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Palladium and nickel catalyzed stereoselective formation of glycosides

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PALLADIUM AND NICKEL CATALYZED STEREOSELECTIVE FORMATION OF GLYCOSIDES

by

Enoch Akuamoah Mensah

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Chemistry
in the Graduate College of
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December 2011

Thesis Supervisor: Assistant Professor Hien M. Nguyen

ABSTRACT

The development of new glycosylation methods for the stereoselective synthesis of β-*O*-glycosides in the absence of the traditional C(2)-ester participatory group on glycosyl donors using cationic palladium catalyst $Pd(PhCN)_2(OTF)_2$, as well as the formation of 1.2-*cis*-2-amino glycosides *via* cationic nickel catalyzed α-selective glycosylation using C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidates is described.

In the formation of β-glycosides, the process relies on the ability of the cationic palladium catalyst $Pd(PhCN)_2(OTF)_2$, generated in situ from $Pd(PhCN)_2Cl_2$ and AgOTf, to direct β-selectivity. The new glycosylation reaction is highly β-selective, and proceeds under mild conditions with 1-2 % of catalyst loading. This β-glycosylation protocol has been applied to a number of glucose donors with benzyl, allyl and *p*-methoxybenzyl groups incorporated at the C(2)-position, as well as xylose and quinovose donors to prepare various disaccharides and trisaccharides with good to excellent β-selectivity. Mechanistic studies suggest that the major operative pathway is likely a seven-membered ring intermediate, wherein the cationic palladium complex coordinates to both the C(1)-imidate nitrogen and the C(2)-oxygen of the trichloroacetimidate donor. Formation of this seven-membered ring complex directs the selectivity, leading to the formation of β-glycosides.

In the formation of 1,2-*cis*-2-amino glycosides, the method relies on the nature of nickel-ligand complex to control α-selectivity. The reactive sites of the nucleophiles as well as the nature of the protecting groups have little effect on the α-selectivity. This protocol is mild, highly α-selective, and has been successfully applied towards the stereoselective synthesis heparin disaccharides, α-GluNAc/GalNAc glycoconjugates, and GPI anchor pseudodisaccharides. The nickel catalyzed glycosylation protocol has also been successfully applied to both disaccharide donors and acceptors to provide the

corresponding oligosaccharides in high yields and with excellent levels of α-selectivity. Mechanistic studies suggests that the presence of the substituted benzylidene functionality at the C(2)-amino position of glycosyl donors is crucial for the high α-selectivity observed in the coupling products.

Abstract Approved: _____
Thesis Supervisor

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Title and Department

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Graduate College
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Iowa City, Iowa

CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph.D. thesis of

Enoch Akuamoah Mensah

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
degree in Chemistry at the December 2011 graduation.

Thesis Committee: _____
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Robert Kerns

To my late Mom and Dad: Reynolds Akuamoah Mensah and Mary Mensah.
For all your love, encouragement and support

It is not the critic who counts: not the man who points out how the strong man stumbles or where the doer of deeds could have done better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood, who strives valiantly, who errs and comes up short again and again, because there is no effort without error or shortcoming, but who knows the great enthusiasms, the great devotions, who spends himself for a worthy cause; who, at the best, knows, in the end, the triumph of high achievement, and who, at the worst, if he fails, at least he fails while daring greatly, so that his place shall never be with those cold and timid souls who knew neither victory nor defeat.

Theodore Roosevelt
Speech given in Paris at the Sorbonne in 1910

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Michael, thank you for being there for me whenever I needed a shoulder or a helping hand. I love you all.

Finally, Glory and Honor goes to Jehovah for his protection, guidance and care throughout all these years, and for helping bring this work to a successful end.

ABSTRACT

The development of new glycosylation methods for the stereoselective synthesis of β-*O*-glycosides in the absence of the traditional C(2)-ester participatory group on glycosyl donors using cationic palladium catalyst $Pd(PhCN)_2(OTF)_2$, as well as the formation of 1.2-*cis*-2-amino glycosides *via* cationic nickel catalyzed α-selective glycosylation using C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidates is described.

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In the formation of 1,2-*cis*-2-amino glycosides, the method relies on the nature of nickel-ligand complex to control α-selectivity. The reactive sites of the nucleophiles as well as the nature of the protecting groups have little effect on the α-selectivity. This protocol is mild, highly α-selective, and has been successfully applied towards the stereoselective synthesis heparin disaccharides, α-GluNAc/GalNAc glycoconjugates, and GPI anchor pseudodisaccharides. The nickel catalyzed glycosylation protocol has also been successfully applied to both disaccharide donors and acceptors to provide the

corresponding oligosaccharides in high yields and with excellent levels of α-selectivity. Mechanistic studies suggests that the presence of the substituted benzylidene functionality at the C(2)-amino position of glycosyl donors is crucial for the high α-selectivity observed in the coupling products.

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LIST OF ABBREVIATIONS

$AgClO_4$	Silver perchlorate
$AgCO_3$	Silver carbonate
AgOTf	Silver trifluoromethanesulfonate (Silver triflate)
$BF_3{\cdot}OEt_3$	Boron trifluoride etherate
BnBr	Benzyl bromide
CH_2Cl_2	Dichloromethane
Cl_3CCN	Tricloroacetonitrile
CSA	Camphor sulfonic acid
Cu $(OTf)_2$	Copper (II) trifluoromethanesulfonate (Copper triflate)
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diaza bicyclo [5.4.0] undec-7-ene
DCE	1,2-Dichloroethane
DIPEA	Diisopropylethyl amine
DMAP	4-(Dimethylamino)pyridine
DMDO	Dimethyl dioxirane
DTBP	2,6-Di-*tert*-butyl pyridine
EtSH	Ethanethiol
K_2CO_3	Potassium carbonate
$LiClO_4$	Lithium perchlorate
LiOTf	Lithium trifluoromethanesulfonate (Lithium triflate)
mg	Milligram
mL	Milliliters
mmol	Millimole

NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NBS	*N*-Bromosuccinamide
$Ni(PhCN)_4(OTf)_2$	Nickel(II) tetrakis benzonitrile bis triflate
$Ni(PhCN)_4Cl_2$	Nickel (II) dichloro tetrakis benzonitrile
NIS	*N*-Iodosuccinamide
Pd $(CH_3CN)_4(BF_4)_2$	Palladium (II) tetrakis acetonitrile bis tetrafluoroborate
Pd $(PhCN)_2(OTf)_2$	Palladium (II) bis benzonitrile bis triflate
PhSOTf	Phenyl sulfenyl triflate
Sm $(OTf)_2$	Samarium triflate
TBSCl	*Tert*-butyl-dimethylsilyl chloride
TBSOTf	*Tert*-butyl-dimethylsilyl trifluoromethanesulfonate
tBuOK	Potassium-*tert*-butoxide
TEA	Triethylamine
TFAA	Trifluoroacetic acid
TfOH	Triflic acid
TLC	Thin-layer chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Yb(OTf)	Ytterbium triflate

CHAPTER 1

INTRODUCTION

1.1. Glycosides: Biological Significance

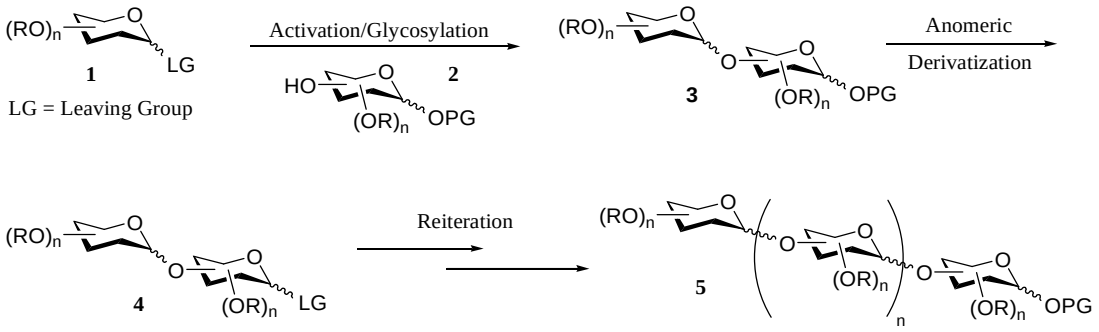
Oligosaccharides and glycoconjugates have fascinated researchers for decades as mediators of complex cellular events.[1] With reference to their structural diversity, they have been known to have capacities that far exceed proteins and nucleic acids. Their variance in structure allows them to encode information for specific molecular recognition events and serve as determinants in protein folding and stability.[1] In cells, most oligosaccharides are linked to other macromolecules, such as proteins and lipids, to form glycoconjugates. The carbohydrate portions of the glycoconjugates usually serve as 'display tags' for a wide array of recognition events in many biological processes.[2-3] Such roles include facilitating cell-cell recognition, cellular transport and to provide a platform for adhesion of bacteria, viruses and toxins. Thus, to better understand this diverse functionality, it is crucial to have access to well defined structures of oligosaccharides and glycoproteins.[1]

The increased understanding of the vital roles that oligosaccharides and glycoconjugates play in biological processes has led to a significant increase in demand for these materials in biological, medicinal and pharmaceutical studies.[4] Unfortunately, only a small quantity of the biologically active carbohydrate natural products can be obtained from nature, thereby limiting a full evaluation and clinical study. As such, a lot of efforts have been made to develop new methods for the synthesis of glycosides, of which the main focus is often the formation of glycosidic linkages.[4] Advancement on this front has also led to the provision of materials necessary for the assessment of glycan function, establishment of structural feature and function relationships, elucidation of

biosynthetic pathways, development of carbohydrate based vaccines as well as the development of inhibitors of glycoconjugate function.[1]

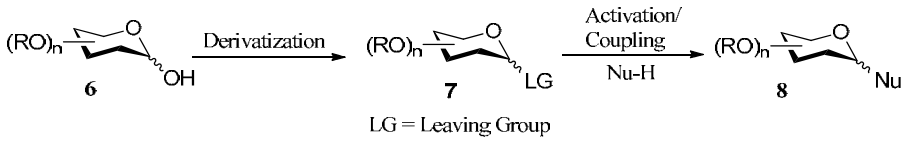
1.2. Glycosylation Methods

The chemical synthesis of oligosaccharides and glycoconjugates is more complex than the synthesis of nucleic acids and peptides because there are a greater number of possibilities to link poly-hydroxyl monomeric units to form oligosaccharides. Thus, the most important reaction in oligosaccharide synthesis is the simple and efficient formation of the glycosidic linkage. In general, glycosidic bond formation can be achieved in a two-step sequence (Scheme 1.1). First, the latent anomeric leaving group on the glycosyl donor (an electrophile) **1** is activated with a promoter or catalyst and subsequently coupled with a glycosyl acceptor (a nucleophile) **2**, to afford the corresponding disaccharide **3**. The resulting disaccharide **3** then undergoes chemoselective anomeric deprotection and anomeric derivatization steps prior to a sequential coupling iteration to generate oligosaccharide **5** (Scheme 1.1).[5]



Scheme 1.1. Oligosaccharide Synthesis.

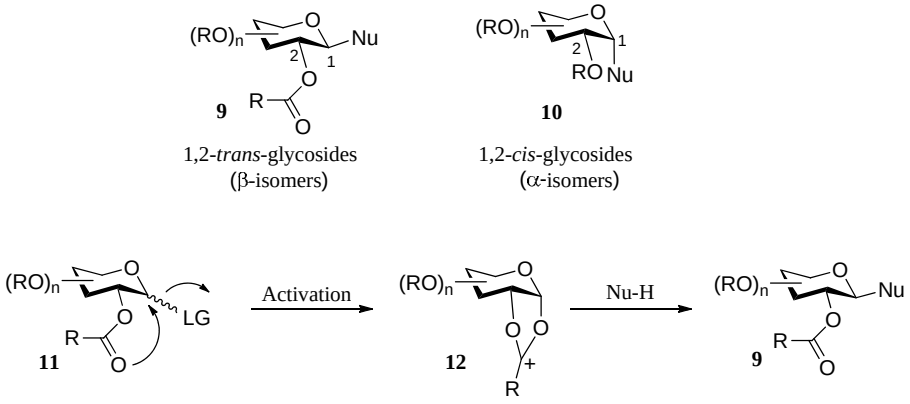
There are numerous challenges in the coupling of a glycosyl donor and a glycosyl acceptor, some of which include 1) the stereoselective formation of glycosidic linkages; 2) the use of a site-selective protected glycosyl acceptor that contains only one free hydroxyl group; and 3) the implementation of orthogonal protection and deprotection of hydroxyl groups of glycosyl donors and acceptors for the assembly of oligosaccharides. In addition, the isolated yield of the coupling process is dependent on the relative reactivities of the glycosyl donors and acceptors.[6] Some of these challenges can be solved by relying on activation of suitably protected glycosyl donors and selectively protected acceptors. Thus, the majority of the efforts in the chemical glycosylation strategies have focused on the development of new methods and reagents for the generation of isolable glycosyl donors, which then undergo anomeric bond formation with glycosyl acceptors.[7-9] In this approach, a C(1)-hemiacetal **6** is initially transformed into a latent anomeric leaving group (LG), and the resultant glycosyl donor **7** can be isolated (Scheme1.2). In the second step, the latent leaving group on **7** is activated with a promoter or catalyst. This process usually occurs in the presence of a nucleophillic acceptor (Nu-H), which effectively displaces the leaving group to form the glycosidic bond in the product **8**.



Scheme 1.2. General Glycosylation Procedure

While the synthesis of 1,2-*trans*-glycosides **9** (Scheme 1.3) could be achieved by employing glycosyl donors with a C(2)-participatory protecting group, the synthesis of 1,2-*cis*-glycosides **10** remains challenging because it requires glycosyl donors with non-

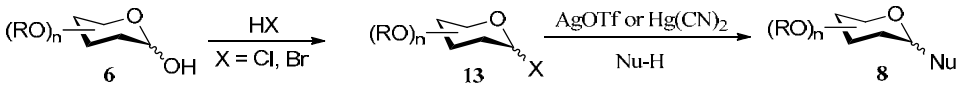
assisting groups at the C(2)-position. In general, the β-stereoselectivity of the newly-formed glycosidic bond in **9** can be achieved when the carbonyl oxygen of the C(2)-acyl protecting group participates with the activated anomeric leaving group at C(1), forming the stabilized carbocation **12** (Scheme 1.3). Subsequent nucleophilic addition of the glycosyl acceptor (Nu-H) can therefore only occur from the equatorial orientation, providing the desired β-glycosides **9**.



Scheme 1.3. Stereoselective Formation of Glycosidic Bonds.

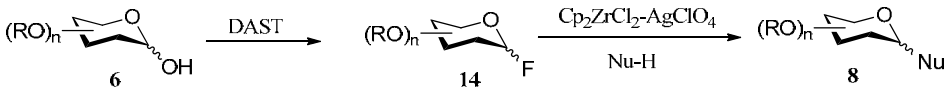
The first viable method for the formation of glycosidic bond was the *Koenigs-Knorr* method that was introduced in 1901.[10] The first step in this mode of glycosylation requires the exchange of the hydroxyl group at the anomeric position with either chlorine or bromine to form the corresponding glycosyl halide **13** (Scheme 1.4). In the second step, the resulting glycosyl donor **13** can be activated with a stoichiometric amount of heavy metal salts such as AgOTf or $Hg(CN)_2$.[11] Although this valuable methodology has been reviewed extensively [5,12,13] since it was first reported in 1901, there are several inherent disadvantages to this method. These include the intrinsic instability of the glycosyl halides, the toxicity of the heavy metal salts used, the requirement of at least an

equimolar quantity of the heavy metal salt promoters for each glycosylation, and the problems associated with the disposal of the heavy metal waste materials. All these have made this mode of glycosylation increasingly less popular, and certainly not very economical for use in large scale synthesis of glycosides.[11] This drawback of the Koenigs-Knorr glycosylation has necessitated the need for alternate methods in the synthesis of glycosidic linkages.



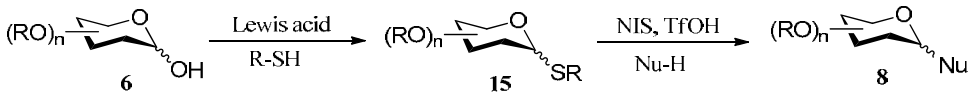
Scheme 1.4. Koenigs-Knorr Glycosylation Method.

Closely related to the Koenigs-Knorr glycosylation is the introduction of fluorine as the latent anomeric leaving group (Scheme 1.5). [14-19] This was developed by Mukaiyama and co-workers in 1981.[15] The introduction of fluorine as a leaving group serves as a good alternative to the Koenigs-Knorr method of glycosylation due to the relative stability of the C – F bond, and consequently, glycosyl fluorides **14** (Scheme 1.5) are easier to handle than their glycosyl chloride and bromide counterparts.[15] In addition, they can be easily synthesized from hemiacetals **6** in the presence of diethylaminosulfur trifluoride (DAST). The glycosyl fluorides **14** are generally activated with the reagent combination of Cp_2ZrCl_2 and $AgClO_4$. Due to the typically low donor properties of the glycosyl fluorides, this method has also not gained wide acceptance and application in the synthesis of complex carbohydrates and glycoconjugates.[20]



Scheme 1.5. Glycosyl Fluoride Glycosylation Method.

Another classical approach that has been widely used in the synthesis of oligosaccharides and glycoconjugates is the thioglycoside methodology (Scheme 1.6). Thioglycosides **15** have been extensively studied as powerful glycosyl donors due to their high stability under a variety of glycosylation conditions. Thioglycosides **15** (Scheme 1.6) can be formed by addition of alkyl- or aryl thiol to hemiacetals **6** under Lewis acid conditions. Glycoside sulfide **15** can be activated with a number of thiophillic reagents such as *N*-bromosuccinimide (NBS), *N*-Iodosuccinimide (NIS), methyl triflate (MeOTf) and methyl iodide (MeI).[21] In addition, the thioglycoside is a good intermediate for the synthesis of the corresponding glycosyl fluoride.



Scheme 1.6. Thioglycoside Glycosylation.

In general, there are three main requirements for an efficient glycosylation methodology. First, the glycosyl donor must be generated in a simple process and then activated by a catalytic amount of a reagent. Second, the glycosylation reaction must be high yielding and stereoselective. Third, the method must be applicable on a large scale.[4] While these requirements were generally not met by the various methods described

above, several other modes of glycosylation have also been recently reported in the synthesis of glycosidic linkages.[11,14,22-31] Among these numerous methodologies, Schmidt's glycosyl imidate glycosylation method is one of the most widely used in the field of synthetic carbohydrate chemistry for the formation of glycosidic linkages.

Of the various synthetic strategies reported in recent years, the synthesis of glycosidic linkages based on *O*-glycosyl imidate donors, with trichloroacetimidate glycosyl donors in particular, are probably one of the most popular.[4] The *O*-glycosyl trichloroacetimidates **16α** and **16β** (Figure 1), which were first introduced by Schmidt and Michel in 1980 [32-34] have been found to exhibit excellent donor properties in terms of their ease of synthesis, their reactivity, as well as their general applicability to the synthesis of a wide variety of glycoconjugates and oligosaccharides, where high yields and excellent anomeric selectivity are usually observed.[4]

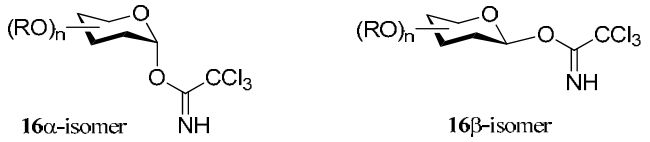
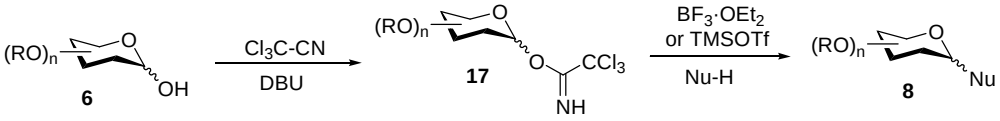


Figure 1.1. α and β-*O*-Glycosyl Trichloroacetimidates

.

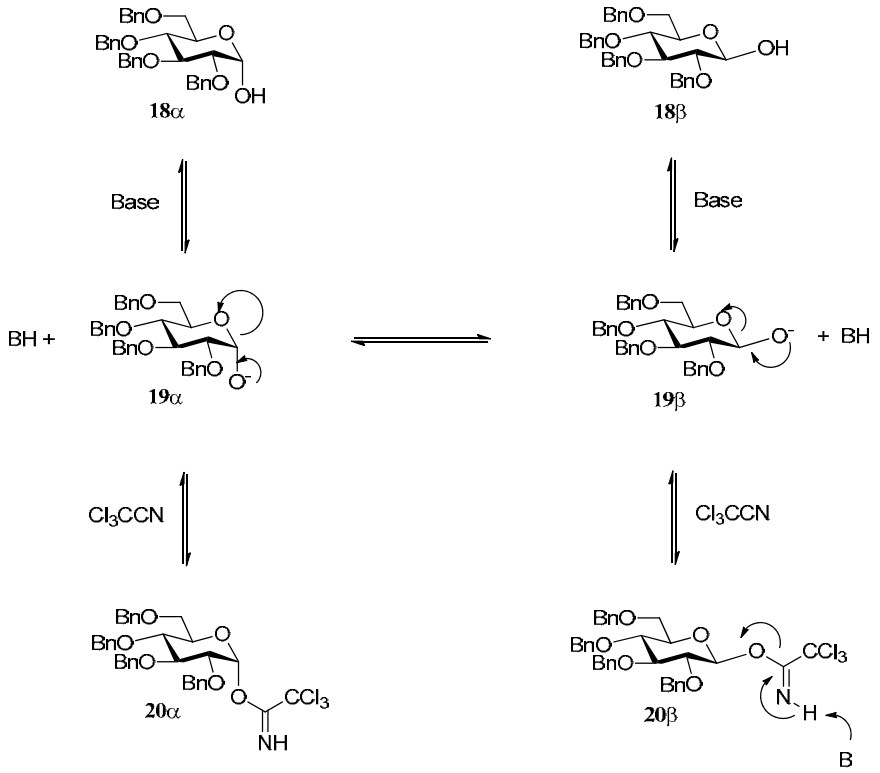
O-glycosyl trichloroacetimidates can be prepared readily by addition of hemiacetal **6** (Scheme 1.7) to trichloroacetonitrile, in the presence of either an inorganic or organic base catalyst (DBU, NaH, or K_2CO_3). Using one of these inorganic or organic bases, both the α- and β-anomers of the glycosyl trichloroacetimidate **17** can be isolated in pure form and in high yield through kinetic and thermodynamic control.[11] Both anomers are thermally stable and therefore easier to handle and store. Furthermore, the electron deficient trichloroacetonitrile is known to undergo direct and reversible base-

catalyzed addition to alcohols, resulting in the formation of *O*-alkyl trichloroacetimidates.[32,35] The synthesis of these glycosyl imidates are advantageous, in that they can be isolated as stable compounds which are less prone to hydrolysis than their corresponding salts.[11] The glycosylation reaction is generally promoted with a stoichiometric or catalytic amount of TMSOTf, TfOH or $BF_3{\cdot}OEt_2$.



Scheme 1.7. Glycosyl Trichloroacetimidate Method

A detailed report [32, 35-37] of the addition of trichloroacetonitrile to β-2,3,4,6-*tetra*-*O*-benzyl-D-glucose **18β** (Scheme 1.8) shows that β-glycosyl trichloroacetimidate **20β** is formed preferentially in a rapid and reversible addition. However, the product **20β** slowly undergoes isomerization under basic conditions, through anomerization of the β-alkoxide **19β** to the corresponding α-anomer **19α** (Scheme 1.8), followed by re-addition to trichloroacetonitrile to form the α-trichloroacetimidate 2**0α** as the major product by the thermodynamically operating anomeric effect.[11, 32]



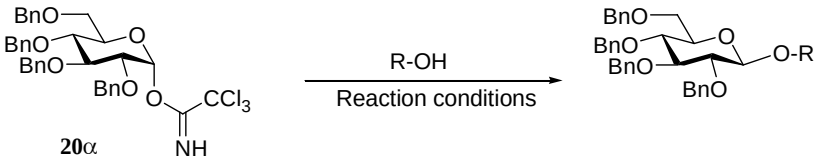
Scheme 1.8. Reversible Formation of Glycosyl Trichloroacetimidates

1.21: *O*-Glucopyranosyl Trichloroacetimidates as Glycosyl Donors

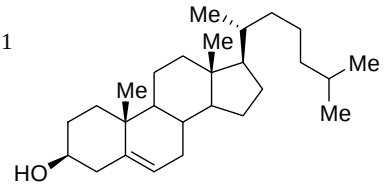
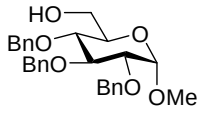
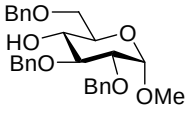
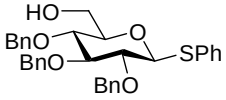
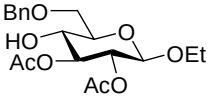
D-Glucose has been known to play an important role in the formation of plant polysaccharides (homoglycans) such as cellulose and starch.[38-39] Also, D-glucose is known to be a constituent in many bacterial, plant, and animal polysaccharides, and also as a repeating unit of heteroglycans in the form of α-and β-glycosidic linkages. It is also found as a constituent of many oligosaccharide moieties of glycosphingolipids and glycoproteins. In glycosphingolipids, D-glucose forms the core region where it is β-linked to a ceramide unit. In *N*-glycoproteins, α-linked D-glucose serves as a terminating signal in the biosynthesis of complex oligosaccharide chains.[11]

The synthesis and application of *O*-glucopyranosyl trichloroacetimidates are generally focused on *O*-benzyl and *O*-acetyl protected derivatives, because the benzyl and acetyl groups have been shown to be the most valuable protecting groups in glycoside synthesis.[32, 40-41] Under Schmidt's glycosylation conditions, *O*-glucopyranosyl trichloroacetimidates are often activated with a variety of Lewis acids.[32,35-36] For instance, boron triflouride etherate ($BF_3{\cdot}OEt_2$) in dichloromethane, or a mixture of dichloromethane and *n*-hexanes as solvent are usually employed. Alternatively, use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) with diethyl ether or acetonitrile as solvent, have also proved to be equally suitable in facile glycosidic bond formation.[40-42] Representative examples of the Schmidt glycosylation method are shown in Table 1.1, which show the coupling of a variety of primary and secondary hydroxyl groups of glycosyl acceptors with α-2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranosyl trichloroacetimidate donor **20α**.[11, 40-44] Overall, the desired glycoconjugates and disaccharides are obtained in moderate to good yields. The selectivity at the newly-formed glycosidic bonds heavily depends on the nature of the nucleophiles and the protecting groups on both coupling partners.

Table 1.1 Glycosylation Between Different Glycosyl Acceptors and *Tetra*-Benzylated-α-D-Glucopyranosyl Trichloroacetimidate Donor.



20α

Entry	Glycosyl Acceptor (R-OH)	Reaction conditions	Yield (%)	(α:β)
1		CH_2Cl_2, $BF_3{\cdot}OEt_2$, -18 °C, 2.5 h	78	1:13
2		CH_2Cl_2, $BF_3{\cdot}OEt_2$, -40 °C, 2 h	85	1:19
		CH_2CN, Me_3.SiOTf, -40 °C , 20 min	89	1:16
3		CH_2Cl_2, $BF_3{\cdot}OEt_2$, -30 °C, 2.5 h	81	1:4
		CH_2CH_2CN, Me_3.SiOTf, -80 °C, 10 min	81	1:19
4		CH_2Cl_2/n-hexane, $BF_3{\cdot}OEt_2$, -10 °C, 3 h	80	0:1
5		CH_2Cl_2, $BF_3{\cdot}OEt_2$, -70 °C, 2 h	46	1:2.5

Application of this glycosylation methodology in the synthesis of α-glycosides have not been extensively investigated, since they are found less frequently in glycoconjugates.[45] However, it has been reported that using β-glycosyl trichloroacetimidate 2**0β** (Scheme 1.8) as a glycosyl donor, in the presence of a stronger

catalyst system such as TMSOTf, the formation of thermodynamically more stable α-glycosides is favored, especially when diethylether is used as solvent.[45]

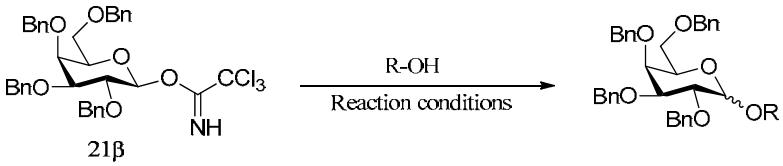
1.22: *O*-Galactopyranosyl Trichloroacetimidates as Glycosyl Donors

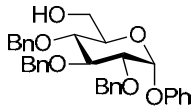
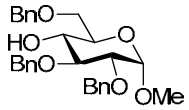
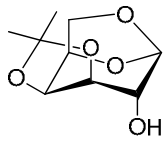
D-Galactose is one of the major constituents of complex sphingolipids and glycoproteins, where they are usually found as terminal or sub-terminal building blocks. [38-39] They form part of the lactosyl ceramide core structure in sphingolipids. In glycoproteins, terminal galactose serves as a signal for the Ashwell receptor, whose function includes the binding of galactosylated glycoproteins to the liver.[11]

C(1)-*O*-unprotected galactose derivatives are readily converted into the corresponding α- and β-galactosyl trichloroacetimidates upon treatment with trichloroacetonitrile and a catalytic amount of base (e.g. DBU). Representative galactosylations examples of a variety of glycosyl acceptors with 2,3,4,6-tetrabenzyl-*O*-galactosyl trichloroacetimidate donors **21β**-isomer (Table 1.2) and **21α**-isomer (Table 1.3), employing Schmidt's glycosylation protocol are as shown. [44, 46-48]

Galactosylations with **21β**-isomer (Table 1.2) and **21α**-isomer (Table 1.3) show that the desired galactosides are formed in good to excellent yields with inversion of the stereochemistry at the newly-formed glycosidic bond.[11] For example, when the galactosyl donor **21β** (Table 1.2) was coupled to various primary and secondary alcohols of glycosyl acceptors in diethyl ether as solvent, the corresponding α-galactosides (Table 1.2) were preferentially formed. The higher tendency of galactosyl donors to favor the α-glycosidic linkage, when compared to their glucosyl donor counterparts may be attributed to the C(4)- axial substituent, blocking the approach of the nucleophile from the top β-face.[5,11] As a result, the nuceophilic acceptors preferentially approach from the bottom face of the activated donors leading to the formation of α-galactoside products (Table 1.2).

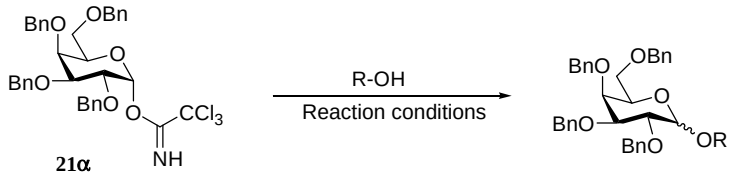
Table 1.2. Glycosylation with a β-Galactosyl Trichloroacetimidate.

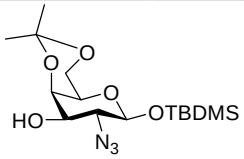
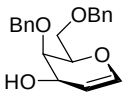
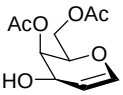
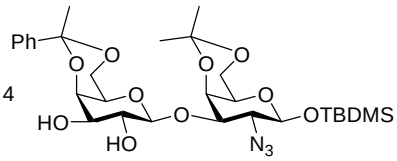


Entry	Glycosyl Acceptor (R-OH)	Reaction conditions	Yield (%)	(α:β)
1		$(C_2H_5)_2O$, TBDMSOTf, rt, 0.75 h	75	5:1
2		$(C_2H_5)_2O$, Me_3SiOTf, rt, 5 h	65	8:1
3		$(C_2H_5)_2O$, Me_3SiOTf, rt, 3.5h	77	8:1

By contrast, when coupling of primary and secondary hydroxyls of carbohydrate acceptors with galactosyl trichloroaceimidate donor **21α** (Table 1.3) was investigated in a mixture of dichloromethane and *n*-hexane as solvent, a reverse in anomeric selectivity was observed, now favoring the formation of β-galactosides.[5, 11]

Table 1.3. Glycosylation with an α-Galactosyl Trichloroacetimidate.



Entry	Glycosyl Acceptor	Reaction conditions	Yield (%)	(α:β)
1		CH_2Cl_2/n-hexane, $BF_3{\cdot}OEt_2$,	84	1:7
2		CH_2Cl_2,/*n*-hexanes Me_3SiOTf, -25 °C	80	1:4
		CH_2CH_2CN, Me_3.SiOTf, -40 °C	75	0:1
3		CH_2Cl_2/n-hexane, $BF_3{\cdot}OEt_2$, -25 °C	83	1:3
4		CH_2Cl_2,/*n*-hexanes Me_3SiOTf, -30 °C	49	1:0

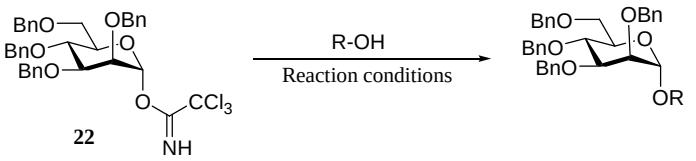
1.23: *O*-Mannopyranosyl Trichloroacetimidates as Donors

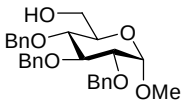
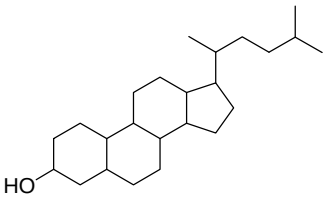
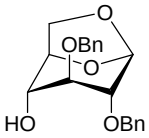
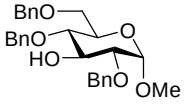
D-Mannose is less frequently encountered in glycosphingolipids, however, it is generally a constituent of *N*-glycoproteins, where it exist as a α-man-(1,6)-[α-man-(1,3)]-man trisacccharide that is β-(1,4)-linked to a chitobiose unit as part of the core structure.[38-39]

C(1)-*O*-mannose substrates are readily converted to the corresponding mannosyl trichloroacetimidate donors prior to their use in glycosylation reactions.[49-50] As a result of

the anomeric effect and the effect of C(2)-axial substituent, the α-mannosyl trichloroacetimidates (e.g. **22**, Table 1.4) are usually formed faster than those observed for the corresponding glucose and galactose derivatives.[32,37,51] When the α-mannosyl trichloroacetimidate donors incorporating C(2)-ether protecting groups (e.g. **22**) were used in the coupling process, a mixture of α-and β-mannopyranoside linkages was observed in the glycosylation to a variety of glycosyl acceptors using $BF_3{\cdot}OEt_2$ or TMSOTf as the promoter (Table 1.4).[42-43]

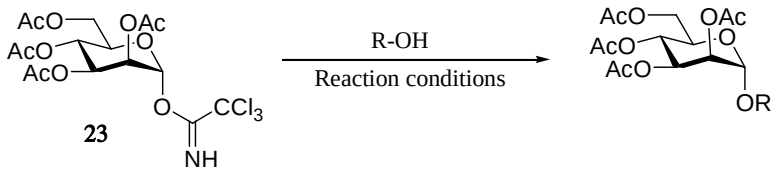
Table 1.4. Glycosylation with an α-Mannosyl Trichloroacetimidate.

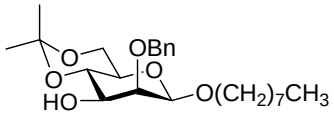
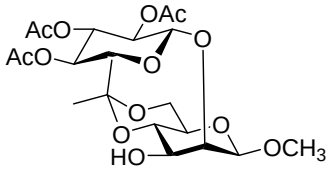
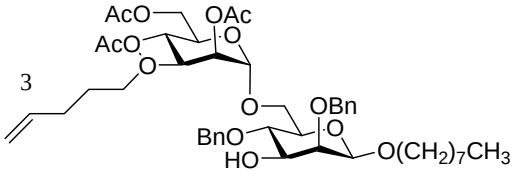
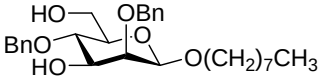


Entry	Glycosyl Acceptor (R-OH)	Reaction conditions	Yield (%)	(α:β)
1		CH_2Cl_2, $BF_3{\cdot}OEt_2$, 20 °C, 20 h	68	1: 0
		CH_2Cl_2/n-hexane, Me_3SiOTf, -80 °C, 20 min	70	3:2
2		CH_2Cl_2, $BF_3{\cdot}OEt_2$, -15 °C, 2 h	83	5:1
		CH_2Cl_2, $BF_3{\cdot}OEt_2$, 20 °C, 5.5h	73	1:0
3		CH_2Cl_2, $BF_3{\cdot}OEt_2$, 20 °C, 4 h	66	1: 0
4		CH_3CH_2CN, Me_3SiOTf, -80 °C, 10 min	71	2:1

In contrast, when the acetyl group is employed as the protecting group at the C(2)-position of α-mannosyl trichloroacetimidates donors (Table 1.5), exclusive α-products were often isolated in high yields. The preferential α-selectivity is presumably due to the C(2)-neighboring group participation (Table 1.5).[52-53]

Table 1.5. Glycosylation with a C(2) Acyl α-Mannosyl Trichloroacetimidate.



Entry	Glycosyl Acceptor (R-OH)	Reaction conditions	Yield (%)	(α:β)
1		CH_2Cl_2, Me_3SiOTf, rt, 10 min	87	1: 0
2		CH_2Cl_2, Me_3SiOTf, -30 °C, 10 min	92	1:0
3		CH_2Cl_2, Me_3SiOTf, -30 °C, 30 min	75	1: 0
4		CH_2Cl_2, Me_3SiOTf, -10 °C, 10 min	82	1:0 α-(1→ 6)

1.24: Other Types of Glycosyl Imidates

In 1984, Schmidt and co-workers reported a new class of glycosyl donors, namely trifluoroacetimidates.[49] Later, a series of *N*-substituted *O*-glycosyl trihaloacetimidates were also synthesized from their corresponding hemiacetals and *N*-substituted trihaloacetimidoyl chlorides.[4] Preliminary studies on these new types of glycosyl donors reveal that glycosylation reactions with *O*-glycosyl trifluoroacetimidates **24** (Figure 2) as donors are less efficient when compared to those of glycosyl trichloroacetimidates in terms of isolated yield of the desired products.[4] Several research groups such as Yu and Tao [54] and Iodonisi and co-workers, [55] have recently explored the use of glycosyl *N*-phenyl-trifluoroacetimidates **25** (Figure 2), and reported promising reactivity on some specific glycosylation reactions. Overall, trifluoroacetimidate donors have been reported to be less reactive than their corresponding trichloroacetamidate counterparts, presumably due to the lower basicity of the nitrogen atom. The presence of a substituent on the nitrogen atom, and the small conformational changes introduced by the trifluoromethyl group, could also influence the reactivity of *N*-phenyl trifluoroacetimidate substrates.[56] In recent years, glycosyl dichlorocyano-acetimidates **26** (Figure 2) have been reported as a new type of glycosyl donor. These glycosyl donors are described as having similar reactivities in glycosylation to those of trichloroacetimidate donors. [57]

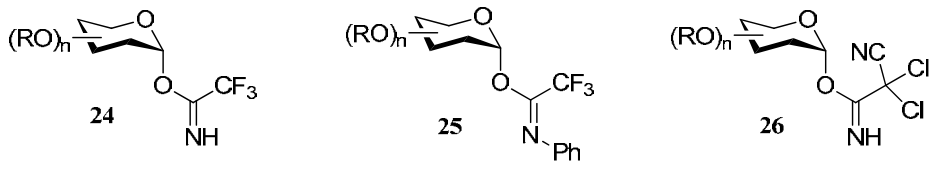
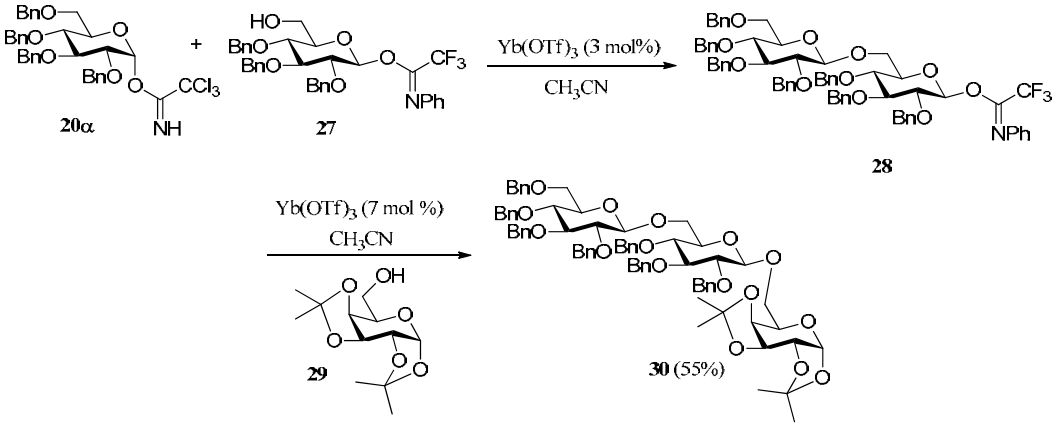


Figure 1.2. New Class of Glycosyl Imidate Donors.

In general, *N*-substituted variants of trifluoroacetimidate donors are more difficult to prepare than the trichloroacetimidates counterparts, as their corresponding reagent, trifluoroacetonitrile, is gaseous at room temperature and also toxic.[58] Of the various trifluoroacetimidates synthesized to date, *N*-phenyl trifluoroacetimidates have received the most attention and have become widely studied.[59] They are usually prepared from anomeric hemiacetals by treatment with *N*-phenyltrifluoroacetimidoyl chloride in the presence of a stoichiometric amount of base. Using potassium carbonate (K_2CO_3) as the base generally favors the formation of the α-anomer of *N*-phenyl trifluoroacetimidates.[59] Conversely, when sodium hydride (NaH) or diisopropylethyl amine (DIPEA) are used as the base, β-products are predominantly formed in the reaction.[59] There are several limitations to the preparation of glycosyl trifluoroacetimidates donors. First, an equimolar amount of salts are generated with the formation of the glycosyl donor.[4] Second, structural assignment of the various peaks by ^{1}H NMR spectroscopy are usually difficult due to the presence of invertomers and signal splitting of the neighboring carbon atoms by fluorine.[4]

In genreal, trimethylsilyl trifluoromethanesulfonate (TMSOTf) and boron trifluoride etherate ($BF_3{\cdot}OEt_2$) are among the most commonly used catalysts or promoters for glycosylation reactions with trihaloacetimidates.[4] However, in the past decade, several new catalysts for the activation of glycosyl trichloroacetimidates have been developed. These catalysts include samarium triflate ($Sm(OTf)_3$),[60] and ytterbium triflate ($Yb(OTf)_3$).[61] Catalytic amounts of $Sm(OTf)_3$ has been reported to be effective in the activation of electron donating glycosyl trichloroacetimidates under very mild conditions,[60] whereas electron withdrawing glycosyl trichloroacetimidates are activated by $Yb(OTf)_3$.[61] The trivalent lanthanide salts are generally stable; and as a result of their stability, they are easy to handle and store for long period.[4] In addition, the nature of the counteranion on the catalyst/promoter has a high impact on the stereoselectivity at the newly formed glycosidic bonds. The reason behind this observation has not yet been

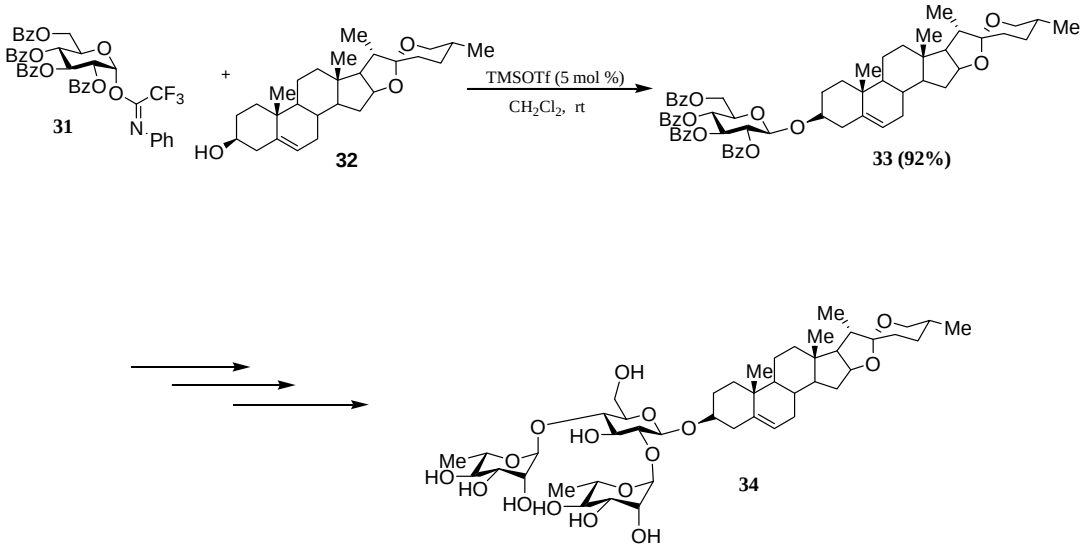
elucidated.[62] The activating reagents, including trimethylsilyl trifluoromethanesulfonate (TMSOTf),[63] boron trifluoride etherate ($BF_3{\cdot}OEt_2$),[64] tertbutyldimethylsilyl trifluoro-methanesulfonate (TBSOTf),[65] ytterbium triflate ($Yb(OTf)_3$),[66-67] and even acid washed molecular sieves,[68] that are often used to activate glycosyl trichloroacetimidates, can also be utilized in the coupling reactions involving *O*-glycosyl *N*-phenyl-trifluoroacetimidates. However, more forceful conditions are often required when trifluoroacetimidates are employed as glycosyl donors in the reaction.[4]



Scheme 1.9. One-Pot Synthesis of Trisaccharide.

The differences in reactivity patterns between glycosyl trichloroacetimidates and glycosyl *N*-phenyltrifluoroacetimidates have been exploited in the synthesis of trisaccharide **30** (Scheme 1.9) using a one-pot multistep protocol, which features the selective activation of α-glycosyl trichloroacetimidate donor **20α** with 3 mol % of ytterbium triflate ($Yb(OTf)_3$), in the presence of the *N*-phenyl-trifluoroacetimidate moiety found within nucleophilic acceptor **27** (Scheme 1.9).[69] Without further purification, the desired disaccharide **28** obtained is subsequently coupled to the primary alcohol of galactosyl acceptor **29** to provide the corresponding trisaccharide **30** in 55% yield (Scheme 1.9).

During the course of the coupling process using trichloroacetimidates as the glycosyl donors, *N*-glycosyl trichloroacetimidate by-products are occasionally formed, as a result of trichloroacetamide liberated in situ from the donor. This side reaction is further pronounced when the glycosyl acceptor is of low nucleophilicity or sterically hindered. These by-products are diminished in *N*-phenyl-trifluoroacetimidates coupling reactions, due to the increased steric hindrance at the *N*-phenyl functionality of the *in situ* liberated *N*-phenyl-trifluoroacetamide.[4] As a result of the lesser tendency of glycosyl *N*-phenyl-trifluoroacetimidate donors to undergo side reactions during glycosylation reactions, this donor has been utilized in the synthesis of a number of oligosaccharides and glycoconjugates.[74-78]



Scheme 1.10. Glycosylation of Diosgenin.

The feasibility of *N*-phenyl-trifluoroacetimidate has been recently employed as an efficient donor in the total synthesis of dioscin **34** (Scheme 1.10). Glycosylation of diosgenin **32** with *N*-phenyl-trifluoroacetimidate glycosyl donor **31** under Lewis acid conditions provided the intermediate glycoconjugate **33** of dioscin in good yield. In this

instance, the use of *N*-phenyl-trifluoroacetimidate donor **31** eliminated the possibility of *N*-glycosyl trichloroacetamide by-products occurring if the corresponding glycosyl trichloroacetimidate donor was employed in the glycosylation. Dioscin **34** (Scheme 1.10) is a trisaccharide steroidal saponin isolated from a number of oriental vegetables, and has been known to demonstrate moderate to good antitumor, antifungal, antiinflamatory as well as immunostimulant activity in humans.[59,70-73]

In spite of the usefulness and popularity of Schmidt's glycosylation protocol, it has several limitations. First, Lewis acids, such as TMSOTf, $BF_3{\cdot}OEt_2$, and TBSOTf, have a high affinity for oxygen. As a result of this oxophilicity, higher catalyst loading usually in stoichiometric quantities, are often required. Second, these Lewis acids are extremely moisture sensitive, and as such, glycosylation reactions have to be carried out under strictly anhydrous conditions, and in most cases, significant cooling conditions (down to -78 °C) are also required, especially when the glycosyl donors and acceptors are incorporated with acid-labile protecting groups.[79] The air and moisture sensitivity of these Lewis acid catalysts makes them very difficult to handle and special precautions are thereby necessary for proper handling and storage. A further drawback is caused by problems associated with chemical compatibility, which are often observed when glycosylations are conducted in the presence of acid labile functional groups.

These limitations make the trichloroacetimidiate methodology inconvenient and cumbersome to use in some cases, which has resulted in the continued development of activating reagents and conditions for the activation of glycosyl trichloroacetimidates. Such improvements began with the use of a stoichiometric amount of silver triflate (AgOTf) to promote the formation of glycosides in good yields.[80] However, such an expensive and potentially toxic metal salt makes this method unattractive. Two other improvements using lithium perchlorate ($LiClO_4$) and lithium triflate (LiOTf) as promoters have also been reported. While the first method requires a large excess of $LiClO_4$ for the glycosylation reaction to proceed,[81] the second method employs a catalytic

amount of LiOTf to provide the desired glycosides, but as a mixture of α- and β-isomers.[82]

These various drawbacks have necessitated the need for the development of a practical and general trichloroacetimidate glycosylation procedure. Recently, our group [79] reported an efficient protocol for the stereoselective formation of glycosides in high yields, and with excellent levels of selectivity at the newly formed glycosidic bonds using air- and moisture-stable and readily available cationic palladium catalyst, $Pd(CH_3CN)_4(BF_3)_2$. The excellent results obtained with this palladium catalyst have prompted an in-depth study of the new glycosylation protocol to access a variety biologically relevant oligosaccharides and glycoconjugates in high yield and excellent stereoselectivity.

1.3. Conclusion

Athough there are a number of current glycosylation procedures, with Schmidt's trihaloacetimidate protocol in particular, that have been extensively applied in the preparation of biologically important oligosaccharides and glycoconjugates, each of these methods has its own advantages and disadvantages. In general, these methods require the use of stoichiometric amount of the activating reagents to activate glycosyl donors. In addition, the glycosylation reactions are often performed under anhydrous conditions. The stereoselectivity at the newly formed glycosidic bond depends solely on the nature of the protecting groups on both the glycosyl donor and acceptor, as well as the nature of the substrate. Thus, there is the need for the development of a general, practical, and stereoselective glycosylation protocol to access a variety of biologically important oligosaccharides and glycoconjugates.

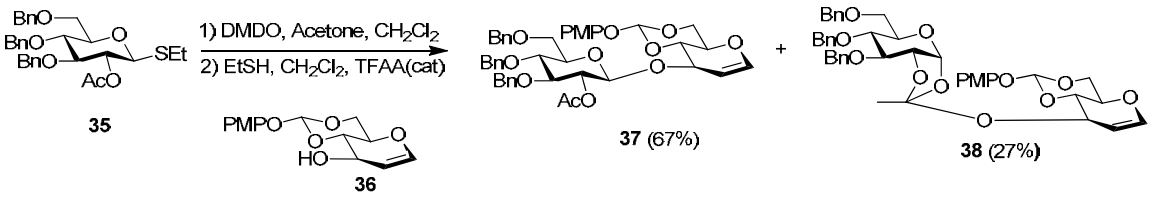
CHAPTER 2

PALLADIUM-CONTROLLED β-SELECTIVE GLYCOSYLATION IN THE ABSENCE OF THE C(2)-ESTER PARTICIPATORY GROUP

2.1: Background

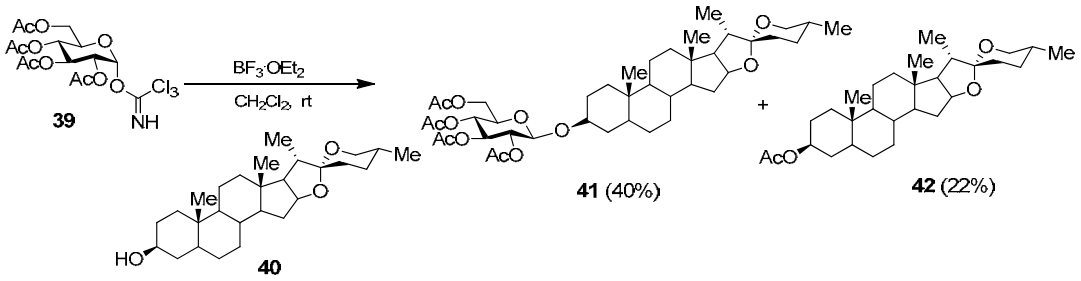
Many biologically active molecules contain sugar molecules with acetal or ketal linkages. Joining two sugar moieties together with diastereomeric selectivity has become an active area of research in recent years. These linkages are commonly formed by glycosylation reactions between an activated electrophilic donor and a nucleophilic acceptor. The necessity to employ reactive glycosyl donors makes these reactions prone to side reactions. Minimizing these side reactions and achieving stereocontrol synthesis of glycosidic linakges are the two main objectives when designing new glycosylation methods in the synthesis of biologically important oligosaccharides and glycoconjugates.

The most common approach in the stereoselective glycosylation reactions is to use neighboring group participation, typically of an ester at the C(2)-position of glycosyl donors to afford β-glycosides, with excellent selectivity.[34, 83-84.] However, as reported by Fraser-Reid and co-workers, the reactivity of many glycosyl donors with a C(2)-ester functionality are significantly decreased within many glycosylation protocols.[85-86] As a result, prolonged reaction times are often required in order to achieve efficient coupling.[87] In addition, yields by this approach are often lower due to the competitive formation of ortho esters as by-products during glycosylation reactions.[88-91] For example, Danishefsky and co-workers reported the coupling of a C(2)-acetyl protected thioglycoside **35** with a glucal nucleophillic acceptor **36** to afford the desired β-linked disaccharide **37** in 67% yield along with competitive formation of an ortho ester **38** in 27% yield as a side product (Scheme 2.1).[90]



Scheme 2.1. Glycosylation with Competitive Formation of an Ortho Ester.

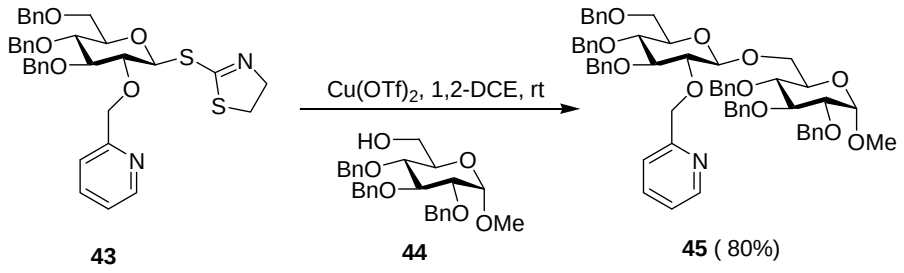
Another side reaction observed with this glycosylation method is that the C(2)-acyl functionality can migrate to both the C(1)-position of the glycosyl donors as well as the reactive sites of the nucleophilic acceptors. This has also been observed under basic conditions, and with many different glycosyl donors under different glycosylation reaction conditions.[92] For instance, Urban and co-workers reported the glycosylation reaction involving 2,3,4,6-*tetra*-*O*-acetyl trichloroacetimidate **39** (Scheme 2.2) as the gylcosyl donor and tigogenin **40** as the nucleophillic acceptor under Lewis acid conditions, to afford the desired glycoconjugate **41** in 40% yield with competitive formation of the acyl transfer product tigogenyl acetate **42** as the major side product (Scheme 2.2).[93]



Scheme 2.2. Glycosylation with C(2)-Acyl Transfer.

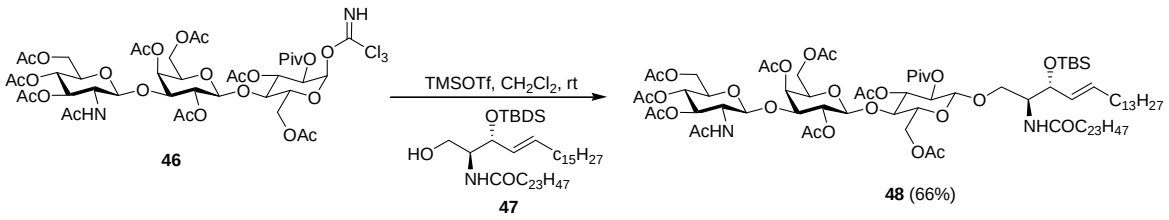
To circumvent this problem, Demchenko and co-workers recently reported the stereoselective synthesis of β-glycosides using copper triflate as a promoter and utilizing

a C(2)-picolyl moiety as a novel neighboring participatory group in the S-thiazolinyl (STaz) glycosyl donor **43**, to afford the glycoconjugate **45** in good yield when the primary alcohol **44** is used as an acceptor (Scheme 2.3).[94]



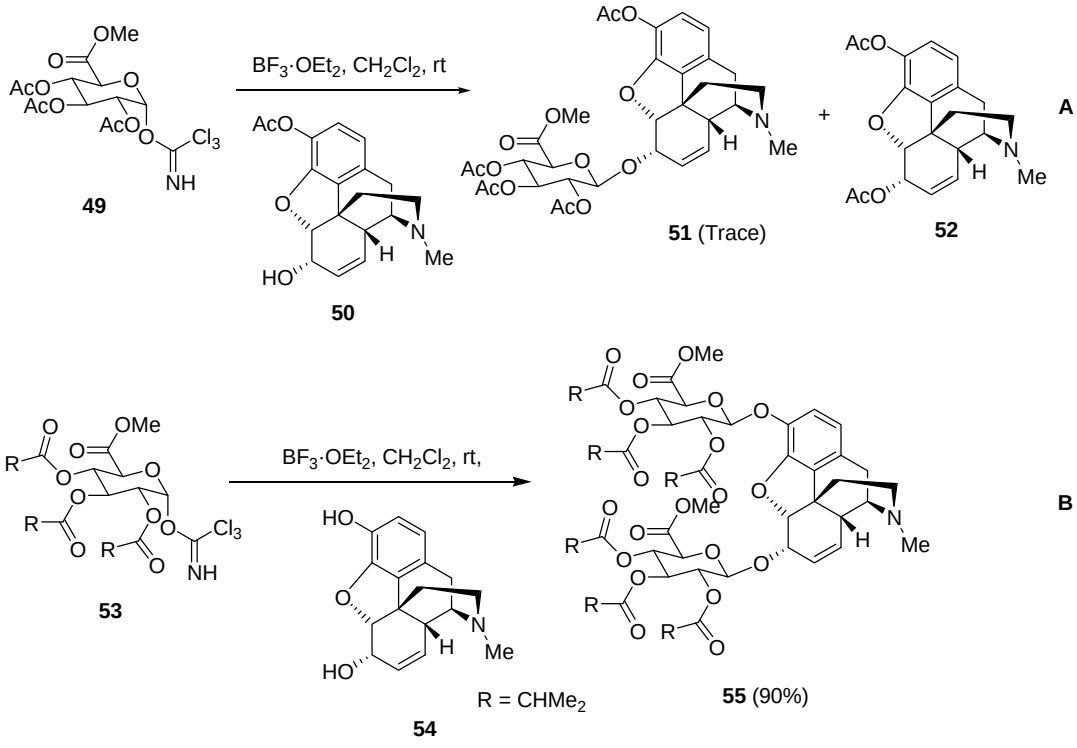
Scheme 2.3. Glycosylation with C(2)-Picolyl Substituent.

Increasing the steric bulk at the C(2)-position on the glycosyl donor has also been known to minimize acyl transfer. For instance, in the total synthesis of sphingolipids, Ogawa and co-workers demonstrated the TMSOTf promoted coupling of ceramide derivative **47** (Scheme 2.4) with the C(2)-pivaloyl protected trisaccharide glycosyl donor **46** to afford the glycoconjugate intermediate **48** in good yields with good β-selectivity. No side product due to acyl transfer was observed (Scheme 2.4).[89] In addition, the use of pivaloyl group at the C(2)-position of the glycosyl donor **46** instead of the acetyl group suppresses the formation of an ortho ester due to the presence of a bulky t-butyl group next to the electrophilic carbon atom, and thereby enhancing the coupling efficiency.[89]



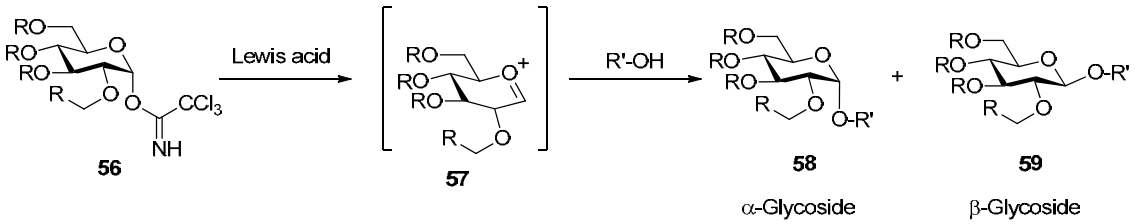
Scheme 2.4. Glycosylation with C(2)-Pivaloyl Trisaccharide Donor.

Brown and co-workers also demonstrated the utility of an isobutyryl group at the C(2)-position of glucuronyl donors to minimize acyl transfer during glycosylation, in the synthesis of morphine-3,6-*di*-β-D-glucuronide, a metabolite of morphine with potent analgesic properties (Scheme 2.5).[97] When Lewis acid catalyzed-coupling of the 3-acetylmorphine acceptor **50** with the glycosyl donor **49** was attempted, the glycosylation reaction resulted in the acetylated 3,6-diacetylmorphine **52** as the major product with a trace amount of the desired glycoconjugate **51** (Scheme 2.5A). On the other hand, the glycosylation reaction proceeded smoothly when the acetyl groups were replaced by isobutyryl groups. Thus, upon coupling of morphine **54** as the acceptor with the tri-isobutyrate glycosyl donor **53**, the desired glycoconjugate **55** was isolated in good yield with a complete stereoselection for the β-isomers (Scheme 2.5B).[97]



Scheme 2.5. Glycosylation with C(2)-Isobutyryl Protected Glycosyl Donor.

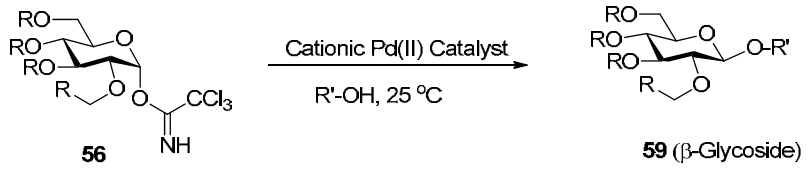
Crich and co-workers have also demonstrated the use of a 3,4-*O*-bisacetal as well as a *trans*-2,3-*O*-group system to direct the formation of β-glycosides.[95-96] On the other hand, ether protecting groups at the C(2)-position of glycosyl donors (e.g **56**, Scheme 2.6) have also been explored in many glycosylation protocols, due to their tendency to enhance reactivity of glycosyl donors. However, because C(2)-ether protected glycosyl donors appears to go through an oxocarbenium ion intermediate **57** (Scheme 2.6), under Lewis acid conditions with **56** as the glycosyl donor, a mixture of α-glycosides **58** and β-glycosides **59** are often formed in the reaction (Scheme 2.6). There has been few reports on the use of nitrile solvent to improve β- selectivity when a glycosyl donor bearing a non-participatory group at the C(2)-position is used in the glycosylation reaction.[98-100]



Scheme 2.6. Lewis Acid Catalyzed Glycosylation Reaction.

In view of these current methods to direct β-selectivity, we propose to investigate the ability of a cationic Pd(II) catalyst to direct β-glycosylation (Scheme 2.7) in the absence of the traditional C(2)-ester neighboring group effects. We hypothesize that the nature of the cationic palladium complex can control the β-selectivity at the newly-formed glycosidic bond. Furthermore, the proposed approach will eliminate the side reactions that are often observed under traditional C(2)-neighboring group conditions. Additionally, the proposed palladium protocol should be milder than the existing Lewis acid conditions.[101] Another advantage of employing the Pd(II) catalyst as the activating reagent is that it does not require strictly anhydrous conditions for the coupling to

proceed. As a result, azeotropic removal of moisture from both glycosyl donors and acceptors using toluene is not required prior to the glycosylation reaction.

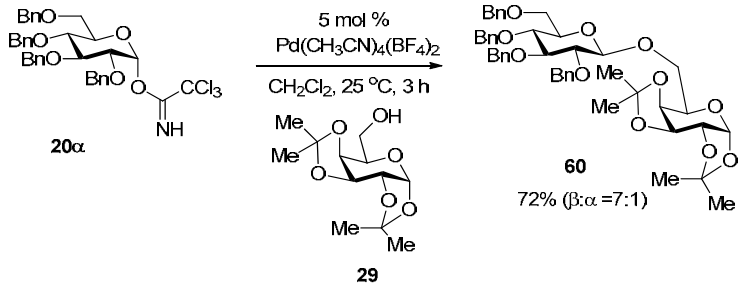


Scheme 2.7. Cationic Palladium(II) Catalyzed Glycosylation.

2.2: Results and Discussion

In order to achieve efficient glycosylation, the cationic Pd(II) catalyst must meet the following criteria: 1) it must act as a Lewis acid to coordinate the C(1)-imidate nitrogen, 2) it must be more nitrophilic than traditional Lewis acid so that it can selectively coordinate to a nitrogen atom over oxygen atoms within glycosyl donors, resulting in higher turnover of the catalyst, and the nature of the ligand on Pd(II) species can influence the selectivity.

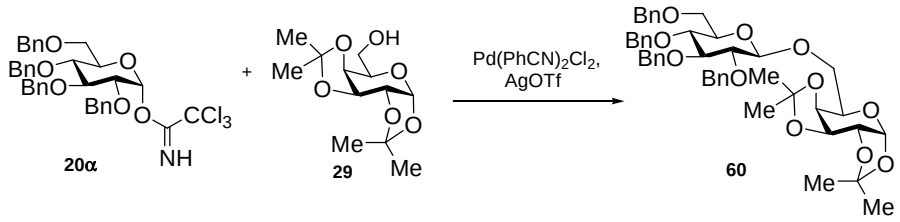
We initially investigated the feasibility of commercially available cationic Pd(II) species, $Pd(CH_3CN)_4(BF_4)_2$, as the efficient activating reagent in the glycosyaltion of 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranosyl acceptor **29** (Scheme 2.8)[79] with 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranosyl trichloroacetimidate **20α** as a glycosyl donor.[37,102-105] Accordingly, treatment of both coupling partners **20α** and **29** (Scheme 2.8) with 5 mol % of $Pd(CH_3CN)_4(BF_4)_2$ in CH_2Cl_2 at 25 ^oC for 3 h, provided the desired disaccharide **60** in 72% yield with good β-selectivity (β:α = 7:1). This result was encouraging because it clearly showed that the cationic Pd(II) catalyst could direct β- glycosylation with the C(2)-benzyl protected donor to provide the desired glycoside with good stereoselectivity.



Scheme 2.8. β-Glycosylation with a C(2)-Non-Participatory Group.

Although the above conditions provided the corresponding disaccharide **60** (Scheme 2.8) in good yield with a good β-selectivity, the commercially available cationic Pd(II) species, $Pd(CH_3CN)_4(BF_4)_2$, is expensive, and at least 5 mol % of the catalyst is required for the reaction to go to completion. In addition, longer reactions times were observed when sterically hindered glycosyl acceptors were used.[101] These limitations prompted us to develop a new cationic Pd(II) catalyst system which utilizes a relatively more reactive palladium catalyst for the stereoselective glycosylation reactions.[106-107] In developing the new catalyst system, we hypothesize that the nature of counterions on cationic Pd(II) complexes could play an important role to effect the reactivity of the catalyst and the stereoselectivity at the newly-formed glycosidic bond. This is because it is widely known that a weakly coordinating counterion to the cationic palladium complex can increase its catalytic activity.[108-109] With this hypothesis in mind, we investigated the use of cationic Pd(II) species, $Pd(PhCN)_2(OTf)_2$ (Table 2.1), which can be generated *in situ* from the readily available neutral Pd(II) species, $Pd(PhCN)_2Cl_2$, and silver triflate (AgOTf). In our preliminary studies, triflate counterion was chosen because it is easier to handle AgOTf than other silver salts.

Table 2.1. $Pd(PhCN)_2(OTf)_2$-Controlled β-Selective Glycosylation.[a]



Entry	Palladium	AgOTf	Additive	Temp	Time	Yield[b]	β:α[c]
1	2 mol %	4 mol%	none	25 °C	15 min	98%	1:1
2	1 mol %	2 mol%	none	25 °C	15 min	96%	1:1
3	1 mol %	2 mol%	none	0 °C	30 min	83%	1:1
4	1 mol %	2 mol%	none	-78 °C	1 h	87%	10:1
5	1 mol %	2 mol%	DTBP	-78 °C	1 h	85%	10:1
6	1 mol %	none	none	-78 °C	8 h	<1 %	
7	none	2 mol%	none	-78 °C	5 h	<1%	

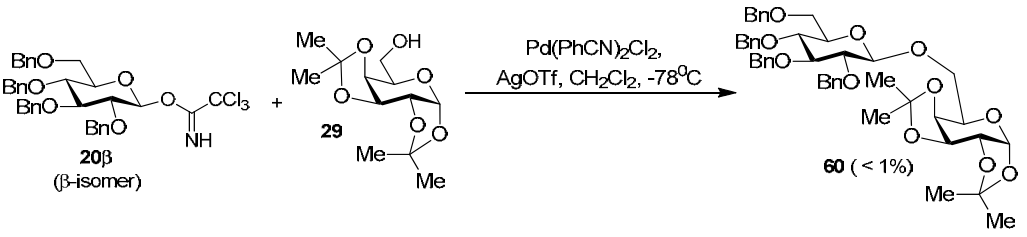
[a] All reactions were carried out in CH_2Cl_2 (0.15 M) with AgOTf and $Pd(PhCN)_2Cl_2$.
[b] Isolated yield. [c] ^1H NMR ratio.

As shown in Table 2.1, coupling of nucleophilic acceptor **29** with the glycosyl trichloroacetimidate donor **20α** in the presence of a preformed solution of 2 mol % $Pd(PhCN)_2(OTf)_2$ formed from 2 mol % $Pd(PhCN)_2Cl_2$ and 4 mol % AgOTf at 25 °C provided the desired disaccharide **60** in 98% yield as a 1:1 mixture of α- and β- isomers (entry 1). Decreasing the catalyst loading to 1 mol % still maintained the yield of **60**, however, the desired product **60** was still isolated as a mixture of α- and β- isomers (entry 2). Lowering the reaction temperature to 0 °C did not have any effect on the stereochemical outcome of the reaction (entry 3). Since the glycosylation reaction was very rapid and completed within 30 min at both 0 °C and 25 °C, the reaction temperature was further lowered to –78 °C (entry 4). This cold temperature reaction significantly increased the β-selectivity, providing the disaccharide **60** in 87% yield with an excellent

β-selectivity (β:α = 10:1) (entry 4). The increase in β-selectivity from 1:1 to 10:1 observed upon cooling the reaction mixture from 0°C to -78°C suggests different mechanisms at each temperature for the glycosylation process. At 0 °C, the reaction appears to go through an oxocarbenium ion intermediate, resulting in a mixture of α- and β-isomers of **60**. In contrast, the reaction is likely to go through an S_N2-like displacement at – 78 °C, where glycosyl acceptor **29** preferentially approaches the β-face of the activated trichloroacetimidate **20α**, leading to the formation of β-glycoside **60**.

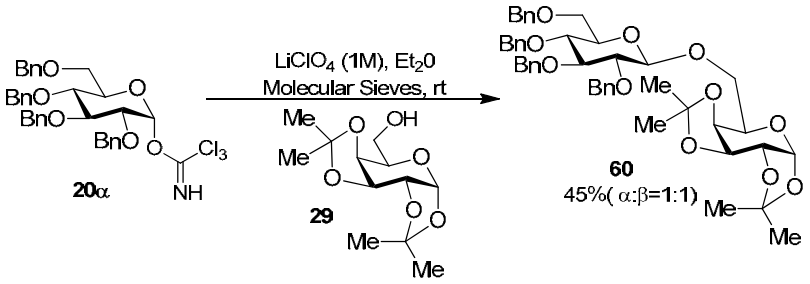
To determine if the source of catalysis originated from triflic acid, which may be generated *in situ* during the formation of $Pd(PhCN)_2(OTf)_2$ from the reaction of $Pd(PhCN)_2Cl_2$ and AgOTf, a control glycosylation was conducted in the presence of 2,6-*di-tert*-butylpyridine (DTBP) (10 mol %) as an acid scavenger (entry 5). In this experiment, disaccharide **60** was isolated in comparable yield and selectivity to that of the coupling reaction without an acid scavenger. A similar glycosylation reaction was attempted with neutral Pd(II) species, $Pd(PhCN)_2Cl_2$ (entry 6). In this case, less than 1% of the desired disaccharide **60** was isolated in the reaction. Since a stoichiometric amount of AgOTf has also been reported to activate trichloroacetimidate donors as demonstrated by Krepinsky and co-workers,[80] a control glycosylation reaction was performed to determine if trichloroacetimidate **20α** was indeed activated by 2 mol % AgOTf at –78 °C (entry 7). In this experiemnt, less than 1% yield of disaccharide **60** was detected. The above results suggest that the source of catalysis was not due to the presence of a triflic acid, neutral palladium or catalytic quantities of silver triflate, but that of the cationic palladium (II) species, $Pd(PhCN)_2(OTf)_2$

The efficacy of this cationic palladium protocol was further investigated to determine whether $Pd(PhCN)_2(OTf)_2$ could activate the β-trichloroacetimidate isomer 20β (Scheme 29). In this instance, less than 1 % of the desired disaccharide **60** was observed in the glycosylation reaction at -78 °C. This may suggest that the α-orientation of the trichloroacetimidate is necessary for the glycosylation to occur.



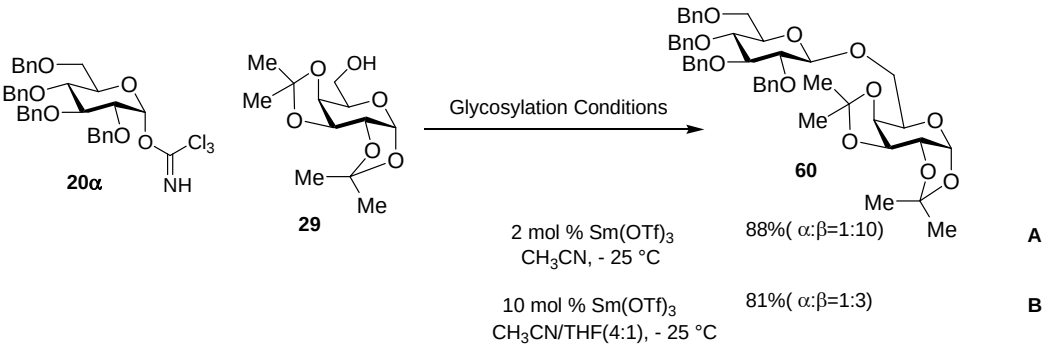
Scheme 2.9. Glycosylation with a β-Glycosyl Donor.

Overall, $Pd(PhCN)_2(OTf)_2$ acts as the efficient catalyst to promote the coupling reaction providing the desired disaccharide **60** in higher yield and β-selectivity than that of $Pd(CH_3CN)_4(BF_4)_2$. In addition, the glycosylation process requires only 1 mol % of $Pd(PhCN)_2(OTf)_2$ compared to the 5 mol % required when $Pd(CH_3CN)_4(BF_4)_2$ was used. In comparison to other glycosylation protocols utilizing trichloroacetimidate **20α** as the glycosyl donor, higher β-selectivity with lower catalyst loadings were observed when $Pd(PhCN)_2(OTf)_2$ was used as the activator. For example, Waldmann and co-workers reported the $LiClO_4$ promoted glycosylation using the glycosyl donor **20α** and the galactose acceptor **29** to afford the corresponding disaccharide **60** in 45% yield, and as a 1:1 mixture of α- and β-isomers (Scheme 2.10).[81]



Scheme 2.10. $LiClO_4$ Promoted Glycosylation.

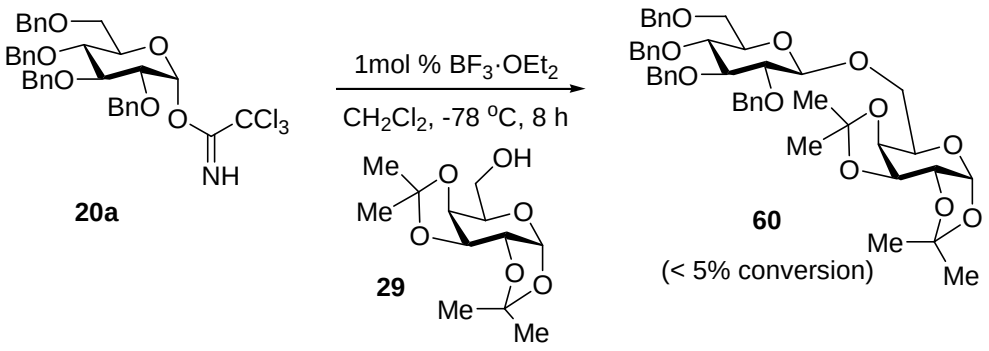
In another example, when LiOTf was used as the promoter in the reaction, disaccharide **60** was isolated in 77% yield and as a 1:1 mixture of α- and β-isomers.[82] When a moisture-stable activating reagent such as $Yb(OTf)_3$ was employed in the glycosylation reaction, disaccharide **60** was isolated in 90% as a 2:1 mixture of α- and β-isomers.[69] With the use of traditional Lewis acid TMSOTf as an activator, disaccharide **60** was obtained in 71% yield and as a 4:1 mixture of α- and β-isomers.[110] Recently, Iadonisi and co-workers[60] reported the use of $Sm(OTf)_3$ (Scheme 2.11) to activate glycosyl trichloroacetimidate **20α**. Although the yield and anomeric selectivity of the desired disaccharide **60** under the $Sm(OTf)_3$ conditions were comparable to those of $Pd(PhCN)_2(OTf)_2$, the glycosylation was performed with relatively higher catalyst loading (10 mol %) and temperature (- 25 ^oC) (Scheme 2.11A). Additionally, acetonitrile was used as the solvent to influence β-selectivity. When THF or a mixture of THF and CH_3CN (1:4) were used as the solvent in the glycosylation reaction, disaccharide **60** was isolated as a 1:3 mixture of α- and β-isomers (Scheme 2.11B).[60]



Scheme 2.11. $Sm(OTf)_3$ Promoted Glycosylation.

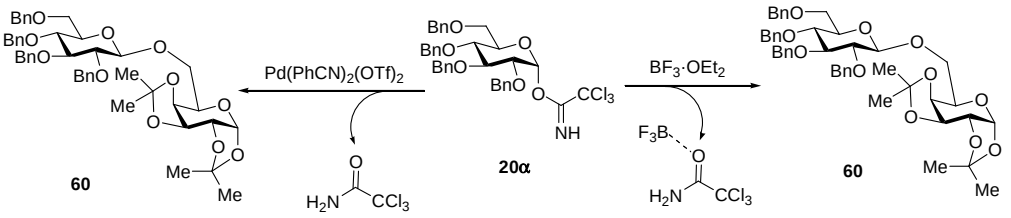
Beause the glycosyl trichloroacetimidate donors are often activated with strong and moisture sensitive Lewis acids such as $BF_3{\cdot}OEt_2$,[64,111-112] TMSOTf,[42,44,63,113-114]

TBSOTf,[65,115] Tf_2O,[116] and $ZnBr_2$,[93] glycosylation of galactosyl nucleophile **29** with trichloroacetimidate **20α** was performed with 1 mol % of $BF_3{\cdot}OEt_2$ at – 78 ^oC in order to compare the reactivity and selectivity of $BF_3{\cdot}OEt_2$ to that of cationic Pd(II) species, $Pd(PhCN)_2(OTf)_2$ (Scheme 2.12). $BF_3{\cdot}OEt_2$ was chosen because it is among the most widely used of the Lewis acids.[117-119] In this reaction, less than 5% conversion was observed even after the reaction had been stirring for 8 hours.



Scheme 2.12. $BF_3{\cdot}OEt_2$ Induced Glycosylation.

The outcome of the Lewis-acid experiment (Scheme 2.12) suggests that there is no turnover when $BF_3{\cdot}OEt_2$ was used as the catalyst in the glycosylation reaction. We hypothesize that trichloroacetamide is generated as the by-product (Scheme 2.13) as the reaction is proceeding. As a result of the oxophilicity of $BF_3{\cdot}OEt_2$, it preferentially coordinates to the carbonyl oxygen of trichloroacetamide. This by-product inhibition prevents $BF_3{\cdot}OEt_2$ from turnover. On the other hand, trichloroacetamide may not be a good ligand for $Pd(PhCN)_2(OTf)_2$. As a result, the cationic palladium(II) species can be subsequently regenerated to continue the reaction, ultimately leading to the formation of the desired disaccharide **60** (Scheme 2.13) in high yield.



Scheme 2.13. Cationic Palladium and $BF_3 \cdot OEt_2$ Catalyzed Glycosylation.

To assess the scope and efficacy of this new β-glycosylation protocol in the absence of the traditional C(2)-ester participatory group on the glycosyl donor, a number of primary, secondary and tertiary acceptors **61-65** (Figure 2.1) were investigated with perbenzylated trichloroacetimidate donor **20α**.

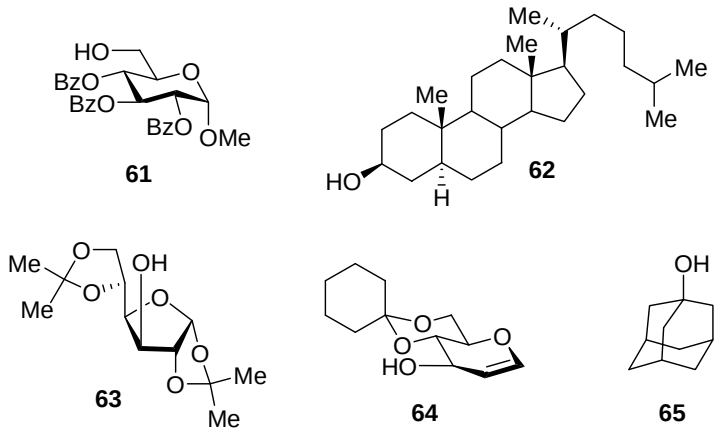
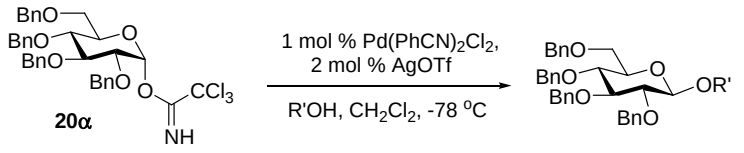


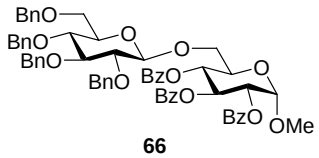
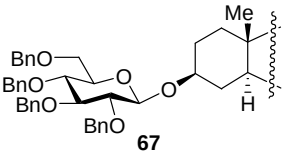
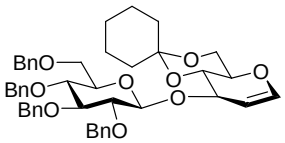
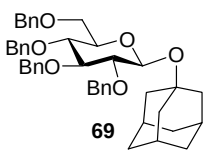
Figure 2.1. Various Nucleophilic Acceptors.

Under standard cationic palladium(II) conditions, the desired disaccharides **66-69** were isolated in good yields and with excellent β-selectivity (Table 2.2). When dihydrocholesterol **62** was used as a nucleophilic acceptor, the glycosylation reaction was performed at - 45^{o}C as the reaction mixture solidified at - 78 ^{o}C (entry 2). With the exception of the dihydrocholesterol **62**, most of these glycosyl acceptors have not been

investigated with the glycosyl donor **20α** under traditional Lewis acid conditions. When dihydrocholesterol **62** was used as a nucleophilic acceptor under cationic palladium(II) conditions, the resulting glycoconjugate **67** (entry 2) was isolated in 85% yield and with excellent β-selectivity (α:β = 1:15). In comparison, the disaccharide **67** was isolated in relatively lower yield and β-selectivity under $BF_3{\cdot}OEt_2$ conditions, [40-41] which also requires higher catalyst loadings and higher temperatures (-40 °C to 25 °C) in comparison to our new glycosylation protocol.

Table 2.2: β-Selective Glycosylation with a C(2)-Benzyl Glucose Donor.[a]

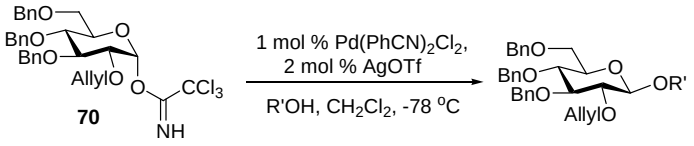


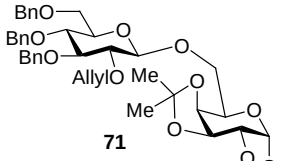
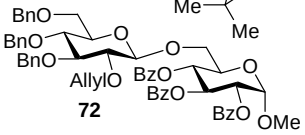
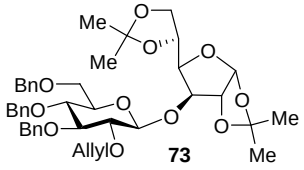
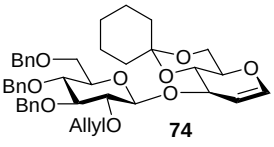
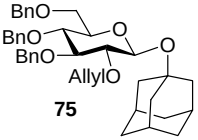
Entry	R'OH	Disaccharides	Yield[b]	β:α[c]
1	**61**	 **66**	83%	β only
2	**62**	 **67**	85%	15:1
3	**64**	 **68**	77%	β only
4	**65**	 **69**	80%	β only

[a] All reactions were performed in CH_2Cl_2 (0.15 M) with 1 mol % $Pd(PhCN)_2Cl_2$ and 2 mol % AgOTf for 1-3 h. [b] Isolated yield [c] ^1H NMR ratio.

Next, we determined the efficacy of this new palladium protocol with C(2)-allyl glycosyl donor **70** (Table 2.3). When galactoside **29** was employed as a glycosyl acceptor, the resulting disaccharide **71** (entry 1) was isolated in 99% yield and with an excellent β-selectivity (13:1). The glycosylation reaction also proceeded smoothly even when sterically hindered nucleophiles **63**, **64** and **65** were employed, affording the respective products **73**, **74** and **75** with moderate to excellent β-selectivity.

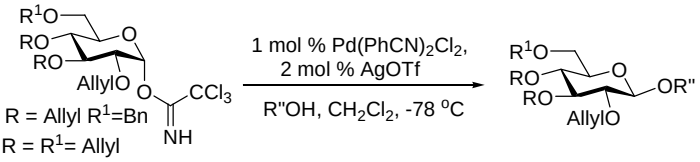
Table 2.3 β-Selective Glycosylation with a C(2)-Allyl Glucose Donor.[a]



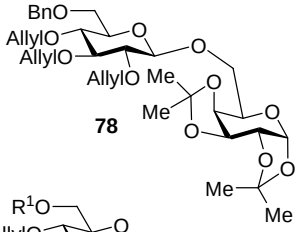
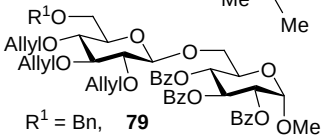
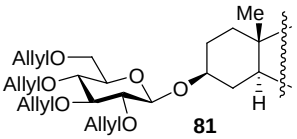
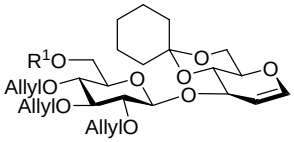
Entry	R'OH	Disaccharides	Yield[b]	β:α[c]
1	**29**	 **71**	99%	13:1
2	**61**	 **72**	73%	β only
3	**63**	 **73**	80%	6:1
4	**64**	 **74**	82%	β only
5	**65**	 **75**	84%	15:1

[a] All reactions were performed in CH_2Cl_2 (0.15 M) with 1 mol % $Pd(PhCN)_2Cl_2$ and 2 mol % AgOTf. [b] Isolated yield. [c] ^1H NMR ratio.

Table 2.4. β-Selective Glycosylation with Allyl Glucose Donors.[a]



76 R = Allyl R^1=Bn
77 R = R^1= Allyl

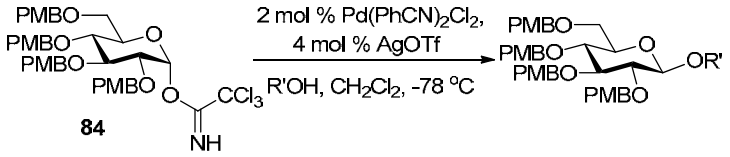
Entry	R'OH	Disaccharides	Yield[b]	β:α[c]
1	**29**	 **78**	97%	13:1
2	**61**	 R^1 = Bn, **79** R^1 = Allyl, **80**	**(79)** 74% **(80)** 72%	13:1 11:1
3	**62**	 **81**	81%	10:1
4	**64**	 R^1 = Bn, **82** R^1 = Allyl, **83**	**(82)** 62% **(83)** 67%	β only 15:1

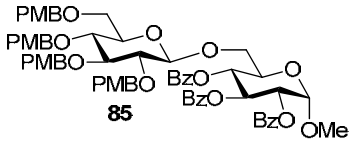
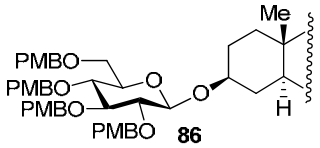
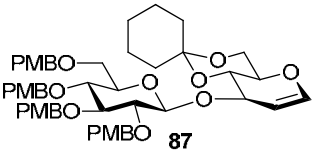
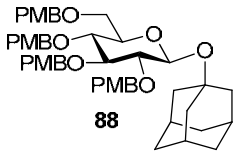
[a] All reactions were performed in CH_2Cl_2 (0.15 M) with 1 mol % $Pd(PhCN)_2Cl_2$ and 2 mol % AgOTf. [b] Isolated yield. [c] ^{1}H NMR ratio.

The excellent results obtained in Table 2.3 prompted us to test the efficacy of this glycosylation protocol with various C(2)-allyl protected glycosyl donors (Table 2.4). Upon coupling of the galactose nucleophile **29** with the glycosyl donor **76**, the disaccharide **78** was isolated in 97% yield and with α:β = 13:1 (entry 1). The glycosylation reaction proceeded smoothly even with hindered nucleophilic acceptors **62** and **64** when C(2)-allyl protected glycosyl donors **77** and **76** are employed. The desired disaccharides **81**, **82** and **83** (entries 3 and 4) were isolated in moderate to good yields

(62% → 81%) and with excellent β-selectivity (10:1 → β only). These results shown in Table 2.3 and 2.4 were encouraging because they suggest that cationic palladium catalyst selectively coordinated to the C(1)-imidate nitrogen in the presence of the allyl protecting group.

Table 2.5. β-Selective Glycosylation with C(2)-PMB-Glucose Donor.[a]



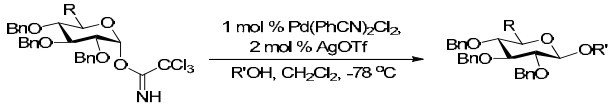
Entry	R'OH	Disaccharides	Yield[b]	β:α[c]
1	**61**	 **85**	75%	9:1
2	**62**	 **86**	90%	8:1
3	**64**	 **87**	71%	10:1
4	**65**	 **88**	71%	6:1

[a] All reactions were performed in CH_2Cl_2 (0.15 M) with 2 mol % $Pd(PhCN)_2Cl_2$ and 4 mol % AgOTf. [b] Isolated yield. [c] ^1H NMR ratio.

The ability of a *p*-methoxybenzyl group to direct β-glycosylation by the cationic palladium catalyst was also investigated, since this protecting group has been extensively employed in a number of glycosylation reactions with reactivity and selectivity similar to

the benzyl group. The *p*-methoxybenzyl group is useful because they can be selectively removed in the presence of the benzyl protecting groups. Accordingly, glycosylation of primary and hindered hydroxyl groups of nucleophilic acceptors **61-65** with 2,3,4,6-*tetra*-*O*-*para*-methoxybenzyl-D-glucopyranosyl trichloroacetimidate donor **84** (Table 2.5) was explored in the presence of $Pd(PhCN)_2(OTf)_2$. The desired products **85-88** were obtained in high yields (71% → 90%) and with good β-selectivity (6:1 → 10:1). In these reactions, the cationic Pd(II) catalyst, $Pd(PhCN)_2(OTf)_2$, had to be increased from 1 mol % to 2 mol % for the coupling reaction to go to completion at - 78 ^oC. Overall, the Pd(II)-catalyzed reaction with the *para*-methoxybenzyl-protected donor **84** was less reactive and less β-selective than that of the benzyl-protected donor **20α**.

Table 2.6. Glycosylation with Benzylated Xylose and Quinovose Donors.[a]

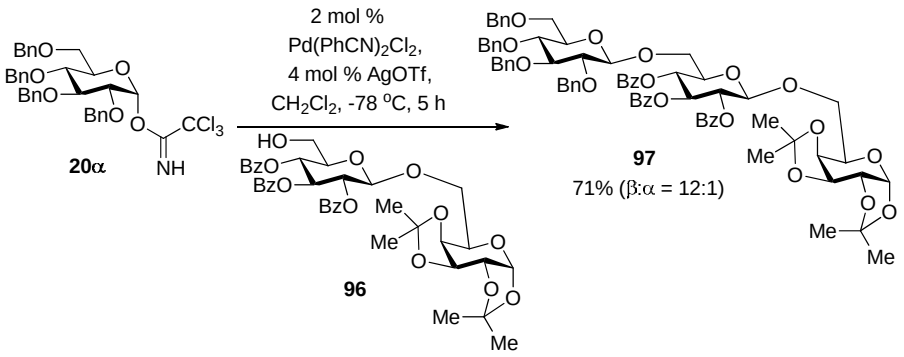


Entry	Donor	R'OH	Disaccharides	Yield[b]	β:α[c]
1	**89**	**61**	**91**	85%	11:1
2	**89**	**62**	**92**	76%	10:1
3	**90**	**61**	**93**	80%	7:1
4	**90**	**62**	**94**	86%	5:1
5	**90**	**65**	**95**	88%	8:1

[a] All reactions (except entries 2 and 4) were carried out in CH_2Cl_2 (0.15 M) with AgOTf and $Pd(PhCN)_2Cl_2$ at -78 ^oC.[b] Isolated yield. [c] ^1H NMR ratio.

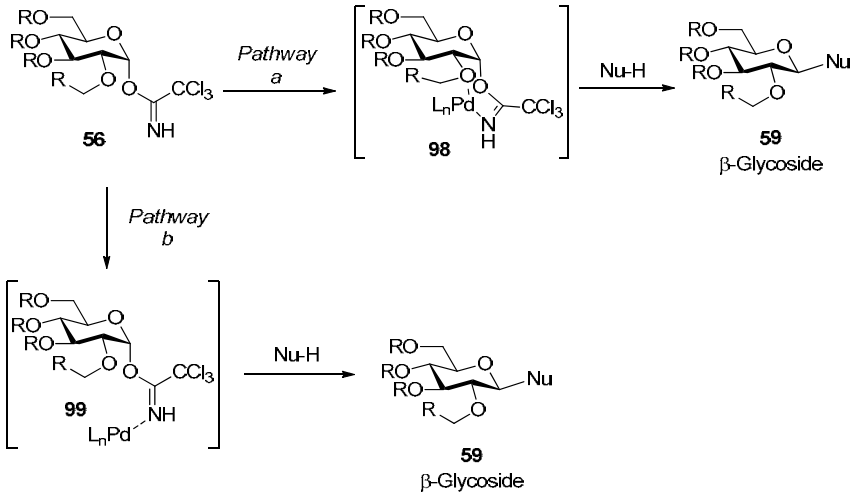
Encouraged by the results obtained with D-glucose donors, the feasibility of this cationic palladium method was further investigated with tribenzylated D-xylose trichloroacetimidate donor **89** and D-quinovose trichloroacetimidate donor **90** (Table 2.6). These carbohydrate moieties are found within a variety of biologically active oligosaccharide and glycoconjugate natural products.[120-122] These substrates lack the protected C(6)-hydroxyl functionality, and so we were interested in what effect this would have on the β-selectivity of the coupling products. Gratifyingly, it was found that both trichloroacetimidate donors **89** and **90** (Table 2.6) were able to couple to primary alcohol acceptor **61** and hindered secondary and tertiaryl acohols **62** and **65** to afford the desired glycoconjugates **91**-**95** in good yields with moderate to good β-selectivity (5:1 → 11:1).

Many current glycosylation methodologies have been known to work well in the synthesis of disaccharides, but fail in oligosaccharide synthesis. To demonstrate the utility of the palladium chemistry in the β-selective synthesis of oligosaccharides and glycoconjugates, it was investigated within the context of trisaccharide synthesis as shown in Scheme 2.14. In this [1+2] approach, the palladium-catalyzed glycosylation of disaccharide nucleophile **96**[102-105] (Scheme 2.14) with glycosyl trichloroacetimidate donor **20α** provided the corresponding trisaccharide **97** in 71% yield with excellent β-selectivity (β:α = 12:1). Notably, the coupling was performed at - 78 ^{o}C with only 2 mol% of $Pd(PhCN)_2(OTf)_2$ as the activating reagent, and the reaction was complete within 5 h. This result clearly demonstrates the efficiency of the cationic palladium(II) method in oligosaccharide synthesis, and it does so with formation of trisaccharide **97** (Scheme 2.14) in high yield and β-selectivity.



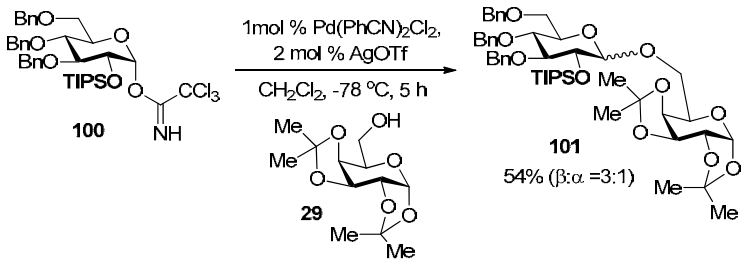
Scheme 2.14. Cationic Palladium(II) Catalyzed Synthesis of a Trisaccharide.

A proposed mechanism for cationic palladium(II) controlled β-glycosylation in the absence of the traditional C(2)-ester participatory group is outlined in Scheme 2.15. It is hypothesized that the reaction might operate through a seven-membered ring intermediate such as **98**, where the cationic Pd(II) species coordinates to both C(1)-imidate nitrogen and C(2)-oxygen of trichloroacetimidate donor **56** (Pathway a). Formation of this seven-membered ring intermediate blocks the α-face of the activated complex. As a result, the incoming nucleophilic acceptor approaches from the β-face of the complex **98**, thus leading to the formation of β-glycoside **59** (Scheme 2.15). However, the glycosylation reaction could occur through a simple S_N2 displacement (Pathway 2) of the trichloroacetimidate leaving group by the nucleophilic acceptor to afford the desired β-isomer **59,** without internal chelation of the C(2)-oxygen of **56** to the cationic palladium(II) catalyst as in the intermediate **99**.



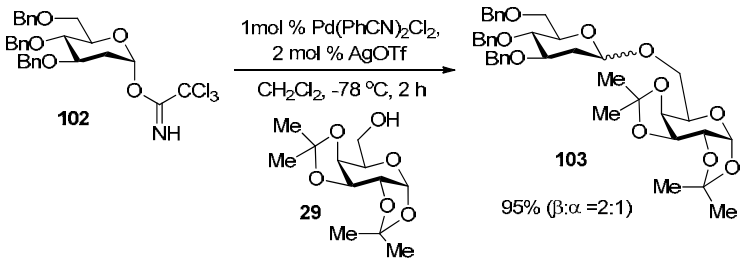
Scheme 2.15. Proposed Cationic Palladium(II) Directed β-Glycosylation.

To differentiate between the two glycosylation reaction pathways, two control experiments were carried out. In the first experiment, galactose nucleophilic acceptor **29** was coupled with C(2)-triisopropylsilyl (TIPS) protected donor **100** (Scheme 2.16). If the seven-membered ring intermediate such as **98** (Scheme 2.15) is the operative pathway, it was anticipated that disaccharide **101** will be formed as a mixture of α- and β-isomers since the bulky TIPS protecting group will prevent the cationic palladium(II) catalyst from coordinating to the C(2)-oxygen of glycosyl donor **100** (Scheme 2.16). Accordingly, treatment of both coupling partners **29** and **100** under standard cationic palladium(II) conditions provided the corresponding disaccharide **101** in 54% yield with a poor β-selectivity (β:α = 3:1). This evidence supports Pathway A (Scheme 2.15) as a likely operative pathway, where activation involves the coordination of cationic Pd(II) species to both C(1)-imidate nitrogen and C(2)-oxygen of the glycosyl donor.



Scheme 2.16. Glycosylation with a TIPS-Protected Glycosyl Donor.

A second control experiment was subsequently performed using 2-deoxy-3,4,6-*tri*-*O*-benzyl trichloroacetimidate as the glycosyl donor **102** (Scheme 2.17). The absence of oxygen functionality at the C(2)-position of glycosyl donor **102** eliminates the possibility of a seven-membered ring intermediate such as **98** (Scheme 2.15, pathway A). Thus, if the seven-membered ring complex (pathway A) is the pathway in operation, disaccharide **103** will be formed as a mixture of α- and β-isomers. On the other hand, if the simple S_N2 pathway without internal chelation is operative (Scheme 2.15, pathway B), β-isomer of the disaccharide **103** will be formed as a major product. Accordingly, glycosylation of **29** with **102** (Scheme 2.17) under cationic palladium(II) conditions resulted in the formation of the disaccharide **103** in excellent yield (95%) but as a mixture of α- and β-isomers (β:α = 2:1). This control experiment suggests that the S_N2 pathway without internal chelation is unlikely to be the major pathway in operation under cationic palladium(II) conditions. The low anomeric selectivity suggests that the reaction may proceed *via* oxocarbenium intermediate, where the primary alcohol of galactoside acceptor **29** can approach from either the α- or β-face of the activated glycosyl donors.



Scheme 2.17. Glycosylation with a C(2)-Deoxy Glycosyl Donor.

The results of the above control experiments enables us to establish the possible mechanistic pathway of the cationic palladium(II) catalyzed β-selective glycosylation. The results obtained from glycosylation with C(2)-TIPS donor **100** (Scheme 2.16) as well as C(2)-deoxy donor **102** (Scheme 2.17) supports the seven-membered ring pathway (Scheme 2.15, pathway A) as likely the major operative pathway, where the cationic palladium(II) species coordinate to both the C(1)-imidate nitrogen and C(2)-oxygen of glycosyl trichloroacetimidate donor.

2.3. Conclusion

In concluding, a novel method for stereoselective synthesis of β-glycosides in the absence of the traditional C(2)-ester neighboring group participation has been developed. This approach relies on the nature of the cationic Pd(II) catalyst, $Pd(PhCN)_2(OTf)_2$, to control the β-selectivity. This new glycosylation protocol is applicable to a wide variety of glucose donors incorporating benzyl, allyl, and *para*-methoxybenzyl ether protecting groups at the C(2)-position, as well as tribenzylated xylose and quinovose donors. The reaction is highly β-selective and proceeds with low catalyst loading (1-2 mol %). The efficiency of this cationic palladium conditions has been applied to the synthesis of a number of disaccharides and trisaccharides with moderate to excellent β-selectivity.

Mechanistic studies suggest that the reaction may operate through a seven-membered ring pathway, in which the cationic Pd(II) species coordinates to both the C(1)-imidate nitrogen and C(2)-oxygen of glycosyl trichloroacetimidate donors. Formation of this seven-membered ring intermediate directs the anomeric selectivity, leading to the formation of β-glycosides.

CHAPTER 3

NICKEL-CATALYZED STEREOSELECTIVE GLYCOSYLATION WITH C(2)-*N*-SUBSTITUTED BENZYLIDENE D-GLUCOSAMINE AND GALACTOSAMINE TRICHLOROACETIMIDATES FOR THE FORMATION OF 1,2-*CIS*-2-AMINO GLYCOSIDES

3.1: C(2)-Amino Glycosides: Biological Significance

The C(2)-aminoglycosides are intergral components of glycoproteins, one of the most important classes of naturally occurring oligosaccharides and glycoconjugates.[123-129] Over half of biologically important proteins are glycosylated in the form of glycoproteins. Many of these C(2)-aminosugars are found on cell surfaces and play useful roles as receptor ligands for macromolecules such as lectins, antibodies, and enzymes.[130-133] Glycoproteins also participate in antibody-antigen interactions and are known to be linked to other sugar residues and serine/threonine amino acids through either 1,2-*cis* or 1,2-*trans*-2-amino *O*-glycosidic linkages (Figure 3.1).

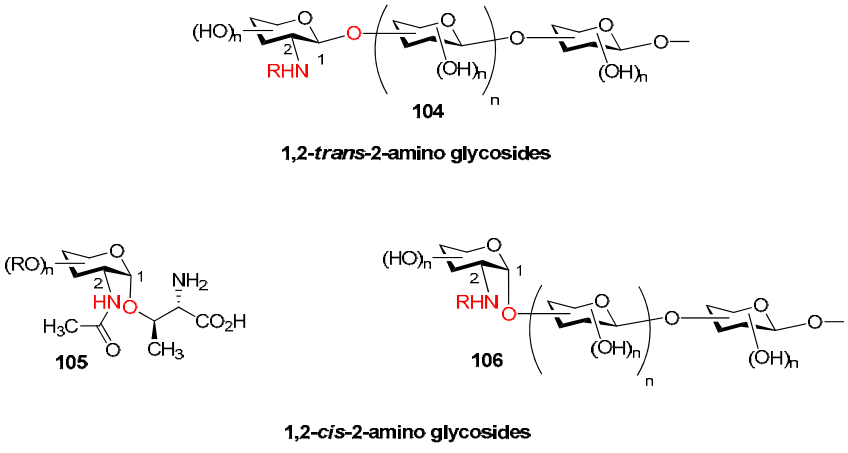


Figure 3.1. Representative Structures of C(2)-Aminosugars.

The C(2)-nitrogen in the vast majority of 2-amino-2-deoxypyranoses is acetylated (Figure 3.2). Some of the most common C(2)-*N*-acetamido-pyranoses include *N*-acetylglucosamine (GlcNAc) **107**, *N*-acetylgalactosamine (GalNAc) **108**, and *N*-acetylmannosamine (ManNAc) **109** (Figure 3.2).

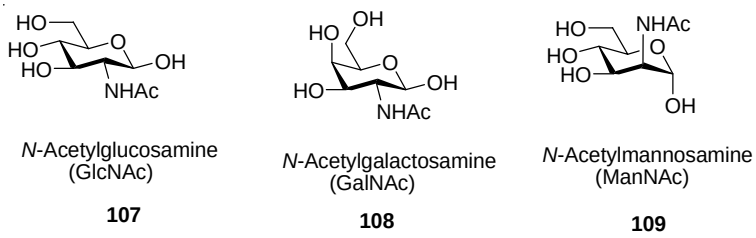


Figure 3.2. Representative Structures of C(2)-Acetaminopyranoses.

The C(2)-aminosugars are central components found in a wide range of naturally occuring oligosaccharides and glycoconjugates including glycoproteins, proteoglycans, glycosaminoglycans, and glycolipids. Glycosaminoglycans are anionic polysaccharides composed of repeating units that incorporate either a sulfated C(2)-acetaminoglycoside or C(2)-sulfoaminoglycoside.[134] Typical examples of glycosaminoglycans include heparin, condrointin-6-sulfate **110**, keratan sulfate **111** and dermatan sulfate **112** (Figure 3.3).

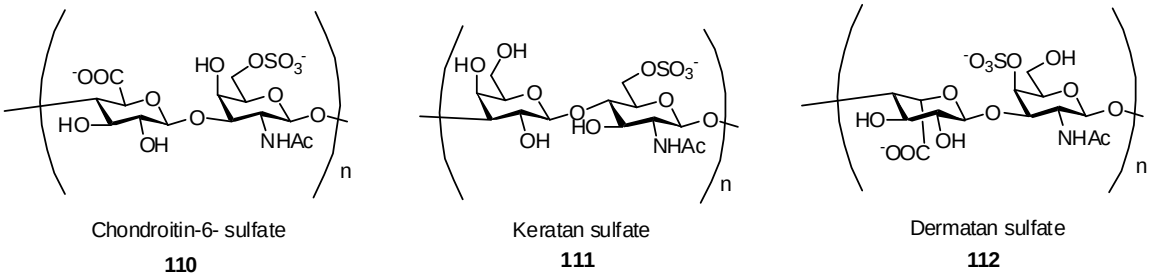


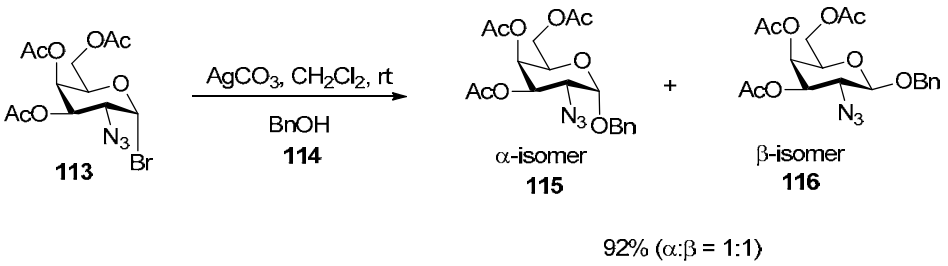
Figure 3.3. Representative Structures of Some Glycosaminoglycans.

Glycosaminoglycans are covalently linked to proteins to form proteoglycans.[135] Glycosaminoglycans and proteoglycans serve as binding sites for a wide variety of enzymes, which are involved in cell growth, damage repair, and adhesion. They also play an important role in adhesion of bacteria and viruses during infections.[136] Proteoglycans are also known to play an important role in the lubrication of joints and in shock absorption.[137]

Glycoproteins, on the other hand, are known to play important role in recognition events, and therefore serve as important targets in disease control. They can be used as haptens to induce immune response and generate antibodies. As a result, several polysaccharide based vaccines have been successfully developed.[126]

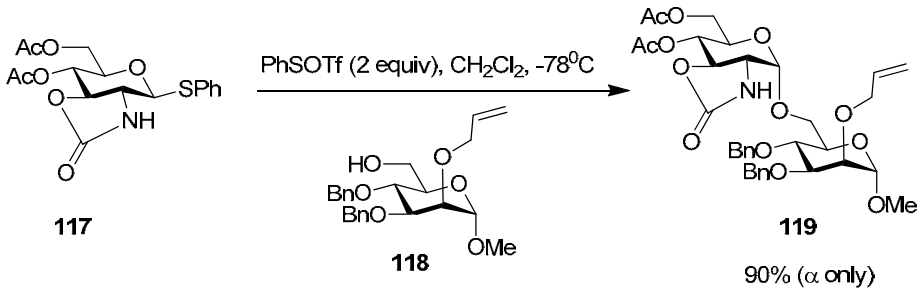
3.2: Glycosylation Methods

Most of the biologically important oligosaccharides and glycoconjugates are known to have core structures partly composed of 1,2-amino glycosides either in a 1,2-*trans* configuration or in a 1,2-*cis* configuration. Despite a variety of methods available, the stereoselective synthesis of 1,2-*cis*-2-amino glycosides continues to be a challenge, because it requires glycosyl donors with non-assisting neighboring groups at the C(2)-amino position. The most commonly used method employs glycosyl donors with a C(2)-azido functionality as the non-participatory group.[138-141] With this method, the anomeric selectivity at the newly-formed glycosidic bond can be difficult to predict, usually providing a mixture of α- and β-isomers. [127] For instance, silver carbonate ($AgCO_3$) promoted galactosylation, as reported by Lemieux and co-workers, [139] between 2-azido galactosyl donor **113** and benzyl alcohol acceptor **114,** afforded the azido galactosides **115** and **116** in excellent yield but without anomeric selectivity (Scheme 3.1).



Scheme 3.1. Glycosylation with a C(2)-Azido Glycosyl Donor.

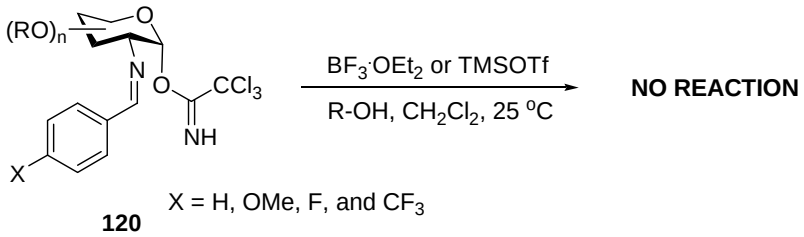
To overcome the challenge of constructing 1,2-*cis*-2-amino glycosides, Kerns and co-workers have recently developed an elegant strategy utilizing a glycosyl donor with an oxazolidinone group spanning the C(2)- and C(3)-positions (Scheme 3.2).[142-143] In this approach, the glycosylation of the primary alcohol acceptor **118** with the donor **117** is promoted by phenylsulfenyltriflate (PST), to afford the disaccharide **119** with exclusive α-selectivity.While this mode of glycosylation is useful, it requires at least two equivalents of the activating reagent (PhSOTf), and undesired side reactions, such as *N*-glycosylation [144] and *N*-sulfenylation, [130-133] are also usually observed. In addition, the stereochemical outcome of the newly-formed glycosidic bond is dependent on the reactivities of alcohol acceptors.[145]



Scheme 3.2. Glycosylation with a Glycosyl Donor Incorporating a C(2)-C(3) Oxazolidinone group.

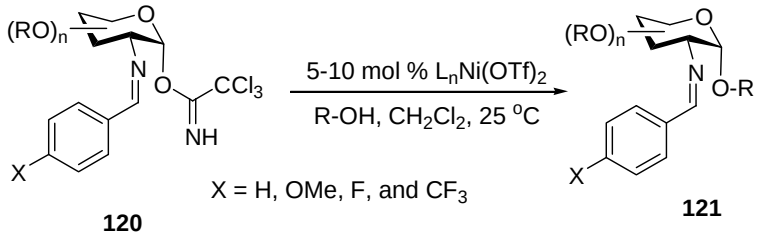
Schmidt and co-workers have also reported the conjugate addition of serine/threonine amino acids to C(2)-nitro-galactals in the presence of *t*-BuOK, to afford 1,2-*cis*-2-amino glycopeptides in good yields.[146] Gin and co-workers also recently reported the opening of aziridines with C(1)-hemiacetal nucleophiles to form the corresponding α-*O*-glycosyl serine conjugates with good selectivity as well.[147] However, the latter two methods are limited in substrate scope.

Alternatively, forty years ago, the use of a *para*-methoxy-benzylidene moiety as the protecting group for the C(2)-nitrogen on a glycosyl bromide to form 1,2-*cis*-2-amino glycosides was also investigated.[148] However, its use was complicated as a result of a multistep synthesis required for the construction of the glycosyl bromide. Additionally, the stereochemical outcome of the coupling process was found to be dependent on the nature of the promoters as well as the alcohol acceptors used. For instance, using stoichiometric amounts of HgCN provided the desired glycosides selectively as either the α-isomers[149] or β-isomers,[150] depending on the nature of the alcohol acceptors. By contrast, use of stoichiometric amount of AgOTf as a promoter provided exclusively β-glycosides. [150] Using *n*-pentenyl glycosyl donor afforded 1,2-*cis*-2-amino glycosides in moderate yields. [151] Conversely, no reaction was observed when C(2)-*para*-methoxy-benzylidene D-glucosamine trichloroacetimidate **120** was used as the glycosyl donor in a glycosylation reaction under the traditional Lewis acid conditions (Scheme 3.3). [150]



Scheme 3.3. Synthesis of 1,2-*Cis* 2-Amino Glycosides Under Lewis Acid Conditions.

With recent increases in the interest of merging transition metal-catalyzed reaction methodology with carbohydrate synthesis to facilitate stereoselective contruction of a variety of α- or β-glycosidic linkages, [79,101,106-107,152-153] the possibility for the synthesis of 1,2-*cis*-2-amino glycosides **121** using transition metal catalysts was therefore explored (Scheme 3.4).



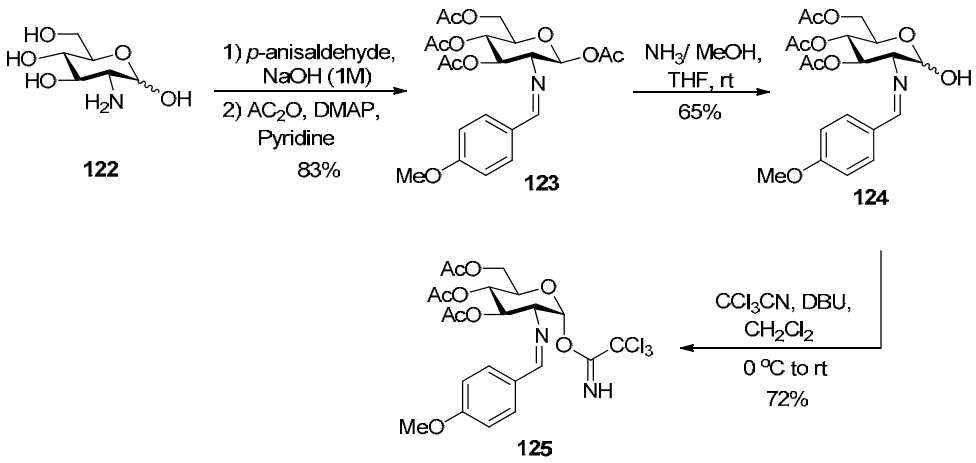
120 **121**

Scheme 3.4. Transition Metal Catalyzed Synthesis of 1,2-*Cis* 2-Amino Glycosides.

The goal was to exploit the ability of transition metal catalyst to direct α-selective glycosylation with C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidate donors **120** (Scheme 3.4) to form 1,2-*cis*-2-aminosugars **121**.[154] In this approach, we hypothesize that the α-selectivity at the newly-formed glycosidic bond is controlled by the nature of the transition metal-ligand complex. Thus, the proposed glycosylation protocol (Scheme 3.4) is a marked departure from the current state-of-the-art methodologies because it does not solely depend on the nature of the protecting groups on the substrates to influence the anomeric selectivity. If successful, we anticipate that this transition metal approach would overcome the current problems associated with the synthesis of the challenging 1,2-*cis*-2-amino glycosides.

3.3: Results and Discussion

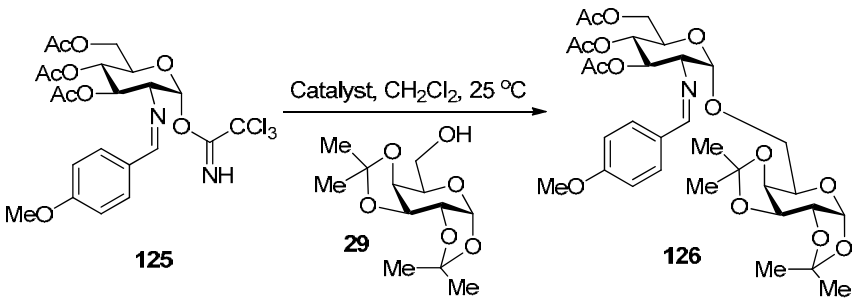
Because C(2)-*para*-methoxy-benzylidene D-glucosamine **125** (Scheme 3.5) has been previously studied as a glucosamine donor under Lewis acid conditions, we began our initial studies with this donor to probe the reactivity and selectivity of the coupling process under the transition-metal catalyzed conditions. To begin, we developed a simple and efficient procedure for the synthesis of **125** (Scheme 3.5). The synthesis of **125** began using the commercially available D-glucosamine **122**. Exposure of **122** to *p*-anisaldehyde and NaOH (1M) afforded the Schiff base intermediate which was subsequently acetylated to afford **123** in 83% over two steps.[155-157] Selective C(1)-*O*-deacetylation using ammonia in methanol at room temperature afforded the hemiacetal intermediate **124** in 65% yield. This hemiacetal was next converted to the corresponding glycosyl trichloroacetimidate **125** upon treatment of **124** with trichloroacetonitrile (Cl_3C-CN) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU). The desired trichloroacetimidate **125** was obtained in 72% yield. Having the glycosyl donor in hand, our attention was shifted to identifying optimal conditions for the stereoselective formation of 1,2-*cis*-2-amino glycosides.



Scheme 3.5. Synthesis of C(2)-*p*-Methoxybenzylidene Glycosyl Donor.

Preliminary studies investigated the glycosylation of galactoside acceptor **29** with C(2)-*N*-*para*-methoxybenzylidene D-glucosamine trichloroacetimidate donor **125** (Table 3.1). Based on the success of the cationic palladium catalyzed β-selective glycosylation project,[101] 5 mol % of $Pd(PhCN)_2(OTf)_2$ was initially employed as the activating reagent (Table 3.1). The reaction was performed at room temperature and methylene chloride was used as a solvent. Although the coupling process was quite sluggish (10 h), the desired disaccharide **126** was still isolated in 60% yield and as a 4:1 mixture of α- and β-isomers (entry 1). This preliminary result is quite encouraging because it validates our hypothesis that we can use the transition metal catalyst to not only activate the glycosyl donor but also control the anomeric selectivity at the newly-formed glycosidic bond. It was envisioned that additional improvements could be made through modification of the catalyst-ligand system. Because nickel has a relatively smaller atomic size and is more nitrophilic than palladium, we postulated that nickel will coordinate better to both the C(2)-benzylidene nitrogen and C(1)-trichloroacetimidate nitrogen of glycosyl donor than its palladium counterpart. As expected, treatment of both coupling partners **125** and **29** with 5 mol % of cationic nickel, $Ni(PhCN)_4(OTf)_2$ (entry 2), generated *in situ* from $Ni(PhCN)_4Cl_2$ and AgOTf in CH_2Cl_2, afforded disaccharide **126** with an improved yield (60% → 95%) and a significantly higher α-selectivity (α:β = 4:1 → 8:1). Additional studies also probed the effect of the ligand on the yields and anomeric selectivity in the coupling products (entries 3-6).[158] Both electron-donating and electron-withdrawing benzonitrile ligands were examined. Gratifyingly, it was found that the more electron-withdrawing substituted benzonitrile ligands, 4-F-PhCN and 4-CF_3-PhCN (entries 3 and 4), shortened the reaction time and increased α-selectivity. For instance, use of 5 mol % $Ni(4\text{-F-PhCN})_4(OTf)_2$ catalyst (entry 4) afforded 93% of the desired disaccharide **126** in 3 h and with an excellent α-selectivity (α:β = 10:1). By comparison, the more electron rich 4-methoxy-benzonitrile ligand (entry 5) increased the reaction time (4 h → 6 h).

Table 3.1. Optimization of Reaction Conditions for Selective Formation of 1,2-*Cis*-2-Amino Glycosides.[a]



Entry	Catalyst	Loading(mol%)	Time(h)	Yield(%)[b]	α:β[c]
1	$Pd(PhCN)_2(OTf)_2$	5	10	60	4:1
2	$Ni(PhCN)_4(OTf)_2$	5	4	95	8:1
3	$Ni(4\text{-}CF_3\text{-}PhCN)_4(OTf)_2$	5	3	90	10:1
4	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5	3	93	10:1
5	$Ni(4\text{-}MeOPhCN)_4(OTf)_2$	5	6	76	10:1
6	$Ni(dppe)(OTf)_2$	5	7	95	8:1
7	$Ni(4\text{-}F\text{-}PhCN)_4Cl_2$	5	10	-	-
8	AgOTf	10	10	<1	-
9	TfOH	10	5	10	3:1

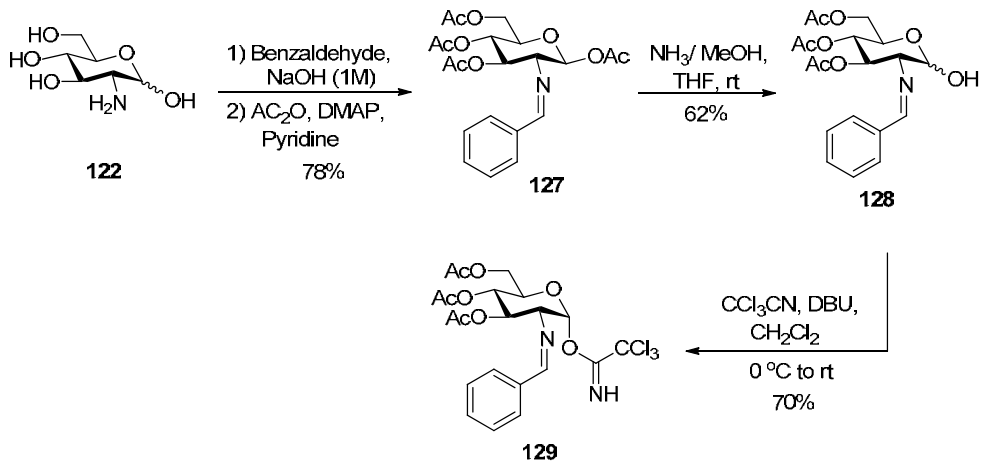
[a] The reactions were performed with 5 mol % of $LnNi(OTf)_2$ which was generated *in situ* from 5 mol % L_nNiCl_2 and 10 mol% AgOTf. [b] Isolated yield. [c] ^1H NMR ratio.

Next, a series of control experiments were conducted to determine the important role of the cationic nickel catalyst to effect the coupling process (Table 3.1, entries 7 – 9). First, a similar coupling reaction was attempted using neutral $Ni(PhCN)_4Cl_2$ (entry 7). With this catalyst, the desired disaccharide **126** was not observed in the glycosylation reaction, validating the important role of the cationic nickel in the coupling process. Since a stoichiometric amount of AgOTf had been reported by Krepinsky and co-workers

to activate glycosyl trichloroacetimidate donors,[80] a control experiment was performed to determine whether C(2)-*N*-benzylidene D-glucosamine **125** was indeed activated by 10 mol% of AgOTf (entry 8). In this experiment, less than 1% conversion was detected. To determine whether the presence of triflic acid, possibly generated *in situ* from the cationic nickel catalyst was the source of catalysis, the coupling of **29** with **125** was performed employing 10 mol % of triflic acid as the activating agent (entry 9). Use of triflic acid resulted in in less than 10% isolated yield of the desired disaccharide **126**, and the anomeric selectivity at the newly-formed glycosidic bond was poor (α:β = 3:1). The results obtained from these studies suggest that the presence of the cationic nickel is crucial in directing the anomeric selectivity and is not just simply acting as a Lewis acid.

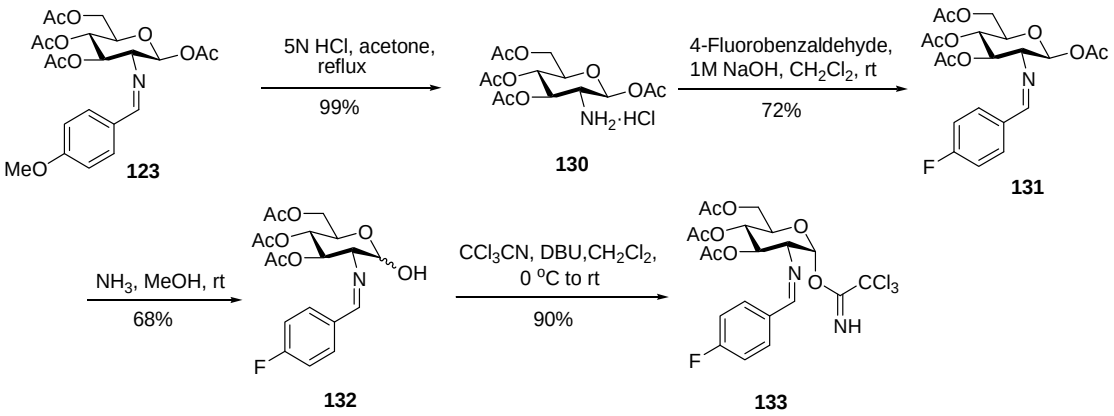
The glycosylation of galactoside acceptor **29** with C(2)-*N*-4-methoxybenzylidene trichloroacetimidate donor **125** was also explored with other Lewis acids or transition metal catalysts. Use of mild Lewis acids, $Zn(OTf)_2$ and $Cu(OTf)_2$, and transition metal catalysts, $Au(PPh_3)(OTf)$ and $RhCOD_2OTf$, provided the desired disaccharide **126** in poor yield (20% □ 26%) and a mixture of α- and β-isomers (1:1 → 2:1).

The nickel catalyzed 1,2-*cis*-2-amino glycosylation method was extended to other *N*-substituted benzylidene glucosamine trichloroacetimidate donors **129**, **133** and **136** (Table 3.2)**.** Glycosyl donor **129** (Scheme 3.6) was prepared using the similar route that has been used for preparation of trichloroacetimidate **125** (Scheme 3.5). The synthesis began employing D-glucosamine **122** as the starting material. Treatment of **122** with benzaldehyde in the presence of 1M sodium hydroxide (NaOH) afforded the Schiff base intermediate, which was subsequently acetylated to provide **127** in 78% yield over two steps. Selective C(1)-*O*-deacetylation of **127** with ammonia in methanol afforded the hemiacetal intermediate **128** in 62% yield. This hemiacetal was then converted to the corresponding glycosyl trichloroacetimidate donor **129** in 70% yield upon treatment with trichloroacetonitrile and DBU (Scheme 3.6).



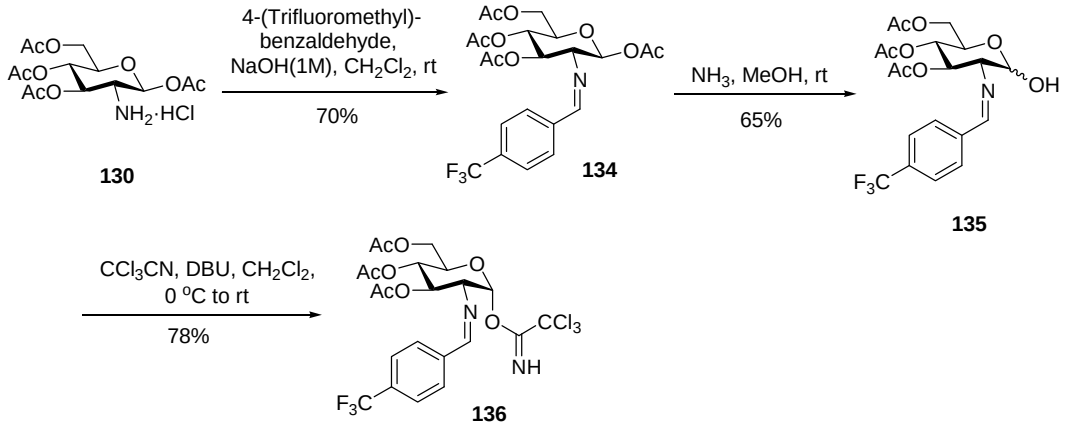
Scheme 3.6. Synthesis of C(2)-*N*-Benzylidene Glucosamine Imidate **129**.

The standard protocol for preparation of both glycosyl donors **125** (Scheme 3.5) and **129** (Scheme 3.6) was not applicable for the synthesis of 4-fluorobenzylidene donor **133** (Scheme 3.7), because the formation of the Schiff base intermediate from condensation of glucosamine **122** (Scheme 3.6) with 4-fluorobenzaldehyde did not occur as anticipated. We hypothesize that this is due to the strong hydrogen bonding between fluoride atom and water (F---H-O-H). Thus, a new route needed to be devised for the preparation of glycosyl donor **133.** The new synthesis of the glycosyl donor **133** commenced with the acetylated Schiff base intermediate **123** (Scheme 3.5) as the starting material. Removal of the C(2)-*p*-methoxybenzylidene with 5N HCl afforded the amine hydrochloride salt **130** (Scheme 3.7)[155] in quantitative yield. This amine salt was subsequently condensed with 4-fluorobenzaldehyde in the presence of 1M sodium hydroxide (NaOH) to afford the corresponding 4-fluorobenzylidene intermediate **131** in 72% yield. Selective C(1)-*O*-deacetylation of **131** using ammonia in methanol provided the hemiacetal **132** in 68% yield, which was then converted to the glycosyl donor **133** in 90% yield upon treatment with Cl_3C-CN and DBU (Scheme 3.7).



Scheme 3.7. Synthesis of C(2)-4-Fluorobenzylidene Glucosamine Imidate **133**.

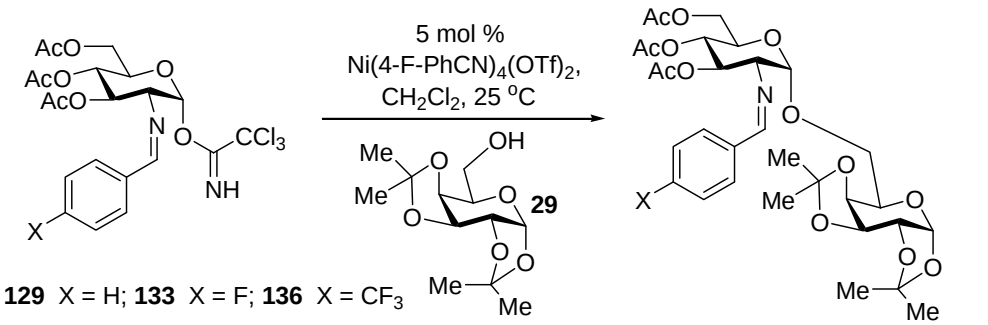
A similar route was then applied toward the synthesis of the glycosyl donor **136**, using the amine hydrochloride salt intermediate **130** as the starting material (Scheme 3.8). Condensation of 4-(trifluoromethyl)benzaldehyde with the amine hydrochloride salt **130** in 1M sodium hydroxide (NaOH) afforded C(2)-4-(trifluoromethyl)benzylidene intermediate **134** in 70% yield. Selective C(1)-*O*-deacetylation of **134** with ammonia in methanol yielded the hemiacetal intermediate **135** in 65% yield. Exposure of **135** to Cl_3C-CN and DBU afforded the corresponding trichloroacetimidate **136** in 78% yield (Scheme 3.8).



Scheme 3.8. Synthesis of C(2)-4-(Trifluoromethyl)benzylidene Glycosyl donor.

With the *N*-substituted benzylidene trichloroacetimidate glucosamine donors **129**, **133** and **136** at hand, the efficacy of the nickel-catalyzed 1,2-*cis*-2-amino-glycosylation reaction was further investigated (Table 3.2).

Table 3.2. Selective Formation of 1,2-*Cis*-2-Amino Glycosides with *N*-Substituted Benzylidene Glucosamine Trichloroacetimidate Donors.



129 X = H; **133** X = F; **136** X = CF_3

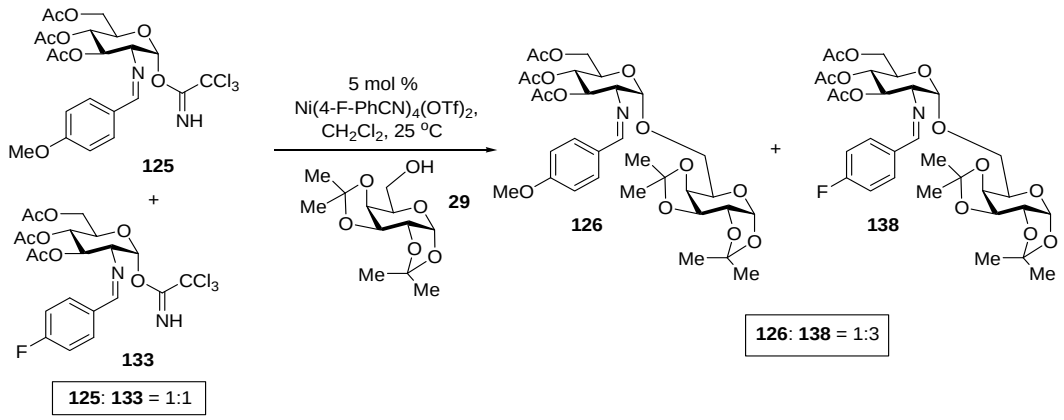
137 X = H; **138** X = F; **139** X = CF_3

Entry	X	Catalyst [a]	Loading(mol %)	Time(h)	Yield(%)[b]	α:β[c]
1	H	$Ni(4\text{-F-PhCN})_4(OTf)_2$	5	3	92	10:1
2	CF_3	$Ni(4\text{-F-PhCN})_4(OTf)_2$	5	1	87	9:1
3	F	$Ni(4\text{-F-PhCN})_4(OTf)_2$	5	1	96	9:1

[a] The reactions were performed with 5 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ which was generated *in situ* from 5 mol % $Ni(4\text{-F-PhCN})_4Cl_2$, and 10 mol % AgOTf. [b] Isolated yield. [c] ^1H NMR ratio.

Accordingly, coupling of the galactoside acceptor **29** with C(2)-*N*-benzylidene glycosyl donor **129** provided the desired disaccharide **137** (Table 3.2, entry 1) in 92% yield and with high α-selectivity (α:β = 10:1). Switching to the relatively more electron-withdrawing *N*-substituted benzylidene donors **133** and **136** shortened the reaction time from 3 h to 1 h, affording the desired disaccharides **138** and **139** (entries 2 and 3) in excellent yields (87% → 96%) and α-selectivities. These results suggest that electron-

withdrawing benzylidene donors accelerate the rate of the glycosylation reaction. To test this hypothesis, a control experiment was performed using a 1:1 mixture of both electron donating 4-methoxybenzylidene D-glucosamine donor **125** and electron withdrawing 4-fluorobenzylidene D-glucosamine donor **133** (Scheme 3.9). In the presence of the galactoside nucleophilic acceptor **29** acting as a limiting reacgent, the glycosylation reaction proceeded to provide the desired disaccharides **126** and **138** in a 1:3 ratio under standard nickel conditions.



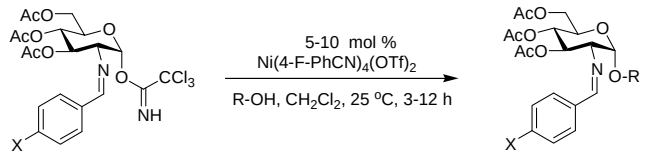
Scheme 3.9. Competitive Studies

Overall, these results demonstrate the efficacy of cationic nickel catalyst in activating C(2)-*N*-substituted benzylidene D-glucosamine donors **125**, **129**, **133** and **136**, affording the corresponding disaccharide products **126**, **137**, **138** and **139** in high yields and with excellent α-selectivity. By comparison, coupling of the glycosyl acceptor **29** with C(2)-azido derivative of the glycosyl donors **125**, **129**, **133** and **136** afforded the desired disaccharides in good yields but with poor α-selectivity (3:1) as reported by Boons and co-workers.[159]

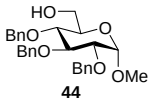
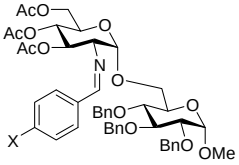
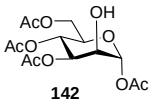
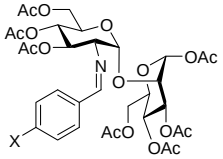
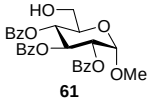
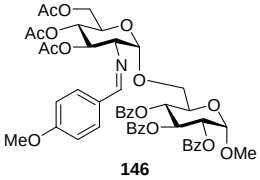
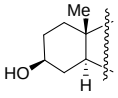
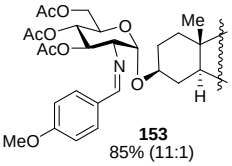
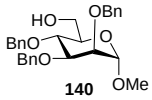
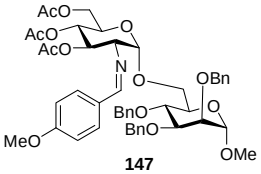
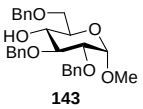
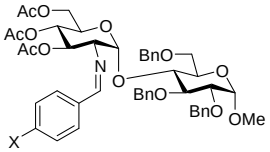
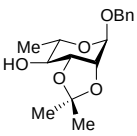
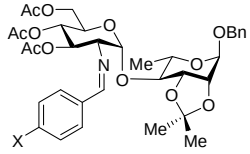
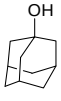
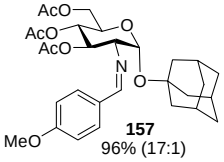
With the optimal conditions at hand, the efficacy of this new α-glycosylation protocol was investigated by glycosylation of a number of primary and hindered alcohols

44, **61, 62, 65** and **140-143** with C(2)-*N*-substituted-benzylidene D-glucosamine trichloroacetimidate donors **125**, **129**, **133** and **136** (Table 3.3).

Table 3.3. α-Selective Coupling with C(2)-*N*-Substituted Benzylidene D-Glucosamine Donors.[a]



125 X = OMe; **129** X = H; **133** X = F; **136** X = CF_3

Entry	R-OH	Products - Yield[b] (α:β)[c]	Entry	R-OH	Products - Yield[b] (α:β)[c]
1	 **44**	 X = OMe **144** 77% (20:1) X = F **145** 76% (16:1)	5	 **142**	 X = OMe **150** 97% (α only) X = H **151** 87% (α only) X = F **152** 89% (α only)
2	 **61**	 **146** 78% (15:1)	6	 **62**	 **153** 85% (11:1)
3	 **140**	 **147** 82% (10:1)	7	 **143**	 X = OMe **154** 76% (6:1) X = F **155** 80% (10:1) X = CF_3 **156** 84% (α only)
4	 **141**	 X = OMe **148** 93% (12:1) X = F **149** 88% (13:1)	8	 **65**	 **157** 96% (17:1)

[a] The reactions were performed with 5-10 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ in CH_2Cl_2 at 25 °C.
[b] Isolated yield. [c] ^1H NMR ratio.

For instance, glycosylation of **44** with **125** proceeded smoothly to afford the desired disaccharide **144** in 77% yield with an excellent α-selectivity (α:β = 20:1) (Table 3.3, entry 1). In contrast, coupling of **44** with **125** did not occur in the presence of TMSOTf as a promoter, and the use of $BF_3{\cdot}OEt_2$ only resulted in decomposition along with a trace amount of the desired disaccharide **144** (entry 1).[150] The new glycosylation protocol using cationic nickel catalyst is more α-selective than other existing methods. For example, coupling of **44** with a glycosyl bromide derivative of donor **125** in the presence of AgOTf (1.5 equiv) as a promoter, afforded the disaccharide **144** with the β-isomer as the major product (α:β = 1:9).[150] On the other hand, coupling of **44** with C(2)-oxazolidinone thioglycoside donor provided the disaccharide in 81% yield with moderate α-selectivity (α:β = 3:1).[160] The efficacy of the nickel method was further explored with the electron-withdrawing nucleophilic acceptor **61** (entry 2). When coupled with the glycosyl donor **125**, the desired disaccharide **146** (entry 2) was isolated in 78% yield with α:β = 15:1. By comparison, when **61** was coupled with C(2)-azido derivative of donor **125** under $BF_3{\cdot}OEt_2$-mediated conditions, the azido glycoside was isolated in moderate yields with an 8:1 mixture of α- and β-isomers, as reported by Boons and co-workers.[159] We next investigated whether secondary alcohols **141**, **142**[167] and **62** might be viable nucleophilic acceptors in glycosylation reaction under cationic nickel conditions (entries 4-6). Accordingly, coupling of C(2)-hydroxyl group of mannoside acceptor **142** with C(2)-*N*-substituted benzylidene trichloroacetimidate donors **125**, **129** and **133** under cationic nickel conditions afforded the respective disaccharides **150**-**152** in good yields (87 → 97%) and with exclusively α-selectivities (entry 5). With Kochetkov's C(2)-azido thiocyanate donor, coupling of the glycosyl acceptor **142** also afforded the α-isomer as the major product, albeit in lower yield (72%).[161] When dihydrocholesterol **62** was employed as a nucleophilic acceptor, the corresponding glycoconjugate **153** was obtained in 85% yield with α:β = 11:1 (entry 6). Under the Oscarson's oxazolidinone method of glycosylation, the glycoconjugate was formed exclusively as a β-isomer using dihydro-

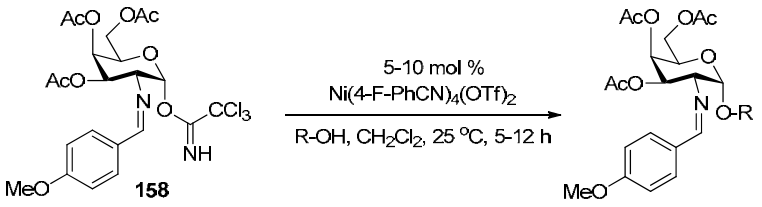
cholesterol as the acceptor.[162] The α-isomer, however, could be obtained when a large quantity of AgOTf (0.4 equivalent) was employed to promote the anomeric epimerization of the kinetic β-isomer into the corresponding thermodynamic α-isomer.[162]

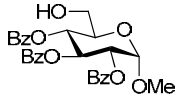
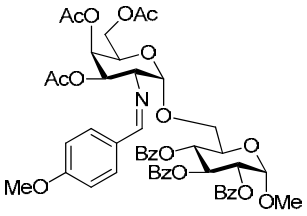
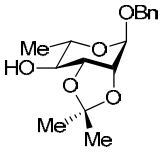
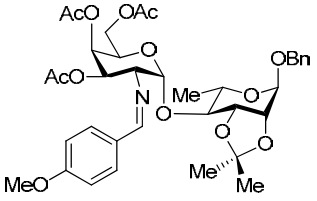
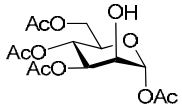
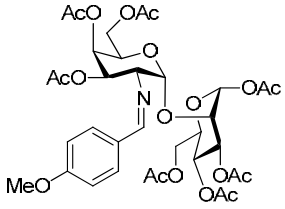
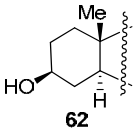
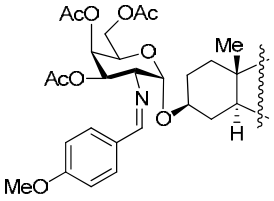
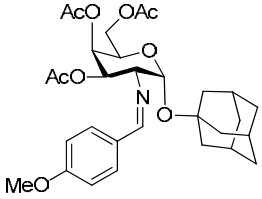
The sterically hindered alcohol acceptor **143** (Table 3.3, entry 7) is known to provide coupling products with either poor yields and/or α-selectivity.[159,163] For instance, coupling of **143** with C(2)-oxazolidinone thioglycoside donor afforded the desired disaccharide in 82% yield with poor α-selectivity (α:β = 2:1) as reported by Geng and co-workers.[163] Under the C(2)-azido method as reported by Boons and co-workers, coupling of **143** with C(2)-azido glycosyl donor provided the expected disaccharide exclusively as α-isomer, albeit in lower yield (40%).[159] To demonstrate that the C(4)-hydroxyl functionality of D-glucopyranoside **143** can be used as a viable nucleophile under the cationic nickel conditions, it was coupled with glycosyl donors **125**, **133**, and **136** (entry 7). The desired disaccharides **154**-**156** were obtained in good yields and with moderate to excellent levels of α-selectivity (6:1 → α only). These results clearly show that the nature of the benzylidene groups on glycosyl donors plays an important role in directing anomeric selectivity of the coupling products. To illustrate, use of an electron-donating 4-methoxybenzylidene donor **125** provided disaccharide **154** in good yields with a good α-selectivity (α:β = 6:1) (entry 7). On the other hand, coupling of glycosyl acceptor **143** with an electron-withdrawing 4-(trifluoromethyl)-benzylidene donor **136** afforded the corresponding disaccharide **156** in excellent yield (84%) and exclusively as α-isomer (entry 7). The efficiency of the cationic nickel protocol was further explored using tertiary alcohol **65** (entry 8). In this glycosylation reaction, the desired glycoconjugate **157** was obtained in 96% yield and with α:β = 17:1. Overall, the nickel-catalyzed α-selective glycosylation with C(2)-*N*-substituted benzylidene D-glucosamine donors **125**, **129**, **133** and **136** provided a practical approach to access a variety of disaccharides and glycoconjugates in high yields and excellent levels of α-selectivity. Additionally, it does not require PhSEt as a putative nucleophile (the azide method), [159]

nor does it require a large quantity of AgOTf (the oxazolidinone method) [162] in order to improve the α-selectivity. Instead, only catalytic amounts of cationic nickel (5-10 mol %) is required to activate glycosyl donors **125**, **129**, **133** and **136**.

Similarly, C(2)-*N*-4-methoxybenzylidene D-galactosamine **158** was also found to be a viable glycosyl donor under the cationic nickel catalyzed glycosylation reaction conditions, with a variety of primary alcohol **61**, secondary alcohols **141, 142** and **62** as well as tertiary alcohol **65** (Table 3.4) containing both electron-withdrawing and electron-donating protecting groups. Each coupling reaction afforded the desired product in high yield (74% → 93%) and with excellent levels of α-selectivity (10:1 → > α only), regardless of the position of the hydroxyl group and the nature of the protecting groups on the glycosyl acceptors. In addition, only 5 – 10 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ was required for the coupling reaction to go to completion at room temperature. For example, glycosylation of the nucleophilic acceptor **142** with the galactosamine trichloroacetimidate **158**, provided the disaccharide **161** (entry 3) in 93% yield and with exclusive α-selectivity. The efficacy of the nickel methodology was further tested with a hindered tertiary alcohol acceptor **65** (entry 5). In this case also, the glycosylation reaction proceeded smoothly to afford the corresponding glycoconjugate **163** in 84% yield and with excellent α-selectivity (α:β = 12:1).

Table 3.4. α-Selective Coupling with D-Galactosamine Trichloroacetimidate.[a]

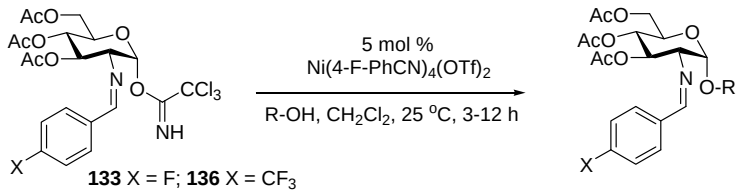


Entry	R-OH	Products	Yield[b] (α:β)[c]
1	 **61**		**159** 74% (14:1)
2	 **141**		**160** 80% (12:1)
3	 **142**		**161** 93% (α only)
4	 **62**		**162** 80% (10:1)
5	 **65**		**163** 84% (12:1)

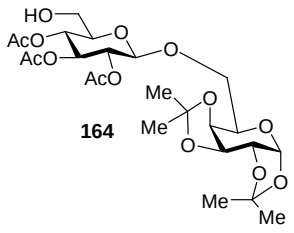
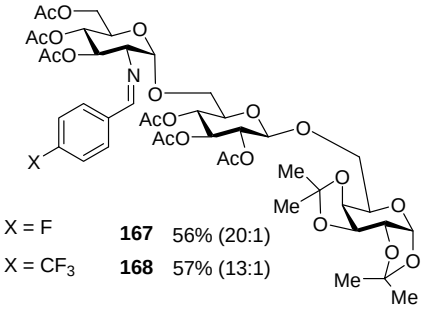
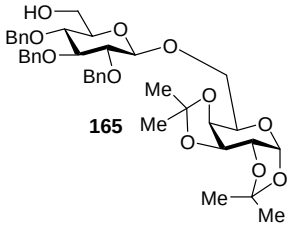
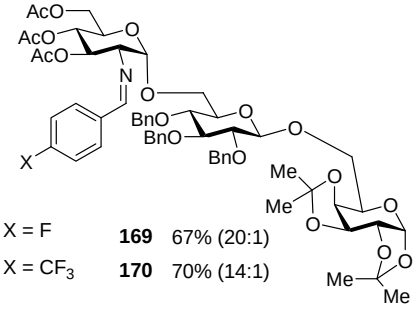
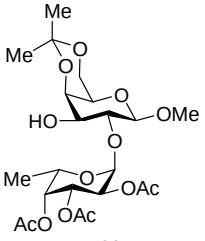
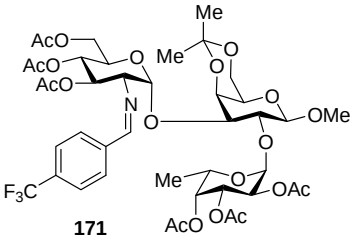
[a] The reactions were performed with 5-10 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^1H NMR ratio.

Since most glycosylation protocols works well when applied to the synthesis of disaccharides, but usually fails when extended to oligosaccharides synthesis, the nickel catalyzed α-selective glycosylation method was also extended to the preparation of oligosaccharides. To demonstrate its efficacy in oligosaccharides synthesis, a number of trisaccharides and tetrasaccharides were synthesized from disaccharide acceptors (Table 3.5) as well as disaccharide donors (Table 3.6). The prospect of trisaccharide synthesis was first evaluated with disaccharide nucleophiles **164**-**166** (Table 3.5) in a [1+2] convergent strategy. The reaction of the disaccharide acceptor **164**[164-165] with C(2)-*N*-4-fluorobenzylidene D-glucosamine donor **133** afforded the desired trisaccharide **167** (Table 3.5, entry 1) in 56% yield and with excellent levels of α-selectivity (α:β =20:1). Similarly, coupling of **164** with C(2)-*N*-4-(trifluoromethyl)benzylidene glycosyl donor **136** also afforded the trisaccharide **168** (entry 1) in 57% yield and with α:β = 13:1. Upon switching to a more electron rich disaccharide acceptor **165** (entry 2), [164-165] there was an improvement in the isolated yields of the corresponding trisaccharides **169** and **170** (entry 2) and with excellent α-selectivities (14:1 → 20:1). Secondary alcohol of disaccharide acceptor **166** (entry 3)[166] was also found to be a viable nucleophile, and upon coupling with the glycosyl donor **136**, the desired trisaccharide **171** (entry 3) was isolated in 76% yield with a 11:1 α:β ratio. Only electron withdrawing glycosyl donors **133** and **136** were explored in this instance, because they were found to undergo glycosylation reactions at a faster rate than that of an electron rich 4-methoxybenzylidine glycosyl donor **125.**

Table 3.5. α-Selective Glycosylation of Disaccharide Acceptors.[a]

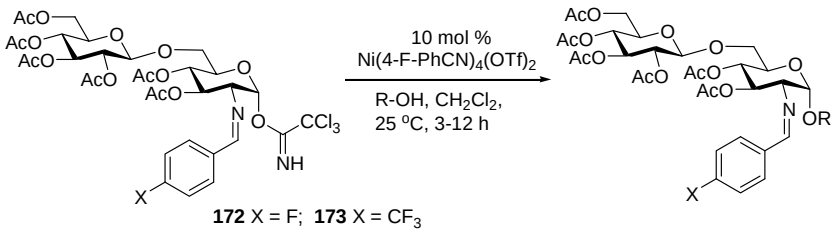


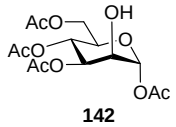
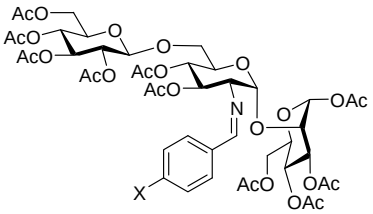
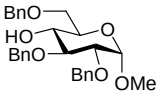
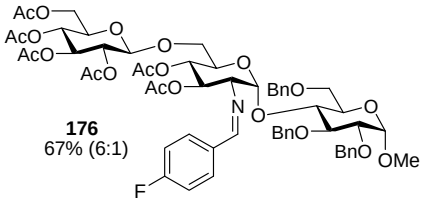
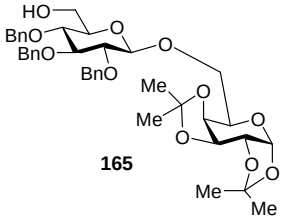
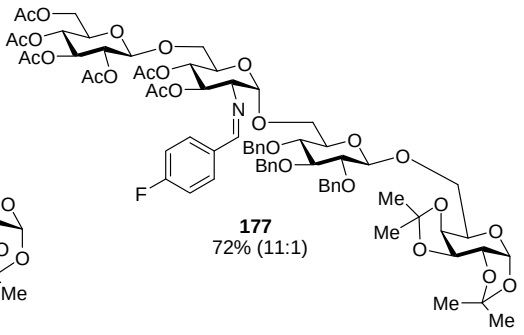
133 X = F; **136** X = CF_3

Entry	Disaccharide Acceptors (R-OH)	Products - Yield[b] (α:β)[c]
1	 **164**	 X = F **167** 56% (20:1); X = CF_3 **168** 57% (13:1)
2	 **165**	 X = F **169** 67% (20:1); X = CF_3 **170** 70% (14:1)
3	 **166**	 **171** 76% (11:1)

[a] The reactions were performed with 5-10 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^{1}H NMR ratio.

Table 3.6. α-Selective Glycosylation with Disaccharide Donors.[a]



Entry	Nucleophilic Acceptors (R-OH)	Products - Yield[b] (α:β)[c]
1	 **142**	 X = F **174** 70% (24:1) X = CF_3 **175** 57% (20:1)
2	 **143**	 **176** 67% (6:1)
3	 **165**	 **177** 72% (11:1)

[a] The reactions were performed with 5-10 mol % of $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^1H NMR ratio.

In [2+1] and [2+2] convergent approach (Table 3.6), disaccharides **172** and **173** were investigated as viable glycosyl donors. In the [2+1] strategy, coupling of mannosyl acceptor **142** with disaccharide donors **172** and **173** afforded the trisaccharides **174** and

175 (entry 1), respectively, in moderate to good yields (57% →70%), and with excellent α-selectivity (α:β > 20:1). The glycosylation reaction proceeded smoothly even with more sterically hindered secondary alcohol of carbohydrate acceptor **143**, affording the desired trisaccharide **176** (entry 2) with lower α-selectivity (6:1) than when the glycosyl acceptor **142** was used (entry 1). In the [2+2] approach, coupling of disaccharide acceptor **165** with disaccharide donor **172** proceeded smoothly to provide tetrasaccharide **177** (entry 3) in 72% yield and with high α-selectivity (11:1). The above results clearly demonstrate the efficacy of the cationic nickel method in the stereoselective synthesis of oligosaccharides.

The encouraging results obtained in the nickel-catalzyed formation of a number of oligosaccharides and glycoconjugates (Tables 3.3 - 3.6) even with extremely hindered C(4)-hydroxyl group of carbohydrate nucleophiles, prompted us to extend this nickel method to the synthesis of more complex oligosaccharides such as heparin (Figure 3.4) and tumor-associated mucin antigens (Figure 3.7).

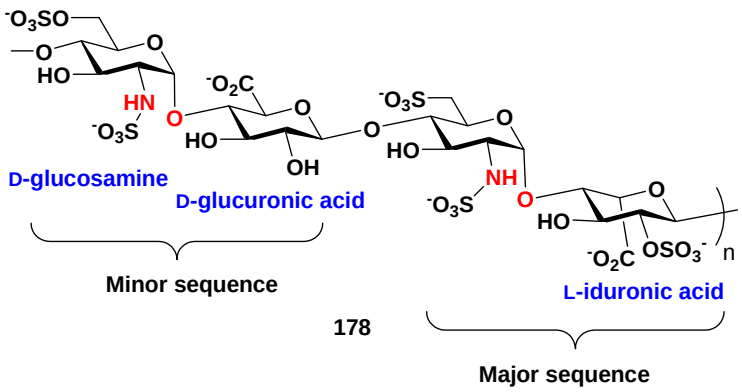


Figure 3.4. A Representative Structure of Heparin Oligosaccharide.

Heparin is a sulfated and anionic polysaccharide consisting of alternating α-(1→4)-linked-disaccharide units of L-iduronic acid or D-glucuronic acid and D-

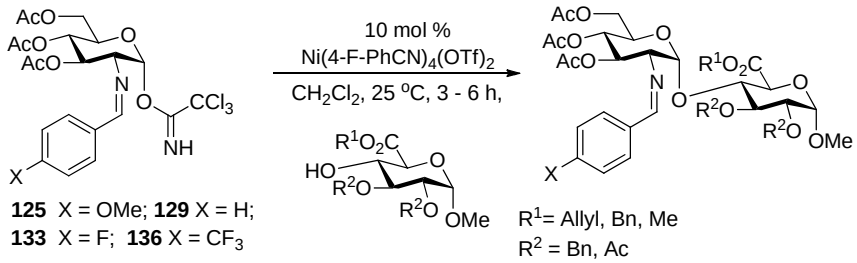
glucosamine components (Figure 3.4).[123, 150, 168-171] This polysaccharide was discovered in 1916 and was introduced into clinical use in 1935 to prevent blood clotting.[162] In addition, it has been widely reported to participate in a variety of important biological functions including blood anticoagulation, cell differentiation, cell growth, inflammation, and pathogen infection.[172-174] Currently, more than one hundred heparin binding proteins have been discovered.[175] However, for most heparin binding proteins, a detailed knowledge of the ligand requirements for binding and mediating biological activity is lacking.[176] This is due to the micro-hetereogeneity of heparin structure, and the difficulties associated with the synthesis of well-defined heparin oligosaccharides.[177] Hence, to gain understanding of heparin structure on its biological activity, well-defined heparin sequences are required. One method for obtaining well-defined low molecular weight heparins (LMWH) is through chemical synthesis.[178-180] There have been remarkable advances in the synthesis of heparin oligosaccharides, but these preparations are still limited by long synthetic steps, low yields, and anomeric mixtures.[181-183] One of the major challenges in the preparation of well-defined heparin oligosaccharides is to achieve high selectivity in the synthesis of the 1,2-*cis*-2-amino glycosidic bond that connects D-glucuronic acid to D-glucosamine unit via α-(1→4)-linkage.

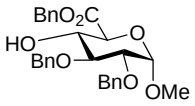
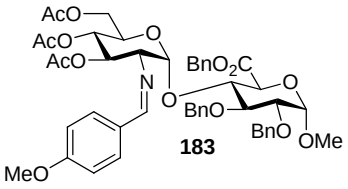
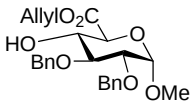
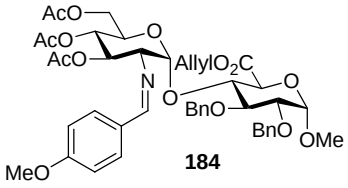
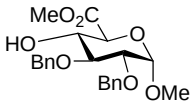
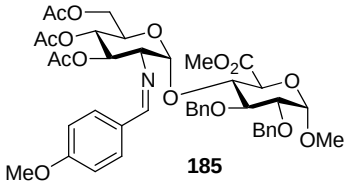
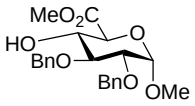
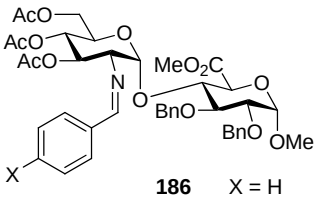
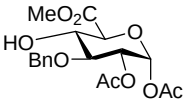
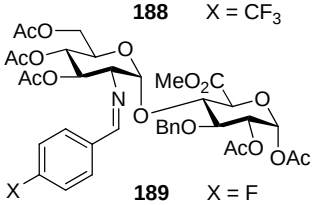
Thus, the goal in this endeavor is to investigate how D-glucuronic acid acceptors **179**-**182**[178-180, 184] would react in the cationic nickel-catalyzed α-selective glycosylation with C(2)-*N*-substituted benzylidene D-glucosamine donors **125**, **129**, **133** and **136** (Table 3.7). The C(4)-hydroxyl group of these D-glucuronic acid acceptors are not only sterically hindered, but also less reactive than other C(4)-hydroxyl groups of carbohydrate acceptors due to the presence of the carboxylate functionality at the C(5)-position. Accordingly, the coupling of glucuronic acid acceptors **179**-**180** with C(2)-*para*-methoxy-benzylidene glucosamine trichloroacetimidate donor **125** (entries 1 and 2) was investigated with 10 mol % $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$. The coupling reactions proceeded smoothly to provide the desired disaccharides **183** and **184,** respectively, in moderate to

good yields (55 → 84%), and with excellent α-selectivity (9:1 → 14:1). Use of glucuronic acid methyl ester **181** provided disaccharide **185** with an exclusive α-selectivity (entry 3). These impressive results prompted us to further investigate the glycosylation of methyl ester D-glucuronic acid acceptor **181** with other C(2)-*N*-substituted benzylidene glycosyl donors **129**, **133** and **136** (entry 4). Of the three glycosylation reactions performed, the C(2)-*N*-*para*-trifluoromethyl-benzylidene derivative **136** was found to be the most effective glycosyl donor, and the desired disaccharide **188** was isolated in excellent yield (87%) and with an exclusive α-selectivity. The scope of this nickel method were also tested with a relatively electron poor acceptor **182** (entry 5).[184] Coupling of D-glucuronic acid acceptor **182** with glycosyl donors **133** and **136** provided the desired disaccharides **189** and **190** (entry 5), respectively, in good yields (74% → 76%), and with excellent α-selectivity (>19:1).

Compared to other reported protocols, [181-183] our nickel method is much more α-selective. For instance, Seeberger and coworkers reported a modular synthesis of heparin oligosaccharides that involves the coupling of D-glucuronic acid acceptor with a C(2)-azido trichloroacetimidate donor to afford the disaccharide in 57% yield but with poor α-selectivity (α:β = 3:1.) [181] Under dehydrative glycosylation conditions, coupling of D-glucuronic acid acceptor **181** with a C(1)-hydroxyl glucoazido donor also afforded the desired disaccharide in 76% yield with 7:1 α:β ratio. [182,185-186] Because of their low reactivity, D-glucuronic acid derivatives are often masked as D-glucopyranosides, that are selectively oxidized at the C(6)-hydroxyl group after the assembly of the oligosaccharide chain. With this type of strategy, glycosylation of D-glucopyranoside acceptor with a C(2)-azido trichloroacetimidate afforded the coupling product in 78% yield, but with poor α-selectivity (α:β = 3:1.).[183]

Table 3.7. α-Selective Glycosylation of Glucuronic Acid Acceptors.[a]

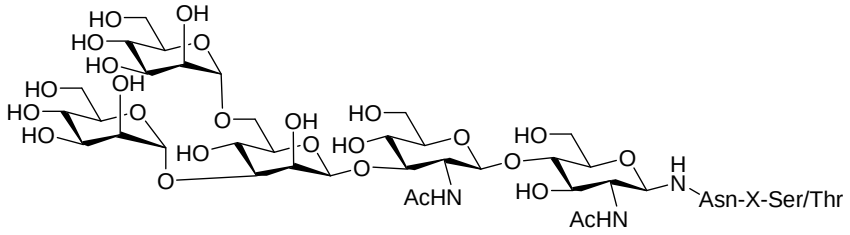


Entry	Glucuronic Acid Esters	Products		Time	Yield [b] (α:β) [c]
1	 **179**	 **183**		5 h	55% (14:1)
2	 **180**	 **184**		6 h	84% (9:1)
3	 **181**	 **185**		6 h	71% (α only)
4	 **181**		**186** X = H	5 h	68% (α only)
			187 X = F	4 h	70% (α only)
			188 X = CF_3	3 h	87% (α only)
5	 **182**		**189** X = F	5 h	76% (19:1)
			190 X = CF_3	5 h	74% (20:1)

[a] The couplings were performed with 5 mol % of Ni(4-F-PhCN)$_{4(}$OTf)$_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^{1}H NMR ratio.

These encouraging results prompted us to extend the nickel catalyzed 1,2-*cis*-2-amino glycosylation method to the stereoselective synthesis of glycopeptides. In nature, over half of biologically important proteins are glycosylated to form glycoproteins. Based on the site of peptide glycosylation, glycoproteins can be broadly divided into two major classes: *N*-linked, and *O*-linked glycoproteins.

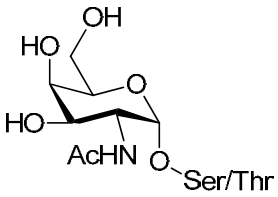
The *N*-linked glycoproteins share the common core structure **191** shown in Figure 3.5. In this structure, the amide nitrogen of the asparagine side chain in the peptide is glycosylated. The site of the glycosylation has been known to be composed of an Asn-X-Ser/Thr sequence where X can be any amino acid except proline.[187] The pentsaccharide core **191** (Figure 3.5) is composed of a disaccharide with two *N*-acetylglucosamine (GlcNAc) units and a trisaccharide with three mannose (Man) residues. The amide side chain of asparagine amino acid is β-linked to the anomeric carbon of the terminal GlcNAc unit.



191

Figure 3.5. Core Structure of *N*-linked Glycoproteins.

In the *O*-linked glycoproteins, the oligosaccharide moiety is usually linked to an oxygen atom on the side chain of either serine (Ser) or threonine (Thr) amino acid (Figure 3.6). However, tyrosine and hydroxylysine have also been observed. [188] Although the oligosaccharide portion of *O*-linked glycopeptide lacks a conserved oligosaccharide core structure, an α-GalNAc **192** (Figure 3.6) is often the first monosaccharide unit.



192

Figure 3.6. Representative Structures of *O*-linked Glycoproteins.

The oligosaccharide portions of the *O*-linked glycoproteins have been reported to play an important role in a variety of recognition events. As a result, these glycopeptides serve as biologically important targets in disease control.[189] *O*-linked glycoproteins are also a vital component in carbohydrate-based tumor associated mucin antigens used in the development of cancer vaccine therapies.[190]

Due to the importance of *O*-linked glycopeptides, and the need for efficient stereoselective synthesis of these materials, we extended our nickel procedure to the synthesis of α-GlcNAc and α-GalNAc-Serine/Threonine derivatives of the family of the glycopeptides **193-196**, which are known tumor associated mucin antigens (Figure 3.7).[126, 191] All mucins are cell surface proteins often associated with tumors in epithelial tissues.[126] Branching of the α-GalNAc-Ser/Thr core structure **192** (Figure 3.6) can occur at the C(3)-position and/or the C(6)-position of the D-galactosamine unit to give rise to a diverse array of mucin-type glycopeptides (e.g. **193-196**, Figure 3.7). These mucin-type glycopeptides carry many of the Lewis and blood group antigens, and serve as receptor ligands for L- and P-selectins.[192] As a result, these glycans are crucial mediators in normal and disease processes and have received attention in cancer vaccine therapies.[190] Procuring an adequate supply of these glycopeptides in homogenous form from natural sources is challenging. In many cases, well-defined mucin-type glycans can only be obtained from chemical approaches.

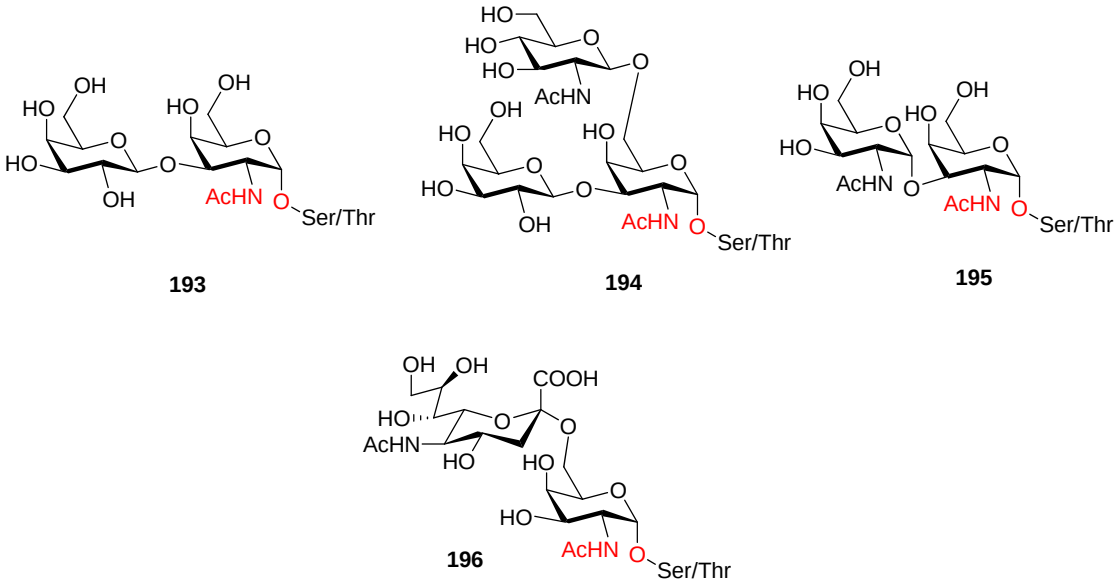
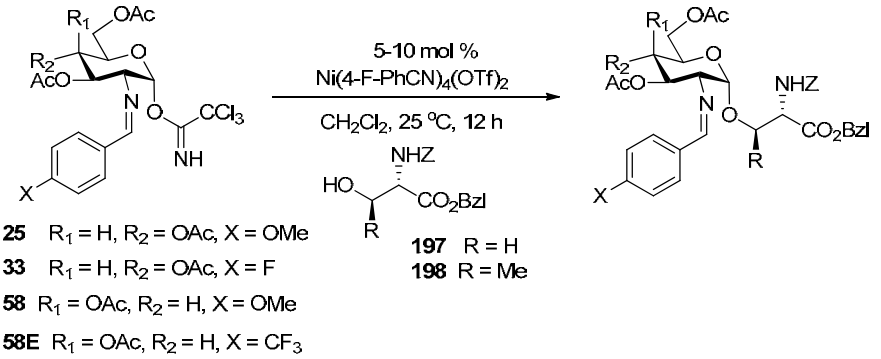
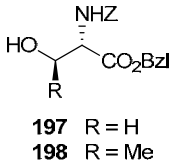
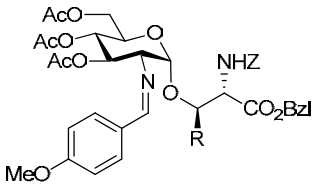
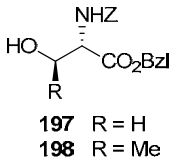
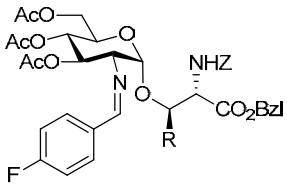
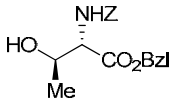
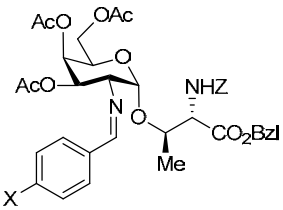


Figure 3.7. Some Carbohydrate Based Tumor-Associated Mucin Antigens.

One of the major challenges in the synthesis of mucin *O*-linked glycoproteins is to achieve high α-selectivity in the connection of the *N*-acetylgalactosamine unit to the serine (Ser) or threonine (Thr) amino acid in **192** (Figure 3.6). Even with simple monosaccharide galactosamine donors, the stereochemical outcome of the newly-formed glycosidic bond can be difficult to predict and often results in moderate α-selectivity.[193-194] For instance, coupling of threonine with C(2)-oxazolidinone thiogalactoside donor has been reported to provide glycopeptides as a 1:1 mixture of α- and β-isomers.[144] In the synthesis of mucin-related T_N and T_F *O*-linked antigens, Danishefsky and co-workers reported the coupling of threonine with C(2)-azido galactosamine donor to afford the desired glycopeptide as a 4:1 mixture of α- and β-isomers.[193] Thus, this warrants the discovery of general and efficient strategies for the stereoselective synthesis of α-GalNAc core structure **192** (Figure 3.6).

Table 3.8. α-Selective Coupling of Serine and Threonine Amino Acids.[a]



Entry	Serine/Threonine	Glycopeptides			Yield[b] (α:β)[c]
1	 **197** R = H, **198** R = Me		R = H	**199**	65% (8:1)
			R = Me	**200**	73% (10:1)
2	 **197** R = H, **198** R = Me		R = H	**201**	83% (9:1)
			R = Me	**202**	75% (14:1)
3	 **198**		X = OMe	**203**	74% (14:1)
			X = CF_3	**204**	81% (15:1)

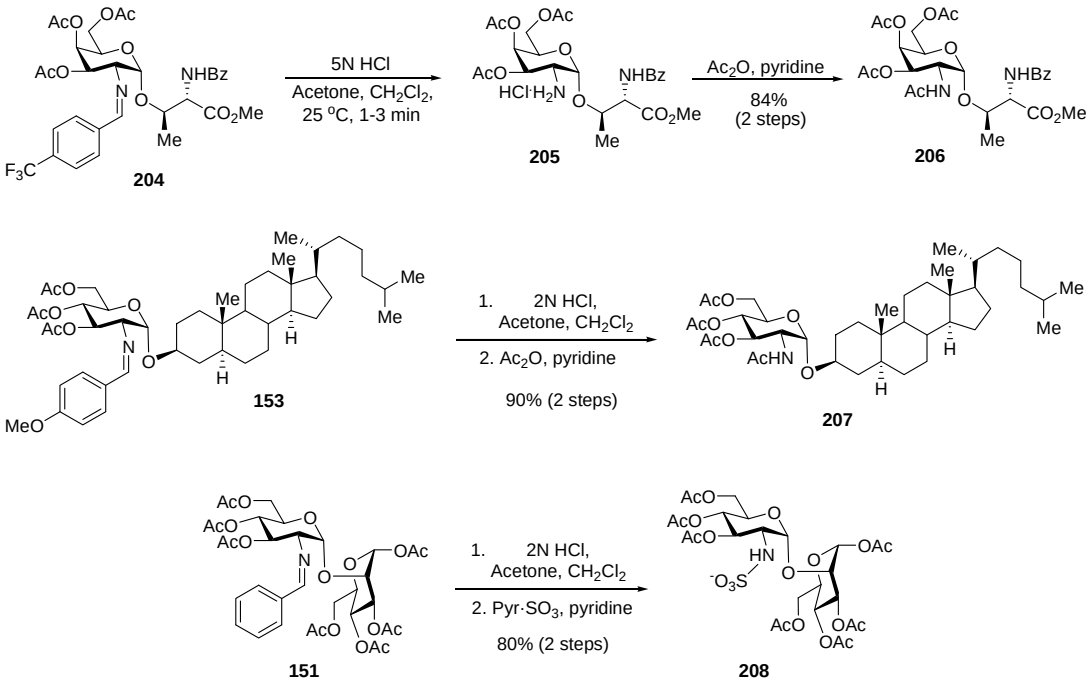
[a] The couplings were performed with 5-10 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^1H NMR ratio.

We began our study by investigating the ability of C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidates to serve as viable donors for the stereoselective synthesis of both α-GlcNAc- and α-GalNAc- Ser/Thr derivatives **199** - **204** (Table 3.8). Under our nickel conditions, coupling of serine **197** and threonine **198**

with C(2)-*N*-4-methoxybenzylidene D-glucosamine trichloroacetimidate donor **125** (entry 1) provided the corresponding glycopeptides **199** and **200**, respectively, in good yields (65% - 73%) and α-selectivity (α:β = 8:1 - 10:1). The use of an electron-withdrawing C(2)-*N*-4-fluorobenzylidene D-glucosamine donor **133** (entry 2) improved both the yields (75% - 83%) and α-selectivities (α:β = 9:1 - 14:1) of the resulting glycopeptides **201** and **202** (entry 2). Encouraged by the results obtained with D-glucosamine donors **125** and **133**, we further explored the efficacy of the nickel methods in the coupling of threonine **198** with both D-galactosamine donors **158** and **158E** (entry 3). In this case, the glycosylation reaction afforded the desired galactopeptides **203** and **204** in good yields (74% - 81%) and with excellent α-selectivities (α:β = 14:1 - 15:1). Although both donors **158** and **158E** provided the galactopeptides with comparable yield and α-selectivity, the reaction was faster with electron-withdrawing benzylidene donor **158E**. Overall, our chemistry has been found to be much more α-selective than the current state-of-the-art methods (e.g. C(2)-azido (α:β = 4:1)[193] and the C(2)-oxazolidinone (α:β = 1:1)[144] derived donors) in accessing this family of α-glycosides.

Although it will be of interest to study the biological properties of these *N*-benzylidene oliogsaccharides and glycoconjugates, it is also vital to investigate whether they could be converted to the corresponding *N*-acetyl or other functionalities. Since the current conditions[155-157] (5 N HCl) for removal of the benzylidene protecting groups would not work well with certain acid-sensitive oligosaccharides and glycoconjugates, we proceeded to explore a number of relatively mild conditions for removing the benzylidine group by screening several acids (TsOH, TfOH, 1N and 2N HCl). It was found that the optimal conditions needed to remove the benzylidene functionality were the use of 2N HCl (1.1 equiv) in acetone/CH_2Cl_2 at 25 ^oC for 5 minutes. For example, treatment of glycopeptides **204** with 2N HCl in acetone/CH_2Cl_2 at 25 ^oC for 3 minutes, followed by acetylation of the resulting amine salt intermediate **205** afforded the fully protected α-GalNAc **206** (Scheme 3.10) in 84% yield over two steps. This

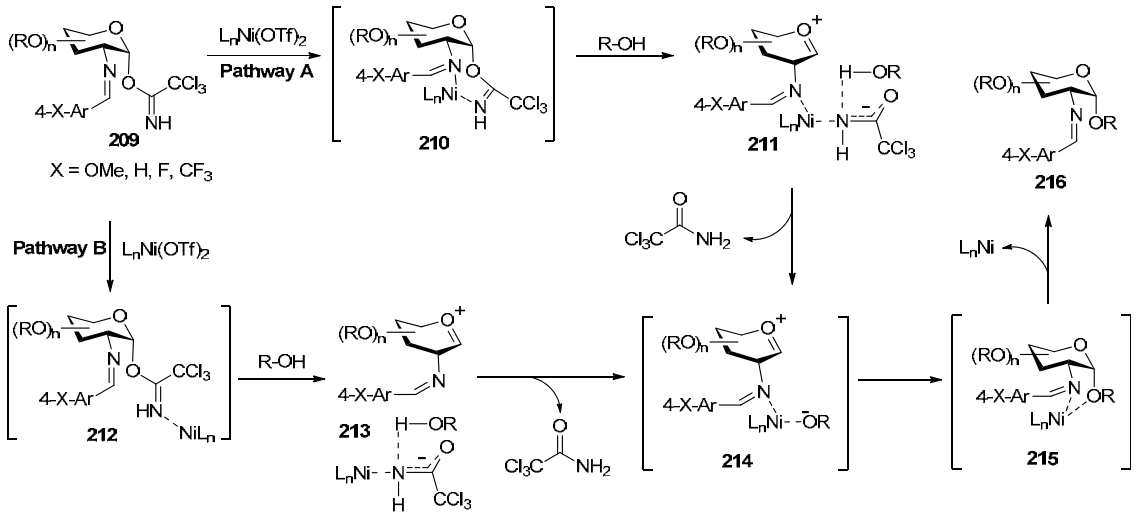
glycoconjugate **206** is the fully protected structure of T_N-tumor associated mucin antigen.[193] Similarly, removal of *N*-benzylidene functionality of **153** and **151** followed by acetylation or sulfation of the resulting amine salt intermediates, afforded the glycoconjugates **207** and **208**, respectively, in good overall yields (Scheme 3.10).



Scheme 3.10. Facile Removal of Benzylidene Functionality.

Although an exact mechanism that explains the stereochemical outcome of our nickel-catalyzed α-selective glycosylation forming 1,2-*cis*-2-amino glycosides requires further study, a working hypothesis is outlined in Scheme 3.11. In pathway A, cationic nickel reversibly coordinates to both the C(1)-trichloroacetimidate nitrogen and C(2)-benzylidene nitrogen of glycosyl donor **209** to provide the seven-membered ring complex **210**. We reasoned that hydrogen bonding between the external oxygen nucleophile and trichloroacetamide could facilitate ionization of **210** to form the complex **211**. Ligand

exchange, followed by dissociation of trichloroacetamide would lead to the formation of the corresponding ion-pair intermediate **214** (Scheme 3.11), which then recombines in a stereoelectronically favored mode to form a five-membered ring intermediate **215**. Dissociation of the cationic nickel catalyst from **215** would then provide 1,2-*cis*-2-amino glycoside **216**.

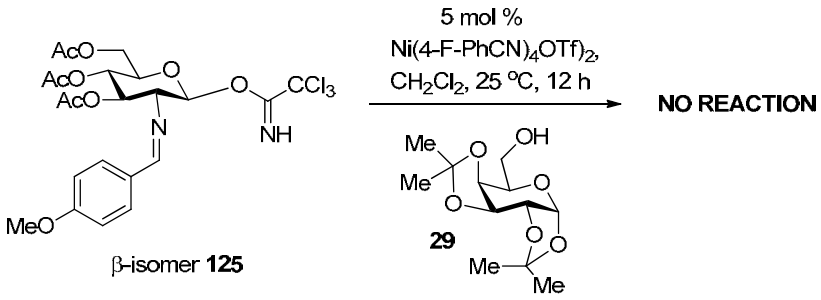


Scheme 3.11 Proposed Mechanism for Nickel-Catalyzed Selective Formation of 1,2-*Cis*-2-Amino Glycosides.

Alternatively, nickel can act as a mild Lewis acid (pathway B, Scheme 3.11). This pathway could involve reversible coordination of $L_nNi(OTf)_2$ to the C(1)-trichloro-acetimidate nitrogen of **209** to form the corresponding complex **212**. Hydrogen bonding between the external oxygen nucleophile and trichloroacetamide group would promote ionization of **212**, leading to the formation of the oxocarbenium ion intermediate **213**. Subsequent ligand exchange between the external oxygen nucleophile and trichloro-acetamide followed by coordination of $L_nNi(OTf)_2$ to the C(2)-benzylidene nitrogen would provide the ion pair intermediate **214** (Scheme 3.11), which recombines forming

the five membered ring complex **215**. Dissociation of the nickel catalyst from **215** would then lead to the desired 1,2-*cis*-2-amino glycoside **216**.

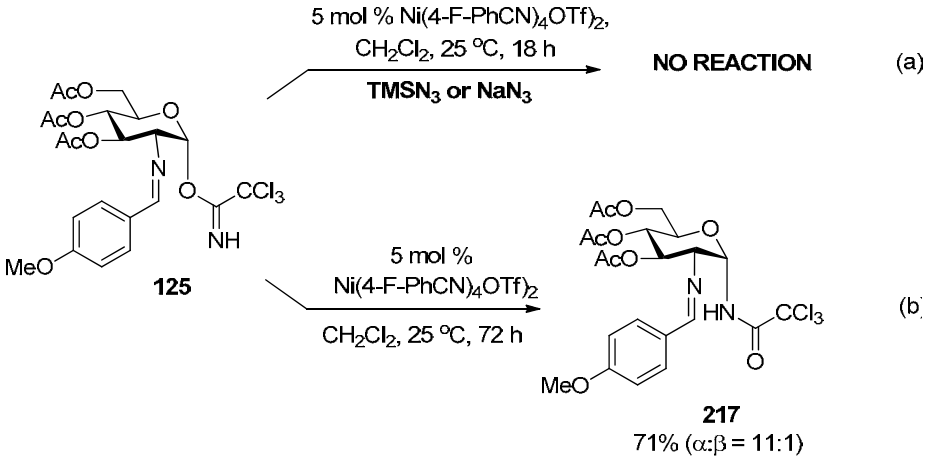
In order to probe the possible mechanism of this nickel catalyzed stereoselective glycosylation method, we first determined if the α-orientation of the trichloroacetimidate leaving group was crucial for ionization and subsequent formation of the corresponding 1,2-*cis*-2-amino glycoside product. Accordingly, coupling of galactose acceptor **29** with β-trichloroacetimidate donor **125** (Scheme 3.12) was attempted in the presence of 5 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$. The coupling reaction did not proceed even after 12 h at 25 ^oC. These results show that the α-orientation of the imidate is indeed crucial for ionization of the imidate and subsequent formation of the amino glycoside.



Scheme 3.12. Glycosylation with a β-Glycosyl Trichloroacetimidate.

As previously discussed (Scheme 3.11), hydrogen bonding between the external oxygen nucleophile and the trichloroacetamide group is proposed for facile ionization of seven-membered ring intermediate **210** (Scheme 3.11, pathway A) or Lewis acid complex **212** (Scheme 3.11, pathway B). To verify this hypothesis, the glycosylation of $TMSN_3$ or NaN_3 which lacks an acidic hydrogen was performed with the C(2)-*N*-*para*-methoxybenzylidene D-glucosamine glycosyl donor **125** (Scheme 3.13a). In this control experiment, no coupling products were observed in the reaction. A second control study was performed in the absence of an external oxygen nucleophile (Scheme 3.13b). In this

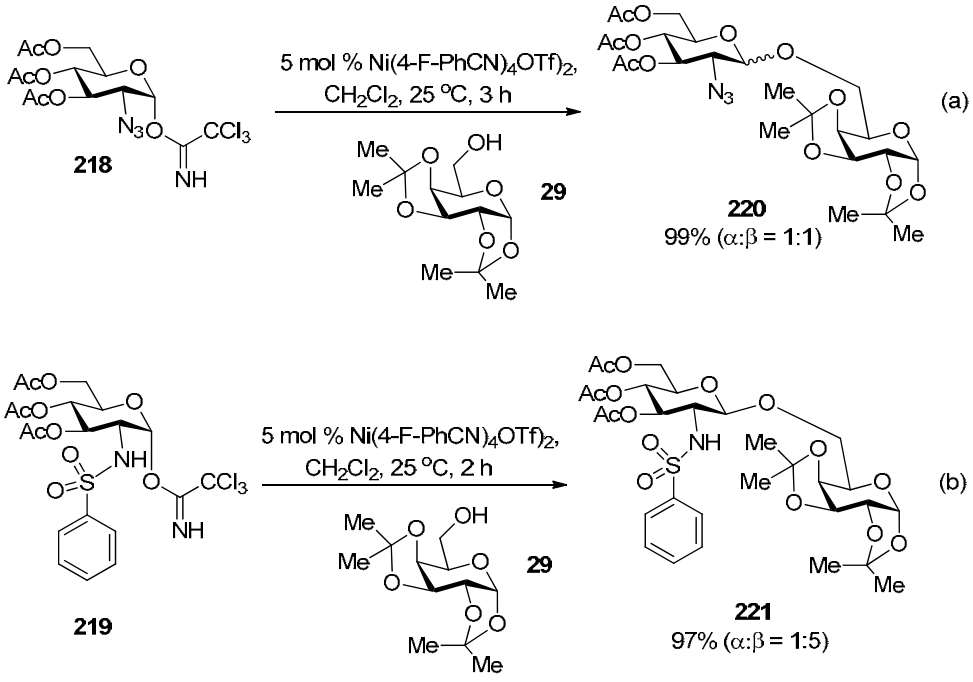
reaction, the trichloroacetamide product **217** was obtained in 71% yield. These results support the hypothesis that both the α-orientation of the trichloroacetimidate leaving group and hydrogen bonding are important factors that promote ionization of the activated glycosyl trichloroacetimidate donor.



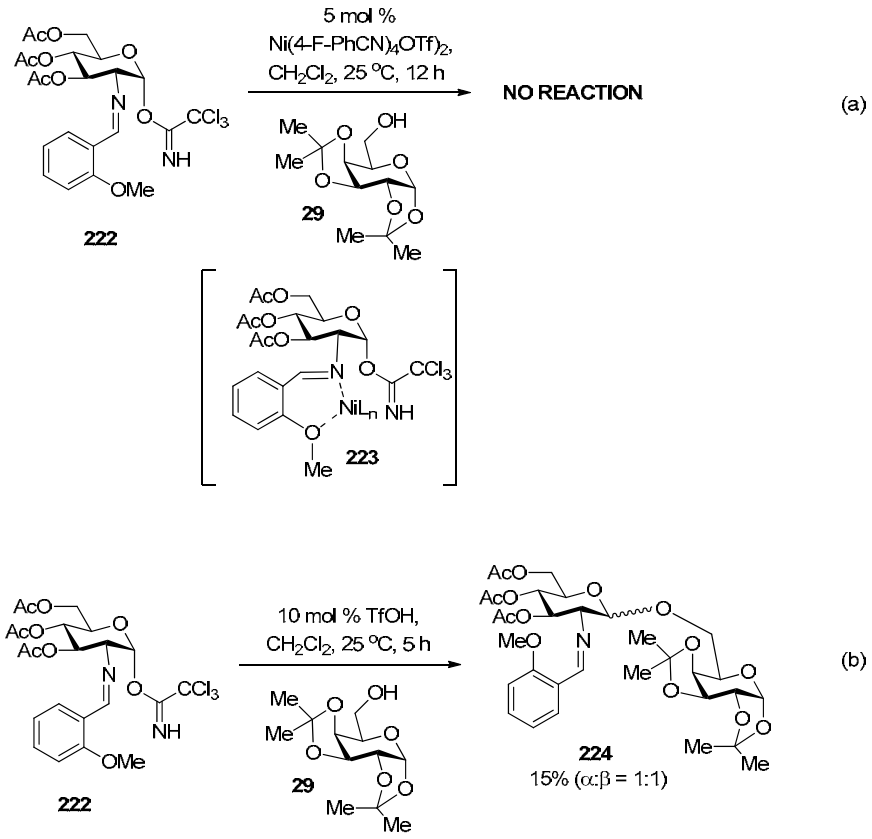
Scheme 3.13. Glycosylations with $TMSN_3$ or NaN_3 and in the Absence of an External Oxygen Nucleophile.

Next, we designed control experiments to determine if the presence of the benzylidene functionality at the C(2)-position of glycosyl trichloroacetimidate donor was necessary for the high levels of α-selectivity observed in the coupling products. The first control experiment was performed with C(2)-azido trichloroacetimidate **218** (Scheme 3.14a). This donor is the most commonly used substrate under the traditional Lewis acid conditions to form the corresponding 1,2-*cis*-2-amino glycosides. Glycosylation of the nucleophilic acceptor **29** with the azido donor **218** in the presence of 5 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ at 25 ^{o}C afforded the disaccharide **220** as a 1:1 mixture of α- and β-isomers. We also explored the use of C(2)-*N*-phenylsulfonamide trichloroacetimidate

donor **219** (Scheme 3.14b) as the electrophilic donor because phensylsulfonamide has been used as a directing group for palladium-catalyzed C-H activation reactions.[195] Upon coupling galactoside acceptor **29** with glycosyl donor **219**, the β-isomer of the disaccharide **221** (Scheme 3.14b) was isolated as the major product (α:β = 1:5) under the cationic nickel conditions. These two control experiments clearly demonstrate the critical role the C(2)-*N*-substituted benzylidene functionality plays in the cationic nickel-catalyzed α-selective glycosylation reaction.



Scheme 3.14. Glycosylation Reactions to Investigate the Crucial Role of C(2)-*N*-Substituted Benzylidene Functionality.

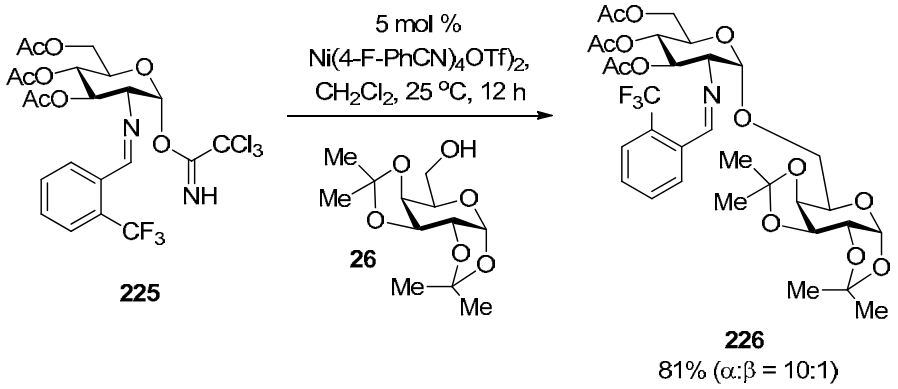


Scheme 3.15. A Control Reaction to Demonstrate the Crucial Role of Nickel Catalyst in the Stereoselective α-Glycosylation.

We continued our investigation by determining whether coordination of cationic nickel to both the C(1)-trichloroacetimidate nitrogen and C(2)-benzylidene nitrogen of the activated glycosyl donor is essential for the coupling process to occur. Accordingly, glycosylation of galactoside acceptor **29** with C(2)-*N*-*ortho*-methoxy-benzylidene D-glucosamine trichloroacetimdiate **222** was attempted under our nickel reaction conditions (Scheme 3.15a). The coupling products were not observed in this reaction, likely due to the preferential coordination of nickel to both C(2)-benzylidene nitrogen and *ortho*-methoxy functionality of **222** to form a six-membered nickel complex **223** (Scheme 3.15a). Formation of this nickel complex **223** prevents nickel from coordinating to the

C(1)-trichloroacetimidate nitrogen of glycosyl donor **222**. This same donor was subjected to glycosylation in the presence of 10 mol % of triflic acid (Scheme 3.15b). In this coupling reaction, the desired disaccharide **224** was isolated in 15% yield with poor α-selectivity (α:β = 1:1).

If the oxygen functionality at the *ortho*-position of the benzylidene group on glycosyl donor **222** shuts down the coupling process, then glycosylation of galactoside acceptor **29** with C(2)-*ortho*-trifluoromethyl-benzylidene D-glucosamine donor **225** under the nickel conditions would validate this hypothesis (Scheme 3.16). Indeed, the coupling process proceeded smoothly in the presence of 5 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ to afford the desired disaccharide **226** in 81% yield and with excellent level of α-selectivity (α:β = 10:1).



Scheme 3.16. Glycosylation with C(2)-*Ortho*-Trifluoromethyl-Benzylidene D-Glucosamine Trichloroacetimidate Donor.

3.4. Conclusion

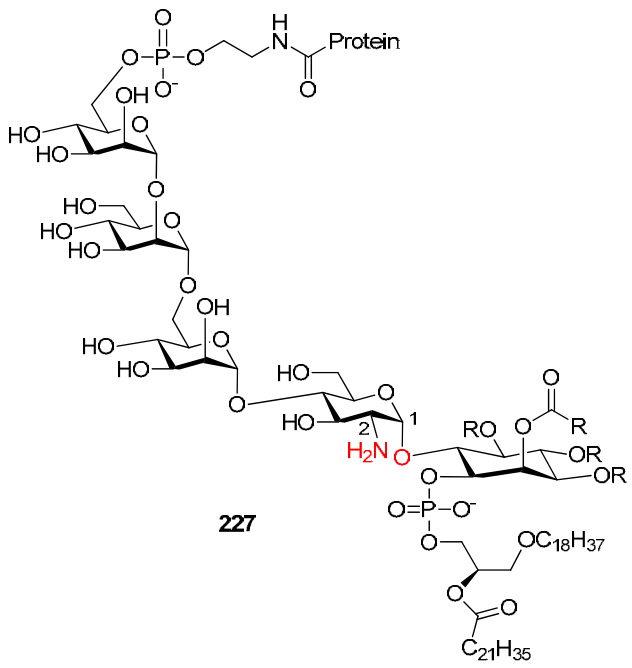
In concluding, a novel method for the stereoselective synthesis of 1,2-*cis*-2-amino glycosides *via* cationic nickel-catalyzed α-selective glycosylation with a variety of C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidate donors has been developed. These glycosyl donors are able to couple to a number of primary and hindered secondary and tertiary alcohols to provide the corresponding oliogsaccharides and glycoconjugates in good yields and with excellent α-selectivity. The current nickel method relies on the nature of the nickel-ligand complex to control the α-selectivity. The reactive sites of the nucleophiles or the nature of the protecting groups have little effect on the selectivity. Additionally, only a catalytic amount of the nickel (5-10 mol %) is required for the coupling reaction to occur at room temperature. This method has also been applied to both disaccharide donors and acceptors to provide the corresponding oligosaccharides in high yields and with excellent levels of α-selectivity. The efficiency of the nickel chemistry has been extended to the synthesis of high yielding and α-selective heparin disaccharides and α-GluNAc/GalNAc derivatives. Mechanistic studies suggest that the presence of the substituted benzylidene functionality at the C(2)-amino position of glycosyl donors is crucial for the high α-selectivity observed in the coupling products. Furthermore, it has been demonstrated that the α-orientation of the C(1)-trichloroacetimidate group as well as the presence of the external oxygen nucleophile are necessary for the facile ionization of the activated glycosyl trichloroacetimidate donors.

CHAPTER 4

NICKEL-CATALYZED STEREOSELECTIVE GLYCOSYLATION WITH C(2)-*N*-SUBSTITUTED BENZYLIDENE D-GLUCOSAMINE TRICHLOROACETIMIDATES FOR THE FORMATION OF GPI ANCHOR PSEUDODISACCHARIDES

4.1: GPI Anchors: Biological Significance

Glycosylphosphatidylinositol (GPI) anchors are a large family of glycolipids that serve to attach many eukaryotic proteins onto the outer surfaces of cell membranes.[196-198] They are known to share a highly conserved common core structure **227** as shown in Figure 4.1.[199]



227

Figure 4.1. A Representative Core Structure of GP1 Anchor.

In the GPI-linked proteins, the proteins are invariably attached to the phosphor-ethanolamine moiety at the non-reducing end of the GPI core glycan.[128, 200-201] This phosphoethanolamine moiety is linked to a trimannose-glucosamine-inositol backbone and a hydrophobic lipid layer that anchors the system to the membrane.[202] The oligosaccharide core structure within the GPI anchor family can be further modified with specific sugars, lipid unit, and phosphoethanolamine group. Proteins containing GPI anchors are known to be functionally diverse and play important roles in a wide range of biological processes, including signal transduction, prion disease pathogenesis, immune response, and the pathobiology of trypanosomal parasites.[203-204] Protozoan parasites, for example, are known to cause several devastating diseases such as malaria (*Plasmodium*), sleeping sickness (*Trypanosoma brucei*), Chagas disease (*Trypanosoma cruzi*) and leishmaniasis (*Leishmania*).[205-206] All of these parasites are known to exhibit high levels of GPI-anchored molecules on their cell surfaces, which are essential for their virulence and survival in the host tissue.[207] While treatment and prevention of such diseases still remains very unsatisfactory, intense research into the biosynthetic intermediates of these GPI anchors and their involved enzymes, with special focus on species dependent specificity, could ultimately lead to accessing potential drug targets for the treatment of some parasitic and fungal diseases.[208]

4.2: Glycosylation Methods

Due to the structural complexity of GPI anchors and their limited quantities, the relationship between the structure of GPI anchors and their biological function in mammalian cells is usually difficult to study. In an effort to define their functional importance, several total syntheses of GPI anchors have been reported.[209] One of the major challenges in the total synthesis of naturally occurring GPI anchors is the stereoselective construction of 1,2-*cis*-2-amino glycosidic bond (Figure 4.1), that

connects D-glucosamine and inositol components to form the corresponding pseudodisaccharide unit with excellent α-selectivity.[209] For instance, Fraser-Reid and co-workers reported in 1993 that glycosylation of inositol nucleophilic acceptor with C(2)-azido glycosyl bromide, in the presence of the stoichiometric amount of $AgClO_4$ as the activating reagent, provided the corresponding pseudodisaccharide as a 3:1 mixture of α- and β-isomers.[210] Although switching to *n*-Bu_4NBr as the activating reagent provided the coupling product exclusively as the α-isomer, it took 72 h for the reaction to go to completion.[210, 202] In the total synthesis of the *P. falciparum* GPI anchor, Seeberger and coworkers reported that coupling of inositol with a C(2)-azido trichloroacetimidate provided the pseudodisaccharide with a 4:1 α:β ratio.[211] In the synthesis of GPI anchor bearing unsaturated lipid chains, as reported by Guo and co-workers, the desired pseudodisaccharide intermediate was formed as a 1.2:1 mixture of α- and β-isomers.[212]

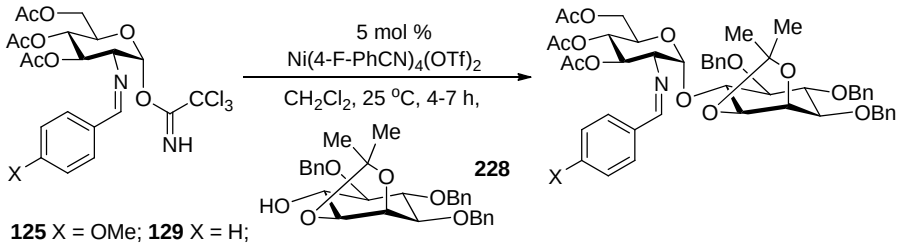
Thus, designing of a new and efficient protocol for the α-selective construction of the pseudodisaccharide unit of D-glucosamine and inositol components, as depicted in Figure 4.1, will be crucial, and will ultimately provide access to the facile synthesis of naturally occurring GPI anchors and their analogues.

4.3: Results and Discussion

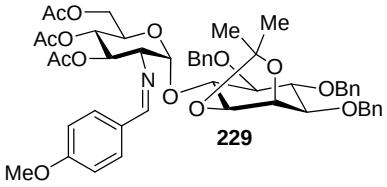
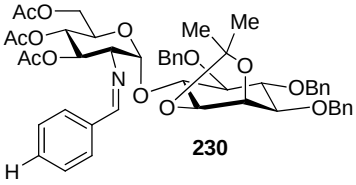
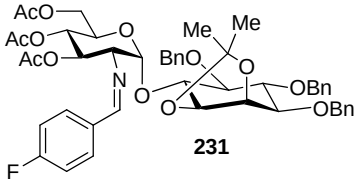
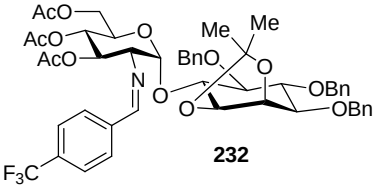
To address the challenges involved in the stereoselective construction of the pseudodisaccharide unit found within the core structure of GPI anchors, we investigated the glycosylation of inositol nucleophile **228**[199] (Table 4.1) with C(2)-*N*-substituted benzylidene D-glucosamine trichloroacetimidate donors **125**, **129**, **133**, and **136**. Due to the earlier successes we had in the glycosylation process using cationic nickel to provide 1,2-*cis*-2-amino glycosides, we proceeded to test the viability of the inositol nucleophilic acceptor **228**,[199] when it is coupled with glycosyl donors **125** and **129** under the same

nickel conditions**.** To our delight**,** the pseudodisaccharides **229** and **230** (Table 4.1, entries 1 and 2) were isolated in good yields (64% - 67%) and with exclusive α-selectivity.

Table 4.1. α-Selective Glycosylation of Inositol Acceptor **228**.[a]



125 X = OMe; **129** X = H;
133 X = F; **136** X = CF_3

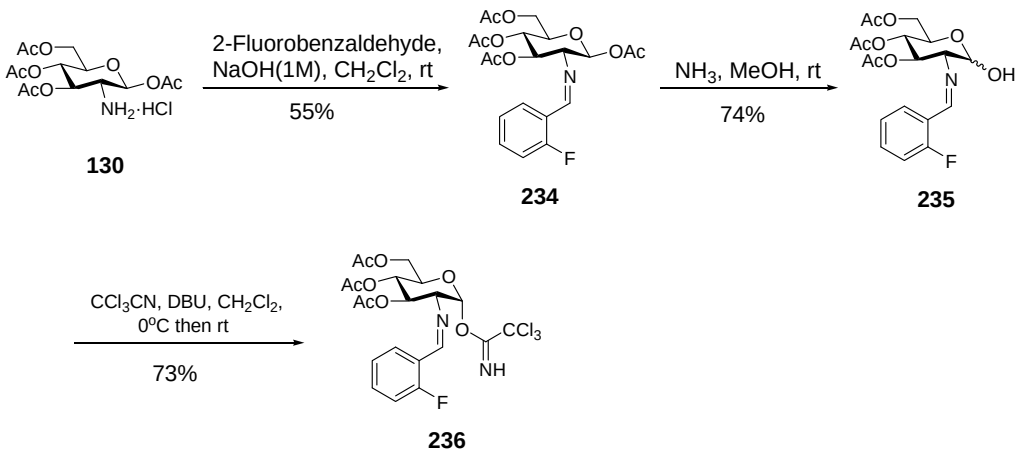
Entry	Trichloroacetimidates	Pseudodisaccharides	Time	Yield (α:β)
1	**125**	 **229**	7 h	67% (α only)
2	**129**	 **230**	6 h	64% (α only)
3	**133**	 **231**	4 h	70% (α only)
4	**136**	 **232**	4 h	62% (12:1)

[a] The couplings were performed with 5 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^1H NMR ratio.

Upon switching to the electron-witdrawing 4-substituted benzylidene glycosyl donors **133** and **136** (Table 4.1, entries 3 and 4), there was significant reduction in the reaction times affording the pseudodisaccharides **231** and **232**, respectively, in good yields (62% - 70%) and with excellent α-selectivity. Overall, the best result for this glycosylation protocol was obtained when C(2)-*N*-4-fluorobenzylidene D-glucosamine donor **133** (entry 3) was used in the reaction, and the desired pseudodisaccharide **231** was isolated in 70% yield and exclusively as the α-anomer.

These encouraging results, and the reduced reaction times observed when the glycosyl donors **133** and **136** were employed, led us to once again test the efficacy of this nickel method when a relatively more hindered and conformationally flexible inositol nucleophile **233** (Table 4.2) was used as the nucleophilic acceptor. To test the scope and limitation of the nickel catalyzed 1,2-*cis*-2-amino glycosylation reaction, the C(2)-*N*-*ortho*-fluoro/trifluoromethyl benzylidene D-glucosamine trichloroacetimidates **236** and **225** (Table 4.2) were investigated as glycosyl donors.

While synthesis of acyclic inositol acceptor **233** was prepared according to literature procedure,[199] preparation of the glycosyl donor **236** (Scheme 4.1) commenced with the amine hydrochloride **130** as the starting material. Condensation of glucosamine hydrochloride **130** with 2-fluorobenzaldehyde afforded the benzylidene intermediate **234** in 55% yield. Selective C(1)-*O*-deacetylation using a solution of ammonia in methanol provided the desired hemiacetal intermediate **235** in 74% yield (Scheme 4.1). This hemiacetal was subsequently converted to the corresponding trichloroacetimidate **236** upon treatment with Cl_3C-CN and DBU. A similar reaction route was also used in the synthesis of the glycosyl donor **225** (Table 4.2).

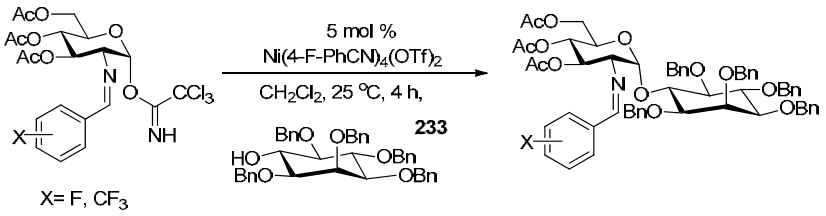


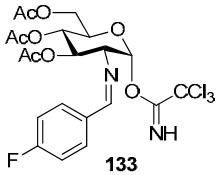
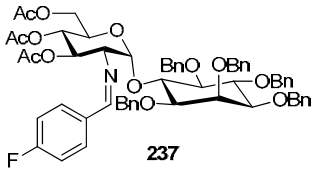
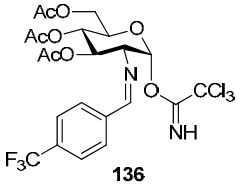
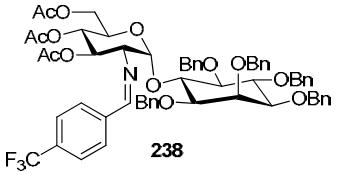
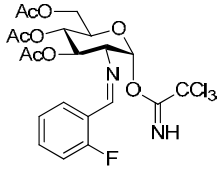
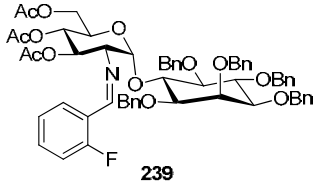
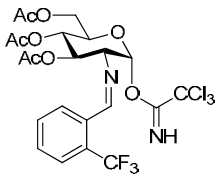
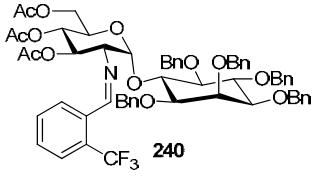
Scheme 4.1. Synthesis of C(2)-*Ortho*-Fluorobenzylidene Glycosyl Donor.

With the glycosyl donors **236** and **225** in hand, the application of the nickel catalyzed 1,2-*cis*-2-amino glycosylation method was investigated in the coupling of the inositol nucleophile **233**[199] (Table 4.2). We first examined the glycosylation of inositol **233** with *N-para*-substituted-benzylidine glycosyl trichloroacetimidate donors **133** and **136** (Table 4.2) to establish the efficacy of the nickel method. The coupling reaction proceeded smoothly under standard nickel conditions to provide the corresponding pseudodisaccharides **237** and **238** (entries 1 and 2) in good yields (68% - 72%) and with excellent α-selectivity (α:β=11:1). The use of this conformationally flexible inositol acceptor **233** resulted in comparable isolated yields and anomeric selectivity of the desired pseudodisaccharides **237** and **238** (Table 4.2, entries 1 and 2) when compared to those obtained from the conformationally rigid inositol nucleophile **228** to afford the pseudodisaccharides **231** and **232** (Table 4.1, entries 3 and 4). Encouraged by these results, we decided to further examine the versatility of this nickel protocol with the C(2)-*N-ortho*-subsituted benzylidine trichloroacetimidates **236** and **225** (Table 4.2, entries 3 and 4) as glycosyl donors in the glycosylation reaction. To our delight, the coupling process proceeded to completion within 4 h to provide the peudodisaccharides **239** and **240**, respectively, in good yields (66% - 80%) and with excellent α-selectivity (α:β =

15:1 – 16:1). To reiterate, this nickel protocol is α-selective and allows for the facile contruction of the 1,2-*cis* pseudodisaccharide units of the GPI anchor.

Table 4.2. α-Selective Glycosylation with a Highly Hindered Inositol Acceptor.[a]



Entry	Trichloroacetimidates	Pseudodisaccharides	Yield (α:β)
1	 **133**	 **237**	68% (11:1)
2	 **136**	 **238**	72% (11:1)
3	 **236**	 **239**	66% (16:1)
4	 **225**	 **240**	80% (15:1)

[a] The couplings were performed with 5 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^1H NMR ratio.

4.4: Conclusion

One of the major challenges in the synthesis of naturally occurring GPI anchors is the stereoselective contruction of the pseudodisaccharide unit of D-glucosamine and inositol components with high α-selectivity. We have demonstrated the efficacy of the nickel catalyzed 1,2-*cis*-2-amino glycosylaiton protocol at constructing the corresponding pseudodisaccharides with excellent α-selectivity, a challenge that had yet to be overcome by previous methods. Although the excellent results obtained using this nickel protocol is preliminary, we anticipate that this breakthrough will ultimately provide access to the facile syntheis of a variety of GPI anchors and their analogues. Overall, the nickel protocol is α-selective and requires only 5 mol % of the catalyst loading. In addition, the glycosylation reaction proceeds at room temperature, and are applicable to a number of both cyclic and acyclic inositol acceptors as well as substituted benzylidene glucosamine trichloroacetimidates donors.

CHAPTER 5

SUMMARY AND FUTURE DIRECTIONS

In our quest to build complex oligosaccharides and glycoconjugates from simple monomers, the single key step is the stereoselective formation of glycosidic linkages. While the stereoslective synthesis of β-*O*-glycosides may first appear to be a simple task by employing a traditional C(2)-ester functionality on a glycosyl donor to direct β-selectivity, several limitations associated with the use of such glycosyl donors in glycosylation reactions have to be addressed. First, the reactivity of glycosyl donors incorporating a C(2)-directing groups is significantly reduced within many glycosylation procedures. As a result, prolong glycosylation times are usually observed. Second, the coupling protocols incorporating a C(2)-ester directing group has been known to also suffer from the competitive formation of ortho esters, thereby reducing their overall utility and the isolated yield of the β-glycoside. Third, under basic conditions, C(2)-directing groups such as the acyl group has the propensity to migrate to the C(1)-position of glysosyl donors as well as the reactive sites of the glycosyl acceptors, and thereby reducing the synthetic utility of the glycosylation methods that utilizes those donors. Alternatively, while the use of ether protecting groups at the C(2)-position of glycosyl donors can overcome the various limitations outlined above, the use of such glycosyl donors usually results in the formation of mixtures of α- and β- glycosidic linkages due to the absence of C(2)-neighboring participation. Additionally, under traditional Schmidt's glycosylation methods, the glycosyl trichloroacetimidate donors are generally activated by strong and moisture sensitive Lewis acids. Thus, these Lewis acids operate under water-free and low temperature conditions, especially if such glycosyl donors and acceptors are incorporated with acid labile protecting groups. Furthermore, stoichiometric amount of Lewis acids are often required in the reaction, since these Lewis acids are quite oxophilic.

In view of these limitations under the existing systems, the work disclosed herein has summarized the successful development of a new and efficient methodology for the stereoselective contruction of β-glycosidic bonds using cationic palladium catalyst and in the absence of the traditional C(2)-neighboring group participation. This new transition metal catalyzed-β-selective glycosylation method, with glycosyl trichloroacetimidate donors containing a C(2)-nonparticipatory ether protecting group, overcomes those limitations associated with the use of glycosyl donors incorporated with C(2)-ester directing group, as well as the use of the traditional Lewis acids as activating reagents. Although the cationic palladium catalyst acts as a mild Lewis acid, it is air- and moisture-stable. Because the palladium catalyst is not as oxophilic as the traditional Lewis acids, only a catalytic amount has been utilized to activate glycosyl trichloroacetimidates. This new palladium-catalyzed glycosylation protocol is applicable to a wide variety of glucose donors incorporating benzyl, allyl, *p*-methoxybenzyl ether protecting groups at the C(2) position, as well as non-glucose tribenzylated xylose and quinovose donors to provide the corresponding oligosaccharides in high yields and with good to excellent β-selectivity. Furthermore, the new transition metal method is highly β-selective and proceeds under low temperature with low catalyst loading. Mechanistic studies suggest that the major pathway in operation is likely a seven-membered ring intermediate, where the cationic palladium complex coordinates to both the C(1)-imidate nitrogen and the C(2)-oxygen of the glycosyl donor. Formation of this seven-membered ring intermediate directs the formation of β-glycosides.

We hope to apply our recently developed method of cationic palladium(II)-catalyzed stereoselective glycosylation in the absence of C(2)-neighboring participation to construct all of the β-glycosidic bonds found within the tetrasaccharide component of the resin glycoside antibiotic orizabin family.[120] Orizabins are members of the resin glycoside family present in the roots of the Mexican Scammony, which has been used to treat a variety of diseases. When tested against two effluxing strains (SA-1199B and XU-

212), one methicillin-resistant strain (EMRSA-15) and *S. aureus* strain ATCC 25933, all of the tetrasaccharides in the orizabin series exhibited inhibitory activity with MIC values of 4-64 μg/mL. Furthermore, when tested in the presence of 2 μg/mL of norfloxacin (an antibacterial agent), orizabins at 25 μg/ml reverse norfloxacin resistance 4-fold for SA-1199B, and at 1 μg/ml completely inhibit SA-1199B growth, indicating remarkable synergistic effects.[120] These results demonstrate the potential that these orizabins have with regard to treatment of *S. aureus*. The spread of both hospital and community-acquired bacterially resistant pathogens continues to increase each year.[214] One such pathogen, methicillin-resistant *Staphylococcus aureus* (MRSA), has been successfully treated under last-resort scenarios with vancomycin. However, this method has become ineffective with the advent of MRSA strains that are resistant to vancomycin.[215] The ever-increasing threat of vancomycin resistant MRSA strains represents a significant health concern. MRSA is found worldwide, and in the US alone is estimated to be responsible for approximately 19,000 deaths per year; more than even the AIDS virus.[216] These figures could potentially pale in comparison to a situation in which vancomycin resistant MRSA becomes dominant and the available options for treatment are not expanded. Thus, the need for a new class of compounds that can effectively treat MRSA and other multi-drug resistant strains of *Staphylococcus aureus* is paramount.

In the synthesis of orizabin series, if the traditional ester protecting groups are employed at the C(2)-position of glycosyl donors to control β-selectivity, they will be exchanged with other protecting groups prior to the final stage of deprotection, due to the presence of other ester side chains within orizabins. Therefore, it is necessary to select the differentiated oligosaccharide protecting groups that can be removed without disrupting the sensitive ester functionality of the side chains. Our cationic palladium-catalyzed β-selective glycosylation with the ether protecting group at the C(2)-position of glycosyl trichloroacetimidate donors will streamline the need for exchange of the acetyl group

with other protecting group prior to the introduction of the side chains incorporated with the base-labile ester bonds.

The 1,2-*cis*-2-amino glycosides are also important structural units found within a variety of biologically important oligosaccharides and glycoconjugates such as heparin polysaccharides, kenanmycin B as well as tumor associated mucin antigens. While this basic structural unit is prevalent in many biologically important aminoglycosides, their stereoselective synthesis is considered to be quite challenging, because it requires a non-participatory group at the C(2)-amino functionality on the glycosyl donor to direct α-selectivity. Although remarkable advances has been made in the synthesis of 1,2-*cis*-2-aminosugars, the limitations of the current reported methods include limited substrate scope, low yields, long reaction times as well as the formation of mixtures of α- and β-isomers. Hence, the stereoselective synthesis of 1,2-*cis*-2-amino glycosides continues to be a challenge.

In view of these limitations, we successfully developed a new method for the streoselective synthesis of 1,2-*cis*-2-amino glycosides, using cationic nickel catalyst with a wide variety of C(2)-*N*-substituted benzylidene glycosyl trichloroacetimidates. These glycosyl donors were able to couple a number of nucleophilic acceptors to provide the desired disaccharides and glycoconjugates in high yields and excellent α-selectivity. In addition, only catalytic amounts of the cationic nickel (5 - 10 mol %) was required to drive the glycosylation reaction to completion at room temperature. The reactive sites of the nucleophilic acceptors as well as the nature of protecting groups were found to have little effect on the α-selectivity at the newly-formed glycosidic bond. This novel nickel method was also extended to the synthesis of a number of oligosaccharides in high yields and with excellent α-selectivities, using disaccharide donors and acceptors. The new

transition metal-catalyzed glycosylation protocol was also successfully applied in the synthesis of the α-(1→4)-linkages between D-glucosamine and D-glucuronic acid esters as found in heparin disaccharides. Synthesis of this glycosidic linkage will ultimately provide access to the efficient preparation of well-defined heparin oligosaccharides, which are otherwise challenging to synthesize. The efficacy of the nickel protocol was further extended to the synthesis of the protected structures of T_N mucin antigens, as well as the α-(1→6)-linkages of D-glucosamine unit and the inositol component found in the pseudodisaccharide unit of GPI anchors in high yields and with excellent α-selectivity. Synthesis of this pseudodisaccharide unit of GPI anchors will ultimately provide access for the facile preparation of naturally occurring GPI anchors and their analogues, which have been known to play an important role in signal transduction, immune response and pathobiology of parasites.

In the nickel catalyzed 1,2-*cis*-2-amino glycosylation method, mechanistic studies suggest that the α-orientation of the C(1)-trichloroacetimidate group as well as the C(2)-substituted benzylideneamino functionality on the C(2)-*N*-subsituted benzylidene glycosyl donor, plays a crucial role in the high α-selectivity observed in the coupling products. To further gain insight in the mechanism of the nickel catalyzed 1,2-*cis*-2-amino glycosylation reaction with C(2)-*N*-substituted benzylidene glycosyl imidate donors, we will look at the nature of counterions on nickel catalysts because it is known that a more weakly coordinating counterion can further increase catalyst activity.[108-109] Thus, the effect of other counterions (BF_4, PF_6, and SbF_6) on the reactivity and selectivity of the glycosylation process will be explored. We hypothesize that use of these counterions on nickel will accelerate the reaction because they are more weakly

coordinating than triflate (OTf).[48] We will also study the effect of the ligand because initial results suggest that electron-withdrawing ligand accelerates the reaction rate and increases the α-selectivity of the coupling product. Furthemore, because we have recently established that in the absence of the external oxygen nucleophile, it took 72 h for glycosyl trichloroacetimidate donor to undergo rearrangement into the corresponding trichloroacetamide (Scheme 3.13), it may be possible to isolate the seven-membered ring complex proposed in Scheme 3.11. In designing seven-membered ring complexes, we will incorporate ligands that would both stabilize nickel(II) species and promote coordination of nickel to both C(2)-benzylidene nitrogen and C(1)-imidate nitrogen of glycosyl donor. In this regard, a rigid ligand (e.g. bipyridine) ligand will be sought because it coordinates tightly to nickel, and therfore, undesired ligand exchange will be reduced.

In view of the remarkable breakthrough made in using the cationic nickel protocol to access 1,2-*cis*-2-aminosugars, which is applicable to a wide variety of nucleophilic acceptors and electrophilic donors at room temperature, future direction of this research endeavor will be to extend this new glycosylation protocol in the synthesis of well-defined heparin oligosaccharides with low or no binding affinity to PF4 (platelet-factor-4) while the binding affinity to AT (antithrombin) and anticoagulant activity remains unchanged. Heparin is used to treat and prevent arterial and venous thrombosis, the two major causes of heart attack, strokes and cardiovascular-associated death.[217] Heparin binds to a variety of different proteins, including antithrombin (AT) and platelet-factor-4 (PF4).[174] The desired anticoagulant function results from heparin-antithrombin interaction, while the serious complication heparin-induced thrombocytopenia (HIT)

associated life-threatening thrombosis, is caused by antibodies against heparin-platelet-factor-4 (PF4) complexes.[172-174,218] This side effect develops in 20-50 percent of patients [219] and is very difficult to eliminate because the methods used to obtained heparin are not as refined as they are for many other drugs.

Heparin polysaccharide is harvested in its unfractionated form from porcine mucosa membrane;[220] unfractionated heparin has significant anticoagulant activity, but has a high prevalence of HIT as well as potential for contamination.[221] In 2008, 113 deaths were attributed to contaminated heparin that contains over-sulfated chondroitin sulfates that caused adverse effects in patients.[222] Unfractionated heparin can be further chemically and enzymatically depolymerized to low molecular weight heparins (LMWH)[223] which has less risk of HIT,[218a] but can lose much of the anticoagulant activity.[224] The medical research community has been attempting to remedy the HIT side effect, while maintaining the anticoagulant function, by deriving a method to synthetically produce heparin in a strictly regulated fashion. The current achievement in this area is a drug marketed as Arixtra, in use since 2002, which has reduced the risk of HIT. However, Arixtra is extremely time consuming and expensive to produce. It is the result of more than sixty low-yielding chemical steps and is highly target-oriented.[123, 225]

Studies show that binding of PF4 to heparin occurs by non-specific interactions between the cationic amino acids of PF4 and the anionic sulfate groups of heparin sequence.[226, 227] The highly sulfated iduronic acid-glucosamine region is responsible for binding to PF4, which leads to HIT.[227,228] We will take advantage of this fact in our synthetic attempts, by altering these sulfate patterns to reduce the PF4 affinity.

CHAPTER 6

EXPERIMENTAL SECTIONS

General Experimental Conditions. All reactions in non-aqueous solvents were performed in oven-dried Schlenk flasks fitted with glass stoppers under a positive pressure of argon and with magnetic stirring. Organic solutions were concentrated by rotary evaporation below 40 ^{o}C at 25 torr. Analytical thin-layer chromatography (TLC) was routinely used to monitor the progress of the reactions using pre-coated glass plates with 230-400 mesh silica gel impregnated with a fluorescent indicator (250 nm). Visualization was achieved using UV light, iodine, or ceric ammonium molybdate. Flash chromatography was performed using 230-400 mesh silica gel. Dichloromethane, and $BF_3.OEt_2$ were distilled from calcium hydride under argon atmosphere at 760 torr. All other chemicals were obtained from commercial vendors and used without further purification.

Instrumentation. All proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on 300, 400 and 500 MHz spectrometers. All carbon (^{13}C) nuclear magnetic resonance spectra were recorded on 75, 100 and 125 MHz NMR spectrometers. Chemical shifts were expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.26 ppm, δ 77.2 ppm; C_6D_6: δ 7.16 ppm, δ 128.4 ppm). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet), integration, and coupling constant in hertz (Hz). Infrared (IR) spectra were reported in cm^{-1}. High resolution (ESI) mass spectrometry was performed to identify the purity of the compounds.

2,3,4,6-*Tetra*-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2,3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (60). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **20α** (102 mg, 0.150 mmol, 1.0 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (51 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to –78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^oC for 1 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, hexane/ethyl acetate) to give the desired disaccharide **60** (103 mg, 87%) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.44 - 7.14 (m, 20H), 5.58 (d, *J* = 5.0 Hz, 1H), 5.07 (d, *J* = 11 Hz, 1H), 4.97 (d, *J* = 11 Hz, 1H), 4.82 (d, *J* = 11 Hz, 1H), 4.79 (d, *J* = 11 Hz, 1H), 4.73 (d, *J* = 11 Hz, 1H), 4.65 - 4.58 (m, 2H), 4.55 (s, 1H), 4.51 (d, *J* = 11 Hz, 1H), 4.47 (d, *J* = 7.5 Hz, 1H), 4.33 - 4.31 (m, 1H), 4.25 (d, *J* = 8.0 Hz, 1H), 4.17 (dd, *J* = 11, 3.5 Hz, 1H), 4.1 (m, 1H), 3.83 - 3.68 (m,3H), 3.67 - 3.58 (m, 2H), 3.49 - 3.45 (m, 2H), 1.51 (s, 3H), 1.46 (s, 3H), 1.32 (2s, 6H). ^1H NMR data matches with the literature report. ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.7, 138.2, 128.7, 128.4, 128.2, 128.0, 127.9, 127.7, 127.6, 127.55, 127.5, 109.4, 108.6, 104.4, 96.4, 84.6, 81.6, 77.7, 75.7, 75.0, 74.8, 74.4, 73.5, 71.5,70.8, 70.5, 69.7, 68.8, 67.4, 26.1, 26.0, 25.1, 24.5. ^{13}C NMR data matches with the literature report. $J(^{13}CH)$ = 156 Hz (104.4 ppm); 179 Hz (96.4 ppm). IR (film cm^{-1}) 2902, 1454, 1381, 1255, 1211.

Methyl-2,3,4,6-*tetra*-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside (66). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **20α** (102 mg, 0.150 mmol, 1.0 equiv), Methyl 2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside **61** (99 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to –78

^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at - 78 ^{o}C for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/1, hexane/ethyl acetate) to give the desired disaccharide **66** (128 mg, 83%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.96 (d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* = 7.0 Hz, 2H), 7.84 (d, *J* = 7.0 Hz, 2H), 7.51 - 7.13 (m, 29H), 6.16 (t, *J* = 10 Hz, 1H), 5.48 (t, *J* = 10 Hz, 1H), 5.25 (dd, *J* = 10, 3.5 Hz, 1H), 5.20 (d, *J* = 2.5 Hz, 1H), 5.05 (d, *J* = 11 Hz, 1H), 4.90 (d, *J* = 11 Hz, 1H),4.82 - 4.74 (m, 2H), 4.68 (d, *J* = 10 Hz, 1H), 4.53 - 4.35 (m, 5H), 4.12 (d, *J* = 10 Hz, 1H), 3.80 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.64 - 3.57 (m, 4H), 3.49 - 3.40 (m, 2H), 3.37 (s, 3H). 1H NMR matches withthe literature report. ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 165.9, 165.8, 165.5, 138.6, 138.5, 138.1, 138.0, 133.4, 133.3, 133.1, 130.0, 129.9, 129.7, 129.2, 129.1, 128.9, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 104.0, 96.8, 84.5, 82.3, 81.7, 77.7, 75.7, 75.0, 74.9, 74.8,73.4, 72.1, 70.5, 69.9, 69.0, 68.8, 68.6, 55.5. ^{13}C NMR matches with the literature report. *J*(^{13}CH) = 155 Hz (104.0 ppm); 173 Hz (96.8 ppm). IR (film, cm^{-1}) 2916, 1730.

1-*O*-Dihydrocholesterolyl-2,3,4,6-*tetra*-*O*-benzyl-β-D-glucopyranoside (67). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **20α** (102 mg, 0.150 mmol, 1.0 equiv), 3β-Cholestanol **62** (76 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 40 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at - 40 ^{o}C for 1 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (9/1, hexane/ethyl acetate) to give the desired glycoconjugate **67** (123 mg, 85%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.35-7.15 (m, 20H),

4.96 (d, *J* = 11 Hz, 1H), 4.91 (d, *J* = 11 Hz, 1H), 4.81 (d, *J* = 11 Hz, 1H), 4.77 (d, *J* = 11 Hz, 1H), 4.71 (d, *J* = 11 Hz, 1H), 4.61 - 4.51 (m,3H), 4.51 (d, *J* = 8.0 Hz, 1H), 3.74 (d, *J* = 11 Hz, 1H), 3.65 - 3.60 (m, 3H), 3.52 (t, *J* = 9.0 Hz,1H), 3.46 - 3.40 (m, 2H), 1.98 - 0.58 (m, 47H). ^{1}H NMR matches with the literature report. ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.7, 138.6, 138.3, 138.2, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 101.9, 84.9, 82.4, 79.1, 78.1, 75.7, 75.0, 74.8,73.4, 69.3, 56.5, 56.3, 54.4, 44.8, 42.6, 40.1, 39.5, 37.1, 36.2, 35.8, 35.6, 35.5, 34.8, 32.1, 29.7, 28.8, 28.3, 28.0, 24.2, 23.8, 22.8, 22.6, 21.2, 18.7, 12.3, 12.1. ^{13}C NMR matches with the literature report. IR (film, cm^{-1}) 2931, 2866, 1453, 1360.

Disaccharide (68). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **20α** (102 mg, 0.150 mmol, 1.0 equiv), glucal nucleophile **64** (44 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^{o}C for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (5/1, hexane/ethyl acetate) to give the desired disaccharide **68** (85 mg, 77%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.35 – 7.24 (m, 18H), 7.18 (d, *J* = 6.5 Hz, 2H), 6.32 (d, *J* = 6.0 Hz, IH), 4.95 – 4.91 (m, 2H), 4.82 – 4.80 (m, 3H), 4.75 (d, *J* = 11 Hz, 1H), 4.65 – 4.62 (m, 2H), 4.58 – 4.56 (m, 2H), 4.52 (d, *J* = 7.5 Hz, 1H), 4.08 (t, *J* = 9.5 Hz, 1H), 3.95 – 3.92 (m, 1H), 3.85(t, *J* = 11 Hz, 1H), 3.77 – 3.74 (m, 3H), 3.70 – 3.63 (m, 2H), 3.47 – 3.44 (m, 2H), 2.03 – 1.26 (m, 10H). ^{13}C NMR ($CDCl_3$, 75MHz) δ (ppm) 144.7, 128.4, 128.1, 127.9, 127.7, 127.6, 101.7, 101.5, 99.8, 84.9, 82.6, 77.8, 75.6, 75.3, 75.1, 75.0, 73.6, 70.7, 70.0, 68.8, 60.9, 37.9, 27.6, 25.6, 22.8, 22.4. IR (film, cm^{-1}) 3089, 3063, 3032, 2935, 2863, 1639, 1499,

1454, 1363, 1235, 1076. $J(^{13}CH)$ = 158 Hz (101 ppm). HRMS (ESI): calc. for $C_{46}H_{52}O_9Na$ (M+Na) 771.35035; found: 771.34910.

1-*O*-Adamantanolyl-2,3,4,6-*tetra*-*O*-benzyl-β-D-glucopyranoside (69). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **20α** (102 mg, 0.150 mmol, 1.0 equiv), 1-adamantanol **65** (30 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was then added. The reaction mixture was stirred at – 78 ^oC for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (9/1, hexane/ethyl acetate) to give the desired glycoconjugate **69** (81 mg, 80%) as white solids. ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 7.30 –7.17 (m, 20H), 4.99 (d, *J* = 11 Hz, 1H), 4.89 (d, *J* = 11 Hz, 1H), 4.82 – 4.77 (m, 2H), 4.73 – 4.66 (m, 2H), 4.60 – 4.45 (m, 2H), 4.45 (m, 1H), 3.71 (d, *J* = 10 Hz, 1H), 3.65 – 3.60 (m, 2H), 3.52 – 3.38 (m, 3H), 2.13 - 1.52 (m, 16H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.7, 128.4, 128.3, 128.2, 129.0, 127.9, 127.7, 127.6, 127.5, 96.3, 85.2, 82.4, 78.3, 75.7, 75.3, 74.9, 74.6, 73.4, 69.9, 42.8, 42.5, 36.3, 30.8. IR (film, cm^{-1}) 3088, 3065, 2909, 2856, 1495, 1457, 1358, 1305, 1210, 1074, 906. $J(^{13}CH)$ = 160 Hz, (101.5 ppm).

2-*O*-Allyl-3,4,6-*tri*-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2,3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (71). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-*O*-Allyl-3,4,6-*tri*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **70** (95 mg, 0.150 mmol, 1.0 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (51 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2

mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^oC for 2h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, hexane/ethyl acetate) to give the desired disaccharide **71** (111 mg, 99%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.35 – 7.24 (m, 13H), 7.13 (d, *J* = 5.5 Hz, 2H), 5.99 – 5.86 (m, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 5.32 (s, 1H), 5.29 (d, *J* = 4.5 Hz, 1H), 5.14 (d, *J* = 10 Hz, 1H), 4.95(d, *J* = 11 Hz, 1H), 4.80 (d, *J* = 11 Hz, 1H), 4.76 (d, *J* = 11 Hz, 1H), 4.63 – 4.57 (m, 2H), 4.50 (t, *J* = 11 Hz, 3H), 4.37 (d, *J* = 8.0 Hz, 1H), 4.30 – 4.29 (m, 1H), 4.23 (d, *J* = 9.5 Hz, 1H), 4.20 – 4.18 (m, 1H), 4.11 (dd, *J* = 10.5, 3 Hz, 1H), 4.02 – 4.01 (m, 1H), 3.71 – 3.66 (m, 3H), 3.61 – 3.50(m, 2H), 3.41 (m, 1H), 3.36 – 3.32 (m, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 1.31 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.7, 138.2, 135.4, 128.4, 127.9, 127.8, 127.7, 127.6, 117.1, 109.4, 108.6, 104.3, 96.3, 84.5, 81.5, 77.6, 75.7, 75.0, 74.7, 73.5, 73.4, 71.4, 70.7, 70.5, 69.7,68.6, 67.4, 26.0, 25.0, 24.4. IR (film, cm^{-1}) 3063, 3033, 2987, 2935, 2904, 1733, 1601, 1495, 1457,1379, 1257, 1212,1072, 1004. HRMS (ESI): calc for $C_{42}H_{52}O_{11}Na$ (M + Na) 755.34018; found: 755.34045.

Methyl-2-*O*-Allyl-3,4,6-*tri*-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside (72). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-*O*-Allyl-3,4,6-*tri*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **70** (95 mg, 0.150 mmol, 1.0 equiv), Methyl 2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside **61** (99 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to –78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at –78 ^oC for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, hexane/ethyl acetate) to give the desired disaccharide **72** (107 mg, 73%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.69 **(** d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* =

7.5 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.49 (m, 2H), 7.44 – 7.25 (m, I8H), 7.23 – 7.21 (m, 2H), 7.14 – 7.13 (m 2H), 6.15 (t, *J* = 9.5 Hz, 1H), 5.99 – 5.94 (m, 1H), 5.45 (t, *J* = 10 Hz, 1H), 5.30 – 5.27 (m, 1H), 5.25 – 5.21(m, 2H), 5.15 (d, *J* = 11 Hz, 1H), 4.93 (d, *J* = 11 Hz, 1H), 4.79 (d, *J* = 11 Hz, 1H), 4.75 (d, *J* = 11 Hz, 1H), 4.52 – 4.47 (m, 3H), 4.43 (s, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 4.38 (s, 1H), 4.33 – 4.30 (m, 1H), 4.20 – 4.16 (dd, *J* = 12, 6 Hz, 1H), 4.07 (d, J = 9.5 Hz, 1H), 3.77 – 3.73 (dd, J =7.5, 11 Hz, 1H), 3.65 – 3.52 (m, 4H), 3.44 (s, 3H), 3.42 – 3.36 (m, 1H), 3.31 (t, *J* = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 165.9, 165.8, 165.4, 165.3, 135.2, 133.4, 133.1, 129.9, 129.7, 129.3, 129.1, 128.9, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 116.9, 103.9, 96.8, 84.6, 82.0, 77.6, 75.7, 75.0, 74.9, 73.7, 73.4, 72.1, 70.6, 69.8, 69.0, 68.7. IR (film, cm^{-1}) 3249, 3192, 3063, 3032, 2916, 2871, 1730, 1605, 1499, 1454, 1450, 1360, 1277, 1099. HRMS (ESI**)**: calc. for $C_{58}H_{58}O_{14}Na$ (M+Na) 1001.37188; found 1001.37873.

2-*O*-Allyl-3,4,6-*tri*-*O*-benzyl-β-D-glucopyranosyl-(1→3)-1,2,5,6-*di*-*O*-isopropylidene-α-D-glucofuranoside (73). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-*O*-Allyl-3,4,6-*tri*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **70** (95 mg, 0.150 mmol, 1 equiv), diacetone-D-glucose **63** (51 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^{o}C for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, hexane/ethyl acetate) to give the desired disaccharide **73** (88 mg, 80%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.35 – 7.24 (m, 13H), 7.12 (d, *J* = 7.5 Hz, 2H), 5.95 – 5.86 (m,2H), 5.28 (d, *J* = 16 Hz, 2H), 5.15 (d, *J* = 11 Hz, 1H), 5.14 (d, *J* = 10 Hz, 1H), 4.93 (d, *J* = 11 Hz, 1H), 4.82 (d, *J* = 11 Hz, 1H), 4.76 (d, *J* = 11 Hz, 1H), 4.63 – 4.60 (m, 2H), 4.49 – 4.43 (m, 3H), 4.23 (d, *J* = 15 Hz, 1H), 4.21 – 4.04 (m, 5H), 3.88 (t, *J* = 9.5Hz, 1H), 3.78 – 3.66

(m, 3H), 3.62 (t, *J* = 9.5Hz, 1H), 3.46 (dd, *J* =10, 3.5 Hz, 1H), 1.47 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.23(s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.7, 138.0, 137.9, 134.7, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 117.1, 111.8, 109.6, 105.2, 97.8, 83.9, 81.4, 80.1, 79.8, 77.6, 75.6, 75.3,73.5, 71.1, 68.6, 67.2, 26.9, 26.8, 26.1, 25.5. IR (film, cm^{-1}) 3372, 3319, 3245, 3187, 1693, 1617, 1265, 1108, 1071, 1026, 835. HRMS (ESI): calc for $C_{42}H_{52}O_{11}Na$ (M + Na) 755.34073; found: 755.34357.

Disaccharide (74). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-*O*-Allyl-3,4,6-*tri*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **70** (95 mg, 0.150 mmol, 1.0 equiv), glucal nucleophile **64** (44 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^{o}C for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, hexane/ethyl acetate) to give the desired disaccharide **74** (90 mg, 82%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.36 – 7.24 (m, 13H), 7.16 (d, *J* = 7.5 Hz, 2H), 6.30 (d, *J* = 6.0Hz, 1H), 5.99 – 5.91 (m, 1H), 5.28 (t, *J* = 10 Hz, 1H), 5.16 (d, *J* = 11 Hz, 1H), 4.92 (d, *J* = 11Hz, 1H), 4.83 – 4.76 (m, 3H), 4.61 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 9.0 Hz, 3H), 4.47 (d, *J* = 9.0Hz, 1H), 4.38 (dd, *J* = 13, 5.5 Hz, 1H), 4.22 (dd, *J* = 12, 6.0 Hz, 1H), 4.04 (dd, *J* = 11, 7.5Hz, 1H), 3.91 (dd, *J* = 11, 6.0 Hz, 1H), 3.83 (t, *J* = 11 Hz, 1H), 3.76 – 3.69 (m, 3H), 3.63 – 3.56 (m, 2H), 3.40 (dt, *J* = 9.5, 6.5 Hz, 1H), 3.30 (t, *J* = 8.5 Hz, 1H), 2.03 – 2.01 (bs, 1H), 1.88 - 1.85 (m,1H), 1.60 – 1.52 (m, 5H), 1.40 – 1.38 (m, 2H), 1.29 – 1.23 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 144.6, 138.7, 138.3, 138.2, 135.1, 128.3, 128.0, 127.9, 127.8,127.7, 127.6, 127.5, 116.9, 101.7, 101.6, 99.8, 84.8, 82.2, 77.7, 75.6, 75.2, 75.0, 74.2, 73.7, 73.5,70.6, 69.9, 68.8, 60.9, 37.8, 27.6, 25.6, 22.7, 22.3. IR (film, cm^{-1}) 3064,

3029, 2935, 2862, 1641, 1453, 1364, 1233, 1152, 1098, 1070, 1027, 1004, 736, 697. HRMS (ESI)**:** calc for $C_{42}H_{50}O_9Na$ (M + Na) 721.33470; found: 721.33871.

1-*O*-Adamantanolyl-2-*O*-allyl-3,4,6-*tri*-*O*-benzyl-β-D-glucopyranoside (75). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-*O*-Allyl-3,4,6-*tri*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **70** (95 mg, 0.150 mmol, 1.0 equiv), 1-adamantanol **65** (30 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^oC for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, hexane/ethyl acetate) to give the desired glycoconjugate **75** (79 mg, 84%) as white solids. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.35 – 7.22 (m, 13H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.99 – 5.91 (m,1H), 5.27 (dd, *J* = 17, 1.5 Hz, 1H), 5.15 (d, *J* = 11 Hz, 1H), 4.92 (d, *J* = 11 Hz, 1H), 4.81 (d,*J* = 11 Hz, 1H), 4.76 (d, *J* = 11 Hz, 1H), 4.61 (d, *J* = 8.0 Hz, 1H), 4.58 – 4.51 (m, 3H), 4.44 (dd, *J* = 12, 5.5 Hz, 1H), 4.20 (dd, *J* = 12, 6.0 Hz, 1H), 3.71 (d, *J* = 11.0 Hz, 1H), 3.58 (dd, *J* = 9.5, 5.0 Hz, 2H), 3.47 – 3.44 (m, 2H), 3.28 (t, *J* = 8.0 Hz, 1H), 2.13 (bs, 3H), 1.90 (bd, *J* = 12 Hz, 3H), 1.79 (bd, *J* = 12 Hz, 3H), 1.64 – 1.56 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.6, 138.4, 138.2, 135.1, 128.4, 128.3, 128.0, 127.9, 127.7,127.6, 127.5, 127.4, 116.9, 96.1, 85.1, 81.9, 78.1, 75.7, 74.9, 74.6, 73.7, 73.3, 69.5, 42.7, 36.3,30.7. IR (film, cm^{-1}) 3063, 3029, 2907, 2852, 1496, 1453, 1354, 1305, 1208, 1072, 1028, 733. HRMS (ESI): calc for $C_{40}H_{48}O_6Na$ (M + Na) 647.33431; found: 647.3345.

2,3,4-*Tri*-*O*-Allyl-6-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2,3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (78). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4-*tri*-*O*-allyl-6-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **76** (80 mg, 0.15 mmol, 1 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-

galactopyranose **29** (51 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL).The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^oC for 1 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (5/1, hexane/ethyl acetate) to give the desired disaccharide **78** (92 mg, 97%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.32 – 7.25 (m, 5H), 5.96 – 5.89 (m, 2H), 5.83 – 5.76(m,1H),5.51 (d, J = 5 Hz, 1H), 5.26 (t, J = 15.5 Hz, 2H), 5.17 – 5.07 (m, 5H), 4.62 – 4.48 (m, 4H), 4.43(dd, J = 12.5, 6 Hz, 1H), 4.35 (dd, *J* = 13, 6 Hz, 1H), 4.31 (d, J = 7.5 Hz, 1H), 4.28 (dd, *J* = 5.0 ,2.5 Hz, 2H), 4.25 – 4.19 (m, 3H), 4.15 (dd, *J* = 13, 6.5 Hz, 1H), 4.08 (dd, *J* = 11, 4.0 Hz, 1H),4.00 – 3.97 (m, 2H), 3.71 – 3.62 (m, 4H), 3.37 – 3.34 (m, 3H), 3.21 (t, *J* = 8.5 Hz, 1H), 1.49 (s,3H), 1.41 (s, 3H), 1.29 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.2, 135.5, 135.3, 134.8, 128.3, 127.9, 127.6, 116.9, 116.8,116.7, 109.3, 108.5, 104.2, 97.1, 96.3, 84.1, 81.5, 81.1, 76.8, 74.7, 74.5, 73.8, 73.5, 73.3, 71.4,70.7, 70.6, 70.5, 704, 69.6, 68.8, 67.3, 26.0, 25.9, 25.0, 24.4. IR (film, cm^{-1}) 3080, 2985, 2909, 1651, 1457, 1381, 1255, 1210, 1069, 1005, 921. HRMS (ESI): calc for $C_{34}H_{48}O_{11}Na$ (M + Na) 655.30888; found: 655.31010.

Methyl-2,3,4-*tri*-*O*-allyl-6-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside (79). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4-*tri*-*O*-allyl-6-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **76** (80 mg, 0.150 mmol, 1 equiv), Methyl 2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside **61** (99 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at -78 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography

(4/1, hexane/ethyl acetate) to give the desired disaccharide **79** (96 mg, 74%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.96 (d, *J* = 7.0 Hz, 2H), 7.91 (d, *J* = 7.0 Hz, 2H), 7.84 (d, *J* = 7.5Hz, 2H), 7.49 – 7.48 (m, 2H), 7.40 – 7.33 (m, 6H), 7.26 (m, 6H), 6.15 (t, *J* = 9 Hz, 1H), 5.94 –5.93 (m, 2H), 5.81 – 5.80 (m, 1H), 5.45 (t, *J* = 9.5 Hz, 1H), 5.29 – 5.21 (m, 4H), 5.18 – 5.07 (m,5H), 4.53 (d, *J* = 13 Hz, 1H), 4.44 (d, *J* =12 Hz, 2H), 4.34 – 4.29 (m, 3H), 4.23 (m, 2H), 4.15(dd, *J* = 12, 5.5 Hz, 1H), 4.05 (d, *J* = 11 Hz, 1H), 3.99 (dd, *J* = 12, 5Hz, 1H), 3.73 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.65 – 3.58 (m, 2H), 3.44 (s, 3H), 3.34 – 3.32 (m, 3H), 3.20 (t, *J* = 7.5 Hz,1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 165.9, 165.8, 165.4, 138.2, 135.3, 134.9, 133.4, 133.1, 133.1, 130.0, 129.9, 129.7, 129.3, 129.2, 129.0, 128.6, 128.4, 128.3, 127.7, 127.6, 116.9, 116.8, 116.7,103.9, 96.8, 84.2, 81.7, 75.0, 74.5, 73.8, 73.6, 73.5, 72.2, 70.6, 69.8, 69.1, 68.8, 55.6. IR (film, cm^{-1}) 3072, 2921, 2871, 1730, 1602, 1586, 1457, 1320, 1282, 1095, 1073, 920,825. HRMS (ESI): calc for $C_{50}H_{54}O_{14}Na$ (M + Na) 901.34058; found: 901.34115.

Methyl-2,3,4,6-*tetra*-*O*-allyl-β-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside (80). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-allyl-α-D-glucopyranosyl trichloroacetimidate **77** (73 mg, 0.150 mmol, 1.0 equiv), Methyl 2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside **61** (99 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^{o}C for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (5/1, hexane/ethyl acetate) to give the desired disaccharide **80** (89 mg, 72%) as white solids. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.96 **(**d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.50 – 7.48 (m, 2H), 7.41 – 7.34 (m, 5H), 7.27 (d, *J* = 7.5 Hz, 2H), 6.13 (t, *J* = 9.5 Hz,1H), 5.97 – 5.85 (m, 3H), 5.79 – 5.74 (m, 1H), 5.42 (t, *J* = 10 Hz, 1H), 5.27 (d,

J = 5.5 Hz, 1H),5.22 (m, 5H), 5.16 – 5.12 (m 4H), 5.06 (d, *J* = 10.5 Hz, 1H), 4.43 (dd, *J* = 12, 5 Hz, 1H), 4.35 – 4.21 (m, 5H), 4.15 – 4.12 (dd, *J* = 12, 5.5 Hz), 4.07 (dd, *J* = 12, 5.5 Hz, 1H), 4.02 (d, *J* = 11 Hz, 1H), 3.96 (dd, *J* = 13, 4.5 Hz, 1H), 3.89 (dd, *J* = 13, 5.0 Hz, 1H), 3.71 (t, *J* = 8.0 Hz, 1H), 3.61 (d, *J* = 11 Hz, 1H), 3.53 (dd, *J* = 11, 3.5 Hz, 1H), 3.44 (s, 3H), 3.38 – 3.30 (m, 3H), 3.19 (t, *J* = 8Hz, 1H). ^{13}CNMR ($CDCl_3$, 125 MHz) δ (ppm) 165.8, 165.7, 165.4, 135.3, 135.2, 134.8, 134.6, 133.4, 133.3,133.1, 129.9, 129.8, 129.6, 129.2, 129.1, 128.8, 128.6, 128.4, 128.2, 116.9, 116.8, 116.7, 116.6,103.8, 96.7, 84.1, 81.6, 74.8, 74.4, 73.8, 73.6, 72.3, 72.1, 70.5, 69.7, 68.9, 68.7, 68.6, 66.6, 55.5 IR (film, cm^{-1}) 3075, 2917, 2868, 1730, 1647, 1602, 1586, 1453, 1316, 1278, 1095, 1069. HRMS (ESI)**:** calc for $C_{46}H_{52}O_{14}Na$ (M + Na) 851.32493; found: 851.32144.

1-*O*-Dihydrocholesterolyl-2,3,4,6-*tetra*-*O*-allyl-β-D-glucopyranoside (81). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-allyl-α-D-glucopyranosyl trichloroacetimidate **77** (73 mg, 0.150 mmol, 1.0 equiv), 3β-Cholestanol **62** (76 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL).The resulting solution was cooled to – 40 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was then added. The reaction mixture was stirred at – 40 ^{o}C for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (15/1, hexane/ethyl acetate) to give the desired glycoconjugate **81** (86 mg, 81%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 5.96 – 5.85 (m, 4H), 5.28 – 5.21 (m, 4H), 5.15 – 5.15 (m, 4H),4.36 – 4.31 (m, 3H), 4.27 (dd, *J* = 12, 5.5 Hz, 1H), 4.22 (dd, *J* = 12, 5.5 Hz, 1H), 4.14 (dd, *J* =13, 6 Hz, 1H), 4.07 (dd, *J* = 13, 5.5 Hz, 1H), 4.04 – 3.98 (m, 2H), 3.67 (d, *J* = 11 Hz, 1H), 3.58 – 3.54 (m, 2H), 3.35 – 3.24 (m, 3H), 3.15 (t, *J* = 8.0 Hz, 1H), 1.94 – 0.56 (m, 47H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 135.3, 135.2, 134.9, 116.9, 116.8, 116.7, 116.6, 101.9, 84.3,81.7, 79.1, 77.7, 74.8, 74.4, 73.8, 73.6, 72.4, 69.2, 56.5, 56.3, 54.4, 44.7, 42.6, 40.0, 39.5, 37.0,36.2, 35.8, 35.6, 35.5, 34.7, 32.1,

29.6, 28.8, 28.0. 24.2, 23.8, 22.6, 21.2, 18.7, 12.3, 12.1 IR (film, cm^{-1}) 3080, 2932, 2863, 1647, 1465, 1354, 1146, 1130, 1080, 997, 920. HRMS (ESI): calc for $C_{45}H_{74}O_6Na$ (M + Na) 733.53776; found: 733.53816.

Disaccharide (82). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4-*tri*-*O*-allyl-6-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **76** (80 mg, 0.150 mmol, 1 equiv), glucal nucleophile **64** (44 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated in *situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) *in* CH_2Cl_2 (1 mL) was then added. The reaction mixture was stirred at – 78 ^oC for 4 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (15/1, Benzene/ethyl acetate) to give the desired disaccharide **82** (56 mg, 62%) as white solids. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.32 – 7.29 (m, 4H), 7.27 – 7.24 (m, 1H), 6.28 (d, *J* = 6.5 Hz,1H), 5.97 – 5.89 (m, 2H), 5.88 – 5.80 (m, 1H), 5.25 (d, *J* = 18 Hz, 2H), 5.19 – 5.08 (m, 4H),4.78 (dd, *J* = 6.0, 1.5 Hz, 1H), 4.61 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 13 Hz, 1H), 4.47 (d, *J* = 8.0 Hz, 1H), 4.43 (d, *J* = 7.5 Hz, 1H), 4.31 (dd, *J* = 12, 5.5 Hz, 2H), 4.26 – 4.22 (m, 2H), 4.18 (dd, *J* =13, 6.5 Hz, 1H), 4.03 – 4.00 (m, 2H), 3.91 (dd, *J* = 11, 5.5 Hz, 1H), 3.82 (t, *J* = 11 Hz, 1H), 3.72 – 3.66 (m, 3H), 3.40 – 3.29 (m, 3H), 3.17 (t, *J* = 8.5 Hz, 1H), 2.01 (m, 1H), 1.86 (m, 1H),1.59 – 1.50 (m, 5H), 1.38 – 1.36 (m, 2H), 1.27 – 1.23 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 163.5, 144.5, 138.2, 135.2, 135.1, 134.8, 128.3, 127.9, 127.6,101.7, 101.5, 99.8, 84.2, 81.9, 77.4, 75.1, 74.3, 74.2, 73.8, 73.7, 73.5, 70.6, 69.9, 68.6, 60.8, 37.8,27.5, 25.6, 22.7, 22.3. IR (film, cm^{-1}) 3373, 3323, 3251, 3191, 2935, 2864, 1643, 1613, 1457, 1362, 1232, 1106, 1073, 1001, 929, 829. HRMS (ESI): calc for $C_{34}H_{46}O_9Na$ (M + Na) 621.30340; found: 621.30113.

Disaccharide (83). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-allyl-α-D-glucopyranosyl trichloroacetimidate **77** (73 mg, 0.15 mmol, 1.0 equiv), glucal nucleophile **64** (44 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^oC for 4 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (15/1, Benzene/ethyl acetate) to give the desired disaccharide **83** (58 mg, 67%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 6.28 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.97 – 5.83 (m, 5H), 5.28 - 5.26(m, 2H), 5.25 – 5.23 (m, 2H), 5.15 – 5.12 (m, 4H), 4.76 (dd, *J* = 6.5, 2.0 Hz, 1H), 4.46 (d, *J* = 8.0Hz, 1H), 4.41 (d, *J* = 8.0 Hz, 1H), 4.32 - 4.21 (m, 4H), 4.16 (dd, *J* = 13, 6.0 Hz, 1H), 4.12 – 4.05(m, 2H), 4.04 – 3.98 (m, 2H), 3.89 (dd, *J* = 11, 5.5 Hz, 1H), 3.82 (t, *J* = 11 Hz, 1H), 3.70 (dd, *J* = 11, 5.5 Hz, 1H), 3.68 – 3.60 (m, 2H), 3.40 – 3.32 (m, 2H), 3.29 – 3.27 (m, 1H), 3.15 (t, *J* = 8.5,5.5 Hz, 1H), 2.07 – 1.85 (m, 2H), 1.58 – 1.54 (m, 4H), 1.47 – 1.30 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 144.5, 135.3, 135.2, 134.9, 116.9, 116.8, 116.6, 101.8, 101.6, 99.8, 84.3, 81.9, 75.2, 74.4, 73.8, 73.7, 72.6, 70.7, 69.9, 68.8, 60.9, 37.9, 27.6, 25.6, 22.8, 22.4. IR (film, cm^{-1}) 2935, 2862, 1643, 1233, 1116, 1096, 1076, 997, 924. HRMS (ESI): calc for $C_{30}H_{44}O_9Na$ (M + Na) 571.28775; found: 571.29078.

Methyl-2,3,4,6-*tetra*-*O*-*p*-methoxybenzyl-β-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside (85). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl trichloroacetimidate **84** (121 mg, 0.150 mmol, 1.0 equiv), Methyl 2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside **61** (99 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (1.73 mg, 0.0045 mmol, 3 mol %) and AgOTf (2.31

mg, 0.009 mmol, 6 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^oC for 4 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (9/1, benzene/ethyl acetate) to give the desired disaccharide **85** (129 mg, 75%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.96 (d, *J* = 7.5 Hz, 2H), 7.91 (d, *J* = 7.0 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.51 – 7.47 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.38 – 7.30 (m, 5H), 7.27 (d, *J* = 8.0 Hz,2H), 7.18 (dd, *J* = 16, 8.5 Hz, 4H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.85 – 6.77 (m, 9H), 6.15 (t, *J* = 10 Hz, 1H), 5.46 (t, *J* = 10 Hz, 1H), 5.25 (dd, *J* = 10, 3.5 Hz, 1H), 5.20 – 5.18 (m, 1H), 4.96 (d, *J* =10.5 Hz, 1H), 4.81 (d, *J* = 10.5 Hz, 1H), 4.69 – 4.66 (m, 2H), 4.59 (d, *J* = 10 Hz, 1H), 4.45 (d, *J*= 12 Hz, 1H), 4.41 (d, *J* = 8 Hz 1H), 4.37 – 4.30 (m, 3H), 4.10 (d, *J* = 10.5 Hz, 1H), 3.80 – 3.74(m, 13H), 3.59 – 3.53 (m, 3H), 3.49 (t, *J* = 9.5 Hz, 1H), 3.40 (t, *J* = 4 Hz, 1H), 3.37 – 3.34 (m,4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 165.8, 165.7, 165.5, 159.2, 159.1, 133.3, 133.1, 130.9, 130.3,130.1, 129.9, 129.8, 129.7, 129.6, 129.5, 129.2, 129.1, 128.4, 128.3, 113.8, 113.7, 104.0, 96.8, 84.3, 82.1, 75.3, 74.9, 74.6, 74.4, 73.1, 72.1, 70.5, 69.9, 69.0, 68.9, 68.3, 55.5, 55.3. IR (film, cm^{-1}) 3068, 3038, 3004, 2943, 2840, 1731, 1609, 1586, 1514, 1456, 1362, 1278, 1255, 1179, 1095, 1073, 1034, 822. HRMS (ESI): calc for $C_{66}H_{68}O_{18}Na$ (M + Na) 1171.42979; found: 1171. 42687.

1-*O*-Dihydrocholesterolyl-2,3,4,6-*tetra*-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (86). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl trichloroacetimidate **84** (81 mg, 0.10 mmol, 1.0 equiv), 3β-cholestanol **62** (51 mg, 0.13 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 50 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (1.15 mg, 0.003 mmol, 3. mol %) and AgOTf (1.54 mg, 0.006 mmol, 6 mol %) in CH_2Cl_2 (0.8 mL) was added. The reaction mixture was stirred at – 50 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (15/1, benzene/ethyl acetate) to give the

desired glycoconjugate **86** (93 mg, 90%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.27 – 7.26 (m, 2H), 7.23 – 7.20 (m, 4H), 7.04 (d, *J* = 8 Hz,2H), 6.83 (d, *J* = 8.0 Hz, 6H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.86 (d, *J* = 11 Hz, 1H), 4.81 (d, *J* = 11Hz, 1H), 4.69 (t, *J* = 9.0 Hz, 2H), 4.63 (d, *J* = 11 Hz, 1H), 4.52 (d, *J* = 12 Hz, 1H), 4.47 – 4.44 (m, 2H), 4.39 (d, *J* = 11 Hz, 1H), 3.78 (s, 6H), 3.77 (s, 6H), 3.67 – 3.63 (m, 2H), 3.57 – 3.52(m, 2H), 3.43 (t, *J* = 9.5 Hz, 1H), 3.39 – 3.35 (m, 2H), 1.96 – 0.59 (m, 47H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 159.1, 129.9, 129.7, 129.5, 129.4, 113.7, 101.9, 84.6, 82.1, 79.0, 77.8, 75.3, 74.6, 74.5, 73.0, 56.5, 56.3, 55.3, 54.4, 44.7, 42.6, 40.0, 39.5, 36.2, 35.8, 35.6, 35.5, 34.8, 29.7, 28.8, 28.3, 28.0, 23.8, 22.8, 22.6, 18.7, 12.3, 12.1. IR (film, cm^{-1}) 2939, 2856, 2361, 2339, 1613, 1510, 1460, 1362, 1305, 1251, 1175, 1099, 1061, 1038. HRMS (ESI): calc for $C_{65}H_{90}O_{10}Na$ (M + Na) 1053.64262; found: 1053.63873.

Disaccharide (87). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl trichloroacetimidate **84** (81 mg, 0.10 mmol, 1.0 equiv), glucal nucleophile **64** (30 mg, 0.13 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL).The resulting solution was cooled to – 78 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (1.15 mg, 0.003 mmol, 3 mol %) and AgOTf (1.54 mg, 0.006 mmol, 6 mol %) in CH_2Cl_2 (0.8 mL) was added. The reaction mixture was stirred at – 78 ^{o}C for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (13/1, benzene/acetonitrile) to give the desired disaccharide **87** (62 mg, 71%) as white solids. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.26 – 7.24 (m, 2H), 7.22 (d, *J* = 8.5 Hz, 4H), 7.05 (d, *J* = 8.5Hz, 2H), 6.84 – 6.83 (m, 6H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.31 (d, *J* = 6 Hz, 1H), 4.83 – 4.80 (m,3H), 4.70 (dd, *J* = 11, 8.5 Hz, 2H), 4.65 (d, *J* = 11 Hz 1H), 4.57 – 4.54 (m, 2H), 4.49 (d, *J* = 9.0 Hz, 1H), 4.44 (t, *J* = 11 Hz, 1H), 4.05 (dd, *J* = 11, 7.5 Hz, 1H), 3.92 (dd, *J* = 11, 5.5 Hz, 1H), 3.78 (s, 6H), 3.77 (s, 6H), 3.75 – 3.69 (m, 2H), 3.66 (d, *J* = 2 Hz, 2H), 3.57 – 3.53 (m, 2H), 3.39 – 3.36 (m, 2H), 2.01 – 1.23 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 159.2, 159.1,

144.6, 130.7, 130.4, 129.8, 129.7, 129.5, 129.4, 113.8, 113.7, 101.8, 101.5, 99.8, 84.6, 82.2, 77.5, 75.3, 75.2, 74.6, 73.9, 73.2, 70.7, 69.9, 68.4, 60.9, 55.3, 37.8, 27.5, 25.6, 22.7, 22.3. IR (film, cm^{-1}) 2930, 2862, 1641, 1612, 1587, 1511, 1462, 1362, 1299, 1246, 1174, 1070, 1035, 823. HRMS (ESI): calc for $C_{50}H_{60}O_{13}Na$ (M + Na) 891.39261; found: 891.39153.

1-*O*-Adamantanolyl-2,3,4,6-*tetra*-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (88). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl trichloroacetimidate **84** (81 mg, 0.10 mmol, 1.0 equiv), 1-adamantanol **65** (20 mg, 0.13 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to –78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (1.15 mg, 0.003 mmol, 3 mol %) and AgOTf (1.54 mg, 0.006 mmol, 6 mol %) in CH_2Cl_2 (0.8 mL) was added. The reaction mixture was stirred at – 78 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (15/1, benzene/ethyl acetate) to give the desired glycoconjugate **88** (56 mg, 71%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.26 – 7.24 (m, 4H), 7.24 – 7.22 (m, 2H), 6.99 (d, *J* = 8.5 Hz,2H), 6.84 (t, *J* = 8.5 Hz, 5H), 6.78(t, *J* = 7.5 Hz, 3H), 5.19 (d, *J* = 3.5 Hz, 1H), 4.87 (d, *J* = 10.5Hz, 1H), 4.70 (dd, *J* = 10, 3.5 Hz, 2H), 4.60 – 4.57 (m, 3H), 4.34 (d, *J* = 12 Hz, 1H), 4.30 (d, *J* = 11 Hz, 1H), 3.92 (t, *J* = 9.5 Hz, 2H), 3.79 (s, 6H), 3.76 (s, 3H), 3.74 (s, 3H), 3.70 (dd, *J* = 11,3.5 Hz, 1H), 3.57 (t, *J* = 9.5 Hz, 1H), 3.52 (d, *J* = 9 Hz, 1H), 3.46 (dd, *J* = 9.5, 3.5 Hz, 1H), 2.10(m, 3H), 1.83 – 1.75 (m, 6H), 1.61 – 1.59 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 159.2, 129.7, 129.5, 129.4, 113.7, 113.6, 89.9, 81.8, 79.8,77.8, 75.2, 74.7, 74.4, 73.0, 72.5, 69.6, 68.2, 55.3, 55.2, 42.4, 36.3, 30.6. IR (film, cm^{-1}) 2905, 2852, 1613, 1514, 1457, 1354, 1301, 1248, 1175, 1035, 822. HRMS (ESI): calc for $C_{48}H_{58}O_{10}Na$ (M + Na) 817.39222; found: 817.39067.

Methyl-2,3,4-*tri*-*O*-benzyl-β-D-xylopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside (91). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4-*tri*-*O*-benzyl-α-D-xylopyranosyl trichloroacetimidate **89** (85 mg, 0.150 mmol, 1.0 equiv), Methyl 2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside **61** (99 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/1, hexane/ethyl acetate) to give the desired disaccharide **91** (116 mg, 85%) as white solids. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.97 (d, *J* = 7.5 Hz, 2H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* =7.5 Hz, 2H), 7.50 (t, *J* = 7.0 Hz, 2H), 7.42 – 7.25 (m, 19H), 7.23 – 7.18 (m, 3H), 6.14 (t, *J* = 9.0 Hz,1H), 5.48 (t, *J* = 10 Hz, 1H), 5.22 – 5.19 (m, 2H), 4.83 (dd, *J* = 18, 11 Hz, 2H), 4.75 (d, *J* = 12 Hz, 1H), 4.70 (d, *J* = 12 Hz, 1H), 4.61 – 4.57 (m, 3H), 4.33 – 4.30 (m, 1H), 3.87 (t, *J* = 9.5 Hz,1H), 3.81 (dd, *J* = 11, 7 Hz, 1H), 3.62 – 3.60 (m, 1H), 3.56 – 3.50 (m, 3H), 3.43 (s, 3H), 3.39 (dd, *J* = 6, 9.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 165.8, 165.3, 138.9, 138.5, 138.4, 138.1, 133.3, 133.0, 129.9, 129.7, 129.3, 129.1, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 104.4, 97.3, 96.8, 96.7, 83.6, 81.9, 81.0, 79.7, 78.0, 77.7, 75.6, 74.9, 73.3, 72.2, 72.0, 70.6, 70.5, 69.8, 69.7, 68.9, 68.6, 66.8, 63.9, 60.1, 55.6. IR (film, cm^{-1}) 3297, 3176, 3063, 2935, 1730, 1601, 1496, 1454, 1450, 1276, 1174, 1095. HRMS (ESI): calc. for $C_{54}H_{52}O_{13}Na$ (M+Na) 931.33001; found 931.32788.

1-*O*-Dihydrocholesterolyl-2,3,4-*tri*-*O*-benzyl-β-D-xylopyranoside (92). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4-*tri*-*O*-benzyl-α-D-xylopyranosyl trichloroacetimidate **89** (85 mg, 0.150 mmol, 1.0 equiv), 3β-cholestanol **62** (76 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled

to – 50 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.0030 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was then added. The reaction mixture was stirred at – 78 ^{o}C for 2 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (15/1, hexane/ethyl acetate) to give the desired glycoconjugate **92** (90 mg, 76%) as white solids. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.36 – 7.25 (m, 15H), 4.92 (d, *J* = 11 Hz, 1H), 4.84 (d, *J* = 11 Hz, 1H), 4.80 (d, *J* = 3.5 Hz, 1H), 4.75 (d, *J* = 8 Hz, 1H), 4.73 (d, *J* = 7.5 Hz, 1H), 4.63 (d, *J* = 11 Hz, IH), 4.61 (d, *J* = 11.5 Hz, 1H), 3.89 (t, *J* = 9.0 Hz, 1H), 3.61 – 3.59 (m, 1H), 3.56 – 3.53 (m, 2H), 3.51 – 3.46 (m, 1H), 3.41 (dd, *J* = 9.5, 3.5 Hz, 1H), 1.95 – 0.56 (m, 47H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 139.1, 138.4, 128.8, 128.3, 128.1, 128.0, 127.8, 127.5, 94.8, 81.5, 79.7, 78.3, 76.1, 75.7, 73.5, 73.1, 59.9, 56.5, 56.3, 54.4, 45.2, 42.6, 40.0, 39.5, 36.9, 36.2, 35.9, 35.8, 35.7, 35.5, 32.1, 28.7, 28.3, 28.0, 27.4, 24.2, 23.8, 22.8, 22.6, 21.4, 18.7, 12.4, 12.1. IR (film, cm^{-1}) 2931, 2863, 1495, 1454, 1363, 1076, 1030. HRMS (ESI): calc. for $C_{53}H_{74}O_5Na$ (M+Na) 813.54285; found 813.54443.

Methyl-2,3,4-*tri*-*O*-benzyl-β-D-quinovopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside (93). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4-*tri*-*O*-benzyl-α-D-quinovopyranosyl trichloroacetimidate **90** (115 mg, 0.20 mmol, 1 equiv), Methyl 2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside **61** (132 mg, 0.26 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to –78 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.76 mg, 0.002 mmol, 1 mol %) and AgOTf (1.02 mg, 0.004 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^{o}C for 4 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, hexane/ethyl acetate) to give the desired disaccharide **93** (148 mg, 80%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.97 – 7.92 (m, 4H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.51 – 7.48

(m,2H), 7.47 – 7.16 (m, 22H), 6.13 (t, *J* = 11 Hz, 1H), 5.50 (t, *J* = 10 Hz, 1H), 5.22-5.19 (m, 2H),4.87 (t, *J* = 11 Hz, 2H), 4.73 (d, *J* = 13 Hz, 2H), 4.61 (d, *J* = 7.0 Hz, 1H), 4.59 (d, *J* = 11.0Hz, 1H), 4.30 (ddd, *J* = 9.5, 7.0, 2.0 Hz, 1H), 3.90 (t, *J* = 9.0 Hz, 1H), 3.82 – 3.79 (m, 2H), 3.55 (dd, *J* = 12, 2.0 Hz, 1H), 3.46 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.43 (s, 3H), 3.06 (t, *J* = 9 Hz, 1H), 1.10 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 165.9, 165.8, 165.3, 138.8, 138.5, 138.4, 133.3, 133.0, 129.9, 129.7, 129.3, 129.1, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 97.0, 96.7, 83.7, 81.4, 80.3, 75.5, 75.0, 73.0, 72.2, 70.6, 69.7, 68.6, 66.8, 66.7, 55.6, 17.7. IR (film, cm^{-1}) 3087, 3063, 3030, 2923, 2875, 1730, 1279, 1262, 1105, 1094, 1071, 1027, 738, 709. HRMS (ESI): calc for $C_{55}H_{54}O_{13}Na$ (M + Na) 945. 34566; found: 945.34236.

1-*O*-Dihydrocholesterolyl-2,3,4-*tri*-*O*-benzyl-β-D-quinovopyranoside (94). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4-*tri*-*O*-benzyl-α-D-quinovopyranosyl trichloroacetimidate **90** (115 mg, 0.20 mmol, 1.0 equiv), 3β-cholestanol **62** (116 mg, 0.30 mmol, 1.5 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to – 50 ^{o}C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.76 mg, 0.002 mmol, 1 mol %) and AgOTf (1.02 mg, 0.004 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was then added. The reaction mixture was stirred at – 50 ^{o}C for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (15/1, hexane/ethyl acetate) to give the desired glycoconjugate **94** (138 mg, 86%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.35 – 7.25 (m, 15H), 4.98 (d, *J* = 11 Hz, 1H), 4.88 (d, *J* =11 Hz, 1H), 4.80 (d, *J* = 4.0 Hz, 1H), 4.78 (d, *J* = 11 Hz, 1H), 4.73 (d, *J* = 12 Hz, 1H), 4.63(d, *J* = 12 Hz, 1H), 4.60 (d, *J* = 11 Hz, 1H), 3.94 (t, *J* = 9.5 Hz, 1H), 3.85 – 3.79 (m, 1H), 3.48(dd, *J* = 10.0, 6.0 Hz, 2H), 3.09 (t, *J* = 9.5 Hz, 1H), 1.95 – 1.93 (m, 1H), 1.81 – 1.76 (m, 2H), 1.72 (m, 1H), 1.64 – 1.61 (m, 1H), 1.55 – 1.40 (m, 6H), 1.32 – 1.21 (m, 9H), 1.18 (d, *J* = 9.0 Hz, 3H), 1.11 – 0.91 (m, 10H), 0.89 – 0.83 (m, 11H), 0.79 (s, 3H), 0.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.9,

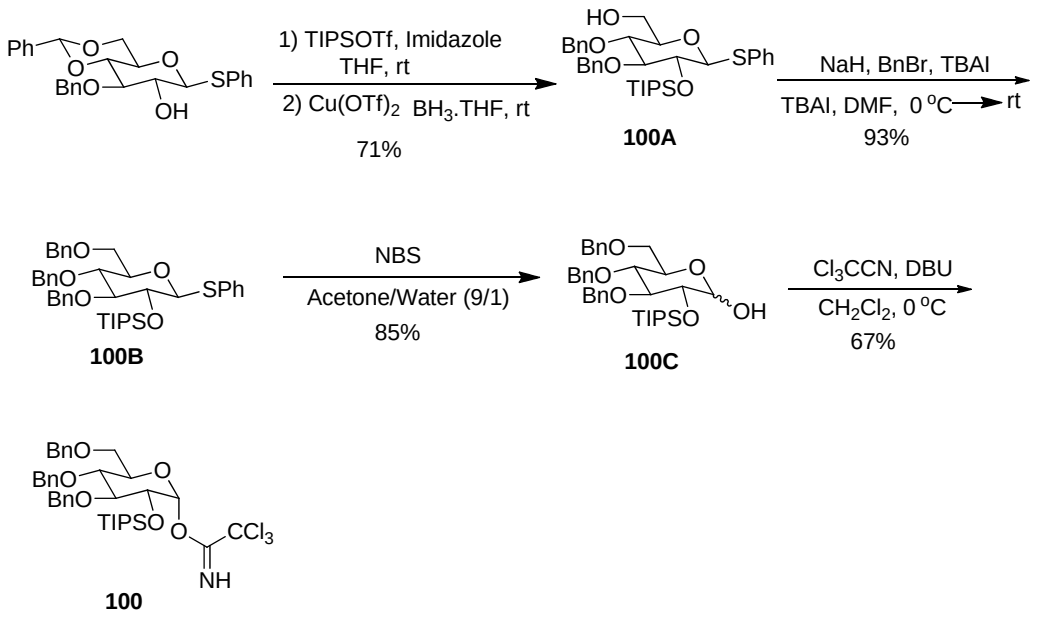
138.3, 128.4, 128.1, 128.0, 127.8, 127.7, 127.5, 94.4, 84.0, 81.8, 80.3, 76.0, 75.7, 75.4, 72.9, 66.5, 56.5, 56.3, 54.4, 45.1, 42.6, 40.0, 39.5, 36.9, 36.1, 35.9, 35.8, 35.7, 35.5, 32.1, 28.7, 28.2, 28.0, 27.4, 24.2, 23.8, 22.8, 22.6, 21.2, 18.7, 17.9, 12.4,12.1. IR (film, cm^{-1}) 2931, 2865, 1453, 1073, 1028, 733, 697. $J(^{13}CH)$ = 166 Hz (94.4 ppm). HRMS (ESI): calc for $C_{54}H_{76}O_5Na$ (M + Na) 827.55850; found: 827.55389.

1-*O*-Adamantanolyl-2,3,4-*tri*-*O*-benzyl-β-D-quinovopyranoside (95). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4-*tri*-*O*-benzyl-α-D-quinovopyranosyl trichloroacetimidate **90** (115 mg, 0.20 mmol, 1 equiv), 1-adamantanol **65** (40 mg, 0.26 mmol, 1.3 equiv) and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to –78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.76 mg, 0.002 mmol, 1 mol %) and AgOTf (1.02 mg, 0.004 mmol, 2 mol %) in CH_2Cl_2 (1 mL) was then added. The reaction mixture was stirred at – 78 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (9/1, hexane/ethyl acetate) to give the desired glycoconjugate **95** (101 mg, 88%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.35 – 7.25 (m, 15H), 5.15 (d, *J* = 3.5 Hz, 1H), 4.96 (d, *J* =11 Hz, 1H), 4.88 (d, *J* = 11 Hz, 1H), 4.78 (d, *J* = 11 Hz, 1H), 4.67 (s, 2H), 4.60 (d, *J* = 11 Hz, 1H), 3.98 – 3.94 (m, 2H), 3.46 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.09 (t, *J* = 9.0 Hz, 1H), 2.12 (bs, 3H), 1.84 – 1.76 (m, 6H), 1.63 – 1.57 (m, 6H), 1.19 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.4, 89.5, 84.4, 81.8, 80.4, 75.5, 75.4, 74.3, 72.8, 66.0, 42.4, 36.3, 30.6, 17.9. IR (film, cm^1) 2907, 2851, 1453, 1354, 1073, 1035, 1014, 734, 697. $J(^{13}CH)$ = 164 Hz (89.5 ppm). HRMS (ESI): calc for $C_{37}H_{44}O_5Na$ (M + Na) 591.30810; found: 591.30977.

Trisaccharide (97). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2,3,4,6-*tetra*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **20α** (102 mg, 0.150 mmol, 1.0 equiv), Disaccharide nucleophile **96**[102-105] (143 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (0.8 mL). The resulting solution was cooled to –78 ^oC, and a

preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (1.15mg, 0.003 mmol, 2 mol %) and AgOTf (1.54 mg, 0.006 mmol, 4 mol %) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at – 78 ^oC for 5 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/1, hexane/ethyl acetate) to give the desired trisaccharide **97** (134 mg, 71%) as pale yellow oil. ^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm) 7.94 (d, *J* = 7.0 Hz, 2H), 7.90 (d, *J* = 7.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.12 (m, 29H), 5.85 (t, *J* = 9.5 Hz, 1H), 5.48 (t, *J* = 8.5 Hz, 1H), 5.41 (t, *J* = 9.5 Hz, 1H), 5.36 (d, *J* = 4.5 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.91 (d, *J* = 8.5 Hz, 1H), 4.88 (d, *J* = 8.5 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.73 (d, *J* = 11 Hz, 1H), 4.68 (d, *J* = 11 Hz, 1H), 4.53 (d, *J* = 13 Hz, 1H), 4.47 (d, *J* = 7.0 Hz, 1H), 4.41 (d, *J* = 12 Hz, 1H), 4.37 (d, *J* = 8.0 Hz, 1H), 4.16 – 4.04 (m, 3H), 3.97 – 3.91 (m, 2H), 3.87 – 3.72 (m, 4H), 3.62 – 3.51 (m, 5H), 3.39 (t, *J* = 7.5 Hz, 2 H), 1.30 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 165.7, 165.4, 165.2, 138.6, 138.5, 138.1, 133.4, 133.3, 133.1, 133.0, 130.1, 129.8, 129.7, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 109.1, 108.3, 103.8, 101.3, 96.1, 84.6, 82.0, 77.6, 75.7, 74.9, 74.8, 74.7, 74.0, 73.4, 73.1, 71.8, 70.8, 70.5, 70.4, 70.2, 68.7, 68.6, 68.5, 67.3, 25.8, 25.6, 24.8, 24.1. IR (film, cm^{-1}) 3063, 3030, 2986, 2922, 1733, 1452, 1281, 1260, 1093, 1069, 1027, 709. HRMS (ESI): calc for $C_{73}H_{76}O_{19}Na$ (M + Na) 1279.48730; found: 1279.47682.

6.1. Synthesis of C(2)-Triisopropylsilyl Glycosyl Donor



Scheme 6.1 Synthesis of 2-*O*-Triisopropylsilyl-3,4,6-*Tri*-*O*-Benzyl-α-D-Glucopyranosyl Trichloroacetimidate.

Phenyl-3,4-*di*-*O*-benzyl-2-*O*-triisopropylsilyl-1-thio-β-D-glucopyranoside (100A). An oven-dried and argon flushed 25 mL Schlenk flask was charged with Phenyl 3-*O*-benzyl-4,6-benzylidene-1-thio-α-D-glucopyranoside [213] (273 mg, 0.607 mmol, 1.0 equiv.), THF(4 mL) and imidazole (124 mg, 1.821 mmol, 3.0 equiv.). The resulting mixture was cooled to 0 °C and TIPSOTf (0.50 mL, 1.820 mmol, 3 equiv.) was added. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was quenched with water (30 mL), and extracted with diethyl ether (3 x 40 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to form the crude C(2)-silylated product (364 mg) as pale yellow oil. This crude product was used in the next step without further purification.

To this C(2)-silylated product (364 mg, 0.606 mmol 1 equiv.) in an oven-dried and argon flushed 25 mL Schlenk flask was added BH_3·THF (3.94 mL, 1M, 6.5 equiv.), the reaction mixture was stirred for about 10 min, after which $Cu(OTf)_2$ (24.2 mg, 0.067 mmol, 0.11 equiv.) was also added. The resulting reaction mixture was stirred for 1.5 h at room temperature. When the reaction was complete as indicated by TLC, the reaction was cooled to 0 ^oC and quenched by slow addition of triethylamine (0.1 mL) and methanol (1 mL). The resulting mixture was concentrated *in vacuo*, and co-evaporated with methanol, and then purified by silica gel flash column chromatography (7/1, hexanes/ethyl acetate $\rightarrow$ 3/2, hexanes/ethyl acetate) to provide the desired primary alcohol **100A** (262 mg, 71%) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.45 (d, J = 7.5, 2H), 7.37 – 7.24(m, 13H), 4.89 (d, J = 12 Hz, 1H), 4.74 (d, J = 12 Hz, 1H), 4.69 (d, J = 9.0 Hz, 1H), 3.84 – 3.80 (m, 2H), 3.73 (dd, J = 12, 5.5 Hz, 1H), 3.61 (t, J = 9.0, 2H), 3.44 – 3.35 (m, 3H), 1.27 – 1.20 (m, 4H), 1.12 – 1.03 (m, 18H). IR (film, cm^{-1}) 3385, 2939, 2868, 1586, 1465, 1365, 1146, 1050, 886, 799.

Phenyl-3,4,6-*tri*-*O*-benzyl-2-*O*-triisopropylsilyl-1-thio-β-D-glucopyranoside (100B). An oven dried and argon flushed 25 mL Schlenk flask was charged with the primary alcohol **100A** (208 mg, 0.342 mmol, 1.0 equiv) and anhydrous DMF (3 mL). The resulting solution was cooled to 0 ^oC and NaH (12.3 mg, 0.513 mmol, 1.5 equiv.) was added portion wise for 30 minutes. BnBr (61 μL, 0.513 mmol, 1.5 equiv) was also added dropwise, followed by the addition of tetrabutylammonium iodide (6.32 mg, 0.017 mmol, 5 mol %). The resulting reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was cooled to 0 ^oC, and quenched with methanol (0.5 mL) and then poured into water (30 mL). The mixture was extracted with diethyl ether (3 x 30 mL) and the combined organic layer was washed with water (1 x 30 mL), then brine (1 x 30 mL), and then dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product as yellow oil. The crude product was then purified by

silica gel flash column chromatography (18/1, hexanes/ ethyl acetate) to provide the fully benzylated product **100B** (221 mg, 93%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.53 – 7.51 (m, 2H), 7.34 – 7.29(m, 10H), 7.24 – 7.20(m, 6H), 7.08 (t, *J* = 3.0 Hz, 2H), 4.99 (d, *J* = 12 Hz, 1H), 4.74 (d, *J* = 12 Hz, 1H), 4.66 (d, *J* = 11 Hz, 1H), 4.63 – 4.59 (m, 1H), 4.54 (t, *J* = 12 Hz, 3H), 3.84 (t, *J* = 9.0 Hz, 1H), 3.75 (d, *J* = 11 Hz, 1H), 3.70 – 3.64 (m, 2H), 3.55 – 3.50 (m, 2H), 1.28 – 1.25 (m, 1H), 1.21 – 1.13 (m, 1H), 1.06 (d, *J* = 7.5 Hz, 9H), 1.02 (d, *J* = 7.5 Hz, 9H), 0.88-0.82 (m, 1H). IR (film, cm^{-1}) 3027, 2943, 2868, 1457, 1362, 1168, 1062, 1027, 886.

3,4,6-*Tri*-*O*-benzyl-2-*O*-triisopropylsilyl-D-glucopyranose (100C). A 25 mL round bottom flask was charged with **100B** (217 mg, 0.301 mmol, 1.0 equiv.) in acetone (1.6 mL). To this solution was added acetone/water (3.13 mL, 9/1) followed by N-bromosuccinamide (NBS) (111 mg, 0.621 mmol, 2.0 equiv.) in one portion. The resulting reaction mixture was stirred at room temperature for 5 minutes and quenched with solid $NaHCO_3$ (228 mg). Stirring was continued for about 10 minutes, after which the mixture was concentrated in vacuo, dissolved in ethyl acetate (20 mL), and washed with water until the pH of the organic layer is neutral. The organic layer was then washed with brine (1 x 10 mL), dried with anhydrous $MgSO_4$, filtered, and finally concentrated *in vacuo* to yield the crude product as yellow oil. The crude product was purified by silica gel flash column chromatography (5/1, hexanes/ethyl acetate) to afford the hemi acetal **100C** (161 mg, 85%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.34 – 7.26 (m, 12H), 7.24 – 7.21(m, 5H), 7.04 – 7.01(m, 3H), 5.21 (s, 1H), 4.88 – 4.85 (m, 3H), 4.73 – 4.70 (m, 1.5H), 4.68 – 4.59 (m, 2H), 4.53 – 4.42 (m, 3H), 3.84 (d, *J* = 10 Hz, 1H), 3.90 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.77-3.72 (m, 2H), 3.70 – 3.62 (m, 3H), 3.55 –3.52 (m, 1.3H), 2.96 (s, 1H), 1.16 – 1.11 (m, 1.7H), 1.08 – 1.04 (m, 27H). IR (film, cm^{-1}) 3422, 3031, 2943, 2871, 1498, 1461, 1369, 1206, 1149, 1069, 921, 886.

3,4,6-*Tri*-*O*-benzyl-2-*O*-triisopropylsilyl-α-D-glucopyranosyl trichloroacetimidate (100). An oven-dried and argon flushed 10 mL Schlenk flask was charged with the hemi-acetal **100C** (157 mg, 0.259 mmol, 1.0 equiv.) and anhydrous CH_2Cl_2 (1.3 mL). The resulting mixture was cooled to 0 ^oC and trichloroacetonitrile (78 μL, 0.776 mmol, 3.0 equiv.) was added, followed by 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (20 μL, 0.13 mmol, 0.5 equiv.). The resulting reaction mixture was stirred at 0 ^oC for 4 h, and purified by silica gel flashed column chromatography (11/1, hexanes/ethyl acetate + 1% triethylamine) to provide the desired C(2)-triisopropylsilyl imidate **100** (127 mg, 67%) as pale yellow oil. ^1H NMR (CDCl3, 500 MHz) δ (ppm) 8.59 (s, 1H), 7.34 – 7.22 (m, 13H), 7.02(s, 2H), 4.91 (dd, *J* = 20, 12 Hz, 2H), 4.75 (d, *J* = 10 Hz, 1H), 4.61 (d, *J* = 13 Hz, 1H), 4.48 – 4.45 (m, 2H), 4.09 – 4.07 (m, 1H), 3.96 – 3.93 (m, 2H), 3.78 – 3.76 (m, 2H), 3.64 (d, *J* = 11 Hz, 1H), 1.21 – 1,24 (m, 1H), 1.05 – 1.102 (m, 20H). IR (film, cm^{-1}) 3421, 3031, 2943, 2840, 1498, 1463, 1369, 1246, 1149, 1069, 886.

3,4,6-*Tri*-*O*-benzyl-2-*O*-triisopropylsilyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (101). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 3,4,6-*tri*-*O*-benzyl-2-*O*-triisopropylsilyl-α-D-glucopyranosyl trichloroacetimidate **100** (60 mg, 0.08 mmol, 1.0 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (27 mg, 0.10 mmol, 1.3 equiv), and CH_2Cl_2 (0.6 mL). The resulting solution was cooled to – 78 ^oC, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.31mg, 0.0008 mmol, 1 mol %) and AgOTf (0.41 mg, 0.0016 mmol, 2 mol %) in CH_2Cl_2 (0.4 mL) was added. The reaction mixture was stirred at – 78 ^oC for 5 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (6/1, hexane/ethyl acetate) to give the desired disaccharide **60** (37 mg, 54%, β:α = 3:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.34 – 7.26 (m, 9H), 7.22 – 7.20(m, 4H), 7.07 (t, *J* = 3.5 Hz, 1H), 7.02 – 7.01 (m, 1H), 5.49 (d, *J* = 5.0 Hz, 1H), 5.48 (d, *J* = 5.0 Hz, 0.3H), 4.93 (d, *J* = 12 Hz, 1H),

4.87 (d, *J* = 11 Hz, 1H), 4.83 – 4.80 (m, 1H), 4.74 – 4.69 (m, 1H),4.65 – 4.62 (m, 1H), 4.59 – 4.58 (m, 1H), 4.55 – 4.52 (m, 1H), 4.49 – 4.45 (m, 1H), 4.42 (d, *J* = 11 Hz, 1H), 4.29 – 4.25 (m,2H), 4.11 (dd, *J* = 10, 5.0 Hz, 0.3H), 3.99 (t, *J* = 7 Hz, 1H), 3.89 (d, *J* = 3.0 Hz, 0.3H), 3.88 (d, *J* = 3.5 Hz, 1H), 3.85 (d, *J* = 8.5 Hz, 1H), 3.83 – 3.80 (m, 1H), 3.77 – 3.74 (m, 2H), 3.71 – 3.69 (m, 1H), 3.67 – 3.60 (m, 3H), 3.56 (dd, *J* = 11, 7.5 Hz, 0.3H), 3.51 (t, *J* = 8.5 Hz, 0.3H), 3.44 (d, *J* = 10.5 Hz, 0.3H), 1.51 (d, *J* = 16.5 Hz, 3H), 1.40 (s, 3H), 1.32-1.29 (m, 6H), 1.21 – 1.16 (m, 1H), 1.06 – 1.03 (m, 20H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 139.3, 139.0, 138.4, 138.2, 138.0, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.6, 127.5, 127.2, 127.1, 109.2, 109.1, 108.6, 108.4, 103.7, 99.8, 96.3, 96.2, 86.6, 82.8, 78.2, 78.0, 75.6, 75.4, 75.2, 74.9, 74.8, 74.7, 73.9, 73.6, 73.5, 71.5, 70.9, 70.7, 70.5, 70.4, 70.2, 68.8, 68.5, 67.1, 66.7, 66.6, 26.1, 26.0, 25.9, 24.8, 24.6, 24.4, 18.2, 18.1, 18.0, 13.1, 12.7; IR (film, cm^{-1}) 2939, 2868, 1498, 1457, 1377, 1252, 1214, 1160, 1005, 917, 883, 735, 692. HRMS (ESI) calcd for $C_{48}H_{68}O_{11}Si$ Na (M + Na) 871.44231, found 871.44197.

2-Deoxy-3,4,6-*tri*-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (103). A 10 mL oven-dried Schlenk flask was charged with 2-deoxy-3,4,6-*tri*-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate **102** (75 mg, 0.129 mmol, 1.0 equiv),1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (44 mg, 0.168 mmol, 1.3 equiv), and CH_2Cl_2 (1 mL). The resulting solution was cooled to – 78 °C, and a preformed solution of $Pd(PhCN)_2(OTf)_2$, generated *in situ* from $Pd(PhCN)_2Cl_2$ (0.50 mg, 0.00129 mmol, 1 mol %) and AgOTf (0.66 mg, 0.00258 mmol, 2 mol %) in CH_2Cl_2 (0.2 mL) was added. The reaction mixture was stirred at – 78 °C for 2 h, diluted with benzene (1 mL), and purified by silica gel flash chromatography (4/1, hexane/ethyl acetate) to give the desired disaccharide **103** (83 mg, 95%, β:α = 3:1) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.32 – 7.27 (m, 14), 7.18 (d, *J* = 4.5 Hz, 3H) 5.54 (d, *J* = 21 Hz,1H), 5.53 (d, *J* = 20, 0.3H), 5.03 (s, 0.3H), 4.90 – 4.87 (m, 2H), 4.69 –

4.58 (m, 6H), 4.54 – 4.50 (m, 5H), 4.31 (s, 2H), 4.21 (d, *J* = 6.5 Hz, 2H), 4.09 (d, *J* = 12 Hz, 1H), 4.00 – 3.94 (m, 2H), 3.79 (t, *J* = 9.0 Hz, 1H), 3.72-3.65 (m, 6H), 3.54 (t, *J* = 9.0 Hz, 1H), 3.39 (d, *J* = 8.0 Hz, 1H), 2.48 (d, *J* = 11 Hz, 1H), 2.33 (d, *J* = 13 Hz, 0.3H), 1.74 (d, *J* = 13 Hz, 0.3H), 1.65 (dd, *J* = 23, 12 Hz, 1H), 1.53 (s, 3H), 1.51 (s, 1H), 1.43 (s, 5H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.7, 138.5, 138.4, 138.3, 138.2, 138.1, 138, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 109.4, 109.3, 108.7, 108.6, 100.5, 97.3, 96.3, 79.3, 78.2, 77.9, 77.5, 75.0, 74.9, 71.8, 71.5, 71.2, 71.0, 70.9, 70.7, 70.6, 70.4, 69.1, 68.9, 68.7, 67.7, 65.7, 65.4, 36.5, 35.4, 26.2, 26.1, 26.0, 25.0, 24.9, 24.6, 24.4. IR (film, cm^{-1}) 3061, 3031, 2988, 2939, 2900, 2863, 1603, 1496, 1454, 1381, 1255, 1209, 1068; HRMS (ESI) calcd for $C_{39}H_{48}O_{10}Na$ (M + Na) 699.31397, found 699.31658.

2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranose (124). A 50 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranose 123 [155] (3.5 g, 7.52 mmol, 1.0 equiv.) and THF (38 mL). The solution was cooled to 0 ^{o}C, and a solution of NH_3 in methanol (7N, 16.1 mL, 112.79 mmol, 15 equiv.) was slowly added. The resulting mixture was warmed to 25 ^{o}C and stirred for 2 h. The mixture was concentrated *in vacuo*, and the residue purified by silica gel flash chromatography (1/1 hexane/ethyl acetate + 1% triethylamine → 1/2 hexane/ethyl acetate + 1% triethylamine) to provide the hemiacetal **124** (2.42 g, 76%) as a pale yellow solid**.** ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.16 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.37 (t, *J* = 9.5 Hz, 1H), 5.12 – 5.06 (m, 2H), 4.24 (dd, *J* = 13, 5.0 Hz, 1H), 4.17 – 4.10 (m,1H), 3.87 – 3.82 (m, 2H), 3.81 (s, 3H), 3.26 (t, *J* = 8.0 Hz, 1H), 2.08 (s, 3H), 2.01 (s, 3H), 1.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 170.1, 169.5, 164.3, 162.2, 130.2, 128.2, 114.2, 95.9, 93.2, 75.3, 73.2, 72.0, 68.5, 62.4, 55.4, 20.8, 20.7, 20.5. IR (film, cm^{-1}) 3452, 1749, 1642, 1608, 1512, 1368, 1246, 1168, 1032.

2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (125). A 100 mL oven-dried Schlenk was charged with hemiacetal **124** (2.4 g, 5.67 mmol, 1.0 equiv.) and dichloromethane (30 mL). The solution was cooled to 0 ^{o}C, and trichloroacetonitrile (1.7 mL, 17.01 mmol, 3.0 equiv.) was added, followed by DBU (0.42 mL, 2.84 mmol, 0.5 equiv.). The resulting mixture was stirred at this temperature for 4 h, diluted with toluene (2 mL), and then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to provide the trichloroacetimidate **125** (2.32 g, 72%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 8.56 (s, 1H), 8.22 (s, 1H), 7.61 (d, *J* = 10 Hz, 2H), 6.86 (d, *J* = 10 Hz, 2H), 6.38 (s, 1H), 5.67 (t, *J* = 10 Hz, 1H), 5.20 (t, *J* = 10 Hz, 1H), 4.34 – 4.32 (m, 2H), 4.13 (d, *J* = 10 Hz, 1H), 3.80 (s, 3H), 3.80 – 3.77 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 170.0, 169.7, 163.9, 162.3, 160.8, 130.2, 128.6, 113.9, 95.8, 91.1, 71.0, 70.8, 70.4, 68.3, 61.8, 55.4, 20.7, 20.6. IR (film, cm^{-1}) 3334, 2961, 2839, 1752, 1674, 1642, 1605, 1579, 1512, 1246, 1065, 1021. HRMS (ESI): calc. for $C_{22}H_{25}C_{l3}N_2O_9$ (M+Na): 589.0518 ; found: 589.0525.

2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (126). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.15 mmol, 1.0 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (50.7 mg, 0.19 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 3 h, diluted with benzene (2 mL),

and purified by silica gel flash column chromatography (3/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **126** (93 mg, 93%, α:β = 10:1). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.17 (s, 1H), 7.64 (d, *J* = 10 Hz, 2H), 6.86 (d, *J* = 10 Hz, 2H), 5.61 (t, *J* = 10 Hz, 1H), 5.46 (d, *J* = 5.0 Hz, 1H), 5.08 (t, *J* = 10 Hz, 1H), 4.89 (d, *J* = 5.0 Hz, 1H), 4.46 (d, *J* = 10 Hz, 1H), 4.34 (dd, *J* = 10, 4.0 Hz, 1H), 4.28 – 4.23 (m, 3H), 4.07 (d, *J* = 10 Hz, 1H), 4.01 (t, *J* = 5.0 Hz 1H), 3.80 (s, 3H), 3.80 (m, 1H), 3.72 – 3.70 (m, 1H), 3.54 (dd, *J* = 10, 3.2 Hz, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.83 (s, 3H), 1.52 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 1.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.9, 170.1, 169.9, 163.6, 163.5, 162.1, 130.2, 128.6, 128,3, 114.0, 108.9, 108.7, 100.5, 96.2, 72.2, 71.5, 70.7, 70.4, 68.9, 67.8, 67.7, 66.4, 62.3, 55.4, 26.2, 25.9, 24.9, 24.0, 20.8, 20.76, 20.6. IR (film, cm^{-1}**)** 3427, 3349, 2987, 2935, 1745, 1642, 1608, 1513, 1376, 1251, 1165, 1110, 1069, 1029. *J*(^{13}CH) = 171 Hz (100.5 Hz). HRMS (ESI): calc. for $C_{32}H_{43}NO_{14}$ (M+H): 666.2756; found: 666.2753.

2-Benzylideneamino-2-deoxy-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranose (127). A 250 mL round bottom flask was charged with D-glucosamine hydrochloride (3.0 g, 13.912 mmol, 1.0 equiv) and NaOH (1M, 14.4 mL, 1.05 equiv.). To this resulting clear solution was added benzaldehyde (1.43 mL, 14.051 mmol, 1.01 equiv.). The reaction mixture was stirred vigorously as room temperature for 4 h, and then stirred at 0 ^{o}C overnight. The resulting pale yellow crystals were filtered and washed with diethyl ether (2 x 12 mL), resulting in the benzylidene intermediate as white solids. This intermediate was dried overnight and used in the next step without further purification. To this benzylidene intermediate in an oven dried and argon flushed 50 mL Schlenk flask was added anhydrous pyridine (12 mL). The resulting mixture was cooled to 0 ^{o}C and acetic anhydride (5.6 mL, 59.14 mmol,) was added, followed by DMAP (21.7 mg, 0.18 mmol). The reaction mixture was slowly warmed back to room temperature and stirred overnight. The reaction mixture was poured into ice (66 mL), and the resulting white crystals was

vacuum filtered, washed with cold water (2 x 5 mL), diethyl ether (2 x 5 mL) and dried under vacuum forming the desired product **127** (4.7 g, 78%) as white solids. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.22 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.44 - 7.37 (m, 3H), 5.95 (d, *J* = 8.5 Hz, 1H), 5.43 (t, *J* = 9.5 Hz 1H), 5.13 (t, *J* = 10, Hz, 1H), 4.37 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.11 (dd, *J* = 13. 1.5 Hz, 1H), 3.98 - 3.95 (m, 1H), 3.48 (t, *J* = 8.5 Hz, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H) 1.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 169.9, 169.5, 168.7, 165.1, 135.3, 131.5, 128.7, 128.6, 93.1, 73.1, 73.0, 72.8, 68.0, 61.8, 20.8, 20.76, 20.7, 20.5. IR (film, cm^{-1}**)** 2951, 2876, 1753, 1646, 1368, 1221, 1073, 1036.

2-Benzylideneamino-2-deoxy-3,4,6-*tri*-*O*-acetyl-D-glucopyranose (128). A 50 mL oven-dried and argon flushed Schlenk flask was charged with 2-benzylideneamino-2-deoxy-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranose **127** (2.1 g, 4.82 mmol, 1.0 equiv.) and THF (24 mL). The solution was cooled to 0 ^{o}C, and a solution of NH_3 in methanol (7N, 10 mL, 72.3 mmol, 15 equiv.) was slowly added. The resulting mixture was warmed to 25 ^{o}C and stirred for 2 h. The mixture was concentrated *in vacuo* at room temperature, and the residue was purified by silica gel flash column chromatography (1/1 hexane/ethyl acetate + 2% triethylamine → 1/2 hexane/ethyl acetate + 2% triethylamine) to provide the hemiacetal 128 (1.18 g, 62%) as pale yellow solids. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.26 (s, 0.6H), 8.23 (s, 1H), 7.70 - 7.67 (m, 3H), 7.45 - 7.33 (m, 5H), 5.53 (t, *J* = 9.5 Hz, 0.5H), 5.39 (t, *J* = 10 Hz, 1H), 5.21 (d, *J* = 3 Hz, 0.6H) 5.12 - 5.06 (m, 2H), 4.42 (d, *J* = 10 Hz, 1H), 4.35 (dd, *J* = 13, 4.0 Hz, 1H), 4.23 (dd, *J* = 13, 5.0 Hz, 1H), 4.16 - 4.10 (m,1H), 3.84 - 3.82 (m, 1H), 3.55 (dd, *J* = 10, 3.5 Hz, 0.6H), 3.30 (t, *J* = 9.5 Hz, 1H), 2.09 (s, 1.7H), 2.07 (s, 3H), 2.01 (s, 4.6H), 1.85 (s, 1.7H), 1.84 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.0, 169.9, 169.7, 165.4, 165.1, 135.3, 134.8, 131.9, 131.5, 128.8, 128.7, 128.6, 95.7, 93.2, 75.4, 73.1, 72.4, 72.0, 71.0, 68.5, 68.3, 68.0, 62.4,

62.2, 20.8, 20.7, 20.5. IR (film, cm^{-1}) 3461, 2947, 2876, 1749, 1642, 1450, 1368, 1231, 1147, 1033.

2-Benzylideneamino-2-Deoxy-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (129). A 25 mL oven-dried and argon flushed Schlenk flask was charged with the hemiacetal **128** (0.84 g, 2.12 mmol, 1.0 equiv.) and dichloromethane (11 mL). The solution was cooled to 0 ^{o}C, and trichloroacetonitrile (0.70 mL, 6.37 mmol, 3.0 equiv.) was added, followed by DBU (0.16 mL, 1.06 mmol, 0.5 equiv.). The reaction mixture was stirred at this temperature for 3 h, after which it was slowly warmed back to room temperature and stirred for additional 2 h. This resulting dark brown reaction mixture was then diluted with toluene (2 mL), and concentrated *in vacuo* at room temperature. The resulting residue was purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to provide the trichloroacetimidate **129** (0.80 g, 70%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 8.58 (s, 1H), 8.31 (s, 1H), 7.67 (d, *J* = 7.0 Hz, 2H), 7.42 - 735 (m, 3H), 6.41 (d, *J* = 4 Hz 1H), 5.71 (t, *J* = 10 Hz, 1H), 5.22 (t, *J* = 10 Hz, 1H), 4.36 - 4.32 (m, 2H), 4.14 (d, *J* = 11 Hz, 1H), 3.83 (m, 1H), 2.08 (s, 3H), 2.04 (s, 3H), 1.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 170.0, 169.7, 164.8, 160.9, 135.5, 131.4, 128.6, 70.9, 70.4, 68.2, 61.8, 20.7, 20.6. IR (film, cm^{-1}) 3338, 2965, 2866, 1753, 1675, 1646, 1453, 1368, 1228, 1147, 1061, 1024.

2-Deoxy-2-*p*-fluorobenzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranose (131). A 100 mL round bottom flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranoside **123** [155] (2.728 g, 5.861 mmol, 1.0 equiv) and acetone (13.4 mL). The resulting solution was heated under reflux at 85 ^{o}C. To this refluxing solution was added 5N HCl (1.34 mL, 6.691 mmol, 1.14 equiv). After the reaction mixture had been stirring for about one minute, a white thick

precipitate was formed. The mixture was cooled to room temperature, and stirring was continued for about 25 min. The precipitate was filtered, washed with hexanes (3x10 mL), acetone (5 mL), and diethyl ether (2 x 5 mL). The crude product was dried under vacuum overnight to provide the crude amine hydrochloride salt **130** [155] (2.25 g).

To a 100 mL round bottom flask was charged with the crude amine hydrochloride salt **130** (2.25 g, 5.86 mmol, 1.0 equiv), 1M NaOH (6.07 mL, 6.07 mmol, 1.04 equiv), and CH_2Cl_2 (8 mL). To this resulting pale yellow solution was added 4-fluorobenzaldehyde (0.74 mL, 6.862 mmol, 1.17 equiv). The resulting mixture was stirred at room temperature for 3 h, concentrated *in vacuo*, and dried by azeotropic removal of water using benzene (3x10 mL). The resulting residue was purified by silica gel flash column chromatography (2/1 hexane/ethyl acetate + 1% triethylamine → 1/2 hexane/ethyl acetate + 1% triethylamine) to provide the desired product **131** (1.92 g, 72%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.17 (s, 1H), 7.68 (t, *J* = 6.5 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 2H), 5.92 (d, *J* = 8.0 Hz, 1H), 5.41 (t, *J* = 10 Hz 1H), 5.12 (t, *J* = 9.5, Hz, 1H), 4.35 (dd, *J* = 13, 4.0 Hz, 1H), 4.10 (d, *J* = 13 Hz, 1H), 3.95 (d, *J* = 7.5 Hz, 1H), 3.45 (t, *J* = 9.0 Hz, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H) 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 169.9, 169.5, 168.7, 165.8, 163.8, 163.6, 131.6, 130.61, 130.6, 116.0, 115.8, 93.0, 73.1, 72.84, 72.8, 67.9, 61.8, 20.8, 20.79, 20.7, 20.5. IR (film, cm^{-1}**)** 2876, 1752, 1645, 1602, 1509, 1368, 1225, 1077, 1036**.** HRMS (ESI): calc. for $C_{21}H_{25}FNO_9$ (M+H): 454.1508 ; found: 454.1514.

2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranose (132).

A 50 mL oven-dried Schlenk flask was charged with **131** (1.485 g, 3.275 mmol, 1.0 equiv) and THF (16 mL). The solution was cooled to 0 ^oC, and a solution of NH_3 in methanol (7N, 7.02 mL, 49.15 mmol, 15 equiv.) was then slowly added. The resulting mixture was warmed to 25 ^oC and stirred for 2 h. The mixture was concentrated *in vacuo*, and the resulting residue was purified by silica gel flash column chromatography (1/1

hexane/ethyl acetate + 1% triethylamine →1/2 hexane/ethyl acetate + 1% triethylamine) to provide hemiacetal **132** (0.98 g, 73%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.20 (s, 1H), 7.70 (m, 2H), 7.06 (m, 2H), 5.38 (t, *J* = 9.5 Hz, 1H), 5.12 - 5.06 (m, 2H), 4.25 (dd, *J* = 12.0, 5.0 Hz, 1H), 4.17 - 4.10 (m, 1H), 3.98 (s, 1H), 3.86 - 3.85 (m, 1H), 3.29 (t, *J* = 8.5 Hz, 1H), 2.08 (s, 3H), 2.01 (s, 3H), 1.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 169.8, 169.6, 165.7, 163.8, 163.5, 131.5, 130.6, 115.9, 95.7, 93.1, 75.2, 73.3, 72.0, 68.2, 62.4, 20.8, 20.7, 20.5. IR (film, cm^{-1}) 3445, 2950, 2868, 1749, 1645, 1601, 1512, 1368, 1231, 1154, 1032. HRMS (ESI): calc. for $C_{19}H_{22}FNO_8$ (M+H): 412.1402 ; found: 412.1407.

2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (133). A 50 mL oven-dried Schlenk flask was charged with the hemiacetal **132** (0.86 g, 2.092 mmol, 1.0 equiv.) and dichloromethane (11 mL). The solution was cooled to 0 ^{o}C, and trichloroacetonitrile (0.63 mL, 6.277 mmol, 3.0 equiv.) was then added, followed by DBU (0.16 mL, 1.046 mmol, 0.5 equiv.). The resulting reaction mixture was stirred at this temperature for 3 h, diluted with toluene (2 mL) and then concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (3/2, hexane/ethyl acetate + 1% triethylamine) to provide D-glucosamine trichloroacetimidate **133** (1.05 g, 90%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.57 (s, 1H), 8.26 (s, 1H), 7.66 (dd, *J* = 8.0, 6.0 Hz, 2H), 7.04 (t *J* = 8.5 Hz, 2H), 6.39 (d, *J* = 3.5 Hz, 1H), 5.68 (t, *J* = 9.5 Hz, 1H), 5.21 (t, *J* = 10 Hz, 1H), 4.35 - 4.31 (m, 2H), 4.13 (d, *J* = 11 Hz, 1H), 3.82 (dd, *J* = 10, 3.5 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 169.9, 169.6, 165.7, 163.3, 160.8, 131.7, 130.6, 130.5, 115.8, 115.7, 95.7, 70.8, 70.7, 70.4, 68.1, 61.7, 20.7, 20.5. IR (film, cm^{-1}) 3338, 2961, 2861, 1749, 1674, 1645, 1597, 1509, 1368, 1228, 1150, 1021. HRMS (ESI): calc. for $C_{21}H_{23}C_{l3}FN_2O_8$ (M+H): 555.0499; found: 555.0492.

2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranose (134). A 100 mL round bottom flask was charged with the amine hydrochloride salt **130** [155] (2.26 g, 5.86 mmol, 1.0 equiv), 1M NaOH (6.09 mL, 6.09 mmol, 1.04 equiv), and CH_2Cl_2 (8 mL). To this resulting pale yellow solution was added 4-(Trifluoromethyl) benzaldehyde (0.9 mL, 6.86 mmol, 1.17 equiv). The resulting mixture was stirred vigorously at room temperature for 2 h, concentrated *in vacuo*, and then dried by azeotropic removal of water using benzene (3 x 10 mL). The resulting residue was purified by silica gel flash column chromatography (2/1 hexane/ethyl acetate + 1% triethylamine) to provide the desired product **134** (2.1 g, 70%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.27 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 5.95 (d, *J* = 8.0 Hz, 1H), 5.44 (t, *J* = 9.5 Hz 1H), 5.14 (t, *J* = 10 Hz, 1H), 4.37 (dd, *J* = 13, 4.5 Hz, 1H), 4.11 (d, *J* = 12 Hz, 1H), 3.98 (dd, *J* = 9.5, 2.0 Hz, 1H), 3.51 (t, *J* = 9.0 Hz, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H) 1.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 169.9, 169.5, 168.7, 163.6, 138.2, 133.0, 128.8, 125.7, 92.9, 72.96, 72.9, 72.8, 67.9, 61.7, 20.8, 20.7, 20.5. IR (film, cm^{-1}**)** 2948, 2880, 1753, 1650, 1372, 1324, 1221, 1169, 1128, 1065, 1034**.**

2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranose (135). A 50 mL oven-dried Schlenk flask was charged with **134** (1.91 g, 3.789 mmol, 1.0 equiv) and THF (19 mL). The solution was cooled to 0 ^{o}C, and a solution of NH_3 in methanol (7N, 8.1 mL, 56.833 mmol, 15 equiv.) was slowly added. The resulting mixture was warmed to 25 ^{o}C and stirred for 2 h. The mixture was concentrated *in vacuo*, and the residue was purified by silica gel flash column chromatography (1/1 hexane/ethyl acetate + 1% triethylamine →1/2 hexane/ethyl acetate + 1% triethylamine) to provide the hemiacetal **135** (1.14 g, 65%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.29 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 5.38 (t, *J* = 10 Hz, 1H), 5.14 - 5.08 (m, 2H), 4.26 (dd, *J* = 13, 7.5 Hz, 1H), 4.18 - 4.12 (m, 1H), 3.88 - 3.86

(m, 1H), 3.35 (t, *J* = 9.0 Hz, 1H), 2.09 (s, 3H), 2.02 (s, 3H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 169.9, 169.6, 163.8, 163.6, 163.5, 138.3, 128.6, 128.8, 125.71, 125.7, 124.8, 95.6, 93.1, 75.3, 72.9, 72.1, 68.4, 62.4, 20.8, 20.7, 20.5. IR (film, cm^{-1}) 3439, 2954, 2876, 1749, 1645, 1323, 1231, 1169, 1228, 1066, 1033.

2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (136). A 25 mL oven-dried Schlenk flask was charged with hemiacetal **135** (0.77 g, 1.678 mmol, 1 equiv.) and dichloromethane (8 mL). The solution was cooled to 0 ^{o}C, and trichloroacetonitrile (0.5 mL, 5.035 mmol, 3 equiv.) was added followed by DBU (0.1 mL, 0.839 mmol, 0.5 equiv.). The resulting reaction mixture was stirred at this temperature for 3 h, diluted with toluene (2 mL), and then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (5/1, benzene/ethyl acetate + 1% triethylamine) to provide the imidate **136** (0.8 g, 78%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.58 (s, 1H), 8.35 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 6.42 (d, *J* = 3.0 Hz, 1H), 5.72 (t, *J* = 9.5 Hz, 1H), 5.22 (t, *J* = 10.0 Hz, 1H), 4.36 - 4.32 (m, 2H), 4.15 (d, *J* = 10.0 Hz, 1H), 3.87 (dd, *J* = 10.0, 3.5 Hz, 1H), 2.08 (s, 3H), 2.04 (s, 3H), 1.87 (s, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 169.9, 169.6, 165.7, 163.4, 160.8, 138.4, 128.7, 125.6, 95.3, 70.8, 70.7, 70.4, 68.1, 61.7, 20.7, 20.5. IR (film, cm^{-1}) 3338, 2961, 2876, 1749, 1678, 1649, 1368, 1323, 1228, 1168, 1128, 1065, 1024.

2-Benzylideneamino-2-deoxy-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (137). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **129** (80.7 mg, 0.150 mmol, 1.0 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (50.8 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from

$Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/1, benzene/ethyl acetate + 1% triethylamine) to give the desired disaccharide **137** (87 mg, 92%, α:β = 10:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.24 (s, 1H), 7.68 (d, *J* = 7.0 Hz, 2H), 7.39 - 7.30 (m, 3H), 5.64 (t, *J* = 10 Hz, 1H), 5.43 (d, *J* = 5.0 Hz, 1H), 5.08 (t, *J* = 10 Hz, 1H), 4.89 (d, *J* = 3.0 Hz, 1H), 4.44 (d, *J* = 7.5 Hz, 1H), 4.34 (dd, *J* = 12, 4.0 Hz, 1H), 4.25 (d, *J* = 10 Hz, 2H), 4.22 (d, *J* = 2.5 Hz, 1H), 4.07 (d, *J* = 12 Hz, 1H), 3.99 (t, *J* = 6.0 Hz 1H), 3.80 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.69 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.58 (dd, *J* = 11, 3.0 Hz, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 1.83 (s, 3H), 1.52 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.1, 169.9, 165.2, 164.5, 163.6, 135.5, 131.3, 128.6, 128.5, 128.3, 108.9, 108.6, 100.3, 96.2, 72.2, 71.4, 70.6, 70.5, 70.4, 68.8, 67.8, 66.3, 62.2, 26.1, 25.8, 24.9, 23.9, 20.8, 20.7, 20.6. IR (film, cm^{-1}) 2987, 2935, 1745, 1642, 1372, 1231, 1069, 1032. HRMS (ESI): calc. for $C_{31}H_{41}NO_{13}$ (M+H): 636.2651; found: 636.2659.

2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (138). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1.0 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (50.8 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 1 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/1,

benzene/ethyl acetate + 1% triethylamine) to give the desired disaccharide **138** (94 mg, 96%, α:β = 9:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.21 (s, 1H), 7.70 (t, *J* = 6.5 Hz, 2H), 7.04 (t, *J* = 8.0 Hz, 2H), 5.63 (t, *J* = 9.5 Hz, 1H), 5.43 (d, *J* = 4.0 Hz, 1H), 5.07 (t, *J* = 9.5 Hz, 1H), 4.88 (bs, 1H), 4.44 (d, *J* = 8.0 Hz, 1H), 4.34 (dd, *J* = 12.4, 4.0 Hz, 1H), 4.22 - 4.19 (m, 3H), 4.08 - 4.03 (m, 1H), 3.99 (t, *J* = 5.9 Hz, 1H), 3.80 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.69 (dd, *J* = 10, 7.5 Hz, 1H), 3.57 (dd, *J* = 10, 2.9 Hz, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.84 (s, 3H), 1.52 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 0.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.0, 169.8, 165.6, 163.6, 162.7, 131.9, 130.5, 130.4, 115.8, 115.6, 108.9, 108.6, 100.2, 96.2, 71.9, 71.4, 70.6, 70.5, 70.4, 68.8, 67.7, 66.3, 62.2, 26.1, 25.8, 24.9, 24.0, 20.8, 20.7, 20.6**.** IR (film, cm^{-1}**)** 2987, 2938, 1749, 1645, 1597, 1509, 1372, 1231, 1154, 1069, 1032. HRMS (ESI): calc. for $C_{31}H_{40}FNO_{13}$ (M+H): 654.2556; found: 654.2549.

2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (139). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **136** (90.9 mg, 0.150 mmol, 1.0 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (50.8 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 1 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/1, benzene/ethyl acetate + 1% triethylamine) to give the desired disaccharide **138** (93 mg, 87%, α:β = 9:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.30 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.5 Hz, 2H), 5. 67 (t, *J* = 10 Hz, 1H), 5.43 (d, *J* = 4.5 Hz, 1H), 5.09 (t, *J* = 10 Hz, 1H), 4.90 (bs,

1H), 4.45 (d, *J* = 7.0 Hz, 1H), 4.34 (dd, *J* = 13, 4.0 Hz, 1H), 4.26 - 4.21 (m, 3H), 4.09 - 4.03 (m, 1H), 3.99 (t, *J* = 5.9 Hz, 1H), 3.81 (dd, *J* = 11, 6.0 Hz, 1H), 3.69 - 3.64 (m, 2H), 2.07 (s, 3H), 2.00 (s, 3H), 1.85 (s, 3H), 1.52 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz**)** δ (ppm) 170.7, 170.0, 169.7, 163.7, 162.6, 138.7, 128.8, 128.7, 128.3, 125.5, 108.9, 108.7, 100.0, 96.2, 71.9, 71.2, 70.5, 70.4, 68.7, 67.8, 67.7, 66.2, 62.1, 26.1, 25.8, 24.8, 24.0, 20.8, 20.7, 20.6. IR (film, cm^{-1}) 2987, 2935, 1749, 1645, 1372, 1320, 1231, 1164, 1128, 1069. HRMS (ESI): calc. for $C_{32}H_{40}$ F_3NO_{13} (M+H): 704.2525; found: 704.2519.

Methyl-2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzyl-α-D-glucopyranoside (144). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), methyl 2,3,4-*tri*-*O*-benzyl-α-D-glucopyranoside **44**[159] (90.6 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (8/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **144** (101 mg, 77%, α:β = 20:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.17 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.39 – 7.21 (m, 13H), 7.06 (bs, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 5.68 (t, *J* = 10 Hz, 1H), 5.15 (d, *J* = 3.0 Hz, 1H), 5.09 (t, *J* = 9.5 Hz, 1H), 5.04 (d, *J* = 12 Hz, 1H), 4.87 - 4.80 (m, 3H), 4.37 (d, *J* = 12 Hz, 1H), 4.33 – 4.27 (m, 2H), 4.20 – 4.15 (m, 2H), 4.12 – 4.05 (m, 2H), 3.92 - 3.88 (m, 2H), 3.85 – 3.81 (m, 2H), 3.69 (d, *J* = 9.5 Hz, 1H), 3.56 (s, 3H), 3.27 (s, 3H), 3.06 (dd, *J* = 9.5, 3 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.1, 169.8, 163.3,

162.1, 139.2, 138.7, 138.3, 130.4, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 114.2, 99.5, 98.0, 81.9, 80.3, 76.8, 75.6, 75.5, 75.0, 73.5, 72.5, 71.4, 71.3, 69.0, 67.7, 65.4, 62.3, 55.4, 55.2, 20.8, 20.7. IR (film, cm^{-1}) 2938, 1749, 1642, 1605, 1512, 1453, 1364, 1246, 1161, 1073, 1028**.** $J(^{13}CH)$ = 171.9 Hz (98.0 Hz) HRMS (ESI**)**: calc. for $C_{48}H_{55}NO_{14}$ (M+H): 870.3695; found: 870.3696.

Methyl-2-deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzyl-α-D-glucopyranoside (145). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1 equiv), methyl 2,3,4-*tri*-*O*-benzyl-α-D-glucopyranoside **44**[159] (90.6 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (11/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **145** (98 mg, 76%, α:β = 16:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz)) δ (ppm) 8.20 (s, 1H), 7.75 - 7.73 (m, 2H), 7.38 – 7.22 (m, 13H), 7.06 (bs, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.68 (t, *J* = 9.5 Hz, 1H), 5.15 (d, *J* = 3.0 Hz, 1H), 5.09 (t, *J* = 10 Hz, 1H), 5.01 (d, *J* = 12 Hz, 1H), 4.87 - 4.78 (m, 3H), 4.46 (d, *J* = 12 Hz, 1H), 4.35 (d, *J* = 3.5 Hz, 1H), 4.30 – 4.18 (m, 3H), 4.11 – 4.09 (m, 1H), 3.96 (t, *J* = 9.5 Hz, 1H), 3.92 - 3.82 (m, 3H), 3.70 (d, *J* = 7.0 Hz, 1H), 3.56 (dd, *J* = 10, 3.0 Hz, 1H), 3.27 (s, 3H), 3.03 (dd, *J* = 9.5, 3.5 Hz, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 170.0, 169.7, 165.6, 163.6, 162.6, 138.8, 138.6, 138.1, 131.7, 130.7, 130.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.67, 127.64, 116.0, 115.8, 99.1, 97.9, 81.8, 80.2, 76.8, 75.7, 75.0, 73.4, 72.3, 71.2, 71.0, 68.9, 67.7, 65.4, 62.2, 55.0, 20.7, 20.6. IR (film, cm^{-1})

2935, 2872, 1749, 1645, 1597, 1509, 1453, 1368, 1231, 1154, 1073, 1021. $J(^{13}CH)$ = 176.04 Hz HRMS (ESI): calc. for $C_{47}H_{52}FNO_{13}$ (M+H): 858.3495; found: 858.3506.

Methyl-2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside (146). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), methyl 2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside **61** (98.7 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (7/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **146** (107 mg, 78%, α:β = 15:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.21 (s, 1H), 7.93 (t, *J* = 8.5 Hz, 4H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.55 – 7.48 (m, 3H), 7.39 (t, *J* = 7.0 Hz, 1H), 7.36 – 7.33 (m, 3H), 7.27 (t, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 8.0 Hz 2H), 6.13 (t, *J* = 9.5 Hz, 1H), 5.68 (t, *J* = 9.5 Hz, 1H), 5.51 (t, *J* = 10 Hz, 1H), 5.19 (s, 1H), 5.12 – 5.06 (m, 2H), 4.93 (d, *J* = 2.7 Hz, 1H), 4.37 – 4.34 (m, 2H), 4.28 (dd, *J* = 12, 4.5 Hz, 1H), 4.10 (d, *J* = 12 Hz, 1H), 3.93 – 3.89 (m, 1H), 3.81 – 3.74 (m, 1H), 3.70 (s, 3H), 3.60 (dd, *J* = 10, 2.8 Hz, 1H), 3.45 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.1, 169.7, 165.8, 165.7, 165.3, 163.9, 162.1, 133.5, 133.3, 133.1, 130.2, 129.9, 129.7, 128.43, 128.40, 128.29, 113.99, 113.94, 99,1, 96.6, 92.6, 72.3, 72.1, 71.3, 71.1, 70.5, 69.5, 69.0, 68.7, 67.9, 66.5, 62.3, 55.5, 55.2, 20.8, 20.7. IR (film, cm^{-1}) 2961, 2939, 1735, 1606, 1513, 1453, 1364, 1251, 1098, 1025. $J(^{13}CH)$ = 176 Hz (96.6 Hz) HRMS (ESI): calc. for $C_{48}H_{49}NO_{17}$ (M+H): 912.3074; found: 912.3092.

Methyl-2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzyl-α-D-mannopyranoside (147). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1 equiv), methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **140** (90.6 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (7/1, benzene/ethyl acetate + 1% triethylamine) to give the desired disaccharide **147** (107 mg, 82%, α:β = 10:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.06 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.34 - 7.15 (m, 15H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.68 (t, *J* = 9.7 Hz, 1H), 5.20 (d, *J* = 3.0 Hz, 1H), 5.10 (t, *J* = 9.5 Hz, 1H), 4.94 (d, *J* = 12 Hz, 1H), 4.76 - 4.49 (m, 6H), 4.32 - 4.26 (m, 2H), 4.16 - 4.13 (m, 2H), 4.02 (d, *J* = 9.7 Hz, 1H), 3.94 - 3.76 (m, 4H), 3.74 (s, 3H), 3.55 (dd, *J* = 10, 3.0 Hz, 1H), 3.27 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.1, 169.7, 164.4, 163.4, 161.8, 138.7, 138.6, 138.4, 130.2, 130.1, 128.3, 128.2, 127.9, 127.6, 127.4, 113.7, 102.2, 98.8, 98.4, 80.3, 75.0, 74.8, 74.6, 72.6, 71.8, 71.3, 69.0, 67.7, 66.1, 62.4, 55.3, 54.6, 20.8, 20.7, 20.6. IR (film, cm^{-1}) 3063, 3030, 2935, 2912, 1749, 1642, 1609, 1576, 1513, 1455, 1336, 1245, 1032. $J(^{13}CH)$ = 171.9 Hz HRMS (ESI): calc. for $C_{48}H_{55}NO_{14}$ (M+H): 870.3695; found: 870.3696.

Disaccharide (148). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), benzyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside **141** (57.4 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A

preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (7/1, benzene/acetonitrile + 2% triethylamine) to give the desired disaccharide **148** (98 mg, 93%, α:β = 12:1) as pale yellow oil. ^{1}H NMR (CDCl$_3$, 500 MHz) δ (ppm) 8.19 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.34 – 7.30 (m, 5H), 6.98 (d, *J* = 8.5Hz, 2H), 5.62 (t, *J* = 9.7Hz, 1H), 5.19 (t, *J* = 9.9 Hz, 1H), 5.05 (s, 1H), 4.95 (d, *J* = 2.6 Hz, 1H), 4.69 (d, *J* = 12 Hz, 1H), 4.48 – 4.46 (m 3H), 4.28 (t, *J* = 5.8 Hz, 1H), 4.18 (d, *J* = 5.4 Hz, 1H), 4.08 (d, *J* = 11.4Hz, 1H), 3.88 – 3.86 (m, 1H), 3.82 (s, 3H), 3.57 (dd, *J* = 10.2, 2.9Hz, 1H), 3.36 (t, *J* = 8.1Hz, 1H), 2.10 (s, 3H), 2.01 (s, 3H), 1.84 (s, 3H), 1.52 (s, 3H), 1.32 (s, 3H), 1.20 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ (ppm) 170.9, 170.1, 169.7, 163.9, 162.4, 137.0, 130.2, 128.5, 128.3, 128.2, 127.9, 114.1, 109.2, 100.6, 95.9, 82.1, 76.2, 72.6, 71.3, 69.0, 68.6, 67.7, 66.0, 65.2, 61.7, 55.4, 28.2, 26.5, 20.8, 20.77, 20.6, 16.9. IR (film, cm^{-1}) 3065, 3032, 2987, 2939, 1749, 1642, 1608, 1576, 1513, 1457, 1380, 1309, 1247, 1165, 1147, 1029. *J*(^{13}CH) = 170.0 Hz (96.0 Hz) HRMS (ESI): calc. for $C_{36}H_{45}NO_{13}$ (M+H): 700.2964; found: 700.2977.

Disaccharide (149). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1.0 equiv), benzyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside **141** (57.4 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (9/1, benzene/acetonitrile + 1% triethylamine) to

give the desired disaccharide **149** (91 mg, 88%, α:β = 13:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.22 (s, 1H), 7.71 (t, *J* = 6.5 Hz, 2H), 7.34 - 7.24 (m, 5H), 7.08 (t, *J* = 8.5 Hz, 2H), 5.61 (t, *J* = 9.5 Hz, 1H), 5.19 (t, *J* = 10 Hz, 1H), 5.02 (s, 1H), 4.95 (d, *J* = 2.6 Hz, 1H), 4.68 (d, *J* = 12 Hz, 1H), 4.48 – 4.44 (m 3H), 4.26 (t, *J* = 6.0 Hz, 1H), 4.18 (d, *J* = 5.5 Hz, 1H), 4.09 (d, *J* = 12.0 Hz, 1H), 3.86 – 3.83 (m, 1H), 3.61 (d, *J* = 7.0 Hz, 1H), 3.35 (t, *J* = 8.5 Hz, 1H), 2.09 (s, 3H), 2.01 (s, 3H), 1.84 (s, 3H), 1.51 (s, 3H), 1.31 (s, 3H), 1.76 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.0, 169.6, 165.7, 163.6, 163.1, 162.9, 136.9, 131.7, 130.5, 130.4, 128.5, 128.3, 128.1, 127.9, 115.9, 115.7, 109.1, 100.3, 95.9, 82.1, 76.2, 75.9, 72.4, 71.1, 69.0, 68.4, 67.7, 65.1, 61.6, 28.2, 26.4, 20.8, 20.7, 20.6, 16.8. IR (film, cm^{-1}) 2991, 2935, 1752, 1642, 1601, 1509, 1456, 1375, 1231, 1146, 1073, 1032. HRMS (ESI): calc. for $C_{35}H_{42}FNO_{12}$ (M+H): 688.2764; found: 688.2769.

2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→2)-1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranoside (150). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), 1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranose **142**[167] (67.9 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 6 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, benzene/acetonitrile + 2% triethylamine) to give the desired disaccharide **150** (109 mg, 97%, α only) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 8.17 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.78 (s, 1H), 5.68 (t, *J* = 9.5 Hz, 1H), 5.53 (t, *J* = 9.0 Hz, 1H), 5.10 (t, *J* = 9.5 Hz, 1H), 5.05 (d, *J* = 9.0 Hz, 1H), 4.93 (s, 1H), 4.64

(d, *J* = 9.5 Hz, 1H), 4.37 (d, *J* = 12 Hz, 1H), 4.21 – 4.17 (m, 3H), 4.01 (d, *J* = 12 Hz, 1H), 3.79 (s, 3H), 3.75 (m, 1H), 3.53 (d, *J* = 9.0 Hz, 1H), 2.12 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.82 (s, 3H), 1.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 171.2, 170.7, 170.1, 169.9, 169.7, 169.1, 168.5, 163.3, 162.1, 130.6, 128.6, 113.9, 100.2, 91.2, 73.7, 73.4, 72.7, 72.5, 70.9, 68.8, 68.0, 66.2, 61.9, 55.4, 21.0, 20.7, 20.6, 20.2. IR (film, cm^{-1}**)** 2961, 2939, 1745, 1642, 1606, 1513, 1368, 1231, 1036. $J(^{13}CH)$ = 171.5 Hz (100.3 Hz) HRMS (ESI): calc. for $C_{34}H_{43}NO_{18}$ (M+H): 754.2553; found: 754.2554.

2-Benzylideneamino-2-Deoxy-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→2)-1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranoside (151). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **129** (80.7 mg, 0.150 mmol, 1.0 equiv), 1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranose **142**[167] (67.9 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **151** (95 mg, 87%, α only) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.26 (s, 1H), 7.79 (d, *J* = 6.5 Hz, 2H), 7.04 - 7.36 (m, 3H), 5.76 (s, 1H), 5.72 (t, *J* = 9.5 Hz, 1H), 5.54 (t, *J* = 9.0 Hz, 1H), 5.12 (t, *J* = 9.5 Hz, 1H), 5.05 (dd, *J* = 10, 2.5 Hz, 1H), 4.95 (d, *J* = 3.0 Hz, 1H), 4.66 (d, *J* = 10 Hz, 1H), 4.39 (dd, *J* = 12, 3.5 Hz, 1H), 4.24 - 4.17 (m, 3H), 4.02 (d, *J* = 11.0 Hz, 1H), 3.75 - 3.73 (m, 1H), 3.60 (dd, *J* = 11, 3.5 Hz, 1H), 2.13 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.83 (s, 3H), 1.58 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz**)** δ (ppm) 171.1, 170.6, 170.0, 169.7, 169.5, 168.9, 168.4, 164.1, 135.5, 131.3, 128.9, 128.6, 128.3,

100.1, 91.1, 73.8, 73.4, 72.6, 72.5, 70.7, 68.7, 67.9, 66.1, 61.9, 21.0, 20.7, 20.65, 20.61, 20.2. IR (film, cm^{-1}**)** 2950, 2857, 1749, 1645, 1450, 1430, 1368, 1228, 1172, 1132, 1083, 1032. HRMS (ESI): calc. for $C_{33}H_{41}NO_{17}$ (M+H): 724.2448; found: 724.2472.

2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl-(1→2)-1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranoside (152). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1 equiv), 1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranose **142**[167] (67.9 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 4 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **152** (99 mg, 89%, α only) as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.22 (s, 1H), 7.81 (t, *J* = 8.5 Hz, 2H), 7.06 (t, *J* = 10 Hz, 2H), 5.77 (s, 1H), 5.69 (t, *J* = 10 Hz, 1H), 5.53 (t, *J* = 10 Hz, 1H), 5.11 (t, *J* = 10 Hz, 1H), 5.05 (dd, *J* = 9.5, 2.0 Hz, 1H), 4.93 (d, *J* = 3.0 Hz, 1H), 4.66 (d, *J* = 10 Hz, 1H), 4.39 (dd, *J* = 12, 3.5 Hz, 1H), 4.23 - 4.16 (m, 3H), 4.01 (d, *J* = 11 Hz 1H), 3.72 (d, *J* = 8.5 Hz, 1H), 3.56 (dd, *J* = 11, 3.5 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.82 (s, 3H), 1.59 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 171.0, 170.6, 169.9, 169.6, 169.4, 169.0, 168.3, 165.7, 163.7, 162.5, 131.8, 131.0, 130.9, 128.3, 115.8, 115.6, 100.1, 91.1, 73.8, 73.3, 72.8, 72.3, 70.7, 68.7, 67.9, 66.0, 61.8, 20.9, 20.7, 20.5, 20.2. IR (film, cm^{-1}) 2954, 2861, 1749, 1642, 1601, 1509, 1372, 1228, 1154, 1083, 1032. HRMS (ESI): calc. for $C_{33}H_{40}FNO_{17}$ (M+H): 742.2314; found: 742.2380.

1-*O*-Dihydrocholesterolyl-2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranoside (153). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), 3-β-cholestanol **62** (75.8 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 8 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (12/1, benzene/acetonitrile + 2% triethylamine) to give the desired glycoconjugate **153** (101 mg, 85%, α:β = 11:1) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.19 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.63 (t, *J* = 10 Hz, 1H), 5.06 (t, *J* = 9.0 Hz, 1H), 4.92 (d, *J* = 3.5 Hz, 1H), 4.28 (d, *J* = 9.5 Hz, 1H), 4.10 (d, *J* = 10 Hz, 1H), 3.82 (s, 3H), 3.58 (dd, *J* = 11, 3.0 Hz, 1H), 3.44 – 3.48 (m, 1H), 2.08 (s, 3H), 2.01 (s, 3H), 1.84 (s, 3H), 1.76 – 0.54 (m, 47H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.1, 169.8, 164.0, 163.3, 162.0, 130.1, 128.8, 114.0, 98.4, 78.9, 71.8, 71.4, 69.4, 67.7, 62.5, 56.4, 56.3, 55.4, 54.3, 45.1, 42.6, 40.0, 39.5, 36.9, 36.1, 36.0, 35.8, 35.6, 35.5, 34.7, 32.1, 28.9, 28.6, 28.2, 28.0, 27.7, 24.2, 23.8, 22.8, 22.6, 21.2, 20.8, 20.78, 20.7, 18.7, 12.3, 12.1. IR (film, cm^{-1}) 2939, 2866, 1749, 1646, 1606, 1583, 1513, 1465, 1368, 1306, 1251, 1169, 1033. *J*(^{13}CH) = 170.7 Hz (98.4 Hz) HRMS (ESI): calc. for $C_{47}H_{71}NO_9$ (M+H): 794.5202; found: 794.5210.

Methyl-2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→4)-2,3,6-*tri*-*O*-benzyl-α-D-glucopyranoside (154). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), methyl 2,3,6-*tri*-*O*-benzyl-α-D-glucopyranoside **143** (90.6 mg, 0.195 mmol, 1.3

equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 6 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired disaccharide **154** (99 mg, 76%, α:β = 6:1) as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.85 (s, 1H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.36 – 7.11 (m, 13H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.79 - 6.78 (m, 2H), 5.75 (d, *J* = 3.5 Hz, 1H), 5.46 (t, *J* = 9.9 Hz, 1H), 5.01 (t, *J* = 9.9 Hz, 1H), 4.85 (d, *J* = 12 Hz, 1H), 4.61 - 4.51 (m, 5H), 4.41 (d, *J* = 12 Hz, 1H), 4.15 (dd, *J* = 10, 6.0 Hz, 1H), 4.07 – 3.70 (m, 7H), 3.82 (s, 3H), 3.44 (dd, *J* = 9.3, 5.5 Hz, 1H), 3.37 (s, 3H), 3.35 (dd, *J* = 10, 3.9 Hz, 1H), 2.02 (s, 3H), 1.98 (s, 3H), 1.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.1, 169.8, 163.3, 162.1, 139.2, 138.7, 138.3, 130.4, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 114.2, 99.5, 98.0, 81.9, 80.3, 76.8, 75.6, 75.5, 75.0, 73.5, 72.5, 71.4, 71.3, 69.0, 67.7, 65.4, 62.3, 55.4, 55.2, 20.8, 20.7. IR (film, cm^{-1}**)** 3430, 3349, 3287, 2935, 1745, 1638, 1601, 1512, 1453, 1364, 1246, 1161, 1102, 1032, 829, 740, 696. HRMS (ESI): calc. for $C_{48}H_{55}NO_{14}$ (M+H): 870.3695; found: 870.3727.

Methyl-2-deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→4)-2,3,6-*tri*-*O*-benzyl-α-D-glucopyranoside (155). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1.0 equiv), methyl 2,3,6-*tri*-*O*-benzyl-α-D-glucopyranoside **143** (90.6 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the

solution. The resulting mixture was stirred under argon at 25 ^{o}C for 6 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired disaccharide **155** (103 mg, 80%, α:β = 10:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.86 (s, 1H), 7.55 (d, *J* = 5.5 Hz, 2H), 7.33 – 7.13 (m, 13H), 7.02 (t, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 3.5 Hz, 2H), 5.76 (d, *J* = 3.0 Hz, 1H), 5.48 (t, *J* = 9.5 Hz, 1H), 5.02 (t, *J* = 10 Hz, 1H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.73 - 4.57 (m, 4H), 4.52 (d, *J* = 14 Hz, 2H), 4.38 (d, *J* = 12 Hz, 1H), 4.20 (dd, *J* = 12, 2.5 Hz, 1H), 4.07 – 3.88 (m, 4H), 3.81- 3.71 (m, 3H), 3.52 - 3.50 (m, 1H), 3.40 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 169.8, 169.6, 163.9, 163.6, 162.9, 138.6, 138.0, 137.7, 131.5, 130.7, 130.6, 130.5, 130.4, 128.4, 128.1, 127.9, 127.6, 127.4, 126.6, 125.7, 115.8, 115.6, 98.8, 97.5, 81.9, 80.3, 73.9, 73.5, 73.2, 72.6, 70.8, 69.3, 69.2, 68.4, 68.2, 61.8, 55.2, 55.2, 20.7, 20.5. IR (film, cm^{-1}**)** 2928, 1754, 1746, 1727, 1645, 1366, 1324, 1230, 1164, 1130. HRMS (ESI): calc. for $C_{47}H_{52}FNO_{13}$ (M+H): 858.3495; found: 858.3515.

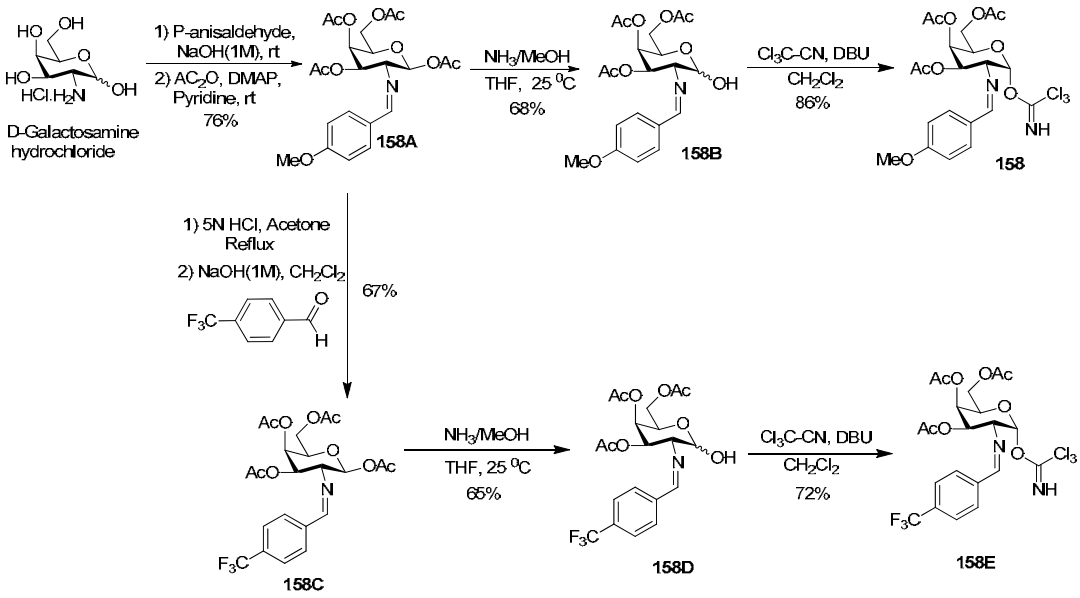
Methyl-2-deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→4)-2,3,6-*tri*-*O*-benzyl-α-D-glucopyranoside (156). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **136** (90.9 mg, 0.150 mmol, 1 equiv), methyl 2,3,6-*tri*-*O*-benzyl-α-D-glucopyranoside **143** (90.6 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 6 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, hexane/ethyl acetate + 1% triethylamine) to

give the desired disaccharide **156** (114 mg, 84%, α only) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.96 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.29 (m, 10H), 7.17 - 7.15 (m, 3H), 6.78 (dd, *J* = 6.8, 2.0 Hz, 2H), 5.79 (d, *J* = 3.6 Hz, 1H), 5.55 (t, *J* = 9.6 Hz, 1H), 5.06 (t, *J* = 10 Hz, 1H), 4.89 (d, *J* = 12 Hz, 1H), 4.67 - 4.58 (m, 4H), 4.53 (d, *J* = 12 Hz, 1H), 4.38 (d, *J* = 12 Hz, 1H), 4.22 (dd, *J* = 12, 3.6 Hz, 1H), 4.09 (ddd, *J* = 10, 5.2, 2.0 Hz, 1H), 4.03 (t, *J* = 9.6 Hz, 1H), 3.98 – 3.90 (m, 2H), 3.86 - 3.79 (m, 2H), 3.75 (dd, *J* =11, 1.6 Hz, 1H), 3.53 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.48 (dd, *J* = 10, 3.6 Hz, 1H), 3.44 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.80 (s, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.6, 169.8, 169.5, 162.9, 138.6, 138.1, 137.7, 128.7, 128.5, 128.4, 128.1, 127.9, 127.6, 127.4, 126.7, 125.6, 125.5, 114.2, 98.7, 97.5, 82.0, 80.3, 74.1, 73.9, 73.2, 72.7, 70.6, 69.4, 69.2, 68.4, 68.2, 61.8, 55.2, 55.2, 20.75, 20.7, 20.5. IR (film, cm^{-1}) 2928, 1754, 1744, 1727, 1646, 1453, 1366, 1324, 1229, 1164, 1128, 1106, 1064, 1028, 912, 836. HRMS (ESI): calc. for $C_{48}H_{52}F_3NO_{13}$ (M+H): 908.3464; found: 908.3508.

1-*O*-Adamantanolyl-2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranoside (157). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1 equiv), 1-adamantanol **65** (29.7 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 7 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (5/1, benzene/ethyl acetate + 1% triethylamine) to give the desired glycoconjugate **157** (81 mg, 96%, α:β = 17:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.18 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.5Hz,

2H), 5.66 (t, *J* = 10 Hz, 1H), 5.19 (d, *J* = 3.0 Hz, 1H), 5.05 (t, *J* = 9.5 Hz, 1H), 4.37 (d, *J* = 10 Hz, 1H), 4.32 (dd, *J* = 12, 4.5 Hz, 1H), 4.05 (d, *J* = 12 Hz 1H), 3.82 (s, 3H), 3.62 (dd, *J* = 11, 3 Hz, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 1.84 (s, 3H), 1.78 – 1.52 (m, 15H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.2, 170.0, 163.7, 162.9, 162.0, 130.1, 113.9, 92.3, 75.0, 71.5, 69.6, 67.3, 62.6, 55.4, 42.4, 36.2, 30.6, 20.8. IR (film, cm^{-1}) 2913, 2854, 1745, 1642, 1606, 1513, 1453, 1368, 1247, 1165. *J*(^{13}CH) = 167.3 Hz (92.3 Hz) HRMS (ESI): calc. for $C_{30}H_{39}NO_9$ (M+H): 558.2698; found: 558.2695.

6.2. Galactosamine Trichloroacetimidate Donors



Scheme 6.2. Synthesis of Galactosamine Trichloroacetimidate Donors **158** and **153E**.

2-Deoxy-2-*p*-methoxybenzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-galactopyranose (158A). A100 mL round bottom flask was charged with D-galactosamine hydrochloride (2 g, 9.275 mmol, 1.0 equiv) and NaOH (1M, 9.6 mL, 1.05 equiv.). To this resulting clear

solution was added benzaldehyde (1.2 mL, 9.368 mmol, 1.01 equiv.). The reaction mixture was stirred vigorously as room temperature for 2 h, and then stirred at 0 ^{o}C for 1 h. The resulting pale white crystals were filtered and washed cold water (2 x 8mL), then a 1:1 mixture of methanol and diethyl ether (2 x 3 mL) resulting in the benzylidene intermediate as white solids. This intermediate was dried overnight and used in the next step without further purification. To this benzylidene intermediate in an oven dried and argon flushed 50 mL Schlenk flask was added anhydrous pyridine (8 mL). The resulting mixture was cooled to 0 ^{o}C and acetic anhydride (3.4 mL, 40.823 mmol,) was added followed by DMAP (15 mg, 0.120 mmol). The reaction mixture was slowly warmed back to room temperature and stirred overnight. The mixture was poured into ice (42 mL), and the resulting white crystals was vacuum filtered, washed with cold water (2 x 3 mL), diethyl ether (2 x 3 mL), and dried under vacuum to form the desired product **158A** (3.3 g, 76%) as white solids. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.19 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.90 (d, *J* = 8.0 Hz, 1H), 5.44 (s, 1H), 5.23 (d, *J* = 10 Hz, 1H), 4.20 - 4.15 (m, 3H), 3.79 - 3.82 (m 3H), 3.59 (t, *J* = 8.5 Hz, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.1, 169.7, 168.8, 164.4, 162.2, 130.2, 128.4, 114.0, 93.5, 71.8, 71.6, 68.8, 65.9, 61.3, 55.4, 20.8, 20.7, 20.5, 20.5. IR (film, cm^{-1}**)** 2938, 2984, 1749, 1645, 1608, 1513, 1368, 1250, 1220, 1065, 1043.

2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-β-D-galactopyranose (158B). A 50 mL oven-dried Schlenk flask was charged with **158A** (2 g, 4.354 mmol, 1.0 equiv) and THF (22 mL). The solution was cooled to 0 ^{o}C, and a solution of NH_3 in methanol (7N, 9.3 mL, 65.304 mmol, 15 equiv.) was slowly added. The resulting mixture was warmed to 25 ^{o}C and stirred for 3 h. The mixture was concentrated *in vacuo*, and the residue purified by silica gel flash column chromatography (1/1 hexane/ethyl acetate + 1% triethylamine →1/2 hexane/ethyl acetate + 1% triethylamine) to provide hemiacetal

158B (1.25 g, 68%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.22 (s, 1H), 7.65 (d, *J* = 8.5 Hz 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.39 (d, *J* = 2.2 Hz, 1H), 5.18 (dd, *J* = 11, 3 Hz, 1H), 5.06 (d, *J* = 7.5 Hz, 1H), 4.21 - 4.16 (m, 2H), 4.03 (t, *J* = 12 Hz, 1H), 3.88 - 3.81 (m, 4H), 3.43 (t, *J* = 8.0 Hz, 1H), 2.15 (s, 3H), 2.06 (s, 3H), 1.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 170.2, 169.9, 164.8, 164.2, 162.5,162.1, 130.3, 130.2, 114.1, 114.0, 96.2, 93.8, 71.5, 71.3, 71.1, 68.8, 67.4, 67.0, 66.9, 66.3, 62.1, 55.4, 55.38, 20.8, 20.6, 20.5. IR (film, cm^{-1}) 3434, 2938, 1745, 1642, 1605, 1513, 1372, 1246, 1164, 1073. 1032.

2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (158). A 50 mL oven-dried Schlenk flask was charged with the hemiacetal **158B** (0.9 g, 2.092 mmol, 1.0 equiv.) and dichloromethane (10 mL). The solution was cooled to 0 ^{o}C, and trichloroacetonitrile (0.6 mL, 6.277 mmol, 3.0 equiv.) was added, followed by DBU (0.2 mL, 1.046 mmol, 0.5 equiv.). The resulting reaction mixture was stirred at this temperature for 3 h, warmed back to room temperature, and stirred for an additional 1 h. The mixture was then diluted with toluene (2 mL) and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to provide D-galactosamine trichloroacetimidate **158** (1.02 g, 86%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.53 (s, 1H), 8.27 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.39 (d, *J* = 3.3 Hz, 1H), 5.57 - 5.53 (m, 2H), 4.54 (t, *J* = 6.2 Hz, 1H), 4.20 (dd, *J* = 11, 6.6 Hz, 1H), 4.10 (dd, *J* = 12, 6.7 Hz, 1H), 3.98 (dd, *J* = 11, 3.5 Hz, 1H), 3.81 (s, 3H), 2.17 (s, 3H), 2.02 (s, 3H), 1.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.4, 170.1, 169.9, 164.1, 162.1, 161.0, 130.2, 128.7, 113.9, 96.5, 69.3, 68.8, 66.7, 66.1, 61.7, 55.4, 20.74, 207.73, 20.7**.** IR (film, cm^{-1}**)** 3345, 2961, 2938, 1749, 1674, 1642, 1605, 1512, 1372, 1250, 1061, 1032. HRMS (ESI): calc. for $C_{22}H_{25}C_{l3}N_2O_9$ (M+Na): 589.0518; found: 589.0522.

2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-galactopyranose (158C). A 100 mL round bottom flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-galactopyranoside **158A** (2.8 g, 6.016 mmol, 1.0 equiv) and acetone (14 mL). The resulting solution was refluxed at 85 ^{o}C. To this refluxing solution was added 5N HCl (1.4 mL, 6.982 mmol, 1.1 equiv). After the reaction mixture had been stirring for about a minute, a white thick precipitate was formed. The mixture was cooled to room temperature, and stirring was continued for another 25 min. The precipitate was filtered, washed with hexane (3 x 10 mL), acetone (1 x 5 mL), and diethyl ether (2 x 5 mL). The crude product was dried under vacuum overnight to provide the crude amine hydrochloride salt **130** (2.1 g) as white solid.

A 100 mL round bottom flask was charged with the crude amine hydrochloride salt **130** (2.1 g, 5.465 mmol, 1.0 equiv), 1M NaOH (5.7 mL, 5.656 mmol, 1.04 equiv), and CH_2Cl_2 (8 mL). To this resulting pale yellow solution was added 4-(trifluoromethyl) benzaldehyde (0.9 mL, 6.394 mmol, 1.17 equiv). The resulting mixture was stirred at room temperature for 3 h, concentrated *in vacuo*, and dried by azeotropic removal of water using benzene (3 x 10 mL). The resulting residue was purified by silica gel flash column chromatography (2/1 hexane/ethyl acetate + 1% triethylamine) to provide the desired product **158C** (2.1 g, 67%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.32 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 5.93 (d, *J* = 8.0 Hz, 1H), 5.44 (d, *J* = 2.5 Hz 1H), 5.25 (dd, *J* = 11, 3 Hz, 1H), 4.2 – 4.13 (m, 3H), 3.67 (t, *J* = 8.5 Hz, 1H), 2.15 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H) 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.4, 170.1, 170.0, 168.6, 163.8, 138.3, 133.1, 132.8, 128.7, 125.7, 93.2, 71.8, 71.3, 68.9, 65.7, 61.2, 20.7, 20.5. IR (film, cm^{-1}**)** 2939, 2888, 1753, 1653, 1372, 1324, 1221, 1165, 1128, 1062, 1043**.**

2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-D-galactopyranose (158D). A 50 mL oven-dried Schlenk flask was charged with **158C** (1.7

g, 3.298 mmol, 1 equiv) and THF (17 mL). The solution was cooled to 0 ^{o}C, and a solution of NH_3 in methanol (7N, 7.1 mL, 49.462 mmol, 15 equiv.) was slowly added. The resulting mixture was warmed to 25 ^{o}C and stirred for 2 h. The mixture was concentrated *in vacuo*, and the residue was purified by silica gel flash column chromatography (1/1 hexane/ethyl acetate + 1% triethylamine →1/2 hexane/ethyl acetate + 1% triethylamine) to provide the hemiacetal **158D** (1.144 g, 65%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.35 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 5.41 – 5.40 (m, 1H), 5.14 - 5.08 (m, 2H), 5.22 (dd, *J* = 11, 3.0 Hz, 1H), 5.07 (d, *J* = 7.5 Hz 1H), 4.21 - 4.08 (m, 3H), 4.05 (t, *J* = 6.5 Hz, 1H), 3.51 (dd, *J* = 10, 8.0 Hz, 1H), 2.15 (s, 3H), 2.06 (s, 3H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 170.2, 169.8, 163.8, 163.6, 164.0, 163.7, 138.4, 128.8, 128.7, 125.8, 125.7, 95.9, 93.6, 71.4, 71.1, 68.4, 67.8, 67.0, 66.8, 66.1, 62.1, 20.7, 20.5. IR (film, cm^{-1}) 3435, 2891, 1749, 1650, 1372, 1328, 1235, 1168, 1128, 1069.

2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (158E). A 25 mL oven-dried Schlenk flask was charged with hemiacetal **158D** (0.9 g, 2.011 mmol, 1.0 equiv.) and dichloromethane (10 mL). The solution was cooled to 0 ^{o}C, and trichloroacetonitrile (0.6 mL, 6.034 mmol, 3.0 equiv.) was added followed by DBU (0.2 mL, 0.839 mmol, 0.5 equiv.). The resulting reaction mixture was stirred at this temperature for 3 h, diluted with toluene (2 mL) and then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (10/1, benzene/acetonitrile + 1% triethylamine) to provide the desired imidate **158E** (0.9 g, 72%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.55 (s, 1H), 8.40 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 6.44 (d, *J* = 3.5 Hz, 1H), 5.58 (s, 2H), 4.57 (t, *J* = 6.5 Hz, 1H), 4.23 - 4.19 (m, 1H), 4.13 – 4.06 (m, 2H), 2.17 (s, 3H), 2.02 (s, 3H), 1.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.4, 170.1, 169.8, 163.6, 160.9, 138.6, 132.7, 128.7, 125.6, 96.1, 69.4, 68.6, 66.5, 66.3, 61.6,

20.7, 20.6. IR (film, cm^{-1}) 3342, 2969, 2880, 1752, 1675, 1650, 1372, 1324, 1231, 1169, 1132, 1066, 1033.

Methyl-2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-galactopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside (159). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **158** (62.5 mg, 0.11 mmol, 1 equiv), methyl 2,3,4-*tri*-*O*-benzoyl-α-D-glucopyranoside **61** (72.4 mg, 0.143 mmol, 1.3 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (6.8 mg, 0.011 mmol, 10 mol %) and AgOTf (5.7 mg, 0.022 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 6 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (10/1, benzene/acetonitrile + 2% triethylamine) to give the desired disaccharide **159** (74 mg, 78%, α:β = 14:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.26 (s, 1H), 7.94 (t, *J* = 8.0 Hz, 3H), 7.85 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.49 – 7.47 (m, 2H), 7.39 – 7.34 (m, 6H), 7.28 (t, *J* = 7.5 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.12 (t, *J* = 9.5 Hz, 1H), 5.60 – 5.54 (m, 2H), 5.51 (s, 1H), 5.17 (d, *J* = 2.5 Hz, 1H), 5.09 (dd, *J* = 11, 3.5 Hz, 1H), 4.96 (d, *J* = 2.5 Hz, 1H), 4.48 (m, 1H), 4.29 (t, *J* = 7.5 Hz, 1H), 4.14 – 4.13 (m, 1H), 4.07 – 4.03 (m, 1H), 3.92 – 3.90 (m, 1H), 3.84 – 3.82 (m, 1H), 3.78 (s, 1H), 3.69 (s, 3H), 3.41 (s, 3H), 2.14 (s, 3H), 2.00 (s, 3H), 1.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 170.2, 169.9, 168.8, 165.7, 165.2, 164.4, 163.7, 162.0, 133.4, 133.3, 133.1, 130.2, 130.0, 129.9, 129.87, 129.7, 129.3, 129.1, 129.0, 128.8, 128.6, 128.5, 128.4, 128.34, 128.29, 113.98, 113.92, 99.84, 96.7, 93.3, 72.2, 70.5, 69.4, 69.2, 68.8, 68.7, 67.6, 67.4, 66.9, 66.7, 66.3, 62.3, 61.6, 55.5, 55.2, 20.79, 20.7. IR (film, cm^{-1}) 2961, 2939, 2844, 1739, 1642, 1606, 1579, 1512, 1450, 1372, 1250, 1165,

1095, 1029. $J(^{13}CH)$ = 172.5 Hz (96.7 Hz) HRMS (ESI): calc. for $C_{48}H_{49}NO_{17}$ (M+H): 912.3074; found: 912.3103.

Disaccharide (160). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **158** (62.5 mg, 0.11 mmol, 1.0 equiv), benzyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside **141** (42.1 mg, 0.143 mmol, 1.3 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (6.76 mg, 0.011 mmol, 10 mol %) and AgOTf (5.65 mg, 0.022 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 4 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (8/1, benzene/acetonitrile + 2% triethylamine) to give the desired disaccharide **160** (62 mg, 80%, α:β = 12:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.24 (s, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.34 – 7.27 (m, 5H), 6.92 (d, *J* = 8.5 Hz, 2H), 5.53 – 5.49 (m, 2H), 5.02 (s, 1H), 4.95 (d, *J* = 3.0 Hz, 1H), 4.69 (d, *J* = 12 Hz, 1H), 4.66 – 4.64 (m 1H), 4.47 (d, *J* = 12 Hz, 1H), 4.27 (t, *J* = 6.0 Hz, 1H), 4.21 – 4.13 (m, 3H), 3.87 – 3.80 (m, 2H), 3.81 (s, 3H), 3.36 (t, *J* = 8.0 Hz, 1H), 2.15 (s, 3H), 2.03 (s, 3H), 1.85 (s, 3H), 1.52 (s, 3H), 1.33 (s, 3H), 1.19 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.4, 170.2, 169.8, 163,9, 162.1, 137.0, 130.2, 128.6, 128.5, 128.3,128.2, 127.9, 114.0, 109.3, 101.2, 96.0, 81.8, 76.9, 72.2, 69.0, 68.8, 68.1, 67.1, 66.4, 65.2, 64.2, 60.7, 55.4, 28.1, 26.4, 20.8, 20.6, 16.9. IR (film, cm^{-1}) 2991, 2935, 1749, 1642, 1608, 1513, 1376, 1251, 1136, 1088, 1047. $J(^{13}CH)$ = 168.0 Hz (96.0 Hz) HRMS (ESI**)**: calc. for $C_{36}H_{45}NO_{13}$ (M+H): 700.2964; found: 700.2963.

2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-tri-*O*-acetyl-D-galactopyranosyl-(1→2)-1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranoside (161). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-

3,4,6-*tri*-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **158** (62.5 mg, 0.11 mmol, 1 equiv), 1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranose **142**[167] (49.8 mg, 0.143 mmol, 1.3 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (6.76 mg, 0.011 mmol, 10 mol %) and AgOTf (5.65 mg, 0.022 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 5 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, benzene/acetonitrile + 2% triethylamine) to give the desired disaccharide **161** (77 mg, 93%, α only) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 8.24 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 5.78 (s, 1H), 5.59 (d, *J* = 9.0 Hz, 1H), 5.50 – 5.47 (m, 2H), 5.05 (d, *J* = 9.0 Hz, 1H), 4.94 (s, 1H), 4.84 (m, 1H), 4.18 – 4.14 (m, 4H), 4.09 – 4.05 (m, 1H), 3.81 (s, 3H), 3.78 (m,1H), 3.74 – 3.72 (m, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.84 (s, 3H), 1.59 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 171.0, 170.34, 170.3, 169.9, 169.8, 169.2, 168.7, 163.3, 162.0, 130.6, 128.7, 113.9, 100.9, 91.2, 73.4, 73.3, 72.8, 68.6, 68.0, 66.9, 66.8, 66.4, 62.3, 61.3, 55.4, 20.78, 20.71, 20.2. IR (film, cm^-1) 2943, 1745, 1646, 1606, 1513, 1368, 1228, 1169, 1043. $J(^{13}CH)$ = 172.2 Hz (100.9 Hz) HRMS (ESI): calc. for $C_{34}H_{43}NO_{18}$ (M+H): 754.2553; found: 754.2565.

1-*O*-Dihydrocholesterolyl-2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-O-acetyl-D-galactopyranoside (162). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **158** (62.5 mg, 0.11 mmol, 1 equiv), 3-β-cholestanol **62** (55.6 mg, 0.143 mmol, 1.3 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (6.76 mg, 0.011 mmol, 10 mol %) and AgOTf (5.65 mg, 0.022 mmol, 20 mol %) in dichloromethane (1 mL) was then added. The resulting mixture was stirred under argon at

25 ^{o}C for 6 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (12/1, benzene/acetonitrile + 2% triethylamine) to give the desired glycoconjugate **162** (70 mg, 80%, α:β = 10:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.23 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5Hz, 2H), 5.51 – 5.49 (m, 2H), 4.93 (d, *J* = 3.0 Hz, 1H), 4.47 (t, *J* = 6.0 Hz, 1H), 4.14 – 4.08 (m, 2H), 3.82 (s, 3H), 3.83 – 3.80 (m, 1H), 3.48 – 3.45 (m, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 1.84 (s, 3H), 1.77 – 0.54 (m, 47H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 170.3, 169.9, 164.1, 163.3, 161.9, 130.1, 129.9, 113.9, 99.3, 78.9, 69.1, 67.7, 67.3, 66.8, 66.1, 62.5, 56.5, 56.3, 55.3, 54.3, 45.1, 42.6, 40.0, 39.5, 36.9, 36.1, 36.0, 35.8, 35.6, 35.4, 34.8, 32.1, 29.9, 28.8, 28.4, 28.0, 27.8, 24.2, 23.8, 22.8, 22.6, 21.2, 20.8, 20.7, 18.6, 12.3, 12.1. IR (film, cm^{-1}) 2935, 2866, 1749, 1646, 1608, 1583, 1513, 1465, 1372, 1251, 1165, 1036. *J*(^{13}CH**)** = 168.1 Hz (99.3 Hz) HRMS (ESI): calc. for $C_{47}H_{71}NO_9$ (M+H): 794.5201; found: 794.5188.

1-*O*-Adamantanolyl-2-deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-galactopyranoside (163). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **158** (62.5 mg, 0.11 mmol, 1 equiv), 1-adamantanol **65** (21.8 mg, 0.143 mmol, 1.3 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (6.76 mg, 0.011 mmol, 10 mol %) and AgOTf (5.65 mg, 0.022 mmol, 20 mol %) in dichloromethane (1 mL) was then added. The resulting mixture was stirred under argon at 25 ^{o}C for 12 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/1, hexane/ethyl acetate + 1% triethylamine) to give the desired glycoconjugate **163** (51 mg, 84%, α:β = 12:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.22 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.54 (d, *J* = 11 Hz, 1H), 5.49 (s, 1H), 5.20 (d, *J* = 3.0 Hz, 1H), 4.55 (t, *J* = 6.5 Hz, 1H), 4.14 – 4.10

(m, 2H), 3.84 (d, *J* = 3.0 Hz 1H), 3.82 (s, 3H), 2.13 (s, 3H), 2.03 (s, 3H), 1.84 (s, 3H), 1.78 – 168 (m, 7H), 1.60 – 1.55 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.5, 170.3, 170.1, 163.8, 162.9, 161.9, 130.0, 113.9, 93.1, 74.8, 69.2, 67.7, 67.1, 66.4, 62.3, 55.4, 42.3, 36.2, 30.6, 20.79, 20.74, 20.7. IR (film, cm^{-1}) 2910, 2854, 1745, 1646, 1606, 1549, 1517, 1453, 1368, 1309, 1250, 1165, 1124. *J*(^{13}CH) = 168.2 Hz (93.1 Hz) HRMS (ESI): calc. for $C_{30}H_{39}NO_9$ (M+H): 558.2698; found: 558.2707.

2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (167). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1 equiv), 2,3,4-*tri*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranose **164**[152-153] (107 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 3 h, diluted with toluene (1 mL), and purified by silica gel flash column chromatography (4/1, toluene/ethyl acetate + 1% triethylamine) to give the desired trisaccharide **167** (78 mg, 56%, α:β = 20:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.24 (s, 1H), 7.80 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.09 (t, *J* = 8.8 Hz, 2H), 5.63 (t, *J* = 9.6 Hz, 1H), 5.46 (d, *J* = 4.8 Hz, 1H), 5.17 (t, *J* = 9.2 Hz, 1H), 5.11 - 5.01 (m, 2H), 4.95 (d, *J* = 3.2 Hz, 1H), 4.80 (dd, *J* = 9.6, 8.0 Hz, 1H), 4.58 - 4.53 (m, 2H), 4.32 - 4.26 (m, 3H), 4.17 - 4.11 (m, 2H), 3.92 (dd, *J* = 11, 3.6 Hz, 1H), 3.86 - 3.84 (m, 1H), 3.77 - 3.70 (m, 3H), 3.69 - 3.58 (m, 2H), 2.11 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.84 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.29 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.7, 170.2, 170.0, 169.5, 169.43, 169.42, 165.9, 163.2, 131.8, 130.7,

130.6, 128.2, 115.9, 115.7, 109.3, 108.5, 101.3, 99.0, 96.1, 73.0, 72.7, 71.6, 71.0, 70.95, 70.3, 70.5, 70.4, 69.2, 69.1, 68.8, 67.9, 67.6, 66.4, 62.2, 26.0, 25.9, 25.0, 24.2, 20.8, 20.7, 20.6, 20.6. IR (film, cm^{-1}) 2988, 2939, 1754, 1745, 1717, 1699, 1683, 1652, 1646, 1635, 1601, 1510, 1435, 1376, 1228, 1153, 1036, 913. HRMS (ESI): calc. for $C_{44}H_{56}NO_{21}FNa$ (M+Na): 964.3229; found: 964.3227.

2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (168). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **136** (90.9 mg, 0.150 mmol, 1.0 equiv), 2,3,4-*tri*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranose **164**[152-153] (107 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 3 h, diluted with toluene (1 mL), and purified by silica gel flash column chromatography (1/1, hexane/ethyl acetate + 1% triethylamine) to give the desired trisaccharide **168** (85 mg, 57%, α:β =13:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.34 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 5.65 (t, *J* = 9.9 Hz, 1H), 5.46 (d, *J* = 4.9 Hz, 1H), 5.16 (d, *J* = 9.4 Hz, 1H), 5.13 - 5.06 (m, 2H), 5.03 (d, *J* = 3.4 Hz, 1H), 4.67 (dd, *J* = 9.1, 8.2 Hz, 1H), 4.56 (dd, *J* = 7.4, 5.0 Hz, 1H), 4.52 (d, *J* = 8.0 Hz, 1H), 4.32 - 4.24 (m, 3H), 4.14 - 4.07 (m, 3H), 3.89 (dd, *J* = 10.8, 3.7 Hz, 1H), 3.76 - 3.66 (m, 3H), 3.58 (dd, *J* = 10.9, 7.3 Hz, 1H), 2.10 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.95 (s, 3H), 1.85 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.29 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.0, 170.5, 170.3, 169.9, 169.7, 169.6, 163.9, 163.5, 138.7, 132.7, 129.2, 126.0, 125.9, 109.6, 108.8,

101.5, 99.1, 96.3, 92.4, 73.4, 72.9, 71.8, 71.2, 71.0, 70.9, 70.8, 70.5, 69.2, 69.1, 68.9, 68.1, 67.7, 66.0, 62.4, 60.6, 26.2, 26.1, 25.2, 24.5, 21.0, 20.9, 20.9, 20.84, 20.82. IR (film, cm^{-1}) 2988, 2939, 1791, 1754, 1744, 1726, 1700, 1683, 1652, 1646, 1635, 1430, 1376, 1324, 1222, 1167, 1128, 1066, 1036, 915, 836. $J(^{13}CH)$ = 175.3 Hz HRMS (ESI**)**: calc. for $C_{44}H_{57}NO_{21}F_3$ (M+H): 992.3392; found: 992.3375.

2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (169). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (56 mg, 0.10 mmol, 1.0 equiv), 2,3,4-*tri*-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranose **165**[152-153] (90 mg, 0.13 mmol, 1.3 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 3 h, diluted with toluene (1 mL), and purified by silica gel flash column chromatography (4/1, toluene/acetonitrile + 1% triethylamine) to give the desired trisaccharide **169** (73 mg, 67%, α:β = 20:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.26 (s, 1H), 7.78 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.41 - 7.27 (m, 15H), 6.85 (t, *J* = 8.6 Hz, 2H), 5.74 (t, *J* = 9.8 Hz, 1H), 5.55 (d, *J* = 5.0 Hz, 1H), 5.28 (d, *J* = 3.5 Hz, 1H), 5.13 (t, *J* = 9.8 Hz, 1H), 4.99 (d, *J* = 12 Hz, 1H), 4.88 (d, *J* = 11 Hz, 1H), 4.83 (d, *J* = 11 Hz, 1H), 4.76 (d, *J* = 11 Hz, 1H), 4.70 (d, *J* = 11 Hz, 1H), 4.60 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.38 - 4.31 (m, 3H), 4.26 - 4.19 (m, 3H), 4.13 (dd, *J* = 12.2, 2.0 Hz, 1H), 4.03 (t, *J* = 9.5 Hz, 1H), 3.98 - 3.94 (m, 4H), 3.65 - 3.59 (m, 2H), 3.54 (t, *J* = 9.2 Hz, 1H), 3.39 - 3.36 (m, 1H), 2.81 (t, *J* = 8.1 Hz, 1H), 2.13 (s, 3H), 2.06 (s, 3H), 1.89 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.0,

170.3, 170.0, 163.1, 139.1, 138.9, 138.8, 131.0, 130.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 116.2, 116.0, 109.6, 108.7, 104.0, 99.7, 96.5, 84.4, 82.1, 75.9, 75.8, 75.2, 74.7, 72.2, 71.5, 71.4, 70.9, 70.7, 69.1, 68.8, 67.9, 67.1, 65.4, 62.5, 26.3, 26.2, 25.2, 24.7, 21.1, 21.0, 20.9. IR (film, cm^{-1}) 2983, 2935, 1748, 1643, 1603, 1509, 1455, 1364, 1231, 1149, 1067, 1022. J(^{13}CH) = 173.3 Hz HRMS (ESI**)**: calc. for $C_{58}H_{69}NO_{18}F$ (M+H): 1086.4509; found: 1086.4499.

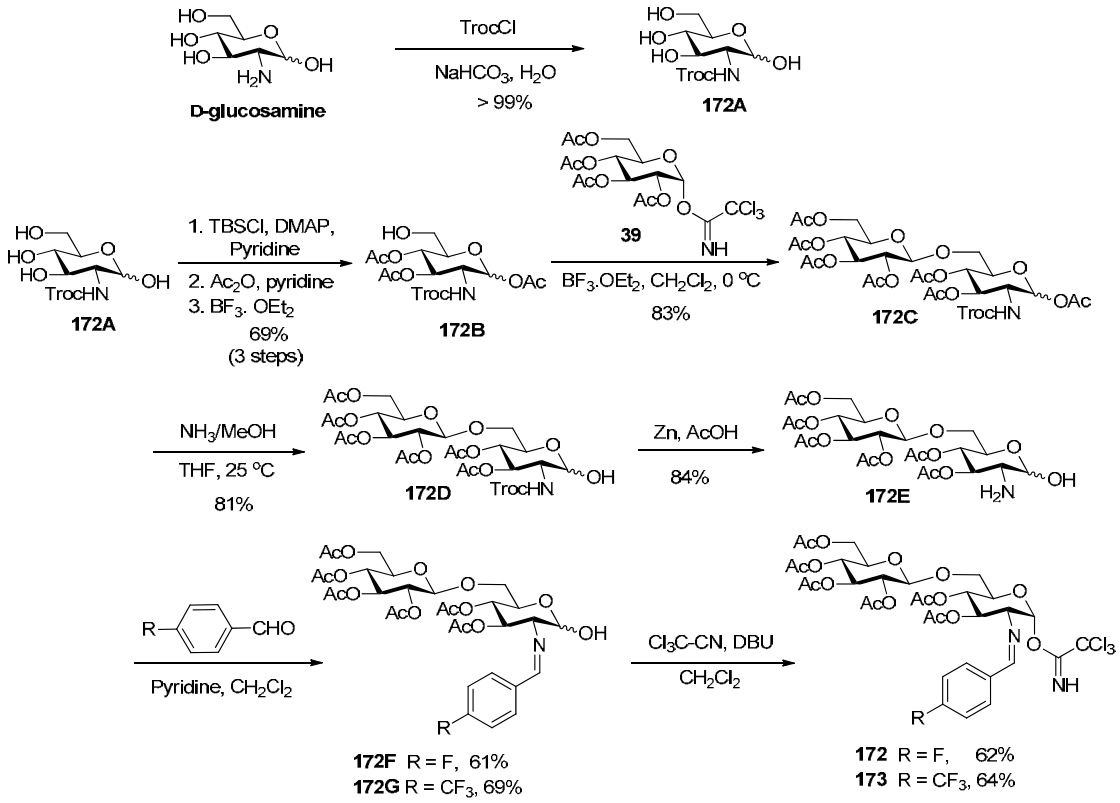
2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-*tri*-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (170). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **136** (109 mg, 0.18 mmol, 1.2 equiv), 2,3,4-*tri*-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranose **165**[152-153] (104 mg, 0.15 mmol, 1 equiv), and CH_2Cl_2 (1.2 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (5.53 mg, 0.009 mmol, 5 mol %) and AgOTf (4.63 mg, 0.018 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 3 h, diluted with toluene (1 mL), and purified by silica gel flash column chromatography (10/1, toluene/acetonitrile + 1% triethylamine) to give the desired trisaccharide **170** (119 mg, 70%, α:β = 14:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.36 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.47 - 7.20 (m, 17H), 5.77 (t, *J* = 9.9 Hz, 1H), 5.55 (d, *J* = 5.0 Hz, 1H), 5.32 (d, *J* = 3.4 Hz, 1H), 5.15 (d, *J* = 10 Hz, 1H), 5.04 (d, *J* = 11 Hz, 1H), 4.90 (d, *J* = 11 Hz, 1H), 4.84 (d, *J* = 11 Hz, 1H), 4.77 (d, *J* = 11 Hz, 1H), 4.61 - 4.58 (m, 2H), 4.39 - 4.29 (m, 3H), 4.27 - 4.24 (m, 1H), 4.23 - 4.13 (m, 3H), 4.08 (t, *J* = 9.5 Hz, 1H), 3.99 - 3.94 (m, 4H), 3.67 - 3.61 (m, 2H), 3.55 (t, *J* = 9.2 Hz, 1H), 3.38 (d, *J* = 9.6 Hz, 1H), 2.75 (dd, *J* = 9.1, 8.0 Hz, 1H), 2.14 (s, 3H), 2.07 (s, 3H), 1.89 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100

MHz) δ (ppm) 171.0, 170.3, 169.9, 163.2, 138.9, 138.8, 138.7, 129.3, 128.7, 128.6, 128.5, 128.4, 128.32, 128.3, 127.9, 127.7, 126.1, 126.0, 109.6, 108.7, 103.9, 99.6, 96.5, 84.5, 82.1, 76.0, 75.9, 75.1, 74.7, 72.4, 71.4, 70.9, 70.6, 69.0, 68.6, 68.0, 67.0, 65.4, 62.5, 26.3, 26.2, 25.2, 24.7, 21.1, 21.0, 20.9. IR (film, cm^{-1}) 2987, 2936, 1754, 1700, 1646, 1453, 1370, 1324, 1226, 1167, 1128, 1066, 1027, 900, 840. $J(^{13}CH)$ = 175.2 Hz. HRMS (ESI): calc. for $C_{59}H_{69}NO_{18}F_3$ (M+H): 1136.4467; found: 1136.4467.

Trisaccharide (171). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **136** (109 mg, 0.18 mmol, 1.2 equiv), disaccharide nucleophile **166**[154] (75 mg, 0.15 mmol, 1.0 equiv), and CH_2Cl_2 (1.2 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (5.43 mg, 0.0085 mmol, 5 mol %) and AgOTf (4.55 mg, 0.0180 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 4 h, diluted with toluene (1 mL), and purified by silica gel flash column chromatography (7/1, toluene/acetonitrile + 1% triethylamine →3/1, toluene/acetonitrile + 1% triethylamine) to give the desired trisaccharide **171** (106 mg, 76%, α:β = 11:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.31 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 5.68 (t, *J* = 9.8 Hz, 1H), 5.21 - 5.09 (m, 3H), 5.01 (dd, *J* = 10, 3.5 Hz, 1H), 4.93 (d, *J* = 3.3, Hz, 1H), 4.73 (d, *J* = 8.1 Hz, 1H), 4.36 - 4.30 (m, 2H), 4.19 - 4.12 (m, 4H), 4.05 - 3.92 (m, 2H), 3.77 - 3.72 (m, 2H), 3.65 (dd, *J* = 10, 3.2 Hz, 1H), 3.56 (dd, *J* = 7.7, 6.3 Hz, 1H), 3.51 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.84 (s, 3H), 1.43 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.1, 170.9, 170.5, 170.1, 169.9, 169.8, 163.4, 138.6, 128.9, 125.9, 125.8, 110.1, 103.4, 101.2, 98.9, 79.4, 73.5, 72.5, 71.6, 71.5, 71.2, 70.4, 69.5, 69.4, 68.9, 68.0, 66.8, 62.3, 57.2, 27.9, 26.3, 21.1, 21.0, 20.9, 20.89, 20.8, 16.1 IR (film, cm^{-1}) 2987, 2938, 1745, 1645, 1367, 1323, 1218, 1167,

1129, 1063, 1026. $J(^{13}CH)$ = 175.3 Hz HRMS (ESI): calc. for $C_{42}H_{55}NO_{20}F_3$ (M+H): 950.3274; found: 950.3270.

6.3. Synthesis of Disaccharide Donors



Scheme 6.3. Synthesis of Disaccharide Donors **172** and **173**

2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucose (172A). To a solution of D-glucosamine hydrochloride (6.5 g, 30 mmol) in 100 mL of 0.75 N $NaHCO_3$ aq. was added 2,2,2-trichloroethyl chloroformate (6.0 mL, 45 as mmol) dropwise at 0 ^oC. The reaction mixture was stirred at room temperature overnight. The resulting white precipitate formed was filtered, washed with cold distilled H_2O, and dried *in vacuo* to

provide the desired product **172A (**10.5 g, >99%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ (ppm) 5.13 (d, *J* = 3.6 Hz, 1H), 4.84 (d, *J* = 12 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 3.84 - 3.75 (m, 2 H), 3.74 - 3.64 (m, 2H), 3.60 - 3.55 (m, 1H), 3.36 (t, *J* = 9.2 Hz, 1H).

1,3,4-*Tri*-*O*-acetyl-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranose (172BB). A 250 mL oven dried and argon flushed round-bottom flask was charged with 2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucose **172A** (10.5 g, 30 mmol) and anhydrous pyridine (25 mL). To this solution was added DMAP (183 mg, 1.5 mmol) and 4 Å MS (6.0 g) under argon, and stirred at room temperature for 0.5 h. TBSCl (5.42 g, 36 mmol) was added to the reaction mixture, and stirred overnight at 40 ^{o}C. Pyridine (30 mL) and acetic anhydride (25 mL) was added and stirred again at room temperature overnight. The reaction mixture was coevaporated with toluene, and purified by silica gel flash column chromatography (5/1, toluene/ethyl acetate) to afford the desired product **172BB** (14.9 g, 83%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.23 (d, *J* = 3.6 Hz, 1H), 5.27 (t, *J* = 9.6 Hz, 1H), 5.20 (t, *J* = 9.6 Hz, 1H), 5.14 - 5.08 (m, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.10 (m, 1H), 3.86 - 3.81 (m, 1H), 3.70 - 3.65 (m, 2H), 2.18 (s, 3H), 2.04 (s, 6H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

2-Deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-1,3,4-*tri*-*O*-acetyl-D-glucopyranose (172B). To a solution of 1,3,4-*tri*-*O*-acetyl-6-*O*-(*tert*-butyl-dimethylsilyl)-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranose **172BB** (16.8 g, 28.3 mmol) in acetonitrile (200 mL) was added $BF_3{\cdot}Et_2O$ (7.2 mL, 56.6 mmol) dropwise at 0 ^{o}C. After all of $BF_3{\cdot}Et_2O$ has been added, the mixture was stirred at 0 ^{o}C. When the reaction was complete as monitored by TLC, the reaction mixture was concentrated *in vacuo*, and purified by silica gel flash column chromatography (1/1, hexane/ethyl acetate) to afford

the desired product **172B** (11.2 g, 83%) as white solids. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.24 (d, *J* = 3.6 Hz, 1H), 5.33 (t, *J* = 9.6 Hz, 1H), 5.18 - 5.13 (m, 2H), 4.81 (d, *J* = 12 Hz, 1H), 4.63 (d, *J* = 12 Hz, 1H), 4.23 - 4.15 (m, 1H), 3.85 - 3.82 (m, 1H), 3.75 - 3.69 (m, 1H), 3.60 - 3.53 (m, 1H), 2.20 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H).

2,3,4,6-*Tetra*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-1,3,4-*tri*-*O*-acetyl-D-glucopyranoside (172C). An oven dried and argon flushed 250 mL round-bottom flask was charged with 2,3,4,6-*tetra*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **39** (7.8 g, 15.8 mmol), 2-Deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-1,3,4-*tri*-*O*-acetyl-D-glucopyranose **172B** (6.3 g, 13.2 mmol) and CH_2Cl_2 (80 mL). The resulting solution was cooled to 0 ^oC, and $BF_3{\cdot}Et_2O$ (0.2 mL, 1.6 mmol) was added. The solution was stirred at 0 ^oC. When the reaction was complete as monitored by TLC, the reaction mixture was quenched with triethylamine (3 mL), concentrated *in vacuo*, and purified by silica gel flash column chromatography (4/1, toluene/acetonitrile) to afford the desired disaccharide **172C** (8.8 g, 83%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.20 (d, *J* = 3.6 Hz, 1H), 5.28 - 5.15 (m, 3H), 5.09 - 4.93 (m, 3H), 4.80 (d, *J* = 12 Hz, 1H), 4.61 (d, *J* = 12 Hz, 1H), 4.50 (d, *J* = 8.0 Hz, 1H), 4.26 (dd, *J* = 12, 4.4 Hz, 1H), 4.17 - 4.08 (m, 2H), 3.98 - 3.88 (m, 2H), 3.69 - 3.62 (m, 1H), 3.52 - 3.47 (m, 1H), 2.19 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H).

2,3,4,6-*Tetra*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-3,4-*di*-*O*-acetyl-D-glucopyranoside (172D). An oven dried and argon flushed 250 mL round-bottom flask was charged with disaccharide **172C** (5.7 g, 7.0 mmol) and THF (80 mL). To this solution was added ammonia in methanol (7N, 15 mL, 105 mmol) and stirred at room temperature. When the reaction was complete as monitored by TLC, the reaction mixture concentrated *in vacuo*, and purified

by silica gel flash chromatography (2/1, hexane/ethyl acetate → 1/2, hexane/ethyl acetate) to afford the desired disaccharide hemiacetal **172D** (4.4 g, 81%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.39 - 5.28 (m, 3H), 5.21 (t, *J* = 9.6 Hz, 1H), 5.10 (t, *J* = 9.6 Hz, 1H), 4.97 (t, *J* = 9.6 Hz, 1H), 4.90 (t, *J* = 9.6 Hz, 1H), 4.81 (d, *J* = 12 Hz, 1H), 4.63 (d, *J* = 12 Hz, 1H), 4.56 (d, *J* = 7.6 Hz, 1H), 4.32 - 4.10 (m, 4H), 4.04 - 3.93 (m, 1H), 3.83 (d, *J* = 10 Hz, 1H), 3.73 - 3.68 (m, 1H), 3.63 (dd, *J* = 7.6, 10 Hz, 1H), 2.10 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.2, 170.88, 170.86, 170.2, 169.8, 169.5, 154.2, 101.0, 95.3, 91.4, 74.4, 72.5, 71.9, 71.1, 70.9, 68.9, 68.2, 68.1, 61.6, 54.1, 21.0, 20.7, 20.6, 20.5. IR (film, cm^{-1}) 3343, 2955, 1742, 1532, 1432, 1367, 1215, 1033.

2,3,4,6-*Tetra*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-3,4-*di*-*O*-acetyl-2-deoxy-2-amino-D-glucopyranoside (172E). To a solution of disaccharide hemiacetal **172D** (4.1 g, 5.3 mmol) in acetic acid (70 mL) was added activated zinc (10.3 g, 165 mmol) portion-wise. After all of zinc was added, the mixture was stirred at room temperature overnight. The excess zinc was filtered, washed with CH_2Cl_2 (20 mL), and the filtrate co-evaporated with toluene. The residue was diluted with CH_2Cl_2 (30 mL), washed with saturated aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The resultant residue was purified by silica gel flash column chromatography (10/1, ethyl acetate/methanol) to afford the desired disaccharide amine **172E** (2.7 g, 84%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.25 - 5.15 (m, 3H), 5.08 (t, *J* = 9.6 Hz, 1H), 4.98 (t, *J* = 9.6 Hz, 1H), 4.83 (t, *J* = 9.6 Hz, 1H), 4.55 (d, *J* = 8.0 Hz, 1H), 4.24 - 4.16 (m, 3H), 3.89 - 3.84 (m, 1H), 3.72 - 3.67 (m, 1H), 3.58 (dd, *J* = 6.4, 11 Hz, 1H), 2.90 (dd, *J* = 10, 3.9 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.019 (s, 3H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.0, 170.7, 170.2, 169.8, 169.7, 169.3, 100.8, 92.9, 74.3, 72.6, 71.8, 70.9, 69.3, 68.3, 68.2, 68.0, 61.7, 54.3, 20.8, 20.7, 20.6, 20.5. IR (film, cm^{-1}**)** 3367, 2943, 1742, 1366, 1215, 1031.

2,3,4,6-*Tetra*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-3,4-*di*-*O*-acetyl-2-deoxy-2-*p*-fluorobenzylideneamino-D-glucopyranoside (172F). An oven dried 50 mL Schlenk flask was charged with the disaccharide **172E** (592 mg, 1.0 mmol), 4-fluorobenzaldehyde (0.12 mL, 1.1 mmol), and anhydrous pyridine (0.81 mL, 10.0 mmol) in CH_2Cl_2 (6 mL). The reaction was stirred under reflux overnight. The reaction mixture was concentrated *in vacuo*, and purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine → 1/2, hexane/ethyl acetate + 1% triethylamine) to afford desired 4-fluorobenzylidene disaccharide hemiacetal **172F** (429 mg, 61%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.18 (s, 1H), 7.73 - 7.65 (m, 2H), 7.08 - 6.99 (m, 2H), 5.35 (t, *J* = 9.6 Hz, 1H), 5.25 - 5.17 (m, 2H), 5.13 - 4.91 (m, 3H), 4.60 (d, *J* = 8.0 Hz, 1H), 4.24 - 4.20 (m, 2H), 3.89 (d, *J* = 10 Hz, 1H), 4.76 (t, *J* = 6.4 Hz, 1H), 3.68 - 3.55 (m, 2H), 3.23 (t, *J* = 9.6 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.00 (s, 6H), 21.98 (s, 3H), 1.82 (s, 3H). IR (film, cm^{-1}) 3480, 2943, 1747, 1644, 1601, 1509, 1367, 1219, 1035.

2,3,4,6-*Tetra*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-3,4-*di*-*O*-acetyl-2-deoxy-2-*p*-(trifluoromethyl)benzylideneamino-D-glucopyranoside (172G). A mixture of disaccharide **172E** (220 mg, 0.37 mmol), 4-trifluoromethyl benzaldehyde (0.06 mL, 0.41 mmol), and anhydrous pyridine (0.30 mL, 3.7 mmol) in CH_2Cl_2 (2.0 mL) was stirred under reflux overnight. The reaction mixture was concentrated in vacuo, and purified by silica gel flash column chromatography (2/1hexane/ethyl acetate + 1% triethylamine → 1/2hexane/ethyl acetate + 1% triethylamine) to afford the desired 4-trifluoromethyl benzylidene disaccharide hemiacetal **172G** (193 mg, 69%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.27 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 5.39 (t, *J* = 9.6 Hz, 1H), 5.24 - 5.17 (m, 2H), 5.13 - 4.91 (m, 3H), 4.60 (d, *J* = 8.0 Hz, 1H), 4.27 - 4.13 (m, 2H), 3.94 - 3.90 (m, 1H), 3.83 - 3.78 (m, 1H), 3.72 - 3.55 (m, 2H), 3.29 (dd, *J* = 8.0, 9.6 Hz, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 2.008 (s, 3H),

2.00 (s, 3H), 1.83 (s, 3H). IR (film, cm^{-1}) 3470, 2965, 1749, 1647, 1370, 1323, 1220, 1032.

2,3,4,6-*Tetra*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-3,4-*di*-*O*-acetyl-2-deoxy-2-*p*-fluorobenzylideneamino-α-D-glucopyranosyl trichloroacetimidate (172). A 25 mL oven dried Schlenk flask was charged with the disaccharide hemiacetal **172F** (285 mg, 0.41 mmol) in CH_2Cl_2 (1.5 mL), trichloroacetonitrile (0.20 mL, 2.0 mmol), and DBU (0.03 mL, 0.20 mmol). The resulting reaction mixture was stirred at room temperature. When the reaction was complete as monitored by TLC, the reaction mixture was quenched with Et_3N (0.5 mL), concentrated *in vacuo* at room temperature, and the residue purified by silica gel flash column chromatography (5/1 toluene/ethyl acetate +1% triethylamine) to afford the desired imidate **172** (206 mg, 60%) as pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.56 (s, 1H), 8.26 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.38 (d, *J* = 3.6 Hz, 1H), 5.67 (t, *J* = 9.6 Hz, 1H), 5.20 - 4.97 (m, 4H), 4.56 (d, *J* = 8.0 Hz, 1H), 4.31-4.23 (m, 2H), 4.16 - 4.01 (m, 2H), 3.77 (dd, *J* = 3.2, 10 Hz, 1H), 3.72 - 3.66 (m, 1H), 3.59 (dd, *J* = 3.6, 11 Hz, 1H), 2.07 (s, 6H), 2.03 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.6, 170.2, 169.67, 169.65, 169.5, 169.3, 165.1 (d, J_{CF} = 251.4 Hz), 163.3, 160.8, 130.8 (d, J_{CF} = 3.0 Hz), 130.5 (d, J_{CF} = 8.8 Hz), 129.0, 128.2, 115.7 (d, J_{CF} = 21.7 Hz), 100.5, 95.6, 91.0, 72.7, 71.8, 71.3, 70.90, 70.89, 70.6, 68.3, 68.2, 67.3, 61.7, 20.69, 20.67, 20.6, 20.5. IR (film, cm^{-1}) 3340, 2942, 1748, 1674, 1645, 1601, 1509, 1366, 1217, 1034. HRMS (ESI): calc. for $C_{33}H_{38}N_2O_{16}FCl_3Na$ (M+Na): 865.1170; found: 865.1169.

2,3,4,6-*Tetra*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-3,4-*di*-*O*-acetyl-2-deoxy-2-*p*-(trifluoromethyl)benzylideneamino-α-D-glucopyranosyl trichloroacetimidate (173). A 25 mL Schlenk flask was charged with the disaccharide hemiacetal **172G** (185 mg,

0.25 mmol) in anhydrous CH_2Cl_2 (1.0 mL), trichloroacetonitrile (0.12 mL, 1.2 mmol), and DBU (0.02 mL, 0.12 mmol). The resulting reaction mixture was stirred at 0 ^oC. When the reaction was complete as monitored by TLC, the reaction mixture was quenched with Et_3N (0.5 mL), concentrated *in vacuo* at room temperature, and purified by silica gel flash column chromatography (5/1toluene/ethyl acetate +1% triethylamine) to afford the desired imidate **173** (142 mg, 64%) as pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.57 (s, 1H), 8.36 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 3.6 Hz, 1H), 5.70 (t, *J* = 9.6 Hz, 1H), 5.19 (t, *J* = 9.6 Hz, 1H), 5.16 (t, *J* = 9.6 Hz, 1H), 5.08 (t, *J* = 9.6 Hz, 1H), 5.01 (t, *J* = 9.6 Hz, 1H), 4.56 (d, *J* = 8.0 Hz, 1H), 4.33 - 4.24 (m, 2H), 4.17 - 4.04 (m, 2H), 3.84 (dd, *J* = 3.6, 10.0 Hz, 1H), 3.72 - 3.65 (m, 1H), 3.59 (dd, *J* = 11, 4.4 Hz, 1H), 2.08 (s, 6H), 2.04 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.7, 170.2, 169.67, 169.65, 169.6, 169.4, 163.5, 163.4, 160.7, 128.7, 125.6 (t, J_{CF} = 3.3 Hz), 100.5, 95.4, 91.0, 72.7, 71.8, 71.3, 70.9, 70.8, 70.7, 68.2, 67.2, 61.8, 20.7, 20.67, 20.6, 20.54, 20.5. IR (film, cm^{-1}) 3342, 2942, 1751, 1674, 1649, 1367, 1323, 1223, 1128, 1035. HRMS (ESI): calc. for $C_{34}H_{38}N_2O_{16}F_3Cl_3Na$ (M+Na): 915.1145; found: 915.1137.

2,3,4,6-*Tetra*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-3,4-*di*-*O*-acetyl-2-deoxy-2-*p*-(trifluoromethyl)benzylideneamino-D-glucopyranosyl-(1→2)-1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranoside (174). A 10 mL oven-dried and argon flushed Schlenk flask was charged with the disaccharide donor **173** (45 mg, 0.05 mmol, 1 equiv), 1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranose **142**[167] (21 mg, 0.06 mmol, 1.2 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (3.1 mg, 0.005 mmol, 10 mol %) and AgOTf (2.7 mg, 0.010 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 6 h, diluted with toluene (1 mL), and purified by silica gel

flash column chromatography (9/1, toluene/acetonitrile + 1% triethylamine) to give the desired trisaccharide **174** (31 mg, 57%, α:β = 20:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.35 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 5.83 (s, 1H), 5.74 (t, *J* = 10 Hz, 1H), 5.56 (t, *J* = 10 Hz, 1H), 5.22 (t, *J* = 9.6 Hz, 1H), 5.10 - 4.96 (m, 5H), 4.70 - 4.63 (m, 1H), 4.49 (d, *J* = 9.6 Hz, 1H), 4.29 - 4.20 (m, 4H), 4.14 (dd, *J* = 12, 2.4 Hz, 1H), 4.04 (dd, *J* = 10, 2.0 Hz, 1H), 3.79 - 3.74 (m, 1H), 3.71 - 3.66 (m, 1H), 3.62 (dd, *J* = 10, 3.6 Hz, 1H), 3.48 (dd, *J* = 10, 4.0 Hz, 1H), 2.18 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.85 (s, 3H), 1.66 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.1, 170.6, 170.2, 169.8, 169.60, 169.56, 169.5, 169.4, 169.1, 168.5, 162.7, 129.1, 125.7 (d, J_{CF} = 4.0 Hz), 100.7, 99.6, 90.9, 73.3, 73.1, 72.5, 72.2, 71.8, 70.8, 70.7, 68.8, 68.4, 68.3, 67.4, 66.0, 61.9, 61.8, 21.0, 20.8, 20.74, 20.70, 20.6, 20.60, 20.57, 20.3. IR (film, cm^{-1}**)** 2924, 1748, 1647, 1367, 1324, 1221, 1167, 1037. HRMS (ESI): calc. for $C_{46}H_{57}NO_{25}F_3$ (M+H): 1080.3194; found: 1080.3172.

2,3,4,6-*Tetra*-*O*-acetyl-β-D-glucopyranosyl-(1→6)-3,4-*di*-*O*-acetyl-2-deoxy-2-*p*-fluorobenzylideneamino-D-glucopyranosyl-(1→2)-1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranoside (175). A 10 mL oven-dried and argon flushed Schlenk flask was charged with the disaccharide donor **172** (42 mg, 0.05 mmol, 1 equiv), 1,3,4,6-*tetra*-*O*-acetyl-α-D-mannopyranose **142**[167] (21 mg, 0.06 mmol, 1.2 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (3.1 mg, 0.005 mmol, 10 mol %) and AgOTf (2.7 mg, 0.010 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 6 h, diluted with toluene (1 mL), and purified by silica gel flash column chromatography (9/1, toluene/acetonitrile + 1% triethylamine) to give the desired trisaccharide **175** (36 mg, 70%, α:β = 24:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.25 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.11

(d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 5.83 (s, 1H), 5.71 (t, *J* = 10 Hz, 1H), 5.56 (t, *J* = 10.0 Hz, 1H), 5.22 (t, *J* = 9.6 Hz, 1H), 5.10 - 4.98 (m, 4H), 4.95 (d, *J* = 3.6 Hz, 1H), 4.67 - 4.61 (m, 1H), 4.48 (d, *J* = 8.0 Hz, 1H), 4.27 - 4.18 (m, 4H), 4.13 (dd, *J* = 12.4, 2.4, Hz, 1H), 4.04 (dd, *J* = 10, 2.0 Hz, 1H), 3.79 - 3.74 (m, 1H), 3.71 - 3.66 (m, 1H), 3.56 (dd, *J* = 10, 3.6 Hz, 1H), 3.47 (dd, *J* = 10, 4.8 Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.85 (s, 3H), 1.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.1, 170.6, 170.2, 169.8, 169.7, 169.5, 169.4, 169.1, 168.5, 163.4, 162.6, 131.8 (d, J_{CF} = 3.1 Hz), 130.9 (d, J_{CF} = 8.8 Hz), 129.0, 128.2, 115.7 (d, J_{CF} = 21.5 Hz), 100.7, 99.8, 90.9, 73.3, 73.2, 73.0, 72.1, 71.8, 70.9, 70.8, 68.9, 68.4, 68.3, 67.5, 66.0, 61.9, 61.8, 21.4, 21.0, 20.8, 20.73, 20.69, 20.67, 20.64, 20.60, 20.56, 20.2. IR (film, cm^{-1}**)** 2931, 1748, 1644, 1602, 1509, 1431, 1367, 1221, 1036. HRMS (ESI): calc. for $C_{45}H_{56}NO_{25}FNa$ (M+Na): 1052.3033; found: 1052.3023.

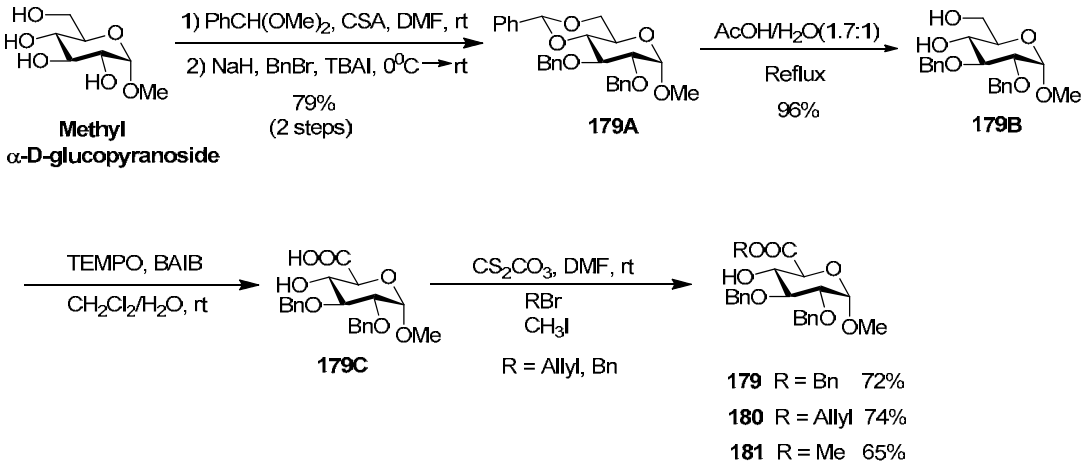
Trisaccharide (176). A 10 mL oven-dried and argon flushed Schlenk flask was charged with the disaccharide donor **172** (42 mg, 0.05 mmol, 1 equiv), methyl 2,3,6-*tri*-*O*-benzyl-α-D-glucopyranoside **143** (28 mg, 0.06 mmol, 1.2 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (3.1 mg, 0.005 mmol, 10 mol %) and AgOTf (2.7 mg, 0.010 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 7 h, diluted with toluene (1 mL), and purified by silica gel flash column chromatography (9/1, hexane/ethyl acetate + 1% triethylamine) to give the desired trisaccharide **176** (38 mg, 67%, α:β = 6:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.21 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.40 - 7.23 (m, 15H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 5.66 (t, *J* = 9.6 Hz, 1H), 5.22 (t, *J* = 9.6 Hz, 1H), 5.14 (d, *J* = 3.6 Hz, 1H), 5.10 - 5.00 (m, 5H), 4.88 - 4.77 (m, 3H), 4.53 (d, *J* = 8.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 3.6 Hz, 1H), 4.27 - 4.21 (m, 2H), 4.05 - 3.97 (m, 3H), 3.92 - 3.80 (m, 3H), 3.70 - 3.65 (m, 2H), 3.52 - 3.47

(m, 2H), 3.29 (s, 3 H), 3.03 (dd, J = 9.2, 3.6 Hz, 1H), 2.08 (s, 6H), 2.02 (s, 6H), 2.01 (s, 3H), 1.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.7, 170.3, 169.9, 169.8, 169.5, 169.4, 162.6, 138.9, 138.7, 130.7 (d, J_{CF} = 8.2 Hz), 128.5, 128.4, 128.3, 128.2, 128.13, 128.05, 128.0, 127.9, 127.8, 127.7, 127.63, 127.57, 115.9 (d, J_{CF} = 21.9 Hz), 101.0, 99.0, 97.9, 81.8, 80.3, 75.7, 75.0, 73.4, 72.7, 72.1, 71.8, 71.4, 71.2, 70.9, 69.0, 68.4, 68.3, 68.0, 65.0, 61.8, 20.80, 20.77, 20.7, 20.63, 20.61**.** IR (film, cm^{-1}) 2924, 1752, 1644, 1600, 1508, 1454, 1366, 1226, 1035. HRMS (ESI): calc. for $C_{59}H_{69}NO_{21}F$ (M+H): 1146.4356; found: 1146.4346.

Tetrasaccharide (177). A 10 mL oven-dried and argon flushed Schlenk flask was charged with the disaccharide donor **172** (42 mg, 0.05 mmol, 1 equiv), the disaccharide acceptor **165**[152-153] (42 mg, 0.06 mmol, 1.2 equiv), and CH_2Cl_2 (0.7 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (3.1 mg, 0.005 mmol, 10 mol %) and AgOTf (2.7 mg, 0.010 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 7 h, diluted with toluene (1 mL), and purified by silica gel flash column chromatography (9/1, toluene/acetonitrile + 1% triethylamine) to give the desired tetrasaccharide **177** (52 mg, 76%, α:β = 11:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.24 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.39 - 7.10 (m, 15H), 6.82 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 5.70 (t, J = 10 Hz, 1H), 5.53 (d, J = 5.2 Hz, 1H), 5.27 - 5.20 (m, 2H), 5.11 - 4.95 (m, 5H), 4.87 (d, J = 11 Hz, 1H), 4.79 (d, J = 11 Hz, 1H), 4.73 (d, J = 11 Hz, 1H), 4.66 (d, J = 11 Hz, 1H), 4.57 - 4.52 (m, 2H), 4.31 - 4.24 (m, 3H), 4.20 - 4.10 (m, 4H), 4.08 - 4.02 (m, 2H), 3.97 - 3.89 (m, 4H), 3.72 - 3.67 (m, 1H), 3.60 - 3.50 (m, 3H), 3.33 (d, J = 9.6 Hz, 1H), 2.75 (t, J = 8.8 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.85 (s, 3H), 1.48 (s, 3H), 1.44 (s, 3 H), 1.32 (s, 3 H), 1.31 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.7, 170.3, 169.9, 169.8, 169.6, 169.4, 162.8, 138.9, 138.63, 138.62, 130.7 (d, J_{CF} = 8.2

Hz), 128.4, 128.3, 128.24, 128.20, 128.17, 128.03, 128.00, 127.7, 127.62, 127.58, 127.5, 127.4, 115.8 (d, J_{CF} = 21.5 Hz), 109.3, 108.5, 103.7, 100.9, 99.4, 96.3, 84.2, 81.9, 75.7, 75.5, 74.9, 74.4, 72.7, 71.8, 71.7, 71.4, 71.1, 70.9, 70.6, 70.4, 69.0, 68.5, 68.3, 67.8, 66.8, 64.9, 61.8, 26.03, 25.96, 24.9, 24.4, 20.79, 20.76, 20.69, 20.67, 20.6. IR (film, cm^{-1}) 2932, 1752, 1644, 1600, 1508, 1455, 1368, 1215, 1067, 1035. *J* (^{13}CH) = 179 Hz (103.7 Hz), 159 (100.9 Hz), 176 (99.4 Hz), 165 (96.3 Hz). HRMS (ESI): calc. for $C_{70}H_{85}NO_{26}F$ (M+H): 1374.5363; found: 1374.5344.

6.4. Synthesis of C(4)-Hydroxyl Glucuronic Acid Ester Acceptors.



Scheme 6.4. Synthesis of Benzyl, Allyl and Methyl Esters of C(4)-Hydroxyl Glucuronic Acid

Methyl-2,3-*di*-*O*-benzyl-4,6-benzylidene-α-D-glucopyranoside (179A). An oven dried and argon flushed 100 mL Schlenk flask was charged with methyl α-D-glucopyranoside (5.0 g, 25.749 mmol, 1.0 equiv.) and anhydrous DMF (40 mL). Benzaldehyde dimethyl acetal (4.6 mL, 30.899 mmol, 1.2 equiv) was added, followed by camphor sulfonic acid (CSA) (0.6 g, 2.575 mmol, 0.1 equiv.). The resulting colorless reaction mixture was

stirred at room temperature overnight. The reaction mixture was quenched with triethylamine (0.5 mL), and concentrated *in vacuo* resulting in pale yellow oil as the C4 - C6 benzylidene protected intermediate. To this crude product in a 100 mL oven dried Schlenk flask was added anhydrous DMF (38 mL). This solution was cooled to 0 °C, and sodium hydride (60% dispersion in mineral oil) (2.5 g, 61.993 mmol) was added portionwise over an hour. Benzyl bromide (7.4 mL, 61.993 mmol) was then added dropwise, followed by tetrabutylammonium iodide (0.3 g, 0.886 mmol, 5 mol %). The reaction mixture was slowly warmed back to room temperature and stirred overnight. The reaction mixture was cooled to 0°C, and methanol (10 mL) was slowly added. The entire reaction mixture was poured into water (300 mL), and the resulting white solution was extracted with diethyl ether (4 x 100 mL). The combined organic layer was washed with water (2 x 100 mL), dried with anhydrous magnesium sulfate, and concentrated *in vacuo* to form pale yellow oil as the crude product. The crude product was purified by silica gel flash column chromatography (5/1, hexane/ethyl acetate) to afford the desired product **179A** (8.5 g, 71%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 7.48 (m, 2H), 7.39 - 7.26 (m, 13H), 5.54 (s, 1H), 4.91 (d, *J* = 11 Hz, 1H), 4.84 (t, *J* = 11 Hz, 2H), 4.69 (d, *J* = 12 Hz, 1H), 4.58 (d, *J* = 3.5 Hz, 1H), 4.26 (dd, *J* = 10, 5 Hz, 1H), 4.04 (t, *J* = 9 Hz 1H), 3.82 – 3.80 (m, 1H), 3.70 (t, *J* = 10 Hz, 1H), 3.60 (t, *J* = 9.5 Hz, 1H), 3.51 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.39 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.7, 138.1, 137.4, 128.9, 128.5, 128.3, 128.2, 128.1, 128.05, 127.9, 127.6, 126.0, 101.2, 99.2, 82.1, 79.1, 78.6, 75.4, 73.8, 69.1, 62.3, 55.4. IR (film, cm^{-1}) 3065, 3027, 2910, 2869, 1498, 1453, 1372, 1088, 1054.

Methyl-2,3-*di*-*O*-benzyl-α-D-glucopyranoside (179B). A 250 mL round bottom flask was charged with **179A** (3.6 g, 7.827 mmol, 1.0 equiv.), acetic acid (8.2 mL) and water (4.8 mL). The resulting white suspension was heated under reflux. When the reaction was complete as monitored by TLC, heating was discontinued, and the reaction mixture was

cooled to room temperature, then concentrated *in vacuo*. The residue was co-evaporated with benzene resulting in a colorless liquid as the crude product. The crude product was purified by silica gel flash column chromatography (1/1, hexane/ethyl acetate → 100% ethyl acetate) to provide the desired diol **179B** (2.8 g, 96%) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 7.36 - 7.29 (m, 10H), 5.01 (d, *J* = 12 Hz, 1H), 4.75 (d, *J* = 12 Hz, 1H), 4.69 (d, *J* = 11 Hz, 2H), 4.64 (d, *J* = 13 Hz, 1H), 4.57 (d, *J* = 3.0 Hz, 1H), 3.79 – 3.70 (m, 3H), 3.60 – 3.58 (m, 1H), 3.51 – 3.46 (m, 2H), 3.56 (s, 3H), 2.41 (s, 1H), 2.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 138.7, 137.9, 128.7, 128.5, 128.1, 128.0, 127.9, 128.0, 98.2, 81.3, 79.8, 75.4, 73.2, 70.7, 70.4, 62.4, 55.3. IR (film, cm^{-1}) 3420, 3061, 3031, 2928, 1498, 1453, 1361, 1195, 1186, 1154, 1051.

Glucuronic acid (179C). A 250 mL round bottom flask was charged with the diol **179B** (2.8 g, 7.449 mmol, 1 equiv.), methylene chloride/water (3/1, 74 mL), 2,2,6,6-tetramethyl piperidinyloxy (TEMPO) (0.2 g, 1.490 mmol, 0.2 equiv.) and bis(acetoxy)iodo benzene (BAIB) (6.0 g, 18.623 mmol, 2.5 equiv.). The resulting bi-phasic mixture was stirred vigorously at room temperature for 45 min. The reaction mixture was quenched by the addition of sodium thiosulfate (1M) (55 mL). The layers were separated, and the organic layer was diluted with ethyl acetate /acetic acid (24/1) (100 mL), washed with water (1 x 50 mL) and dried over anhydrous magnesium sulfate. The dried organic layer was concentrated *in vacuo* to yield the crude **179C** as pale-brown oil. This crude product was used in the next step without further purification.

Benzyl Ester (179). An oven dried and argon flushed 25 mL Schlenk flask was charged with the crude **179C** (1.4 g, 3.499 mmol, 1.0 equiv.), anhydrous DMF (10 mL) and cesium carbonate (1.2 g, 3.499 mmol, 1.0 equiv.). The resulting reaction mixture was stirred at room temperature for 5 min, and benzyl bromide (0.4 mL, 3.150 mmol, 0.9 equiv.) was added, followed by tetrabutylammonium iodide (65 mg, 0.175 mmol, 5 mol

%). The reaction mixture was stirred at room temperature. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with ethyl acetate (250 mL) and washed with water (3 x 75 mL). The organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to form pale-yellow oil as the crude product. This product was purified by silica gel flash column chromatography (3/1, hexane/ethyl acetate) to afford the desired product **179** (1.2 g, 72%) as pale-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 7.35 - 7.28 (m, 15H), 5.21 (d, *J* = 2.0 Hz, 2H), 4.89 (d, *J* = 12 Hz, 1H), 4.78 (d, *J* = 9.5 Hz, 2H), 4.67 – 4.63 (m, 2H), 4.20 (d, *J* = 8.5 Hz, 1H), 3.83 – 3.81 (m, 2H), 3.55 – 3.52 (m, 1H), 3.41 (s, 3H), 2.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.0, 138.5, 137.9, 135.1, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 98.6, 80.3, 78.4, 75.4, 73.6, 71.7, 70.9, 67.3, 55.9. IR (film, cm^{-1}) 3489, 3061, 3031, 2935, 1749, 1494, 1453, 1187, 1055.

Allyl Ester (180). An oven dried and argon flushed 25 mL Schlenk flask was charged with the crude **179C** (1.0 g, 2.550 mmol, 1.0 equiv.), anhydrous DMF (7 mL) and cesium carbonate (0.8 g, 2.550 mmol, 1.0 equiv.). The resulting reaction mixture was stirred at room temperature for 5 min, and allyl bromide (0.24 mL, 2.805 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (3 x 75 mL). The organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to form pale-yellow oil as the crude product. This product was purified by silica gel flash column chromatography (3/1, hexane/ethyl acetate) to afford the desired product **180** (0.8 g, 74%) as a pale-yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 7.36 - 7.26 (m, 10H), 5.89 (m, 1H), 5.32 (dd, *J* = 17, 1.0 Hz, 1H), 5.28 - 5.23 (m, 1H), 4.90 (d, *J* = 11 Hz, 1H), 4.78 (dd, *J* = 11, 2.5 Hz 2H), 4.67 – 4.62 (m, 4H), 4.16 (d, *J* = 8.5 Hz 1H), 3.84 – 3.77 (m, 2H), 3.52 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.41 (s, 3H), 2.82 (d, *J* = 2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm)

169.9, 138.6, 138.0, 131.3, 128.5, 128.2, 128.1, 128.0, 127.8, 119.2, 98.7, 80.4, 78.5, 75.5, 73.7, 71.8, 70.8, 66.2, 55.9. IR (film, cm^{-1}) 3497, 3065, 2935, 1745, 1453, 1191, 1055.

Methyl Ester (181). An oven dried and argon flushed 25 mL Schlenk flask was charged with the crude **179C** (1.3 g, 3.416 mmol, 1.0 equiv.), anhydrous DMF (9 mL) and cesium carbonate (1.1 g, 3.416 mmol, 1.0 equiv.). The resulting reaction mixture was stirred at room temperature for 5 min, and methyl iodide (0.19 mL, 3.074 mmol, 0.9 equiv.) was added. The reaction mixture was stirred at room temperature. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with ethyl acetate (250 mL), and washed with water (3 x 75 mL). The organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to form pale-yellow oil as the crude product. This product was purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate) to afford the desired product **181** (0.9 g, 65%) as pale-yellow solids. ^{1}H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 7.35 - 7.23 (m, 10H), 4.90 (d, *J* = 12 Hz, 1H), 4.79 (dd, *J* = 12, 3.5 Hz, 2H), 4.64 - 4.62 (m, 2H), 4.14 (d, *J* = 9.0 Hz, 1H), 3.83 – 3.79 (m, 2H), 3.78 (s, 3H), 3.51 (dd, *J* = 9.0, 3.0 Hz 1H), 3.41 (s, 3H), 2.85 (d, *J* = 2.0 Hz, 1H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 138.6, 137.9, 128.5, 128.2, 128.1, 128.0, 127.8, 98.7, 80.4, 78.4, 75.5, 73.6, 71.8, 70.5, 55.9, 52.7. IR (film, cm^{-1}) 3490, 2928, 1749, 1453, 1358, 1199, 1055.

6.5. Synthesis of Heparin Disaccharides

Disaccharide (183). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), benzyl ester acceptor **179**

(93.3 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 5 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (7/1, benzene/ethyl acetate + 1% triethylamine) to give the desired disaccharide **183** (73 mg, 55%, α:β = 14:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.88 (s, 1H), 7.55 (d, *J* = 9.0 Hz, 2H), 7.42 - 7.27 (m, 10H), 7.22 - 7.13 (m, 3H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 1.5 Hz, 2H), 5.69 (d, *J* = 4.0 Hz, 1H), 5.53 (t, *J* = 9.5 Hz, 1H), 5.18 (d, *J* = 13 Hz, 1H), 5.15 (d, *J* = 13 Hz, 1H), 5.02 (t, *J* = 10 Hz, 1H), 4.83 (d, *J* = 12 Hz, 1H), 4.64 (d, *J* = 13 Hz, 1H), 4.55 (d, *J* = 3.0 Hz, 1H), 4.50 (d, *J* = 12 Hz, 2H), 4.39 (d, *J* = 9.5 Hz, 1H), 4.26 (dd, *J* = 12, 3.5 Hz, 1H), 4.18 (t, *J* = 9.0 Hz, 1H), 4.11 - 4.08 (m, 2H), 3.89 - 3.86 (m, 1H), 3.82 (s, 3H), 3.55 (dd, *J* = 11, 3.0 Hz, 1H), 3.40 (s, 3H), 3.40 - 3.37 (m, 1H), 2.10 (s, 3H), 1.88 (s, 3H), 1.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.9, 169.8, 169.5, 163.7, 162.1, 138.5, 137.5, 134.7, 130.2, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 126.7, 125.9, 114.0, 113.9, 99.0, 98.4, 81.2, 79.4, 75.0, 74.2, 73.5, 72.4, 70.9, 69.7, 68.5, 68.1, 67.5, 61.7, 55.6, 55.3, 20.8, 20.6, 20.5. IR (film, cm^{-1}**)** 3027, 2935, 1749, 1642, 1605, 1512, 1453, 1364, 1246, 1028. HRMS (ESI): calc. for $C_{48}H_{53}NO_{15}$ (M+H): 884.3488; found: 884.3484.

Disaccharide (184). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), allyl ester acceptor **180** (83.6 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25

^{o}C for 6 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired disaccharide **184** (105 mg, 84%, α:β = 9:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.86 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.23 - 7.15 (m, 7H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.78 - 6.77 (m, 3H), 5.95 - 5.92 (m, 1H), 5.64 (d, *J* = 3.5 Hz, 1H), 5.46 (t, *J* = 9.5 Hz, 1H), 5.38 (dd, *J* = 17, 1.0 Hz, 1H), 5.25 (d, *J* = 11 Hz, 1H), 5.00 (t, *J* = 9.5 Hz, 1H), 4.81 (d, *J* = 12 Hz, 1H), 4.65 - 4.61 (m, 3H), 4.54 (d, *J* = 3.0 Hz, 1H), 4.48 (dd, *J* = 12, 6.5 Hz, 2H), 4.34 (d, *J* = 9.5 Hz, 1H), 4.26 (dd, *J* = 12, 3.5 Hz, 1H), 4.12 - 4.03 (m, 3H), 3.83 - 3.80 (m, 1H), 3.81 (s, 3H), 3.53 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.40 (s, 3H), 3.35 (dd, *J* = 11, 3.5 Hz, 1H), 2.08 (s, 3H), 1.96 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.9, 169.7, 169.5, 164.4, 164.0, 163.6, 162.2, 138.4, 137.5, 131.1, 130.3, 128.4, 128.2, 128.1, 128.0, 127.9, 126.7, 126.0, 119.3, 114.2, 114.0, 98.8, 98.4, 81.2, 79.4, 74.8, 74.2, 73.5, 72.4, 70.8, 69.6, 68.4, 68.0, 66.2, 61.7, 55.6, 55.3, 20.8, 20.6, 20.5. IR (film, cm^{-1}) 3349, 3293, 2946, 1745, 1638, 1605, 1512, 1364, 1246, 1032. HRMS (ESI): calc. for $C_{44}H_{51}NO_{15}$ (M+H): 834.3331; found: 834.3359.

Disaccharide (185). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), methyl ester acceptor **181** (78.5 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 6 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (1/1, hexane/ethyl acetate + 1% triethylamine) to give the desired disaccharide **185** (86 mg, 71%, α only) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.88 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.24 - 7.12 (m, 8H), 6.84 (d, *J* = 8.5 Hz,

2H), 6.80 (d, *J* = 4.0 Hz, 2H), 5.62 (d, *J* = 3.0 Hz, 1H), 5.48 (t, *J* = 10 Hz, 1H), 5.01 (t, *J* = 9.5 Hz, 1H), 4.81 (d, *J* = 12 Hz, 1H), 4.63 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 3.0 Hz, 1H), 4.52 - 4.48 (m, 2H), 4.33 (d, *J* = 9.5 Hz, 1H), 4.29 (dd, *J* = 13, 3.5 Hz, 2H), 4.11 - 4.06 (m, 2H), 4.02 (t, *J* = 9.5 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.53 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.41 (s, 3H), 3.36 (dd, *J* = 10, 3.5 Hz, 1H), 2.09 (s, 3H), 1.97 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.1, 169.8, 169.6, 163.6, 162.1, 138.5, 137.5, 130.2, 128.4, 128.3, 128.2, 128.0, 127.9, 126.7, 126.0, 113.9, 98.9, 98.4, 81.2, 79.3, 75.1, 74.2, 73.5, 72.4, 70.8, 69.6, 68.5, 68.0, 61.7, 55.6, 55.3, 52.1, 20.8, 20.6, 20.5. IR (film, cm^{-1}) 3031, 2938, 2843, 1749, 1642, 1605, 1575, 1512, 1456, 1442, 1368, 1246, 1161, 1095, 1032. $J(^{13}CH)$ = 170.2 Hz HRMS (ESI): calc. for $C_{42}H_{49}NO_{15}$ (M+H): 808.3175; found: 808.3172.

Disaccharide (186). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **129** (80.7 mg, 0.150 mmol, 1.0 equiv), methyl ester acceptor **181** (78.5 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 5 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/2, hexane/ethyl acetate + 1% triethylamine) to give the desired disaccharide **186** (80 mg, 68%, α only) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.95 (s, 1H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.42 - 7.32 (m, 4H), 7.23 - 7.12 (m, 7H), 6.75 (d, *J* = 5.5 Hz, 2H), 5.63 (d, *J* = 3.5 Hz, 1H), 5.51 (t, *J* = 9.5 Hz, 1H), 5.01 (t, *J* = 9.5 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 3.0 Hz, 1H), 4.48 (d, *J* = 12 Hz, 2H), 4.33 (d, *J* = 10 Hz, 1H), 4.30 (dd, *J* = 13, 3.5 Hz, 2H), 4.12 - 4.07 (m, 2H), 3.83 (d, *J* = 9.0 Hz, 1H), 3.77 (s, 3H), 3.53 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.41

(s, 3H), 3.41 - 3.40 (m, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.1, 169.8, 169.6, 164.5, 138.5, 137.5, 135.2, 131.3, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 126.7, 125.8, 98.9, 98.4, 81.2, 79.4, 75.1, 74.2, 73.5, 72.4, 70.7, 69.6, 68.5, 68.0, 61.7, 55.7, 52.5, 20.8, 20.7, 20.5. IR (film, cm^{-1}) 3061, 3027, 1752, 1642, 1453, 1368, 1231, 1047, 1028. $J(^{13}CH)$ = 172.5 Hz HRMS (ESI): calc. for $C_{41}H_{47}NO_{14}$ (M+H): 778.3069; found: 778.3086.

Disaccharide (187). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1.0 equiv), methyl ester acceptor **181** (78.5 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 4 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired disaccharide **187** (84 mg, 70%, α only) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.89 (s, 1H), 7.55 (dd, *J* = 8.0, 5.5 Hz, 2H), 7.34 - 7.12 (m, 8H), 7.00 (t, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 5.0 Hz, 2H), 5.62 (d, *J* = 3.5 Hz, 1H), 5.49 (t, *J* = 10 Hz, 1H), 5.02 (t, *J* = 10 Hz, 1H), 4.82 (d, *J* = 12 Hz, 1H), 4.62 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 3.0 Hz, 1H), 4.48 (d, *J* = 12 Hz, 1H), 4.45 (d, *J* = 12 Hz, 1H), 4.32 - 4.28 (m, 2H), 4.09 (t, J = 9.5 Hz, 2H), 4.00 (t, *J* = 9.5 Hz, 1H), 3.83 (d, *J* = 9.5 Hz, 1H), 3.76 (s, 3H), 3.52 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.45 (s, 3H), 3.44 - 3.38 (m, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.9, 170.1, 169.8, 169.6, 165.6, 163.6, 162.9, 138.4, 137.5, 131.5, 130.5, 130.4, 128.4, 128.2, 128.0, 127.9, 126.7, 125.8, 115.8, 115.6, 98.9, 98.4, 81.2, 79.3, 75.2, 74.2, 73.5, 72.4, 70.6, 69.6, 68.4, 68.0, 61.7, 55.7, 52.5, 20.8, 20.7,

20.5. IR (film, cm^{-1}) 2938, 2861, 1752, 1645, 1601, 1509, 1368, 1231, 1047, 1028. HRMS (ESI): calc. for $C_{41}H_{46}FNO_{14}$ (M+Na): 809.2975; found: 809.2718.

Disaccharide (188). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **136** (90.9 mg, 0.150 mmol, 1 equiv), methyl ester acceptor **181** (78.5 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added. The resulting mixture was stirred under argon at 25 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired disaccharide **188** (110 mg, 87%, α only) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.96 (s, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.24 - 7.10 (m, 8H), 6.75 (d, *J* = 7.0 Hz, 2H), 5.64 (d, *J* = 3.5 Hz, 1H), 5.53 (t, *J* = 10 Hz, 1H), 5.03 (t, *J* = 10 Hz, 1H), 4.82 (d, *J* = 12 Hz, 1H), 4.61 (d, *J* = 12 Hz, 1H), 4.56 (d, *J* = 3.0 Hz, 1H), 4.48 (d, *J* = 12 Hz, 1H), 4.31 (d, *J* = 12 Hz, 1H), 4.30 (d, *J* = 10 Hz, 2H), 4.11 - 4.08 (m, 2H), 3.98 (t, *J* = 9.0 Hz, 1H), 3.85 (d, *J* = 10 Hz, 1H), 3.78 (s, 3H), 3.53 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.46 (dd, *J* = 10, 3.0 Hz, 1H), 3.41 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.8, 170.0, 169.8, 169.5, 162.9, 138.4, 138.1, 137.4, 128.6, 128.4, 128.2, 128.1, 128.0, 126.7, 125.6, 125.5, 98.8, 98.4, 81.2, 79.4, 75.4, 74.3, 73.5, 72.5, 70.5, 69.6, 68.3, 68.1, 61.6, 55.7, 52.5, 20.8, 20.6, 20.5. IR (film, cm^{-1}) 2942, 1749, 1645, 1453, 1438, 1368, 1323, 1231, 1164, 1128, 1047, 1028. $J(^{13}CH)$ = 172.7 Hz HRMS (ESI): calc. for $C_{42}H_{46}F_3NO_{14}$ (M+H): 846.2943; found: 846.2905.

Disaccharide (189). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (108.4 mg, 0.195 mmol, 1.3 equiv), methyl ester acceptor **182**[184] (57.4 mg, 0.150 mmol, 1.0 equiv), and CH_2Cl_2 (1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (6.0 mg, 0.0098 mmol, 5 mol %) and AgOTf (5.0 mg, 0.0195 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 5 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (4/1, toluene/ethyl acetate + 1% triethylamine) to give the desired disaccharide **189** (88 mg, 76%, α:β = 19:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.04 (s, 1H), 7.63 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.19 – 7.15 (m, 3H), 7.06 (t, *J* = 8.6 Hz, 2H), 6.85 – 6.83 (m, 2H), 6.32 (d, *J* = 3.5 Hz, 1H), 5.59 (t, *J* = 10 Hz, 1H), 5.53 (d, *J* = 3.5 Hz, 1H), 5.11 – 5.05 (m, 2H), 4.65 – 4.51 (m, 3H), 4.35 – 4.25 (m, 2H), 4.15 – 4.13 (m, 2H), 3.96 – 3.92 (m, 1H), 3.81 (s, 3H), 3.47 (dd, *J* = 11, 3.6 Hz, 1H), 2.24 (s, 3H), 2.12 (s, 3H), 2.03 (s, 3H), 1.87 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.0, 169.98, 169.87, 169.8, 162.01, 168.96, 138.2, 131.8, 131.79, 130.8, 130.75, 128.4, 127.4, 126.0, 116.2, 116.0, 99.8, 89.5, 79.5, 75.8, 74.8, 73.0, 72.5, 71.5, 70.0, 68.8, 68.6, 61.9, 53.0, 21.2, 21.0, 20.9, 20.8, 20.7. IR (film, cm^{-1}) 2955, 2870, 1745, 1644, 1600, 1509, 1367, 1227, 1213, 1151, 1022.

Disaccharide (190). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **136** (118.1 mg, 0.195 mmol, 1.3 equiv), methyl ester acceptor **182**[184] (57.4 mg, 0.150 mmol, 1.0 equiv), and CH_2Cl_2 (1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (6.0 mg, 0.0098 mmol, 5 mol %) and AgOTf (5.0 mg, 0.0195 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred

under argon at 25 ^{o}C for 5 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired disaccharide **190** (92 mg, 74%, α:β = 20:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.10 (s, 1H), 7.71 (d, *J* = 7.6, Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.15(m, 3H), 6.78 (d, *J* = 6.4 Hz, 2H), 6.32 (d, *J* = 3.2 Hz, 1H), 5.62 (t, *J* = 10 Hz, 1H), 5.55 (d, *J* = 2.8 Hz, 1H), 5.13 – 5.05 (m, 2H), 4.57 (s, 2H), 4.52 (d, *J* = 9.6 Hz, 1H), 4.34 (dd, *J* = 13, 3.6, Hz, 1H), 4.28 (t, *J* = 9.2 Hz, 1H), 4.14 (d, *J* = 12 Hz, 1H), 4.06 (t, *J* = 9.2 Hz, 1H), 3.95 (d, *J* = 10 Hz, 1H), 3.82 (s, 3H), 3.53 (dd, *J* = 10, 2.8 Hz, 1H), 2.25 (s, 3H), 2.14 (s, 3H), 2.04 (s, 3H), 1.88 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.8, 169.8, 169.6, 169.61, 168.8, 168.7, 163.5, 137.8, 128.7, 128.2, 127.1, 125.7, 125.6, 99.5, 89.2, 79.2, 75.6, 74.5, 72.9, 72.2, 71.3, 70.4, 68.5, 68.2, 61.6, 52.8, 21.0, 20.8, 20.7, 20.5. IR (film, cm^{-1}) 2955, 2924, 1746, 1644, 1367, 1324, 1222, 1164, 1126, 1024.

6.6. Synthesis of α-GluNAC and GalNAC Derivatives.

Glycopeptide (199). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), benzyloxycarbonyl-L-serine benzyl ester **197** (64.2 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 4 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (6/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **199** (72 mg, 65%, α:β = 8:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.10 (s, 1H), 7.63 (d, *J* = 10 Hz, 2H), 7.36 - 7.16 (m, 10H), 6.77 (d, *J*

= 10 Hz, 2H), 6.24 (d, *J* = 10 Hz, 1H), 5.53 (t, *J* = 10 Hz, 1H), 5.13 (bs, 2H), 5.04 (t, *J* = 10 Hz, 1H), 4.99 (d, *J* = 10 Hz, 1H), 4.97 (d, *J* = 15 Hz, 1H), 4.75 (d, *J* = 4.0 Hz 1H), 4.57 (d, *J* = 10 Hz, 1H), 4.27 (dd, *J* = 15, 5.0 Hz, 1H), 4.12 - 4.06 (m, 3H), 3.98 (dd, *J* = 10, 3.0 Hz, 1H), 3.75 (s, 3H), 3.48 (dd, *J* = 10, 5.0 Hz, 1H), 2.06 (s, 3H), 2.01 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 170.7, 170.0, 169.8, 169.7, 164.0, 162.2, 156.2, 136.3, 135.1, 130.3, 128.5, 128.3, 128.1, 128.0, 114.0, 100.3, 71.9, 71.0, 69.4, 68.8, 68.3, 67.4, 67.1, 62.1, 55.3, 54.5, 20.7, 20.6. IR (film, cm^{-1}) 3349, 2950, 2839, 1745, 1638, 1605, 1512, 1456, 1368, 1246, 1168, 1028. *J*(^{13}CH) = 170.2 Hz

Glycopeptide (200). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), benzyloxycarbonyl-L-threonine benzyl ester **198** (67 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 6 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (9/1, benzene/acetonitrile + 1% triethylamine) to give the desired glycopeptide **200** (81 mg, 73%, α:β = 10:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.03 (s, 1H), 7.64 (d, *J* = 5.0 Hz, 2H), 7.37 - 7.28 (m, 4H), 7.24 - 7.22 (m, 3H), 7.08 (d, *J* = 10 Hz, 2H), 6.63 (d, *J* = 10 Hz, 2H), 6.44 (d, *J* = 10 Hz, 1H), 5.48 (t, *J* = 10 Hz, 1H), 5.20 (d, *J* = 15 Hz, 1H), 5.13 (d, *J* = 15 Hz, 1H), 5.01 (t, *J* = 10 Hz, 1H), 4.91 (d, *J* = 15 Hz 1H), 4.79 - 4.76 (m, 2H), 4.45 - 4.44 (m, 1H), 4.35 (d, *J* = 5 Hz, 1H), 4.28 (dd, *J* = 10, 5.0 Hz, 1H), 4.21 - 4.19 (m, 1H), 4.08 (d, *J* = 10 Hz, 1H), 3.82 - 3.78 (m, 1H), 3.68 (s, 3H), 3.33 (dd, *J* = 10, 3 Hz, 1H), 2.08 (s, 3H), 2.01 (s, 3H), 1.80 (s, 3H), 1.35 (d, *J* = 5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 170.5, 170.0, 169.8, 164.6, 162.2, 157.0, 136.5, 135.1, 130.5, 128.6, 128.5, 128.4, 128.2, 128.1,

128.0, 127.9, 114.0, 99.5, 75.1, 72.5, 71.1, 68.9, 68.2, 67.06, 67.0, 62.3, 58.8, 55.3, 20.7, 20.6, 19.5. IR (film, cm^{-1}**)** 3354, 2942, 1749, 1638, 1606, 1513, 1368, 1239, 1169, 1033. $J(^{13}CH)$ = 170.1 Hz (99.5 Hz) HRMS (ESI): calc. for $C_{39}H_{44}N_2O_{13}$ (M+H) 749.2916; found: 749.2920.

Glycopeptide (201). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1.0 equiv), benzyloxycarbonyl-L-serine benzyl ester **197** (64.2 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (7/1, benzene/acetonitrile + 1% triethylamine) to give the desired glycopeptide **201** (89 mg, 83%, α:β = 9:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.12 (s, 1H), 7.66 (d, *J* = 6.0 Hz, 2H), 7.34 - 7.15 (m, 10H), 6.90 (t, *J* = 6.8 Hz, 2H), 6.12 (d, *J* = 8.0 Hz, 1H), 5.53 (t, *J* = 10.0 Hz, 1H), 5.11 (bs, 2H), 5.05 - 4.94 (m, 3H), 4.74 (d, *J* = 3.0 Hz 1H), 4.56 (d, *J* = 8.0 Hz, 1H), 4.27 (dd, *J* = 12, 4.0 Hz, 1H), 4.10 - 4.05 (m, 3H), 3.99 (d, *J* = 8.0 Hz, 1H), 3.50 (dd, *J* = 10, 7.0 Hz, 1H), 2.06 (s, 3H), 2.00 (s, 3H), 1.83 (s, 3H). ^{13}**C** NMR ($CDCl_3$, 75 MHz) δ (ppm) 170.7, 169.9, 169.8, 169.7, 165.6, 164.3, 163.6, 163.3, 156.1, 136.1, 134.9, 131.5, 130.7, 130,6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 115.8, 115.7, 100.0, 71.7, 70.8, 69.2, 68.6, 68.2, 67.3, 67.1, 62.0, 54.4, 20.7, 20.5. IR (film, cm^{-1}) 3345, 2954, 2890, 1745, 1642, 1601, 1509, 1453, 1368, 1231, 1028. $J(^{13}CH)$ = 170.2 Hz HRMS (ESI): calc. for $C_{37}H_{39}FN_2O_{12}$ (M+H) 723.2560; found: 723.2573.

Glycopeptide (202). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1.0 equiv), benzyloxycarbonyl-L-threonine benzyl ester **198** (67 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0015 mmol, 10 mol %) in dichloromethane (1 mL) was then added. The resulting mixture was stirred under argon at 25 ^oC for 4 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (9/1, benzene/acetonitrile + 1% triethylamine) to give the desired glycopeptide **202** (82 mg, 75%, α:β = 14:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.04 (s, 1H), 7.65 (d, *J* = 6.0 Hz, 2H), 7.35 - 6.99 (m, 10H), 6.73 (t, *J* = 8.0 Hz, 2H), 6.27 (d, *J* = 8.5 Hz, 1H), 5.48 (t, *J* = 10 Hz, 1H), 5.18 (d, *J* = 12 Hz, 1H), 5.09 (t, *J* = 12 Hz, 1H), 5.00 (t, *J* = 9.5 Hz, 1H), 4.90 (d, *J* = 13 Hz 1H), 4.80 (d, *J* = 13 Hz, 1H), 4.76 (d, *J* = 2.0 Hz, 1H), 4.44 (d, *J* = 5.5 Hz, 1H), 4.34 (d, *J* = 8.0 Hz, 1H), 4.28 (dd, *J* = 12, 4.5 Hz, 1H), 4.19 (d, *J* = 9.5 Hz, 1H), 4.08 (d, *J* = 12 Hz, 1H), 3.34 (d, *J* = 7.5 Hz, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.80 (s, 3H), 1.35 (d, *J* = 6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 170.5, 170.0, 169.7, 165.6, 163.9, 163.6, 156.9, 136.3, 134.9, 131.2, 130.8, 130.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 115.08, 115.6, 99.2, 75.1, 72.2, 70.8, 68.7, 68.1, 67.1, 62.2, 58.7, 20.7, 20.5, 19.4. IR (film, cm^{-1}) 3349, 2979, 2942, 1745, 1645, 1601, 1509, 1368, 1228, 1028. HRMS (ESI): calc. for $C_{38}H_{41}FN_2O_{12}$ (M+H) 737.2716; found: 737.2720.

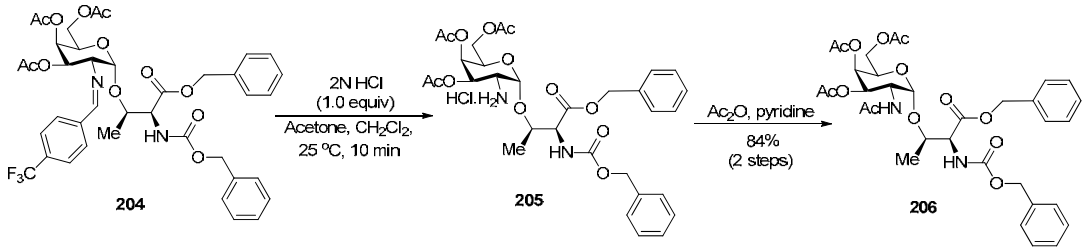
Glycopeptide (203). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **158** (62.5 mg, 0.110 mmol, 1.0 equiv), benzyloxycarbonyl-L-threonine benzyl ester **198** (49.1 mg, 0.143 mmol, 1.3 equiv), and CH_2Cl_2 (0.7 mL). A

preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (6.76 mg, 0.011 mmol, 10 mol %) and AgOTf (5.65 mg, 0.022 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 5 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (9/1, benzene/acetonitrile + 2% triethylamine) to give the desired glycopeptide **203** (59 mg, 74%, α:β = 14:1) as pale yellow oil. ^{1}H NMR (CDCl$_3$, 500 MHz**)** δ (ppm) 8.09 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.37 - 7.28 (m, 5H), 7.24 - 7.23 (m, 2H), 7.08 (d, *J* = 6.0 Hz, 2H), 6.65 (d *J* = 8.0 Hz, 2H), 6.29 (d, *J* = 8.5 Hz, 1H), 5.44 (s, 1H), 5.37 (d, *J* = 11 Hz, 1H), 5.19 (d, *J* = 13 Hz, 1H), 5.14 (d, *J* = 12 Hz, 1H), 4.90 (d, *J* = 13 Hz 1H), 4.83 (d, *J* = 3.0 Hz, 1H), 4.73 (d, *J* = 13 Hz, 1H), 4.45 - 4.44 (d, *J* = 4.5 Hz, 1H), 4.38 – 4.34 (m, 2H), 4.10 (d, *J* = 6.5 Hz, 1H), 3.83 - 3.75 (m, 1H), 3.69 (s, 3H), 3.58 (dd, *J* = 10, 3 Hz, 1H), 2.17 (s, 3H), 2.04 (s, 3H), 1.82 (s, 3H), 1.35 (d, *J* = 6Hz, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ (ppm) 170.5, 170.2, 169.9, 164.6, 162.1, 157.0, 135.1, 130.5, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 113.9, 100.3, 74.9, 68.7, 67.9, 67.2, 67.1, 67.0, 62.2, 58.8, 55.3, 20.8, 20.7, 20.6, 19.4. IR (film, cm^{-1}) 3353, 2938, 2844, 1745, 1642, 1606, 1513, 1457, 1372, 1247, 1169, 1066, 1033. *J*(^{13}CH**)** = 173.3 Hz HRMS (ESI): calc. for $C_{39}H_{44}N_2O_{13}$ (M+H): 749.2916; found: 749.2925.

Glycopeptide (204). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **158E** (90.9 mg, 0.150 mmol, 1.0 equiv), benzyloxycarbonyl-L-threonine benzyl ester **198** (69.0 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 3 h, diluted with benzene (1 mL), and purified by silica gel flash column chromatography (9/1, benzene/acetonitrile + 2%

triethylamine) to provide the desired glycopeptide **204** (95 mg, 81%, α:β = 15:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz**)** δ (ppm) 8.18 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.36 - 7.20 (m, 12H), 7.07 (d, *J* = 6.5 Hz, 2H), 6.11 (d, *J* = 9.0 Hz, 1H), 5.45 (bs, 1H), 5.38 (dd, *J* = 11, 2.5 Hz, 1H), 5.18 (d, *J* = 12 Hz, 1H), 5.09 (d, *J* = 12 Hz, 1H), 4.91 (d, *J* = 13 Hz 1H), 4.81 - 4.76 (m, 2H), 4.46 (d, *J* = 6.0 Hz, 1H), 4.39 - 4.33 (m, 2H), 4.11 - 4.10 (m, 2H), 3.62 (dd, *J* = 11, 3.5 Hz, 1H), 2.13 (s, 3H), 2.03 (s, 3H), 1.81 (s, 3H), 1.35 (d, *J* = 6Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.6, 170.1, 169.8, 164.3, 164.1, 156.9, 138.0, 136.1, 134.8, 128.8, 128.7, 128.5, 128.4, 128.34, 128.3, 128.1, 127.9, 125.9, 125.5, 99.6, 74.7, 68.4, 67.9, 67.2, 67.1, 66.9, 62.2, 58.6, 20.8, 20.5, 19.4. IR (film, cm^{-1}**)** 3353, 2938, 1745, 1645, 1372, 1327, 1235, 1168, 1132. *J*(^{13}CH) = 170.34 Hz HRMS (ESI): calc. for $C_{39}H_{41}FN_2O_{13}$ (M+H): 787.2684; found: 787.2709.

6.7. Removal of Benzylidene Protecting Group



Scheme 6.5. Removal of Benzylidene Protecting Group.

Glycopeptide (206). A 10 mL round bottom flask was charged with a fully protected glycopeptide **204** (94.4 mg, 0.12 mmol, 1.0 equiv), acetone (1.6 mL), and methylene chloride (0.2 mL). Aqueous 2N HCl (60 μL, 0.12 mmol, 1.0 equiv) was added, and the resulting yellow solution was stirred at room temperature for 10 min. The reaction

mixture was diluted with toluene (5 mL), and concentrated *in vacuo* to provide the crude product **205** as yellow oil. This crude product was dried by azeotropic removal of water using toluene (3 x 5 mL). The dried crude product **205** was dissolved in pyridine (0.6 mL) and cooled to 0 ^{o}C, acetic anhydride (56.7 μL, 0.60 mmol, 5.0 equiv) was added, followed by DMAP (0.35 mg, 0.00288 mmol, 2.4 mol %). The ice bath was removed, and the resulting mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (3 mL) was added dropwise to the reaction mixture. The mixture was stirred at room temperature for 1 h, and then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (2/1, benzene/acetonitrile + 1 % triethylamine) to provide *N*-acetyl glycopeptide **206** (67.6 mg, 84%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.34 – 7.30 (m, 10H), 5.80 (d, *J* = 9.5 Hz, 1H), 5.59 (d, *J* = 9.5 Hz, 1H), 5.34 (s, 1H), 5.16 (d, *J* = 12 Hz, 1H), 5.11 (d, *J* = 7.5 Hz 2H), 5.05 – 5.01 (m, 2H), 4.77 (s, 1H), 4.49 (t, *J* = 8.5 Hz, 1H), 4.43 (d, *J* = 9.0, Hz, 1H), 4.22 (d, *J* = 4.5 Hz, 1H), 4.16 – 4.14 (m, 1H), 4.04 – 4.02 (m, 2H), 2.13 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.9, 170.8, 170.3, 156.4, 129.0, 128.9, 128.6, 128.4, 128.3, 128.1, 99.9, 77.3, 68.4, 67.8, 67.4, 67.3, 67.2, 62.1, 58.6, 47.5, 23.2, 20.7, 20.6, 18.2. IR (film, cm^{-1}) 3331, 3061, 2938, 1749, 1668, 1531, 1372, 1306, 1231, 1169, 1132, 1043. *J*(^{13}CH) = 172.3 Hz (99.9 Hz). HRMS (ESI): calc. for $C_{33}H_{40}N_2O_{13}$ (M+H): 673.2603; found: 673.2590.

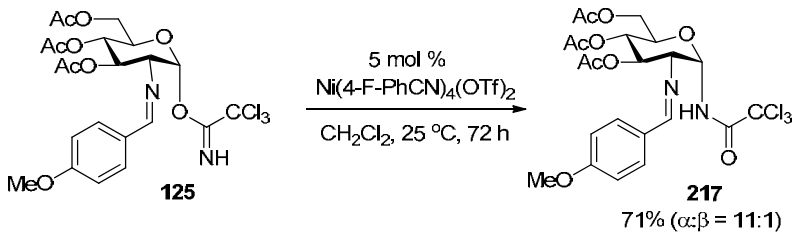
Disaccharide (207). A 10 mL round bottom flask was charged with **153** (58.1 mg, 0.07 mmol, 1.0 equiv), acetone (1.0 mL), and methylene chloride (0.2 mL). Aqueous 2N HCl (42 μL, 0.07 mmol, 1.0 equiv) was added, and the resulting yellow solution was stirred at room temperature for 10 min. The reaction was diluted with toluene (5 mL), and

concentrated *in vacuo* to provide the crude product as yellow oil. This crude product was dried by azeotropic removal of water using more toluene (3 x 5 mL). The dried crude product was dissolved in pyridine (0.4 mL), and the resulting solution was cooled to 0 ^{o}C. Acetic anhydride (34.5 μL, 0.36 mmol, 5.0 equiv) was then added to the reaction mixture, followed by DMAP (0.21 mg, 0.0018 mmol, 2.4 mol %). The ice bath was removed, and the resulting mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (3 mL) was added dropwise to the reaction mixture, and stirred at room temperature for 1 h. The resulting solution was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (2/1, benzene/acetonitrile) to provide the disaccharide **207** (47.2 mg, 90 %) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 5.60 (d, *J* = 9.5 Hz, 1H), 5.17 (t, *J* = 9.5 Hz, 1H), 5.07 (t, *J* = 10 Hz, 1H), 4.93 (d, *J* = 3.0 Hz, 1H), 4.28 (t, *J* = 10 Hz, 1H), 4.18 (dd, *J* = 12, 4.0 Hz, 1H), 4.08 (bs, 1H), 4.05 - 4.02 (m, 1H), 3.51 - 3.47 (m, 1H), 2.06 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.92 (s, 3H), 1.76 – 0.54 (m, 47H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 171.4, 170.7, 169.8, 169.3, 96.0, 78.3, 71.4, 68.2, 67.7, 62.1, 56.3, 56.2, 55.2, 51.8, 44.9, 42.5, 39.9, 39.4, 36.6, 36.1, 35.9, 35.7, 35.5, 35.4, 31.7, 28.7, 28.2, 27.9, 27.8, 24.1, 23.8, 23.2, 22.8, 22.5, 21.1, 20.7, 20.6, 18.6, 12.3, 12.0. IR (film, cm^{-1}) 3323, 2935, 2868, 1749, 1671, 1531, 1450, 1368, 1231, 1124, 1032. $J(^{13}CH)$ = 171.72 Hz

Disaccharide (208). A 10 mL round bottom flask was charged with **151** (182.4 mg, 0.25 mmol, 1.0 equiv), acetone (2.5 mL), and methylene chloride (0.4 mL). Aqueous 2N HCl (126.0 μL, 0.25 mmol, 1.0 equiv) was added, and the resulting yellow solution was stirred at room temperature for 20 min. The reaction was diluted with toluene (5 mL), and concentrated in vacuo to provide the crude product as pale yellow oil. This crude product was dried by azeotropic removal of water using more toluene (3 x 5 mL), resulting in a

pale yellow foamy solid. The dried crude product was dissolved in anhydrous pyridine (3.0 mL), and sulfur trioxide in pyridine (Pyr·SO_3) (0.4 g, 1.26 mmol, 5.0 equiv) was added. The reaction mixture was stirred at room temperature for 4 h. When the reaction was complete as indicated by TLC, saturated aqueous $NaHCO_3$ (2 mL) was added dropwise to quench it. The resulting reaction mixture was extracted with ethyl acetate/methanol (10:1) (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered, and concentrated *in vacuo*. The pale green residue was purified by silica gel flash column chromatography (4/1, benzene/methanol + 1 % triethylamine) to provide the disaccharide **208** (144 mg, 80 %) as white solids. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 5.71 (s, 1H), 5.34 – 5.29 (m, 2H), 5.21 (t, *J* = 10 Hz, 1H), 5.15 (dd, *J* = 9.4, 2.0 Hz, 1H), 5.07 (t, *J* = 10 Hz, 1H), 4.36 (d, *J* = 10 Hz, 1H), 4.27 – 4.24 (m, 1H), 4.21 – 4.18 (m, 1H), 4.17 – 4.09 (m, 4H), 3.77 (d, *J* = 10 Hz 1H), 3.63 (t, *J* = 10 Hz, 1H), 3.08 (q, *J* = 15, 5 Hz, 8H), 2.21 (s, 3H), 2.09 (s, 6H), 2.01 (s, 3H), 1.99 (s, 6H), 1.99 (s, 3H), 1.31 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.9, 170.8, 170.75, 170.6 169.6, 169.3, 168.8, 100.2, 91.2, 73.0, 71.6, 70.9, 68.7, 68.1, 65.7, 61.8, 57.0, 46.2, 21.1, 20.9, 20.8, 20.7, 20.65, 8.6. IR (film, cm^{-1}) 3335, 2994, 2954, 1745, 1437, 1370, 1228, 1080, 1037. *J*(^{13}CH**)** = 176.0 Hz (100.2 Hz). HRMS (ESI): calc. for $C_{26}H_{36}NO_{20}S$ (M+H+2Et_3N+H): 918.4112; found: 918.4117.

6.8. Mechanistic Studies

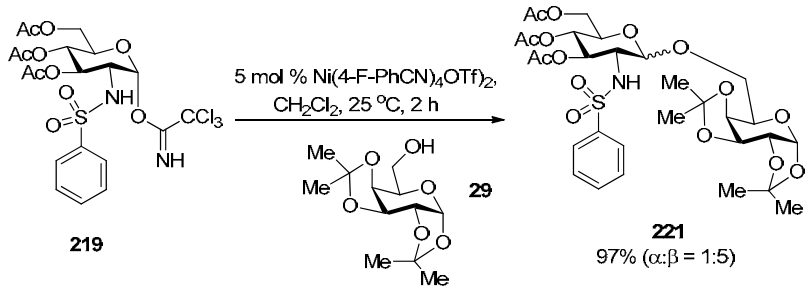


Scheme 6.6. A [1, 3]-Rearrangement of 2-Deoxy-2-*p*-Methoxybenzylideneamino-3,4,6-*Tri*-*O*-Acetyl-α-D-Glucopyranosyl Trichloroacetimidate.

2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetamide (217). A 10 mL oven-dried Schlenk flask was charged with D-glucosamine trichloroacetimidate donor **125** (85.2 mg, 0.150 mmol, 1.0 equiv) and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from a reaction of Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) for 30 min, was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C for 72 h, diluted with benzene (2 mL), and purified by silica gel flash column chromatography (7/1, benzene/acetonitrile + 1% triethylamine) to give the desired glycosyl trichloroacetamide **217** (60.1 mg, 71%, α:β = 11:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.16 (s, 1H), 8.01 (s, 1H), 7.61 (d, *J* = 5.0 Hz, 2H), 6.90 (d, *J* = 5.0 Hz, 2H), 5.47 (t, *J* = 5.0 Hz, 1H), 5.33 (t, *J* = 10 Hz, 1H), 5.11 (t, *J* = 10 Hz, 1H), 4.37 (dd, *J* = 10, 5.0 Hz, 1H), 4.12 - 4.06 (m, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 10, 5.0 Hz, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 1.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 170.7, 169.8, 169.7, 164.4, 162.7, 162.5, 152.3, 144.2, 130.2, 129.6, 128.3, 127.5, 114, 79.5, 71.6, 69.2, 68.8, 68.1, 61.8, 55.4, 20.7, 20.6, 20.5. IR (film, cm^{-1}) 3356, 2957, 1745,

1645, 1608, 1512, 1368, 1242, 1231, 1168, 1039. $J(^{13}CH)$ = 170.04 Hz (79.5 Hz). HRMS (ESI): calc. for $C_{22}H_{25}Cl_3N_2O_9$ (M+Na): 589.0518; found: 589.0525.

Azido disaccharide (**220**). A 10 mL oven-dried Schlenk flask was charged with 2-azido-2-deoxy-3,4-6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **218**[139] (71.4 mg, 0.150 mmol, 1.0 equiv),1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (50.8 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from a reaction of Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.015 mmol, 10 mol %) in dichloromethane (1 mL) for 30 min, was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 3 h, diluted with benzene (2 mL), and purified by silica gel flash column chromatography (7/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **220**[159] (85.2 mg, 99 %, α:β = 1:1) as pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.51 (d, *J* = 5.04 Hz, 1H), 5.49 (d, *J* = 4.96 Hz, 1H), 5.43 (dd, *J* = 10, 9.3 Hz, 1H), 5.02 - 4.94 (m, 4H), 4.59 - 4.53 (m, 3H), 4.30 – 4.21 (m, 6H), 4.15 - 3.95 (m, 6H), 3.85 - 3.72 (m, 3H), 3.64 - 3.62 (m, 21H), 3.48 (t, *J* = 9.9 Hz, 1H), 3.27 (dd, *J* = 11, 3.5 Hz, 1H), 2.06 (s, 6H), 2.05 (s, 3H), 2.04 (s, 1.5H), 2.01 (s, 3H), 1.98 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.30 (s, 12H). IR (film, cm^{-1}) 2988, 2113, 1752, 1373, 1225, 1068.



Scheme 6.7. Glycosylation Reaction with C(2)-*N*-Phenylsulfonamide Glycosyl Donor

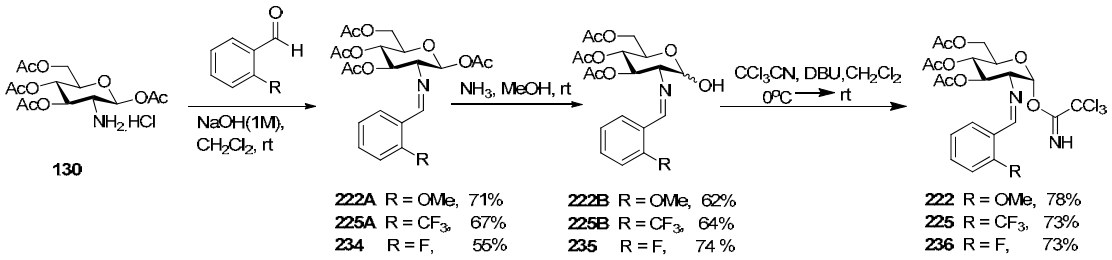
A 10 mL oven-dried Schlenk flask was charged with a C(2)-*N*-phenylsulfonamide glycosyl donor **219**[177](88.5 mg, 0.150 mmol, 1 equiv),1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (50.8 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from the reaction of Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC for 2 h, diluted with benzene (2 mL), and purified by silica gel flash column chromatography (7/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **221**(100.1 mg, 97 %, α:β = 1:5) as pale yellow oil.

Disaccharide (221α). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.88 - 7.85 (m, 2H), 7.56 - 7.50 (m, 3H), 5.52 - 5.50 (m, 3H), 5.14 (t, *J* = 10 Hz, 1H), 4.98 (t, *J* = 9.7 Hz, 1H), 4.68 (dd, *J* = 7.8, 2.3 Hz, 1H), 4.62 (d, *J* = 3.5 Hz, 1H), 4.36 - 4.32 (m, 2H), 4.23 (dd, *J* = 13, 4.8 Hz, 1H), 4.03 - 4.00 (m, 3H), 3.86 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.55 (dd, *J* = 9.1, 7.6 Hz, 1H), 3.49 (dd, *J* = 10, 3.5 Hz, 1H), 2.07 (s, 3H), 1.98 (s, 3H), 1.72 (s, 3H), 1.56 (s, 3H), 1.52 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.6, 170.5, 169.3, 141.1, 132.7, 129.2, 128.9, 126.8, 109.8, 108.7, 98.4, 96.1, 70.6, 70.4, 70.3, 70.2, 68.0, 67.9, 65.4, 61.6, 55.9, 26.1, 25.8, 24.8, 24.1, 20.6, 20.5, 20.3. IR (film, cm^{-1}) 3260, 2936, 1745, 1449, 1372, 1161, 1213, 1039, 913, 730. HRMS (ESI): calc. for $C_{30}H_{41}NO_{15}SNa$ (M+Na): 710.2092; found: 710.2095.

Disaccharide (221β). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.88 - 7.85 (m, 2H), 7.52 - 7.47 (m, 3H), 5.52 (d, *J* = 5.1 Hz, 1H), 5.05 (t, *J* = 9.2 Hz, 1H), 5.01 (t, *J* = 9.2 Hz, 1H), 4.89 (d, *J* = 7.7 Hz, 1H), 4.59 (d, *J* = 8.2 Hz, 1H), 4.55 (dd, *J* = 7.8, 2.2 Hz, 1H), 4.28 (dd, *J* = 5.1, 2.3 Hz, 1H), 4.28 (dd, *J* = 7.5, 4.7 Hz 1H), 4.13 - 4.05 (m, 2H), 3.91 - 3.84 (m, 1H), 3.76 (dd, *J* = 11.8, 3.9 Hz, 1H), 3.67 - 3.63 (m, 2H), 3.51 (dd, *J* = 18, 8.0 Hz, 1H), 2.05 (s, 3H), 1.98 (s, 3H), 1.86 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.0, 170.5, 169.2, 141.2, 132.3, 128.7,

127.3, 109.2, 108.6, 101.4, 96.2, 73.0, 71.9, 70.9, 70.6, 70.2, 68.6, 68.1, 67.8, 62.0, 60.3, 57.8, 26.0, 25.9, 24.7, 24.3, 20.9, 20.6, 20.5, 20.4. IR (film, cm^{-1}) 3267, 2982, 1745, 1448, 1373, 1213, 1162, 1041, 912, 727. HRMS (ESI): calc. for $C_{30}H_{42}NO_{15}S$ (M+H): 688.2269; found: 688.2275.

6.9. Synthesis of *Ortho*-Substituted Benzylideneamino Glycosyl Donors



Scheme 6.8. Synthesis *Ortho*-Substituted Glycosyl Donors **222**, **225** and **236**

2-Deoxy-2-*O*-methoxybenzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranose (222A). A 100 mL round bottom flask was charged with 2-amino-2-deoxy-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranosyl hydrochloride **130** [155] (2.25 g, 5.861 mmol, 1.0 equiv), 1M NaOH (6.07 mL, 6.070 mmol, 1.04 equiv), and CH_2Cl_2 (8 mL). To this resulting pale yellow solution was added 2-methoxybenzaldehyde (0.83 mL, 6.857 mmol, 1.17 equiv). The resulting mixture was stirred at room temperature for 3 h. When the reaction was complete as indicated by TLC, the reacton mixture was concentrated *in vacuo*, and dried by azeotropic removal of water using benzene (3 x 10 mL). The resulting residue was purified by silica gel flash column chromatography (2/1 hexane/ethyl acetate + 1% triethylamine → 1/2 hexane/ethyl acetate + 1% triethylamine) to provide the desired

product **222A** (1.94 g, 71%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.66 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.37 - 7.35 (m, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.4 Hz 1H), 5.95 (d, *J* = 8.4, Hz, 1H), 5.40 (t, *J* = 10 Hz, 1H), 5.12 (t, *J* = 10 1H), 4.35 (dd, *J* = 12, 4.8 Hz, 1H), 4.11 (dd, *J* = 12, 1.6 Hz, 1H) 3.96 - 3.93 (m, 1H), 3.85 (s, 3H), 3.48 (t, *J* = 9.6 Hz, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 1.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.5, 169.7, 169.5, 168.6, 161.3, 158.8, 132.6, 127.7, 123.8, 120.8, 110.8, 93.1, 68.0, 61.8, 55.4, 20.7, 20.6, 20.56, 20.4. IR (film, cm^{-1}**)** 2951, 2876, 1753, 1646, 1368, 1221, 1073, 1036.

2-Deoxy-2-*O*-methoxybenzylideneamino-3.4,6-*tri*-*O*-acetyl-D-glucopyranose (222B). A 50 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*O*-methoxybenzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranose **222A** (1.9 g, 4.082 mmol, 1.0 equiv.) and THF (21 mL). The solution was cooled to 0 ^{o}C, and a solution of NH_3 in methanol (7N, 8.8 mL, 61.23 mmol, 15 equiv.) was slowly added. The resulting mixture was warmed to 25 ^{o}C and stirred for 2 h. When the reaction was complete as indicated by TLC, the mixture was concentrated *in vacuo*, and the residue was purified by silica gel flash chromatography (1/1 hexane/ethyl acetate + 1% triethylamine → 1/2 hexane/ethyl acetate + 1% triethylamine) to provide the hemiacetal **222B** (1.07 g, 62%) as a pale yellow solid**.** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.75 (s, 1H), 7.87 (dd, *J* = 7.6 Hz, 1H), 7.41 – 7.37 (m, 1H), 6.95 – 6.86 (m, 3H), 5.39 (t, *J* = 10 Hz, 1H), 5.25 – 5.11(m, 2H), 4.28 (dd, *J* = 12, 5.2 Hz, 1H), 4.20 - 4.17 (m,1H), 3.87 - 3.86 (m, 5H), 3.26 (dd, *J* = 10, 8.0 Hz, 1H), 2.10 (s, 3H), 2.03 (s, 3H), 1.89 (s, 3H). IR (film, cm^{-1}) 3446, 2949, 1747, 1635, 1601, 1244, 1033.

2-Deoxy-2-*O*-methoxybenzylideneamino-3.4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (222). A 100 mL oven-dried Schlenk flask was charged with hemiacetal **222B** (1.0 g, 2.362 mmol, 1.0 equiv.) and methylene chloride (12 mL). The

solution was cooled to 0 ^{o}C, and trichloroacetonitrile (0.7 mL, 7.086 mmol, 3.0 equiv.) was added followed by DBU (0.18 mL, 1.181 mmol, 0.5 equiv.). The resulting mixture was stirred at this temperature for 4 h, diluted with toluene (2 mL), and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to provide the imidate **222** (1.05 g, 78%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz**)** δ (ppm) 8.77 (s, 1H), 8.56 (s, 1H), 7.85 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.40 – 7.38 (m, 1H), 6.94 – 6.87 (m, 2H), 6.42 (d, *J* = 3.6 Hz, 1H), 5.69 (t, *J* = 10 Hz, 1H), 5.23 (t, *J* = 10 Hz, 1H), 4.35 – 4.33 (m, 2H), 4.18 – 4.15 (m, 1H), 3.86 – 3.83 (m, 4H), 2.09 (s, 3H), 2.06 (s, 3H), 1.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.6, 169.9, 169.7, 161.0, 160.8, 158.9, 132.6, 127.6, 123.9, 120.7, 110.8, 95.8, 91.0, 71.0, 70.9, 70.3, 68.2, 61.8, 55.4, 20.6, 20.5. IR (film, cm^{-1}) 3339, 2964, 1744, 1672, 1636, 1600, 1366, 1222, 1019.

2-Deoxy-2-*O*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranoside (224). A 10 mL oven-dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*O*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **222** (85.2 mg, 0.150 mmol, 1.0 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (50.7 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). To this solution was added triflic acid (1.3 μL, 0.015 mmol, 10 mol %) in CH_2Cl_2 (1 mL). The resulting mixture was stirred under argon at 25 ^{o}C. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with benzene (2 mL), and purified by silica gel flash column chromatography (3/1, benzene/acetonitrile + 1% triethylamine) to give the desired disaccharide **224** (15 mg, 15%, α:β = 1:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.73 (s, 0.5H), 8.66 (s, 1H), 7.95 (dd, *J* = 7.6, 1.6 Hz, 0.5H),7.89 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.41 - 7.37 (m, 1.5H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 5.67 (t, *J* = 10 Hz, 1H), 5.50 (d, *J* = 4.8 Hz, 0.5), 5.46 (d, *J* = 4.8 Hz, 1H), 5.38 (t, *J* = 9.6 Hz, 1H), 5.14 (d, *J* =

9.6 Hz, 1H), 5.09 (d, *J* = 9.6 Hz, 1H), 4.94 (d, *J* = 3.6 Hz, 0.5H), 4.84 (d, *J* = 8.0 Hz, 1H), 4.50 (dd, *J* = 8.0, 2.0 Hz, 0.5H), 4.39 (dd, *J* = 7.9, 2.2 Hz, 1.5H), 4.36 – 4.31 (m, 2.5H), 4.27 (dd, *J* = 5.0, 2.3 Hz, 0.5H), 4.23 (dd, *J* = 4.9, 2.0 Hz 1H), 4.18 - 4.14 (m, 2.7H), 4.08 - 4.04 (m, 1H), 3.99 - 3.90 (m, 2.7H), 3.86 (s, 1.5H), 3.85 (s, 3H), 3.82 - 3.73 (m, 2.7H), 3.62 (dd, *J* = 10, 3.5 Hz, 0.5H), 3.39 (dd, *J* = 9.6, 7.9 Hz, 1H), 2.12 (s, 1.5H), 2.11 (s, 3H), 2.06 (s, 1.5H), 2.03 (s, 3H), 1,92 (s, 3H), 1.90 (s, 1.5H), 1.69 (s, 1.5H), 1.58 (s, 1.5H), 1.43 (s, 3H), 1.39 (s, 3H), 1.37 (s, 1.5H), 1.33 (s, 1.5H), 1.29 (s, 3H), 1.19 (s, 3H). IR (film, cm^{-1}) 2987, 2937, 1725, 1636, 1600, 1370, 1315, 1245, 1228, 1164, 1113, 1067, 1029. HRMS (ESI): calc. for $C_{32}H_{43}NO_{14}$ (M+H): 666.2756; found: 666.2753.

2-Deoxy-2-*O*-(trifluoromethyl)benzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranose (225A). A 100 mL round bottom flask was charged with 2-amino-2-deoxy-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranosyl hydrochloride **130** [155] (2.26 g, 5.864 mmol, 1.0 equiv), 1M NaOH (6.09 mL, 6.09 mmol, 1.04 equiv), and CH_2Cl_2 (8 mL). To this resulting pale yellow solution was added 2-(Trifluoromethyl) benzaldehyde (0.9 mL, 6.862 mmol, 1.17 equiv). The resulting mixture was stirred vigorously at room temperature. When the reaction was complete as monitored by TLC, the reaction mixture was concentrated *in vacuo*, and dried by azeotropic removal of water using benzene (3 x 10 mL). The resulting residue was purified by silica gel flash column chromatography (2/1 hexane/ethyl acetate + 1% triethylamine) to provide the desired product **225A** (1.98 g, 67%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.62 (d, *J* = 1.2 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.69 – 7.67 (m, 1H), 7.61 – 7.53 (m, 2H), 5.99 (d, *J* = 8.2 Hz 1H), 5.49 (t, *J* = 9.6 Hz, 1H), 5.17 (t, *J* = 10 Hz, 1H), 4.37 (dd, *J* = 12, 4.5 Hz, 1H), 4.16 – 4.12 (m, 1H), 4.00 – 3.97 (m, 1H), 3.58 (dd, *J* = 9.8, 8.3 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H) 1.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.2, 169.4, 169.3, 168.3, 161.6, 133.3, 133.1, 133.09, 132.0, 130.6, 128.4, 125.3, 125.29, 125.2, 125.17,

92.5, 72.8, 72.6, 72.5, 67.7, 61.4, 20.3, 20.26, 20.2, 20.0. IR (film, cm^{-1}**)** 2948, 2880, 1753, 1650, 1372, 1324, 1221, 1169, 1128, 1065, 1034**.**

2-Deoxy-2-*O*-(trifluoromethyl)benzylideneamino-3.4,6-*tri*-*O*-acetyl-D-glucopyranose (225B). A 50 mL oven-dried Schlenk flask was charged with **225A** (1.91 g, 3.789 mmol, 1.0 equiv) and THF (19 mL). The solution was cooled to 0 ^{o}C, and a solution of NH_3 in methanol (7N, 8.1 mL, 56.833 mmol, 15 equiv.) was slowly added. The resulting mixture was warmed to 25 ^{o}C and stirred. When the reaction was complete as monitored by TLC, the mixture was concentrated *in vacuo*, and the residue was purified by silica gel flash column chromatography (1/1 hexane/ethyl acetate + 1% triethylamine $\rightarrow$1/2 hexane/ethyl acetate + 1% triethylamine) to provide the hemiacetal **225B** (1.12 g, 64%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.62 (d, J = 2.4 Hz, 1H), 8.15 (d, J = 7.2 Hz, 1H), 7.69 – 7.67 (m, 1H), 7.58 – 7.56 (m, 3H), 5.42 (t, J = 9.6 Hz, 1H), 5.16 – 5.14 (m, 2H), 4.29 (dd, J = 12, 4.8 Hz, 1H), 4.22 – 4.17 (m, 1H), 3.95 – 3.98 (m, 1H), 3.40 (dd, J = 10, 7.6 Hz, 1H), 2.11 (s, 3H), 2.04 (s, 3H), 1.90 (s, 3H). IR (film, cm^{-1}) 3451, 2945, 1747, 1643, 1368, 1315, 1230, 1170, 1121, 1034.

2-Deoxy-2-*O*-(trifluoromethyl)benzylideneamino-3.4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (225). A 25 mL oven-dried Schlenk flask was charged with hemiacetal **225B** (0.77 g, 1.678 mmol, 1 equiv.) and CH_2Cl_2 (8 mL). The solution was cooled to 0 ^{o}C, and trichloroacetonitrile (0.5 mL, 5.035 mmol, 3 equiv.) was added, followed by DBU (0.1 mL, 0.839 mmol, 0.5 equiv.). The resulting reaction mixture was stirred at this temperature for 3 h, diluted with toluene (2 mL), and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (5/1, benzene/ethyl acetate + 1% triethylamine) to provide the imidate **225** (0.74 g, 73%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.69 (d, J = 2.4 Hz, 1H), 8.65 (s, 1H), 8.14 – 8.12 (m, 1H), 7.68 – 7.66 (m, 1H), 7.62 – 7.54 (m, 2H),

6.49 (d, *J* = 3.6 Hz, 1H), 5.70 (t, *J* = 9.6 Hz, 1H), 5.26 (t, *J* = 10 Hz, 1H), 4.37 - 4.34 (m, 2H), 4.2 – 4.17 (m, 1H), 3.93 (dd, *J* = 10, 3.2 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H), 1.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.5, 169.8, 169.6, 161.3, 161.2, 160.8, 133.2, 133.18, 132.1, 130.8, 129.4, 129.1, 128.5, 125.5, 125.4, 125.3, 95.3, 91.0, 71.0, 70.6, 70.4, 68.1, 61.7, 20.6, 20.58, 20.3. IR (film, cm^{-1}) 3342, 2959, 1748, 1674, 1314, 1224, 1120, 1128, 1022.

2-Deoxy-2-*O*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranosyl-(1→6)-1,2:3,4-*di*-*O*-isopropylidene-α-D-galactopyranoside (226). A 10 mL oven dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*O*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **225** (90.9 mg, 0.150 mmol, 1.0 equiv), 1,2:3,4-*di*-*O*-isopropylidene-D-galactopyranose **29** (50.8 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting reaction mixture was stirred under argon at 25 ^{o}C. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with benzene (1 mL), and purified by silica gel flash column chromatography (3/1, benzene/ethyl acetate + 1% triethylamine) to give the desired disaccharide **226** (85.9 mg, 81%, α:β = 10:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.64 (d, *J* = 2.0 Hz, 1H), 8.22 (d, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.58 - 7.75 (m, 2H), 5.68 (t, *J* = 10 Hz, 1H), 5.48 (d, *J* = 4.8 Hz, 1H), 5.14 (t, *J* = 10 Hz, 1H), 4.94 (d, *J* = 3.6 Hz, 1H), 4.52 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.37 (dd, *J* = 12, 4.1 Hz, 1H), 4.31 - 4.27 (m, 3H), 4.16 (dd, *J* = 14, 3.3 Hz 1H), 4.07 - 4.03 (m, 1H), 3.86 (dd, *J* = 10, 6.0 Hz, 1H), 3.76 (dd, *J* = 10, 7.2 Hz, 1H), 3.70 (d, *J* = 10, 3.4 Hz, 1H), 2.10 (s, 3H), 2.03 (s, 3H), 1.89 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 170.2, 170.1, 160.9, 138.7, 133.8,

132.2, 130.8, 129.2, 128.9, 128.4, 125.7, 125.6, 109.3, 108.8, 100.1, 96.4, 72.5, 71.3, 70.9, 70.7, 69.0, 68.0, 67.9, 66.5, 62.4, 26.3, 26.1, 25.1, 24.3, 21.0, 20.9, 20.6.

IR (film, cm^{-1}) 2988, 2938, 1747, 1643, 1578, 1371, 1314, 1213, 1164, 1115, 1067, 1028, 1008. J(^{13}CH) = 172.29 Hz. HRMS (ESI): calc. for $C_{32}H_{41}F_3NO_{13}$ (M+H): 704.2534; found: 704.2530.

6.10. Synthesis of GPI Anchor Pseudodisaccharides.

Pseudodisaccharide (229). A 10 mL oven dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-methoxybenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **125** (85.2 mg, 0.150 mmol, 1.0 equiv), myo-inositol derivative **228**[199] (88.3 mg, 0.180 mmol, 1.2 equiv) and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in CH_2Cl_2 (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with toluene (1 mL), and purified by silica gel flash column chromatography (5/1, toluene/ethyl acetate + 1% triethylamine) to give the desired pseudo-disaccharide **229** (89.8 mg, 67%, α only) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.22 (s, 1H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.40 - 7.27 (m, 15H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.69 (t, *J* = 9.9 Hz, 1H), 5.49 (d, *J* = 3.5 Hz, 1H), 5.07 (t, *J* = 10 Hz, 1H), 4.93 (d, *J* = 11 Hz, 1H), 4.86 - 4.73 (m, 5H), 4.38 (ddd, *J* = 10, 5.3, 3.0 Hz, 1H), 4.20 (dd, *J* = 5.3, 3.8 Hz, 1H), 4.15 - 4.11 (m, 2H), 3.98 - 3.90 (m, 2H), 3.85 (s, 3H), 3.82 (dd, *J* = 9.0, 1.9 Hz, 1H), 3.73 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.59 - 3.51 (m, 2H), 2.05 (s, 3H), 1.91 (s, 3H), 1.88 (s, 3H), 1.52 (s, 3H), 1.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 170.1, 170.0, 163.7, 162.4, 138.6, 138.5, 138.3, 130.2, 129.3, 129.2, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 114.1, 110.1, 97.6, 81.2, 80.7, 79.3, 78.3, 75.1,

74.8, 73.6, 72.0, 71.7, 69.6, 67.6, 62.2, 55.6, 27.8, 25.8, 21.0, 20.93, 20.91. IR (film, cm^{-1}) 2985, 2938, 2873, 1745, 1640, 1604, 1512, 1455, 1366, 1306, 1241, 1221, 1024. $J(^{13}CH)$ = 172.56 Hz. HRMS (ESI): calc. for $C_{50}H_{58}NO_{14}$ (M+H): 896.3850; found: 896.3857.

Pseudodisaccharide (230). A 10 mL oven dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **129** (80.7 mg, 0.150 mmol, 1.0 equiv), myo-inositol derivative **228**[199] (88.3 mg, 0.180 mmol, 1.2 equiv) and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in CH_2Cl_2 (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with toluene (1 mL), and purified by silica gel flash column chromatography (6/1, toluene/ethyl acetate + 1% triethylamine) to give the desired pseudo-disaccharide **230** (83.2 mg, 64%, α only) as pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.32 (s, 1H), 7.76 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.46 - 7.27 (m, 18H), 5.73 (t, *J* = 10 Hz, 1H), 5.52 (d, *J* = 3.6 Hz, 1H), 5.09 (t, *J* = 10 Hz, 1H), 4.95 (d, *J* = 11 Hz, 1H), 4.87 - 4.77 (m, 5H), 4.40 (ddd, *J* = 10, 5.2, 3.0 Hz, 1H), 4.20 (dd, *J* = 5.3, 3.8 Hz, 1H), 4.16 - 4.09 (m, 2H), 3.98 - 3.93 (m, 2H), 3.85 (dd, *J* = 12, 1.9 Hz, 1H), 3.74 (dd, *J* = 7.9, 3.6 Hz, 1H), 3.63 (dd, *J* = 10, 3.5 Hz, 1H), 3.53 (dd, *J* = 9.3, 8.2 Hz, 1H), 2.06 (s, 3H), 1.93 (s, 3H), 1.90 (s, 3H), 1.52 (s, 3H), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 170.1, 170.0, 164.5, 138.6, 138.5, 138.3, 136.1, 131.3, 129.2, 128.8, 128.7, 128.66, 128.65, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 110.1, 97.5, 81.2, 80.7, 79.3, 78.4, 75.14, 75.1, 74.8, 73.6, 71.9, 71.7, 68.9, 67.7, 62.1, 27.8, 25.7, 21.0, 20.9. IR (film, cm^{-1}**)** 3030, 2985, 2936, 2871, 1745, 1643, 1496, 1453, 1366, 1220, 1024. $J(^{13}CH$**)** = 175.1 Hz. HRMS (ESI): calc. for $C_{49}H_{56}NO_{13}$ (M+H): 866.3755; found: 866.3752.

Pseudodisaccharide (231). A 10 mL oven dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (37.8 mg, 0.07 mmol, 1.0 equiv), myo-inositol derivative **228**[199] (40 mg, 0.08 mmol, 1.2 equiv) and CH_2Cl_2 (0.8 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (2.09 mg, 0.003 mmol, 5 mol %) and AgOTf (1.75 mg, 0.007 mmol, 10 mol %) in dichloromethane (0.5 mL) was then added to the solution.The resulting mixture was stirred under argon at 25 ^{o}C. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with toluene (1 mL), and purified by silica gel flash column chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired pseudodisaccharide **231** (42 mg, 70%, α only) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.27 (s, 1H), 7.74 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.40 - 7.27 (m, 15H), 7.11 (t, *J* = 11 Hz, 2H), 5.69 (t, *J* = 9.8 Hz, 1H), 5.49 (d, *J* = 3.5 Hz, 1H), 5.07 (t, *J* = 10 Hz, 1H), 4.95 (d, *J* = 11 Hz, 1H), 4.87 - 4.73 (m, 5H), 4.38 (ddd, *J* = 10, 5.3, 3.0 Hz, 1H), 4.18 (t, *J* = 5.0 Hz, 1H), 4.14 - 4.05 (m, 2H), 3.97 - 3.90 (m, 2H), 3.81 (dd, *J* = 12, 1.8 Hz, 1H), 3.72 (dd, *J* = 8.1, 3.6 Hz, 1H), 3.59 (dd, *J* = 10, 3.5 Hz, 1H), 3.51 (t, *J* = 8.6 Hz, 1H), 2.05 (s, 3H), 1.91 (s, 3H), 1.89 (s, 3H), 1.52 (s, 3H), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 170.2, 170.0, 163.1, 138.6, 138.5, 138.3, 132.4, 132.3, 130.7, 130.6, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 116.0, 115.8, 110.1, 97.4, 81.2, 80.5, 79.4, 78.4, 75.2, 74.8, 73.6, 71.9, 71.6, 68.7, 67.6, 62.0, 27.9, 25.8, 21.1, 20.1, 20.9. IR (film, cm^{-1}) 2936, 2870, 1745, 1644, 1601, 1509, 1454, 1366, 1222, 1152, 1125, 1025. *J*(^{13}CH) = 175.0 Hz. HRMS (ESI): calc. for $C_{49}H_{55}NO_{13}F$ (M+H): 884.3669; found: 884.3657.

Pseudodisaccharide (232). A 10 mL oven dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-

glucopyranosyl trichloroacetimidate **136** (90.9 mg, 0.150 mmol, 1.0 equiv), myo-inositol derivative **228**[199] (88.3 mg, 0.180 mmol, 1.2 equiv) and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.008 mmol, 5 mol %) and AgOTf (3.85 mg, 0.015 mmol, 10 mol %) in CH_2Cl_2 (1 mL) was then added to the solution.The resulting mixture was stirred under argon at 25 ^oC. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with toluene (1 mL), and purified by silica gel flash column chromatography (9/1, toluene/acetonitrile + 1% triethylamine) to give the desired pseudodisaccharide **232** (86.3 mg, 62%, α:β = 12:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.36 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.40 - 7.27 (m, 15H), 5.73 (t, *J* = 9.9 Hz, 1H), 5.52 (d, *J* = 3.6 Hz, 1H), 5.08 (t, *J* = 10 Hz, 1H), 4.95 (d, *J* = 11 Hz, 1H), 4.85 - 4.73 (m, 5H), 4.39 (ddd, *J* = 10, 5.2, 2.7 Hz, 1H), 4.19 (dd, *J* = 5.7, 3.8 Hz, 1H), 4.13 (dd, *J* = 9.9, 7.0 Hz, 1H), 4.05 (dd, *J* = 13, 6.2 Hz, 1H), 3.97 - 3.91 (m, 2H), 3.83 (dd, *J* = 12, 1.9 Hz, 1H), 3.72 (dd, *J* = 7.9, 3.6 Hz, 1H), 3.66 (dd, *J* = 10, 3.5 Hz, 1H), 3.50 (dd, *J* = 9.9, 8.0 Hz, 1H), 2.05 (s, 3H), 1.92 (s, 3H), 1.89 (s, 3H), 1.52 (s, 3H), 1.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.8, 170.1, 169.9, 162.9, 138.5, 138.4, 138.3, 129.2, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 125.8, 125.7, 110.1, 97.4, 81.2, 80.6, 79.4, 78.4, 75.2, 75.1, 74.8, 73.6, 71.9, 71.5, 68.7, 67.7, 62.0, 27.8, 25.8, 21.0, 20.9. IR (film, cm^{-1}) 2985, 2937, 2873, 1746, 1644, 1497, 1454, 1366, 1322, 1221, 1165, 1124, 1063, 1025. J(^{13}CH) = 175.0 Hz. HRMS (ESI): calc. for $C_{50}H_{55}NO_{13}F_3$(M+H): 934.3614; found: 934.3626.

2-Deoxy-2-*O*-fluorobenzylideneamino-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranose (234). A 250 mL round bottom flask was charged with 2-amino-2-deoxy-1,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranosyl hydrochloride **130** [155] (3.5 g, 9.120 mmol, 1.0 equiv), 1M NaOH (9.4 mL, 9.44 mmol, 1.04 equiv), and CH_2Cl_2 (13 mL). To this resulting pale yellow solution was added 2-fluorobenzaldehyde (1.1 mL, 10.670 mmol, 1.17 equiv).

The resulting mixture was stirred vigorously at room temperature. When the reaction was complete as monitored by TLC, the reaction mixture was concentrated *in vacuo*, and dried by azeotropic removal of water using benzene (3 x 10 mL). The resulting residue was purified by silica gel flash column chromatography (2/1 hexane/ethyl acetate + 1% triethylamine) to provide the desired product **234** (2.27 g, 55%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.56 (s, 1H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 9.6 Hz, 1H), 5.98 (d, *J* = 8.3 Hz 1H), 5.44 (t, *J* = 9.6 Hz, 1H), 5.16 (t, *J* = 9.9 Hz, 1H), 4.39 (dd, *J* = 12, 4.4 Hz, 1H), 4.13 (dd, *J* = 12, 1.8 Hz, 1H), 4.00 – 3.96 (m, 1H), 3.53 (t, *J* = 9.6 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H) 1.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 170.1, 169.8, 169.0, 163.9, 161.3, 158.8, 158.78, 133.5, 133.4, 128.3, 124.8, 124.81, 123.3, 123.2, 119.0, 115.8, 93.2, 73.2, 73.17, 73.0, 68.1, 62.0, 21.1, 21.0, 20.9, 20.7. IR (film, cm^{-1}**)** 1748, 1642, 1615, 1582, 1485, 1365, 1210, 1155, 1075, 1030**.**

2-Deoxy-2-*O*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-D-glucopyranose (235). A 100 mL oven dried Schlenk flask was charged with **234** (2.1 g, 4.632 mmol, 1.0 equiv) and THF (23 mL). The solution was cooled to 0 ^{o}C, and a solution of NH_3 in methanol (7N, 9.9 mL, 69.472 mmol, 15 equiv.) was slowly added. The resulting mixture was warmed to 25 ^{o}C and stirred. When the reaction was complete as monitored by TLC, the mixture was concentrated *in vacuo*, and the residue was purified by silica gel flash column chromatography (1/1 hexane/ethyl acetate + 1% triethylamine →1/2 hexane/ethyl acetate + 1% triethylamine) to provide the hemiacetal **235** (1.41 g, 74%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.62 (s, 0.5H), 8.56 (s, 1H), 7.94 – 7.89 (m, 1.5H), 7.46 – 7.34 (m, 1.5H), 7.19 – 7.05 (m, 3.3H), 5.55 (t, *J* = 9.8 Hz, 0.5H), 5.40 (t, *J* = 9.6 Hz, 1H), 5.27 (d, *J* = 3.4 Hz, 0.5H), 5.16 – 5.09 (m, 2.5H), 4.47 – 4.43 (m, 0.5H), 4.36 (dd, *J* = 12, 4.2 Hz, 0.5H), 4.26 (dd, *J* = 12, 5 Hz, 1H), 4.19 – 4.09 (m, 2H), 3.86 – 3.84 (m, 1H), 3.62 (dd, *J* = 9.9, 3.4 Hz, 0.5H), 3.36 (dd, *J* = 9.8, 7.8 Hz, 1H), 2.11 (s,

1.5H), 2.10 (s, 3H), 2.04 (s, 4.5H), 1.92 (s, 1.5H), 1.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.2, 171.1, 170.3, 170.2, 170.1, 170.0, 164.0, 163.9, 161.5, 161.3, 159.0, 158.9, 158.85, 158.8, 133.8, 133.75, 133.4, 133.3, 128.3, 128.25, 128.2, 124.9, 124.8, 124.75, 124.7, 123.3, 123.2, 122.9, 122.8, 116.2, 116.1, 116.0, 115.9, 96.0, 93.3, 75.7, 73.2, 72.7, 72.2, 71.1, 68.7, 68.5, 68.2, 62.6, 62.4, 21.1, 21.0, 20.9, 20.8. IR (film, cm^{-1}) 3441, 2951, 2896, 1743, 1640, 1614, 1581, 1485, 1457, 1366, 1222, 1026.

2-Deoxy-2-*O*-fluorobenzylideneamino-3.4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (236). A 50 mL oven dried Schlenk flask was charged with hemiacetal **235** (1.4 g, 3.403 mmol, 1 equiv.) and CH_2Cl_2 (17 mL). The solution was cooled to 0 ^{o}C, and trichloroacetonitrile (1 mL, 10.209 mmol, 3.0 equiv.) was added, followed by DBU (0.26 mL, 1.702 mmol, 0.5 equiv.). The resulting reaction mixture was stirred at this temperature for 3 h, diluted with toluene (2 mL), and concentrated *in vacuo.* The residue was purified by silica gel flash column chromatography (3/1, hexane/ethyl acetate + 1% triethylamine) to provide the imidate **236** (1.38 g, 73%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.66 (s, 1H), 8.63 (s, 1H), 7.92 – 7.88 (m, 1H), 7.45 – 7.39 (m, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 9.8 Hz, 1H), 6.46 (d, *J* = 3.5 Hz, 1H), 5.71 (t, *J* = 9.8 Hz, 1H), 5.25 (t, *J* = 10 Hz, 1H), 4.41 - 4.34 (m, 2H), 4.2 – 4.16 (m, 1H), 3.89 (dd, *J* = 10, 3.5 Hz, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 1.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 170.2, 170.0, 164.0, 161.1, 158.6, 133.4, 133.3, 128.2, 128.17, 124.8, 124.7, 123.4, 123.3, 116.0, 115.8, 95.8, 91.4, 71.3, 71.0, 70.7, 68.4, 62.0, 21.0, 20.98, 20.8. IR (film, cm^{-1}) 3336, 1747, 1674, 1643, 1486, 1457, 1366, 1223, 1149, 1020.

Pseudodisaccharide (237). A 10 mL oven dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **133** (83.4 mg, 0.150 mmol, 1.0 equiv), myo-inositol

derivative **233**[199] (123 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in CH_2Cl_2 (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^oC. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with toluene (1 mL), and purified by silica gel flash column chromatography (14/1, toluene/acetonitrile + 1% triethylamine) to give the desired pseudodisaccharide **237** (104 mg, 68%, α:β = 11:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.93 (s, 1H), 7.55 – 7.51 (m, 2H), 7.42 - 7.31 (m, 13H), 7.29 – 7.27 (m, 2H), 7.25 – 7.11 (m, 8H), 7.03 (t, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 6.8 Hz, 2H), 5.72 – 5.67 (m, 2H), 5.24 (d, *J* = 11 Hz, 1H), 5.06 – 4.99 (m, 2H), 4.88 (dd, *J* = 12, 4.0 Hz, 2H), 4.80 (d, *J* = 12 Hz, 2H), 4.88 – 4.60 (m, 2H), 4.47 – 4.44 (m, 1H), 4.39-4.34 (m, 2H), 4.24 – 4.18 (m, 2H), 4.00 (t, *J* = 2 Hz, 1H), 3.65 – 3.59 (m, 3H), 3.51 – 3.42 (m, 3H), 2.04 (s, 3H), 1.90 (s, 3H), 1.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.6, 169.8, 169.7, 162.5, 138.7, 138.6, 138.5, 138.2, 137.8, 131.8, 131.81, 130.4, 130.3, 129.1, 128.6, 128.5, 128.4, 128.35, 128.3, 128.25, 128.2, 128.1, 128.0, 127.8, 127.77, 127.7, 127.6, 127.5, 127.4, 127,0, 126.9, 126.0, 125.4, 125.3, 115.6, 115.4, 99.0, 82.1, 82.0, 81.2, 80.9, 75.9, 75.6, 75.4, 74.3, 73.4, 72.9, 72.7, 71.7, 71.5, 68.3, 67.1, 61.4, 20.8, 20.6. IR (film, cm^{-1}) 3063, 3031, 2936, 2870, 1744, 1644, 1602, 1508, 1497, 1454, 1363, 1228, 1021. *J*(^{13}CH) = 178.8 Hz.

Pseudodisaccharide (238). A 10 mL oven dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*p*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **136** (90.9 mg, 0.150 mmol, 1.0 equiv), myo-inositol derivative **233**[199] (123 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in

dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with toluene (1 mL), and purified by silica gel flash column chromatography (13/1, toluene/acetonitrile + 1% triethylamine) to give the desired pseudodisaccharide **238** (116 mg, 72%, α:β = 11:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm) 7.98 (s, 1H), 7.59 (d, *J* = 2.8 Hz, 4H), 7.42 – 7.30 (m, 14H), 7.27 - 7.25 (m, 3H), 7.21 – 7.17 (m, 4H), 7.12 (t, *J* = 7.6 Hz, 2H), 6.81 (d, *J* = 7.1 Hz, 2H), 5.75 – 5.70 (m, 2H), 5.24 (d, *J* = 12 Hz, 1H), 5.06 – 4.99 (m, 2H), 4.88 (d, *J* = 11, 2H), 4.79 (d, *J* = 7.1 Hz, 2H), 4.64 (d, *J* = 6.8 Hz, 2H), 4.46 (d, *J* = 11 Hz, 1H), 4.39 - 4.31 (m, 2H), 4.23 – 4.14 (m, 2H), 4.00 (t, *J* = 2 Hz, 1H), 3.65 – 3.59 (m, 3H), 3.55 (dd, *J* = 10, 3.6 Hz, 1H), 3.44 (dd, *J* = 9.7, 1.7 Hz, 2H), 2.04 (s, 3H), 1.91 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.8, 170.0, 169.9, 162.6, 138.9, 138.8, 138.7, 138.6, 138.5, 137.9, 130.4, 129.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.2, 127.1, 125.9, 125.6, 125.5, 99.2, 82.4, 82.3, 81.4, 81.2, 76.1, 76.0, 75.7, 74.5, 73.3, 73.0, 71.7, 68.5, 67.4, 61.6, 21.0, 20.9, 20.8. IR (film, cm^{-1}) 3031, 2872, 1747, 1645, 1497, 1455, 1364, 1323, 1223, 1167, 1019. $J(^{13}CH)$ = 175.5 Hz.

Pseudodisaccharide (239). A 10 mL oven dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*O*-fluorobenzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **236** (83.4 mg, 0.150 mmol, 1.0 equiv), myo-inositol derivative **233**[199] (123 mg, 0.195 mmol, 1.3 equiv) and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-F-PhCN})_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.0150 mmol, 10 mol %) in CH_2Cl_2 (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 ^{o}C. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with toluene (1 mL), and purified by silica gel flash column chromatography (14/1, toluene/acetonitrile + 1% triethylamine) to give the desired

pseudodisaccharide **239** (101.3 mg, 66%, α:β = 16:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.32 (s, 1H), 8.04 – 8.02 (m, 1H), 7.42 - 7.31 (m, 14H), 7.25 – 7.23 (m, 5H), 7.21 – 7.10 (m, 6H), 7.00 (t, *J* = 9.8 Hz, 1H), 6.87 (d, *J* = 7.1 Hz, 2H), 5.71 – 5.65 (m, 2H), 5.23 (d, *J* = 12 Hz, 1H), 5.06 – 4.98 (m, 2H), 4.88 (t, *J* = 11 Hz, 2H), 4.85 – 4.78 (m, 2H), 4.75 – 4.69 (m, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.48 - 4.45 (m, 1H), 4.37 (t, *J* = 10 Hz, 2H), 4.29 (d, *J* = 12 Hz, 1H), 4.20 (t, *J* = 9.6 Hz, 1H), 3.99 (t, *J* = 2.0 Hz, 1H), 3.67 – 3.59 (m, 3H), 3.53 (dd, *J* = 10, 3.6 Hz, 1H), 3.48 (dd, *J* = 9.8, 2.2 Hz, 1H), 3.43 (dd, *J* = 9.8, 2.2 Hz, 1H), 2.03 (s, 3H), 1.8 (s, 3H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 170.0, 169.9, 157.6, 157.5, 139.0, 138.9, 138.8, 138.5, 137.9, 131.8, 128.6, 128.57, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.58, 127.5, 127.4, 127,2, 126.4, 99.0, 82.5, 82.3, 81.5, 81.2, 76.1, 75.8, 75.6, 74.6, 73.9, 73.6, 73.0, 72.2, 71.6, 68.6, 67.3, 61.7, 21.0, 20.9, 20.85. IR (film, cm^{-1}) 3031, 2935, 2873, 1745, 1638, 1454, 1364, 1225, 1125. $J(^{13}CH)$ = 177.4 Hz.

Pseudodisaccharide (240). A 10 mL oven dried and argon flushed Schlenk flask was charged with 2-Deoxy-2-*O*-(trifluoromethyl)benzylideneamino-3,4,6-*tri*-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **225** (48.5 mg, 0.080 mmol, 1.5 equiv), myo-inositol derivative **233**[199] (33.6 mg, 0.053 mmol, 1.0 equiv) and CH_2Cl_2 (0.7 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (2.46 mg, 0.004 mmol, 5 mol %) and AgOTf (2.06 mg, 0.008 mmol, 10 mol %) in CH_2Cl_2 (0.5 mL) was then added to the solution.The resulting mixture was stirred under argon at 25 ^{o}C. When the reaction was complete as monitored by TLC, the reaction mixture was diluted with toluene (1 mL), and purified by silica gel flash column chromatography (3/1, hexane/ethyl acetate + 1% triethylamine → 2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired pseudodisaccharide **240** (45.3 mg, 80%, α:β = 15:1) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.44 (d, *J* = 2.2 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.59 - 7.53 (m, 2H), 7.41 – 7.33

(m, 12H), 7.30 – 7.24 (m, 8H), 7.21 – 7.18 (m, 1H), 7.05 (t, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 7.1 Hz, 2H), 5.72 (d, *J* = 3.6 Hz, 1H), 5.64 (t, *J* = 7.2 Hz, 1H), 5.21 (d, *J* = 12, 1H), 5.04 (dd, *J* = 10, 9.5 Hz, 1H), 4.98 (d, *J* = 11 Hz, 1H), 4.91 – 4.87 (m, 2H), 4.86 – 4.78 (m, 2H), 4.67 - 4.60 (m, 2H), 4.50 – 4.46 (m, 1H), 4.41 – 4.37 (m, 2H), 4.32 (t, *J* = 13 Hz, 1H), 4.19 (t, *J* = 9.6 Hz, 1H), 3.99 (t, *J* = 2.1 Hz, 1H), 3.71 (dd, *J* = 13, 2 Hz, 1H), 3.66 – 3.58 (m, 3H), 3.49 (dd, *J* = 9.8, 2.2 Hz, 1H), 3.43 (dd, *J* = 9.8, 2.3 Hz, 1H), 2.03 (s, 3H), 1.86 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 170.02, 170.0, 160.5, 139.1, 138.8, 138.78, 138.5, 137.7, 133.6, 132.0, 130.9, 129.3, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.9, 127.7, 127.6, 127.5, 127.1, 126.7, 98.6, 82.5, 82.3, 81.6, 81.1, 76.1, 75.6, 74.1, 73.4, 72.9, 72.4, 71.3, 68.5, 67.3, 61.7, 21.0, 20.8, 20.7. IR (film, cm^{-1}) 3032, 2883, 1747, 1498, 1454, 1364, 1314, 1227, 1165, 1124, 1025. $J(^{13}CH)$ = 174.9 Hz.

APPENDIX

NMR SPECTRA

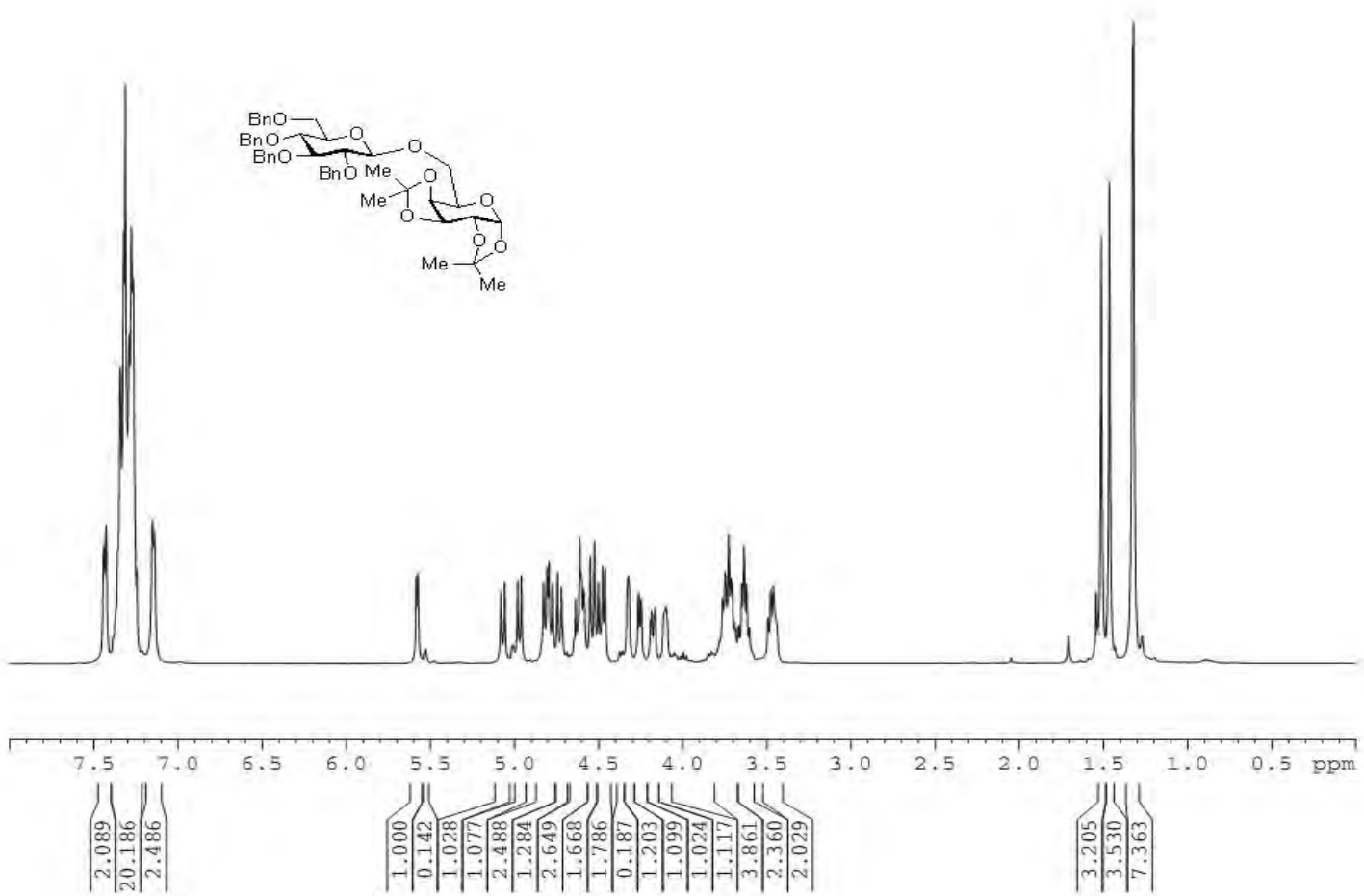


Figure A1. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **60**

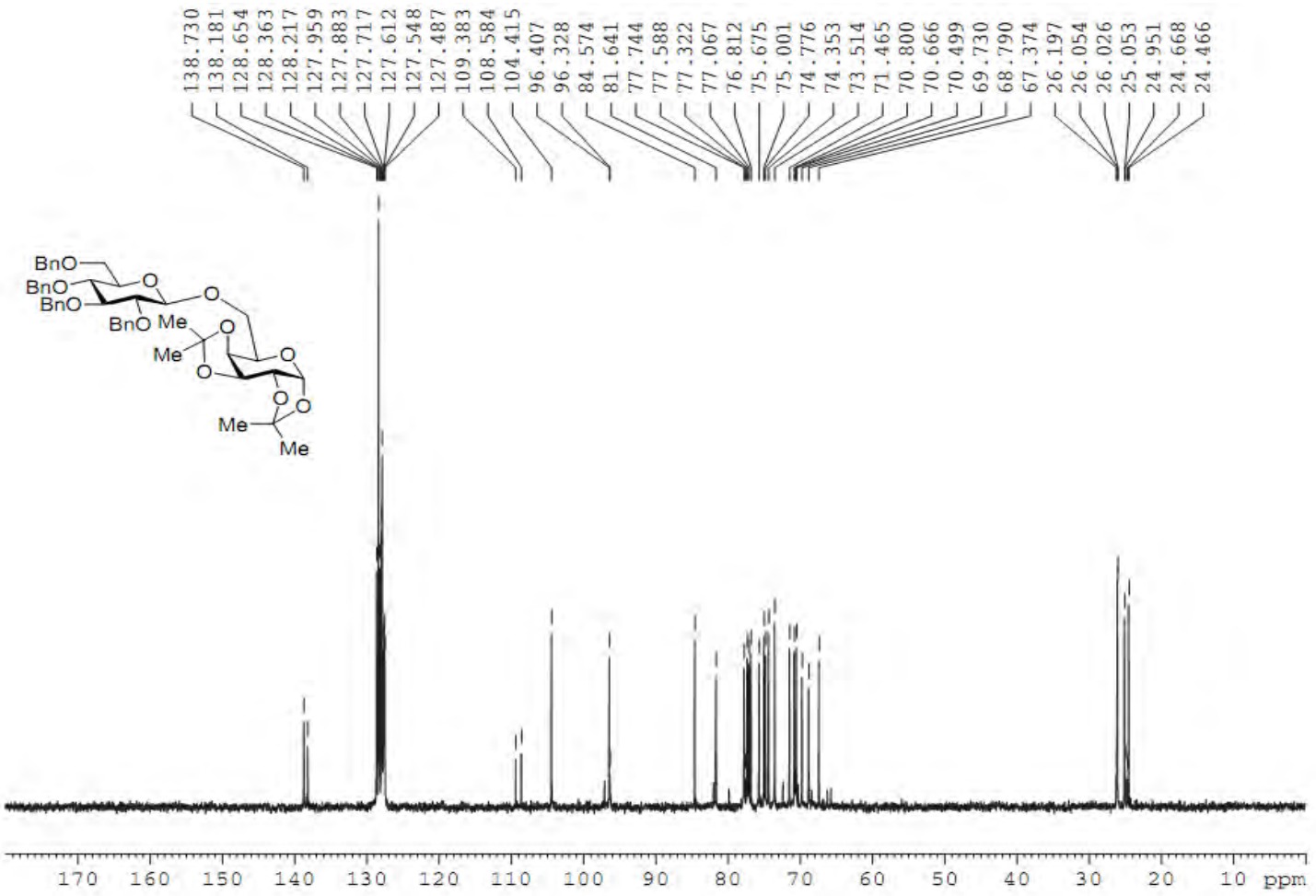


Figure A2. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **60**

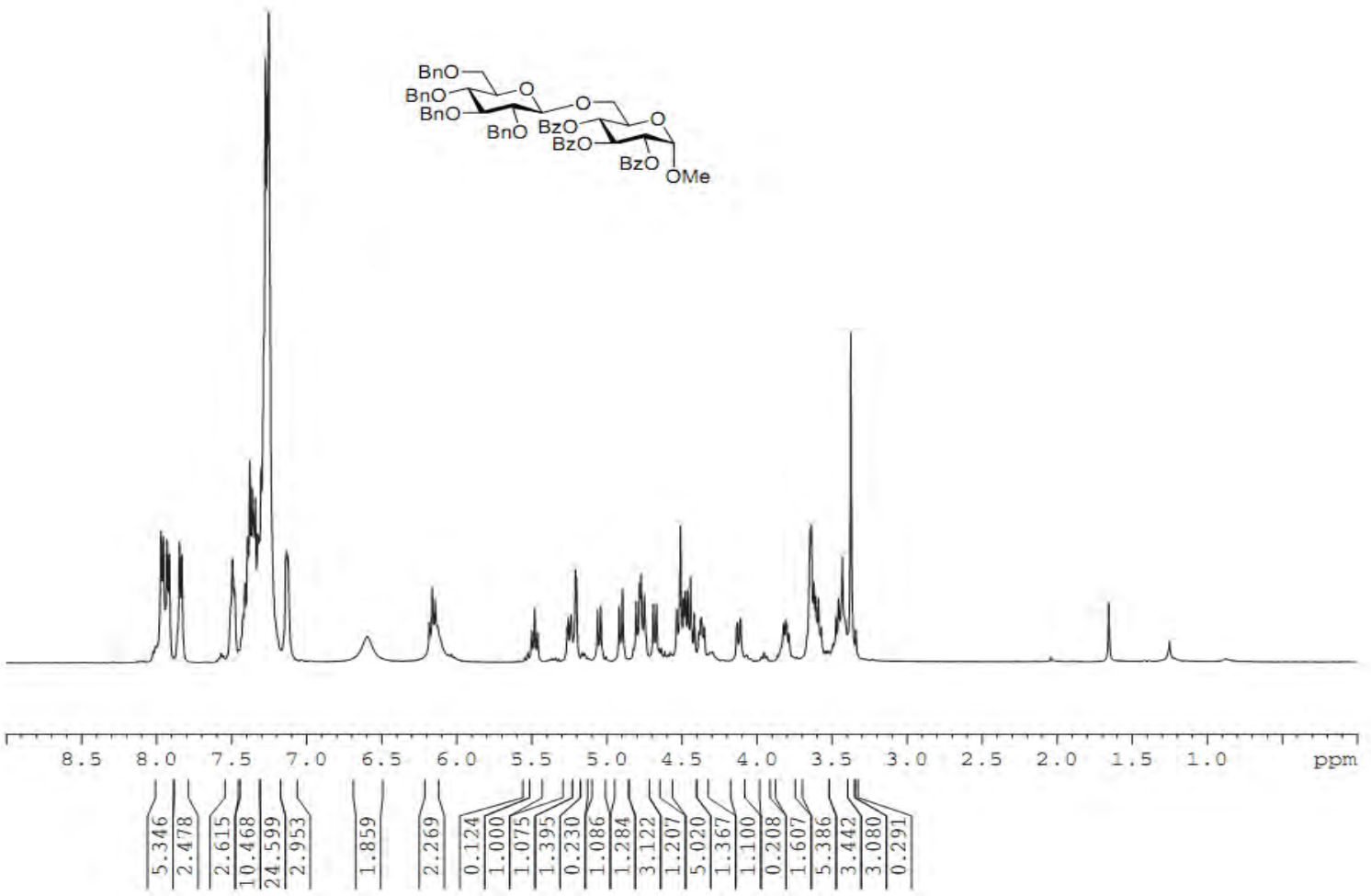


Figure A3. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **66**

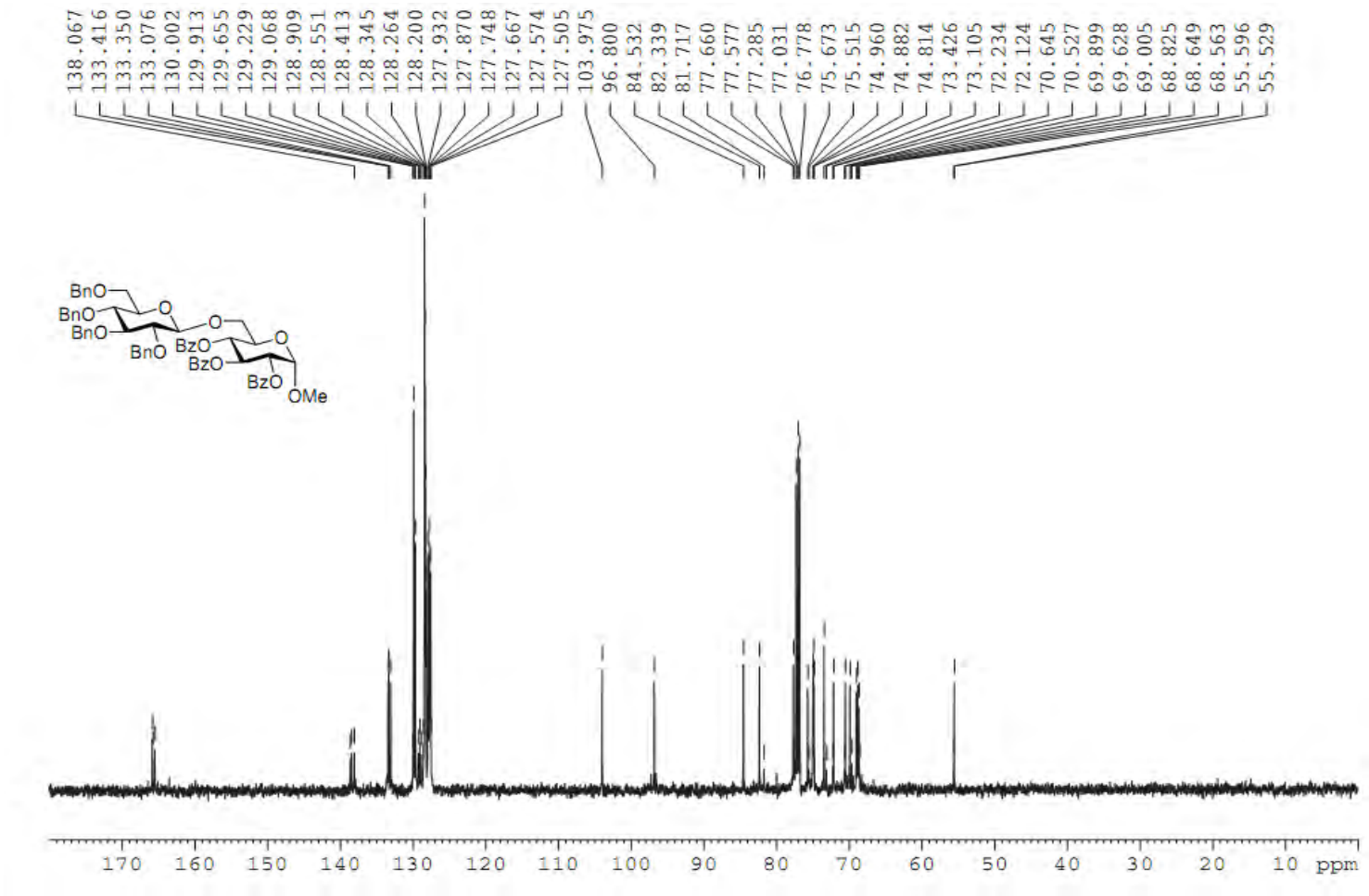


Figure A4. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **66**

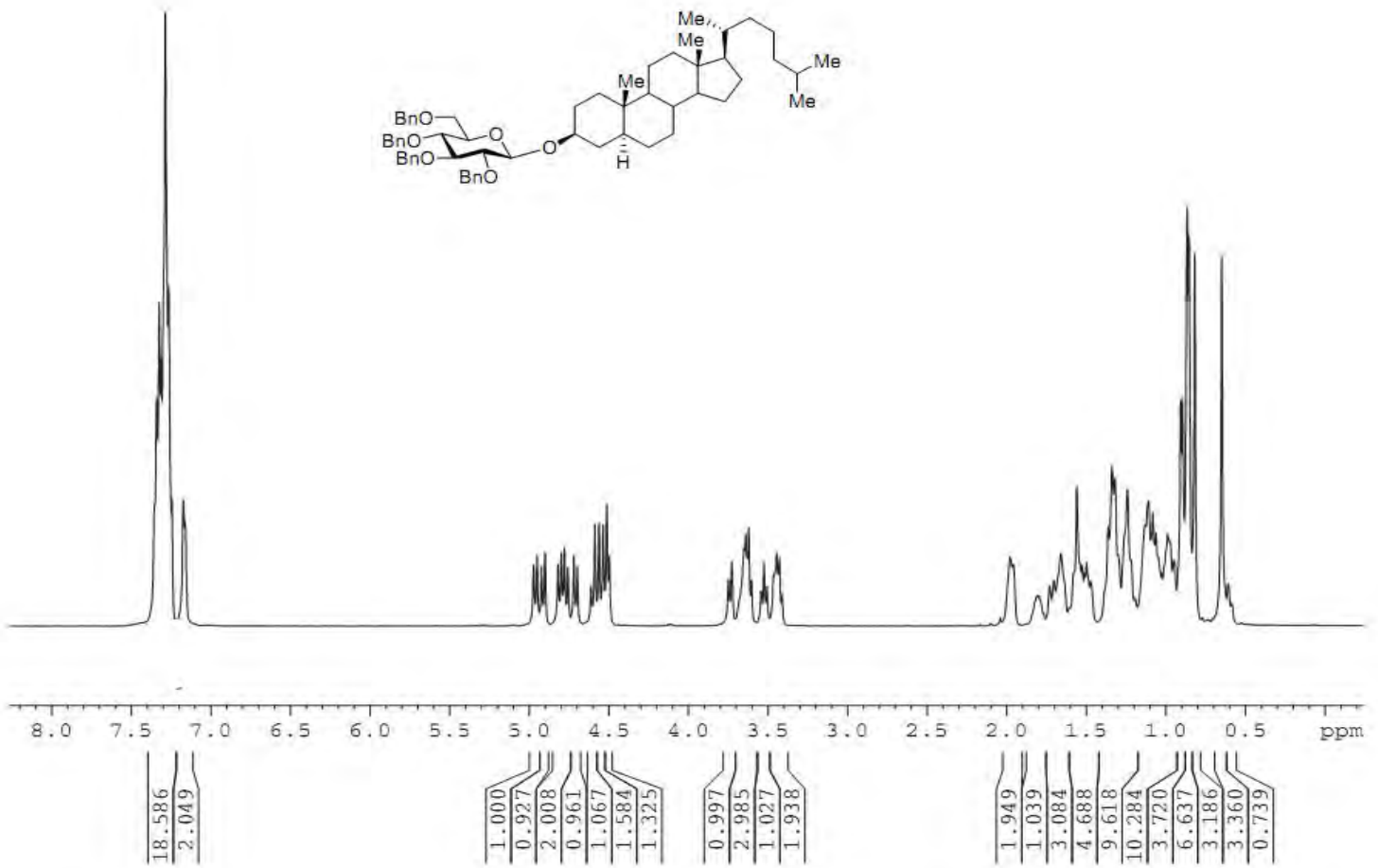


Figure A5. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **67**

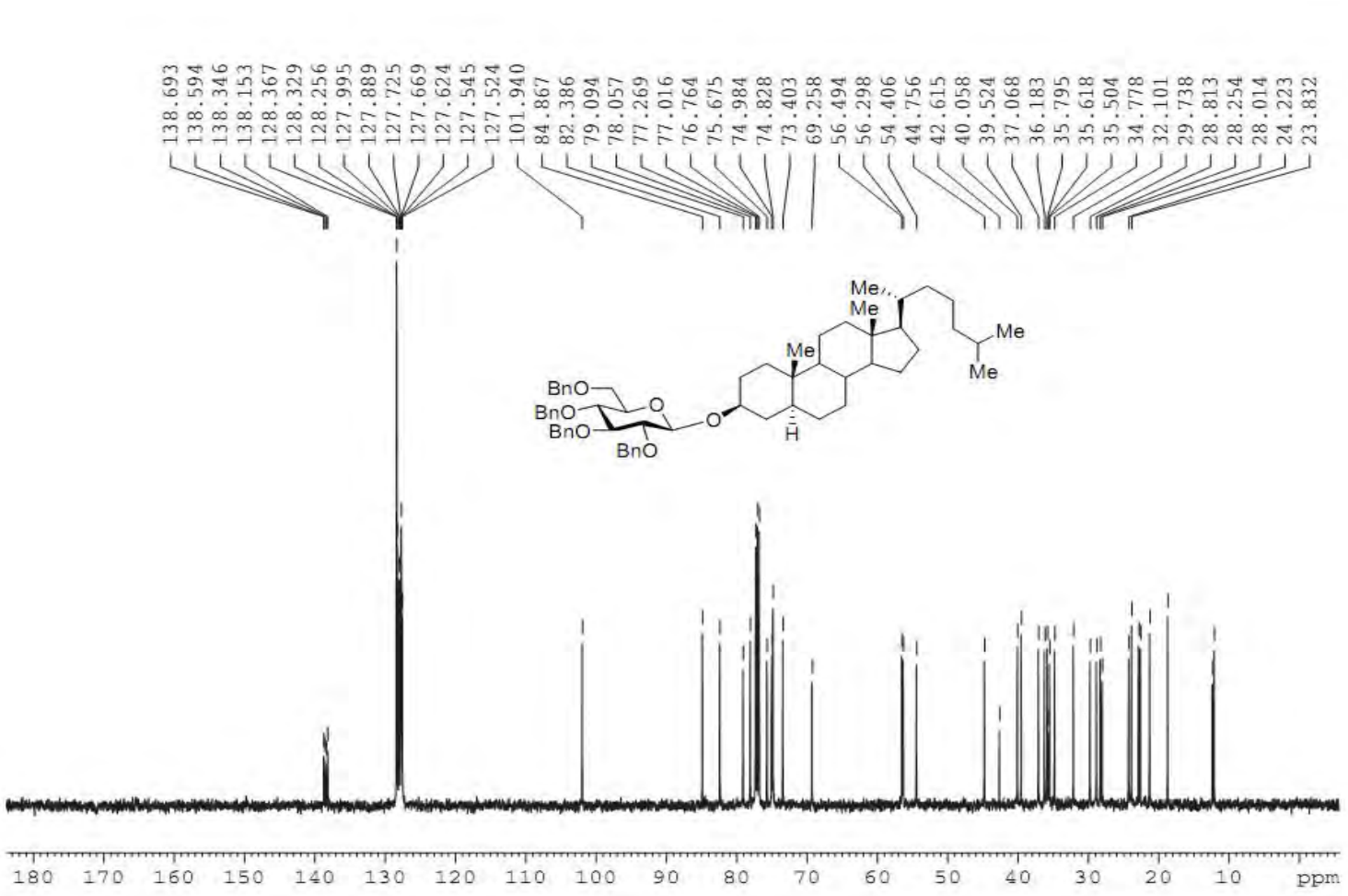


Figure A6. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **67**

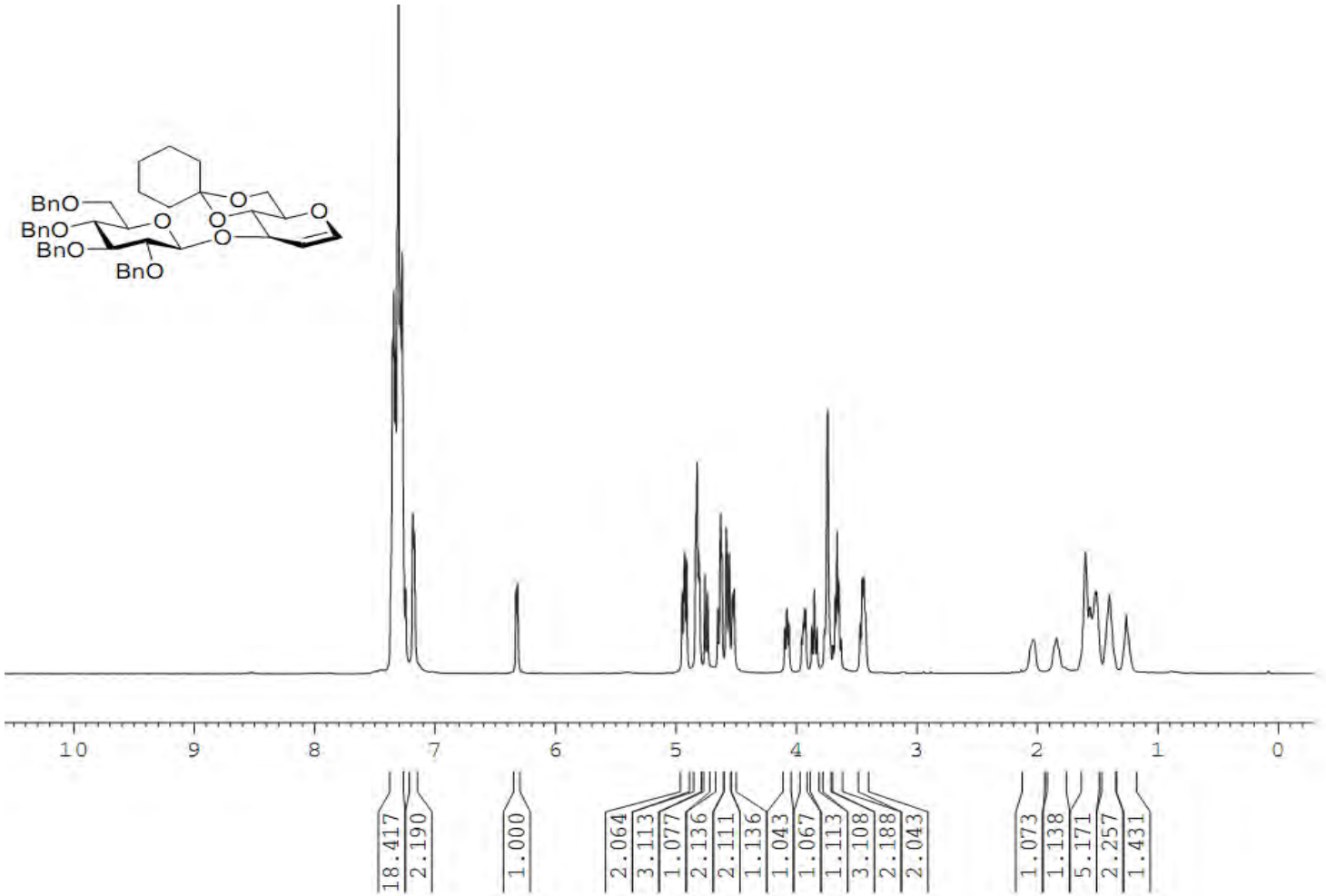


Figure A7. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **68**

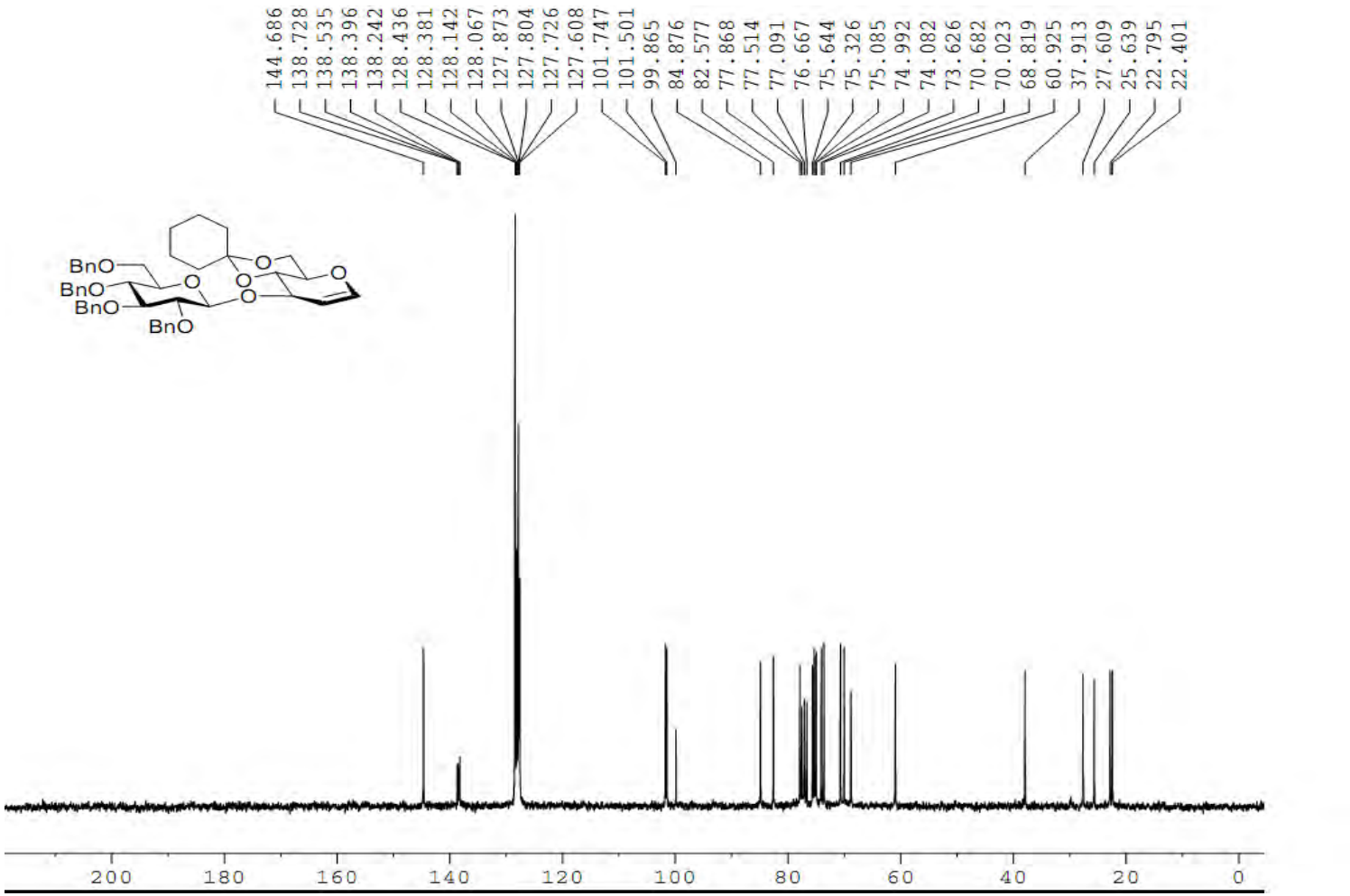


Figure A8. 75 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **68**

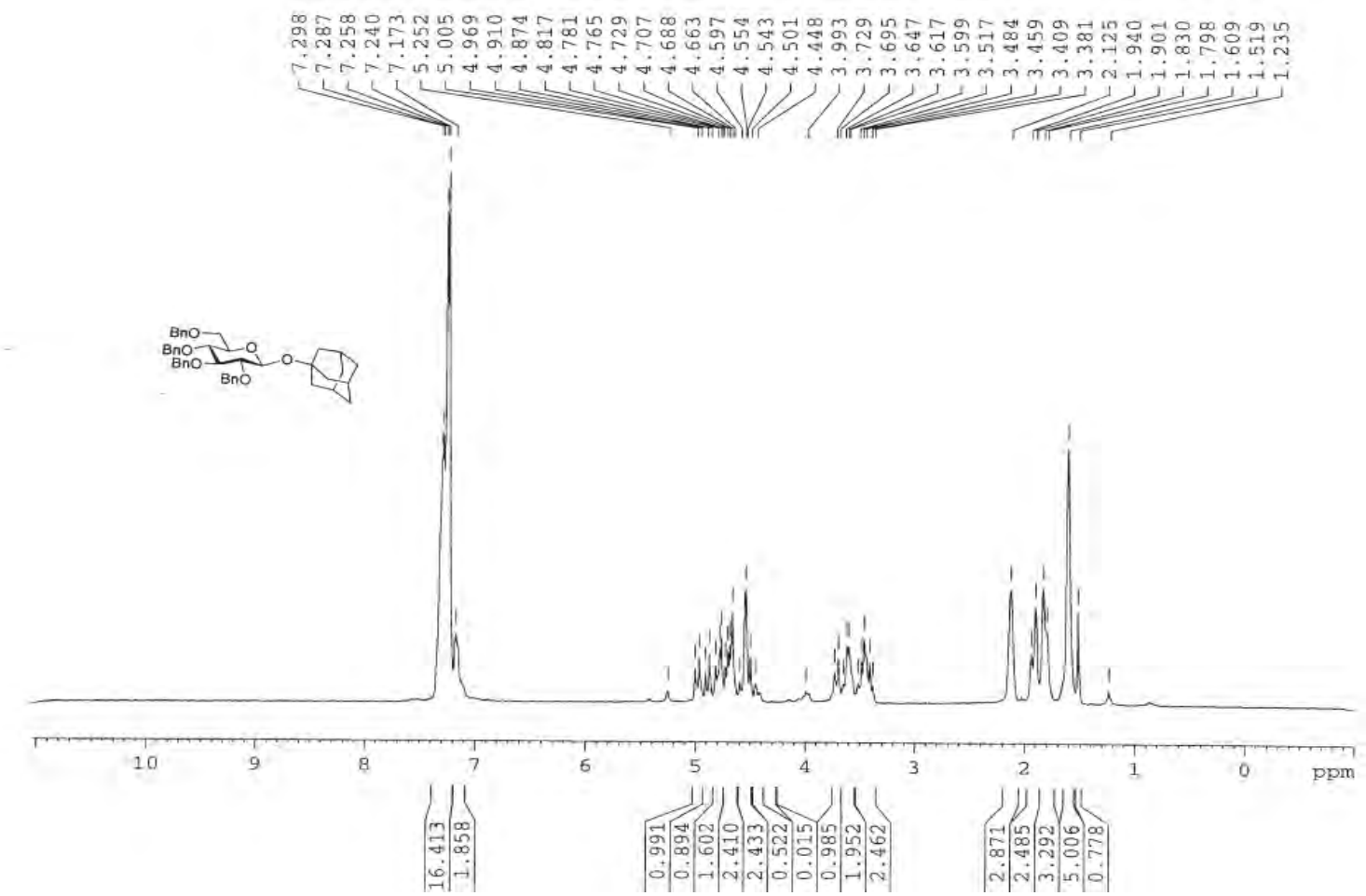


Figure A9. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **69**

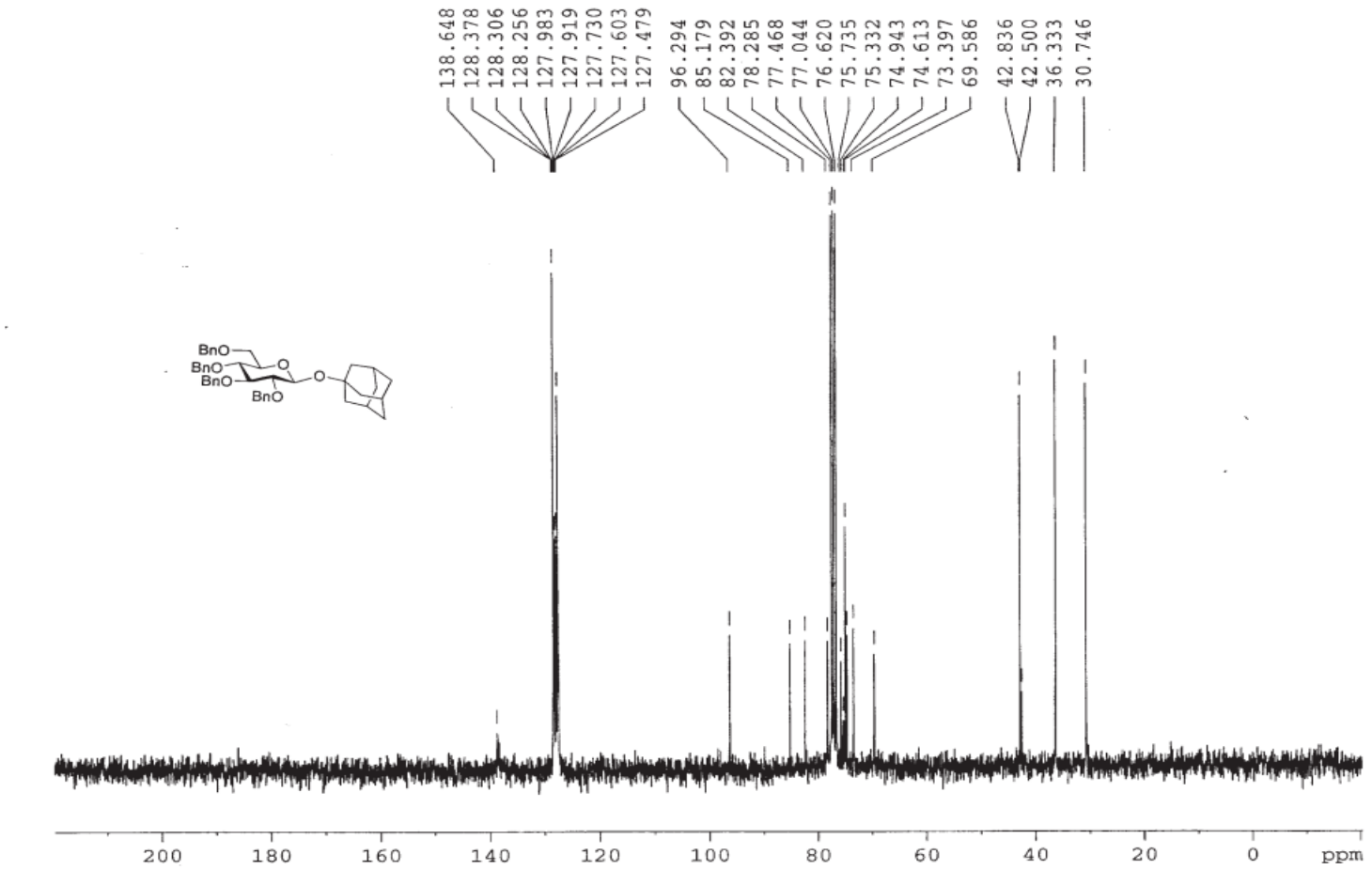


Figure A10. 75 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **69**

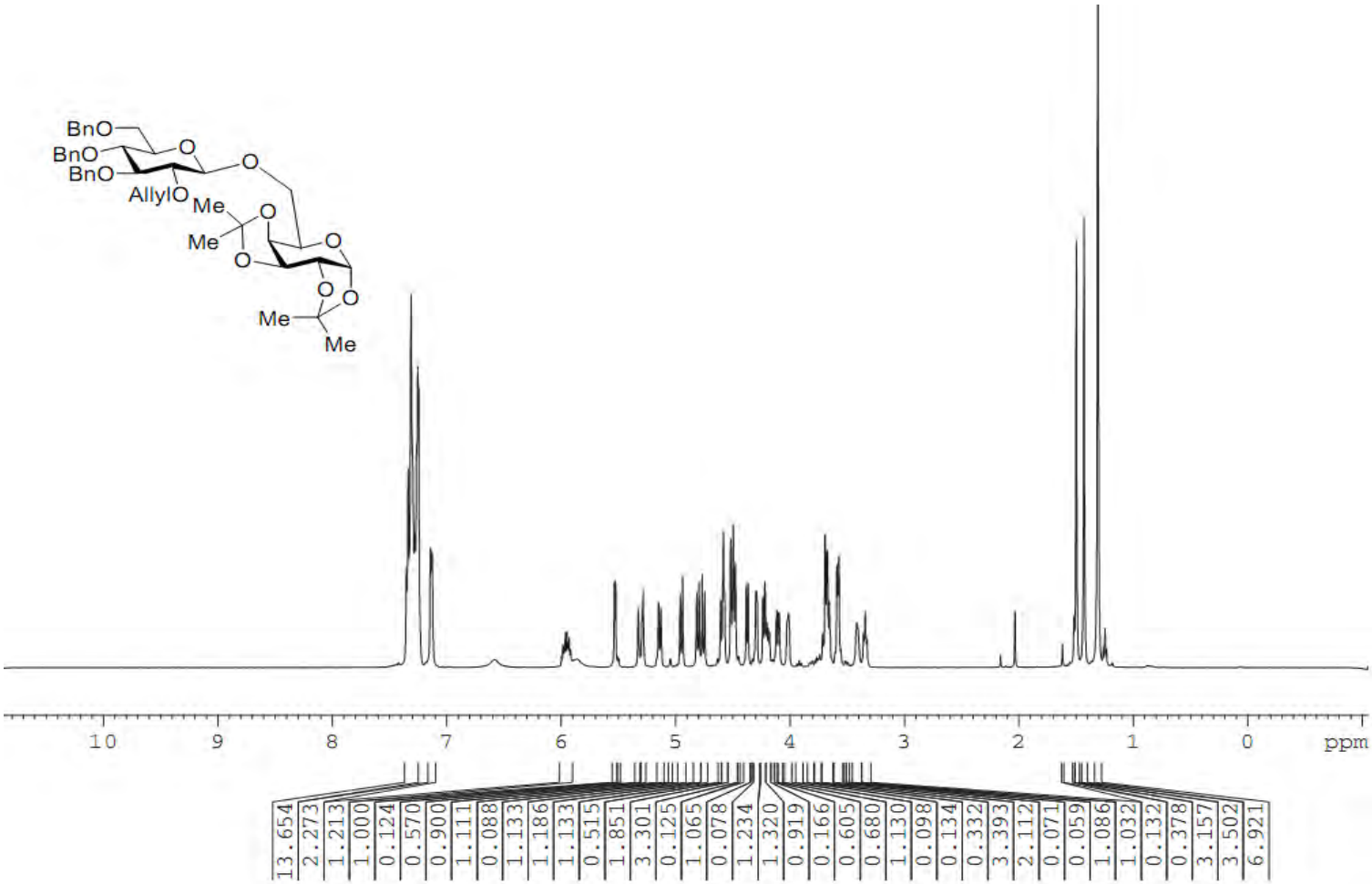


Figure A11. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **71**

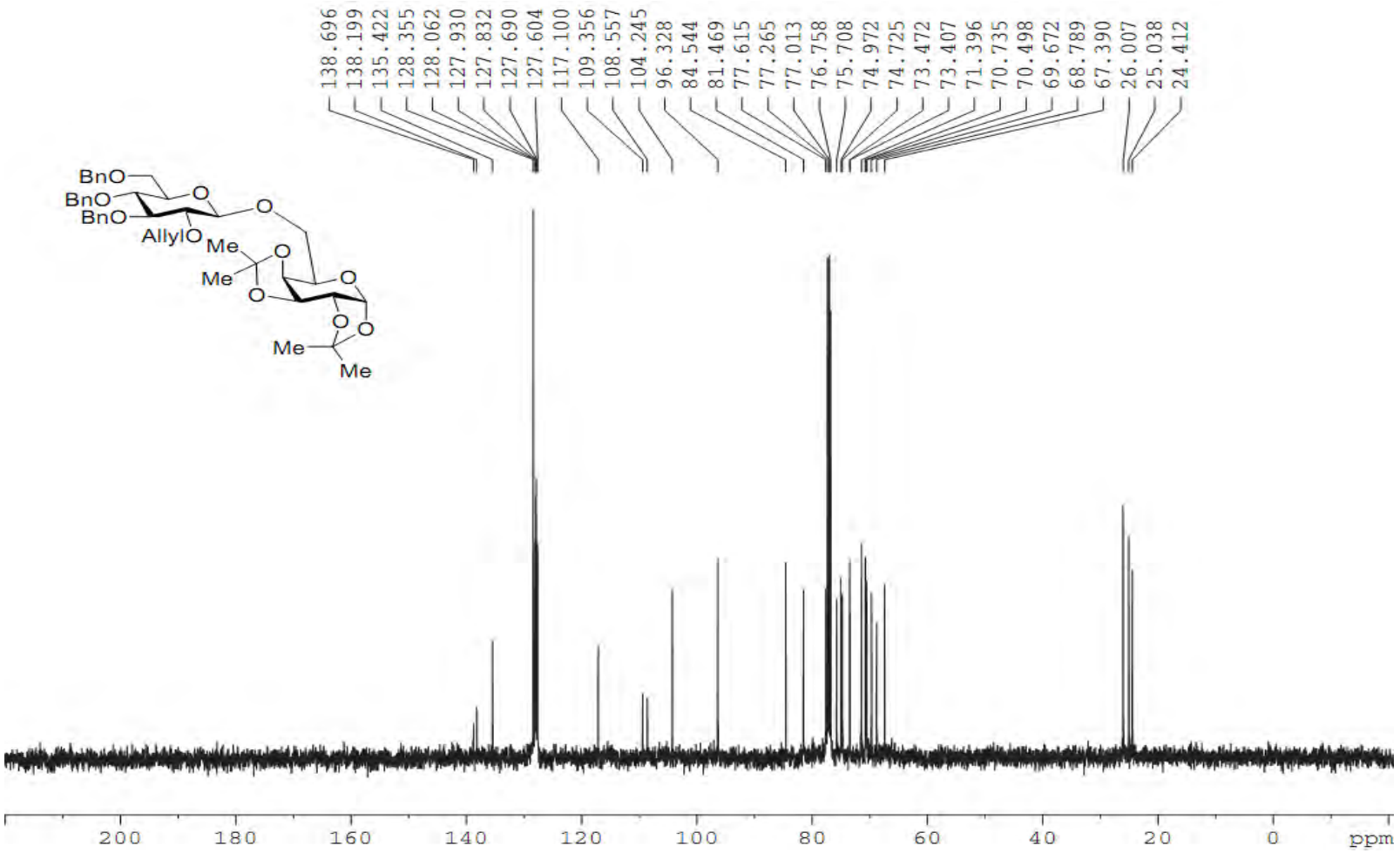


Figure A12. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **71**

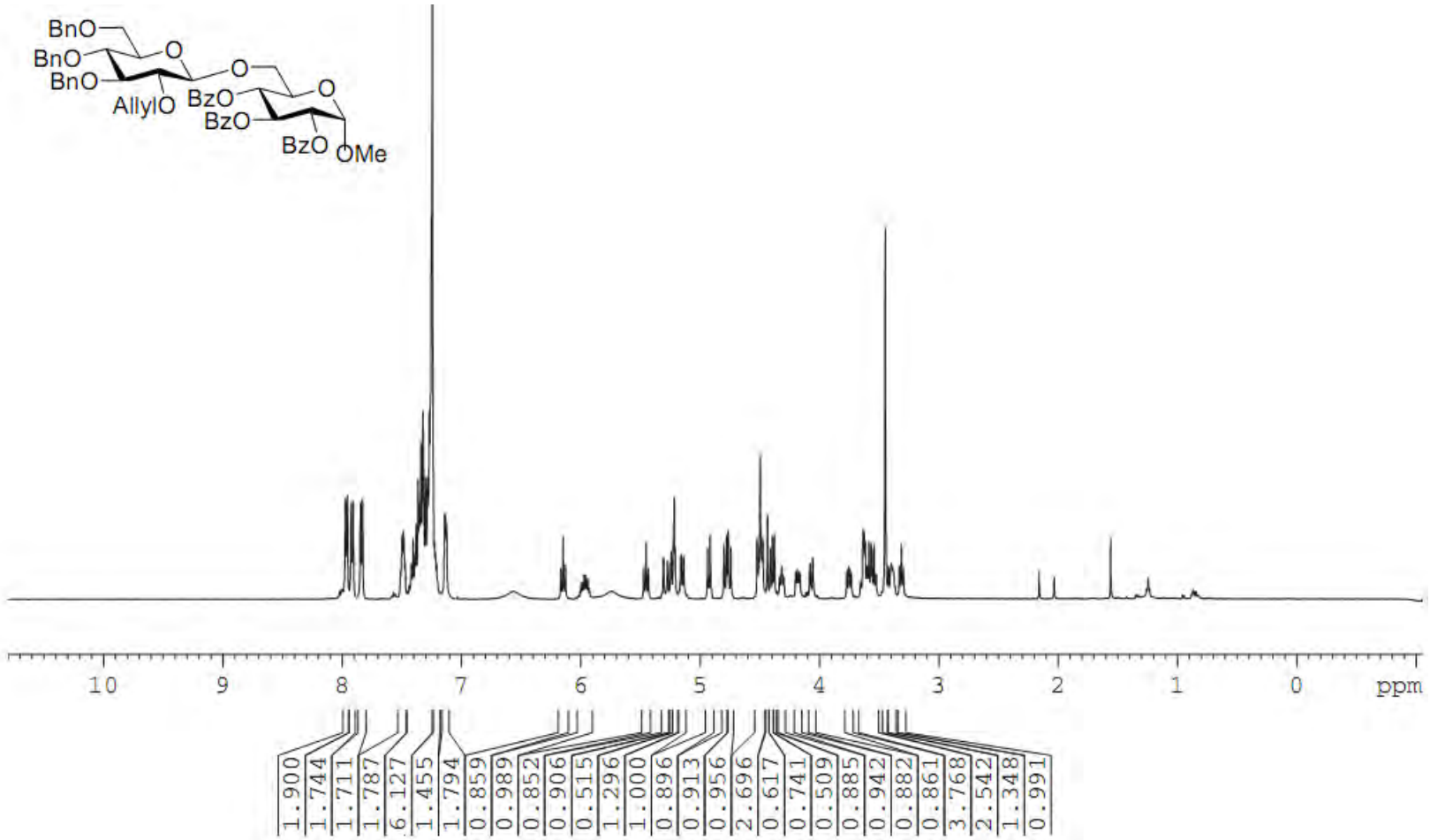


Figure A13. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **72**

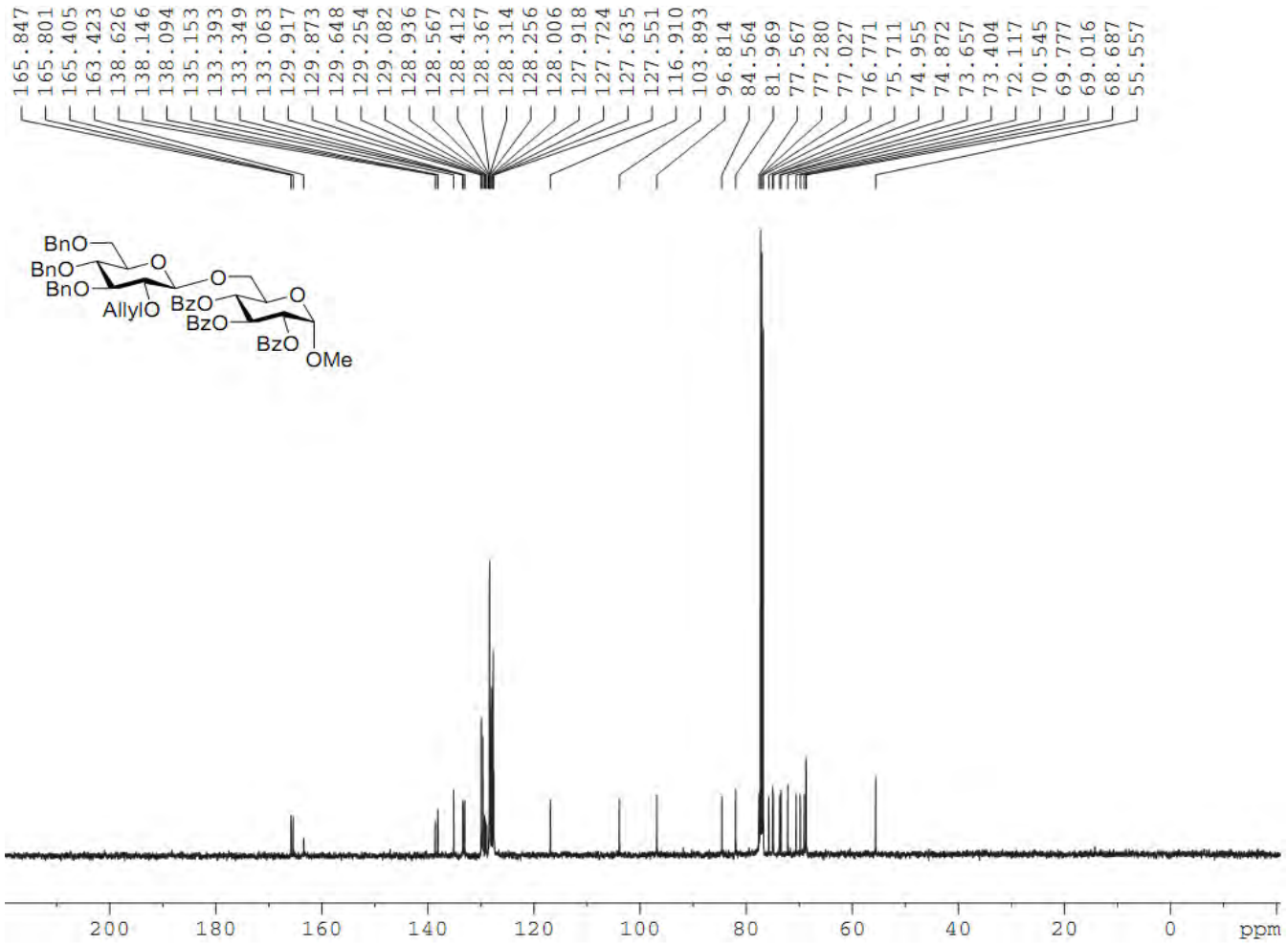


Figure A14. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **72**

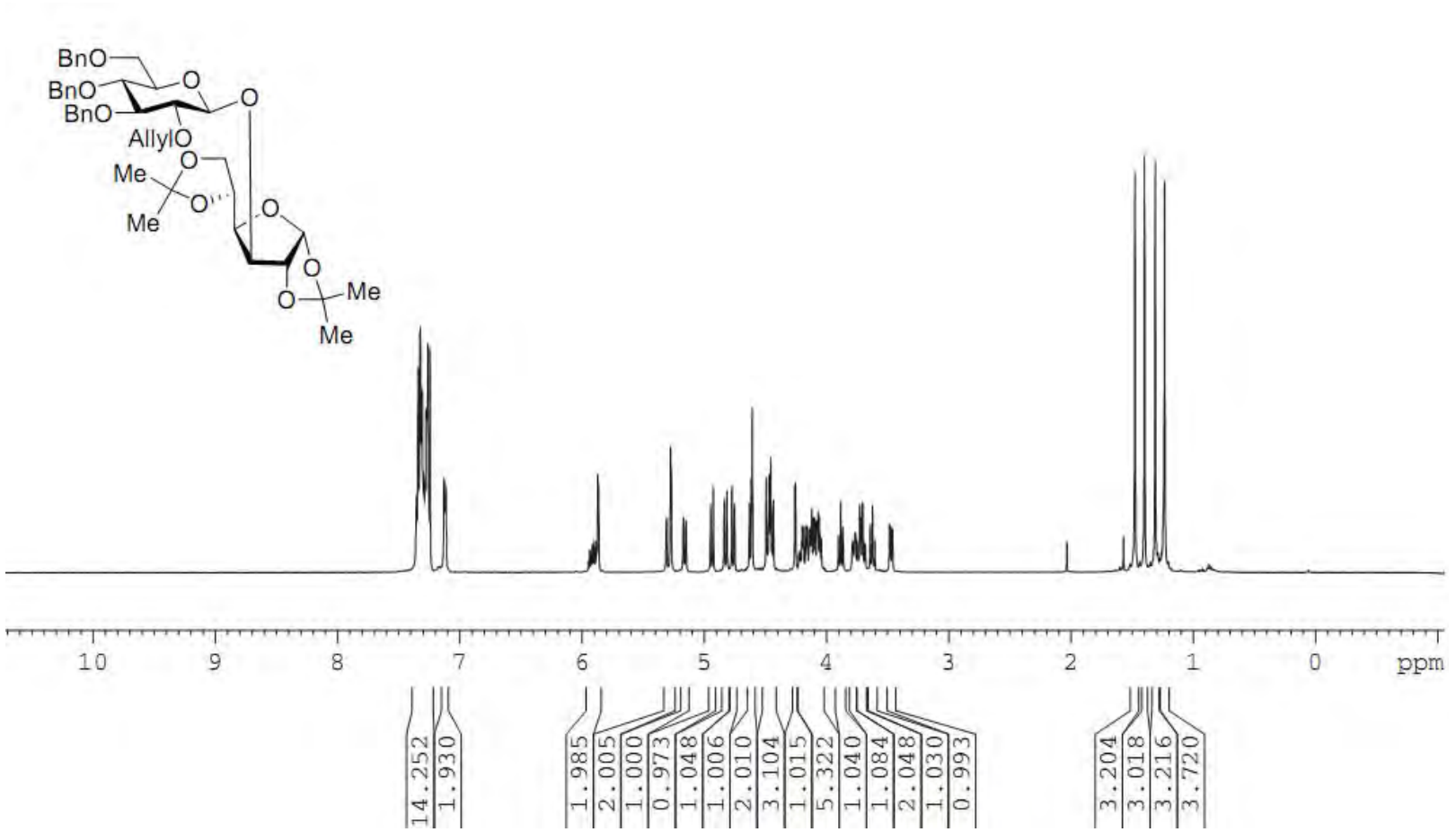


Figure A15. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **73**

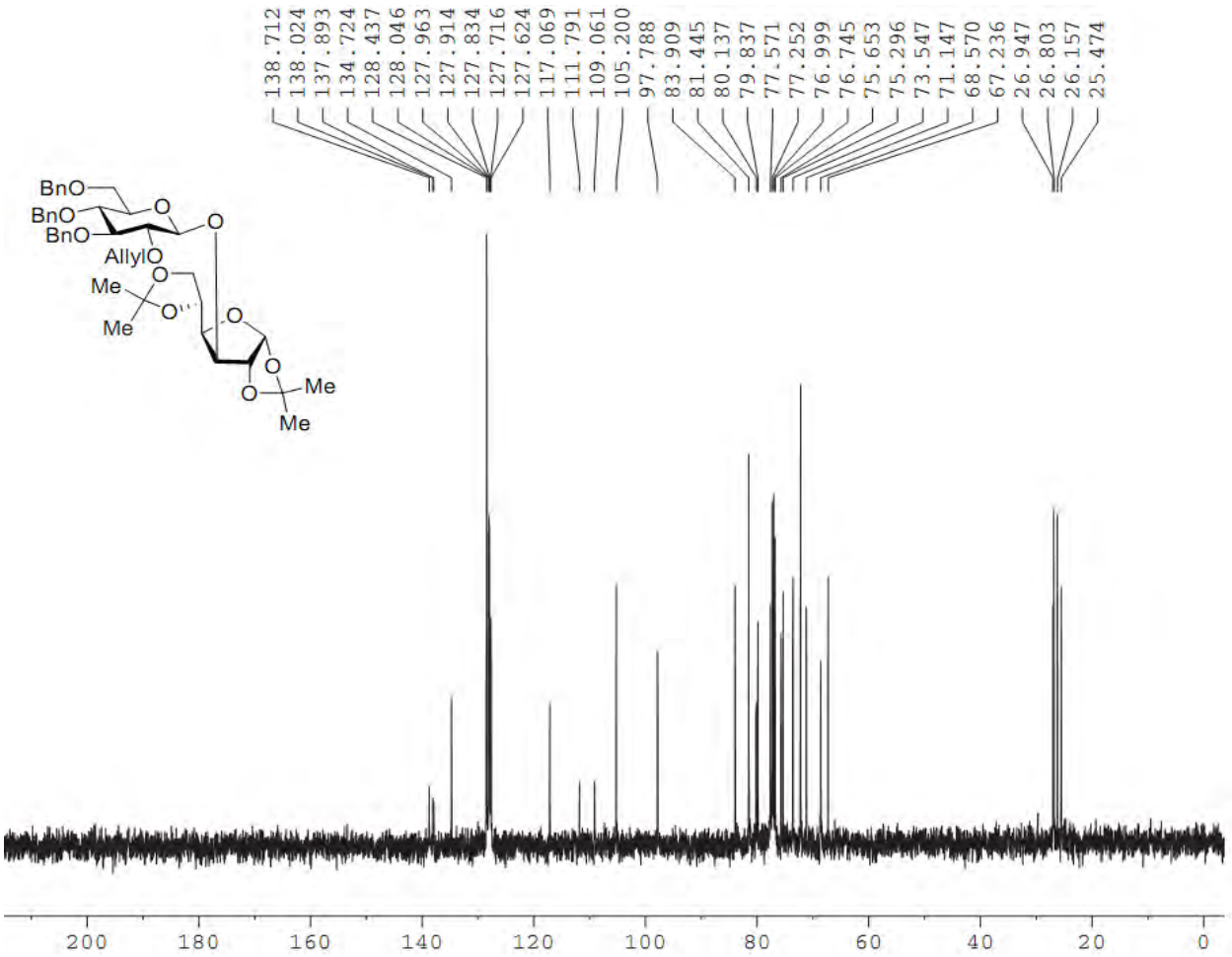


Figure A16. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **73**

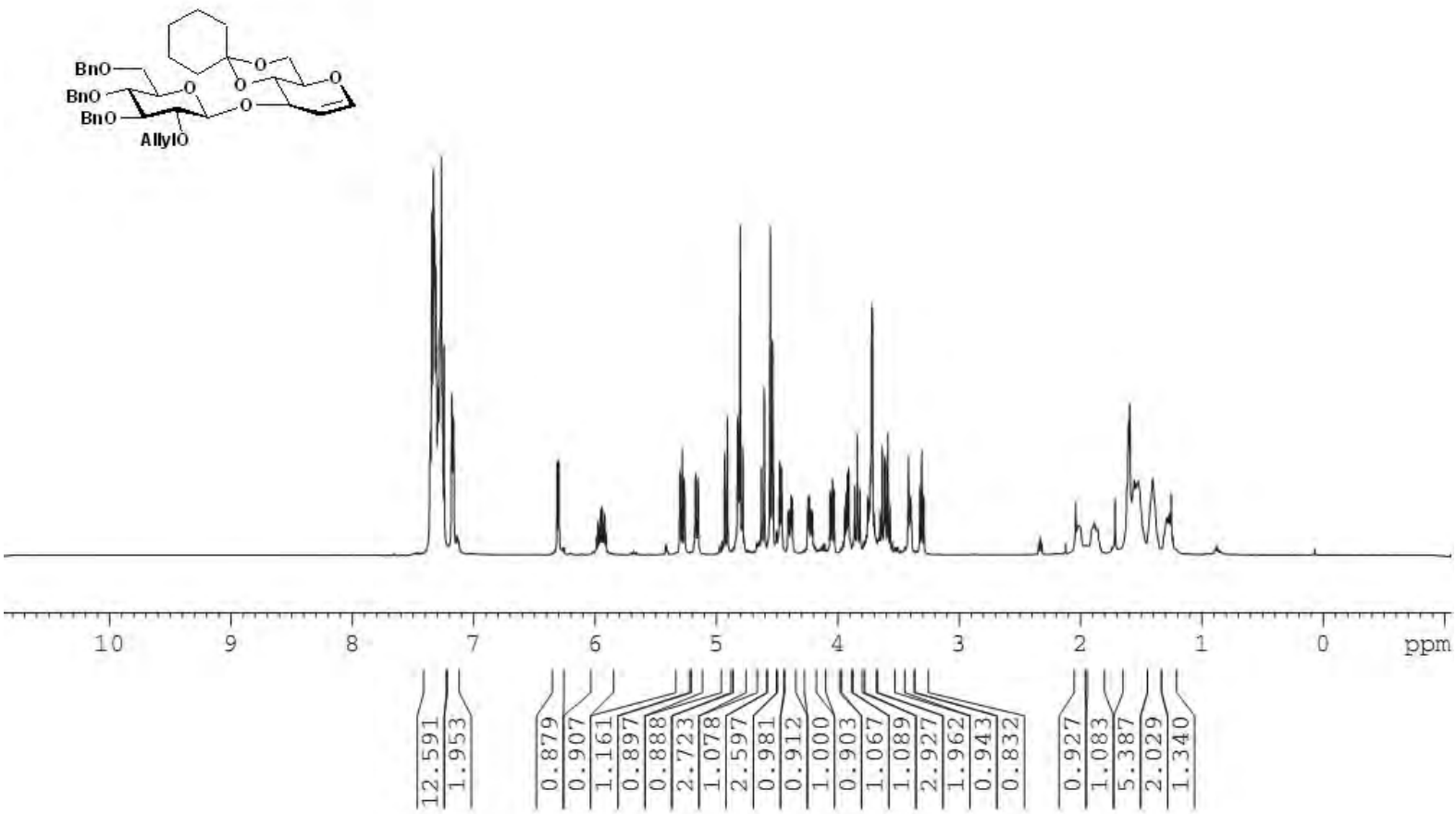


Figure A17. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **74**

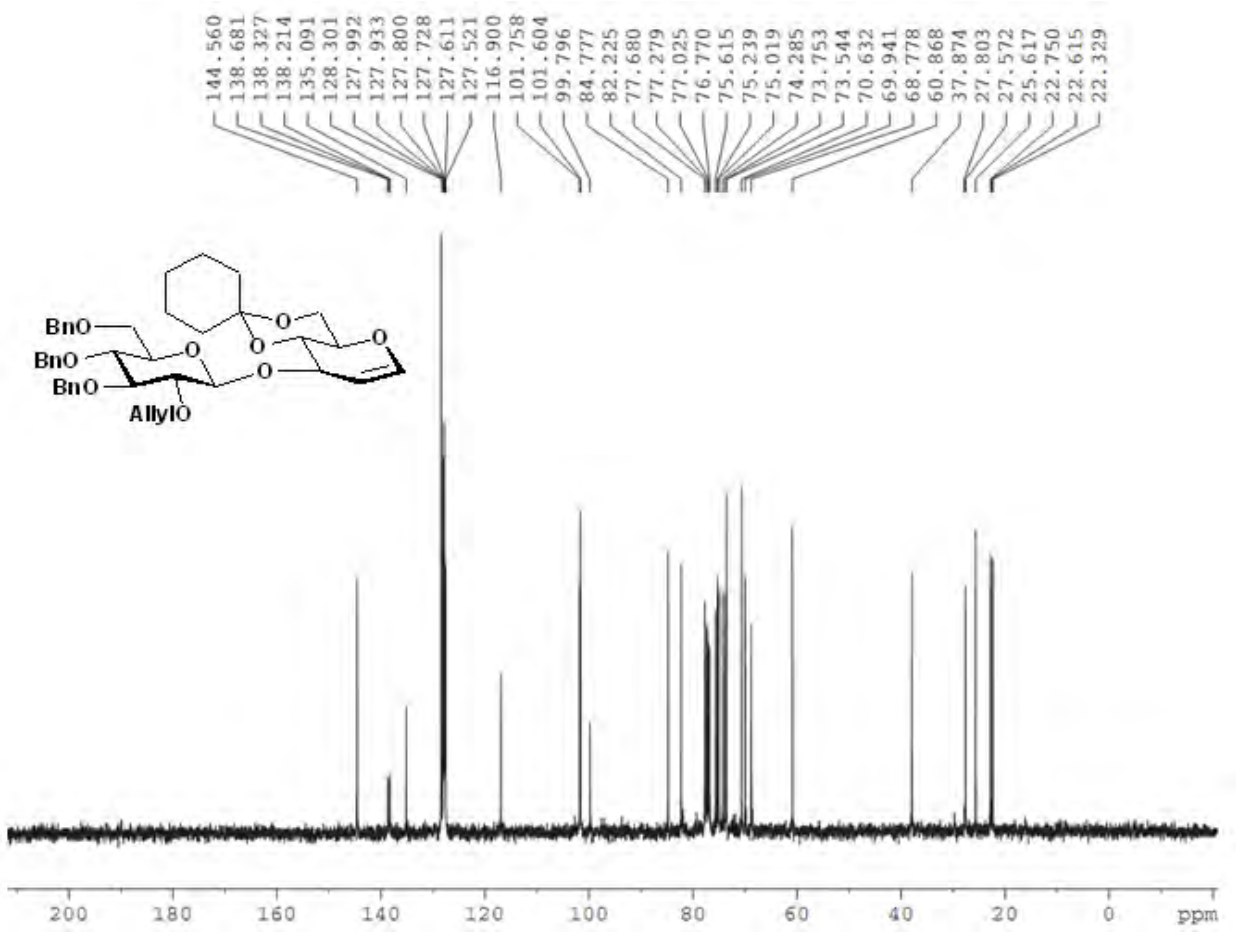


Figure A18. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **74**

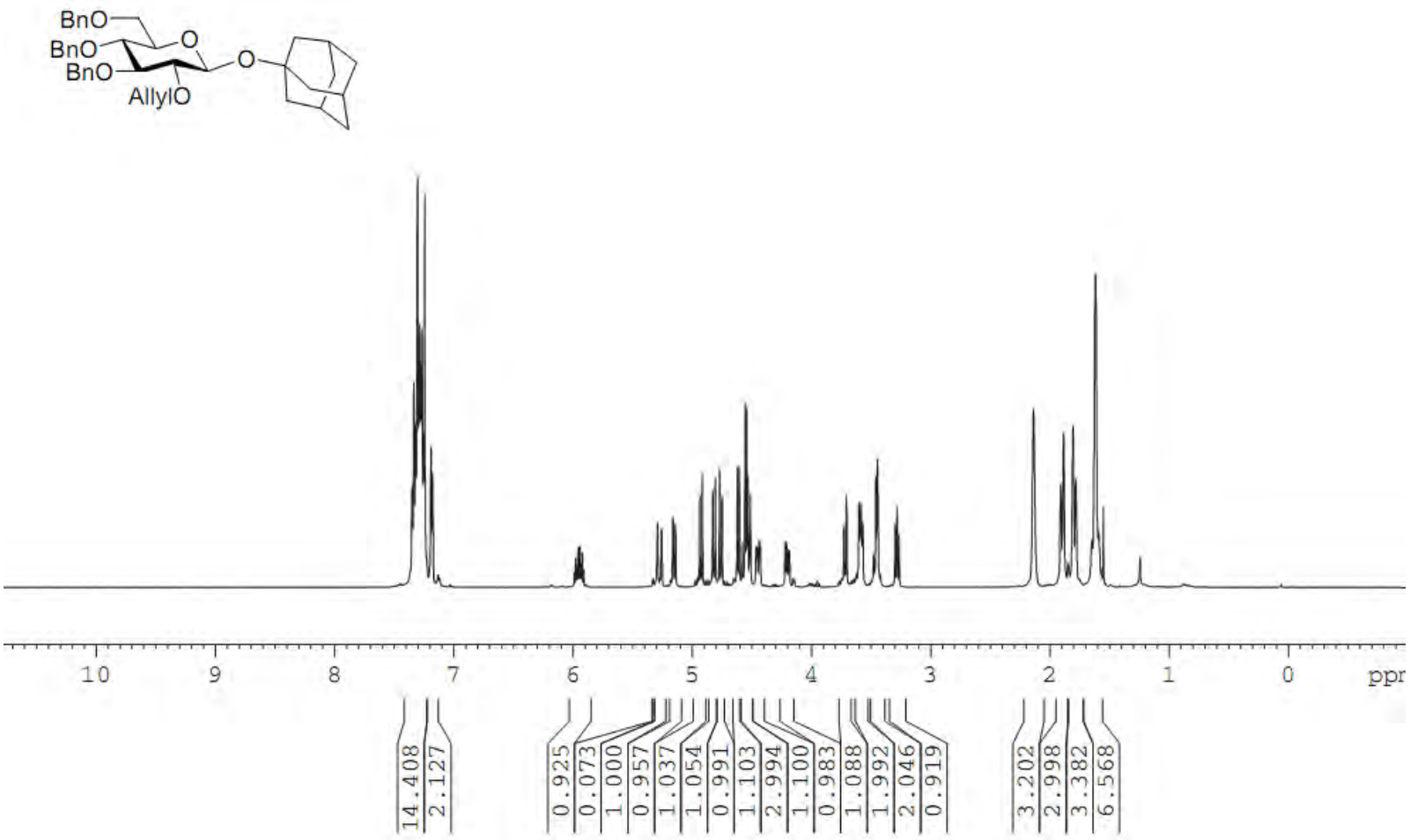


Figure A19. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **75**

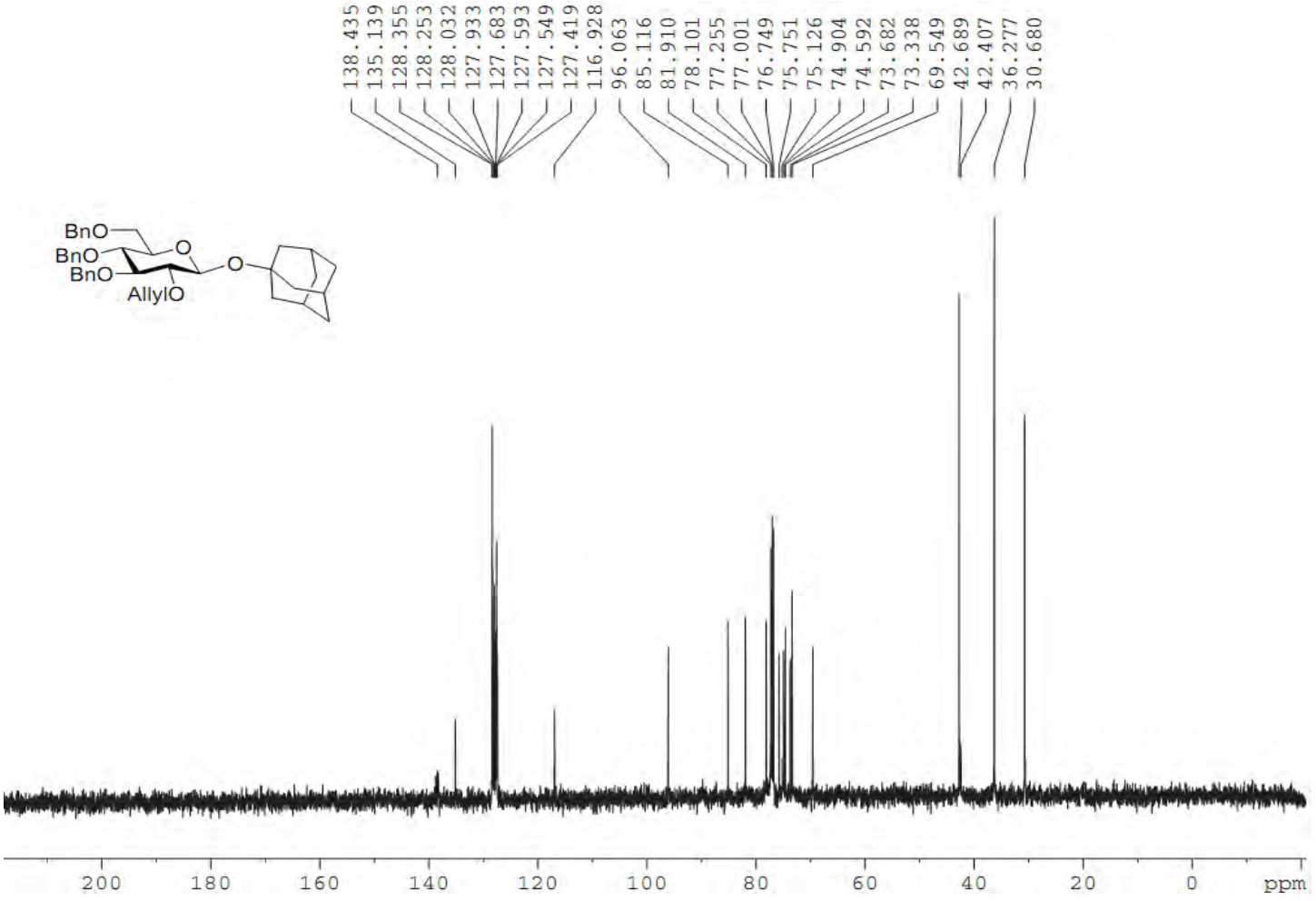


Figure A20. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **75**

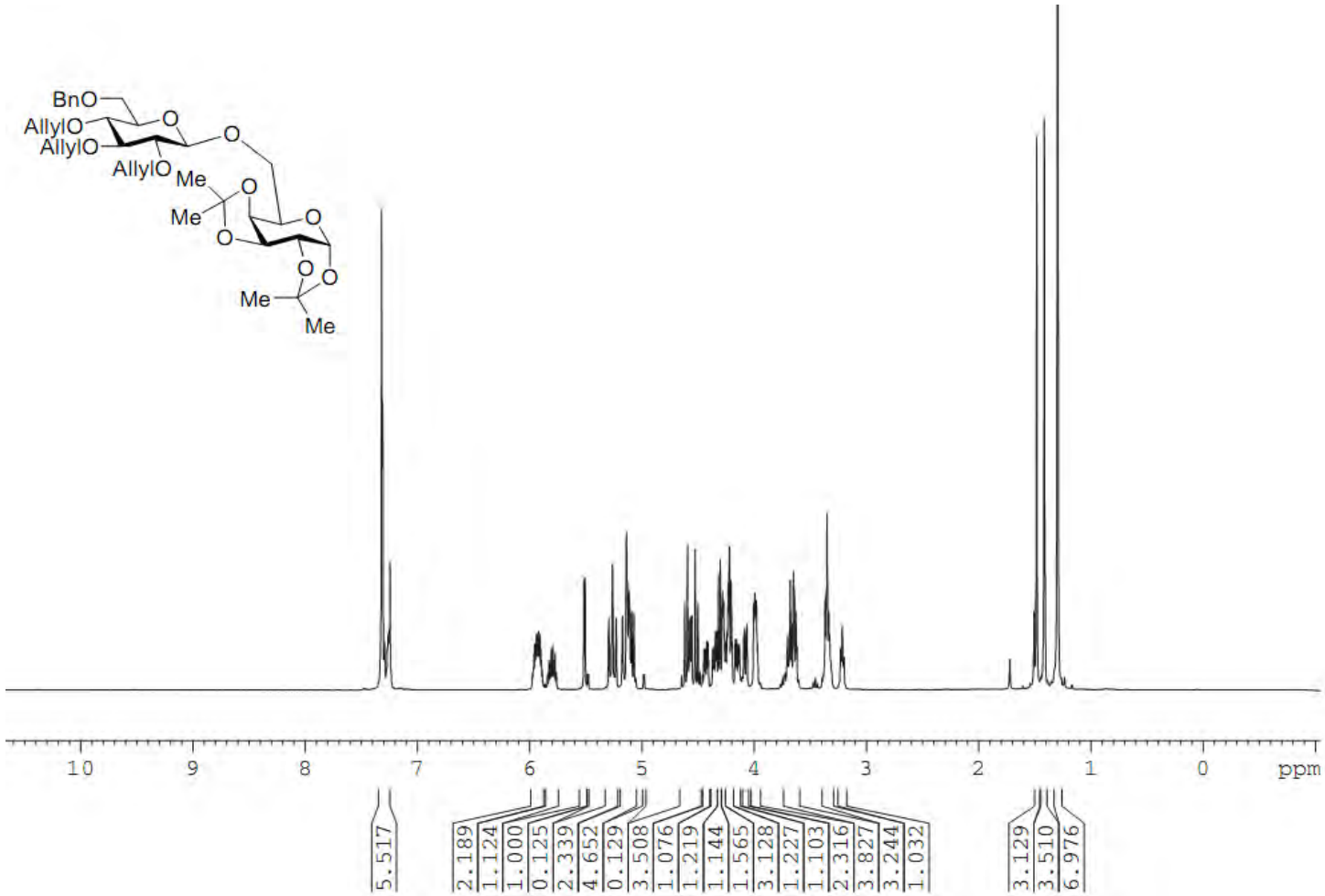


Figure A21. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **78**

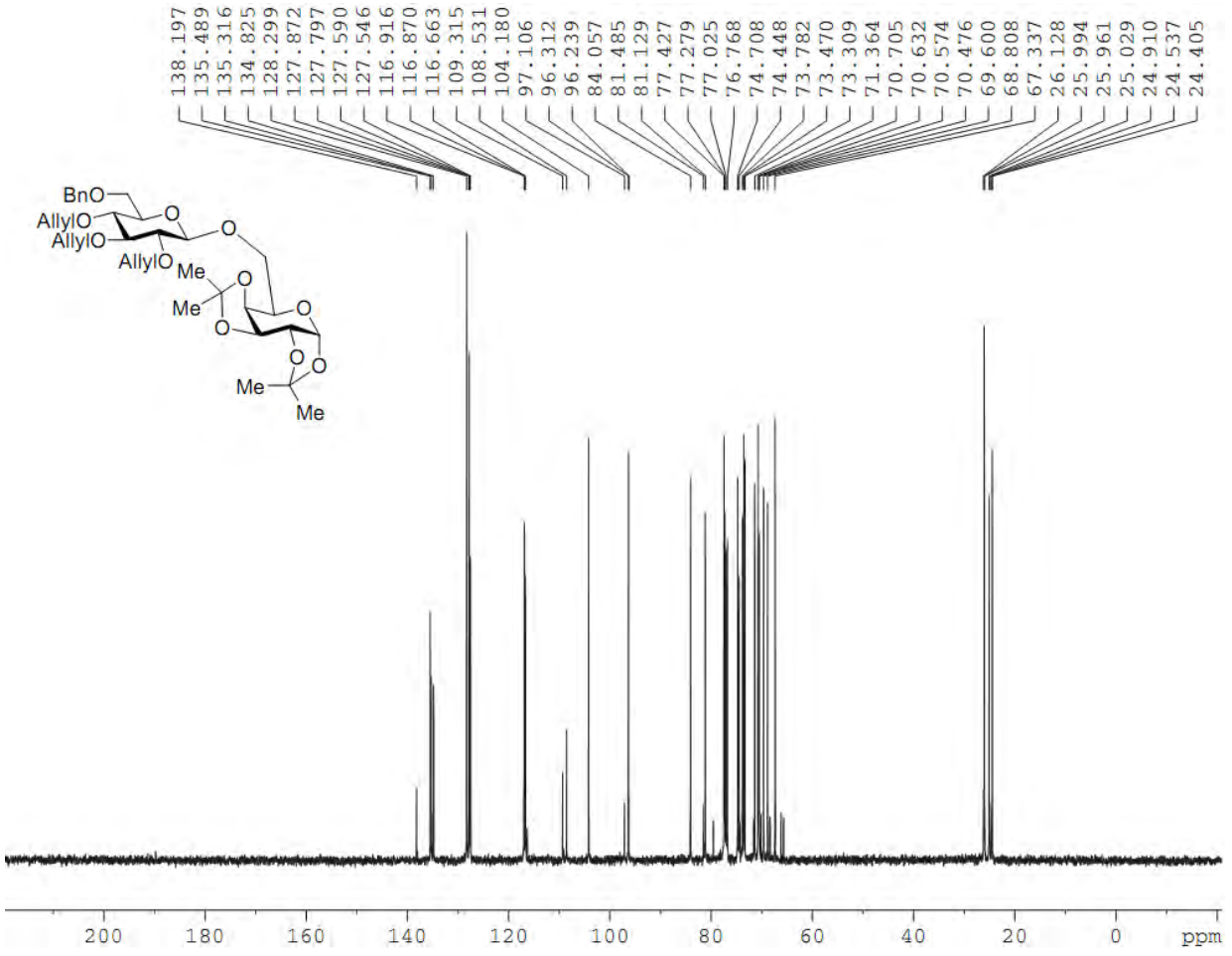


Figure A22. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **78**

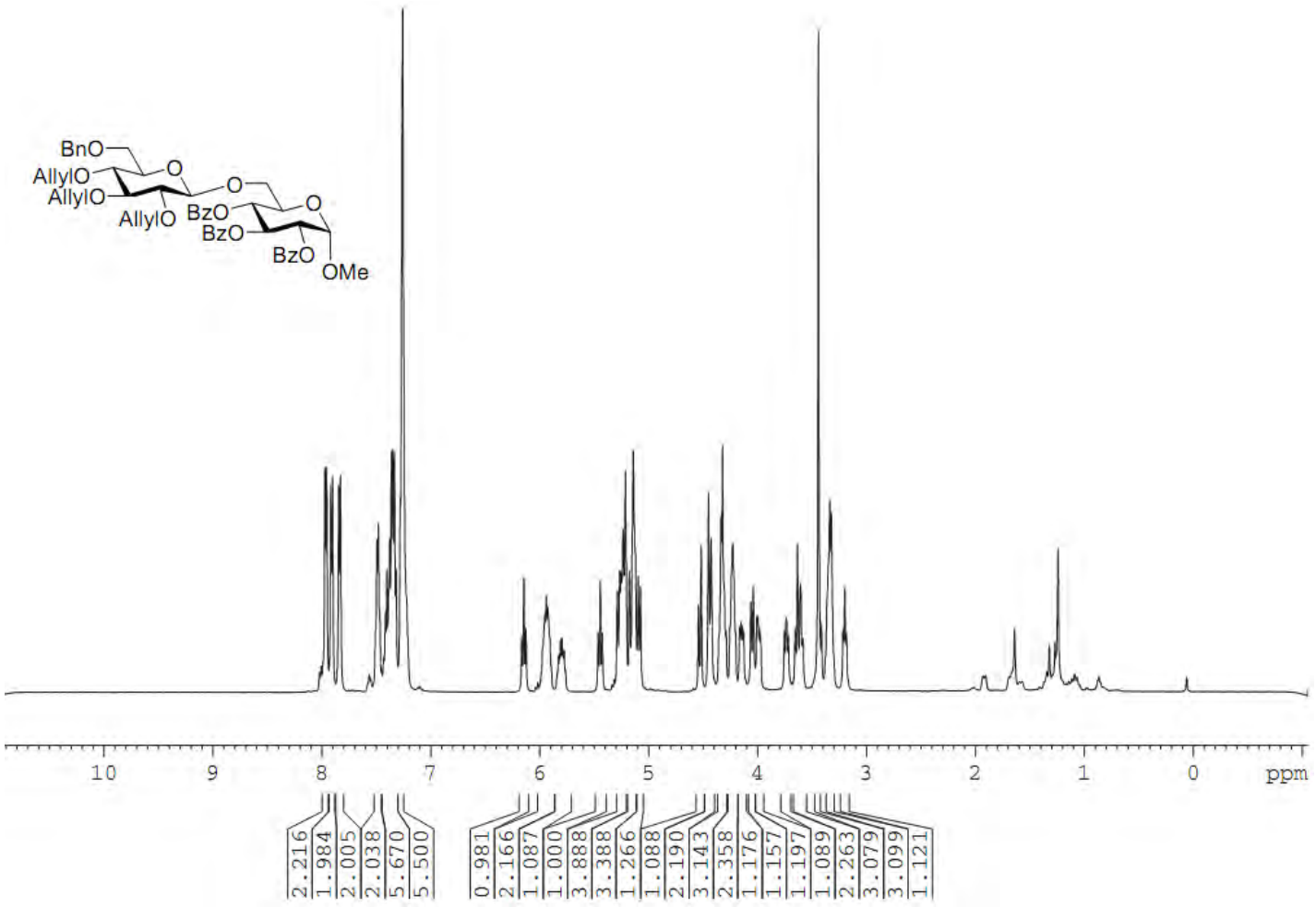


Figure A23. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **79**

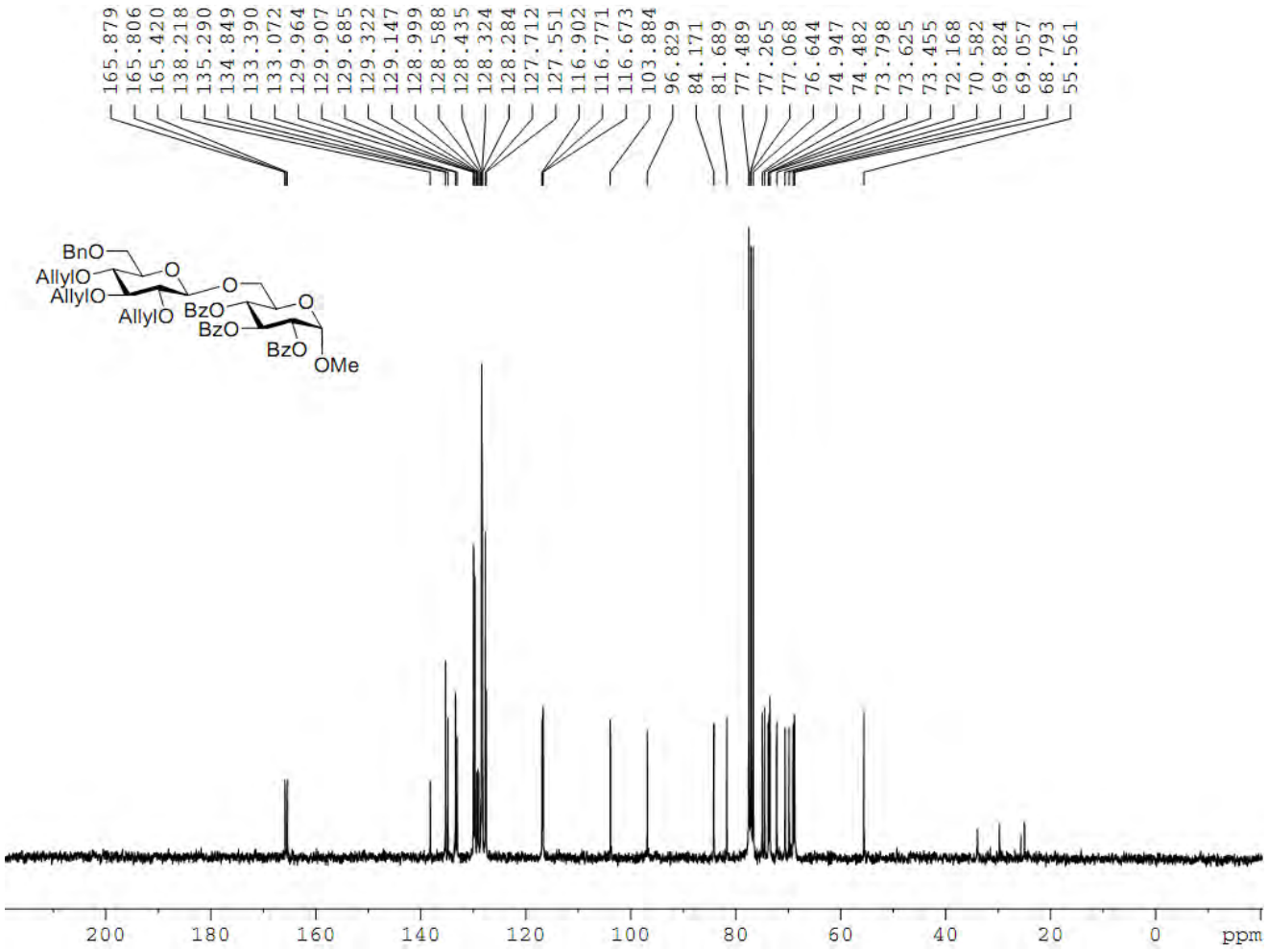


Figure A24. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **79**

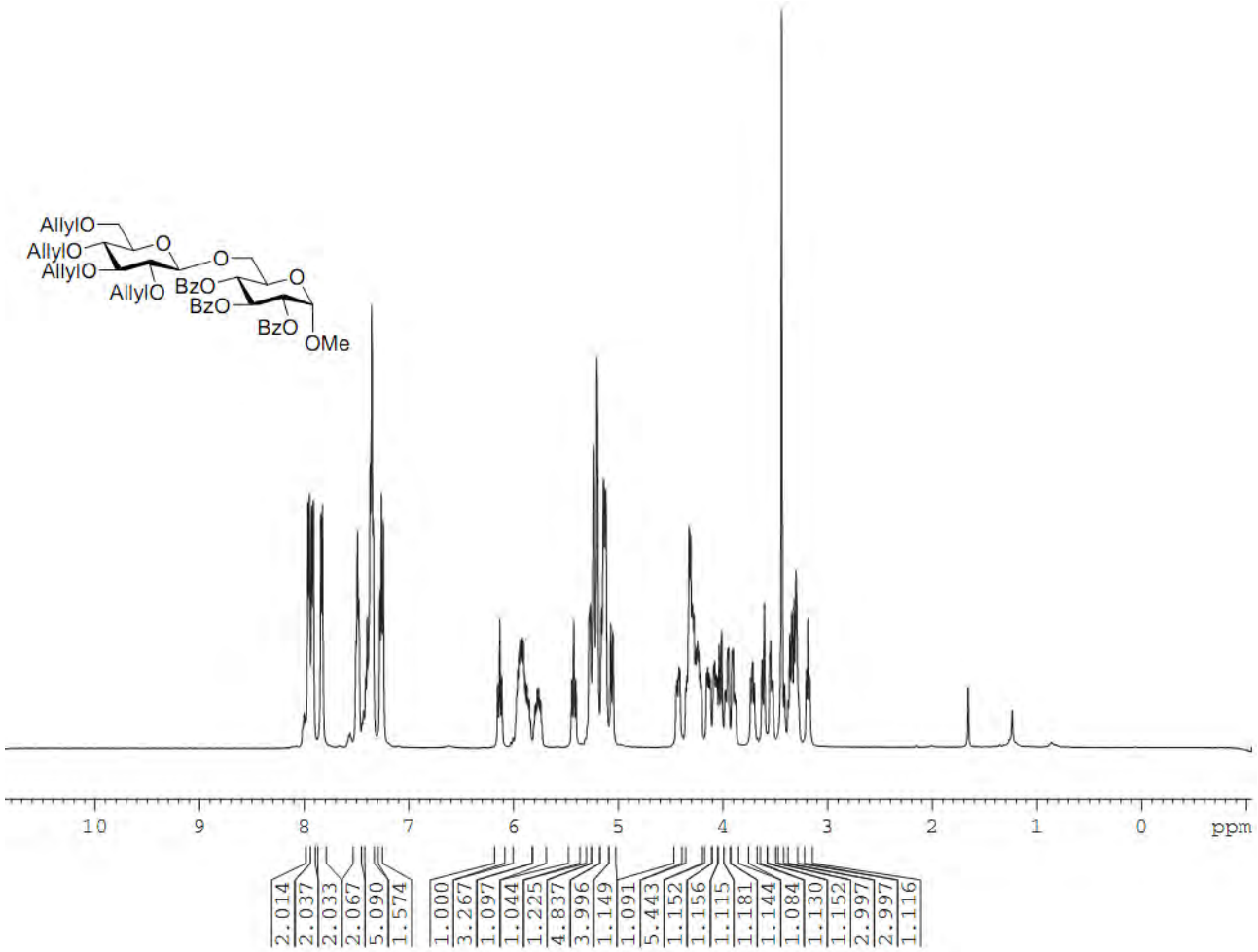


Figure A25. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **80**

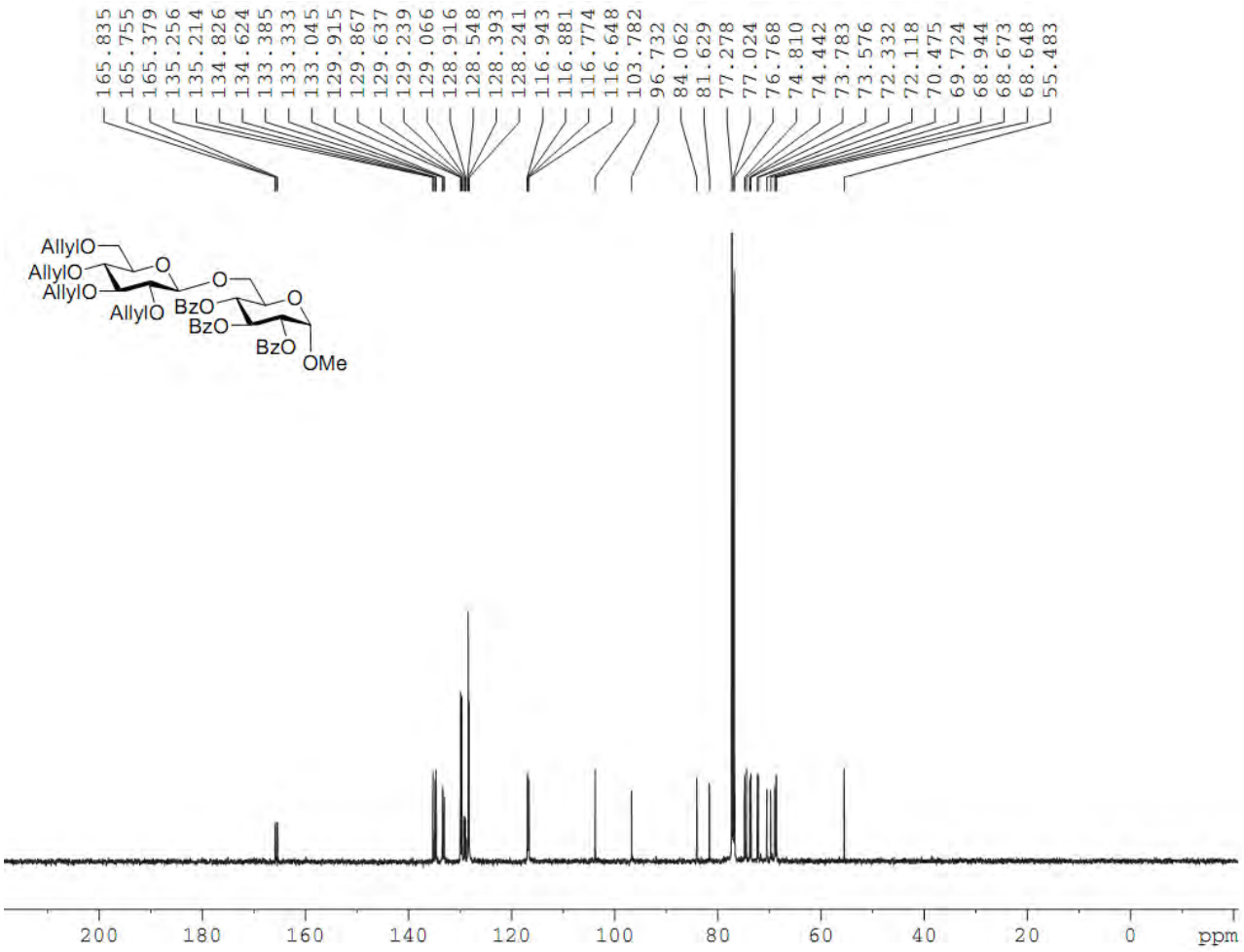


Figure A26. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **80**

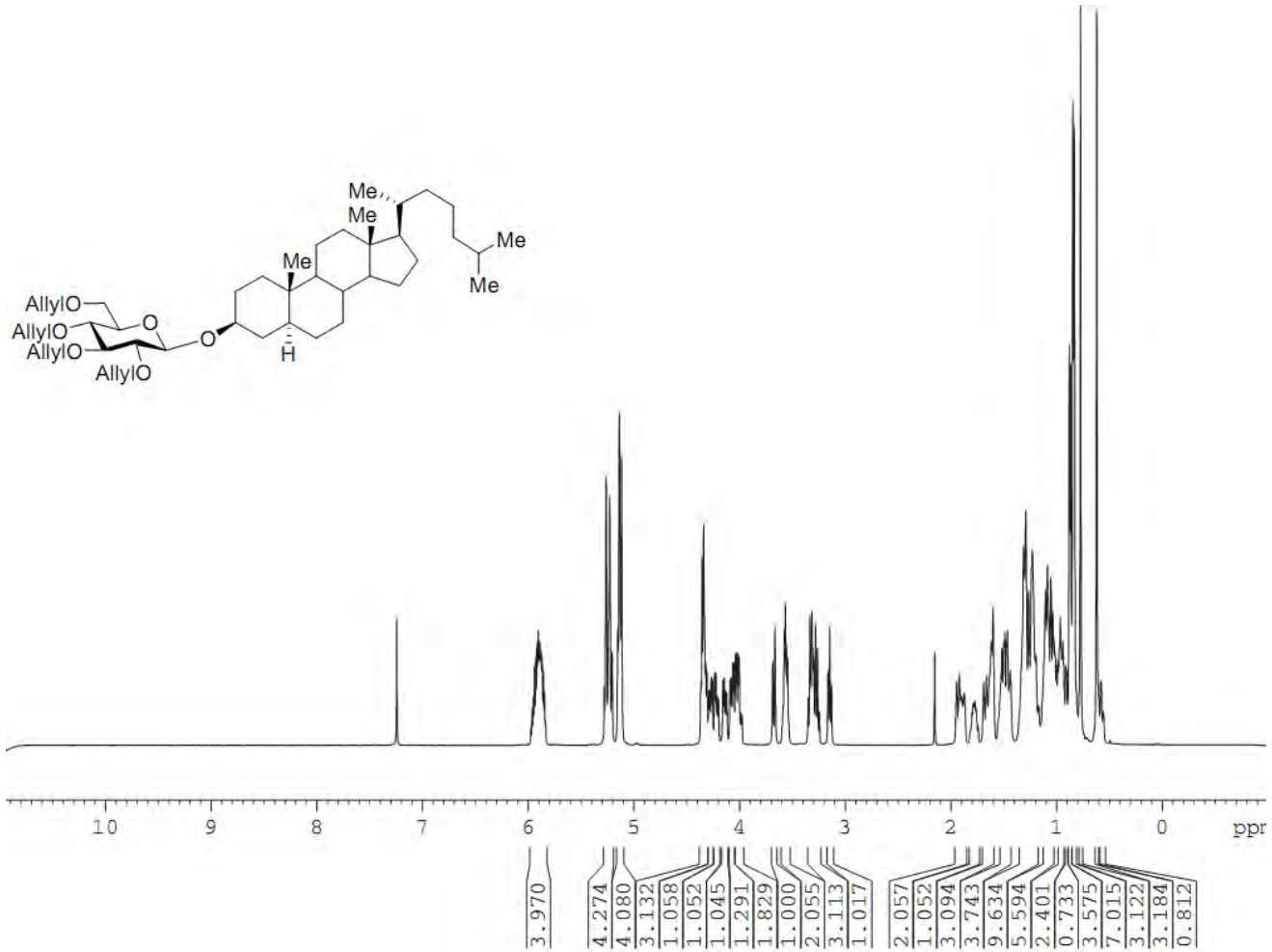


Figure A27. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **81**

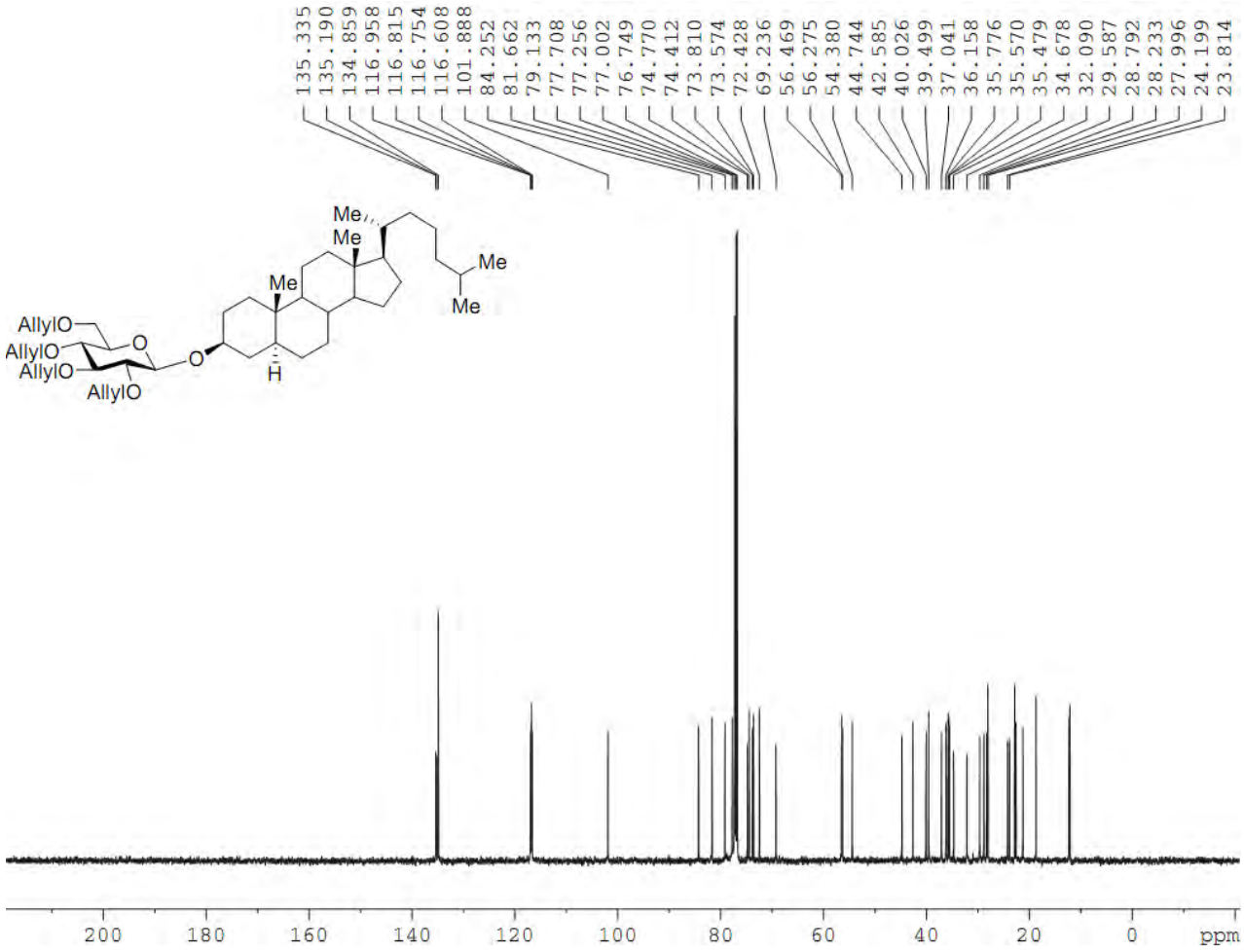


Figure A28. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **81**

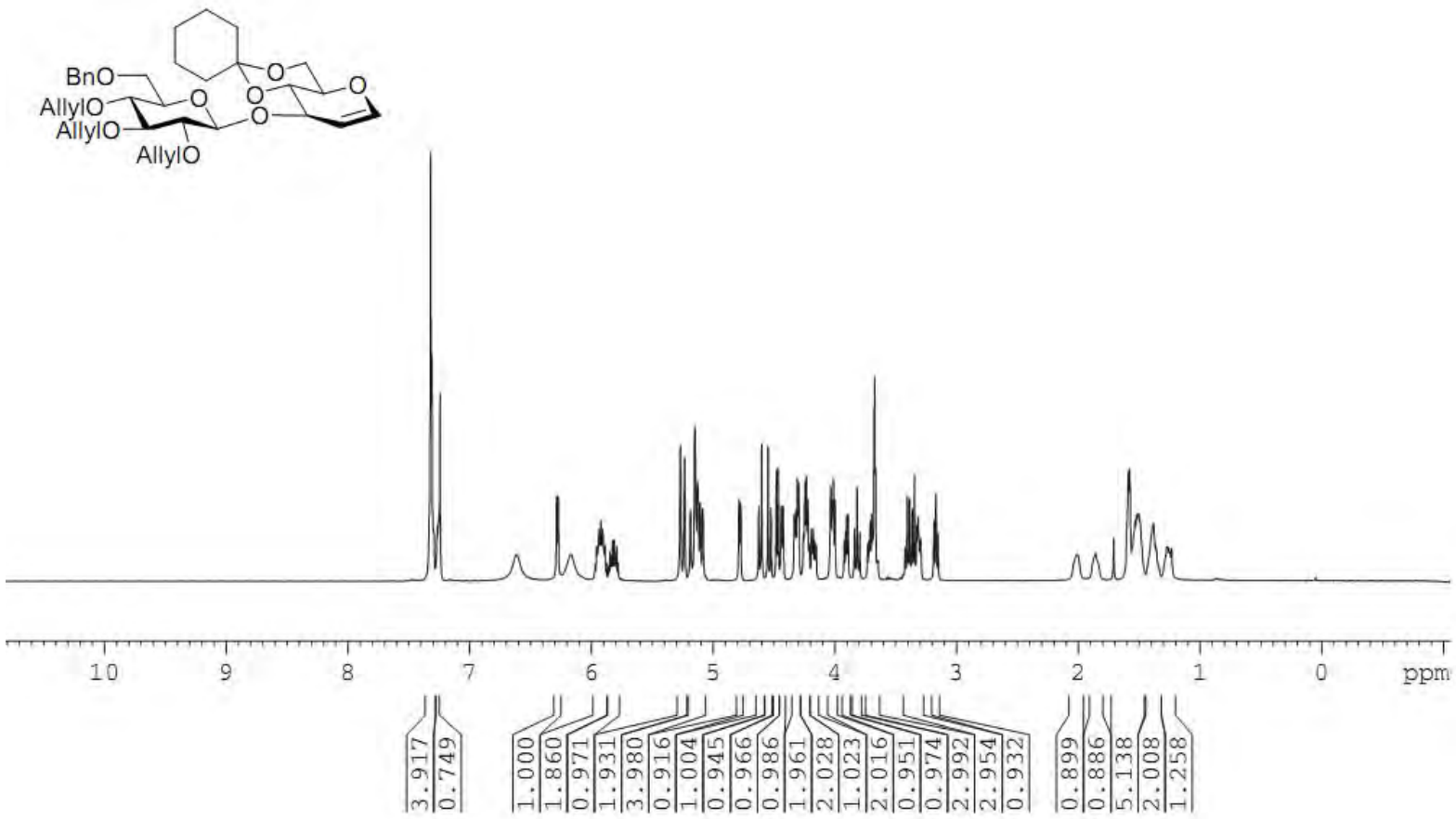


Figure A29. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **82**

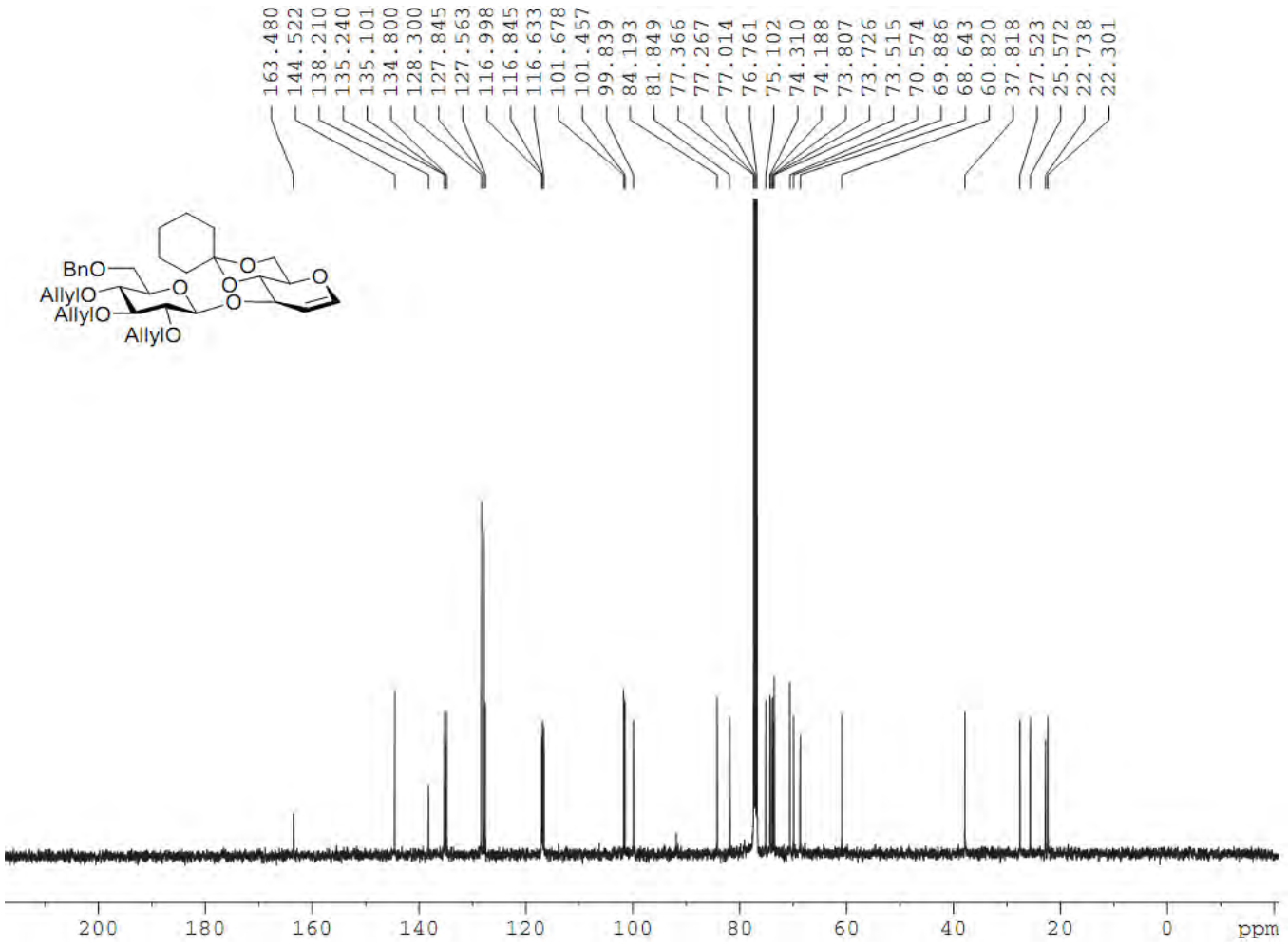


Figure A30. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **82**

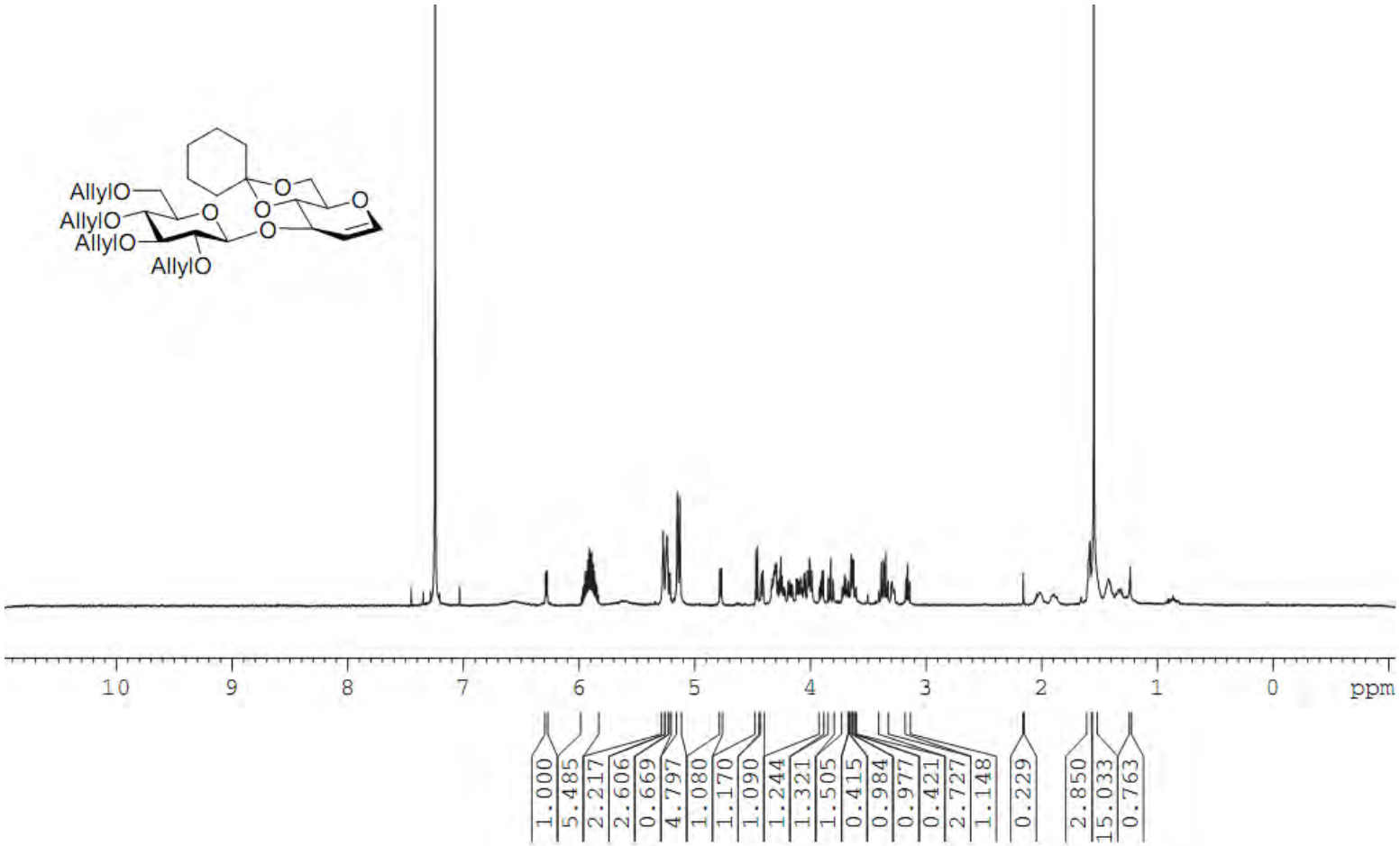


Figure A31. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **83**

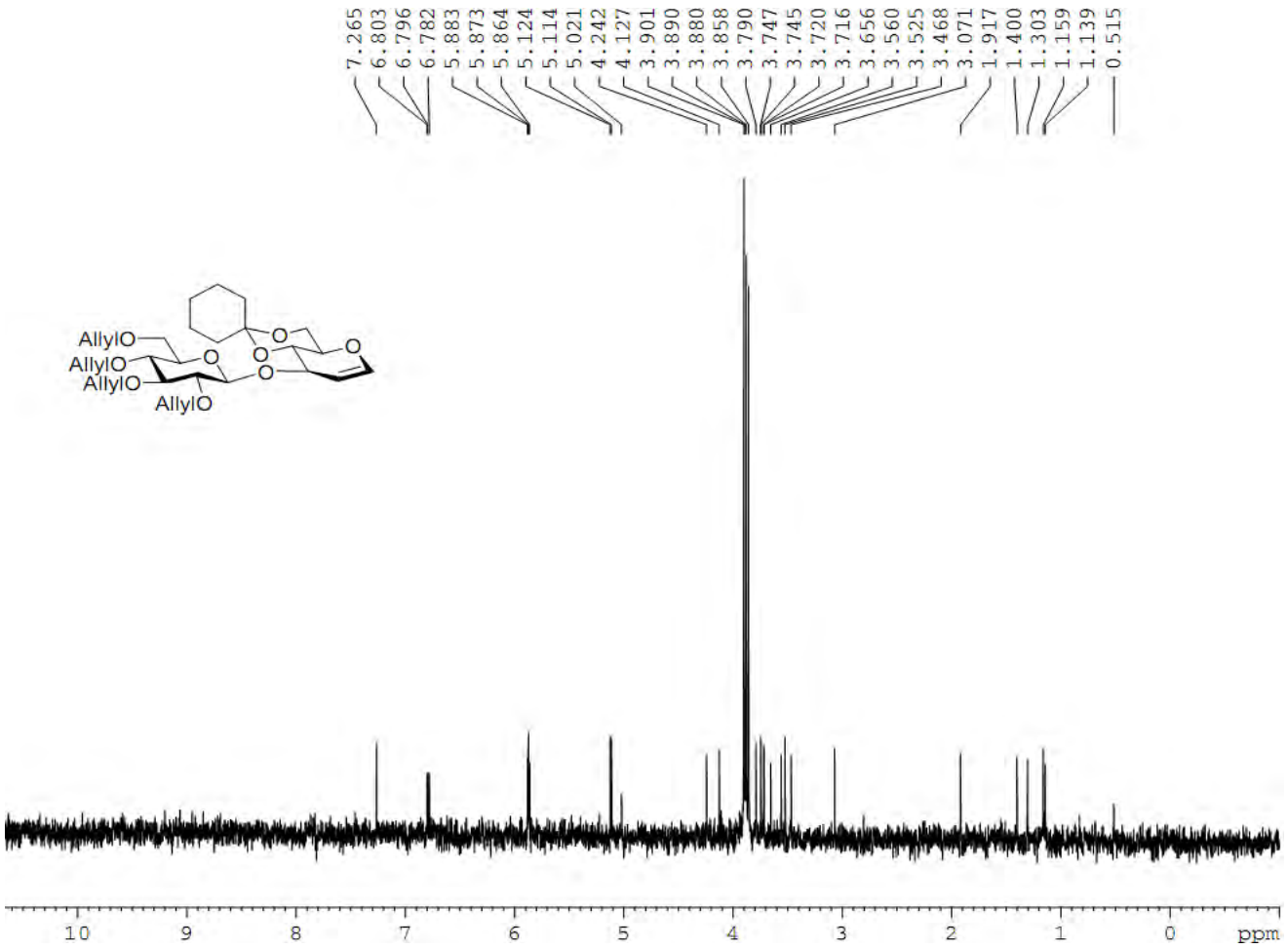


Figure A32. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **83**

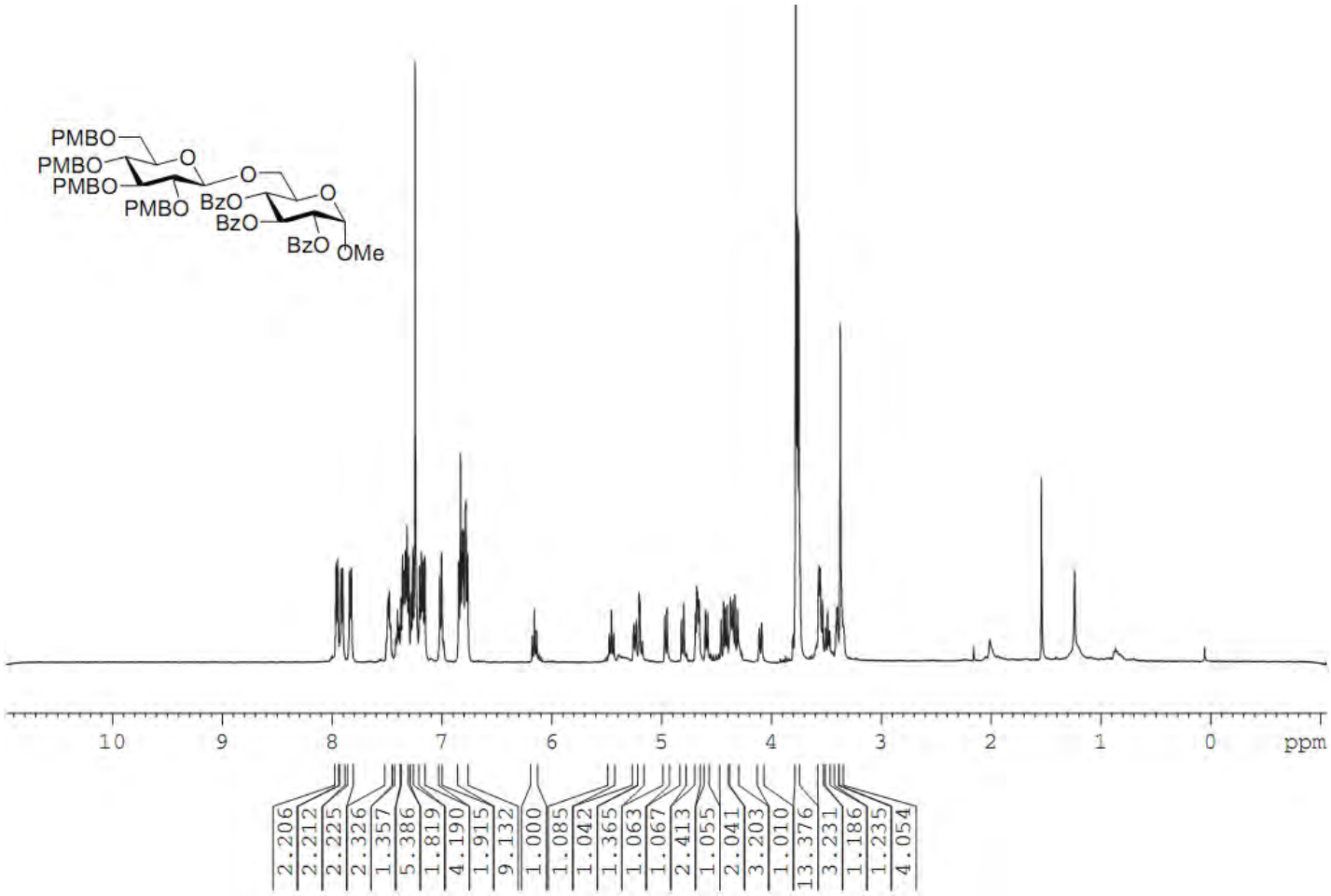


Figure A33. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **85**

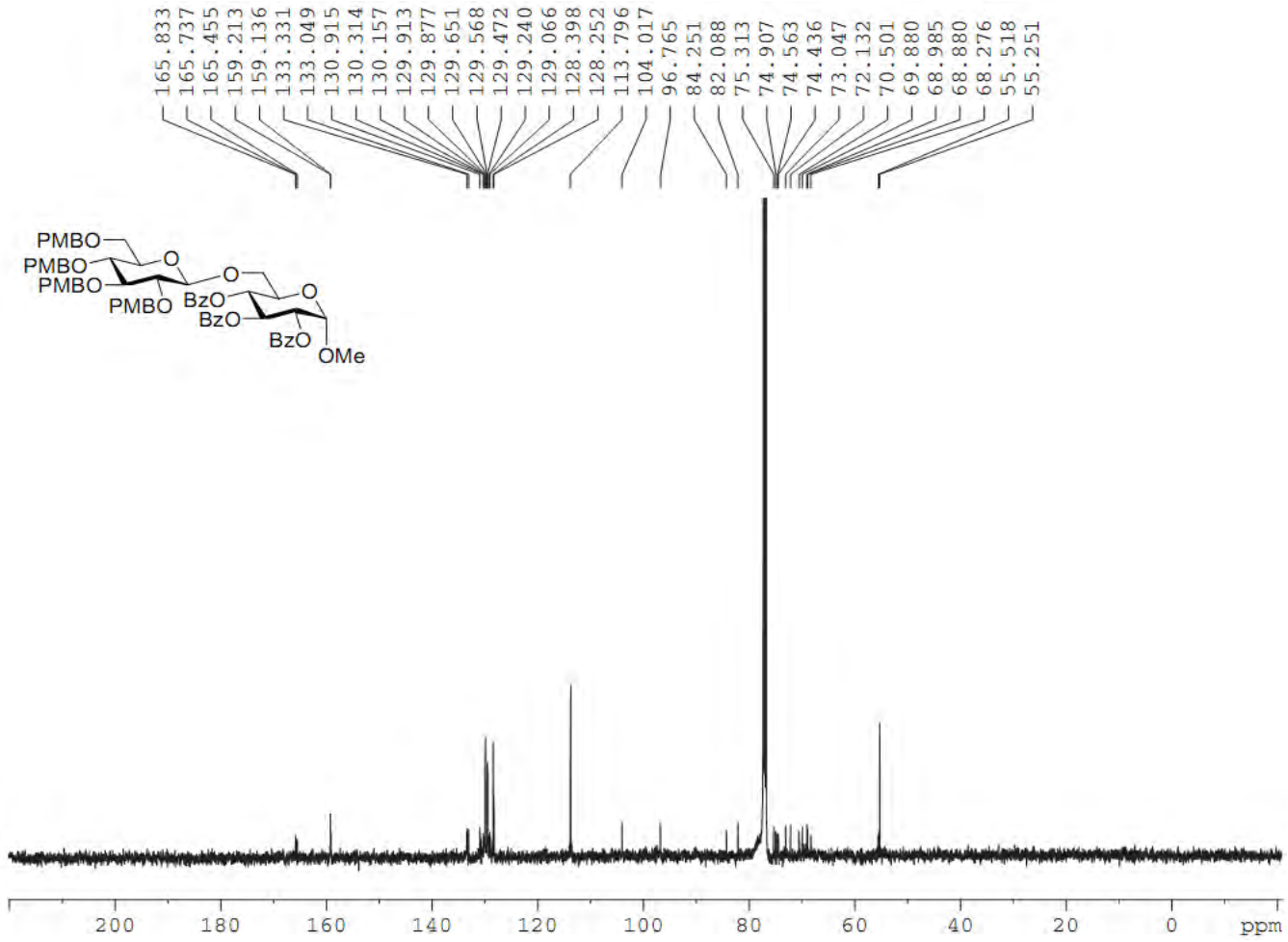


Figure A34. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **85**

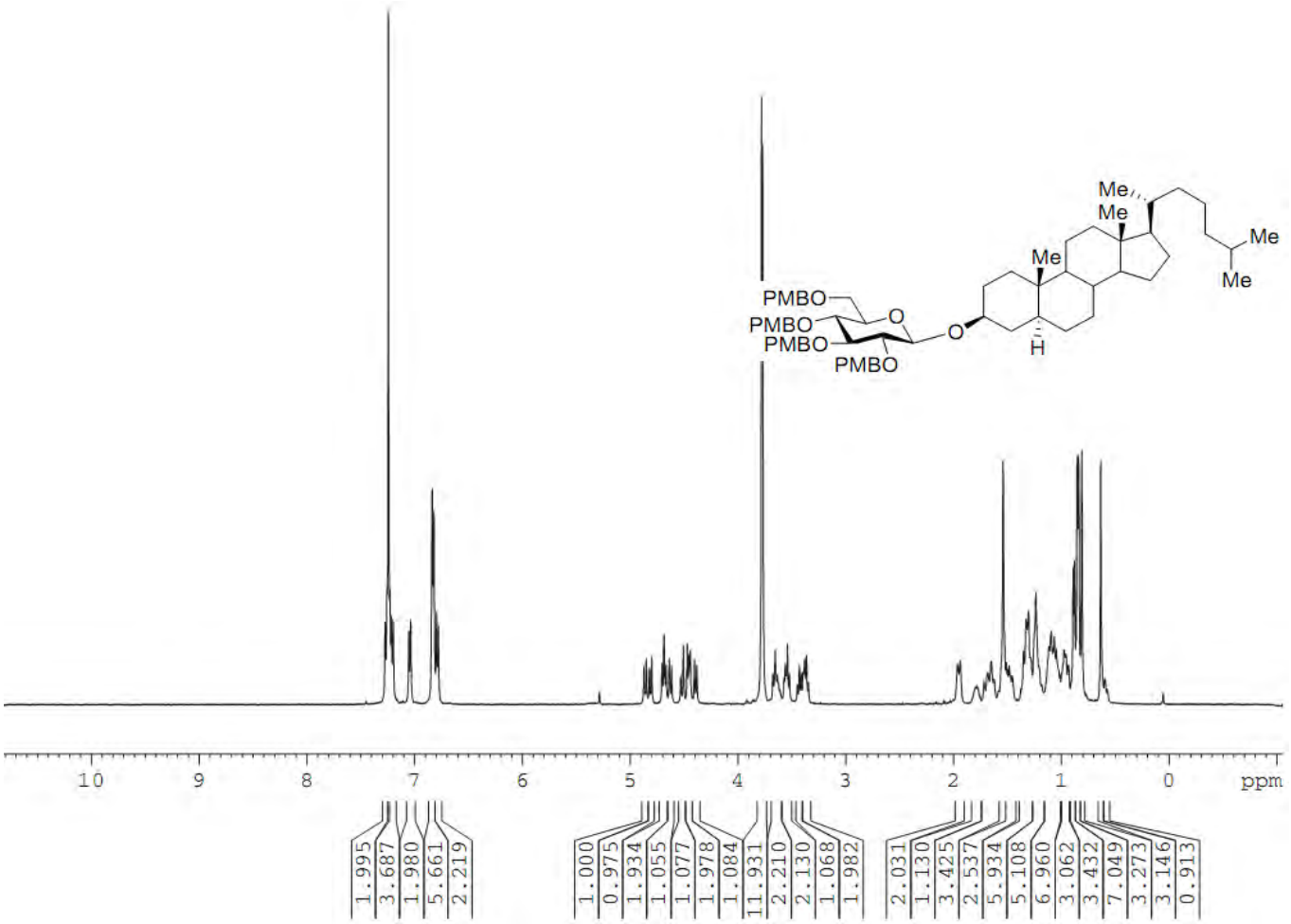


Figure A35. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **86**

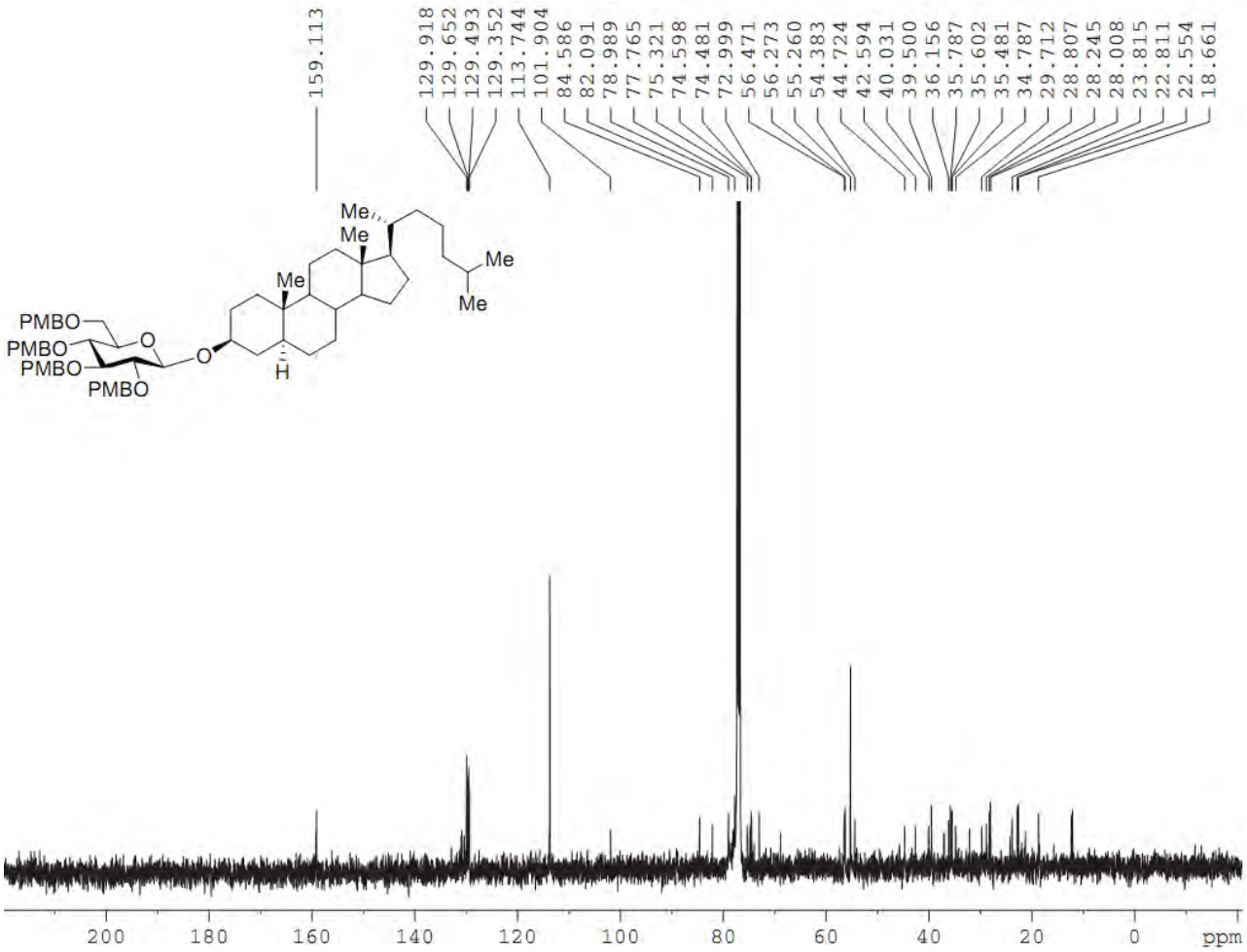


Figure A36. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **86**

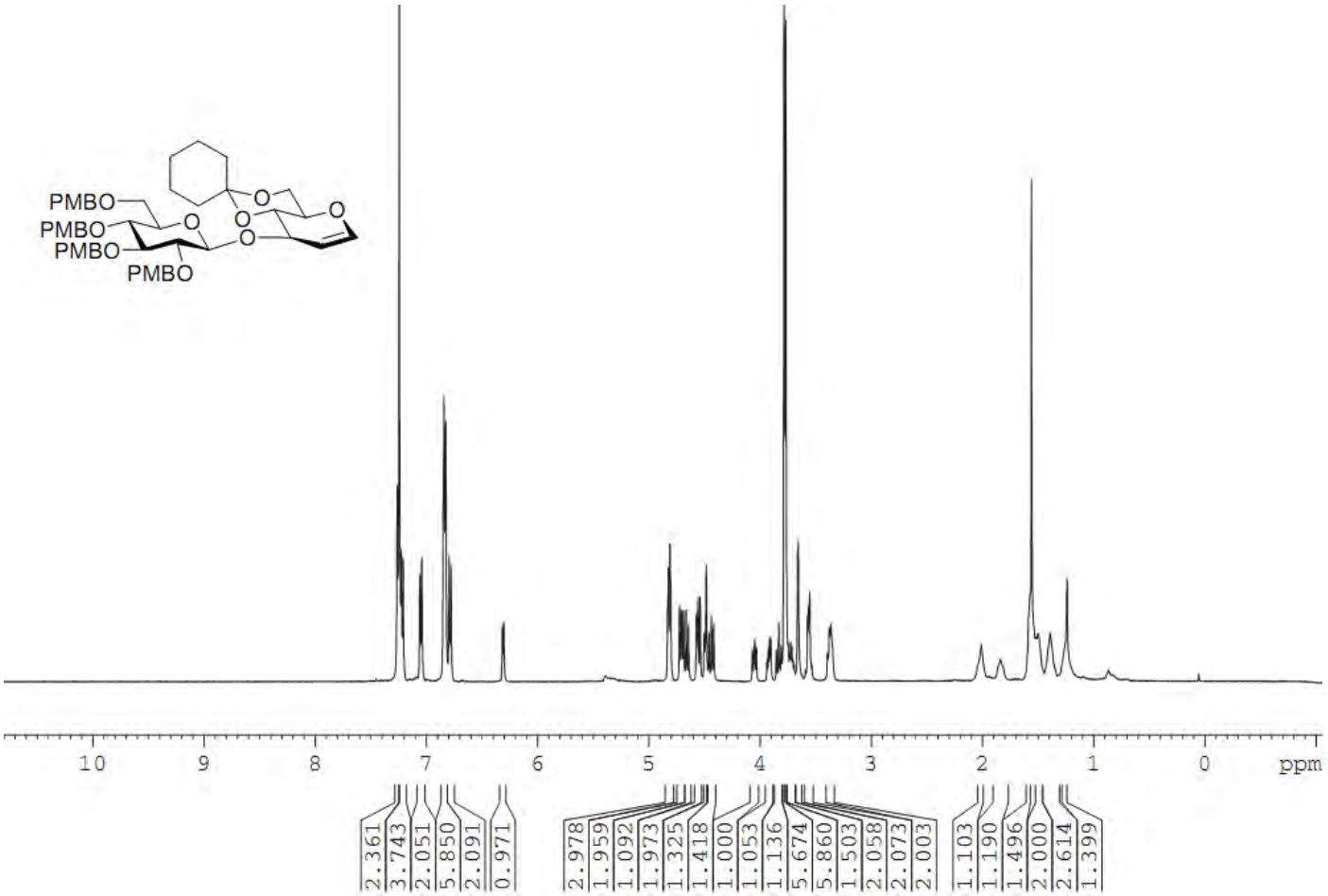


Figure A37. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **87**

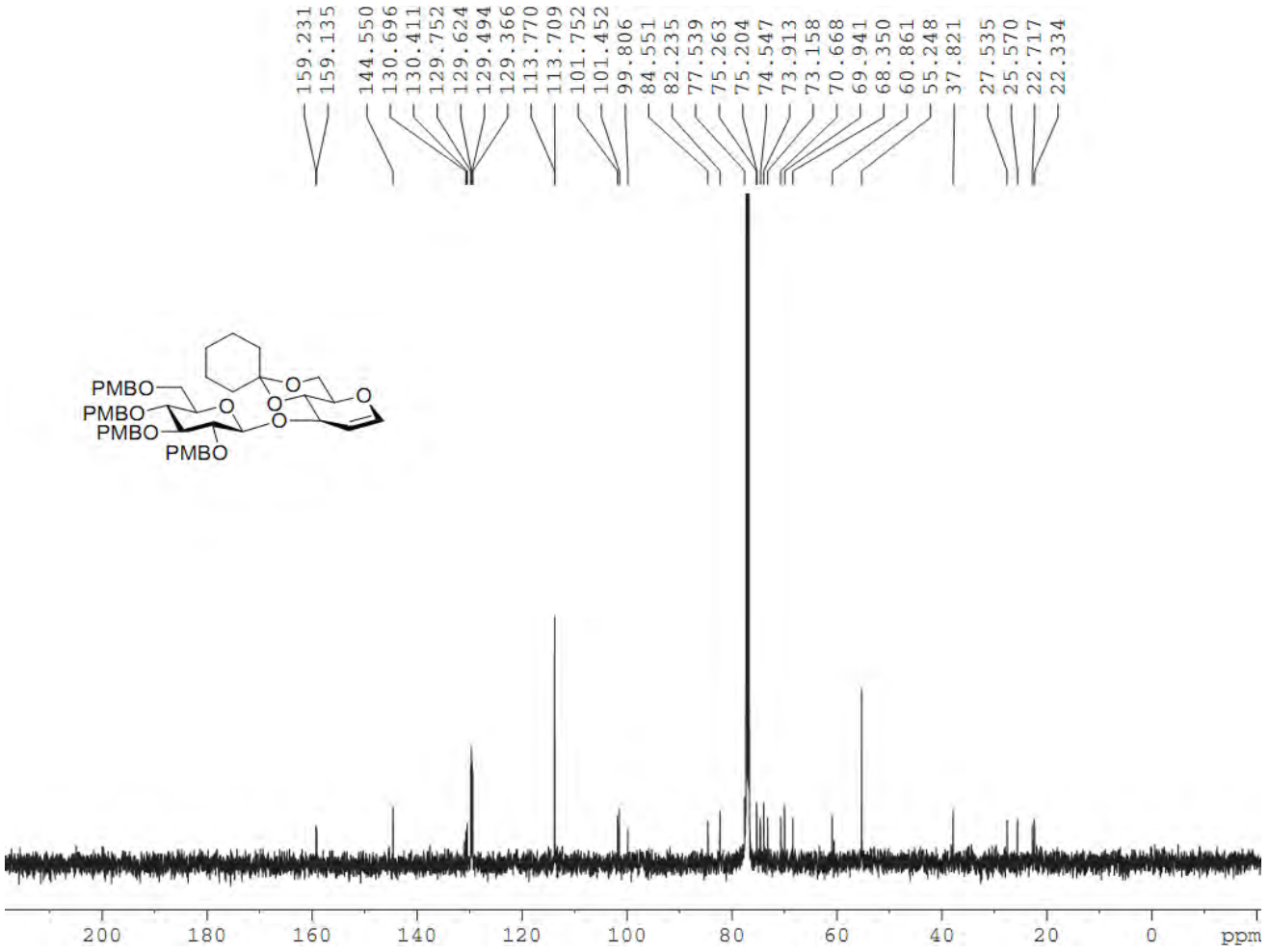


Figure A38. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **87**

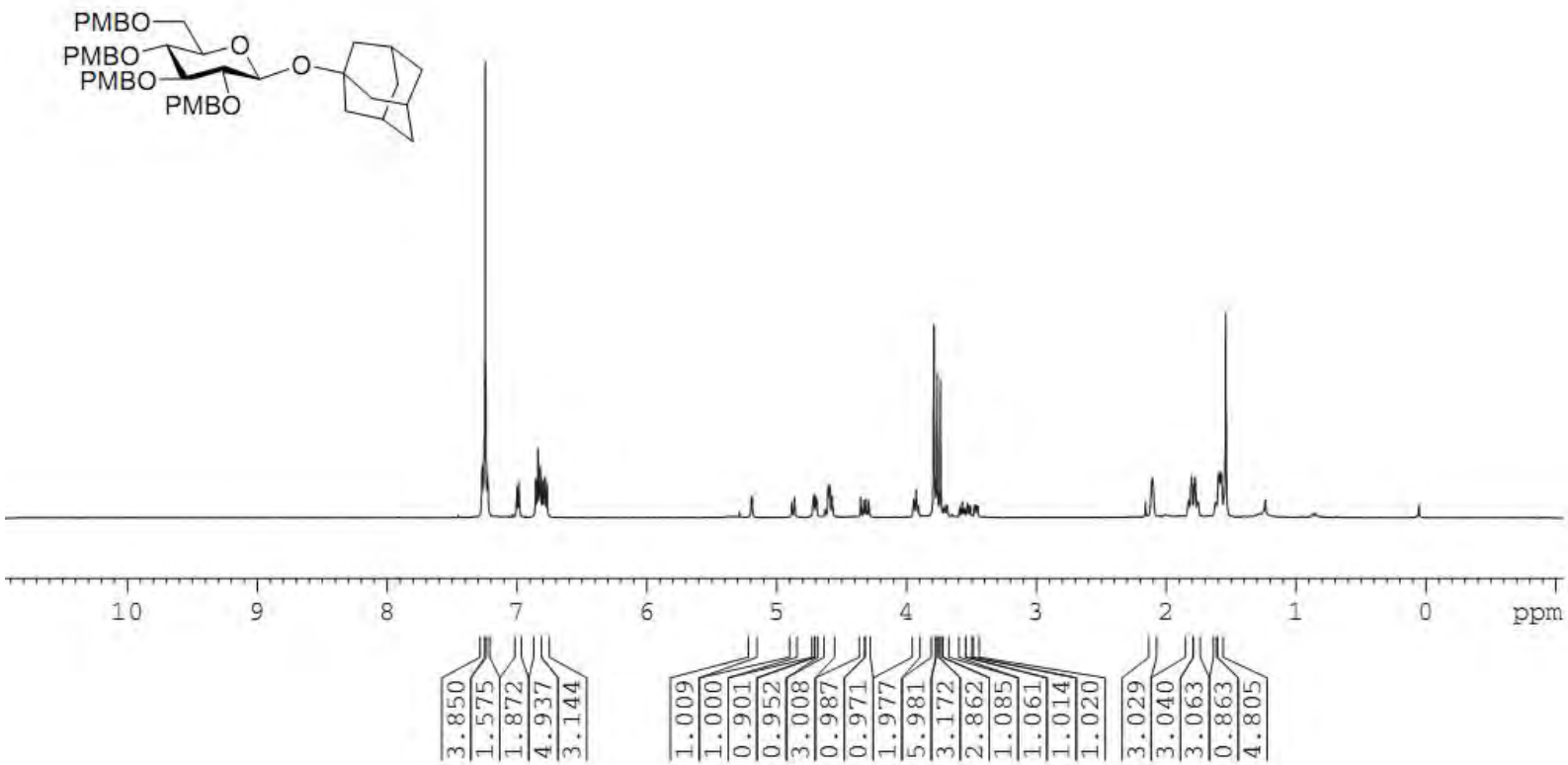


Figure A39. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **88**

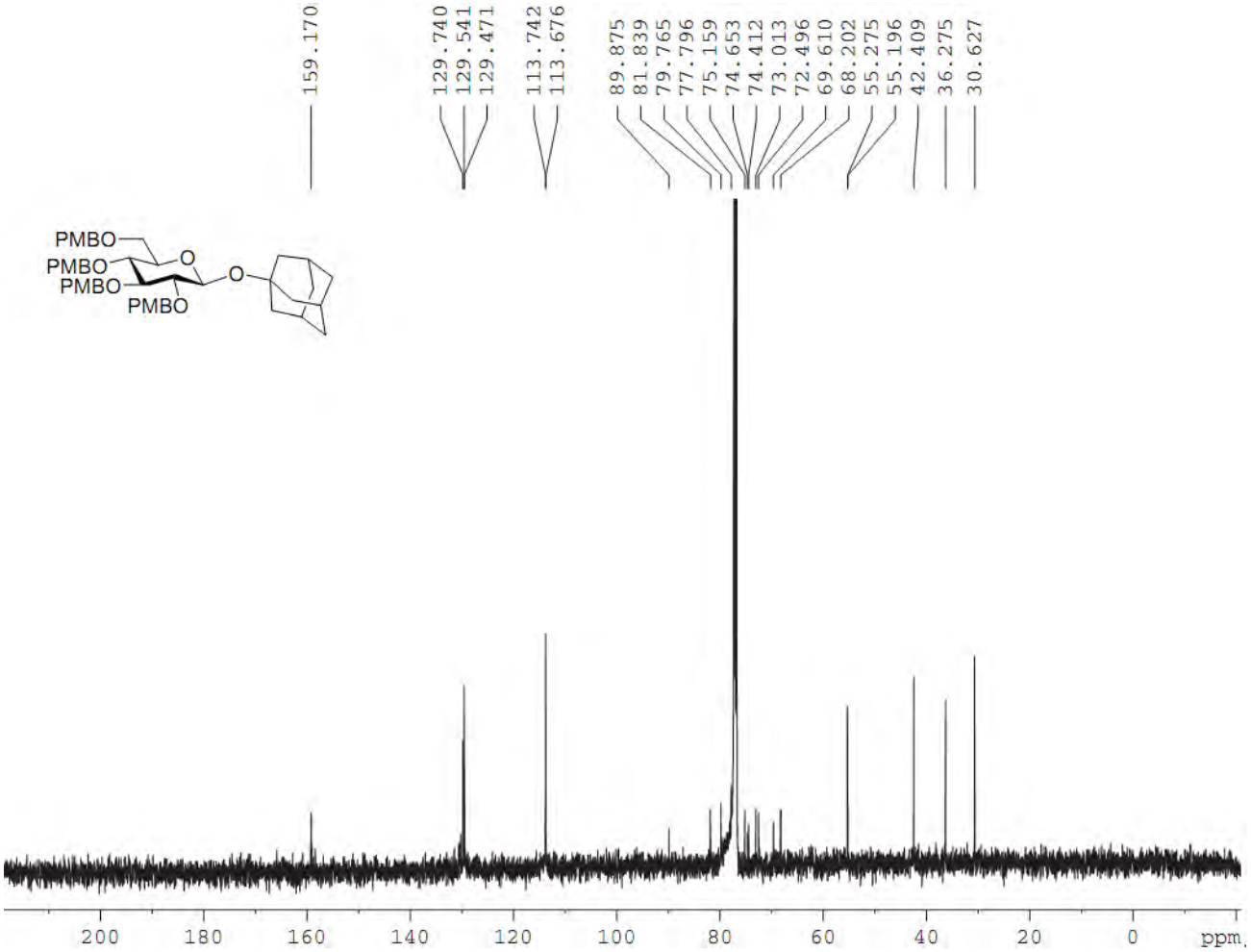


Figure A40. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **88**

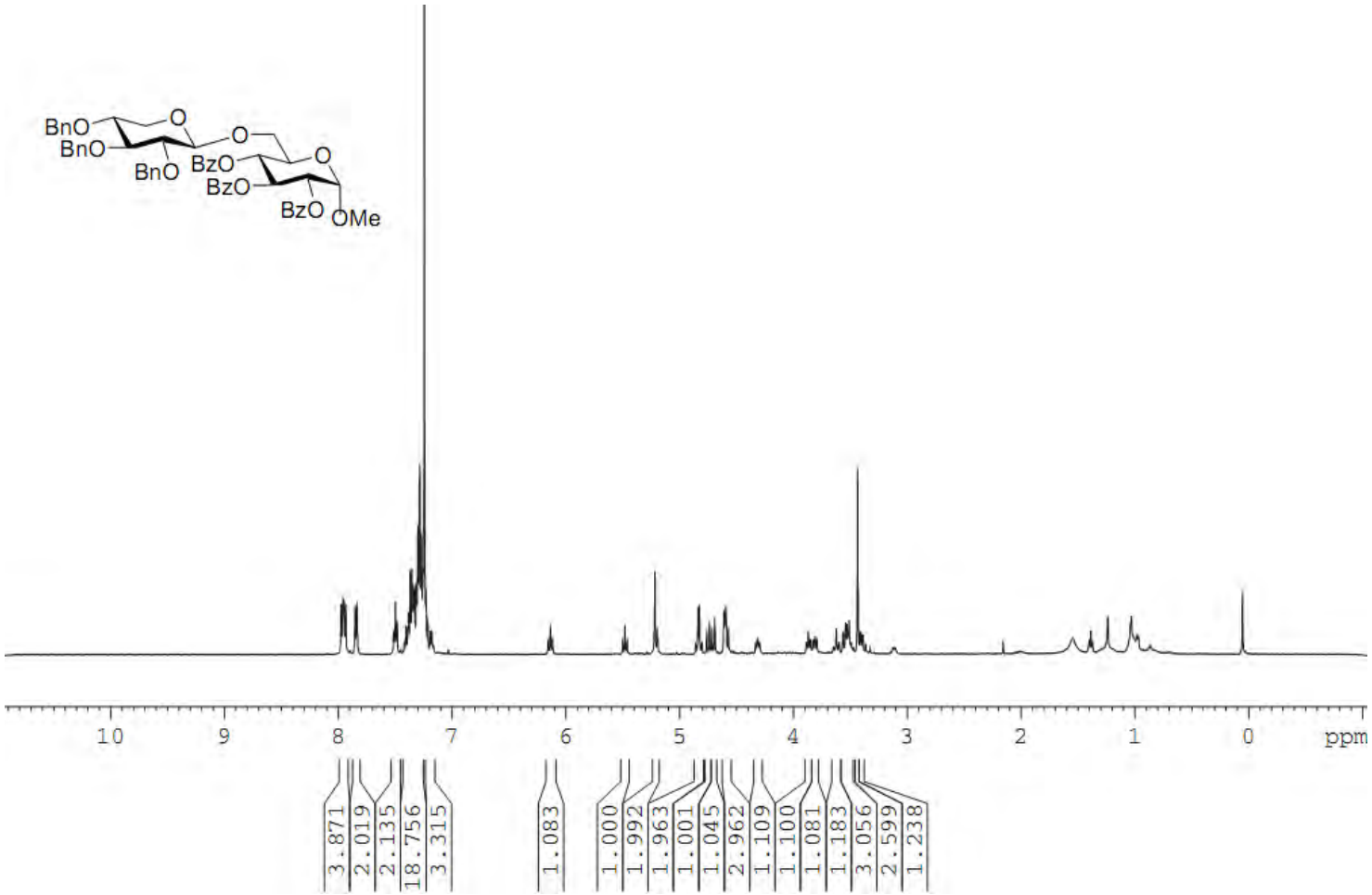


Figure A41. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **91**

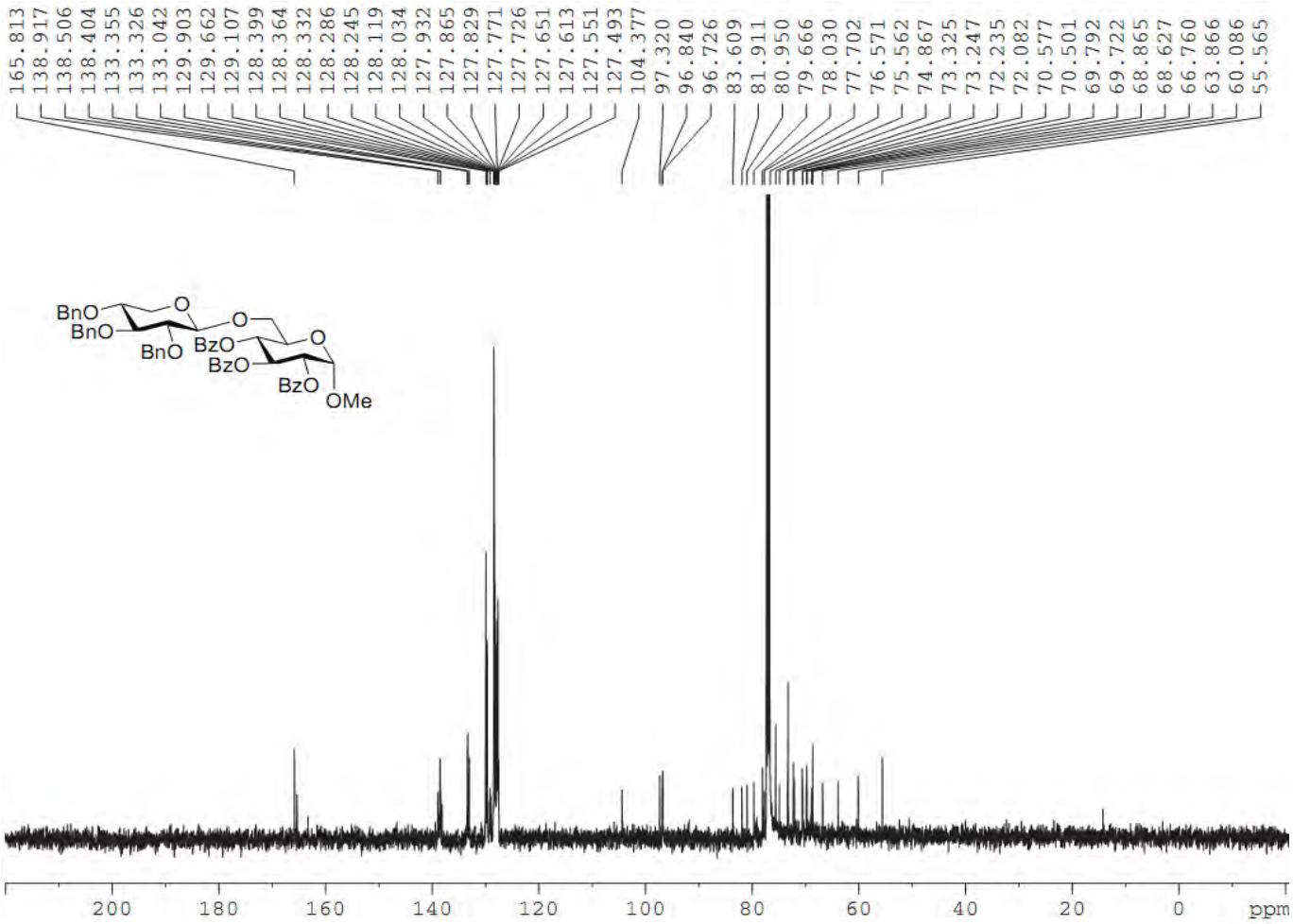


Figure A42. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **91**

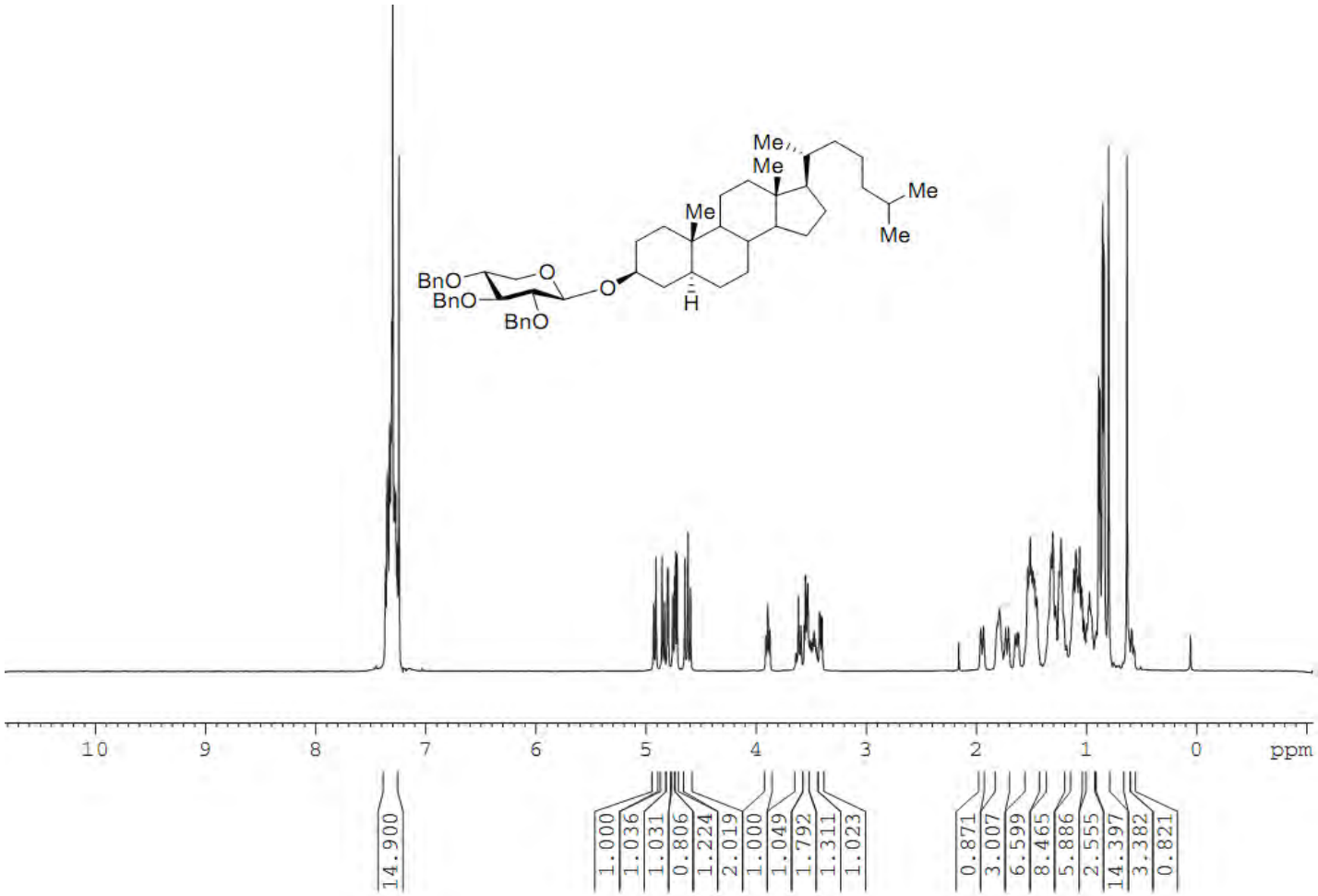


Figure A43. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **92**

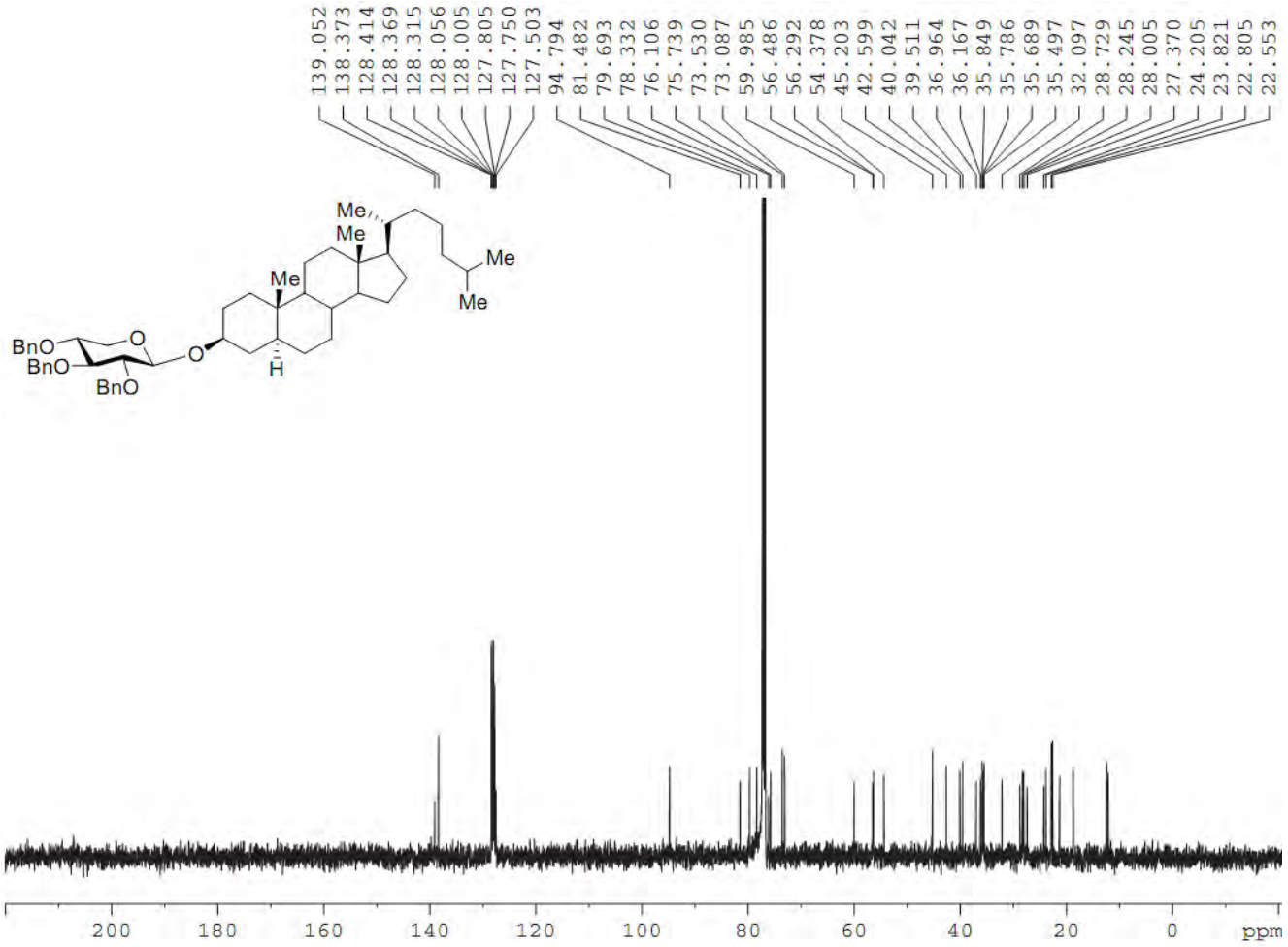


Figure A44. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **92**

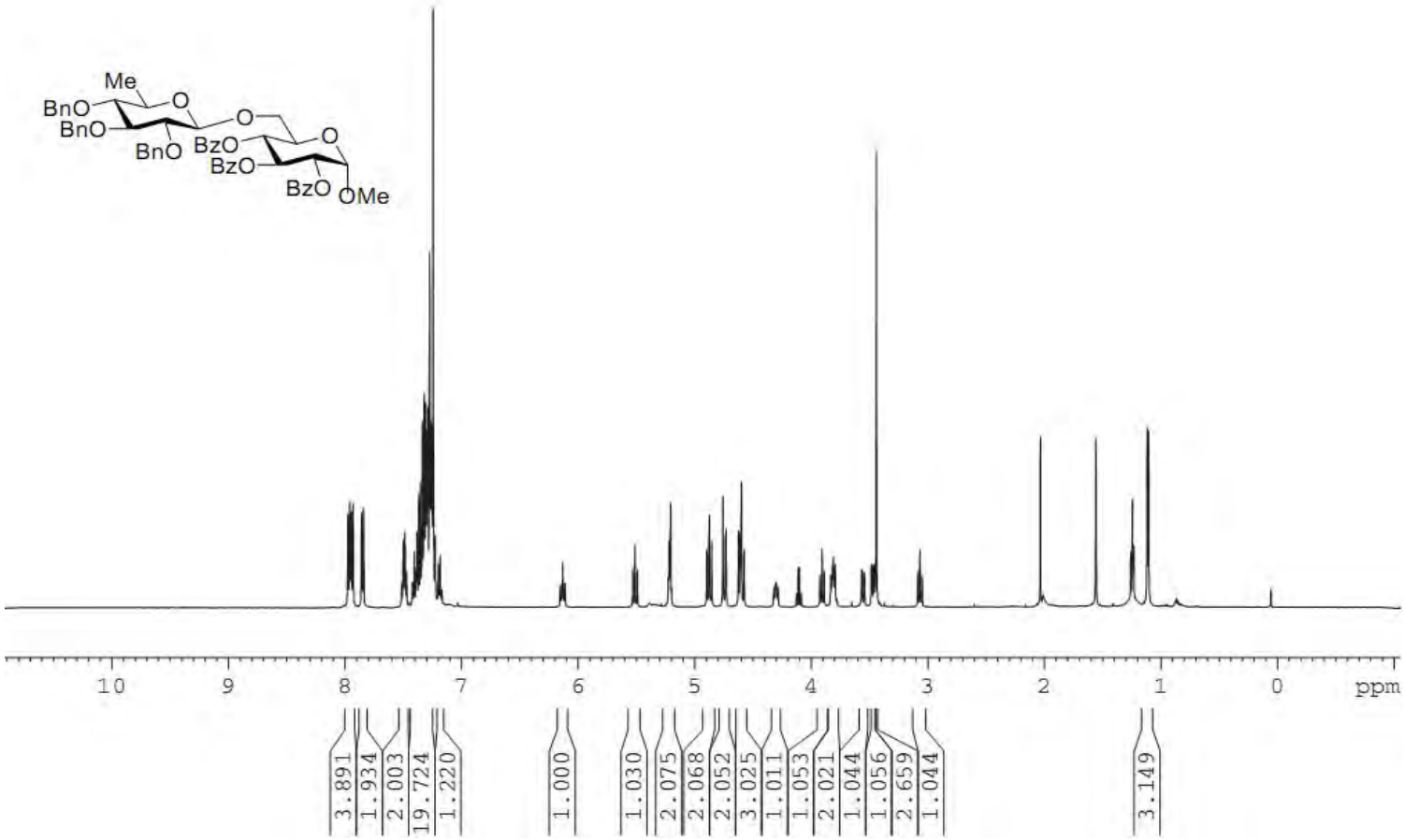


Figure A45. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **93**

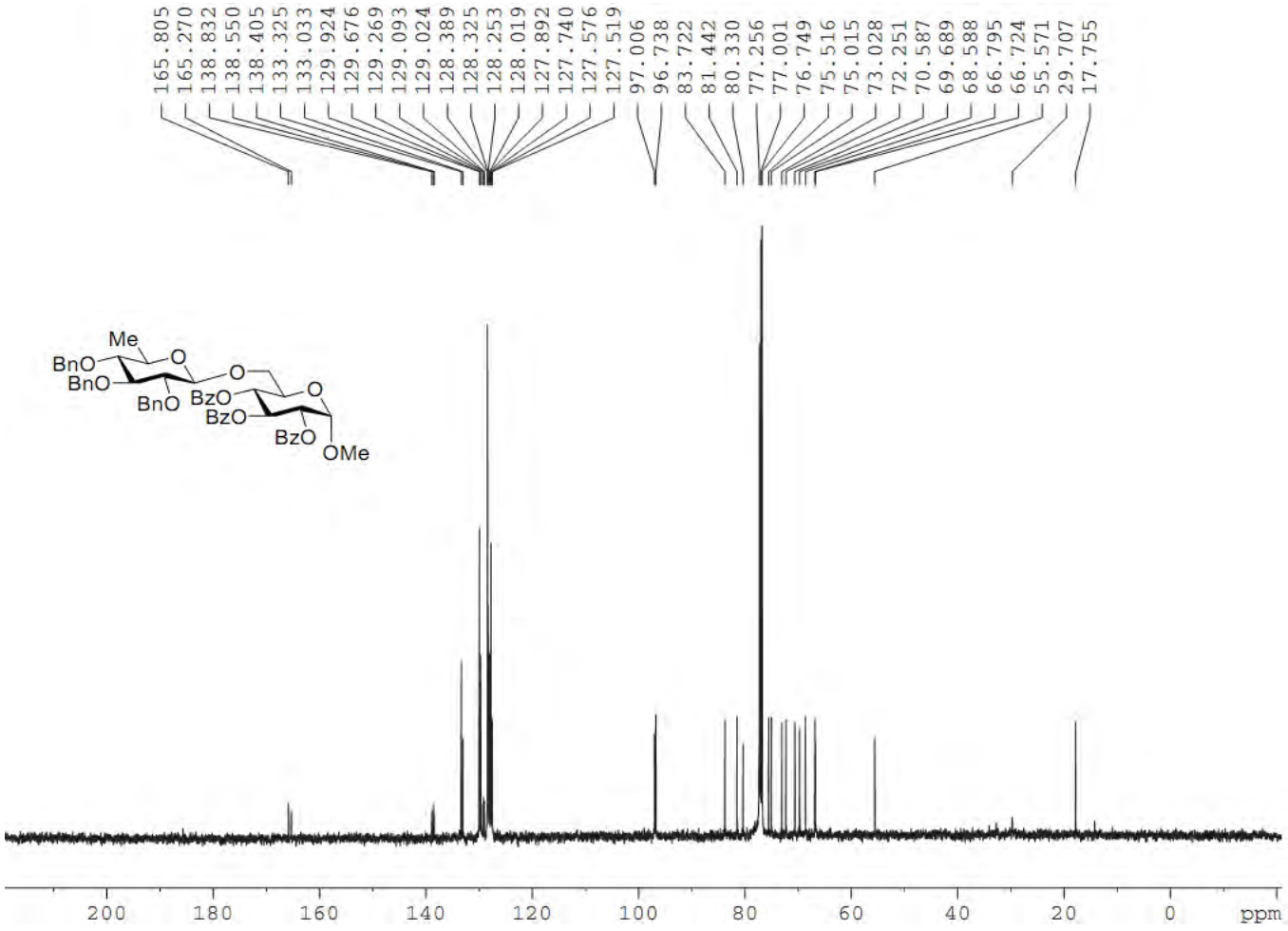


Figure A46. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **93**

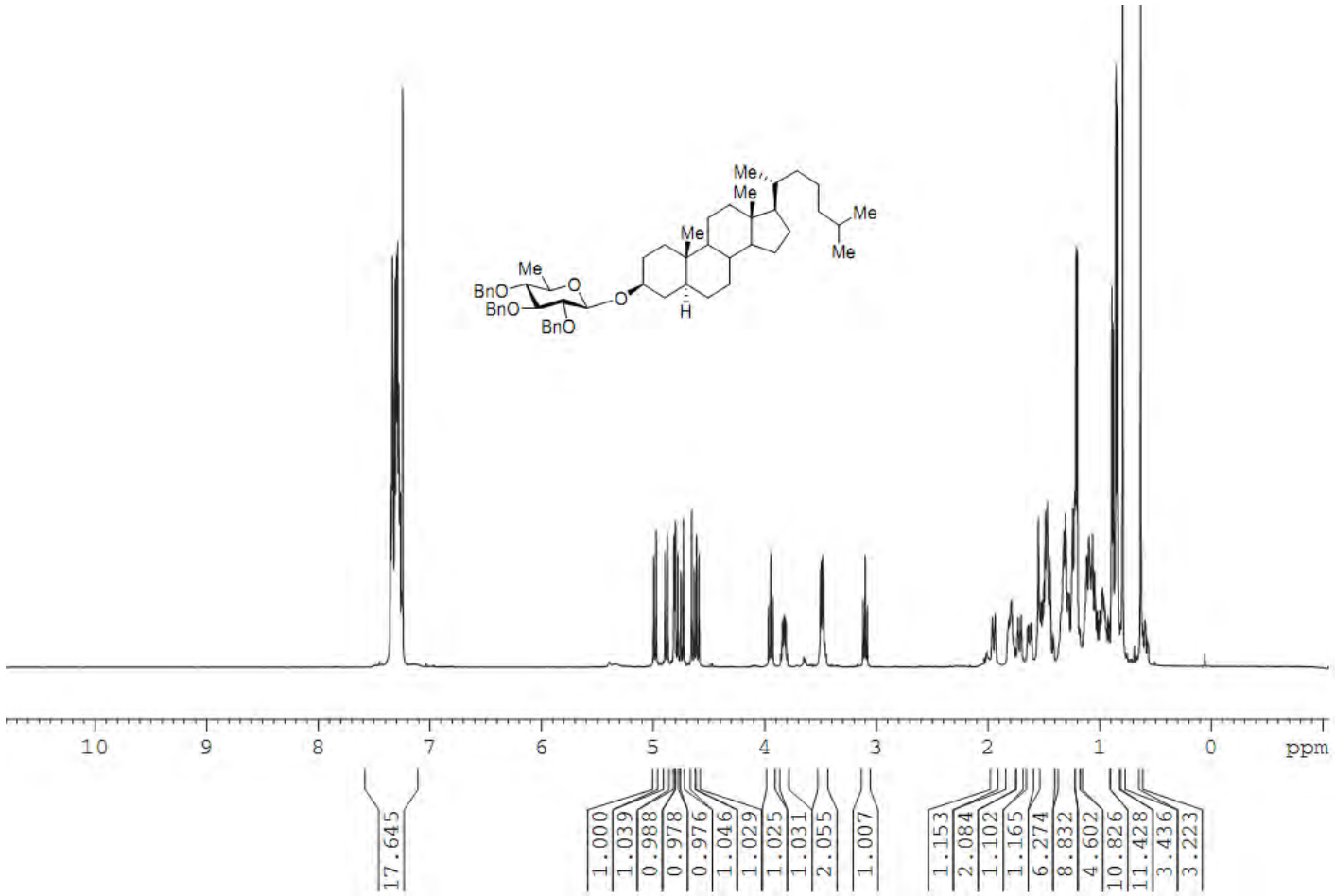


Figure A47. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **94**

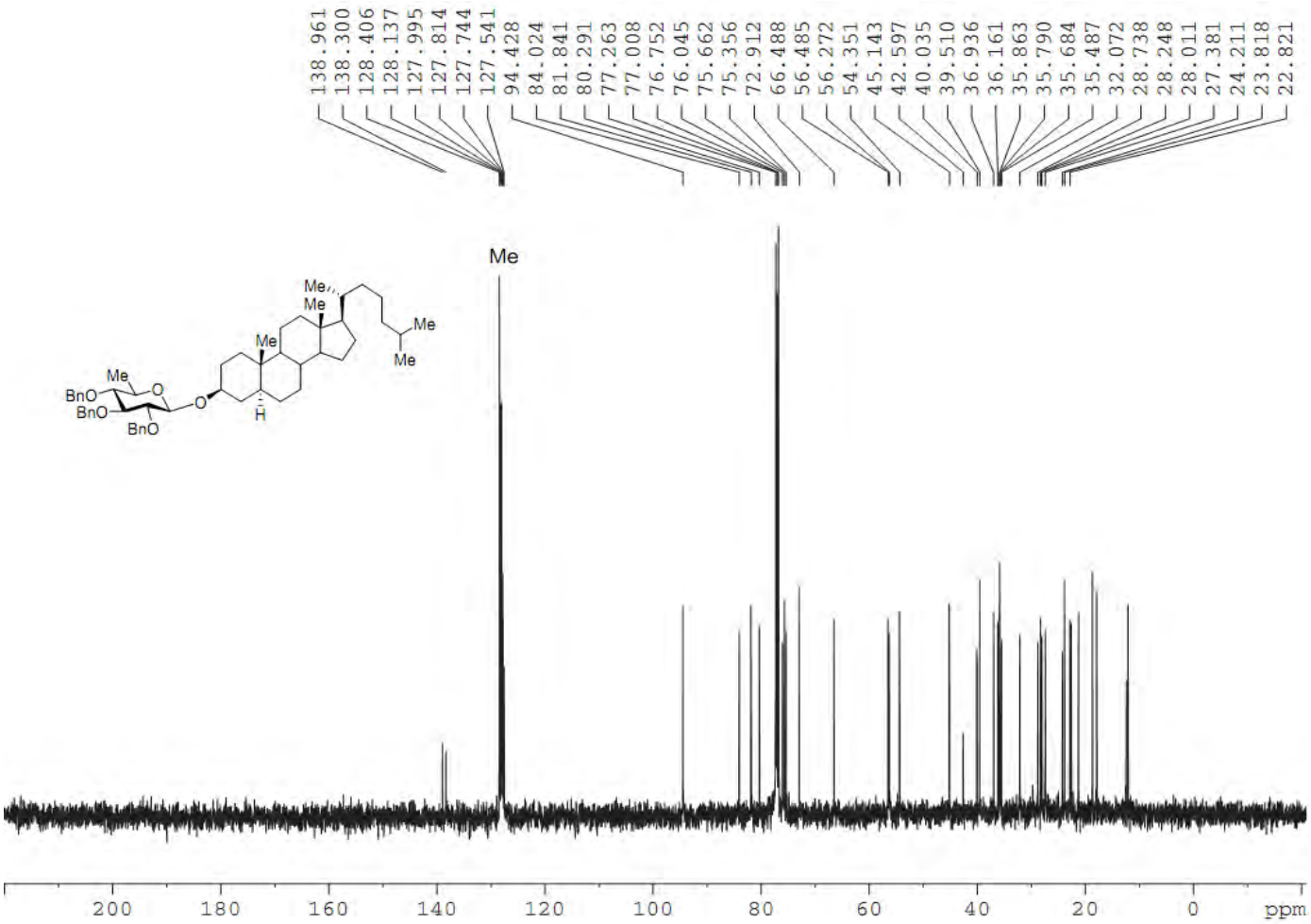


Figure A48. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **94**

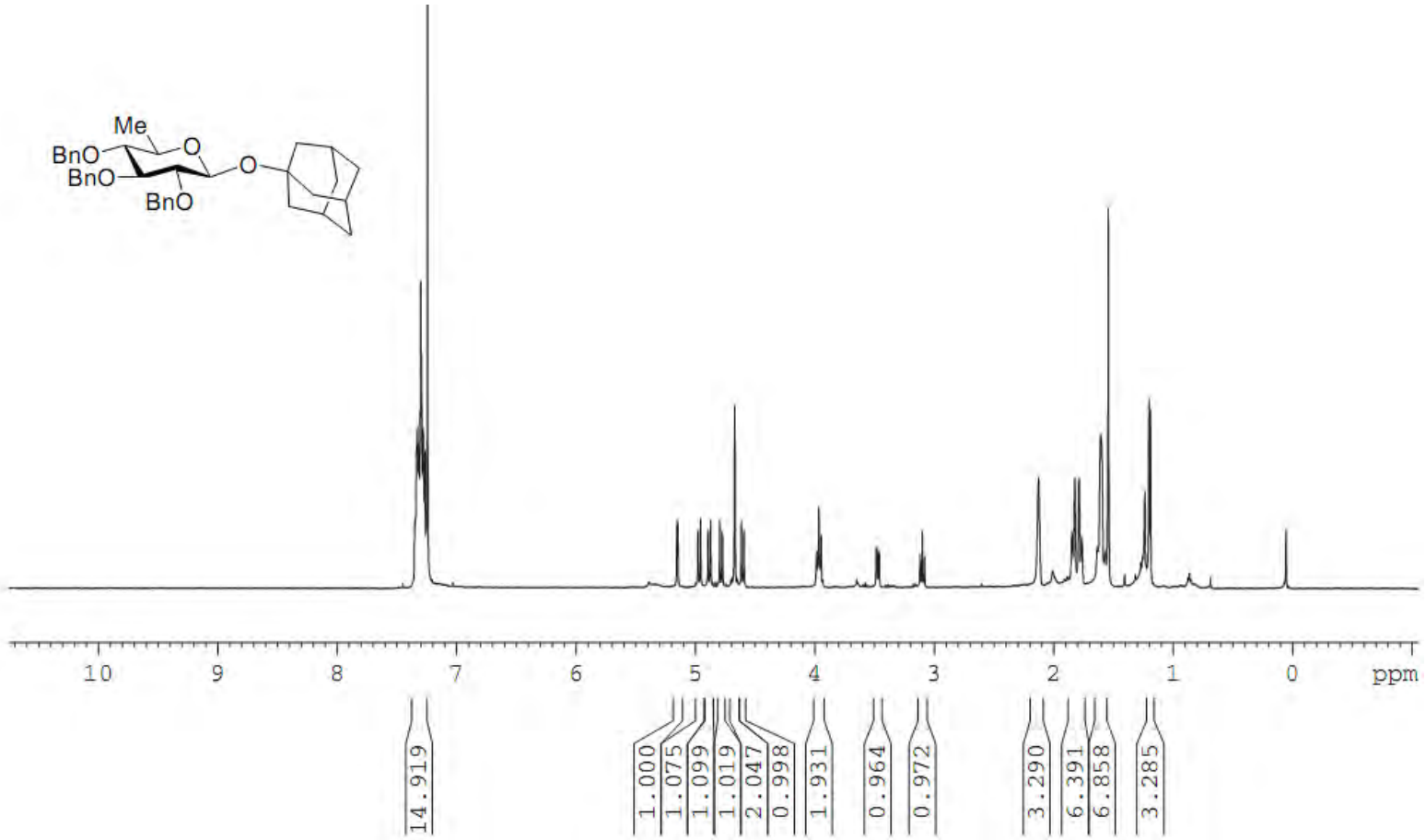


Figure A49. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **95**

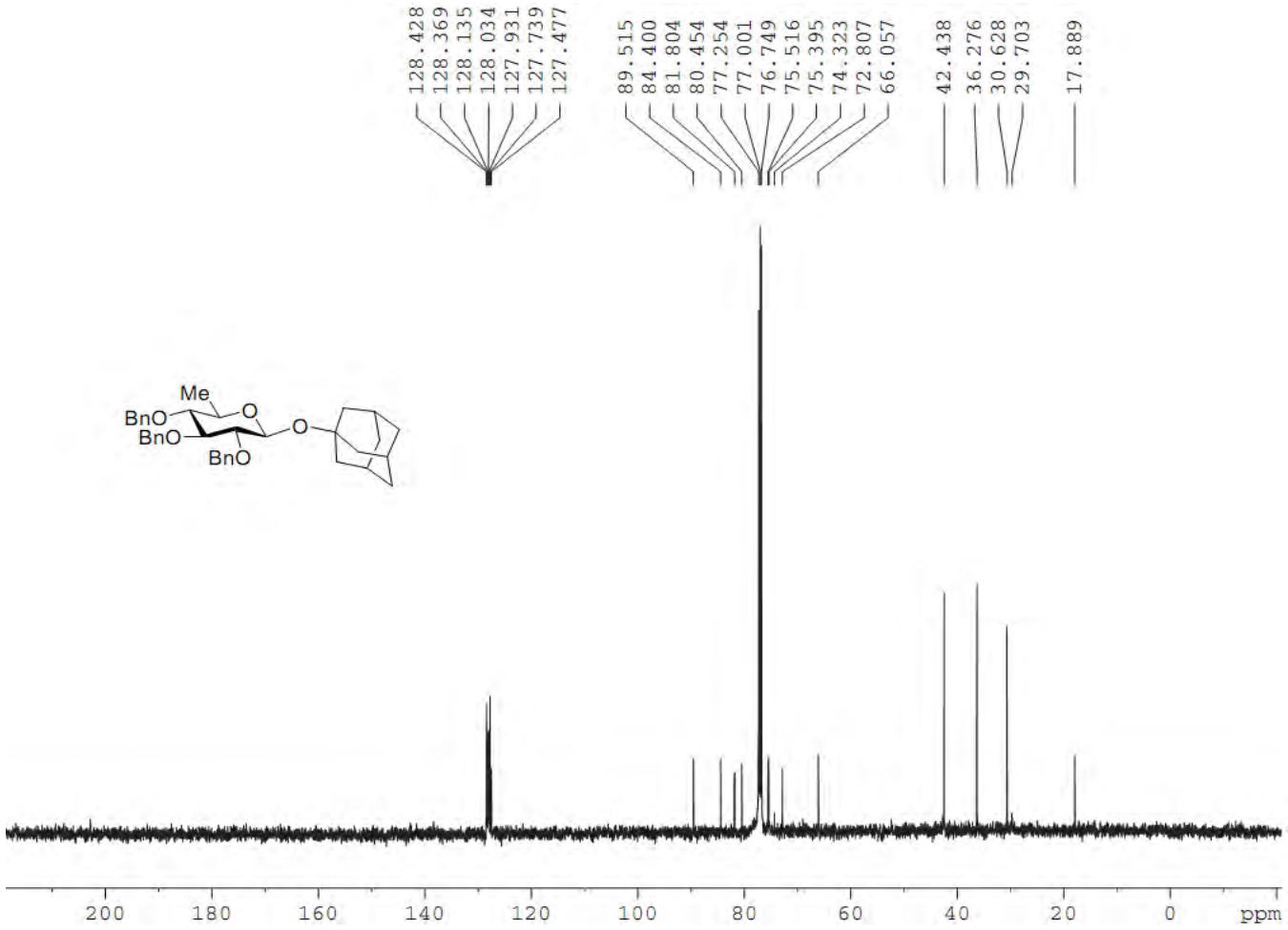


Figure A50. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **95**

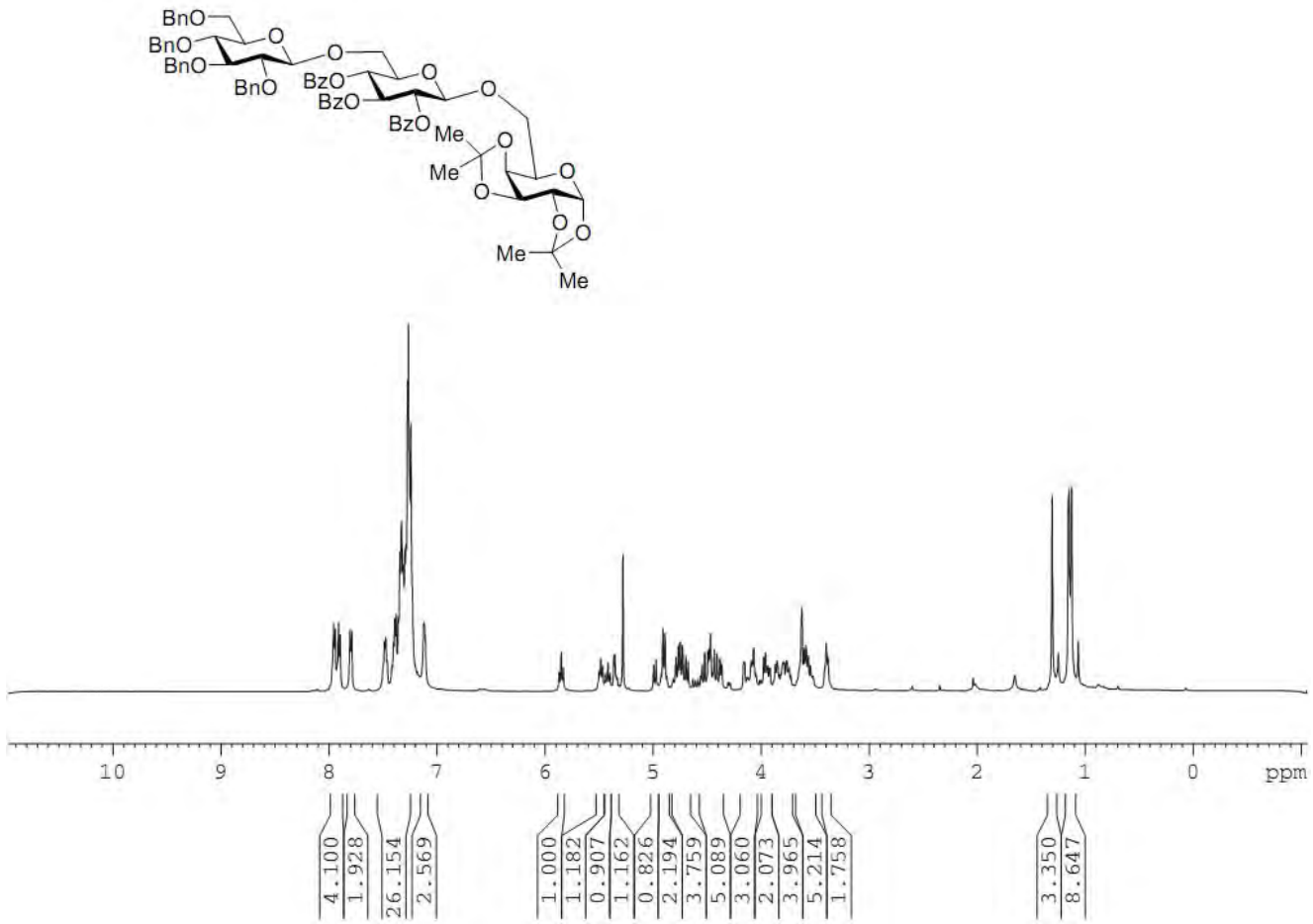


Figure A51. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **97**

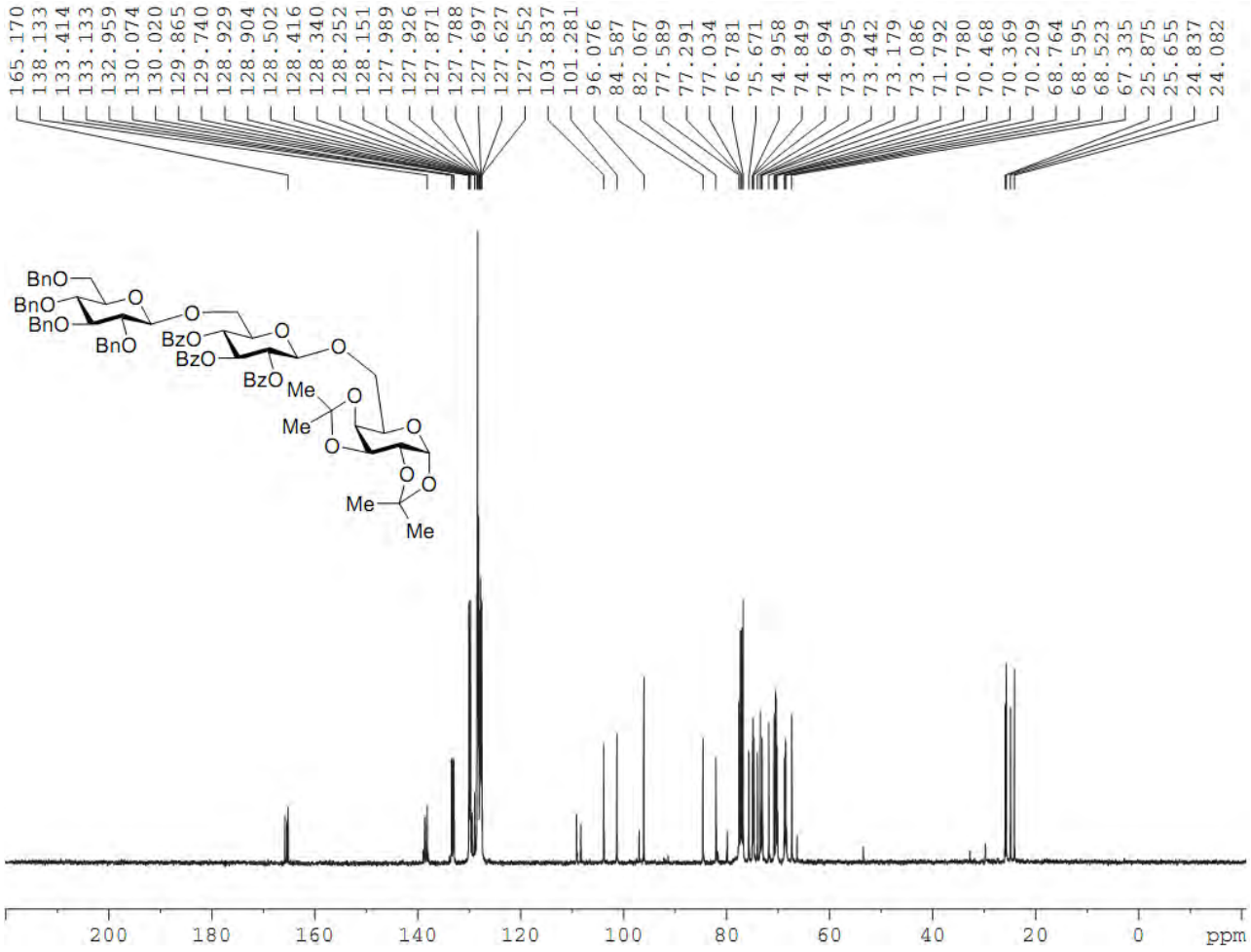


Figure A52. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **97**

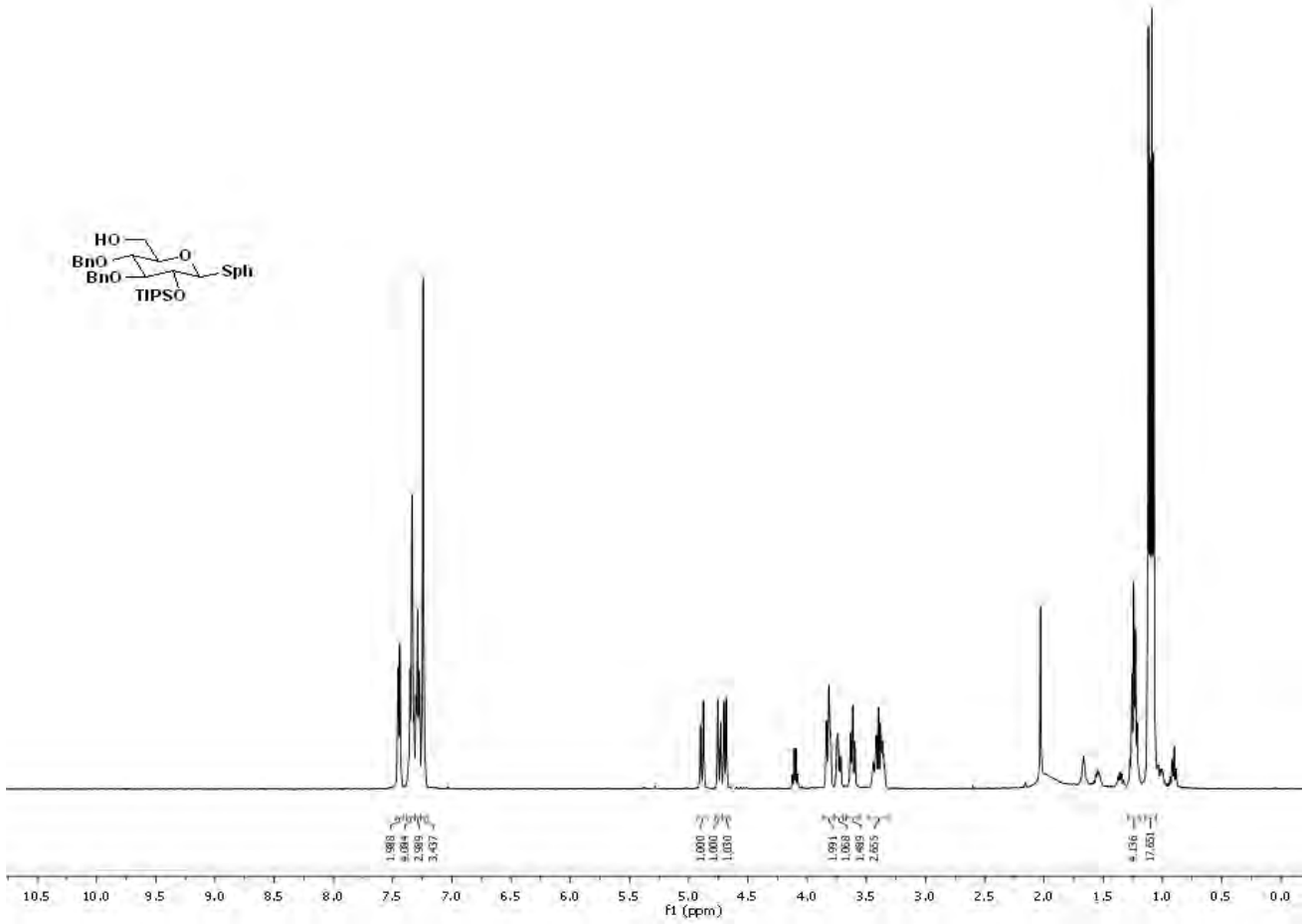


Figure 53A. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **100A**

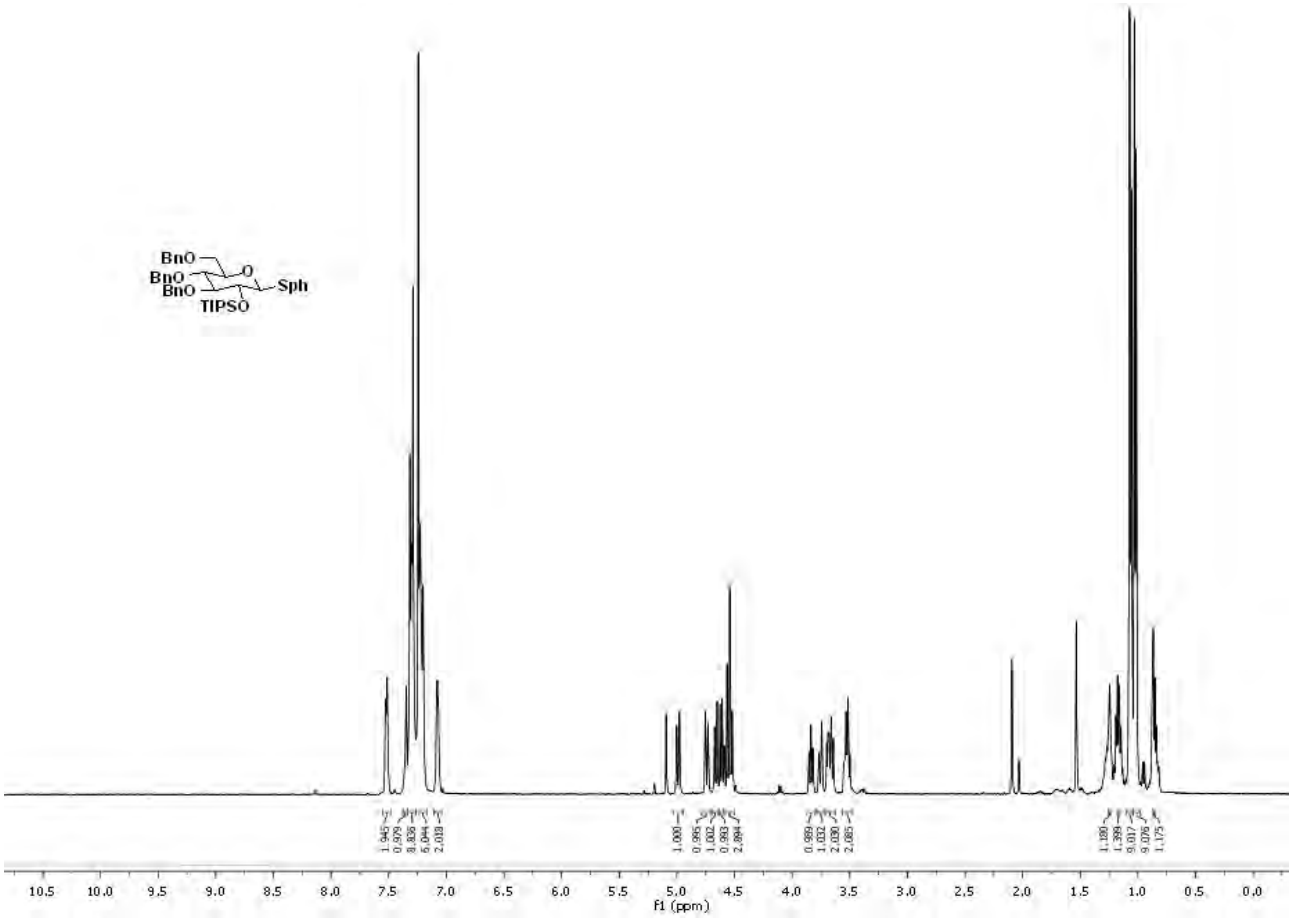


Figure A54. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **100B**

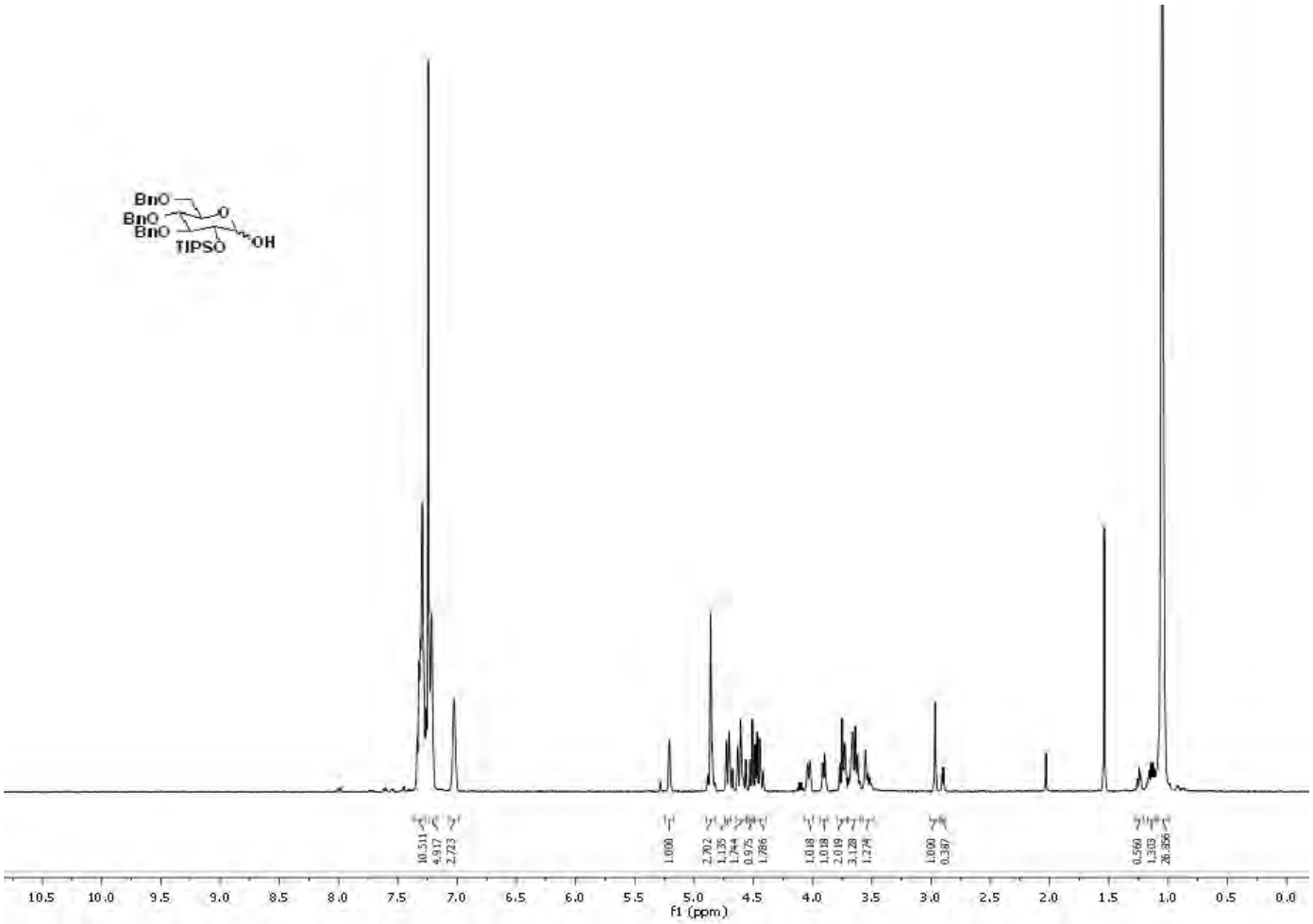


Figure A55. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **100C**

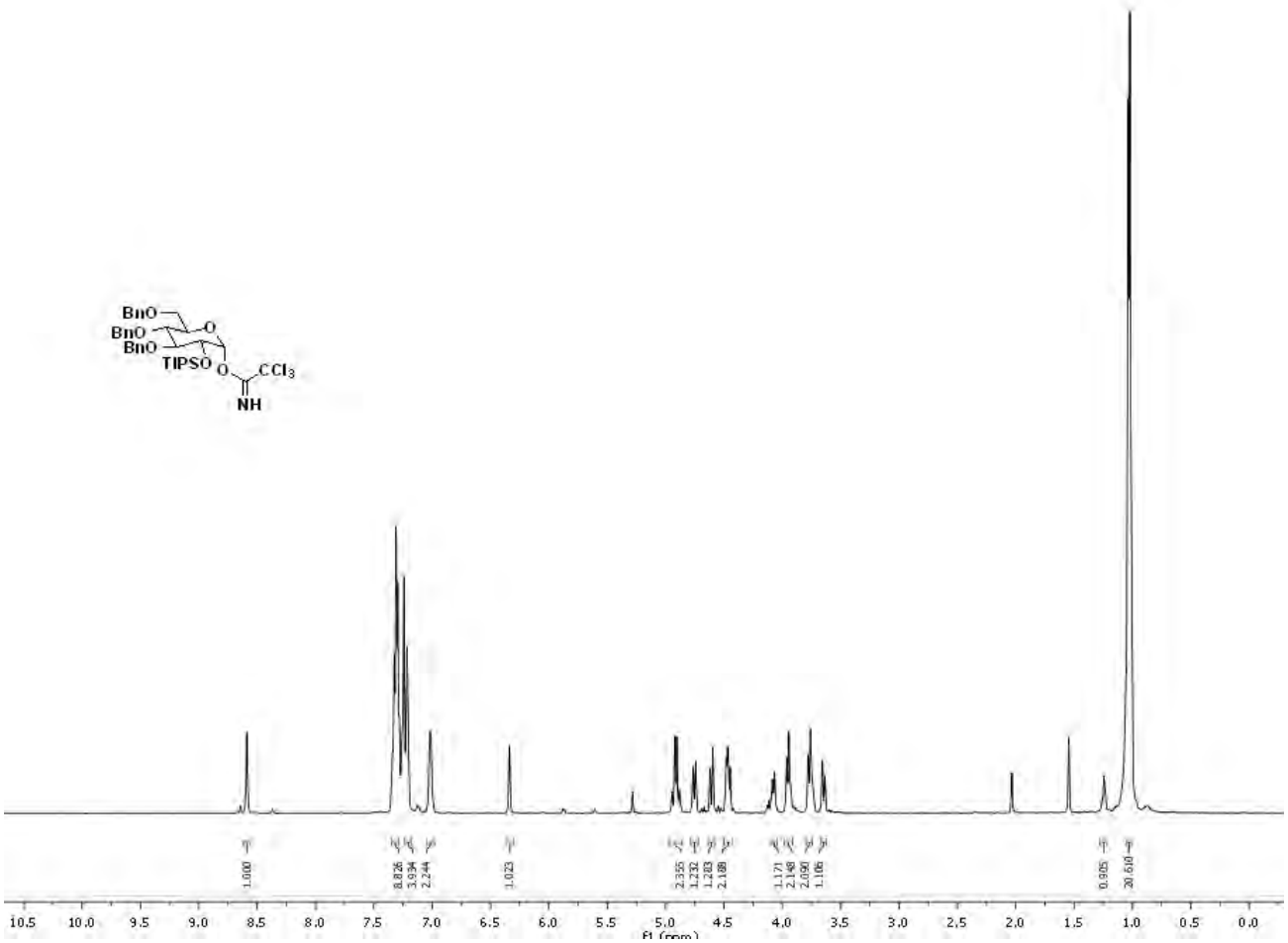


Figure A56. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **100**

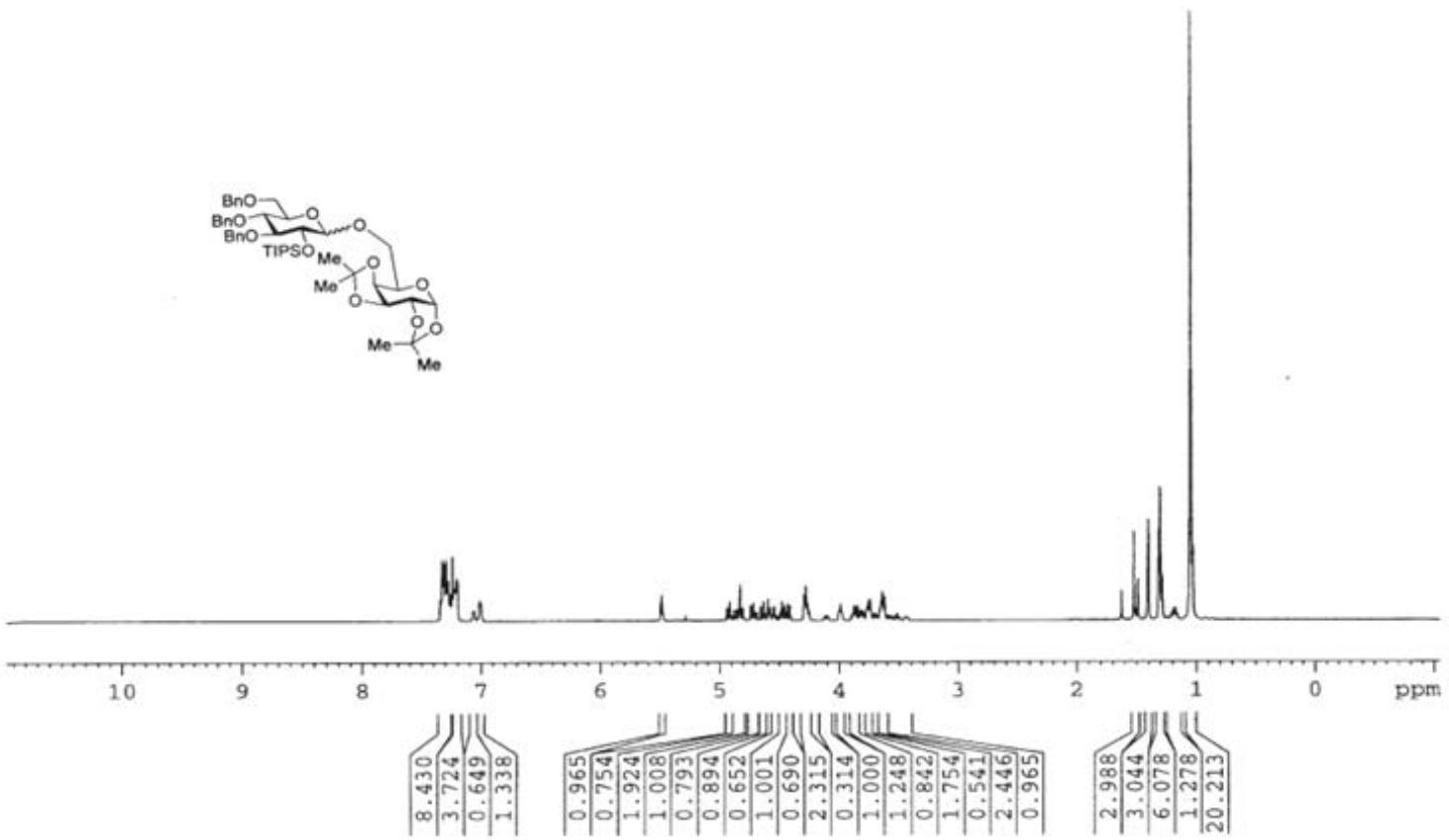


Figure A57. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **101**

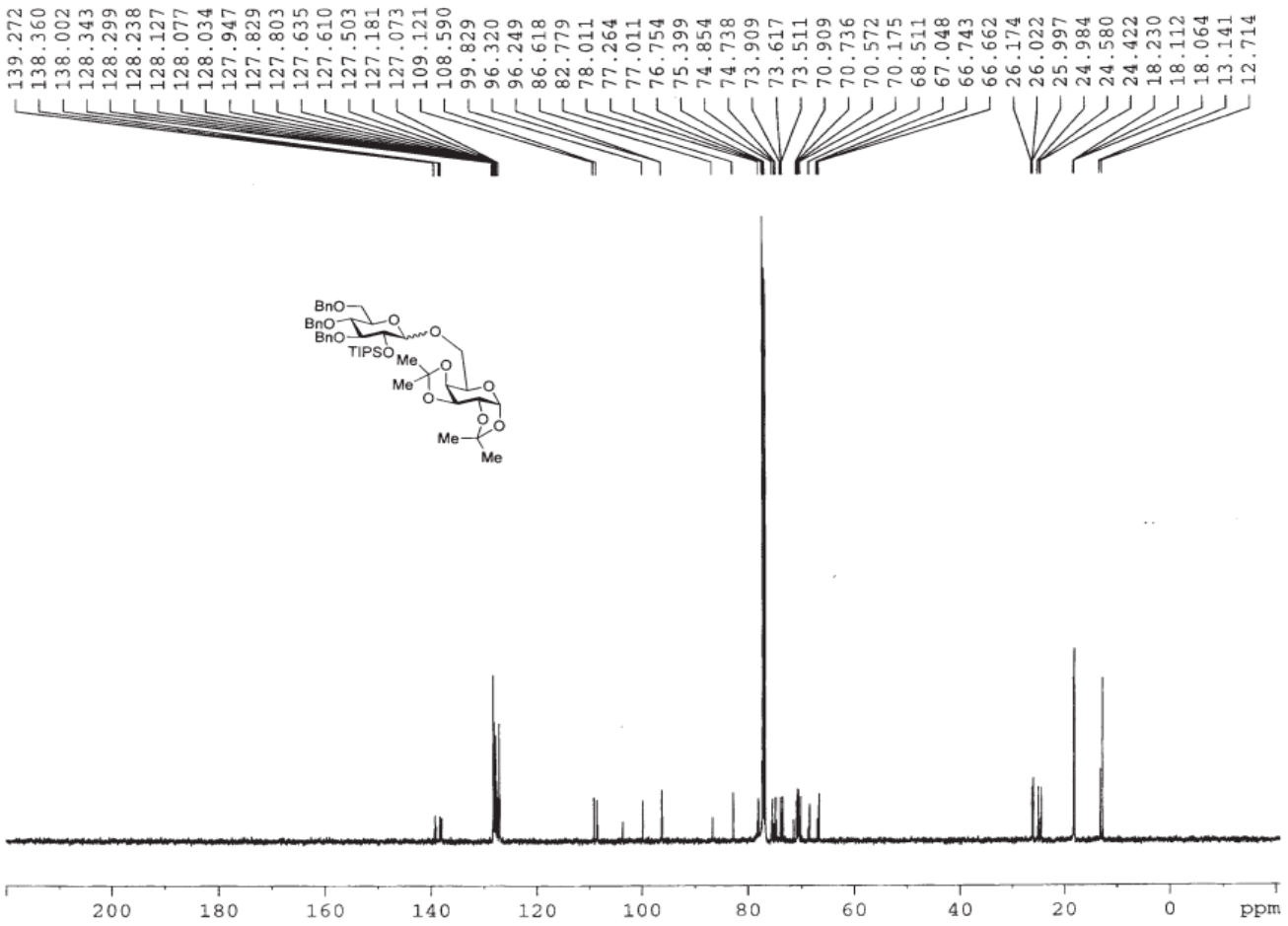


Figure A58. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **101**

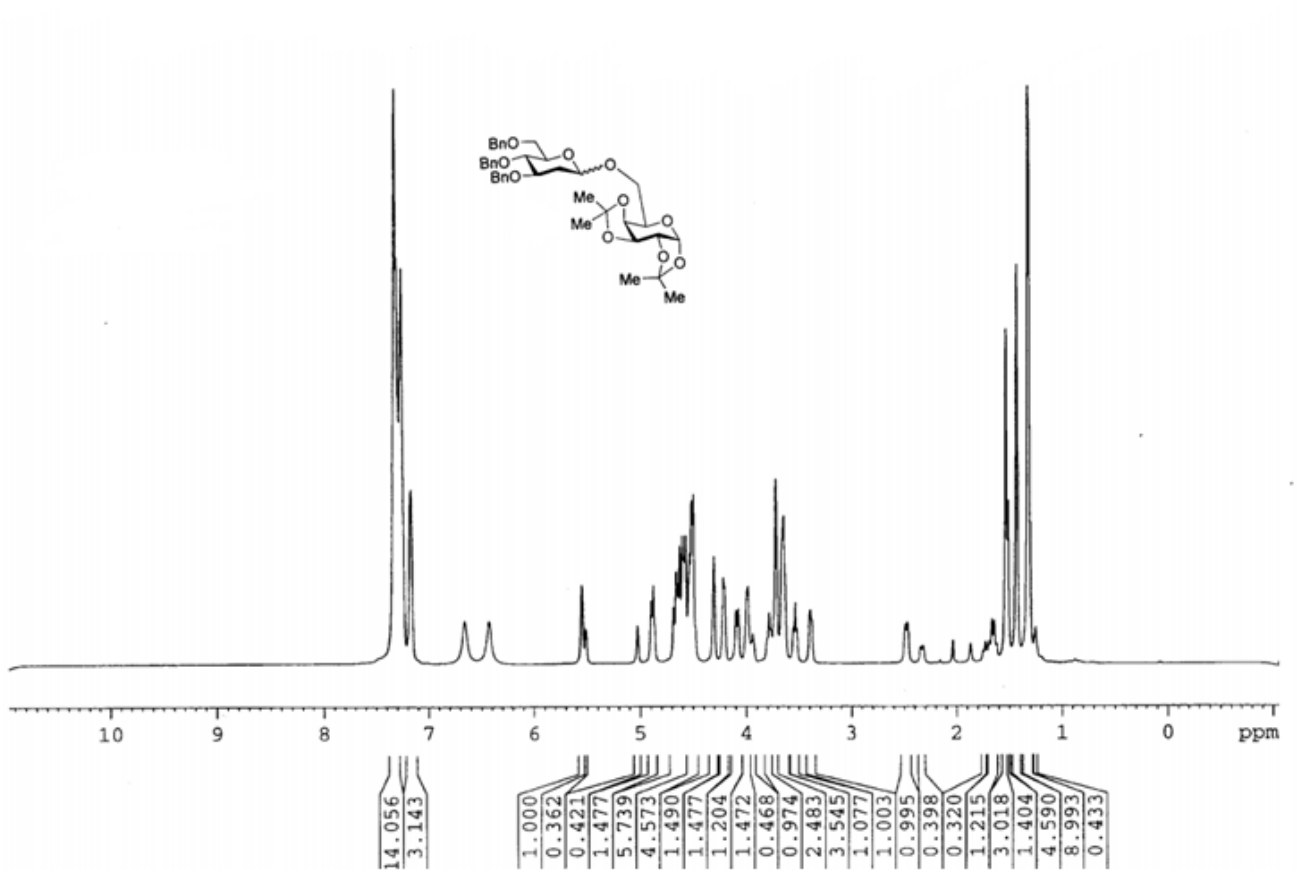


Figure A59. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **103**

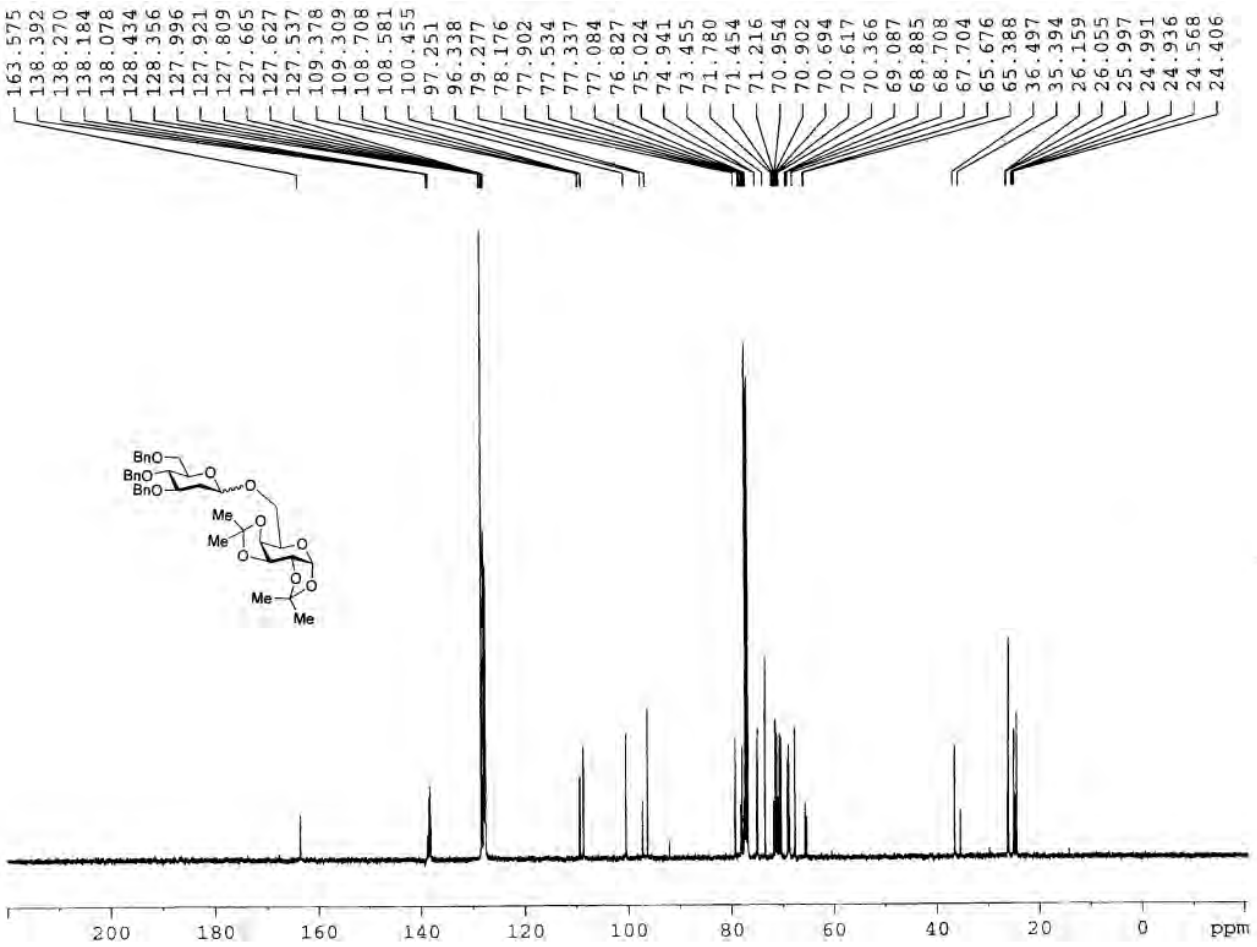


Figure A60. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **103**

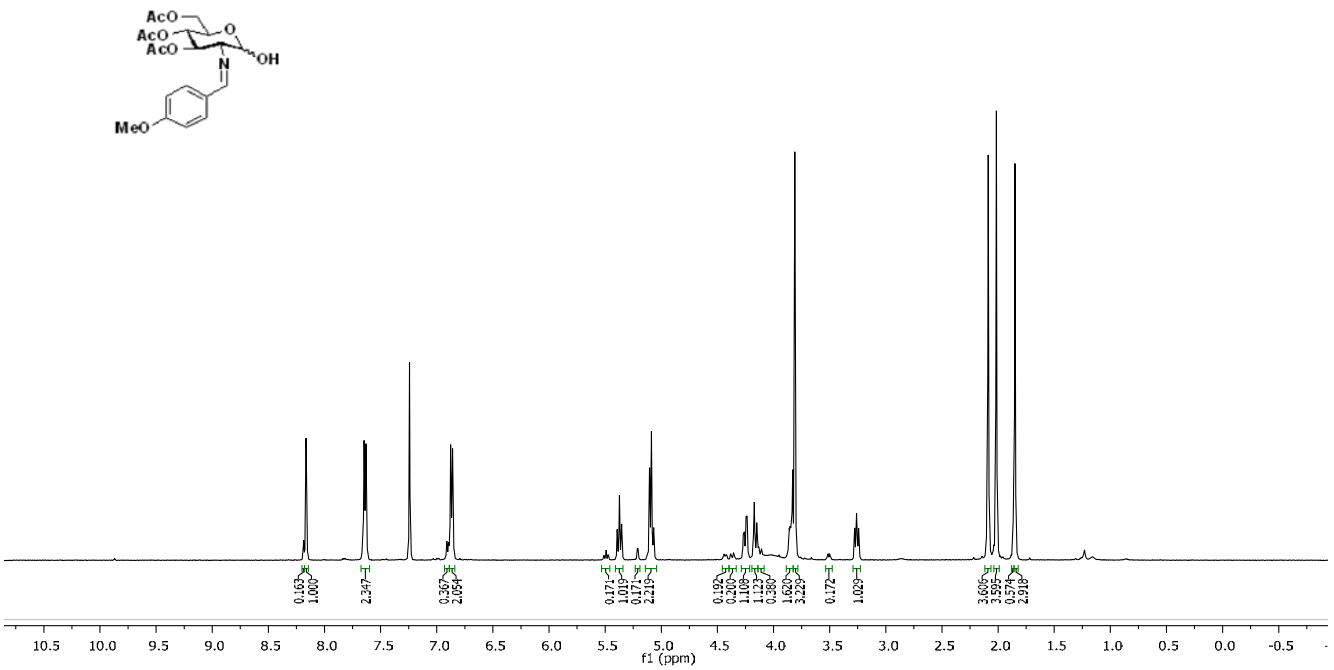


Figure A61. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **124**

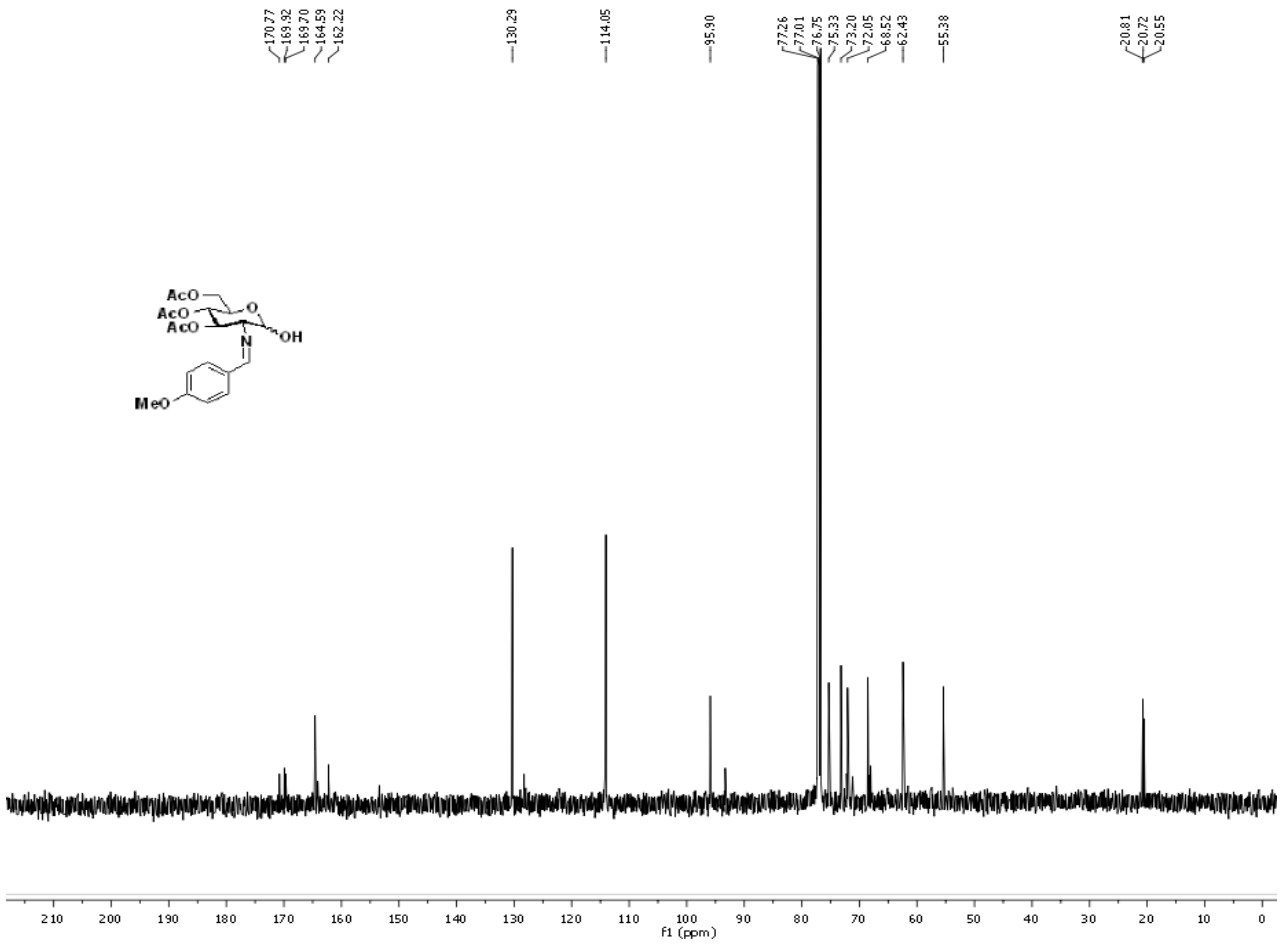


Figure A62. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **124**

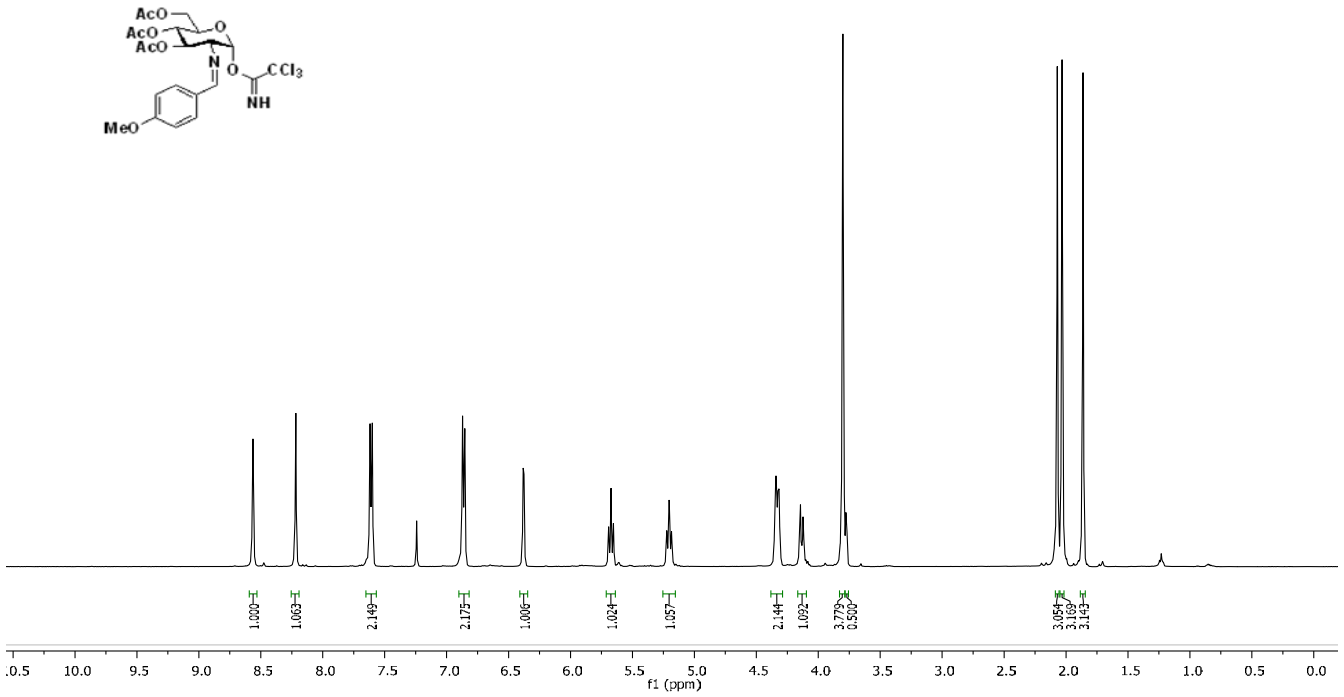


Figure A63. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **125**

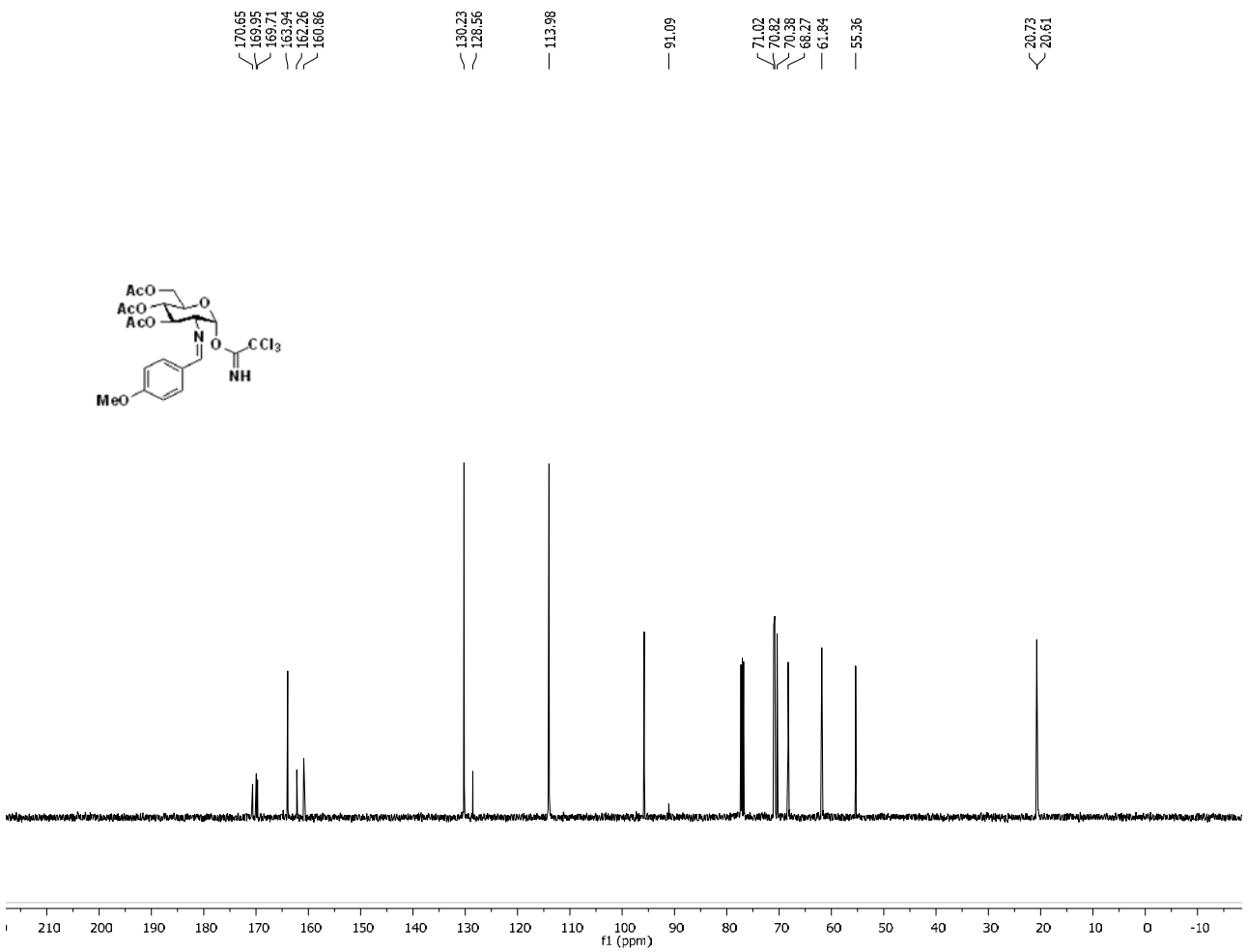


Figure A64. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **125**

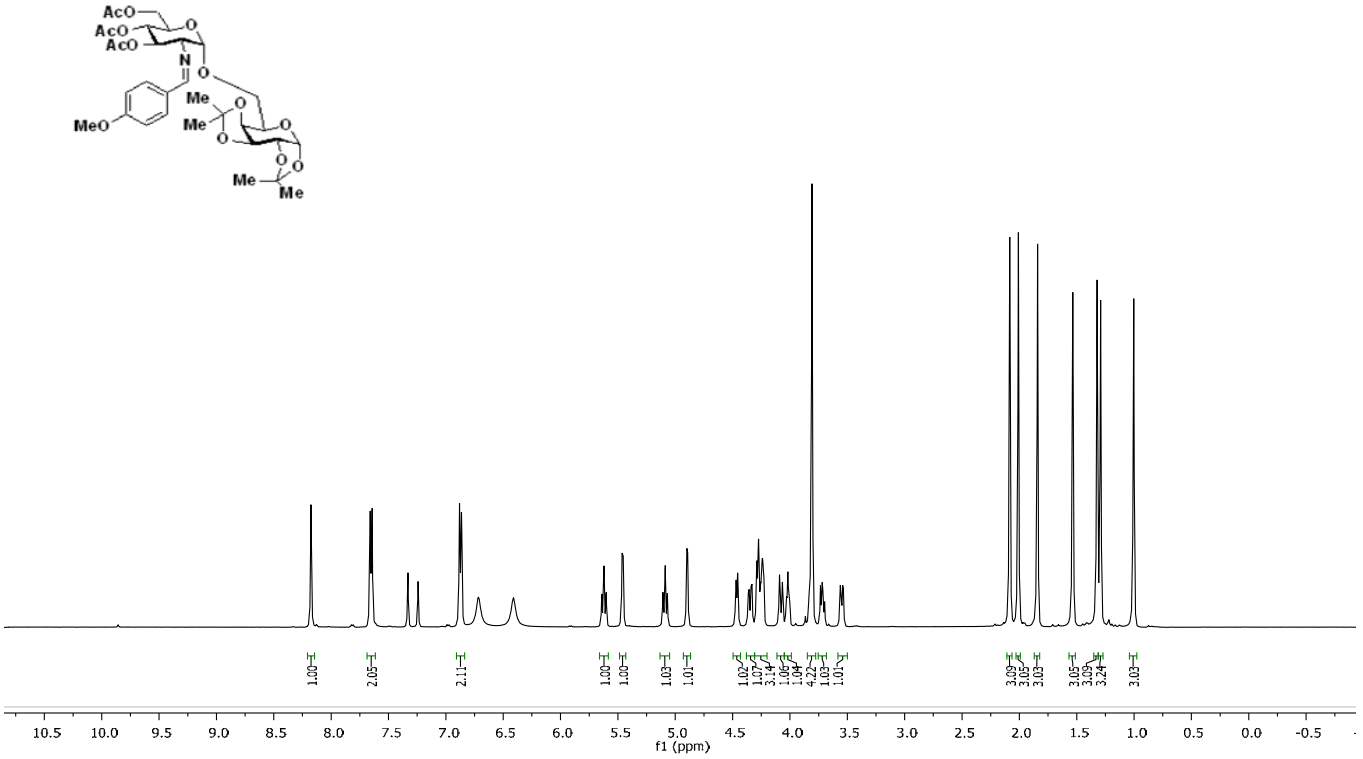


Figure A65. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **126**

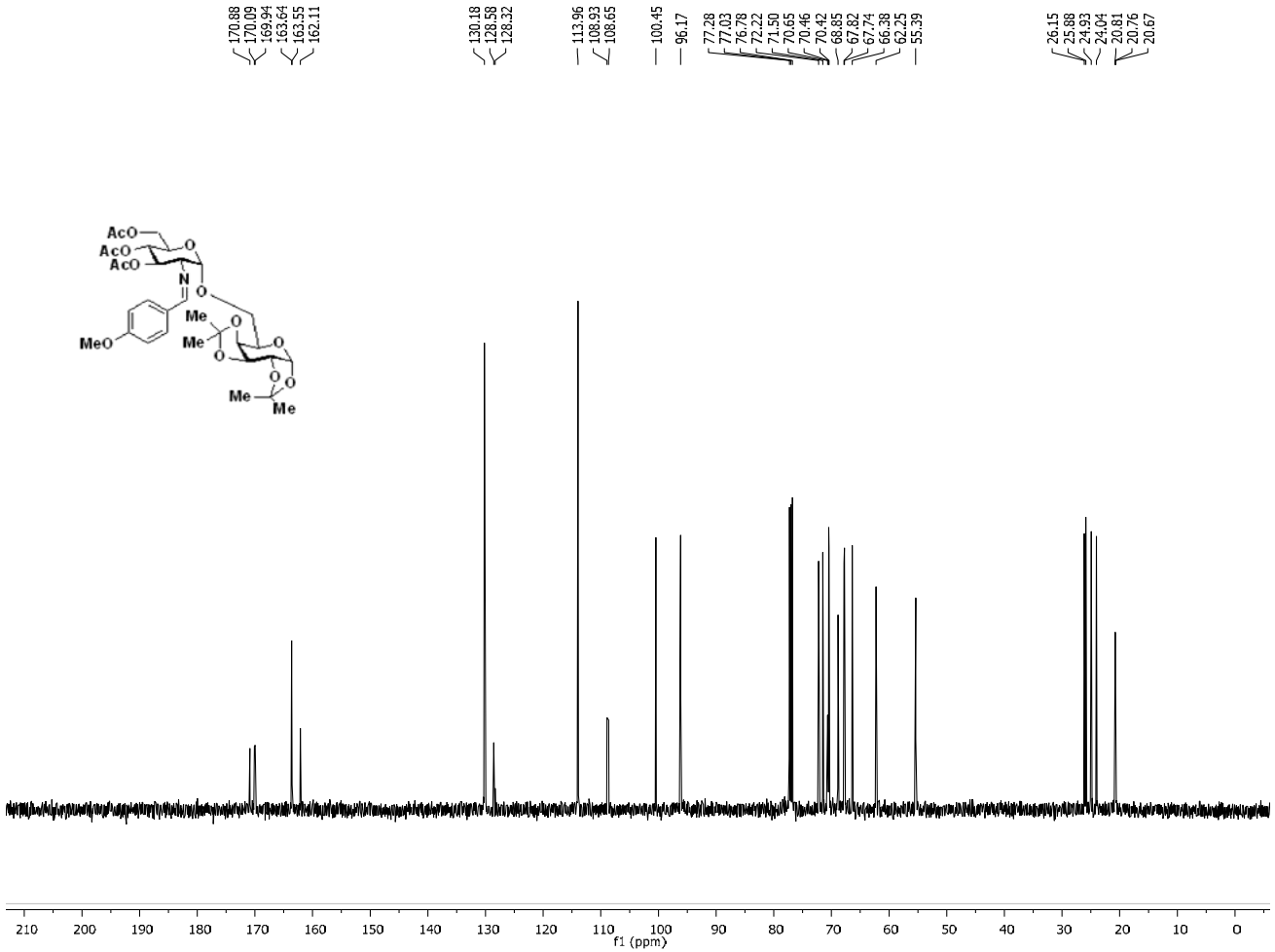


Figure A66. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **126**

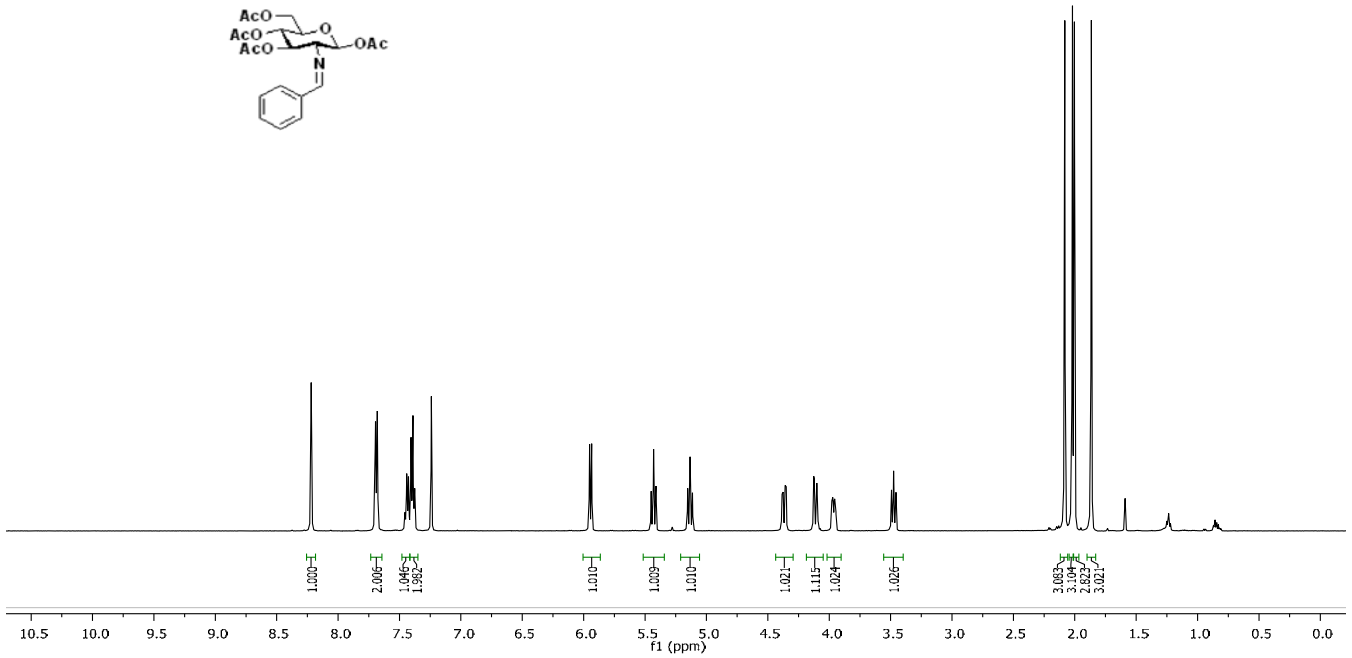


Figure A67. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **127**

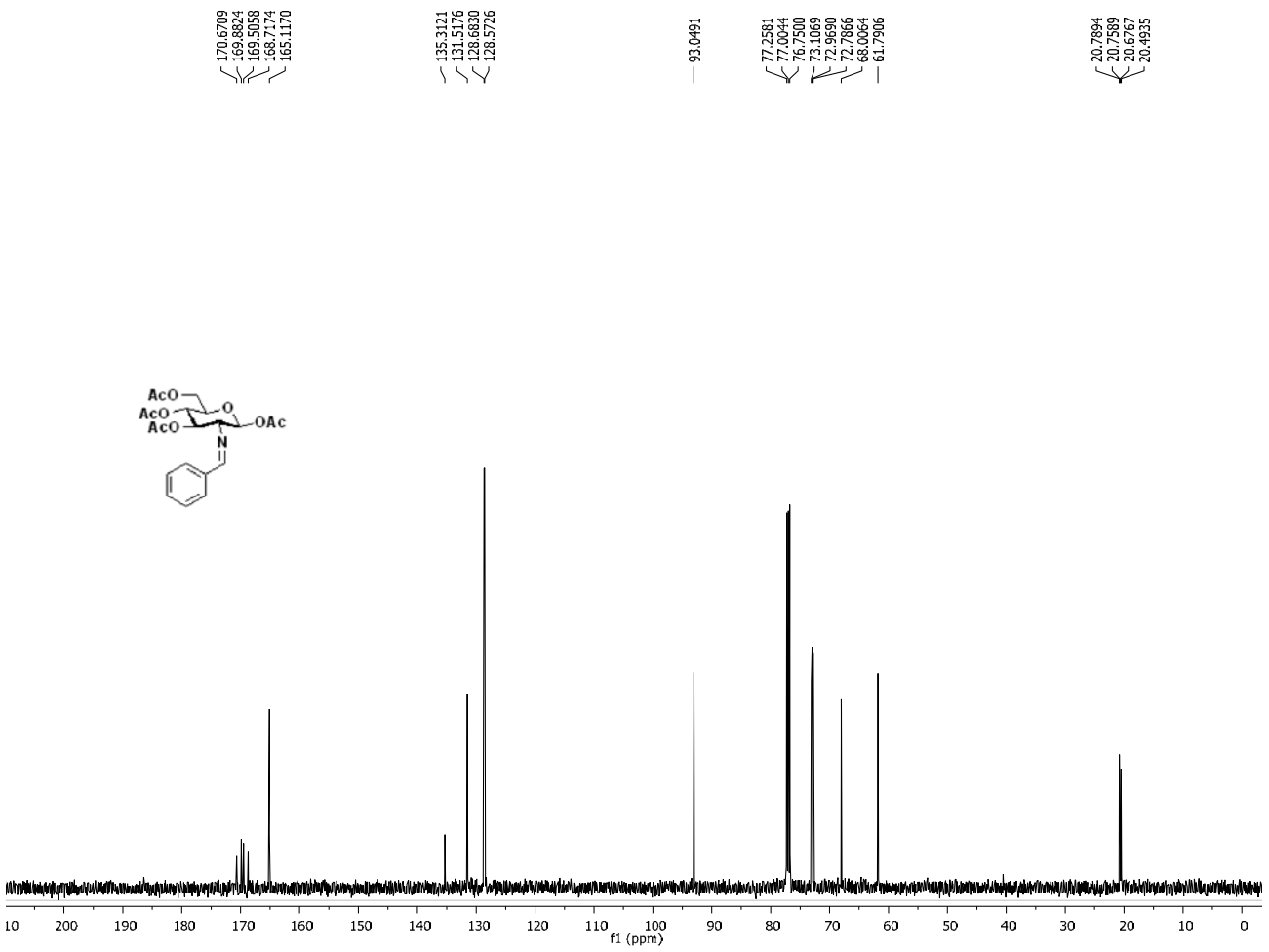


Figure A68. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **127**

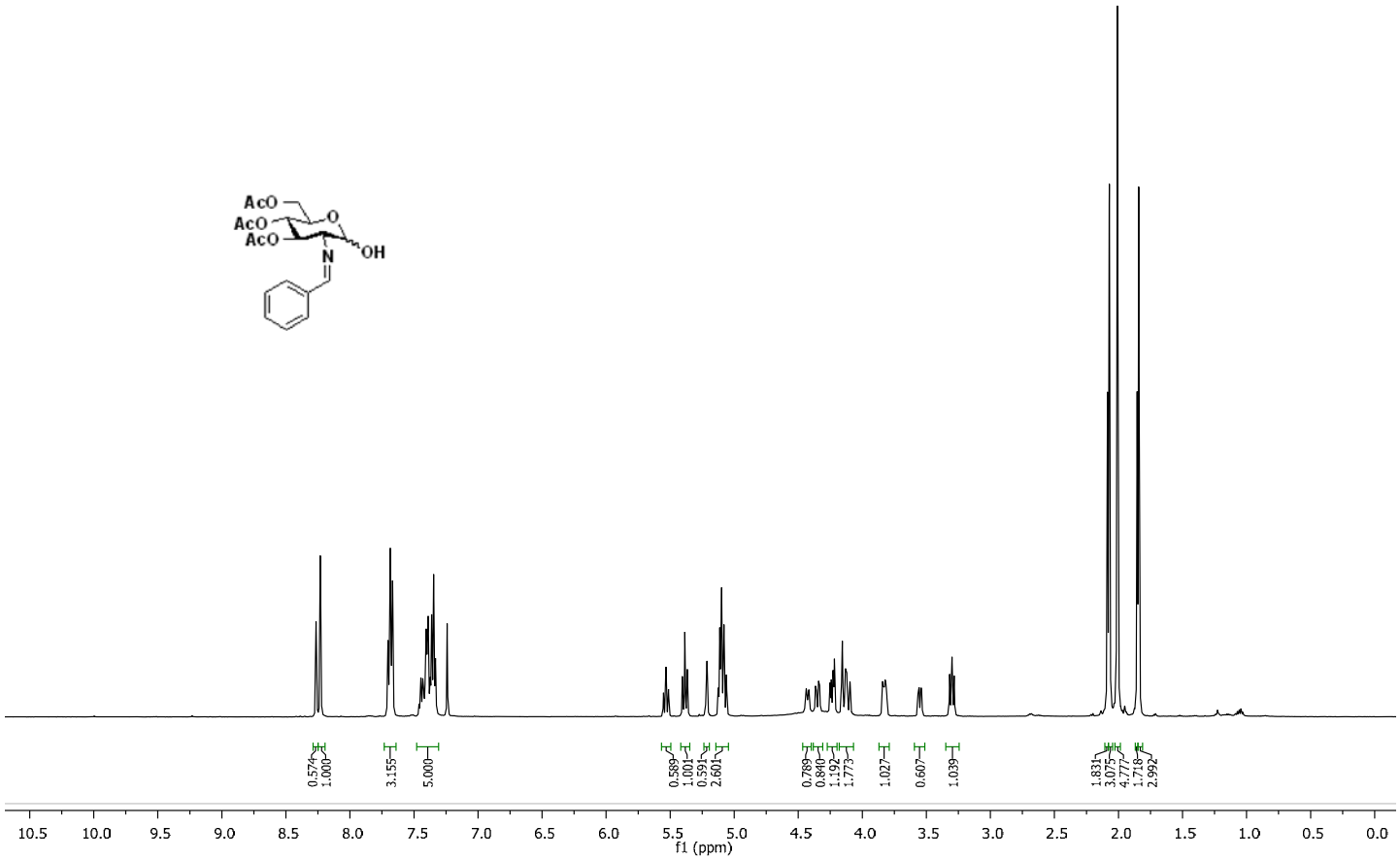


Figure A69. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **128**

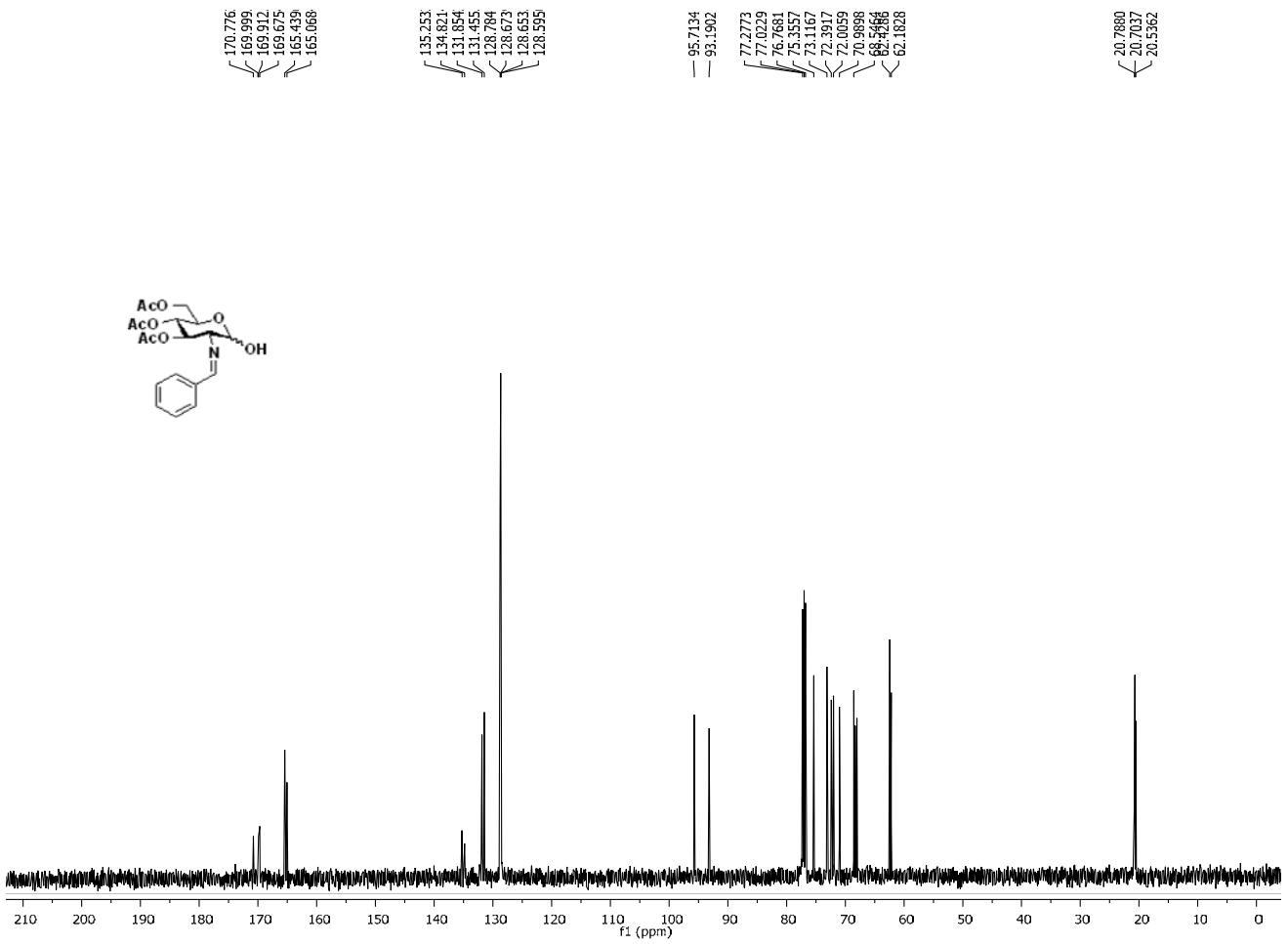


Figure A70. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **128**

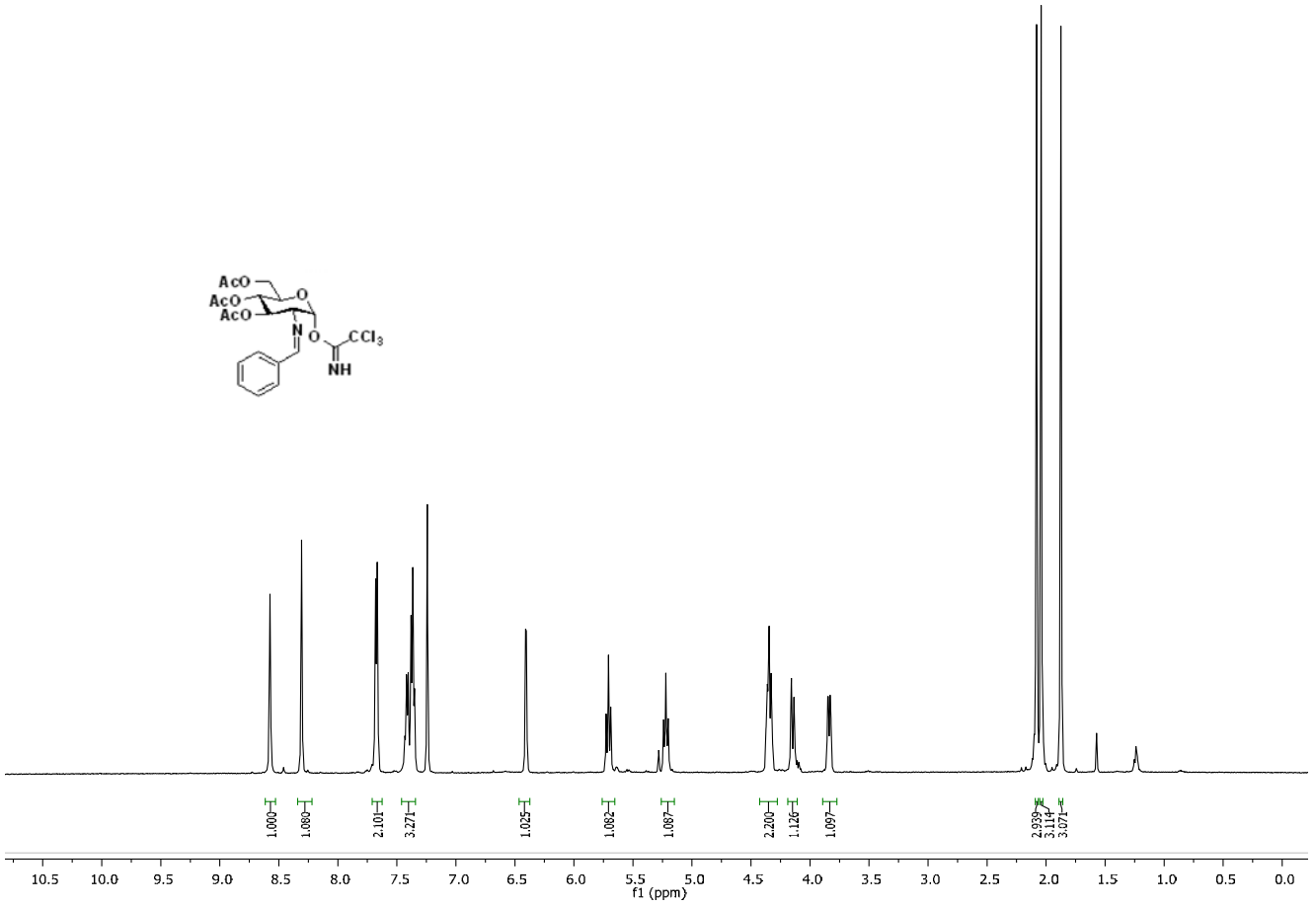


Figure A71. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **129**

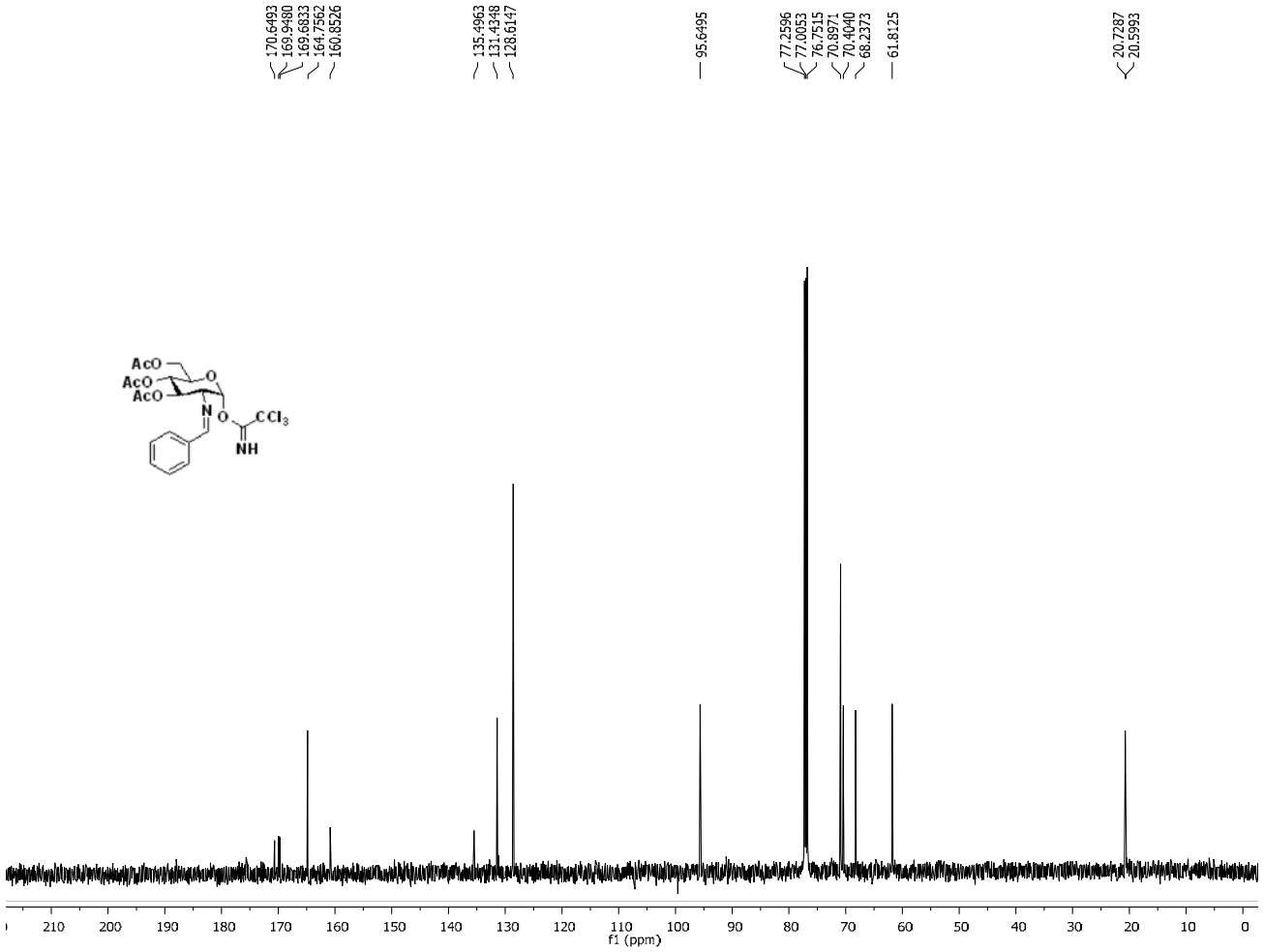


Figure A72. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **129**

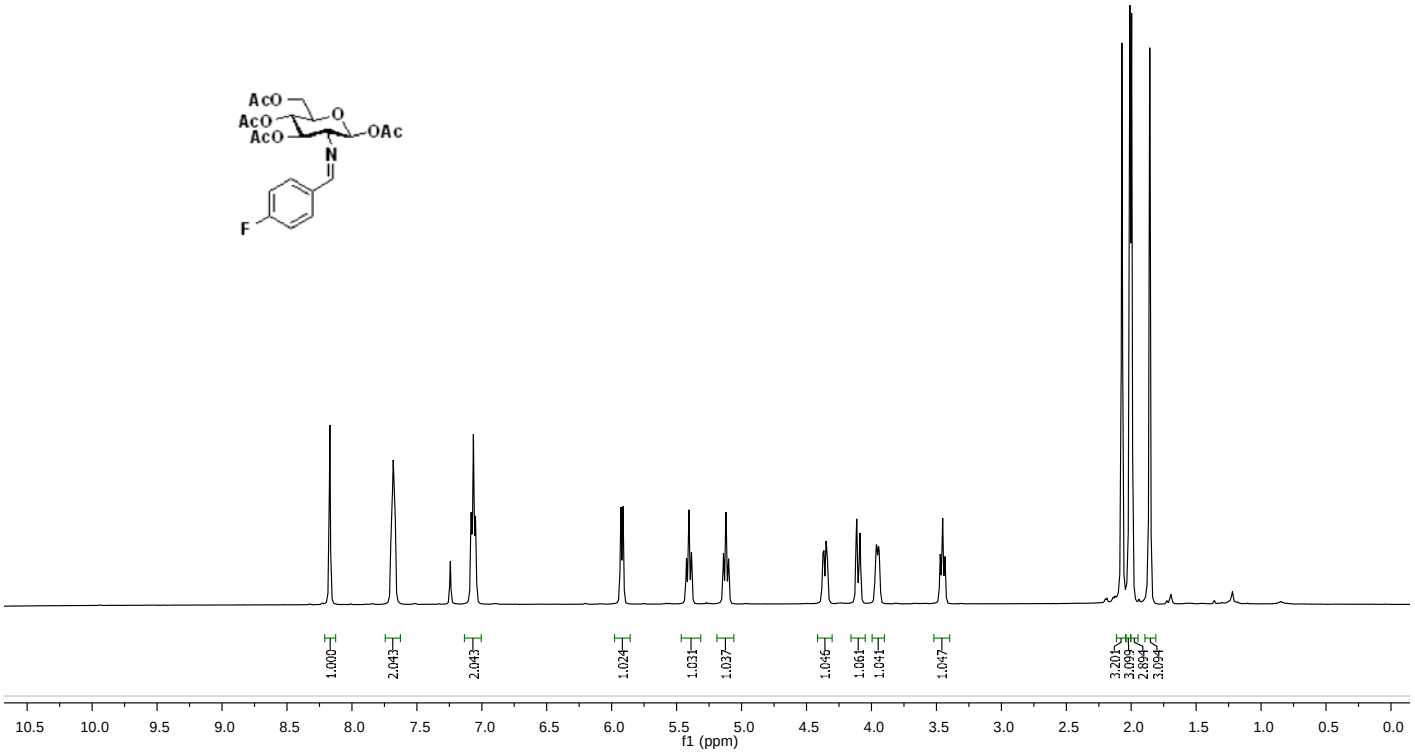


Figure A73. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **131**

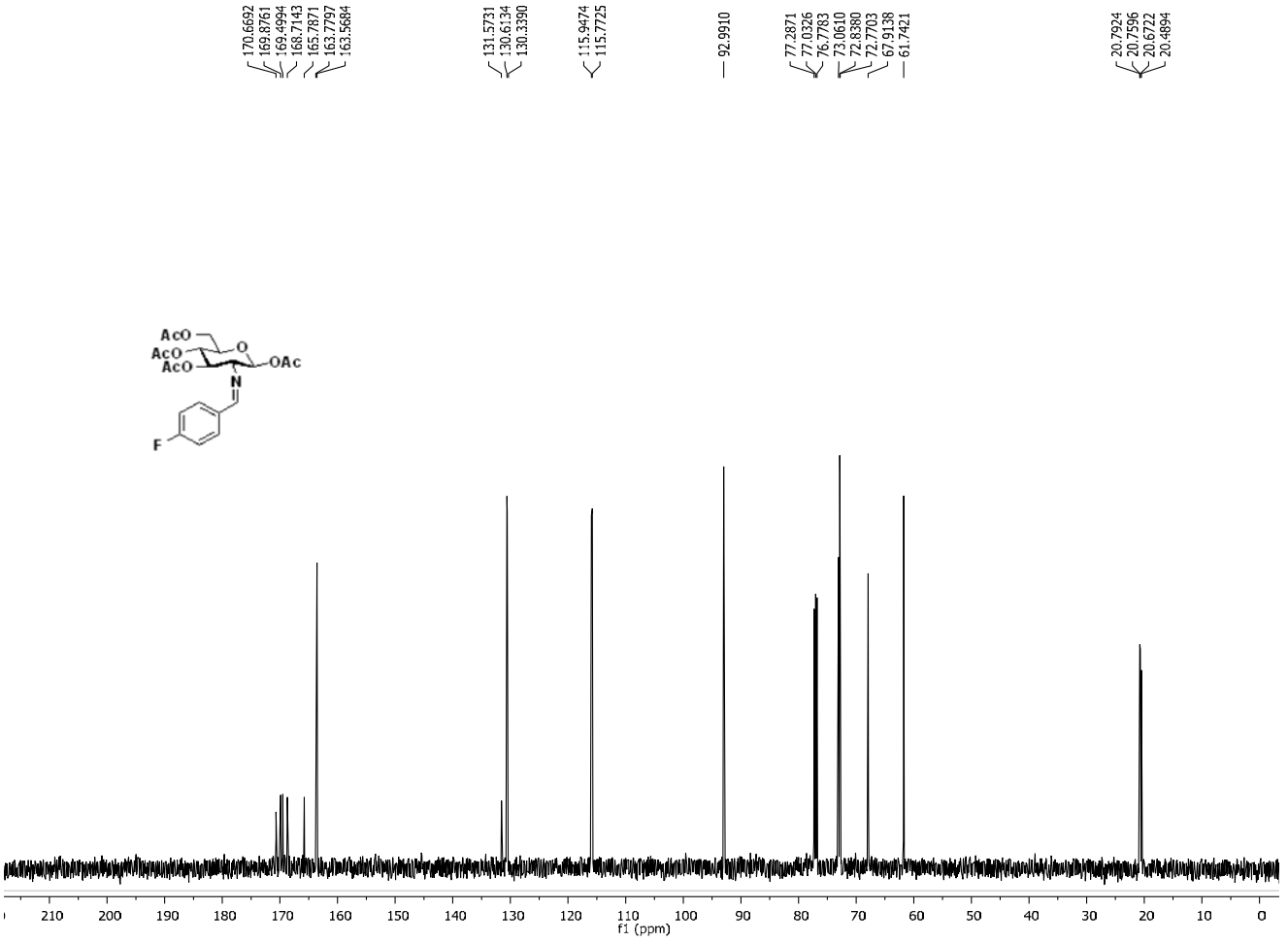


Figure A74. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **131**

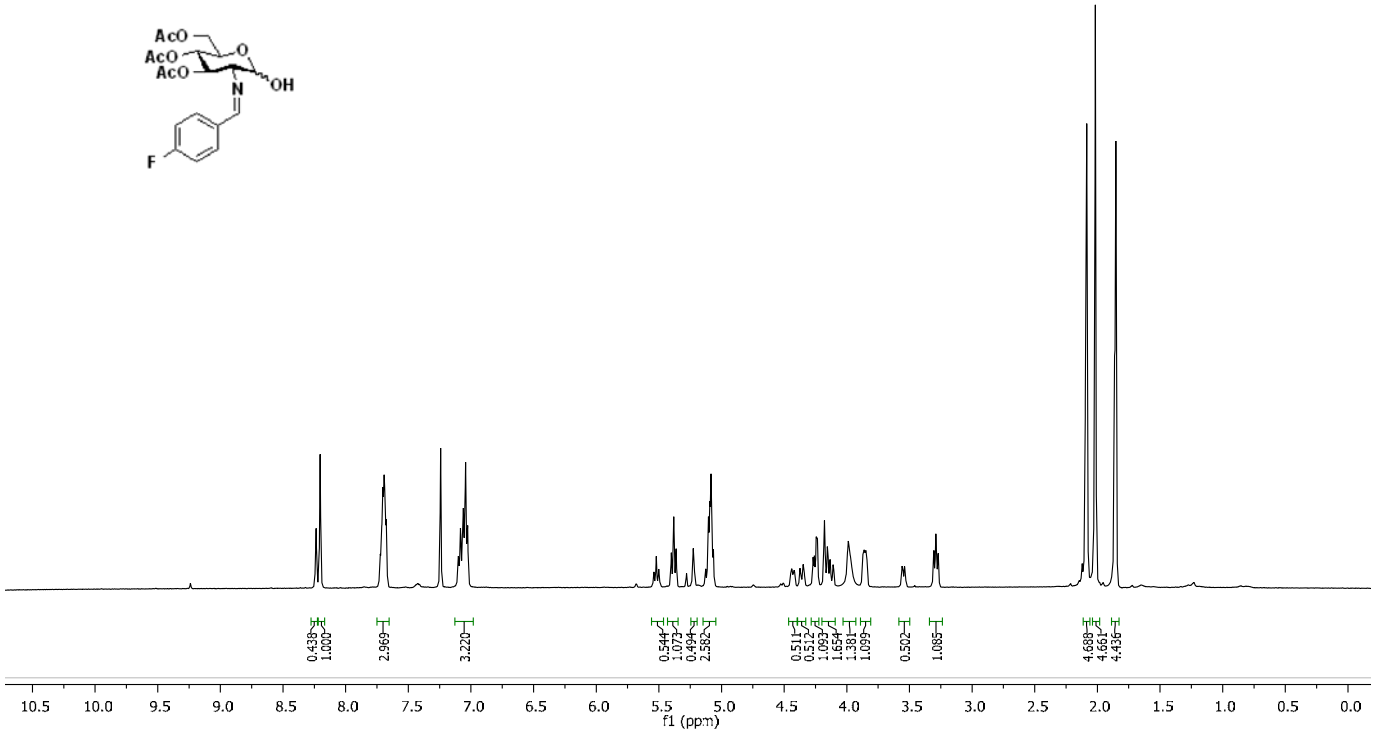


Figure A75. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **132**

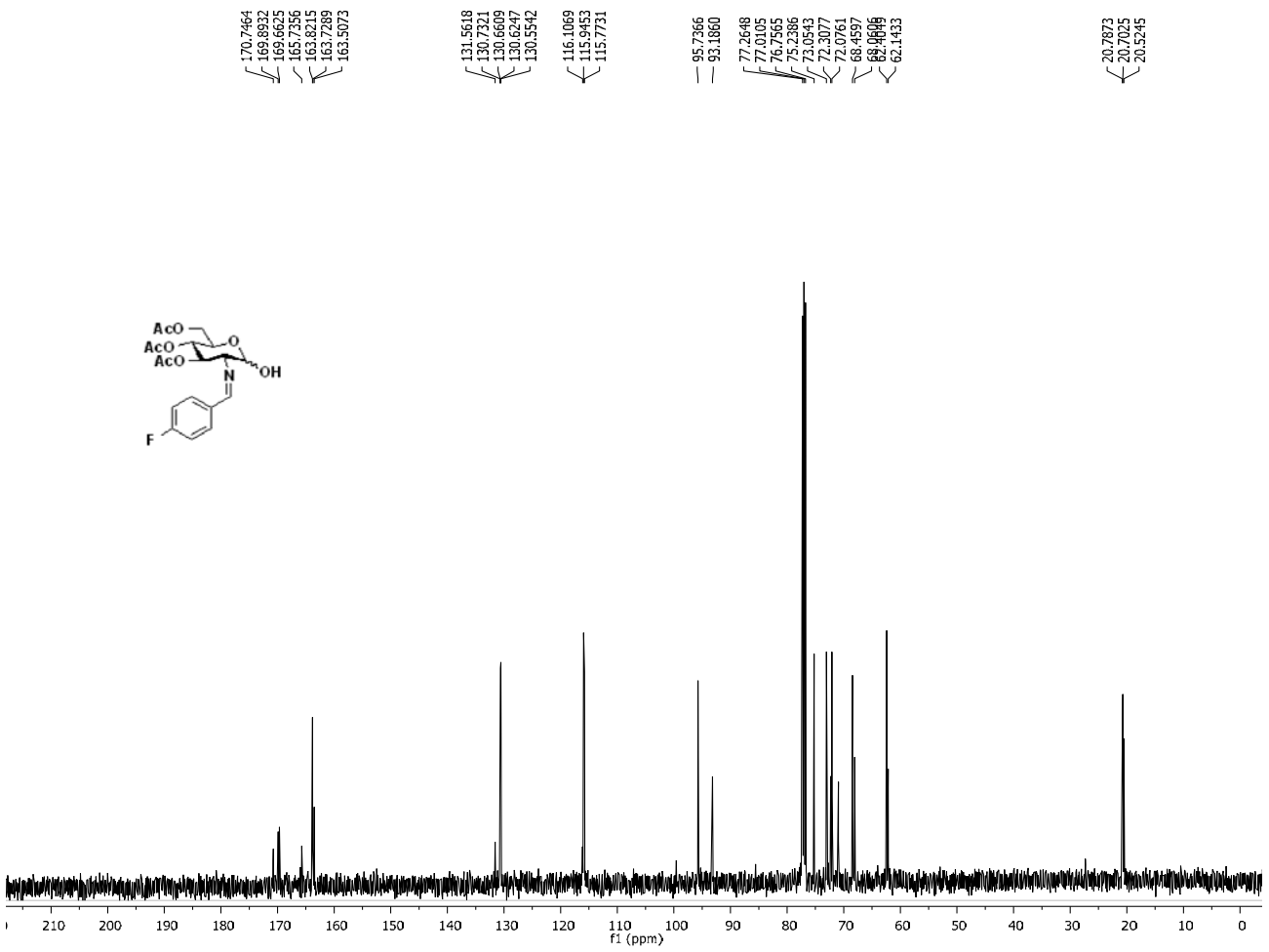


Figure A76. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **132**

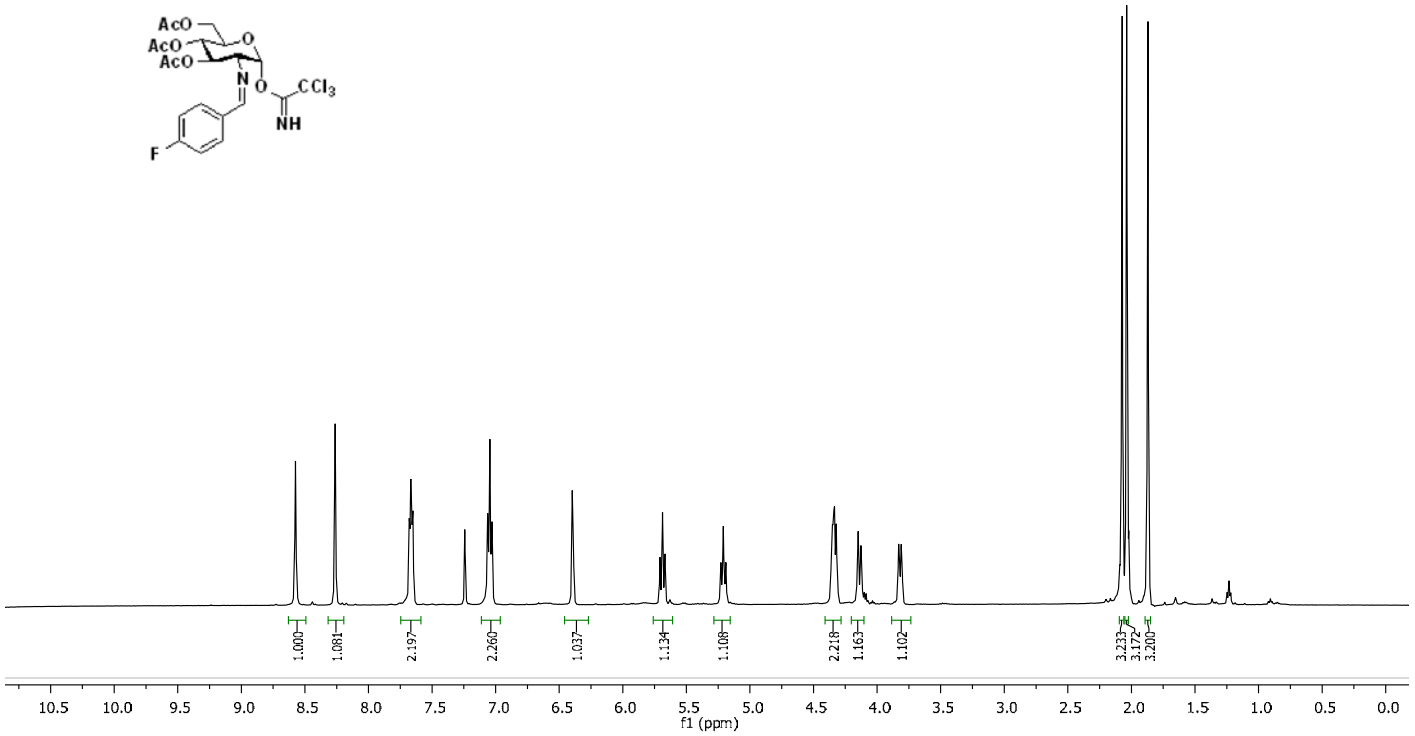


Figure A77. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **133**

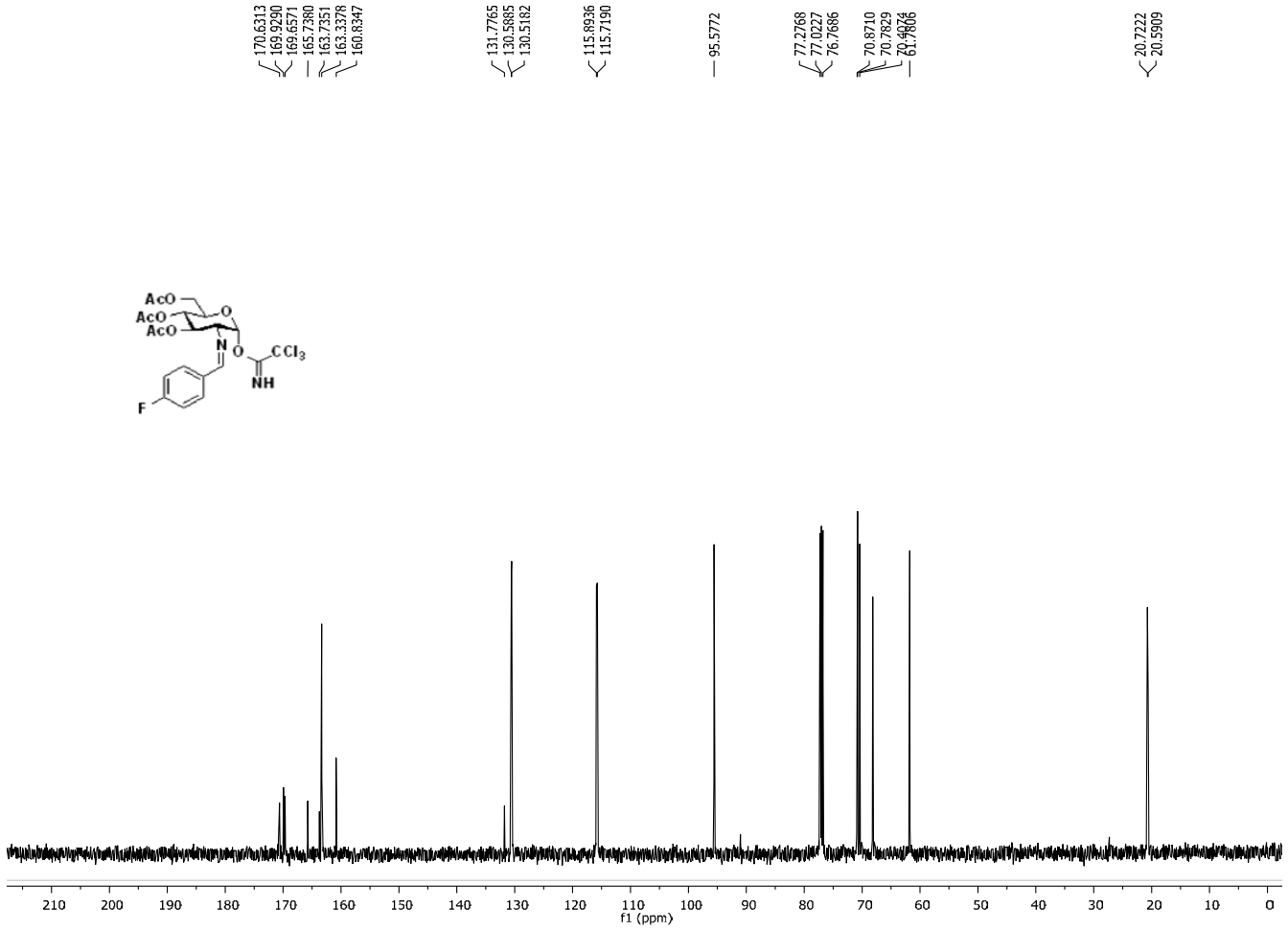


Figure A78. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **133**

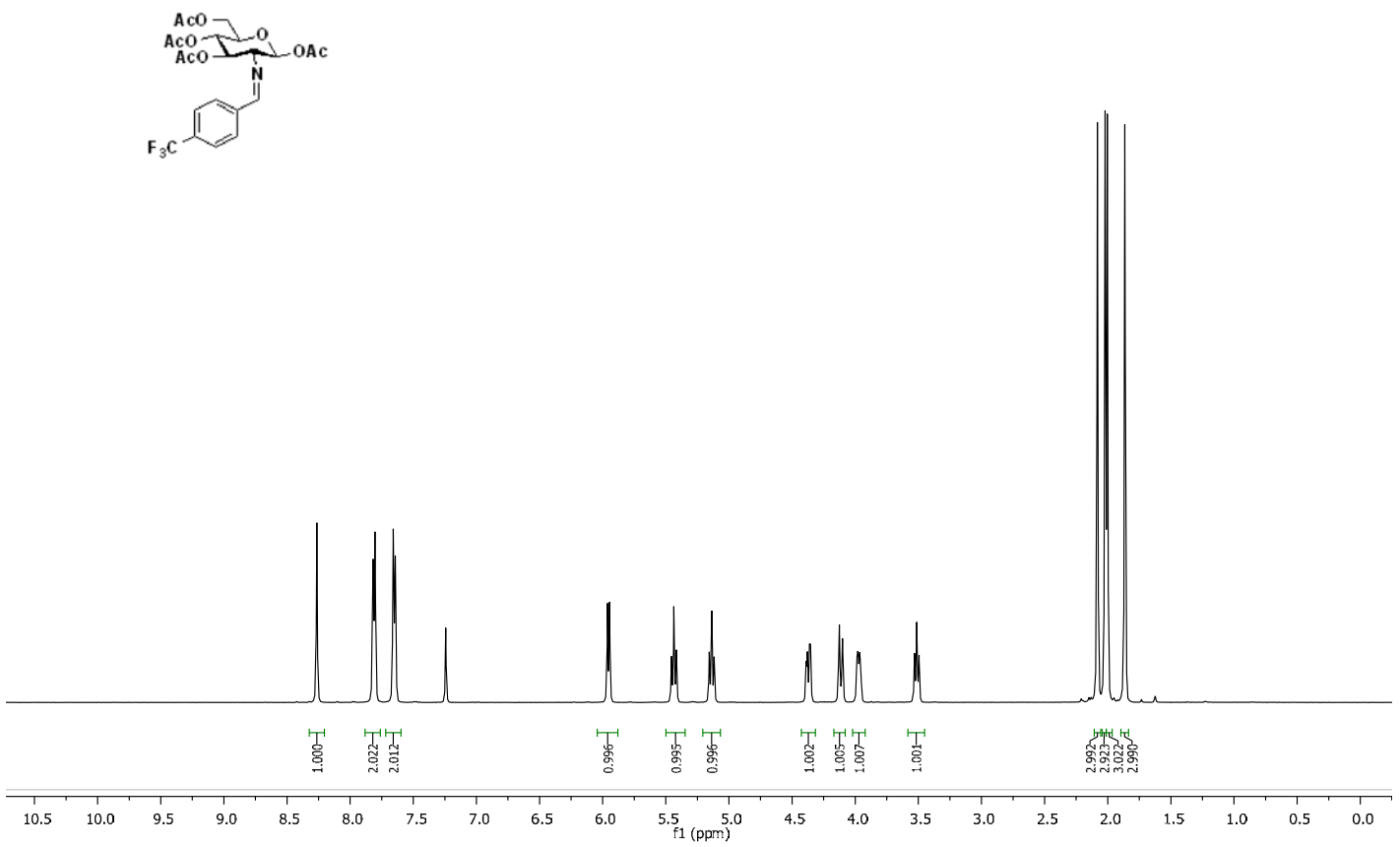


Figure A79. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **134**

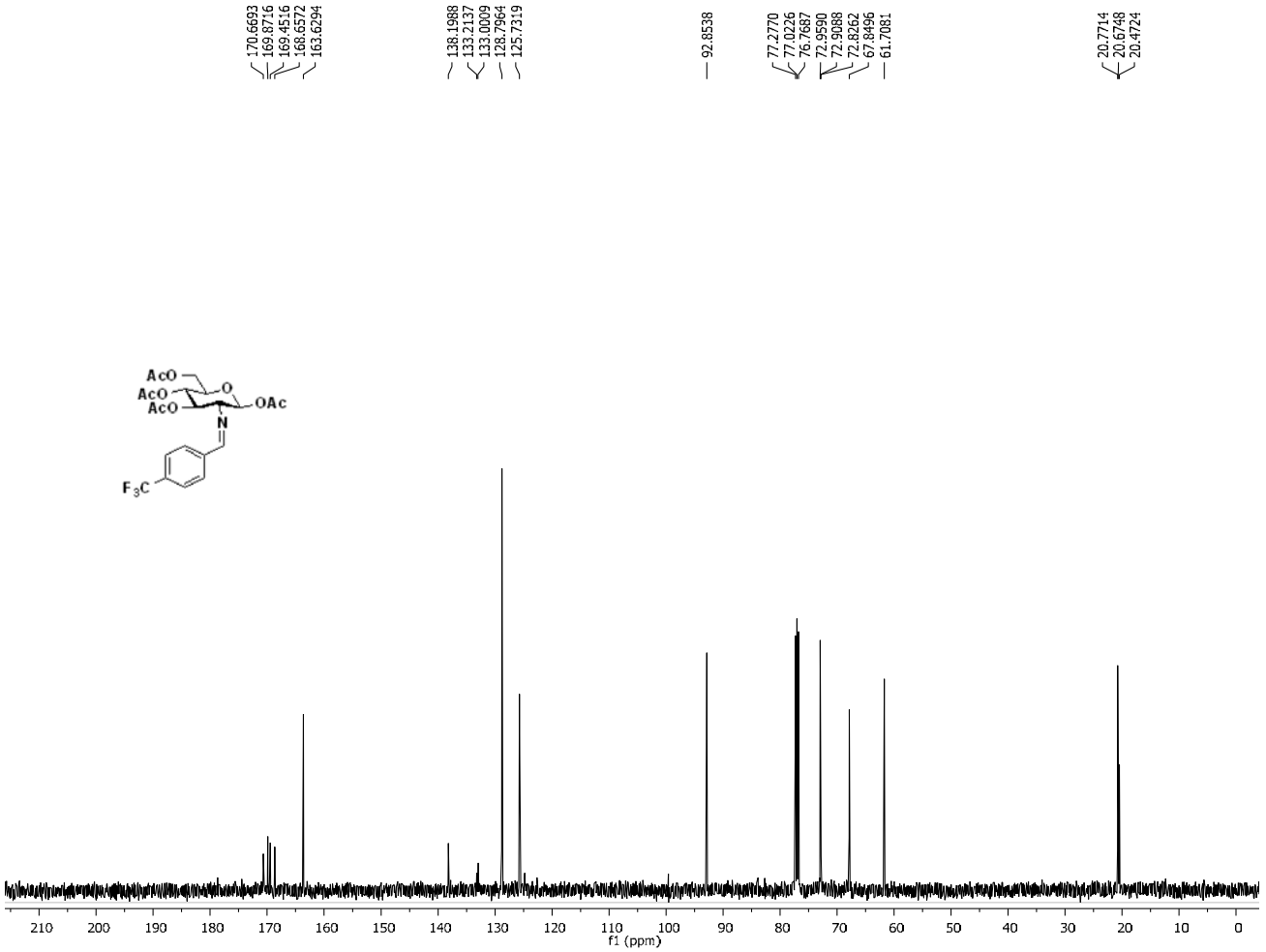


Figure A80. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **134**

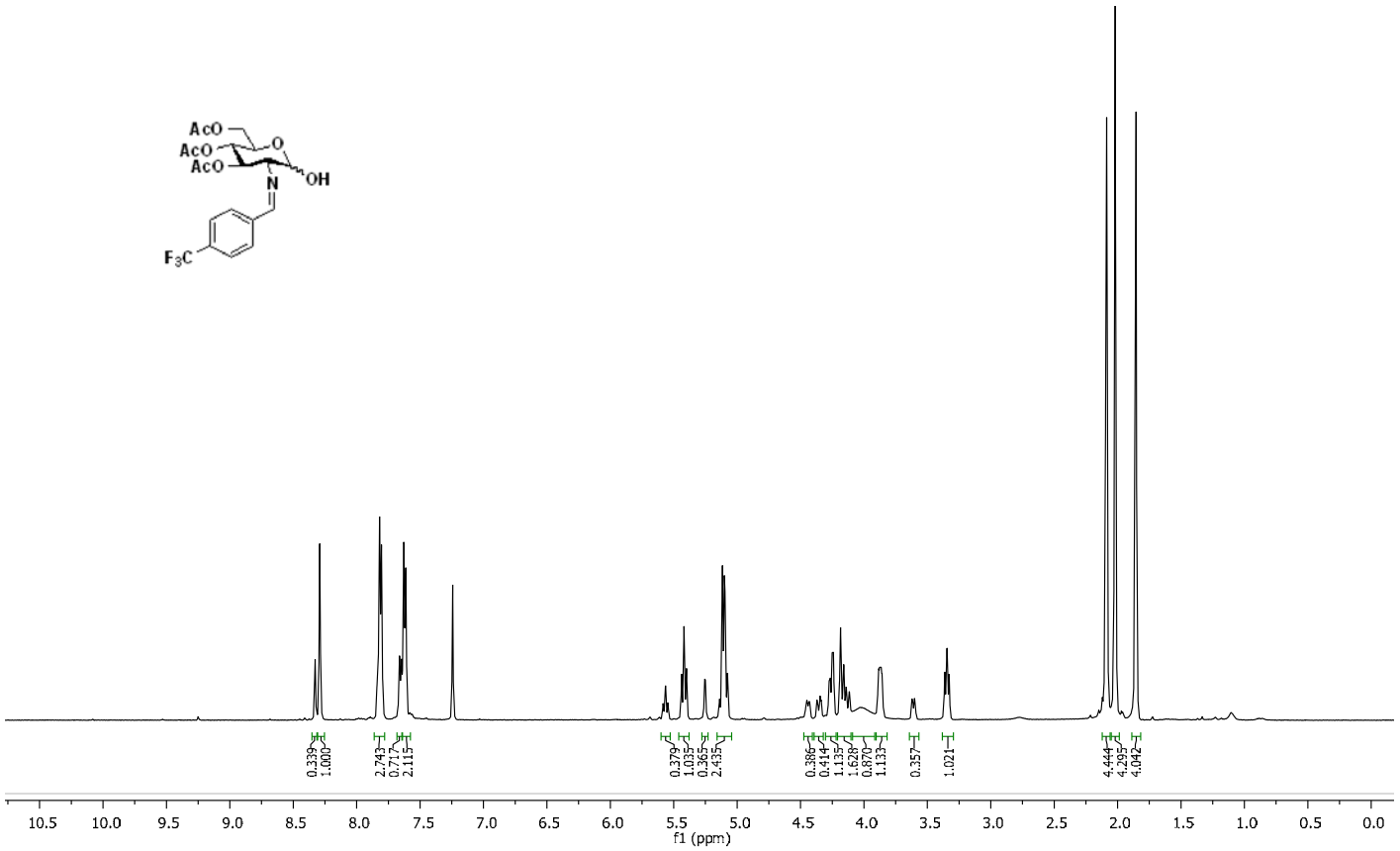


Figure A81. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **135**

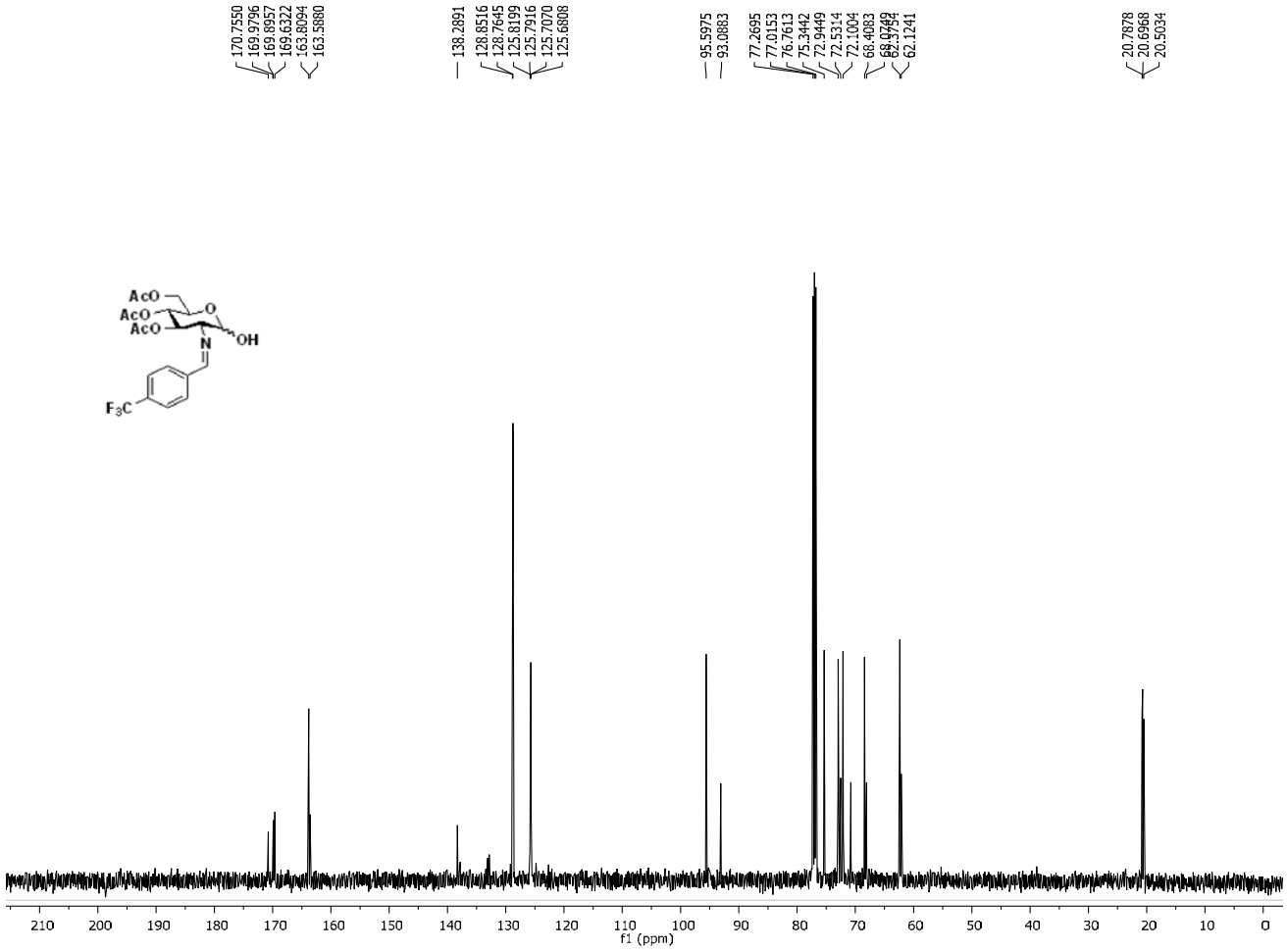


Figure A82. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **135**

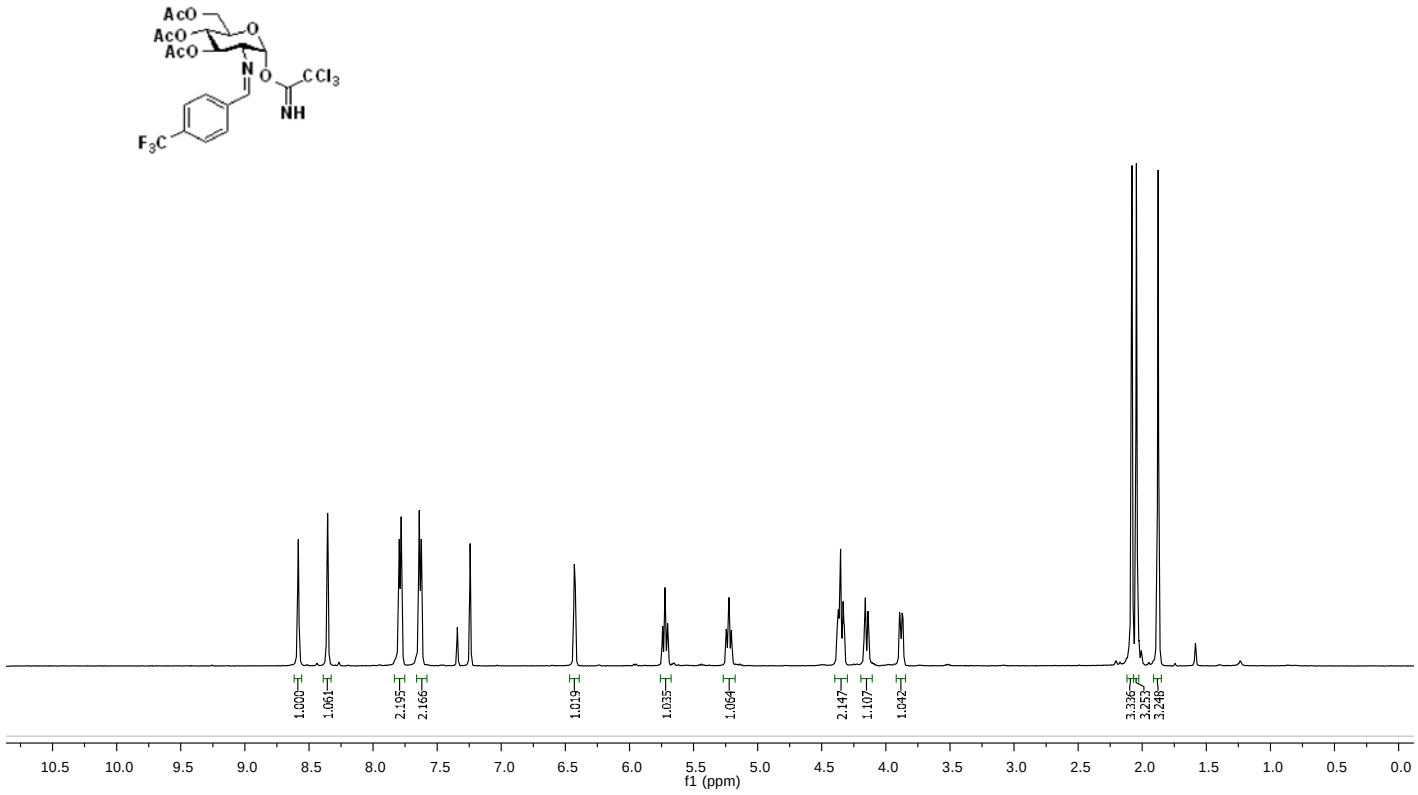


Figure A83. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **136**

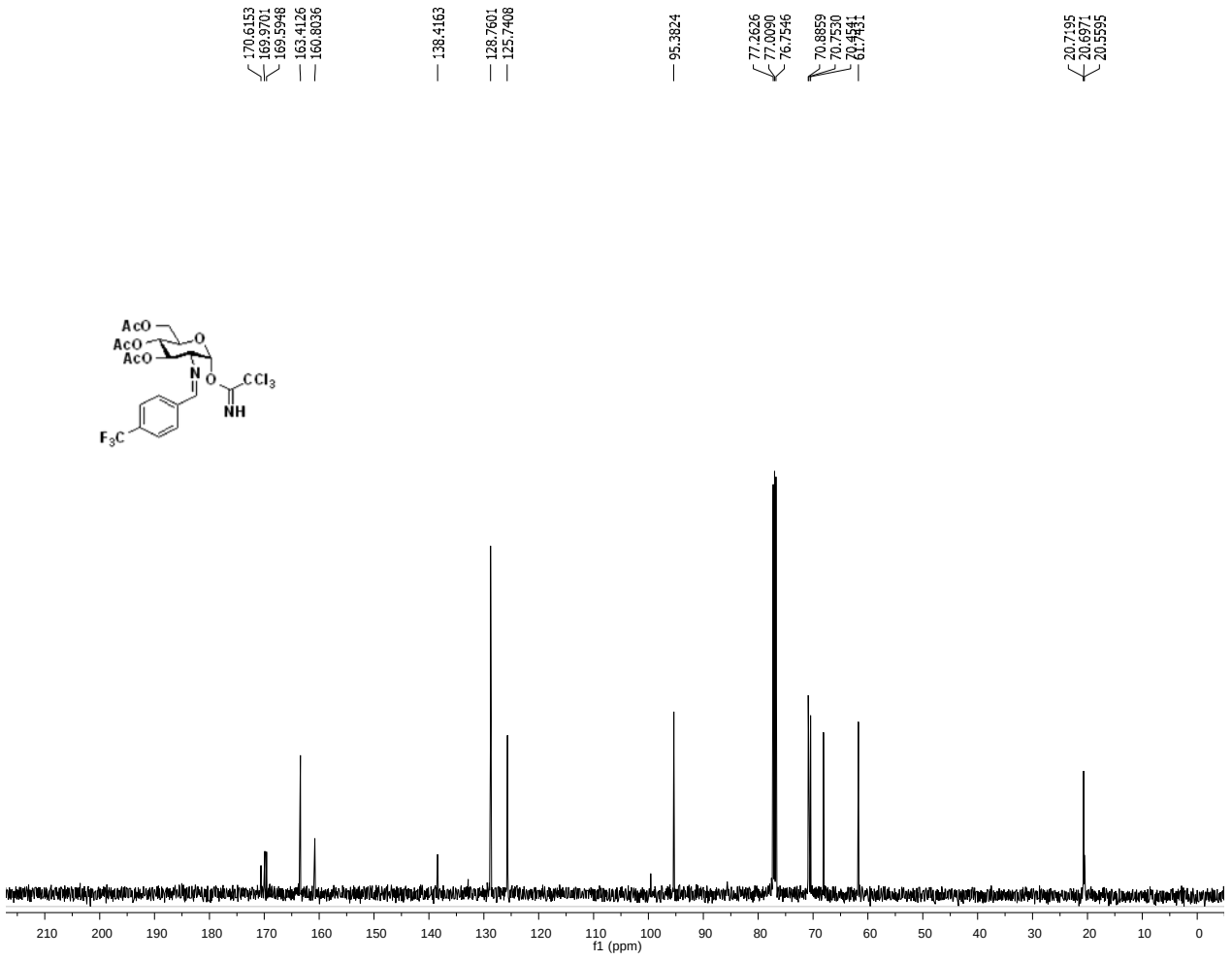


Figure A84. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **136**

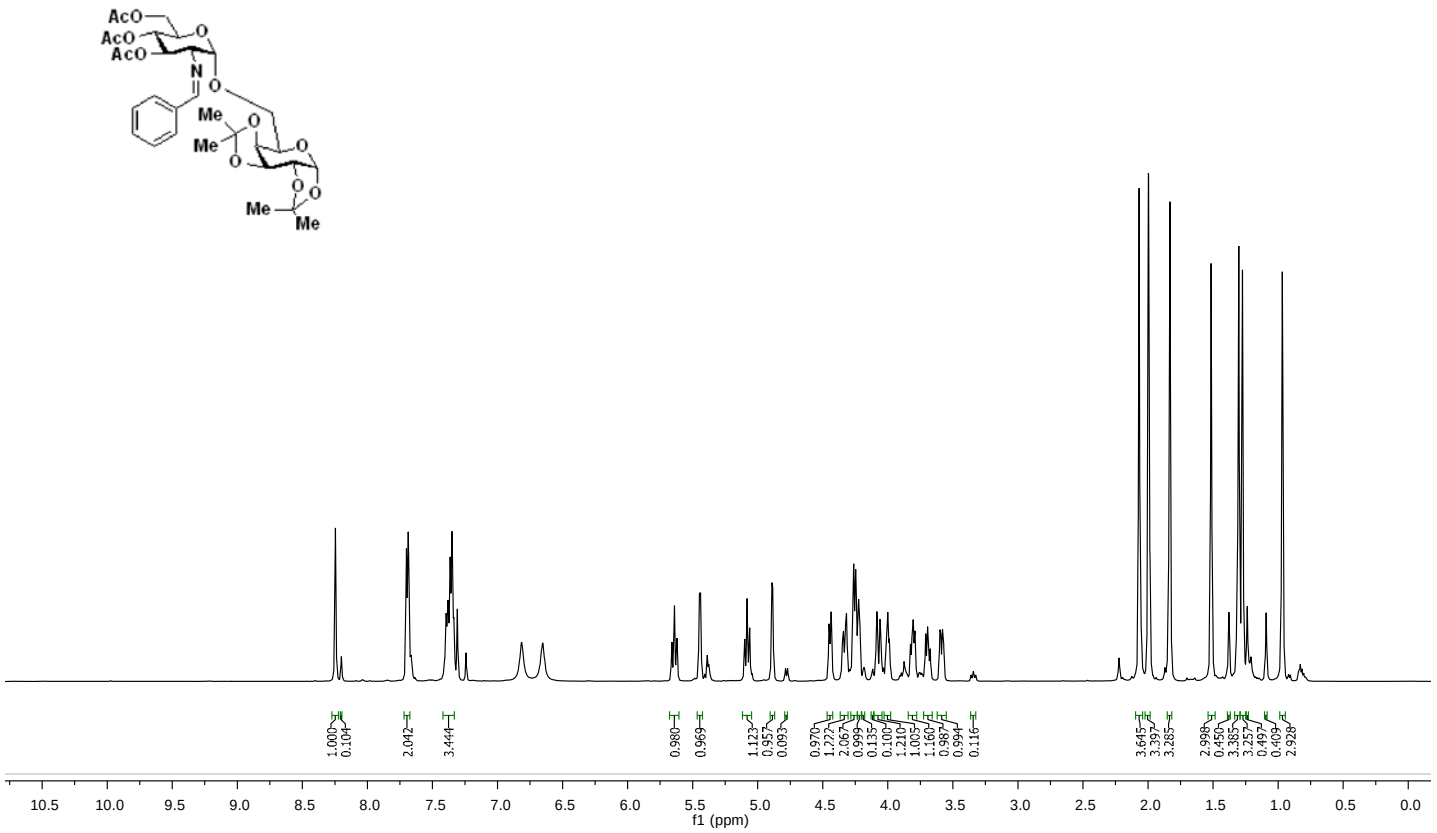


Figure A85. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **137**

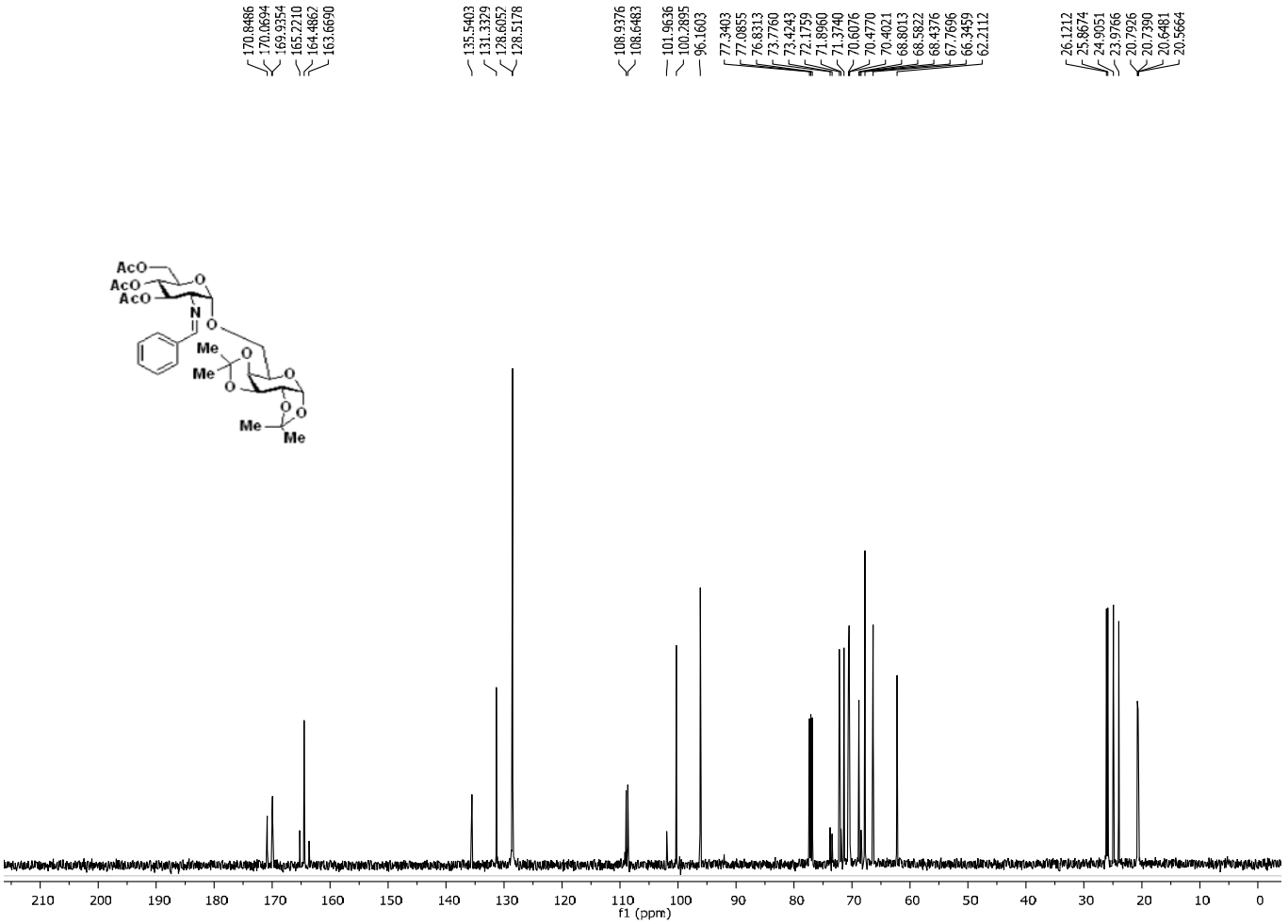


Figure A86. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **137**

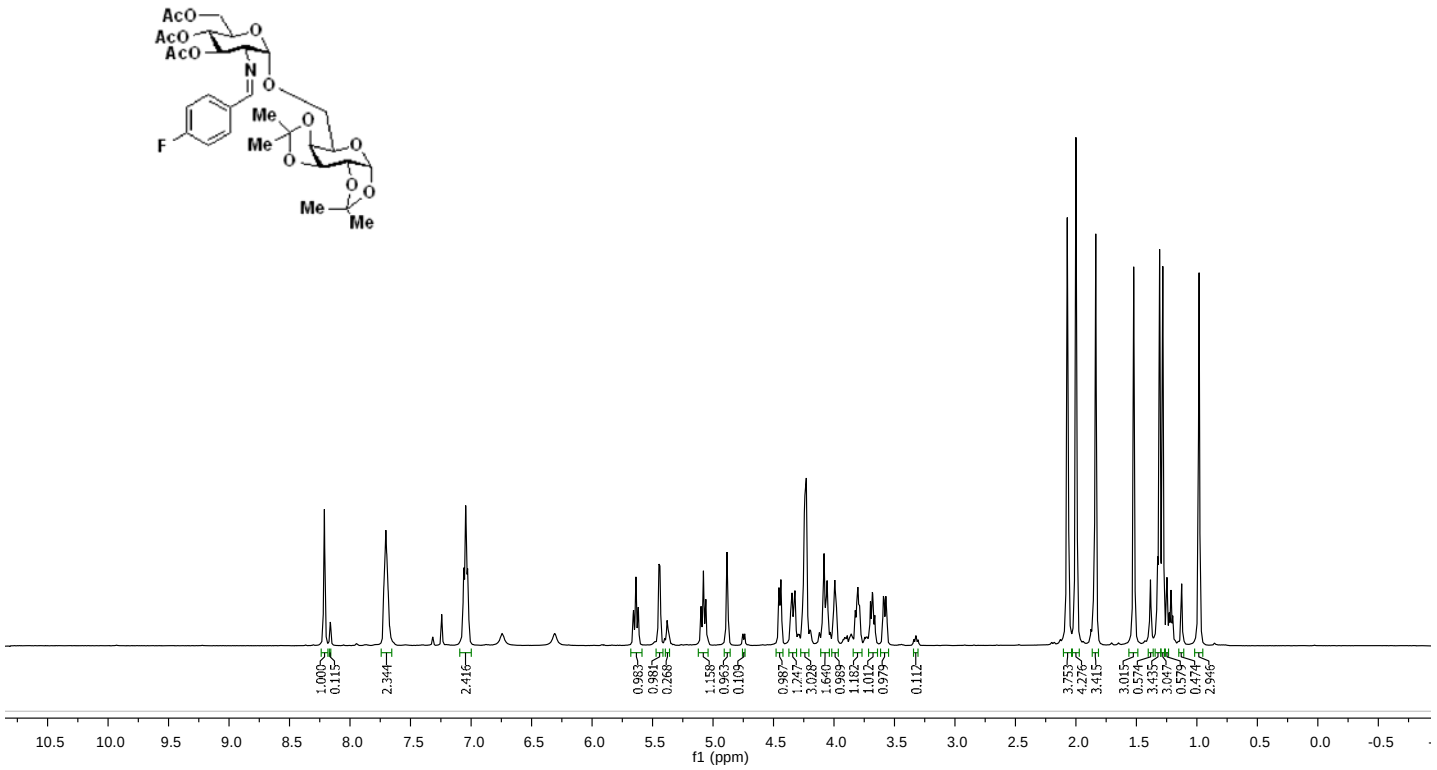


Figure A87. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **138**

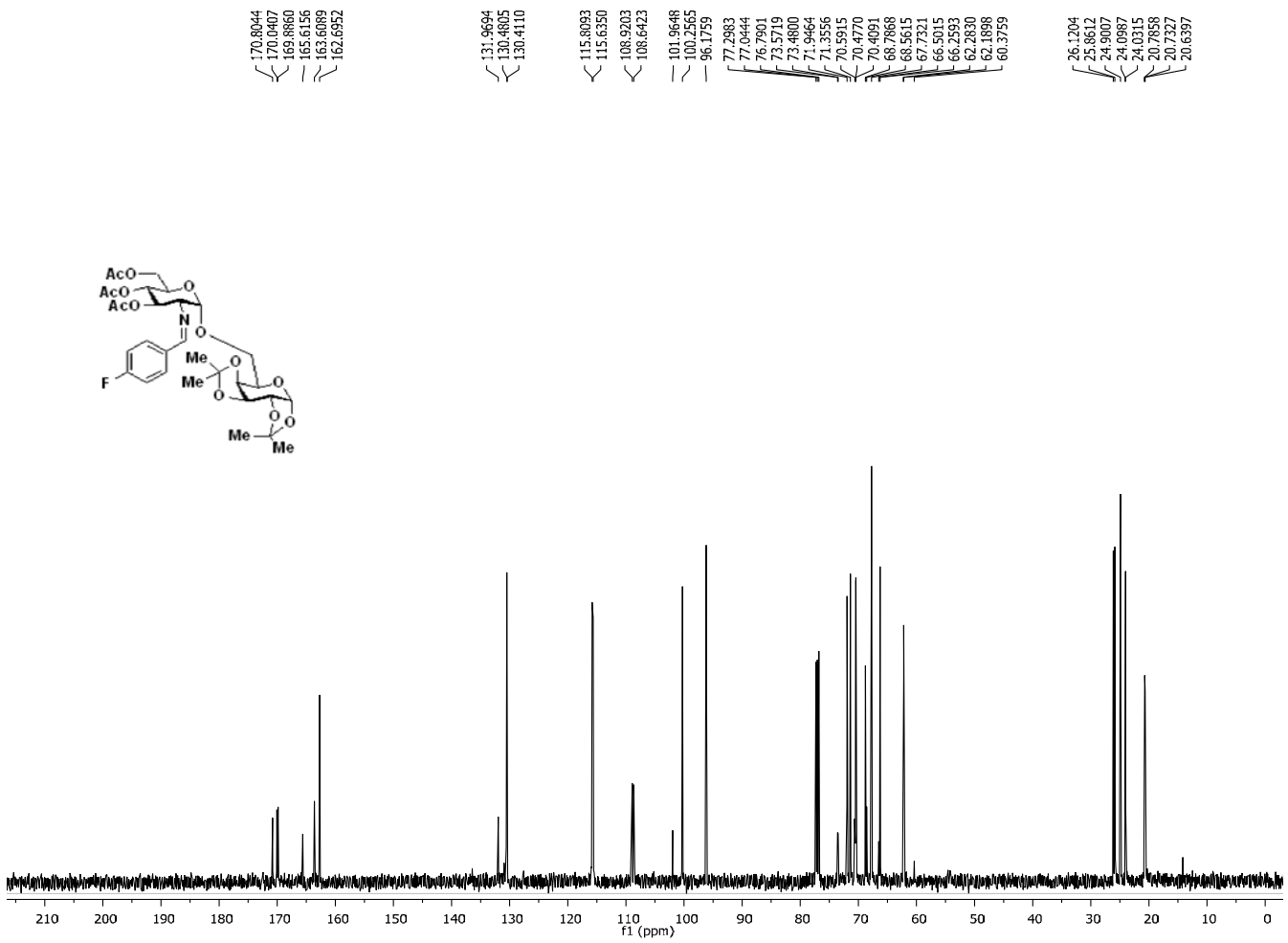


Figure A88. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **138**

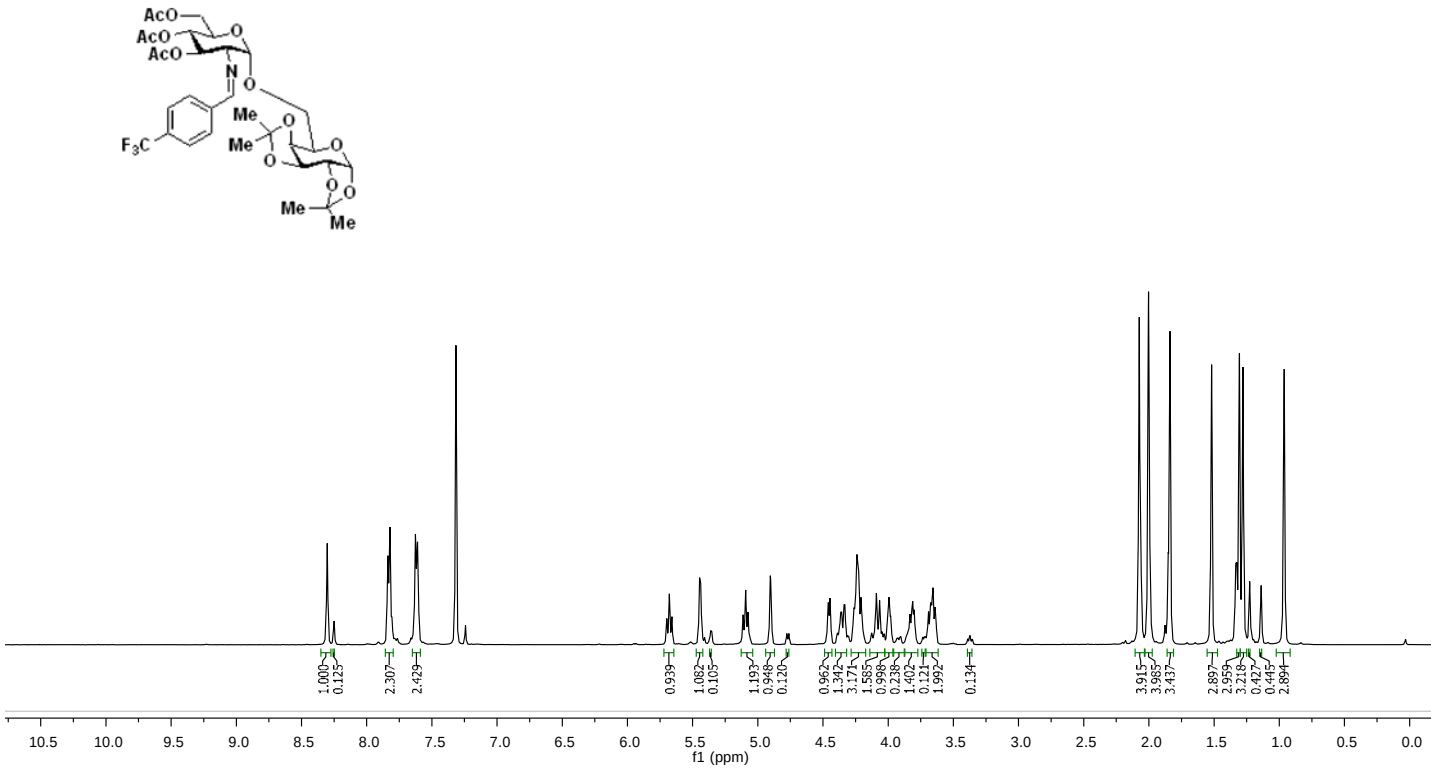


Figure A89. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **139**

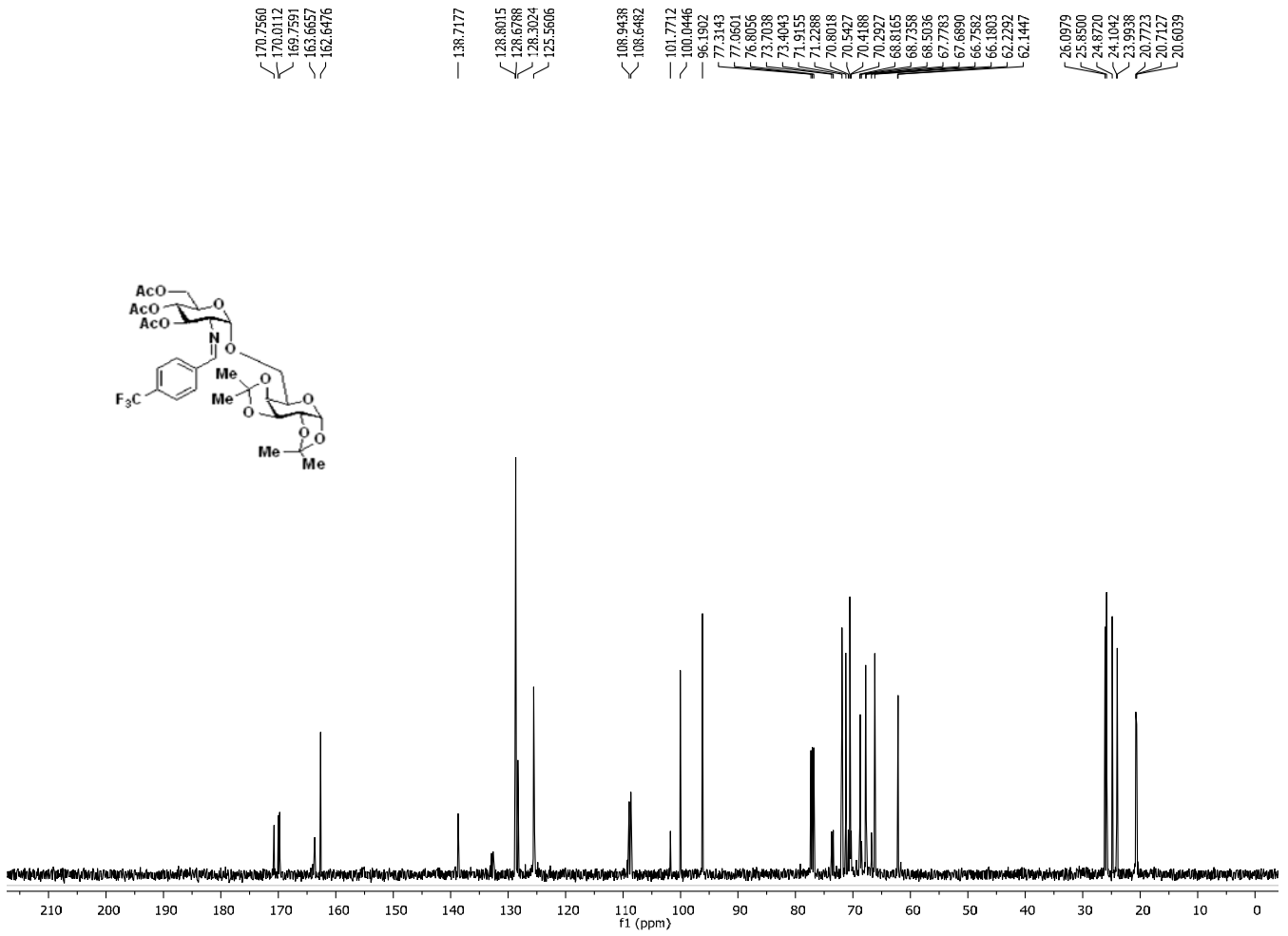


Figure A90. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **139**

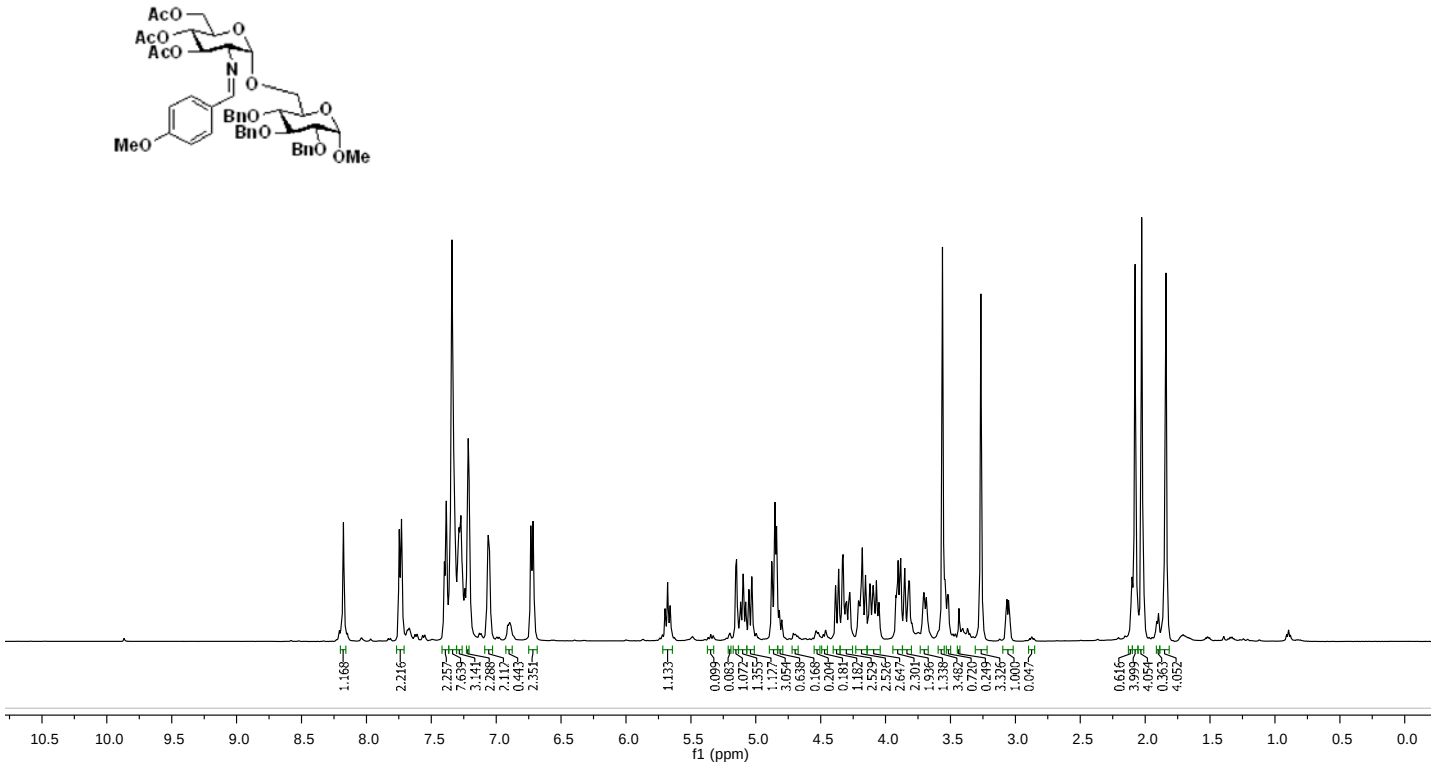


Figure A91. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **144**

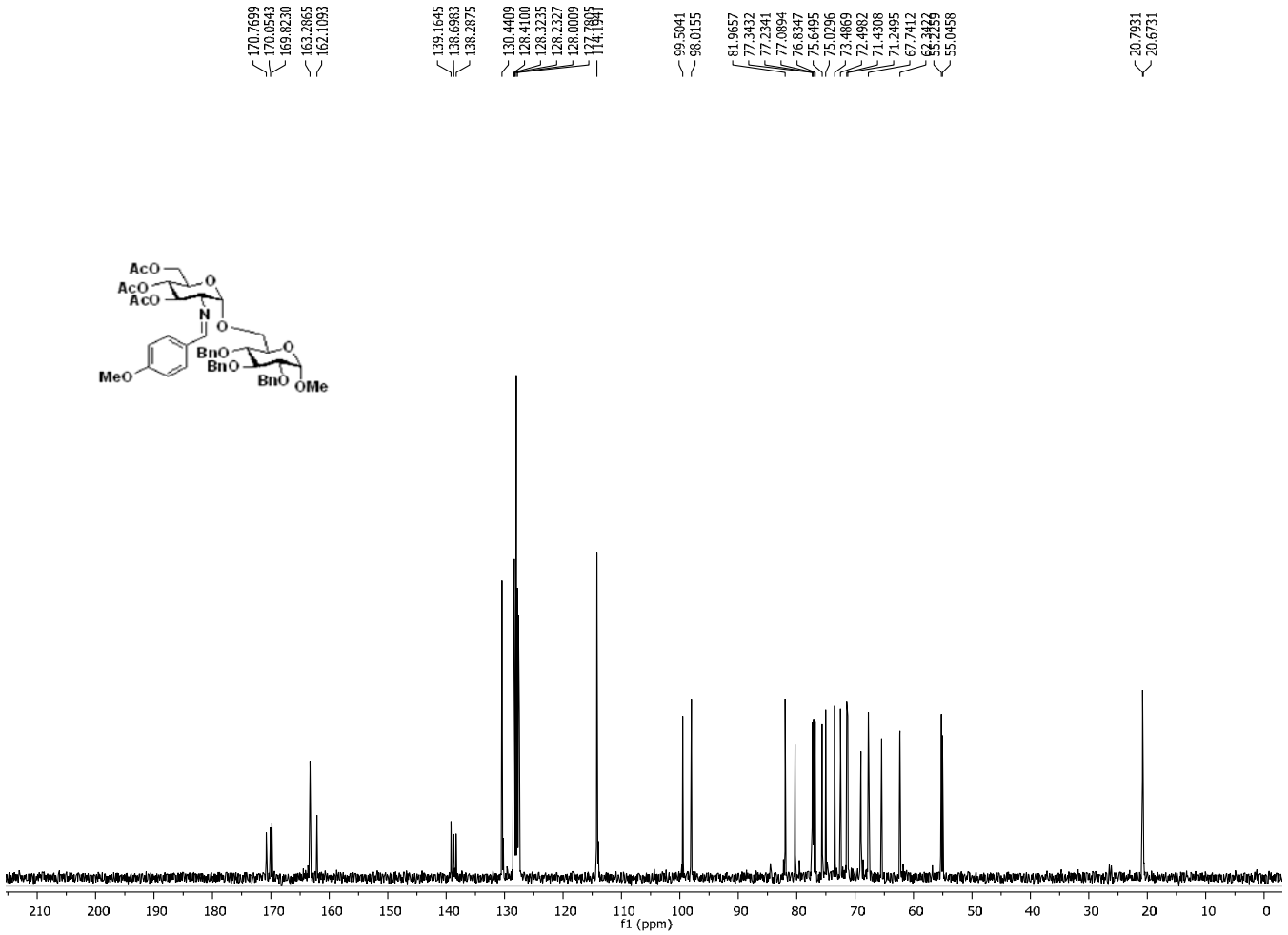


Figure A92. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **144**

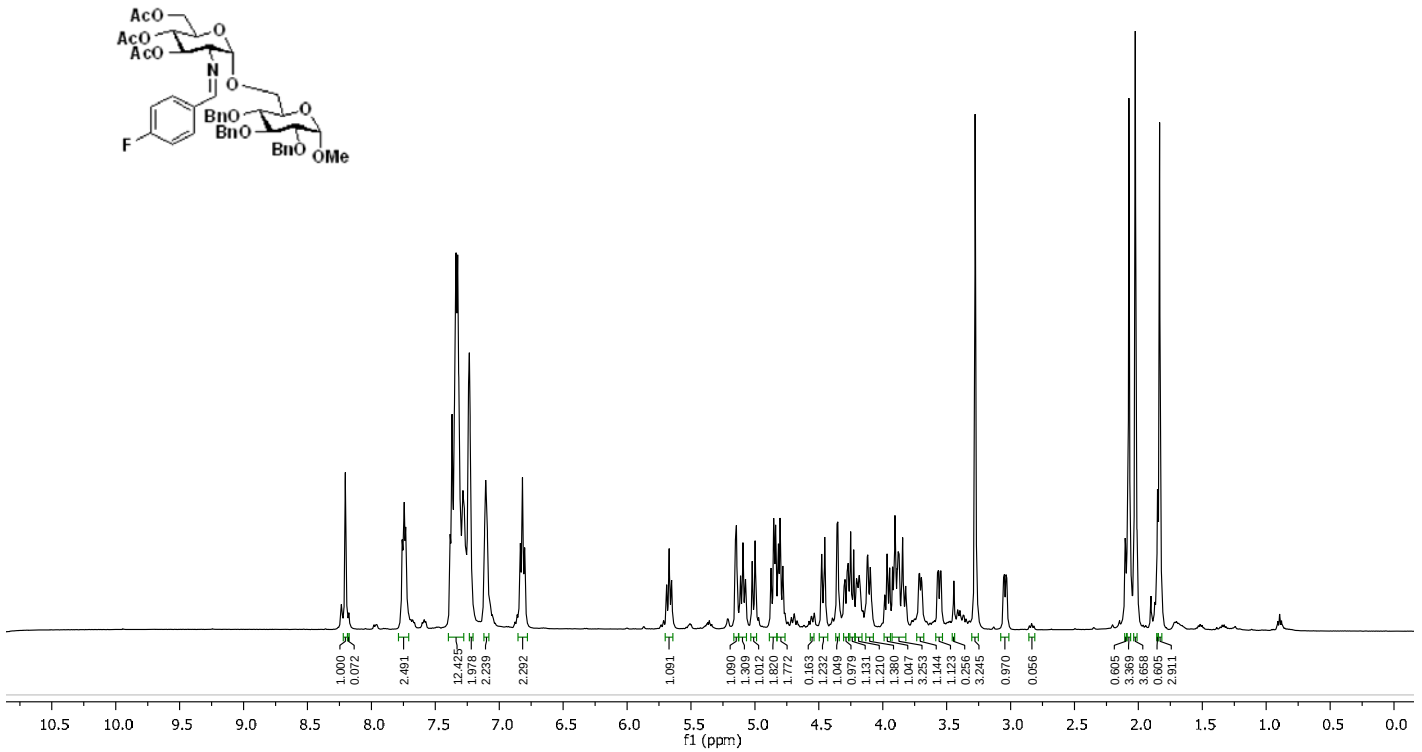


Figure A93. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **145**

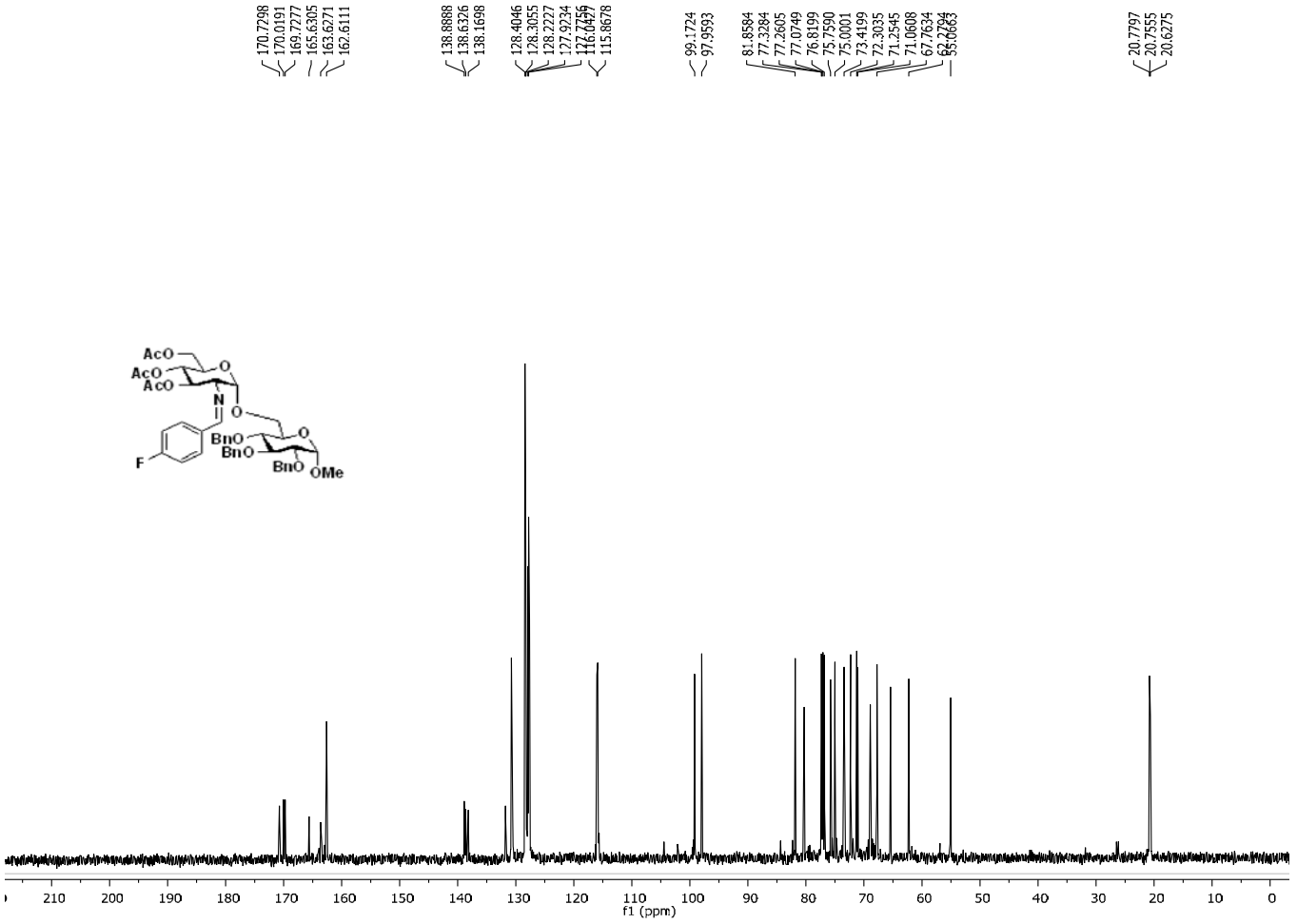


Figure A94. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **145**

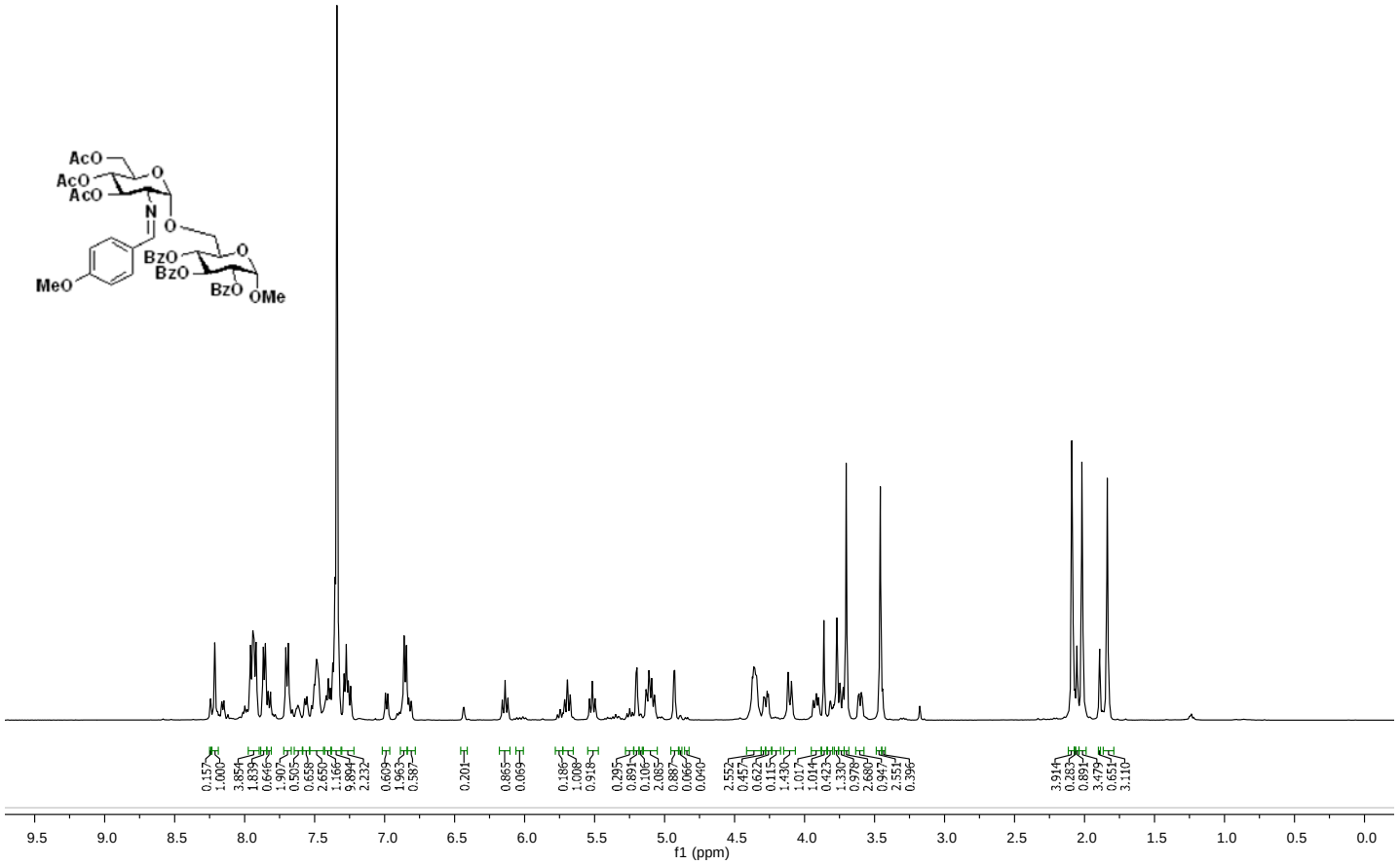


Figure A95. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **146**

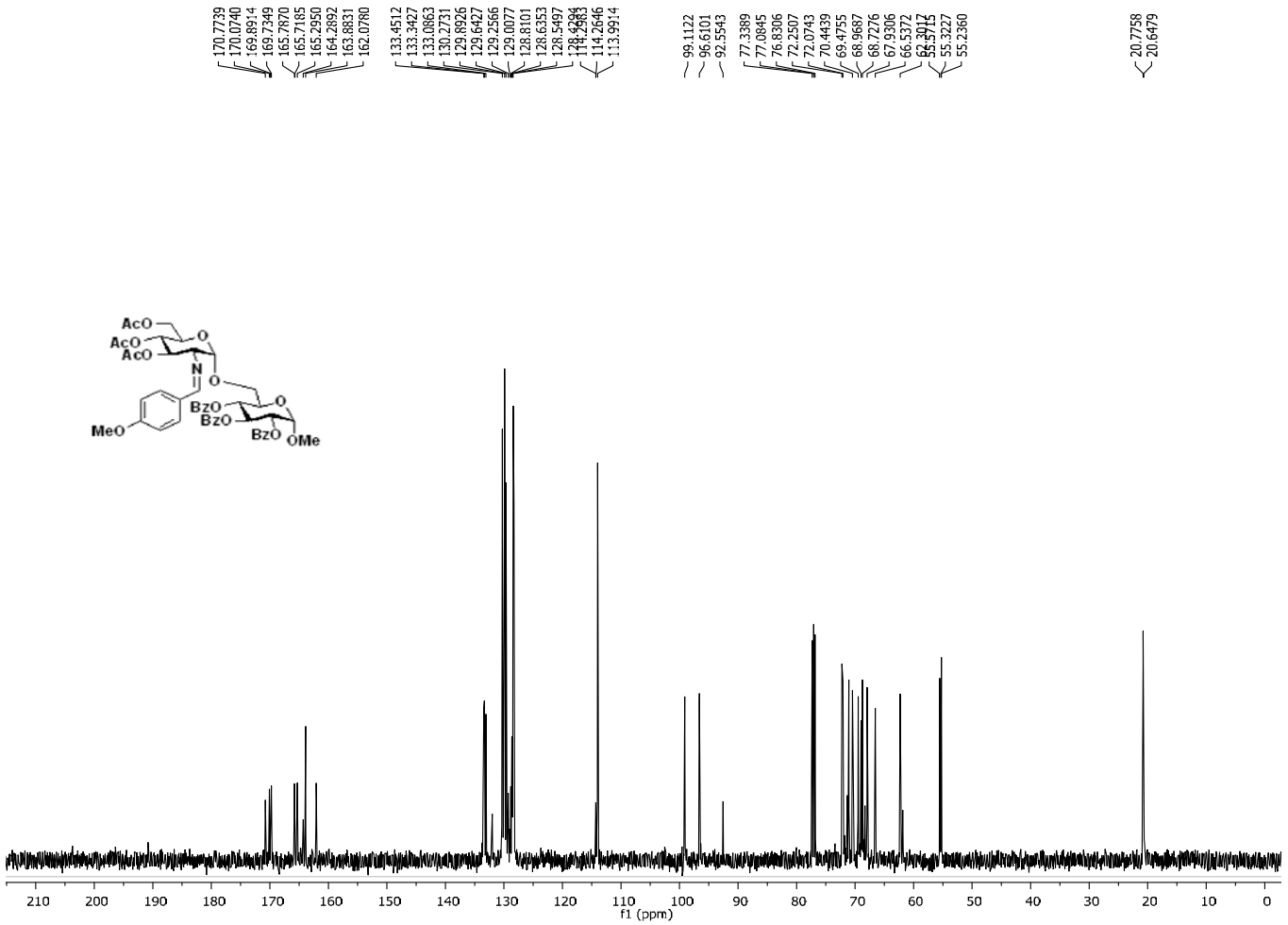


Figure A96. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **146**

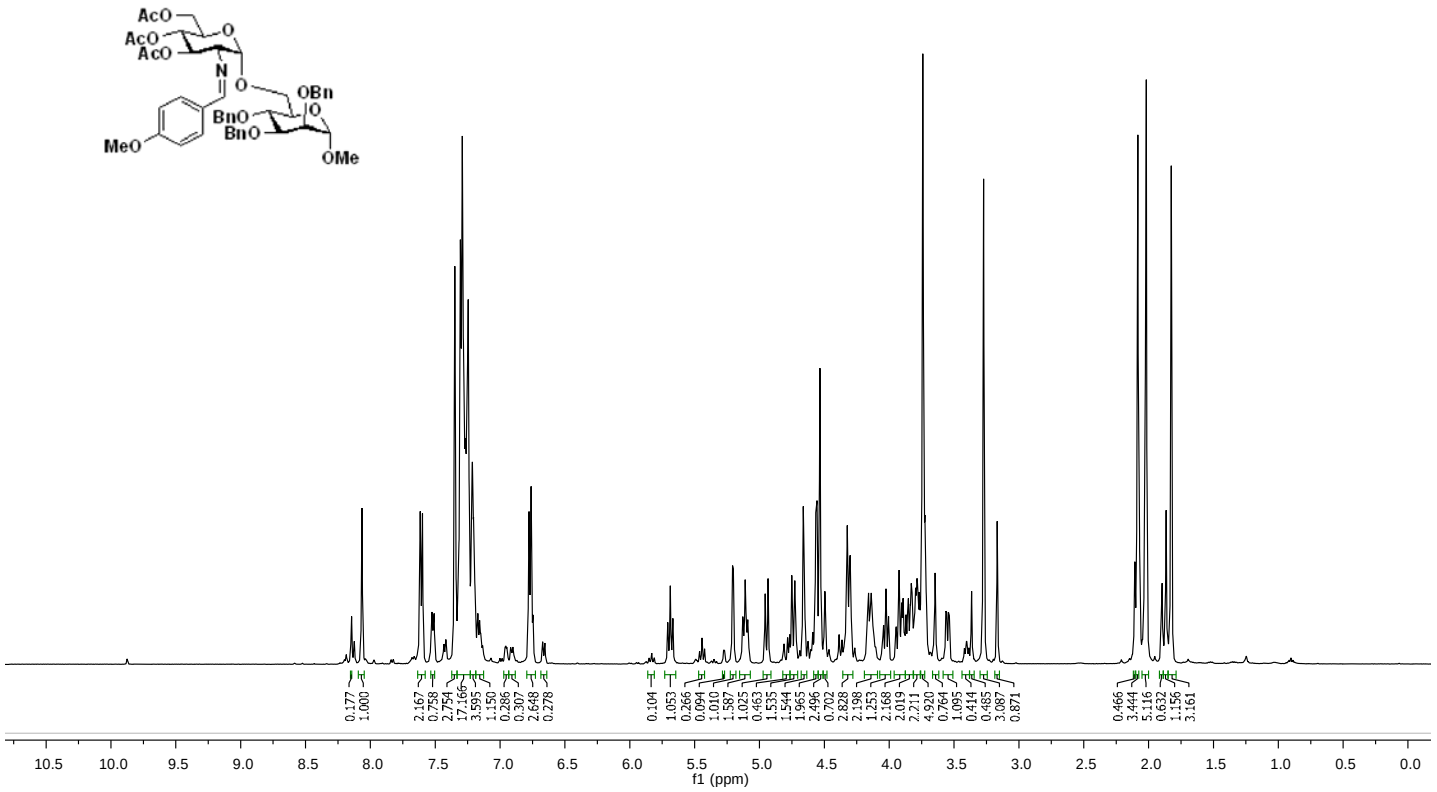


Figure A97. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **147**

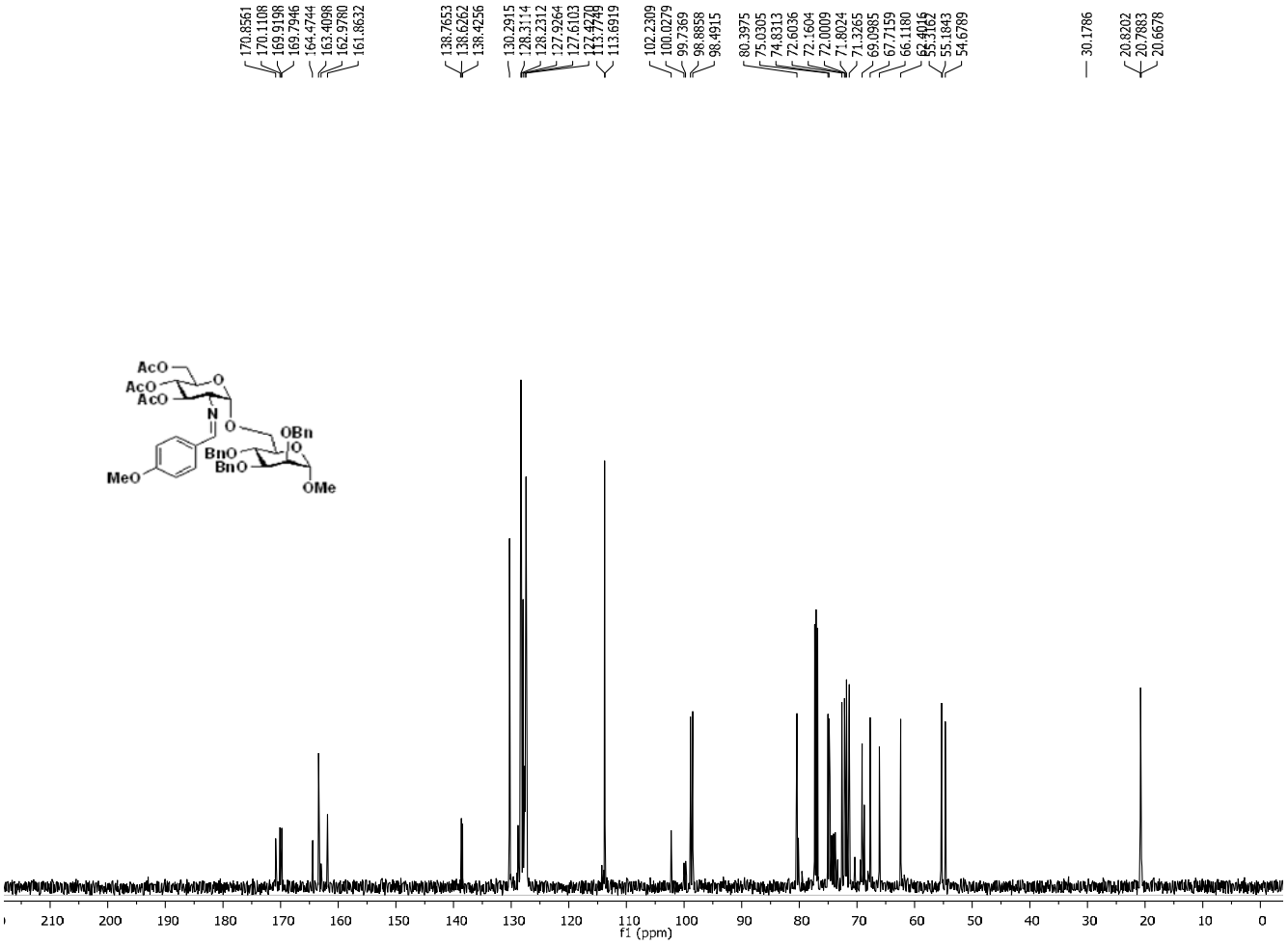


Figure A98. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **147**

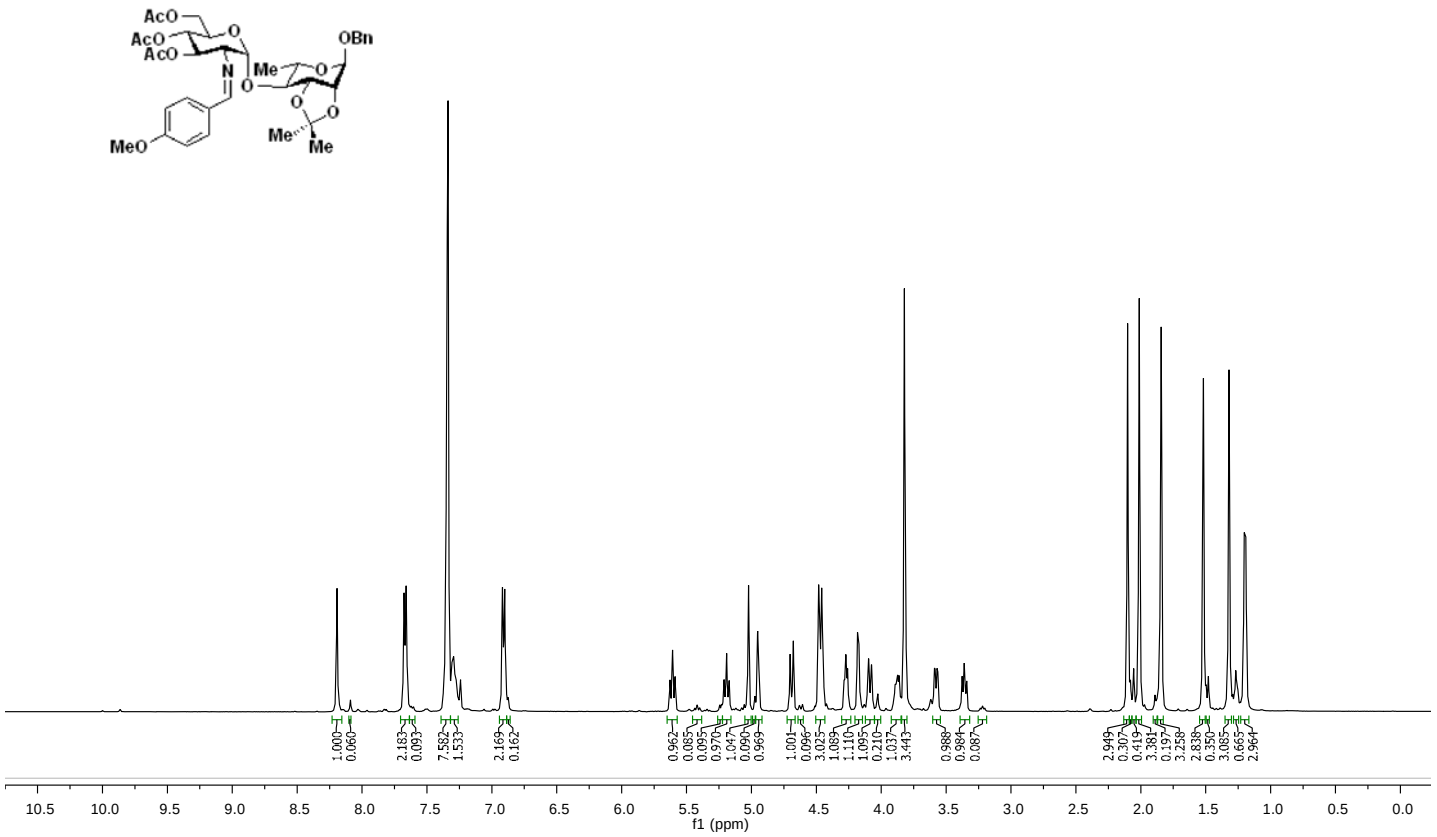


Figure A99. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **148**

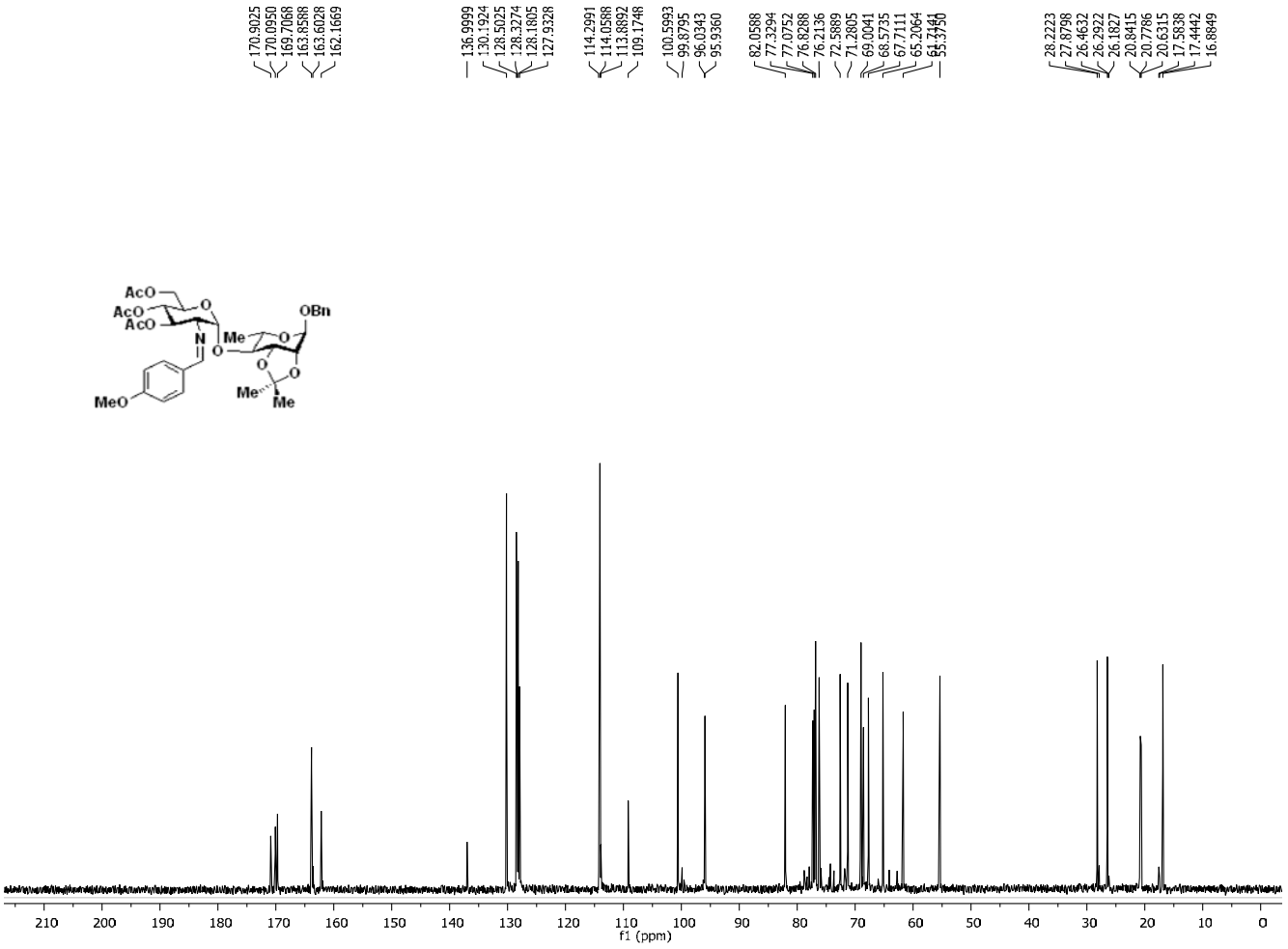


Figure A100. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **148**

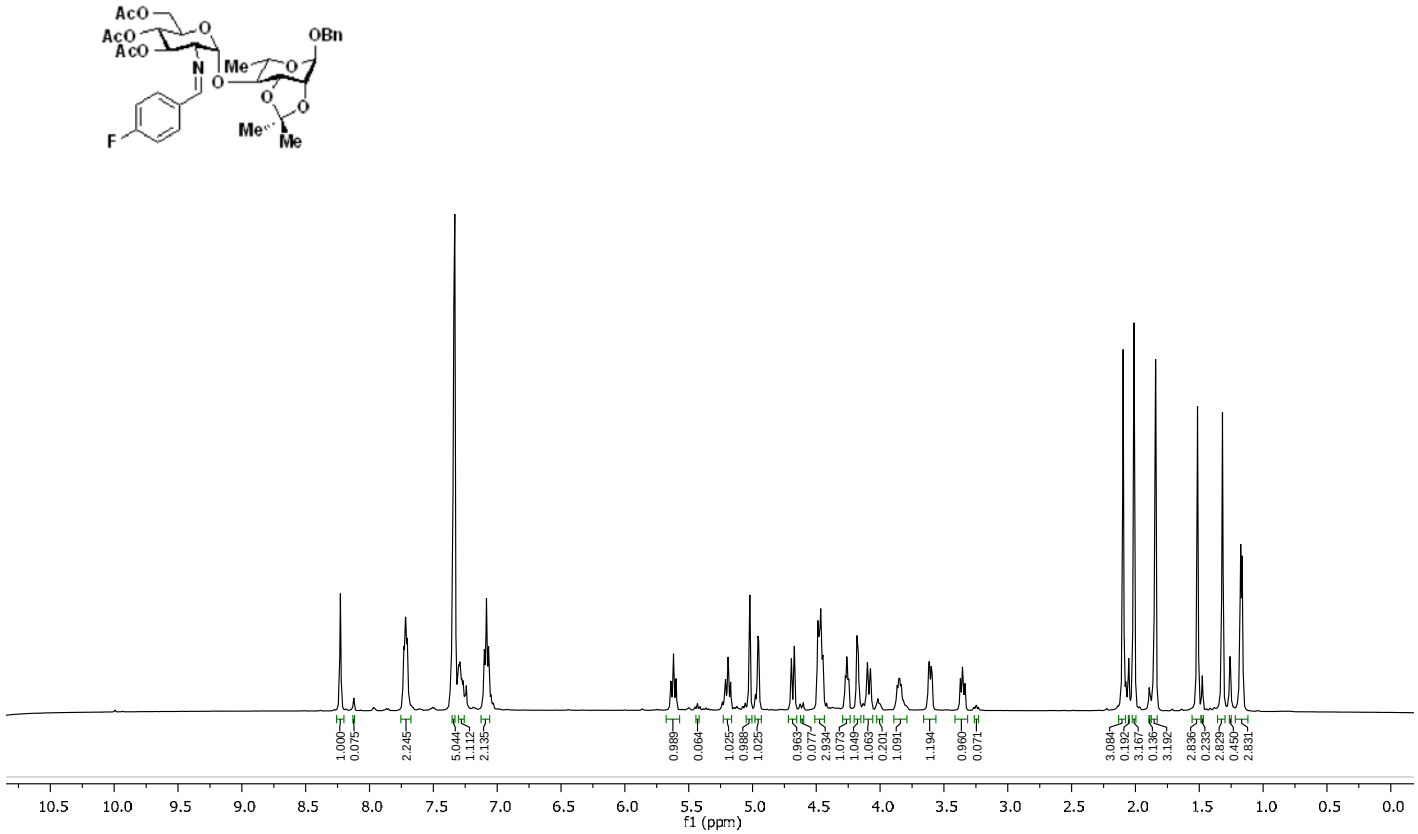


Figure A101. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **149**

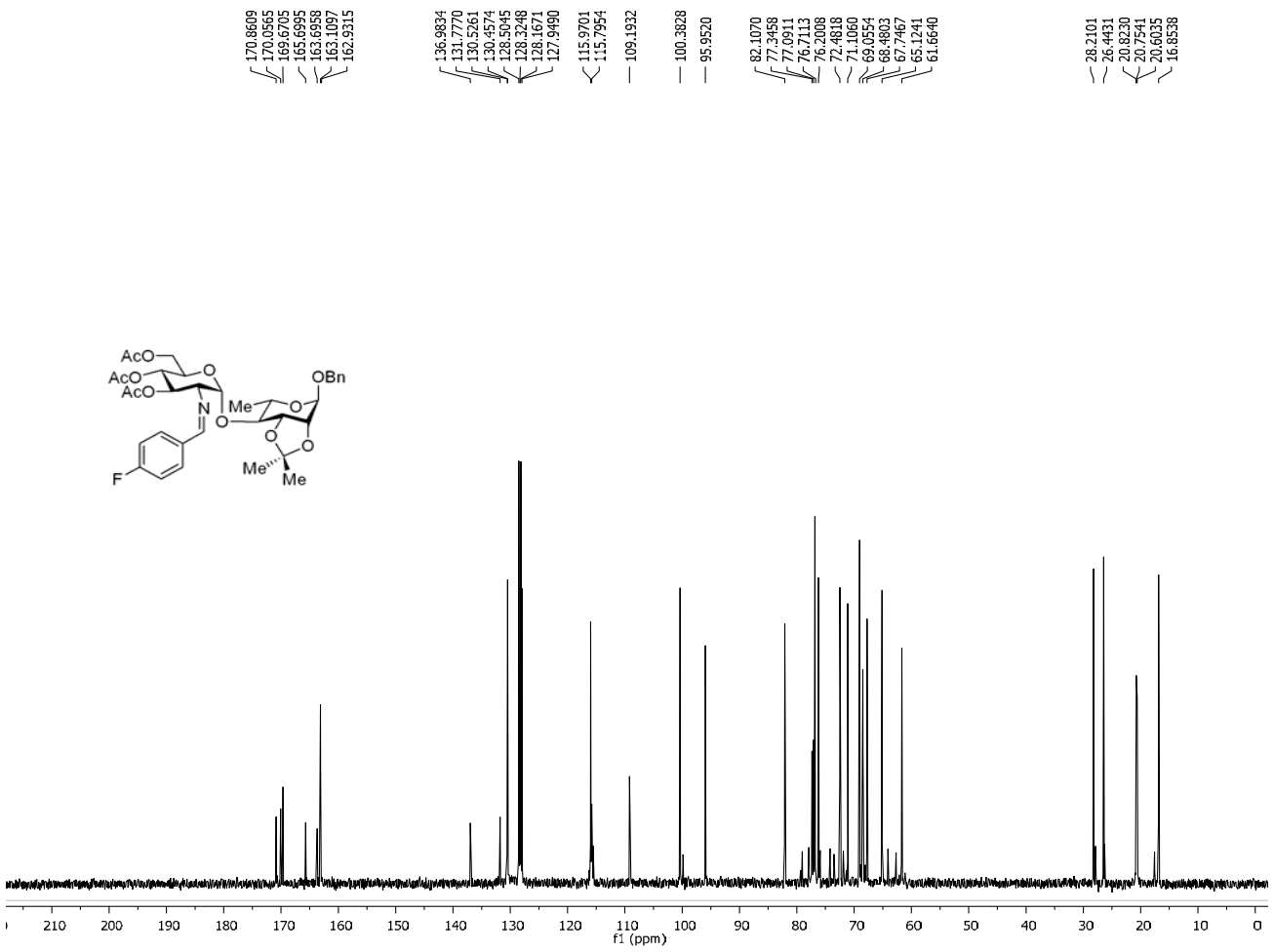


Figure A102. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **149**

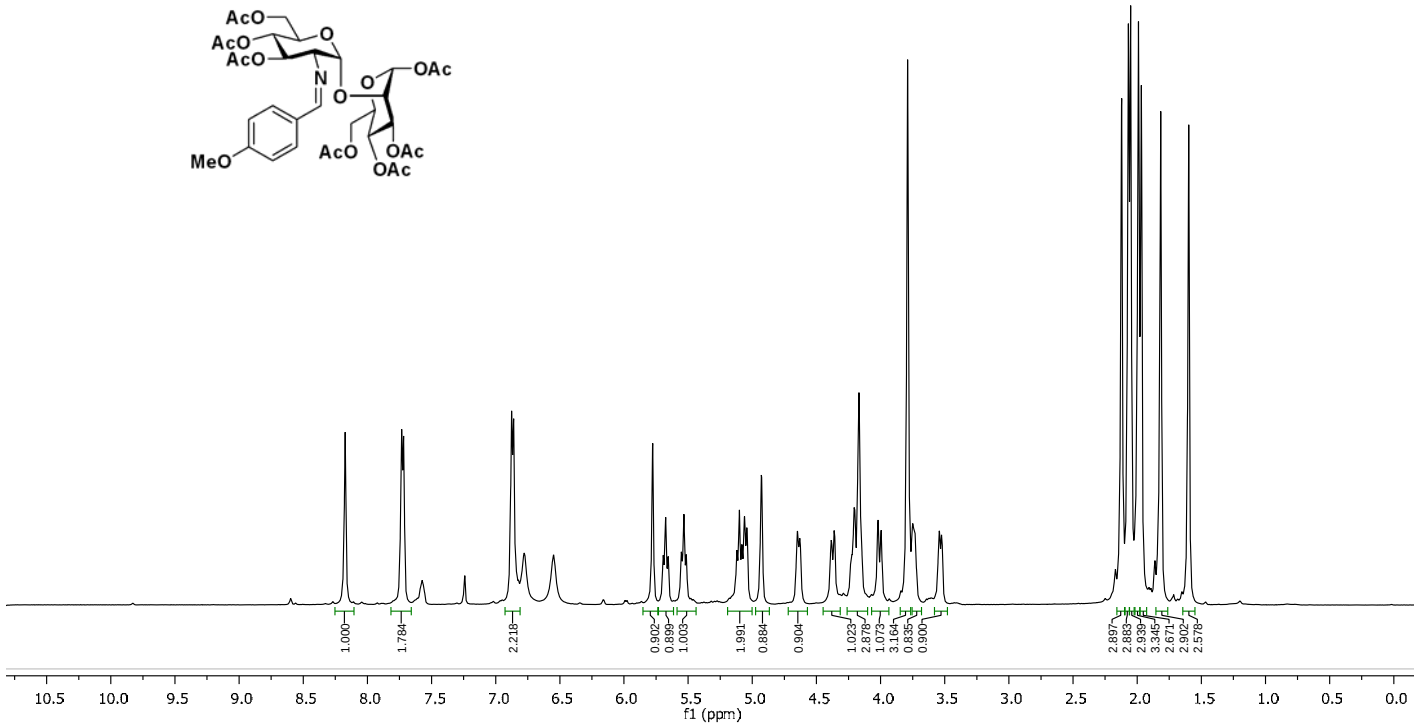


Figure A103. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **150**

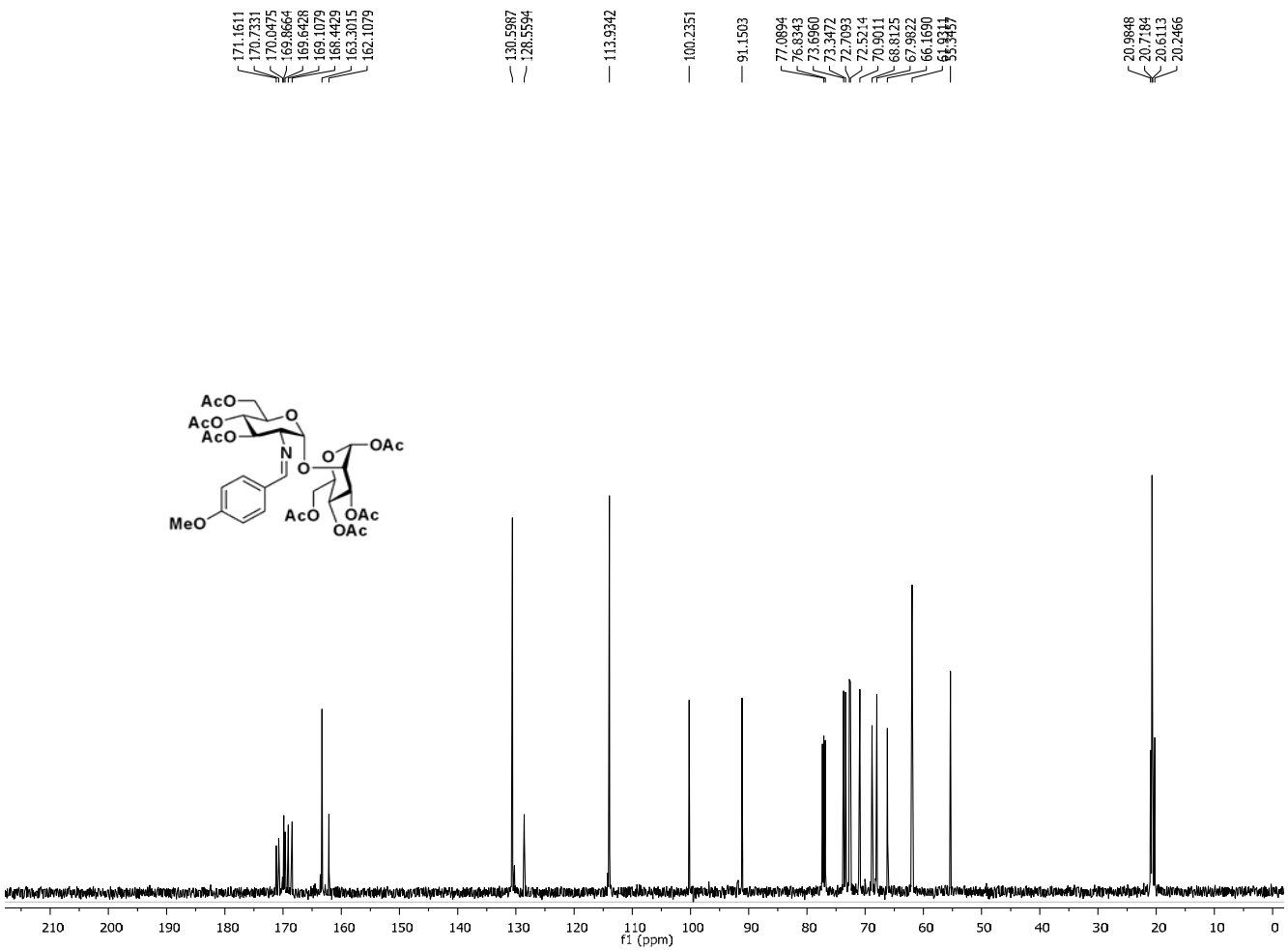


Figure A104. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **150**

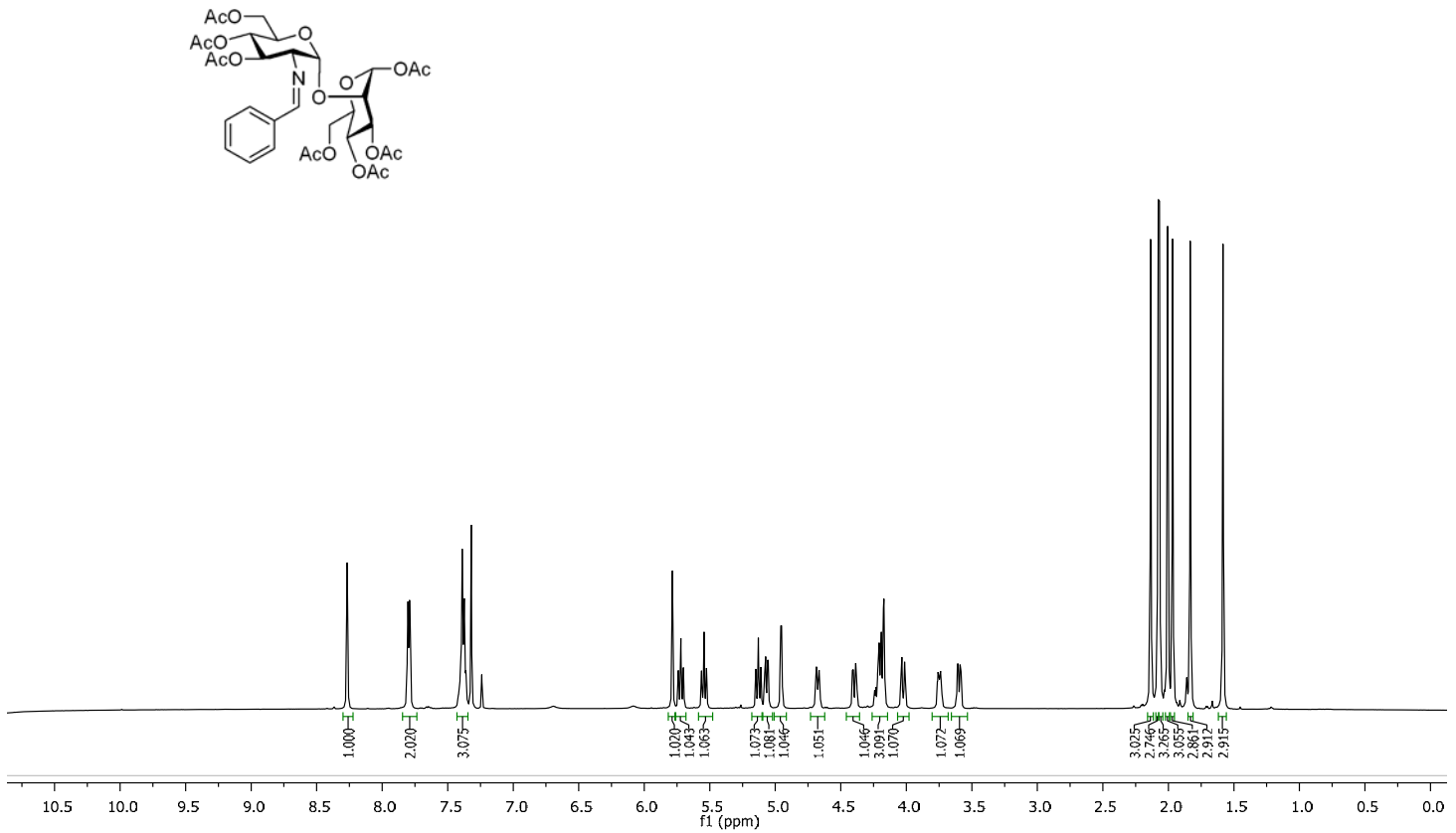


Figure A105. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **151**

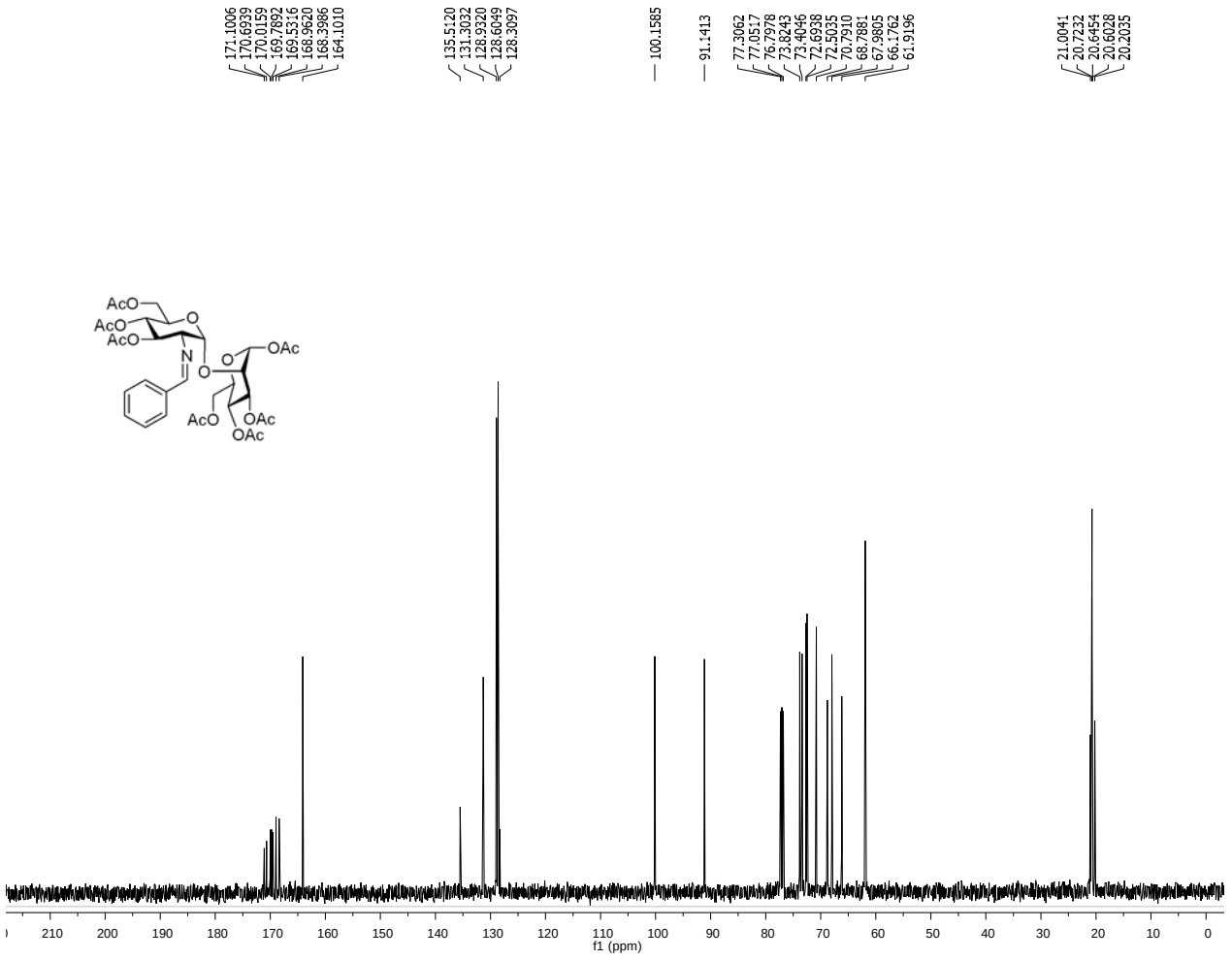


Figure A106. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **151**

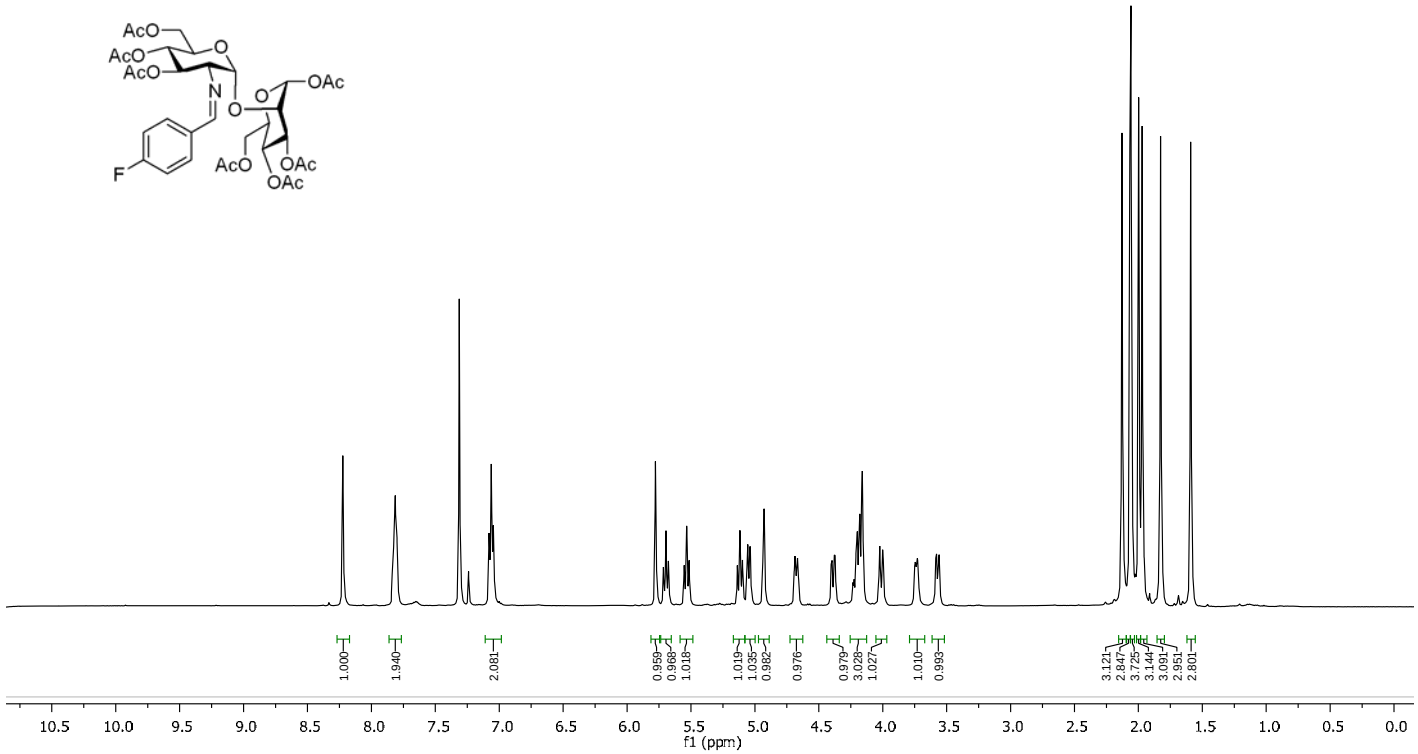


Figure A107. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **152**

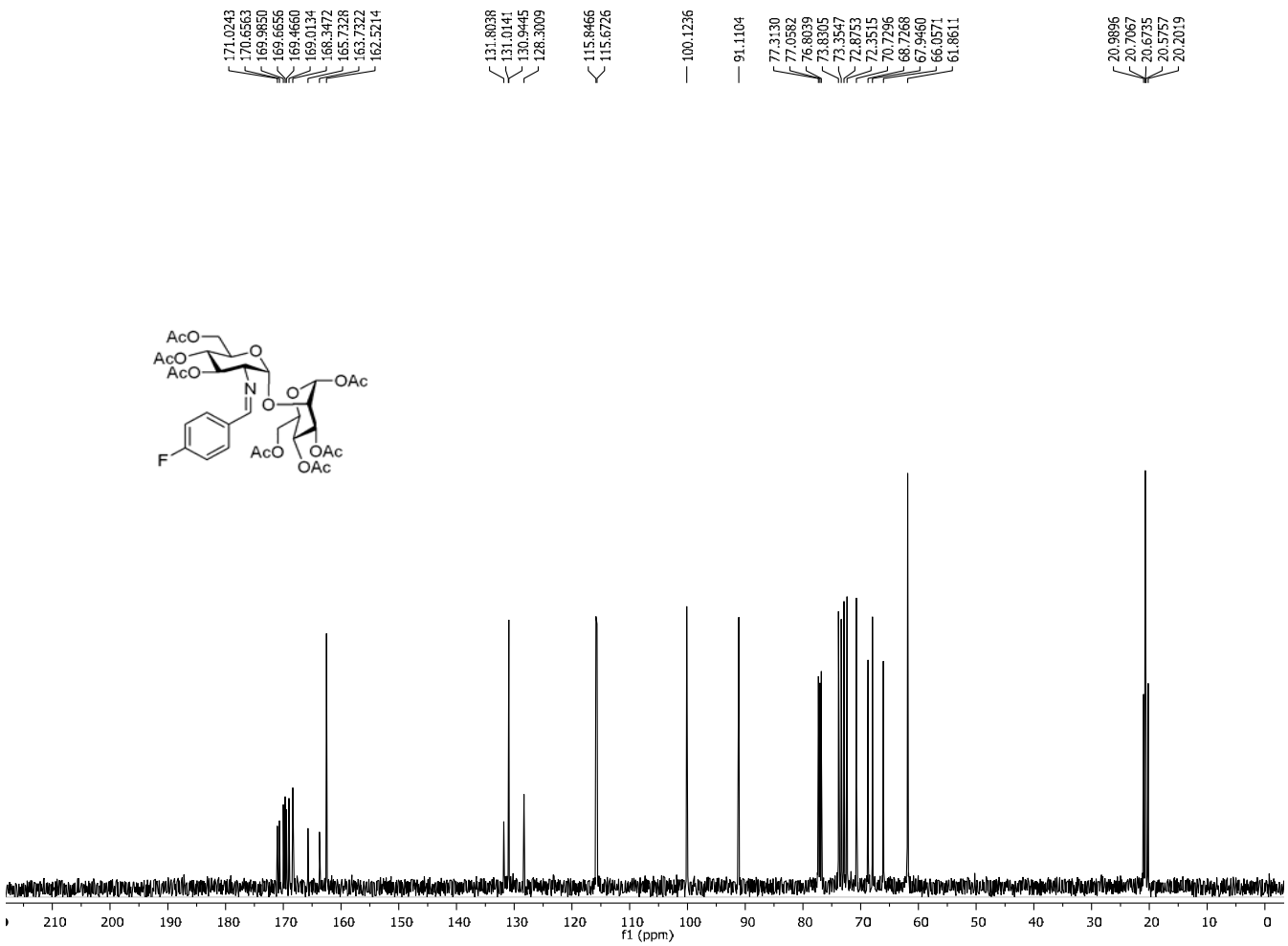


Figure A108. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **152**

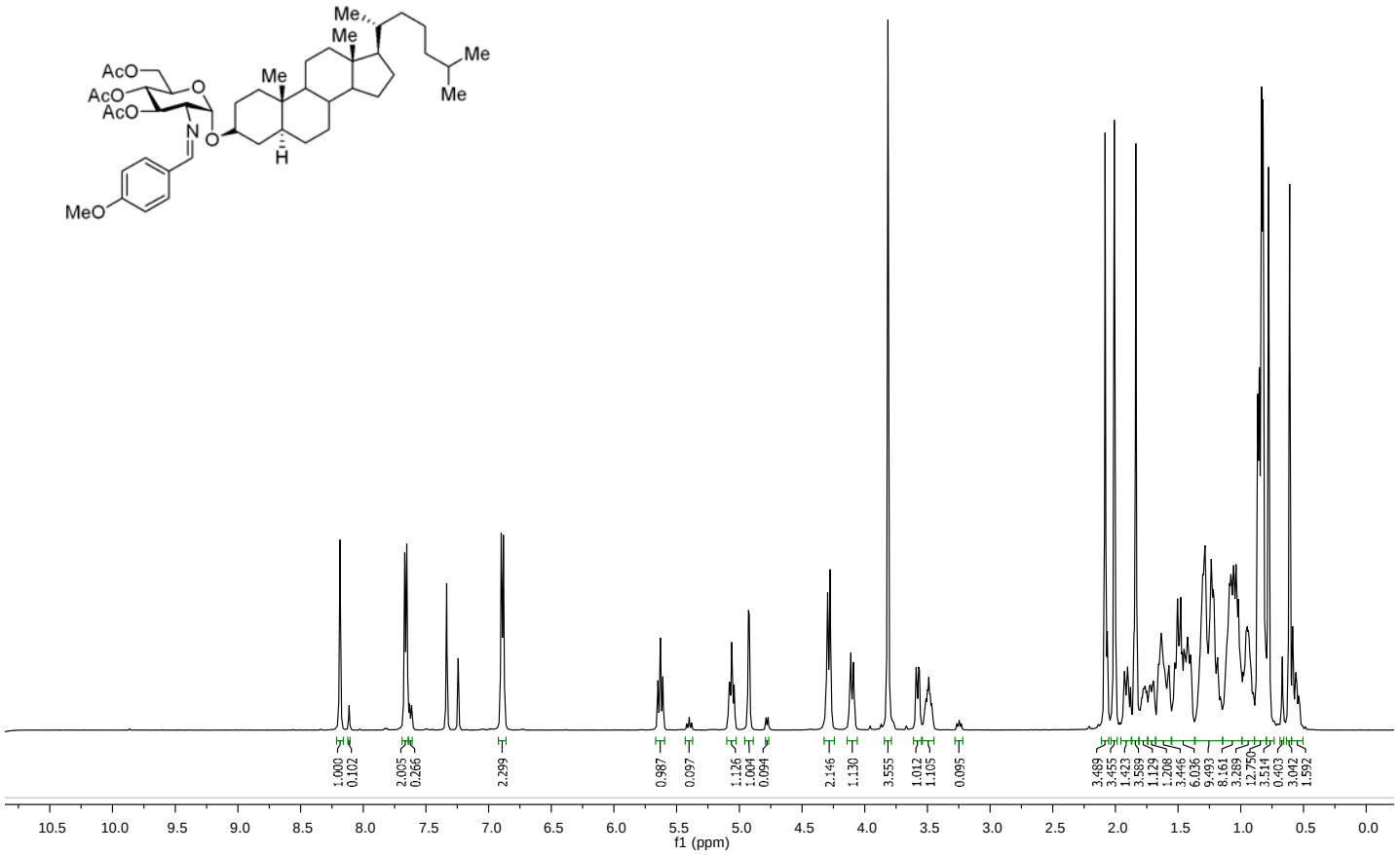


Figure A109. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **153**

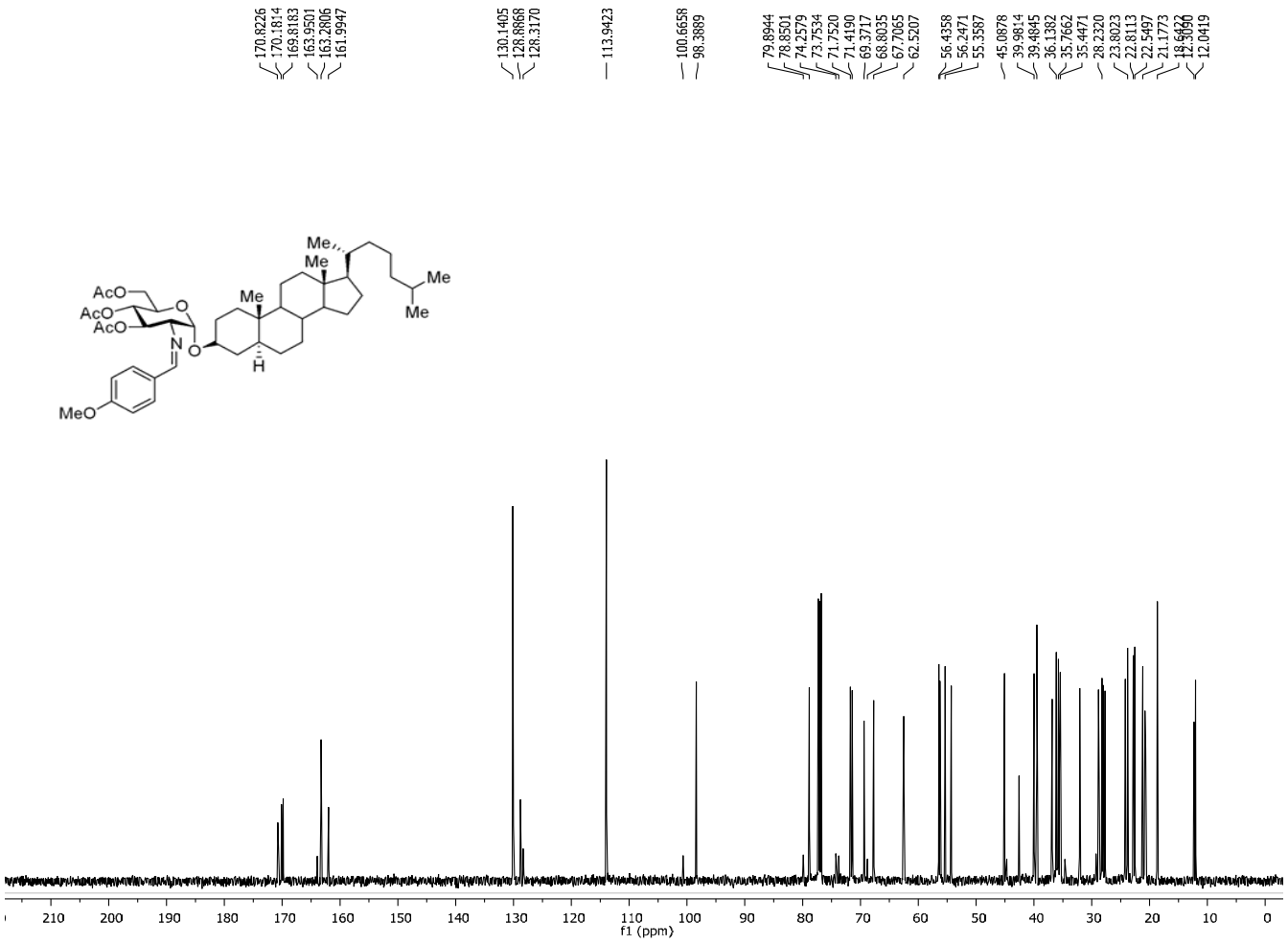


Figure A110. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **153**

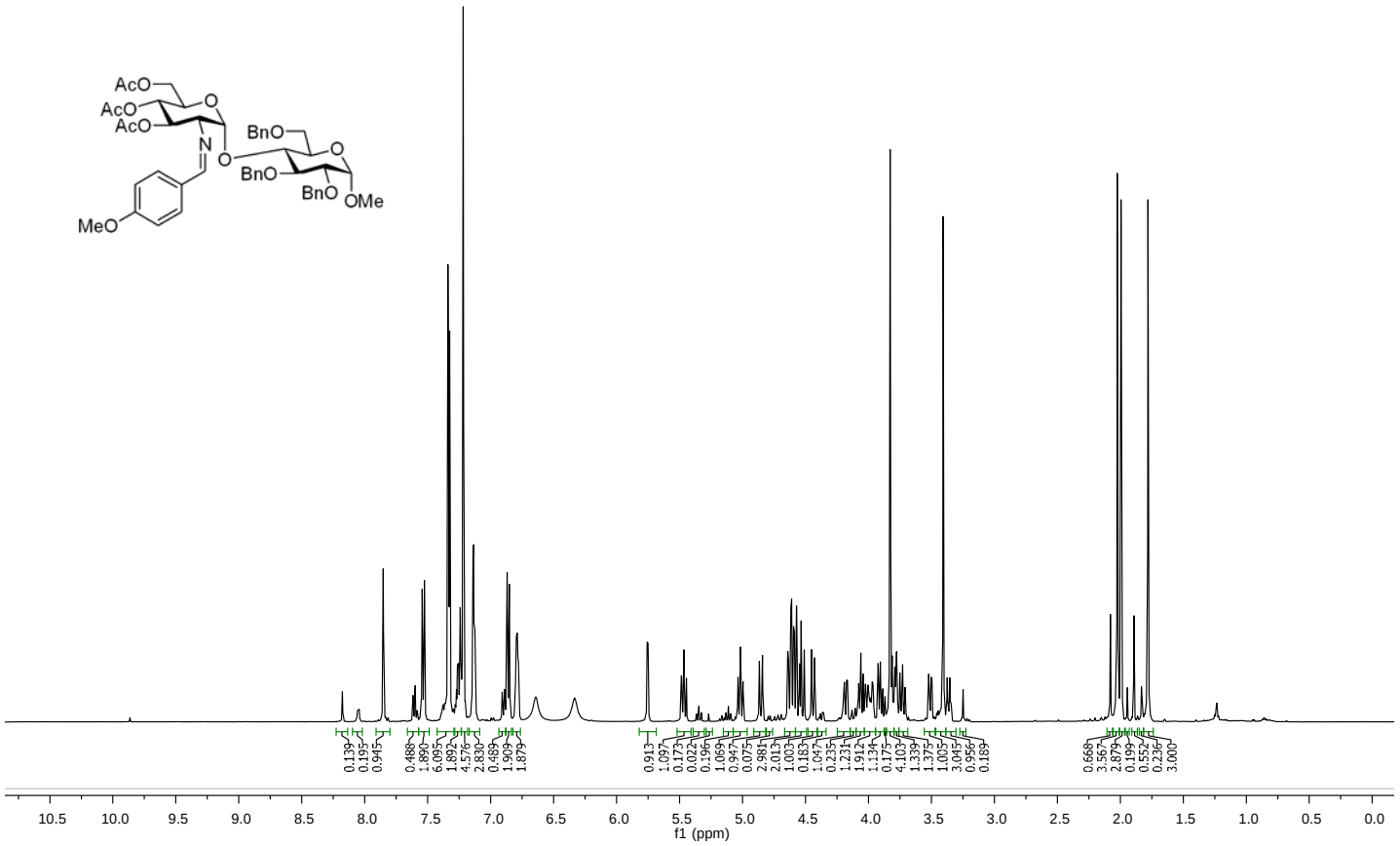


Figure A111. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **154**

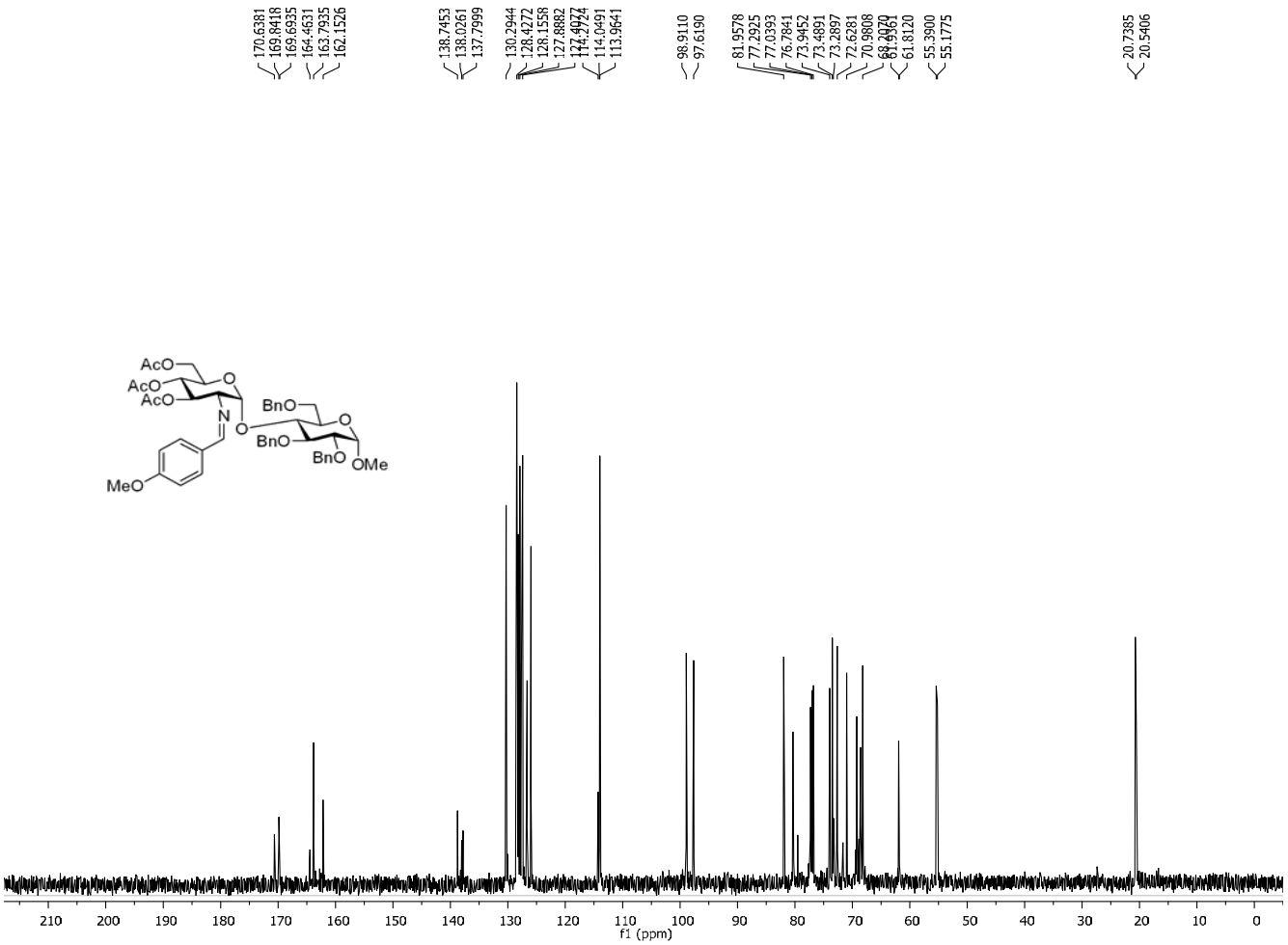


Figure A112. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **154**

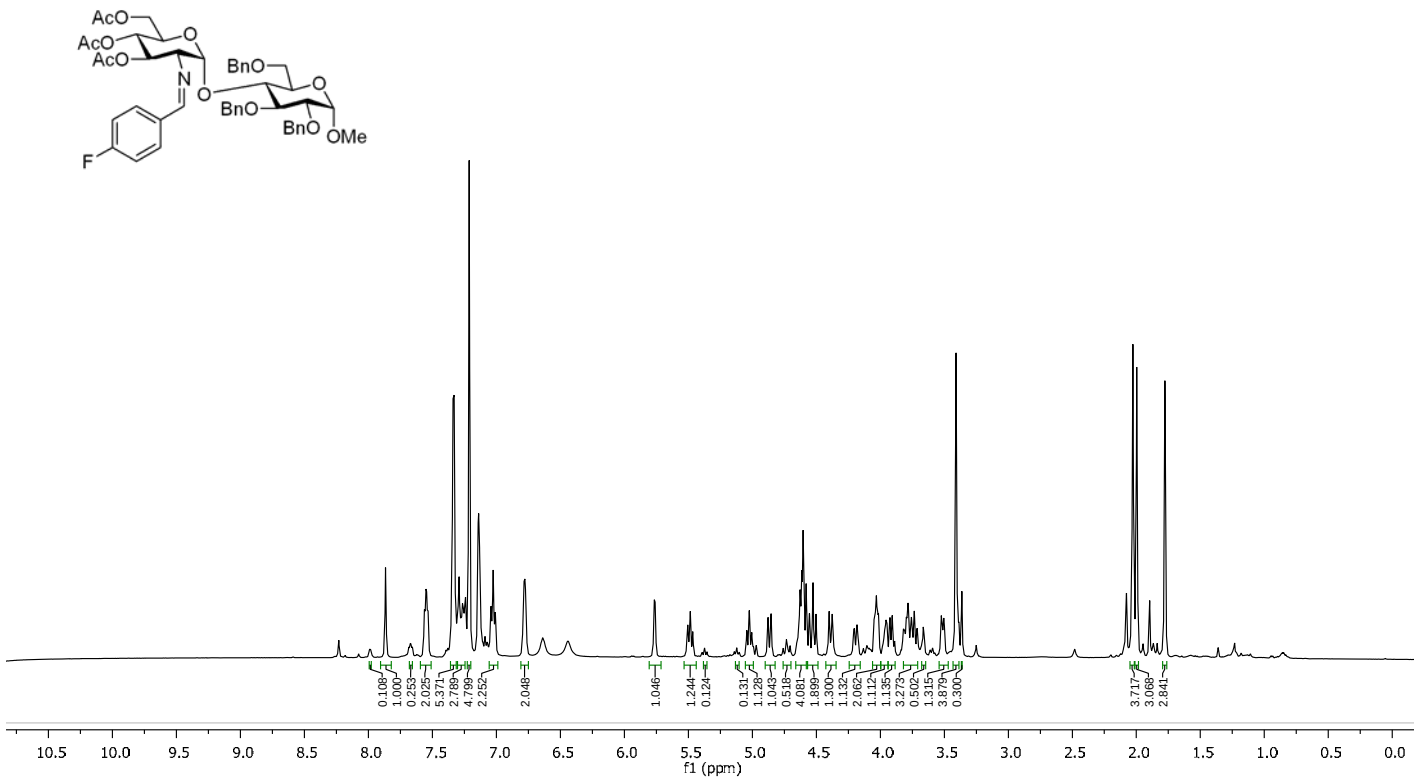


Figure A113. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide 155

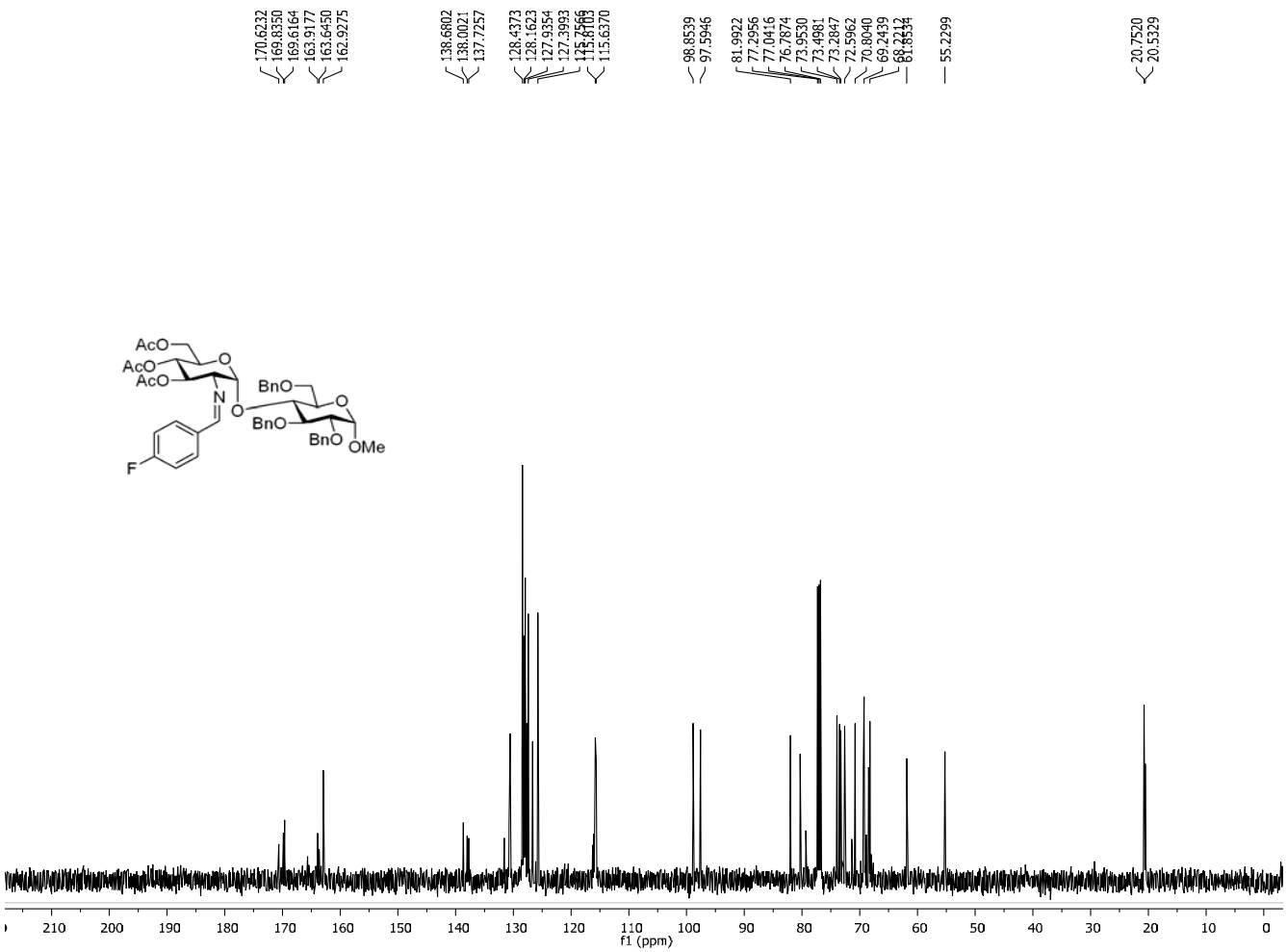


Figure A114. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **155**

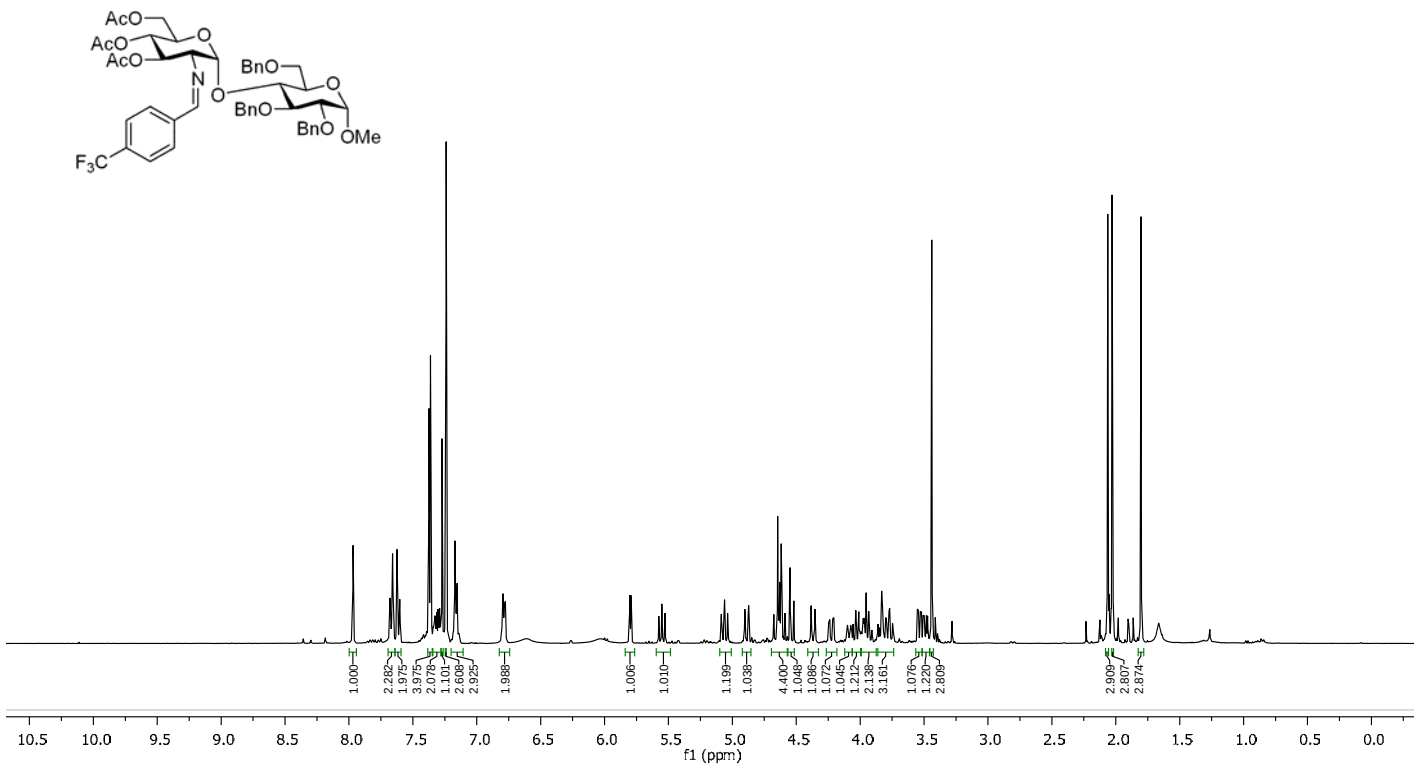


Figure A115. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide 156

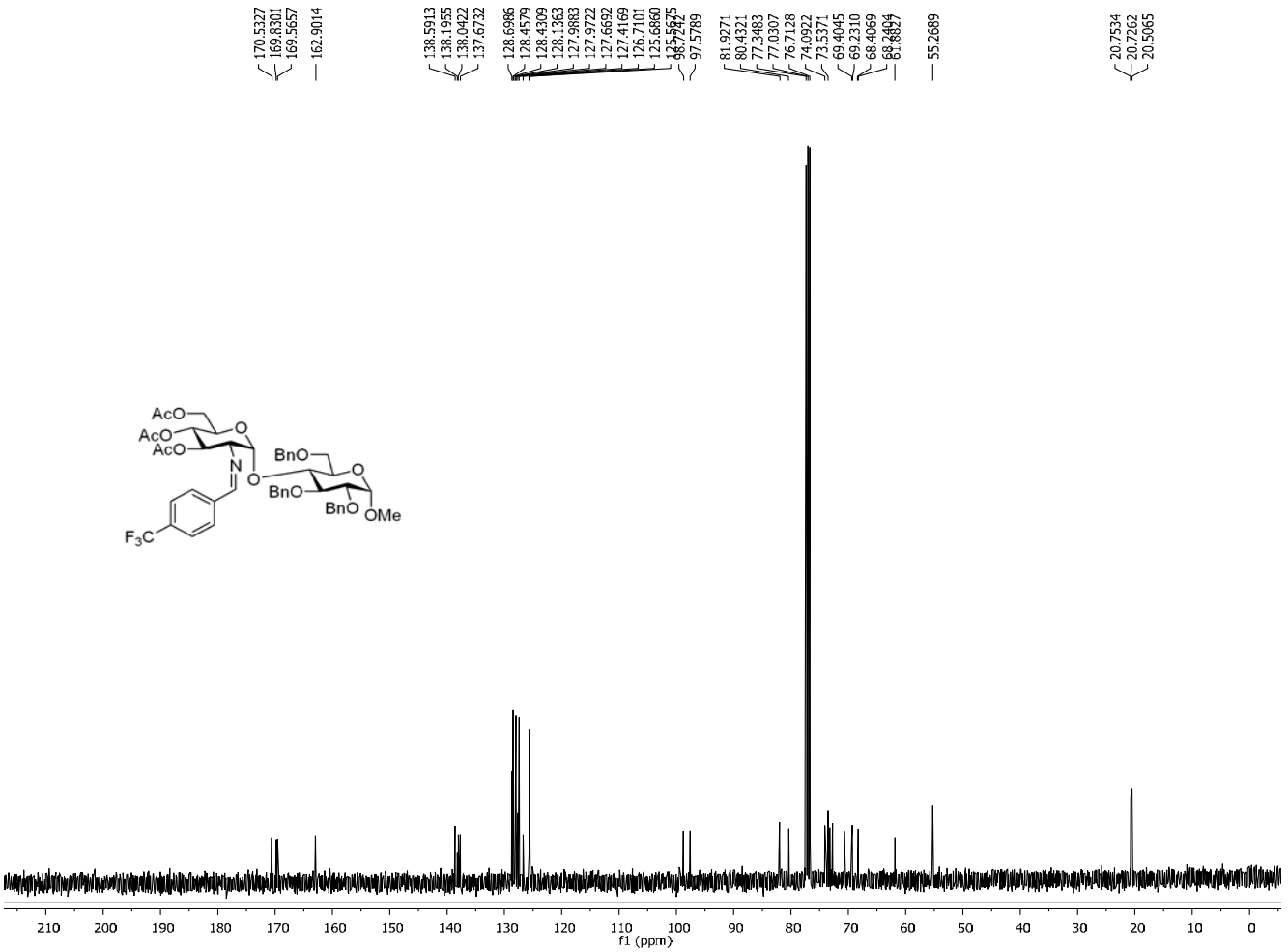


Figure A116. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **156**

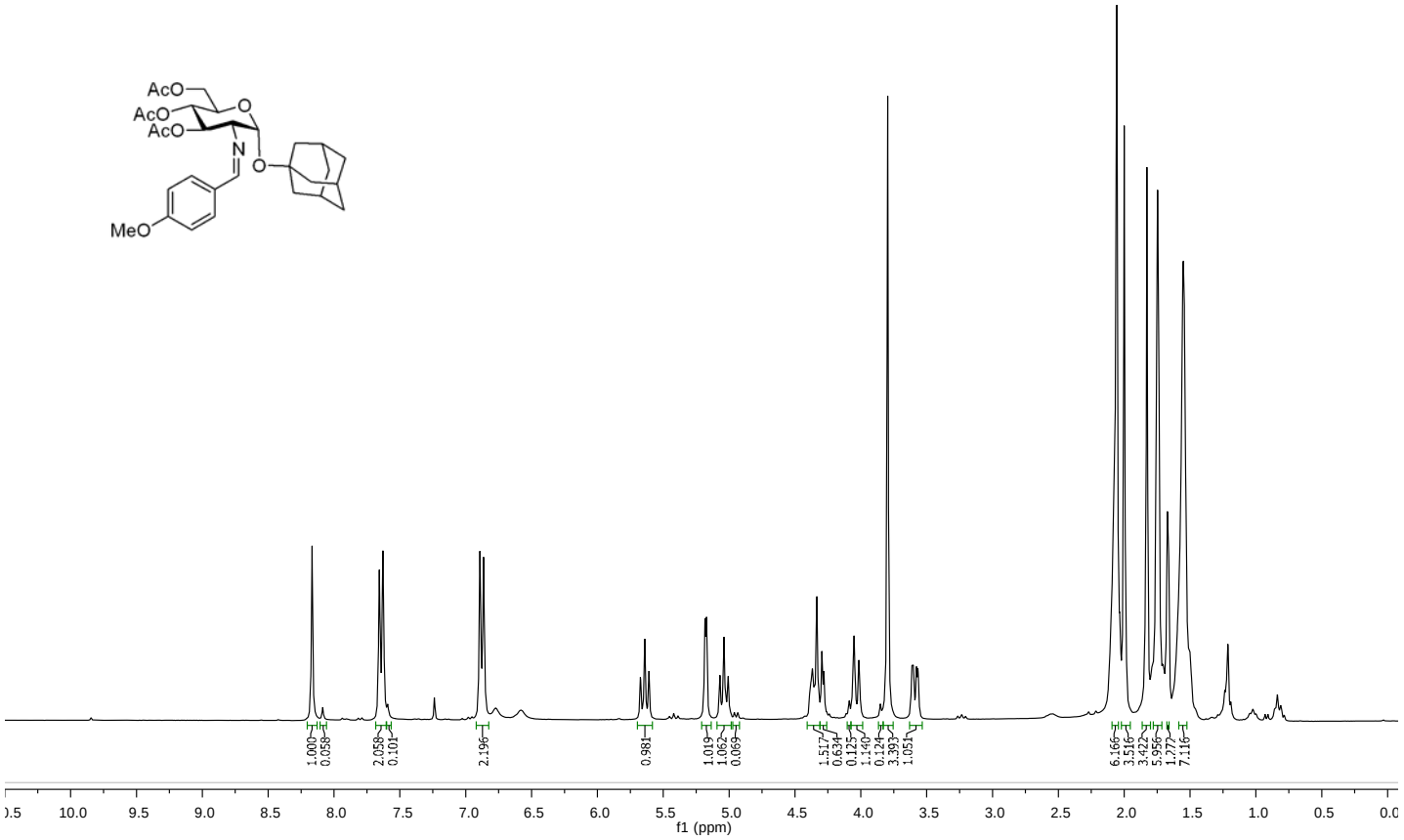


Figure A117. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate 157

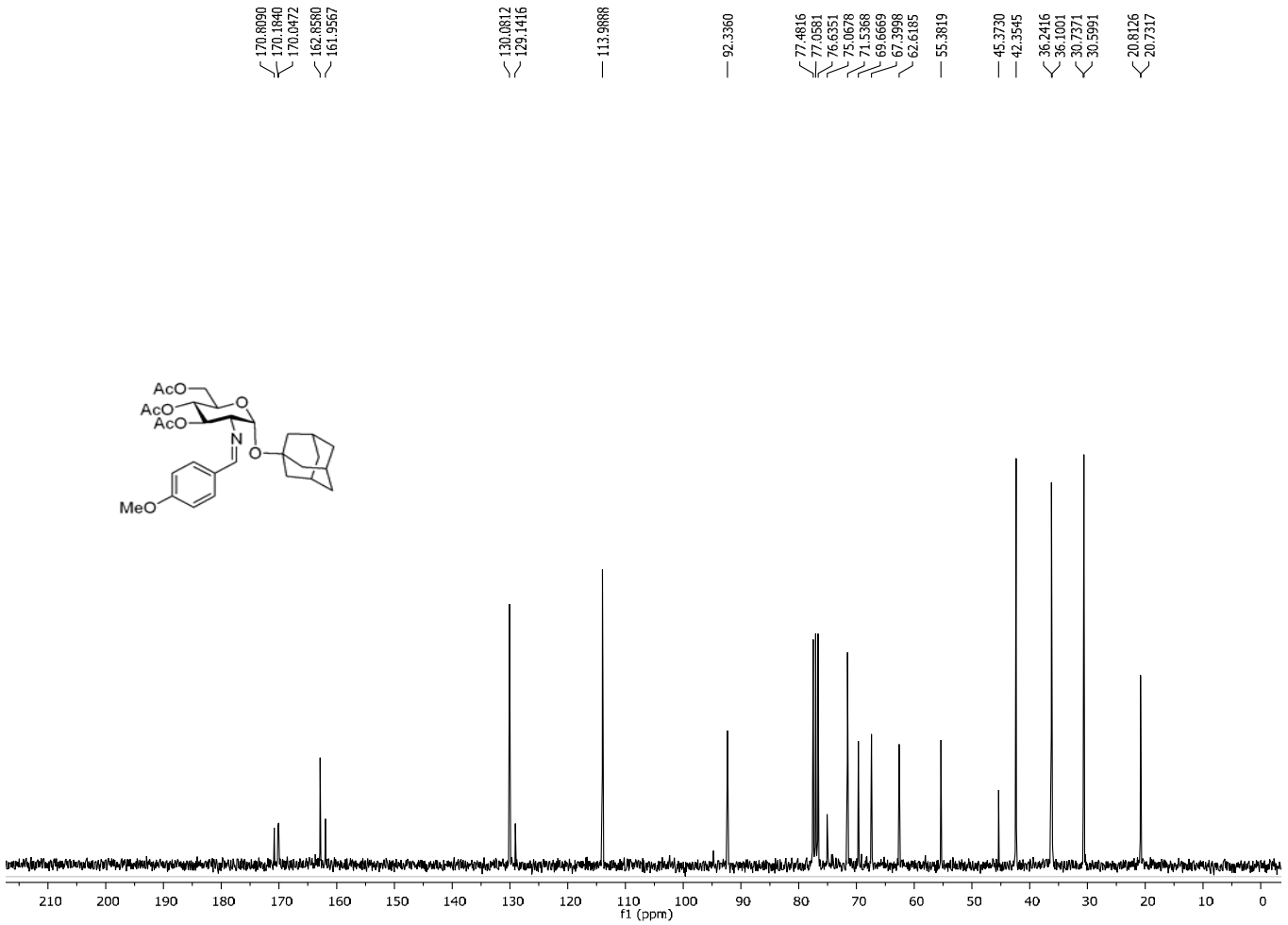


Figure A118. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **157**

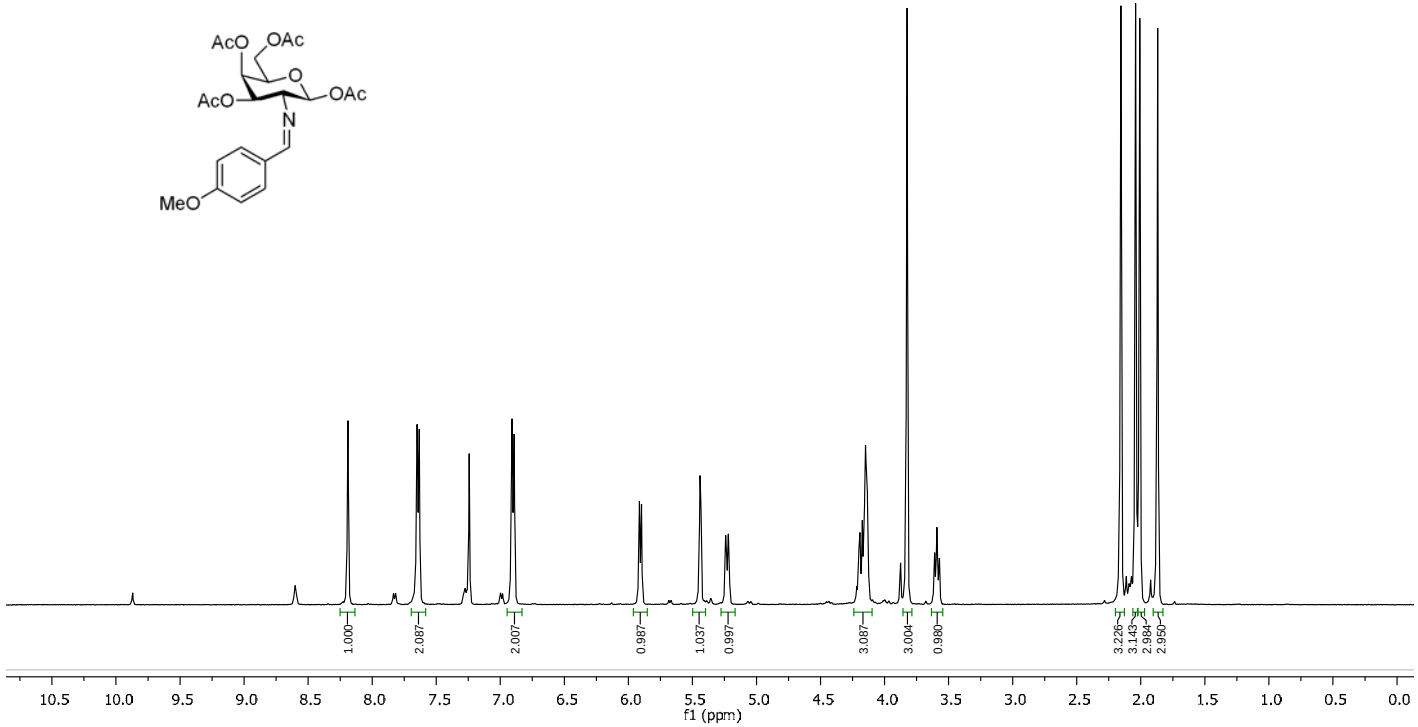


Figure A119. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound 158A

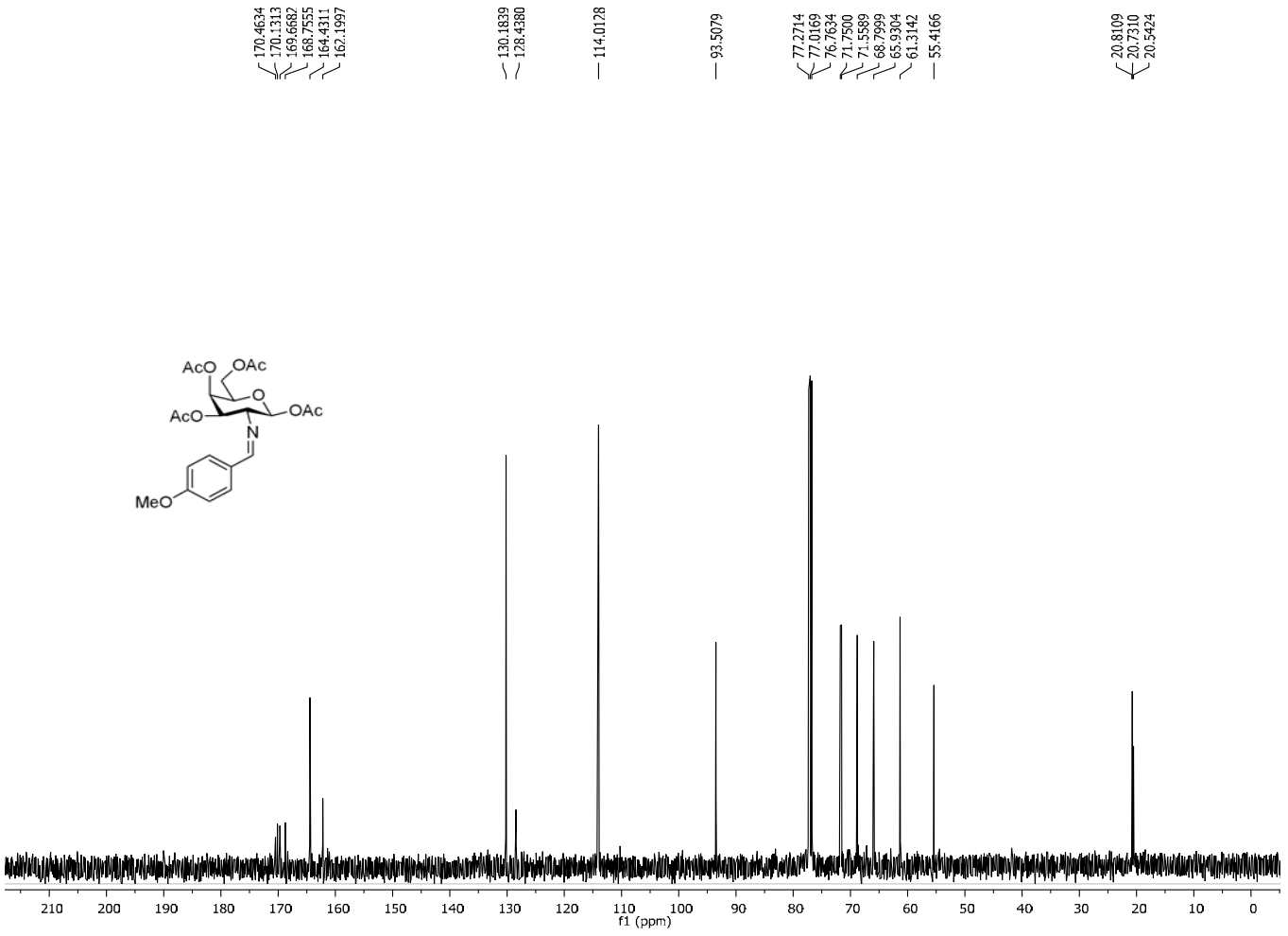


Figure A120. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **158A**

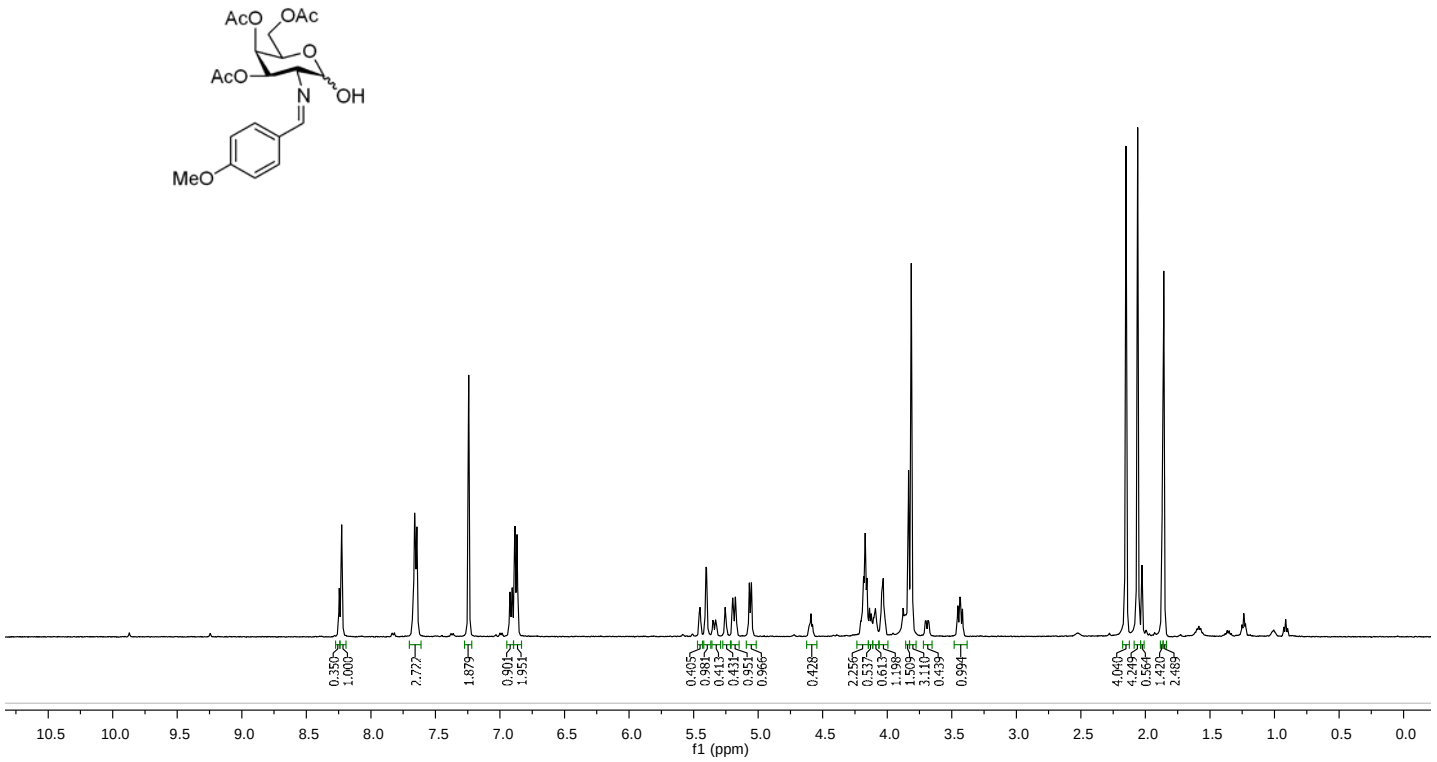


Figure A121. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal 158B

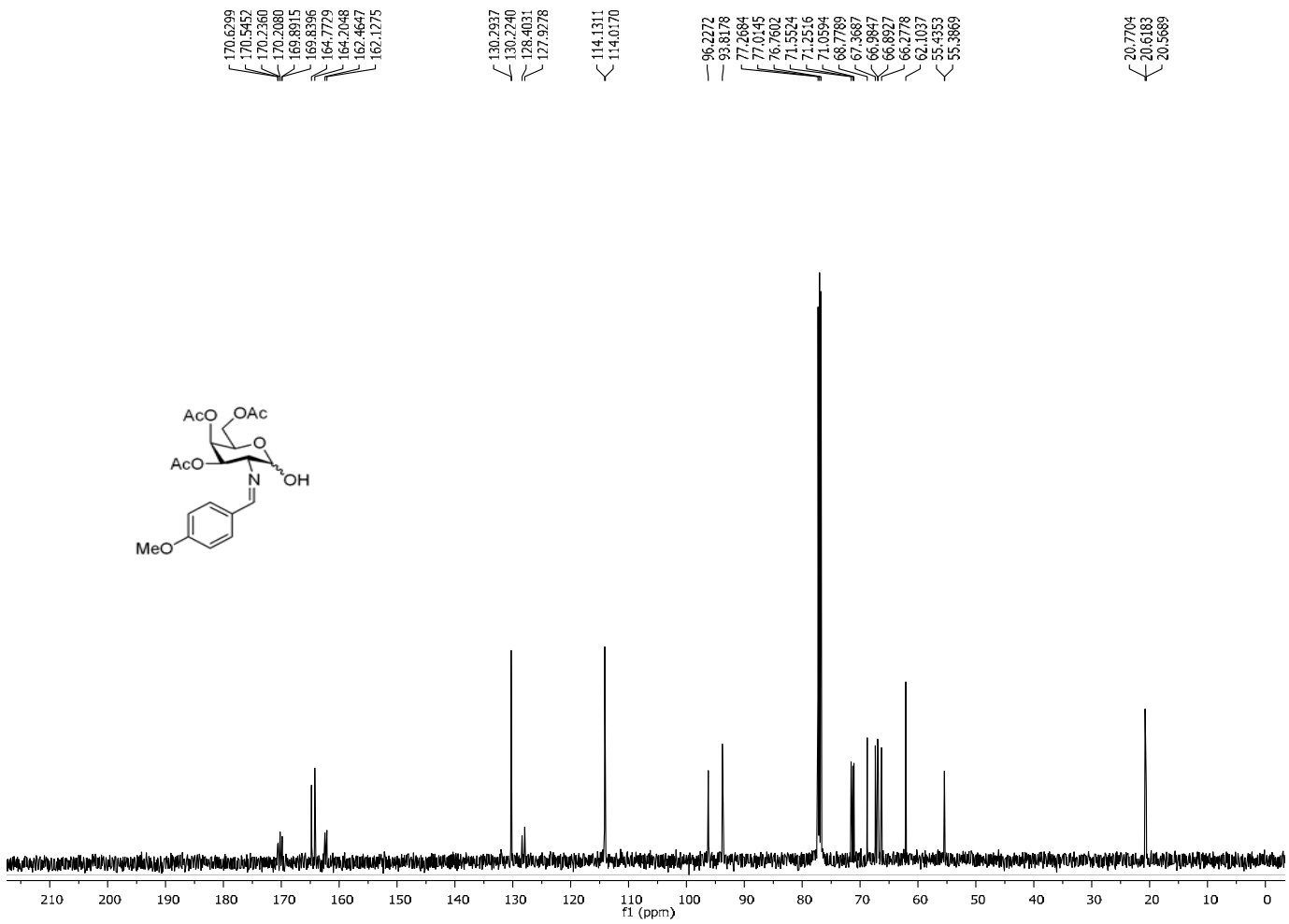


Figure A122. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **158B**

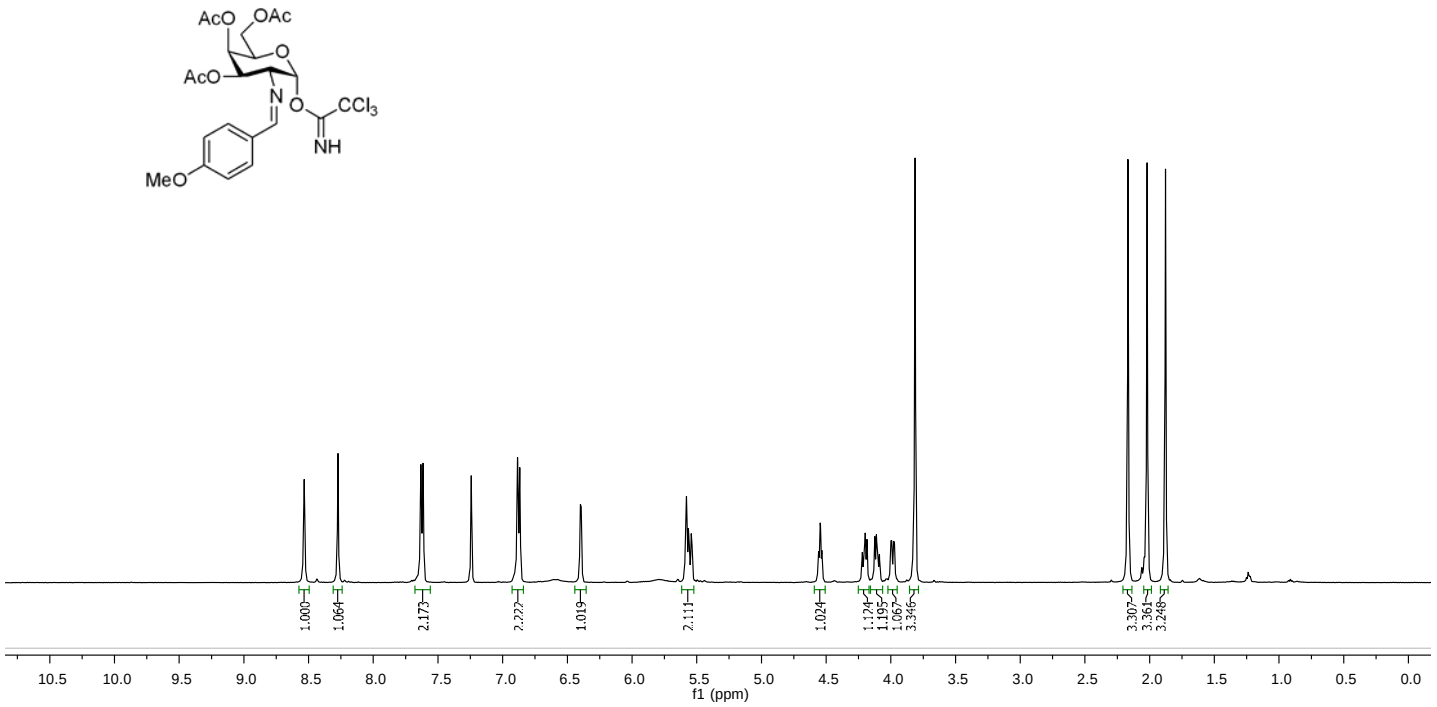


Figure A123. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **158**

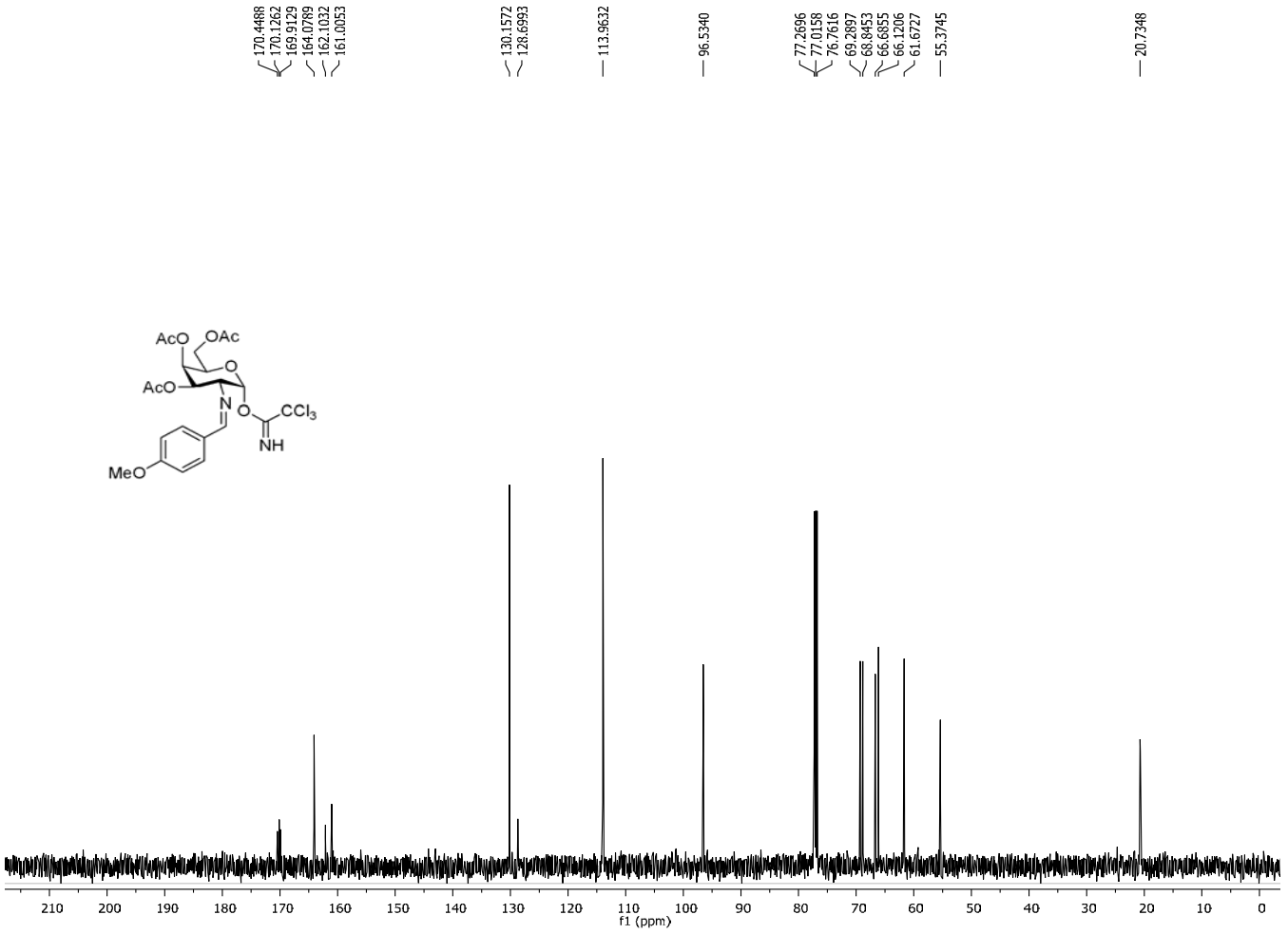


Figure A124. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **158**

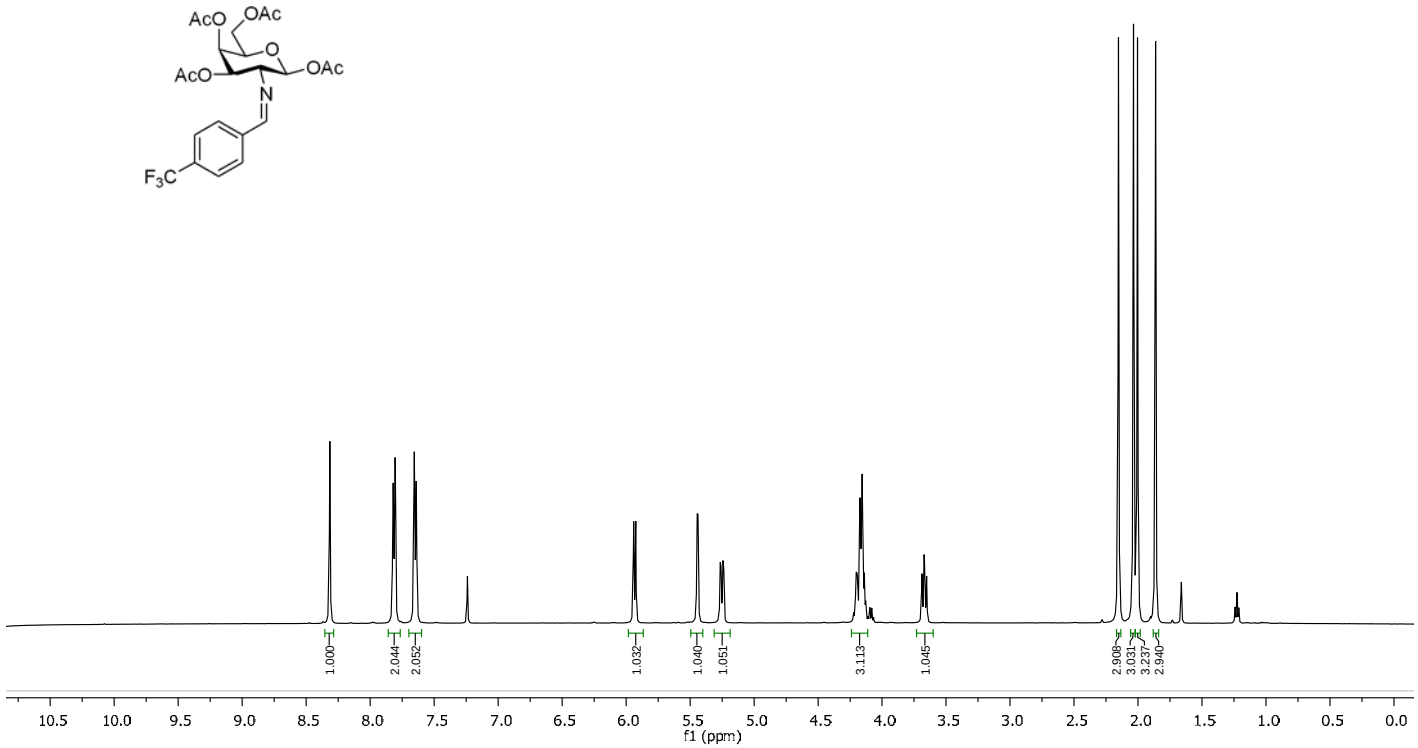


Figure A125. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **158C**

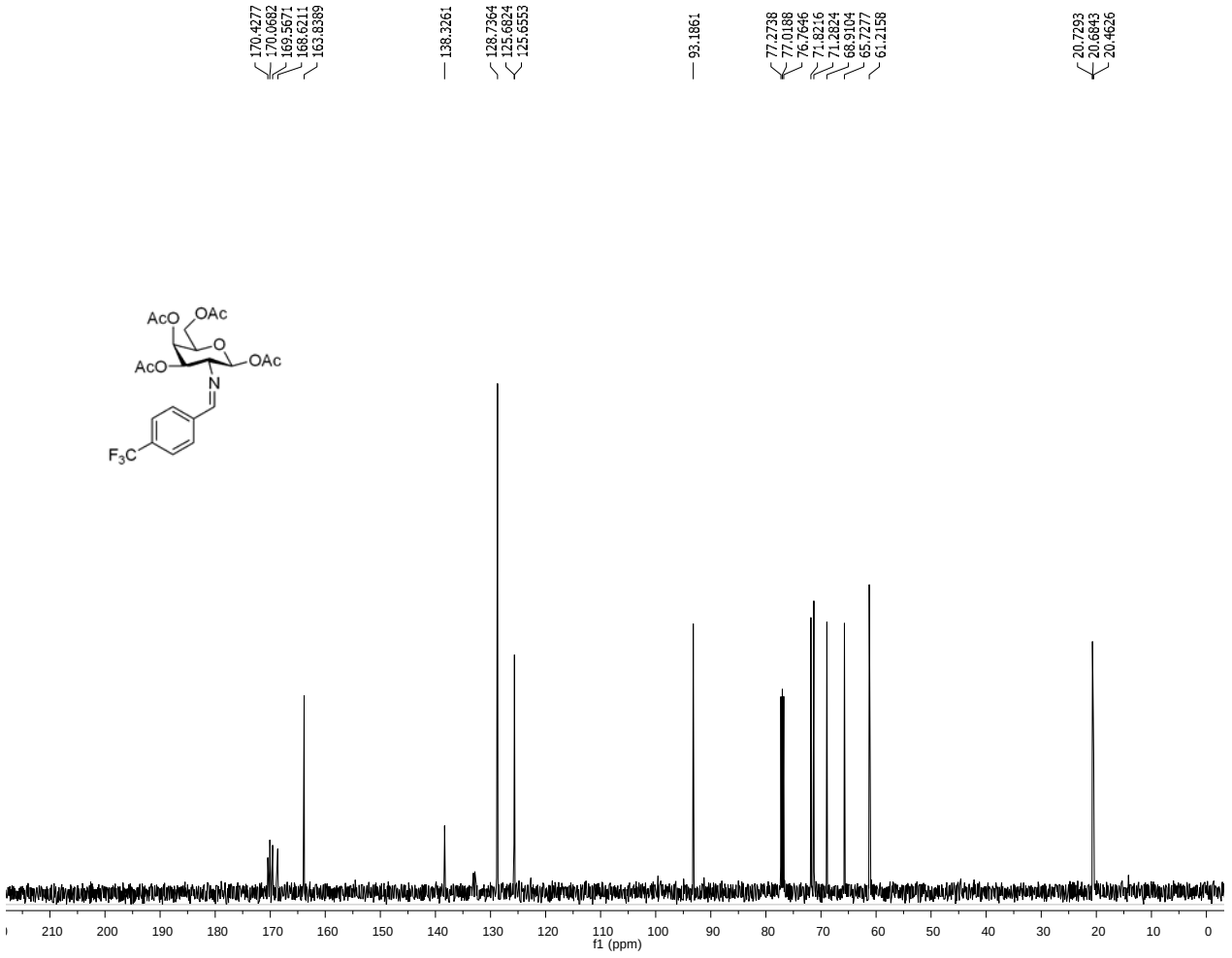


Figure A126. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **158C**

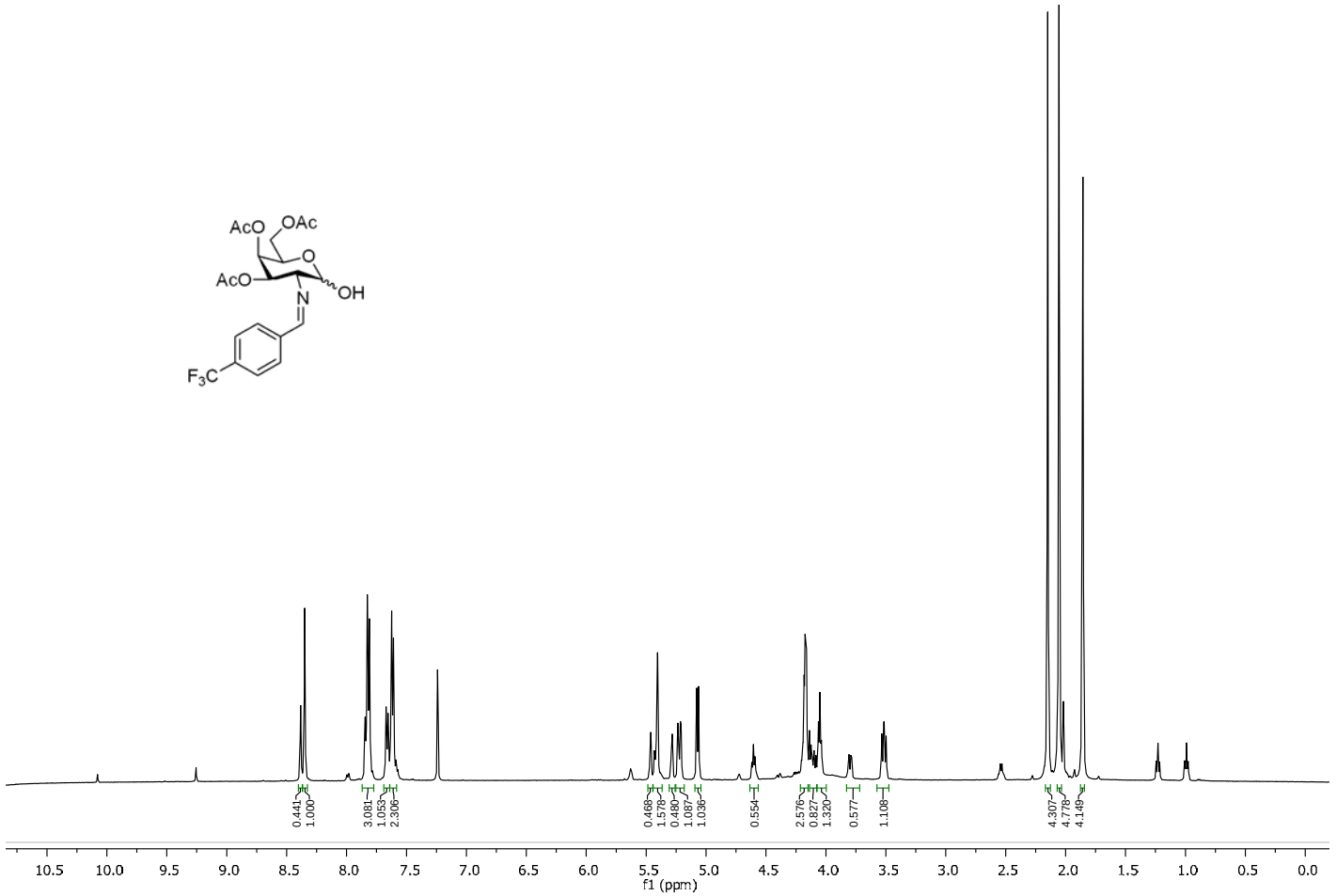


Figure A127. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **158D**

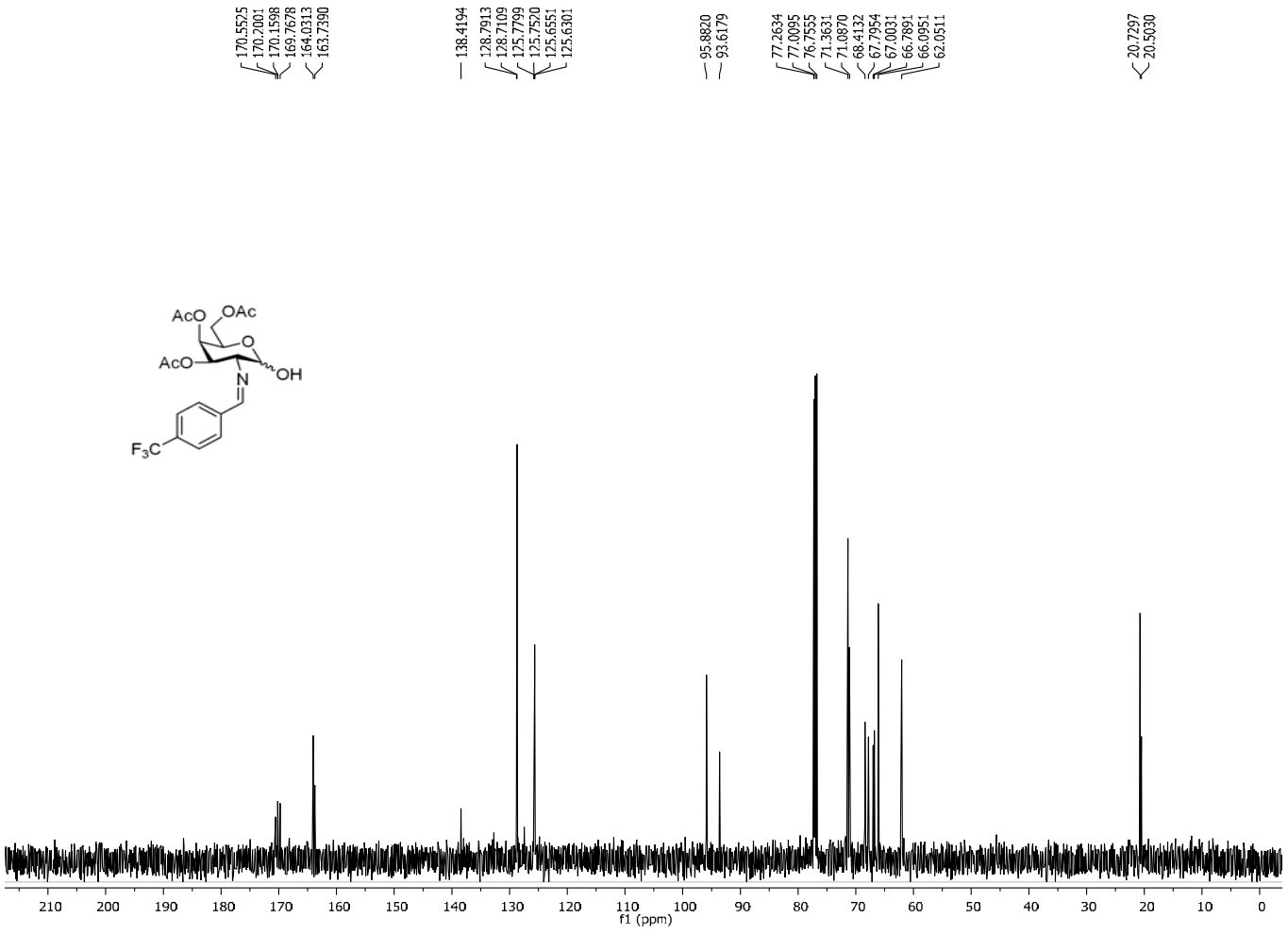


Figure A128. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **158D**

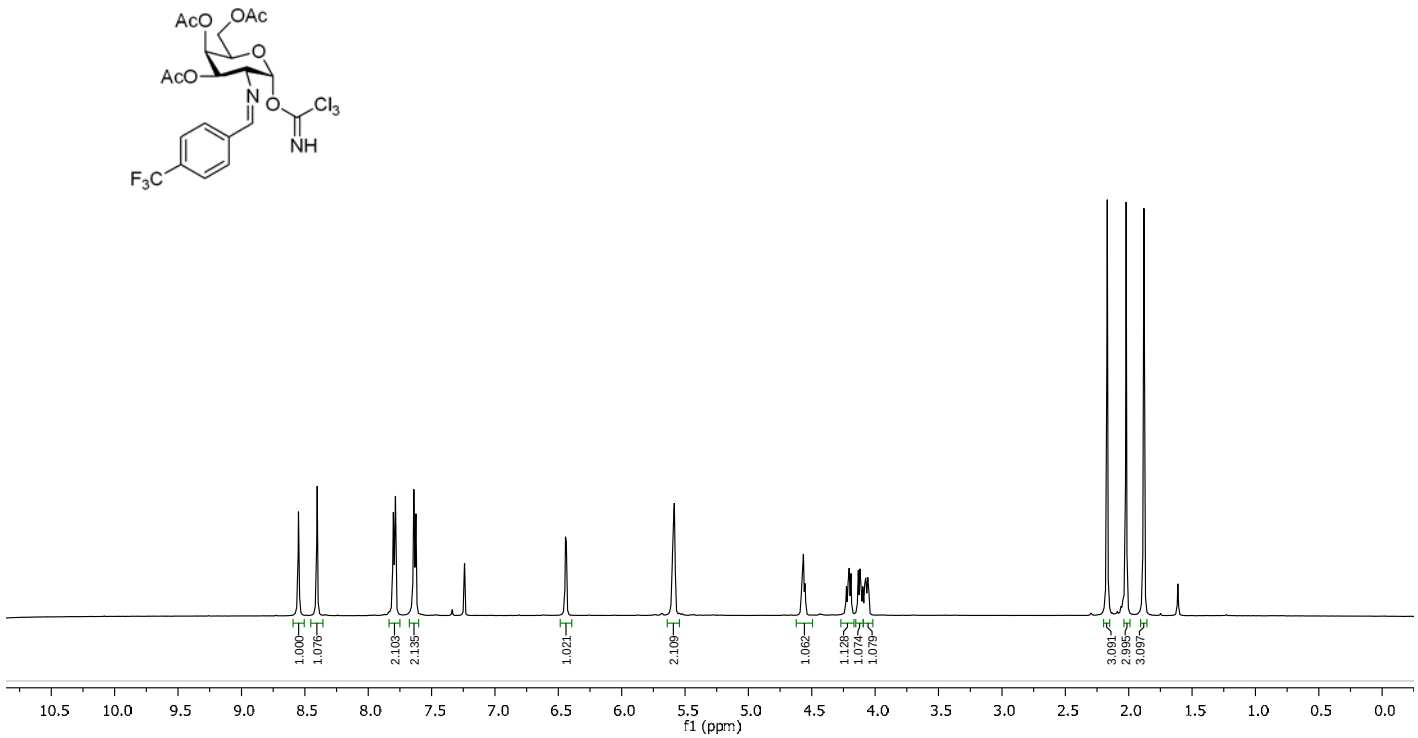


Figure A129. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **158E**

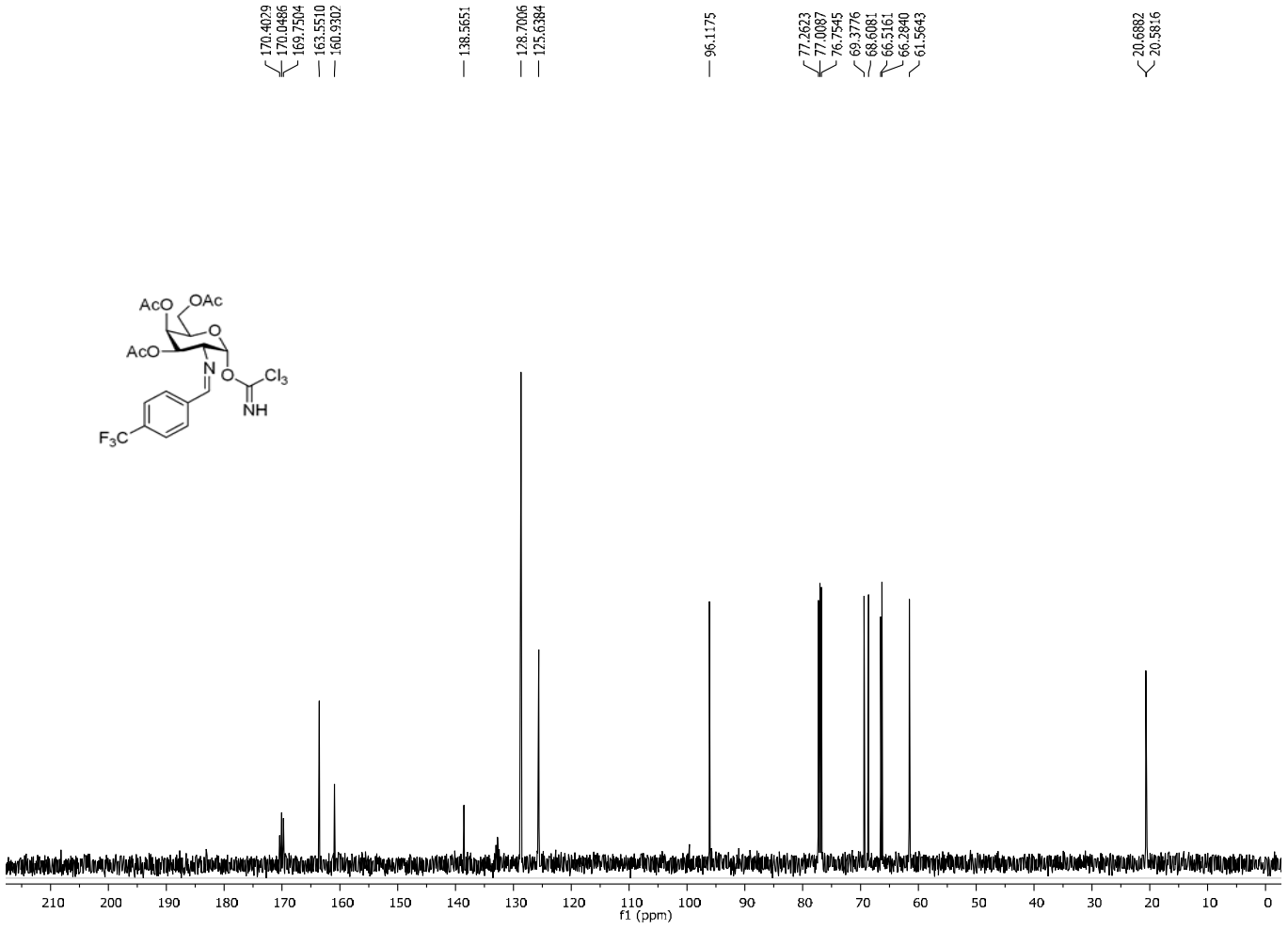


Figure A130. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **158E**

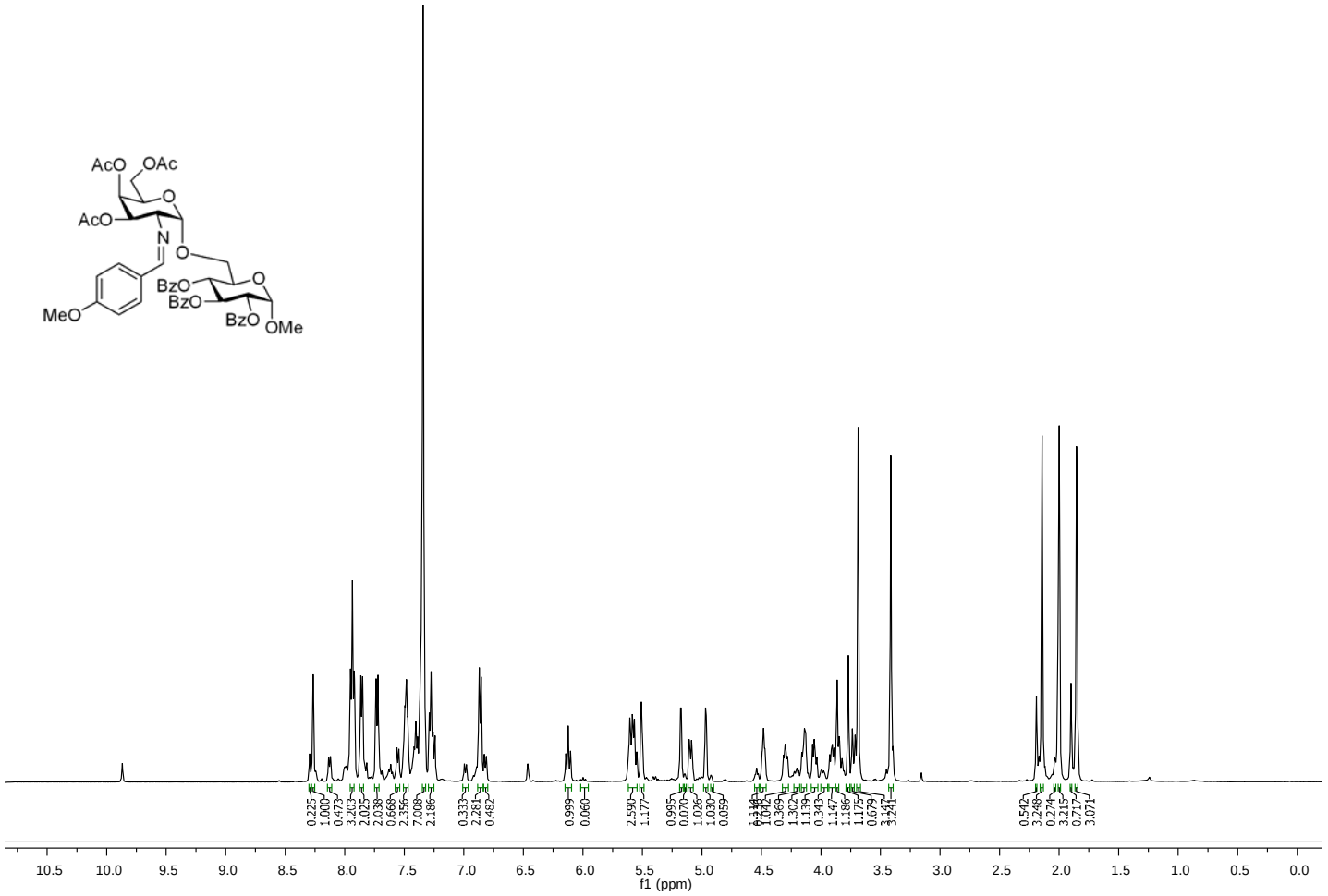


Figure A131. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **159**

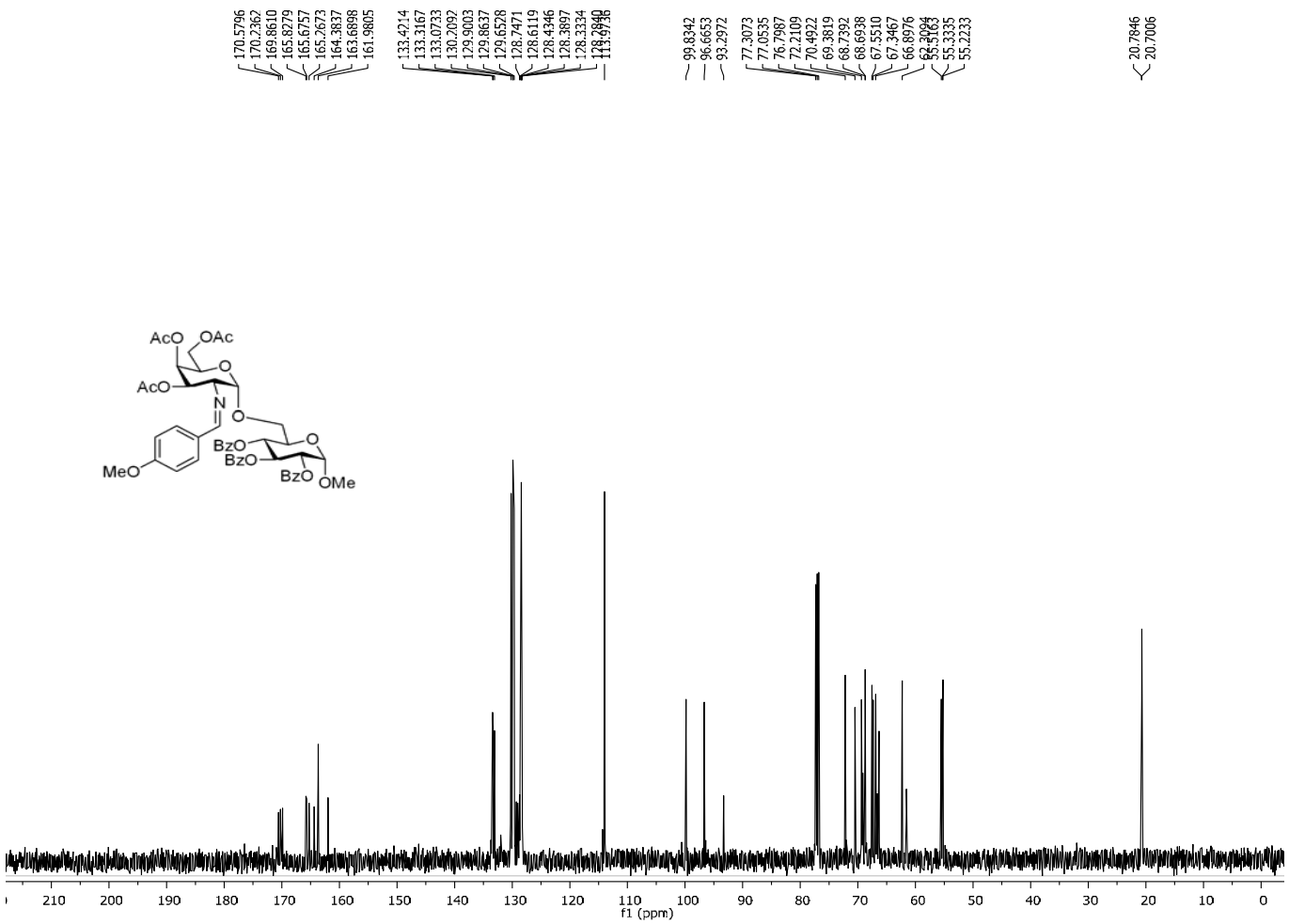


Figure A132. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **159**

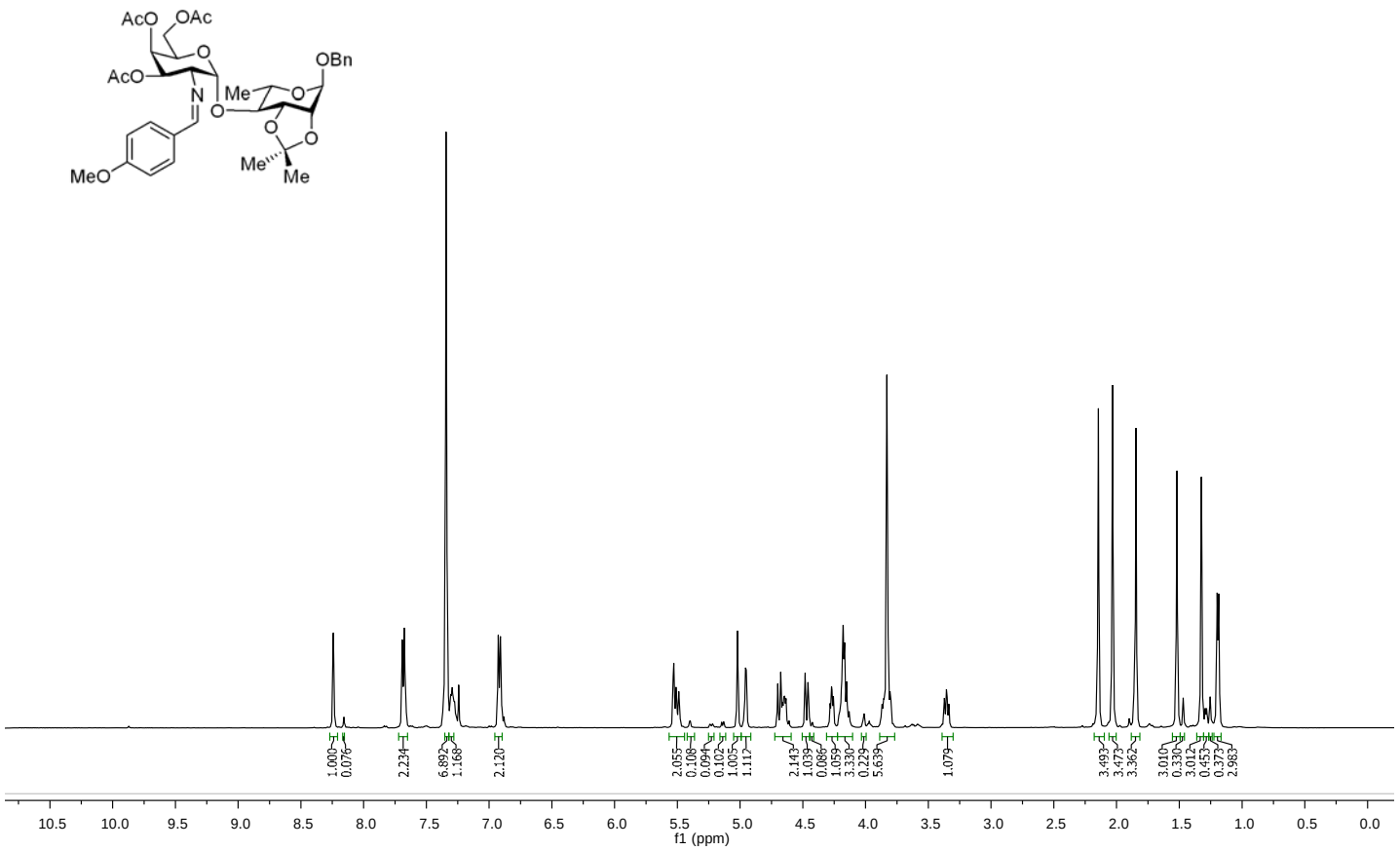


Figure A133. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **160**

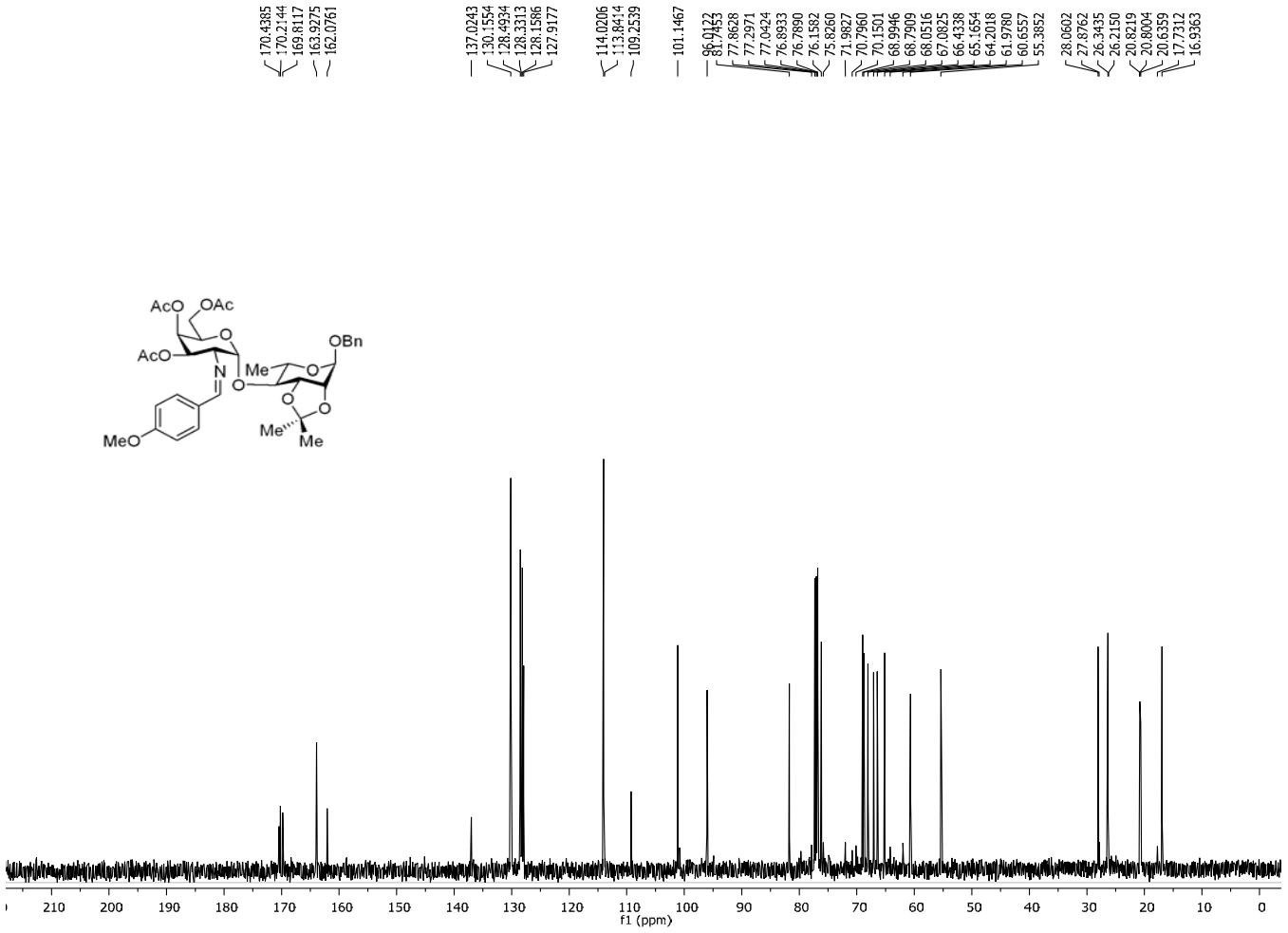


Figure A134. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **160**

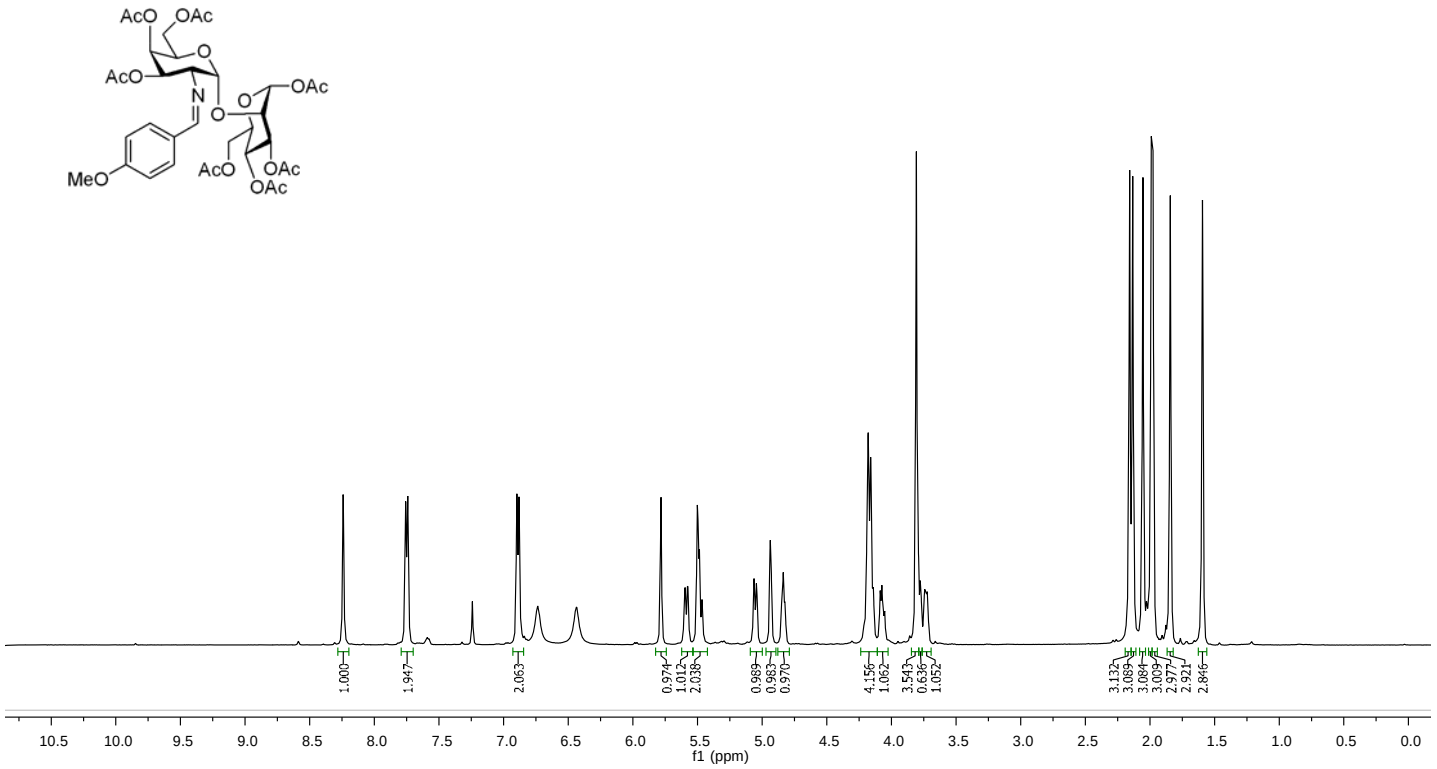


Figure A135. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **161**

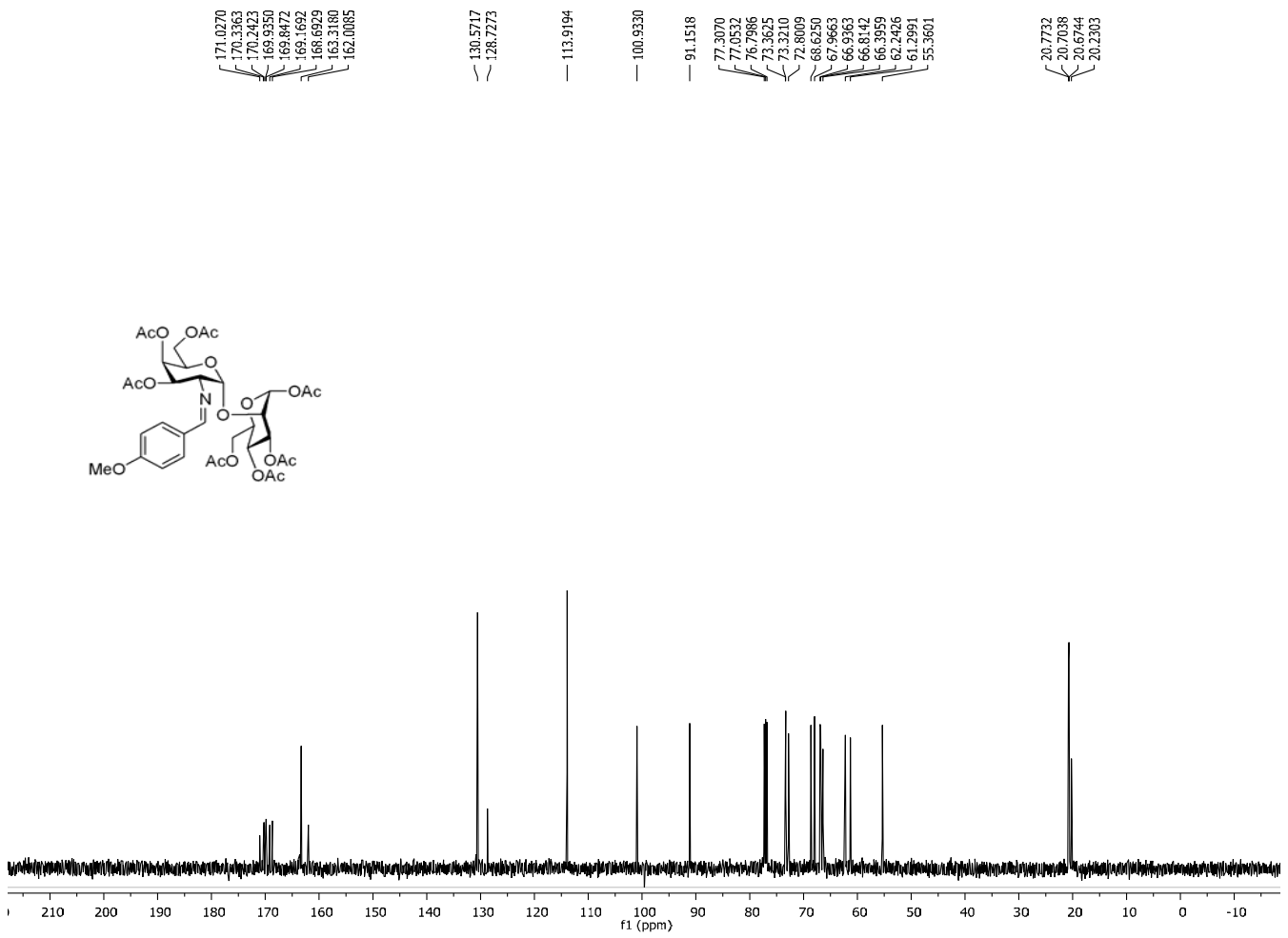


Figure A136. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **161**

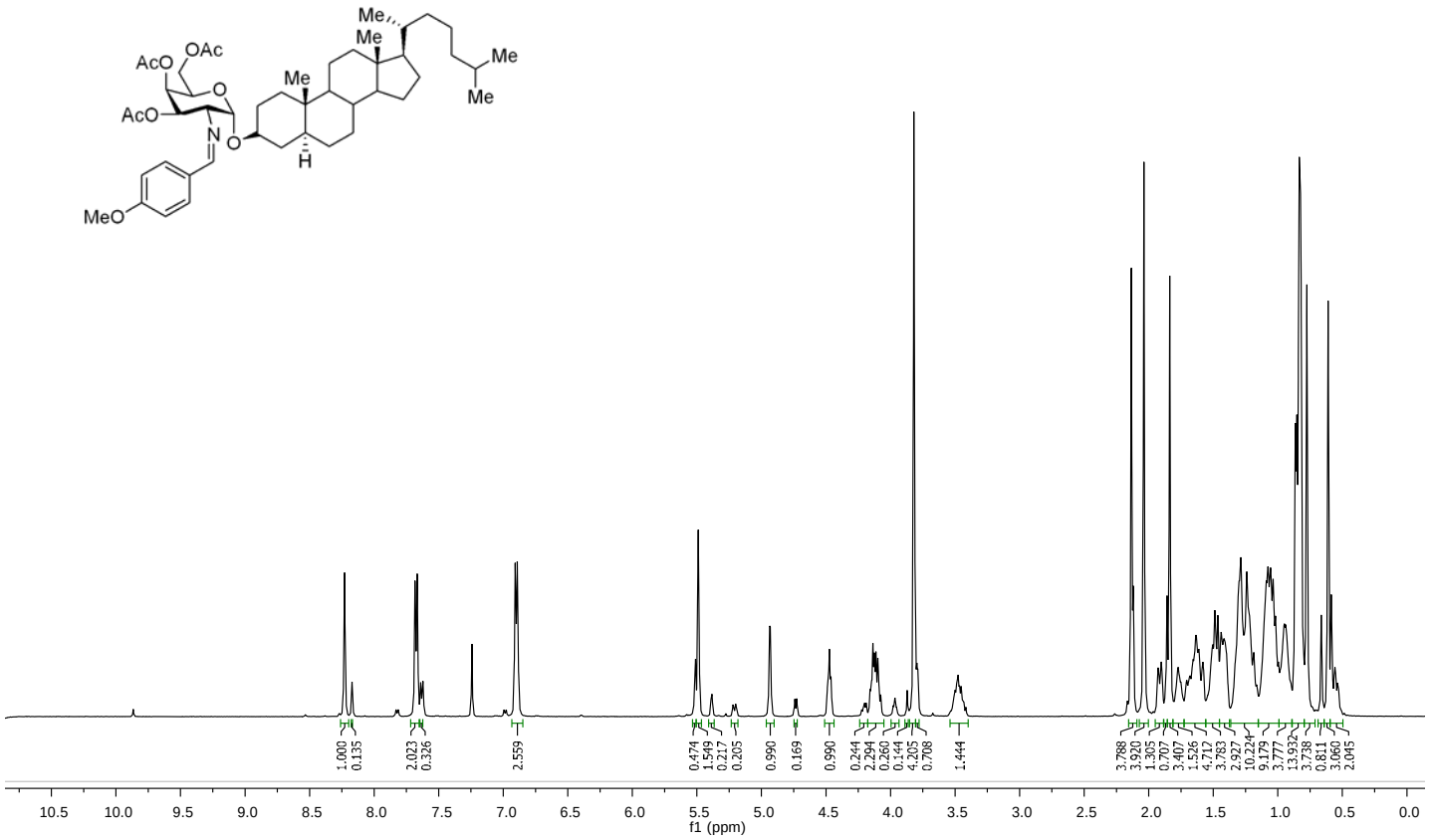


Figure A137. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **162**

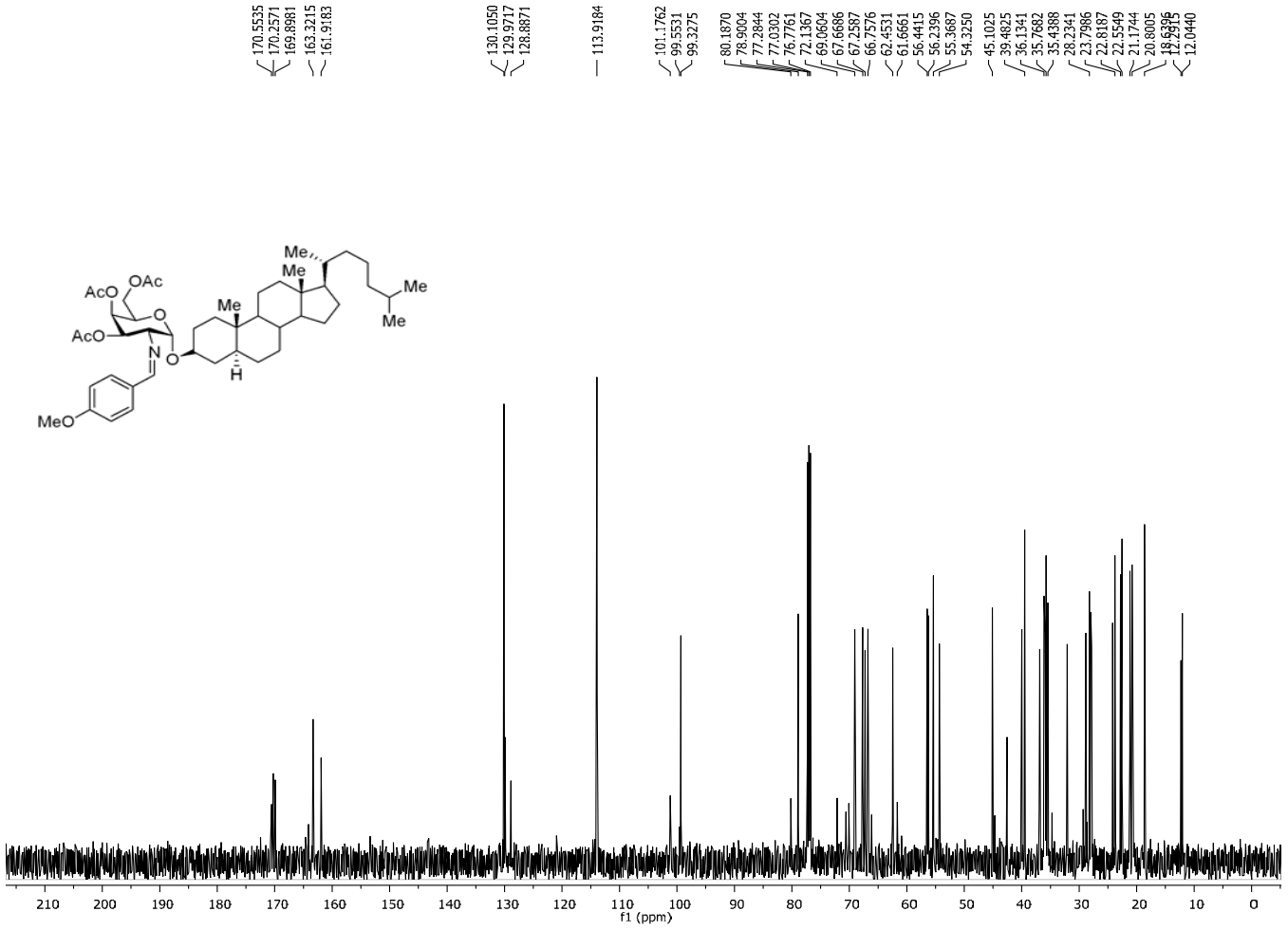


Figure A138. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **162**

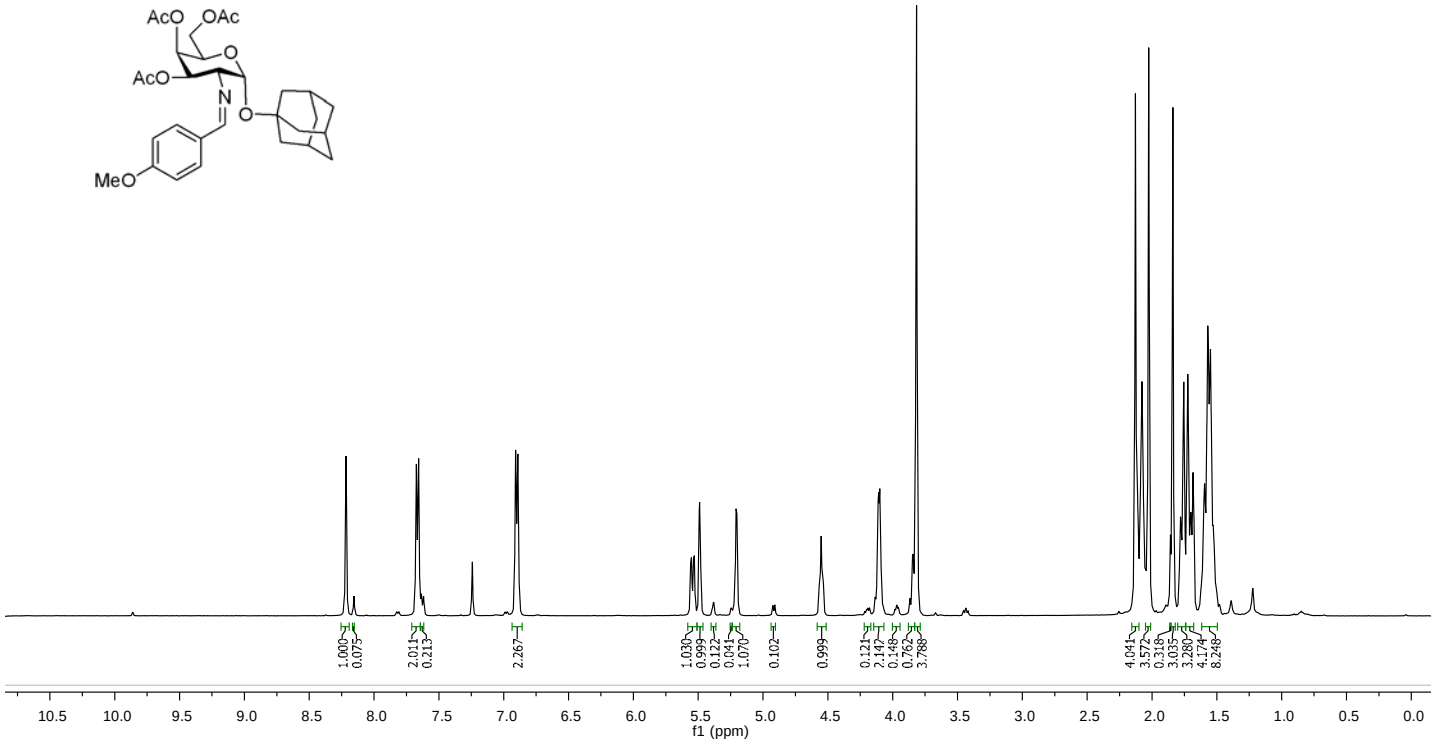


Figure A139. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **163**

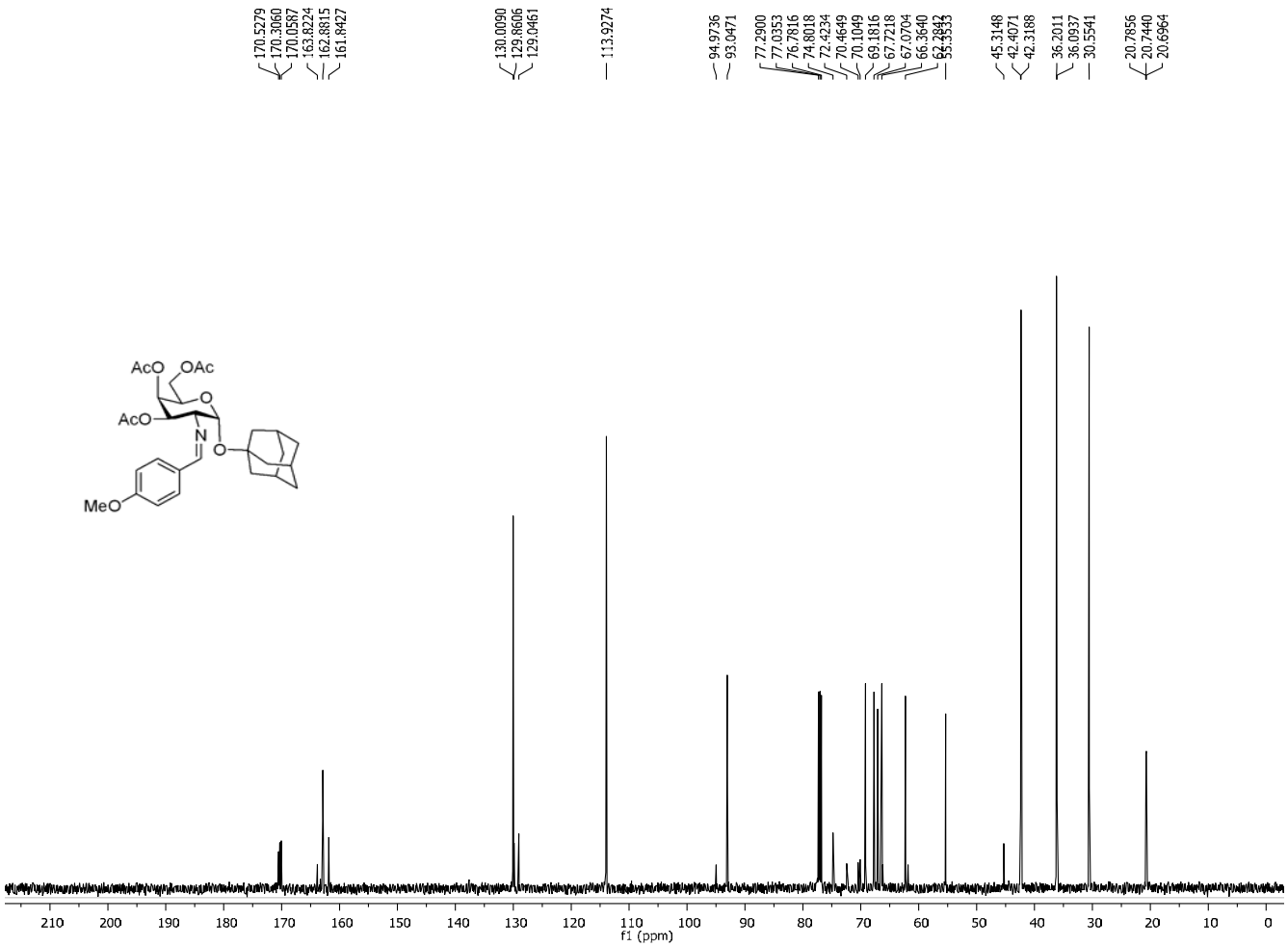


Figure A140. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **163**

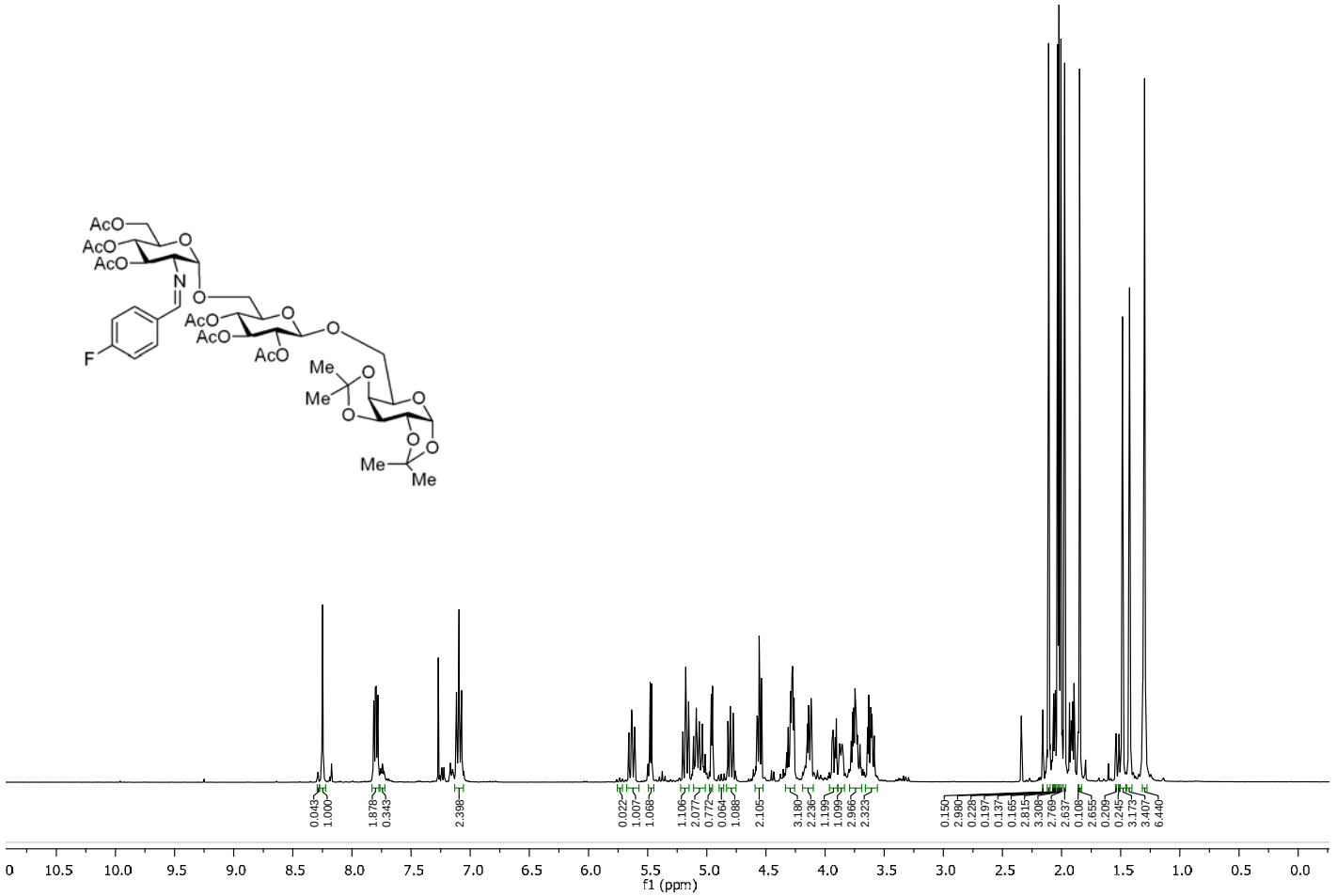


Figure A141. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **167**

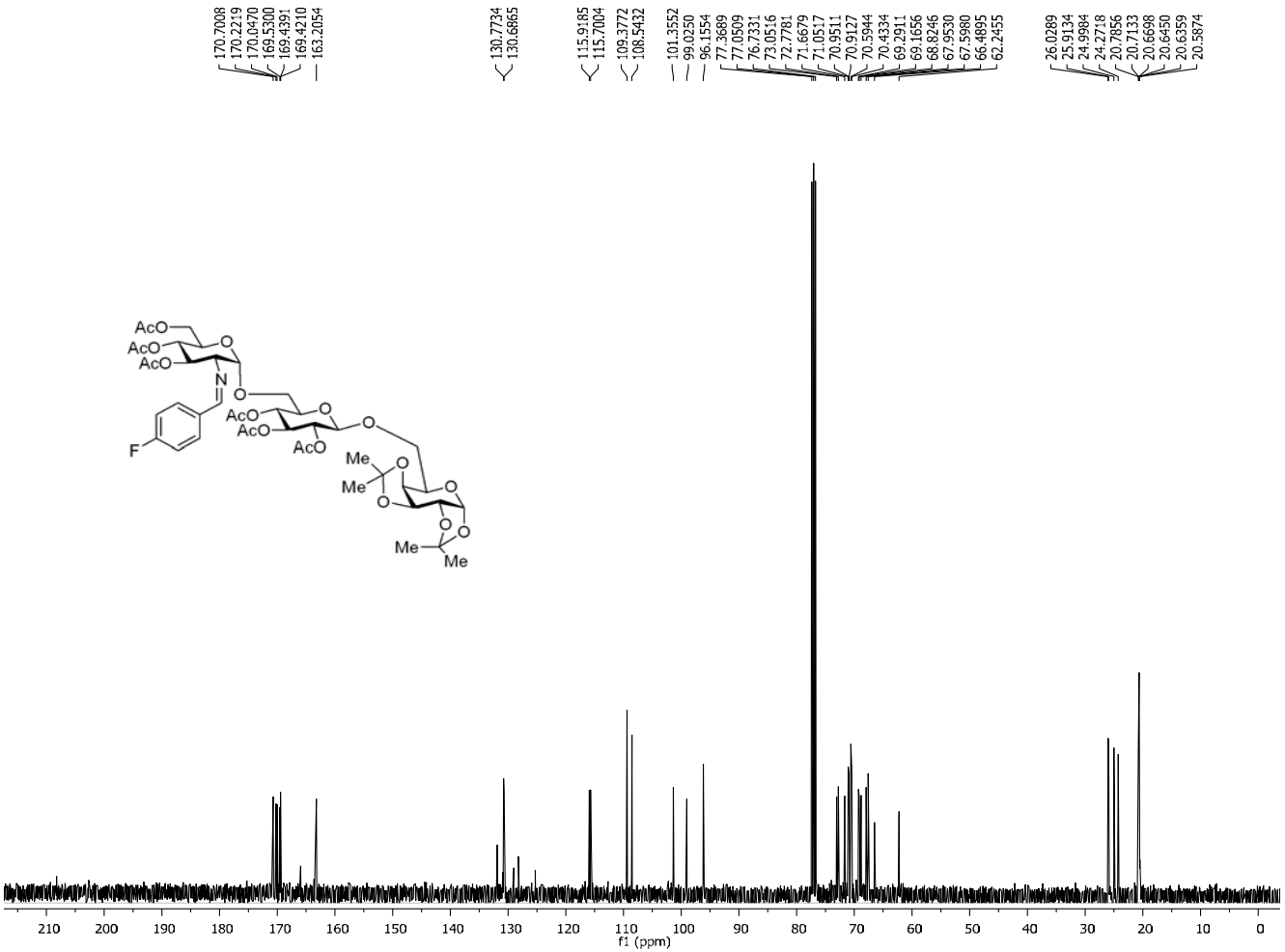


Figure A142. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **167**

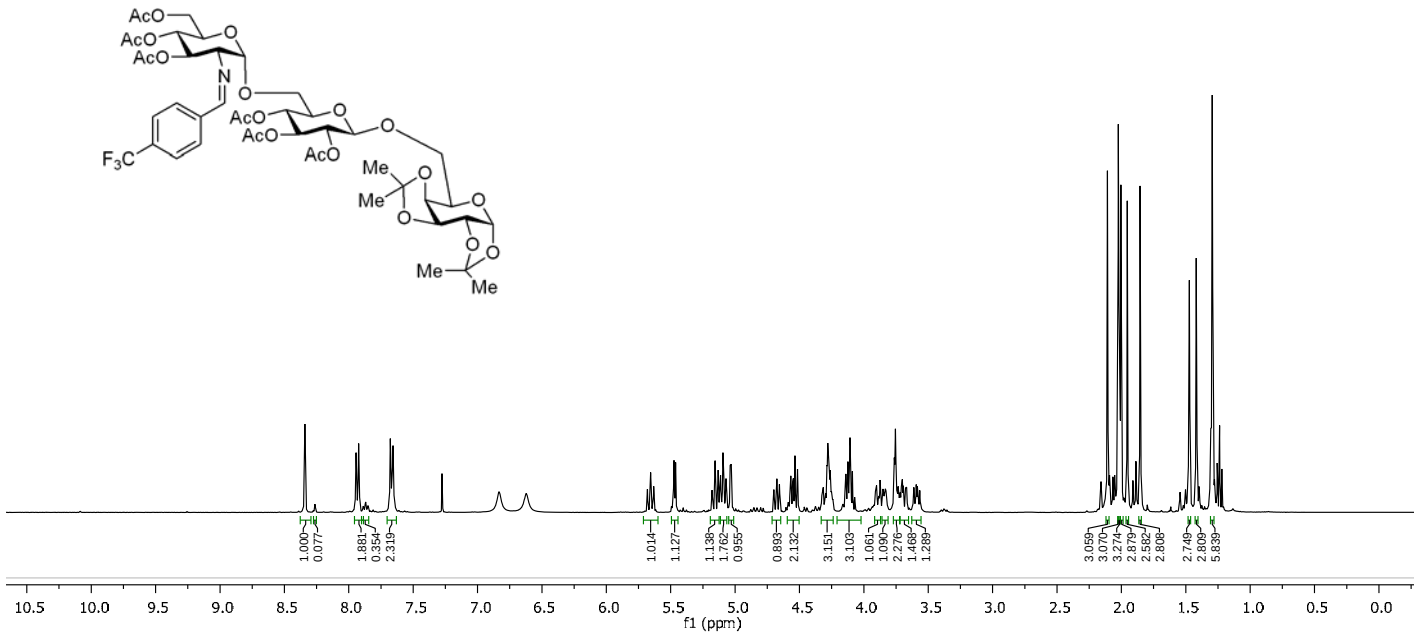


Figure A143. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **168**

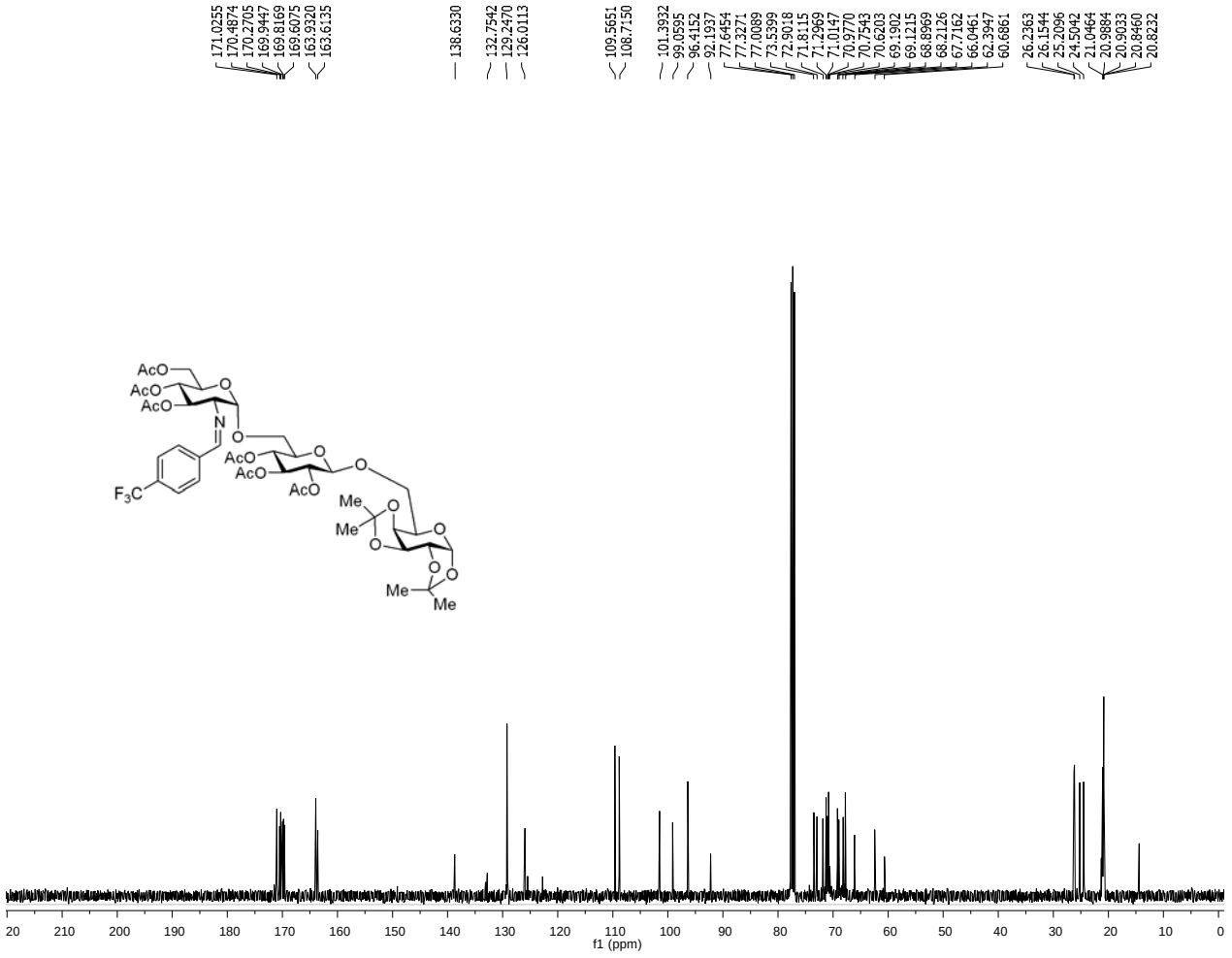


Figure A144. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **168**

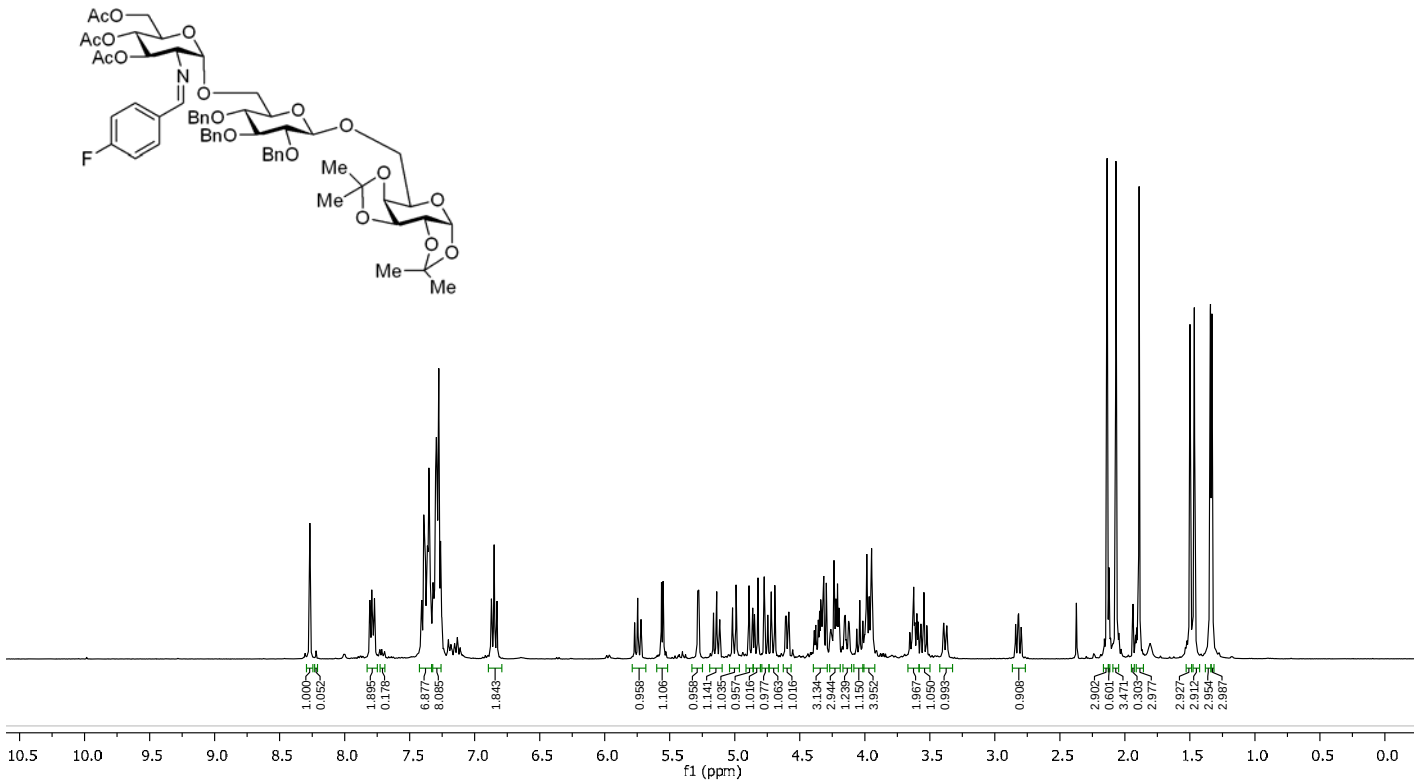


Figure A145. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **169**

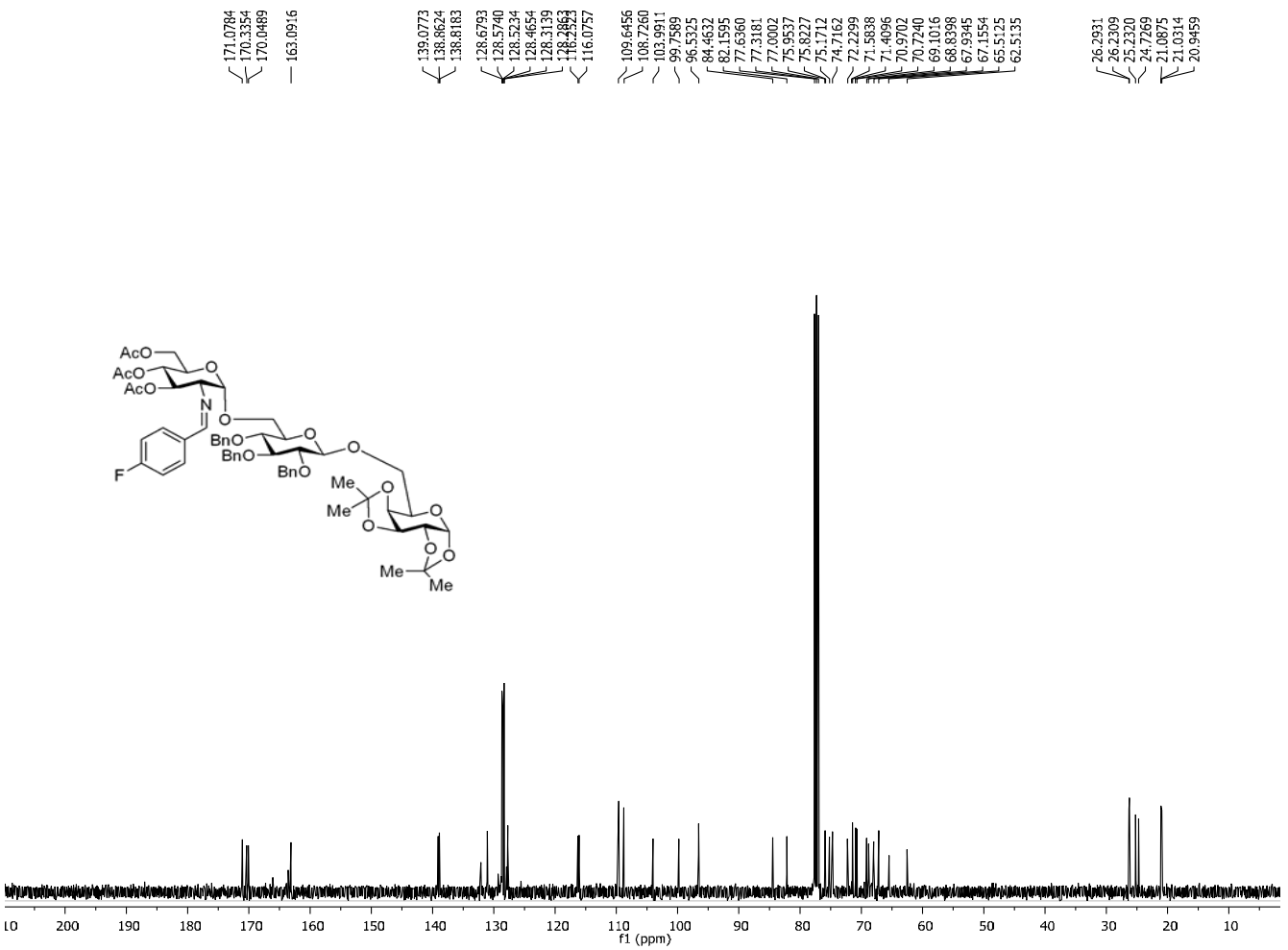


Figure A146. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **169**

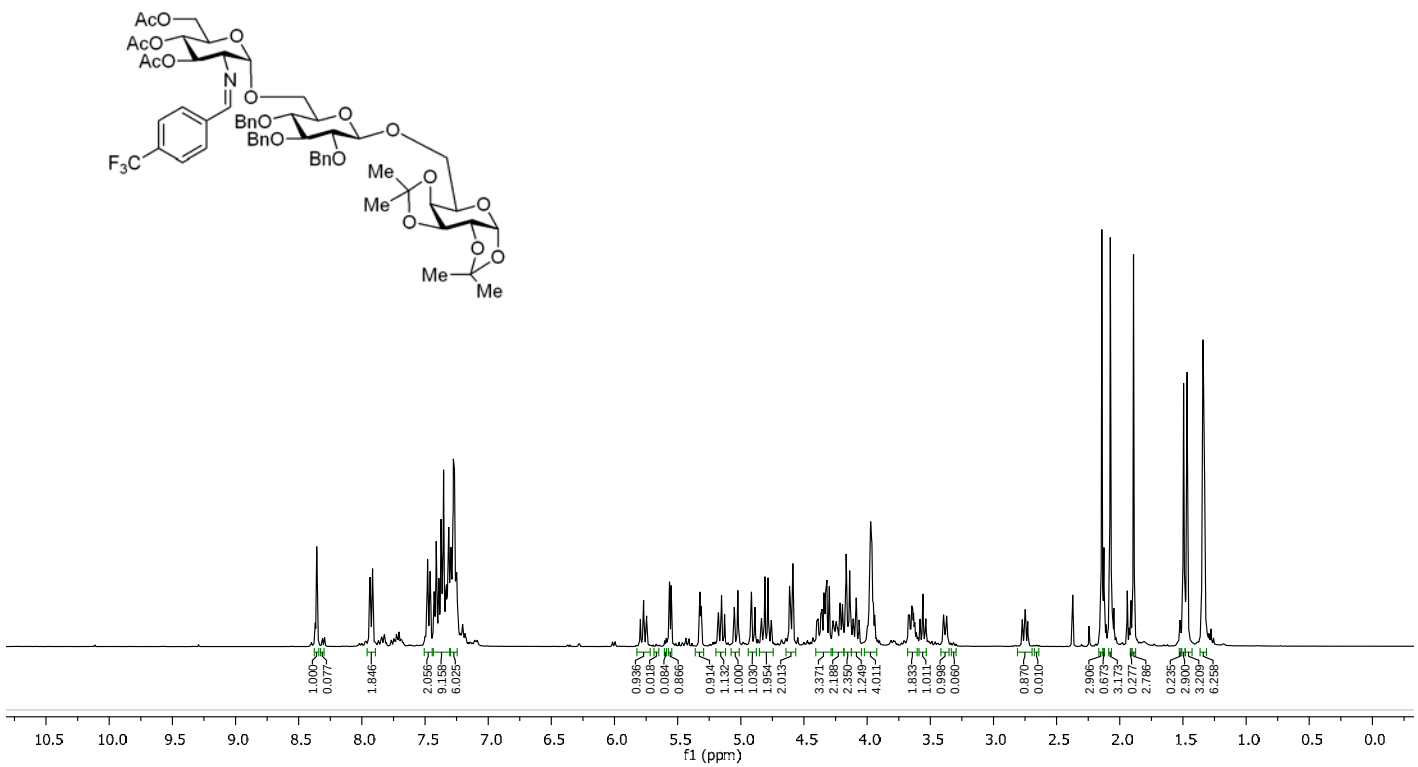


Figure A147. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **170**

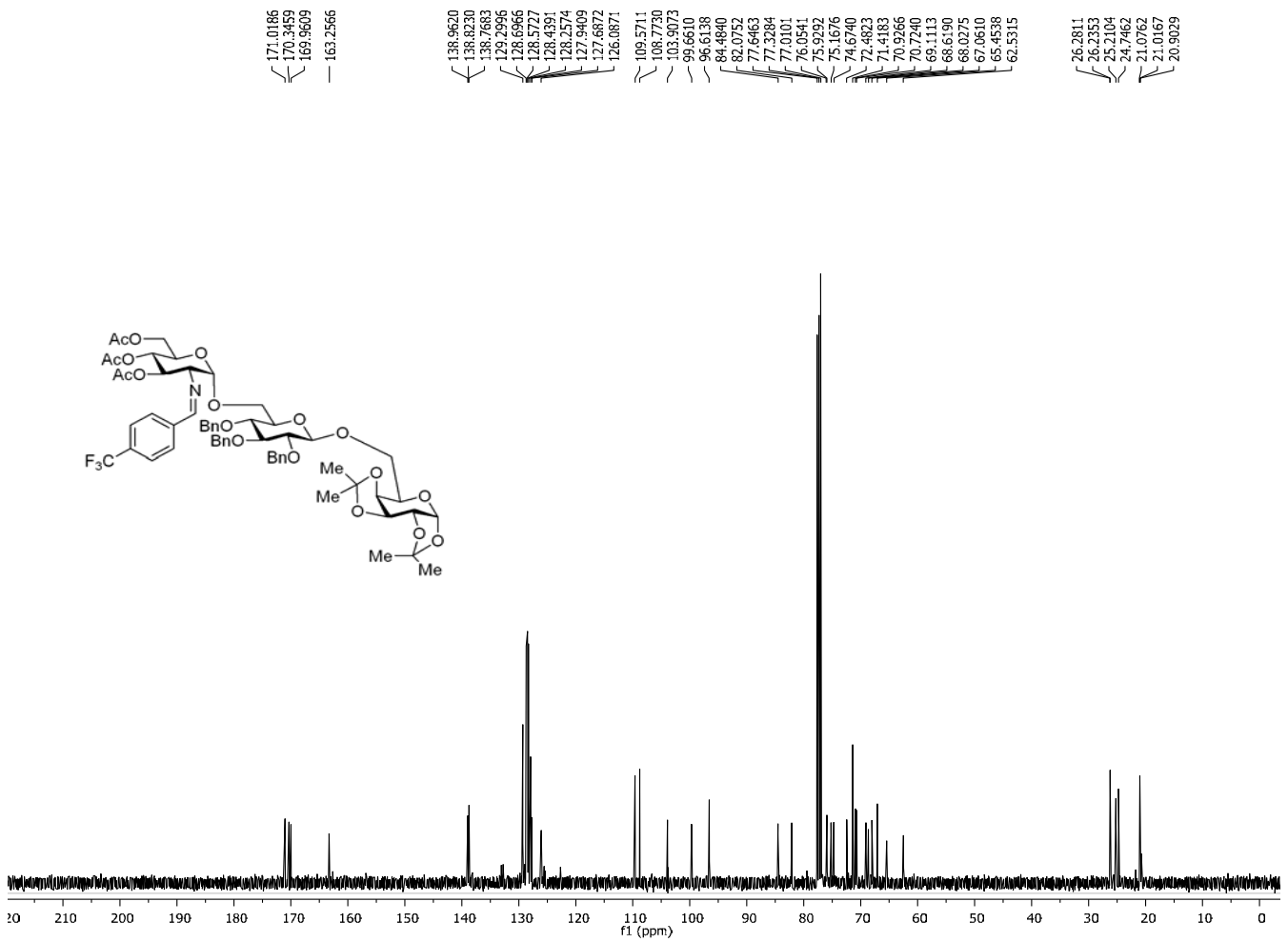


Figure A148. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **170**

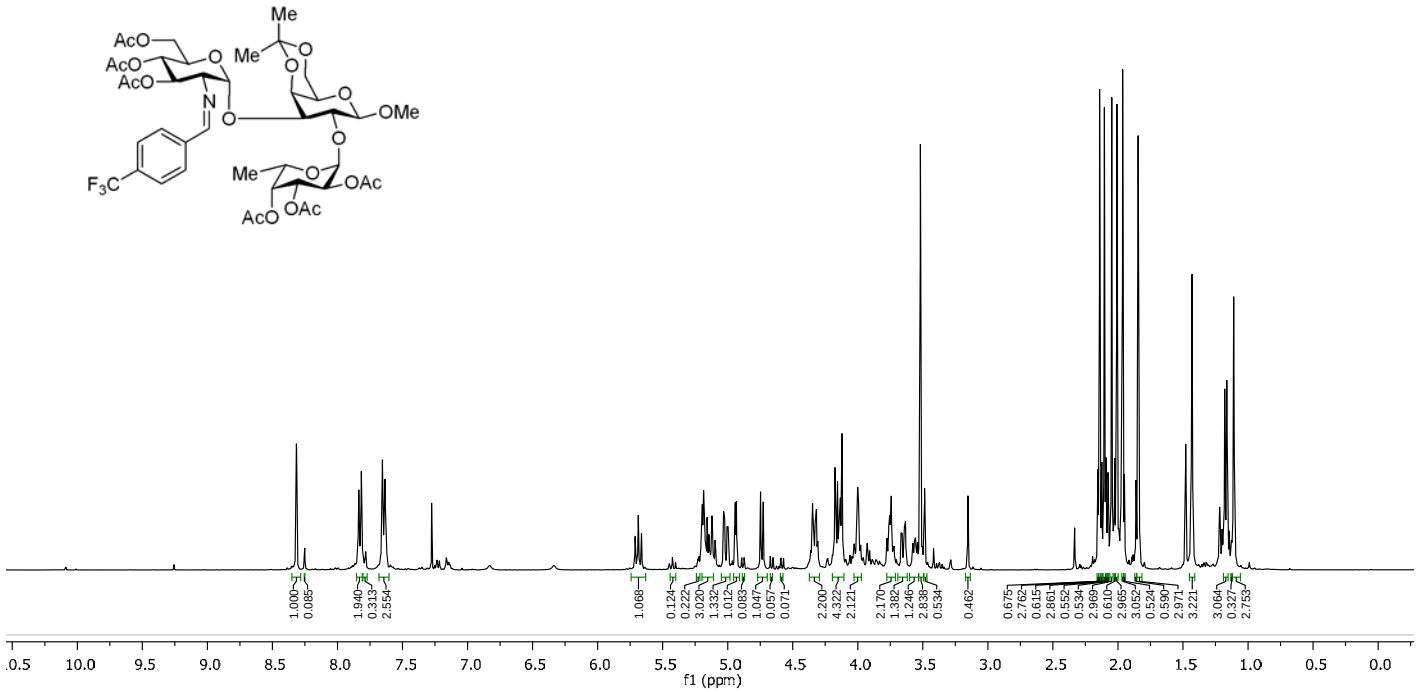


Figure A149. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **171**

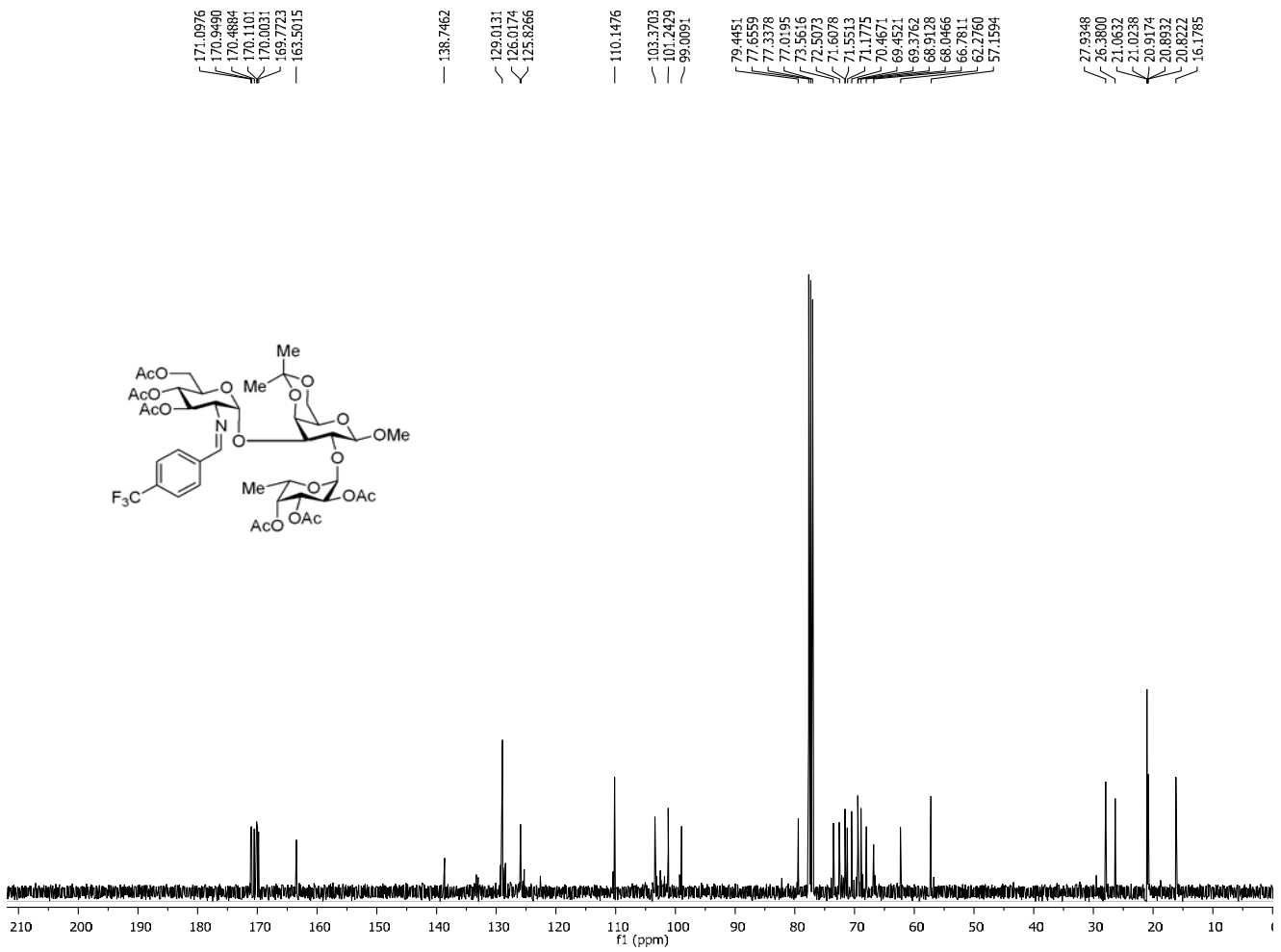


Figure A150. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **171**

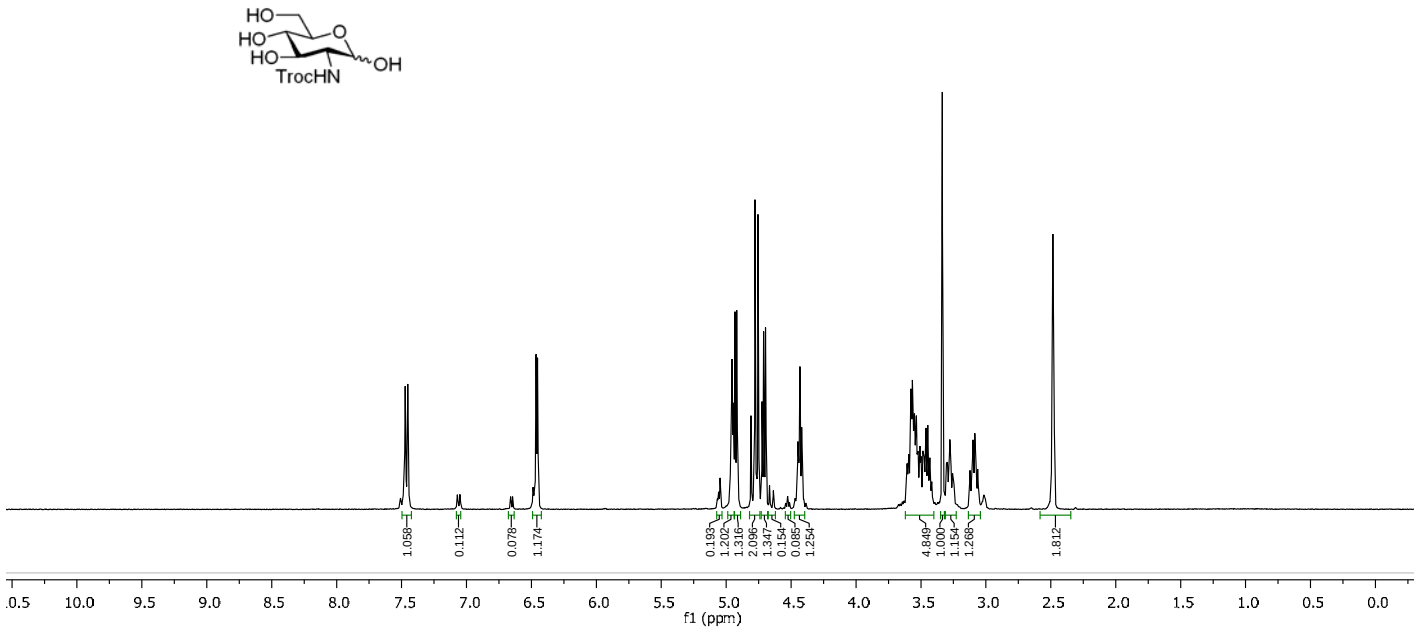


Figure A151. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **172A**

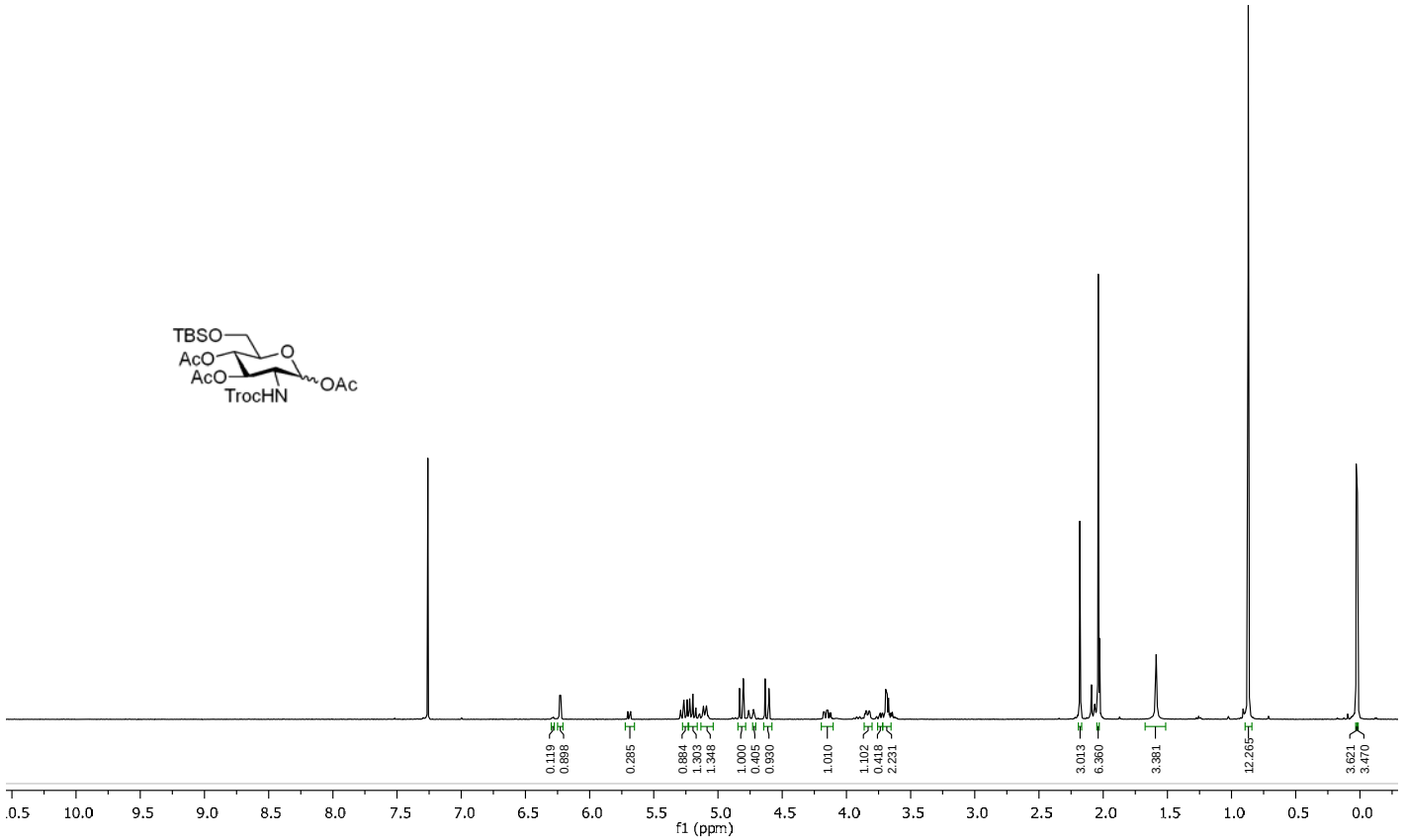


Figure A152. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **172B**

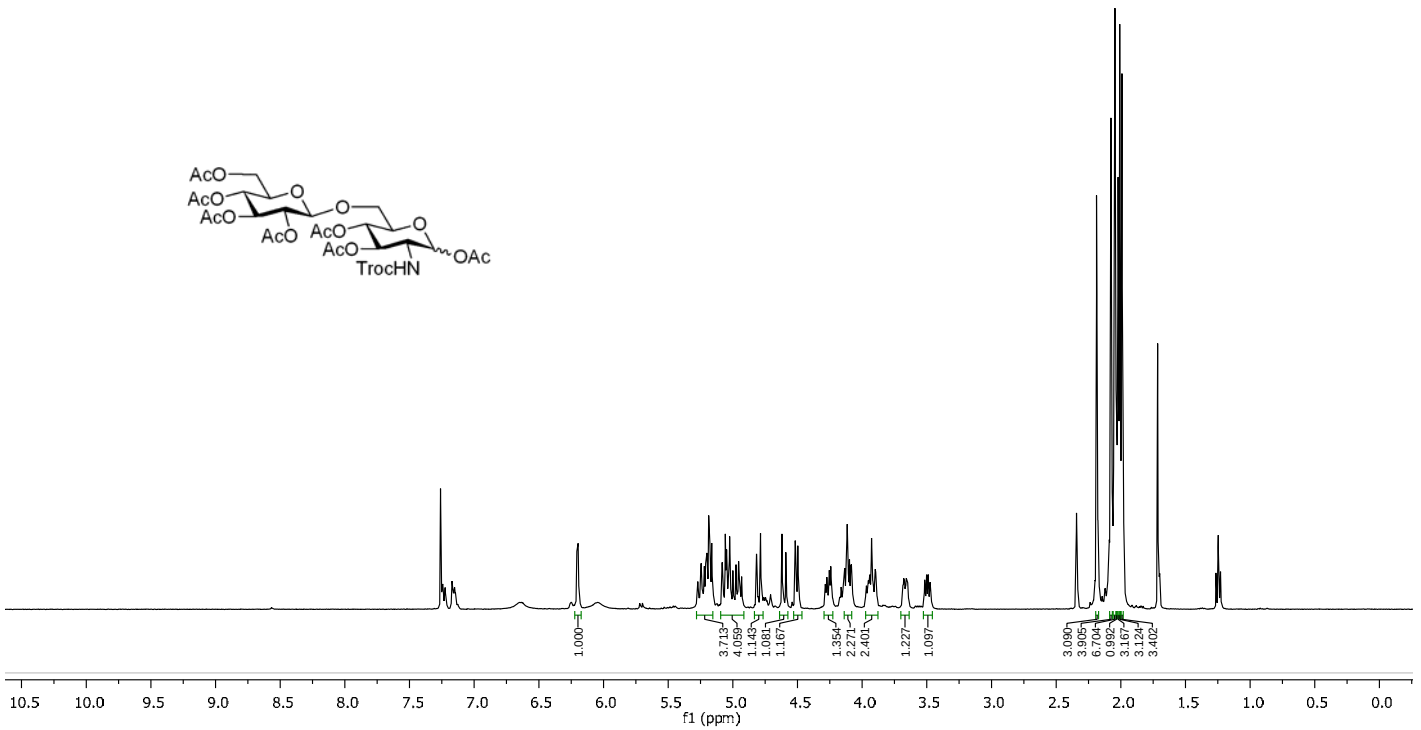


Figure A153. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **172C**

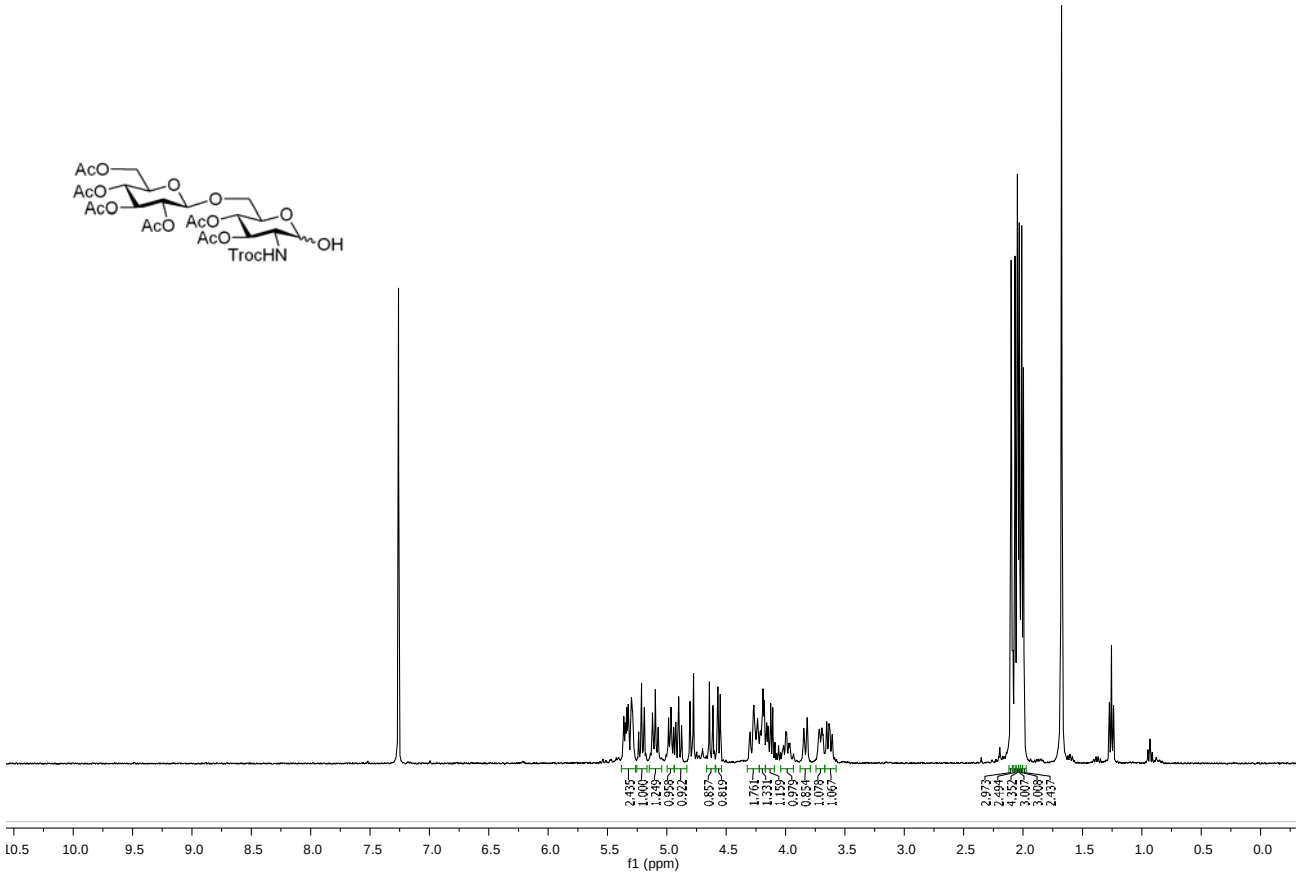


Figure A154. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **172D**

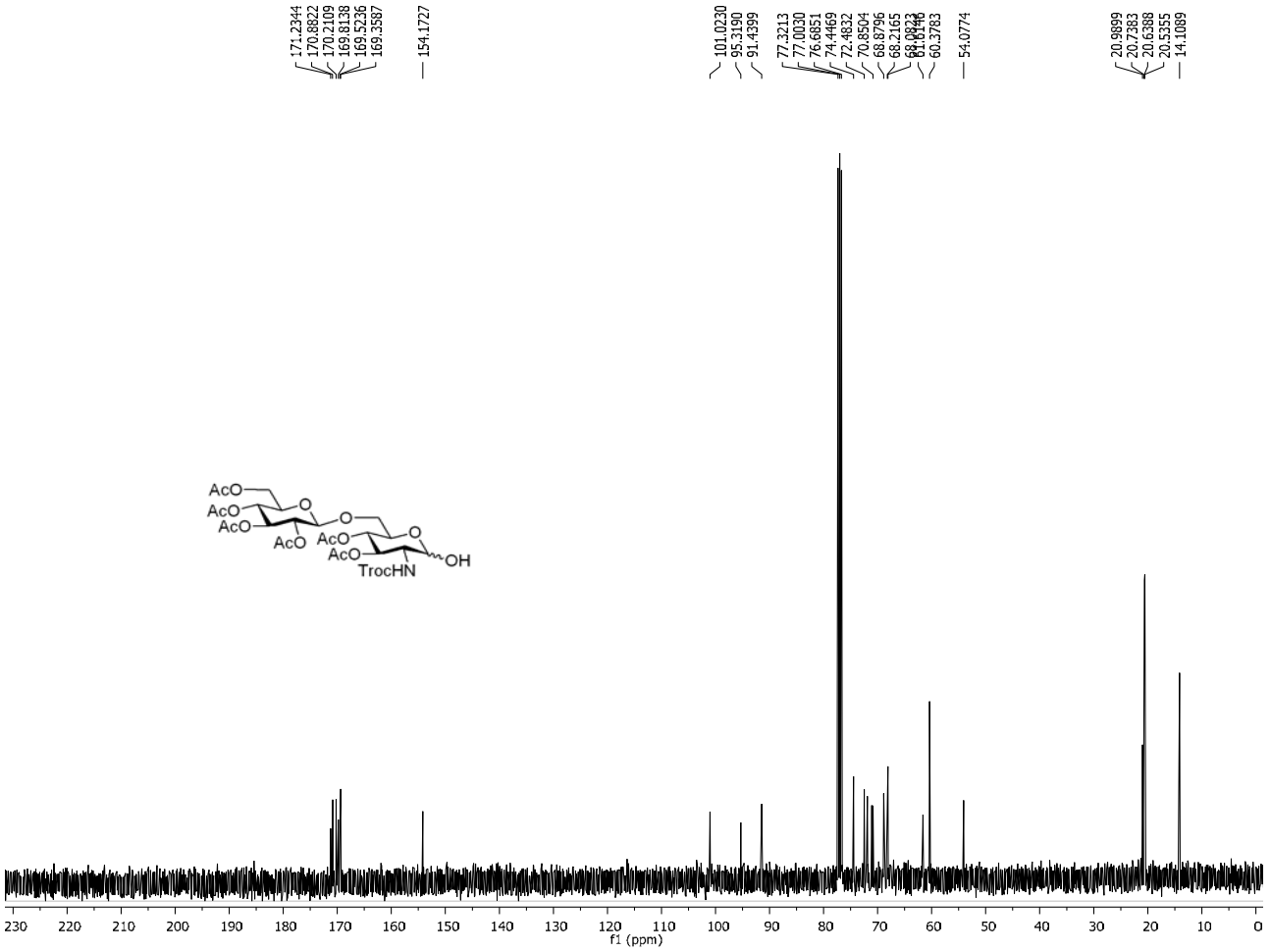


Figure A155. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **172D**

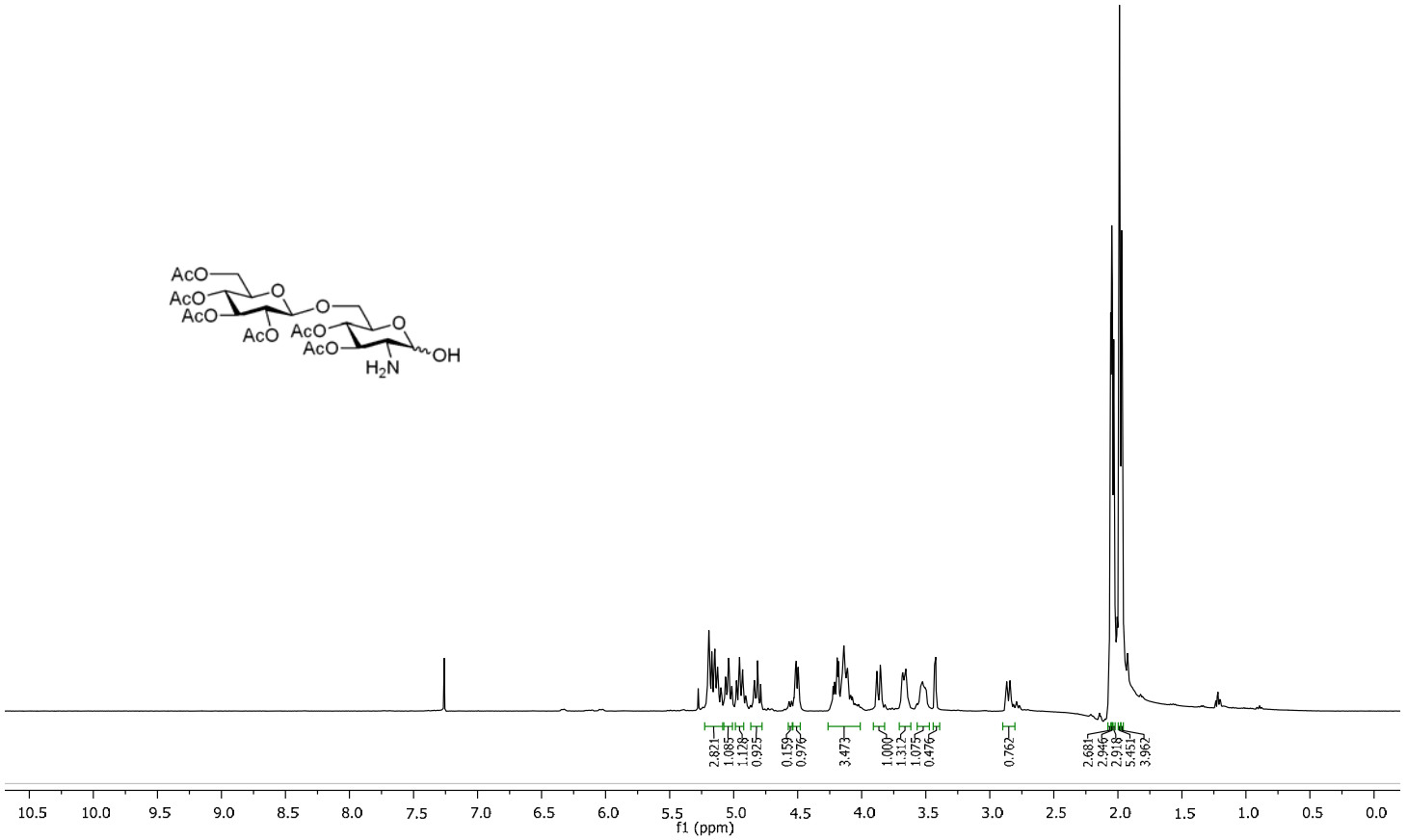


Figure A156. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Amine **172E**

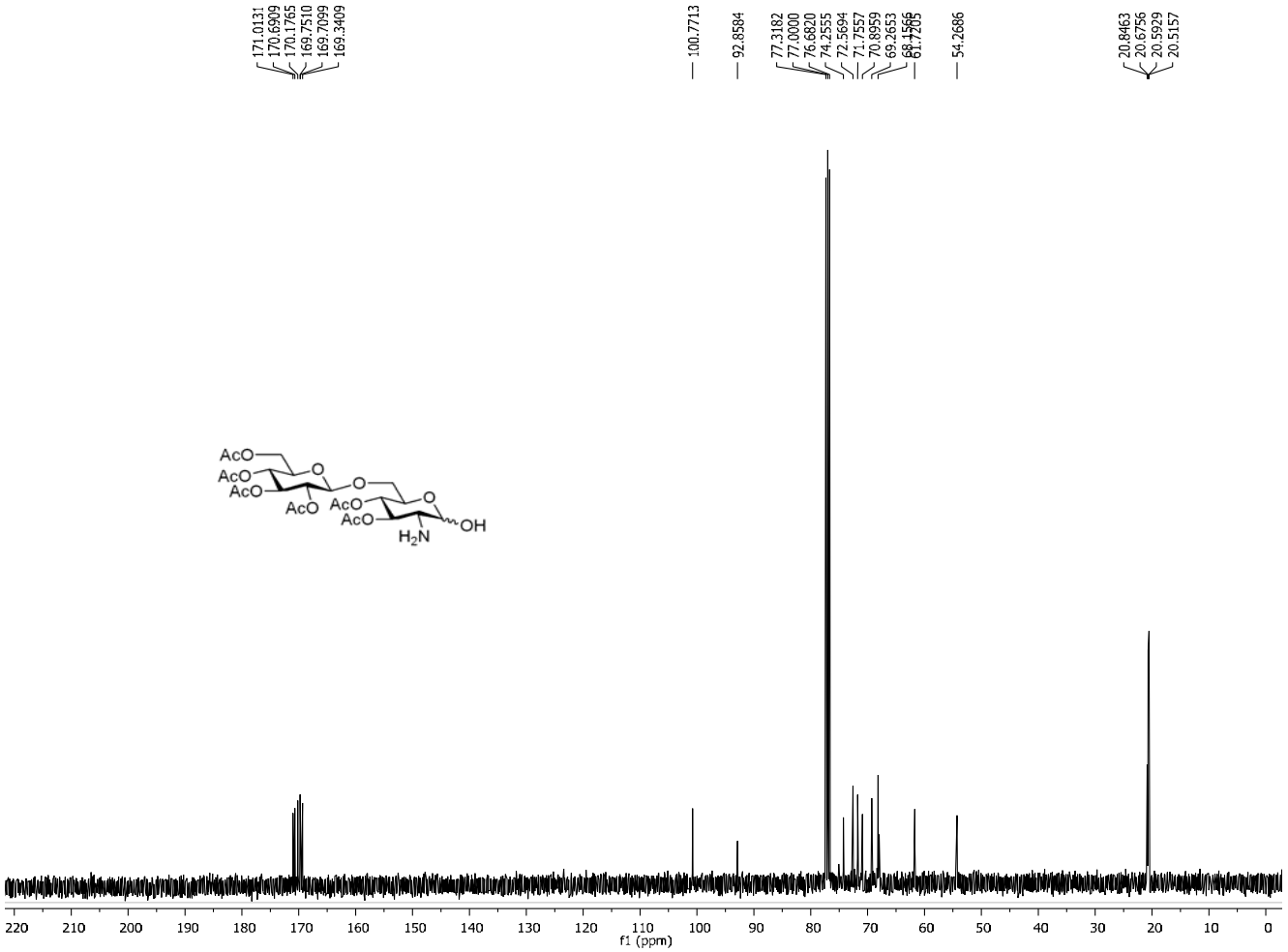


Figure A157. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Amine **172E**

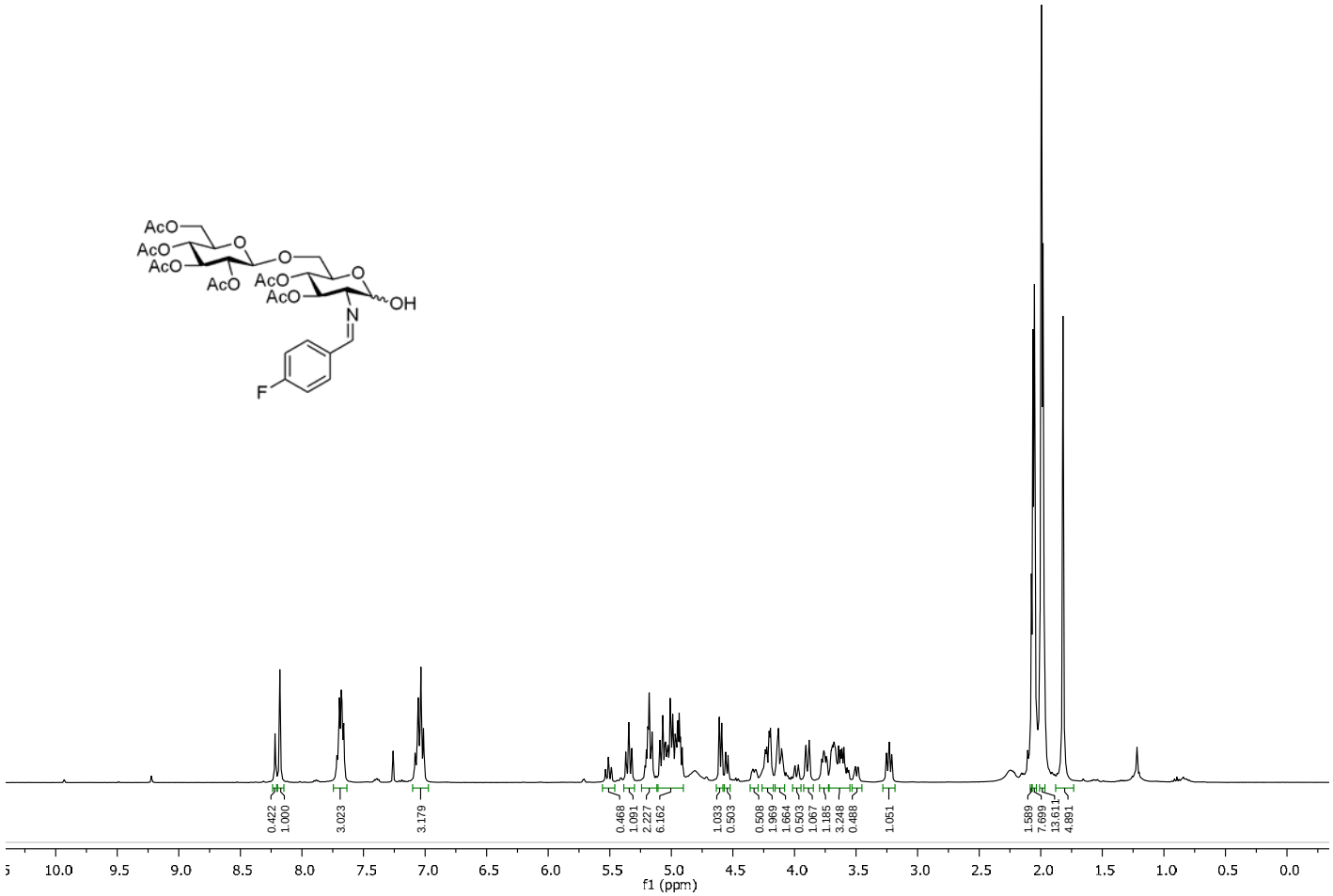


Figure A158. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **172F**

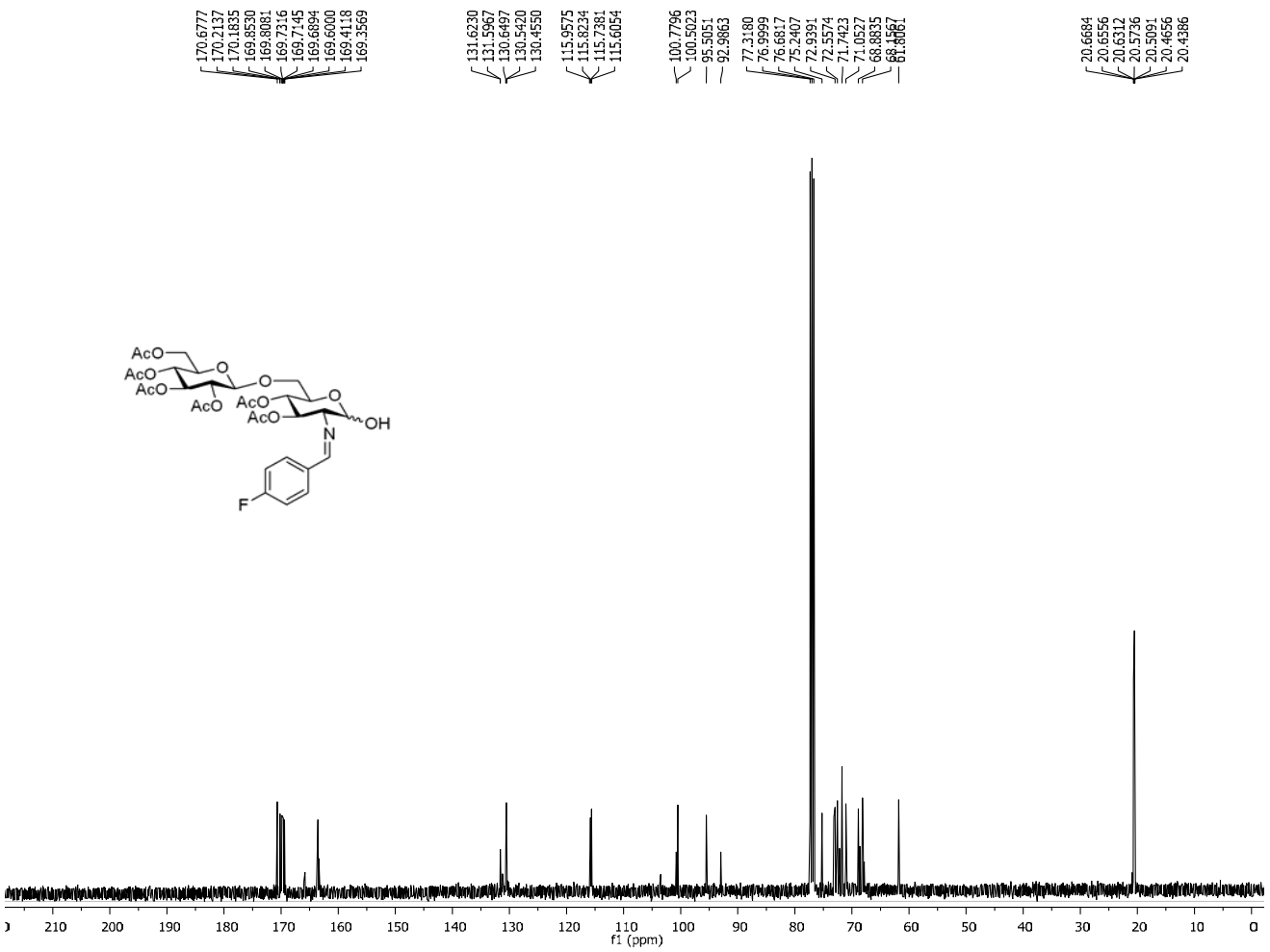


Figure A159. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **172F**

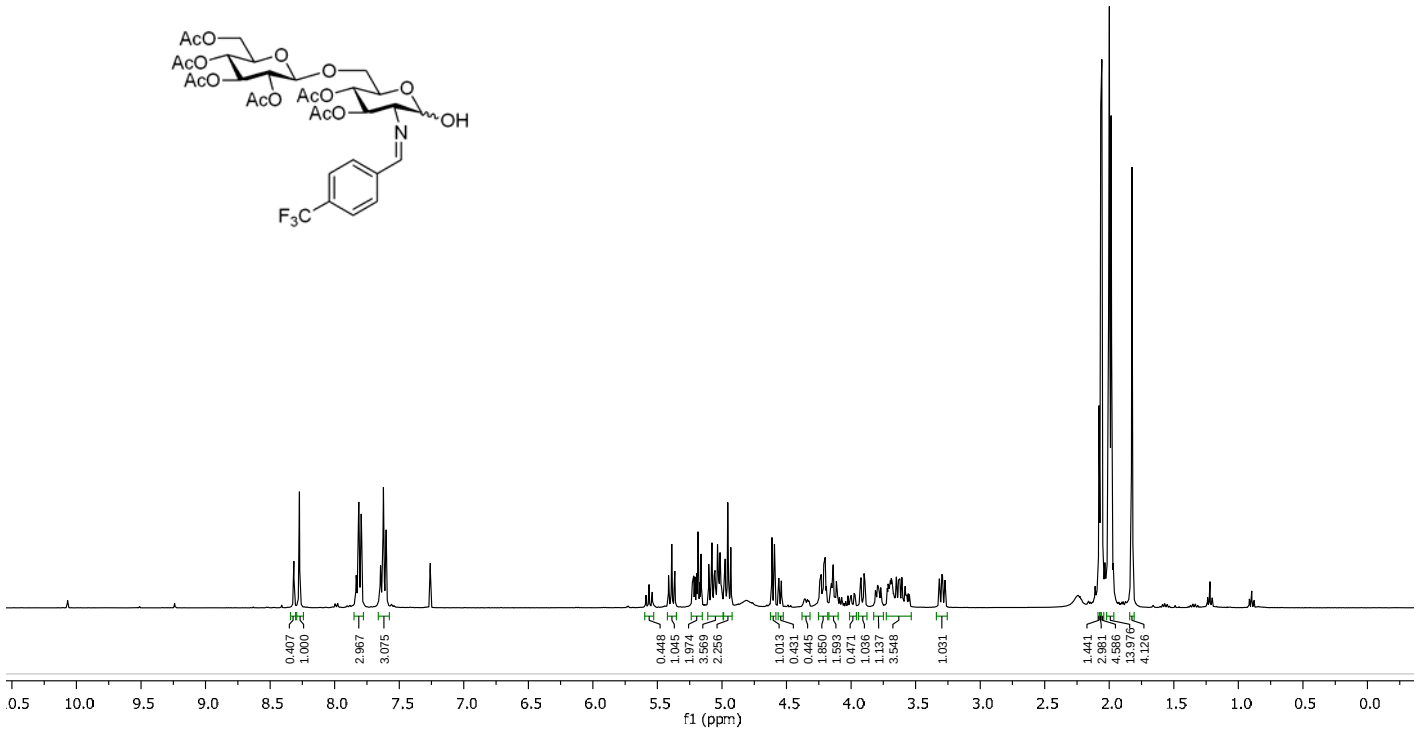


Figure A160. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **172G**

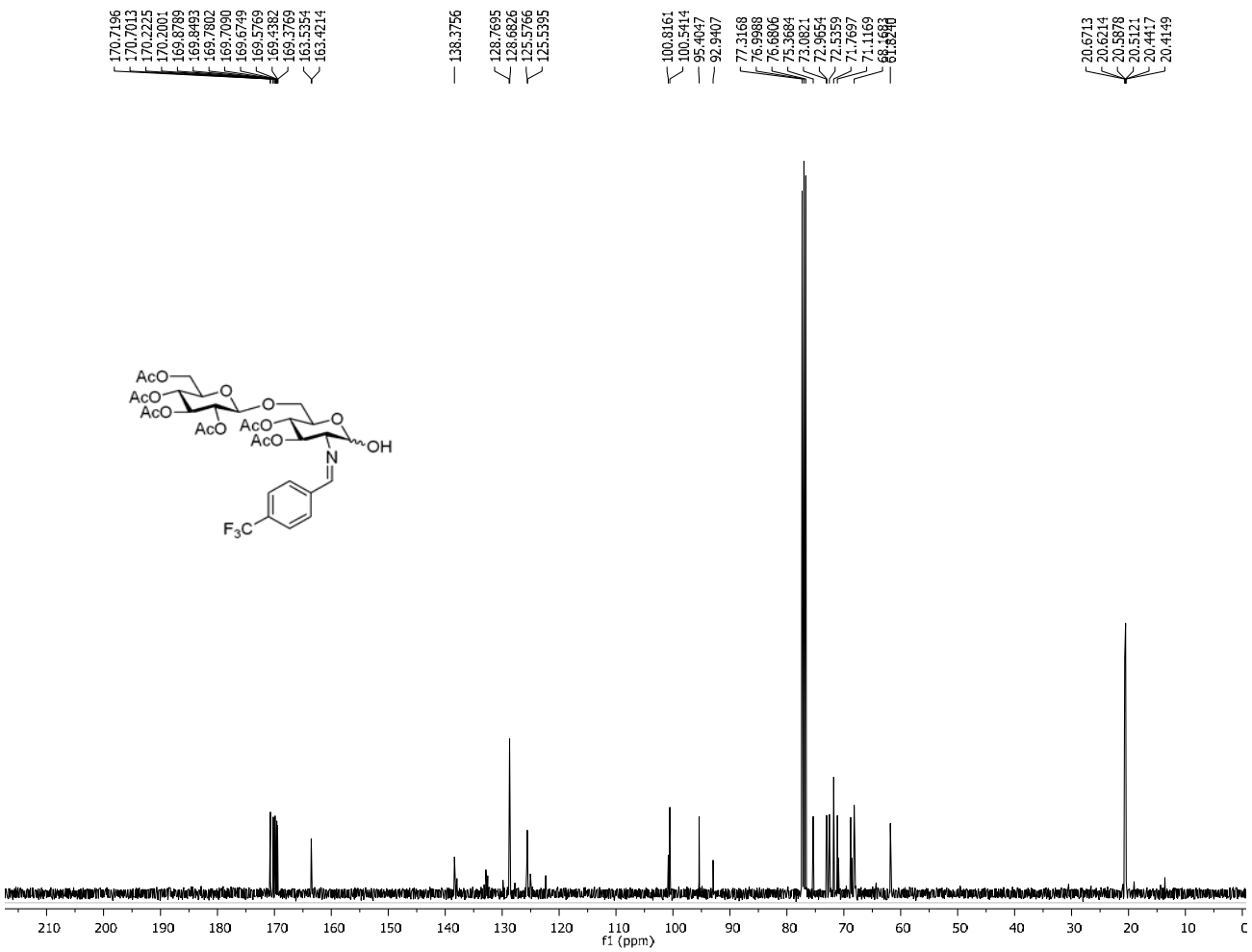


Figure A161. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **172G**

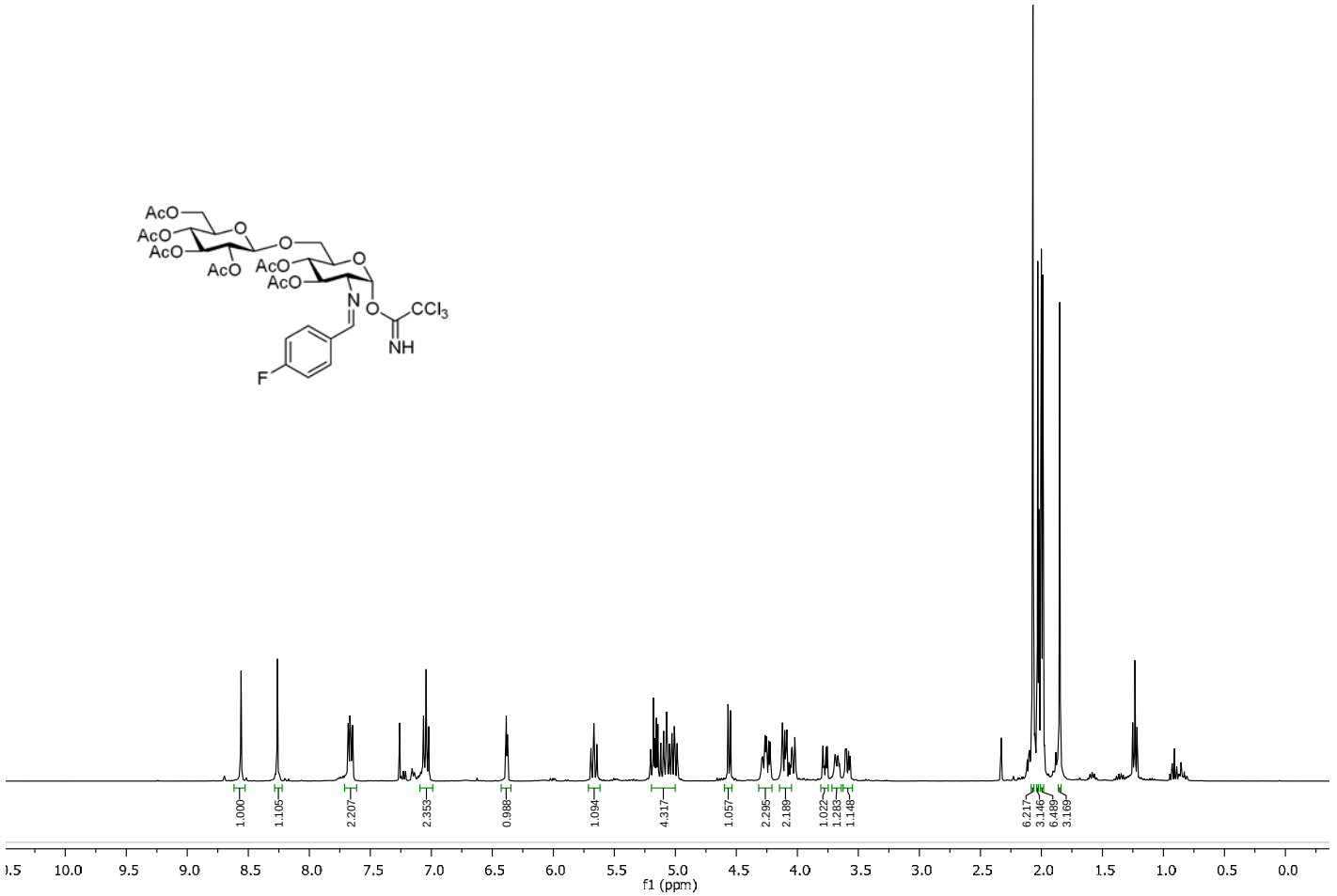


Figure A162. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **172**

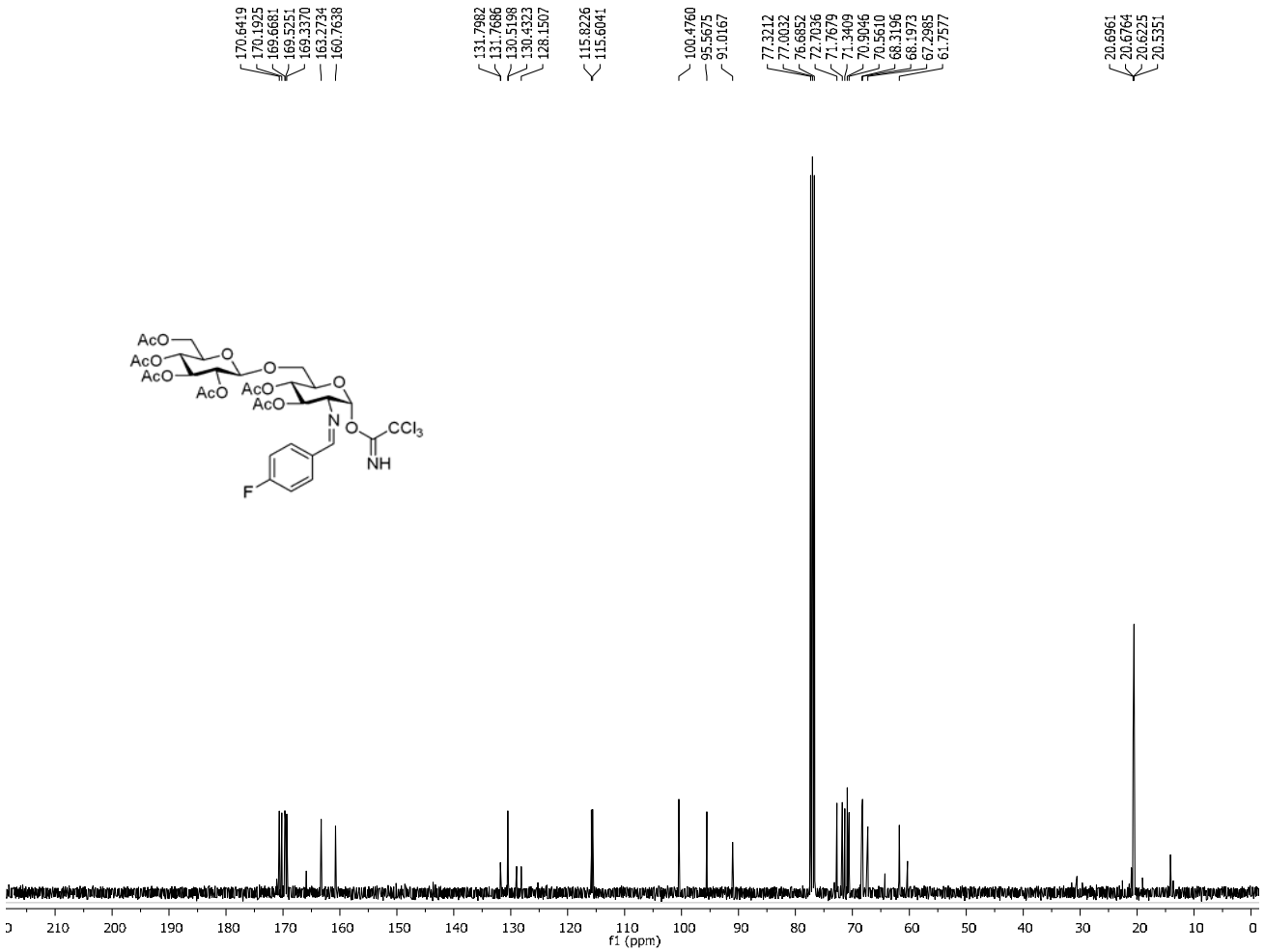


Figure A163. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **172**

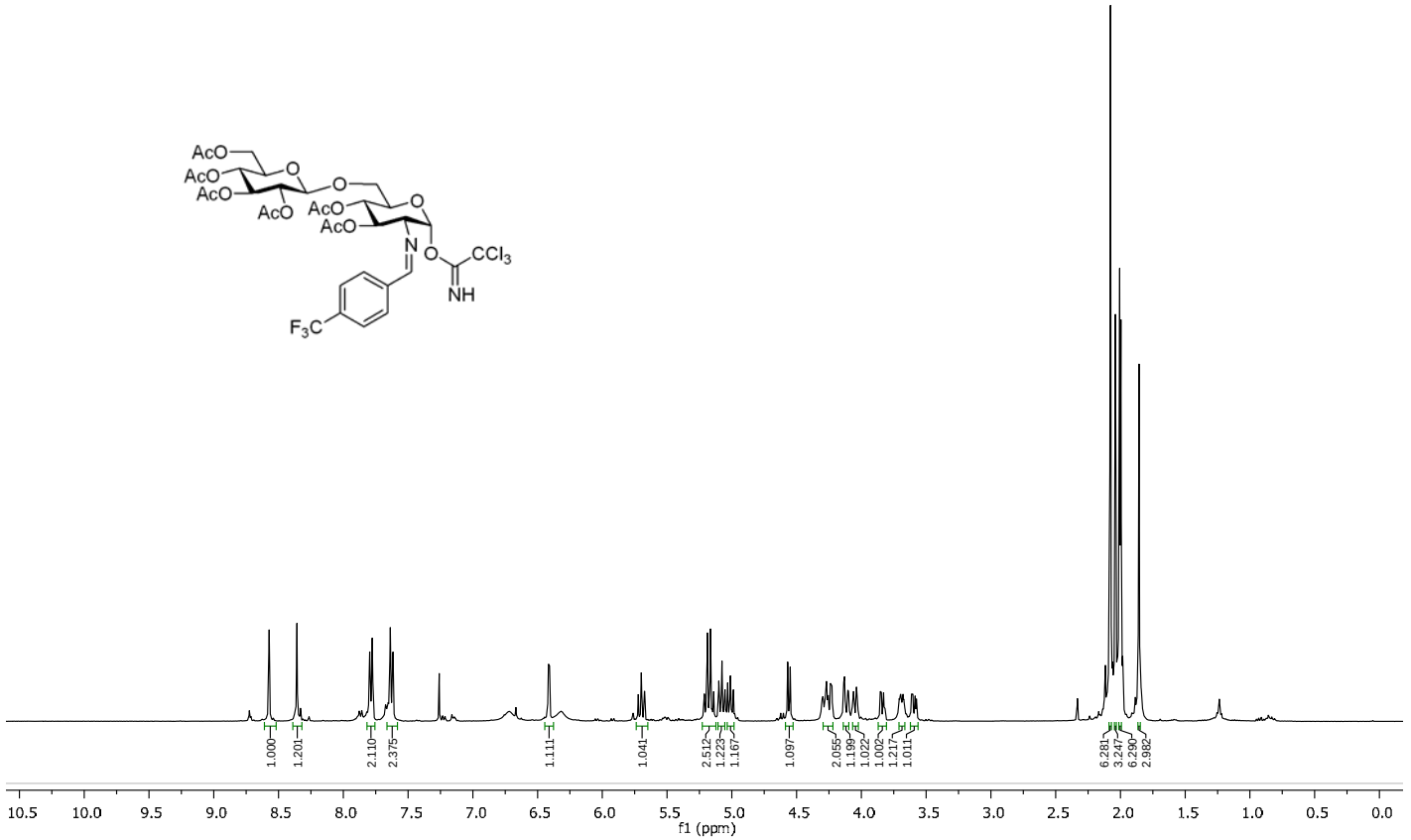


Figure A164. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **173**

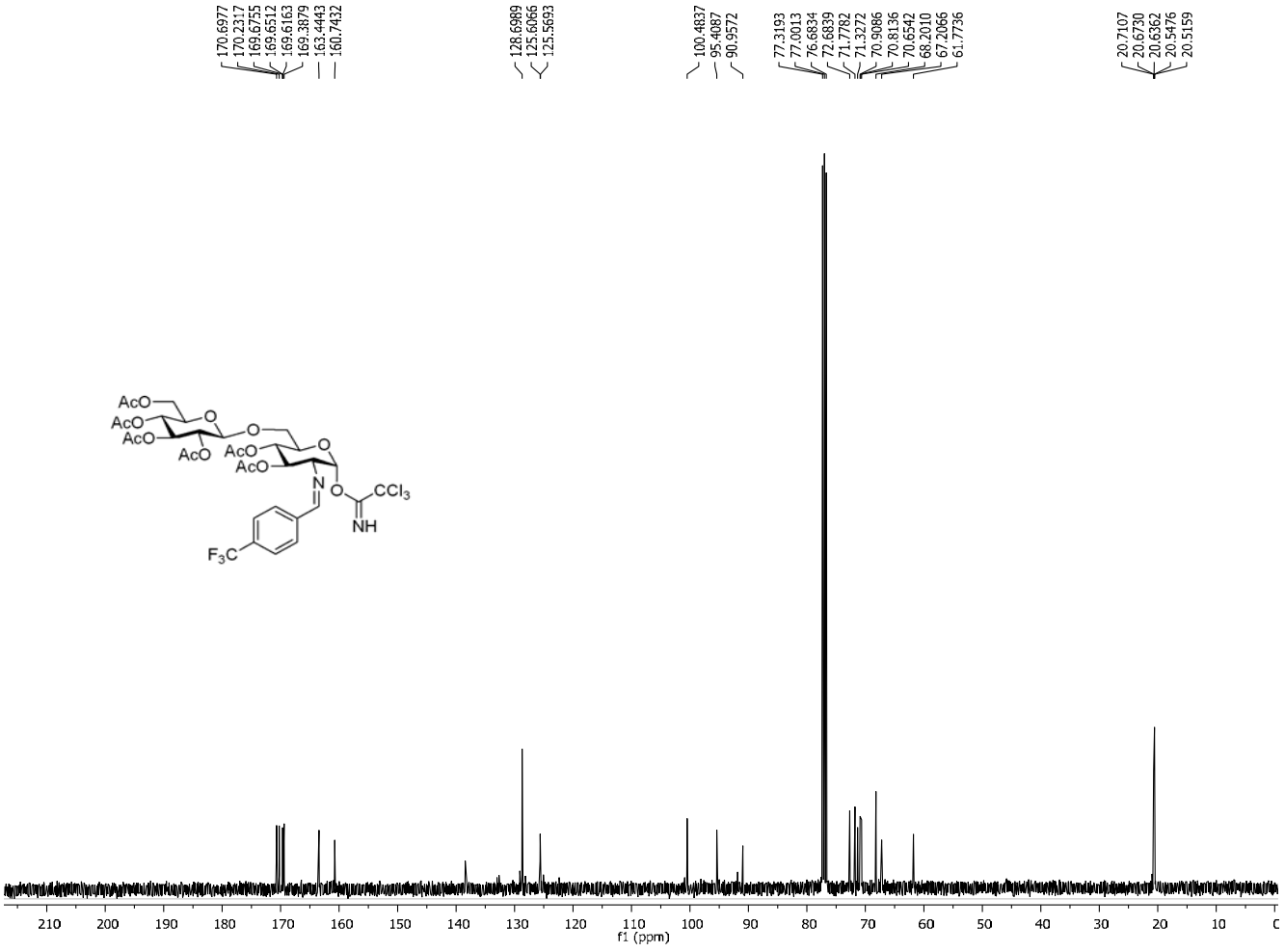


Figure A165. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **173**

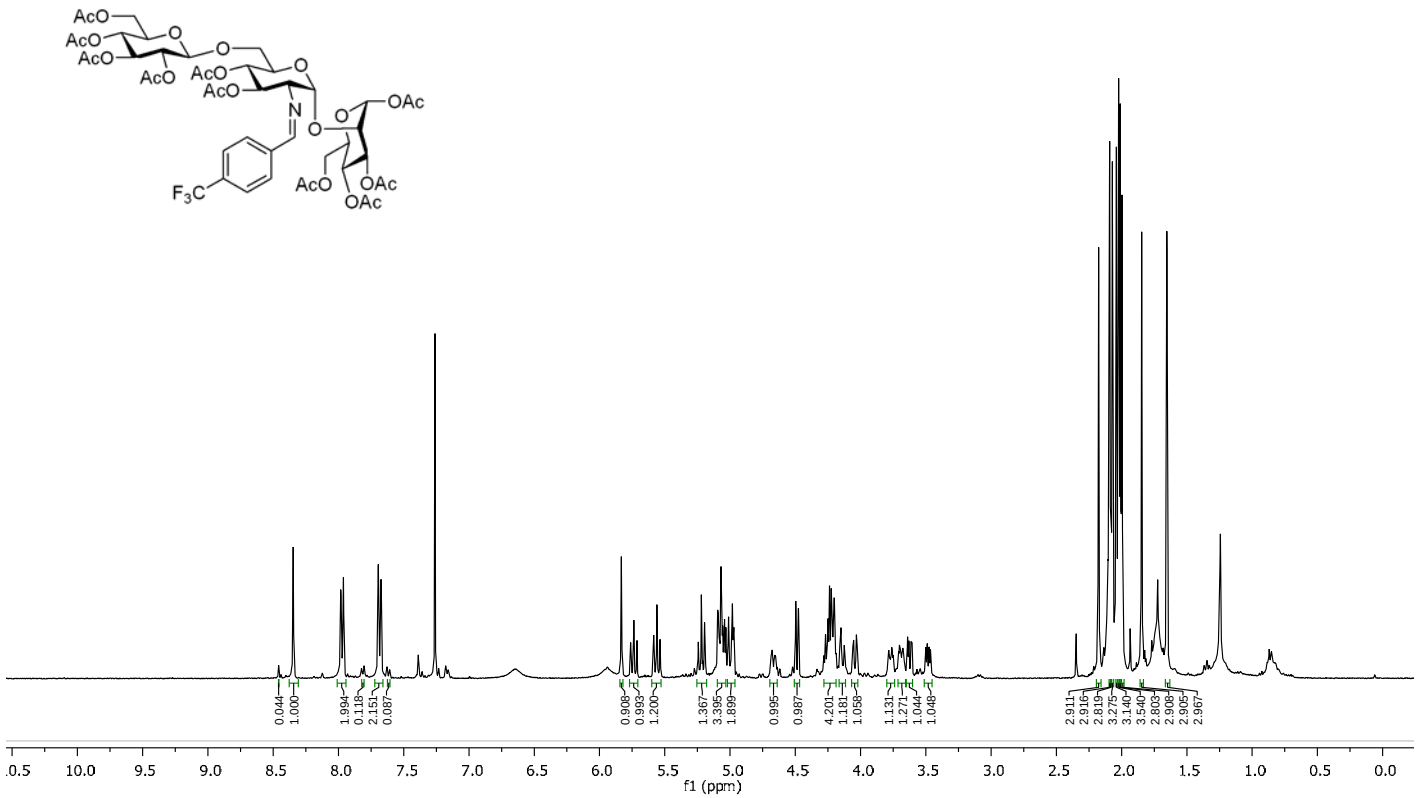


Figure A166. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **174**

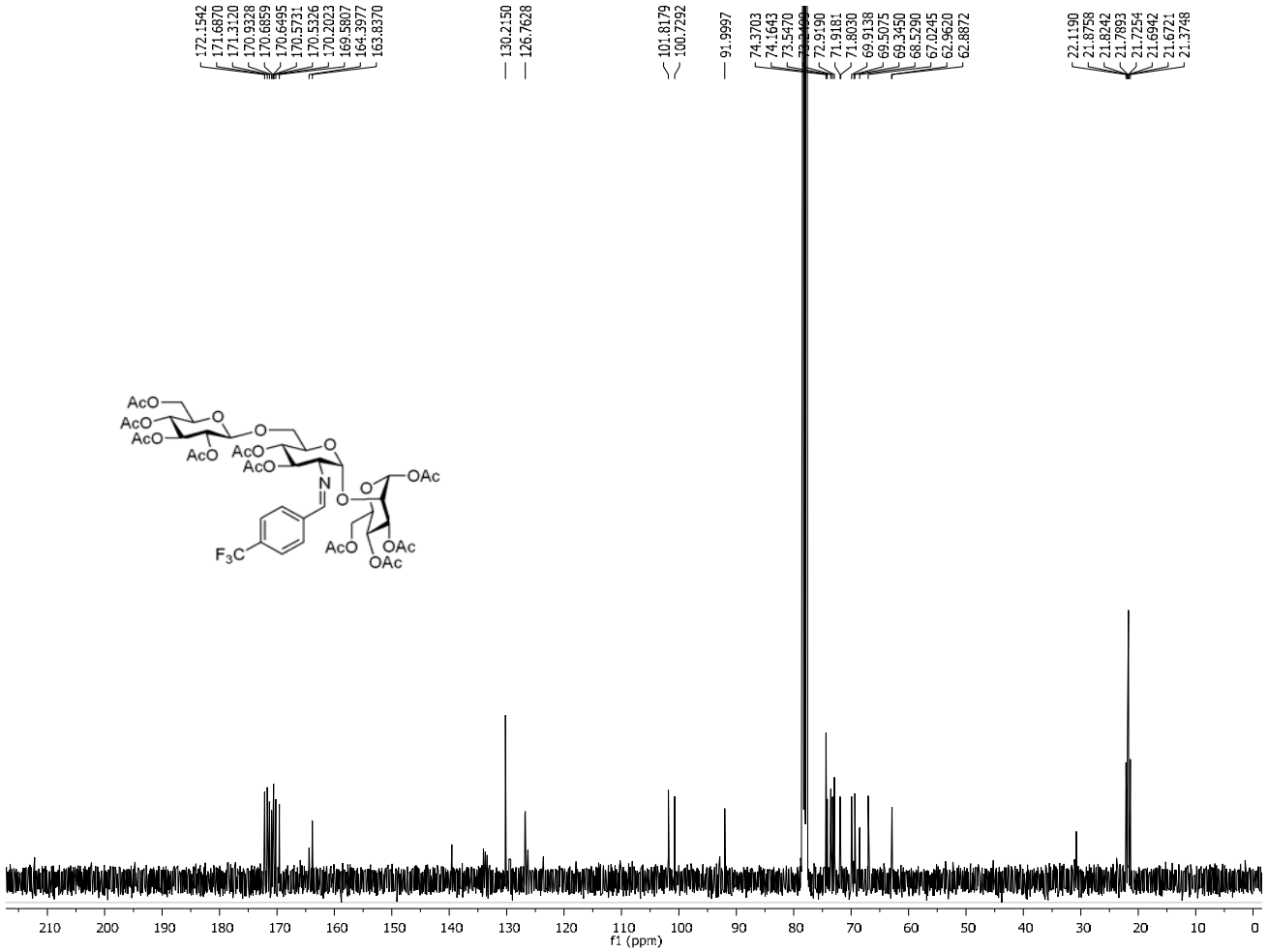


Figure A167. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **174**

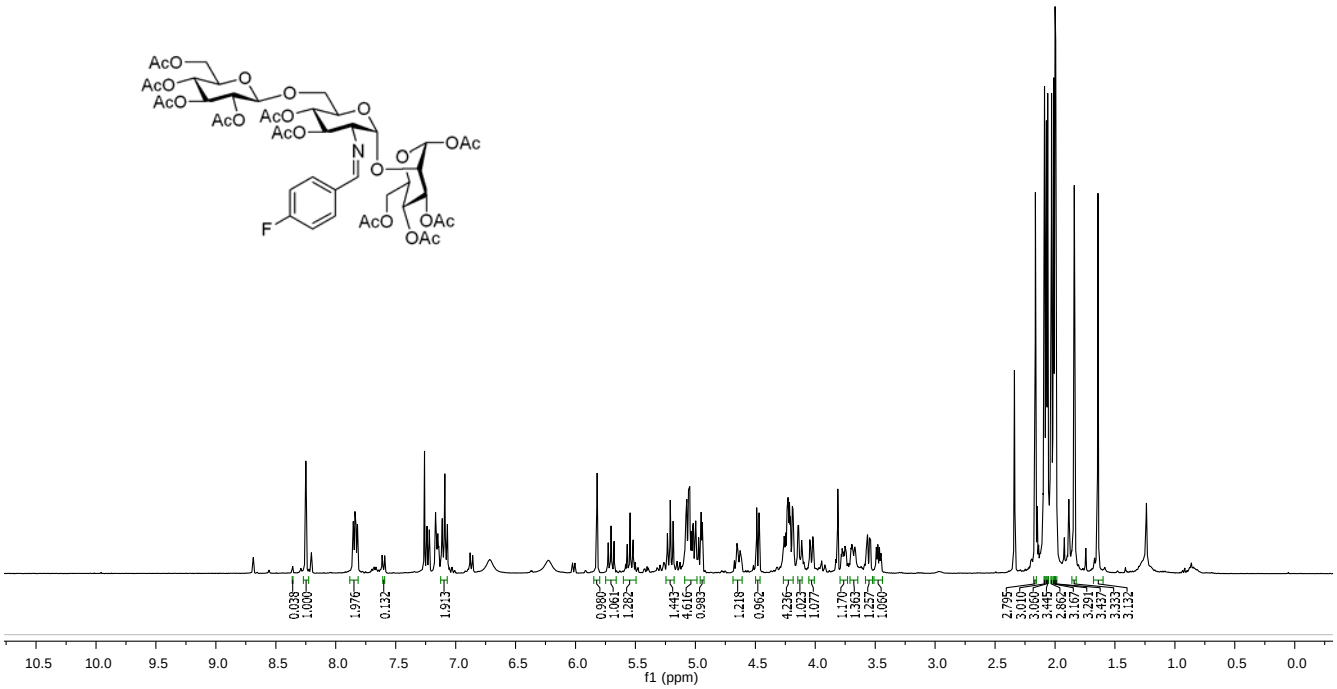


Figure A168. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **175**

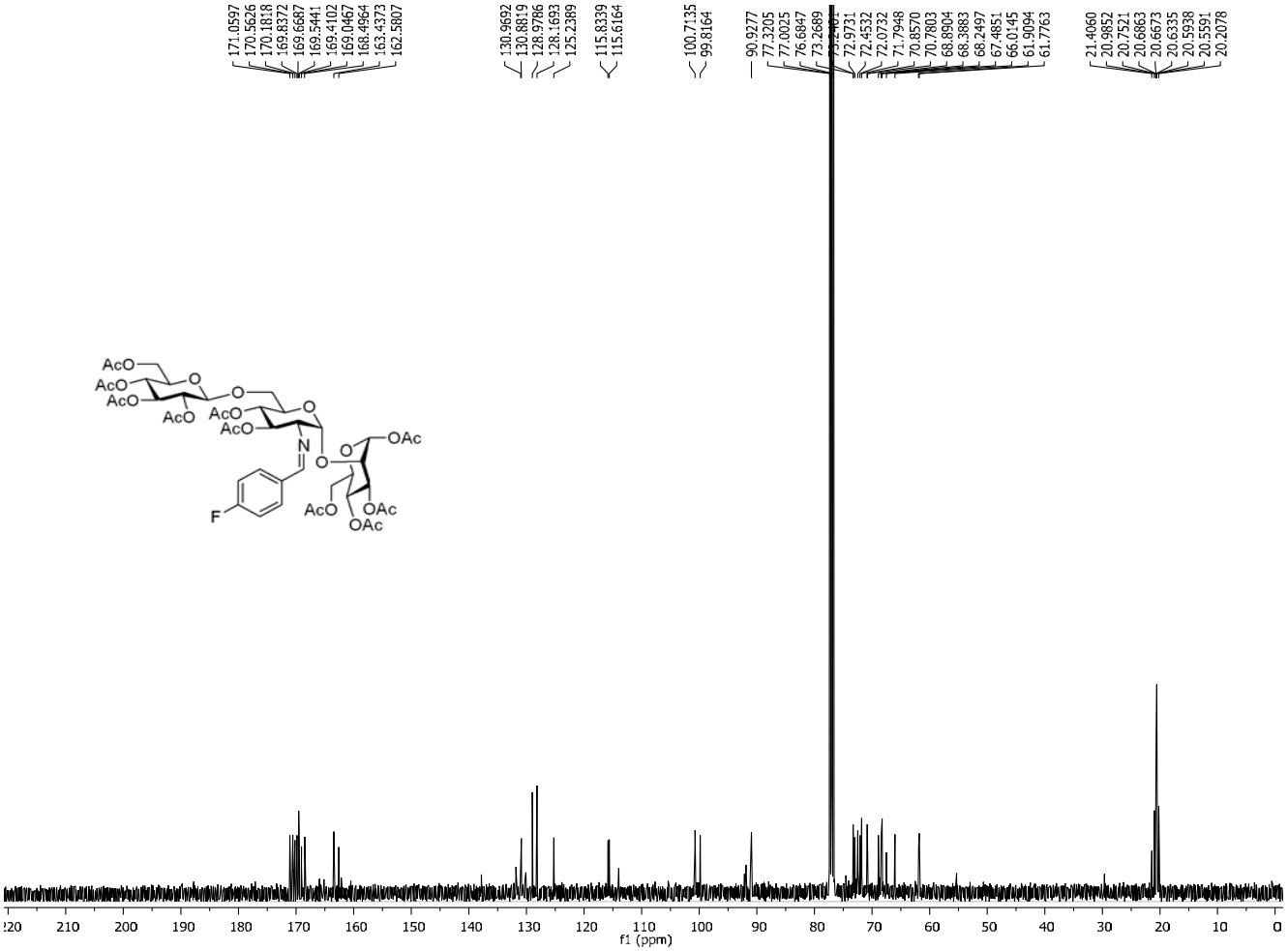


Figure A169. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **175**

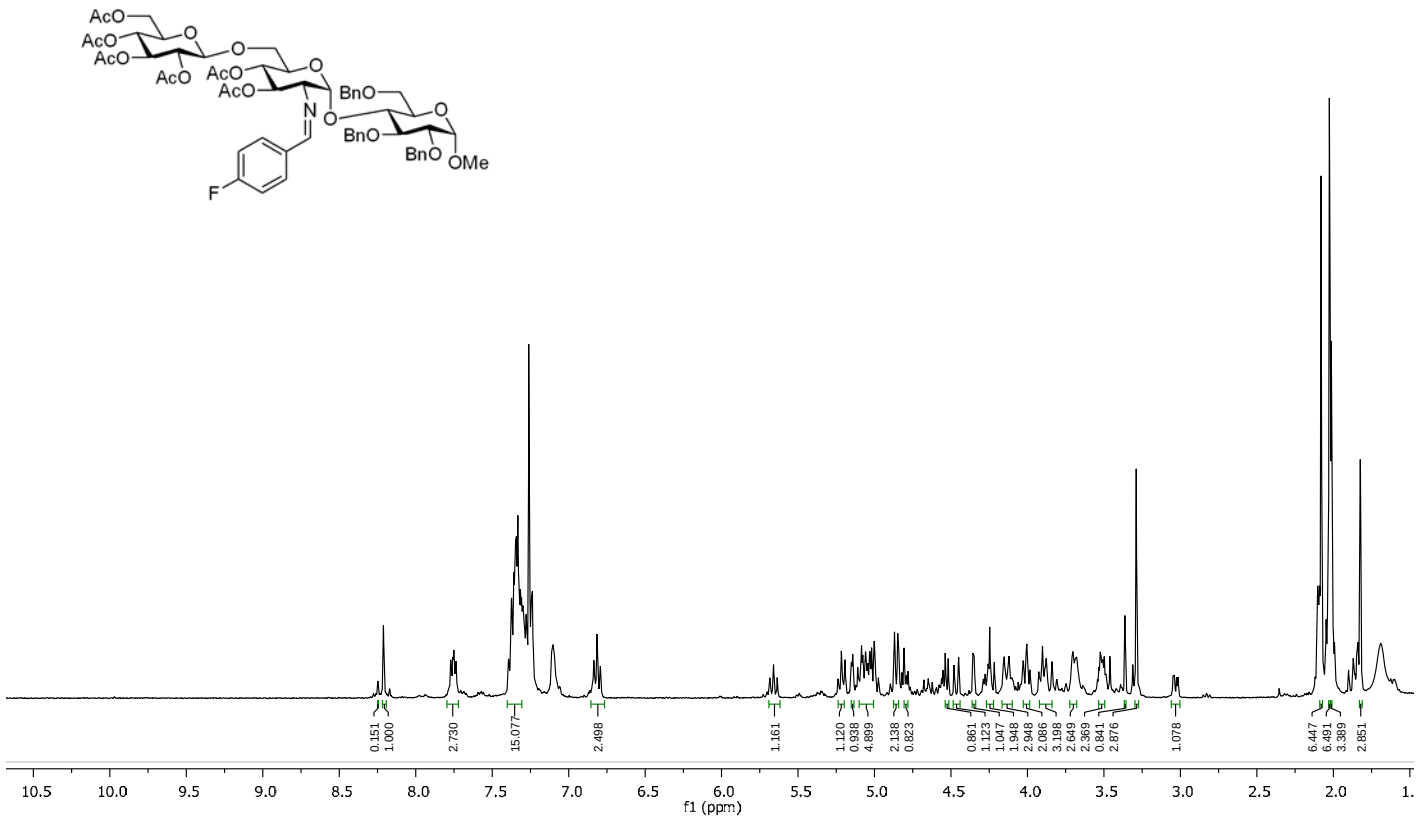


Figure A170. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **176**

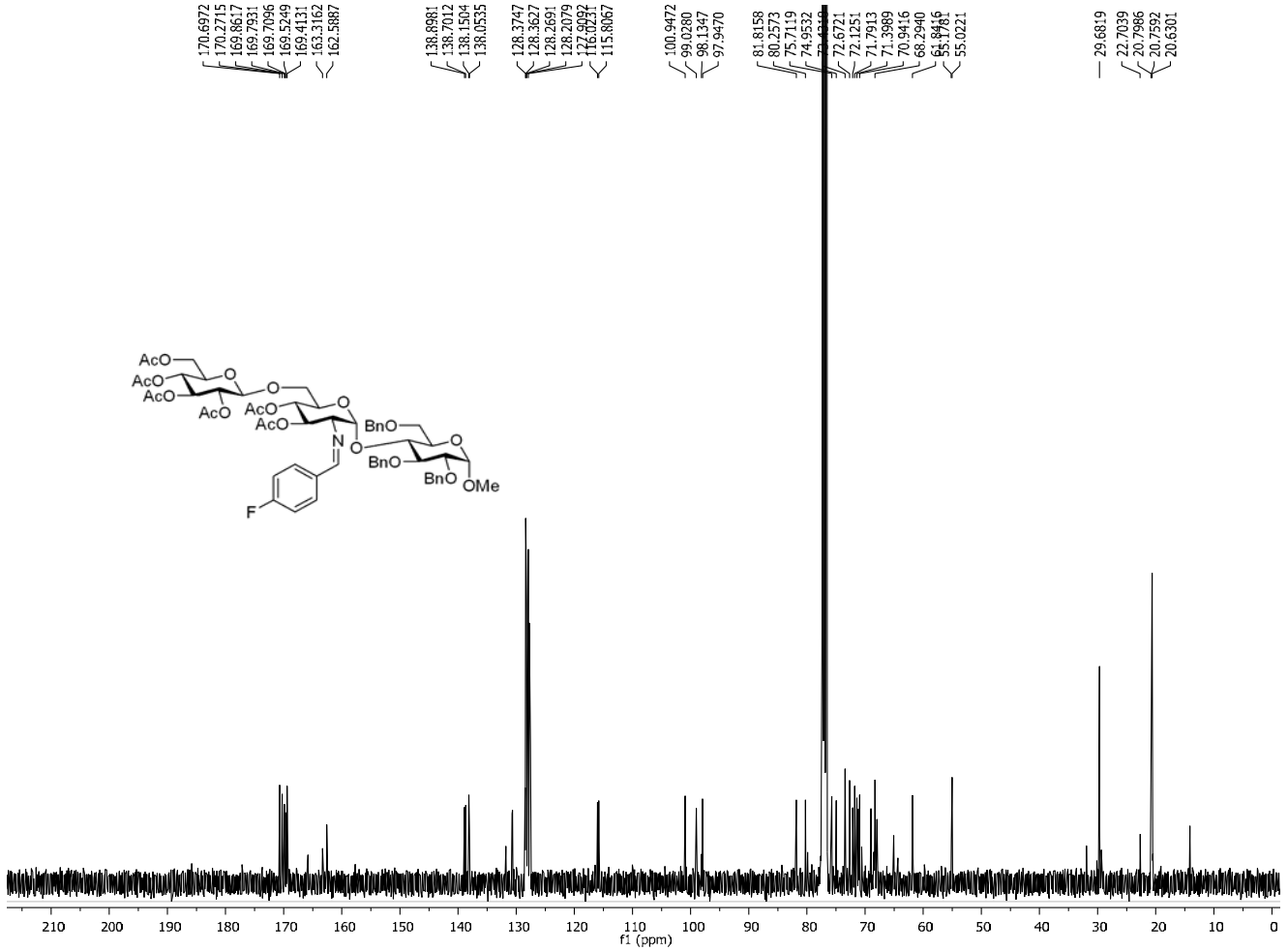


Figure A171. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **176**

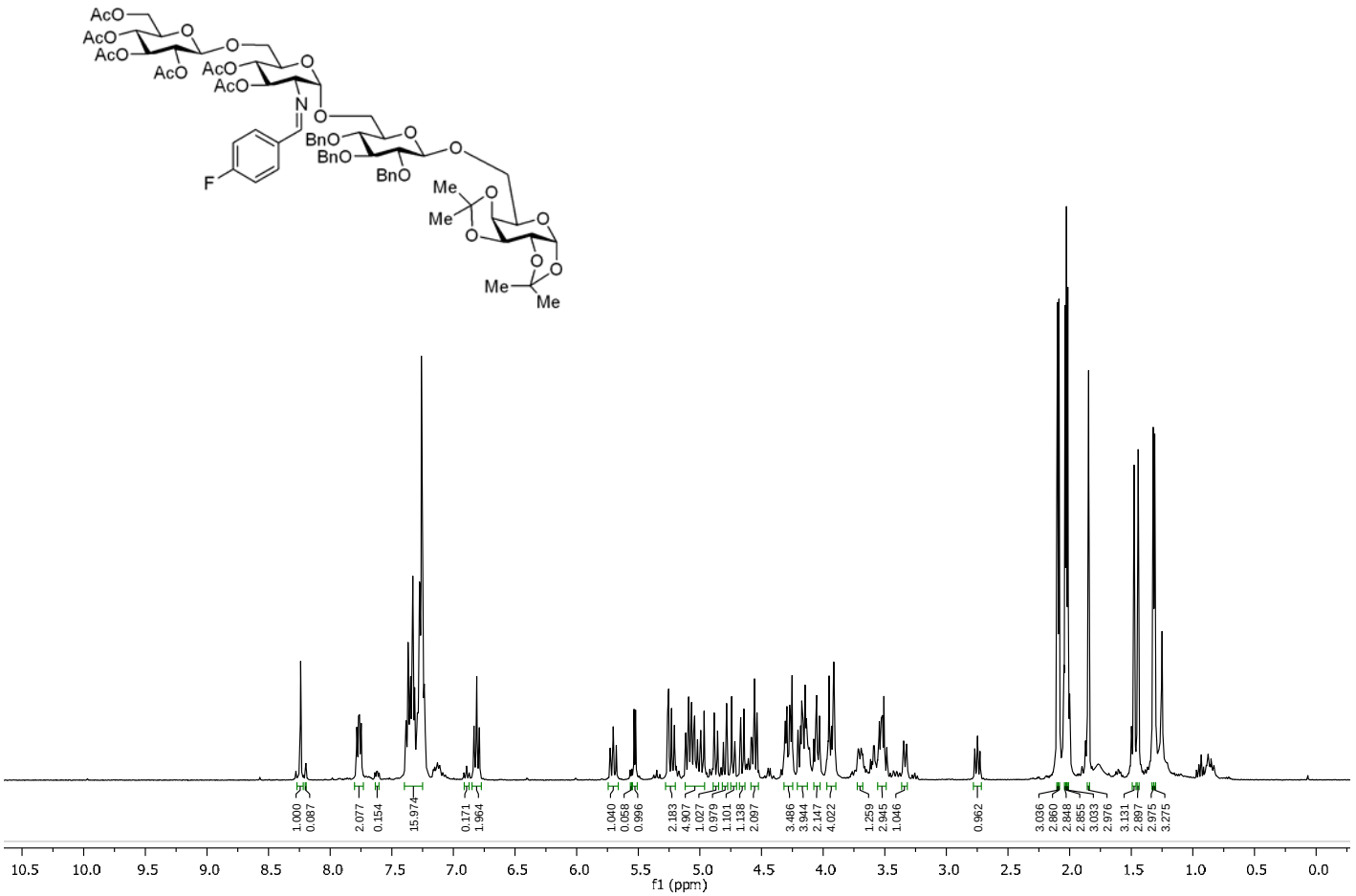


Figure A172. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of *Tetra*saccharide **177**

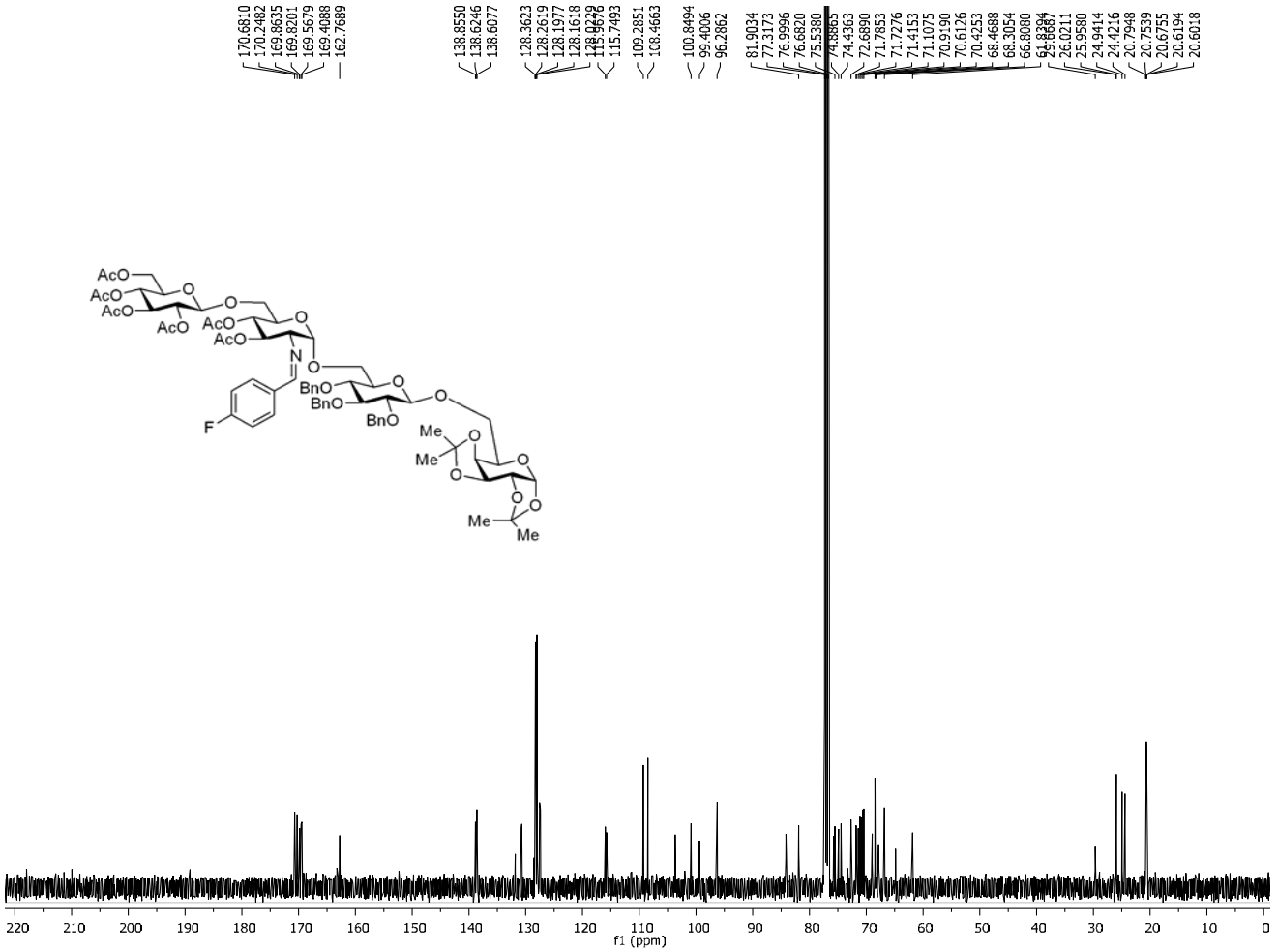


Figure A173. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of *Tetra*saccharide **177**

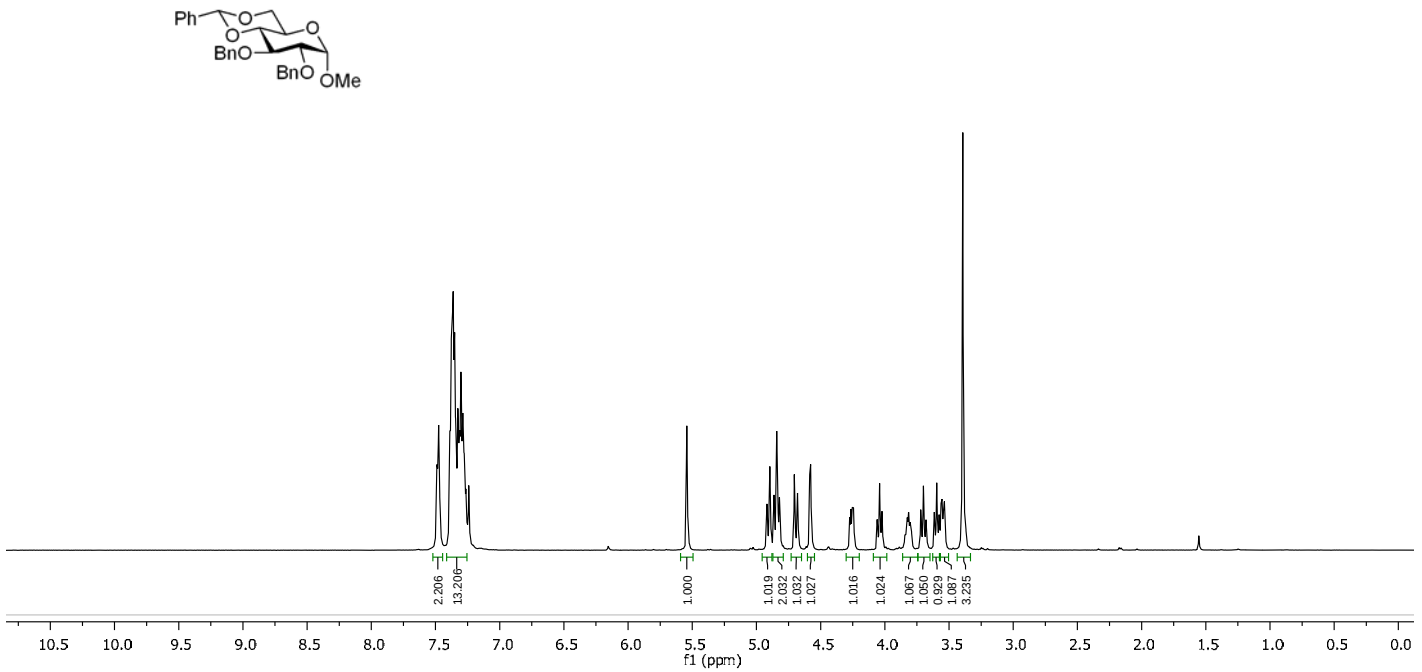


Figure A174. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **179A**

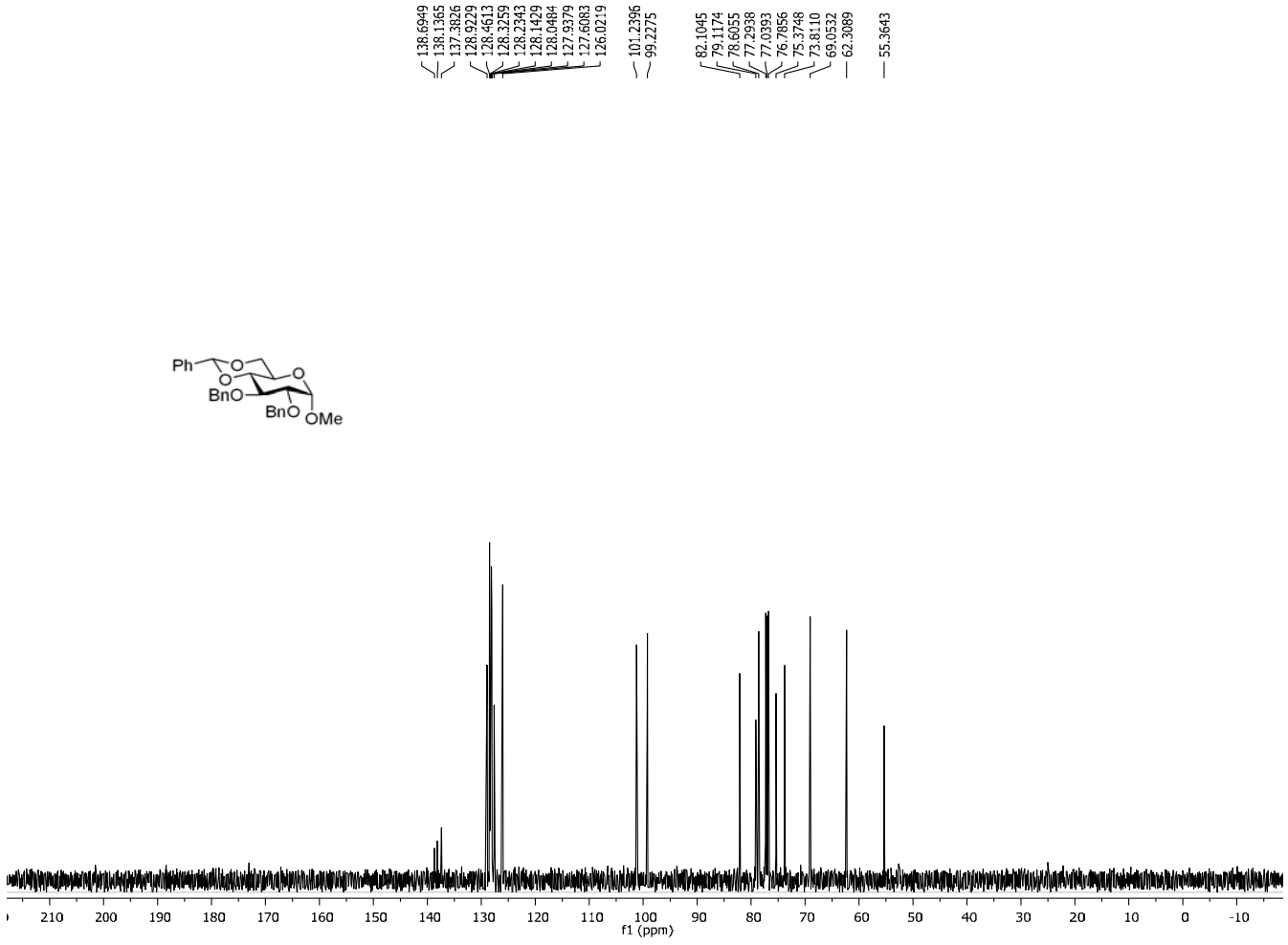


Figure A175. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **179A**

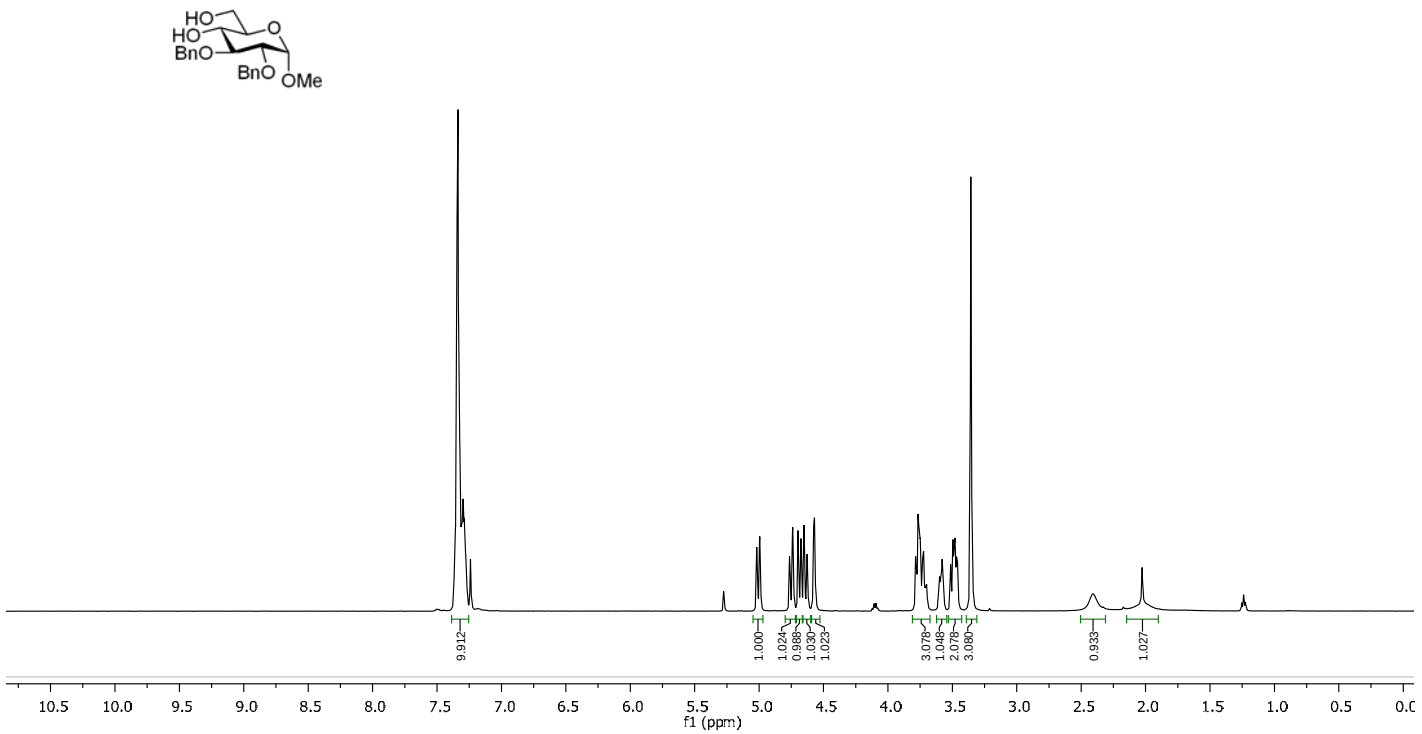


Figure A176. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Alcohol **179B**

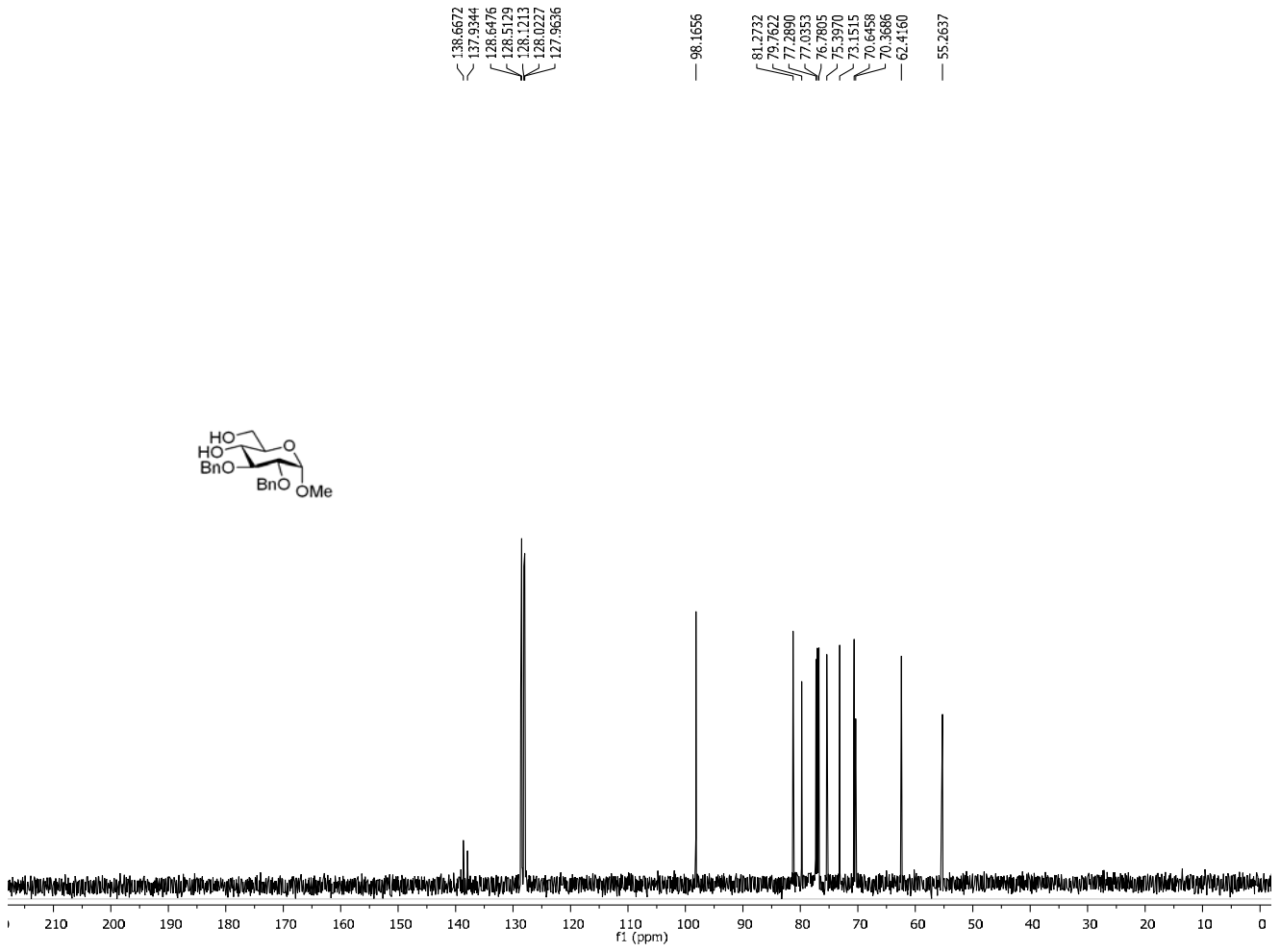


Figure A177. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Alcohol **179B**

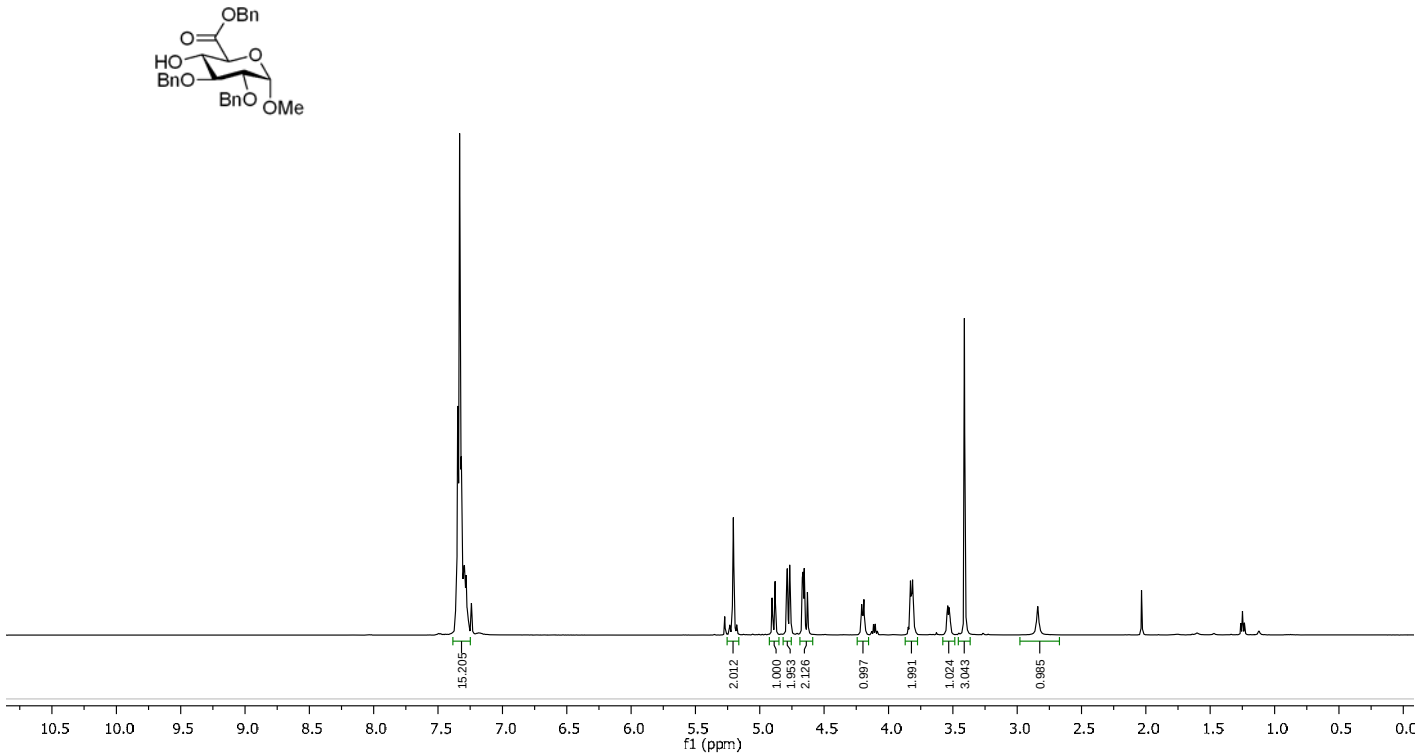


Figure A178. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of the Benzyl Ester **179**

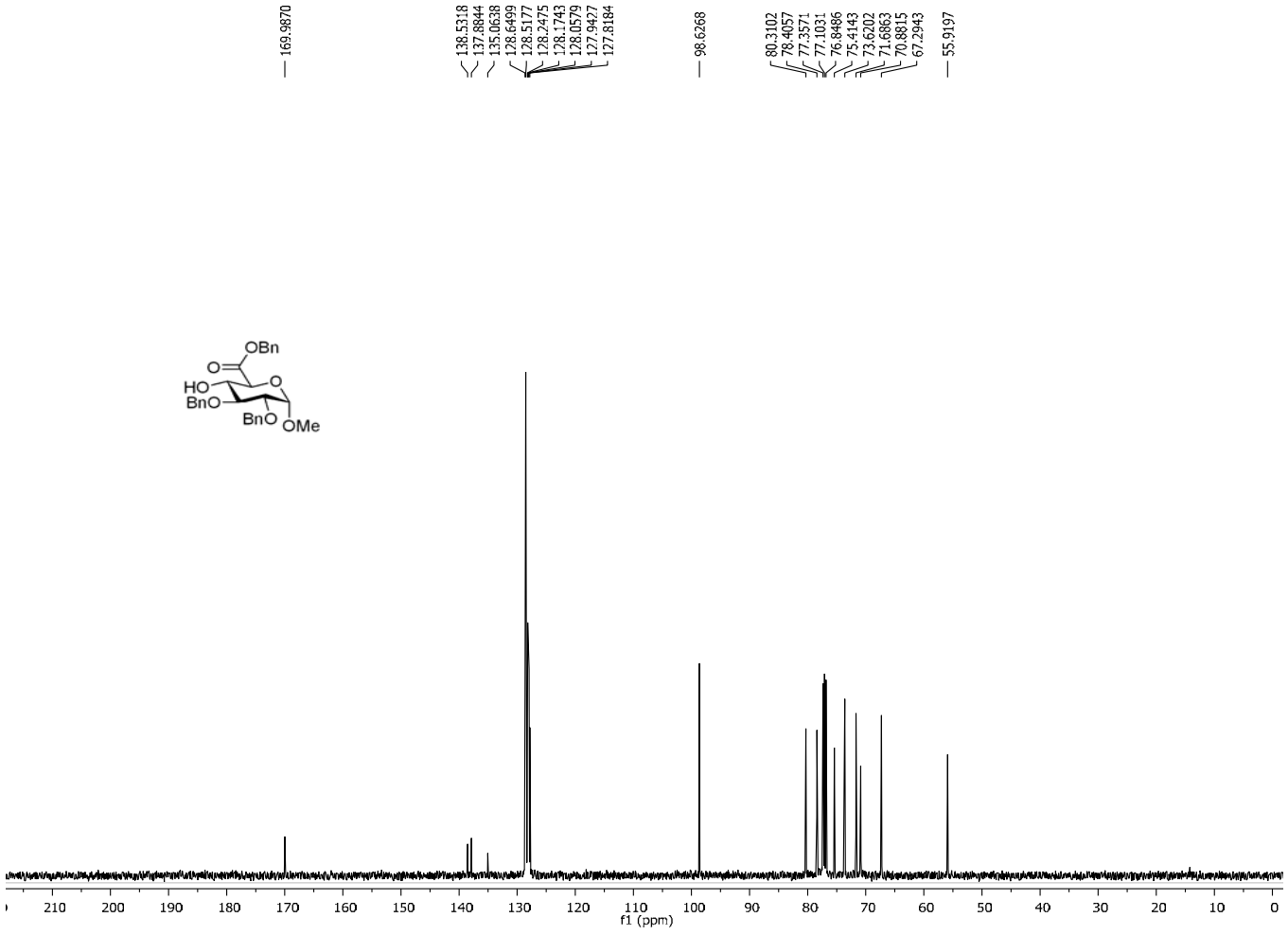


Figure A179. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Benzyl Ester **179**

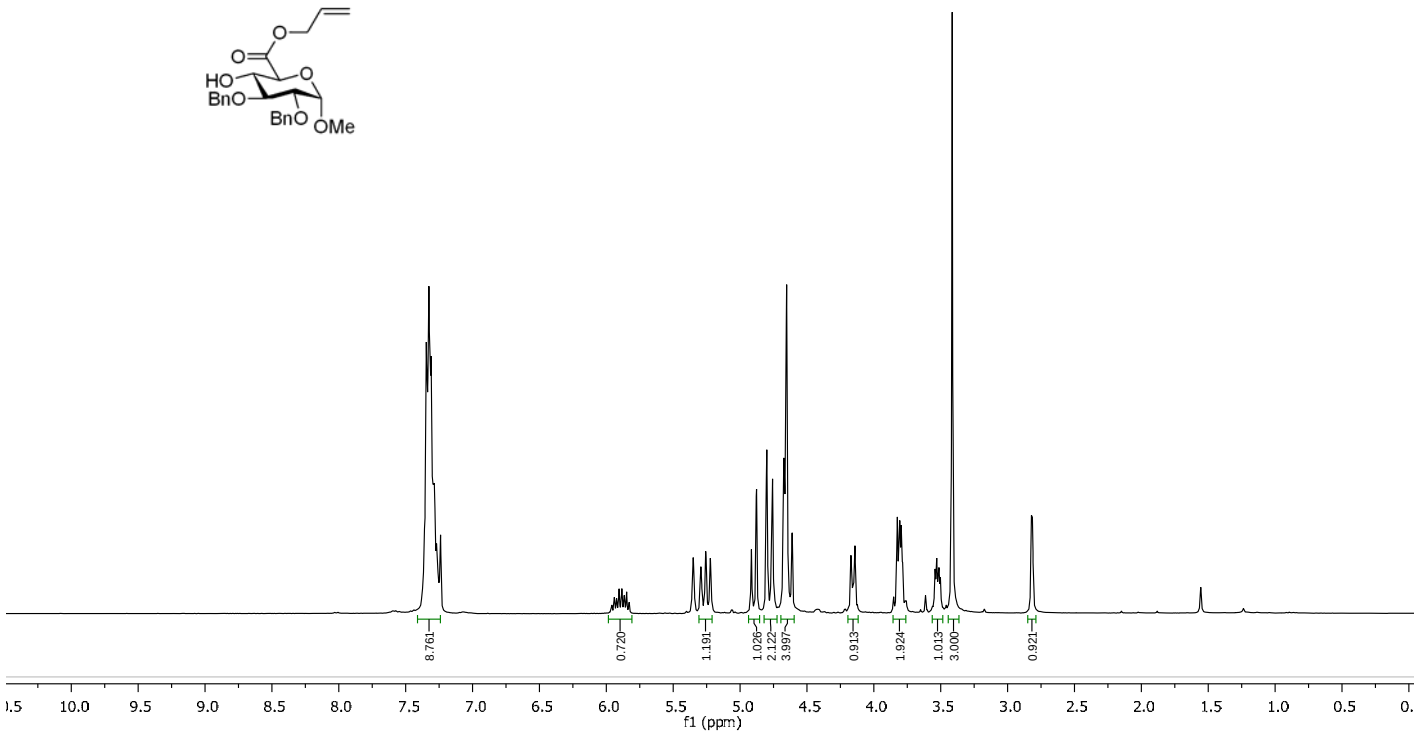


Figure A180. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of the Allyl Ester **180**

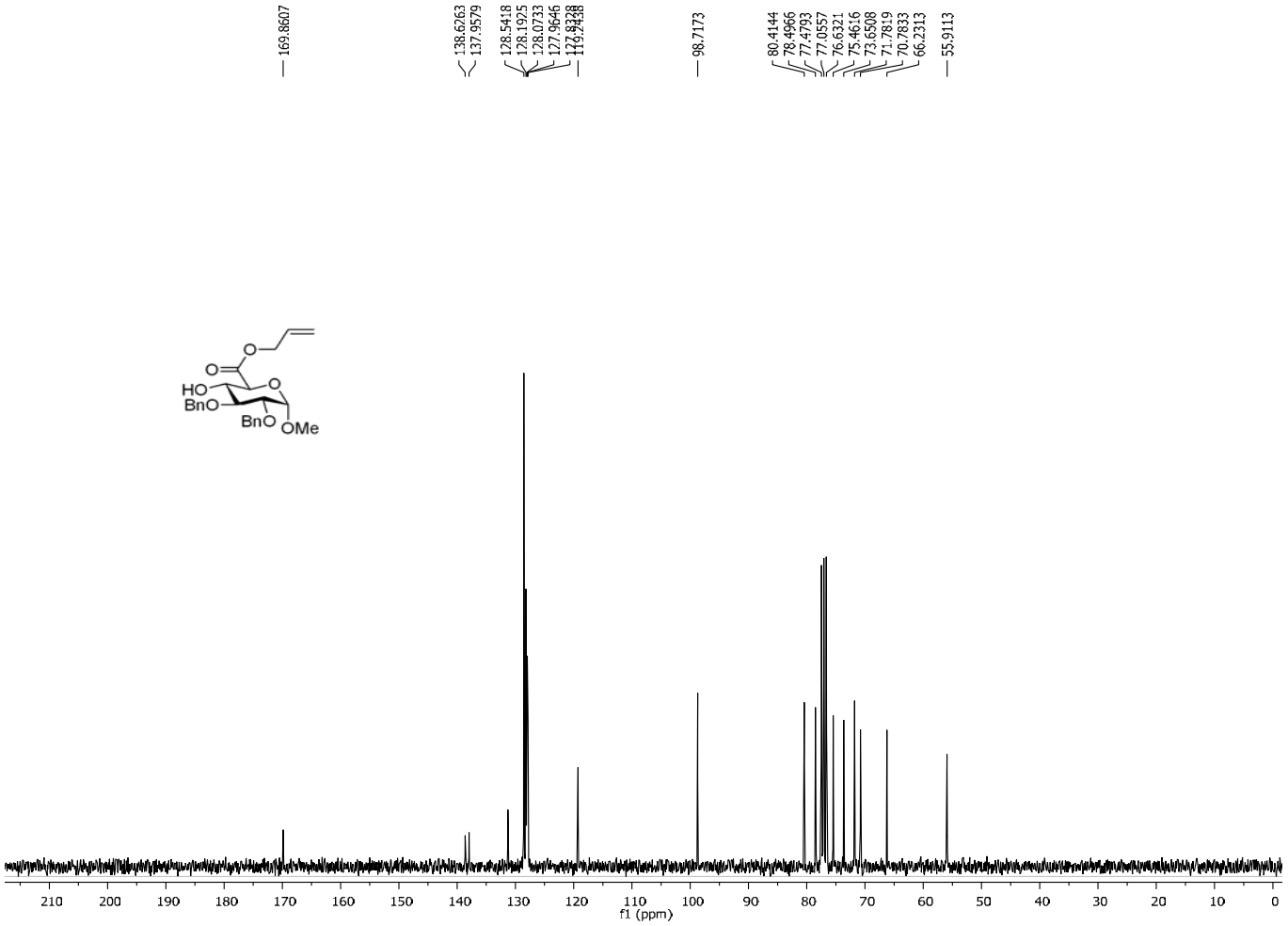


Figure A181. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Allyl Ester **180**

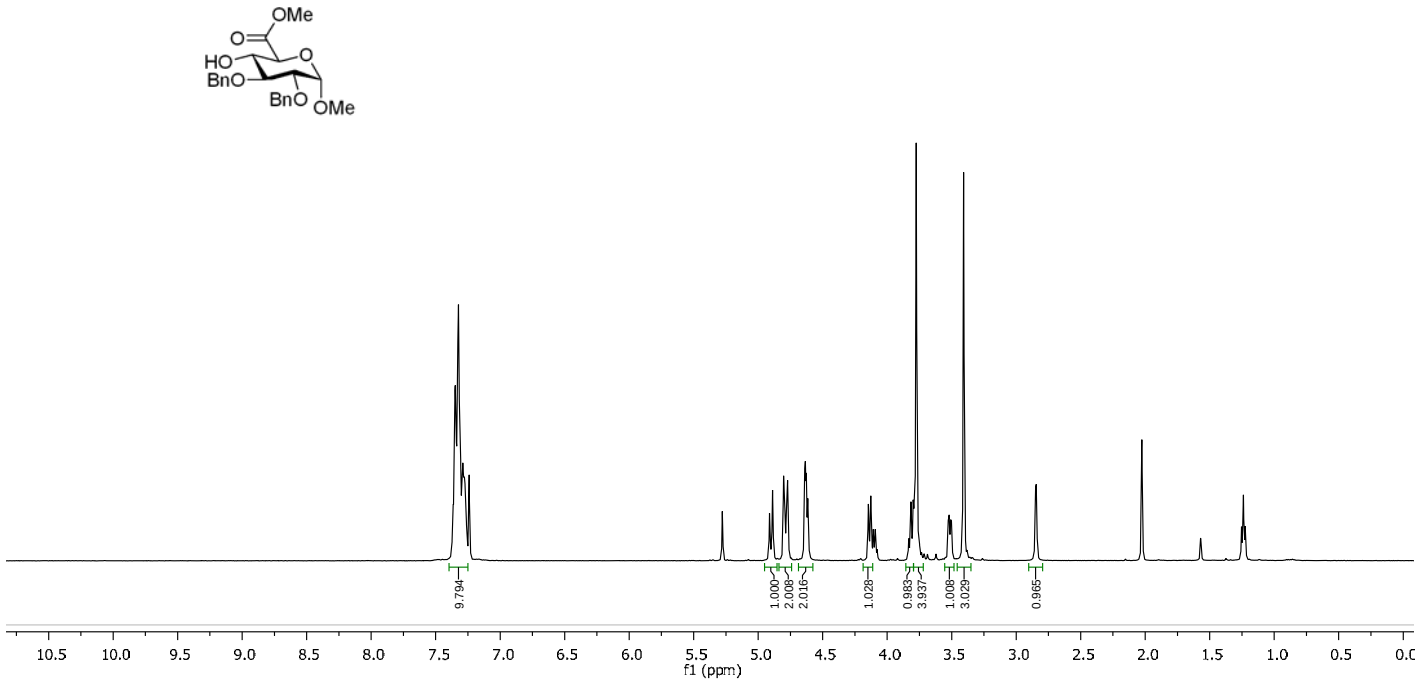


Figure A182. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Methyl Ester **181**

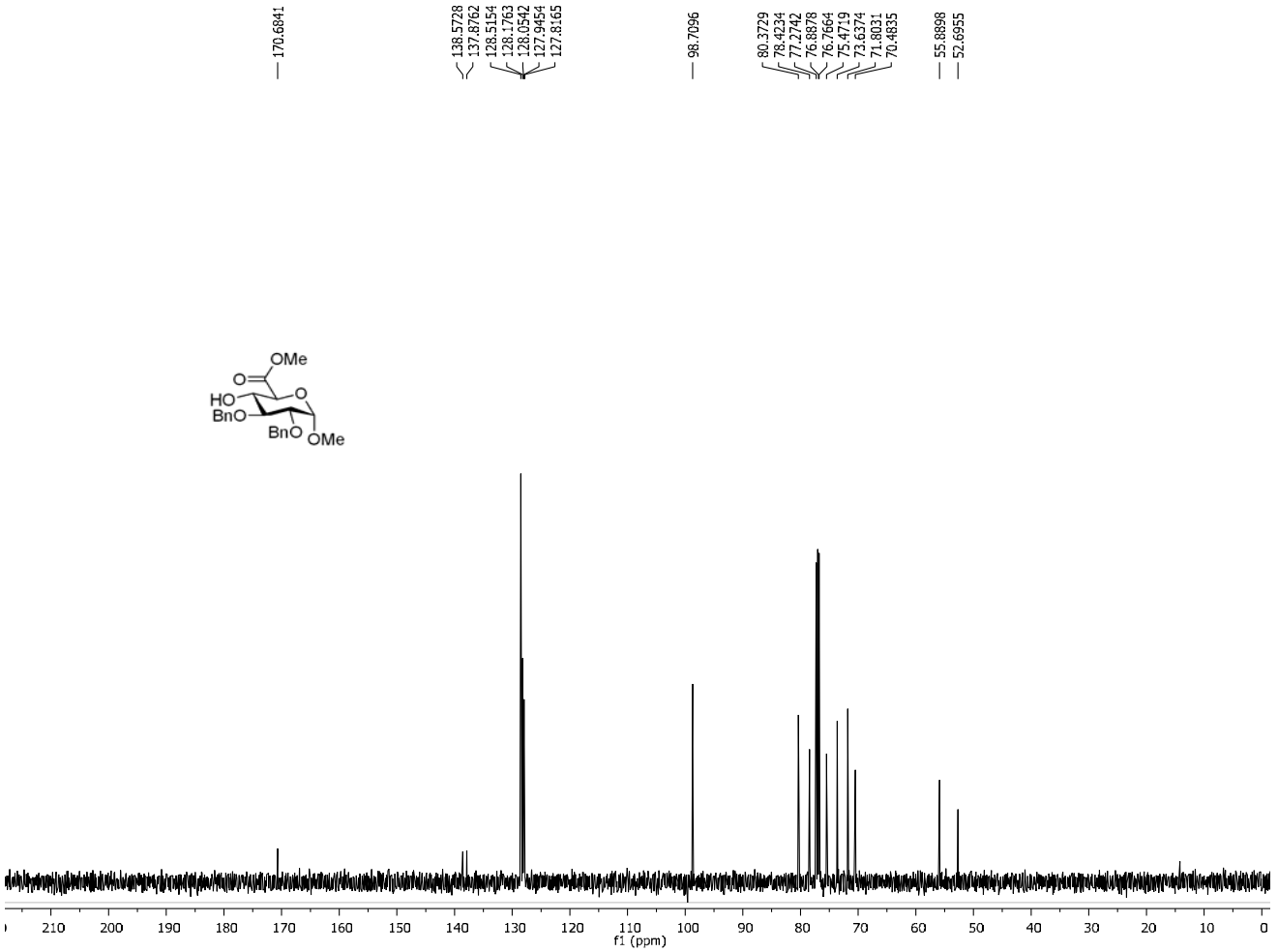


Figure A183. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Methyl Ester **181**

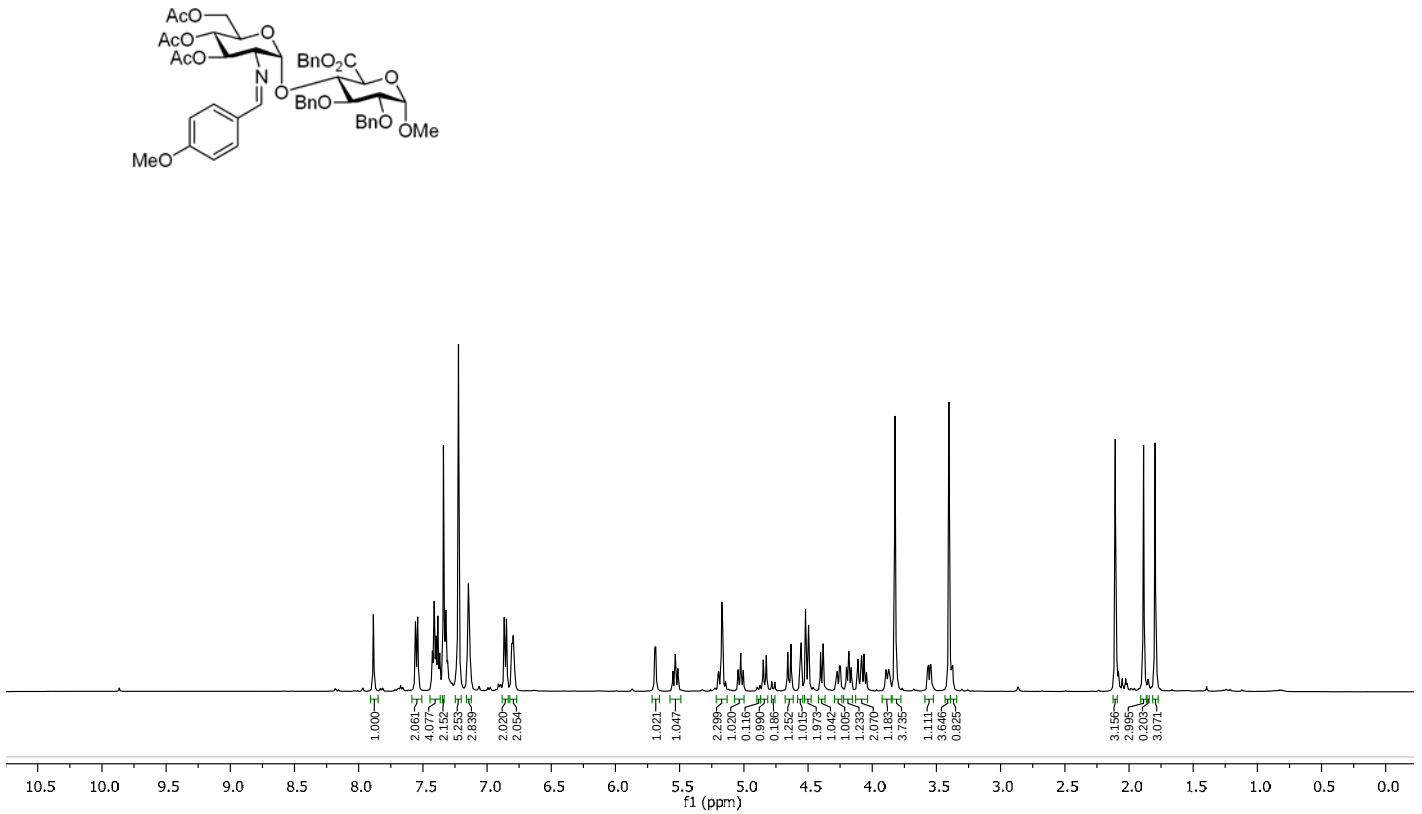


Figure A184. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **183**

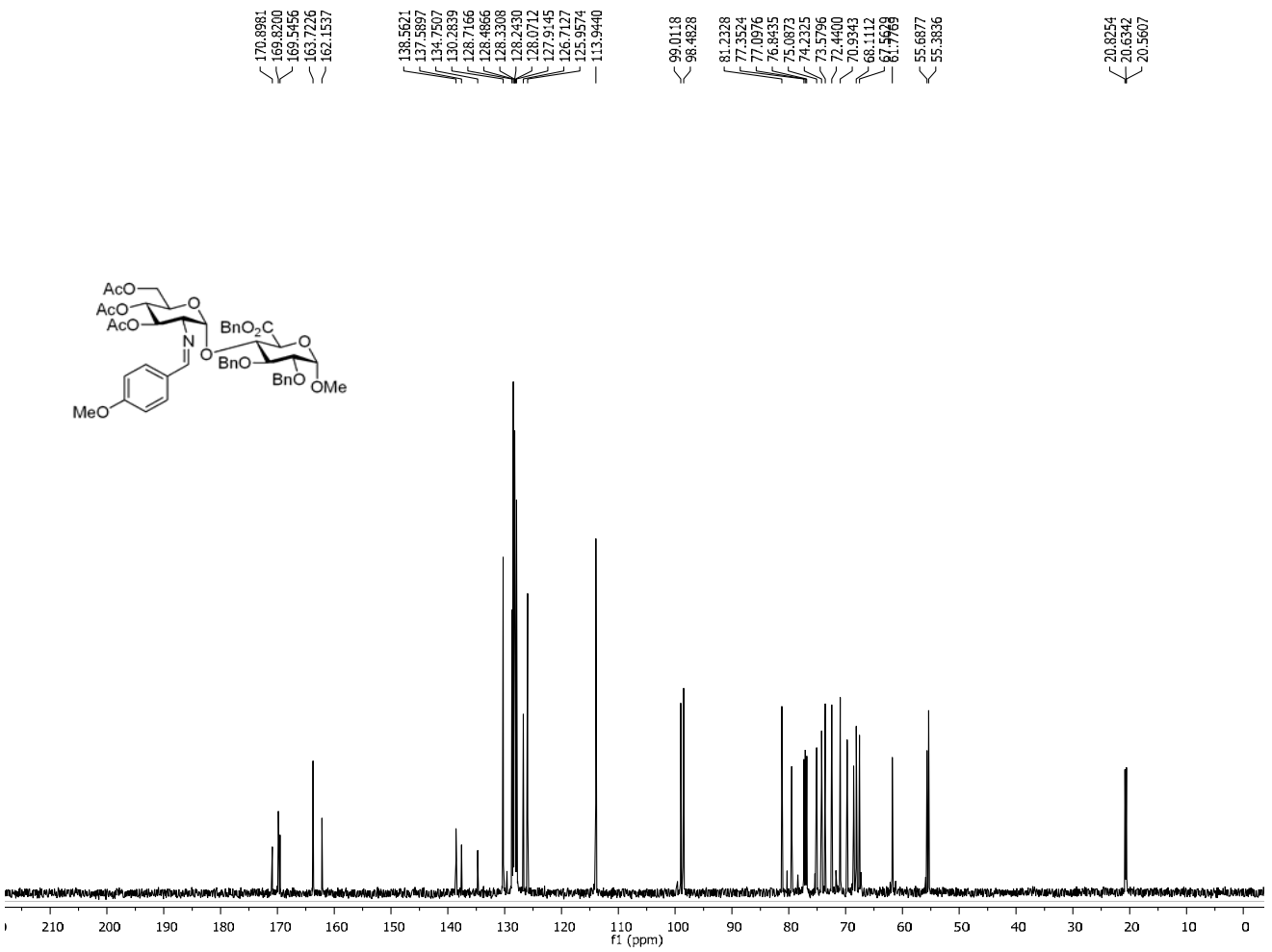


Figure A185. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **183**

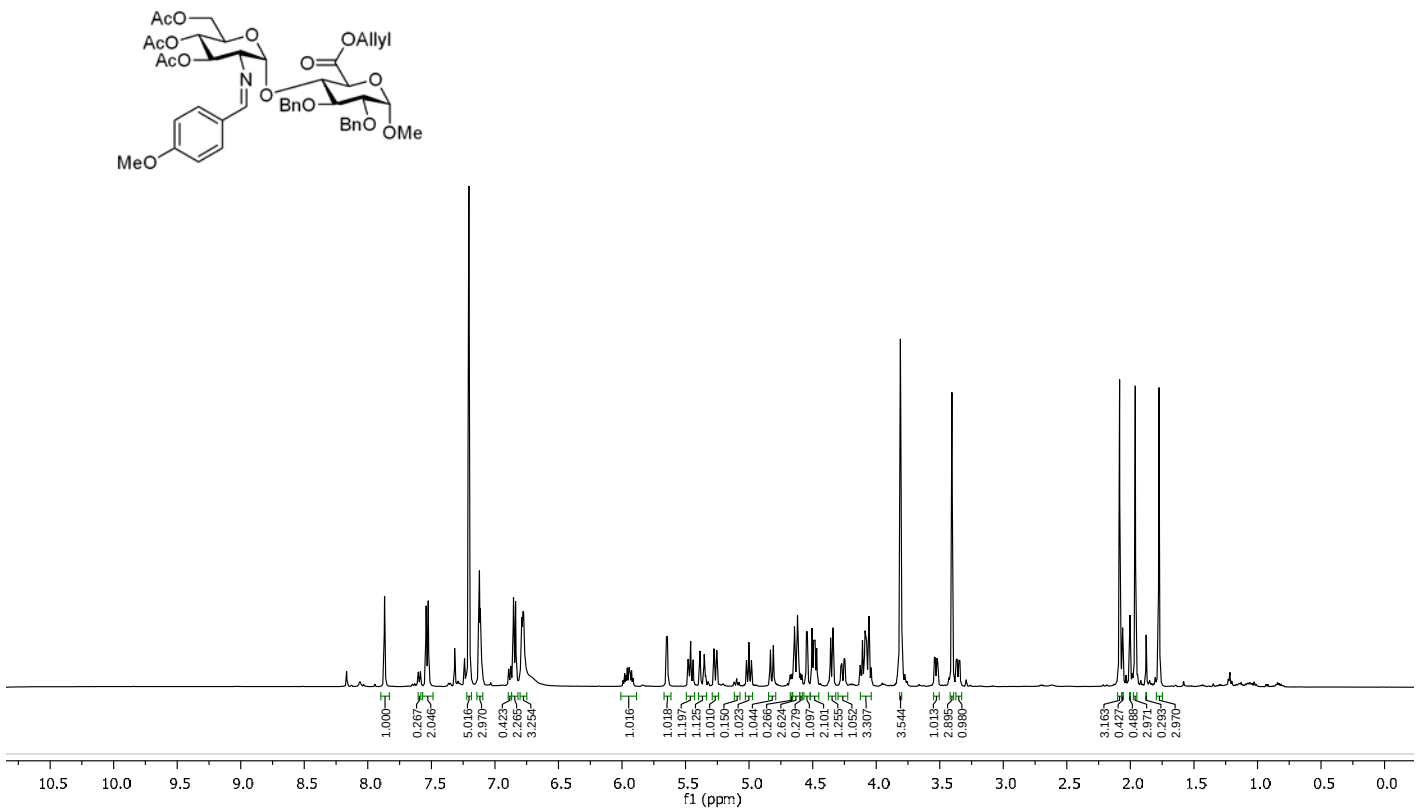


Figure A186. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **184**

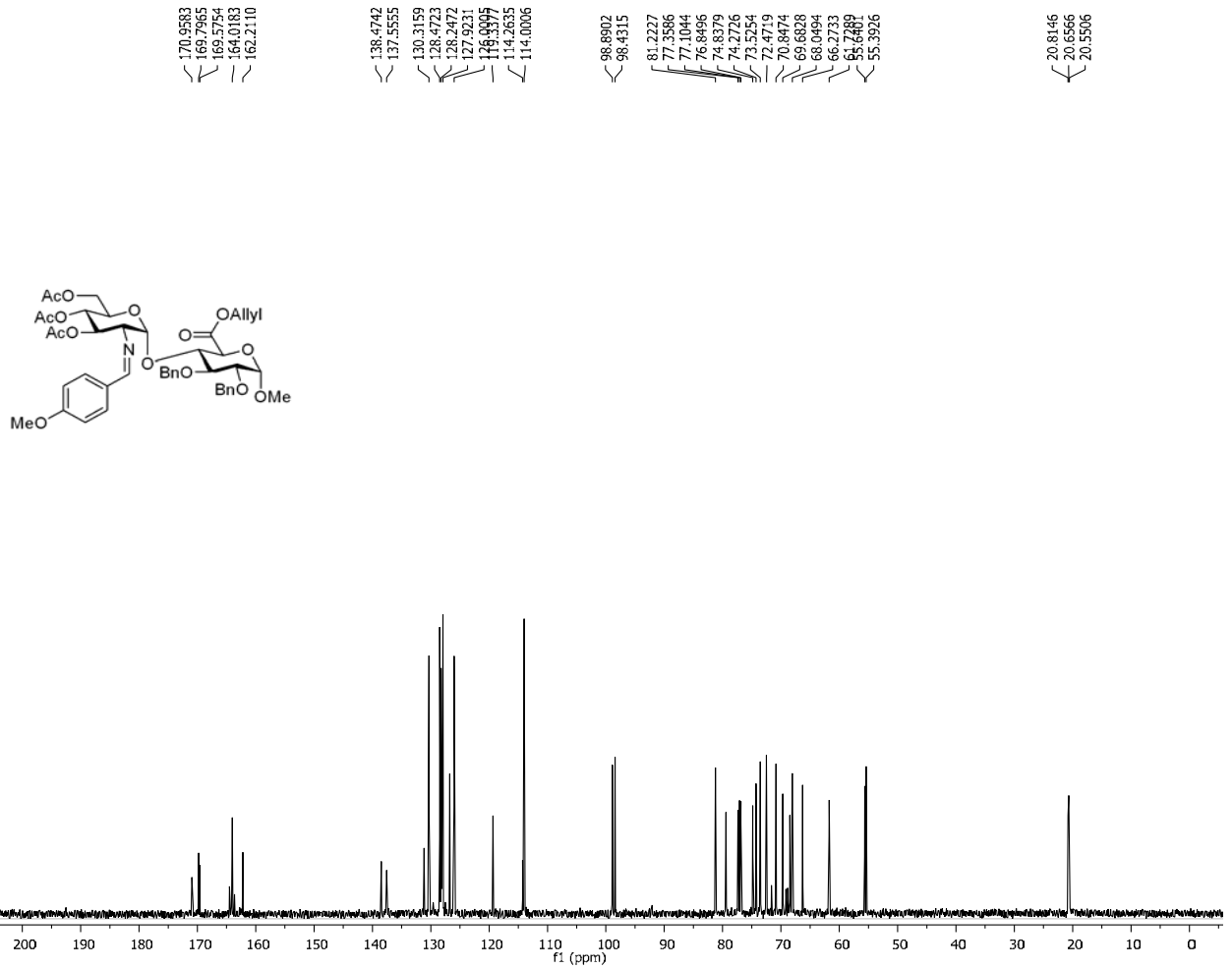


Figure A187. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **184**

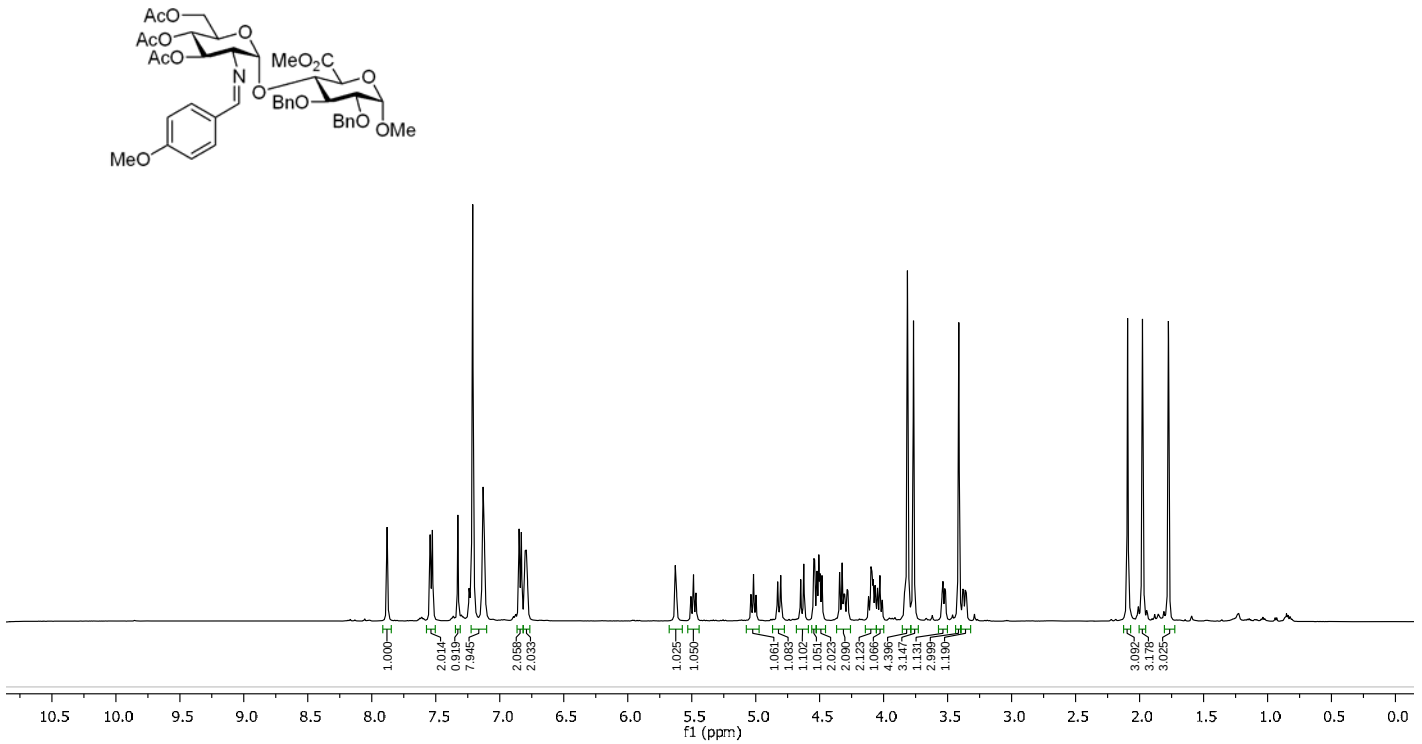


Figure A188. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **185**

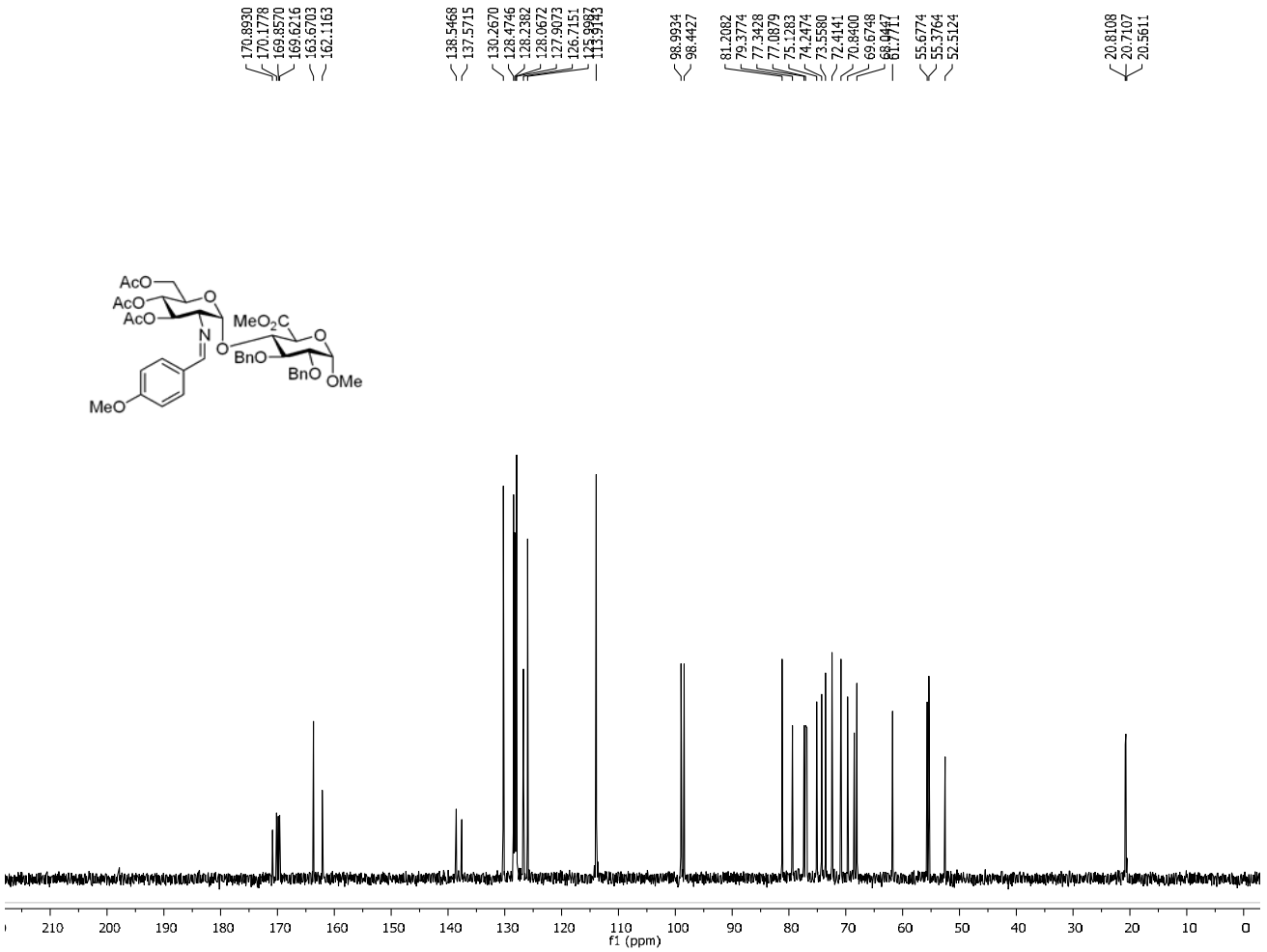


Figure A189. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **185**

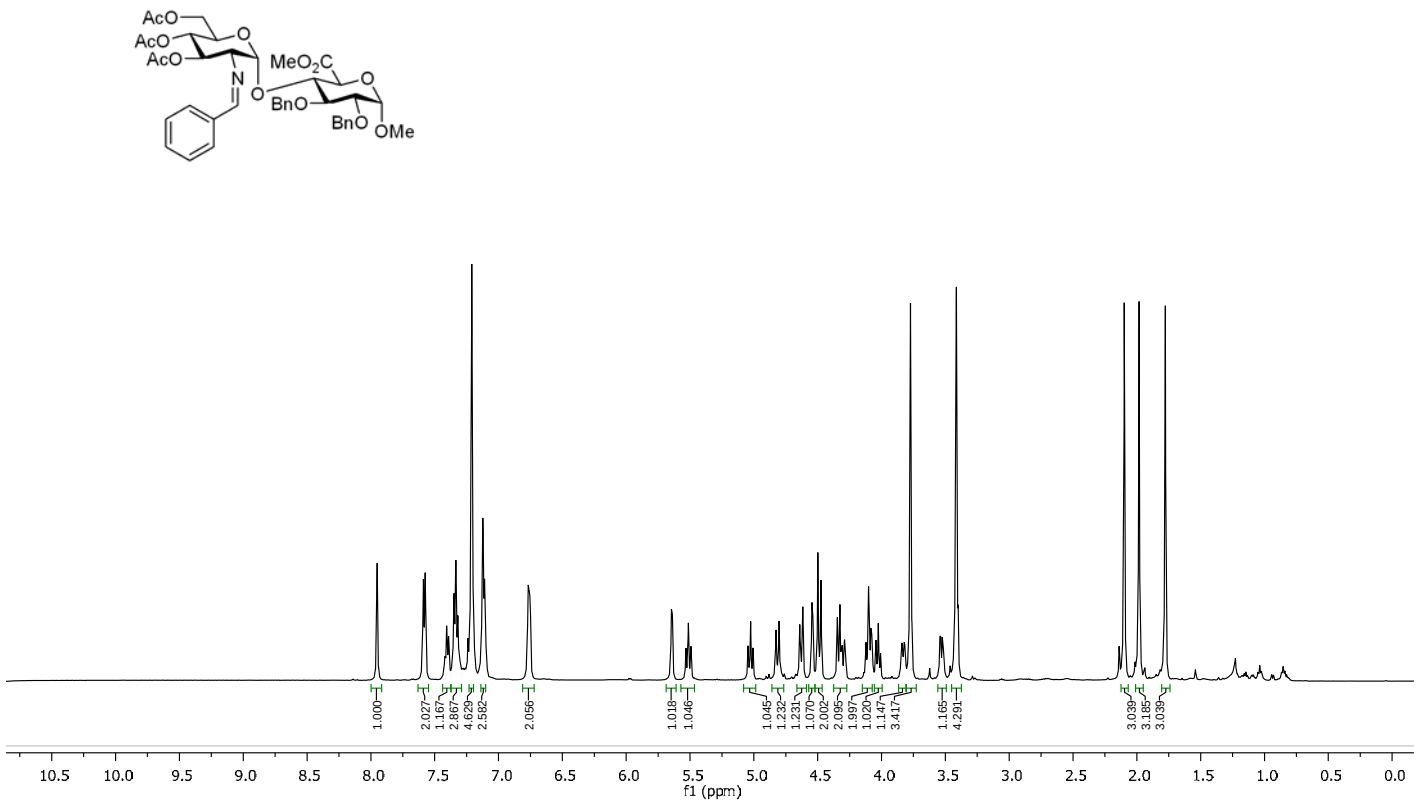


Figure A190. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **186**

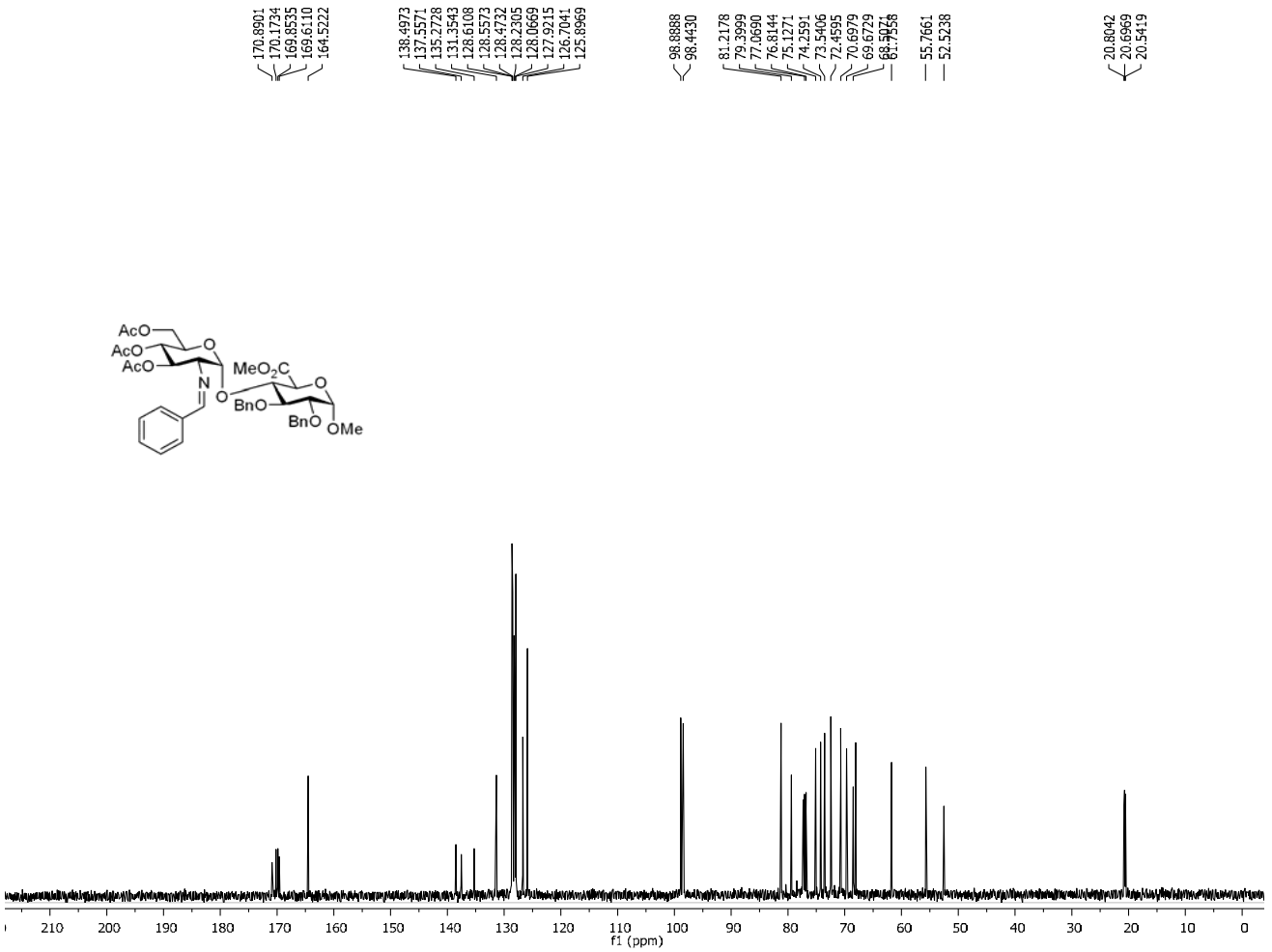


Figure A191. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **186**

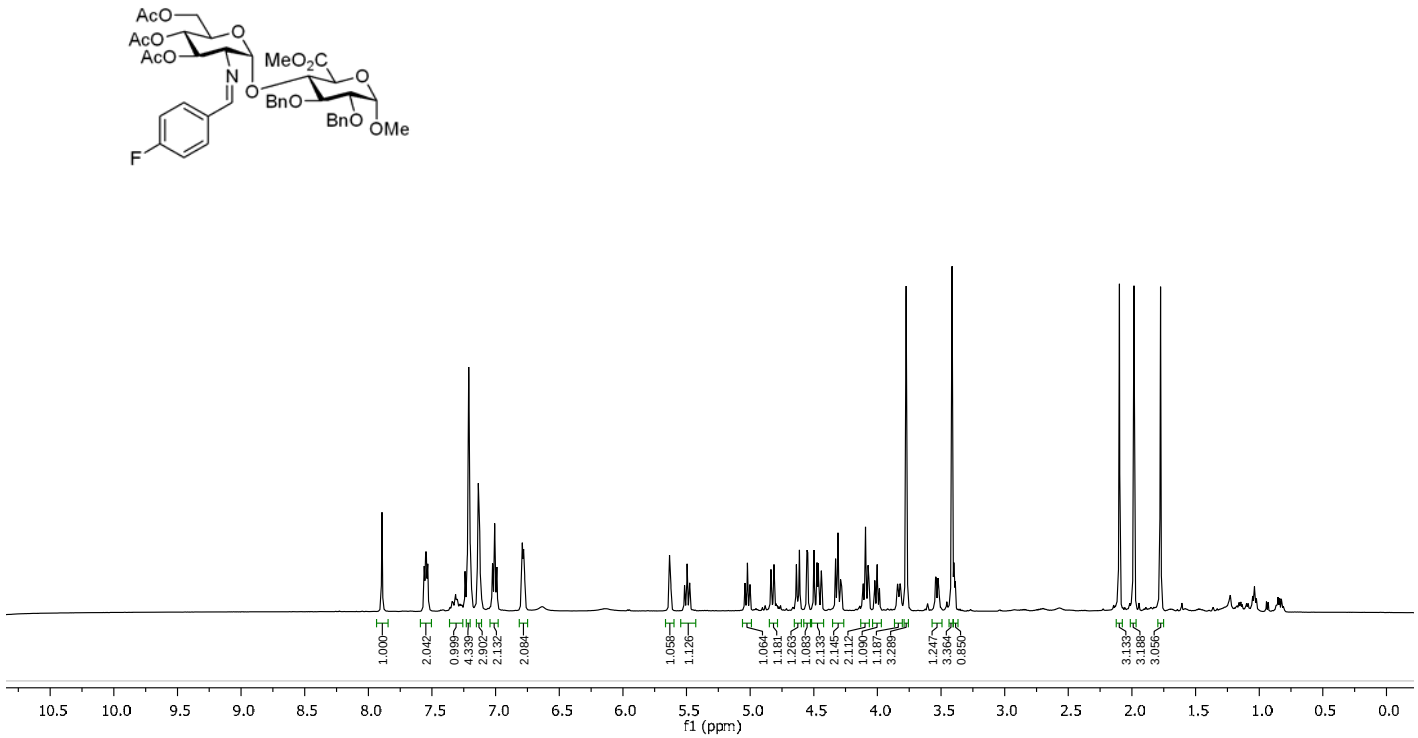


Figure A192. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **187**

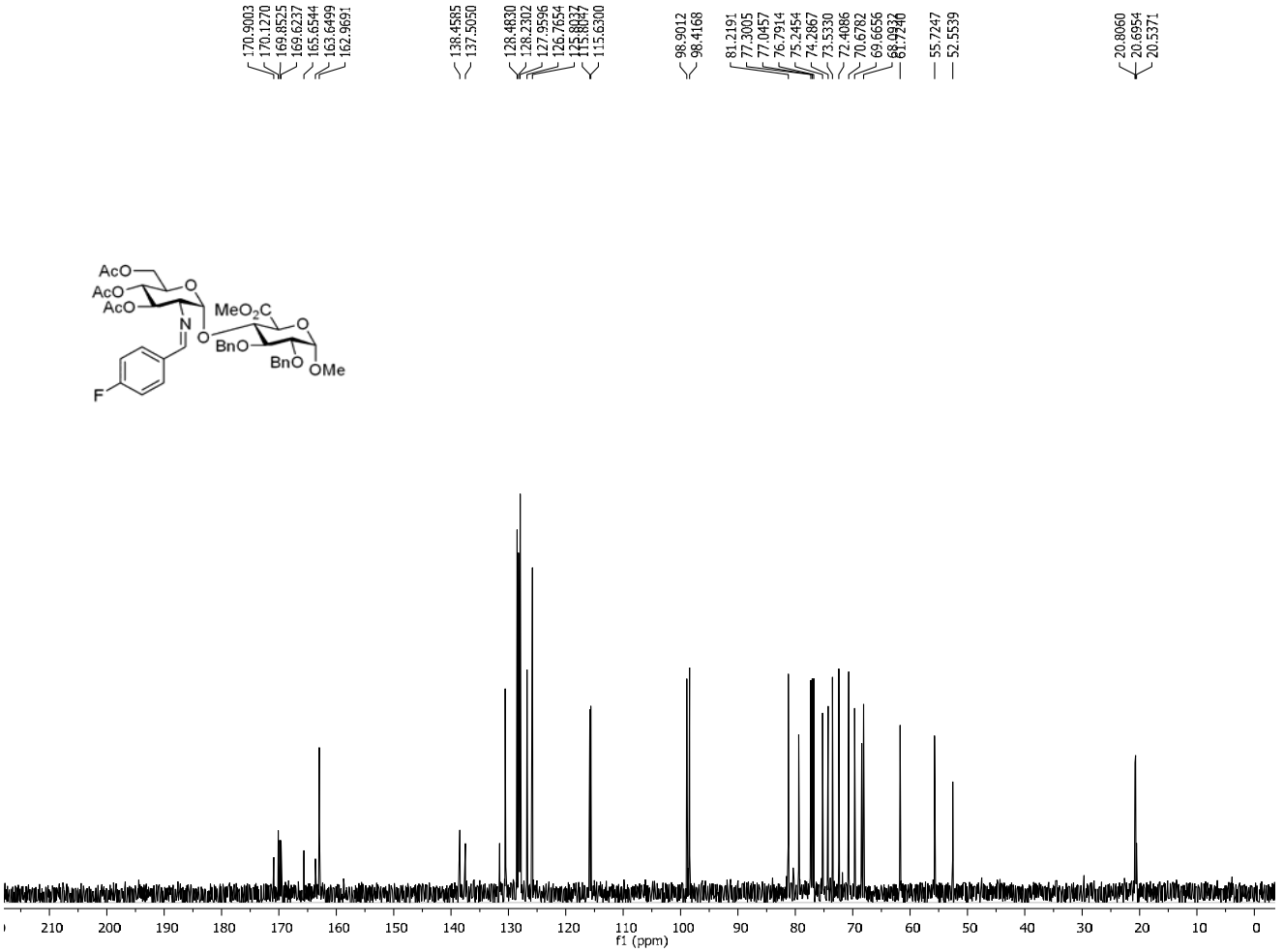


Figure A193. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **187**

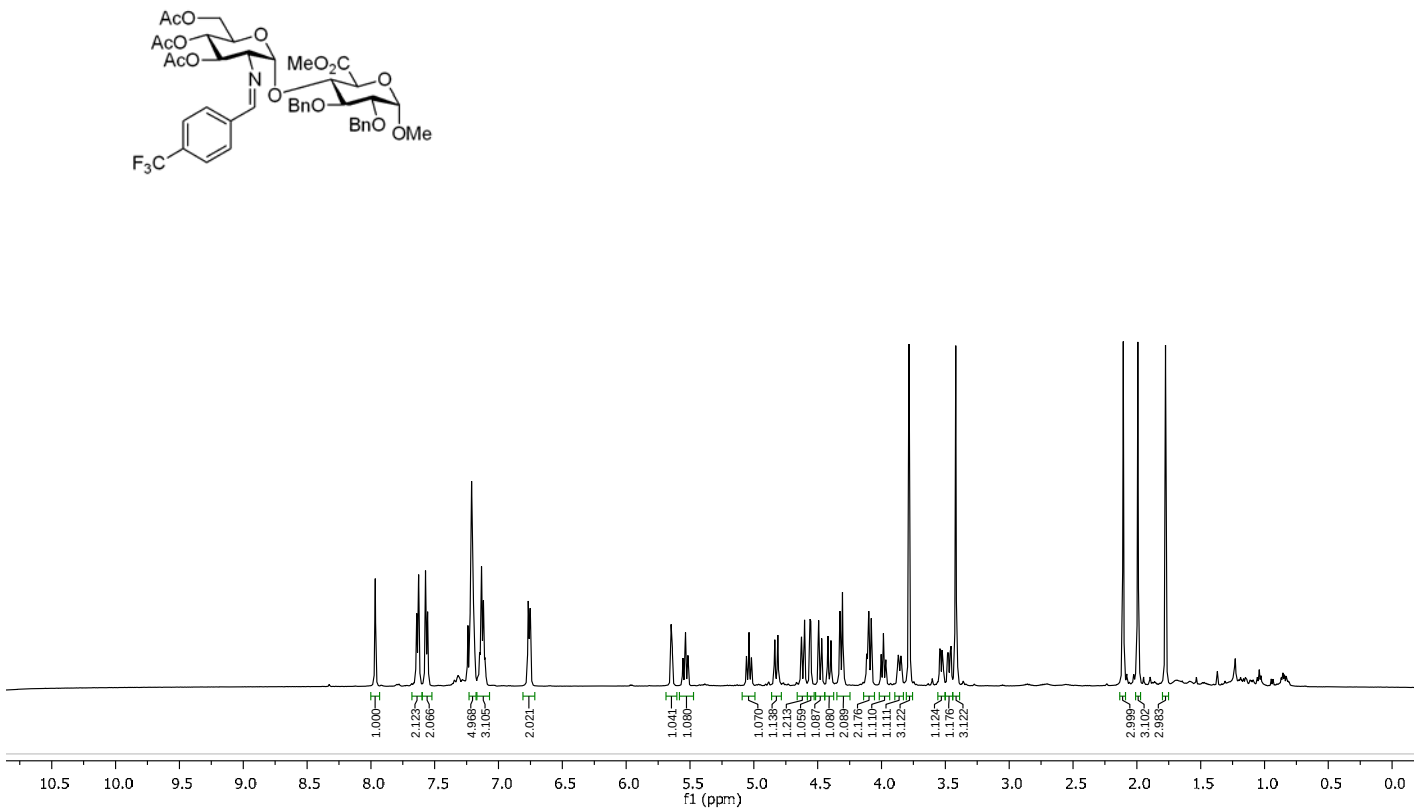


Figure A194. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **188**

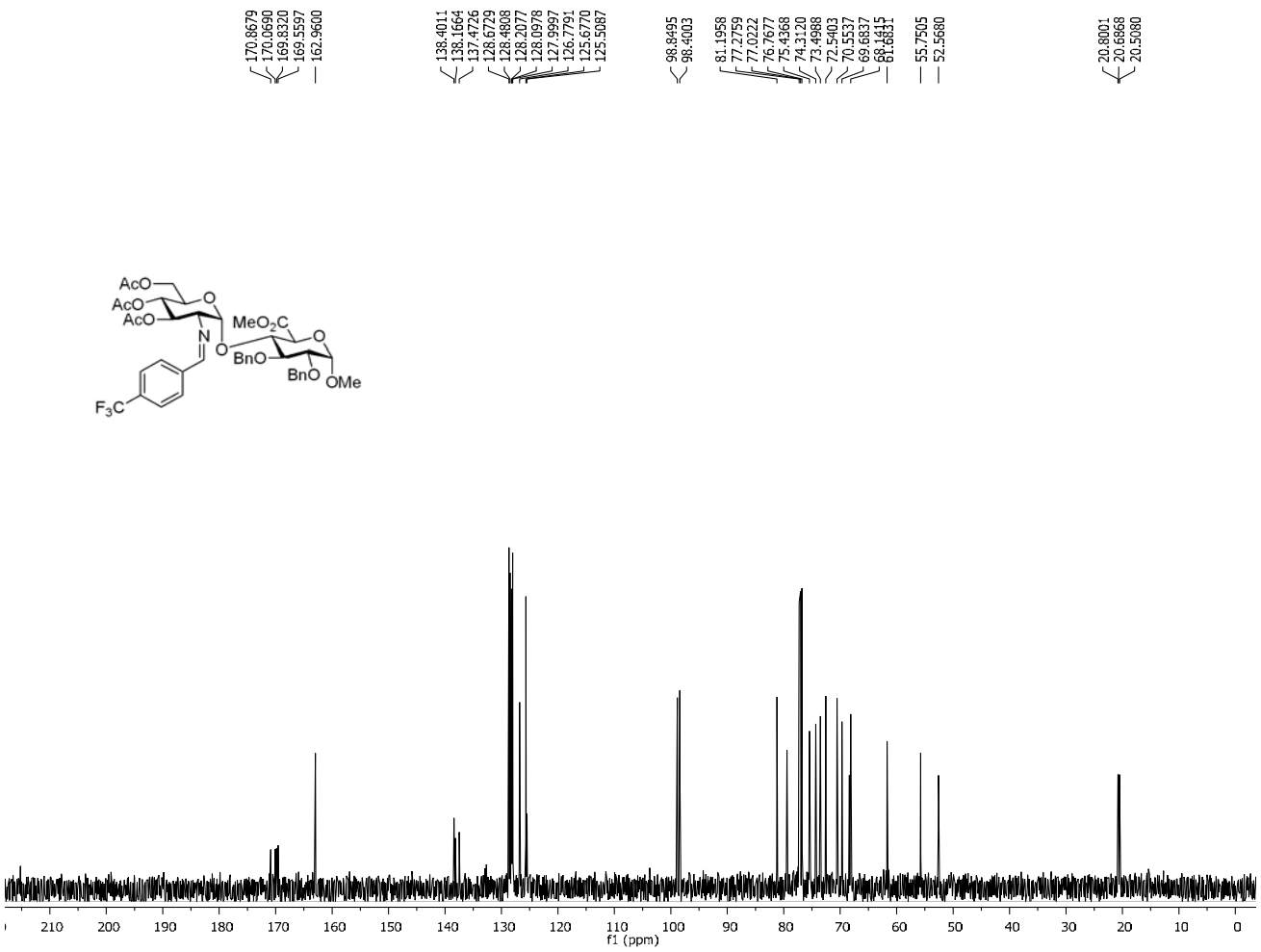


Figure A195. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **188**

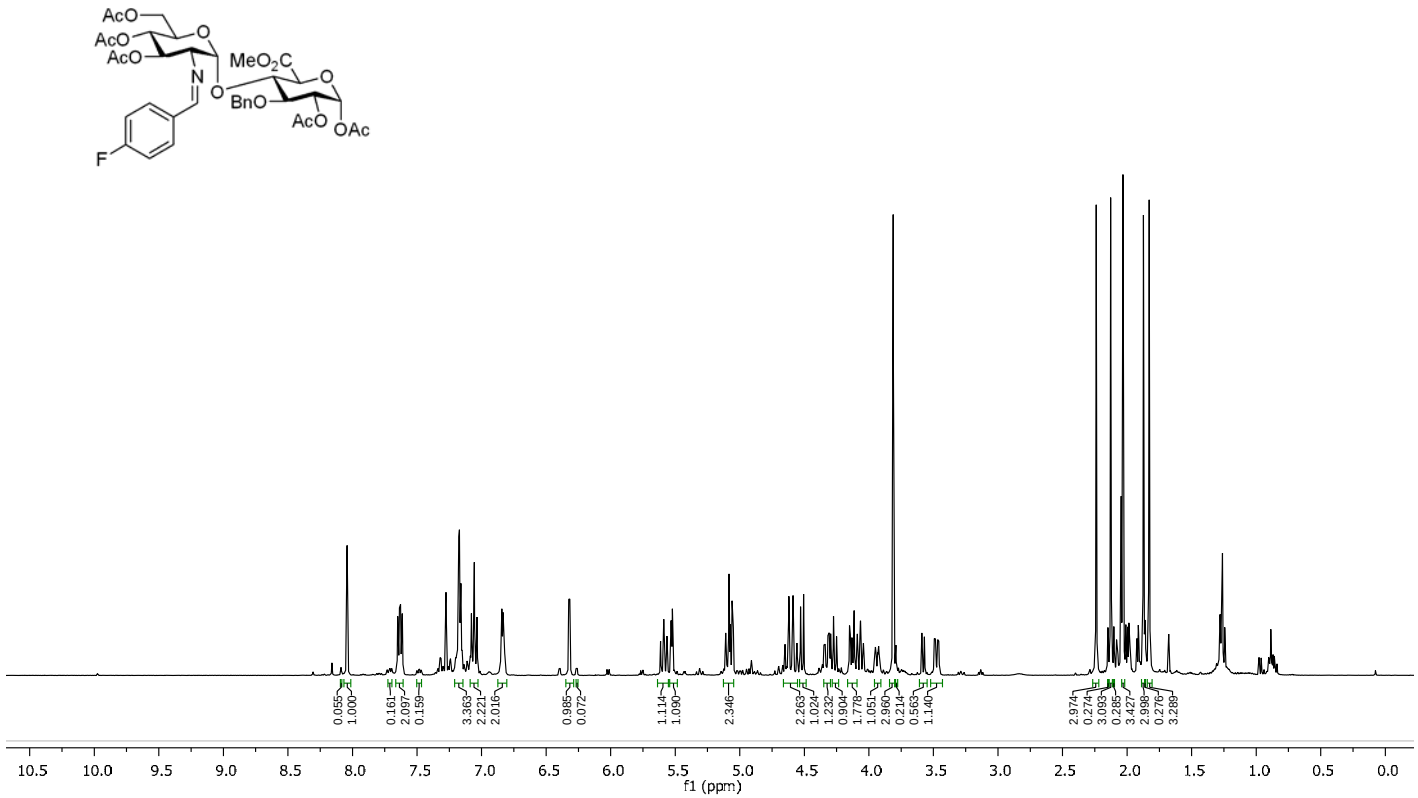


Figure A196. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **189**

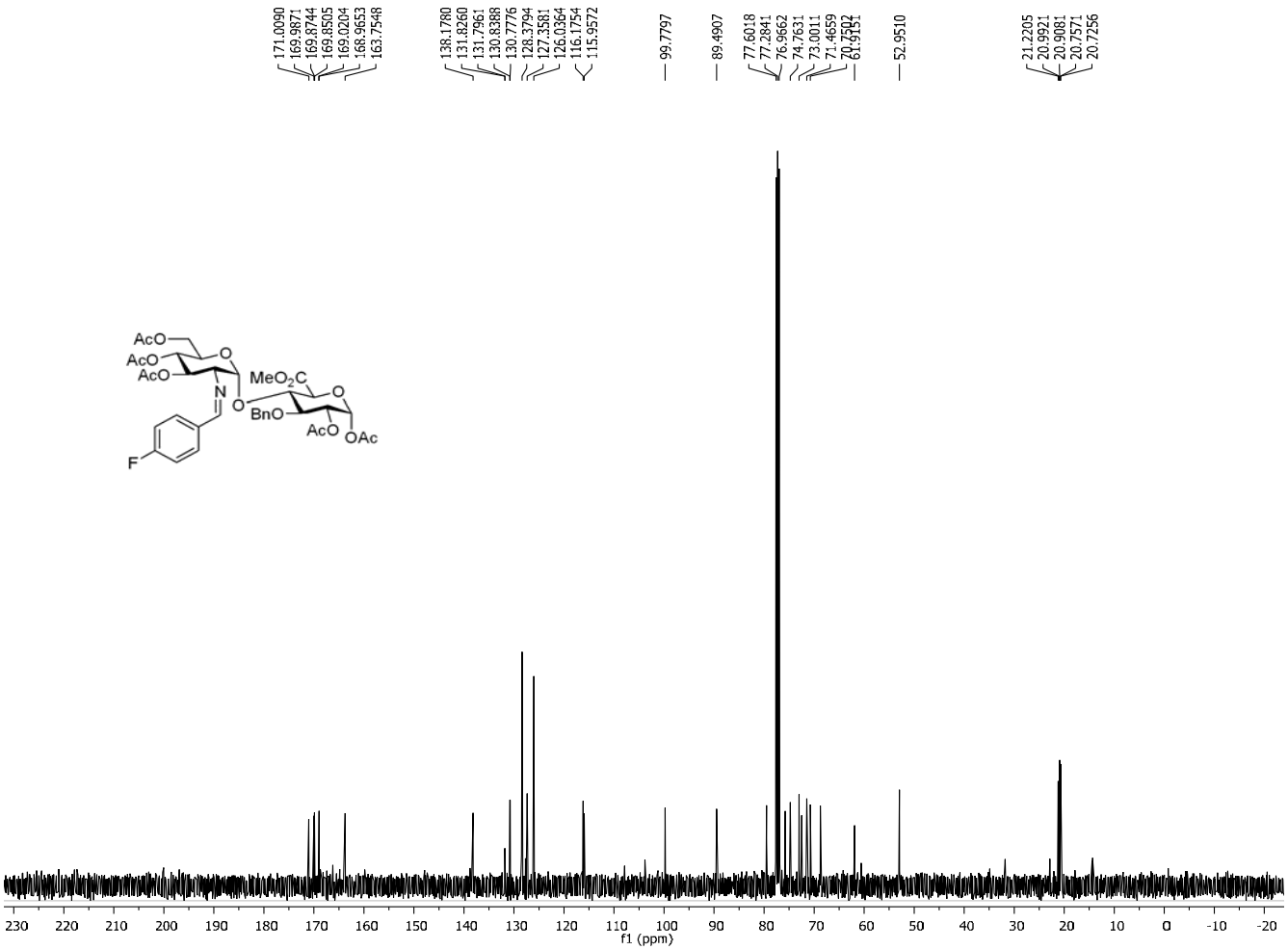


Figure A197. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **189**

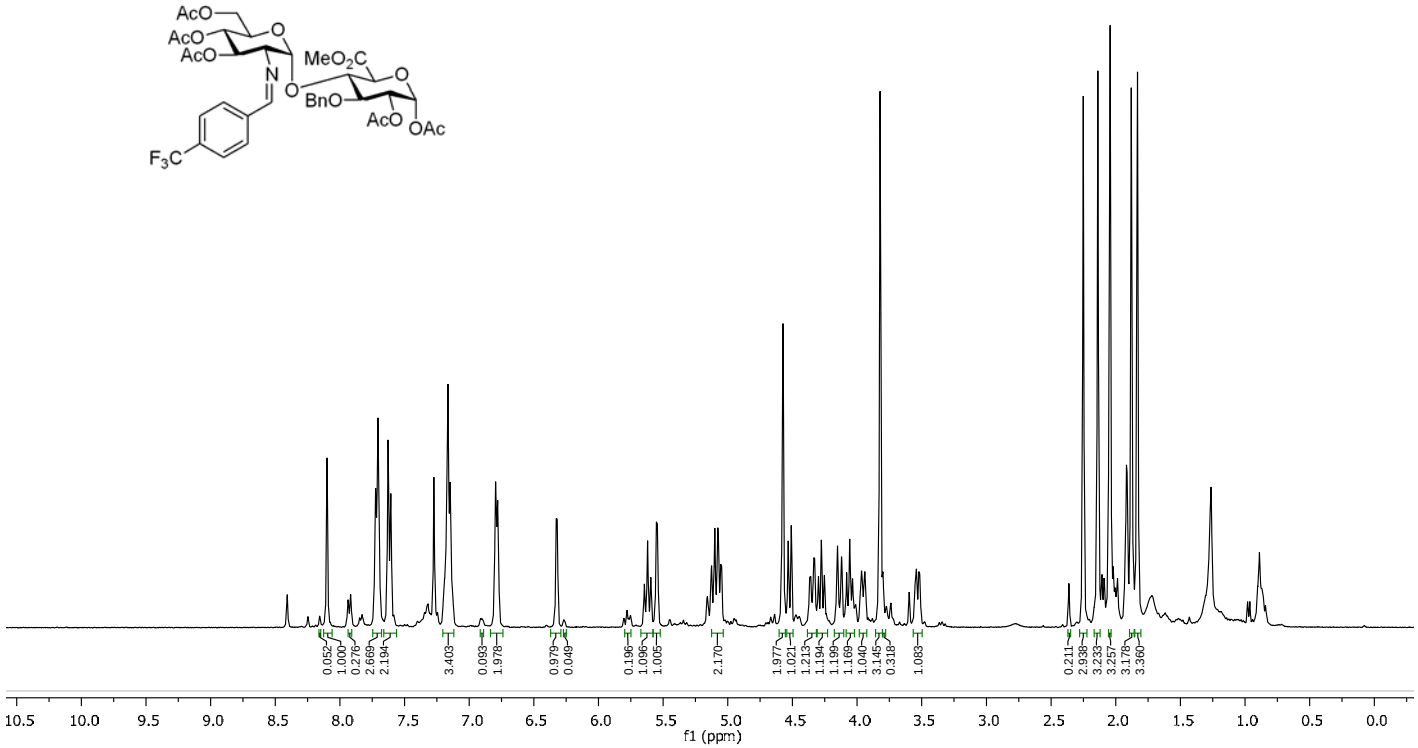


Figure A198. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **190**

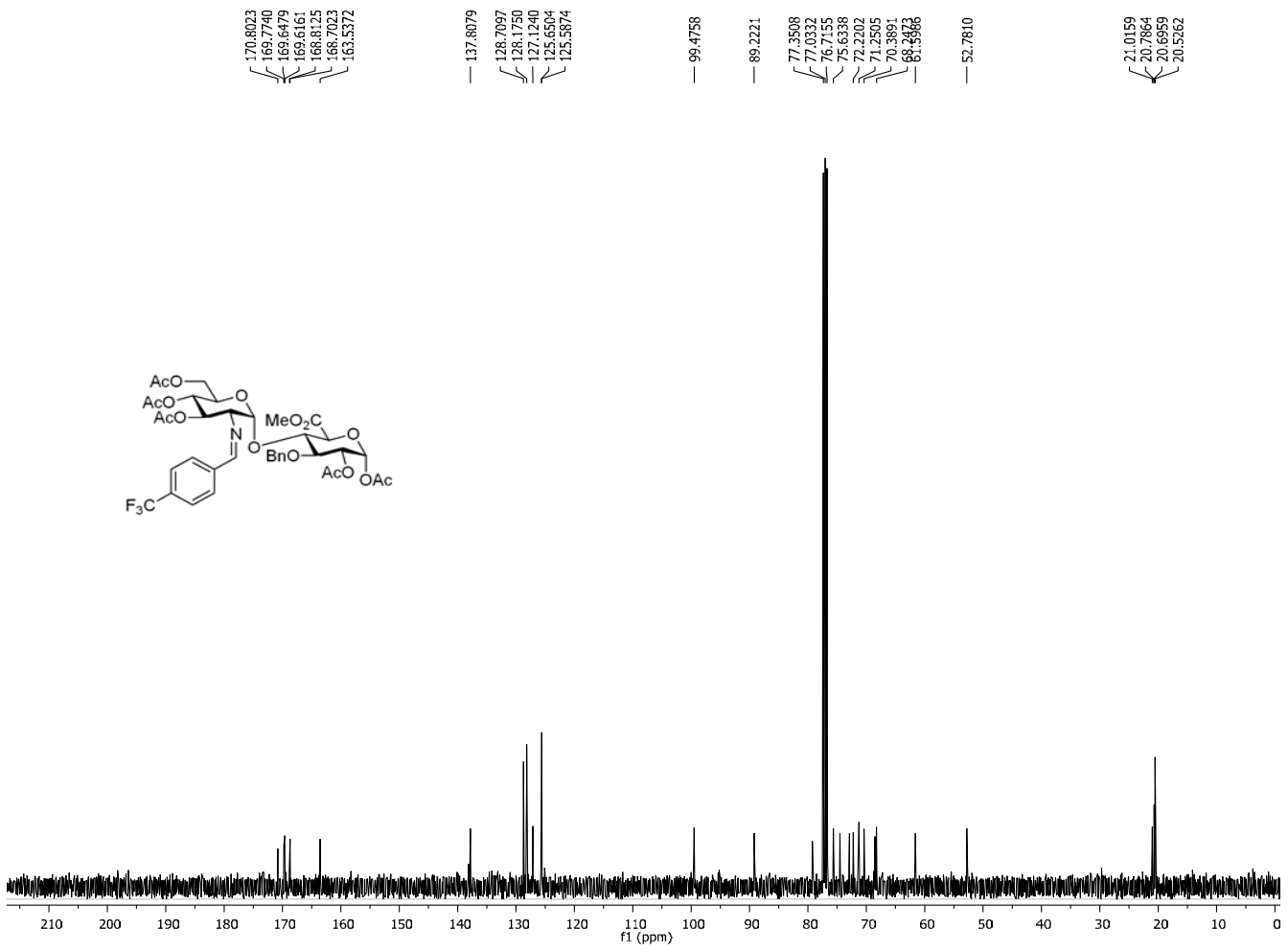


Figure A199. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **190**

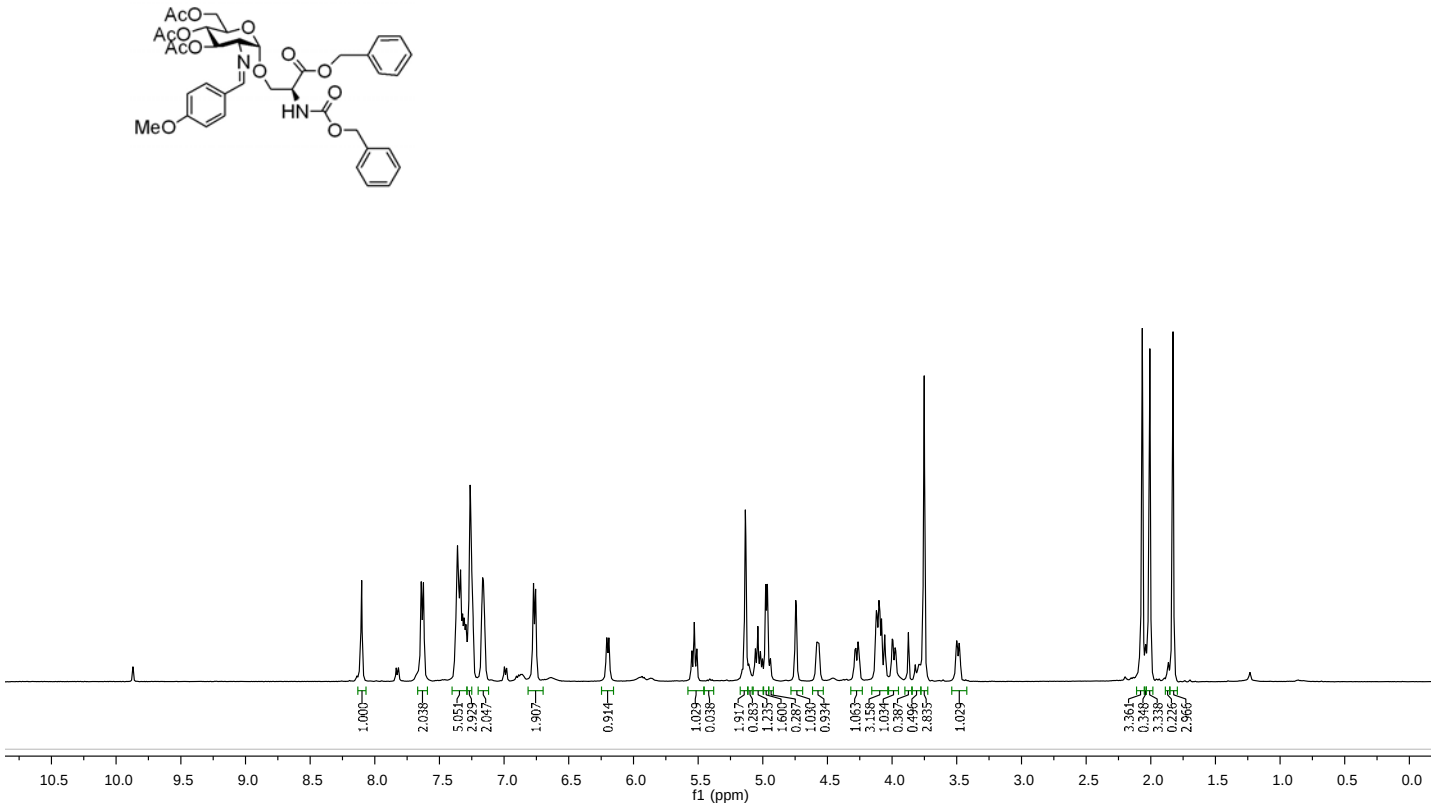


Figure A200. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycopeptide **199**

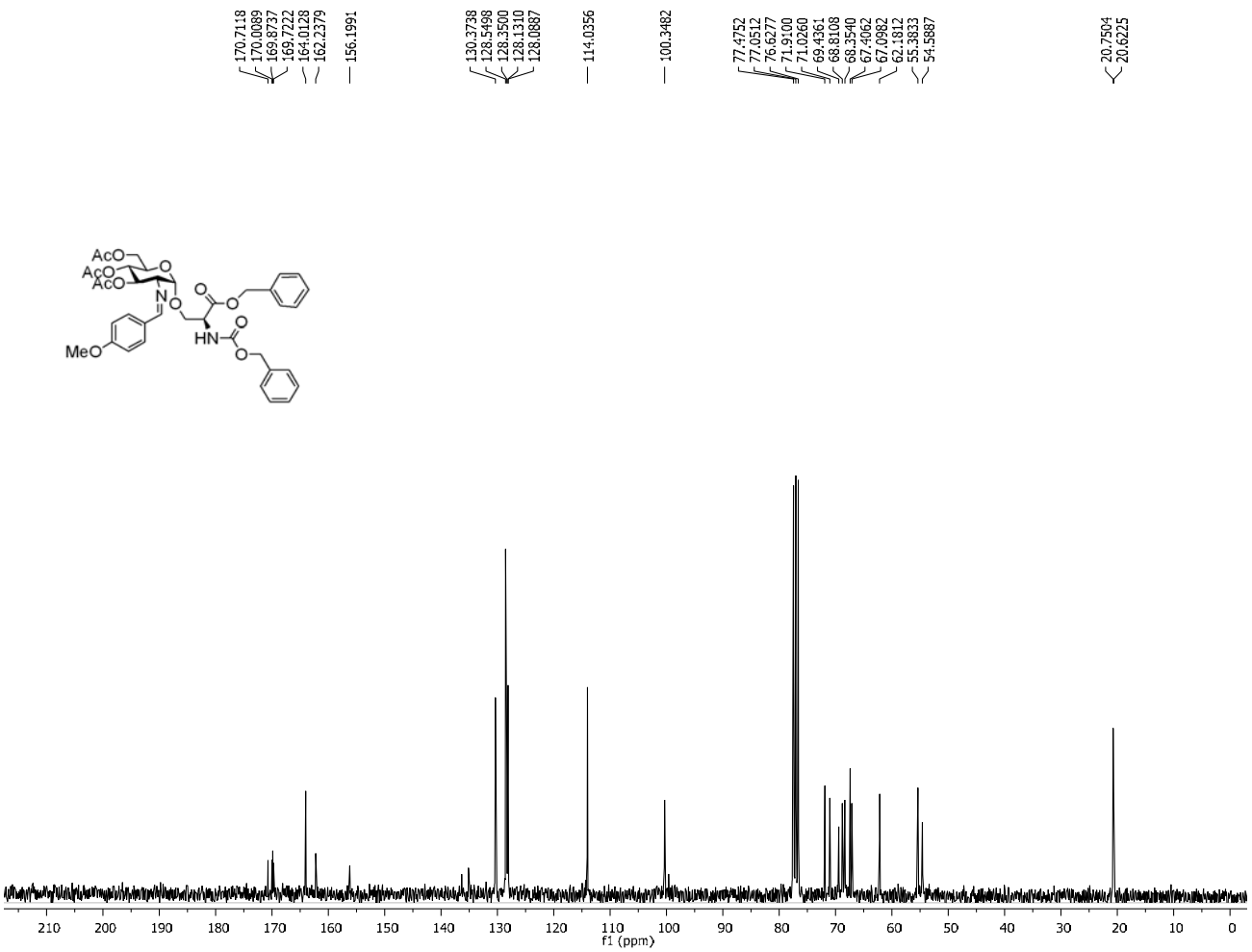


Figure A201. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycopeptide **199**

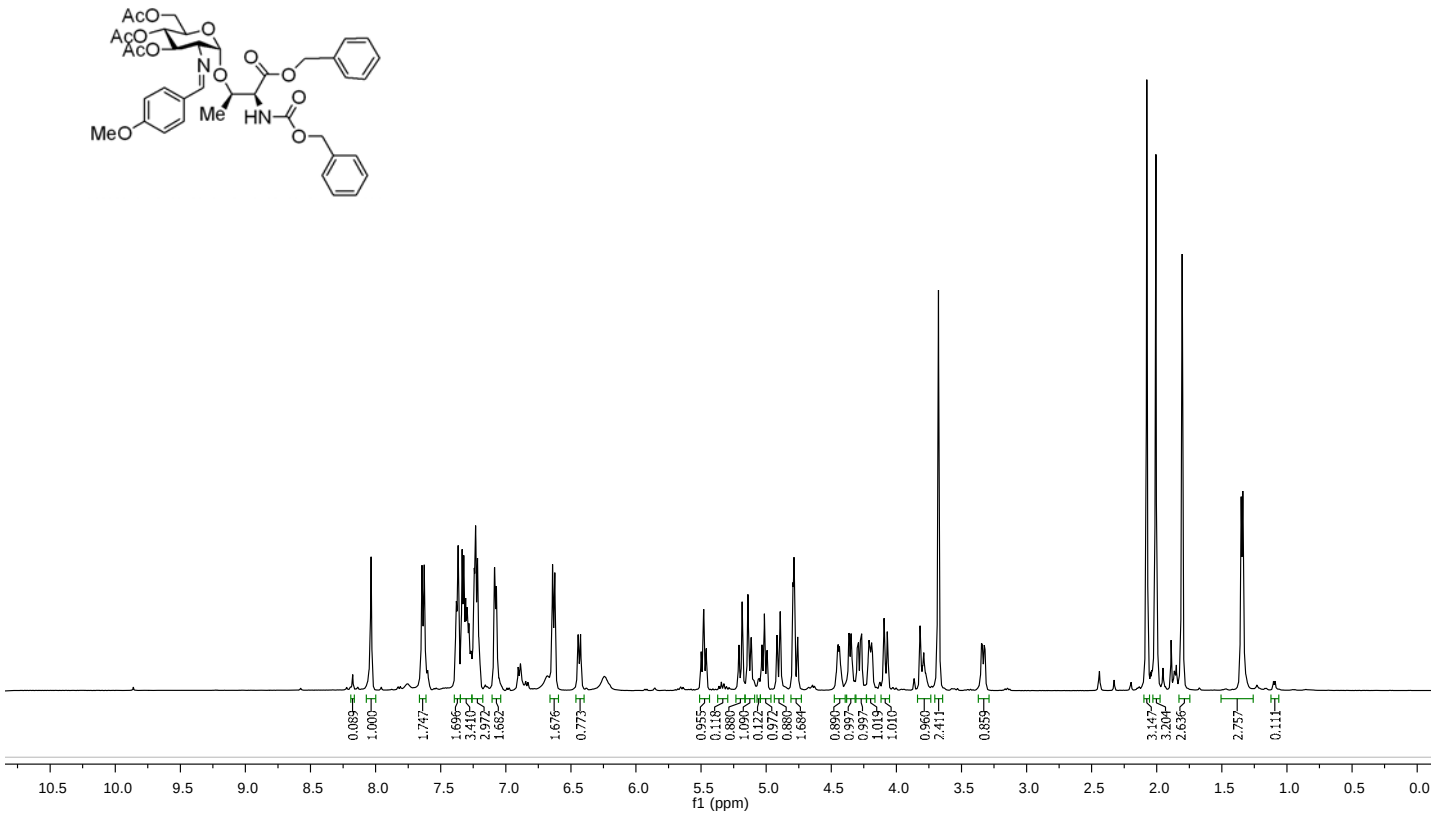


Figure A202. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycopeptide **200**

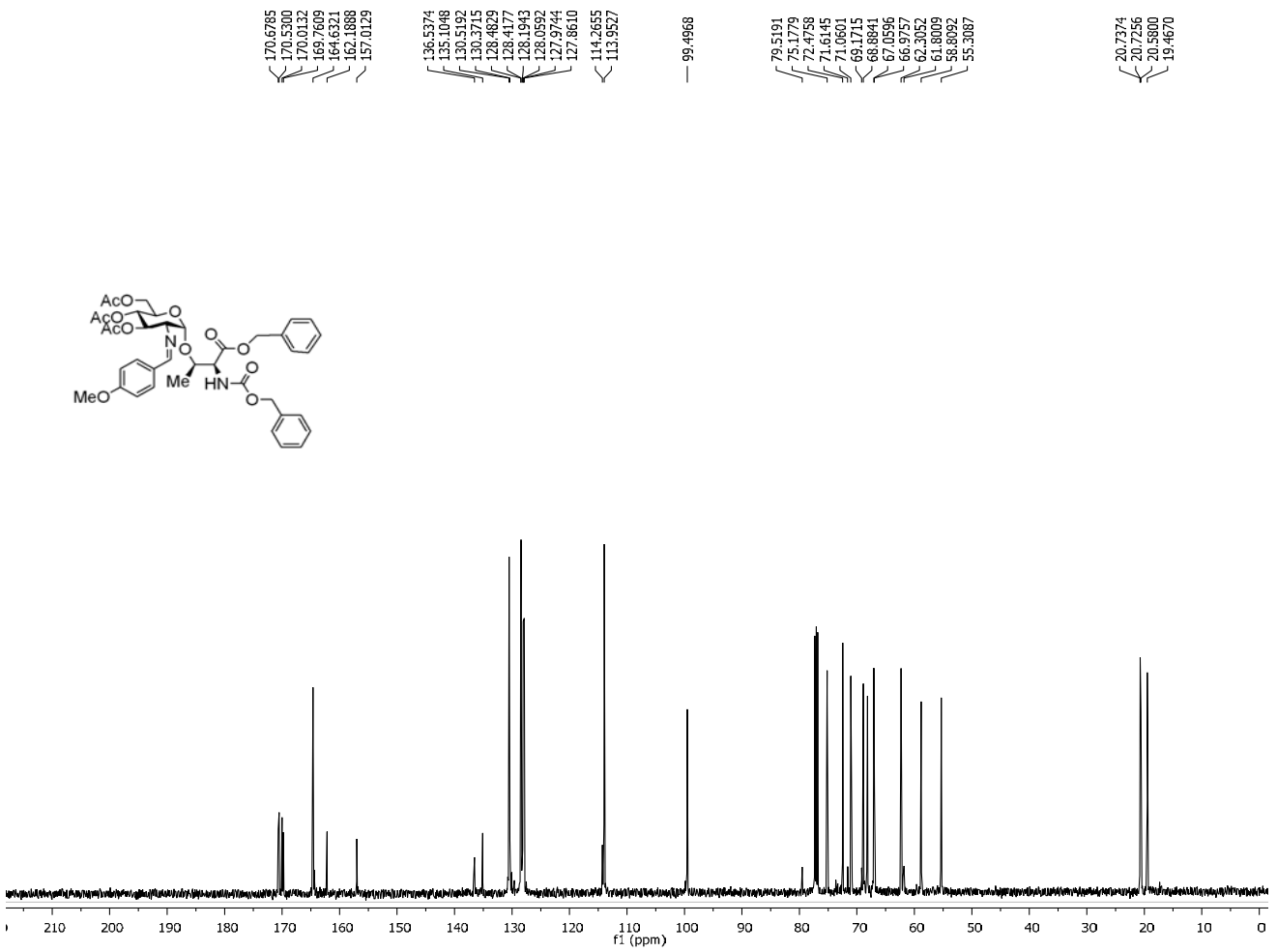


Figure A203. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycopeptide **200**

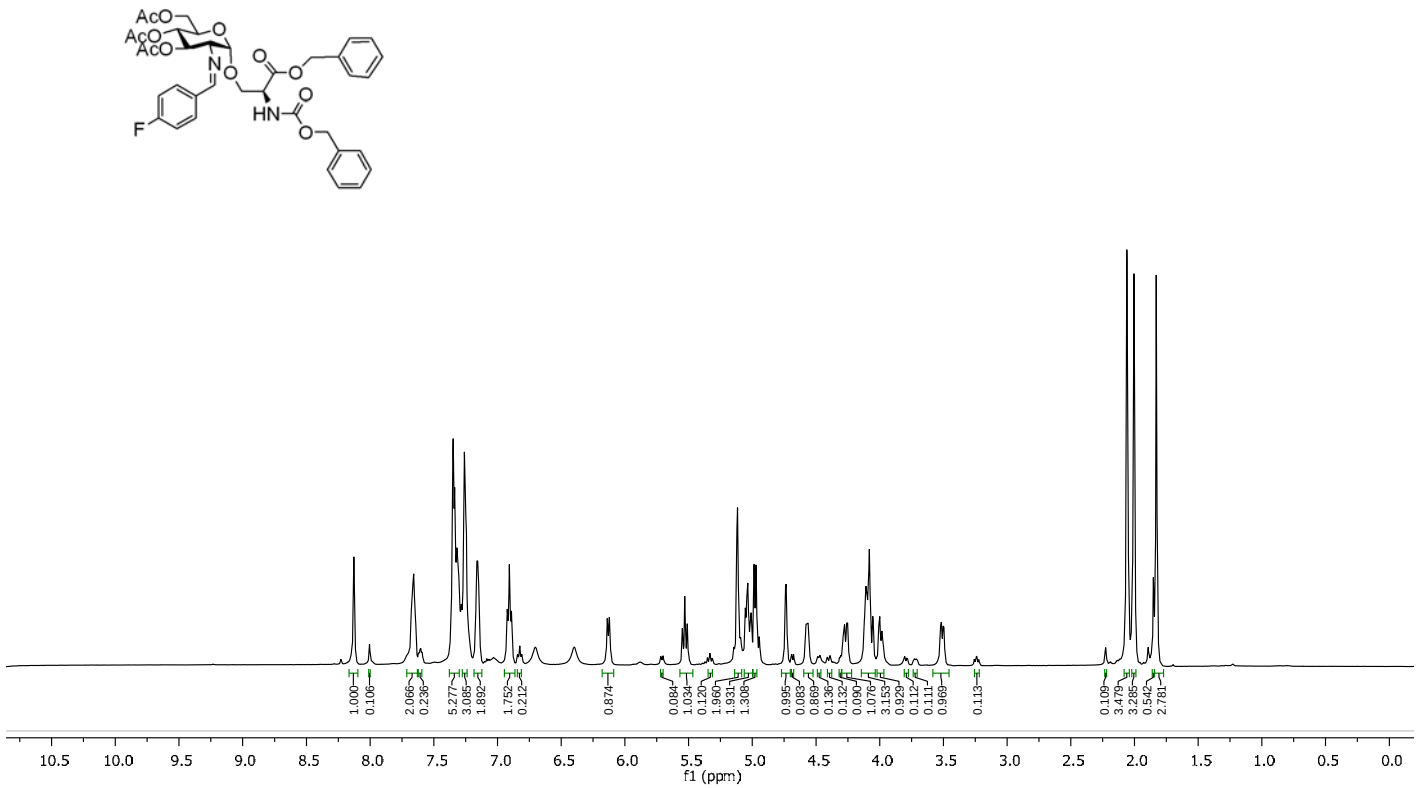


Figure A204. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycopeptide **201**

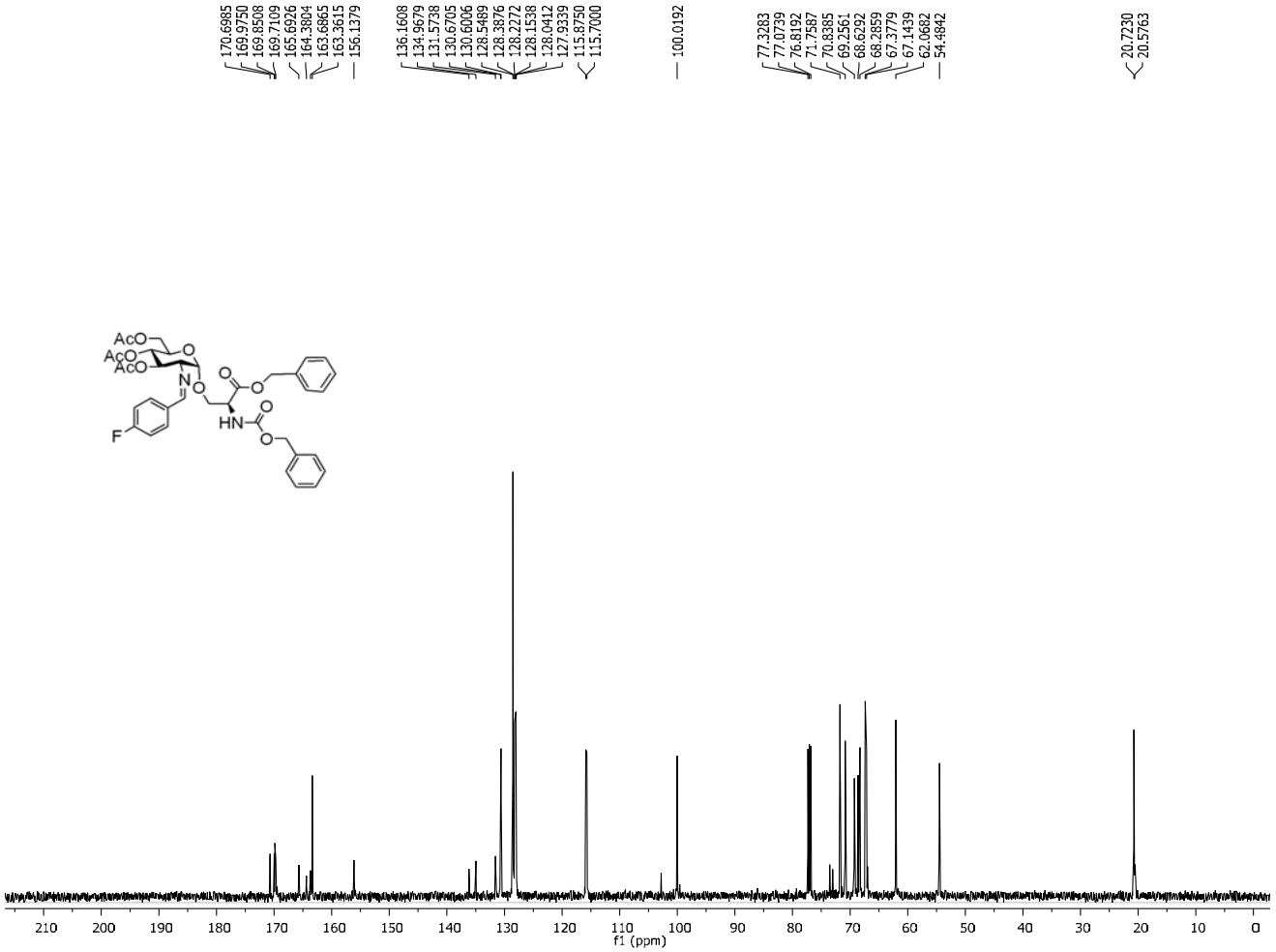


Figure A205. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycopeptide **201**

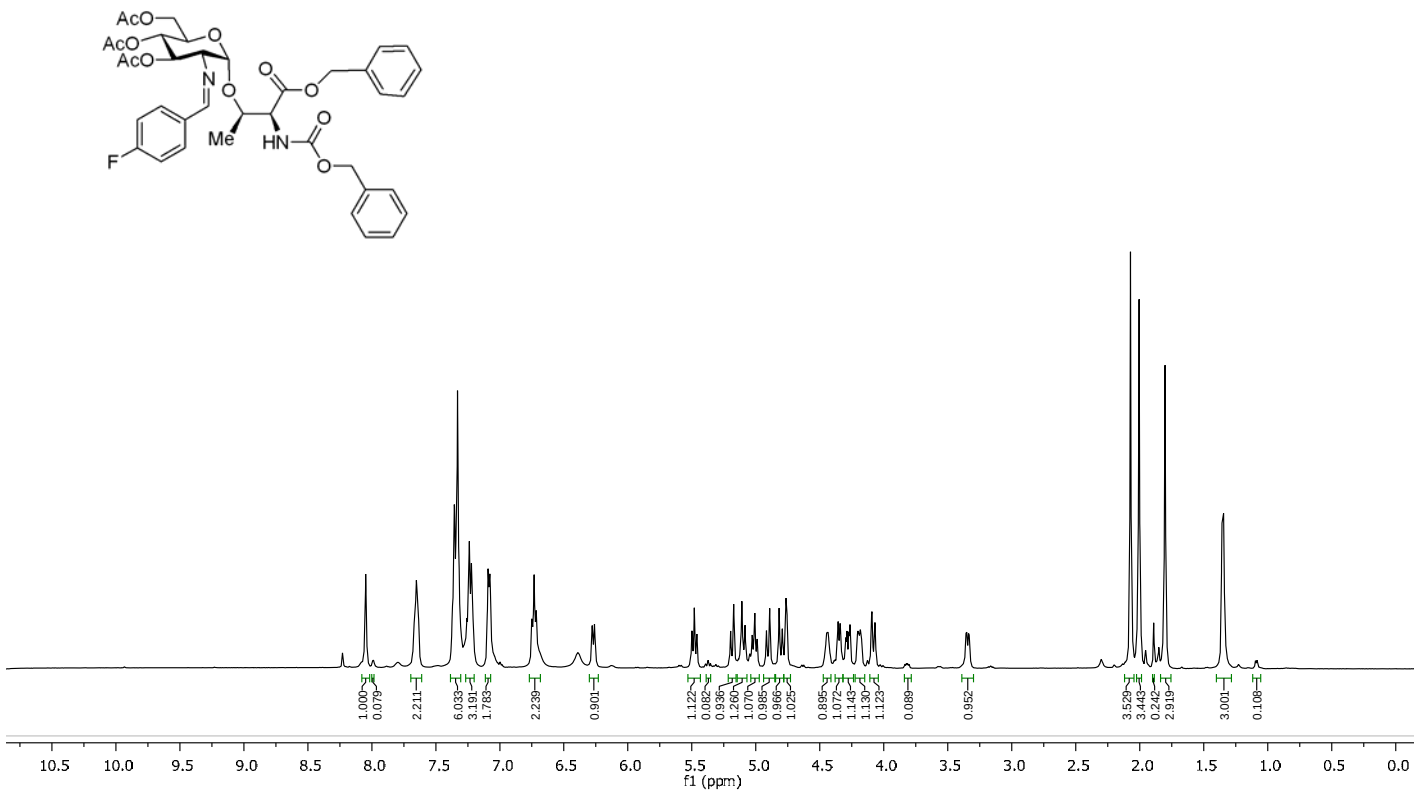


Figure A206. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycopeptide **202**

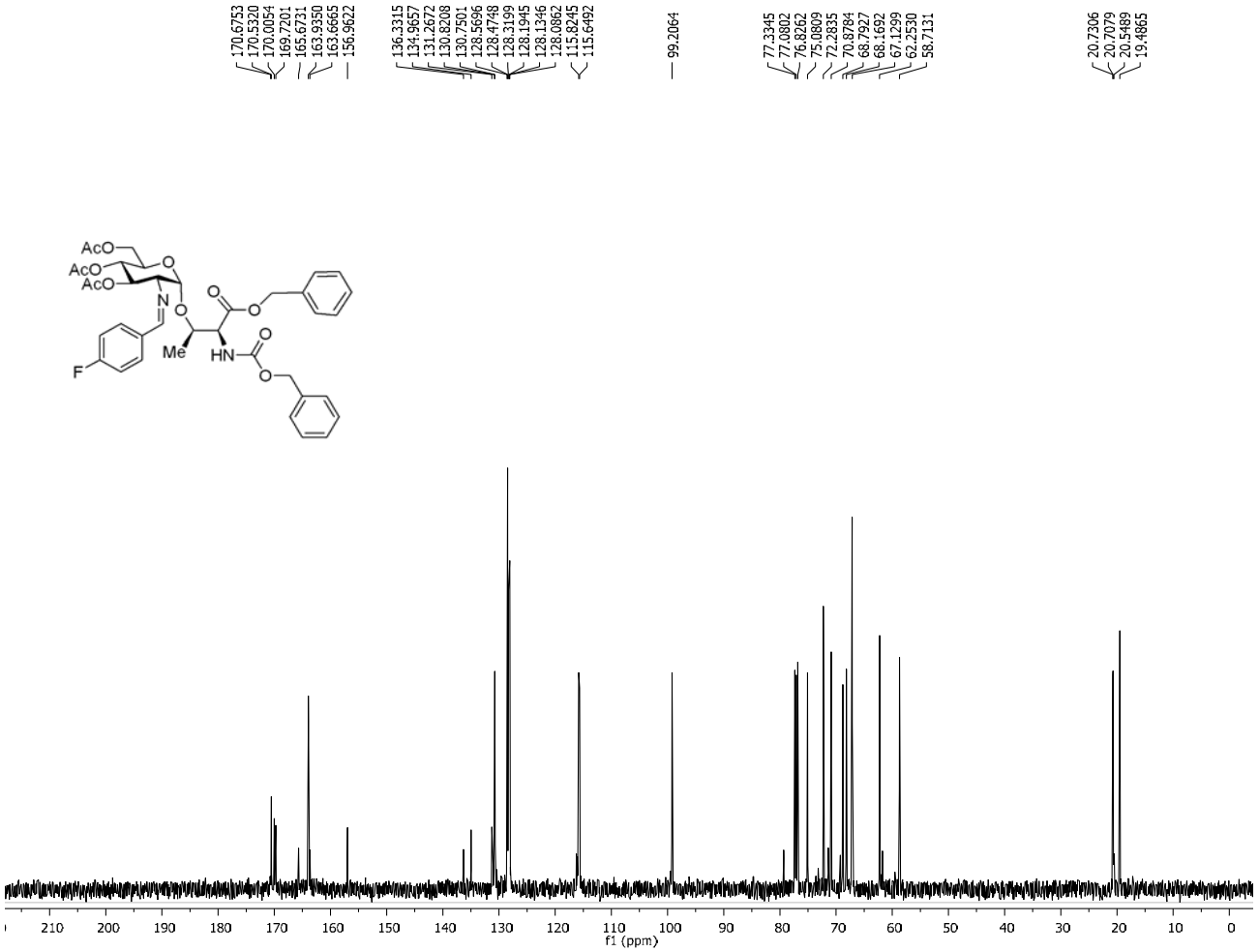


Figure A207. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycopeptide **202**

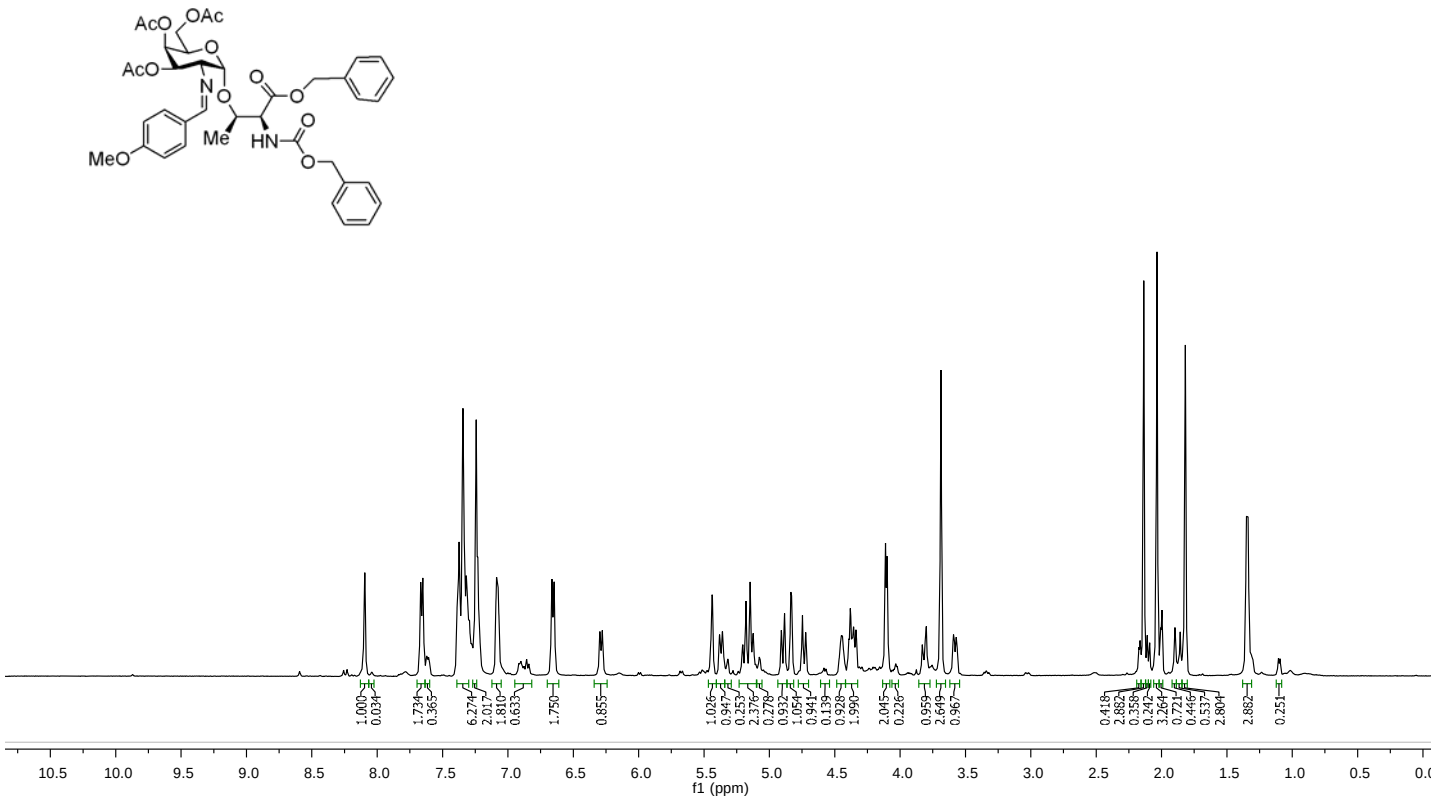


Figure A208. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycopeptide **203**

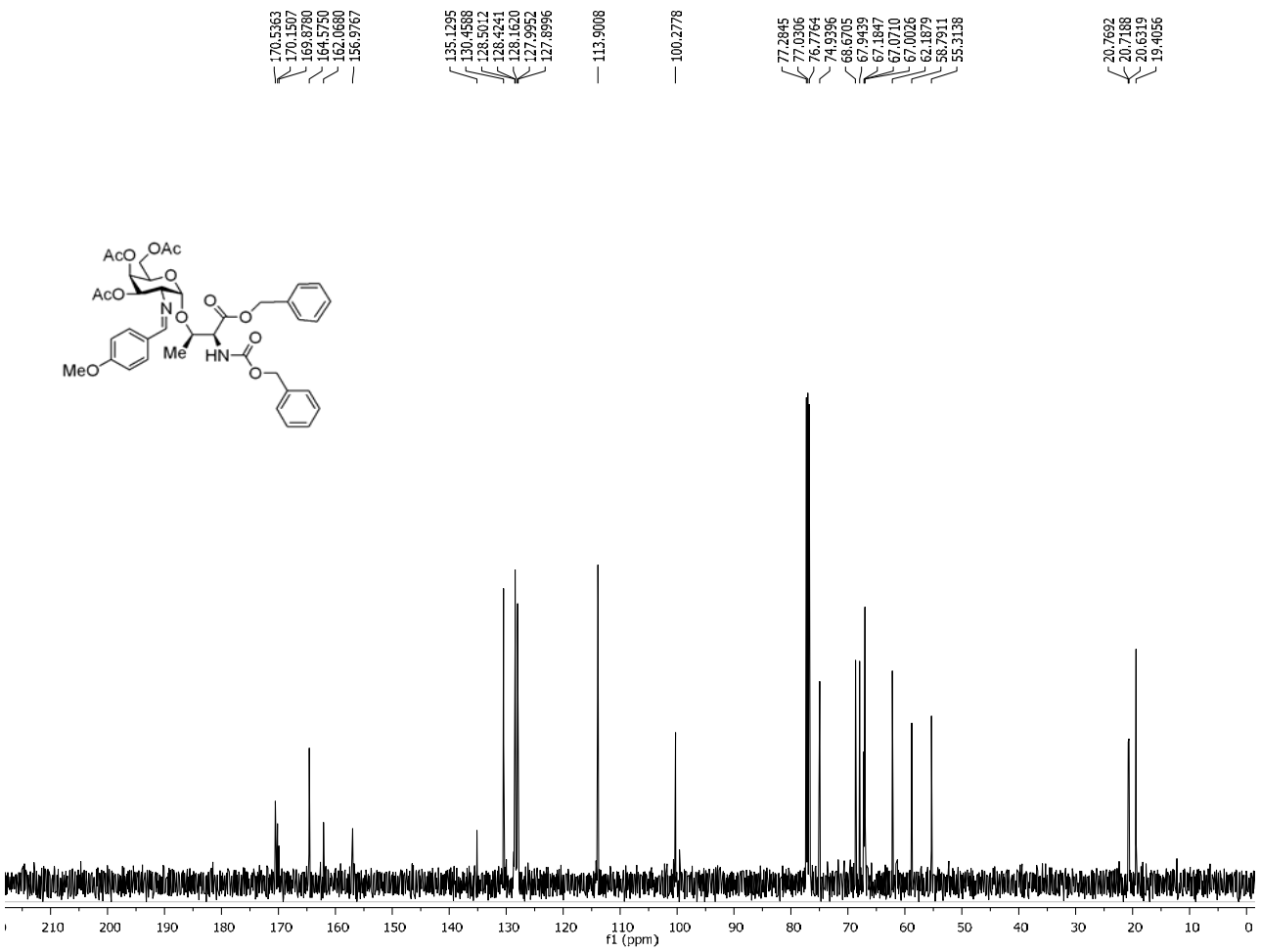


Figure A209. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycopeptide **203**

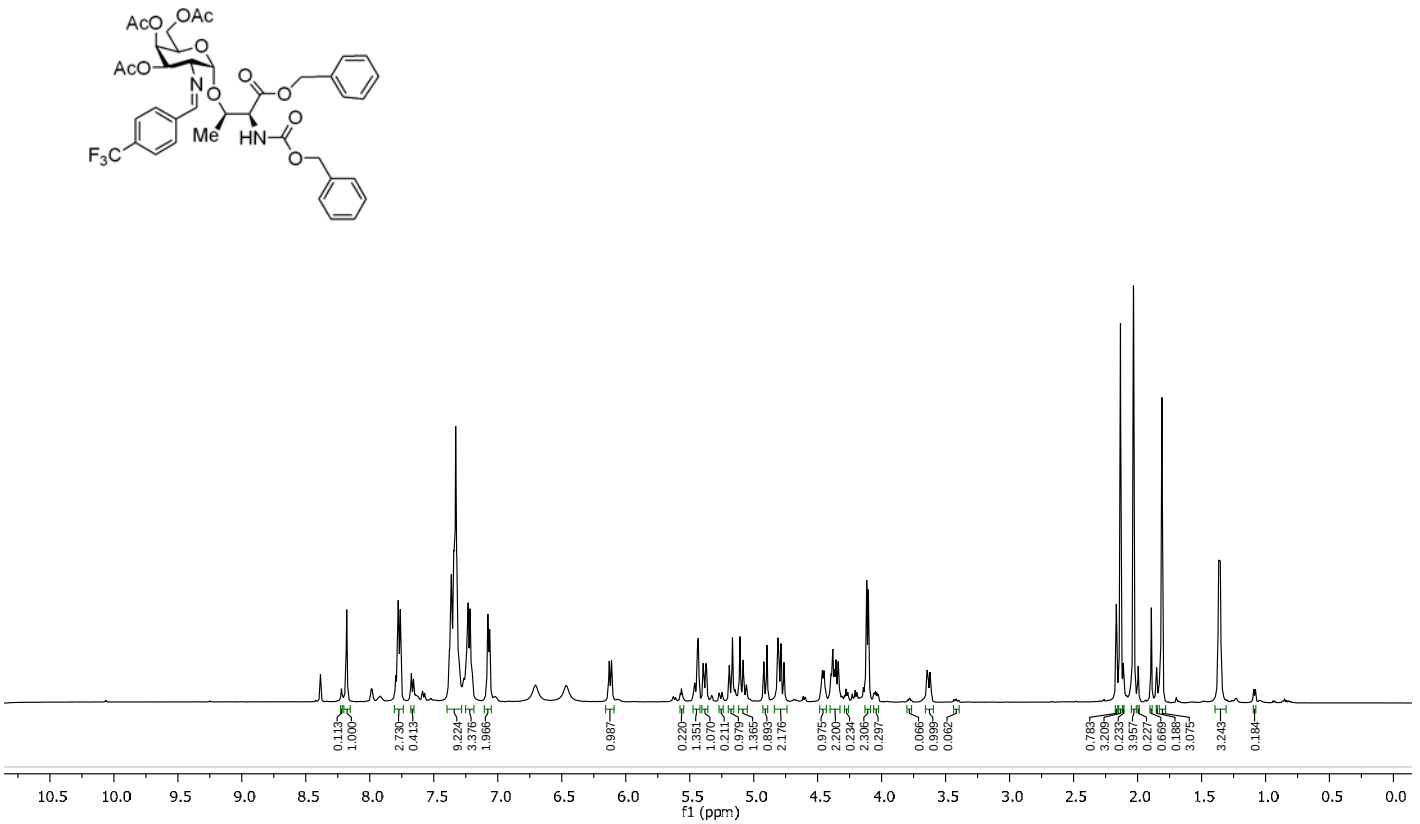


Figure A210. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycopeptide **204**

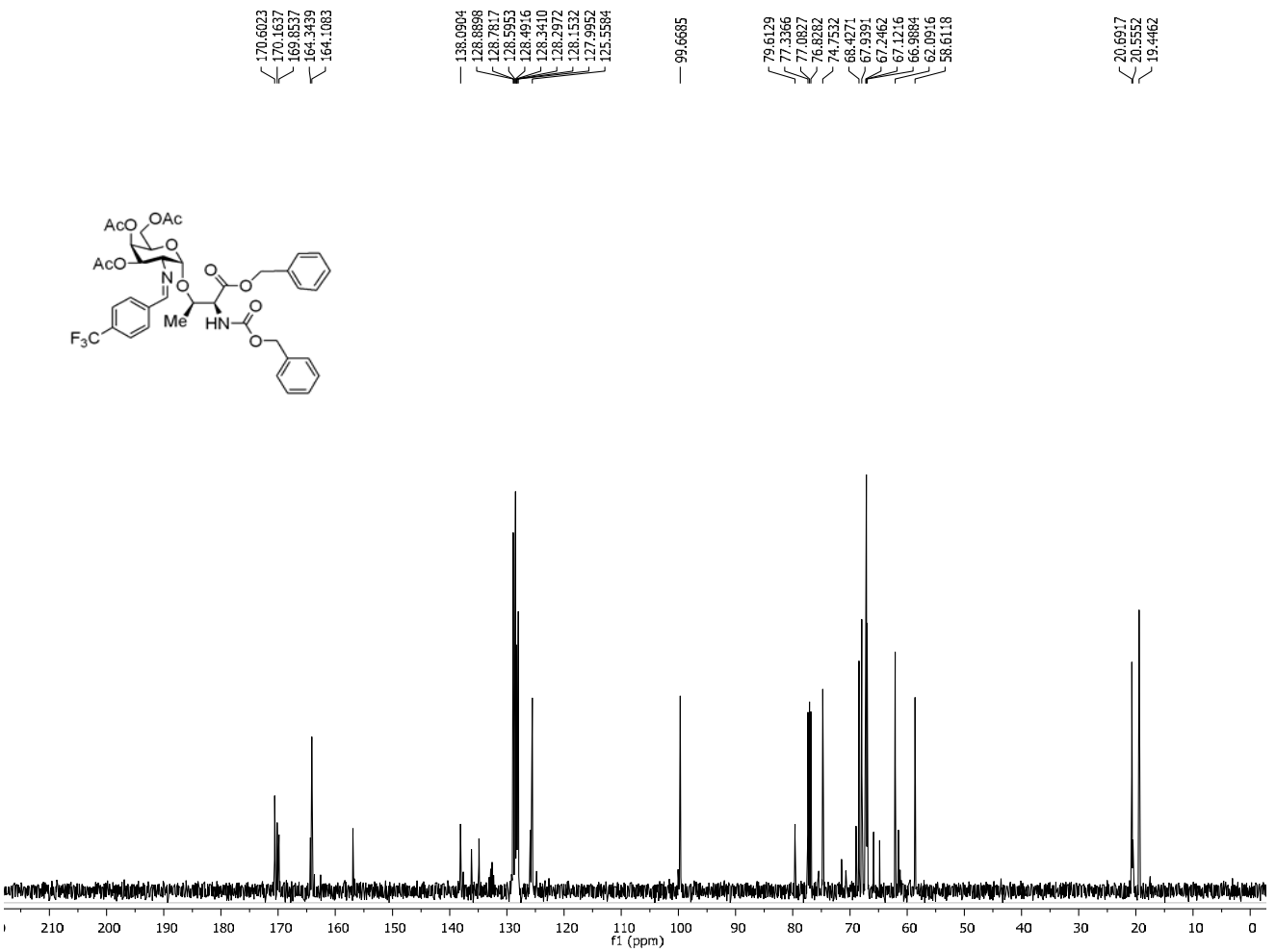


Figure A211. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycopeptide **204**

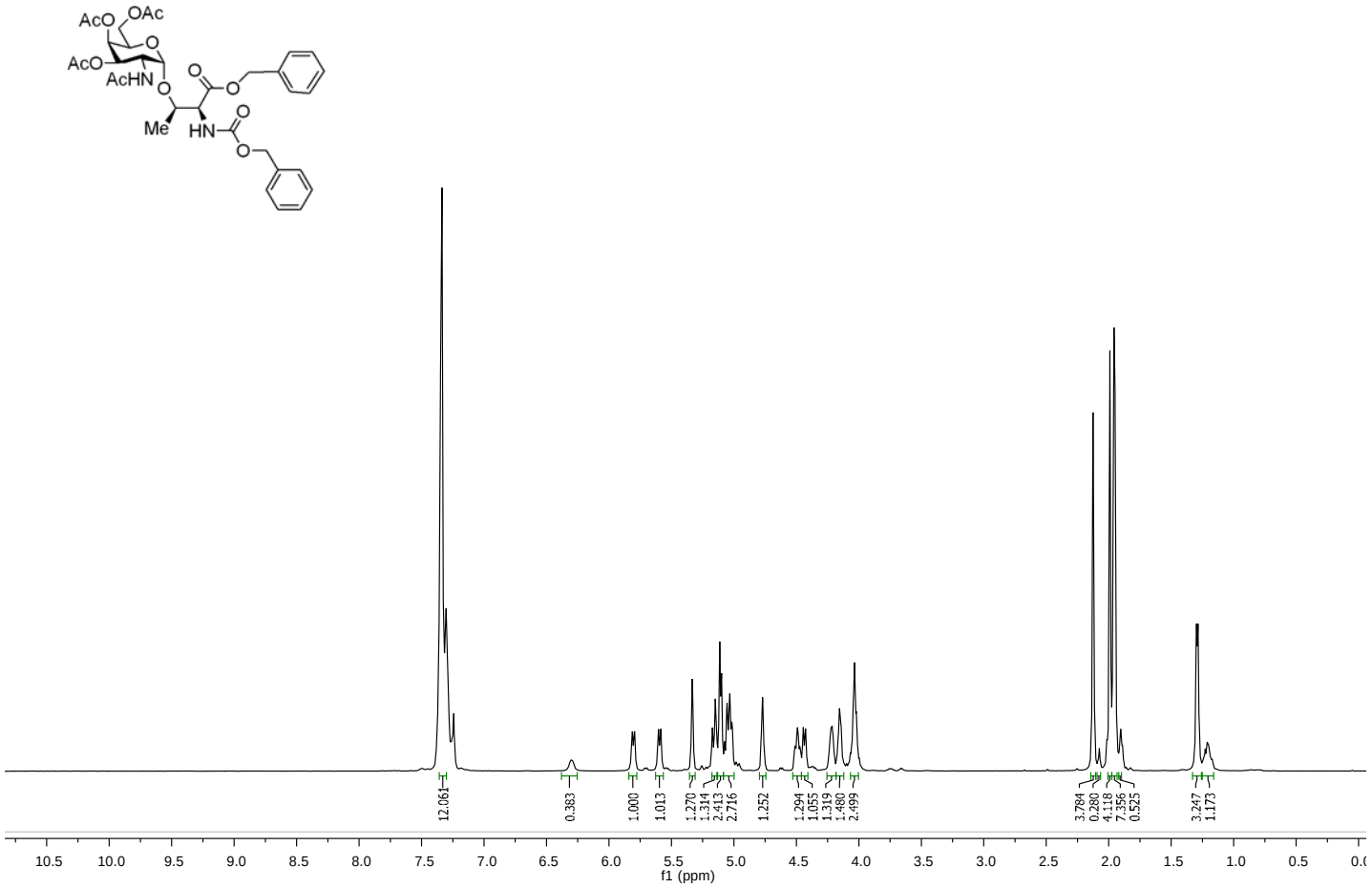


Figure A212. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycopeptide **206**

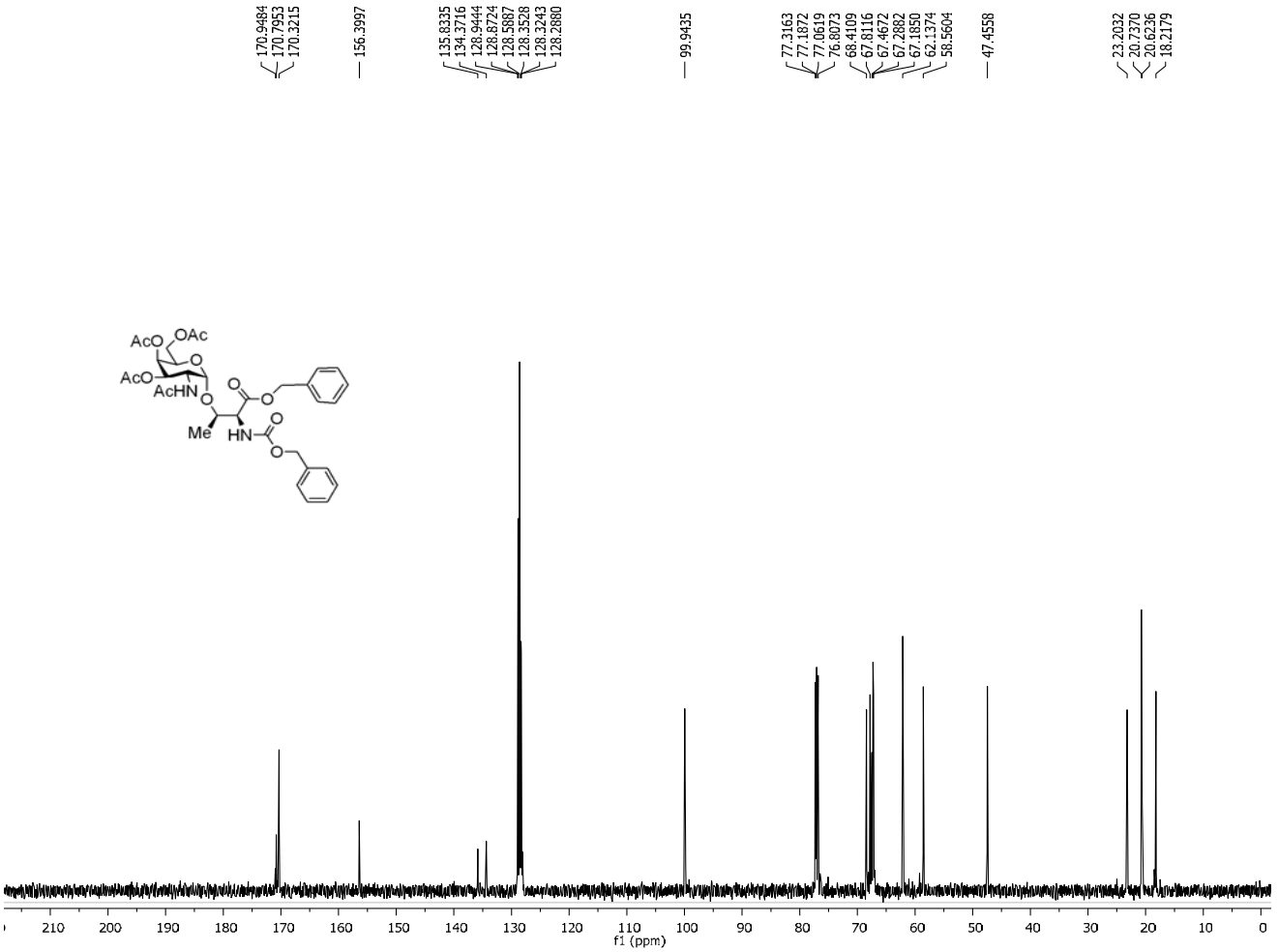


Figure A213. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycopeptide **206**

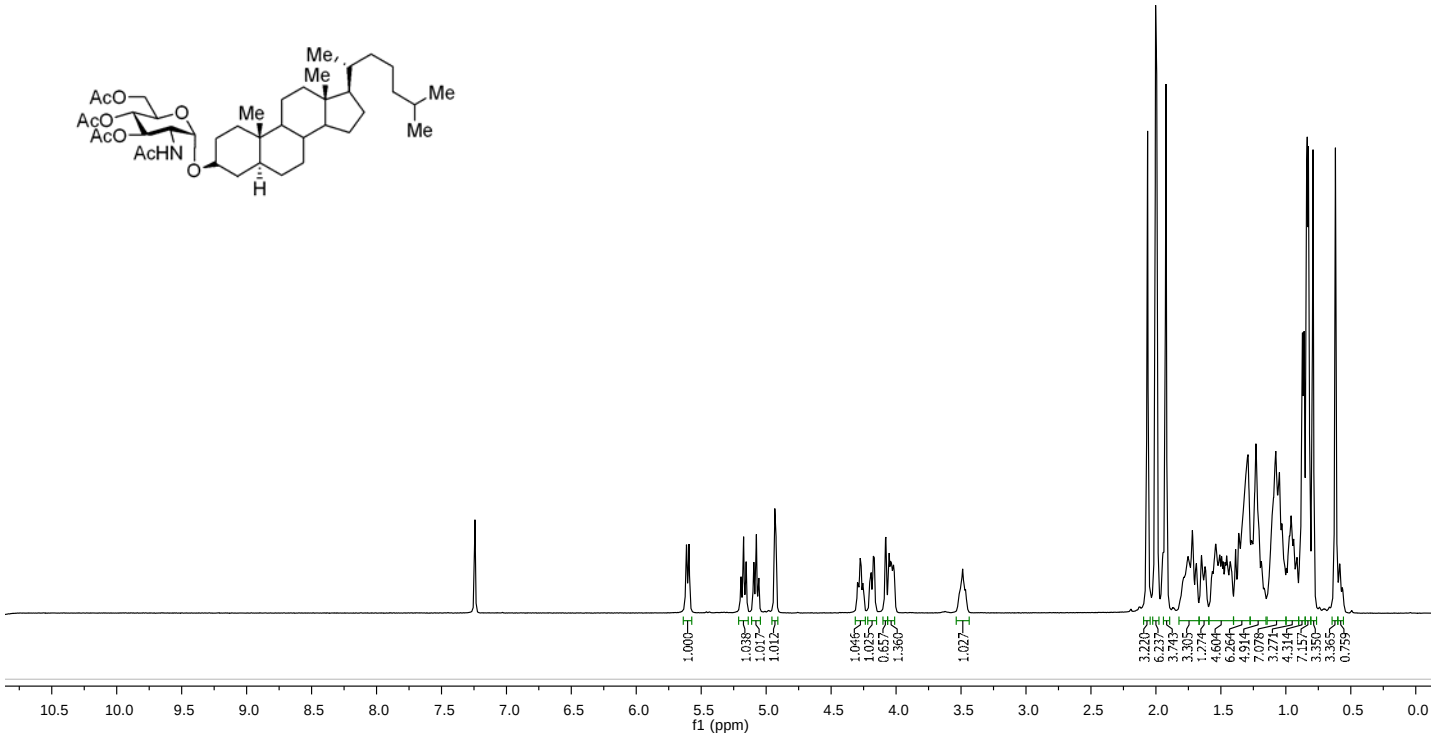


Figure A214. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **207**

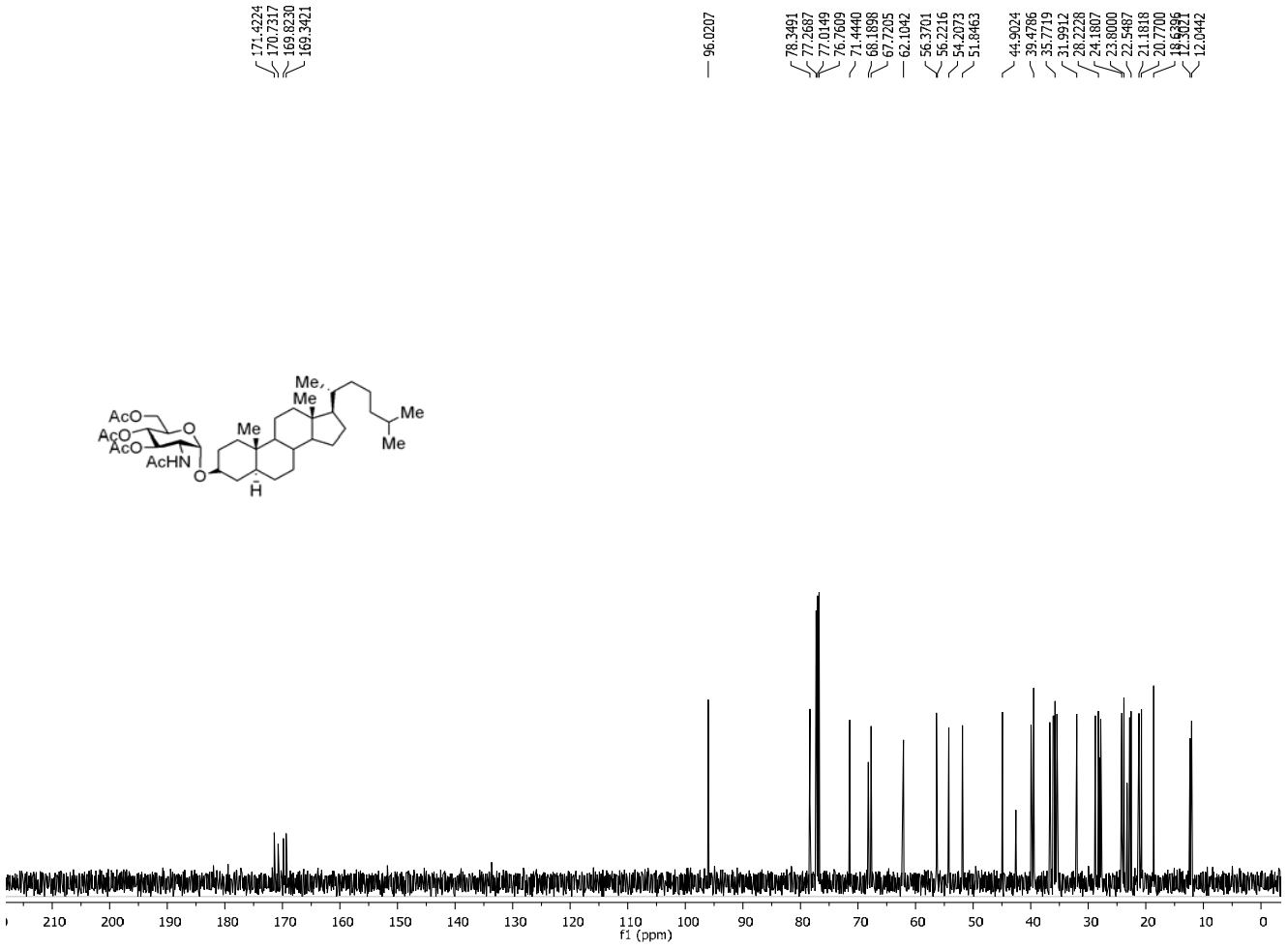


Figure A215. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **207**

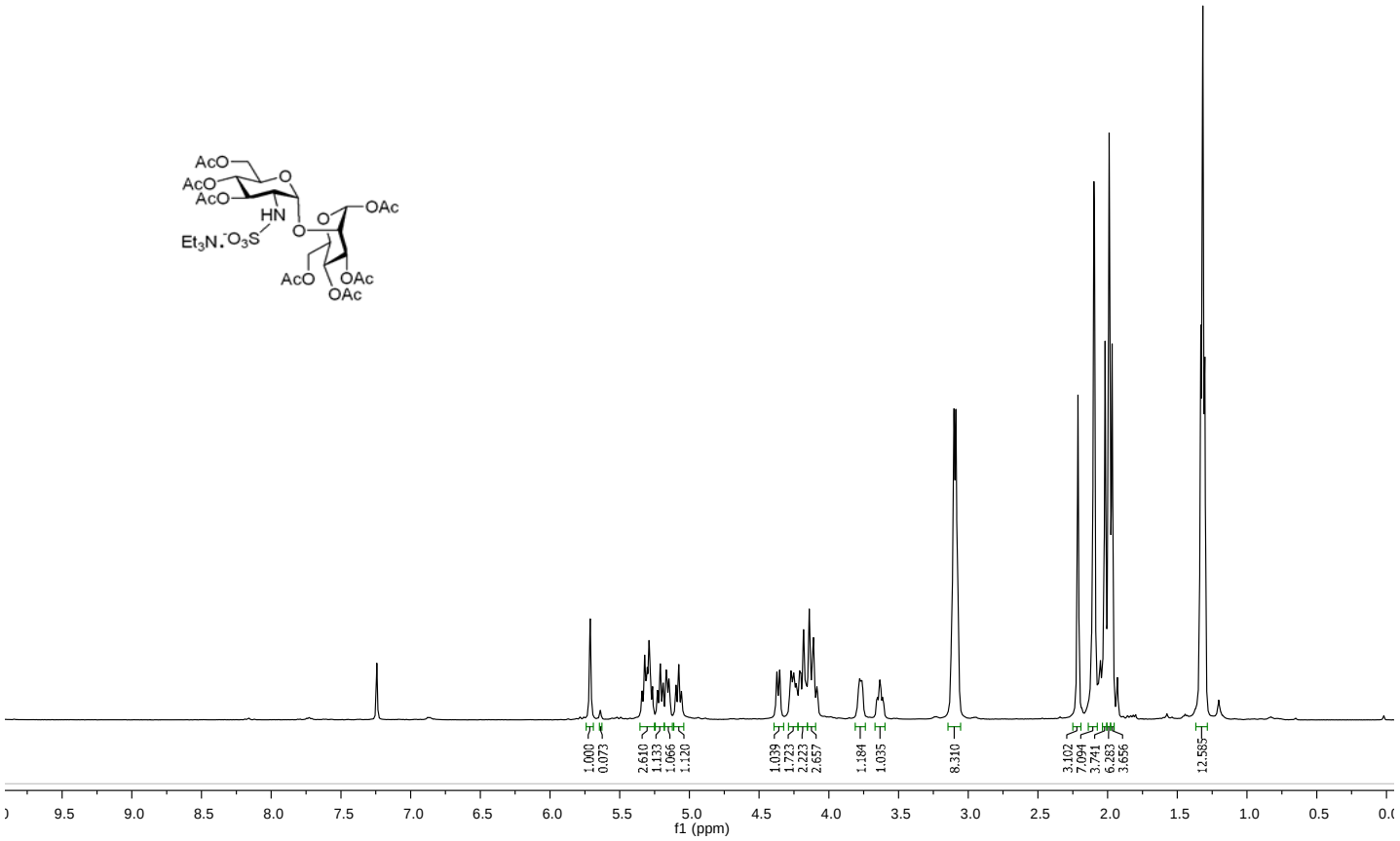


Figure A216. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **208**

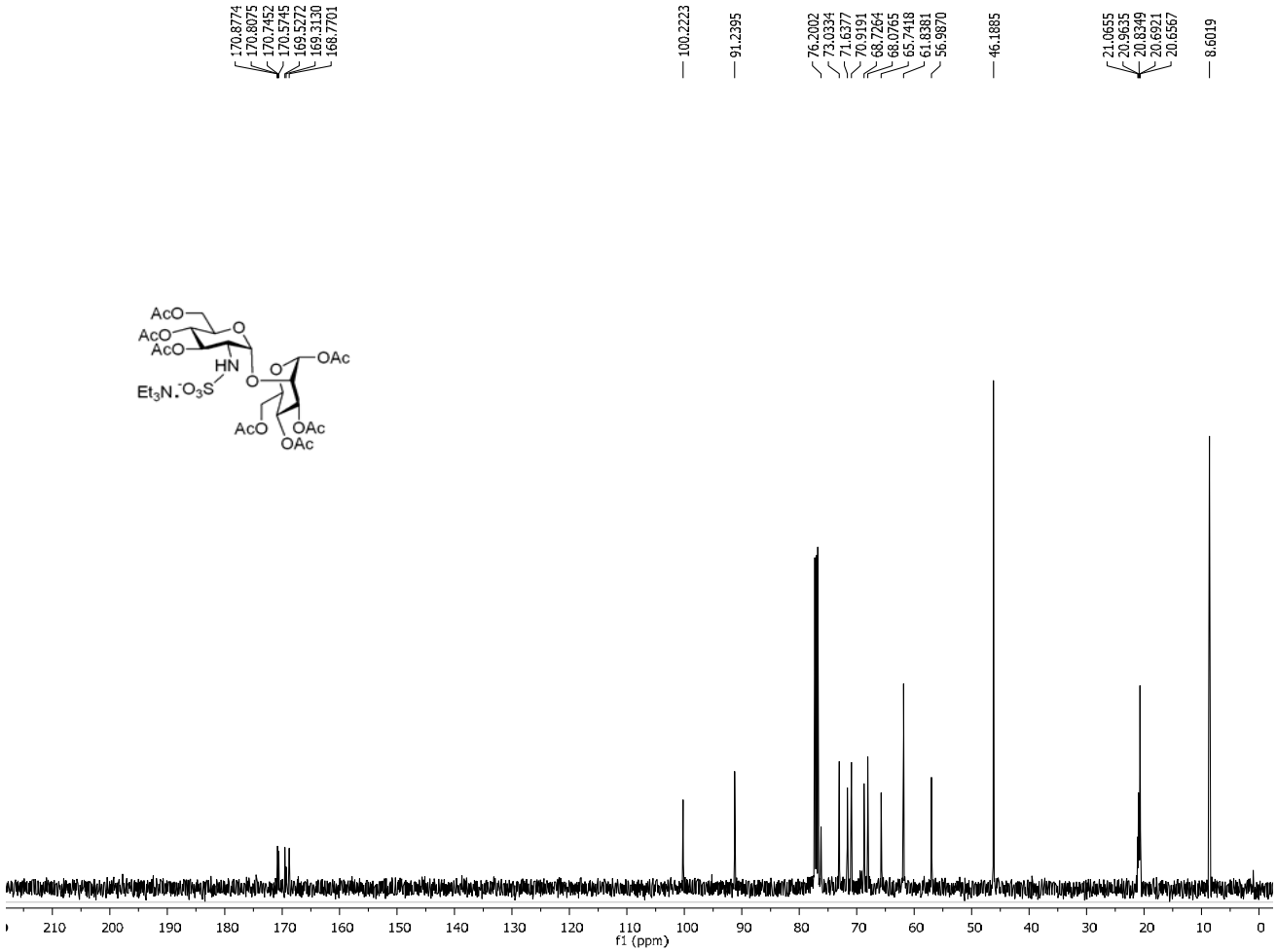


Figure A217. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **208**

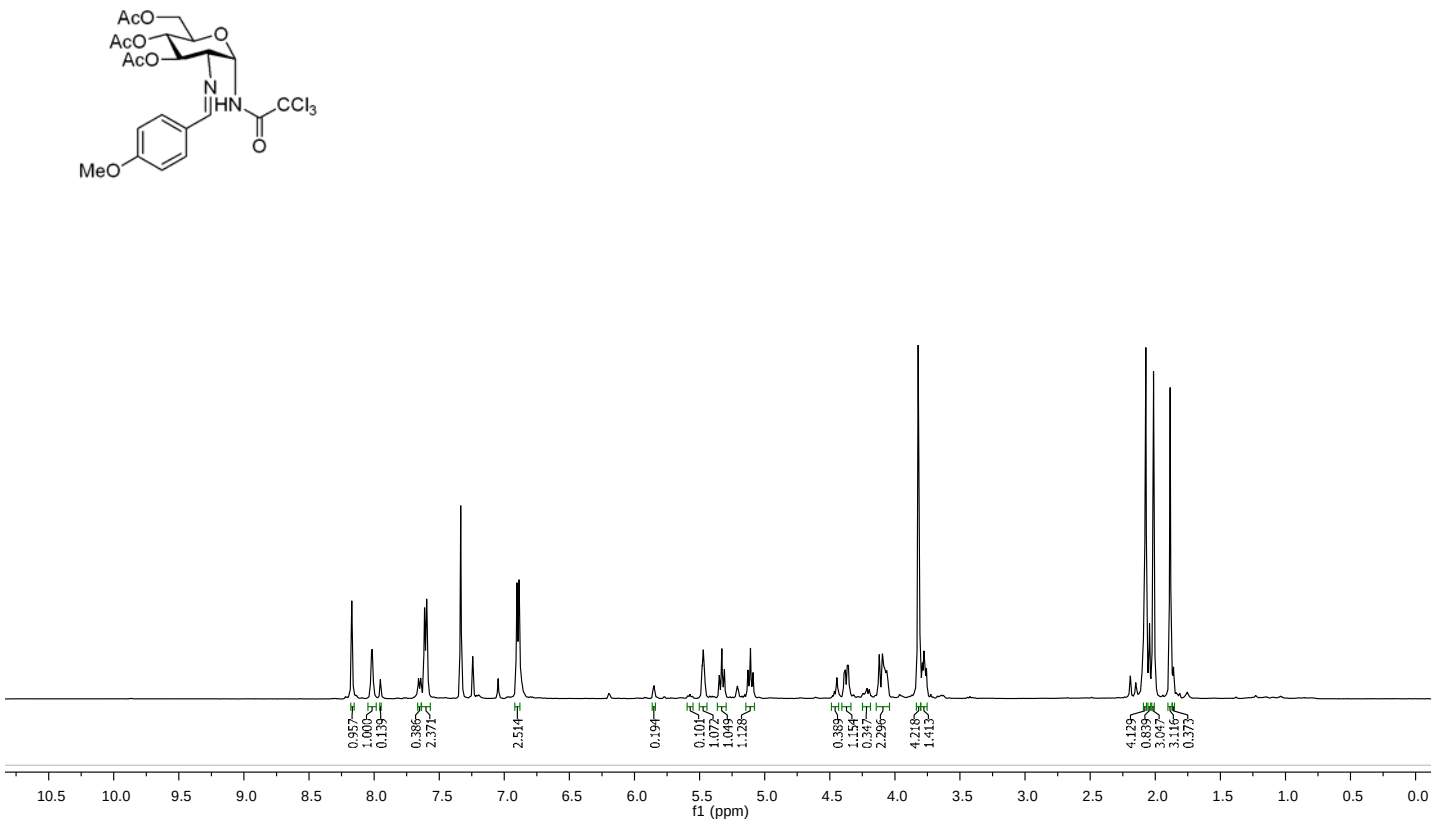


Figure A218. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trichloroacetamide **217**

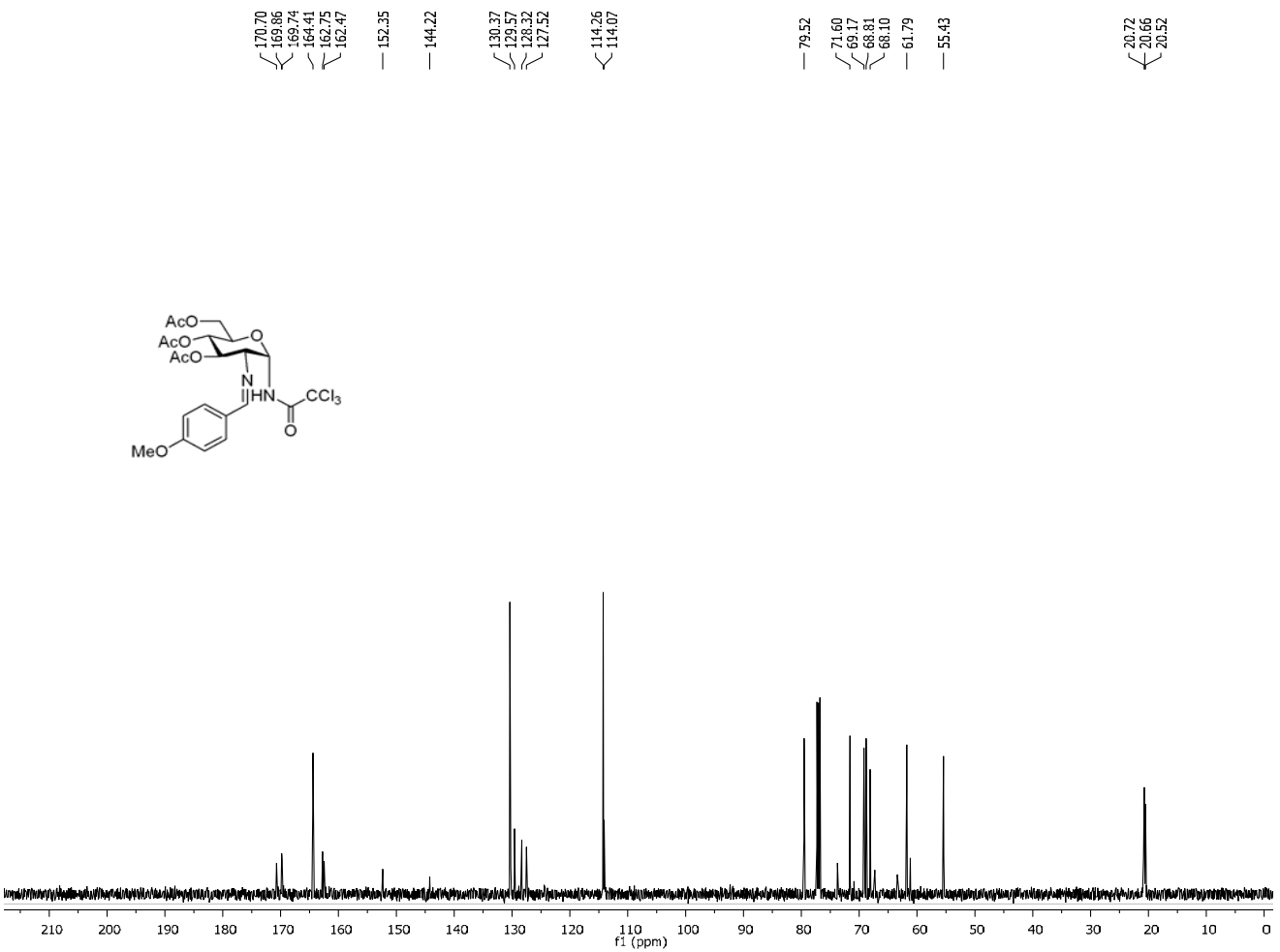


Figure A219. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trichloroacetamide **217**

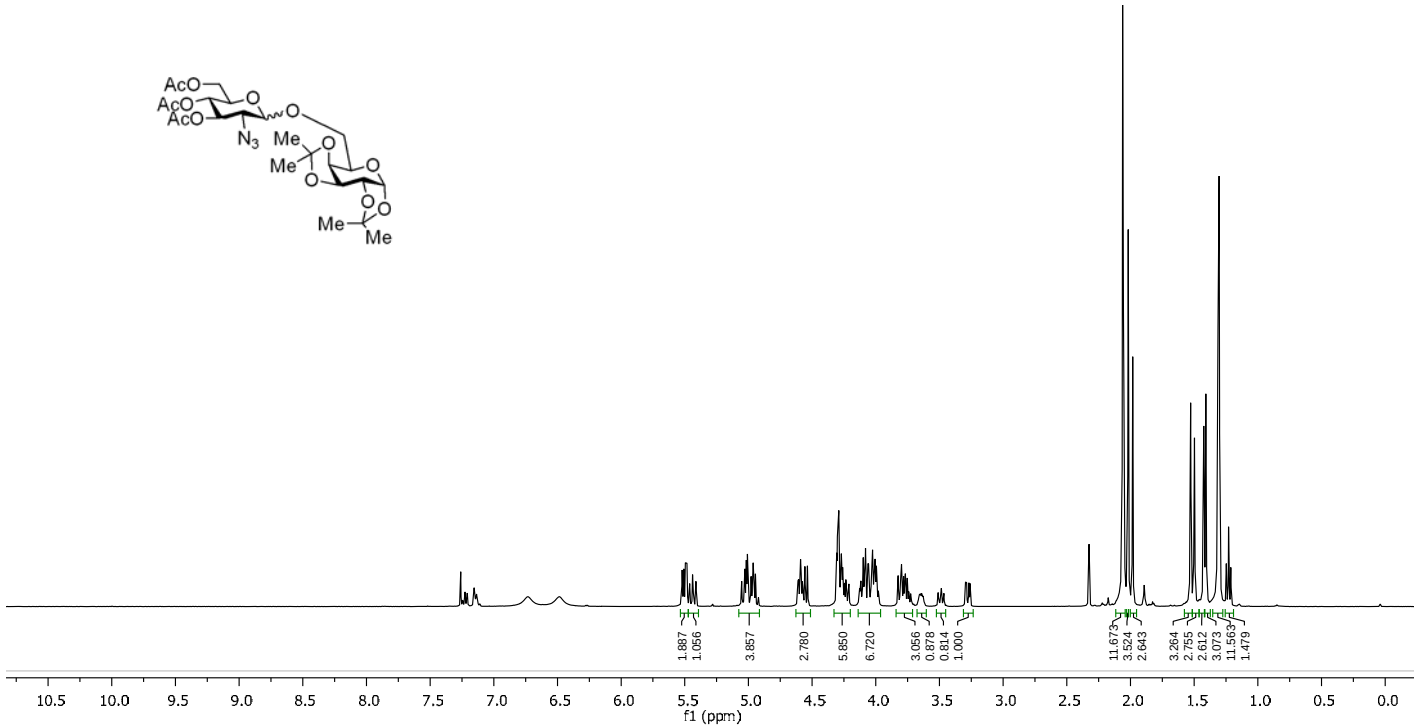


Figure A220. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **220**

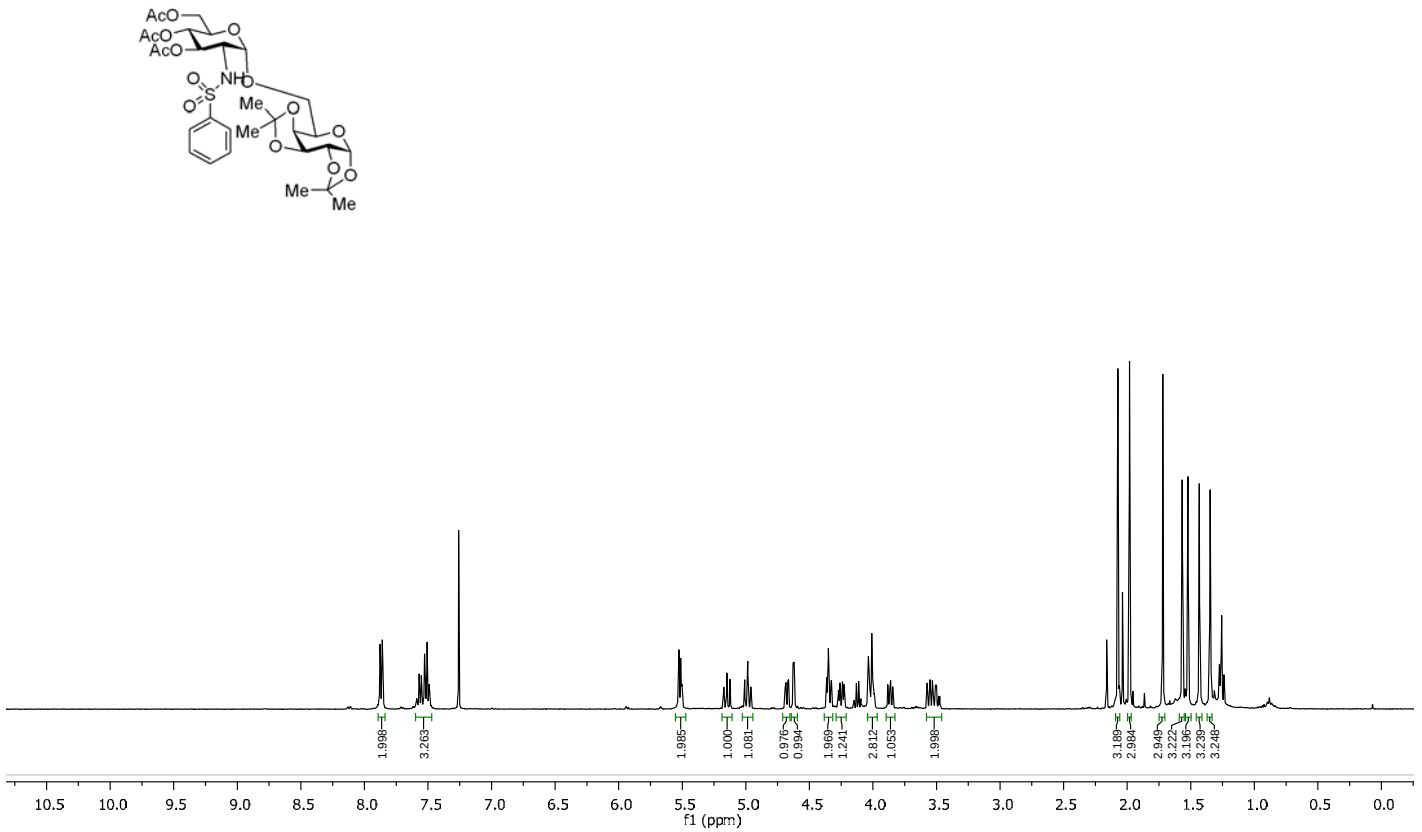


Figure A221. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **221α**

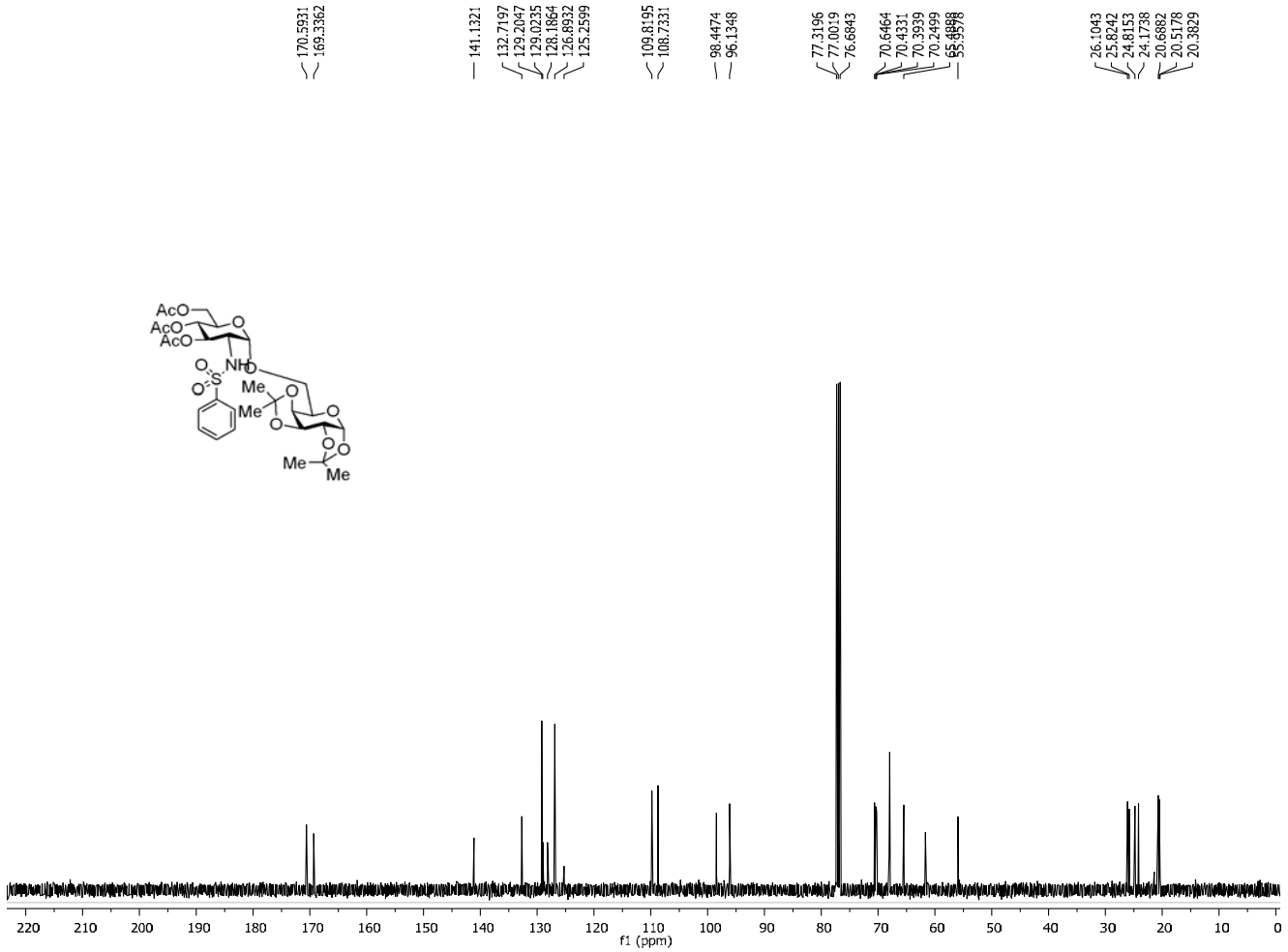


Figure A222. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **221α**

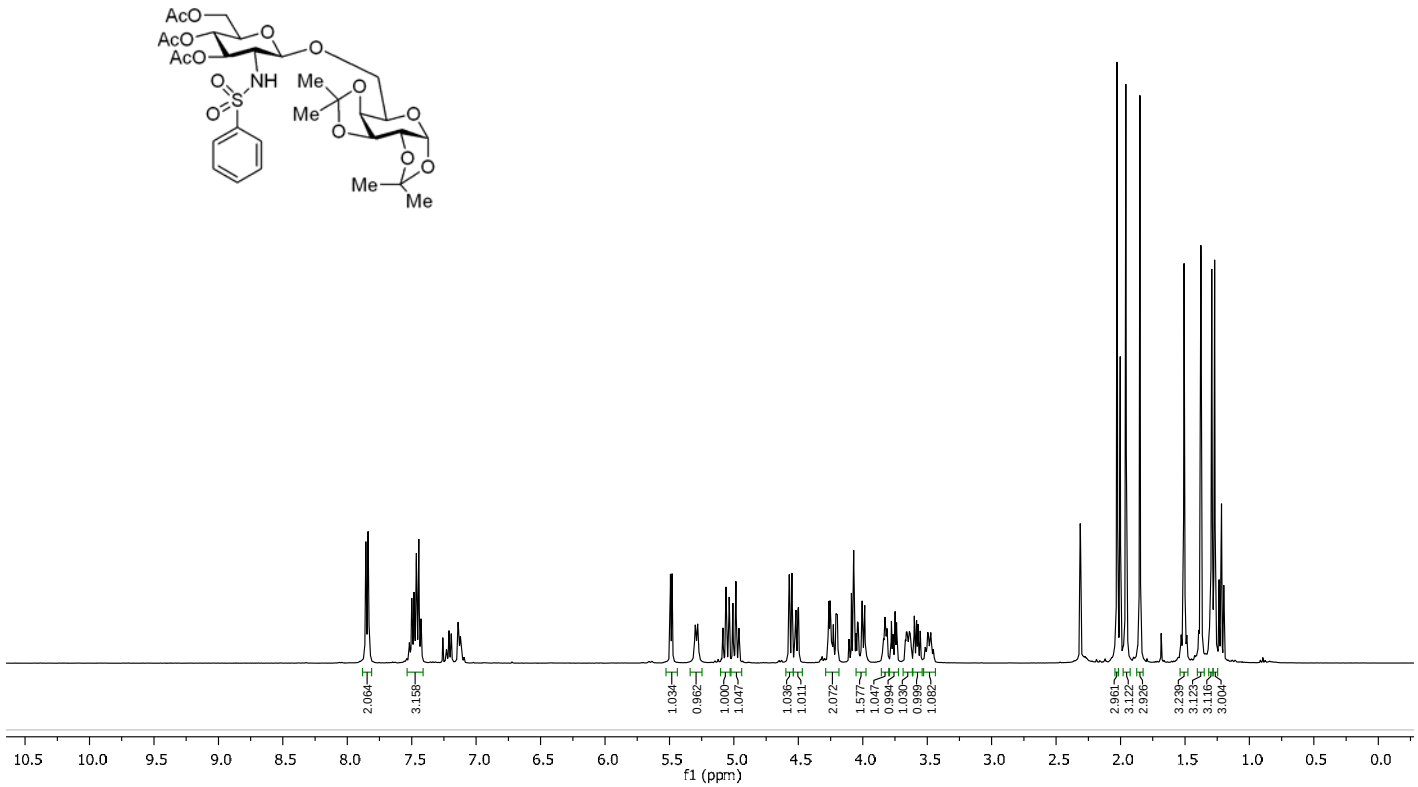


Figure A223. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **221β**

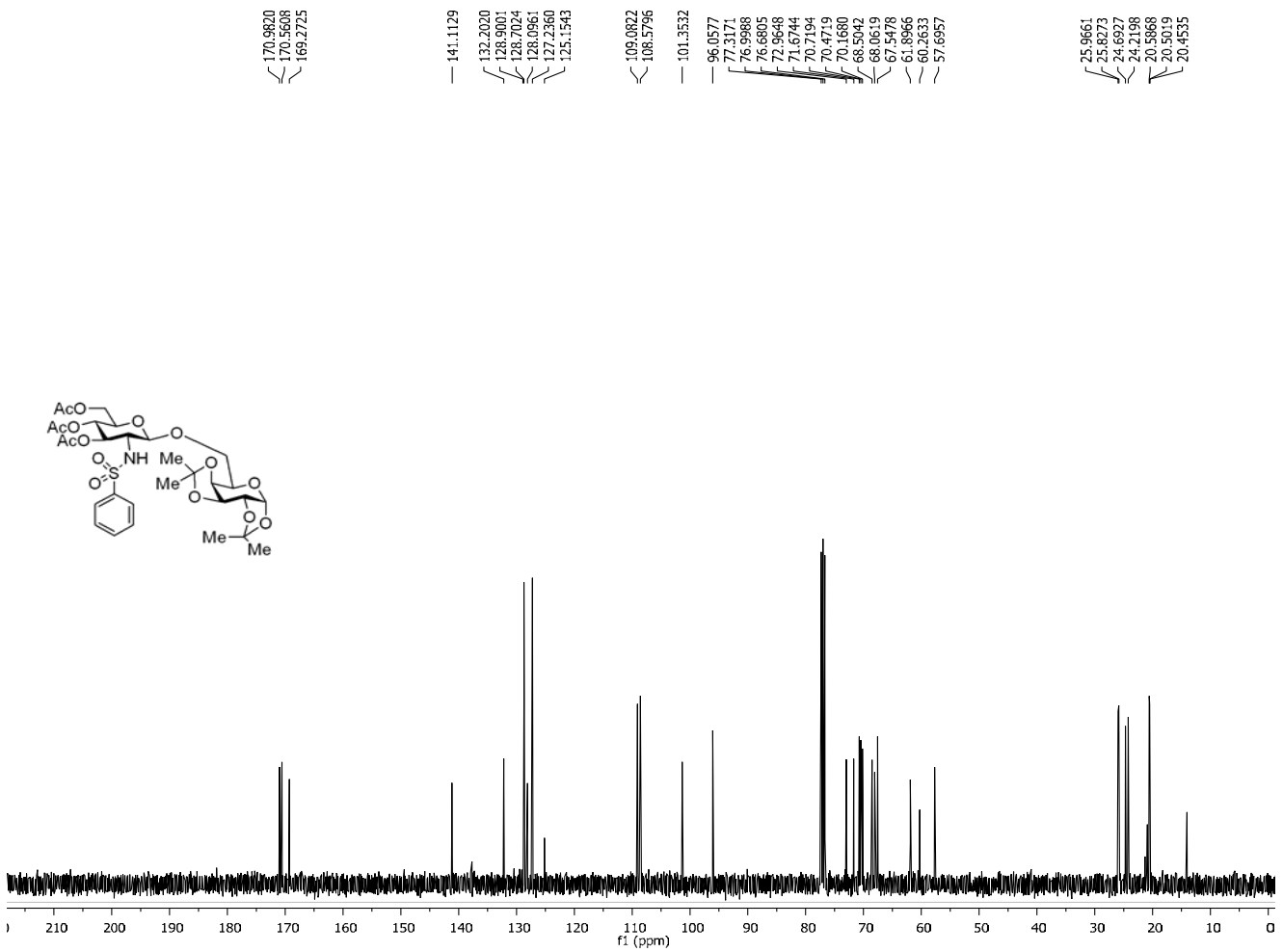


Figure A224. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **221β**

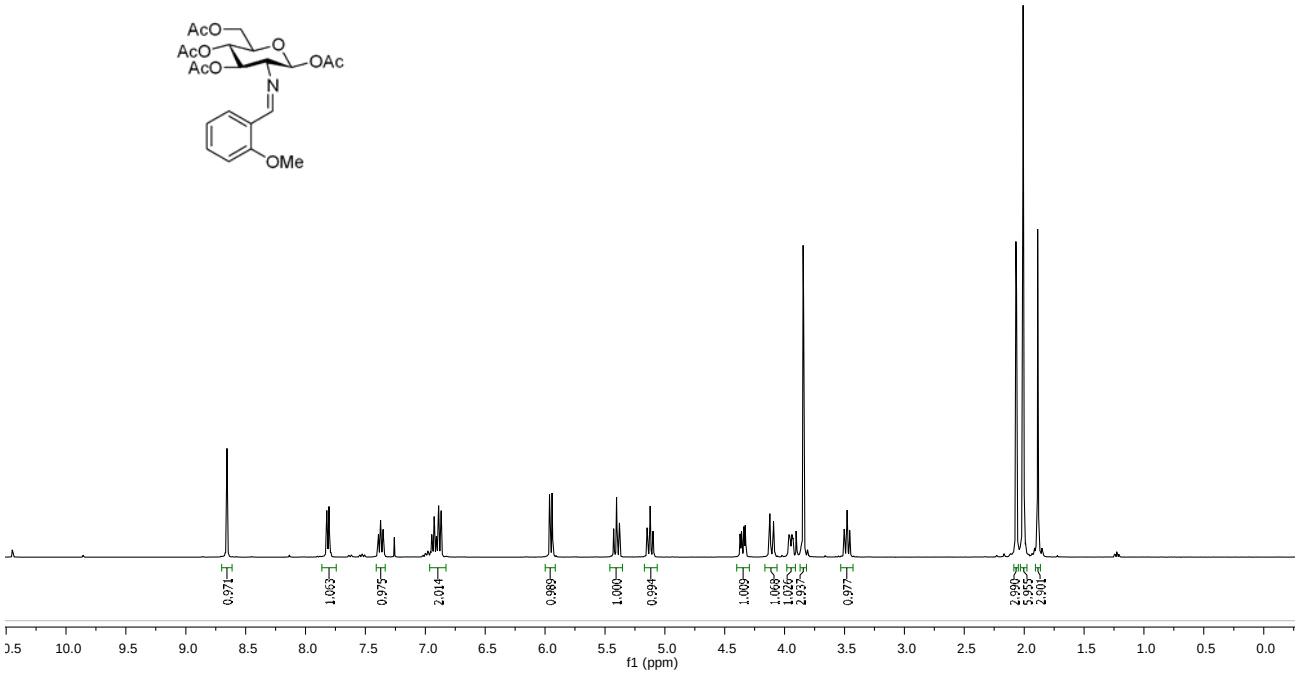


Figure A225. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **222A**

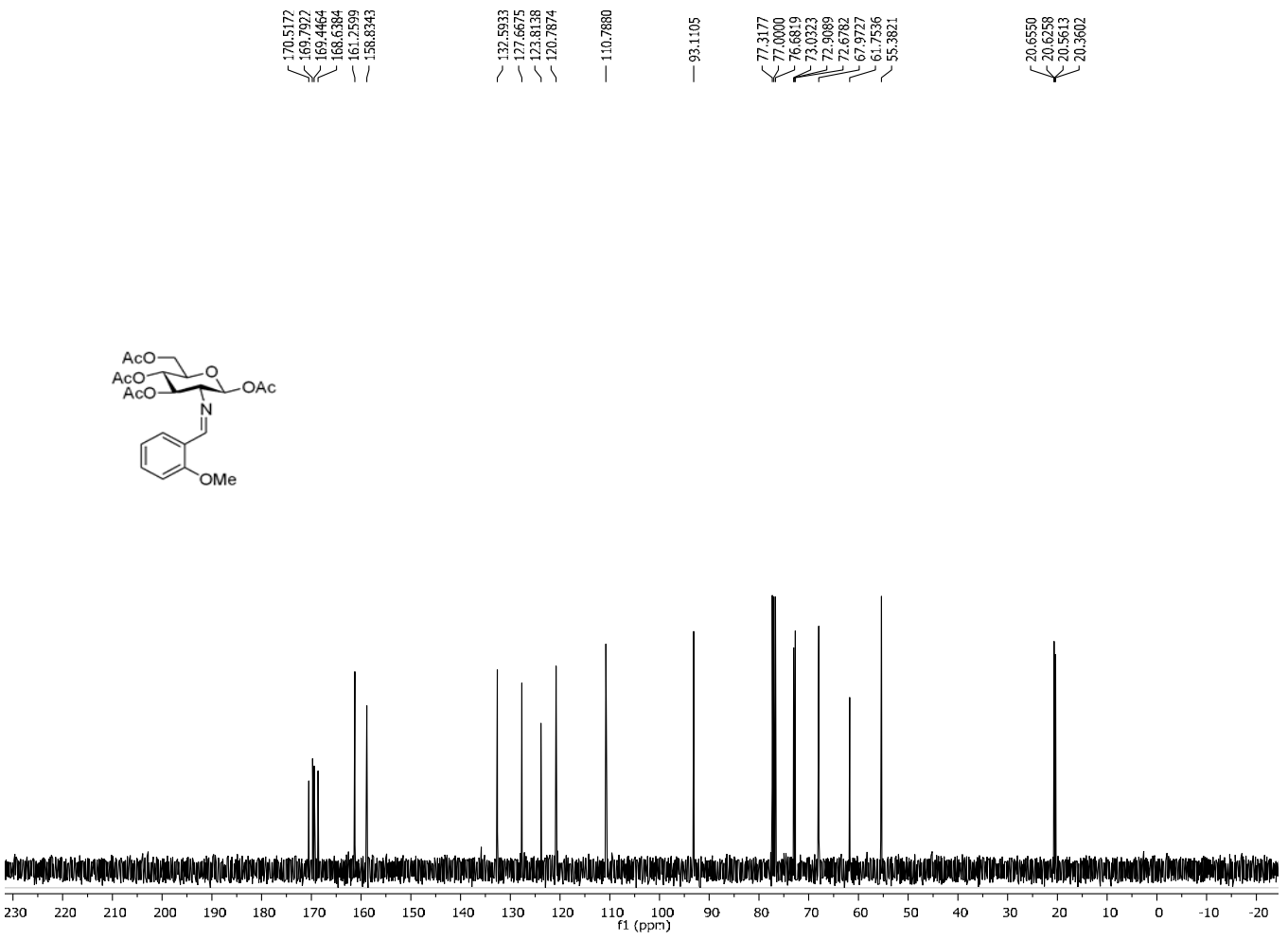


Figure A226. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **222A**

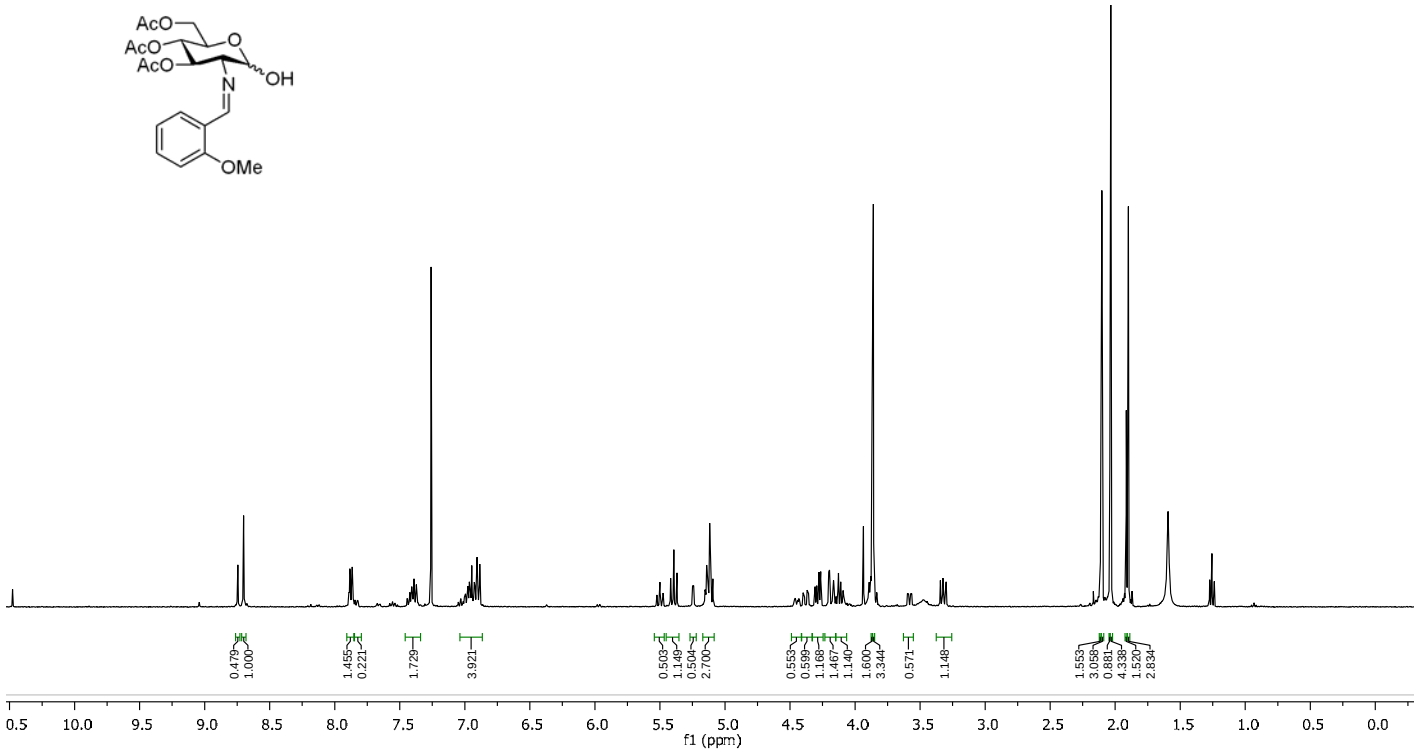


Figure A227. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **222B**

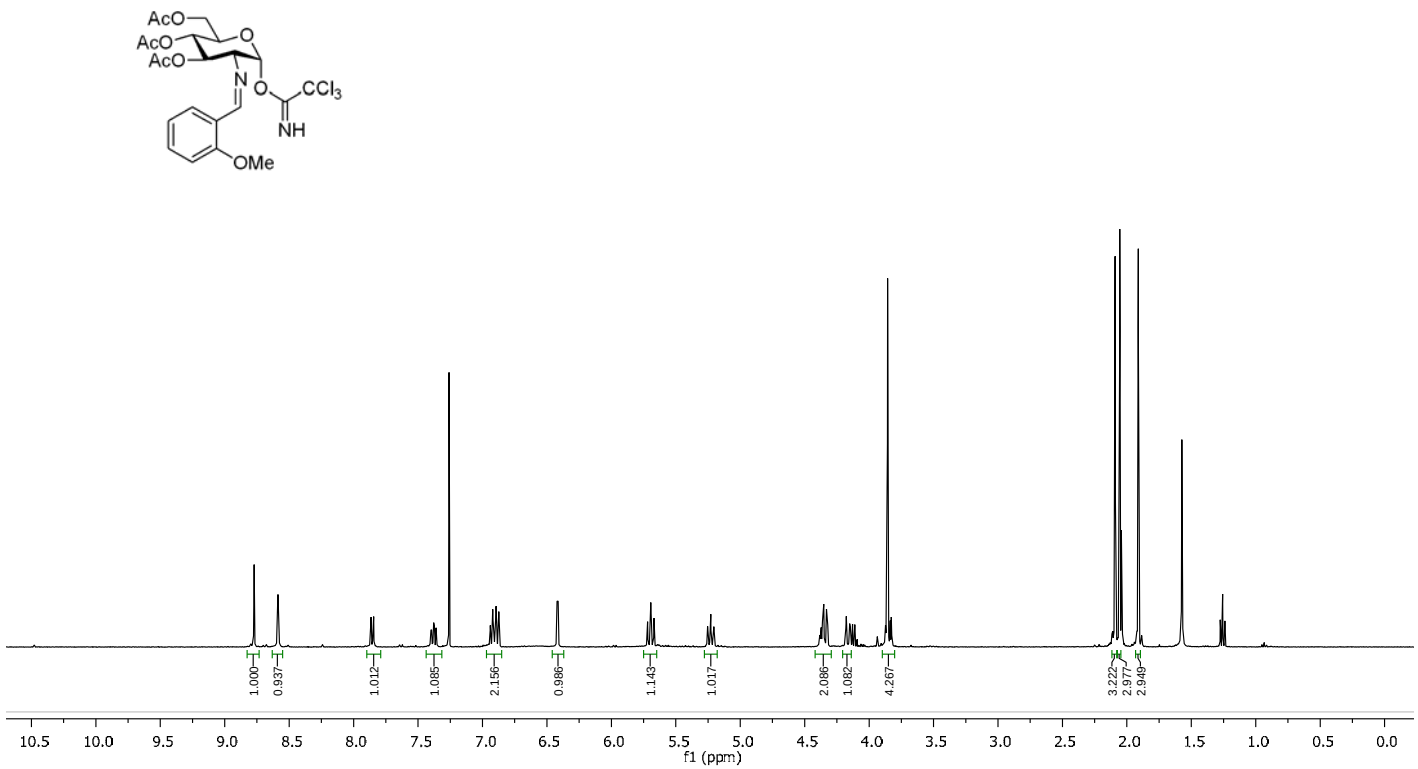


Figure A228. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **222**

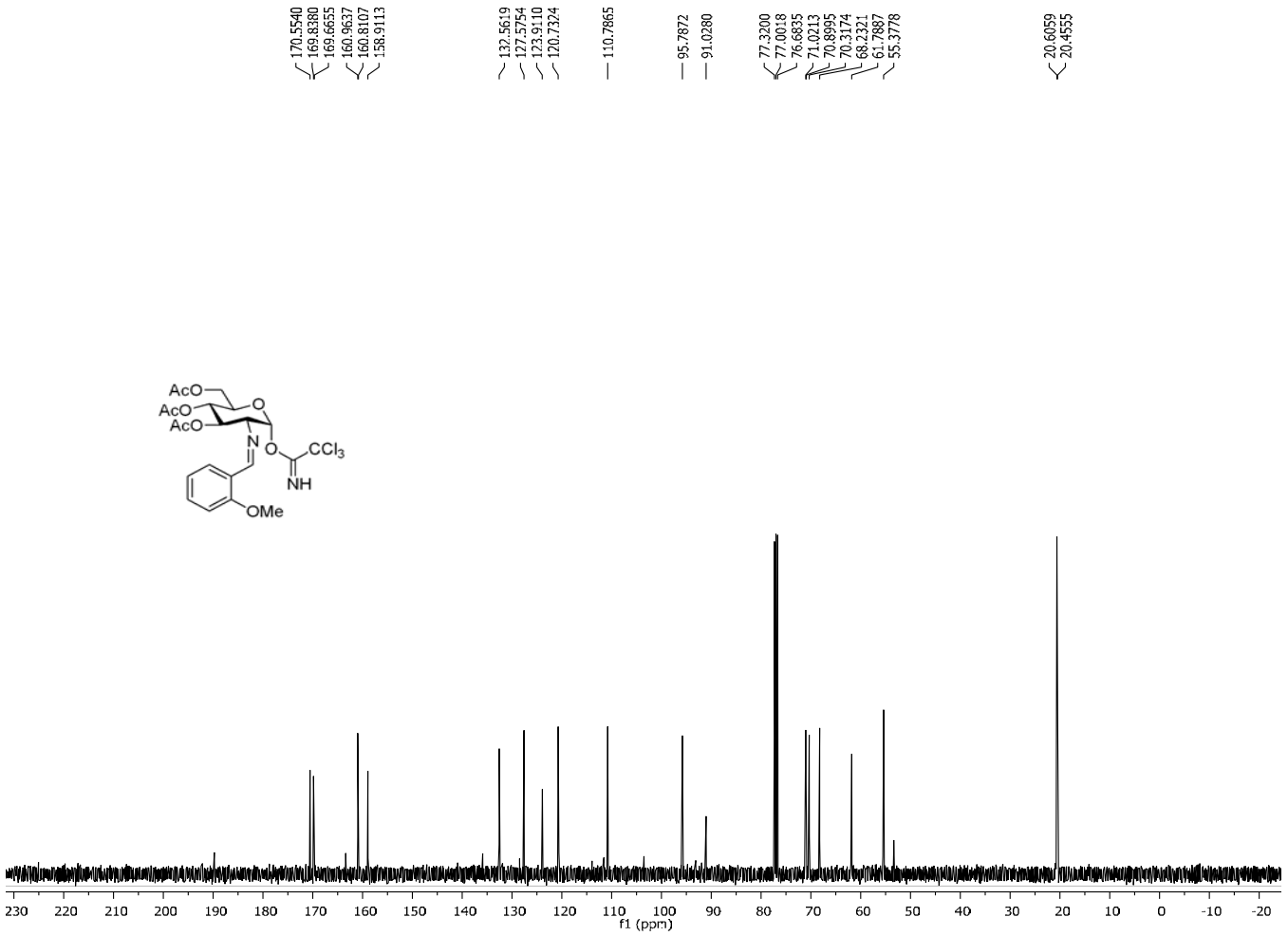


Figure A229. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **222**

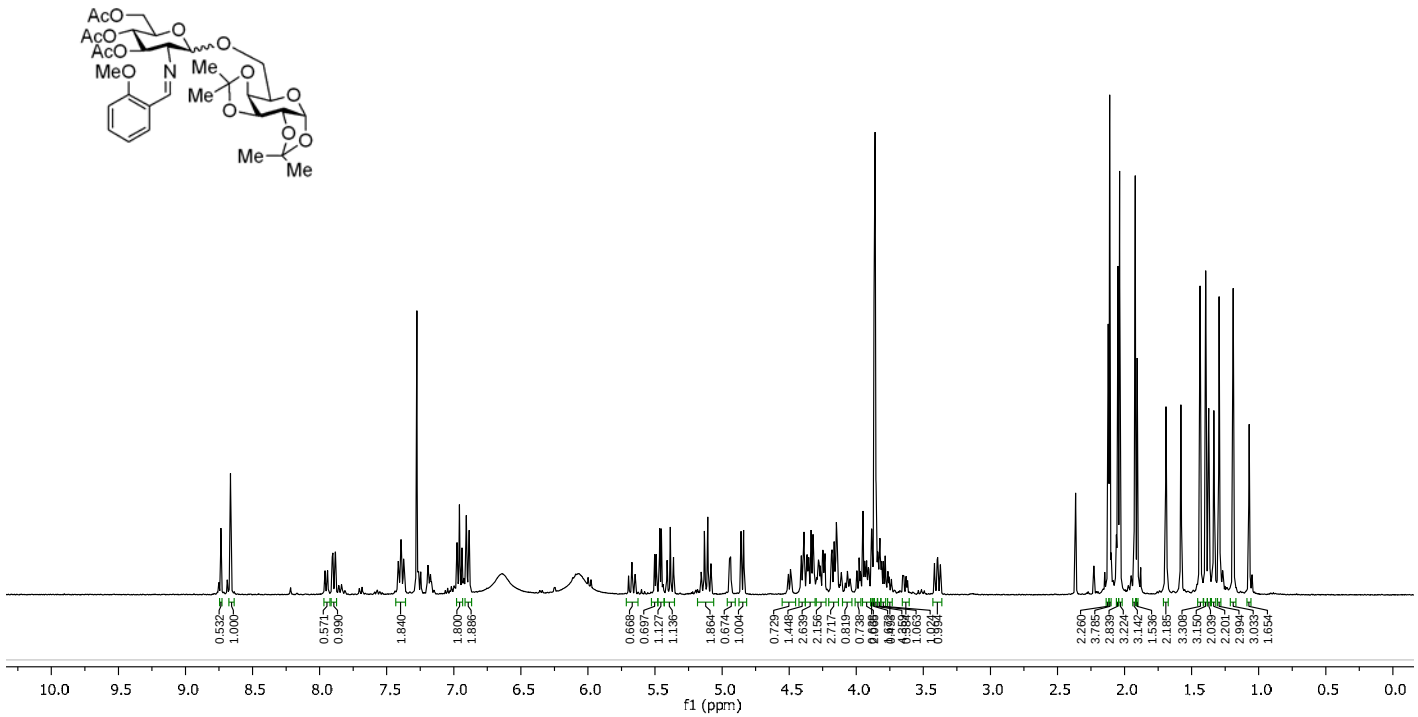


Figure A230. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **224**

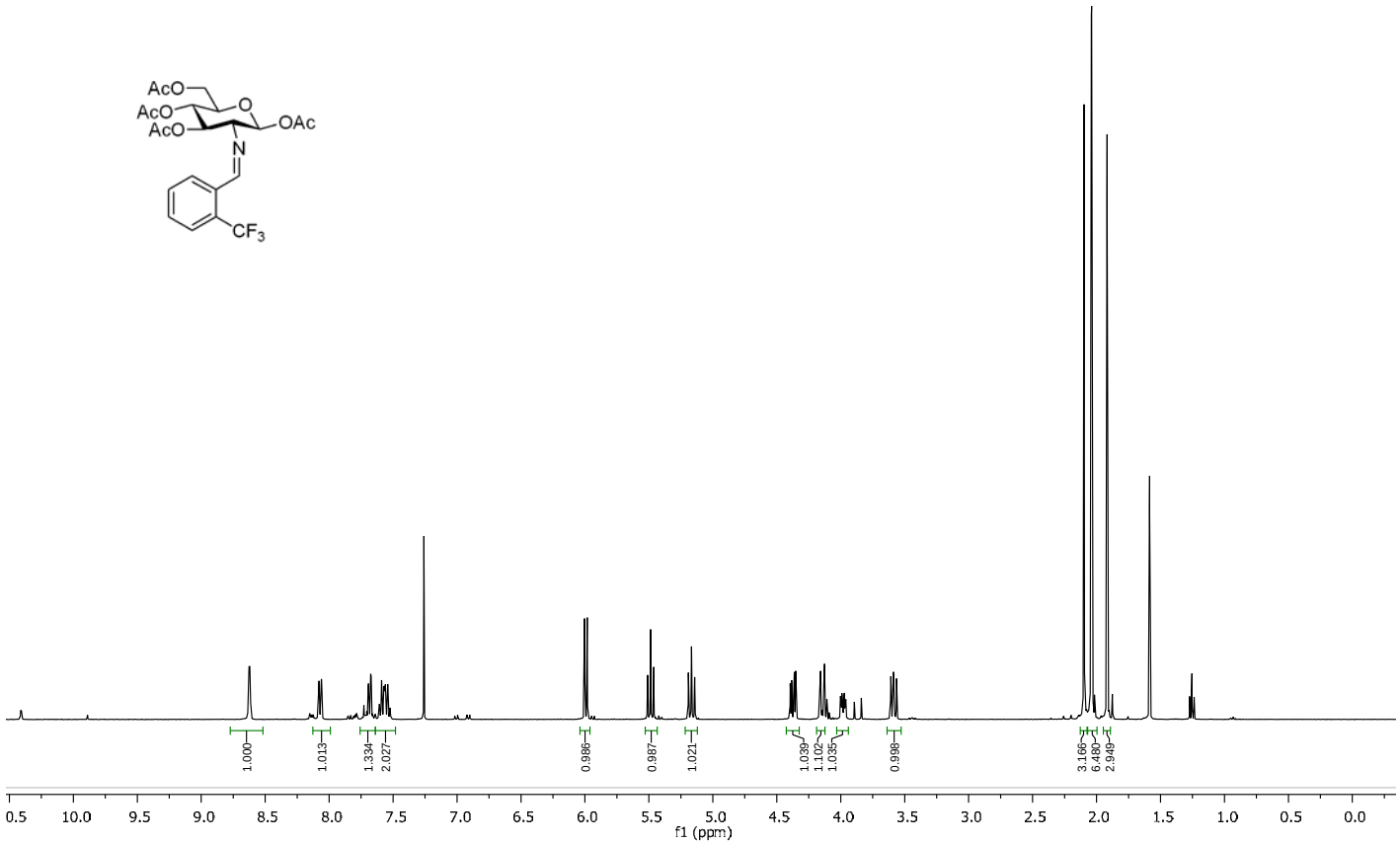


Figure A231. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **225A**

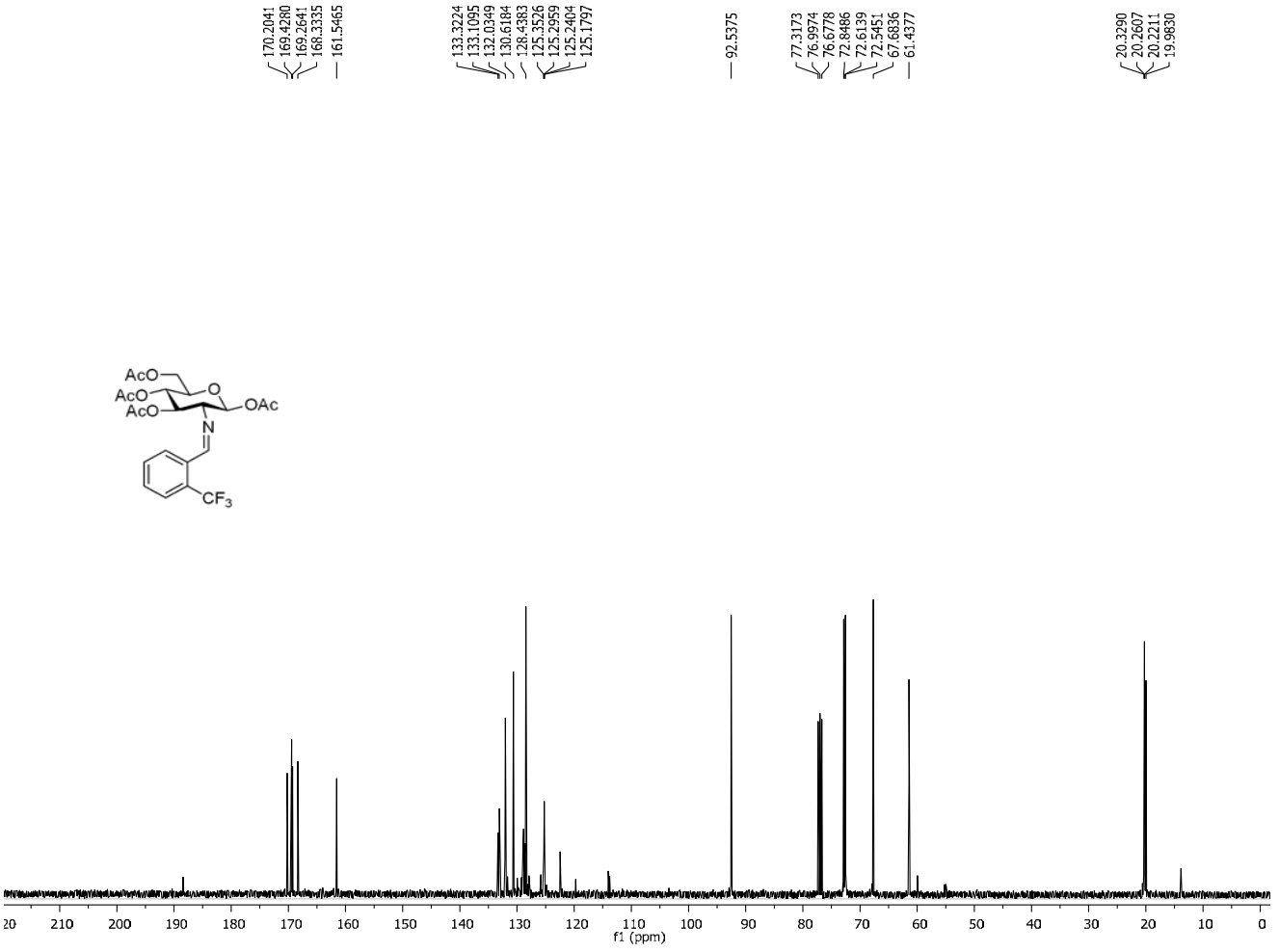


Figure A232. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **225A**

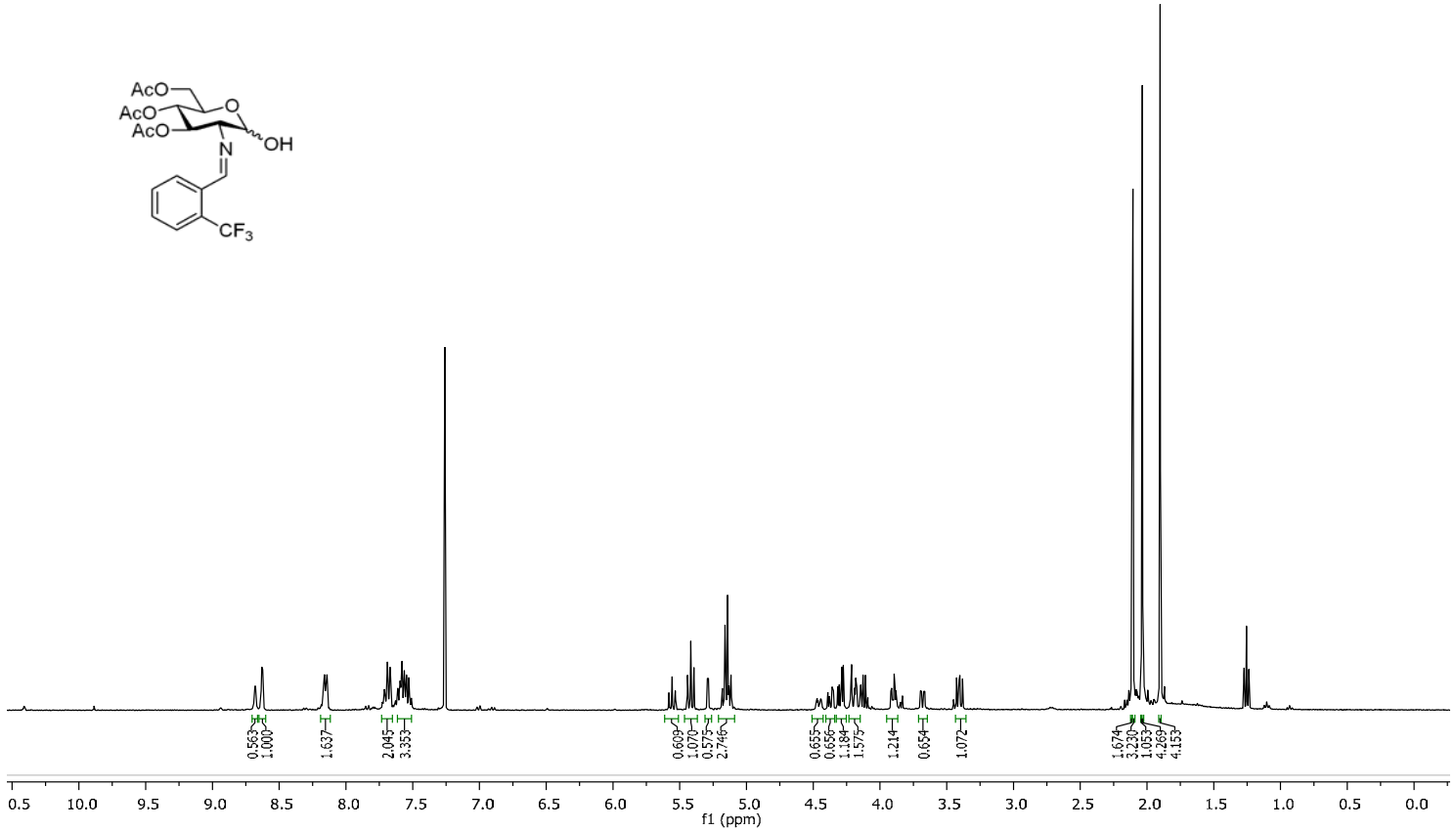


Figure A233. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **225B**

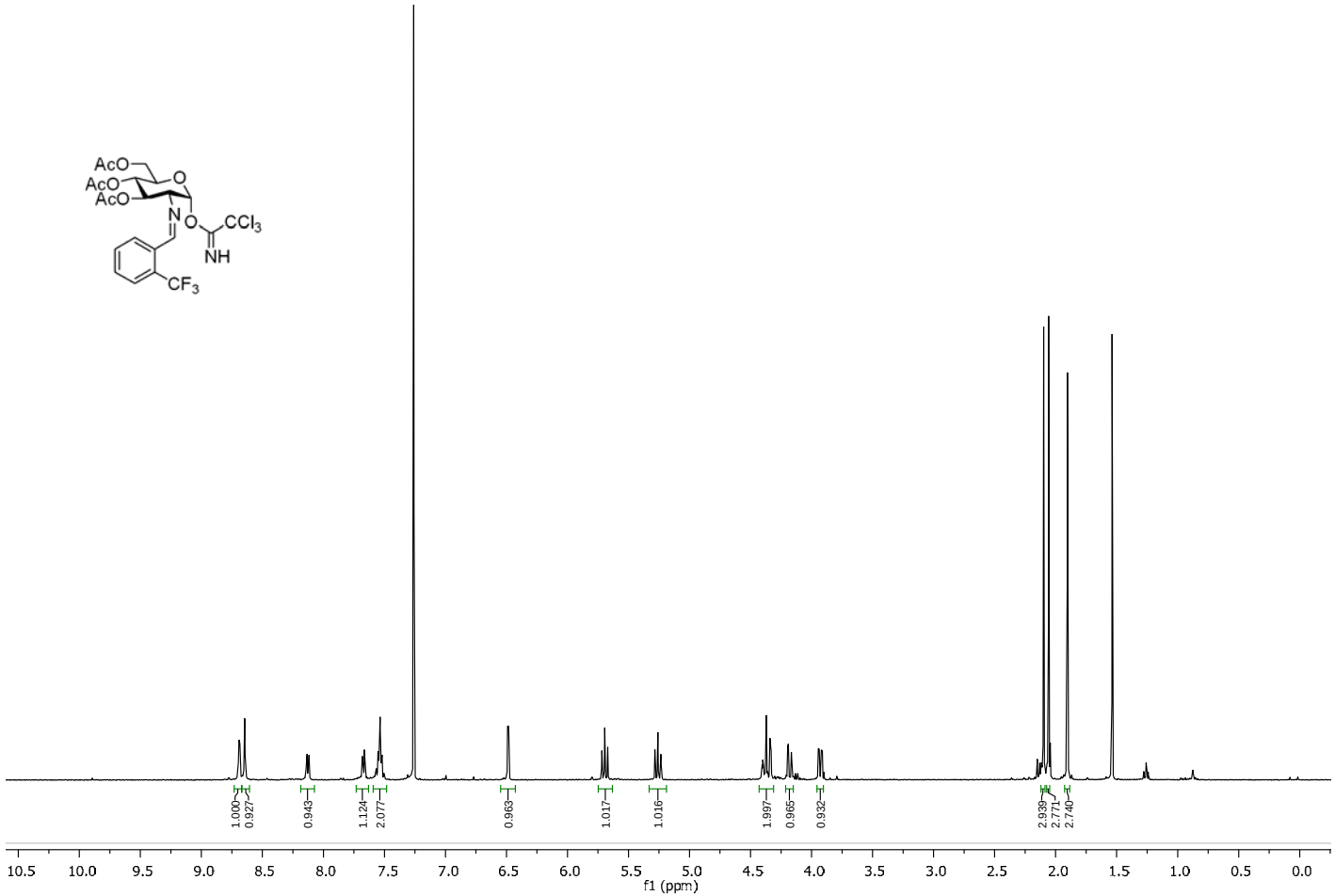


Figure A234. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **225**

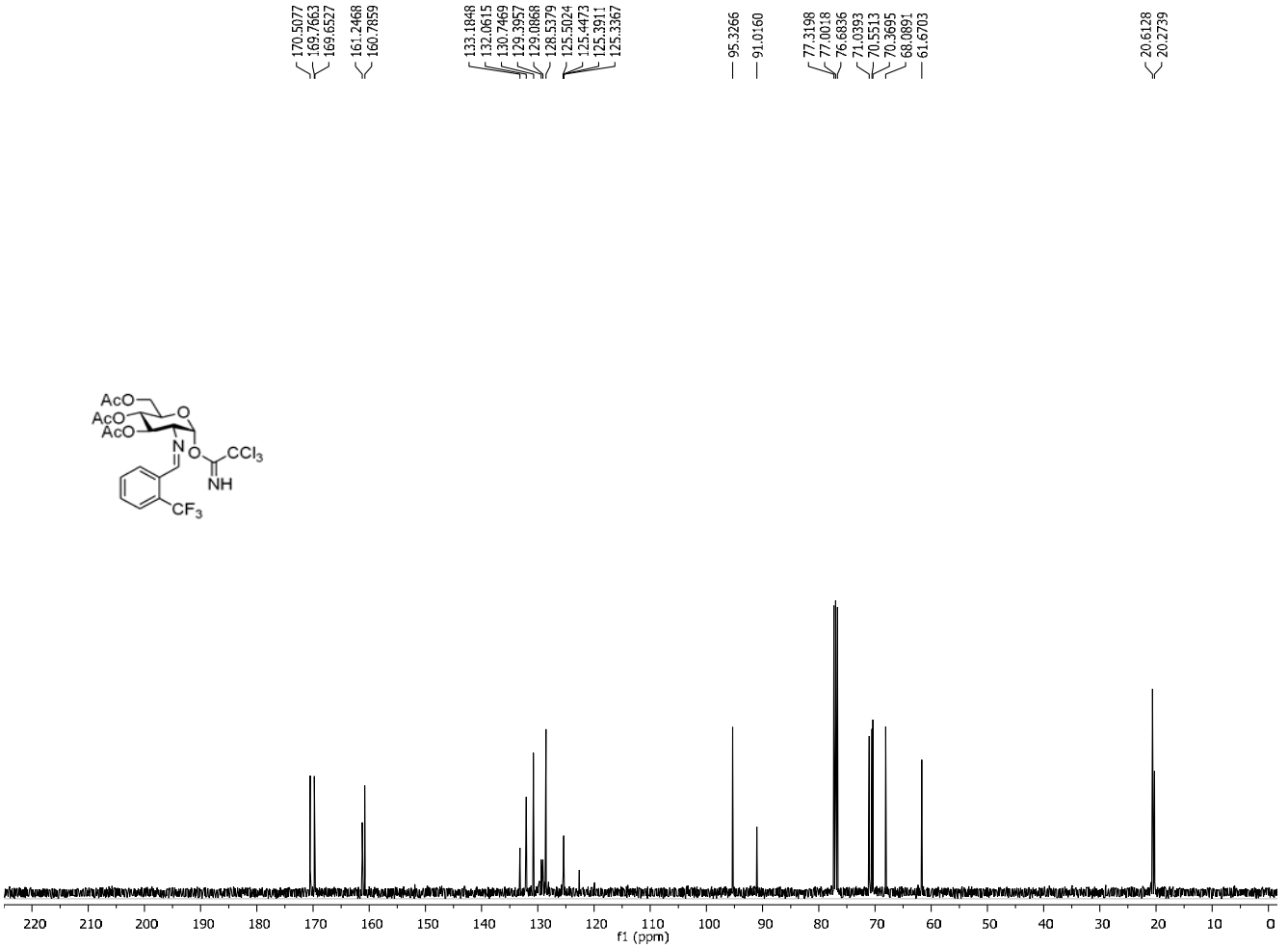


Figure A235. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **225**

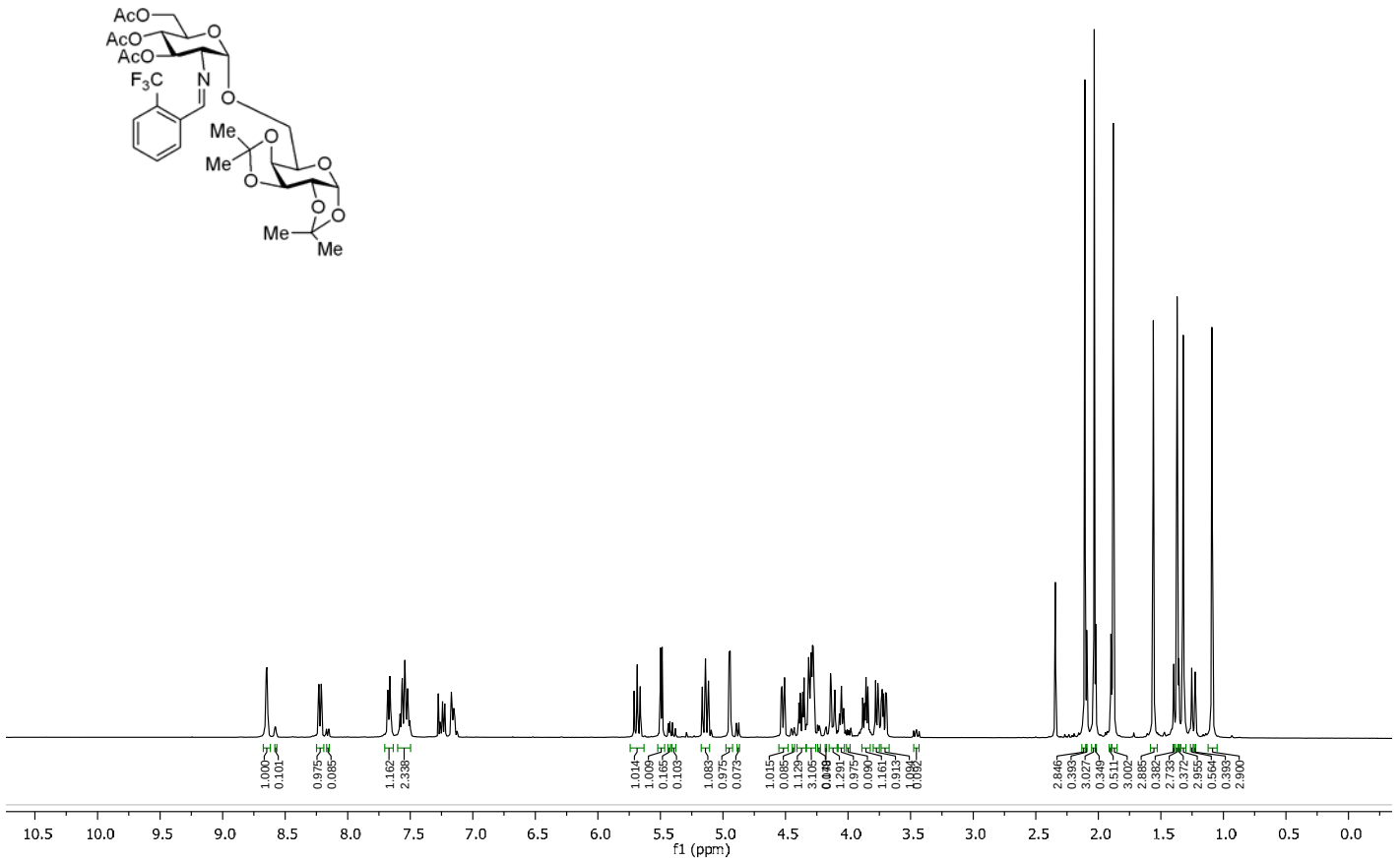


Figure A236. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **226**

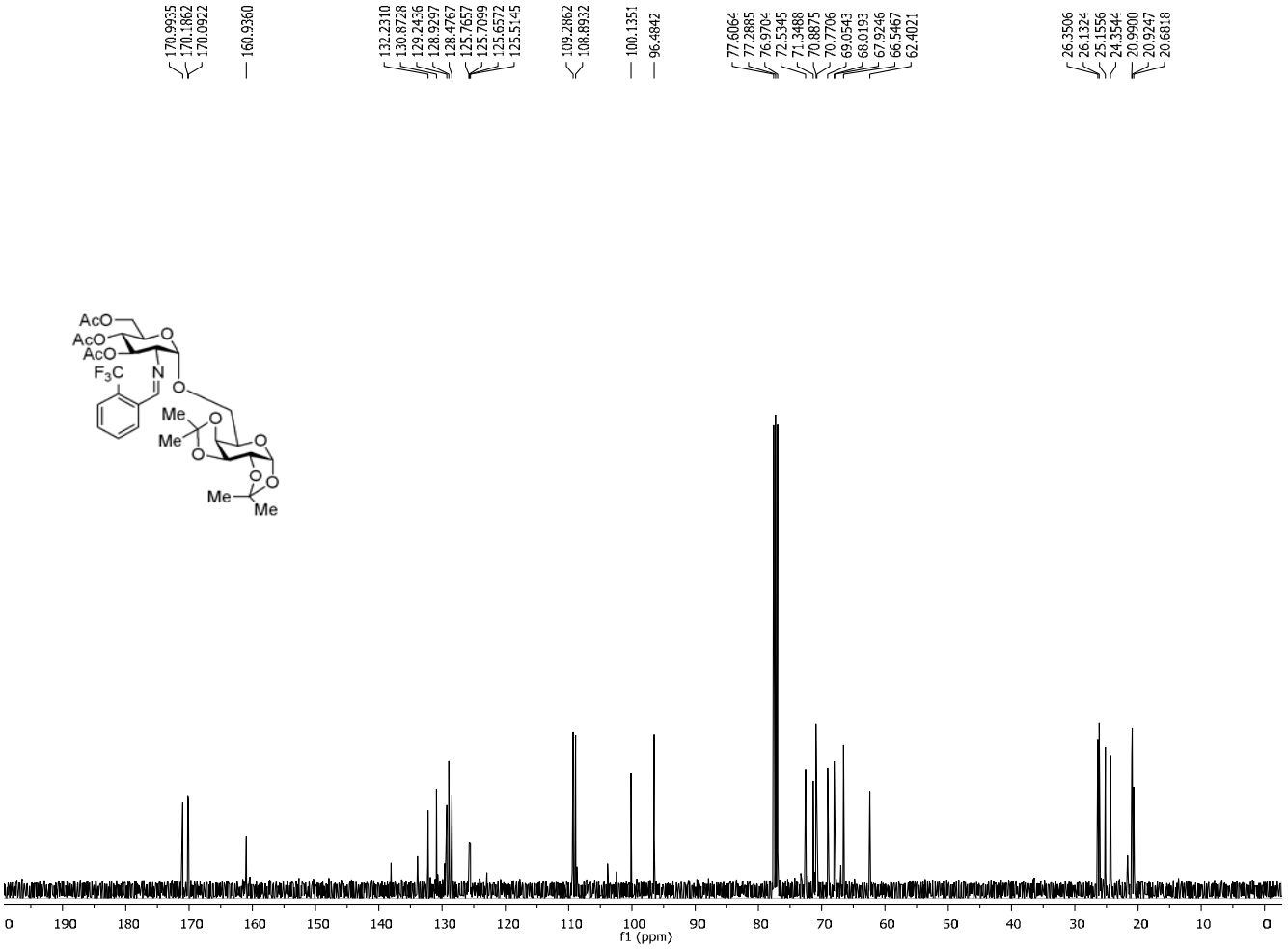


Figure A237. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **226**

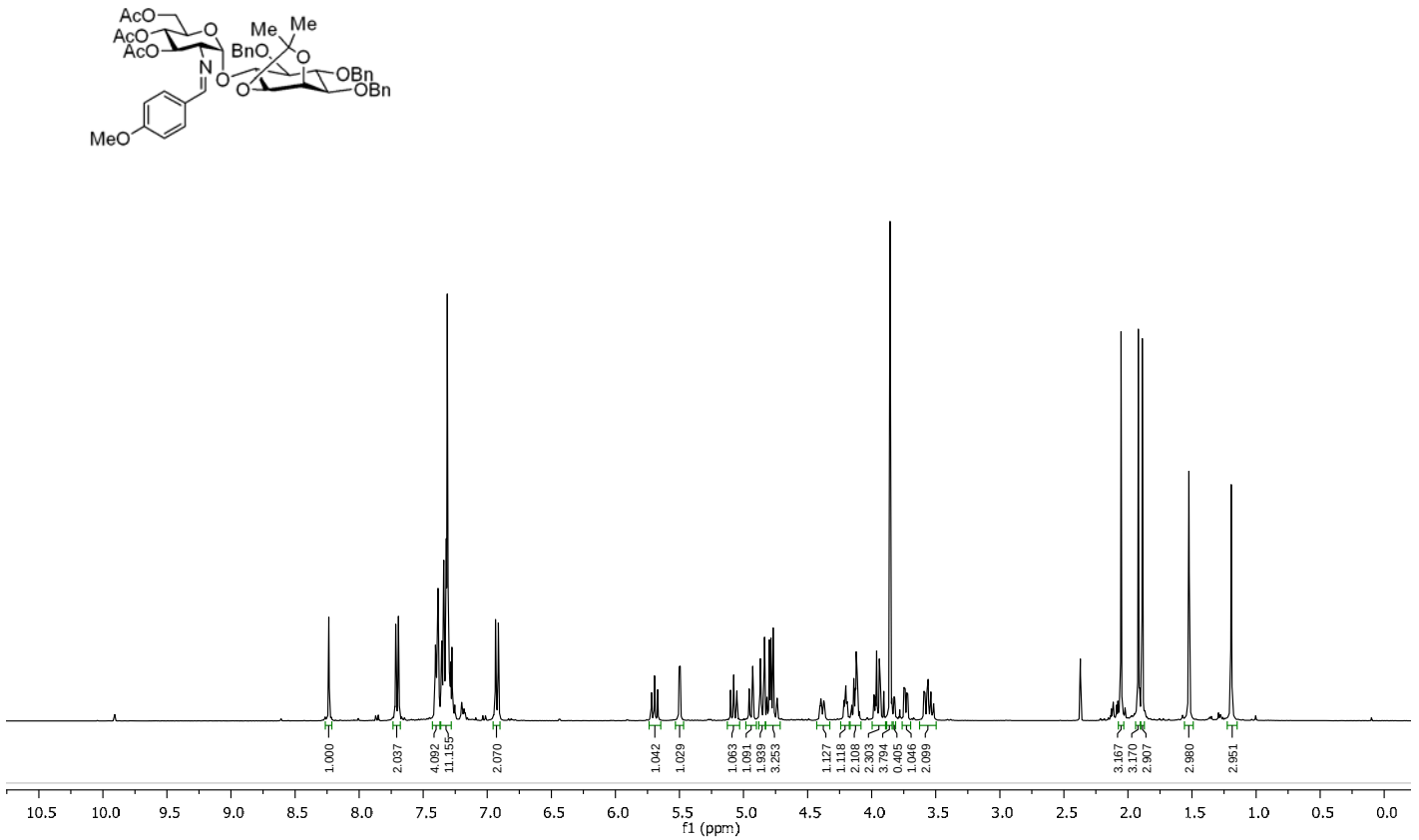


Figure A238. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **229**

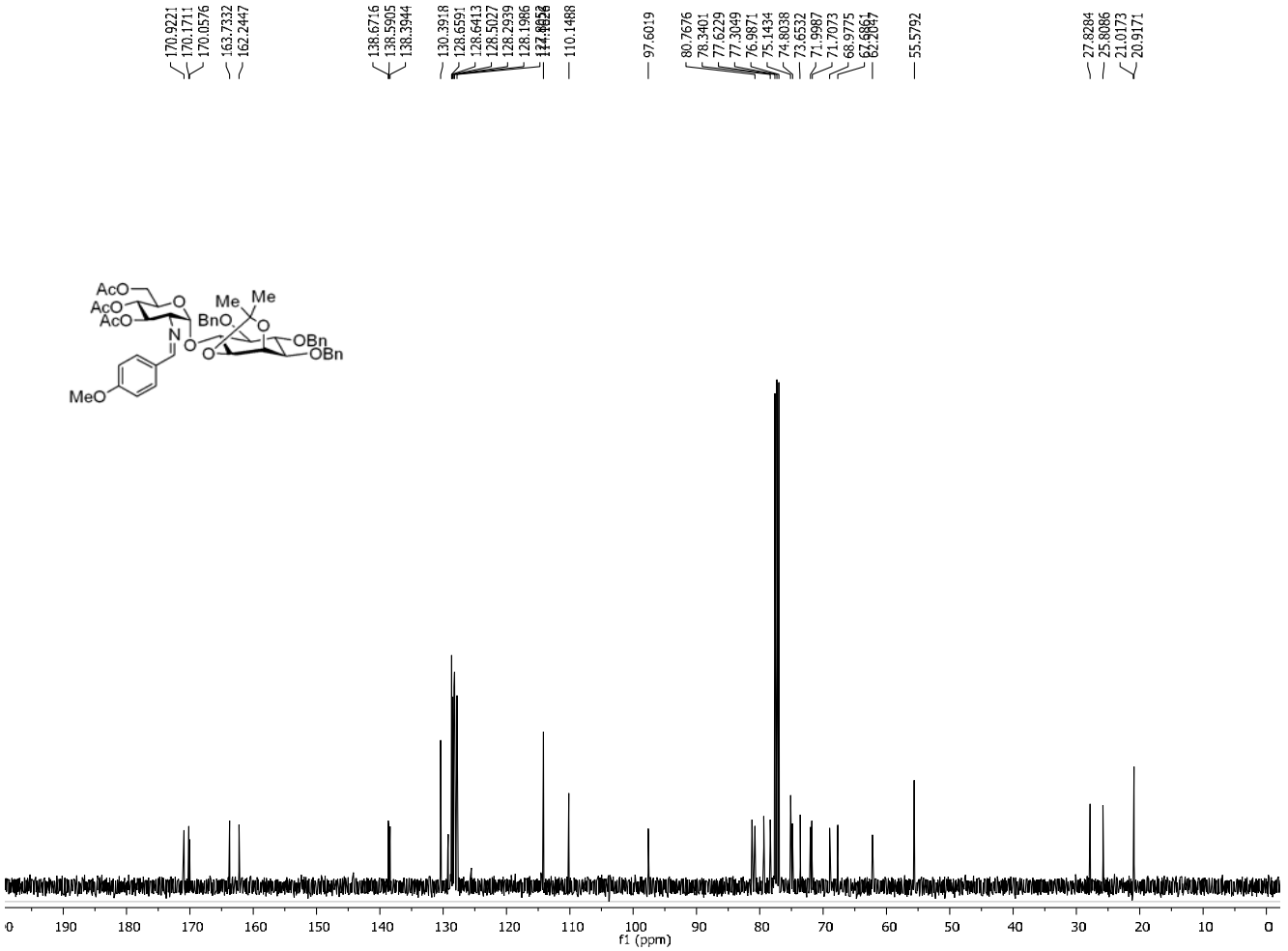


Figure A239. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **229**

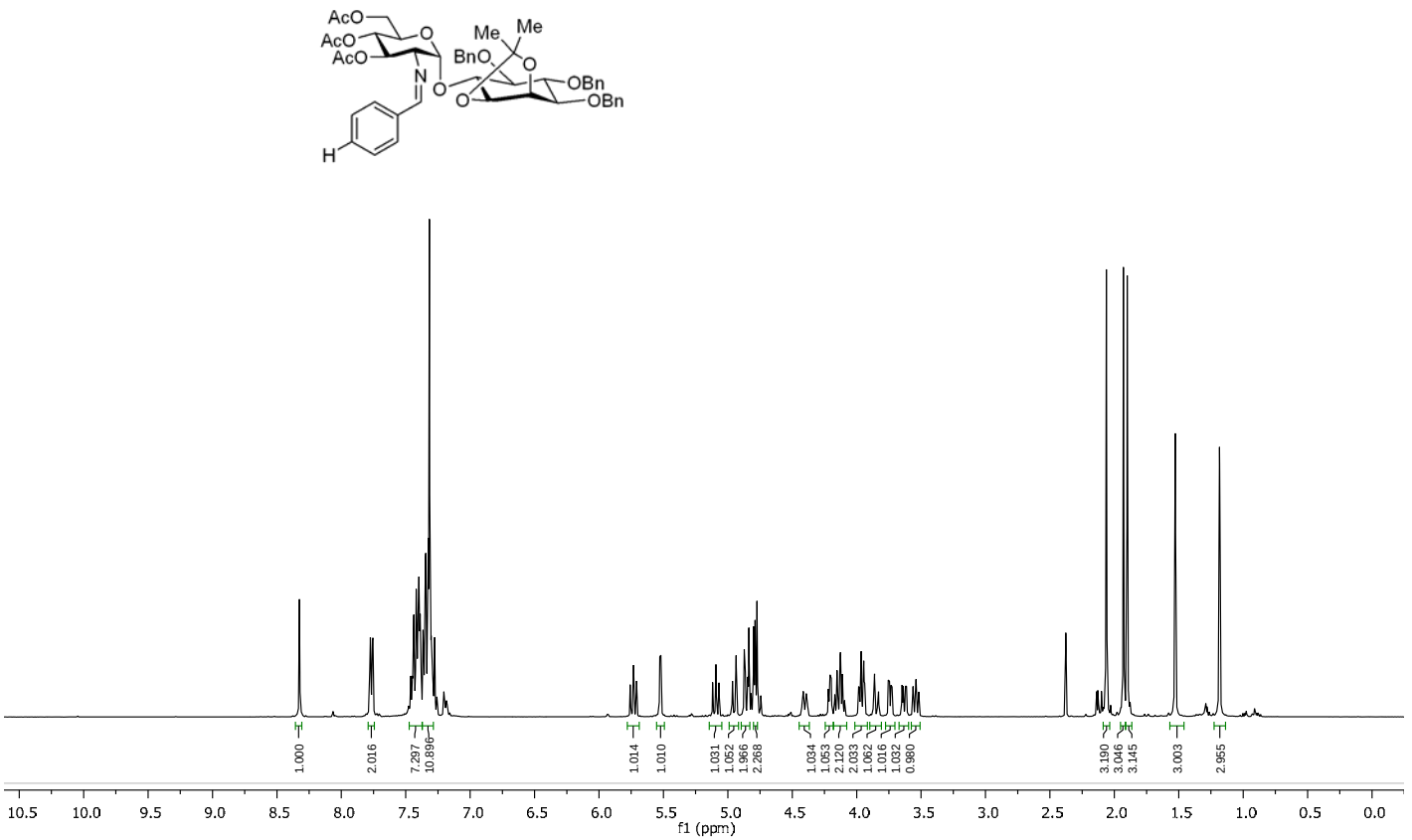


Figure A240. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **230**

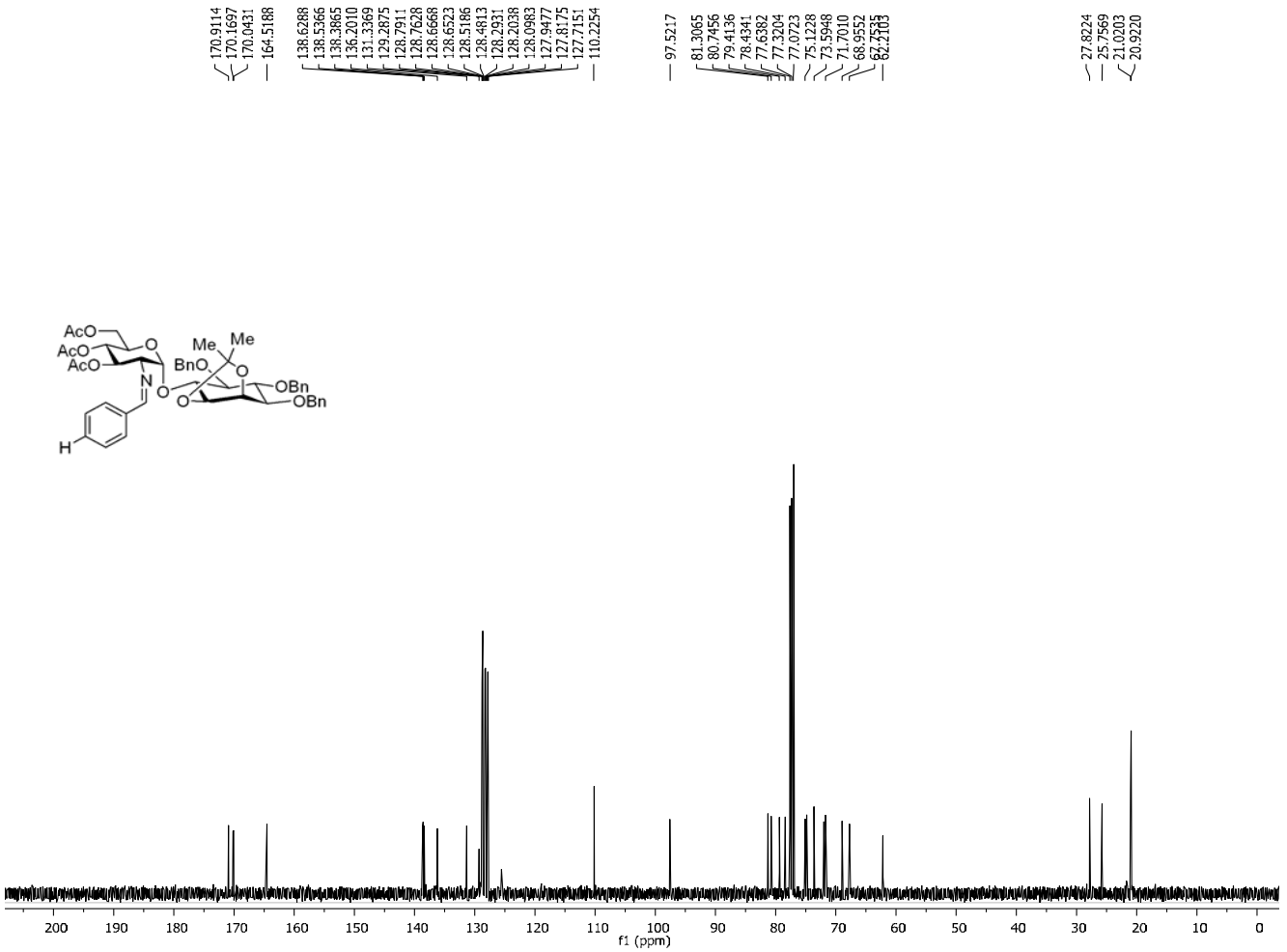


Figure A241. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **230**

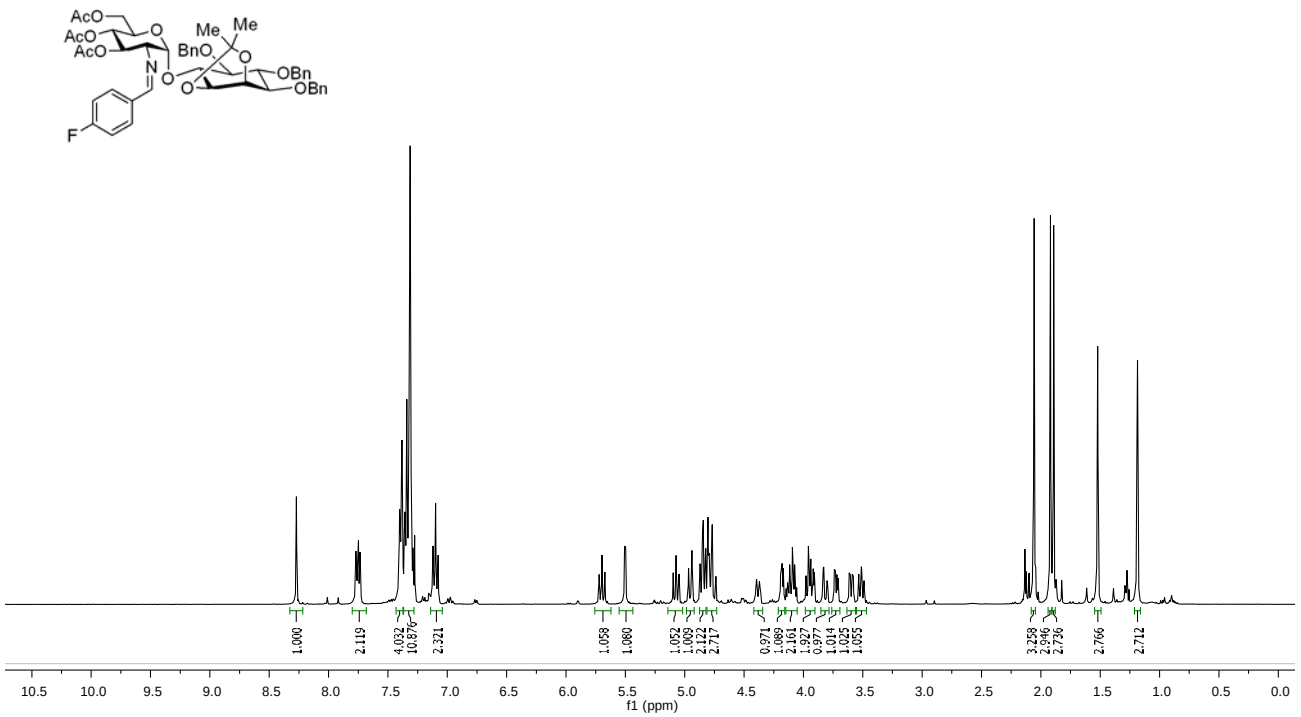


Figure A242. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **231**

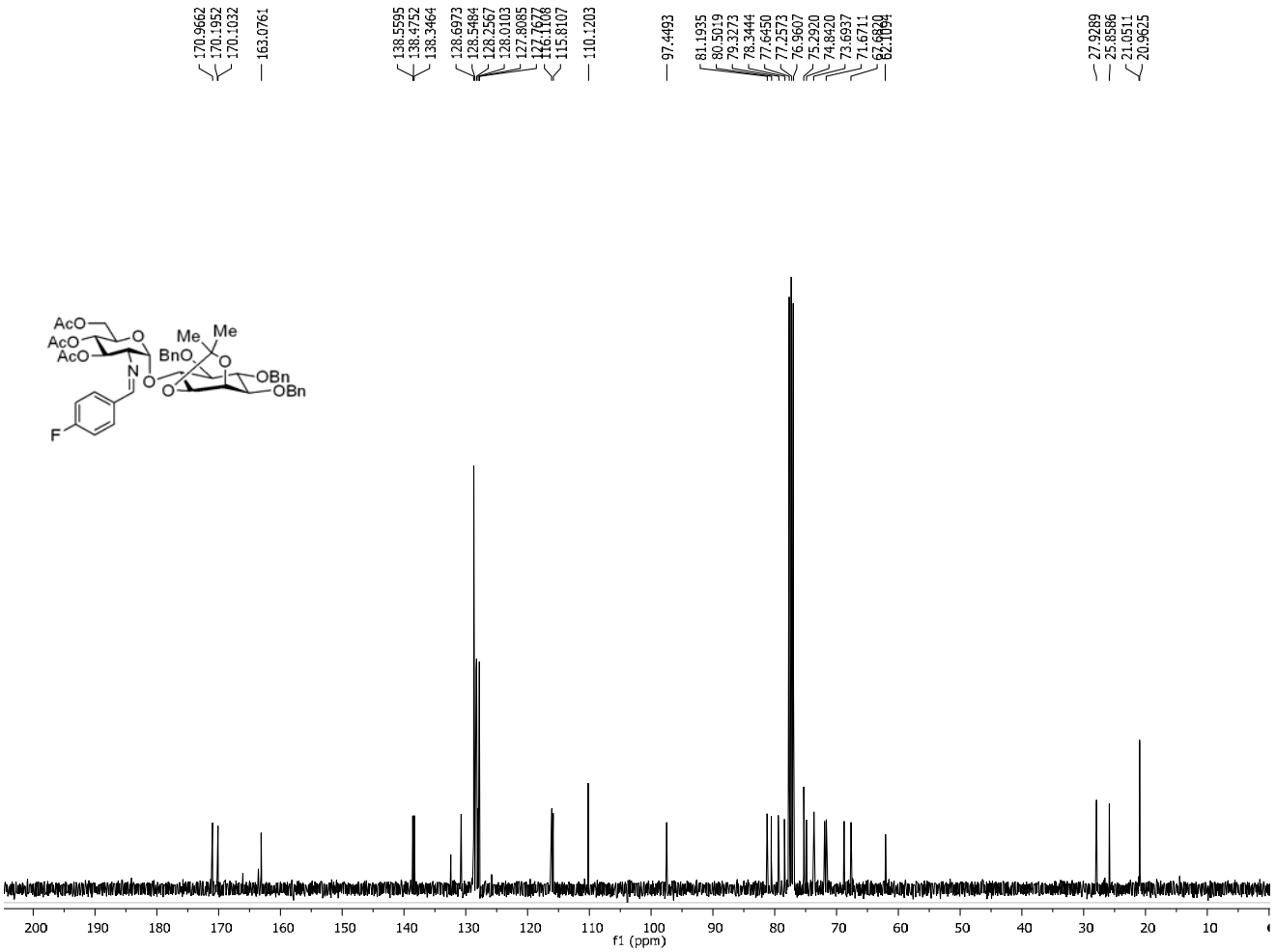


Figure A243. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **231**

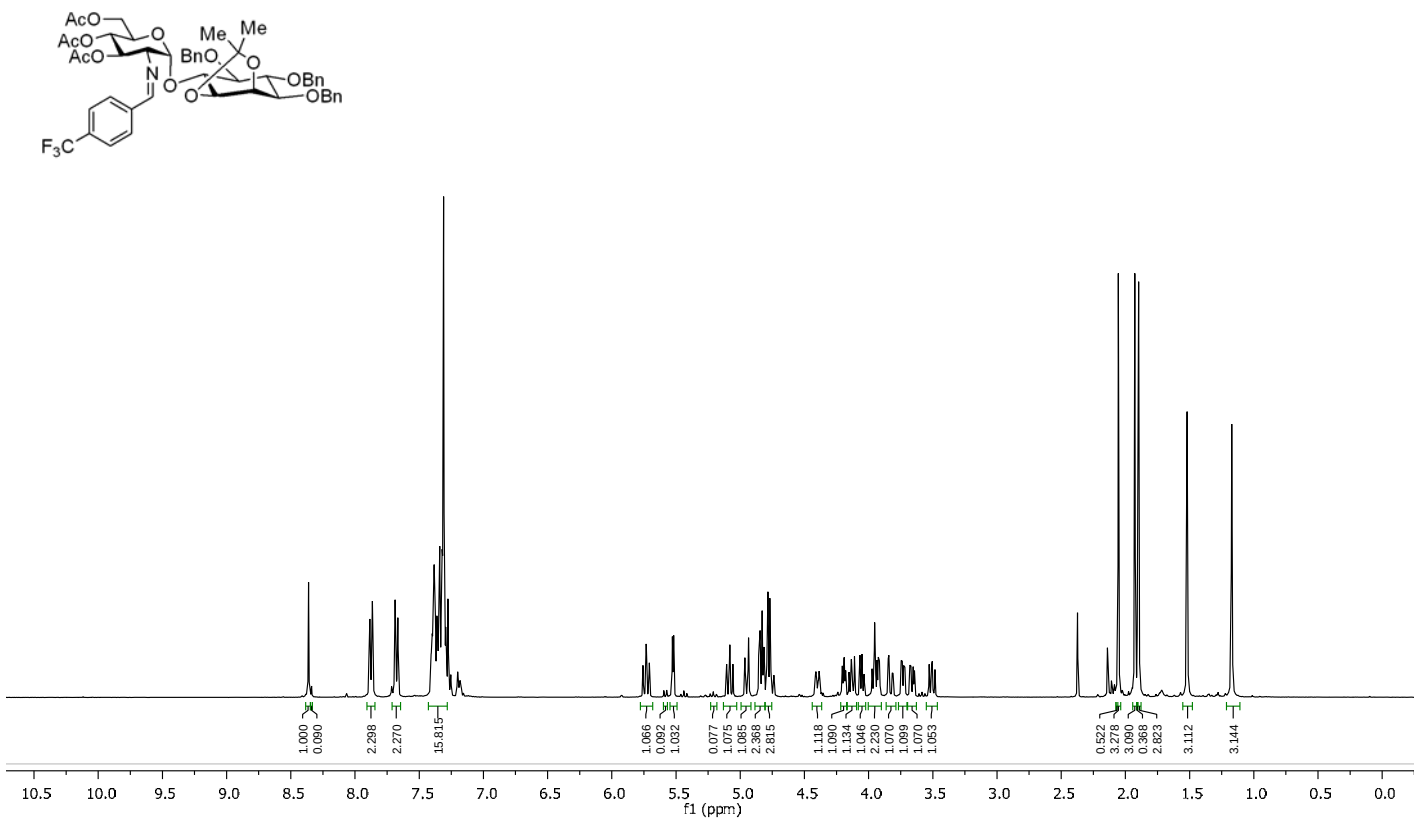


Figure A244. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **232**

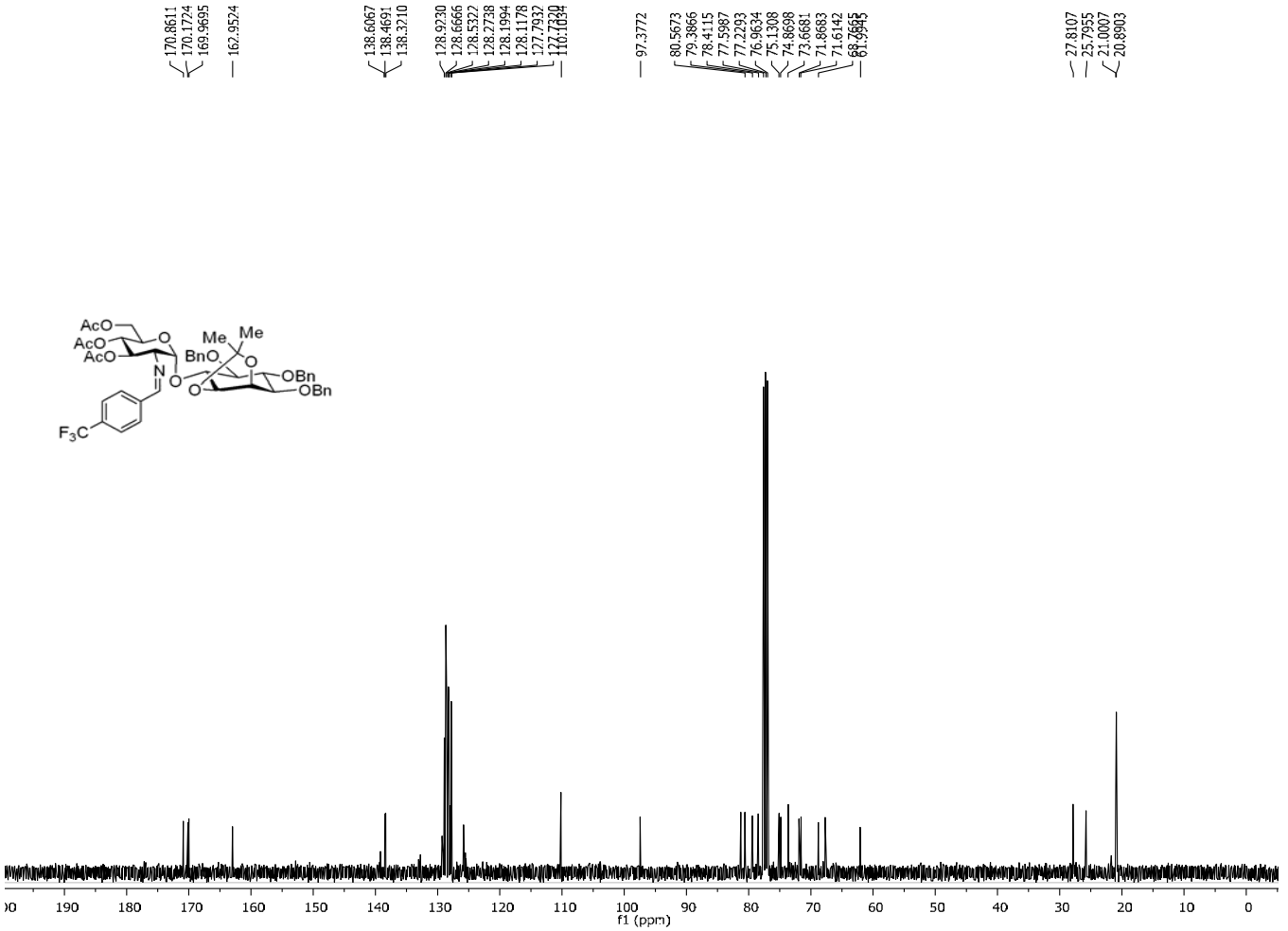


Figure A245. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **232**

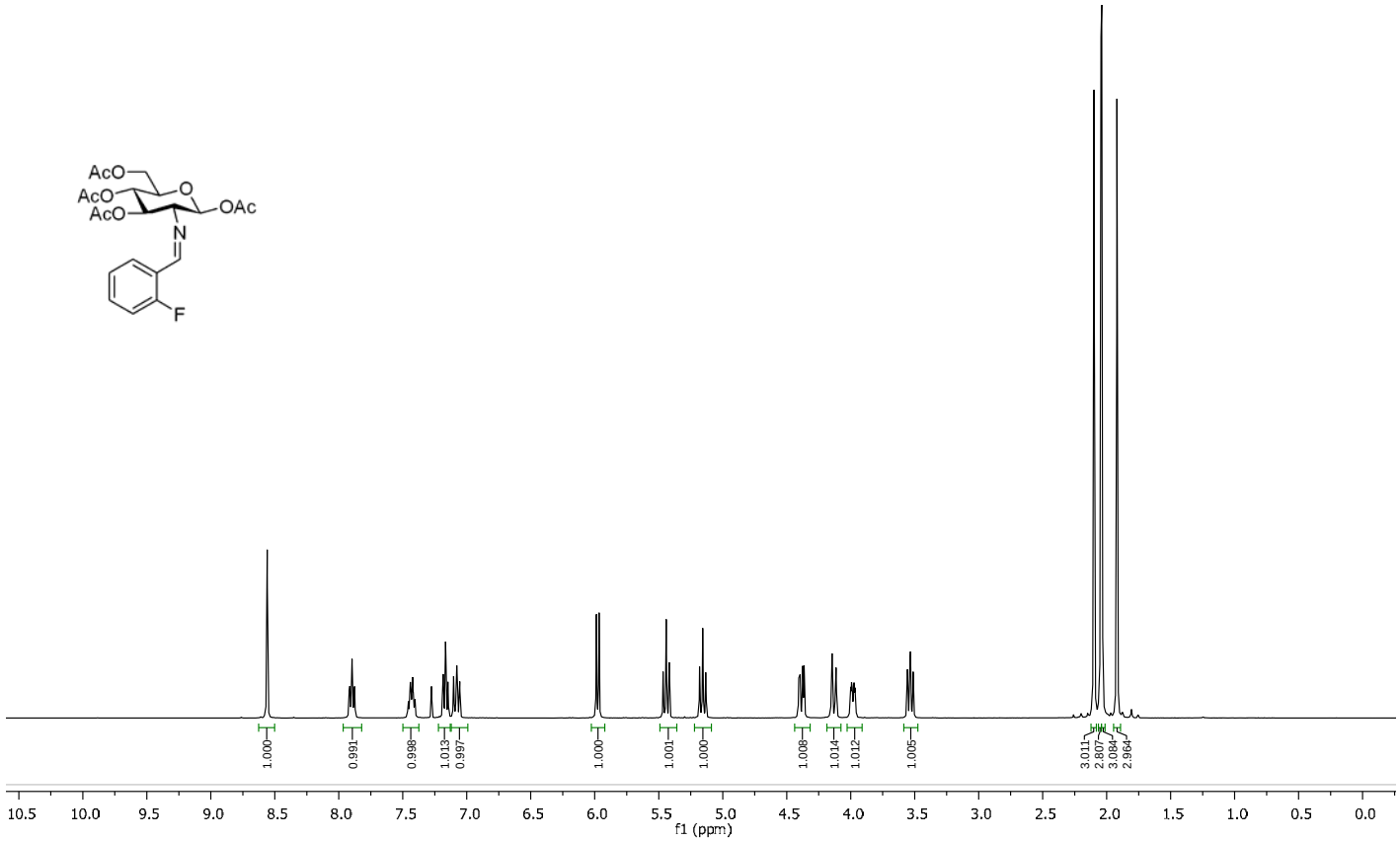


Figure A246. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **234**

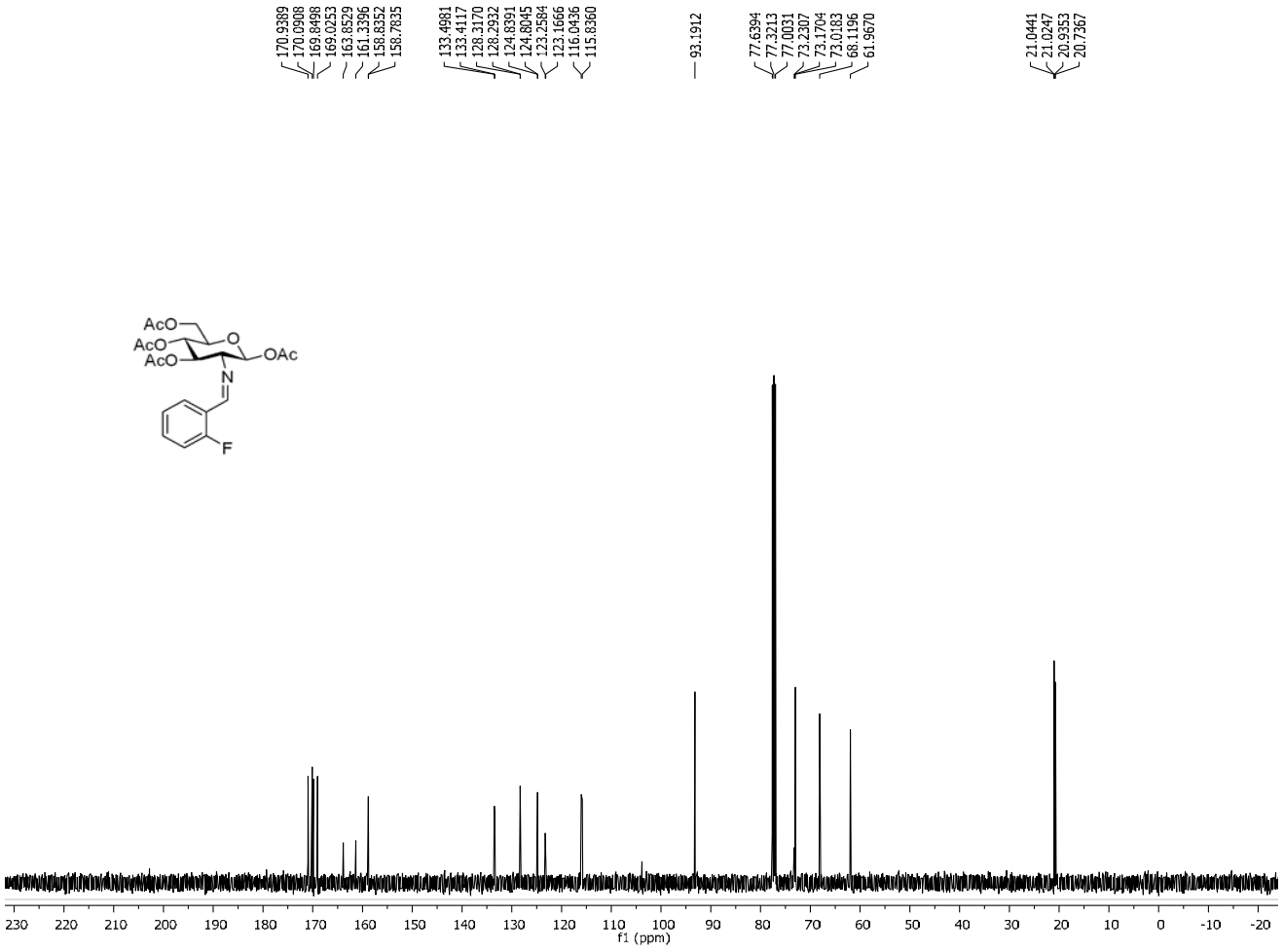


Figure A247. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **234**

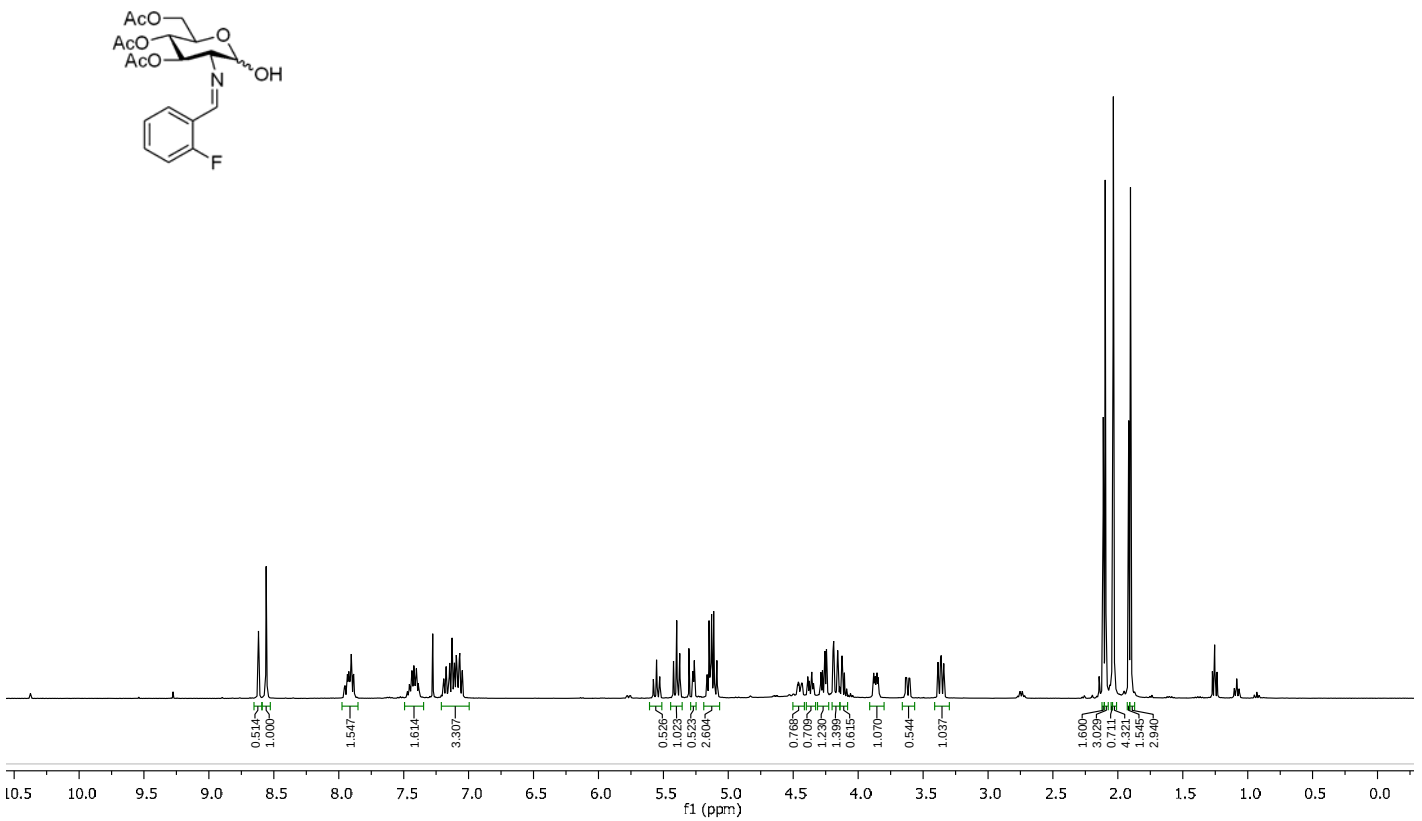


Figure A248. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Hemiacetal **235**

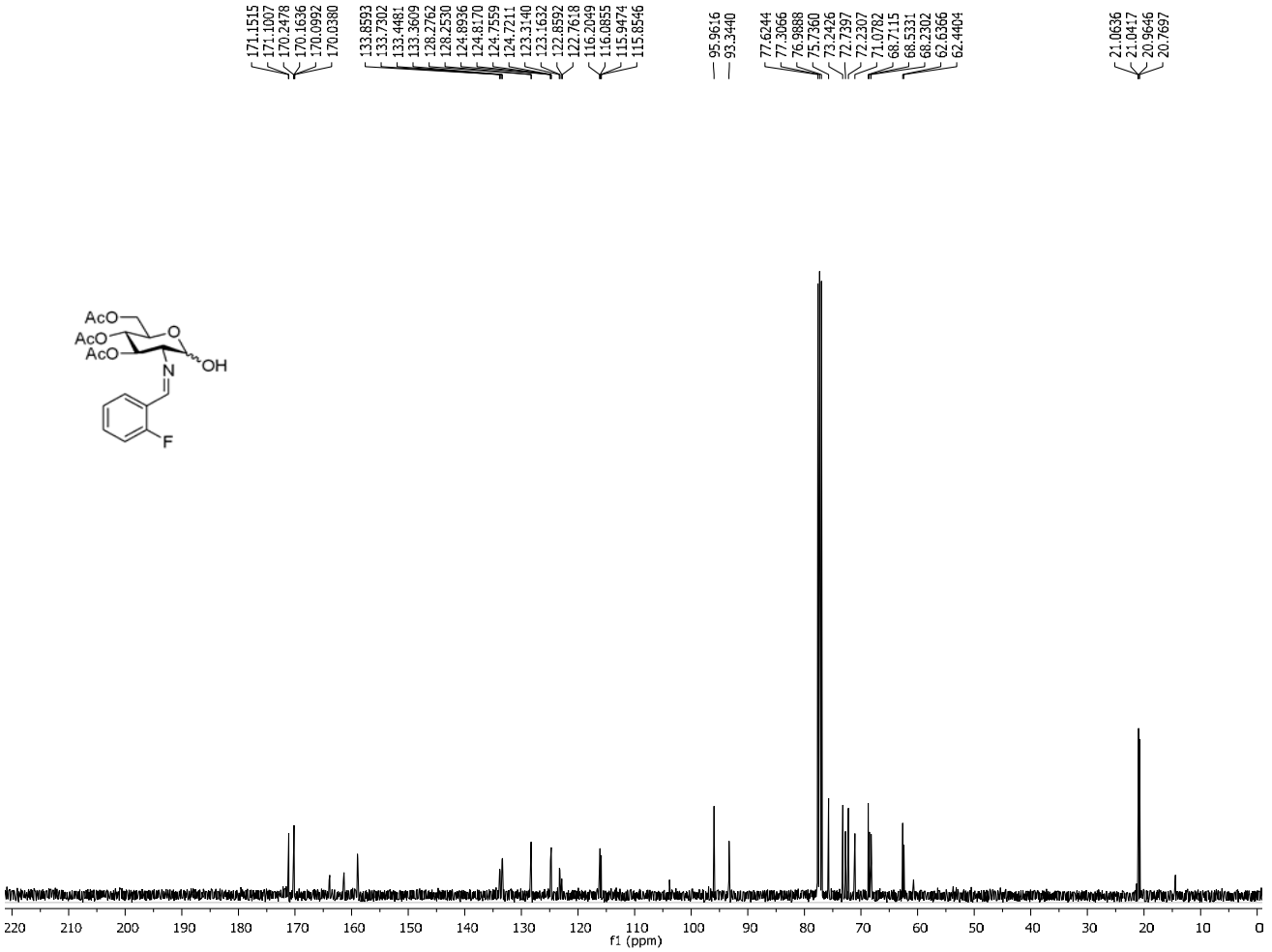


Figure A249. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Hemiacetal **235**

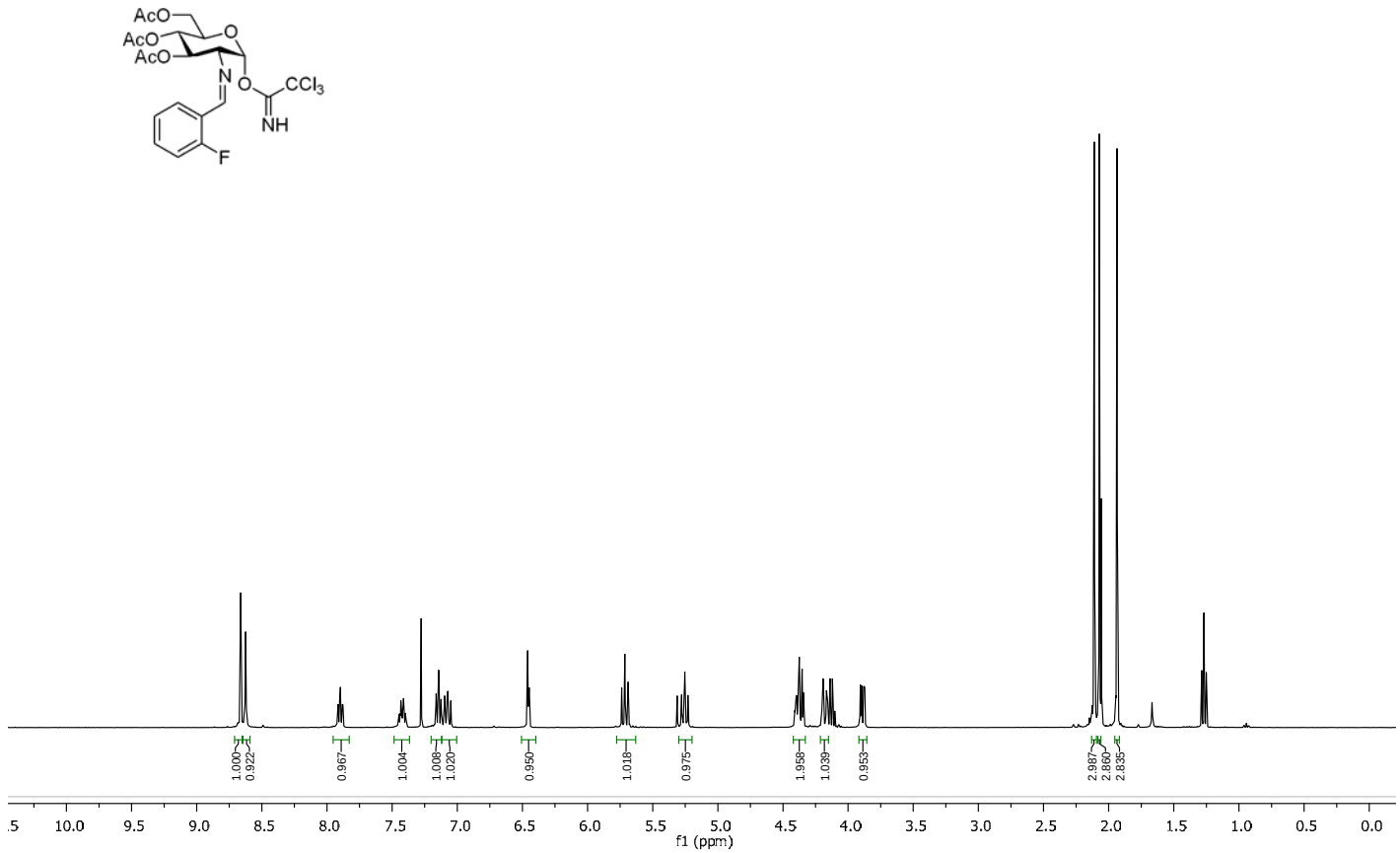


Figure A250. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **236**

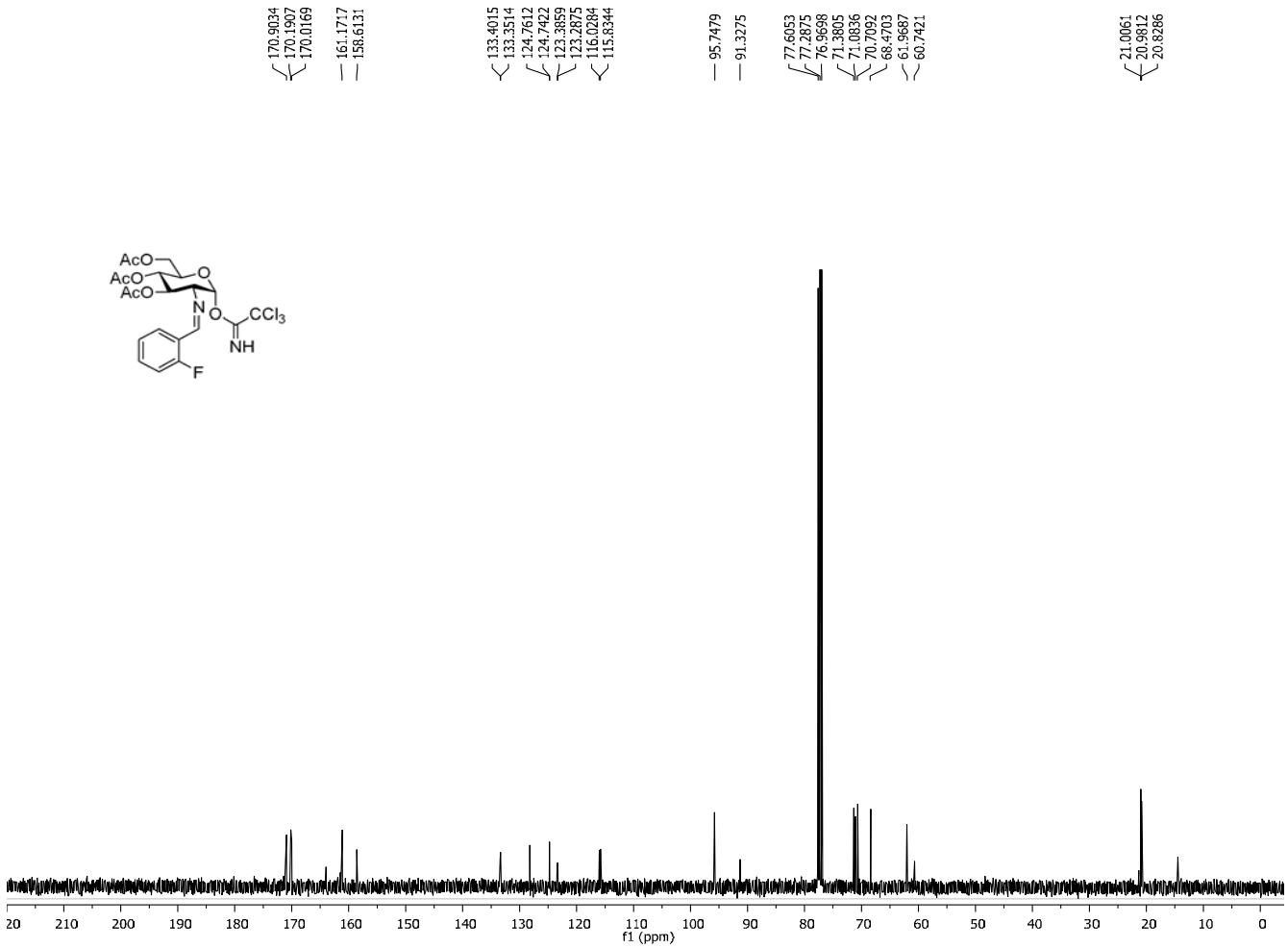


Figure A251. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **236**

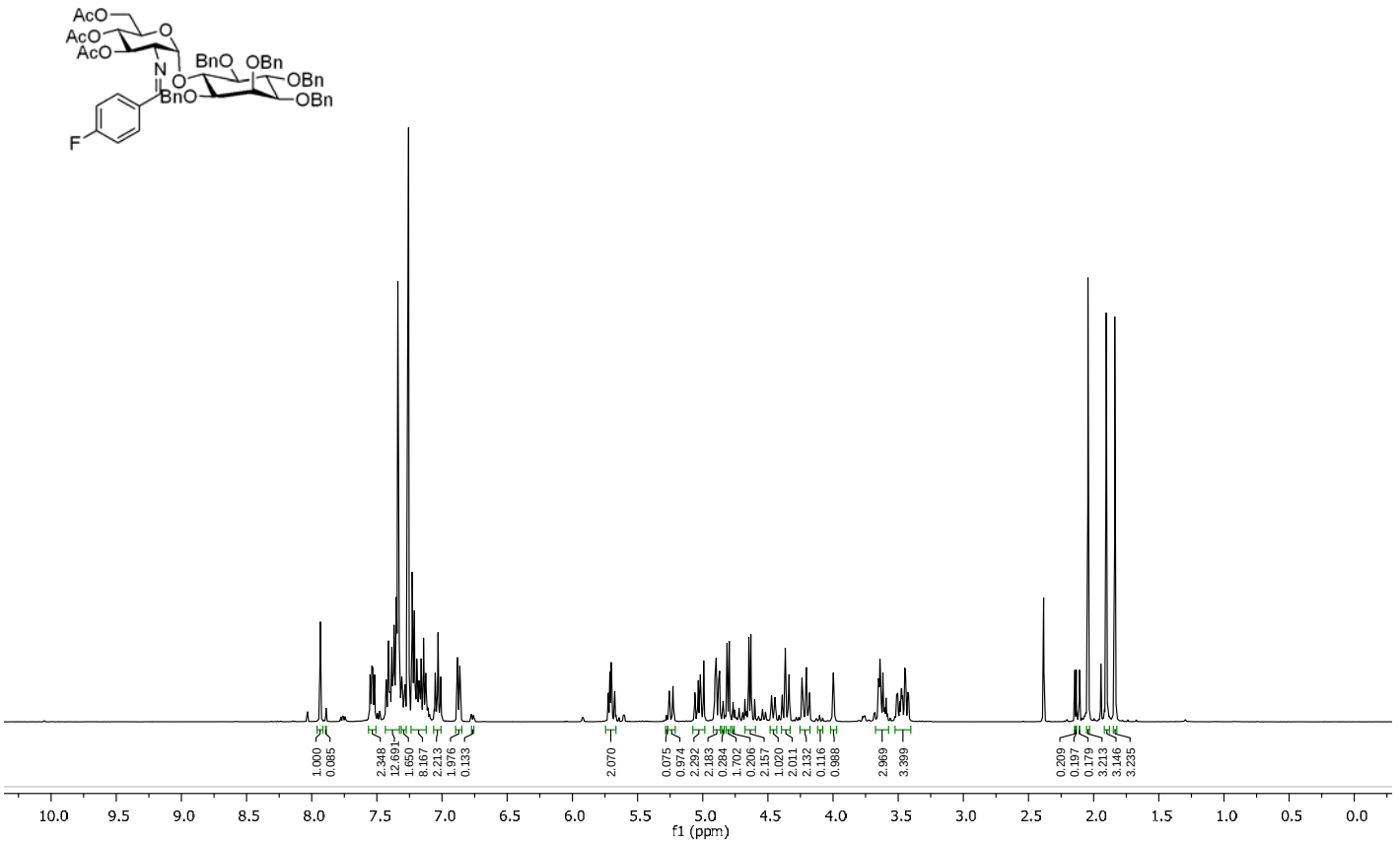


Figure A252. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **237**

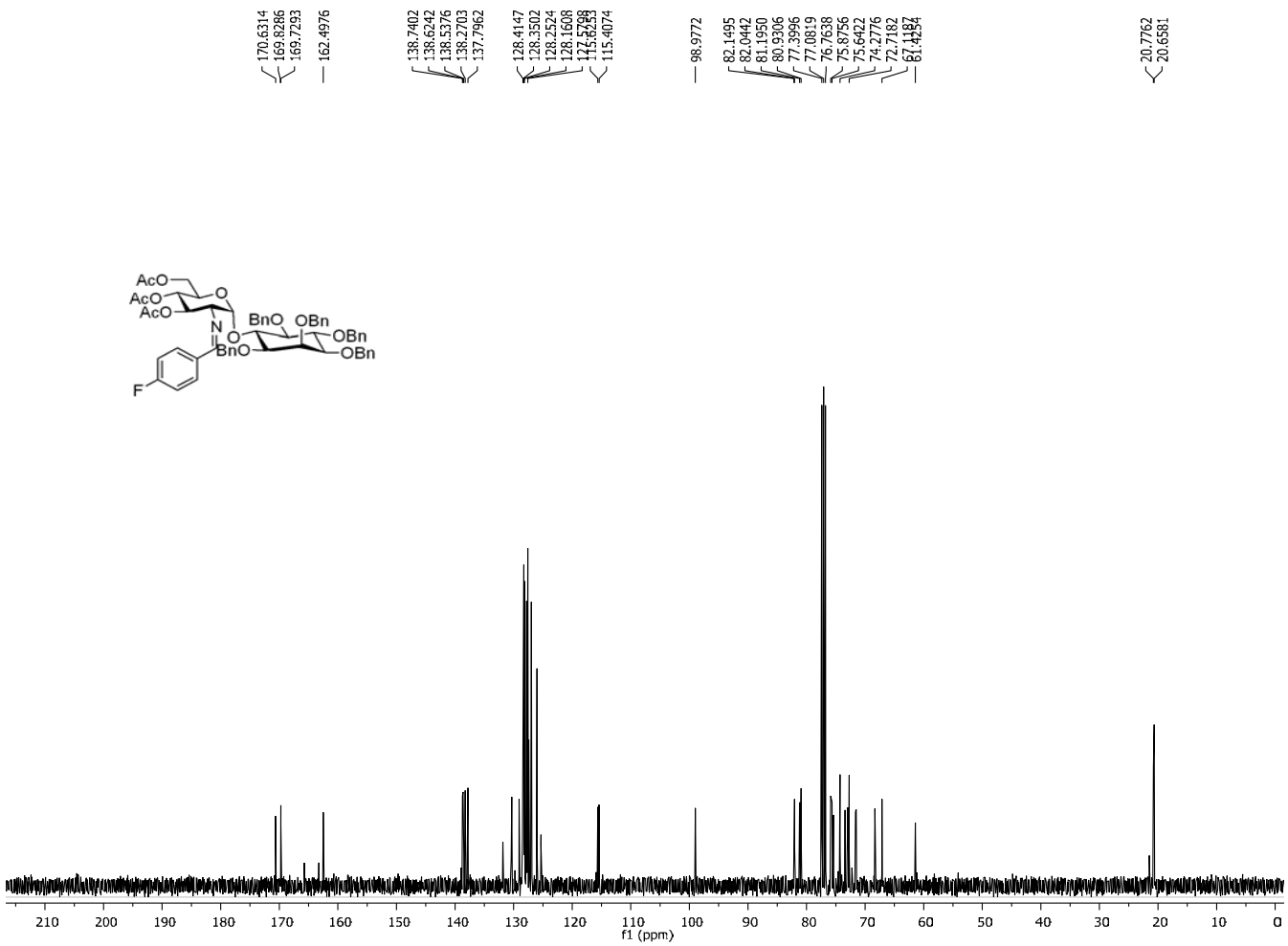


Figure A253. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **237**

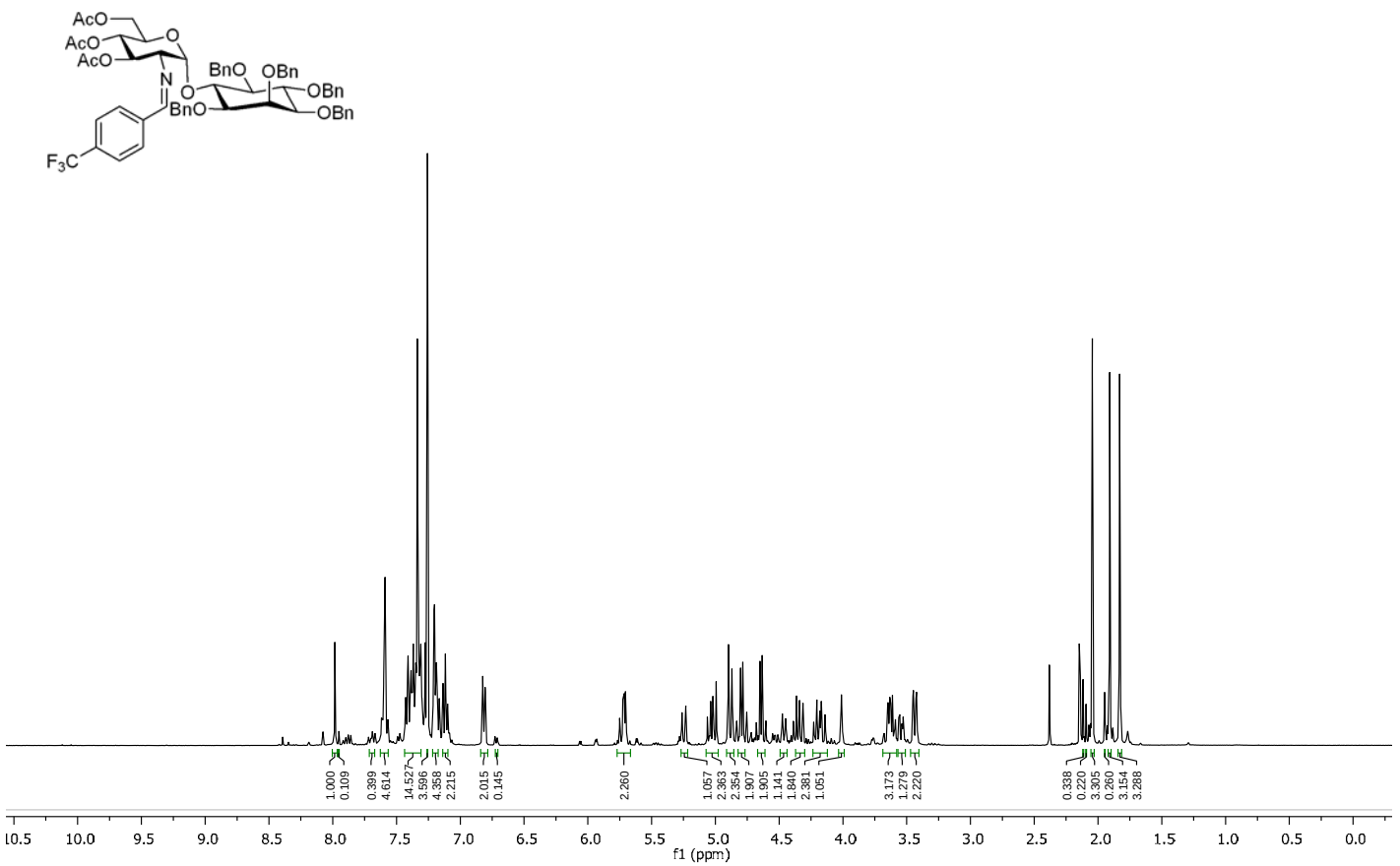


Figure A254. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **238**

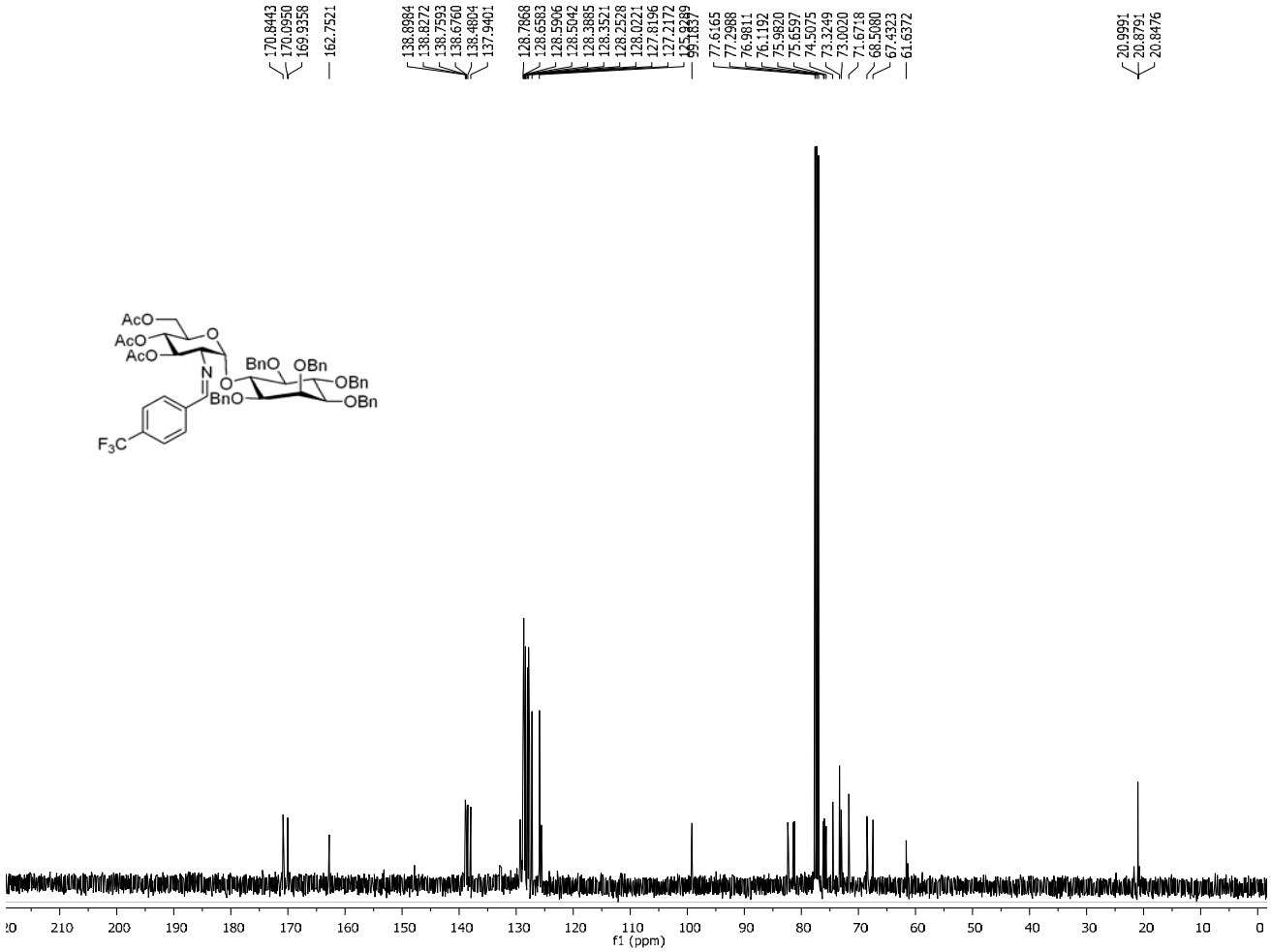


Figure A255. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **238**

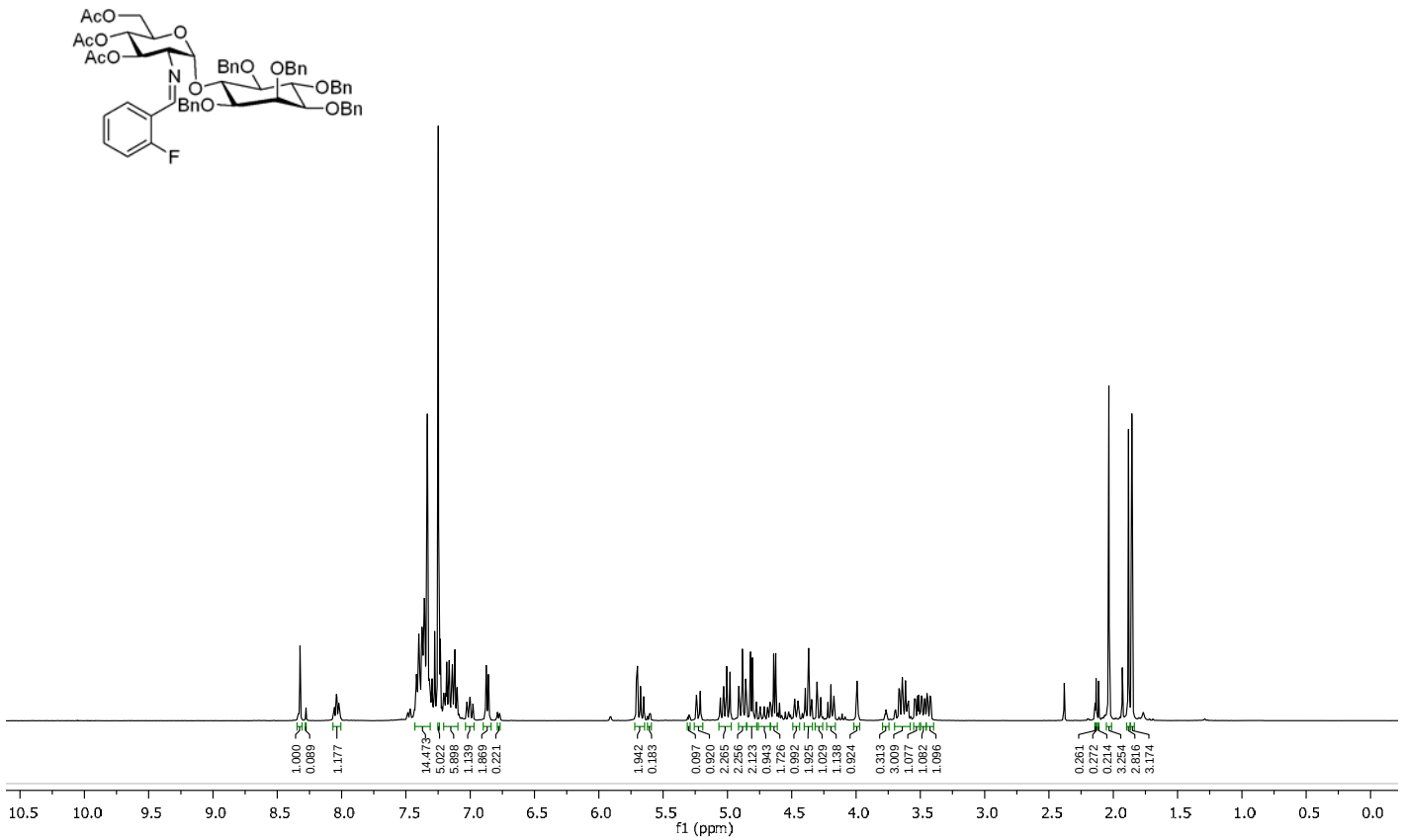


Figure A256. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **239**

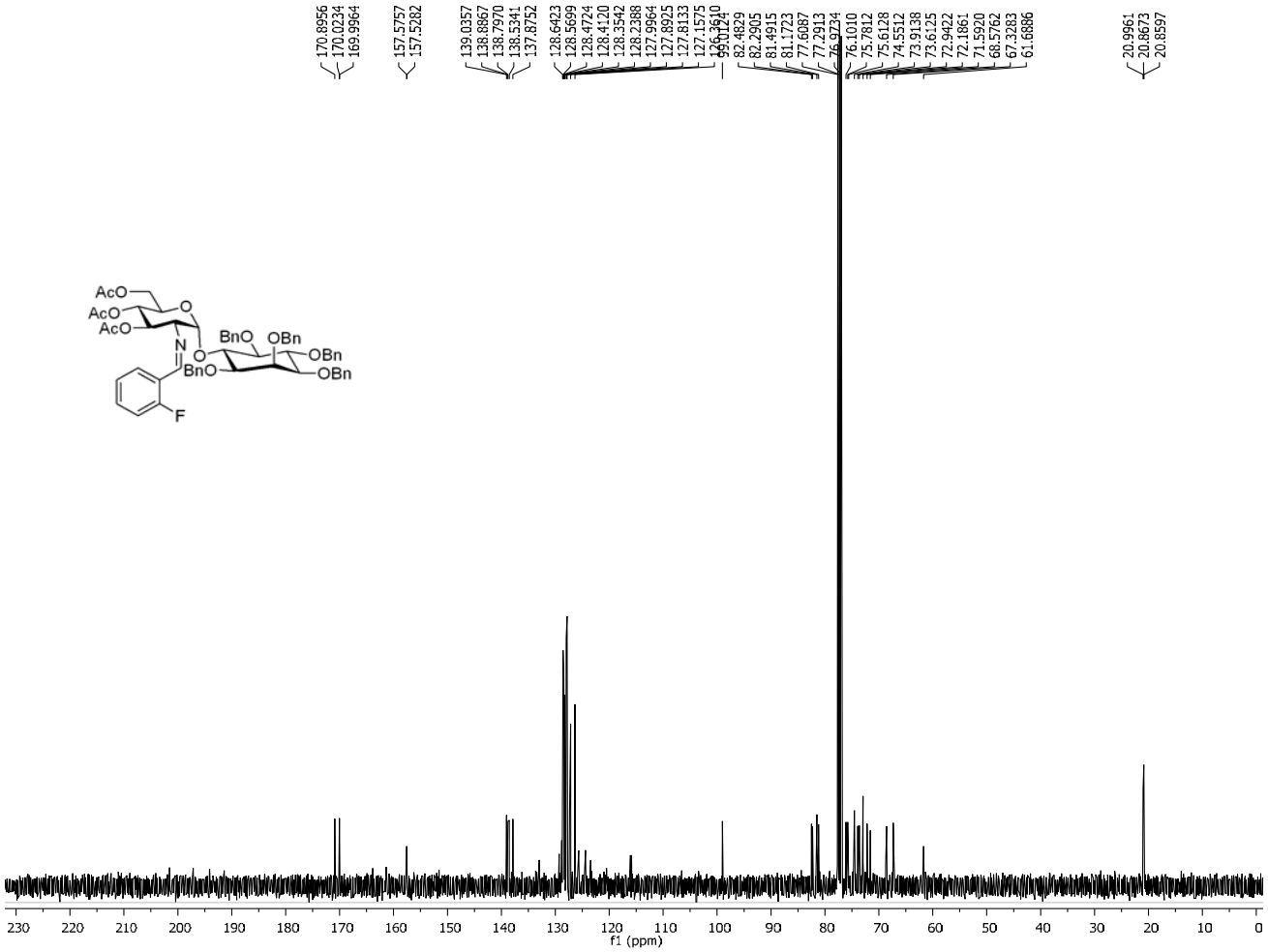


Figure A257. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **239**

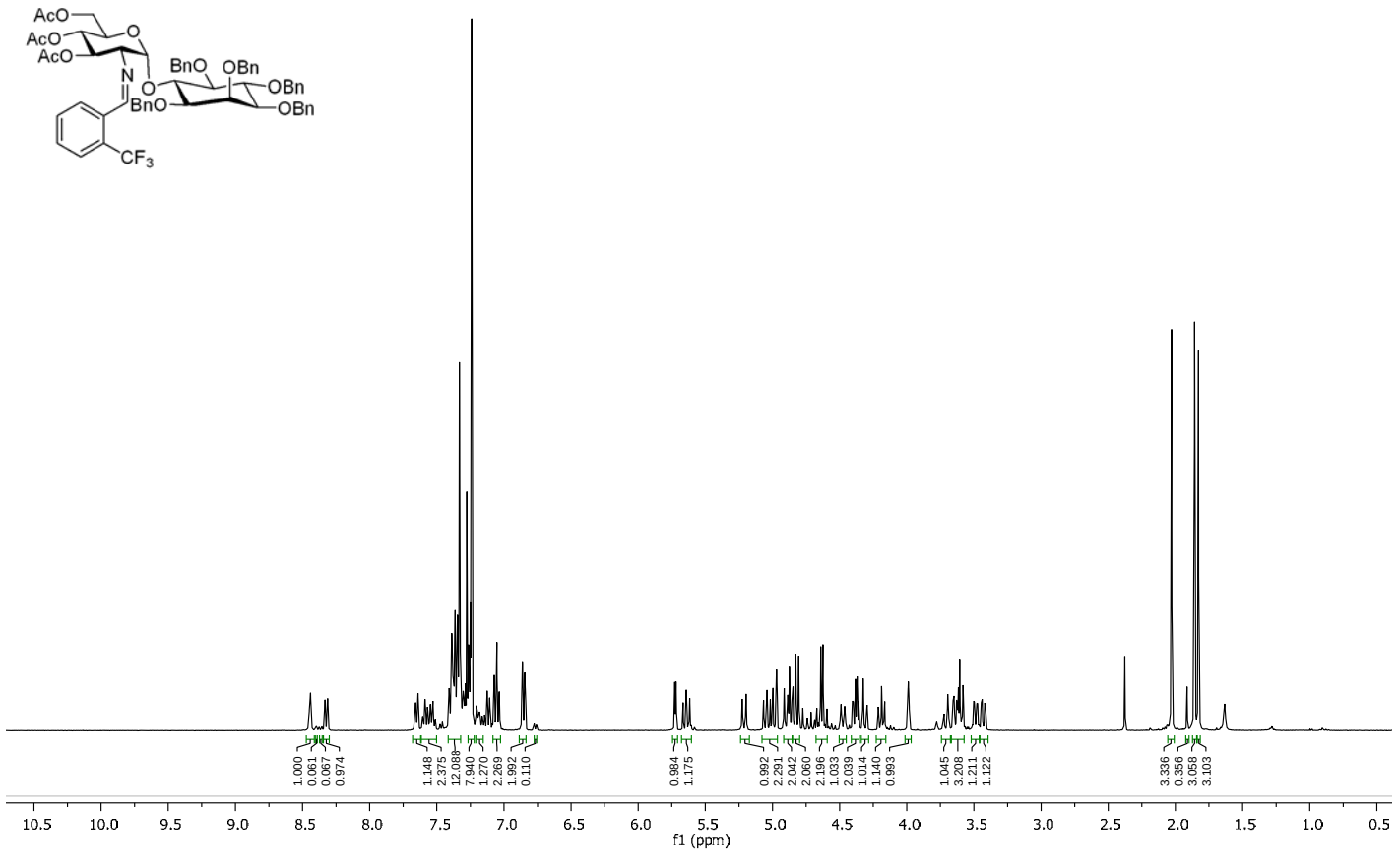


Figure A258. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **240**

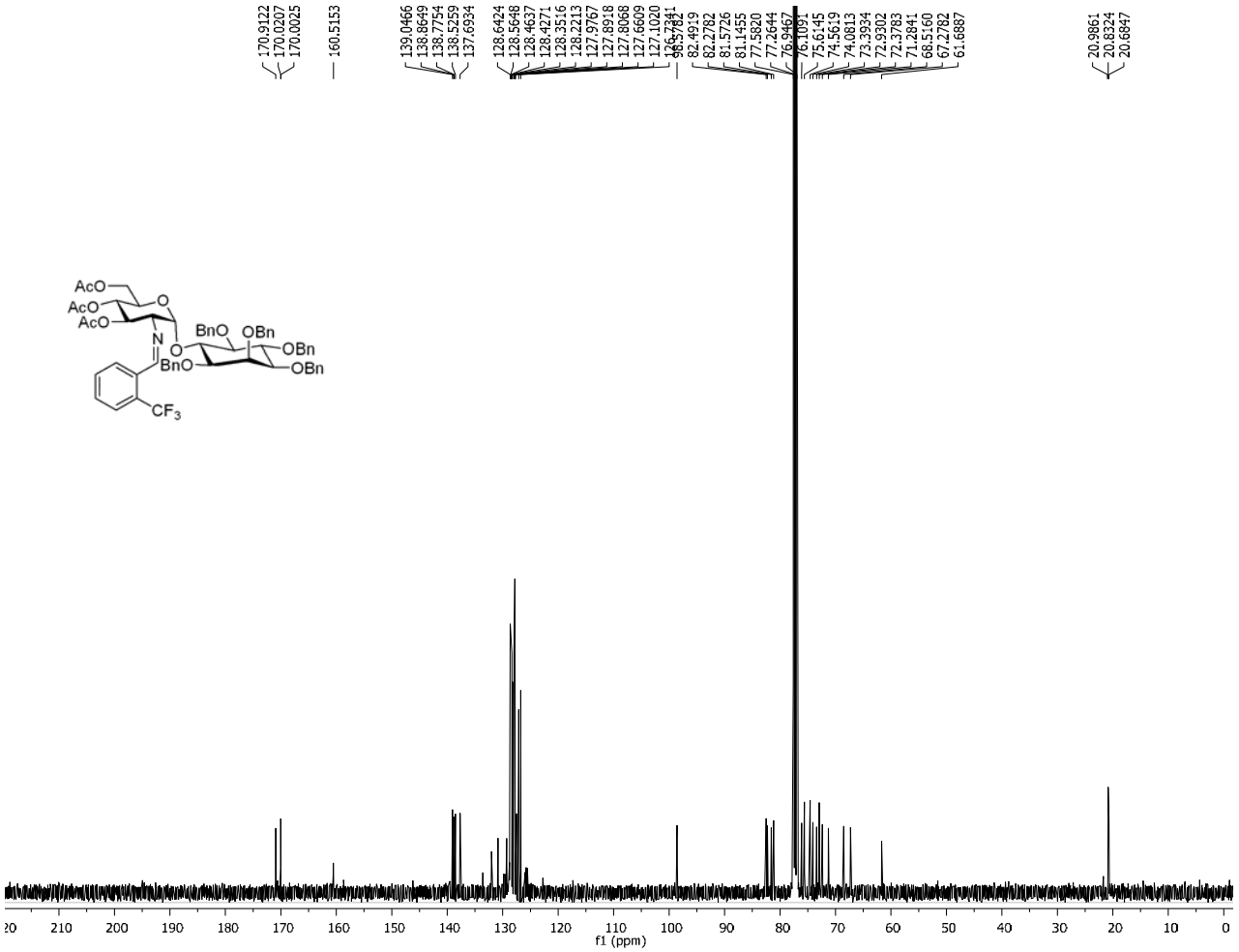


Figure A259. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Pseudodisaccharide **240**

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