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Rational Design and Synthesis of Sialyl Lewis X Mimetics and other Glycomimetics

by

Xuhong Cheng

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

2001

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

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Abstract

Rational Design and Synthesis of Sialyl Lewis X Mimetics and other glycomimetics

By

Xuhong Cheng

Adviser: Professor David R. Mootoo

Sialyl Lewis X (sLe^x) is a tetrasaccharide expressed on the surface of neutrophils and tumor cells. It was identified to be the smallest recognizable ligand for selectins. The interaction between sLe^x and selectins initializes the inflammatory cascade for recruitment of leukocytes to a site of tissue damage, which causes the inflammatory diseases. Related adhesion is involved in metastasis. A large number of sLe^x mimetics have been developed as biological probes or potential therapeutics. An 1,1-Gal-Man disaccharide which emerged from Wong's group was reported to be more active than sLe^x in binding to E- and P-selectin.

In this thesis the synthesis of the C-, carba- and aza-C- disaccharide analogues of the molecule is reported. These natural structuresare topographically similar to the parent O-saccharide and are of special interest because of their stability to enzymatic and chemical hydrolysis. The methodology used for the synthesis of the target compounds involved the use of 1-thio-1,2-O-isopropylidene acetals (TIA's) as precursors. A key reaction is the oxocarbenium ion-enol ether cyclization to form a cyclic enol ether. This chemistry was also applied to glycomimetics of glycosyinositols and other important disaccharides. The conformational and selectin binding properties of the O- and C-glycoside analogues of the aforementioned sLe^x mimetics, as well as two novel galactoside analogues for the gp-120 binding affinity are reported.

Acknowledgments

The harvest season of a doctoral thesis is always an embodiment of a number of people's contributions, in ways of enthusiastic support and valued friendship. I would like to express my gratitude to all those who made my graduate life an enjoyable one.

Foremost, I deeply thank my dear advisor, Dr. David R. Mootoo, who teaches me the soul of chemistry. His unique and gifted insight to chemistry directed me all the way; He influenced me to become an earnest researcher by his profound thought and professional attitude, which has always been, and will always be a great stimulus in my career; His guidance, infinite encouragement, and inspiration made possible accomplishments that I thought I could not achieve.

I would like to sincerely thank the members of my committee, Dr. William W. Berkowitz, and Dr. Richard. W. Franck, for their invaluable suggestions and comments.

I am truly grateful to Dr. Klaus Grohmann for his deep care, giving me strength and faith in so many ways.

My appreciation also goes to Dr. Michael Blumenstein, who taught me sophisticated NMR techniques and shared his invaluable expertise in structure interpretation. I also thank Dr. Clifford E. Soll for his help in MS analysis. Our research collaborators, Dr. Jimenez Barbero and Jacques Fantini are also gratefully acknowledged.

I especially thank the chemistry department for giving me this great opportunity to accomplish my doctoral degree.

I wish to thank all my colleagues in Hunter college, for creating a wonderful working environment and providing generous help whenever and wherever I need: Mr. Haiyun Xiao, Drs. Zheming Ruan, Hang Zhao, Noshena Khan, Mohindra Seepersaud, Kumaran Govindaraj, and Mr. Darren Dabidene, Lei Zhu, Liang Bao, Ms. Sunej Hans, Fatou Mata, Line Augustin.

Finally, I would like to thank my family: my parents Jinlin Cheng and Suxia Chen for their love and support, no matter the time and space, my brother, Sicong Cheng, for his love and care and my husband, Chunxin Ji, for the power of love we hold on together.

To my parents, who encourage me
my husband, who loves me and
my teachers, who enable me...

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Symbols and Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
AgOTf	silver trifluoromethanesulfonate
$BF_3{\cdot}Et_2O$	boron trifluoride etherate
Bn	benzyl
Boc	*t*-butyloxycarbonyl
Brine	saturated aqueous sodium chloride solution
br	broad
Bu	butyl
Bz	benzoyl
^oC	degree Celsius
ca.	about
calcd	calculated
Cbz	benzyloxycarbonyl
^{13}C NMR	carbon-13 nuclear magnetic resonance spectrometry
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
δ	chemical shift in ppm
d	doublet
DABCO	1,4-diazabicyclo octane
DEAD	diethyl azodicarboxylate
DIB	iodobenzene diacetate
DCC	dicyclohexylcarbodiimide
DUPHOS	2,5-dimethyl phospho benzene
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
ee	enantiomer excess
ELAM-1	endothelial leukocyte adhesion molecule

Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
eq	equivalent
FCC	flash column chromatography
Fuc	L-fucose
g	gram
Gal	D-galactose
Glc	glucose
GluNAc	N-acetyl-D-glucosamine
h	hour
^1H NMR	proton nuclear magnetic resonance spectrometry
HOAc	acetic acid
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	concentration of inhibitor resulting in the reduction of bonding to 50% of Maximum
IDCP	iodonium dicollidine perchlorate
J	coupling constant in hertz
L	liter
Le^x	Lewis X
m	multiplet
M	molar
Me	Methyl
MeOH	methanol
mg	milligram
min	minute
mL	milliliter
mmol	millimole
MM3	force fields for molecular mechanics calculations
MS	molecular sieves

man	mannopyranoside
NOE	nuclear overhauser effect
Ph	phenyl
ppm	parts per million
Psi	pounds per square inch
q	quartet
rt	room temperature
s	singlet
sLe^a	sialyl lewis a
sLe^x	sialyl lewis X
t	triplet
TBS	*tert*-butyl diphenylsilyl
TIA	1-thio-1,2-O-isopropylidine acetal
TfOH	trifluoromethanesulfonic acid (triflic acid)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethyl trifluoromethanesulfonate
Ts	toluenesulfonyl
vs	versus

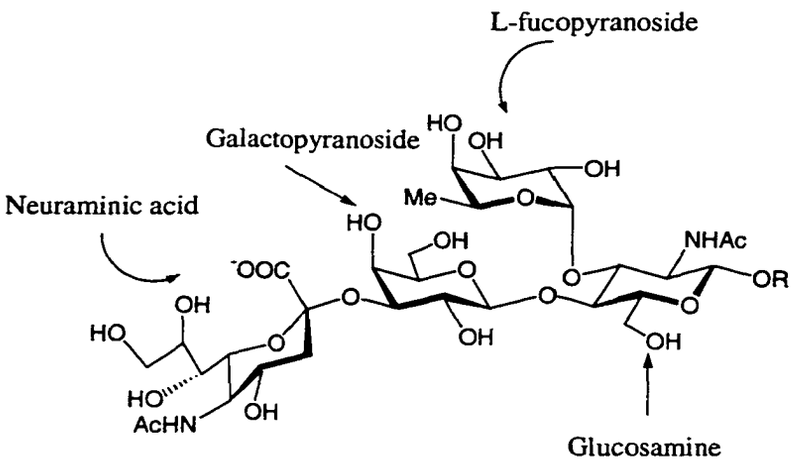
Chapter 1

Introduction

1.1 Background[1]

Sialyl Lewis X (sLe^x) (Figure 1.1) is a tetrasaccharide expressed on the surface of neutrophils and tumor cells. Interaction between sLe^x on neutrophils and selectins on the surface of endothelial cells occurs at the early stage of the inflammatory response. Related adhesion processes are believed to be involved in metastasis.

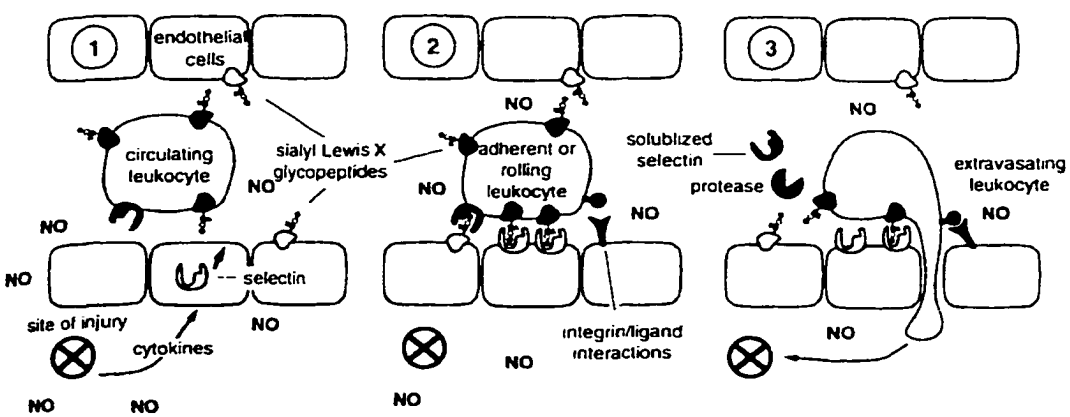
Figure 1.1 Sialyl Lewis X (sLe^x)



Acute inflammatory conditions following stroke, reperfusion injury during surgery and organ transplantation, and chronic diseases, such as psoriasis and rheumatoid arthritis, are results of the body's overzealous recruitment of

lymphocytes. The inflammatory cascade begins when cytokines that are released at the site of tissue injury stimulate the endothelium to express two proteins, E-[2] and P-selectin[3] transiently on the endothelial lining.[4] Selectins E and P recognize sLe^x and related oligosaccharides on the surface of the leukocytes[5] and promote leukocyte adhesion to the affected endothelial cells.[6] L-selectin is constitutively expressed on leukocytes, and it recognizes similar carbohydrate ligands displayed on the endothelium. "Rolling" by the leukocytes across the affected endothelium leads to further adhesion events between integrins on the leukocytes[7] and an endothelial protein, ICAM-1 (intercellular adhesion molecule-1).[8] This stronger interaction leads to the migration of the leukocytes through the endothelial layer (extravasation) to the site of the injury. Proteolytic cleavage of L-selectin from the surface of leukocytes occurs, and leukocytes then accumulate at the site of injury. If too many white blood cells are recruited to the site of injury, normal (i.e. not injured) cells can be damaged, resulting in inflammation (Figure 1.2).

Figure 1.2 Inflammatory Cascade



Therefore, an attractive strategy for treating inflammation-related diseases, such as the aforementioned, and, perhaps, for suppressing metastasis of cancer cells, is to inhibit the selectin-ligand interaction that initiates these processes. Since sLe^x is difficult to synthesize and binds weakly, there has been an intensive effort to develop simple molecules, such compounds are also less likely to be affected by problems relating to drug delivery.

1.2 Selectins[9]

Selectins are a class of carbohydrate binding glycoproteins, previously known as the murine lymph node homing receptors. Selectins are a small group in the carbohydrate-binding lectin family. Since selectins are dependent on calcium, they are referred to as C-type lectins. There are three different selectins, E-, P- and L-selectin, according to the cell type on which each was initially found (i.e. endothelium, platelets and leukocyte).

Each of the selectins comprises five domains: a cytosolic tail that may play a role in signal transduction, a transmembrane domain, a series of complement-like modules (CR), an epidermal growth factor domain (EGF), and an N-terminal, calcium-dependent carbohydrate recognition domain (CRD) (Figure 1.3).

Both the EGF and CRD domains are required for binding the carbohydrate ligand, although the site of binding has been localized to the CRD domain.[10] The EGF region is believed to exert its effect by holding portions of the lectin domain

in the proper conformation.[11] The CRD is a globular structure that recognizes its ligands in a shallow depression that contains a Ca^{2+} ion (Figure 1.4).

Figure 1.3 Selectins

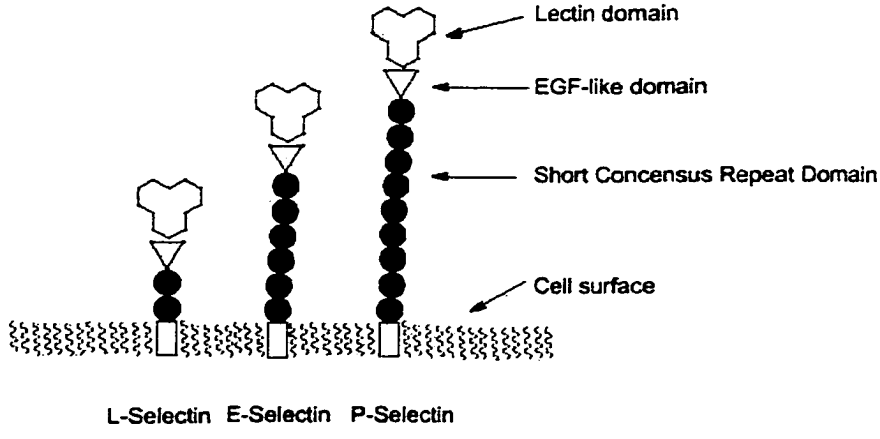
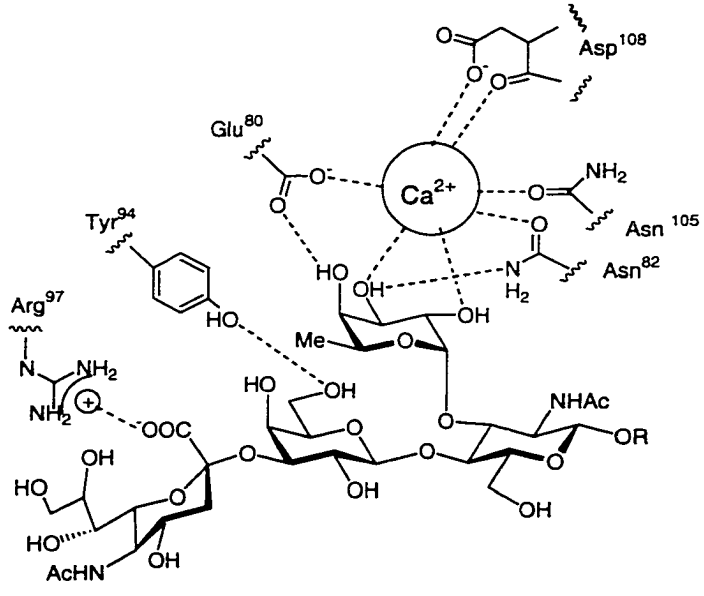


Figure 1.4 Hypothesized Binding Site for sLe^x on E-selectin



E-selectin was known as the endothelial leukocyte adhesion molecule 1(ELAM-1). It is activated by cytokines such as interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), and is expressed on the cell surface a few hours after activation.[12]

Table 1.1 Nomenclatures and Properties of Selectins

Selectins	old names	Distribution	Regulation
E-selectin	ELAM-1	Endothelial cells	IL 1-β TNF Interferon-γ
P-selectin	CD62 GMP-140 PADGEM	Endothelial cells platelets	Thrombin Histamine H_2O_2
L-selectin	MEL-14 LECAM-1	Leukocytes	Constitutive surface expression TNF

P-selectin was termed as granule membrane protein 140 (GMP-140), CD62, or platelet activation-dependent granule external membrane protein (PADGEM). It is a 140 kDa glycoprotein expressed on platelets and endothelial cells. P-selectin is rapidly expressed to its maximum concentration in about ten minutes following stimulation by thrombin, phorbol histamine, peroxide radicals, or other mediators.[13]

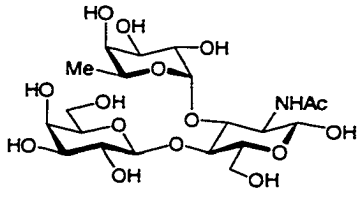
L-selectin was called MEL-14/LAM-1 antigen. In contrast to E- and P-selectins, it is expressed on the surface of leukocytes. lymphocytes, monocytes, and myeloid cells. High levels of phorbol 12-myristate 13-acetate (PMA), LPS, calcium ionophores, or tumor necrosis factor α (TNF-α) can induce the release of L-selectin. L-selectin is involved in the recirculation of lymphocytes in peripheral lymph nodes but also in the recruitment of leukocytes at the infection site (Table 1.1).

1.3 Natural carbohydrate ligands for the selectins[14]

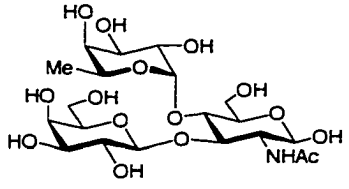
The carbohydrate determinants recognized by selectins are typically located at the nonreducing terminal carbohydrate groups of glycoproteins and/or glycolipids. The sialylated and fucosylated tetrasaccharide antigens, sLe^x, sialyl Lewis a (sLe^a), and VIM-2 (Figure 1.5) are common ligands for selectins. Of these, sLe^x is usually the most critical. sLe^x comprises fucose, galactose, glucosamine (GlcNAc) and neuraminic acid (NeuAc). The 2- and 3-hydroxyl groups of fucose coordinate in a calcium-dependent manner with E-selectin; The 4-OH of fucose and hydroxyl groups of galactose interact via hydrogen bonding with acid, tyr94, or amino acid side chains; The carboxylate and the glycosidic oxygen of the NeuAc forms a salt bridge with an arg97 side chain (Figure 1.4). The GlcNAc residue does not play a critical role in these interactions, but is believed to be important for preorganizing the residues of the tetrasaccharide. The binding to P-selectin is essentially similar. The 2 and 4-hydroxyl groups of fucose were originally thought to be not as critical as in E-selectin-sLe^x binding, but this premise has recently been

challenged.[1c]

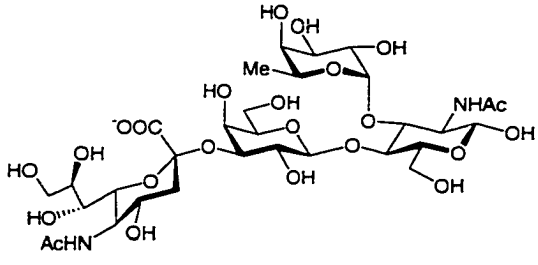
Figure 1.5 Ligands for Selectins



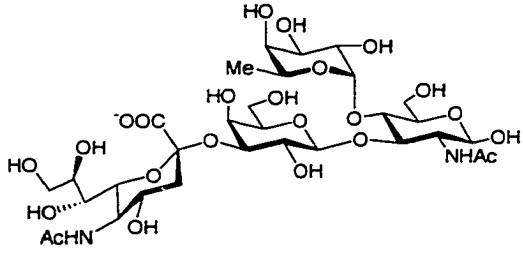
Lewis X trisaccharide (Le^x)
Galβ1-4(Fucα1-3)GlcNAc



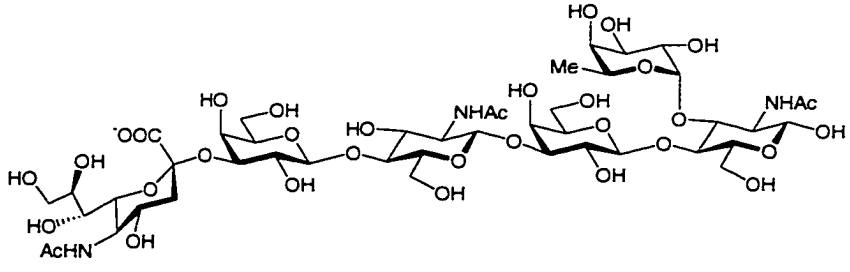
Lewis a trisaccharide (Le^a)
Galβ1-3(Fucα1-4)GlcNAc



Sialyl Lewis X tetrasaccharide (sLe^x)
NeuAcα2-3Galβ1-4(Fucα1-3)GlcNAc



Sialyl Lewis a tetrasaccharide (sLe^a)
NeuAcα2-3Galβ1-3(Fucα1-4)GlcNAc

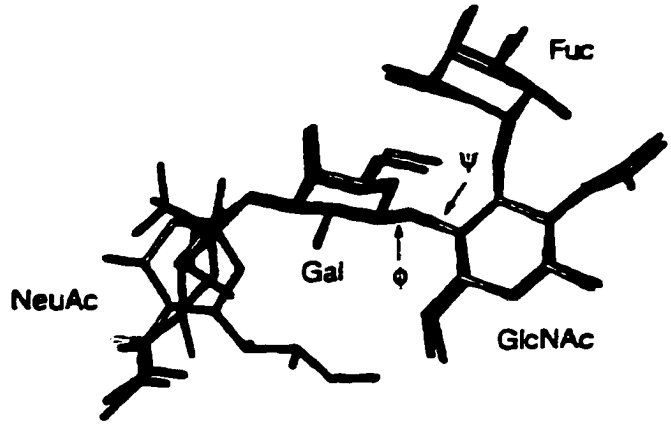


VIM-2
NeuAcα2-3Galβ1-4GlcNAcβ1-3Galβ1-4(Fucα1-3)GlcNAc

The solution[15] and bound[16] E-selectin conformations of sLe^x have been deduced by transfer NOE NMR studies (Figure 1.6). The glycosidic torsion angles (Φ/Ψ) of NeuAc-Gal, Gal-GlcNAc and Fuc-Gal for the solution form are 167/-63, 48/15 and 23/30, and for the bound conformation are –76/6, 39/12 and 38/26. These data indicated that the relative orientation of fucose, N-acetylglucose amine,

and galactose is very similar in bound and unbound states. However, the conformations of the linkage to the NeuAc are quite different.

Figure 1.6 Bound/Unbound Conformations of sLe^x



Since the bound conformation has been estimated to cost 1.5 kcal/mol, which suggests that it is plausible to design sLe^x mimetics with constrained conformations (to mimic the bound form of sLe^x), or with flexible conformations (with low energy barriers), to improve the binding affinity.

1.4 Sialyl Lewis X mimetics

The following groups of sLe^x mimetics (Figure 1.7) have been designed and synthesized based on the foregoing structure-activity hypotheses.

Deletion of NeuAc[17] When the complex neuraminic group was replaced by a simple negatively charged group, such as phosphate or sulfate, on the 3 position of galactose, similar binding affinities to sLe^x was observed, e.g. **1.1**.

Deletion of NeuAc and GlcNAc[18] It has been established that glucosamine

contains none of the functional groups critical for binding, but important for preorganizing the tetrasaccharide. Compound **1.2**, in which the glucosamine group was simplified with β-linked ether, and neuraminic acid was replaced by "CH_2COO^-", was almost as effective as sLe^x. While in compound **1.3**, with a more rigid cyclohexyl ring as the linker between *Gal* and *L-Fucose*, showed 10 fold more active than sLe^x.

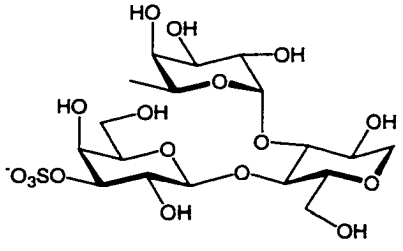
Deletion of GlcNAc and Gal[16c-e] Compound **1.4**, in which fucose and sialic acid residue are tethered by a reasonably rigid phenyl linker, showed 20 fold less active than sLex. This example reinforces the importance of the hydroxyl groups of galactose and the relatively flexible linker group.

Deletion of NeuAc, GlcNAc and Gal: L-Fucose-Based Inhibitors[19] In compound **1.5**, the glucosamine-galactose linker to the carboxylate anion was replaced by a *trans*-cyclohexanediol and a rigid aromatic spacer. This molecule showed slightly increased activity relative to sLe^x.

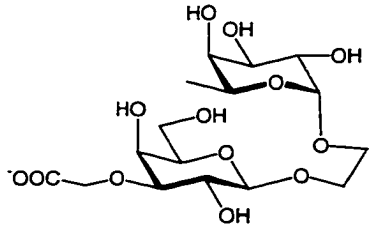
Replacement of GlcNAc and Fucose Segment[20] A novel 1,1-linked O-disaccharide **1.6** was designed to provide a similar orientation of the hydroxyl groups on the fucose and galactose moieties as in the active conformation of sLe^x. A carboxymethyl group was incorporated into the 3-OH group of the galactose residue. The simple and flexible carboxymethyl group was used because of the observation that only the carboxyl group of sialic acid is essential for binding.[21] This O-disaccharide **1.6** was found to be five times as active as sLe^x in binding with E- selectin, and 4000 times more active with P- selectin.

In this thesis the syntheses of sLe^x mimetics which are closely related to this O- disaccharide will be presented.

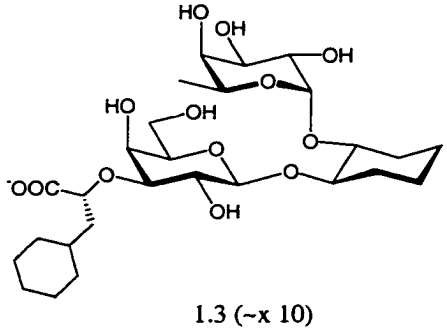
Figure 1.7 Representative of sLe^x Mimetics



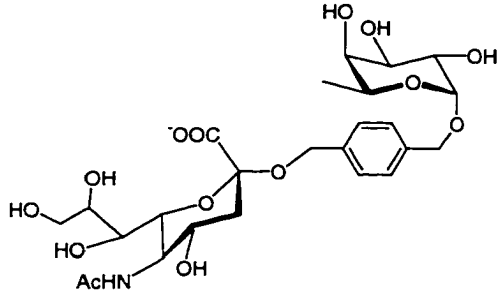
1.1 (~x 1)



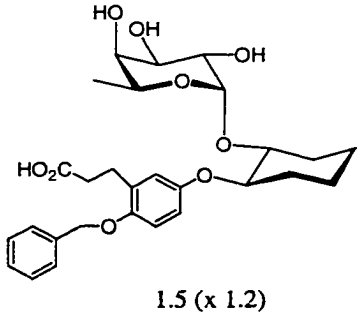
1.2 (~x 1)



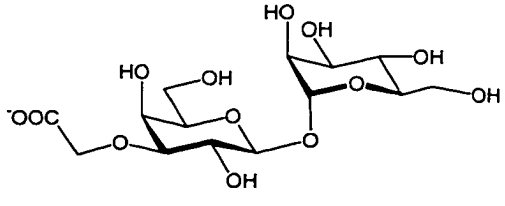
1.3 (~x 10)



1.4 (< 0.05)



1.5 (x 1.2)



1.6 (x 5)

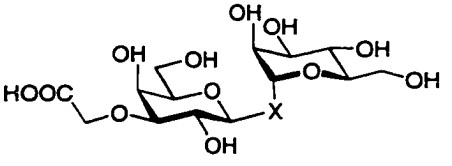
Chapter 2

Synthesis of C-linked disaccharides

2.1 Background

As mentioned earlier, the O-linked 1,1-Gal-Man disaccharide **1.6**[20] was reported to bind E-selectin more strongly than the natural ligand, sLe^x. We were interested in the C-glycoside analogue **2.1** (Figure 2.1), since it is expected to be more flexible about the intersaccharide linkage[22] and this could result in higher binding affinity. In addition, C-glycosides are attractive drug candidates due to their stability to chemical and enzymic hydrolysis.[23]

Figure 2.1 O- and C- Disaccharide as sLe^x Mimetics



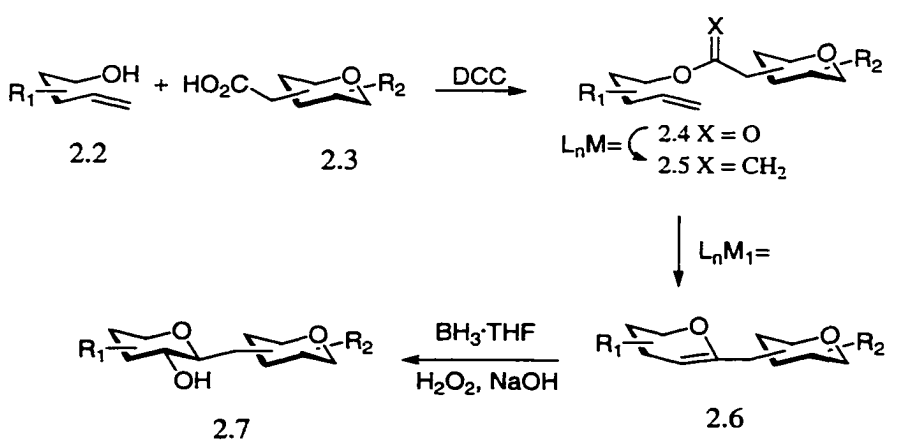
1.6 X = O, O-Glycoside sLe^x Mimetic
2.1 X = CH_2, C-Glycoside sLe^x Mimetic

Conventional approaches[24-26] to C-glycosides with complex aglycone segments involve the addition of C1 nucleophiles to aglycone aldehydes, C1 radicals to activated or tethered aglycone alkenes, and aglycone nucleophiles to C1 electrophiles.[27] These methods are often limited by experimentally difficult or low yielding coupling protocols. Strategies based on C1-nucleophiles with aglycone aldehydes are the most general but only reliable for 2-deoxy and man-α-C-

glycosides. Extension to the *gluco* and *galacto* series is severely hampered by competing elimination of the 2-substituent. 2-Phenyl-sulfinyl-lithio glycals have been used to overcome this drawback, and high yields with complex aldehydes have been obtained. However, the synthesis and handling of these lithio reagents are not trivial, and the conversion of the coupled product to the C-glycoside is somewhat lengthy. A novel approach based on the Ramberg-Bäcklund reaction has recently been described. To date this method has been used for relatively simple aglycone segments, but it shows promise for application to more complex systems.[25b, 25c]

Approaches which involve the cyclization of the sugar ring have also been described. The metathesis-based strategy by Postema[28] is noteworthy. (Scheme 2.1) In this method, DCC mediated coupling of sugar based alcohol **2.2** and sugar acid **2.3** delivered the complex ester **2.4**, which was transformed to an acyclic enol ether **2.5** via a modified Takai procedure. Ring closing metathesis gave the requisite C-disaccharide glycal **2.6** and subsequent hydroboration-oxidation accomplished the

Scheme 2.1



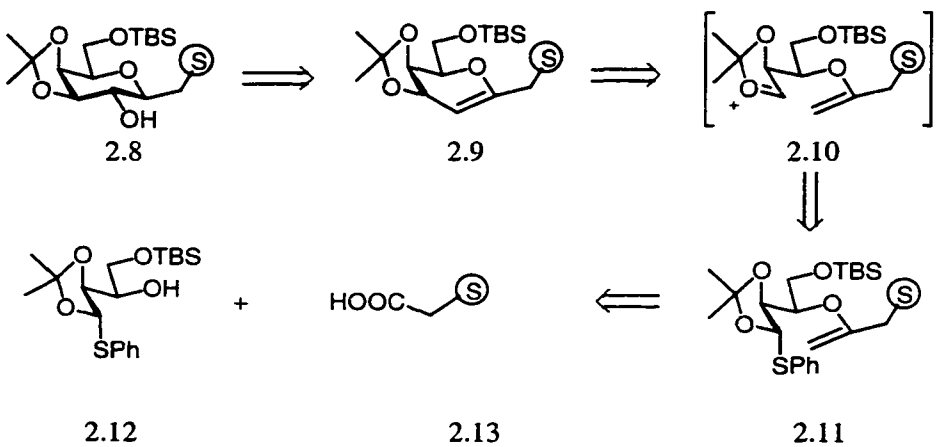
2.2 2.3 2.7 2.6

desired C-disaccharide **2.7** in good yields. β-C-gluco- and β-C-galacto-disaccharides have been published via this protocol.

2.2 Retro-synthesis and model studies

Like the Postema methodology, our approach[29] requires the stereoselective hydroboration of a complex C1-substituted glycal. Our glycal synthesis is, however, different. The glycal **2.9** is formed via an intramolecular oxocarbenium ion-alkene cyclization of acetal-enol ether precursor **2.11**. This idea originated from successes with related dioxolenium ion cyclizations, [30] suggesting that acyclic enol ether **2.11** could be constructed in a convergent fashion from a 1-thio-1, 2-O-isopropylidene acetal (TIA) **2.12** and a carboxylic acid **2.13** (Scheme 2.2).

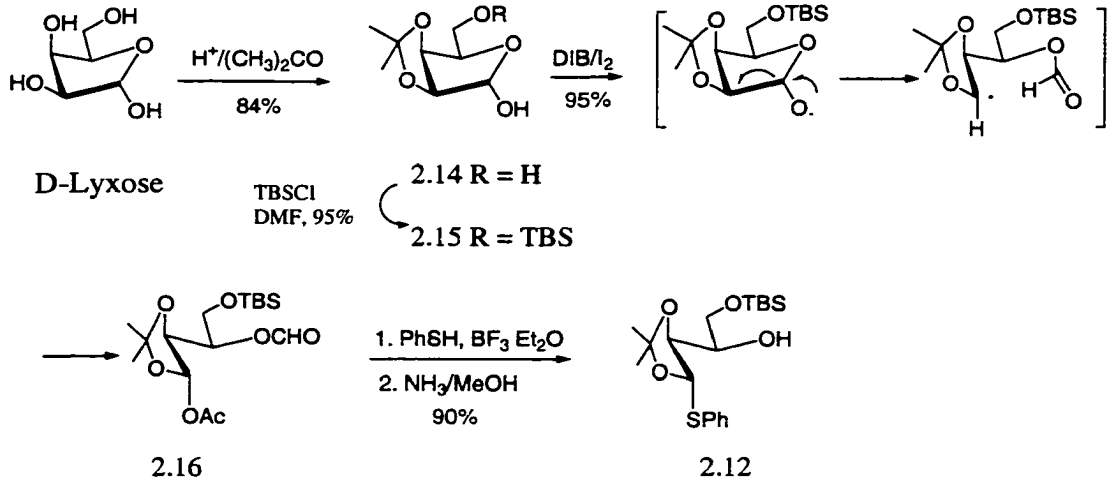
Scheme 2.2



The first goal was the synthesis of the TIA alcohol component **2.12**. The key reaction in this synthesis was the Suarez fragmentation of an anomeric alkoxy radical derived from **2.15**.[31] Acetonation[32] of D-lyxose in the presence of a catalytic

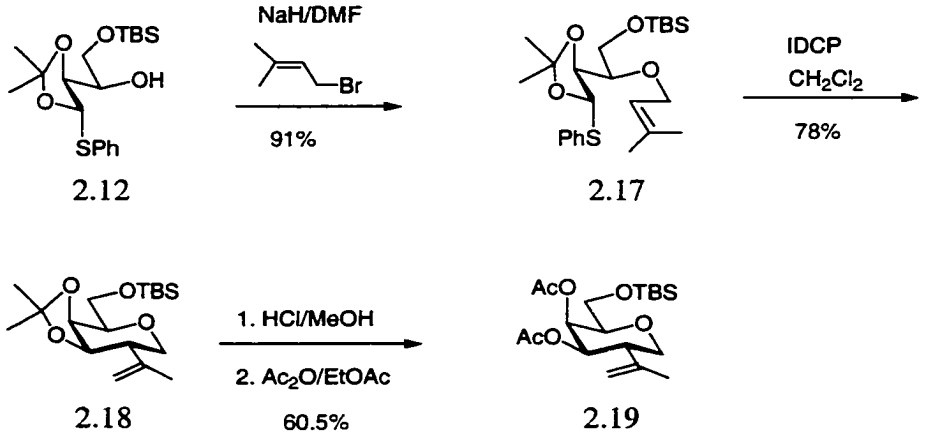
amount of sulfuric acid provided diol **2.14** in 84% yield. Selective silylation of the primary alcohol was achieved by treatment with TBSCl (1.1 eq) at rt for 10 minutes. Reaction of **2.15** with iodobenzene diacetate (DIB) led to formate **2.16** in 95% yield. Acetyl exchange with thiophenyl followed by hydrolysis of the formate accomplished acetal **2.12** in 90%. The overall yield for the conversion of D-lyxose to **2.12** was 65% (Scheme 2.3).

Scheme 2.3



A simple model system was used to test the key oxocarbenium ion cyclization. Allyl ether **2.17** was prepared by alkylation of thioacetal **2.12** with 4-bromo-2-methyl-2-butene. Activation of the thiophenyl group with IDCP yielded **2.18** as the single diastereomer in 78% yield. (Scheme 2.4) The stereochemistry of **2.18** was established by the coupling constants in acetate **2.19** ($J_{1a,\ 2}$ = 11.4, $J_{2,\ 3}$ = 11.4, $J_{3,\ 4}$ = 2.7, $J_{4,\ 5}$ = 2.4 Hz) for vicinal pairs of H_1, H_2 and H_3, H_4. This indicates the isopropenyl substituent was trans to the cis-isopropylidenedioxy residue.

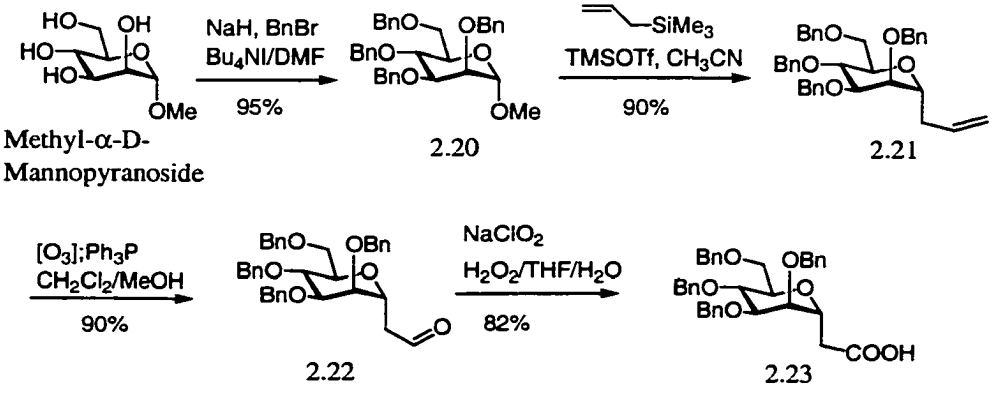
Scheme 2.4



2.3 Synthesis of sLe^x mimetics 2.1

Next we turned to the acid component for C-glycoside **2.1**. Benzylation of the readily available methyl-α-D-mannopyranoside provided benzyl ether **2.20** in 95% yield. Allyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside **2.21** was prepared through a known procedure[33] employing allyltrimethylsilane and trimethylsilyl

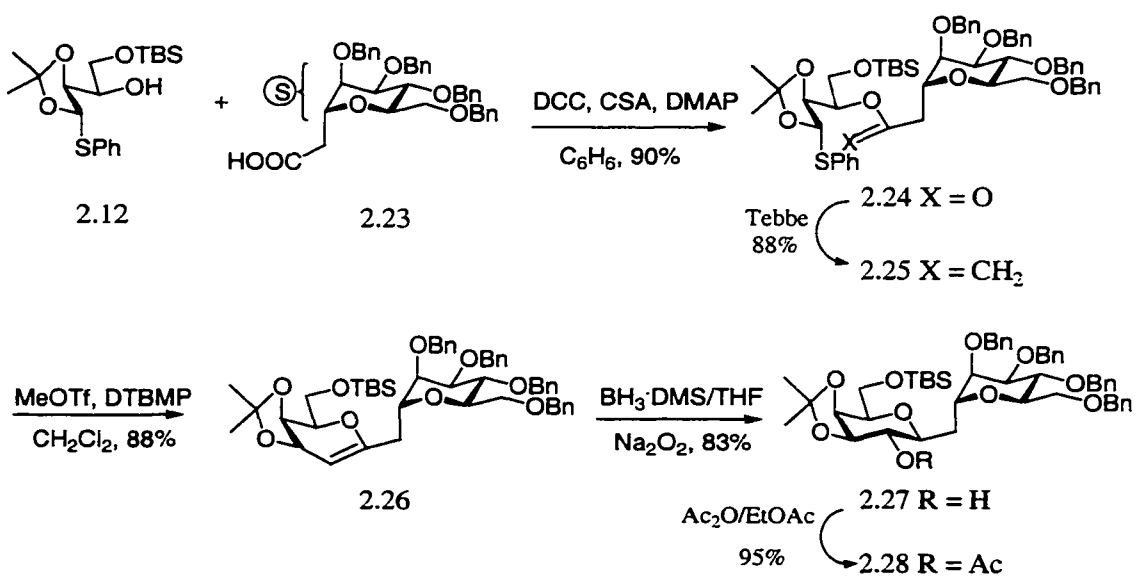
Scheme 2.5



triflate in anhydrous acetonitrile. Ozonolysis of **2.21** in CH_2Cl_2 at –78 °C followed by reductive work up with triphenylphosphine gave the aldehyde **2.22**. Oxidation[34] of the resultant aldehyde **2.22** using sodium chlorite delivered acid **2.23** in 82% yield (Scheme 2.5).

DCC-mediated coupling[35] of **2.12** and **2.23** in the presence of camphorsulfonic acid (CSA) proceeded in excellent yield (90%) to form ester **2.24**. The presence of CSA was found to be important in improving the efficiency of this reaction.[35b] Exposure of the complex ester **2.24** to Tebbe reagent[36] at –78 °C generated the enol ether **2.25** in 88% yield. Methyl triflate promoted cyclization led exclusively to glycal **2.26** as a single stereo- and regioisomer in 88% yield (Scheme 2.6). The efficiency of this reaction is likely due to entropy ring strain effects of the isopropylidene residue in **2.10**.

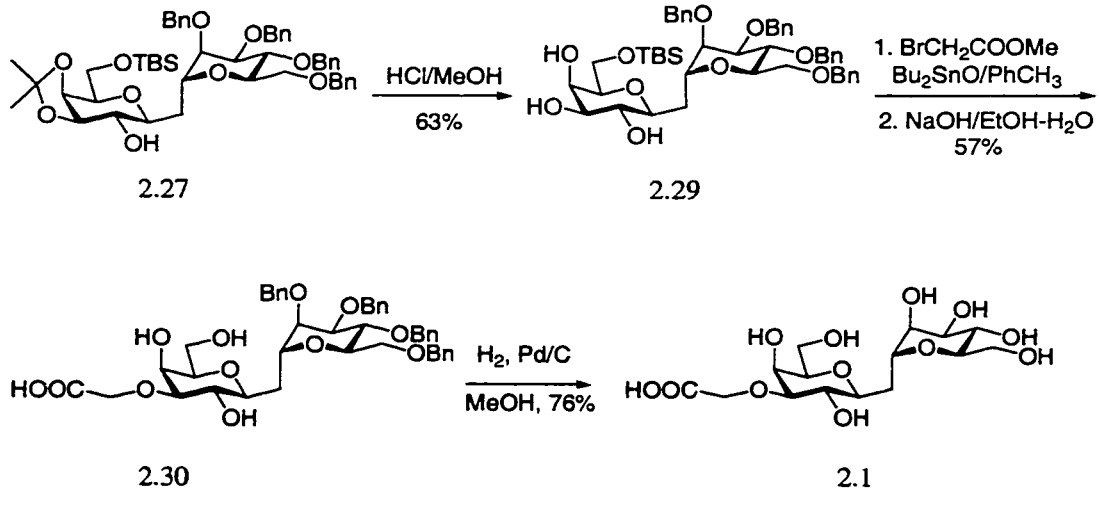
Scheme 2.6



Hydroboration of **2.26** provided the C-glycoside **2.27** as a single diastereomer in 83% yield. The structure of **2.27** was confirmed by ^{1}H COSY analysis of the acetate **2.28**. The coupling constants ($J_{1',2'}$ = 9.2, $J_{2',3'}$ = 7.5, $J_{3',4'}$ = 5.1, and $J_{4',5'}$ = 2.2 Hz) are in agreement with those expected for the 3, 4-O-isopropylidene 1β-galacto residue ($J_{1',2'}$ = 9.9, $J_{2',3'}$ = 7.2, $J_{3',4'}$ = 4.5, and $J_{4',5'}$ = 2.2 Hz).[37]

Alcohol **2.27** was next converted to the target **2.1**. Acidic hydrolysis of **2.27** afforded triol **2.29**, which was subjected to selective alkylation[20] of the 3-OH, using methyl bromoacetate and dibutyltin oxide. Chromatography of the product gave a mixture of two products (1 : 1). The ^{1}H NMR of this mixture did not show the methoxy signals for the expected alkylation product, and it was presumed that the components were the regiosomeric O-2 and O-4 lactone derivatives of **2.30**. Indeed, basic hydrolysis and acidification of the mixture afforded the desilylated acid **2.30** as a single product in 57% overall yield from **2.29**. Exhaustive hydrogenolysis of

Scheme 2.7



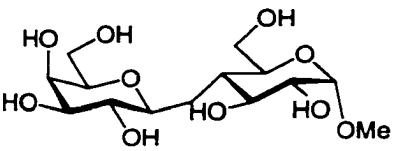
2.27 2.29

2.30 2.1

2.30 provided **2.1** in 76% yield. The identity of **2.1** was confirmed by ^{1}H COSY, ^{13}C NMR and MS (Scheme 2.7).

2.4 Synthesis of C-Lactose Derivative

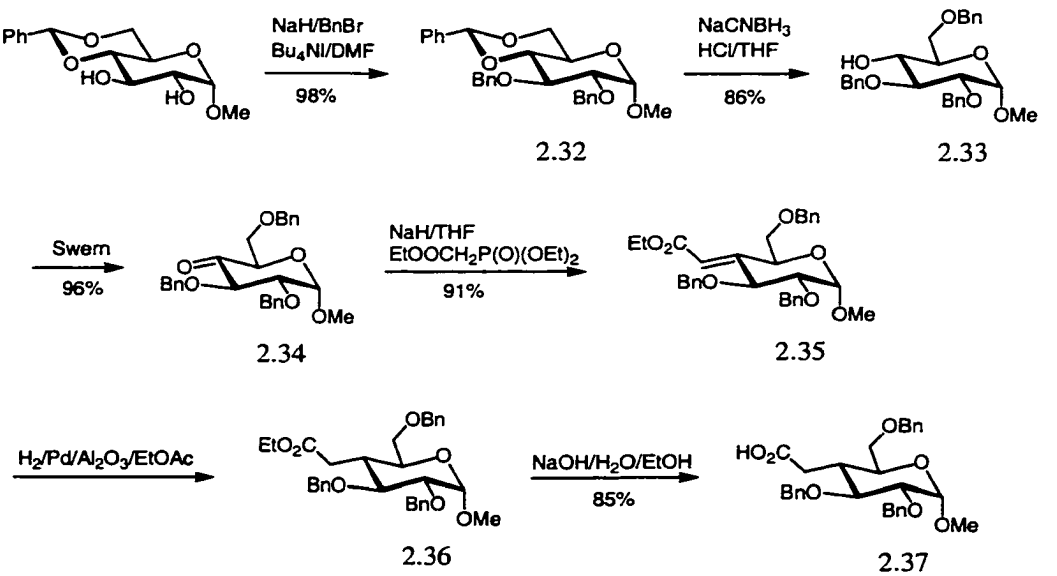
Figure 2.2 C-Lactose



2.31 C-lactose

The above C-glycosidation methodology was also applied to the synthesis of C-lactose **2.31** and other C-disaccharides. The preparation of C-lactose required

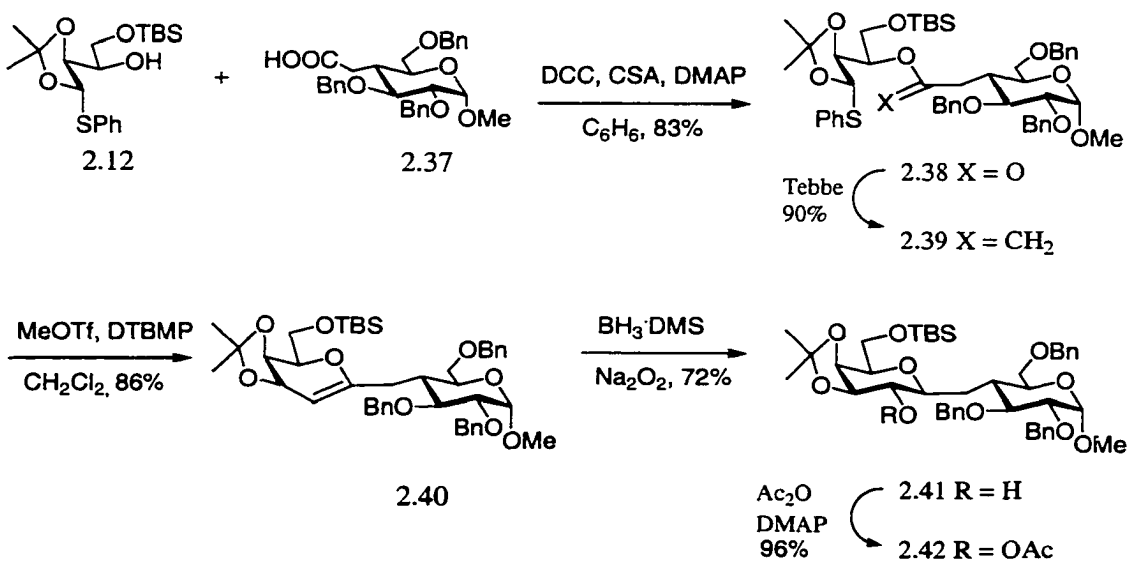
Scheme 2.8



the glucose derived carboxylic acid **2.37**. Standard benzylation on 4,6-benzylidene glucose provided the protected glucose **2.32** in 98% yield. Reaction of benzyl ether **2.32** with sodium cyanoborohydride and hydrochloric acid in anhydrous ether led to alcohol **2.33** in 89% yield. Swern oxidation of alcohol **2.33** was followed by Emmons-Horner reaction of ketone **2.34** to provide α,β unsaturated ester **2.35**. The yields for these reactions were 82% and 91% respectively. Hydrogenation of **2.35** with 5% Pd on alumina in ethyl acetate, and subsequent hydrolysis, furnished the carboxylic acid **2.37** (Scheme 2.8). It should be noted that hydrogenation of **2.35** with palladium on carbon resulted in a mixture of partial debenzylation products.

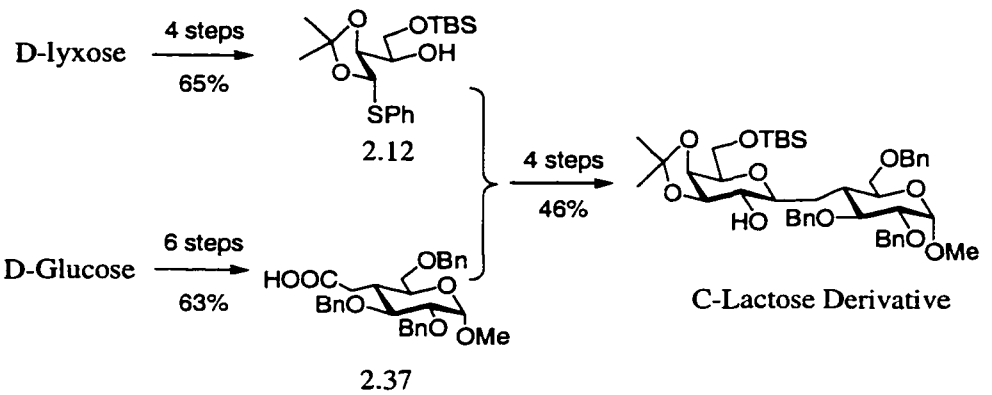
DCC-mediated coupling[35b] of **2.12** and **2.37** afforded ester **2.38** in 83% yield. Tebbe reaction transformed ester **2.38** to enol ether **2.39** in 90% yield.

Scheme 2.9



Treatment of **2.39** with methyl triflate and DTBMP led to glycal **2.40** in 86% yield (Scheme 2.9). Hydroboration of glycal **2.40** with borane-dimethylsulfide and oxidation with sodium peroxide provided C-lactose derivative **2.41** as a single diastereomer in 77% yield. The structure of **2.41** was confirmed by ^{1}H COSY analysis of the acetate **2.42**. The coupling constants ($J_{1',2'}$ = 9.6, $J_{2',3'}$ = 9.0 Hz, $J_{3',4'}$ = 6.0, and $J_{4',5'}$ = 2.2 Hz) are in consistent with the β-galacto configuration.[37]

Scheme 2.10

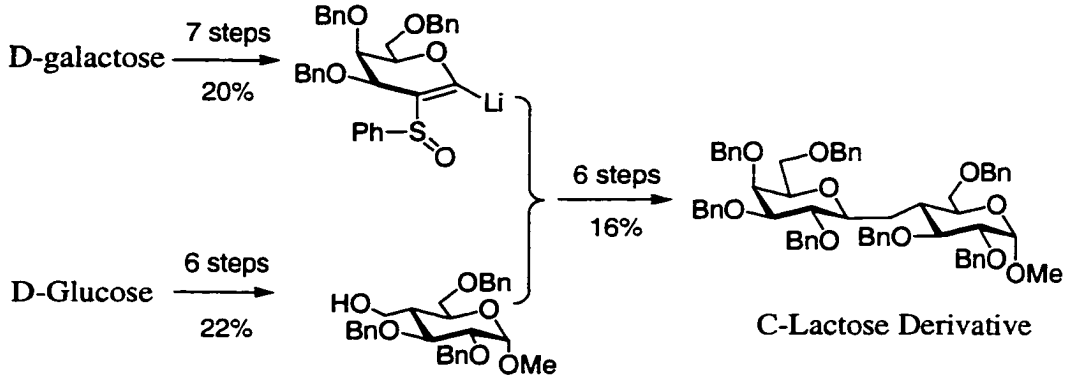


2.5 Conclusion

In summary, TIA **2.12** is a synthon for β-C-galactosides. The acid component may be changed, making this approach general for a variety of C-galactosides. The good overall coupling yield and the high stereoselectivity are attractive features. This method compares favorably with the approaches[38] for C-disaccharides. By using this methodology, a total of 14 steps were taken to accomplish the synthesis of the protected C-lactose, in a total of 29% yield.

(Scheme 2.10) While a total of 19 steps, were taken in Schmidt's synthesis, in a total of 3% yield (Scheme 2.11).

Scheme 2.11



2.6 Experimental section

General Experimental-Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in oven dried flasks. Dry THF and diethyl ether were distilled from potassium and sodium benzophenone ketyl respectively. Dry methylene chloride was distilled from phosphorus pentoxide. Dry DMF, acetonitrile, pyridine and Et_3N were distilled from calcium hydride. Dry acetone was distilled from calcium sulfate, and dry methanol from magnesium. Benzene and toluene were dried by azeotropic removal of water.

^1H and ^{13}C NMR spectra were obtained using a GE QE 300 (300 MHz), JEOL 400 (400 MHz) or Unity Plus 500 (500 MHz) spectrometer. Chemical shifts are reported relative to the deuterated solvent peak or the TMS peak (0.00 ppm).

The following format was used to report peaks: chemical shifts in ppm (on the δ scale relative to TMS), multiplicity (b=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant (J, in Hz), and number of protons.

Infrared (IR) spectra were obtained on a Perkin-Elmer 710B and reported in cm^{-1}. High resolution mass spectrometry data (HRFABMS) was performed on 70-4F spectrometer at University of Illinois, Chicago. Optical rotations were recorded on a Rudolph Research AUTOPOL III automatic polarimeter and were determined in solutions of chloroform, unless otherwise stated. Thin-layer chromatograms (TLC) were performed on silica gel 60 HF_{254} (E, Merck) and short and long-wave ultraviolet was used to visualize the spots. Unless otherwise stated, silica gel 60 (230-400 mesh) was used for flash column chromatography (FCC).

2,3-O-Isopropylidene D-lyxofuranose 2.14

To a solution of D-lyxose (5 g, 0.034 mmol) was added conc. sulfuric acid (0.2 mL) under an argon atmosphere. The reaction mixture was stirred at rt for 2.5 hr, at which time calcium hydroxide (1.84 g) was added. The suspension was then filtered and the filtrate was concentrated under reduced pressure. The residue was purified by FCC to give **2.14** (5.9 g, 84%): colorless oil; R_f = 0.20 (ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 1.30, 1.52 (both s, 3H ea), 2.47 (m, 1H, -OH), 3.18 (br s, 1H), 3.95 (m, 2H), 4.28 (dt, 1H), 4.67 (dd, J = 2.0, 4.1 Hz, 1H), 4.81 (dd, J = 1.8, 4.4 Hz, 1H), 5.45 (d, J = 2.0 Hz, 1H).

5-O-*tert*-Butyl diphenyl silyl-2, 3-O-isopropylidene-O-lyxofuranose 2.15

A solution of 2,3-O-isopropylidene-D-lyxofuranose **2.14** (2.7 g, 14 mmol), TBDPSCl (3.7 mL, 14 mmol), imidazole (1.9 g, 28 mmol) in anhydrous DMF (25 mL) was stirred at RT for 20 min. The reaction mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give **2.15** (5.7 g, 95%): colorless oil; R_f = 0.20 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.26, 1.35 (both s, 3H ea), 3.94 (m, 2H), 4.33 (m, 1H), 4.58 (d, J = 7.0 Hz, 1H), 4.75 (m, 1H), 5.35 (s, 1H), 7.38, 7.70 (both m, 10H).

1-O-Acetate-1, 2-O-isopropylidene formate 2.16

A solution of **2.15** (9.5 g, 21.6 mmol) in anhydrous cyclohexane (120 mL) containing diacetoxyiodobenzene (8.54 g, 26.5 mmol) and iodine (5.89 g, 23.2 mmol), was stirred under an atmosphere of argon, at rt for 3h. The reaction mixture was then diluted with water and extracted with ether. The organic phase was washed with aqueous $Na_2S_2O_3$ and brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give **2.16** (10.0 g, 95%): clear oil; R_f = 0.45 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.46, 1.505 (both s, 3H ea), 2.10 (s, 3H), 3.82 (m, 2H), 4.51 (m, 1H), 4.58 (d, J = 7.0 Hz, 1H), 5.25 (m, 1H), 6.21 (d, J = 1.5 Hz, 1H), 7.40, 7.60 (both m, 10H), 8.05 (s, 1H); ESMS 509 (M + Na).

1-Thio-1, 2-isopropylidene Acetal 2.12

$BF_3 \cdot OEt_2$ (1.3 mL, 12.4 mmol) was slowly added to a solution of **2.16** (5 g, 10.3 mmol) and thiophenol (2.12 mL, 20.6 mmol) in anhydrous CH_2Cl_2 (50 mL), at -78°C under an atmosphere of argon. The reaction mixture was warmed to -40°C and stirred at this temperature for 1h, or until TLC indicated complete disappearance of the starting material. Triethylamine (5 mL) was then added and the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The organic phase was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude material was dissolved in methanolic ammonia (100 mL) and stirred at rt for 30 min. Most of the solvent was removed under reduced pressure and the residue diluted with water, and extracted with ether. The organic phase was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. FCC of the residue provided **2.12** (4.7 g, 90%); colorless oil; R_f = 0.50 (10% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.47, 1.49 (both s, 6H), 2.32 (br s, 1H, D_2O ex), 3.80 (m, 3H), 4.18 (dd, J = 2.0, 7.0 Hz, 1H), 5.44 (d, J = 7.0 Hz), 7.20-7.80 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 26.3, 27.1, 27.5, 65.3, 70.1, 80.4, 85.4, 111.5, 127.6, 127.9, 129.1, 129.9, 132.0, 133.3, 134.0, 135.7; ESMS 531 (M + Na); FABHRMS: calcd for $C_{23}H_{31}O_4Si$ (M-SC_6H_5) 399.1992, found 399.1992.

Thioacetal alkene 2.17

To a solution of thioacetal **2.12** (100 mg, 0.2 mmol) in anhydrous THF (2 mL) was added sodium hydride (32 mg, 0.8 mmol) at rt, under an atmosphere of argon. The reaction mixture was stirred at rt for 20 min. 4-Bromo-2-methyl-2-butene (0.14 mL, 1.2 mmol) was then added and stirring continued for an additional 0.5 h at rt. Water was then carefully added and the mixture was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give **2.17** (113 mg, 91%): colorless oil; R_f = 0.25 (15% ethyl acetate:petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.50, 1.52, 1.60, 1.69 (all s, 12H), 3.51 (m, 1H), 3.80 (m, 2H), 3.95 (dd, J = 9.8, 10.6 Hz, 1H), 4.09 (dd, J = 8.8, 11.6 Hz, 1H), 4.20 (dd, J = 3.2, 7.8 Hz, 1H), 5.21 (br t, 8.8 Hz, 1H), 5.38 (d, J = 7.8 Hz, 1H) 7.35-8.05 (m, 10H); ESMS 599 (M + Na).

Tetrahydropyran 2.18

To a mixture of **2.17** (113 mg, 0.2 mmol), and freshly activated, powdered 4A molecular sieves (200 mg) in anhydrous CH_2Cl_2 (5 mL), was added IDCP (277 mg, 0.6 mmol); The reaction mixture was stirred at rt for 20 min, and was then diluted with ether. The mixture was filtered, and the filtrate was washed with saturated, aqueous $Na_2S_2O_3$ solution and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by FCC to give **2.18** (82 mg, 78%): clear oil; R_f = 0.75 (2% ethyl ether: dichloromethane); ^1H NMR

(400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.29, 1.42, 1.61 (all s, 9H), 2.49 (ddd, J = 4.4, 11.2, 15.6 Hz, 1H), 2.90 (t, J = 11.2 Hz, 1H), 3.67 (dt, J = 6.4 Hz, 1H), 3.76 (dd, J = 4.4, 11.2 Hz, 1H), 3.81 (dd, J = 7.2, 10.0 Hz, 1H), 4.04 (dd, J = 3.6, 7.2 Hz, 1H), 4.20 (m, 2H), 4.68 (s, 1H), 4.82 (s, 1H), 7.3 (m, 8H), 7.82 (m, 2H).

Diacetate 2.19

To a solution of **2.18** (50mg, 0.11mmol) in dry methanol (3 mL) was added HCl (0.2 mL, 1M solution in ether, 0.2 mmol). The reaction mixture was stirred at room temperature for 20 min, and then neutralized by addition of sodium methoxide. Removal of the volatiles under reduced pressure and the crude material was treated with acetic anhydride (0.1 mL, 1.0 mmol), DMAP (5 mg, 0.04 mmol) in ethyl acetate. The reaction mixture was stirred at rt for 20 min, and methanol (1 mL) was added. Removal of the volatiles under reduced pressure and FCC of the residue provided **2.19** (30 mg, 60.5%): clear oil; R_f = 0.5 (50% ethyl acetate:petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.50, 1.68, 1.79 (all s, 9H), 2.89 (ddd, J = 4.4, 11.4, 15.6 Hz, 1H), 3.00 (t, J = 11.4 Hz, 1H), 3.50 (t, J = 6.4 Hz, 1H), 3.76 (dd, J = 4.4, 11.2 Hz, 1H), 3.83 (dd, J = 7.2, 10.0 Hz, 1H), 3.94 (dd, J = 7.2, 10.0 Hz, 1H), 4.76 (m, 2H), 5.22 (dd, J = 2.7, 11.4 Hz, 1H), 5.84 (d, J = 2.4 Hz, 1H), 7.3 (m, 8H), 7.82 (m, 2H).

2,3,4,6-Tetra-O-benzyl-methyl-α-D-mannopyranoside 2.20

To a solution of methyl-α-D-mannopyranoside (5.0 g, 25.8 mmol) in dry DMF (50 mL) at 0 °C was added NaH (5.15 g, 60% in mineral oil, 0.13 mol) and Bu_4NI (0.95 g, 0.26 mmol), followed by BnBr (0.13 mol, 15.3 mL). The reaction mixture was stirred for 0.5 h at rt under argon atmosphere. The reaction was quenched with H_2O, and extracted with ether (2 x 50 mL). The organic layer was washed with H_2O (10 x 5 mL), dried (Na_2SO_4) and then concentrated in *vacuo*. The residue was purified by FCC to give **2.20** (13.6 g, 95%): clear oil; TLC R_f = 0.80 (15% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 3.3 (s, 3H), 3.8 (m, 6H), 4.7 (m, 9H), 7.4 (m, 20H).

1-C-allyl manno-D-α-pyranoside 2.21

A solution of **2.20** (11.2 g, 20.2 mmol) and allyltrimethylsilane (6.5 mL, 40.5 mmol) in anhydrous acetonitrile (50 mL) was added trimethylsilyl triflate (1.8 mL, 10.1 mmol) dropwise at 0°C under an atmosphere of argon. The solution was then warmed up to rt and stirred for additional 16h. The resulting deep-orange solution was diluted with CH_2Cl_2 (250 mL) and quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give **2.21** (9.4 g, 90%): colorless oil; R_f = 0.20 (5% ethyl acetate:petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 2.38-2.29 (m, 2H), 3.62 (dd, J = 3.5, 4.6 Hz, 1H), 3.70 (dd, J = 3.5, 10.3 Hz, 1H), 3.85 (m, 2H), 3.82 (m, 1H), 3.87 (dd, J = 6.8, 13.0 Hz, 1H), 4.05 (ddd, J = 4.8, 6.2, 7.8 Hz, 1H),

4.51-4.61 (m, 7H), 4.70 (d, J = 11.3 Hz, 1H), 5.00-5.03 (m, 2H), 5.75 (m, 1H), 7.18-7.34 (m, 20H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 34.6, 69.1, 71.5, 72.2, 72.3, 73.2, 73.6, 73.9, 74.8, 75.1, 76.9, 117.2, 127.4, 127.6, 127.8, 128.0, 128.1, 128.3, 134.3, 138.2, 138.4.

Aldehyde 2.22

A solution of allyl mannoside **2.21** (2.0 g, 3.5 mmol) in 5:1 CH_2Cl_2:MeOH (60 mL) was cooled to -78 °C. A stream of O_3 in O_2 was bubbled through the solution until the starting material was not detectable by TLC (20% ethyl acetate:petroleum ether). The mixture was flushed with argon and then triphenylphosphine (1.0 g, 4.2 mmol) was added. The solution was warmed to rt, stirred for 2 h, and concentrated in *vacuo*. The residue was purified by FCC to give the aldehyde **2.22** (1.8 g, 89.7%): clear oil; R_f = 0.1 (20% ethyl acetate:petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (ddd, J = 2.5, 8.0, 16.4 Hz, 1H), 2.68 (ddd, J = 2.0, 5.0, 16.4 Hz, 1H), 3.60 (dd, J = 7.8, 2.1 Hz, 1H), 3.71 (dd, J = 5.5, 10.1 Hz, 1H), 3.78 (m, 2H), 3.83 (dd, J = 6.7, 10.1 Hz, 1H), 3.99 (m, 1H), 5.00-5.03 (m, 9H), 7.18-7.34 (m, 20H), 9.97 (s, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 45.5, 66.1, 68.1, 71.3, 72.4, 73.2, 73.9, 74.1, 74.4, 75.6, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 137.6, 137.8, 137.9, 138.2, 200.6.

Acid 2.23

A solution of aldehyde **2.22** (1.8 g, 3.2 mmol) in acetone (50 mL) was cooled to 0 °C. Jones reagent (20 mL, 0.32 M, 6.4 mmol) was added dropwise to the solution. The reaction mixture was diluted with brine and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by FCC to give acid **2.23** (1.5 g, 82%): clear oil; R_f = 0.45 (40% ethyl acetate:petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (dd, J = 9.2, 20.2 Hz, 1H), 2.82 (dd, J = 8.0, 20.2 Hz, 1H), 3.54 (dd, J = 9.0, 20.2 Hz, 1H), 3.62 (m, 2H), 3.78 (m, 1H), 3.92 (t, J = 12.1 Hz, 1H), 4.1 (m, 1H), 4.30 (m, 1 H), 4.46 (m, 8H), 7.2 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.3, 68.3, 68.4, 71.4, 72.3, 73.4, 74.5, 127.6, 127.8, 127.9, 127.9, 128.0, 128.1, 128.4, 128.4, 128.5, 128.5, 128.7, 131.8, 132.1, 132.3, 132.8, 138.1, 138.2, 173.4; FAB HRMS calcd for $C_{36}H_{38}O_7$ (M + Na) 605.2515, found 605.2512.

Thioacetal Ester 2.24

DCC (1.2 g, 5.15 mmol) was added at 0 °C to a solution of alcohol **2.12** (2 g, 3.94 mmol), acid **2.23** (2.2 g, 3.94 mmol) and DMAP (48.3 mg, 0.40 mmol), CSA (96.6 mg, 0.4 mmol) in anhydrous benzene (80 mL). The reaction mixture was warmed to rt and stirred for 1.5 h. The mixture was then diluted with ether (15 mL) and filtered. The filtrate was washed with 0.1N aqueous HCl and brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give **2.24** (3.8 g, 90%): colorless oil; R_f = 0.60 (15% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.38, 1.40

(both s, 6H), 2.52 (dd, J = 8.0, 14.0 Hz, 1H), 2.65 (dd, J = 4.8, 14.0 Hz, 2H), 3.63 (m, 2H), 3.75 (m, 4H), 3.86 (m, 1H), 4.20-4.60 (m, 11H), 5.24 (m, 1H), 5.30 (d, J = 6.6 Hz, 1H), 7.10-7.70 (m, 35H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 27.2, 27.7, 28.1, 37.3, 63.0, 69.6, 69.7, 72.2, 72.6, 72.9, 73.9, 74.1, 75.0, 76.3, 76.4, 80.0, 85.7, 112.3, 128.2, 128.4, 128.5, 128.7, 129.0, 129.1, 129.7, 130.5, 133.4, 133.7, 133.8, 134.2, 136.3, 136.4, 138.7, 138.8, 139.0, 139.3, 170.8; FABHRMS calcd for $C_{65}H_{72}O_{10}SSiNa$ (M + Na) 1095.4513, found 1095.4514.

Thioacetal Enol Ether 2.25

A solution of Tebbe reagent in THF (15.3 mL, 0.5M, 7.65 mmol) was added dropwise, under an argon atmosphere, at -78 °C, to the ester **2.24** (4.1 g, 3.8 mmol) and pyridine (0.3 mL), in anhydrous 3:1 toluene:THF (10 mL). The reaction mixture was warmed to rt and stirred at this temperature for 1 h, or until TLC indicated complete disappearance of the starting material. The reaction mixture was then slowly poured into a solution of 1N aqueous NaOH at 0 °C, and the resulting suspension extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue on basic alumina provided enol ether **2.25** (3.6 g, 88%): colorless oil; R_f = 0.65 (15% ethyl acetate:petroleum ether); $[\alpha]_D$ = 22 (c = 1.44, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.38, 1.44 (both s, 6H), 2.20 (dd, J = 6.4, 14.3 Hz, 1H), 2.34 (dd, J = 8.4, 14.3 Hz, 1H), 3.54-3.94 (m, 10H), 4.19 (m, 1H), 4.38-4.55 (m, 8H), 4.77 (d, J = 9.8 Hz, 1H), 5.45 (d, J = 7.0 Hz, 1H),

7.3 (m, 35H); ^{13}C NMR (75 MHz, C_6D_6) δ 19.9, 27.1, 27.6, 28.1, 36.8, 62.4, 70.8, 71.7, 72.3, 72.4, 74.1, 74.7, 74.8, 75.4, 76.1, 77.2, 79.3, 80.9, 85.3, 112.3, 127.8, 128.2, 129.5, 130.4, 130.5, 132.7, 133.8, 134.0, 135.0, 136.4, 139.6, 139.7, 139.9, 140.1, 159.0; FABHRMS calcd for $C_{66}H_{74}O_9SSiNa$ (M + Na) 1093.4721, found 1093.4719.

Glycal 2.26

Enol ether **2.25** (3.6 g, 3.36 mmol), 2,6-di-tert-butyl-4-methylpyridine (6.3 g, 40.3 mmol), and freshly activated, powdered 4A molecular sieves (300 mg) in anhydrous CH_2Cl_2 (100 mL), was stirred for 15 min, at rt, under an argon atmosphere, then cooled to 0 °C. Methyl triflate (3.73 mL, 33.6 mmol) was then introduced, and the mixture was warmed to rt, and stirred for an additional 18 h, at which time, triethylamine (5 mL) was added. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC of the residue on basic alumina (Brockmann I, 150 mesh) provided **2.26** (2.8 g, 88%): clear oil; R_f = 0.55 (15% ethyl acetate:petroleum ether); $[\alpha]_D$ 18 (c = 1.3, $CHCl_3$); IR (neat) 1689, 1682 cm^{-1} ^1H NMR (400 MHz, C_6D_6) δ 1.18 (s, 9H), 1.35, 1.54 (both s, 6H), 2.25 (m, 2H), 3.74 (dd, J = 2.9, 4.0 Hz, 1H), 3.8 (dd, J = 2.9, 7.7 Hz, 1H), 3.90 (m, 4H), 4.14 (m, 2H), 4.21 (t, J = 7.3 Hz, 1H), 4.29 (d, J = 6.2 Hz, 1H), 4.42-4.58 (m, 9H), 4.64 (d, J = 2.6 Hz, 1H), 4.74 (apparent d, J = 12 Hz, 1H), 7.00-7.40 (m, 26H), 7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 27.0, 25.5, 35.0, 63.0, 69.6, 69.7, 71.4, 71.6,

71.7, 72.1, 73.6, 74.0, 74.1, 75.1, 75.4, 75.7, 76.8, 100.0, 110.2, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 128.5, 130.0, 135.7, 135.8, 138.5, 138.6, 152.5; FABHRMS calcd for $C_{60}H_{69}O_9Si$ (M + H) 961.4711, found 961.4708.

Alcohol 2.27

$BH_3{\cdot}Me_2S$ (10 mL, 1M solution in CH_2Cl_2, 10 mmol) was added at 0 °C to a solution of glycal **2.26** (180 mg, 0.27 mmol) in anhydrous THF (50 mL) under an atmosphere of argon. The mixture was warmed to rt and stirred for an additional 1 h, or until TLC indicated complete disappearance of the starting material. At that time the solution was recooled to 0 °C and treated with a mixture of 3N NaOH (10 mL) and 30% aqueous H_2O_2 (10 mL) for 30 min. The solution was then diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC of the residue provided **2.27** (2 g, 83%): white solid; R_f = 0.30 (15% ethyl acetate:petroleum ether); $[\alpha]_D$ 23 (c = 2.1, $CHCl_3$); IR (neat) 3391 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.41, 1.58 (both s, 6H), 1.56 (m, buried under s at δ 1.58), 2.22 (m, 1H), 3.19 (m, 1H), 3.56 (m, 2H), 3.64-4.22 (m, 9H), 4.12 (d, J = 5.5 Hz, 1H, D_2O ex), 4.36 (d, J = 5.5 Hz, 1H), 4.42-4.84 (m, 9H) 7.10-7.85 (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 27.3, 27.6, 29.3, 30.4, 63.7, 70.2, 70.5, 72.2, 72.5, 72.9, 73.6, 74.1, 74.6, 74.9, 76.1, 76.9, 77.6, 77.8, 78.9, 80.7, 109.9, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 129.1, 130.2, 134.2, 134.4, 136.2, 136.3, 136.4, 138.3, 138.8, 138.9; FABHRMS: calcd for $C_{60}H_{71}O_{10}Si$ (M + H) 979.4817, found 979.4818.

Acetate 2.28

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.28, 1.61 (both s, 6H), 1.70 (s, 3H), 2.08 (m, 1H), 3.58 (dt, J = 4.8, 9.4 Hz, 1H), 3.73 (dd, J = 2.6, 5.5 Hz, 1H), 3.76-3.92 (m, 4H), 3.98 (dd, J = 5.1, 7.3 Hz, 1H), 4.08 (m, 3H), 4.17 (dd, J = 7.7, 9.5 Hz, 1H), 4.20 (dd, J = 2.2, 5.1 Hz, 1H), 4.34-4.54 (m, 8H), 4.59 (apparent d, J = 12.1 Hz, 1H), 5.38 (dd, J = 7.7, 9.2 Hz, 1H), 7.10-7.90 (m, 26H), 7.82 (m, 4H)

Triol 2.29

A solution of 1M HCl in ether (3 mL) was added to a solution of **2.27** (500 mg, 0.51 mmol) in dry methanol (50 mL). The reaction mixture was stirred at rt for 20 min, and then neutralized by addition of sodium methoxide. Removal of the volatiles under reduced pressure and FCC of the residue provided **2.29** (300 mg, 62.6%): clear oil; R_f = 0.5 (50% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.39 (br d, J = 14 Hz, 1H), 2.20 (m, partially hidden under br s at δ 2.24, 1H), 2.24 (br s, 1H, D_2O, ex), 2.52 (br s, 1H, D_2O, ex), 3.17 (m, 1H), 3.31 (br d, J = 9.2Hz, 1H), 3.45 (t, J = 5.5 Hz, 1H), 3.51 (br s, 1H), 3.65 (m, 3H), 3.72-3.98 (m, 5H), 4.1 (m, 2H, D_2O, ex 1H), 4.40-4.70 (m, 8H), 4.80 (apparent d, J = 11.1 Hz, 1H), 7.15-7.55 (m, 26H), 7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 27.5, 27.6, 29.9, 61.1, 64.1, 69.7, 69.9, 70.6, 70.7, 70.8, 71.0, 72.5, 72.6, 72.7, 72.8, 73.0, 73.3, 73.4, 74.4, 75.0, 75.7, 75.9, 76.1, 76.3, 76.5, 76.6, 78.2, 78.5, 78.9, 79.2, 128.2, 128.3, 128.5, 128.6, 128.7, 128.9, 129.1, 129.1, 129.3,

129.4, 129.5, 130.3, 133.9, 134.2, 136.2, 136.3, 136.6, 136.7, 138.0, 138.8; ESMS 961.5 (M + Na).

Acid 2.30

A mixture of triol **2.29** (130 mg, 0.14 mmol), dibutyltin oxide (32 mg, 0.14 mmol) was refluxed in dry toluene in a Dean-Stark apparatus for 1hr. The solvent was evaporated in *vacuo*, and the residue was dissolved in dry toluene (3 mL), and then refluxed with n-Bu_4NI (40 mg, 0.14 mmol) and methyl 2-bromo acetate (0.1 mL, 0.42 mmol) for 1hr. The volatiles were then removed under reduced pressure to give a brown syrup. Partial purification of this material by FCC provided an approximately 1:1 mixture (100 mg) of two components: clear oil; TLC, R_f = 0.35, 0.45 (30% ethyl acetate:petroleum ether).

The mixture obtained in the previous step was treated with a 1:1 mixture of aqueous 3 N NaOH/ethanol (2 mL). After 1 hr, the reaction mixture was neutralized with aqueous 2 N HCl. The solvent was then removed under reduced pressure, and the residue was purified by FCC to give **2.30** (60 mg, 57% from **2.29**): clear oil; R_f = 0.2 (30% methanol:ethyl acetate); IR (neat), 3368, 1729 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.86 (m, 1H), 2.14 (m, 1H), 3.14 (br t, J = 7.0 Hz, 1H), 3.30 (m, 1H), 3.38 (t, J = 6.5 Hz, 1H), 3.64-3.86 (m, 9H), 4.08 (d, J = 3.0 Hz, 1H), 4.19 (ABq, Δδ = 0.13 ppm, J = 14.4 Hz, 2H), 4.36 (m, 1H), 4.45-4.58 (m, 6H), 4.63, 4.72 (both apparent d, J = 12.0, 11.0 Hz resp, 1H ea), 7.30 (m, 20H); ^{13}C NMR (75 MHz, CD_3OD): 35.0, 64.9, 70.4, 72.4, 73.3, 74.3, 74.5, 74.9, 76.2, 76.6,

77.1, 78.1, 78.9, 80.7, 81.3, 81.4, 87.0, 87.3, 130.4, 130.9, 131.1, 141.2, 141.4, 141.5, 179.5; FABHRMS calcd for $C_{48}H_{50}O_{12}Na$ (M + Na) 781.3200, found 781.3202.

Compound 2.1

A mixture of acid **2.30** (35 mg, 0.05 mmol), 20% Pd on carbon (35 mg), formic acid (0.1 mL) in methanol (2 mL) was stirred under an atmosphere of hydrogen (balloon) for 12 hour. The mixture was then purged with argon and filtered through a bed of celite. The filtrate was concentrated in *vacuo*, and the residue was purified by Sephadex LH-20 chromatography (H_2O) and lyophilized to give **2.1** (14 mg, 76.2%): white powder; $[\alpha]_D$ 57 (c = 0.8, Methanol : H_2O = 1:1) ^1H NMR (400 MHz, D_2O) δ 1.9 (dt, J = 7.5, 15.0 Hz, 1H), 2.11 (ddd, J = 1.5, 7.5, 15.0 Hz, 1H), 3.31 (dt, J = 3.0, 8.0 Hz, 1H), 3.4(dt, J = 3.0, 9.5 Hz, 1H), 3.53-3.74 (m, 7H), 3.79 (m, 2H), 3.91 (br s, 1H), 4.08 (d, J = 3.0 Hz, 1H), 4.11 (ABq, J = 12.0 Hz, Δδ = 0.04 ppm, 2H), 4.19 (t, J = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.1, 64.7, 65.0, 69.4, 70.8, 71.6, 73.2, 73.9, 74.3, 77.5, 79.0, 80.8, 81.7, 86.6 ESMS 421 (M + Na).

Benzyl ether 2.32

Methyl-4,6-O-benzylidene-Glucopyranoside (3.0 g, 10.6 mmol) was subjected to the standard benzylation procedure as detailed in preparation of **2.20**. FCC purification of the product provided benzyl ether **2.32** (4.8 g, 98%): clear oil;

R_f = 0.80 (30% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 3H), 3.58 (dd, J = 3.0, 7.1 Hz, 1H), 3.65 (ABq, J = 11.7 Hz, Δδ = 0.13 ppm, 2H), 3.85 (dd, J = 4.0, 9.0 Hz, 1H), 4.09 (t, J = 9.0, 18.1 Hz, 1H), 4.31 (dd, J = 4.1, 9.2 Hz, 1H), 4.68 (d, J = 4.1 Hz, 1H), 4.71-4.98 (m, 4H), 5.58 (s, 1H), 7.4 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 62.5, 69.2, 73.9, 75.5, 78.7, 79.4, 82.3, 99.3, 101.3, 126.1, 127.6, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.9.

Alcohol 2.33

To a mixture of benzyl ether **2.32** (4.8 g, 0.01 mol), freshly activated, powdered molecular sieves, $NaCNBH_3$ (10.32 g, 0.16 mol) in anhydrous THF (100 mL) was added a saturated solution of hydrogen chloride in anhydrous ether until the evolution of gas has ceased. (~pH 3). The reaction mixture was diluted with CH_2Cl_2, filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by FCC to give alcohol **2.33** (4.1g, 86%): clear oil; R_f = 0.40 (20% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.55 (dd, J = 3.1, 10.2Hz, 1H), 3.65 (br d, 1H), 3.68 (m, 3H), 3.79 (t, J = 11.2 Hz, 1H), 4.52-5.0 (m, 7H), 7.4 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 55.4, 69.5, 69.7, 70.1, 70.7, 70.8, 70.8, 70.9, 71.0, 73.7, 75.5, 79.8, 81.6, 98.3, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 138.1, 138.8, 138.9.

Ketone 2.34

To a solution of oxalyl chloride (4.5 mL, 0.05 mol) in CH_2Cl_2 (30 mL) at – 78 °C was added DMSO (4.25 mL, 0.06 mol) dropwise. The mixture was stirred for 20 min at this temperature and then a solution of alcohol **2.33** (4.8 g, 0.01 mol) in CH_2Cl_2 (20 mL) was slowly introduced. After stirring at this temperature for an additional 20 min, Et_3N (14.6 mL, 0.1 mol) was added, the solution was warmed up to rt, and then poured into saturated aqueous $NaHCO_3$. The mixture was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC to give ketone **2.34** (4.6 g, 96%): clear oil; R_f = 0.4 (15% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 3.48 (s, 3H), 3.65 (dd, J = 6.2, 10.2 Hz), 3.80 (dd, J = 3.0, 10.2 Hz, 1H), 3.90 (m, 1H), 4.28 (m, 1H), 4.40-4.96 (m, 8H), 7.31(m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.8, 61.1, 68.4, 73.5, 74.4, 74.6, 77.9, 78.0, 80.8, 83.3, 99.1, 128.3, 128.5, 128.7, 129.1, 138.4, 138.5, 202.6.

Ester 2.35

To a solution of NaH (344 mg, 8.6 mmol) in anhydrous THF (20 mL) was added triethylphosphonoacetate (2.6 mL, 12.9 mmol) dropwise at 0 °C. The mixture was stirred for 30 min at this temperature, then a solution of ketone **2.34** (2.0 g, 4.3 mmol) in anhydrous THF (20 mL) was added. The mixture was warmed to rt and stirred for additional 30 min. The reaction was quenched by water and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by FCC to give ester

2.35 (2.1 g, 91%): clear oil; R_f = 0.40 (2% ethyl ether:methylene chloride); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 5.1 Hz, 3H), 3.42 (s, 3H), 3.95 (m, 3H), 4.18 (m, 3H), 4.42-4.90 (m, 6H), 5.78 (br d, 1H), 5.80 (s, 1 H), 7.32 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 57.2, 61.3, 70.8, 70.9, 72.1, 73.1, 73.4, 79.7, 81.6, 97.0, 122.2, 127.5, 128.0, 128.1, 128.3, 128.4, 128.5, 128.7, 128.9, 129.1, 129.2, 129.3, 137.9, 138.6, 139.2, 150.4, 165.5

Acid 2.37

A mixture of unsaturated ester **2.35** (6.0 g, 11.4 mmol), Pd/Al_2O_3 (5 g 5% w) in EtOAc (80 mL) was stirred under an atmosphere of H_2 (balloon) for 3 h. The reaction mixture was purged with argon and filtered through a short plug of celite and the filtrate was concentrated in *vacuo*. The crude product (5 g, 9.4 mmol) obtained in the previous step was treated with a 1:1 mixture of aqueous 3 N NaOH/ethanol (100 mL). When the reaction was complete (ca. 5 hr), most of EtOH was removed under reduced pressure. The resulting was acidified by Con. HCl to pH 4-5, and extracted by ethyl acetate (4 x). The combined organic layer was concentrated in *vacuo*. The residue was purified by FCC to give acid **2.37** (4.0 g, 85%): clear oil; R_f = 0.10 (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (m, 2H), 2.55 (m, 1H), 3.40 (s, 3H), 3.62 (m, 3H), 3.85 (m, 2H), 4.42-5.10 (m, 7H), 7.32 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.0, 56.0, 61.1, 70.5, 71.0, 73.7, 74.1. 75.9, 78.8, 82.4, 99.2, 128.1, 128.2, 128.5, 128.6, 128.8, 128.9, 129.1, 138.7, 138.8, 139.5, 172.5.

Ester 2.38

Alcohol **2.12** (3.6 mg, 7.1 mmol), acid **2.37** (3.62 g, 7.1 mmol) was converted via coupling procedure as detailed in the preparation of **2.24**, to ester **2.38** (5.9 g, 83.3%): colorless oil; $R_f = 0.60$ (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (s, 9H), 1.41, 1.43 (both s, 3H ea), 2.22 (m, 2H), 2.70 (dd, J = 3, 10 Hz, 1H), 3.3 (s, 3H), 3.51 (m, 3H), 3.77 (m, 2H), 3.9 (br d, 1H), 4.30 (m, 2H), 4.50-4.90 (m, 7H), 5.15 (d, J = 3.0 Hz, 1H), 5.30 (d, J = 8.0 Hz, 1H), 7.4 (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 26.5, 27.0, 27.5, 31.9, 40.4, 55.3, 62.3, 69.8, 70.3, 72.4, 73.0, 73.5, 75.5, 77.9, 79.2, 82.0, 85.2, 98.7, 111.9, 127.6, 127.7, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 129.0, 129.9, 132.4, 133.1, 133.8, 135.7, 138.2, 138.4, 138.5, 138.8, 170.3.

Enol ether 2.39

Ester **2.38** (4.8 g, 4.8 mmol) was converted via the Tebbe reaction detailed in the preparation of **2.25**, to enol ether **2.39** (4.32 g, 90%): colorless oil; $R_f = 0.65$ (20% ethyl acetate:petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.45, 1.55 (both s, 3H ea), 2.11 (m, 2H), 2.5 (dd, J = 4, 11 Hz, 1H), 3.22 (s, 3H), 3.47 (dd, J = 4, 9 Hz, 1H), 3.62 (dd, J = 3, 9 Hz, 1H), 3.68 (m, 2H), 3.80 (m, 2H), 3.92 (m, 3H), 4.32 (s, br, 1H), 4.4-5.03 (m, 8H), 5.35 (d, J = 8 Hz, 1H); $^{13}CNMR$ (75 MHz, $CDCl_3$) δ 19.3, 26.1, 27.0, 27.4, 32.1, 40.7, 54.8, 60.7, 70.0, 72.6, 73.0, 73.3, 74.9, 78.9, 82.4, 83.9, 84.8, 98.2, 110.8, 127.2, 127.4, 127.6, 127.7, 127.7,

127.9, 128.2, 128.3, 128.9, 129.8, 129.9, 132.6, 133.0, 133.1, 133.4, 136.6, 138.2, 138.5, 139.3, 159.3.

Glycal 2.40

Enol ether **2.39** (0.2 g, 0.2 mmol) was converted via cyclization procedure detailed in the preparation of **2.26**, to glycal **2.40** (153 mg, 86%): clear oil; R_f = 0.45 (15% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, C_6D_6) δ 1.18 (s, 9H), 1.35, 1.54 (both s, 6H), 2.40 (m, 3H), 3.22 (s, 3H), 3.66 (dd, J = 2.92, 8.0 Hz, 1H), 3.8 (m, 2H), 4.2 (t, J = 14.0 Hz, 1H), 4.1 (m, 2H), 4.20 (m, 2H), 4.34 (s, 1H), 4.46 (m, 4H), 4.69 (br s, 1H), 4.80 (br d, 2H), 5.23 (d, J = 8.1 Hz, 1H), 7.3 (m, 30H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.38, 1.41 (both s, 6H), 2.13 (m, 2H), 2.39 (dd, J = 4.8, 14.8 Hz, 1H), 3.33 (s, 3H), 3.60 (m, 2H), 3.85 (m, 2H), 3.95 (m, 2H), 4.44-4.76 (m, 9H), 4.92 (ABq, J = 10.4 Hz, Δδ = 0.45 ppm, 2H), 7.20 (m, 22H), 7.70 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 26.8, 27.1, 28.4, 31.1, 40.9, 55.2, 62.9, 69.6, 70.2, 71.3, 73.0, 73.5, 75.0, 75.8, 76.9, 77.4, 77.5, 82.3, 98.4, 101.1, 110.0, 127.5, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 129.9, 133.2, 133.4, 135.6, 135.8, 138.3, 139.3, 153.9.; FABHRMS calcd for $C_{54}H_{65}O_9Si$ (M + H) 885.4398, found 885.4402.

Alcohol 2.41

Glycal **2.39** (153 mg, 0.17 mmol) was converted via hydroboration procedure detailed in the preparation of **2.27**, to the alcohol **2.41** (120 mg, 77%):

colorless oil; R_f = 0.10 (30% ethyl acetate:petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.1 (s, 9H), 1.35, 1.53 (both s, 6H), 1.95 (m, 1H), 2.12 (m, 1H), 2.60 (br s, -OH, 1H), 3.15 (ddd, J = 3.2, 9.6, 10.8 Hz, 1H), 3.29 (s, 3H), 3.58 (m, 3H), 3.70 (m, 5H), 3.84 (m, 2H), 4.29 (dd, J = 2.2, 6.0 Hz, 1H), 4.48 (ABq, J =11.7 Hz, Δδ = 0.13 ppm, 2H), 4.61 (m, 3H), 4.65 (ABq, J = 11.7 Hz, Δδ = 0.13 ppm, 2H), 4.81 (ABq, J =11.7 Hz, Δδ = 0.26 ppm, 2H), 7.4 (m, 25 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 26.7, 27.1, 28.7, 29.7, 39.6, 55.2, 62.7, 70.4, 71.1, 73.0, 73.5, 73.6, 74.4, 75.4, 76.2, 76.3, 78.9, 80.0, 82.0, 98.4, 109.6, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 128.5, 128.6, 129.8, 129.8, 133.4, 133.6, 135.7, 135.8, 138.3, 138.4, 138.9.

Acetate 2.42

^{1}H NMR (400 MHz, C_6D_6) δ 1.98 (s, 9H), 1.28, 1.53, 1.61 (all s, 9H), 1.80 (m, 1H), 2.11 (m, 1H), 2.42 (m, 1H), 3.18 (s, 3H), 3.39 (t, J = 10.0 Hz, 1H), 3.60 (m, 2H), 3.66 (dt, J = 4.9, 9.6 Hz, 1H), 3.73 (m, 1H), 3.88 (dd, J = 3.3, 5.9 Hz, 1H), 4.02 (dd, J = 5.1, 7.3 Hz, 1H), 4.12 (m, 2H), 4.30 (m, 6H), 4.77 (d, J = 2.2 Hz, 1H), 4.95 (ABq, J = 10.7 Hz, Δδ = 0.55 ppm, 2H), 5.26 (dd, J = 9.0, 9.6 Hz, 1H), 7.10-7.90 (m, 25H).

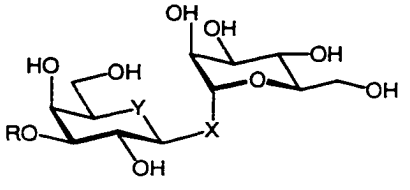
Chapter 3

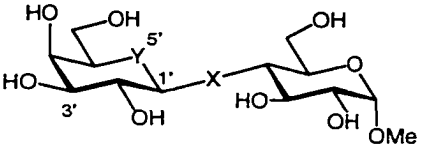
Synthesis of carbagalactosides as Sialyl Lewis X mimetics

3.1 Background[39, 40]

Carbasugars are pseudo-saccharides in which the ring oxygen of a cyclic monosaccharide is replaced by a methylene group. They have been shown to be inhibitors against β-galactosidases and galactosyl transferases involved in the biosynthesis of complex oligosaccharides. Carbasugars, like C-glycosides,[24] are expected to have topographical features similar to the parent O-glycoside, and to be stable to chemical and enzymic hydrolysis.[41] The oxygens of the acetal linkages are generally believed to be intimately involved in carbohydrate-receptor interactions.[42]

Figure 3.1 Acetal Analogues of Disaccharides





1.6 X = O, Y = O, R = CH_2COOH
(3-O-carboxymethyl)–β-D-gal (1'-1)-α-D-mannopyranoside

2.1 X = CH_2, Y = O, R = CH_2COOH
(3-O-carboxymethyl)–β-D-gal (1'-1)-C-α-D-mannopyranoside

3.1 X = O, Y = CH_2, R = H
5a'-carba-β-D-gal (1'-1)-α-D-mannopyranoside

2.31 X = CH_2, Y = O
β-D-gal (1'-4)-C-α-D-glucopyranoside

3.2 X = O, Y = CH_2
5a'-carba-β-D-gal (1'-4)-α-D-glucopyranoside

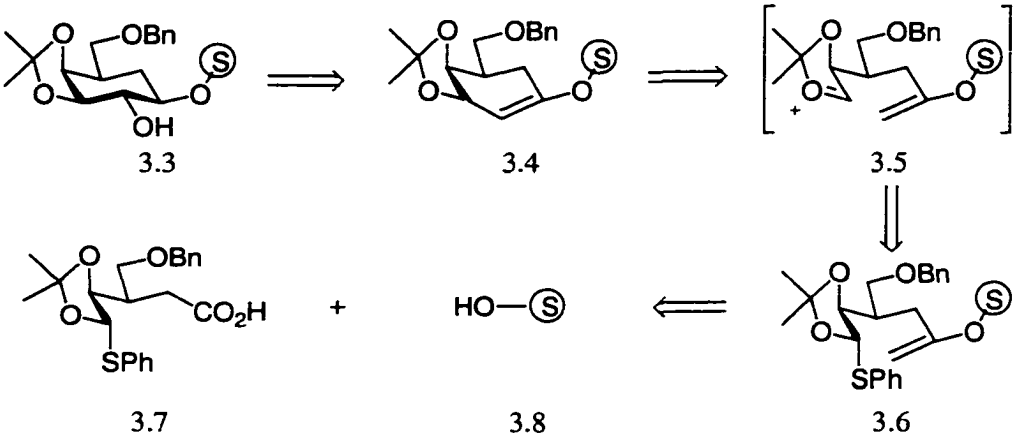
Accessibility of carba sugar and C-glycoside partners of a given O-glycoside could be important for assessment of the role of the individual acetal oxygens.[43] Therefore, having already prepared the C-glycoside of **2.1** and C-Lactose derivative **2.41**, we undertook the synthesis of carbasugars **3.1** and **3.2** (Figure 3.1).

3.2 First synthesis of 5a'-carba-α-D-gal (1'-1)-α-D-mannopyranoside

A number of approaches[39] to carba-disaccharides have been developed. These usually involve the coupling of an epoxysugar or epoxycyclitol with an alcohol partner. However, these methods are lengthy and give low yields in the coupling step when secondary alcohols are used.

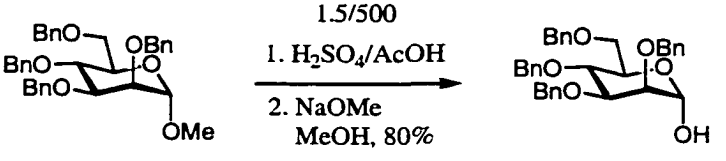
Retrosynthetic plan Our strategy centers on the stereoselective hydroboration of the cyclic enol ether which may be obtained from cyclization of oxocarbenium ion **3.5**. Intermediate **3.5** should be accessible from 1-thio-2,3-isopropylidene acetal (TIA) derived enol ether **3.6**, which would come from acid **3.7** and alcohol **3.8.** Thus, construction of carbadisaccharide **3.3** should be possible via the same sequence of reactions as that used for C-galacto-C-disaccharides: esterification of the acid and sugar alcohol components, Tebbe olefination, methyltriflate activated cyclization, and finally hydroboration of the enol ether. The difference from C-glycoside synthesis[29] lies in the location of the alcohol and acid residues. Here the carboxyl group is on the TIA, (**3.7**, Scheme 3.1) while the hydroxyl group is on the sugar. (**3.8**, Scheme 3.1)

Scheme 3.1



Preparation of 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside Acetolysis[20d] of benzyl ether **2.20** followed by Zemplen deacetylation gave the hemiacetal **3.9**[44] in 80% yield (Scheme 3.2).

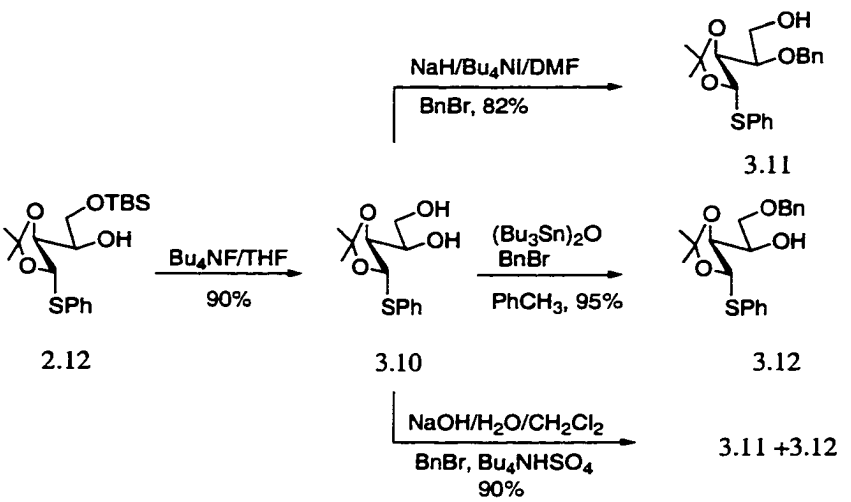
Scheme 3.2



Synthetic study of TIA acid component Our initial plan was to derive the TIA acid **3.7** from thioacetal **2.12**. The TBS protecting group was first replaced with a benzyl group. Treatment of **2.12** with tetrabutylammonium fluoride gave the diol **3.10** in 90% yield. The primary hydroxyl in **3.10** was selectively protected with benzyl bromide and bis-tributyl tin oxide[45] in 95% yield. Surprisingly,

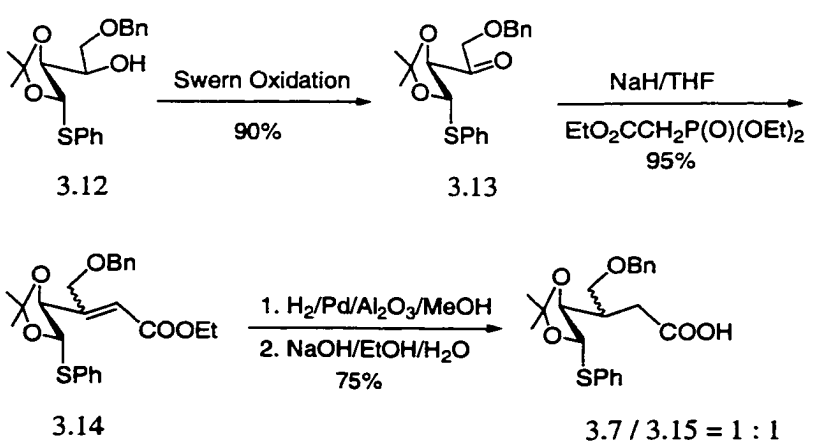
standard benzylation using sodium hydride as base gave exclusively the secondary benzyl ether **3.11**. With sodium hydroxide, a 1:1 mixture of primary and secondary benzyl ethers were obtained (Scheme 3.3).

Scheme 3.3



Swern oxidation of **3.12** afforded ketone **3.13**, which was subjected to Emmons-Horner reaction to form a single α,β- unsaturated ester **3.14** of

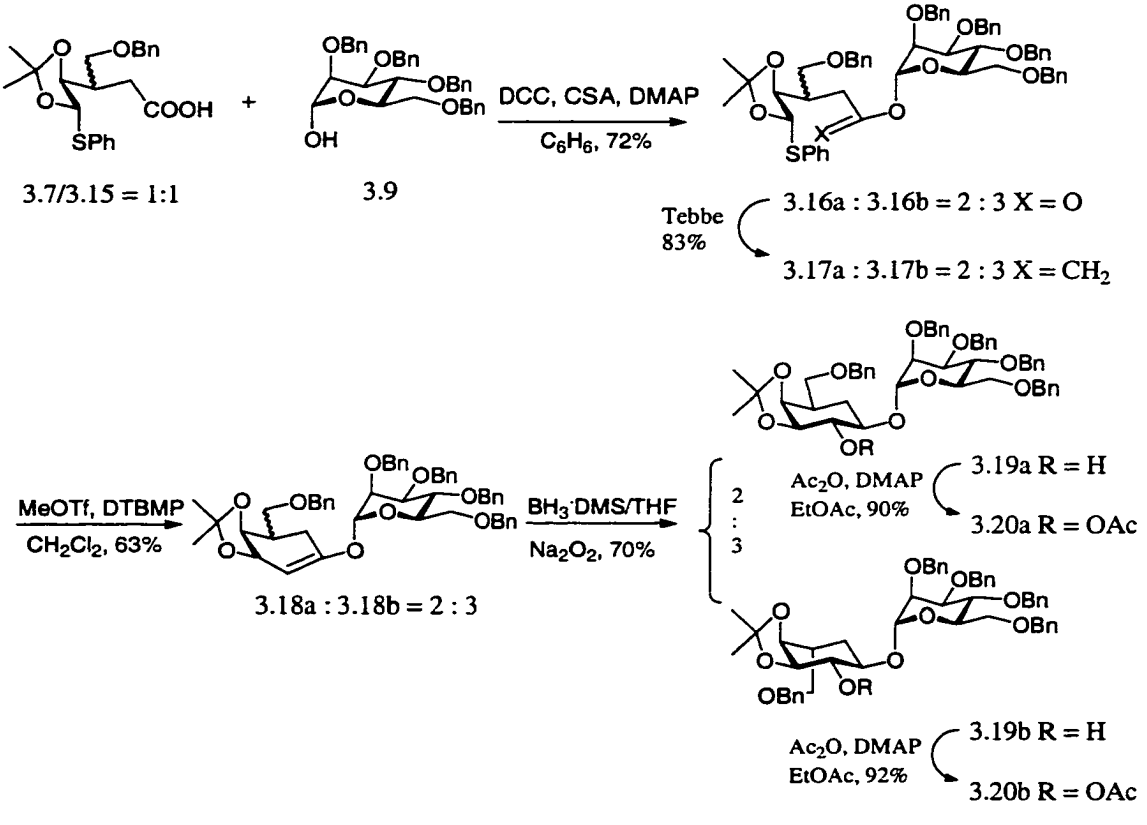
Scheme 3.4



undetermined configuration. Hydrogenation of **3.14** with 5% palladium on alumina, followed by hydrolysis of the crude product gave a 1:1 mixture of diastereoisomeric acids **3.7** and **3.15** in an overall yield of 75% (Scheme 3.4).

DCC esterification[35b] of the mixture of acids **3.7** and **3.15** and alcohol **3.9** provided an inseparable 2:3 mixture of esters **3.16a** and **3.16b**. A single anomer of each compound was obtained. Treatment of **3.16a** and **3.16b** with Tebbe reagent furnished a 2:3 mixture of enol ethers **3.17a** and **3.17b** in 83% yield. Activation of the thiophenyl group in **3.17a/b** with MeOTf led to cyclization products **3.18a** and **3.18b** in 63% yield. Hydroboration of the mixture with borane-methyl disulfide afforded a mixture of **3.19a** and **3.19b**. FCC purification provided **3.19a** and **3.19b**

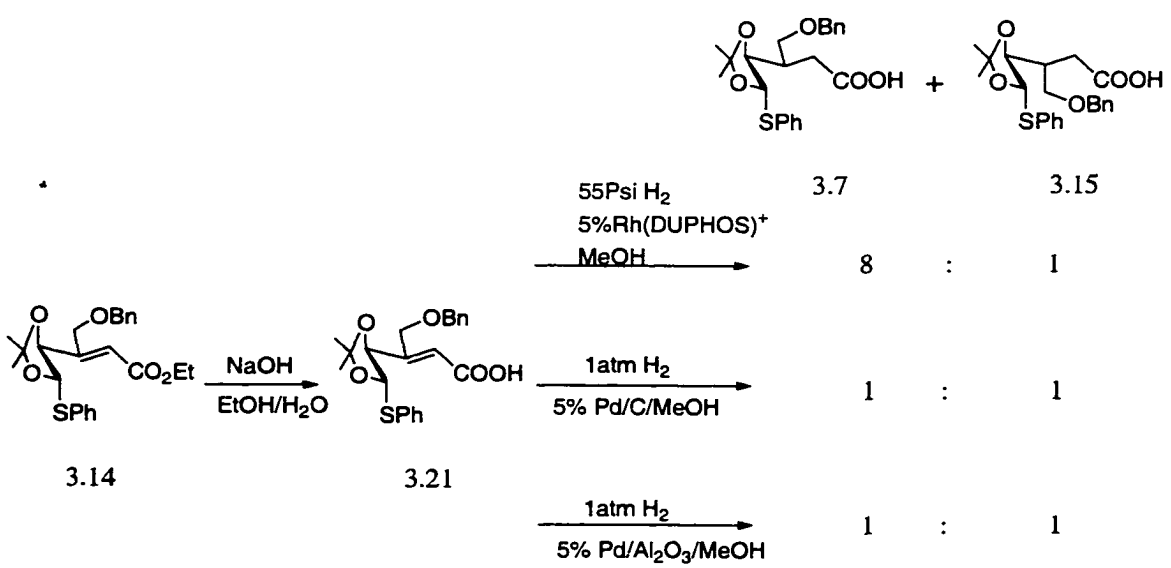
Scheme 3.5



in 28% and 42% yields respectively. The configurations of **3.19a** and **3.19b** were established by the coupling constants of the acetate derivatives **3.20a** ($J_{1,2}$ = 10.0, $J_{2,3}$ = 8.0, $J_{3,4}$ = 4.0, $J_{4,5}$ = 3.5 Hz) and **3.20b** ($J_{1,2}$ = 10.0, $J_{2,3}$ = 8.0, $J_{3,4}$ = 4.0, $J_{4,5}$ = 1.2 Hz). Diastereomers **3.20a** and **3.20b** were distinguished by observation of NOE effects between H-1, H-3, and H-5 in **3.20a**, but not in **3.20b**. Therefore, we concluded that all the minor products in this sequence of reactions possess the desired stereochemistry "**R**" at C-5', while the major products have "**S**".

A more stereoselective synthesis of **3.7** was next attempted. Asymmetric hydrogenation was initially tested on the α,β-unsaturated acid **3.21**, which was obtained from hydrolysis of **3.14**. Utilizing rhodium DUPHOS[46] as catalyst, an 8:1 mixture of acids **3.7** and **3.15** was obtained in 90% yield (Scheme 3.6). The stereochemistry of **3.7** and **3.15** was confirmed by conversion to the previously

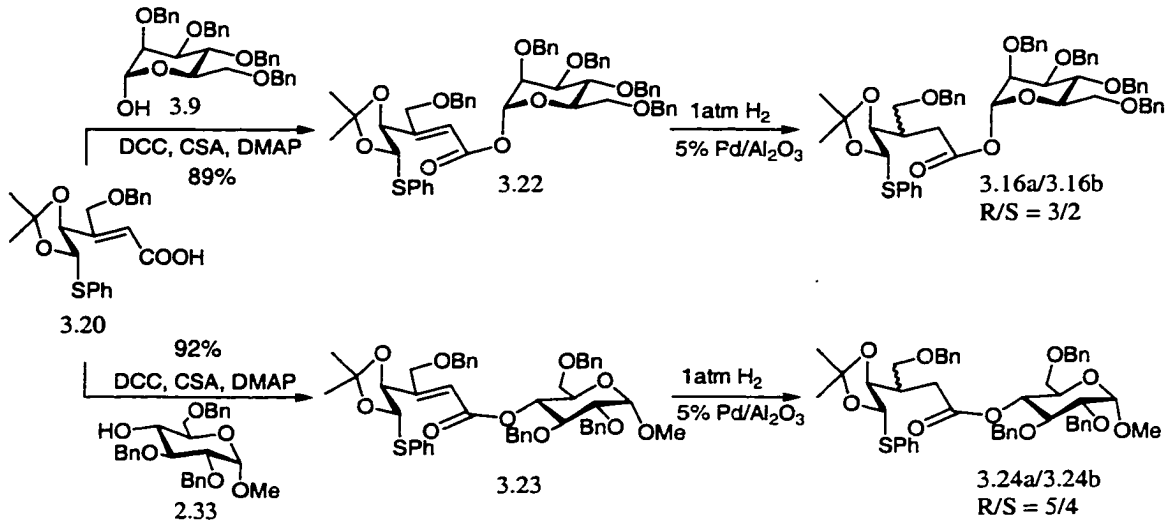
Scheme 3.6



prepared esters **3.16a** and **3.16b**.

Hydrogenation of acid **3.21** using 5% Pd/C or Pd/Al_2O_3 were less selective, leading to a 1:1 ratio of products in both cases. Hydrogenation on the monosaccharide linked esters **3.22** or **3.23** with 5% Palladium/Al_2O_3 also showed low selectivity: 3:2 for **3.16a** : **3.16b**, and 5:4 for **3.24a** : **3.24b** (Scheme 3.7).

Scheme 3.7



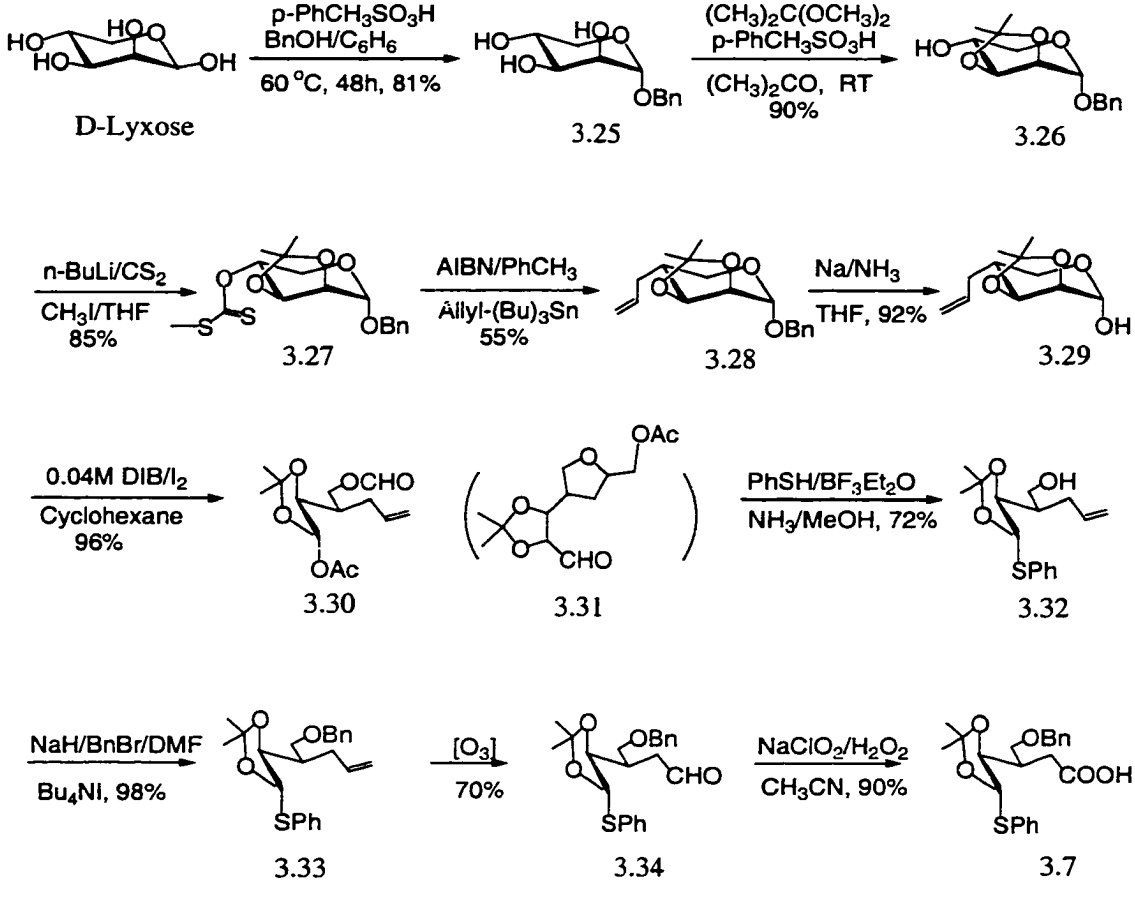
3.3 Improved synthesis of carbasugars

Although the asymmetric hydrogenation induced by rhodium DUPHOS was relatively high, the reaction was sluggish and often didn't occur, especially on a large scale. Therefore an alternative synthetic route from the known D-lyxose derivative **3.29** was attempted.[47, 48]

Reaction of D-lyxose with benzyl alcohol in the presence of *p*-toluenesulfonic acid yielded a mixture of benzyl glycoside **3.25** in 81% yield.[47] Acetonation of **3.25** by treatment with dimethoxypropane and p-TsOH provided

3.26 in 90% yield. The free hydroxyl group in **3.26** was converted to the xanthate[48] **3.27** under standard conditions. Allylation of **3.27** with allyltributylstannane in toluene at 90 °C, using AIBN as initiator led to the desired C-allyl derivative **3.28** in 55% yield. Freshly recrystalized AIBN reagent improved the reaction yield. Birch reduction of the benzyl ether in **3.28** delivered lactol **3.29** in 92%.

Scheme 3.8

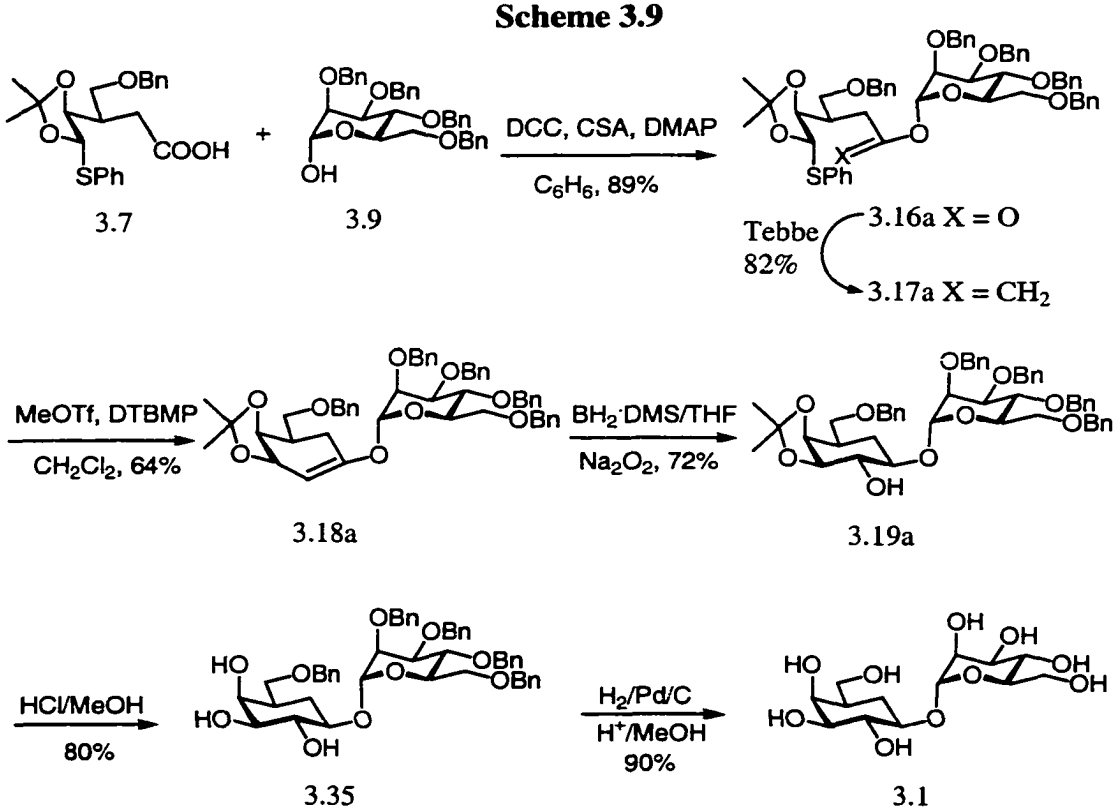


Treatment of **3.29** with DIB[49] according to previously described Suarez methodology[31] led to 1,2-O-isopropylidene acetate **3.30** in 96% yield. The yield of this reaction is highly dependent on concentration. Concentrations higher than 0.04

M of DIB led to formation of byproduct **3.31**, resulting from intramolecular iodoetherification reaction of the alkene.[49b] Acetal exchange on **3.30** with thiophenol, followed by basic hydrolysis of the crude product afforded alcohol **3.32** in overall 72% yield. A sequence of benzylation, ozonolysis and chlorite oxidation[50] applied to **3.34** furnished TIA acid **3.7** in an overall 60% yield (Scheme 3.8).

Manno carbasugar DCC mediated esterification[35] of TIA acid **3.7** and manno alcohol **3.9** led to ester **3.16a** in 89% yield. As previously noted, this ester was found to be a single anomer with respect to the mannose linkage. This was determined to be the α-glycoside from the H-H and C-H coupling constants ($J_{H1, H2}$ = 2.0, $J_{C1, H1}$ = 175 Hz).[51] Enol ether transformation under Tebbe conditions yielded

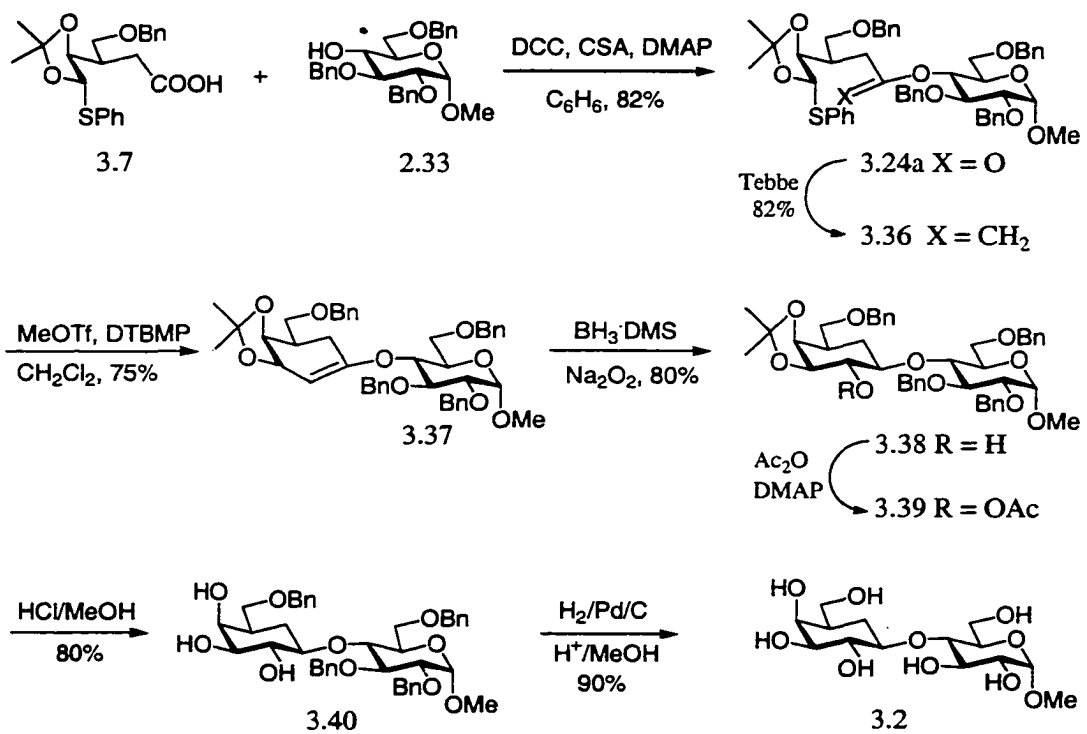
Scheme 3.9



3.16a in 82% yield. Oxocarbenium ion cyclization promoted by methyl triflate and DTBMP furnished carbaglycal **3.18a** in 64% yield. Stereoselective hydroboration on **3.18a** provided carbadisaccharides **3.19a** in 72% yield. The acetonide group in **3.19a** was cleaved by acidic hydrolysis to provide triol **3.35** in 80% yield. Final debenzylation under hydrogenolysis conditions led to carbasugar **3.1** in 90% yield (Scheme 3.9).

Gluco carbasugar The gluco carbasugar **3.2** was obtained from gluco pyranoside **2.33**[52] and TIA acid **3.7**. Coupling of **3.7** and **3.29** gave ester **3.23a** in 82% yield. Enol ether **3.36** was obtained in 82% yield from **3.24a** under Tebbe conditions. Cyclization in the presence of methyl triflate and DTBMP furnished

Scheme 3.10

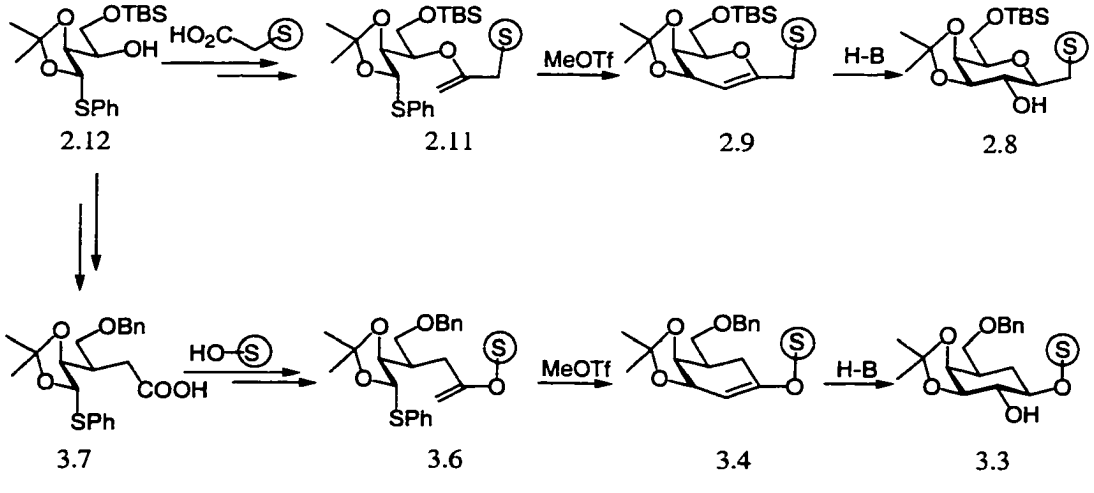


carbaglycal **3.37** in 75% yield. Stereoselective hydroboration on **3.37** provided carbadisaccharides **3.38** in 80% yield. The configuration of **3.38** was established by the *J* values for the acetate derivative **3.39** ($J_{1,2}$ = 10.5, $J_{2,3}$ = 8.5, $J_{3,4}$ = 3.5, $J_{4,5}$ = 3.5 Hz), which were similar to the data for the acetate derivative **3.20a** of manno carbasugar. As before, carbasugar **3.38** was converted via two steps (72%) to **3.2** (Scheme 3.10).

3.4 Summary

The TIA methodology provides a general protocol for conversion of a given glycosyl acceptor **3.8** to either its β-C-galactoside **2.8** or β-carbagalactoside **3.3**. In both the C-glycoside and carbasugar synthesis, the key glycone-aglycone coupling step is an esterification reaction. The reliability of this coupling reaction should allow for the synthesis of β-galacto mimetics with wide diversity (Scheme 3.11).

Scheme 3.11



3.5 Experimental section

Benzyl ether 3.9

To a solution of **2.20** (5.4 g, 9.75 mmol) in acetic anhydride (18.6 mL) was added acetic acid (17.7 mL), and AcOH-H_2SO_4 (500:1.5, 15.4 mL) dropwise. When TLC indicated complete disappearance of the starting material (ca. 4 h), the mixture was poured into saturated, aqueous $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4), and concentrated in *vacuo*. The crude material was dissolved in dry methanol (20 mL) and treated with a solution of NaOMe in MeOH (20 mL, 1M) for 0.5 h. A solution of 10% HCl/MeOH was then carefully added to a pH of 8. The mixture was concentrated in *vacuo* and the residue was partitioned between ether and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by FCC gave **3.9** (4.1 g, 80%): clear oil; R_f = 0.10 (15% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (m, 6H), 4.60 (m, 8H), 5.25 (s, 1H), 7.30 (m, 20H).

Diol 3.10

A solution of alcohol **2.12** (600 mg, 1.2 mmol) in THF (10 mL) containing Bu_4NF (2.3 mL of 1M solution in THF, 2.3 mmol), was stirred under an atmosphere of argon at rt for 1h. The reaction mixture was then diluted with water and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was

purified by FCC to give product **3.10** (300 mg, 90%): clear oil; R_f = 0.15 (30% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (br s, 6H), 3.20 (br, 1H, -OH), 3.71 (m, 2H), 3.80 (m, 1H), 4.02 (dd, J = 1.0, 3.2 Hz, 1H), 5.42 (d, J = 3.8 Hz, 1H), 7.23-7.80 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 27.3, 64.5, 70.3, 81.3, 85.4, 111.7, 127.6, 127.7, 129.0, 131.7.

Benzyl ether 3.12

A mixture of diol **3.10** (1.1 g, 4.26 mmol), bis-tributylstannyl oxide (1.65 mL, 3.2 mmol), and anhydrous toluene (200 mL) was heated at reflux in a Dean-Stark apparatus for 2 h. The solvent was then concentrated to half volume. BnBr (1.52 mL, 12.8 mmol) and Bu_4NBr (689 mg, 2.1 mmol) was then added and the solution was heated at 80 °C for 16 h. The reaction mixture was diluted with $CHCl_3$ and washed with saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. FCC purification of the residue provided benzyl ether **3.12** (1.4 g, 95%): colorless oil; R_f = 0.80 (25% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 6H), 2.92 (d, J = 3.8 Hz, -OH, 1H), 3.65 (m, 2H), 3.98 (m, 1H), 4.17 (dd, J = 2.8, 4.2 Hz, 1H), 4.59 (d, J = 3.8 Hz, 2H), 5.54 (d, J = 4.2 Hz, 1H), 7.23-7.55 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 28.1, 69.8, 72.3, 74.2, 81.6, 85.9, 112.2, 128.1, 128.5, 129.1, 129.7, 132.4, 134.8, 138.5.

Ketone 3.13

Benzyl ether **3.12** (4 g, 11.5 mmol) was subjected to the Swern oxidation procedure as detailed in preparation of **2.34**. Purification of the product provided ketone **3.13** (3.5 g, 90%): colorless oil; R_f = 0.75 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42, 1.53 (both s, 6H), 4.40 (d, J = 3.0 Hz, 2H), 4.52 (d, J = 4.2 Hz, 1H), 4.61 (s, 2H), 5.58 (d, J = 4.2 Hz, 1H), 7.23-7.55 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 28.1, 72.6, 73.6, 83.7, 85.8, 128.1, 128.0, 128.6, 129.2, 132.4, 203.2.

Unsaturated Ester 3.14

Ketone **3.13** (2.0 g, 5.75 mmol) was subjected to the Emmons-Horner reaction procedure as detailed in preparation of **2.35**. Purification of the product provided ester **3.14** (1.9 g, 95%). colorless oil; R_f = 0.85 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.56, 1.63 (both s, 6H), 4.20 (q, J = 7.4 Hz, 2H), 4.61 (br s, 2H), 4.85 (d, J = 6.7 Hz, 1H), 4.75 (ABq, J = 10.5 Hz, Δδ = 0.4 ppm, 2H), 5.52 (d, J = 6.8 Hz, 1H), 6.3 (s, 1H), 7.30-7.60 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 26.3, 27.4, 60.4, 65.0, 73.0, 81.2, 88.2, 111.8, 119.4, 127.2, 127.5, 127.8, 128.0, 128.8, 131.5, 134.0, 137.7, 151.7, 165.4.

Acid 3.7 and 3.15 (ratio 1:1)

Ester **3.14** (400 mg, 0.96 mmol) was subjected to hydrogenolysis and hydrolysis procedure as detailed in preparation of **2.37**. FCC Purification of the product gave a 1:1 mixture of acids **3.7** and **3.15** (296 mg, 75% for two steps): colorless oil; R_f = 0.1 (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, C_6D_6) δ 1.4, 1.5 (both s, 6H), 2.6 (m, 3H), 3.45 (br d, 2H), 4.3 (m, 3H), 5.53 (d, J = 6.0 Hz, 1H), {5.60 (d, J = 6.0 Hz, 1H) for the other isomer}, 7.0-7.6 (m, 10H, Ar-H's).

Acid 3.7 and 3.15 (ratio 8:1)

Ester **3.14** (580 mg, 1.4 mmol) was subjected to hydrolysis procedure as detailed in preparation of **2.37**. FCC Purification of the product gave acid **3.21** (550 mg, 93%): colorless oil; R_f = 0.1 (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.56, 1.63 (both s, 6H), 4.63 (br s, 2H), 4.85 (d, J = 6.7 Hz, 1H), 4.72 (ABq, J = 10.5 Hz, Δδ = 0.4 ppm, 2H), 5.52 (d, J = 6.8 Hz, 1H), 6.3 (s, 1H), 7.30-7.60 (m, 10H).

A Fisher-Porter bottle was charged with acid **3.21** (500 mg, 1.3 mmol), MeOH (5 mL), and Rh(DUPHOS)OTf (2.6 mg, 3.9 μmol). After five vacuum/H_2 cycles, the tube was pressurized to an initial pressure of 55 psi H_2. The reaction was allowed to shake at rt for 5 days, or until no further hydrogen uptake was observed. Then the reaction mixture was purged in N_2 by five vacuum/ N_2 cycles, and concentrated under reduced pressure. FCC purification of the residue provided a

8:1 mixture of acids **3.7** and **3.15** (450 mg, 90%): colorless oil; $R_f = 0.1$ (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, C_6D_6) δ 1.4, 1.5 (both s, 6H), 2.6 (m, 3H), 3.45 (br d, 2H), 4.3 (m, 3H), 5.53 (d, J = 6.0 Hz, 1H), {5.60 (d, J = 6.0 Hz, 1H) for the other isomer}, 7.0-7.6 (m, 10H, Ar-H's).

Ester 3.16a

Alcohol **3.9** (34 mg, 0.063 mmol), acid **3.7** (34 mg, 0.085 mmol) were subjected to coupling procedure as detailed in preparation of **2.24**. Purification of the product gave ester **3.16a** (52 mg, 89.4% from alcohol): colorless oil; $R_f = 0.50$ (15% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.4, 1.5 (both s, 6H), 1.5 (m, buried, 1H), 2.5 (m, 2H), 3.5 (d, J = 5.6Hz, 1H), 3.73 (m, 5H), 4.1 (m, 2H), 4.5 (m, 8H), 4.7 (m, 2H), 4.9 (d, J = 10.6 Hz, 1H), 5.37 (d, J = 6.6Hz, 1H), 6.27 (d, J = 1.8 Hz, 1H), 7.3-7.5 (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 27.2, 33.2, 38.7, 69.0, 69.8, 72.2, 72.6, 73.3, 73.6, 74.4, 73.8, 74.6, 75.4, 79.2, 80.8, 86.4, 92.1, 111.0, 127.8, 128.0, 128.4, 128.5, 129.0, 131.8, 134.6, 138.3, 138.5, 170.5; FABHRMS: calcd for $C_{56}H_{60}O_{10}S$ (M + Na) 947.3806, found 947.3804.

Enol ether 3.17a

Ester **3.16a** (50 mg, 0.054 mmol) was subjected to the Tebbe reaction as detailed in preparation of **2.25**. Purification of the product gave enol ether **3.17a** (41 mg, 82%): colorless oil; $R_f = 0.8$ on basic Al_2O_3 (10% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.42, 1.50 (both s, 6H), 2.1 (m, 3H), 3.5-4.0

(m, 6H), 4.1 (m, 2H), 4.4-4.8 (m, 13H), 4.81 (d, J = 5.0 Hz, 1H), 5.32 (br s, 1H), 5.50 (d, J = 6.6Hz, 1H), 7.32 (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 27.8, 33.0, 39.5, 69.2, 69.7, 72.5, 72.8, 73.2, 73.4, 73.6, 74.9, 75.0, 80.2, 81.4, 86.7, 88.4, 95.7, 110.7, 127.0, 127.3, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 128.8, 131.3, 138.3, 138.4, 138.5, 138.6, 157.9; FABHRMS calcd for $C_{57}H_{62}O_9S$ (M + Na) 945.3997, found 945.4012.

Glycal 3.18a

Enol ether **3.17a** (35 mg, 0.038 mmol), was subjected to cyclization procedure as detailed in preparation of **2.26.** Purification of the product provided glycal **3.18a** (20 mg, 64.3%): clear oil; R_f = 0.4 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32, 1.34 (both s, 6H), 1.92 (dd, J = 4.8, 16.1Hz, 1H), 2.04 (ABq, J = 11.6 Hz, 1H), 2.13 (m, 1H), 3.52 (t, J = 9.2Hz, 1H), 3.61 (dd, J = 7.0, 9.2Hz, 1H), 3.73 (m, 1H), 3.82 (m, 2H), 3.94 (dd, J = 2.9, 9.5 Hz, 1H), 4.08 (t, J = 9.5 Hz, 1H), 4.33 (br d, J = 5.1 Hz, 1H), 4.5-4.9 (m, 11H), 5.03 (br s, 1H), 5.42 (br s, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 26.0, 26.9, 28.3, 37.9, 69.5, 72.0, 72.6, 72.8, 73.0, 73.1, 73.4, 73.6, 74.3, 75.0, 75.1, 75.3, 80.3, 95.3, 99.6, 108.6, 127.5, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 138.5, 138.7, 138.8, 154.1; FABHRMS calcd for $C_{51}H_{56}O_9$ (M + Na) 835.3815, found 835.3822.

Alcohol 3.19a

Glycal **3.18a** (20 mg, 0.02 mmol) was subjected to hydroboration procedure as detailed in preparation of **2.27**. Purification of the product provided alcohol **3.19a** (15 mg, 72%): colorless oil, R_f = 0.45 (40% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.35(m buried under at 1.35, 1H), 1.49 (s, 3H), 1.97 (m, 1H), 2.07 (m, 1H), 2.33 (br s, 1H, D_2O ex), 3.33 (m, 2H), 3.50 (m, 2H), 3.71 (m, 3H), 3.85 (m, 4H), 4.27 (t, J = 4.0 Hz, 1H), 4.40-4.70 (m, 9H), 4.86 (apparent d, J = 11.0 Hz, 1H), 5.08 (br s, 1H), 7.30 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.64, 29.8 (2C), 36.1, 69.7, 71.2, 72.5, 72.6, 72.7, 73.4, 73.6, 74.1, 75.2, 75.3, 77.4, 79.9, 80.0, 80.5, 99.5, 109.4, 138.3, 138.5, 138.5, 138.6; FABHRMS calcd for $C_{51}H_{58}O_{10}$ (M + Na) 853.3931, found 853.3927.

Acetate 3.20a

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.33 (s, 3H), 1.51 (m, 1H), 1.84 (s, 3H), 2.06 (m, 2H), 3.32 (m, 1H), 3.48 (dt, J = 3.0, 10.0 Hz, 1H), 3.56 (t, J = 8.5 Hz, 1H), 3.63 (t, J = 2.0 Hz, 1H), 3.72 (m, 2H), 3.89 (m, 4H), 4.29 (t, J = 4.0 Hz, 1H), 4.46 (m, 3H), 4.65 (m, 6H), 4.84 (apparent d, J = 11.0 Hz, 1H), 4.94 (br s, 1H), 5.02 (dd, J = 8.0, 10.0 Hz, 1H), 7.30 (m, 25H).

^{1}H NMR (500 MHz, C_6D_6) δ 1.21 (s, 3H), 1.58 (s, 3H), 1.61 (m, buried under s at δ 1.58 and 1.65, 1H), 1.65 (s, 3H), 1.82 (m, 1H), 2.14 (dt, J = 4.4, 12.7 Hz, 1H), 3.21 (m, 1H), 3.44 (dt, J = 4.0, 10.5 Hz, 1H), 3.50 (t, J = 8.5 Hz, 1H), 3.80 (m, 4H), 4.10 (br t, J = 3.0, 1H), 4.14 (m, 3H), 4.28 (ABq, J = 12.0 Hz, Δδ = 0.04

ppm, 2H), 4.38 (apparent d, J = 11.5 Hz, 1H), 4.48 (m, 4H), 4.65 (ABq, J = 12.0 Hz, $\Delta\delta$ = 0.09 ppm, 2H), 4.93 (apparent d, J = 11.5 Hz, 1H), 5.14 (br s, 1H), 5.44 (t, J = 10.0 Hz, 1H), 7.20 (m, 25H). NOE between δ 2.14 (H5) and 3.44 (H1) and 3.80 (H3 buried in multiplet).

Triol 3.35

Alcohol **3.19a** (30 mg, 0.036 mmol) was subjected to acidic hydrolysis procedure as detailed in preparation of **2.29**, purification of the product provided triol **3.35** (22 mg, 80%): clear oil; R_f = 0.5 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (m, 3H), 3.30 (dd, J = 1.8, 8.2 Hz, 1H), 3.45 (m, 2H), 3.68 (m, 5H), 3.82 (m, 2H), 3.96 (br t, J = 8.0 Hz, 1H), 4.12 (d, J = 1.8 Hz, 1H), 5.12 (d, J = 2.0 Hz, 1H), 7.30-7.60 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7, 37.3, 69.4, 69.5, 71.8, 72.1, 72.4, 72.8, 73.7, 73.8, 74.4, 75.1 (2C), 73.3, 79.9, 80.1, 97.8, 127.2-129.4 (many lines), 138.0, 138.1, 128.8, 138.9.

Carba disaccharide 3.1

A mixture of triol **3.35** (22 mg, 0.028 mmol), 10% Pd (50 mg), formic acid (0.1 mL) in methanol (2 mL) was stirred under an atmosphere of hydrogen (balloon) for 12 h. The reaction mixture was then purged with argon and filtered through a bed of Celite. The filtrate was concentrated in vacuo, and the residue was purified by Sephadex LH-20 chromatography (H_2O) and lyophilized to give **3.1** (8.5mg, 90%): white foamy solid; mp 130-135 °C; R_f = 0.50 (50% methanol: ethyl

acetate); ^{1}H NMR (400 MHz, D_2O) δ 1.40 (dt, J = 11.3, 12.7 Hz, 1H), 1.75 (m, 1H), 1.88 (br d, J = 13.2 Hz, 1H), 3.42 (dd, J = 2.9, 9.5 Hz, 1H), 3.47 (dd, J = 8.6, 11.0 Hz, 1H), 3.45-3.65 (m, 4H), 3.70 (m, 2H), 3.78 (dd, J = 3.3, 9.5 Hz, 1H), 3.85 (br d, J = 9.5 Hz, 1H), 3.99 (m, 2H), 5.04 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 38.6, 61.3, 62.5, 67.2, 69.4, 70.4, 70.7, 73.3, 74.2 (2C), 80.6, 102.0; ESMS 363.2 (M + Na).

Alcohol 3.29[48]

Liquid NH_3 was condensed into a solution of isopropylidene-4-allyl-D-lyxose **3.28** (3.4 g, 11.2 mmol) in THF (30 mL) at -78°C under an atmosphere of argon. Sodium was then added to this solution slowly until the blue color was persistent for several minutes. After slowly warming up to rt, the reaction was quenched with solid NH_4Cl, and filtered. The filtrated was concentrated in *vacuo*, and purified by FCC to give alcohol **3.29** (2.2 g, 92%): clear oil; R_f = 0.3 (30% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33, 1.50 (both s, 6H), 1.91 (m, 1H), 2.12 (m, 1H), 2.32 (m, 1H), 3.61 (d, J = 6.0 Hz, 2H), 3.81 (d, J = 4.5 Hz, 1H), 3.90 (t, J = 6.0 Hz, 1H), 4.05 (t, J = 7.0 Hz, 1H), 5.05 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 26.0, 28.1, 34.2, 38.5, 62.1, 76.4, 75.3, 95.5, 109.3, 117.2, 135.0.

Formate 3.30

A solution of 2,3-isopropylidene-4-allyl-D-lyxose **3.29** (1.15 g, 5.4 mmol) in anhydrous cyclohexane (153 mL) containing diacetoxyiodobenzene (2.07 g, 6.42 mmol) and iodine (1.49 g, 5.88 mmol), was stirred under an atmosphere of argon at rt for 1h. The reaction mixture was then diluted with water and extracted with ether. The organic phase was washed with aqueous $Na_2S_2O_3$ and brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give product **3.30** (1.41 g, 95.9%): clear oil; R_f = 0.75 (20% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4 (br s, 6H), 2.0 (s, 3H), 2.2 (m, 3H), 4.1 (m, 2H), 4.3 (m, 1H), 5.1 (m, 1H), 5.8 (m, 2H), 6.2 (d, 1H), 8.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 31.1, 32.7, 36.7, 39.4, 63.0, 79.5, 81.9, 93.5, 97.2, 117.7, 134.9, 160.5, 207.3.

Thioacetal 3.32

$BF_3{\cdot}OEt_2$ (0.78 mL, 6.12 mmol) was slowly added to a solution of **3.30** (1.4 g, 5.15 mmol) and thiophenol (1.06 mL, 10.3 mmol) in anhydrous CH_2Cl_2 (25 mL), at -78 °C under an atmosphere of argon. The reaction mixture was warmed to –40 °C and stirred at this temperature for 20 min, then recooled to –78 °C, and stirred at this temperature for additional 20 min. Triethylamine (2 mL) was then added and the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude material was dissolved in methanolic ammonia

(25 mL) and stirred at rt for 30 min. Most of the solvent was removed under reduced pressure, the residue was diluted with water, and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. FCC of the residue provided thioacetal **3.32** (1.08 g, 72%); colorless oil; R_f = 0.80 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45, 1.53 (both s, 6H), 1.95 (m, 1H), 2.21 (m, 2H), 3.70 (m, 2H), 4.21 (t, J =7.5 Hz, 1H), 5.06 (m, 2H), 5.38 (d, J =7.0 Hz, 1H), {Ratio of the two doublet at 5.38 is 10:1}, 5.81 (m, 1H), 7.30 (m, 3H), 7.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 27.5, 31.4, 42.8, 62.9, 82.1, 86.9, 110.9, 117.0, 127.5, 129.1, 131.5, 131.6, 134.4, 136.3.

Benzyl ether 3.33

Alcohol **3.32** (1.00 g, 3.4 mmol) was subjected to the standard benzylation procedure as detailed in preparation of **2.20**. FCC purification of the product provided benzyl ether **3.33** (1.28 g, 98%). R_f = 0.90 (5% EtOAc/PE); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.52, 1.63 (both s, 6H), 2.10 (m, 1H), 2.25 (m, 1H), 2.41 (m, 1H), 3.56 (m, 2H), 4.20 (m, 1H), 4.51 (s, 2H), 5.10 (m, 2H), 5.53 (d, J =7.0 Hz, 1H), {Ratio of the two doublet at 5.53 is 10:1}, 5.85 (m, 1H), 7.34-7.5 (m, 10H, Ar-H's); ^{13}C NMR (75MHz, $CDCl_3$) δ 26.1, 27.7, 32.0, 41.5, 69.9, 73.3, 81.5, 87.1, 110.8, 116.9, 127.1, 127.6, 127.7, 128.4, 129.0, 131.4, 136.3.

Aldehyde 3.34

Alkene **3.33** (1.2 g, 3.1 mmol) was subjected to standard ozonolysis procedure as detailed in preparation of **2.22**. FCC purification of the product provided aldehyde **3.34** (0.84g, 70.2%). R_f = 0.5 (10% EtOAc/PE); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.41, 1.50 (both s, 6H), 2.61 (br s, 3H),), 3.53 (m, 2H), 4.12 (m,1H), 4.50 (s, 2H), 5.32 (d, J = 5.1 Hz, 1H), {Ratio of the two doublet at 5.32 is 10:1}, 7.3-7.46 (m, 10H, Ar-H's), 9.75 (s, 1H, -CHO) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 27.5, 37.4, 42.7, 70.3, 73.3, 80.9, 81.1, 111.1, 127.4, 127.7, 128.4, 129.0, 131.6, 134.3, 137.9, 201.0.

Acid 3.7

Aldehyde **3.34** (0.38 g, 1.0 mmol) was subjected to chlorite oxidation procedure as detailed in preparation of **2.23** to give acid **3.7** (0.35 g, 89.7%): Clear oil; R_f = 0.1 (20% ethyl acetate:petroleum ether). Acid **3.7** was determined to be a mixture of thioacetal isomers by integration of protons at 5.55 and 5.60 (ratio 10:1). The major compound was identical to sample obtained from rhodium DUPHOS hydrogenation of **3.21**. Major isomer: ^{1}H NMR (300 MHz, C_6D_6) δ 1.4, 1.5 (both s, 6H), 2.60 (m, 3H), 3.45 (br d, 2H), 4.3 (m, 3H), 5.53 (d, J = 6.0 Hz, 1H), 7.0-7.6 (m, 10H, Ar-H's); ^{13}C NMR (75MHz, C_6D_6) δ 26.5, 28.0, 33.5, 39.9, 70.5, 73.8, 81.8, 81.9, 88.3, 111.6, 127.7, 127.8, 128.2, 128.9, 129.3, 129.4,129.5, 129.7132.0, 132.3, 135.7, 139.0; FABHRMS calcd for $C_{22}H_{26}O_5S$ (M + K) 441.1139, found 441.1139.

Ester 3.24a

Alcohol **3.31** (122.2 mg, 0.26 mmol), acid **3.7** (320 mg, 0.79 mmol) were subjected to coupling procedure as detailed in preparation of **2.24**. Purification of the product gave ester **3.24a** (181 mg, 82.0% from alcohol): colorless oil; R_f= 0.50 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41, 1.52 (both s, 6H), 2.40 (m, 3H), 3.35 (s, 3H), 3.48 (m, 4H),3.56 (dd, J = 3.9 Hz, 1H), 3.80 (m, 1H), 3.90 (t, J = 9.3 Hz, 1H), 4.16 (m, J = 6.1 Hz, 1H), 4.31 (m, 2H), 4.46 (s, 2H), 4.65 (m, 3H), 4.82 (m, 2H), 5.06 (t, J = 7.0 Hz, 5.38 (d, J = 6.2 Hz, 1H), 7.32 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 27.6, 32.5, 38.4, 55.6, 69.0, 69.2, 69.9, 70.9, 73.2, 73.6, 73.7, 75.3, 79.4, 79.8, 80.8, 87.1, 98.3, 111.1, 127.4, 127.6, 127.7, 127.8, 128.0, 128.2, 128.4, 128.6, 129.0, 131.6, 134.6, 138.1, 138.2, 137.7, 171.2; FABHRMS calcd for $C_{50}H_{56}O_{10}S$ (M + K) 887.3229, found 887.3231.

Enol ether 3.36

Ester **3.24a** (170mg, 0.2mmol) was subjected to Tebbe reaction as detailed in preparation of **2.25**. Partial chromatography purification of the product on alumina (Brockmann I, 150 mesh) gave enol ether **3.36** (150 mg, 82%): yellowish oil; R_f = 0.8 on basic alumina plate (10% ethyl acetate:petroleum ether); FABHRMS: calcd for $C_{51}H_{56}O_{10}S$ (M + Na) 869.3697, found 869.3699.

Glycal 3.37

Enol ether **3.36** (130mg, 0.15 mmol), was subjected to cyclization procedure as detailed in preparation of **2.26**. Purification of the product on basic alumina provided glycal **3.37** (85 mg, 75.2%): clear oil; R_f = 0.55 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3, 1.4 (both s, 6H), 1.99 (m, 2H), 2.07 (m, 1H), 3.41 (m, 1H), 3.82 (m, 1H), 3.73 (s, 3H), 3.92 (t, J = 9.0 Hz, 1H), 4.21 (t, J = 9.6 Hz, 1H), 4.34 (m, 1H), 4.41-4.86 (m, 8H), 5.03 (br s, 1H), 7.34 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 27.1, 28.5, 37.8, 69.2, 70.1, 71.9, 72.7, 72.8, 73.5, 73.6, 73.8, 74.5, 74.6, 74.7, 74.8, 75.8, 79.6, 81.2, 96.9, 98.4, 128.5, 127.7, 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 138.2, 138.4, 138.7, 138.9, 156.0.

Alcohol 3.38

Glycal **3.37** (50 mg, 0.05 mmol) was subjected to hydroboration procedure as detailed in preparation of **2.27**. Purification of the product provided alcohol **3.38** (41 mg, 80%): colorless oil; R_f = 0.25 (40% ethyl acetate:petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (m, 1H), 1.33, 1.48 (both s, 6H), 1.72 (m, 1H), 1.82 (dt, J = 2.0, 12.8 Hz, 1H), 3.15 (dd, J = 6.2, 8.4 Hz, 1H), 3.30-3.34 (m, 4H), 3.35 (s, 3H), 3.50 (dd, J = 3.0, 11.0 Hz, 1H), 3.68-3.82 (m, 5H), 3.94 (dd, J = 2.2, 10.8 Hz, 1H), 4.16 (t, J = 4.0 Hz, 1H), 4.36-4.80 (m, 8H), 5.0 (apparent d, J = 11.4 Hz, 1H), 7.3 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 28.5, 28.7, 35.7, 55.4, 68.7, 70.6, 71.2, 73.3, 73.6, 73.9, 74.1, 75.9, 76.2, 77.0, 77.4, 78.1, 80.4, 80.5, 80.9,

81.8, 98.3, 109.2, 127.5, 127.6, 127.7, 128.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 137.7, 138.3; FABHRMS calcd for $C_{45}H_{55}O_{10}$ (M + H) 755.3795, found 755.3795.

Triol 3.40

Alcohol **3.38** (40 mg, 0.053 mmol) was subjected to acidic hydrolysis procedure as detailed in preparation of **2.29**, purification of the product provided triol **3.40** (30 mg, 80%): clear oil; R_f = 0.6 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (m, 1H), 1.46 (m, 1H), 1.60 (m, 1H), 3.20 (m, 2H), 3.36 (s, 3H), 3.58 (m, 6H), 3.85 (m, 2H), 4.08 (m, 2H), 4.42 (s, 2H), 4.68 (m, 6H), 5.08 (d, J = 10.5 Hz, 1H), 7.30-7.60 (m, 20 H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 28.3, 36.4, 55.3, 69.0, 69.2, 70.5, 71.3, 73.7, 73.8, 74.2, 75.1, 76.2 (2C), 80.6, 81.1, 82.8, 98.3, 127.0, 128.8, 136.2, 138.2, 138.3, 138.9.

Acetate 3.39

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (m, 1H), 1.32 (s, 3H), 1.54 (s, 3H), 1.77 (m, 1H), 2.00 (s, 3H), 2.02 (m, buried under s at δ 2.00, 1H), 3.11 (dd, J = 6.0, 9.0 Hz, 1H), 3.16 (dd, J = 3.0, 11.0 Hz, 1H), 3.36 (s, 3H), 3.36 (m, buried under s at δ 3.36, 1H), 3.44 (m, 2H), 3.52 (br d, J = 9.0 Hz, 1H), 3.59 (br d, J = 10.5 Hz, 1H), 3.65 (dd, J = 5.0, 8.0 Hz, 1H), 3.72 (t, J = 9.5 Hz, 1H), 3.81 (dd, J = 3.0, 10.5 Hz, 1H), 4.17 (br t, J = 3.5 Hz, 1H), 4.42 (m, 3H), 4.57 (d, J = 3.5 Hz, 1H), 4.62

(apparent d, J = 12.0 Hz, 1H), 4.72 (m, 3H), 4.91 (apparent d, J = 11.0 Hz, 1H), 4.95 (dd, J = 8.5, 10.5 Hz, 1H), 7.30 (m, 20H).

Carba disaccharide 3.2

Triol **3.40** (25 mg, 0.035 mmol) was subjected to hydrogenation procedure as detailed in preparation of **3.1.** Purification of the product provided **3.2** (10 mg, 90%): white, amorphous solid; mp 159-168 °C; R_f = 0.40 (30% methanol: ethyl acetate); ^{1}H NMR (400 MHz, D_2O) δ 1.31 (q, J = 12.4 Hz, 1H), 1.72 (m, 1H), 1.98 (br d, J = 13.2 Hz, 1H), 3.39 (s, 3H), 3.40-3.74 (m, 9H), 3.90 (m, 2H), 4.00 (br s, 1H), 4.78 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3, 38.3, 55.2, 60.5, 60.9, 69.3, 71.2, 71.4, 72.9, 74.4, 74.5, 77.0, 81.4, 99.3; ESMS 377.2 (M + Na).

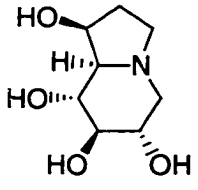
Chapter 4

Synthesis of aza-C-glycosides as Sialyl Lewis X mimetics

4.1 Background[53]

Azasugars are sugars in which the ring oxygen is replaced by NH. They are of interest as potential glycosidase inhibitors.[54] Naturally occurring azasugar

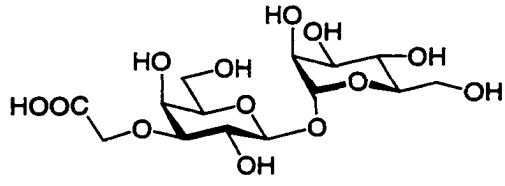
Figure 4.1 Castanospermine



analogues such as castanospermine (Figure 4.1) have been evaluated in therapies for viral infections,[55] cancer,[56] diabetes,[57] and obesity.[57] The activity of azasugars is attributed to their conformational resemblance to natural sugars, and their ability to mimic the oxonium ion transition state involved in glycoside hydrolysis, as a result of the heterocyclic nitrogen being protonated at physiological pH.[58] Aza-C-glycosides,[59] azasugars linked to an aglycone component via a C-glycosidic bond, have the additional benefit of stability towards chemical and enzymic hydrolysis. The goal of this part of the project was the synthesis of the aza C-glycoside **4.2**, which could be useful for gaining a clearer insight on structure-activity factors in sLe^x-selectin binding. The C-glycoside **4.3** also has alternative potential for

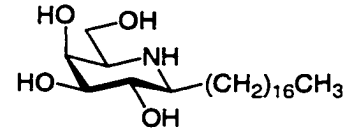
studying the mechanism of glycosidase inhibitors. Before the synthesis of these two compounds was undertaken, the relatively simple lipid imino glycoside **4.1** was targeted as a model compound. Related compounds have received attention as potential anti-HIV agents (Figure 4.2).

Figure 4.2 Aza-C-Glycosides Mimetics



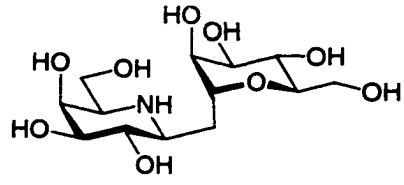
1.6

O-Glycoside sLe^{x}Mimetics



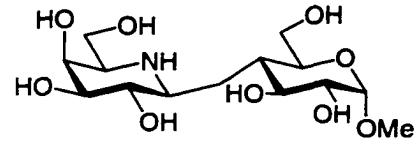
4.1

1-stearic-β-C-Galactoside



4.2

Aza-α-D-gal (1'-1)-α-D-Mannnopyranoside



4.3

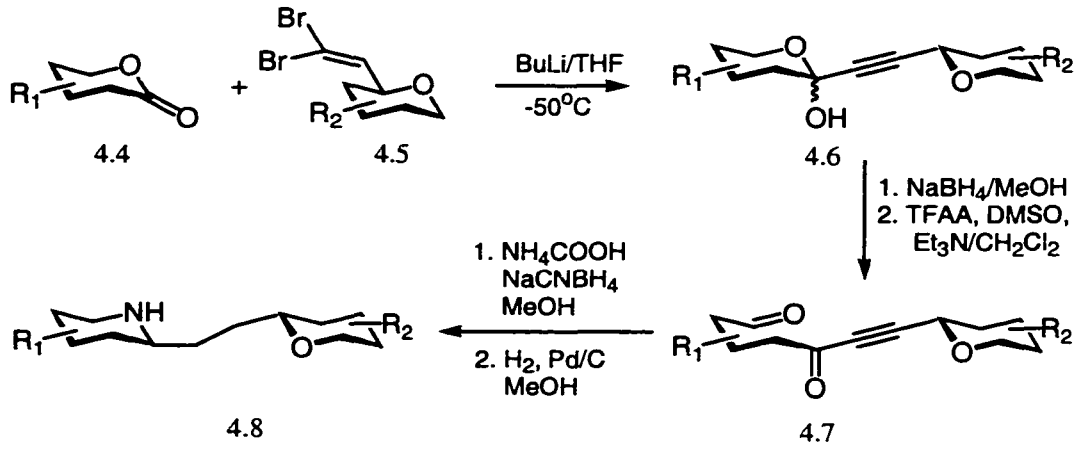
Aza-α-D-gal (1'-4)-α-D-Glucopyranoside

4.2 Retro-Synthetic plan

We envisaged double reductive amination[61] to construct the azasugar ring, based on previous results in this laboratory and others.[62] In a closely related study,[62c] the aza-β-(1→6)–C-disaccharide **4.8**, was obtained via the reductive amination of dicarbonyl sugars **4.7**. The diketone substrate **4.7** was derived from a ketal precursor **4.6**, which was obtained via addition of monosaccharide lithio acetylides **4.5** to pyranolactones **4.4**. This method is applicable to the 1→6 ethylene linked aza-C-disaccharide system, however, the organometallic coupling strategy is

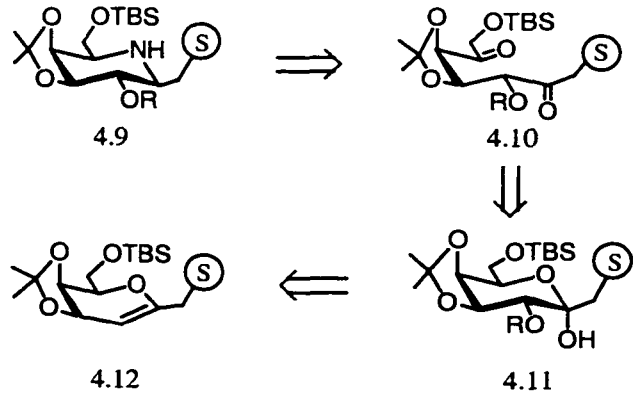
not generally applicable to methylene linked structures (e.g. 1→2, 1→3, 1→4 linked disaccharide analogues).

Scheme 4.1



In our approach, the ketal precursors **4.11** was obtained through dihydroxylation of a C1-substituted galactal **4.12**, which was previously used in our C-glycoside synthesis (Scheme 4.2).

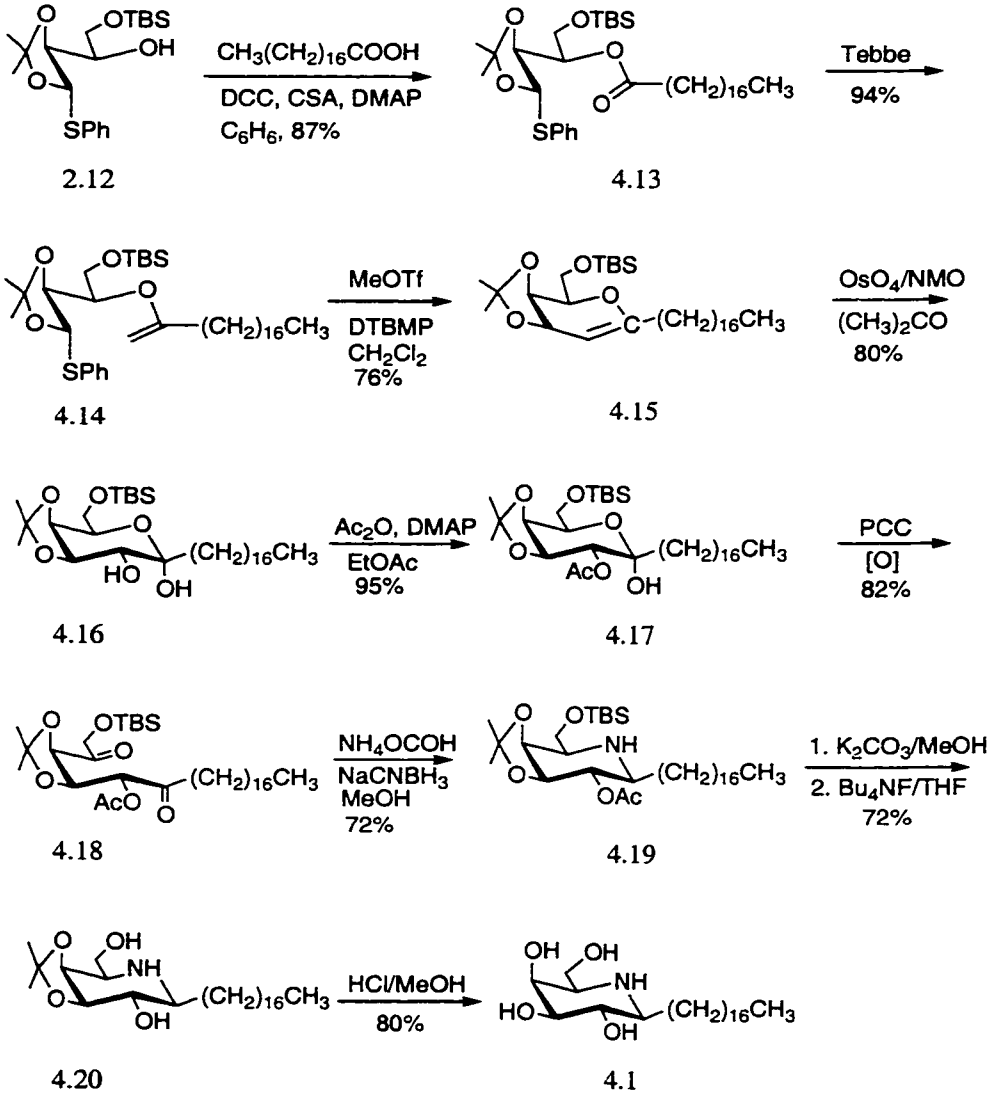
Scheme 4.2



4.3 Synthesis of 1-heptadecyl-β- aza-C-galactoside

The synthesis of azasugar **4.1** started from the DCC mediated coupling of excess stearic acid and thioacetal **3.12**, which led to ester **4.13** in 87% yield. Tebbe reaction on **4.13** resulted in the enol ether **4.14** in 94% yield. Methyl triflate

Scheme 4.3



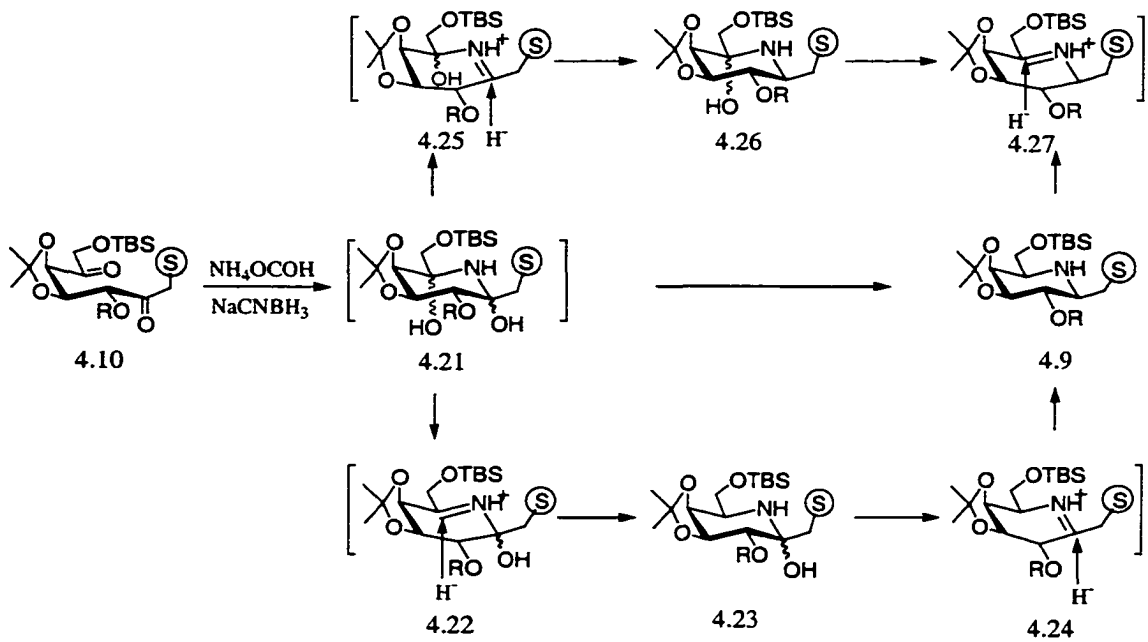
promoted cyclization in the presence of DTBMP afforded glycal **4.15** in 76% yield (Scheme 4.3). Dihydroxylation[63] of glycal **4.15** with osmium tetroxide-NMO proceeded with complete α-selectivity to provide diol **4.16** in 80% yield. Selective acetylation of **4.16** followed by PCC oxidation of the monoacetate **4.17** resulted in diketone **4.18** in 78% yield from **4.16**. Double reductive amination of **4.18** with ammonium formate and sodium cyanoborohydride in the presence of freshly activated 4A molecular sieves, furnished the desired azasugar **4.19** as a single isomer in 72% yield. Subsequent ester hydrolysis followed by the removal of silyl group delivered diol **4.20** in overall yield 72% from **4.19**. Finally, the acetonide was deprotected under acidic condition to give 1-heptadecyl-β-aza-C-galactoside **4.1** in 80% yield (Scheme 4.3).

The stereochemistry of **4.19** was assigned on the basis of *J* values ($J_{1,2}$ = 9.9, $J_{2,3}$ = 7.7, $J_{3,4}$ = 5.1, $J_{4,5}$ = 2.2 Hz)[37] and observation of NOE effects between H_1 and H_3, H_1 and H_5.

The high stereoselectivity of the reductive amination may have been a result of hydride delivery on the cyclic iminium ions.[67] A first formed bis-hemiaminal **4.21** gave the cyclic iminium ion **4.22** or **4.25**, then the first hydride was delivered from the bottom face of **4.22** due to the steric hindrance of the top face by the isopropylidene group, and the second hydride was again delivered from the bottom face of **4.24** due to preference for axial delivery in a chair like conformation. A single isomer, **4.9**, was formed (Scheme 4.4); The order of hydride delivery could

be reversed but the same reasons for the stereochemical outcome apply. The binding of **4.1** with gp-120 was evaluated (Chapter 6).

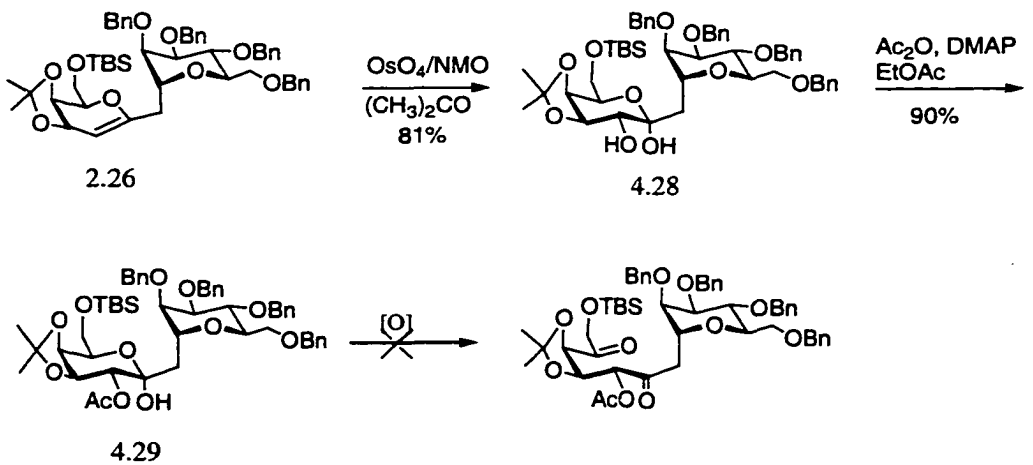
Scheme 5.4



4.4 Synthesis of aza galacto β-C-mannoside

The synthesis of aza-C-mannoside **4.2** was accomplished in a similar fashion. Dihydroxylation of galactal **3.24** gave diol **4.28** in 81% yield. However, the desired monoacetate **4.29** was unreactive under PCC and various other oxidative methods.[62] The lactol **4.29** was therefore reduced to the diol, which was oxidized. This reaction was low yielding, probably due to the acetate protecting group (Scheme 4.5). Therefore, a benzyl protecting group was selectively introduced on **4.28**, using silver triflate[66] and benzyl bromide in the presence of collidine and 4A molecular sieves.

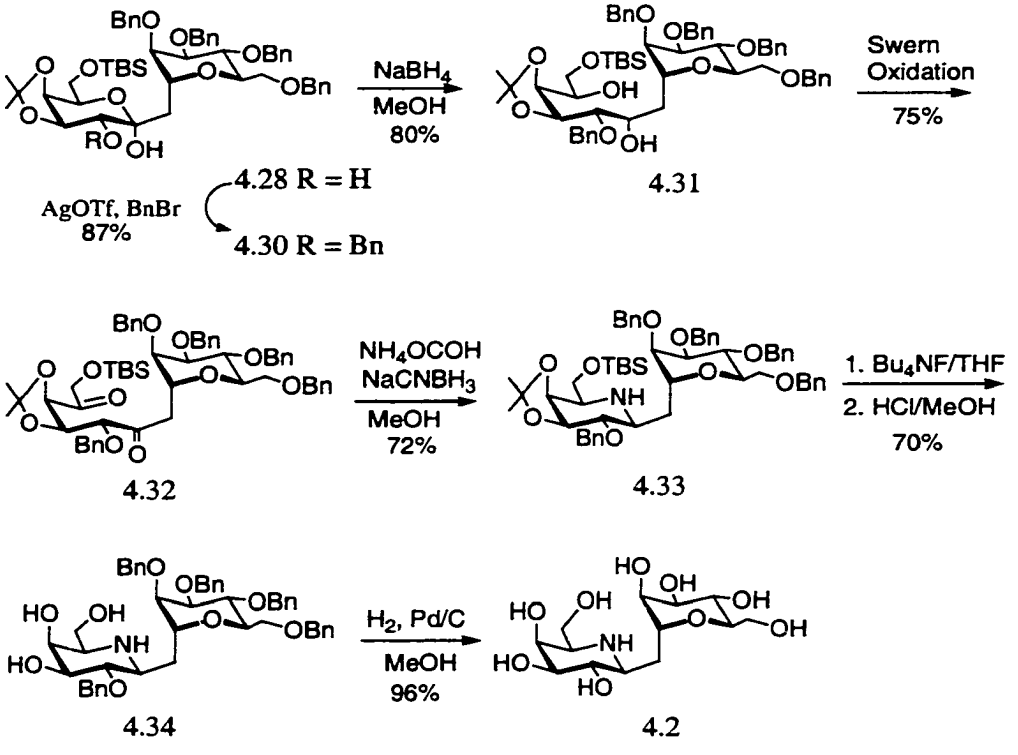
Scheme 4.5



2.26 4.28 4.29

Benzyl ether **4.30** was reduced with sodium borohydride to diol mixture **4.31**. Swern oxidation of **4.31** provided the complex diketone **4.32** in 75% overall yield from **4.30**. Double reductive amination of **4.32** in the presence of 1.8 equivalent ammonium formate and 2.2 equivalents sodium cyanoboronhydride, led to **4.33** as a single isomer in 72% yield. Excess sodium cyanoboronhydride led to byproducts resulting from aldol type reaction. The NOE effects between H1/H3 and H1/H5 confirmed the configuration of the aza-β-C-galactose ring. Finally, a sequence of desilylation, deacetonization and debenzylation on **4.33** provided the target aza-galacto β-C-mannoside **4.2** in a 70% overall yield (Scheme 4.6).

Scheme 4.6



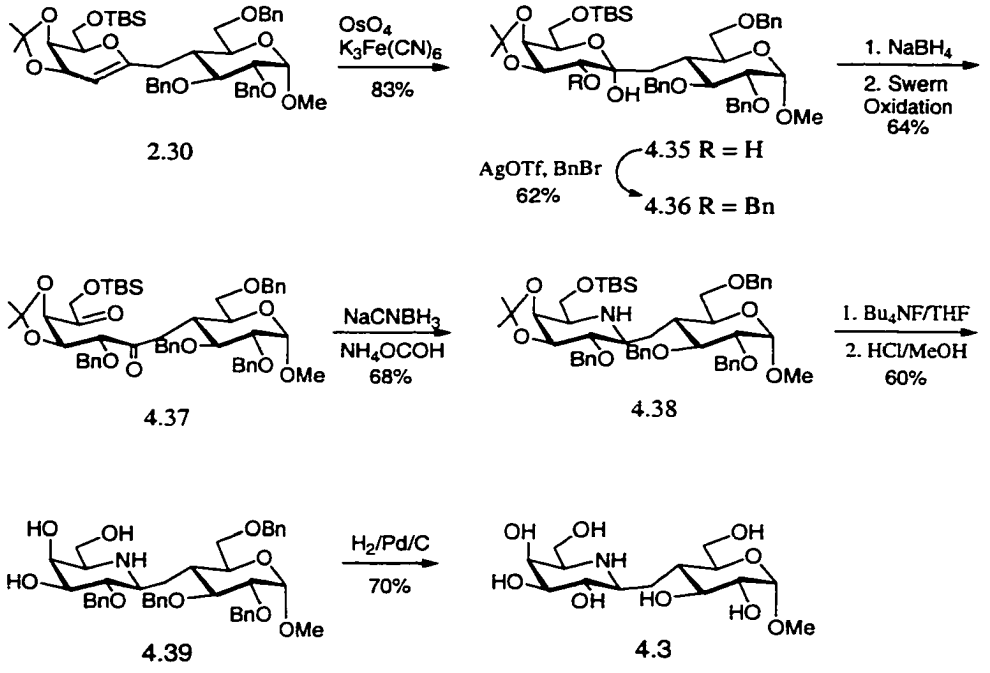
4.5 Synthesis of aza-galacto β(1→4)-C-glucoside

A similar sequence of reactions was adopted for azasugar **4.3**. However, dihydroxylation of **3.38** with osmium tetroxide and NMO was low yielding. Potassium ferricyanide and DABCO,[67] gave much improved results, providing hydroxyl ketal **4.35** in 83% yield.

Regioselective benzylation and the ensuing reduction/oxidation sequence, as mentioned earlier, yielded the expected diketone **4.37** in a total yield of 33%. Double reductive amination on **4.37** in the presence of 3.6 equivalent ammonium formate and 8 equivalent sodium cyanoborohydride, over 24 hour, provided the

fully protected azasugar **4.38** in 68% yield. Standard deprotection procedures led to aza-Galacto β(1→4)-C-glucoside **4.3** in a total of 43% yield. A NOE effect between H1 and H5 was clearly observed, proving the configuration of aza-β-C-galactoside **4.3** (Scheme 4.7). An NOE between H1 and H3 observed in the other two aza-β-C-galactosides was not observable due to severe overlapping.

Scheme 4.7

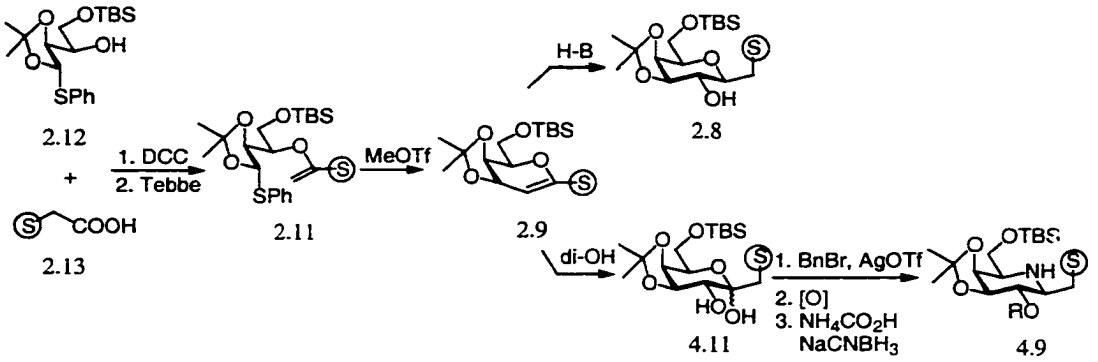


4.6 Conclusion

In conclusion, highly stereoselective double reductive amination reactions were used for the construction of aza-C-glycosides. The ketone precursors are derived from C1-substituted glycals. These are therefore common intermediates for C-glycosides and aza-C-glycosides. The easy accessibility of diverse sugar acids

2.13 allow for the synthesis of a variety of β-aza-C-glycosides with aglycone segments (Scheme 4.8).

Scheme 4.8



4.7 Experimental Section

Ester 4.13

TIA **2.12** (804 mg, 1.58 mmol) and stearic acid (450 mg, 1.58 mmol) were subjected to the coupling procedure as detailed in preparation of **2.24**. FCC purification of the product gave ester **4.13** (1.04 g, 86.4%): colorless oil; $R_f = 0.60$ (10% ethyl acetate:petroleum ether); $[\alpha]_D$ –39.9 (c 5.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3H), 1.02 (s, 9H), 1.25 (m, 28H), 1.42, 1.47 (both s, 3H ea), 1.56 (m, 2H), 2.29 (m, 2H), 4.32 (dd, J = 3.6, 6.6 Hz, 1H), 5.26 (m, 2H), 7.20-7.70 (m, 15H).

Enol ether 4.14

Ester **4.13** (455 mg, 0.646 mmol) was subjected to Tebbe reaction as detailed in preparation of **2.25**. Purification of the product on basic alumina gave enol ether **4.14** (470 mg, 94%): colorless oil; $R_f = 0.65$ (2% ethyl acetate:petroleum ether); $[\alpha]_D$ –57.0 (c 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3H), 1.03 (s, 9H), 1.25 (m, 28H), 1.40 (m, partly buried under singlets at 1.43 and 1.45, 2H), 1.43, 1.45 (both s, 3H ea), 1.98 (m, 2H), 3.72, 3.77 (both br s, 1H ea.), 3.84 (m, 2H), 4.41 (dd, J = 1.8, 7.0 Hz, 1H), 5.35 (d, J = 7.0 Hz, 1H), 7.20-7.70 (m, 15H).

Glycal 4.15

Enol ether **4.15** (300 mg, 0.39 mmol) was subjected to cyclization procedure as detailed in preparation of **2.26**. Purification of the product on basic alumina gave glycal **4.15** (195 mg, 76%): colorless oil; R_f = 0.55 (2% ethyl acetate:petroleum ether); $[\alpha]_D$ +18.0 (c 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3H), 1.03 (s, 9H), 1.23 (m, 28H), 1.34 (both s, 3H ea), 1.42 (m, partly buried under singlets at 1.34 and 1.39, 2H), 1.99 (m, 2H), 3.95 (m, 3H), 4.38 (br d, J = 7.0 Hz, 1H), 4.58 (br s, 1H), 4.68 (dd, J = 3.0, 7.0 Hz, 1H), 5.35 (d, J = 8.3 Hz, 1H), 7.38-7.70 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 19.5, 23.0, 23.2, 26.9, 27.6, 28.5, 29.5, 29.7, 29.8, 30.0, 32.2, 34.2, 63.4, 70.2, 71.5, 75.9, 86.9, 91.3, 97.6, 110.0, 127.8, 133.6,133.7, 135.8, 156.5 FAB HRMS calcd for $C_{42}H_{65}O_4Si$ (M-H) 761.4652, found 761.4649.

Diol 4.16

N-methylmorpholine-N-oxide (0.57 mL, 60 wt% in H_2O, 3.32 mmol) and osmium tetroxide (2.08 mL 2.5 wt% in t-Butanol, 0.17 mmol) were added to a solution of **4.15** (1.1 g, 1.66 mmol) in acetone (20 mL). The reaction mixture was stirred at rt for 0.5 h, at which time a solution of sodium bisulfite (0.57 mL, 1 N) was added and the mixture was stirred for additional 0.5 h. Most of the solvent was evaporated *in vacuo*, the residue was diluted with water and extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4), filtered, and evaporated *in vacuo*. FCC of the residue gave a mixture of anomers **4.16** (0.93 g, 80.4%): colorless oil; R_f = 0.10 (10% ethyl acetate:petroleum ether); FAB HRMS calcd for $C_{42}H_{68}O_6Si$ (M + Na) 719.4684, found 719.4683.

Acetate 4.17

To a solution of anomer mixture **4.16** (0.9 g, 1.3 mmol) and DMAP (15.9 mg, 0.13 mmol) in ethyl acetate (10 mL) was added acetic anhydride (0.16 mL, 1.56 mmol) dropwise, the reaction mixture was stirred at rt for 5 min and was then diluted with methanol (0.5 mL). The mixture was evaporated under reduced pressure, and the residue was purified by FCC to give **4.17** (0.91 g, 95%): clear oil; R_f = 0.85 (20% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.10 (s, 9H), 1.25 (s, 30H), 1.32, 1.53 (both s, 3H ea) 2.12 (s, 3H), 3.85, 3.96 (both m, 1H ea), 4.32 (m, 3H), 4.95 (d, J = 7.50Hz, 1H), 7.40, 7.60 (both m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6, 21.4, 22.1, 23.0, 26.9, 27.0,

27.1, 27.2, 28.0, 29.7, 29.8, 30.0, 30.2, 30.2, 32.2, 38.3, 63.2, 69.2, 73.4, 73.7, 75.3, 76.8, 97.9, 109.7, 127.7, 127.8, 127.9, 128.0, 128.1, 129.7, 129.8, 130.0, 133.1, 133.7, 133.8, 135.8, 170.3; FAB HRMS calcd for $C_{44}H_{71}O_5SiN$ 722.5180, found 722.5183.

Diketone 4.18

To a mixture of PCC (147 mg, 0.136 mmol), celite (147mg), florisil (15mg), sodium acetate (56 mg, 0.68 mmol) and freshly activated 4A molecular sieves (200 mg) in CH_2Cl_2 (3 mL) was added a solution of **4.17** (100 mg, 0.136 mmol) in CH_2Cl_2 (2 mL) The reaction mixture was stirred at rt for 3 hr under an argon atmosphere, and was then filtered through a bed of celite. The filtrate was concentrated under reduced pressure, and the residue was purified by FCC to give **4.18** (82mg, 82%): colorless oil; $R_f = 0.80$ (10% ethyl acetate:petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.10 (s, 9H), 1.25 (br s, 30H), 1.27, 1.5 (both s, each 3H) 2.08 (s, 3H), 2.42 (m, 2H), 4.40 (ABq, J = 17.0 Hz, $\Delta\delta$ = 0.15 ppm, 1H), 4.66 (d, J = 2.2 Hz, 1H), 4.95 (dd, J = 2.2, 8.4 Hz, 1H), 5.17 (d, J = 8.4 Hz, 1H), 7.40, 7.60 (both m, 10H); FAB HRMS calcd for $C_{44}H_{68}O_7Si$ (M + Na) 759.4629, found 759.4632.

Azasugar 4.19

To a mixture of **4.18** (250 mg, 0.34 mmol), ammonium formate (38.0 mg, 0.6 mmol) and 4A powdered molecular sieves (100 mg) was added sodium

cyanoborohydride (75 mg, 1.1 mmol) in one portion. The reaction mixture was stirred for 30 min at rt under an argon atmosphere. The solids were then removed by filtration through a bed of celite, and washed by ether, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether (20 mL) and washed successively with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC purification of the residue gave **4.19** (176.3 mg, 72%): clear oil; R_f = 0.45 (15% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (br t, J = 7.0 Hz, 3H), 1.1 (s, 9H), 1.25 (s, 30H), 1.3, 1.6 (both s, each 3H), 1.2-1.4 (m, buried 2H), 2.45 (t, J = 9.3 Hz, 1H), 3.11 (m, 1H), 3.82 (m, 2H), 3.98 (m, 1H), 4.18 (m, 1H), 4.83 (dd, J = 7.8, 9.9 Hz, 1H), 7.40, 7.60 (both m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 19.5, 21.4, 23.0, 25.9, 26.8, 26.9, 27.1, 28.1, 29.6, 29.9, 30.0, 31.6, 32.2, 57.3, 57.8, 64.4, 74.1, 76.5, 78.7, 86.9, 109.9, 127.8, 129.8, 133.5, 133.6, 134.9, 135.7, 170.3; FAB HRMS calcd for $C_{44}H_{71}O_5SiN$ (M + H) 722.5183, found 722.5179.

Diol 4.20

To a solution of **4.19** (150 mg, 0.21 mmol) in anhydrous methanol (5mL) was added potassium carbonate (21 mg, 0.21 mmol), the reaction mixture was stirred at rt for 0.5 h under an argon atmosphere. The resulting solution was evaporated in *vacuo* to dryness. The crude material was treated with Bu_4NF (0.4 mL, 1M in THF) in THF (5 mL) and stirred at rt for 1h under an atmosphere of argon. The reaction mixture was diluted with water and extracted with ether. The

organic phase was washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC purification of the residue gave diol **4.20** (64.1 mg, 72%): clear oil; R_f = 0.1 (40% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (br t, J = 7.0 Hz, 3H), 1.25 (br s, 32H), 1.32, 1.52 (both s, each 3H), 2.42 (m, 1H), 3.11 (m, 1H), 3.32 (dd, J = 7.8, 9.9 Hz, 1H), 3.82 (m, 2H), 3.98 (m, 1H), 4.18 (m, 1H).

Azasugar 4.1

Diol **4.20** (60 mg, 0.14 mmol) was subjected to hydrolysis procedure as detailed in the preparation of **2.29**. FCC purification of the product gave **4.1** (43.5 mg, 80%): clear oil; R_f = 0.1 (20% methanol:ethyl acetate). ^1H NMR (500 MHz, CD_3OD) δ 0.90 (br t, J = 7.0 Hz, 3H), 1.30 (m, 28H), 1.50 (m, 2H), 1.62 (m, 1H), 1.94 (m, 1H), 2.00 (s, 1H, -NH), 2.78 (m, 1H), 3.15 (t, J = 6.5 Hz, 1H), 3.42 (dd, J = 3.0, 8.5 Hz, 1H), 3.62 (t, J = 10.0 Hz, 1H), 3.78 (m, 2H), 4.00 (br s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.6, 23.9, 26.8, 30.6, 30.7, 30.9, 31.1, 32.0, 32.2, 60.9, 61.2, 61.5, 68.9, 71.7, 75.6. FAB HRMS calcd for $C_{23}H_{48}NO_4$ (M + H) 402.3583, found 402.3584.

Diol 4.28

N-methylmorpholine-N-oxide (0.5 mL, 60 wt% in H_2O, 2.92 mmol) and osmium tetroxide (2.03 mL 2.5 wt% in t-Butanol, 0.16 mmol) were added to a solution of **3.24** (1.4 g, 1.46 mmol) in acetone (15 mL). The reaction mixture was

stirred at rt for 0.5 h, at which time sodium bisulfite (0.5 mL, 1N aq solution, 0.5 mmol) was added and the reaction mixture was stirred for additional 0.5 h. Most of the solvent was evaporated in *vacuo*, the residue was diluted with water and extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4), filtered, and evaporated in *vacuo*. FCC of the residue gave **4.28** (1.18 g, 81.2%): colorless oil; R_f = 0.20 (30% ethyl acetate:petroleum ether); ^{1}H NMR (75 MHz, $CDCl_3$) δ 1.0 (s, 9H), 1.38, 1.42 (both s, each 3H), 1.69 (m, 1H), 2.15 (dd, J = 12.0, 20.0 Hz, 1H), 3.41 (d, J = 6.96 Hz, 1H), 3.55 (m, 5H), 3.72 (m, 2H), 3.82 (s, 1H), 3.91 (m, 2H), 4.11 (m, 1H), 4.52 (m, 9H), 7.41, 7.70 (m, 30H).

Benzyl ether 4.30

To a mixture of diol **4.28** (850 mg, 0.86 mmol), dry collidine (0.55 mL, 4.13 mmol), benzyl bromide (0.395 mL, 3.32 mmol) and powdered 4A molecular sieves (400 mg) was added silver triflate (853 mg, 3.32 mmol) at 0°C. The reaction mixture was stirred for 30 min at this temperature under an argon atmosphere. The ice bath was then removed and the reaction was stirred at rt for additional 4 h. The solids were then removed by filtration through a bed of celite, and washed by ether, and the filtrate was washed successively with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue gave **4.30** (0.80 g, 87%): clear oil; R_f = 0.8 (20% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (s, 9H), 1.42, 1.53 (both s, each 3H), 2.02 (m, 2H), 3.41 (d, J = 6.96 Hz, 1H), 3.62 (m, 1H), 3.69 (m, 1H), 3.82 (m, 4H),

3.98 (m, 4H), 4.41-5.0 (m, 12H), 7.4, 7.7 (m, 35H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 26.7, 27.1, 28.6, 38.6, 63.0, 68.2, 68.9, 69.0, 71.5, 72.4, 73.3, 73.5, 74.1, 74.8, 76.2, 76.4, 78.0, 81.0, 97.7, 108.9, 127.5, 127.7, 127.8, 127.9, 128.0, 128.4, 129.0, 129.7, 133.6, 133.8, 135.7, 135.8, 138.2, 138.4, 138.5. FAB HRMS calcd for $C_{67}H_{76}O_{11}Si$ 1107.5055, found 1107.5047.

Diol 4.31

Diol **4.30** (100 mg, 0.09 mmol) and $NaBH_4$ (11 mg, 0.14 mmol) in anhydrous ethanol was stirred at rt for 1.5 h, under an atmosphere of argon. Ethanol was then removed under reduced pressure. The residue was diluted with ether and washed with saturated aqueous NH_4Cl, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue gave a mixture of diol stereoisomers **4.31** (80 mg, 80%): clear oil; R_f = 0.2, 0.3 (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) for first isomer: δ 1.1 (s, 9H), 1.35, 1.48 (both s, each 3H), 1.69 (m, 1H), 2.10 (m, 1H), 3.54 (dd, J =2.6, 6.2 Hz, 1H), 3.60 (dd, J = 4.0, 9.9 Hz, 1H), 3.67-4.0 (m, 9H), 4.16 (m, 1H), 4.25 (d, J =6.9 Hz, 1H), 4.34 (t, J = 6.2, 12.5 Hz, 1H), 4.41-5.0 (m, 10H), 7.4, 7.7 (m, 35H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 25.2, 26.7, 27.1, 33.6, 65.5, 68.7, 70.0, 71.9, 72.7, 73.1, 73.3, 73.4, 73.8, 74.4, 74.9, 75.1, 75.6, 76.4, 79.3, 79.7, 118.2, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.6, 128.8, 128.9, 129.6, 133.7, 135.7, 138.0, 138.3; FAB HRMS calcd for $C_{67}H_{78}O_{11}Si$ 1109.5211, found 1109.5214.

^{1}H NMR (300 MHz, $CDCl_3$) for second isomer: δ 1.1 (s, 9H), 1.32, 1.48 (both s, each 3H), 1.75 (m, 2H), 3.61-4.01 (m, 12H), 4.22 (m, 2H), 4.41-4.48 (m, 10H), 7.4, 7.7 (m, 35H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 25.5, 27.0, 27.2, 35.2, 65.2, 68.1, 68.9, 69.0, 70.2, 71.8, 72.5, 73.4, 73.5, 74.0, 75.8, 76.2, 77.5, 77.7, 79.2, 108.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.5, 128.6, 129.0, 129.8, 133.6, 135.8, 138.3, 138.4.

Diketone 4.32

To a solution of oxalyl chloride (0.068 mL, 0.74 mmol) in CH_2Cl_2 (2 mL) at -78°C was added DMSO (0.06 mL, 0.88 mmol) dropwise, after the mixture was stirred for 20 min, a solution of diol mixture **4.31** (80 mg, 0.074 mmol) in CH_2Cl_2 (2 mL) was added in one portion, and stirred for additional 20 min. Then Et_3N (2 mL) was added to the reaction mixture to get yellowish suspension, and the reaction was allowed to rise to rt within 1 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether, the organic layer was washed successively with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC to give **4.32** (60 mg, 75%): clear oil; R_f = 0.4 (20% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.22 (s, 6H), 3.10 (d, J = 6.20 Hz, 1H), 3.88 (m, 2H), 3.91 (m, 2H), 3.94 (d, J = 9.52 Hz, 1H), 4.10 (m, 1H), 4.18 (d, J = 2.2 Hz, 1H), 4.50-4.63 (m, 13H), 5.02 (dd, J = 6.4, 12.8 Hz, 1H), 5.11 (d, J = 18.7 Hz, 1H), 7.4, 7.7 (m, 35H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 25.0, 27.6, 68.9, 69.1, 70.1, 71.9, 72.8, 73.1, 73.5, 74.0,

75.4, 75.8, 76.9, 77.2, 80.3, 80.5, 83.8, 111.1, 126.6, 129.4, 129.5, 129.6, 129.7, 130.3, 130.5, 133.8, 134.3, 136.2, 136.4, 136.5, 138.4, 139.4, 139.5, 139.7, 205.8, 208.9; FAB HRMS calcd for $C_{67}H_{74}O_{11}Si$ 1105.4898, found 1105.4899.

Azasugar 4.33

To a mixture of **4.32** (60 mg, 0.06 mmol), ammonium formate (7.0 mg, 0.11mmol) and powdered 4A molecular sieves (80.0 mg) was added sodium cyanoborohydride (14.0 mg, 0.22 mmol) in one portion. The reaction mixture was stirred for 1 h at rt under an argon atmosphere. The solids were then removed by filtration through a bed of celite, and washed by ether, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether and washed successively with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC to give **4.33** (45.3mg, 72%): clear oil; R_f = 0.50 (15% ethyl acetate:petroleum ether). ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.35, 1.52 (both s, 6H), 1.72 (m, 1H), 2.32 (m, 1H), 2.65 (m, 1H), 3.18 (m, 1H), 3.40 (dd, J = 6.96, 9.92 Hz, 1H), 3.62 (dd, J = 2.9, 4.8 Hz, 1H), 3.77 (m, 3H), 3.83 (m, 1H), 3.99 (t, J = 6.9 Hz, 1H), 4.05 (m, 3H), 4.23 (m, 1H), 4.30 (d, J = 1.6 Hz, 1H), 4.43 (m, 7H), 4.68 (m, 2 H), 5.13 (d, J = 11.7Hz, 1H), 7.4, 7.7 (m, 35H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 27.3, 27.7, 27.8, 29.1, 33.1, 58.7, 58.9, 65.5, 70.3, 72.3, 72.9, 73.5, 73.7, 74.1, 74.4, 74.9, 76.2, 78.1, 78.6, 82.1, 83.6, 108.9, 129.9, 130.1, 130.3, 130.4, 134.4, 136.3,

136.5, 139.6, 139.7, 140.0; FAB HRMS calcd for $C_{67}H_{77}NO_9Si$ 1068.5446, found 1068.5442.

Triol 4.34

A solution of **4.33** (70 mg, 0.066 mmol) and Bu_4NF (0.13 mL, 1M solution in THF, 0.13 mmol) in THF (5 mL) was stirred at rt for 0.5 h, under an atmosphere of argon. The mixture was then diluted with water and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. To a solution of the above crude material in dry methanol (3 mL) was added HCl (0.8 mL, 1M solution in ether, 0.8 mmol) dropwise. The reaction mixture was stirred at room temperature for 20 min, and then neutralized by sodium methoxide. Removal of the volatiles under reduced pressure and FCC of the residue provided triol **4.34** (36.4 mg, 70%): clear oil; R_f = 0.3 (10% methanol:ethyl acetate); FAB HRMS calcd for $C_{48}H_{55}NO_9$ (M + H) 790.3955, found 790.3955

Azasugar 4.2

A mixture of triol **4.30** (34 mg, 0.043 mmol), 10% Pd on carbon (60 mg) and formic acid (0.1 mL) in methanol (2 mL) was stirred under an atmosphere of hydrogen (balloon) for 12 h. The reaction mixture was then purged with argon and filtered through a bed of celite. The filtrate was concentrated in vacuo, and the residue was purified by Sephadex LH-20 chromatography (H_2O) and lyophilized to

give **4.1** (14 mg, 96%): white powder; ^{1}H NMR (500 MHz, D_2O) δ 2.05 (m, 1H), 2.32 (br d, J = 15.5 Hz, 1H), 3.29 (br t, J = 9.5 Hz, 1H), 3.45 (t, J = 6.5 Hz, 1H), 3.63 (dd, J = 3.0, 9.5 Hz, 1H), 3.68-3.90 (m, 9H), 4.15 (br s, 1H), 4.20 (m, 1H); ^{13}C NMR (90 MHz, D_2O) δ 28.7, 59.0, 59.7, 60.1, 66.8, 68.0, 69.5, 70.4, 70.5, 73.2, 74.9, 76.0; FAB HRMS calcd for $C_{67}H_{77}O_9NSi$ (M + H) 340.1608, found 340.1608.

Diol 4.35

To a solution of **2.40** (600 mg, 0.68 mmol) in t-Butanol (5 mL) and H_2O (5 mL) was added $K_3Fe(CN)_6$ (660 mg, 2.04 mmol), K_2CO_3 (277 mg, 2.04 mmol), 1,4-diazabicyclo-octane (20 mg, 0.2 mmol) and osmium tetroxide (0.11 mL 2.5 wt% in t-Butanol, 8 μmol). The reaction mixture was stirred at rt for 18h. At which time solid sodium sulfite (200 mg) was then added and the stirring was continued for additional 4 h. The pale blue solution obtained was diluted with water and extracted with ethyl acetate (4x). The combined organic phase was dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was purified by FCC to give **4.35** (500 mg, 83.3%): colorless oil; R_f = 0.20 (30% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.0 (s, 9H), 1.31, 1.43 (both s, 6H), 1.46 (m, buried, 1H), 1.71 (dd, J = 5.84, 15.76 Hz, 1H), 2.1 (m, 1H), 3.12 (d, J =3.6 Hz, -OH, 1H), 3.32 (s, 3H), 3.47 (m, 2H), 3.68 (m, 5H), 3.93 (t, J = 9.2, 18.4Hz, 1H), 4.16 (m, 1H), 4.23 (m, 1H), 4.4 (m, 1H), 4.66 (m, 6H), 5.07(d, J = 11.2 Hz, 1H), 5.7 (s, -OH, 1H), 7.4, 7.7 (both m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 26.2, 27.0, 28.2, 38.1, 39.4, 55.4, 62.9, 68.4, 70.2, 71.5, 72.9, 73.9, 74.4, 76.5, 77.4, 81.3, 81.6, 96.3,

98.2, 108.9, 127.6, 127.7, 127.9, 128.1, 128.2, 128.5, 128.6, 128.8, 129.6, 129.7, 133.6, 133.8, 135.7, 135.8, 137.0, 137.5, 138.0; FAB HRMS calcd for $C_{54}H_{66}O_{11}Si$ (M + H) 941.4272, found 941.4275.

Benzyl ether 4.36

To a mixture of **4.35** (200 mg, 0.22 mmol), dry collidine (0.30 mL, 1.98 mmol), benzyl bromide (0.196 mL, 1.65 mmol) and powdered 4A molecular sieves (300 mg) was added silver triflate (423 mg, 1.65 mmol) at 0°C. The reaction mixture was stirred for 30 min at this temperature under an argon atmosphere. Then the ice bath was removed and the reaction was stirred at rt for additional 5 h. The solids were then removed by filtration through a bed of celite, and washed by ether, and the filtrate was washed successively with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC to give **4.36** (136 mg, 62%): clear oil; R_f = 0.7 (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (s, 9H), 1.31, 1.43 (both s, 6H), 1.46 (m, buried, 1H), 1.91 (dd, J = 5.84, 15.76 Hz, 1H), 2.2 (m, 1H), 3.26 (m, 2H), 3.31 (s, 3H), 3.50 (m, 2H), 3.58 (m, 3H), 3.79 (m, 1H), 3.92 (m, 2H), 4.3 (m, 1H), 4.6 (m, 7H), 5.0 (m, 2H), 5.45 (s, -OH, 1H), 7.3, 7.7 (both m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6, 26.7, 27.1, 28.7, 37.4, 37.9, 55.4, 63.0, 68.4, 70.8, 72.1, 73.0, 73.1, 73.6, 73.8, 75.5, 78.2, 80.7, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.1, 129.7, 133.7, 133.8,

135.8, 135.9, 137.8, 138.3, 138.4, 138.7; ESMS 1026 (M + NH_4); FAB HRMS calcd for $C_{61}H_{72}O_{11}Si$ (M + H) 1031.4742, found 1031.4741.

Diketone 4.37

Acetal **4.36** (100 mg, 0.1 mmol) was subjected to reduction procedure as detailed in the preparation of **4.31**. Partial purification by FCC gave a mixture of diol stereoisomers (85 mg, 85%): clear oil; R_f = 0.2, 0.22 (20% ethyl acetate:petroleum ether); FAB HRMS calcd for $C_{61}H_{74}O_{11}Si$ (M + H) 1033.4891, found 1033.4893.

To a solution of oxalyl chloride (0.07 mL, 0.75 mmol) in CH_2Cl_2 (2 mL) at –78 °C was added DMSO (0.07 mL, 0.9 mmol) dropwise under an atmosphere of argon, after the mixture was stirred for 20 min, a solution of the above diol mixture (75 mg, 0.075 mmol) in CH_2Cl_2 (2 mL) was added in one portion, and stirred for additional 20 min at –78 °C. Then the reaction mixture was allowed to warm up to –50 °C within 1 h and stirred at this temperature for another 20 min. This reaction mixture was then cooled back to –78 °C, and added Et_3N (2 mL). The mixture was warmed up to rt within 1h and was poured into saturated aqueous $NaHCO_3$ and extract with ether, the organic layer was washed successively with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC to give **4.37** (60 mg, 75%): clear oil; R_f = 0.3 (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, C_6D_6) δ 1.0 (s, 9H), 1.11, 1.33 (both s, 6H), 2.35 (m, 1H), 2.65 (dd, J = 5.6, 30 Hz, 1H), 2.85 (dd, J = 5.6, 30.0 Hz, 1H),

3.39 (s, 3H), 3.50 (m, 2H), 3.58 (m, 1H), 3.75 (t, J = 12.5 Hz, 1H), 3.92 (m, 2H), 4.05 (m, 2H), 4.3 (m, 2H), 4.4 (m, m, 3H), 4.6 (m, 5H), 4.95 (d, J = 5.0 Hz, 1H), 7.3, 7.7 (both m, 30H); FAB HRMS calcd for $C_{61}H_{70}O_{11}Si$ (M + H) 1029.4585, found 1029.4598.

Azasugar 4.38

To a mixture of **4.37**(55 mg, 0.06 mmol), ammonium formate (28 mg, 4.4 mmol) and powdered 4A molecular sieves (60 mg) was added sodium cyanoborohydride (56 mg, 0.88 mmol) in one portion. The reaction mixture was stirred for 24 h at rt under an argon atmosphere. The solids were then removed by filtration through a bed of celite, and washed by ether, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether and washed successively with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC to give **4.38** (37 mg, 68%): clear oil; R_f = 0.80 (20% ethyl acetate:petroleum ether); ^1H NMR (400 MHz, C_6D_6) δ 1.2 (s, 9H), 1.31, 1.48 (both s, 6H), 1.4 (buried, m, 1H), 2.51 (m, 1H), 3.05 (m, 1H), 3.18 (s, 3H), 3.2 (buried, 1H), 3.60 (m, 1H), 3.75 (m, 4H), 3.86 (m, 1H), 3.98 (m, 2H), 4.08 (m, 1H), 4.4 (m, 4H), 4.6 (m, 2H), 4.75 (d, J = 4.2 Hz, 1H), 5.1 (m, 1H), 7.7 (both m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 27.3, 27.7, 29.0, 31.8, 31.8, 55.4, 58.8, 59.4, 65.3, 66.3, 67.4, 72.9, 73.2, 73.8, 75.2, 76.0, 76.3, 79.7, 83.7, 84.4, 99.1, 109.6; FAB HRMS calcd for $C_{61}H_{73}O_9NSi$ (M + H) 992.5131, found 992.5132.

Triol 4.39

4.38 (30 mg, 0.03 mmol) was subjected to desilylation and deacetonization procedure as detailed in preparation of **4.34**. FCC of the product gave triol **4.39** (12 mg, 60%): clear oil; $R_f = 0.3$ (10% methanol:ethyl acetate).

Azasugar 4.3

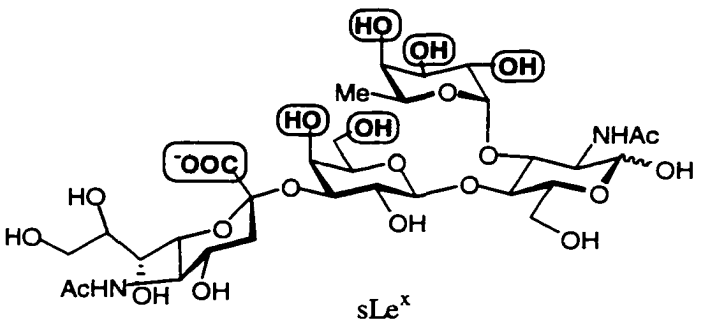
The above triol **4.35** (8 mg, 0.01 mmol) was subjected to hydrogenation procedure as detailed in preparation of **4.2**. The residue was purified by Sephadex LH-20 chromatography and lyophilized to give **4.3** (4 mg, 70%): white powder; ^{1}H NMR (500 MHz, D_2O) δ 1.29 (m, 1H), 1.67(m, 1H), 2.09 (br d, J = 16.0 Hz, 1H), 2.44 (t, J = 10.0 Hz, 1H), 2.83 (t, J = 6.5 Hz, 1H), 3.36 (t, J = 10.0 Hz, 1H), 3.41 (s, 3H), 3.50-3.70 (m, 6H), 3.83 (m, 2H), 4.01 (d, J = 3.0 Hz, 1H), 4.83 (d, J = 3.5 Hz, 1H); ^{13}C NMR (90 MHz, D_2O) δ 31.6, 42.6, 55.1, 58.2, 59.3, 61.6, 61.9, 69.5, 71.9, 72.1, 72.3, 72.6, 75.0, 99.6; ESMS 354.2 (M + H). FAB HRMS calcd for $C_{14}H_{28}O_9N$ (M + H) 354.1765, found 354.1764.

Chapter 5

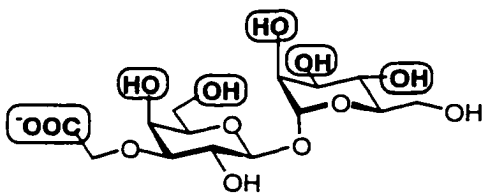
Synthesis of O-linked 1,1-gal-man disaccharide

5.1 Background

Figure 5.1 sLe^x and O-linked 1,1-Gal-Man Disaccharide



sLe^x



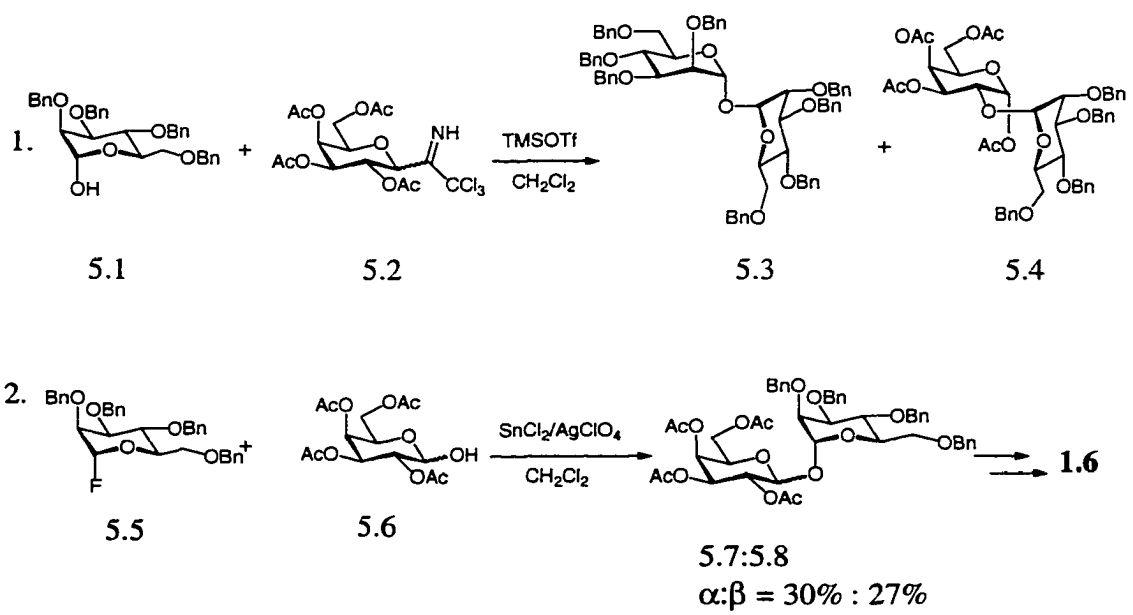
1.6

O-linked disaccharide **1.6** was designed to mimic the active conformation of sLe^x (Figure 2.1). In order to obtain a sample of the O-disaccharide **1.6** for NMR and biological studies, we designed an original synthesis of fully protected O-linked 1,1-gal-man disaccharide **5.8**, which is a key precursor to the sLe^x mimetic, **1.6**.

5.2 Previous synthesis of O-linked 1,1-gal-man disaccharide

Wong and coworkers pursued two approaches[20] to a protected β-D-galactopyranosyl-α-D-mannopyranoside precursor to **1.6**: β-D-galactopyranosylation of 2,3,4,6-tetra-O-benzyl D-mannose (entry 1 in Scheme 5.1) and α-D-mannosylation of 2,3,4,6-tetra-O-acetyl-D-galactose (entry 2 in Scheme 5.1). Neighboring group participation is expected to favor β-galactoside formation in the former reaction, and anomeric effect was expected to lead to the α-mannoside in the latter reaction. The reaction between the galactosyl donor **5.2** and mannosyl acceptors **5.1** in the presence of TMSOTf or $BF_3{\cdot}Et_2O$ afforded the unexpected α-D-mannosyl α-D-Mannoside **5.3** and α-D-Mannopyranosyl-(1→2)-D-galactopyranoside **5.4**; Reaction of 2,3,4,6-tetra-O-acetylgalactose **5.6** and

Scheme 5.1

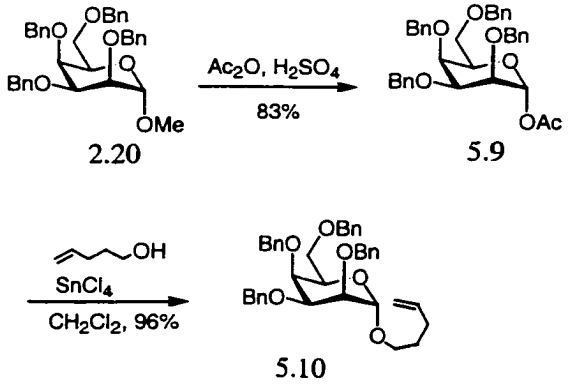


mannosyl donor **5.5**, activated with $SnCl_2$-$AgClO_4$, gave a mixture of 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside (30%) **5.7** and 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl 2,3,4,6- tetra-O-benzyl α-D-mannopyranoside **5.8** (27%) (Scheme 5.1). Disaccharide **5.8** was converted to the desired carboxylic acid **1.6** as described later.

5.3 New synthesis of O-linked 1,1-gal-man disaccharide 5.8

Our strategy is to explore pentenyl mannoside **5.10** as the glycosyl donor.[68] This approach overcomes the complexity of making the mannopyranosyl fluoride and simplifies the coupling procedure. Preparation of **5.10** is as follows: Acetolysis of benzyl ether **2.20** by careful treatment of a mixture of 500:1.5 (AcOH-H_2SO_4) in acetic anhydride, led to the desired acetate **5.9** in 83% yield. This reaction is highly dependent on the acid ratio and the amount of acid mixture that is used. Excess acid would result in partial debenzylation. Acetate **5.9** was smoothly converted to

Scheme 5.2

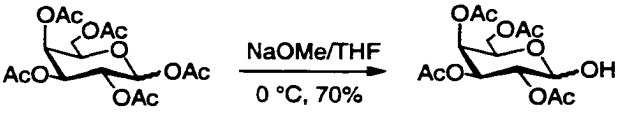


2.20 5.9 5.10

pentenyl glycoside **5.10** in 96% yield, by employing 4-penten-1-ol and tin(IV) chloride.[69] (Scheme 5.2)

The glycosyl acceptor **5.6** was synthesized from selective deprotection of penta-acetylgalactose **5.11** with sodium methoxide in THF solution at 0 °C in 70% yield (Scheme 5.3).[70]

Scheme 5.3

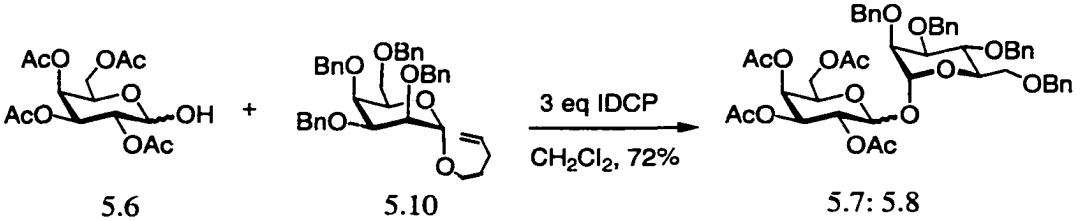


penta-O-acetylgalactose

5.11 5.6

Iodonium dicollidine perchlorate (IDCP) mediated coupling[68] of subunits **5.10** and **5.6** (1:1) in anhydrous methylene chloride afforded a 2:1 α/β mixture of galactosides. The total yield for both isomers was 72%, and the desired β isomer **5.8** was separable from α isomer **5.7** by chromatography. The stereochemistries of the α-, and β-isomer were established by comparison of ^{1}H NMR spectra ($J_{1,2\,(gal)}$ = 2.6 Hz for **5.7** vs. 7.6 Hz for **5.8**) (Scheme 5.4).

Scheme 5.4



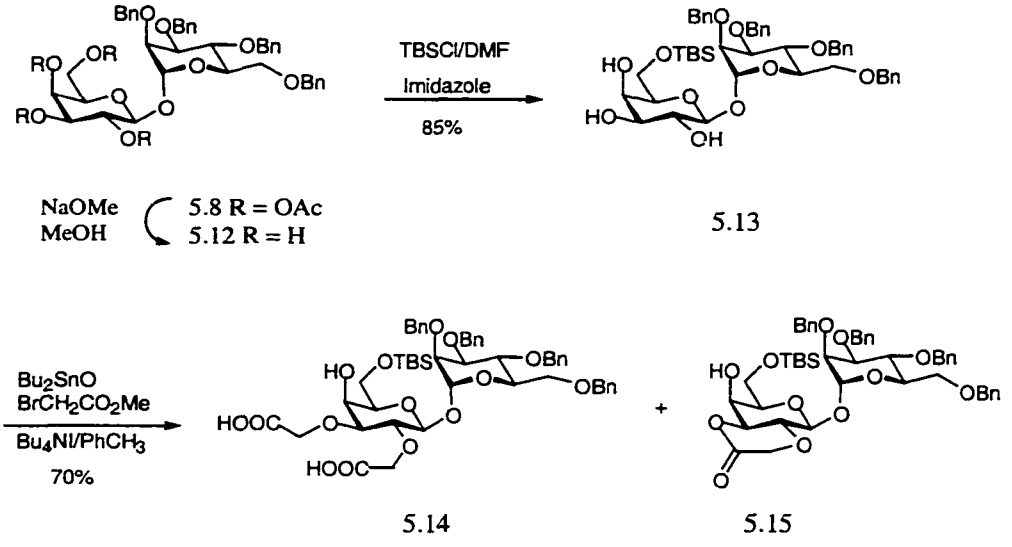
5.6 5.10 5.7: 5.8

α:β = 48% : 24 %

5.4 Incorporation of O-acetic acid at C-3 position of galactose

Disaccharide **5.8** was deacetylated to give tetra-ol **5.12**. Our initial plan for the introduction of the 3-O-acetic acid residue involved selective alkylation of silyl ether **5.13** in the presence of dibutyl tin oxide and methyl 2-bromo acetate. Unfortunately, all attempts at this procedure resulted in a mixture of 2-alkylated and the 2,3-di-alkylated products (Scheme 5.5).

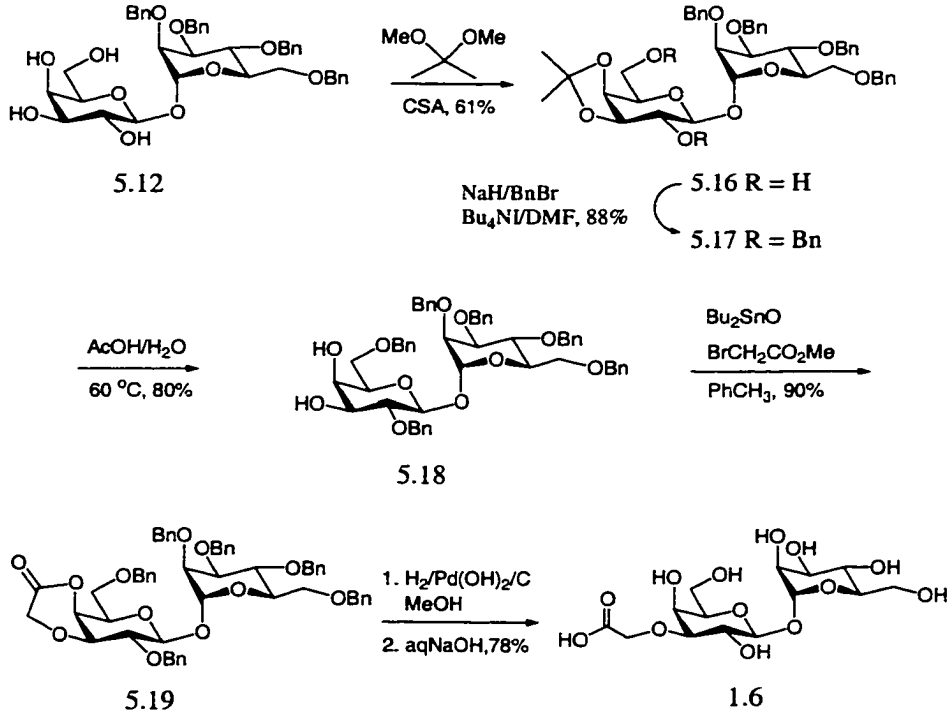
Scheme 5.5



Consequently, we used the method developed by Wong and coworkers.[20] Therefore, the 3- and 4-hydroxy groups in **5.12** were protected as the acetonide. The resulting diol **5.16** was transformed to dibenzyl ether **5.17**. After cleavage of the acetonide, the diol **5.18** was reacted with di-*n*-butyltin oxide and alkylated with methyl α-bromoacetate to afford lactone **5.19** in 90% yield. Hydrogenation over

Pearlman's catalyst followed by saponification with sodium hydroxide furnished **1.6**. The overall yield for the two steps was 78% (Scheme 5.6).

Scheme 5.6



5.5 Experimental section

2,3,4,6-tetra-O-acetylgalactose 5.6

To a suspension of sodium methoxide (38 mg, 0.70 mmol) in of THF (5 mL) in an ice-salt bath was added β-D-galactose pentaacetate **5.11** (1.12 g, 2.8 mmol). The mixture was stirred at 0 °C for 6 h, then quenched by addition of acetic acid (1 mL). The solution was evaporated to dryness under reduced pressure. The crude product was dissolved in CH_2Cl_2, and washed with water (3x). The organic phase was dried ($MgSO_4$), and evaporated to dryness. The residue was purified by

FCC to give **5.6** (0.7 g, 70%): clear oil; TLC R_f = 0.10 (35% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91, 2.01, 2.05, 2.11 (all s, 3H ea), 3.83 (dt, J = 1.0, 6.7 Hz, 1H), 4.12 (m, 2H), 4.43 (dd, J = 2.6, 10.9 Hz, 1H), 5.12 (dd, J = 2.3, 10.9 Hz, 1H), 5.42 (m, 2H).

2,3,4,6-Tetra-O-acetyl-α/β-D-galactopyranosyl-2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside 5.7 and 5.8

To a mixture of **5.6** (0.7 g, 2.01 mmol), **5.10** (1.1 g, 2.01 mmol) and freshly activated 4A molecular sieves in CH_2Cl_2 (20 mL) was added IDCP (1.27 g, 8.04 mmol), at rt under an argon atmosphere. When the starting material had completely disappeared as monitored by TLC (ca. 1h), the reaction mixture was filtered through a bed of celite. The filtrate was washed with saturated, aqueous $Na_2S_2O_3$, brine, dried (Na_2SO_4), and concentrated in *vacuo*. The residue was purified by FCC to give a mixture of **5.7** (α-anomer, 0.8g, 48%) and **5.8** (β-anomer, 0.4g, 24%).

α-anomer **5.7**, clear oil; TLC R_f = 0.20 (30% ethyl acetate:petroleum ether) ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.98, 1.99, 2.04, 2.14 (each s, 12H), 3.53 (dd, 1H), 3.60-3.78 (m, 3H), 3.85 (br t, 1H), 3.87 (m, 1H), 3.93 (t, J = 9.6 Hz, 1H), 3.95 (m, 1H), 4.03 (dd, J = 6.9, 10.9 Hz, 1H), 4.55 (ABq, J = 12.2 Hz, Δδ = 0.10 ppm, 2H), 4.70 (ABq, J = 11.7 Hz, Δδ = 0.12 ppm, 2H), 4.66 (ABq, J = 12.5 Hz, Δδ = 0.10 ppm, 2H), 4.65 (ABq, J = 10.9 Hz, Δδ = 0.34 ppm, 2H), 5.06 (d, J = 2.0 Hz, 1H), 5.18 (d, J = 2.3 Hz, 1H), 5.22 (dd, J = 2.6, 10.6 Hz, 1H), 5.33 (d, J = 2.6, 1H), 5.40 (br s, 1H), 7.09-7.48 (m, 20H).

β-anomer **5.8**, clear oil; R_f = 0.25 (30% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.84, 1.97, 2.04, 2.14, (each s, 12H), 3.65 (m, 2H), 3.78 (br dd, J = 10.6 Hz, 1H), 3.85 (br t, 1H), 3.91 (m, 1H), 4.10 (m, 4H), 4.57 (d, J = 7.6 Hz, 1H), 4.58 (ABq, J = 11.9 Hz, Δδ = 0.16 ppm, 2H), 4.65 (ABq, J = 12.1 Hz, Δδ = 0.10 ppm, 2H), 4.70 (ABq, J = 12.5 Hz, Δδ = 0.13 ppm, 2H), 4.60 (ABq, J = 12.1 Hz, Δδ = 0.38 ppm, 2H), 4.96 (dd, buried, 1H), 4.98 (d, J = 2.3 Hz, 1H), 5.09 (dd, J = 7.6, 10.6 Hz, 1H), 5.33 (d, J = 3.3, 1H), 7.09-7.48 (m, 20H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.2, 170.0, 139.1, 138.4, 138.2, 128.4-127.5, 100.6, 100.4, 80.0, 75.1, 73.4, 72.7, 74.6, 73.9, 72.6, 70.9, 70.8, 69.0, 68.7, 66.8, 61.0, 20.3, 20.6, 20.5, 20.5.

2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl acetate 5.9

To a solution of **2.20** (5.4 g, 9.75 mmol) in acetic anhydride (18.6 mL) was added acetic acid (17.7 mL), and AcOH-H_2SO_4 (500:1.5, 15.4 mL) dropwise. When the starting material had completely disappeared by TLC(ca. 4h), the mixture was poured into saturated, aqueous $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was further washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by FCC to give **5.9** (4.8 g, 83%): clear oil; TLC R_f = 0.20 (15% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 2.0 (s, 3H), 3.8 (m, 5H), 4.08 (t, J = 12.8 Hz, 1H), 4.72 (m, 8H), 6.21(br s, 1H), 7.3 (m, 20H).

4-Penten-1-yl-α-D-mannopyranoside 5.10

To a solution of **5.9** (1.2 g, 2.06 mmol) in CH_2Cl_2 (20 mL) was added $SnCl_4$ (0.5 mL, 4.12 mmol) and 4-penten-1-ol (0.44 mL, 4.12 mmol) under an argon atmosphere. The reaction was monitored by TLC until disappearance of the starting material (ca. ~5 min), then quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4). and concentrated in *vacuo*. The residue was purified by FCC to give **5.10** (1.2 g, 96%): clear oil; TLC $R_f = 0.80$ (15% ethyl acetate:petroleum ether); ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.60 (m, 2H), 2.08 (m, 2H), 3.4 (m, 1H), 3.8 (m, 5H), 3.98(m, 2H), 4.8 (m, 11H), 5.8 (m, 1H). 7.4 (m, 20H).

3,4-O-Isopropylidene-β-D-galactopyranosyl-2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside 5.12

To a solution of **5.8** (350 mg, 0.50 mmol) in dry methanol (3 mL) and chloroform (0.5 mL) was added powdered sodium methoxide (12 mg, 0.23 mmol). When the starting material had completely disappeared as shown by TLC (ca. 0.5 h), a solution of 1M HCl/MeOH was carefully added to adjust the pH to 8. The solution was concentrated in *vacuo* and the residue was partitioned between chloroform and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in *vacuo*. The residue was dissolved in 2,2-dimethoxypropane (1 mL) and treated with camphorsulfonic acid (~20 mg). The mixture was stirred at rt for 1 h, and then the solvent was evaporated. The residue

was dissolved in methanol (3 mL), stirred for 5 min, and neutralized with NaOMe. the solvent was then evaporated, and the residue was purified by FCC to give **5.12** (0.24 g, 61%): clear oil; TLC R_f = 0.5 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33, 1.52 (both s, 3H ea), 2.72 (d, J = 2.72 Hz, -OH, 1H), 3.40 (dd, J = 2.3, 10.6 Hz, 1H), 3.47 (dd, J = 8.3, 9.9 Hz, 1H), 3.56 (ddd, 1H), 3.69 (t, 1H), 3.60-3.73 (m, 2H), 3.75 (t, 1H), 3.82-3.97 (m, 2H), 3.92 (dd, J = 3.0, 9.2 Hz, 1H), 4.05 (m, 1H), 4.07 (s, 1H), 4.15 (br t, 1H), 4.36 (d, J = 8.6 Hz, 1H), 4.55 (ABq, J = 12.5 Hz, Δδ = 0.16 ppm, 2H), 4.63 (ABq, J = 11.9 Hz, Δδ = 0.08 ppm, 2H), 4.68-4.83 (m, 4H), 5.17 (d, J = 1.7 Hz, 1H), 7.09-7.42 (m, 20H).

2,6-Di-O-benzyl-3,4-O-Isopropylidene-β-D-galactopyranosyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside 5.17

Diol **5.16** (20 mg, 0.03 mmol) was subjected to the standard benzylation procedure as detailed in preparation of **2.20**. Purification of the product afforded **5.17** (22 mg, 88%): clear oil; TLC R_f = 0.80 (40% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32, 1.38 (both s, 3H ea), 3.37-3.77 (m, 1H), 3.57-3.73 (m, 4H), 3.75 (m, 1H), 3.91 (m, 1H), 3.95 (m, 1H), 4.10 (m, 4H), 4.43 (d, J = 8.3 Hz, 1H), 4.48-4.88 (m, 12H), 5.17 (d, J = 1.3 Hz, 1H), 7.10-7.41 (m, 30H).

2,6-Di-O-benzyl-β-D-galactopyranosyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside 5.18

A solution of **5.17** (20 mg, 0.02 mmol) in acetic acid (1 mL) and water (0.26 mL) was stirred at 60 °C for 3 h, then most of the solvent was removed in *vacuo*. The residue was purified by FCC to give **5.18** (15 mg, 80%): clear oil; TLC R_f = 0.10 (40% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69 (d, -OH, 1H), 3.40 (d, J = 5.3 Hz, -OH, 1H), 3.44 (dd, J = 9.2 Hz, 1H), 3.66 (m, 1H), 3.51-3.72 (m, 5H), 3.71 (dd, J = 3.5, 10.8 Hz, 1H), 3.94 (dd, J = 3.0, 8.9 Hz, 1H), 3.99 (t, J = 3.0 Hz, 1H), 4.06 (t, J = 8.9 Hz, 1H), 4.20 (m, 1H), 4.48-4.88 (m, 13H), 5.14 (d, J = 1.7 Hz, 1H), 7.10-7.44 (m, 30H).

2,6-Di-O-benzyl-3,4-O-(2-carbonylethylene)-β-D-galactopyranosyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside 5.19

A solution of **5.18** (20 mg, 0.02 mmol) and dibutyltin oxide (10 mg, 0.04 mmol) in dry toluene was heated at refluxed in a Dean-Stark apparatus for 1 h. The solvent was evaporated in *vacuo*, and the residue was dissolved in dry toluene (3 mL). *n*-Bu_4NI (10 mg, 0.02 mmol) and methyl 2-bromo acetate (0.08 mL, 0.2 mmol) were added, and the solution was heated at reflux for 1 h, at which time the volatiles were removed under reduced pressure to give a brown syrup. The residue was purified by FCC to give lactone **5.19** (19 mg, 90%): clear oil; TLC R_f = 0.60 (40% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48 (dd, J = 7.6, 9.9 Hz, 1H), 3.60 (m, 6H), 3.86 (dd, J = 4.0, 9.9 Hz, 1H), 3.92 (m, 2H), 4.05

(m, 2H), 3.95 (ABq, J = 18.1 Hz, $\Delta\delta$ = 0.20 ppm, 2H), 4.37-4.90 (m, 13H), 5.14 (d, J = 1.7 Hz, 1H), 7.11-7.41 (m, 30H).

3-O-(Carbonylethyl)-β-D-galactopyranosyl -α-D-mannopyranoside 1.6

A mixture of lactone **5.19** (19 mg, 0.02 mmol), 20% w $Pd(OH)_2/C$ in methanol (1 mL) was stirred under 1 atm H_2 for 4 h. The resulting solution was filtered through a short plug of celite and concentrated in *vacuo*. The residue was dissolve in 0.25 N aqueous NaOH (0.5 mL) and stirred at rt for 10 min. The reaction mixture was neutralized with 1N HCl/MeOH and evaporated under reduced pressure. The residue was purified by Sephadex LH-20 chromatography (H_2O) and lyophilized to give **1.6** (7 mg, 78%). TLC R_f = 0.40 (20% acetic acid:methanol, indicated to be dark blue by *p*-anisaldehyde); $[\alpha]^{23}_D$ 40.5 (c = 0.12, MeOH:H_2O = 1:1); ^{1}H NMR (400 MHz, D_2O) δ 3.5 (dd, J = 1.4, 9.9 Hz, 1H), 3.71 (m, 5H), 3.84 (m, 2H), 3.93 (m, 1H), 4.05 (t, J = 1.6 Hz, 1H), 4.08 (br d, 1H), 4.11 (s, 2H), 4.60 (d, J = 8.1 Hz, 1H), 5.14 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 61.7, 61.9, 66.0, 67.5, 69.2, 70.5, 7.05, 71.1, 74.3, 76.0, 82.7, 102.3, 103.5, 170.3. FABMS 423 (M + Na).

Chapter 6

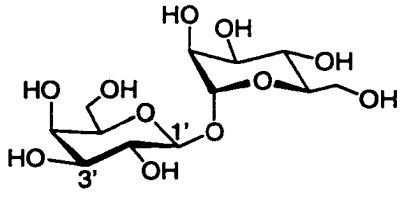
Conformational and biological studies on prepared glycomimetics

6.1 Introduction

Carbohydrate-protein[71] interactions are involved in a number of biological recognition events, for instance, the sLe^x-selectin interaction in inflammatory response,[1] and the hydrolysis of saccharides by glycohydrolysis. In the previous chapters, we have described our efforts towards the synthesis of stable glycomimetics which may function as inhibitors of selectins or glycosidase. A variety of related O-, C-glycosides, carbasugars and aza-C-glycosides have been synthesized by other laboratories.[33, 72]

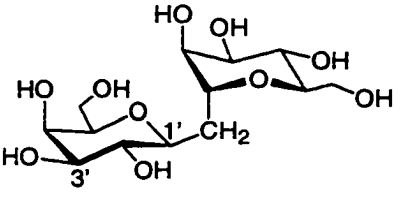
It has been suggested that a primary requirement for activity of a glycomimetic is similar conformational behavior as the bound natural ligand. This property minimizes the entropic cost of the recognition process.[73] In this context, many studies[74] with respect to conformational behavior and activity have been

Figure 6.1



O-Glycoside

6.1



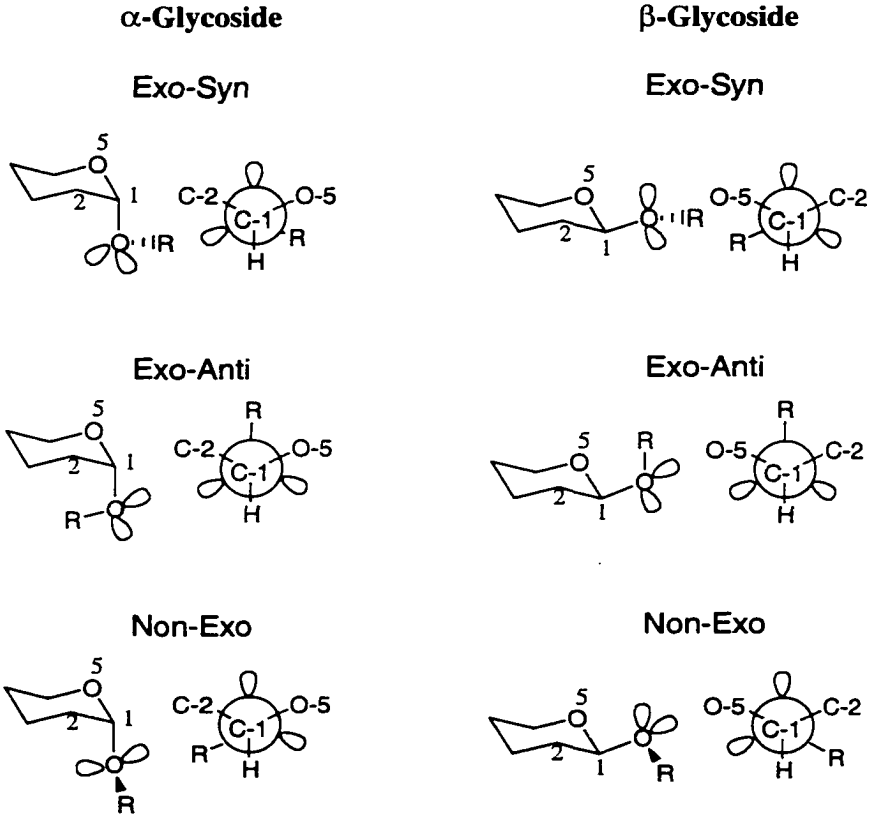
C-Glycoside

6.2

undertaken. However, the conformational similarity between C- and O-glycosides[76] have been under debate. In this view, we undertook, in collaboration with Jimenez Barbero, NMR analysis of galactose-β-O-(1→1)-α-mannoside **6.1** and galactose-β-C-(1→1)-α-mannoside **6.2**[75](Figure 6.1).

General concepts There are three staggered, low energy conformers about the C1-O bond. They are *exo-syn*, *non-exo* and *exo-anti* respectively (Figure 6.2). *Exo-syn* is the rotamer with the R group gauche to C1-O5 and C1-H bond, and one lone pair

Figure 6.2



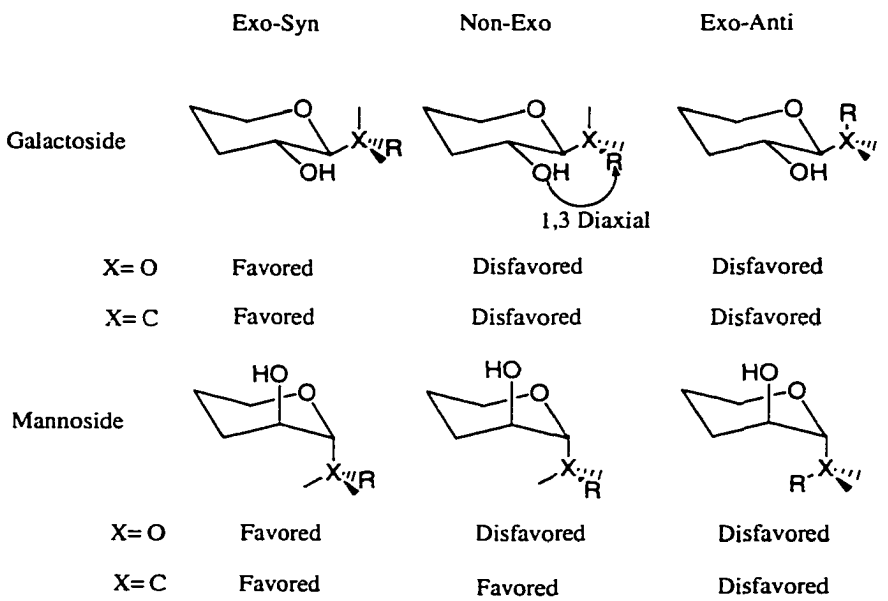
on O-1 periplanar to the C-1-O-5 bond; *Exo-anti* is the rotamer with the R group gauche to C1-O5 and C1-C2 bond, and one lone pair on O-1 periplanar to the C-1-O-5 bond; *Non-exo* is the rotamer with the R group gauche to C1-C2 and C1-H bond, in this case neither of the lone pairs is periplanar to the C-1-O-5 bond. It has been generally observed that the preferred conformation in both α and β glycosides is the exo-syn. This is referred to as the *exo-anomeric effect*[79] and has been explained in terms of stereoelectronic and steric effects. Of the three conformations the exo-anti is least favored because of steric factors. The preference for the exo-syn over the non-exo has been explained by both steroelectronic and steric effects. The stereoelectronic effect stablizes the exo-syn due to n-σ* delocalization by the O lone pair and the C1-O5 bond. Alternatively, the preference for the exo-syn over the non-exo may be due to less sterically demanding, gauche interaction between R and O5 compared with R and C2 (Figure 6.2).

The stereoelectronic effect,[77] disappears in C-glycoside.[78] In addition, since the substitution of an oxygen by a methylene group results in changes to both the coordination of the linking moiety and the intersaccharide bond length, steric factors are different.[74a] Therefore, the flexibility around the Φ/Ψ torsional angles is expected to be different for O- *vs* C-glycosides (Φ is the dihedral angle H1'-C1'-O-C1, or H1'-C1'-C-C1 and Ψ is C1'-O-C1–H1 or C1'-C-C1–H1).

Conformational analysis For α-O-mannopyranosides and β-O-galactosides, the *exo-syn* configuration is favored both on stereoelectronic and steric grounds. *Ab*

initio calculations *in vacuo* by Houk[74] showed that the relative stablization of of the *exo-syn vs non-exo* forms, increased from 0.7 to 2.2 kcal/mol when 1,3-type interaction was added. According to this data, the 1,3-syn-diaxial destabilization should equal to about 1.5 Kcal/mol. The relative stablization of of the *exo-syn vs exo-anti* forms is about 0.8 kcal/mol. In the case α-C-mannopyranosides and β-C-galactosides, the stereoelectronic effect is absent. The *exo-anti* should again be highly disfavored because of the steric hindrance between the two sugar residues. The relative proportions of *exo-syn* and *non-exo* rotamers should depend mainly on gauche interactions involving the C2 position *vs* O5 in the respective mannoside or galactoside.

Figure 6.3 Low Energy Conformations

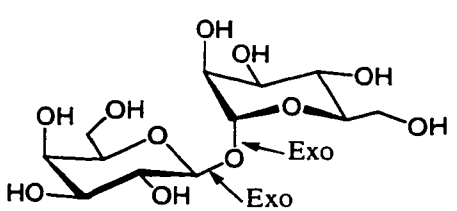


For the galactopyranoside, the relative preference among the three rotamers is different from that of mannoside because of the additional 1,3-diaxial interaction. Thus, in the case of O-galactoside, *exo-syn* is favored because of n-σ* stablization and destablization of the *non-exo* rotamer due to 1,3-diaxial interaction. The *exo-anti* is disfavored because of steric effect between two sugar moiety.

In the case of C-galactoside, there is no n-σ* stablization. The *exo-syn* should be still favored over *non-exo* due to steric effects, but by a less amount than for the O-galactosides. A similar situation should exist for the O- *vs* C-mannoside linkage. However, because of the absence of 1,3-diaxial type interactions in the *non-exo* conformer, the relative proportion of *exo-syn* and *non-exo* for the C-mannoside should be similar.

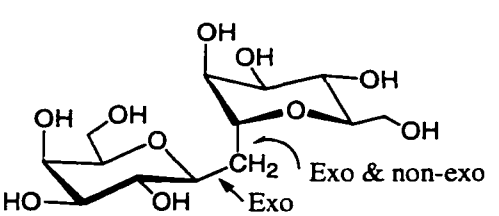
Based on the forgoing discussion, the following hypothesis can be made: For the O-glycoside **6.1**, the preferred conformation around both glycosidic bonds should be *exo-syn*. For the C-glycoside **6.2**, the preferred conformation for the glycosidic bond around galactose should be *exo-syn*; For the bond around mannoglycoside, *exo-syn* and *non-exo* should be equally populated (Figure 6.4).

Figure 6.4



O-Glycoside

6.1



C-Glycoside

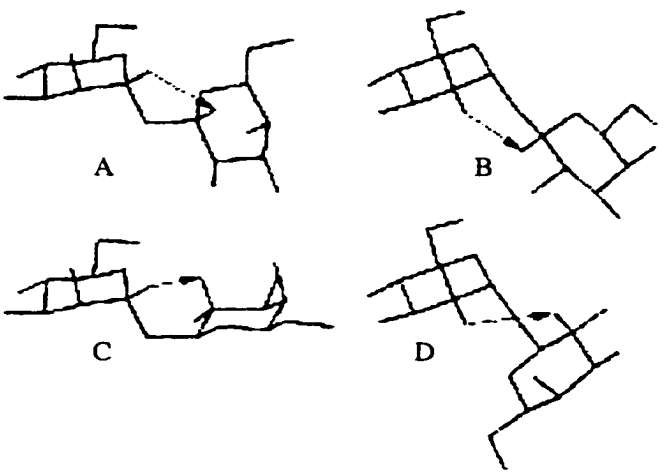
6.2

6.2 Results and disscussion[75]

The following study was carried out by Jesus Jimenez-Barbero.

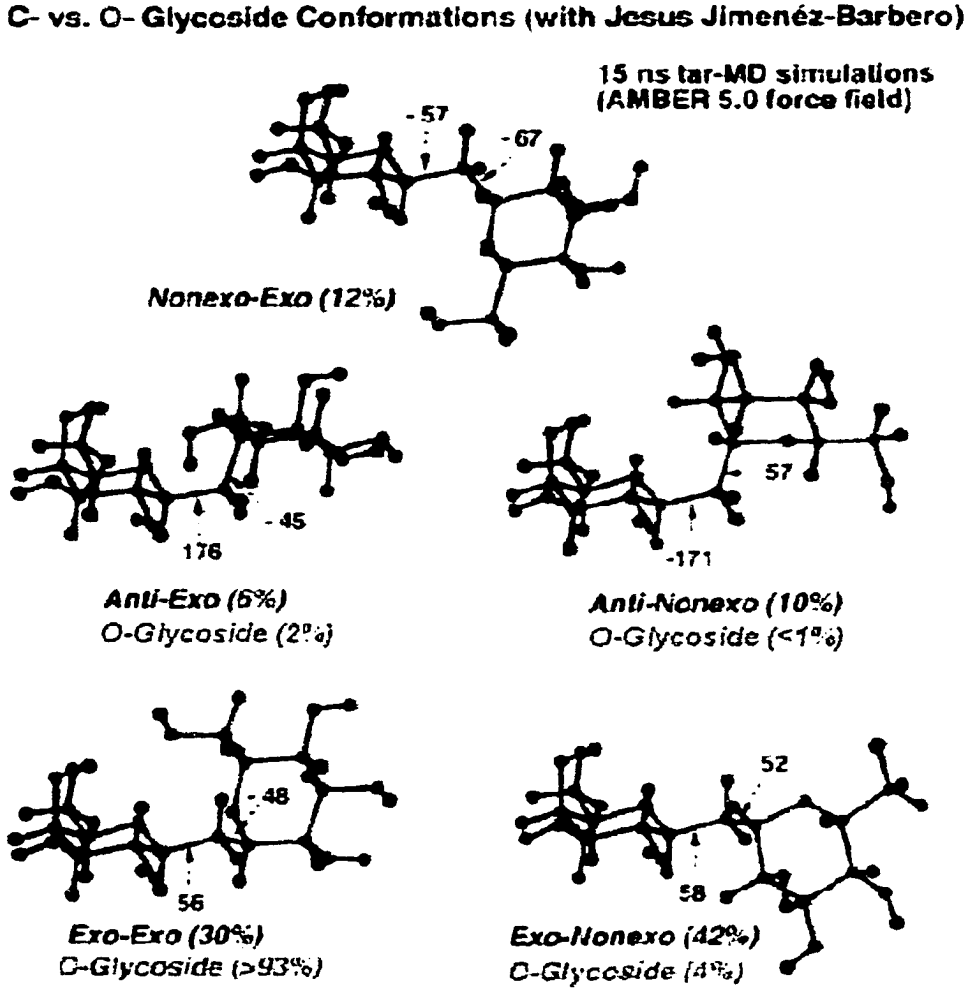
NOEs and J values A qualitative conformational analysis of **6.1** and **6.2** was done, based on exclusive[80] interresidue NOEs[81] and J coupling data that characterize minimum A-D (Figure 6.5). For **6.1** and **6.2**, the relavant NOEs are H1'-H1 (A), H2'-H1 (B), H1'-H2 (C) and H2'-H2 (D). Since the NOE intensities are sensitive to the respective conformer populations, a first indication of the population distribution could be obtained by focusing on these key NOEs. For **6.1**, the strong H1'-H1 NOE shows qualitatively that the global minimum A (exo-syn/exo-syn) is highly populated. The additional small NOEs indicate a very minor presence of conformers B and C. By contrast, compound **6.2** shows medium-large H1'-H1 and H2'-H1, and medium H1'-H2 NOEs with different mixing times. In addition, for compound **6.2**, interglycosidic proton-proton J values were derived from the potential energy surface ($J_{H1',HR}$ = 7.1, $J_{H1',Hs}$ = 7.4, $J_{H1,HR}$ = 3.1, $J_{H1,Hs}$ = 8.0 Hz).

Figure 6.5 Major Low Energy Conformers for Compound 6.1 and 6.2



These data qualitatively shows the existence of minimum A (*exo-syn/exo-syn*) for **6.1**, but minimum A (*exo-syn/exo-syn*), B (*non-exo/exo-syn*), as well as C (*exo-syn/exo-anti*) for **6.2**. This demonstrates an enhanced flexibility of C-glycoside **6.2** in comparison to O-glycoside **6.1**.

Figure 6.6



In order to get the best experimental conformer distribution for **6.1** and **6.2**, time averaged restrained (tar)-MD simulations[81a] were carried out using the

AMBER 5.0 force field and the experimental NOE/J information.[82] The major distribution for the O-galactoside bond is *exo-syn* (97%), exo-anti (2%). For the C-galactoside, *exo-syn* conformations account for 72% of all populations, compared with 12% for *non-exo* and 16% for *exo-anti* conformations. For the O-mannoside bond the distribution was exo-syn (>93%), non-exo (4%), exo-anti (2%) and anti-non (<1%). For the C-mannoside the distribution was exo-syn (48%), non-exo (52%).

6.3 Biological data for glycomimetics 1.6 and 2.1

The following sLe^x-mimetics-P-selectin binding assay were carried out by Wyeth Research (Boston) on a BIAcore analyzer.

Both O- and C- glycosides (**1.6** and **2.1**) mimetics show similar inhibition to sLe^x-selectin interaction at 6mM; (Table 6.1) These values were similar to that obtained with sLe^x (IC_{50} = 8 mm).

Therefore, It is unlikely that both O- and C- disaccharide analogues adopt an exo-exo conformation in bound state (if it is, O-glycoside would be expected to have stronger binding affinity); It is possible that O-glycoside binds in an exo-exo conformation and C-glycoside binds in some other conformation; Alternatively, they may both bind in a single conformation which is different from exo-exo conformation; or, each of them binds in a different conformation, neither of them is exo-exo conformation.

Closer investigation is ongoing with the use of conformational restrained analogues of C-glycoside **2.1**.

Table 6.1

	Concentration (mM)	Percentage% Inhibition	sd
O-Glycoside **1.6**	6	35	1.12
	3	21	1.66
	1.5	10	1.34
	0.75	6	0.87
C-Glycoside **2.1**	6	37	0.17
	3	20	0.91
	1.5	10	1.33
	0.75	6	0.56

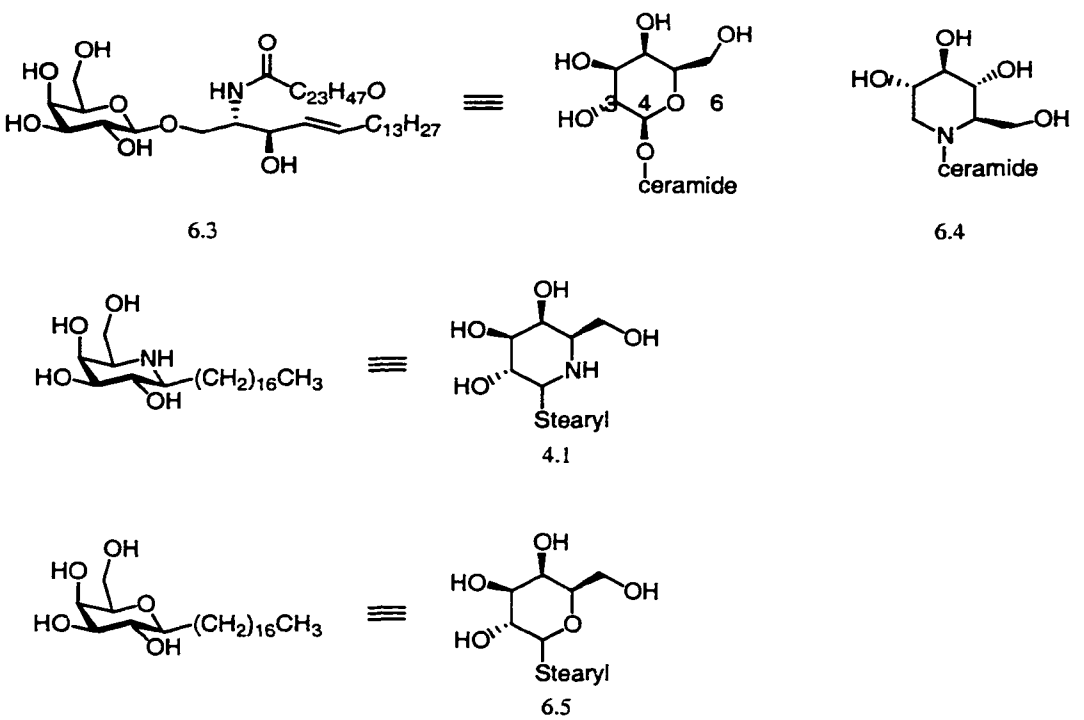
6.4 Biological data for glycomimetics 4.1 and its parent C-glycoside 6.5

The following assay was done by Prof. Jacques Fantini (Faculté des Sciences St Jérôme, 13013 Marselle).

HIV-1 has been shown to infect CD4 negative cells by binding of HIV gp120 to the glycolipid galactosylceramide **6.3**.[63c] The reported X-ray structure of **6.3** presented the 3-, 4-, and 6-OH groups interacting with gp120. Several analogues were prepared to investigate the structure-activity in terms of gp120

binding. Experiments to investigate the specificity of penetration was conducted with each analog. In these studies, the increase in surface pressure ΔΠ caused by penetration of gp120 (10 nM) into the monolayer was measured as a function of initial surface pressure Π! of the monolayer. The most active analog was glucosylceramide **6.4**, which display a potent and specific affinity with gp120 equal to **6.3** (Figure 6.7).

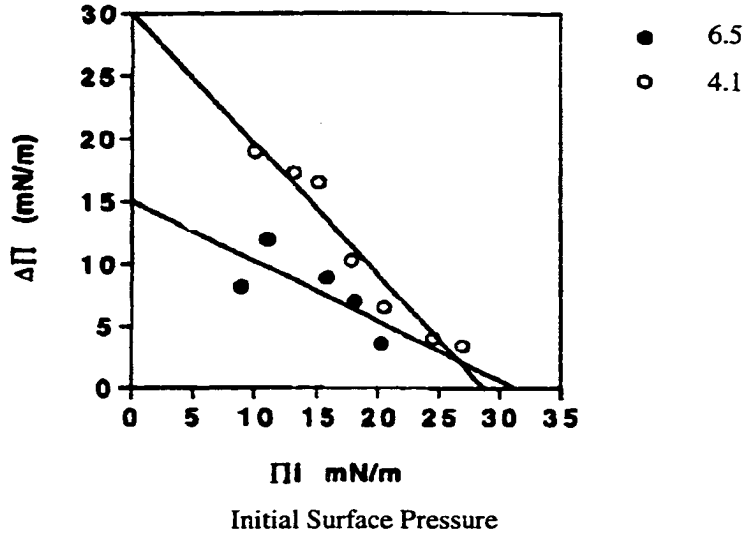
Figure 6.7 Glycolipid Analogues for gp120 Binding



Our heptadecyl C-glycoside **6.5** and its aza-C-glycomimics **4.1** were also tested under the same assay. Interestingly, azasugar **4.1** displayed potent and specific affinity for gp120, even better than ceramide **6.4** (Figure 6.8). This

indicated that azasugar **4.1** may adopt a conformation better resembling the orientation of GalCer **6.3**; C-glycoside **6.5** is less active than its aza anaologue **4.1** .

Figure 6.8 Specificity of gp120 binding to glycolipid analogues



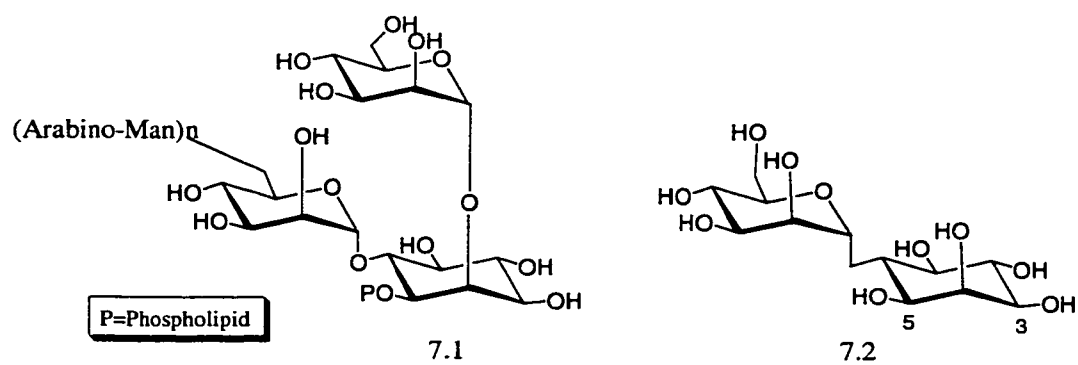
Chapter 7

Synthesis of inositol glycomimetics

7.1 Background[83]

Inositol phosphates function as secondary messengers in cells. They regulate a variety of cellular functions, such as those of insulin, growth factor and hormones. Inositol phosphates also comprise the glycosyl phosphatidyl inositol (GPI) component of the protective cell surface coat in protozoa and bacteria. Pseudo-trisaccharide **7.1**[84] was identified as the antigenic core of the causative agent "*Mycobactarium tuberculosis*". Mimetics of this molecule have been of interest in connection with the development of anti-tuberculosis vaccine. Consequently, we were interested in the synthesis of the C-glycoinositol **7.2**. In addition, substitution of the 5-OH of **7.2** with a phosphate group leads to a

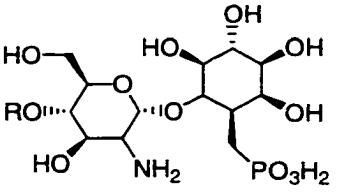
Figure 7.1 Glycosyl Phosphatidyl Inositol (GPI) Mimetic



Antigenic Core of Mycobacterium Tuberculosis

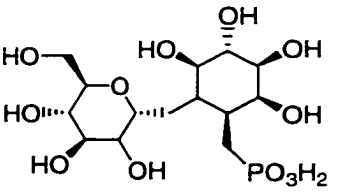
glycomimetic **7.4**, which is an analogue of GPI **7.3**.[85] Compound **7.4** could mimic the role of GPI in the biosynthesis of the GPI-anchoring system used by parasites, such as those responsible for the African sleeping sickness.[86]

Figure 7.2 GPI Analogues



7.3

R=High mannose glycan

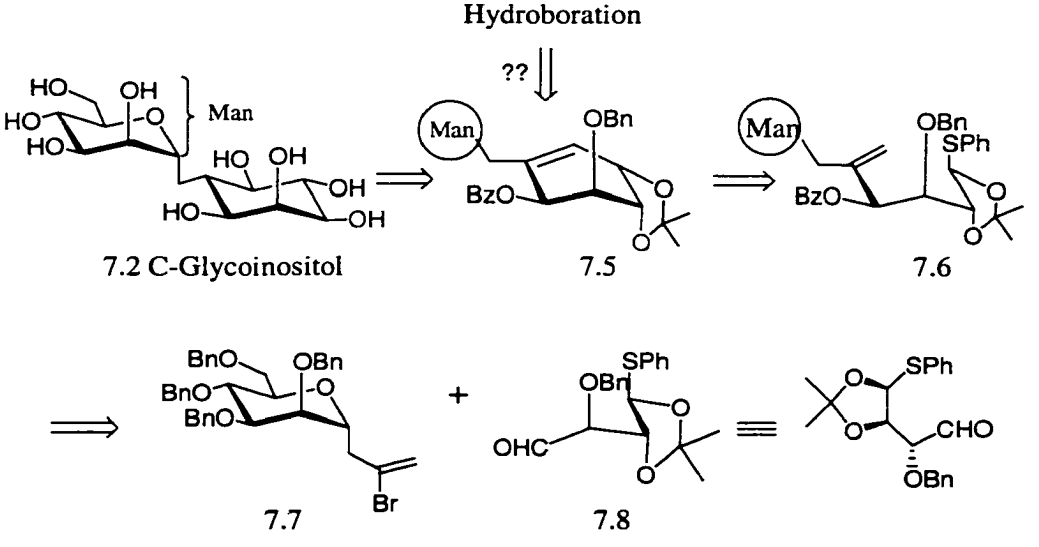


7.4

7.2 Retrosynthetic plan and model studies

Our plan centers on the stereoselective hydroboration on a highly oxygenated cyclohexene, which could be constructed by ring closure of **7.6** based on our oxocarbenium cyclization methodology. The key precursor **7.6** was

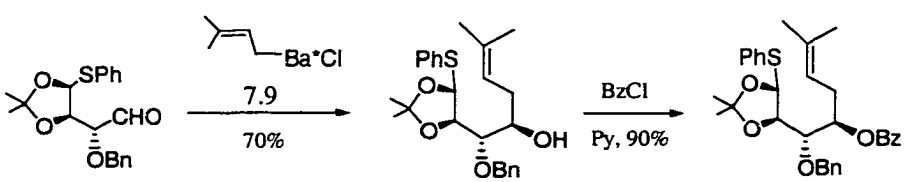
Scheme 7.1



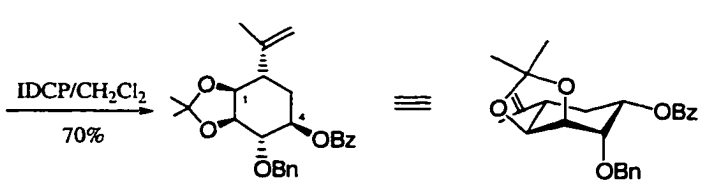
envisaged from the Nozaki coupling[87] of a bromo compound **7.7** and aldehyde **7.8**. A mixture of the coupling products was expected in the coupling step. In this plan, the cis acetonide group was expected to direct the hydroboration of the olefine from the desired top face. However, this plan will lead to the incorrect configuration at C-3, and this will have to be reversed (Scheme 7.1).

Synthesis The key oxocarbenium ion cyclization strategy was first tested on two simple model systems. Thus, treatment of aldehyde **7.8** with the allylic organobarium[88] reagent **7.19**, provided in 70% yield, a 10:1 mixture of allylic alcohol **7.10** and its epimer. The organobarium[88] reagent **7.9** was generated *in situ* from the addition of 1-chloro-3-methyl-2-butene to freshly activated barium iodide, in the presence of lithium biphenylide. Benzoylation of the free hydroxyl group in **7.10** provided benzoate **7.11** in 90% yield. IDCP mediated cyclization[89] provided the funtionalized cyclohexane **7.12** in 70% yield. The coupling constants ($J_{2,3} = J_{3,4} = 3.6$ Hz) was in agreement with the structure shown (Scheme 7.2).

Scheme 7.2



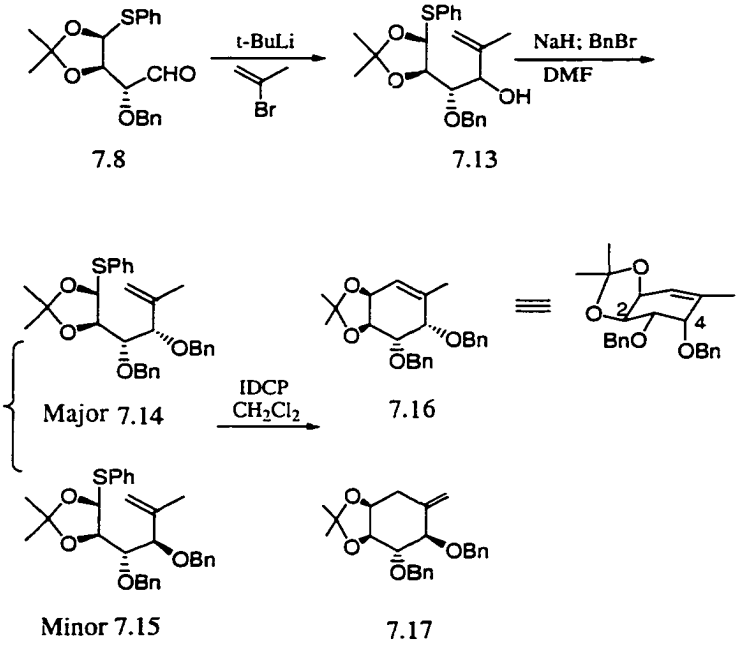
7.8 7.10 7.11



7.12

The cyclization of **7.14** is an even closer model study of the required ring closure. Reaction of aldehyde **7.8** with the lithiated isopropene[90] leads to a mixture of inseparable alcohol isomers **7.13**. Standard benzylation of **7.13** provided a mixture which was partially separable. The major isomer **7.14** was treated with IDCP. Cyclohexene **7.16** was obtained as the major product in 65% yield. The stereochemistry of **7.16** was established on the basis of the J value ($J_{2,3}$ = 10.1 Hz). The other minor product was identified by COSY to be the undesired exocyclic alkene **7.17**. This result indicates that S configuration at C-4 leads to be the desired alkenic product (Scheme 7.3).

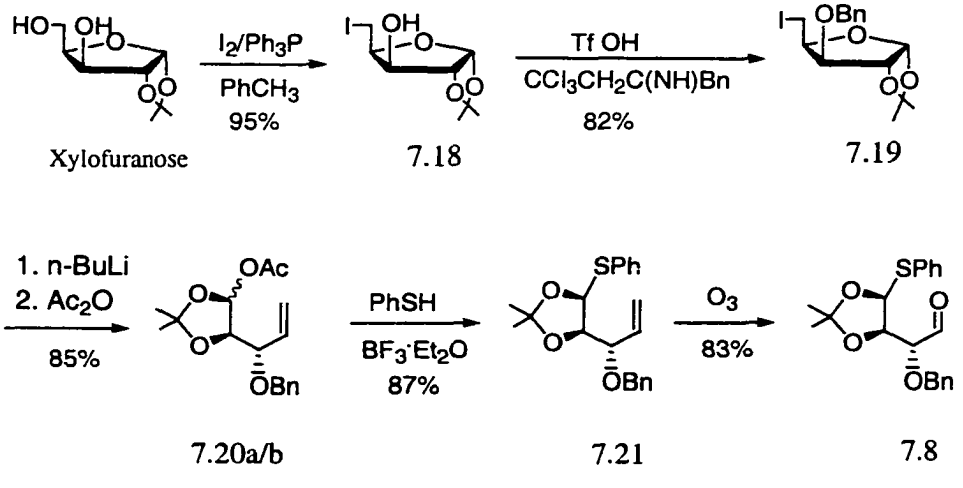
Scheme 7.3



7.3 Synthesis of C-manno-inositol 7.2

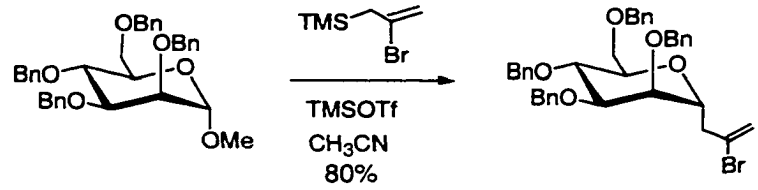
Aldehyde and bromo-allyl mannoside component Synthesis of aldehyde **7.8** started with iodination[91] of 1,2-isopropylidene xylofuranose. The secondary hydroxyl in the resulting iodide **7.18** was benzylated with benzyl trichloroimidate in the presence of catalytic triflic acid, in a mixture of cyclohexane and dichloromethane (4:1). Benzyl ether **7.19** was obtained in 82% yield. Reductive elimination of **7.19** with *n*-butyl lithium, followed by acylation[92] of the lactol product provided **7.20a** and **7.20b** in a total yield of 85%. Exchange of acetate with thiophenyl was accomplished by treatment with thiophenol and borontrifluoroetherate. The acetal **7.21** was obtained as a single isomer in 87% yield. Ozonolysis of the terminal alkene in **7.21** furnished aldehyde **7.8** in 83% yield (Scheme 7.4). There was no evidence for oxidation of the thiophenyl group under this condition.

Scheme 7.4



The 2-bromo-allylated mannoside **7.7** was obtained in 80% yield, by allylation of benzylated mannoside **2.20** via the known procedure[93] (Scheme 7.5).

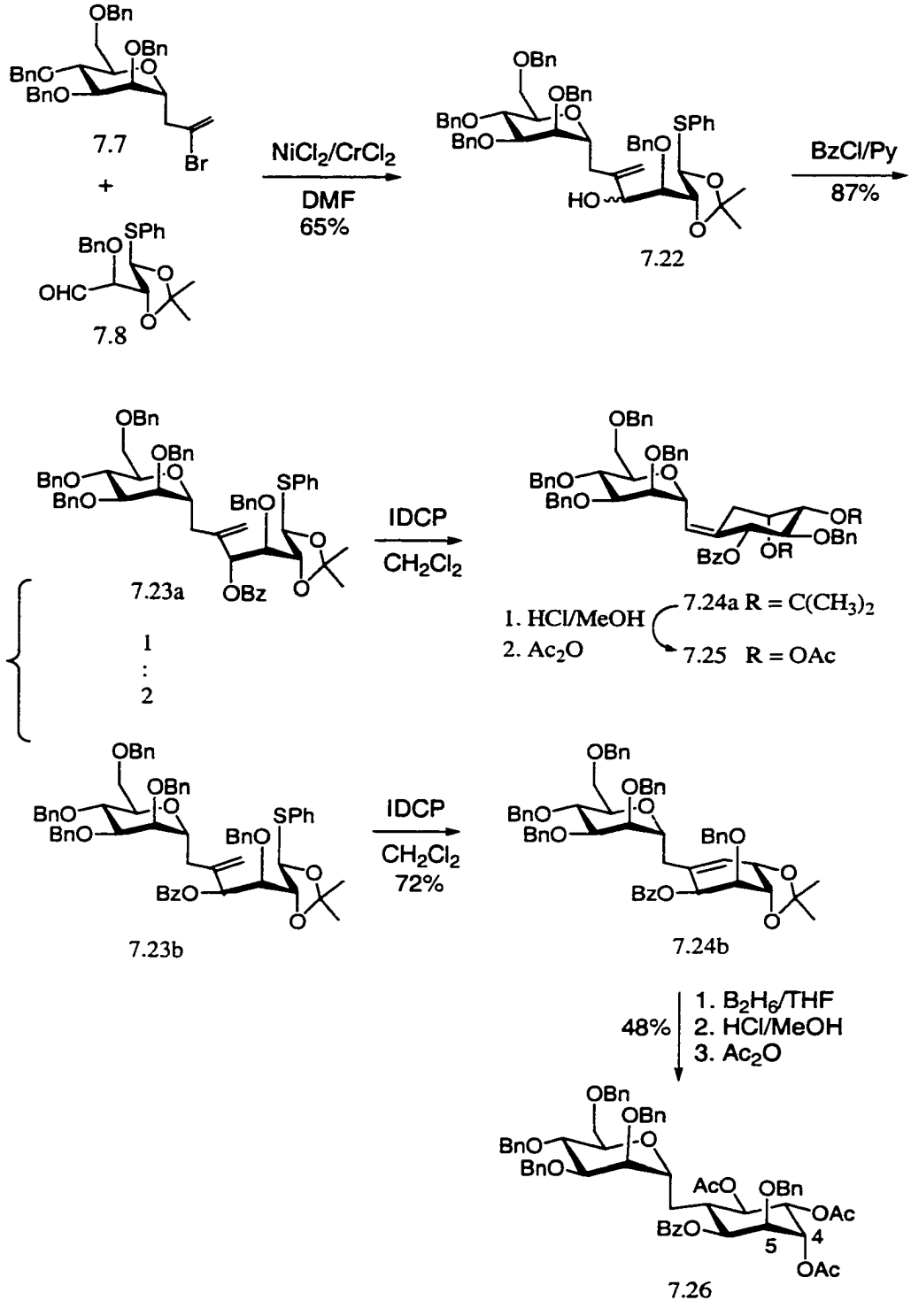
Scheme 7.5



2.20 7.7

Coupling of aldehyde and bromo components The Ni(II)/Cr(II) mediated Nozaki coupling of aldehyde **7.8** and bromo-allyl mannoside **7.7** under an atmophere of argon, led to an inseparable 1:2 mixture of diastereomers **7.22** in 65% yield. The best result was obtained when the exposure of reagents to the air was minimized. Bezoylation of the free hydroxyl group in **7.22** afforded **7.23a** and **7.23b** in a total yield of 78% as a partially separable mixture. Pure **7.23a**, as well as a 1:1 mixture of **7.23a** and **7.23b** were individually subjected to IDCP mediated cyclization. The major isomer **7.23b** formed the desired cyclohexene derivatives **7.24b** in 72% yield. The mixture of isomers **7.23a** and **7.23b** yielded both **7.24a** and **7.24b** in a 70% yield. Based on these results, we concluded that minor isomer **7.23a** produced **7.24a** in the cyclization step, and **7.23b** produced **7.24b**. The configuration of **7.24a** was established on the basis of of J value of diacetates **7.25** ($J_{2,3}$ = 8.8 Hz), COSY, as well as NOE experiments (NOE effect between H4-OAc and H2-OBz). Hydroboration of **7.24b**,[94] followed by deprotection and acylation,

Scheme 7.6



furnished triacetate **7.26** in a total yield of 48% for these three steps. The stereochemistry of **7.26** was elucidated by the NOE effects between H1 and H3, as well as J values ($J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 3.3 Hz, $J_{1,2}$ = 11.0, $J_{1,6}$ = 11.0 Hz) (Scheme 7.6).

7.4 Experimental section

1-(2-bromo-allyl)-2,3,4,6,-O-tetrabenzyl-mannoside 7.7

A solution of **2.20** (1.3 g, 2.35 mmol) and 2-bromoallyltrimethylsilane (1.0 g, 4.7 mmol) in anhydrous acetonitrile (10 mL) was added trimethylsilyl triflate (0.08 mL, 0.5 mmol) dropwise at 0°C under an atmosphere of argon. The solution was then warmed up to rt and stirred for additional 16h. The resulting deep-orange solution was diluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give 1-(2-bromo-allyl)-Mannopyranoside **7.7** (1.1 g, 80%): clear oil; R_f = 0.5 (15% ethyl acetate:petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 2.7 (m, 2H), 3.82 (m, 7H), 4.55 (m, 10H), 7.3 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.0, 70.0, 71.2, 72.8, 73.2, 74.8, 75.0, 75.8, 76.0, 76.2, 79.9, 120.0, 128.2, 128.6, 128.9, 129.2, 129.4, 130.2; ESMS (M + Na) 665.2.

1-Thio-1,2-O-isopropylidene-3-O-benzyl-4-butyl aldehyde 7.8

Bromide **7.7** (450 mg, 1.26 mmol) was subjected to ozonolysis procedure as detailed in the preparation of **2.2**. FCC of the product gave aldehyde **7.8** (380 mg, 83%). R_f = 0.6 (5% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43, 1.47 (both s, 3H ea), 3.98 (d, J = 3.0 Hz, 1H), 4.4 (dd, J = 3.0, 7.0 Hz, 1H), 4.6 (ABq, J = 11.5 Hz, 2H), 5.42 (d, J = 7.0 Hz, 1H), 7.3(m, 5H), 9.8 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 27.1, 73.5, 80.5, 81.2, 84.6, 112.2, 127.8, 128.5, 132.2, 136.6, 201.7.

Activated barium organo reagent 7.9

Lithium biphenylide Freshly cut lithium (30 mg, 4.4 mmol) and biphenylide (700 mg, 4.6 mmol) were placed into a flasked charged with dry THF (10 mL), the mixture was stirred at RT for 2 hr resulting a dark green solution with the disappearance of lithium.

$BaI_2 \cdot 2H_2O$ (989 mg, 2.2 mmol) was heated at 150 °C for 2 hr under reduced pressure (<10 Torr) to get BaI_2 (860 mg, 2.2 mmol), which was then cooled down to RT and covered with anyhydrous THF (10 mL) under N_2, to the resulting yellowish solution was added the prepared lithium biphenylide solution via a stainless steel cannula under N_2 stream. The reaction mixture was stirred for 30 min at RT, the resulting solution was freshly used for the following coupling reaction.

1-thio-1,2-O-isopropylidene alkene 7.14

To the above-obtained barium solution was slowly added a solution of 1-chloro-3-methyl-2-butene (0.23 mL, 2.0 mmol) in anhydrous THF (3 mL) at –78 °C under an atmosphere of argon. The mixture was stirred for 20 min at this temperature and then a solution of **7.8** (71 mg, 0.2 mmol) in THF (2 mL) was slowly introduced. After stirring for additional 20 min, the reaction mixture was then poured into 1N HCl solution (10 mL), and extracted by ethyl ether (3 x), the combined organic layer was successively washed by saturated $Na_2S_2O_3$, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue gave **7.10** (53 mg, 70%). R_f = 0.20 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5 (s br, 6H), 1.6, 1.7 (both s, 3 ea), 2.2-2.4 (m, 3H, CH_2 & -OH hidden), 3.5 (dd, J = 6.0, 6.8 Hz, 1H), 3.8 (m, 1H), 4.3 (dd, J = 6.0, 7.2 Hz), 4.7 (ABq, J = 10.5 Hz, Δδ = 0.17 ppm, 2H), 5.1 (br t, J = 9.8 Hz), 5.4 (d, J = 8.0 Hz), 7.2-7.6 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.34. 26.12, 26.3, 27.37, 32.61, 71.52, 73.58, 78.53, 81.03, 85.34, 111.64, 119.97, 127.62, 128.03, 128.20, 128.23, 128.59, 131.82.

Benzoate 7.11

A solution of benzoyl chloride (0.1 mL) and1-thio-1,2-O-isopropylidene alkene **7.10** (35 mg, 0.1 mmol) in pyridine (1 mL) was stirred at RT for 2 hr. The reaction mixture was then diluted with ethyl ether, then washed by saturated aqueous $NaHCO_3$, brine and dried (Na_2SO_4), filtered, concentrated under reduced

pressure. FCC of the residue gave **7.11** (38 mg, 90%). R_f = 0.45 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3 (m, 2H), 1.50, 1.56 (both s, 3H ea), 1.63, 1.68 (both s, 3H ea), 2.60 (m, 2H), 3.81 (dd, J = 6.2, 7.0 Hz, 1H), 4.32 (dd, J = 6.2, 8.0 Hz, 1H), 4.5 (br s, 2H), 5.36 (t, J = 9.8 Hz, 1H), 5.46 (m, 2H), 7.2-7.6 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 26.0, 26.2, 27.4, 29.3, 66.2, 74.3, 74.5, 77.6, 77.8, 80.6, 85.5, many lines from 127.5 to 133.0.

1-isopropene-2,3-O-isopropylidene-4-O-benzyl-5-O-benzoyl-cyclohexane 7.12

To a mixture of **7.11** (25 mg, 0.05 mmol) and freshly activated molecular sieves (30 mg) in anhydrous CH_2Cl_2 (2 mL) was added IDCP (80 mg, 0.17 mmol) under an atmosphere of argon. The mixture was stirred at rt for 10 min, then poured into saturated, aqueous $Na_2S_2O_3$, and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated in *vacuo*. FCC of the residue afforded **7.14** (16 mg, 70%). R_f = 0.27 (30% EtOAc/PE); ^{1}H NMR (300 MHz, C_6D_6), δ 1.4 (s, 3H), 1.6 (s, 3H), 1.8 (s, 3H), 2.8 (m, 2H), 4.2 (m, 2H), 4.32 (t, J = 3.6 Hz, 1H), 4.9 (m, 3H), 5.6 (m, 1H), 7.3-8.0 (m, 10H).

1-thio-1,2-O-isopropylidene alkene 7.13 and 7.14

To a solution of 2-bromopropene (0.37 mL, 4.2 mmol) in anhydous THF (3 mL) was added t-butyl lithium (5.25 mL, 1.6 M, 8.4 mmol) dropwise at –78 °C under an atmosphere of argon. This reaction mixture was warmed up to 0 °C, and stirred for additional 30 min at this temperature. This freshly generated 2-lithiated

propene solution was cooled back to –78 °C and a solution of aldehyde **7.8** (150 mg, 0.42 mmol) in THF (4 ml) was then slowly introduced. This reaction mixture was warmed up to 0 °C over a period of 30 min, and quenched by addition of satuarated aqueous NH_4Cl, extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated in *vacuo*. FCC of the residue afforded an inseparable mixture of isomers **7.13** (100 mg). R_f= 0.50 (30% EtOAc/PE).

Alcohol mixture **7.13** (100 mg, 0.25 mmol) was subjected to standard benzylation procedure as detailed in preparation of **2.20**. FCC of the residue afforded an inseparable 10:1 mixture of isomers (70 mg, 60%) R_f = 0.50 (30% EtOAc/PE); Major isomer **7.14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3, 1.4 (both s, 3H ea), 1.5 (s, 3H), 3.7 (m, 1H), 4.02-4.6 (m, 6H), 5.2 (m, 2H), 5.4 (d, J = 3.6 Hz, 1H), 7.3-7.6 (m, 15H).

1-methyl-2,3-O-dibenzyl 4,5-O-isopropylidene cyclohexane 7.16

Benzyl ether **7.14** (25 mg, 0.05 mmol) was subjected to cyclization procedure as detailed for the preparation of **7.12**, FCC of the residue afforded **7.16** (14 mg, 65%). R_f = 0.40 (30% EtOAc/PE); ^{1}H NMR (300 MHz, C_6D_6) δ 1.3 (s, 3H), 1.45 (s, 3H), 1.6 (s, 3H), 3.7 (dd, J = 3.0, 10.1 Hz, 1H), 3.8 (d, J = 3.0 Hz, 1H), 4.5 (ABq, J = 10.5 Hz, Δδ = 0.17 ppm, 2H), 4.62 (m, 1H), 4.75 (dd, J = 4.1, 10.3 Hz, 1H), 5.55 (d, J = 3.0 Hz, 1H), 7.3-8.0 (m, 10H).

5-Deoxy-5-iodo-1,2-O-isopropylidene-α-D-xylofuranose 7.18

A solution of 1,2-O-isopropylidene-α-D-xylofuranose (5.0g, 26.3 mmol), triphenylphosphine (6.9 g, 26.3 mmol), imidazole (3.6 g, 52.9 mmol) and iodine (6.7 g, 26.4 mmol) in anhydrous toluene(200 mL) was heated at reflux for 1 h under an atmosphere of argon. The mixture was then cooled to rt, and diluted with ether (500 mL), filtered through a bed of celite, the filtrated was concentrated in *vacuo*, the residue was purified by FCC to give **7.18** (7.6 g, 95%) as a white solid: R_f = 0.50 (50% EtOAc/PE); mp 107-108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.60 (s, 3H), 3.33 (m, 2H), 4.12 (apparent d, J = 4.8 Hz, 1H), 4.48 (m, 1H), 4.56 (m, 1H), 6.02 (d, J = 6.2 Hz).

5-Deoxy-5-iodo-1,2-O-isopropylidene-3-O-Benzyl-α-D-xylofuranose 7.19

To a solution of 5-Deoxy-5-iodo-1,2-O-isopropylidene-α-D-xylofuranose **7.18** (600 mg, 2 mmol) and benzyl trichloroimidate (1.5 mL, 4 mmol) in a co-solvent cyclohexane/methylene chloride (2:1, 6 mL) was added a catalytic amount of triflic acid (0.05 mL of solution 0.25 mL/5 mL CH_2Cl_2) at 0 °C under an atmosphere of argon, the reaction mixture was then stirred at RT for additional 30 min, then poured into saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated in *vacuo*. FCC of the residue afforded **7.19** (550 mg, 82%). R_f = 0.40 (10% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.60 (s, 3H), 3.33 (m, 2H), 4.12 (apparent d, J = 4.8 Hz, 1H), 4.52 (m, 1H), 4.60 (m, 3H), 6.05 (d, J = 6.2 Hz, 1H), 7.3-7.6 (m,

5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.22, 28.55, 73.05, 81.3, 82.5, 83.7, 107.2, 112.5, 129.5, 130.0, 137.5.

1-O-acetyl-1,2-O-isopropylidene-3-O-benzyl-4-pentene 7.20

To a solution of 5-Deoxy-5-iodo-1,2-O-isopropylidene-3-O-Benzyl-α-D-xylofuranose **7.19** (450 mg, 1.19 mmol) in THF (5 mL) was added n-BuLi (2.2 mL of 1.6 M solution in THF, 3.48 mmol) dropwise at –78 °C, under an atmosphere of argon. The reaction was stirred at this temperature for 1 h and then pyridine (0.27 mL, 3.48 mmol), acetic anhydride (0.45 mL, 4.68 mmol), DMAP (150 mg, 1.2 mmol) were added. This reaction mixture was slowly warmed up to – 40 °C, and stirred for additional 1 hr at this temperature. The reaction mixture was then poured into saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated in *vacuo*. FCC of the residue afforded two diastereomers **7.20a/b** (450 mg, 85%). R_f = 0.1, 0.2 (10% EtOAc/PE); First isomer **7.20a**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.43, 1.46 (both s, 3H ea), 2.05 (s, 3H), 3.92 (br t, J = 8.0 Hz, 1H), 4.3 (m, 1H), 4.6 (ABq, J = 12.2 Hz, Δδ = 0.30 ppm, 2H), 5.4 (m, 2H), 5.8 (m, 1H), 6.2 (d, J = 4.0 Hz, 1H), 7.3(m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 25.5, 25.8, 46.5, 71.6, 80.0, 84.5, 96.5, 113.2, 123.1, 128.4, 128.6, 129.5, 130.8, 134.3.

Second isomer **7.20b**: ^1H NMR (300 MHz, CDCl3) δ 1.43, 1.56 (both s, 3H ea), 2.05 (s, 3H), 4.2 (m, 2H), 4.6 (ABq, J = 10.3 Hz, Δδ = 0.30 ppm, 2H), 5.4 (m,

2H), 5.7 (m, 1H), 6.2 (d, J = 4.0 Hz, 1H), 7.3(m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 26.5, 28.8, 70.6, 79.0, 82.5, 94.5, 117.2, 122.1, 128.4, 128.6, 129.5, 133.3.

1-Thio-1,2-O-isopropylidene-3-O-benzyl-4-pentene 7.21

Acetate mixture **7.20** (440 mg, 1.44 mmol) was subjected to the procedure as detailed for the preparation of **2.12**. FCC of the residue afforded single isomer **7.21** (450 mg, 87%). R_f = 0.6 (10% EtOAc/PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.48, 1.56 (both s, 3H ea), 3.92 (dd, J = 6.6, 8.0 Hz, 1H), 4.2 (br t, J = 6.6 Hz, 1H), 4.6 (ABq, J = 12.0 Hz, Δδ = 0.35 ppm, 2H), 5.4 (m, 3H), 5.9 (m, 1H), 7.3(m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 27.9, 70.0, 79.8, 83.6, 87.0, 113.2, 120.0, 127.5, 127.9, 128.3, 129.1, 129.8, 132.3, 134.6.

Alcohol 7.22

A mixture of 0.5% $NiCl_2$ in $CrCl_2$ (300 mg) was heated at 180 °C for 48 hr under high vacumn (<10 torr). The mixture was then cooled down to rtT and protected by N_2. A solution of aldehyde **7.8** (100 mg, 0.28 mmol) and bromide **7.7** (537 mg, 0.84 mmol) in anhydrous co-solvent THF and DMF (4:1, 3 mL) was added to the above catalysts mixture to obtain dark green suspension, which was then stirred at RT for 24 hr under an atmosphere of argon. The reaction mixture was then diluted with ethyl acetate and washed with saturated aqueous NH_4Cl, brine, dried ($MgSO_4$) and evaporated in *vacuo*. FCC of the residue afforded a mixture of 2:1 inseparable isomers **7.22** (170 mg, 65%), clear oil; R_f = 0.2 (15%

ethyl acetate:petroleum ether). For characterization purpose, the major isomer was obtained from deprotection of the major bezoate diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45, 1.47 (both s, 3H ea), 2.48 (m, 2H), 3.59 (dd, J = 2.6, 5.2 Hz, 1H), 3.62 (dd, J = 2.6, 6.6 Hz, 1H), 3.71 (m, 5H), 3.98 (m, 1H), 4.15 (m, 1H), 4.30 (dd, J = 2.6, 7.32 Hz, 1H), 4.50 (m, 10H), 5.11 (br s, 1H), 5.34 (m, 2H), 7.3 (m, 30H); ESMS (M + Na) 945.4.

Benzoate 7.23

Alcohol **7.22** (100 mg, 0.1 mmol) was subjected to the benzoylation procedure as detailed for the preparation of **7.11**. FCC of the product gave a 2:1 mixture of inseperable diastereomers, benzoate **7.23a** and **7.23b** (100 mg, 87%). clear oil; R_f = 0.8, 0.82 (2% ethyl ether/ dichloromethane), these two isomers are barely seperated, only part of the major isomer **7.23b** can be cleanly isolated: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45, 1.55 (both s, 3H ea), 2.47 (m, 2H), 3.75 (m, 7H), 4.20 (dd, J = 3.4, 6.8 Hz, 1H), 4.30 (m, 1H), 4.52 (m, 10H), 5.10 (br s, 1H), 5.26 (d, J = 6.8 Hz, 1H), 5.34 (s, 1H), 5.66 (d, J = 6.0 Hz, 1H), 7.4 (m, 35 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.96, 28.05, 34.62, 69.96, 72.31, 72.68, 72.74, 74.00, 74.36, 74.41, 74.52, 75.58, 76.18, 77.29, 80.89, 85.36, 111.92, 116.48, 127.86, 127.93, 127.99, 128.07, 128.19, 128.31, 128.41, 128.45, 128.53, 128.57, 128.68, 128.85, 128.92, 128.97, 129.10, 129.48, 130.37, 130.43, 130.82, 132.35, 133.58, 134.30, 134.35, 139.06, 139.12, 142.75; ESMS (M + NH_4) 1044.5.

Diacetate 7.25

To a mixture of **7.23b** (40 mg, 0.039 mmol) and freshly activated molecular sieves (80 mg) in dry CH_2Cl_2 (2 mL) was added IDCP (55 mg, 0.12 mmol). The mixture was stirred at rt for 10 min, then filtered through a bed of celite, the filtrate was poured into saturated, aqueous $Na_2S_2O_3$, and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated in *vacuo*. FCC of the residue afforded **7.24b** (25 mg, 72%). R_f = 0.30 (10% EtOAc/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.38 (s, 3H), 2.40 (m, 2H), 3.55 (dd, J = 3.0, 5.6, 1H), 3.72 (m, 3H), 3.86 (m, 2H), 4.12 (m, 2H), 4.45 (m, 10H), 4.74 (m, 2H), 5.88 (m, 2H), 7.3-8.0 (m, 30H); ESMS (M + Na) 939.4.

A mixture of inseparable (~1:1) **7.23a** and **7.23b** (60 mg) was also subjected to cyclization using the same procedure. Two products were formed, with R_f = 0.25, 0.30 (10% EtOAc/PE), corresponding to **7.24a** and **7.24b** respectively.

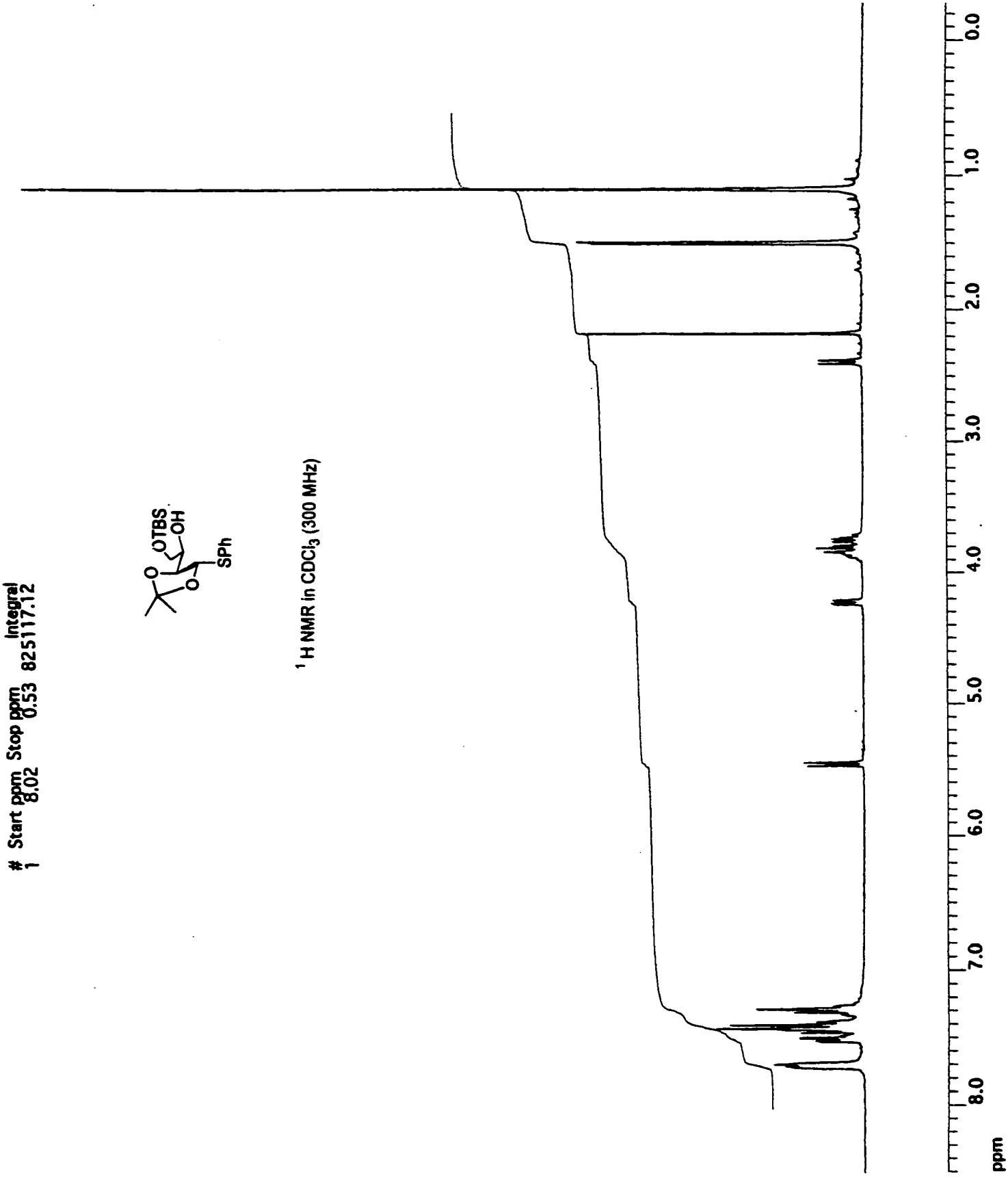
A solution of 1M HCl in ether (0.2 mL) was added to a solution of **7.24a** (~10 mg) in dry methanol (1 mL). The reaction mixture was stirred at rt for 20 min, and then neutralized by addition of sodium methoxide. The solvent was removed under reduced pressure. A solution of this crude material and acetic anhydride (1 mL) and DMAP (5 mg) in ethyl acetate (2 mL) was stirred at rt for 20 min. Methanol (0.1 mL) was added to quench the reaction. Most of the solvent was removed under the reduced pressure, the residue was purified by FCC to give diacetate **7.25** (4 mg, 45% for 3 steps) R_f = 0.5 (15% ethyl acetate:petroleum ether); ^{1}H NMR (400 MHz, C_6D_6) δ 1.72, 1.78 (s, 3H ea), 2.42 (m, 1H), 2.78 (dd, J = 5.2,

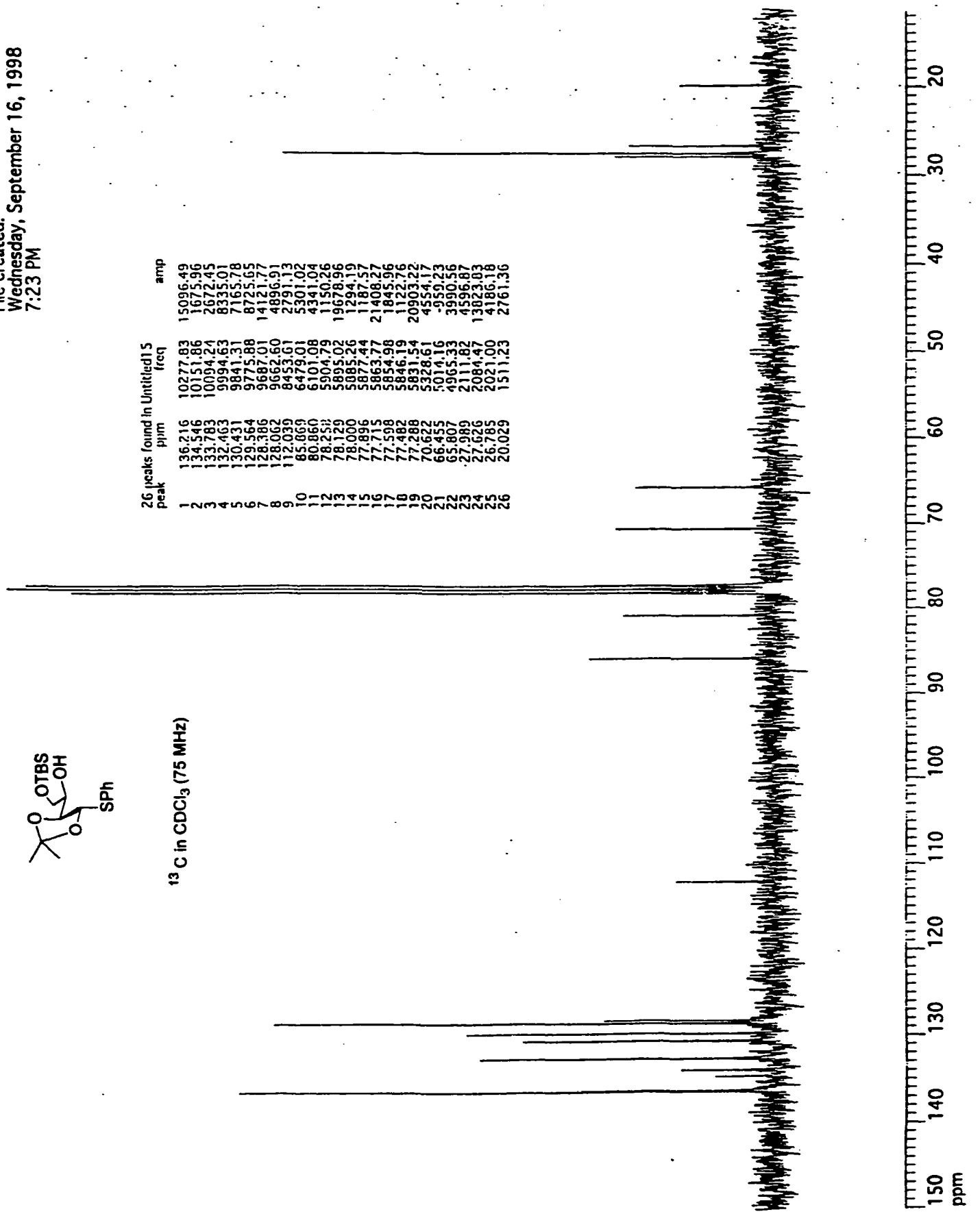
14.4 Hz, 1H), 3.84 (m, 1H), 3.87 (m, 3H), 4.10 (m, 2H), 4.13 (t, J = 4.4Hz, 1H), 4.47 (m, 10H), 4.88 (t, J = 6.0 Hz, 1H), 5.62 (m, 1H), 5.83 (dd, J = 3.3, 8.8 Hz, 1H), 6.19 (m, 2H), 7.3 (m, 30H).

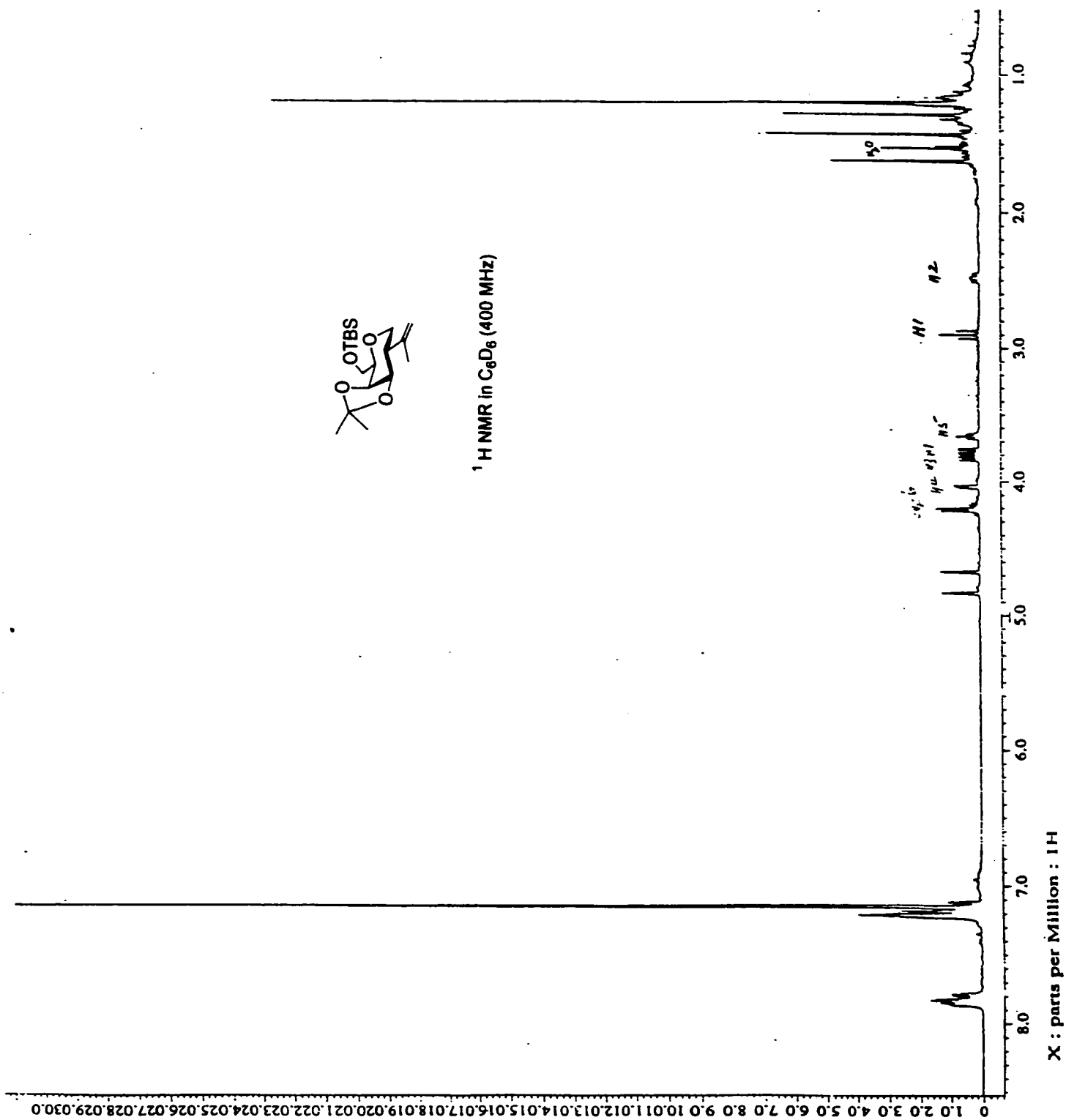
Triacetate 7.26

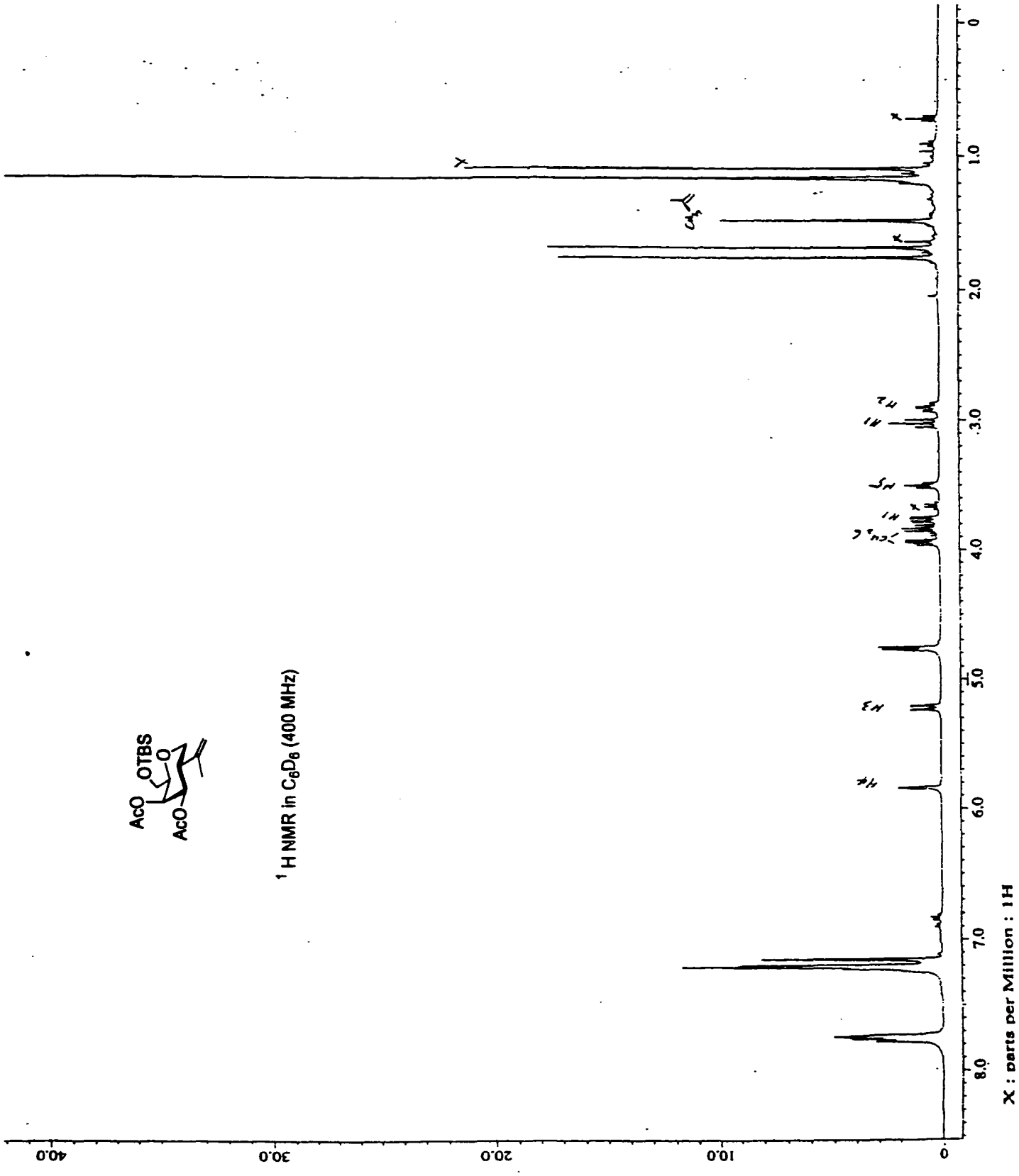
To a solution of olefin **7.24b** (22 mg, 0.02 mmol) in anhydrous THF (1 mL) was added borane (1 mL, 1M solution in THF, 1 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 4 hr at this temperature, followed by addition of aqueous sodium peroxide dropwise (mixture of 0.5 mL 3N NaOH and 0.5 mL of 30% H_2O_2). This mixture was slowly warmed up to RT over 0.5 hr, diluted with water, and extracted with ether. The combined organic layer was washed with aqueous $NaHSO_3$, brine, and dried (Na_2SO_4), filtered, evaporated *in vacuo*. This crude material was subjected to deacetonization and acetylation procedure as detailed in the preparation of **7.25**. FCC of the product gave triacetate **7.26** (10 mg, 48% for 3 steps); R_f = 0.5 (15% ethyl acetate:petroleum ether); ^1H NMR (400 MHz, C_6D_6) δ 1.56 (m, 1H), 1.64, 1.76, 1.81 (s, 3H ea), 2.0 (m, 1H), 3.24 (m, 1H), 3.46 (m, 1H), 3.75 (dd, J = 2.4, 6.8 Hz, 1H), 3.95 (m, 3H), 4.13 (t, J = 4.4 Hz, 1H), 4.17 (dd, J = 3.3, 4.0 Hz, 1H), 4.50 (m, 11H), 5.78 (m, 2H), 5.87 (dd, J = 3.3, 9.9 Hz, 1H), 5.95 (t, J = 4.0 Hz, 1H), 7.3 (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 21.55, 21.72, 37.55, 68.87, 70.04, 71.79, 72.34, 72.071, 73.75, 73.91, 74.13, 74.22, 74.38, 74.66, 75.66127.91, 127.98, 128.10, 128.17, 128.21,

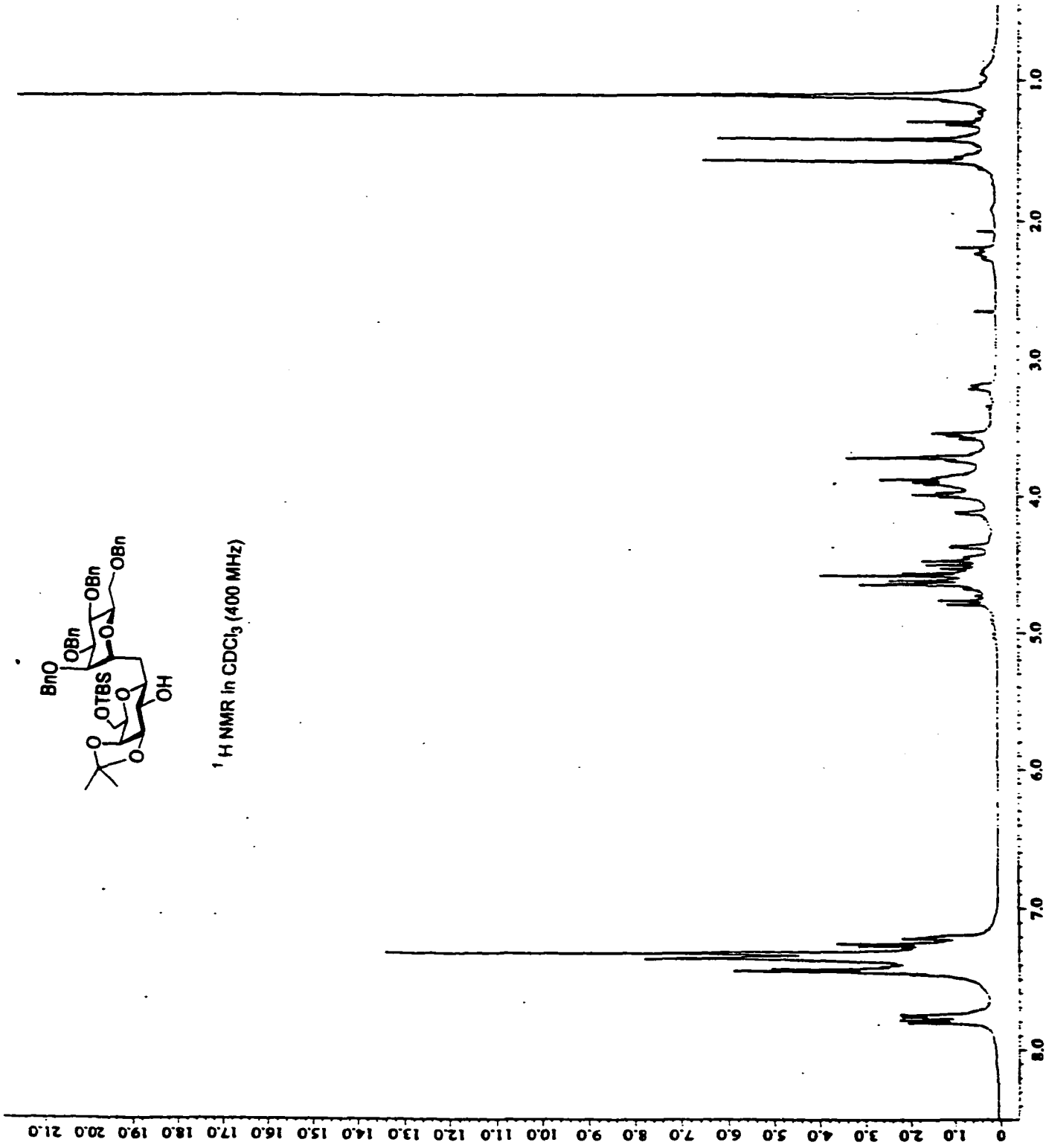
128.24, 128.30, 128.45, 128.75, 128.87, 128.96, 129.18, 130.22, 130.42, 133.94, 137.81, 138.99, 139.17, 166.13, 170.53, 170.90; ESMS ($M + NH_4$) 1038.6.

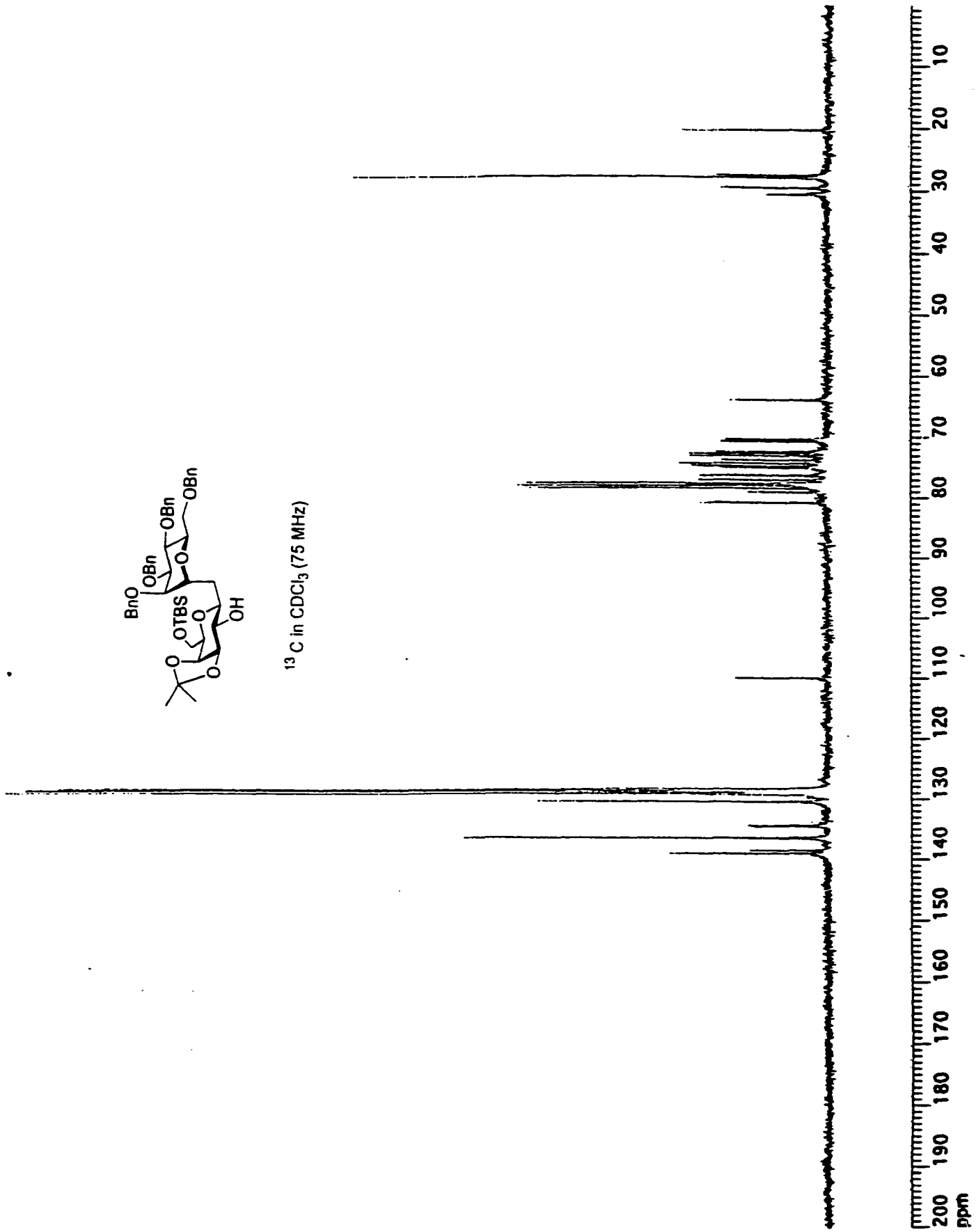


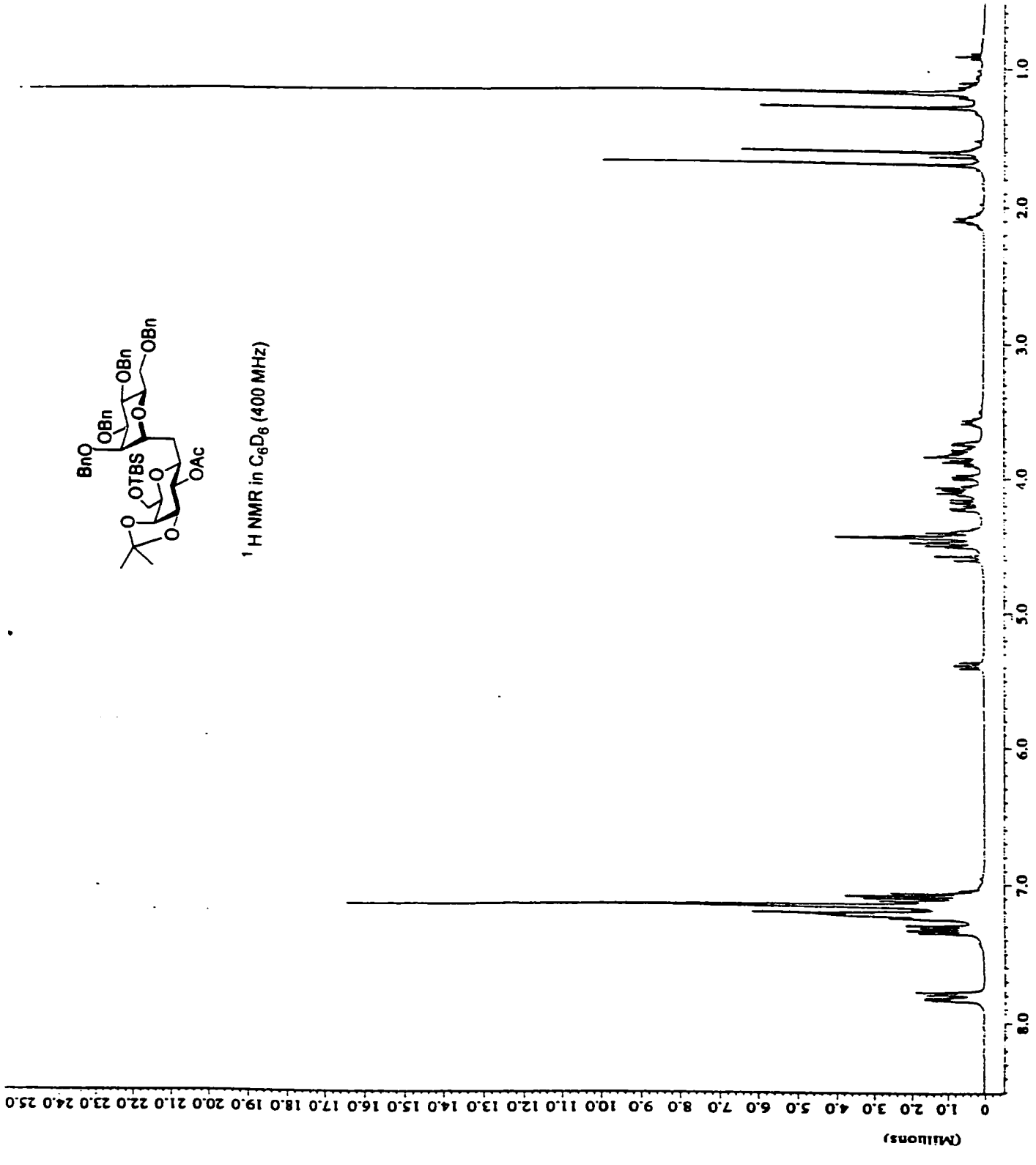


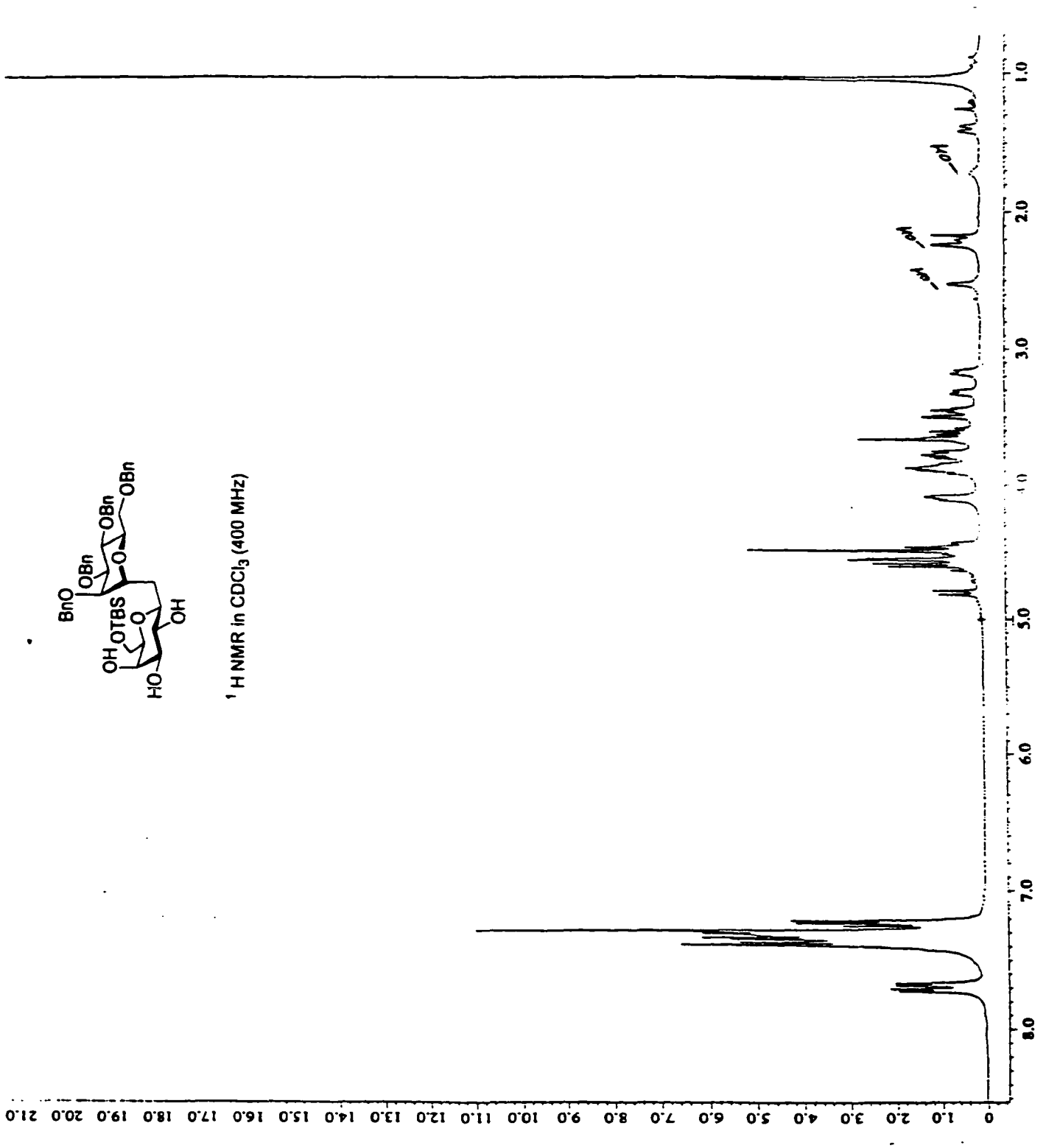


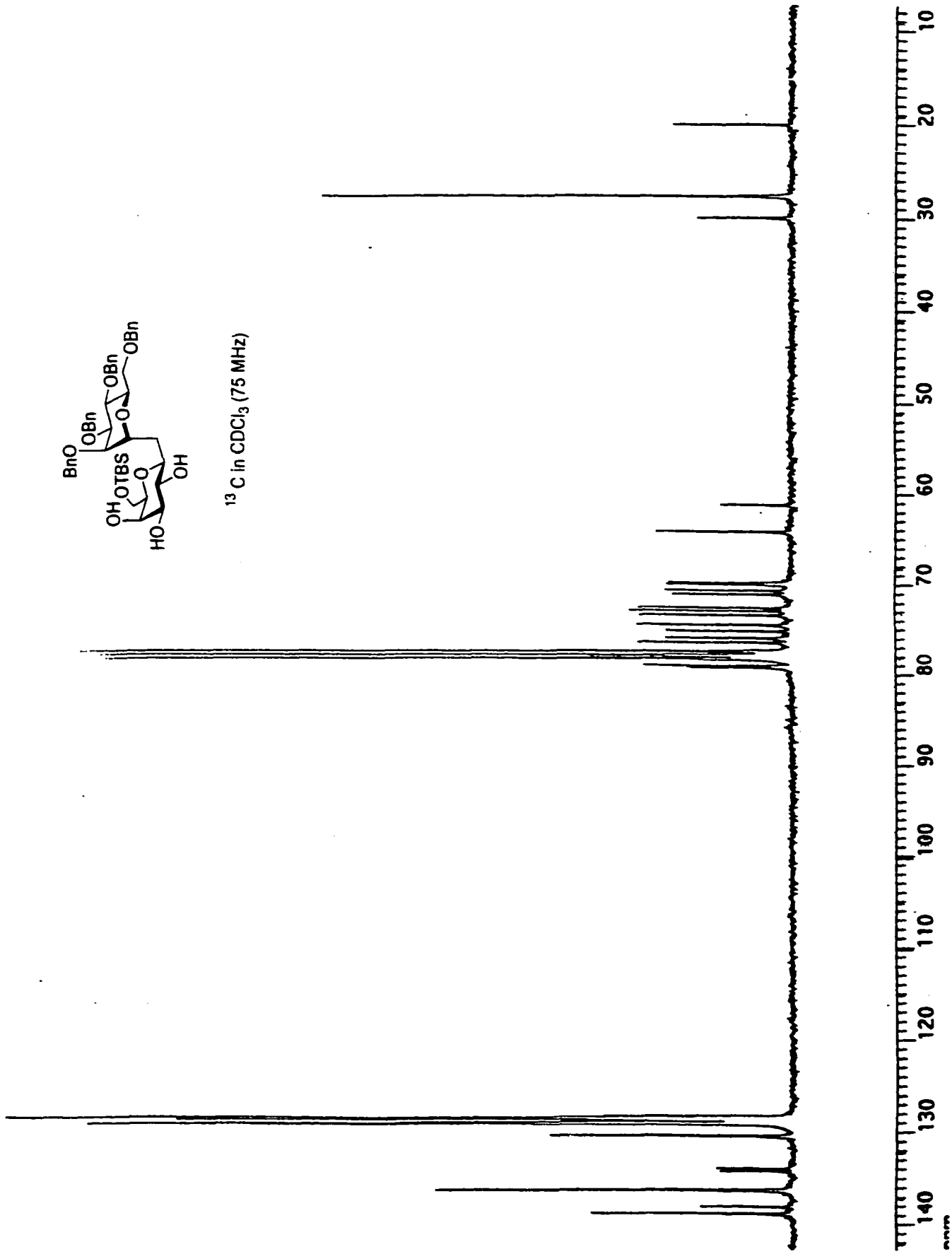


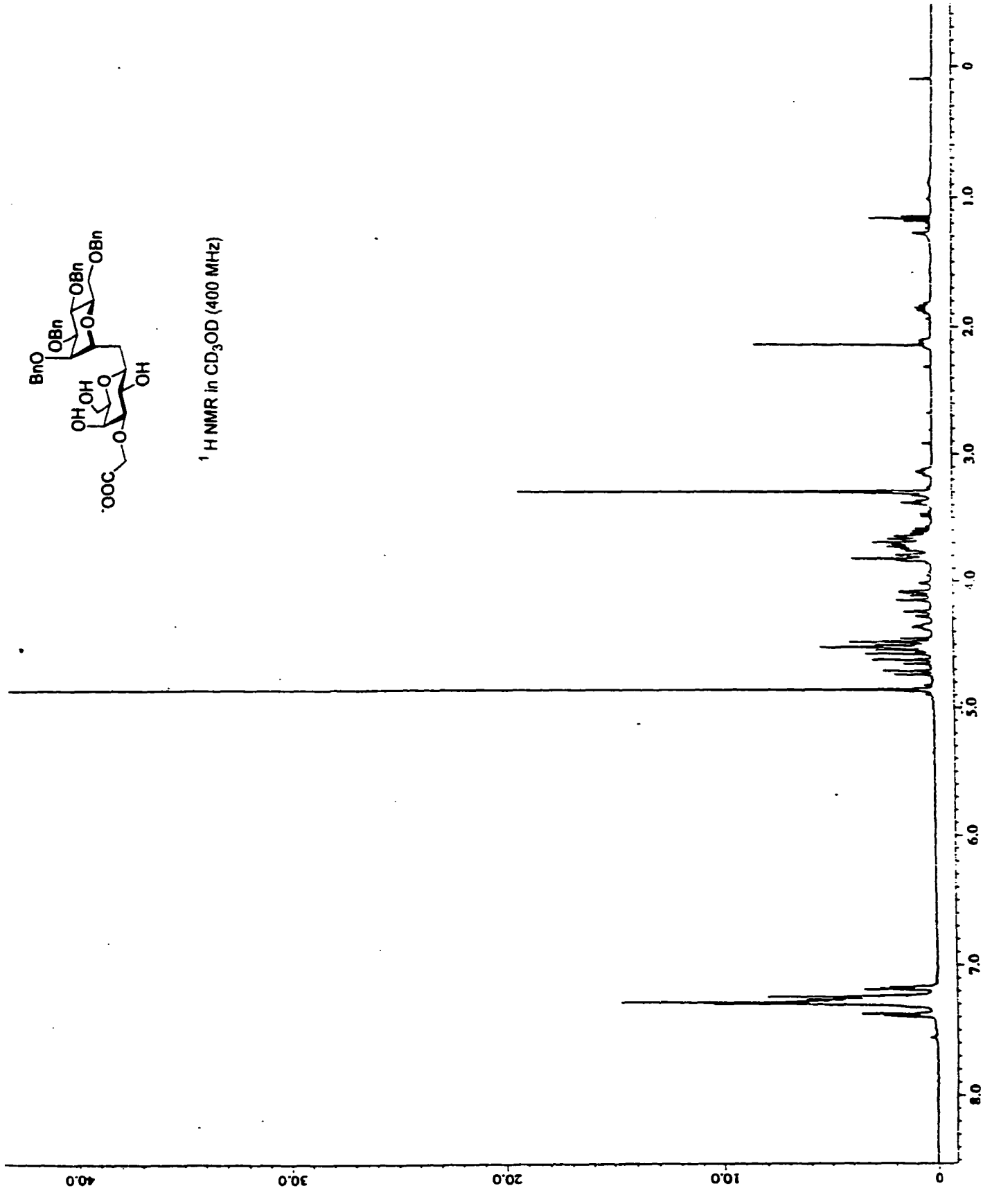


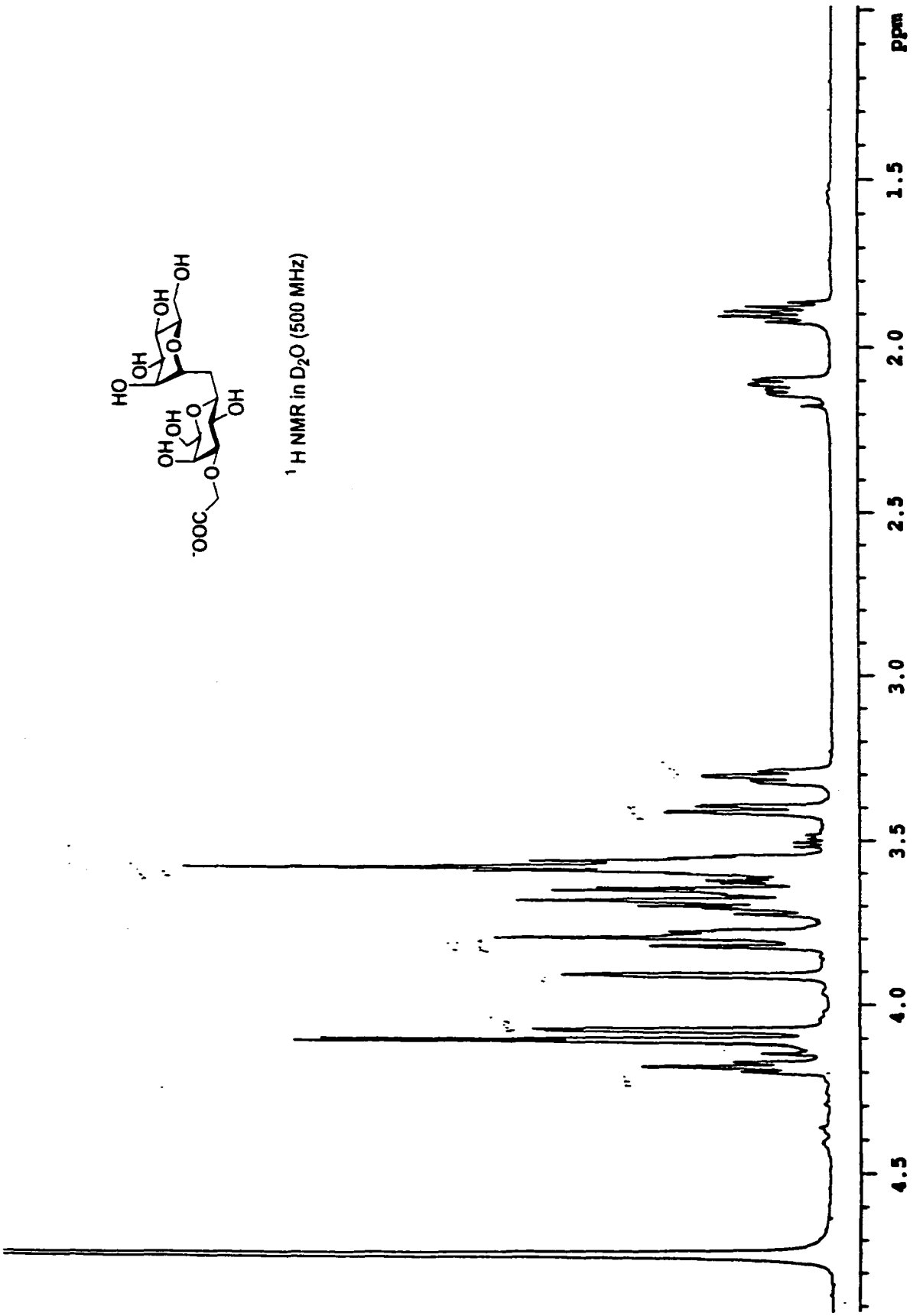












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6	77.482	5846.19	573386.00
7	74.311	5606.93	530535.12
8	73.936	5578.61	514931.00
9	73.159	5520.02	554816.38
10	71.567	5399.90	407258.59
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12	69.393	5235.84	503051.84
13	64.953	4900.88	544636.25
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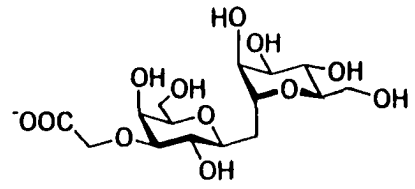

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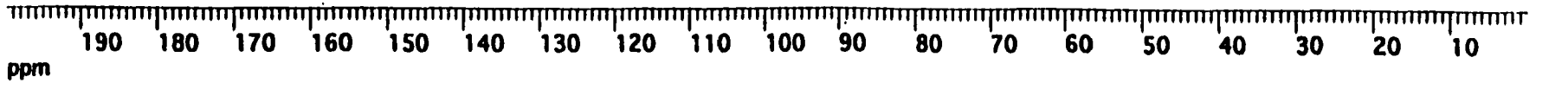

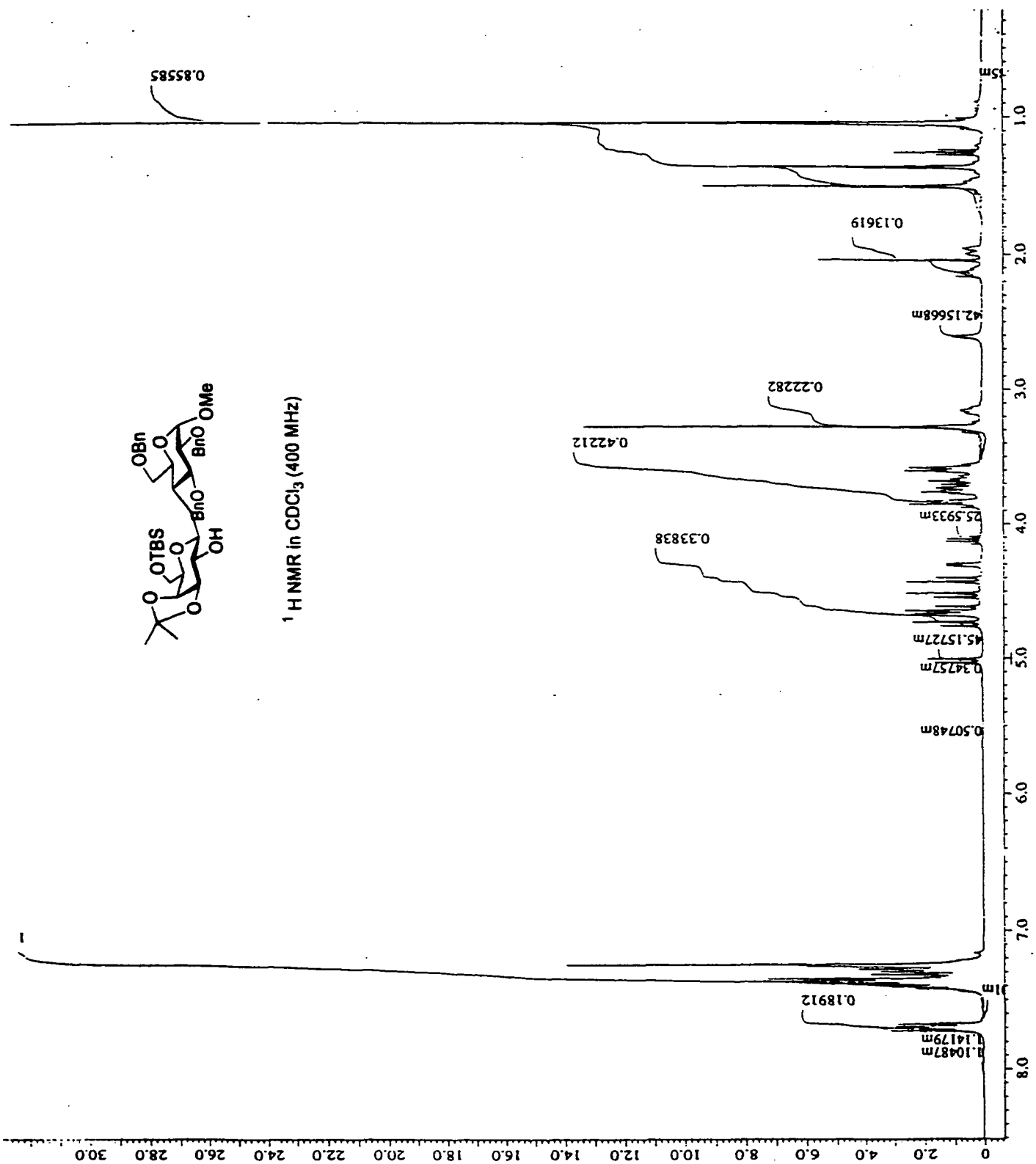

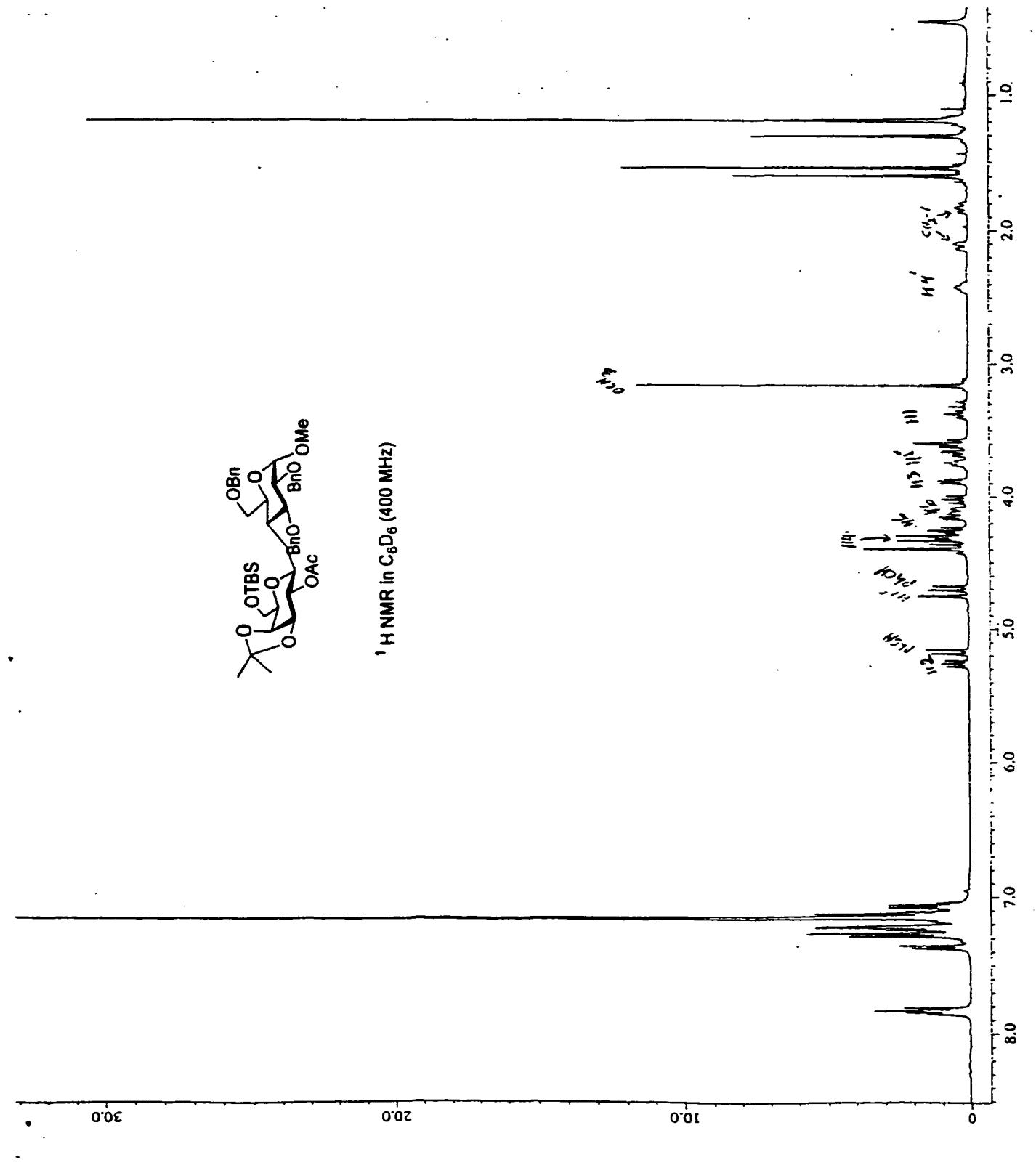

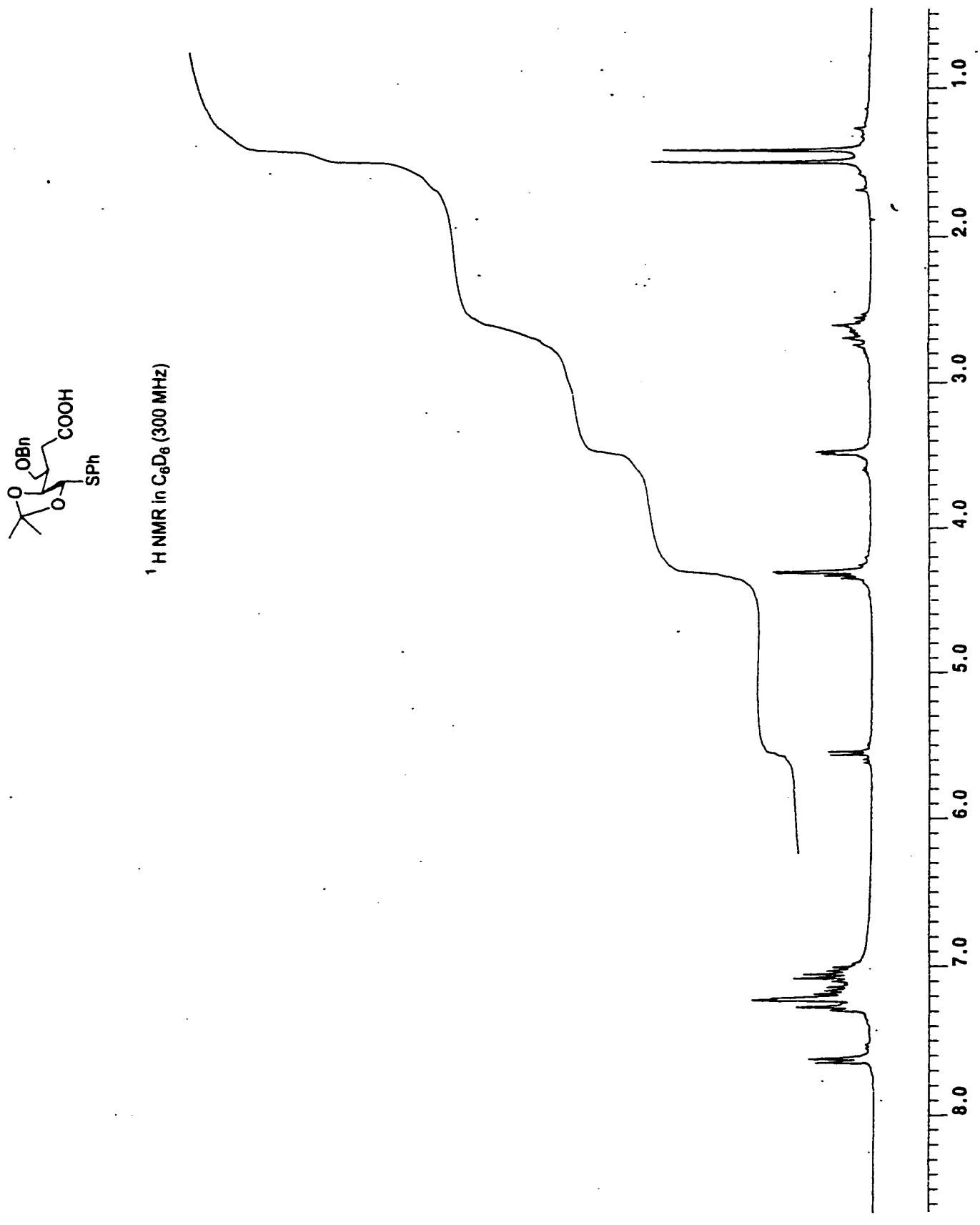

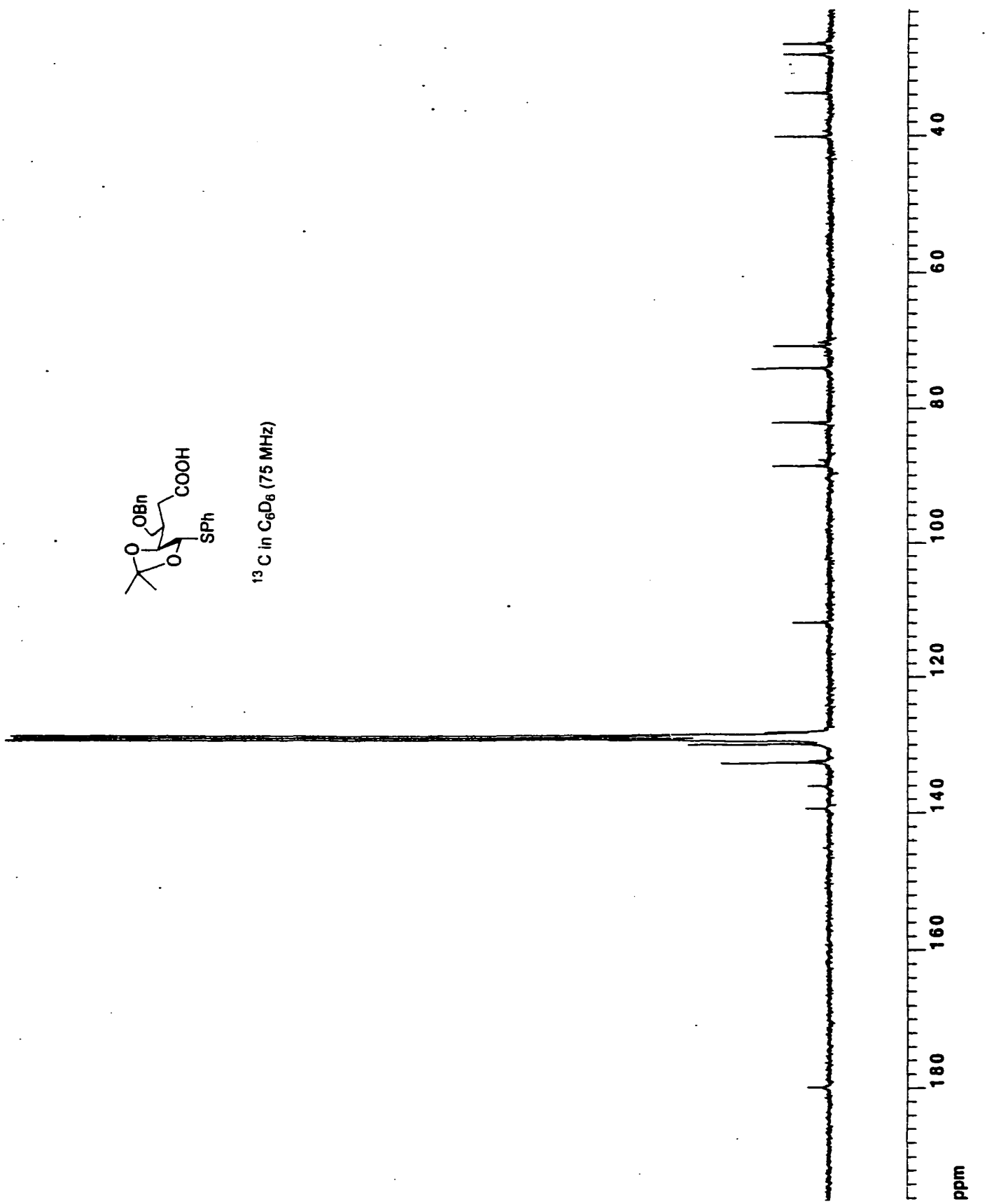

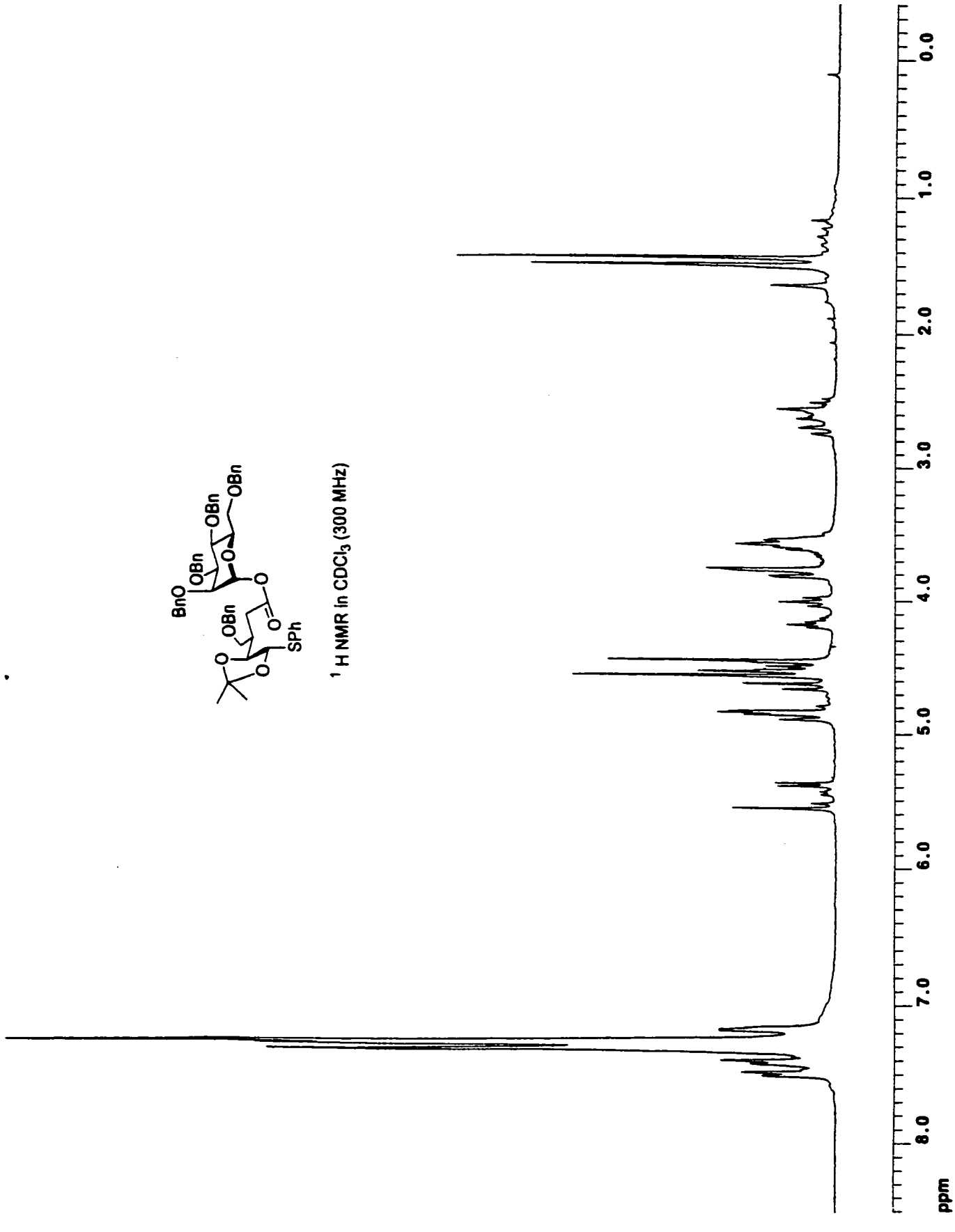

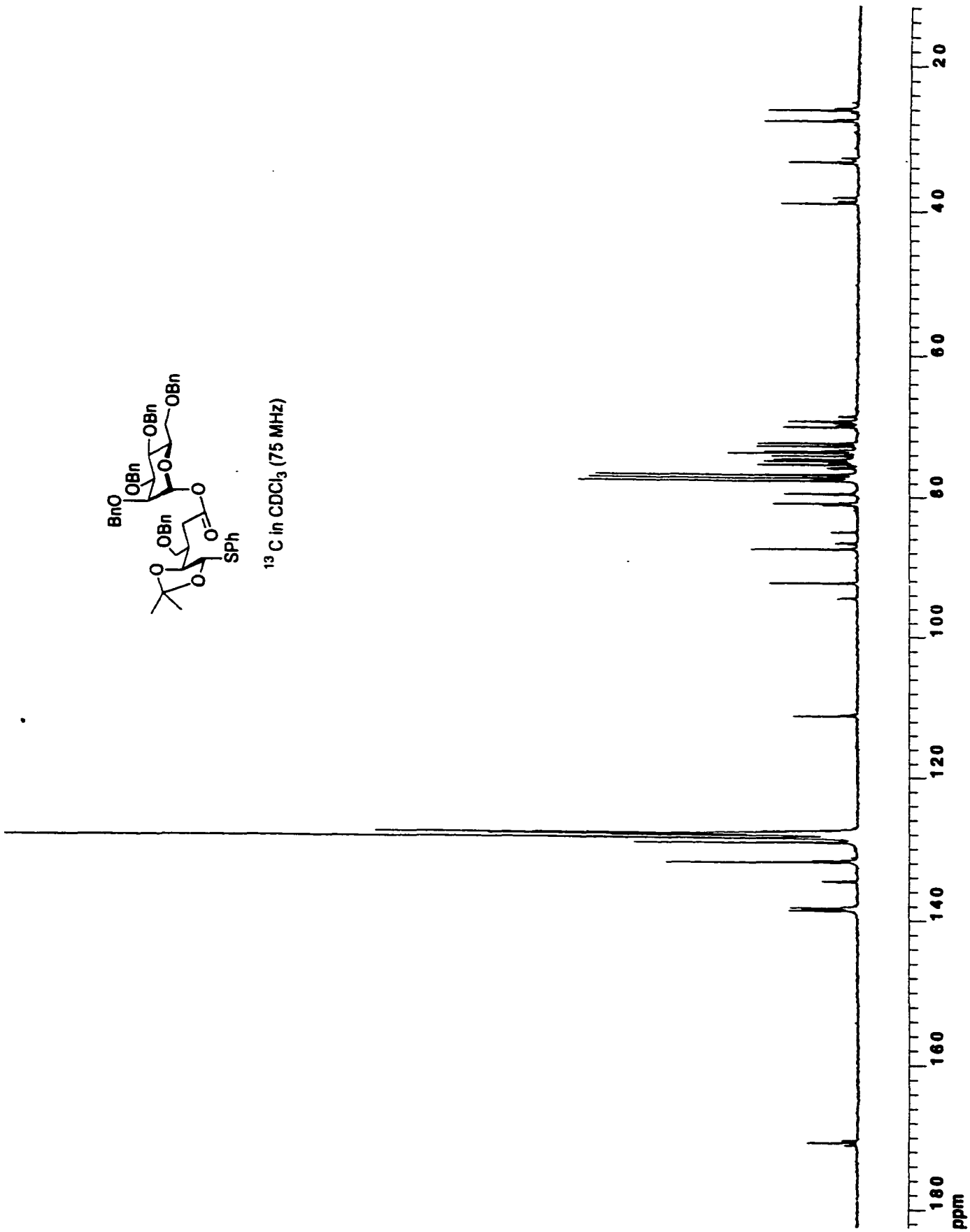

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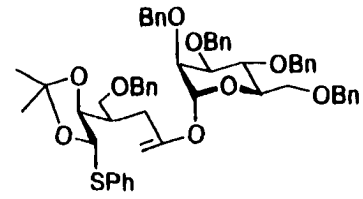
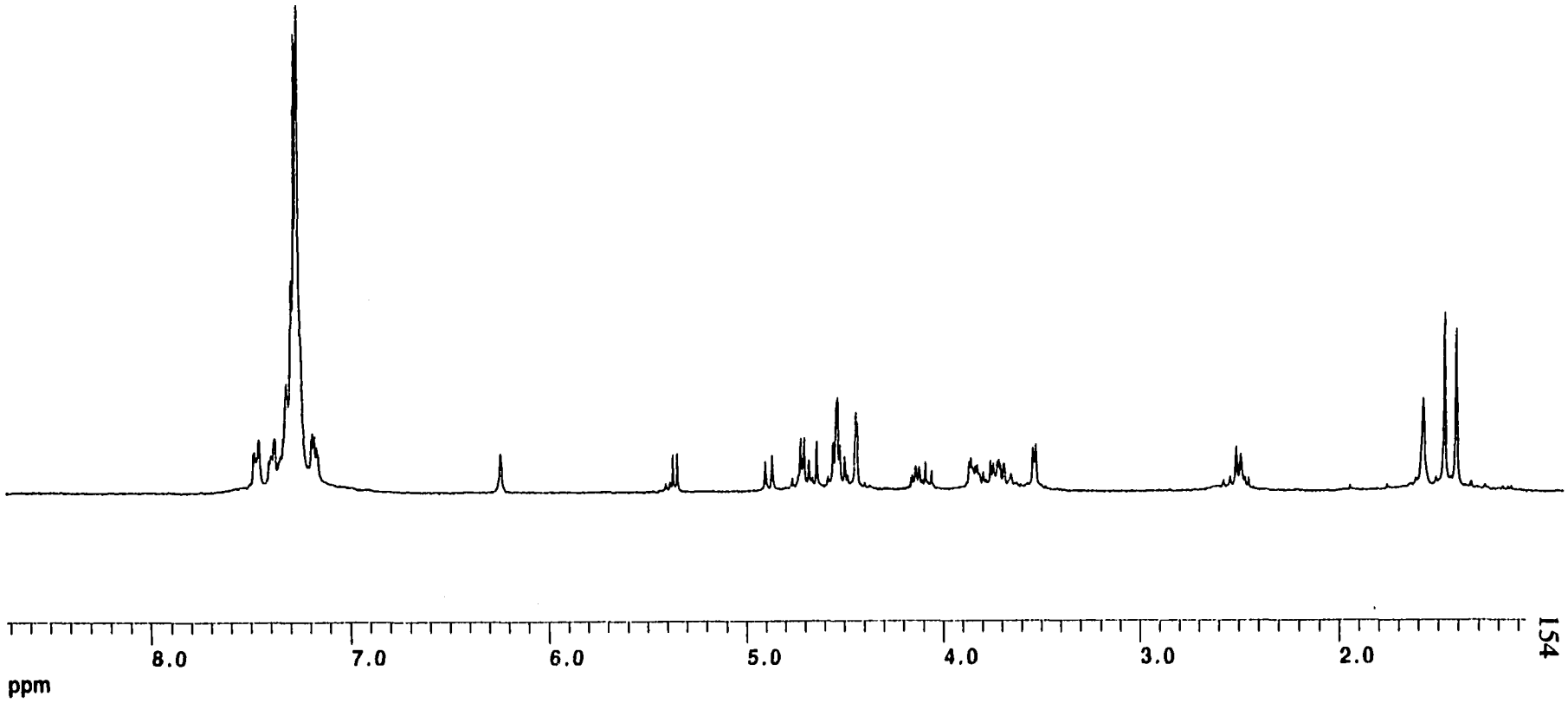
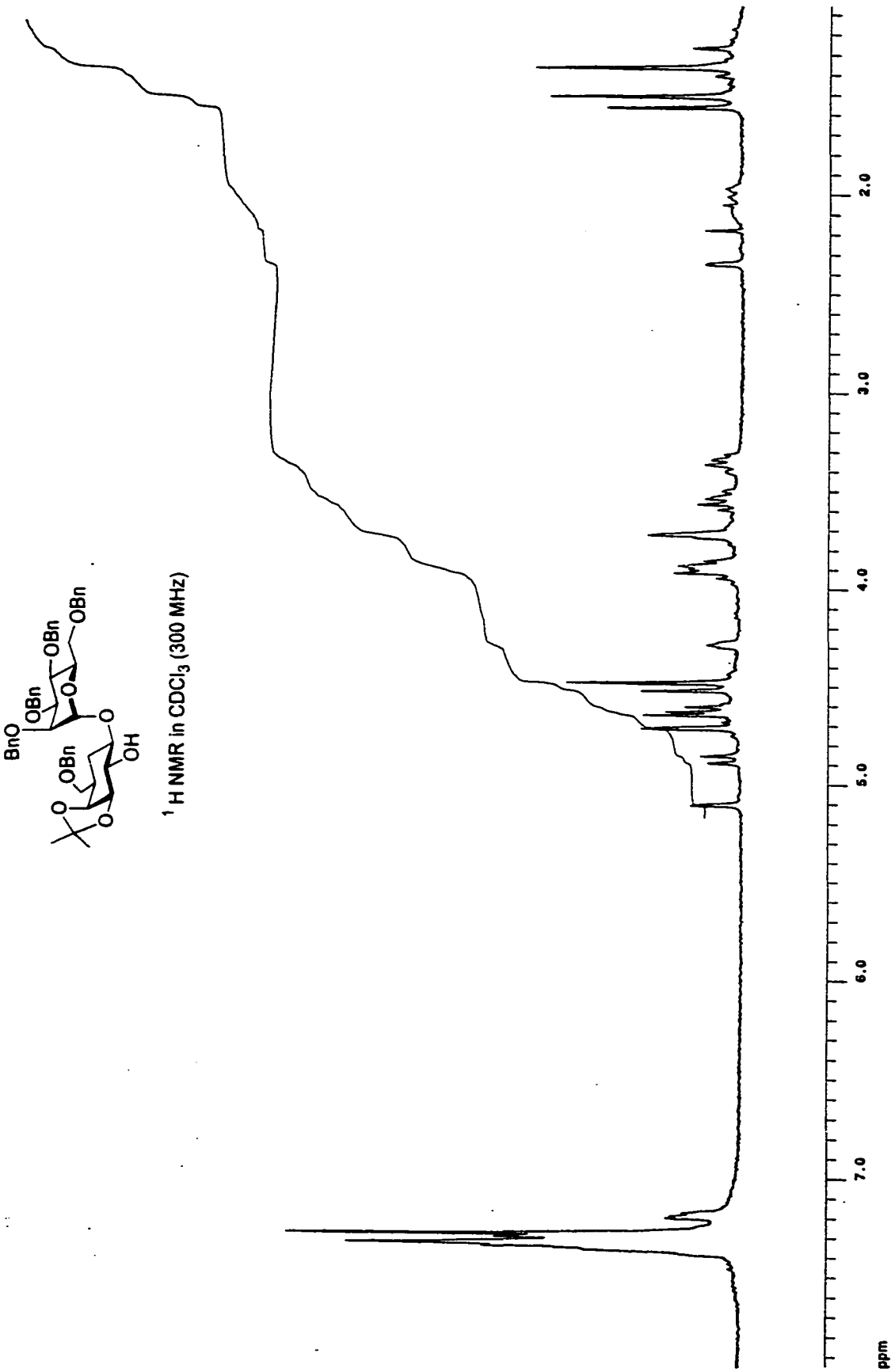
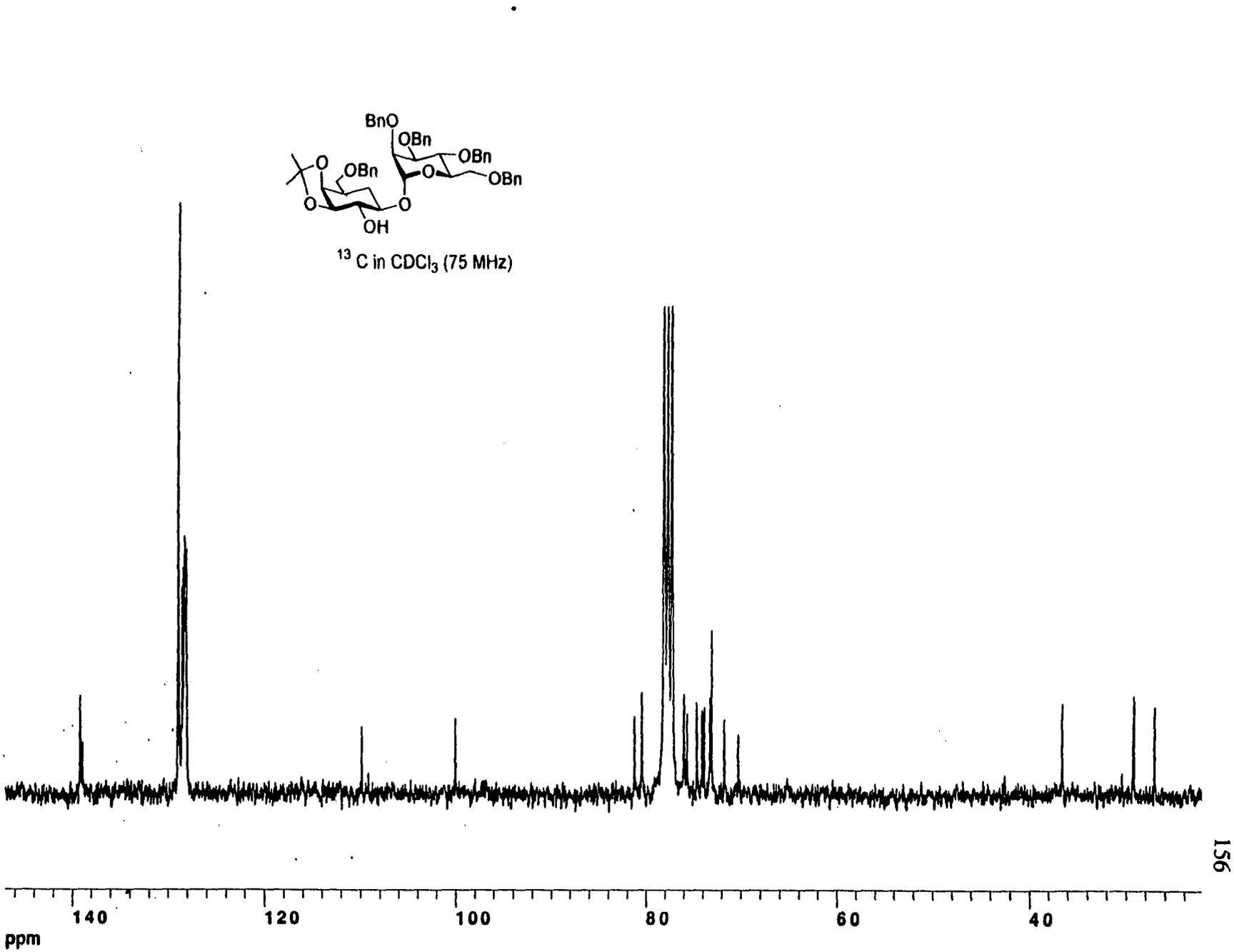
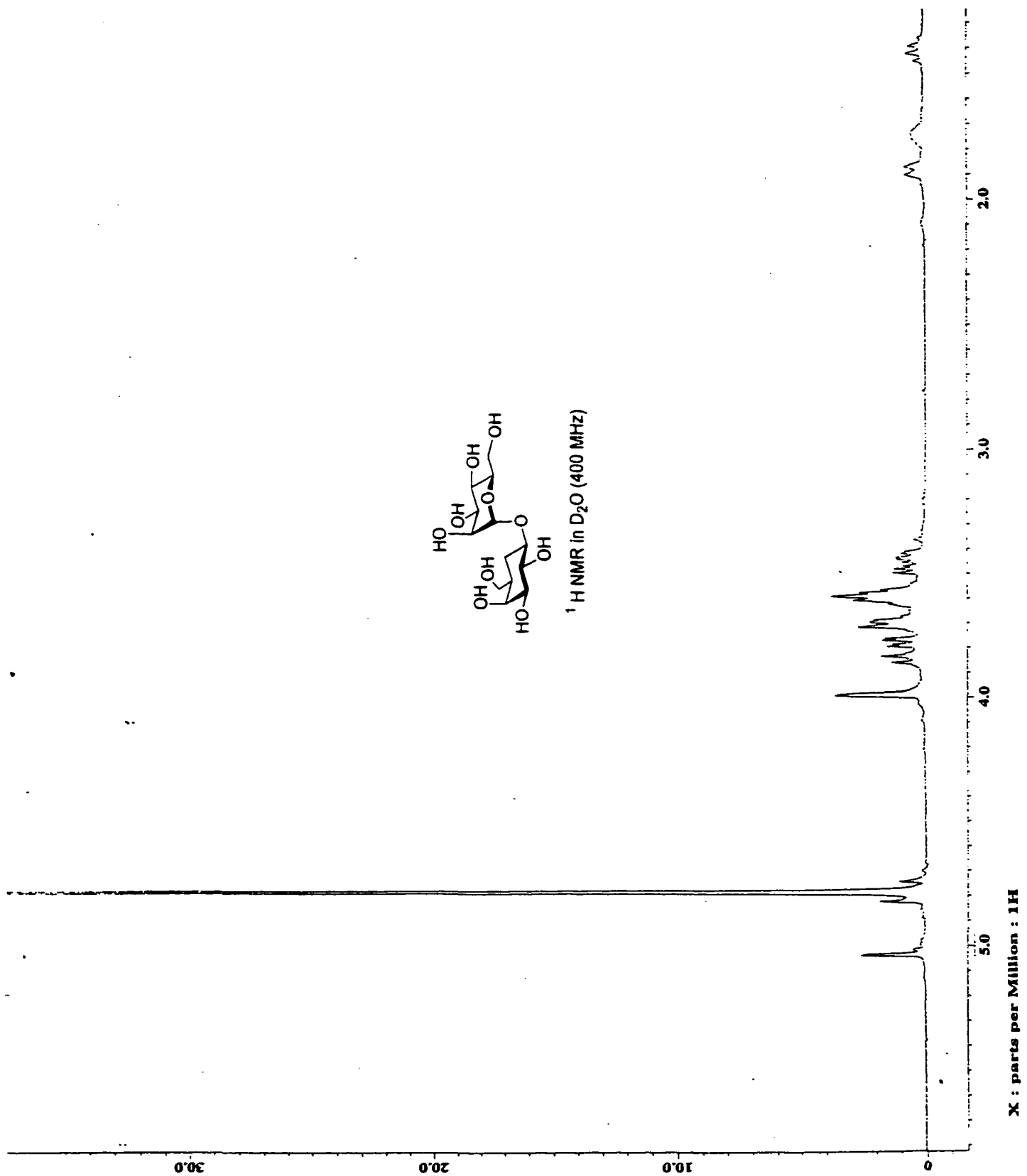


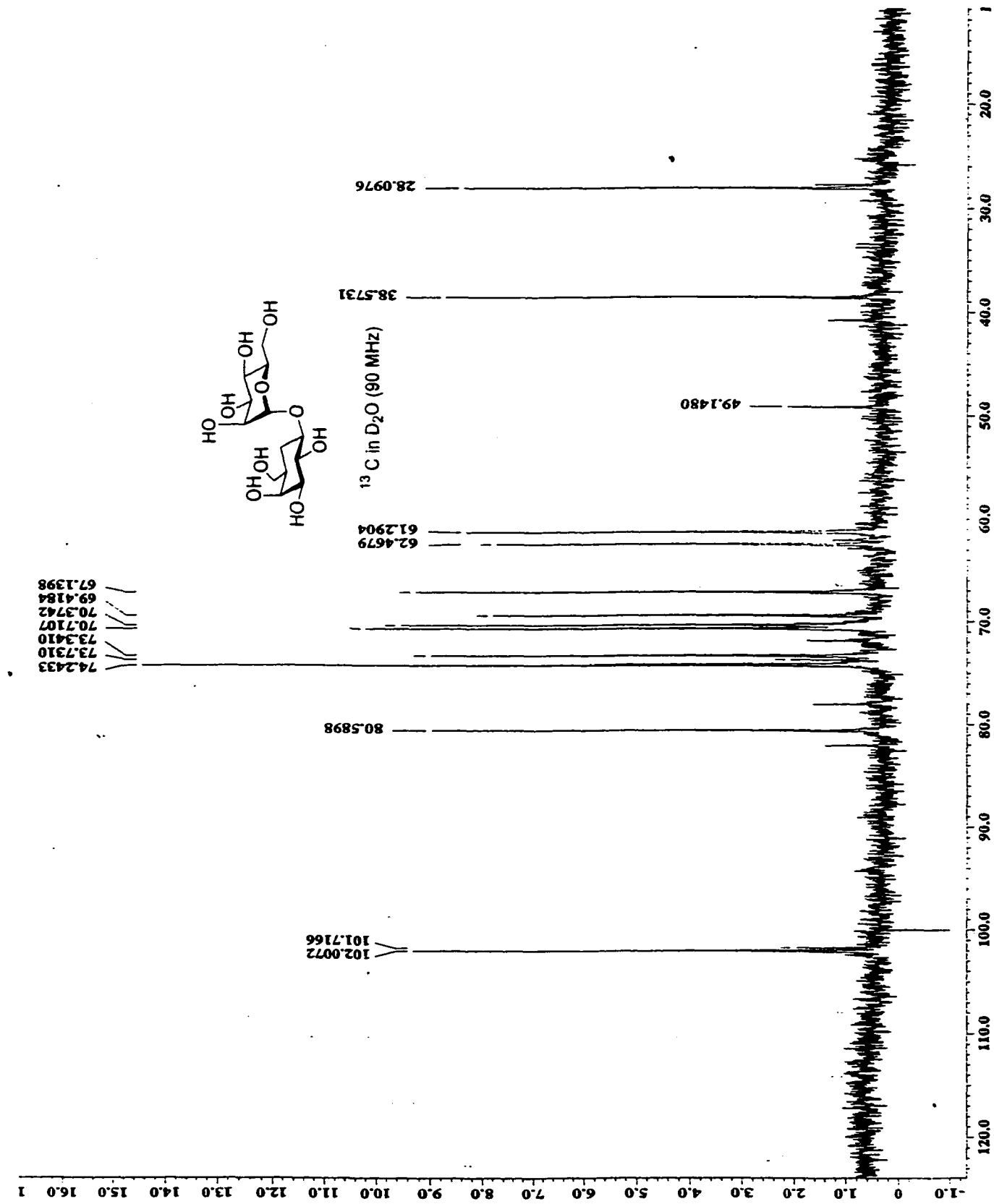
^{1}H NMR in $CDCl_3$ (300 MHz)

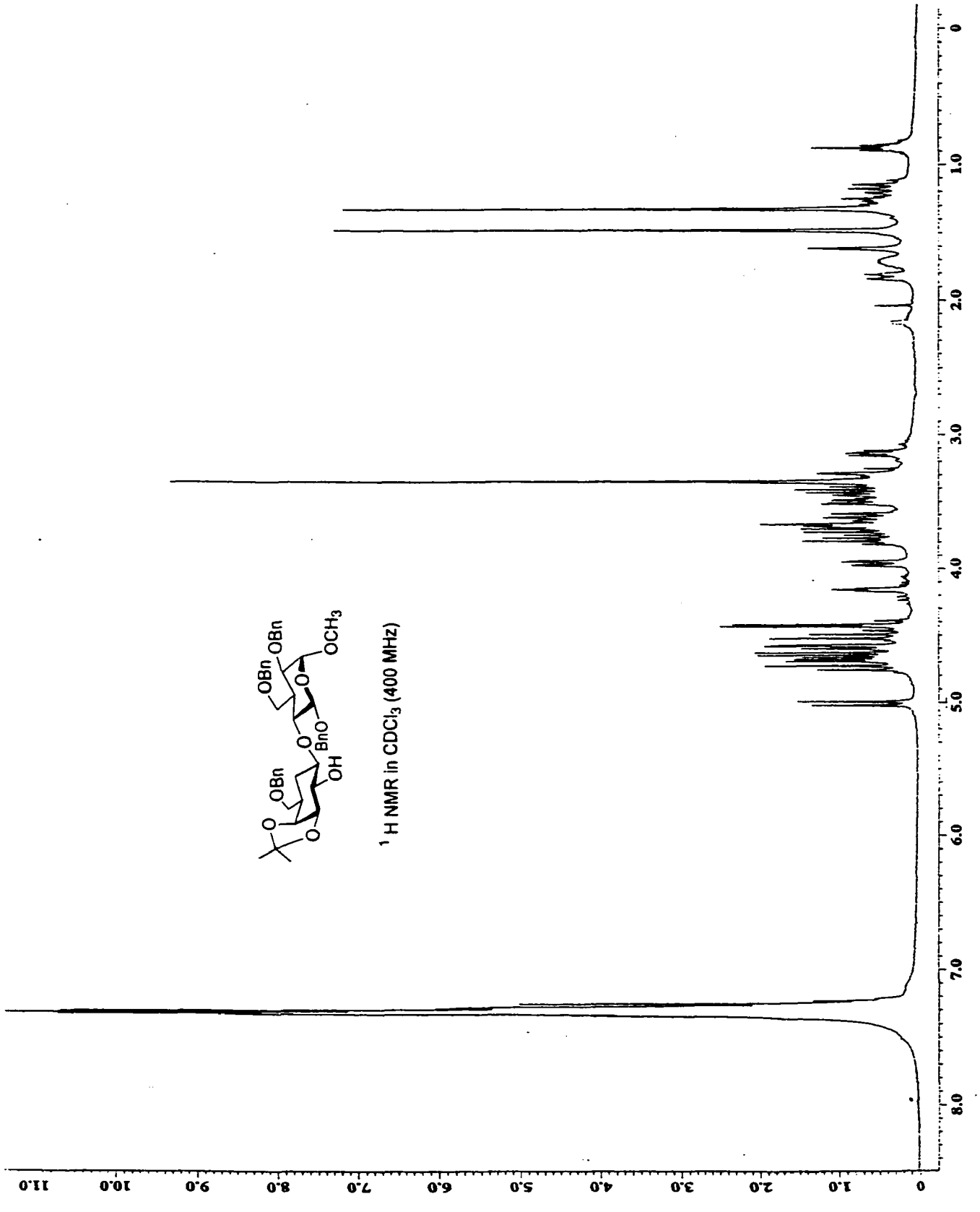


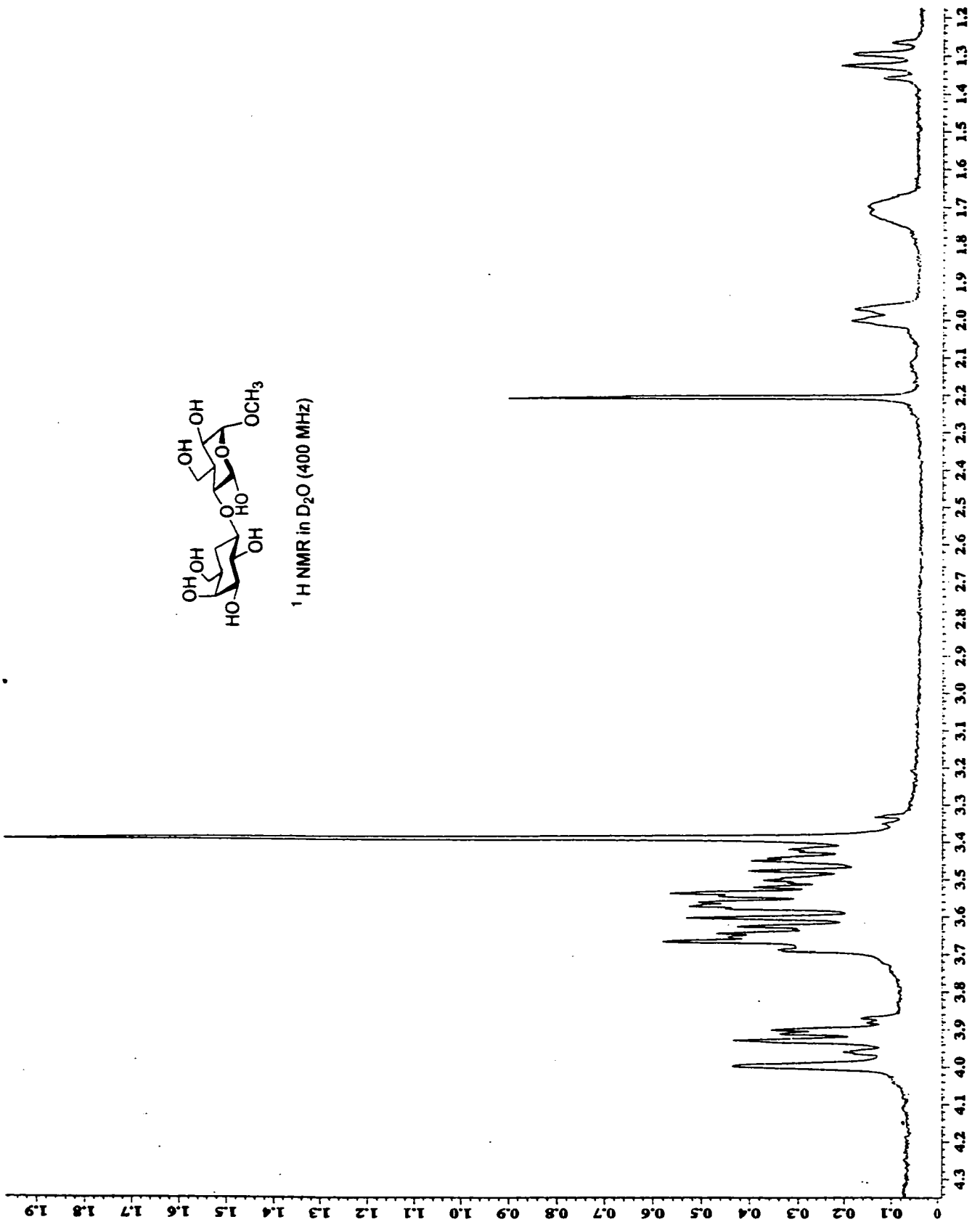


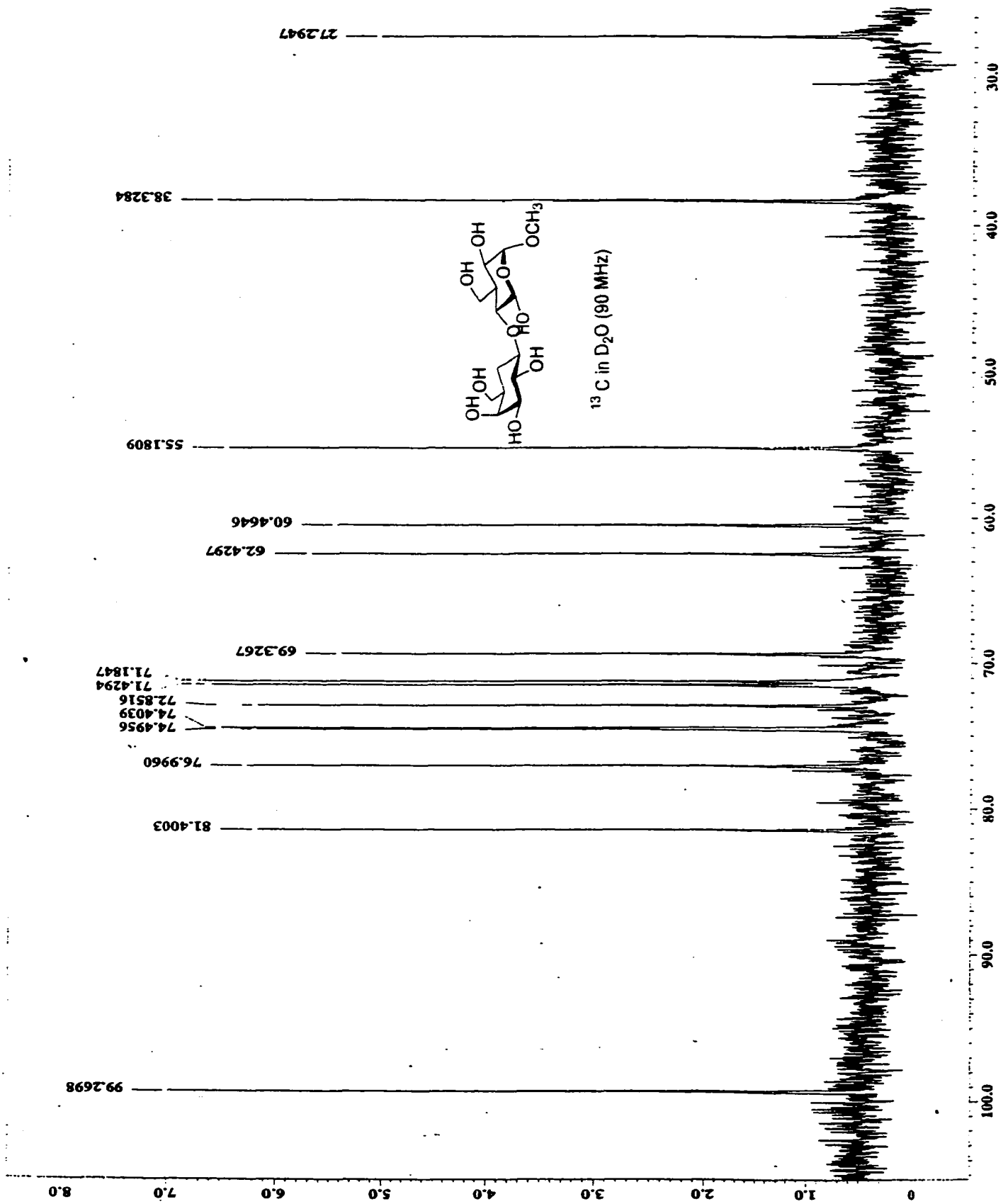


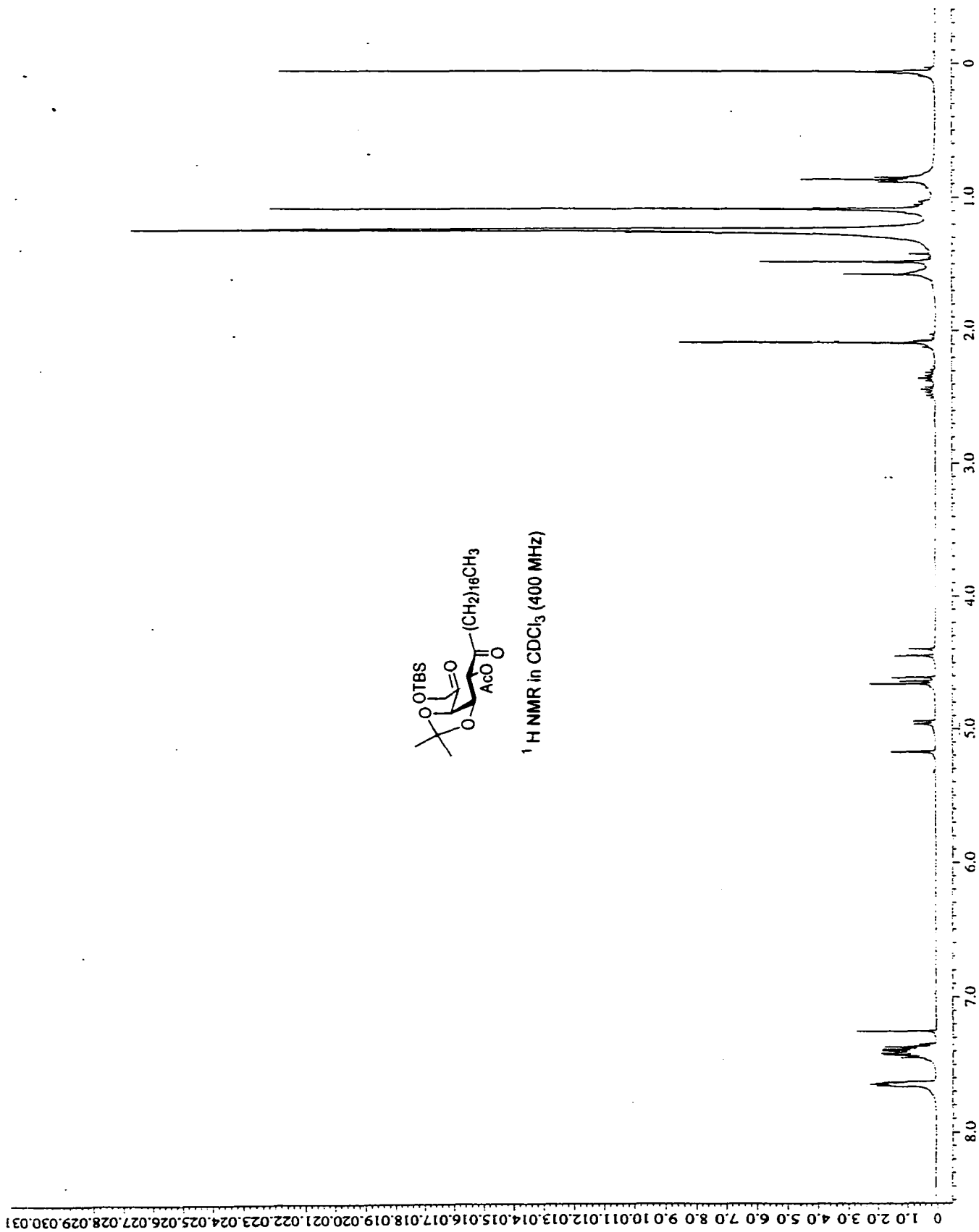


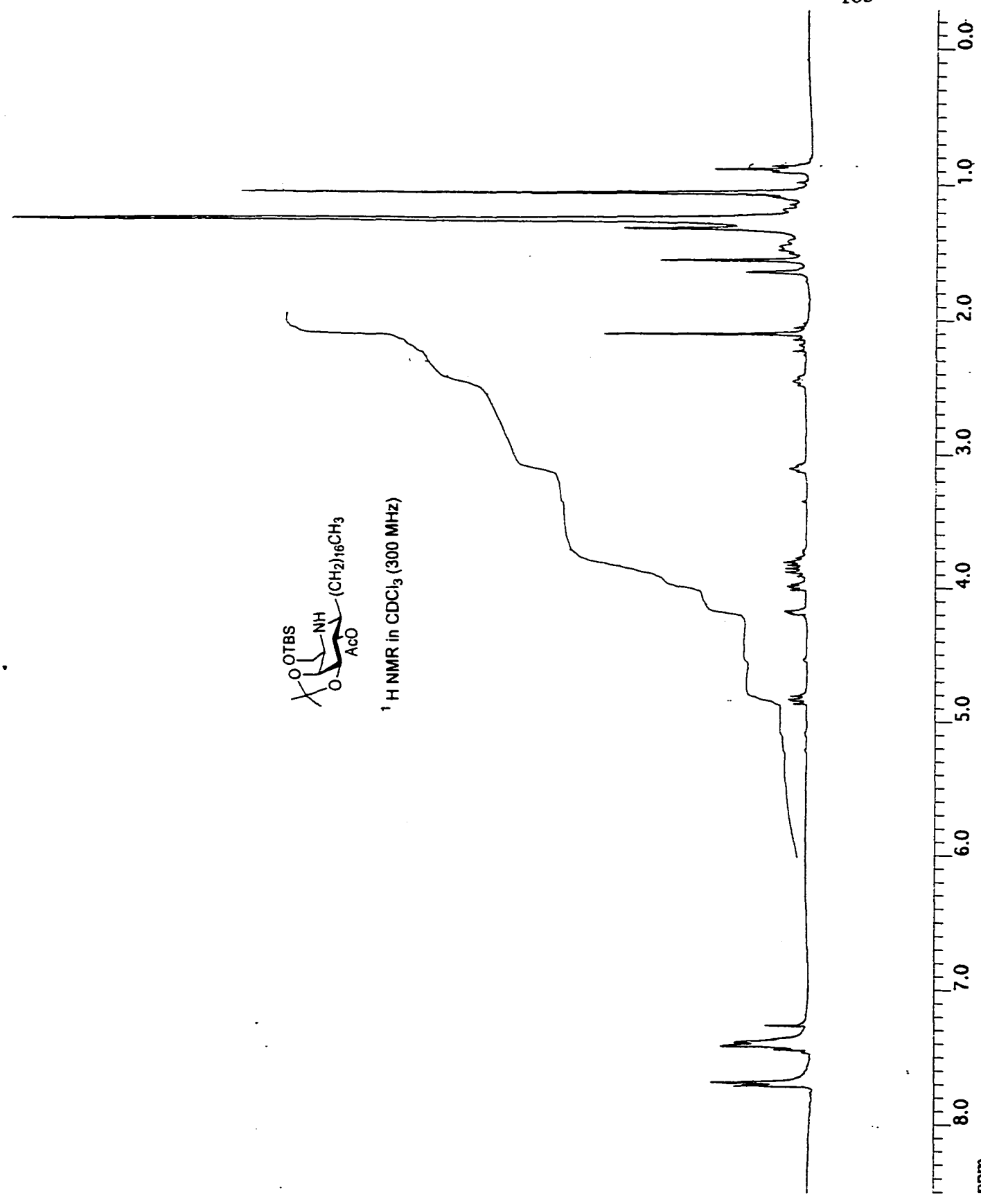


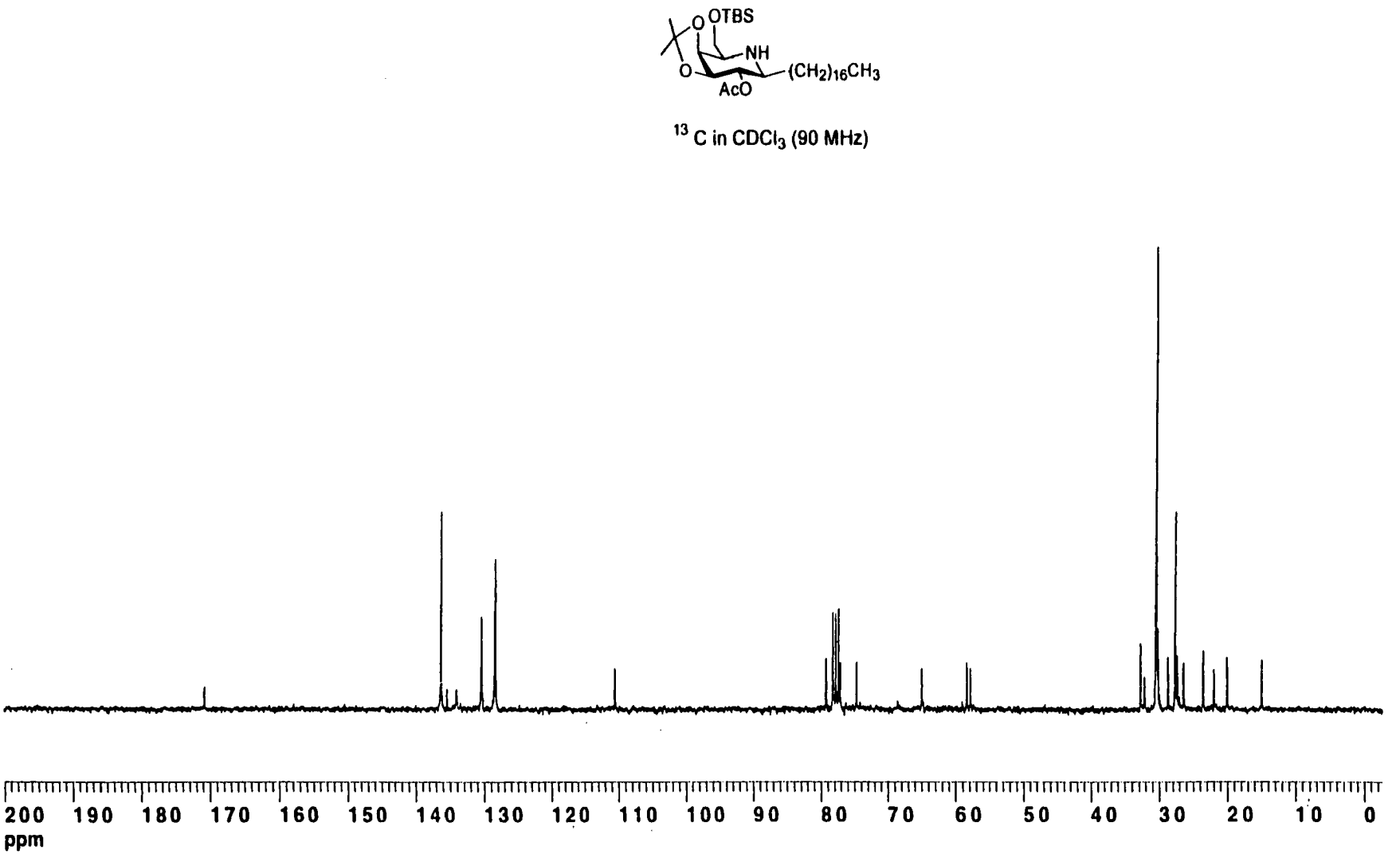


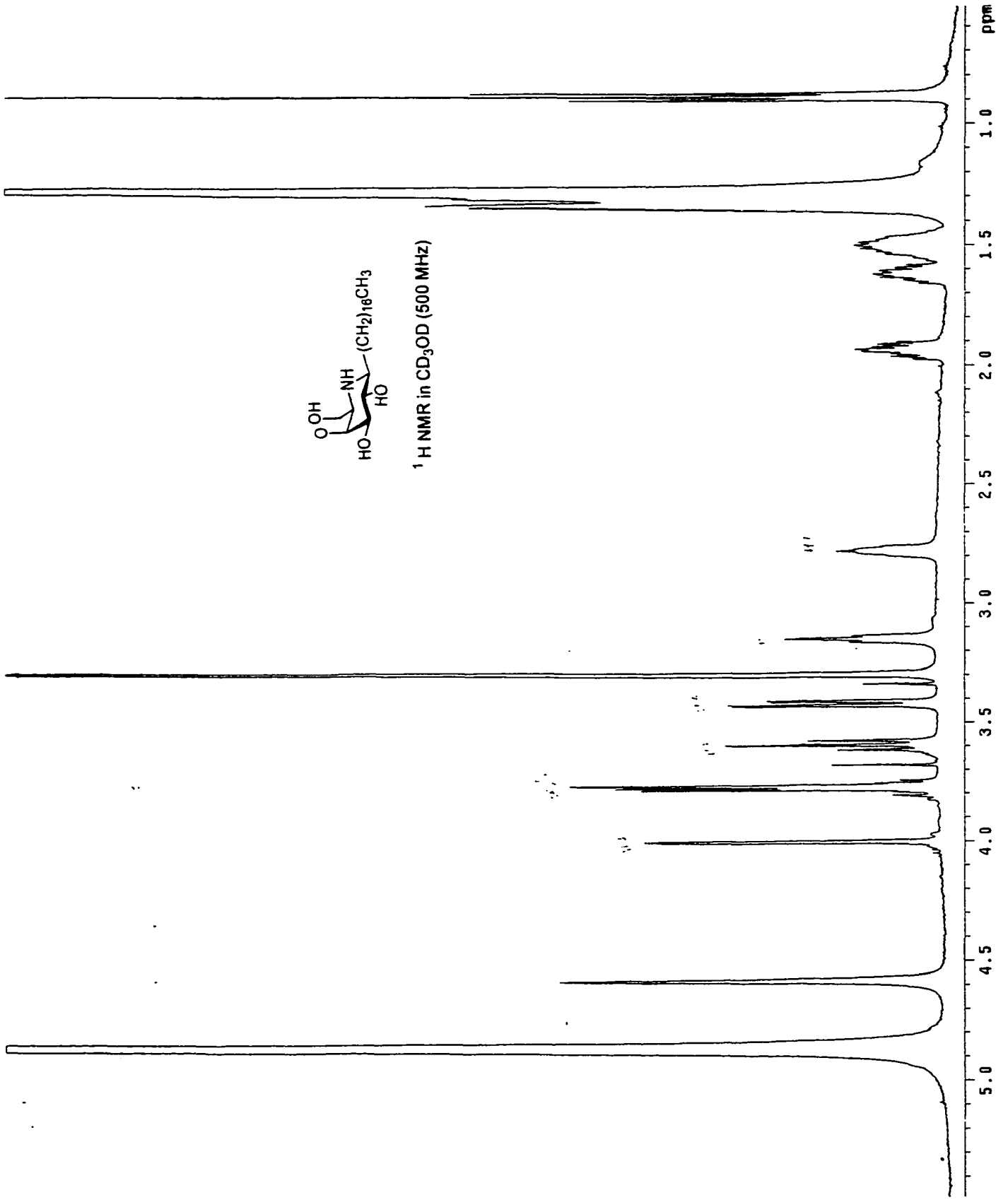


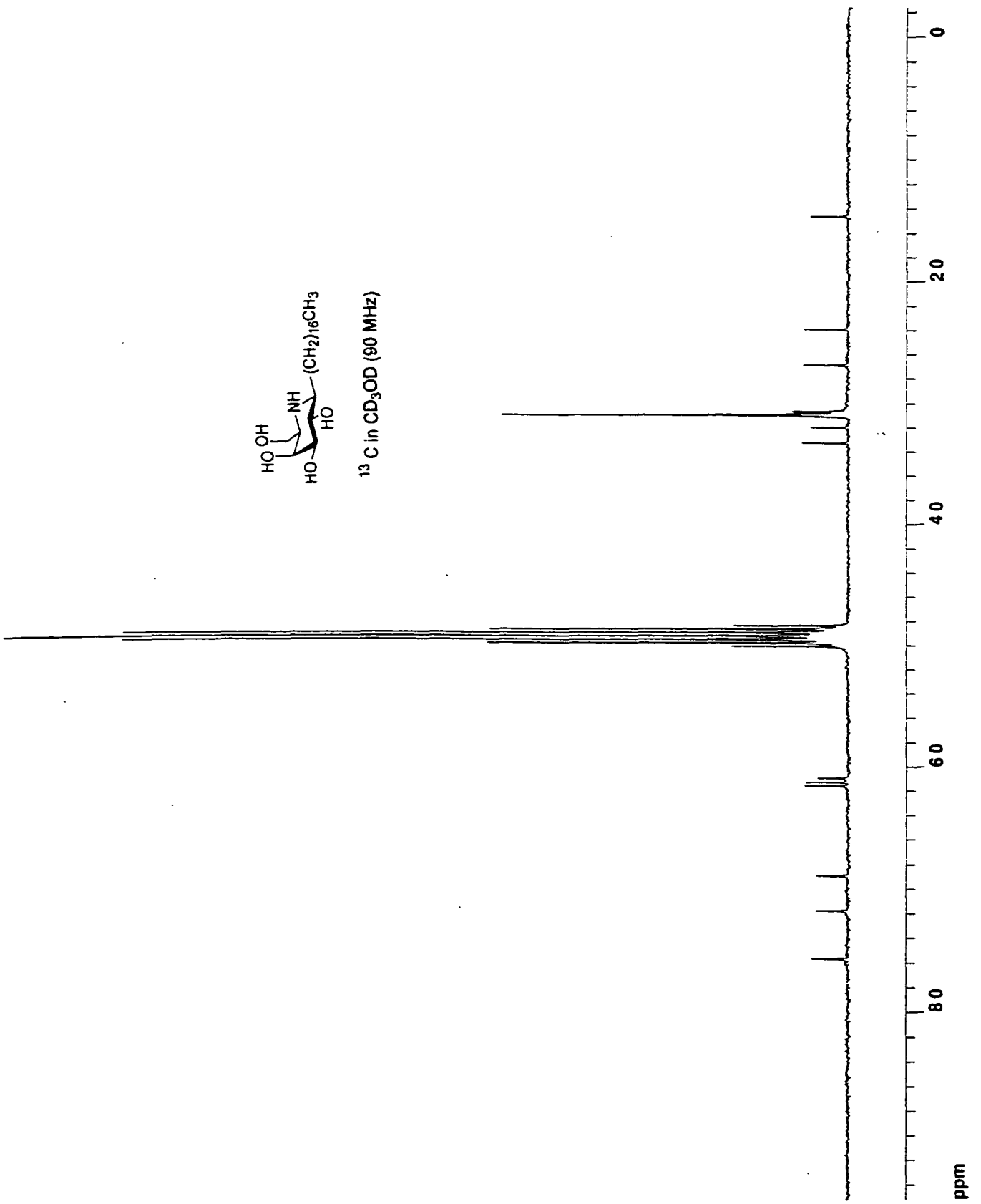


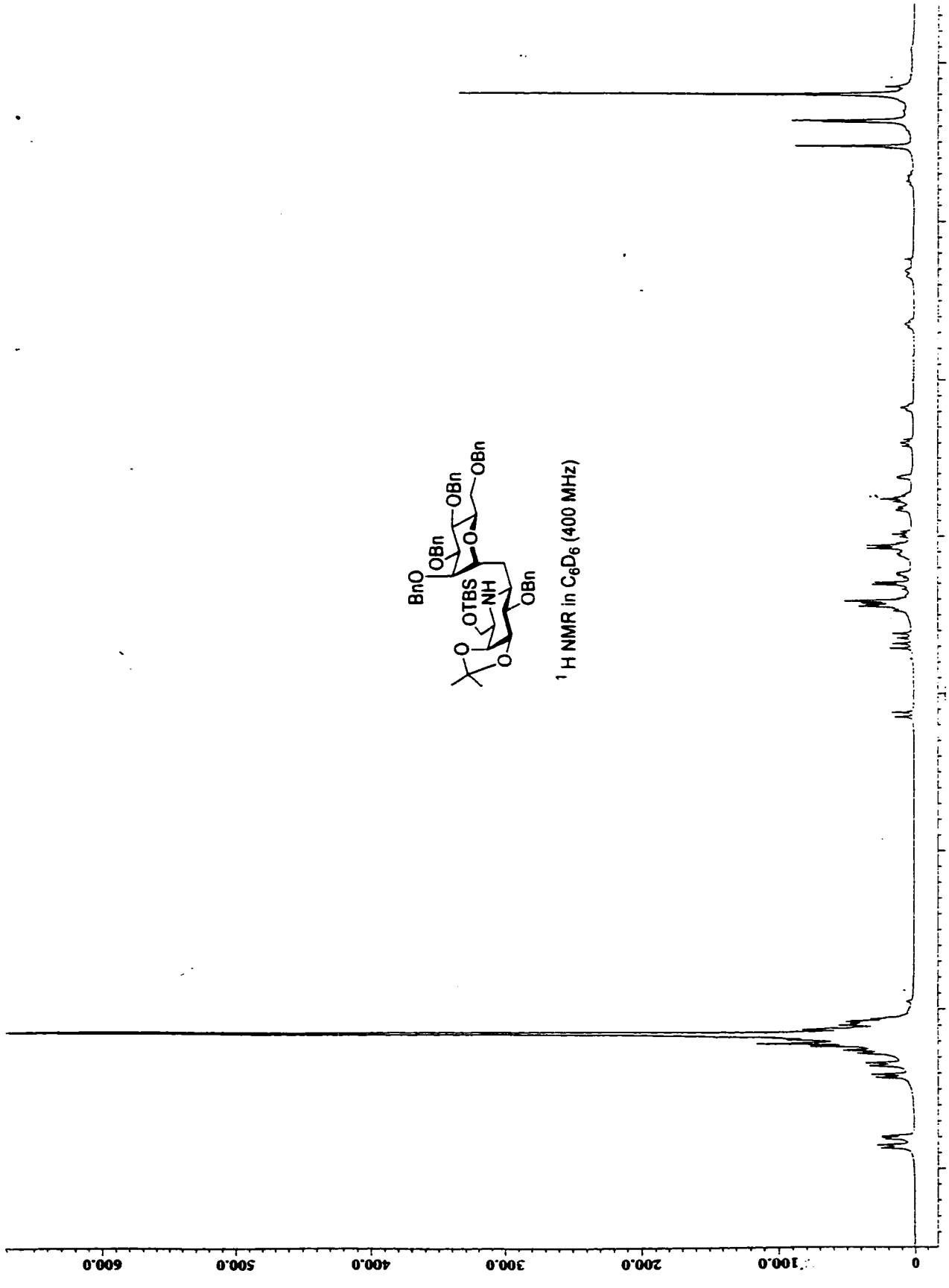


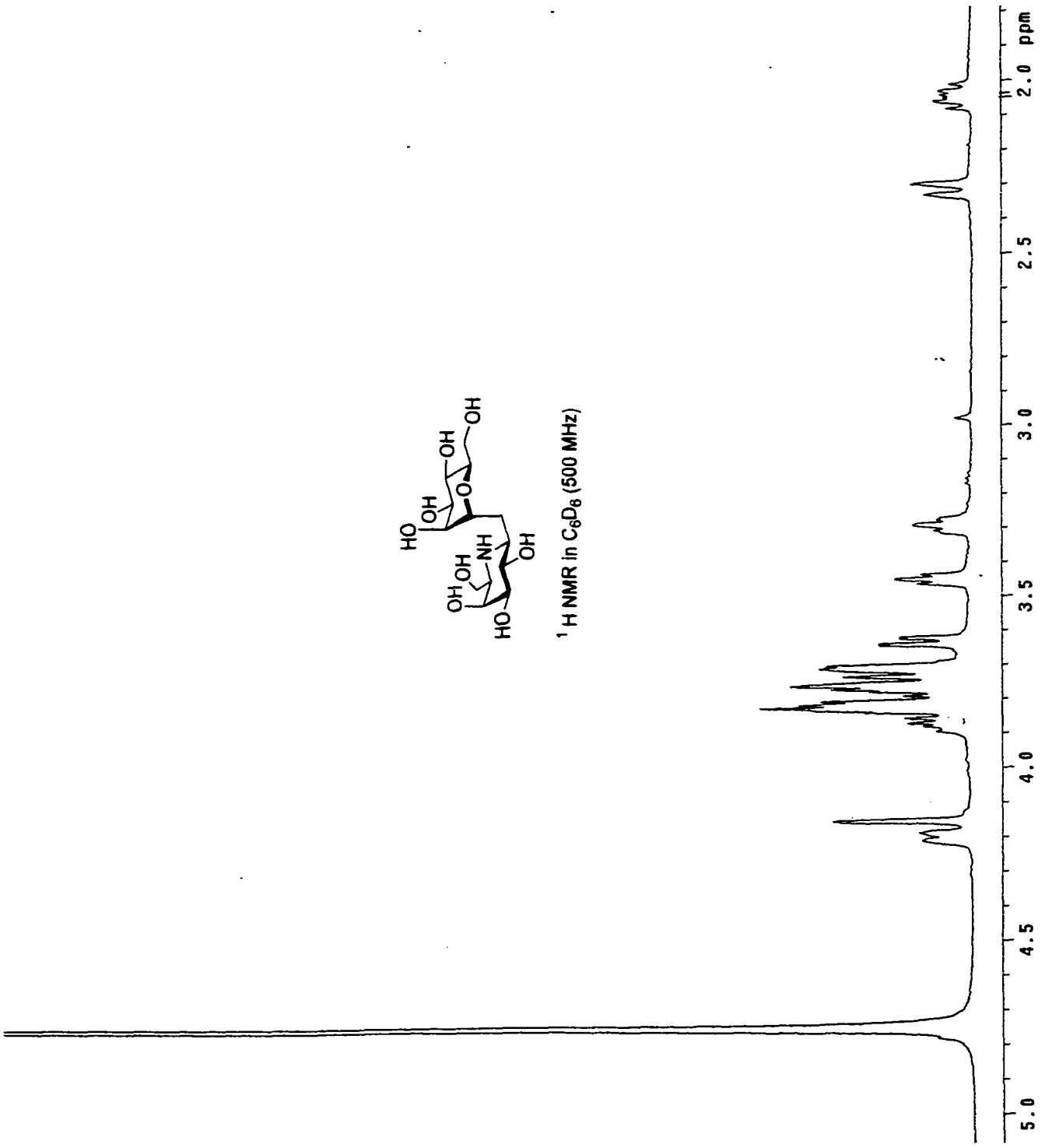


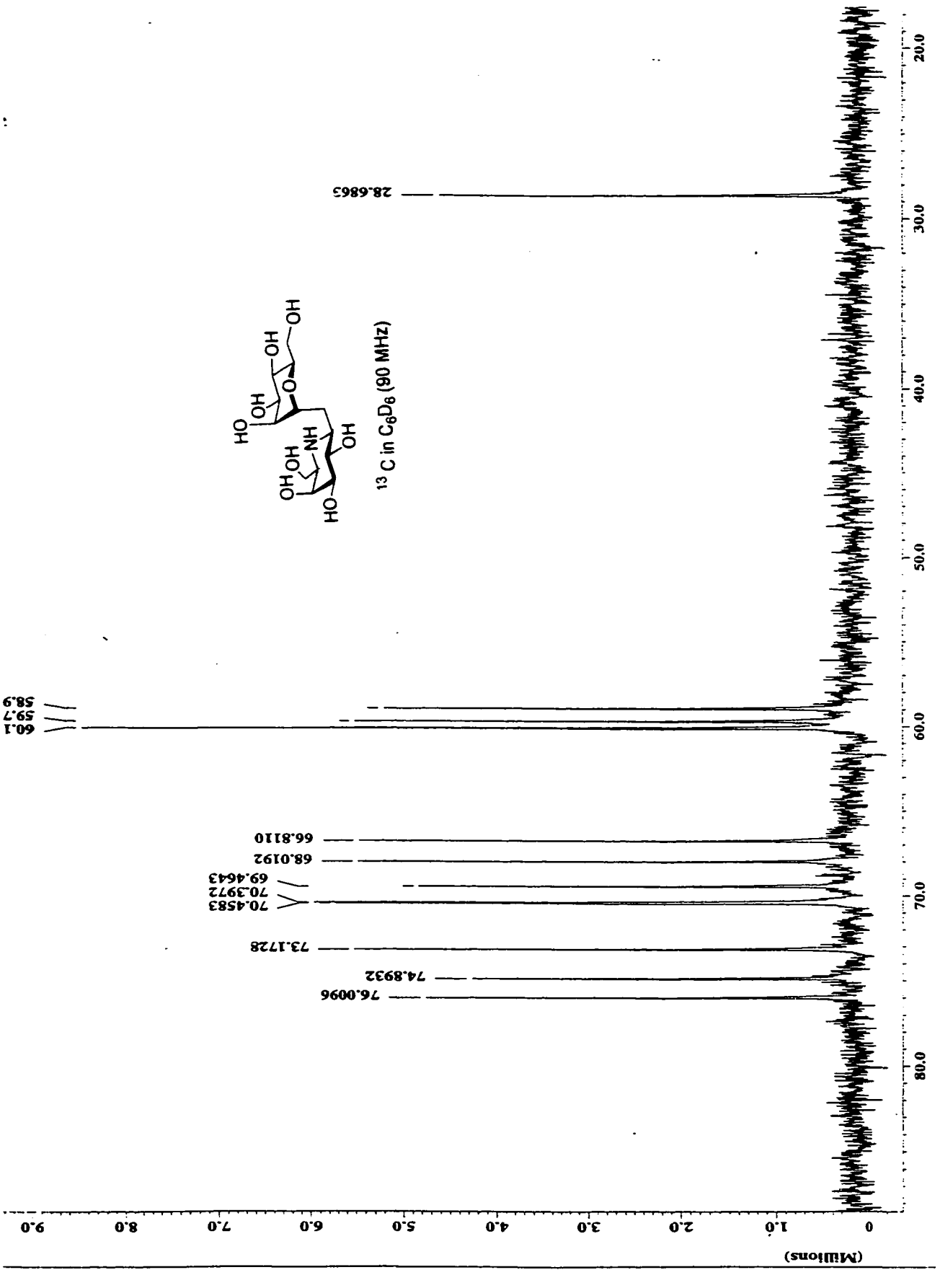


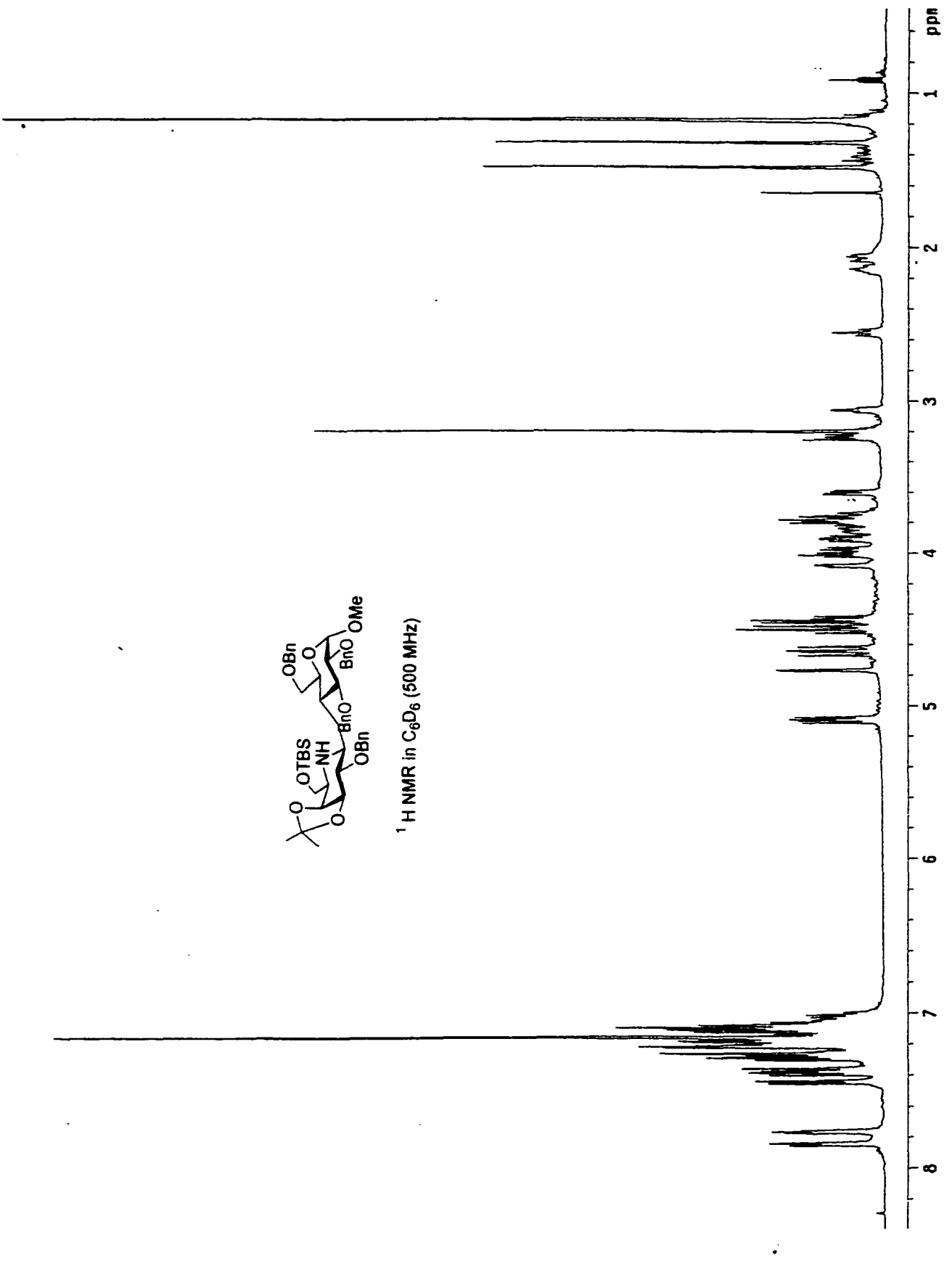


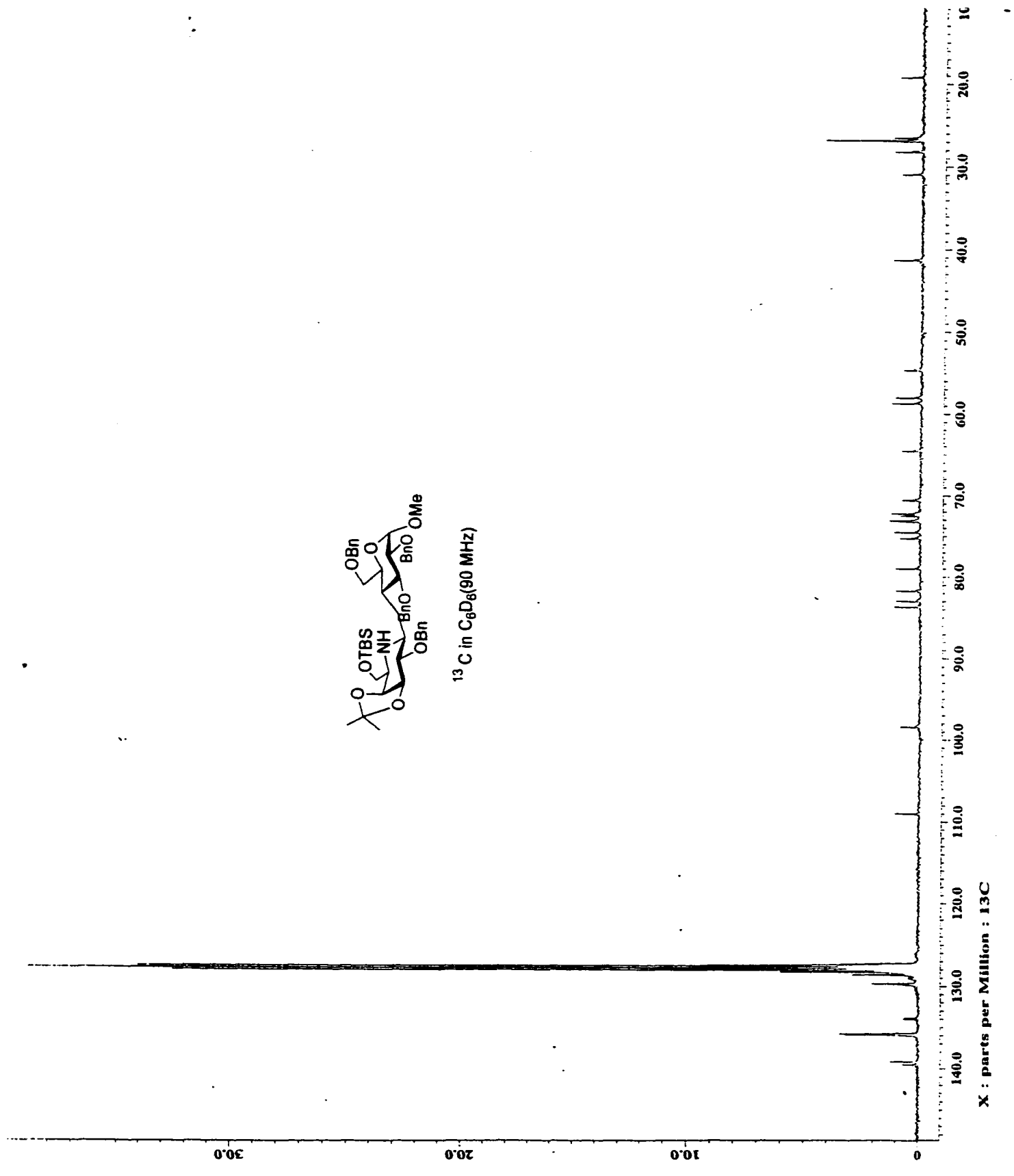


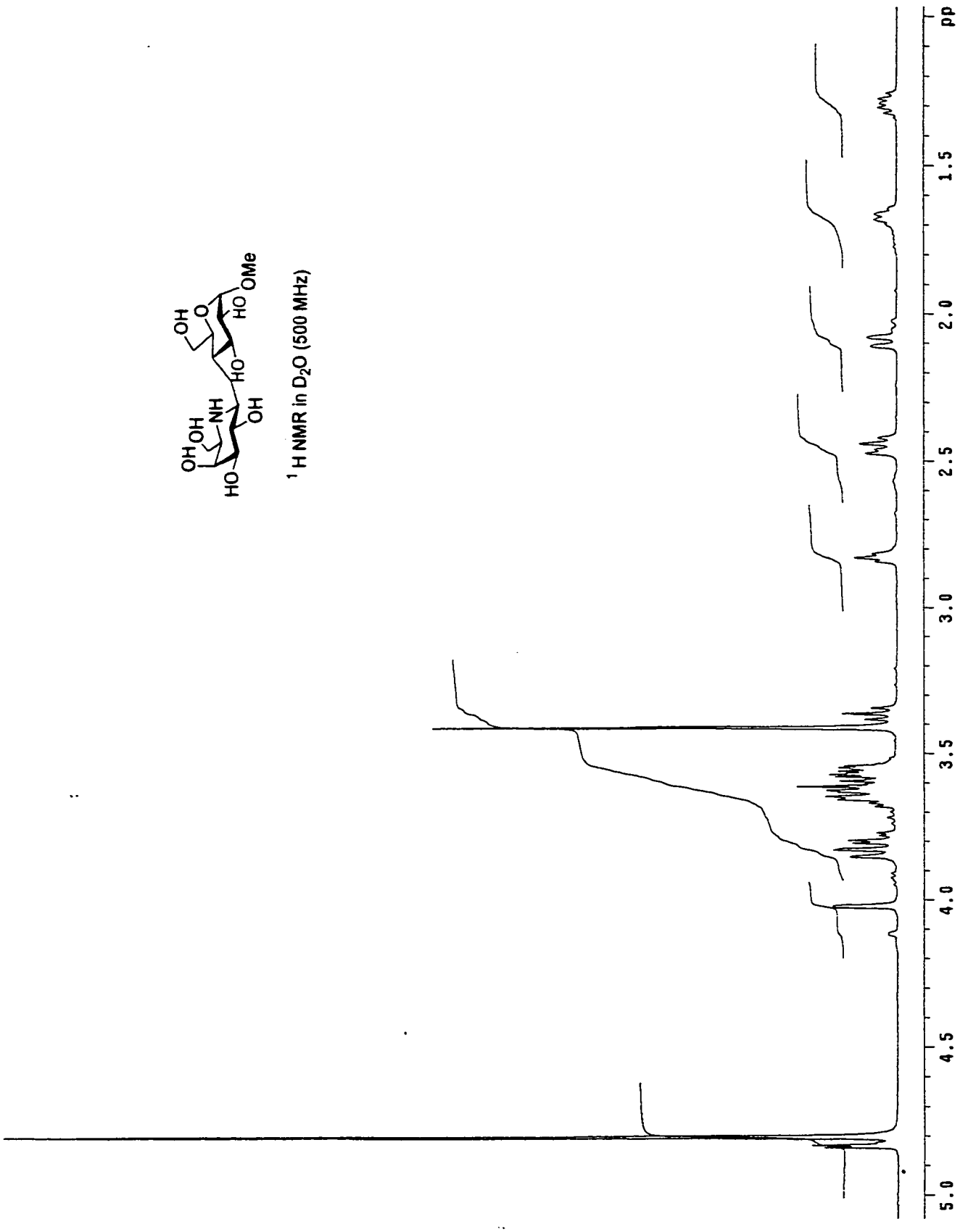


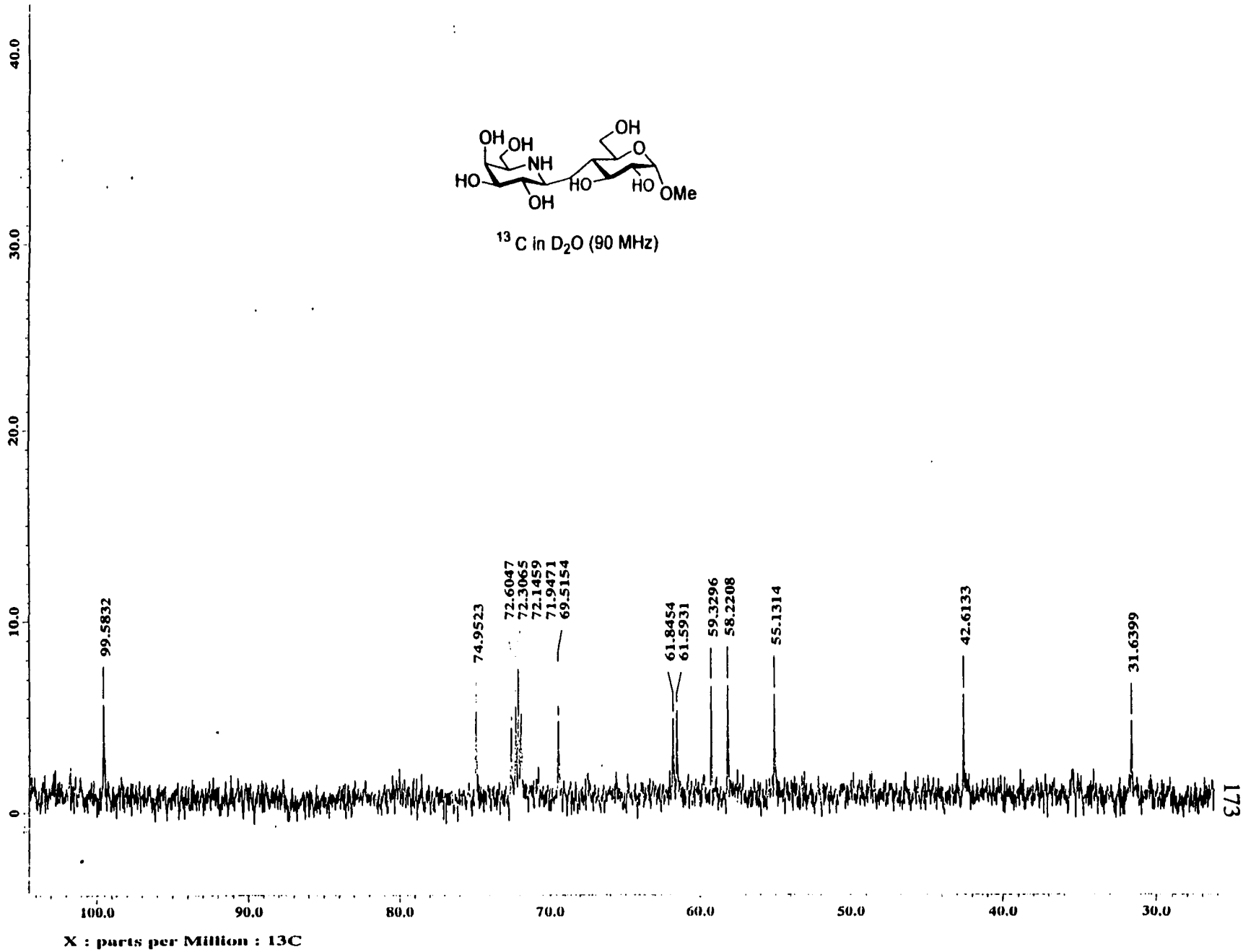


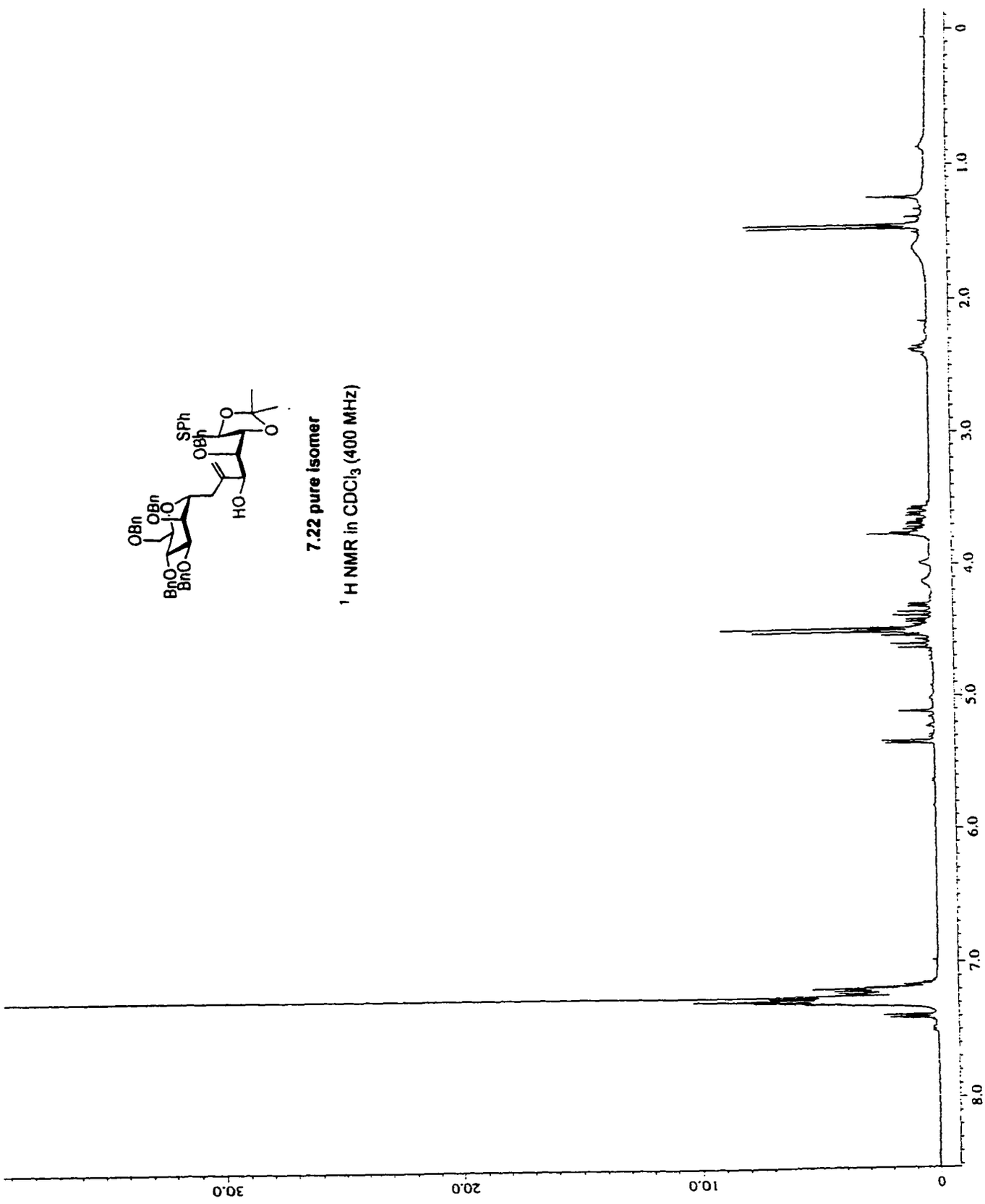


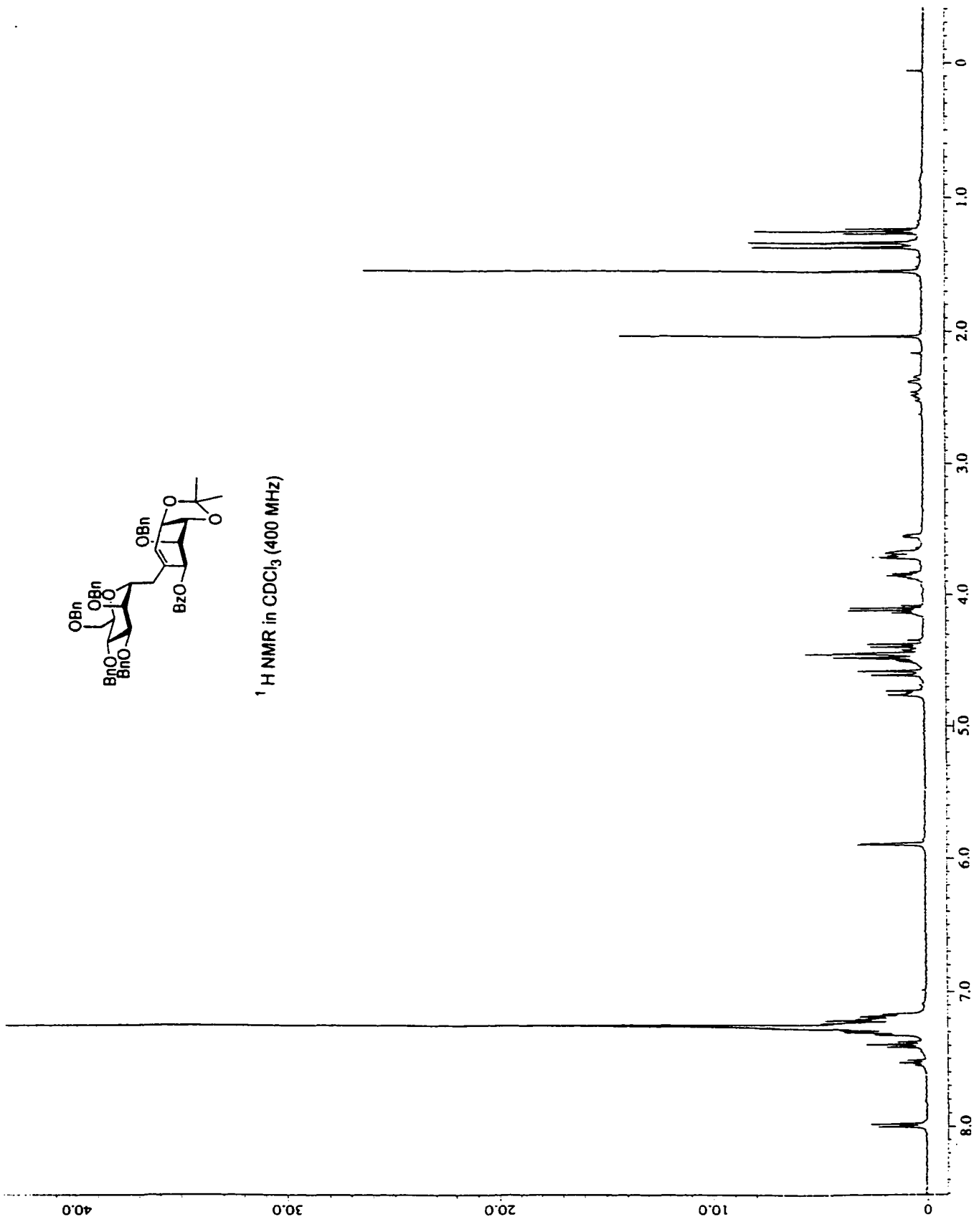


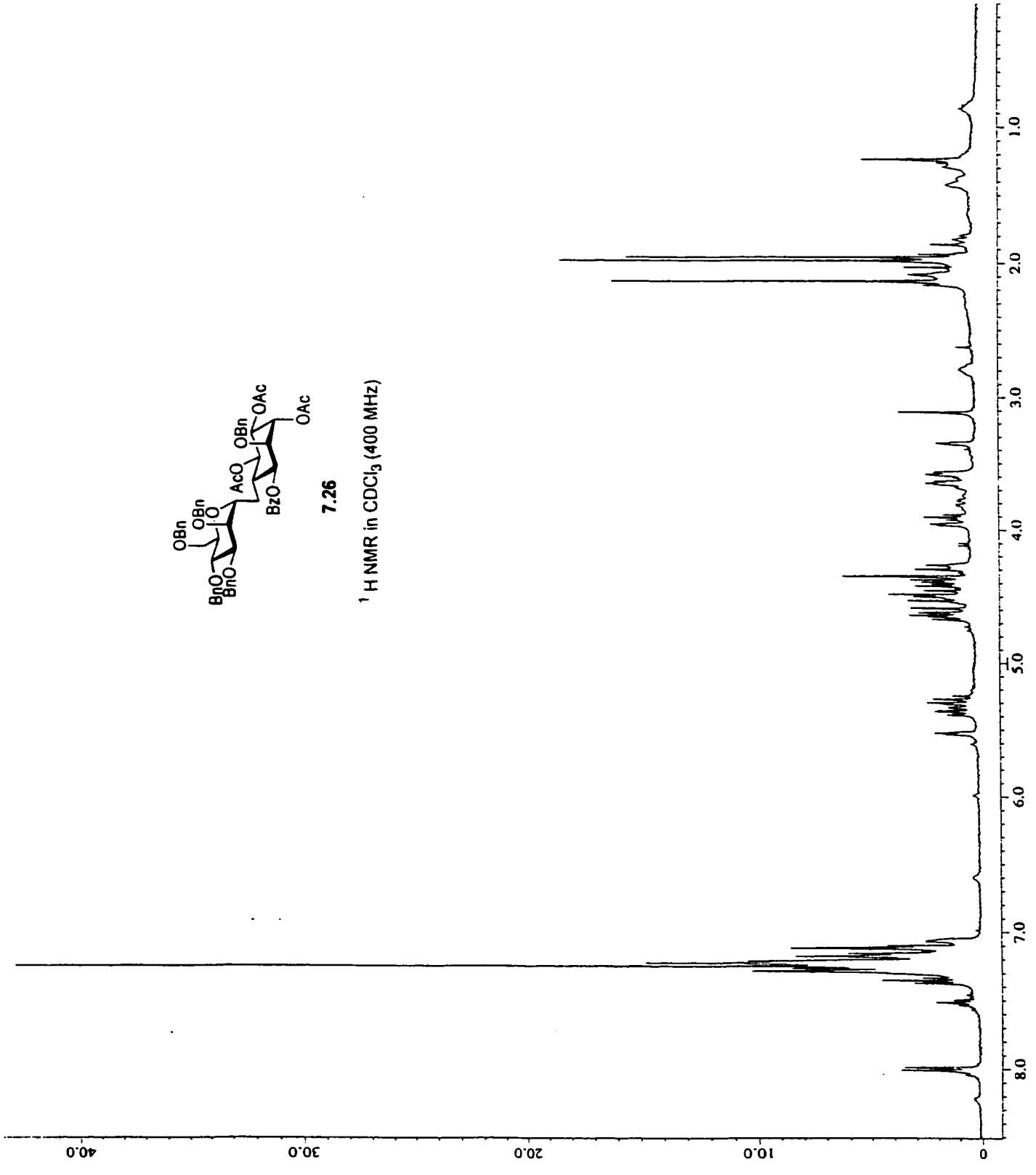












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