

Synthesis of Biologically important C-glycoinositols

by

Sunej Hans

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

2009

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

Prof. David R. Mootoo

1/29/09

Date

Chair of Examining Committee

Prof. Mahesh Lakshman

1/29/09

Date

Executive Officer

Prof. Alexander Greer

Prof. Akira Kawamura

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

ABSTRACT

Synthesis of biologically important glycoinositols

By

Sunej Hans

Mentor: Professor David R. Mootoo

Glycosylinositol subunits comprise important glycoproteins on eukaryotic cell membranes and oligosaccharide components of the cell wall of mycobacteria. Glycosylinositols are also believed to function as secondary messengers in cellular processes, such as the mediation of insulin action. Analogues of glycoinositols in which the ring or glycosidic oxygen of the acetal residue is replaced with a methylene group (C- and carba- glycoside respectively), have attracted interest as mechanistic probes because of their greater hydrolytic stability and different conformational behavior compared with the native *O*-glycosides.

Chapter 1 of this thesis presents an overview of selected biologically important glycoinositols, and of previous synthetic approaches to C- and carba- glycosides. Chapters 2, 3 and 4 describes the synthesis of the *C*-glycosides of 6-*O*- (α -mannosyl)-myo-inositol and 4-*O*- (2-amino-2-deoxy- β -D-galactopyranosyl)-3-*O*-methyl-D-chiro-inositol (also called **INS-2**), and the carba-glycoside of **INS-2**.

The synthetic strategy for these complex C- and carba- glycosides centers on formulation of the “sugar” or “glycone” component from a highly oxygenated cyclic enol ether in which the enolic oxygen is endo- or exo- cyclic, respectively. A key innovative element in these syntheses is an oxocarbenium ion cyclization strategy wherein these enol ethers are produced with complete stereocontrol from highly substituted thioacetal-enol ether precursors. An appealing aspect of this plan is that the cyclization precursors may be accessed in a convergent fashion starting from the esterification of “glycone” and “aglycone” components, thereby allowing for the preparation of a variety of C- or carba- inositols with different sugar and inositol residues.

ACKNOWLEDGMENTS

This thesis arose from many years of research that has been done in Dr. David R. Mootoo's lab. Over all these years, I have worked with a great number of people who made great contribution toward my achievement of the Ph.D degree. I would like to express my deep and sincere gratitude to every one of them.

In the first place I would like to express my deep gratitude to my mentor Dr. David Mootoo for his supervision, advice, and guidance from the very early stage of this research as well as giving me most valuable experience through out the work. He has been very encouraging in all difficult paths of the research.

Many thanks go to my committee members: Dr. Alexander Greer and Dr. Akira Kawamura for their constructive comments on my thesis. I am thankful that they have accepted to be members of the committee.

I gratefully thank Dr. Klaus Grohman for being there all the time when I needed his help.

I wish to express many thanks to Dr. Clifford E. Soll, Dr. Michael Blumenstein and Dr. Matthew Devany for their help with mass and NMR experiment.

I would like to express my special thanks to the chemistry department of the Hunter College and the Graduate Center of CUNY for giving me the opportunity to obtain the Ph.D degree. I am very thankful to Ms. Mirela Settenhofer, Ms. Nala Fernando and Mrs. Diane Adebawale for their encouragement and well wishes.

My very special thanks go to the members of Dr. Mootoo's group: Dr. Govindaraj Kumaran, Dr. Darrin Dabideen, Dr. Xuhong Cheng, Dr. Lei Zhu, Dr. Richard Denton,

Dr. Xiaohua Li, Clayton Mattis, Steawart Bachan, Feng Wang, Rong Wang, and Jialiang Li.

I would like to especially thank Dr. Line Augustin, Dr. Tony Kurissery, and Dr. Fatoumata Camara for their support and help in tough times.

My parents Satnam Hans and Balbir Kaur deserve special mention for their support and prayers. It was their dream that I would get higher education, and they have worked very hard to bring me up to this point. Thanks to my brother Lakhwinder Hans, his wife Surjit Kaur, and my younger brother Bharat Hans. I also would to thank my parents in law: Harmail Chohan and Manjit Kaur for their well wishes and prayers.

Finally, I own my loving thanks to my husband Sandeep Singh, my sons Sahejdeep Chohan and Sahibdeep Chohan. Without their encouragement and understanding it would have been impossible to finish my Ph.D work.

TABLE OF CONTENTS

Title	Page
Acknowledgments	
Table of Content	
List of Symbols and Abbreviations	
List of Tables	
List of Figures	
Chapter 1: Biological activity and previous syntheses	1
1.1 Introduction	2
1.2 Background-biology	
1.2.1 6-D-mannopyranosyl-D- <i>myo</i> -inositol	2
1.2.2 4-C-(2-amino-2-deoxy- β -D-galactopyranosyl)-3-O-methyl-D- <i>Chiro</i> -inositol (4.15)	7
1.3 Background-Synthesis	12
1.3.1 C-Glycosides	12
1.3.2 Carbasugars	15
1.4 Our Synthetic Approach	19
1.5 Summary	20
Chapter 2: Synthesis of C-branched <i>Myo</i> -inositol	21
2.1 Retrosynthesis	22
2.2 Results and discussion	24
2.2.1 Model study: Synthesis of <i>D-chiro</i> inositol and <i>Neo</i> -inositol	24

2.2.2	Stereochemical analysis of cyclization products 2.23 and 2.26	28
2.2.3	Synthesis of <i>myo</i> -inositol	30
2.2.4	Stereochemical analysis of cyclization products	33
2.3	Computational studies on conformations of cyclization products	36
2.4	Discussion	40
2.5	Alternative synthesis for a C-brached <i>myo</i> -Inositol	43
2.6	Summary	44
2.7	Experimental Section	45
Chapter 3:	Synthesis of the C-pseudodisaccharide of 6- α -D- <i>mannopyranosyl</i> -D- <i>myo</i> -Inositol	68
3.1	Introduction	69
3.2	Synthesis of the C-pseudodisaccharide of 6- α -D- <i>mannopyranosyl</i> -D- <i>myo</i> -inositol	69
3.2.1	First route: cyclization of the inositol segment	69
3.2.2	Second route: Coupling of pre-formed <i>mannose</i> and inositol segments	71
3.2.3	Third route: Cyclization of the <i>mannose</i> segment from a hydroxy alkene precursor	73
3.3	Formation of the <i>mannose</i> segment via an oxocarbenium ion cyclization	76
3.4	NMR Analysis of 3.46 and 3.47	83
3.5	Summary	84
3.6	Experimental	85

Chapter 4	Synthesis of <i>D-chiro</i> -Inositol-Galactosamine mimetics	101
4.1	Background	102
4.2	Results and discussion	102
4.2.1	Synthesis of C-INS-2	102
4.2.2	Synthesis of the aglycone component	104
4.2.3	Coupling of the glycone and aglycone components	105
4.2.4	Introduction of the 2-amino substituent	106
4.3	Synthesis of Carba-INS-2	109
4.3.1	Coupling of the glycone and aglycone components	110
4.3.2	Introduction of the 2-amino group	111
4.4	Summary	113
4.5	Experimental	114
Appendix		133
References		199

LIST OF SYMBOLS and ABBREVIATIONS

Ac	Acetyl
Ac ₂ O	acetic anhydride
BF ₃ .Et ₂ O	boron trifluoride etherate
Bn	benzyl
Brine	saturated aqueous sodium chloride solution
brs	broad singlet
Bu	butyl
⁰ C	degree Celsius
calcd	calculated
¹³ C NMR	carbon-13 nuclear magnetic resonance spectrometry
CSA	camphorsulfonic acid
δ	chemical shift in ppm
d	doublet
DIB	iodobenzene diacetate
DCC	dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
ee	enantiomeric excess
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol

eq	equivalent
FCC	flash column chromatography
g	gram
h	hour
^1H NMR	proton nuclear magnetic resonance spectrometry
Hz	hertz
IDCP	iodonium dicollidine perchlorate
J	coupling constant
m	multiplet
M	molar
Me	methyl
MeOH	methanol
MeOTf	methyl triflate
mg	milligram
min	minute
mL	milliliter
mmol	millimole
MS	molecular sieves
NOE	Nuclear Overhauser effect
Ph	phenyl
ppm	parts per million
PPTS	para-pyridinium toluenesulfonate
q	quartet

rt	room temperature
s	singlet
t	triplet
TBDPS	tert-butyl diphenyl silyl
TIA	1-thio-1,2-isopropylidene acetal
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	toluenesulfonyl
Vs	versus

LIST OF FIGURES

Figure 1.1	Examples of biological important glycoinositol analogues	3
Figure 1.2	Model of mycobacterium cell wall	5
Figure 1.3	Schematic overview of insulin's signaling in a target cell	8
Figure 1.4	INS-2	
Figure 1.5	INS-2 and a model phosphopeptide substrate docked into the β -sandwich of PP2C	10
Figure 1.6	INS2 hydrogen bonding to Asp146, Asp163, Asp243, and Lys165 in PP2C	11
Figure 1.7	Synthetic strategies of C-pseudo disaccharides	12
Figure 1.8		16
Figure 2.1	Spectroscopic analysis of <i>D-chiro</i> -inositol and <i>neo</i> -inositol	29
Figure 2.2		37
Figure 2.3		38
Figure 2.4		39
Figure 2.5		40
Figure 2.6	Transition state models of oxocarbenium ion cyclizations	42
Figure 3.1	O- and C- Psueduodisaccharide as PIM Mimetics	69
Figure 3.2	NMR analysis of α -C-linked altroside and α -C-linked <i>mannoside</i>	83
Figure 4.1		108

LIST OF TABLES

Table 2.1	37
Table 2.2	38
Table 2.3	39
Table 2.4	40

Chapter 1 Introduction

Biological activity and previous syntheses

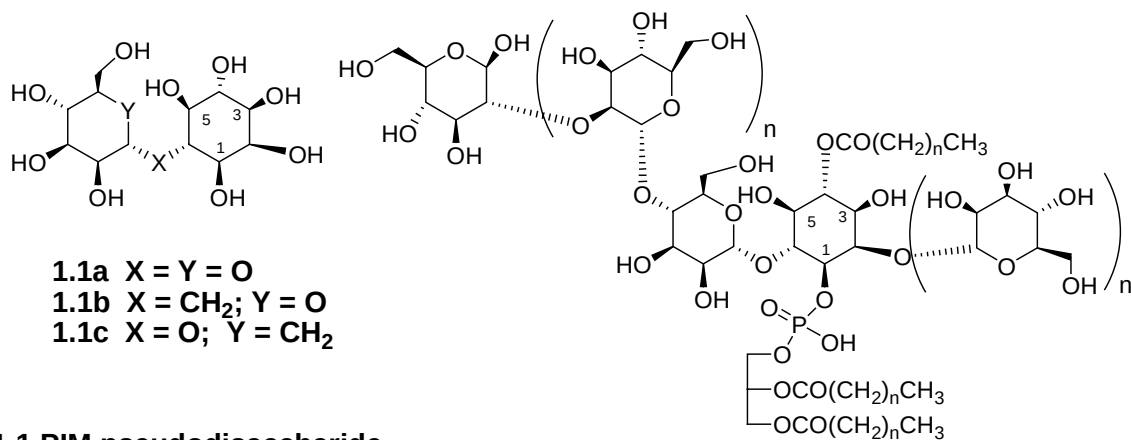
1.1 Introduction

Carbohydrates have become the focus of considerable research because of their involvement in various pathological processes.¹ C-glycosides and carba-glycosides are carbohydrate analogues in which the exocyclic and endocyclic acetal oxygen respectively is replaced by a methylene (e.g. **1.1b**, **1.1c** **Figure 1.1**). These unnatural compounds are interesting mechanistic probes because they are more stable than O-glycosides and have different conformational properties with respect to the intersaccharide bonds.² Thus the hydrolytic stability of the pseudo glycoside bond in carba and C-glycosides may be useful in probing whether biological activity is related to, or affected by glycoside cleavage. In addition their constitutional and conformational differences may lead to changes in their interaction with biological receptors compared to O-glycosides.³ In this thesis, the synthesis of C- and carba-glycosides of biologically important glycoinositols will be presented. Specifically, the synthesis of **1.1b**, the C-glycoside of 6- α -D-mannopyranosyl-D-myoinositol **1.1a**, and **1.5b** and **1.5c**, the C- and carba-glycoside respectively, of 2-amino-2-deoxy- β -D-galactopyranosyl-D-chiro inositol **1.5a**, will be described (**Figure 1.1**).

1.2 Background-biology

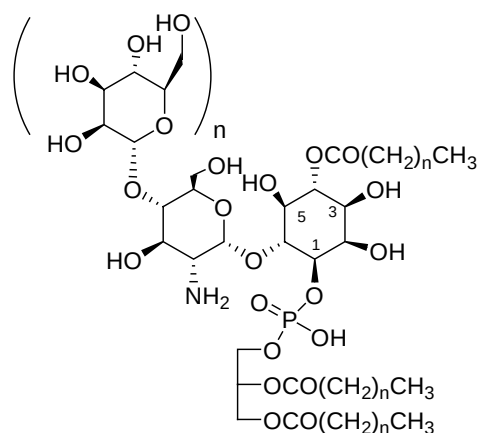
1.2.1 6- α -D-mannopyranosyl-D-myoinositol

Clinical management of human acquired immune deficiency syndrome (AIDS) is greatly hindered because of drug resistance to established antimycobacterial agents.⁴ The problem has been correlated with increase in the incidence of tuberculosis.

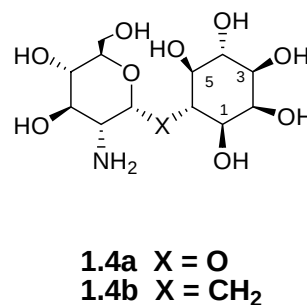


1.1 PIM pseudodisaccharide analogue

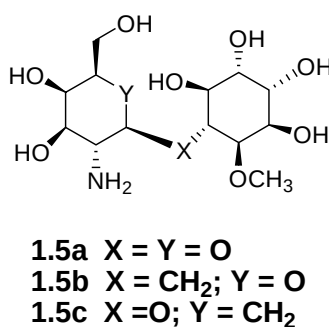
1.2 PIM from mycobacteria^{8,10}



1.3 GPI from fungi and protozoan parasites^{2,10}



1.4 Glu-myo pseudodisaccharide analogues



1.5. Gal-*Chiro* pseudo-disaccharide¹⁶ analogues

Figure 1.1 Examples of biologically important glycoinositol analogues

Despite the urgent need for new chemotherapeutic agents only a small number of promising leads have been discovered in the recent years. These include the tuberculostatic agents Upjohn oxazolidinone (U-100480) and bicyclic nitroimidazole (CGT 17341).

Many of the known antimycobacterials act on the mycobacterial cell wall either by inhibiting the RNA's synthesis or later steps in the biosynthesis of the cell wall.⁵ Accordingly, structural information on the mycobacterial cell wall has been valuable in the design of new antibacterial agents.⁶ The mycobacterium cell wall contains numerous components that are necessary for survival in the host (**Figure 1.2**). The lipoarabinomannan (LAM) subunit is composed of an outermost arabinomannan segment linked to a PIM (phosphatidylinositol *mannoside*) region (cf **1.2**, **Figure 1.1**). LAM has been implicated in the suppression of the host immune response thereby contributing to pathogenesis and many of the clinical manifestations of tuberculosis.⁷ The glycoinositol residue that is found at the reducing end of LAM is believed to function as a membrane anchor through the phospholipid and fatty acid residues on the inositol ring.

In view of the unique and complex architecture of the triacyl the pseudotrisaccharide PIM₂ **1.7** and its critical function in the bacterial survival, identification of inhibitors of PIM₂ biosynthesis could lead to both potent and highly specific antimycobacterial agents (**Scheme 1.1**). The α -mannose transferase that catalyzes the synthesis of **1.7** from GDP-mannose and triacyl-PIM₁ **1.6** has recently been isolated, and this presents an opportunity for rational drug design (**Scheme 1.1**).⁸ For example, *manno*- α -C-glycosides analogues of **1.7** that contain substitutes for the phospholipid and *mannose* residues at O1 and O2 of the inositol ring, could act as inhibitors of this step (cf **1.8**, **Scheme 1.2**).

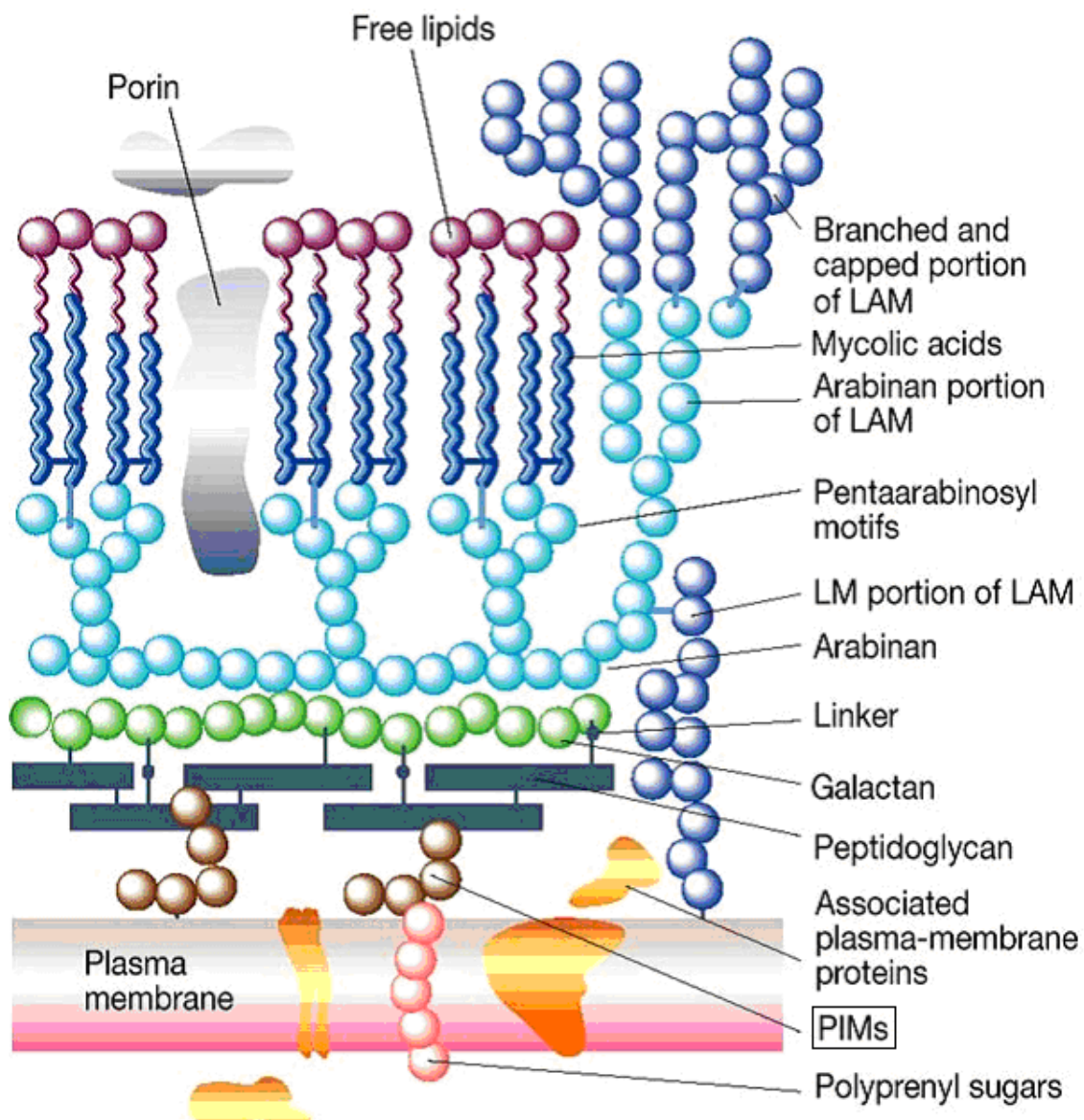
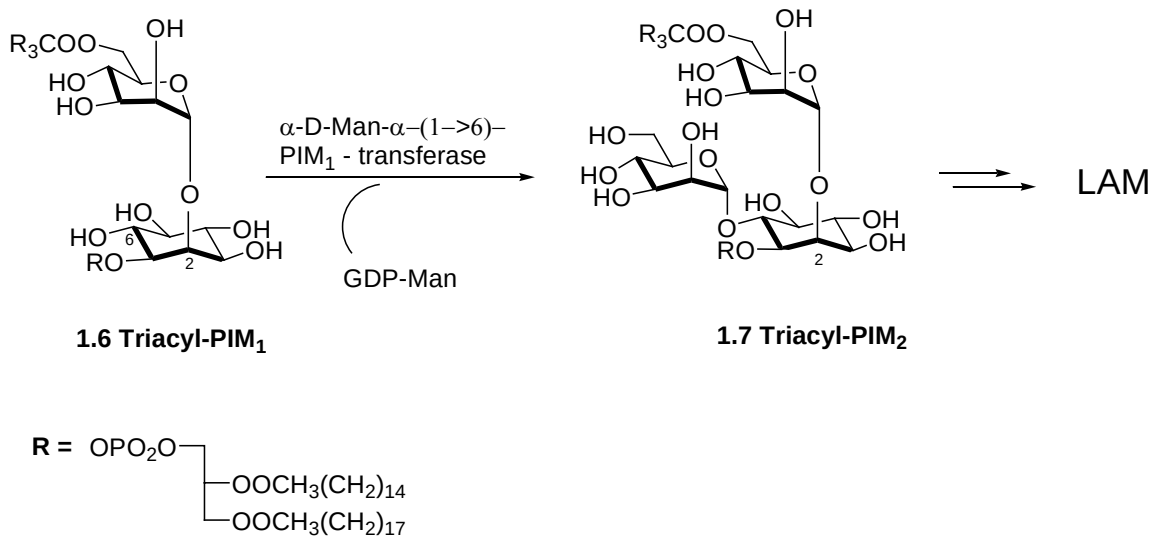
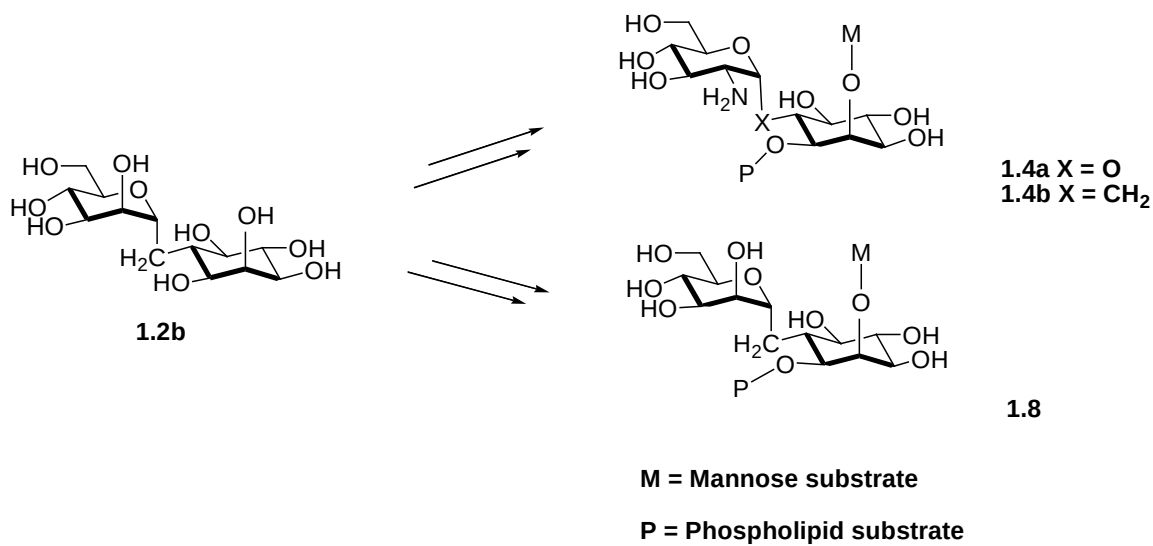


Figure 1.2⁹ Model of mycobacterium cell wall

The related pseudodisaccharide 6- α -glucosamine-myoinositol (i.e. **1.4a**, **Figure 1.1**) occurs at the reducing terminus of the glycosyl phosphatidyl inositol (GPI)¹⁰ anchor that covalently links certain proteins to the outer leaflet of eukaryotic cell membranes.



Scheme 1.1 Biosynthesis of lipoarabinomannan (LAM) subunit in mycobacteria



Scheme 1.2 *Manno- α -C*-pseudodisaccharide 1.2b as a precursor to biologically interesting GPI mimetics

This pseudodisaccharide is attached at O4 of the glucosamine residue to a trimannan chain. The *myo*-inositol segment is connected at O1 to a phosphatidyl-diacylglycerol residue. The O2 position bears a fatty acid ester. The hydrophobic nature of the *myo*-inositol residue is believed to facilitate lipid clustering and translocation in the bilayer surface, and the specificity of aggregation is likely controlled by lipid substitution and the conformation of this subunit.¹¹ The formation of such lipid microdomains has been associated with signaling mechanisms.¹² Parasites such as *Trypanosoma brucei*, have a similar GPI anchoring system that provides a protective protein coating. This GPI undergoes antigenic variation and constitutes a defense mechanism against the host immune response.^{2,10} Against this background the C-glycoside of **1.4a** (i.e. **1.4b**) is another interesting C-glycoside target (**Scheme 1.2**). The target C-pseudodisaccharide **1.2b** is a potential precursor to both **1.4b** and **1.8**.

1.2.2 4-C-(2-amino-2-deoxy- β -D-galactopyranosyl)-3-O-methyl-D-Chiro-inositol (**4.15**)

Insulin transduction is controlled by a tyrosine phosphorylation cascade mechanism (**Figure 1.3**).¹³ It has been suggested that a secondary messenger mechanism operates together with, or independently of the tyrosine phosphorylation pathway. This secondary messenger pathway has been the subject of much debate. Inositol phosphate glycans (IPG's) have been suggested as secondary messengers.¹⁴ It has been proposed that these small, ionic oligosaccharides are released from the external surface of the insulin sensitive cells in response to binding of insulin to its receptor. This hypothesis is

supported by the finding that IPG's induce similar effects to those regulated by insulin, both in the presence and the absence of insulin.

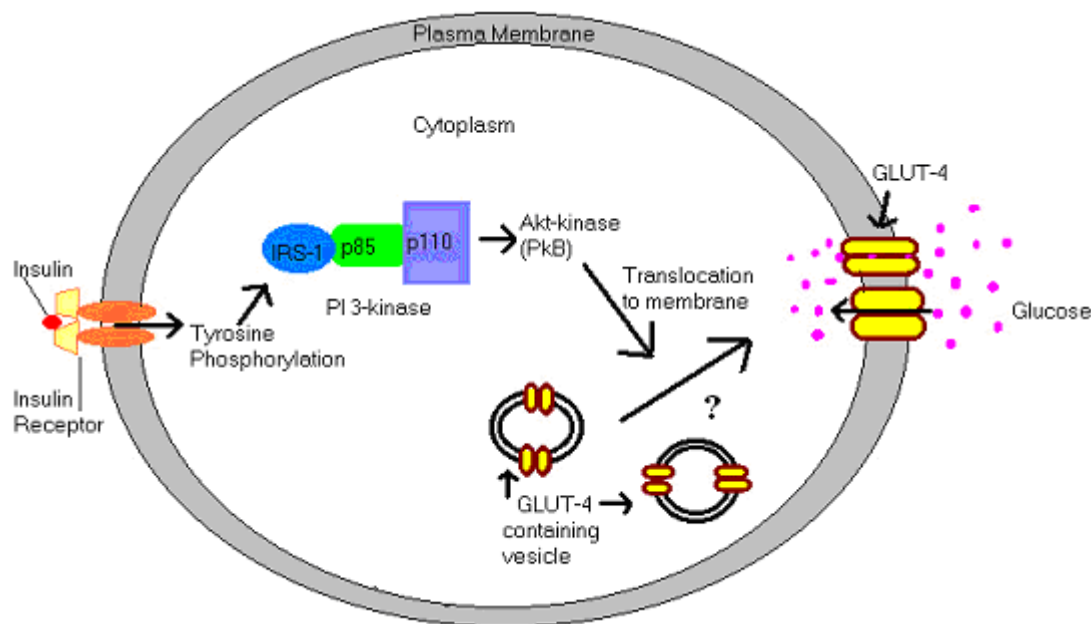


Figure 1.3¹⁵. Schematic overview of insulin's signaling in a target cell

The mechanism of action by which IPG's mimic the action of insulin is not clear. Alvarez had demonstrated that natural IPG's are transported to the cytoplasm.¹⁶ Once these IPG's are in the cytosol, they may start regulating the metabolic processes of the cells. In support of this hypothesis IPG's have been shown to modulate the activities of several insulin-responsive enzymes, including c-AMP phosphodiesterase, pyruvate dehydrogenase phosphatase, protein phosphatase 2C, c-AMP-dependent protein kinase, and adenylate cyclase in cell-free assays.^{17,18} Two types of inositol glycan species have been identified. Type-A, which contains *myo*-inositol and glucosamine, inhibits cAMP-

kinase. Type-P, contains *D-chiro*-inositol and galactosamine, stimulates PDH phosphatase, PP2C, and indirectly PP1¹⁹.

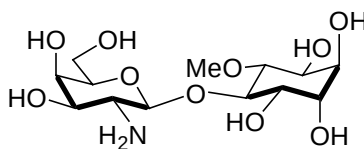


Figure 1.4 INS-2

Larner and co-workers have isolated the type P pseudo-disaccharide INS-2 (**Figure 1.4**) from rat liver.²⁰ INS2 elicited dose-dependent reduction of hyperglycemia in streptozotocin (STZ) diabetic rats at low micromolar concentrations. INS-2 activated PDH phosphatase in vitro and enhanced insulin-stimulated incorporation of glucose into glycogen in hepatoma H4 cells. Molecular modeling was used to locate an energetically favorable site for binding of INS2 to PP2C.²⁰ The residues proposed to be interacting with INS2 are in three surface loops that connect $\beta 8$ and $\alpha 3$ (top left, containing Asp 163 and Lys 165) distal to the catalytic site, $\beta 6$ and $\beta 7$ (center, containing Asp 146) bottom of the *allosteric* pocket, and $\beta 10$ and $\alpha 5$ (right, containing Asp 243) proximal to the catalytic site (**Figure 1.5**). Residue Asp 163 interacts with pinitol portion of INS-2 by hydrogen bonding with the hydroxyl groups on C1' and C2' (**Figure 1.6**). Asp 146 interacts with the hydroxyl on C6' and Asp 243 interacts with C5' on the pinitol portion and NH₂ on the galactosamine. Asp 163 interacts with vicinal cis hydroxyls on the pinitol component of the INS2.

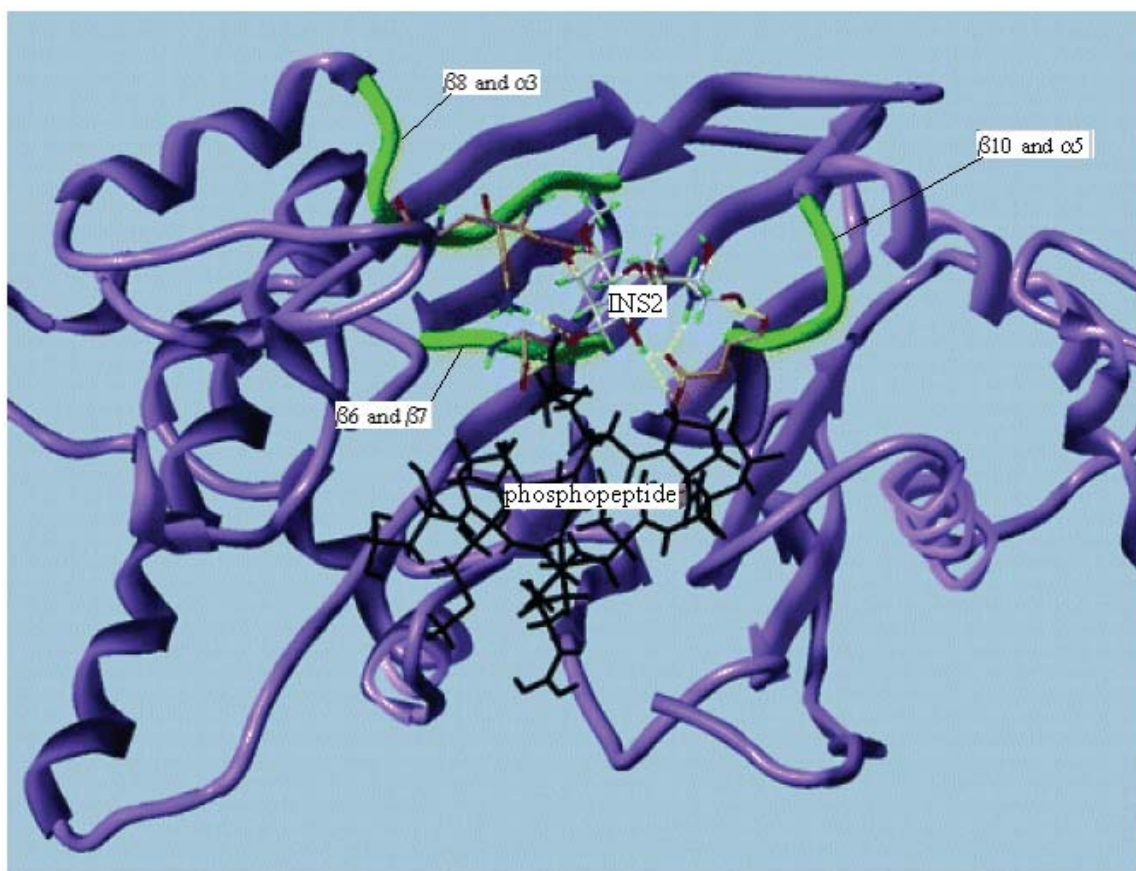


Figure 1.5²⁰ INS-2 and a model phosphopeptide substrate docked into the β -sandwich of PP2C

These workers proposed that *allosteric* activation arises from a conformational shift in the β 10 and α 5 loop due to an interaction between Asp 243 and INS-2. It was also suggested that the INS-2-Asp243 interaction prevents Asp 243 from interfering with the portion of the phosphopeptide substrate in the catalytic center. Thus, both a conformational change and a better substrate alignment are believed to contribute to higher PPC activity in the presence of INS-2.

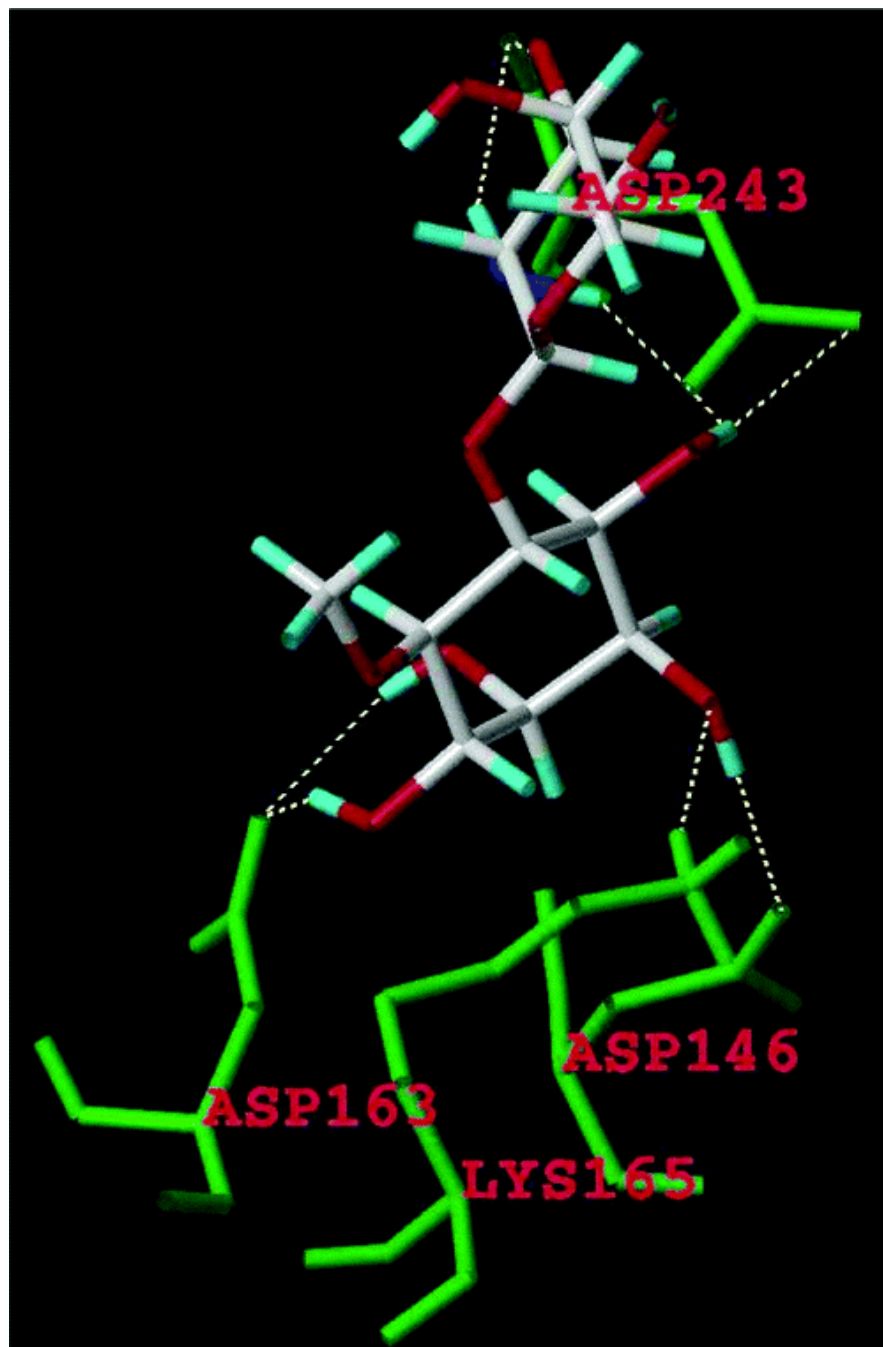


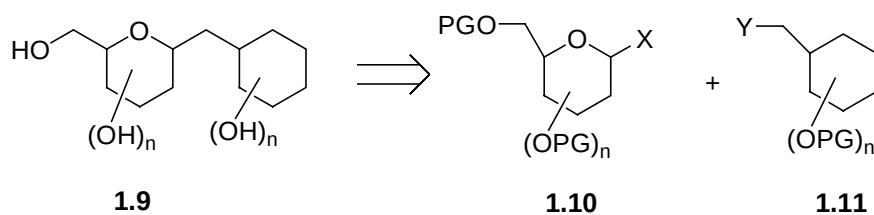
Figure 1.6²⁰ INS2 hydrogen bonding to Asp146, Asp163, Asp243, and Lys165 in PP2C

Our synthetic target *C*-INS-2 may be more active INS-2 because it has different conformational properties. The hydrolytic stability of *C*-INS-2 over INS-2 could also contribute to higher activity.

1.3 Background-Synthesis

1.3.1 C-Glycosides

1. Coupling of preformed sugar and inositol segments



2. Cyclization of monocyclic sugar or inositol precursors

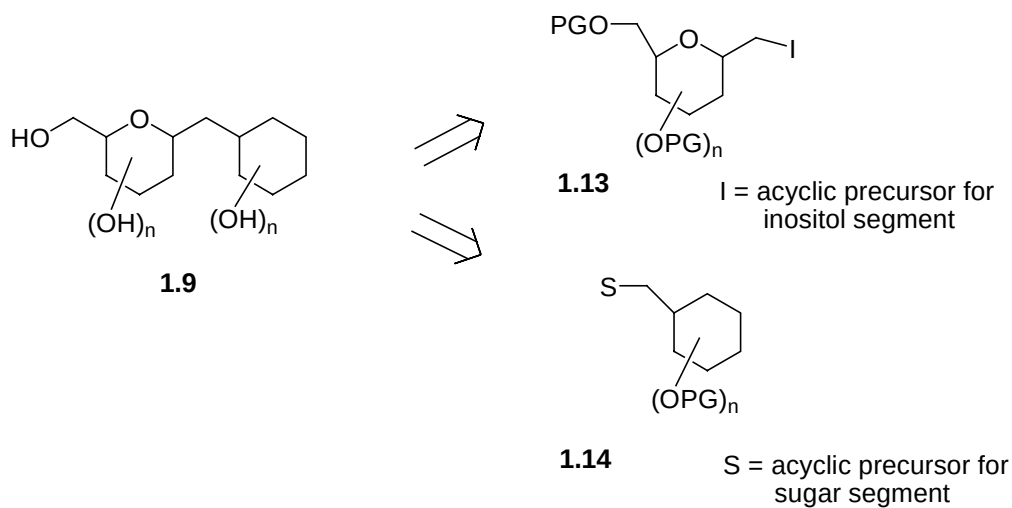


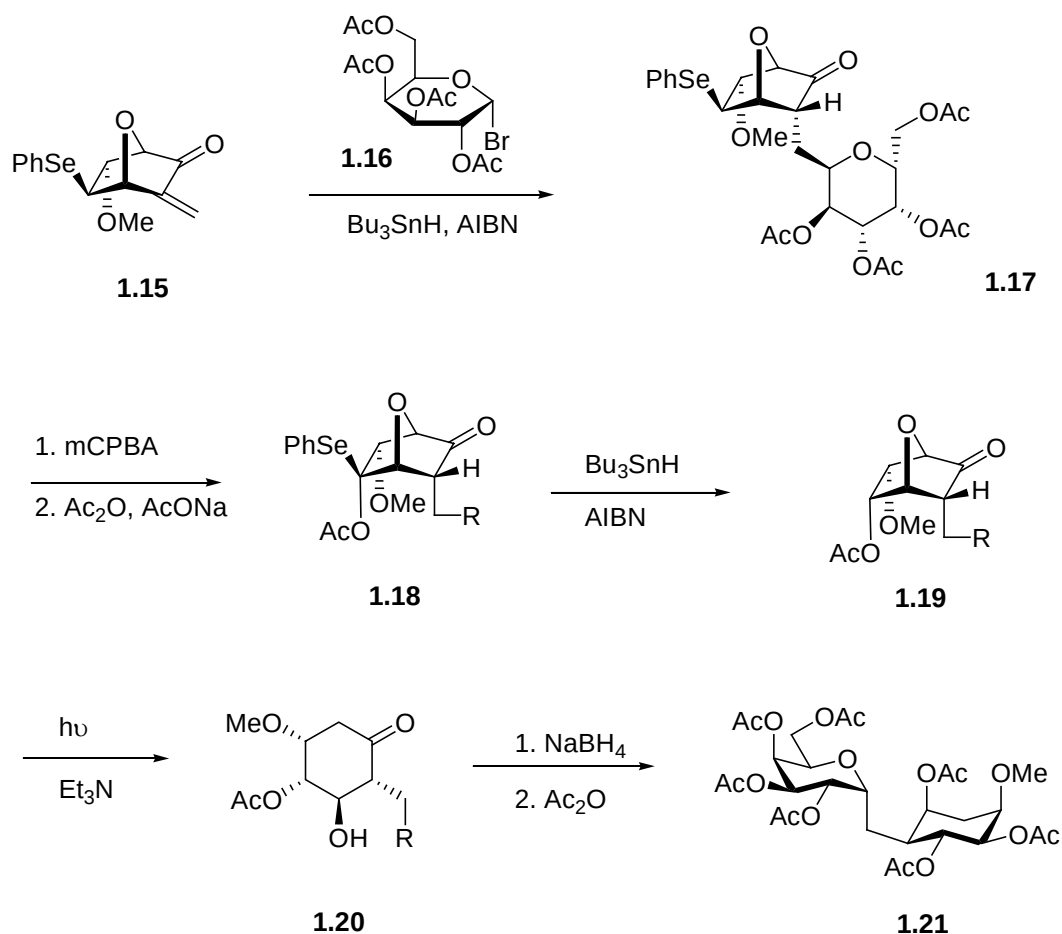
Figure 1.7 Synthetic strategies of *C*-pseudo disaccharides

C-glycoinositol pseudo-disaccharides may be prepared by coupling of preformed sugar **1.10** and inositol segments **1.11**, or through the cyclization of monocyclic sugar **1.13** or inositol precursors **1.14** (**Figure 1.7**). These strategies are well established for C-disaccharides,²¹ but have not been widely used for C-pseudodisaccharides, presumably because of the novelty of these analogs. There are syntheses of C-branched cyclitols,²² which are based on the modification of naturally occurring cyclitols, the de novo formation of the cyclitol framework through cyclization of acyclic precursors,²³ or cycloadditions²⁴ strategies, which could be modified to the synthesis of C-pseudodisaccharides. The majority of C-disaccharide syntheses utilize the first approach and center on the coupling reactions of glycosyl electrophiles, nucleophiles and radicals.^{25,26,27,28}

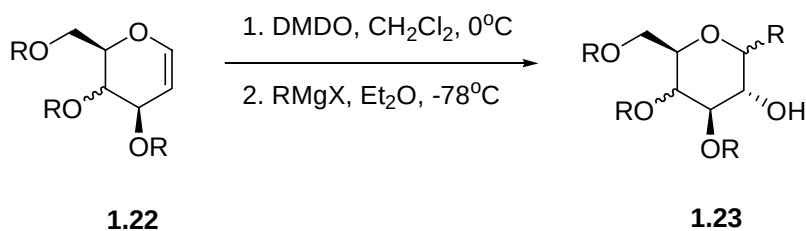
The Vogel group has reported one of the few syntheses of a complex C-glycoinositol pseudo disaccharide (**Scheme 1.3**)²⁹. This synthesis used the modular-type C-glycoside strategy on a glycosyl radical. Treatment of radical precursor **1.16** and enone **1.15** with Bu₃SnH and AIBN afforded **1.17**. Oxidation of selenide, followed by seleno-Pummerer rearrangement led to formation of **1.18** (82%). Deselenation to give **1.19** and irradiation of **1.19** in isopropanol in the presence of Et₃N led to a mixture from which **1.20** was isolated in 28% yield, together with 67% of unreacted **1.19**. Reduction of ketone **1.20** followed by esterification provided **1.21** (46%).

The Vazquez's group has developed a modular-type approach in which carbon nucleophiles were added to 1,2-anhydrosugars (**Scheme 1.4**).³⁰ C-glycoside derivatives were prepared in three steps: (i) O-alkylation of D-glucal or D-glactal, (ii) epoxidation using dimethyldioxirane in CH₂Cl₂,^{31,32} and (iii) epoxide opening with

Grignard reagents or diorganocuprates.³³ By using an inositol derivative as the nucleophile this strategy could be used for the synthesis of C-glycoinositols.

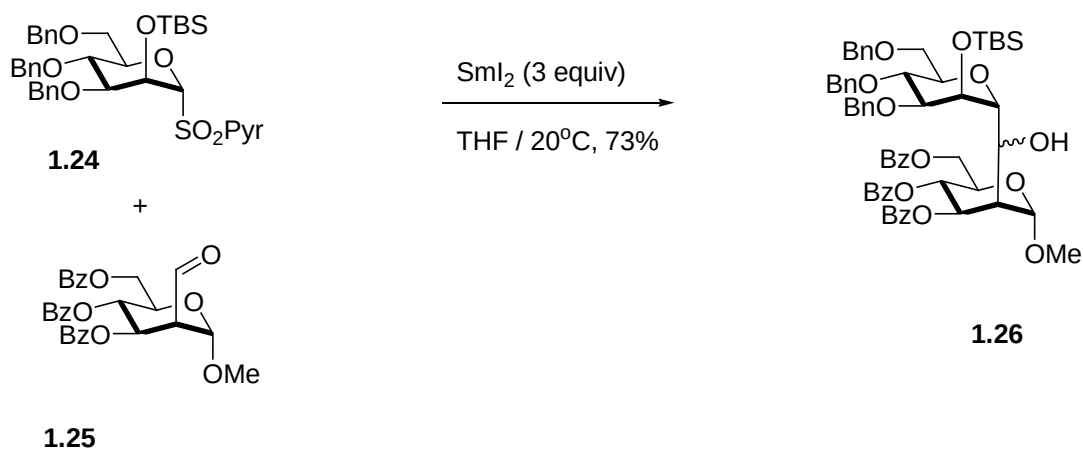


Scheme 1.3



Scheme 1.4: Synthesis of C-gluco- and C-galactopyranoside

Jean-Marie Beau reported a C-glycoside synthesis that is based on the umpolung of the anomeric center (**Scheme 1.5**).³⁴ This reductive samariation of anomeric 2-pyridyl sulfones in the presence of carbonyl compounds provides a versatile approach to C-glycosyl compounds. This synthetic approach could be also used for C-glycoinositols wherein an inositol derivative is the aldehyde component.

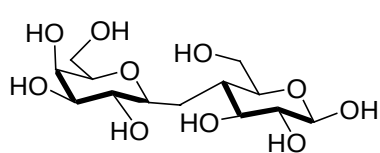


Scheme 1.5

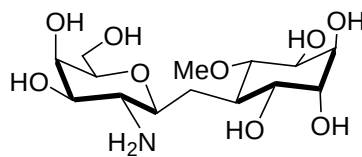
1.3.2 Carbasugars

Carbasugars are glycoside in which the ring oxygen is replaced with a methylene. Figure 1.8 illustrates compares the structure of C- and carba-disaccharide **1.27** and **1.28** with glycoinositol analogues **1.5b** and **1.5c**, which may be regarded as C- and carba-pseudodisaccharides. Carbasugars have similar potential biological applications as C-glycosides. Several approaches have been used for the synthesis of carbasugars, such as transformation of natural sugars, electrophilic cyclizations³⁵, nucleophilic cyclizations³⁶, radical cyclizations³⁷ and Diels-Alder reactions³⁸. As for C-glycosides, these synthetic

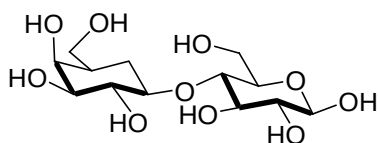
strategies could be modified for the synthesis of carba-pseudodisaccharides like **1.5c** (Figure 1.8).



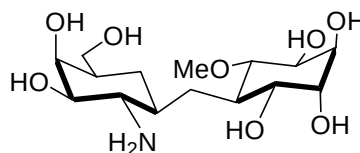
1.27 C-disaccharide



**1.5b C-pseudodisaccharide
(C-glycoinositol)**



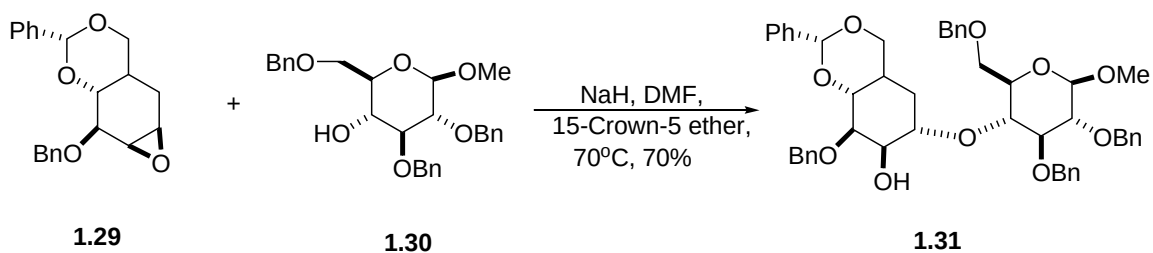
1.28 carba-disaccharide



1.5c carba-pseudodisaccharide

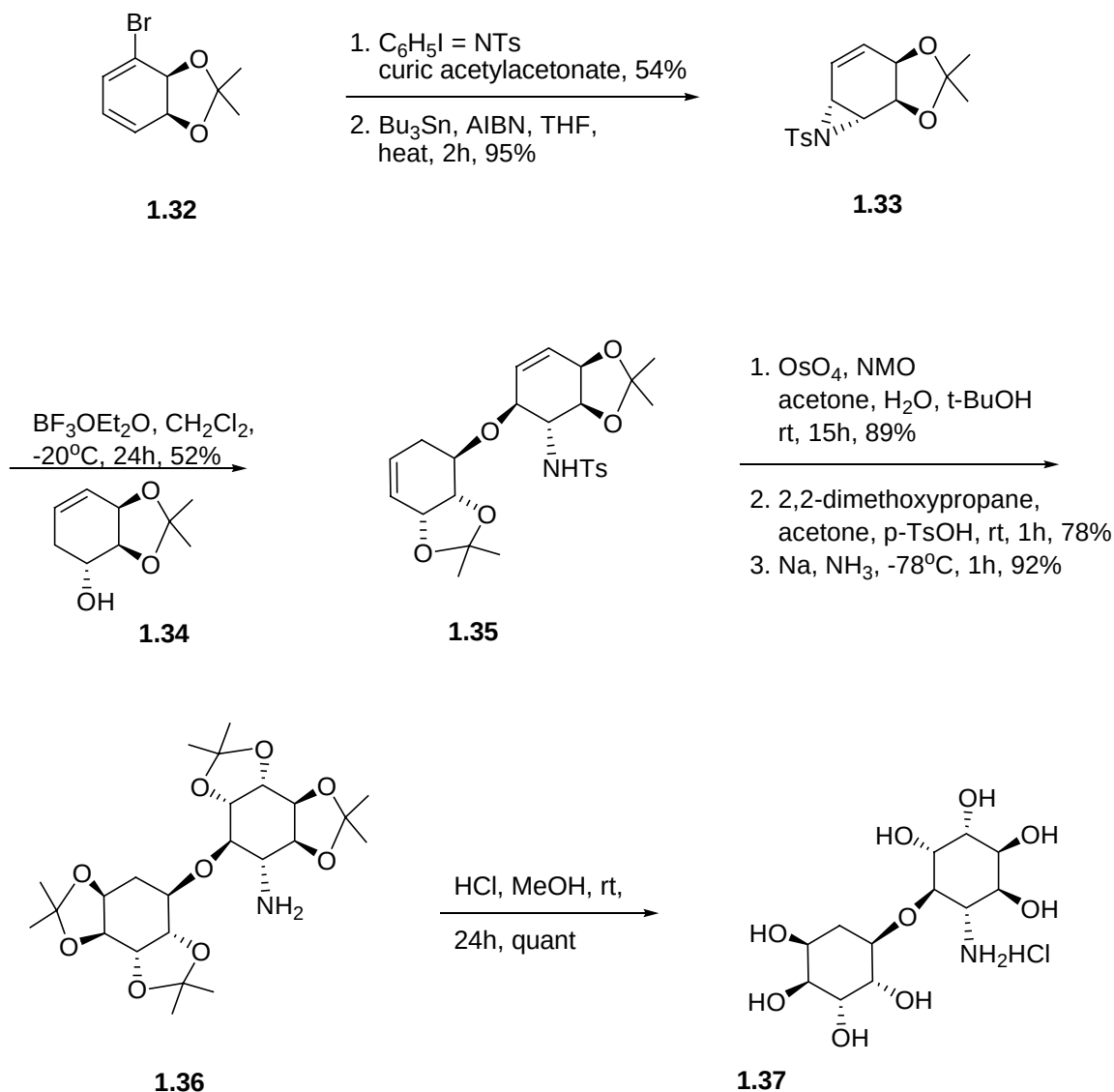
Figure 1.8

Ogawa and co-workers prepared carbadisaccharide derivative **1.31** (Scheme 1.6)³⁹. The treatment of alcohol **1.30** with NaH in DMF followed by addition of the epoxide **1.29** afforded **1.31** in reasonable yield.



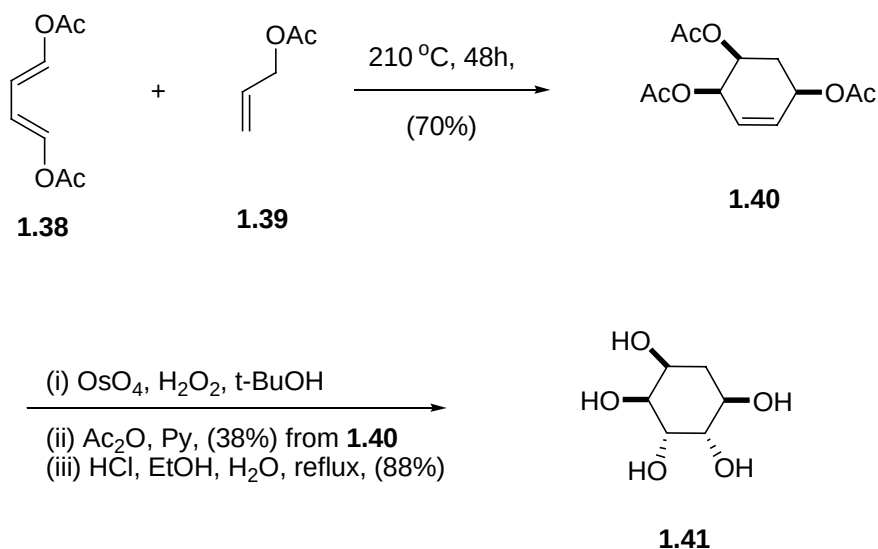
Scheme 1.6

Hudlicky reported the synthesis of a carba-pseudo-disaccharide **1.37** (Scheme 1.7).⁴⁰ Lewis-acid catalysed coupling of aziridine **1.33** and alcohol **1.34** provided ether **1.35**. Double dihydroxylation of **1.35**, protection of the resulting tetraol with isopropylidenes followed by birch reduction has lead to amine **1.36**. Removal of the protecting groups provided **1.37**.



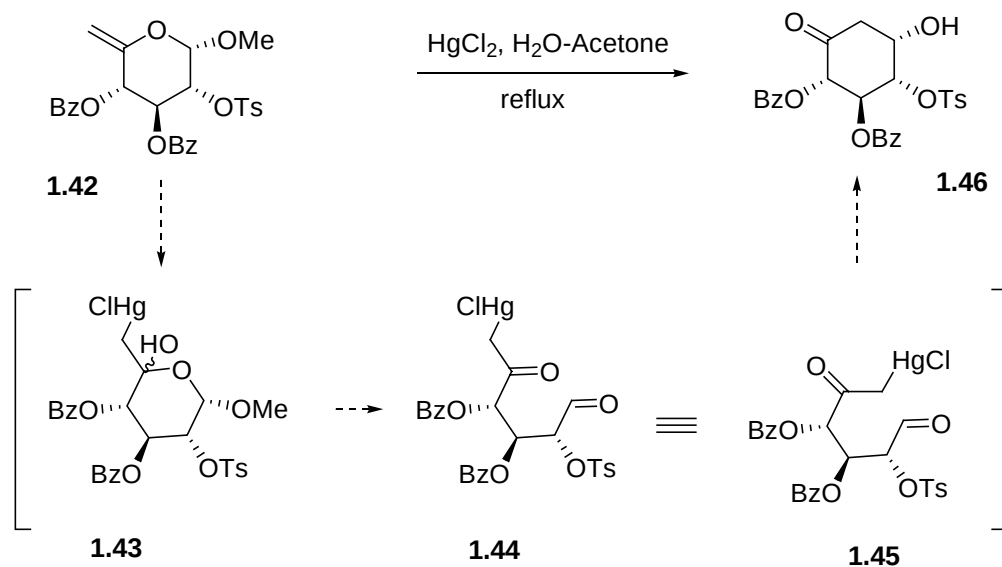
Scheme 1.7

McCasland³⁸ and co-workers worked out the synthesis of 5a-carba- α -D-glucopyranose **1.41** (Scheme 1.8). Diels-Alder cycloaddition of 1,4-diacetoxy-1,3-butadiene **1.38** and allyl acetate **1.39** provided **1.40**. Dihydroxylation of **1.40** followed by acetylation and hydrolysis afforded the free carbasugar in 33% overall yield.



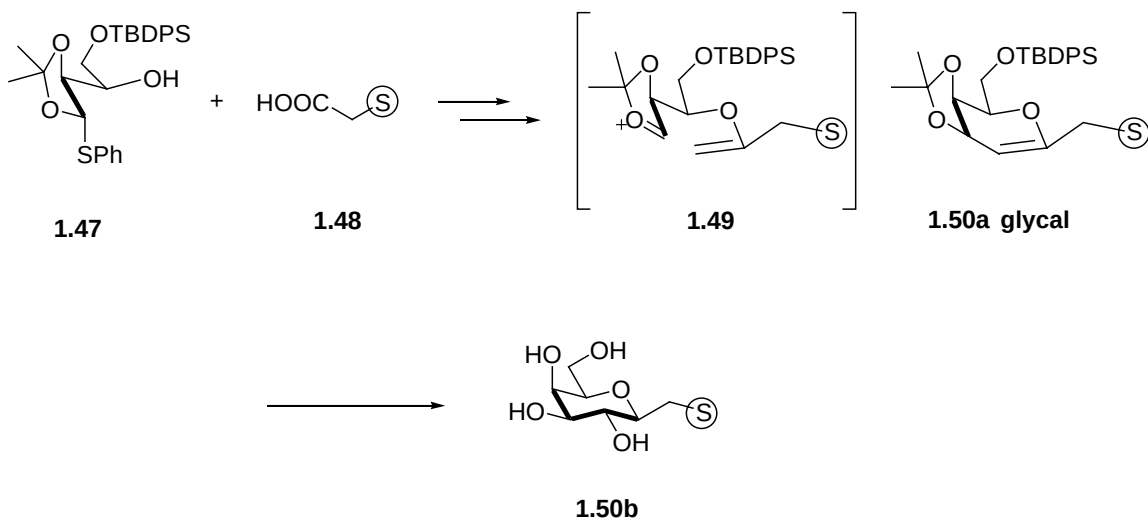
Scheme 1.8

Ferrier described the mercury (II) mediated transformation of hex-5-enopyranoside **1.42** to substituted cyclohexanes **1.46** (Scheme 1.9).⁴¹ The reaction involves the regiospecific hydroxymercuration of the vinyl ether moiety of **1.42** to give the unstable hemiacetal **1.43** which loses methanol to afford dicarbonyl intermediate **1.44**. Then aldol-like intramolecular cyclization takes place to give cyclohexane **1.46**.



Scheme 1.9

1.4 Our Synthetic Approach



Scheme 1.10: Previous work: C-glycoside via oxocarbenium-ion cyclization

Our synthetic strategy centers on a C1-substituted glycal, which is formed via a novel intramolecular oxocarbenium ion based enol ether cyclization (**Scheme 1.10**). This route is well suited for *C*-glycosides with complex aglycone segment and has been applied to several *C*-disaccharides.^{42,43} A variation of the concept was used for carba-disaccharides. This chemistry will be applied to the synthetic targets in this thesis.

1.5 Summary

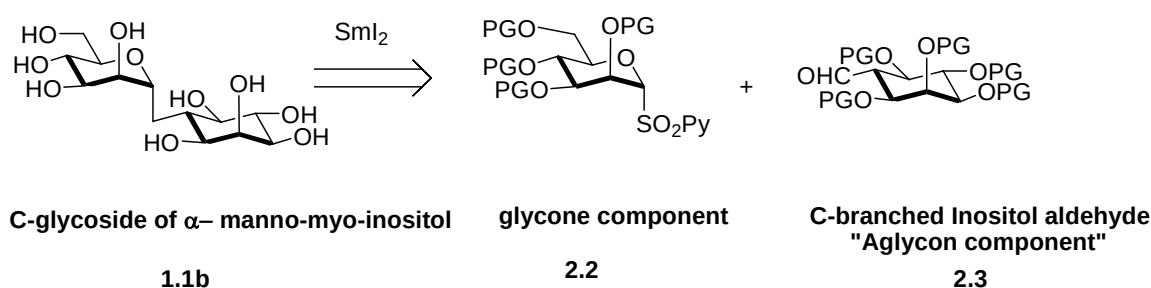
Naturally occurring glycoinositols are *O*-glycosides. Our work is focused on the synthesis of *C*-glycoinositols. The hydrolytic stability and different conformation properties of *C*-glycosides compared to *O*-glycosides make these *C*-glycoinositols interesting biological probes. The synthesis of *C*-glycosides has received more attention than carba-glycosides. Several *C*-glycoside syntheses that are based on the chemistry of glycosyl radicals, nucleophiles and cations have been developed. The extension of these methods to the *C*-glycoinositols has not been extensively explored. In this thesis we will apply an oxocarbenium ion-enol ether cyclization strategy for *C*-glycosides that was previously discovered in this laboratory, to the synthesis of *C*- and carba glycoinositols.

CHAPTER 2

Synthesis of C-branched *Myo*-inositol

2.1 Retrosynthesis

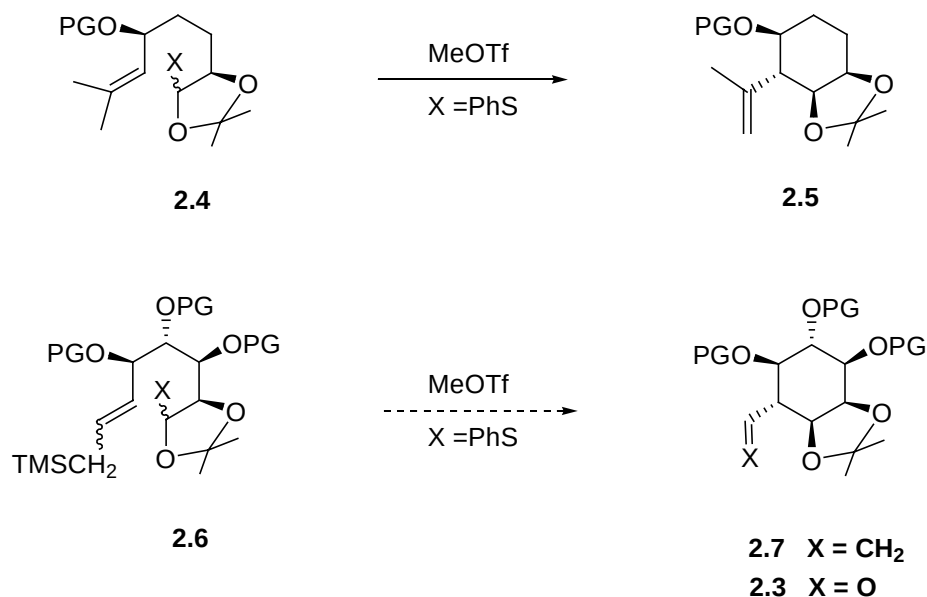
The C-glycoside of α -manno-*myo*-inositol **1.1b** may be synthesized through the samarium diiodide promoted coupling of *mannosyl* sulfone **2.2** and C-branched *myo*-inositol aldehyde **2.3** (Scheme 2.1). The first challenge was the synthesis of the *myo*-inositol, which is chiral. Our plan for the synthesis of **2.3** centers on the oxocarbenium ion-alkene cyclization strategy described earlier.



Scheme 2.1 Retrosynthesis C-glycoside of α -manno-*myo*-inositol

It was previously observed that treatment of thioacetal-alkene **2.4** with methyl triflate led to one of the four possible diastomeric cyclization products, **2.5** (Scheme 2.2).⁴⁴ The favored isomer contained a cis-fused *O*-isopropylidene and a vicinal isopropenyl substituent that was trans to the isopropylidene residue.⁴⁵ The stereoselectivity of this transformation was rationalized in terms of the cyclic nature of the oxocarbenium ion intermediate and conformational factors in the transition state leading to **2.5**. By analogy, we envisaged that cyclization of a precursor such as **2.6** should lead to the C-branched *myo*-inositol **2.7** with high stereoselectivity. While an

allylsilane in **2.6** place of the isobutenyl residue in **2.4**, was expected to facilitate the trapping of the oxocarbenium ion, the more complex substitution in **2.6** compared with **2.4** led to concerns about competing side reactions and stereoselectivity.



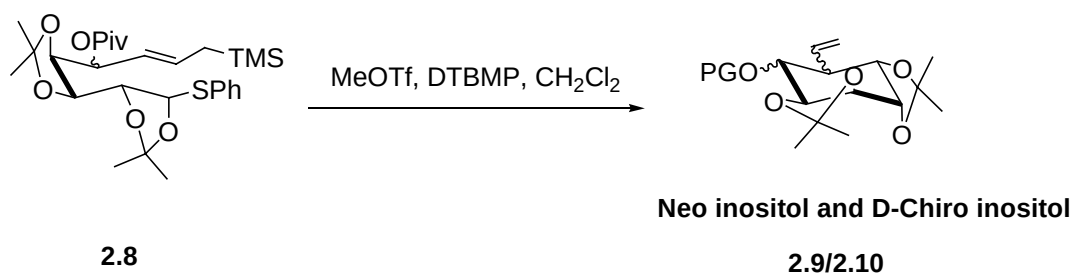
Scheme 2.2 Oxocarbenium ion cyclizations for C-branched inositols

Indeed, preliminary investigations on derivatives of **2.6** with benzyl ether or ester protecting groups suggested that products arising from attack on the intermediate oxocarbenium ion by neighboring oxygen substituents were predominant. We argued that strategic positioning of cyclic and ester-protecting groups would limit these processes because of unfavorable ring strain and electronic effects in the cyclization

reaction. We reasoned that using a conformationally restrained substrate may solve these problems, and tested this strategy on the cyclization of model substrate **2.8** (Scheme 2.3).

2.2 Results and discussion

2.2.1 Model study: Synthesis of *D-chiro* inositol and *Neo*-inositol

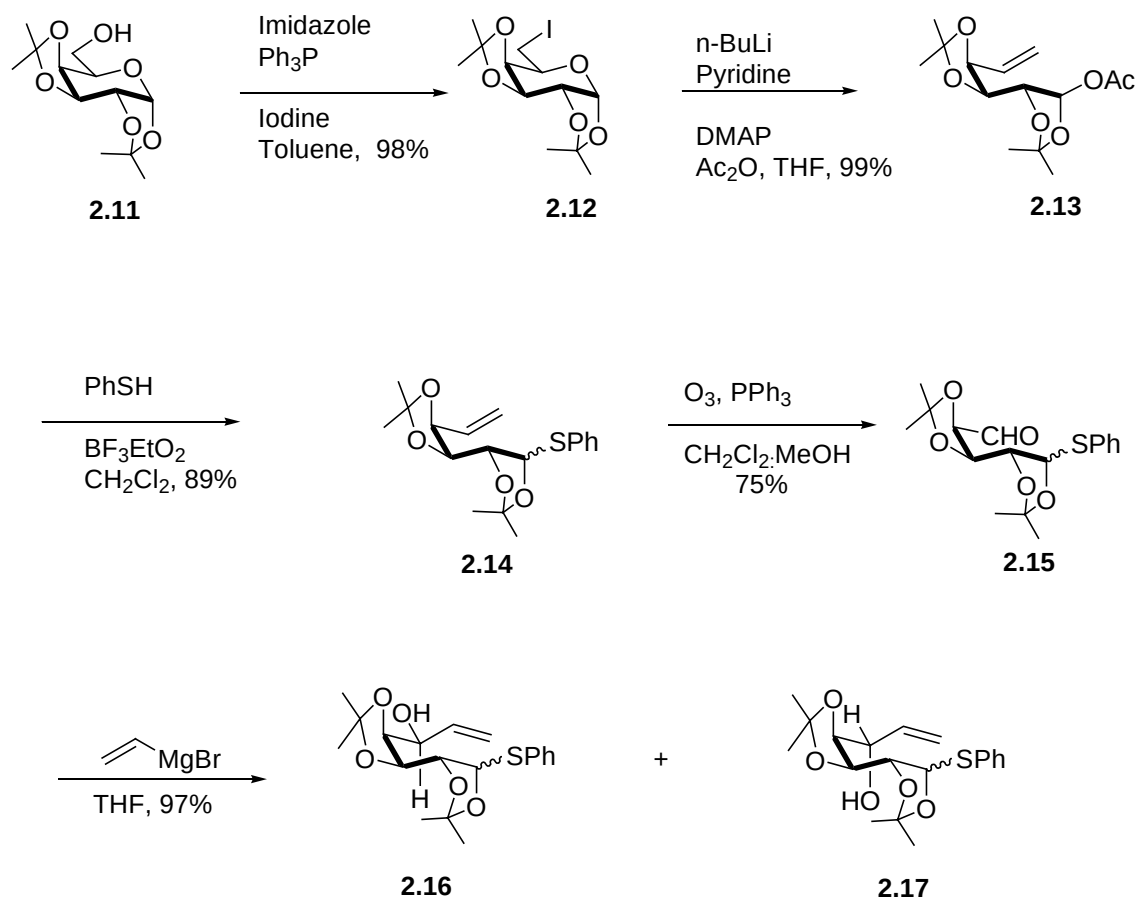


Scheme 2.3

Test compounds of the type **2.8** were easily obtained from 1,2: 3,4-di-*O*-isopropylidene-*D*-glactopyranose **2.11** (Scheme 2.4). Iodination⁴⁶ of **2.11** provided **2.12** in 98% yield (Scheme 2.4). Reductive elimination of Iodide **2.12** with *n*-butyllithium, followed by addition of the acetic anhydride⁴⁷ to trap the alkene lactal intermediate provided the di-*O*-isopropylidene alkene **2.13**. Acetate/phenyl thiolate exchange under controlled conditions gave a 1:1 mixture of acetal isomers **2.14** in 89% yield. Ozonolysis of **2.14** in CH₂Cl₂ at –78 °C followed by reductive work up with triphenylphosphine gave the aldehyde **2.15** in 75% yield.

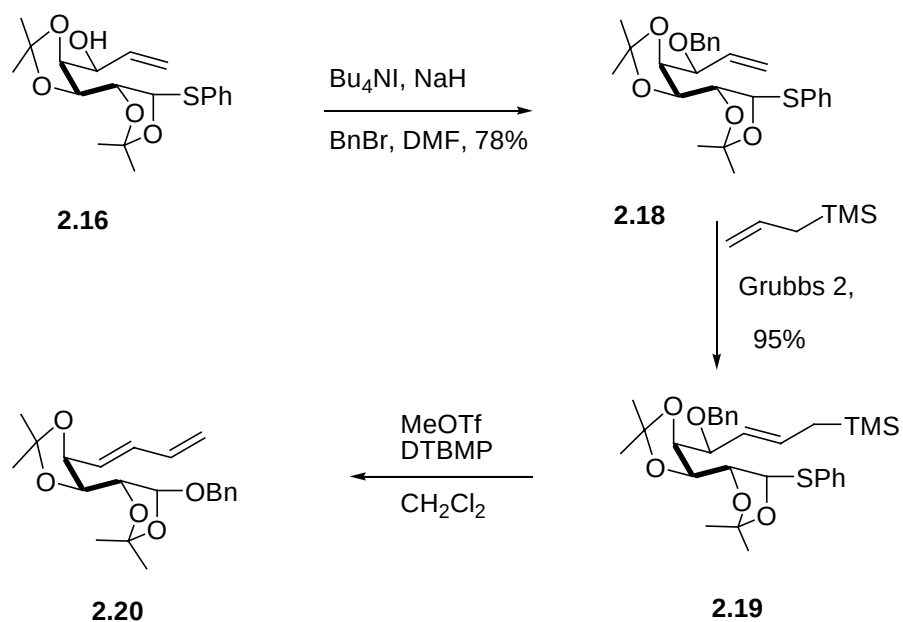
Addition of vinylmagnesium bromide in dry THF to **2.15** afforded *epimeric* alcohols **2.16** and **2.17**, each as a mixture of phenylthio-*O*-isopropylidene acetals. The individual mixture **2.16** and **2.17** were separated and taken separately through later steps. Allylic

alcohol **2.16** was protected as the benzyl ether **2.18**, which was treated with Grubbs second-generation catalyst and allyltrimethylsilane⁴⁹ in dry CH₂Cl₂ to give the cyclization precursor **2.19** in 95% yield (Scheme 2.5).

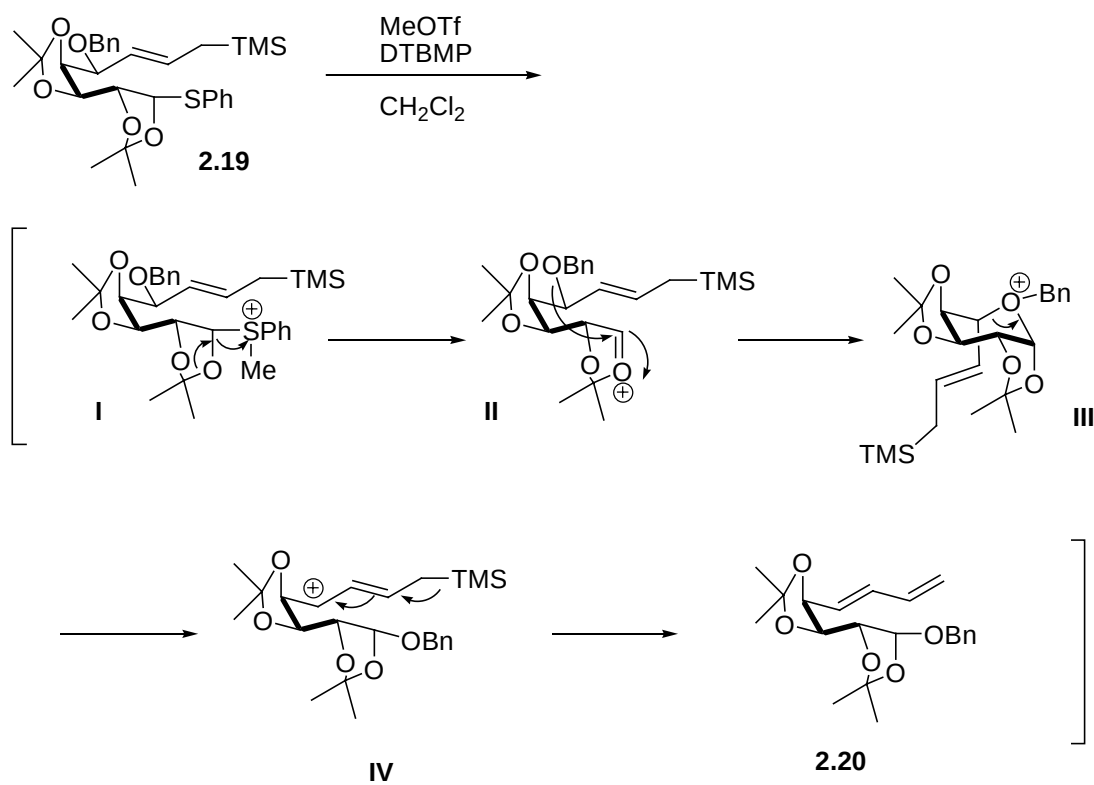


Scheme 2.4

The key cyclization step was attempted by treatment of alkene **2.19** with methyl triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), 4Å molecular sieves and dry dichloromethane. The desired compound was not achieved, but instead the diene **2.20** was obtained. We speculate that the participation of the benzyl group in this reaction led to compound **2.20** (Scheme 2.6).



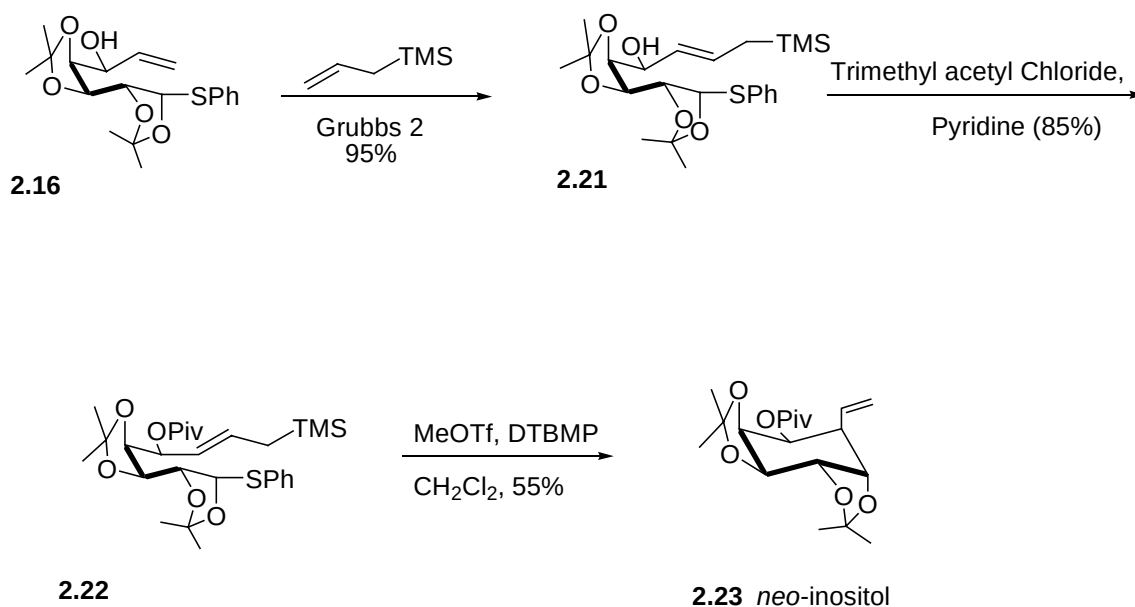
Scheme 2.5



Scheme 2.6 Suggested mechanism for formation of diene 2.20

Activation of the thiophenyl group leads to oxocarbenium ion II, which was trapped by *O*-benzyl group to form III. Fragmentation of III gives IV, which undergoes desilylation to form **2.20** (Scheme 2.6).

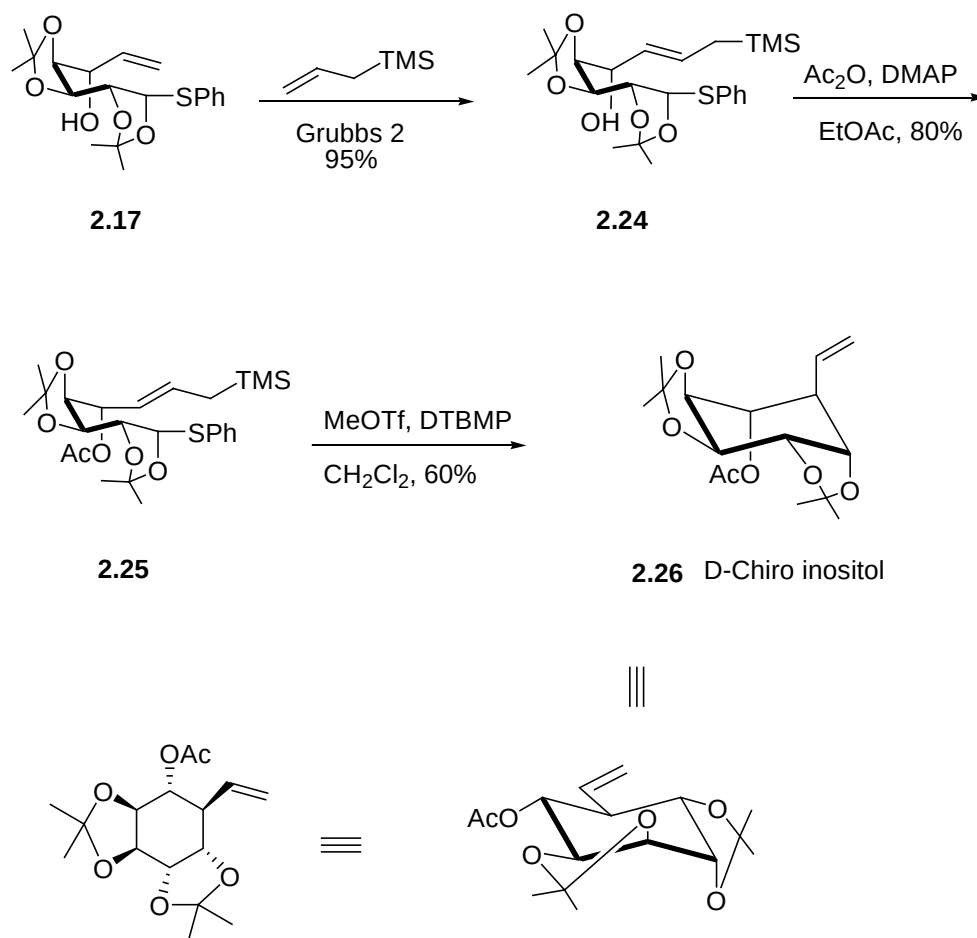
In view of the mechanism we reasoned that use of an ester protecting would reduce *O*-participation and prevent diene formation. Accordingly pivalate **2.22** was prepared and subjected to the standard cyclization conditions (Scheme 2.7). The *C*-branched *neo*-inositol **2.23** was obtained. The stereochemical assignment for **2.23** will be discussed later.



Scheme 2.7

This strategy was next attempted on the epimeric cyclization precursor **2.24**. However, the preparation of pivalate ester was problematic. Therefore, **2.24** was protected as the acetate **2.25** (Scheme 2.8). Exposure of **2.25** to the standard cyclization conditions

gave the C-branched *D-chiro* inositol **2.26** as a single isomer. The stereochemical analysis of the cyclization products **2.23** and **2.26** is discussed in the following section.



Scheme 2.8

2.2.2 Stereochemical analysis of cyclization products **2.23** and **2.26**

The stereocenter at C2, C3 and C4 of **2.23** and **2.26** is set in the synthetic precursor **2.15** (Figure 2.1). The C5 center is formed in the Grignard reaction and C1 and C6 are formed in the cyclization step. The configuration at C1, C5 and C6 in **2.26**

was assigned by consideration of the known stereochemistry at C2, C3 and C4 and analysis of the HNMR of **2.26**. Thus, values for $J_{4,5}$, $J_{5,6}$ and $J_{1,2}$ of 12.0, 9.2, and 3.0 Hz respectively supported the *chiro* configuration. Because of poor resolution in the ^1H NMR of **2.23**, as well as conformational ambiguities due to the two isopropylidene rings, **2.23** was converted to the penta acetate **2.27** for NMR analysis. $J_{4,5}$, $J_{5,6}$, $J_{1,2}$ values of 3.0, 11.3 and 3.0 Hz were in agreement with the *neo* configuration.

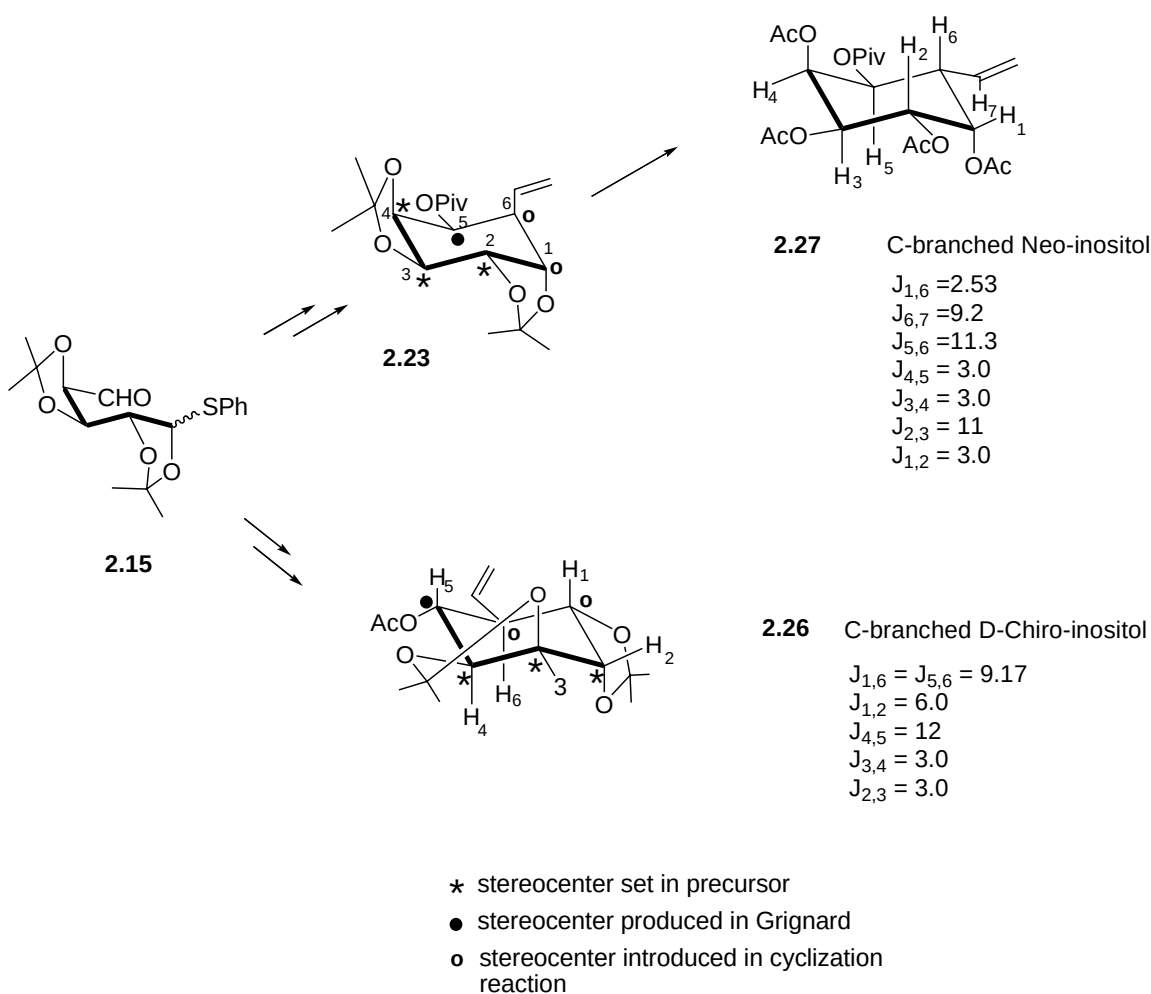


Figure 2.1: Spectroscopic analysis of *D-chiro*-inositol and *neo*-inositol

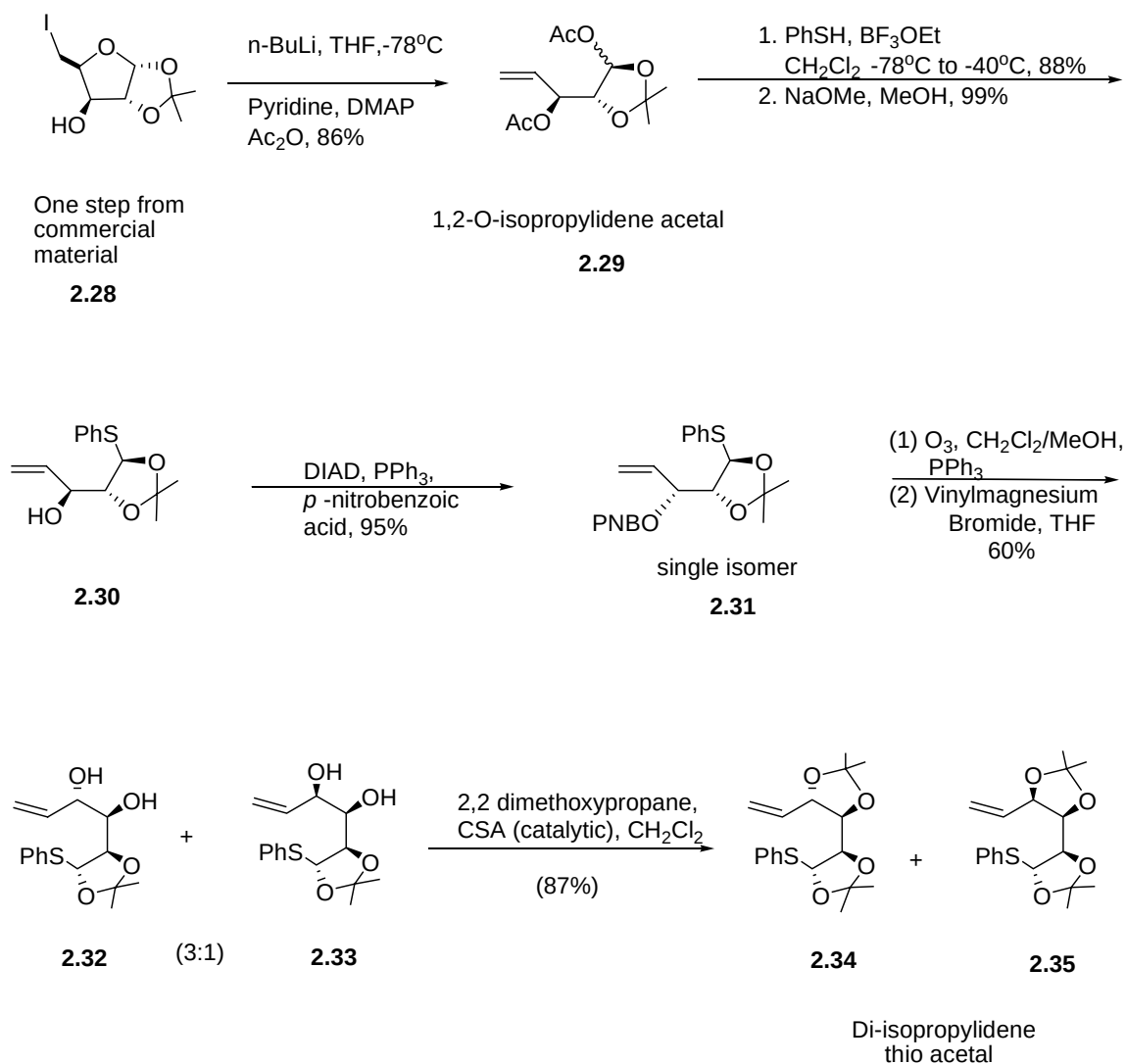
2.2.3 Synthesis of *myo*-inositol

With the feasibility of the key cyclization established, we next targeted the *C*-branched *myo*-inositol **2.42** and diastereomeric analogues. The precursors for the cyclization were prepared from 1,2-*O*-isopropylidene xylofuranose (**Scheme 2.9**).

1,2-*O*-isopropylidene xylofuranose was converted to iodide compound **2.28** (**Scheme 2.9**)⁴⁶. Reductive elimination of iodide **2.28** with *n*-butyllithium, followed by addition of the acetic anhydride⁴⁸ to trap the alkene lactal intermediate provided the di-*O*-isopropylidene alkene **2.29** in 86% yield. Acetate/phenyl thiolate exchange under controlled conditions gave a single acetal isomer in 88% yield. The deprotection of the acetate group produced alcohol **2.30**. Alcohol **2.30** was subjected to Mitsunobu reaction conditions to invert the C3 center, thereby giving the required stereochemistry for the *C*-branched *myo*-inositol target. Ozonolysis of **2.31** afforded the crude aldehyde, which was treated with vinylmagnesium bromide. This reaction led to **2.32** and **2.33** (3:1) mixture of alcohols. The *p*-nitrobenzoate ester was deprotected under the same reaction conditions. Protection of diol mixture as the isopropylidene using 2,2-dimethoxypropane and catalytic amount of camphorsulfonic acid provided **2.34** and **2.35** in 87% yield. The configuration at the newly formed carbinol centers in **2.34** and **2.35** was assigned in the subsequent cyclization products, the structures of which were analyzed through ¹H NMR analysis (*vide infra*). The major isomer **2.34** corresponds to the stereochemistry required for the *myo*-inositol target.

Ozonolysis of alkenes **2.34** and **2.35** followed by the vinylmagnesium bromide addition to the aldehyde products led to 2:1 mixture of alcohols **2.36** and **2.37** from **2.34**, and a single isomer **2.38** from **2.35** (**Scheme 2.10**). Once again, the configuration at the

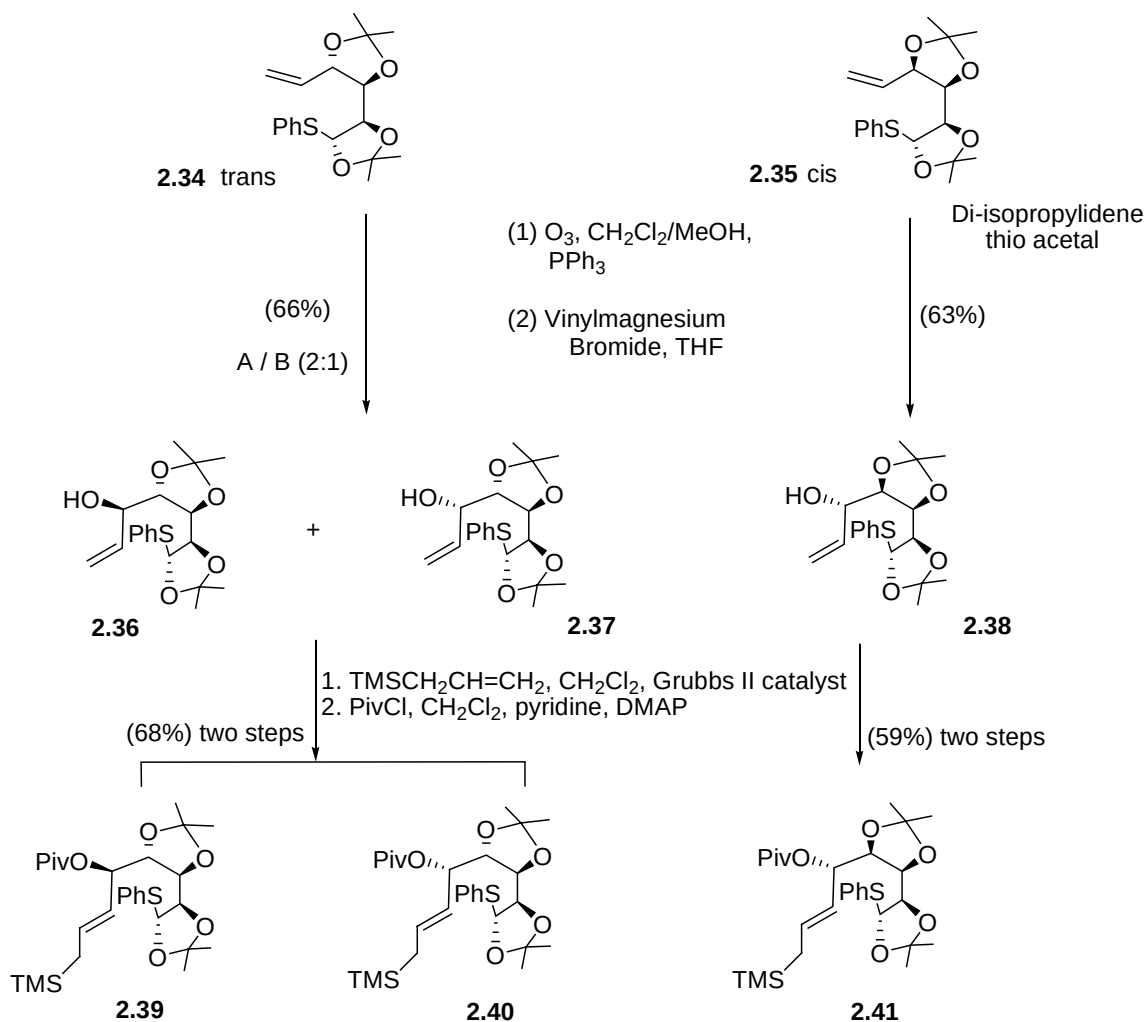
newly introduced stereogenic center relied on the assignment of stereochemistry in the later cyclization products.



Scheme 2.9

Olefin cross-metathesis with allyltrimethylsilane⁴⁹ and the unseparated mixture of alcohols, followed by the protection of resulting allylic alcohol as the pivalate ester provided cyclization precursors **2.39** and **2.40** in 68% yield, as an inseparable mixture (**Scheme 2.10**). The ^1H NMR analysis of this mixture suggested that the stereoselectivity

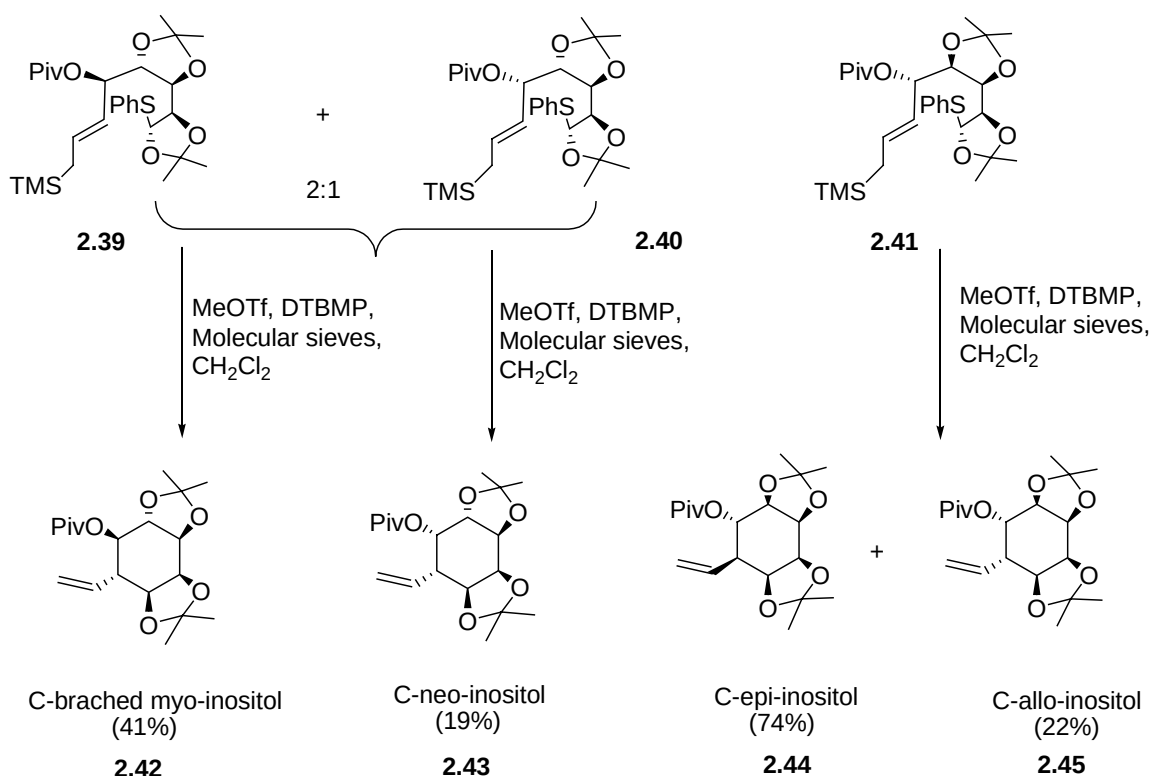
of the cross-metathesis was greater than 90% in favor of the E-alkene. Similarly, allylic alcohol **2.38** was transformed to the cyclization precursor **2.41** in 59% yield.



Scheme 2.10

The cyclization reaction on unseparated mixture **2.39/2.40** and **2.41** were promoted with methyl triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) and freshly activated 4Å molecular sieves in anhydrous dichloromethane. An approximately 2:1 mixture of **2.39/2.40** afforded **2.42** (41%) and **2.43** (19%). Thus, the

reaction of **2.39** and **2.40** were both highly stereoselective, giving in each case single diastereomer in which the newly formed *O*-isopropylidene was cis-fused to the cyclitol ring, and the adjacent isopropenyl substituent was trans to the isopropylidene ring. The cyclization of **2.41** was less selective giving a mixture of products, which also contained a cis-fused *O*-isopropylidene, but differed with respect to the configuration at the ethenylated carbon.

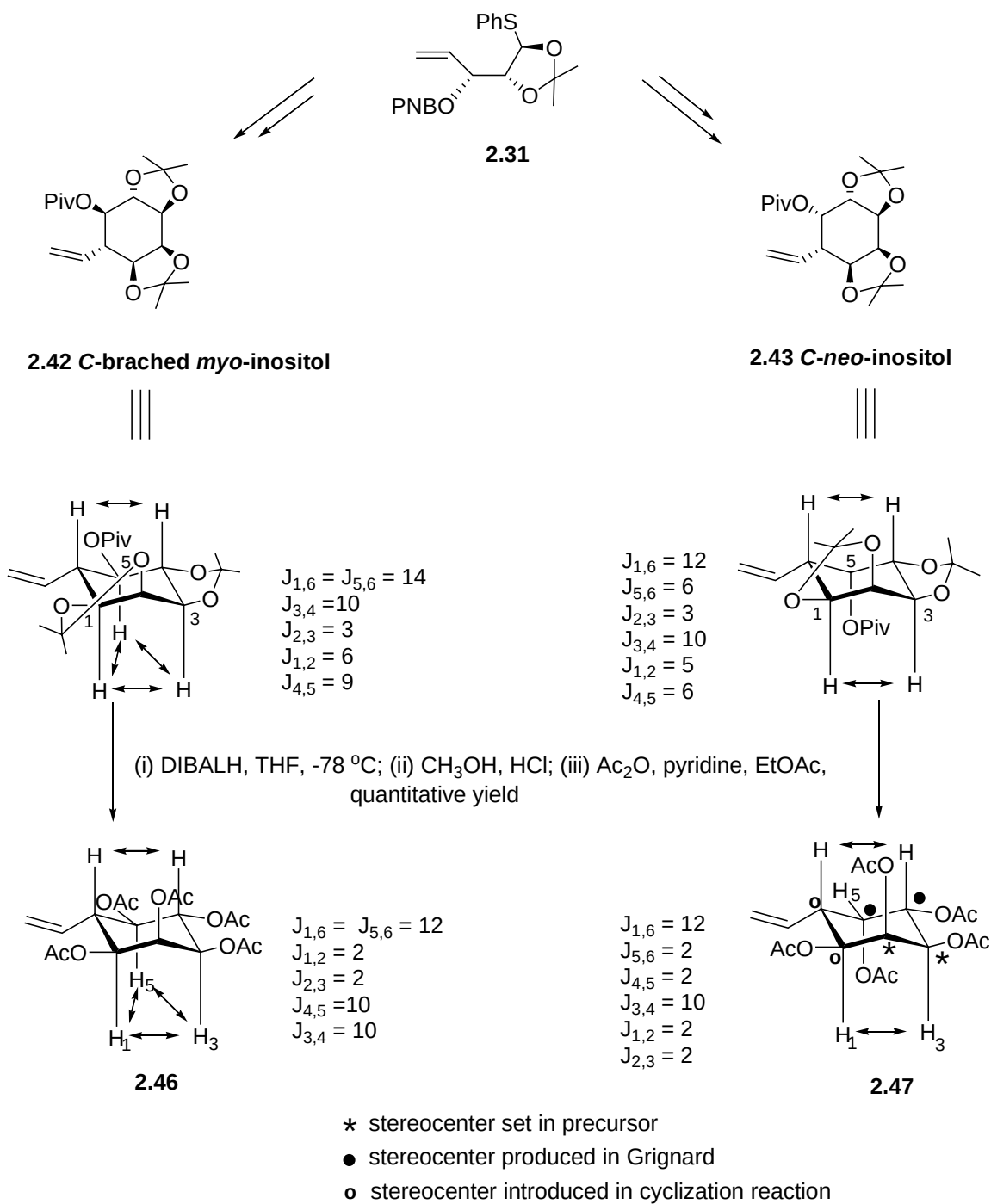


Scheme 2.11

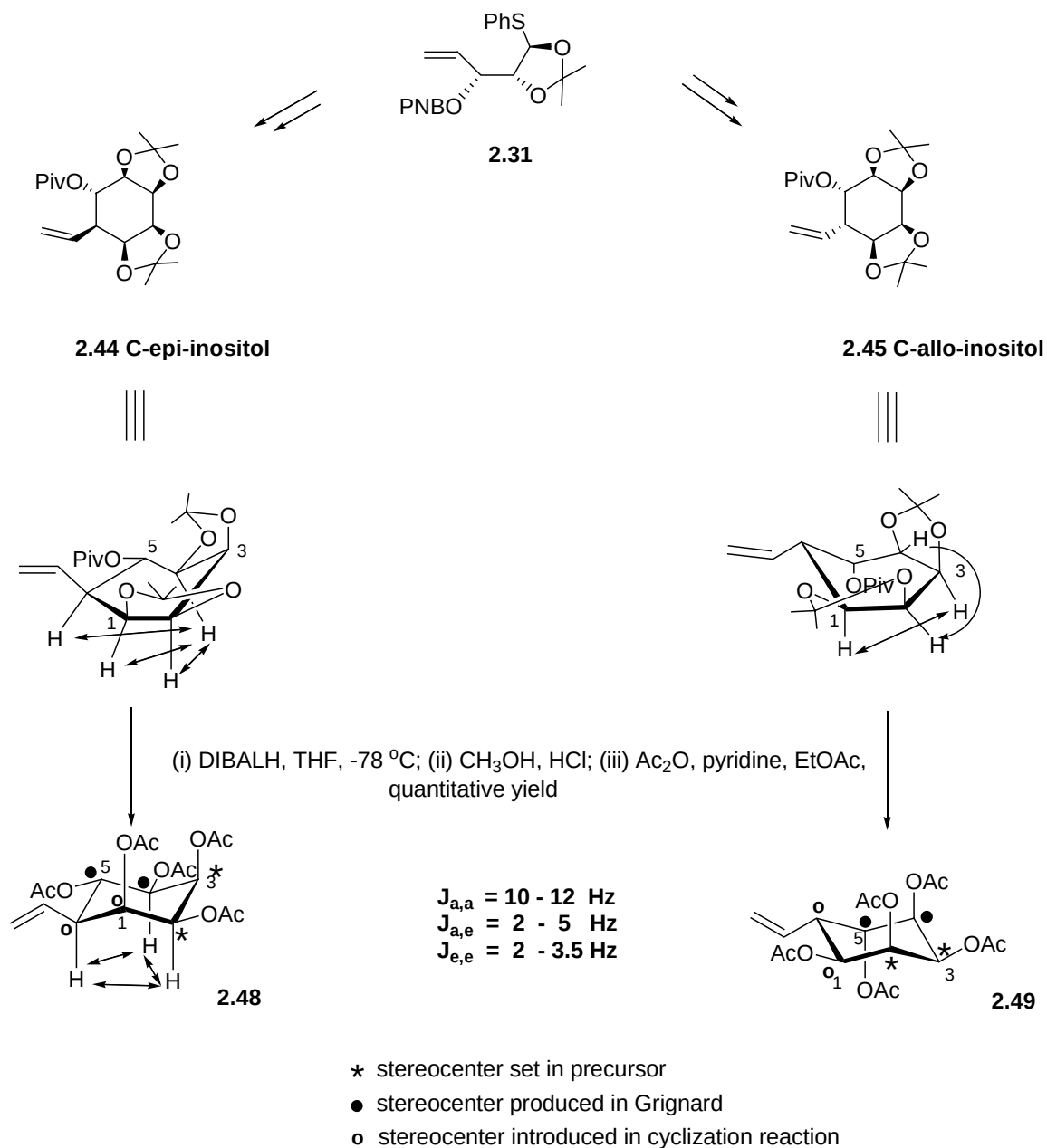
2.2.4 Stereochemical analysis of cyclization products

The stereochemistry at C2 and C3 of **2.42**, **2.43**, **2.44** and **2.45** is set in precursor **2.31**. Stereocenters C4 and C5 were formed in the Grignard reaction. C1 and C6 were

introduced in the cyclization step. The configuration at C1, C4, C5 and C6 was assigned by consideration of the known stereochemistry at C2 and C3 and analysis of ^1H NMR and NOESY data.



Scheme 2.12: ^1H NMR analysis



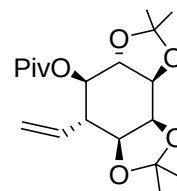
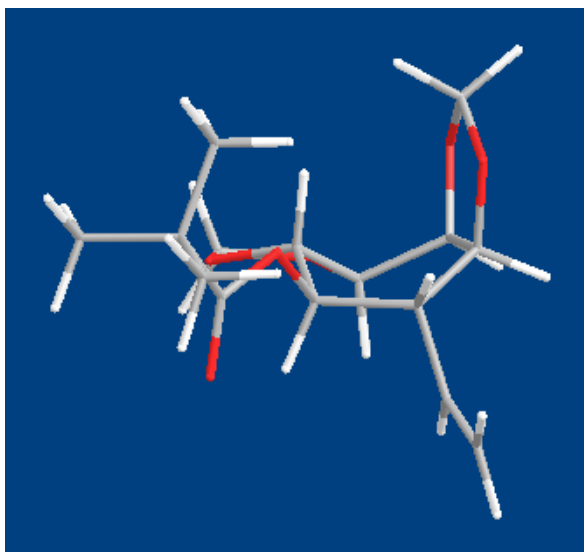
Scheme 2.13

Thus, values for $J_{1,6}$, $J_{5,6}$, $J_{3,4}$, $J_{2,3}$, $J_{4,5}$ of 14.0, 10.0, 3.0, and 9.0 Hz respectively supported the *myo* configuration, except for $J_{1,2} = 6$ Hz which was ambiguous possibly because of conformational distortion. Therefore, removal of isopropylidenes and

derivitization as the acetate penta-ester **2.46** was performed (**Scheme 2.12**). Now the coupling constant was in agreement with our *myo*-inositol system. As for **2.42** the stereochemistry of **2.43**, **2.44** and **2.45** was also assigned by ^1H NMR analysis of the individual penta-ester derivatives and consideration of the synthetic routes (**Scheme 2.12**, **2.13**).

2.3 Computational studies on conformations of cyclization products

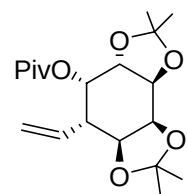
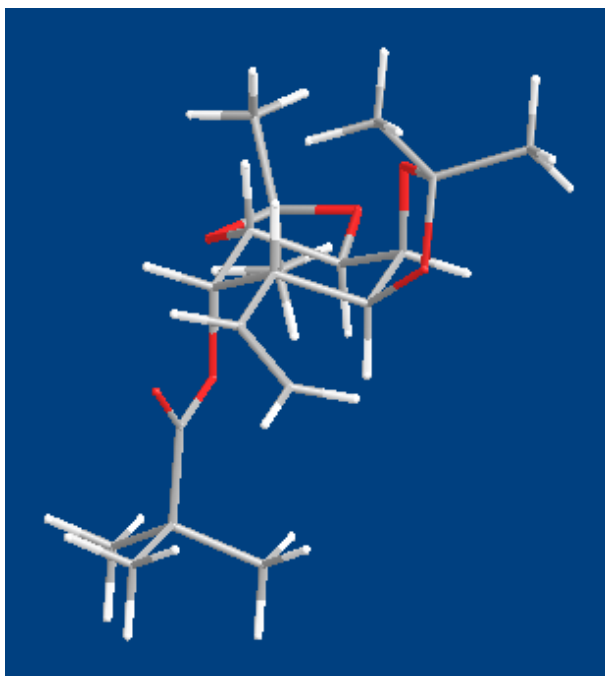
J values were obtained from application of the Karplus-Altona equation to preferred conformation obtained from molecular modeling with Hyper Chem 7.5 (TM of Hypercube Inc; performed with a semiempirical AM1 method as algorithm).^{50,51} The theoretical J values were generally close to the experimental NMR data. Conformational averaging and solvent effects on chemical shifts may contribute to the differences between the calculated and observed values.



C-branched myo-inositol

2.42**Figure 2.2****Table 2.1:** twist boat Potential Energy = -109977KJ

	Dihedral angles	Calculated $J_{H,H}$	Experimental $J_{H,H}$
H-C6-C1-H	156.3	7.81	6.8
H-C1-C2-H	-40.5	4.15	5.3
H-C2-C3-H	57.6	2.44	3.1
H-C3-C4-H	178.4	8.62	10.1
H-C4-C5-H	174.9	8.15	9.3
H-C5-C6-H	-167.7	9.85	8.1



C-neo-inositol

2.43**Figure 2.3****Table 2.2:** Chair Potential Energy = -109973KJ

	Dihedral angles	Calculated $J_{H,H}$	Experimental $J_{H,H}$
H-C1-C2-H	-52.2	2.95	4.6
H-C2-C3-H	58.3	2.37	2.7
H-C3-C4-H	169.3	8.95	10.1
H-C4-C5-H	56.8	2.51	2
H-C5-C6-H	-60.6	1.63	2.9
H-C6-C1-H	172	9.44	8.4

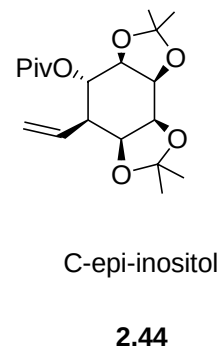
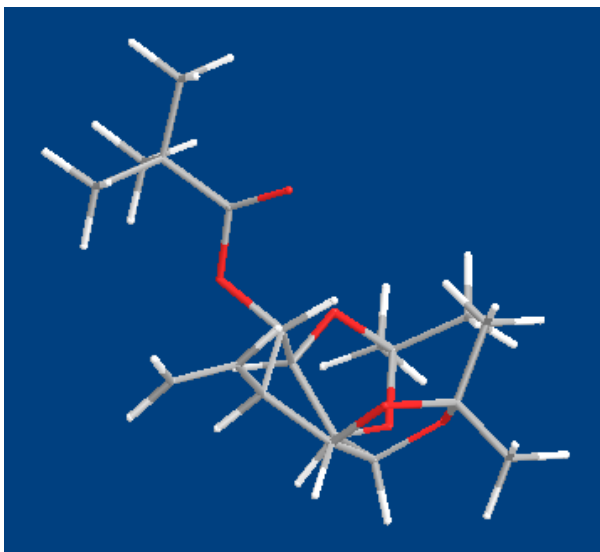
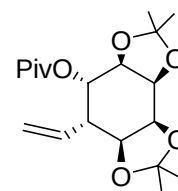
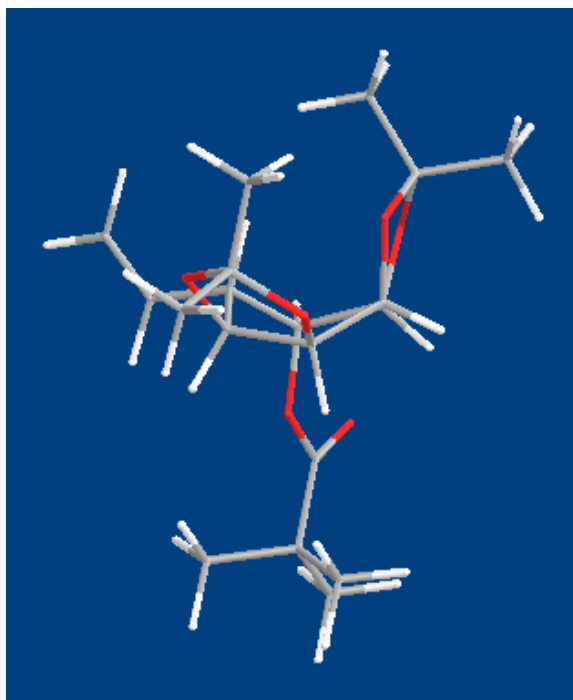


Figure 2.4

Table 2.3: twist half chair Potential Energy = -109983KJ

	Dihedral angles	Calculated $J_{H,H}$	Experimental $J_{H,H}$
H-C1-C2-H	-51.3	2.6	3.8
H-C2-C3-H	-8.4	6.57	3.6
H-C3-C4-H	37	4.5	6.8
H-C4-C5-H	-10.8	6.49	7.4
H-C5-C6-H	-155.3	5.91	7.3
H-C6-C1-H	-169.1	8.27	12.4



C-allo-inositol

2.45**Figure 2.5****Table 2.4:** twist half chair Potential Energy = -109984KJ

	Dihedral angles	Calculated $J_{H,H}$	Experimental $J_{H,H}$
H-C1-C2-H	12.1	6.44	7.3
H-C2-C3-H	-41.5	4.04	3.9
H-C3-C4-H	14.1	6.34	6.9
H-C4-C5-H	-74.5	2.2	2.2
H-C5-C6-H	-70.8	0.92	1.5
H-C6-C1-H	161.5	8.45	7.6

2.4 Discussion

The stereochemistry of the cyclization reaction appears to be controlled by conformational factors. Thus, the high stereoselectivity observed for the reactions of

2.39 and **2.40** is consistent with a clear preference for chair-like transition states **A** and **B** respectively, over the other diastereomeric possibilities (**Figure 2.6**). The particular flip chair conformation in these structures is determined by 3,4-*O*-isopropylidene residue (in which the oxygens of the cyclic acetal are in a trans diequatorial relationship in the forming six-membered ring). The configuration at C1 is controlled by the preference for a 1,2 *O*-isopropylidene that is cis-fused (vs. trans-fused) in the resulting tricyclic framework. The constraints imposed by the two cyclic acetal residues are met in a pair of low energy transition states, **A/A'** and **B/B'** corresponding to precursors **2.39** and **2.40** respectively. Of these **A** and **B**, in which the C6 substituent adopts the pseudo equatorial (vs. the pseudo axial orientation in **A'** and **B'**), in the forming six-membered ring are expected to highly favored, thereby leading to single cyclization products from **2.39** and **2.40** respectively.

Analysis of transition states for the cyclization of **2.41** is complicated by the fact that the both *O*-isopropylidene rings in the diastereomeric products **2.44** and **2.45**, are cis-fused, and therefore a wider range of low energy conformations are possible, compared to the cyclizations leading to **2.42** and **2.43**. In addition, chair-like geometries would probably be disfavored because of severe 1,3-diaxial interactions between oxygen substituents of the two-isopropylidene rings. Assuming a half-chair like geometry, four low energy pathways **C/D'** and **D/C'** corresponding to pairs of 'flip' conformations may be considered for **2.44** and **2.45** (**Figure 2.4**), respectively. Of these **C** and **D**, in which the alkene substituent adopts a pseudo-equatorial position, are expected to be favored (over **C'** and **D'**). While **C** should be preferred over **D**, and as a result **2.44** should predominate over **2.45**, the high degree of steric congestion in both structures would be

expected to have a leveling effect on their relative energies, thereby leading to low product selectivity. The observed ratio of **2.44/2.45** (3:1) appears to be consistent with this argument.

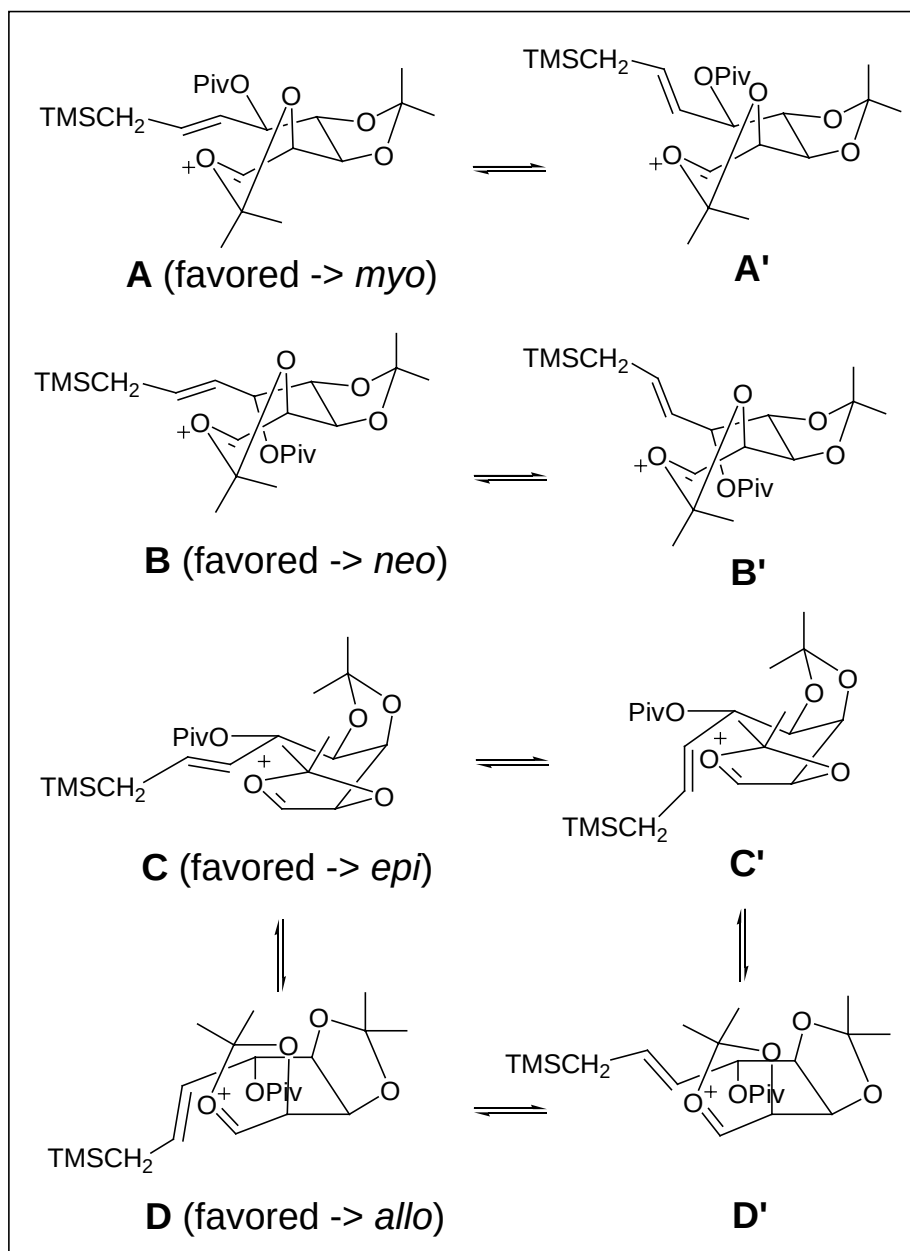
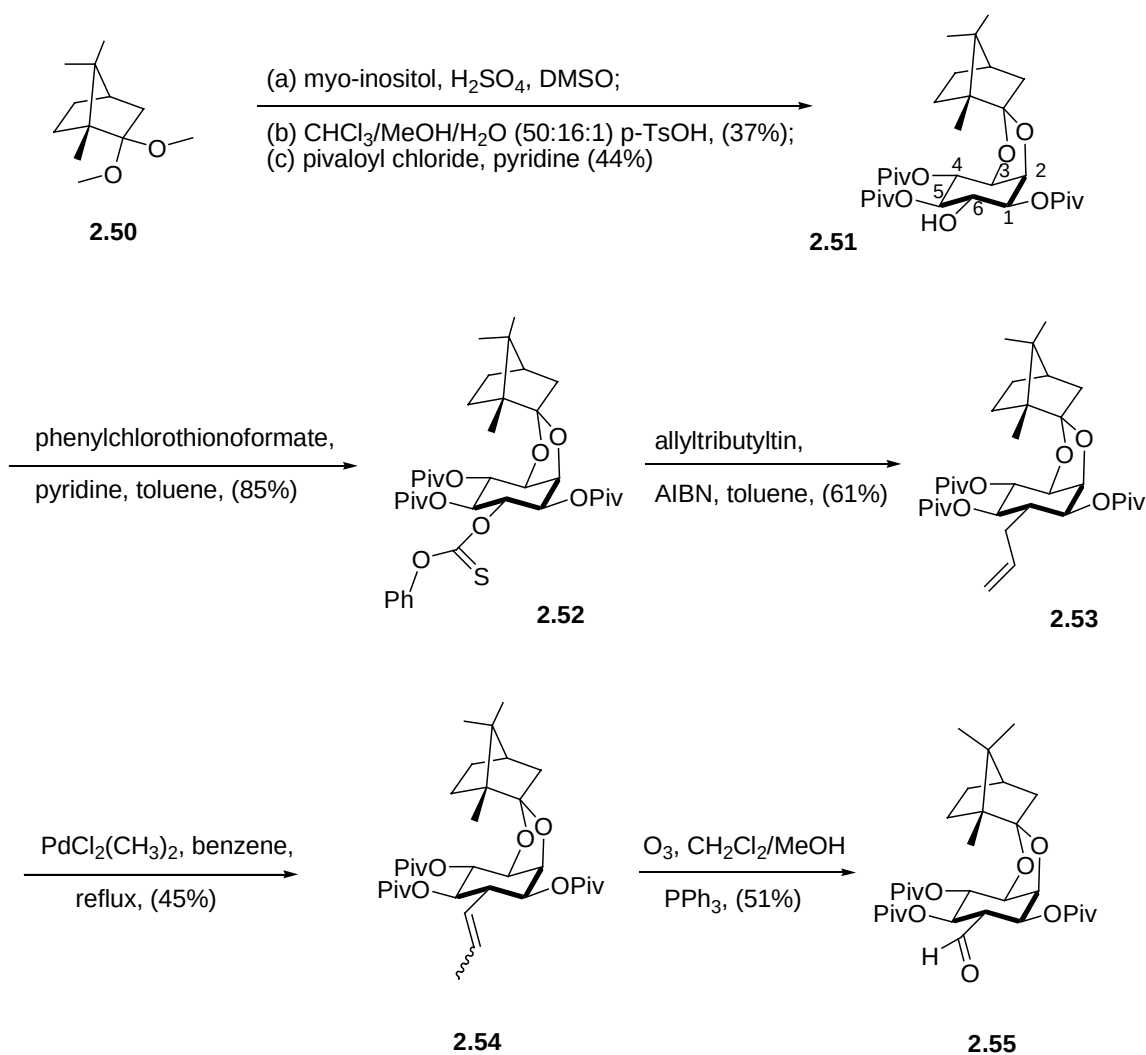


Figure 2.6: Transition state models of oxocarbenium ion cyclizations

2.5 Alternative synthesis for a C-branched *myo*-Inositol

The foregoing strategy led to a C-branched *myo*-inositol and three diastereomers. Since the *myo* derivative was required for C-glycoinositol target **2.42** (Scheme 2.14), a more streamlined synthesis of this isomer was next investigated. This synthesis started from the *myo*-inositol derivative **2.51**, which was obtained via an established protocol on *myo*-inositol.



Scheme: 2.14

Treatment of alcohol **2.51** with phenylchlorothionoformate and pyridine in toluene afforded thiocarbonate **2.52** in 85%. Exposure **2.54** to allyltributytin in the presence of AIBN gave the C-allyl derivative **2.53**. Isomerization of the allyl residue in *myoinositol* **2.53** using catalytic bis(acetonitrile) dichloropalladium (II) provided an E/Z mixture of the 6-C-propenyl products **2.54** in 45% yield. Finally, **2.54** was converted to aldehyde **2.55** by ozonolysis.

2.6 Summary

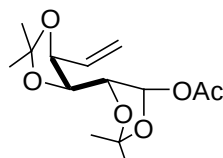
Our approach to C-branched inositol involves formation of the inositol ring via an oxocarbenium ion alkene cyclization. This strategy was first tested on two model substrates **2.22** and **2.25** that were easily obtained from 1,2,3,4, di-O-isopropylidenegalactopyranose. The key cyclization reactions on **2.22** and **2.25** produced C-ethenyl-branched- D- neo- (**2.23**) and D-chiro- (**2.26**) inositols respectively.

With this result in hand **2.39**, the cyclization precursor for the C-branched *myoinositol* was prepared from 1,2-O-isopropylidene-D-glucofuranose. Two diastereomeric cyclization precursors **2.40** and **2.41** were also obtained from the synthetic sequence leading to **2.39**. The cyclizations of **2.39** and **2.41** produced C-ethenyl-myo-D- and C-ethenyl-neo-D- inositol derivatives respectively, as the only detectable cyclization products. The reaction of **2.41** gave a 3:1 mixture of C-ethenyl-epi- and C-ethenyl-allo-inositol derivatives. The stereochemistry of the cyclization products was assigned by consideration of the synthetic route and analysis of NMR data. Finally the computed conformations of the cyclization products were found to be in general agreement with the conformations

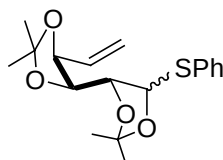
2.7 Experimental Section

General Experimental

Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe and septa technique. Optical rotations were recorded at room temperature using a Rudolph Autopol III polarimeter. ^1H and ^{13}C NMR spectra were obtained on a Varian Unity Plus 500 (500 MHz) spectrometer. Chemical shifts are relative to the deuterated solvent peak or the tetramethylsilane (TMS) peak at (δ 0.00) and are in parts per million (ppm). Assignments for selected nuclei were determined from ^1H COSY experiments. High-resolution mass spectrometry (HRMS) was performed on an Ultima Micromass Q-ToF instrument at the Mass Spectrometry Laboratory of the University of Illinois, Urbana-Champaign, and also on an Agilent 6210 instrument at Hunter College, CUNY. Thin layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel HF₂₅₄ aluminum sheets. Chromatograms were observed under UV (short and long wavelength) light, and/or were visualized by heating plates that were dipped in a solution of ammonium (VI) molybdate tetrahydrate (12.5 g) and cerium (IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulphuric acid (500 mL). Flash column chromatography (FCC) was performed using silica gel 60 (230-400 mesh) and employed a stepwise solvent polarity gradient, correlated with TLC mobility.

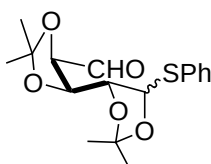
**2.13****Alkene (2.13)**

To a solution of **2.12** (6.00 g, 16.2 mmol) in THF (100 mL) was added *n*-BuLi (6.48 mL of a 2.5 M solution in THF, 16.2 mmol) dropwise at -78°C , under an atmosphere of argon. The reaction was stirred at this temperature for 1 h, then pyridine (3.93 mL, 48.6 mmol), acetic anhydride (6.62 mL, 70.0 mmol) and DMAP (2.18 g, 17.8 mmol) were added. The mixture was warmed to -40°C , stirred for additional 1 h at this temperature, then poured into ice-cold 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 **2.13** as an approximately 1:1 mixture of diastereomers (4.89 g, 99 %). A portion of this mixture was subjected to further FCC for characterization purposes. ^1H NMR (CDCl_3) δ (less polar) 1.40 (4s, 12H), 2.0 (s, 3H), 4.0-4.30 (m, 2H), 4.60 (t, 1H), 5.27 (dd, 2H), 5.82-5.95 (m, 1H), 6.04 (bs, 1H); (more polar) 1.40 (4s, 12H), 2.02 (s, 3H), 4.12 (bd, 1H), 4.43 (bt, 2H), 5.23 (bd, 2H), 5.6-5.95 (m, 1H), 6.21 (bd, 1H).

**2.14****Thioacetal alkene (2.14)**

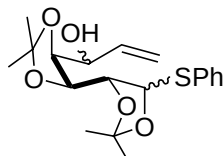
$\text{BF}_3 \cdot \text{OEt}_2$ (2.05 mL, 19.9 mmol) was slowly added at -78°C , under argon, to a solution of **2.13** (4.92 g, 16.3 mmol) and thiophenol (3.35 mL, 32.6 mmol), in anhydrous CH_2Cl_2

(160 mL). The mixture was warmed to $-40\text{ }^{\circ}\text{C}$, and stirring was continued at this temperature for 1 h (or until the TLC indicated complete disappearance of the starting material). The reaction mixture was quenched by addition of Et_3N (3 mL), then poured into 1N aqueous NaOH and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. FCC of the residue gave mixture (1:1) **2.14** (5.04 g, 88%); ^1H NMR (CDCl_3) (less polar) 1.42 (4s, 12H), 3.86 (d, 1H), 4.26 (d, 1H), 4.70 (bt, 1H), 5.35 (dd, 3H), 5.90-6.15 (m, 1H), 7.25 (bd, 3H), 7.49 (bd, 2H); (more polar) 1.50 (4s, 12H), 4.25 (dd, 1H), 4.55 (dd, 1H), 4.83 (t, 1H), 5.25 (dd, 2H), 5.50 (d, 1H), 5.75-5.92 (m, 1H), 7.13-7.40 (m, 3H), 7.40-7.60 (m, 2H).

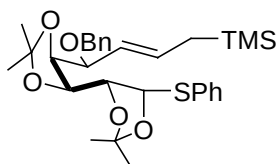
**2.15**

Thioacetal aldehyde (2.15)

Alkene **2.14** (5.31 g, 1.51 mmol) was dissolved in a 5/1 mixture of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10 mL). The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and treated with a stream of O_3 in O_2 until TLC indicated the complete disappearance of the starting material. The reaction was then purged with nitrogen, and Ph_3P (0.792 g, 3.02 mmol) was added. The mixture was warmed to rt, stirred for 1 h at this temperature, and concentrated under reduced pressure. FCC of the residue gave mixture **2.15** (0.396 g, 74 %); ^1H NMR (CDCl_3) (less polar) 1.45 (4s, 12H), 4.25 (dd, 1H), 4.60 (m, 2H), 5.65 (d, 1H), 7.25 (bd, 3H), 7.50 (d, 2H), 9.70 (s, 1H).

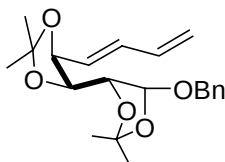
**2.16/2.17****Thioacetal alkene (2.16/2.17)**

The aldehyde **2.15** (0.404 g, 1.15 mmol) was dissolved in anhydrous THF (10 mL). The resulting solution was added dropwise at 0 °C, to a mixture of vinylmagnesium bromide (3 mL of a 1M solution in THF, 3.42 mmol) in THF (10 mL). The reaction was stirred for 1 h at this temperature then poured into saturated aqueous NH₄Cl and extracted with ether. The organic phase was washed with brine, dried (Na₂SO₄), and concentrated *in vacuo*. FCC of the residue afforded **2.16/2.17** as a 1:2 mixture (0.417 g, 96%). Further FCC of the mixture provided separate samples of **2.16** and **2.17**. For **2.16**: ¹H NMR (CDCl₃) δ (less polar) 1.50 (4s, 12H), 2.78 (t, 1H), 4.30 (dd, 2H), 4.50 (bd, 1H), 5.25 (d, 1H), 5.45 (d, 2H), 5.96-6.10 (m, 1H), 7.15-7.35 (m, 3H), 7.45-7.55 (m, 2H); **2.17** (more polar) 1.45 (4s, 12H), 3.0 (s, 1H), 4.0 (d, 1H), 4.19 (t, 1H), 4.29 (d, 2H), 4.40 (bt, 1H), 5.23 (d, 1H), 5.36 (dd, 2H), 5.70-5.99 (m, 1H), 7.15-7.35 (m, 3H), 7.39-7.61 (m, 2H)

**2.19****Allylsilane (2.19)**

Grubb's catalyst 2nd generation, (34 mg, 0.04 mmol) in CH₂Cl₂ (5 mL) was injected at rt, into a degassed solution of **2.18** (105 mg, 0.20 mmol) and allyltrimethylsilane (0.19 mL, 1.2 mmol), in CH₂Cl₂ (5 mL). After 2 h at this temperature, the reaction was quenched

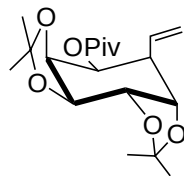
by addition of DMSO (1 mL), stirred for an additional 5 h and concentrated *in vacuo*. The residue was purified by FCC to afford **2.19** (0.115 g, 94 %); ^1H NMR (CDCl_3) δ 0.0 (s, 9H), 1.35 (2s, 6H), 1.50 (2s, 6H), 1.60 (d, 2H), 2.05 (d, 1H), 4.05-4.25 (m, 2H), 4.31 (d, 1H), 4.40 (d, 1H), 4.63 (d, 1H), 5.29 (dd, 1H), 5.44 (dd, 1H), 5.78-5.99 (m, 1H), 7.15-7.45 (m, 9H), 7.5-7.65 (d, 1H).



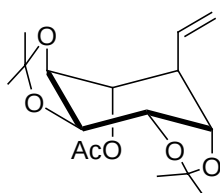
2.20

Diene (2.20)

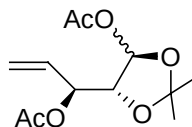
Compound **2.19** (200 mg, 0.30 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.6 g, 2.7 mmol), and freshly activated, powdered 4A molecular sieves (600 mg) in anhydrous CH_2Cl_2 (6 mL), was stirred under an argon atmosphere for 15 min at rt., then cooled to 0 °C. Methyl triflate (0.26 mL, 2.1 mmol) was introduced, and the reaction warmed to rt and stirred for an additional 18 h, at which time, Et_3N (1 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 afforded **2.20** (105 mg, 88 %). ^1H NMR (C_6D_6) δ 1.37 (d, 6H), 1.60 (d, 6H), 4.01 (dd, 1H), 4.37 (d, 1H), 4.45-4.63 (m, 2H), 4.73 (d, 1H), 4.98-5.20 (m, 3H), 5.56 (d, 1H), 5.85 (dd, 1H), 6.13-6.35 (m, 1H), 7.15-7.59 (m, 5H); ^{13}C NMR (C_6D_6) δ 25.9, 27.3, 28.5, 29.3, 69.3, 78.5, 79.7, 98.8, 109.6, 110.9, 119.5, 129.1, 129.4, 129.8, 134.2, 135.9, 137.2.

**2.23** *neo*-inositol**6-deoxy-1,2,3,4-di-*O*-isopropylidene-5-*O*-pivaloyl-6-*C*-ethenyl-*D*-neo-inositol (2.23)**

Compound **2.22** (0.12 mmol, 0.060 g), 2,6-di-*tert*-butyl-4-methylpyridine (1.1 mmol, 0.22 g), and freshly activated, powdered 4Å molecular sieves (250 mg) in anhydrous CH₂Cl₂ (2 mL), was stirred under an argon atmosphere for 15 min at rt, then cooled to 0 °C. Methyl triflate (0.82 mmol, 0.093 ml) was introduced, and the reaction warmed to rt and stirred for an additional 18 h, at which time, Et₃N (1 mL) was added. The mixture was diluted with ether, washed with saturated aqueous NaHCO₃ and brine, dried (Na₂SO₄), filtered and evaporated under reduced pressure. FCC of the residue afforded **2.20** (30 mg, 75 %). ¹H NMR (300MHz, CD₃OD): δ 1.1 (s, 6H), 1.42 (s, 3H), 1.52 (s, 3H), 1.76 (s, 3H), 2.99 (ddd, 1H), 4.28 (q, 1H), 4.4 (d, 1H), 4.55 (s, 1H), 5.2 (m, 2H), 5.6 (d, 1H), 6.18 (m, 1H).

**2.26** *D*-Chiro inositol**6-deoxy-1,2,3,4-di-*O*-isopropylidene-5-*O*-pivaloyl-6-*C*-ethenyl-*D*-chiro-inositol (2.26)**

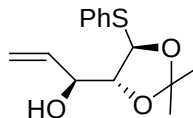
Allylsilane **2.25** (0.12 mmol, 0.055 g) was subjected to the procedure that was used for the preparation of **2.23**. FCC of the crude product afforded **2.26** (25 mg, 69%). ¹H NMR (500MHz, CD₃OD): δ 1.3 (d, 6H), 1.5 (s, 3H), 1.6 (s, 3H), 1.8 (s, 3H), 2.4 (t, 1H), 3.95 (q, 1H), 4.29 (q, 1H), 4.42 (q, 1H), 4.58 (q, 1H), 5.23 (m, 3H), 5.75 (m, 1H).



1,2-O-isopropylidene acetal

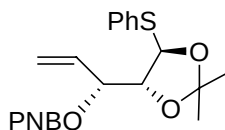
2.29**1,3-Di-O-Acetyl-1,2-O-isopropylidene-4,5-dideoxy-4-eno-L-threo-pentose (2.29)**

To a solution of **2.28** (6.24 g, 20.8 mmol) in THF (100 mL) was added *n*-BuLi (33 mL of a 2.5 M solution in THF, 83.2 mmol) dropwise at -78°C , under an atmosphere of argon. The reaction was stirred at this temperature for 1 h, then pyridine (6.73 mL, 83.2 mmol), acetic anhydride (15.7 mL, 83.2 mmol) and DMAP (2.50 g, 20 mmol) were added. The mixture was warmed to -40°C , stirred for additional 1 h at this temperature, then poured into ice-cold 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 **2.29** as an approximately 1:1 mixture of diastereomers (4.60 g, 86%). A portion of this mixture was subjected to further FCC for characterization purposes. For less polar component: $R_f = 0.80$ (20% EtOAc/PE); $[\alpha]_D -20.6$ (*c* 2.5, CHCl_3); ^1H NMR (CDCl_3) δ 1.41, 1.51 (s, 3H), 2.09, 2.13 (2s, 6H), 4.23 (dd, 1H, $J = 3.4$, $J = 3.5$ Hz), 5.31 (d, 1H, $J = 10.6$ Hz), 5.39 (d, 1H, $J = 17.2$ Hz), 5.53 (t, 1H, $J = 7.6$ Hz), 5.73 (m, 1H), 6.20 (d, 1H $J = 3.4$ Hz); ^{13}C NMR (CDCl_3) δ 21.0, 21.1, 27.1, 30.5, 73.1, 82.8, 96.3, 113.7, 120.1, 131.9, 170.2, 170.2. ESMS (*m/z*) 281.1 ($\text{M}+\text{Na}$). For more polar component: $R_f = 0.70$ (20% EtOAc/PE); $[\alpha]_D -80.3$ (*c* 4.0, CHCl_3); ^1H NMR (CDCl_3) δ 1.40, 1.51 (both s, 6H), 2.80, 2.11 (both s, 3H each), 4.23 (dd, 1H, $J = 3.5$, $J = 10.6$ Hz), 5.29 (d, 1H $J = 10.6$ Hz), 5.37 (d, 1H, $J = 17.3$ Hz), 5.54 (t, 1H, $J = 7.7$ Hz), 5.70 (m, 1H), 5.20 (d, 1H, $J = 3.5$ Hz); ^{13}C NMR (CDCl_3) δ 21.3, 21.4, 26.2, 28.3, 72.9, 80.1, 93.4, 113.0, 120.3, 131.9, 169.9, 170.0; ESMS (*m/z*) 281.1 ($\text{M}+\text{Na}$).

**2.30**

3-O-Acetyl-1,2-O-isopropylidene-4,5-dideoxy-4-eno-L-threo-pentose-S-phenyl-monothiohemiacetal (2.30)

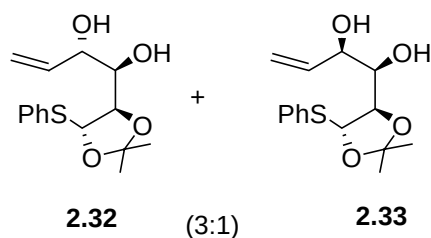
BF₃.OEt₂ (3.05 mL, 24.2 mmol) was slowly added at -78°C , under argon, to a solution of **2.29** (4.17 g, 16.2 mmol) and thiophenol (4.15 mL, 40.4 mmol), in anhydrous CH₂Cl₂ (70 mL). The mixture was warmed to -40°C , and stirring was continued at this temperature for 1 h (or until the TLC indicated complete disappearance of the starting material). The reaction mixture was quenched by addition of Et₃N (3 mL), then poured into 1N aqueous NaOH and extracted with ether. The organic phase was washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. FCC of the residue gave **2.30** (4.40 g, 88%); $R_f = 0.7$ (15% EtOAc/PE); $[\alpha]_D +118.7$ (c 1.2, CHCl₃); ¹H NMR (CDCl₃) δ 1.50, 1.57 (each 3H, both s), 2.12 (3H, s), 4.25 (1H, t, $J = 5.6$ Hz), 5.34 (1H, d, $J = 6.5$ Hz), 5.35 (1H, d, $J = 10.8$ Hz), 5.42 (1H, d, $J = 17.6$ Hz), 5.49 (1H, t, $J = 5.9$ Hz), 5.79 (1H, m), 7.34 (3H, m), 7.54 (2H, d, $J = 7.1$ Hz); ¹³C NMR (CDCl₃) δ 21.6, 26.8, 27.8, 74.1, 82.2, 86.2, 112.9, 120.9, 128.2, 129.6, 132.5, 132.5, 134.6, 170.4; ESMS (m/z) 331.1 (M+Na).

**2.31**

1,2-O-isopropylidene-3-O-p-nitrobenzoyl-4,5-dideoxy-4-eno-D-erythro-pentose-S-phenyl-monothiohemiacetal (2.31)

NaOMe (100 mg, 1.85 mmol) was added to a solution of **2.30** (2.23 g, 7.24 mmol) in anhydrous MeOH (20 mL). The reaction was stirred at rt for 2 h and the pH was then adjusted to 7 by addition of a solution of HCl in methanol. The mixture was concentrated under reduced pressure and the residue purified by FCC to give the derived alcohol (1.93 g, 99%); $R_f = 0.50$ (15% EtOAc/PE); $[\alpha]_D +158$ (c 0.9, CHCl₃); ¹H NMR (CDCl₃) δ 1.40, 1.43 (each 3H, both s), 2.19 (1H, bs), 3.96 (1H, dd, $J = 4.0$ Hz), 4.13 (1H, m), 5.18 (1H, dt, $J = 1.2, 10.5$ Hz), 5.31 (1H, dt, $J = 1.4, 17.2$ Hz), 5.33 (1H, d, $J = 6.6$ Hz), 5.84 (1H, m), 7.20 (3H, m), 7.43 (2H, d, $J = 7.1$ Hz); ¹³C NMR (CDCl₃) δ 26.2, 27.5, 71.9, 83.4, 85.8, 112.1, 117.4, 127.7, 128.5, 129.2, 131.8, 134.2, 136.8; ESIHRMS calcd for C₁₄H₁₈O₃NaS (M+Na) 289.0874, found 289.0887.

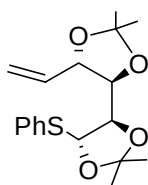
Diisopropylazodicarboxylate (2.05 mL, 10.6 mmol) was added dropwise at 0 °C to a mixture of the product from the previous step (1.88 g, 7.05 mmol), Ph₃P (2.2 g, 8.46 mmol) and *p*-nitrobenzoic acid (1.77 g, 10.6 mmol) in anhydrous toluene (30 mL). The reaction was maintained at this temperature for 2 h, then quenched with saturated aqueous NaHCO₃. The mixture was then extracted with ether and the organic phase was washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. FCC of the residue gave **2.31** (2.81 g, 98%); $R_f = 0.85$ (15% EtOAc/PE); $[\alpha]_D +142$ (c 0.65, CHCl₃); ¹H NMR (CDCl₃) δ 1.34, 1.47 (each 3H, both s), 4.26 (1H, q, $J = 4.3$ Hz), 5.35 (1H, d, $J = 10.6$ Hz), 5.38 (1H, d, $J = 6.3$ Hz), 5.37-5.42 (1H, d, $J = 17.2$ Hz), 5.70 (1H, t, $J = 5.4$ Hz), 5.95 (1H, m), 7.24 (3H, m), 7.41 (2H, dd, $J = 1.1, 1.5$ Hz), 8.20 (2H, d, $J = 8.7$ Hz), 8.24 (2H, d, $J = 8.7$ Hz); ¹³C NMR (CDCl₃) δ 26.3, 27.5, 75.4, 82.2, 85.9, 112.6, 120.6, 123.8, 128.0, 129.3, 131.1, 131.4, 132.3, 135.5, 152.1, 164.1; ESIHRMS calcd for C₂₁H₂₁NO₆NaS (M+Na) 438.0987, found 438.0996.



1,2-O-isopropylidene-5,6-dideoxy-5-eno-L-lyxo-hexose-S-phenyl-monothiohemiacetal (2.32) and 1,2-O-isopropylidene-5,6-dideoxy-5-eno-D-ribo-hexose-S-phenyl-monothiohemiacetal (2.33)

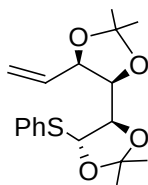
Alkene **2.31** (2.71 g, 6.28 mmol) was dissolved in a 5/1 mixture of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (35 mL). The solution was cooled to -78°C and treated with a stream of O_3 in O_2 until TLC indicated the complete disappearance of the starting material. The reaction was then purged with nitrogen, and Ph_3P (3.29 g, 12.5 mmol) was added. The mixture was warmed to rt, stirred for 1 h at this temperature, and concentrated under reduced pressure. The crude material was dried under high vacuum and dissolved in anhydrous THF (30 mL). The resulting solution was added dropwise at 0°C , to a mixture of vinylmagnesium bromide (50 mL of a 1M solution in THF, 50.0 mmol) in THF (60 mL). The reaction was stirred for 1 h at this temperature then poured into saturated aqueous NH_4Cl and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. FCC of the residue afforded **2.32/2.33** as a 3:1 mixture (0.90 g, 60%). Further FCC of the mixture provided separate samples of **2.32** and **2.33**. For **2.32**: $R_f = 0.53$ (40% EtOAc/PE); $[\alpha]_D +127.4$ (c 0.9, CHCl_3); ^1H NMR (CDCl_3) δ 1.40, 1.47 (each 3H, both s), 2.40 (2H, bd, $J = 7.7$ Hz), 3.62 (1H, bd, $J = 4.4, 8.8$ Hz), 4.14 (1H, t, $J = 5.3$ Hz), 4.25 (1H, bs), 5.24 (1H, dt, $J = 1.3, 10.6$ Hz), 5.4 (1H, dt, $J = 1.4, 17.3$ Hz), 5.51 (1H, d, $J = 6.0$ Hz), 5.90 (1H, m), 7.22 (3H, m), 7.45 (2H, m); ^{13}C NMR (CDCl_3) δ 26.1, 27.7, 71.8, 74.1, 81.6, 86.0, 111.9, 118.0, 127.6, 129.2, 131.7, 134.7, 136.8;

ESIHRMS calcd for $C_{15}H_{20}O_4NaS$ ($M+Na$) 319.0980, found 319.1031. For **2.33**: R_f = 0.30 (40% EtOAc/PE); $[\alpha]_D +392.5$ (c 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.49, 1.55 (each 3H, both s), 2.29 (1H, d, J = 3.6 Hz), 2.38 (1H, d, J = 4.4 Hz), 3.81 (1H, m), 4.23 (1H, t, J = 5.7 Hz), 4.30 (1H, m), 5.30 (1H, dt, J = 1.2, 10.5 Hz), 5.40 (1H, dt, J = 1.3, 17.3 Hz), 5.65 (1H, d, J = 5.9 Hz), 6.01 (1H, m), 7.30 (3H, m), 7.51 (2H, d, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 26.1, 27.7, 73.8, 74.0, 81.6, 85.8, 111.9, 118.3, 127.7, 129.2, 131.7, 134.3, 136.5; ESIHRMS calcd for $C_{15}H_{20}O_4NaS$ ($M+Na$) 319.0980, found 319.0982.

**2.34**

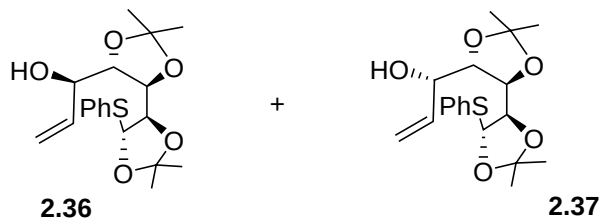
1,2,3,4-Di-O-isopropylidene-5,6-dideoxy-5-eno-L-lyxo-hexose-S-phenyl-monothiohemiacetal (2.34)

A solution of diol **2.32** (0.599 g, 2.16 mmol), dimethoxypropane (5.30 mL, 43.2 mmol) and camphorsulphonic acid (0.05 g, 0.22 mmol) in anhydrous CH_2Cl_2 (20 mL) was stirred at 0 °C for 1 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The organic extract was dried (Na_2SO_4) and concentrated under reduced pressure. FCC of the residue provided **2.34** (0.592 g, 87%); R_f = 0.70 (15% EtOAc/PE); $[\alpha]_D -11.3$ (c 0.16, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34, 1.36, 1.39, 1.47 (each 3H, all s), 3.85 (1H, dd, J = 4.7, 8.1 Hz), 4.14 (1H, dd, J = 4.8, 5.6 Hz), 4.42 (1H, dd, J = 7.0, 7.9 Hz), 5.19 (1H, dt, J = 1.0, 10.4 Hz), 5.38 (1H, dt, J = 1.1, 17.2 Hz), 5.48 (1H, d, J = 5.7 Hz), 5.81 (1H, m), 7.22 (5H, m), 7.45 (2H, m); ^{13}C NMR ($CDCl_3$) δ 26.5, 27.1, 27.3, 27.8, 79.5, 80.4, 81.3, 85.5, 110.1, 112.2, 119.0, 127.6, 129.2, 131.8, 134.5, 135.7; ESMS (m/z) 359.1 ($M+Na$).

**2.35**

1,2,3,4-Di-O-isopropylidene-5,6-dideoxy-5-eno-D-ribo-hexose-S-phenyl-monothiohemiacetal (2.35)

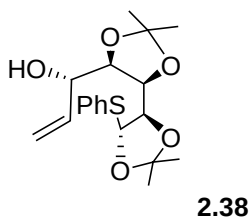
Treatment of diol **2.33** (0.232 g, 0.84 mmol) following the procedure that was described for **2.34**, provided **2.35** (0.23 g, 82%); $R_f = 0.60$ (15% EtOAc/PE); ^1H NMR (CDCl_3) δ 1.37, 1.45, 1.52, 1.58 (each 3H, all s), 4.09 (1H, dd, $J = 6.0, 8.6$ Hz), 4.17 (1H, dd, $J = 4.2, 9.6$ Hz), 4.72 (1H, t, $J = 6.2$ Hz), 5.32 (1H, dt, $J = 1.4, 10.5$ Hz), 5.45 (1H, dt, $J = 1.5, 17.2$ Hz), 5.66 (1H, d, $J = 4.2$ Hz), 6.01 (1H, m), 7.30 (3H, m), 7.51 (2H, d, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ 25.7, 26.9, 28.0, 28.3, 78.7, 79.0, 80.1, 87.7, 109.4, 112.6, 118.4, 127.3, 129.1, 129.2, 131.5, 133.0, 135.3. ESIHRMS calcd for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{NaSSi}$ ($\text{M}+\text{Na}$) 359.1293, found 359.1297.



1,2,3,4-Di-O-isopropylidene-6,7-dideoxy-6-eno-D-gulo-heptose-S-phenyl-monothiohemiacetal (2.36) and 1,2,3,4-Di-O-isopropylidene-6,7-dideoxy-6-eno-L-manno-heptose-S-phenyl-monothiohemiacetal (2.37)

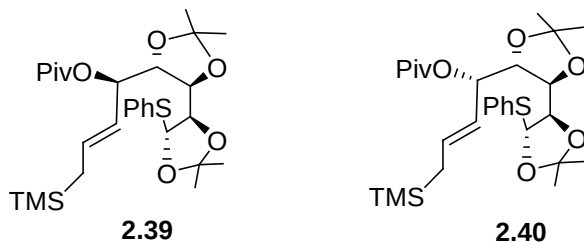
Treatment of alkene **2.34** (0.592 g, 1.9 mmol) following the ozonolysis-Grignard reaction sequence that was described for the preparation of **2.32/2.33** provided **2.36/2.37** as an approximately 2/1 inseparable mixture of alcohols (0.42 g, 66%); $R_f = 0.55$ (25%

EtOAc/PE). ^1H NMR (CDCl_3) δ 1.40, 1.41, 1.43, 1.44, 1.47, 1.49, 1.57, 1.58, 1.60 (12H, all s), 2.40 (0.5H, bd, $J = 8.3$ Hz), 2.59 (0.5H, bs, $J = 3.6$ Hz), 4.04 (1H, dd, $J = 6.4$, 11.5 Hz), 4.09 (1H, dd, $J = 6.8$, 10.4 Hz), 4.16 (0.5H, t, $J = 5.7$ Hz), 4.20 (0.5H, t, $J = 5.6$ Hz), 4.25 (1H, m), 5.26 (0.5H, dt, $J = 1.4$, 10.6 Hz), 5.27 (0.5H, dt, $J = 1.4$, 10.5 Hz), 5.40 (1H, dt, $J = 1.5$, 17.3 Hz), 5.61 (1H, dd, $J = 3.7$, 5.1 Hz), 5.97 (1H, m), 7.31 (3H, m), 7.65 (2H, m); ^{13}C NMR (CDCl_3) δ 26.4, 26.7, 27.2, 27.3, 27.4, 27.4, 27.7, 27.9, 29.8, 71.8, 73.2, 78.9, 81.7, 81.8, 82.1, 82.5, 86.4, 86.8, 110.4, 110.5, 112.4, 112.6, 116.9, 117.4, 127.6, 129.2, 131.7, 134.5, 136.4, 137.3; ESIHRMS calcd for $\text{C}_{19}\text{H}_{26}\text{O}_5\text{NaS}$ ($\text{M}+\text{Na}$) 389.1399, found 389.1396.



1,2,3,4-Di-O-isopropylidene-6,7-dideoxy-6-eno-L-talo-heptose-S-phenyl-monothiohemiacetal (2.38)

Treatment of alkene **2.35** (0.208g, 0.66mmol) following the ozonolysis-Grignard reaction sequence that was described for the preparation of **2.32/2.33** provided alcohol **2.38** (0.15 g, 63%); $R_f = 0.76$ (20% EtOAc/PE); $[\alpha]_D +89$ (c 0.97, CHCl_3); ^1H NMR (CDCl_3) δ 1.26, 1.37, 1.45, 1.51 (each 3H, all s), 2.47 (1H, d, $J = 6.9$ Hz), 4.02 (1H, dd, $J = 6.1$, 9.1 Hz), 4.10 (1H, dd, $J = 4.0$, 6.0 Hz), 4.48-4.50 (2H, m), 5.15 (1H, dt, $J = 1.6$, 10.6 Hz), 5.36 (1H, dt, $J = 1.6$, 17.3 Hz), 5.53 (1H, d, $J = 4.5$ Hz), 5.96 (1H, m), 7.23 (3H, m), 7.46 (2H, d, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ 25.2, 26.8, 27.6, 28.3, 69.6, 78.4, 79.6, 80.1, 88.3, 109.3, 112.8, 116.0, 127.4, 129.1, 131.6, 135.2, 137.9; ESIHRMS calcd for $\text{C}_{19}\text{H}_{26}\text{O}_5\text{NaS}$ ($\text{M}+\text{Na}$) 389.1399, found 389.1385.

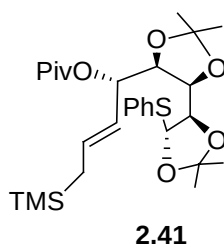


1,2,3,4-Di-O-isopropylidene-5-O-pivaloyl-6,7,8-trideoxy-8-trimethylsilyl-6(E)-eno-D-*gulo*-octose-S-phenyl-monothiohemiacetal (2.39) and 1,2,3,4-Di-O-isopropylidene-5-O-pivaloyl-6,7,8-trideoxy-8-trimethylsilyl-6(E)-eno-L-*manno*-octose-S-phenyl-monothiohemiacetal (2.40)

Grubb's catalyst 2nd generation, (39 mg, 0.05 mmol) in CH₂Cl₂ (3 mL) was injected at rt, into a degassed solution of mixture **2.36/2.37** (320 mg, 0.93 mmol) and allyltrimethylsilane (0.89 mL, 10.8 mmol), in CH₂Cl₂ (10 mL). After 2 h at this temperature, the reaction was quenched by addition of DMSO (1 mL), stirred for an additional 5 h and concentrated *in vacuo*. The residue was purified by FCC to afford an approximately 2:1 mixture of products (0.369 g, 95%); *R_f* = 0.82 (15% EtOAc/PE); ¹H NMR (CDCl₃) δ 0.0 (9H, s), 1.37, 1.38, 1.39, 1.48, 1.53 (12H, all s), 1.39-1.50 (2H, m), 2.25 (1H, bm), 3.90-4.22 (4H, m), 5.35 (1H, m), 5.55 (0.4H, d, *J* = 5.3 Hz), 5.56 (0.6H, d, *J* = 5.5 Hz), 5.75 (1H, m), 7.22-7.30 (3H, m), 7.50 (2H, m); ¹³C NMR (CDCl₃) δ 1.68, 1.71, 23.2, 23.3, 26.5, 26.6, 27.2, 27.5, 27.8, 73.0, 73.8, 82.1, 82.3, 86.4, 110.2, 110.4, 112.3, 126.5, 127.1, 127.5, 127.6, 129.2, 131.5, 131.8, 132.0, 134.7; ESIHRMS calcd for C₂₃H₃₆O₅NaSSi (M+Na) 475.1950, found 475.1938.

DMAP (15 mg, 0.12 mmol), pyridine (0.34 mL, 4.2 mmol) and pivaloyl chloride (0.44 mL, 3.6 mmol) were added to a solution of the product from the previous step (269 mg, 0.59 mmol), in dry dichloromethane (10 mL). The mixture was stirred at rt for 12 h and then poured into water and extracted with ether. The organic phase was washed with

brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. FCC of the residue gave an approximately 2:1 inseparable mixture of **2.39/2.40** (220mg, 72%); R_f = 0.85 (15% EtOAc/PE); ¹H NMR (CDCl₃) δ 0.0 (9H, s), 1.21 (9H, s), 1.39, 1.41, 1.43, 1.44, 1.48, 1.54, 1.56 (12H, all s), 1.45-1.52 (2H, m buried under singlets), 4.00 (0.65H, t), 4.04 (0.35H, dd, J = 5.5, 6.8 Hz), 4.19 (2H, m), 5.28-5.39 (2H, m), 5.57 (1H, d, J = 5.2 Hz), 5.85 (1H, m), 7.29 (3H, m), 7.54 (2H, m); ¹³C NMR (CDCl₃) δ -1.78, 23.4, 23.5, 26.3, 26.6, 27.4, 27.5, 27.6, 27.7, 27.9, 74.0, 74.9, 80.2, 80.8, 82.1, 82.3, 85.9, 86.2, 110.5, 110.6, 112.3, 112.4, 122.4, 123.0, 127.5, 127.6, 129.1, 131.7, 131.8, 134.4, 134.5, 135.1; ESIHRMS calcd for C₂₈H₄₄O₆NaSSi (M+H) 559.2526, found 559.2528.

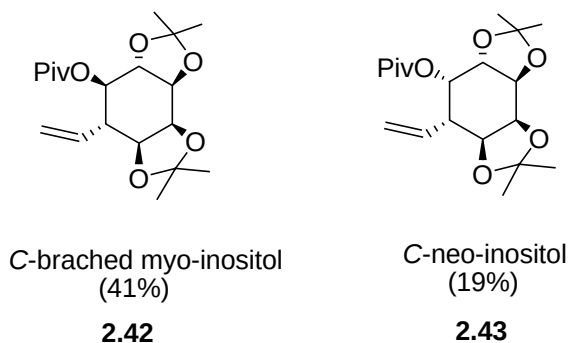


1,2,3,4-Di-*O*-isopropylidene-5-*O*-pivaloyl-6,7,8-trideoxy-8-trimethylsilyl-6(*E*)-eno-*L*-talo-octose-*S*-phenyl-monothiohemiacetal (2.41)

Allylic alcohol **2.38** (63 mg, 0.18mmol) was subjected to the metathesis procedure that was used in the preparation of **2.38/2.40**. FCC of the crude product afforded the cross-metathesis product (0.074 g, 90%); R_f = 0.67 (10%EtOAc/PE). $[\alpha]_D$ +51.2 (c 0.66, CHCl₃); ¹H NMR (CDCl₃) δ 0.0 (9H, s), 1.32, 1.44, 1.55, 1.57 (each 3H, all s), 1.45-1.50 (2H, m buried under singlets), 2.40 (1H, bd, J = 5.7), 4.03 (1H, dd, J = 6.1, 8.6 Hz), 4.09 (1H, dd, J = 4.6, 5.9 Hz), 4.42-4.47 (1H, m), 4.50 (1H, dd, J = 4.3, 8.6 Hz), 5.45 (1H, dd, J = 6.3, 15.4 Hz), 5.62 (1H, d, J = 4.3), 5.79 (1H, m), 7.22-7.30 (3H, m), 7.51 (2H, m). ¹³C NMR (CDCl₃) δ -1.62, 23.3, 25.4, 27.0, 27.7, 28.3, 69.9, 78.4, 79.9, 80.8, 88.3, 109.1,

112.8, 127.4, 128.0, 129.2, 129.9, 131.6, 135.4; ESIHRMS calcd for $C_{23}H_{36}O_5NaSSi$ (M+Na) 451.1974, found 451.1955.

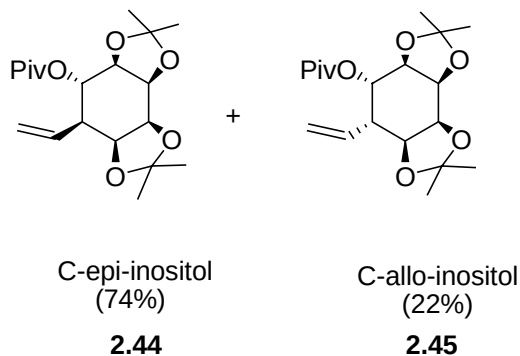
Treatment of a sample of the material from the previous step (152 mg, 0.34 mmol) following the pivaloylation procedure that was used for **2.36/2.37**, provided **2.41** (141 mg, 65%); $R_f = 0.84$ (15% EtOAc/PE); ^1H NMR ($CDCl_3$) δ 0.0 (9H, s), 1.24 (9H, s), 1.34, 1.44, 1.53, 1.57 (each 3H, all s), 1.47-1.53 (2H, m, buried under singlets), 4.03 (1H, dd, $J = 6.0, 9.3$ Hz), 4.21 (1H, dd, $J = 3.1, 6.0$ Hz), 4.26 (1H, dd, $J = 4.2, 9.3$ Hz), 5.42 (1H, m), 5.55 (1H, dd, $J = 4.0, 7.5$ Hz), 5.62 (1H, d, $J = 4.2$ Hz), 5.85 (1H, m), 7.27 (3H, m), 7.53 (2H, m); ^{13}C NMR ($CDCl_3$) δ 1.77, 23.3, 25.6, 26.9, 27.2, 27.4, 28.4, 39.1, 72.0, 78.2, 79.7, 79.8, 88.4, 109.4, 112.8, 124.1, 127.2, 129.1, 131.5, 132.9, 178.2; ESMS (m/z) 554.2 (M+NH₄).



6-Deoxy-1,2,3,4-di-O-isopropylidene-5-O-pivaloyl-6-C-ethenyl-D-myo-inositol (2.42)
and **6-deoxy-1,2,3,4-di-O-isopropylidene-5-O-pivaloyl-6-C-ethenyl-D-neo-inositol (2.43)**

A mixture of **2.39/2.40** (316 mg, 0.61 mmol) was subjected to the procedure that was used for the preparation of **2.23**. FCC of the residue afforded **2.42** (79 mg, 41%) and **2.43** (37 mg, 19%). For **2.42**: $R_f = 0.22$ (15% EtOAc/PE); $[\alpha]_D -27.5$ (c 1.0, $CHCl_3$); ^1H NMR (C_6D_6) δ 1.18 (3H, s), 1.2 (9H, s), 1.38, 1.41, 1.45 (each 3H, all s), 2.61 (1H, dt, $J =$

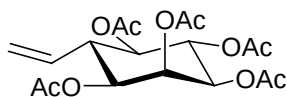
7.3, 6.3 Hz), 3.37 (1H, dd, $J = 3.1, 10.0$ Hz), 3.80 (1H, dd, $J = 5.4, 6.5$ Hz), 4.27 (1H, dd, $J = 3.1, 5.2$ Hz), 4.48 (1H, t, $J = 9.7$ Hz), 5.50 (1H, bd, $J = 10.6$ Hz), 5.12 (1H, bd, $J = 17.1$ Hz), 5.21 (1H, t, $J = 8.9$ Hz), 5.70 (1H, ddd, $J = 17.3, 10.3, 7.9$ Hz); ^{13}C NMR (CDCl_3) δ 25.4, 26.9, 27.2, 27.3, 27.6, 38.9, 51.2, 72.4, 73.0, 74.6, 75.3, 78.8, 111.4, 111.6, 118.6, 135.9, 177.9; ESIHRMS calcd for $\text{C}_{19}\text{H}_{31}\text{O}_6$ ($\text{M}+\text{H}$) 355.21, found 355.21. For **2.43**: $R_f = 0.39$ (15% EtOAc/PE); $[\alpha]_D -6.7$ (c 0.18, CHCl_3); ^1H NMR (C_6D_6) δ 1.15 (9H, s), 1.23, 1.33, 1.36, 1.45 (each 3H, all s), 2.27 (1H, m), 3.92 (1H, dd, $J = 4.6, 8.4$ Hz), 4.01 (1H, dd, $J = 1.9, 10.1$ Hz), 4.05 (1H, dd, $J = 2.7, 10.1$ Hz), 4.42 (1H, dd, $J = 2.7, 4.5$ Hz), 5.09 (1H, dt, $J = 1.3, 10.6$ Hz), 5.19 (1H, dt, $J = 1.4, 17.4$ Hz), 5.63 (1H, t, $J = 2.5$ Hz), 5.71 (1H, ddd, $J = 17.2, 10.6, 6.3$ Hz); ^{13}C NMR (C_6D_6) δ 27.0, 27.5, 27.6, 28.0, 29.1, 39.6, 48.4, 69.4, 73.7, 74.3, 74.4, 79.0, 111.2, 111.9, 117.9, 136.0, 176.8; ESIHRMS calcd for $\text{C}_{19}\text{H}_{31}\text{O}_6$ ($\text{M}+\text{H}$) 355.2121, found 355.2119.



1-Deoxy-2,3,4,6-di-O-isopropylidene-6-O-pivaloyl-1-C-ethenyl-D-epi-inositol (2.44)
and 6-deoxy-1,2,3,4-di-O-isopropylidene-5-O-pivaloyl-6-C-ethenyl-D-allo-inositol (2.45)

Allylsilane **2.41** (88 mg, 0.17 mmol) was subjected to the procedure that was used for the preparation of **2.23**. FCC of the crude product afforded recovered **2.41** (10 mg), **2.44** (40 mg, 74% based on recovered **2.41**) and **2.45** (12 mg, 22% based on recovered **2.45**). For

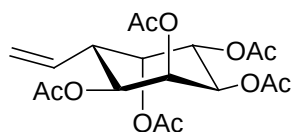
2.44: $R_f = 0.59$ (15% EtOAc/PE); $[\alpha]_D -94.0$ (c 2.2, CHCl_3); ^1H NMR (C_6D_6) δ 1.11 (3H, s), 1.18 (9H, s), 1.30 (3H, s), 1.63 (6H, s), 1.77 (1H, ddd, $J = 3.8, 9.4, 12.7$ Hz), 3.81-3.86 (2H, m), 4.16 (1H, dd, $J = 3.6, 6.8$ Hz), 4.24 (1H, t, $J = 7.4$ Hz), 4.98 (1H, dd, $J = 2.1, 17.2$ Hz), 5.02 (1H, dd, $J = 2.1, 10.2$ Hz), 5.88 (1H, dd, $J = 7.1, 12.4$ Hz), 6.08 (1H, ddd, $J = 2.4, 9.9, 17.2$ Hz); ^{13}C NMR (C_6D_6) δ 24.7, 26.3, 26.8, 27.1, 27.8, 39.0, 48.4, 71.1, 74.5, 74.5, 76.8, 78.9, 109.7, 111.1, 118.4, 136.1, 177.2; ESIHRMS calcd for $\text{C}_{19}\text{H}_{31}\text{O}_6$ ($\text{M}+\text{H}$) 355.2121, found 355.2129. For **2.45:** $R_f = 0.63$ (15% EtOAc/PE) $[\alpha]_D +32.1$ (c 0.95, CHCl_3); ^1H NMR (CDCl_3) δ 1.18 (9H, s), 1.34, 1.41, 1.52, 1.57 (each 3H, s), 2.95 (1H, ddd, $J = 1.5, 6.3, 7.7$ Hz), 4.13 (1H, dd, $J = 2.1, 6.9$ Hz), 4.33 (1H, t, $J = 7.4$ Hz), 4.38 (1H, dd, $J = 3.9, 7.2$ Hz), 4.55 (1H, dd, $J = 3.9, 6.9$ Hz), 4.99 (1H, bs), 5.20 (1H, d, $J = 10.5$ Hz), 5.25 (1H, d, $J = 16.3$ Hz), 5.83 (1H, ddd, $J = 6.4, 10.5, 17.1$ Hz); ^{13}C NMR (CDCl_3) δ 24.3, 25.5, 26.6, 26.8, 27.3, 39.1, 41.2, 73.3 (2C), 73.4, 74.8, 75.2, 109.8, 110.1, 117.3, 136.8, 177.1; ESIHRMS calcd for $\text{C}_{19}\text{H}_{31}\text{O}_6$ ($\text{M}+\text{H}$) 355.2121, found 355.2117.

**2.46**

6-Deoxy-1,2,3,4,5-penta-O-acetyl-6-C-ethenyl-D-myo-inositol (2.46)

Compound **2.42** (37 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (2 mL), and DIBALH (0.16 mL, 0.14 mmol) was introduced at -78°C . The reaction was warmed to rt, stirred an additional 3 h at this temperature, then quenched by addition of saturated aqueous potassium sodium tartrate tetrahydrate. The mixture was stirred until the appearance of two layers, then extracted with CH_2Cl_2 . The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was

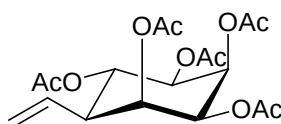
filtered through a plug of silica gel, and the filtrate evaporated to dryness. The residue was dissolved in MeOH (2 mL) and concentrated HCl (0.05 mL) added to the solution. The mixture was stirred for 6 h, then adjusted to pH 7 by addition of a solution of NaOMe in MeOH. The solvent was removed *in vacuo* and pyridine (0.2 mL), EtOAc (2 mL), Ac₂O (0.28 mL, 3 mmol) and DMAP (6 mg, 0.05 mmol) were added to the residue. The reaction mixture was stirred at rt for 12 h, then quenched with MeOH (0.2 mL) and concentrated under reduced pressure. The residue was purified by FCC to afford **2.46** (40 mg, 86%); R_f = 0.42 (30% EtOAc/PE); $[\alpha]_D$ +5.5 (*c* 3.0, CHCl₃); ¹H NMR (C₆D₆) δ 1.61, 1.65, 1.68, 1.72, 1.78 (each 3H, s), 2.93 (1H, dt, J = 11.2, 9.4 Hz), 4.94 (1H, dd, J = 2.6, 11.5 Hz), 4.99 (1H, dd, J = 1.5, 10.0 Hz), 5.06 (1H, dd, J = 1.0, 16.7 Hz), 5.12 (1H, t, J = 10.3 Hz), 5.19 (1H, dd, J = 2.8, 10.5 Hz), 5.52 (1H, ddd, J = 2.3, 9.7, 17.1 Hz), 5.80 (1H, t, J = 10.1 Hz), 5.87 (1H, t, J = 2.6 Hz); ¹³C NMR (C₆D₆) δ 20.5 (3C), 20.6, 20.7, 47.6, 69.0, 69.9, 70.0, 71.2, 71.4, 120.4, 135.1, 169.2, 169.5, 169.5, 170.0, 170.0; ESIHRMS calcd for C₁₈H₂₅O₁₀ (M+H) 401.1448, found 401.1443.

**2.47**

6-Deoxy-1,2,3,4,5-penta-O-acetyl-6-C-ethenyl-D-neo-inositol 2.47

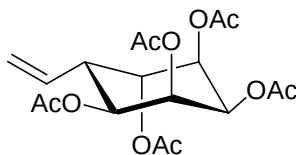
Treatment of **2.43** (37 mg, 0.10 mmol) following the identical three-step procedure that was used for **2.42**, provided **2.47** (38 mg, 90%); R_f = 0.45 (30% EtOAc/PE); $[\alpha]_D$ -6.7 (*c* 0.18, CHCl₃); ¹H NMR (C₆D₆) δ 1.54, 1.60, 1.63, 1.72, 1.74 (each 3H, all s), 3.13 (1H, ddd, J = 2.6, 8.0, 11.1 Hz), 4.89 (1H, d, J = 17.3 Hz), 4.9 (1H, d, J = 10.1 Hz), 5.62 (1H, ddd, J = 7.9, 10.6, 17.2 Hz), 5.6 (1H, dd, J = 2.8, 11.7 Hz), 5.62 (1H, dd, J = 2.9, 10.9

Hz), 5.72 (1H, dd, $J = 2.9, 10.9$ Hz), 5.79 (1H, t, $J = 2.8$ Hz), 6.12 (1H, t, $J = 2.8$ Hz); ^{13}C NMR (CDCl_3) δ 20.8, 20.9 (3C), 21.0, 43.0, 67.9, 68.0, 69.6, 69.7, 70.3, 120.1, 132.7, 169.9, 170.0, 170.2 (2C), 170.5; ESIHRMS calcd for $\text{C}_{18}\text{H}_{25}\text{O}_{10}$ ($\text{M}+\text{H}$) 401.1448, found 401.1439.

**2.48**

1-Deoxy-2,3,4,6-penta-O-acetyl-6-C-ethenyl-D-*epi*-inositol **2.48**

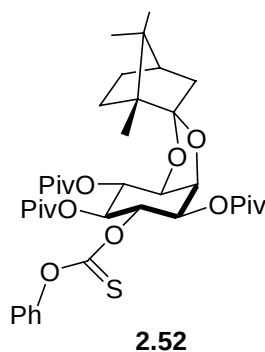
Treatment of **2.44** (74 mg, 0.20 mmol) following the identical three-step procedure that was used for **2.46**, provided **2.48** (66 mg, 80%); $R_f = 0.34$ (30% EtOAc/PE); $[\alpha]_D -8.84$ (c 1.9, CHCl_3); ^1H NMR (C_6D_6) δ 1.66, 1.68, 1.69 (each 3H, all s), 1.73 (6H, s), 1.93 (1H, ddd, $J = 2.9, 8.5, 11.2$ Hz), 4.84 (1H, t, $J = 3.34$ Hz), 4.92 (1H, d, $J = 17.2$ Hz), 4.97 (1H, d, $J = 10.3$ Hz), 5.06 (1H, dd, $J = 3.3, 10.3$ Hz), 5.48 (1H, bt, $J = 3.3$ Hz), 5.68 (1H, ddd, $J = 8.4, 10.3, 17.3$ Hz), 5.8 (1H, t, $J = 10.7$ Hz), 5.84 (1H, bt, $J = 3.3$ Hz); ^{13}C NMR (C_6D_6) δ 20.5, 20.6, 20.7, 20.8, 46.6, 68.2, 68.9, 70.1, 71.2, 71.8, 119.9, 133.6, 169.3, 169.7, 169.8, 169.9, 170.1; ESIHRMS calcd for $\text{C}_{18}\text{H}_{25}\text{O}_{10}$ ($\text{M}+\text{H}$) 401.1448, found 401.1439.

**2.49**

6-Deoxy-1,2,3,4-penta-O-acetyl-6-C-ethenyl-D-*allo*-inositol **2.49**

Treatment of **2.45** (19 mg, 0.05 mmol) following the identical three-step procedure that was used for **2.46**, provided **2.49** (18 mg, 86%); $R_f = 0.32$ (30% EtOAc/PE); $[\alpha]_D +1.92$

(c 1.25, CHCl_3); ^1H NMR (3% v/v $\text{CDCl}_3/\text{C}_6\text{D}_6$) δ 1.58, 1.73, 1.74, 1.74, 1.79 (each 3H, all s), 3.16 (1H, m), 5.03 (1H, dt, $J = 1.1, 10.5$ Hz), 5.11 (1H, dt, $J = 1.2, 17.3$ Hz), 5.38 (1H, t, $J = 3.4$ Hz), 5.41 (1H, dd, $J = 3.6, 5.0$ Hz), 5.46-5.51 (2H, m), 5.60 (1H, ddd, $J = 7.9, 10.5, 17.3$ Hz), 5.69 (1H, bt, $J = 3.4$ Hz); ^{13}C NMR (3% v/v $\text{CDCl}_3/\text{C}_6\text{D}_6$) δ 20.3, 20.6, 20.7 (2C), 20.8, 41.5, 67.9, 68.1 (2C), 69.2, 71.3, 120.0, 133.6, 169.2, 169.4, 169.6, 169.8, 170.0; ESIHRMS calcd for $\text{C}_{18}\text{H}_{25}\text{O}_{10}$ (M+H) 401.1448, found 401.1435.

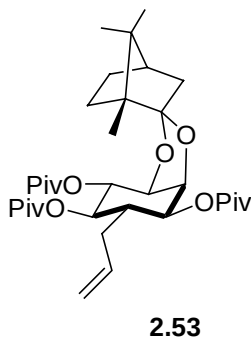


Thionoformate (**2.52**)

Phenyl chlorothionoformate (0.10 mL, 0.77 mmol) was added dropwise to a suspension of the alcohol **2.51** (196 mg, 0.35 mmol) and DMAP (4 mg, 0.04 mmol), in dry toluene (10 mL) at rt. Pyridine (0.14 mL, 1.75 mmol) was then added and the resulting suspension was stirred for 2h at rt. The reaction mixture was then washed with HCl (0.1M) and saturated NaHCO_3 , and the organic extract dried (Na_2SO_4) and concentrated in *vacuo*. FCC of the residue gave **2.52** (0.20 g, 83 %). $R_f = 0.50$ (10 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 0.88 (s, 3H), 0.99 (s, 3H), 1.25 (4s, 27H), 1.40-1.50 (m, 3H), 1.68-1.80 (m, 2H), 1.83-1.98 (m, 3H), 4.10 (t, 1H, $J = 5.97$ Hz), 4.65 (dd, 1H, $J = 4.30, J = 6.38$ Hz), 5.24-5.35 (m, 3H), 6.31 (dd, 1H, $J = 7.7, J = 10.7$ Hz), 6.98-7.26 (m, 2H), 7.28-7.45 (m, 4H); ^{13}C NMR (500 MHz, CDCl_3) δ 9.93, 20.2, 20.2, 26.9, 26.9, 27.0, 27.0, 27.1, 29.3, 38.8, 44.0, 45.1, 48.0, 69.4, 71.8, 72.1, 72.2, 72.9,

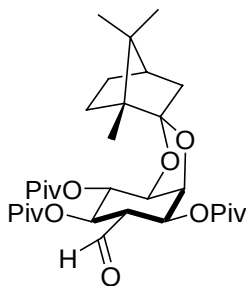
76.8, 77.0, 77.3, 79.0, 121.7, 126.6, 129.5, 129.5, 153.4, 176.5, 177.0, 177.6, 194.5.

HRMS (EI) m/z calcd for $C_{38}H_{54}NaO_{10}S$ ($M + Na$)⁺ 725.3334, found 725.3334.



C-allyl *myo*-inositol (2.53)

A solution of **2.52** (167 mg, 0.24 mmol), allyltributyltin (0.22 mL, 0.72 mmol), AIBN (7.88 mg, 0.05 mmol) and toluene (3.5 mL) was heated at reflux for 18h. The solution was concentrated after which FCC of the residue gave **2.53** (0.85 g, 61%). R_f = 0.69 (10 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (s, 3H), 0.97 (s, 3H), 1.02 (s, 3H), 1.21 (2s, 27H), 1.28-1.47 (m, 2H), 1.60-1.76 (m, 3H), 1.76-1.87 (m, 2H), 2.12-2.30 (m, 2H), 2.46-2.59 (m, 1H), 3.97 (t, 1H, J = 6.21 Hz), 4.44 (dd, 1H, J = 4.38, J = 5.27 Hz), 4.83-5.01 (m, 3H), 5.03-5.13 (m, 2H), 5.60-5.75 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.55, 20.2, 20.3, 26.9, 27.0, 27.1, 27.1, 27.2, 29.2, 30.6, 38.1, 38.7, 38.8, 38.9, 45.0, 45.1, 48.0, 51.7, 68.7, 69.7, 72.8, 73.7, 74.5, 76.8, 77.0, 77.3, 118.1, 119.0, 132.6, 177.0, 177.0, 177.5. HRMS (EI) m/z calcd for $C_{34}H_{54}NaO_8$ ($M + Na$)⁺ 613.3710, found 613.3712.

**2.55****Aldehyde (2.55)**

Treatment of alkene **2.54** (0.070g, 0.12mmol) following the ozonolysis reaction that was described for the preparation of **2.32/2.33** provided aldehyde **2.55** (0.35 g, 51%); R_f = 0.76 (10% EtOAc/PE); ^1H NMR (CDCl_3) δ 0.86 (s, 3H), 0.97 (s, 3H), 1.02 (s, 3H), 1.21 (2s, 27H), 1.28-1.47 (m, 2H), 1.60-1.76 (m, 3H), 1.76-1.87 (m, 2H), 2.12-2.30 (m, 2H), 2.46-2.59 (m, 1H), 4.25 (dd, 1H, J = 5.7, J = 7.56 Hz), 4.51 (dd, 1H, J = 5.23, J = 7.56 Hz), 5.61 (dd, 1H, J = 3.34, J = 5.65 Hz), 5.81 (d, 1H, J = 5.2 Hz), 6.78 (d, 1H, J = 3.34 Hz), 9.67 (s, 1H); ^{13}C NMR (500 MHz, CDCl_3) δ 9.84, 20.1, 20.4, 27.0, 27.0, 27.1, 29.6, 30.9, 38.8, 43.4, 45.2, 47.8, 51.5, 63.8, 70.6, 70.6, 72.4, 74.3, 118.5, 139.9, 147.2, 188.7.

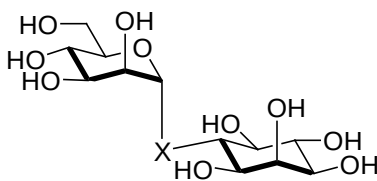
CHAPTER 3

Synthesis of the *C*-pseudodisaccharide of 6- α -D-mannopyranosyl-D-*myo*-inositol

3.1 Introduction

Although several syntheses of the *O*-glycosides subunit of PIM have been reported, the synthesis of a *C*-glycoside analog is not known^{52,53,54}. Recently, Seeberger achieved the first total synthesis of the native PIM₂ and PIM₆ present in the cell wall of *M. tuberculosis*⁵⁵. Herein we present our studies on the synthesis of the *C*-pseudodisaccharide of 6- α -D-mannopyranosyl-D-*myo*-inositol **1.1b**.

3.2 Synthesis of the *C*-pseudodisaccharide of 6- α -D-mannopyranosyl-D-*myo*-inositol



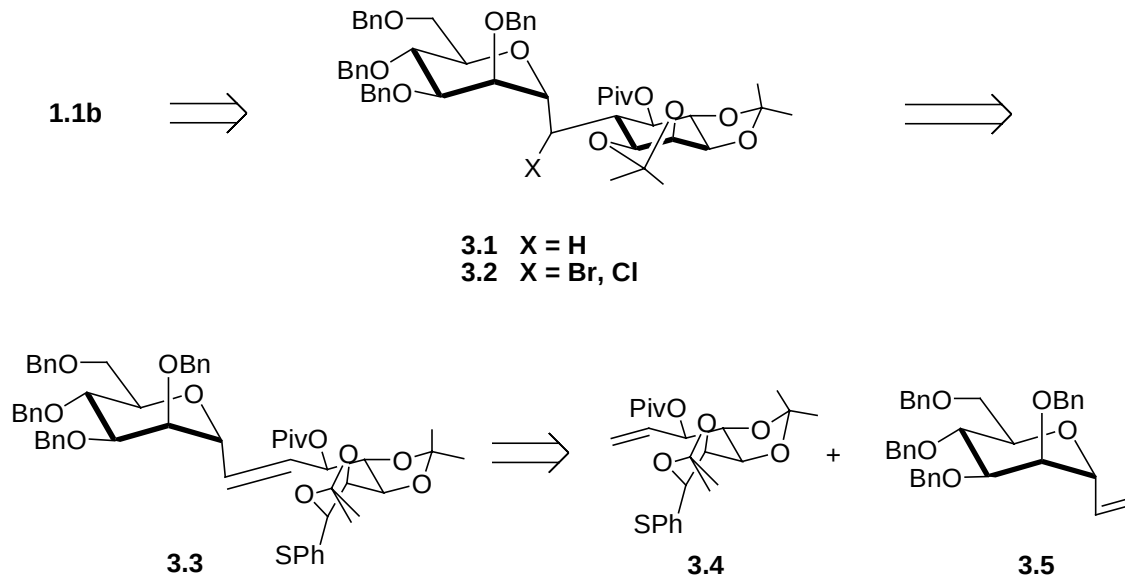
1.1a X = O

1.1b X = CH₂

Figure 3.1 *O*- and *C*- Psueduodisaccharide as PIM Mimetics

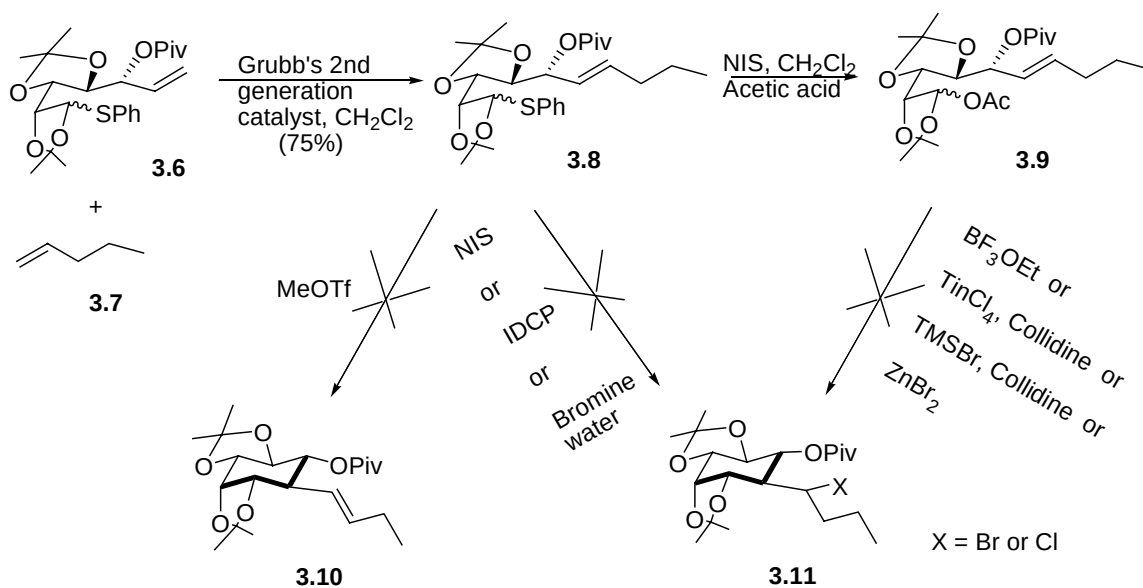
3.2.1 First route: cyclization of the inositol segment

The first approach to the *C*-glycoside **1.1b** was an extension of the *C*-branched inositol synthesis described in Chapter 2. The difference is that the cyclization precursor **3.3** should contain an intact *C*-linked *mannose* segment (**Scheme 3.1**). Precursor **3.3** can be synthesized from **3.4** and **3.5** by cross metathesis reaction.



Scheme 3.1

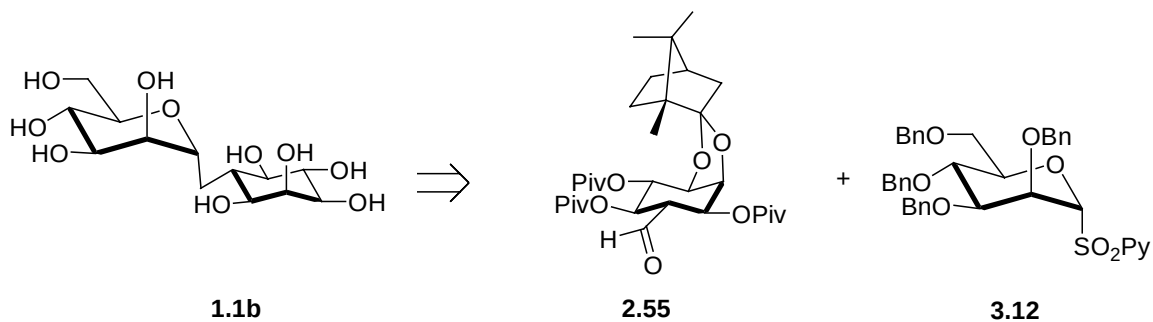
We decided to test these ideas on a model substrate (**Scheme 3.2**). Cross metathesis of **3.6** (obtained by pivaloylation of previously prepared **2.17** (**Scheme 2.4**)) and 1-pentene gave **3.8** in 75% yield. However, treatment of **3.8** under the standard cyclization conditions gave an inseparable mixture of several products. These problems may be due to the low reactivity of the unactivated alkene nucleophile. Different thiophenyl activators like N-bromosuccinimide, IDCP, and bromine water were attempted, but with no success. The thiophenyl group was next replaced with acetate, which could be activated with Lewis acids at lower temperatures. Again the desired product was not obtained.



Scheme 3.2

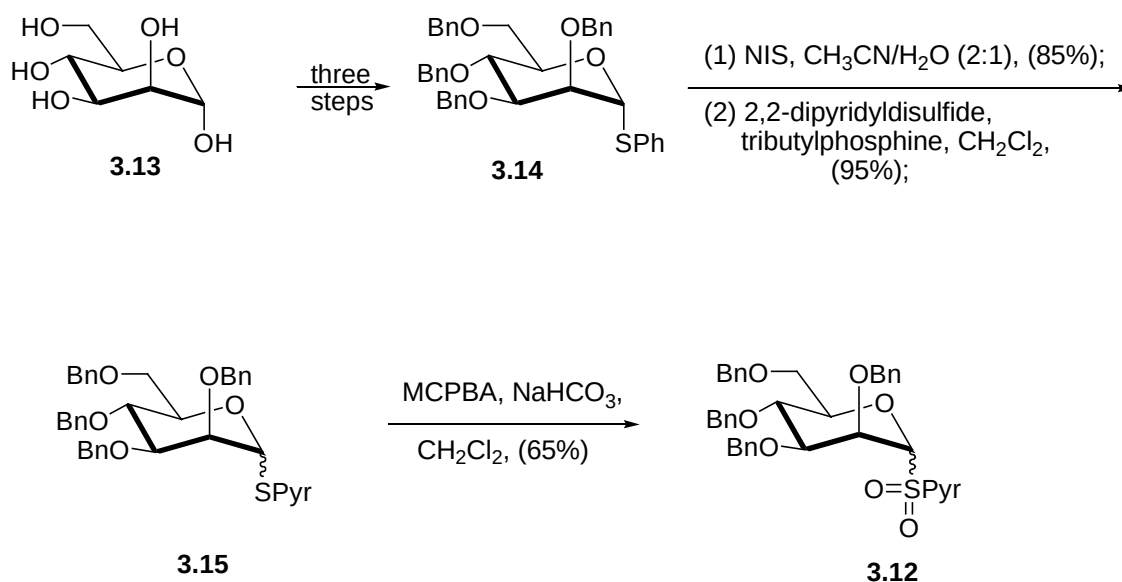
3.2.2 Second route: Coupling of pre-formed *mannose* and *inositol* segments

An alternative route based on glycosyl samarium precursors was next investigated (Scheme 3.3). This psuedo-disaccharide inositol **1.1b** could be realized from aldehyde **2.55** and glycosyl sulfone **3.12**.



Scheme 3.3

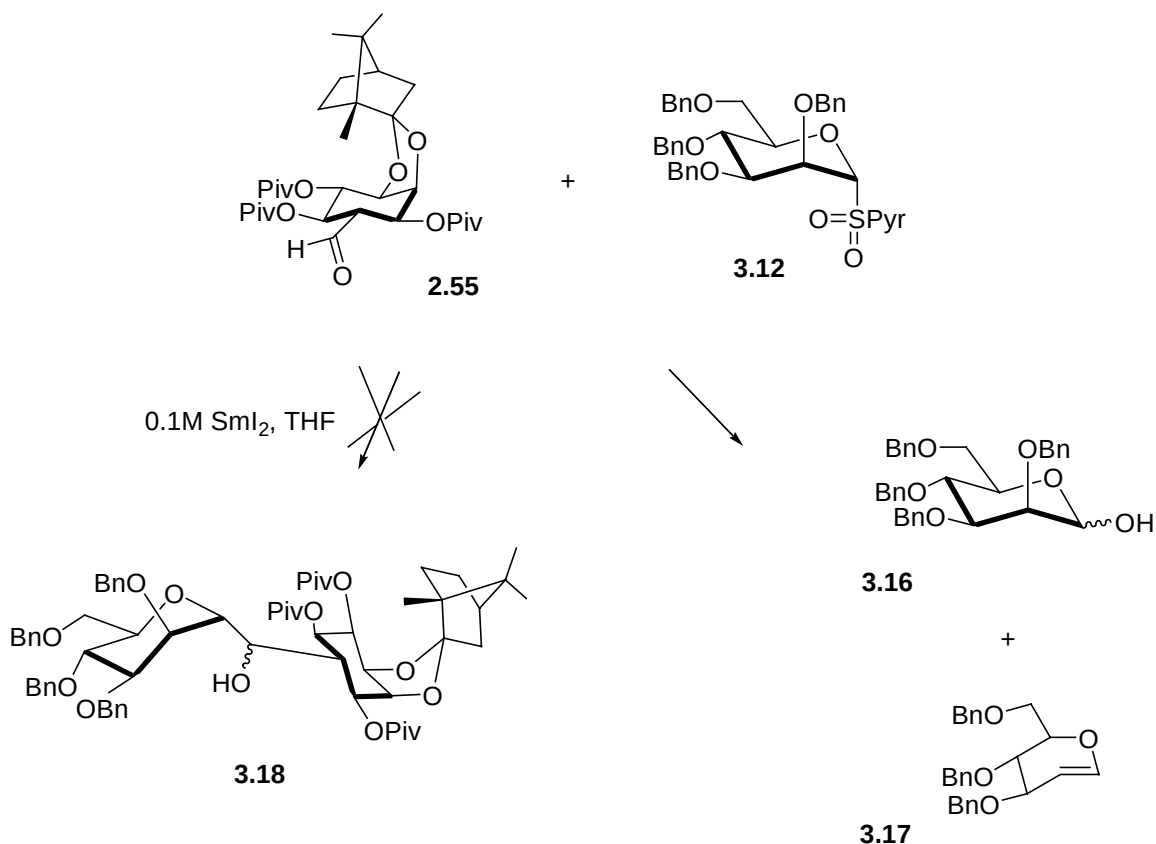
Thioglycoside **3.14** was prepared from *D*-mannose **3.13**, over three steps via a known procedure (**Scheme 3.4**). Treatment of **3.14** with NIS gave the lactol derivative, which was reacted with 2,2-dipyridyldisulfide and tributylphosphine to produce pyridyl sulfide **3.15** as a 1:1 mixture of α and β anomers in 81% yield for two steps. Oxidation of **3.15** with MCPBA provided pyridyl sulfone **3.12** in 65% yield.



Scheme 3.4

The glycosyl samarium coupling of sulfone **3.12** and the previously prepared aldehyde **2.55** was next examined (**Scheme 3.5**). Thus **3.12** and **2.55** were treated under Barbier⁵⁶ conditions using 0.1M SmI₂ in THF. Unfortunately the desired product **3.18** was not obtained. Instead the hemiacetal **3.16** and glycal **3.17** were produced, and the aldehyde **2.55** was recovered. We speculated that the failure of the reaction was due to low reactivity of the aldehyde due to steric hindrance. In order to confirm that we were carrying out the procedure properly, we studied the reaction of **3.12** with two less

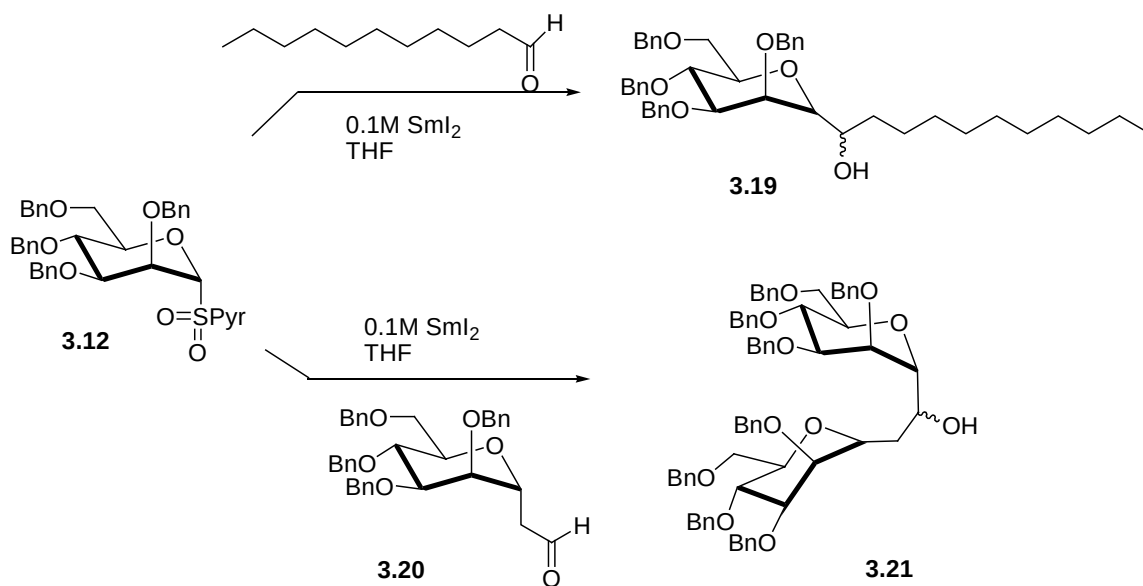
substituted aldehydes undecanal and **3.20** (Scheme 3.6). In both cases the desired compounds were obtained in approximately 85% yield.



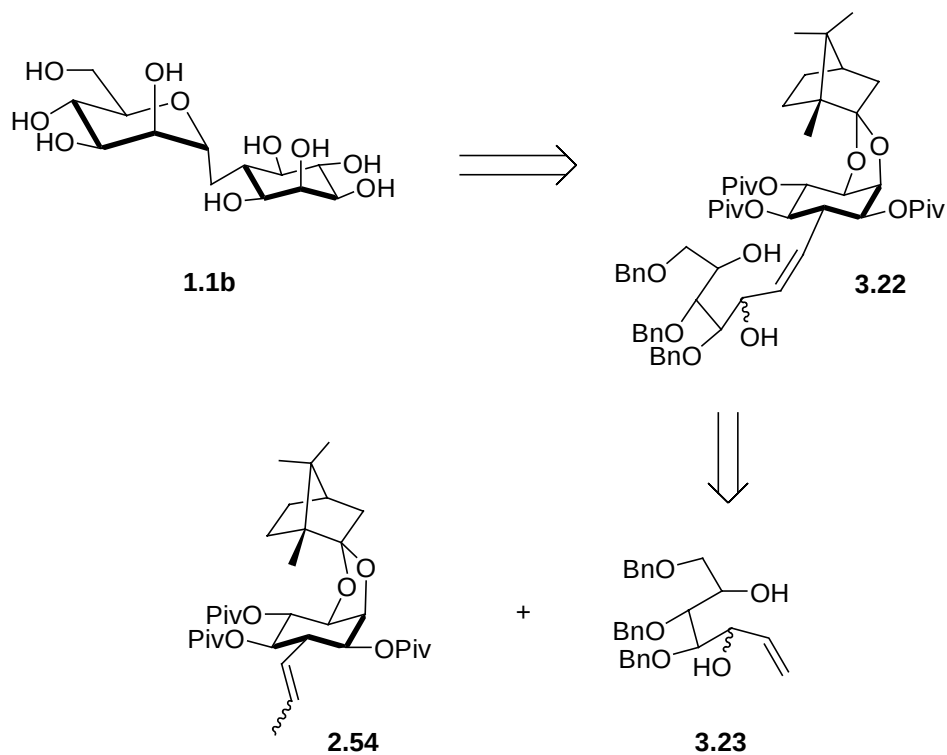
Scheme 3.5

3.2.3 Third route: Cyclization of the *mannose* segment from a hydroxy alkene precursor

The next plan was to obtain the *mannose* segment via the iodo-etherification of an acyclic precursor. An appropriate precursor may be obtained from cross metathesis of previously prepared *myo*-inositol **2.54** and the diol **3.23** (Scheme 3.7). The synthesis of **3.23** will be first discussed (Scheme 3.8).



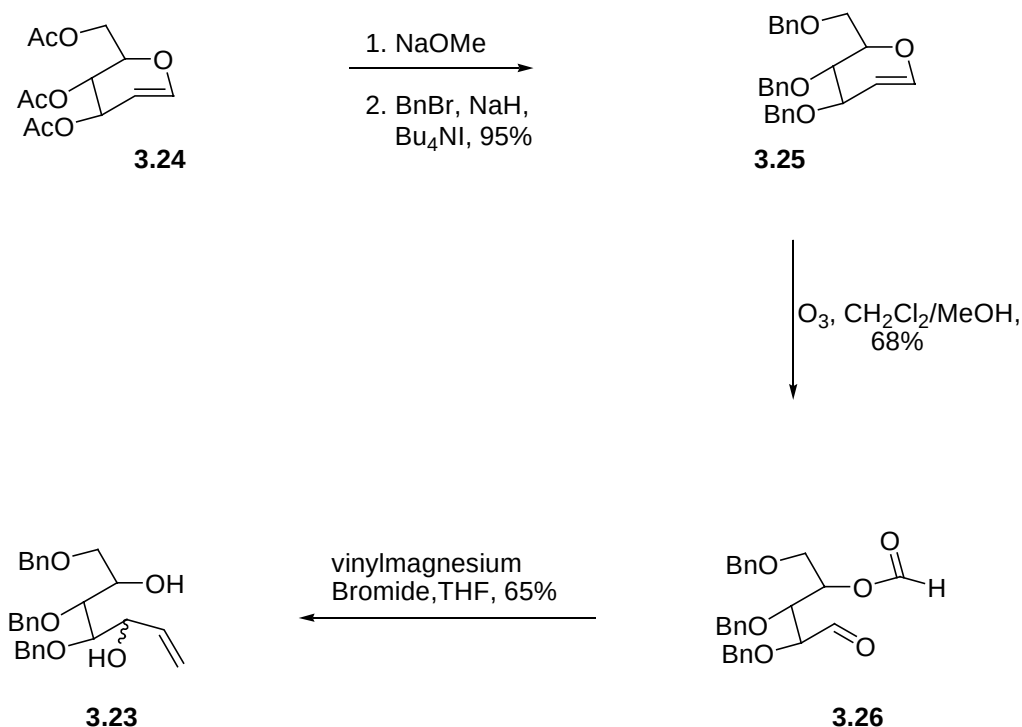
Scheme 3.6



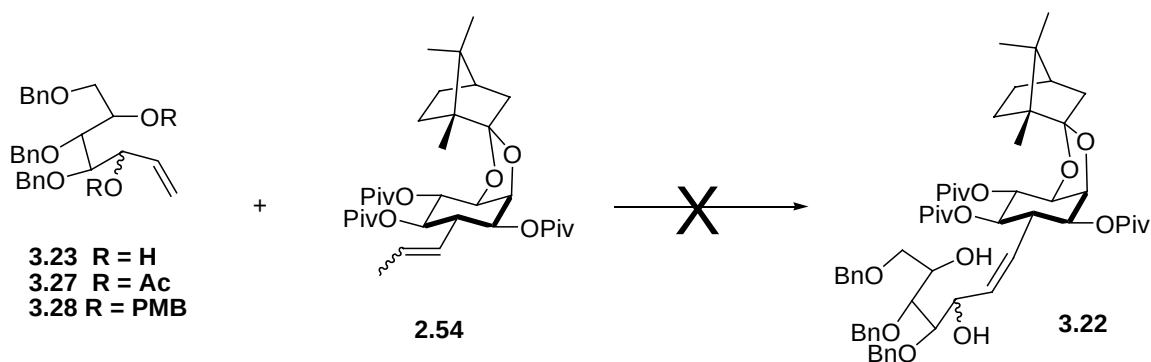
Scheme 3.7

Triacetoxyl glucal **3.24** was deprotected by exposure to sodium methoxide (**Scheme 3.8**). Protection of the resulting triol using benzyl bromide, sodium hydride and tetrabutylammonium iodide in dry DMF gave tri-O-benzyl-D-glucal **3.25**.⁵⁷ Glucal **3.25** was next subjected to ozonolytic cleavage. Treatment of the product with excess vinyl magnesium bromide gave a 1:1 mixture of allylic alcohol **3.23** in 65% yield.

With diol **3.23** and *myo*-inositol **2.54** in hand, we next attempted cross metathesis using Grubb's II catalyst (**Scheme 3.9**). The desired product **3.22** was not obtained. Instead the dimer of **3.23** was formed. The reaction of **2.54** with the acetate derivative **3.27** and di-PMB ether **3.28** were also unsuccessful.



Scheme 3.8

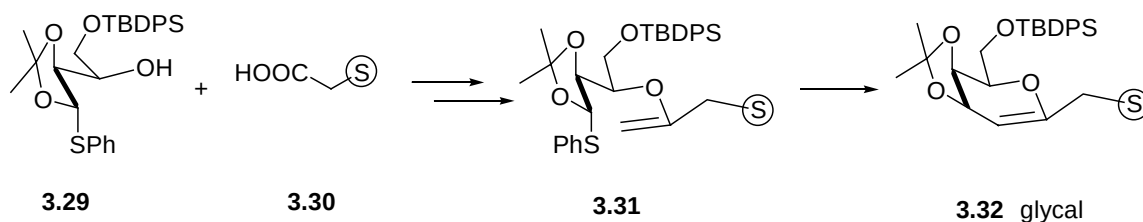


Scheme 3.9

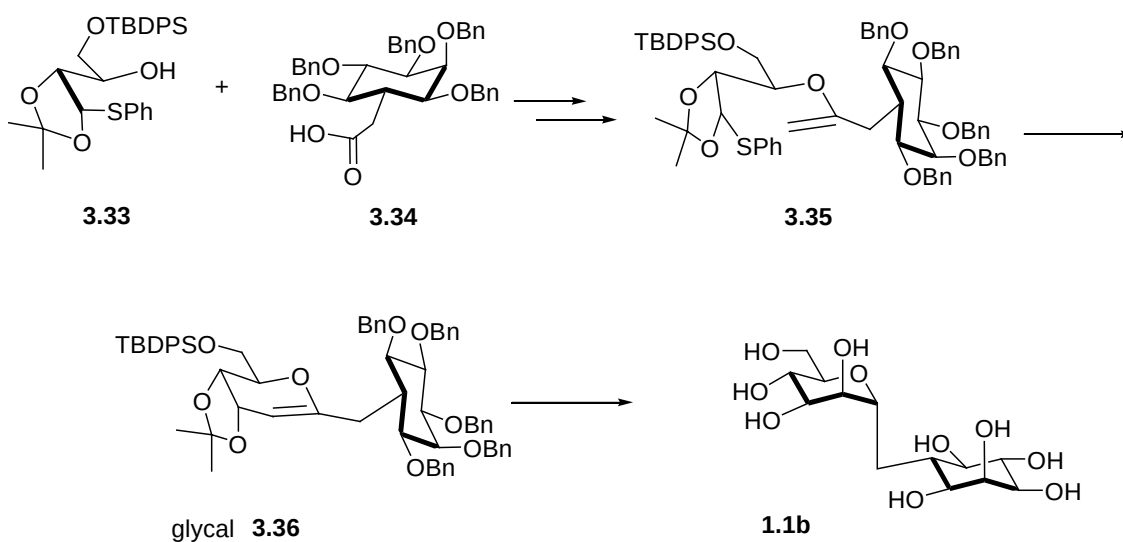
3.3 Formation of the *mannose* segment via an oxocarbenium ion cyclization

As discussed earlier C1 substituted glycals like **3.32** are available through the oxocarbenium ion cyclization of precursors like **3.31** (Scheme 3.10). The glycal **3.32** could be assembled over two steps glycone and aglycone components, **3.29** and **3.30**. We envisaged that the strategy would be applied to the glycal **3.36**, from which the required *manno*- α -C-glycoside **1.1b** could be obtained. The cyclization precursor **3.35** can be derived from alcohol **3.33** and acid **3.34**.

Previous work: C-glycosides via oxocarbenium ion cyclizations



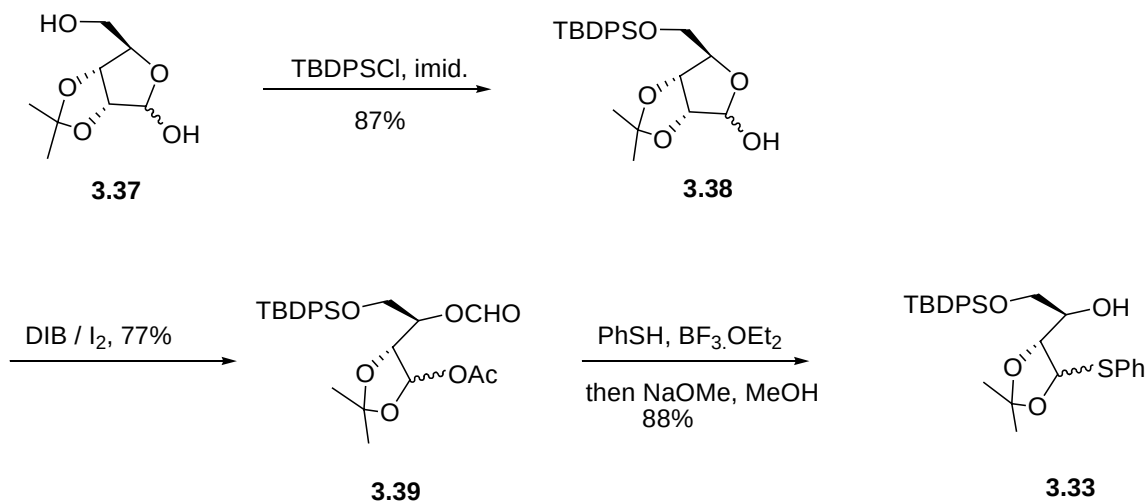
Extension to C-linked glycoinositols



Scheme 3.10

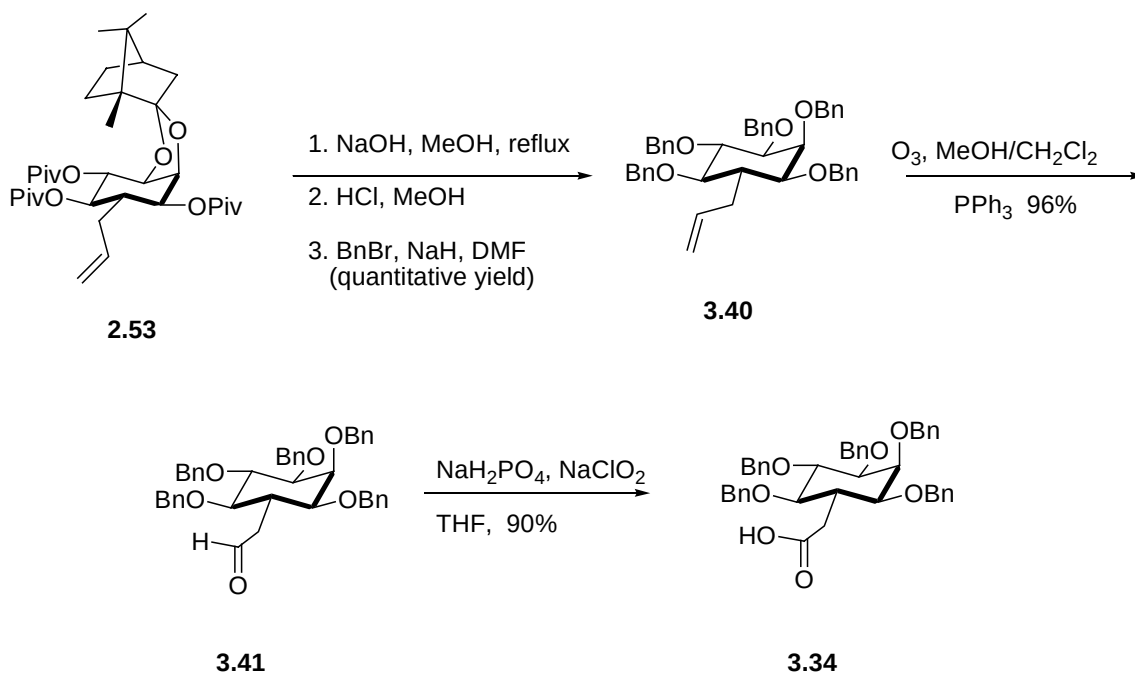
The first goal was the synthesis of the TIA alcohol component **3.33** (**Scheme 3.12**). The key reaction in this synthesis was the Suarez fragmentation of the anomeric alkoxy radical derived from **3.38**.⁵⁸ Acetonation of D-ribose in the presence of catalytic amount of sulfuric acid provided diol **3.37** in 85% yield.⁵⁹ Selective silylation of the primary alcohol was performed by treatment of **3.37** with TBDPSCl (1.1 eq) at rt for 1h.

Exposure of **3.37** to diacetoxy iodobenzene (DIB) and iodine in cyclohexane afforded **3.39** in 77% yield. Thiophenyl exchange of **3.39** was carried out in the presence of benzenethiol and $\text{BF}_3\cdot\text{OEt}_2$, which afforded **3.33** in 88% yield.



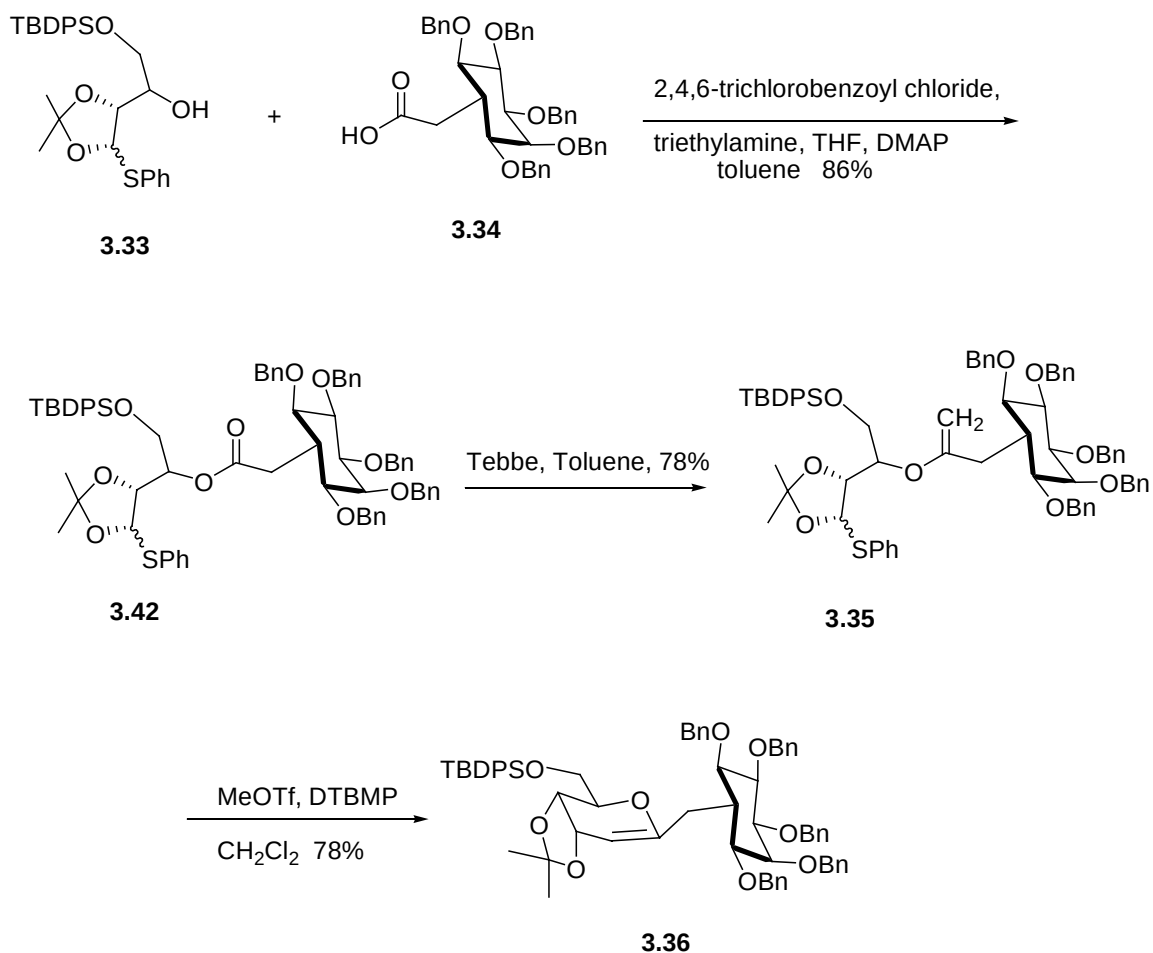
Scheme 3.12

The aglycone segment was next prepared. First protecting group transformation was performed on the allyl *C-myo*-inositol **2.53**. Hydrolysis of the pivalate with sodium hydroxide in dry methanol, followed by the removal of camphor acetal with methanolic hydrochloric acid gave the pentaol derivative. The crude material was protected as the penta-*O*-benzyl ether **3.40**. Oxidative cleavage of alkene **3.40** provided aldehyde **3.41**, which was further oxidized to acid **3.34** upon the treatment with sodium chlorate.



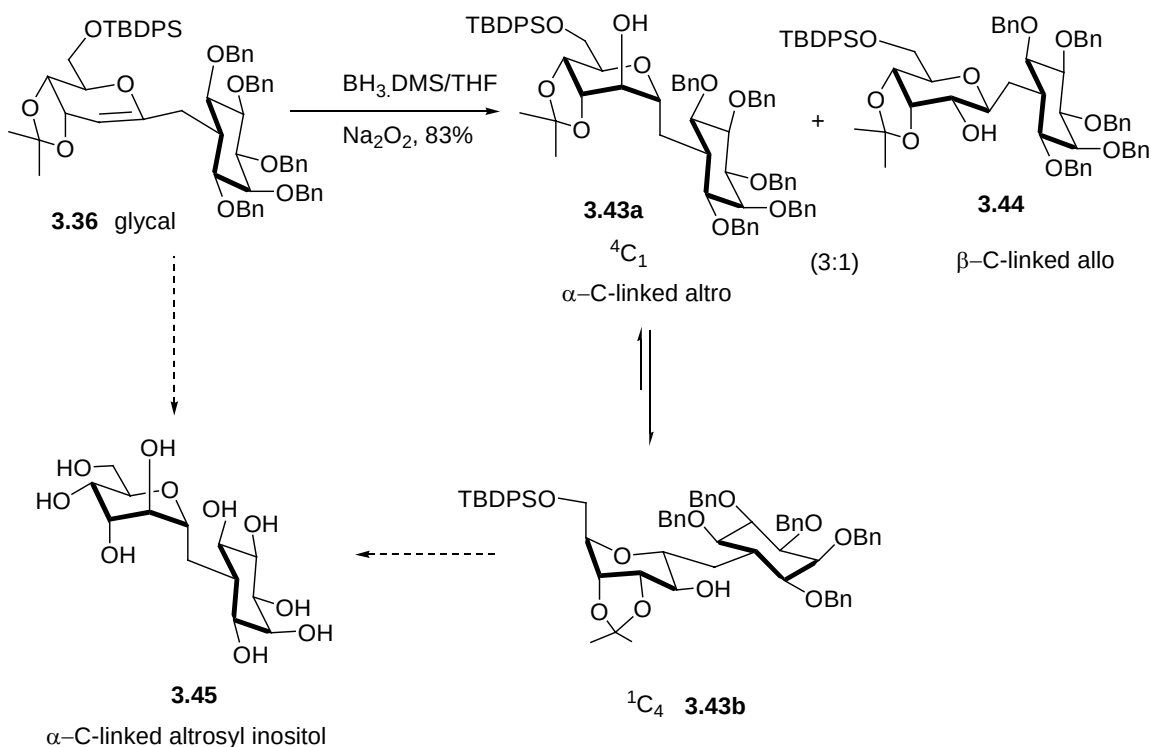
Scheme 3.13

With alcohol **3.33** and acid **3.34** in hand DCC mediated esterification was next attempted (**Scheme 3.14**).⁶⁰ However, the product was obtained in low yield. The Yamaguchi was more successful, providing ester **3.42** in 86% yield. Reaction of **3.42** with the Tebbe reagent yielded **3.35** in 78% yield. Oxocarbenium ion cyclization promoted by methyl triflate and DTBMP furnished **3.36** in 78% yield.



Scheme 3.14

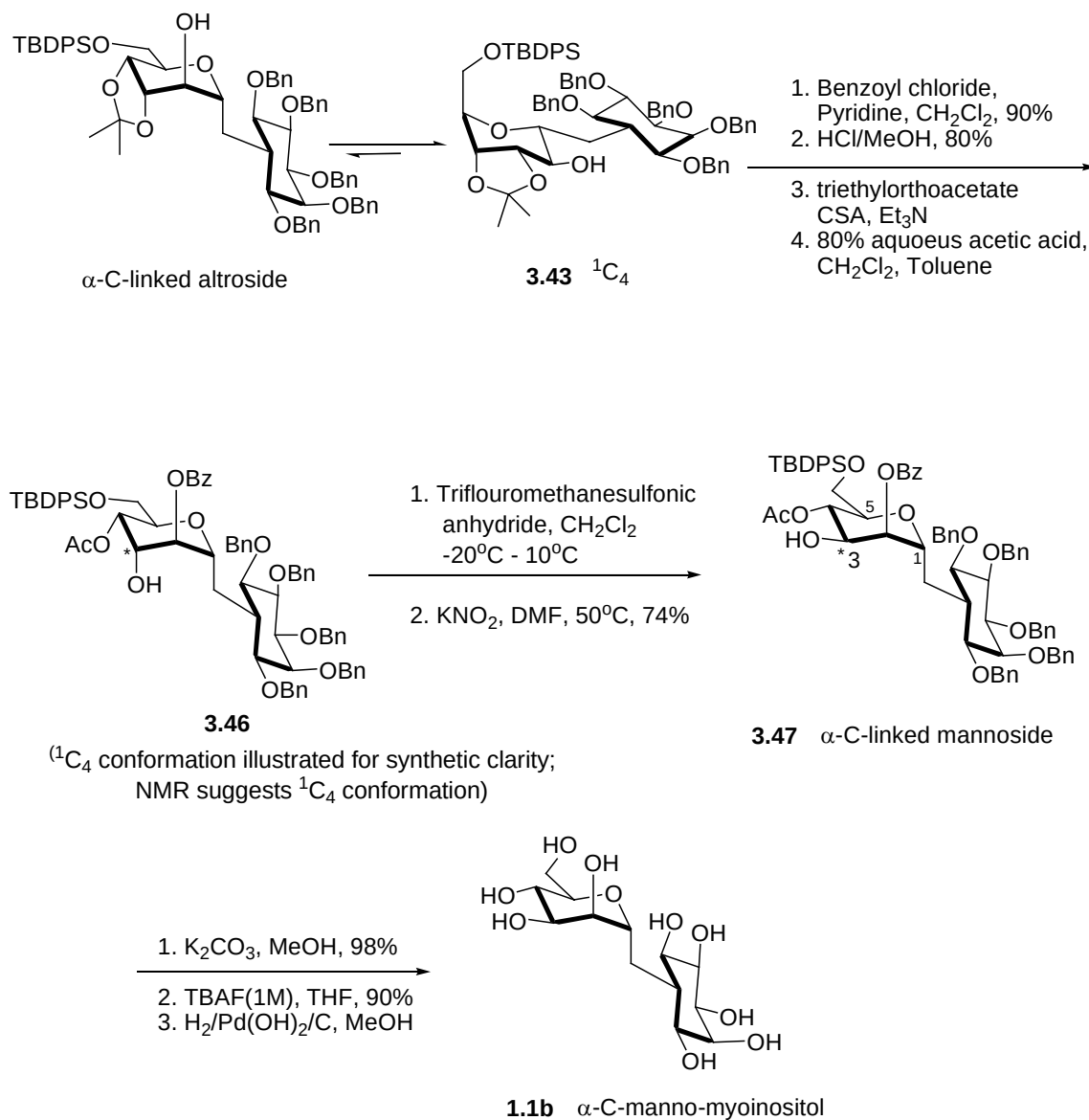
Hydroboration of **3.36** provided α -C-altro-*myo*-inositol **3.43** a and β -C-*allo*-*myo*-inositol **3.44** as a 3:1 mixture in 83% yield. ^1H NMR analysis suggested that the α -linked anomer favors the $^1\text{C}_4$ conformation.



Scheme 3.15

Since the alcohol **3.43** has the α -altro configuration in the glycone segment, the C3 center has to be inverted to obtain the required α -mannose derivative. This was achieved through reaction of a C-3-O-triflate.⁶¹ It has been reported that an ester group on the adjacent carbon is essential for best results in this reaction. Therefore the alcohol in **3.43** was protected as the benzoate ester. Next the acetonide group was cleaved by acidic hydrolysis to provide the diol in 80% yield. Selective protection of the C4 (axial hydroxyl group) was done in two steps. Treatment of the diol with triethylorthoacetate, CSA and triethylamine first gave the orthoester, which on reaction with 80% aqueous acetic acid, dichloromethane and toluene led to alcohol **3.46**. Interestingly **3.46** appears to favor the $^4\text{C}_1$ conformation. Reaction of **3.46** with trifluoromethanesulfonic anhydride

and dry dichloromethane at $-20\text{ }^{\circ}\text{C}$ to $10\text{ }^{\circ}\text{C}$ afforded the triflate derivative. The crude product was treated with potassium nitrite in DMF at $50\text{ }^{\circ}\text{C}$ to give the desired alcohol **3.47** in 74% yield over two steps. Straightforward removal of alcohol protecting groups gave the target α -C-mannopyranosyl-myoinositol **1.1b**.



Scheme 3.16

3.4 NMR Analysis of 3.46 and 3.47

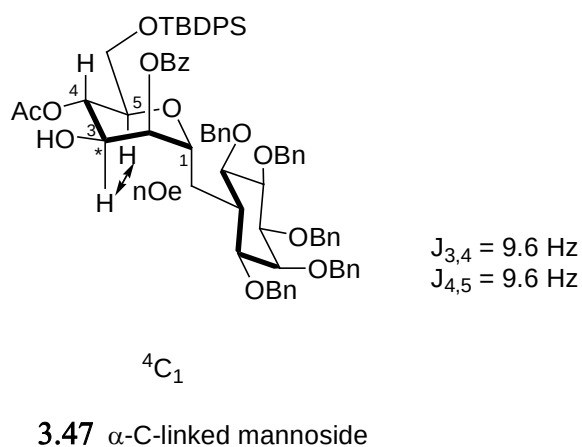
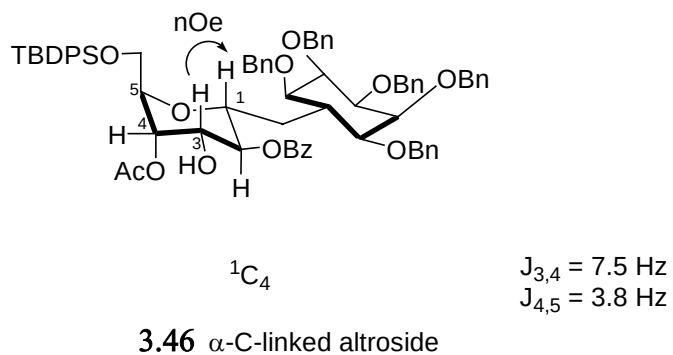
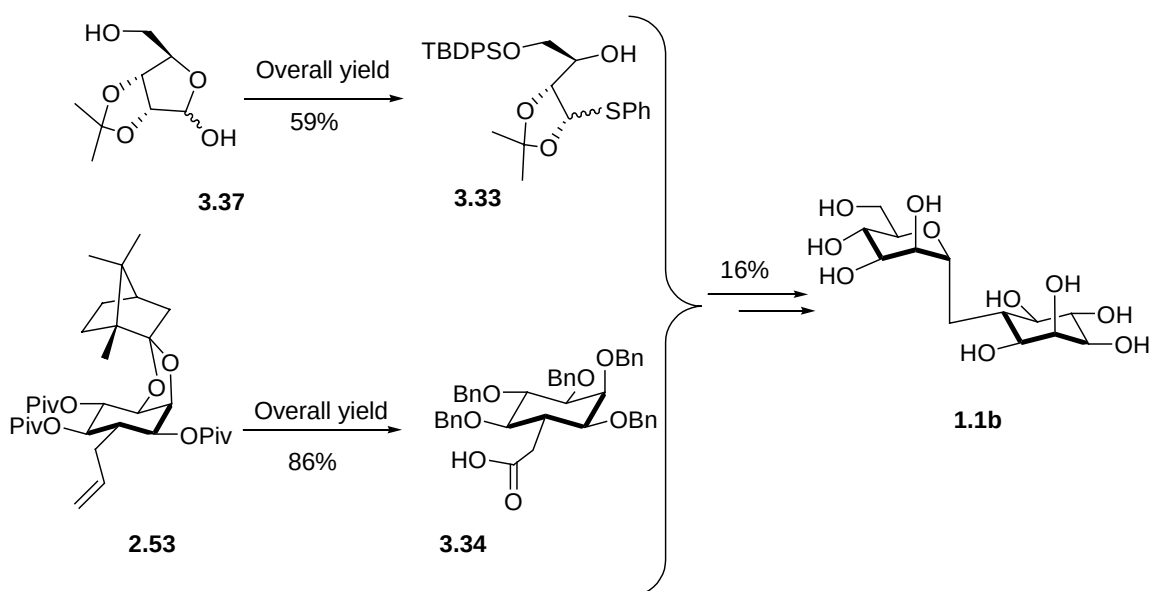


Figure 3.2 NMR analysis of α -C-linked altroside and α -C-linked mannoside

A $J_{4,5}$ value of 3.8 Hz and nOe between H_1 and H_3 supported the α -C-altro configuration in the ${}^1C_4$ conformation for **3.46** (Figure 3.2). The $J_{3,4}$ value of 7.5 Hz is consistent with distortion of the chair geometry. For **3.47** $J_{3,4}$ and $J_{4,5}$ values of 9.6 Hz and a nOe between H_3 and H_5 were in agreement with a mannose configuration in the ${}^4C_1$ conformation.

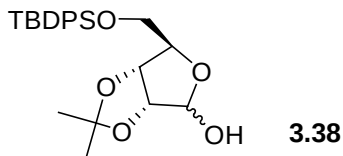
3.5 Summary

The synthesis of the C-pseudodisaccharide of 6- α -D-mannopyranosyl-D-*myo*-inositol **1.1b** was realized from alcohol **3.33** and acid **3.34** over 13 steps and 23% yield. The key steps in this sequence were an oxocarbenium ion-enol ether cyclization to give a C-altral, stereoselective hydroboration-oxidation of the glycal to a α -C-altrose product, and configuration inversion of the latter at the C-3 position via a triflate derivative (**Scheme 3.17**).



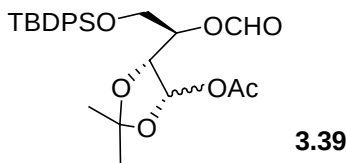
Scheme 3.17

3.6 Experimental



2,3-O-Isopropylidene-5-O-tert-butyldiphenylsilyl- α/β -D-ribofuranose (**3.38**)

A solution of 2,3-O-isopropylidene-D-ribofuranose **3.37** (7.86 g, 41.0 mmol), TBDPSCl (11.4 ml, 41.0 mmol), and imidazole (5.64 g, 85.0 mmol) in anhydrous DMF (100 mL) was stirred at 50 °C for 1.5 h. 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 concentrated under reduced pressure. The residue was purified by FCC to give **3.38** as an inseparable mixture of anomers (15.2 g, 87%): colorless oil; R_f = 0.42 (20% EtOAc/petroleum ether); IR (neat) 3423 cm^{-1} . For **3.38** α : ^1H NMR (300 MHz, CDCl_3) δ 1.06 (s, 9H), 1.33, 1.48 (both s, 3H ea), 3.66 (dd, 1H, J = 2.6, 11.4 Hz), 3.83 (dd, 1H, J = 2.6, 11.4 Hz), 4.29 (bs, 1H), 4.54 (d, 1H, J = 10.6 Hz), 4.61 (d, 1H, J = 6.2 Hz), 4.72 (d, 1H, J = 5.9 Hz), 5.38 (d, 1H, J = 10.3 Hz), 7.43-7.80 (m, 10H); ^{13}C NMR (75 MHz CDCl_3) δ 25.3, 26.8, 27.2, 65.8, 82.0, 87.4, 87.5, 103.6, 112.3, 128.0, 135.9. For **3.38** β : ^1H NMR (300 MHz, CDCl_3) δ (selected Signals) 1.06 (s, 9H), 1.41, 1.56 (both s, 3H ea), 3.94 (d, 1H, J = 11.4 Hz), 4.16 (bs, 1H), 5.67 (dd, 1H, J = 4.0, 11.4); ^{13}C NMR (75 MHz, CDCl_3) δ 25.1, 26.5, 27.2, 66.2, 79.8, 81.6, 82.2, 98.2, 113.3; HRMS(EI) m/z calcd for $\text{C}_{23}\text{H}_{29}\text{O}_5\text{Si}$ (M- CH_3) 413.1777, found 413.1773.

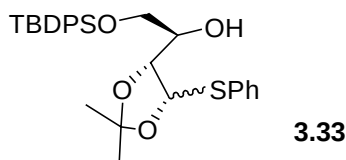


1-O-Acetyl-4-O-tert-butyl-1-diphenylsilyl-3-O-formyl-1,2-O-isopropylidene-D-erythrohemiacetal (3.39)

A solution of compound **3.38** (5.82 g, 13.6 mmol) in anhydrous cyclohexane (90 mL) containing diacetoxyiodosobenzene (4.39 g, 15.2 mmol) and iodine (3.45 g, 13.5 mmol) was stirred under an atmosphere of argon at rt for 4 h. The reaction mixture was then diluted with water and extracted with ether. The organic phase was washed with aqueous Na₂SO₃ and brine, then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was separated using FCC to give major (4.00 g, 61%) and minor (1.08g, 16%) isomers of **3.39**. The major isomer was isolated as a white solid; R_f = 0.23 (5% EtOAc/petroleum ether); IR (film) 1732, 1752 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.09 (s, 9H), 1.41, 1.50 (both s, 3H ea), 2.04 (s, 3H), 3.91 (m, 2H), 4.52 (dd, 1H, J = 1.8, 5.9 Hz), 5.18 (q, 1H, J = 4.8 Hz), 6.27 (d, 1H, J = 1.8 Hz), 7.38-7.70 (m, 10H), 8.02 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 21.9, 27.5, 28.1, 62.9, 73.4, 81.2, 96.8, 113.6, 128.4, 130.4, 133.6, 136.2, 160.3, 170.2. HRMS (EI) m/z calcd for C₂₄H₃₁O₅Si (M-C₂H₃O₂) 427.1941, found 427.1932.

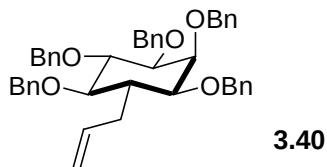
The minor isomer was isolated as a colorless oil; R_f = 0.28 (5% EtOAc/petroleum ether); ¹H NMR (300 MHz, CDCl₃) δ 1.09 (s, 9H), 1.42, 1.51 (both s, 3H ea), 2.04 (s, 3H), 3.98 (m, 2H), 4.54 (dd, 1H, J = 3.3, 9.2 Hz), 5.33 (m, 1H), 6.33 (d, 1H, J = 3.3 Hz), 7.40-7.70 (m 10H), 7.91 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 21.3, 26.3, 27.1, 28.4,

63.4, 71.3, 76.0, 93.5, 112.7, 127.8, 129.9, 133.3, 135.7, 159.5, 170.0; ESMS m/z 504.3 $[M + NH_4]^+$.



4-O-tert-Butyldiphenylsilyl-1,2-O-isopropylidene-D-erythro-S-phenyl monothiohemiacetal (3.33)

$BF_3 \cdot OEt_2$ (1.60 mL, 12.7 mmol) was slowly added to a solution of **3.39** (4.10 g, 8.4 mmol) and thiophenol (2.16 mL, 21.1 mmol) in anhydrous CH_2Cl_2 (40 mL) at $-78^\circ C$ under a atmosphere of argon. The reaction was warmed at $-40^\circ C$ and stirred at this temperature for 1 h, or until TLC indicated complete disappearance of the starting material. Triethylamine (6.0 mL) was then added, and the reaction mixture was diluted with satd. Aq $NaHCO_3$ and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was dissolved in methanol (50 ml) and treated with a solution of NaOMe in methanol at rt for 30 min. Most of the solvent was then removed under reduced pressure. FCC of the residue provided **3.33** (3.49 g, 81%) as a colorless oil; $R_f = 0.42$ (10% EtOAc/petroleum ether); IR (neat) 3485 cm^{-1} ; ^1H NMR (300 MHz $CDCl_3$) δ 1.07 (s, 9H), 1.40-1.53 (both s, 3H ea), 2.55 (d, 1H, $J = 4.4\text{ Hz}$), 3.81 (m, 3H), 4.18 (t, 1H, $J = 5.7\text{ Hz}$), 5.58 (d, 1H, $J = 5.5\text{ Hz}$), 7.26-7.71 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.8, 27.1, 27.8, 64.6, 72.4, 81.2, 86.0, 111.7, 127.2-135.6; HRMS(EI) m/z calcd for $C_{23}H_{31}O_4Si$ (M-SPh) 399.1992, found 399.1996.

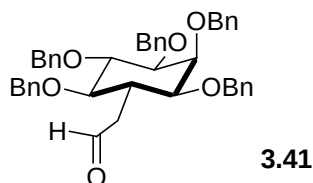


C-allyl *myo*-inositol (**3.40**)

Sodium hydroxide (0.65 g, 16.5 mmol) was added to the solution of **2.53** (0.24 g, 0.41 mmol) in dry methanol (5 mL). The reaction mixture was heated at reflux for 3h. Methanol was then evaporated and the reaction mixture was treated with water and neutralized with 1M HCl in methanol. The organic layer was washed with ethyl acetate (2 x 10 mL), dried (Na₂SO₄) and concentrated in *vacuo*. The residue was purified by FCC to give the desired triol. ¹H NMR (500 MHz, CDCl₃) δ 0.90 (2s, 6H), 1.01 (s, 3H), 1.20-1.31 (m, 2H), 1.36-1.49 (m, 1H), 1.51 (d, 1H, J = 13.0 Hz), 1.70-1.82 (m, 2H), 1.83-1.98 (m, 1H), 1.98-2.10 (m, 3H), 2.18 (d, 1H, J = 6.9 Hz), 2.44 (t, 2H, J = 6.4 Hz), 2.51 (d, 1H, J = 3.4 Hz), 2.75 (d, 1H, J = 2.9 Hz), 3.19-3.27 (m, 1H), 3.75-3.83 (m, 2H), 3.85 (t, 1H, J = 6.8 Hz), 4.26 (dd, 1H, J = 4.0, 6.5 Hz), 5.13 (dd, 1H, J = 1.4, 17.0), 5.22 (dd, 1H, J = 1.4, 17.6 Hz), 5.87-6.01 (m, 1H); ¹³C NMR (500 MHz, CDCl₃) δ 9.89, 20.3, 20.5, 27.0, 30.0, 33.0, 44.1, 44.5, 45.1, 48.0, 51.6, 69.0, 71.8, 75.5, 76.3, 76.4, 117.8, 117.9, 135.3.

A solution of HCl in methanol (ca 2M) was added to a methanolic solution of the product from the previous step until a pH of 2 was reached. The reaction was stirred overnight. The mixture was neutralized with sodium hydroxide in methanol and concentrated in *vacuo*. To a solution of the crude product (1.50 g, 7.35 mmol) in dry DMF (15 mL) at 0°C was added NaH (1.24 g, 60% in mineral oil, 51.5 mmol) and Bu₄NI (0.54 g, 1.47 mmol), followed by BnBr (47.8 mmol, 5.7 mL). The reaction mixture was stirred for 0.5 h at rt under an argon atmosphere. The reaction was quenched with H₂O, and extracted

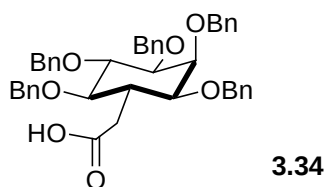
with ether (2 x 20 mL). The organic layer was washed with H₂O (2 x 10 mL), dried (Na₂SO₄) and then concentrated in *vacuo*. The residue was purified by FCC to give **3.40** (4.45g, 93%): clear oil; $R_f = 0.75$ (10% ethyl acetate: petroleum ether); ¹H NMR (500 MHz, CDCl₃) δ 2.50-2.68 (m, 3H), 3.15 (dd, 1H, $J = 1.73, 11.1$ Hz), 3.25-3.40 (m, 2H), 4.10-4.25 (m, 2H), 4.38 (d, 1H, $J = 11.4$ Hz), 4.53-4.61 (m, 1H), 4.61-4.75 (m, 3H), 4.75-4.95 (m, 3H), 4.95-5.15 (m, 4H), 5.68-5.80 (m, 1H), 7.18-7.48 (m, 24H), 7.48-7.55 (m, 1H); ¹³C NMR (500 MHz, CDCl₃) δ 30.3, 41.2, 71.4, 72.7, 73.1, 73.7, 74.5, 75.6, 76.8, 77.0, 77.2, 77.3, 79.5, 81.5, 83.6, 117.6, 127.3, 127.5, 127.6, 127.6, 127.7, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.4, 135.0, 138.1, 138.5, 138.9, 139.0, 139.2, 139.2. HRMS (EI) m/z calcd for C₄₄H₄₇O₅ (M + H)⁺ 655.3418, found 655.3421.



Aldehyde (**3.41**)

A solution of **3.40** (1.53 g, 2.34 mmol) in 5:1 CH₂Cl₂: MeOH (72 mL) was cooled to –78°C. A stream of O₃ in O₂ was bubbled through the solution until the starting material was not detectable by TLC. The mixture was flushed with argon and then triphenylphosphine (1.22 g, 4.68 mmol) was added. The solution was warmed to rt, stirred for 2h, and concentrated in *vacuo*. The residue was purified by FCC to give aldehyde **3.41** (1.47 g, 96%): clear oil; $R_f = 0.79$ (30% ethyl acetate: petroleum ether); ¹H NMR (500 MHz, CDCl₃) δ 2.40-2.56 (m, 2H), 2.80-3.00 (m, 1H), 3.07 (dd, 1H, $J = 2.0, 11.2$ Hz), 3.20 (dd, 1H, $J = 9.0, 10.7$ Hz), 3.37 (dd, 1H, $J = 2.2, 9.85$ Hz), 4.07 (bt, 1H, $J = 2.2, 9.85$ Hz), 4.07 (bt, 1H, $J = 2.2, 9.85$ Hz).

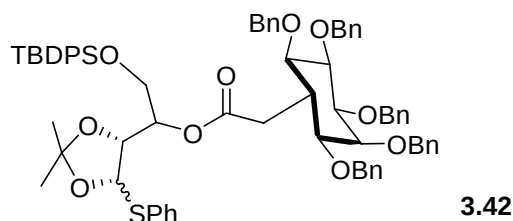
= 2.0 Hz), 4.08-4.19 (m, 2H), 4.30 (d, 1H, J = 11.5 Hz), 4.50 (dd, 2H, J = 2.0, 10.7 Hz), 4.75 (ABq, $\Delta\delta$ = 0.08, J = 11.8 Hz), 4.82 (d, 2H, J = 10.9 Hz), 8.87 (d, 1H, J = 11.9 Hz), 8.88 (d, 1H, J = 10.7 Hz), 5.01 (d, 1H, J = 10.8 Hz), 7.20-7.50 (m, 25H), 9.55 (t, 1H, J = 2.6 Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 38.8, 44.2, 71.6, 72.8, 73.0, 74.0, 74.9, 75.6, 78.4, 81.2, 81.4, 83.3, 127.4, 127.5, 127.7, 127.7, 127.9, 128.0, 128.1, 128.2, 128.2, 128.4, 128.4, 128.5, 128.5, 137.2, 138.0, 138.2, 138.8, 138.9, 202.0.



Acid (**3.34**)

A solution of aldehyde **3.41** (1.47 g, 2.23 mmol), in THF (22.3 mL) was cooled to 0 °C. A solution of 2,3-dimethyl-2-butene (1.1 mL, 2M in THF) was then added followed by aqueous 1M sodium biphosphate (2.20 mL, 2.20 mmol), and aqueous 1M sodium chlorate (2.20 mL, 2.20 mmol). The reaction mixture was warmed to rt and stirred for 2h. The mixture was extracted with ethyl acetate. 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 **3.34** (1.37 g, 93%); R_f = 0.48 (30 % ethyl acetate: petroleum ether); ^1H NMR (500 MHz, CDCl_3) δ 2.68 (d, 2H, J = 4.9 Hz), 2.70-2.78 (m, 1H), 3.30-3.34 (dd, 1H, J = 1.9, 11.4 Hz), 3.38 (dd, 1H, J = 2.3, 9.8 Hz), 3.40 (dd, 1H, J = 8.9, 10.9 Hz), 3.70-4.02 (m, 1H), 4.03-4.20 (m, 2H), 4.37 (d, 1H, J = 11.4 Hz), 4.52 (d, 1H, J = 11.4 Hz), 4.60 (d, 1H, J = 11.0 Hz), 4.61 (ABq, $\Delta\delta$ = 0.08, J = 8.3 Hz), 4.75-4.90 (m, 3H), 5.00 (t, 2H, J = 10.9 Hz), 7.20-7.49 (m, 25H); ^{13}C NMR (500 MHz, CDCl_3) δ 23.9, 29.1,

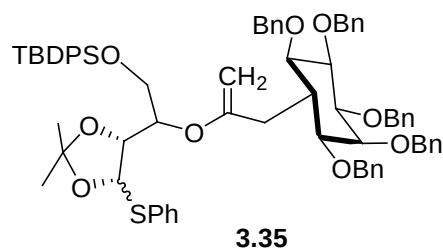
32.0, 39.2, 67.7, 71.6, 72.8, 72.9, 73.8, 75.0, 75.6, 77.8, 80.2, 81.3, 83.4, 108.0, 127.3, 127.5, 127.6, 127.7, 127.7, 127.9, 127.9, 127.9, 128.0, 128.2, 128.4, 128.4, 128.4, 128.4, 128.5, 137.6, 138.4, 138.4, 138.8, 139.0.



Thioacetal ester (3.42)

A mixture of acid **3.34** (0.38 g, 0.56 mmol) 2,4,6-trichlorobenzoyl chloride (0.09 mL, 0.56 mmol) and triethylamine (0.16 mL, 1.13 mmol) in THF (30 mL) was stirred for 3.5h at 0 °C. Alcohol **3.33** (0.29 g, 0.56 mmol) and DMAP (89.5 mg, 0.73 mmol) in toluene were added, and stirring continued for 1h. The mixture was then diluted with ether (50 mL), washed with saturated aqueous NaHCO₃ and brine, dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give ester **3.42** (0.57 g, 86%): colorless oil; *R*_f = 0.58 (15% ethyl acetate: petroleum ether); ¹H NMR (500 MHz, CDCl₃) δ 1.02 (s, 9H), 1.37 (s, 3H), 1.44 (s, 3H), 2.68-2.85 (m, 3H), 3.38 (dd, 1H, *J* = 2.3, 9.9 Hz), 3.45-3.55 (m, 2H), 3.70-3.83 (m, 2H), 4.03-4.15 (m, 2H), 4.33 (dd, 1H, *J* = 4.5, 6.7 Hz), 4.40 (d, 1H, *J* = 11.4 Hz), 4.48 (d, 1H, *J* = 11.4 Hz), 4.52 (d, 1H, *J* = 10.9 Hz), 4.64 (d, 2H, *J* = 4.2 Hz), 4.75-4.85 (m, 3H), 4.90 (d, 1H, *J* = 10.8 Hz), 5.01 (d, 1H, *J* = 10.9 Hz), 5.23 (q, 1H, *J* = 5.0 Hz), 5.50 (d, 1H, *J* = 6.7 Hz), 7.15-7.73 (m, 40H); ¹³C NMR (500 MHz, CDCl₃) δ 19.1, 26.0, 26.8, 27.3, 31.5, 39.4, 62.1, 62.1, 71.7, 72.6, 72.8, 73.2, 73.7, 75.0, 75.4, 77.6, 79.4, 80.1, 81.3, 83.5, 84.9, 111.5, 127.6, 127.7, 127.7,

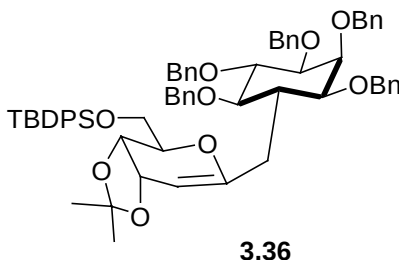
127.7, 127.8, 127.9, 127.9, 128.1, 128.3, 128.3, 128.4, 128.4, 128.4, 129.0, 132.0, 135.6, 135.6, 139.1, 172.0. HRMS (EI) m/z calcd for $C_{72}H_{78}NaO_{10}SiS$ ($M + Na$)⁺ 1185.4977, found 1185.4977.



Thioacetal enol ether (3.35)

To a mixture of ester **3.42** (1.35 g, 1.16 mmol), and pyridine (0.10 mL) in anhydrous 3:1 toluene: THF (30 mL), was added, under an argon atmosphere and at -78 °C, Tebbe reagent (5.71 mL, 0.5M in THF). The reaction mixture was warmed to rt and stirred at this temperature for 1h. 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 in *vacuo*. FCC of the residue on basic alumina provided enol ether **3.35** (0.70 g, 78% based on recovered starting material) as light yellow oil: R_f (on alumina plate) = 0.45 (10% ethyl acetate: petroleum ether); ^1H NMR (500 MHz, C_6D_6) δ 1.16 (s, 9H), 1.40 (s, 3H), 1.51 (s, 3H), 2.61-3.00 (m, 3H), 3.47 (dd, 1H, $J = 2.1, 10.0$ Hz), 3.60 (dd, 1H, $J = 1.8, 11.3$ Hz), 3.77 (t, 1H, $J = 9.1$ Hz), 4.06 (dd, 1H, $J = 4.8, 10.8$ Hz), 4.10-4.20 (m, 2H), 4.20-4.26 (m, 3H), 4.40 (t, 1H, $J = 9.5$ Hz), 4.45-4.55 (m, 6H), 4.56 (q, 1H, $J = 4.6$ Hz), 4.61-4.77 (m, 2H), 4.80-5.11 (m, 5H), 5.26 (d, 1H, $J = 11.4$ Hz), 5.53 (s, 1H), 5.90 (d, 1H, $J = 6.3$ Hz), 6.87-7.85 (m, 40H); ^{13}C NMR (500 MHz, C_6D_6) δ 19.7, 23.1, 26.5, 27.4, 27.5, 28.0, 30.4, 32.2, 34.8, 41.9, 62.7, 71.9, 73.2, 74.7, 74.9, 74.9, 75.9, 76.8,

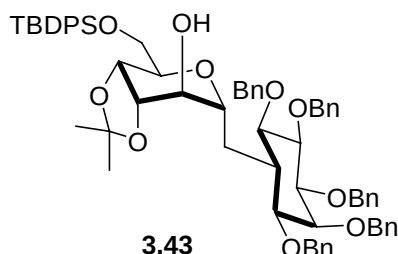
79.1, 80.6, 80.7, 82.5, 85.0, 86.0, 86.4, 112.5, 112.6, 127.9, 127.9, 128.0, 128.1, 128.1, 128.1, 128.3, 128.5, 128.7, 128.7, 128.8, 128.8, 128.9, 129.0, 129.0, 129.6, 130.6, 130.6, 132.0, 133.8, 135.4, 136.4, 139.6, 139.7, 140.3, 140.3, 140.8, 160.8. HRMS(EI) m/z calcd for $C_{73}H_{80}O_9NaSiS$ ($M + Na$)⁺ 1183.4184, found 1183.5188.



6-Deoxy-1,2,3,4,5-penta-O-benzyl-6-C-(2,6-anhydro-7-O-tert-butyldiphenylsilyl-4,5-O-isopropylidene-1,3-dideoxy-D-ribo-hept-2-enitol-1-C-yl)-D-myo-inositol (3.36)

A mixture of enol ether **3.35** (0.49 g, 0.42mmol), 2,6-di-tert-butyl-4-methylpyridine (1.02 g, 5.0 mmol), and freshly activated, powdered 4Å molecular sieves (1.47 g) in anhydrous CH_2Cl_2 (20 mL), was stirred for 15 min, at rt, under an atmosphere of argon, then cooled to 0 °C. Methyl triflate (0.47 mL, 4.2 mmol) was then introduced, and the mixture warmed to rt, and stirred for an additional 18h, at which time, triethylamine (1 mL) was added. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated in *vacuo*. FCC of the residue provided glycal **3.36** (0.35 g, 78%) as light yellow oil. R_f (on alumina plate) =0.35 (10% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, C_6D_6) δ 1.16 (s, 9H), 1.23 (s, 3H), 1.32 (s, 3H), 2.70 (dd, 1H, J = 5.0, 14.3 Hz), 2.91 (dd, 1H, J = 3.1, J = 14.3 Hz), 2.94-3.02 (m, 1H), 3.40 (dt, 2H, J = 1.5, 10.4 Hz), 3.50-3.63 (m, 1H), 3.69 (dd, 1H, J = 9.1, 10.8 Hz), 3.96-4.05 (m, 2H), 4.08 (t, 1H, J = 10.5Hz), 2.21 (bt, 1H, J = 1.9 Hz), 4.24 (t, 1H, J = 5.2

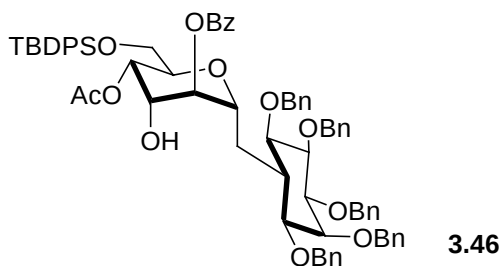
Hz), 4.41 (t, 1H, $J = 9.5$ Hz), 4.46 (ABq, 2H, $\Delta\delta = 0.04$ ppm, $J = 11.1$ Hz), 4.55 (ABq, 2H, $\Delta\delta = 0.04$ ppm, $J = 11.9$ Hz), 4.80 (d, 1H, $J = 10.9$ Hz), 4.92 (ABq, 2H, $\Delta\delta = 0.03$ ppm, $J = 12.1$ Hz), 5.00-5.10 (m, 3H), 5.30 (d, 1H, $J = 11.3$ Hz), 7.00-7.28 (m, 21H), 7.31 (d, 2H, $J = 1.2$ Hz), 7.38 (d, 2H, $J = 7.5$ Hz), 7.46 (d, 4H, $J = 7.5$ Hz), 7.52 (d, 2H, $J = 7.3$ Hz), 7.84 (dt, 4H, $J = 1.4, 7.9$ Hz); ^{13}C NMR (500 MHz, C_6D_6) δ 21.0, 27.2, 28.6, 30.2, 32.8, 42.6, 64.7, 70.7, 71.2, 72.9, 74.2, 75.4, 76.0, 76.1, 77.2, 78.7, 80.4, 82.3, 83.5, 85.8, 98.9, 109.5, 128.9, 129.0, 129.1, 129.2, 129.3, 129.4, 129.5, 129.6, 129.7, 129.7, 129.8, 129.9, 129.9, 130.0, 131.4, 137.4, 137.5, 141.2. HRMS (EI) m/z calcd for $\text{C}_{67}\text{H}_{75}\text{O}_9\text{Si}$ ($M + \text{H}$) $^+$ 1051.5174, found 1051.5159.



6-Deoxy-1,2,3,4,5-penta-O-benzyl-6-C-(2,6-anhydro-4,5-O-isopropylidene-7-O-tert-butylidiphenylsilyl-1-deoxy-D-glycero-D-altro-heptitol-1-C-yl) -D-myo-inositol (3.43)

$\text{BH}_3 \cdot \text{Me}_2\text{S}$ (1.3 mL, 1M solution, 1.3 mmol) was added at 0 °C to a solution of glycal **3.36** (0.35 g, 0.33 mmol) in anhydrous THF (15 mL) under an atmosphere of argon. The mixture was warmed to rt and stirred for an additional 1 h. At that time the solution was recooled to 0 °C and treated with a mixture of 3N NaOH (2.4 mL) and 30% aqueous H_2O_2 (2.4 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 **3.43** in (0.30 g, 83%): $R_f = 0.36$ (20%

ethyl acetate: petroleum ether); ^1H NMR (500 MHz, CDCl_3) δ 1.05 (s, 9H), 1.34 (s, 3H), 1.46 (s, 3H), 1.51-1.81 (m, 1H), 1.81-1.90 (m, 1H), 2.52-2.69 (m, 1H), 2.08-3.20 (m, 3H), 3.30 (dd, 1H, $J = 2.1, 9.89$ Hz), 3.40-3.49 (m, 1H), 3.52-3.63 (m, 1H), 3.71 (dd, 1H, $J = 4.8, 10.5$ Hz), 3.78 (dd, 1H, $J = 6.7, 10.6$ Hz), 3.87-4.01 (m, 2H), 4.05 (bs, 1H), 4.09 (t, 1H, $J = 9.2$ Hz), 4.26 (d, 1H, $J = 11.3$ Hz), 4.31 (dd, 1H, $J = 3.6, 6.10$ Hz), 4.48 (d, 1H, $J = 11.2$ Hz), 4.58-4.70 (m, 3H), 4.72-4.89 (m, 5H), 4.95 (t, 2H, $J = 2.3$ Hz), 7.06-7.15 (m, 3H), 7.2-7.48 (m, 28H), 7.61-7.69 (m, 4H); ^{13}C NMR (500 MHz, CDCl_3) δ 19.2, 25.8, 26.9, 28.0, 33.2, 37.7, 64.1, 71.9, 72.6, 72.8, 73.5, 73.5, 73.6, 73.7, 74.8, 74.8, 75.4, 77.6, 80.3, 81.5, 82.4, 83.3, 108.8, 125.3, 127.6, 127.6, 127.7, 127.8, 127.8, 127.8, 127.8, 128.0, 128.0, 128.1, 128.2, 128.2, 128.2, 128.3, 128.4, 128.4, 128.6, 129.8, 129.8, 133.3, 135.6, 137.1, 138.5, 138.6, 138.9, 138.9. HRMS (EI) m/z calcd for $\text{C}_{67}\text{H}_{77}\text{O}_{10}\text{Si}$ ($\text{M} + \text{H}$) $^+$ 1069.5280, found 1069.5266.



α -C-altrose alcohol (3.46)

Alcohol **3.43** was dissolved in CH_2Cl_2 (20 mL), and pyridine (0.06 mL, 0.69 mmol) and benzoyl chloride (0.03 mL, 0.3 mmol) were added to the reaction mixture. The reaction was monitored by TLC. The mixture was diluted with dichloromethane, washed with saturated aqueous NaHCO_3 and brine, dried (Na_2SO_4), filtered and evaporated in *vacuo*. FCC of the residue provided the benzoate in quantitative yield: ^1H NMR (500 MHz,

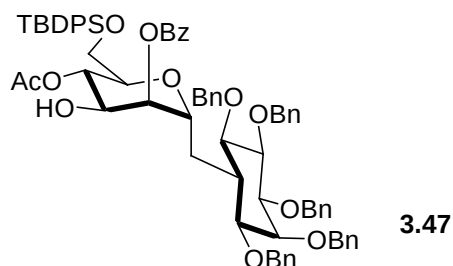
CDCl₃) δ 1.11 (s, 9H), 1.28 (s, 3H), 1.49 (s, 3H), 1.51-1.70 (m, 1H), 2.15-2.26 (m, 1H), 2.55-2.74 (m, 1H), 3.14-3.24 (m, 2H), 3.26 (dd, 1H, J = 2.2, 9.9 Hz), 3.82 (dd, 1H, J = 4.2, 10.9 Hz), 3.89 (dd, 1H, J = 4.8, J = 10.9 Hz), 4.00 (q, 1H, J = 4.4 Hz), 4.03 (bt, 1H, J = 2.0 Hz), 4.15 (t, 1H, J = 9.3 Hz), 4.23 (t, 1H, J = 6.1 Hz), 4.26-4.33 (m, 2H), 4.35 (t, 1H, J = 5.1 Hz), 4.46 (d, 1H, J = 11.6 Hz), 4.55-4.65 (m, 3H), 4.75 (d, 1H, J = 10.7 Hz), 4.81 (s, 2H), 4.97 (t, 2H, J = 9.6 Hz), 5.22 (t, 1H, J = 6.9 Hz), 7.09-7.49 (m, 19H), 7.49-7.56 (m, 7H), 7.56-7.76 (m, 7H), 7.99 (dd, 2H, J = 1.0, 8.1 Hz), 8.19 (dd, 5H, J = 1.4, 3.19 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 19.5, 26.4, 27.1, 27.2, 27.9, 30.4, 37.8, 64.7, 71.5, 72.5, 72.5, 72.8, 72.9, 73.1, 73.5, 74.3, 74.4, 75.6, 81.1, 81.1, 81.6, 83.4, 109.5, 127.6, 127.8, 127.8, 128.0, 128.0, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.7, 130.4, 134.0, 135.9, 136.0, 138.8, 165.8, 171.9. HRMS(EI) m/z calcd for C₇₄H₈₁O₁₁Si (M + H)⁺ 1173.5542, found 1173.5525.

A solution of 1M HCl in ether (0.05 mL) was added to a solution of the product from the previous step (0.02 g, 0.03 mmol), in dry methanol (1 mL). The reaction mixture was stirred at rt for 20 min. The mixture was neutralized by addition of sodium methoxide. Removal of the volatiles under reduced pressure and FCC of the residue provided the diol derivative: R_f = 0.54 (30% ethyl acetate: petroleum ether): ¹H NMR (500 MHz, CDCl₃) δ 1.10 (s, 9H), 1.49-1.59 (m, 1H), 1.60 (s, 1H), 2.49-2.63 (m, 2H), 2.67 (d, 1H, J = 3.1 Hz), 2.93 (d, 1H, J = 4.0 Hz), 3.12-3.33 (m, 2H), 3.33 (dd, 1H, J = 2.3, J = 9.9 Hz), 3.80 (dd, 1H, J = 6.8, 10.3 Hz), 3.83 (dd, 1H, J = 4.3, J = 10.8 Hz), 3.85-3.98 (m, 1H), 3.98-4.03 (m, 1H), 4.03-4.13 (m, 2H), 4.18 (t, 1H, J = 9.3 Hz), 4.25-4.39 (m, 2H), 4.51 (d, 1H, J = 11.5 Hz), 4.53-4.70 (m, 3H), 4.75-4.81 (m, 3H), 5.03 (d, 1H, J = 5.6 Hz), 5.04 (d, 1H, J = 6.3 Hz), 4.15 (dd, 1H, J = 3.7, J = 4.8 Hz), 7.12-7.25 (m, 12H), 7.25-7.41 (m, 27H), 7.52-

7.55 (m, 1H), 7.63-7.73 (m, 4H), 7.90-8.00 (m, 2H); ^{13}C NMR (500 MHz, CDCl_3) δ 19.2, 26.9, 27.0, 30.0, 37.2, 65.1, 69.0, 69.2, 69.3, 71.4, 72.6, 72.6, 73.3, 73.5, 74.0, 75.4, 75.5, 77.3, 81.4, 81.5, 81.8, 83.6, 127.5, 127.5, 127.7, 127.9, 128.0, 128.0, 128.1, 128.3, 128.3, 128.3, 128.4, 128.4, 129.9, 129.9, 130.0, 135.6, 135.7, 135.7, 166.0. HRMS (EI) m/z calcd for $\text{C}_{71}\text{H}_{77}\text{O}_{11}\text{Si}$ ($\text{M} + \text{H}$) $^{+}$ 1133.5229, found 1133.5215.

A solution of the diol from the previous step (0.041 g, 0.036 mmol) in dry benzene (6 mL) and triethyl orthoacetate (6 mL) was treated with CSA (1.1 mg) at rt. The mixture was stirred for 1h and then triethylamine (3 mL) was added followed by cold water (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL), washed with saturated aqueous NaHCO_3 (10 mL), water (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and treated with 80% aqueous acetic acid (20 mL). The mixture was stirred at rt for 35 min. Toluene (3 x 8 mL) was added and the mixture was evaporated under reduced pressure. FCC of the residue afforded **3.46** (0.035 g, 58% from **3.43**): R_f = 0.73 (20% ethyl acetate: petroleum ether); ^1H NMR (500 MHz, CDCl_3) δ 1.10 (s, 9H), 1.62-1.71 (m, 1H), 2.10 (dd, 1H, J = 6.4, 10.4 Hz), 2.12 (s, 3H), 2.18-2.26 (m, 1H), 2.58-2.69 (m, 1H), 3.14-3.21 (m, 2H), 3.26 (dd, 1H, J = 2.2, 9.9 Hz), 3.76 (dd, 1H, J = 4.7, 10.9 Hz), 3.81 (dd, 1H, J = 6.0, 10.9 Hz), 3.99-4.05 (m, 2H), 4.05-4.17 (m, 2H), 4.23-4.30 (m, 2H), 1.48 (d, 1H, J = 11.4 Hz), 4.55-4.65 (m, 3H), 4.73-4.81 (m, 3H), 5.47 (dd, 2H, J = 6.8, 11.0 Hz), 5.13 (m, 1H, J = 7.5 Hz), 5.43 (t, 1H, J = 3.8 Hz), 7.18-7.46 (m, 33H), 7.50-7.53 (m, 1H), 7.68 (dd, 2H, J = 1.4, J = 7.8 Hz), 7.70-7.74 (m, 2H), 7.86 (dd, 2H, J = 1.0, J = 8.2 Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 19.2, 21.1, 26.8, 30.6, 37.3, 62.4, 68.9, 71.2, 71.4, 72.6, 72.8, 73.3, 74.5, 74.7, 75.5, 81.0, 81.2, 81.4, 83.3,

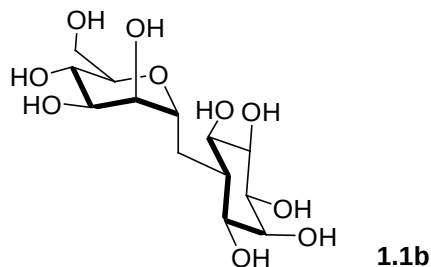
127.2, 127.5, 127.6, 127.7, 127.7, 127.8, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 129.8, 129.9, 133.2, 135.6, 135.7, 139.1, 166.5, 170.2. HRMS (EI) m/z calcd for $C_{15}H_{24}NaO_6$ ($M + Na$)⁺ 323.1468, found 323.1468.



Protected α -C-manno pseudodisaccharide (**3.47**)

To a solution of **3.46** (0.025 g, 0.021 mmol), in CH_2Cl_2 (0.3 mL) was added pyridine (0.03 mL) at $-20\text{ }^{\circ}C$. Trifluoromethanesulfonic anhydride (0.007 mL, 0.021) in CH_2Cl_2 (0.5 mL) was then added dropwise, and the mixture warmed $10\text{ }^{\circ}C$ over 2 h. The solution was subsequently diluted with CH_2Cl_2 and washed with 1M HCl, aqueous $NaHCO_3$, water and brine. The organic phase was dried (Na_2SO_4) and concentrated in *vacuo* at rt. KNO_2 (5 equiv) was added to a solution of the crude product in dry DMF (1 mL). After stirring at $50\text{ }^{\circ}C$ for 6h, the mixture was diluted with CH_2Cl_2 and washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in *vacuo*. Purification of the residue by FCC afforded **3.47**. $R_f = 0.60$ (30% ethyl acetate: petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.32-1.49 (m, 1H), 1.49-2.15 (m, 4H), 1.30 (d, 1H, $J = 9.9$ Hz), 2.50-2.61 (m, 1H), 3.09-3.24 (m, 2H), 3.31 (dd, 1H, $J = 2.1, 9.9$ Hz), 3.51 (dd, 1H, $J = 3.5, 11.3$ Hz), 3.62-3.74 (m, 2H), 3.81-3.92 (m, 1H), 4.09-4.20 (m, 2H), 4.26 (d, 1H, $J = 11.6$ Hz), 4.52-4.65 (m, 4H), 4.66 (d, 1H, $J = 6.9$ Hz), 4.77 (d, 1H, $J = 10.7$ Hz), 4.82 (s, 2H), 5.01 (d, 1H, $J = 10.7$ Hz), 5.03 (d, 1H, $J = 11.2$ Hz), 5.28 (t, 1H, $J = 1.3$ Hz), 5.49 (t,

1H, J = 9.6 Hz), 7.16-7.48 (m, 33H), 7.55 (t, 1H, J = 7.41), 7.69 (dd, 2H, J = 1.1, 7.7 Hz), 7.71 (dd, 2H, J = 1.2, 7.8 Hz), 8.09 (d, 2H, J = 7.3 Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 19.3, 21.0, 26.7, 26.8, 28.1, 37.2, 62.7, 69.7, 70.2, 71.0, 71.2, 72.4, 72.6, 73.4, 74.5, 75.2, 75.2, 75.4, 80.6, 81.3, 81.3, 83.7, 127.2, 127.5, 127.6, 127.6, 127.7, 127.7, 127.9, 128.0, 128.1, 128.1, 128.3, 128.4, 128.4, 128.5, 130.0, 135.7, 135.8, 138.6, 166.0, 171.4. HRMS (EI) m/z calcd for $\text{C}_{15}\text{H}_{24}\text{NaO}_6$ ($\text{M} + \text{Na}$) $^+$ 323.1468, found 323.1468.



To a solution of **3.47** (0.010 g, 0.01 mmol), in methanol (5 mL) and treated with a solution of NaOMe in methanol at rt for 30 min. Most of the solvent was then removed under reduced pressure. FCC of the residue gave triol derivative in quantitative yield. Treatment of triol (0.007 g, 0.006 mmol) in dry THF (1 mL), was added TBAF (0.012 mL, 0.012 mmol) at rt. The reaction was stirred for 5 h at rt, then diluted with saturated aqueous NaHCO_3 and extracted with ether. The combined organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. FCC of the residue afforded tetraol derivative (0.004 g, 82%) as a colorless oil.

To a solution of tetraol (0.004g, 0.01 mmol) in 20% Pd on carbon (0.0123 g), and methanol (1 mL) was stirred under an atmosphere of hydrogen (balloon), for 12 h. The reaction mixture was purged with argon and filtered through a bed of Celite. The filtrate was concentrated in *vacuo*, and the residue was purified by FCC to give **1.1b** (0.0015g, 88%); ^1H NMR (500 MHz, CDCl_3) δ 1.58-1.67 (m, 1H), 1.77-1.86 (m, 1H), 2.05-2.15

(m, 1H), 3.35 (dd, 1H, $J = 1.8, 9.2$ Hz), 3.48-3.54 (m, 1H), 3.56-3.68 (m, 6H), 3.76-3.83 (m, 1H), 3.85 (bd, 1H, $J = 1.9$ Hz), 3.93 (bd, 1H, $J = 2.7$ Hz), 4.35-4.45 (m, 1H); ^{13}C NMR (500 MHz, CDCl_3) δ 26.5, 39.2, 61.3, 67.3, 70.6, 71.0, 71.1, 71.9, 72.7, 73.2, 73.5, 74.0, 76.7.

CHAPTER 4

Synthesis of *D-chiro*-Inositol-Galactosamine mimetics

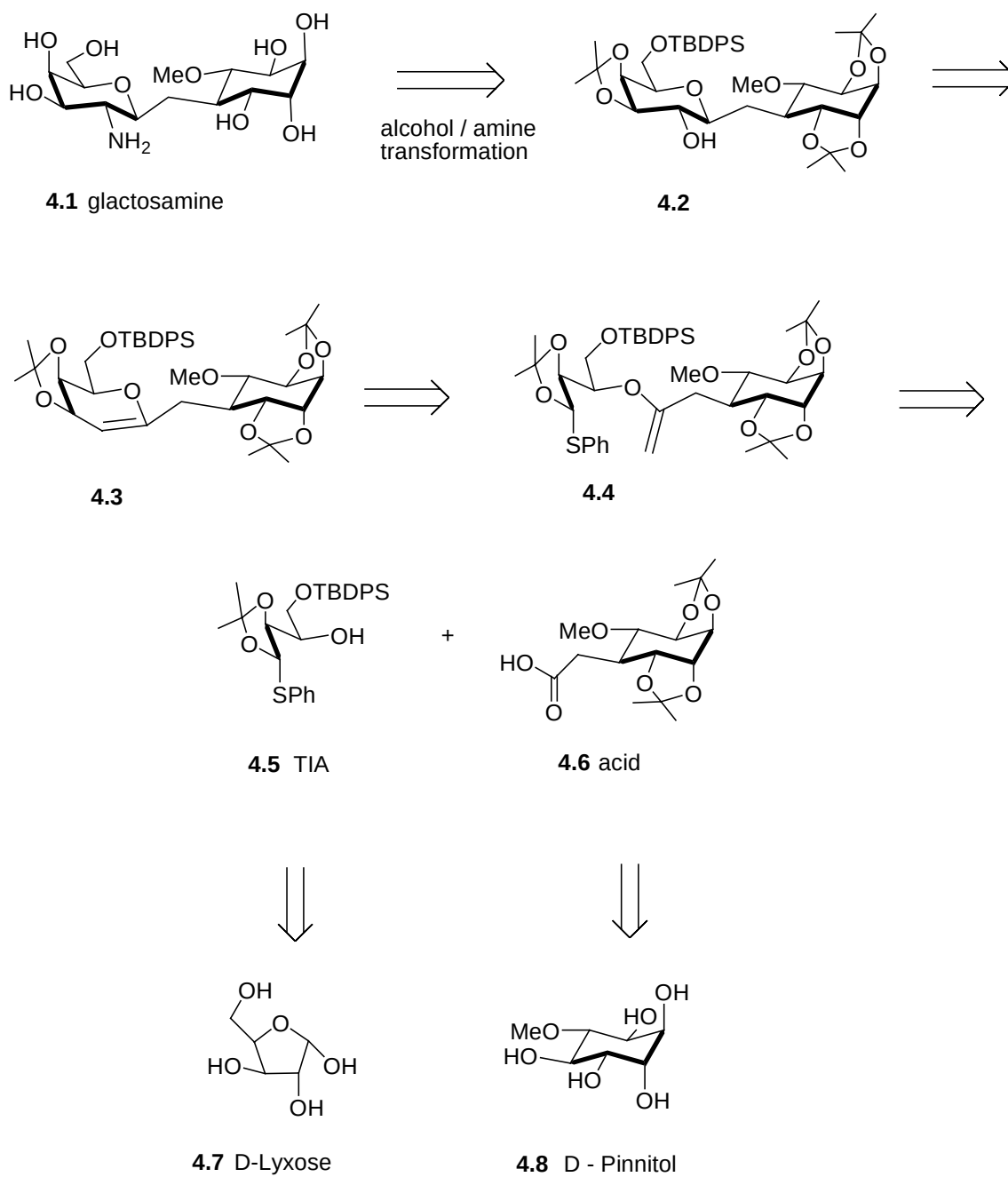
4.1 Background

Glycoconjugates such as glycoproteins and glycolipids are vital components in cellular recognition processes. For example, cell surface carbohydrates not only mediate cell-cell communication but also act as receptors for viral and bacterial pathogens. 2-Amino 2-deoxy sugars are important subunit of many glycoconjugates such as glycoproteins,⁶² chitin,⁶³ and heparin.⁶⁴ Inositol phosphate glycans (IPG's) are small, ionic oligosaccharides that are released from the exterior surface of insulin-sensitive cells in response to insulin stimulation.⁶⁵ It has been proposed that IPG's act as second messengers of insulin action. The glycan 4-O-(2-amino-2-deoxy- β -D-galactopyranosyl)-*D-chiro*-inositol (INS-2) **4.1** was earlier isolated from liner as a putative insulin second messenger. A synthetic sample was later found to be both insulin mimetic and insulin sensitizing in rats.¹⁹ The C-glycosides and carboglycoside analogs of INS-2 are of interest as metabolically stable analogs for therapeutic applications, and also as structure activity probes. This chapter describes the synthesis C-INS-2 and carba-INS-2.

4.2 Results and discussion

4.2.1 Synthesis of C-INS-2

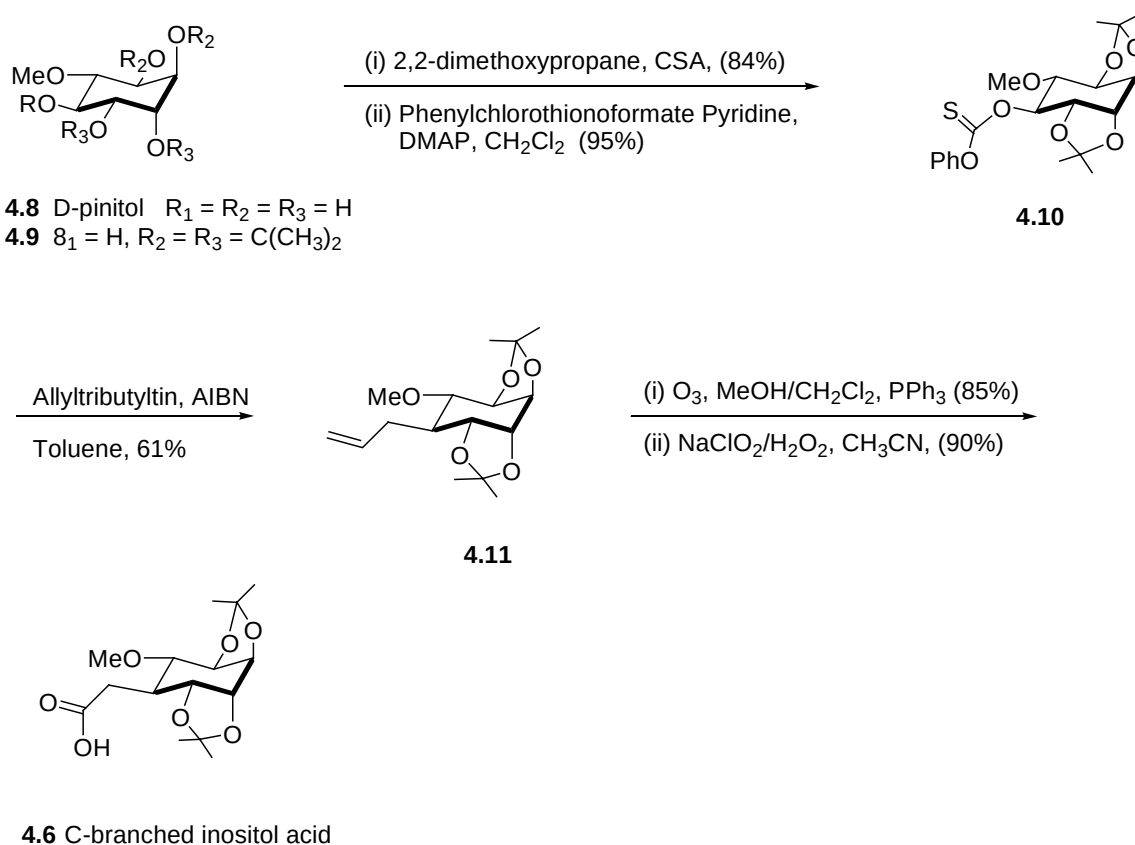
The synthesis of C-INS-2 **4.1** could be realized by transformation of alcohol **4.2** to the amine (**Scheme 4.1**). Hydroboration of glycal **4.3** leads to **4.2**. The previously described oxocarbenium ion cyclization of enol ether **4.4** gives **4.3**. Enol ether **4.4** can be prepared from TIA **4.5** and acid **4.6** over two steps. TIA **4.5** can be obtained from D-lyxose **4.7** and acid **4.6** can be synthesized from D-pinnitol **4.8**.



Scheme 4.1

4.2.2 Synthesis of the aglycone component

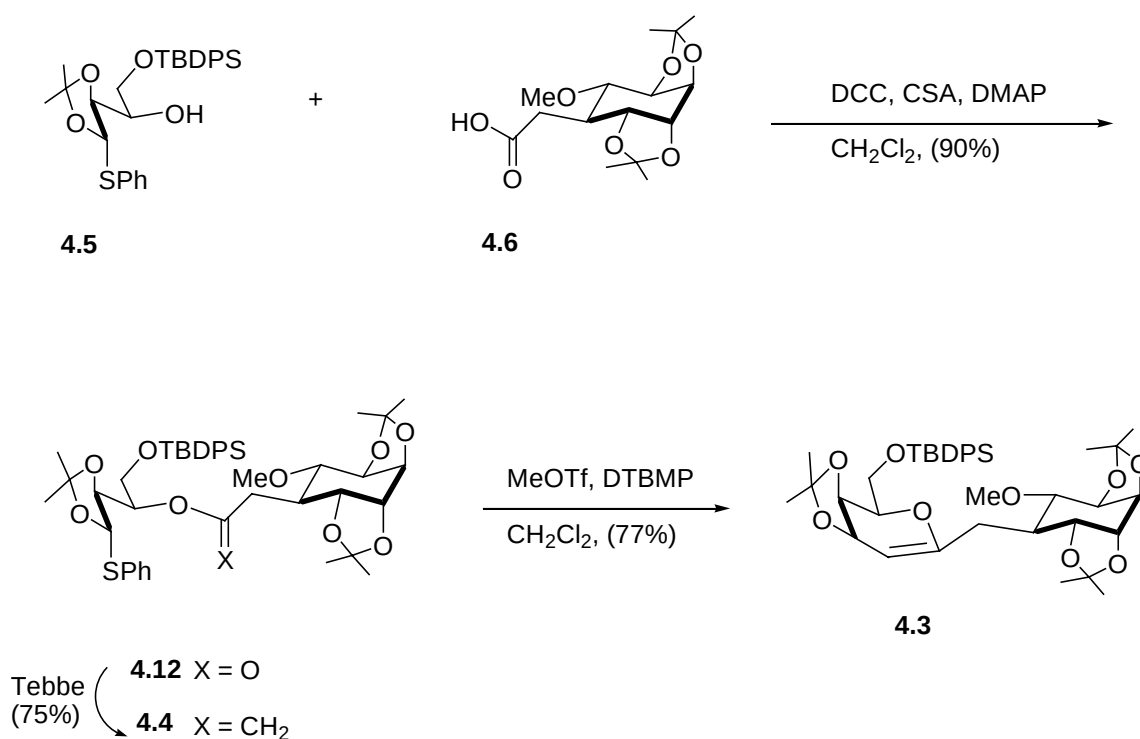
Thionoformate **4.10** was obtained from commercially available D-pinitol **4.1** over two steps (**Scheme 4.2**). First treatment of D-pinitol with 2,2-dimethoxypropane and catalytic camphorsulfonic acid in dry dichloromethane gave the di-O-isopropylidene derivative **4.9** in 84% yield. Treatment of **4.9** with phenylchlorothionoformate, pyridine and DMAP in dichloromethane led to **4.10** in 95% yield. The reaction of thionoformate **4.10** with allyltributyltin in the presence of AIBN, in toluene afforded the C-allyl inositol **4.11** in 61% yield. Transformation of **4.11** to acid **4.6** was performed over two steps: cleavage of the alkene to the aldehyde, followed by oxidation of the aldehyde to the acid.



Scheme 4.2

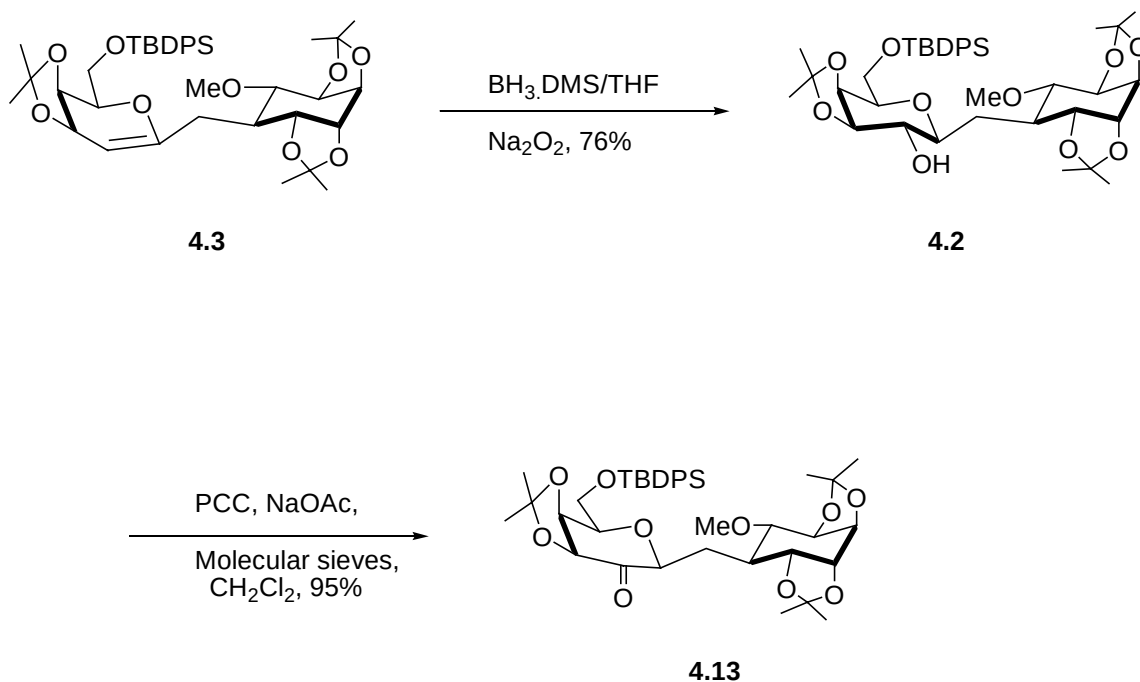
4.2.3 Coupling of the glycone and aglycone components

Coupling of alcohol **4.5** and acid **4.6** was done using DCC, CSA, and DMAP in dichloromethane, which lead to ester **4.12** in 90% yield. Tebbe olefination on **4.12** provided enol-ether **4.4** (Scheme 4.3). Glycal **4.3** was obtained by exposing enol-ether **4.4** to the standard cyclization conditions.



Scheme 4.3

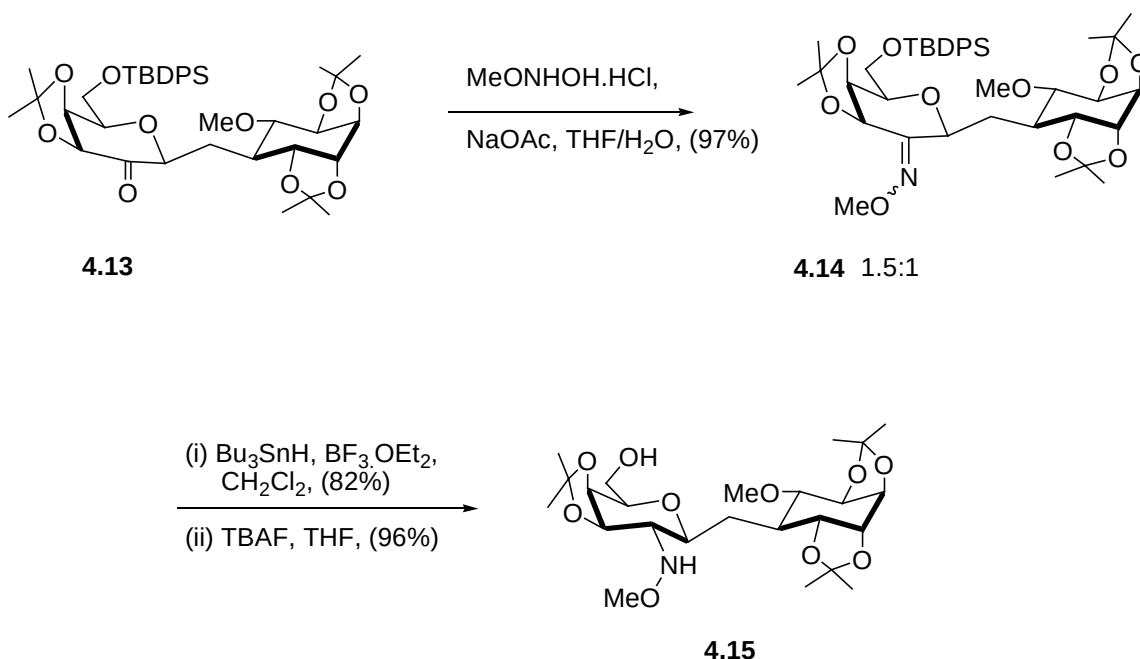
Glycal **4.3** was treated with BH₃.Me₂S complex and H₂O₂/NaOH to give alcohol **4.2** as a single isomer in 75% yield (Scheme 4.4).⁶⁶ Alcohol **4.2** was oxidized to ketone **4.13** by using PCC, NaOAc, and molecular sieves in dichloromethane.



Scheme 4.4

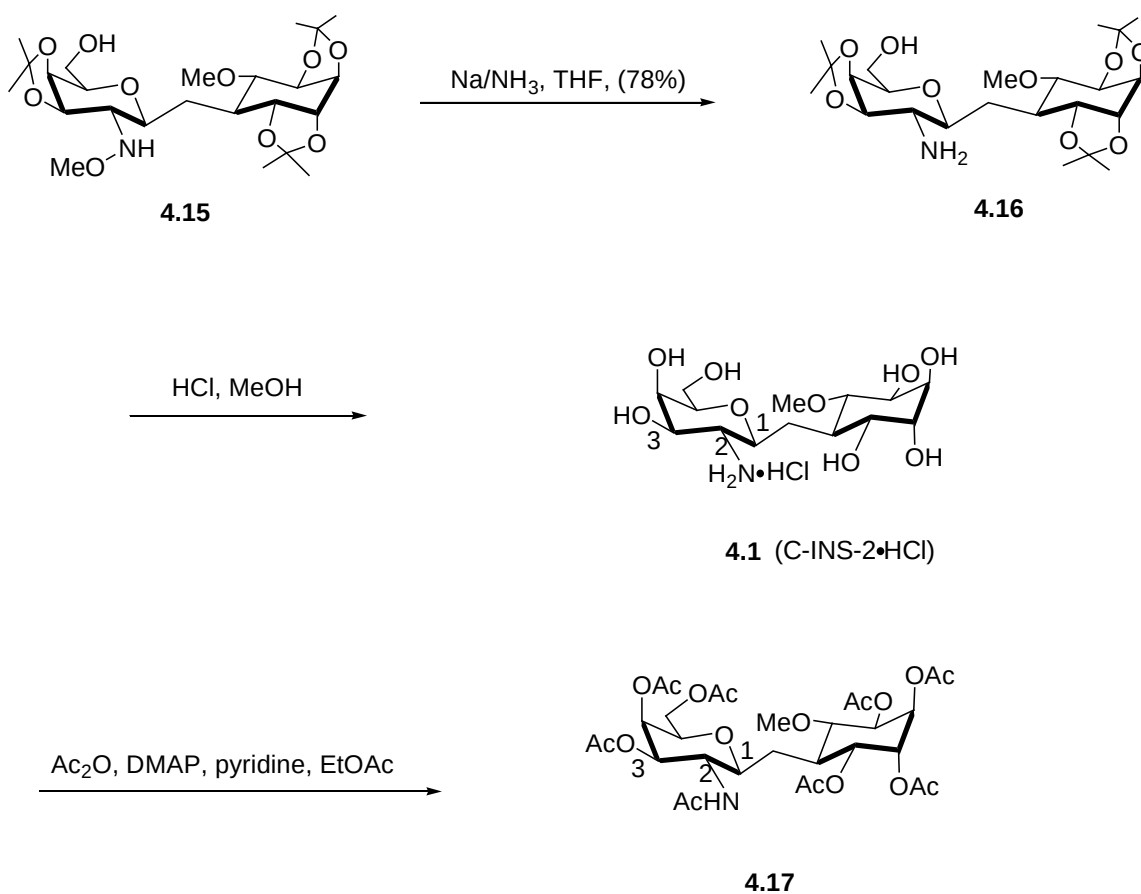
4.2.4 Introduction of the 2-amino substituent

Treatment of ketone **4.13** with $\text{MeONHOH} \cdot \text{HCl}$,⁶⁷ and sodium acetate in a 1:1 mixture of THF and H_2O afforded oxime **4.14** in 97% yield (**Scheme 4.5**). Oxime **4.14** was obtained as inseparable E/Z mixture (1.5:1). The next task was to reduce the oxime stereoselectively. Treatment of oxime **4.14** with Bu_3SnH (4 mole eq) and $\text{BF}_3 \cdot \text{OEt}_2$ (2 mole eq) in anhydrous CH_2Cl_2 at $-20\text{ }^\circ\text{C}$ provided a single methosyamine in 82% yield. It should be noted that the reaction proceeded smoothly at $-20\text{ }^\circ\text{C}$, but if the temperature was elevated to $0\text{ }^\circ\text{C}$ acetonide cleavage was observed. The silyl protecting group was next removed via using TBAF in dry THF, which resulted in alcohol **4.15**.



Scheme 4.5

Next, Birch reduction on methoxy amine **4.15** provided amine **4.16** in 78% yield (**Scheme 4.6**). Hydrolysis of the isopropylidene groups in **4.16** gave the target compound as the hydrochloride salt **4.1**. For characterization a sample of **4.1** was converted to the penta acetylated derivative **4.17**. Stereochemical analysis of the acetate **4.17** was done through ^1H NMR and ^1H NOESY data (**Figure 4.1**).



Scheme 4.6

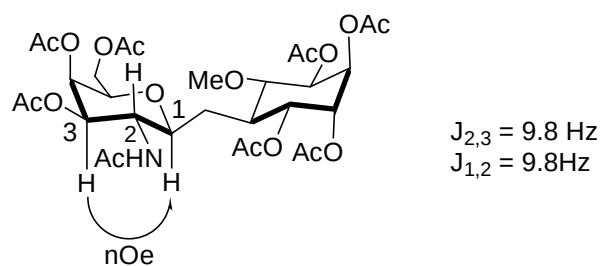
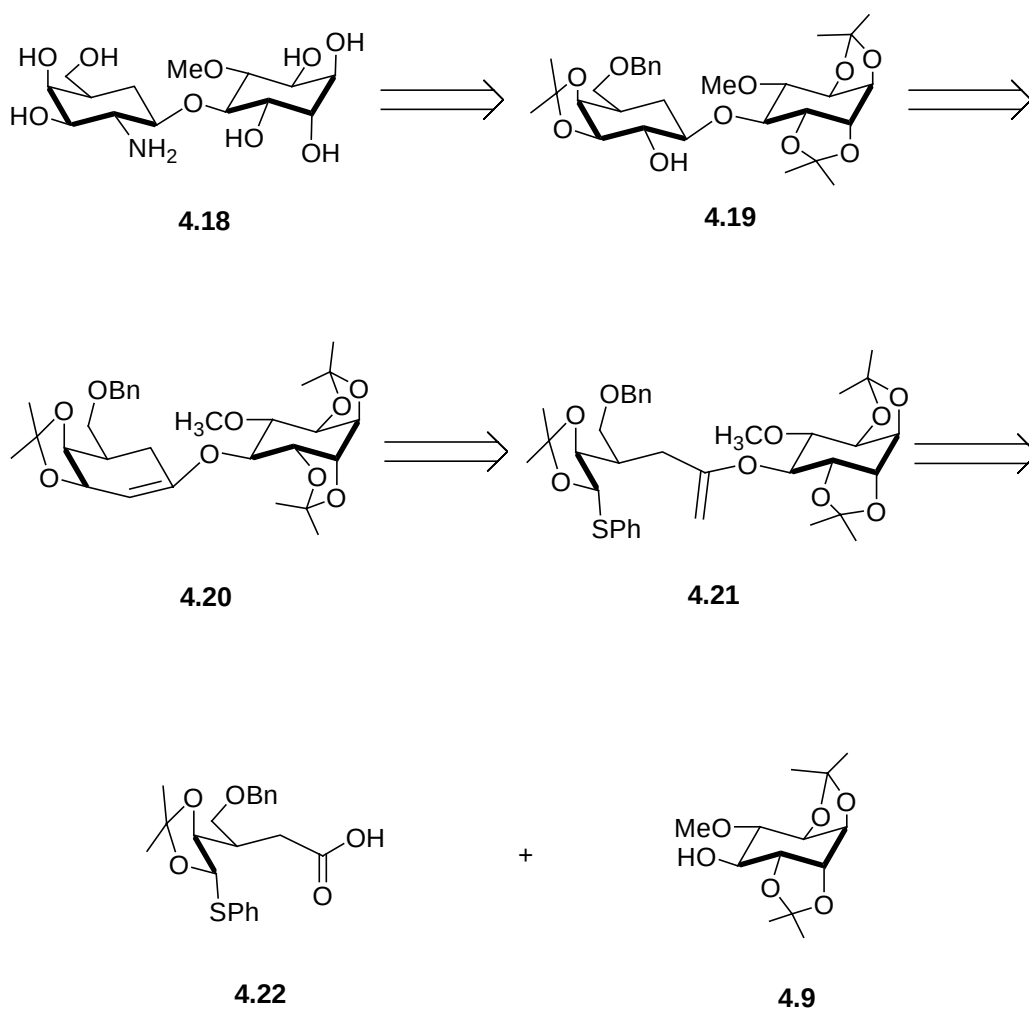
4.17 2-amino- β -C-galactoside

Figure 4.1

4.3 Synthesis of Carba-INS-2

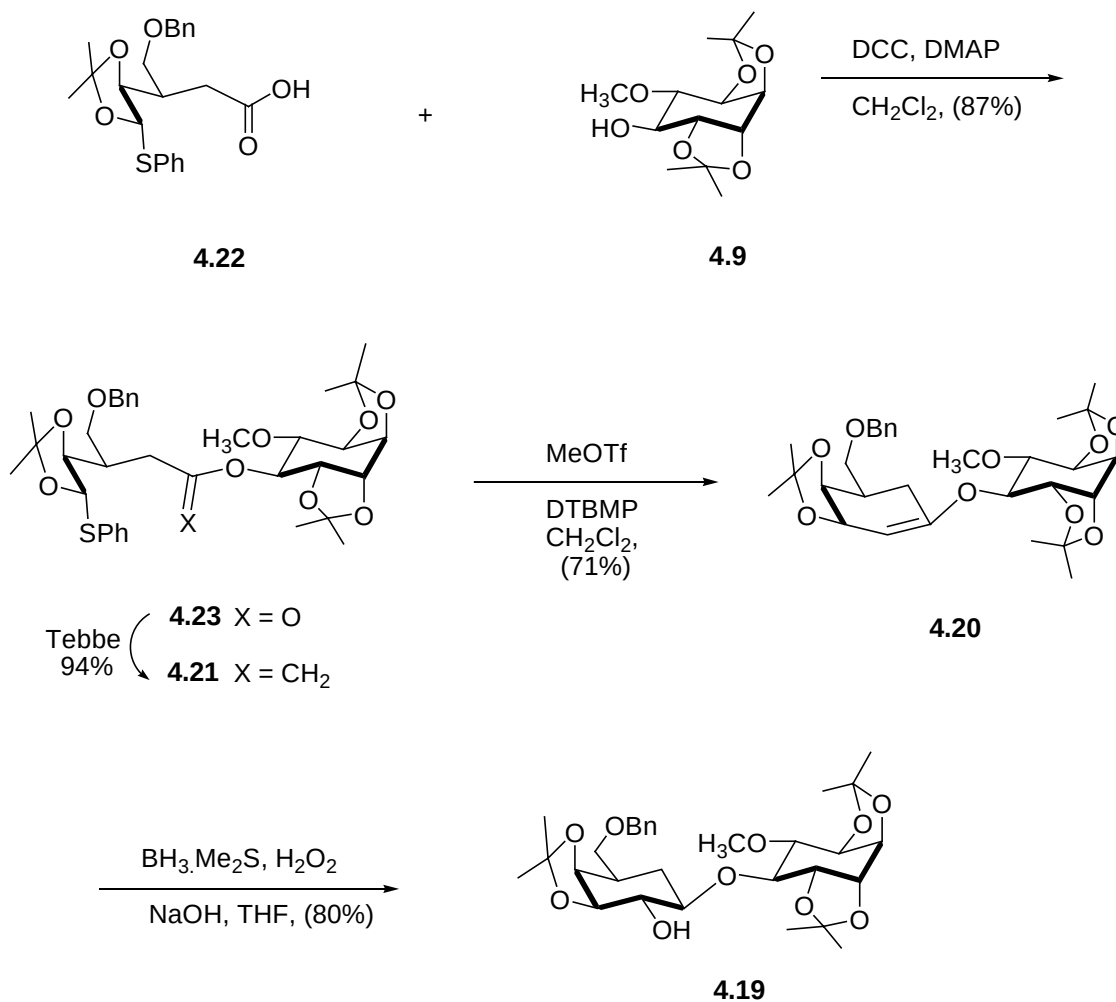
Compound **4.18**, the carbasugar of INS-2 can be synthesized via a variation of the oxocarbenium ion cyclization strategy that was used for the C-glycoside analog of INS-2 (Scheme 4.7). Thus alcohol **4.19** may be obtained from cyclic enol ether **4.20**, which may be derived from the cyclization of thioacetal-enol ether **4.21**. The latter can be prepared from acid **4.22** and alcohol **4.9**. The final target **4.18** could be accessed from alcohol **4.19** using a strategy similar to that described for C-INS-2.



Scheme 4.7

4.3.1 Coupling of the glycone and aglycone components

A synthesis of the glycone segment **4.22** was previously developed in the laboratory (Scheme 4.8).⁶⁸ The glycone alcohol segment **4.9** is identical to the intermediate in the C-glycoside synthesis (Scheme 4.2). Formation of ester **4.23** was accomplished by treatment of **4.9** and **4.22** with DCC and DMAP.



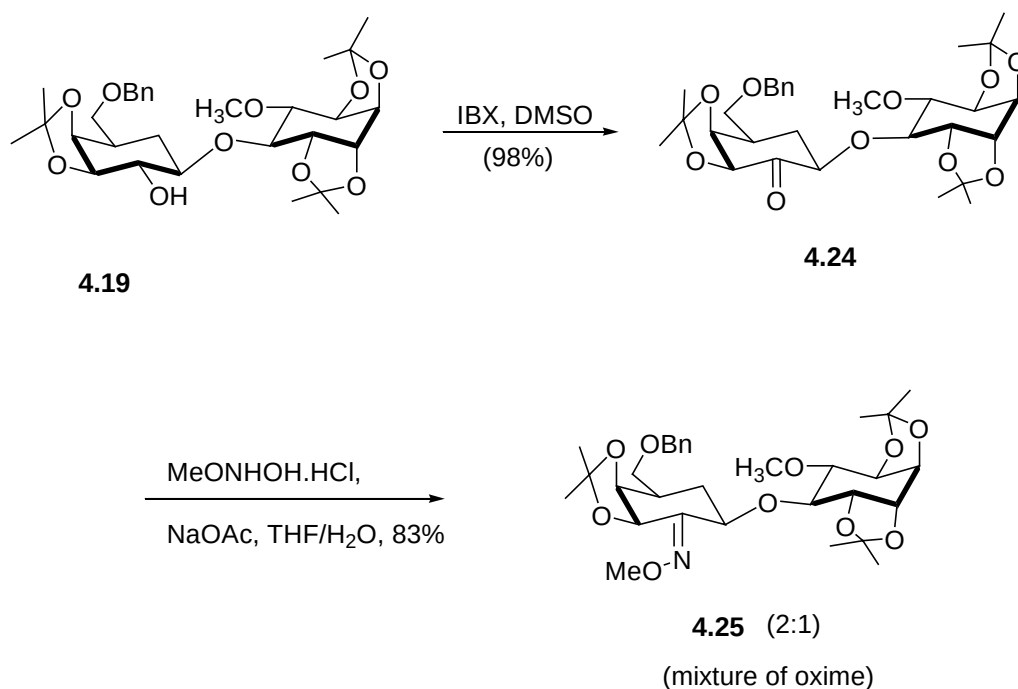
Scheme 4.8

The transformation of ester **4.23** to enol-ether **4.21** was performed under Tebbe olefination conditions. Exposure of **4.21** to the standard cyclization conditions provided

the cyclic enol ether **4.20** in 71% yield. The hydroboration of enol ether **4.20** was carried out with borane-sulfide complex to give alcohol **4.19** in 80% yield.

4.3.2 Introduction of the 2-amino group

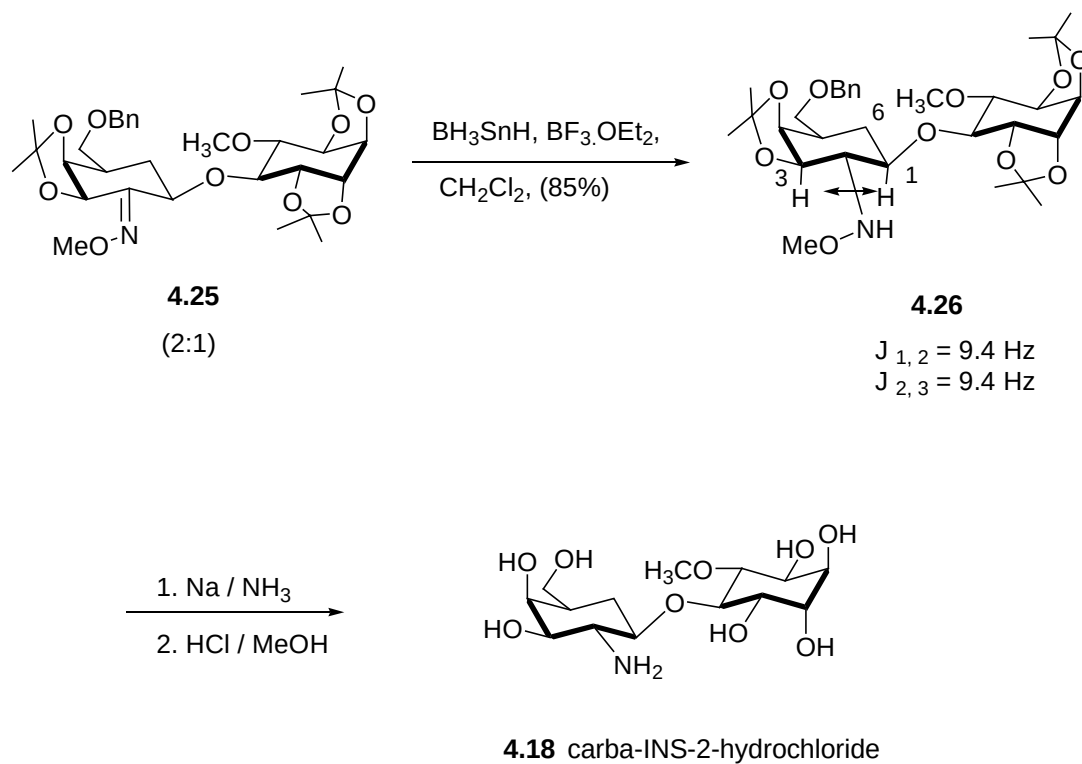
The next task was to oxidize alcohol **4.19** to ketone **4.24** (Scheme 4.9). Most widely used procedures like PCC and DesMartin oxidation did not give the desired product. Finally the reaction of **4.19** with IBX in DMSO provided ketone **4.24** in 98% yield. Treatment of **4.24** with MeONHOH.HCl and NaOAc gave an E/Z mixture of oximes **4.25** in 83% yield.



Scheme 4.9

Stereoselective reduction of **4.25** with tributyltinhydride and borane trifluoride etherate at $-20\text{ }^{\circ}\text{C}$ provided a single isomer of methoxy amine **4.26** in 85% yield (Scheme 4.10). J

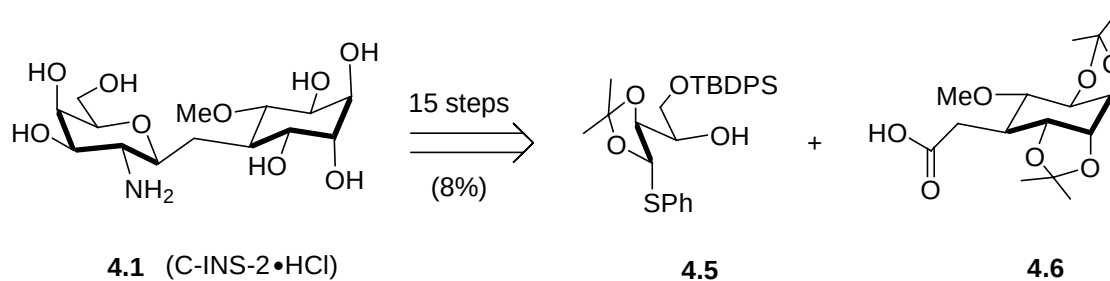
values and nOe data supported the equatorial position of the amino group. Treatment of **4.26** with Na/NH₃, followed by acid hydrolysis of the product lead to carba-INS-2 as the hydrochloride salt **4.18**.



Scheme 4.10

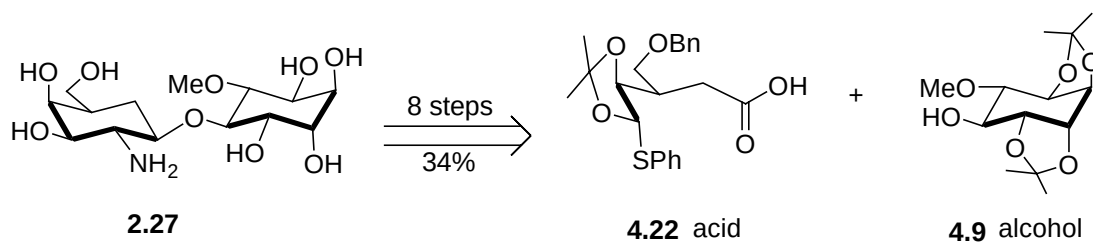
4.4 Summary

The synthesis of the C-glycoside and carba-glycoside analogs of INS-2 was accomplished via an oxocarbenium ion-enol ether cyclization strategy. C-INS-2 hydrochloride **4.1** was realized from TIA alcohol **4.6** and acid **4.5** over 15 steps with an overall yield of 8% (**Scheme 4.11**). These precursors were prepared from commercially available D-lyxose and D-pinitol respectively.



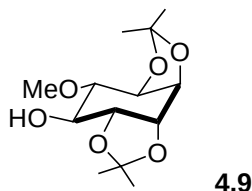
Scheme 4.11

The carba-INS-2 hydrochloride **4.18** was accomplished from TIA acid **4.22** and alcohol **4.9** in 8 steps in an overall yield of 34% (**Scheme 4.12**).



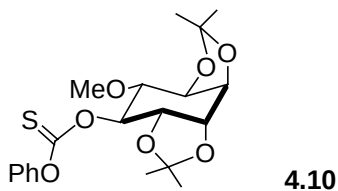
Scheme 4.12

4.5 Experimental



Alcohol (4.9)

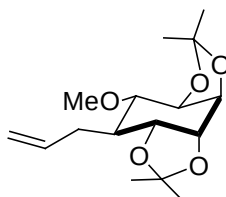
p-Toluenesulfonic acid (0.245 g, 1.29 mmol) was added to a suspension of alcohol **4.8** (2.50 g, 12.9 mmol) and dimethoxypropane (6.32 mL, 51.5 mmol) in dry acetone (30 mL) at rt. The mixture was stirred for 6h, then washed with saturated aqueous NaHCO₃. The organic extract was dried (Na₂SO₄) and concentrated under reduced pressure. FCC of the residue gave **4.9** (3.25 g, 84%). $R_f = 0.47$ (45% ethyl acetate: petroleum ether). ¹H NMR (500 MHz, CDCl₃) δ 1.40 (2s, 6H), 1.55 (2s, 6H), 2.80 (bs, 1H), 3.23 (dd, 1H, $J = 6.6, 10.0$ Hz), 3.60-3.65 (m, 4H), 4.20-4.29 (m, 4H); ¹³C NMR (500 MHz, CDCl₃) δ 25.1, 25.3, 27.6, 27.8, 59.2, 71.5, 76.7, 77.2, 78.4, 79.0, 81.3, 109.9, 110.1. HRMS (EI) m/z calcd for C₁₃H₂₂O₆Na (M + Na)⁺ 297.1308, found 297.1316.



Thionoformate (4.10)

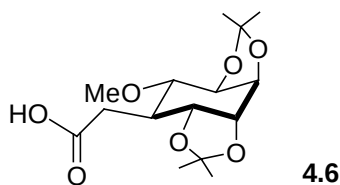
Phenyl chlorothionoformate (8.75 mL, 64.7 mmol) was added dropwise to a solution of alcohol **4.9** (8.05 g, 29.4 mmol) and DMAP (0.72 g, 5.87 mmol), in dry toluene (120 mL) at rt. Pyridine (12.0 mL, 147 mmol) was then added, the resulting mixture stirred for 2h at rt, then washed with 0.1M HCl and saturated aqueous NaHCO₃. The organic extract was dried (Na₂SO₄) and concentrated in *vacuo*. FCC of the residue gave **4.10** (11.5 g,

96%). $R_f = 0.43$ (10% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 2.40 (s, 6H), 2.6 (2s, 6H), 3.09 (dd, 1H, $J = 7.5$, $J = 10.9$ Hz), 4.39 (t, 1H, $J = 7.9$ Hz), 4.48-4.51 (m, 3H), 5.6 (dd, 1H, $J = 7.1$, 10.9 Hz), 6.86 (d, 1H, $J = 7.1$ Hz), 7.16 (d, 2H, $J = 8.4$ Hz), 7.25 (dd, 1H, $J = 6.9$, 8.0 Hz), 7.31 (t, 1H, $J = 7.4$ Hz), 7.44 (t, 2H, $J = 7.9$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 25.4, 25.5, 27.5, 27.8, 60.2, 75.4, 75.5, 76.0, 78.4, 80.4, 82.5, 109.5, 110.0, 115.4, 120.4, 122.0, 126.6, 129.5, 129.6, 153.6, 195.0. HRMS (EI) m/z calcd for $\text{C}_{20}\text{H}_{27}\text{O}_7\text{S}$ ($\text{M} + \text{H}$) $^+$ 411.1472, found 411.1471.

**4.11**

Allyl (4.11)

A solution of **4.10** (4.17 g, 10.2 mmol), allyltributyltin (9.35 mL, 30.6 mmol), AIBN (0.33 g, 2.04 mmol) and toluene (18 mL) was heated reflux for 4h. The solution was then concentrated in *vacuo*. FCC of the residue gave **4.11** (1.70 g, 56%). $R_f = 0.64$ (10% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, ca 1% C_6D_6 / CDCl_3 , v/v) δ 1.40 (2s, 6H), 1.51 (2s, 6H), 1.79-1.87 (m, 1H), 2.54-6.67 (m, 2H), 3.02 (dd, 1H, $J = 6.8$, 12.4 Hz), 3.54 (s, 3H), 4.06 (dd, 1H, $J = 6.9$, 9.2 Hz), 4.15 (t, 1H, $J = 6.3$ Hz), 4.21 (t, 1H, $J = 7.1$ Hz), 4.30 (t, 1H, $J = 6.6$ Hz), 5.20 (d, 1H, $J = 10.1$ Hz), 5.27 (d, 1H, $J = 17.1$ Hz); ^{13}C NMR (500 MHz, ca 1% C_6D_6 / CDCl_3 , v/v) δ 25.1, 25.2, 27.8, 27.8, 32.7, 41.5, 58.4, 75.9, 77.2, 77.8, 79.2, 81.1, 108.7, 108.9, 117.3, 135.2.



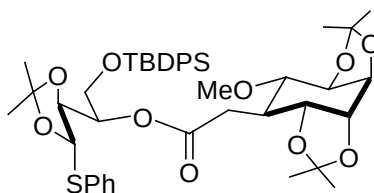
Acid (4.6)

Alkene **4.11** (1.35 g, 4.55 mmol) was dissolved in a 5/1 v/v mixture of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (24 mL). The solution was cooled to $-78\text{ }^\circ\text{C}$ and treated with a stream of O_3 in O_2 until TLC indicated complete disappearance of the starting material. The reaction was then purged with nitrogen, and Ph_3P (2.64 g, 9.09 mmol) was added. The mixture was warmed to rt, stirred for 1 h at this temperature, and concentrated under reduced pressure. FCC of the residue gave the derived aldehyde (1.15 g, 85%). $R_f = 0.16$ (10% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.30 (2s, 6H), 1.51 (2s, 6H), 2.09-2.18 (m, 1H), 2.48 (m, 1H), 2.23 (dd, 1H, $J = 4.7, 16.2$ Hz), 3.15 (dd, 1H, $J = 6.7, 12.1$ Hz), 3.45 (s, 3H), 4.04 (dd, 1H, $J = 6.5, 9.7$ Hz), 4.18-4.25 (m, 2H), 4.36 (dd, 1H, $J = 4.7, 6.7$ Hz), 9.65 (d, 1H, $J = 2.1$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 25.3, 25.4, 27.8, 27.8, 39.1, 43.9, 59.1, 76.4, 76.8, 80.2, 80.5, 109.3, 200.9. HRMS (EI) m/z calcd for $\text{C}_{15}\text{H}_{24}\text{NaO}_6$ ($M + \text{Na}$) $^+$ 323.1468, found 323.1468.

To a solution of aldehyde from the previous step (1.4 g, 4.68 mmol) in mixture of $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (85:17mL), at $0\text{ }^\circ\text{C}$ was added $\text{NaH}_2\text{PO}_4 \cdot 3\text{H}_2\text{O}$ (6.46 g, 46.8 mmol), and a solution of NaClO_2 (0.51 g, 5.62 mmol) in H_2O (85 mL) and H_2O_2 (0.55 mL). The mixture was stirred at $0\text{ }^\circ\text{C}$ until TLC indicated the disappearance of the starting material. Solid Na_2SO_3 was then added to the reaction. The reaction mixture was diluted with water and the organic phase was extracted with ether. The combined extract was dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified

by FCC to give acid **4.6** (1.10 g, 75%). $R_f = 0.16$ (25% ethyl acetate: petroleum ether).

^1H NMR (500 MHz, CDCl_3) δ 1.39 (2s, 6H), 1.62 (2s, 6H), 2.02-2.12 (m, 1H), 2.52 (dd, 1H, $J = 7.0, 15.7$ Hz), 2.71 (dd, 1H, $J = 4.3, 15.7$ Hz), 3.16 (dd, 1H, $J = 7.3, 12.2$ Hz), 3.54 (s, 3H), 4.14 (dd, 1H, $J = 6.4, 9.9$ Hz), 4.22-4.27 (m, 2H), 4.38 (dd, 1H, $J = 4.7, 6.7$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 25.4, 25.4, 27.7, 27.8, 33.5, 39.7, 59.5, 76.4, 76.5, 76.7, 76.9, 76.9, 80.3, 80.4, 109.3, 109.3, 176.9.

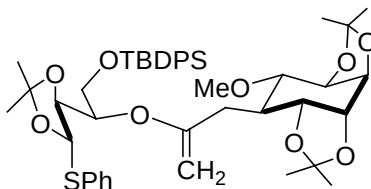


4.12

Thioacetal-ester (**4.12**)

DCC (0.50 g, 2.42 mmol) was added at 0 °C to a mixture of TIA alcohol **4.5** (1.23 g, 2.42 mmol), acid **4.6** (0.64 g, 2.02 mmol) and DMAP (74.0 mg, 0.61 mmol) in dry dichloromethane (10 mL). The reaction mixture was warmed to rt and stirred for 6 h. The mixture was then diluted with ether and filtered. The filtrate was successively washed with 0.1 N aqueous HCl and brine, dried (Na_2SO_4), filtered, and evaporated in *vacuo*. FCC of the residue gave ester **4.12** (1.45 g, 89% from acid) as colorless oil. $R_f = 0.38$ (10% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.05 (s, 9H), 1.26 (s, 3H), 1.27 (s, 3H), 1.28 (s, 3H), 1.56 (2s, 6H), 2.09-2.17 (m, 1H), 2.34 (dd, 1H, $J = 7.9, 16.5$ Hz), 2.69 (dd, 1H, $J = 3.8, 15.4$ Hz), 3.06 (dd, 1H, $J = 7.1, 12.2$ Hz), 3.20 (s, 3H), 3.8 (dd, 1H, $J = 7.3, 10.0$ Hz), 3.85 (dd, 1H, $J = 6.0, 9.9$ Hz), 4.55 (dd, 1H, $J = 6.6, 9.8$ Hz), 4.17 (dd, 1H, $J = 6.6, 9.8$ Hz), 4.17 (dd, 1H, $J = 5.4, 6.2$ Hz), 4.19 (t, 1H, $J = 7.0$ Hz), 4.42 (dd, 1H, $J = 2.4, 7.7$ Hz), 5.22-5.27 (m, H), 5.50 (d, 1H, $J = 6.8$ Hz), 7.24-7.34

(m, 4H), 7.37-7.49 (m, 6H), 7.56 (m, 2H), 7.67-7.74 (m, 4H); ^{13}C NMR (500 MHz, CDCl_3) δ 20.0, 25.3, 25.5, 26.2, 26.7, 27.3, 27.7, 27.9, 34.5, 39.9, 59.0, 62.0, 70.8, 76.5, 76.6, 78.9, 80.4, 80.5, 84.4, 109.3, 111.5, 127.5, 127.9, 127.8, 128.9, 129.7, 129.7, 132.3, 133.1, 133.1, 133.7, 135.6, 135.7, 171.4. HRMS (EI) m/z calcd for $\text{C}_{44}\text{H}_{58}\text{O}_{10}\text{SSiNa}$ ($\text{M} + \text{Na}$) $^+$ 829.3420, found 829.3423.

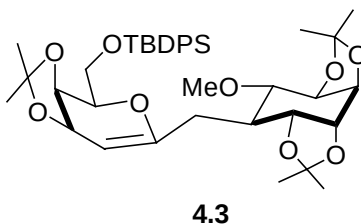


4.4

Thioacetal-enol ether (4.4)

To a solution of ester **4.12** (0.592 g, 0.735 mmol), and pyridine (0.3 mL) in a anhydrous mixture of toluene: THF (10:5 mL), was added, under an argon atmosphere and at -78°C , Tebbe reagent (3.7 mL, 0.5M in THF). The reaction mixture was warmed to rt and stirred at this temperature for 1 h. The mixture was then slowly poured into a solution of 1M 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 in *vacuo*. FCC of the residue on basic alumina provided enol ether **4.12** (0.44 g, 75%) as light yellow oil. R_f = 0.49 (alumina, 10% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.07 (s, 9H), 1.29 (s, 3H), 1.35 (s, 6H), 1.48 (s, 3H), 1.50 (s, 3H), 1.51 (s, 3H), 1.80-1.93 (m, 1H), 2.31 (dd, 1H, J = 5.6, 14.4 Hz), 2.45 (dd, 1H, J = 5.2, 14.3 Hz), 3.14 (dd, 1H, J = 6.9, 12.5 Hz), 3.81 (d, 1H, J = 2.2 Hz), 3.85-3.93 (m, 3H), 3.97 (t, 1H, J = 6.3 Hz), 4.10 (dd, 1H, J = 7.9, 8.9 Hz), 4.13-4.18 (m, 2H), 4.22-4.27 (m, 1H), 4.49 (dd, 1H, J = 3.2, 8.0 Hz), 5.49 (d, 1H, J = 7.0 Hz), 7.25-7.34 (m,

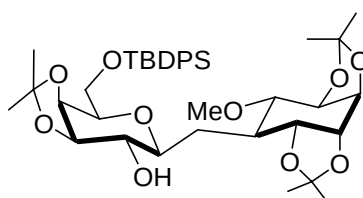
4H), 7.37-7.48 (m, 4H), 7.51-7.58 (m, 2H), 7.67-7.73 (m, 5H); ^{13}C NMR (500 MHz, CDCl_3) δ 19.1, 25.2, 25.3, 26.1, 26.7, 26.8, 26.9, 27.4, 27.8, 27.8, 29.7, 30.9, 34.3, 39.3, 58.6, 61.1, 74.2, 76.0, 76.6, 76.8, 77.5, 79.6, 79.7, 81.0, 83.7, 84.3, 109.0, 109.3, 111.3, 112.0, 127.3, 127.7, 127.8, 129.0, 129.7, 129.8, 131.8, 131.8, 133.0, 133.3, 134.1, 135.6, 159.4. HRMS (EI) m/z calcd for $\text{C}_{45}\text{H}_{60}\text{O}_9\text{NaSSi}$ ($\text{M} + \text{Na}$) $^+$ 827.3625, found 827.3625.



6-Deoxy-1,2,3,4-diisopropylidene-5-O-methy-6-C-(2,6-anhydro-7-O-tert-butylidiphenylsilyl-4,5-O-isopropylidene-1,3-dideoxy-D-galacto-hept-2-enitol-1-C-yl)-D-chiro-inositol (4.3)

A mixture of enol ether **4.4** from the previous step (5.22 g, 6.49 mmol), 2,6-di-tert-butyl-4-methylpyridine (20.0 g, 97.3 mmol), and freshly activated, powdered 4Å molecular sieves (15.3 g) in anhydrous CH_2Cl_2 (200 mL), was stirred for 15 min, at rt, under atmosphere of argon, then cooled to 0 °C. Methyl triflate (9.50 mL, 84.4 mmol) was then introduced, and the mixture warmed to rt, and stirred for an additional 18 h, at which time, triethylamine (15 mL) was added. The mixture was diluted with ether, washed with saturated aqueous NaHCO_3 and brine, dried (Na_2SO_4), filtered and evaporated in *vacuo*. FCC of the residue provided glycol **4.3** (2.66 g, 77 % based on recover glycol 1.22 g) as a light yellow oil. R_f = 0.58 (basic alumina, 10 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, C_6D_6) δ 1.29 (2s, 12H), 1.34 (s, 3H), 1.50 (s, 3H), 1.56 (s, 3H), 1.66 (s, 3H), 2.11-2.20 (m, 1H), 2.89 (d, 1H, J = 10.2 Hz), 3.07(dd, 1H, J = 6.9, 12.0 Hz), 3.56 (s,

3H), 4.1 (t, 1H, $J = 6.9$ Hz), 4.21-4.28 (m, 3H), 4.33 (dd, 2H, $J = 1.6, 6.4$ Hz), 4.36 (t, 1H, $J = 6.4$ Hz), 4.47 (d, 1H, $J = 6.4$ Hz), 4.73 (dd, 1H, $J = 2.93, 6.3$ Hz), 7.31-7.41 (m, 6H), 7.87 (m, 4H); ^{13}C NMR (500 MHz, C_6D_6) δ 19.3, 25.2, 25.4, 26.8, 27.0, 27.8, 28.0, 28.4, 34.1, 39.8, 58.5, 63.8, 71.0, 75.9, 76.9, 77.3, 77.8, 80.0, 81.1, 100.5, 108.8, 110.0, 129.8, 133.6, 133.6, 135.8, 135.8, 157.1. HRMS (EI) m/z calcd for $\text{C}_{39}\text{H}_{54}\text{O}_9\text{NaSi}$ ($M + \text{Na}$) $^+$ 717.3429, found 717.3422.

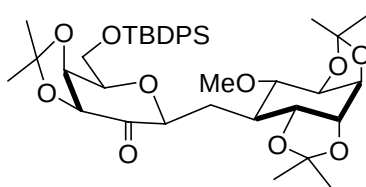


4.2

6-Deoxy-1,2,3,4-diisopropylidene-5-O-methyl-6-C-(2,6-anhydro-7-O-tert-butylidiphenylsilyl-4,5-O-isopropylidene-1,3-dideoxy-D-galacto-hept-2-enitol-1-C-yl)-D-chiro-inositol (4.2)

$\text{BH}_3 \cdot \text{Me}_2\text{S}$ (1.1 mL, 1M solution in THF, mmol) was added at 0 °C to a solution of glycal **4.3** (0.191 g, 0.275 mmol) in anhydrous THF (8 mL) under an atmosphere of argon. The mixture was warmed to rt and stirred for an additional 1 h. At that time the solution was recooled to 0 °C and treated with a mixture of 3N NaOH (2 mL) and 30% aqueous H_2O_2 (2 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 **4.2** (0.149 g, 76 %). $R_f = 0.51$ (25 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.06 (s, 9H), 1.33 (2s, 6H), 1.4 (s, 3H), 1.44 (s, 3H), 1.52 (2s, 6H), 1.71-1.78 (m, 1H), 1.95-2.08 (m, 1H), 2.42 (d, 1H, $J = 3.4$ Hz), 3.01 (dd, 1H, $J = 6.3, 12.2$ Hz), 3.42-3.46 (m, 2H), 3.49 (s, 3H), 3.81-3.92 (m,

3H), 4.03 (t, 1H, $J = 5.6$ Hz), 4.05-4.09 (m, 2H), 4.16-4.24 (m, 2H), 4.39 (dd, 1H, $J = 1.8$, 5.3 Hz), 7.35-7.46 (m, 6H), 7.67-7.75 (m, 4H); ^{13}C NMR (500 MHz, CDCl_3) δ 19.2, 25.3, 25.4, 26.4, 26.7, 27.7, 27.8, 28.4, 32.7, 37.5, 58.7, 62.7, 73.8, 74.8, 75.5, 76.1, 77.2, 79.1, 80.1, 80.3, 80.3, 109.2, 109.4, 109.6, 127.6, 127.7, 129.6, 135.6, 135.6. HRMS (EI) m/z calcd for $\text{C}_{39}\text{H}_{56}\text{O}_{10}\text{NaSi}$ ($M + \text{Na}$) $^+$ 735.3534, found 735.3537.

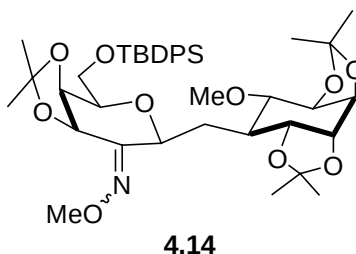


4.13

C-pseudodisaccharide ketone (4.13)

To a mixture of PCC (0.401 g, 1.87 mmol), florisil (0.996 g), sodium acetate (0.15 g, 1.87 mmol), freshly activated, powdered 4A molecular sieves (0.996 g) and Celite (0.996 g) in dry dichloromethane (15 mL), was added dropwise a solution of alcohol **4.2** (0.322 g, 0.466 mmol) in dry dichloromethane (5 mL). The reaction mixture was stirred at rt until TLC indicated total consumption of the starting material. The mixture was then diluted with ether and filtered through a column of florisil. The filtrate was evaporated in *vacuo* and the residue purified by FCC to afford ketone **4.13** (0.315 g, 95%) as colorless oil. $R_f = 0.51$ (25% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.07 (s, 9H), 1.30 (s, 3H), 1.35 (s, 3H), 1.42 (2s, 6H), 1.51 (s, 3H), 1.60 (s, 3H), 1.76-1.85 (m, 1H), 1.85-1.95 (m, 1H), 2.19-2.29 (m, 1H), 3.01 (dd, 1H, $J = 6.3$, 12.1 Hz), 3.34 (s, 3H), 3.90-3.99 (m, 2H), 4.01-4.13 (m, 3H), 4.15-4.24 (m, 2H), 4.26 (dd, 1H, $J = 3.8$, 9.2 Hz), 4.47 (d, 1H, $J = 5.8$ Hz), 4.77 (dd, 1H, $J = 1.7$, 5.8 Hz), 7.32-7.56 (m, 6H), 7.67-7.99 (m, 4H); ^{13}C NMR (500 MHz, CDCl_3) δ 19.2, 25.3, 25.4, 26.1, 26.8, 27.2, 27.7, 27.9, 29.8,

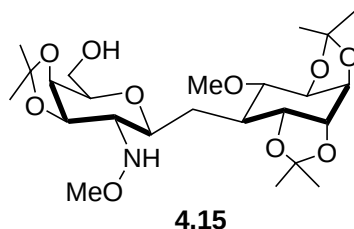
38.3, 58.9, 62.5, 76.7, 76.7, 77.1, 77.5, 77.8, 79.0, 79.1, 80.0, 80.3, 109.2, 109.4, 110.8, 127.7, 127.7, 128.3, 129.7, 135.5, 135.6, 204.6. HRMS (EI) m/z calcd for $C_{39}H_{54}O_{10}SiNa$ ($M + Na$)⁺ 733.3393, found 733.3393.



C-pseudodisaccharide oxime (4.14)

To a solution of ketone **4.13** (0.312 g, 0.439 mmol) in a 1:1 mixture THF/MeOH (5.5 mL), was added a solution of O-methyl hydroxylamine hydrochloride (0.367 g, 4.39 mmol) and NaOAc (0.397 g, 4.82 mmol) in water (2.75 mL), adjusted to pH = 4.5 with glacial acetic acid. The reaction mixture was stirred at rt for 4 h, then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give **4.14** as a 1.5:1 mixture of oxime O-methyl ethers (0.280 g, 86%), as colorless oil. R_f = 0.60 (20 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.25-1.45 (4s, 12H), 1.49 (s, 3H), 1.59 (s, 3H), 1.70-1.79 (m, 1H, minor), 1.79-1.88 (m, 1H, major), 1.97-2.11 (m, 2H, major), 2.34-2.45 (m, 1H, major), 2.45-2.54 (m, 1H, minor), 3.07 (dd, 1H, J = 6.2, 12.4 Hz, minor), 3.12 (dd, 1H, J = 6.7, 12.5 Hz, major), 3.38-3.41 (m, 1H, major), 3.48 (s, 3H), 3.80-3.86 (m, 3H, major), 3.93(s, 3H), 4.03 (t, 1H, J = 7.0 Hz, major), 4.06 (t, 1H, J = 6.1 Hz, minor), 4.14 (t, 1H, J = 7.3 Hz, major), 4.16 (t, 1H, J = 7.3 Hz, major), 4.34 (dd, 1H, J = 7.0, 8.1 Hz, major), 4.46 (dd, 1H, J = 1.6, 7.8 Hz, minor), 4.51 (dd, 1H, J = 1.7, 7.9 Hz, major), 4.62 (dd, 1H, J = 2.9, 10.9 Hz, minor), 4.78 (d, 1H, 7.8 Hz, major),

5.09 (d, 1H, $J = 9.4$ Hz, major), 5.51 (d, 1H, 7.8 Hz, major), 7.36-7.48 (m, 6H), 7.68-7.75 (m, 4H); ^{13}C NMR (500 MHz, CDCl_3) δ 19.2, 19.2, 25.2, 25.3, 25.3, 25.4, 25.4, 25.5, 26.0, 26.2, 26.8, 27.8, 27.9, 34.0, 37.0, 37.9, 38.6, 58.4, 58.6, 62.2, 62.3, 62.5, 62.6, 65.8, 72.5, 73.6, 74.2, 75.1, 75.6, 76.0, 76.6, 76.7, 77.1, 77.2, 77.5, 78.9, 79.0, 79.5, 79.8, 80.3, 80.5, 109.1, 109.2, 109.3, 109.5, 110.8, 111.2, 127.6, 127.7, 128.3, 129.6, 133.4, 133.5, 133.5, 133.6, 135.6, 135.7, 135.7, 154.8, 156.1. HRMS (EI) m/z calcd for $\text{C}_{40}\text{H}_{57}\text{NO}_{14}\text{NaSi}$ ($M + \text{Na}$) $^{+}$ 762.3643, found 762.3643.

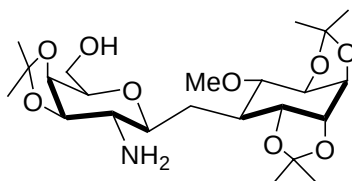


6-Deoxy-1,2,3,4-diisopropylidene-5-O-methyl-6-C-(2,6-anhydro-7-O-tert-butylidiphenylsilyl-4,5-O-isopropylidene-1,3-dideoxy-D-galacto-hept-2-deoxy-2-amino-1-C-yl)-D-chiro-inositol (4.15)

To a mixture of oxime *O*-methyl ether **4.14** (0.092 g, 0.124 mmol), and Bu_3SnH (0.065 mL, 0.248 mmol) in CH_2Cl_2 (3 mL), was added at -20 °C, $\text{BF}_3\cdot\text{OEt}_2$ (0.015 mL, 0.124 mmol). The mixture was stirred at -20 °C for 2h, then diluted with saturated aqueous NaHCO_3 and extracted with CH_2Cl_2 . The combined organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. FCC of the residue afforded the methoxy amine derivative (0.075 g, 82%) as a colorless oil. $R_f = 0.81$ (25 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.06 (s, 9H), 1.33 (s, 3H), 1.35 (s, 3H), 1.38 (s, 3H), 1.46 (s, 3H), 1.51 (2s, 6H), 1.78-1.88 (m, 1H), 2.01-2.11 (m, 2H), 2.59 (dd, 1H, $J = 8.1, 9.3$ Hz), 3.05 (dd, 1H, $J = 6.1, 12.3$ Hz), 3.49 (s, 3H), 3.56 (s, 3H), 3.73 (m, 1H), 3.80-3.88 (m, 2H), 3.91 (dd, 1H, $J = 7.5, 9.0$ Hz), 4.06 (t, 1H, $J = 6.5$ Hz), 4.13 (dd, 1H, $J = 7.2, 8.6$

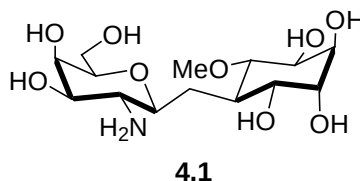
Hz), 4.17-4.22 (m, 2H), 4.36-4.43 (m, 2H), 6.01 (bs, 1H), 7.31-7.51 (m, 6H), 7.71-7.82 (m, 4H); ^{13}C NMR (500 MHz, CDCl_3) δ 19.2, 25.3, 26.4, 26.8, 27.8, 27.8, 28.5, 33.2, 37.8, 58.5, 62.3, 62.9, 65.7, 72.9, 73.2, 73.7, 75.9, 77.4, 79.1, 79.9, 80.4, 109.2, 109.2, 109.4, 127.6, 127.7, 129.6, 133.5, 133.6, 135.6, 135.6. HRMS (EI) m/z calcd for $\text{C}_{40}\text{H}_{59}\text{NO}_{10}\text{SiNa}$ ($\text{M} + \text{Na}$) $^{+}$ 764.3688, found 764.3688.

To a solution of product from the previous step (0.033 g, 0.046 mmol) in dry THF (1 mL), was added TBAF (0.09 mL, 0.09 mmol) at rt. Reaction was stirred for 5 h at rt, diluted with saturated aqueous NaHCO_3 and extracted with ether. The combined organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. FCC of the residue afforded **4.15** (0.022 g, 95%) as a colorless oil. R_f = 0.20 (50 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.36 (s, 9H), 1.52 (3s, 9H), 1.77-1.86 (m, 1H), 2.05-2.17 (m, 2H), 2.44 (dd, 1H), 2.61-2.69 (m, 2H), 3.10 (dd, 1H, J = 6.5, 12.3 Hz), 4.06 (t, 1H, J = 7.1 Hz), 4.12 (t, 1H, J = 6.9 Hz), 4.17 (dd, 1H, J = 1.8, 5.5 Hz), 4.21 (t, 1H, J = 7.4 Hz), 4.25 (t, 1H, J = 4.2 Hz), 4.39 (dd, 1H, J = 5.5, 8.2 Hz), 5.97 (d, 1H, J = 1.3 Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 25.3, 25.5, 26.4, 27.8, 28.0, 28.0, 28.3, 29.4, 33.4, 37.8, 54.9, 58.6, 62.4, 63.0, 65.7, 69.8, 73.3, 73.3, 75.3, 76.5, 77.4, 77.5, 78.3, 80.2, 80.5, 109.5, 109.7, 109.9.

**4.16**

6-Deoxy-1,2,3,4-diisopropylidene-5-O-methyl-6-C-(2,6-anhydro-7-O-tert-butylidiphenylsilyl-4,5-O-isopropylidene-1,3-dideoxy-D-galacto-hept-2-deoxy-2-amino-1-C-yl)-D-chiro-inositol (4.16)

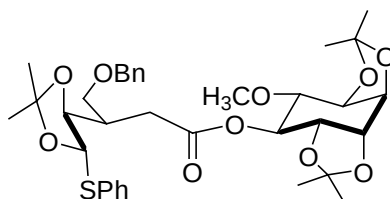
Liquid NH_3 was condensed into a solution of methoxyamine **4.15** (0.122 g, 0.242 mmol) in THF (4 mL) at $-78\text{ }^\circ\text{C}$ under an atmosphere of argon. Sodium was then slowly added to the solution until the blue color was persistent for several minutes. After warming to rt, the reaction was quenched with solid NH_4Cl , and filtered. The organic phase was concentrated in *vacuo*. FCC of the residue afforded **4.16** (0.090 g, 78%) as a colorless oil. $R_f = 0.48$ (25 % methanol: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 0.69 (3S, 9H), 0.85 (3S, 9H), 1.42 (m, 2H), 2.09 (t, 1H, $J = 8.8$ Hz), 2.47 (dd, 1H, $J = 6.4, 12.3$ Hz), 2.55 (t, 1H, $J = 9.2$ Hz), 2.85 (s, 3H), 3.05 (m, 2H), 3.21 (m, 2H), 3.37 (t, 1H, $J = 7.0$ Hz), 3.41 (m, 2H), 3.52 (t, 1H, $J = 7.4$ Hz), 3.60 (t, 1H, $J = 7.0$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 24.6, 24.9, 25.9, 27.2, 27.4, 27.7, 32.3, 37.0, 56.1, 57.9, 62.3, 72.9, 75.4, 76.0, 76.8, 77.6, 79.4, 79.8, 80.1, 108.9, 109.1, 109.4.



Amine (4.1)

A solution of amine **4.16** (0.052g, 0.11 mmol) in dry methanol (3mL) adjusted to pH 2-3 by addition of a solution of HCl in ether. The mixture was stirred over 18 h, then diluted with methanol, evaporated under reduced pressure. Dissolution of the residue in methanol and removal of the volatiles was repeated three times to give **4.1** (0.038 g, 98 %); $R_f = 0.67$ (4:4:1:2 of 2-propanol: pyridine: acetic acid: water). ^1H NMR (500 MHz, D_2O) δ 1.77 (ddd, 1H, $J = 2.6, 7.5, 14.8$ Hz), 1.85 (ddd, 1H, $J = 1.8, 9.9, 14.7$ Hz), 2.05 (m, 1H), 3.05 (t, 1H, $J = 10.3$ Hz), 3.52 (t, 1H, $J = 3.2$ Hz), 3.40 (s, 3H), 3.57 (dd, 1H, $J = 3.7, 8.1$ Hz), 3.61 (dd, 1H, $J = 4.1, 11.8$ Hz), 3.69 (dd, 1H, $J = 8.0, 11.8$ Hz), 3.75 (dd,

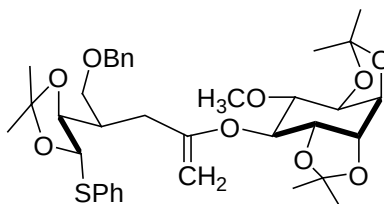
1H, J = 3.3, 10.6 Hz), 3.77 (t, 1H, J = 3.2 Hz), 3.80 (t, 1H, J = 3.1 Hz), 3.81 (dd, 1H, J = 3.4, 7.0 Hz), 3.87 (d, 1H, J = 3.2 Hz), 3.90 (t, 1H, J = 3.7 Hz); ^{13}C NMR (500 MHz, D_2O) δ 30.9, 36.6, 54.0, 57.5, 61.3, 68.0, 70.3, 70.4, 71.2, 71.9, 72.1, 75.2, 78.5, 79.8. HRMS (EI) m/z calcd for $\text{C}_{14}\text{H}_{27}\text{NO}_9$ ($\text{M} + \text{H}$) $^+$ 355.1762, found 355.1760.



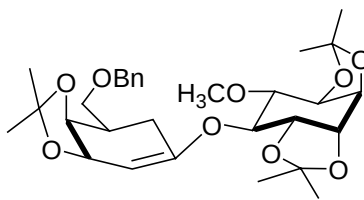
4.23

TIA ester (4.23)

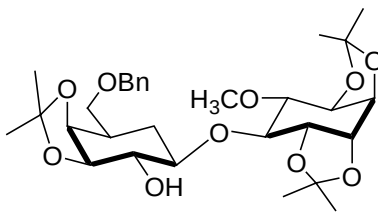
The TIA acid **4.22** (77.2 mg, 0.19 mmol) and alcohol **4.9** (68.2 mg, 0.25 mmol) was subjected to the procedure that was used for the preparation of **4.12**. FCC of the crude product afforded the TIA ester **4.23** (0.11 g, 87%) as colorless oil. R_f = 0.60 (15% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.32 (s, 3H), 1.39 (s, 3H), 1.46 (s, 9H), 1.55 (s, 3H), 2.59-2.79 (m, 3H), 3.22 (dd, 1H, J = 7.4, 11.4 Hz), 3.47 (s, 3H), 3.55-3.75 (m, 2H), 4.20-4.32 (m, 3H), 4.38 (dd, 1H, J = 4.2, 6.0 Hz), 4.42 (dd, 1H, J = 4.2, 6.4 Hz), 4.45-4.60 (m, 2H), 5.07 (dd, 1H, J = 8.2, 11.4 Hz), 5.48 (d, 1H, J = 6.6 Hz), 7.22-7.41 (m, 8H), 7.45-7.53 (m, 2H); ^{13}C NMR (500 MHz, CDCl_3) δ 25.4, 25.6, 25.8, 27.3, 27.4, 25.6, 27.9, 32.3, 38.5, 59.6, 59.7, 69.5, 72.3, 72.3, 73.1, 75.8, 75.8, 75.9, 76.4, 78.8, 80.0, 80.0, 80.6, 87.1, 109.5, 109.8, 110.9, 127.2, 127.5, 127.6, 127.7, 127.7, 128.3, 128.4, 128.4, 128.4, 128.9, 129.0, 129.0, 131.5, 134.6, 138.3, 171.7. HRMS (EI) m/z calcd for $\text{C}_{35}\text{H}_{46}\text{O}_{10}\text{NaS}$ ($\text{M} + \text{Na}$) $^+$ 681.2703, found 681.2684.

**4.21****TIA enol ether (4.21)**

The TIA ester **4.23** (1.10 g, 1.70 mmol) was subjected to the procedure that was used for the preparation of **4.4**. FCC of the crude product afforded the enol ether **4.2** (1.04 g, 94%) as the light yellow oil. $R_f = 0.80$ (alumina, 20 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, C_6D_6) δ 1.16 (s, 6H), 1.41 (s, 3H), 1.46 (2s, 6H), 1.52 (s, 3H), 2.42 (dd, 1H, $J = 8.6, 13.8$ Hz), 2.65-2.80 (m, 2H), 3.13-3.22 (m, 1H), 3.48 (s, 3H), 3.65 (dd, 1H, $J = 7.1, 9.4$ Hz), 3.75 (dd, 1H, $J = 3.8, 9.3$ Hz), 4.01-4.10 (m, 2H), 4.10-4.20 (m, 4H), 4.24 (d, 1H, $J = 1.5$ Hz), 4.37 (ABq $\Delta\delta = 0.07$, $J = 9.9$ Hz), 4.55-4.61 (m, 1H), 4.63 (dd, 1H, $J = 5.3, 6.4$ Hz), 5.88 (d, 1H, $J = 6.6$ Hz), 7.89-7.38 (m, 8H), 7.56-7.67 (m, 2H); ^{13}C NMR (500 MHz, C_6D_6) δ 25.7, 25.8, 26.3, 28.0, 28.3, 28.3, 34.2, 39.7, 60.2, 70.5, 73.7, 77.3, 77.4, 78.9, 79.2, 79.5, 81.9, 82.1, 87.0, 88.0, 109.6, 111.3, 127.3, 127.9, 128.2, 128.7, 128.9, 129.0, 128.9, 129.5, 129.5, 129.5, 131.6. HRMS (EI) m/z calcd for $\text{C}_{36}\text{H}_{48}\text{O}_9\text{NaS}$ ($M + \text{Na}$) $^+$ 679.2908, found 679.2928.

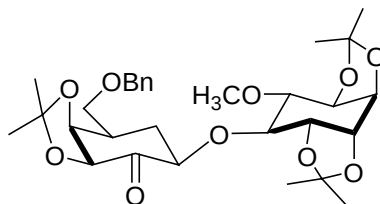
**4.20****Enol ether (4.20)**

Reaction of **4.21** (0.100 g, 0.15 mmol) under the condition that were used for the synthesis of (**4.3**) provided **4.20** (0.055g, 71%) as light yellow oil. $R_f = 0.55$ (alumina, 20% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, C_6D_6) δ 1.15 (s, 9H), 1.41 (3s, 9H), 2.09-2.19 (m, 1H), 2.32 (dd, 1H, $J = 5.3, 16.2$ Hz), 2.37-2.50 (m, 1H), 3.28 (dd, 1H, $J = 7.3, 11.1$ Hz), 3.39-3.49 (m, 5H), 3.61 (d, 1H, $J = 7.2, 8.8$ Hz), 4.02-4.26 (m, 9H), 4.31 (s, 2H), 4.72 (m, 1H), 5.28 (t, 1H, $J = 2.8$ Hz), 7.04-7.29 (m, 5H); ^{13}C NMR (500 MHz, C_6D_6) δ 25.6, 25.7, 27.5, 27.9, 28.2, 28.3, 28.9, 38.0, 60.3, 72.7, 73.5, 73.5, 75.4, 77.5, 77.7, 78.1, 79.2, 79.5, 82.0, 98.5, 109.6, 109.6, 128.0, 128.1, 128.7, 128.8, 128.9, 139.7, 156.7.

**4.19****Carba pseudodisaccharide alcohol (4.19)**

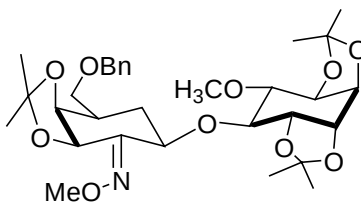
Hydroboration of the glycal **4.20** (0.060g, 0.11 mmol) under the conditions described in the synthesis (**4.2**) lead to alcohol **4.19** (0.048g, 80%) $R_f = 0.74$ (alumina, 30 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.38 (2s, 9H), 1.55 (2s, 9H), 2.01-2.09 (m, 1H), 2.11-2.22 (m, 1H), 3.1 (dd, 1H, $J = 7.0, 11.2$ Hz), 3.29-3.40 (m, 1H),

3.47-3.47 (m, 9H), 3.92 (dd, 1H, $J = 5.0, 7.6$ Hz), 4.19 (t, 1H, $J = 6.7$ Hz), 4.21-4.39 (m, 6H), 4.49 (s, 2H), 7.29-7.40 (m, 5H); ^{13}C NMR (500 MHz, C_6D_6) δ 25.0, 25.4, 26.4, 27.3, 27.8, 28.3, 28.5, 35.1, 59.8, 71.4, 73.1, 74.1, 76.3, 76.4, 76.7, 76.8, 78.3, 78.7, 79.7, 80.3, 81.6, 82.1, 83.6, 109.2, 109.5, 110.1, 127.1, 127.4, 127.5, 128.4, 138.6. HRMS (EI) m/z calcd for $\text{C}_{30}\text{H}_{43}\text{O}_{10}\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 587.2826, found 587.2815.

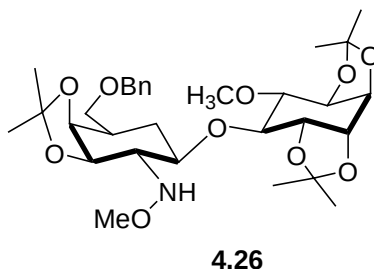
**4.24**

Caba pseudodisaccharide ketone (4.24)

Alcohol **4.19** (0.043 g, 0.076 mmol), was dissolved in DMSO (1 ml). IBX (0.06 g, 0.20 mmol) was added to the solution and the reaction was heated at 55 °C over 18 h. The mixture was then diluted with saturated aqueous NaHCO_3 and extracted with ether. Organic extract was dried and evaporated in *vacuo*. The residue was purified by FCC to give ketone **4.24** (0.042 g, 98%) as the colorless oil. $R_f = 0.79$ (30% ethyl acetate: petroleum ether). ^1H NMR (500 MHz, C_6D_6) δ 1.18 (2s, 6H), 1.25 (s, 3H), 1.41 (2s, 6H), 1.50 (s, 1H), 1.92 (q, 1H, $J = 12.7$ Hz), 2.00-2.11 (m, 1H), 2.25-2.32 (m, 1H), 3.30 (dd, 1H, $J = 7.1, 8.8$ Hz), 3.29 (m, 1H), 3.46-3.55 (m, 3H), 3.56 (s, 3H), 3.99 (d, 1H, $J = 5.0$ Hz), 4.05-4.18 (m, 4H), 4.18-4.25 (m, 2H), 4.27 (ABq $\Delta = 0.07\text{ppm}$, $J = 12.2$ Hz), 4.50 (t, 1H, $J = 6.9$ Hz), 7.07-7.33 (m, 10H); ^{13}C NMR (500 MHz, C_6D_6) δ 25.5, 25.8, 26.8, 27.8, 28.2, 28.3, 31.9, 36.1, 60.5, 71.3, 73.7, 77.6, 78.0, 78.1, 79.7, 80.0, 80.3, 81.7, 81.8, 82.2, 109.8, 109.8, 110.3, 128.1, 128.9, 139.4, 204.5. HRMS (EI) m/z calcd for $\text{C}_{30}\text{H}_{42}\text{O}_{10}\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 585.2670, found 585.2676.

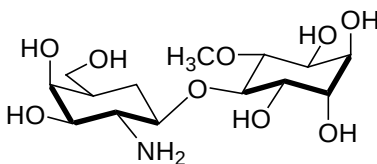
**4.25****Carba pseudodisaccharide oxime (4.25)**

Ketone **4.24** (0.017 g, .03 mmol) was converted to mixture of oxime **4.25** (0.015g, 83%) under the condition that were used in the synthesis of (**4.14**). $R_f = 0.65$ (20 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.34 (s, 3H), 1.54 (s, 3H), 1.39 (s, 3H), 1.51 (s, 3H), 1.53 (s, 3H), 1.55 (s, 3H), 1.61 (s, 3H), 1.85-1.95 (m, 2H), 2.07-2.20 (m, 2H), 3.31 (dd, 1H, $J = 7.1, 11.1$ Hz), 3.41 (dd, 1H, $J = 6.8, 9.1$), 3.61 (s, 3H), 3.78 (dd, 1H, $J = 6.0, 11.2$ Hz), 3.92 (s, 3H), 4.09-4.23 (m, 5H), 4.35 (t, 1H, $J = 6.1$ Hz), 4.49 (t, 1H, $J = 5.5$ Hz), 4.51-4.61 (m, 4H), 4.76(d, 0.30H, $J = 7.8$ Hz, minor), 4.93 (dd, 0.31H, $J = 8.2, 9.8$ Hz, minor), 5.53 (d, 1H, $J = 7.6$ Hz), 5.63 (dd, 0.32H, $J = 1.9, 6.0$ Hz, minor) 7.25-7.40 (m, 5H); ^{13}C NMR (500 MHz, CDCl_3) δ 23.8, 23.8, 23.9, 24.2, 25.0, 25.1, 25.3, 25.5, 25.6, 25.8, 27.7, 27.7, 28.0, 29.1, 35.3, 35.8, 60.5, 60.7, 62.1, 62.3, 66.4, 67.3, 67.7, 70.6, 70.9, 73.2, 74.0, 74.6, 75.7, 76.6, 77.8, 78.6, 78.7, 79.5, 80.5, 81.2, 109.5, 109.7, 109.9, 110.1, 127.6, 127.6, 128.4, 138.4, 153.2. HRMS (EI) m/z calcd for $\text{C}_{31}\text{H}_{46}\text{NO}_{10}$ ($\text{M} + \text{H}$) $^+$ 592.3116, found 592.3122.



Carba pseudodisaccharide methoxyamine (4.26)

Oxime **4.25** (0.004 g, 0.024 mmol) provided compound **4.26** (0.012 g, 85%) under the conditions that were used in the synthesis of (**4.15**). $R_f = 0.62$ (35 % ethyl acetate: petroleum ether). ^1H NMR (500 MHz, C_6D_6) δ 1.15 (s, 3H), 1.20 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 1.51 (s, 3H), 1.74 (q, 1H, $J = 12.3, 12.4$ Hz), 2.80-2.10 (m, 1H), 2.37-2.45 (m, 1H), 2.96 (t, 1H, $J = 9.4$ Hz), 3.13 (dd, 1H, $J = 6.9, 11.1$ Hz), 3.51 (s, 3H), 3.67 (s, 3H), 3.77-3.90 (m, 1H), 3.95-4.05 (m, 2H), 4.08-4.24 (m, 4H), 4.30-4.41 (m, 3H), 7.01-7.42 (m, 5H); ^{13}C NMR (500 MHz, C_6D_6) δ 25.3, 25.6, 27.2, 27.9, 28.2, 29.1, 30.3, 30.4, 36.7, 59.7, 63.3, 70.3, 72.6, 73.5, 75.0, 76.3, 76.8, 77.7, 77.8, 79.4, 80.4, 80.4, 80.5, 83.3, 109.1, 109.6, 109.9, 127.9, 127.9, 127.9, 128.9, 139.8. HRMS (EI) m/z calcd for $\text{C}_{31}\text{H}_{48}\text{NO}_{10}$ ($M + \text{H}$) $^+$ 594.3272, found 592.3283.



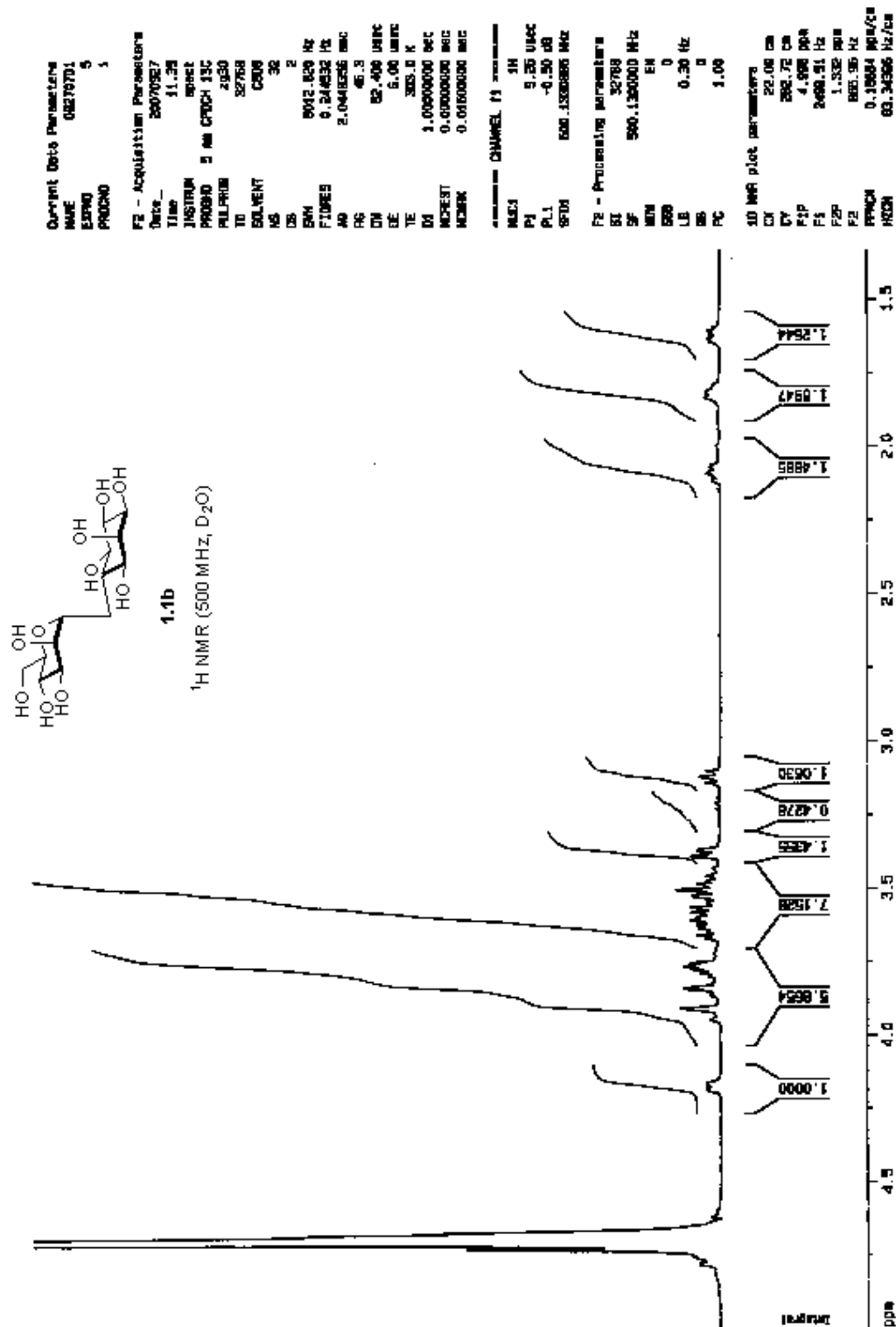
4.18 carba-INS-2-hydrochloride

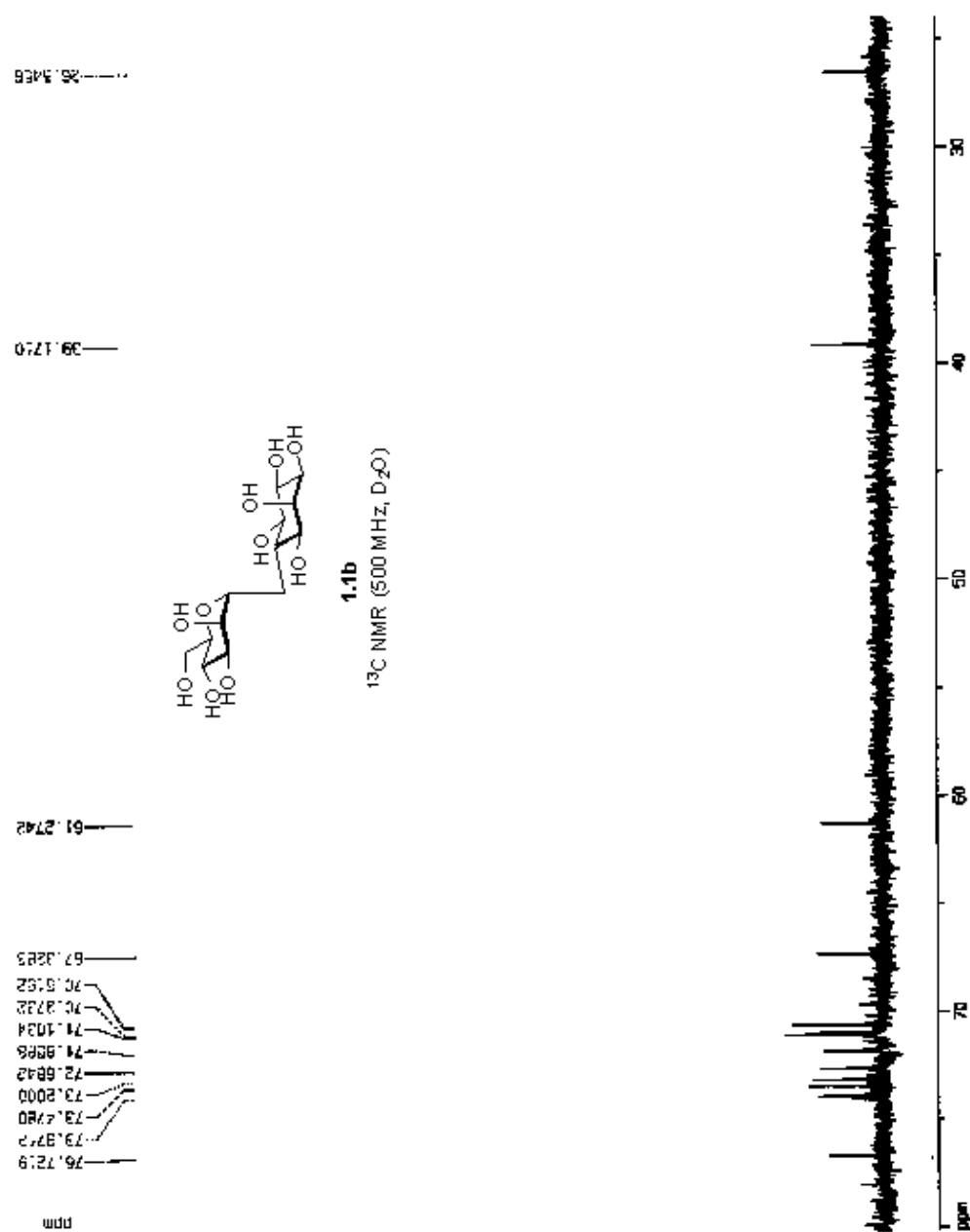
Amine 4.18

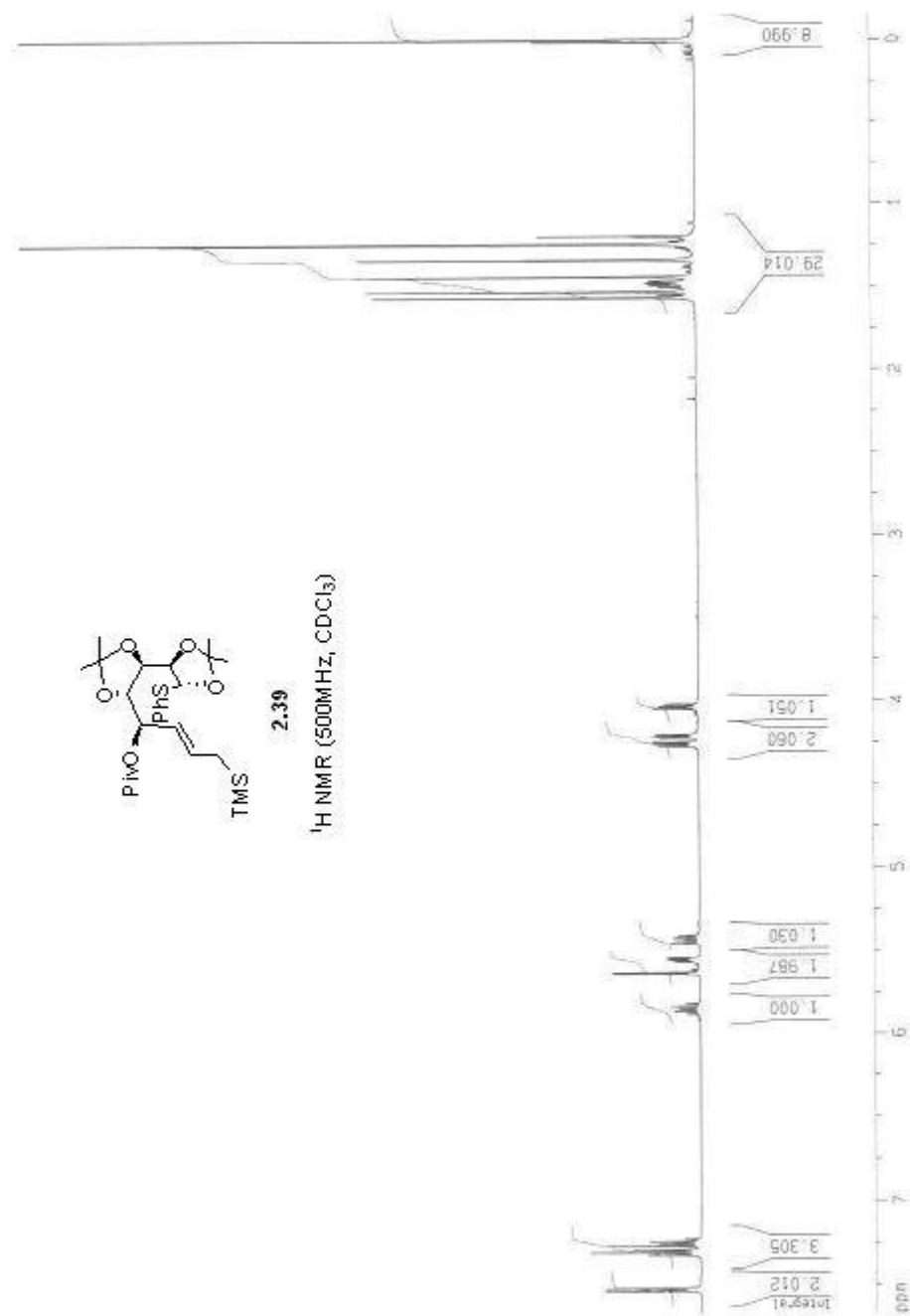
The compound **4.26** (0.010 g, 0.020 mmol) was carried out under the procedure discussed for (**4.16**). FCC of the residue afforded amine (0.006 g, 75%).

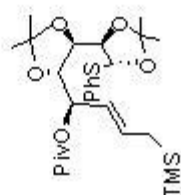
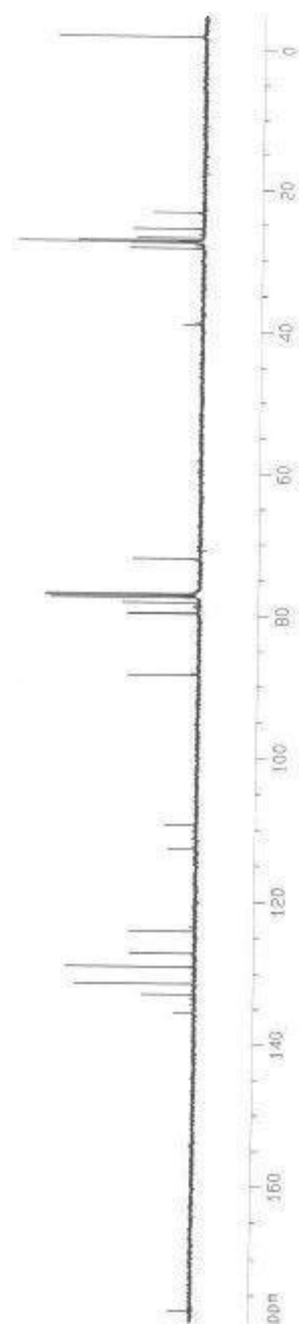
Product from the previous step (0.005g, 0.01 mmol) was treated in similar conditions as for **4.1**. FCC of the residue afforded **4.18** (0.0037 g, 95 %); ^1H NMR (500 MHz, D_2O) δ 1.42-1.51 (m, 1H), 1.63-1.75 (bs, 1H), 1.99-2.14 (bm, 1H), 3.15-3.23 (m, 1H), 3.24-3.30 (m, 1H), 3.48-3.78 (m, 8H), 3.81-4.13 (m, 2H); ^{13}C NMR (500 MHz, D_2O) δ 38.0, 46.7, 60.0, 60.7, 62.0, 69.8, 70.1, 70.3, 70.5, 71.5, 71.6, 72.1, 81.0, 82.0.

Appendix



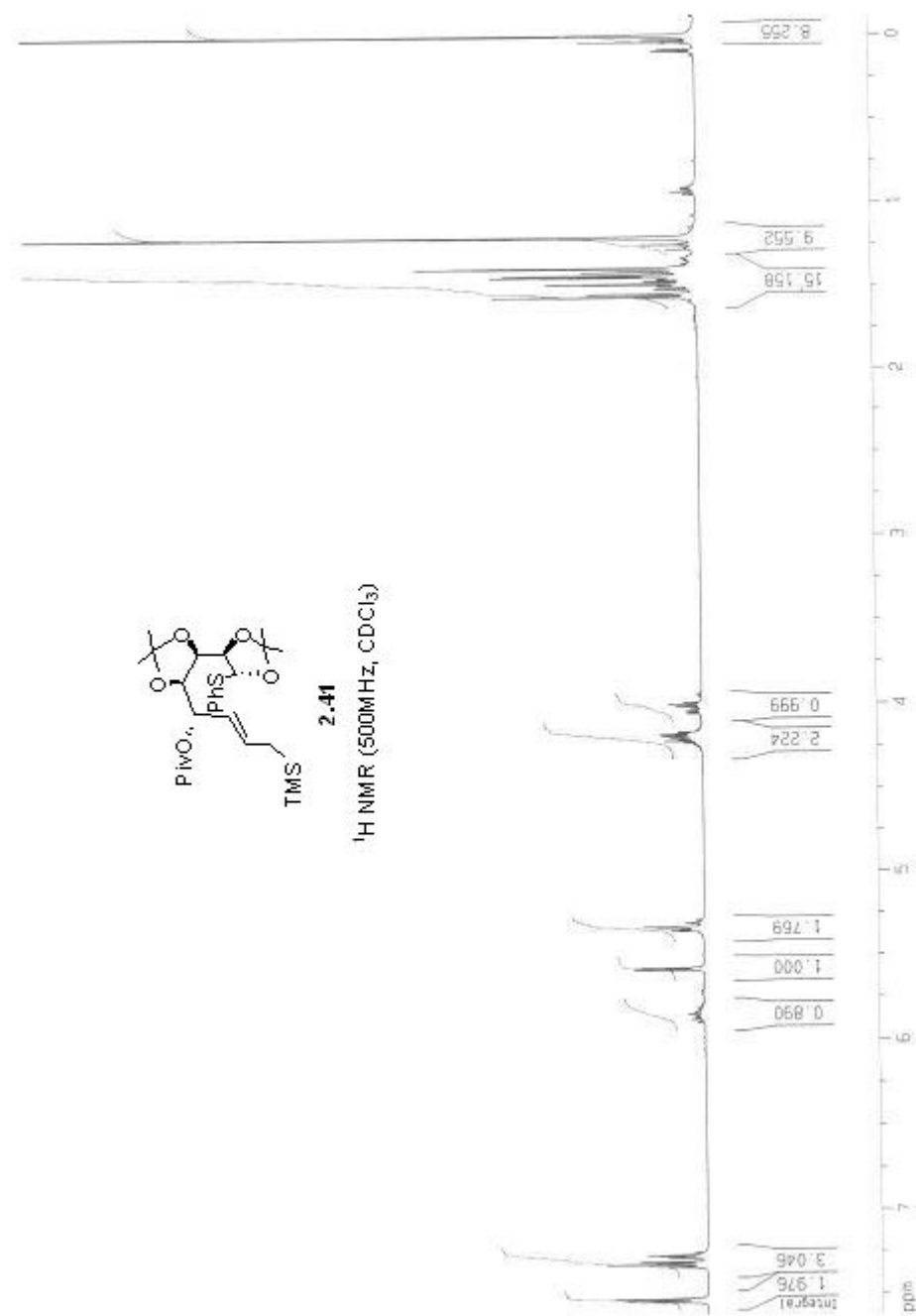


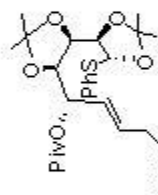




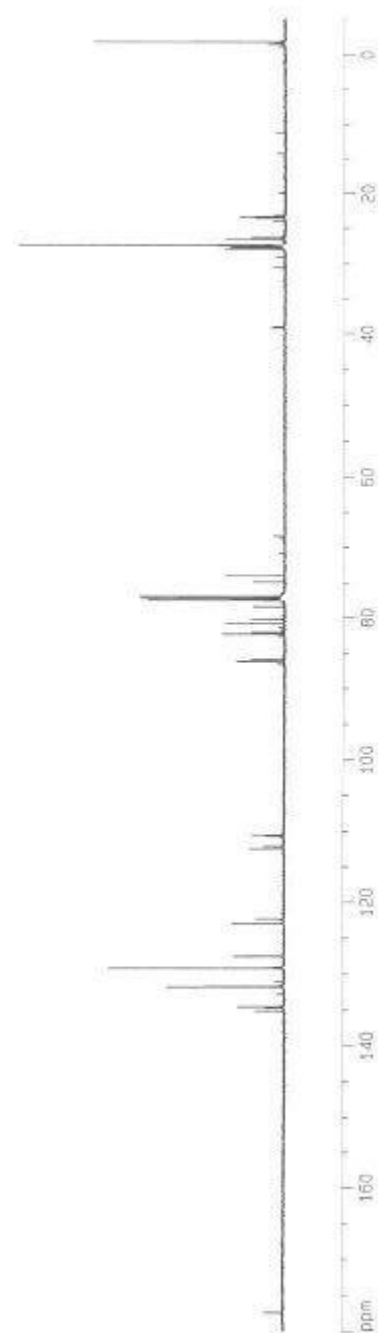
2.39

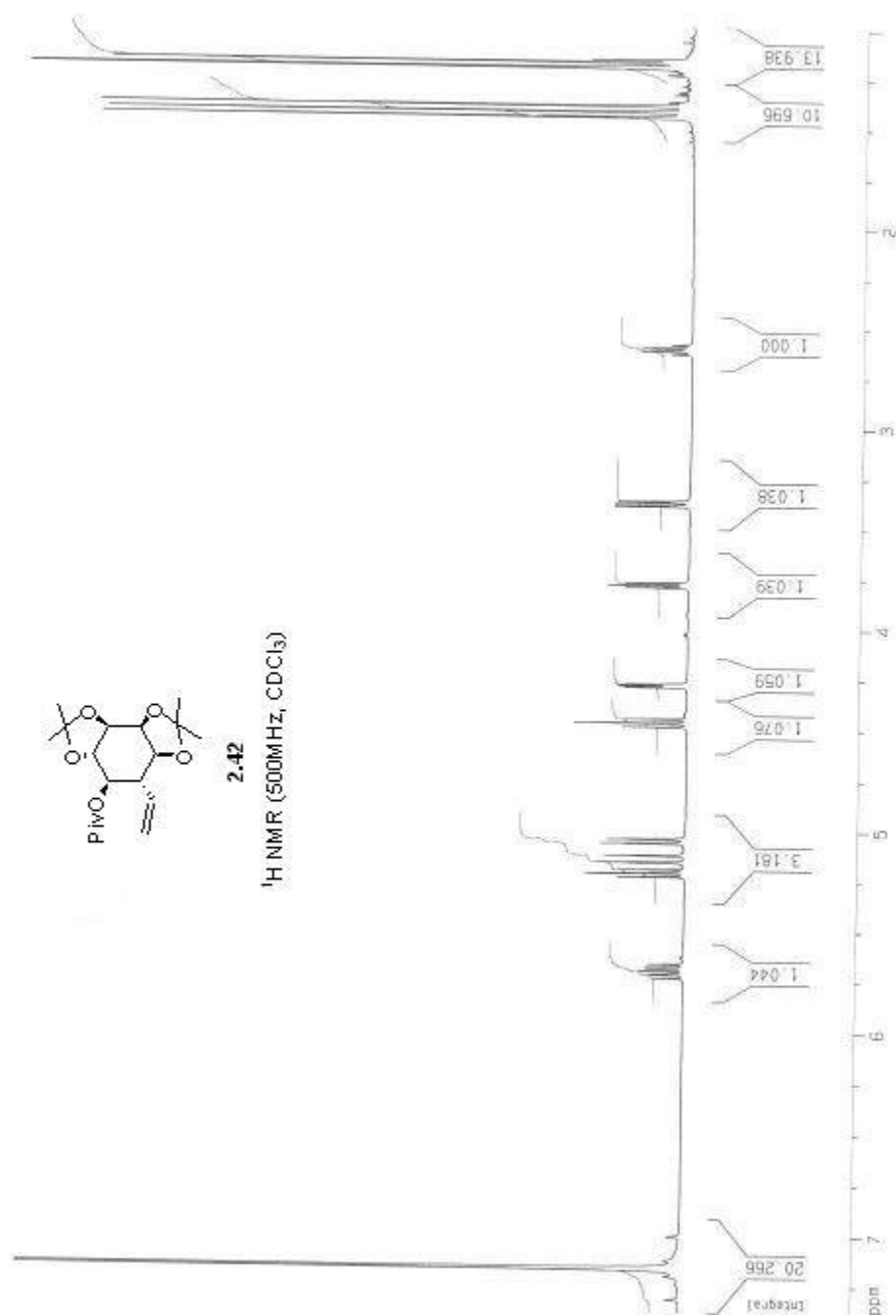
 ^{13}C NMR (500MHz, CDCl_3)



**2.41**

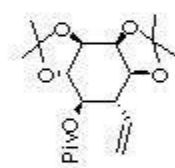
¹³C NMR (500MHz, CDCl₃)



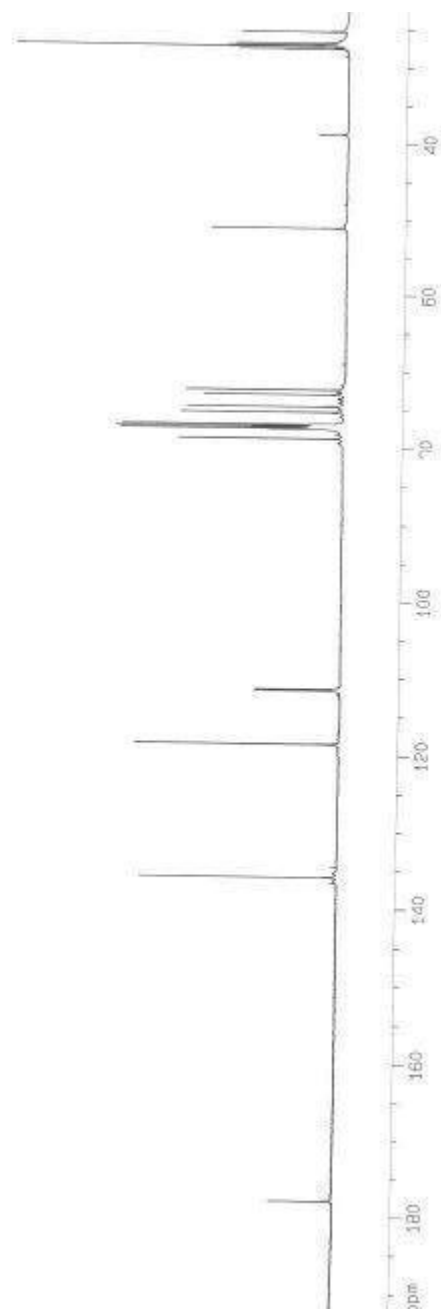


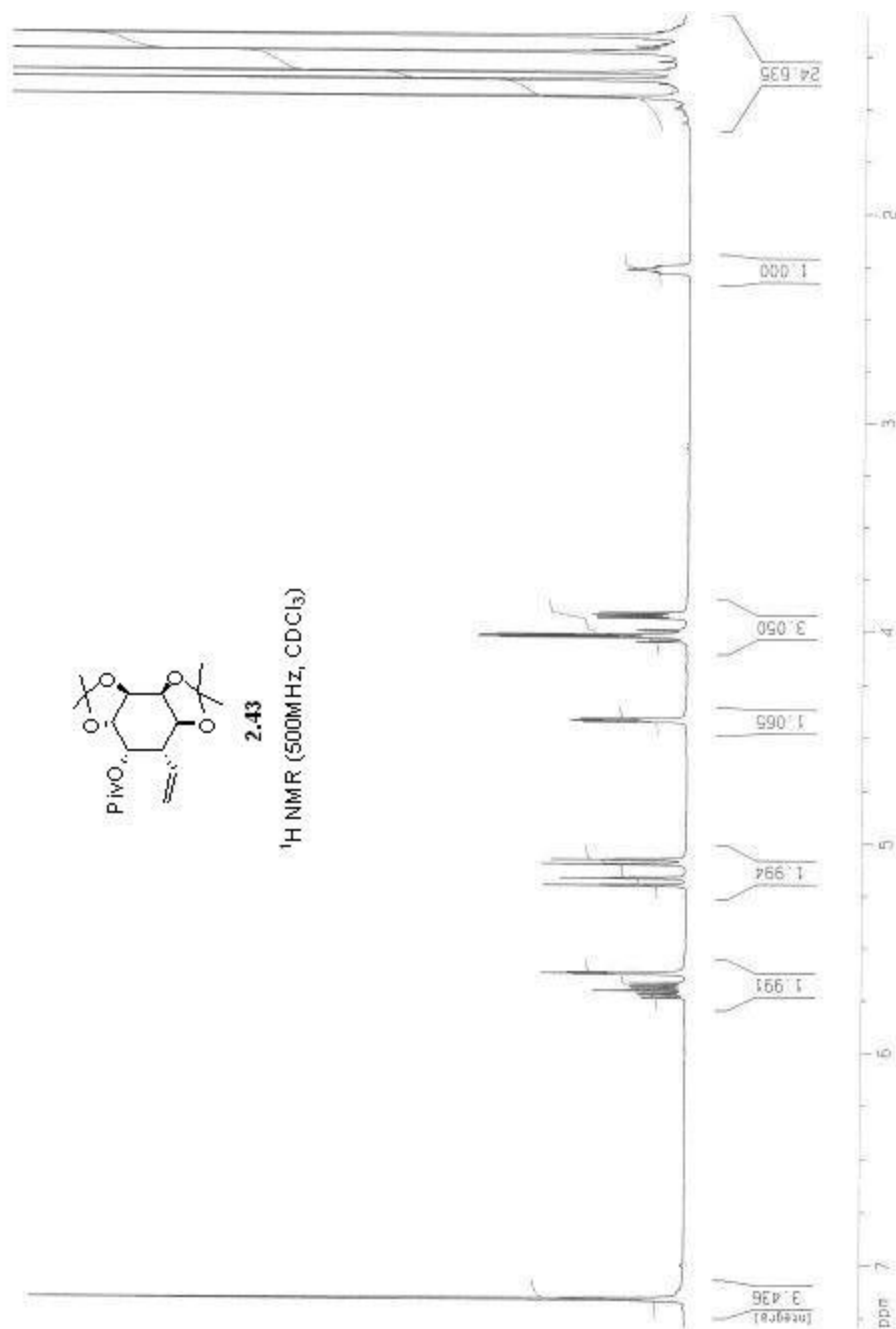


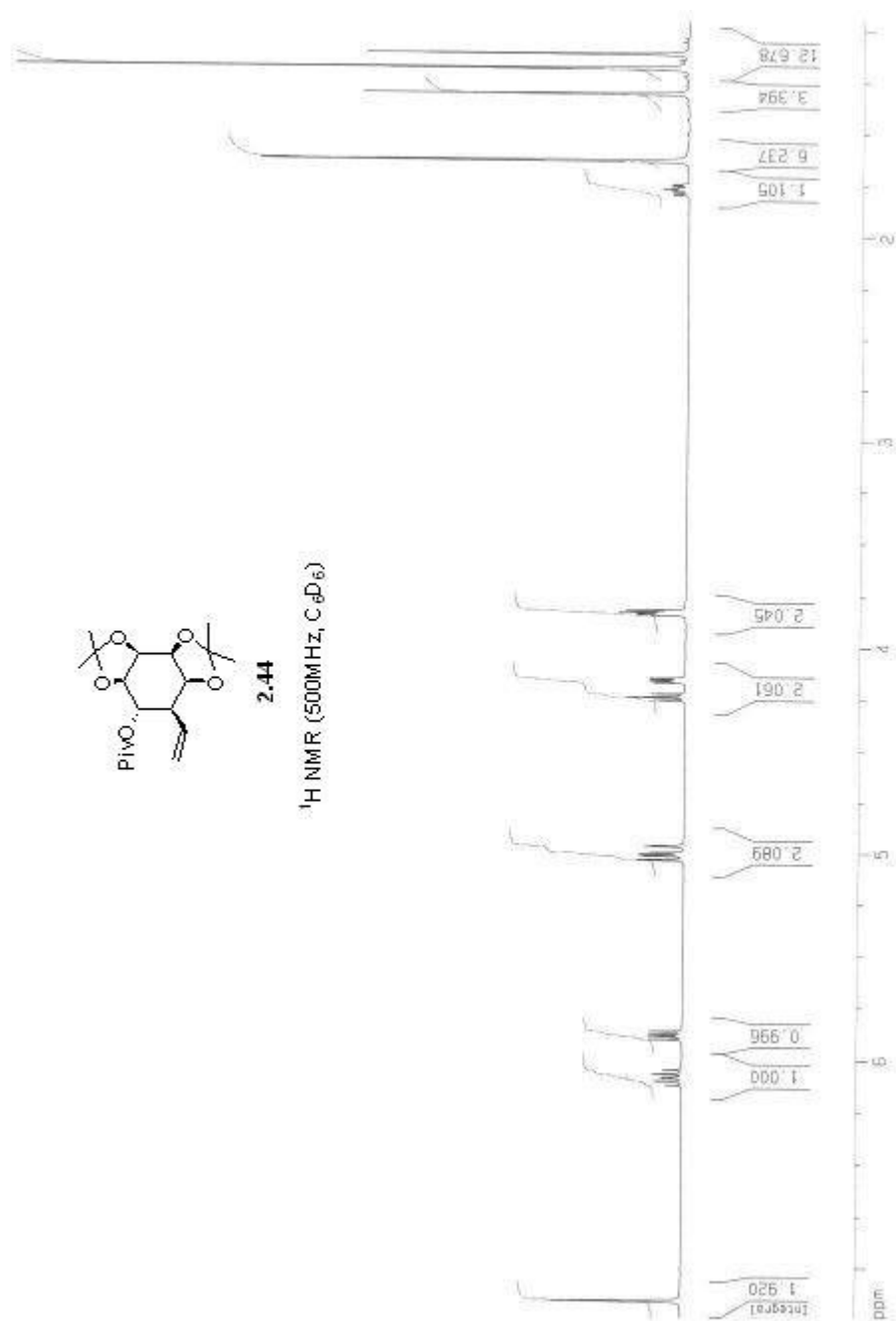
150

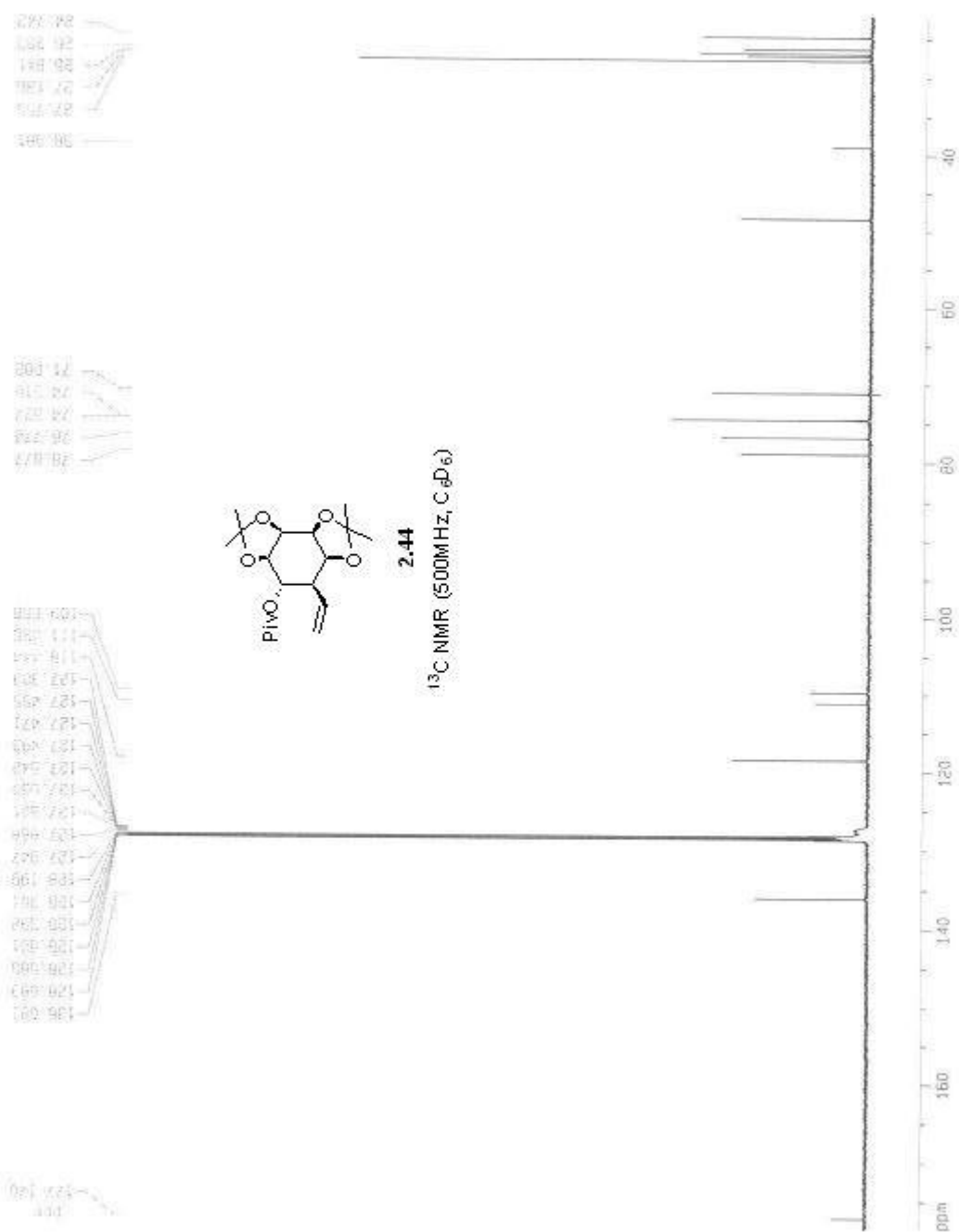


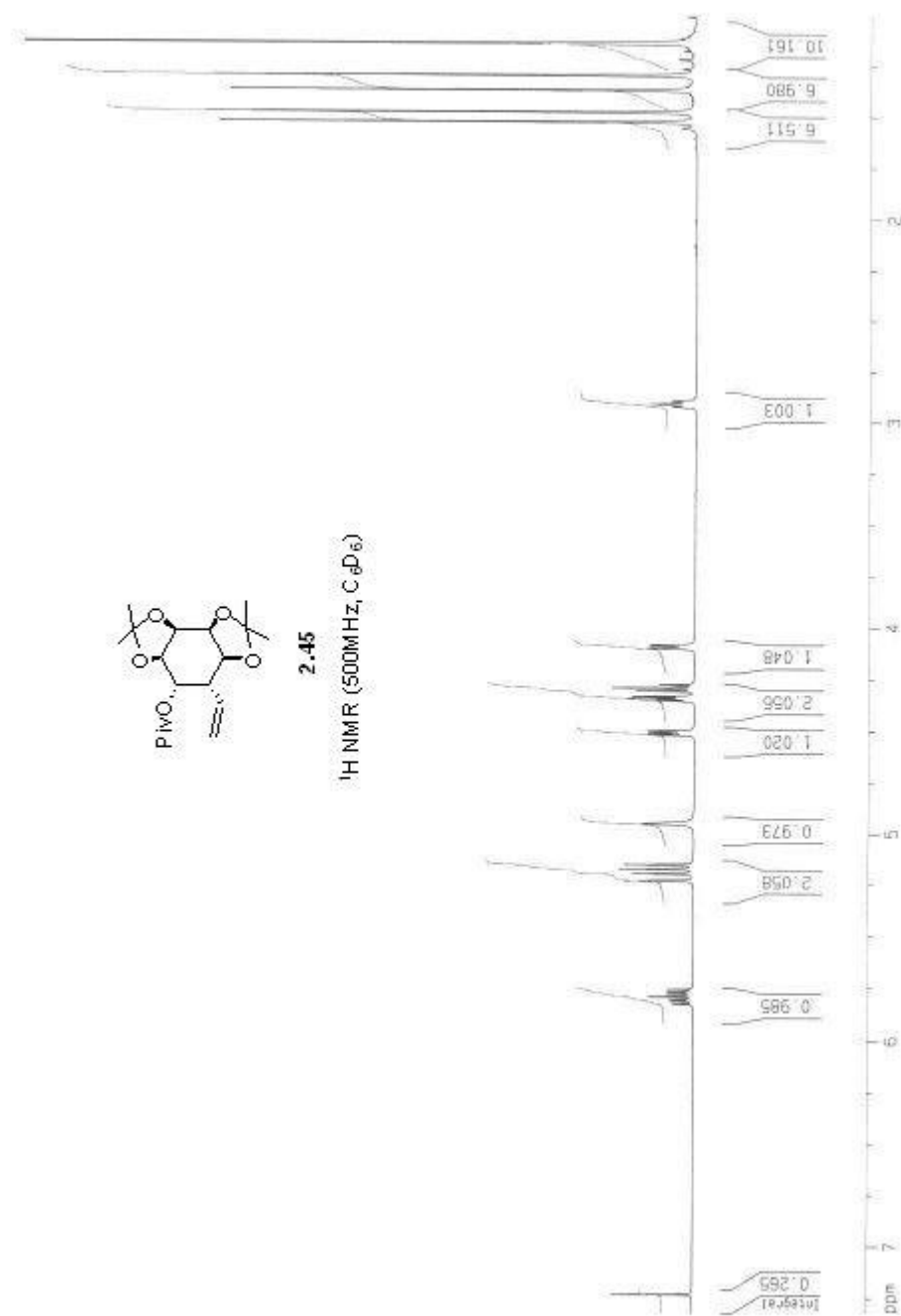
2.42

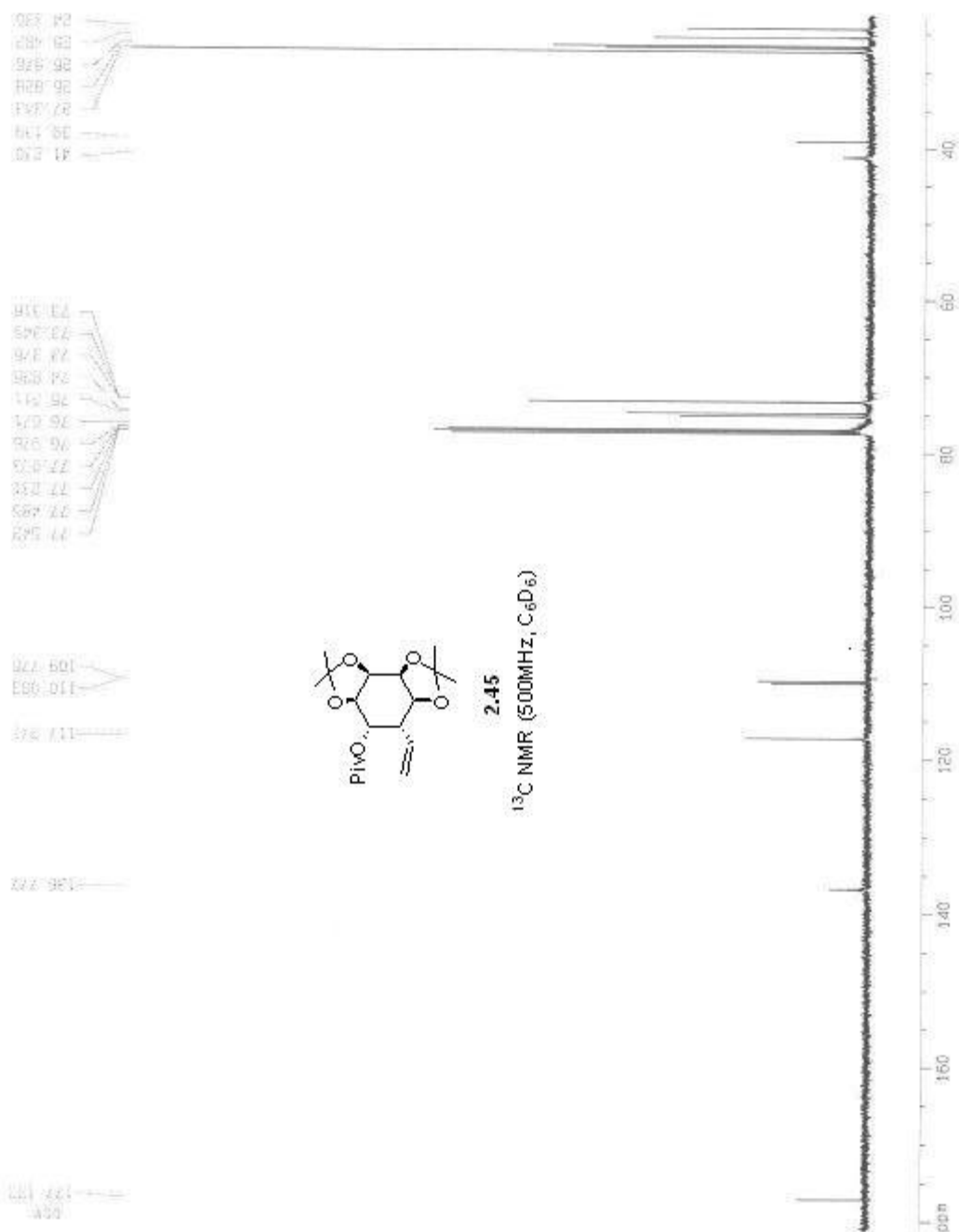
 ^{13}C NMR (500MHz, CDCl_3)

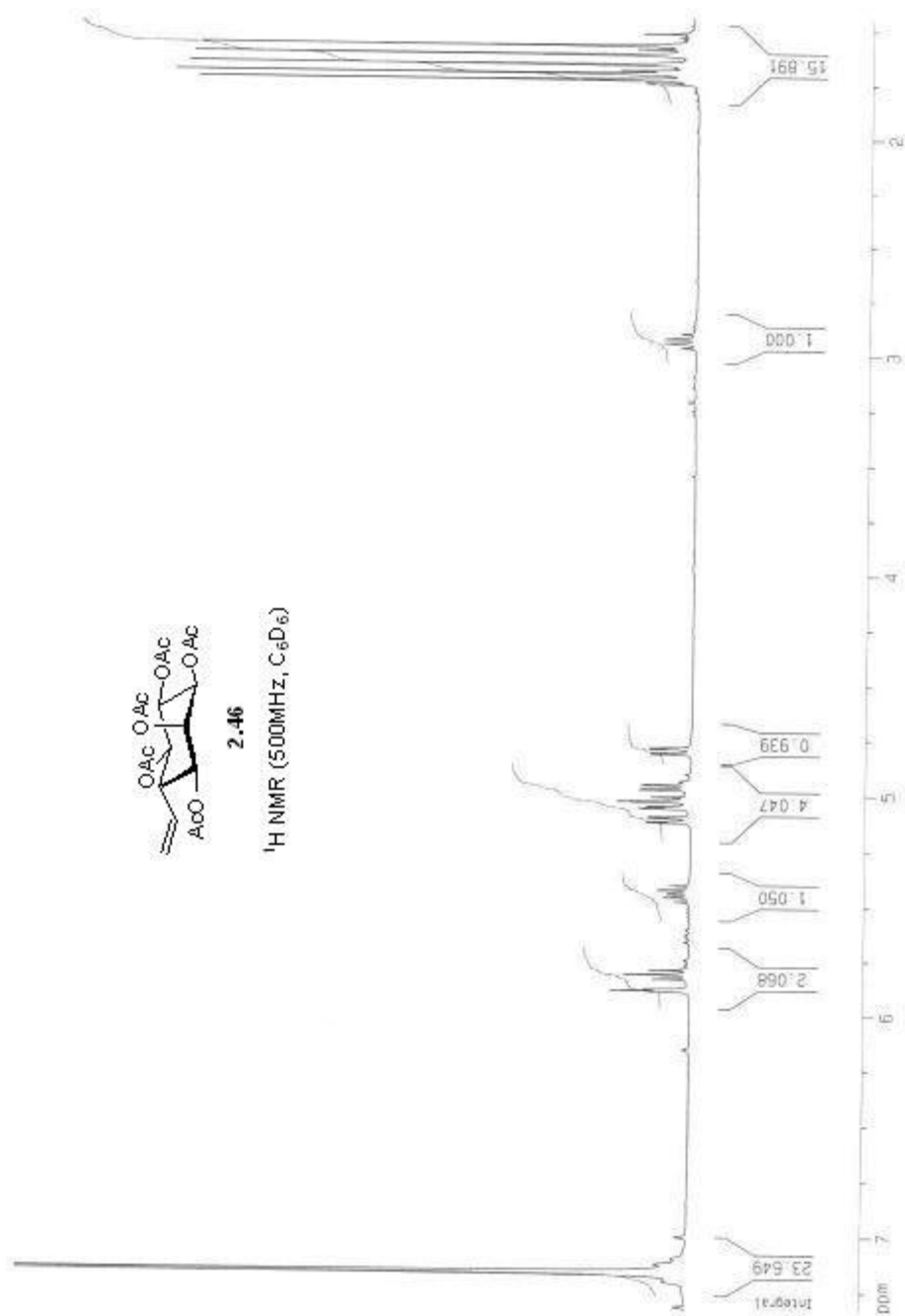


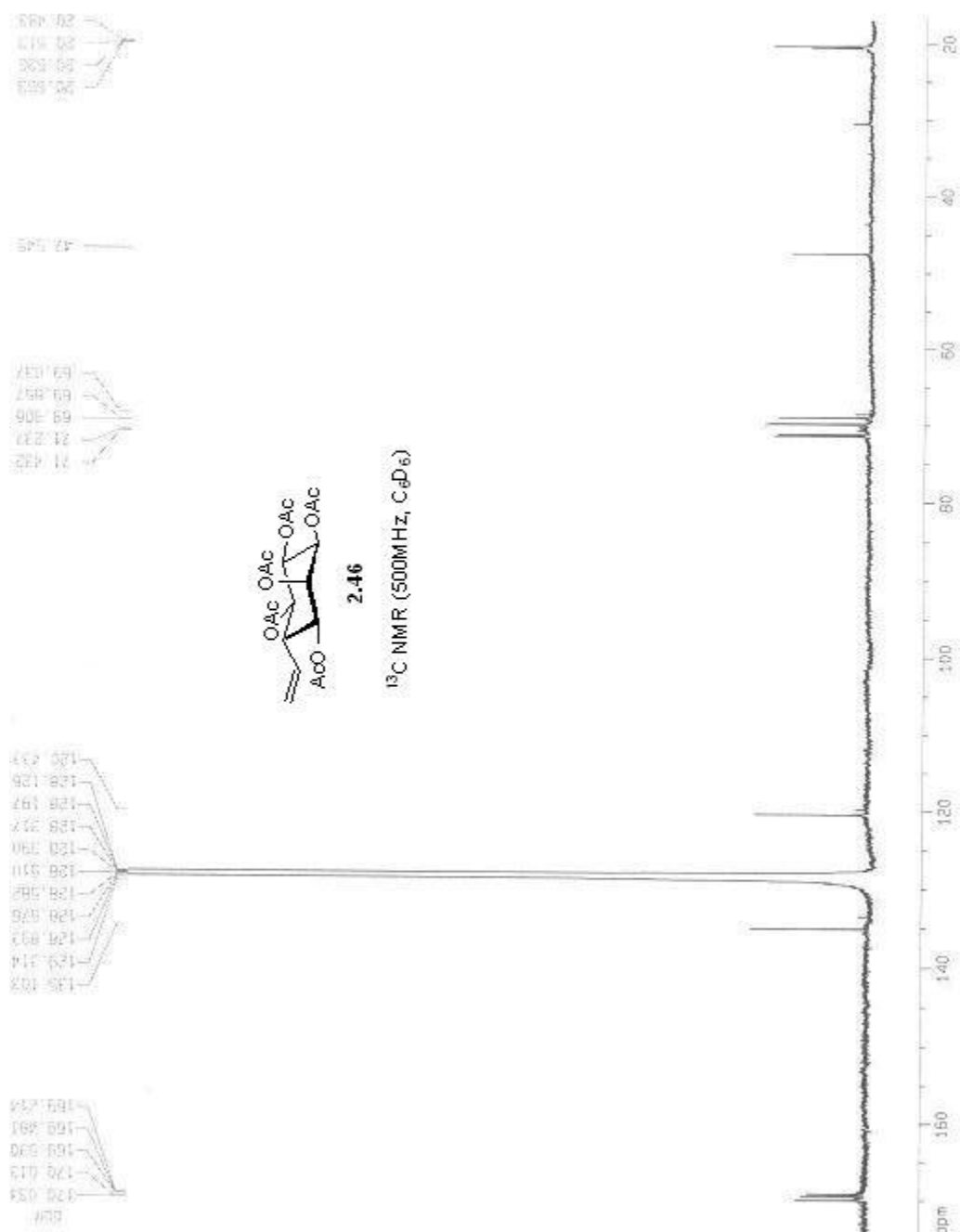


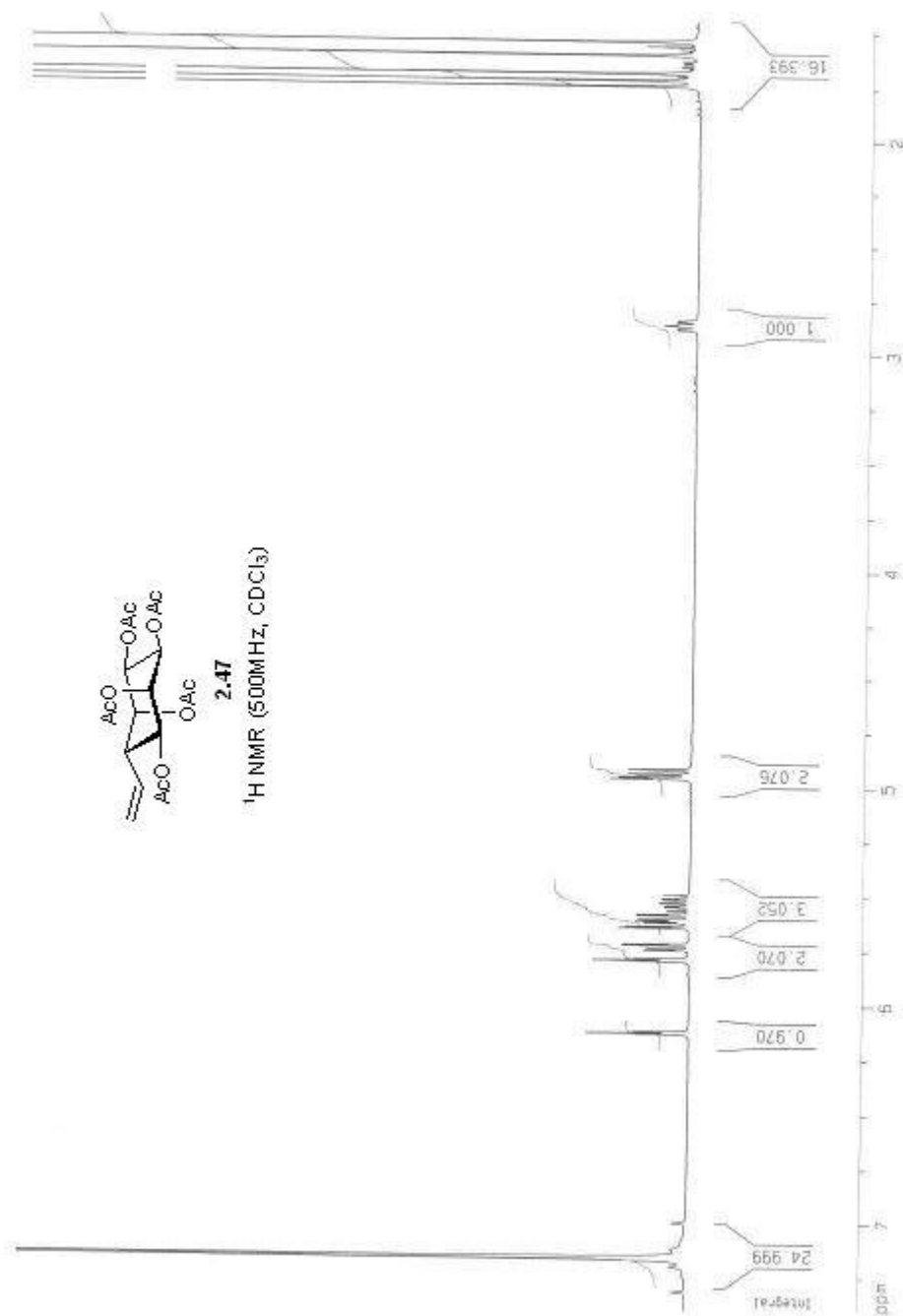


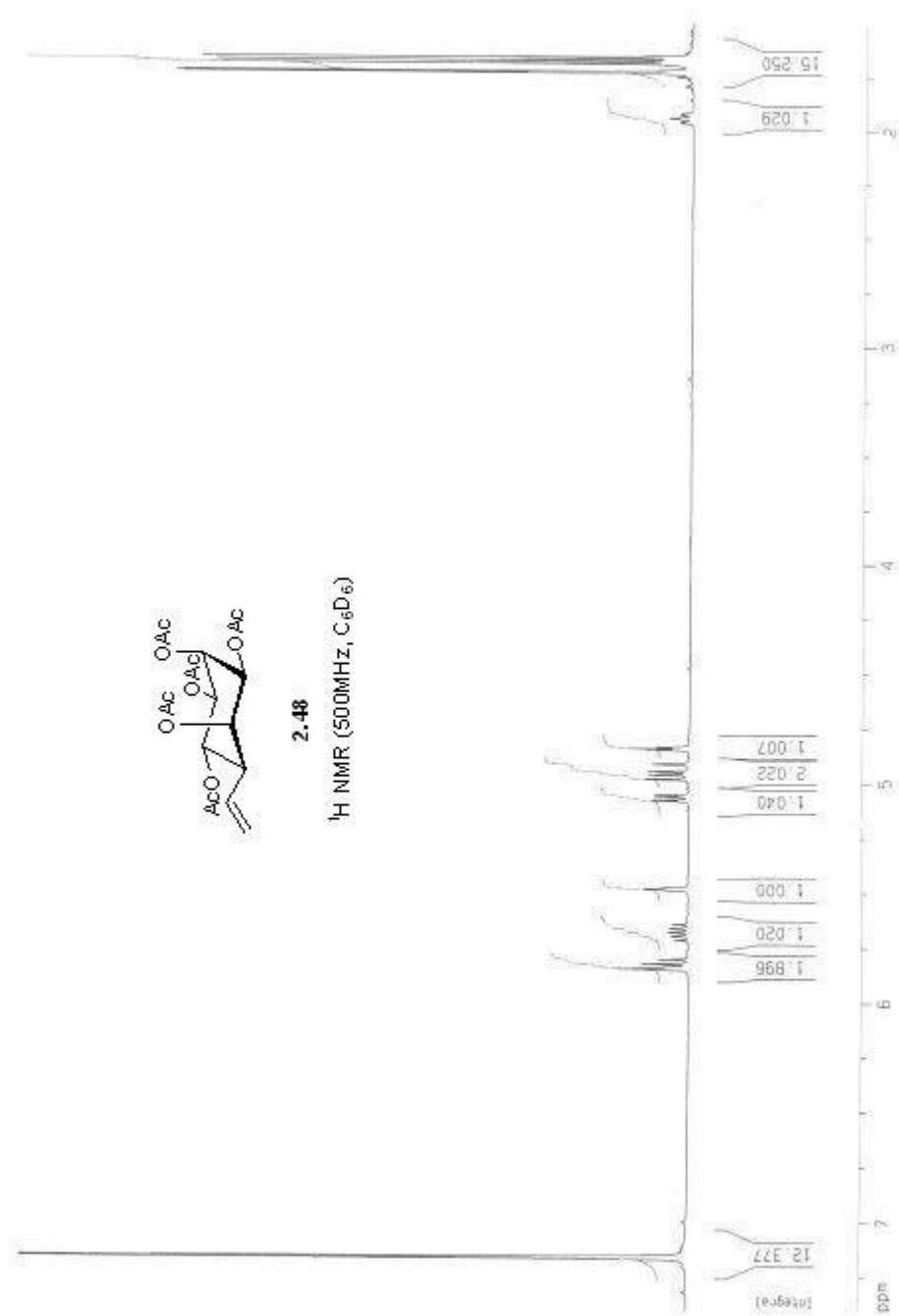


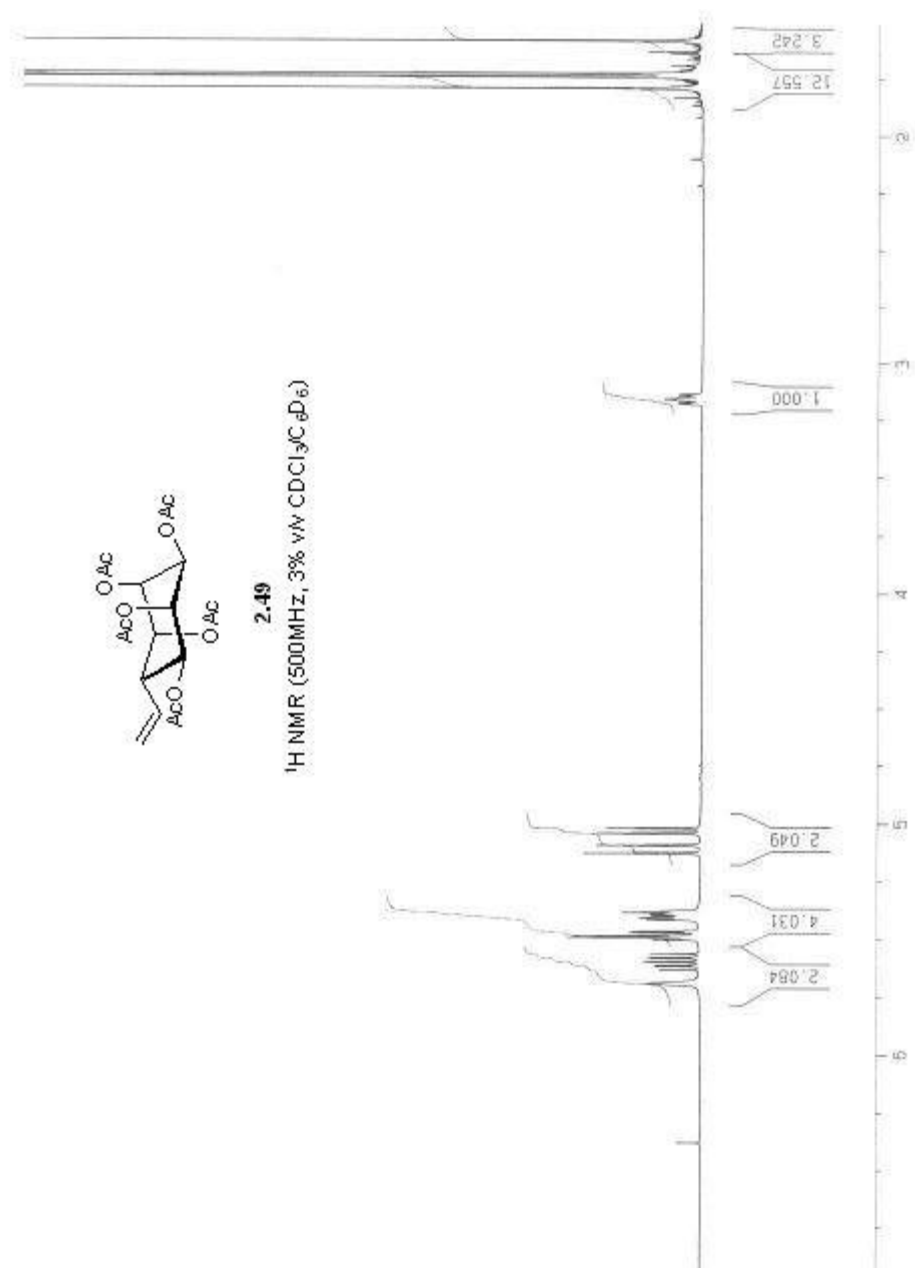


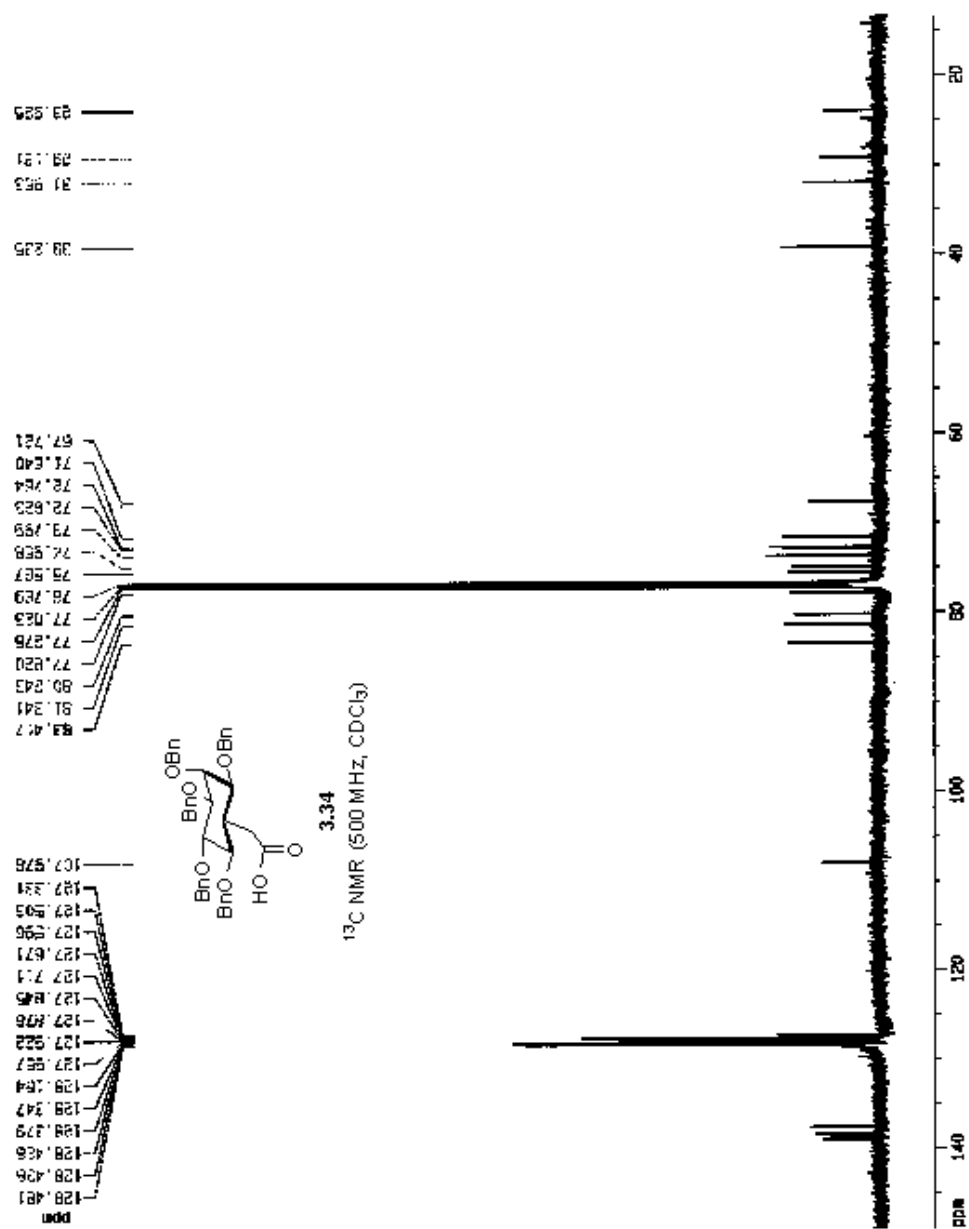


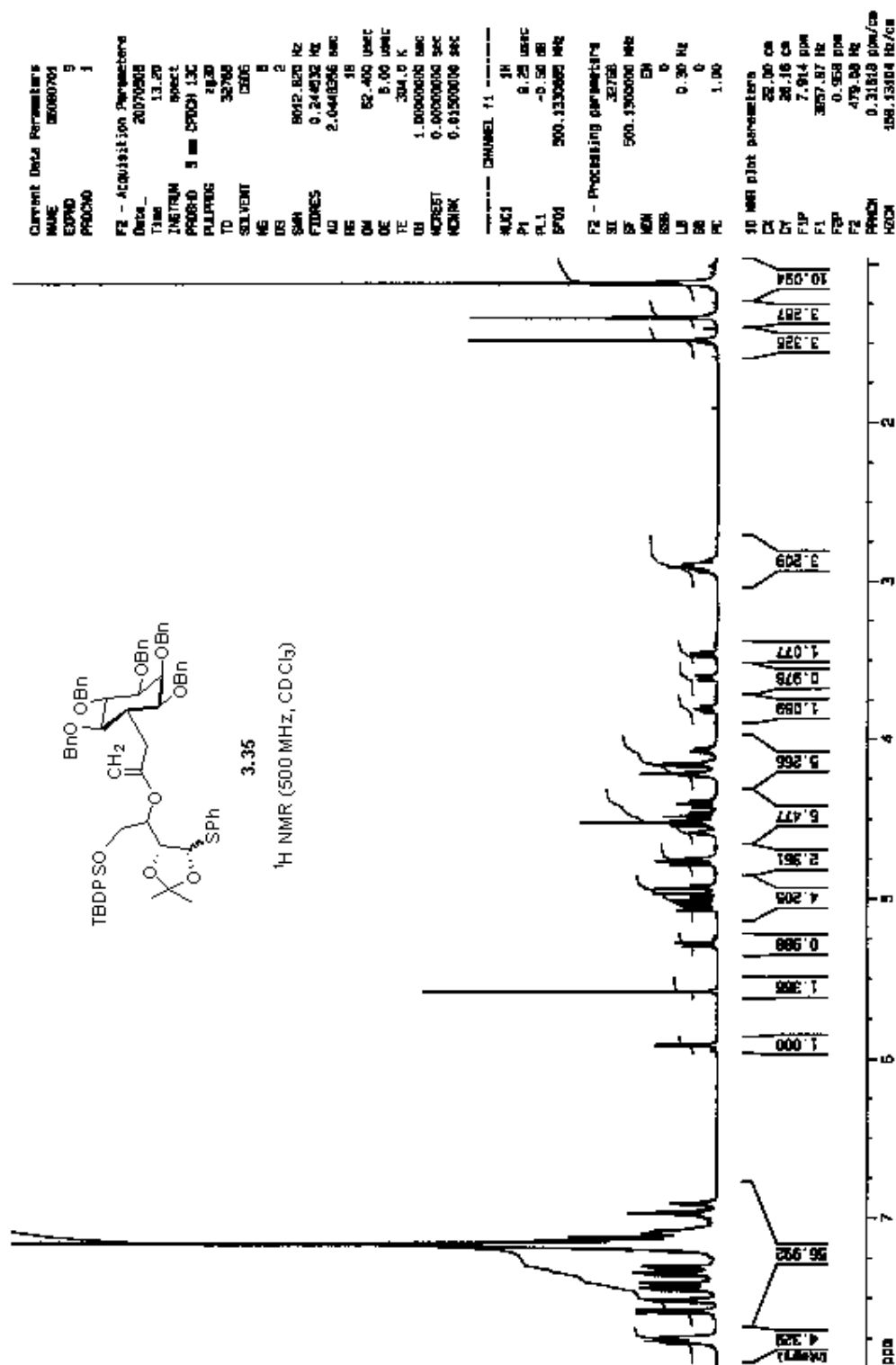


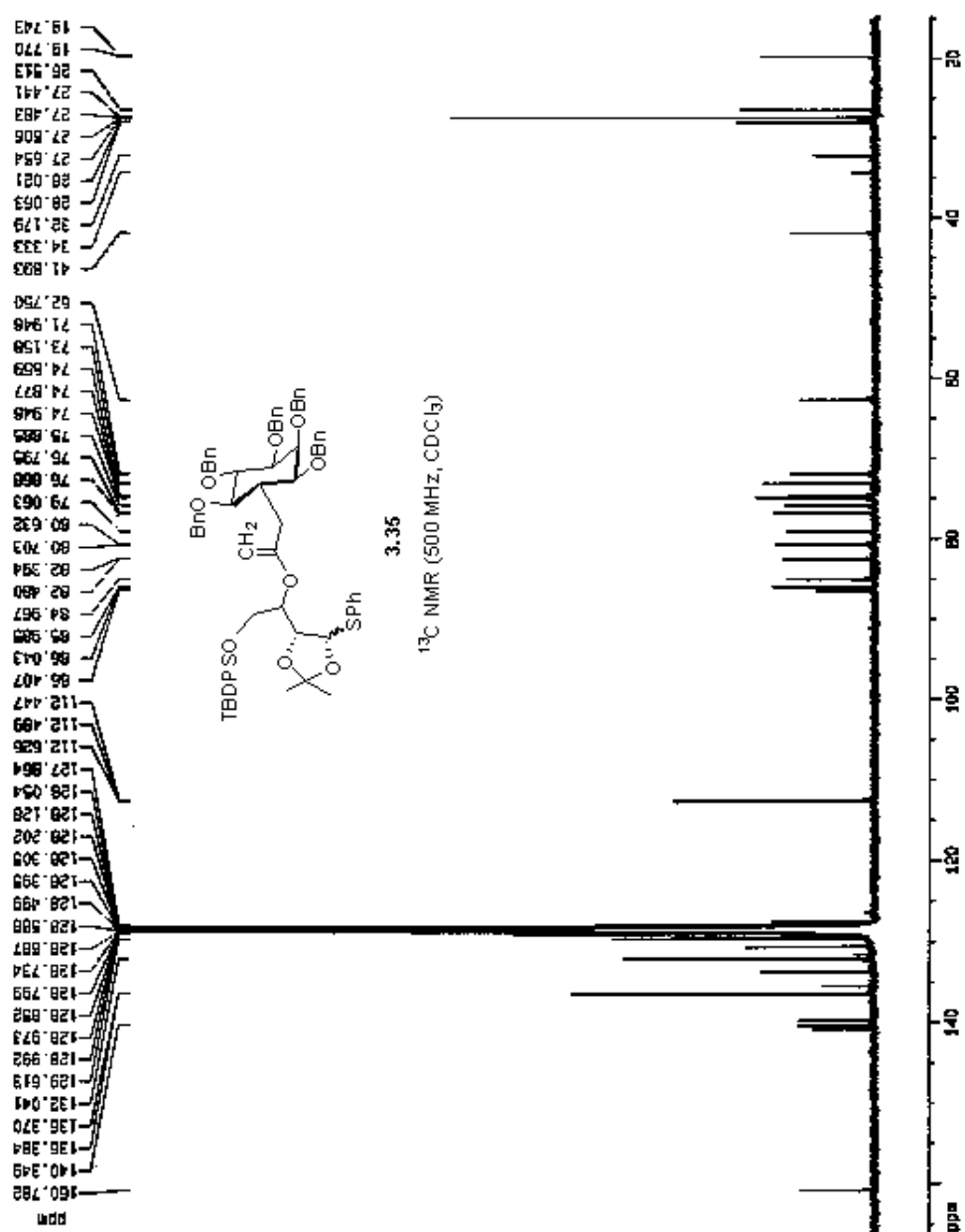


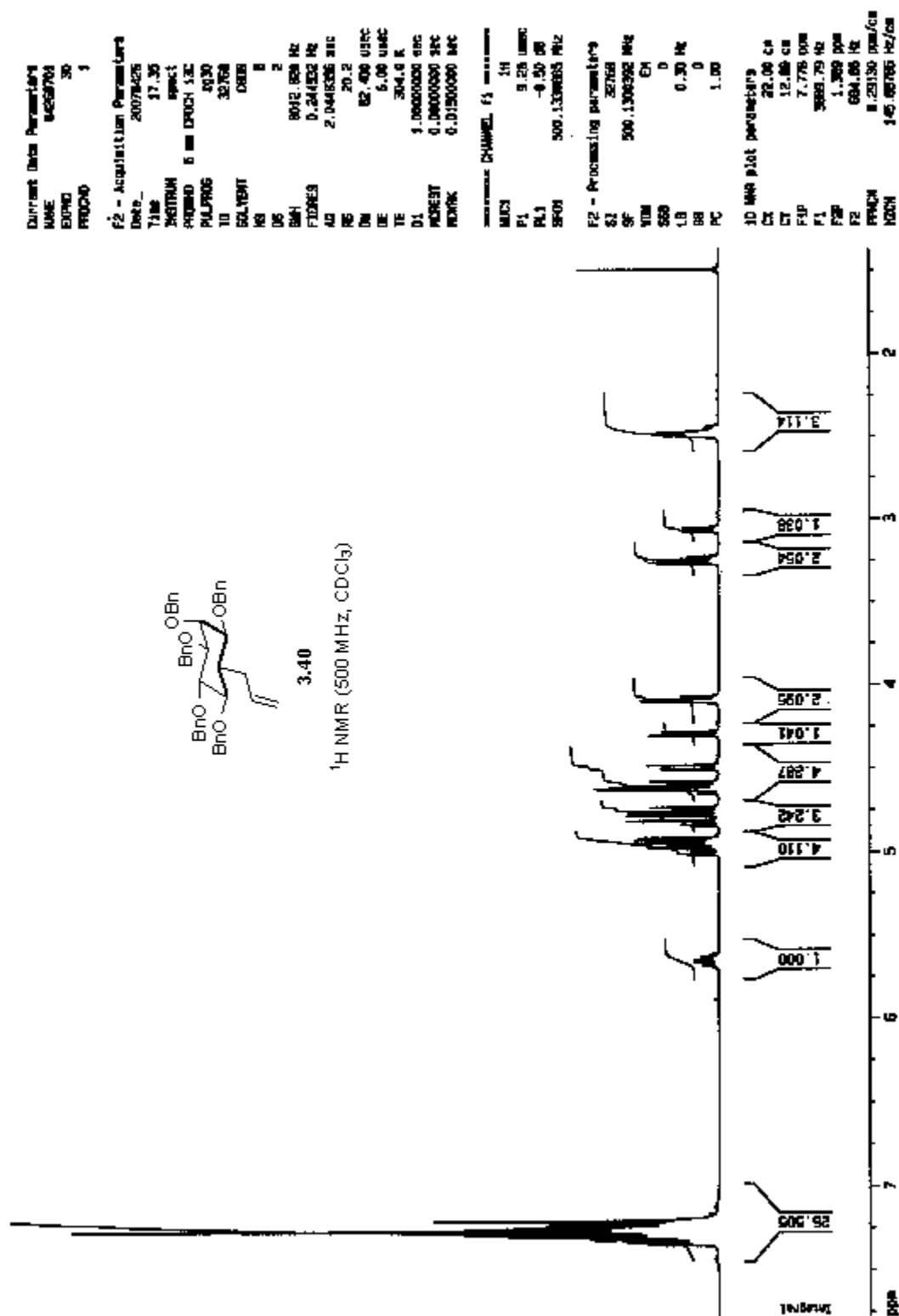


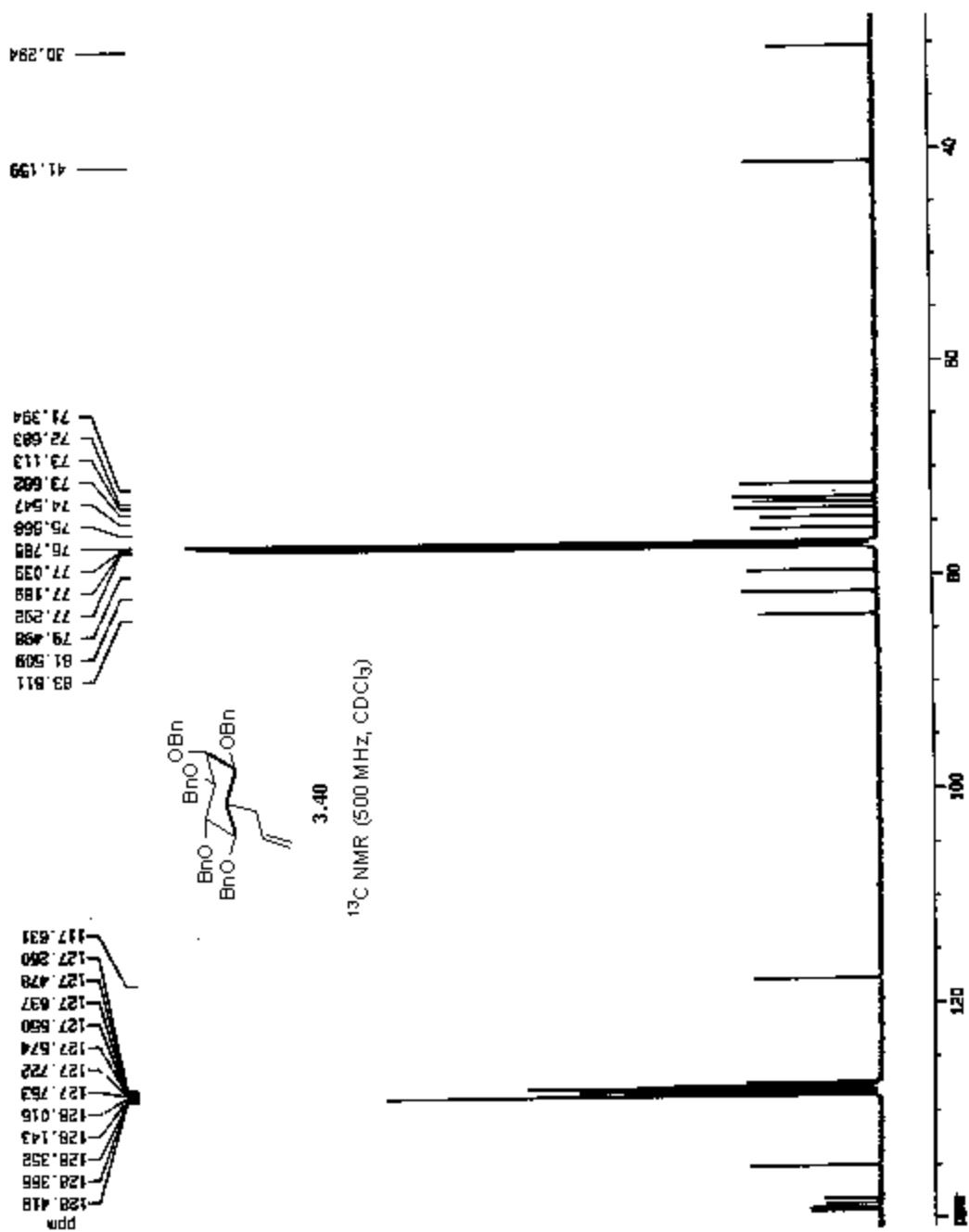


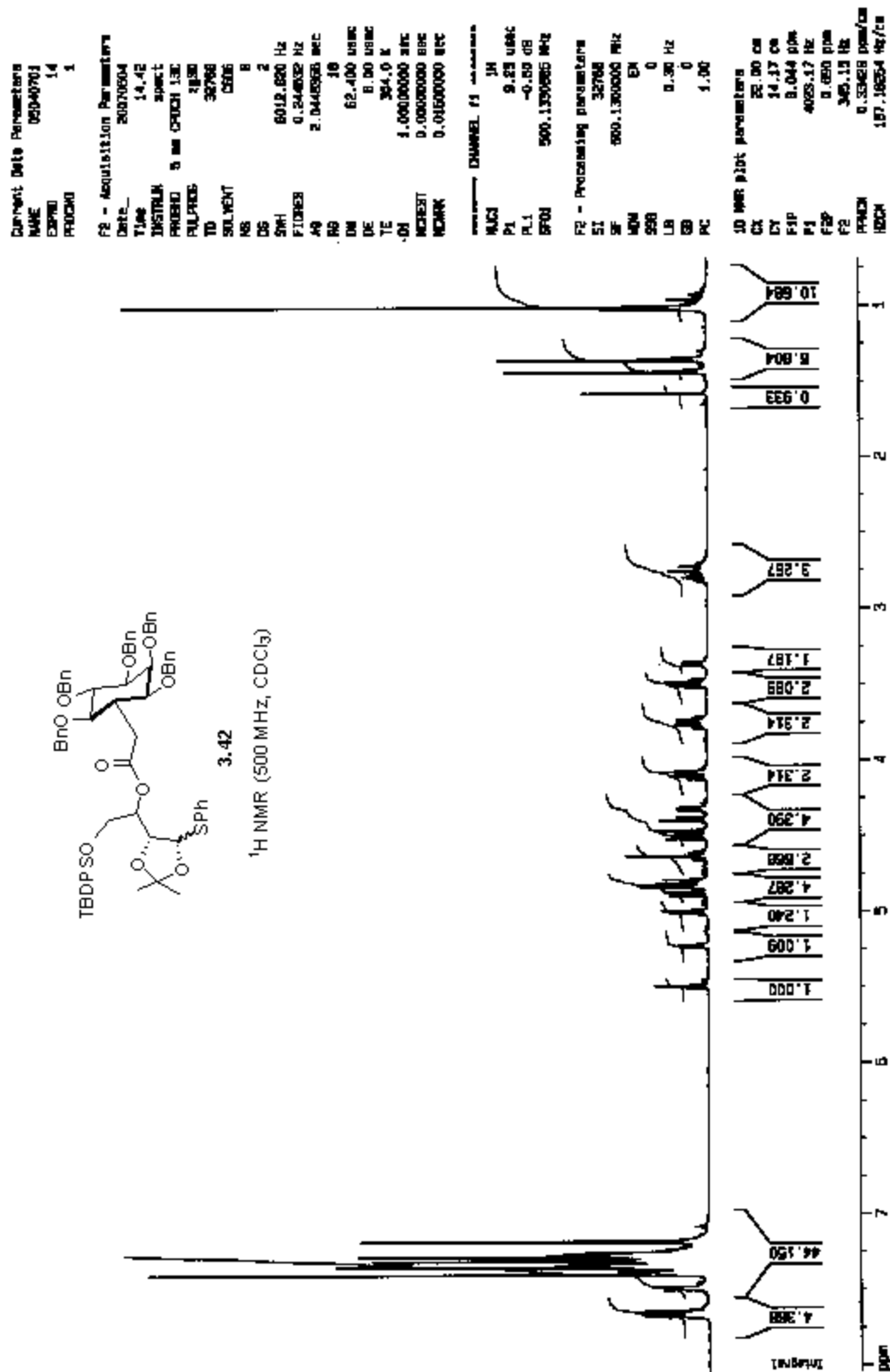


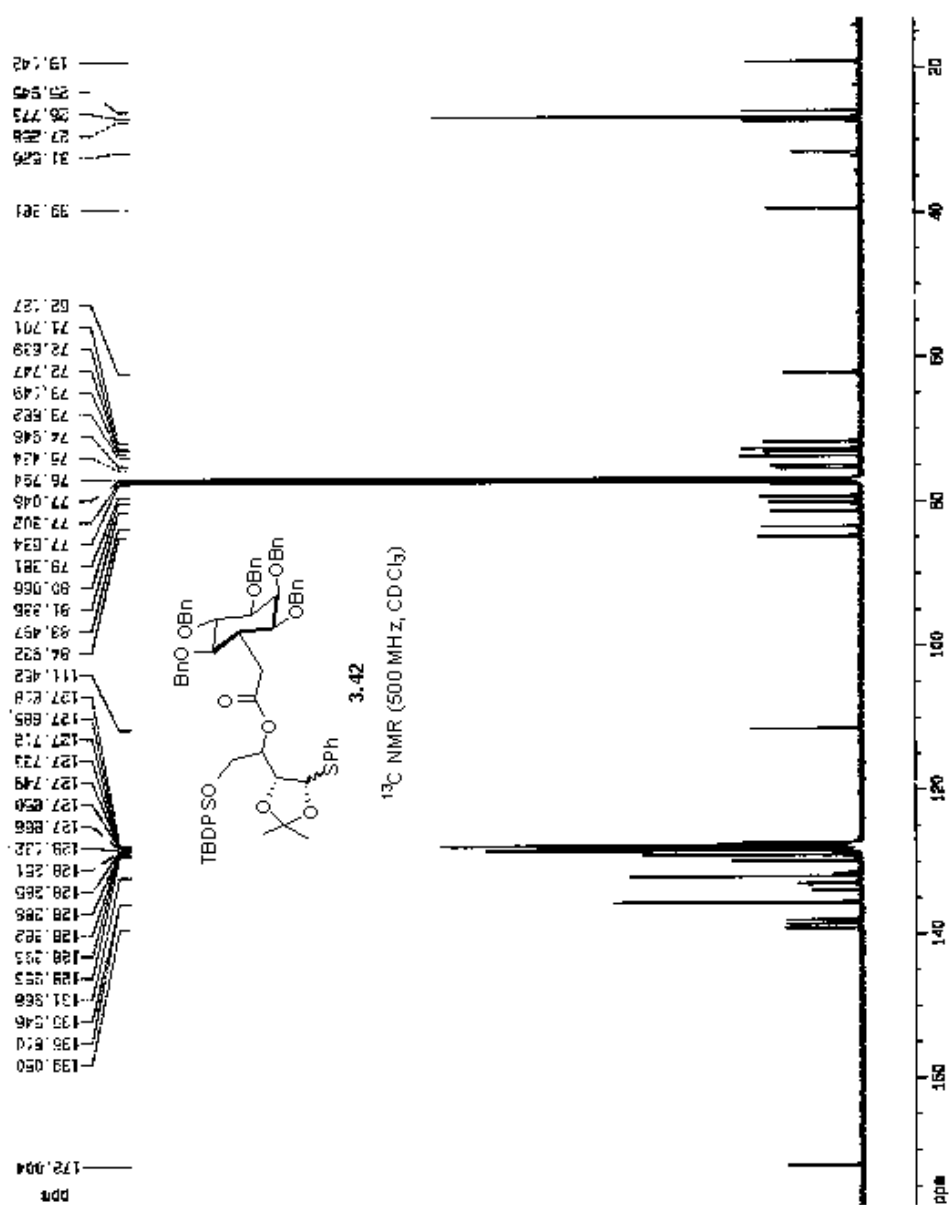


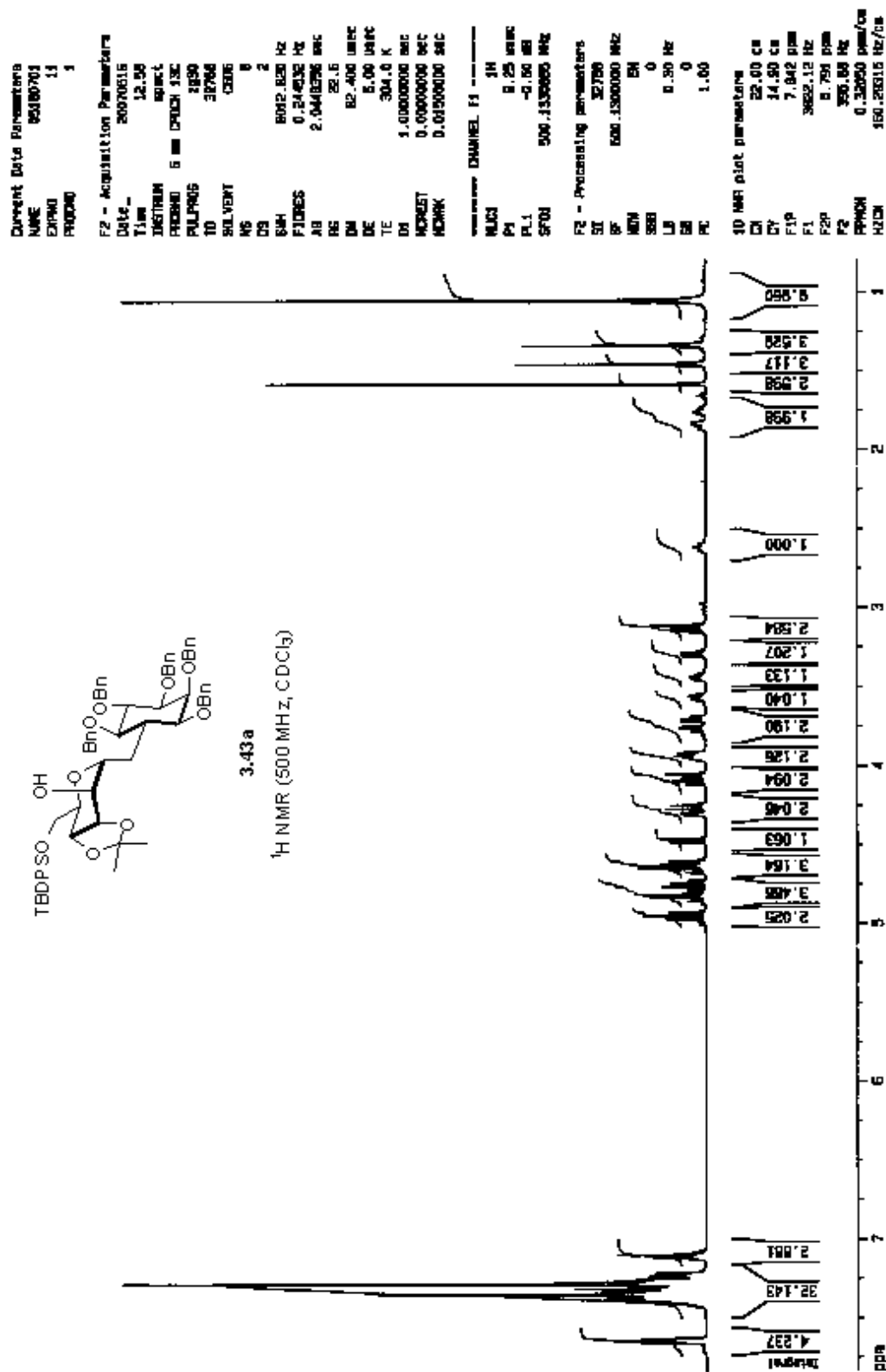


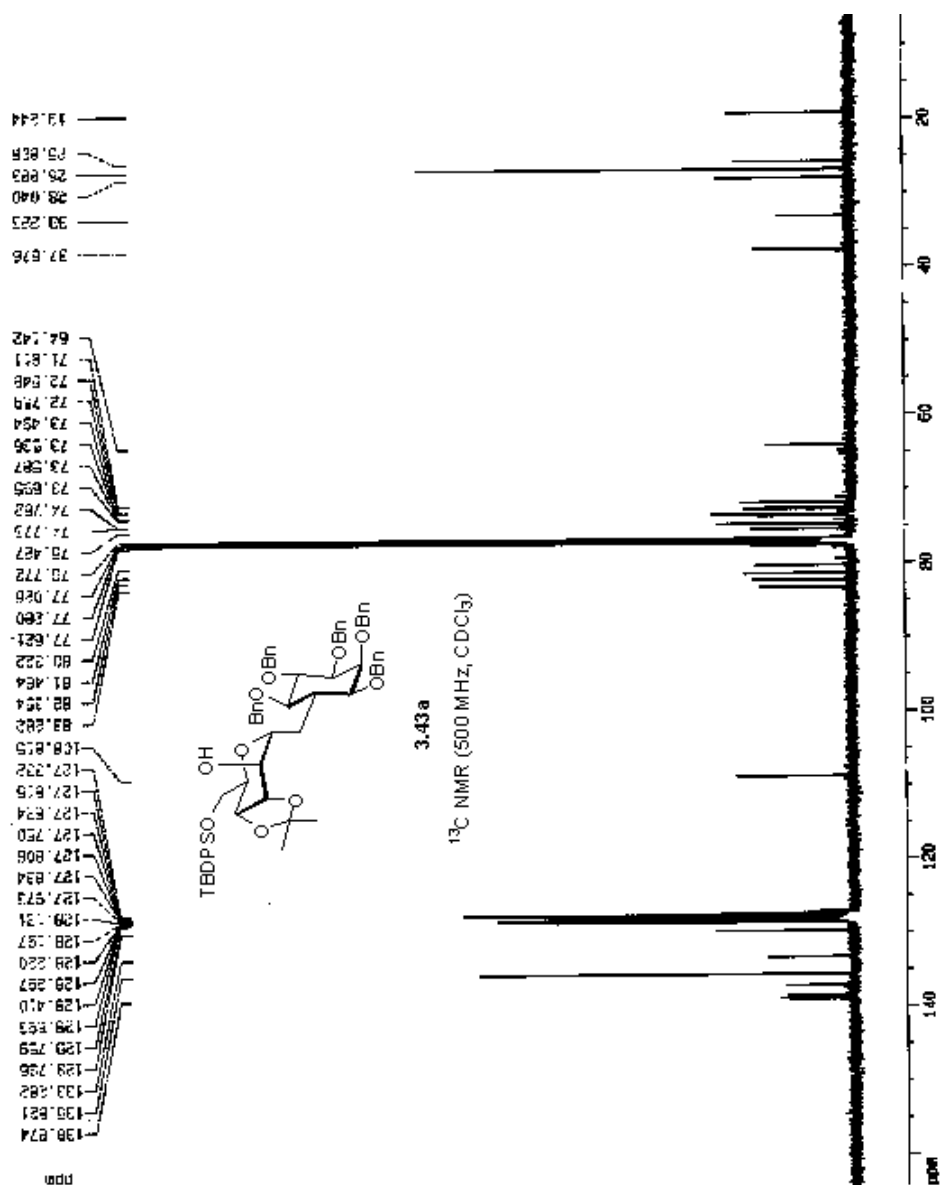












Current Data Parameters
NAME 08210701
EXPNO 28
PROCNO 1

F2 - Acquisition Parameters
Date_ 20070521
Time 17.54

INSTRUM spect
PROBHD 5 mm CPDCH-13C
PULPROG zgpg30

TD 32768
SOLVENT CDCl₃
NS 8

DS 2
SWH 6012.820 Hz
FIDRES 0.244532 Hz

AQ 2.0448766 sec
RG 64
DM 62.400 uMBC

DE 5.00 uMBC
TE 304.0 K
D4 1.00000000 sec

RG 64
DE 5.00 uMBC
TE 304.0 K

D4 1.00000000 sec
RG 64
DE 5.00 uMBC

TE 304.0 K
D4 1.00000000 sec
RG 64

DE 5.00 uMBC
TE 304.0 K
D4 1.00000000 sec

RG 64
DE 5.00 uMBC
TE 304.0 K

D4 1.00000000 sec
RG 64
DE 5.00 uMBC

TE 304.0 K
D4 1.00000000 sec
RG 64

DE 5.00 uMBC
TE 304.0 K
D4 1.00000000 sec

RG 64
DE 5.00 uMBC
TE 304.0 K

D4 1.00000000 sec
RG 64
DE 5.00 uMBC

TE 304.0 K
D4 1.00000000 sec
RG 64

DE 5.00 uMBC
TE 304.0 K
D4 1.00000000 sec

RG 64
DE 5.00 uMBC
TE 304.0 K

D4 1.00000000 sec
RG 64
DE 5.00 uMBC

TE 304.0 K
D4 1.00000000 sec
RG 64

DE 5.00 uMBC
TE 304.0 K
D4 1.00000000 sec

RG 64
DE 5.00 uMBC
TE 304.0 K

D4 1.00000000 sec
RG 64
DE 5.00 uMBC

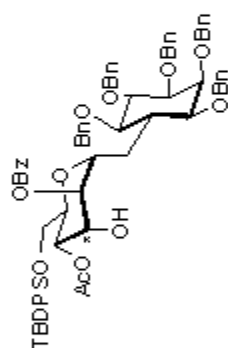
TE 304.0 K
D4 1.00000000 sec
RG 64

DE 5.00 uMBC
TE 304.0 K
D4 1.00000000 sec

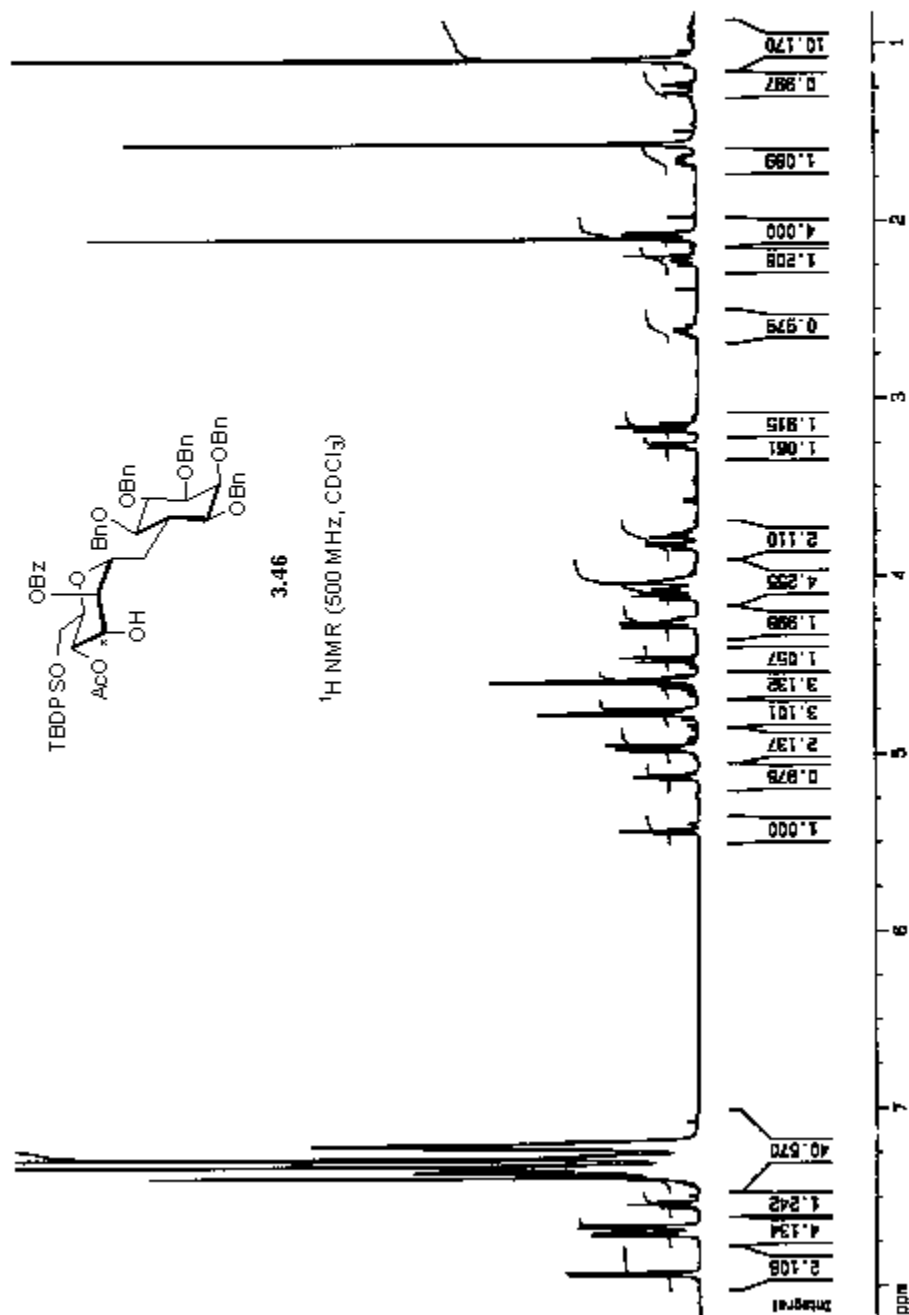
RG 64
DE 5.00 uMBC
TE 304.0 K

D4 1.00000000 sec
RG 64
DE 5.00 uMBC

TE 304.0 K
D4 1.00000000 sec
RG 64



3.46

¹H NMR (500 MHz, CDCl₃)

10 MHz plot parameters
CX 22.00 cm
CY 20.15 cm

P1 8.186 mm
F1 4025.00 Hz
F2 0.623 mm

F2 415.88 Hz
F2 0.33356 mm/cm
F2 188.72324 Hz/cm

10 MHz plot parameters
CX 22.00 cm
CY 20.15 cm

P1 8.186 mm
F1 4025.00 Hz
F2 0.623 mm

F2 415.88 Hz
F2 0.33356 mm/cm
F2 188.72324 Hz/cm

10 MHz plot parameters
CX 22.00 cm
CY 20.15 cm

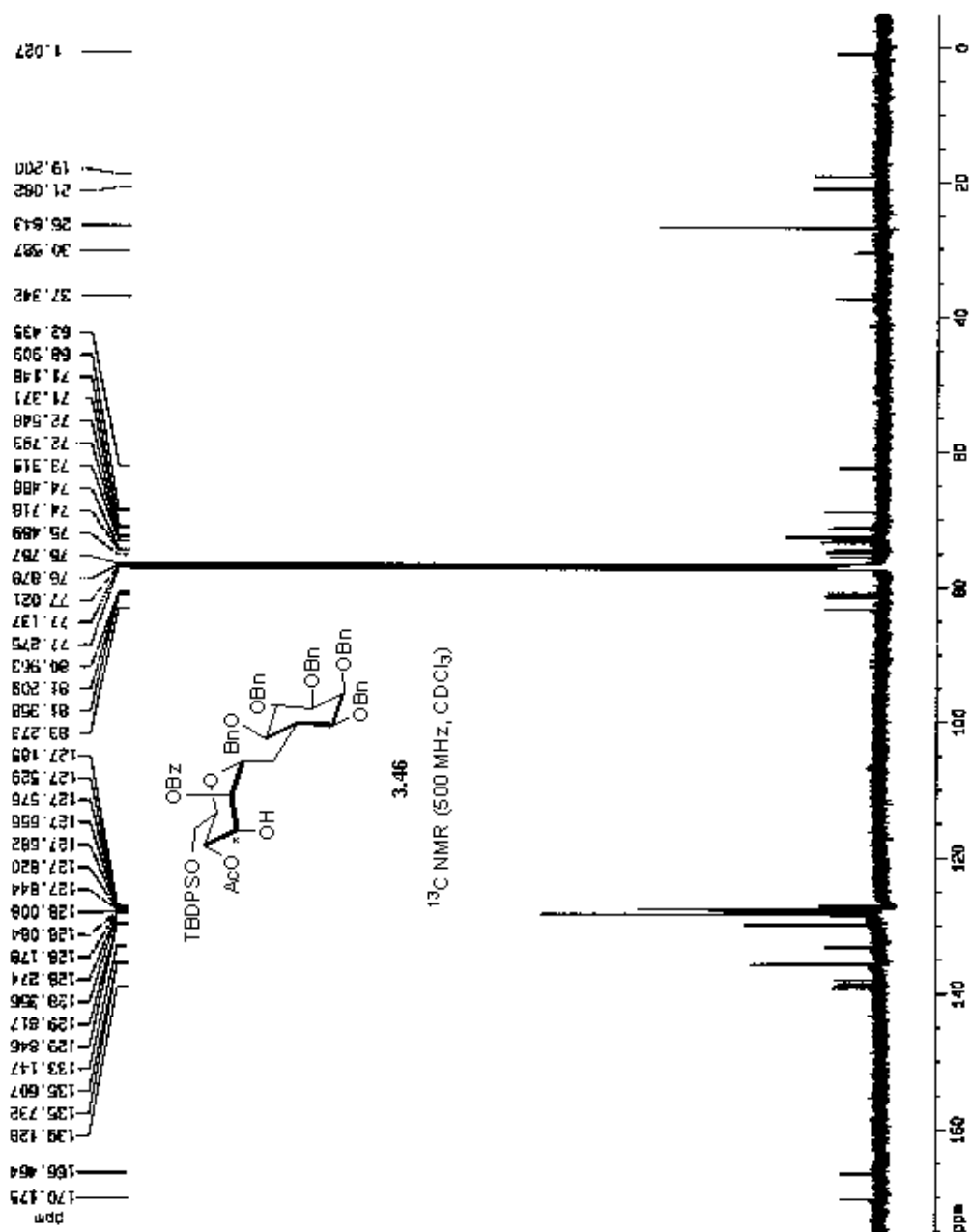
P1 8.186 mm
F1 4025.00 Hz
F2 0.623 mm

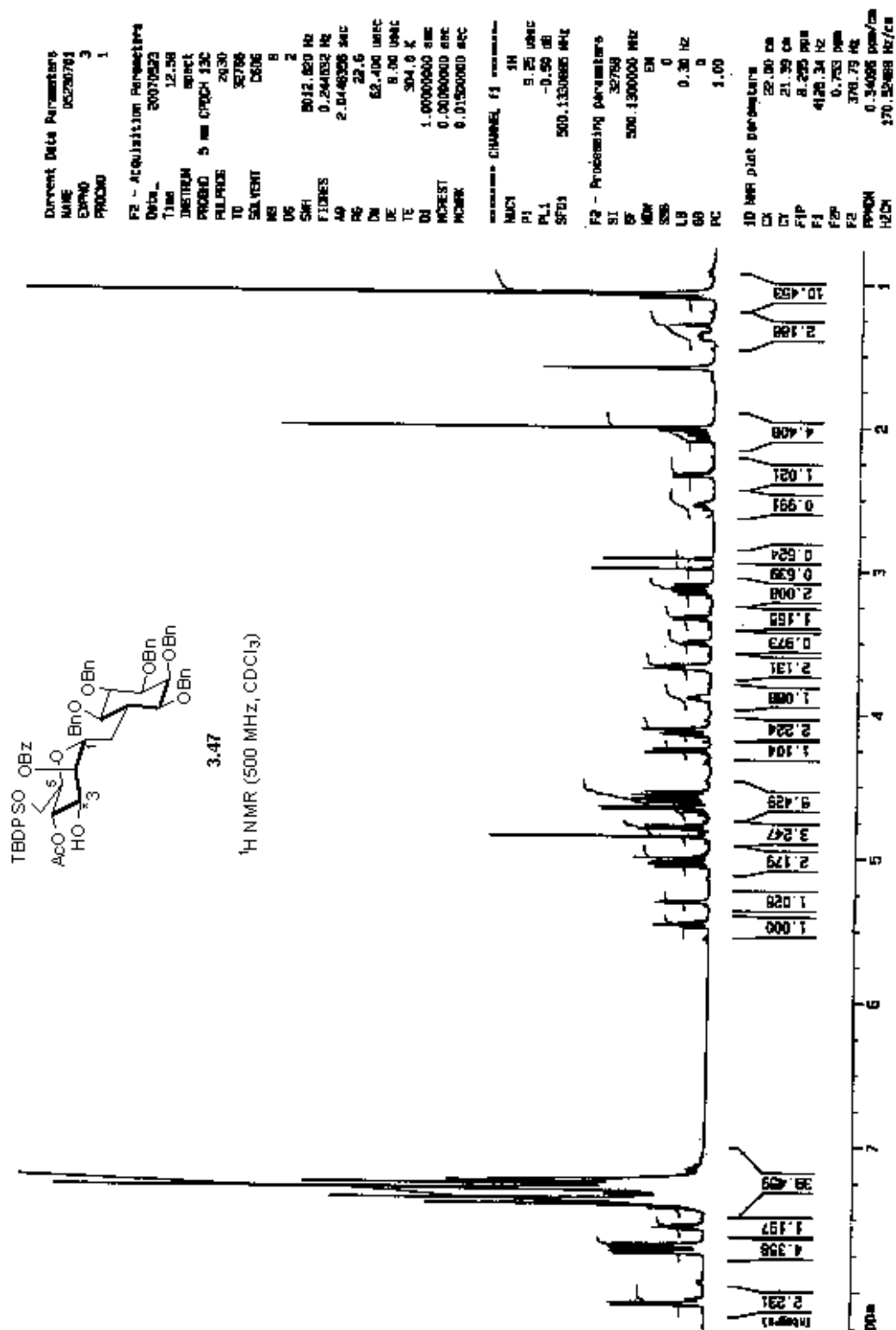
F2 415.88 Hz
F2 0.33356 mm/cm
F2 188.72324 Hz/cm

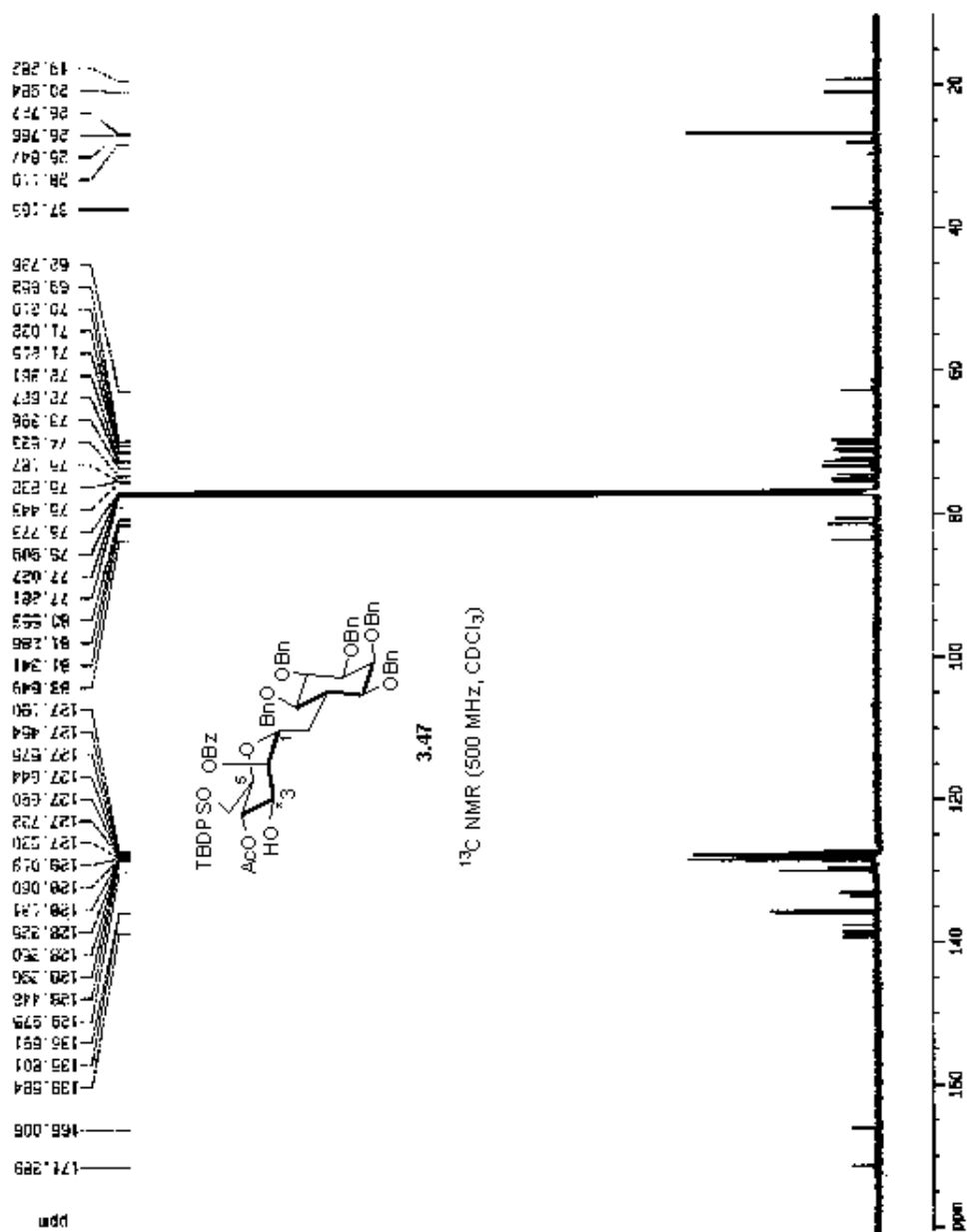
10 MHz plot parameters
CX 22.00 cm
CY 20.15 cm

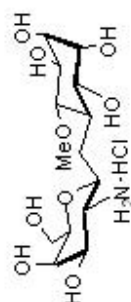
P1 8.186 mm
F1 4025.00 Hz
F2 0.623 mm

F2 415.88 Hz
F2 0.33356 mm/cm
F2 188.72324 Hz/cm

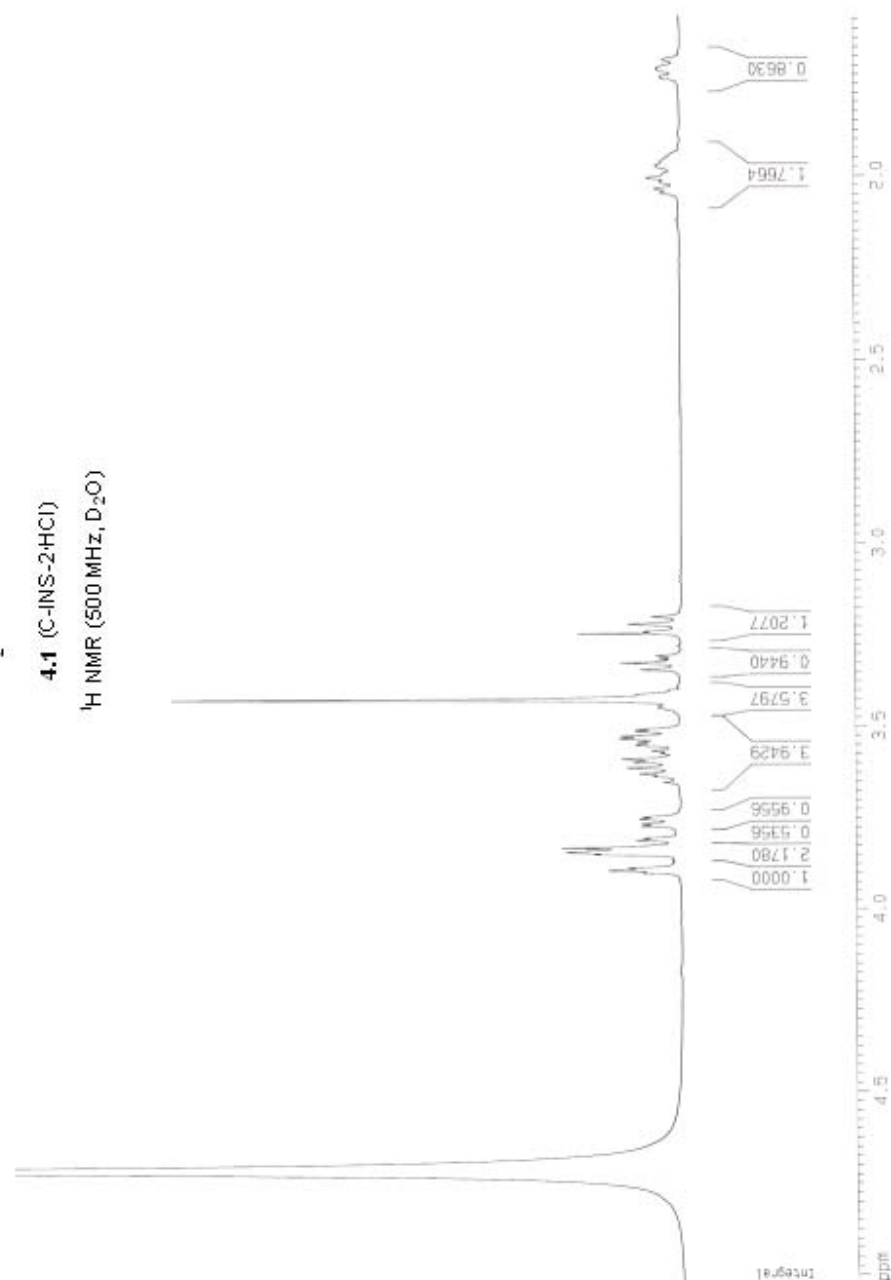








4.1 (C-INS-2-HCl)
¹H NMR (500 MHz, D₂O)



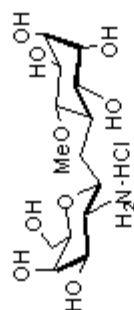
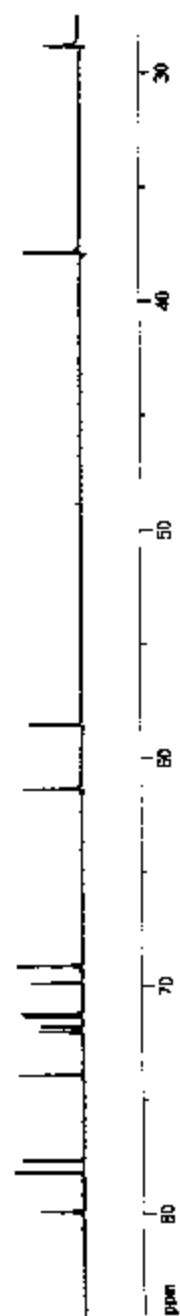
Current Data Parameters
 NAME 20080328
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20080328
 Time 11:24
 INSTRUM spect
 PROBHD 5 mm QNPCH 13C
 PULPROG zg30
 TD 32768
 SOLVENT C5D5
 NS 8
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.244532 Hz
 AQ 2.0448356 sec
 RG 35.9
 DM 62.400 usec
 DE 6.00 usec
 TE 303.0 K
 D1 1.00000000 sec
 MCHRG 0.00000000 sec
 MCWIR 0.01500000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 8.25 usec
 PL1 -0.50 dB
 SF01 500.1300885 MHz

F2 - Processing parameters
 SI 32768
 SF 500.1300000 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

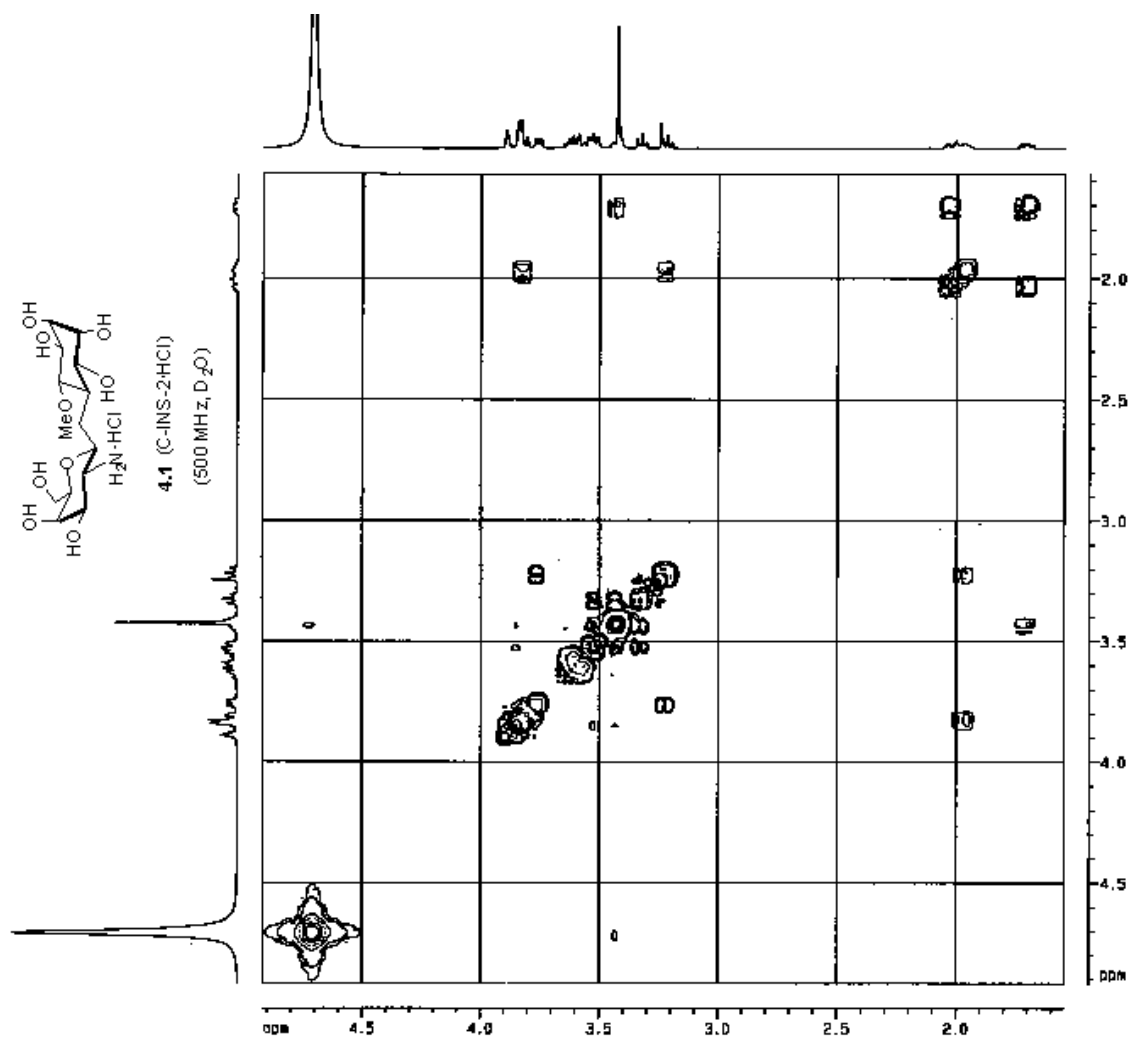
1D NMR plot parameters
 CX 22.00 cm
 CY 16.38 cm
 F1P 5.020 ppm
 F1 2510.70 Hz
 F2P 1.563 ppm
 F2 781.89 Hz
 PPMX 0.10712 tps/cm
 HZCX 78.58234 Hz/cm

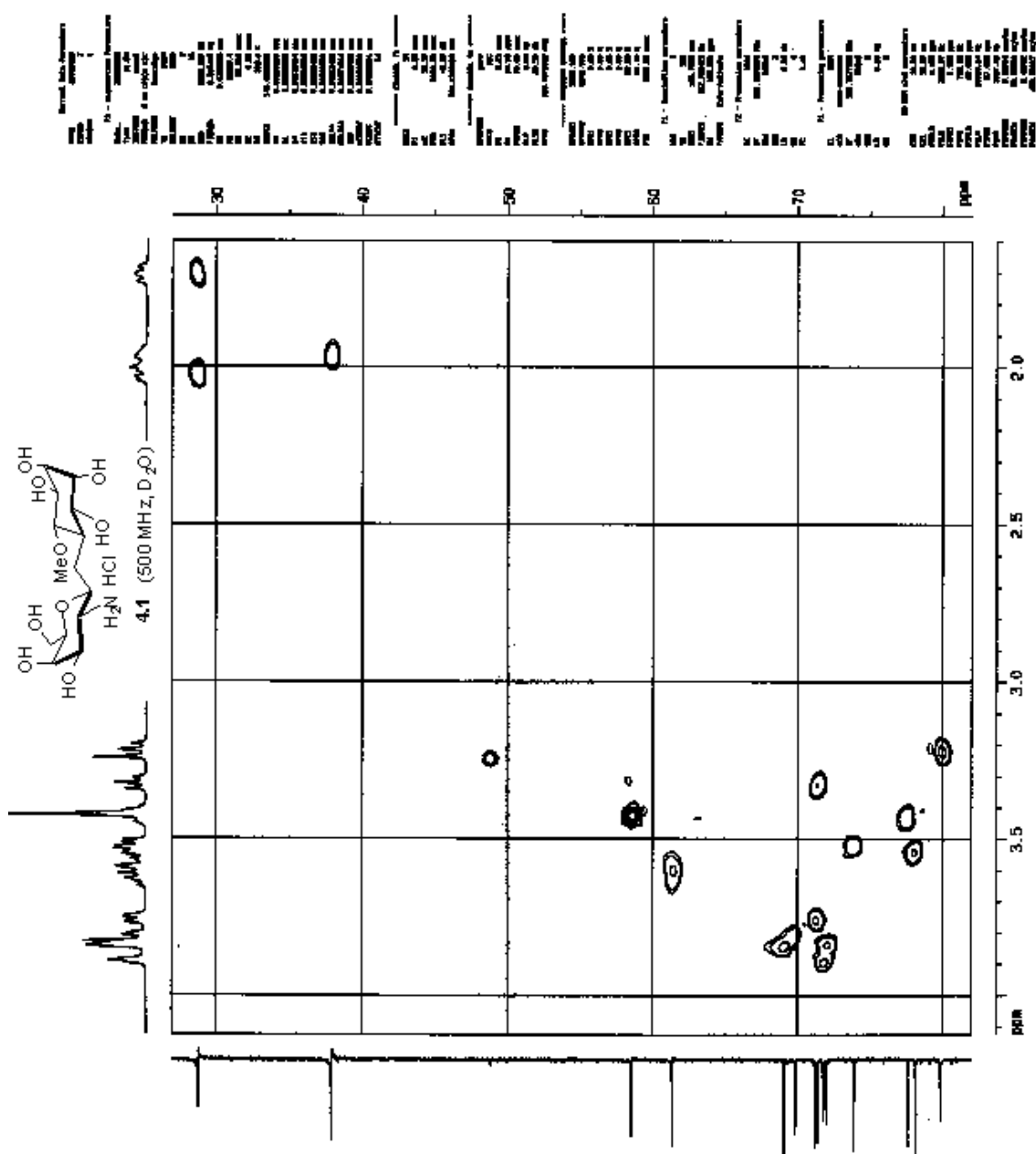


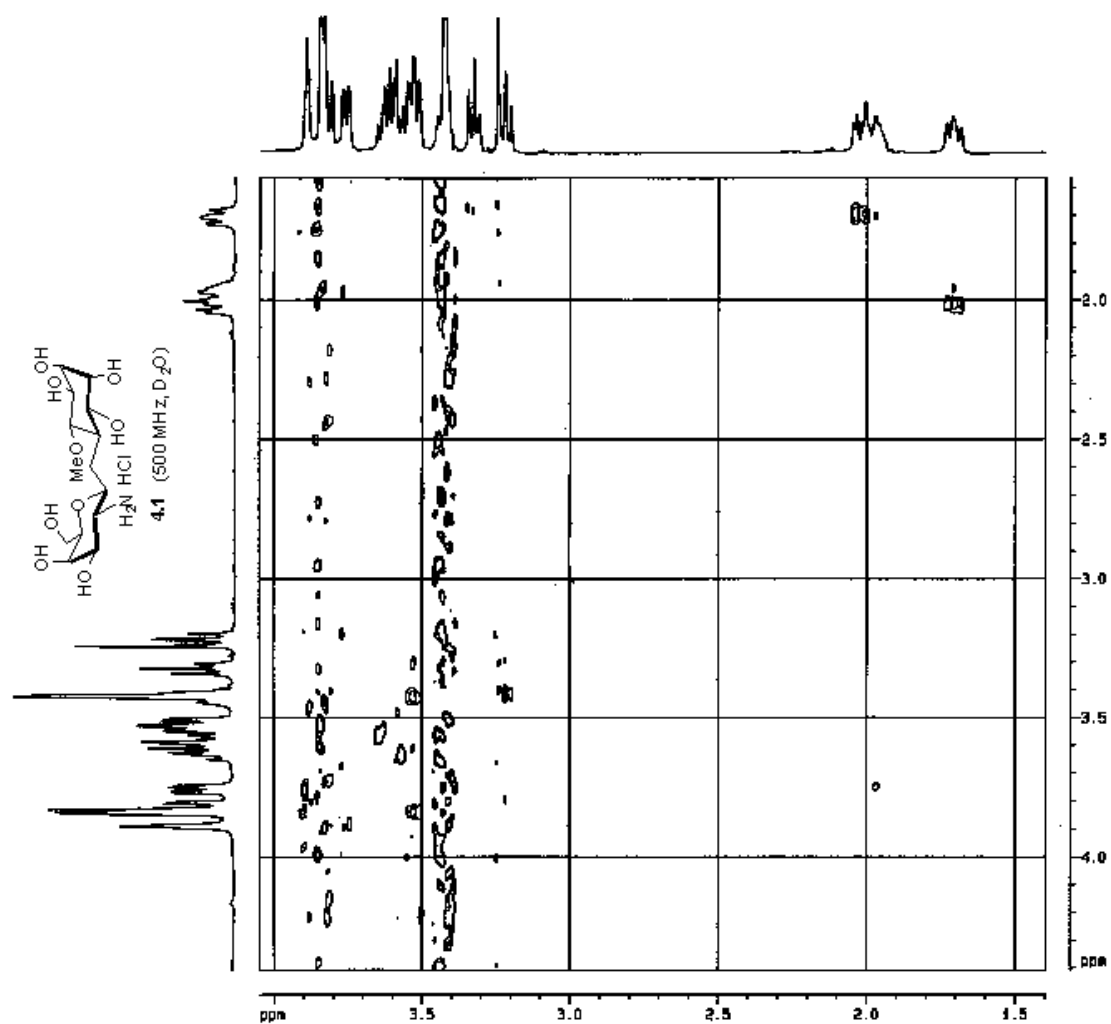
4.1 (C-INS-2HCl)

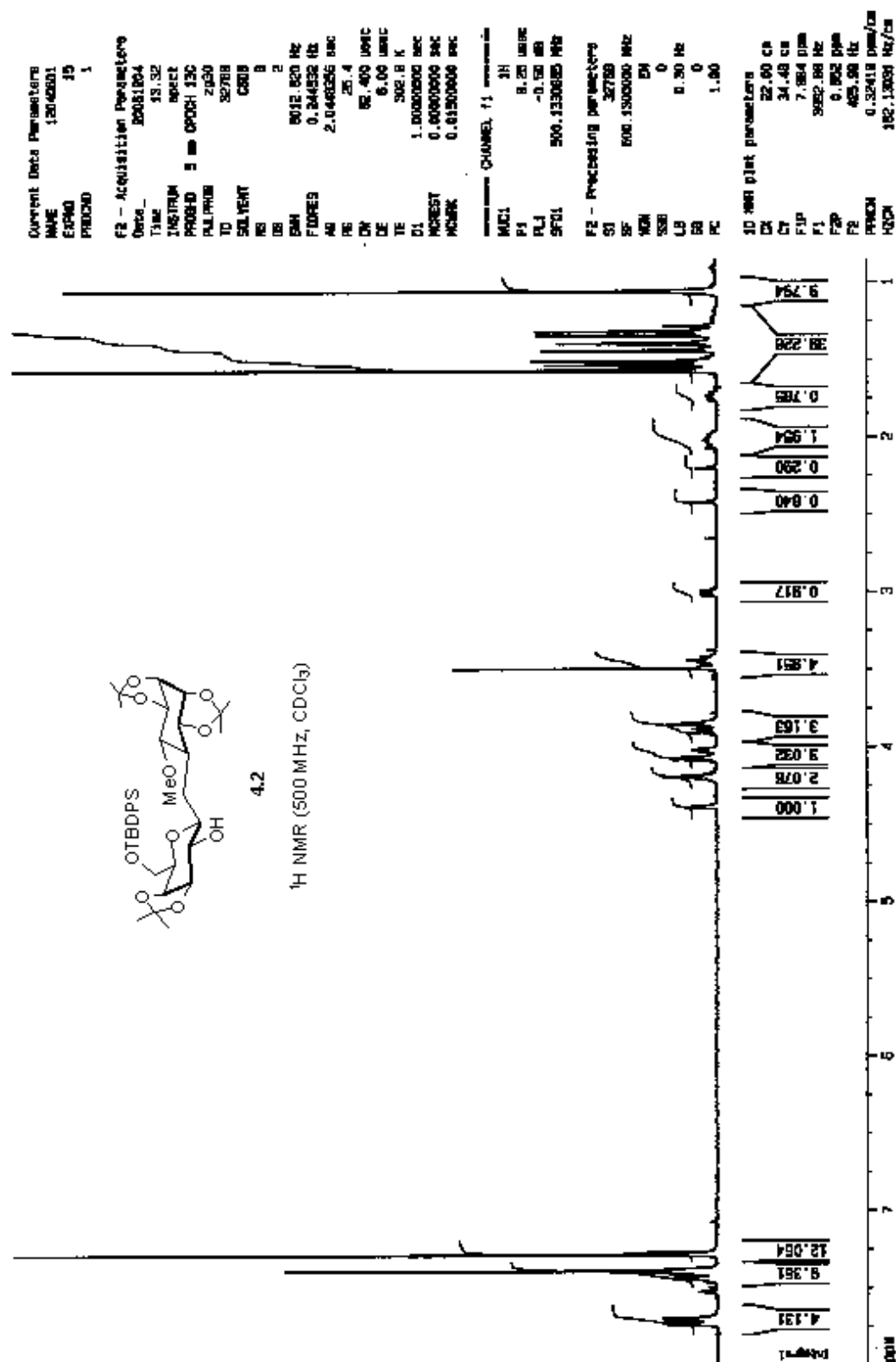
^{13}C NMR (500 MHz, D_2O)

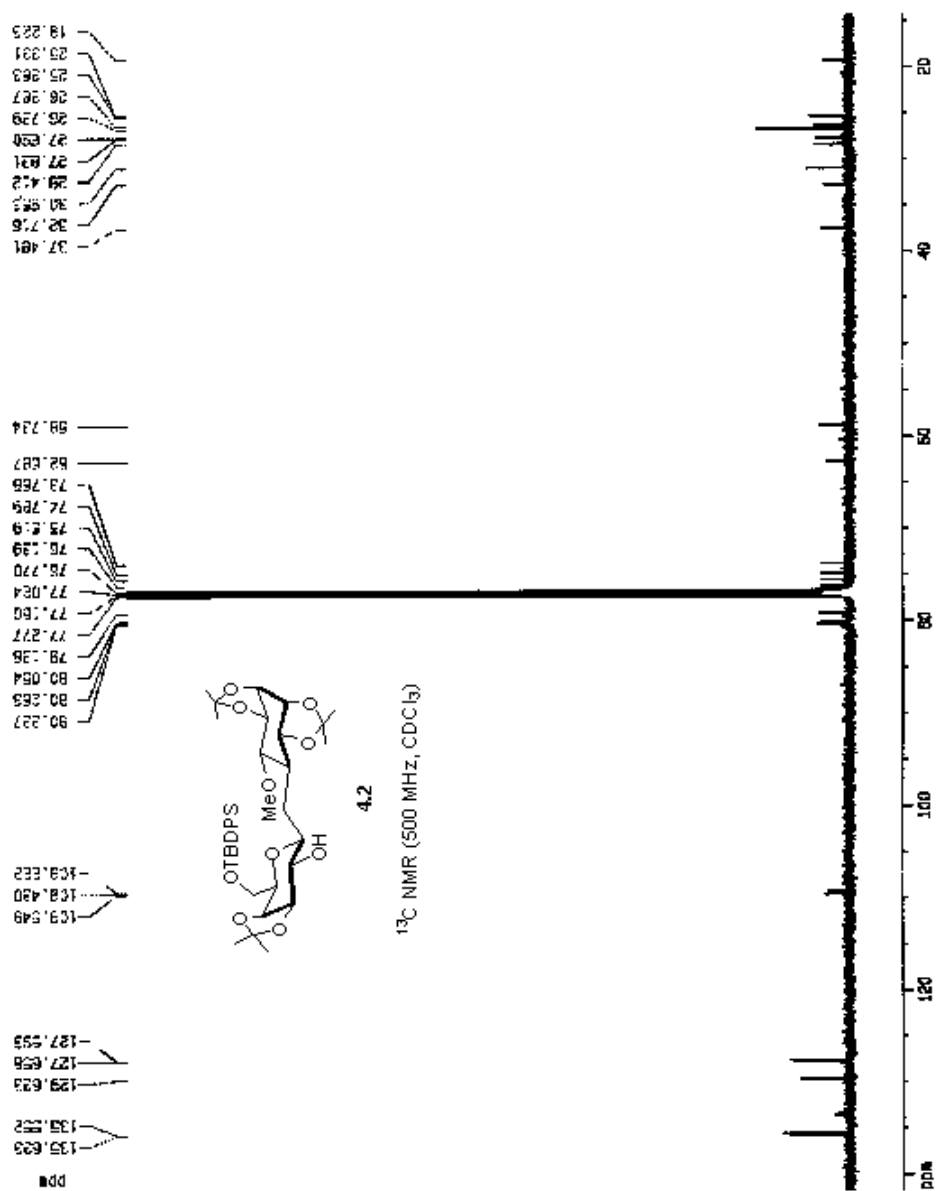


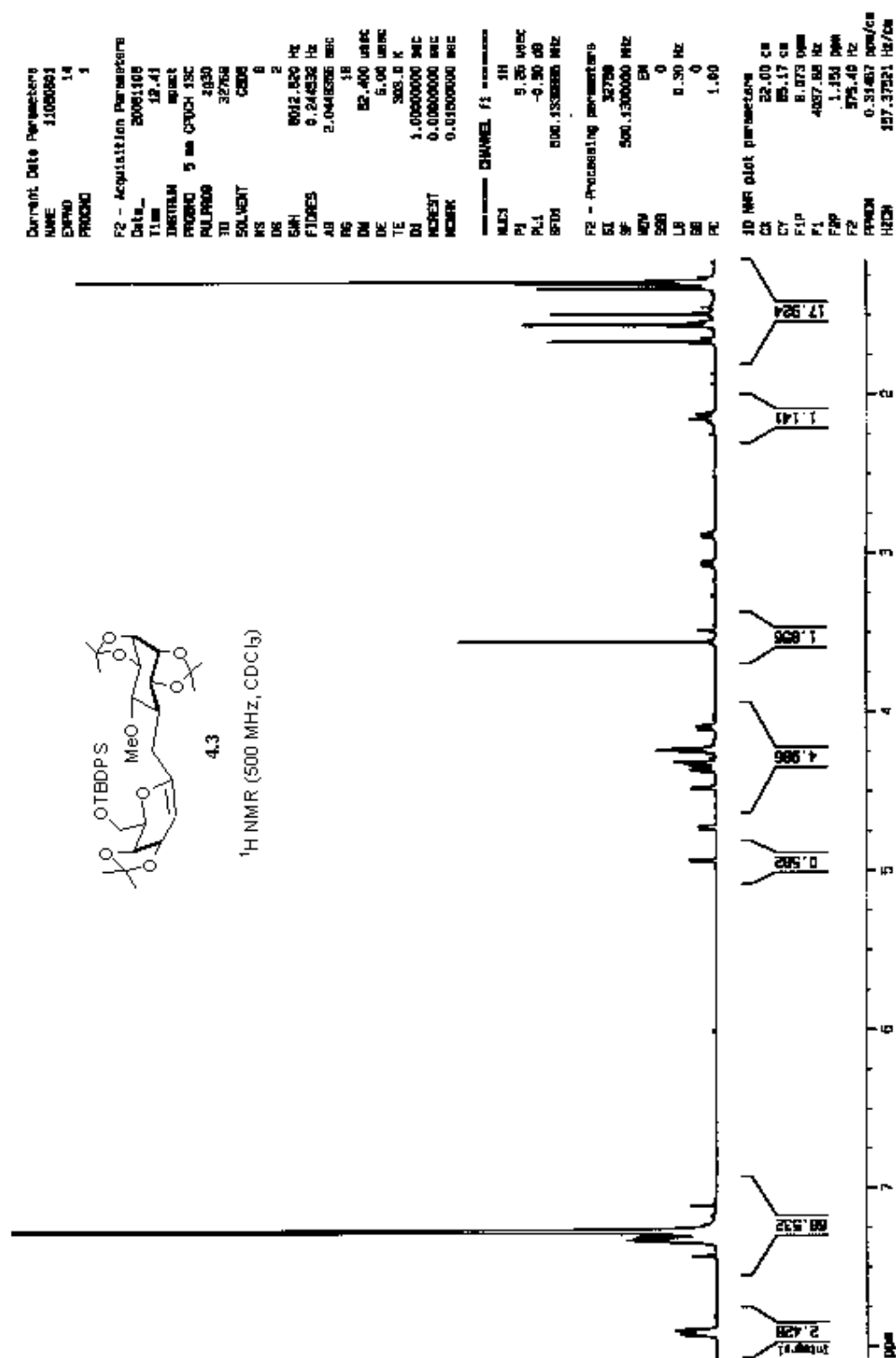


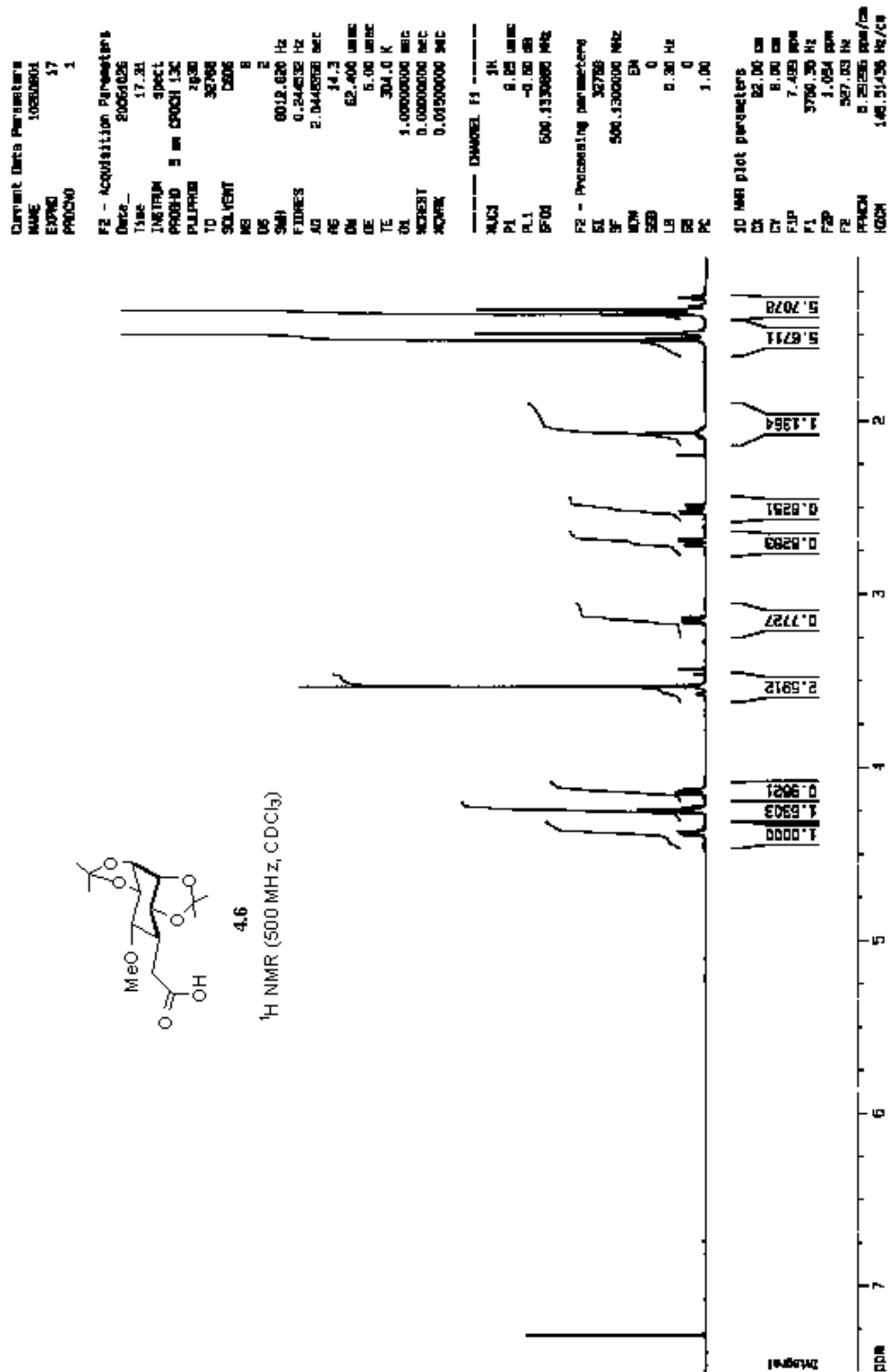


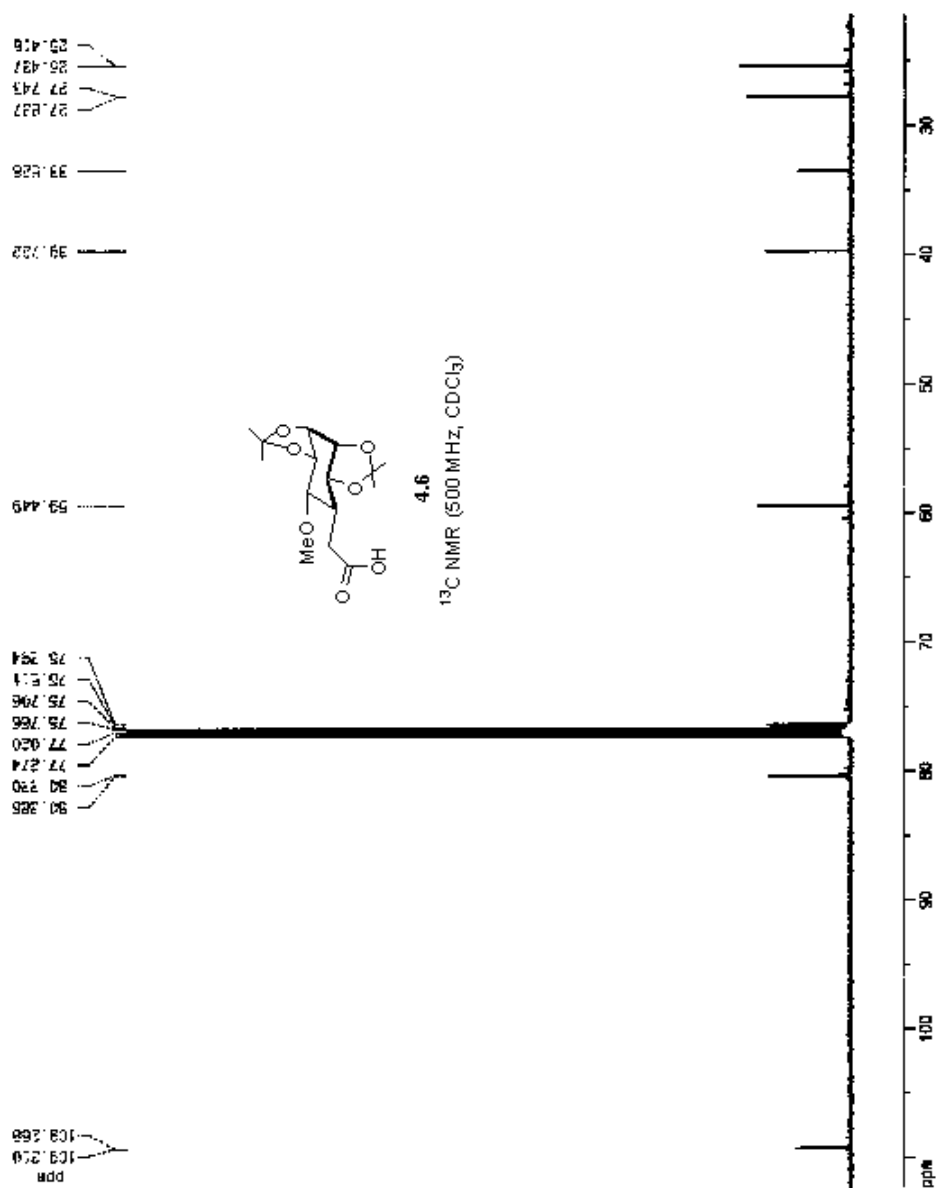


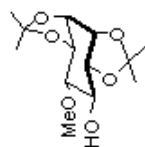




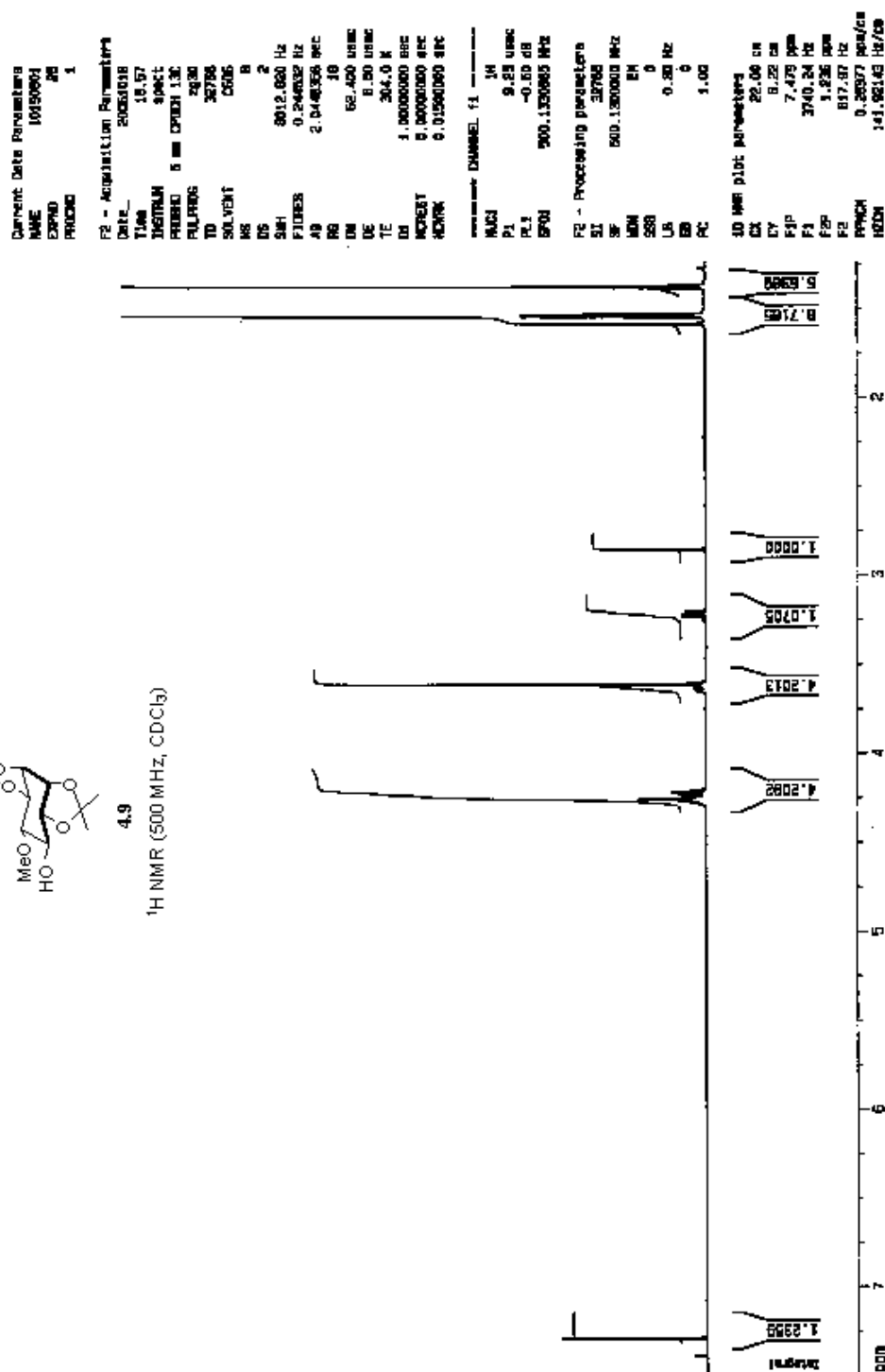


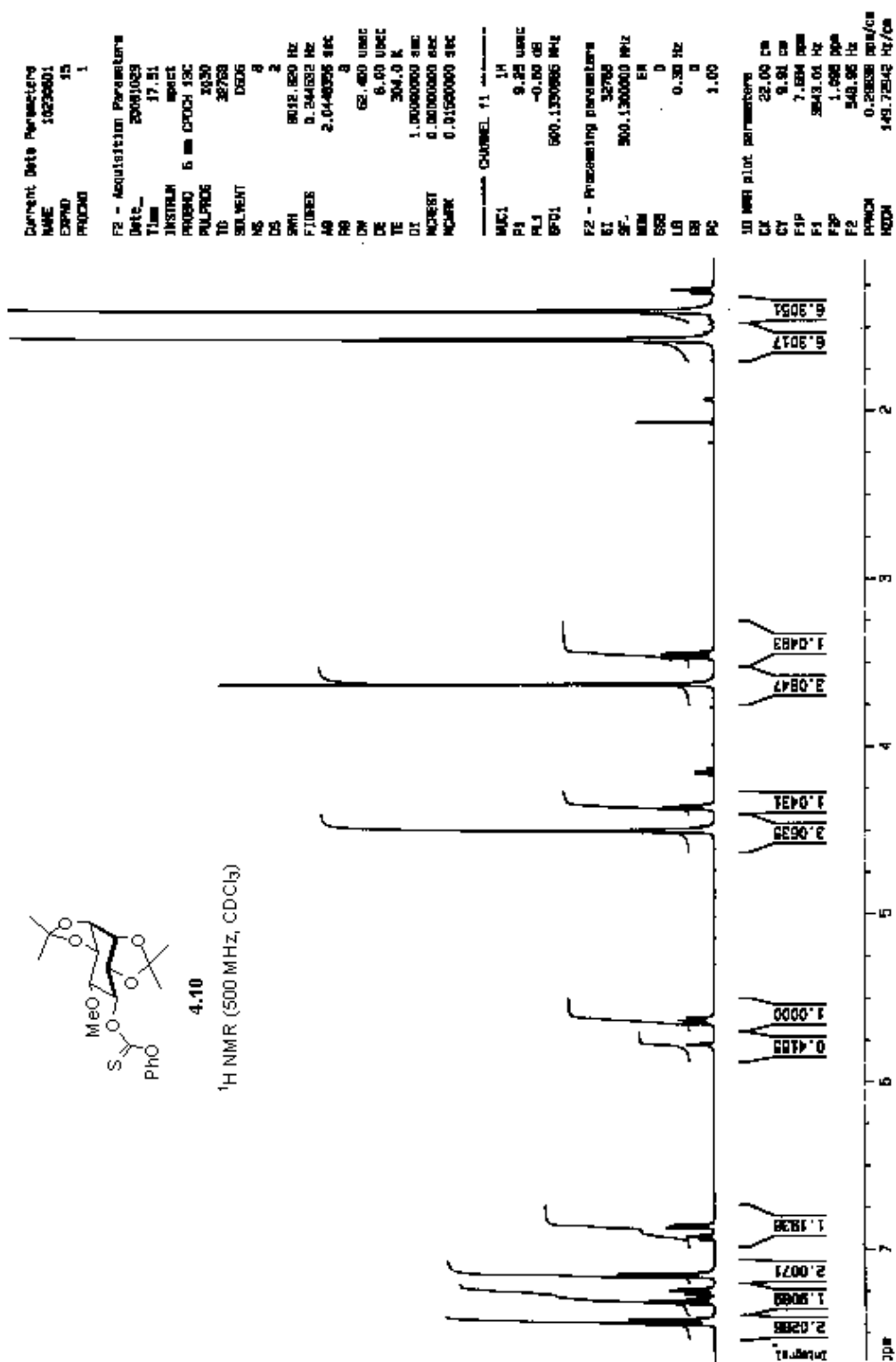


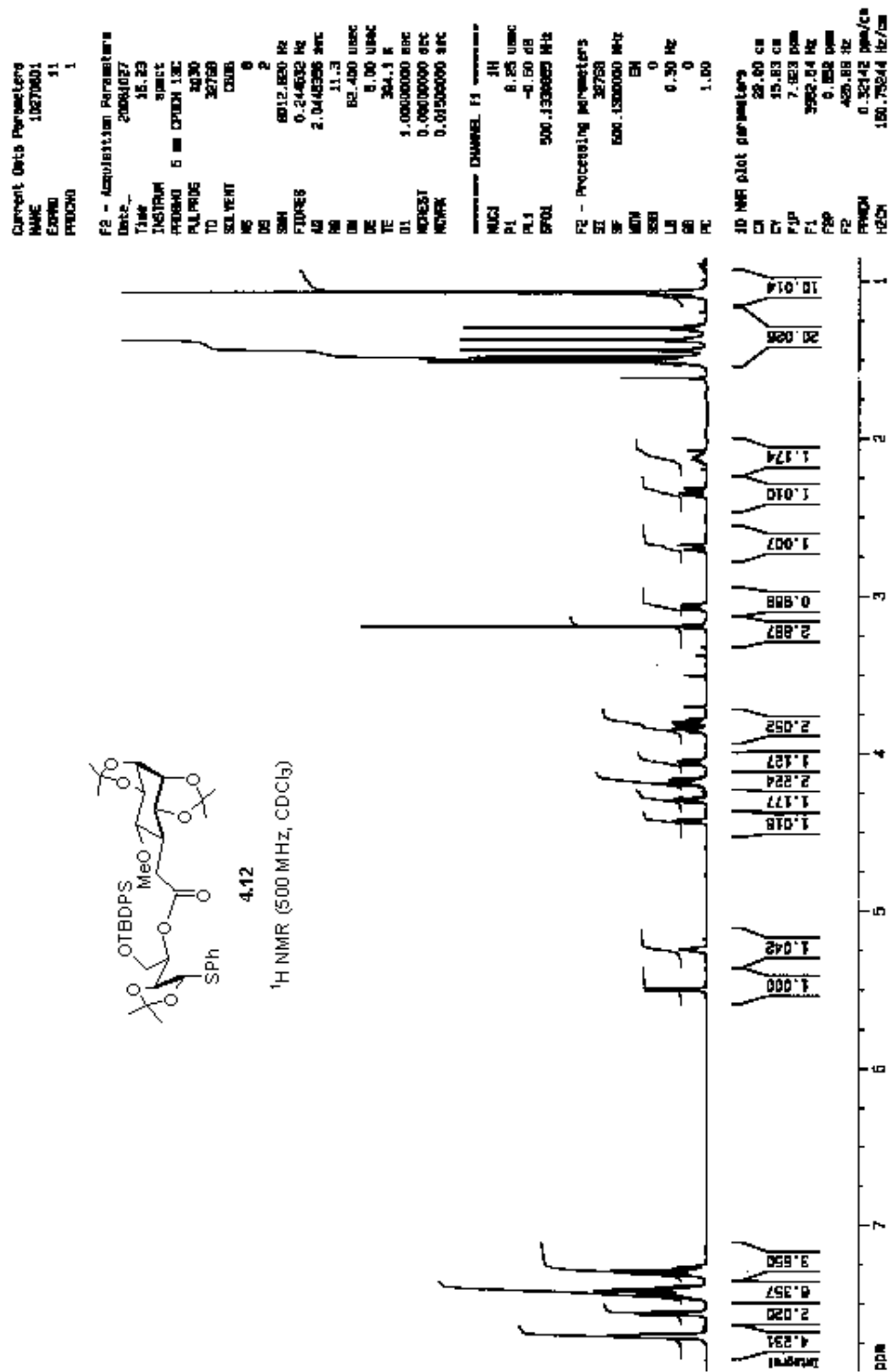


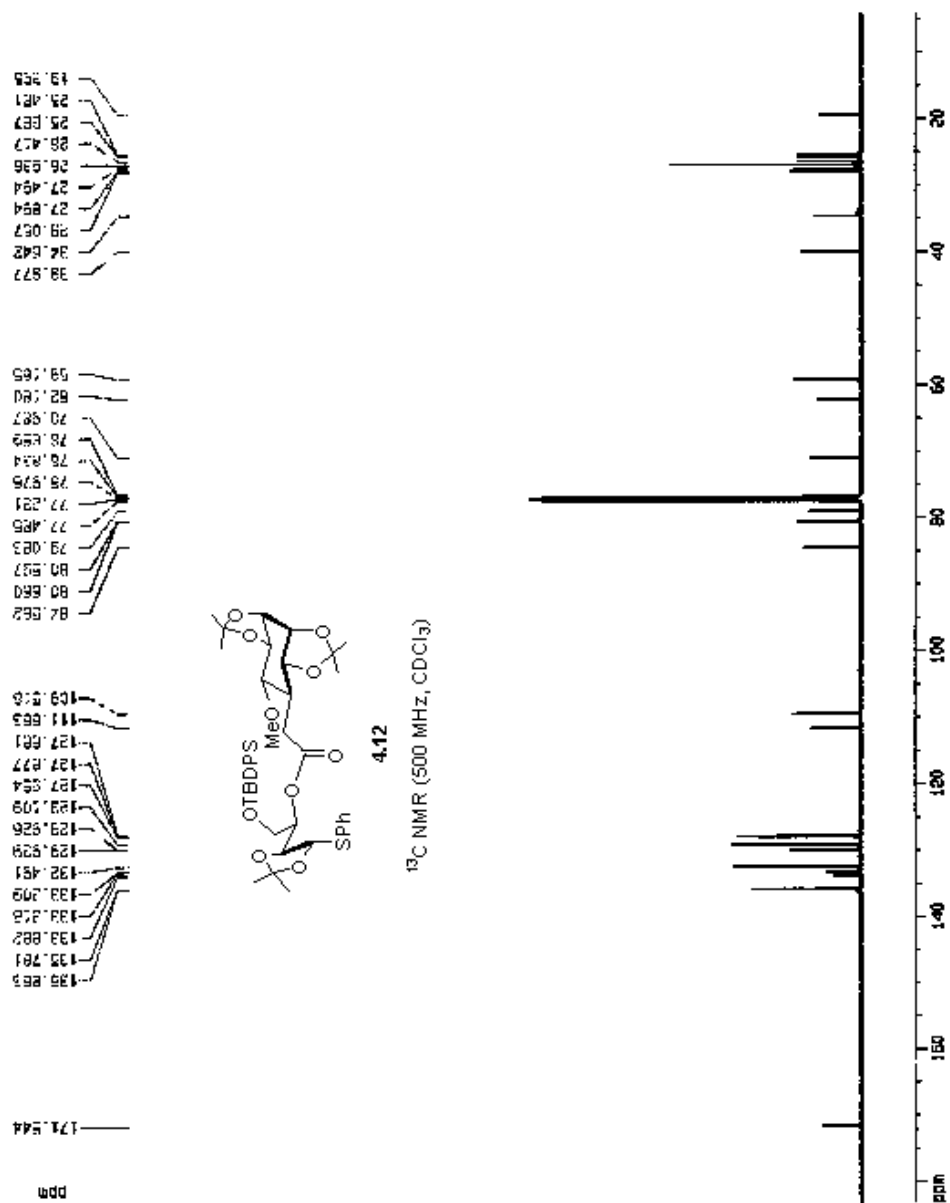


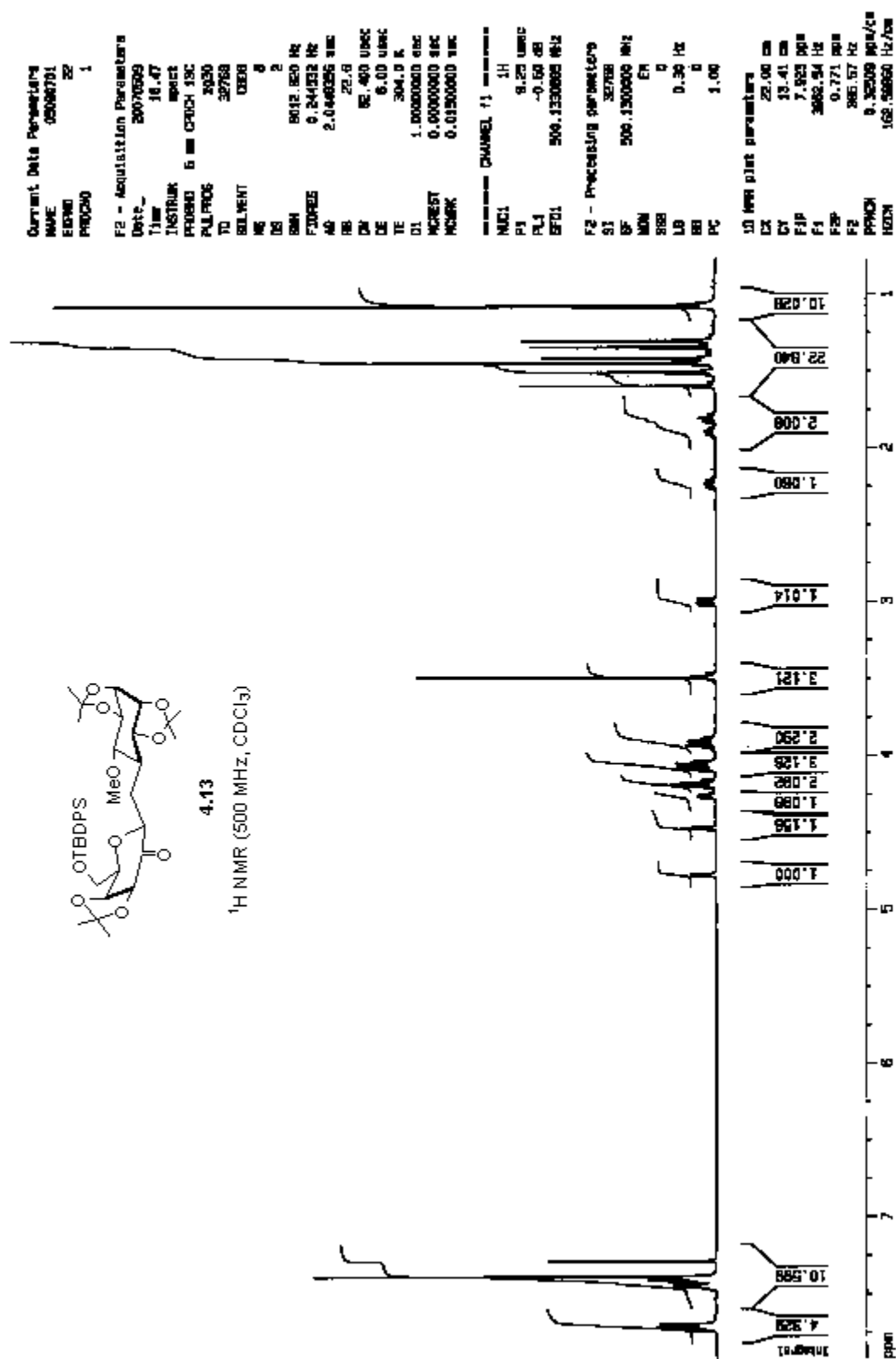
4.9
¹H NMR (500 MHz, CDCl₃)

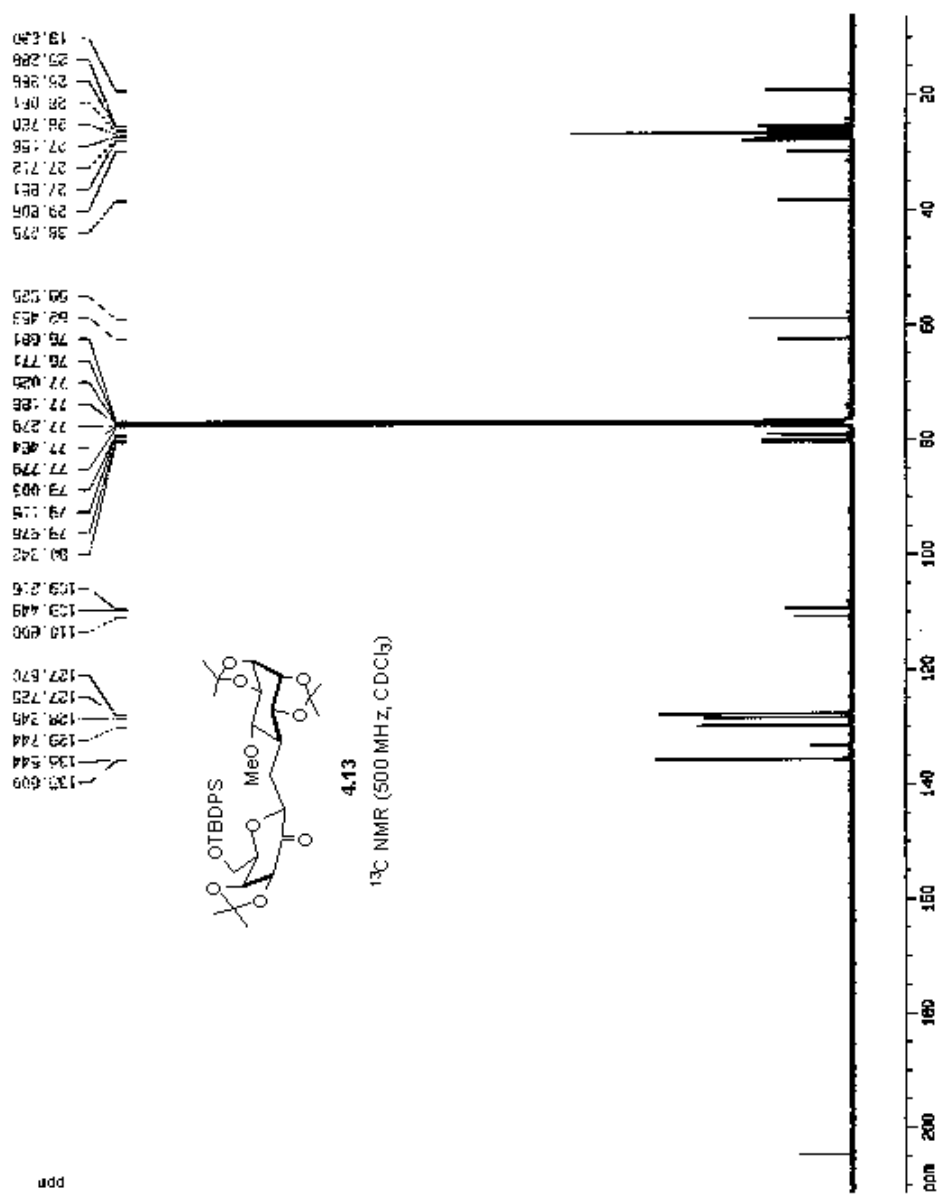


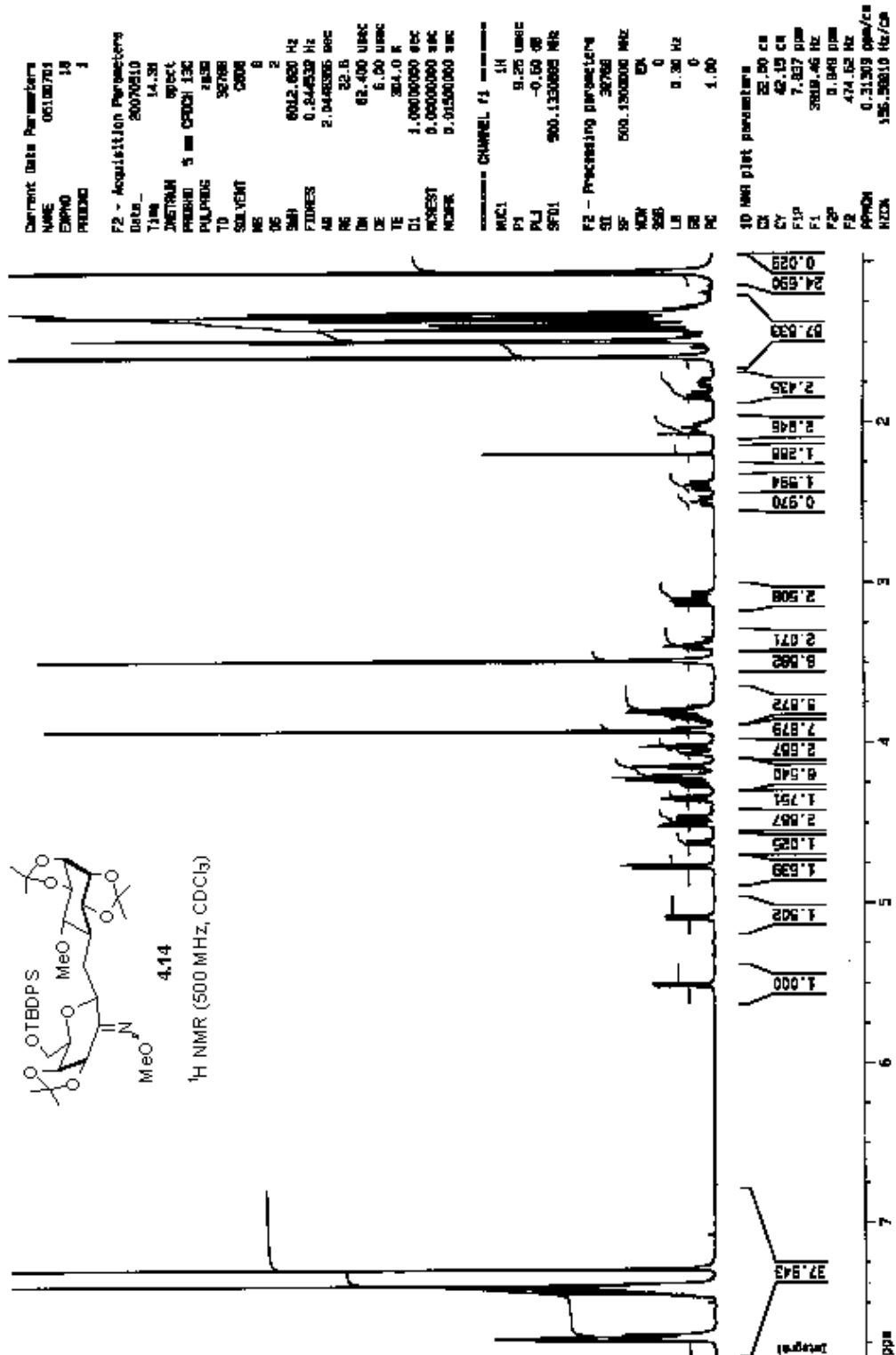


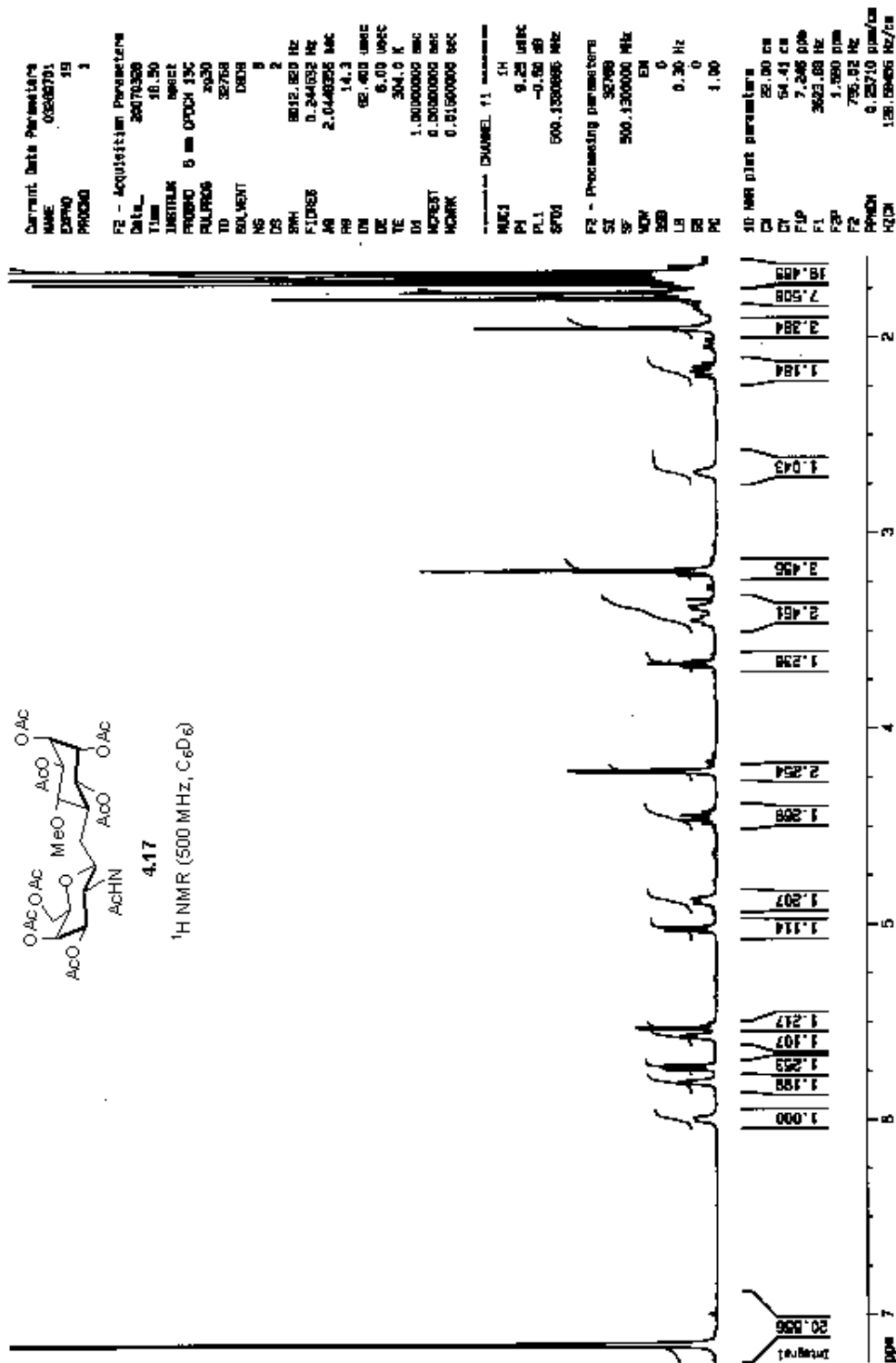


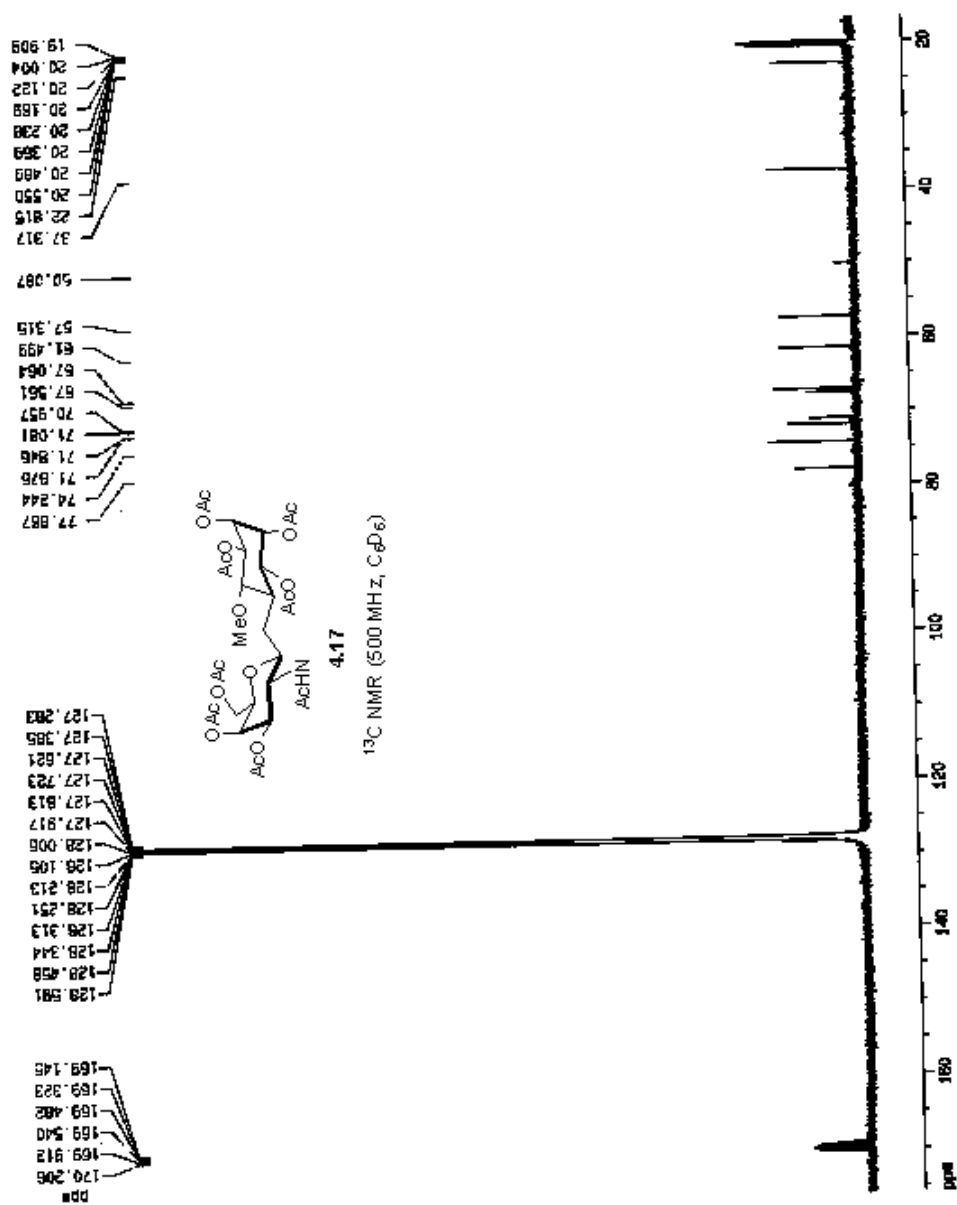


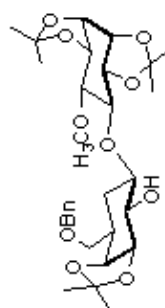




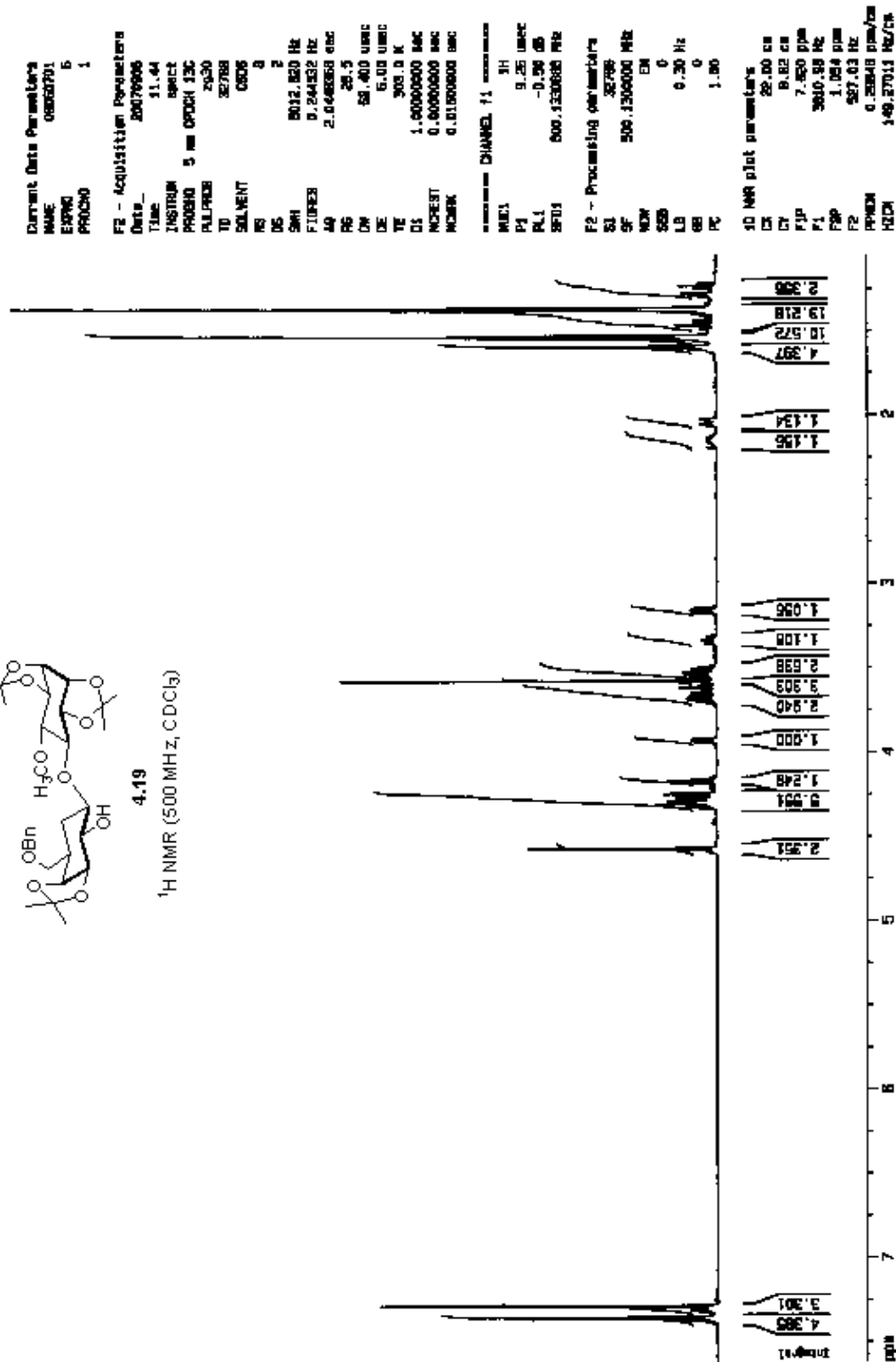


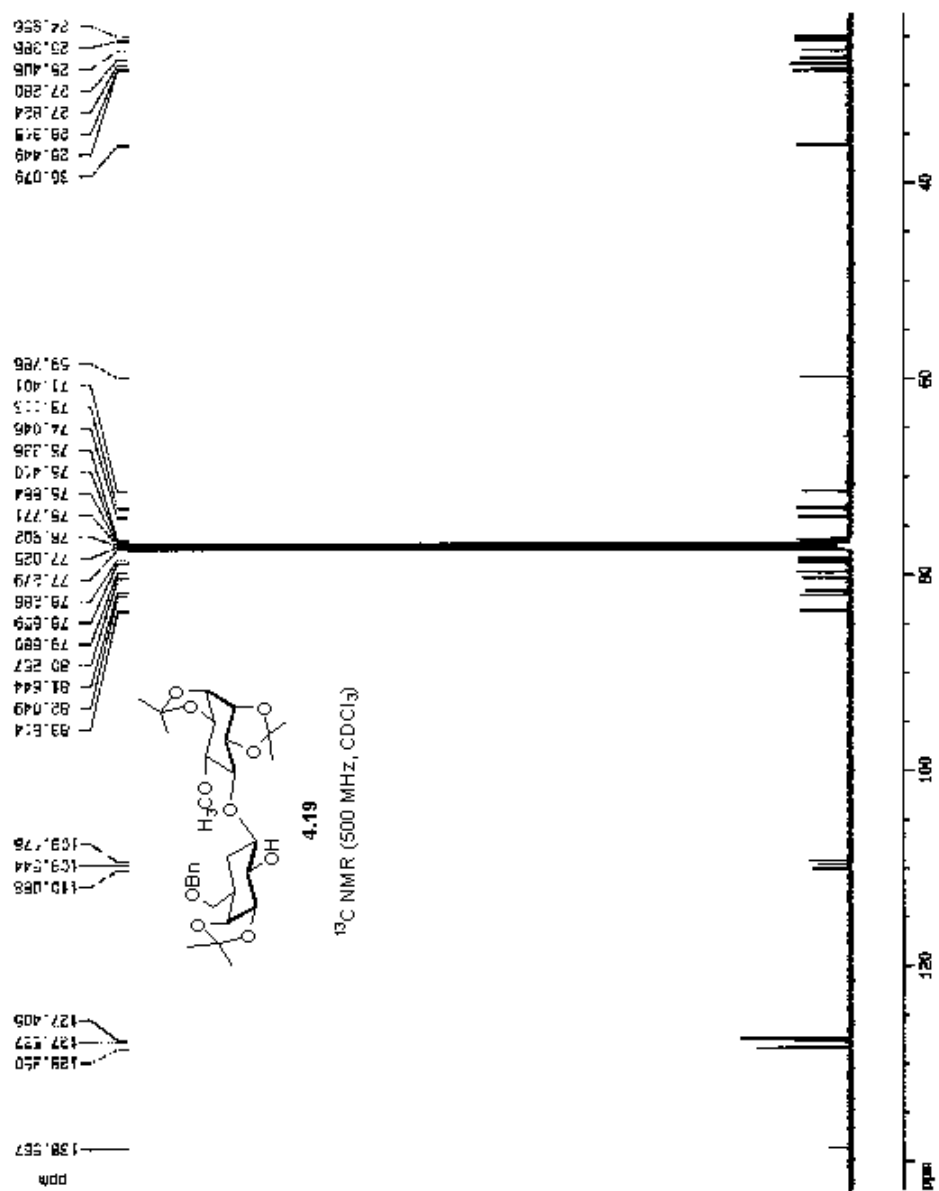


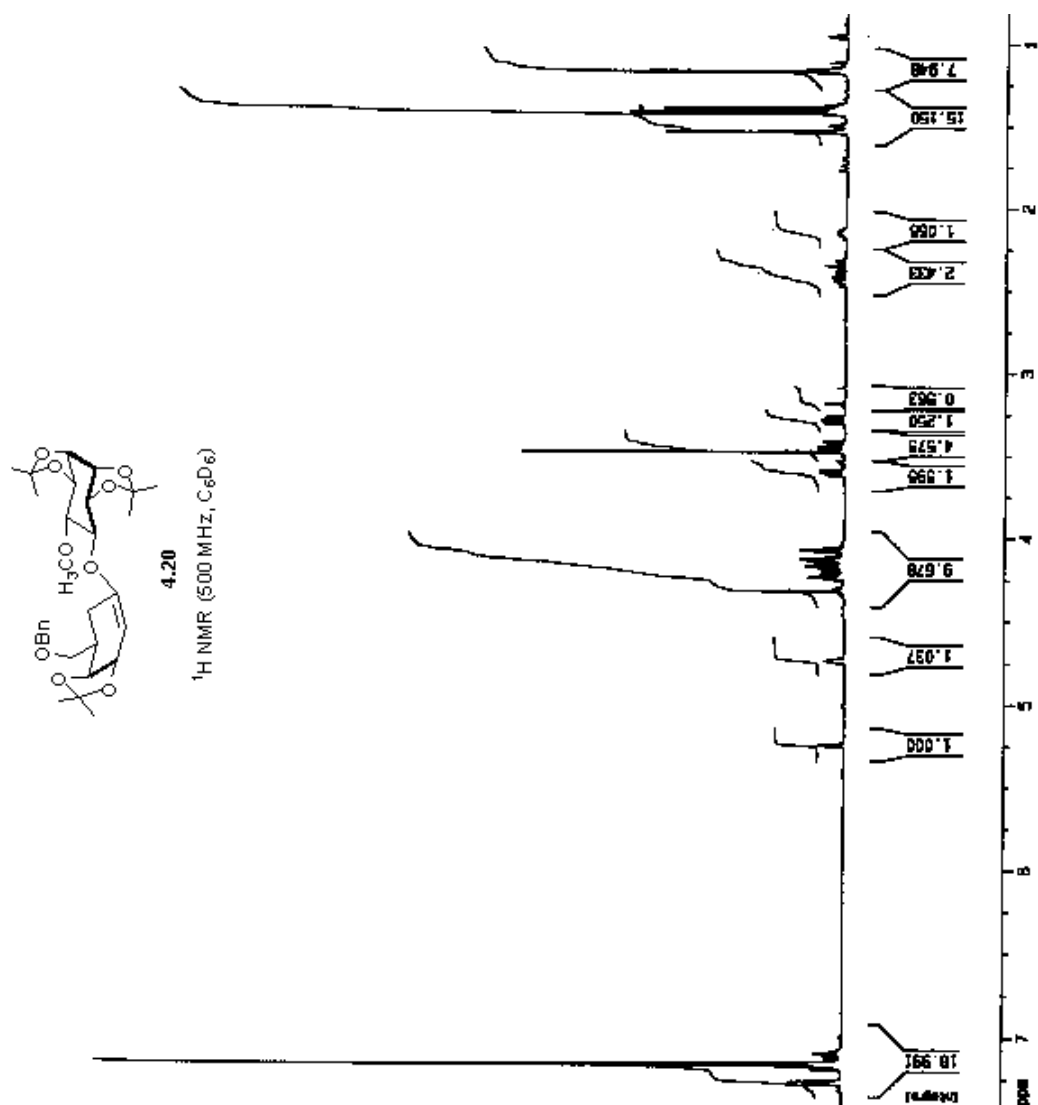


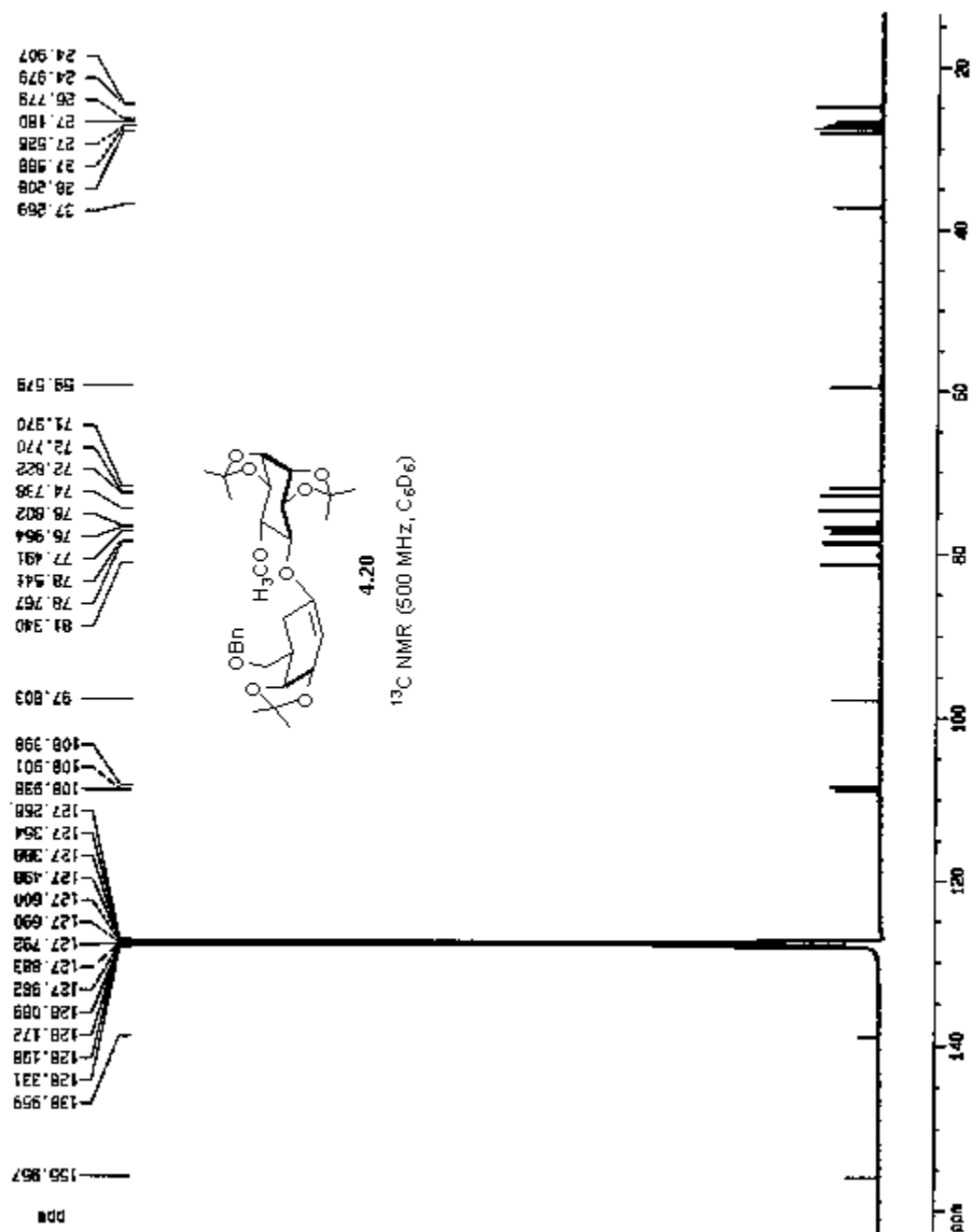


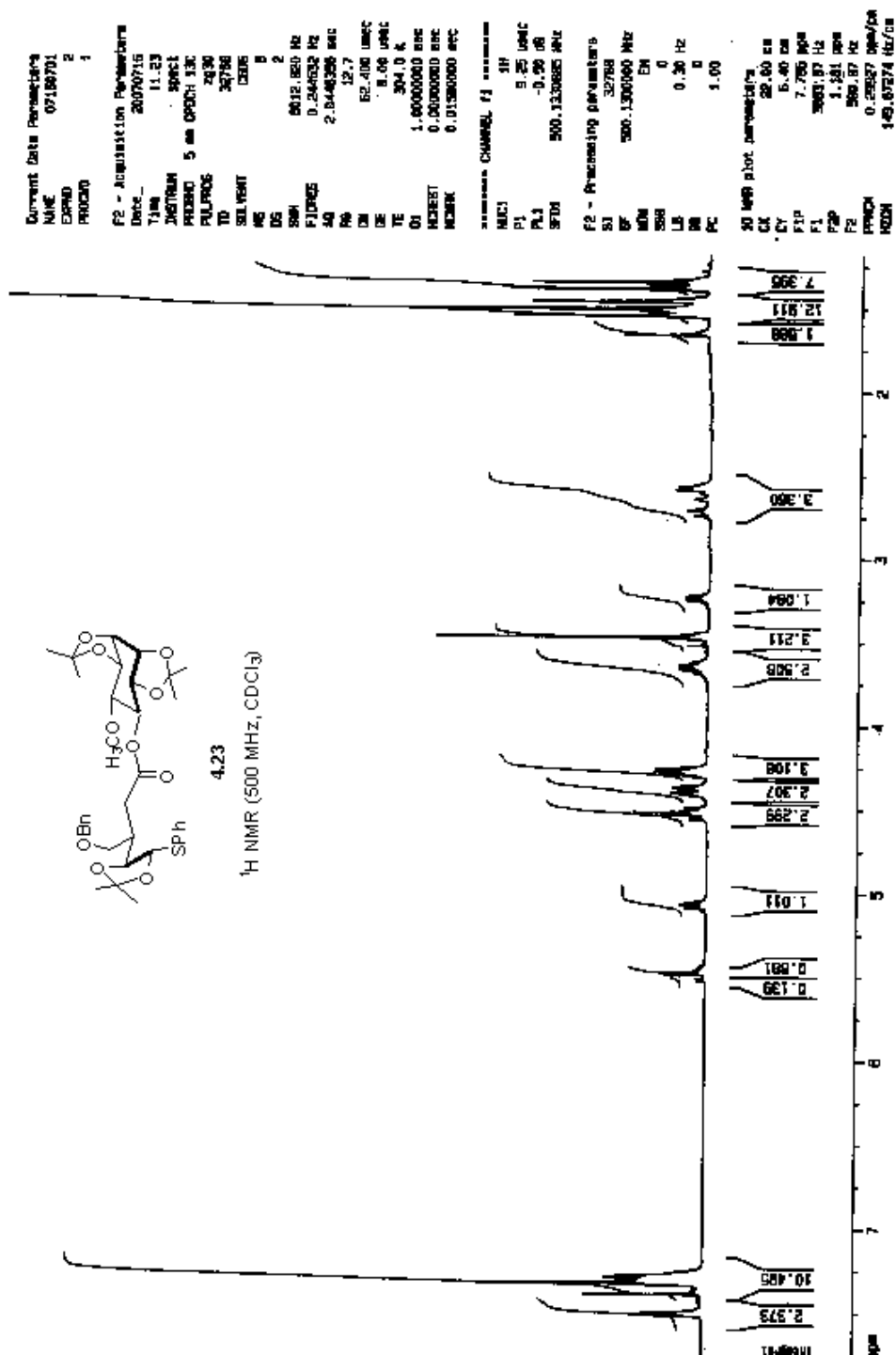
4.19

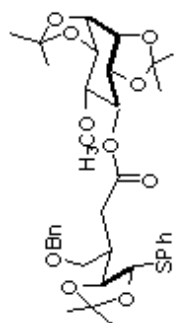
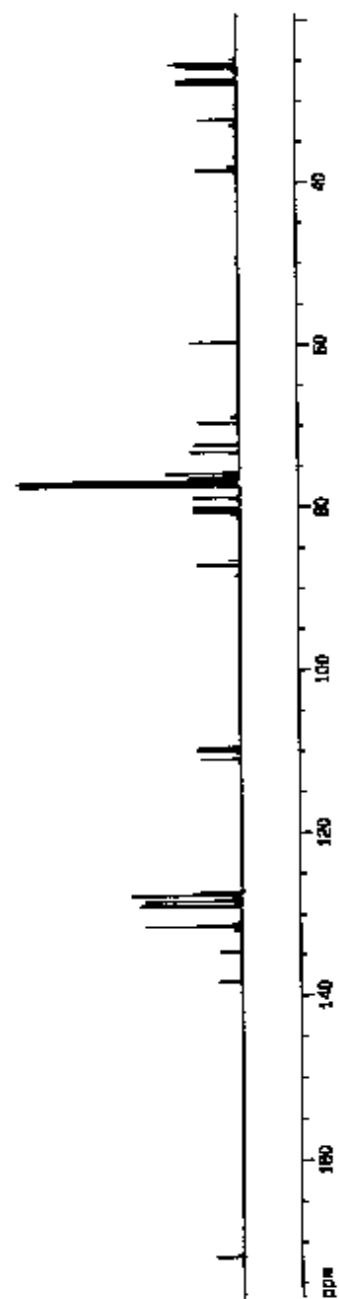
¹H NMR (500 MHz, CDCl₃)



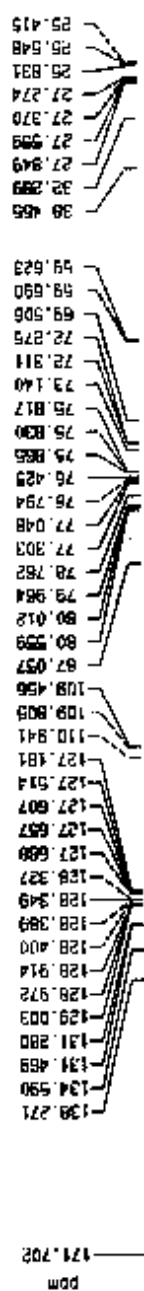


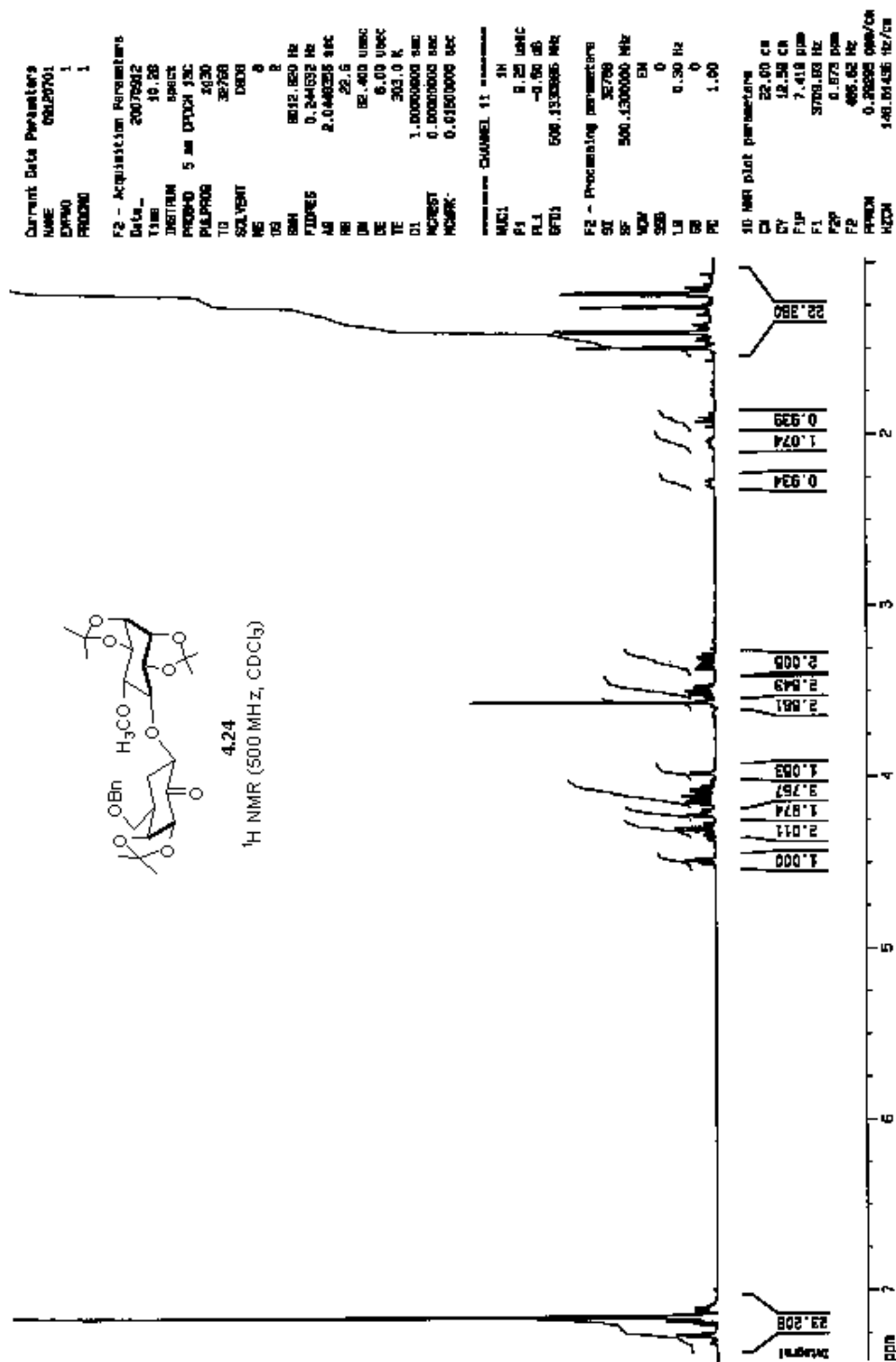


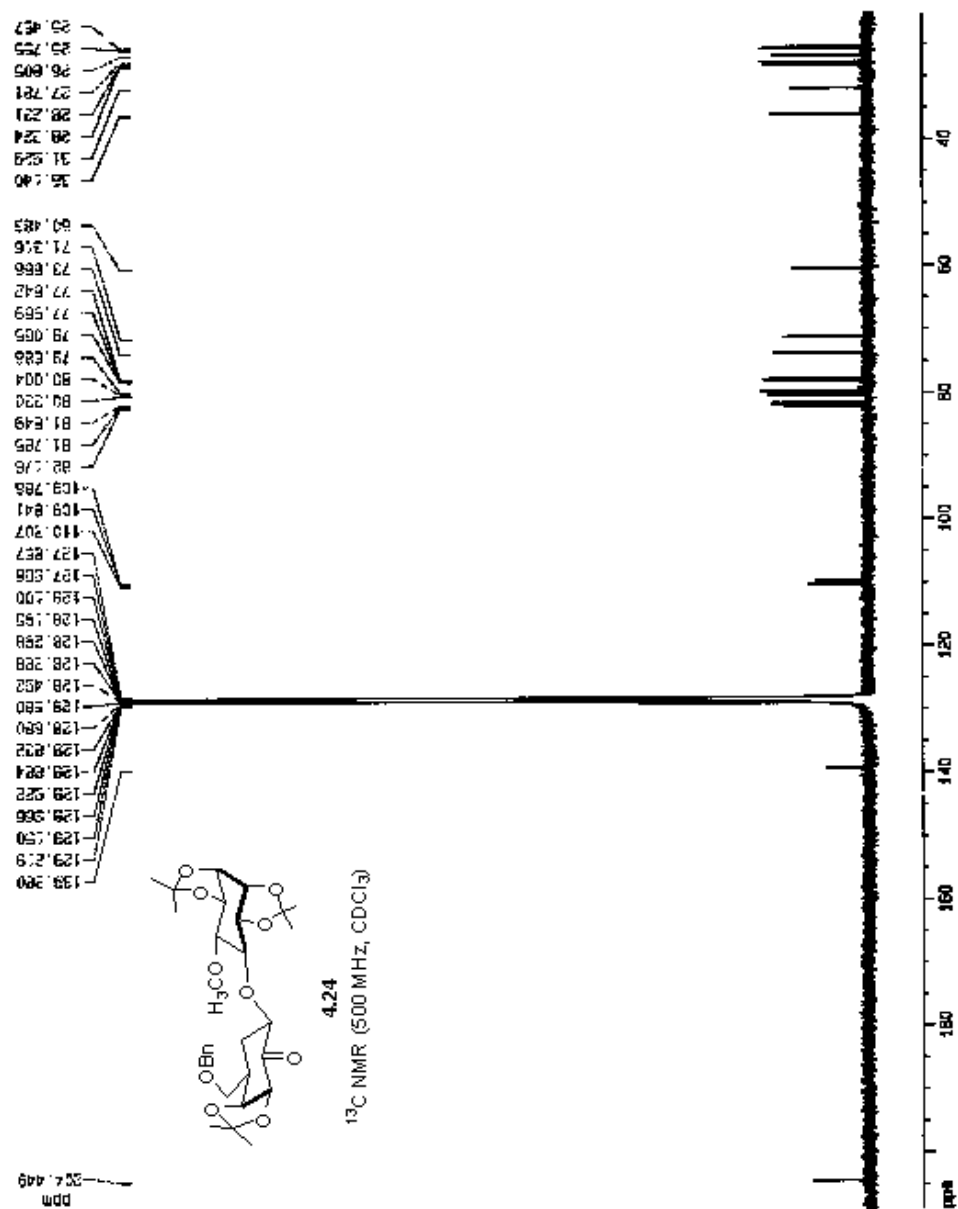


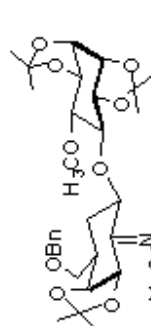


4.23

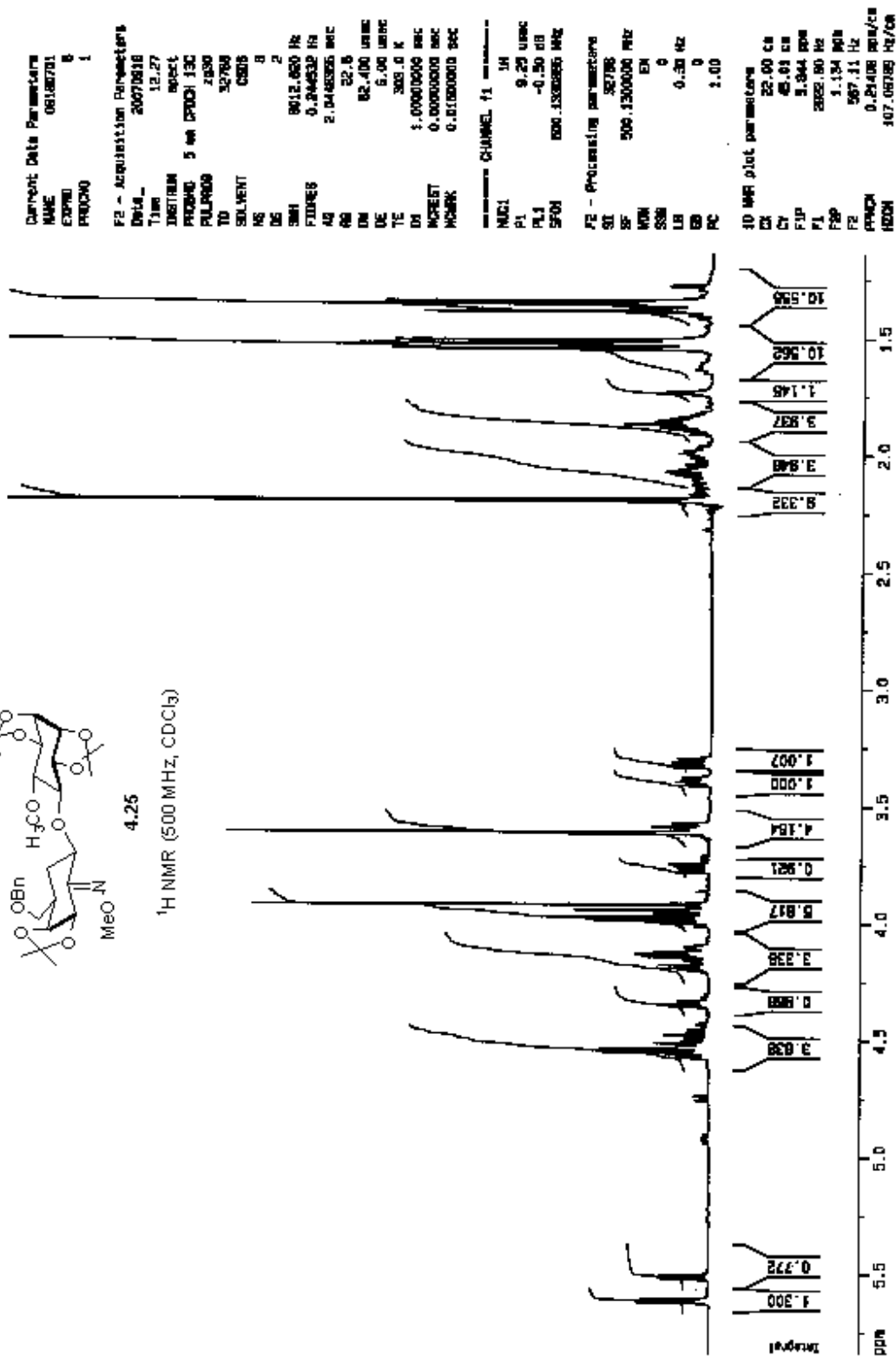
 ^{13}C NMR (500 MHz, CDCl_3)

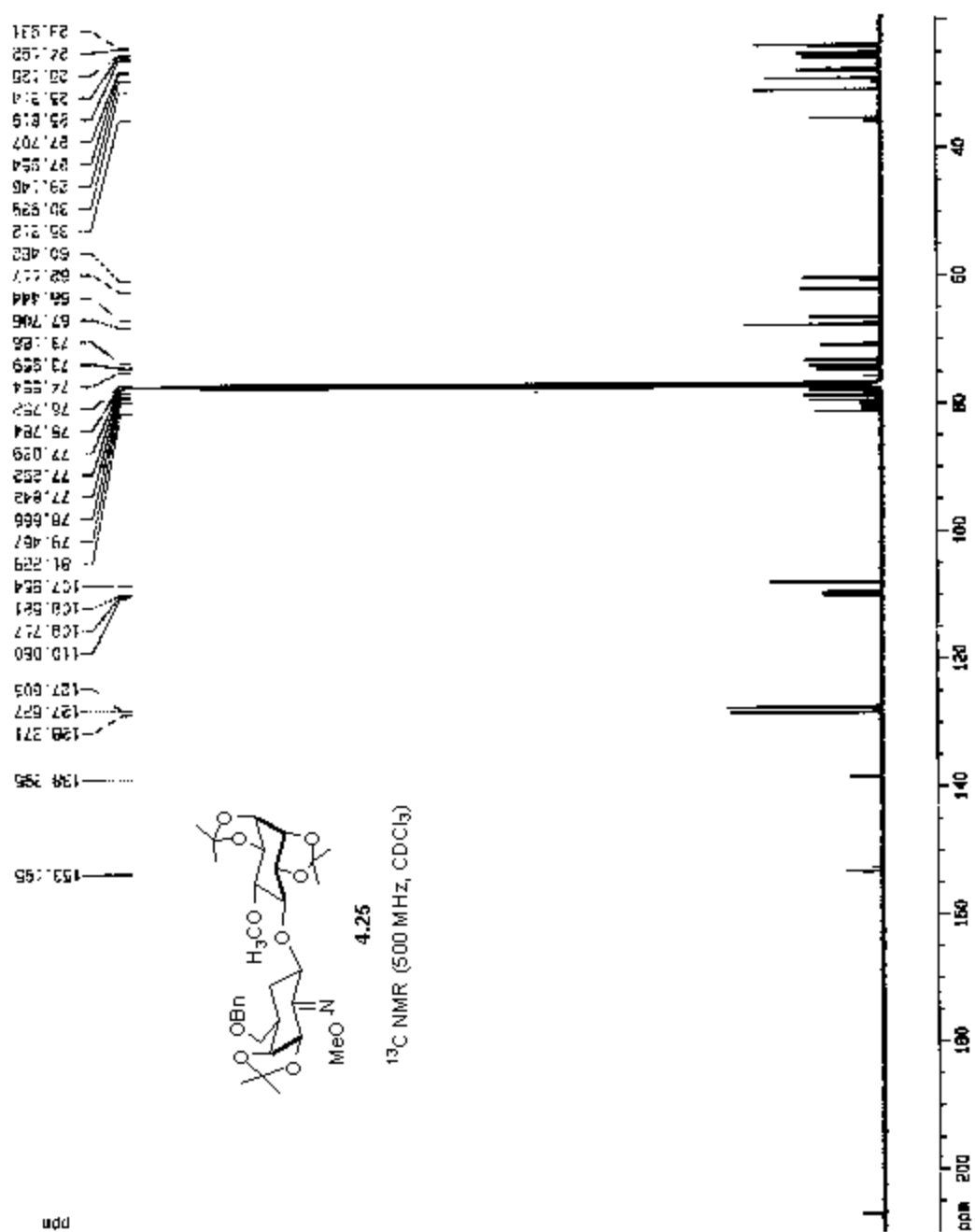






4.25

¹H NMR (500 MHz, CDCl₃)



-
- ¹ Ben, N. R.; Orellana, A.; Arya, P. *J. Org. Chem.* **1998**, 63, 4817-4820.
- ² For reviews of chemistry and applications of C-glycosides: Postema, M.H.D. *C-Glycoside Synthesis*, CRC Press, Boca Raton 1995. Levy, D.; Tang, C. *The Synthesis of C-Glycosides*, Elsevier/Pergamon, Oxford 1995. Skrydstrup, T.; Vauzeilles, B.; Beau, J.-M. Synthesis of C-oligosaccharides in *Carbohydrates in Chemistry and Biology*, Vol. 1; Eds. Ernst, B.; Hart, G. W.; Sinaÿ, P., Wiley-VCH, Weinheim, 2000, p 495-530. Jiménez-Barbero, J.; Espinosa, J. F.; Asensio, J. L.; Cañada, F. J. *Adv. Carbohydr. Chem. Biochem.* **2001**, 56, 235-284.
- ³ For an example where O- and C- glycosides bind in different conformations with respect to the intersaccharide torsions: Espinosa, J. f.; Montero, E.; Vian, A.; Garcia, J. L.; Dietrich, H.; Schmidt, R. R.; Martin-Lomas, M.; Imberty, A.; Canada, F. J.; Jimenez-Barbero, J. *J. Am. Chem. Soc.* **1998**, 120, 1309-1318.
- ⁴ Santo, D.R.; Costi, R.; Artico, M.; Massa, S.; Lampis, G.; Deidda, D.; Pompei, R. *Bioorganic & Medicinal Chemistry Letters.* **1998**, 8, 2931-2936.
- ⁵ Gundersen, L.-L.; Meyer, N.J.; Spilsberg, B. *J. Med. Chem.* **2002**, 45, 1383-1386.
- ⁶ Chatterjee, D. *Curr Opin Chem Biol.* **1997**, 1, 579-588.
- ⁷ Chatterjee, D.; Khoo, K.-Y. *Glycobiology* **1998**, 8, 113-120.
- ⁸ Nagafuku, M.; Kabayama, K.; Oka, D.; Kato, A.; Tani-ichi, S.; Shimada, Y.; Ohno-Iwashita, Y.; Yamasaki, S.; Saito, T.; Iwabuchi, K.; Hamaoka, T.; Inokuchi, J.; Kosugi, A. *J. Biol. Chem.* **2003**, 278, 5192-51927. Denny, P. W.; Field, M. C.; Smith, D. F. *FEBS Lett.* **2001**, 491, 47-50. Benting, J. H.; Rietveld, A. G.; Simons, K. J. *Cell. Biol.* **1999**, 146, 313-320. Ilangumaran, S.; Arni, S.; van Echten-Deckert G.; Borisch, B.;

Hoessli, D. C. *Mol. Biol. Cell* **1999**, *10*, 891-905. Shroeder, R. J.; Ahmed, S. N.; Zhu, Y.; London, E.; Brown, D. A. *J. Biol. Chem.* **1998**, *273*, 1150-1157.

⁹ Park, S.-H.; Bendelac, A. *Nature* **2000**, *406*, 788-792.

¹⁰ Ferguson, M. A. J. *J. Cell Sci.* **1999**, *112*, 2799-2809.

¹¹ Sharom, F. J.; Lehto, M. T. *Biochem. Cell Biol.* **2002**, *80*, 535-549.

⁸ Nagafuku, M.; Kabayama, K.; Oka, D.; Kato, A.; Tani-ichi, S.; Shimada, Y.; Ohno-Iwashita, Y.; Yamasaki, S.; Saito, T.; Iwabuchi, K.; Hamaoka, T.; Inokuchi, J.; Kosugi, A. *J. Biol. Chem.* **2003**, *278*, 5192-51927. Denny, P. W.; Field, M. C.; Smith, D. F. *FEBS Lett.* **2001**, *491*, 47-50. Benting, J. H.; Rietveld, A. G.; Simons, K. J. *Cell. Biol.* **1999**, *146*, 313-320. Ilangumaran, S.; Arni, S.; van Echten-Deckert G.; Borisch, B.; Hoessli, D. C. *Mol. Biol. Cell* **1999**, *10*, 891-905. Shroeder, R. J.; Ahmed, S. N.; Zhu, Y.; London, E.; Brown, D. A. *J. Biol. Chem.* **1998**, *273*, 1150-1157.

¹³ Turner, D. I.; Chakraborty, N.; d'Alarcao, M., *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2023-2025.

¹⁴ (a) Jones, D. R.; Varela-Nieto, I., *Int. J. Biochem. Cell Biol.* **1998**, *30*, 313-326. (b) Stralfors, P., *BioEssays*, **1997**, *19*, 327-335. (c) Field, M. C., *Glycobiology* **1997**, *7*, 161-168. (d) Varela-Nieto, I.; Leon, Y.; Caro, H. N. *Comp. Biochem. Pysiol. B: Biochem.* **1996**, *115*, 223-241.

¹⁵ (a) Del Aguila, L. F. et.al. *Am. J. Physiol. Endocrinol. Metab.* **2000**, *279*, E206-E212. (b) Shepherd, P. R., B. B. Kahn. *N. Eng. J. Med.* **1999**, *341*, 248-257.

¹⁶ Alvarez, J. F.; Sanchez-Arias, J. A.; Guadano, A.; Estevez, F.; Varela, I.; Feliu, J. E.; Mato, J. M. *Biochem. J.* **1991**, *274*, 369-374.

-
- ¹⁷ Thompson, M. P., Larner, J., Kilpatrick, D., *Mol. Cell. Biochem.* **1984**, 62, 67-75.
- ¹⁸ Malchoff, C. D., Huang, L., Gillespie, N., Villar-Palasi, C., Schwartz, C. F. W., Cheng, K., Hewlett, E. L., and Larner, J., *Endocrinology*, **1987**, 120, 1327-1333.
- ¹⁹ Larner, J., Price, J. D., Heimark, D., Smith, L., Rule, G., Piccariello, T., Fronteles, M. C., Pontes, C., Vale, D., Huang, L., *J. Med. Chem.* **2003**, 46, 3283-3291 and the ref. therein.
- ²⁰ Brautigan, D. L.; Brown, M.; Grindrod, S.; Chinigo, G.; Kruszewski, A.; Lukasik, S. M.; Bushweller, J. H.; Horal, M.; Keller, S.; Tamura, S.; Heimark, D. B.; Price, J.; Larner, A. N.; Larner, J. *Biochemistry* **2005**, 44, 11067-11073.
- ²¹ (a) Smoliakova, I. P. *Curr. Org. Chem.* **2000**, 4, 589-608. (b) Du, Y.; Linhardt, R. J.; Vlahov, J. R. *Tetrahedron* **1998**, 54, 9913-9959. (c) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700-717. (d) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995. (e) Levy, D.; Tang, C. *The Synthesis of C-Glycosides*; Elsevier/Pergamon: Oxford, 1995.
- ²² (a) Riley, A. M.; Murphy, C. T.; Lindley, C. J.; Westwick, J.; Potter, B. V. L. *Bioorg. Med. Chem. Lett.* **1996**, 6, 2197-2200; (b) Sun, H.; Reddy, G. B.; George, C.; Meuillet, E. J.; Berggren, M.; Powis, G.; Kozikowski, A. P. *Tetrahedron Lett.* **2002**, 43, 2835-2838.
- ²³ (a) Kan, T.; Nara, S.; Ozawa, T.; Shirahama, H.; Matsuda, F. *Angew. Chem. Int. Ed.* **2000**, 39, 355-357; (b) Kan, T.; Hosokawa, S.; Nara, S.; Tamiya, H.; Shirahama, H.; Matsuda, F. *J. Org. Chem.* **2004**, 69, 8956-8958; (c) Gomez, A. M.; Moreno, E.; Danelon, G. O.; Valverde, S.; Lopez, J. C. *Tetrahedron: Asymmetry* **2003**, 14, 2961-2974; (d) Soengas, R. G.; Estevez, J. C.; Estevez, R. *J. Org. Lett.* **2003**, 5, 4457-4459; (e)

Ishikawa, T.; Shimizu, Y.; Kodoh, T.; Saito, S. *Org. Lett.* **2003**, 5, 3879-3882; (f) Kireev, A. S.; Breithaupt, A. T.; Collins, W.; Nadein, O. N.; Kornienko, A. *J. Org. Chem.* **2005**, 70, 742-745.

²⁴ Jacques, F.; Dupeyroux, H.; Joly, J.-P.; Chapleur, Y. *Tetrahedron Lett.* **1997**, 38, 73-76.

²⁵ Glycosyl nucleophiles: Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, 187, 1-54.

²⁶ Glycal nucleophiles: Eisele, T.; Ishida, M.; Hummel, G.; Schmidt, R. *Liebigs Ann.* **1995**, 2113-2121.

²⁷ C1 radicals: Rubinstenn, G.; Mallet, J.-M.; Sinay, P. *Tetrahedron Lett.* **1998**, 39, 3697-3700.

²⁸ C1 electrophiles: Rouzad, D.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1353-1354. Preuss, R.; Schmidt, R. *J. Carbohydr. Chem.* **1991**, 10, 887-900.

²⁹ Ferritto, R.; Vogel, P. *Tetrahedron Letters*, **1995**, 36, 3517-3518.

³⁰ Sanhueza, C.; Mayato, C.; Garcia-Chicano, M.; Diaz-Penate, R.; Dorta, R.; Vazquez, J. *T. Bio. & Med. Chem. Lett.*, **2006**, 16, 4223-4227.

³¹ Danishefsky, S. J.; Halcomb, R. L., *J. Am. Chem. Soc.* **1989**, 111, 6661-6666.

³² Murray, R.; Singh, M. *J. Org. Chem.* **1993**, 58 (19), 5076-5080.

³³ Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, 58, 1997-2009.

³⁴ Palmier, S.; Vauzeilles, B.; Beau, J.-M. *Org. Biomol. Chem.* **2003**, 1, 1097-1098.

³⁵ (a) Mini Review: Pearce, A. J.; Sinay, P. *Trends Org. Chem.* **2000**, 8, 129-135. (b) Das, S. K.; Mallet, J.-M.; Sinay, P. *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 493-496.

³⁶ Paulsen, H.; von Dein, W. *Liebigs Ann. Chem.* **1987**, 125-131.

-
- ³⁷ Schmid, W.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, 112, 9670-9671.
- ³⁸ McCasland, G. E.; Furuta, S.; Dulham, L. J. *J. Org. Chem.* **1968**, 33, 2835-2841.
- ³⁹ Ogawa, S.; Matsunaga, N.; Palcic, M. M. *Carbohydr. Lett.* **1997**, 2, 299-306. Ogawa, S.; Hirai, K.; Yamazaki, T.; Nakajima, A.; Matsunaga, N. *Carbohydr. Lett.* **1996**, 2, 183-186. Ogawa, S.; Hirai, K.; Ohno, M.; Furuya, T.; Sasaki, S.-I.; Tsunoda, H. *Liebigs Ann. Chem.* **1996**, 673-677. Arjona, O.; Gomez, A. M.; Lopez, J. C.; Plumet, J. *Chem Rev.* **2007**, 107, 1919-2036.
- ⁴⁰ Hudlicky, T.; Abboud, K. A.; Entwistle, D. A.; Fan, R.; Maurya, R.; Thorpe, A. J.; Bolonick, J.; Myers, B. *Synthesis*, **1996**, 7, 897-911.
- ⁴¹ Ferrier, R. J.; Haines, S. R. *J. Chem. Soc., Perkin Tans. 1*, **1984**, 1689-1692.
- ⁴² Khan, N.; Xiao, H.; Zhang, B.; Cheng, X.; Mootoo, D. R. *Tetrahedron* **1999**, 55, 8303-8312; Shan, W.; Wilson, P.; Liang, B.; Mootoo, D. R. *J. Org. Chem.* **1999**, 59, 7986-7992.
- ⁴³ Denton, R. W.; Tony, K. A.; Hernandez, J. J.; Canada, F. J.; Jimenez-Barbero, J.; Mootoo, D. R. *Carbohydr. Res.* **2007**, 342, 1624-1635. Denton, R. W.; Cheng, X.; Tony, K. A.; Dilhas, A.; Hernandez, J. J.; Canales, A.; Jimenez-Barbero, J.; Mootoo, D. R. *Eur. J. Org. Chem.* **2007**, 645-654. Tony, K. A.; Denton, R. W.; Dilhas, A.; Jimenez-Barbero, J.; Mootoo, D. R. *Org. Lett.* **2007**, 9, 1441-1444.
- ⁴⁴ Hans, S.; Mootoo, D. R. *Carbohydrate Research* **2006**, 341, 1322-1332.
- ⁴⁵ Camara, F.; Angarita, J.; Mootoo, D. R. *J. Org. Chem.* **2005**, 70, 6870-6875.
- ⁴⁶ Wilson, P.; Jammalama; Mootoo, D. R. *J. Carb. Chem.* **1994**, 13 (6), 841.
- ⁴⁷ Dahanukar, V. H.; Rychnovsky, S. D. *J Org. Chem.* **1996**, 61, 8317-8320.
- ⁴⁸ Dahanukar, V. H.; Rychnovsky, S. D. *J Org. Chem.* **1996**, 61, 8317-8320.

-
- ⁴⁹ For an example of olefin cross-metathesis with allyltrimethylsilane and carbohydrate alkene: Roy, R.; Dominique, R.; Das, S. DK. *J. Org. Chem.* **1999**, 64, 5408-5412.
- ⁵⁰ Fernandez de la Pradilla, R.; Jaramillo, C.; Jimenez-Barbeero, J.; Martin-Lomas, M.; Penades, S.; Zapata, A. *Carbohydr. Res.* **1990**, 207, 249-257.
- ⁵¹ Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron Lett.* **1980**, 36, 2783-2793.
- ⁵² Elie, C. J. J.; C. E.; Verduyn, R.; Vandermarel, G. A.; Van Boom, J. H. *Tetrahedron* **1989**, 45, 3477-3486. Elie, C. J. J.; Vanduyun, R.; Dreef, C. E.; Brounts, D. M.; Vandermarel, G. A.; Van Boom, J. H. *Tetrahedron* **1990**, 46, 8243-8254. Elie, C. J. J.; Verduyn, R.; Dreef, C. E.; Vandermarel, G. A.; Van Boom, J. H. *J. Carbohydr. Chem.* **1992**, 11, 715-739.
- ⁵³ Watanabe, Y.; Yamamoto, T.; Ozaki, S. *J. Org. Chem.* **1996**, 61 14-15. Watanabe, Y.; Yamamoto, T.; Okazaki, T. *Tetrahedron* **1997**, 53, 903-918.
- ⁵⁴ Stadelmaier, A.; Schmidt, R. R. *Carbohydrate Res.* **2003**, 338, 2557-2569. Jayaprakash, K. N.; Lu, J.; Fraser-Reid, B. *Bioorg. Med. Chem. Lett.* **2004**, 14, 3815-3819. Stadelmaier, A.; Biskup, M. B.; Schmidt, R. R. *Eur. J. Org. Chem.* **2004**, 3292-3303.
- ⁵⁵ Liu, X.; Stocker, B. L.; Seeberger, P. H. *JACS* **2006**, 3638-3648.
- ⁵⁶ Palmier, B.; Vauzeilles, B.; Beau, J-M. *Org. Biomol. Chem.* **2003**, 1, 1097-1098.
- ⁵⁷ Seeberger, P.H. *Aldrichimica Acta.* **1997**, 30 (3), 75-92.
- ⁵⁸ (a) De Armas, P.; Francisco, C. G.; Suarez, E. *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 772-774. (b) Francisco, C. G.; Friere, R.; Gonzalez, C. C.; Surez, E. *Tetrahedron Asymmetry* **1997**, 8, 1971-1972.

-
- ⁵⁹ Levene, P. A.; Tipson, R. S. *J. Biol. Chem.* **1936**, 115, 731-747.
- ⁶⁰ (a) Neises, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 522-523. (b) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Reddy, K.; Defrees, S. A.; Reddy, D. R.; Awartani, R. A.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, 117, 41, 10227-10238.
- ⁶¹ (a) Lattrell, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 904-920. (b) Dong, H.; Pei, Z.; Ramstrom, O. *J. Org. Chem.* **2006**, 71, 3306-3309.
- ⁶² Paulson, J. C. *Trends Biochem. Sci.* **1989**, 14, 272.
- ⁶³ Austin, P. R.; Brine, C. J.; Castle, J. E.; Zikakis, J. P. *Science*, **1981**, 212, 749.
- ⁶⁴ Roden, L. *In The Biochemistry of Glycoprotein and proteoglycans*; Lennarz, W. J.; Ed; Plenum: New York, **1980**; p 321.
- ⁶⁵ Turner, D. I.; Chakroborty, N.; d'Alarcao, M. *Bioor. & Medi. Chem. Lett.* **2005**, 15, 2023-2025.
- ⁶⁶ Denton, R. W.; Cheng, X.; Tony, K. A.; Dilhas, A.; Hernandez, J. J.; Carnales, A.; Jimenez-Barbero, J.; Mootoo, D. R. *Eur. J. Org. Chem.* **2007**, 4, 645.
- ⁶⁷ Nicotra, F et al. *Eur. J. Org. Chem.* **1999**, 3437.
- ⁶⁸ Cheng, X.; Khan, N.; Kumaran, G.; Mootoo, D. R. *Org. Lett.* **2001**, 3(9), 1323-1325.