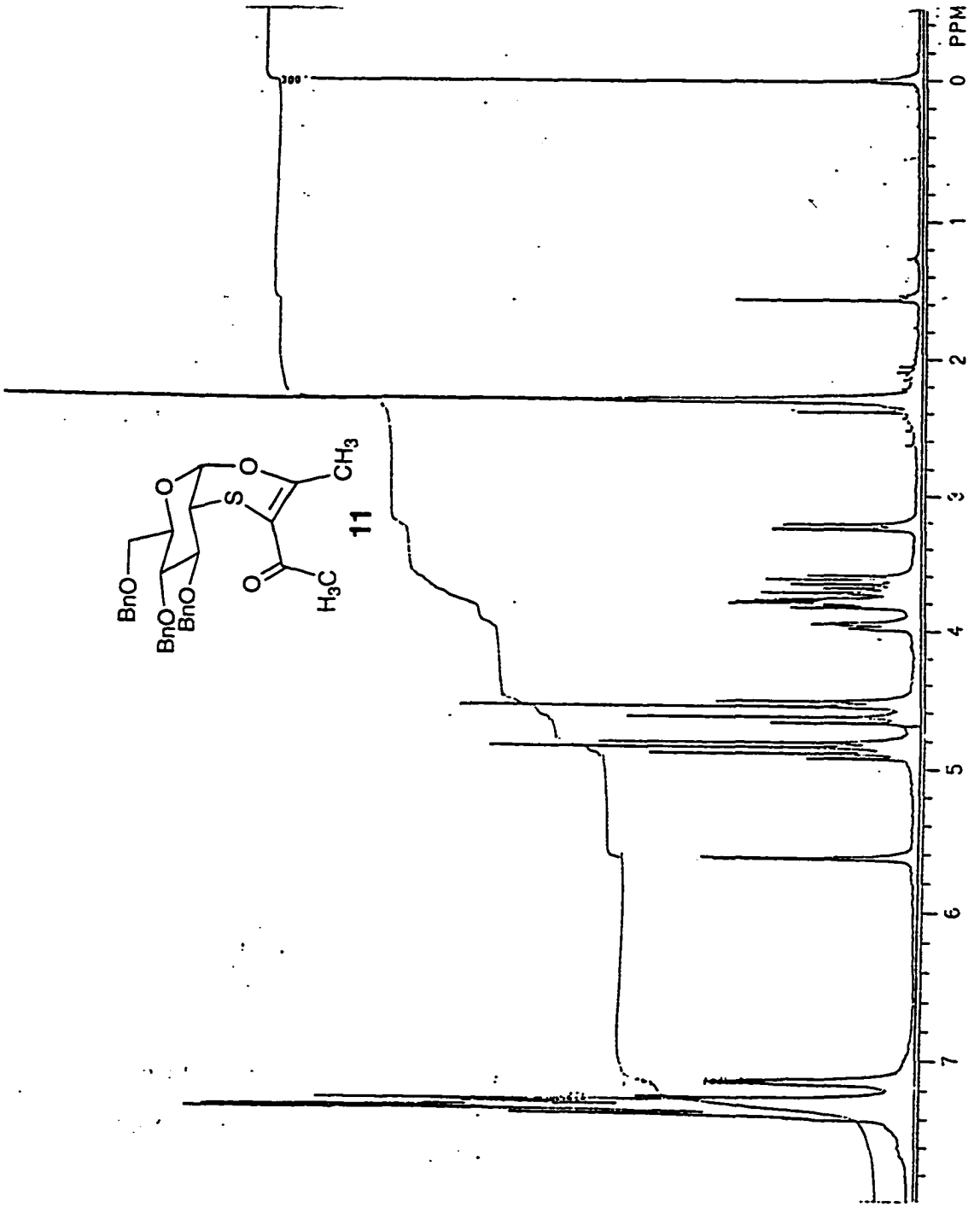
^{1}HNMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.07 (s, 6H), 0.10 (s, 12H), 0.87 (s, 12H), 0.88 (s, 12H), 0.89 (s, 6H), 0.90 (s, 6H), 1.85 (s, 6H), 1.86 (s, 6H), 2.26 (d, J=3.6 Hz, 1H), 2.57 (s, 1H), 3.30-3.40 (m, 2H), 3.60-4.10 (m, 11H), 4.14 (d, J=2.1 Hz, 1H), 4.91 (d, J=1.0 Hz, 2H), 5.05 (d, J=1.5 Hz, 2H), 5.49 (dd, J=2.4 Hz, 1H), 5.54 (d, J=3.0 Hz, 1H); ^{13}CNMR (300 MHz, $CDCl_3$) δ -11.4, -5.4, -5.3, -4.8, -4.6, -4.3, -4.1, 18.1, 18.2, 18.3, 18.5, 18.6, 18.7, 22.7, 23.0, 25.7, 25.7, 25.8, 25.9, 26.1, 26.2, 26.4, 29.7, 40.5, 40.7, 61.2, 61.8, 67.0, 68.8, 68.9, 69.3, 71.6, 73.8, 94.9, 95.1, 117.6, 117.7, 140.8, 140.9, 141.4, 143.3.

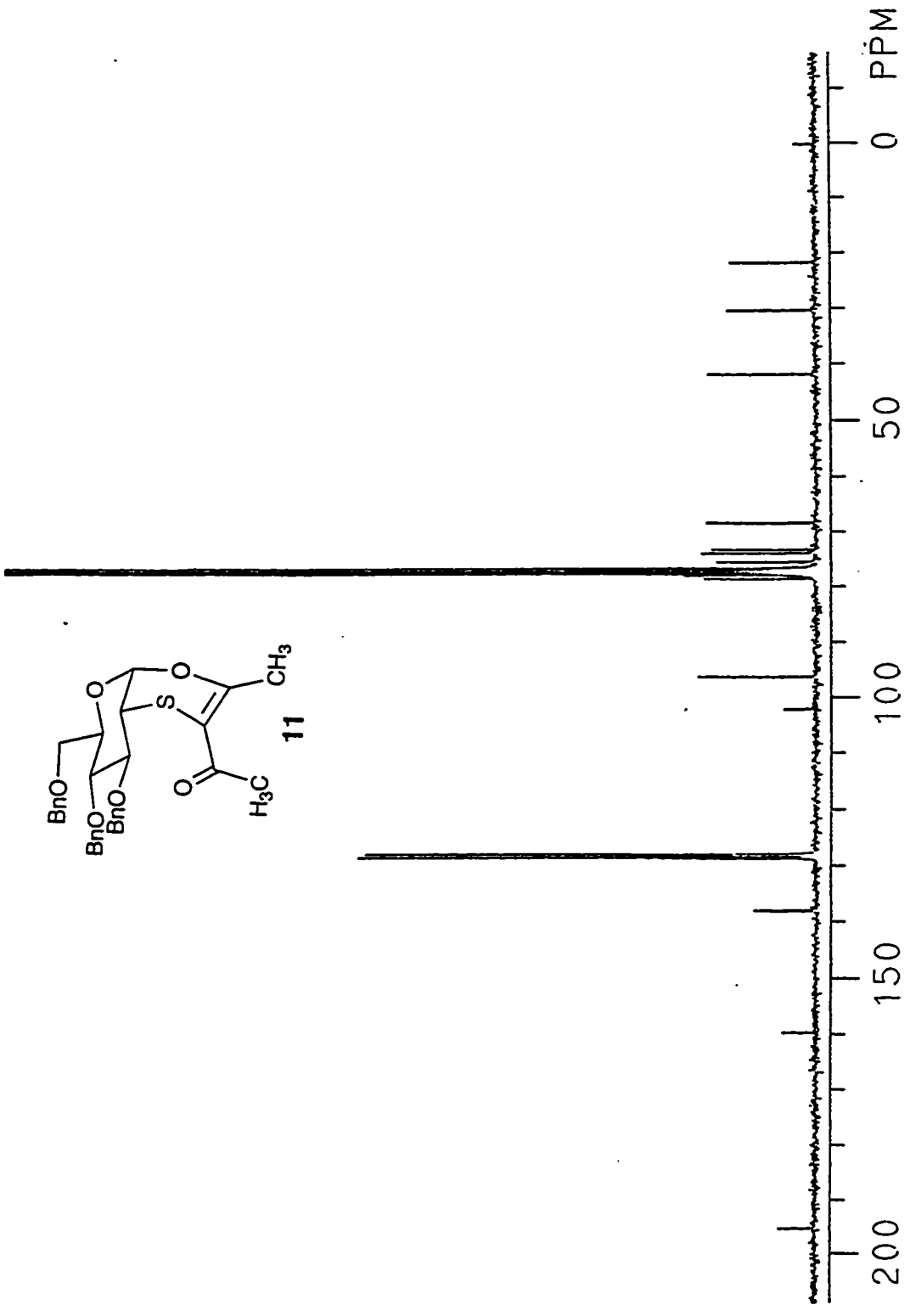
Preparation of 1-O, 2-S-(2-(2-propanoloxy)-1-methyl-1, 2-ethenediyl)-3, 4-O-β-(trimethylsilyl)ethoxymethyl-6-thiophenyl-2-thio-α-D-galactopyranose (69).

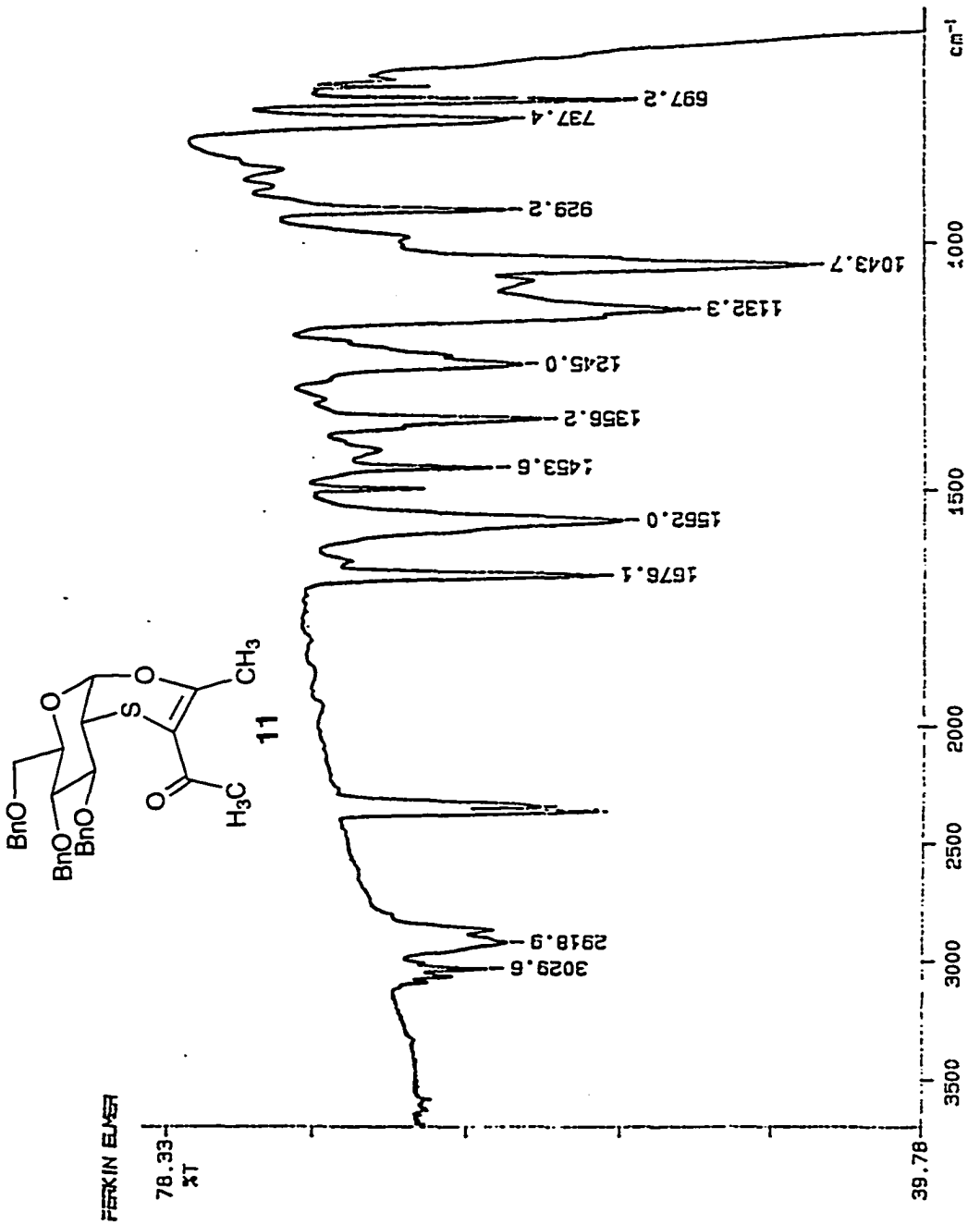
A Wittig reaction was run on compound **79** (0.1613 g; 0.26 mmol; 1 eq) in the usual way, and after purification by flash chromatography (EtOAc-P.E (10:90)) the amount of pure adduct **69** recovered was 0.087 g (58% yield).

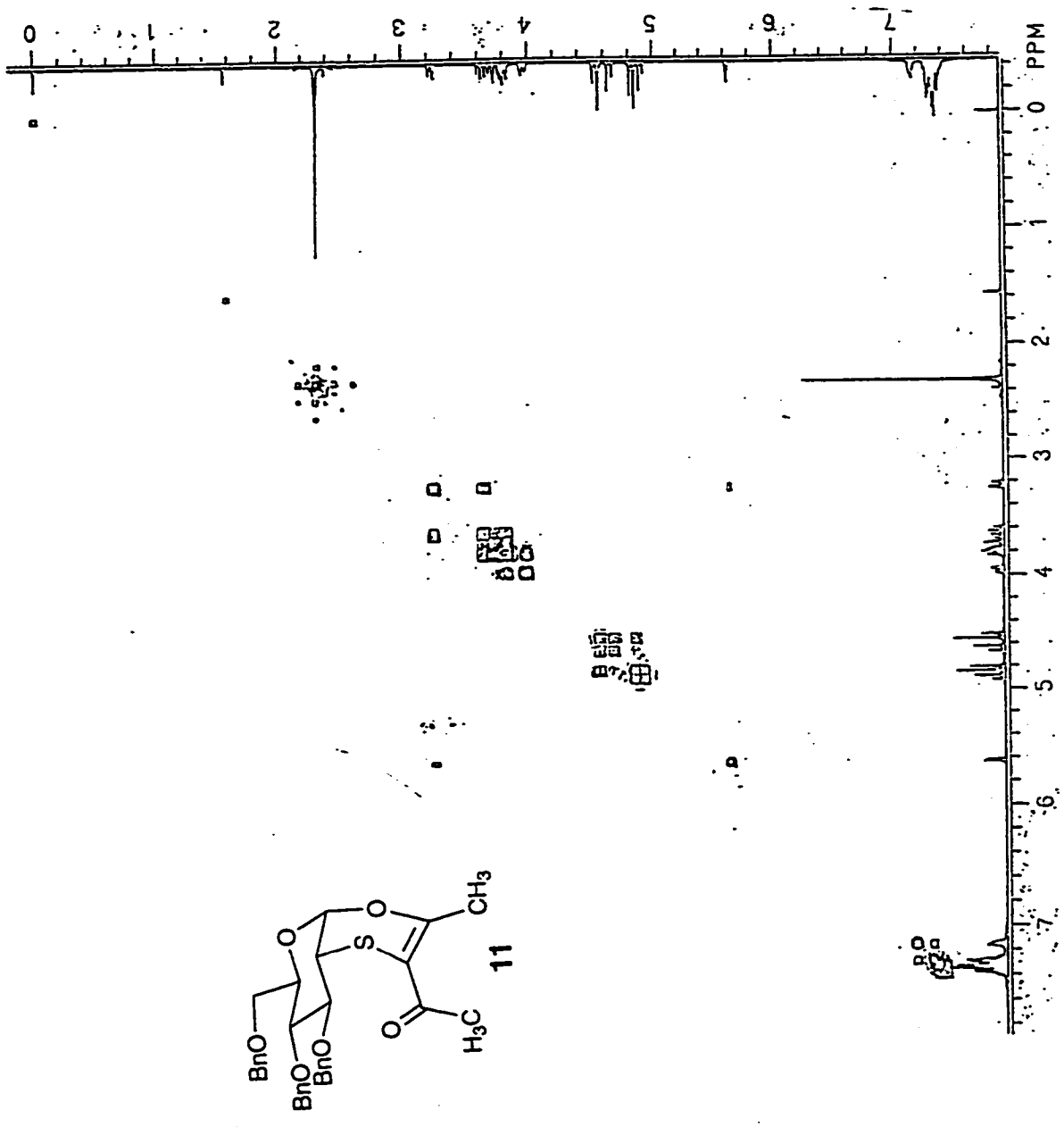
^{1}HNMR (300 MHz, $CDCl_3$) δ 0.02 (s, 18H), 0.85-0.98 (m, 4H), 1.81 (s, 3H), 1.85 (s, 3H), 3.10-3.24 (m, 2H), 3.45-3.80 (m, 6H), 4.12 (dd, J=6.6, 6.6 Hz, 1H), 4.15 (d, J=2.4, 1H), 4.83 (dd, 3, 3.5 Hz, 2H), 4.89-5.06 (m, 4H), 5.59 (d, J=3 Hz, 1H), 7.21-7.40 (m, 5H); ^{13}CNMR (300 MHz, $CDCl_3$) δ -1.2, 18.3, 18.4, 23, 34.2, 39.5, 66.2, 66.4, 71.2, 73.9, 95.3, 96.3, 97.6, 117.8, 126.6, 129.3, 129.9, 133.8, 134.1, 140.9; IR (neat, cm^{-1}) 3070, 2951, 1632, 1429, 1245, 1053, 1017, 856, 832, 689.

APPENDIX









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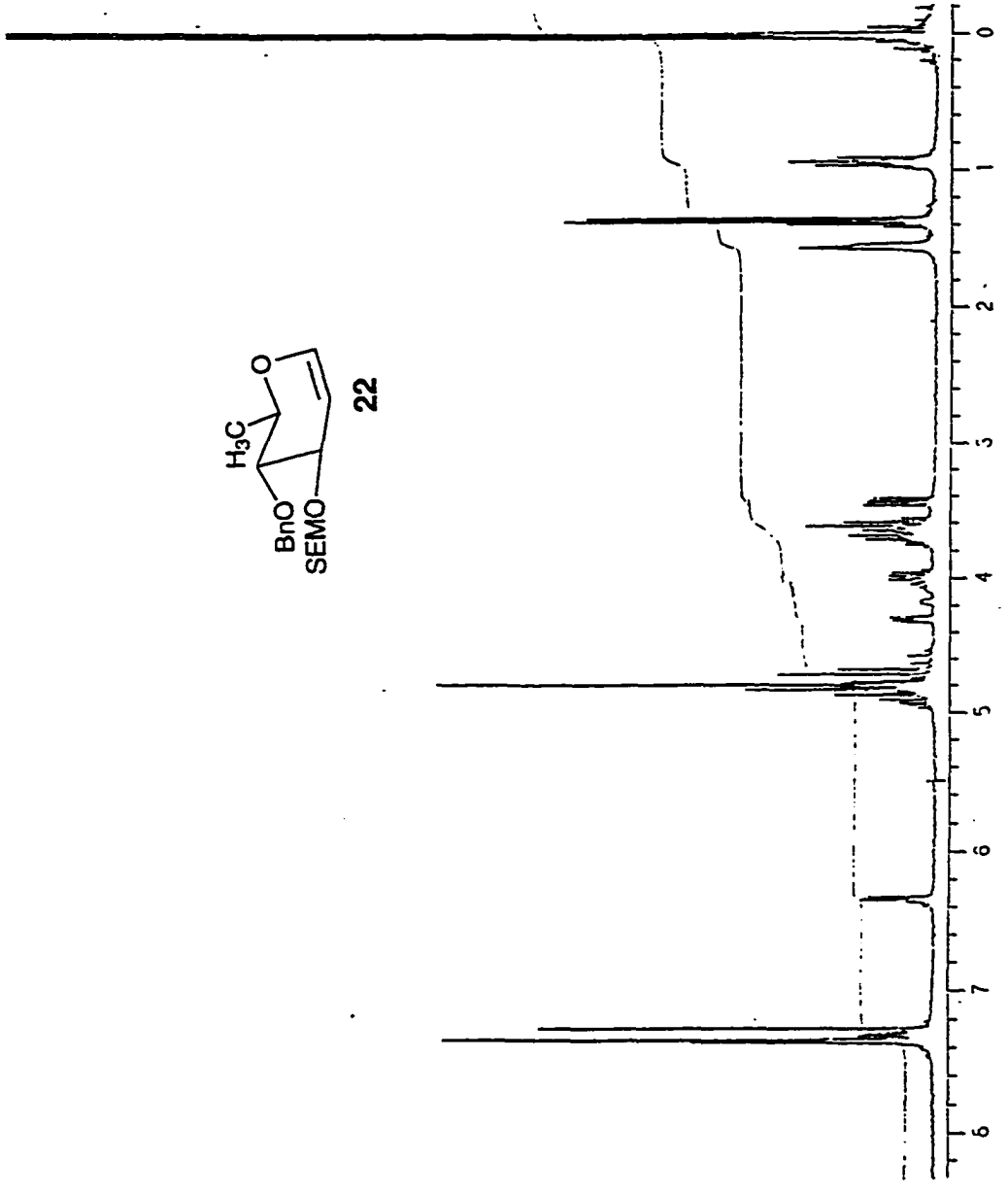

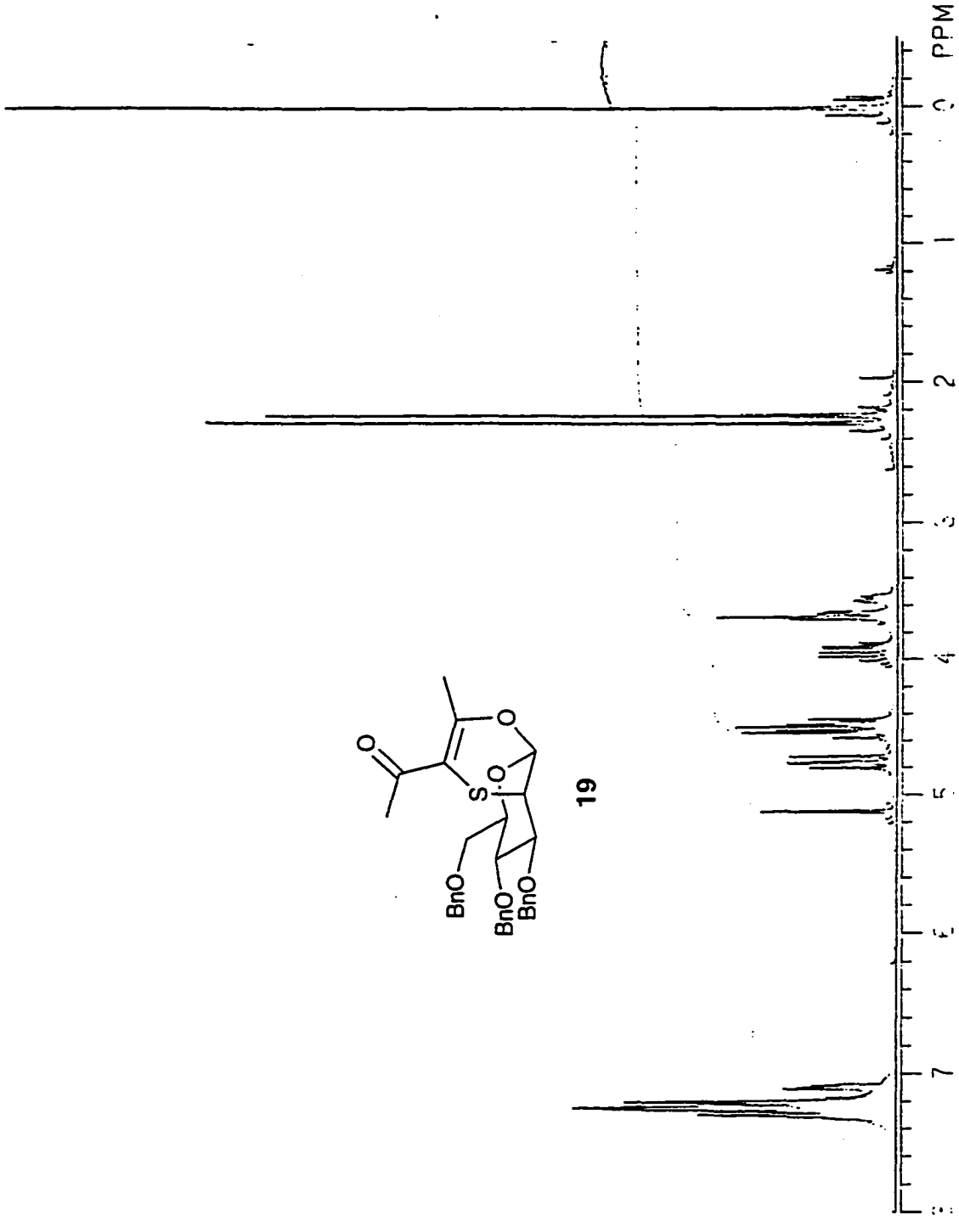

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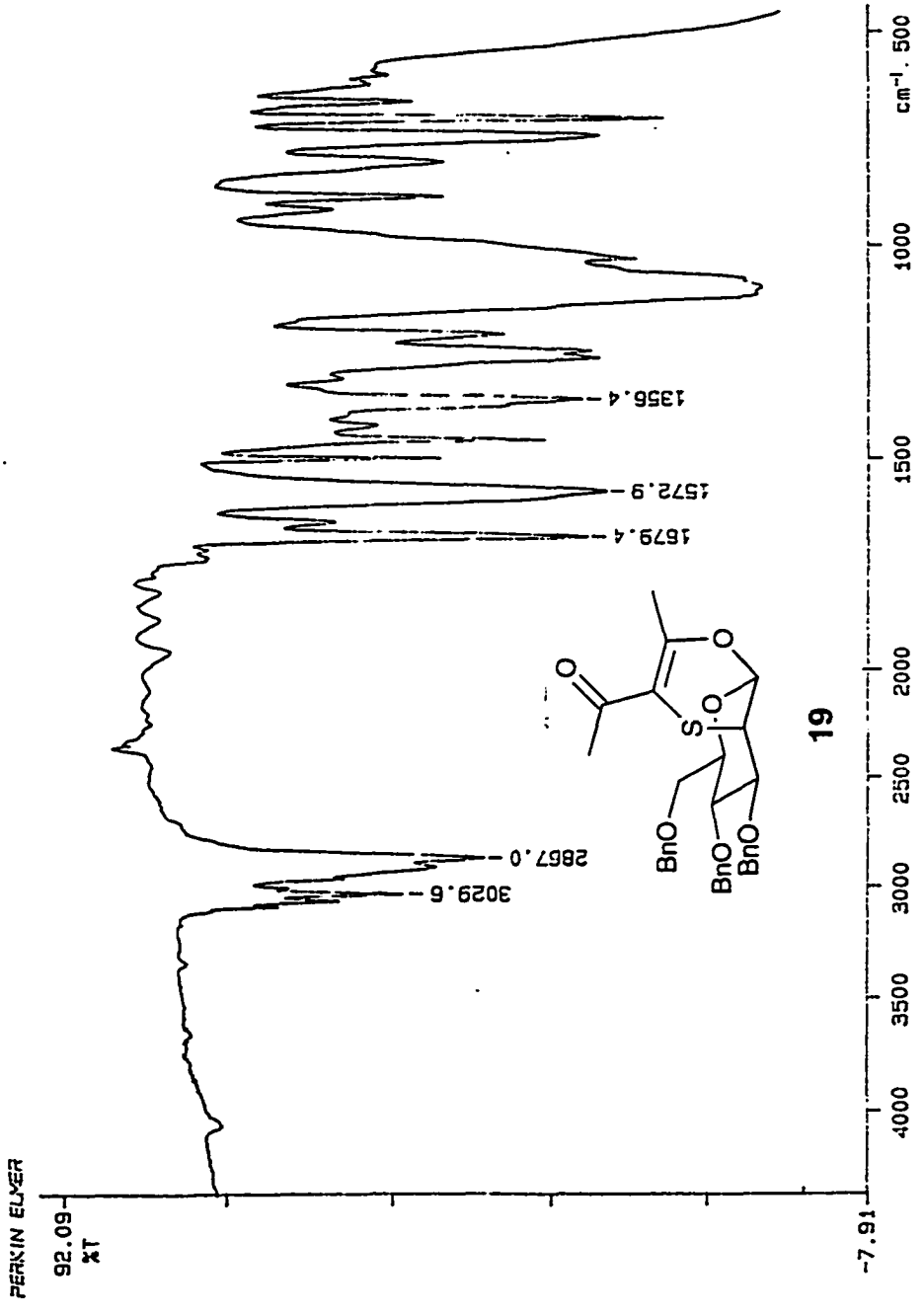

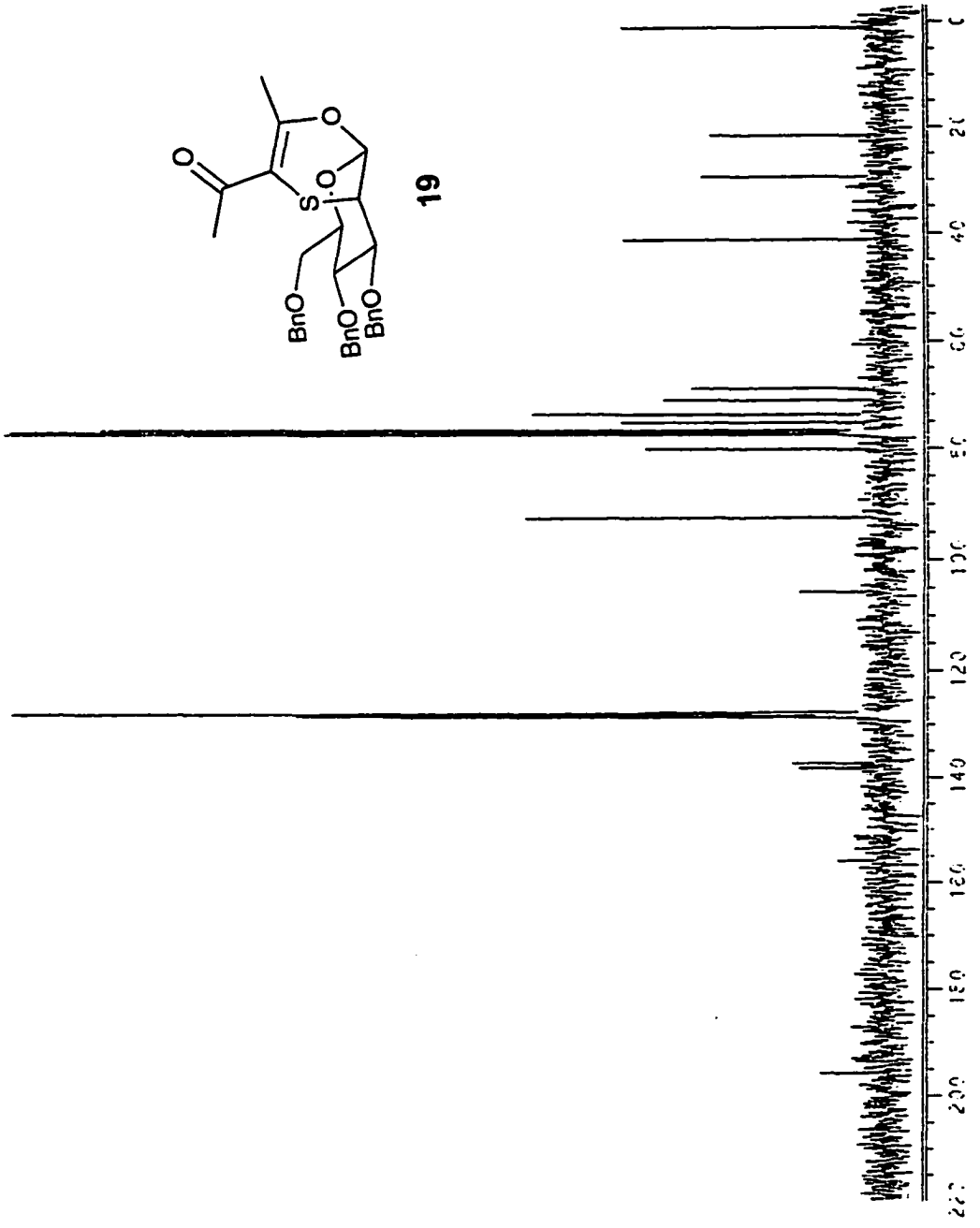

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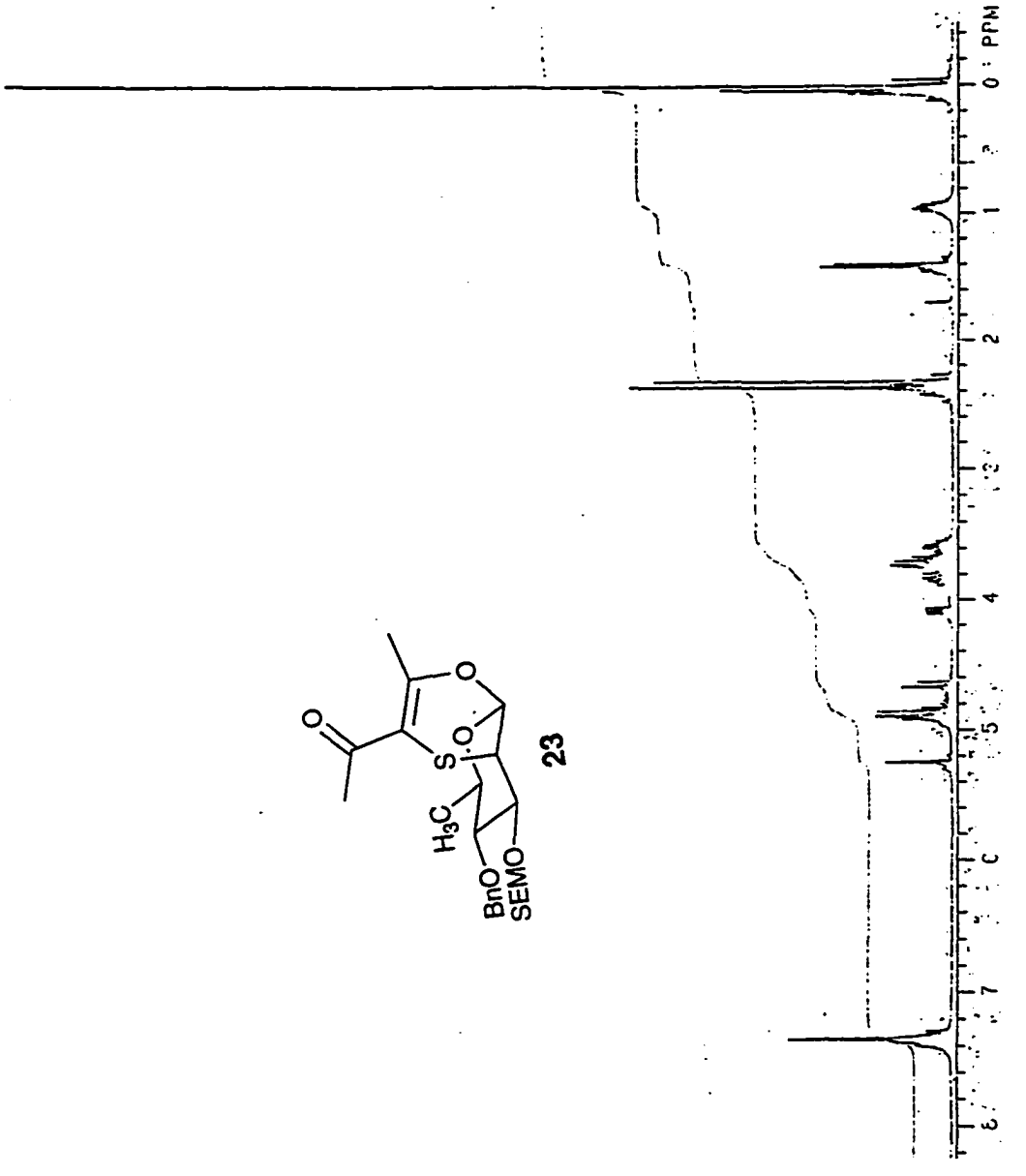

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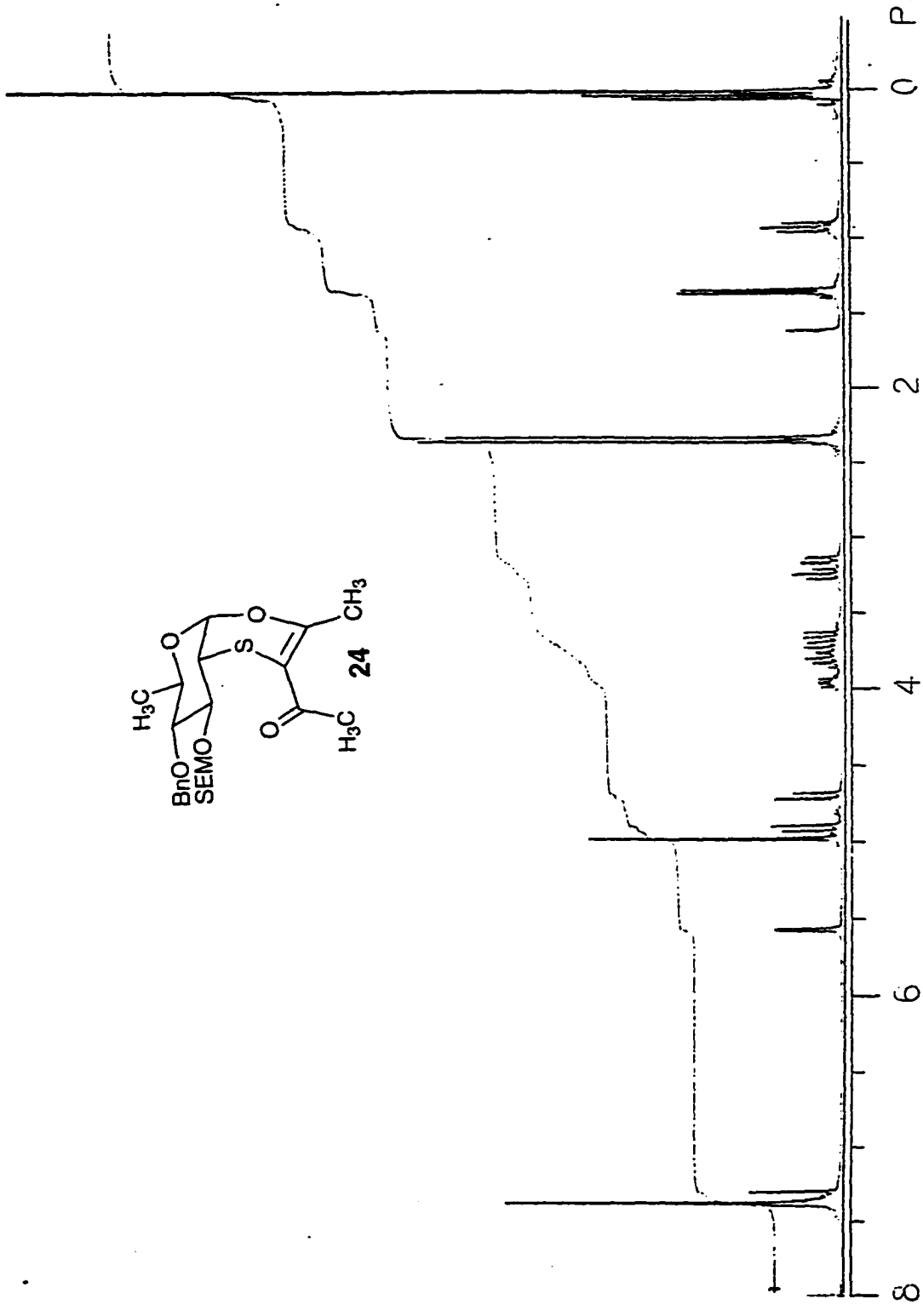

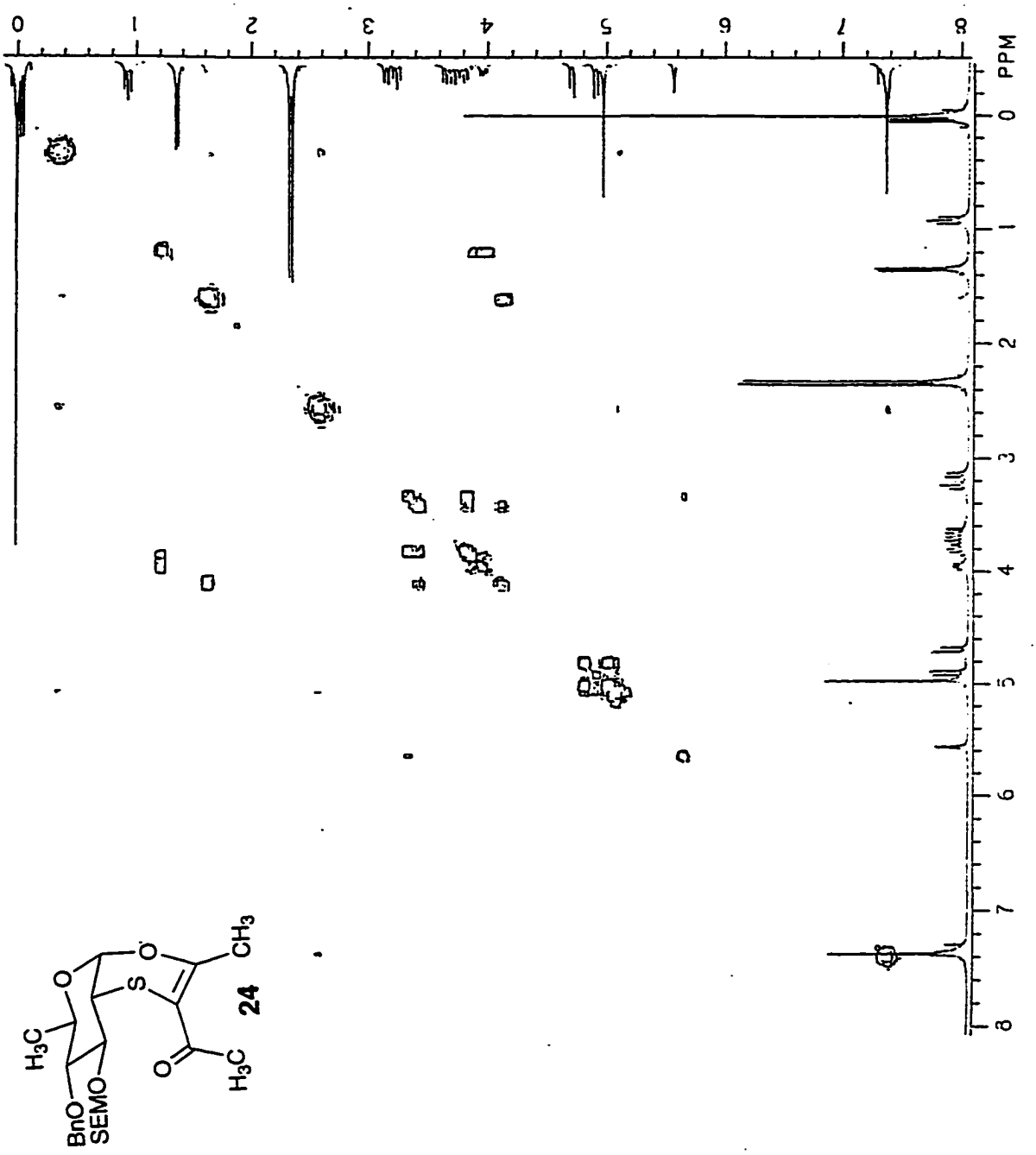

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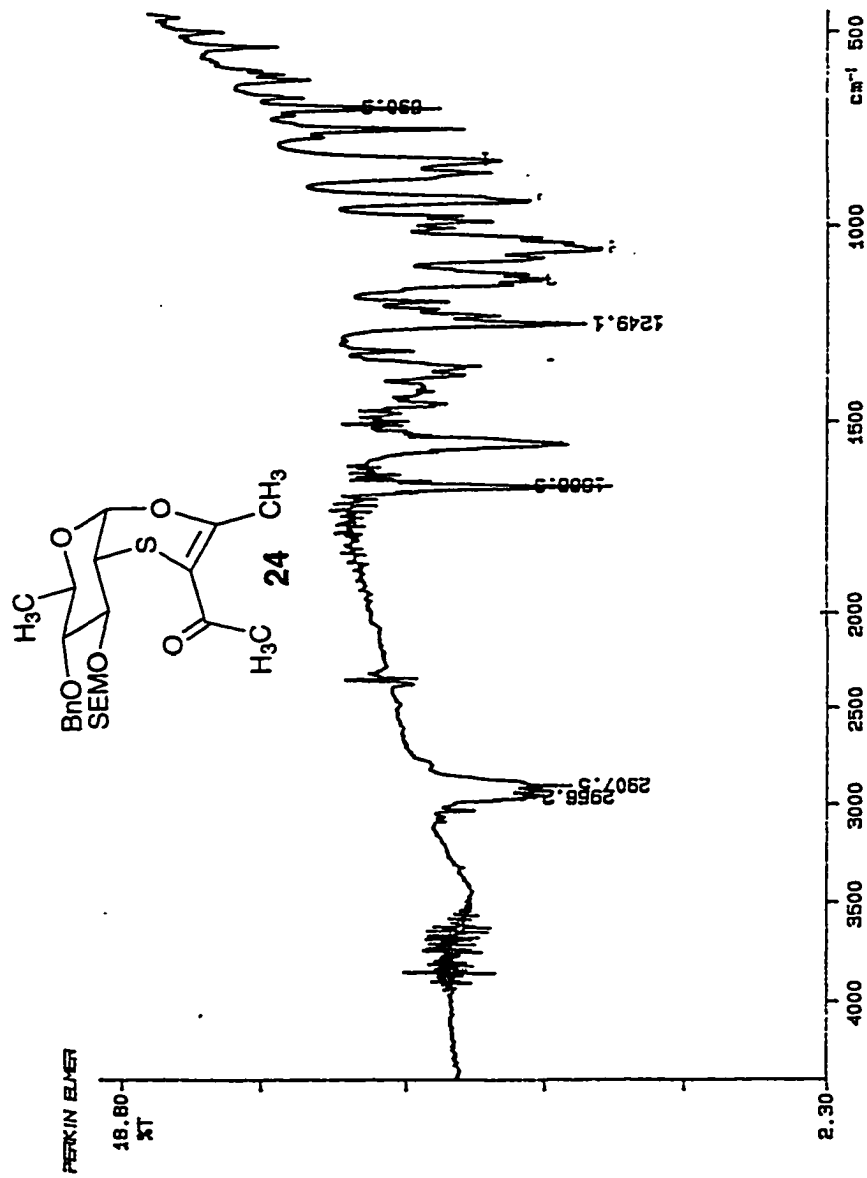

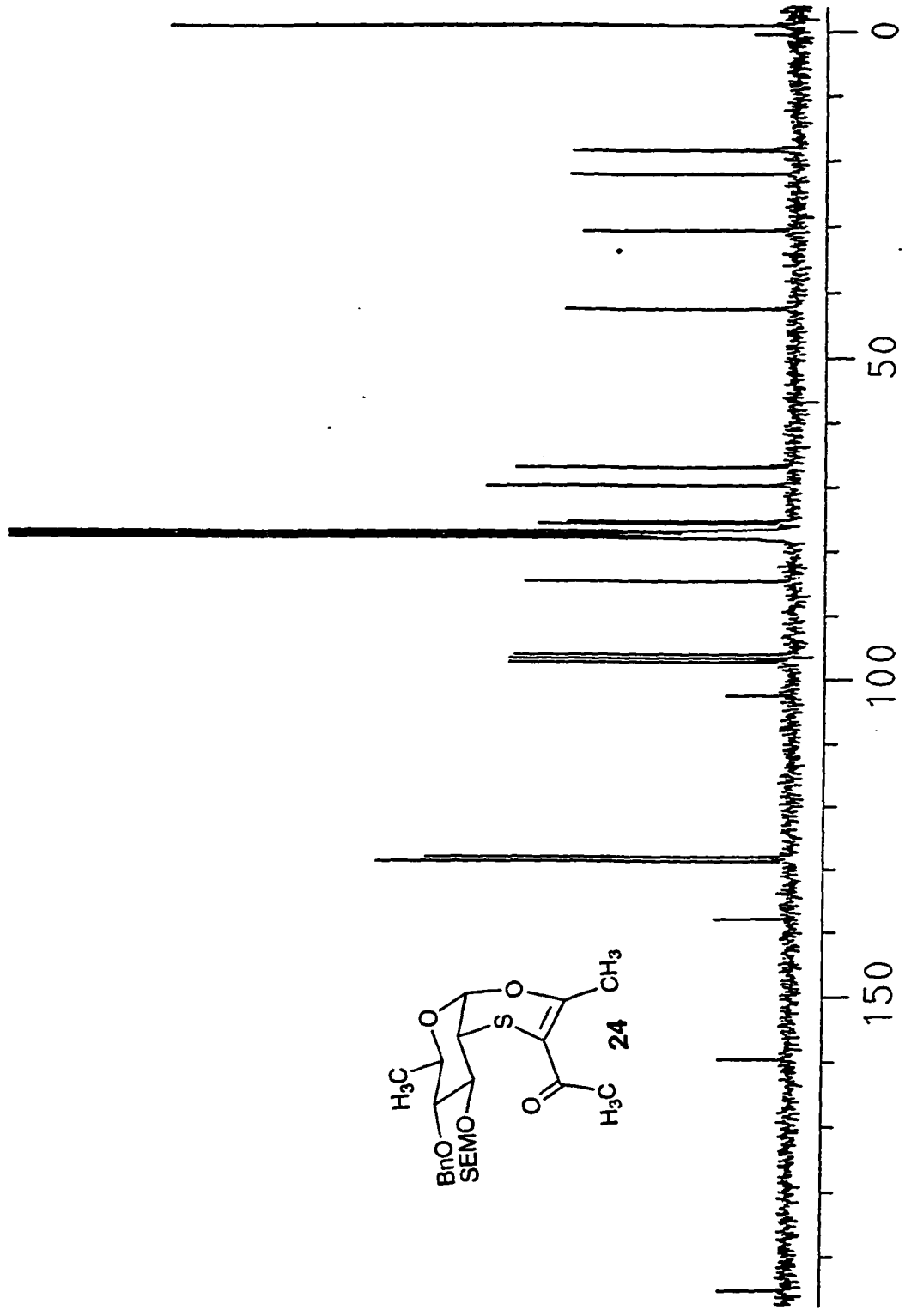

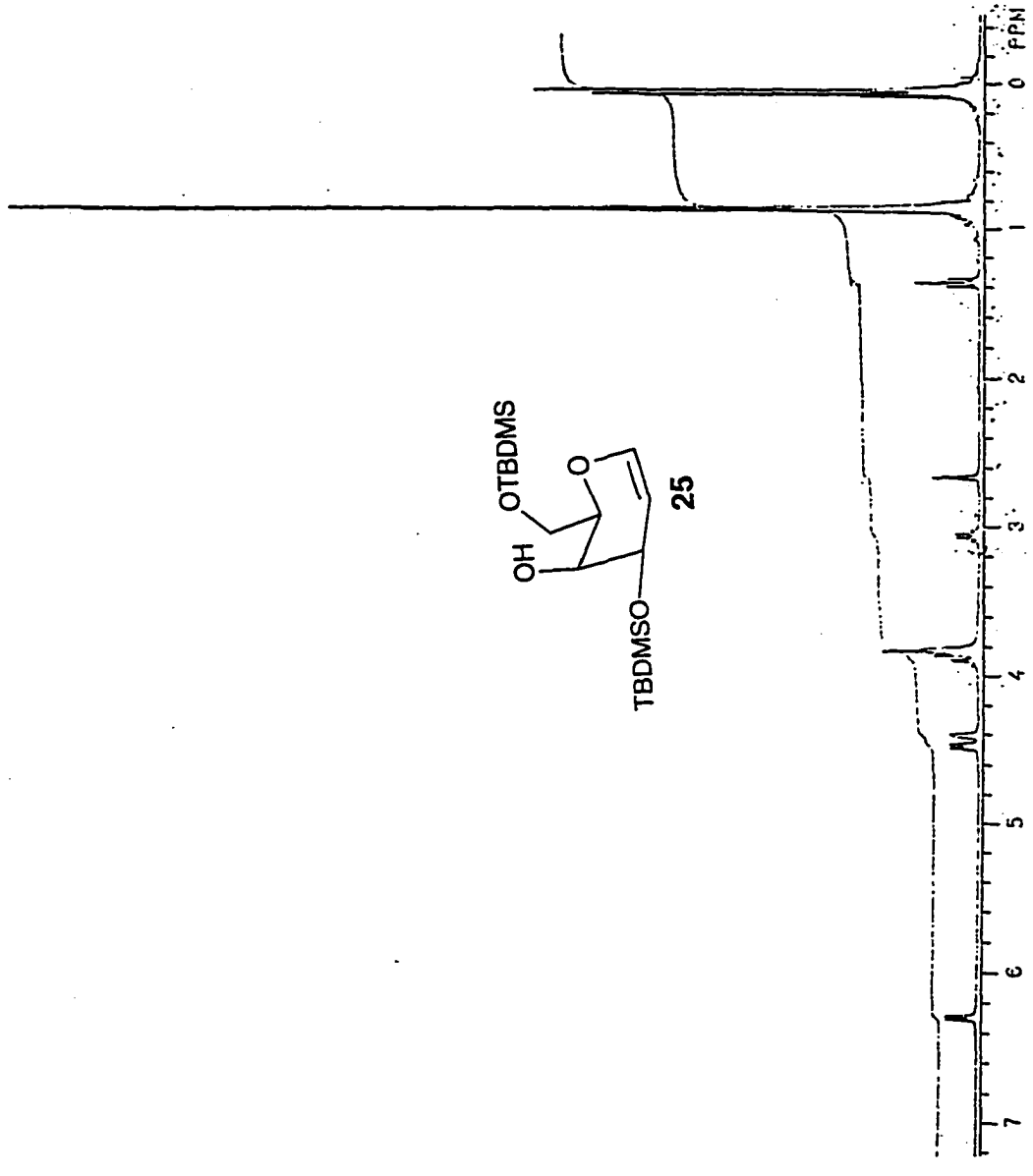

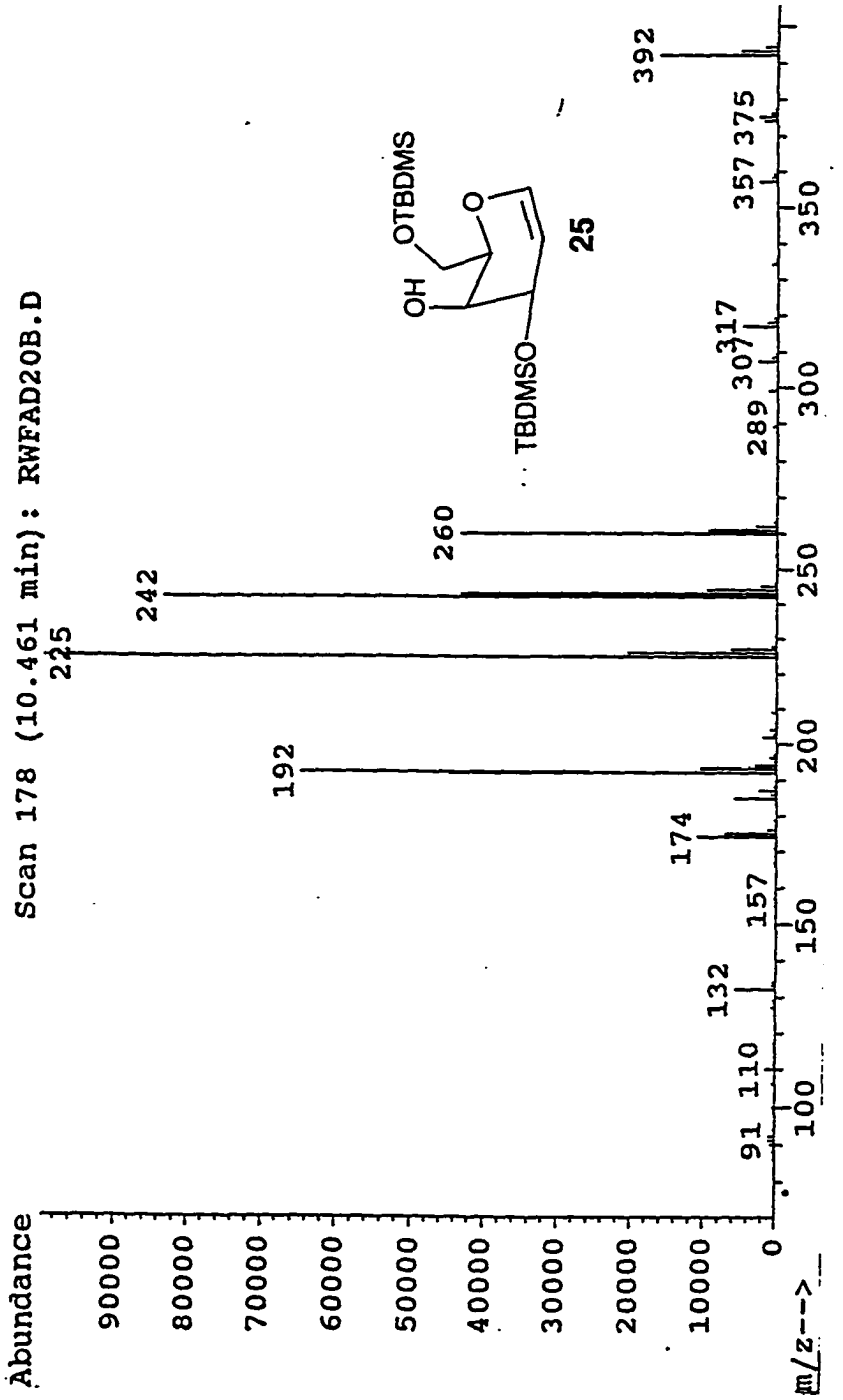

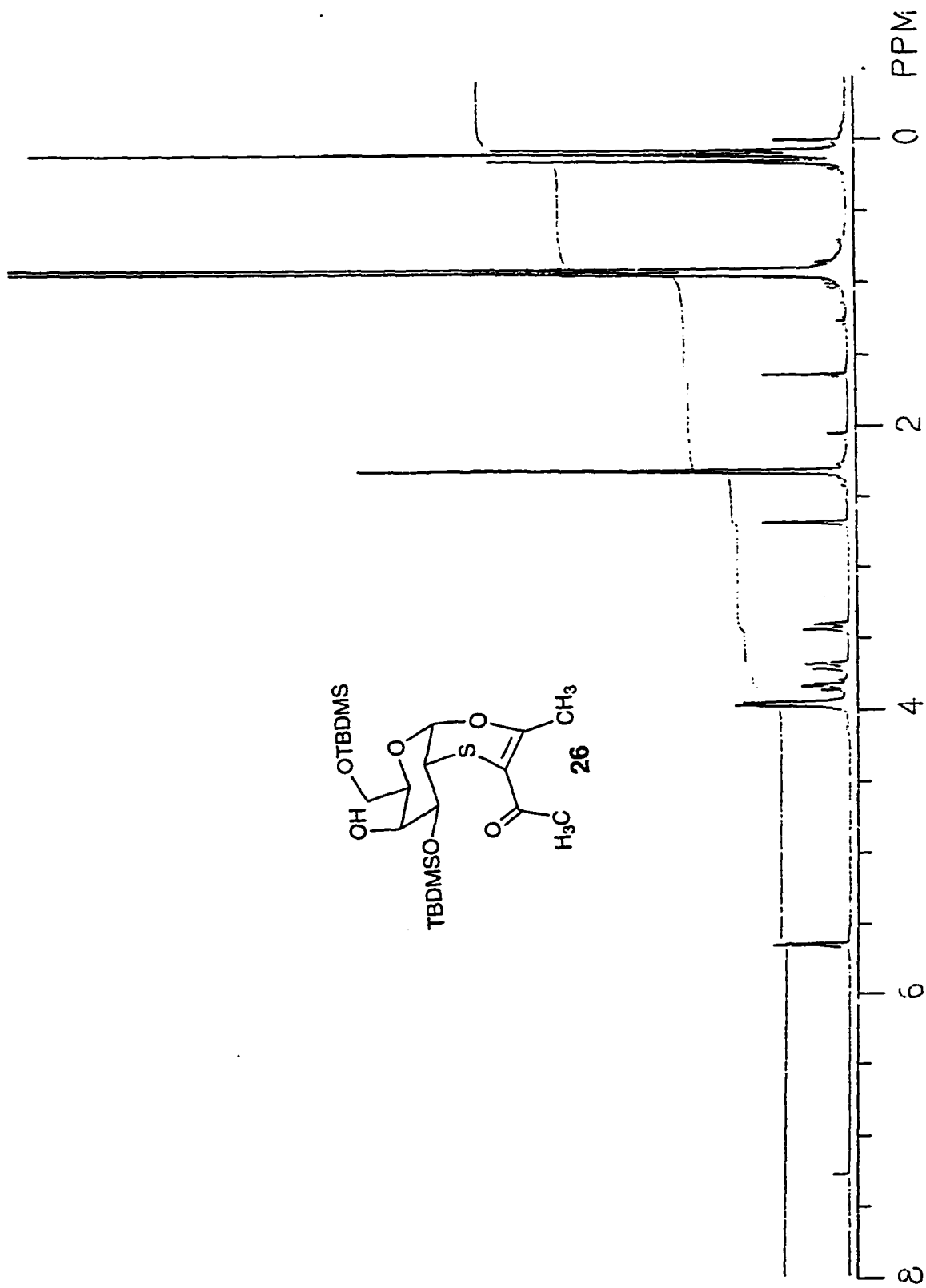

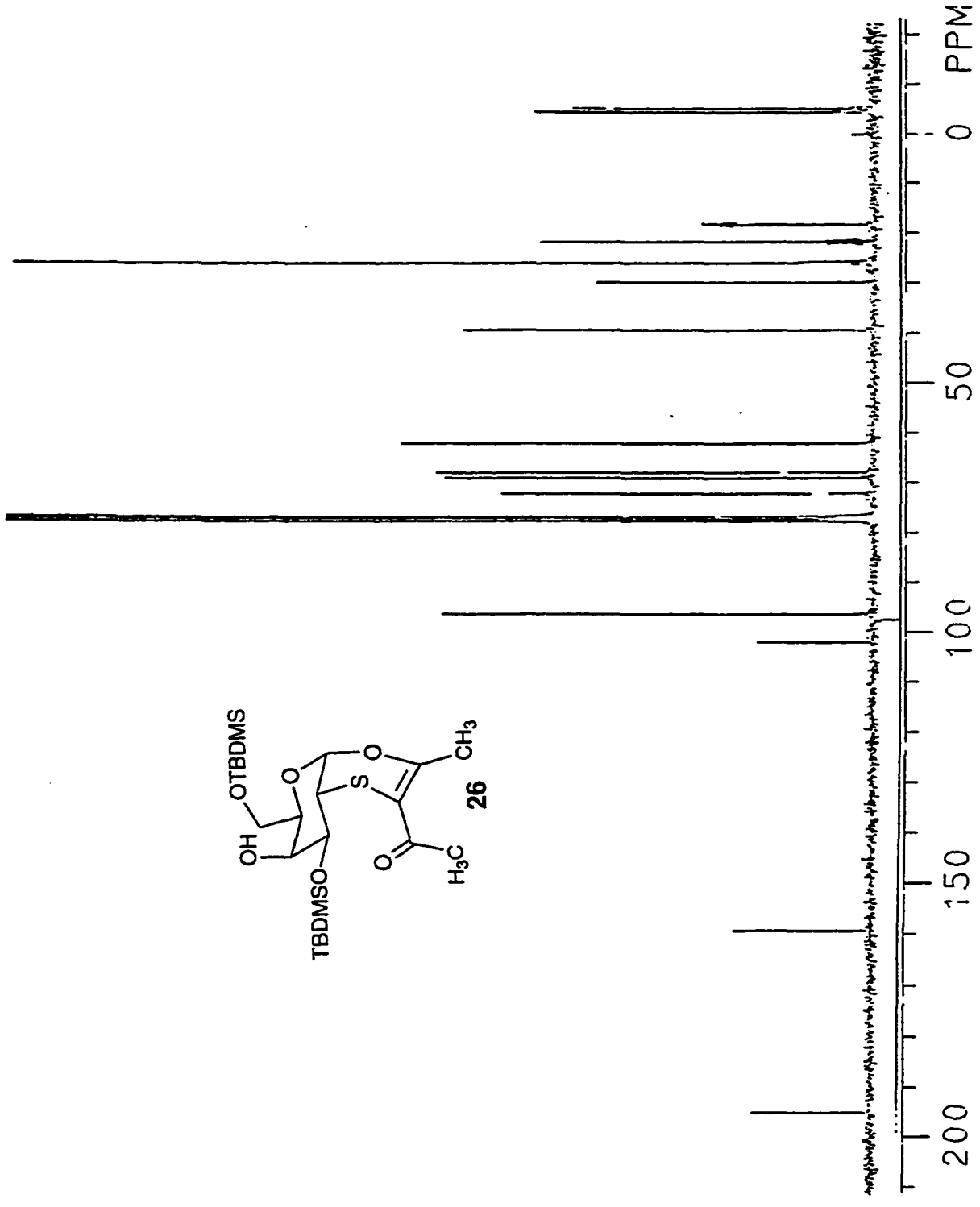

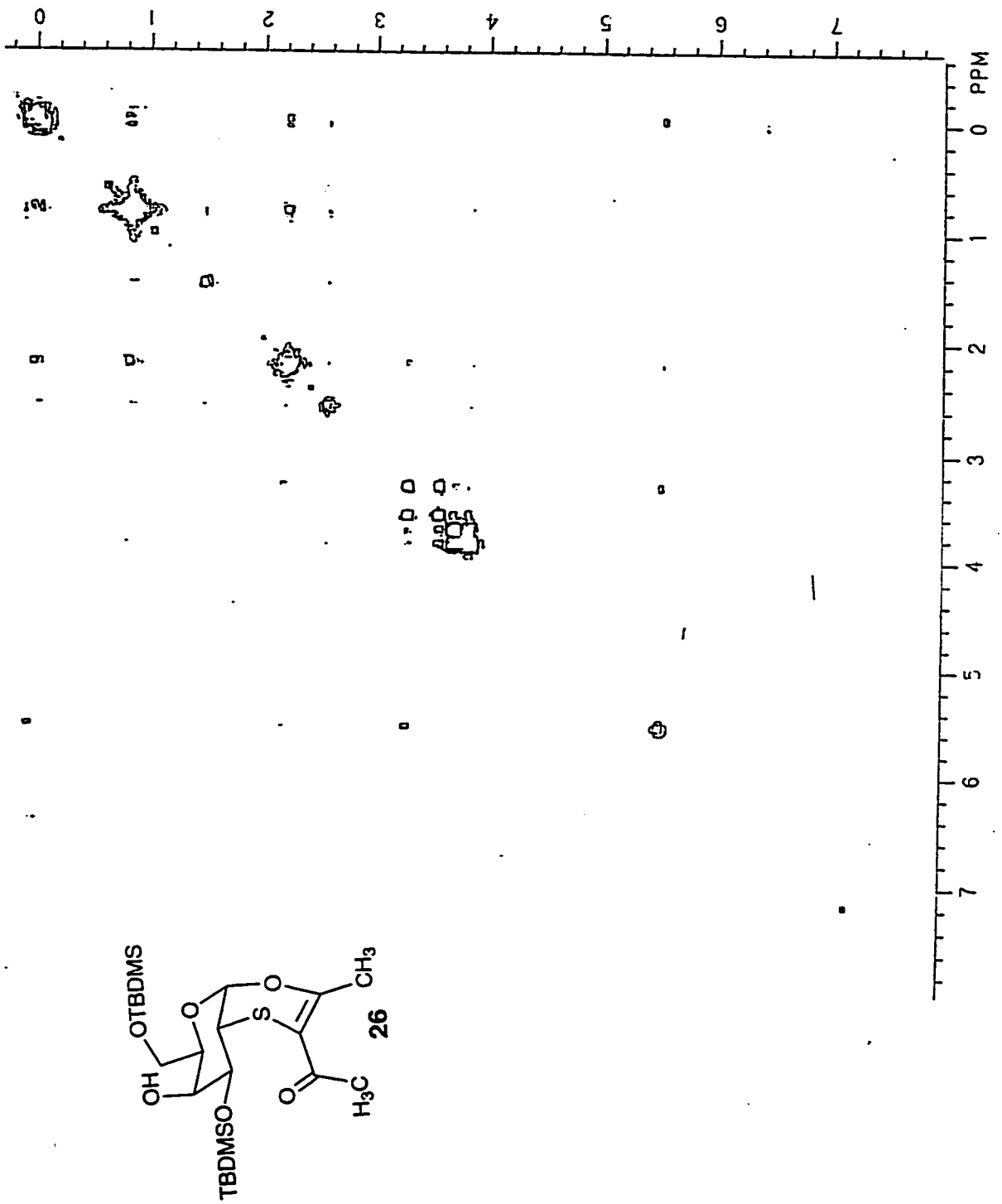

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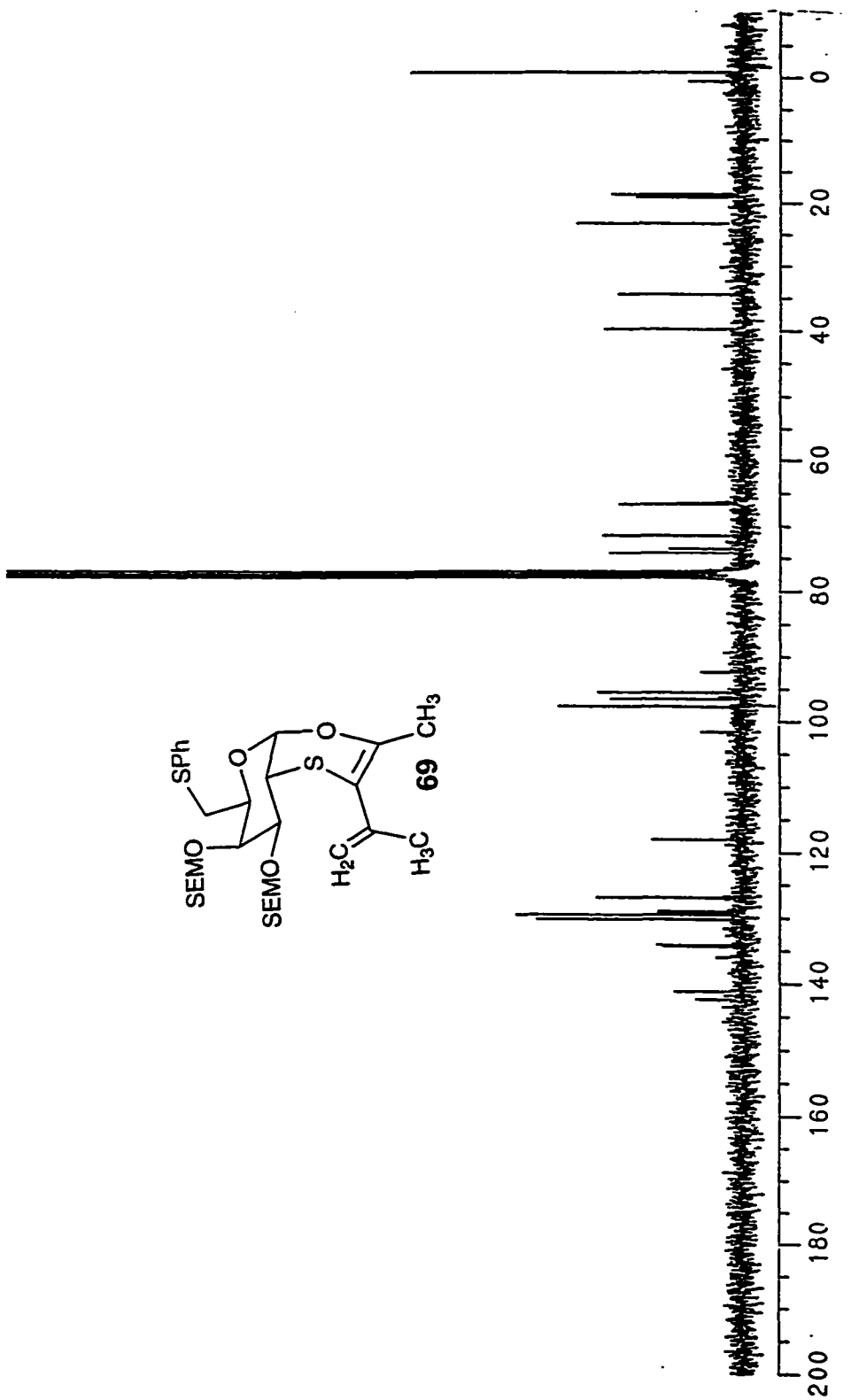

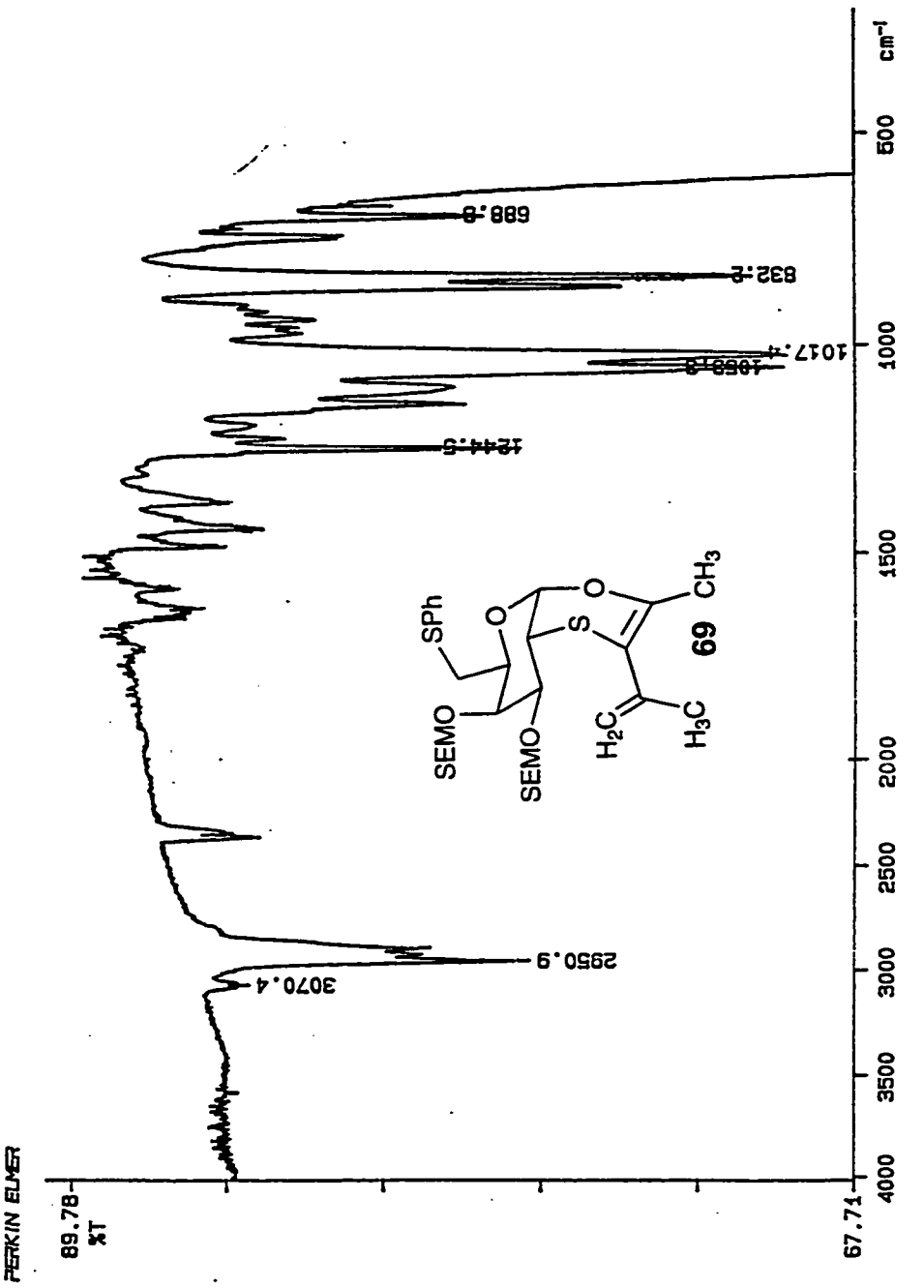

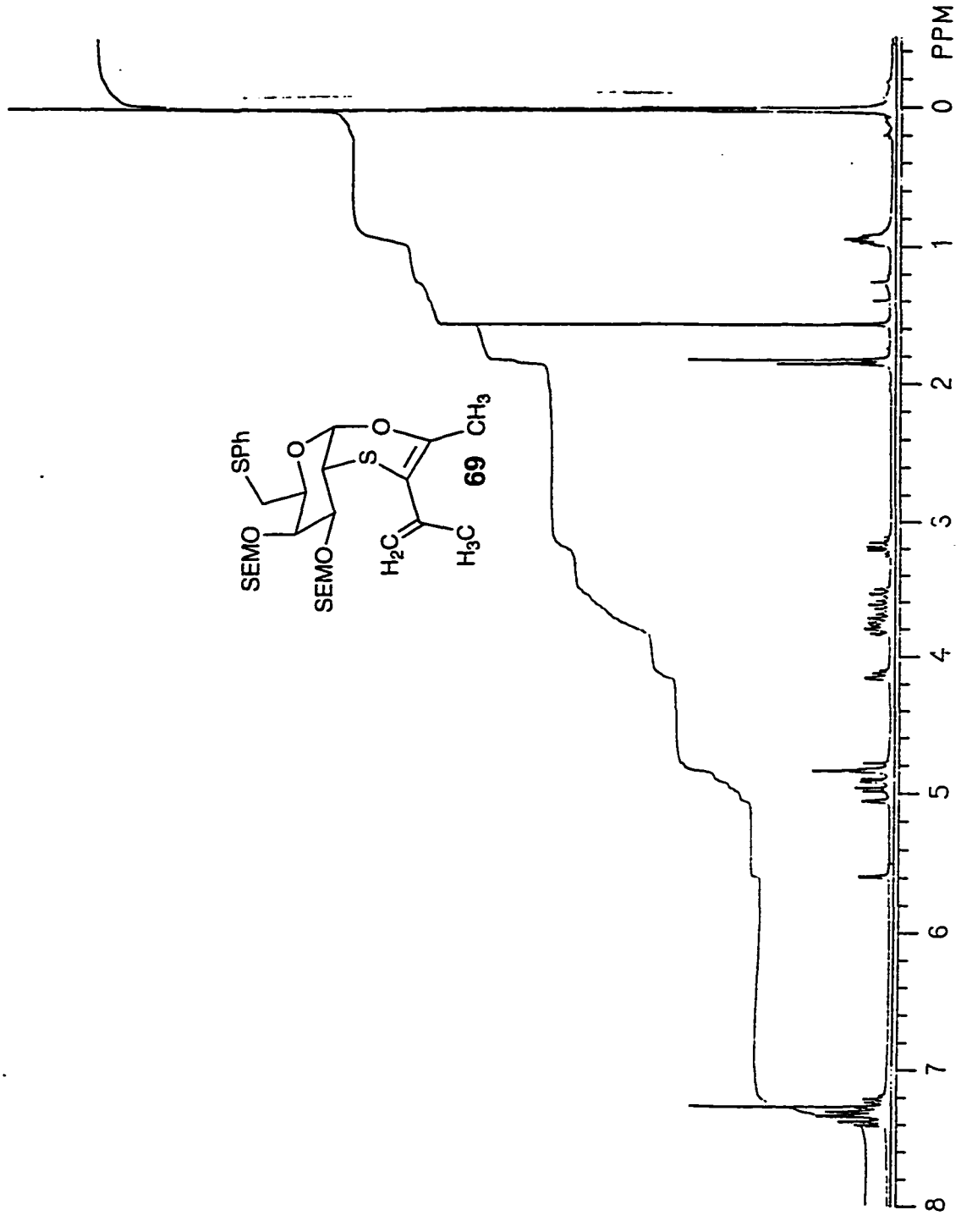

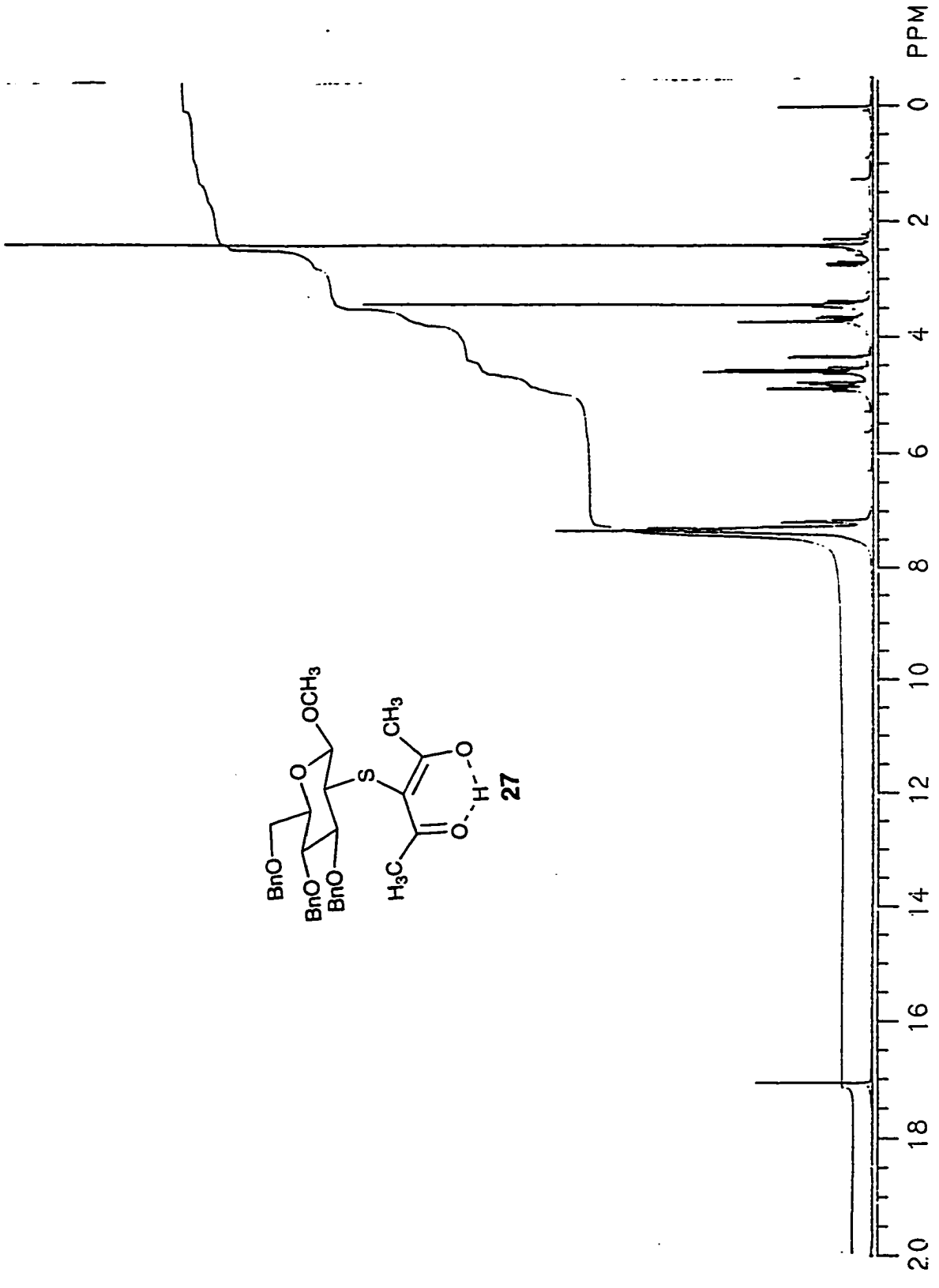

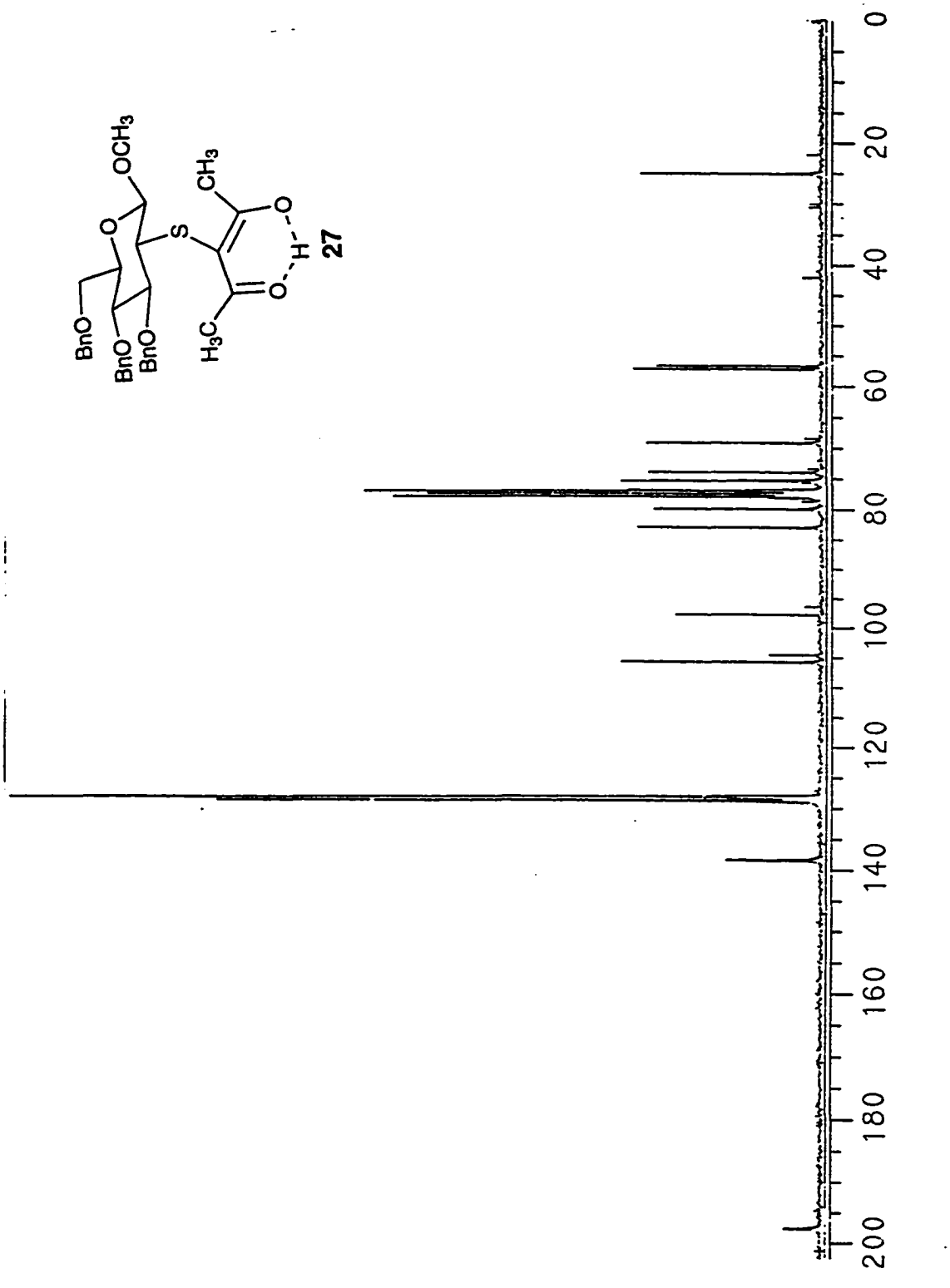

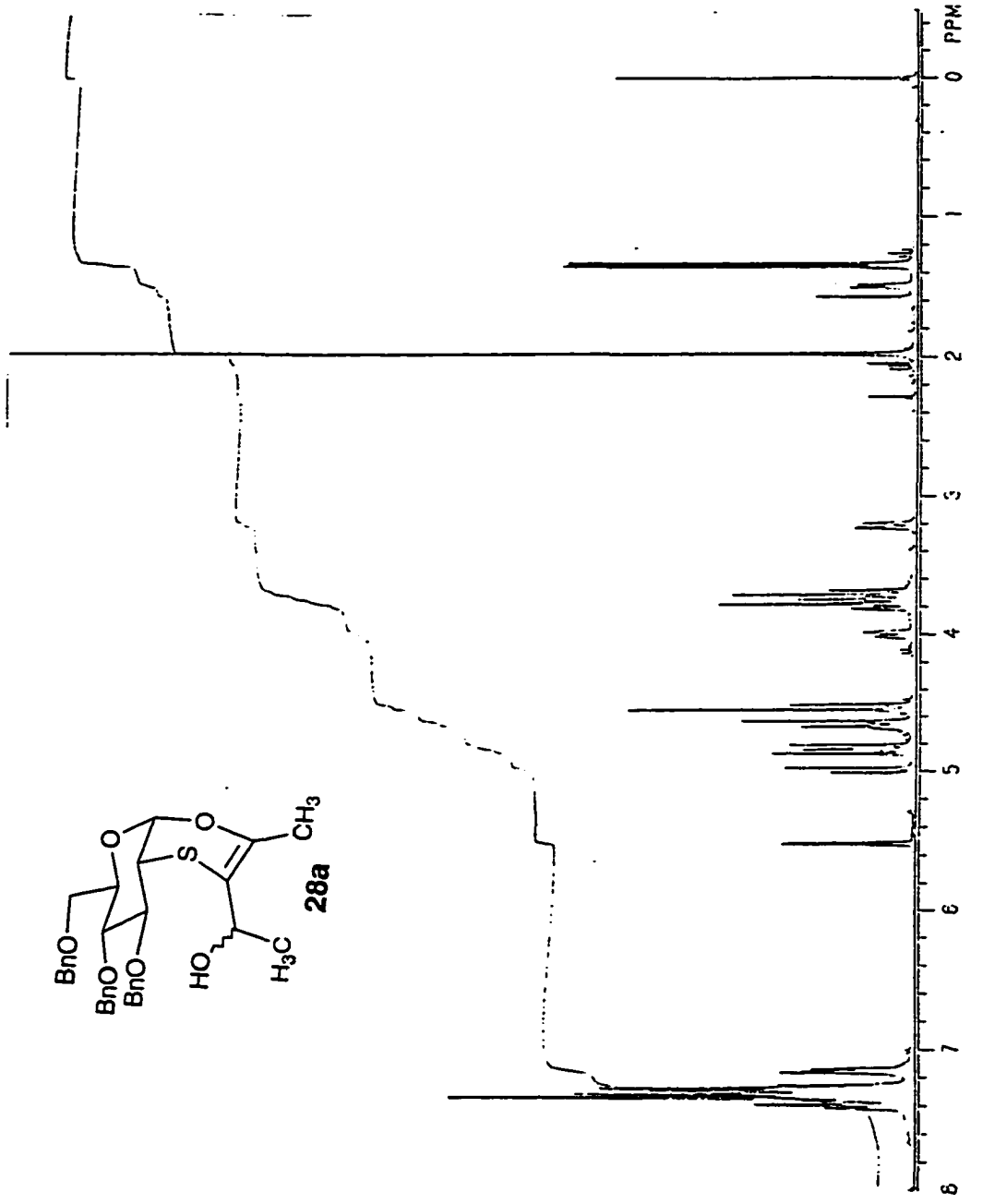

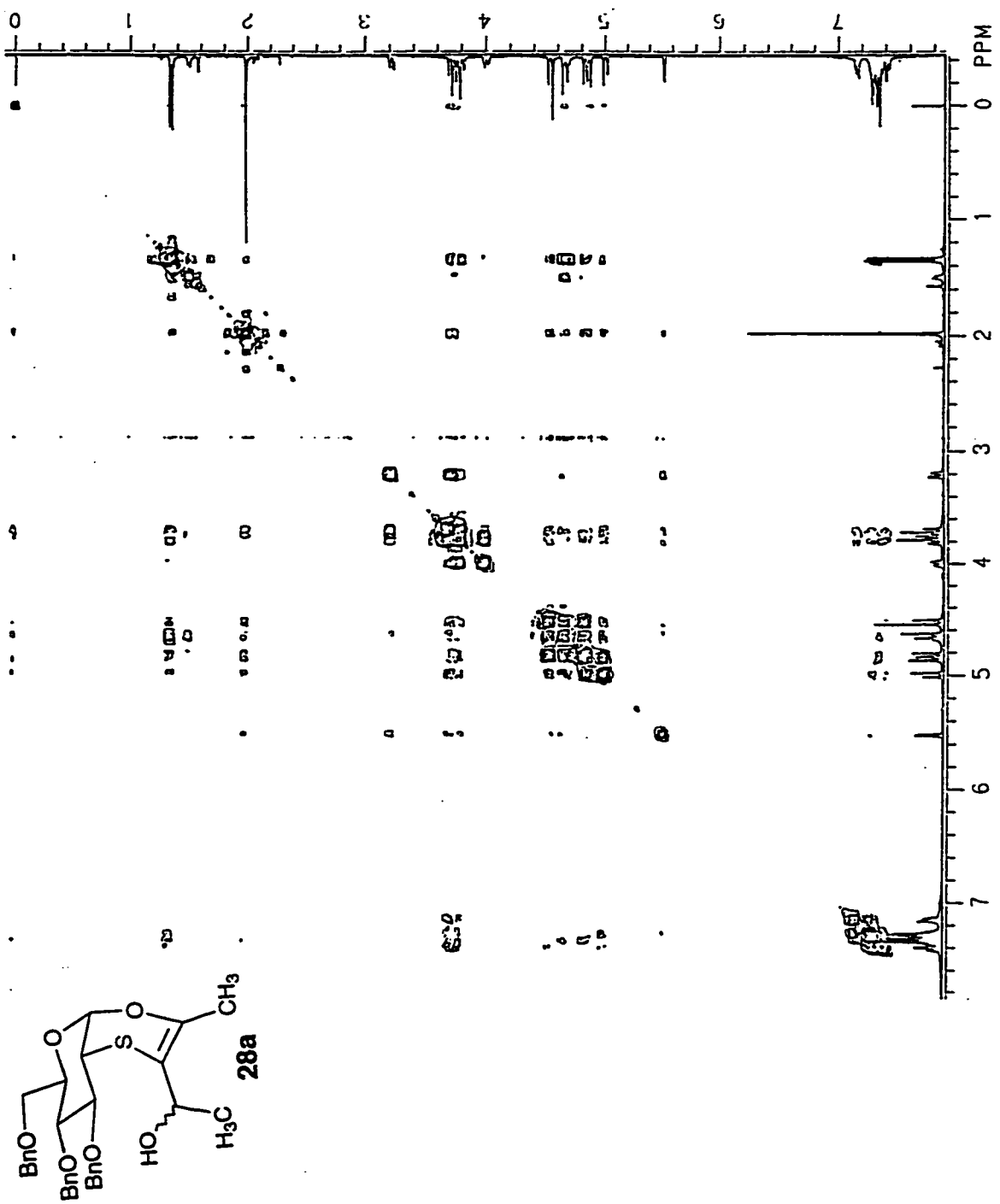

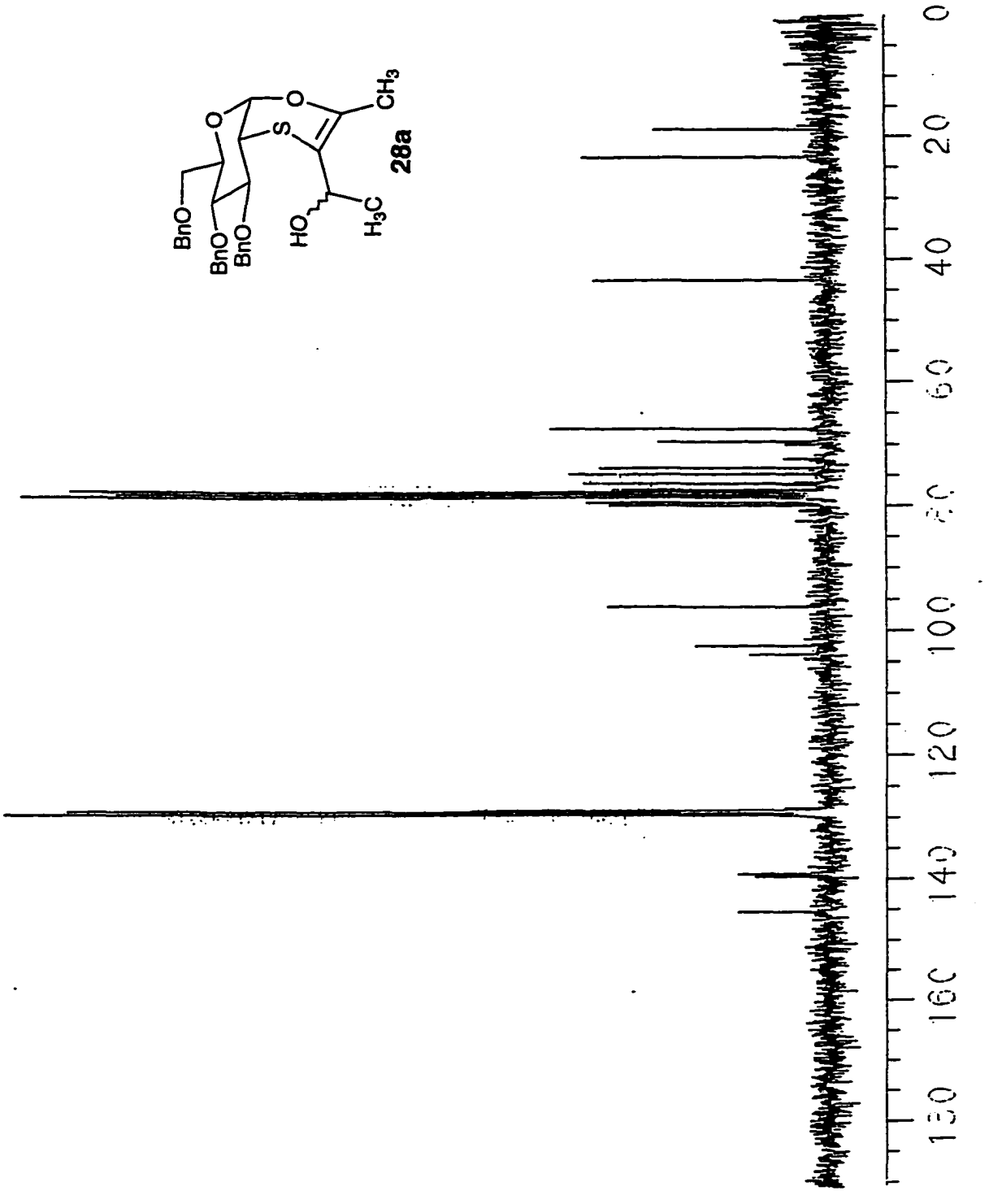

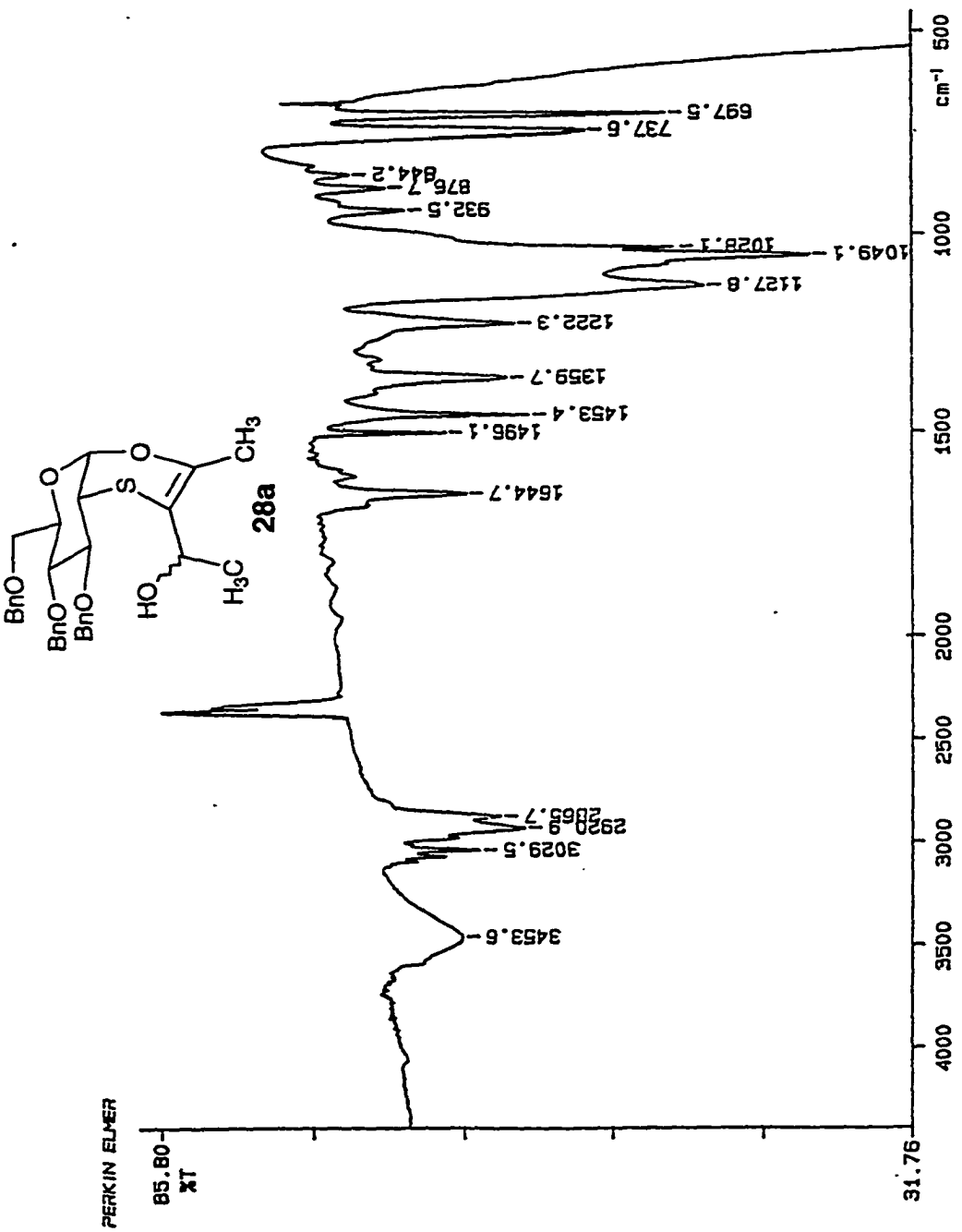

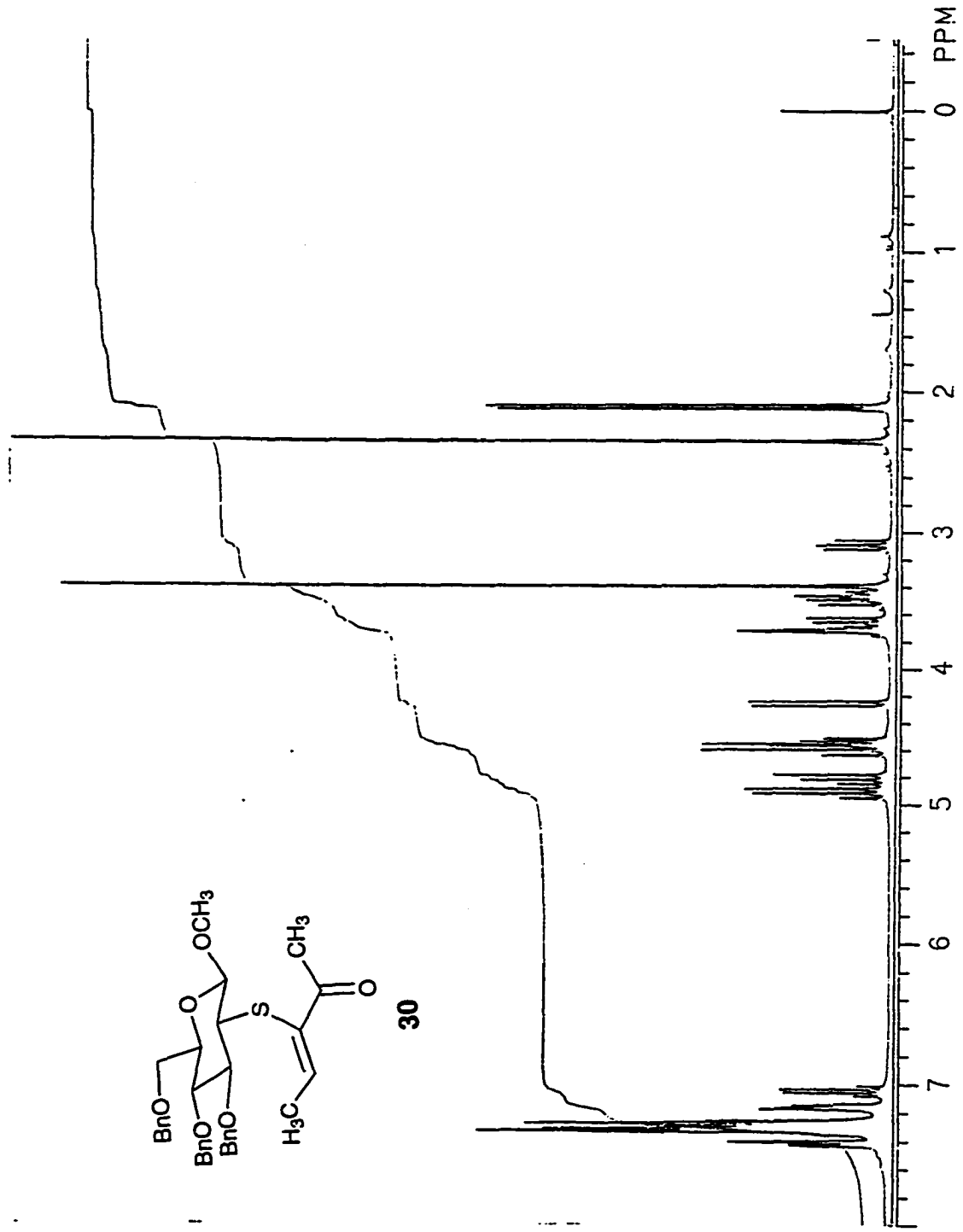

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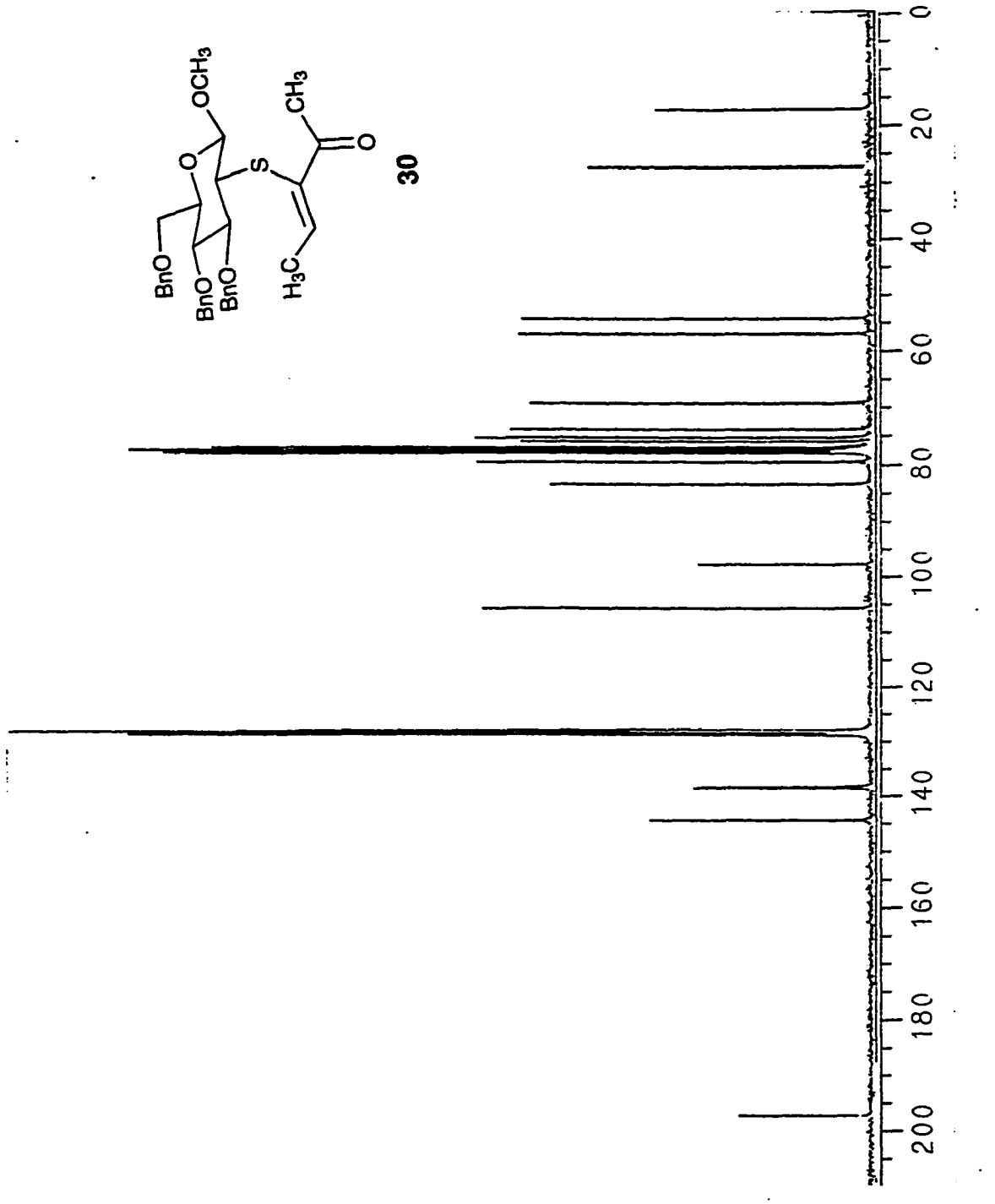

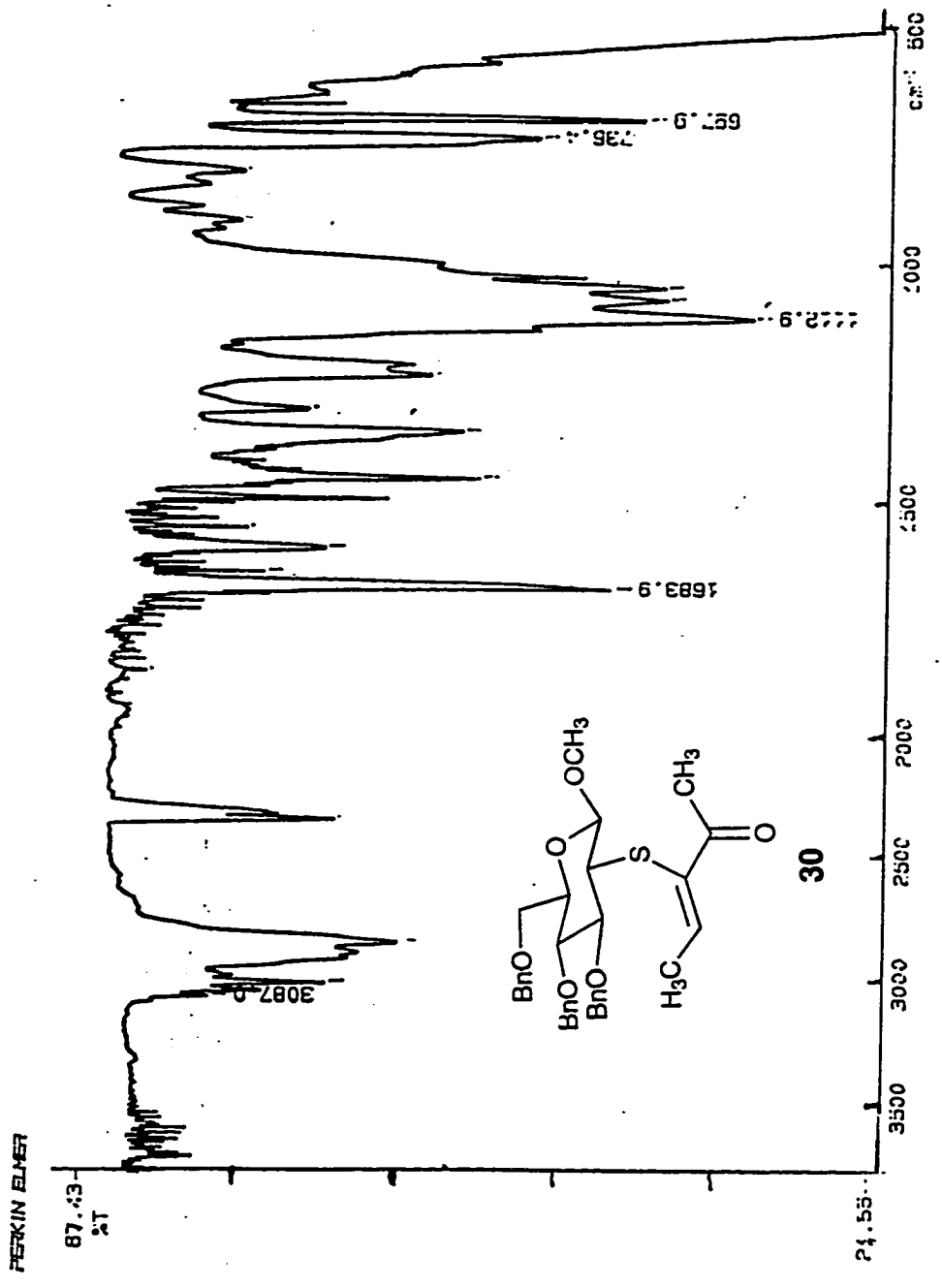

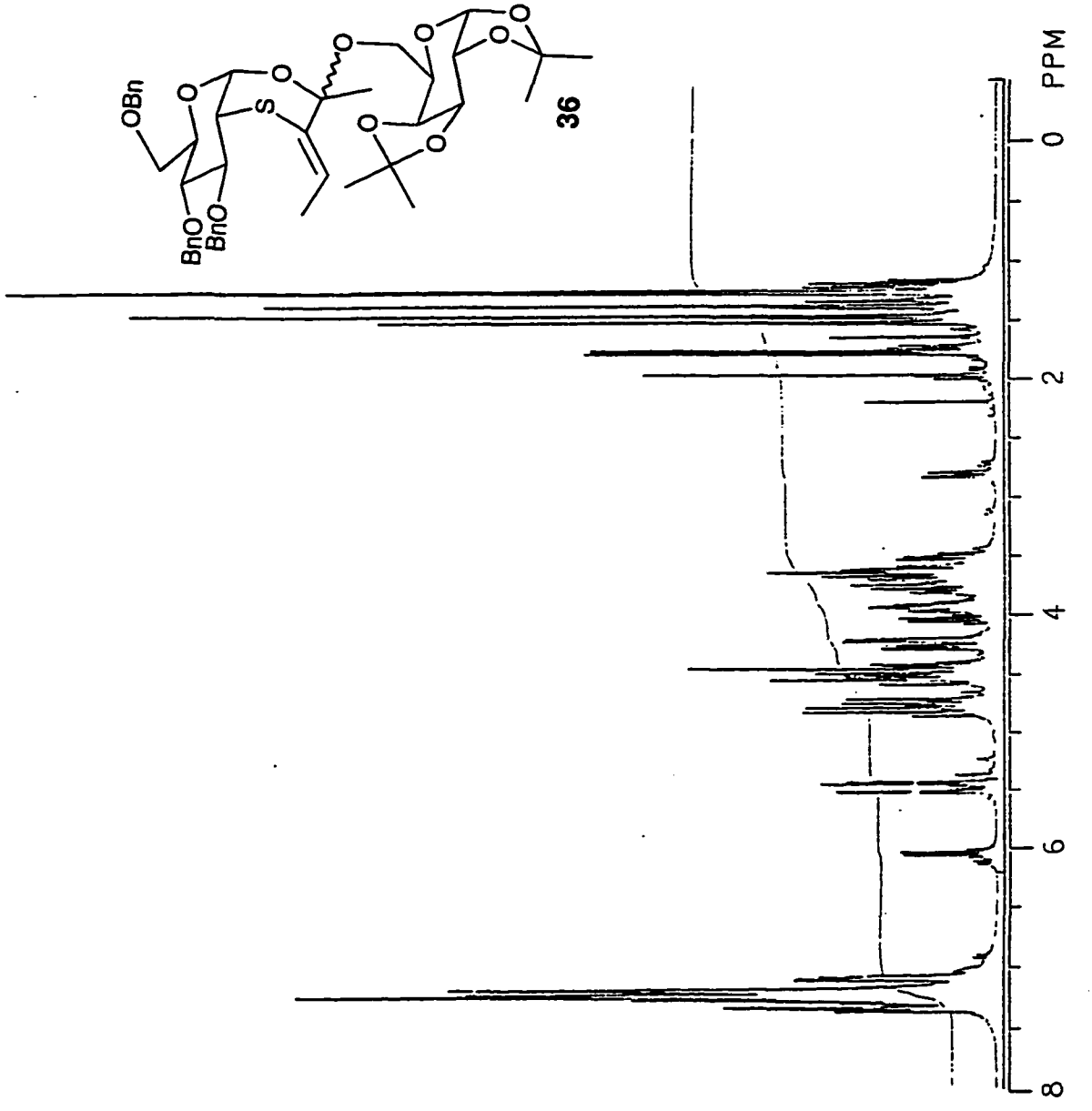

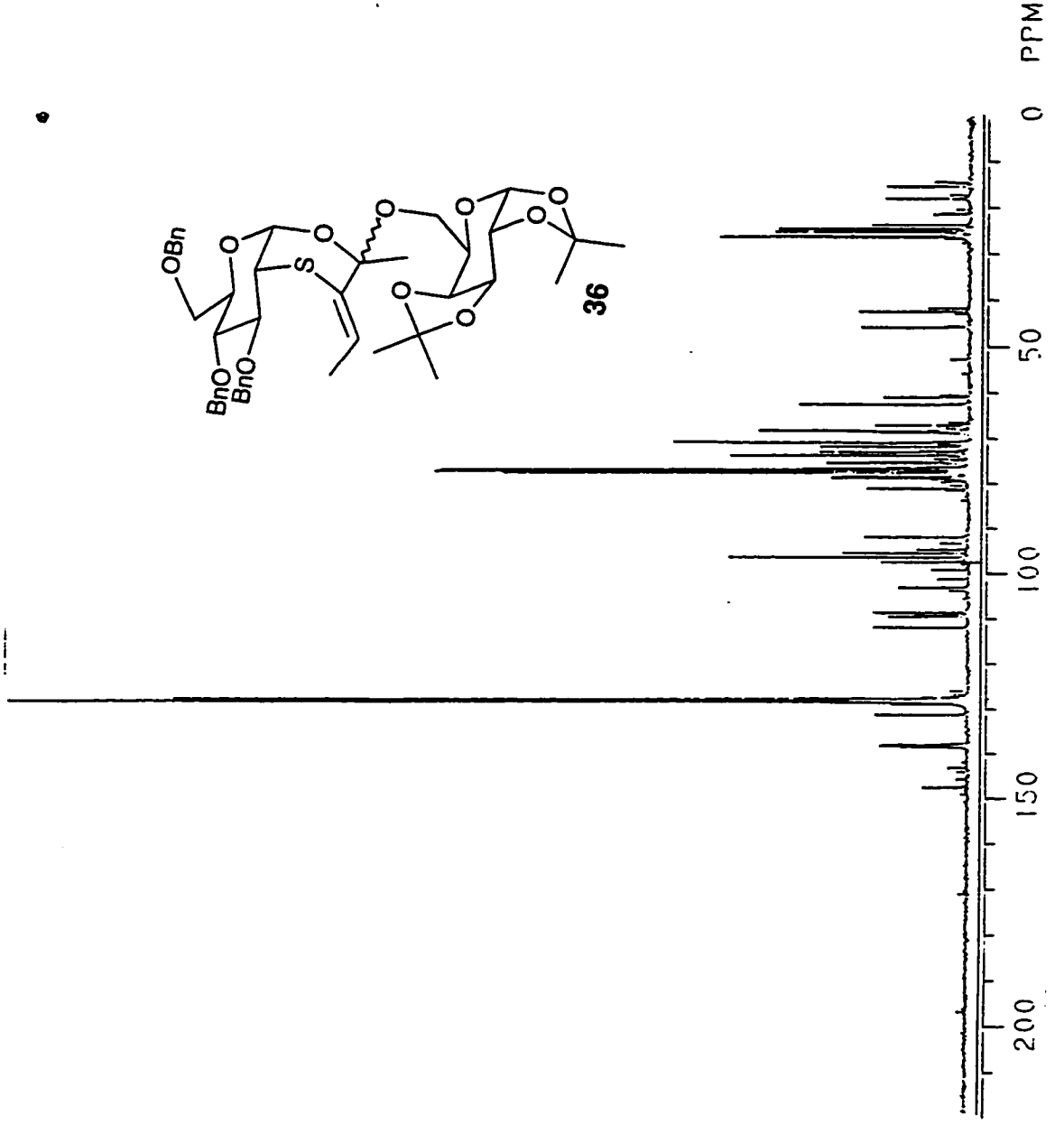

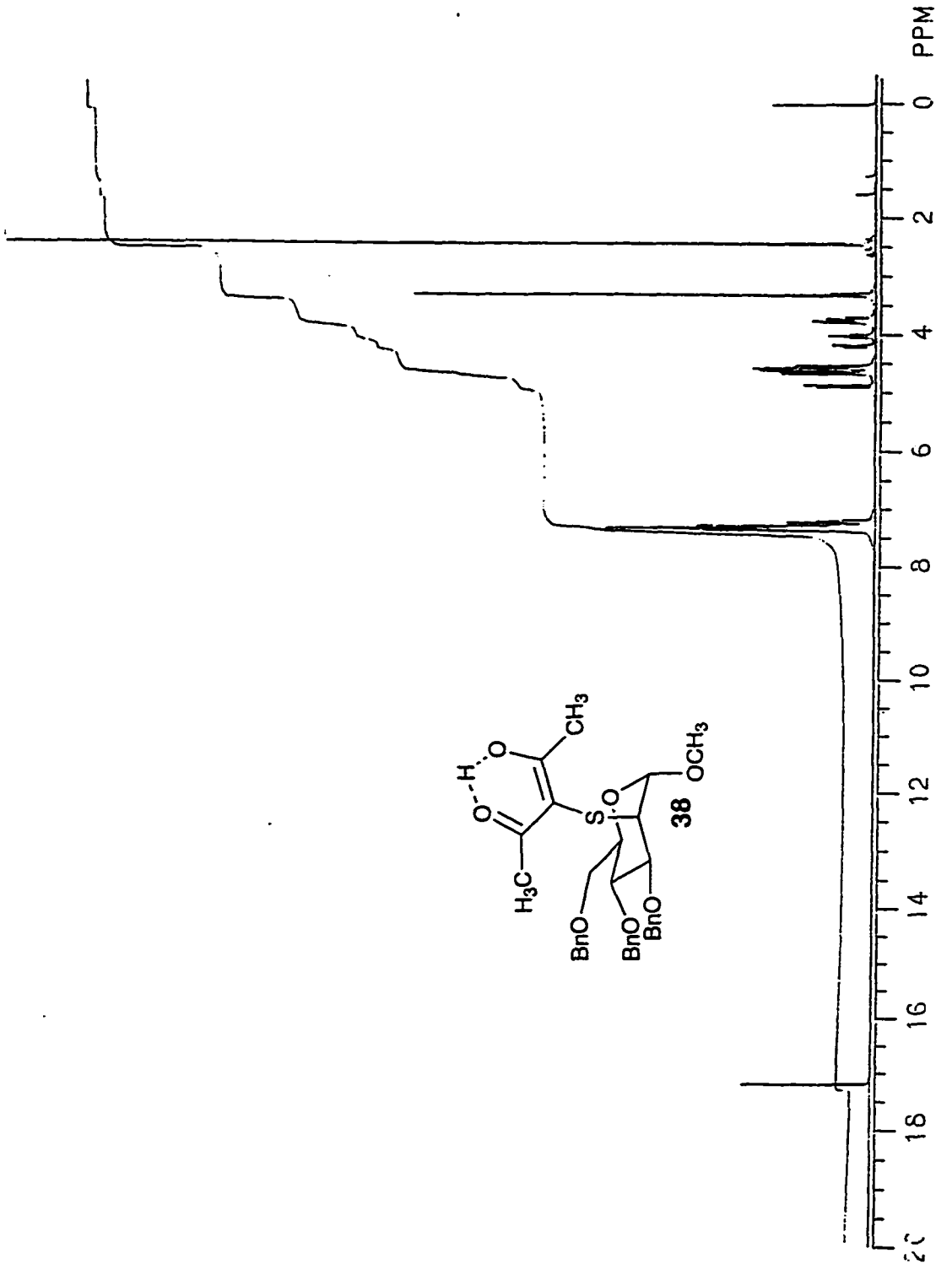

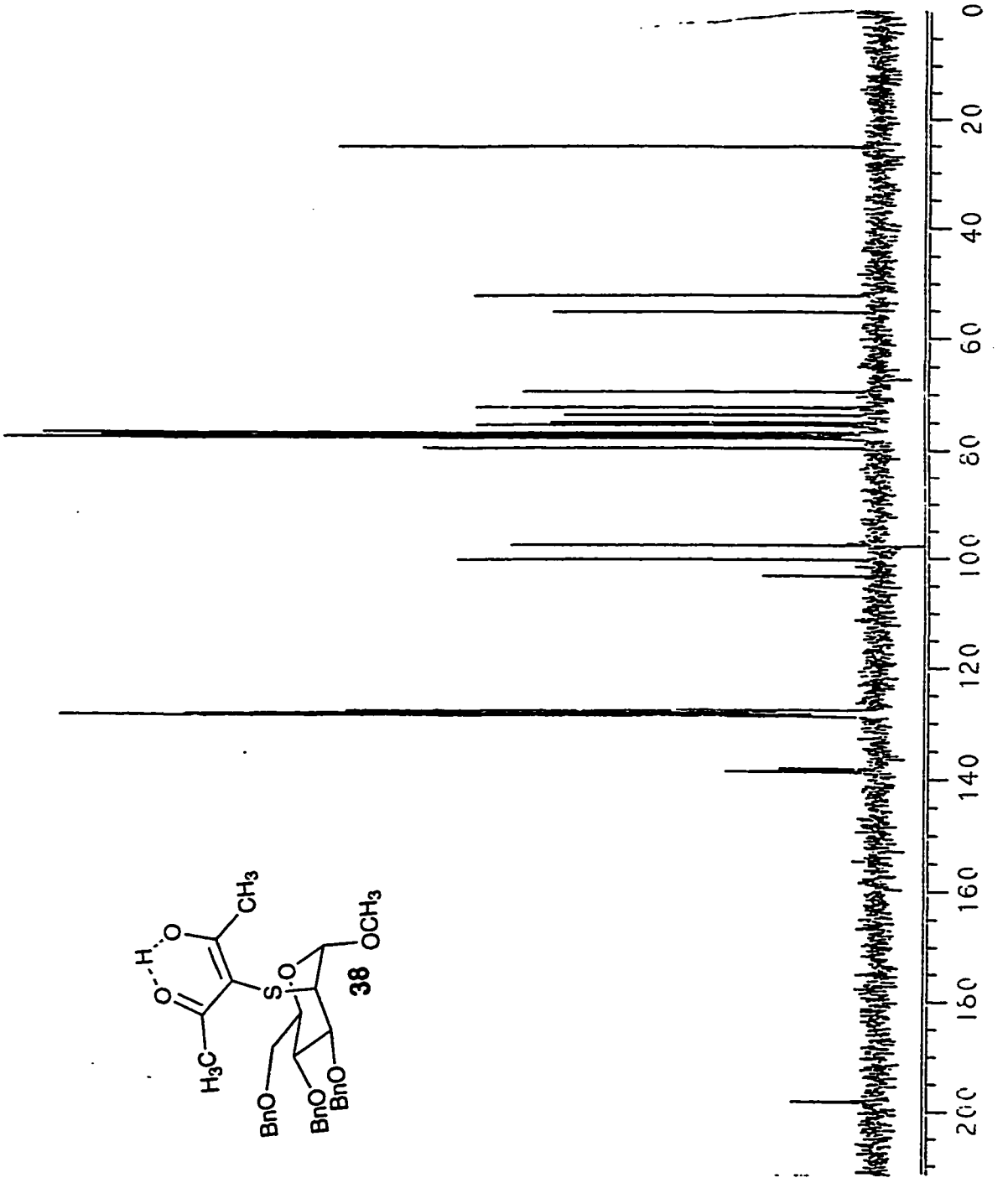

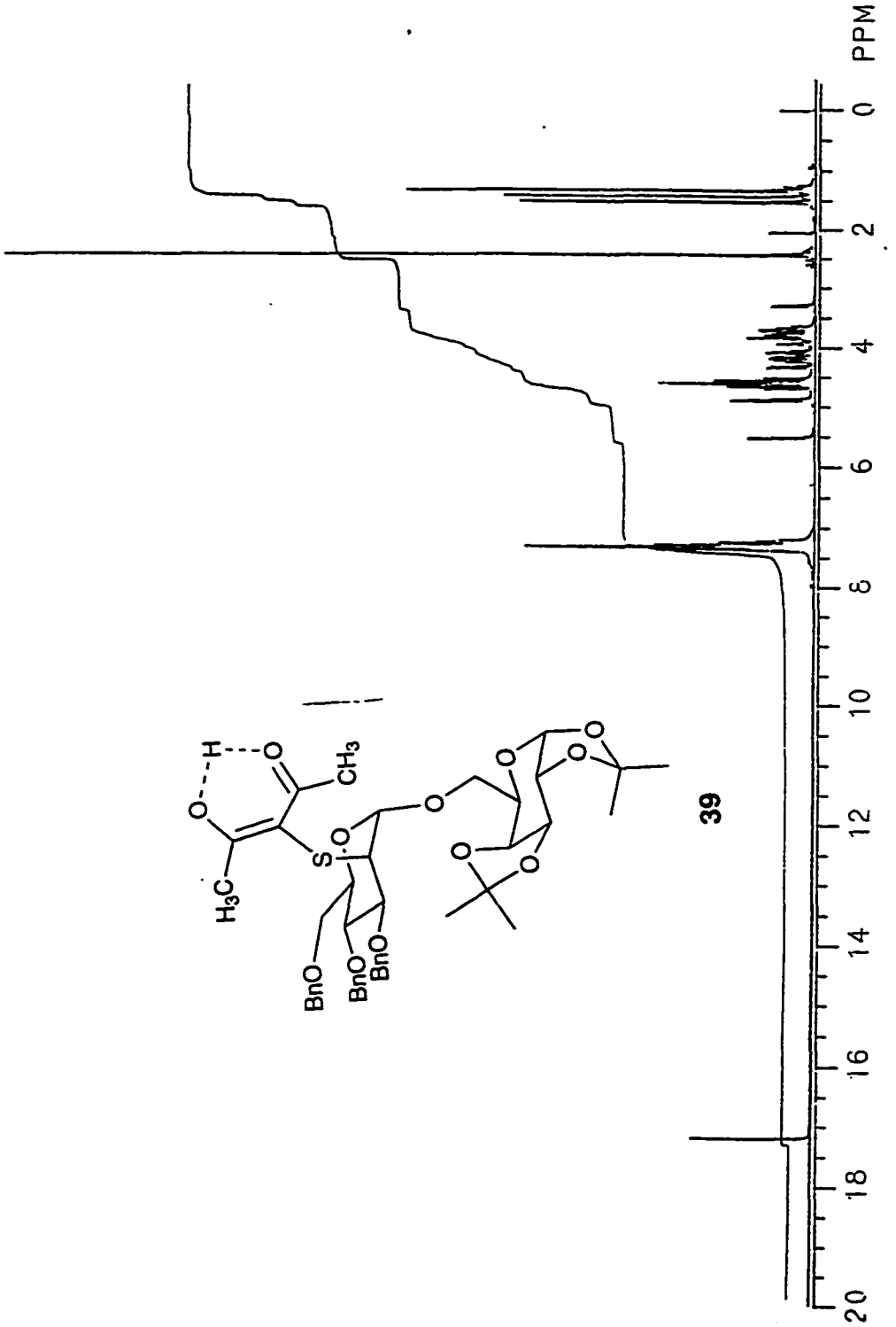

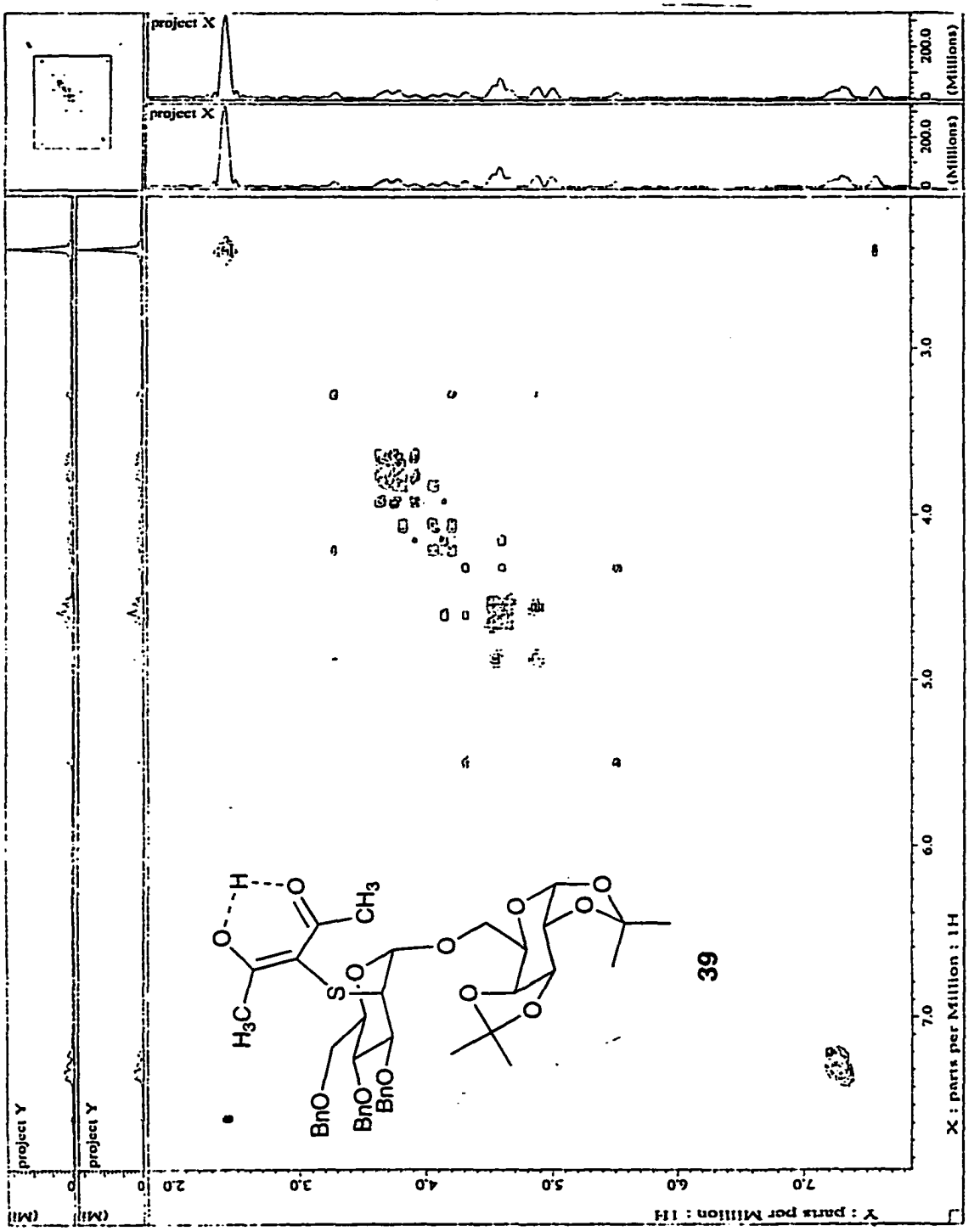

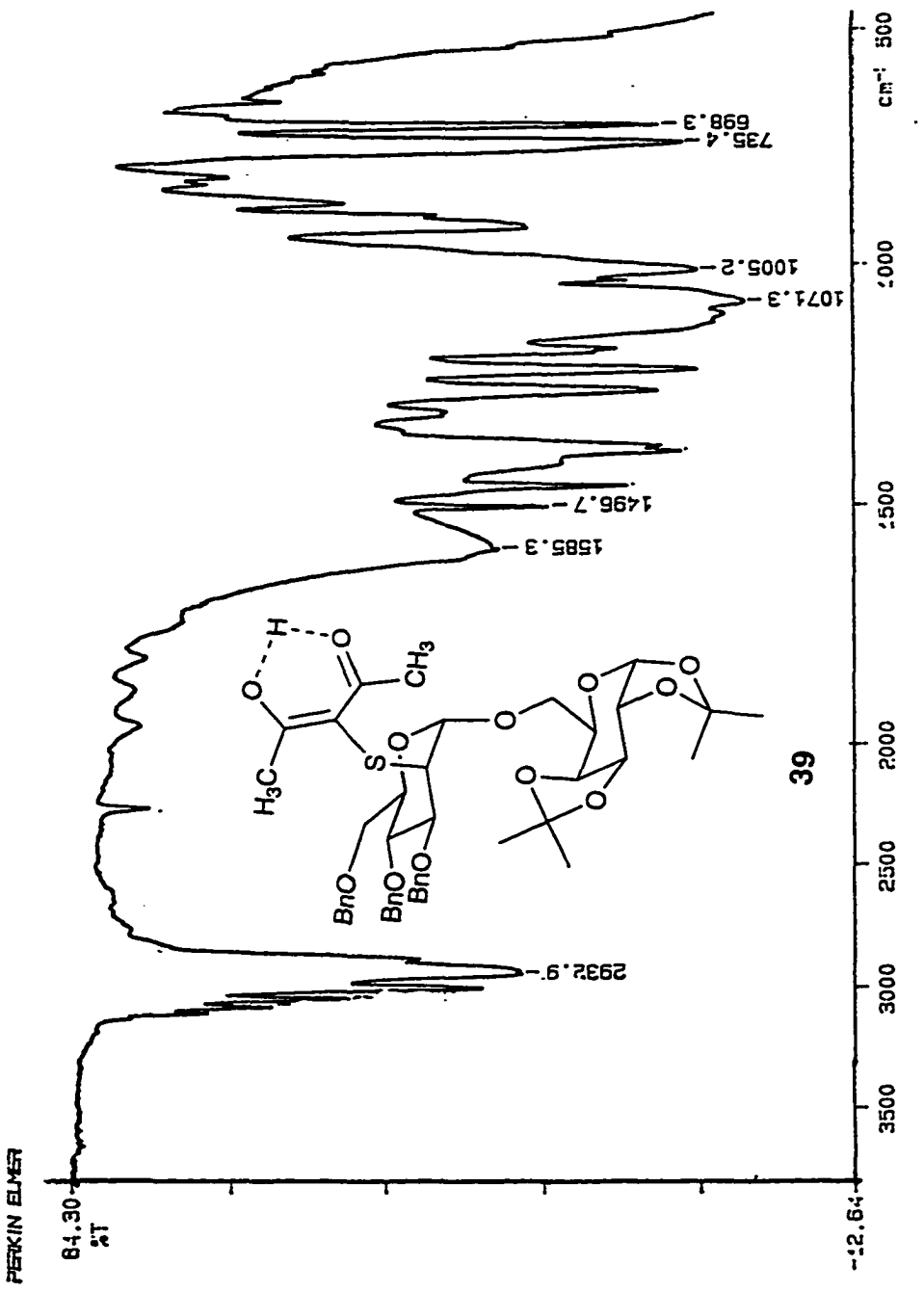

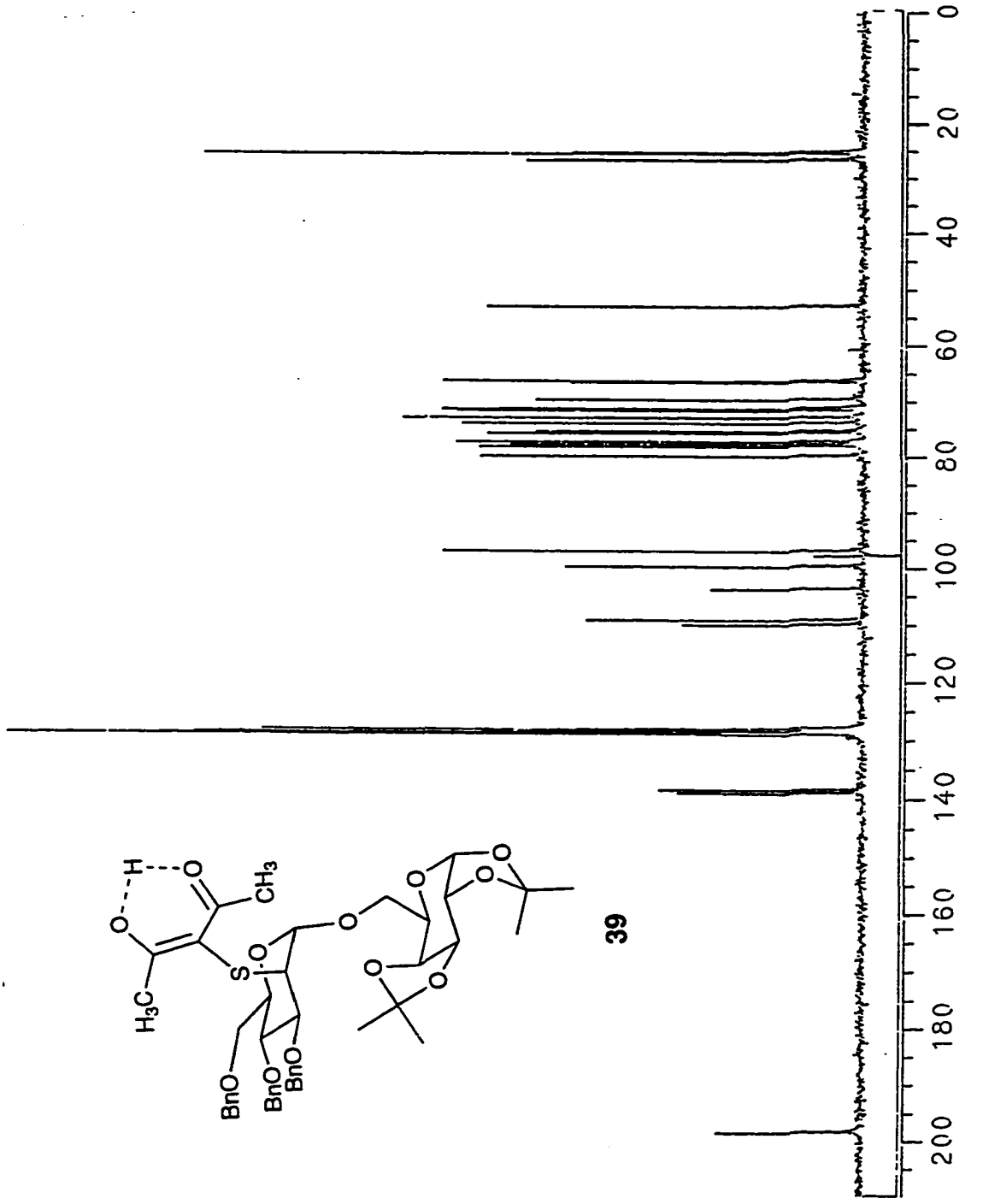

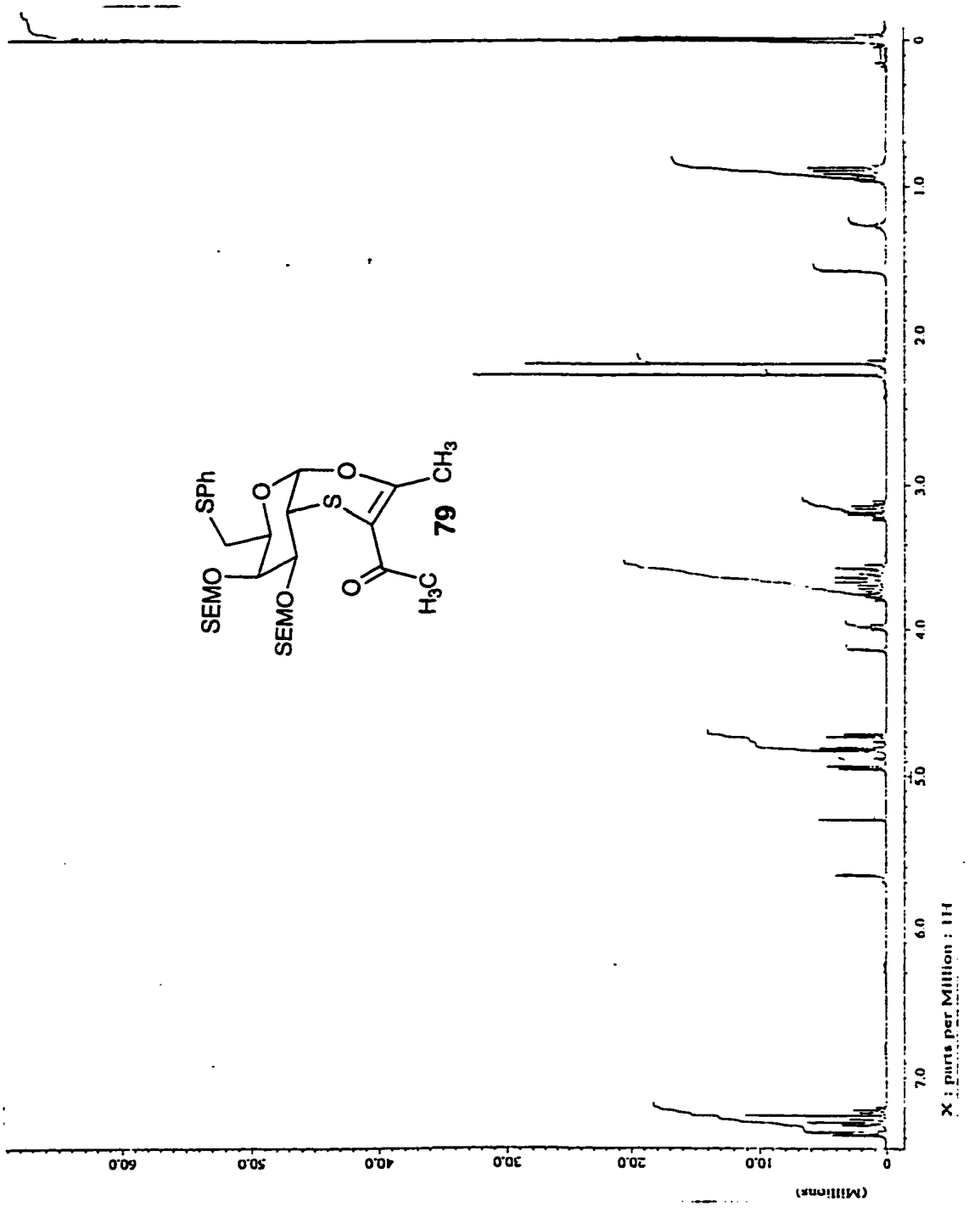

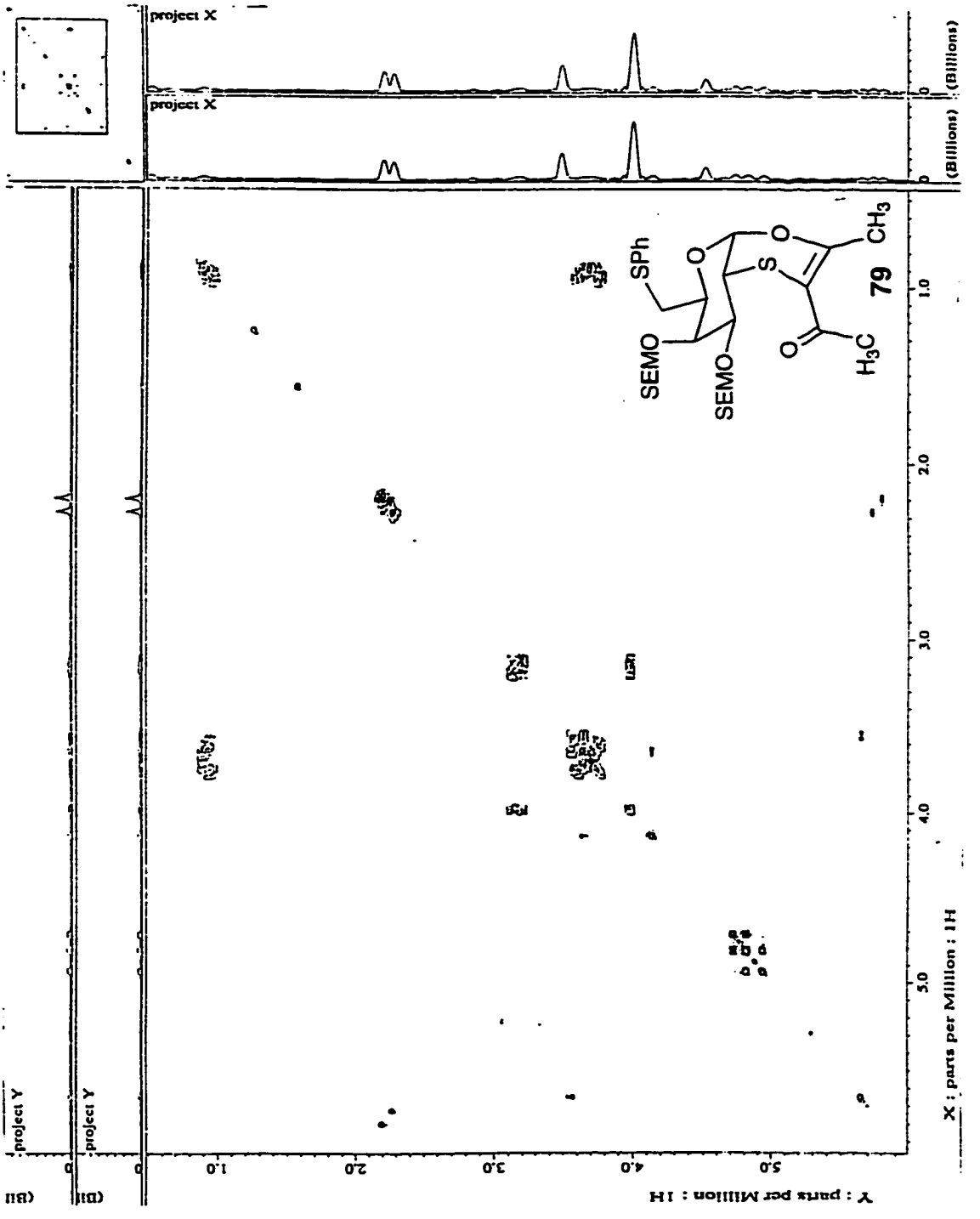

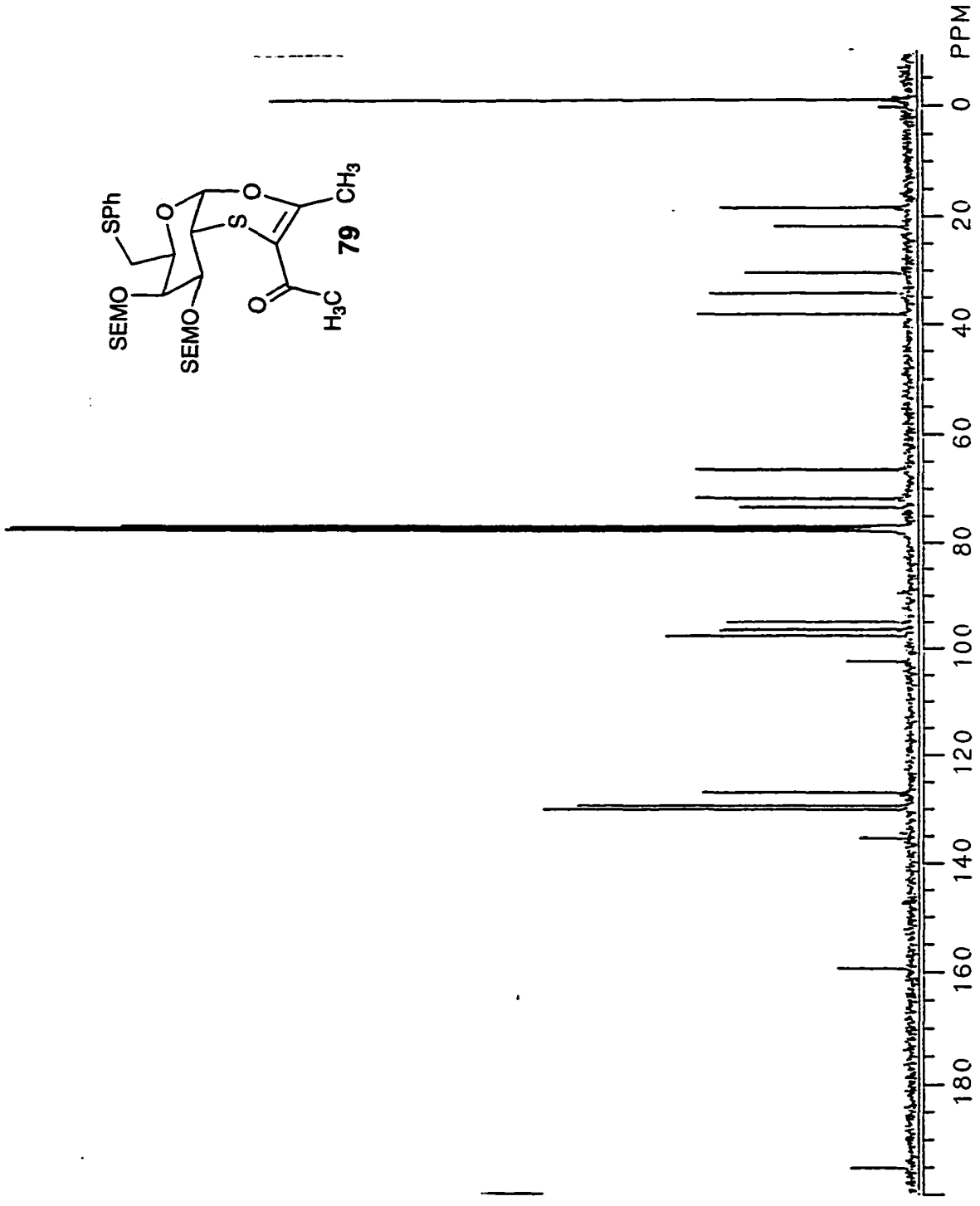

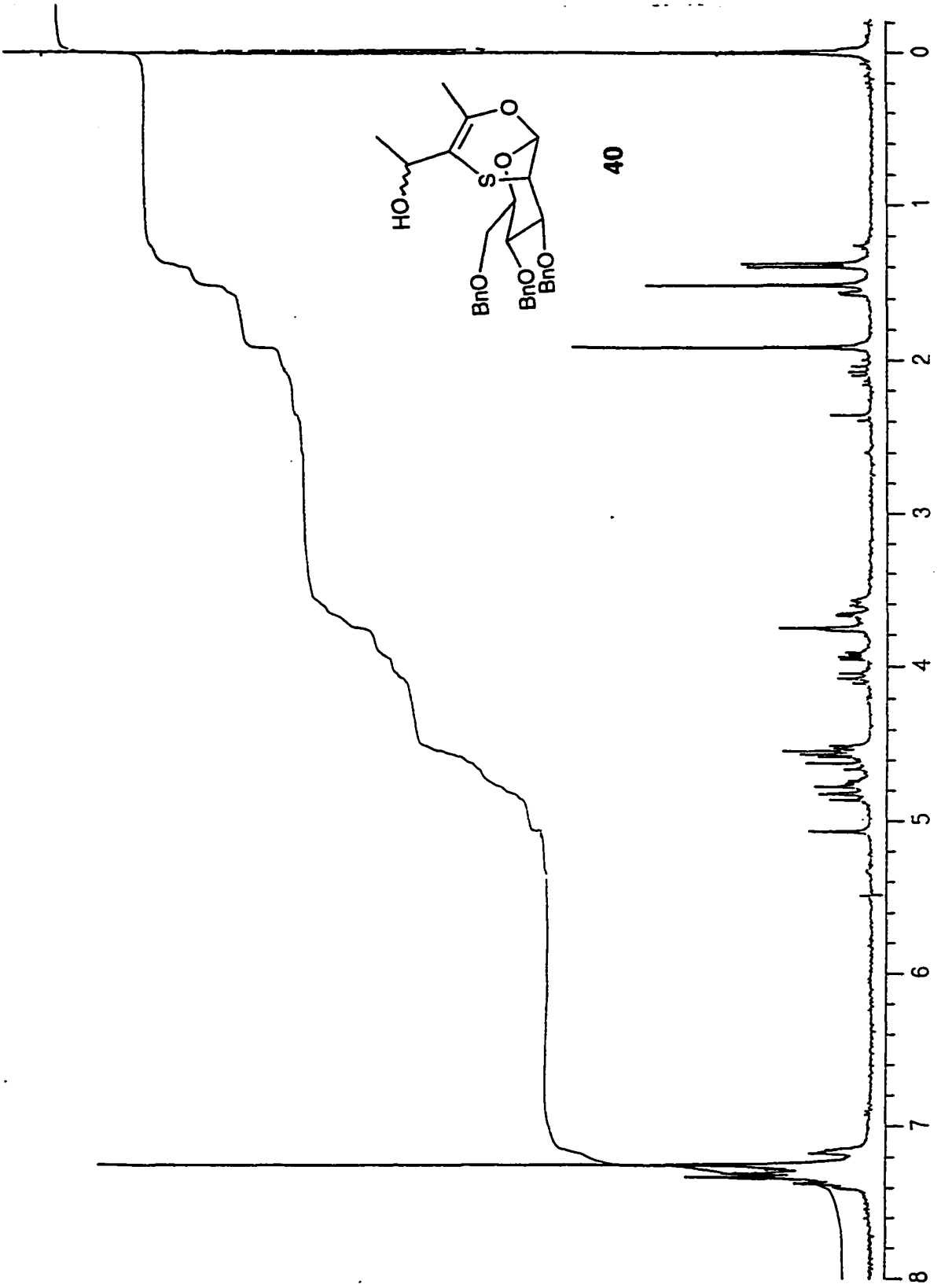

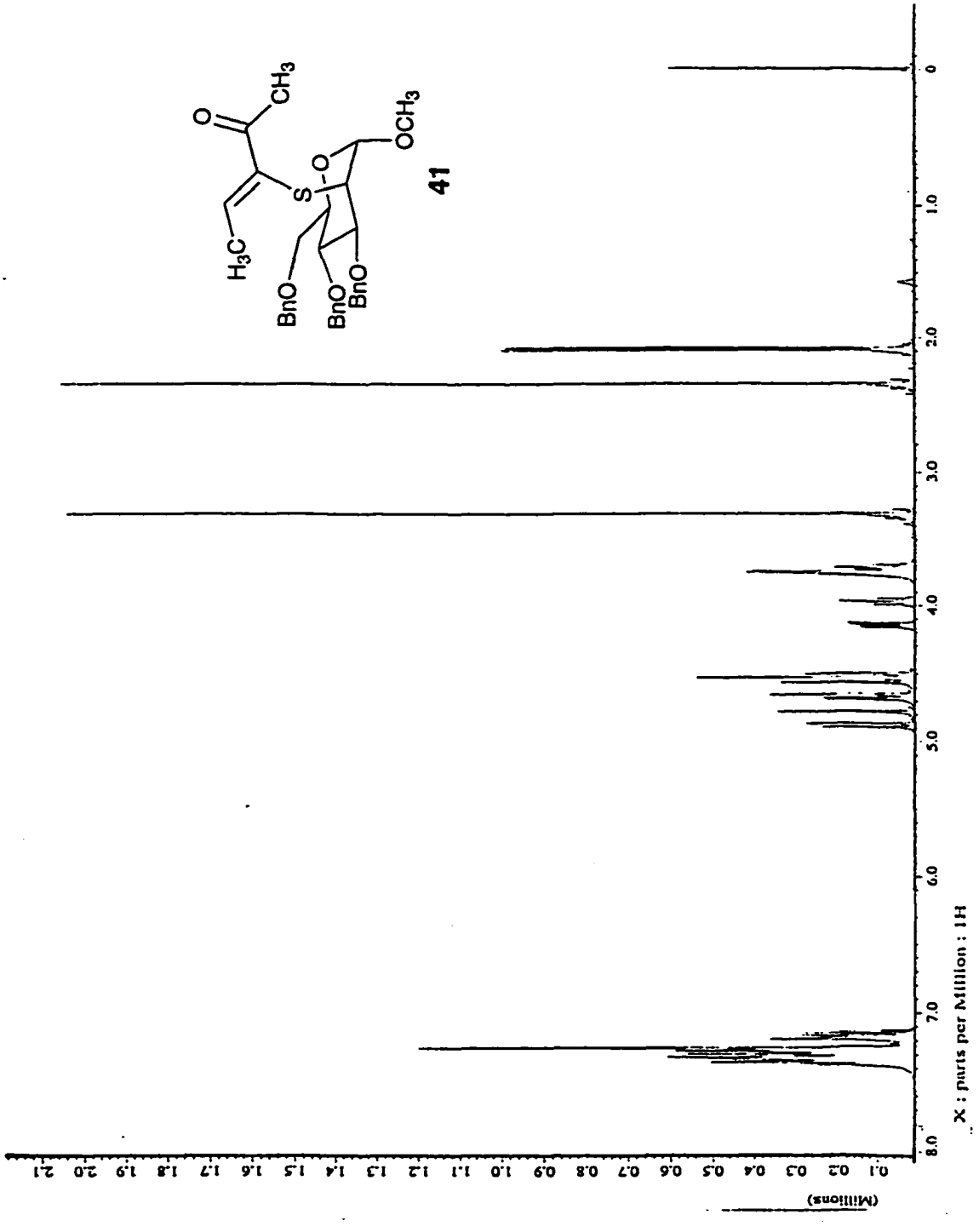

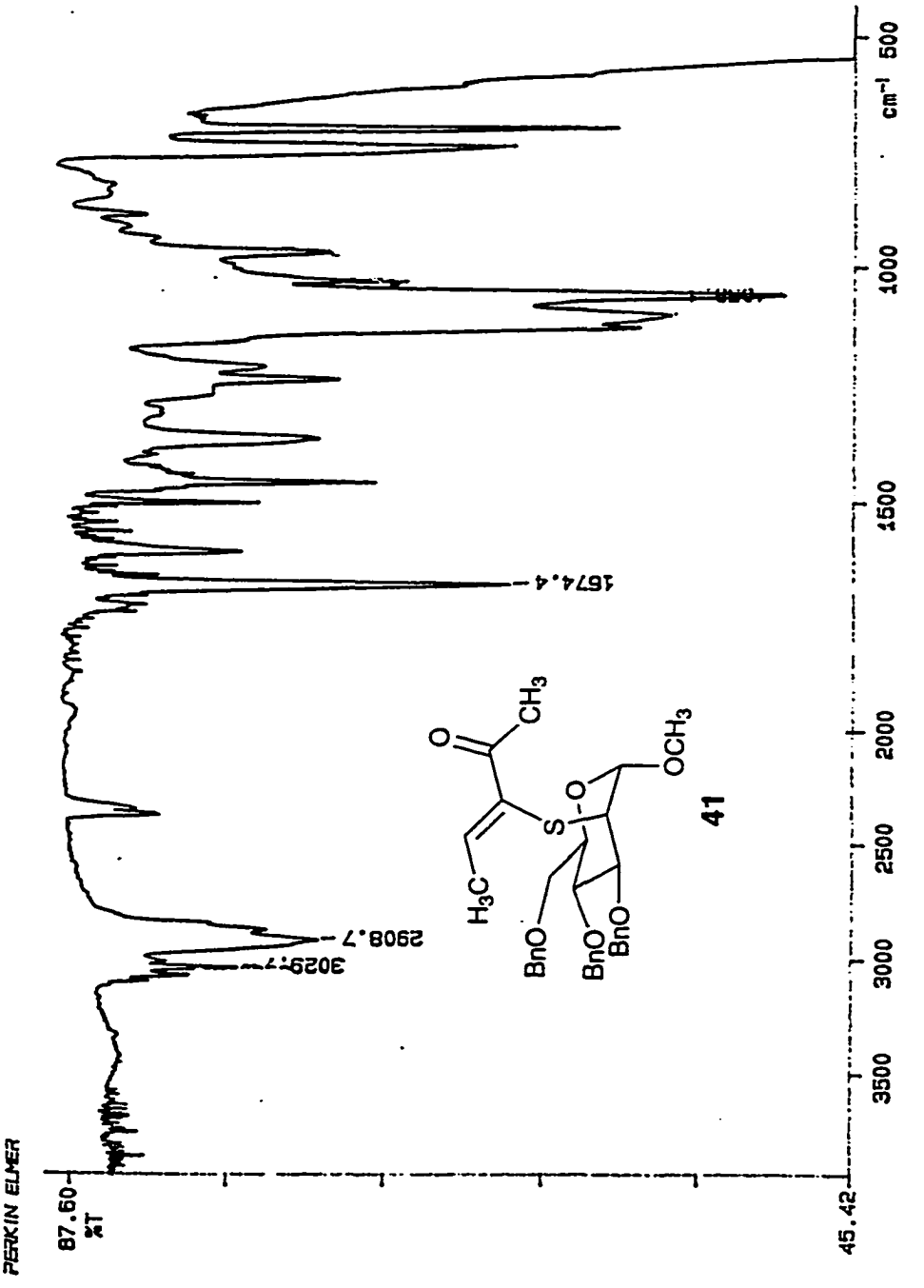

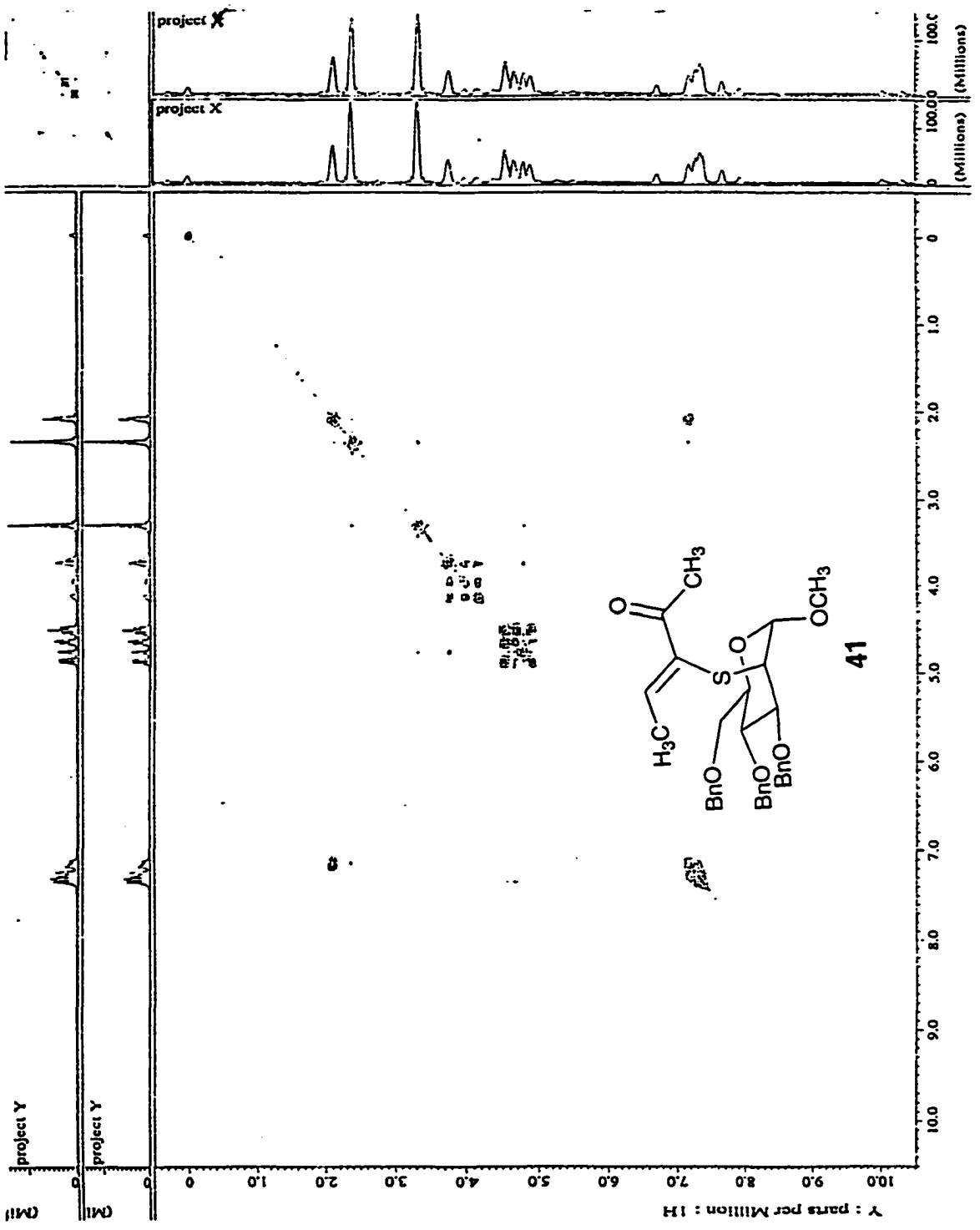

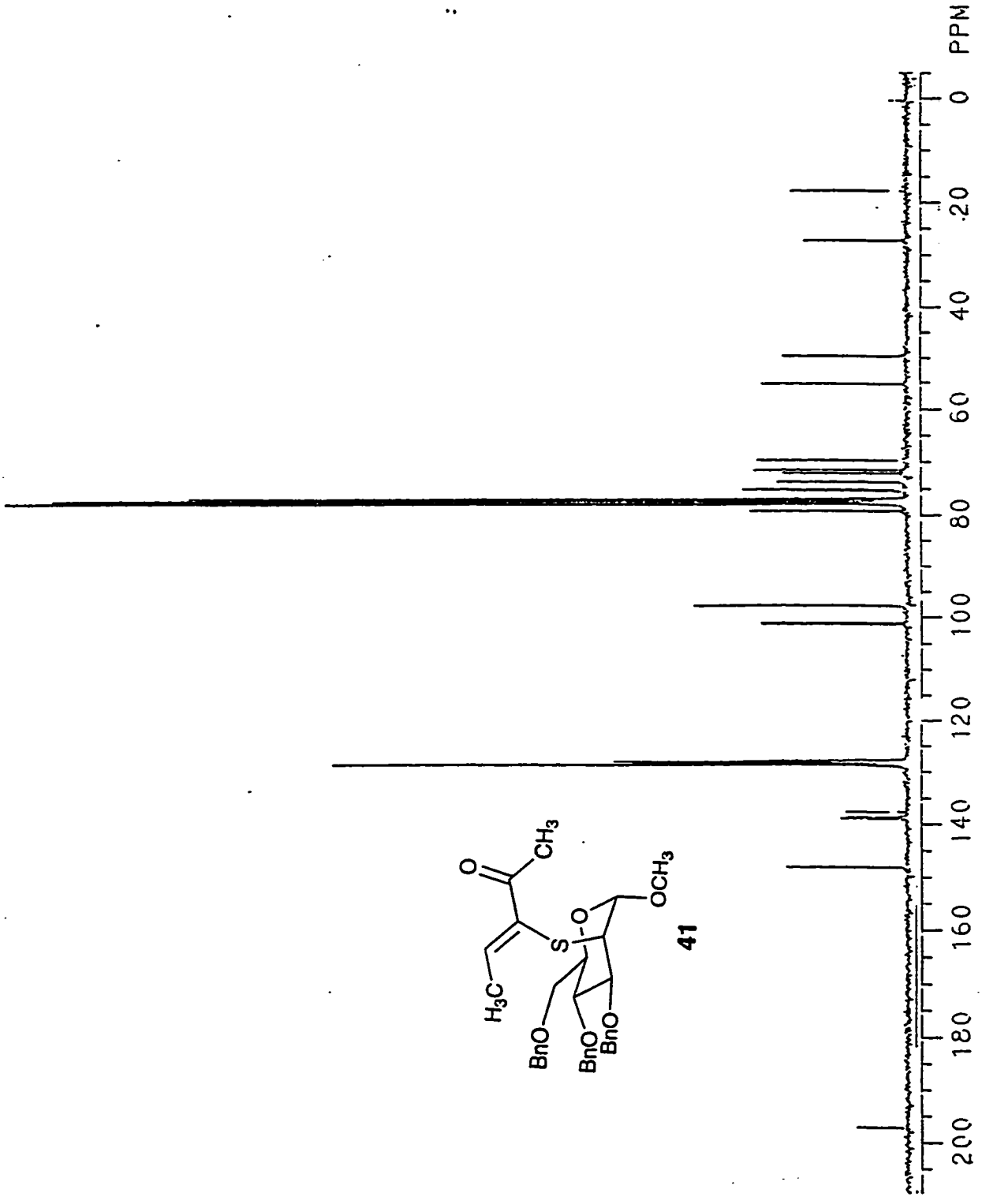

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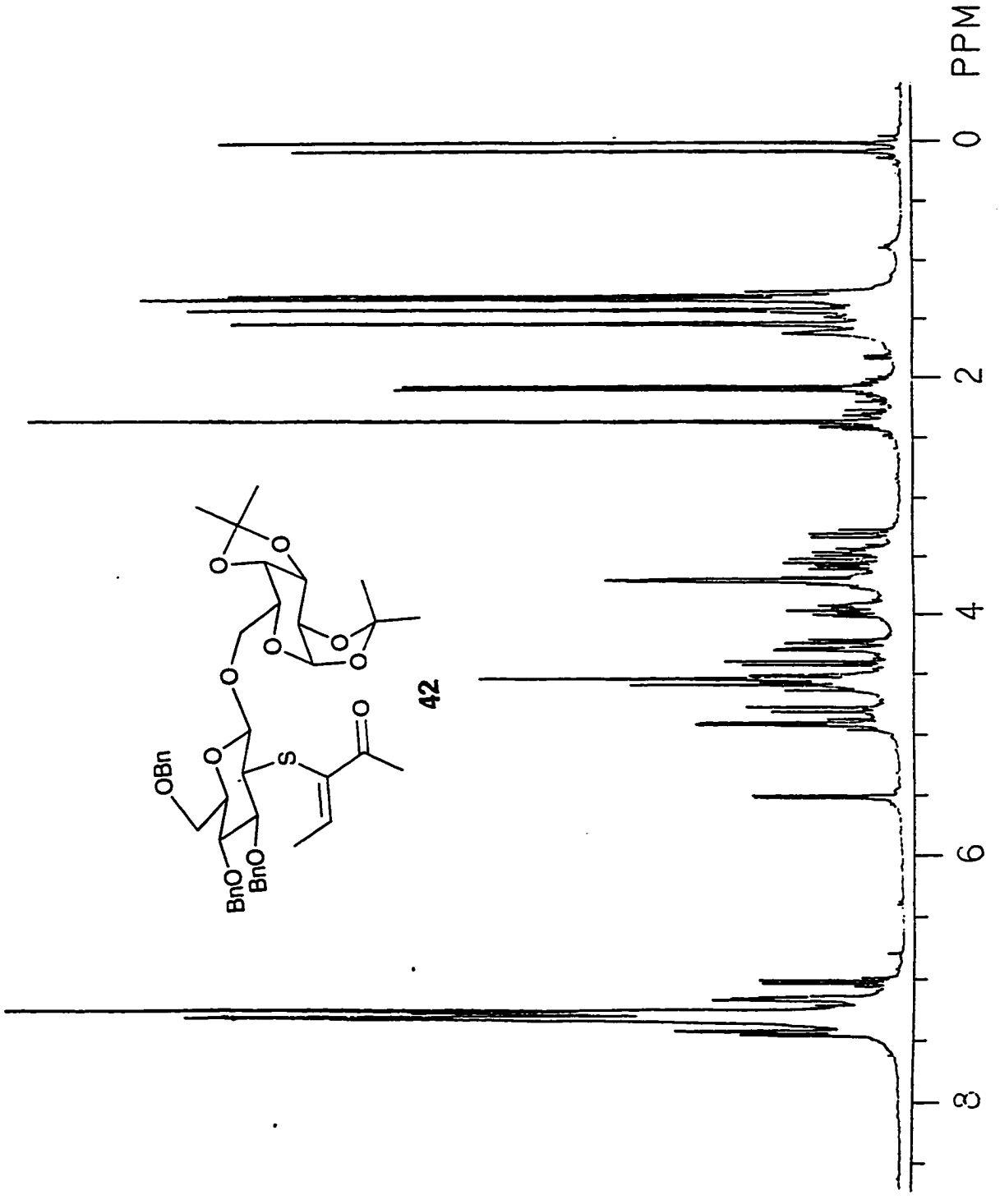

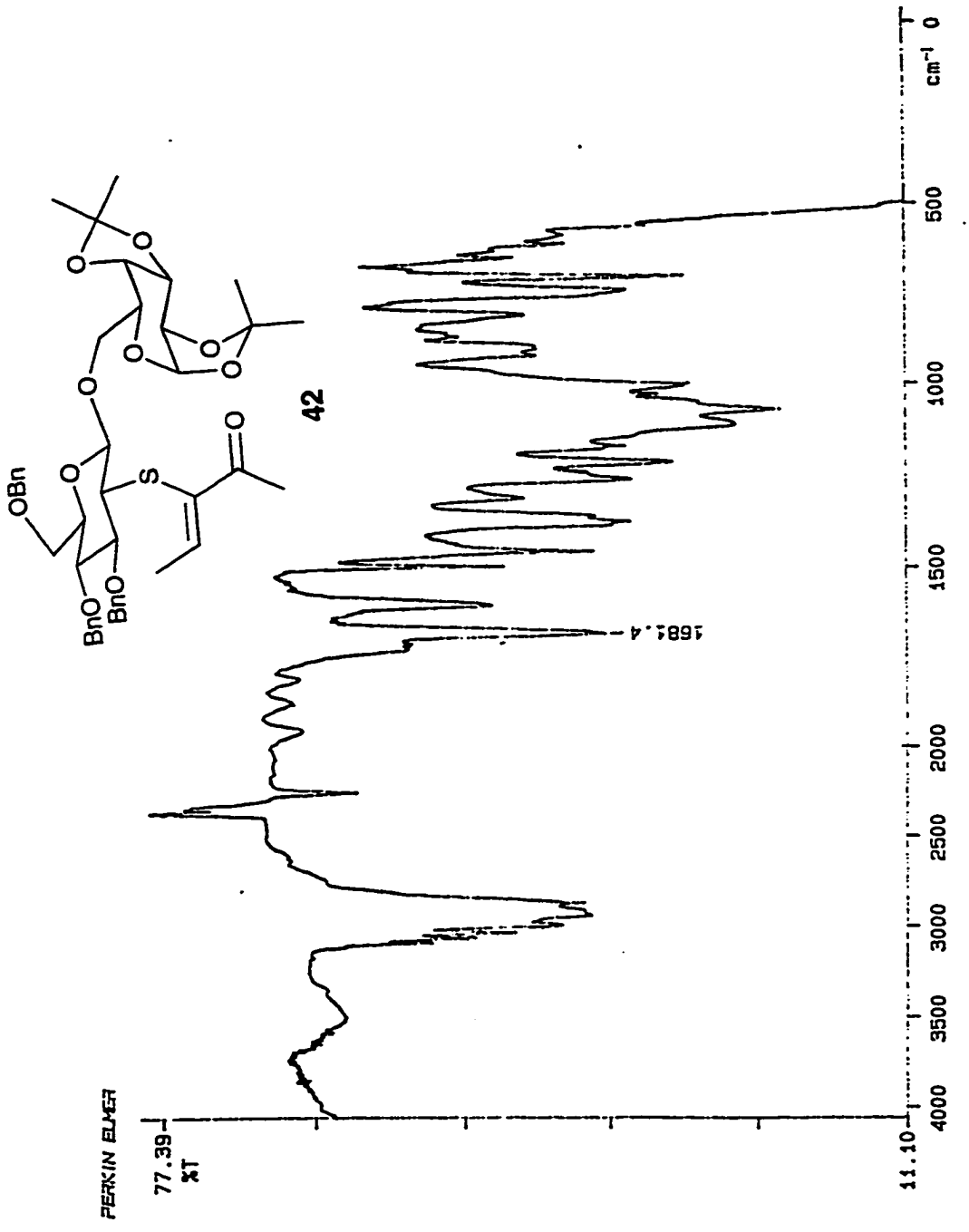

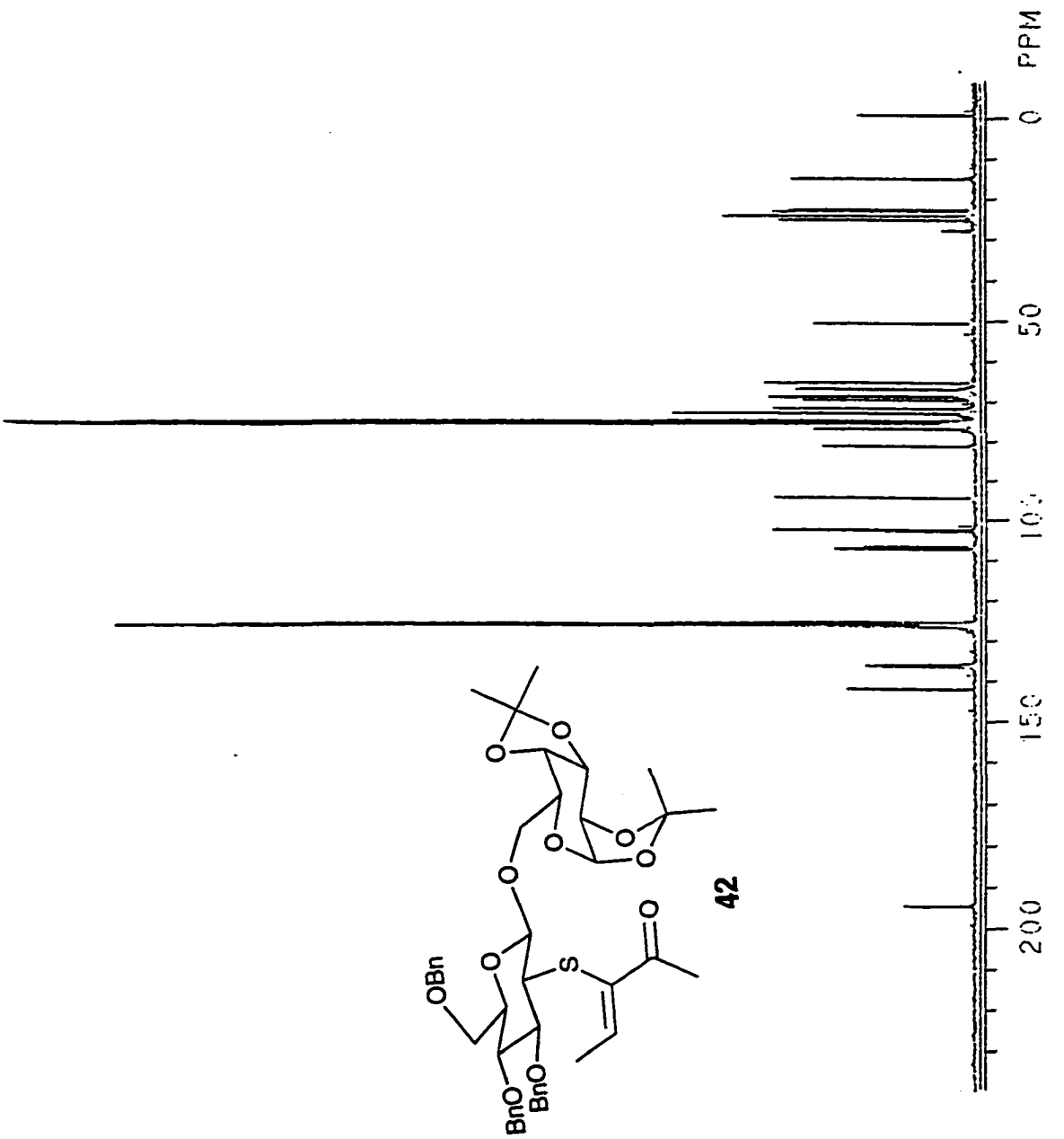

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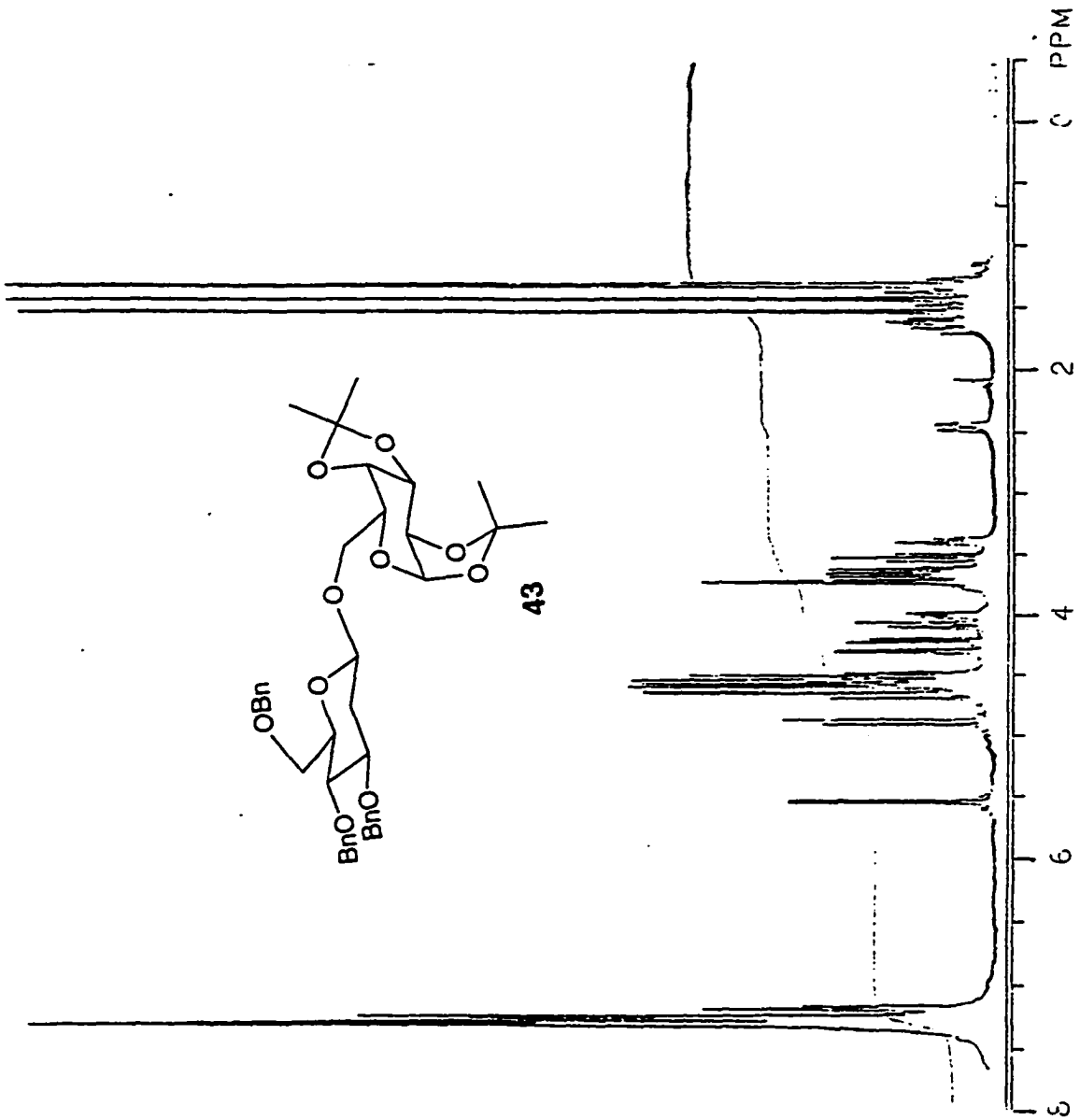

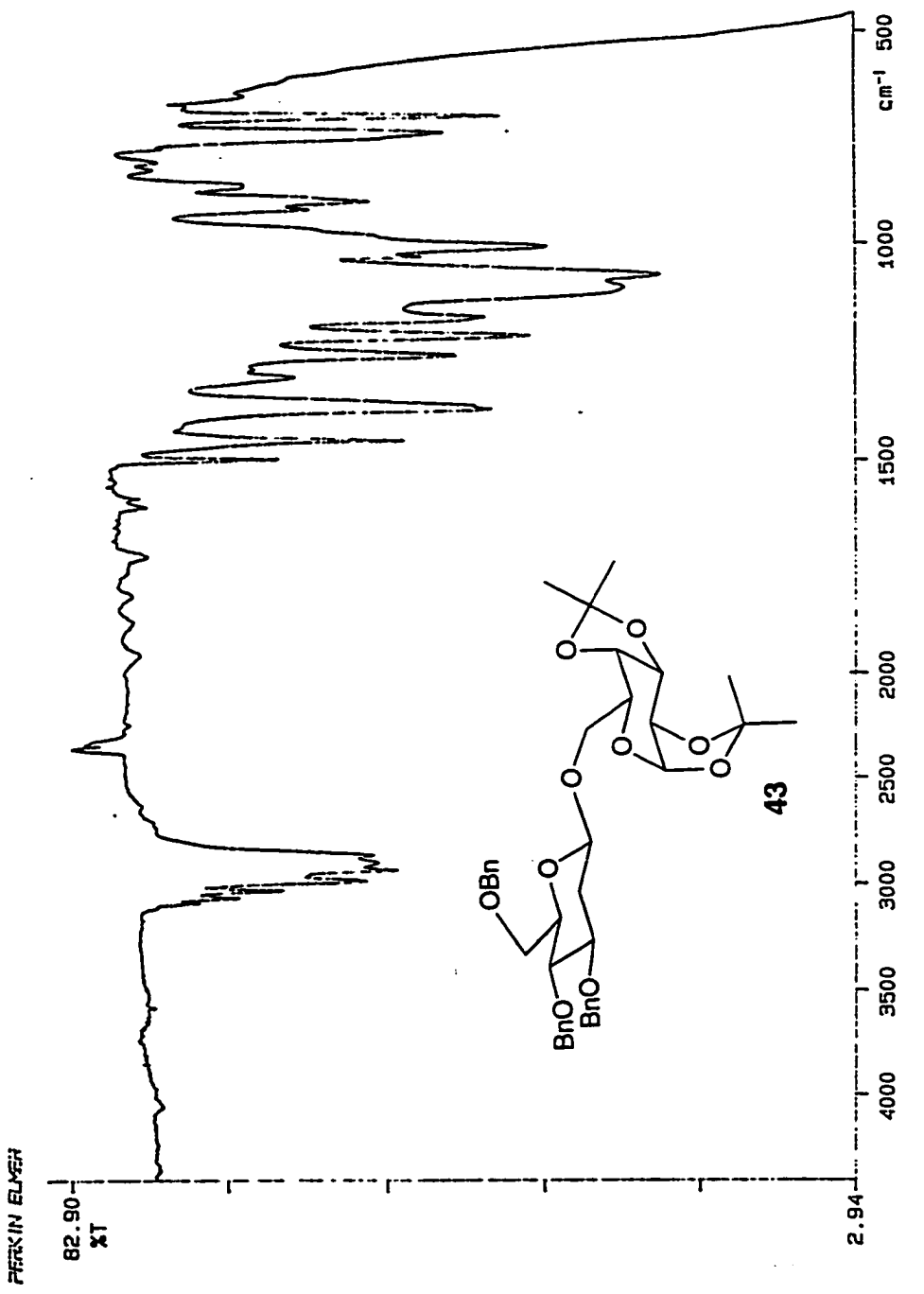

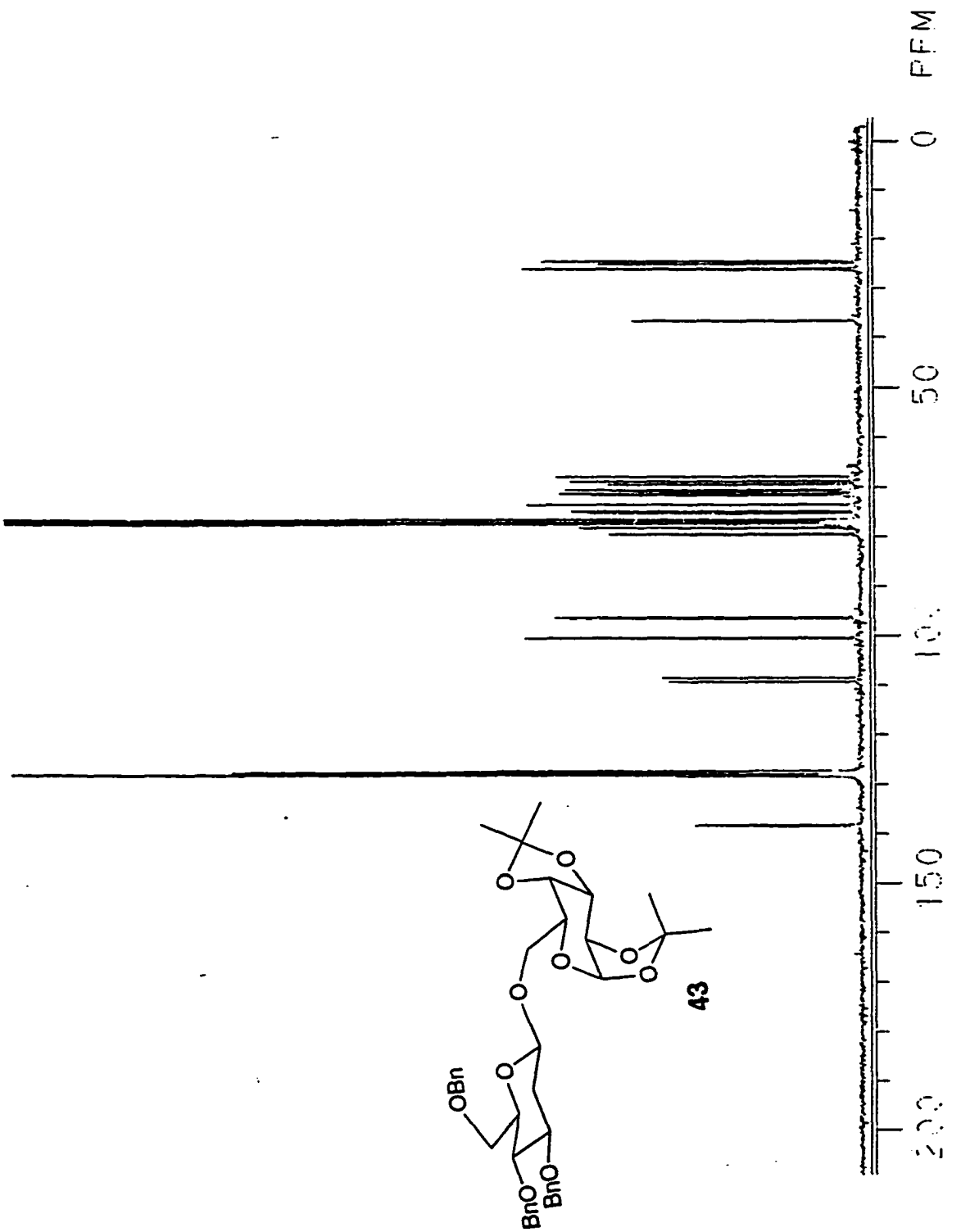

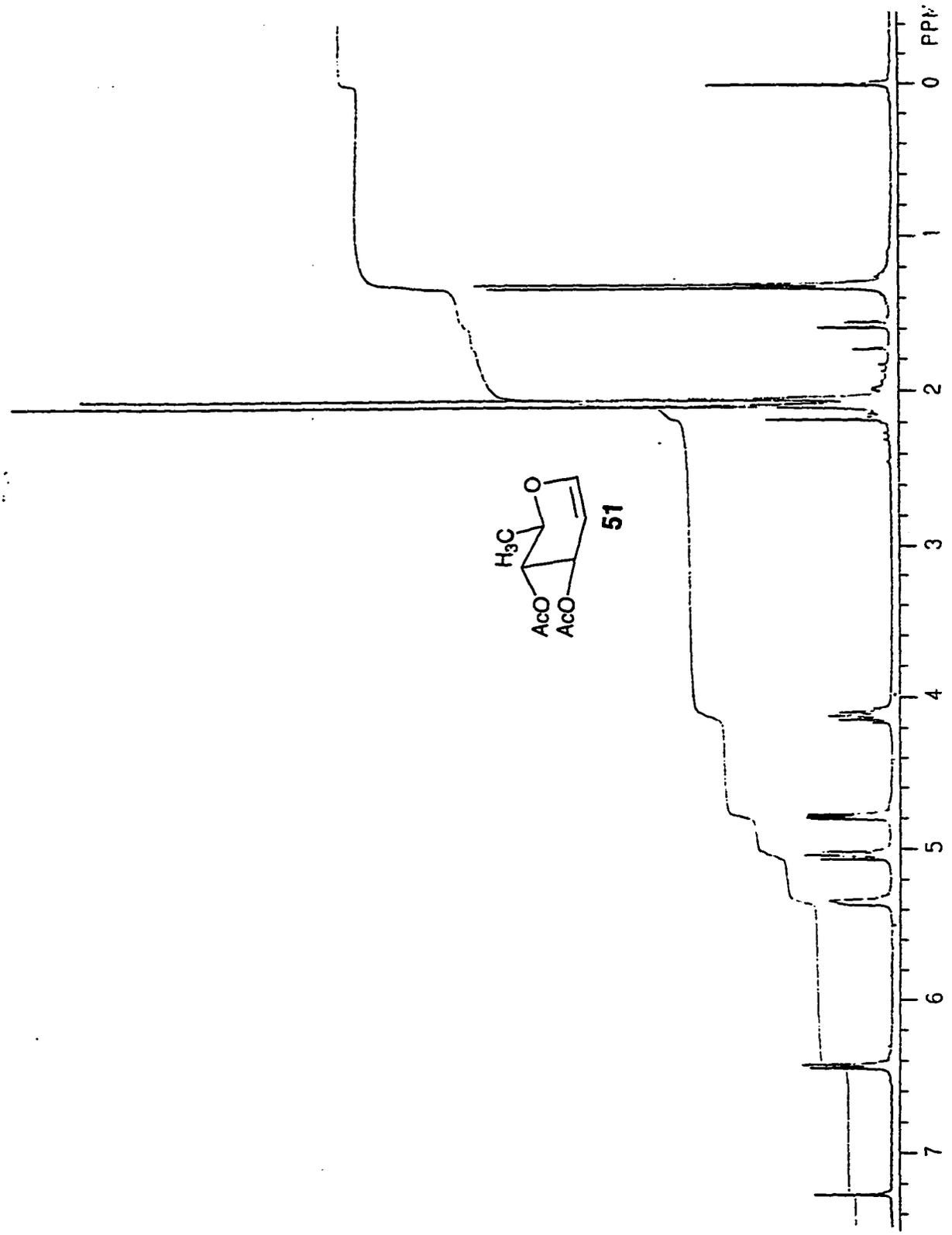

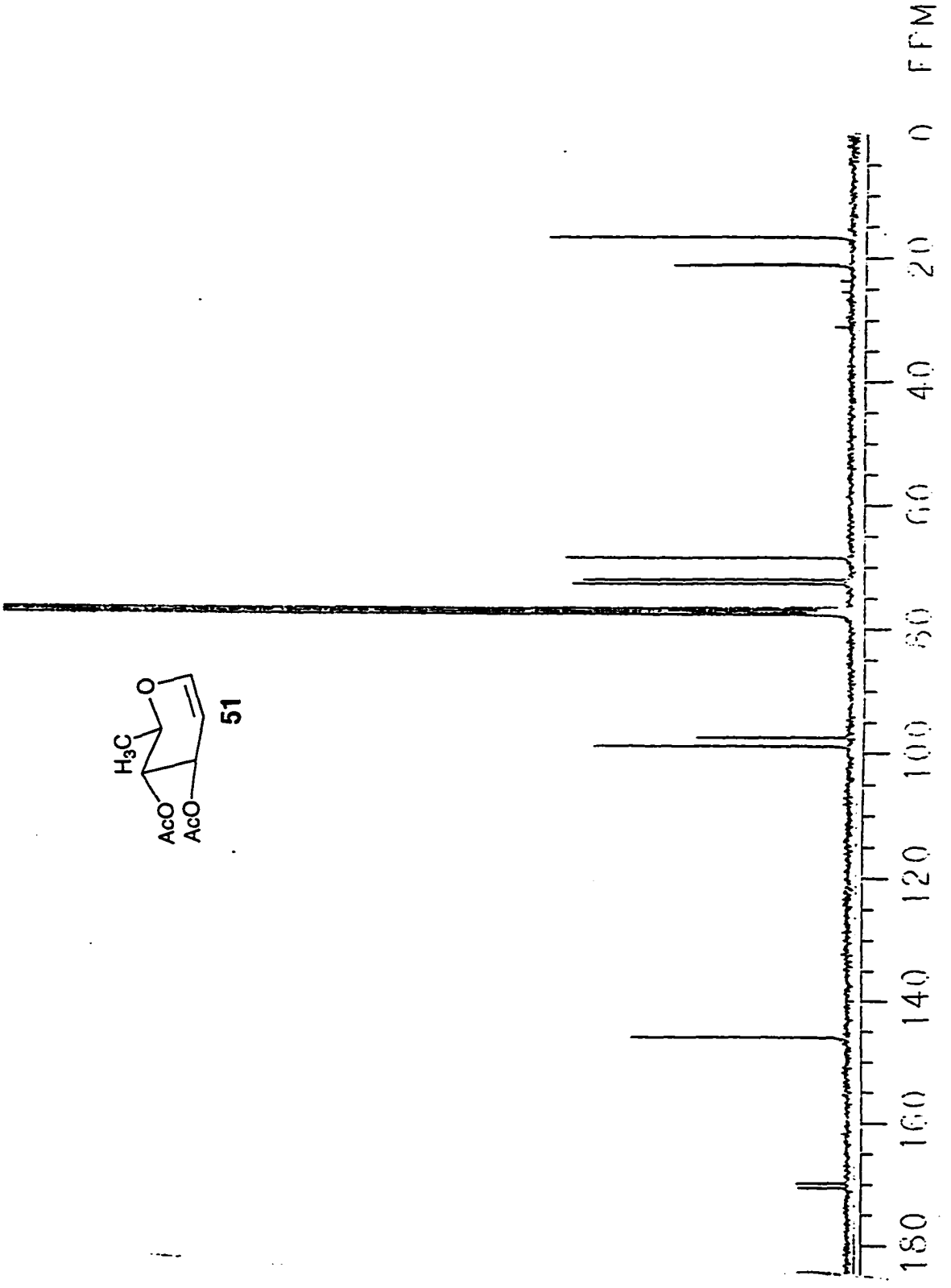

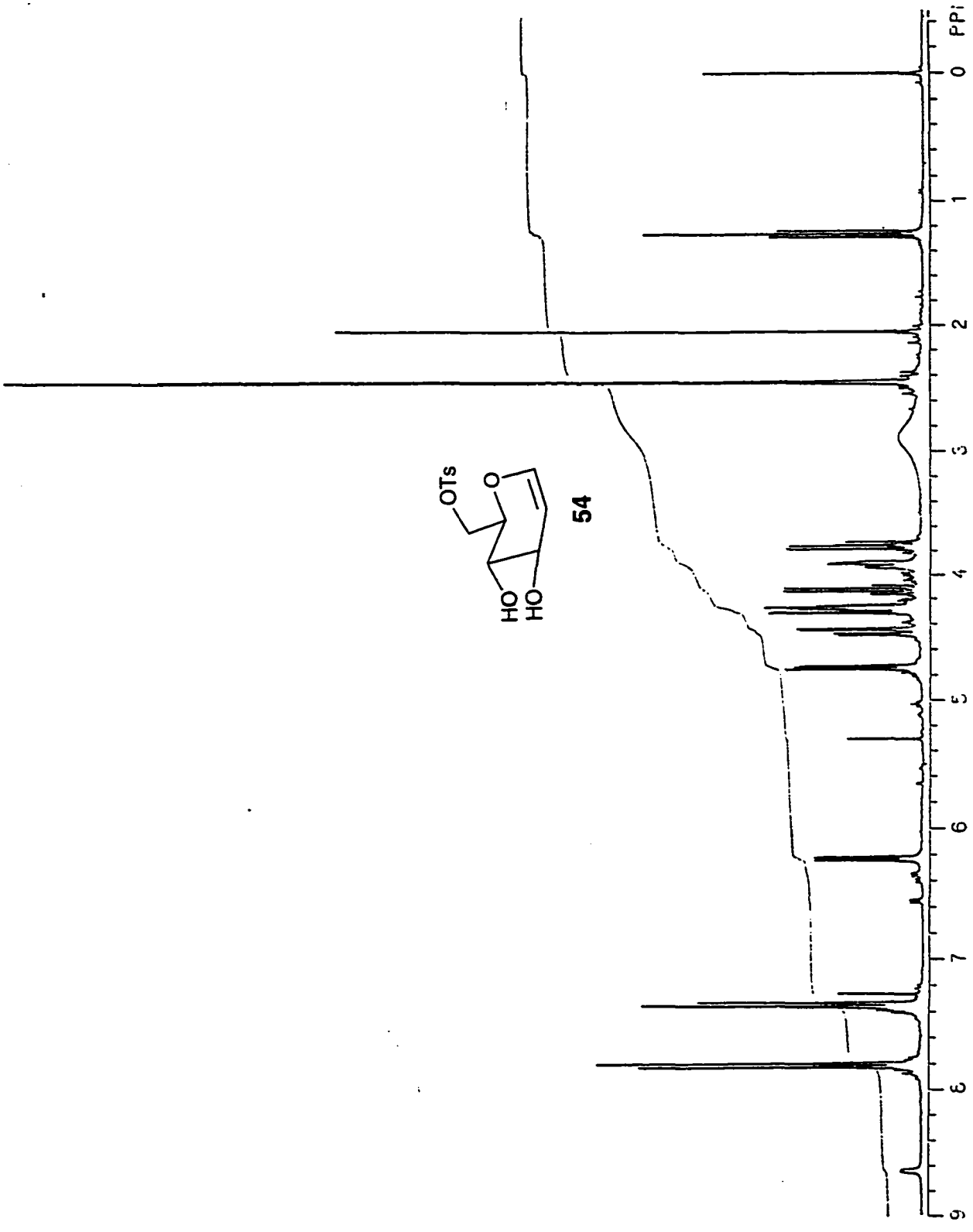

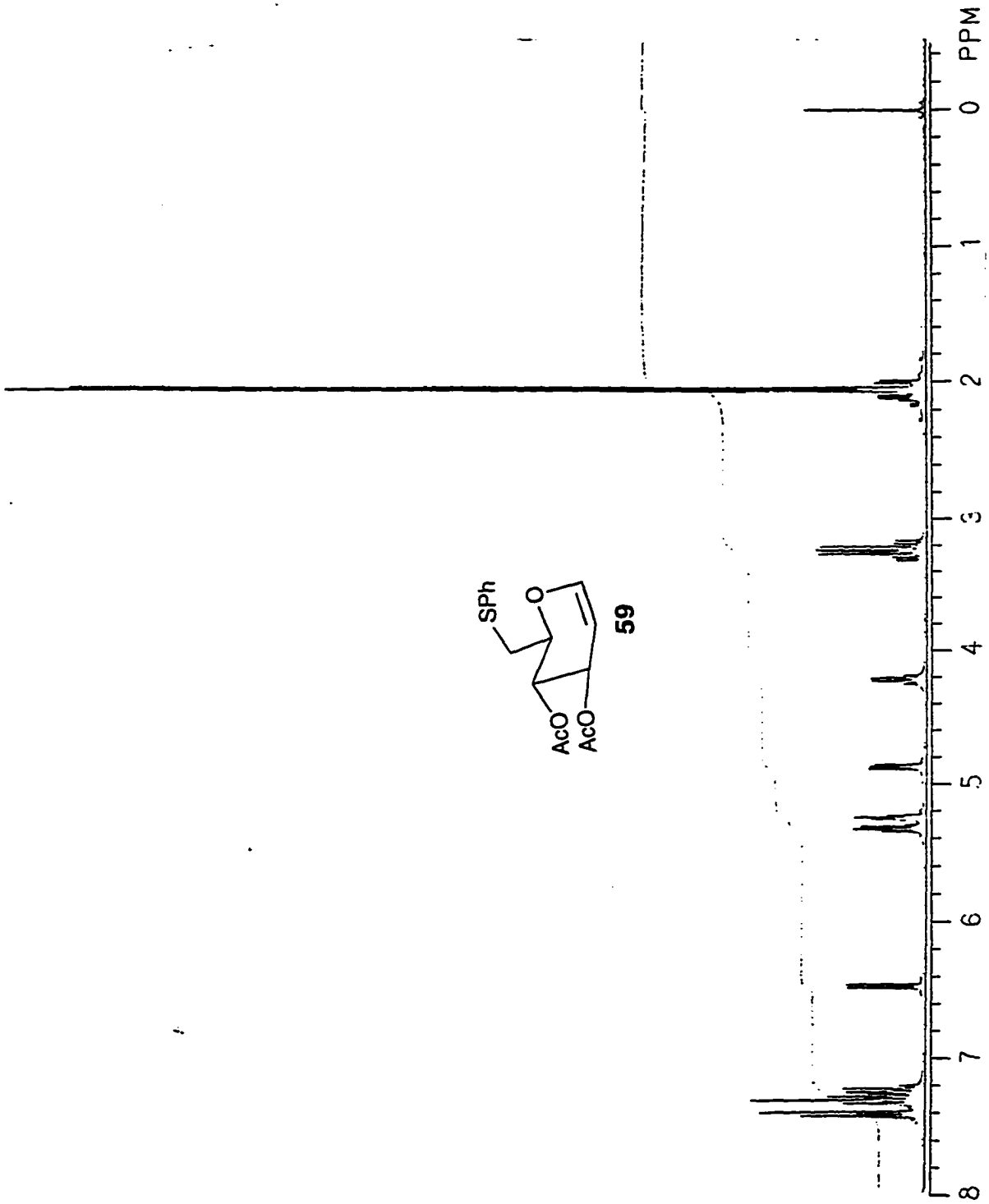

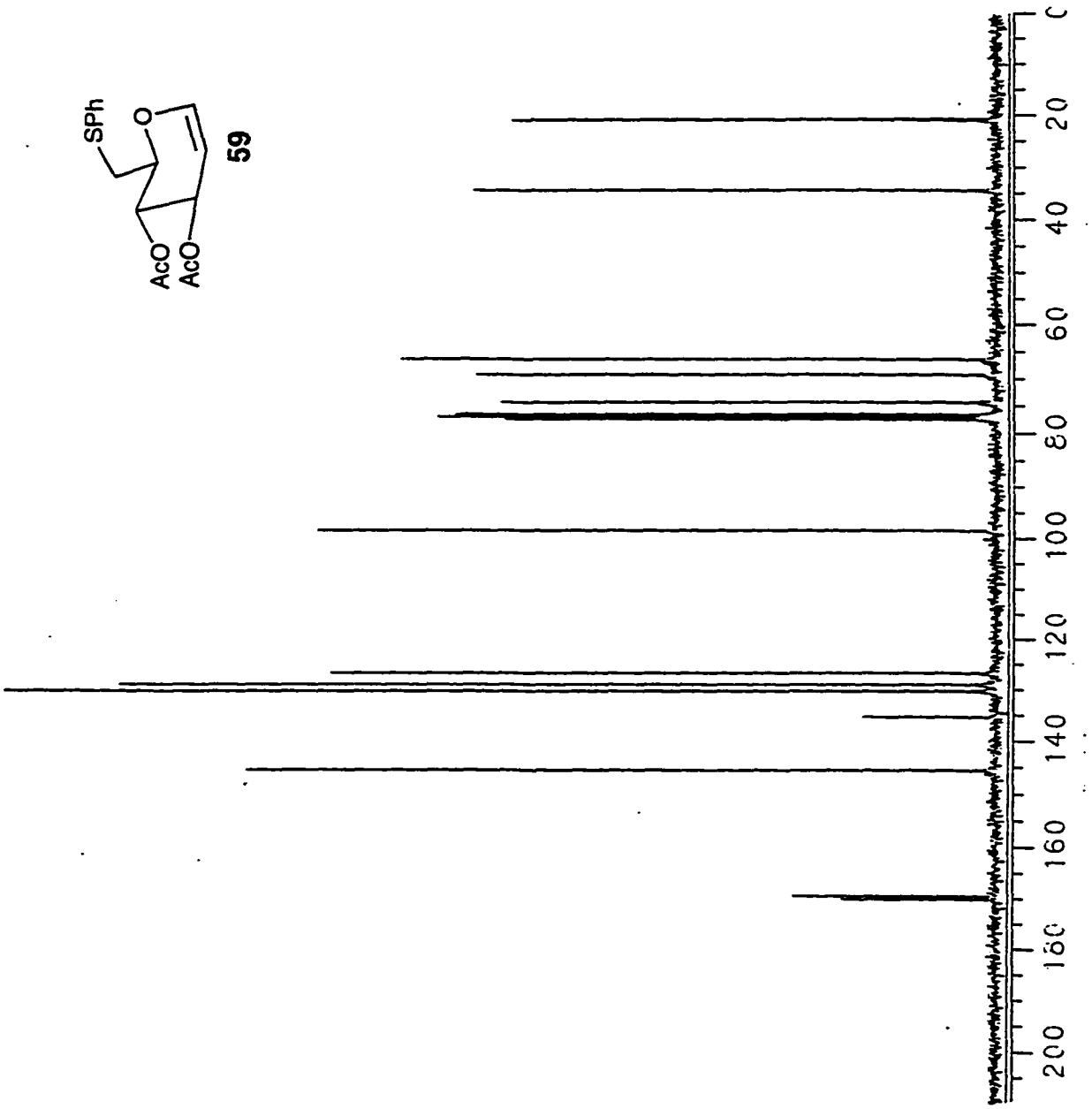

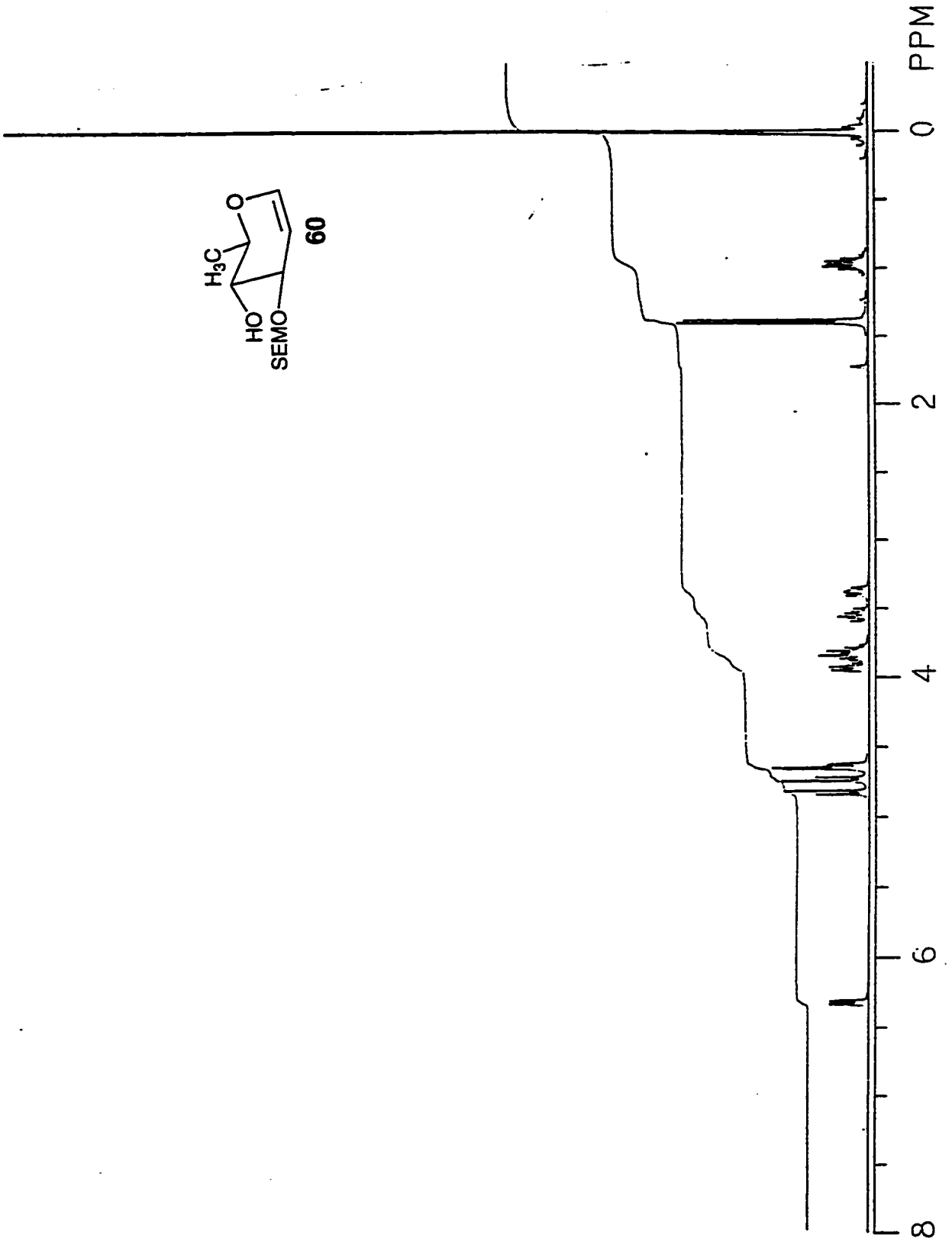

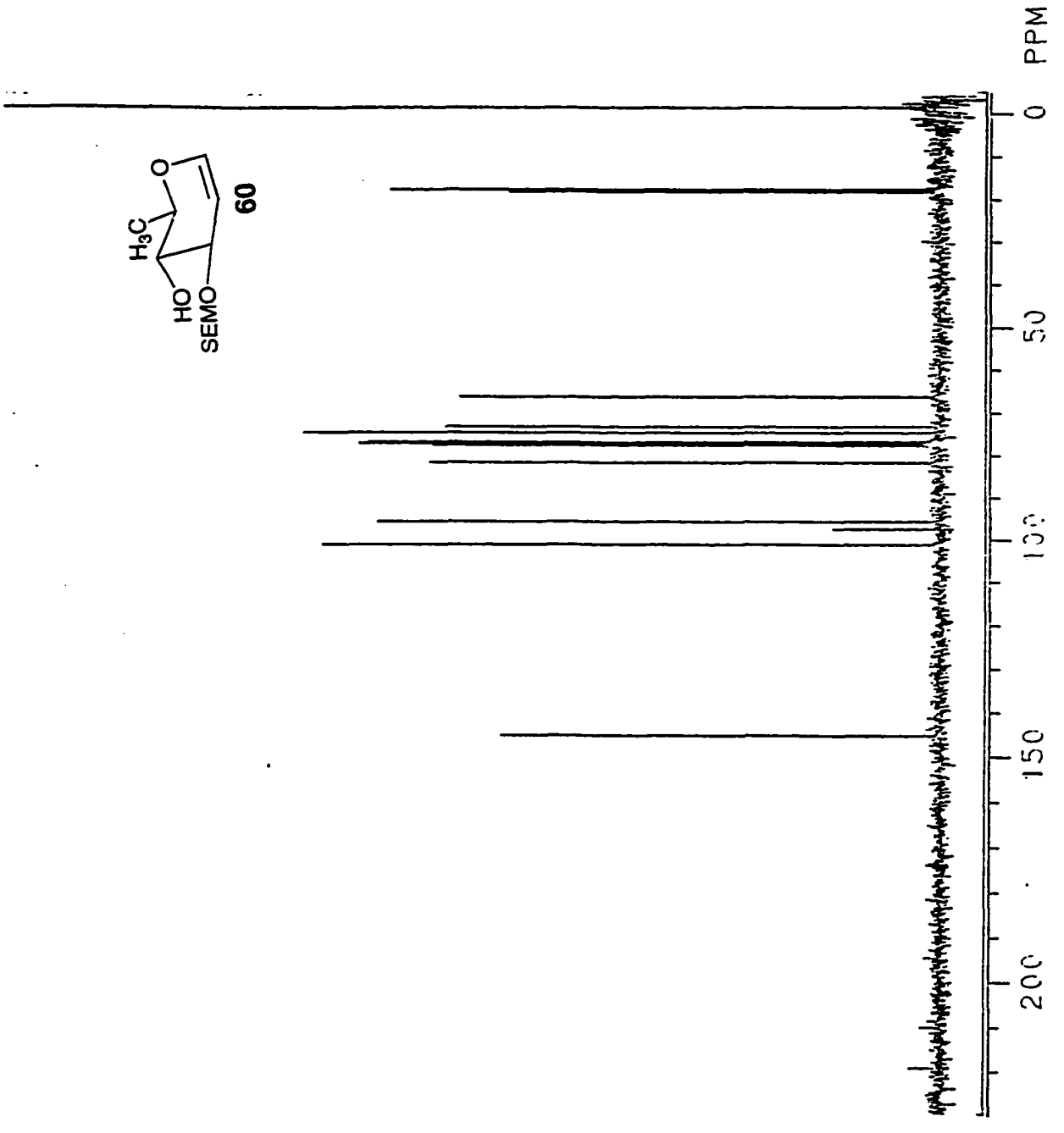

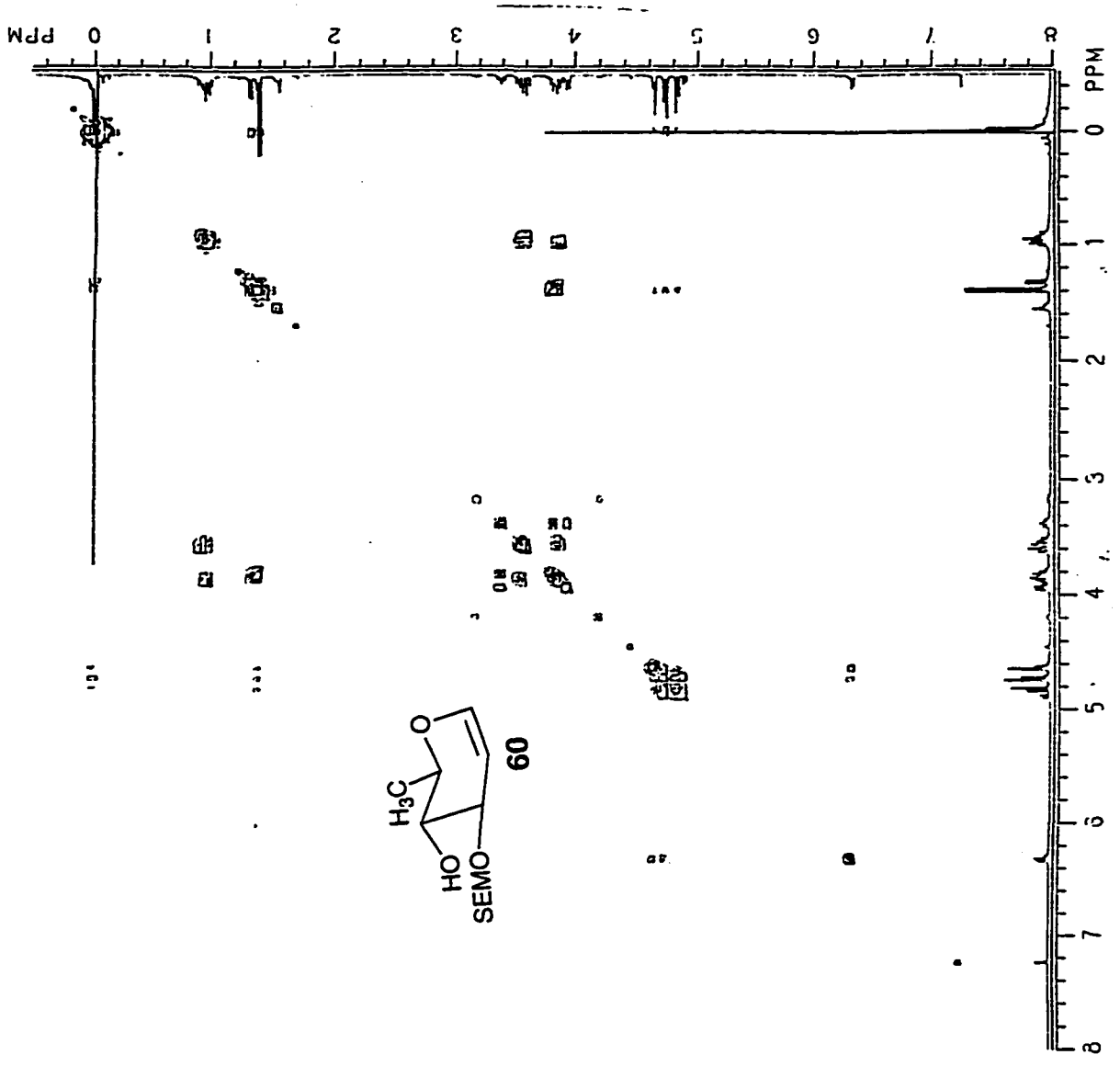

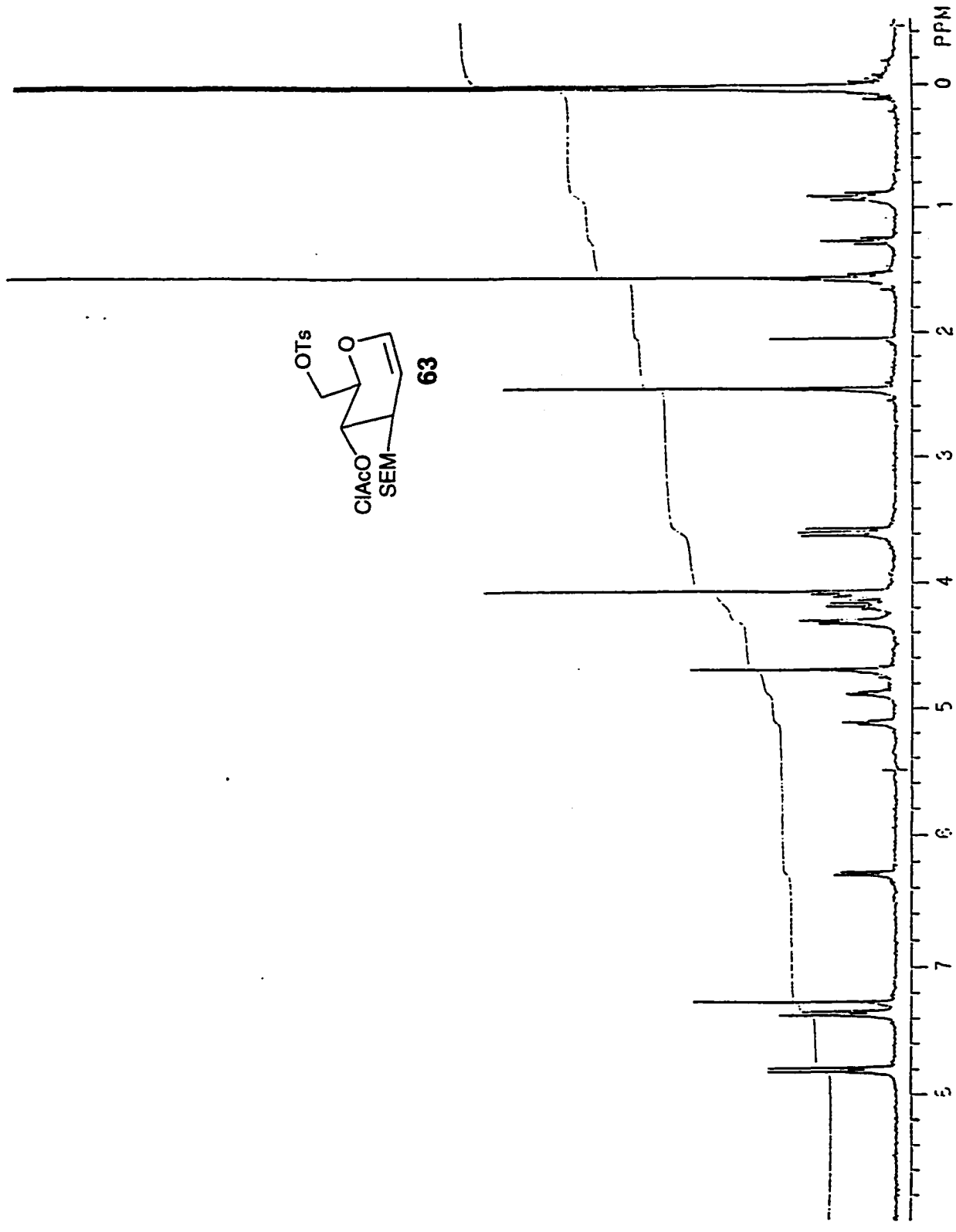

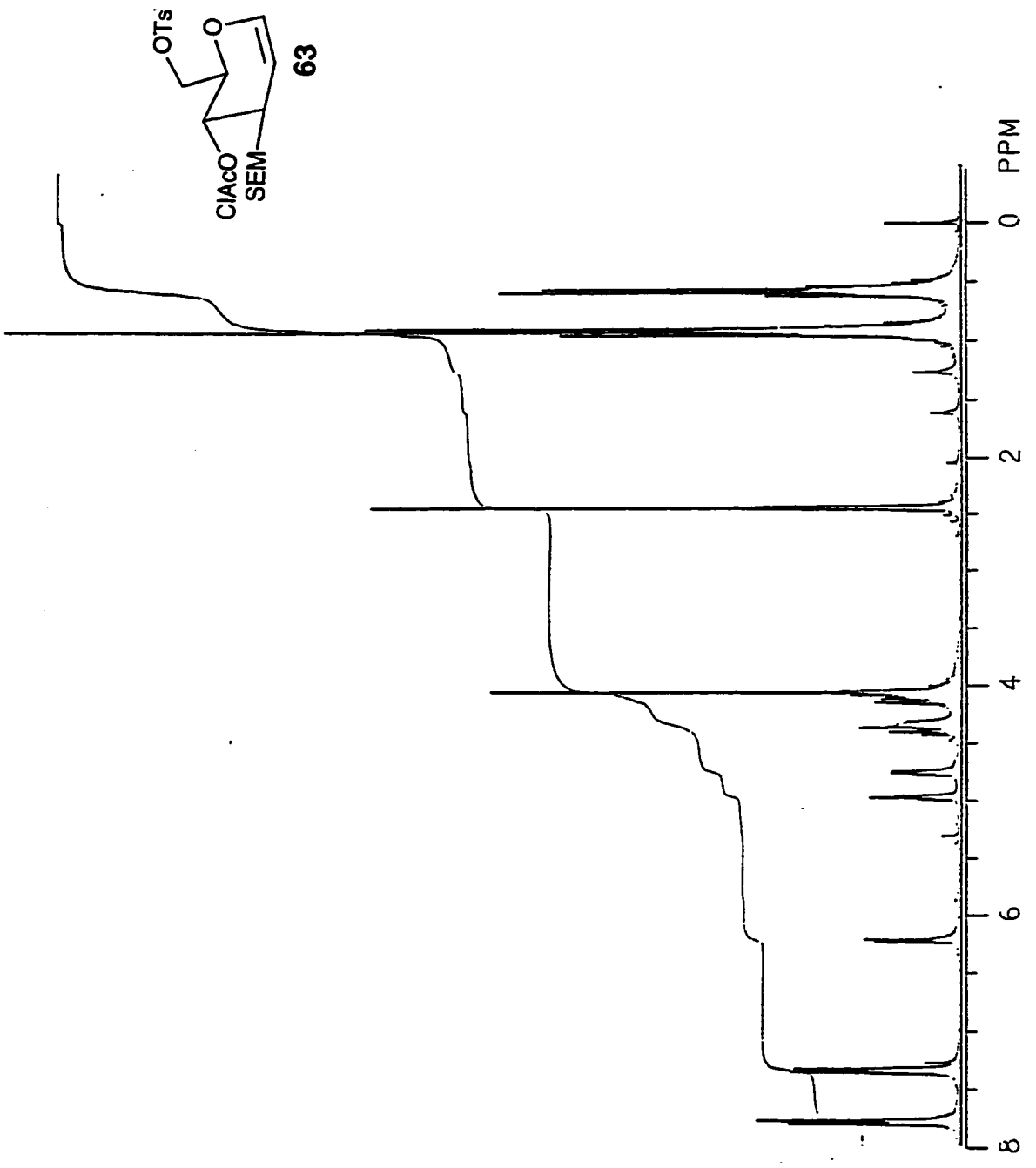

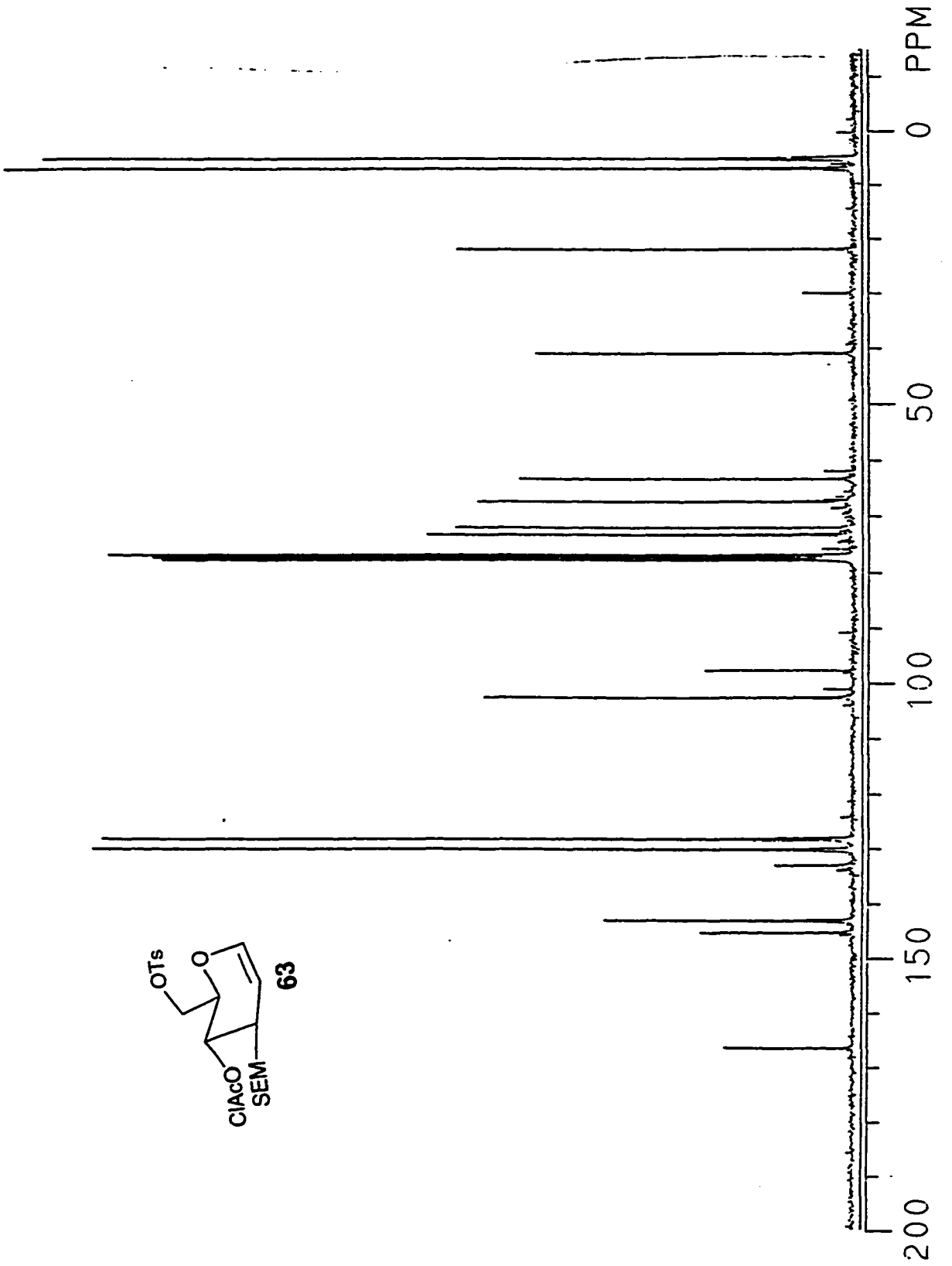

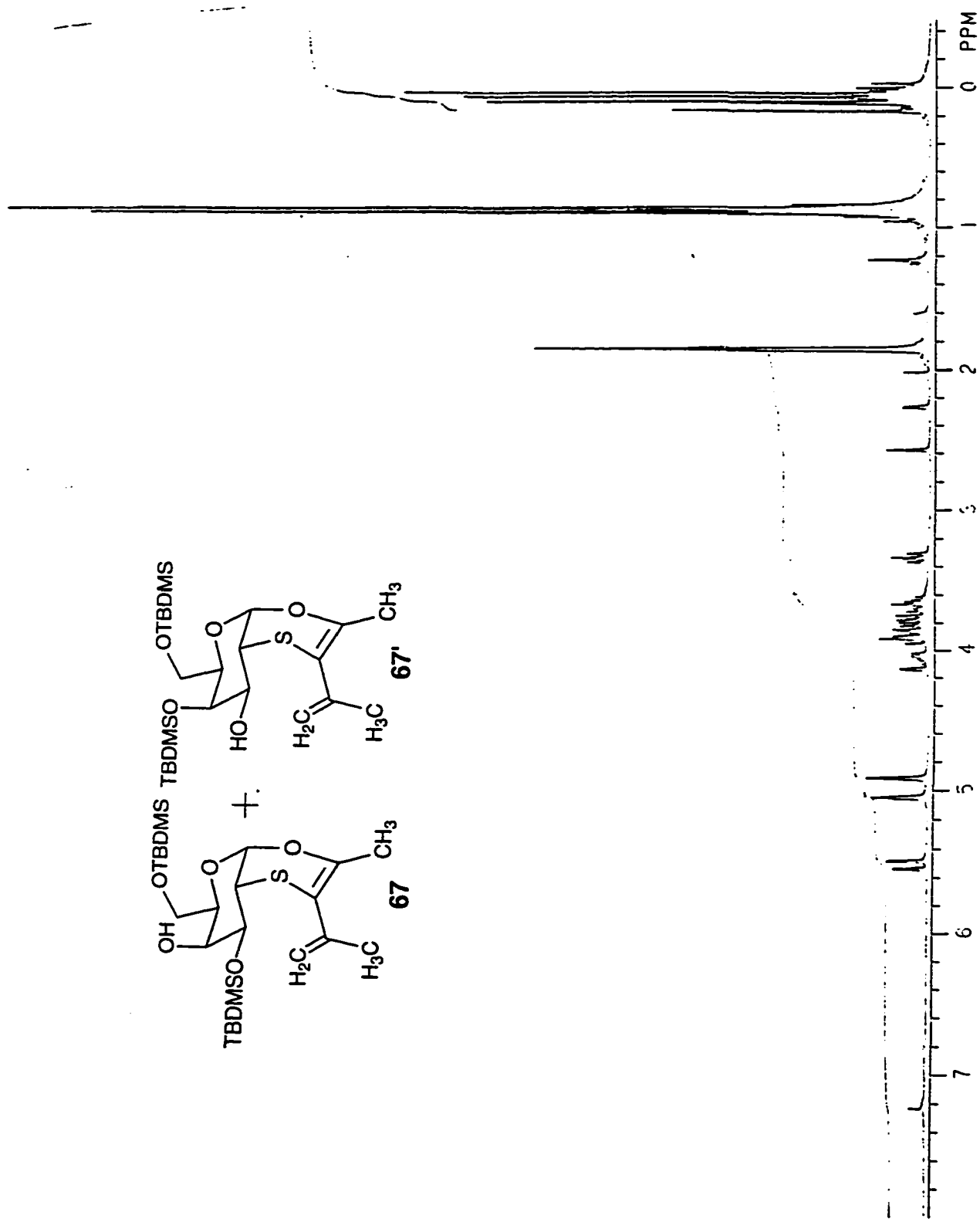

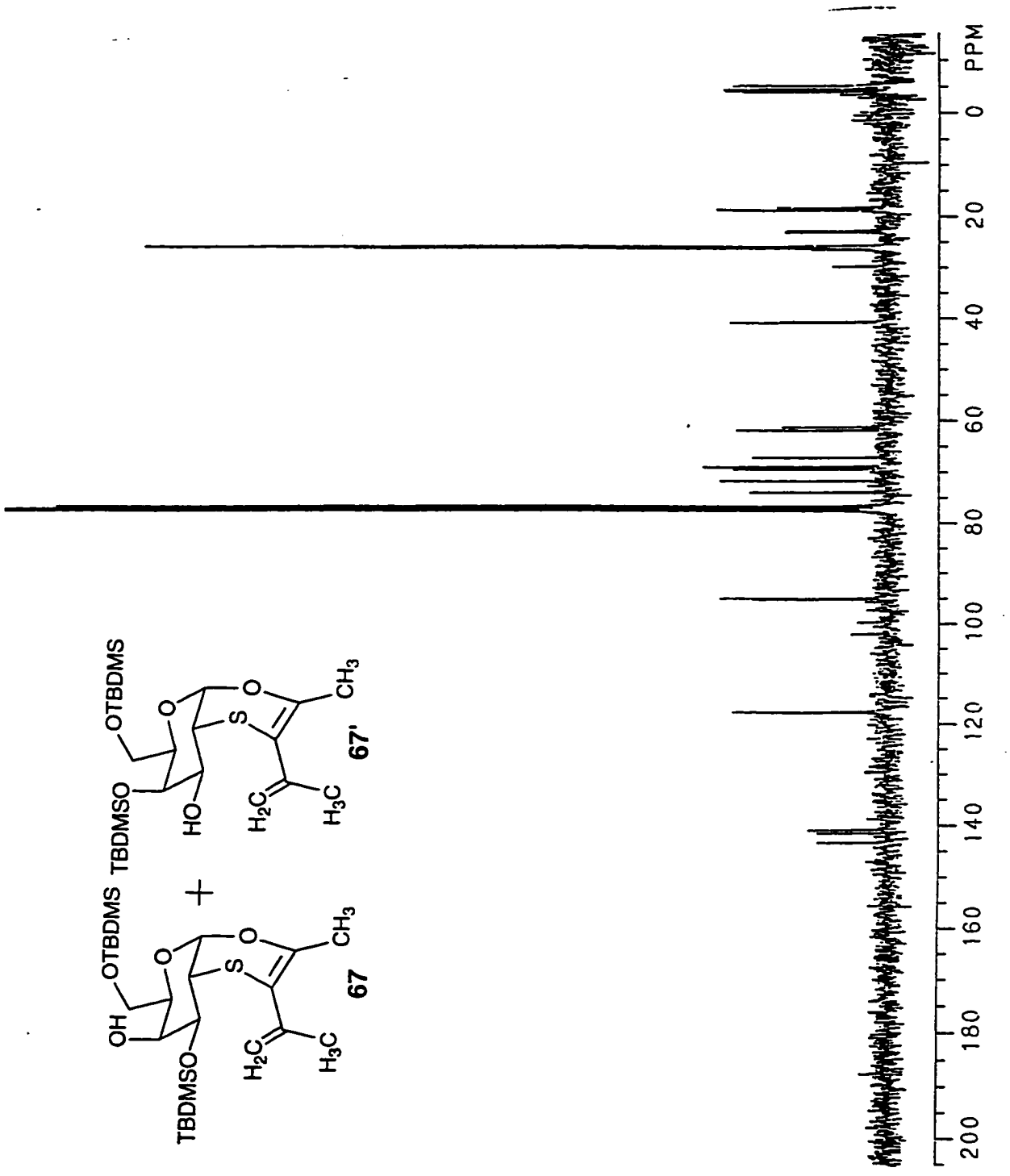

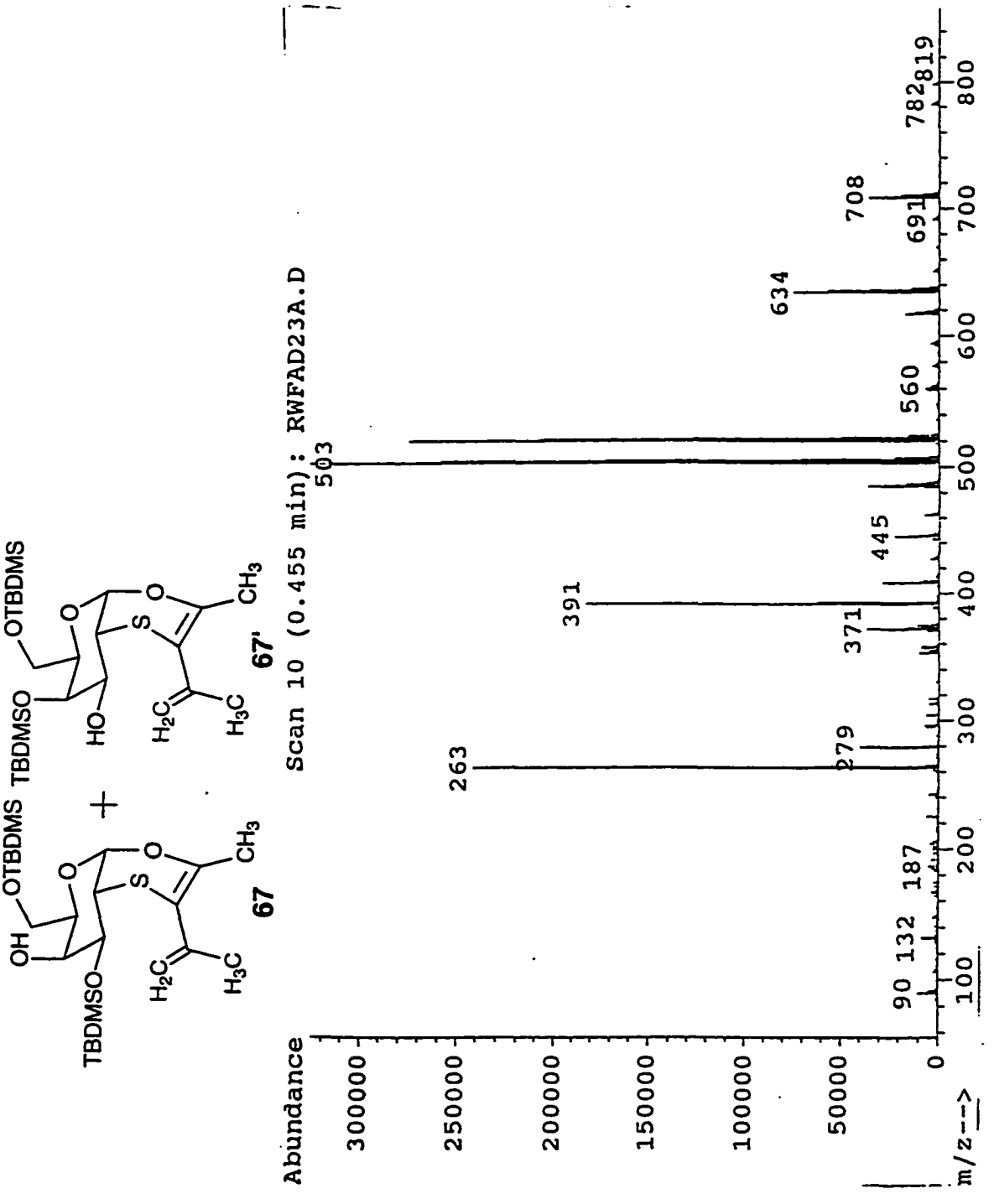

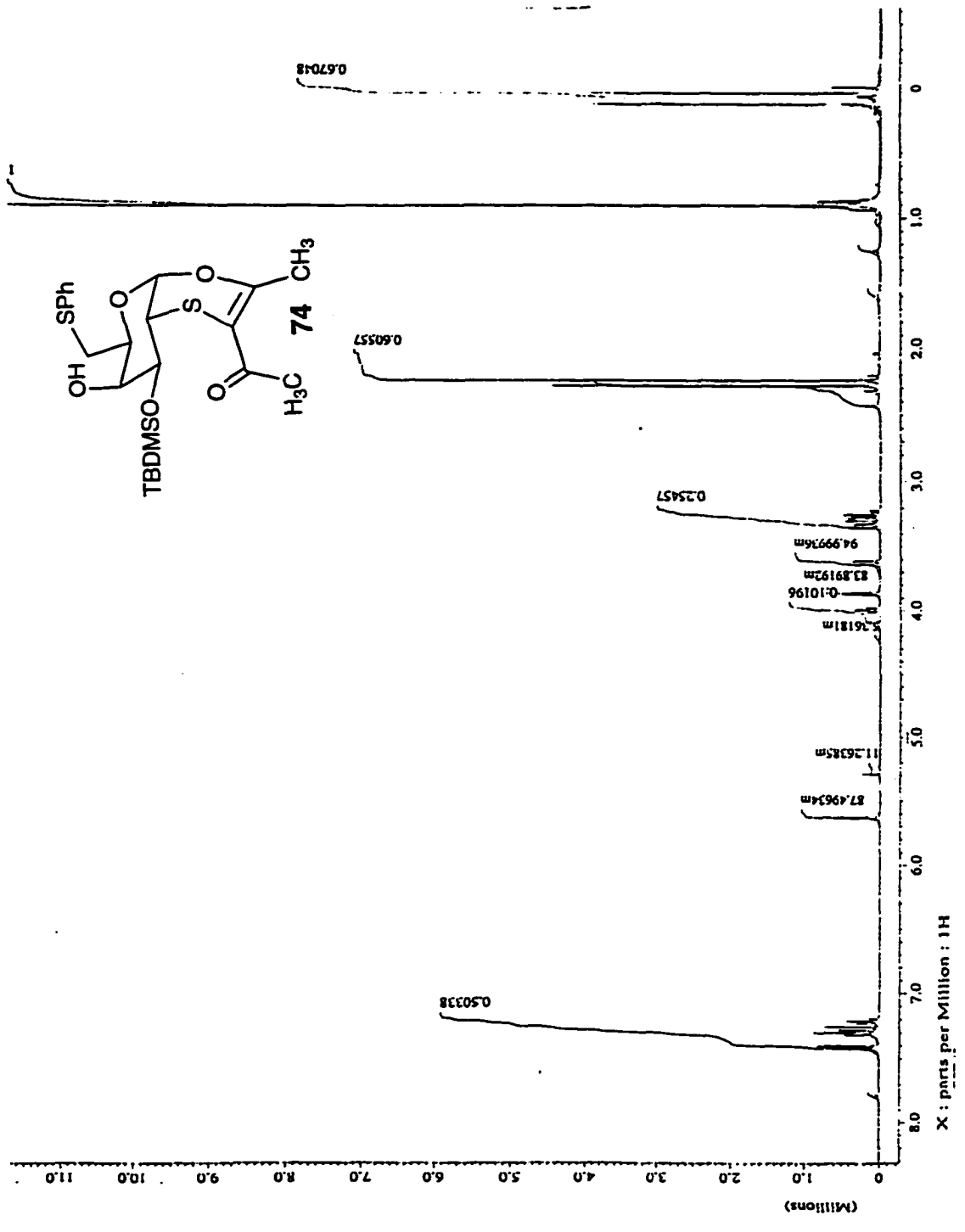

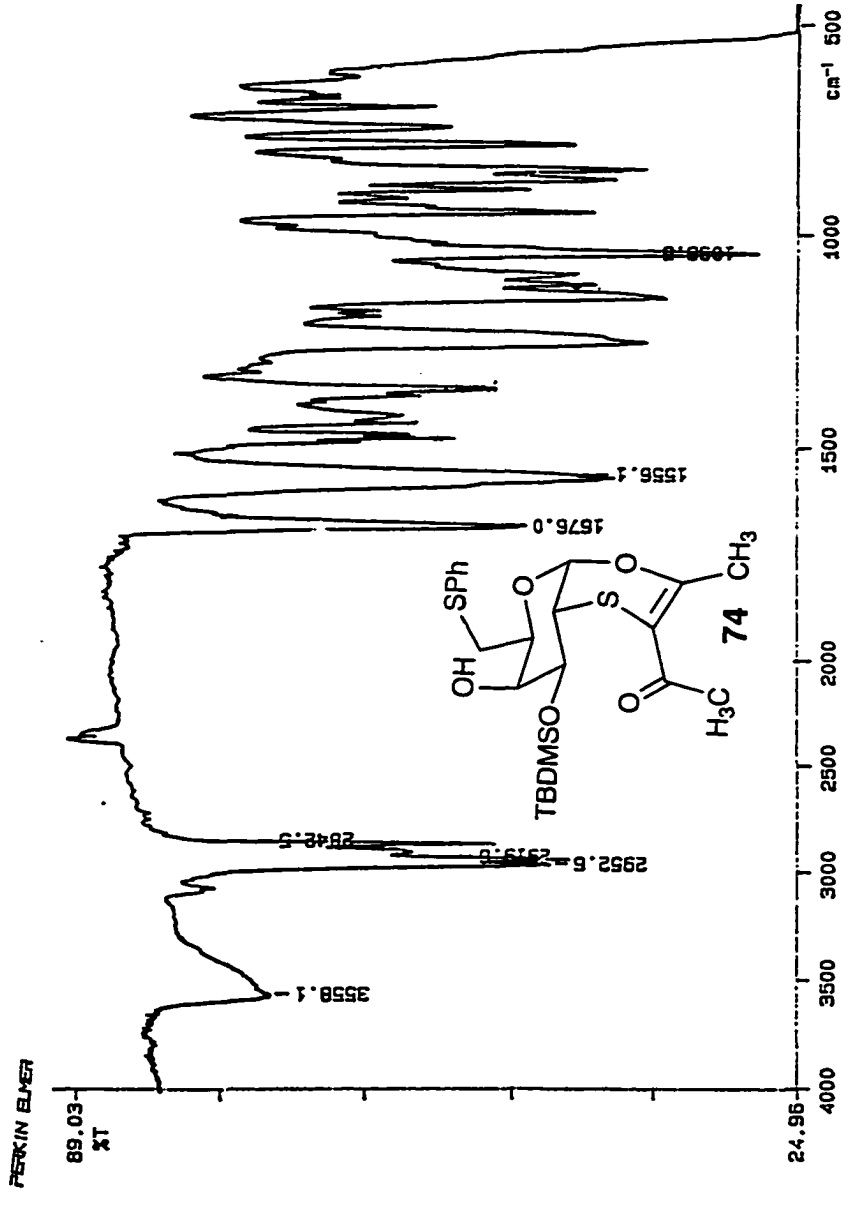

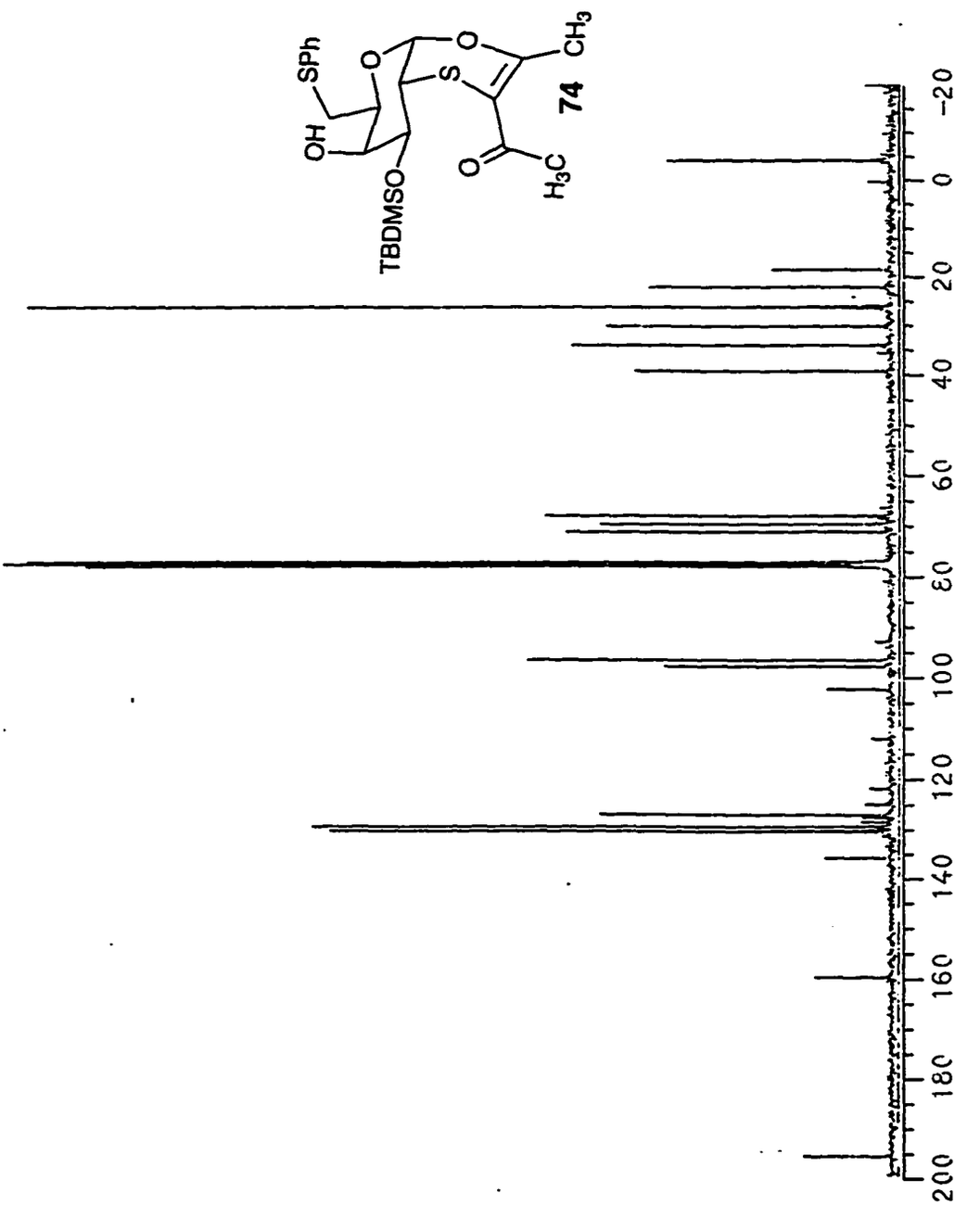

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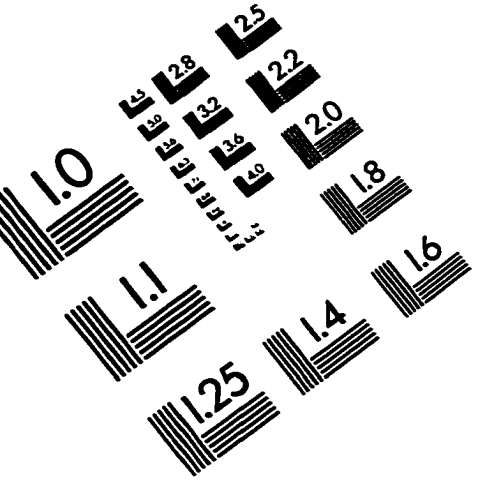

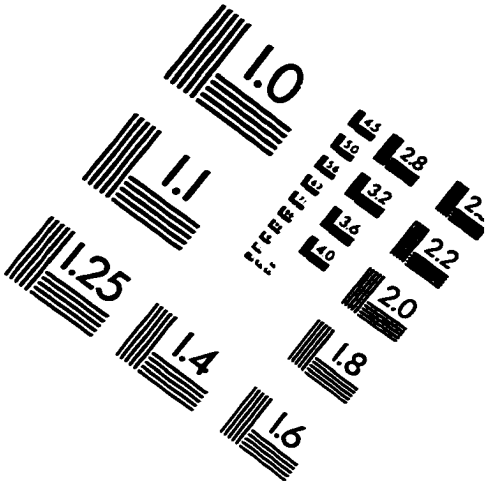

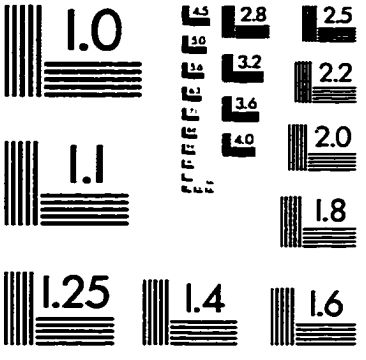

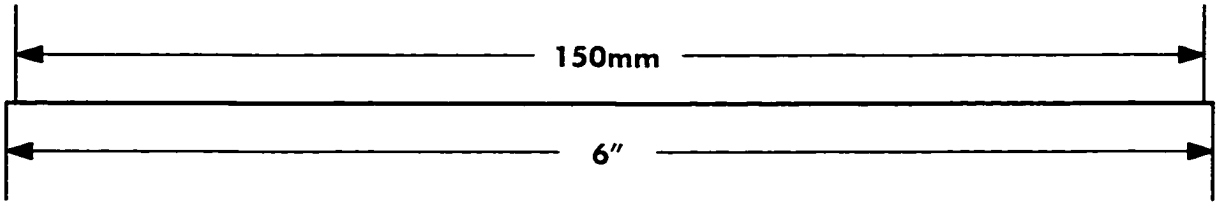

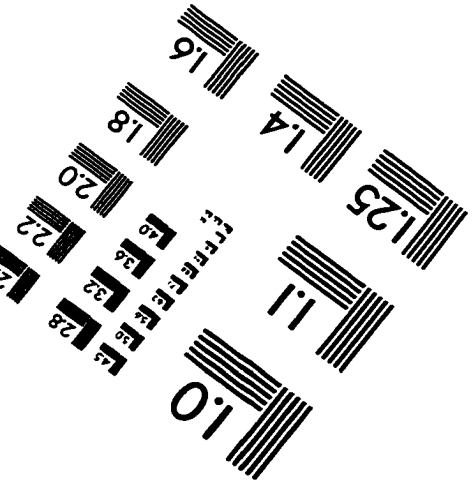

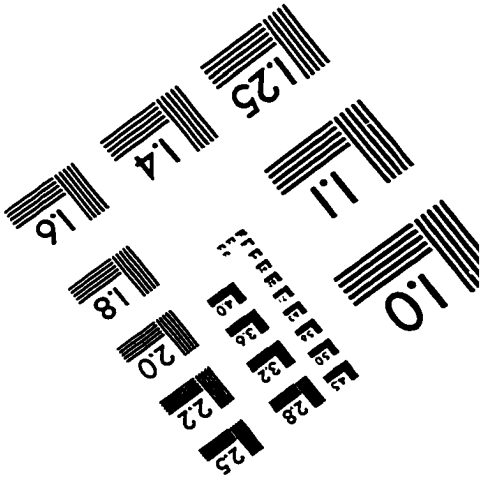

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