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I am submitting herewith a dissertation written by Sean K. Hamilton entitled "Synthesis of the S- and C-linked Disaccharide Analogues Related to Hyaluronic Acid." I have examined the final paper copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.



David C. Baker, Major Professor

We have read this dissertation
and recommend its acceptance:



Accepted for the Council:



Vice Provost and Dean of
Graduate Studies

**Synthesis of the S and C-linked Disaccharide
Analogues Related to Hyaluronic Acid**

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Sean K Hamilton
December 2001

This dissertation is dedicated to my mother Joan,
my father Fitzroy, my sister Saonjie,
and my daughter Amani.

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ABSTRACT

Hyaluronic acid is a ubiquitous glycosaminoglycan found in several mammalian tissues. It has been implicated in the development and progression of cancer by interacting with a cell's CD 44 receptor. Our goal was to synthesize small molecules that are hyaluronic acid mimics, which contain CH₂ and S groups strategically placed, as to render the molecules hydrolytically stable. Described in this dissertation are the synthetic efforts involved in assembling the disaccharide units related to hyaluronic acid that can potentially serve as building blocks for the synthesis of long-chain, enzymatically stable, oligosaccharide mimics. Both the S- and CH₂- linked disaccharide analogues proved synthetically formidable. However, they were successfully synthesized. The C-disaccharide, after several methods were attempted, was obtained from the coupling of a glycosyl tin derivative with an aldehyde derived from methyl α -D-glucopyranoside. The S-disaccharide was successfully accomplished through an S_N2 displacement of an axial triflate by a thiol.

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ABBREVIATIONS AND ACRONYMS

AcOH	Acetic Acid
ADMA	Anisaldehyde dimethyl acetal
AIBN	Azoisobutyronitrile
All	Allyl
BAIB	Bis(acetoxy)iodobenzene
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
CAN	Ceric ammonium nitrate
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ESIMS	Electrospray-ionization mass spectrometry
EtOAc	Ethyl acetate
GlcA	D-Glucuronic acid
GlcNAc	<i>N</i> -acetyl-D-glucosamine

HA	Hyaluronic acid
<i>m</i> CPBA	3-Chloroperoxybenzoic acid
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
Phth	Phthalimido
PMB	<i>p</i> -Methoxybenzyl
SAR	Structure-activity relationship
TBS	<i>tert</i> -Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl

I. INTRODUCTION

A. Biological Background

Hyaluronic acid (HA) (Figure 1) is a linear, high molecular weight, widely distributed, polysaccharide, specifically, a glycosaminoglycan, first isolated by Meyer and Palmer 66 years ago from the vitreous humor of cow eyes.¹ HA consists of repeating disaccharide units of *N*-acetyl-D-glucosamine (GlcNAc) and D-glucuronic acid (GlcA) linked via β (1 $\rightarrow$ 4)- and β (1 $\rightarrow$ 3) glycosidic bonds. It is synthesized at the cell surface in the plasma membrane and is secreted into the extracellular matrix,² which is made up of many proteins and complex macromolecules known as proteoglycans. These ubiquitous macromolecules contain a core protein tightly bound to a glycosaminoglycan. Hyaluronic acid is considered an "honorary proteoglycan".³

In addition to the vitreous humour, hyaluronic acid is found in vast quantities in the synovial fluid, rooster comb, umbilical cord, extracellular matrix and other soft connective tissues.³ Some bacterial strains like Streptococci also consist of ample quantities of the biopolymer.³ Hyaluronic acid seems to play a significant role in coordinating the tissue in young and developing extracellular matrix, joint lubrication,⁴ cell adhesion, cell growth and migration, in inflammation and wound healing, and in the inhibition of fetal scarring.⁵ Furthermore, many malignant tumors consist of elevated HA levels, and this has resulted in HA's being implicated in the development and progression of cancer. Recently, it has been linked to glioma, one of the deadliest of tumors and most invasive form of

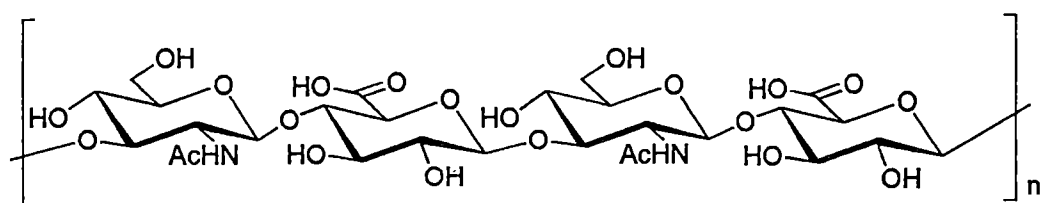


Figure 1. Hyaluronic Acid.

brain cancer.⁶

Cancer cannot be considered a single disease, but rather, as a conglomeration of countless maladies that share key features. These features of cancer are exemplified by four stages, (1) uncontrolled cell growth (2) an absence of cell differentiation, (3) intrusion into neighboring tissues, and (4) metastasis, the ability to disseminate to distant sites in the body.⁷ This insidious aspect makes cancer so extremely deadly, and it is the hallmark of malignancy. In order for cells to metastasize effectively, they must detach from their primary sites and cross the basement membrane enclosing a blood vessel, including the endothelial cells lining it; diffuse by way of the bloodstream; affix to the cell wall in a new tissue; extravasate by maneuvering through the basal lamina, and navigate through to other tissue and establish a new cellular colony.⁸⁻¹¹ It appears that HA plays a prominent role in the event of cancer cell migration through the extracellular matrix. Evidence has implicated the interaction between CD 44, a major cell-surface receptor and HA in cancer metastasis. Moreover, this interaction has been proven vital for tumor development because it mediates attachment of tumor cells to peripheral tissue or to other remote sites.¹² Remarkably, Miyake et al.¹³ have shown that this interaction regulates human prostate cancer development. CD44, which is expressed in numerous cell types, is a cell-surface adhesion molecule that is broadly distributed and is engrossed in countless physiological activities, including immune responses,

cellular adhesion and migration, leucocyte differentiation and circulation,¹⁴ and HA degradation.¹⁵

Alternative splicing of CD44 during transcription spawns an extensive array of CD44 isoforms, which are found on tumor cells, and most have significant affinity for binding HA.¹⁶ Multiple studies¹⁷⁻¹⁹ have indicated that malignant cells undoubtedly use these isoforms to facilitate migration, thus spreading cancerous tumors. A current model of this interaction between HA and CD44 in metastasis is described as follows: Migrating cancer cells discharge growth factors that galvanize neighboring cells to increase production of extracellular hyaluronic acid. These newly synthesized HA strands are used by the cancer cells CD44 receptors to bind to and migrate to distant locales, consequently spreading malignancy to new tissues. Upon examination of this modest blueprint for metastasis, a novel therapeutic approach that is based on the introduction of a CD44 receptor antagonist that would adeptly impede a malignant cell from binding to HA could be conceived. Unlike several conventional strategies that consist of cytotoxic agents that target the cell cycle, this approach would involve essentially cell-surface phenomena. A metastatic inhibitor would be acutely beneficial in cases where the tumor is highly metastatic or the primary tumor is untreatable. Most remarkably, current cancer therapeutics being investigated such as protease and collagenase inhibitors, target metalloproteases and collagenases, respectively, both of which are suspected as agents in enabling cancer cells to metastasize or spread.²⁰

B. Antimetastatic Agents Derived from the Enzymatic Degradation of HA

As was elucidated earlier, the interaction of HA and CD44 has been implicated in cancer metastasis. Based on this premise and on our preliminary work, our group submitted a grant proposal to the Medicinal Chemistry Study Section of the National Institutes of Health in June 1996, which was eventually funded, duly entitled "Antimetastatic Oligosaccharides from Hyaluronic Acid." We advanced the idea that small molecules derived from enzymatic degradation of HA could conceivably be utilized to interlude in the binding of HA to CD44 and therefore limit metastasis. Accordingly, it was proposed that an oligosaccharide, of unspecified length, could serve as a probe for investigating the role of CD44-HA binding in metastasis providing that it would (a) contain the required functionality to bind to the tumor cell's CD44 receptor (b) be readily acquired from HA by enzymatic or hydrolytic cleavage, and (c) would function as a model for development of a hydrolytically stable, synthetic analogue.

To this end, a series of experiments was conducted by our collaborator, Dr. Richard L. Cysyk of the National Cancer Institute, to ascertain whether oligosaccharides derived from HA would serve as antagonists for the CD44 receptor. A summary of the experiments staged is discussed below. Highly metastatic B16F10 melanoma cells were incubated in vitro (10^5 cell count) with a mixture of HA oligosaccharides (1mg/mL) derived from the enzymatic degradation of hyaluronic acid by hyaluronate lyase (EC 4.2.2.1) and injected i.v. into the tail vein of mice. After 10 days, the lungs of the mice, along with the

lungs of a group of control mice that only received B16F10 melanoma cells, were removed and the noticeable metastatic colonies were counted. We were optimistic that a depletion in the metastatic sites on the lungs of the mice that were treated with B16F10 melanoma cells, premixed with HA oligosaccharides, would be observed. Astonishingly, there was practically a total absence of metastatic colonies on these lungs. On the untreated lungs, numerous tumors were evident. To determine if these results were accurate, the experiments were duplicated with a variety of controls, and similar results were achieved. In the HA-oligosaccharide-treated sample, the viability of the B16F10 melanoma cells was checked, as well as other consequential factors. No toxicity was detected from cell viability analyses on the melanoma cells, even when the concentration of the oligosaccharides (up to 3mg/mL) was doubled and tripled. While HA itself (1mg/mL) shows antimetastatic effect, these experiments affirm that a relatively small molecule can behave as an antimetastatic probe, which is essential to our proposed research. Ongoing work will determine the structure-activity relationships (SAR) among the oligosaccharides. Exploratory investigations show activity setting in with the 8-mer (DP = 8).

C. Design of Stabilized Oligosaccharides Related to HA

Several lines of evidence suggest HA is degraded, in the liver, in the lymph nodes, as well as in local tissues, by acid hydrolases.^{3,21-24} There are three major enzymes that degrade HA in mammalian tissues, they are (1)

hyaluronidase (EC 3.2.1.35), which is an endoglycosidase, and whose substrate specificity is for a glycosidic bond containing C-1 of a GlcNAc residue, (2) β -D-glucuronidase (EC 3.2.1.31) which expunges the GlcA residue from the nonreducing end of the polymer, and (3) 2-acetamido-2-deoxy-D-hexosaminidase (EC 3.2.1.30), which removes the GlcNAc unit from the nonreducing end of the chain (Figure 2).

It has been well established that substituting the glycosidic -O- linkages with -CH₂- or -S- linkages render oligosaccharides resistant to enzymatic cleavage.²⁵ Although synthesizing an all -S-linked oligosaccharide is relatively difficult, an all -CH₂- linked oligosaccharide is a much greater task and is virtually impractical. To date, only a C-trisaccharide related to the Type II O(H) blood group determinant has been achieved.²⁶ Since making both an all S-linked and an all C-linked oligosaccharide would be essentially impossible, we proposed to synthesize "mixed" oligosaccharides. These compounds would have the C- or S-linkages strategically placed as to render the oligosaccharides resistant to the degrading enzymes and also contain the regular glycosidic O-linkages, principally to aid in ready synthesis. As Figure 3 illustrates, on a hexasaccharide for example, C or S-linkages would be placed at every reducing end of a GlcNAc residue and at the first linkage of the nonreducing end of the oligomer, regardless of the residue. To this end, a convergent "block synthesis" approach would be appropriate wherein a lone S or C-linked disaccharide is

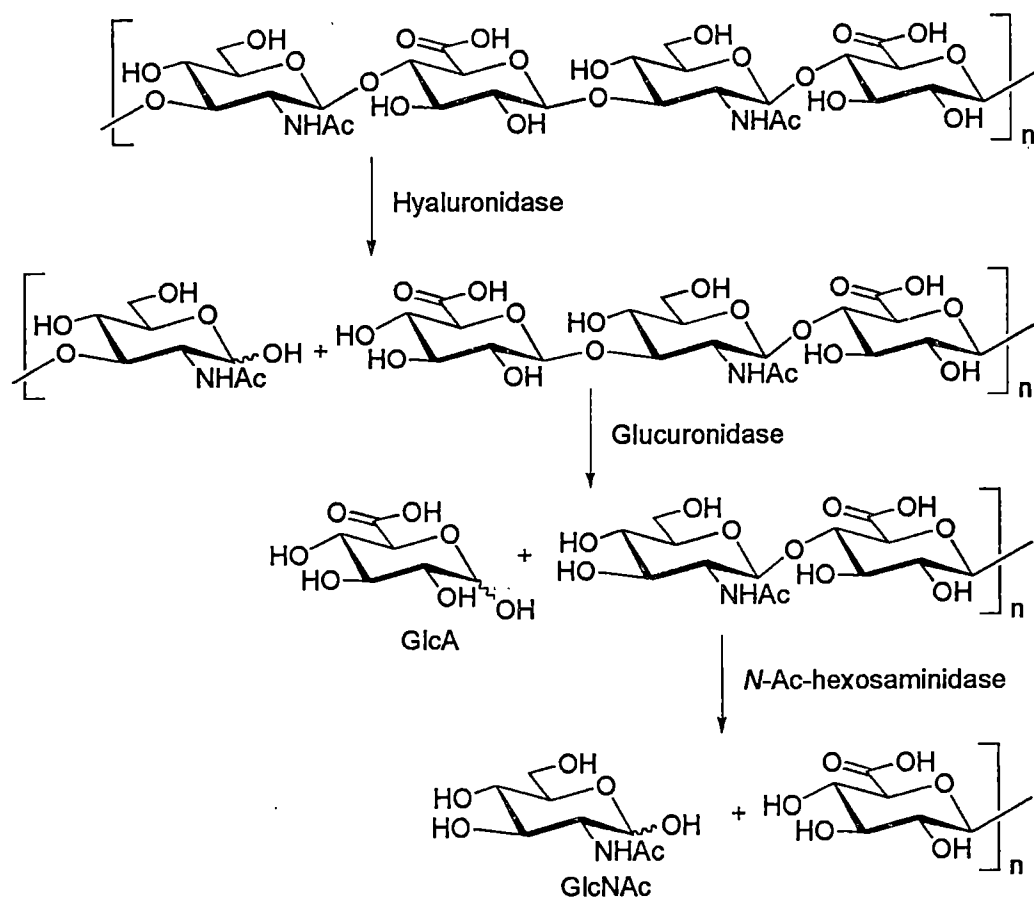


Figure 2. Enzyme degradation of HA.

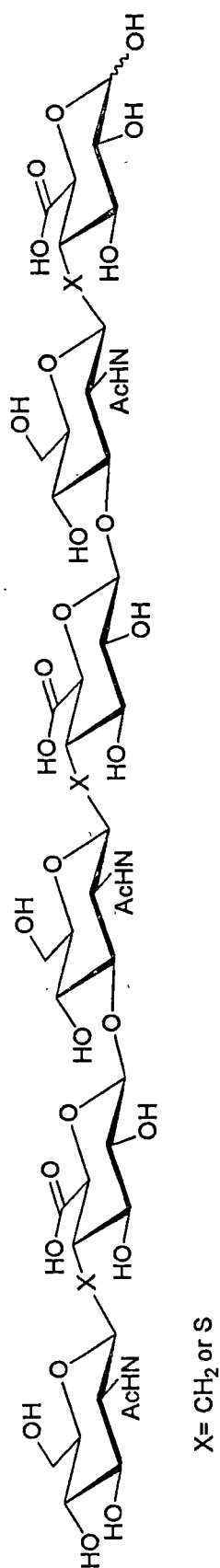


Figure 3. "Mixed" hexasaccharides.

linked once, twice, or more times *via* normal O-glycosidation techniques to produce oligomers of specified length (of either 4,6, or eight residues, etc.).

Knowing the specificity of the three major HA-degrading enzymes that were previously mentioned, the GlcNAc-X-GlcA (where X = -CH₂- or -S-) block unit is the best possible synthetic target, as this repeat unit eliminates any vulnerability to glucuronidase activity.

II. STATEMENT OF THE PROBLEM

A. Objectives

The major focus of this dissertation is the design and synthesis of the C-linked and S-linked analogues of the repeating, GlcNAc-(1→4)-GlcA, disaccharide unit of hyaluronic Acid. These disaccharide units will be useful as they will be used for NMR and molecular modeling studies. Further, the chemistry developed for these mimics will lay the foundation for the synthesis of higher order oligosaccharides, in the hopes of making potential anti-metastatic agents.

B. Research Plan

1. Retrosynthetic analysis

As previously stated, the "mixed" oligosaccharides will be assembled from a single disaccharide intermediate, GlcNAc-X-GlcA (where X = -CH₂- or -S-) that is strategically protected. This disaccharide unit will be adopted as the glycosyl acceptor, having the 3'-hydroxyl group free or as a C-1 glycosyl donor, activated as a trichloroacetimidate (Figure 4). Standard glycosidation methods, for example the use of silver triflate (AgOTf) or trimethylsilyl triflate (TMSOTf), will facilitate coupling of the disaccharide units. The primary alcohol, i.e., the 6-OH group of the GlcA moiety, will be selectively protected to allow for installation of the carboxylic acid at a late stage in the synthesis. In summary, the principal considerations for the synthesis of the disaccharide block unit are as follows:

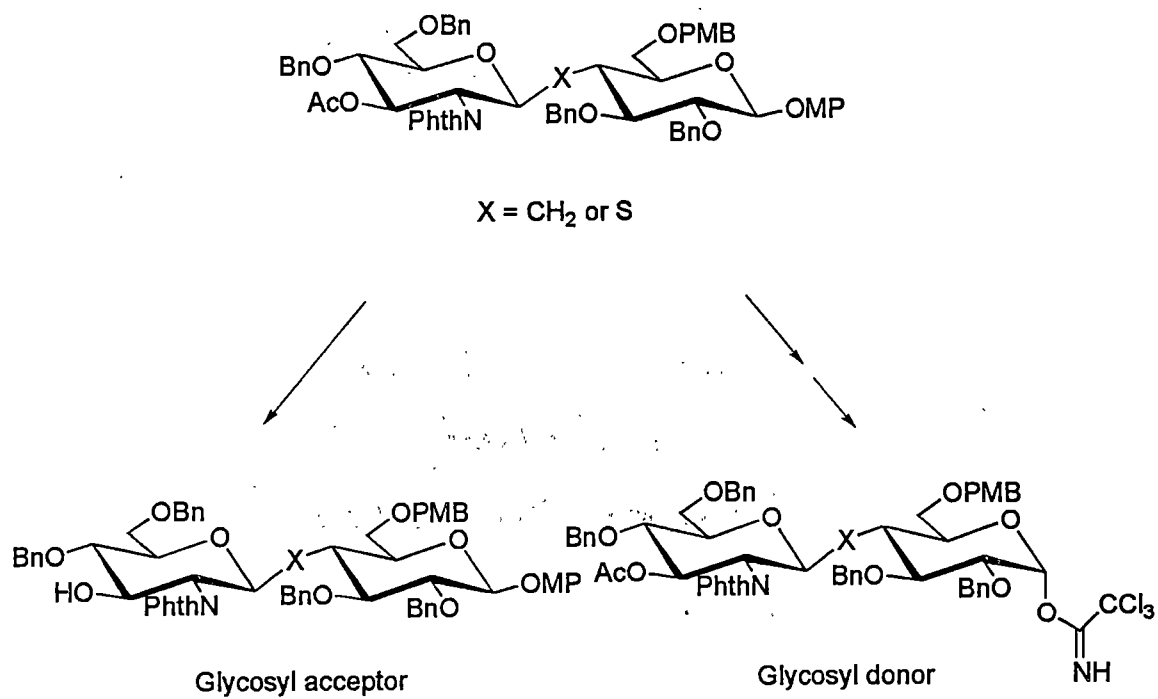


Figure 4. Building blocks for S and C-linked oligosaccharides.

- establishment of the CH₂- or S-linkage
- selective protection/deprotection of the 6-OH for later oxidation
- adequate protection at the 3'-OH which will serve as the acceptor
- differential protection at C-1 to function as the glycosyl donor
- suitable protection of the amine at C-2

Below the retrosynthetic analysis for the C and S-linked disaccharides is discussed.

1.1. Retrosynthetic analysis of the C-linked disaccharide related to HA

The occurrence of C-disaccharides (technically "C-glycosylic compounds"), compounds in which the interglycosidic oxygen bond is replaced by a methylene group or by a substituted carbon atom, in nature is quite negligible. According to Postema,²⁷ the term C-disaccharide is only applicable when the anomeric carbon of one sugar is bonded via one carbon atom to any position on another sugar. Researchers have shown immense interest in their potential as enzyme inhibitors and their capacity to withstand hydrolysis. Thus, a voluminous amount of effort has been shown toward the synthesis of these types of compounds.²⁸⁻³² Many of the methods currently being exploited for C-disaccharide synthesis were recently reviewed.²⁷ Several of these approaches are applicable toward our target.

Careful examination of the HA C-linked disaccharide revealed two sites of disconnection. As indicated by the arrows site 1 is between C-1 of the GlcNAc residue and the CH₂ group and site 2 is between the CH₂ group and C-4 of the

GlcA unit (Figure 5). As detailed in Bin Jiang's dissertation³³ these disconnections provide a cornucopia of reactive combinations. It was therefore prudent to evaluate a limited number of these possibilities. Our initial strategy was inspired by Martin's nitrosugar approach, and is extensively covered in Ken Price's dissertation³⁴ and the NIH grant application. Martin et al. have successfully synthesized both a β -C-(1 $\rightarrow$ 6)-linked (Scheme 1) and a β,β -C-(1 $\rightarrow$ 1)-linked (Scheme 2) disaccharide systems.^{35,36} Recently, Spak and Martin have also accomplished a mixed O/C-linked trisaccharide using this methodology.³⁷ Kobertz et al. also utilized the nitroaldol reaction to synthesize the C-linked analog of the biologically potent inducer of the *lac* repressor protein, allolactose.³⁸ Likewise, Julina³⁹ and Gross⁴⁰ have carried out pioneering work in the use of nitrosugars in the synthesis of C-glycosides and C-disaccharides under similar conditions. Briefly, our plan as described in Scheme 3 called for the potassium fluoride-mediated condensation of a differentially protected acyclic aldehyde and an activated nitrosugar, in the presence of 18-crown-6 in acetonitrile. After coupling, free-radical denitration and an unusual ring closure, the versatile disaccharide intermediate with the desired β stereochemistry between the C-1 of the GlcNAc unit and the newly formed methylene group should be formed. A bulky protecting group on the amine at C-2 will assist in providing the necessary stereochemistry. The invaluable aldehydo sugar will be prepared in several steps from glucosamine hydrochloride in which the key step

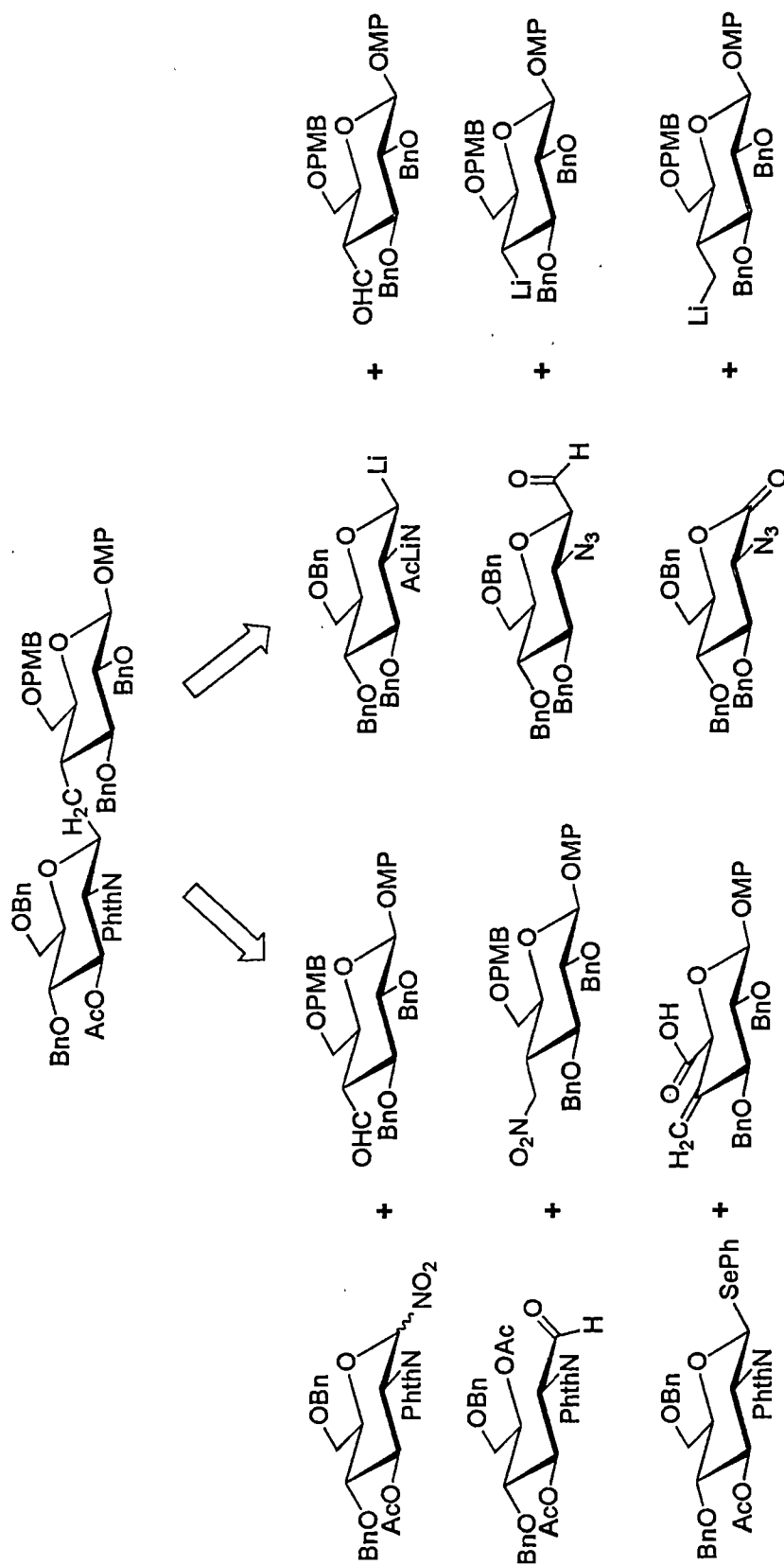
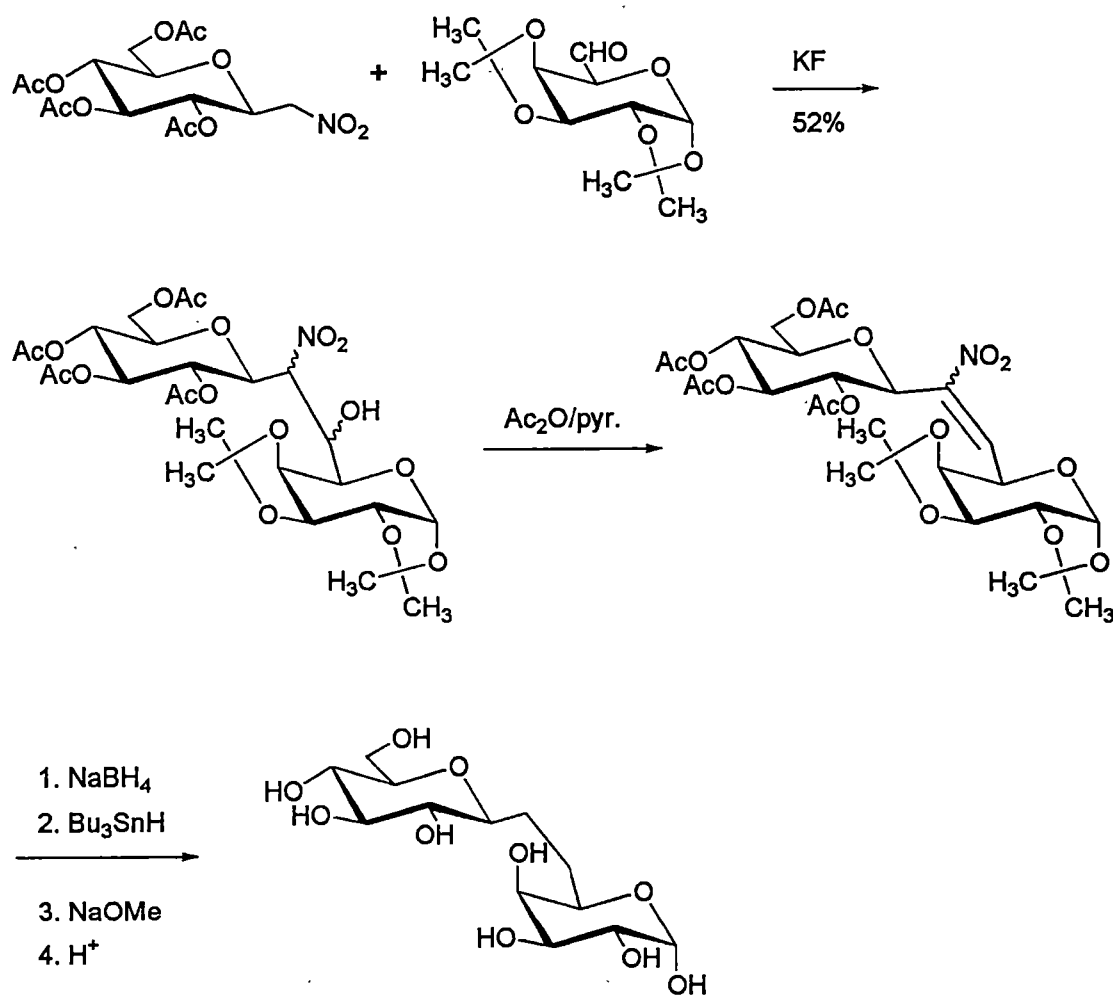
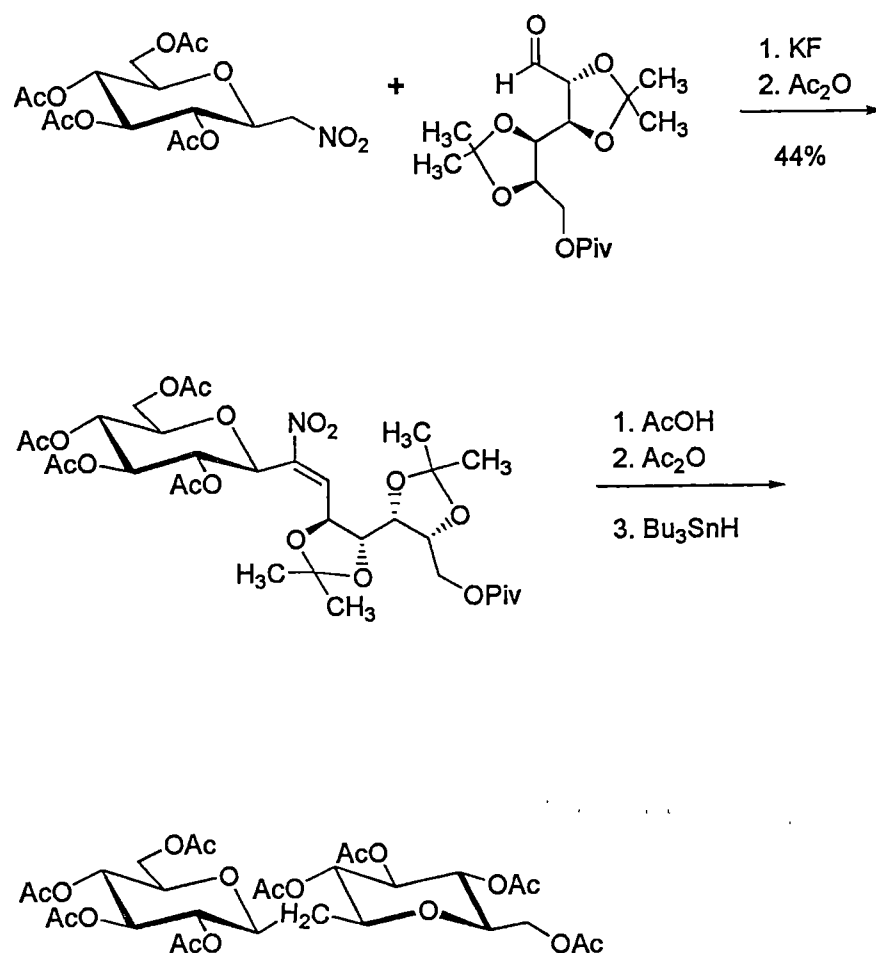


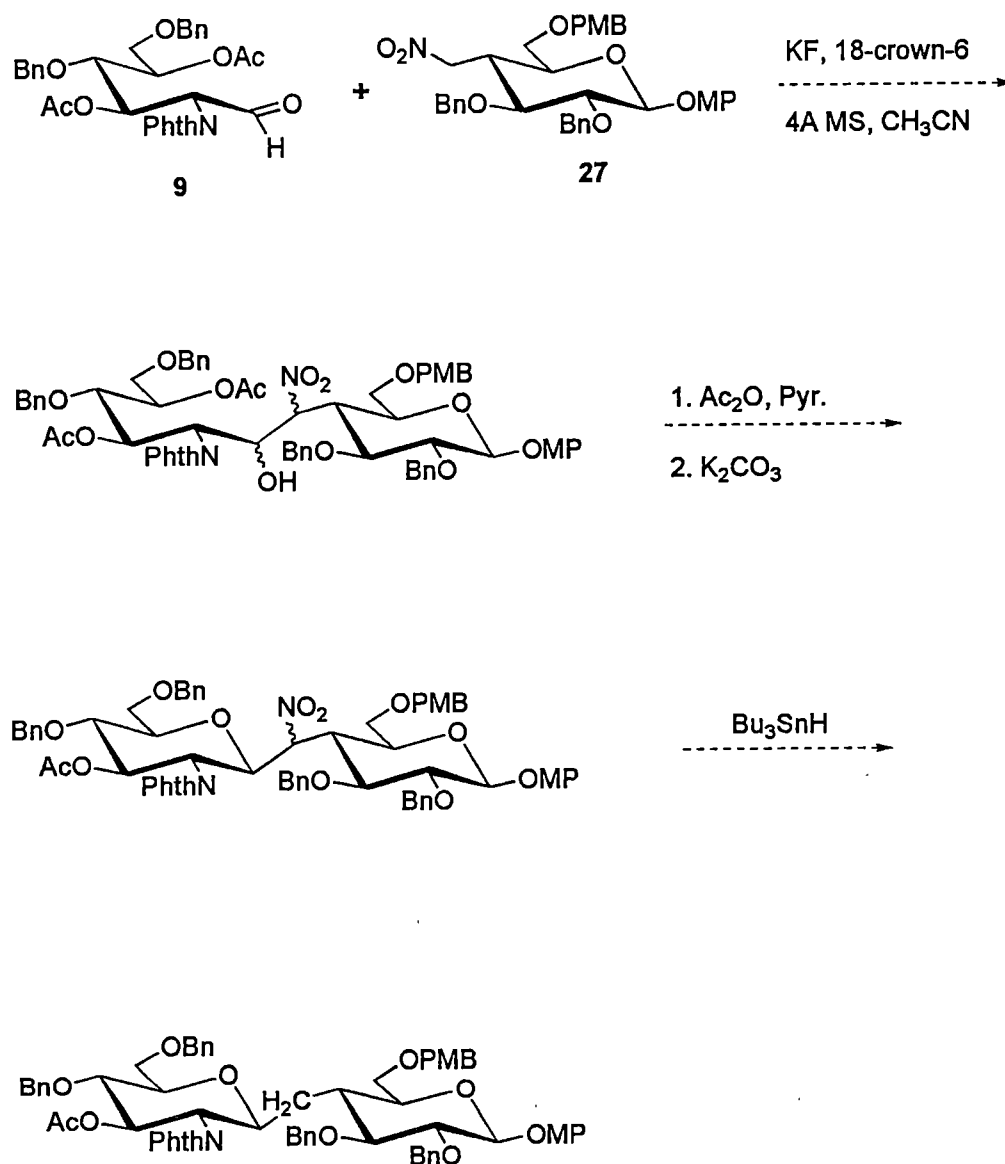
Figure 5. Retrosynthetic Analysis for C-disaccharide.



Scheme 1. Martin's approach to β -C-(1 $\rightarrow$ 6)-linked disaccharide.



Scheme 2. Martin's approach to β -C-(1 $\rightarrow$ 1)-linked disaccharide.

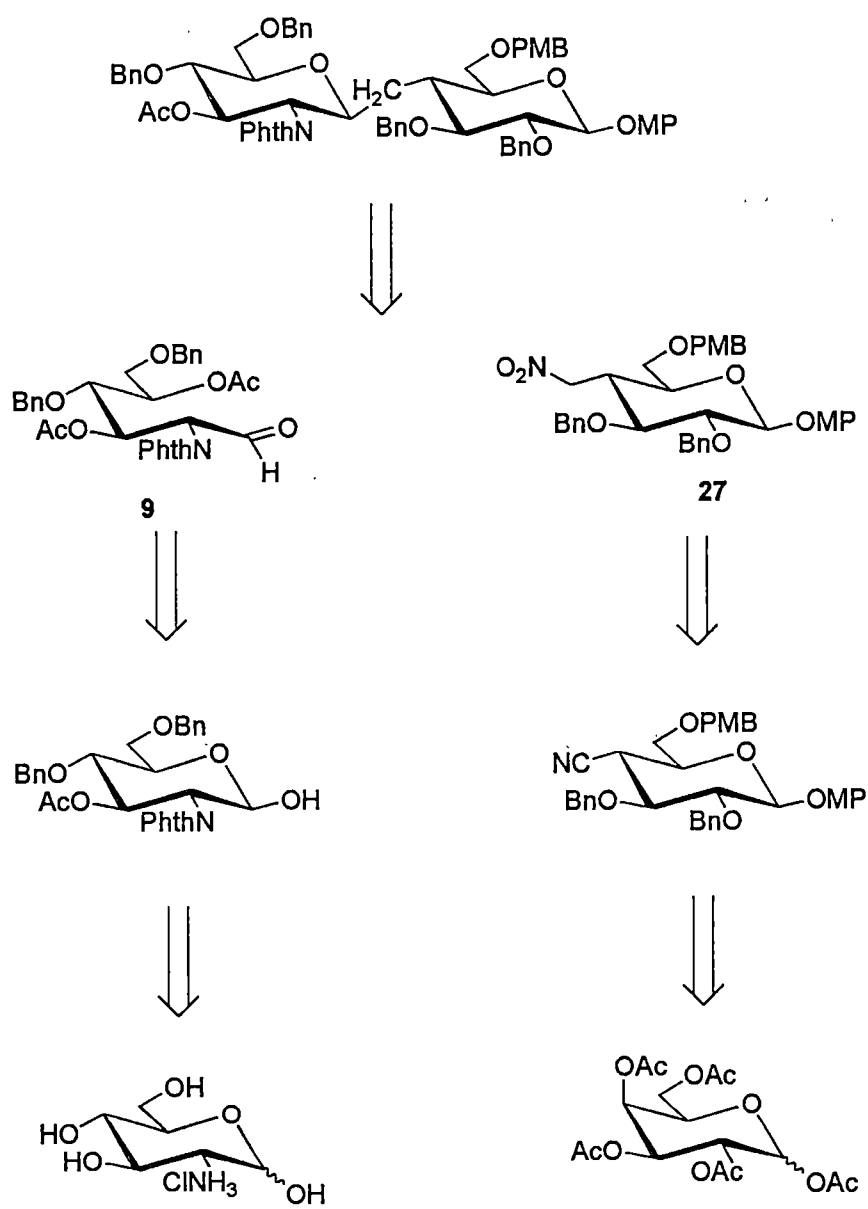


Scheme 3. Proposed nitrosugar approach to β -C-(1 $\rightarrow$ 4)-linked disaccharide.

is generation of the open-chain diethyl dithioacetal from treatment of the appropriately protected GlcNAc pyranose with ethanethiol in acid (Scheme 4). The resulting 5-OH compound will be protected and subsequently treated under Wolfrom's conditions⁴¹ to give the distinctly masked acyclic aldehyde. Galactose pentaacetate will serve as the starting material for the C-glycoside acceptor (Scheme 4). The stereochemistry around C-4 of the GlcA moiety will be established prior to coupling from an S_N2 cyanide displacement of an axially substituted triflate, followed by lithium aluminum hydride (LAH) reduction and *m*-CPBA or dimethyldioxirane oxidation to furnish the nitrosugar.

1.2. Retrosynthetic analysis of the S-linked disaccharide analogue of HA

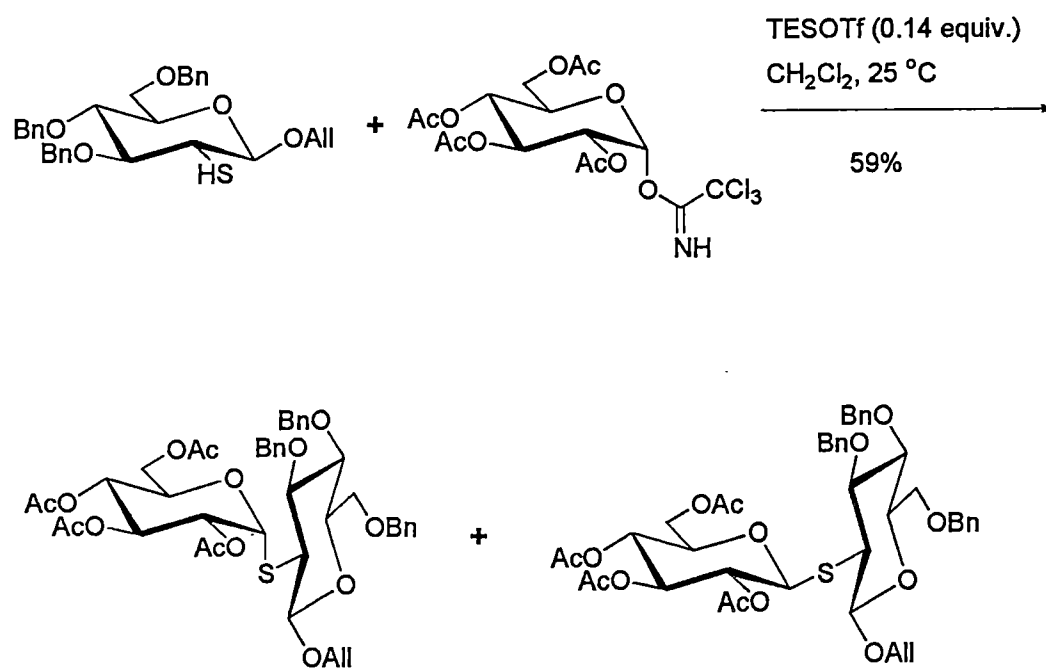
Thiodisaccharides are unnatural analogues of O-linked disaccharides in which the interglycosidic linkage is replaced with a sulfur atom. Like their C-linked counterparts, thiodisaccharides are more resistant to hydrolysis than their O-linked equivalents, and are excellent tools for studying various enzymatic systems.⁴²⁻⁴⁴ Additionally these compounds are frequently stable to chemical or enzymatic degradation and are inclined to behave as enzyme inhibitors.^{45,46} Early endeavors into the synthesis of the S-linked mimic of hyaluronic acid by Ken Price, which is covered comprehensively in his dissertation,³⁴ utilized a modified Schmidt's trichloroacetimidate strategy.⁴⁷ This method took full advantage of a 2-phthalimido-1-trichloroacetimidate as a glycosyl donor and a 4-SH glycosyl acceptor to generate a uniquely protected S-disaccharide. To our knowledge this was the first occasion that Schmidt's methodology was used for



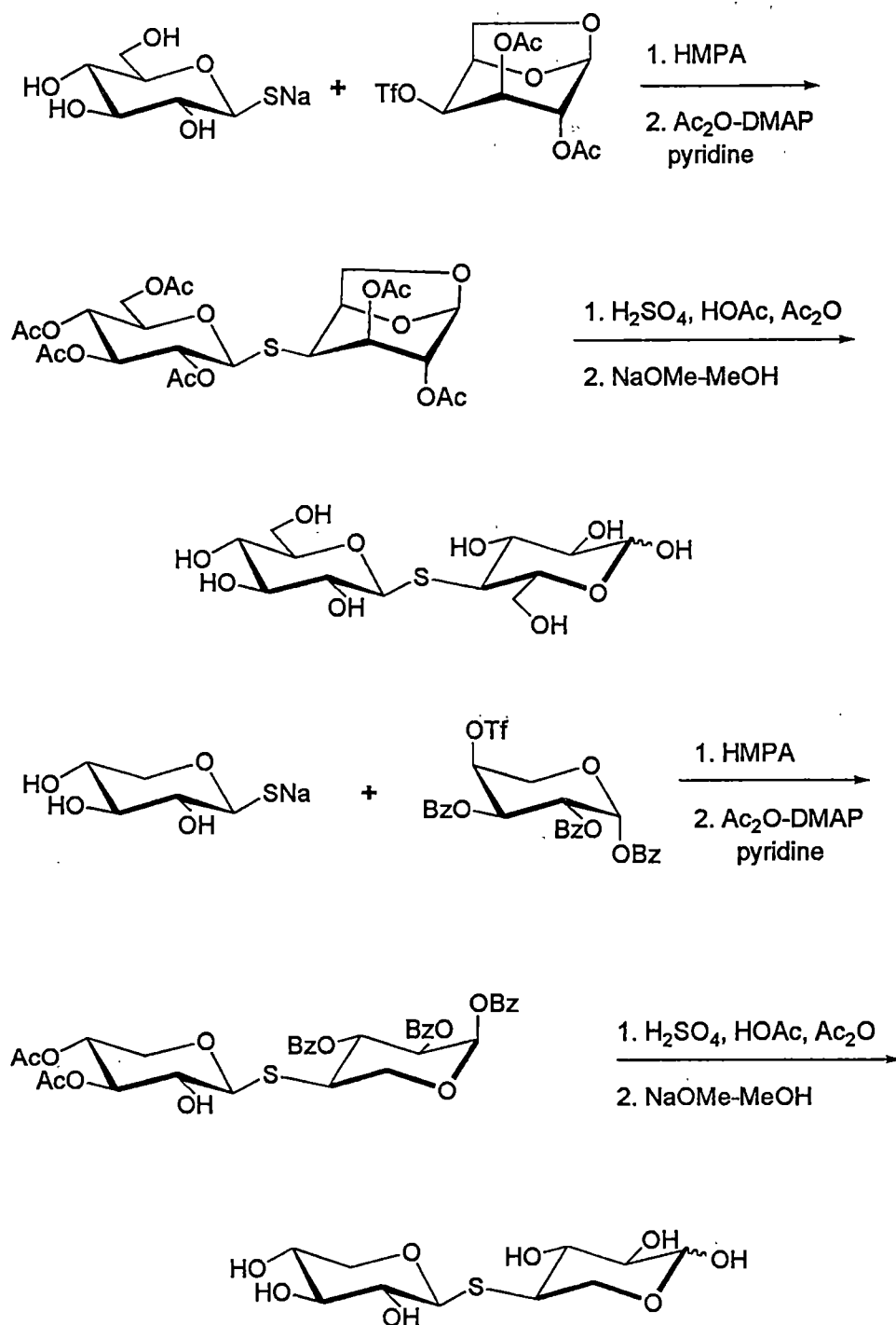
Scheme 4. Retrosynthetic analysis for aldehyde **9** and nitrosugar **27**.

this purpose. Unfortunately, manipulation of the protecting groups, particularly at C-1, was arduous; hence, the S-oligosaccharide was not made. We decided to focus our attention toward making the S-disaccharide first, and then longer chain oligosaccharides. Andrews and Pinto⁴⁸ published the application of this procedure in their synthesis of kojibioside, a potential glucosidase inhibitor (Scheme 5). Their synthesis commenced with a series of steps to provide the glycosyl 2-SH acceptor. Upon treatment of the acceptor with 0.14 equivalents triethylsilyltriflate in the presence of the acetylated α -trichloroacetimidate, both α and β disaccharides were formed. However, at lower catalyst concentrations only the orthoester was isolated. The orthoester then rearranged under added triethylsilyltriflate to give both α and β thio-linked disaccharides. Schmidt and co-workers have also developed this method toward the synthesis of a mimic of the highly studied sialyl Lewis X.⁴⁹

Price had also attempted the coupling of a thiolate anion with a monosaccharide that possessed an axial triflate leaving group in accord with Driguez' method.⁵¹⁻⁵³ Driguez has done considerable work in this area (Scheme 6) and has reviewed published synthesis of thiooligosaccharides.⁵³ The most acclaimed of these procedures applied S_N2 type substitutions in which thiolate anions are used to displace a good leaving group on a monosaccharide moiety. With our disaccharide target, two types of thiolate anions can be formed from the two disconnection points labeled A and B (Figure 6). Disconnection at point A, which is between the C-1 of the glucosamine unit and the sulfur atom, provides a



Scheme 5. Pinto's approach to S-linked disaccharides.



Scheme 6. Driguez' method to S-linked disaccharides.

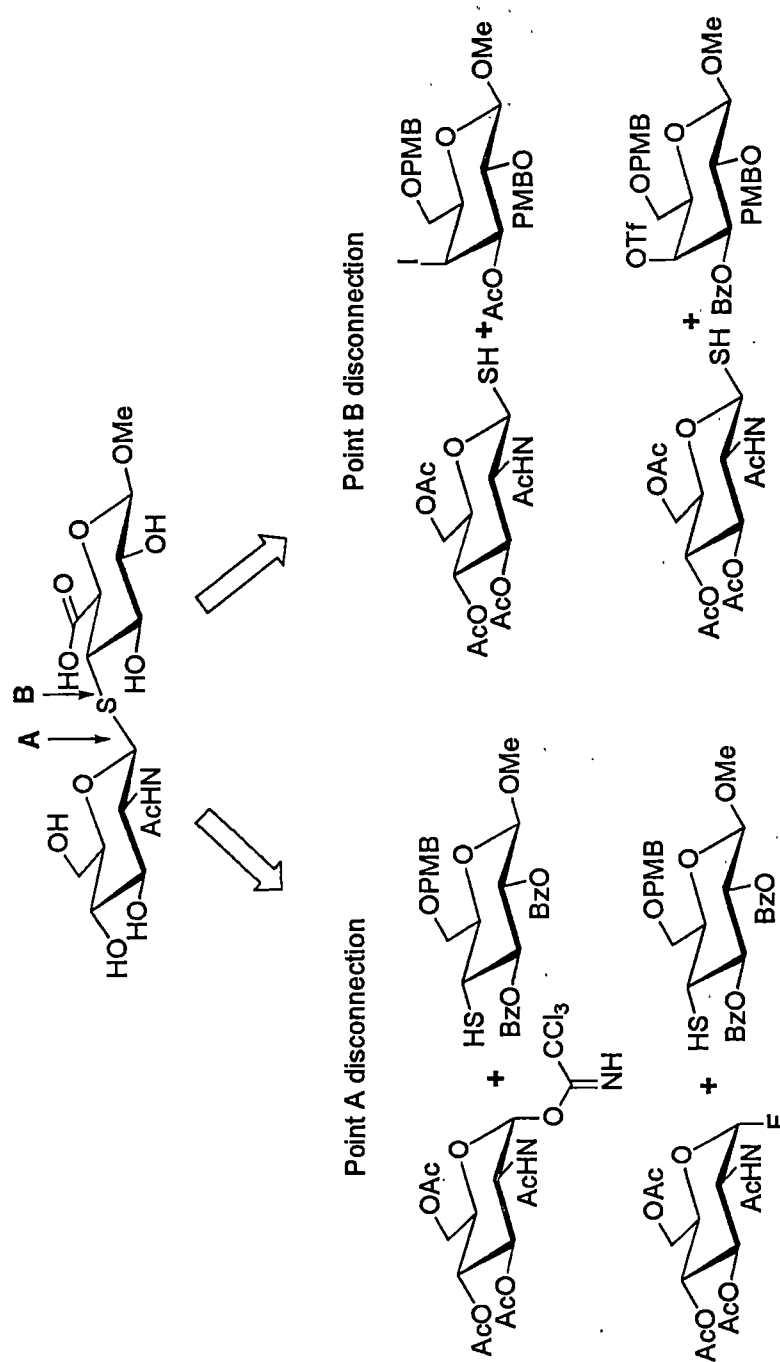
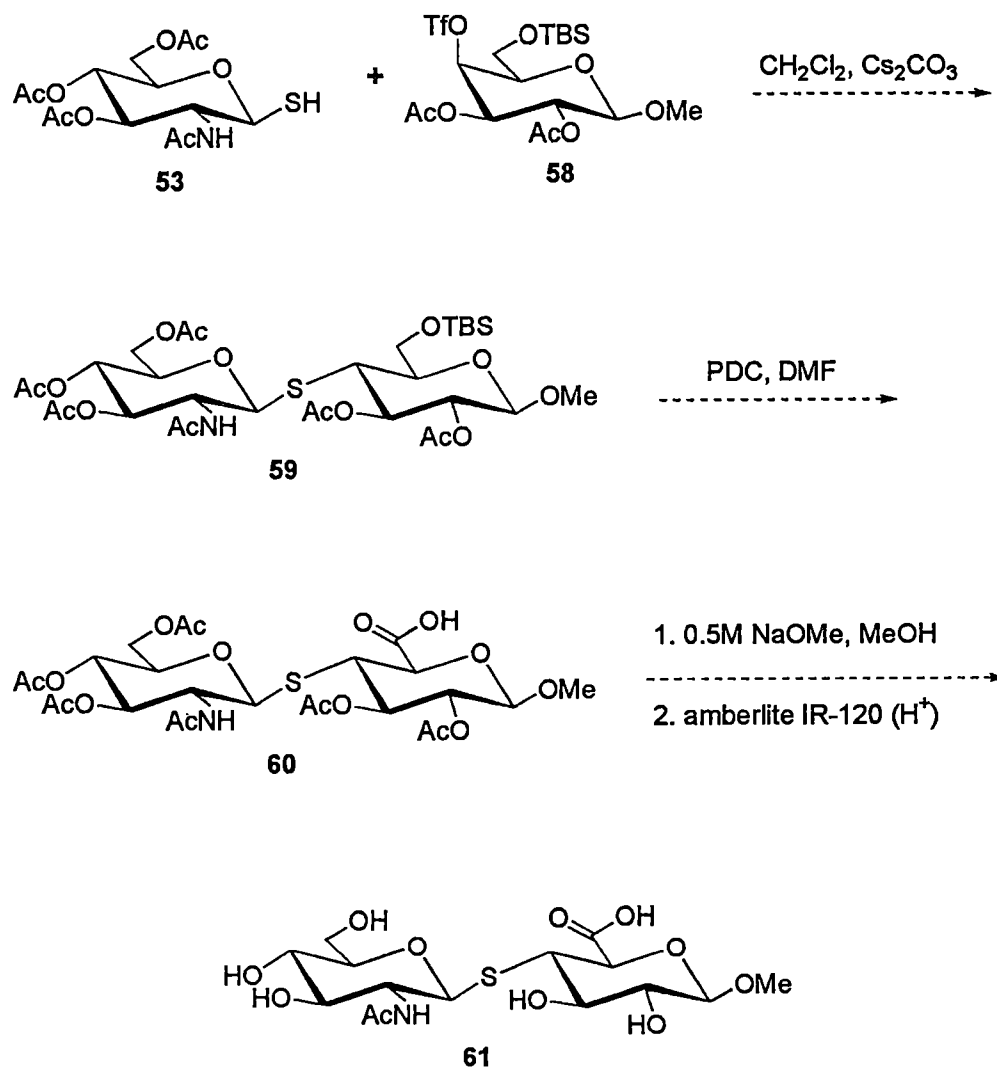


Figure 6. Retrosynthetic analysis for S-linked disaccharide.

4-thiolate anion and an amino C-1 electrophile. Point B disconnection, between the sulfur atom and the C-4 of the glucuronic acid residue, affords an amino 1-thiolate anion and a C-4 electrophile.

Although Price had little success via the 2-phthalimido-1-thiolate anion displacement of a C-4 triflate, we were confident this popular methodology could work. In his dissertation Price alluded to the C-4 triflate as the unreactive fragment. Consequently, we postulated that protecting groups, such as acetates on the C-4 triflate would increase its reactivity. For convenience, we decided to use only acetyl protecting groups on the thiol. Our strategy (Scheme 7) was to perform a base-mediated coupling of thiol **53** with an axial C-4 triflate distinctively protected at the 2- and 3-positions with acetyl groups and the 6-position with *tert*-butyldimethylsilyl (TBS). Pyridinium dichromate (PDC) oxidation of the TBS-protected 6-hydroxy group to the carboxylic acid should furnish **60**. Ester hydrolysis and acetyl group removal should award the S-disaccharide. With confirmation that the protecting groups on the triflate were the problem, a revised route to longer chain oligosaccharides could be planned. The major advantage of this method over the trichloroacetimidate is the simplicity of making the coupling partners, the thiol and the triflate, as well as their increased stability.

Procurement of the thiol would occur according to the procedure of Wang and Lee.⁵⁴ Thus, 2-acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine) will be



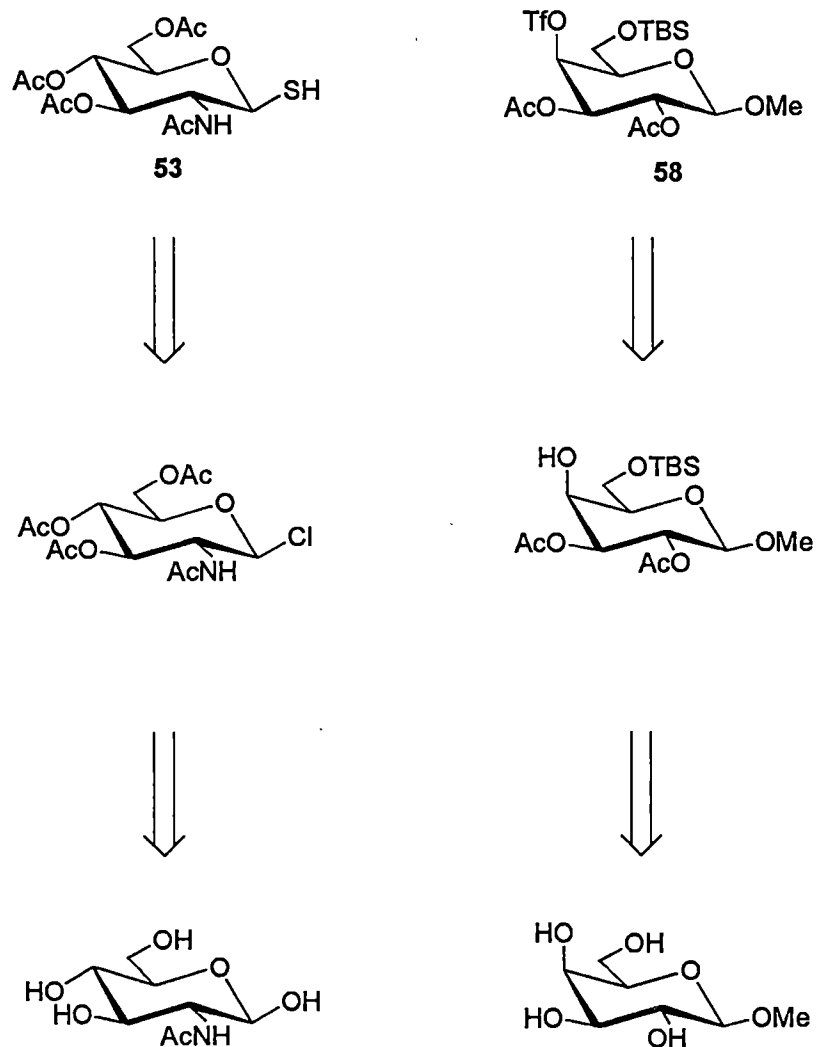
Scheme 7. Proposed approach to S-linked disaccharide of HA.

converted in three steps to the thiol. However, the desired C-4 triflate requires a great deal more effort (Scheme 8). It can be built from treatment of the exposed 4-OH compound with triflic anhydride, which can be garnered through a series of protecting group manipulations from methyl β -D-galactopyranoside.

Our alternative plan was to adopt Santoyo-Gonzalez⁵⁵ approach. Santoyo-Gonzalez has used the cyclic sulfate method popularized by Sharpless and co-workers⁵⁶ to synthesize thio-linked disaccharides. Accordingly, an O-acetyl protected 1-thioglycose was reacted in the presence of cesium carbonate with various cyclic sulfates. For example, when the 1- β -thioglycose was reacted with a α -4,6-cyclic sulfate a β -(1 $\rightarrow$ 4)-thioglycosidic linkage was established. Moreover, only the β -(1 $\rightarrow$ 3)-linkage was observed when a β -4,6-cyclic sulfate was employed. This was owing to steric factors. Both O/S "mixed" linked and all -S-linked oligosaccharides can be made *via* this route.

C. Significance

Synthesis of the C-linked and S-linked disaccharides related to hyaluronic acid presents three inimitable challenges which are as follows: (1) generation of the desired β stereochemistry (2) selective oxidation of the 6-OH group to the carboxylic acid and (3) manipulation of the amino function. Incorporating the *N*-acetylglucosamine moiety at the nonreducing end of a C-disaccharide is horribly complex. Only a handful of instances exist in the literature. Many of these methods are not stereoselective, and most give mixtures of α and β products,



Scheme 8. Retrosynthetic analysis of thiol **53** and triflate **58**.

with the α anomer predominating. Therefore, an alternative approach, that can predominately provide the β anomer would be useful. Additionally, the HA mimics have a carboxylic acid moiety that substantially boosts the difficulty of the synthesis. In the case of the S-linked analogue, if coupling occurs prior to introduction of the carboxylic entity, the methods of oxidation are limited, since most oxidizing agents oxidize both oxygen and sulfur. With respect to the C-linked mimic, establishment of the carboxylic acid group before coupling diminishes the coupling possibilities owing in part to electronic effects.

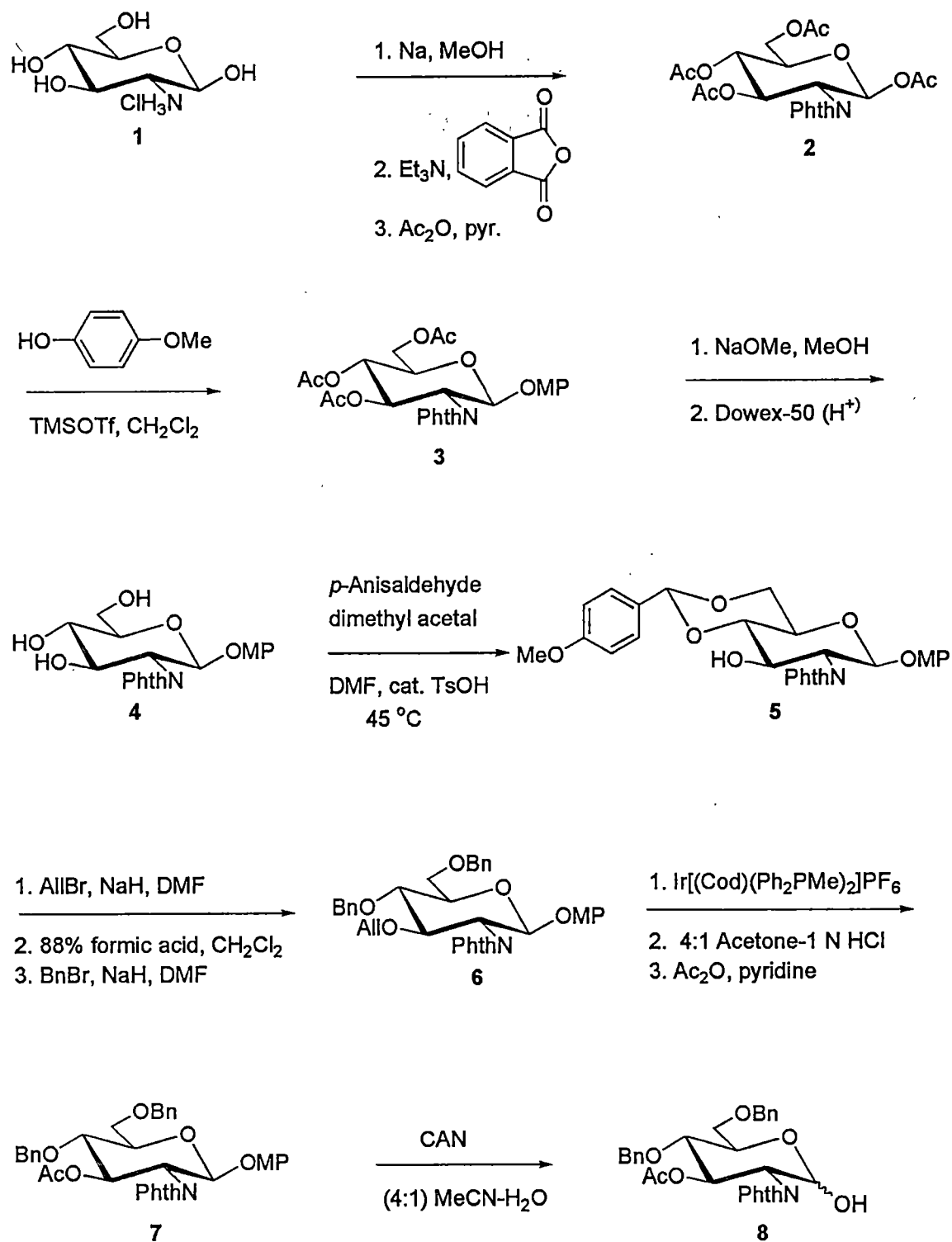
III. RESULTS AND DISCUSSION

A. C-Disaccharide Synthesis: The Nitro Sugar Approach

1. Attempted synthesis of acyclic aldehyde **9**

Ken Price³⁴ designed our initial strategy for the synthesis of the C-disaccharide mimic of hyaluronic acid. As stated earlier, this approach was based on Martin's methodology for the synthesis of C-disaccharides.³⁵ It involves coupling of an orthogonally protected nitro sugar with an appropriately masked aldehyde. With great enthusiasm we embarked on our synthetic pursuit toward this novel C-disaccharide with the intent of making longer chain oligosaccharides.

Thus, compound **3** was prepared as described by Lemieux and co-workers⁵⁷ (Scheme 9). D-Glucosamine hydrochloride was added to a solution of methanolic sodium, followed by triethylamine and phthalic anhydride, and subsequently, treatment with acetic anhydride and pyridine, provided tetraacetate **2**. Next, *p*-methoxyphenol and trimethylsilyl trifluoromethanesulfonate (TMSOTf) were introduced to a solution of crystalline **2** in dry dichloromethane at 0 °C, to provide compound **3**. Deacetylation of **3** in the conventional way with sodium methoxide proceeded smoothly to the anticipated triol **4**, which was used without further purification in the ensuing reaction. Thus, transacetalation was induced with *p*-anisaldehyde dimethylacetal in anhydrous *N,N*-dimethylformamide (DMF) at 45 °C with a catalytic quantity of *p*-toluenesulfonic acid (TsOH) under reduced pressure to



Scheme 9. Synthesis of alcohol 8.

afford **5**. At this stage, the exposed alcohol was easily protected as the allyl ether. Hence, alcohol **5** was treated with allyl bromide and sodium hydride (NaH), which furnished the fully protected monosaccharide. Acidic expulsion of the acetal with formic acid at room temperature, and subsequent benzylation of the diol under standard conditions (BnBr and NaH in DMF), gave **6** as a pale-yellow oil after column chromatography. To access the essential C-1 alcohol **8**, compound **6** was deallylated using an activated iridium catalyst, and the resultant propenyl glycoside was exposed to acidic conditions to liberate the 3-hydroxy group. Subsequently, the hydroxy group, which will serve as the glycosyl acceptor, was reprotected as the acetate ester *via* acetic anhydride and pyridine to afford **7**. The *p*-methoxyphenyl group of **7** was readily discharged with ceric ammonium nitrate (CAN) in 4:1 MeCN-H₂O,⁵⁸ thus freeing the anomeric carbon to yield **8**. The removal of the *p*-methoxyphenyl group was easily confirmed by ¹H NMR spectroscopy. The singlet at δ 3.71 and the doublets at 6.68 and 6.84 corresponding to the methoxy and aromatic protons disappeared.

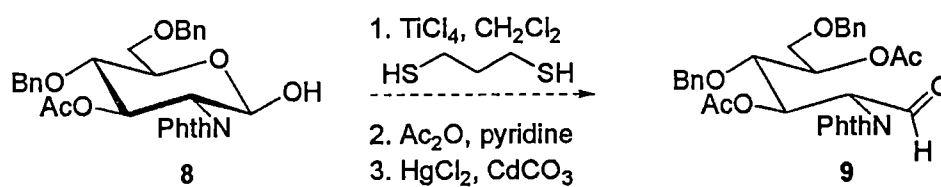
Although a milestone had been reached, we were faced with two important concerns: (1) the length of the synthesis, which we thought could be shortened by amending our protecting group strategy, and (2) the cost of employing the iridium catalyst. Although it proved quite effective, it was not advantageous for large-scale reactions. Because we had ample quantities of compound **5**, we envisioned altering the protecting strategy beyond this point. Several protecting groups were considered to conceal the 3-OH group, but we choose with some

apprehension, the robust *tert*-butyldimethylsilyl (TBS) group because it was expected to survive both the acetal removal and benzylation steps. Our excitement for this group was short lived, however. Although it survived acetal removal, it migrated under the alkaline conditions of benzylation. Consequently, we looked at introducing the benzyl groups under neutral conditions using freshly generated silver oxide as catalyst.^{59,60} This procedure failed and no dibenzylated product was observed; however, the 6-OH group was benzylated and this compound was isolated in poor yield.

Our focus shifted to alternative methods of isomerizing the allyl group. There are numerous methods in the literature for accomplishing this task, including, the use of Wilkinson's catalyst, potassium *tert*-butoxide, and stoichiometric amounts of PdCl₂ with stoichiometric quantities of CuCl₂,⁶¹ and trisphenylphosphine rhodium chloride (RhCl(PPh₃)₃),⁶² however, in our hands, none of these methods gave good yields of the 3-OH compound. The iridium catalyst proved superior for our purpose.

Armed with adequate amounts of **8**, the path to the desired acyclic aldehyde seemed uncomplicated since there are countless examples of ring-opening approaches for carbohydrates utilizing dithiane chemistry. With the aldehyde moiety concealed as the dithiane or thioacetal, the next step would be the protection of the newly formed hydroxyl group at position 5, followed by release of the aldehyde with the application of a mercury reagent. Frustratingly, masking the aldehyde proved formidable. Several procedures were examined,

including boron trifluoride etherate ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) in 1,3-propanedithiol, zinc chloride (ZnCl_2) in ethanethiol, dry hydrochloric acid (HCl) with ethanethiol,⁶³ and titanium tetrachloride (TiCl_4) as the Lewis acid promoter in conjunction with both ethanethiol and ethanedithiol.⁶⁴ Only TiCl_4 as promoter in ethanedithiol gave any of the desired product in moderate isolated yield (Scheme 10). In many cases no reaction was observed or the thioglycoside was produced. In the case of BF_3 as Lewis acid in ethanethiol, very polar products were detected on thin-layer chromatography, perhaps due to debenzylation of the monosaccharide. Fletcher and Diehl have demonstrated that this combination of reagents is an efficient method for the removal of *O*-benzyl groups from carbohydrates.⁶⁵ Following protection of the free hydroxy group as the acetate ester, all attempts at depositing the dithiane to furnish **9** failed. Various established procedures were tried, such as $\text{HgCl}_2\text{--HgO}$, NBS,⁶⁶ $\text{BF}_3 \cdot \text{Et}_2\text{O--HgO}$, HgClO_4 , and bis-(trifluoroacetoxy)-iodobenzene.⁶⁷ In most cases the products were unidentifiable. We could not rule out the possibility that trace amounts of the product were formed; therefore, we attempted to detect the presence of the aldehyde from these products using purpaldTM, (4-amino-3-hydrazino-5-mercapto-1,2,4-triazole, 4-amino-5-hydrazino-4*H*-1,2,4-triazole-3-thiol).^{68,69} Unfortunately, no detectable aldehyde was observed. The intrinsic electron-withdrawing capacity of the phthalimido group influences significantly the reactivity of the monosaccharide. Unequivocally it affects the oxidation of the dithiane. Further investigation is needed to assess the complete role of the



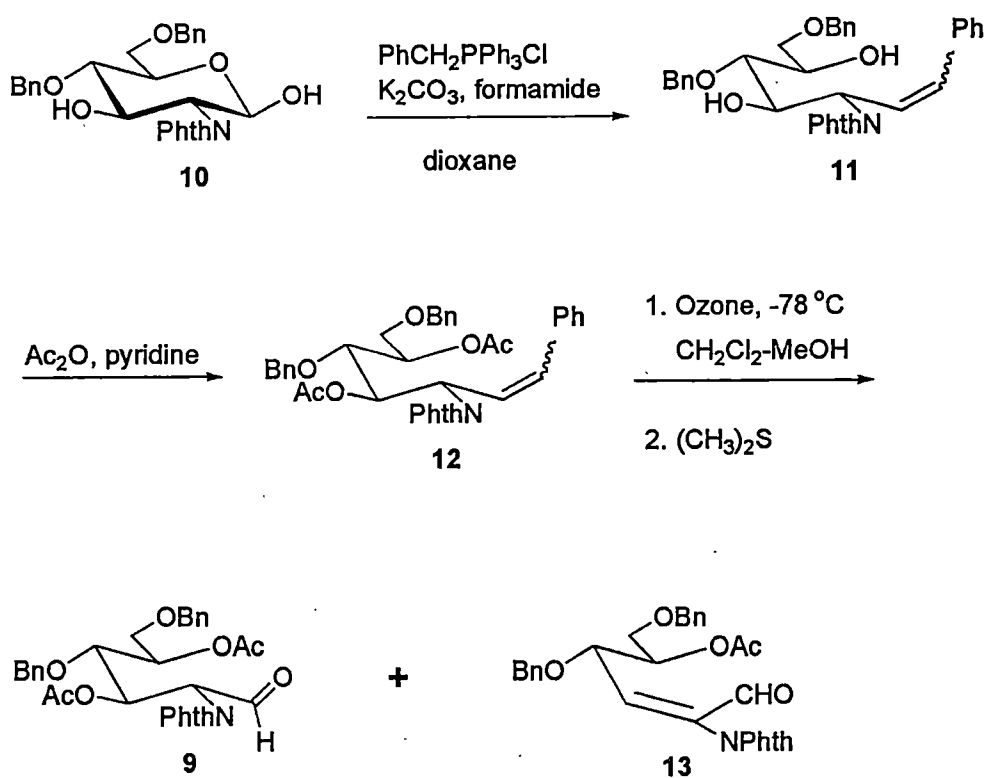
Scheme 10. Attempted synthesis of acyclic aldehyde **9**.

phthalimido group in these types of reactions. It became apparent that our original methodology for aldehyde construction was defunct.

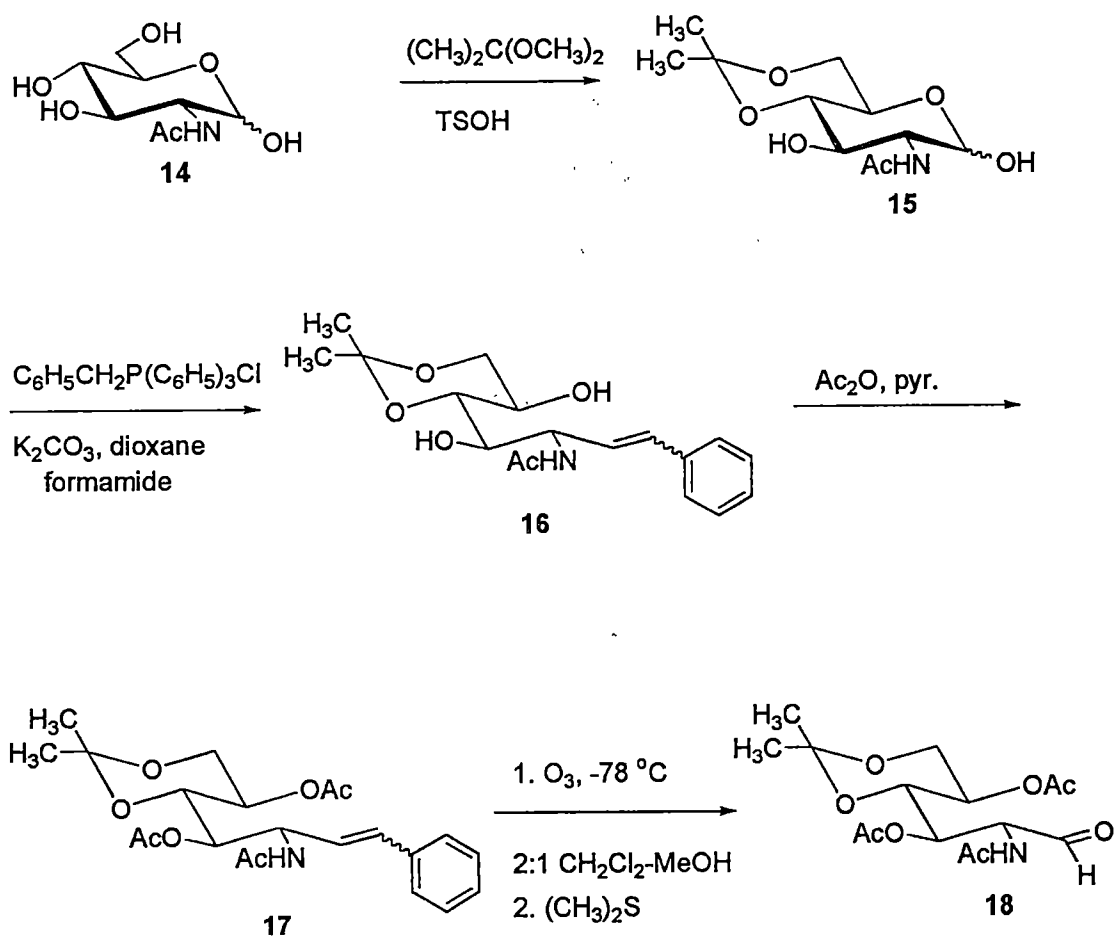
At this stage we became cognizant of an alternative protocol for generating the desired aldehyde. Gannis et al.⁷⁰ used a Wittig-type reaction on an analogous substrate as ours to spawn an alkene, which when subjected to ozonolysis, afforded the corresponding aldehyde. In addition, the method was also successful with unprotected carbohydrates utilizing semi-stabilized ylides.⁷¹ Fortunately, intermediates **8** and **10** which were synthesized through a three-step sequence from compound **6**, were prime candidates for application of this methodology. Accordingly, pyranose **10** was refluxed in dry dioxane in the presence of benzyltriphenylphosphonium chloride, powdered potassium carbonate and distilled formamide to give alkene **11** (*E/Z* mixture) as a syrup (Scheme 11). Agitating the alkene in anhydrous pyridine and acetic anhydride furnished **12** in quantitative yields. Oxidation of **12** under ozone at -78 °C in chloroform-methanol, followed by treatment with dimethyl sulfide, gave **9**. However, compound **9** spontaneously eliminated to yield **13**. While this was disheartening, we were confident that the phthalimido group contributed to the rapid elimination of the aldehyde moiety; therefore an appropriate change in the amino protecting group would cease or at least significantly delay the onset of elimination. We were proven correct.

2. Synthesis of acyclic aldehyde **18**

As delineated in Scheme 12, aldehyde **18** was effortlessly assembled from



Scheme 11. Attempted synthesis of acyclic aldehyde **9** via Wittig reaction.



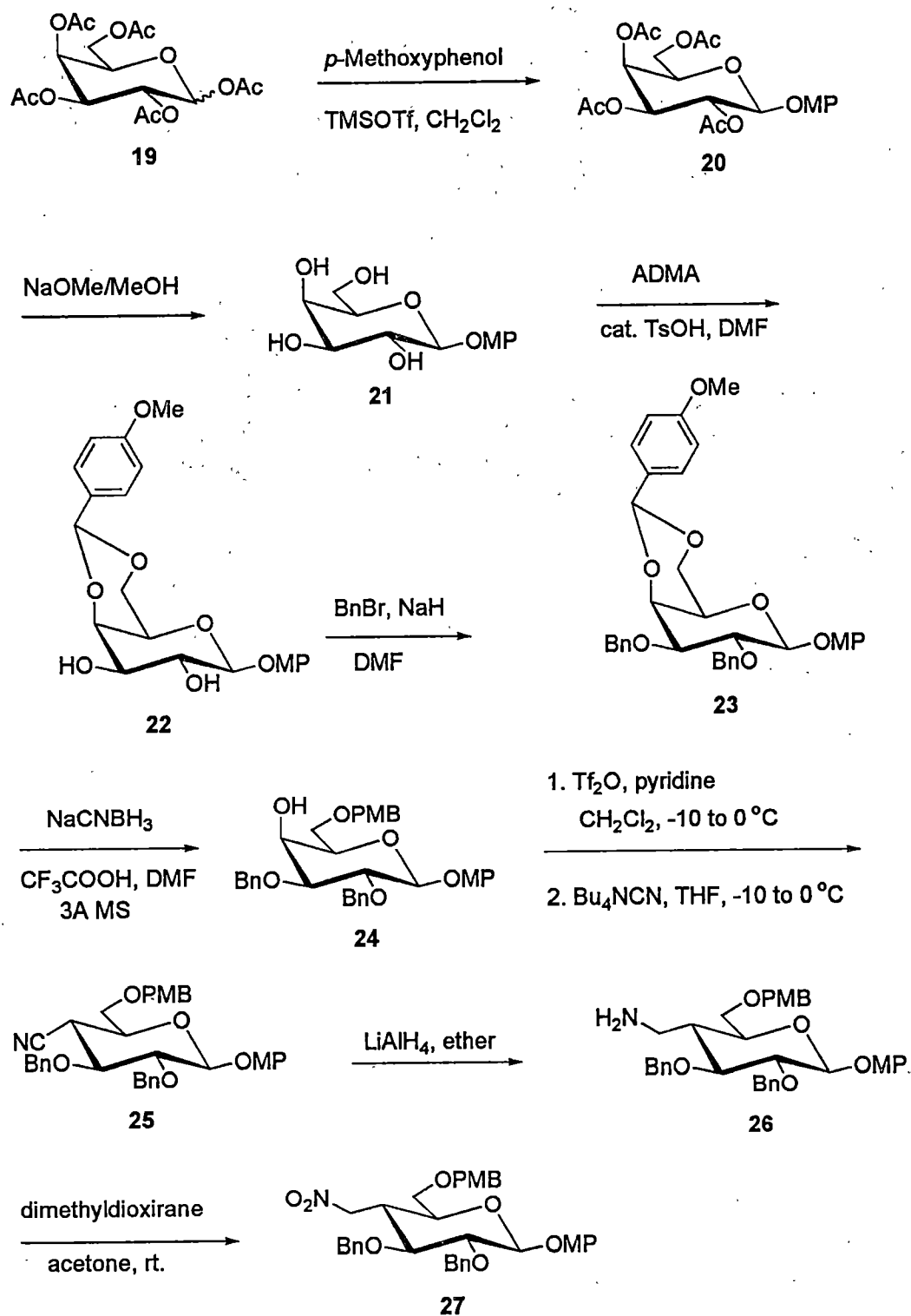
Scheme 12. Synthesis of aldehyde **18** via Wittig reaction.

commercially available *N*-acetyl-D-glucosamine (**14**). Hence, when compound **14** was stirred in the presence of 2,2-dimethoxypropane ((CH₃)₂C(OCH₃)₂) and *p*-toluenesulfonic acid, the 4,6-*O*-isopropylidene acetal **15** was acquired. Treatment of **15** in an identical process as detailed above for intermediate **10** afforded **16** as a mixture of isomers, which were immediately subjected to pyridine and acetic anhydride at room temperature to provide the diacetate **17** as a mixture of isomers. The isomers were separable at this stage, but this was unnecessary because olefin **17**, after ozonolysis, was smoothly transformed to a single product **18**. Rapid column chromatography of compound **18** in the presence of an alcohol provided the pure aldehyde. It is believed that the alcohol helps stabilize aldehydo sugars by adding to the carbonyl group producing a hemiacetal and rendering H-2 less acidic; therefore, the aldehyde can survive during chromatography.⁷² Furthermore, chromatography of the aldehyde over silica gel impregnated with 25% (w/w) water, helped prevent β -elimination; however, resolution was compromised. β -Elimination of **18** was observed following contact with silica gel over extended periods of time to provide **18b** (not shown, NMR data is provided in the experimental section). In their study, Martin and Lai³⁶ alluded to the observation that under mildly alkaline conditions 5-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-*aldehydo*-D-glucose experienced considerable β -elimination. Whereas, when the 2-OH and 3-OH formed an isopropylidene moiety, the aldehydo sugar was significantly less inclined to eliminate. Miljkovic⁷² also found that aminodeoxy-*aldehydo*-sugars were

extremely labile and could not withstand chromatography on fully active silica gel.

3. Synthesis of nitrosugar 27

At this juncture, an abbreviated summary of the demanding steps toward the synthesis of compound **27**, which was made by my co-worker, Bin Jiang, is essential (Scheme 13). Our starting material for this segment was the commercially available penta-O-acetyl-D-galactopyranose. This compound was easily manipulated to accord the fully protected 4,6-O-(*p*-methoxybenzylidene) glycoside **23**. Regioselective reductive ring opening of the acetal by means of sodium cyanoborohydride (NaBH_3CN) and trifluoroacetic acid⁷³ in the presence of molecular sieves gave the galacto derivative **24** that bears the 4-OH group exposed. To obtain the necessary gluco configuration that we required at C-4, we took advantage of $\text{S}_{\text{N}}2$ chemistry. Accordingly, **24** was effortlessly converted to its axial triflate, followed by displacement utilizing tetrabutylammonium cyanide in tetrahydrofuran (THF) to provide the one-carbon branched chain pyranoside **25** along with its complimentary elimination product. Significant work was mandatory to optimize this reaction to favor formation of the cyano product and is summarized in Price's³⁴ and Jiang's³³ dissertations. Conversion of **25** to the essential coupling partner **27** was actualized in two steps: (1) **25** was treated with lithium aluminum hydride (LiAlH_4), which granted the amine **26**, and (2) oxidation of the amine with dimethyldioxirane in acetone at room temperature furnished **27**.



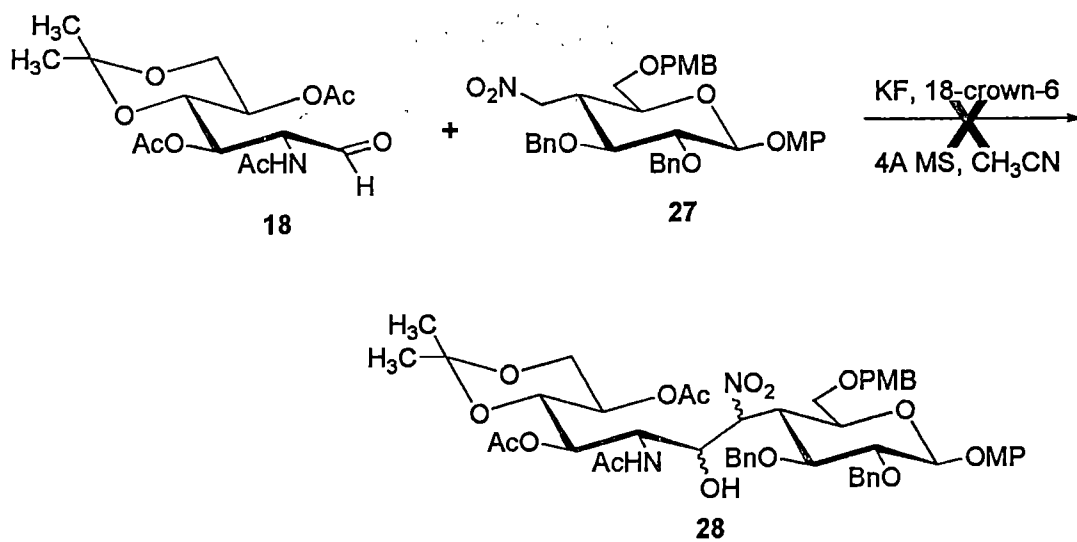
Scheme 13. Synthesis of nitrosugar 27.

4. Attempted coupling of aldehyde **18** with nitrosugar **27**

With the requisite aldehyde **18** and its coupling partner **27** in hand, the necessary chemistry for condensation of the monosaccharides was set in motion. Acyclic aldehyde **18** and the nitrosugar **27** were treated with potassium fluoride as promoter via Martin's protocol. Unfortunately, no detectable coupling products were obtained (Scheme 14). We suspect that the *N*-protecting group, through β -participation, significantly influenced the reactivity of the aldehyde. At this point, we were compelled to pursue alternate avenues toward our objective.

D. Investigation into Alternative Approaches to the C-Disaccharide

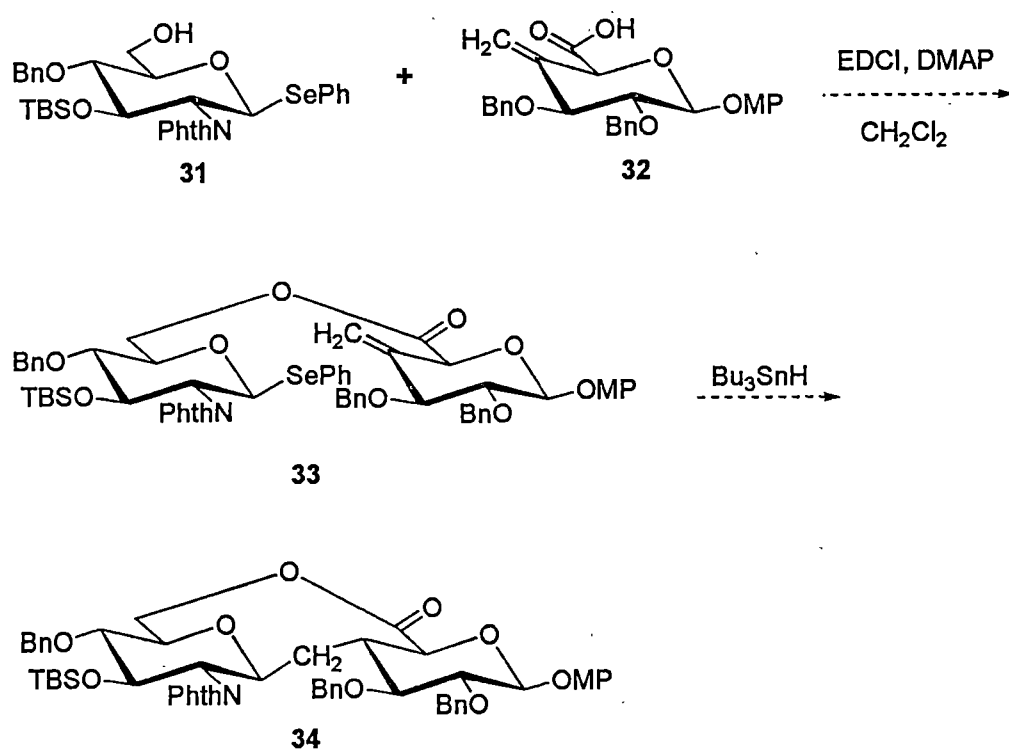
After investigation into a variety of options, several approaches emerged which we perceived would make our goal readily attainable. The first was the silicon tether strategy of Sinaÿ et al.^{74,75} in which they made numerous C-disaccharides including methyl α -C-maltoside. The C-glycosidic analogue of adenophostin A, a very potent IP₃ receptor agonist, was also synthesized using this method by Abe et al.⁷⁶ Sinaÿ in his method, shrewdly applied an intramolecular radical cyclization reaction between a selenophenyl sugar and an easily obtainable alcohol temporarily connected *via* a silicon tether. Although the regioselectivity of the reaction was contrary to what we coveted, we hoped that with adequate protecting groups the selectivity could be reversed. It is well known that protecting a 2-amino-2-deoxy sugar with the phthalimido group generally dictates that reaction at the 1-position results in the formation of the β



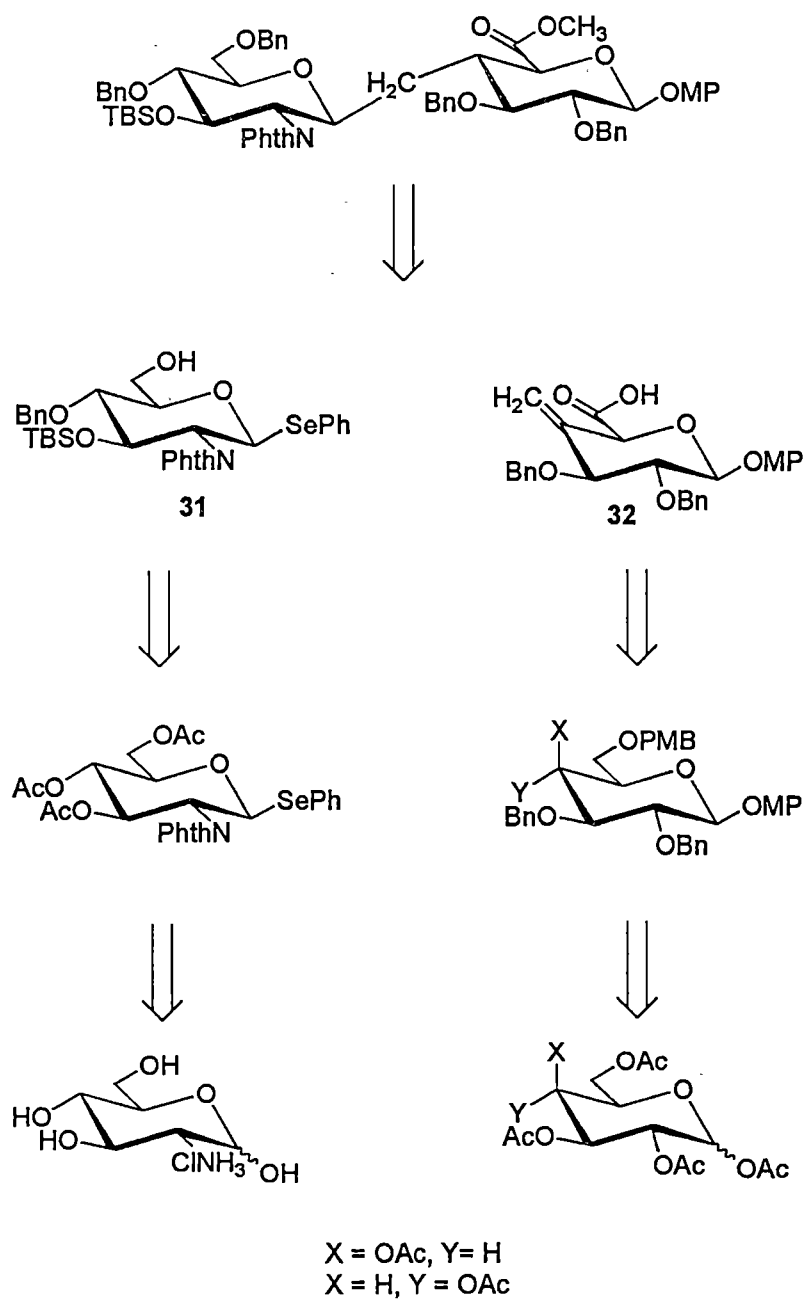
Scheme 14. Attempted Henry coupling of aldehyde **18** and nitrosugar **27**.

anomer of the products. Our proposed approach as outlined in Scheme 15 used a phenylseleno sugar with the hydroxyl group at the 6 position bare and a non-activated exomethylene pyranoside which has incorporated within its structure a carboxylic acid moiety at position-5. Coupling of these two units would be effected using EDCI/DMAP in dichloromethane to form an ester tether, joined at position-6 of both structures. Subsequently, we expected to perform an intramolecular radical addition reaction adopting tributyltin hydride ($n\text{-Bu}_3\text{SnH}$) and azoisobutyronitrile (AIBN) as the radical initiator, to generate the disaccharide with the correct stereochemistry. Hence, we envisioned synthesizing from glucosamine hydrochloride the phenyl 2-deoxy-2-phthalimido-1-seleno- β -D-glucopyranoside (**31**) that has an exposed 6-OH group, which will be used for tethering (Scheme 16). Its coupling partner alkene **32** with the carboxylic acid already in place could be readily conceived from penta-O-acetyl-D-glucopyranose in a limited number of steps (Scheme 16). The advantages of this method are (1) that the synthesis of the monosaccharides is relatively short and (2) the utterly important carboxylic acid, which would be produced from oxidation of the alcohol using bisacetoxiodobenzene (BAIB), would already be in place. The obvious disadvantage of this method is the uncertainty as to whether the cyclization would confer the β stereochemistry we require.

Because our initial protocol required a C-1 electrophile, it seemed logical in an alternate strategy to apply a C-1 nucleophile. This approach rests on the use of Kessler's dianion⁷⁷⁻⁷⁹ made from glycosyl tin derivative **37** as a nucleophile.



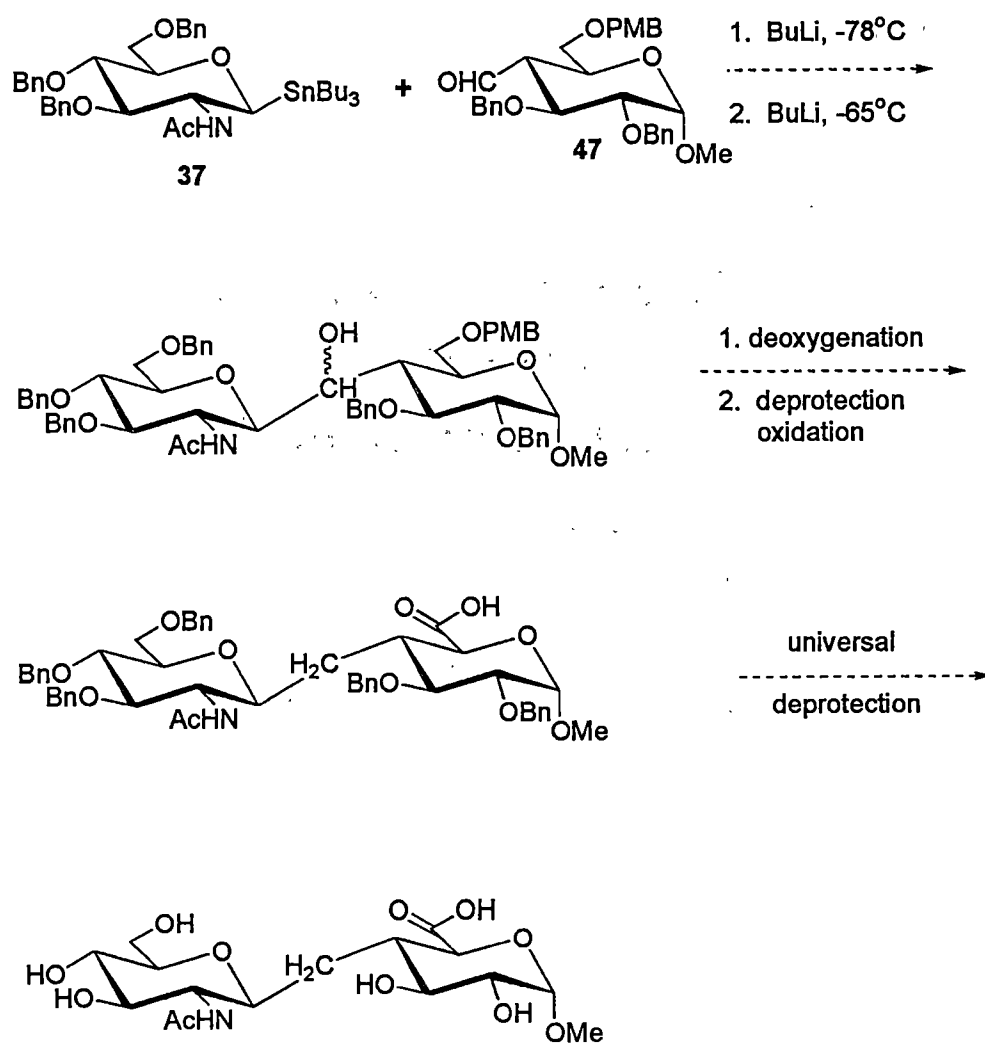
Scheme 15. Proposed tether strategy to C-disaccharide.



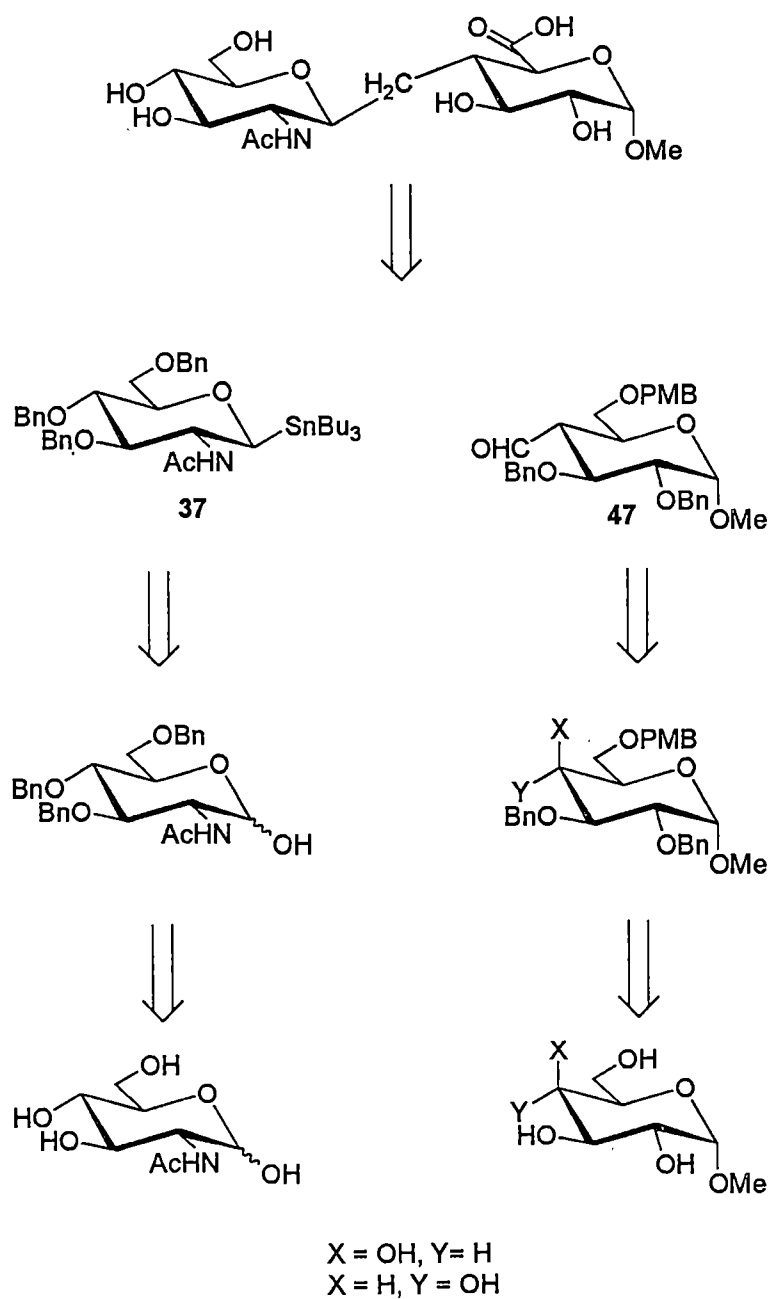
Scheme 16. Retrosynthetic analysis for phenyl selenoglycoside **31** and alkene **32**.

The aldehyde **47**, which is similar to the aldehyde utilized by Schmidt and Dietrich⁸⁰ in their synthesis of the C-disaccharide of lactose, acts as the electrophile. Coupling of the monosaccharide segments can be carried out via treatment with methyllithium and butyllithium. Barton deoxygenation, followed by liberation and oxidation of the 6-hydroxyl group and universal deprotection, should furnish the C-disaccharide (Scheme 17). Glycosyl tin derivative **37** could rapidly be made from *N*-acetylglucosamine in six steps. The aldehyde **47** can be derived from methyl α -D-glucopyranoside (Scheme 18). The key steps in this sequence are hydroboration/oxidation of the exomethylene, followed by Swern oxidation of the primary alcohol. Alternatively, the aldehyde can be synthesized from methyl α -D-galactopyranoside. In this case, the critical procedures would include cyanide displacement of an axial triflate to establish the equatorial configuration around C-4 and DIBAL-H reduction of the cyanide to the expected aldehyde.

This approach provides several advantages: (1) the stereochemical outcome is known, and only the required β anomer would be obtained. (2) The equatorial nature of the aldehyde (C-4 of the GlcA) is established prior to coupling. (3) Protection of the amide is not required; hence, there is no need for an additional deprotection step, and (4) the sequence does not require ring opening or ring closure. Although this method has been applied to the synthesis of alkyl C-glycosides, to our knowledge no one has exploited this chemistry to assemble C-disaccharides.



Scheme 17. Proposed C-disaccharide synthesis via dianion approach.



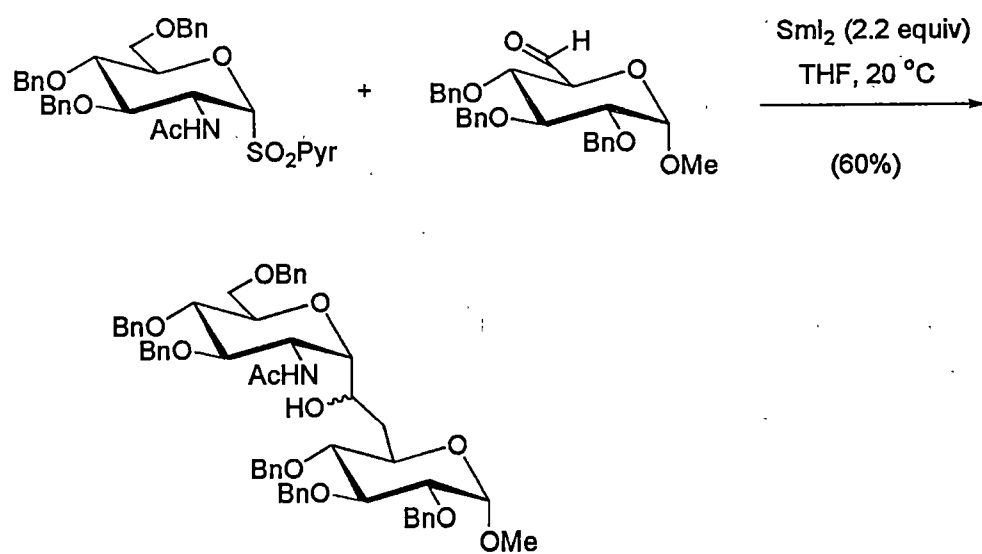
Scheme 18. Retrosynthetic analysis of glycosyl tin derivative **37** and aldehyde.

Finally, Skrydstrup and co-workers⁸¹ have produced a α C-disaccharide, that contains an *N*-acetylglucosamine subunit at the nonreducing end, the first of its kind, via samarium iodide coupling of an α -D-glycosyl-2-pyridylsulfone with a simple aldehyde (Scheme 19). Interestingly, Hung et al.⁸² have described the utilization of samarium iodide as a very mild and efficient reagent in the coupling of glycosyl phosphates to aldehydes to produce C-disaccharides. We suspect that the β isomer of the 2-pyridylsulfone would give predominately the β -C-disaccharide. Our procedure would utilize a strategically protected β -2-pyridylsulfone, which could then be coupled to an adequately masked aldehyde.

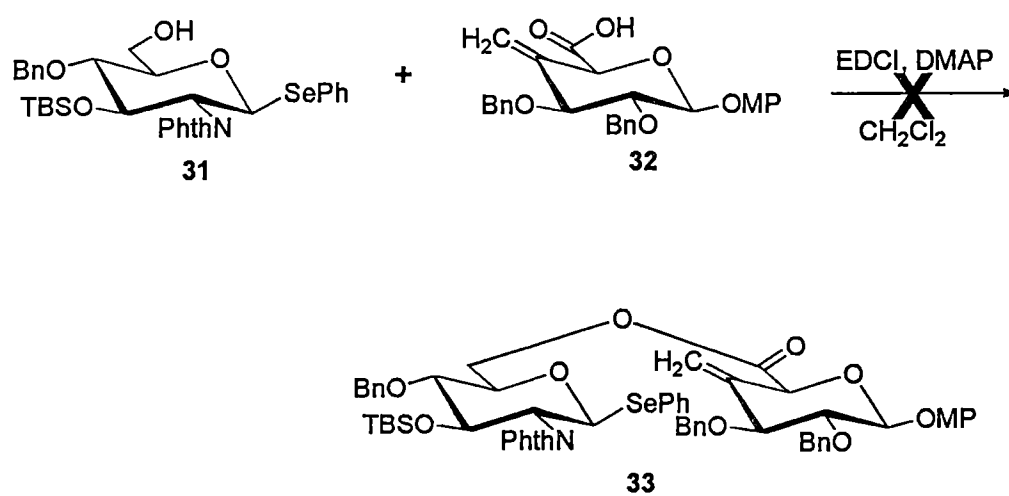
The resulting alcohol could be deoxygenated using Barton's procedure, followed by protecting group manipulation that could either yield the HA C-disaccharide or allow entry into long-chain oligosaccharides. This method, developed by Dr. Z. X. Ren in our laboratory, has shown significant promise and will be described elsewhere.

E. C-Disaccharide Synthesis. The Tether Approach

Phenyl selenoglycoside **31** was made by my co-worker Karen Welch and the carboxylic acid **32** by Bin Jiang³³ (Scheme 20). The synthesis of both compounds is described in Bin Jiang's dissertation.³³ Frustratingly, all attempts at effecting coupling proved futile. Coupling was attempted using EDCI/DMAP/CH₂Cl₂, 1,1'-carbonyl-bis(3-methylimidazolium) bis(trifluoromethanesulfonate) and (COCl)₂/pyridine; however, compound **32**



Scheme 19. Skrydstrup approach to C-disaccharides.



Scheme 20. Attempted coupling of phenyl selenoglycoside **31** and alkene **32**.

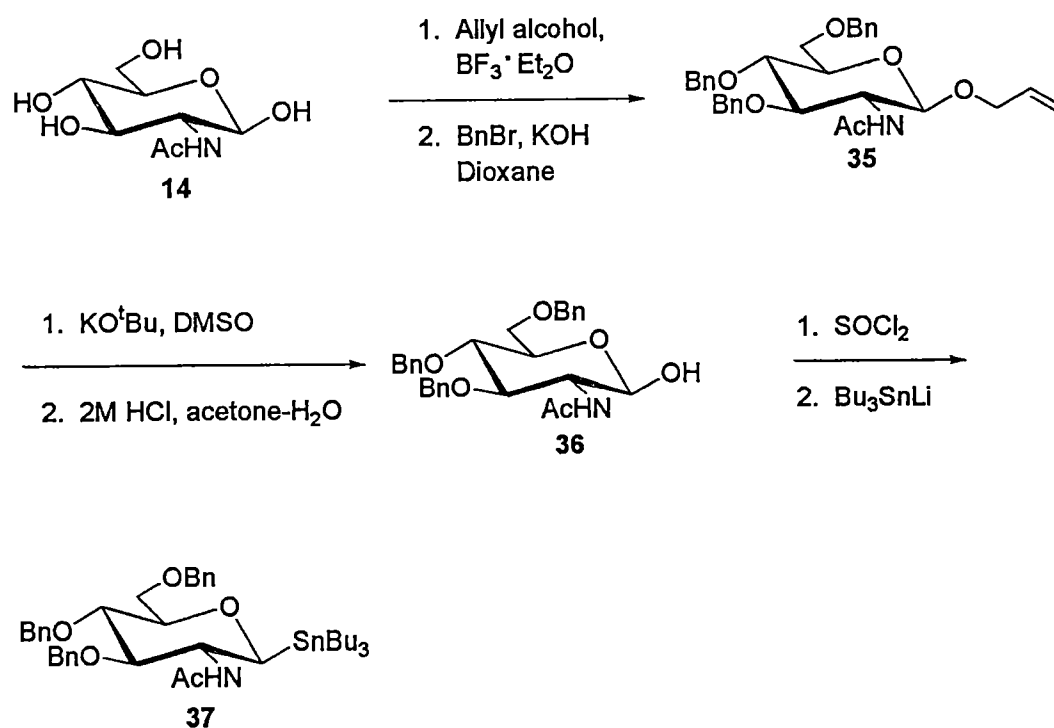
decomposed under these reaction conditions.

F. C-Disaccharide Synthesis. The Dianion Approach

1. Synthesis of glycosyl tin derivative **37**

With our limited success we needed to find a method to rapidly make the disaccharide unit. Our aim at this stage was to achieve a coupled product. As such, we turned to a modest protecting group strategy. Only the 6-OH group would be uniquely masked, and all other hydroxyl groups would be concealed as benzyl ethers. Furthermore, the aldehyde residue would be made from methyl α -D-glucopyranoside because of cost and other factors. If this strategy proved fruitful, then the more expensive methyl β -D-glucopyranoside would be employed to match the O-linked disaccharide synthesized by Jiang.³³

Consequently, the glycosyl tin derivative **37** was prepared according to the procedure adopted by Kessler and co-workers.⁷⁷⁻⁷⁹ and is depicted in Scheme 21. Hence, 2-acetamido-2-deoxy-D-glucose was refluxed in allyl alcohol in the presence of boron trifluoride etherate until all of the starting sugar was consumed (TLC monitoring), which provided the anticipated allyl glycoside. Treatment of this intermediate with powdered potassium hydroxide and benzyl bromide in refluxing dioxane provided compound **35**, which was not purified. Removal of the allyl group of **35** occurred in two steps: (1) isomerization of the double bond with potassium *tert*-butoxide in anhydrous dimethyl sulfoxide and (2) removal of the resultant propenyl glycoside with 2 M hydrochloric acid in a

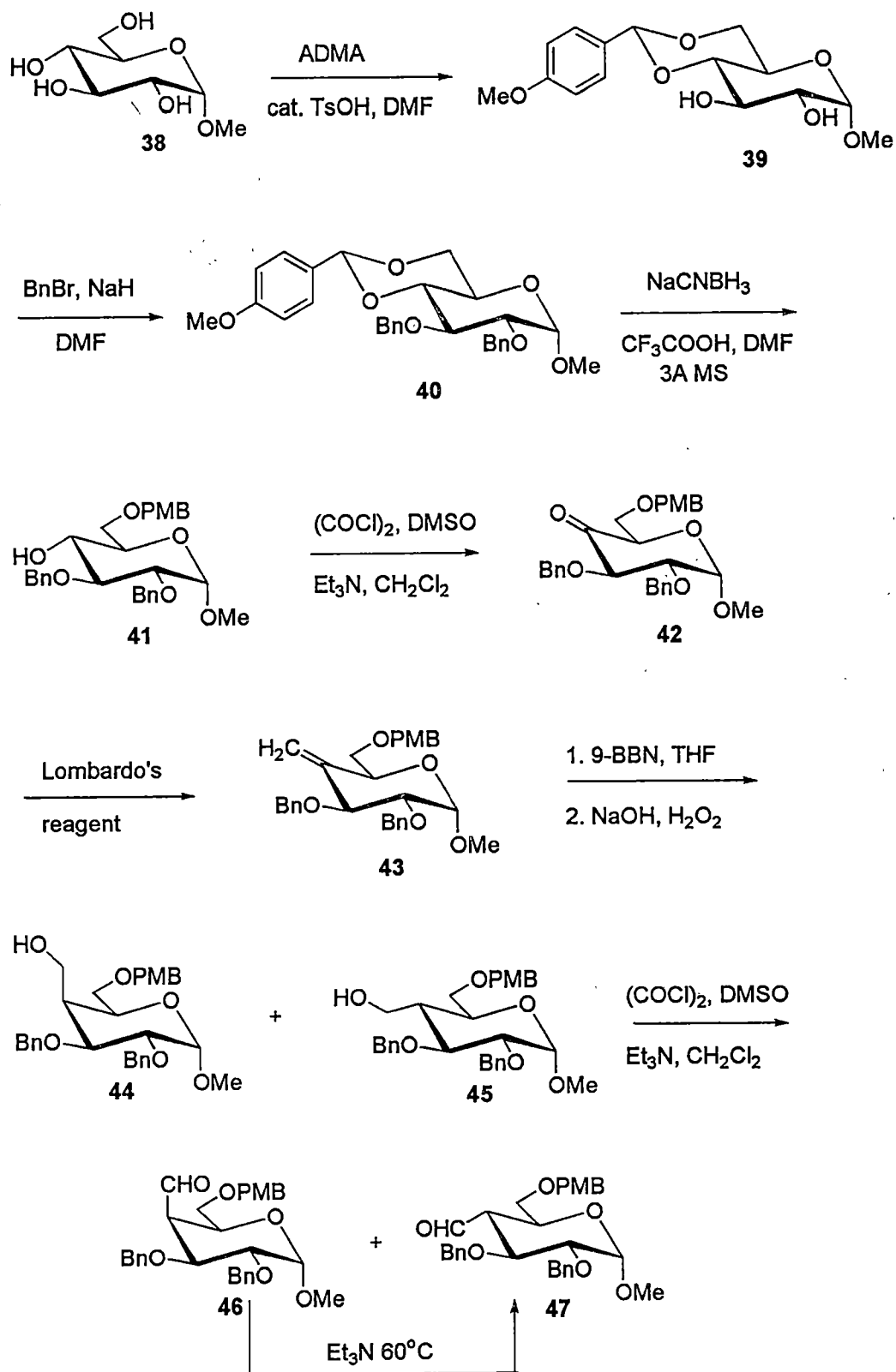


Scheme 21. Synthesis of glycosyl tin derivative **37**.

warm acetone–water mixture. Compound **36**, with its anomeric hydroxyl group exposed, was purified by crystallization from ethanol and then chlorinated with thionyl chloride in dry dichloromethane. The unstable glycosyl chloride was then treated with lithium tributyltin, which was produced from metallic lithium and tributyltin chloride, to furnish **37** in 40% overall yield as the sole product, and with the desired stereochemistry. Any residual acid was removed prior to addition of lithium tributyltin because it impeded the formation of the glycosyl tin compound. Co-evaporating the moisture-sensitive glycosyl chloride with dry toluene and placing it on a vacuum pump over several hours accomplished this. With the realization of the invaluable glycosyl tin derivative our attention shifted to the synthesis of its interesting coupling partner **47**.

2. Synthesis of aldehyde **47**

The synthesis of compound **41** commenced with commercially available methyl α -D-glucopyranoside **38** according to the procedures of Samuelsson and Johansson (Scheme 22).⁷³ Consequently, when a solution of *p*-anisaldehyde dimethyl acetal, a catalytic amount of *p*-toluenesulfonic acid (TSOH), and compound **38** in dry *N,N*-dimethylformamide (DMF) was placed on a rotatory evaporator at 45 °C for 4 h, acetal exchange occurred resulting in the formation of crystalline **39** in 75% yield. Benzylation of the assailable hydroxyl groups of compound **39** via benzyl bromide and sodium hydride easily led to the formation of entirely protected monosaccharide **40** in high yield (80%). Regioselective reductive ring opening of acetal **40** using sodium cyanoborohydride,



Scheme 22. Synthesis of aldehyde 47.

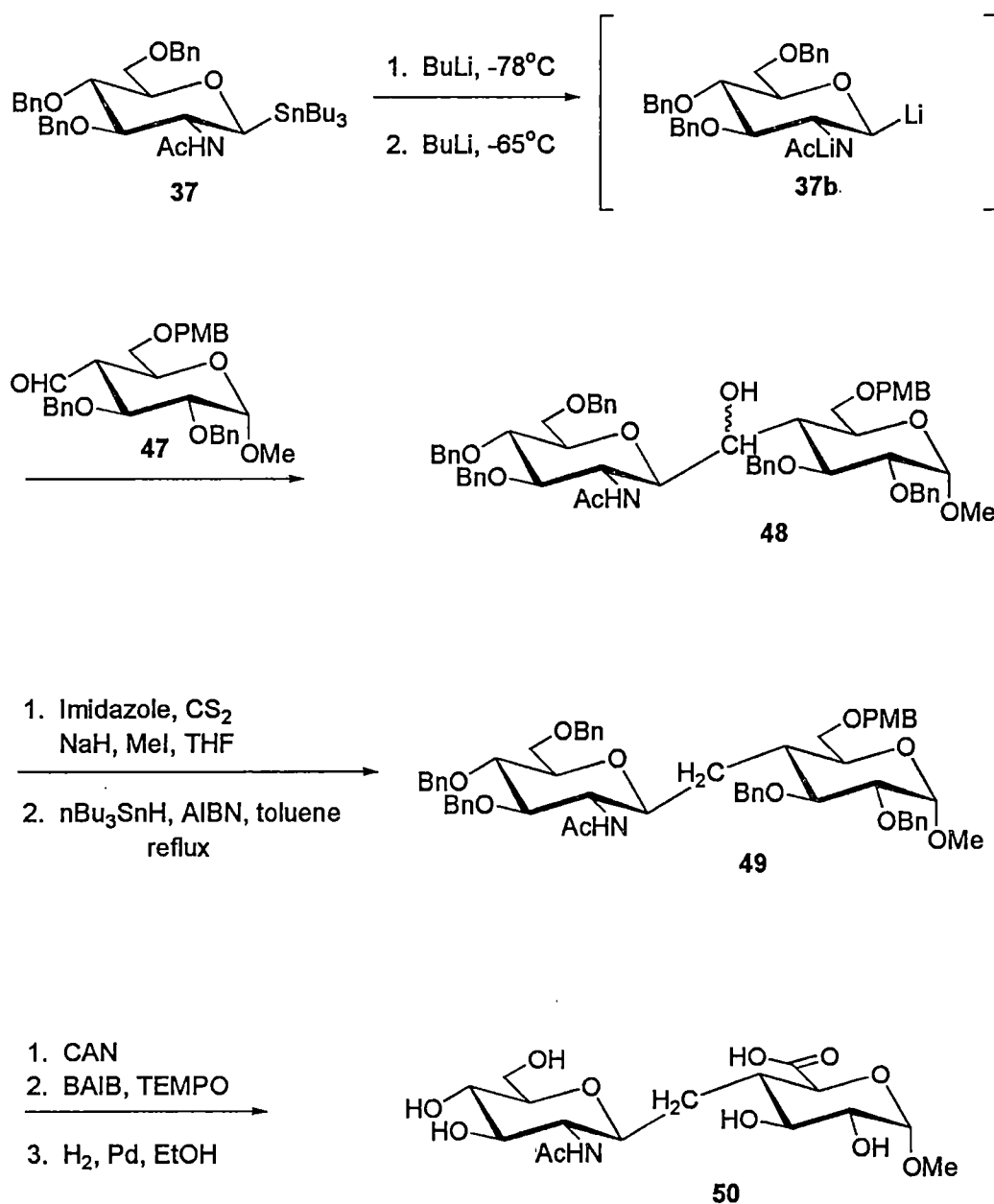
trifluoroacetic acid and 3A molecular sieves in dry DMF provided **41** in 89% yield and its isomer, methyl 2,3-di-O-benzyl-4-O-(6-methoxybenzyl)- α -D-glucopyranoside **41b** (not shown, NMR data is provided in the Experimental section) in only 9% yield. Hollingsworth and co-workers⁸³ had synthesized compound **43** from alcohol **41** in two steps. Swern oxidation or oxidation with Dess–Martin periodinane of **41** afforded ketone **42** in greater than 90% yield. Attempts at oxidizing the alcohol with a mixture of pyridinium chlorochromate (PCC) in conjunction with silica gel in dry dichloromethane, according to the procedure of Luzzio et al.,⁸⁴ generated only a moderate amount of the ketone, and only after stirring for two days. The ketone was readily converted to the exocyclic methylene derivative **43**, via Lombardo's reagent⁸⁵ (Zn dust, CH₂Br₂, TiCl₄, THF) or Wittig olefination using methyl triphenylphosphonium bromide and butyllithium (BuLi) in 92 and 86% yields, respectively. The structure of the alkene was confirmed from its ¹H NMR spectrum, which showed two singlets at δ 4.97 and 5.36 corresponding to the two olefinic protons. Successful transformation of alkene **43** to a 4:1 mixture of primary alcohols **45** and **44**⁸⁰ was accomplished using 9-borabicyclo[3.3.1]nonane (9-BBN) in refluxing tetrahydrofuran (THF), followed by oxidation with hydrogen peroxide and sodium hydroxide. Interestingly, borane (BH₃) yielded a comparable mixture of **44** and the tertiary alcohol (not shown). The newly formed *gluco*-configured hydroxymethyl derivative had the alcohol signal appearing as a broad singlet at δ 1.69 and the methylene signal as a multiplet between δ 1.71–1.76 in the ¹H

NMR spectrum. The desired aldehyde **47** was obtained from both the *gluco* and *galacto*-configured alcohols. Thus, **44** and **45** were oxidized according to Swern's protocol, and the resultant aldehydes were heated in the presence of triethylamine for several hours to furnish the more thermodynamically stable aldehyde **47**. The aldehyde structure was confirmed from its ^1H and ^{13}C NMR spectra. The aldehydic proton signal appeared as a doublet at δ 9.6 in the ^1H NMR spectrum, and in the ^{13}C NMR the carbonyl peak appeared at δ 199.61.

3. Dianion coupling of **37** with **47**.

With both coupling partners in hand, we were confident Kessler's dianion approach would be fruitful. Our enthusiasm was tremendously encouraged by Westermann and co-workers,⁸⁶ recent assembly of several carbohydrate-derived amino C-glycosides using this methodology. Impressively, only β glycosides were procured. This fact boded well for our aim.

The coupling of compounds **37** and **47** proceeded smoothly (Scheme 23). Deprotonation of the glycosyl tin derivative **37** in THF was accomplished with methyllithium at $-78\text{ }^\circ\text{C}$, followed by transmetallation at $-65\text{ }^\circ\text{C}$ using butyllithium, which provided the key dianion intermediate that was promptly treated with aldehyde **47** to afford the expected alcohol **48**, which was easily identified by mass spectrometry (Figure 7). Unfortunately, the stereochemistry was difficult to confirm from the alcohol itself. The stereochemical assignment of the newly formed disaccharide was ascertained from the O-acetylated compound. The ^1H NMR spectrum of the acetylated product proved the conformation of the



Scheme 23. Dianion coupling of glycosyl tin derivative **37** and aldehyde **47**.

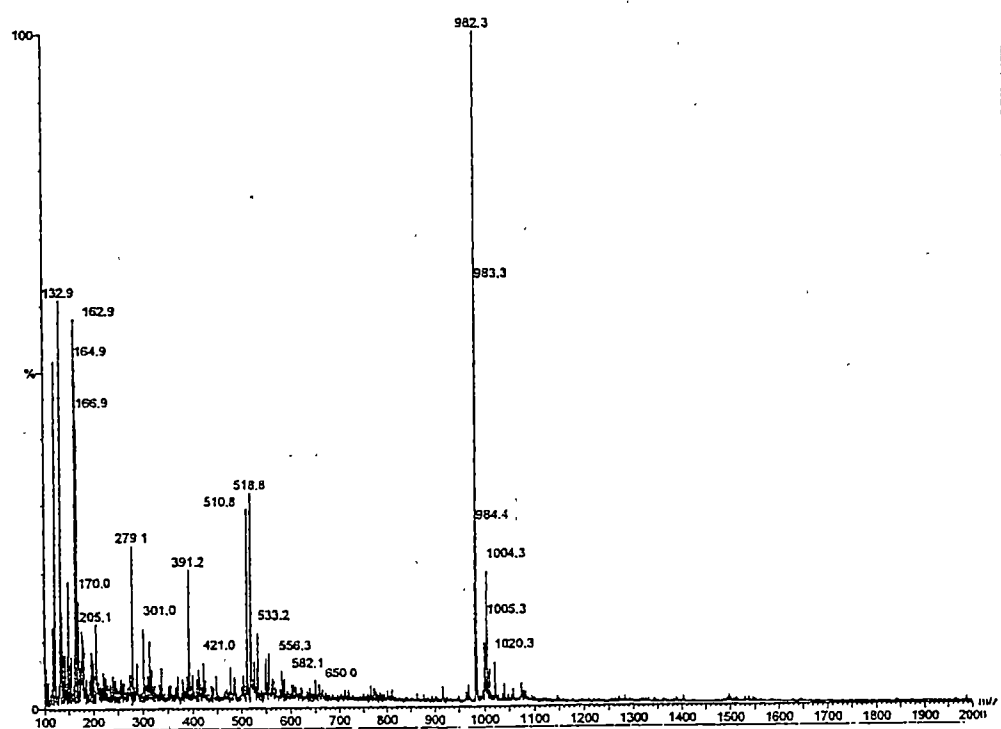


Figure 7. Mass Spectrum of C-disaccharide 48.

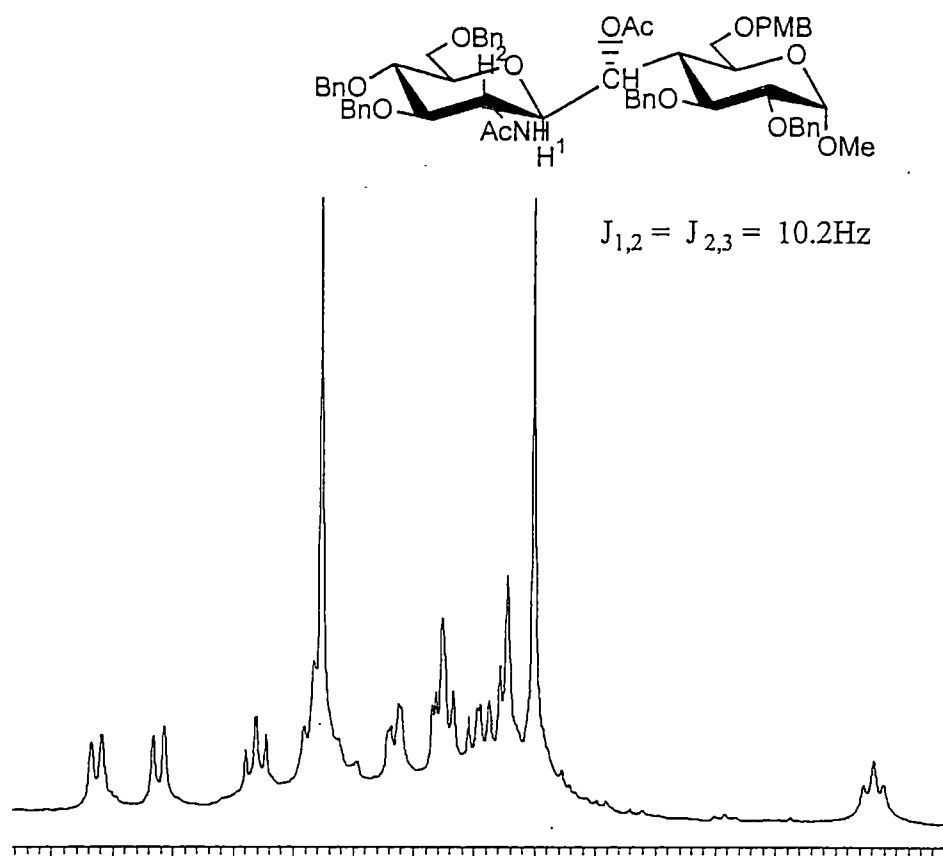


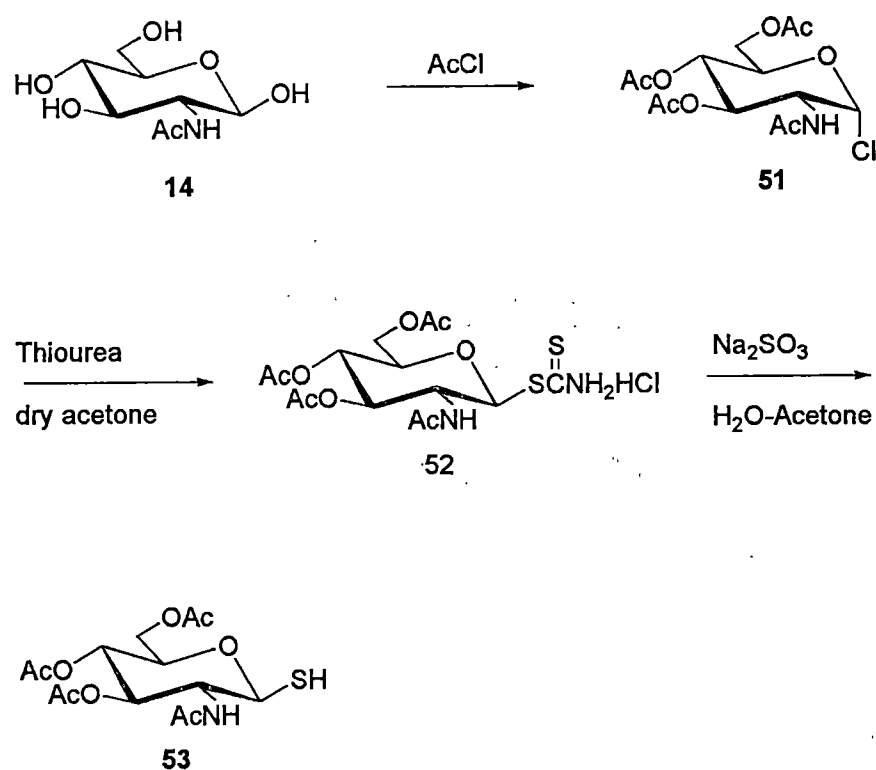
Figure 8. ^1H NMR spectrum of acetylated C-disaccharide.

disaccharide to be β with its coupling constant of $J_{1,2} = J_{2,3} = 10.2$ Hz (Figure 8). Interestingly, formation of the dianion was accompanied by a deep red color, which upon addition of the aldehyde, disappeared. Removal of the hydroxyl moiety on **48** was achieved using a method of Barton and McCombie.^{80,87} Thus, formation of the xanthogenate intermediate from **48** was realized with imidazole, carbon disulfide, sodium hydride, and iodomethane in dry THF. The xanthogenate group was dislodged with tributyltin hydride ($n\text{-Bu}_3\text{SnH}$) and azoisobutyronitrile (AIBN) in refluxing toluene. The deoxygenated disaccharide **49** was subjected to ceric ammonium nitrate (CAN) oxidation to provide the expected primary alcohol in 78% yield. Several methods of oxidizing the primary alcohol directly to the carboxylic acid were investigated; however, the best results were obtained when bis(acetoxy)iodobenzene (BAIB) and TEMPO were used. After the carboxylic acid was installed, hydrogenolytic debenzoylation of the uronic acid in the presence of Pearlman's catalyst, $\text{Pd}(\text{OH})_2$, in ethanol awarded at long last, the elusive disaccharide **50**.

G. Synthesis of the S-Disaccharide

1. Synthesis of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-1-thio- β -D-glucopyranose **53**

As stated earlier, difficulty with manipulating the protecting groups of our sulfur-linked disaccharide stymied any realization of a thio-linked hyaluronic acid analogue. As a result, an alternate route was enacted and is revealed below.

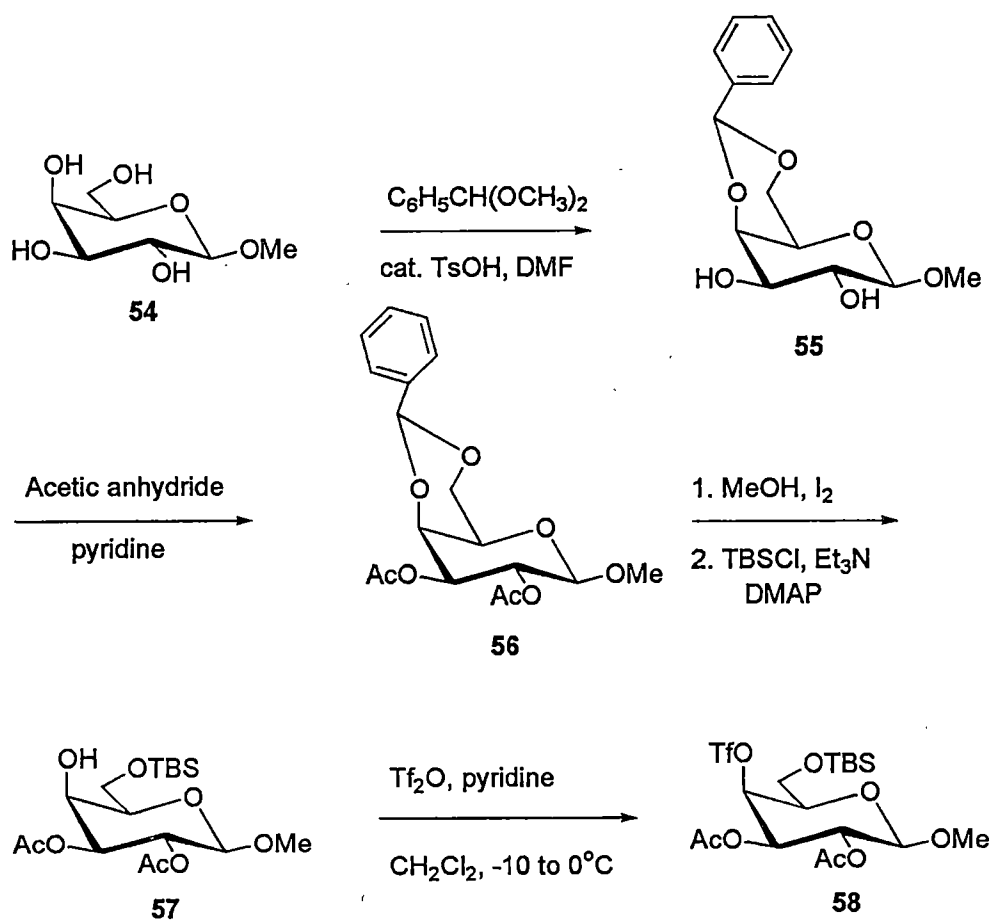


Scheme 24. Synthesis of thiol **53**.

Compound **53** was readily made according to the procedure of Wang and Lee (Scheme 24).⁵⁴ Accordingly, 2-acetamido-2-deoxy-D-glucopyranose was treated with acetyl chloride to afford the anticipated moisture-sensitive, highly crystalline glucopyranosyl chloride **51**. 2-Thiopseudourea hydrochloride **52** was formed when compound **51** was refluxed with thiourea in dry acetone. Next, treatment of **52** with powdered sodium sulfite in a water–acetone mixture resulted in the expected β -thio nucleophile **53** in high isolated yield. The β configuration was confirmed from the coupling constant between H-1(SH) and H-2, $J_{H1,H2} = 9.3$ Hz. Next, our attention turned toward the synthesis of triflate **58**.

2. Synthesis of Triflate **58**

The methyl 4,6-O-benzylidene acetal **55** was made from methyl β -D-galactopyranoside, benzaldehyde dimethyl acetal, and TsOH in DMF in high yield (Scheme 25). Reaction of the crude acetal derivative with pyridine and acetic anhydride furnished the fully protected monosaccharide **56**. Acetate resonances appeared as a singlet at δ 2.07 in the ^1H NMR spectrum. Removal of the benzylidene acetal was best accomplished in 60% acetic acid at 60 °C or with iodine in refluxing methanol.⁸⁸ Alternative acidic treatments (example HCl, H_2SO_4) gave poor yields of the desired product. Selective *tert*-butyldimethylsilyl (TBS) protection of the resulting 6-OH using the standard procedure gave **57** in good yield. Fortuitously, no diprotected TBS product was observed. The synthesis of the triflate was completed when alcohol **57** was stirred at 0 °C for several hours in the presence of triflic anhydride and pyridine to afford the

Scheme 25. Synthesis of triflate **58**.

unstable triflate **58** in good yield.

3. Coupling of thiol **53** and triflate **58**

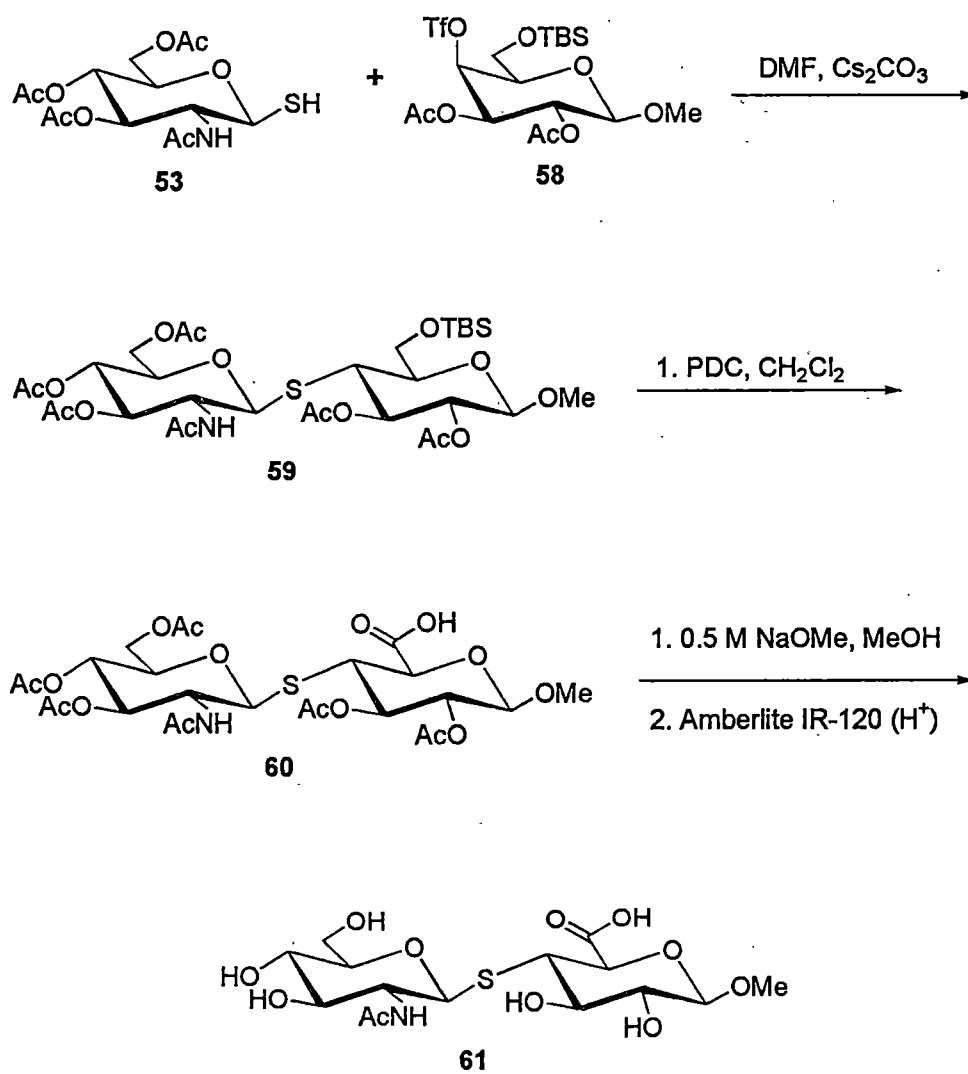
The sequence of reactions to assemble the S-disaccharide is illustrated in Scheme 26. Base-catalyzed S_N2 coupling of thiol **53** and triflate **58** rapidly and efficiently provided disaccharide **59**. The coupling constant $J_{H1',H2'} = 10.2$ Hz confirmed the β stereochemistry of the product. It is well known that a primary OTBS group can be converted, directly to the carboxylic acid via PDC.⁸⁹ Thus, disaccharide **59** was subjected to PDC in dry *N,N*-dimethylformamide to give, after rapid chromatography, pure acid **60**. The sequence was completed with saponification with sodium methoxide and protonation using amberlite IR-120 (H⁺) resin, which gave the desired compound **61**.

H. Synthetic Efforts Toward S-Oligosaccharide: The Gonzalez approach

Because of our preliminary work, significant advances were achieved toward the synthesis of the S-linked mimic of HA and its longer chain oligomers.

Recently, we were alerted to a novel and speedy method for the assembling of thio-linked disaccharides. This procedure, based on Gao and Sharpless⁵⁶ cyclic sulfate chemistry, was adopted by Calvo-Flores et al.⁵⁵ for carbohydrates.

Simply, this process called for a 1-thioglycose nucleophilic displacement of a highly reactive cyclic sulfate. Since an elaborate protecting-group strategy was unnecessary and the coupling was stereoselective and regioselective, this process could easily and promptly be incorporated toward realizing our

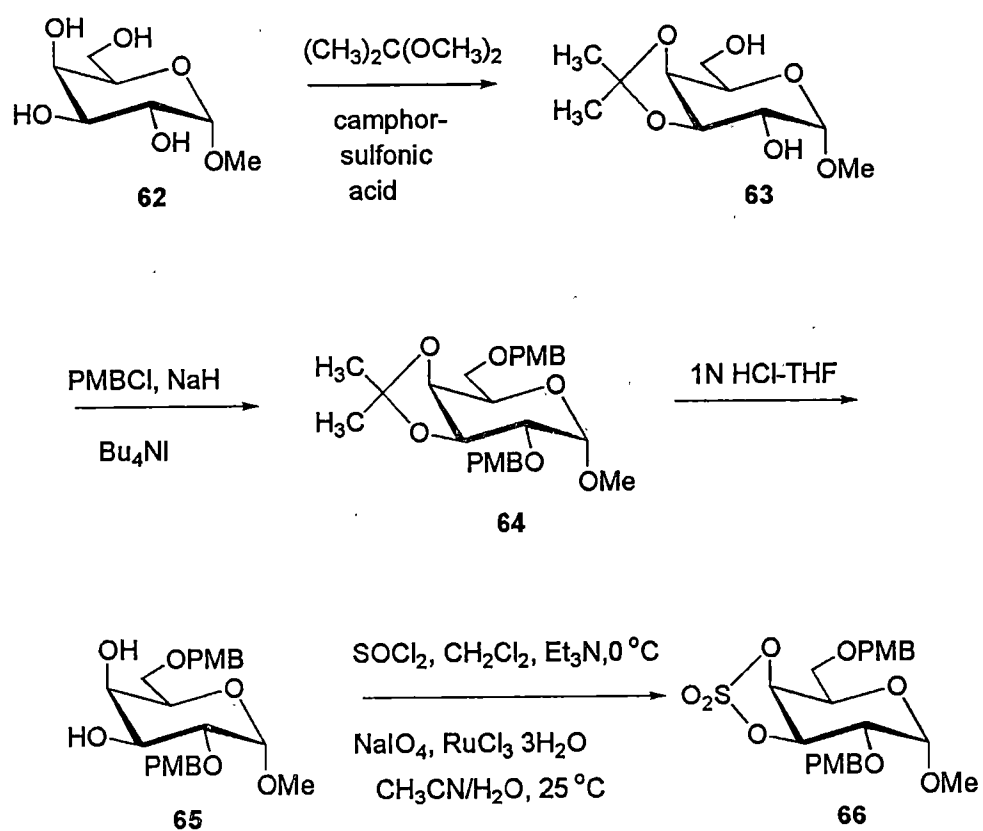


Scheme 26. Coupling of thiol **53** with triflate **58**.

objective. Detailed below is the progress made toward the synthesis of thio-linked oligosaccharides.

1. Synthesis of cyclic sulfate **66**

The synthesis of cyclic sulfate **66** commenced with the commercially available methyl α -D-glucopyranoside (Scheme 27). Compound **62** was smoothly converted to the selectively protected 4,6-O-isopropylidene acetal according to the procedure of Catelani.⁹⁰ Thus, **62** was stirred in the presence of 2,2-dimethoxypropane and dry camphorsulfonic acid for two days, the solvent was evaporated, and the residue was refluxed in a solution of methanol–water for several hours to yield compound **63**. Protection of the assailable hydroxyl groups of **63** with *p*-methoxybenzyl chloride, NaH and tetrabutylammonium iodide (Bu₄NI) in dry DMF, followed by acid hydrolysis in HCl–THF of the dimethyl acetal, bestowed **65**. The reaction was very sluggish in the absence of Bu₄NI. The disappearance of the two methyl signals at δ 1.22 and 1.29 in the ¹H NMR spectrum confirmed the successful removal of the dimethyl acetal. Next, the vicinal diol was cautiously transformed to the delicate cyclic sulfate **66** in two steps: **65** was converted to the cyclic sulfite using thionyl chloride and triethylamine in dichloromethane at 0 °C and subsequently oxidized with sodium metaperiodate (NaIO₄) and ruthenium trichloride tri-hydrate in acetonitrile–water. Mass spectrometry corroborated the formation of the cyclic sulfate. Both the potassium ([M + K] = 534.9) and sodium ([M + Na] = 518.9) species were observed. The cyclic sulfate when exposed to moisture turned pink and



Scheme 27. Synthesis of cyclic sulfate **66**.

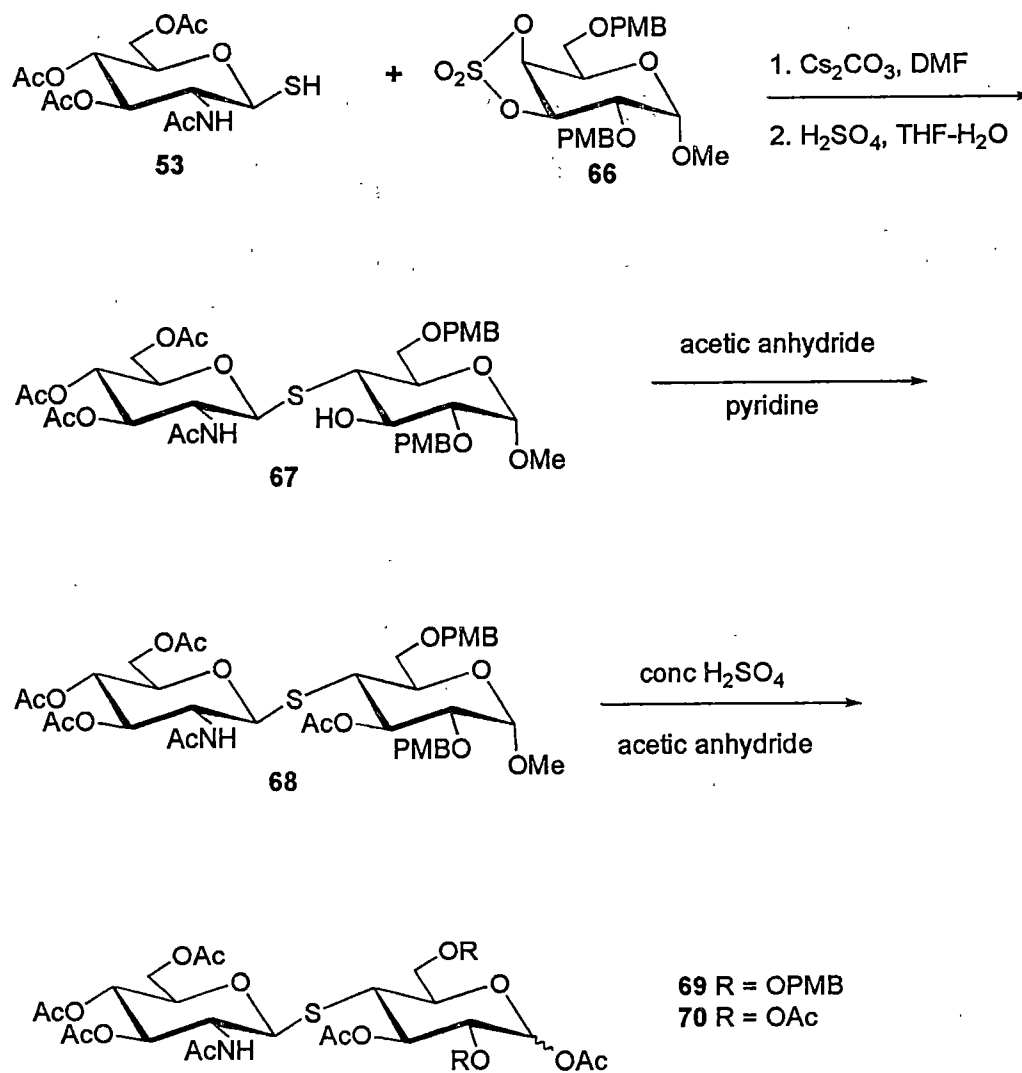
decomposed.

2. Coupling of thiol **53** and cyclic sulfate **66**

The coupling of thiosugar **53** and cyclic sulfate **66** went as proposed (Scheme 28). Hence, treatment of **53** in anhydrous DMF with cesium carbonate and sulfate **66** resulted in the monosulfated thio-linked disaccharide. This compound was stirred in a catalytic amount of H_2SO_4 in a H_2O –THF mixture that yielded the expected monohydroxylated product **67** as the only product with the desired β configuration as affirmed by ^1H NMR spectroscopy ($J_{\text{H1}',\text{H2}'} = 10.2$ Hz). The lone hydroxyl group was protected as the acetate in the usual way to furnish **68**. An acetate group at C-1 could provide entry into “mixed” O/S linked or all -S- oligosaccharides. The acetate group is quite easily manipulated, even in oligosaccharides, at the anomeric (C-1) position of a sugar residue.^{54,91} With this in mind, compound **68** was treated with acetic anhydride and a catalytic amount of H_2SO_4 to afford the unexpected compound **70**, with the *p*-methoxybenzyl groups replaced by acetates, as the only product. This result indicated that, with an appropriate protecting group on the 2- and 6-OH positions of the disaccharide or the methyl ester of the carboxylic acid already established, this method could be useful for synthesizing oligosaccharides related to HA.

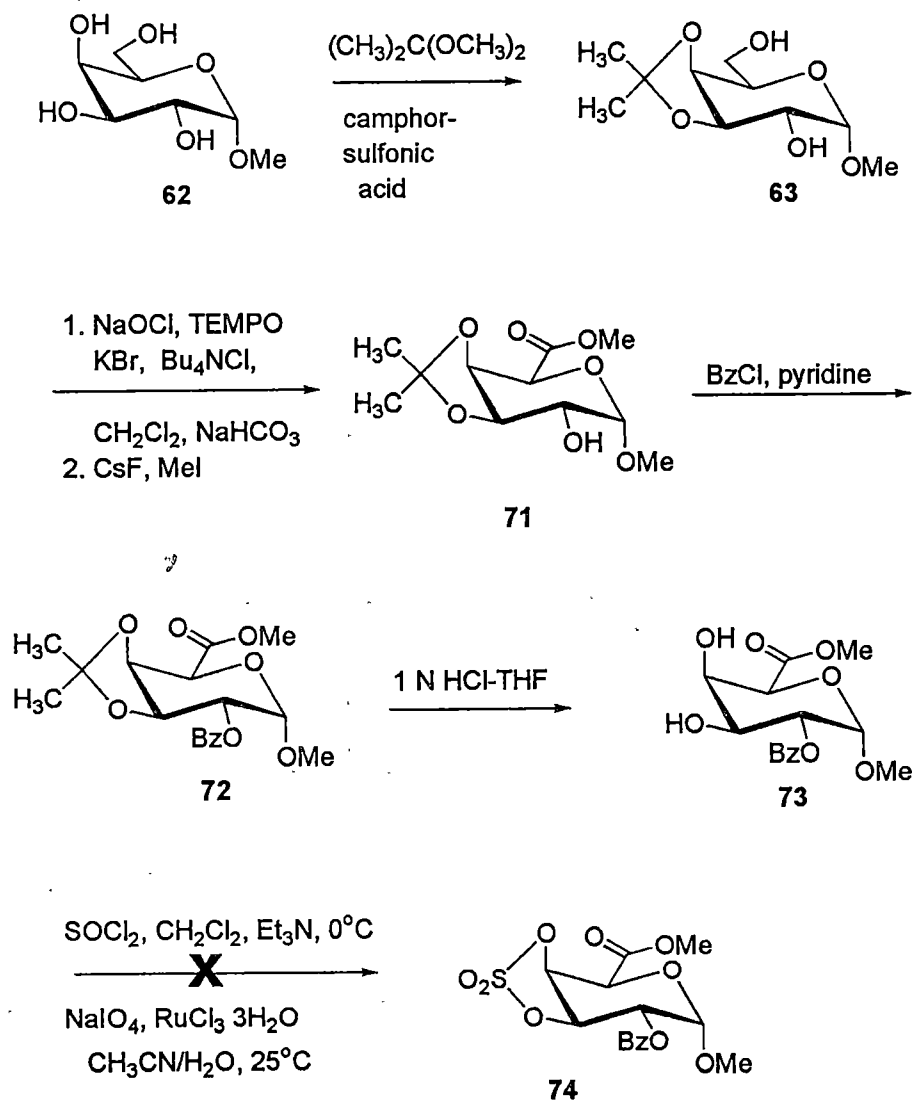
3. Attempted synthesis of cyclic sulfate **74**

To test the above assumption we elected to synthesis the cyclic sulfate with the C-6 methyl ester already in position, and with an appropriate protecting



Scheme 28. Coupling of thiol **53** with cyclic sulfate **66**.

group at C-2. To this end, compound **63** was selectively oxidized with sodium hypochlorite using TEMPO as catalyst to furnish the carboxylic acid, which was effortlessly converted to the methyl ester, by reaction with cesium fluoride⁹² in DMF at 15 °C over 24 h (Scheme 29). Although BAIB worked well for the oxidation, the product was difficult to purify when this method was used. The appearance of the carboxyl signal at δ 168.55 in the ^{13}C NMR spectrum and the newly observed methyl peak at δ 3.76 indicated that the methyl ester was formed. Compound **71**, with the lone hydroxyl group at C-2 was successfully protected as the benzoyl ester derivative **72** as shown. The O-isopropylidene group was then ousted under acidic conditions to provide *vic* diol **73**. Unfortunately, we were unable to generate the cyclic sulfate from the diol using the method previously described.



Scheme 29. Attempted synthesis of methyl ester 74.

IV. CONCLUSIONS

Synthesis of the C-disaccharide equivalent of hyaluronic acid via Martin's nitroaldol chemistry^{35,36} and Sinaÿ silaketal strategy was unsuccessful;^{74,75} however, valuable information was obtained in regards to the synthesis of carbon-linked disaccharides that incorporate the *N*-acetylglucosamine moiety at the nonreducing end. Kessler's dianion procedure⁷⁷⁻⁷⁹ was successfully developed toward achievement of the non-natural analog of the GlcNAc-(1→4)-GIA unit related to HA. To our knowledge, this is the first example of a C-disaccharide made via this route. The strategy elucidated here, relied on the reactivity of a glycosyl tin derivative and an attractive aldehyde. With the realization of a coupling strategy, this should enable us to assemble potential antimetastatic C/O linked oligosaccharides.

With respect to the S-linked analog of hyaluronic acid, a short route was successfully applied to its synthesis. The pivotal feature of this procedure was a base-mediated coupling of a thiol donor and a triflate acceptor. It was determined that the protecting groups were important to the reactivity of the triflate. With benzyl ethers as the protecting groups, the triflate was unreactive toward the coupling conditions. However, acetyl groups, and probably esters in general, increased the reactivity tremendously. This method, along with the cyclic sulfate method, will serve us well in the development of a general strategy toward S/O-linked oligosaccharides.

Both disaccharides can be used for molecular modeling and NMR studies.

The knowledge gained from the synthesis of these compounds, will be used to synthesize oligosaccharides that will be evaluated for their ability to obstruct the activity of hyaluronate lyases and hyaluronidases. Additionally, their potential as antimetastatic agents will be evaluated. If these oligosaccharides prove effective as anticancer agents, they could emerge as potential drug candidates.

V. EXPERIMENTAL

A. General Methods

Optical rotations were measured with a Perkin–Elmer Model 241 automatic polarimeter equipped with sodium and mercury lamps for solutions in a 1-dm cell at the indicated temperature. All reactions were monitored by thin-layer chromatography (TLC) on aluminum-backed plates coated with E. Merck silica gel and detection by 254 nm UV light and/or by charring with *p*-anisaldehyde–sulfuric acid. Melting points are uncorrected and were determined on a Thomas–Hoover melting point instrument equipped with a Cole–Palmer model 8520-50 Digi-Sense digital thermocouple thermometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer unless otherwise designated. Chemical shifts are reported as δ (ppm) relative to the solvent used. All compounds were run in deuterated chloroform, unless otherwise indicated, with 1% tetramethylsilane (TMS) as internal standard. Multiplicities are first-order values in Hz: s, singlet; bs, broad singlet; d, doublet; t, triplet; pt, pseudo triplet; bd, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet. Elemental analyses were performed by Atlantic Microlab, Inc. of Atlanta, GA. Mass spectral analyses were done on a Micromass VG Quattro II electrospray instrument at the University of Tennessee. All chemicals and solvents were reagent grade and were used directly. Anhydrous solvents were freshly distilled from appropriate drying agents prior to use. Moisture-

sensitive reactions were carried out under nitrogen or argon in oven-dried glassware. Removal of solvents occurred under reduced pressure, below 40 °C, on a Büchi rotary evaporator unless otherwise specified.

***p*-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido- β -D-**

glucopyranoside (3).³⁴ To an ice-cooled and magnetically stirred solution of **2** (15.05 g, 31.55 mmol) and *p*-methoxyphenol (5.81 g, 46.70 mmol) in dry CH₂Cl₂ (50 mL) was added dropwise TMS triflate (2.3 mL, 12.7 mmol). Stirring was continued at 0 °C overnight. The reaction mixture was quenched with aq NaHCO₃ (25 mL), and diluted with CH₂Cl₂ (50 mL) and H₂O (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layer was dried with MgSO₄, and the solvent was removed to give a red glassy material. Column chromatography of the crude material (1:1 hexane–ethyl acetate), followed by crystallization from hexanes–ethyl acetate, gave compound **3** as white crystals: mp 143–144 °C; $[\alpha]_D^{23} +52.38^\circ$ (c 0.99, CHCl₃). ¹H NMR: δ 1.89 (s, 3H) 2.05 (s, 3H), 2.11 (s, 3H), 3.72 (s, 3H), 3.91–4.01 (m, 1H), 4.18 (dd, 1H, *J* = 2.2, 10.1 Hz), 4.34 (dd, 1H, *J* = 4.5, 5.1 Hz), 4.57 (dd, 1H, *J* = 2.1, 8.5 Hz), 5.24 (t, 1H, *J* = 9.9 Hz), 5.82–5.90 (m, 2H), 6.72 (d, 2H, *J* = 9.2 Hz), 6.84 (d, 2H, *J* = 9.9 Hz), 7.73–7.76 (m, 2H) 7.85–7.88 (m, 2H). ¹³C NMR; 20.41, 20.69, 54.56, 55.56, 61.99, 68.93, 70.72, 71.99, 97.53, 114.45, 118.91, 123.67, 131.35, 134.35, 150.48, 155.76, 167.64, 169.42, 170.10, 170.58. This compound was reported in Ken Price's

dissertation.³⁴

***p*-Methoxyphenyl 2-deoxy-4,6-*O*-(4-methoxybenzylidene)-2-phthalimido- β -D-glucopyranoside (5).** To a suspension of compound **3** (15.9 g, 29.7 mmol) in reagent grade MeOH (150 mL) at room temperature was added dropwise NaOMe (10 mL of a 0.5 M solution). After TLC indicated the starting material was completely consumed, the reaction was quenched with Dowex-50 (H⁺ form). The mixture was stirred for 15 min and filtered. Evaporation of the solvent yielded the triol, *p*-methoxyphenyl 2-deoxy-2-phthalimido- β -D-glucopyranoside, as a white solid (11.01 g, 89% yield).

A solution of the triol, *p*-methoxyphenyl 2-deoxy-2-phthalimido- β -D-glucopyranoside **4**, (0.71 g, 1.69 mmol), anisaldehyde dimethyl acetal (0.77 mL, 4.22 mmol), *p*-toluenesulfonic acid (16 mg, 0.084 mmol) in dry DMF was rotated under reduced pressure at 45 °C until all of the starting material was consumed. After evaporation of approximately 20 mL of the DMF, Et₃N was added, and the remaining solvent was removed. The resulting residue was washed with PhCH₃ (3 x 20 mL) and dried in vacuo. Column chromatography (2:1:1 hexane–EtOAc–CH₂Cl₂) of the syrup, followed by crystallization from hexane–ethyl acetate, gave **5** as a white solid (0.717 g, 79.8% yield): mp 192 °C; [α]_D²³ = +6.53° (c 0.919, CHCl₃). ¹H NMR: δ 2.57 (d, 1H, *J* = 3.4 Hz, OH), 3.68–3.87 (m, 3H), 4.40 (dd, 1H, *J* = 8.8, 4.0 Hz), 4.5 (dd, 1H, *J* = 9.1, 10.7 Hz), 4.69 (td, 1H, *J* = 7.9, 4.0 Hz, H-3), 5.5 (s, 1H), 5.8 (d, 1H, *J* = 8.7 Hz, H-1), 6.70–6.97 (m, 6H), 7.40 (d, 2H, *J* = 9.1 Hz), 7.70–7.79 (m, 2H), 7.82–7.92 (m, 2H); ¹³C NMR (CDCl₃): δ 55.32,

55.60, 56.48, 66.30, 68.67, 77.95, 82.01, 98.11, 101.96, 113.79, 114.52, 118.61, 123.59, 127.65, 129.38, 131.62, 134.20, 150.60, 155.60, 160.37. This compound was reported in Ken Price's dissertation.³⁴

***p*-Methoxyphenyl 3-*O*-allyl-4,6-di-*O*-benzyl-2-deoxy-2-phthalimido- β -D-glucopyranoside (6).** To a cooled (0 °C) and stirred suspension of NaH

(washed with hexanes), in dry DMF (15 mL) was added dropwise a solution of **5** (3 g) in dry DMF (10 mL). After stirring at 0 °C for 5 min, allyl bromide was introduced. After 2.5 h the mixture was quenched with aq NH₄Cl and extracted with CH₂Cl₂. The organic phase was dried with anhydrous MgSO₄ and filtered, and the solvent was evaporated to dryness. Crystallization from hexanes–ethyl acetate provided *p*-methoxyphenyl 3-*O*-allyl-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-2-phthalimido- β -D-glucopyranoside (2.8 g, 89%): mp 151–152 °C; $[\alpha]_D^{23}$ +27.27° (c 1.0, CHCl₃); ¹H NMR (CDCl₃): δ 3.66–3.94 (m, 4H), 3.71 (s, 3H), 3.81 (s, 3H), 4.01 (dd, 1H, *J* = 14.1, 6.0 Hz), 4.33 (dd, 1H, *J* = 13.0, 4.9 Hz), 4.40 (dd, 1H, *J* = 9.8, 4.9 Hz), 4.48–4.57 (m, 2H), 4.88 (dd, 1H, *J* = 10.8, 1.6 Hz), 5.05 (dd, 1H, *J* = 17.9, 2.1 Hz), 5.48–5.67 (m, 2H), 5.76–5.80 (m, 1H), 6.70–6.97 (m, 6H), 7.43 (d, 2H, *J* = 9.8 Hz), 7.72–7.79 (m, 2H), 7.8–7.93 (m, 2H); ¹³C NMR (CDCl₃): δ 55.16, 55.46, 55.76, 66.31, 66.53, 73.01, 75.02, 82.42, 98.13, 101.19, 113.53, 114.41, 116.93, 118.47, 123.39, 127.27, 129.63, 131.48, 134.12, 134.42, 150.55, 155.51, 159.99; Anal. Calcd for C₃₂H₃₁NO₉: C, 67.01; H, 5.45; N, 2.44. Found: C, 66.94; H, 5.51; N, 2.39. This compound was reported in

Ken Price's dissertation.³⁴

A solution of *p*-methoxyphenyl 3-*O*-allyl-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-2-phthalimido- β -D-glucopyranoside (1.4 g) in CH_2Cl_2 (10 mL) was treated with 88% formic acid (10 mL) and MeOH (2 mL). After the starting material was consumed (10 min), CH_2Cl_2 was added. The organic layer was washed with H_2O , brine and aq NaHCO_3 , dried (MgSO_4), and evaporated to dryness. Flash chromatography of the residue using (3:1,2:1,1:1) CH_2Cl_2 –EtOAc and crystallization gave the diol as a white solid (0.998 g, 90%): mp 149 °C; +19.6° (0.91, CHCl_3). The diol (0.998 g, 2.19 mmol) was added as a solution in dry DMF (10 mL) to a stirred suspension of 60% NaH (2 mL DMF) at 0 °C. After 10 min had elapsed, PhCH_2Br was added and cooling was stopped. The mixture was stirred overnight and quenched with satd NH_4Cl (5 mL) and water (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined extract was dried (MgSO_4), and the solvent was evaporated. Purification by column chromatography (4:1 petroleum ether–acetone) of the yellow syrup gave the title compound **6** as a pale-yellow glass. ^1H NMR (CDCl_3): δ 3.71 (s, 3H), 3.74–3.83 (m, 2H), 3.92 (dd, 1H, J = 6.3 Hz), 4.20–4.53 (m, 4H), 4.57–4.66 (m, 4H), 4.79 (dd, 2H J = 3.4, 6.8 Hz), 4.98 (d, 1H, J = 17.1 Hz), 5.51–5.62 (m, 1H), 5.66 (d, 1H, J = 8.3 Hz), 6.67 (d, 2H, J = 9.0 Hz), 6.85 (d, 2H, J = 9.0 Hz), 7.23–7.33 (m, 10H), 7.71–7.78 (m, 2H), 7.86 (bs, 2H). ^{13}C NMR (CDCl_3): δ 55.50, 55.95, 68.62, 73.42, 73.70, 74.85, 75.26, 78.97, 79.23, 97.60, 114.33, 117.19, 118.64, 123.40, 127.52, 127.68, 127.79, 127.87, 128.28, 128.37, 131.65, 134.10, 134.22,

137.90, 138.12, 150.87, 155.30.

Preparation of 3-O-Acetyl-4,6-di-O-benzyl-2-deoxy-2-phthalimido- β -D-

glucopyranose (8). A solution of compound **6** (334 mg, 0.52 mmol) in dry THF at room temperature was treated with a solution of an activated Ir catalyst⁹³ (53 mg) in dry THF. Iridium catalyst was activated as follows: the catalyst was dissolved in dry THF and treated with hydrogen using a balloon equipped with a long needle. The solution was vigorously shaken under hydrogen until the bright red solution turned brown. Nitrogen was then bubbled into the solution to purge any excess hydrogen. This solution was added to the solution of **6**, and the solution was stirred until all of the starting material was consumed as determined by TLC. The solvent was evaporated, and the residue was dissolved in a solution of 2:1 THF–HCl and warmed gently to 45 °C. After 30 min heating was stopped, and the solution was allowed to cool to room temperature and diluted with CH₂Cl₂. The layers were partitioned, and the aqueous layer was extracted with CH₂Cl₂. The organic layers were combined and washed with a satd solution of NaHCO₃, water and brine, dried, and filtered, and the solvent was evaporated under reduced pressure to yield the alcohol as a glass. The alcohol was pure enough to carry through to the next step. A pure sample was obtained for analytical purposes after column chromatography using 1:1 hexane–ethyl acetate as eluent. ¹H NMR (250 MHz, CDCl₃): δ 3.7 (s, 4H, CH₃), 3.81–3.83 (m, 2H), 4.40–4.51 (m, 3H), 4.60–4.71 (m, 4H, CH₂Ph), 5.68 (d, 1H, J = 8 Hz), 6.69

(d, 2H, $J = 9.1$ Hz ArOMe), 6.86 (d, 2H, $J = 9.1$ Hz, ArOMe), 7.26–7.35 (m, 10H, Ar), 7.70–7.73 (m, 2H, Phth), 7.83–7.85 (m, 2H, Phth).

The alcohol was dissolved in excess pyridine and acetic anhydride and stirred overnight at room temp. The solution was concentrated, the crude syrup (256 mg, 0.40 mmol) was dissolved in 4:1 $\text{CH}_3\text{CN}-\text{H}_2\text{O}$, and CAN (1.1 g, 2.0 mmol) was added. After stirring for 5 min, CH_2Cl_2 and brine were added, and the phases were separated. The organic layer was dried and the solution was concentrated. Column chromatography of the residue using 1:1 petroleum ether–ethyl acetate afforded **8** as a syrup. ^1H NMR (250 MHz, CDCl_3): δ 1.75 (s, 3H, CH_3), 3.74–3.80 (m, 4H, H-4, H-5, H-6a, H-6b), 4.17 (dd, 1H, $J = 10.3$, 8.7 Hz, H-2), 4.48 (m, 4H, CH_2Ph), 5.63 (d, 1H, $J = 8.4$ Hz, H-1), 5.75 (dd, 1H, $J = 8$ Hz, H-3), 7.12–7.32 (m, 10H, Ar), 7.65–7.82 (m, 4H, Phth). ^{13}C NMR (250 MHz, CDCl_3): δ 20.5, 56.5, 68.4, 73.0, 73.5, 74.5, 74.7, 76.6, 92.5, 123.4, 127.6, 127.7, 127.9, 128.4, 131.5, 134.1, 137.7, 137.8, 167.9, 170.0.

(*E/Z*)-4,6-Di-*O*-acetyl-5,7-di-*O*-benzyl-1,2,3-trideoxy-1-phenyl-3-phthalimido-D-*gluco*-hept-1-enitol (12). A mixture of compound **10** (0.10 g, 0.20 mmol), benzyltriphenylphosphonium chloride (0.24 g, 0.61 mmol), dry potassium carbonate (0.085 g, 0.20 mmol) and dry formamide (0.081 mL, 2 mmol) in anhydrous dioxane (10 mL) was allowed to reflux for 8 h. The solution was brought to room temperature, and the precipitate was filtered and washed with dioxane (4 x 10 mL). The filtrate was evaporated, and the residue was

chromatographed on silica gel using CH_3Cl – MeOH as eluent to provide **11** as a colorless syrup ($R_f = 0.28$ 6:1 petroleum ether–acetone) that was directly used in the next reaction.

A solution of **11** in pyridine and acetic anhydride was stirred at room temperature overnight. The solution was poured into a stirred mixture of ice-water, and EtOAc was added to the mixture. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL), the organic layers were combined and dried with MgSO_4 and filtered. The solution was concentrated under reduced pressure to give crude **12** (an *E/Z* mixture) as a glassy material. Flash Chromatography using 4:1:1 hexanes–acetone–toluene as eluent provided pure **12**. Data is given for the *Z* isomer. ^1H NMR (250 MHz CDCl_3): δ 1.75 (s, 3H, OAc), 1.98 (s, 3H, OAc), 3.65–4.01 (m, 5H, H-4, H-5, H-6, H-7a, H-7b), 4.38 (dd, 1H, $J = 10.5, 8.9$ Hz, H-2), 4.49–4.55 (m, 3H), 4.70 (d, 1H, $J = 12.0$ Hz), 5.84 (dd, 1H, $J = 10.5, 8.7$ Hz, H-3), 6.52 (d, 1H, $J = 8.9$ Hz, H-1), 7.12–7.37 (m, 15H), 7.70–7.80 (m, 2H, Phth), 7.81–9.87 (m, 2H, Phth). ^{13}C NMR (250 MHz, CDCl_3): δ 20.4 (CH_3), 20.8 (CH_3), 54.0, 67.8, 72.9, 73.6, 74.5, 75.3, 75.9, 89.9, 123.6, 125.2, 127.7, 128.0, 128.2, 128.4, 129.0, 131.3, 134.2, 137.8, 167.5, 168.7, 170.0. ESIMS (positive-ion mode): $m/z = 648$ ($\text{M} + \text{H}^+$).

Preparation of 5-O-Acetyl-4,6-di-O-benzyl-2,3-dideoxy-2-phthalimido-aldehydo-D-erythro-hex-2-enose (13). A stirred and cooled solution (-78°C) of **12** (1.0 g, 1.7 mmol) in 2:1 CH_2Cl_2 – MeOH was treated with ozone until a

bluish color was evident. A stream of nitrogen was passed through the solution to purge any excess ozone. Methyl sulfide (0.1 mL) was added and cooling was stopped. After room temperature was attained, the solution was stirred for an additional 2 h. The solvent was concentrated under reduced pressure, and the residue was co-evaporated with Et₂O several times. Flash chromatography of the crude material resulted in pure **13** as a colorless syrup (0.52 g, 59% yield).

¹H NMR (250 MHz CDCl₃): δ 2.05 (s, 3H, OAc), 3.86 (m, 2H, H-6a, H-6b), 4.42 (s, 2H, OCH₂Ph), 4.49–4.58 (m, 2H, H-4, 0.5 OCH₂Ph) 4.70 (d, *J* = 11.8 Hz, 0.5 OCH₂Ph), 5.24 (m, 1H, H-5), 7.04 (d, *J* = 8.6 Hz, H-3), 7.12–7.33 (m, 10H), 7.72–7.80 (m, 2H, Phth), 7.82–7.90 (m, 2H, Phth), 9.46 (s, 1H, CHO). ¹³C NMR (250 MHz, CDCl₃): δ 21.0, 67.3, 72.1, 72.6, 73.0, 74.0, 123.8, 127.3, 127.5, 127.8, 128.1, 128.3, 128.4, 128.6, 131.9, 134.4, 134.8, 137.4, 137.6, 151.9, 170.3, 184.2, 186.5.

2-Acetamido-2-deoxy-4,6-O-isopropylidene-α-D-glucopyranose (15). A mixture of 2-acetamido-2-deoxy-α-D-glucose (5.0 g, 22.6 mmol) and 2,2-dimethoxypropane (5.56 mL, 45.2 mmol) was vigorously stirred in the presence of *p*-toluenesulfonic acid monohydrate (56 mg) at room temperature. After 7 h Et₃N was added to neutralize the mixture, and the mixture was filtered. The filtrate was concentrated to dryness to afford compound **15** as a white solid (85 %). ¹H NMR (250 MHz, CD₃OD): δ 1.27(s, 3H), 1.42 (s, 3H), 1.91 (s, 3H), 3.20–

3.30 (m, 1H), 3.45 (t, $J = 8.4$ Hz, 1H, H-2), 3.64–3.75 (m, 3H), 3.80–3.87 (m, 1H, H-6a), 4.50 (bs, 1H, NH), 4.97 (d, $J = 3.6$ Hz, 1H, H-1). ^{13}C NMR (CD_3OD): δ 19.4, 22.61, 29.54, 56.39, 63.64, 64.48, 69.95, 76.42, 93.25, 100.91, 173.66.

Preparation of (*E/Z*)-3-Acetamido-1,2,3-trideoxy- 5,7-*O*-isopropylidene-1-phenyl-D-*gluco*-hept-1-enitol (16**).** A solution of compound **15** (2.04 g, 7.8 mmol), benzyltriphenylphosphonium chloride (9.11 g, 23.4 mmol), dry K_2CO_3 (3.24 g, 23.4 mmol) and dry formamide (3.1 mL, 78 mmol) in freshly distilled dioxane (75 mL) was allowed to reflux for 8 h. The solution was brought to room temperature, and the resulting precipitate was filtered and washed with dioxane (4 x 10 mL). The filtrate was evaporated, and the residue was chromatographed using CH_3Cl –MeOH as eluent to provide **16** as a colorless syrup (90%). ^1H NMR (250 MHz, CDCl_3): δ 1.29–1.43 (m, 5H), 1.88 (s, 1.3H), 2.01 (s, 1.65H), 3.54–3.64 (m, 1.11H), 3.72–3.86 (m, 3.61H), 3.94–4.03 (m, 1.65H), 4.85–4.88 (m, 0.49H), 5.20–5.26 (m, 0.51H), 5.57 (dd, $J = 11.3, 9.5$ Hz, 0.34H), 6.14 (dd, $J = 15.9, 5.8$ Hz, 0.50H), 6.46–6.58 (m, 1.33H), 6.80 (d, $J = 8.5$ Hz, 0.35H), 7.03 (d, $J = 8.7$ Hz, 0.53H), 7.19–7.36 (m, 6H). ^{13}C NMR (250 MHz CDCl_3): δ 19.18, 23.31, 28.45, 50.66, 54.62, 61.76, 64.47, 69.61, 73.98, 74.15, 98.56, 125.76, 126.25, 127.22, 127.35, 127.53, 128.27, 128.42, 131.11, 132.28, 136.06, 136.36, 170.27, 170.56.

(*E/Z*)-3-Acetamido-4,6-di-*O*-acetyl-1,2,3-trideoxy-5,7-*O*-isopropylidene-1-phenyl-D-*gluco*-hept-1-enitol (17**).** A solution of **16** (1.1 g, 3.1 mmol) in excess pyridine and acetic anhydride was stirred at room temperature overnight. The solution was poured into a stirred mixture of ice-water, and EtOAc was added to the mixture. The organic layer was separated, the aqueous layer was extracted with EtOAc (3 x 15 mL), and the organic layers were combined, dried with MgSO₄ and filtered. The solution was concentrated under reduced pressure to give crude **17** as a glassy material. Flash chromatography using 3:1 hexanes–ethyl acetate provided pure **17** (1.2 g, 92% yield). ¹H NMR (250 MHz CDCl₃): δ 1.43–1.52 (m, 7.7 H), 1.93 (s, 1.76 H), 1.95 (s, 1.84H), 2.10 (s, 2.24H), 3.63 (t, 0.98H, *J* = 8.9 Hz), 3.93–4.00 (m, 1H), 4.17–4.20 (m, 0.78H), 4.80–4.85 (m, 0.93H), 5.09–5.12 (m, 1.68H), 5.44–5.52 (m, 0.77H), 6.09 (dd, 0.34H, *J* = 15.9, 5.7 Hz), 6.54–6.62 (m, 1.21H), 6.72 (dd, 0.38H, *J* = 8.2 Hz), 6.89 (d, 0.45H, *J* = 8.1 Hz), 7.22–7.47 (m, 6H). ¹³C NMR (250 MHz, CDCl₃): δ 19.2 (CH₃), 19.4 (CH₃), 20.4 (CH₃), 20.7 (CH₃), 23.0 (OAc), 23.2 (OAc), 27.4 (NHAc), 47.4, 51.7, 61.5, 61.6, 64.0, 64.1, 69.3, 69.4, 69.9, 70.3, 99.4, 99.5, 124.9, 126.1, 126.9, 127.3, 127.6, 128.1, 128.4, 128.5, 131.6, 132.5, 135.5, 136.0, 169.0, 169.3, 169.5, 170.1; ESIMS (positive-ion mode): *m/z* = 419.9 (*M* + H⁺), 441.8 (*M* + Na⁺), 457.9 (*M* + K⁺).

Preparation of 2-Acetamido-3,5-di-O-acetyl-4,6-O-isopropylidene-aldehydo-D-glucose (18). A stirred and cooled solution ($-78\text{ }^{\circ}\text{C}$) of **17** (1.09 g, 2.6 mmol) in 2:1 CH_2Cl_2 –MeOH (15 mL) was treated with ozone until a bluish color was evident. A stream of nitrogen was passed through the solution to purge any excess ozone. Methyl sulfide (0.1 mL) was added, and cooling was stopped. After room temperature was attained, the solution was stirred for an additional 2 h. The solvent was concentrated under reduced pressure, and the residue was co-evaporated with Et_2O several times. Flash chromatography (100:1 CHCl_3 –MeOH) of the crude material resulted in pure **18** (0.52 g, 56%) as a colorless syrup. ^1H NMR (250 MHz CDCl_3): δ 1.46 (s, 3H), 1.51 (s, 3H), 2.03 (s, 3H), 2.08 (s, 3H), 3.41 (d, 1H, $J = 6.0$ Hz), 3.70 (t, 2H $J = 10.0$ Hz), 3.95–4.02 (m, 1H), 4.27 (d, 1H, $J = 9.7$ Hz), 4.78 (t, 1H, $J = 7.2$ Hz), 4.88 (m, 1H), 9.70 (s, 1H, CHO). ^{13}C NMR (250 MHz, CDCl_3): δ 19.5, 20.4, 20.6, 22.8, 60.1, 61.5, 63.8, 70.1, 71.5, 99.8, 169.8, 170.2, 170.3, 196.7. ESIMS (positive-ion mode): $m/z = 346$ ($\text{M} + \text{H}^+$), 368 ($\text{M} + \text{Na}^+$).

2-Acetamido-4,6-di-O-acetyl-5,7-O-isopropylidene-aldehydo-D-erythro-hex-2-enose (18b). Compound **18** when left standing or in contact with silica gel decomposed to afford **18b** as a colorless syrup. ^1H NMR (250 MHz CDCl_3): δ 1.43 (s, 3H), 1.56 (s, 3H), 2.05 (s, 3H), 2.16 (s, 3H), 3.74 (dd, 1H, $J = 11.6, 8.0$

Hz, H-6a), 4.03 (dd, $J = 11.6, 5.3$ Hz, 1H, H6b), 4.79–4.88 (m, 1H), 5.10–5.17 (m, 1H), 6.01 (d, 1H, $J = 6.3$ Hz, H-2), 9.30 (s, 1H, CHO). ^{13}C NMR (250 MHz, CDCl_3): δ 19.9, 20.8, 23.5, 27.9, 61.6, 68.5, 68.8, 99.6, 134.1, 135.7, 167.8, 169.9, 189.1.

Preparation of 2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranoside

(36).^{78,79} To a suspension of 2-acetamido-2-deoxy-D-glucopyranoside (20 g, 90.4 mmol) and allyl alcohol (280 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.64 mL, 20.8 mmol). The mixture was refluxed for 2 h and filtered hot, and the filtrate was evaporated to dryness. The dried residue was suspended in freshly distilled dioxane (500 mL) and benzyl bromide (80 mL) with vigorous stirring. Powdered KOH was then added in small portions, and the mixture was heated under reflux until all the starting material had been consumed (approx. 4 h). Evaporation of the solvent gave an orange residue that was extracted with $\text{CHCl}_3\text{--H}_2\text{O}$. The CHCl_3 layer was dried with MgSO_4 , and the solvent was evaporated. The residue was co-evaporated several times with PhCH_3 (3 x 100 mL), and the solid was dried in vacuo overnight. A vigorously stirred suspension of the crude product **35** in anhydrous DMSO (500 mL) was treated with KO^tBu (12 g) and heated to 100 °C for 3.5 h. The resulting brown solution was cooled, distilled H_2O (500 mL) was added, and the precipitate was filtered off. The brown precipitate was dissolved in acetone (150 mL) and 2 N HCl (150 mL), and the mixture was heated under reflux for 45 min. After diluting with H_2O (200 mL),

the brown precipitate was filtered off and crystallized from MeOH.

Recrystallization from MeOH provided **36** as white needles (18 g, 40% yield).

mp 214–216°. ¹H NMR (250 MHz, CDCl₃): δ 1.82 (s, 3H, CH₃), 3.65 (m, 4H), 3.79 (m, 1H), 4.09 (m, 2H), 4.54 (AB, 5H), 4.79 (AB, 2H), 5.21 (d, 1H, *J* = 3.6 Hz, H-1), 5.35 (d, 1H, *J* = 9 Hz), 7.16–7.41 (m, 15H).

Preparation of (2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-

glucopyranosyl)- tributylstannane (**37**).^{78,79} Bu₃SnCl (3.42 mL) was added to small pieces of Li (0.22 g) in dry THF (20 mL), which resulted in the formation of a dark-green mixture of LiCl and (tributylstannyl)lithium, Bu₃SnLi, after stirring for 5–6 h. The reagent was kept at 0 °C until needed.

Compound **36** (2.0 g, 4.1 mmol) was suspended in PhCH₃ (10 mL) and CHCl₃ (10 mL) under argon and treated with freshly distilled SOCl₂ (14.8 mL) for 40 min to produce the α-D-glucopyranosyl chloride. After evaporation of the solvent, the pale-yellow solid was co-evaporated with anhydr CHCl₃ (3 x 20 mL), and the moisture-sensitive residue was dried overnight in vacuo at 30 °C. The glucopyranosyl chloride was dissolved in dry THF (50 mL) and cooled to -78 °C, at which time the dark-green Bu₃SnLi was added slowly with stirring via syringe.

After consumption of the glucopyranosyl chloride as indicated by TLC (ca. 2 h), cooling was terminated and aq NH₄Cl (15 mL) was added. After warming to room temperature in a sonic bath, H₂O was added, and the mixture was

extracted with CH_2Cl_2 (3 x 500 mL). The organic layers were combined, dried (MgSO_4), and evaporated to dryness, and the oil was purified by flash chromatography (1:0, 5:1, 3:1 hexane–EtOAc) to afford **37** (2.4 g, 76% yield) as a yellow oil that hardened upon standing: mp 56 °C. ^1H NMR (250 MHz, CDCl_3): δ 0.78–1.00 (m, 15H, CH_2 , Me), 1.21–1.36 (m, 6H, CH_2), 1.43–1.55 (m, 6H, CH_2), 1.77 (s, 3H, CH_3), 3.25 (m, H-5), 3.38 (t, 1H, $J = 9.2$ Hz, H-3), 3.44 (d, 1H, $J = 11.6$ Hz, H-1), 3.62 (t, 1H, $J = 9.2$ Hz, H-4), 3.68 (s, 2H, H-6), 4.15 (dt, 1H, $J = 9.4, 11.6$ Hz, H-2), 4.52–4.67 (m, 4H, PhCH_2), 4.80–4.93 (m, 3H, PhCH_2 , NH). ^{13}C NMR (250 MHz, CDCl_3): δ 9.2, 13.7, 27.3, 29.1, 54.7, 69.4, 73.4, 74.6, 74.9, 79.3, 83.4, 85.5, 127.3, 127.7, 127.9, 128.2, 128.3, 128.4, 138.3, 138.6, 169.4. NMR spectral data matches that reported.^{78,79}

Preparation of Methyl 4,6-O-(4-Methoxybenzylidene)- α -D-glucopyranoside

(39).⁷³ Methyl α -D-glucopyranoside (20 g, 103 mmol) and *p*-toluenesulfonic acid (cat. amount) in dry DMF (200 mL) were evaporated under reduced pressure at 45 °C until all of the starting material was consumed. After evaporation of approximately 180 mL of DMF, the solution was poured into a vigorously stirred mixture of ice, NaHCO_3 (75 mL) and Et_2O (75 mL). The resulting residue was filtered, washed with petroleum ether (2x) and H_2O (2x) and dried in vacuo at 30 °C. Crystallization from EtOAc gave **39** as a white solid (24 g, 75% yield). mp 191–192 °C (Lit.,⁷³ mp 194 °C). $[\alpha]_D^{23} +9.16^\circ$ (c 0.8, CHCl_3). ^1H NMR (250 MHz,

DMSO): δ 3.31 (s, 3H), 3.52 (m, 3H), 3.75 (s, 3H), 4.11 (dd, 1H, $J = 4.2, 4.2$ Hz), 4.62 (d, 1H, $J = 3.57$ Hz), 5.01 (d, 1H, $J = 6.65$ Hz), 5.19 (d, 1H, $J = 5.01$ Hz), 5.51 (s, 1H), 6.90 (d, 2H, $J = 8.68$), 7.35 (d, 2H, $J = 8.64$ Hz). ^{13}C NMR (250 MHz, CDCl_3): δ 54.86, 55.21, 62.52, 68.27, 70.04, 72.55, 81.41, 100.64, 100.94, 113.40, 127.84, 130.29, 159.65. NMR spectral data matches that reported.⁷³

Preparation of Methyl 2,3-di-*O*-benzyl-4,6-*O*-(4-methoxybenzylidene)- α -D-glucopyranoside (40).⁷³ To a solution of **39** (10.23 g, 33 mmol) in dry DMF (100 mL) at 0 °C was added portionwise NaH (60% in mineral oil, 6.6 g, 164 mmol). After stirring for 15 min, PhCH_2Br (9.7 mL, 98 mmol) was added, and the mixture was allowed to stir at room temperature. After the reaction was complete, as indicated by TLC, MeOH was slowly added. The mixture was diluted with EtOAc (500 mL) and washed with H_2O (3 x 100 mL). The combined aqueous phase was extracted with Et_2O . The combined organics were dried with MgSO_4 , and the solvent was evaporated to give a white solid.

Crystallization from EtOH gave the title compound **40** (12.9 g, 80% yield). mp 143–144 °C (lit.,⁷³ mp 145–146 °C). $[\alpha]_{\text{D}}^{23} -3.6^\circ$ (c 0.7, CHCl_3). ^1H NMR (250 MHz, CDCl_3): δ 3.39 (s, OCH_3), 3.52–3.77 (m, 3H), 3.79 (s, 4H), 3.99 (t, 1H, $J = 9.2$ Hz), 4.21 (dd, 1H $J = 4.35$ Hz), 4.58 (d, 1H $J = 3.6$ Hz), 4.66 (d, 1H, $J = 12.18$ Hz), 4.80 (m, 3H) 5.5 (s, 1H), 4.88 (d, 2 H, $J = 10$ Hz), 7.26–7.42 (m, 12H).

^{13}C NMR (250 MHz, CDCl_3): δ 55.24, 62.29, 68.95, 73.72, 75.24, 78.55, 79.15,

82.05, 99.17, 101.20, 113.51, 127.28, 127.45, 127.85, 127.95, 128.04, 128.23, 128.37, 129.67, 138.13, 138.71, 159.94. NMR spectral data matches that reported.⁷³

Preparation of Methyl 2,3-di-O-benzyl-6-O-(4-methoxybenzyl)- α -D-glucopyranoside (41) and Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)- α -D-glucopyranoside (41b).⁷³ A solution of trifluoroacetic acid (15.65 mL, 203 mmol) in dry DMF (120 mL) was added dropwise to a stirred mixture of compound **40** (10 g, 20.3 mmol), powdered 3A molecular sieves (3 g), and NaCNBH₃ (6.38 g, 101.5 mmol) in dry DMF (160 mL) at 0 °C. After stirring overnight the mixture was filtered through Celite, and the solution was then poured into ice-cold satd NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 50 mL). The combined organic phases were dried over MgSO₄ and filtered, and the solvent was evaporated. Column chromatography (3:1 PhMe–EtOAc, *R_f* 0.32) of the residue provided **41** as a syrup in 80% yield and its isomer **41b** in 9% yield. Data for compound **41**. ¹H NMR (250 MHz, CDCl₃): δ 2.12 (bs, 1H, OH), 3.37 (s, 3H), 3.49–3.54 (dd, 1H, *J* = 2.5, 2.5 Hz), 3.57–3.64 (m, 4H), 3.77 (s, 3H), 4.47 (d, 2H, *J* = 5 Hz), 4.61–4.80 (m, 4H), 4.96 (d, 1H, *J* = 4 Hz), 6.83–6.86 (d, 2H *J* = 7.5 Hz), 7.21 (d, 2H, *J* = 7.5 Hz), 7.25–7.36 (m, 14H). ¹³C NMR (CDCl₃): δ 55.17, 69.14, 69.77, 70.61, 73.09, 73.17, 75.33, 79.51, 81.39, 98.13, 113.69, 127.74, 127.91, 128.04, 128.39, 128.49, 129.22,

130.01, 138.01, 138.78, 159.15. NMR spectral data matches that reported.⁷³

Data for compound **41b**: ¹H NMR (250 MHz, CDCl₃): δ 1.87 (s, 1H, OH), 3.34 (s, 3H, OCH₃), 3.46–3.54 (m, 2H), 3.60–3.72 (m, 3H), 3.76 (s, 3H, OCH₃), 3.99 (t, 1H, *J* = 9.2 Hz), 4.55–4.67 (m, 3H, CH₂Ar), 4.76 (d, 1H, *J* = 5.3 Hz, H-1), 4.81–4.87 (m, 2H, CH₂Ar), 4.97 (d, 1H, *J* = 10.9 Hz, 0.5 CH₂Ar), 6.82 (d, 2H, *J* = 8.6 Hz, CH₂ArOMe), 7.19 (d, 2H, *J* = 8.4 Hz, CH₂ArOMe), 7.28–7.39 (m, 10H, Ar). ¹³C NMR (CDCl₃): δ 55.0, 55.1, 61.7, 70.6, 73.2, 74.5, 75.6, 79.9, 81.9, 98.0, 113.8, 127.5, 127.8, 128.0, 128.3, 129.6, 130.2, 138.0, 138.7, 159.2. NMR spectral data matched that reported.⁷³

Preparation of Methyl 2,3-di-*O*-benzyl-6-*O*-(4-methoxybenzyl)- α -D-xylo-4-hexulopyranoside (42**).⁸³** A solution of DMSO (5.1 mL, 71.2 mmol) in dry CH₂Cl₂ (25 mL) was added dropwise to a solution of oxalyl chloride (3.1 mL, 35.6 mmol) in dry CH₂Cl₂ (25 mL) at -78 °C. After stirring for 10 min at -78 °C, compound **41** (8.8 g, 17.8 mmol) dissolved in CH₂Cl₂ was added slowly over 15 min. After stirring for an additional 20 min, Et₃N (15 mL, 107 mmol) was added. The reaction was allowed to warm to room temperature until TLC indicated the starting alcohol was completely consumed. The mixture was diluted with CH₂Cl₂ (150 mL), poured into satd aq NH₄Cl (200 mL), and washed with brine (100 mL). The CH₂Cl₂ layer was dried over MgSO₄ and filtered, and the solvent was evaporated. Column chromatography (3:1 PhMe–EtOAc *R*_f = 0.49) on silica gel

gave **42** as an unstable colorless syrup (8 g, 90% yield). ^1H NMR (250 MHz, CDCl_3): δ 3.36 (s, 3H, OCH_3), 3.54 (dd, 1H, $J = 10.6, 6.2$ Hz, H-6b), 3.64 (s, 3H, OCH_3), 3.69 (dd, 1H, $J = 10, 3.4$ Hz, H-2), 3.76 (dd, 1H, $J = 10.8, 3.5$ Hz, H-6a), 4.14 (dd, 1H, $J = 9.5, 3.6$ Hz, H-5), 4.31 (d, 1H, $J = 9.8$ Hz, H-3), 4.37 (s, 1H, 0.5 CH_2Ar), 4.39 (s, 1H, 0.5 CH_2Ar), 4.52 (d, 1H, $J = 2.5$ Hz, 0.5 CH_2Ar), 4.57 (s, 1H, 0.5 CH_2Ar), 4.69 (d, 1H, $J = 3.39$ Hz, H-1), 4.70 (d, 1H, $J = 10.6$ Hz, 0.5 CH_2Ar), 4.83 (1H, d, $J = 11.3$ Hz, 0.5 CH_2Ar), 6.74 (d, 2H, $J = 8.4$ Hz, ArOMe), 7.14 (d, 2H, $J = 8.5$ Hz, ArOMe), 7.17–7.33 (m, 10H, Ar). ^{13}C NMR (CDCl_3): δ 54.98, 55.63, 67.14, 72.58, 73.09, 73.66, 74.12, 79.94, 82.34, 98.18, 113.57, 127.59, 127.79, 127.86, 128.16, 128.25, 129.09, 129.77, 137.63, 159.05, 201.82. ESIMS (positive-ion mode): $m/z = 515.21$ ($\text{M} + \text{Na}^+$), 531.0 ($\text{M} + \text{K}^+$).

Preparation Methyl 2,3-di-O-benzyl-4-deoxy-4-C-(methylene)-6-O-(4-methoxybenzyl)- α -D-xylo-hexopyranoside (43**).⁸³** Preparation of Lombardo's reagent:⁸⁵ TiCl_4 (2.3 mL) was added dropwise to a vigorously stirred suspension of CH_2Br_2 (2.02 mL) and zinc dust (5.75 g) in dry THF (50 mL) at -40°C . The mixture was stirred at 5°C for 3 days to give a thick gray slurry that was shown to be active by effervescing when H_2O was added to an aliquot. The Lombardo's reagent was then added in small portions to a solution of ketone **42** (8.5 g, 17.2 mmol) in dry CH_2Cl_2 (100 mL) at room temperature until TLC indicated complete depletion of the starting material. The mixture was poured

into satd aq NaHCO₃ (100 mL) and Et₂O (200 mL). The mixture was shaken in a separatory funnel, and the clear organic layer was removed. The aqueous phase was extracted several times with Et₂O and the organic extract was dried (MgSO₄), and filtered, and the solvent was evaporated. Flash chromatography (5:1 petroleum ether–EtOAc, *R_f* = 0.3) of the crude product, followed by crystallization from hexane and EtOAc, gave the alkene **43** as white crystals (7.62 g, 90% yield): mp 102 °C. [α]_D²³ +36.19° (c 1.6, CHCl₃). ¹H NMR (600 MHz, CDCl₃): δ 3.43 (s, 3H, OCH₃), 3.49 (dd, 1H, *J* = 4.2, 3.6 Hz, H-2), 3.65 (dd, 1H, *J* = 6 Hz, H-6a), 3.76 (dd, 1H, *J* = 5.4, 4.8 Hz), 3.80 (s, 3H, ArOCH₃), 4.30 (t, 1H, *J* = 4.8, H-5), 4.33 (d, 1H, *J* = 9.6 Hz, H-3), 4.53 (AB, 2H, *J* = 11.4, CH₂Ar), 4.67 (AB, 1H, *J* = 12.6 Hz, CH₂Ar), 4.69 (d, 1H, *J* = 4.2 Hz, H-1), 4.73 (AB, 1H, *J* = 11.4 CH₂Ar), 4.80 (AB, 1H, *J* = 11.4 Hz, CH₂Ar), 4.85 (AB, 1H, *J* = 12 Hz, CH₂Ar), 4.97 (s, 1H, CH₂=CR), 5.36 (s, 1H, CH₂=CR), 6.85 (d, 2H, *J* = 6.75 Hz, ArOCH₃), 7.25–7.40 (m, 12H, Ar). ¹³C NMR (250 MHz, CDCl₃): δ 55.2, 67.7, 69.3, 73.1, 73.5, 73.8, 79.2, 81.6, 98.7, 107.7, 113.8, 127.5, 127.7, 128.0, 128.3, 129.3, 130.0, 138.4, 138.5, 142.7, 159.2. Anal. Calcd for C₃₀H₃₅O₆: C, 73.45; H, 6.99. Found: C, 73.37; H, 6.89.

Methyl 2,3-di-O-benzyl-4-deoxy-4-C-(hydroxymethyl)-6-O-(4-methoxybenzyl)- α -D-galactopyranoside (44**) and methyl 2,3-di-O-benzyl-4-deoxy-4-C-(hydroxymethyl)-6-O-(4-methoxybenzyl)- α -D-glucopyranoside**

(45). A stirred solution of alkene **43** (3.62 g, 7.4 mmol) in dry THF (100 mL) and 60 mL (36.9 mmol) 9-BBN (0.5 M in THF) was heated to reflux for 4 h. The solution was then cooled to 0 °C and treated with a 10% solution of NaOH (20 mL), followed by the addition of a 30% aq hydrogen peroxide solution (20 mL) with stirring for 45 min. The mixture was extracted with Et₂O (3 × 50 mL), and the organic extract was washed with 20% aq NaHSO₃ and brine. The organic layer was dried over MgSO₄, and filtered, and the solvent was evaporated.

Column chromatography of the crude product gave **44** and **45** as syrups (3.2 g, 86% overall yield). Data for compound **44**: ¹H NMR (250 MHz, CDCl₃): δ 2.36 – 2.41 (m, 1H, H-4), 3.36 (s, 3H, OCH₃), 3.56–3.59 (m, 2H, H-6a, H-6b), 3.67 (dd, 1H, *J*_{1,2} = 3.6, *J*_{2,3} = 10.2 Hz, H-2), 3.79 (s, 3H, OCH₃), 3.91 (dd, 1H, *J*_{4,7a} = 6.1, *J*_{7a,7b} = 11.6 Hz, H-7a), 4.02–4.07 (m, 3H, H-3, H-5, H-7b), 4.50 (d, 2H, *J* = 2.4 Hz, CH₂Ph), 4.62–4.83 (m, 6H, H-1, CH₂Ph), 6.82 (d, 2H, *J* = 8.1 Hz, PhOCH₃), 7.21–7.38 (m, 12H, C₆H₅, PhOCH₃). ¹³C NMR (250 MHz, CDCl₃): δ 43.96, 55.51, 58.04, 68.07, 70.45, 73.30, 73.69, 76.82, 78.77, 98.99, 114.13, 127.95–128.68, 129.69, 129.75, 138.53, 138.59, 159.62. ESIMS (positive-ion mode): *m/z* = 531.1 (M + Na⁺).

Data for compound **45**: ¹H NMR (250 MHz, CDCl₃): δ 1.69 (br. s, 1H, OH), 1.71–1.92 (m, 1H, 4-H), 3.36 (s, 3H, Me), 3.56–3.61 (m, 5H, 2-H, 6a-H, 6b-H, 4a'-H, 4b'-H), 3.79–3.90 (m, 5H, 3-H, 5-H, OCH₃), 4.37–5.01 (m, 7H, 1-H, CH₂Ph), 6.83 (d, 2H, PhOMe), 7.20–7.38 (m, 12H, C₆H₅, PhOMe). ¹³C NMR (250 MHz,

CDCl_3): δ 46.25, 55.19, 59.49, 68.20, 70.20, 72.85, 73.14, 75.17, 75.48, 81.48, 98.44, 113.76, 127.82–128.46, 129.40, 129.69, 138.19, 138.44, 159.27. ESIMS (positive-ion mode): m/z = 531.1 ($M + \text{Na}^+$).

Methyl 2,3-di-O-benzyl-4-deoxy-4-C-(formyl)-6-O-(4-methoxybenzyl)- α -D-galactopyranoside (46) and Methyl 2,3-di-O-benzyl-4-deoxy-4-C-(formyl)-6-O-(4-methoxybenzyl)- α -D-glucopyranoside (47). To a stirred solution of oxalyl chloride (1.32 mL, 15.14 mmol) in anhydr CH_2Cl_2 (25 mL) at -78°C was added dropwise a solution of freshly distilled DMSO (2.15 mL, 30.3 mmol) in dry CH_2Cl_2 (25 mL). After 15 min, a solution of **44** and **45** (3.85 g, 7.6 mmol) in dry CH_2Cl_2 (100 mL) was slowly added. Stirring was continued at -78°C for 30 min and then anhydr Et_3N (6.33 mL, 45.4 mmol) was added over 5 min. The reaction mixture was allowed to warm to room temperature, and CH_2Cl_2 was added after 30 min. The mixture was then washed with satd aq NH_4Cl (100 mL) and brine (150 mL). The organic layer was dried over MgSO_4 , filtered and concentrated. The crude residue was dissolved in dry Et_3N (150 mL) and heated for 20 h at 60°C . Concentration of the solution and purification of the residue by flash chromatography yielded predominantly **47** as a colorless syrup (3.6 g, 93% yield) and a small amount of compound **46**. Data for compound **46**: ^1H NMR (250 MHz, CDCl_3): δ 2.98 (ddd, 1H, $J = 2.5$, $J = 5.6$, $J_{4,4'} = 5.6$ Hz, 4-H), 3.38 (s, 3H, OCH_3), 3.48 (dd, 1H, $J = J_{5,6a} = 4.9$, $J_{6a,6b} = 10.4$ Hz, H-6a), 3.55 (dd, 1H, $J_{5,6b}$

= 3.9, $J_{6a,6b}$ = 10.4 Hz, H-6b), 3.79 (s, 3H, OCH₃), 3.98 (dd, 1H, $J_{1,2}$ = 3.8, $J_{2,3}$ = 10.2 Hz, H-2), 4.09–4.15 (m, 2H, H-3, H-5), 4.42 (d, 2H, J = 12.3 Hz, CH₂Ph), 4.61–4.73 (m, 3H, CH₂Ph), 4.77 (d, 1H, J = 3.8 Hz, H-1), 4.86 (d, 1H, J = 12.3 Hz, CH₂Ph), 6.85 (d, 2H, J = 8.0 Hz, PhOCH₃), 7.21 (d, 2H, J = 8.0 Hz, PhOCH₃), 7.28–7.35 (m, 10H, C₆H₅), 9.90 (d, 1H, $J_{4,4'}$ = 5.6 Hz, CHO). ¹³C NMR (300 MHz, CDCl₃): δ 55.02, 55.66, 55.89, 68.06, 70.21, 72.53, 73.69, 74.05, 76.86, 77.77, 99.49, 114.19, 128.11–128.85, 129.91, 129.95, 138.35, 138.54, 159.69, 201.74. ESIMS (positive-ion mode): m/z = 529.2 (M + Na⁺).

Data for compound **47**: ¹H NMR (250 MHz, CDCl₃): δ 2.94 (ddd, $J_{3,4}$ = $J_{4,5}$ = 10.6 Hz, $J_{4,4'}$ = 2.6 Hz, 1H 4-H) 3.36 (s, 3H, OMe), 3.51 (d, $J_{6,5}$ = 4.3 Hz, 2H, 6a-H, 6b-H), 3.56 (dd, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 9.3 Hz, 1H, 2-H), 3.79 (s, 3H, OMe), 3.97–4.03 (m, 1H, 5-H), 4.22 (dd, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 10.6 Hz, 1H, 3-H), 4.35–4.92 (m, 7H, 1-H, CH₂Ph), 6.83 (d, 8.6 Hz, 2H, PhOCH₃), 7.19–7.36 (m, 12H, C₆H₅, PhOCH₃), 9.6 (d, $J_{4,4'}$ = 2.6 Hz, 1H, CHO): ¹³C NMR (250 MHz, CDCl₃): δ 54.59, 54.83, 56.53, 66.51, 69.54, 72.37, 72.54, 74.60, 74.69, 80.24, 97.77, 113.29, 127.22–128.86, 129.21, 137.56, 137.74, 158.79, 199.61. ESIMS (positive-ion mode): m/z = 529.2 (M + Na⁺), 545.1 (M + K⁺).

Methyl 4-C-(2-acetamido-2-deoxy-3,4,6-tri-O-benzyl-β-D-glucopyranosylhydroxymethyl)-2,3-di-O-benzyl-4-deoxy-6-O-(4-methoxybenzyl)-α-D-glucopyranoside (48). To a cooled solution at -78 °C of

the glycosyl tin derivative **37** (1.2 g, 1.6 mmol) in dry THF (30 mL) was added dropwise MeLi (1.2 equiv of 1.0 M MeLi in hexanes). The reaction was allowed to warm to $-65\text{ }^{\circ}\text{C}$, and BuLi (1.0 equiv of a 2.5 M BuLi solution) was then added. The resulting red solution was stirred at this temperature for 10 min, and aldehyde **47** (1.13 g, 5.5 mmol) dissolved in dry THF (50 mL) was added. Addition of the aldehyde caused the solution to turn pale yellow. After 1 h, the reaction was quenched with satd aq NH_4Cl and warmed to room temperature in an ultrasonic bath. H_2O was then added to the reaction mixture, followed by extraction with EtOAc ($3 \times 50\text{ mL}$). The organic layers were combined, dried (MgSO_4) and concentrated. Column chromatography of the residue gave **48** (1.06 g, 68% yield) as a pale-yellow oil. ^1H NMR (250 MHz, CDCl_3): δ 1.47 (s, 3H), 2.22 (t, 1H, $J = 10.3\text{ Hz}$), 3.08 (t, 1H, $J = 9.1\text{ Hz}$), 3.22–3.26 (m, 1H), 3.30 (s, 3H), 3.51–3.68 (m, 4H), 3.75 (s, 3H), 3.77–3.94 (m, 6H), 4.09 (bs, 1H), 4.41–4.53 (m, 8H), 4.62–4.75 (m, 5H), 5.07 (d, 1H, $J = 11.3\text{ Hz}$), 5.11 (bs, 1H), 6.81 (d, 2H, $J = 2.5\text{ Hz}$), 7.18–7.33 (m, 27H). ^{13}C NMR (250 MHz, CDCl_3): δ 22.9, 45.4, 51.8, 54.8, 55.2, 67.9, 68.8, 69.4, 70.5, 72.4, 72.9, 73.4, 74.5, 75.8, 78.5, 79.1, 81.8, 83.3, 97.3, 113.6, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 129.4, 130.7, 137.9, 138.1, 138.4, 138.8, 158.9, 170.7. ESIMS (positive-ion mode): m/z 1004.1 ($\text{M} + \text{Na}$) $^+$, 1020.1 ($\text{M} + \text{K}$) $^+$.

Methyl 4-C-(2-acetamido-2-deoxy-3,4,6-tri-O-benzyl- β -D-glucopyranosylmethyl)-2,3-di-O-benzyl-4-deoxy-6-O-(4-methoxybenzyl)- α -D-glucopyranoside (49). A stirred solution of 48 (727 mg, 0.74 mmol) and imidazole (5 mg) in dry THF (25 mL) at room temperature was treated with NaH (13 g, 3.3 mmol, 60% in mineral oil, washed in dry hexanes). Stirring was continued for 1 h, and CS₂ (0.76 mL, 12.6 mmol) was then added. After another 1 h had elapsed, MeI (0.21 mL, 3.3 mmol) was added with stirring. TLC of the reaction mixture after an additional hour showed complete consumption of the starting alcohol. The mixture was diluted with CH₂Cl₂ and poured into H₂O. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 50 mL). The combined organic layers were dried over anhydr MgSO₄ and evaporated to give a crude material that was chromatographed on a silica gel column (2:1 petroleum ether–EtOAc, *R_f* 0.27) to give the thiocarbonyl compound as a pale-yellow syrup.

The thiocarbonyl compound (650 mg, 0.63 mmol) and AIBN (5 mg) in anhydr degassed PhMe (15 mL) was added to a refluxing solution of Bu₃SnH (0.9 mL, 3.5 mmol) in anhydr degassed PhMe (5 mL). Heating was stopped after 40 min, and the reaction was allowed to cool to room temperature, PhMe was added, and the solvent was evaporated. Flash chromatography of the crude material

gave **49** as a colorless syrup (471 mg, 78% yield). ^1H NMR (250 MHz, CDCl_3): δ 1.46–1.50 (m, 1H), 1.53 (s, 3H), 1.75–1.77 (m, 1H), 2.06 (bs, 1H), 3.11 (t, 1H, J = 9.6 Hz), 3.26 (s, 3H), 3.48–3.72 (m, 10H), 3.77 (s, 3H), 3.97 (d, 1H, J = 9.6 Hz), 4.33–4.77 (m, 18H), 5.04 (d, 1H, J = 12 Hz), 6.85 (d, 2H, J = 7.2 Hz), 7.21–7.33 (m, 22H). ^{13}C NMR (250 MHz, CDCl_3): δ 23.66, 28.57, 40.27, 55.12, 55.39, 55.59, 69.58, 70.06, 72.98, 73.36, 73.79, 74.69, 74.78, 78.97, 79.08, 82.31, 83.79, 98.26, 113.93, 127–128.66, 129.69, 138.22–139.72, 159.22, 169.89. ESIMS (positive-ion mode): m/z = 988.1 ($\text{M} + \text{Na}^+$), 1003.9 ($\text{M} + \text{K}^+$).

Methyl 4-C-(2-acetamido-2-deoxy- β -D-glucopyranosylmethyl)-4-deoxy- α -D-glucopyranosiduronic acid (50**).** Ceric ammonium nitrate (0.37 g, 0.67 mmol) was added all at once to a solution of compound **49** (130 mg, 0.14 mmol) in 4:1 CH_3CN – H_2O (5 mL). After the yellow solution had stirred for 5 min, CH_2Cl_2 (5 mL), H_2O (5 mL), and brine (10 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried, and the solvent was evaporated to dryness to yield a yellow glass that was purified by flash chromatography to give the intermediate alcohol (6-OH) in 78% isolated yield. A vigorously stirred solution of the alcohol (89 mg, 0.11 mmol) in 1:1 CH_3CN – H_2O (1 mL) at room temperature was treated with bis(acetoxy)iodobenzene (75 mg, 0.23 mmol) and a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO, 3

mg, 0.02 mmol). The mixture was stirred until all of the starting alcohol was consumed (TLC 9:1 CH₃Cl–MeOH), CH₂Cl₂ was added, and the phases were separated. After repeated extraction of the aqueous phase, the organic layers were combined, dried over MgSO₄, and filtered, and the filtrate was evaporated to dryness. The crude material was subjected to column chromatography over a short (4 x 1 cm, 5:1 CH₃Cl–MeOH) bed of silica gel to yield the carboxylic acid as a syrup (44 mg, 49% yield).

A mixture of the acid and Pd(OH)₂ in MeOH (Caution! Extreme fire hazard!) was treated with H₂ at 1 atm (balloon) for 24 h and then filtered through Celite. The filtrate was evaporated to give an oil. The yellow oil was subjected to column chromatography (2:1 CHCl₃–MeOH) on Sephadex LH-20 and preparative TLC (3:1 MeOH–2-PrOH) to provide compound **50** (16 mg, 74%). ¹H NMR (600 MHz, D₂O): δ 1.65 (m, 2H, H-7a and 7b), 1.88 (m, 1H, H-4), 1.91 (s, 3H, CH₃), 3.29 (ddd, 1H, *J*_{1',7a} = 10.1, *J*_{1',2'} = 9.9, *J*_{1',7b} = 2.0 Hz, H-1'), 3.32 (m, 1H, H-2, H-5'), 3.39 (m, 1H, H-4'), 3.47 (dd, 1H, *J*_{2',3'} = 9.9, *J*_{3'4'} = 8.8 Hz, H-3'), 3.50 (dd, 1H, *J*_{3,4} = 10.3, *J*_{2,3} = 9.6 Hz, H-3), 3.55 (dd, 1H, *J*_{1',2'} = *J*_{2',3'} = 9.9 Hz, H-2'), 3.67 (dd, 1H, *J*_{6'a,6'b} = 12.5 Hz, *J*_{6'b,5'} = 6.2 Hz, H-6'b), 3.78 (s, 3H, OCH₃), 3.88 (dd, 1H, *J*_{6'a,6'b} = 12.5, *J*_{6'a,5'} = 2.2 Hz, H-6'a), 3.89 (d, 1H, *J*_{4,5} = 10.7 Hz, H-5), 4.82 (d, 1H, *J*_{1,2} = 3.7 Hz). ¹³C NMR (450 MHz, D₂O): δ 22.46, 28.91, 41.54, 55.06, 56.00, 61.23, 70.44, 70.86, 72.65, 75.45, 76.53, 79.60, 99.89, 174.53, 176.83. ESIMS (positive-ion mode): *m/z* 432.1 (M + Na⁺), 448.2 (M + K⁺).

Preparation of 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-1-thio- β -D-

glucopyranose (53).⁵⁴ A solution of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- α -D-glucopyranosyl chloride (**51**) (10 g, 27.3 mmol), thiourea (4.16 g, 54.6 mmol) and dry acetone was (200 mL) refluxed. After 30 min the pseudothiourea hydrochloride precipitated out of solution. The mixture was cooled to 0 °C and filtered. The white solid, S-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- β -D-glucopyranosyl)pseudothiourea hydrochloride (**52**) was washed with several portions of acetone and dried (8.28 g, 69% yield): mp 177–179 °C (lit.,⁵⁴ 178–180 °C). A mixture of the pseudothiourea (6.54 g, 14.8 mmol) and sodium sulfite (3.77g, 30 mmol) in 70 mL 6:1 acetone–H₂O was stirred for 30 min under nitrogen at room temperature. The resulting solution was acidified to pH 4 (litmus paper) by dropwise addition of 10% hydrochloric acid and extracted with CH₃Cl (4 x 50 mL). The combined organic layer was washed with brine and H₂O and dried with MgSO₄. The solvent was evaporated under reduced pressure to yield **53** as a white solid that was crystallized from EtOH (4.12 g, 77%). mp 150–152 °C. $[\alpha]_D^{23}$ –13.58° (c 0.89, CHCl₃) ¹H NMR (250 MHz CDCl₃): δ 1.99 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.11 (s, 3H, NAc), 2.57 (d, 1H, J = 9.3 Hz, SH), 3.73 (m, 1H, H-5), 4.10–4.16 (m, 2H, H-2 and H-6b), 4.25 (dd, 1H, J = 12.3, 4.8 Hz, H-6a), 4.65 (t, 1H, J = 9.7 Hz, H-1), 5.13 (m, 2H, H-3, H-4), 6.16

(d, 1H, $J = 9.4$ Hz, NH). ^{13}C NMR (250 MHz, CDCl_3): δ 21.1, 21.2, 23.7, 57.2, 62.6, 68.7, 73.9, 76.6, 80.6, 169.7, 171.0, 171.2, 171.5. NMR spectral data matches that reported.⁵⁴

Methyl 2,3-di-O-acetyl-4,6-O-benzylidene- β -D-galactopyranoside (56). To a solution of methyl β -D-galactopyranoside (**54**), (1.0 g, 5.1 mmol), benzaldehyde dimethyl acetal (1.1 mL, 7.7 mmol), and *p*-toluenesulfonic acid (90 mg, 0.51 mmol) in dry DMF (5 mL) were rotated under reduced pressure at 45 °C until all of the starting material was consumed as indicated by TLC. Et_3N was added, and the solvent was evaporated. The resulting residue was washed with PhCH_3 (3 x 20 mL) and dried in vacuo at 30 °C. The crude **55** was dissolved in excess acetic anhydride and pyridine and stirred overnight at room temperature. The resulting solution was poured into ice water, and CH_2Cl_2 was added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried with MgSO_4 and filtered, and the solvent was evaporated. Column chromatography of the residue afforded **56** as a white solid (1.2 g, 64%). $[\alpha]_{\text{D}}^{23} +73.27^\circ$ (c 1.6, CHCl_3). ^1H NMR (250 MHz CDCl_3): δ 2.07 (s, 6H, OAc), 3.52 (bs, 4H, OCH_3 , H-5), 4.07 (d, 1H, $J = 12.5$ Hz, H-6a), 4.32–4.38 (m, 2H, H-4, H-6b), 4.42 (d, 1H, $J = 7.9$ Hz, H-1), 4.98 (dd, 1H, $J = 3.6$, H-3), 5.38 (dd, 1H, $J = 8.2$, 2.0 Hz, H-2), 5.51 (s, 1H, CHAr), 7.35–7.37 (m, 3H, Ar), 7.50–7.52 (m, 2H, Ar). ^{13}C NMR (250 MHz, CDCl_3): δ 20.8, 56.2,

66.3, 68.3, 68.8, 72.0, 73.3, 101.0, 101.7, 126.3, 128.1, 129.0, 138.1, 169.4, 170.7. ESIMS (positive-ion mode): m/z = 421.1 ($M + Na^+$), 437.1 ($M + K^+$).
 Anal. Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found C, 58.98; H, 6.04.

Methyl 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl- β -D-galactopyranoside

(57). A solution of **56** (520 mg, 1.42 mmol) in 60% CH_3COOH was heated at 60 °C for 2 h. Heating was stopped, and the solution was allowed to reach room temperature. The solution was concentrated and co-evaporated with $PhCH_3$ (3 x 10 mL). Column chromatography using 1.5:1 acetone–petroleum ether gave the diol that was used in the next reaction. The diol (108 mg, 0.39 mmol) and a catalytic amount of DMAP, were dissolved in dry DMF and cooled to 0 °C. Dry Et_3N (0.06 mL, 0.43 mmol) was added, followed by dropwise addition of TBSCl (70 mg, 0.47 mmol). After TLC indicated the reaction was complete, CH_2Cl_2 was added, and the solution was washed with satd $NaHCO_3$, H_2O , and brine. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was evaporated. Column chromatography of the residue (3:1 petroleum ether–ethyl acetate) afforded pure **57** as a syrup. ^1H NMR (250 MHz $CDCl_3$): δ 0.45 (s, 6H, CH_3), 0.85 (s, 9H, CH_3), 2.01 (s, 3H, OAc), 2.06 (s, 3H, OAc), 3.45 (s, 3H, OCH_3), 3.48 (t, 1H, J = 5.0 Hz, H-5), 3.81–3.93 (m, 2H, 6a and 6b), 4.13 (d, 1H, J = 2.9 Hz, H-4), 4.34 (d, 1H, J = 7.9 Hz H-1), 4.89 (dd, 1H, J = 7.2, 2.9 Hz, H-3), 5.24 (dd, 1H, J = 7.9 Hz, H-2). ^{13}C NMR (250 MHz, $CDCl_3$): δ 0.11, 18.2, 20.7,

20.8 25.7, 56.3, 62.8, 68.0, 69.2, 73.6, 73.7, 101.9, 169.6, 170.3. ESIMS

(positive-ion mode): $m/z = 415.1$ ($M + Na^+$), 431.1 ($M + K^+$).

Methyl S-(2-acetamido-2-deoxy-3,4,6-tri-O-acetyl- β -D-glucopyranosyl)-(1 $\rightarrow$ 4)-2,3-di-O-acetyl-6-O-*tert*-butyldimethylsilyl-4-thio- β -D-glucopyranoside (59).

A solution of alcohol **57** (105 mg, 0.27 mmol) in dry CH_2Cl_2 (2 mL) and pyridine (0.043 mL, 10 equiv) was cooled to 0 °C and $(TfO)_2$ (0.45 mL, 2.7 mmol) was added dropwise. After the reaction was complete as indicated by TLC, the solvent was evaporated. The residue was passed through a plug of silica gel (EtOAc) to provide compound **58** that was used directly in the following reaction.

A mixture of triflate **58** (0.12 g, 0.28 mmol), thiol **53** (0.12 g, 0.33 mmol) and Cs_2CO_3 (0.11 g, 0.33 mmol) in dry DMF (2 mL) were stirred at room temperature until complete consumption of the triflate was observed as indicated by TLC.

The solvent was evaporated, and the residue was chromatographed (EtOAc) to afford the thio disaccharide **59** as a syrup in 69% yield. ^1H NMR (250 MHz $CDCl_3$): δ 0.07 (s, 6H, CH_3), 0.89 (s, 9H, *t*-Bu), 1.91 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.07 (s, 6H, OAc), 2.09 (s, 3H, OAc), 2.99 (t, 1H, $J = 10.8$ Hz, H-4), 3.45 (s, 3H, OCH_3), 3.58–3.68 (m, 3H), 4.72 (d, 1H, $J = 10.2$ Hz), 4.91 (t, 1H, $J = 8.7$ Hz), 5.02 (pt, 2H, $J = 7.8$ Hz), 5.14 (dd, 1H, $J = 9.3, 1.8$ Hz), 5.67 (d, 1H, $J = 9.6$ Hz). ^{13}C NMR (250 MHz, $CDCl_3$): δ -0.24, 0.003, 0.92,

18.32, 20.52, 20.69, 20.87, 22.92, 25.81, 25.88, 45.47, 52.19, 62.23, 62.57, 68.30, 70.56, 72.36, 74.39, 75.64, 76.06, 82.14, 101.14, 169.22, 169.28, 169.49, 170.13, 170.79, 171.43. ESIMS (positive-ion mode): m/z = 760.1 ($M + Na^+$), 776.0 ($M + K^+$), 777.1 ($M + K + H^+$).

Methyl S-(2-acetamido-2-deoxy- β -D-glucopyranosyl)-(1 $\rightarrow$ 4)-4-thio- β -D-glucopyranosiduronic acid (61). To a vigorously stirred solution of **59** (60 mg, 0.08 mmol) in dry DMF (1 mL) at room temperature was added PDC (245 mg, 0.65 mmol). After 2 days Et₂O (10 mL) was added and the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give a pale-yellow solid. Flash chromatography (10:1 CH₃Cl–MeOH) of the residue afforded methyl S-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- β -D-glucopyranosyl)-(1 $\rightarrow$ 4)-2,3-di-O-acetyl-4-thio- β -D-glucopyranosyluronic acid.

To a cold solution (0 °C) of the acid in MeOH (1 mL) was slowly added 0.5 M NaOMe. The solution was gradually warmed to room temperature, and the solution was allowed to stir at this temperature overnight. The reaction was quenched with Dowex-50 (H⁺), and the MeOH was evaporated under reduced pressure. Flash chromatography (CH₃Cl–MeOH) of the crude product afforded **61**. ¹H NMR (300 MHz CDCl₃): δ 1.97 (s, 3H), 2.29 (t, 1H, J = 10.6 Hz), 3.29 (t, 1H, J = 8.0 Hz), 3.35–3.40 (m, 4H), 3.47 (s, 3H), 3.63–3.68 (m, 3H), 3.78 (d, 1H, J = 12.0 Hz), 3.85 (d, 1H, J = 12.0 Hz), 4.30 (d, 1H, J = 8 Hz), 4.56 (d, 1H, J =

10.6 Hz). ^{13}C NMR (250 MHz, CDCl_3): δ 28.7, 54.9, 61.1, 70.0, 73.4, 75.4, 79.5, 80.1, 84.1, 103.9, 107.2, 158.36, 171.14, 174.4. ESIMS (negative-ion mode): $m/z = 426.01$ ($\text{M} - \text{H}^+$).

Methyl 3-4-O-isopropylidene-2-6-di-O-(4-methoxybenzyl)- α -D-

galactopyranoside (64). To a vigorously stirred solution of **63**⁹⁰ (1.0 g, 4.3 mmol) in dry DMF (10 mL) under a nitrogen atmosphere, at 0°C was added portionwise NaH (60% in mineral oil, 0.41g, 10 mmol). After 10 min a catalytic amount of Bu_4NI (0.32 g, 0.87 mmol) was added all at once, followed by dropwise addition of PMBCl (1.74 mL, 13 mmol). After complete conversion of the starting material as indicated by TLC, MeOH was added, the mixture was poured into distilled H_2O , and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried with MgSO_4 and filtered, and the solvent was evaporated under reduced pressure. Column chromatography of the residue using petroleum ether–ethyl acetate as eluent gave compound **64** as a syrup that solidified upon standing. ^1H NMR (250 MHz CDCl_3): δ 1.22 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.28 (s, 3H, OCH_3), 3.40 (dd, 1H, $J = 4.5, 2.4$ Hz), 3.37–3.3.59 (m, 2H), 3.67 (s, 6H, ArOCH_3), 4.02–4.07 (m, 2H), 4.22 (pt, 1H, $J = 7.5$ Hz), 4.33–4.68 (m, 5H, H-1, CH_2ArOMe), 6.75 (d, 4H, $J = 7.2$ Hz, Ar), 7.17 (t, 4H, $J = 8.2$ Hz, Ar). ^{13}C NMR (250 MHz, CDCl_3): δ 26.13, 27.99, 54.96, 55.22, 64.44, 66.23, 69.01, 71.78, 72.82, 73.57, 75.76, 75.85, 98.07, 108.81, 113.51, 113.60, 128.25, 128.95,

129.34, 130.90, 158.97, 159.09. ESIMS (positive-ion mode): m/z = 497.0 ($M + Na^+$), 513.0 ($M + K^+$).

Methyl 2,6-di-O-(4-methoxybenzyl)- α -D-glucopyranoside (65). A mixture of **64** (0.58 g, 1.23 mmol) in 1:1 1 N HCl–THF (20 mL) was maintained at 40 °C until TLC indicated the starting material had disappeared. The mixture was cooled to room temperature and diluted with CH_2Cl_2 and H_2O . The layers were partitioned, and the aqueous layer was extracted repeatedly with CH_2Cl_2 . The combined organic layer was washed successively with H_2O , satd $NaHCO_3$, and brine. The solvent was dried with $MgSO_4$ and filtered, and the solution was evaporated to dryness. The crude product was pure enough for the next reaction (88% yield). A small sample was purified for analysis. Column chromatography from 3:1 petroleum ether–acetone gave **65** as a syrup which solidified on standing. ^1H NMR (250 MHz $CDCl_3$): δ 3.34 (s, 3H, OCH_3), 3.67–3.71 (m, 3H, H-5, H-6a, H-6b), 3.79 (s, 6H, $ArOCH_3$), 3.84–4.01 (m, 2H, H-2, H-3), 4.02 (d, 1H, J = 2.9 Hz, H-4), 4.50 (s, 2H, CH_2ArOMe), 4.61 (d, 2H, J = 1.1 Hz, CH_2ArOMe), 4.66 (d, 1H, J = 3.4 Hz, H-1), 6.85 (d, 4H, J = 8.5 Hz, Ar), 7.26 (t, 4H, J = 8.3 Hz, Ar). ^{13}C NMR (250 MHz, $CDCl_3$): δ 55.21, 68.26, 69.32, 69.60, 69.78, 72.55, 73.28, 76.26, 98.01, 113.81, 113.93, 129.28, 129.65, 129.86, 130.13, 159.27, 159.47.

**Methyl S-(2-acetamido-3,4,6-tri-O-acetyl- 2-deoxy- β -D-glucopyranosyl)-
(1 $\rightarrow$ 4)-3-acetyl-2,6-di-O-(4-methoxybenzyl)-4-thio- α -D-glucopyranoside (68).**

A solution of SOCl_2 (0.12 mL, 1.6 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise over 10 min to a vigorously stirred solution of **65** (0.47 g, 1.08 mmol) in dry CH_2Cl_2 (5 mL) and anhydr Et_3N (0.60 mL) at 0 °C. After stirring for 10 min at 0 °C, the mixture was diluted with cold Et_2O (10 mL) and washed with H_2O (2 x 10 mL) and brine (20 mL). The organic layer was dried (MgSO_4) and filtered, and the solvent was evaporated. The crude product was evaporated with PhCH_3 (3 x 20 mL) and placed on a vacuum pump overnight. The residue was dissolved in 1:1 CCl_4 – CH_3CN (10 mL), and distilled H_2O (5 mL) was added, followed by NaIO_4 (0.35 g, 1.6 mmol), and a catalytic amount of $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ (6 mg, 0.03 mmol). The mixture was stirred at room temperature until all of the starting sulfite was consumed as indicated by TLC. The reaction mixture was diluted with Et_2O , and the layers were separated. The aqueous layer was extracted with Et_2O , and the organic layers were combined, dried with MgSO_4 and filtered. The filtrate was concentrated and the sulfate subjected to column chromatography with 3:1 petroleum ether–acetone as eluent to provide unstable **66** (76% yield) as a syrup.

A mixture of cyclic sulfate **66** (385 mg, 0.77 mmol), thiol **53** (338 mg, 0.93 mmol) and Cs_2CO_3 (303 mg, 0.93 mmol) in dry DMF (5 mL) were stirred at room temperature until complete consumption of the sulfate was observed by TLC.

The solvent was evaporated, and the residue was dissolved in THF and treated with a catalytic amount of concentrated H_2SO_4 (0.5 mol equiv.) and H_2O (1 mol equiv). After the hydrolysis was complete, as indicated by TLC, the residual acid was neutralized with powdered NaHCO_3 . The mixture was filtered through Celite on silica gel, and the filtrate evaporated to dryness to provide a colored solid. The residue was dissolved in excess acetic anhydride and pyridine and stirred for 3 h. The reaction mixture was poured into ice-water and extracted with EtOAc. The organic layer was dried, and filtered and the solvent was evaporated. Flash chromatography (EtOAc) of the solid gave the thiodisaccharide **68** in 69% yield. ^1H NMR (250 MHz CDCl_3): δ 1.91 (s, 3H), 1.99 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.99 (t, 1H, $J = 10.6$ Hz), 3.38 (s, 3H, OCH_3), 3.52–3.67 (m, 3H), 3.80 (s, 6H, ArOCH_3), 3.99–4.20 (m, 6H), 4.46–4.61 (m, 4H), 4.67 (d, 1H, $J = 3.4$ Hz), 4.77 (d, 1H, $J = 10.6$ Hz), 5.00 (m, 2H), 5.4 (t, 1H, $J = 10.6$ Hz), 5.86 (d, 1H, $J = 9.7$ Hz), 6.86 (d, 4H, $J = 8.5$ Hz), 7.20–7.28 (m, 4H). ^{13}C NMR (250 MHz, CDCl_3): δ 20.66, 21.24, 23.04, 45.68, 51.94, 55.33, 55.50, 62.68, 68.45, 68.62, 69.43, 69.82, 72.77, 73.49, 74.77, 75.61, 81.96, 98.21, 113.80, 113.95, 129.50, 129.56, 129.95, 130.13, 160.01, 160.10, 169.78, 169.83, 170.38, 170.68, 171.81. ESIMS (positive-ion mode): $m/z = 844.3$ ($\text{M} + \text{Na}^+$),

Methyl (methyl 3-4-O-isopropylidene- α -D-galactopyranosid)uronate (71). To a vigorously stirred solution of alcohol **63** (0.50 g, 2.13 mmol), KBr (0.13 g, 1.07

mmol), Bu_4NCl (0.34 g, 1.07 mmol), and 2,2,6,6-tetramethyl-1-piperidinyloxiide (TEMPO, 30 mg, 0.21 mmol) in CH_2Cl_2 (8 mL) was added dropwise a solution of NaOCl (6.6 mL) and a solution of NaHCO_3 (9.0 mL) to maintain a pH between 10 and 11. After the reaction was complete (TLC monitoring) CH_2Cl_2 was added, and the layers were partitioned. The organic layer was washed with H_2O and brine, dried with MgSO_4 , and filtered. The filtrate was evaporated to give a pale-yellow glass in 56% yield. Part of the crude material (184 mg, 0.74 mmol) was dissolved in dry DMF (3 mL) and cooled to 15°C . CsF (169 mg, 1.11 mmol) was added, followed by dropwise addition of MeI (0.07 mL, 1.11 mmol). The mixture was stirred for 24 h at 15°C and CH_2Cl_2 (10 mL) was added. The mixture was filtered through Celite, and the filtrate was concentrated to dryness. Column chromatography of the residue provided the ester in 80% yield. ^1H NMR (250 MHz CDCl_3): δ 1.27 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.73 (s, 1H, OH), 3.43 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.87 (bs, 1H, H-2), 4.28 (t, 1H, $J = 6.0$ Hz, H-3), 4.46 (dd, 1H, $J = 8.7, 2.5$ Hz, H-4), 4.57 (d, 1H, $J = 2.4$ Hz, H-5), 4.81, (d, 1H, $J = 3.8$ Hz, H-1). ^{13}C NMR (250 MHz, CDCl_3): δ 25.52, 25.59, 27.06, 52.25, 55.90, 67.96, 68.45, 73.39, 75.09, 98.17, 110.05, 168.55. ESIMS (positive-ion mode): $m/z = 284.9$ ($\text{M} + \text{Na}^+$), 300.9 ($\text{M} + \text{K}^+$).

Methyl (methyl 2-O-benzoyl-3-4-O-isopropylidene- α -D-

galactopyranosid)uronate (72). To a solution of ester **71** (403 mg, 1.62 mmol)

in dry pyridine (5 mL) at 0 °C was added dropwise BzCl (0.75 mL, 6.48 mmol).

The reaction was allowed to stir overnight and satd NaCO₃ was added. The

mixture was extracted with EtOAc (3 x 25 mL), dried and filtered. Column

chromatography of the syrup using 1:1 petroleum ether–EtOAc provided

compound **72** in quantitative yield. ¹H NMR (250 MHz CDCl₃): δ 1.37 (s, 3H,

CH₃), 1.55 (s, 3H, CH₃), 3.43 (s, 3H, CH₃), 3.88 (s, 3H, CH₃), 4.54–4.63 (m, 2H,

H-3, H-4) 4.69 (d, 1H, J = 2.5Hz, H-5), 5.13 (d, 1H, J = 3.6Hz, H-1), 5.23 (d, 1H,

J = 7.4, 3.5Hz, H-2), 7.41–7.47 (m, 2H, Ar), 7.55–7.58 (m, 1H, Ar), 8.07 (d, 2H, J

= 7.3Hz, Ar). ¹³C NMR (250 MHz, CDCl₃): δ 26.36, 27.79, 52.58, 56.31, 67.39,

71.48, 73.36, 73.79, 97.78, 128.34, 129.49, 129.92, 133.28, 165.89, 168.27.

ESIMS (positive-ion mode): m/z = 388.9 (M + Na⁺), 405.0 (M + K⁺), 755.0 (2M + Na⁺).

Methyl (methyl 2-O-benzoyl- α -D-galactopyranosid)uronate (73). A solution of

72 (0.40 g, 1.09 mmol) in 1:1 1 N HCl–THF (25 mL) was maintained at 40 °C

until TLC indicated the starting material had disappeared. The mixture was

cooled to room temperature and diluted with CH₂Cl₂ (20 mL) and H₂O (20 mL).

The layers were partitioned, and the aqueous layer was extracted repeatedly

with CH₂Cl₂ (3 x 25 mL). The combined organic layer was washed successively

with H₂O, satd NaHCO₃, and brine. The solvent was dried with MgSO₄ and filtered, and the solution was evaporated to dryness. The crude product was chromatographed using EtOAc to provide **73** (300 mg, 84%). ¹H NMR (250 MHz CDCl₃): δ 3.35 (s, 3H, CH₃), 3.76 (s, 3H, CH₃), 4.15 (dd, 1H, *J* = 10.2, 3.31Hz, H-3), 4.34 (s, 1H, H-4), 4.43 (s, 1H, H-5), 5.07 (d, 1H, *J* = 3.6Hz, H-1), 5.22 (dd, 1H, *J* = 10.2, 3.6Hz, H-2). ¹³C NMR (250 MHz, CDCl₃): δ 52.64, 56.13, 67.87, 69.67, 70.45, 71.45, 97.92, 128.35, 129.37, 129.69, 133.34, 166.82, 169.22. ESIMS (positive-ion mode): *m/z* = 349.1 (M + Na⁺), 365.1 (M + K⁺).

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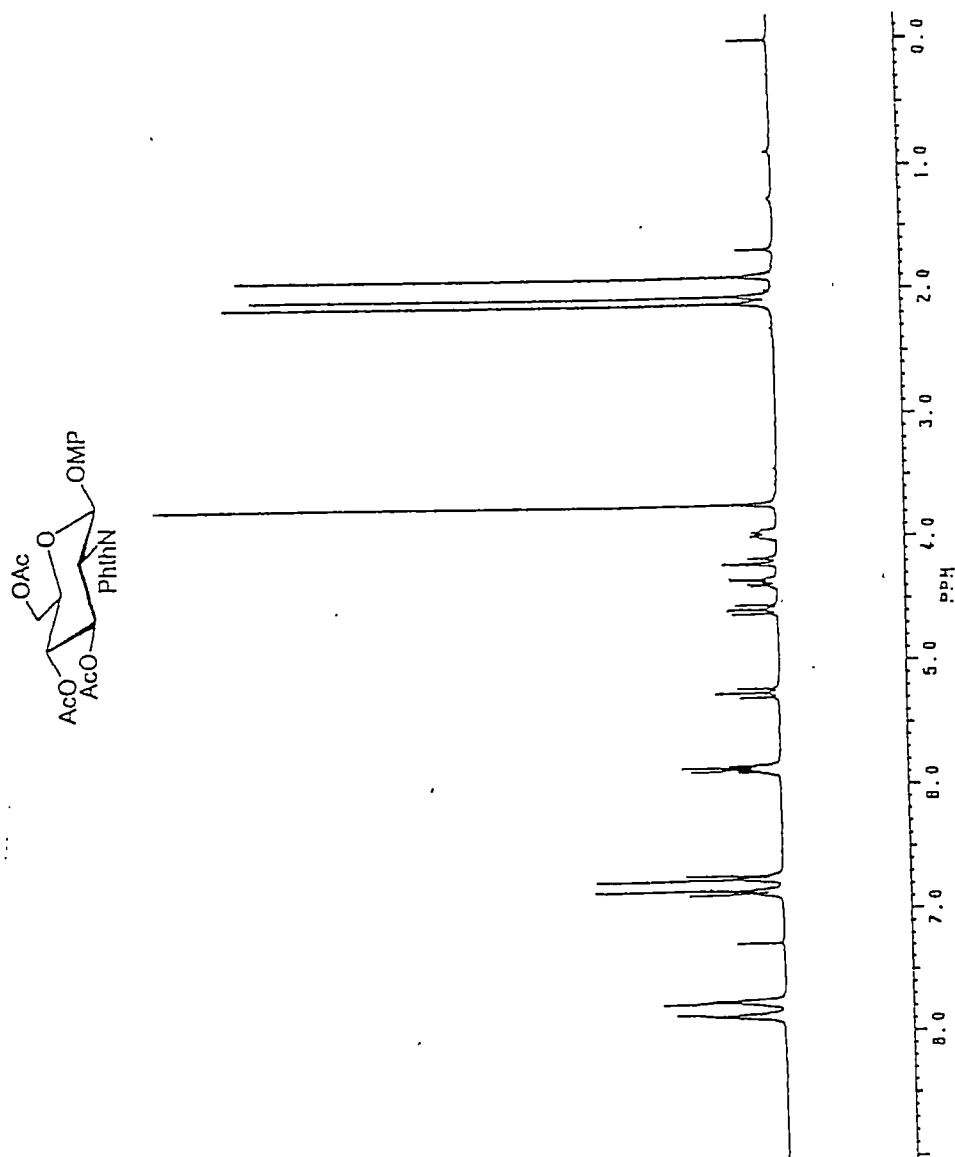
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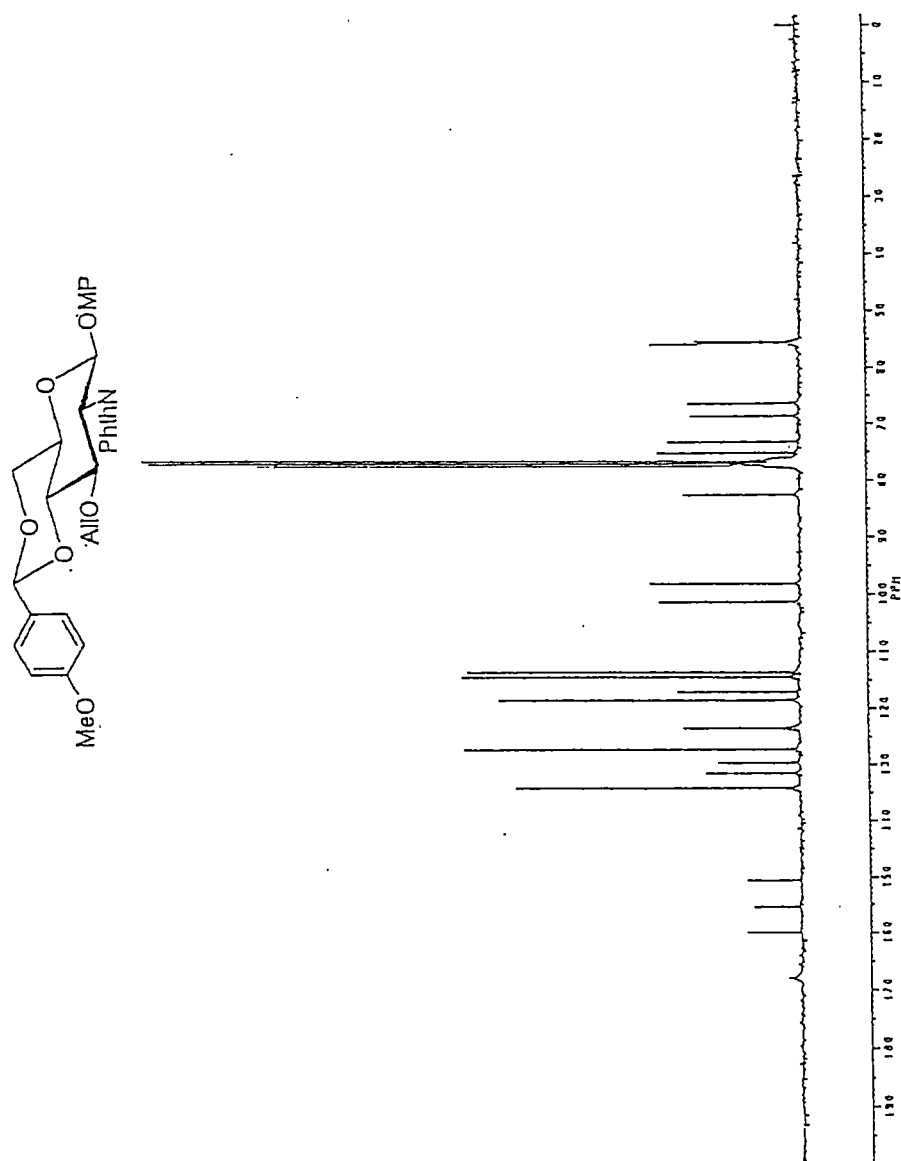
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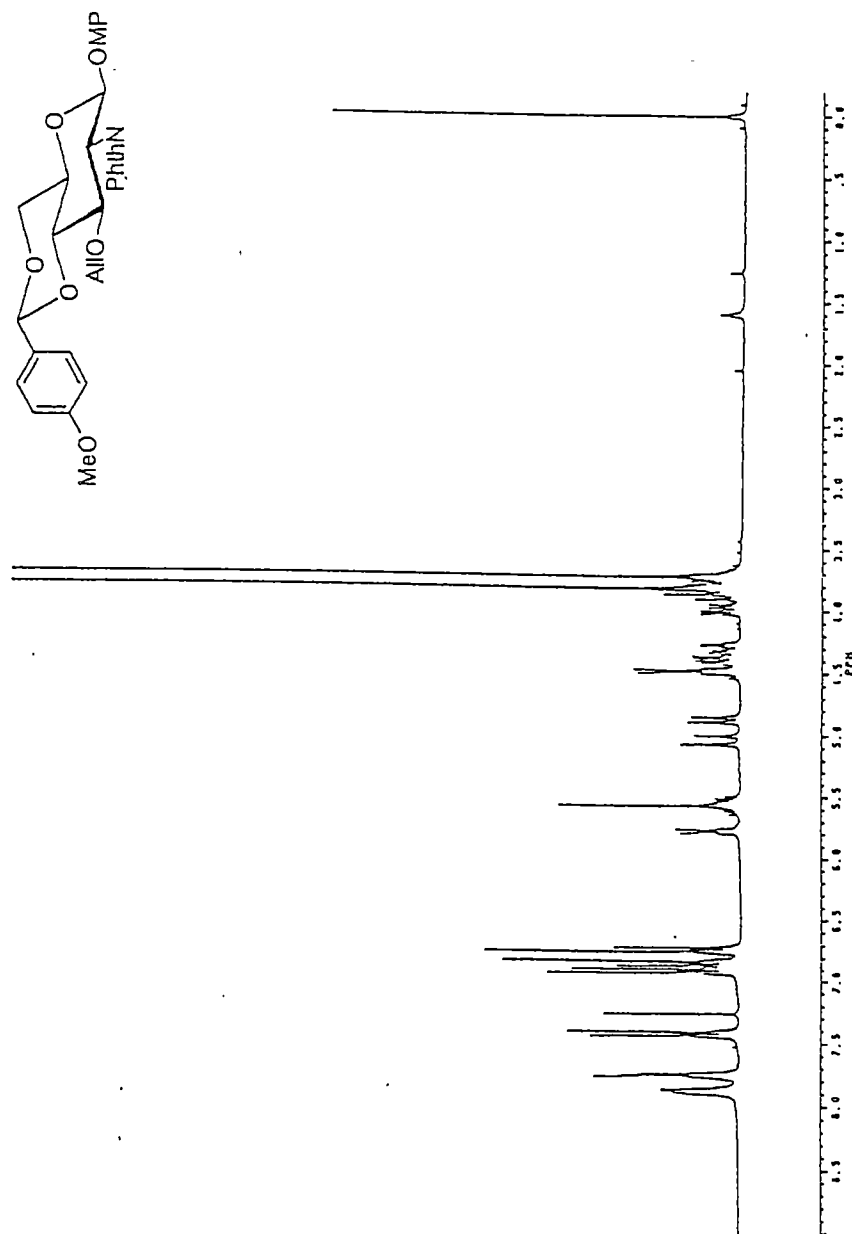
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APPENDIX

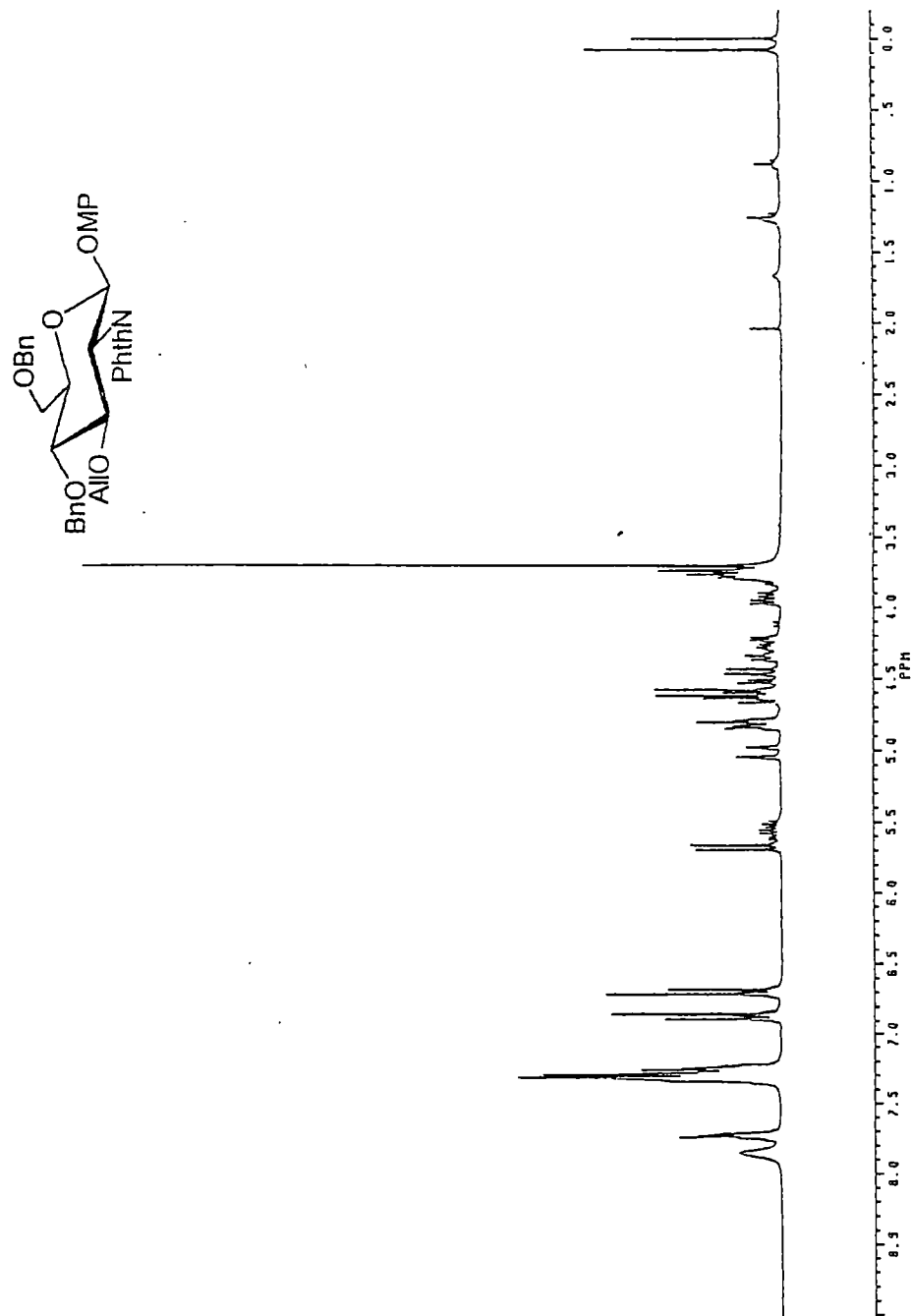




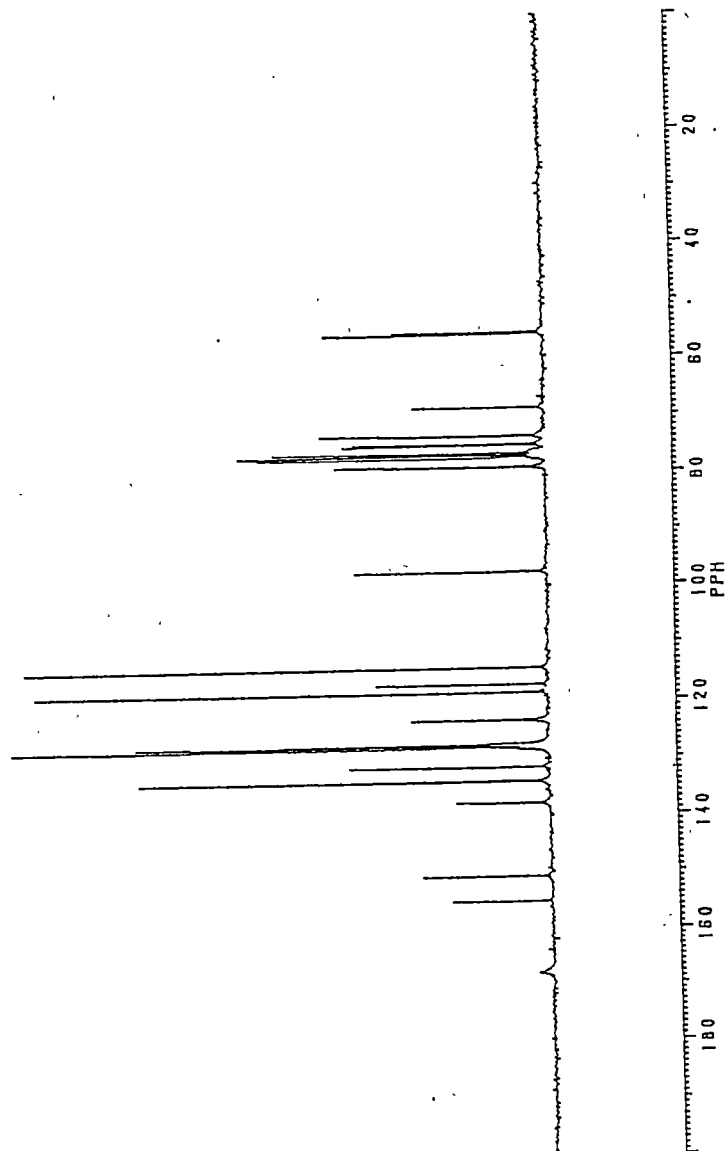
¹³C NMR (250 MHz, CDCl₃) spectrum for *p*-methoxyphenyl 3-*O*-allyl-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-2-phthalimido-β-D-glucopyranoside 5a.



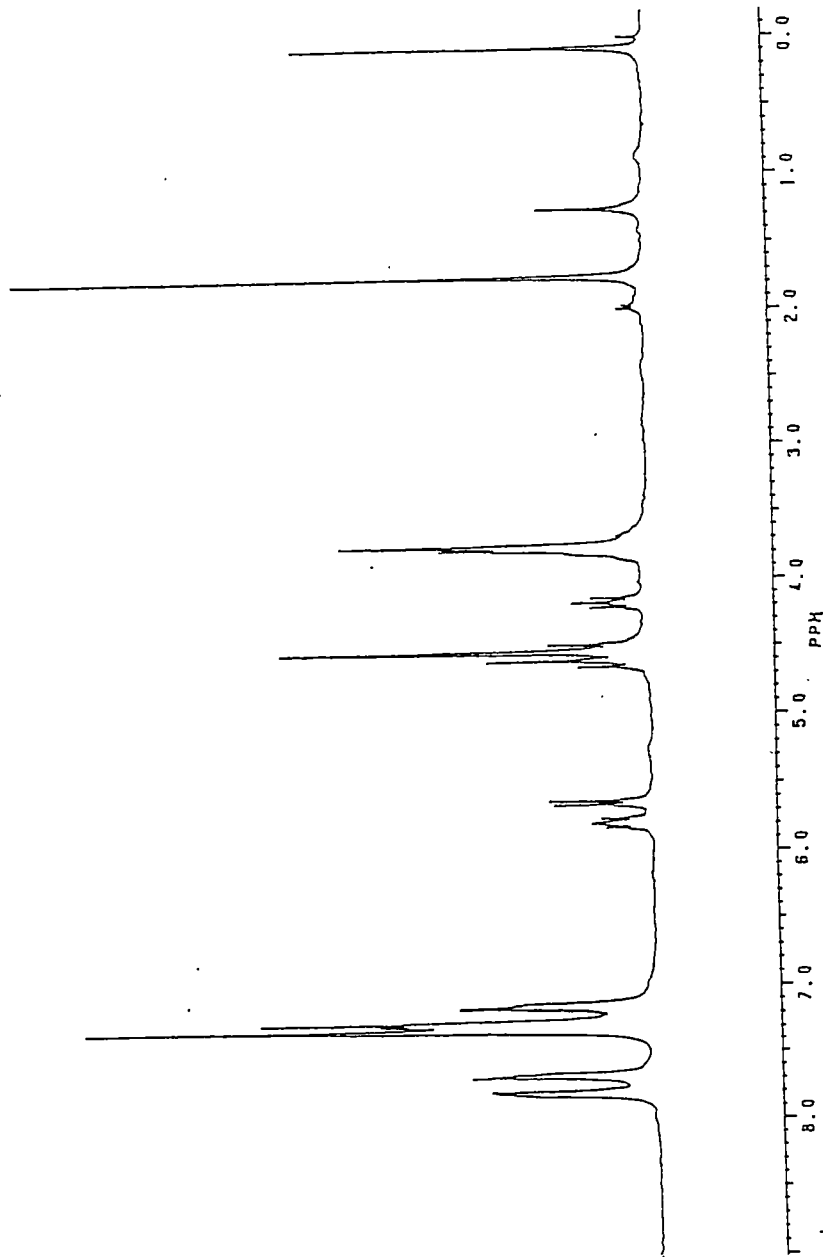
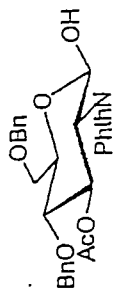
¹H NMR (250 MHz, CDCl₃) spectrum for *p*-methoxyphenyl 3-O-allyl-2-deoxy-4,6-O-(4-methoxybenzylidene)-2-phthalimido-β-D-glucopyranoside **5a**.



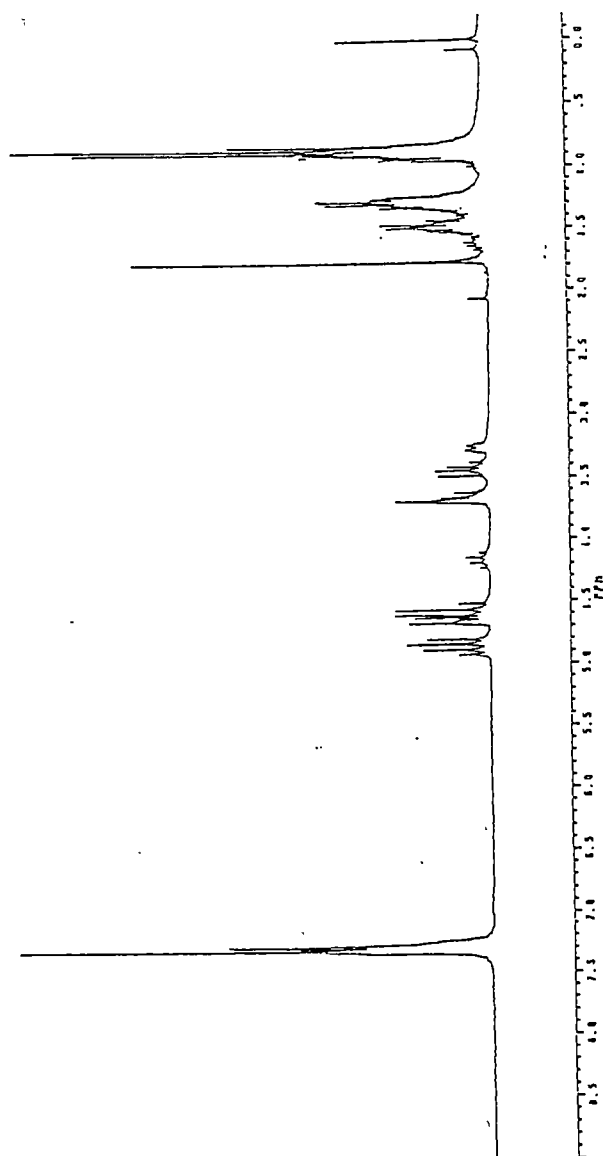
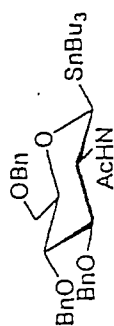
¹H NMR (250 MHz, CDCl₃) spectrum for *p*-methoxyphenyl 3-O-allyl-4,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside **6**.



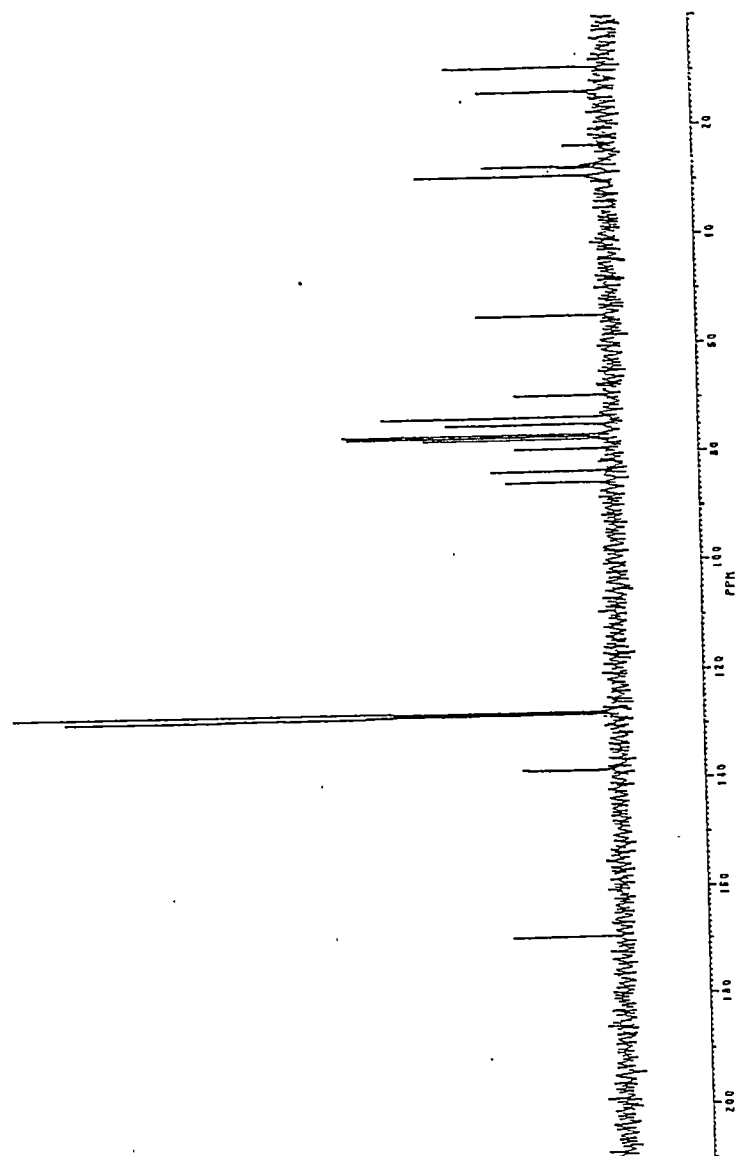
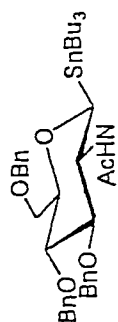
^{13}C NMR (250 MHz, CDCl_3) spectrum for *p*-methoxyphenyl 3-O-allyl-4,6-di-O-benzyl-2-deoxy-2-phthalimido- β -D-glucopyranoside 6.



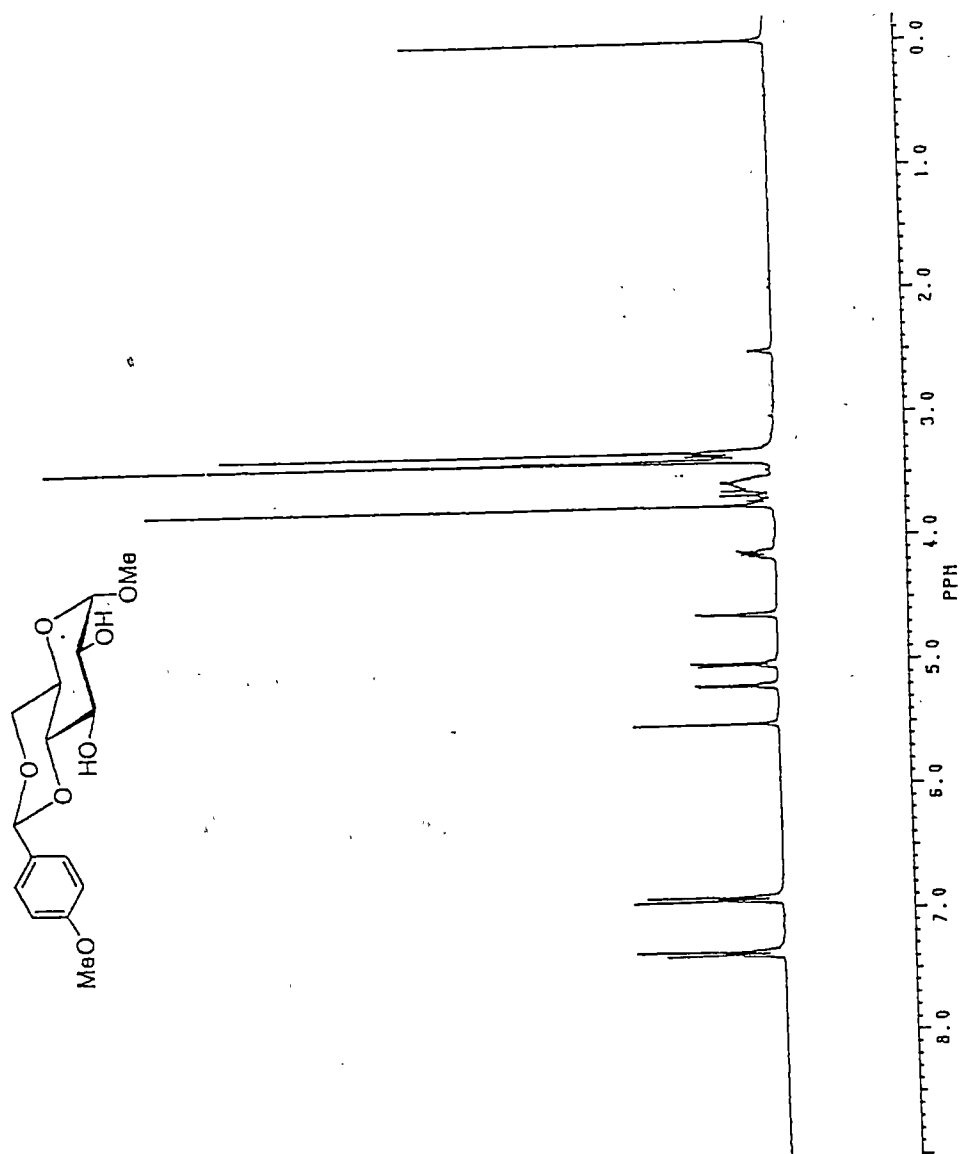
^1H NMR (250 MHz, CDCl_3) spectrum for 3-O-acetyl-4,6-di-O-benzyl-2-phthalimido- β -D-glucopyranose 8.

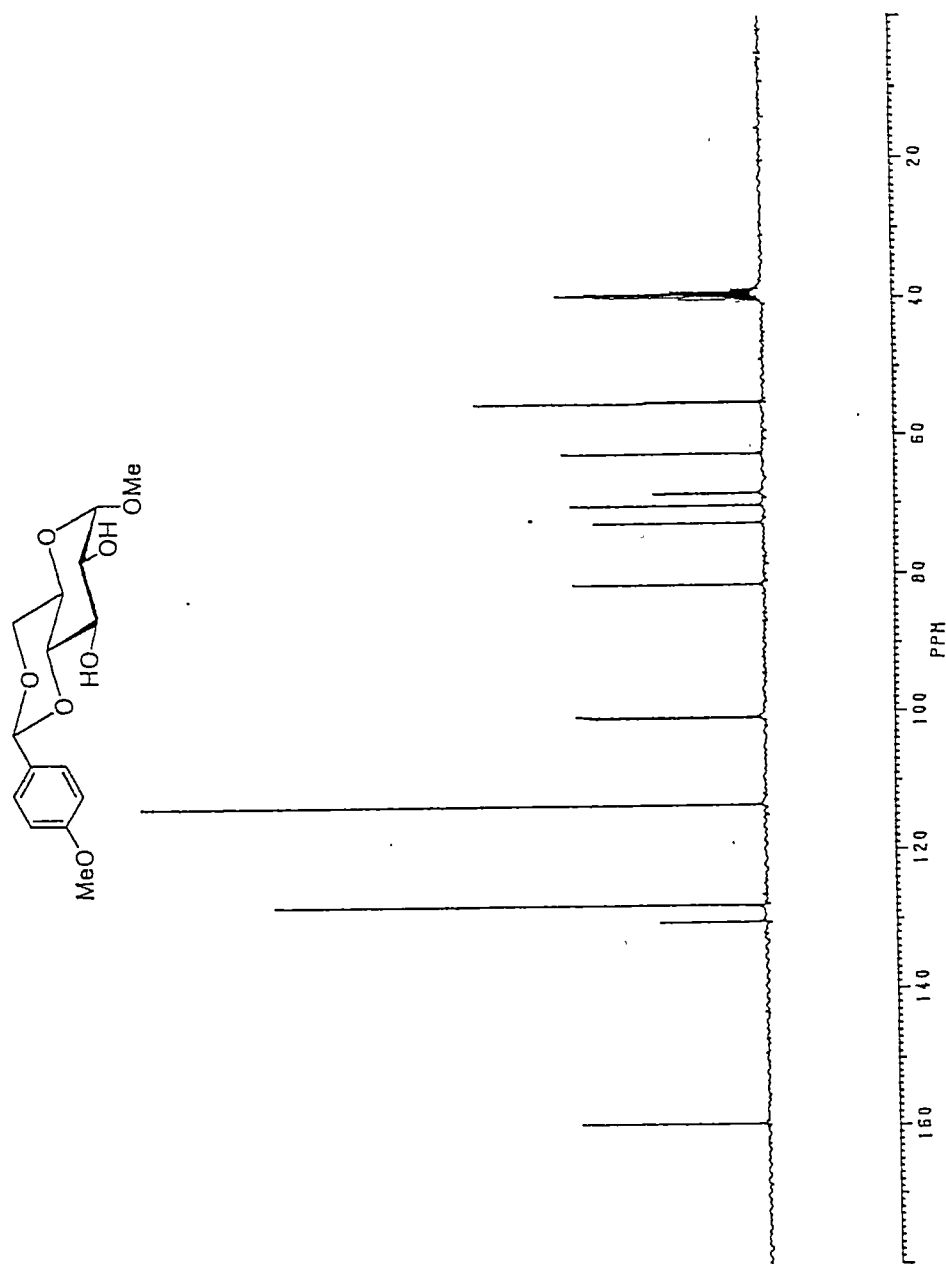


^1H NMR (250 MHz, CDCl_3) spectrum of 2-acetamido-3,4,6-tri-O-benzyl- β -D-glucopyranosyl tributyl stannane 37.

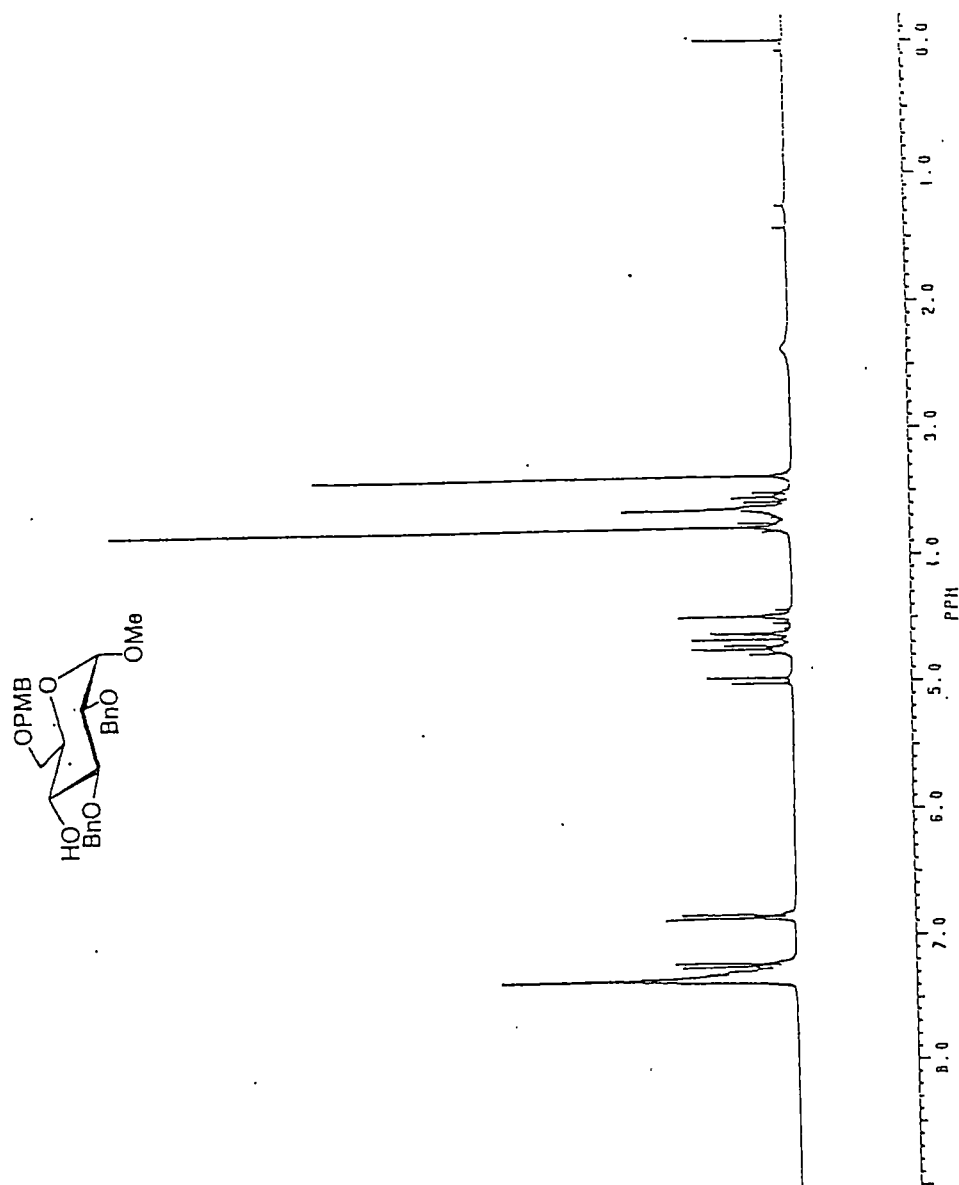


^{13}C NMR (250 MHz, CDCl_3) 2-acetamido-3,4,6-tri-O-benzyl- β -D-glucopyranosyl tributyl stannane **37**.

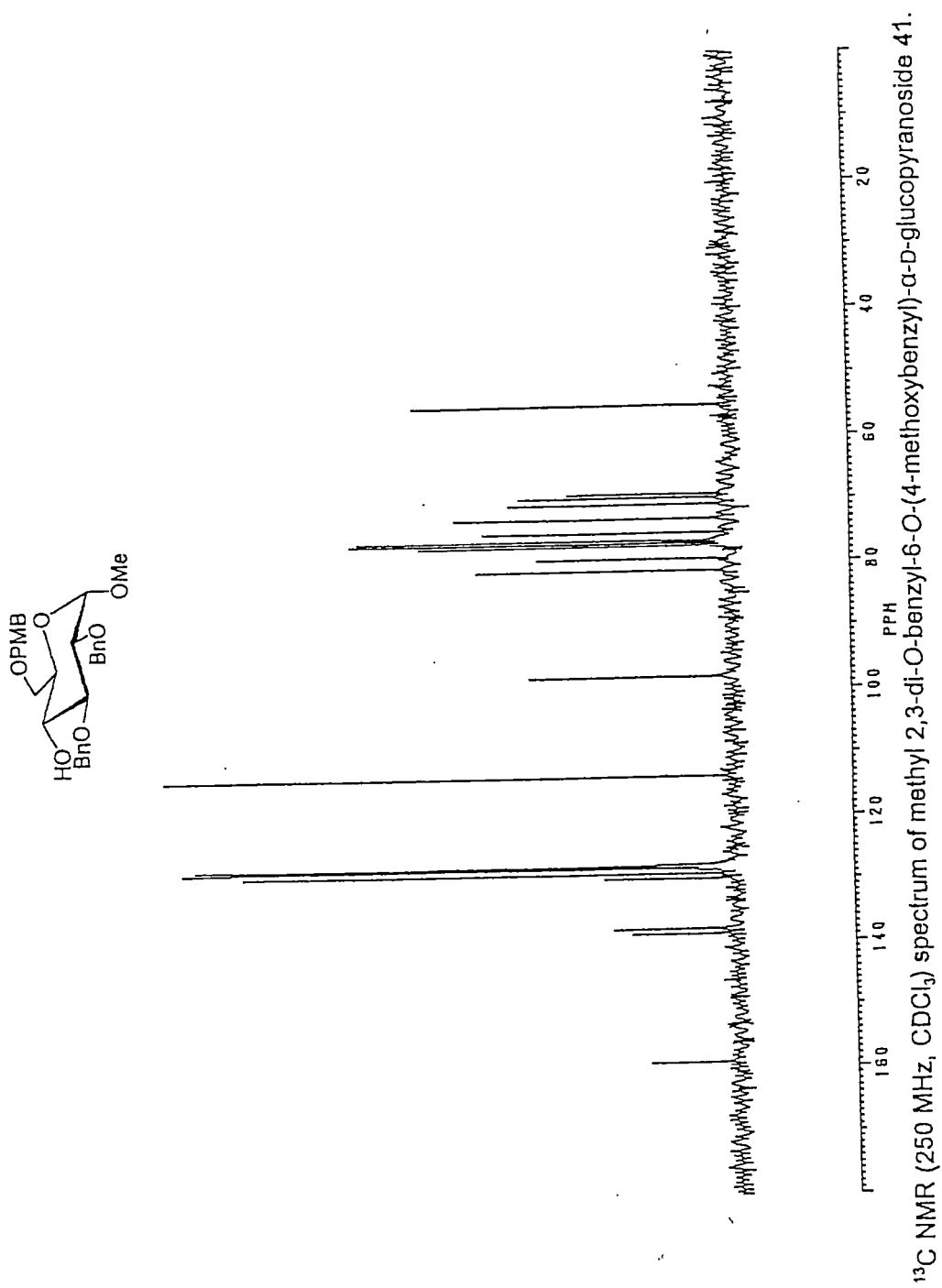


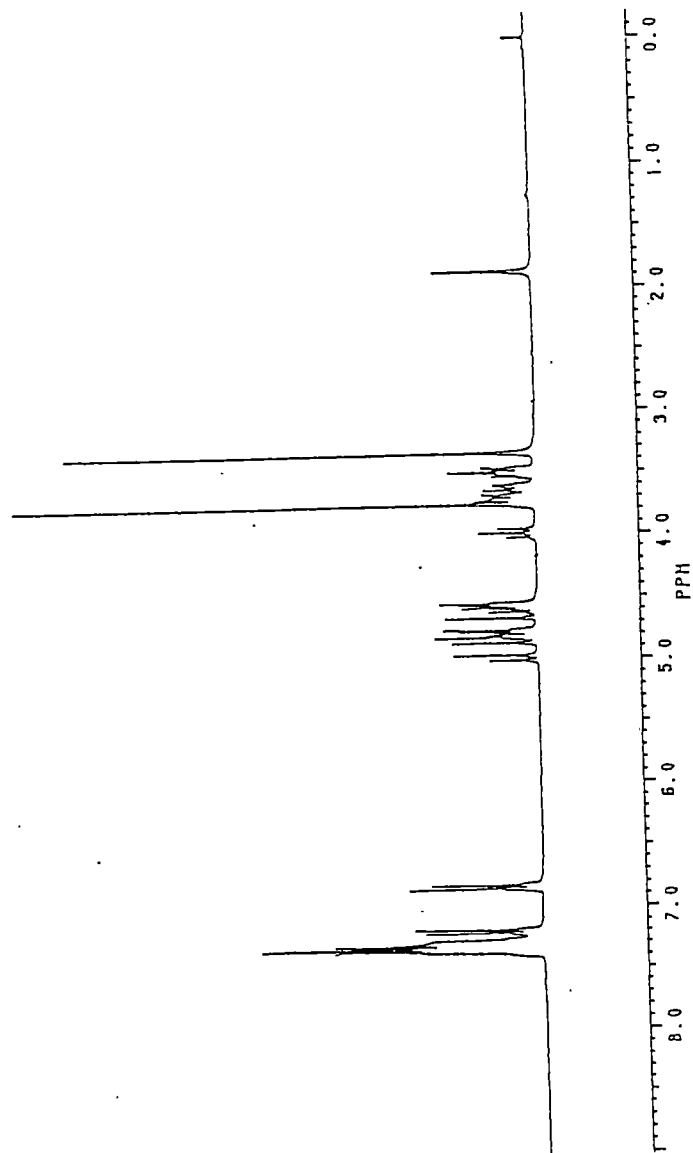
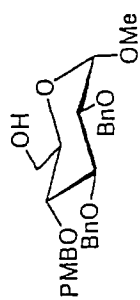


^{13}C NMR (250 MHz, CDCl_3) spectrum of methyl 4,6-O-(4-methoxybenzylidene)- α -D-glucopyranoside 39.

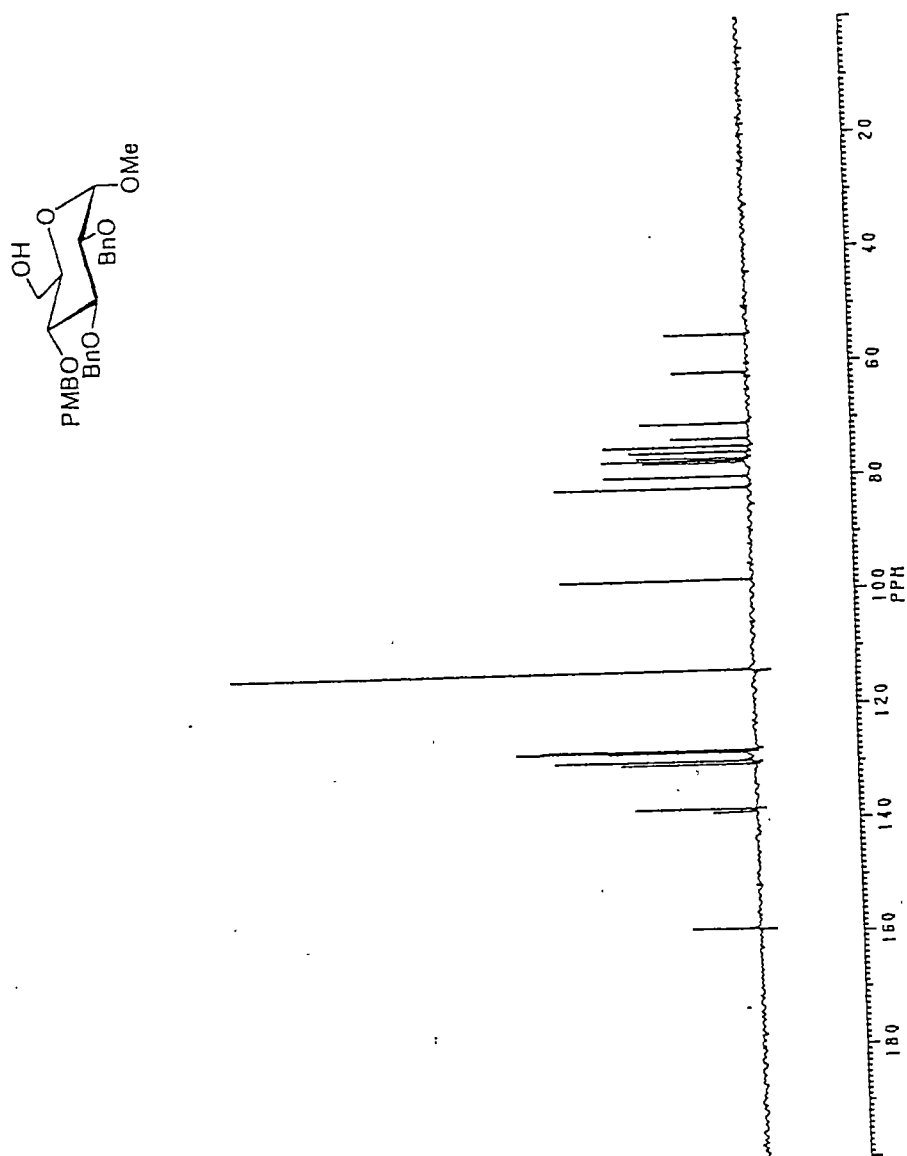


^1H NMR (250 MHz, CDCl_3) spectrum of methyl 2,3-di-O-benzyl-6-O-(4-methoxybenzyl)- α -D-glucopyranoside 41

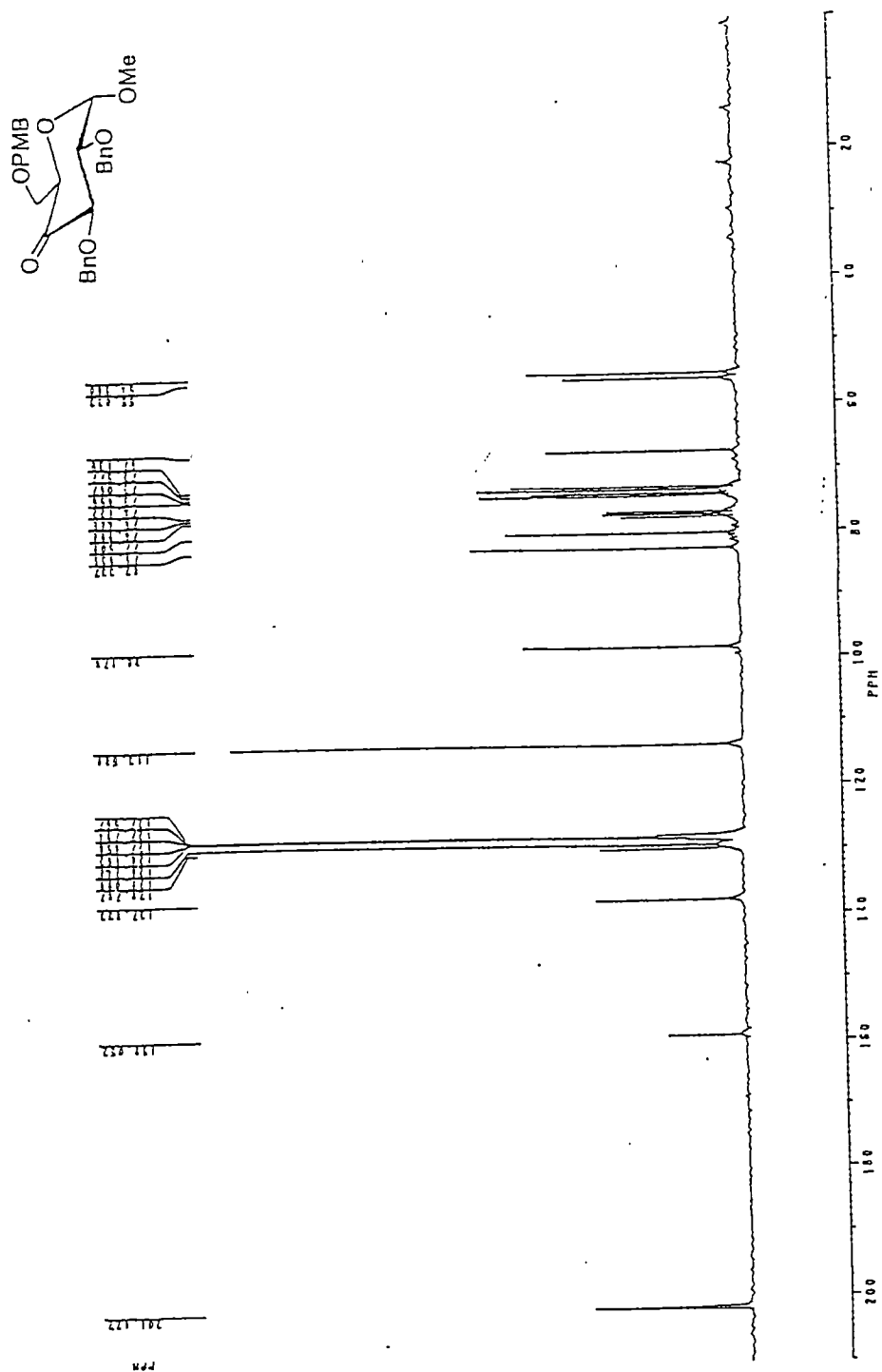




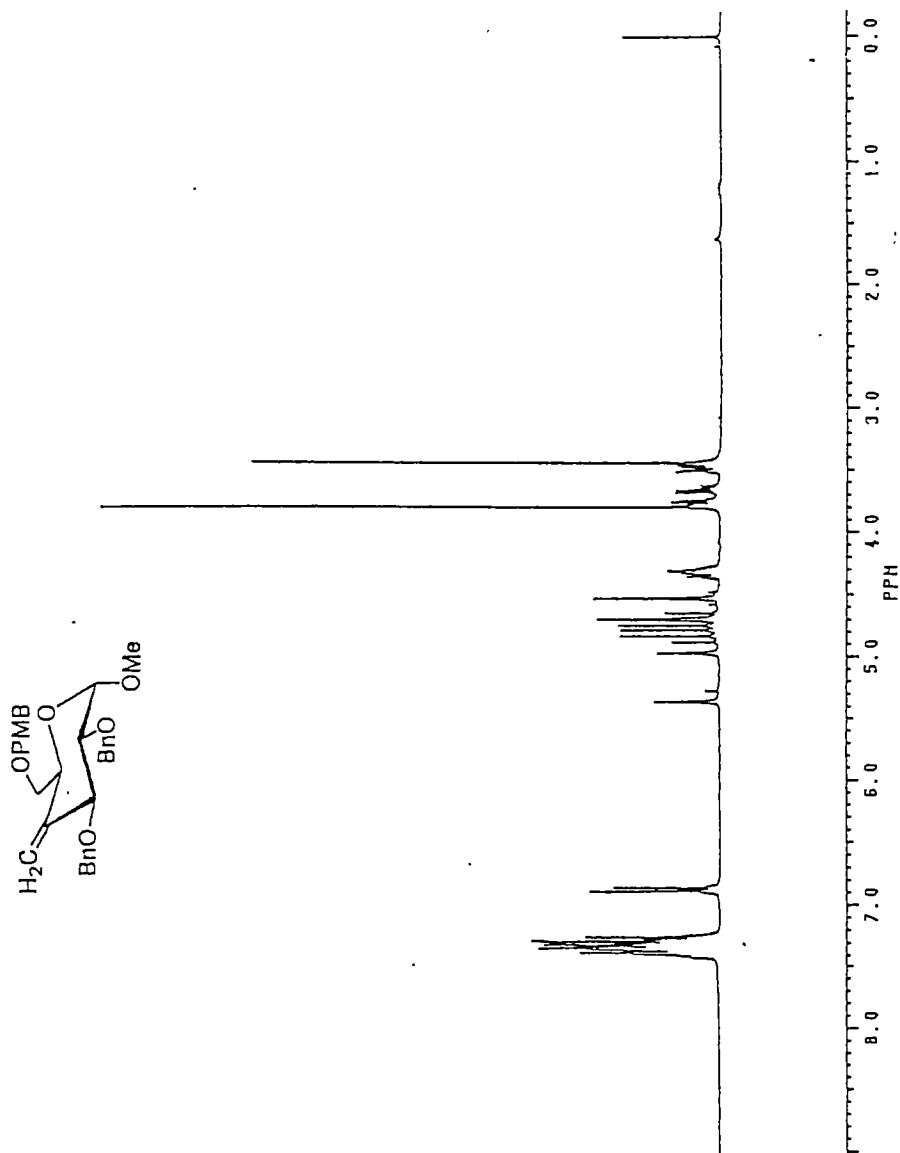
¹H NMR (250 MHz, CDCl₃) spectrum of methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-α-D-glucopyranoside 41b.



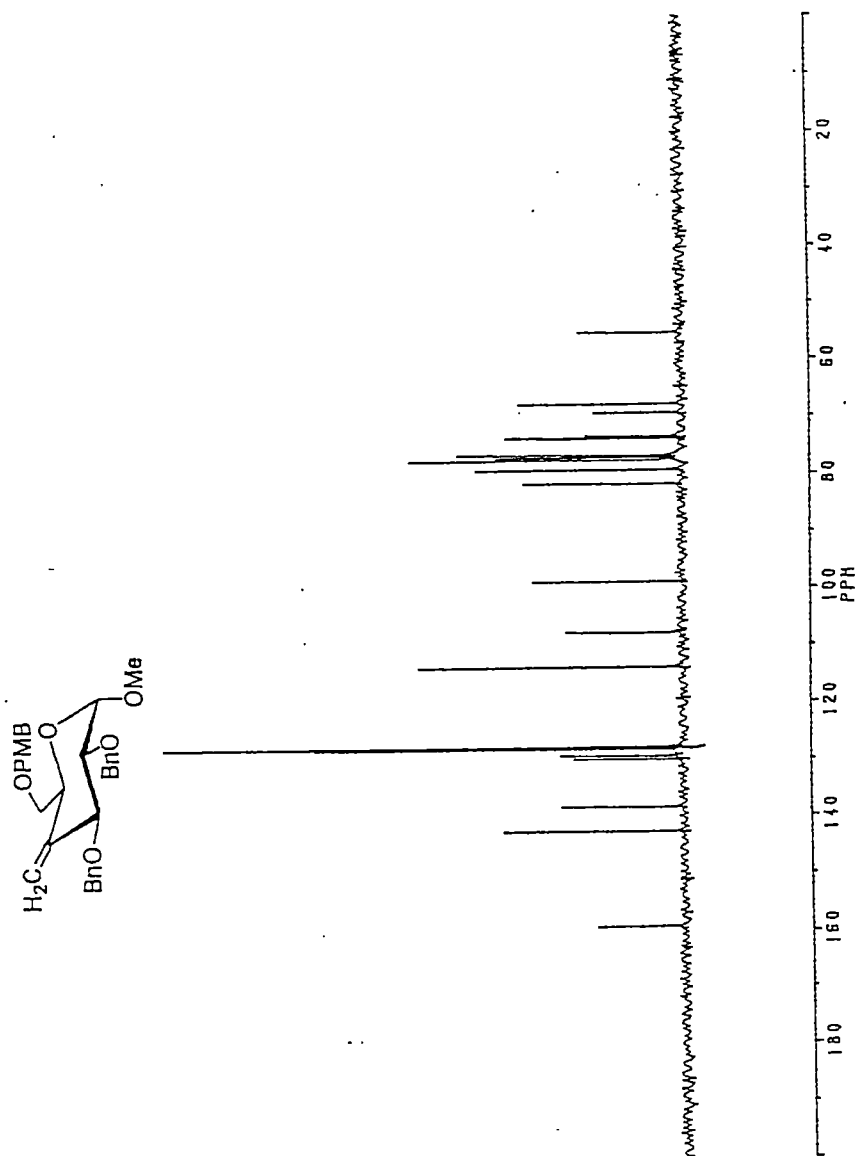
¹³C NMR (250 MHz, CDCl₃) spectrum of methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-α-D-glucopyranoside 41b.



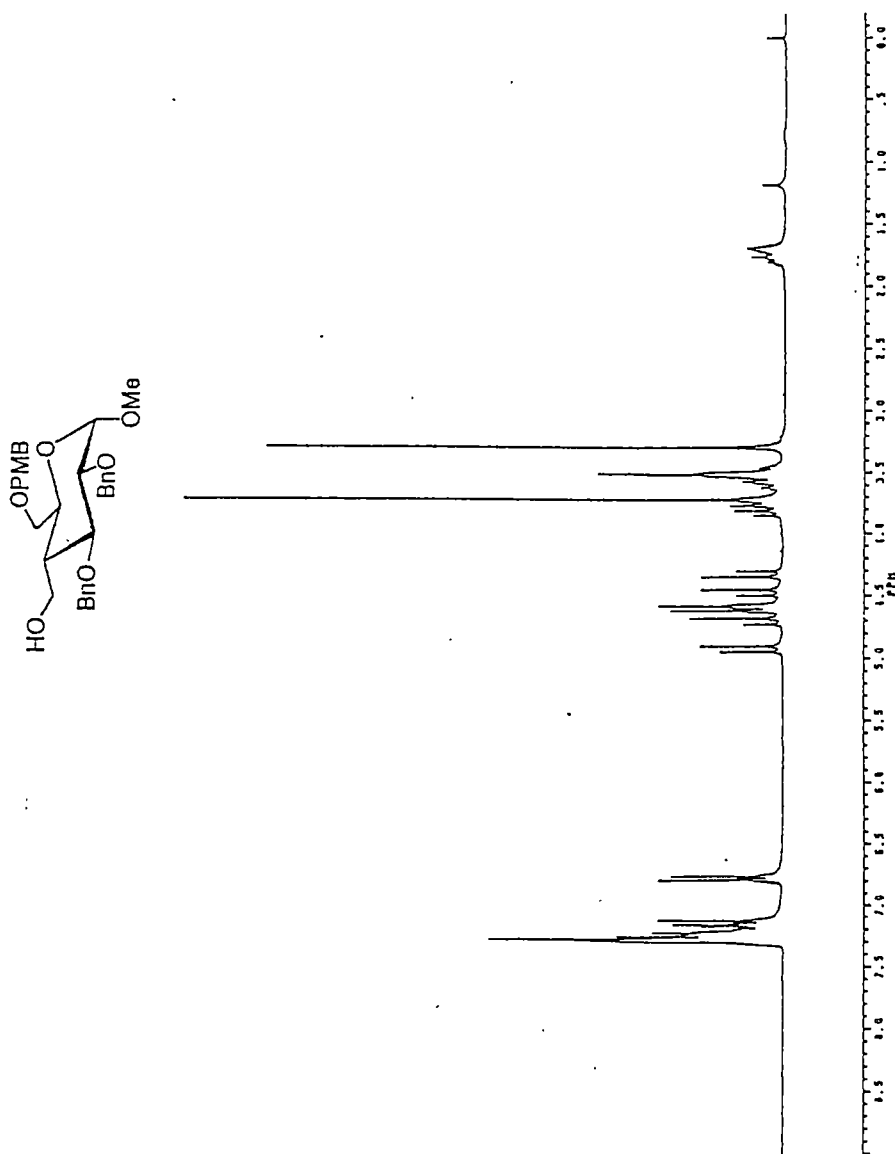
^{13}C NMR (250 MHz, CDCl_3) spectrum of methyl 2,3-di-O-benzyl-6-O-(4-methoxybenzyl)- α -D-xylo-4-hexulopyranoside 42.



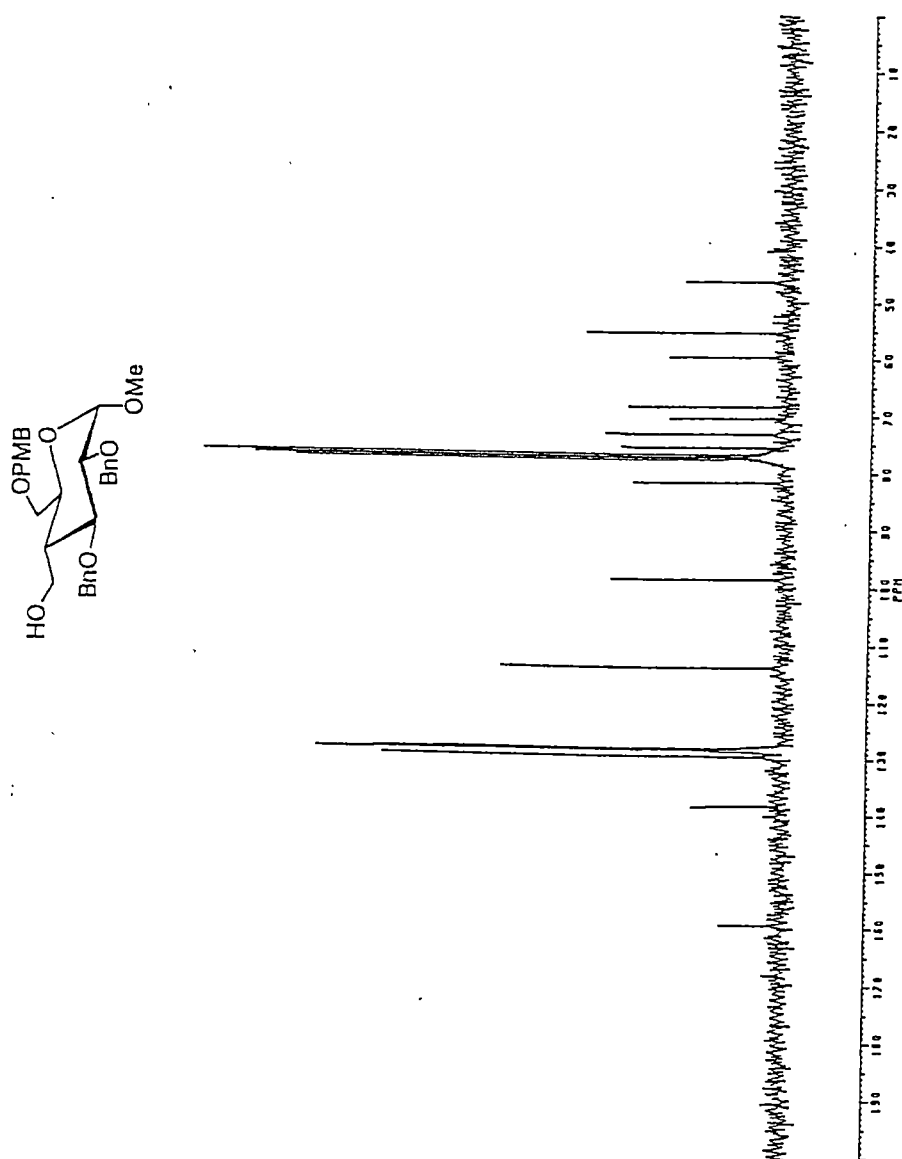
^1H NMR (250 MHz, CDCl_3) spectrum of methyl 2,3-di-O-benzyl-4-deoxy-4-C-(methylene)-6-O-(4-methoxybenzyl)- α -D-xylohexopyranoside 43.



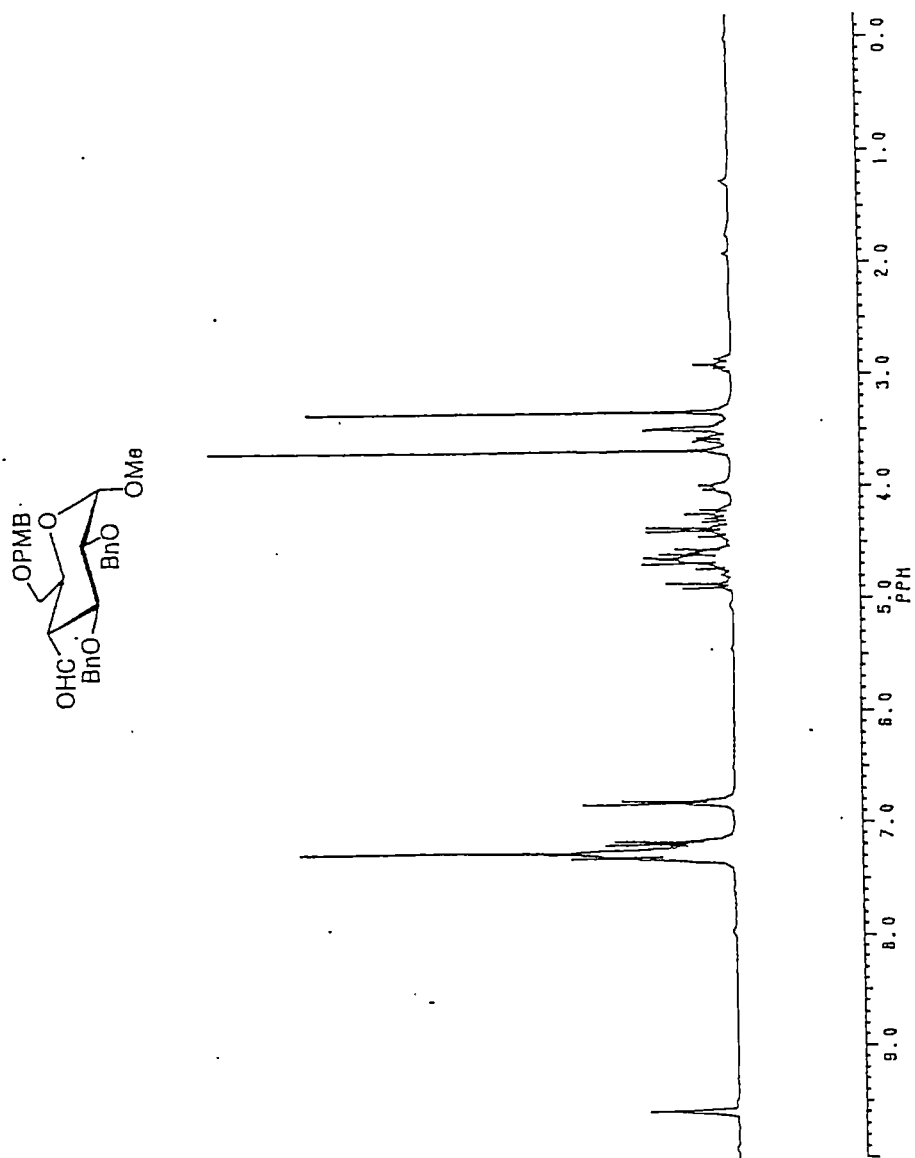
^{13}C NMR (250 MHz, CDCl_3) spectrum for methyl 2,3-di-O-benzyl-4-deoxy-4-C-(methylene)-6-O-(4-methoxybenzyl)- α -D-xylo-hexopyranoside 43.



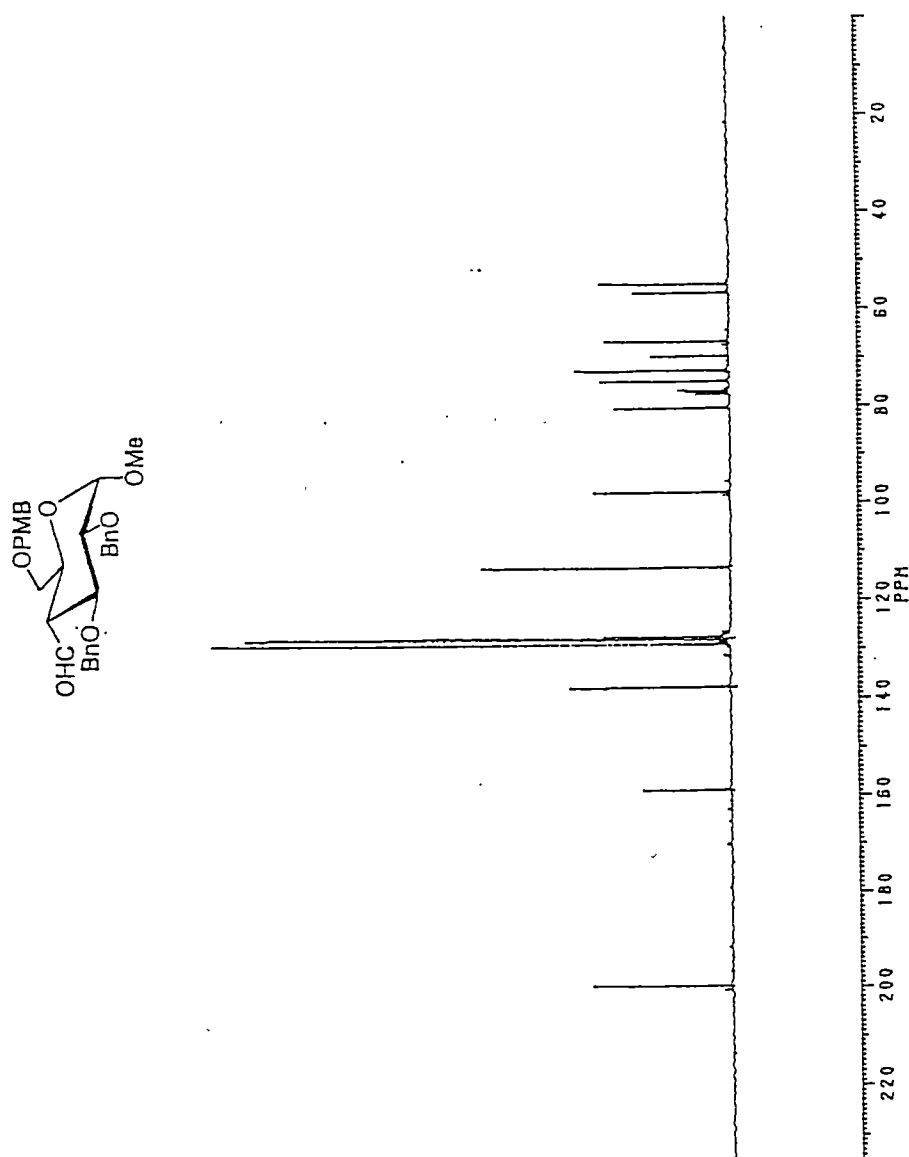
¹H NMR (250 MHz, CDCl₃) spectrum for methyl 2,3-di-O-benzyl-4-deoxy-4-C-(hydroxymethyl)-6-O-(4-methoxybenzyl)-α-D-glucopyranoside 45.



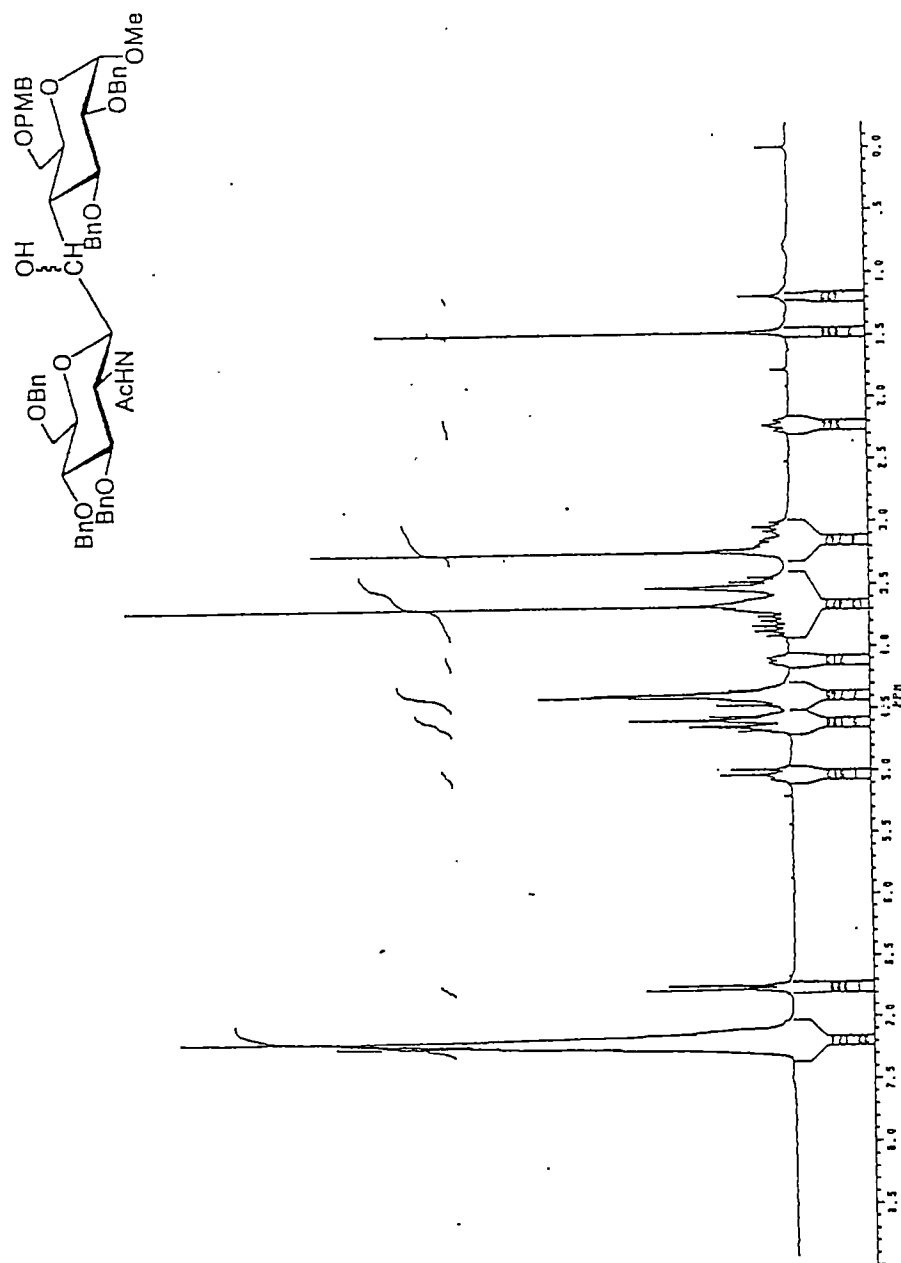
¹³C NMR (250 MHz, CDCl₃) spectrum for methyl 2,3-di-O-benzyl-4-deoxy-4-C-(hydroxymethyl)-6-O-(4-methoxybenzyl)-α-D-glucopyranoside 45.



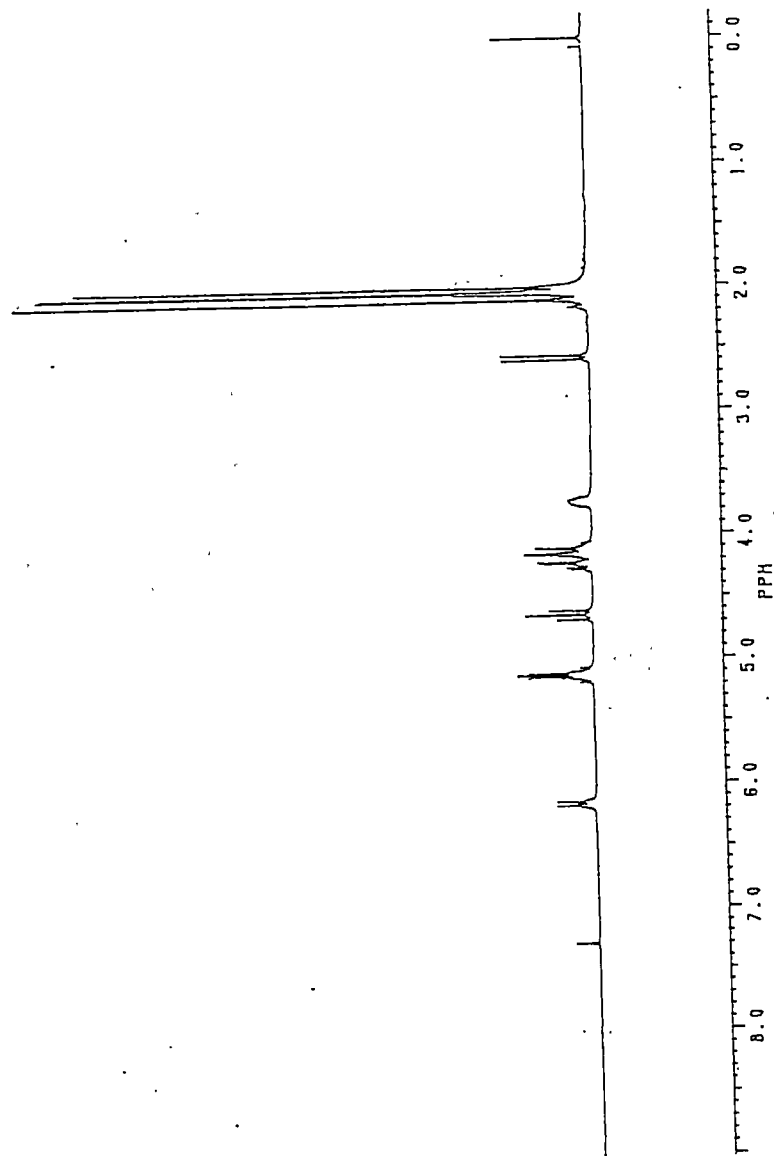
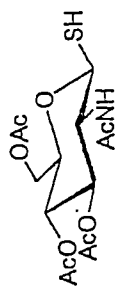
^1H NMR (250 MHz, CDCl_3) spectrum of methyl 2,3-di-O-benzyl-4-deoxy-4-C-(formyl)-6-O-(4-methoxybenzyl)-α-D-glucopyranoside 47.



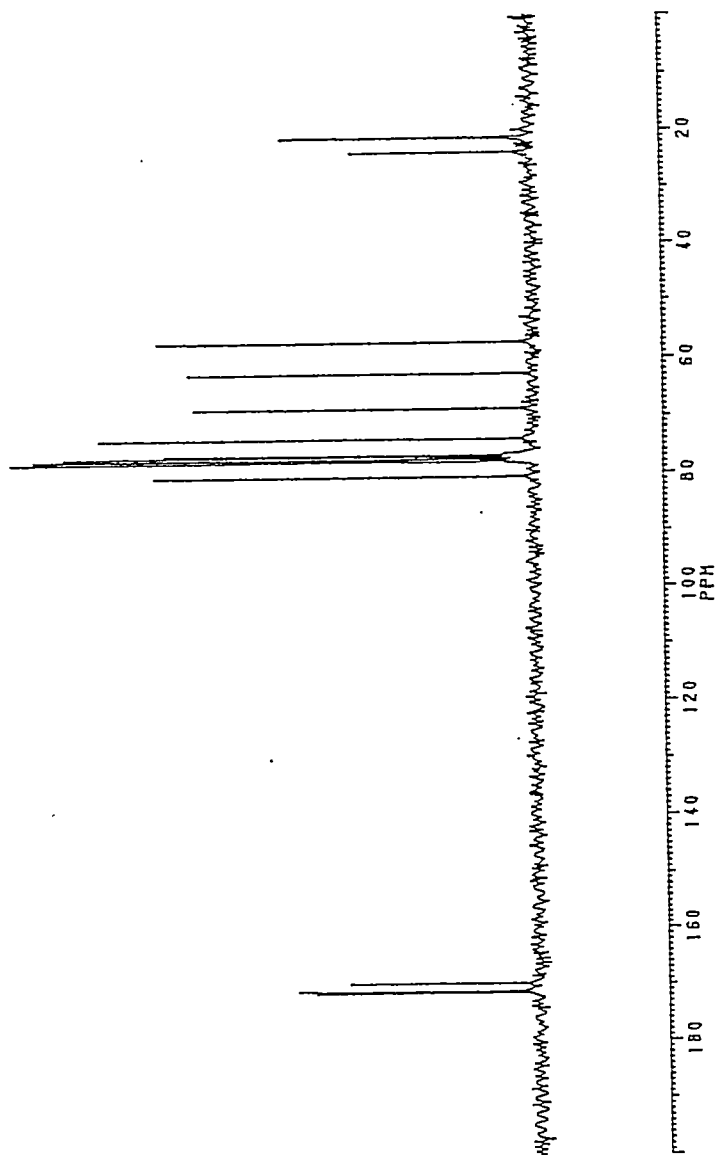
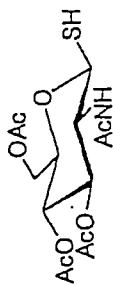
¹³C NMR (250 MHz, CDCl₃) spectrum of methyl 2,3-di-O-benzyl-4-deoxy-4-C-(formyl)-6-O-(4-methoxybenzyl)-α-D-glucopyranoside 47.



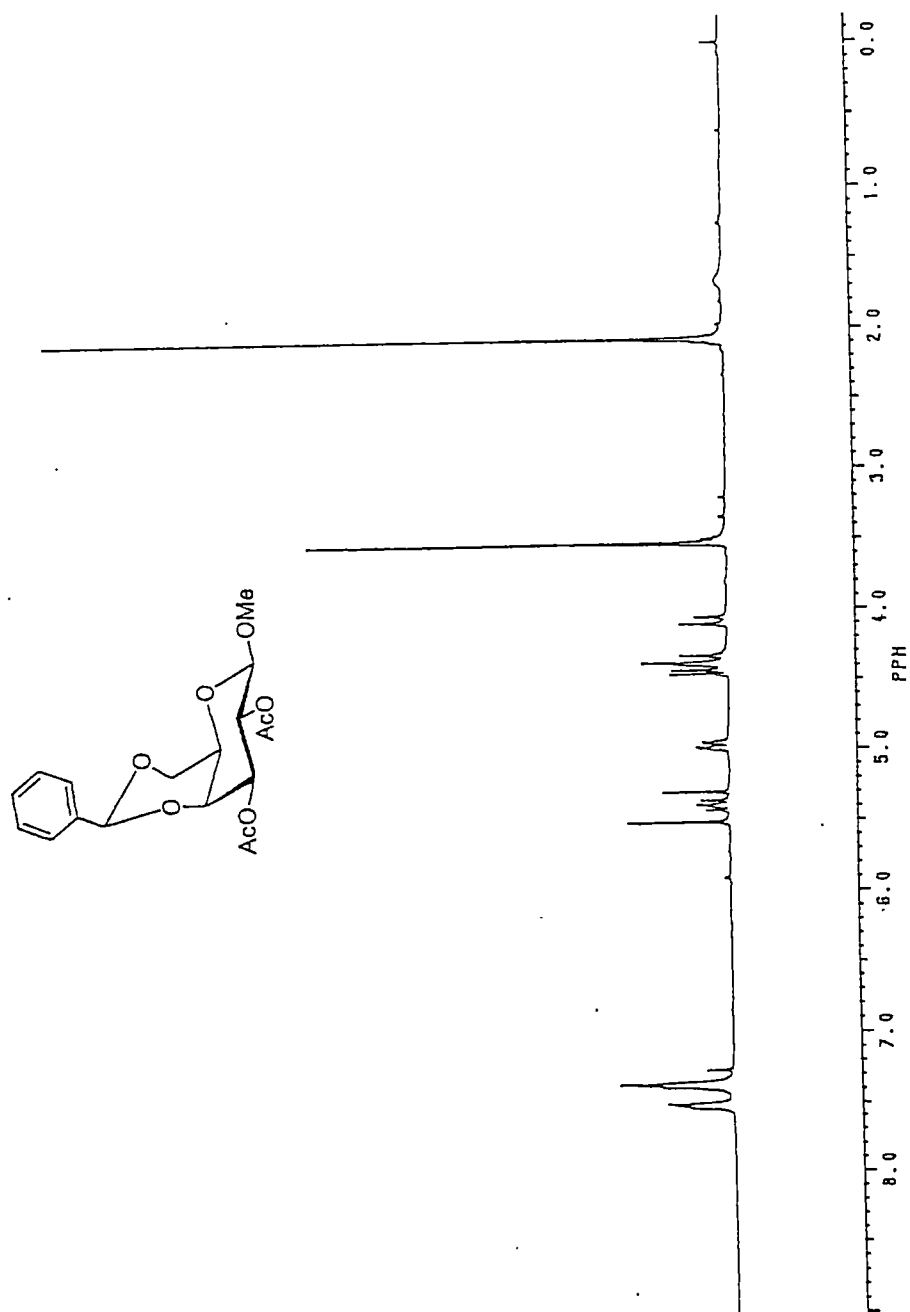
¹H NMR (250 MHz, CDCl₃) spectrum of methyl 4-C-(2-acetamido-2-deoxy-3,4,6-tri-O-benzyl-β-D-glucopyranosylhydroxymethyl)-2,3-di-O-benzyl-4-deoxy-6-O-(4-methoxybenzyl)-α-D-glucopyranoside 48.



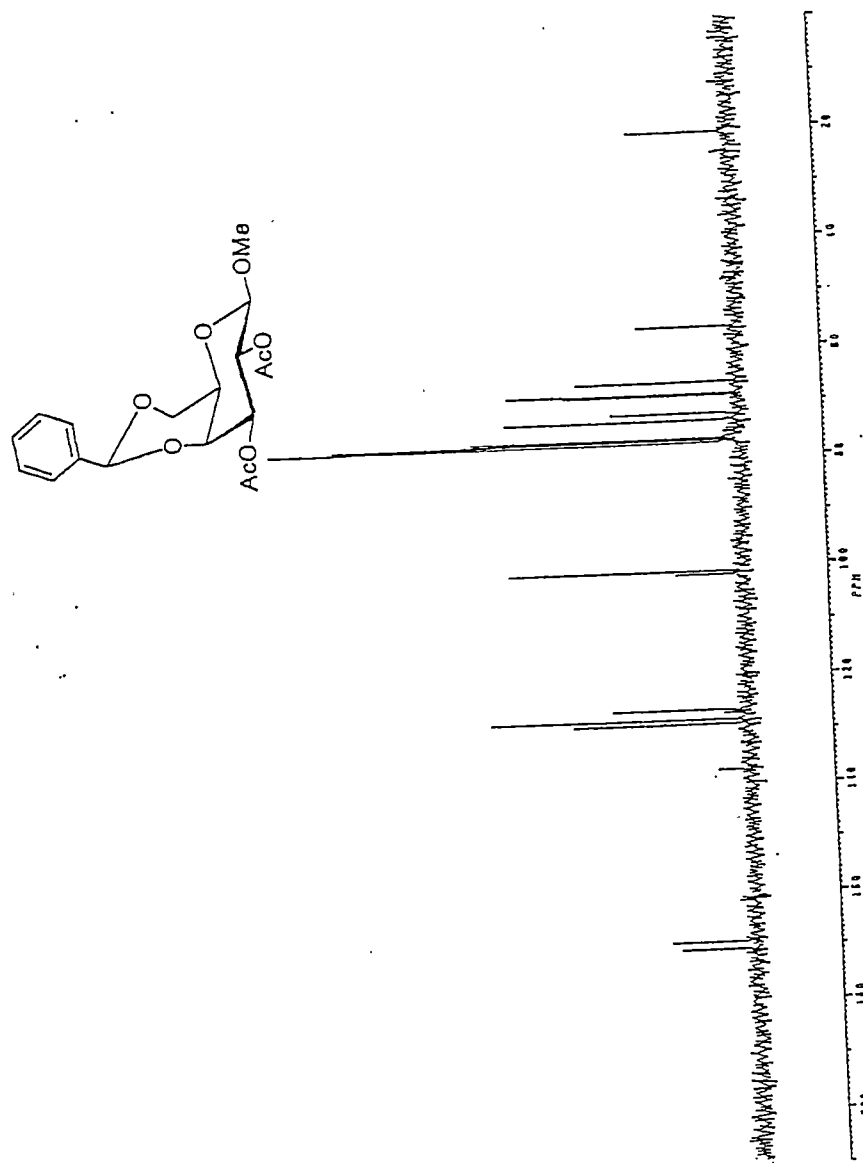
^1H NMR (250 MHz, CDCl_3) spectrum of 2-acetamido-3,4,6-tri-O-acetyl-1-thio- β -D-glucopyranose 53.



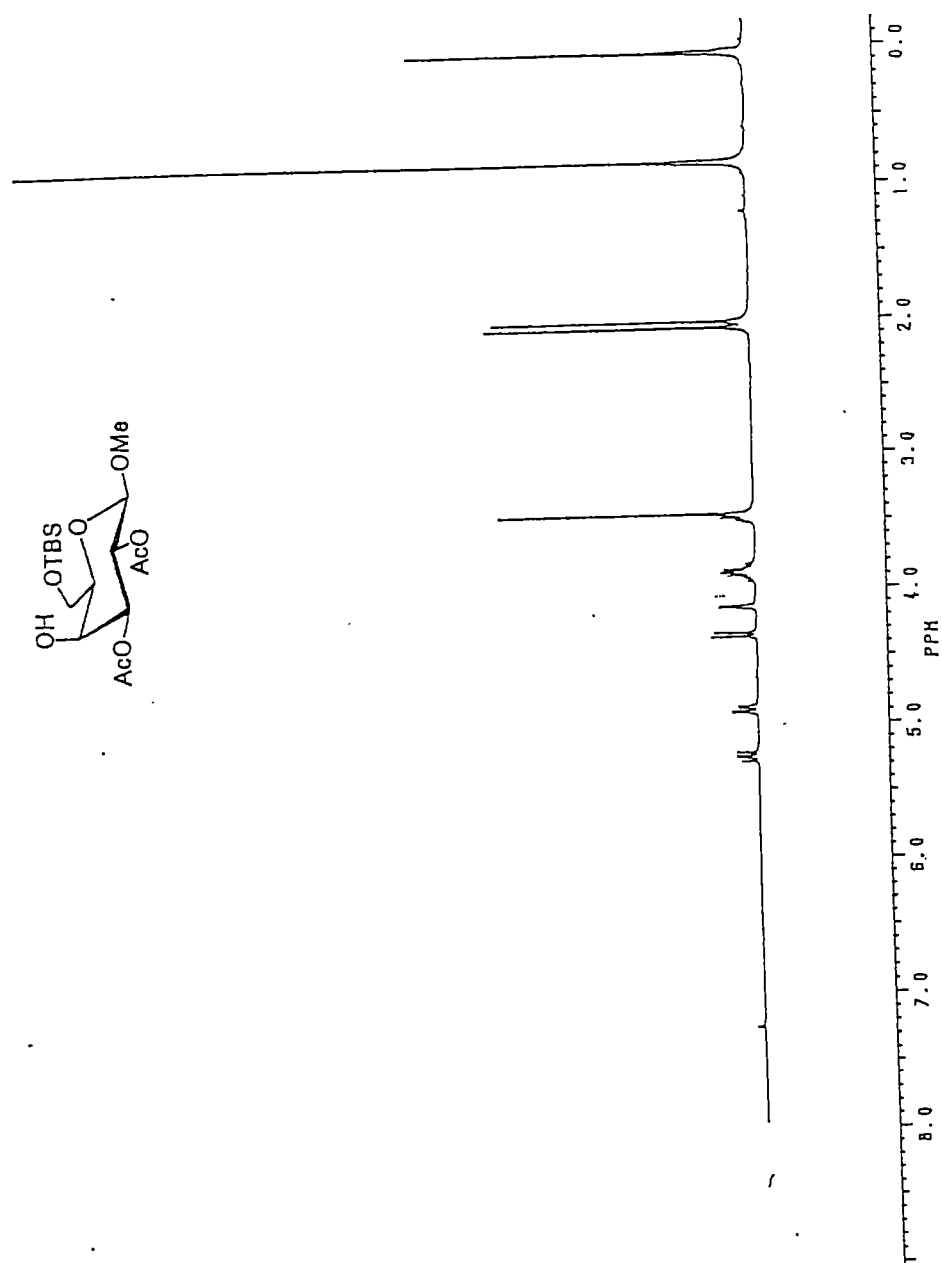
^{13}C NMR (250 MHz, CDCl_3) spectrum 2-acetamido-3,4,6-tri-O-acetyl-1-thio- β -D-glucopyranose **53**.



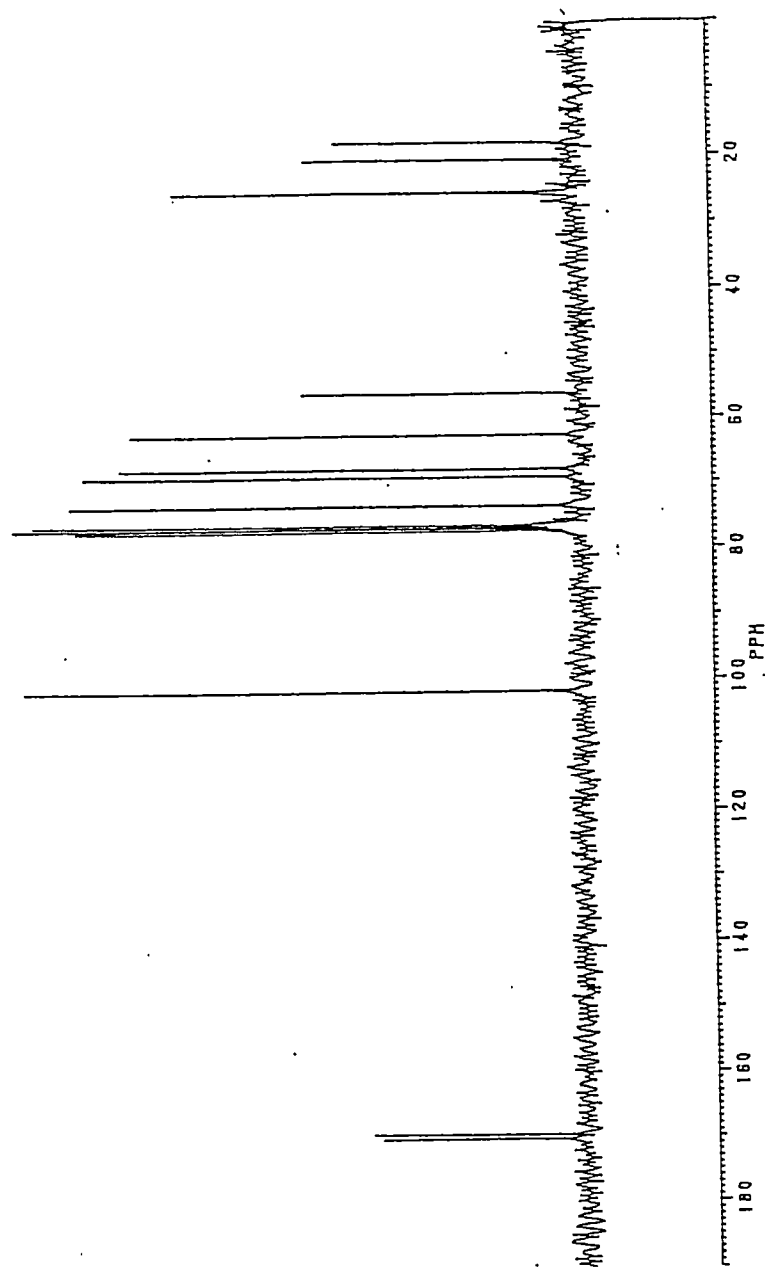
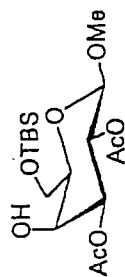
^1H NMR (250 MHz, CDCl_3) spectrum of methyl 2,3-di-O-acetyl-4,6-O-benzylidene- β -D-galactopyranoside 56.



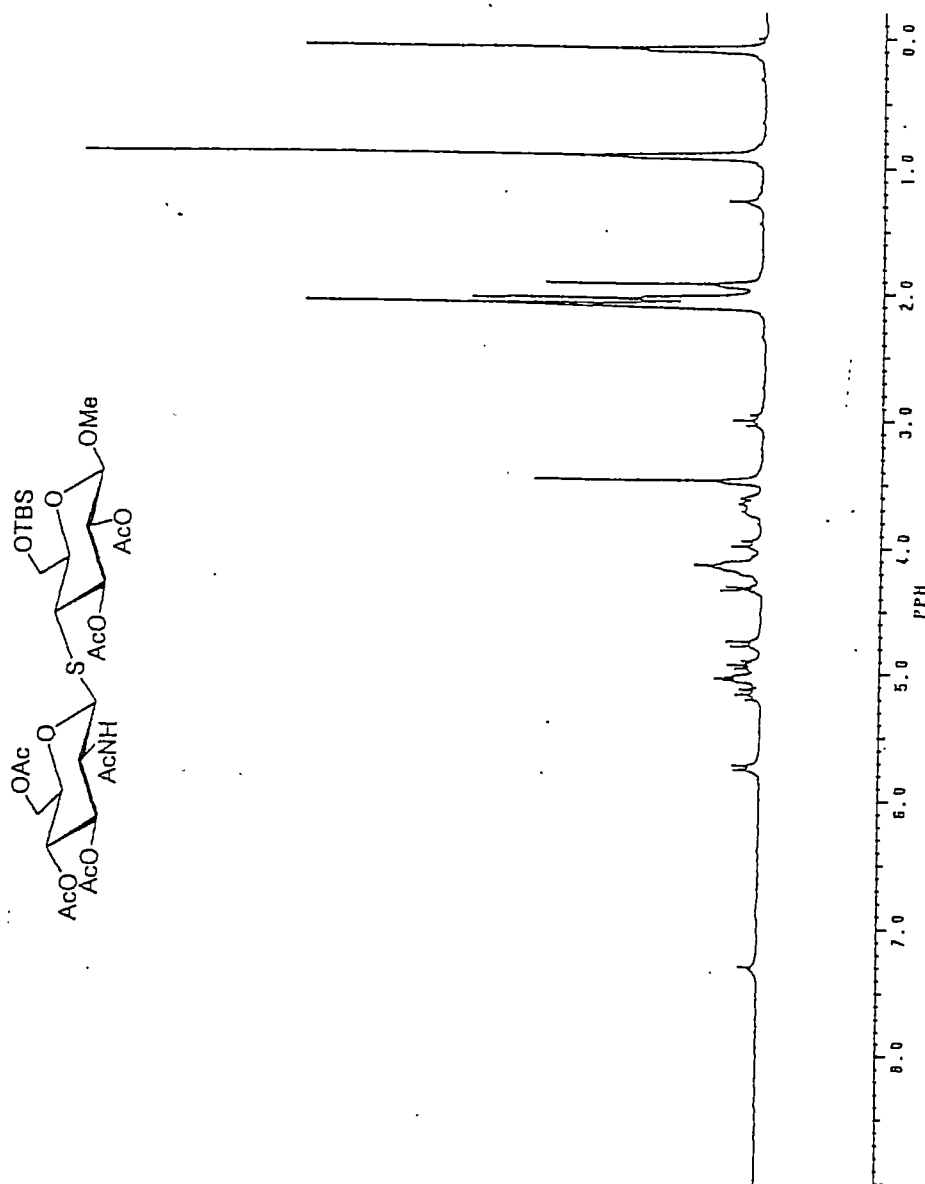
¹³C NMR (250 MHz, CDCl₃) spectrum of methyl 2,3-di-O-acetyl-4,6-O-benzylidene-β-D-galactopyranoside 56.



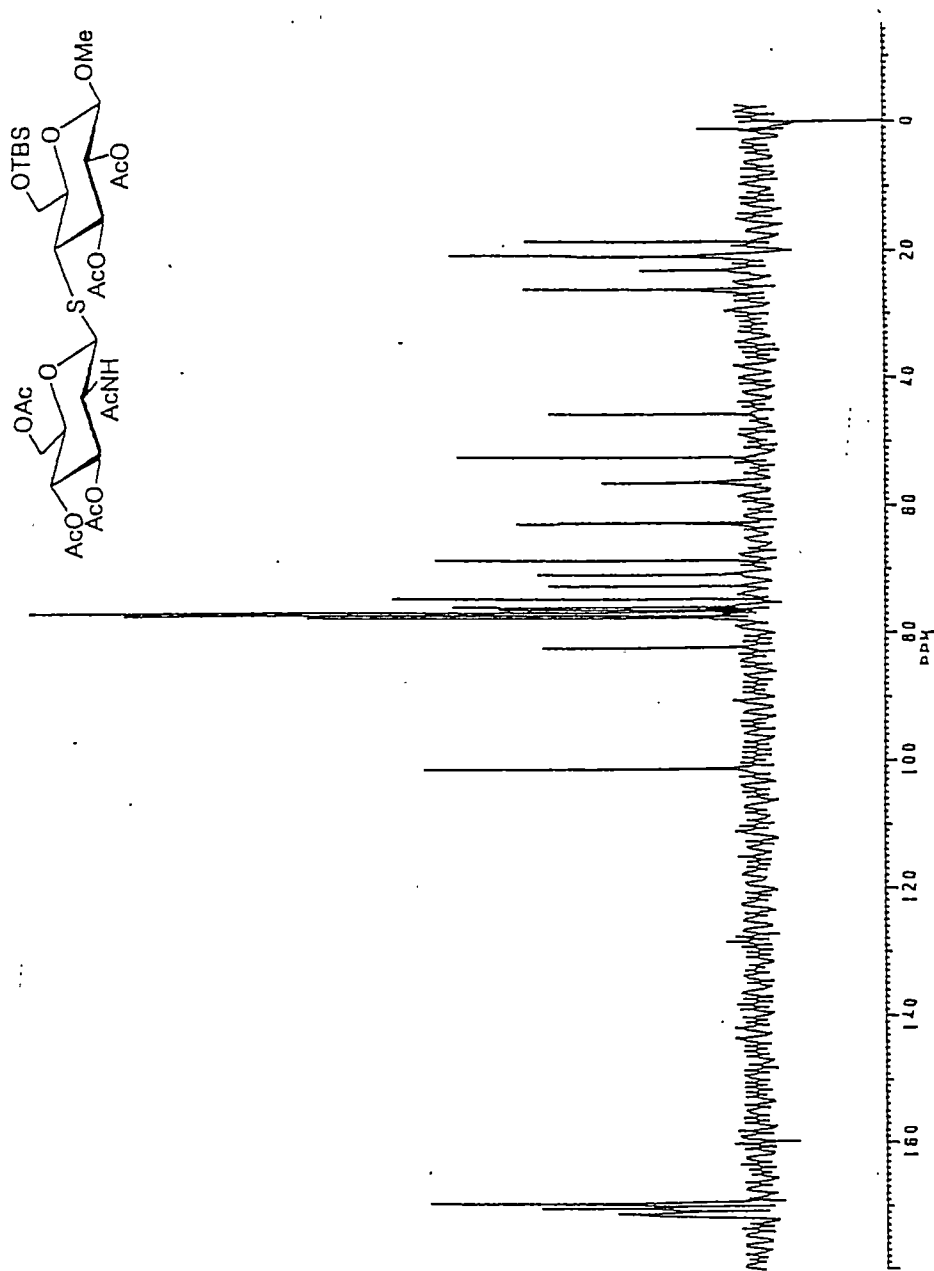
^1H NMR (250 MHz, CDCl_3) spectrum of methyl 2,3-di-O-acetyl-6-O-*tert*-butyldimethylsilyl- β -D-galactopyranoside 57.



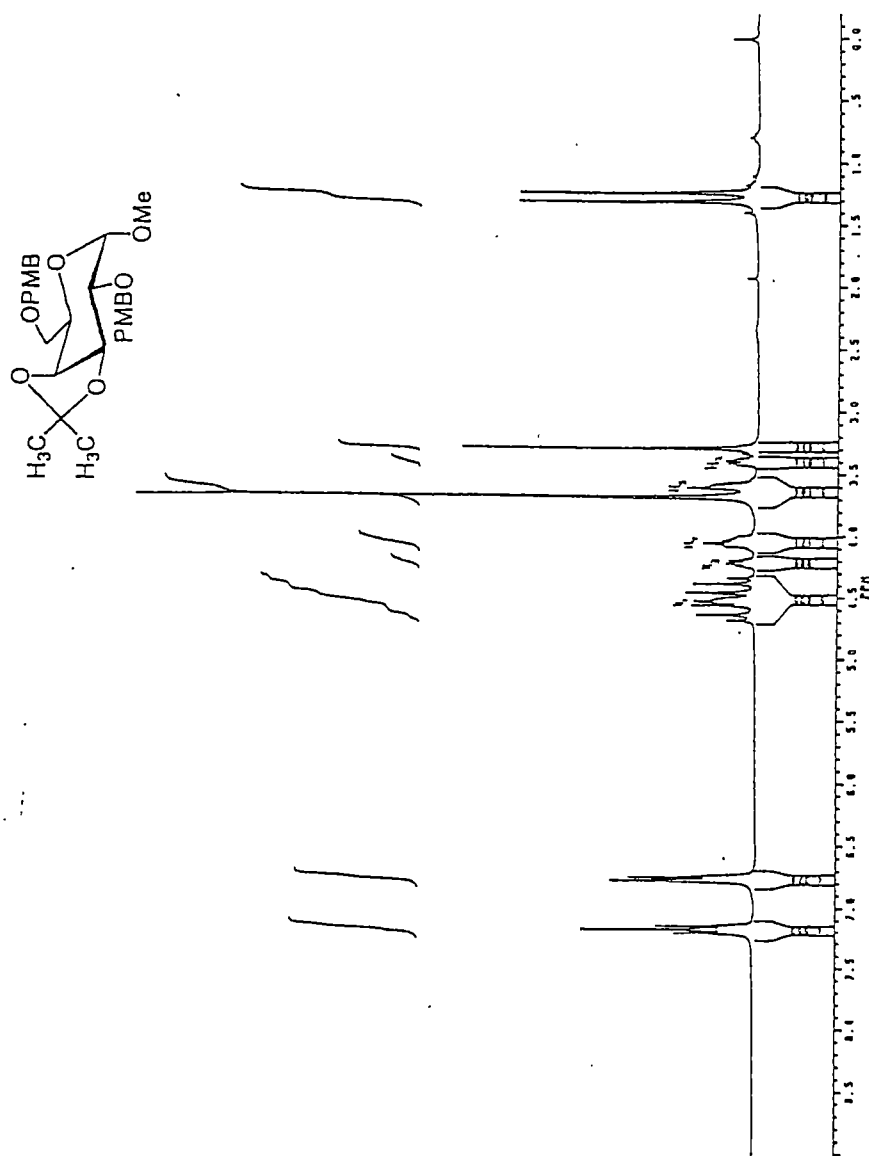
^{13}C NMR (250 MHz, CDCl_3) spectrum of methyl 2,3-di-O-acetyl-6-O-tert-butyltrimethylsilyl- β -D-galactopyranoside **57**.



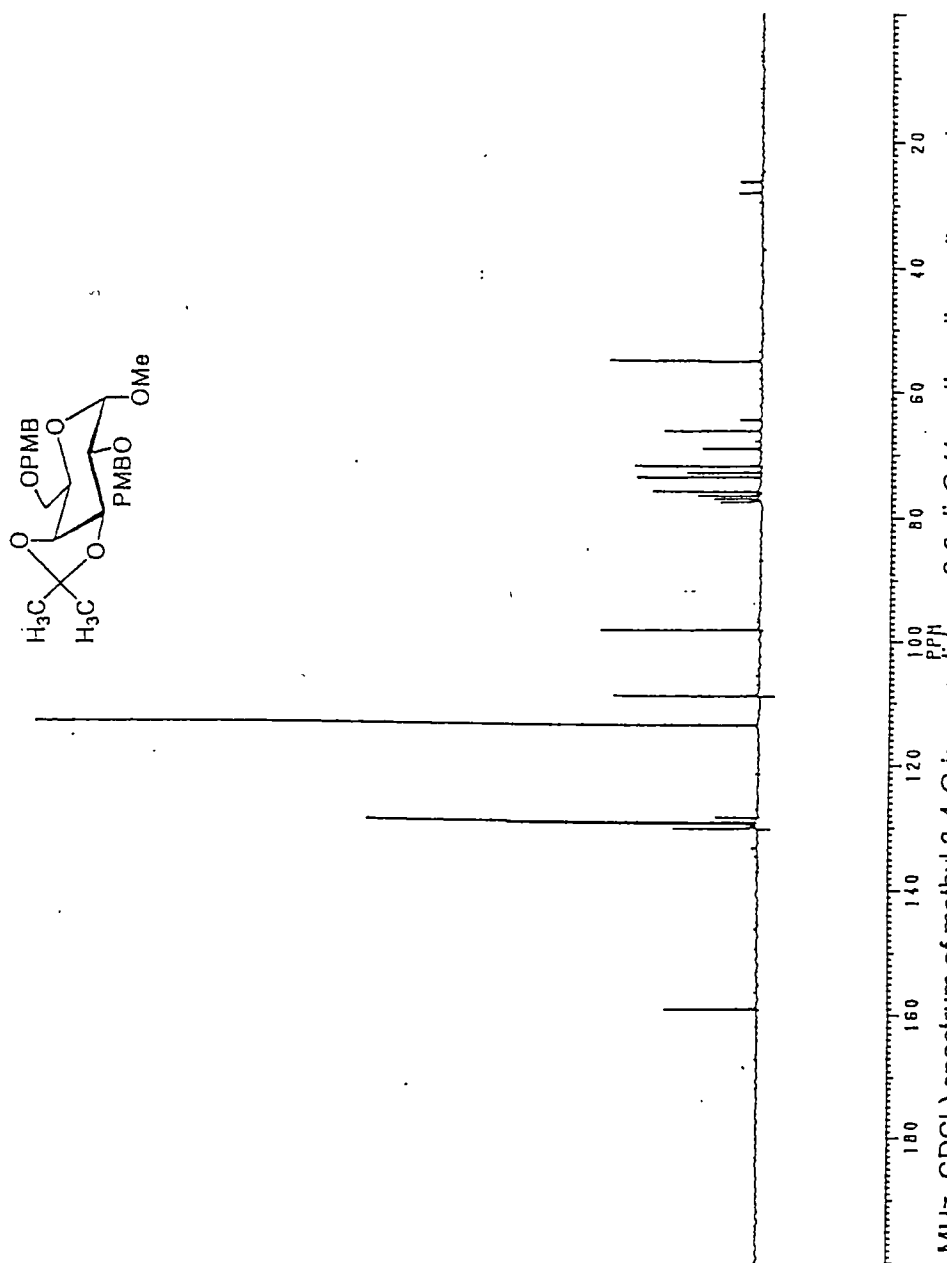
^{13}C NMR (250 MHz, CDCl_3) spectrum of methyl S-(2-acetamido-2-deoxy-3,4,6-tri-O-acetyl- β -D-glucopyranosyl)-(1 $\rightarrow$ 4)-2,3-di-O-acetyl-6-O-tert-butylidimethylsilyl-4-thio- β -D-glucopyranoside 59.



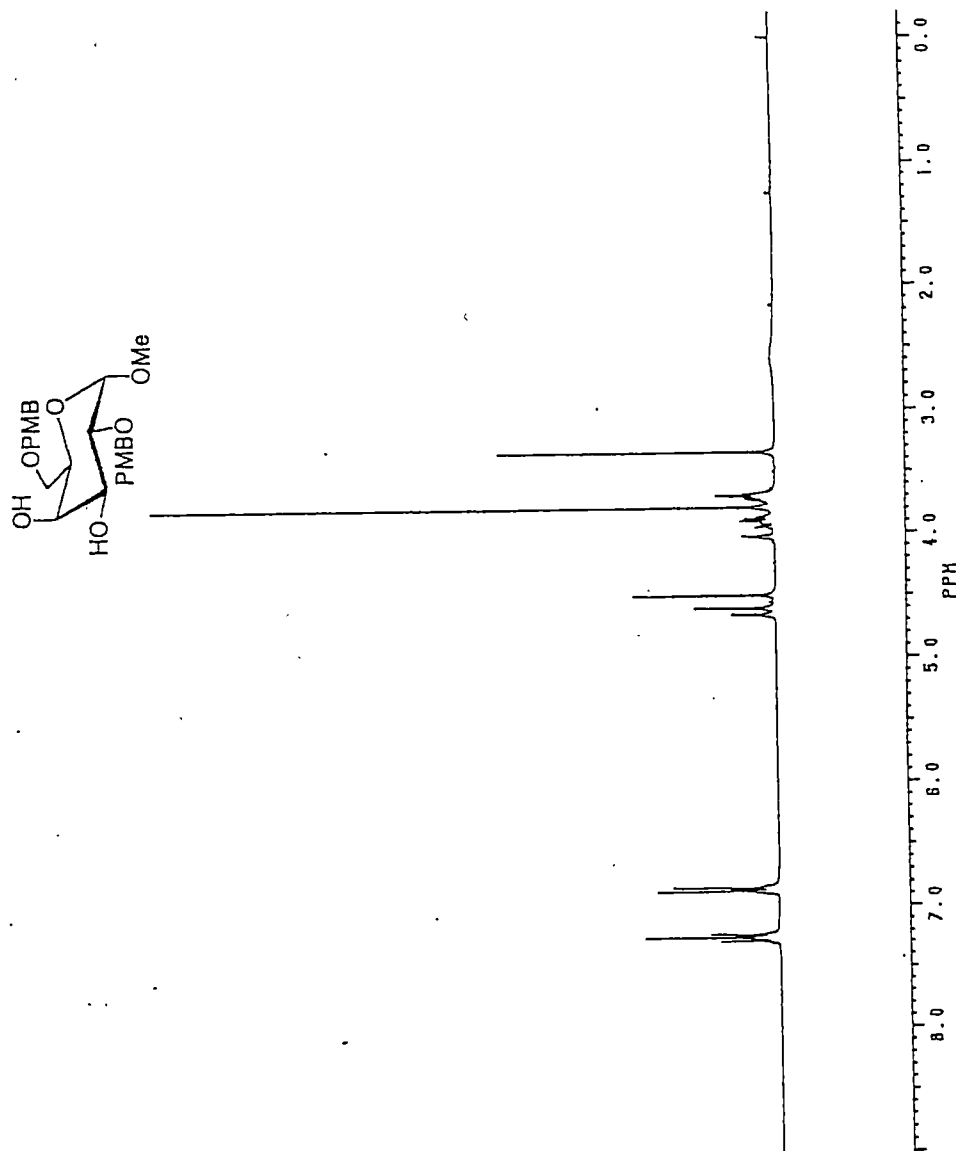
^{13}C NMR (250 MHz, CDCl_3) spectrum of methyl S-(2-acetamido-2-deoxy-3,4,6-tri-O-acetyl- β -D-glucopyranosyl)-(1-4)-2,3-di-O-acetyl-6-O-*tert*-butyldimethylsilyl-4-thio- β -D-glucopyranoside 59.



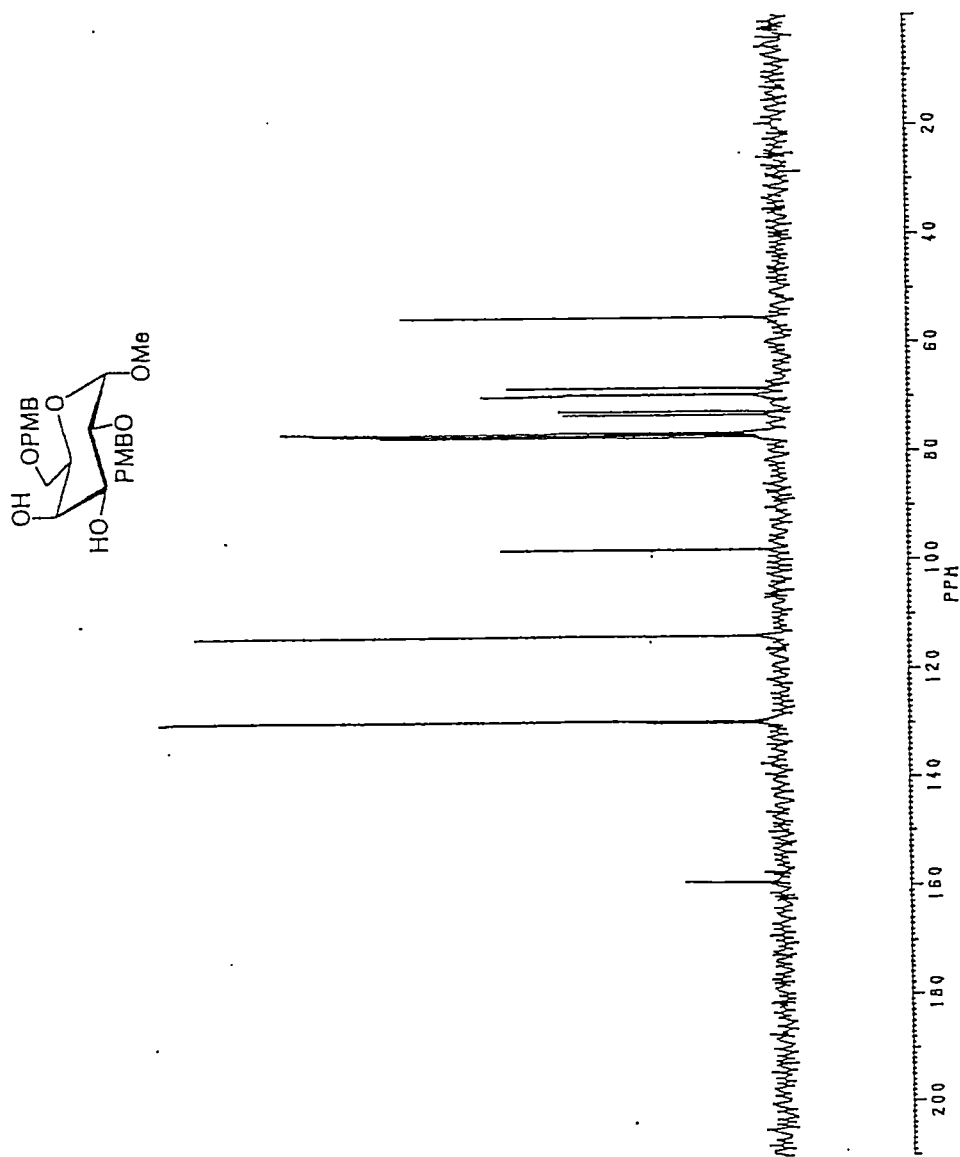
^1H NMR (250 MHz, CDCl_3) spectrum of methyl 3,4-O-isopropylidene-2,6-di-O-(4-methoxybenzyl)-α-D-galactopyranoside 64.



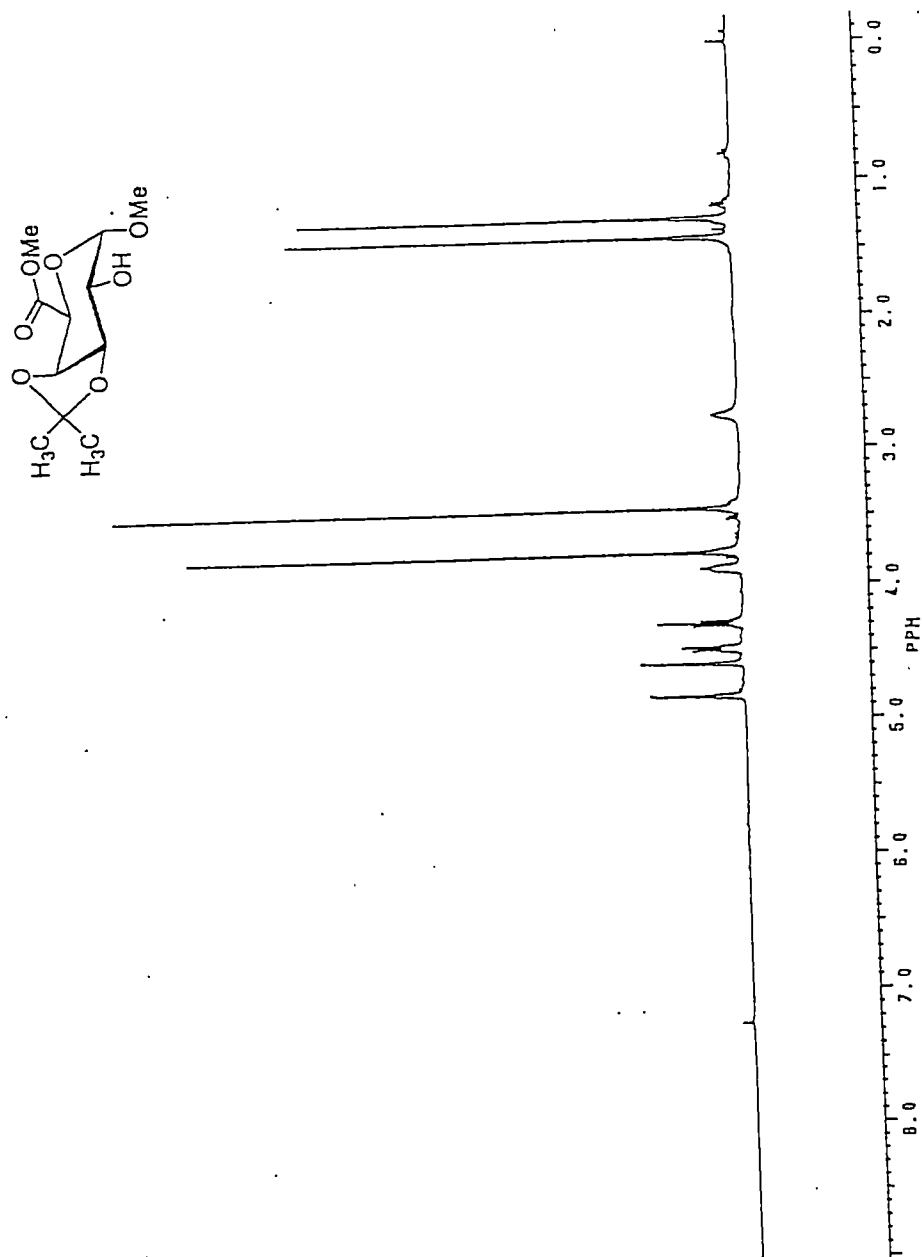
¹³C NMR (250 MHz, CDCl₃) spectrum of methyl 3,4-O-isopropylidene-2,6-di-O-(4-methoxybenzyl)-α-D-galactopyranoside 64.



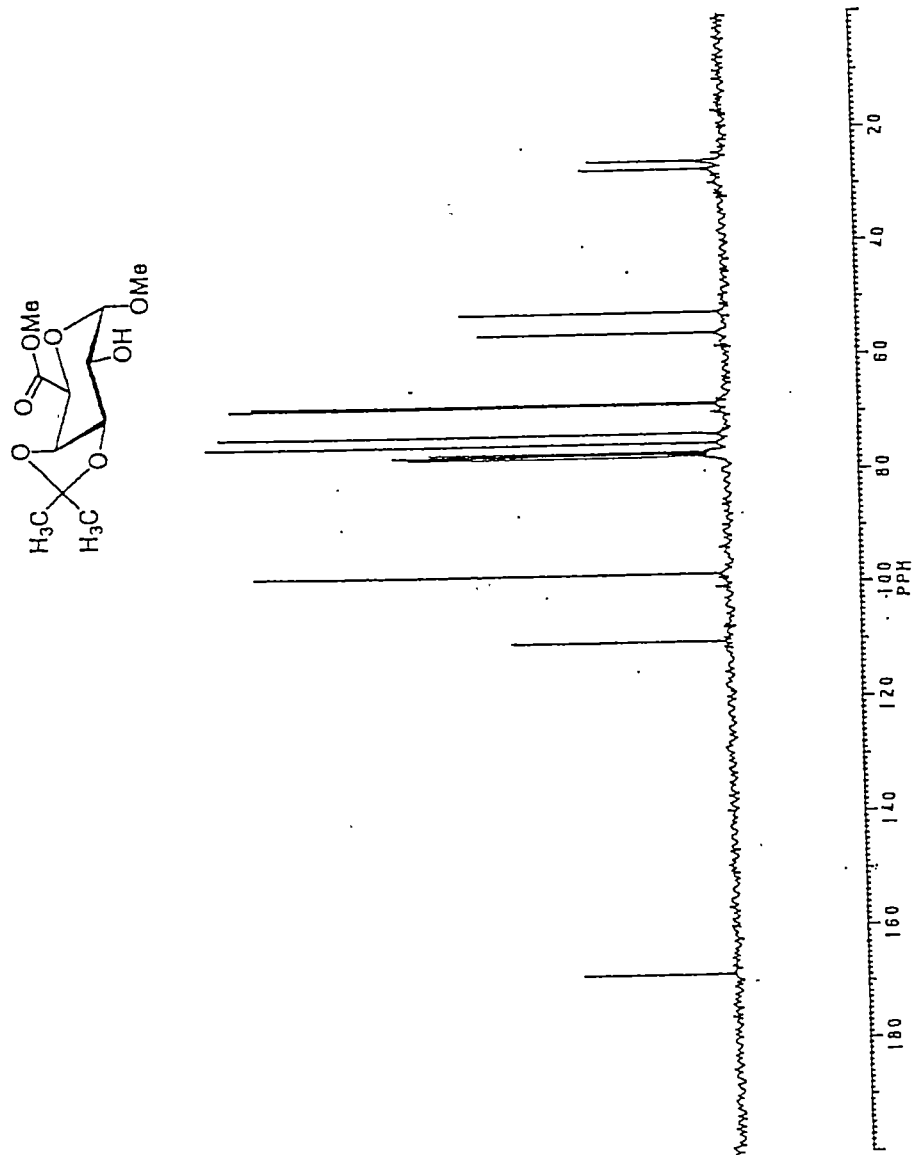
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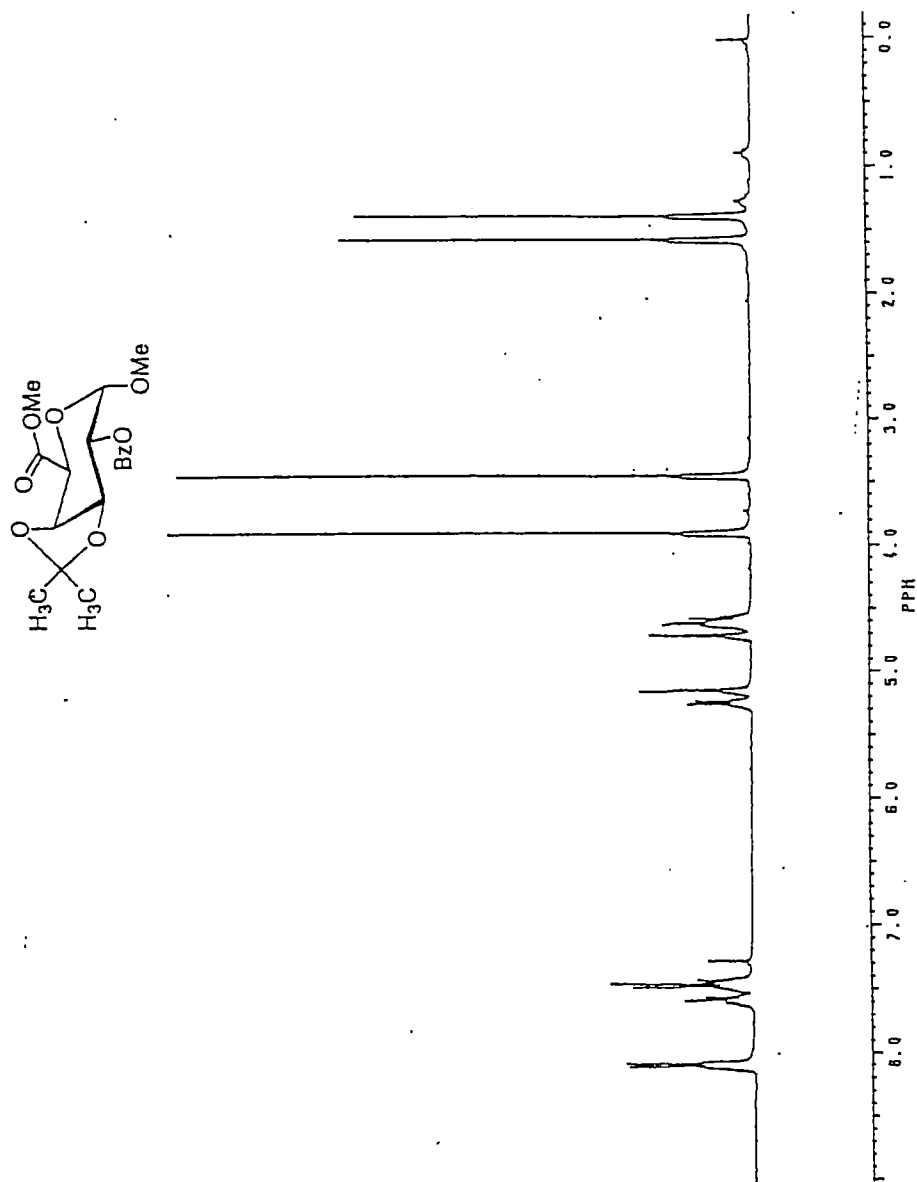
¹³C NMR (250 MHz, CDCl₃) spectrum of methyl 2,6-di-O-(4-methoxybenzyl)-α-D-glucopyranoside 65.



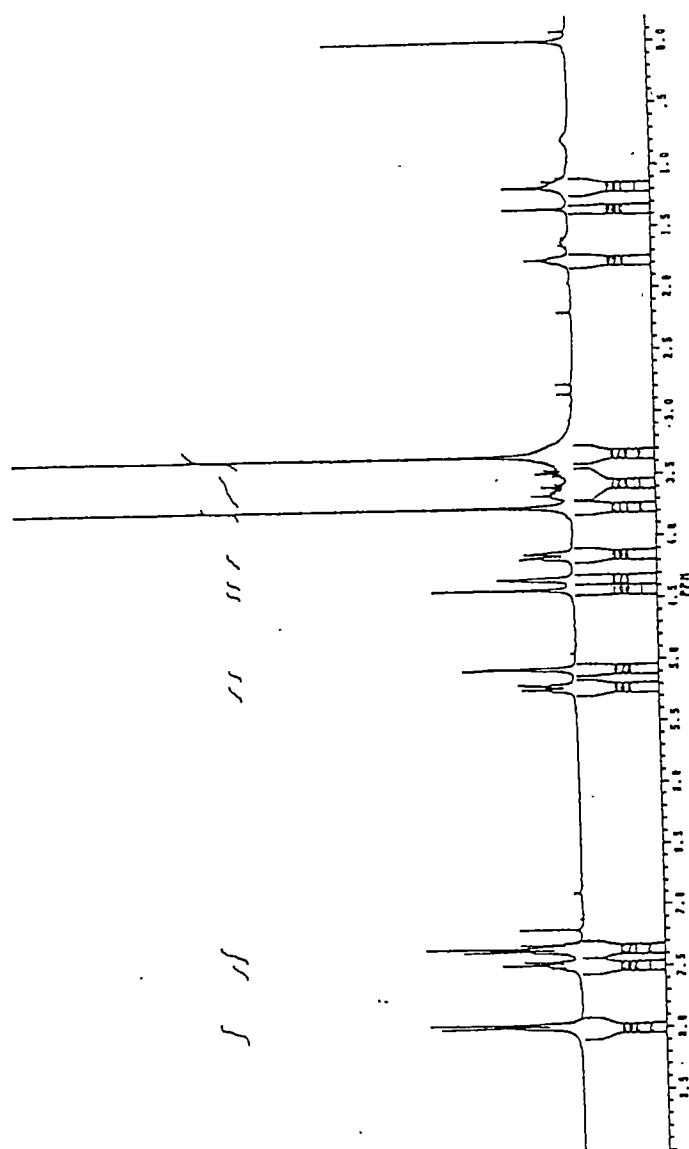
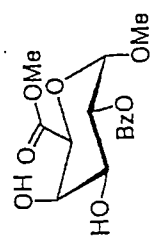
^1H NMR (250 MHz, CDCl_3) spectrum of methyl 3-4-O-isopropylidene- α -D-galactopyranosiduronate 71.



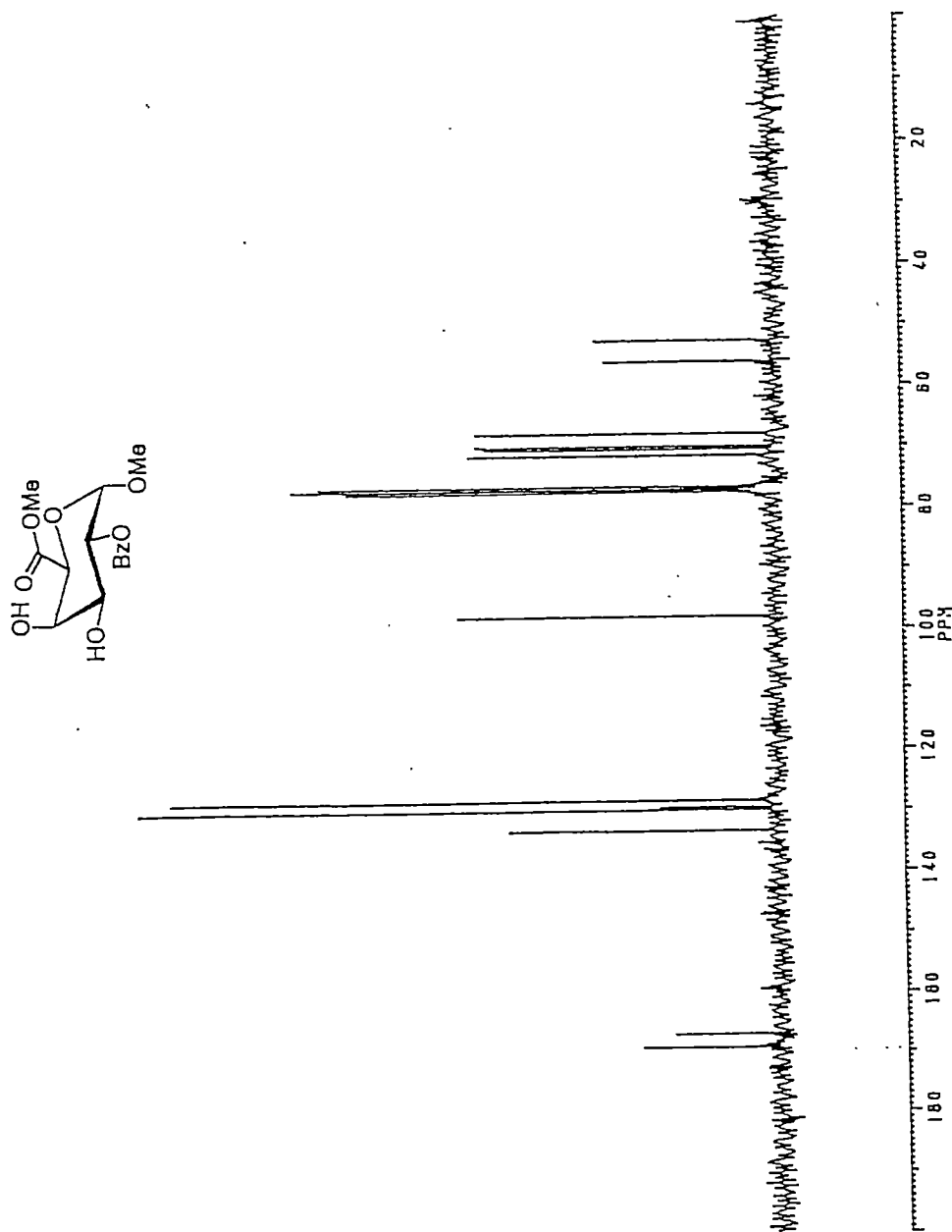
^{13}C NMR (250 MHz, CDCl_3) spectrum of methyl 3-4-O-isopropylidene- α -D-galactopyranosiduronate 71.



^1H NMR (250 MHz, CDCl_3) spectrum of methyl (methyl 2-O-benzoyl-3,4-O-isopropylidene- α -D-galactopyranosid)uronate 72.



^1H NMR (250 MHz, CDCl_3) spectrum of methyl (methyl 2-O-benzoyl- α -D-galactopyranosid)uronate 73.



VITA

Sean Hamilton was born in Stewartville, West Coast Demerara, Guyana in 1968. After completing his early education in Guyana, he migrated to the United States of America. In 1995, he completed his Bachelor's of Science Degree in Chemistry at Long Island University in Brooklyn, New York. While at Long Island University, he conducted undergraduate research in organometallic chemistry under the tutelage of Professor Aderemi Oki who encouraged him to pursue graduate studies. Upon completion of his graduate studies at the University of Tennessee in the laboratory of Professor David C. Baker, he has accepted a position in the Research and Development Department of Guilford Pharmaceuticals Inc. in Baltimore, Maryland.