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Nickel catalyzed formation of 1,2-cis-2-amino sugars to access important biomolecules

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NICKEL CATALYZED FORMATION OF 1,2-CIS-2-AMINO SUGARS TO ACCESS IMPORTANT BIOMOLECULES

by

Matthew McConnell

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Thesis Supervisor: Associate Professor Hien M. Nguyen

Graduate College
The University of Iowa
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

Matthew McConnell

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
degree in Chemistry at the August 2015 graduation.

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Daniel Quinn

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Leonard R. MacGillivray

_____
Scott Shaw

_____
Horacio Olivo

For my Mom, Dad, and Sister
For all your love, encouragement and support
Finally, I get to join the club

Research is to see what everybody else has seen, and to think what nobody else has thought.

Albert Szent-Gyorgyi

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SCHOLARLY ABSTRACT

The stereoselective formation of 1,2-*cis*-2-amino glycosides remains a challenging obstacle for researchers seeking to study glycan function in nature. A variety of techniques to form α-linked C(2)-aminoglycosides are examined herein. The most prominent of these techniques is the nickel catalyzed stereoselective coupling of C(2)-*N*-benzylidine protected trichloroacetimidates to form 1,2-*cis*-2-amino sugars. This protocol demonstrates excellent α-selectivity and is applicable to a large structural variety of C(2)-aminoglycosyl donors and acceptors.

We also describe the effectiveness of the cationic nickel(II) species, $Ni(4\text{-}F\text{-}PhCN)_4OTf_2$, at catalyzing formation of 1,2-*cis*-2-amino glycosidic bonds between C(2)-*N*-substituted benzylidene trihaloacetimidate donors and *myo*-inositol acceptors under mild conditions, allowing rapid access to pseudosaccharides of glycosylphosphatidyl inositol (GPI) anchors and mycothiol (MSH) in good yield and with excellent α-selectivity (α:β = 10:1 – >20:1). In stark contrast, employing conventional Lewis acids, TMSOTf and $BF_3{\cdot}OEt_2$, to activate trichloroacetimidate donors provided the desired pseudodisaccharides as a 1:1 mixture of α- and β-isomers. Additionally, the facile synthesis of both C(1)- and C(6)-hydroxyl *myo*-inositols bearing differentiated protecting groups from a common and easily attainable intermediate allows access to a wide variety of GPI anchor and MSH pseudosaccharides.

The highly α-selective and scalable synthesis of the Fmoc-protected GalNAc-threonine amino acid and T_N antigen in large quantities is also described. The challenging 1,2-*cis*-2-amino glycosidic bond is addressed through a coupling of threonine residues with C(2)-*N*-*ortho*-(trifluoromethyl)benzylidenamino trihaloacetimidates mediated by $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$. The desired 1,2-*cis*-2-amino glycoside was obtained in large quantities with α-only selectivity and subsequently transformed into the Fmoc-protected GalNAc-threonine and T_N antigen.

With the establishment of 1,2-*cis*-selective synthesis of heparan disaccharides, we sought to develop multivalent inhibitors of heparanase. A model study of protein/glycan interactions, in which various macromolecular architectures were examined, was developed using Concanavalin A as the model protein. Preparations of the highly-ordered monoantennary, homofunctional diantennary, and heterofunctional diantennary glycopolymers of α-mannose and β-glucose were achieved via ring opening metathesis polymerization. Isothermal titration calorimetry measurements of these synthetic glycopolymers with Concanavalin A, which has been reported to bind strongly to α-mannose unit, revealed that heterofunctional diantennary architectures bearing both α-mannose and non-binding β-glucose residues, glucose units, enhanced binding affinity. Despite the presence of non-binding β-glucose unit on the polymer chain, a highly-ordered heterofunctional diantennary glycopolymer (K_a = 16.1 x 10^6 M^{-1}) can effectively bind to Concanavalin A comparably to the homofunctional diantennary mannose glycopolymer (K_a = 30 x 10^6 M^{-1}). The monoantennary mannose glycopolymer (K_a = 7.94 x 10^6 M^{-1}) does not bind to ConA as strongly as the heterofunctional diantennary glycopolymer.

PUBLIC ABSTRACT

The stereoselective formation of 1,2-*cis*-2-amino glycosides remains a challenging obstacle for researchers seeking to study glycan function in nature. A variety of techniques to form α-linked C(2)-aminoglycosides are examined herein. The most prominent of these techniques is the nickel catalyzed stereoselective coupling of C(2)-*N*-benzylidine protected trichloroacetimidates to form 1,2-*cis*-2-amino sugars. This protocol demonstrates excellent α-selectivity and is applicable to a large structural variety of C(2)-aminoglycosyl donors and acceptors.

The application of the nickel catalyzed stereoselective coupling of C(2)-*N*-benzylidine protected trichloroacetimidates toward the synthesis of pseudosaccharides of glycosylphosphatidyl inositol (GPI) anchors and mycothiol (MSH) in good yield and with excellent α-selectivity was also examined. In stark contrast, employing conventional Lewis acids to activate trichloroacetimidate donors provided the desired pseudodisaccharides with poor α-selectivity. Additionally, the facile synthesis of both C(1)- and C(6)-hydroxyl *myo*-inositols bearing differentiated protecting groups from a common and easily attainable intermediate allows access to a wide variety of GPI anchor and MSH pseudosaccharides.

The highly α-selective and scalable synthesis of the Fmoc-protected GalNAc-threonine amino acid and T_N antigen in large quantities is also described. The challenging 1,2-*cis*-2-amino glycosidic bond is addressed through a coupling of threonine residues with C(2)-*N*-*ortho*-(trifluoromethyl)benzylidenamino trihaloacetimidates mediated by $Ni(4\text{-F-PhCN})_4(OTf)_2$. The desired 1,2-*cis*-2-amino glycoside was obtained in large quantities with α-only selectivity and subsequently transformed into the Fmoc-protected GalNAc-threonine and T_N antigen.

With the establishment of 1,2-*cis*-selective synthesis of heparan disaccharides, we sought to develop multivalent inhibitors of heparanase. A model study of protein/glycan

interactions, in which various macromolecular architectures were examined, was developed using Concanavalin A as the model protein. Preparations of the highly-ordered monoantennary, homofunctional diantennary, and heterofunctional diantennary glycopolymers of α-mannose and β-glucose were achieved via ring opening metathesis polymerization. Isothermal titration calorimetry measurements of these synthetic glycopolymers with Concanavalin A, which has been reported to bind strongly to α-mannose unit, revealed that heterofunctional diantennary architectures bearing both α-mannose and non-binding β-glucose residues, glucose units, enhanced binding affinity.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

AcCl	Acetyl chloride
Ac_2O	Acetic anhydride
ACN	Acetonitrile
AcOH	Acetic acid
$AgClO_4$	Silver perchlorate
$AgCO_3$	Silver carbonate
AgOTf	Silver trifluoromethanesulfonate (Silver triflate)
AllylBr	Allyl bromide
$BF_3{\cdot}OEt_3$	Boron trifluoride etherate
BnBr	Benzyl bromide
BnOH	Benzyl alcohol
Boc_2O	Di-*t*-butyl-dicarbonate
Bu_2SnO	Dibutyl tin anhydride
CAN	Ceric ammonium nitrate
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
Cl_3CCN	Tricloroacetonitrile
CsF	Cesium fluoride
CuI	Copper (I) iodide
DBU	1,8-Diaza bicyclo [5.4.0] undec-7-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethylazo dicarboxylate
DIPEA	Diisopropylethyl amine
DMF	*N*,*N*-Dimethylformamide

DTBP	2,6-Di-*tert*-butyl pyridine
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOH	Ethanol
g	Gram
HCl	Hydrochloric acid
$HClO_4$	Perchloric acid
HgCN	Mercury (I) cyanide
HNO_3	Nitric acid
K_2CO_3	Potassium carbonate
KH	Potassium hydride
$LiClO_4$	Lithium perchlorate
LiOH	Lithium hydroxide
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram
mL	Milliliters
mmol	Millimole
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NMA	*N*-Methylaniline
NaN_3	Sodium azide
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
NaOMe	Sodium methoxide
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
NPCC	p-Nitrophenylphosphorylcholine
$Pd(CH_3CN)_4(BF_4)_2$	Palladium (II) tetrakis acetonitrile bis tetrafluoroborate
$PdCl_2$	Palladium (II) chloride
$Pd(OH)_2/C$	Pearlman's catalyst
$Pd(Ph_3P)_4$	Tetrakis triphenylphosphine palladium (0)
Ph_3P	Triphenylphosphine
PhSH	Phenolthiol
PhSCl	Phenyl sulfenyl chloride
Ph_2SO	Diphenyl sulfoxide
PhSOTf	Phenyl sulfenyl triflate
SO_3 * TMA	Sulfur trioxide trimethylamine
$SnCl_4$	Tin (IV) chloride
TBAF	Tetrabutyl ammonium fluoride
TBAI	Tetrabutyl ammonium iodide
tBuOH	*Tert*-butanol
tBuOK	Potassium-*tert*-butoxide
TFE	Trifluoroethanol
TEA	Triethylamine
Tf_2O	Triflic anhydride
TfOH	Triflic acid
TfN_3	Triflyl azide
THF	Tetrahydrofuran
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

$TMSCHN_2$	Trimethylsilyl diazomethane
$TrClO_4$	Trityl perchlorate

CHAPTER 1

INTRODUCTION

1.1: Aminoglycosides: Biological Significance

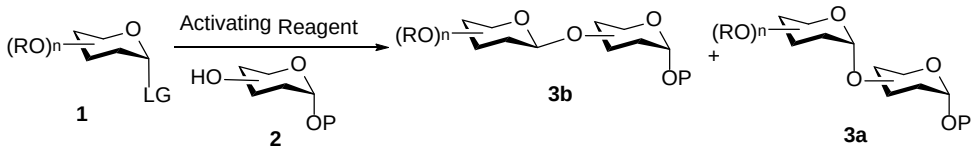
C(2)-aminoglycosides play an important role in a variety of signaling processes in a biological environment.[1] Numerous naturally occurring macromolecules such as proteins and lipids carry covalently attached mono- or oligosaccharide chains typically referred to as glycans.[2] The overall structures of these glycan attached macromolecules are known as glycoconjugates. Many glycans are able to mediate a variety of events in cellular interactions such as cell-cell recognition,[2] cellular transport, adhesion of bacteria, viruses, and toxins because of their position on the outer surface of glycoconjugates. Many of these glycans are typically attached via a glycosidic bond between a protein or lipid and a C(2)-aminoglycoside.[3] Synthetically mimicking the structure of glycans can allow for selective binding of glycan binding proteins that govern important biological processes such as immune response,[4] viral transfection,[5] cancer metastasis,[6] and coagulation processes.[7]

While C(2)-aminoglycosides play a vital role in these processes, the development of chemical glycosylation of C(2)-aminosugars to mimic glycan function is lacking. This is problematic due to the fact that only a small quantity of the biologically active carbohydrate natural products can be obtained from nature, thereby limiting a full evaluation and clinical study. [8-11] Chemical syntheses directed at C(2)-aminoglycosides have advanced the assessment of glycan function, establishment of structure/activity

relationships, elucidation of biosynthetic pathways, development of carbohydrate based vaccines, as well as the development of inhibitors of glycoconjugate function.[12]

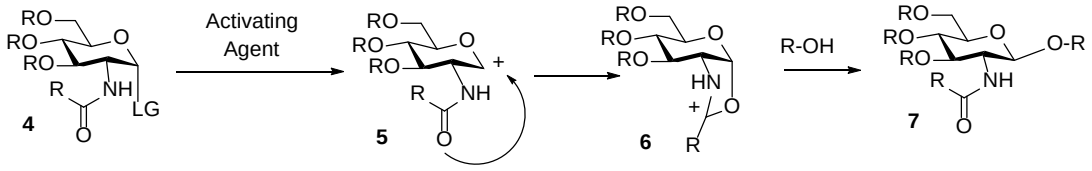
1.2: Glycosylation Methods of C(2)-Aminosugars

Because the vast majority of C(2)-aminosugars found in nature are not in free form but linked to other molecules via the glycosidic bond, researchers have been interested in new glycosylation methodologies. Thus, the most important part of oligosaccharide synthesis is the simple and efficient formation of the glycosidic linkage. The basic anatomy of a glycosylation reaction is presented below (Scheme 1.1).[13,14] A glycosyl donor (an electrophile) **1** with a leaving group at the anomeric position is activated via an activating reagent (typically a Lewis acid promoter) and subsequently coupled with a glycosyl acceptor (a nucleophile) **2** to afford the corresponding disaccharide in either the α- **3a** or β- **3b** stereoisomers. The protecting groups on the resulting disaccharide **3** can then be selectively removed in order to serve as a glycosyl accepter or donor for further coupling.



Scheme 1.1. Disaccharide Synthesis.

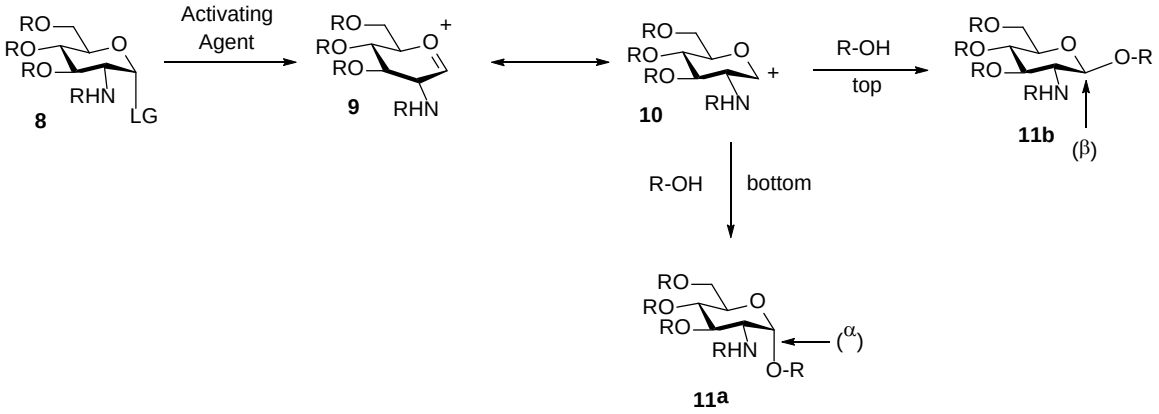
The most important aspect of carbohydrate chemisty is the simple, efficient, and stereoselective formation of glycosidic linkages. In contrast to peptide synthesis, absolute stereocontrol is required in carbohydrate synthesis. Problems with stereoselectivity arise due to the ring oxygen readily stabilizing a resulting oxocarbenium ion at the C(1) position of the glycosyl donor, leading to significant S_N1 character. In relation to C(2)-aminosugars, the two stereochemical outcomes could be considered 1,2-*cis*-2-aminoglycosides (α) or 1,2-*trans*-2-aminoglycosides (β). The stereoselective synthesis of 1,2-*trans*-aminoglycosides can be achieved by using neighboring group participation (Scheme 1.2). The activating agent assisted departure of the leaving group on the glycosyl donor **4** results in carbocation formation **5**. Attack of the acyl oxygen on the bottom face of the carbocation **5** results in the formation of the acyloxonium ion intermediate **6**. The glycosyl acceptor (R-OH) can then react only at the top face of the C(1) position to give 1,2-*trans*-2-aminoglycoside **7**.



Scheme 1.2. Glycosylation With a C(2)-Participatory Protecting Group.

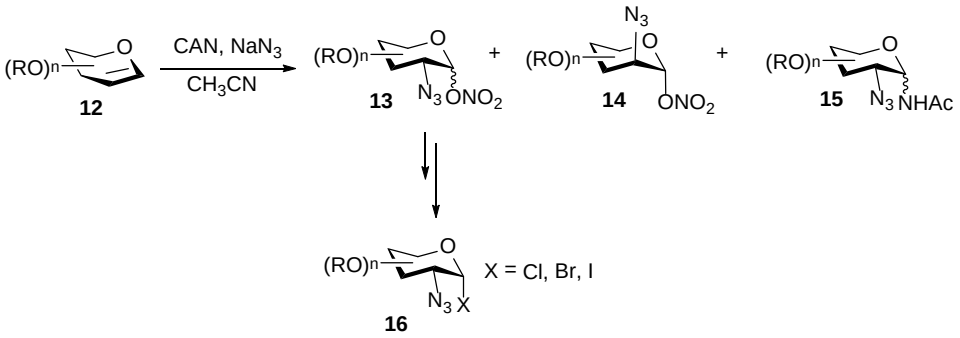
While the synthesis of 1,2-*trans*-2-aminoglycosides can be readily achieved by employing glycosyl donors with a C(2)-participatory protecting group, the synthesis of 1,2-*cis*-2-aminoglycosides remains challenging because it requires glycosyl donors with non-assisting groups at the C(2)-position (Scheme 1.3). Activation of the leaving group

of the glycosyl donor **8** results in the formation of an oxocarbenium ion **9**, which is a resonance form of the carbocation at the C(1) position **10**. Subsequent nucleophilic addition of the glycosyl acceptor (R-OH) can occur from either the top face to give the β-aminoglycoside **11b**, or the bottom face to give the α-aminoglycoside **11a**.



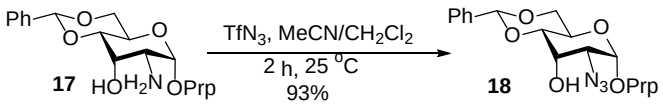
Scheme 1.3. Glycosylation With a C(2)-Nonparticipatory Protecting Group.

While many C(2)-nonparticipatory protecting groups have been examined in efforts to make 1,2-*cis*-2-aminoglycosides, by far the most commonly used protecting group has been the glycosyl azide.[15] While first utilized by Paulsen,[16-18] C(2)-azido glycosyl halides **16** were readily synthesized from the corresponding glycal **12** by Lemieux and coworkers (Scheme 1.4).[19] Azidonitration was performed on the glycal **12** using ceric ammonium nitrate and sodium azide to afford the equatorial C(2)-azido glycosylnitrate intermediate **13** alongside the axial C(2)-azido glycosylnitrate **14** and the C(2)-azido glycosylacetamide **15**. Although **14** and **15** were unwanted side products, **13** was converted into the corresponding C(2)-azido glycosyl halide **16**.



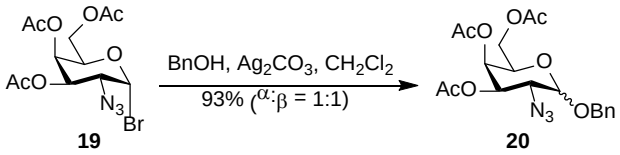
Scheme 1.4. Azidonitration of Glycal **12**.

While **13** is the major product in the case of D-galactal derivatives of **12**, the amount of byproducts **14** and **15** become more significant when D-glucal derivatives were utilized. To overcome this difficulty, diazotransfer conditions of the C(2)-aminosugar to directly give the C(2)-azide with complete retention of stereochemistry were developed by Vaselia and coworkers (Scheme 1.5).[20] In the first example of diazotransfer on a sugar, a glucosamine derivative **17** was mixed with *in situ* generated triflyl azide to give C(2)-glucosylazide **18** in 93% yield. Further examination by the Wong group found that the addition of a catalytic amount of copper (II) sulfate yielded more reproducible diazotransfer conditions.[21]



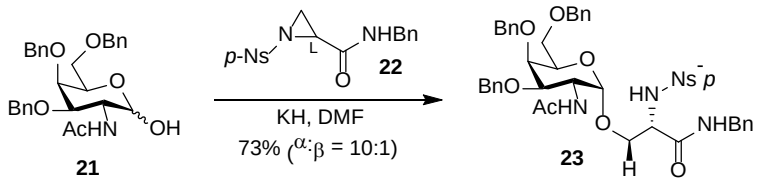
Scheme 1.5. Diazotransfer of Glucosamine Derivative **17**.

Although the use of C(2)-azido glycosyl donors to make 1,2-*cis*-2-aminoglycosides is widespread, stereocontrol of the newly formed glycosidic bond is often absent.[22] For example, Lemieux and co-workers reported the silver carbonate ($AgCO_3$) promoted galactosylation of benzyl alcohol with C(2)-azido galactosyl donor **19** to afford the C(2)-azido galactosides **20** in excellent yield (93%) but poor α-selectivity (α:β = 1:1) (Scheme 1.6).[19] Demchenko determined that in certain cases, α-selectivity can be improved using solvent effects.[23]



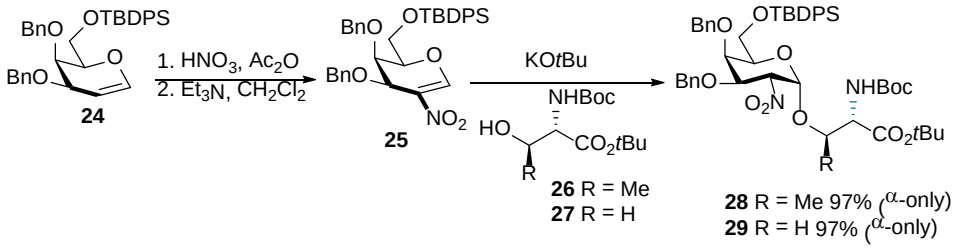
Scheme 1.6. Glycosylation Using C(2)-Azide Donor **19**.

These results have inspired researchers to develop new glycosylation methodologies to synthesize C(2)-aminoglycosides with exclusive α-selectivity. The Gin group has accomplished the stereoselective formation of α-linked tumor associated mucin T_N-antigen derivatives using regioselective ring-opening of aziridine-2-carboxamides using C(1)-*O*-nucleophiles (Scheme 1.7).[24] Nucleophilic attack of the anomeric hydroxyl group of galactosamine **21** on the *p*-nosyl protected L-aziridine **22** gave the 1,2-*cis*-2-aminoglycosyl amino acid **23** in high yield (73%) and excellent α-selectivity (α:β = 10:1). Interestingly, the authors found that varying the solvent from DMF to THF gave almost exclusively β-linked GalNAc-Ser residue.



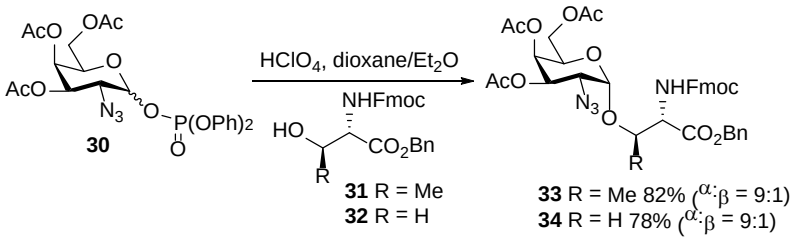
Scheme 1.7. Ring Opening Addition of **21** to Aziridene **22**.

In 2001, Winterfeld and Schmidt prepared α-linked GalNAc-Ser/Thr glycosides using a protected 2-nitrogalactal as the glycosyl donor.[25] The 2-nitrogalactal donor **25** was prepared from the protected galactal **24** using a two step procedure involving installing acetyl nitrate followed by elimination of acetic acid (Scheme 1.8). Conjugate addition of protected threonine **26** and serine **27** amino acids to the donor using potassium *tert*-butoxide gave the T_N-antigens **28** and **29** in excellent yield (97%) of the α-isomer. The authors noted that the sterically demanding *tert*-butyl(diphenyl)silyl ether protecting group installed at the C(6)-position of the donor enhanced reactivity and selectivity.



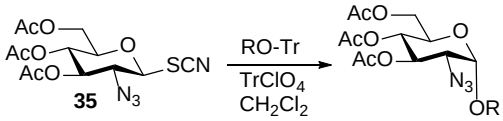
Scheme 1.8. Synthesis and Michael Addition of **25**.

Koshiba also synthesized T_N-antigens using C(2)-azidogalactosyl phosphate ester donors.[26] Glycosyl phosphate **30** was activated using perchloric acid in the presence of Fmoc protected threonine **31** and serine **32** glycosyl acceptors to give the C(2)-azidogalactosyl amino acids **33** and **34** in good yields (**32** = 82%, **34** = 78%) and good selectivity (α:β = 9:1). Interstingly, activation using silyl or metal triflates resulted in poor selectivity.



Scheme 1.9. Glycosylation Using Phosphate Ester Donor **30**.

Kochetkov found that C(2)-azido glycosyl thiocyanates can serve as useful donors for the construction of 1,2-*cis*-aminoglycosides when activated with trityl perchlorate.[27] Entry 1 shows that glycosylation at the C(6)-position of the glycosyl acceptor **36** with C(2)-azido donor **35** gave slightly elevated yield (81%) of the dissacharide **39** when compared to entry 2 and entry 3 in which glycosylation occurs at the C(3) **37** and C(2) **38** positions (Table 1.1). This may be due to the reduced steric encumberance of the C(6) position of acceptor **36**. To explain the α-selectivity, the authors postulate that the reaction proceeds through an S_N2 type mechanism in which attack of the acceptor **42** on the anomeric carbon of the donor **35** and departure of the thiocyanate leaving group to form the disaccharide **43** trityl thioisocyanate **44** are concerted (Scheme 1.10).



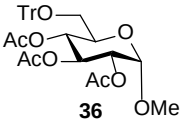
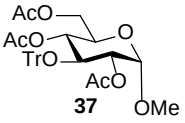
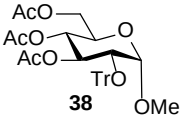
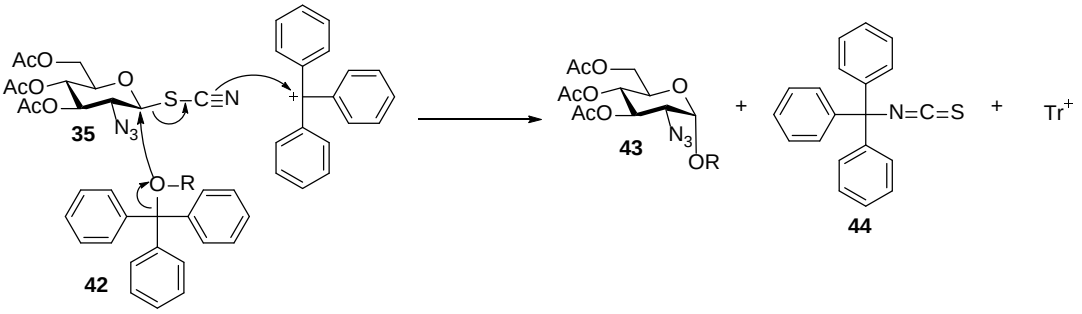
Entry	RO-Tr	Products	Yield (%)	α:β
1		**39**	81	α only
2		**40**	73	α only
3		**41**	72	α only

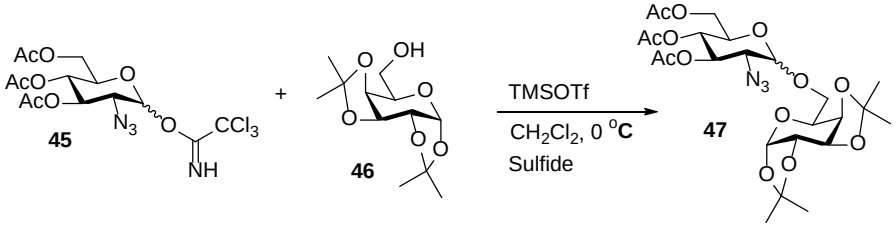
Table 1.1. Glycosylation Using Thiocyanate Donor **35**.



Scheme 1.10. Mechanism of Glycosylation Using Thiocyanate Donor **35**.

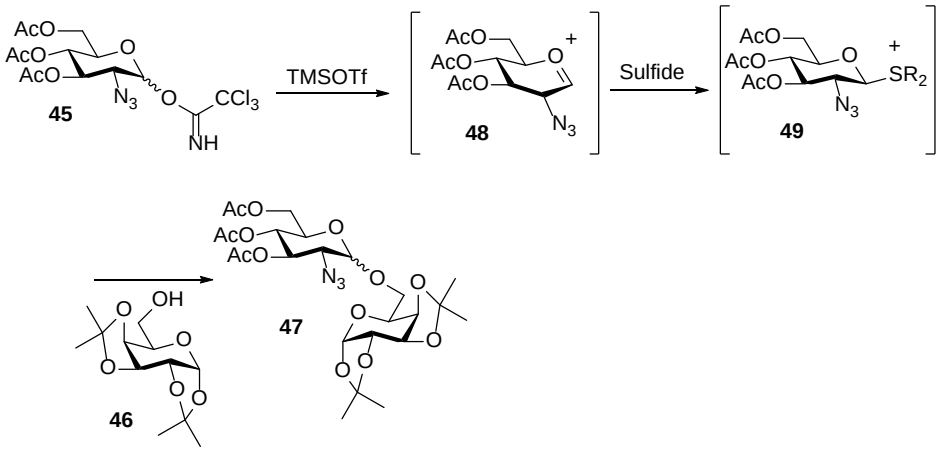
Park found that sulfides can serve as useful additives to facilitate formation of 1,2-*cis*-aminoglycosides from C(2)-azido donors.[28] Glycosylation of acceptor **46** with C(2)-azido donor **45** without sulfide (entry 1) yielded very poor α-selectivity (α:β = 2:1) as expected (Table 1.2). However, glycosylation in the presence of 10 equiv. of phenyl thioethyl ether improved selectivity modestly (α:β = 5:1) (entry 2). A sharp increase in α-selectivity (α:β = 14:1) was observed when thiophene was used as an additive (entry

3). The mechanistic rationale for the increase in α-selectivity is due to nucleophilic displacement of the β-sulfonium intermediate **49** that is generated upon coordination of the sulfide with the oxocarbenium **48** to afford the 1,2-*cis*-2-aminoglycoside **47** (Scheme 1.11).



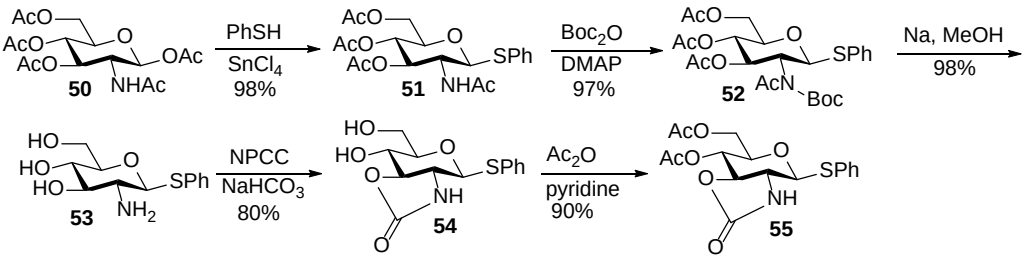
Entry	Sulfide	Yield (%)	α:β
1	None	87	2:1
2	PhSEt	92	5:1
3	Thiophene	95	14:1

Table 1.2. Glycosylation of Acceptor **46** with Sulfide Additives.



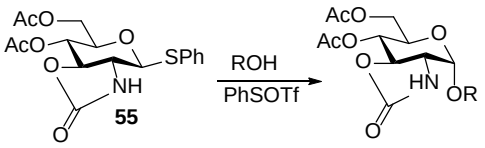
Scheme 1.11. Mechanism of Action of Sulfide Additive.

The Kerns group reported that 2,3-oxazolidinone protected C(1)-arylthioglycosides are useful donors for in preparation of 1,2-*cis*-2-amino sugars.[29] Synthesis of these donors proceeded from simple glucosamine derivative **50** (Scheme 1.12). Glycosylation of phenolthiol (PhSH) with peracetylated glucosamine **50** yielded the C(1)-thioglyoside **51**. Installation of a *t*-butoxycarbonyl (Boc) group on the amine gave the intermediate **53**. Removal of the acetates using sodium and methanol gave the free amine **53**. Treatment of the free amine **53** with *p*-nitro-phenoxycarbonyl chloride followed by acetylation provided the oxazilidinone protected glycosyl donor **55**.



Scheme 1.12. Synthesis of 2,3-Oxazolidinone Donor **55**.

Utilizing phenylsulfenyltriflate to activate the donor **55** gave the 1,2-*cis*-2-aminosugars in high yield (97%) and α-only selectivity (entry 1, Table 1.3). Even a sterically encumbered glycosyl acceptor such as the phthalimide protected C(4)-hydroxyl glucosamine **57**, reacted to form the α-linked disaccharide in high yield (75%). The authors note that the oxazildinone protecting group can then be removed in mildly basic conditions allowing for facile synthesis of deprotected 1,2-*cis*-2-aminoglycosides.



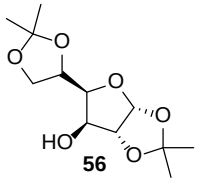
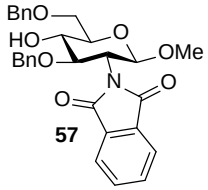
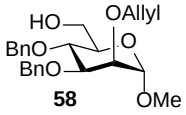
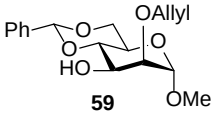
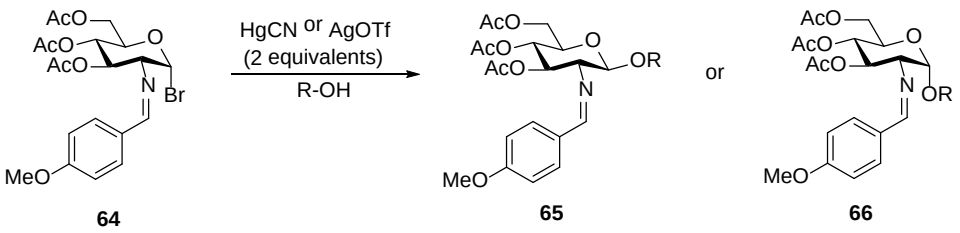
Entry	ROH	Products	Yield (%)	α:β
1		**60**	97	α only
2		**61**	75	α only
3		**62**	90	α only
4		**63**	95	α only

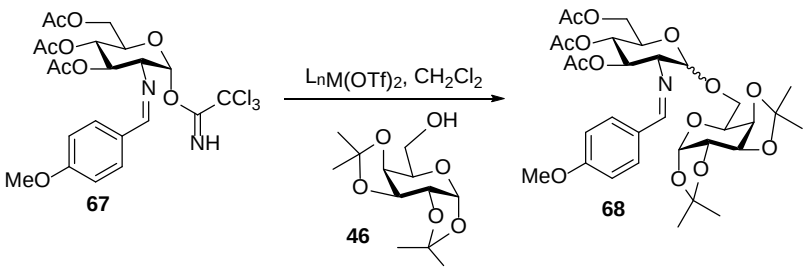
Table 1.3. Glycosylation Using 2,3-Oxazolidinone Donor **55**.

Initially developed by Hardy, the C(2)-*N*-benzylidine non-participatory protecting group has seen use in *cis*-selective glycosylation involving C(2)-aminosugars.[30] Reports of glycosylation using C(2)-*N*-benzylidinamino glycosyl halides **64** as donors, gave either the 1,2-*trans*-2-aminoglycoside[31] **65** or the 1,2-*cis*-2-aminoglycoside[32] **66** depending on the nature of the nucleophile (R-OH) (Scheme 1.13).



Scheme 1.13. Glycosylation Using C(2)-*N*-Benzylidine Donor **64**.

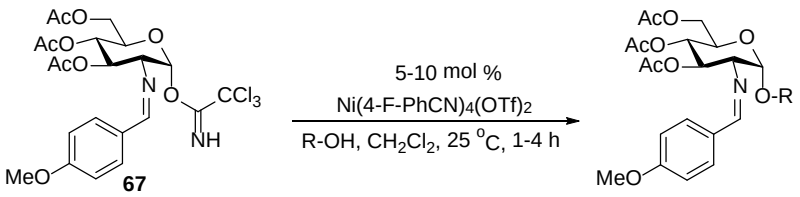
In 2009, Mensah reported the use of C(2)-*N*-benzylidinamino trichloroacetimidate donors to effectively form α-linked C(2)-aminosugars.[33] Cationic transition metal promoters were screened in the glycosylation of alcohol **46** with the imine protected trichloroacetimidate donor **67** (Table 1.4). In each case, the reaction proceeded with a catalytic amount of promoter at or near room temperature. The benzonitrile coordinated palladium (II) triflate $Pd(PhCN)_2(OTf)_2$ gave modest yield (60%) and α-selectivity (α:β = 4:1) (entry 2). Switching to the more nitrophilic nickel catalysts gave markedly increase yields (75 – 95%) and α-selectivities (α:β = 8:1 – 10:1) (entries 3 – 6). $Ni(4\text{-}FPhCN)_4(OTf)_2$ promoted the glycosylation in 3 h reaction time to give highest yield (93%) and α-selectivity (α:β = 10:1) (entry 5).



Entry	Catalyst	Loading	Temperature	Time	Yield	α:β
1	$Pd(PhCN)_2(OTf)_2$	5 mol%	0 °C	15 h	41%	5:1
2	$Pd(PhCN)_2(OTf)_2$	5 mol%	25 °C	6 h	60%	4:1
3	$Ni(PhCN)_4(OTf)_2$	5 mol%	25 °C	4 h	95%	8:1
4	$Ni(4\text{-}CF_3PhCN)_4(OTf)_2$	5 mol%	25 °C	3 h	90%	10:1
5	$Ni(4\text{-}FPhCN)_4(OTf)_2$	5 mol%	25 °C	3 h	93%	10:1
6	$Ni(4\text{-}MeOPhCN)_4(OTf)_2$	5 mol%	25 °C	6 h	75%	10:1

Table 1.4. Catalyst Screening of Glycosylation of **46** with **67**.

The scope of the coupling method using $Ni(4\text{-}FPhCN)_4(OTf)_2$ was then examined using a variety of primary, secondary, and tertiary alchohols (Table 1.5).[33] The desired 1,2-*cis*-2-aminosugars were obtained in excellent yields (73 – 97%) and selectivities (α:β = 10:1 - α only). The glycosylation of primary alcohol **69** gave the disaccharide **75** in high yield (78%) and α-selectivity (α:β = 15:1) (entry 1). When the secondary alcohol **71** was glycosylated with **67** the product **77** formed in excellent yield (97%) and complete α-selectivity (entry 3). When dihydrocholesterol was examined as a glycosyl acceptor **72**, the glycoconjugate **78** was obtained in good yield (85%) and stereoselectivity (α:β = 11:1) (entry 4). Coupling of the protected L-threonine derivative **73** with trichloroimidate **67** provided the the 1,2-*cis*-2-aminoglycopeptide in good yield (73%) and α-selectivity (α:β = 10:1) (entry 5). Using a C(2)-azide trichloroacetimidate donor in the glycosylation of **73** resulted in poor stereoselectivity (α:β = 2.5:1).[34]



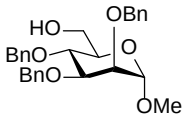
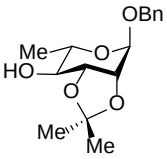
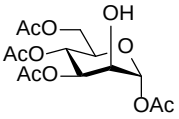
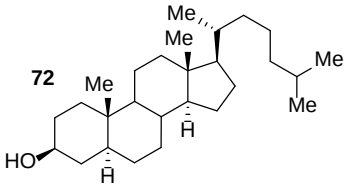
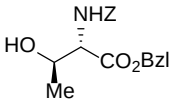
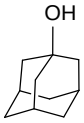
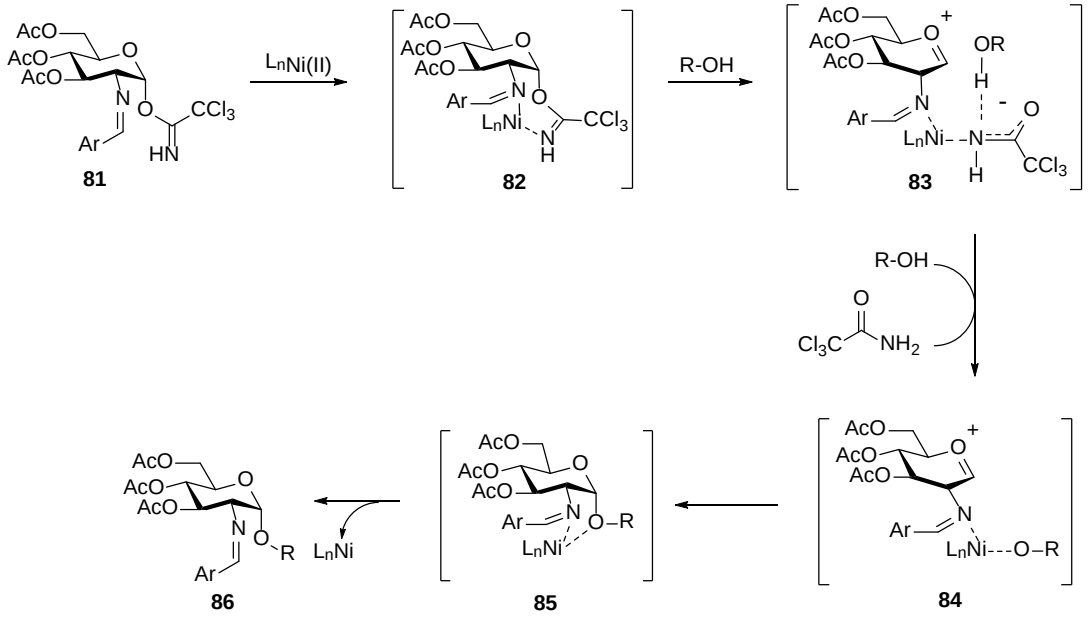
Entry	ROH	Products	Yield (%)	α:β
1	**69** 	**75**	78	15:1
2	**70** 	**76**	93	12:1
3	**71** 	**77**	97	α only
4	**72** 	**78**	85	11:1
5	**73** 	**79**	73	10:1
6	**74** 	**80**	96	17:1

Table 1.5. Glycosylation of Various Acceptors with Donor **67**.

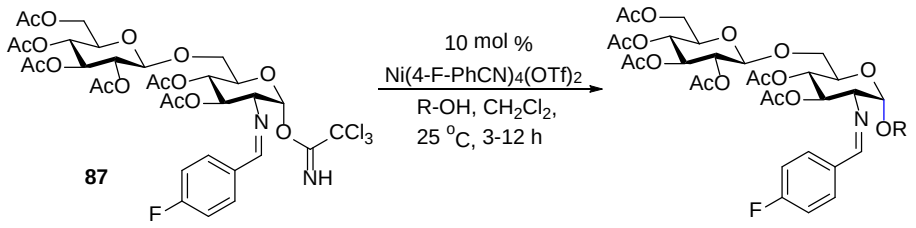
The authors proposed a mechanism for the α-selectivity (Scheme 1.14).[33] Reversible coordination of both the imidate nitrogen and the imine nitrogen of **81** resulted in the seven membered ring complex **82**. Hydrogen bonding of the incoming nucleophile promotes activation of the complex **82** to form the ion pair **83**. Subsequent

ligand exchange results in the Ni coordinated acceptor complex **84** which promotes attack of the nucleophilic oxygen on the α-face of oxocarbenium to form the five membered ring **85**. Disassociation of the nickel catalyst results in 1,2-*cis*-2-aminoglycoside **86** formation.



Scheme 1.14. Mechanistic Rationale for Nickel Catalyzed Glycosylation of Trichloroimidate **81**.

The cationic nickel catalyzed glycosylation methodology using C(2)-*N*-benzylidinamino trichloroimidates was expanded in 2010 to disaccharide donors in order to demonstrate the feasibility of oligosaccharide synthesis using the nickel catalyst (Table 1.6).[35]



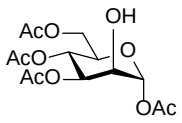
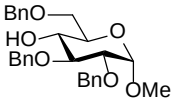
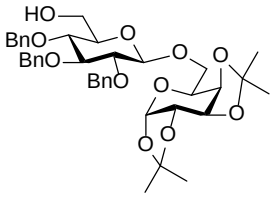
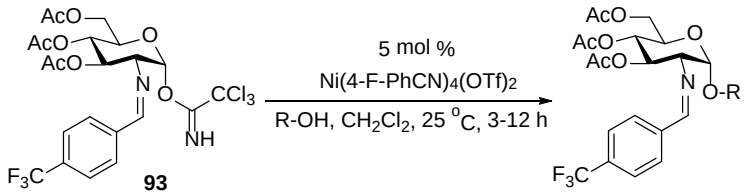
Entry	ROH	Products	Yield (%)	α:β
1	**71** 	**90**	70	24:1
2	**88** 	**91**	67	6:1
3	**89** 	**92**	72	11:1

Table 1.6. Glycosylation with Disaccharide Donor **87**.

Acceptor **71** was glycosylated with disaccharide donor **87** to give trisaccharide **90** in excellent yield (70%) and α-selectivity (α:β = 24:1) (entry 1). A more modest yield (67%) and α-selectivity (α:β = 6:1) was obtained when the more sterically hindered acceptor **88** was glycosylated with donor **87** (entry 2). A [2 + 2] convergent synthesis of α-linked tetrasaccharide **92** using $Ni(4\text{-}FPhCN)_2(OTf)_2$ to glycosylate disaccharide **89** with donor **81** was reported in good yield (72%) and selectivity (α:β = 11:1). Alongside disaccharide donors, glycosylation of disaccharide acceptors was also examined (Table 1.7).[35]



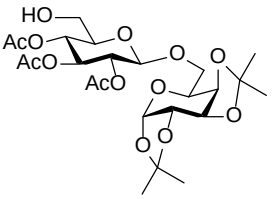
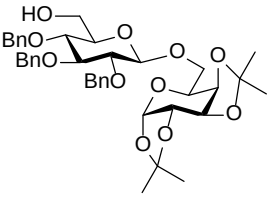
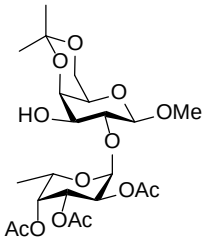
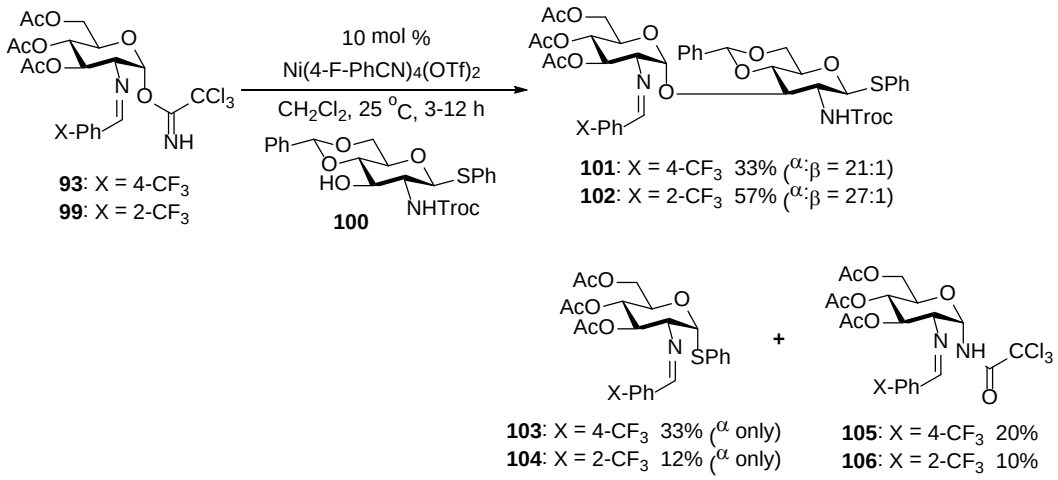
Entry	ROH	Products	Yield (%)	α:β
1	**94** 	**96**	57	13:1
2	**89** 	**97**	70	14:1
3	**95** 	**98**	76	11:1

Table 1.7. Glycosylation of Disaccharide Acceptors.

Glycosylation of tri-*O*-acetyl disaccharide acceptor **94** with C(2)-*N*-4-trifluoromethyl-benzylidine trichloroimidate **93** resulted in modest yield (57%) and good selectivity (α:β = 13:1) (entry 1). Switching to the more electron rich disaccharide nucleophile **89** gave the trisaccharide product **97** in better yield (70%) and selectivity (α:β = 14:1). When a disaccharide acceptor bearing a secondary hydroxyl group **95** was glycosylated with donor **93**, the trisaccharide **98** was obtained in high yield (76%) and good α-selectivity (α:β = 11:1). These results demonstrate the high utility and efficiency

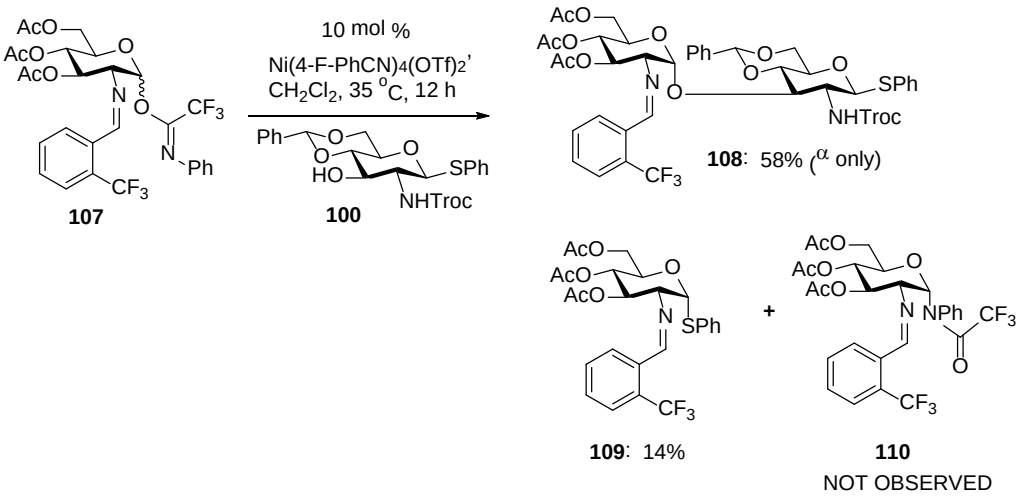
of 1,2-*cis*-2-aminoglycoside formation using $Ni(4\text{-}FPhCN)_4(OTf)_2$ in conjungtion with C(2)-*N*-benzylidinamino trichloroimidates.

It was demonstrated that this method could be used to glycosylate thioglycoside acceptors in high yield and α-selectivity with minimal aglycon transfer.[36] Initial studies using C(2)-*p*-trifluoromethyl- **93** and C(2)-*o*-2-trifluoromethyl-*N*-benzylidine trichloroacetimidate **99** as donors in the glycosylation of thioglycoside acceptor resulted in a complex mixture of the disaccharide **101**, **102**; aglycon transfer **103, 104**; and rearrangement products **105**, **106** (Scheme 1.15).



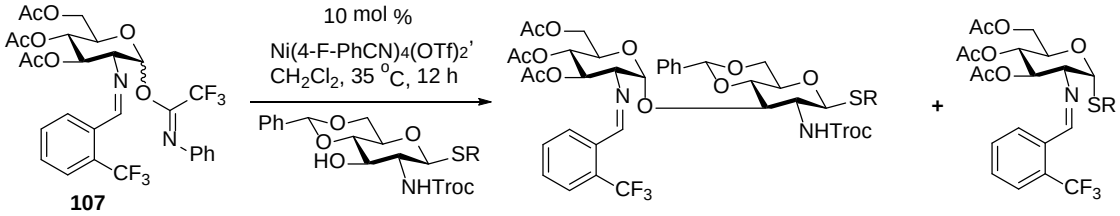
Scheme 1.15. Glycosylation of Thioglycoside **100** with Trichloroacetimidates **93** and **99**.

To avoid obtaining the rearrangement byproduct, glycosylation of thioglycoside **100** with the analogous *N*-phenyl-trifluoroacetimidate donor **107** was explored using similar conditions (Scheme 1.16). Not only was the rearrangement product not formed, but a significant improvement in α-selectivity was observed as well.



Scheme 1.16. Glycosylation of Thioglycoside **100** with *N*-Phenyl-Trifluoroacetimidate **107**.

By varying the steric and electronic effects of the aryl substituent of the thioglycoside, the authors were able to minimize the amount of aglycon transfer observed (Table 1.8).[36] Glycosylation of the electron rich thioglycoside **114** bearing a 4-MeOPh group significantly increased the amount of aglycon transfer product **128** (30%) observed (entry 4). However, thioglycosides bearing an electron poor aryl substituent (entries 5-7) nearly blocked aglycon transfer and increased α-selectivity. The ideal acceptor was identified to be the 2-CF_3-Ph substituted thioglycoside **117**. Glycosylation of **117** provided the disaccharide in good yield (61%) as the α-only isomer with no aglycon transfer product **131** observed. These results demonstrate that this methodology not only orthogonally activates *N*-phenyl-trifluoroimidates over aryl thioglycosides, but controls the α-selectivity as well.



Entry	R	Disaccharide Yield (%) (α:β)	Aglycon Transfer Yield (%)
1	**111**: R = Et	**118**: 43 (10: 1)	**125**: 22
2	**112**: R = 1-Napthyl	**119**: 59 (α only)	**126**: 10
3	**113**: R = 4-Me-Ph	**120**: 38 (11:1)	**127**: 20
4	**114**: R = 4-MeO-Ph	**121**: 37 (11:1)	**128**: 30
5	**115**: R = 4-F-Ph	**122**: 58 (20:1)	**129**: 9
6	**116**: R = 2-F-Ph	**123**: 60 (α only)	**130**: 4
7	**117**: R = 2-CF_3-Ph	**124**: 61 (α only)	**131**: 0

Table 1.8. Glycosylation of Various Thioglycosides with Donor **105**.

1.3: Conclusion

Three criteria are necessary for development of an effective 1,2-*cis*-2-amino glycosylation methodology. First is that the reaction must be highly α-selective in the presence of a diverse array of glycosyl donors and acceptor nucleophiles. The second criteria is that the reaction must proceed under mild conditions that will not affect pH or temperature sensitive protecting groups. Third is that the reaction uses a catalytic amount of activating reagent to minimize wasteful biproducts. While many methodologies exist to provide α-aminoglycosides, only the $Ni(4\text{-}PhCN)_4(OTf)_2$ catalyzed glycosylation using C(2)-*N*-benzylidinamino imidates fits all three criteria. Further chapters will

explore the application of this methodology to synthesize biologically important carbohydrates.

CHAPTER 2

NICKEL-CATALYZED GLYCOSYLATION OF C(1)-HYDROXYL D-*MYO*-INOSITOL: A FORMAL SYNTHESIS OF MYCOTHIOL

2.1: Background

Mycothiol (MSH) (**132**, Figure 2.1), isolated from *Streptomyces* sp. AJ9463,[37] is a protective low molecular weight thiol present in *Mycobacterium tuberculosis* and other actinomycetes.[37] Mycothiol is used by mycobacteria for defense against foreign electrophilc agents such as oxidants, radical, and drugs.[38-39] Since mycothiol was discovered in the 1990s,[40] extensive efforts have been focused on the identification of its biosynthesis and its role in oxidative stress.[41-45] Disruption of mycothiol's metabolic pathways is fatal to *Mycobacterium tuberculosis*, the tuberculosis causative agent. Because *M. tuberculosis* has developed resistance to many therapies at an alarming rate, development of an efficient strategy for the synthesis of mycothiol analogs can provide a promising platform for rational drug design in fighting tuberculosis.[46-51]

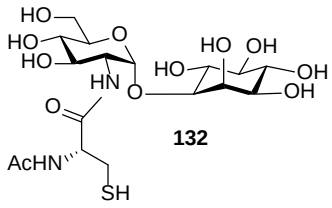
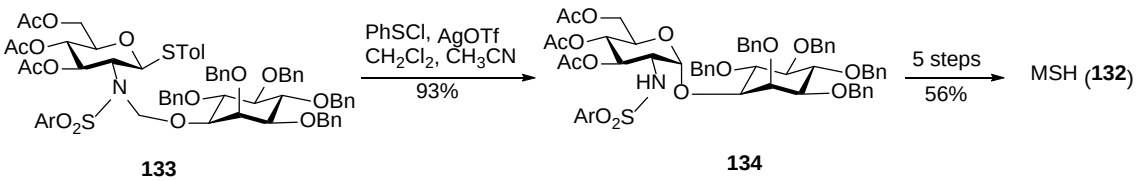


Figure 2.1. Mycothiol (MSH).

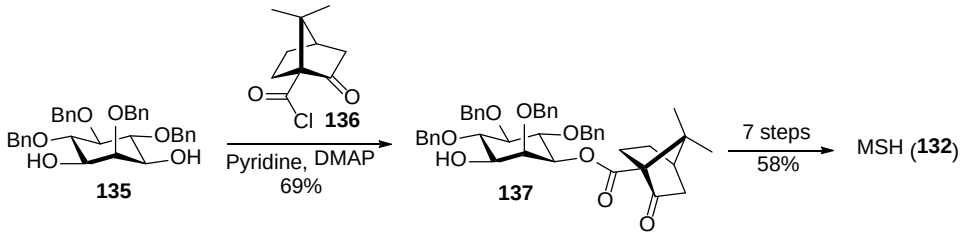
Currently, one liter of the *M. smegmatis* cell culture produces less than 1.5 mg of mycothiol.[52] This limited availability has prompted a number of synthetic efforts.[53-57] There are several challenges to be addressed in the chemical synthesis of MSH: 1) selective preparation of the C(1)-hydroxyl group of D-*myo*-inositol unit, 2) prevention of epimerization of cysteine residue, and 3) α-selective formation of the glycosidic linakge. A number of elegant approaches to prevention of cysteine epimerization and regioselective inositol protection have been reported in several syntheses. However, the stereocontrolled formation of α-glycosidic linkage that connects D-glucosamine residue to inositol remains underdeveloped. The current systems provide the desired pseudo-disaccharide of MSH in poor to moderate selectivity (α:β = 1:1 – 6:1).[55-57]

In 2010, Ajayi demonstrated the α-selective synthesis of mycothiol via an intramolecular α-glucosaminidation strategy.[53] Electrophilic activation of the thioglycoside portion of a protected inositol tethered (*N*-arylsulfonyl)glucosamine donor provided the pseudodisaccharide in excellent yield (93%) exclusively as the α-isomer (Scheme 2.1). The pseudodisaccharide was then converted to MSH in good yield (56%) over five steps.



Scheme 2.1. Intramolecular Glucosaminidation of **133**.

Chung reported the total synthesis of mycothiol in 2011, with the desymmetrization of 2,4,5,6-tetra-*O*-benzyl-D-*myo*-inositol **135** to form the ketopinyl C(1)-hydroxyl inositol **137** as the key step (Scheme 2.2).[54] Coupling of ketopinyl chloride **136** with the 1,3-diol **135** resulted in the C(3)-ketopinate **137** being the major product (63%). The authors note that the C(3)-ketopinate **137** was seperable by silica gel column chromatography. From the key intermediate **137**, total synthesis of MSH was accomplished in 7 steps with a good overall yield (58%).



Scheme 2.2. Desymmetrization of Diol **135**.

Herein, we address current challenges associated with MSH synthesis. This includes development of efficient routes to C(1)- and C(6)-hydroxyl *myo*-inositols from a common starting materials, as well as α-selective formation of the 1,2-*cis*-2-amino pseudosaccharide moieties of MSH using our nickel-catalyzed stereoselective glycosylation method. We proposed to employ building blocks such as D-glucosamine imidate donor **138**,[33, 35-36] inositol acceptor **140**,[58] and cysteine residue **139** (Figure 2.2).[53] The use of these units will allow for efficient preparation of a variety of mycothiol analogs with minimal additional effort.

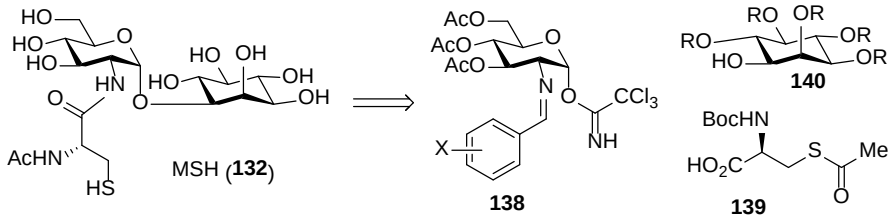
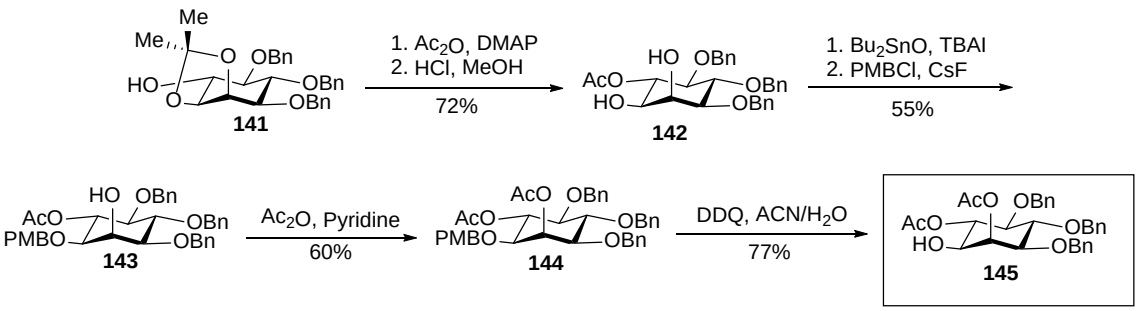


Figure 2.2. Retrosynthetic Analysis of MSH.

2.2: Results and Discussion

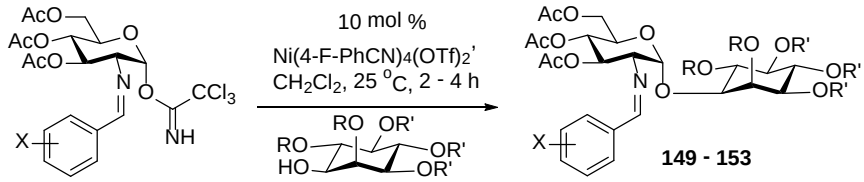
Efficient access to the C(1)-hydroxyl *myo*-inositols will pave the way for preparation of a variety of MSH. To balance the steric and electronic properties of *myo*-inositols for use as glycosyl acceptors in the formation of pseudodisaccharides of MSH,[18d] we choose to protect the C(2)- and C(6)-hydroxyl groups with the acetyl groups (Scheme 2.3). Our synthetic route commenced with an acetyl group being installed onto the C(6)-hydroxyl group of **141**, after which the isopropylidene was removed under acidic conditions, yielding diol **142** in 72% yield over 2 steps. The less sterically encumbered C(1)-hydroxyl of **142** reacted selectively with *p*-methoxybenzyl chloride with the aid of dibutyl tin oxide to form the C(2)-hydroxyl inositol **143** in 55% yield. The C(2) hydroxyl group was then acetylated to form **144** (Scheme 2.3). Finally removal of the PMB protecting group on the C(1)-hydroxyl group with DDQ afforded C(1)-hydroxyl *myo*-inositol **145** in 77% yield.



Scheme 2.3. Synthesis of C(1)-Hydroxyl *myo*-Inositol **145**.

In formulating a reaction design for an α-glycosylation that proceeds with high yield and selectivity, we first explored the coupling of peracetylated inositol **147** (Table 2.1, entry 1) with C(2)-*N*-(4-trifluoromethyl)benzylideneamino trichloroacetimidate **93**. We chose to examine this with donor **93** because it is an effective imidate under nickel conditions.[33, 35] The reaction proceeded with 10 mol% of $Ni(4\text{-F-PhCN})_4(OTf)_2$ to provide the desired pseudodisaccharide **149** (entry 1) in 63% yield and with good α-selectivity (α:β = 8:1). To improve the coupling efficiency and selectivity, the more electron-donating perbenzylated inositol **148** (entry 2) was investigated as the glycosyl acceptor. Unfortunately, the coupling product **150** was not observed. We reasoned that the glycosylation did not proceed because inositol **148** was too sterically hindered to react with donor **93**. Thus, a less hindered and partially reactive inositol **145** (Table 2.1, entry 3) was then explored. Pseudodisaccharide **151** was isolated in 60% yield and with an excellent α-selectivity (α:β = 20:1). A significant decrease in α-selectivity (α:β = 20:1 → 14:1) and yield (66 → 54%) was observed when the coupling process was further examined with another electron-withdrawing benzylidene donor **146** (entry 4), C(2)-*N*-4-fluoro-benzylideneamino trichloroacetimidate. Switching to the C(2)-*N*-(2-

trifluoromethyl)benzylideneamino donor **99** (entry 5) led to the improved yield of the coupling product (66 → 94%).

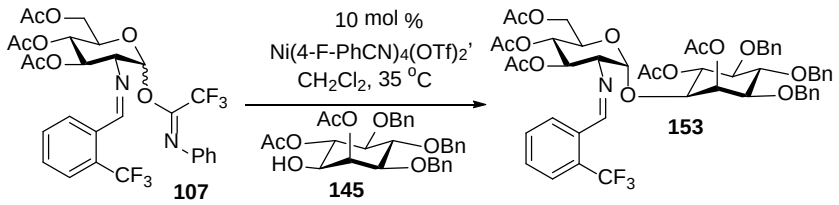


Entry	Donors	Inositols	Products	Yield (%)[b]	α:β[c]
1	**93:** X = 4-CF_3	**147:** R = R' = Ac	**149**	63	6:1
2	**93:** X = 4-CF_3	**148:** R = R' = Bn	**150**	NR	–
3	**93:** X = 4-CF_3	**145:** R = Ac, R' = Bn	**151**	66	20:1
4	**146:** X = 4-F	**145:** R = Ac, R' = Bn	**152**	54	14:1
5	**99:** X = 2-CF_3	**145:** R = Ac, R' = Bn	**153**	94	20:1

[a] All reactions were performed with 1.2 equiv. of inositol. [b] Isolated yield. [c] 1H NMR ratio.

Table 2.1. Initial Studies with Trichloroimidates.[a]

Although α-trichloroacetimidate **99** (Table 2.1, entry 5) was the most effective donor, it was a minor isomer resulting from the reaction of hemiacetal with trichloroacetontrile (α:β = 1:3). Unfortunately, the major β-isomer of **99** did not undergo glycosylation with inositol **145** in the presence of the nickel catalyst, Ni(4-F-PhCN)$_4$(OTf)$_2$, even though the reaction was allowed to stir for a prolonged period. To further improve the efficiency of the glycosylation, *N*-phenyl trifluoroacetimidate **107**[59-61] (Table 2.2) was explored as the glycosyl donor.



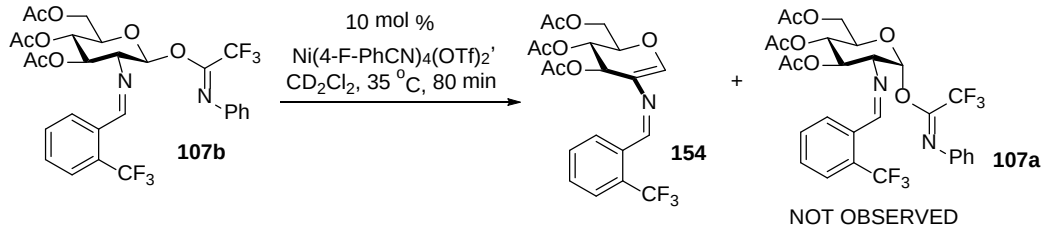
Entry	Imidate Donor	Time (h)	Yield (%)[b]	α:β[c]
1	**107a**	4	77	α only
2	**107b**	4	48	α only
3	**107b**	12	81	α only
4	**107**	18	78	α only

[a] All reactions were performed with 1.5 equiv. of imidate. [b] Isolated yield. [c] 1H NMR ratio.

Table 2.2. Studies with *N*-Phenyl Trifluoroacetimidate **107**.[a]

Because **107** was a less reactive donor than trichloroacetimidate **99**, the reaction was performed at 35 °C. Gratifyingly, it was found that both α- and β-isomers of imdate **107** (entries 1–3) reacted to provide exclusively α-pseudodisaccharide **153**. We hypothesize that because the β-isomer **107b** reacted much slower than its α-isomer counterpart **107a** (entry 1 vs. entry 2), the desired coupling product **153** was obtained in much lower yield (48% vs. 77%). Prolonged glycosylation time allowed β-isomer **107b** to undergo full conversion at 12 h (entry 3), providing **153** in good yield (81%). Based on these results, a mixture of α- and β-isomers **107** (entry 4) was then employed in the reaction, affording **153** in 78% yield and with complete α-selectivity.

To determine if β-isomer imidate **107b** undergoes anomerization to the corresponding α-iosmer prior to the coupling process, β-isomer **107b** was subjected to the nickel conditions in the absence of inositol **145** (Scheme 2.4).



Scheme 2.4. Formation of Elimination product **154**.

^{1}H NMR scans of the reaction mixture at 10 min intervals showed no isomerization of the β-isomer **107b** to the α-isomer **107a**, only direct conversion of **107b** to the elimination product **154** (Figure 2.3). This result suggests that the β-trifluoroimidate **107b** is directly activated by the Ni(4-F-PhCN)$_4$(OTf)$_2$ catalyst to couple with the C(1)-hydroxyl inositol **145** to form the α-linked pseudo-disaccharide **153**.

With optimized conditions and glycosyl donor and acceptor identified, we explored the scope of the nickel-catalyzed α-selective glycosylation with a wide variety of monosaccharide and disaccharide *N*-phenyl trifluoroacetimidate donors **155-159** (Table 2.3). Coupling of the C(1)-hydroxyl group of inositol **145** with tribenzoylated substrate **155** provided pseudodisaccharide **160** (entry 1) in comparable yield (55%) and α-selectivity (13:1) to that of triacetylated donor **107** (Table 2.2). The utility of the current α-glycosylation strategy was also investigated with the galactosamine donors **156** and **157**[33, 35-36] (entries 2 and 3) to evaluate the substrate and protecting group tolerance of the present nickel catalysis. Gratifyingly, the corresponding pseudodisaccharides **161** and **162** were obtained in good yields (56–85%) and with good α-selectivty.

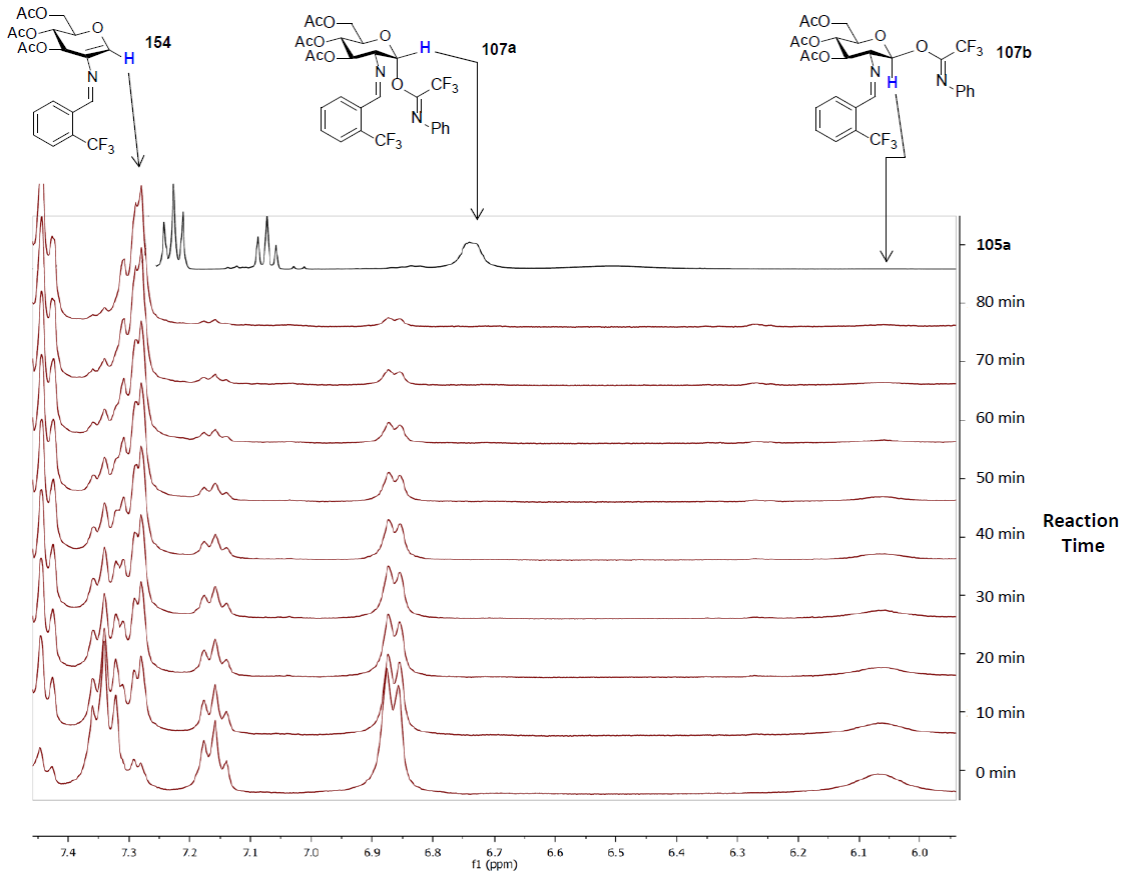
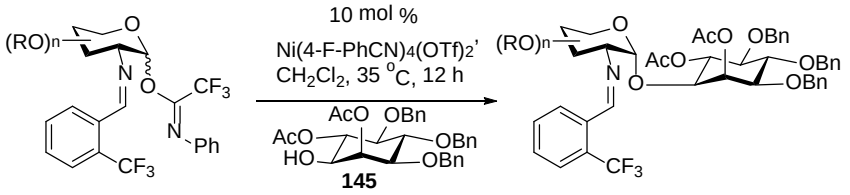
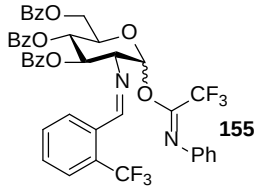
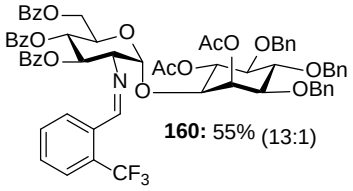
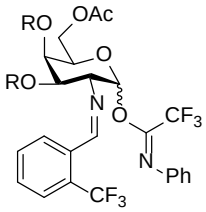
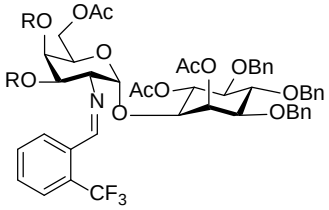
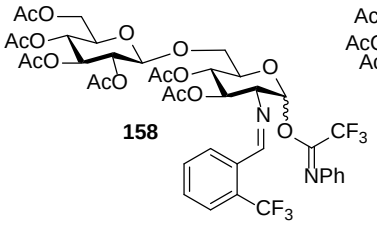
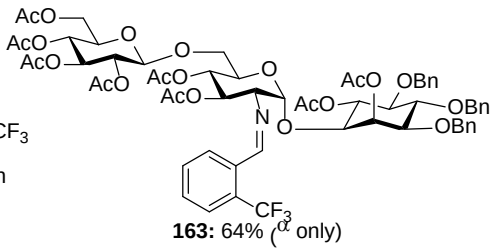
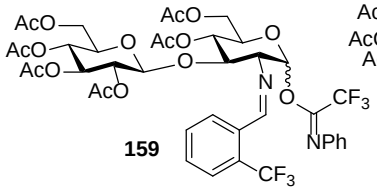
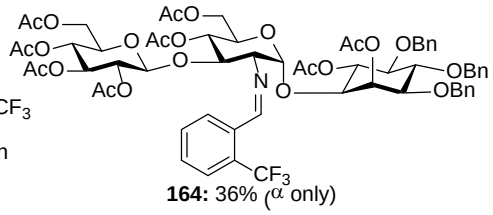


Figure 2.3. ^{1}H NMR Studies of *N*-Phenyl Trifluoroimidate **107b**.

Encouraged by these results, the scope of the glycosylation reaction was further examined with the more challening disaccharide *N*-phenyl trifluoroacetimidates **158** and **159** (entries 4 and 5). Coupling of inositol **145** with 1,6-linked disaccharide donor **158** (entry 4) provided exclusively α-pseudo-trisaccharide **163** in 64% yield. We discovered that 1,3-linked disaccharide **159** (entry 5) did not perform well with 10 mol% of Ni(4-F-PhCN)$_4$(OTf)$_2$. The desired pseudo-trisaccharide **164** (entry 5) was obtained in only 36% yield, albeit exclusively as α-isomer. Overall, the results in Table 2.3 illustrate the efficacy of the nickel catalyst to promote the α-selective glycosylation of inositol **145** with a number of C(2)-*N*-(2-trifluoromethyl)benzylidieneamino donors.

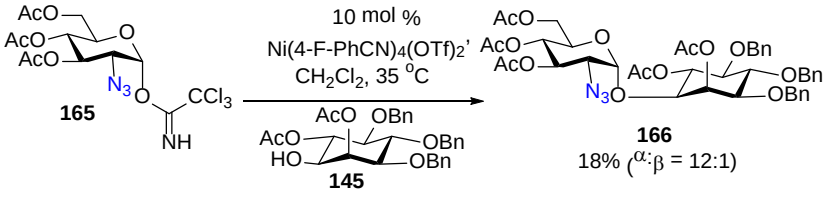


Entry	Donors	Pseudosaccharides Yield[b] (α:β)[c]
1	 **155**	 **160:** 55% (13:1)
2	 **156**: R = Ac	 **161:** R = Ac 85% (α only)
3	**157**: R = Bn	**162:** R = Bn 56% (10:1)
4	 **158**	 **163:** 64% (α only)
5	 **159**	 **164:** 36% (α only)

[a] All reactions were performed with 1.5 equiv. of imidate. [b] Isolated yield. [c] 1H NMR ratio.

Table 2.3. Survey of Saccharide Imidate Donors.[a]

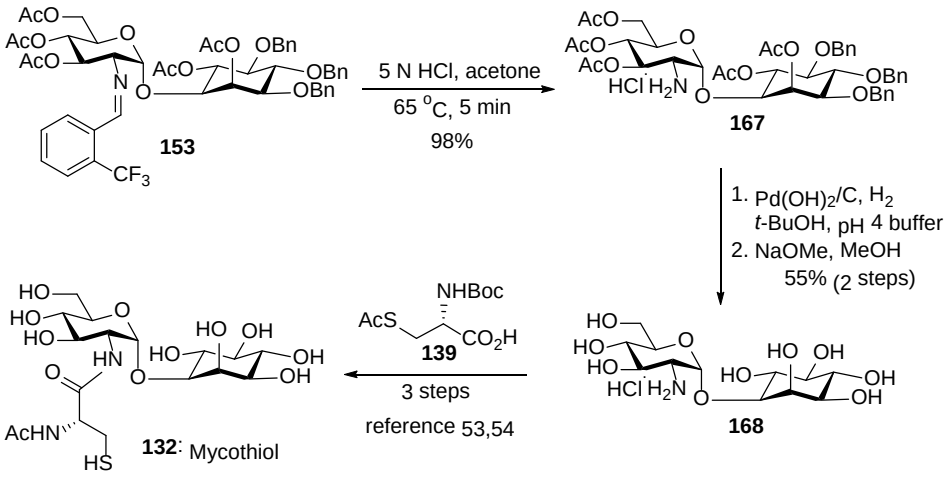
Currently, the most common method for the stereoselective synthesis of the pseudodisaccharide unit of MSH employs the use of C(2)-azido glycosyl donors.[55-57, 60] Although the azido method provides the coupling products in good yields, the α-anomeric selectivity varies (α:β = 1:1 – 6:1). To explore the limitation of the current method, we performed the glycosylation of inositol **145** with C(2)-azido imidate donor **165** (Scheme 2.5). The desired pseudodisaccharide **166** was isolated with excellent α-selectivty ((α:β = 12:1), albeit in much lower yield (18%). This control experiment clearly demonstrates that the nickel catalyst is more efficient and selective for C(2)-*N*-subsituted benzylideneamino imidates than for C(2)-azido donor.



Scheme 2.5. Nickel Catalyzed Coupling with C(2)-Azido Donor **165**.

The synthetic utility of the nickel-catalyzed α-glycosylation strategy was illustrated by the formal synthesis of mycothiol (**132**, Figure 2.1). The 2-trifluoromethyl-benzylidene group in **153** (Scheme 2.6) was removed instantly with 5N HCl in less than 5 minutes to provide the corresponding amine salt **167** in 98% yield. Subsequent hydrogenolysis of the benzyl protecting groups in **167** was carried out using $Pd(OH)_2/C$ and H_2 in a mixture of *t*-BuOH and pH 4 phosphate buffer.[62] Removal of the acetyl groups provided pseudo-disaccharide **168** (Scheme 2.6) in 55% yield over 2 steps. The product **168** showed matching NMR, IR, and mass spectra as previously constructed.[53-54]

Coupling of amine **168** with cysteine residue **139** to form mycothiol will follow methods used in previous synthesis.[53-54]



Scheme 2.6. Formal Synthesis of Mycothiol via Nickel Catalysis.

2.3: Conclusion

We have demonstrated an effective method of generating mycothiol and its analogs in good yields and with excellent α-selectivity utilizing nickel-catalyzed glycosylation of C(2)-*N*-2-trifluoromethyl benzylideneamino imidates with C(1)-hydroxy D-*myo*-inositol. This process was optimized for glycosyl acceptor and donor reactivity and illustrates versatility over a wide range of monosaccharide and disaccahride *N*-phenyl trifluoroacetimidates. Removal of the C(2)-*N*-(2-trifluoromethylphenyl)benzylidene group under mild conditions provides pseudo-disaccharide, completing the formal synthesis of mycothiol. The ability of these mycothiol analogs to act as anti-TB agents are currently under investigated and will be reported in due course.

CHAPTER 3

NICKEL-CATALYZED GLYCOSYLATION OF C(6)-HYDROXYL D-*MYO*-INOSITOL: APPLICATION TO THE SYNTHESIS OF GPI ANCHOR PSEUDO-OLIGOSACCHARIDES

3.1: Background

The glycosylphosphatidyl inositol (GPI) anchor (**169**, Figure 3.1) is a glycophospholipid which is post-translationally tethered to a protein for attachment to a cell membrane.[63] Proteins containing GPI anchor are functionally diverse and play a pivotal role in biochemical processes such as signal transduction, prion disease pathogenesis, immune response, the pathobiology of trypanosomal parasites, and cancer metastasis.[64-65] All GPI structures share the basic core that includes a phosphoethanolamine linker, a tetrasaccharide attached to the C(6)-position of *myo*-inositol, and phospholipid tail.[66] The glycan core of the GPI anchor family can be further modified with specific sugar, lipid, and phosphoethanolamine groups. While studies have shown that the main function of the GPI anchor is to bind proteins to a cell surface, the relationship between structural diversity and biological function is poorly understood.[67-68] Synthetic analogues of the GPI anchor could provide useful insight into this relationship.[69-72]

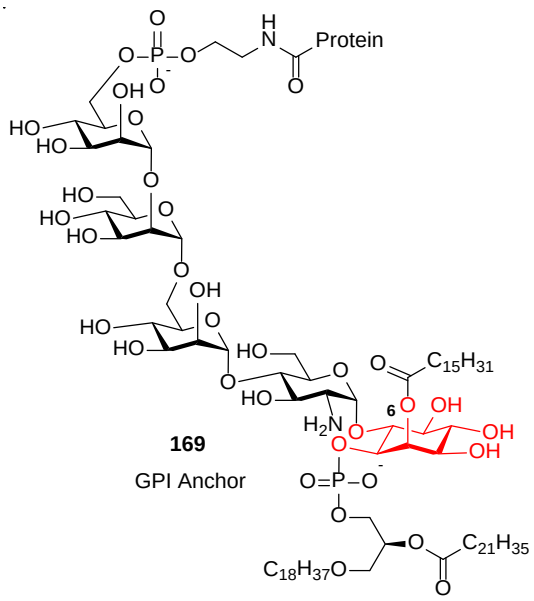


Figure 3.1. Glycosylphosphatidyl Inositol (GPI) Anchor.

Despite remarkable advances in the syntheses of GPI anchors,[73-87] their analogues,[69-72] and other bioactive compounds containing *myo*-inositol unit,[45-48, 50-51, 88-90] there are several key challenges that remain. First is the stereoselective construction of the 1,2-*cis*-2-amino glycosidic bond between the glucosamine unit and *myo*-inositol moiety.[45-48, 50-51, 73-90] Current approaches provide this type of pseudodisaccharide with modest to excellent α-selectivity. Another challenge involves the synthesis of *myo*-inositol moiety with differential protecting groups at C(6)-hydroxyl centers. Several approaches toward the synthesis of C(6)-hydroxyl *myo*-inositols have been reported in an effort to generate GPI anchor.[58, 74, 91-92] For GPI anchor synthesis, the second challenge involves formation of the α-glycosidic linkages which connect the mannose units without the use of C(2)-acyl neighboring group participation in the glycosyl donor unit. This is essential, as the basic conditions employed to remove the acyl groups will also cleave the ester bonds of the lipid chains attached to the *myo*-inositol.

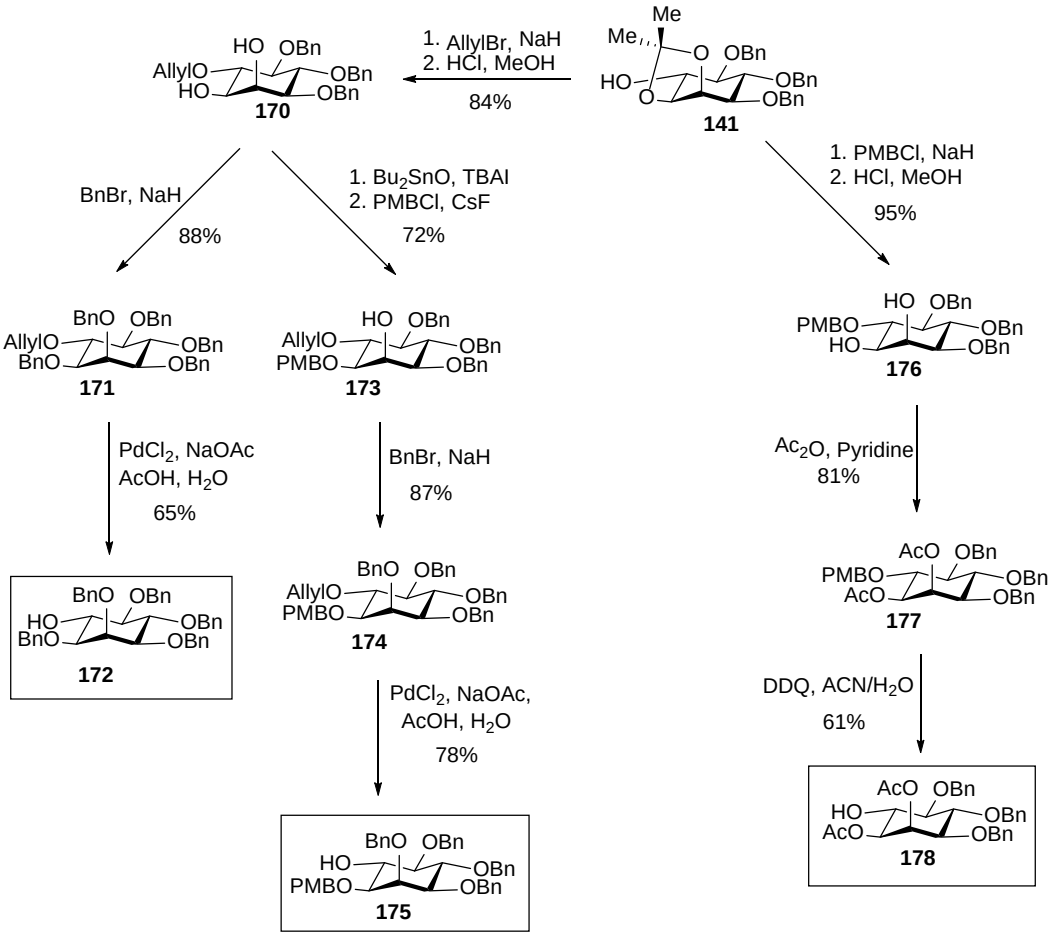
Our goal is to develop a reliable and operationally simple glycosylation procedure that provides straightforward access to a variety of pseudosaccharides of GPI anchors and their analogues. Herein, we present a cationic nickel (II) catalyst, $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$, that efficiently promotes the α-selective pseudosaccharide formation from the C(2)-*N*-benzylideneamino trihaloacetimidate donors and C(6)-hydroxyl *myo*-inositols.

3.2: Results and Discussion

The *myo*-inositols containing a free C(6)-hydroxyl group can serve as useful glycosyl acceptors in the preparation of a number of GPI anchor pseudo-disaccharides and analogues. However, latent protection of the C(6)-hydroxyl functionality must be maintained until the final step. Since the GPI anchor contains a fatty acid ester side chain at C(2) and a phospholipid side chain at C(1), differential protection at those positions would be advantageous. Varying the protecting groups at the C(1)- and C(2)-hydroxyl centers adds a degree of versatility to the preparation of GPI anchor analogues. On the basis of these considerations, the synthesis of three inositol acceptors **172**, **175**, and **178** is outlined in Scheme 3.1.

Glycosyl acceptors **172**, **175**, and **178** were prepared from known intermediate **141** (Scheme 3.1).[58] Allylation of **141** followed by removal of the isopropylidene group resulted in diol **170** in 84% overall yield. Treatment of **170** with benzyl bromide and subsequent removal of the allyl group provided the C(6)-hydroxyl *myo*-inositol **172** in 57% yield over two steps. Alternatively, the diol **170** was converted to **173** via selective protection of the C(1)-hydroxyl group as a *p*-methoxybenzyl (PMB) ether. Subsequent

benzylation of the C(2)-hydroxyl inositol **173** afforded a fully protected *myo*-inositol **174**, after which the allyl group was removed to give the second C(6)-hydroxyl *myo*-inositol **175** in 49% yield over four steps (Scheme 3.1).



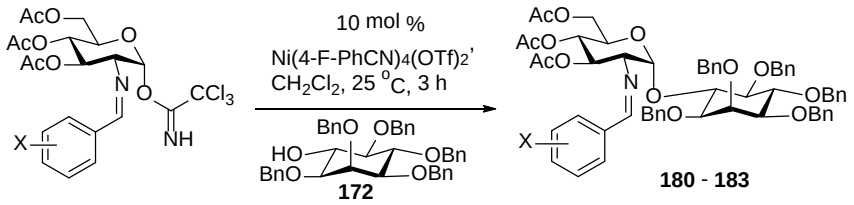
Scheme 3.1. Synthesis of C(6)-Hydroxyl Inositols.

Another C(6)-hydroxyl *myo*-inositol **178** (Scheme 3.1) was synthesized starting from **141** over four steps. A *p*-methoxybenzyl ether (PMB) was installed at C(6) of **141**, and the isopropylidene was removed to form the diol **176**. Subsequent acetylation of **176** provided fully protected inositol **177** in 81% yield. The final step in the synthesis of

C(6)-hydroxyl *myo*-inositol **178** was performed using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to remove the PMB group, delivering **178** in 61% yield.

With access to three different *myo*-inositols **172**, **175**, and **178** (Scheme 3.1), efforts were focused on the α-selective formation of pseudodisaccharides of GPI anchors. Given our previous studies with nickel-catalyzed glycosylations,[33, 35-36, 93] it was prudent to investigate the effects that varying the electronic properties of the C(2)-*N*-substituted benzylidene group would have on yield and α-selectivity in D-glucosamine trichloroacetimidate donors. Our studies have shown that electron-withdrawing substituents on the benzylidene group increase the yield and α-selectivity of the coupling products.[36] To simplify our investigations, we initially tested the efficacy of the cationic nickel catalyst, $Ni(4\text{-F-PhCN})_4(OTf)_2$, to promote the coupling of C(1)-hydroxyl perbenzylated *myo*-inositol **172** (Table 3.1) with four different C(2)-benzylidene D-glucosamine trichloroacetimidate donors **93**, **99**, **146**, **179** at varying donor/acceptor ratios. Overall, the desired pseudodisaccharides **180** – **183** were isolated in good yield (65–79%) and with high α-selectivity (α:β = 10:1–15:1). The 2-trifluoromethyl-benzylidene **99** showed the highest reactivity and α-selectivity (entry 6), affording pseudodisaccharide **183** in 79% yield as a 15:1 α:β ratio. The 2-fluoro-benzylidene substrate **179** (entry 5) showed similar α-selectivity (α:β = 15:1) but with decreased yield (66%). While not ideal, the 4-substituted benzylidene donors **146** and **93** (entries 1 and 2) reacted with C(6)-hydroxyl *myo*-inositol acceptor **172** to provide the coupling products **180** and **181** in good yield (72 → 78%) and with high α-selectivity (α:β =11:1). Use of excess donor **93** relative to acceptor **172** (entry 4) was shown to increase α-selectivity (11:1 → 13:1) but decreased yield (72 → 65%). On the other hand, excess equivalents of

donor **146** (entry 3) only led to a decrease in both α-selectivity (11:1 → 10:1) and yield (78 → 67%).



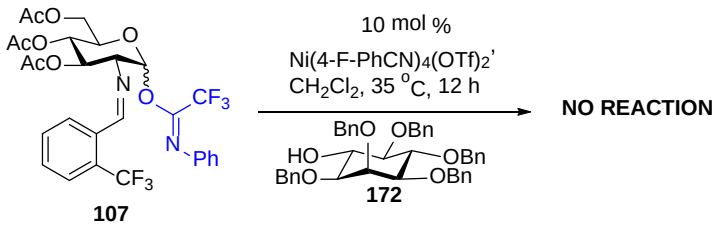
entry	donors	donor/acceptor	products	yield (%)[b]	α:β[c]
1	**146:** X = 4-F	1/1.3	**180**	72	11:1
2	**93:** X = 4-CF_3	1/1.3	**181**	78	11:1
3	**146:** X = 4-F	1.3/1	**180**	67	10:1
4	**93:** X = 4-CF_3	1.3/1	**181**	65	13:1
5	**179:** X = 2-F	1/1.3	**182**	66	15:1
6	**99:** X = 2-CF_3	1/1.3	**183**	79	15:1

[a] All reactions were run at 0.2 M with 10 mol% catalyst at 35 °C. [b] Isolated Yield. [c] ^{1}H NMR ratio.

Table 3.1. Studies with C(6)-Hydroxyl Perbenzylated *myo*-Inositol.[a]

Since the 2-trifluoromethyl-benzylidene donor **99** (Table 3.1, entry 6) showed the highest α-selectivity and yield, it seemed practical to use this glycosyl donor for further studies. Unfortunately, the α-trichloroacetimidate of **99** is the minor product from the reaction of hemiacetal and trichloro-acetonitrile (α:β = 1:3). Since the β-isomer of **99** is unreactive under our nickel conditions,[35] we looked into utilizing *N*-phenyl trifluoroacetimidate donors.[59-61] We have established that a mixture of α- and β-isomer of 2-substituted benzylidene *N*-phenyltrifluoroacetimidate donors effectively reacts with a wide variety of glycosyl acceptors under our nickel conditions.[36] Unfortunately, the glycosylation of inositol acceptor **172** with *N*-phenyl trifluoroacetimidate donor **107**

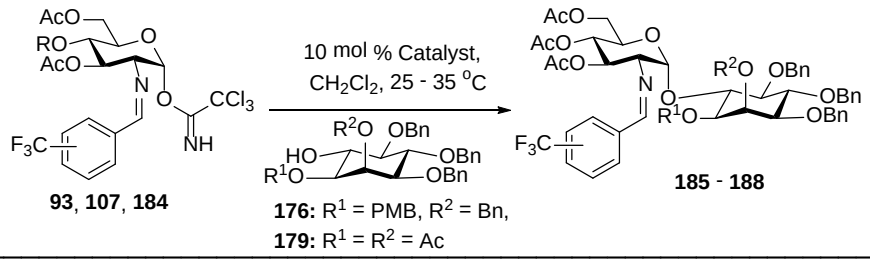
(Scheme 3.2) did not proceed, even at elevated temperature, increased catalyst loading, and extended reaction time.

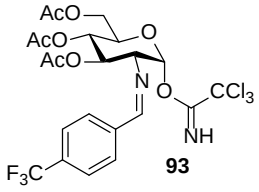
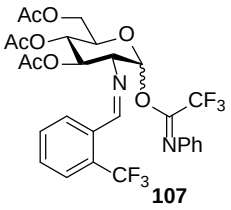
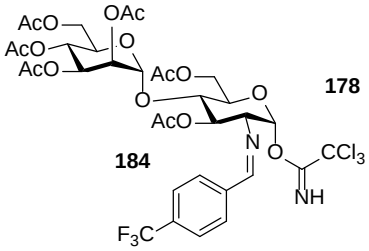


Scheme 3.2. Attempted Coupling with *N*-Phenyl Trifluoroacetimidate **107**.

This may be due to steric encumbrance surrounding the C(6)-hydroxyl group in perbenzylated *myo*-inositol **172**. Since the 4-trifluoromethyl benzylidene **93** gave the next highest α-selectivity (Table 3.1, entry 4), this directing group was employed to examine the substrate scope of various donors reacting with other *myo*-inositols **175** and **178** (Table 3.2).

When the C(6)-hydroxyl tetrabenzylated *myo*-inositol **175** bearing a C(1)-*p*-methoxybenzyl ether (Table 3.2, entry 1) was glycosylated with trichloroacetimidate **93**, a similar yield (71%) and α-selectivity (α:β = 10:1) was observed when compared with the coupling of C(6)-hydroxyl perbenzylated inositol **172** with donor **93** (Table 3.1, entry 2). This led us to believe that inositol **175** would react in a similar manner as acceptor **172**; both too sterically hindered to undergo glycosylation with *N*-phenyl trifluoroacetimidate substrates.



entry	donors	acceptors	catalyst	products	time (h)	yield[b] (%)	α:β[c]
1	 **93**	**175**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	**185**	4	71	10:1
2	**93**	**178**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	**186**	4	79	12:1
3	 **107**	**178**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	**187**	18	72	10:1
4	**93**	**178**	$BF_3 \cdot OEt_2$	**186**	4	40	1:1
5	**93**	**178**	TMSOTf	**186**	4	55	1:1
6	 **184**	**178**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	**188**	4	40	11:1

[a] All reactions were run at 0.2 M with 10 mol% catalyst. All trichloroacetimidate donors were conducted at 25 °C, except for N-phenyl trifluoroacetimidate **105** which was performed at 35 °C. [b] Isolated Yield. [c] ^1H NMR ratio.

Table 3.2. Substrate Scope for Glycosylation of **175** and **178**.[a]

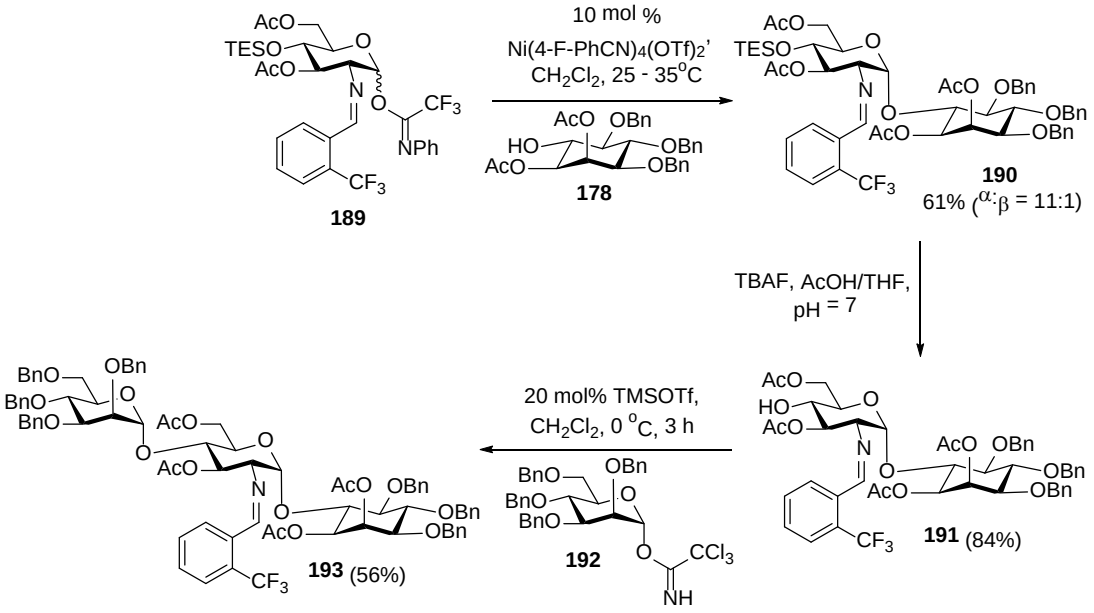
Gratifyingly, *myo*-inositol **178** (Table 3.2, entry 2) showed a marked improvement in yield (71 → 79%) and α-selectivity (10:1 → 12:1) when coupled with

glycosyl donor **93**. We hypothesize that this improvement may be due to a reduction in steric crowding around the C(6)-hydroxyl group of *myo*-inositol resulting from the acetyl groups incorporated at the C(1)- and C(2)-positions in inositol **178** in lieu of the C(1)-PMB ether and C(2)-benzyl ether in inositol **175**. With that in mind, we decided to attempt coupling of inositol **178** with a α/β-mixture of the *N*-phenyltrifluoracetimidate donor **107** (entry 3). To our excitement, after 18 h of reaction time, the desired pseudodisaccharide **187** was isolated in 72% yield and with α:β = 10:1.

To evaluate the unique properties of the cationic nickel catalyst, $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$, to efficiently promote the α-selective glycosylation with *myo*-inositol acceptors, control experiments were performed with traditional Lewis acids, $BF_3.OEt_2$[94-96] and TMSOTf[97-101] (Table 3.2, entries 4 and 5). In these reactions, the desired pseudodisaccharide **186** (entries 4 and 5) was obtained in much lower yield (79→55%) and α-selectivity (12:1→1:1) when compared to the glycosylation performed with the nickel catalyst (entry 2), $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$. Pseudotrisaccharide **188** obtained in entry 6 highlights the efficacy of the nickel-catalyzed glycosylation method. Accordingly, $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$ was applied to the more challenging mannose-α(1,4)-glucosamine disaccharide trichloroacetimidate **184**, chosen for its similar connectivity to that found in GPI anchor **169** (Figure 3.1). Although the glycosylation provided the corresponding pseudotrisaccharide **188** in only moderate yield (40%), a high α-selectivity (11:1) was still observed in the coupling process.

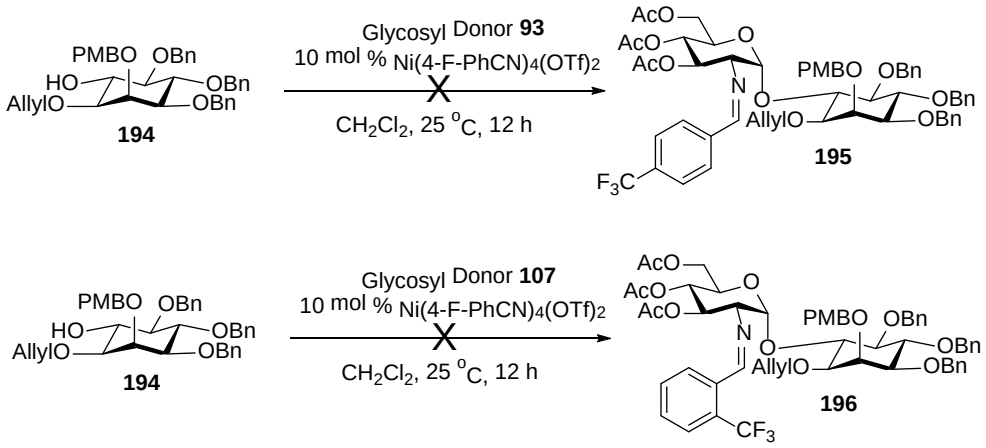
To validate the ability of the C(2)-*N*-substituted benzylidene to serve as effective protecting group in oligosaccharide synthesis and to demonstrate the utility of our pseudodisaccharides as valuable building blocks in GPI anchor synthesis, *N*-phenyl

trifluoroacetimidate **189** (Scheme 3.3), with labile TES protecting group at the C(4) position, was investigated in the glycosylation of C(6)-hydroxyl *myo*-inositol **178**. The coupling process proceeded smoothly, providing pseudodisaccharide **190** in 61% yield and with (α:β = 11:1) good selectivity. The TES group in **190** was subsequently removed using TBAF (Scheme 3.3) to reveal the free C(4)-hydroxyl group of pseudodisaccharide **191**. This acceptor **191** was then used in a glycosylation with tetrabenzylated D-mannose trichloroacetimidate **192** in the presence of TMSOTf as a catalyst to afford α-pseudotrisaccharide **193** exclusively in 47% yield over two steps, highlighting the versatility of the *N*-substituted benzylidene protecting group under various coupling conditions. The benzylidene group can be easily to removed in less than 5 min with HCl and acetone.[36]



Scheme 3.3. Another Approach to a GPI Anchor Pseudotrisaccharide.

Overall, the results obtained in Table 3.2 and Scheme 3.3 demonstrate the efficacy of our nickel catalyst, $Ni(4\text{-F-PhCN})_4(OTf)_2$, to promote the high-yielding and α-selective coupling of a number of C(6)-hydroxyl *myo*-inositols with monosaccharide and disaccharide trihaloacetimidate donors bearing the C(2)-*N*-substituted benzylidene groups. To further explore the scope and limitation under nickel catalysis, the coupling of inositol acceptor **194** bearing the C(1)-allyl and C(2)-PMB groups with both donors **93** and **107** (Scheme 3.4) was examined. Unfortunately, inositol **194** did not perform well with $Ni(4\text{-F-PhCN})_4(OTf)_2$. Pseudodisaccharides **195** and **196** were obtained in very poor yield and selectivity along with other byproducts. In fact, we were unable to fully analyze and characterize compounds **195** and **196**.



Scheme 3.4. Attempted Glycosylation of *myo*-Inositol **194**.

3.3: Conclusion

In summary, we have developed an efficient strategy for the preparation of pseudodisaccharides that are applicable to the synthesis of GPI anchor analogues. We

have addressed a major hurdle that is commonly encountered in the synthesis of these compounds by achieving high α-selectivity in the glycosylation step to form the major pseudosaccharide moieties. The cationic nickel catalyst, $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$, acts as an effective activating reagent for promoting the coupling of *myo*-inositols with a variety of trichloroacetimidate and *N*-phenyl trifluoroacetimidate donors bearing the C(2)-*N*-substituted benzylidene group. The desired 1,2-*cis*-2-amino pseudosaccharides were obtained in moderate to good yields and excellent α-selectivity where the best results were obtained from less sterically encumbered inositols. In addition, both α- and β-isomers of *N*-phenyl trifluoroacetimidates are viable glycosyl donors in the nickel-catalyzed reaction, an important finding for increasing the overall efficiency. In contrast, TMSOTf and $BF_3{\cdot}OEt_2$ coupling of *myo*-inositols with the *N*-substituted benzylidene donors provided pseudodisaccharides as a 1:1 mixture of α- and β-isomers. Lastly, the synthesis of the GPI anchor pseudotrisaccharides highlights the utility of the C(2)-*N*-benzylidine functionality to serve not only as a directing group in nickel-catalyzed glycosylation, but also as a stable protecting group under various conditions.

CHAPTER 4

NICKEL-CATALYZED GLYCOSYLATION OF FMOC-PROTECTED THREONINE AMINO ACIDS: SCALABLE SYNTHESIS OF T_N ANTIGEN

4.1: Introduction

Protein glycosylation can be generally divided into two major classes: *N*-linked and *O*-linked. In *N*-linked glycoproteins, an *N*-acetyl-glucosamine (GlcNAc) unit is β-linked to the amide nitrogen of an asparagine amino acid side chain.[102-103] In *O*-linked glycoproteins, an *N*-acetyl-galactosamine (GalNAc) unit is α-linked to the hydroxyl group of serine or threonine to generate a core structure **197** (Figure 4.1), commonly referred to as the T_N antigen.[104] Branching of this core structure **197** can take place at the C(3)- and/or C(6)-hydroxyl groups of GalNAc to give rise to a diverse array of structural motifs (e.g. TF antigen **198** and ST_N antigen **199**, Figure 4.1). These antigens are widely distributed on cell-surface mucin glycoproteins, which participate in cell adhesion events associated with cancer metastasis.[105] The T_N antigen **197**, in particular, has been found to be highly expressed by mucins on most epithelial cancers.[106-107] As a result, this T_N antigen has been investigated extensively as a biomarker and a therapeutic target for cancer vaccine therapy.[108-117]

In the development of cancer vaccines, well-defined and pure T_N antigen as a single tumor antigen or as a component of a polyvalent vaccine is required. However, acquiring adequate amounts of T_N antigen from natural sources in homogenous form is

challenging. In many cases, high purity T_N antigen can only be obtained by chemical and/or enzymatic synthesis.[118-119]

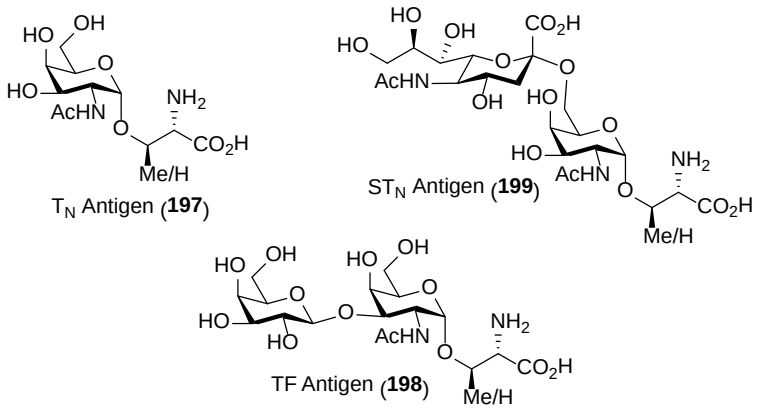
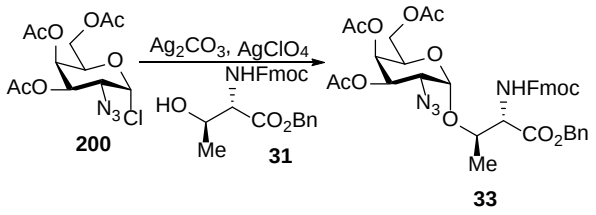


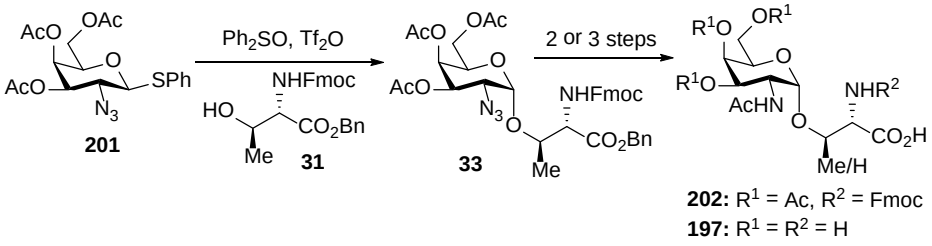
Figure 4.1. Tumor Associated Mucin T_N, TF, and ST_N Antigens.

In the chemical synthesis strategy, C(2)-azido donors are the most commonly used substrates for generating the T_N antigen. Early work utilized a C(2)-azido halo donor **200** (Scheme 4.1) in the presence of the reagent combination of Ag_2CO_3 and $AgClO_4$ as a promoter to ensure α-selectivity (α:β = 4:1) in the glycosylation of Fmoc protected threonine amino acid **31**.[120-123]



Scheme 4.1. Previous Work Involving C(2)-Azido Glycosyl Chloride **200**.

Another efficient synthesis of T_N antigen employed a C(2)-azido thioglycoside donor **201** (Scheme 4.2), and the Ph_2SO/Tf_2O system is employed to promote α-glycosylation reaction.[124] Compound **33** was further converted into Fmoc-protected GalNAc-threonine amino acid **202** (2 steps, for use in the production of full-length glycosylated proteins) and T_N antigen **197** (3 steps). A number of efficient strategies were subsequently developed for generating glycopeptides containing the T_N antigen moiety.[125-138]



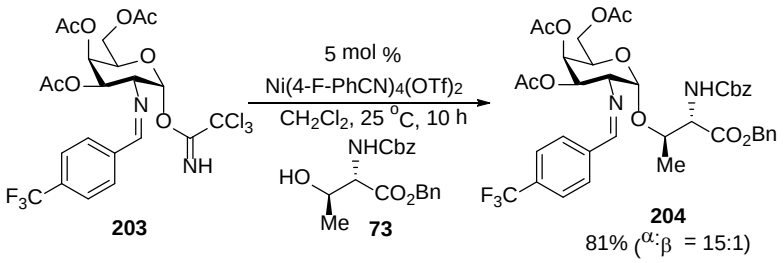
Scheme 4.2. Previous Work Involving C(2)-Azido Glycosyl Thiophenol **201**.

Both glycosyl amino acid **202** and T_N antigen **197** are readily available, but they are expensive to purchase (**202:** $303.50/25 mg and **197:** $250/mg from Sigma-Aldrich). Although high purity T_N antigen can be chemically prepared, it cannot be easily and reproducibly obtained in large quantities. Most of existing glycosylation procedures require stoichiometric amounts of the activating agents to sufficiently activate donors, resulting in excessive waste materials.[120-122, 124-130, 132-136, 138-139] Some of these reagents can be air- and moisture-sensitive (e.g. Ph_2SO/Tf_2O)[8] and potentially explosive (e.g. $AgClO_4$).[125-130, 132-136, 138-139] In addition, the synthesis of the commonly used C(2)-azido donors **200** and **201** (Scheme 4.2) is not trivial. Lemieux's azidonitration method for

preparing **200** and **201** is not very diastereoselective,[19] depending on the nature of the protecting groups on glycal starting material.[140] Alternatively, diazotransfer reaction can be utilized to prepare donors **200** and **201** through direct conversion of galactosamine by the action of either trifluoromethanesulfonyl azide or imidazole-1-sulfonyl azide,[21, 141] which are potentially explosive reagents. Although the diazotransfer method is frequently used nowadays for preparing donors **200** and **201**, it is unlikely to be suitable for large scale synthesis. Herein, we report a scalable and reproducible protocol for the synthesis of the Fmoc-protected GalNAc-threonine amino acid **202** and T_N antigen **197** via the $Ni(4\text{-F-PhCN})_4(OTf)_2$-mediated α-glycosylation of threonine amino acids with C(2)-*N*-*ortho*-(trifluoromethyl)benzylidenamino trihaloacetimidate donors. This operationally simple procedure no longer requires the utilization of C(2)-azido glycosyl donors and is suitable for a gram-scale preparations of **202** and **197**.

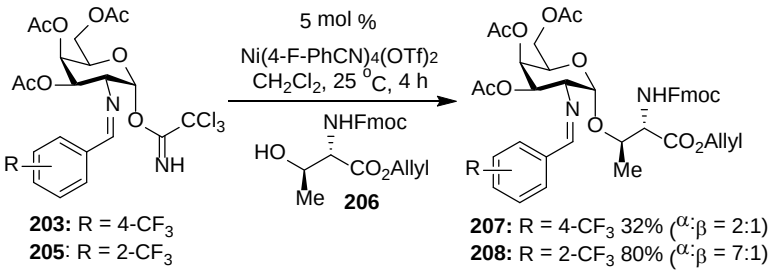
4.2: Results and Discussion

Our group has introduced nickel-catalyzed α-stereoselective glycosylation reaction as a general platform for preparations of a variety of 1,2-*cis*-2-amino glycosides.[33, 35-36, 93, 142-144] Additionally, we have illustrated that $Ni(4\text{-F-PhCN})_4(OTf)_2$ effectively promoted a coupling of Cbz-protected threonine residue **73** with C(2)-*para*-(trifluoromethyl)benzylidenamino trichloroacetimidate donor **203** to afford glycosyl amino acid **204** (Scheme 4.3) in 81% yield with α:β = 15:1.[35]



Scheme 4.3. Nickel-Catalyzed Route to Cbz-Protected GalNAc-Threonine Precursor.

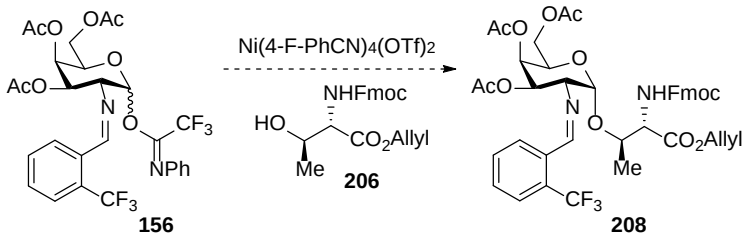
We postulated that an analogous nickel-catalyzed α-selective glycosylation would be possible with Fmoc-protected amino acid **206** (Scheme 4.4). Of two standard methods for the solid-phase peptide synthesis (SPPS) of glycopeptides containing T_N antigen unit, Fmoc-based chemistry is more often utilized than Boc-based chemistry.[102] Unfortunately, employing 5 mol% of $Ni(4\text{-F-PhCN})_4(OTf)_2$ to promote the glycosylation of **206** with donor **203** only resulted in a 32% yield of **207** (Scheme 4.4) with poor α-selectivity (α:β = 2:1). Alternatively, use of C(2)-*N*-*ortho*-(trifluoromethyl)benzylidenamino substrate **205** (Scheme 4.4) improve both yield (32% → 80%) and α-selectivity (α:β = 2:1 → 7:1).



Scheme 4.4. Preliminary Results with Fmoc-Protected Threonine Residue.

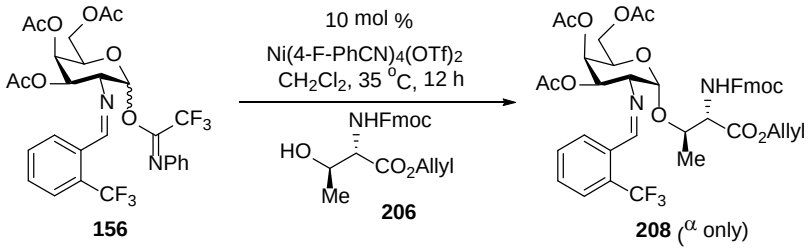
Although α-trichloroacetimidate donor **205** acted as an effective donor, it was a minor anomer resulting from the reaction of hemiacetal with Cl_3CCN and DBU (α:β = 1:3). Unfortunately, reaction of β-anomer of donor **205** with Fmoc-protected threonine amino acid **206** resulted in no reaction. On the basis of our recent successful results with the use of *N*-phenyl trifluoroacetimidates as effective glycosyl donors,[36, 93, 142] we hypothesize that triacetyl galactosamine donor **156** (Scheme 4.5), possessing the C(2)-*N*-*ortho*-(trifluoromethyl)benzylidene functionality, is a suitable starting material for the rapid and gram-scale synthesis of 1,2-*cis*-2-amino glycoside **208**, its corresponding Fmoc-protected threonine amino acid **202** and T_N antigen **197**.

While it was known that $Ni(4\text{-F-PhCN})_4(OTf)_2$ effectively promoted the glycosylation of a wide variety of carbohydrate acceptors with C(2)-*ortho*-(trifluoromethyl)benzylidenamino *N*-phenyl trifluoroacetimidate donors,[60-61, 93, 142] it was uncertain if the reaction of Fmoc-protected threonine amino acid **206** with substrate **156** would proceed with high yield and α-selectivity. Importantly, it was still unclear if the nickel method can be utilized in a large scale preparation of glycosyl amino acid **208** (Scheme 4.5).



Scheme 4.5. Proposed Gram-Scale Synthesis of Fmoc-Protected GalNAc-Threonine.

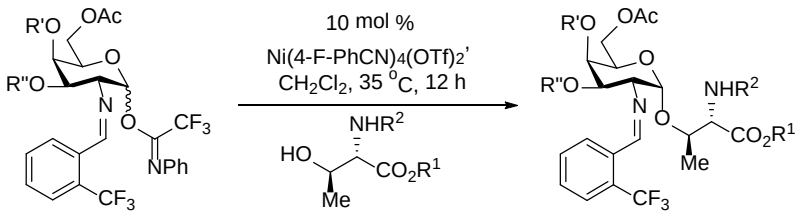
We were delighted to find that employing only 10 mol% $Ni(4\text{-F-PhCN})_4(OTf)_2$ the coupling reaction reached completion in 12 h at 35 °C to afford the desired product **208** in 74% yield with exclusive α-anomeric selectivity (Scheme 4.6a). Purification of the glycosyl amino acid **208**, however, was tedious due to closeness in R_f value of the threonine acceptor **206** to the desired product **208**. In the second trial, we glycosylated **206** with *N*-phenyl trifluoroacetimidate donor **156** on a similar scale (Scheme 4.6b) and got a comparable yield and selectivity (63%, α only). The yield in this second run was slightly lower because we tried two different purification methods (manual and automated chromatography) to separate **208** from unreacted threonine donor **206**. Unfortunately, it was not successful. Anticipating that this problem would be exacerbated in a larger scale, we made the threonine acceptor **206** the limiting reagent (Scheme 4.6c) and isolated 3.77 g of pure product **208** in 66% yield with α-only selectivity. Overall, the results obtained in Scheme 4.6 have illustrated the high α-selectivity and scalability of the nickel-catalyzed glycosylation reaction under mild and operationally simple conditions.



a.	0.808 g (1.0 equiv)	0.585 g (1.2 equiv)	74%, 0.782 g
b.	0.947 g (1.0 equiv)	0.685 g (1.2 equiv)	63%, 0.779 g
c.	5.730 g (1.28 equiv)	2.710 g (1.0 equiv)	66%, 3.77 g

Scheme 4.6. Gram-Scale Synthesis of Glycosyl GalNAc-Threonine Compound **208**.

Further investigation of scope showed that a glycosylation reaction could be realized using 10 mol% of nickel catalyst, $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$, with other donors and a number of Fmoc-protected threonine amino acids to afford the desired 1,2-*cis*-2-amino glycosides **210** – **214** (Table 4.1) in good yields (61 – 86%) with excellent α-selectivity (α:β = 14:1 – α only). The terminal alkyne of product **211** is capable of conjugating to biorthogonal azide, via click chemistry,[145-146] for incorporation into a wide variety of biomolecules.[147] This alkyne can also conjugate to a linker possessing the azide functionality to form the corresponding polymerizable monomer, which can then undergo ring-opening metathesis polymerization (ROMP)[148-151] to generate highly clustered T_N antigens for use as antitumor vaccine candidates.[152-153] On the other hand, both glycosyl amino acids **213** and **214** can be further functionalized to generate ST_N antigen (**199**, Figure 4.1). The Cbz-protected threonine amino acid was also compatible with this nickel system, providing the desired glycoside product **212** (Table 4.1) in 67% yield as a single α-anomer.



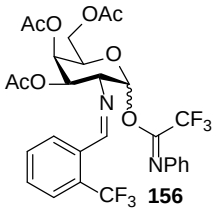
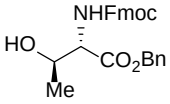
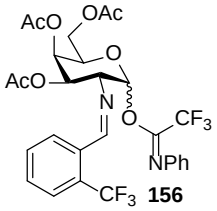
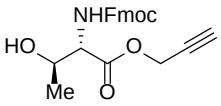
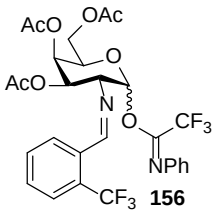
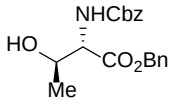
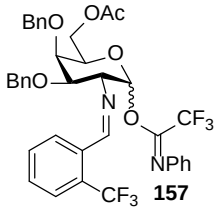
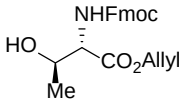
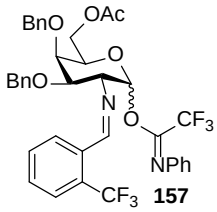
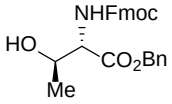
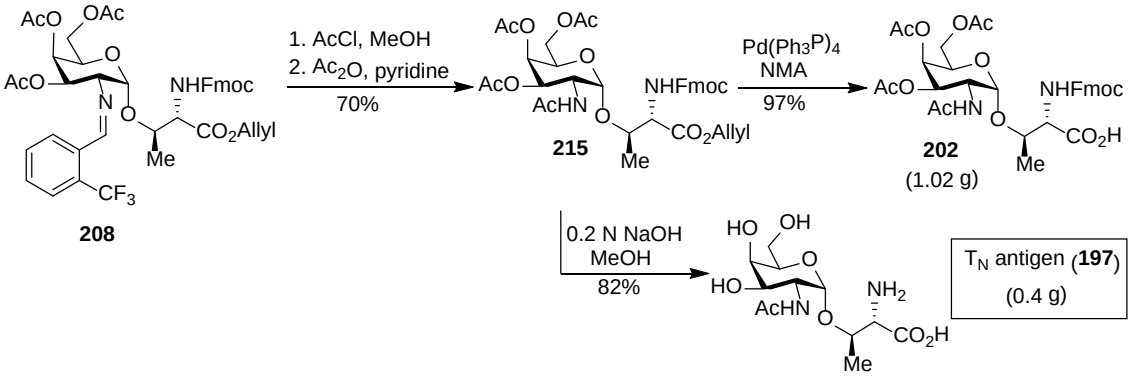
entry	donors	acceptors	products	yield[b]	α:β[c]
1	 **156**	 **31**	**210**	86%	14:1
2	 **156**	 **209**	**211**	78%	α only
3	 **156**	 **73**	**212**	67%	α only
4	 **157**	 **206**	**213**	62%	α only
5	 **157**	 **31**	**214**	69%	α only

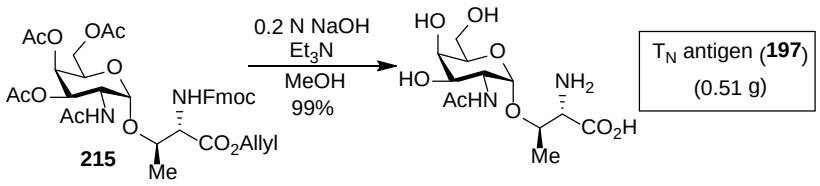
Table 4.1. Scope of the Reaction with Threonine Amino Acids.

Since the Fmoc-protected GalNAc-threonine amino acid **208** (Scheme 4.7) is a useful building block required for SPPS of mucin-type glycopeptides,[102] we next investigated the mild conditions for converting glycosyl amino acid **208** into **202**. The previous conditions (2N – 5N HCl, acetone, 25 – 50 ^{o}C)[25, 154-156] for the exchange of C(2)-N-benzylidenamino functionality with *N*-acetyl group to form **215** (Scheme 4.7) may not be suitable for use in a large scale synthesis. Using the product **208** from Scheme 4.6, we found that the benzylidene group could be removed with acetyl chloride (1.6 equiv) in methanol at 25 ^{o}C. Subsequent acetylation of the amine salt intermediate provided the desired Fmoc-protected GalNAc-threonine **215** in 70% yield (Scheme 4.7). **215** was utilized to synthesize 1.02 g of Fmoc-protected GalNAc-threonine amino acid **202** (97% yield) using $Pd(Ph_3P)_4$ in THF and NMA at 25 ^{o}C for 1 h. Global hydrolysis of **215** with sodium hydroxide in methanol provided 0.4 g of T_N-antigen (**198**) in 82% yield. While a high yield of **197** was obtained, we found these conditions to be insufficient in fully deprotecting Fmoc group.



Scheme 4.7. Gram Scale Synthesis of T_N Antigen and Fmoc Protected GalNAc **202**.

We hypothesized that addition of triethylamine alongside sodium hydroxide in methanol would facilitate quantitative global deprotection of the intermediate **215** to produce the T_N antigen (**197**). Global deprotection of **215** in the presence of triethylamine and sodium hydroxide occurred with almost quantitative yield (99%, Scheme 4.8).



Scheme 4.8. Large Scale Synthesis of the T_N Antigen.

4.3: Conclusion

In summary, we have illustrated a highly α-selective 1,2-*cis*-2-amino glycosylation reaction utilizing substoichiometric amount of $Ni(4\text{-F-PhCN})_4(OTf)_2$ to mediate the coupling of a number of Cbz- and Fmoc-protected threonine amino acids with C(2)-*ortho*-(trifluoromethyl)benzylideneamino *N*-phenyl trifluoroacetimidate donors. This methodology demonstrates the utility of our catalytic, selective glycosylation method for a gram scale preparation of glycosyl 1,2-*cis*-2-amino acids and their subsequent transformation into the corresponding Fmoc-protected GalNAc-threonine amino acid and T_N antigen. This operationally simple procedure no longer requires utilization of the commonly used C(2)-azido donors, which are often prepared via the potentially explosive diazotransfer reaction. As the scalable, catalytic, and

stereoselective synthesis of complex oligosaccharides and glycoconjugates continues to develop, we anticipate that this nickel-catalyzed glycosylation methodology will have an impact on the strategies used for the preparation of biologically active carbohydrate molecules.

CHAPTER 5

CARBOHYDRATE-FUNCTIONALIZED DIANTENNARY POLYMERS TO INVESTIGATE THE PREDICTABLE TUNABILITY OF MULTIVALENT INTERACTIONS

5.1: Introduction

Heparan sulfate (HS) glycosaminoglycans are carbohydrates consisting of alternating units of partially sulfated glucuronic acid (GlcA) and glucosamine (GlcN) (Figure 5.1).[157-159] HS glycosaminoglycans bind to many extracellular proteins that modulate the integrity and normal function of the extracellular matrix (ECM).[157-158] The ECM provides a physical barrier for cells as well as a scaffold for growth, migration, and survival.[160-162] HS linked proteins also serve as a tether for a multitude of growth factors.[161] Cleavage of HS glycosaminoglycans is therefore expected to disrupt the integrity of the ECM which dramatically alters cell and tissue function and release teathered growth factors. Heparanase is a glycosidase that cleaves HS at the GlcA-(β-1,4)-GlcN glycosidic bond (Figure 5.1).[163-167] This enzyme is preferentially expressed in tumor cells and has been correlated with the metastatic potential of tumor cells due to the angiogenic response and remodeling of the ECM caused by cleavage of HS.[168-170] Because of this, heparanase is an attractive clinical target for the development of antimetastatic and antiangiogenic drugs. Despite its clinical attractiveness, progress in fully understanding and characterizing heperanase has remained slow.

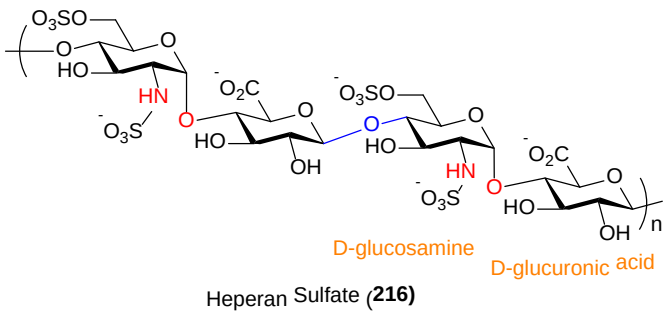


Figure 5.1. Heparan Sulfate (HS) Polysaccharide.

The synthetic strategy for 1,2-*cis*-2-aminoglycoside formation using Ni(4-F-PhCN)$_4$(OTf)$_2$ has been effectively established. Application of this methodology towards heparan disaccharide synthesis has also been explored.[35-36] Since HS serves as part of larger carbohydrate chain, it is important to explore the ability of synthetic HS derivatives to successfully inhibit heperanase activity. Owing to the expense and relatively little understanding of heperanase, development of a model study on the ideal way to express glycan function in terms of protein binding affinity was prudent.

Glycans, such as HS, have a wide variety of roles in cellular processes that require specific recognition by glycan binding proteins (GBPs). Examples of these GBPs include plant,[171] viral lectins,[172] bacterial adhesins,[173] and sulfated glycosaminoglycan binding proteins.[174] In addition, glycan binding proteins can bind to the same glycan at different sites or multiple glycans in solution or on a cell surface.[175-178] Synthetically mimicking the structure of glycans can allow for selective binding of glycan binding proteins that govern important biological processes such as immune response,[179] viral transfection,[180] cancer metastasis,[181-183] and coagulation processes.[184] Many of these proteins are functionally multivalent; in that they have multiple receptors for interacting with glycans. Although individual carbohydrate-protein receptor interactions are generally weak,[185-187]

the summation of these interactions results in an enhanced binding affinity. This global binding affinity has been referred to as "avidity".[188-190]

In order to mimic glycan function, carbohydrates have been chemically displayed on a range of macromolecular architectures including polymers,[181-183] dendrimers,[184] quantum dots,[185-187] and nanoparticles.[188-190] To date, glycopolymers (polymers incorporated with carbohydrate side chains) have illustrated great promise in studying GPB-governed processes. This is due to their ability to vary the length of the polymer chain, length and flexibility of the carbohydrate-polymerizable linker, and individual spacing of the pendant carbohydrate moities.[191] For this work, glycopolymers can be classifed as monoantennary (Figure 5.2a), homofunctional diantennary (Figure 5.2b), or heterobifunctional diantennary (Figure 5.2c). Synthesis of glycopolymers can involve either a post-polymerization attachment of the glycan molecule[192] or polymerization of a monomer bearing a pendant carbohydrate moiety.[193]

Multivalent binding ligand design is still an emerging field. Concanavalin A (Con A), which is known to bind strongly to α-mannose residues, is widely utilized as a model protein to probe multivalent properties due to its low cost and well known structure.[194] Isothermal titration calorimetry (ITC) is emerging as a useful method of examining the binding affinities of GPB-glycan substrates. Many detailed ITC studies of multivalent α-mannose functionalized architectures with Con A have been reported. The Cloninger group has investigated the thermodynamics of the interaction of α-mannose-functionalized dendrimers with Con A using ITC;[195] wherein this study found that the fifth generation mannose-functionalized dendrimer had the highest binding affinity to dimeric Con A.

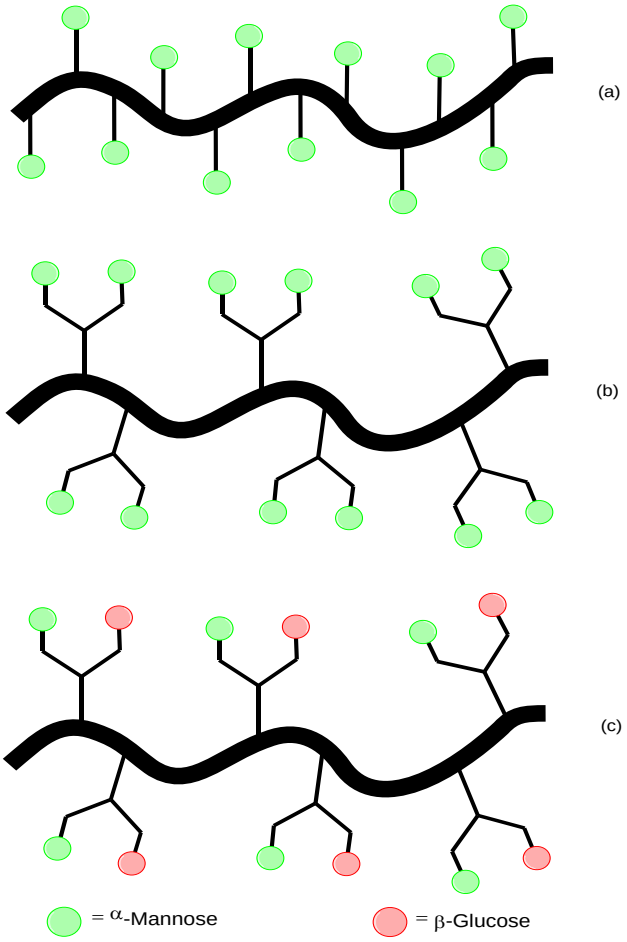


Figure 5.2. Examples of (a) Monoantennary, (b) Homofunctional Diantennary, and (c) Heterobifunctional Diantennary Glycopolymers of α-Mannose and β-Glucose.

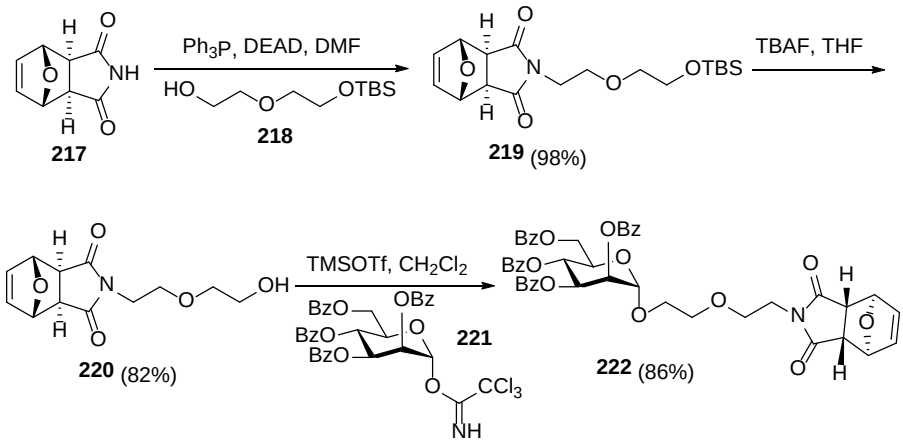
One can infer that mannose moieties were properly spaced such that steric crowding was not present, yet the peripheral α-mannose density was able to effectively chelate Con A. Recently, Wang and coworkers also used ITC to examine the binding affinity of mannose-functionalized nanoparticles to Con A.[196] The Brewer group also thoroughly examined the binding of branched trisaccharides, including 3,6-di-*O*-(α-mannosyl)-α-mannopyranoside, to Con A using ITC, concluding that Con A has a nextended binding site that exhibits high affinity for the branched structure.[197-198]

Herein, we report the synthesis of highly-ordered diantennary glycopolymers (Figure 5.1b – c) from an orthogonally functionalized glycomonomer consisting of α-mannose and non-binding β-glucose. To the best of our knowledge, this study is the first time glycopolymer binding to a lectin has been investigated using ITC measurement. ITC studies were used to examine the avidity and thermodynamics of heterobifunctional diantennary glycopolymers to Con A. These ITC results were then compared to those of homofunctional diantennary glycopolymers as well as monoantennary glycopolymers (Figure 5.1). The aim of this study is to ascertain the ideal architectural parameters for effective glycan mimicking in order to apply them to HS derivatives to give rise to effective inhibition of heparanase.

5.2: Results and Discussion

The synthesis began with the preparation of monoantennary monomer **222** (Scheme 5.1) starting from a known Diels-Alder *exo*-adduct **217**, which was obtained from the reaction of maleimide with furan.[199] We chose this *exo*-norbornene backbone **217** because it is known to undergo ring-opening metathesis polymerization (ROMP) much faster than its *endo*-counterpart,[200-201] and allows for multivalent display of the ligands at defined, chemically controlled intervals to promote multivalent binding.[200] Furthermore, this polymerizable scaffold **217** not only increases the structural rigidity of the resultant glycopolymers, but also allows access to copolymers between α-mannose and β-glucose.[200] Accordingly, the synthetic sequence started with the Mitsunobu coupling of **217** with alcohol linker **218**[202] in DMF for 12 h to lead to the formation of

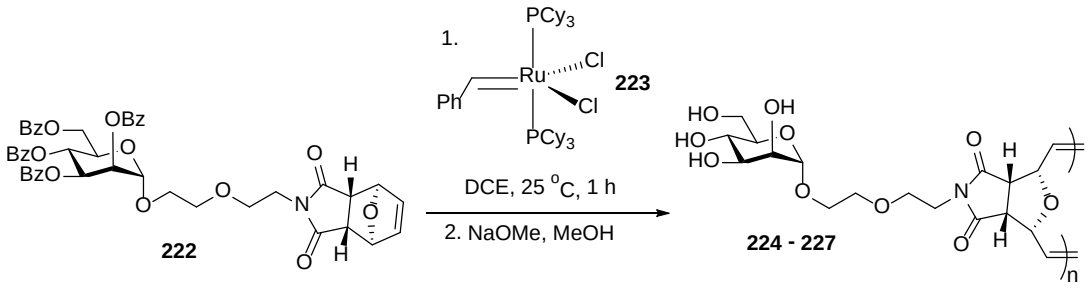
219 in 98% yield. Subsequent removal of the *tert*-butyl silyl (TBS) ether afforded 82% yield of primary alcohol **220**, which served as a glycosyl acceptor in the glycosylation reaction with mannosyl trichloroacetimidate donor **221** mediated by 20 mol% of trimethylsilyl triflate (TMSOTf). The corresponding glycoside **222** was obtained in 86% yield (Scheme 5.1).



Scheme 5.1. Synthesis of α-Mannose Monoantennary Monomer **222**.

Next, ring opening metathesis polymerization of monovalent monomer **222** was investigated using the first generation Grubbs catalyst **223** (Table 5.1). In our design, the benzoyl (Bz) protecting groups were chosen for the mannose hydroxyl groups at C-2, -3, -4, and -6 positions in **222** because aromatic glycopolymers tend to have a high refractive index increment (dn/dc).[202-203] With a higher dn/dc, that is the change in refractive index versus the change in concentration, gel permeation chromatography (GPC) analysis of the glycopolymers using a light scattering detector allowed for accurate absolute molecular weight (M_n) and polydispersity (PDI) determination.[202-203] Additionally, the benzoyl protected monomer **222** can be soluble in non-coordinating, aprotic solvents which are

generally used for ROMP. Gratifyingly, monomer **222** dissolved in dichloroethane (DCE) and polymerization with 5 mol% of **223** led to complete conversion to the corresponding glycopolymer within 1 h (Table 5.1, entry 1, DP = 30, PDI = 1.09, and M_n = 25,290). We also performed a control polymerization of the free-hydroxyl product resulted from hydrolysis of monomer **222** in MeOH. Incomplete conversion and significantly low degree of polymerization (DP = 9) was observed in the reaction. It is probably due to coordination of methanol to the catalyst **223** and reactive intermediates, which could reduce the propagation rate of polymerization and result in premature chain termination. By decreasing the amount of the Grubb's 1st generation catalyst **223** from 5% to 1% (entry 1 – 4), we were able to accomplish a series of the desired glycopolymers from monomer **222** with increasingly larger molecular weights and degrees of polymerization (DP). Although lowering Grubbs catalyst **223** increased molecular weights of polymers, the polydispersities remained relatively narrow (PDI = 1.08 – 1.10), indicating a high uniformity of molecular weight (M_n) in each glycopolymer. All glycopolymers were also analyzed by ^{1}H NMR spectroscopy. All protected glycopolymers were obtained in good yields (Table 5.1, 78 – 83%). Finally, the benzoyl protecting groups were removed using sodium methoxide in methanol to afford glycopolymers **224** – **227** in 40 – 67% yield (Table 5.1).



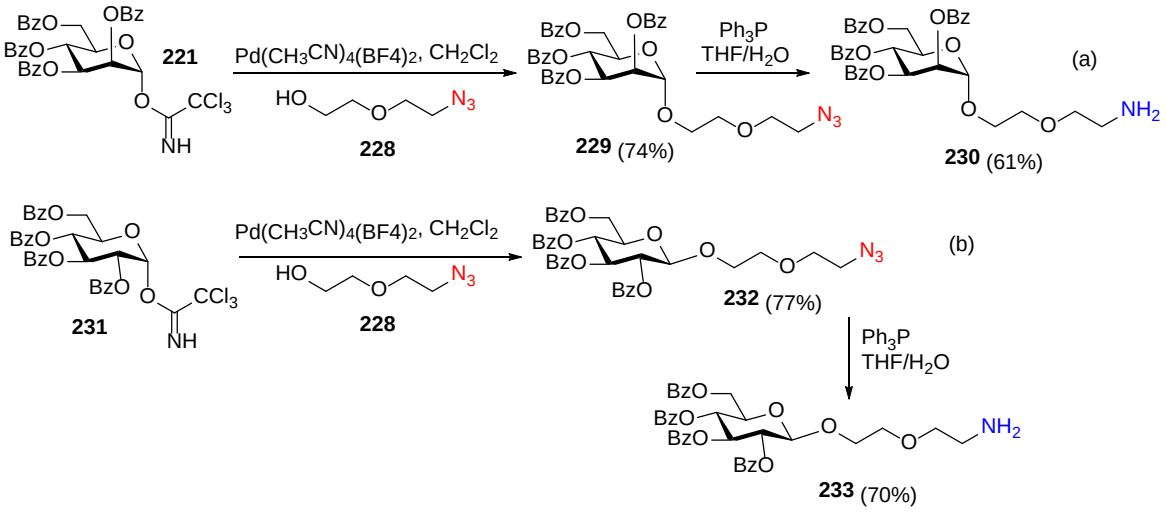
entry	Glycopolymers	**233**	Mn (g/mol)[a]	DP[a]	PDI[a]	ROMP Yield[b]	Hydrolysis Yield[b]
1	**224**	5 mol %	25,290	30	1.09	83%	67%
2	**225**	3 mol %	47,150	57	1.10	80%	65%
3	**226**	2 mol %	147,700	175	1.08	79%	40%
4	**227**	1 mol %	184,300	222	1.08	78%	62%

[a] Number average molecular weight (Mn), degree of polymerization (DP), and polydispersity index (PDI) of glycopolymers were determined by gel permeation chromatography (GPC). [b] Isolated yield.

Table 5.1. ROMP of Monoantennary Monomer **222** using Grubb's Catalyst **223**.

We next studied the synthesis and polymerization of the diantennary glycopolymers. There are two crucial criteria for effective hetero-diantennary glycopolymer design needed to be taken into account. The first is to establish orthogonal reactivity with α-mannoside and β-glucoside moiety that we intend to attach to the bivalent, polymerizable scaffold **234** (Scheme 5.3). To that end, we sought to functionalize both carbohydrates with amine and azido functional groups. While the amine functionality may facilitate an amide coupling to the carboxylic acid of the bifunctional scaffold, the azide group can react with the terminal alkyne of **234**. In addition, an ethylene glycol spacer was employed in the sugars to increase flexibility and solubility of glycopolymers generated from ROMP.

Initially, attempting the TMSOTf-mediated coupling of azido-alcohol **228** with mannosyl trichloroacetimidate **221** resulted in a low yield of the desired product **229** along with the formation of the undesired orthoester (Scheme 5.2). Fortunately, utilizing 5 mol% of readily available $Pd(CH_3CN)_4(BF_4)_2$ catalyst, previously reported in our lab,[204-205] provided **229** in 74% yield (Scheme 2). Subsequent subjection of glycoside **229** to a Staudinger reduction of the azide functionality provided the primary amine **230** in 61% yield. A similar route was used to make β-glucose azide **232** and amine **233**.

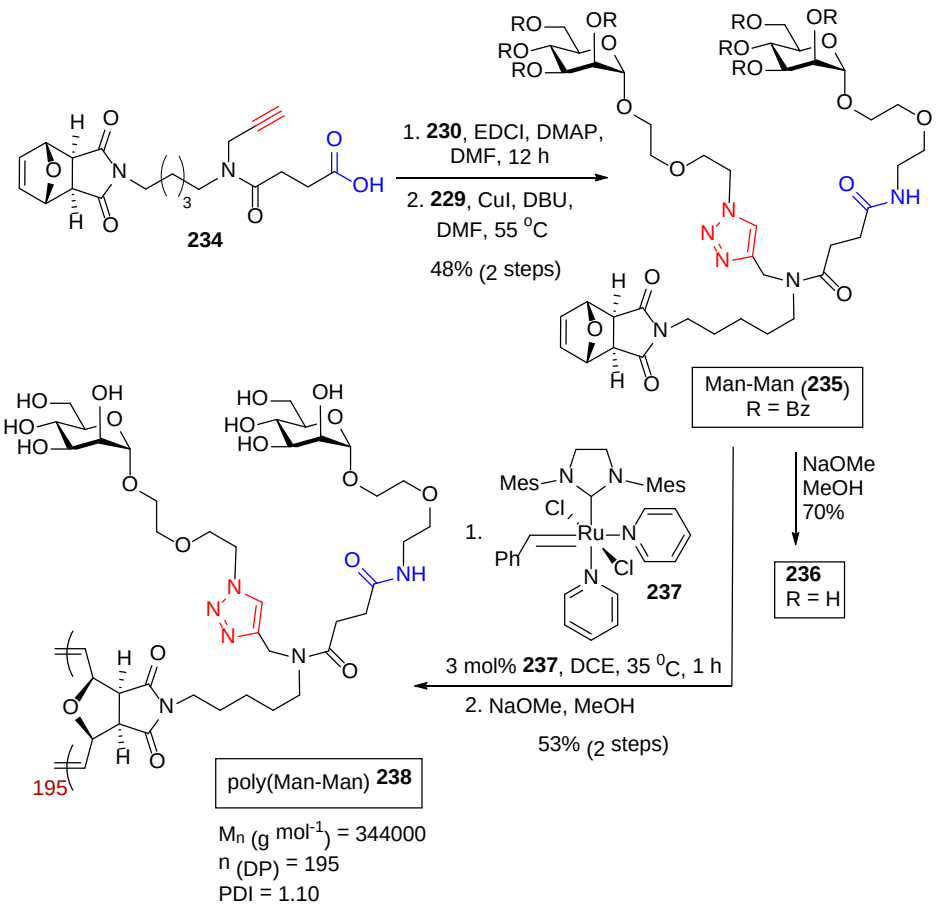


Scheme 5.2. Preperation of α-Mannoside and β-Glucoside Bearing the Azide and Amine Functionality.

The second vital criterion for the efficient heterobifunctional diantennary glycopolymer design involves the spacing between the sugars. Recently, a hetero-bifunctional monomer was synthesized with the calculated spacing between anomeric centers of mannose moieties at about 13 Å using solid state 3D-modeling software.[206] Based on this calculation, we hypothesize that the proximity between two sugar units

facilitates enhanced binding in a similar manner as observed by Mandal and coworkers with branched trisaccharides.[197]

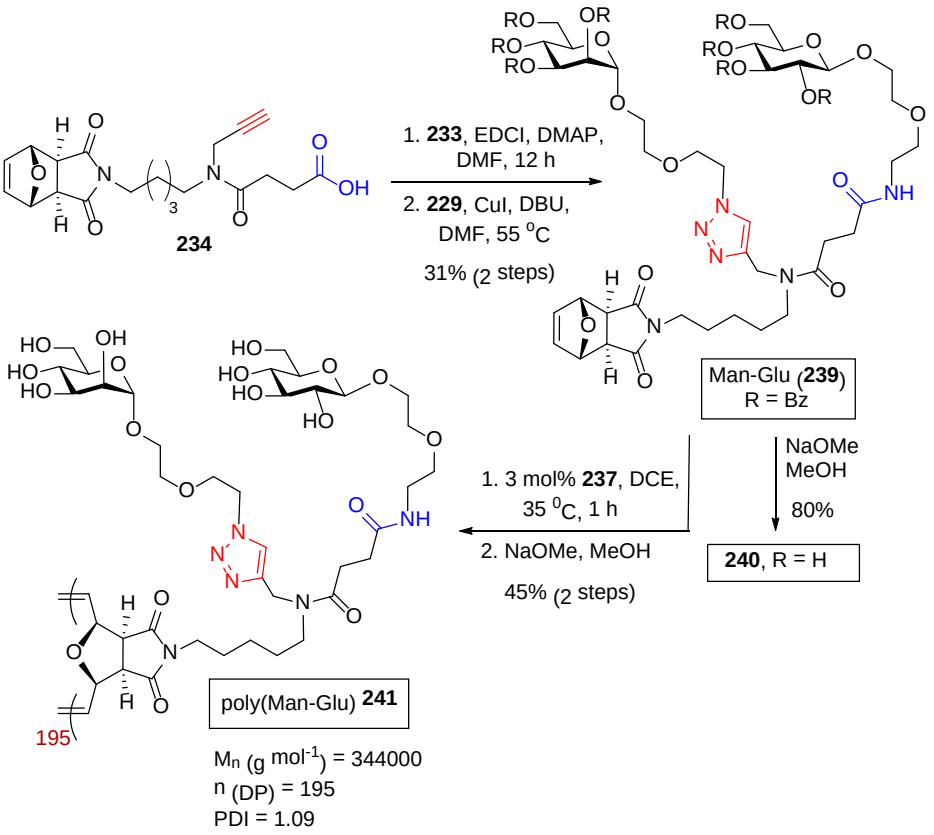
With this approach in mind, each sugar (Scheme 5.2) with its respective orthogonal functionality was sequentially coupled to the diantennary polymerizable scaffold **234** (Schemes 5.3 – 5.5). The synthesis of homofucntional diantennary glycopolymer **238**, poly(Man-Man), (Scheme 5.3) was first investigated. Accordingly, EDCI-mediated amide coupling of linker **234** with mannosyl amine **230** followed by Sharpless-Huisgen azide-alkyne cycloaddition of mannosyl azide **229** produced the homofunctional diantennary monomer, Man-Man (**235**), in 48% yield over two steps. Removal of the benzoyl protecting groups using sodium methoxide gave the deprotected monomer **236** in 70% yield. Unfortunately, Man-Man (**235**) monomer did not undergo polymerization with Grubbs 1st generation catalyst **223**. To address this problem, we investigated ROMP of **235** with the much more reactive Grubbs 3rd generation catalyst **237**. Reaction of **235** with 3 mol% of catalyst **237** in DCE at 35 ^{o}C for 1 h afforded complete conversion to polymer with 195 repeating units and excellent polydispersities (PDI = 1.10). Hydrolysis of the benzoyl protecting groups with NaOMe yielded the homo-diantennary glycopolymer, poly(Man-Man) **238**, in 53% over 2 steps (Scheme 5.3). While higher and lower catalyst loadings were also employed to make larger and smaller homofucntional diantennary glycopolymers (e.g. use of 5 mol% of catalyst **237** provided **238** with DP = 97 and PDI = 1.08), ITC studies of glycopolymers **224** – **227** showed the optimal valency for binding to be 175 repeating units (*vide infra*, Table 2).



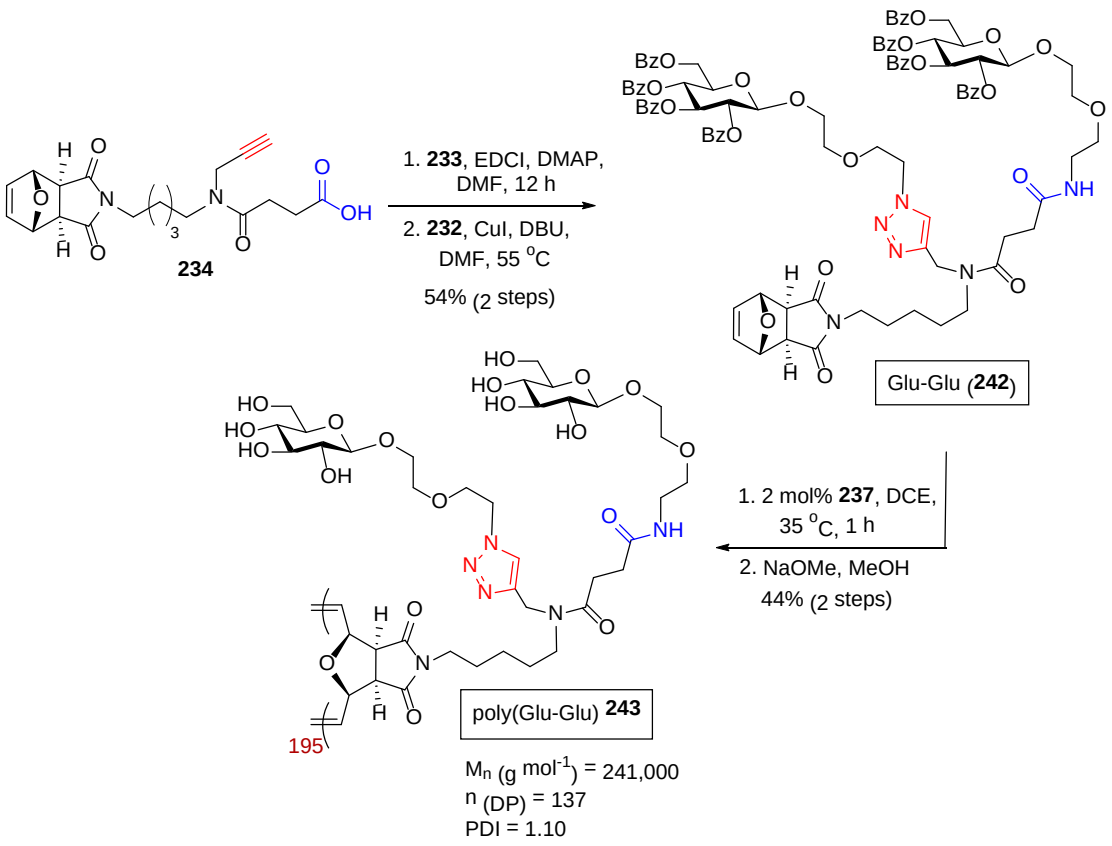
Scheme 5.3. Synthesis and Polymerization of Homofunctional Diantennary Glycomonomer **235**.

The heterobifunctional diantennary glycopolymer **241**, poly(Man-Glu), was prepared similarly to the route used for poly(Man-Man) with the exception of utilizing the amine-functionalized β-glucoside **233** for the amide-bond forming step (Scheme 5.4). Hydrolysis of the benzoyl groups on the heterobifunctional diantennary monomer **239** yielded the deprotected monomer **240** in 80% yield. While slightly less catalyst **237** was used [2.5 mol% vs. 3 mol% for poly(Man-Man)], a similar high valency was accomplished (DP = 195) with a narrow ploydispersity (PDI = 1.09). The poly(Man-Glu)

241 (Scheme 5.4) was formed in 45% yield over two steps. In order to investigate whether polymeric β-glucoside can bind to Con A, we synthesized a homofunctional diantennary glycopolymer poly(Glu-Glu) **243** (Scheme 5.5) in a similar fashion to that for the poly(Man-Man) **238** (Scheme 5.3) and the poly(Man-Glu) **241** (Scheme 5.4). The valency (DP = 137) of poly(Glu-Glu) **243** is somewhat lower than both poly(Man-Man) **238** and poly(Man-Glu) **2341** despite the polymerization being performed with a lower loading of Grubbs III catalyst **237**. Nevertheless, the polydispersities are still narrow (PDI = 1.10).



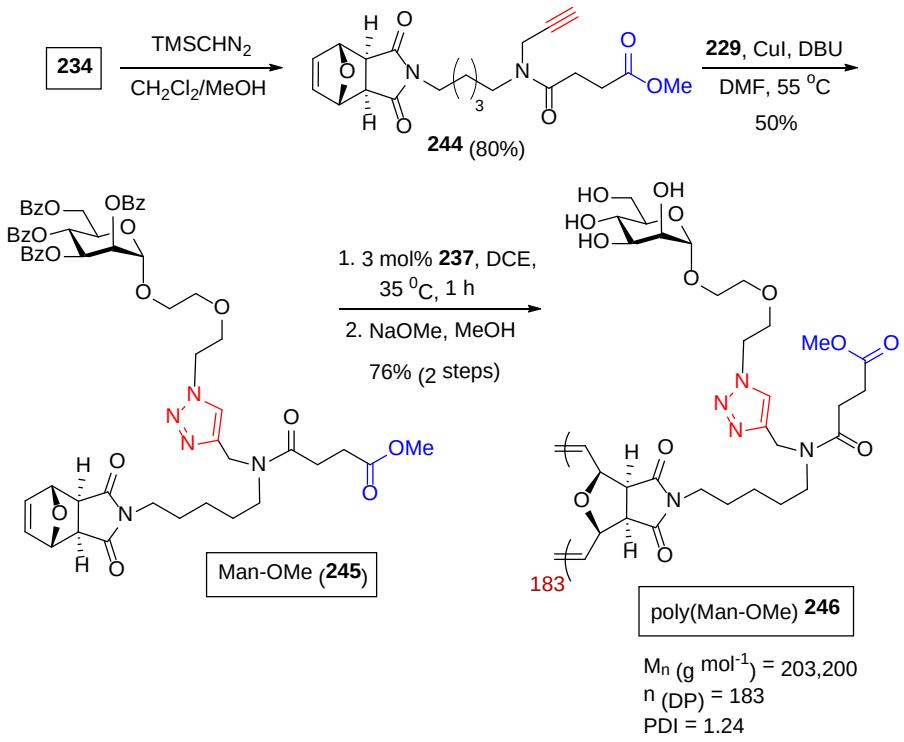
Scheme 5.4. Synthesis and Polymerization of Heterobifunctional Diantennary Glycomonomer **239**.



Scheme 5.5. Synthesis and Polymerization of Homofunctional Diantennary Glycomonomer **242**.

In order to accurately compare the binding affinity of the monoantennary glycopolymers to Con A with the corresponding diantennary glycopolymers, the change in linker must be taken into consideration. A monoantennary glycopolymer **246** (Scheme 5.6) using scaffold **234** as the building block was made as a control experiment for this purpose. The carboxylic acid group in **234** was converted into the methyl ester **244** (Scheme 5.6) using trimethylsilyl diazomethane. Copper(I)-mediated "click" coupling of alkyne **244** with azide **229** provided the monoantennary glycomonomer **245**, Man-OMe, in 50% yield. The monomer **245** was then polymerized using catalyst **237** to form

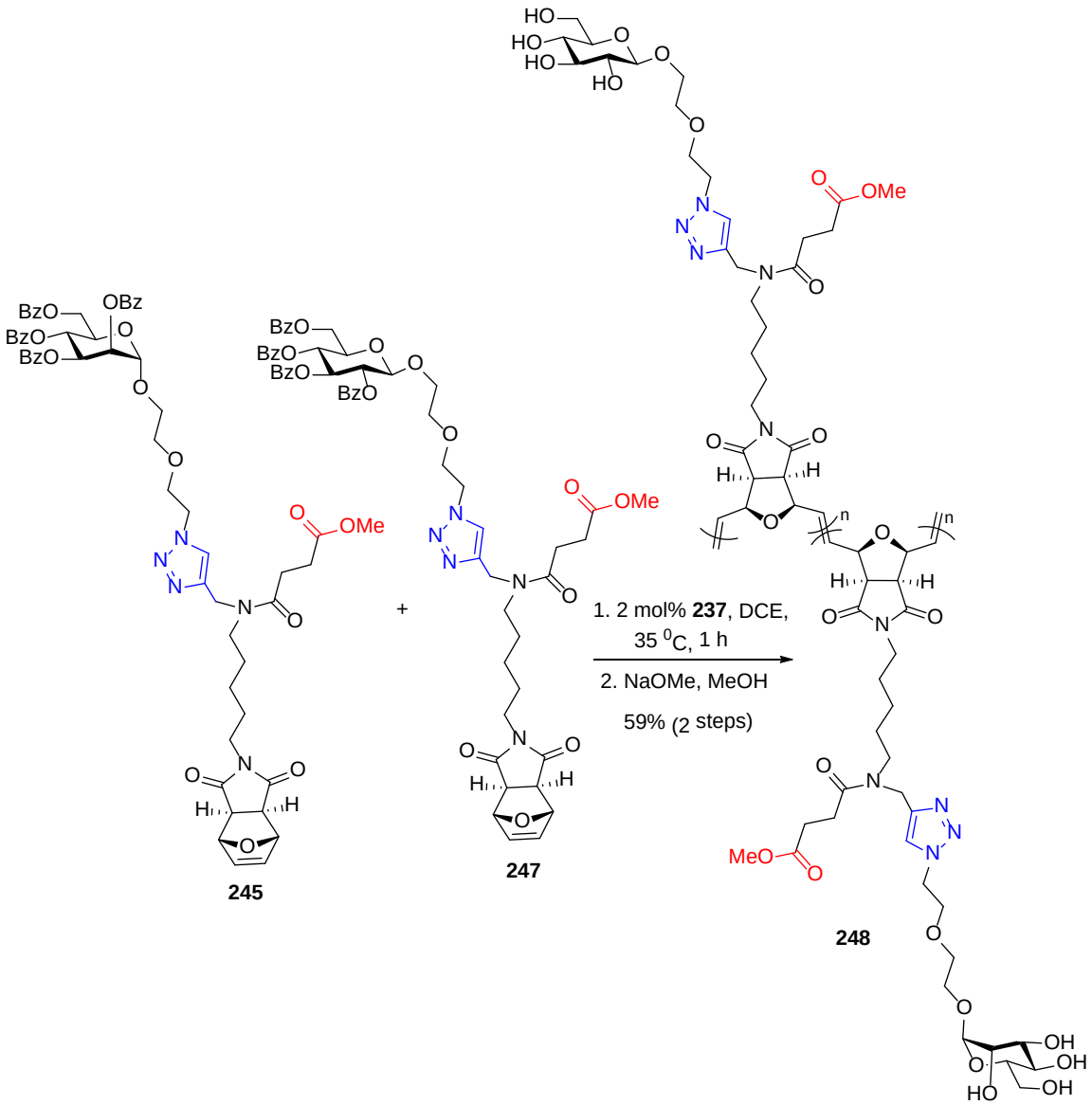
poly(Man-OMe) **246** (Scheme 5.6) with similar valency (DP = 183) and higher polydispersity (PDI = 1.23) to the poly(Man-Man) **238** (Scheme 5.3) and the mono-functional glycopolymer **226** (Table 5.1, entry 3).



Scheme 5.6. Synthesis and Polymerization of Monoantennary Glycomonomer **245**.

We also sought to investigate if the highly-ordered nature of the heterobifunctional glycopolymer poly(Man-Glu) **241** (Scheme 5.4) would enhance binding affinity to Con A. To accomplish this, a control experiment was setup in which a random copolymer of Man-OMe **245** and Glu-OMe **247** (prepared using the same route for **245**) was synthesized in a 1:1 ratio, and subsequent removal of the benzoyl protecting groups provided the co-poly(Man-OMe)-(Glu-OMe) (Scheme 5.7) in 59% yield with a high valency (DP = 173 or about 87 mannose units per polymer) and narrow

polydispersity (PDI=1.05). Given the structural similarity between mannose and glucose unit, we postulated that there is no real difference in reactivity to the Grubb's catalyst **237** between Man-OMe and Glu-OMe monomers. As a result, they are randomly oriented along the polymer chain.



Scheme 5.7. Copolymerization of Monofunctional Glycomonomers **245** and **247**.

With the monofunctional and bifunctional glycopolymers in hand, we next examined the direct measurement of their interactions with Con A by isothermal titration calorimety (ITC). This ITC method can measure the stoichiometry, binding affinity and thermodynamic constants for polymer-Con A interaction in a single experiment.[207-209] For these experiments, a solution of Con A would be injected with aliquots of our synthetic glycopolymers. The concentrations of binding species will be chosen to produce a sigmoidal binding isotherm that comes to saturation. The heat produced or absorbed during the binding reaction would then be determined by measuring the change in the power required to maintain the solution at a constant temperature. These heats are mathematically related to values for change in enthalpy (ΔH), the association constant (K_a) and stoichiometry (n).[207-209] From these constants, the values for the change in Gibbs free energy (ΔG) and the change in entropy (ΔS) can be calculated. The affinity constant (K_d) can be calculated using the equation $K_d = 1/K_a$. Previous studies have illustrated that a lectin with a higher number of binding sites increases the possibility of precipitation.[197] To avoid this problem, we chose to examine the binding affinity of Con A to our glycopolymers at acidic pH, wherein Con A is in its dimeric form rather than tetrameric at higher pH. This is evident in Figure 5.3, in which there is a small amount of noise in the baseline consistent with minimal aggregation. Experimental details are provided in the supporting section. Concentrations of Con A ranged from 0.12 – 0.06 mM and glycopolymer concentrations ranged from 0.338 – 0.017 mM. Titration was done in 100 mM acetate buffer, pH 4.6 in the presence of 1 mM $MnCl_2$, 1 mM $CaCl_2$, and 30 mM NaCl.

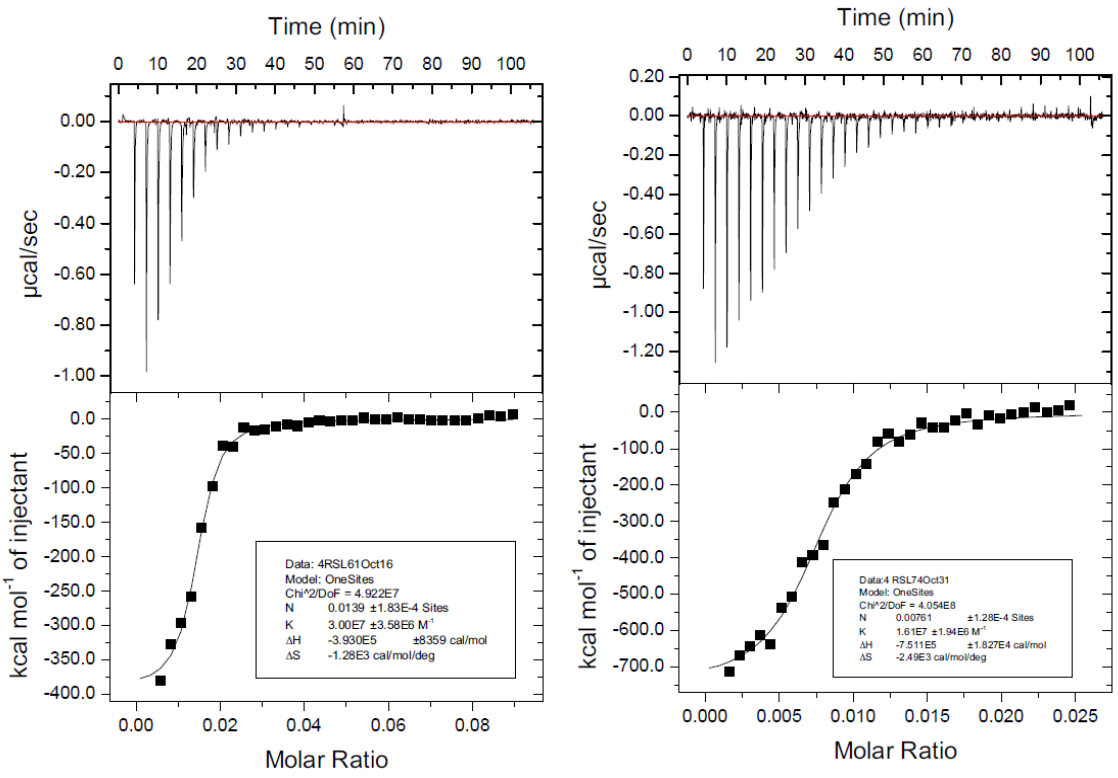


Figure 5.3. Calorimetric Data for (A) poly(Man-Man) **238** and (B) poly(Man-Glu) **241** Binding of Con A. *Top*: Raw Data. *Bottom*: Integrated Data Points with a Best Fit Curve for One Binding Site.

Investigation of ITC values for the glycomonomers and polymers are shown in Table 5.2. The binding affinity (K_a) of methyl mannose is comparable with previously reported values (K_a = 7.6 x 10^3 M^{-1}) (Table 5.2, entry 1).[195] Compared to α-methyl mannose, the K_a of deprotected (Man-Man) **236** was increased about two fold (K_a = 17.3 x 10^3 M^{-1}) (entry 2). Given that two mannose units are present in **236**, this result was expected. A small increase in binding affinity (K_a = 8.6 x 10^3 M^{-1}) of methyl mannose

was observed for deprotected (Man-Glu) **240** (entry 3). This may be due to an additional interaction of the β-glucose unit with Con A.

Upon examining monoantennary glycopolymers **224** – **227** (Table 5.2, entry 4 - 7), we found that increasing the valency resulted in higher binding affinity. For example, glycopolymer **224** (entry 4) with K_a = 537 x 10^3 M^{-1} showed a 70 fold increase in binding affinity over methyl mannoside. The increasing trend continues with glycopolymer **225** (K_a = 3200 x 10^3 M^{-1}) and **226** (K_a = 3880 x 10^3 M^{-1}). However the binding begins to level off with glycopolymer **227** (K_a = 2860 x 10^3 M^{-1}). We hypothesize that steric congestion due to the folding of larger glycopolymers decreases the availability of α-mannose unit. Upon comparison with excellent work reported by the Cloninger group, our synthetic glycopolymers of similar valency to highly branched glycodendrimers have higher binding affinities.[195] For example, the 3rd generation glycodendrimer which displayed 29 mannose units had less binding affinity (K_a = 300 x 10^3 M^{-1}) than that of glycopolymer **224** (K_a = 537 x 10^3 M^{-1}). This may be due to higher conformational flexibility of linear polymer chains than branched dendrimers. The higher flexibility imparts greater availability of α-mannose units. Next, we compare the binding affinity between monoantennary glycopolymer **226** with diantennary polymers **238**, **241**, and **243** (Table 5.2). For instance, poly(Man-Man) **238** (entry 8) (K_a = 30000 x 10^3 M^{-1}) demonstrated a nearly 10-fold increase in binding affinity versus polymer **226** (K_a = 3880 x 10^3 M^{-1}). The increase in binding affinity may due to the interactions of both mannose units with a Con A binding site. Importantly, when one of the mannose units is substituted with non-binding β-glucose poly(Man-Glu) **241** (entry 9), we see a nearly 5-fold increase in binding affinity (K_a = 16100 x 10^3 M^{-1}) from polymer **226**. Although an

enhancement in binding affinity is observed as going from **226** to **241**, the exact mechanism for this increase is unknown at this stage. ITC studies of homofunctional diantennary poly(Glu-Glu) **243** (entry 10), determined that polymeric β-glucose does not, by itself, bind to Con A. This result also demonstrates the polymeric scaffold does not play a role in Con A binding. However, the change in linker from the monoantennary scaffold to the diantennary counterpart did show 2-fold increase in binding when comparing glycopolymer **226** (entry 6) with poly(Man-OMe) **246** (entry 11, K_a = 7940 x 10^3 M^{-1}). This can possibly be attributed to the increase in linker length which allows for increased flexibility and availability of pendant mannose units. It has also been speculated that the triazoles participate in binding to Con A.[191] In comparison, poly(Man-OMe) **246** did not bind as strongly as heterobifunctional diantennary poly(Man-Glu) **241** (bearing a non-binding β-glucose unit), suggesting additional interaction of the β-glucose unit to ConA. In order to examine whether the close proximity of the mannose and glucose moieties in poly(Man-Glu) **241** result in higher avidity, ITC measurements were also performed on the heterobifunctional monoantennary copolymer poly(Man-OMe)-(Glu-OMe) **248**, and its binding affinity (entry 12, K_a = 2340 x 10^3 M^{-1}) was much lower than poly(Man-Glu) **241** (entry 9). This result demonstrates the importance of the highly ordered diantennary architecture.

entry	Polymers	DP[a]	K_a[b]/M^{-1} x 10^3	ΔH[b]/kcal mol^{-1}	ΔH per sugar /kcal mol^{-1}	ΔG/kcal mol^{-1}	$T\Delta S$/kcal mol^{-1}	n[b]	N[c]
1	Man	1	7.60	-7.30	-7.30	-5.2	-2.1	1.120	1
2	**236**	2	7.60	-7.30	-7.30	-5.2	-2.1	0.390	2
3	**240**	2	7.60	-7.30	-7.30	-5.2	-2.1	0.813	1
4	**224**	30	537	-41.40	-1.38	-7.8	-33.6	0.171	6
5	**225**	57	3200	-92.80	-1.63	-9.3	-83.5	0.060	17
6	**226**	172	3880	-196.8	-1.12	-9.6	-187.2	0.030	34
7	**227**	222	2860	-456.4	-2.06	-10.7	-445.7	0.0184	54
8	**238**	195	30000	-786.0	-2.01	-84.0	-701.8	0.0139	72
9	**241**	195	16100	-751.1	-1.93	-69.5	-682.6	0.0140	72
10	**243**	137	No Binding						
11	**246**	183	7940	-414.2	-2.26	-8.72	-405.5	0.0148	67
12	**248**	173	2340	-214.0	-1.24	-8.0	-206.0	0.0331	30

[a] DP = degree of polymerization determined by GPC. [b] Errors for K_a, n, and ΔH are 2 - 15%, 1 - 4%, and 1 - 12%, respectively. [c] Number of binding sites: N = 1/n (n: number of lectin binding sites)

Table 5.2. ITC Studies of Glycopolymers/ConA Binding Affinity.

Our data in Table 5.2 showed that the enthalpy (ΔH) increases almost linearly with valency, meaning there is very little variation in ΔH per mannose residue, (-2.26 kcal/mol for poly(Man-OMe) **246** to -1.12 kcal/mol for monofunctional glycopolymer **226**). However, $T\Delta S$ increases unfavourably with additional valency but is ultimately overcome by a strongly exothermic ΔH value, leading to a negative ΔG in all cases. Similar results have been obtained for different systems by Dam and Wang.[196-197] The stoichiometry (n) defined as the amount of ligands per binding site is generally better expressed as functional valency (N), which describes the binding sites or Con A proteins per polymer chain (Table 5.2). In all cases, the functional valency N is less than valency (DP) of each glycopolymer (entries 4 – 12) suggesting that not all of α-mannose residues

are participating in the binding. For the monofunctional glycopolymers **224** – **227** (Table 5.2), the functional valency (*N)* value does, however, increase as valency (DP) increases up to *N* = 54 for glycopolymer **227** with a valency of 222 (Table 5.2, entry 7). In the case of diantennary glycopolymers, the increased ligand density and valency (DP = 2 x 195 = 380 mannose units per polymer chain) of poly(Man-Man) **238** (entry 8) potentially allowed for the binding of more Con A protein units per glycopolymer *N* = 72. Interestingly, poly(Man-Glu) **241** (entry 9) also showed the same functional valency *N* = 72, despite having half as many mannose residues per polymer chain. Overall, these results may suggest that only the α-mannose moieties in both diantennary glycopolymers **238** and **241** are involved in binding. Although this is further evident by the similar functional valency (*N* = 67) for the poly(Man-OMe) **246** (entry 9), the K_a values for the poly(Man-Man) **238**, poly(Man-Glu) **241**, and poly(Man-OMe) **246** are very different. Taken these data together, we postulated that β-glucose may not be involved in the number of bound Con A proteins but is involved in enhancing overall avidity to Con A.

5.3 Conclusion

In conclusion, we have synthesized a highly ordered hetero-diantennary glycopolymer consisting of binding α-mannose and non-binding β-glucose residues using ROMP. We are the first to report the investigation of linear glycopolymer interaction with a GPB using ITC. We discovered that the bifunctional glycopolymers have a higher binding affinity to Con A protein than monoantennary glycopolymers consisting of only strong binding α-mannose units. Although β-glucose is normally unable to bind to Con

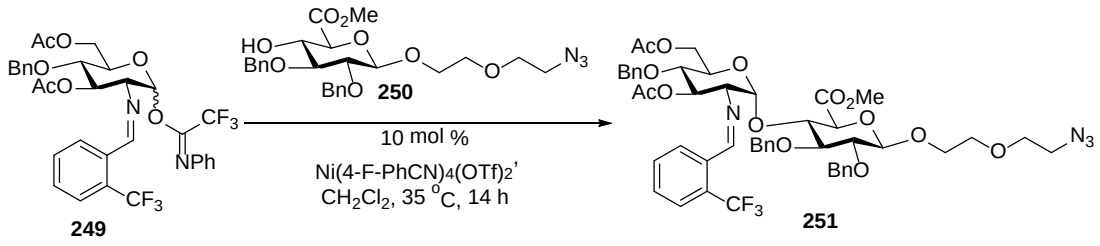
A, the close proximity of the mannose and glucose residues in the synthetic hetero-diantennary glycopolymer enhances overall binding affinity. Further examination of the mechanism of binding enhancement for diantennary poly(Man-Glu) will be reported in due course. The hetero-diantennary architecture represents a unique means of examining other GPBs in the future. This approach presented here, using ITC direct measurements of the affinity constant, thermodynamic parameters, and stoichiometry for carbohydrate-protein interactions, provides a general platform for investigating other interactions between glycopolymers and biomolecules.

CHAPTER 6

PARTIALLY SULFATED HEPARAN DISSACHARIDE-FUNCTIONALIZED GLYCOPOLYMERS AS INHIBITORS OF HEPARANASE: PRELIMINARY RESULTS AND FUTURE DIRECTIONS

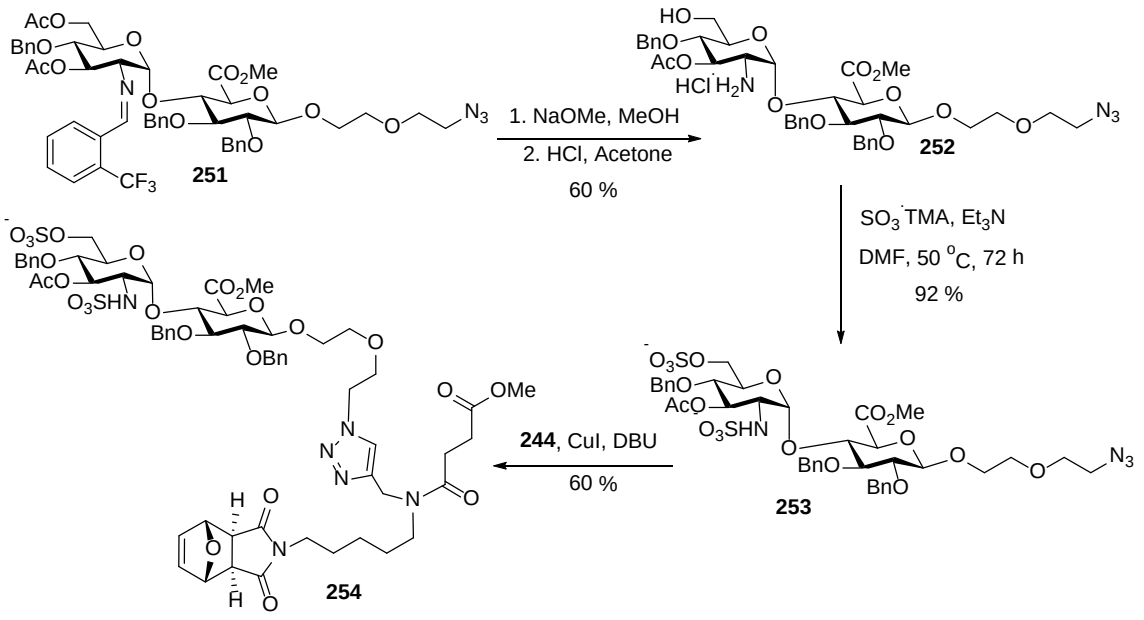
6.1: Preliminary Results

Previous work in our lab had shown that glucuronic acid derivatives can serve as useful acceptors in the α-selective Ni catalyzed coupling with C(2)-*N*-benzylidine protected trichloroacetimidate donors.[35] We have also demonstrated the ability to bind GPBs such as Con A using bifunctional multivalent binding glycopolymers. In our efforts to combine these concepts to create effective heparanase inhibitors, we first sought to glycosylate an azido linked GlcA acceptor **250** with our *N*-phenyl trifluoroimidate donors. We were happy to report that the glycosylation GlcA acceptor **250** with C(2)-*N*-(2-trifluoromethyl)-benzylidine donor **249** proceeded in good yield (85%) with α-only selectivity of the disaccharide **251**.



Scheme 6.1. Glycosylation of GlcA Acceptor **250** Bearing the Azide Functionality.

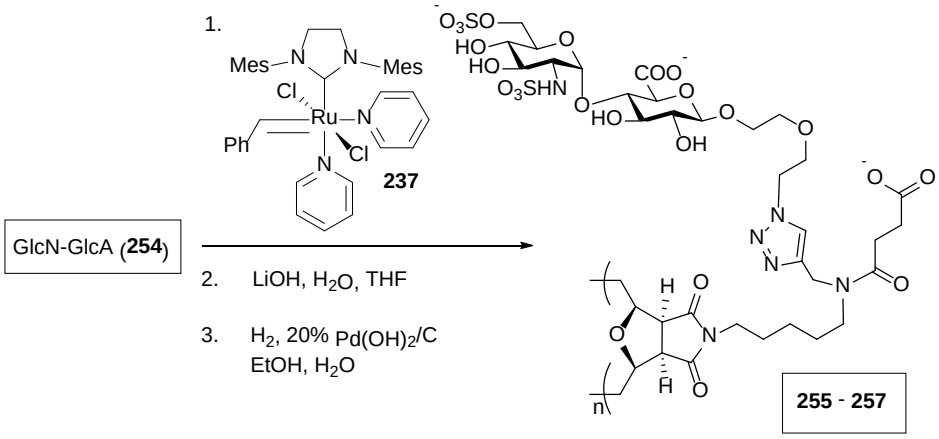
In an effort to make a simple, polymerizable glycomonomer based on the HS disaccharide for initial screening, monoantennary (GlcN-GlcA) **254** glycomonomer was synthesized (Scheme 6.2). The C(6)-acetate and C(2)-*N*-benzylidine of **251** were removed in a one-pot reaction using sodium methoxide in methanol and hydrochloric acid in acetone, respectively, to give the partially deprotected azide **252** in 60% yield. The C(2)-amine and C(6)-hydroxyl groups on **252** were then sulfated using sulfur trioxide trimethyl amine to give the partially sulfated disaccharide **253** in 92% yield. "Click" coupling of the azide **253** with the terminal alkyne in **244** gave the polymerizable (GlcN-GlcA) **254** monomer in 60% yield.



Scheme 6.2. Synthesis of (GlcN-GlcA) **254** Glycomonomer.

The polymerization of (GlcN-GlcA) **254** was carried out using Grubbs' 3rd generation catalyst **237** in a similar fashion as (Man-Man) **238**. At 25 mol % loading of

catalyst **237**, a short oligomer **255** (DP = 9) was made with low PDI (PDI = 1.21) (Table 6.1, entry 1). At lower catalytic loadings (entries 2 and 3), a higher molecular weight and degree of polymerization (DP = 22 and DP = 51) were observed with low PDI (PDI = 1.22 and PDI = 1.29). The acetate and methyl ester of the protected polymers were removed using lithium hydroxide and hydrogen peroxide. Further deprotection of the benzyl ether groups was accomplished via hydrogenolysis in the presence of Pearlman's catalyst (20% $Pd(OH)_2/C$) to afford the deprotected poly(GlcN-GlcA) in moderate yields (33 – 38%).



entry	Polymer	**237**	Mn[a]	DP[a]	PDI[a]	Yield[b]
1	**255**	25 mol %	11 kDa	9	1.21	38%
2	**256**	17 mol %	29 kDa	22	1.22	35%
3	**257**	10 mol %	69 kDa	51	1.29	33%

[a] Number average molecular weight (Mn), degree of polymerization (DP), and polydispersity index (PDI) of glycopolymers were determined by gel permeation chromatography (GPC). [b] Isolated yield.

Table 6.1. ROMP of (GlcN-GlcA) using Grubb's 3rd Generation Catalyst **237**.

6.2: Future Direction

Alongside poly(GlcN-GlcA) different homofunctional monoantennary glycopolymers bearing glucuronic acid β(1-4) linked glucosamine, glucosamine α(1-4) linked iduronic acid, and iduronic acid β(1-4) linked glucosamine will be screened for inhibition of heparanase activity. With the ideal polymer chain length for inhibition determined, homobifunctional and heterobifunctional diantennary glycopolymers consisting of glucuronic acid, glucosamine, and iduronic acid in various permutations will be screened for heparanase inhibition. In order to accurately probe the thermodynamics of heperanase binding, ITC studies will be conducted to measure the binding affinity, enthalpy and functional valency of glycopolymer/heparanase interactions. *In vivo* studies involving cancer cell growth may be conducted depending on the inhibition and ITC results.

Development and advancement of the stereoselective coupling of C(2)-aminosugars using our nickel catalyst will prove vital in preparing the significant amount of glycopolymer required for these studies. Furthermore, the diantennary architecture of glycopolymers, which were determined to have the highest binding affinity in the case of mannose/Con A interactions, allows for a wider range of substrates to be screened.

CHAPTER 7

EXPERIMENTAL PARAGRAPHS

Methods and Reagents. All reactions were performed in oven-dried Schlenk flasks fitted with glass stoppers under a positive pressure of argon. 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 and performed 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 and employed 230-400 mesh silica gel. Dichloromethane was distilled from calcium hydride under an argon atmosphere at 760 torr. All other chemicals were obtained from commercial vendors and used without further purification.

Instrumentation. All proton (^{1}H) nuclear magnetic resonance spectra were recorded on 300, 400, and 500 MHz spectrometers. All carbon (^{13}C) nuclear magnetic resonance spectra were recorded on 75, 100, 125, 150 MHz) NMR spectrometer. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.27 ppm, δ 77.23 ppm; DMSO-d_6: δ 2.50 ppm, δ 39.52 ppm; D_2O: δ 4.79 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. Microcal iTC_{200} from GE health care was used to perform ITC experiments.

Isothermal Titration Calorimetry. Microcal iTC_{200} from GE health care was used to perform ITC experiments. Concanavalin A (Con A) was dialyzed using Slide-A-Lyzer® dialysis cassette with 10000 MW cut off against 100 mM acetate buffer, pH 4.6 in the presence of 1 mM $MnCl_2$, 1 mM $CaCl_2$, and 30 mM NaCl. Concentrations of Con A were determined by spectrophotometry at 280 nm using $A^{1\%,1\ cm} = 12.4$ (expressed in terms of the monomer, MW = 25600 g mol^{-1}) and glycopolymers by colorimetry.[195] Concentrations of Con A ranged from 0.42 – 0.06 mM, glycopolymers from 0.338 – 0.017 mM, and glycomonomers from 7.55 – 8.03 mM. Titrations were performed at 25° C with stirring speed of 1000 rpm. Injections of 1 μL of glycopolymer in the same buffer were added into the sample solution of Con A (cell volume = 200 μL) from a computer controlled 40 μL syringe at an interval of 2 sec. Injections of 2 μL of glycomonomer in the same buffer were added into the sample solution of Con A (cell volume = 200 μL) from a computer controlled 40 μL syringe at an interval of 4 sec. The experimental data were fitted to a theoretical titration curve using software supplied by Microcal. A standard one site model was used with ΔH (enthalpy change in kcal mol^{-1}), Ka (association constant in M^{-1}), and n (number of binding sites per monomer) as variable parameters.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Trifluoromethylbenzylideneamino-D-Glucopyranosyl Trichloroacetimidate 93.[35] A 25 mL oven-dried Schlenk flask was charged with hemiacetal (0.77 g, 1.678 mmol, 1.0 equiv.) and dichloromethane (8 mL).

The solution was cooled 0 ^{o}C, and trichloroacetonitrile (0.5 mL, 5.035 mmol, 3.0 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 **93** (0.8 g, 78%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 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).

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-D-Glucopyranosyl Trichloroacetimidate 99.[35] A 25 mL oven-dried Schlenk flask was charged with the hemiacetal (0.77 g, 1.678 mmol, 1.0 equiv.) and dichloromethane (8 mL). The solution was cooled to 0 ^{o}C and trichloroacetonitrile (0.5 mL, 5.035 mmol, 3.0 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 **99** (0.74 g, 73%) ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.69 (d, *J* = 2.0 Hz, 1H), 8.65 (s, 1H), 7.67 (t, *J* = 6.0 Hz, 1H), 7.55 – 7.52 (m, 2H), 6.49 (d, *J* = 3.6 Hz, 1H), 5.69 (t, *J* = 10.0 Hz, 1H), 5.26 (t, *J* = 9.6 Hz, 1H), 4.39 – 4.33 (m, 2H), 4.19 – 4.17 (m, 1H), 3.93 (dd, *J* = 10.0, 3.2 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H), 1.90 (s, 3H).

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-D-Glucopyranosyl *N*-Phenyl Trifluoroacetimidate 107. A 100 mL round bottom flask was charged with triacetyl D-glucosamine hemiacetal[36] (4.9 g, 10.6 mmol, 1.0 equiv.), 2,2,2-trifluoro-*N*-phenyl-ethanimidoyl chloride (6.66 g, 31.9 mmol, 3.0 equiv.), K_2CO_3 (2.93 g, 21.2 mmol, 2.0 equiv.) and acetone (30 mL). The solution was stirred at room temperature overnight. When the reaction was complete as monitored by TLC (hexane/ethyl acetate = 3/1), the mixture was filtered, evaporated, and then purified by flash chromatography on silica gel (hexane/ethyl acetate = 5/1 → 3/1 with 1% Et_3N) to afford **107** (5.26 g, 80%, α:β = 1:4). **107a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.68 (s, 1 H), 8.22 (d, *J* = 7.6 Hz, 1 H), 7.73-7.52 (m, 3 H), 7.25-7.13 (m, 2 H), 7.12-6.98 (m, 1 H), 6.88-6.65 (m, 2 H), 6.44 (brs, 1 H), 6.65 (t, *J* = 10.0 Hz, 1 H), 5.23 (t, *J* = 10.0 Hz, 1 H), 4.48-4.27 (m, 2 H), 4.22-4.08 (m, 1 H), 3.88-3.77 (m, 1 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.89 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.4, 169.7, 169.5, 161.5, 143.2, 133.1, 132.1, 131.0, 129.4 (q, $J_{C\text{-}F}$ = 30.5 Hz), 128.64, 128.59, 125.6 (q, $J_{C\text{-}F}$ = 5.6 Hz), 124.3, 124.0 (d, $J_{C\text{-}F}$ = 272 Hz), 119.4, 94.7, 71.1, 70.5, 68.0, 61.7, 20.55, 20.50, 20.2; IR (film, cm^{-1}): ν = 2963, 1752, 1644, 1367, 1315, 1212; HRMS (ESI): calc. for $C_{28}H_{26}F_6N_2O_8Na$ (M+Na): 655.1491; found: 655.1497. **107b**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.68 (d, J = 2.4 Hz, 1 H), 8.11 (d, *J* = 7.6 Hz, 1 H), 7.71 (d, *J* = 7.2 Hz, 1 H), 7.68-7.51 (m, 2 H), 7.38-7.27 (m, 2 H), 7.19-7.07 (m, 1 H), 6.82 (d, *J* = 7.6 Hz, 2 H), 6.02 (brs, 1 H), 5.46 (t, J = 10.0 Hz, 1 H), 5.19 (t, *J* = 10.0 Hz, 1 H), 4.34 (dd, *J* = 12.4, 4.8 Hz, 1 H), 4.17 (dd, *J* = 12.4, 2.0 Hz, 1 H), 3.93-3.76 (m, 1 H), 3.71 (t, *J* = 8.8 Hz, 1 H), 2.10 (s, 3 H), 2.04 (s, 3 H), 1.93 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.4, 169.5, 143.2, 133.3, 132.1, 130.9, 129.3 (q, $J_{C\text{-}F}$ = 31.0 Hz), 128.7, 128.6, 125.6 (q, $J_{C\text{-}F}$ = 5.5 Hz), 124.4, 124.0 (d,

$J_{C\text{-}F}$ = 272 Hz), 119.2, 95.7, 73.3, 72.9, 72.7, 68.0, 61.7, 20.53, 20.47, 20.2; IR (film, cm^{-1}): ν = 2887, 1752, 1645, 1489, 1315, 1231; HRMS (ESI): calc. for $C_{28}H_{26}F_6N_2O_8Na$ (M+Na): 655.1491; found: 655.1511.

6-*O*-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-inositol 142.[210] A 100 mL oven-dried, Ar flushed Schlenk flask was charged with **141**[35] (5.1 g, 10.4 mmol, 1.0 equiv.), anhydrous pyridine (35 mL), acetic anhydride (2.9 mL, 31.2 mmol, 3.0 equiv.), and DMAP (63.5 mg, 0.52 mmol, 0.05 equiv.). The resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated by azeotropic removal of pyridine with toluene (2 x 100 mL). The residue was redissolved in CH_2Cl_2 (150 mL) and washed with sat. aq. $CuSO_4$ (3 x 50 mL) and water (1 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to a yellow oil. The yellow oil was dissolved in MeOH (194 mL) in a 500 mL RBF. An aqueous solution of 5 N HCl (5.8 mL, 29.12 mmol, 3.0 equiv.) was added, and the reaction mixture was stirred for approximately 1.5 h. The reaction mixture was quenched with triethylamine (4 mL) and concentrated to form crude **142**. Crude **142** was purified by flash column chromatography (hexane/ethyl acetate = 3/1 → 1/5) to afford **142** (3.47 g, 72%) as a clear, colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36 – 7.26 (m, 15H), 5.33 (t, *J* = 10.0 Hz, 1H), 4.88 – 4.83 (m, 3H), 4.78 – 4.67 (m, 3H), 4.17 (t, *J* = 2.8 Hz, 1H), 3.99 (t, *J* = 9.2 Hz, 1H), 3.50 – 3.45 (m, 3H), 2.58 (bs, 1H), 2.02 (s, 3H), 1.56 (bs, 1H).

6-*O*-Acetyl-3,4,5-Tri-*O*-Benzyl-1-*O*-(4-methoxybenzyl)-*myo*-Inositol 143. An oven dried 50 mL round bottom flask was charged with **142**[210] (100 mg, 0.203 mmol, 1

equiv.), and anhydrous Toluene (4 mL). The solution was heated to 120 ^{o}C under reflux with a Dean-Stark trap. Dibutyl tin oxide (101.5 mg, 0.406 mmol, 2 equiv) was added and the reaction mixture was stirred for 4 h. The reaction mixture was cooled to 25 ^{o}C, and tetrabutylammonium iodide (82.4 mg, 0.223 mmol, 1.1 equiv) and *p*-methoxybenzyl chloride (276.4 µL, 2.03 mmol, 10 equiv) were sequentially added. The mixture was refluxed at 120 ^{o}C for 4 h and then concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (4/1 hexane/ethyl acetate $\rightarrow$ 2/1 hexane/ethyl acetate) to provide pure **143** (68.2 mg, 55%) as a semisolid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.32 (m, 18H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.52 (t, *J* = 9.9 Hz, 1H), 5.37 (t, *J* = 9.9 Hz, 1H), 4.95 (d, *J* = 10.5 Hz, 1H), 4.84 (dd, *J* = 6.6, 4.8 Hz, 2H), 4.76 (s, 2H), 4.62 (t, *J* = 11.7, 2H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.22 (t, *J* = 2.7 Hz, 1H), 4.11 (t, *J* = 9.6 Hz 1H), 3.83 (s, 3H), 3.43 (t, *J* = 9.6 Hz, 2H), 3.30 (dd, *J* = 9.9 Hz, 2.7 Hz, 1H), 2.58 (s, 1H), 1.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.9, 159.4, 138.6, 138.4, 137.9, 129.6, 129.3, 128.5, 128.3, 128.1, 127.9, 127.7, 127.6, 127.6, 113.9, 81.0, 80.9 79.4, 77.2, 76.9, 75.9 75.3, 72.7, 72.7, 71.7, 67.0, 55.3, 21.0. IR (film, cm^{-1}): ν = 3488, 3087, 3062, 3030, 3005, 2908, 2873, 1746, 1612, 1586, 1513, 1496, 1455, 1421, 1364, 1302, 1243, 1174, 1149, 1131, 1086, 1070, 1028. HRMS (ESI): calc. for $C_{37}H_{40}O_8$ (M+Na): 635.2620 ; found: 635.2621.

2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-1-*O*-(4-methoxybenzyl)-*myo*-Inositol 144. A 25 mL oven-dried Schlenk was charged with **143** (2.083 g, 3.4 mmol, 1 equiv.) and anhydrous pyridine (11.3 mL). The solution was cooled to 0 ^{o}C, and acetic anhydride (0.964 mL, 10.2 mmol, 3 equiv) and dimethylaminopyridine (20.7 mg, 0.17 mmol, 0.05

equiv.) were sequentially added. The resulting mixture was stirred at room temperature overnight. The mixture was poured into ice where a precipitate was formed. The precipitate was filtered, dissolved in ethyl acetate, and dried with anhydrous sodium sulfate. The ethyl acetate solution was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (2/1, hexane/ethyl acetate) to provide pure **144** (1.34 g, 60%) as a semisolid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.32 (m, 18H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.81 (t, *J* = 3.0 Hz, 1H), 5.40 (t, *J* = 9.9 Hz, 1H), 4.92-4.73 (m, 4H), 4.63-4.53 (m, 3H), 4.34 (d, *J* = 12.0 Hz, 1H), 3.95 (t, *J* = 9.6 Hz, 1H), 3.82 (s, 3H), 3.48-3.40 (m, 2H), 3.32 (dd, *J* = 10.2, 3.0 Hz, 1H), 2.12 (s, 3H), 1.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.8, 170.4, 169.9, 164.6, 159.3, 138.5, 138.2, 137.5, 132.0, 129.5, 129.4, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 114.3, 113.8, 81.4, 80.9, 78.0, 77.2, 75.9, 75.6, 74.5, 72.8, 72.2, 71.0, 66.1, 55.6, 55.3, 21.1, 21.0. IR (film, cm^{-1}): ν = 3392, 3075, 3065, 3030, 3004, 2950, 2933, 2857, 2803, 1748, 1698, 1685, 1599, 1508, 1455, 1367, 1244, 1180, 1160, 1139, 1095, 1074, 1029. HRMS (ESI): calc. for $C_{39}H_{42}O_9$ (M+Na): 677.2727 ; found: 677.2723.

2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 145. A 250 mL round bottom flask was charged with **144** (1.33 g, 2.031 mmol, 1 equiv.), CH_2Cl_2 (34 mL), H_2O (1.3 mL), and 2,3-dichloro-5,6-dicyanobenzoquinone (691.7 mg, 3.05 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature while being monitored by TLC. After 1 h and 20 min the mixture was concentrated to a dark oil and purified by silica gel flash chromatography (1/1, hexane/ethyl acetate) to provide pure **145** (833.6 mg, 77%) as a viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.35-7.29 (m, 15H), 5.71 (t, *J* = 2.7 Hz,

1H), 5.27 (t, *J* = 9.9 Hz, 1H), 4.90 (t, *J* = 11.1 Hz, 2H), 4.78 (d, *J* = 10.5 Hz, 2H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 3.90 (t, *J* = 9.6 Hz, 1H), 3.66 (t, *J* = 7.2 Hz, 1H), 3.53 (t, *J* = 9.6 Hz, 2H), 2.28 (d, *J* = 8.1 Hz, 1H), 2.21 (s, 3H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.6, 170.5, 138.4, 138.2, 137.5, 128.4, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 81.3, 80.5, 78.0, 77.3, 77.0, 76.7, 75.9, 75.7, 74.9, 72.2, 70.2, 69.6, 21.0, 20.9. IR (film, cm^{-1}): ν = ν = 3449, 2926, 1744, 1455, 1369, 1226, 1051. HRMS (ESI): calc. for $C_{31}H_{34}O_8$ (M+Na): 557.2151; found: 557.2143.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Fluorobenzylideneamino-D-Glucopyranosyl Trichloroacetimidate 146.[35] A 100 mL oven-dried Schlenk was charged with hemiacetal (2.4g, 5.67 mmol, 1 equiv) and dichloromethane (30 mL). The solution was cooled to 0 °C, and trichloroacetonitrile (1.7 mL, 17.01 mmol, 3 equiv) was then added to the reaction mixture followed by DBU (0.42 mL, 2.84 mmol, 0.5 equiv). The resulting mixture was stirred at this temperature for 4 h and then concentrated in vacuo. The residue was purified by silica gel flash chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to provide trichloroacetimidate **146** (2.89 g, 90%) as a yellow solid. ^1H NMR (CDCl3, 500 MHz): δ = 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* = 10.0 Hz, 1H), 4.35-4.31 (m, 2H), 4.13 (d, *J* = 10.5 Hz, 1H), 3.82 (dd, *J* = 10.0, 3.5 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.87 (s, 3H).

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Trifluoromethylbenzylidene-amino-α-D-Glucopyranosyl-(1→1)-2,3,4,5,6-Penta-*O*-Acetyl-*myo*-Inositol 149. A 10 mL oven

dried Schlenk flask was charged with imidate **93**[35] (83.4 mg, 0.138 mmol, 1.0 equiv), inositol **147** (64.6 mg, 0.166 mmol, 1.2 equiv), and dichloromethane (1 mL). A preformed solution of $Ni(4\text{-}PhCN)_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-}F\text{-}PhCN)_4Cl_2$ (8.47 mg, 0.0138 mmol, 10 mol %) and AgOTf (7.09 mg, 0.0276 mmol, 20 mol %) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 °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 → 1/1, hexane/ethyl acetate + 1% triethylamine) to give the desired pseudo-disaccharide **149** (72.4 mg, 63%, α:β = 6:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.29 (s, 1 H), 7.86 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 5.70 (t, *J* = 2.8 Hz, 1 H), 5.72 (t, *J* = 10.4 Hz, 1 H), 5.30 (t, *J* = 10.4 Hz, 1 H), 5.44 (t, *J* = 10.4 Hz, 1 H), 5.16-4.95 (m, 3 H), 4.33(dd, *J* = 12.0, 2.8 Hz, 1 H), 4.26-4.03 (m, 1 H), 4.16-4.09 (m, 2 H), 3.98 (dd, *J* = 10.4, 2.8 Hz, 1 H), 3.59 (dd, *J* = 10.4, 2.8 Hz, 1 H), 2.33 (s, 3 H), 2.14 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 6 H), 2.00 (s, 3 H), 1.82 (s, 3 H), 1.55 (s, 3 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 170.7, 170.3, 170.0, 169.9, 169.7, 169.5, 169.2, 169.0, 163.3, 138.1, 128.9, 125.7, 123.7 (q, $J_{C\text{-}F}$ = 270 Hz), 100.5, 74.4, 72.2, 71.2, 71.1, 70.0, 69.12, 69.09, 69.06, 68.9, 68.3, 62.1, 20.8, 20.64, 20.61, 20.5, 20.4, 20.3. IR (film, cm^{-1}): ν = 2882, 1751, 1644, 1368, 1221. HRMS (ESI): calc. for $C_{36}H_{42}F_3NO_{18}Na$ (M+Na): 856.2252; found: 856.2256.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Fluorobenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2,3,4,5-Penta-*O*-Benzyl-*myo*-Inositol 150. An oven dried, Ar flushed 10 mL Schlenk flask was charged with **93** (83.4 mg, 0.15 mmol, 1.0 equiv), **148** (123 mg, 0.195

mmol, 1.3 equiv), and dichloromethane (1 mL). The resulting mixture was cooled to 0 ^{o}C after which Ni(4-F-Ph-CN)$_4$(OTf)$_2$ (1.0 mL, 0.015 mmol, 10 mol %) was added. The reaction mixture was stirred at room temperature. When the reaction was complete as monitored by TLC (hexane/ethyl acetate = 3/1), the reaction mixture was filtered, evaporated, and purified by flash chromatography on silica gel (hexane/ethyl acetate = 3/1 → 3/2 with 1% Et$_3$N) to give **150** as a yellow solid (104 mg, 78%, α:β = 11:1). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.93 (s, 1H), 7.78 – 7.74 (m, 0.2H), 7.55 – 7.52 (m, 2H), 7.43 – 7.27 (m, 16H), 7.23 – 7.13 (m, 9H), 7.03 (t, *J* = 11.0 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.72 – 5.68 (m, 2H), 5.24 (d, *J* = 14.5 Hz, 1H), 5.04 – 4.99 (m, 2H), 4.88 (dd, *J* = 14.5, 5.0 Hz, 2H), 4.80 (d, *J* = 8.5 Hz, 2H), 4.64 (d, *J* = 8.5 Hz, 2H), 4.46 (d, *J* = 13.0 Hz, 1H), 4.39 – 4.34 (m, 2H), 4.24 – 4.18 (m, 2H), 4.00 (t, *J* = 3.0 Hz, 1H), 3.65 – 3.59 (m, 3H), 3.51 – 3.42 (m, 4H), 2.04 (s, 3H), 1.90 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 170.6, 169.8, 169.7, 162.5, 138.7, 138.6, 138.5, 138.3, 137.8, 131.8, 131.8, 130.4, 130.3, 129.1, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 127.0, 126.0, 125.4, 125.3, 115.6, 115.4, 99.0, 82.1, 82.0, 81.2, 80.9, 77.4, 77.1, 76.8, 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, 20.7. IR (film, cm^{-1}): ν = 3063, 3030, 2869, 1744, 1644, 1601, 1508, 1454, 1363, 1227, 1125, 1048, 1021. HRMS (ESI): calc. for C$_{60}$H$_{63}$ NO$_{13}$F (M+H): 1024.4283; found: 1024.4290.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 151. A 10 mL oven dried Schlenk flask was charged with imidate **93** (16.9 mg, 0.028 mmol, 1.0

equiv.), inositol **145** (17.9 mg, 0.033 mmol, 1.2 equiv.) and CH_2Cl_2 (0.5 mL). A preformed solution of Ni(4-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (0.86 mg, 0.0014 mmol, 5 mol %) and AgOTf (0.72 mg, 0.0028 mmol, 10 mol %) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 °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 pseudo-disaccharide **151** (18 mg, 66%, α:β = 20:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (s, 1 H), 7.85 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 7.33-7.14 (m, 15 H), 5.73 (s, 1 H), 5.53 (t, *J* = 10.0 Hz, 1 H), 5.46 (t, *J* = 10.0 Hz, 1 H), 5.11 (t, *J* = 9.6 Hz, 1 H), 5.00 (d, *J* = 3.2 Hz, 1 H), 4.90-4.72 (m, 4 H), 4.57 (t, *J* = 11.2 Hz, 2 H), 4.42-4.34 (m, 2 H), 4.15-4.09 (m, 1 H), 3.95 (t, *J* = 9.6 Hz, 1 H), 3.72 (dd, *J* = 10.0, 2.4 Hz, 1 H), 3.61-3.50 (m, 2 H), 3.41 (t, *J* = 9.6 Hz, 1 H), 2.27 (s, 3 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.80 (s, 3 H), 1.46 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7, 170.6, 170.1, 169.2, 169.0, 163.2, 138.3, 138.0, 137.3, 129.0, 128.45, 128.38, 128.36, 128.14, 128.07, 128.0, 127.9, 127.7, 125.6, 100.2, 81.3, 80.7, 78.2, 77.2, 76.0, 75.5, 75.1, 72.4, 72.3, 70.2, 68.9, 68.6, 68.5, 62.2, 21.1, 20.8, 20.75, 20.67, 20.5. IR (film, cm^{-1}): ν = 2923, 1744, 1644, 1366, 1323, 1222. HRMS (ESI): calc. for $C_{51}H_{54}F_3NO_{15}$ (M+H): 978.3524; found: 978.3522.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Fluorobenzylideneamino-α-D-Glucopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 152. A 10 mL oven dried Schlenk flask was charged with imidate **146** (25.4 mg, 0.046 mmol, 1.0 equiv.), inositol

145 (29.4 mg, 0.055 mmol, 1.2 equiv.) and CH_2Cl_2 (0.5 mL). A preformed solution of Ni(4-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (1.41 mg, 0.0023 mmol, 5 mol %) and AgOTf (1.18 mg, 0.0046 mmol, 10 mol %) in dichloromethane (0.5 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 (3/1, hexane/ethyl acetate + 1% triethylamine → 1/1, hexane/ethyl acetate + 1% triethylamine) to give the desired pseudo-disaccharide **152** (23 mg, 54%, α:β = 14:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (s, 1 H), 7.73 (dd, *J* = 8.8, 5.6 Hz, 2 H), 7.34-7.18 (m, 15 H), 7.10 (t, *J* = 8.8 Hz, 2 H), 5.72 (t, *J* = 2.8 Hz, 1 H), 5.52 (t, *J* = 10.0 Hz, 1 H), 5.43 (t, *J* = 10.0 Hz, 1 H), 5.09 (t, *J* = 9.6 Hz, 1 H), 4.98 (d, *J* =3.6 Hz, 1 H), 4.88-4.74 (m, 4 H), 4.56 (t, *J* = 10.0 Hz, 2 H), 4.39-4.33 (m, 2 H), 3.94 (t, *J* = 9.6 Hz, 1 H), 3.71 (dd, *J* = 10.0, 2.8 Hz, 1 H), 3.55-3.47 (m, 2 H), 3.40 (t, *J* = 9.6 Hz, 1 H), 2.27 (s, 3 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.81 (s, 3 H), 1.46 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7, 170.6, 170.1, 169.2, 169.0, 163.0, 138.3, 138.1, 137.4, 130.9, 130.8, 128.5, 128.4, 128.15, 128.08, 128.0, 127.8, 127.6, 115.7, 100.5, 81.3, 80.7, 78.2, 77.2, 76.0, 75.5, 75.2, 72.4, 72.3, 70.4, 68.9, 68.6, 68.5, 62.2, 21.1, 20.78, 20.76, 20.6, 20.5. IR (film, cm^{-1}): ν = 2938, 1748, 1644, 1367, 1225. HRMS (ESI): calc. for $C_{50}H_{54}FNO_{15}$ (M+H): 928.3556; found: 928.3539.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 153. A 10 mL oven dried Schlenk flask was charged with imidate **99** (16.4 mg, 0.027 mmol, 1.0

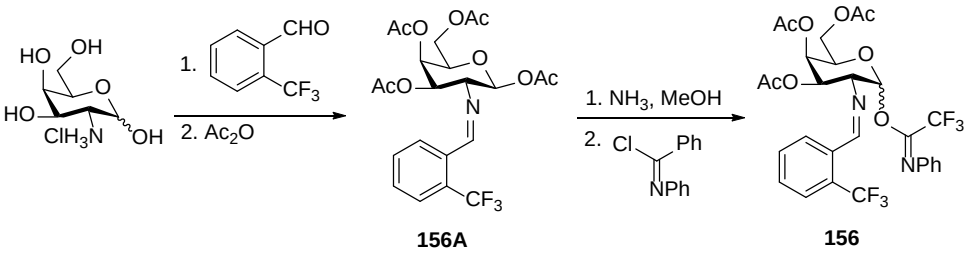
equiv.), inositol **145** (17.4 mg, 0.033 mmol, 1.2 equiv.) and CH_2Cl_2 (0.5 mL). A preformed solution of Ni(4-PhCN)$_4$(OTf)$_2$, which was generated *in situ* from Ni(4-F-PhCN)$_4$Cl$_2$ (0.83 mg, 0.0014 mmol, 5 mol %) and AgOTf (0.69 mg, 0.0027 mmol, 10 mol %) in dichloromethane (0.5 mL) was then 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 (3/1, hexane/ethyl acetate + 1% triethylamine → 1/1, hexane/ethyl acetate + 1% triethylamine) to give the desired pseudo-disaccharide **153** (25 mg, 94%, α:β = 20:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.57 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.32-7.18 (m, 15H), 5.73 (t, *J* = 2.4 Hz, 1H), 5.53 (t, *J* = 10.0 Hz, 1H), 5.44 (t, *J* = 10.0 Hz, 1H), 5.12 (t, *J* = 10.0 Hz, 1H), 5.01 (d, *J* = 3.6 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.82-4.74 (m, 3H), 4.57 (d, *J* = 7.2 Hz, 1H), 4.54 (d, *J* = 7.2 Hz, 1H), 4.40 – 4.33 (m, 2H), 4.11 (d, *J* = 10.4 Hz, 1H), 3.95 (t, *J* = 9.6 Hz, 1H), 3.72 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.60 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.54 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.40 (t, *J* = 10.0 Hz, 1H), 2.26 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.80 (s, 3H), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7, 170.6, 170.1, 163.6, 169.3, 169.0, 160.8, 138.3, 138.1, 137.4, 132.9, 132.4, 131.0, 129.4, 129.2, 128.9, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 125.5, 125.3, 125.3, 122.8, 100.4, 81.3, 80.7, 78.2, 77.3, 76.0, 75.6, 75.2, 72.5, 70.2, 69.0, 68.5, 62.2, 21.1, 20.8, 20.7, 20.6, 20.3. IR (film, cm^{-1}): ν = 3064, 3031, 2933, 2873, 1745, 1642, 1602, 1576, 1497, 1454, 1431, 1367, 1314, 1279, 1165, 1121, 1050, 1027. HRMS (ESI): calc. for $C_{51}H_{55}NO_{15}F_3$ (M+H): 978.3524; found: 978.3535.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 153. A 10 mL oven-dried Schlenk flask was charged with donor **107** (53.1 mg, 0.084 mmol, 1.5 equiv), inositol acceptor **145** (30.0 mg, 0.056 mmol, 1.0 equiv), and CH_2Cl_2 (0.5 mL). Then 0.5 mL of 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$_2$ (3.4 mg, 0.00561 mmol, 10 mol%) and AgOTf (2.9 mg, 0.0112 mmol, 20 mol%) in CH_2Cl_2 for 30 min, was added to the solution. The resulting mixture was stirred at 35 ^oC overnight. When the reaction was complete as monitored by TLC (toluene/acetonitrile = 4/1), the mixture was purified by silica gel flash chromatography (hexane/ethyl acetate = 5/1 → 3/1 → 3/2 → 1/1 with 1% Et_3N) to afford disaccharide **153** (42.8 mg, 78%, α only). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.57 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.32-7.18 (m, 15H), 5.73 (t, *J* = 2.4 Hz, 1H), 5.53 (t, *J* = 10.0 Hz, 1H), 5.44 (t, *J* = 10.0 Hz, 1H), 5.12 (t, *J* = 10.0 Hz, 1H), 5.01 (d, *J* = 3.6 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.82-4.74 (m, 3H), 4.57 (d, *J* = 7.2 Hz, 1H), 4.54 (d, *J* = 7.2 Hz, 1H), 4.40 – 4.33 (m, 2H), 4.11 (d, *J* = 10.4 Hz, 1H), 3.95 (t, *J* = 9.6 Hz, 1H), 3.72 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.60 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.54 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.40 (t, *J* = 10.0 Hz, 1H), 2.26 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.80 (s, 3H), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7, 170.6, 170.1, 163.6, 169.3, 169.0, 160.8, 138.3, 138.1, 137.4, 132.9, 132.4, 131.0, 129.4, 129.2, 128.9, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 125.5, 125.3, 125.3, 122.8, 100.4, 81.3, 80.7, 78.2, 77.3, 76.0, 75.6, 75.2, 72.5, 70.2, 69.0, 68.5, 62.2, 21.1, 20.8, 20.7, 20.6, 20.3. IR (film, cm^{-1}): ν = 3064, 3031, 2933, 2873,

1745, 1642, 1602, 1576, 1497, 1454, 1431, 1367, 1314, 1279, 1165, 1121, 1050, 1027. HRMS (ESI): calc. for $C_{51}H_{55}NO_{15}F_3$ (M+H): 978.3524; found: 978.3535.

3,4,6-Tri-*O*-Benzoyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-D-Glucopyranosyl *N*-Phenyl Trifluoroacetimidate 155. A 100 mL round bottom flask was charged with the tribenzoyl hemiacetal (100 mg, 0.154 mmol, 1.0 equiv), 2,2,2-trifluoro-*N*-phenyl-ethanimidoyl chloride (320.5 mg, 1.54 mmol, 10.0 equiv.), K_2CO_3 (106.7 mg, 0.772 mmol, 5.0 equiv.) and anhydrous acetone (1.0 mL). The solution was stirred at room temperature overnight. When the reaction was complete as monitored by TLC (hexane/ethyl acetate = 3/1), the reaction mixture was filtered, evaporated, and purified by flash chromatography on silica gel (hexane/ethyl acetate = 5/1 with 1% Et_3N) to afford **155** (70.9 mg, 56%, α:β = 1:4). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.76 (s, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 2H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.61 – 7.50 (m, 5H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 4H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.29 – 7.26 (m, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 5.5 Hz, 2H), 6.07 (s, 1H), 5.73 (t, *J* = 9.5 Hz, 1H), 4.66 (dd, *J* = 12.5, 2.5 Hz, 1H), 4.55 – 4.52 (m, 1H), 4.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.4, 165.5, 162.9, 143.4, 133.5, 130.1, 130.0, 129.8, 129.0, 128.9, 128.9, 128.7, 128.6, 128.5, 119.5, 103.8, 77.5, 74.1, 73.5, 73.3, 69.3, 63.2, 30.0. IR (film, cm^{-1}): ν = 3064, 3035, 2954, 2925, 2872, 2853, 1725, 1644, 1601, 1582, 1489, 1452, 1315, 1270, 1212, 1164, 1127, 1109, 1094, 1071, 1026. HRMS (ESI): calc. for $C_{43}H_{32}F_6N_2O_8Na$ (M+Na): 841.1962; found: 841.1961.

7.1. Synthesis of *N*-Phenyl Trifluoroimidate **156**



Scheme 7.1. Synthesis of Galactopyranosyl *N*-Phenyl Trifluoroacetimidate **156**.

C(2)-*N*-*ortho*-Trifluoromethylbenzylideneamino-D-Galactosaminepyranoside

156A.[36] An oven dried 1 L round bottom flask was charged with D-Galactosamine hydrochloride (23.0 g, 1067 mmol, 1 equiv), 2-(trifluoromethyl)-benzaldehyde (42.2 mL, 320.0 mmol, 3.0 equiv), anhydrous pyridine (213 mL), and triethylamine (22.3 mL, 160.05 mmol, 1.5 equiv). The resulting mixture was stirred at 60 ^{o}C for 24 h. The reaction mixture was cooled to room temperature, and acetic anhydride (81.3 mL, 853.6 mmol, 8.0 equiv) was added. The reaction mixture was then stirred at room temperature overnight and concentrated to a dark oil. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate = 5/1 → 3/1 with 1% Et_3N) to afford **156A** as a white solid (12.55 g, 55%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.67 (d, J = 2.1 Hz, 1H), 8.06 (d, J = 7.2 Hz, 1H), 7.70 – 7.67 (m, 1H), 7.61 – 7.51 (m, 2H), 5.98 (d, J = 8.1 Hz, 1H), 5.46 (d, J = 3.3 Hz, 1H), 5.30 (dd, J = 10.5, 3.6 Hz, 1H), 4.23 – 4.15 (m, 3H), 3.72 (dd, J = 10.5, 8.4 Hz, 1H), 2.19 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.91 (s, 3H).

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-D-Galactopyranosyl *N*-Phenyl Trifluoroacetimidate 156.[36] A 500 mL round bottom flask was charged with **156A** (12.55 g, 24.36 mmol, 1 equiv) and anhydrous THF (125 mL). The solution was cooled to 0 ºC, ammonia in methanol solution (7 N, 53.4 mL, 373.96 mmol, 15.0 equiv) was added. The resulting mixture was stirred at room temperature for 2.5 h and monitored by TLC. The round bottom flask was unsealed, and the reaction mixture was stirred under positive air flow for 1 h. The reaction mixture was concentrated to a yellow oil, and the crude hemiacetal used in the next step without further purification. A 250 mL round bottom flask was charged with the yellow-oil hemiacetal, 2,2,2-trifluoro-*N*-phenyl-ethanimidoyl chloride (4.4 mL, 27.3 mmol, 1.1 equiv), diazobicycloundecane (DBU) (2.0 mL, 13.65 mmol, 0.5 equiv) and anhydrous dichloromethane (53 mL). The resulting solution was stirred at room temperature overnight. When the reaction mixture was complete as monitored by TLC (hexane/ethyl acetate = 1/1), the reaction mixture was evaporated and purified by flash chromatography on silica gel (hexane/ethyl acetate = 5/1 → 3/1 with 1% Et_3N) to afford **156** as a white solid (6.30 g, 40%; α:β = 1:2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.73 (d, *J* = 2.4 Hz, 1H), 8.12 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 6.9 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 2H), 6.73 (d, *J* = 7.8 Hz, 0.25H), 6.02 (bs, 0.75H), 5.45 (d, *J* = 3.0 Hz, 1H), 5.28 (bs, 1H), 4.22 (d, *J* = 6.0 Hz, 2H), 4.06 (bs, 1H), 3.85 (t, *J* = 9.3 Hz, 1H), 2.24 (s, 3H), 2.06 (s, 3H), 1.94 (s, 3H).

6-*O*-Acetyl-3,4-Di-*O*–Benzyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-D-Galactopyranosyl *N*-Phenyl Trifluoroacetimidate 157.[36] A 100 mL round bottom flask

was charged with the hemiacetal[36] (291 mg, 0.52 mmol, 1.0 equiv), 2,2,2-trifluoro-*N*-phenyl-ethanimidoyl chloride (325 mg, 1.57 mmol, 3.0 equiv.), K_2CO_3 (144 mg, 1.0 mmol, 2.0 equiv.) and anhydrous acetone (2.6 mL). The solution was stirred at room temperature overnight. When the reaction was complete as monitored by TLC (hexane/ethyl acetate = 3/1), the reaction mixture was filtered, evaporated, and purified by flash chromatography on silica gel (hexane/ethyl acetate = 3/1 → 3/2 with 1% Et_3N) to afford **157** as a viscous oil (377 mg, 99%). ^{1}H NMR (CDCl3, 400 MHz): δ = 8.82 (d, J = 1.2 Hz, 1 H), 8.16 (d, J = 7.6 Hz, 1 H), 7.73 (d, J = 7.6 Hz, 1 H), 7.64−7.53 (m, 2 H), 7.37−7.21 (m, 12 H), 7.06 (t, J = 3.6 Hz, 1 H), 6.76 (d, J = 7.6 Hz, 2 H), 5.91 (brs, 1 H), 5.01 (d, J = 11.6 Hz, 1 H), 4.73−4.57 (m, 3 H), 4.28 (dd, J = 11.2, 6.8 Hz, 1 H), 4.17 (dd, J = 11.2, 5.6 Hz, 1 H), 4.07−4.01 (m, 1 H), 3.90−3.62 (m, 3 H), 1.97 (s, 3 H).

2,3,4,6-Tetra-*O*-Acetyl-α-D-Glucopyranosyl-(1→6)-3,4-Di-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl *N*-Phenyl Trifluoroacetimidate 158. A 100 mL round bottom flask was charged with the disaccharide hemiacetal[35] (2.11 g, 2.8 mmol, 1.0 equiv), 2,2,2-trifluoro-*N*-phenyl-ethanimidoyl chloride (1.776 g, 8.5 mmol, 3.0 equiv.), K_2CO_3 (773 mg, 5.6 mmol, 2.0 equiv.) and anhydrous acetone (15.0 mL). The solution was stirred at room temperature overnight. When the reaction was complete as monitored by TLC (hexane/ethyl acetate = 3/1), the reaction mixture was filtered, evaporated, and purified by flash chromatography on silica gel (hexane/ethyl acetate = 3/1 → 3/2 with 1% Et_3N) to afford **158** (2.179 g, 84%, α:β = 1:3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.63 (s, 1H), 8.18 (d, *J* = 7.6 Hz, 0.3H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.59 – 7.50 (m, 3H), 7.26 (t, *J* = 8.0 Hz,

2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.09 – 6.99 (m, 2H), 6.79 (d, *J* = 7.2 Hz, 2H), 6.69 (d, *J* = 6.4 Hz, 1H), 6.46 (s, 0.25H), 6.02 (s, 0.75H), 5.58 (t, *J* = 9.6 Hz, 0.5H), 5.40 (s, 1H), 5.22 – 4.98 (m, 6H), 4.57 (d, *J* = 8.0 Hz, 1H), 4.25 – 4.21 (m, 2H), 4.14 – 4.01 (m, 2H), 3.93 (d, *J* = 10.4 Hz, 1H), 3.80 (d, *J* = 8.0 Hz, 1H), 3.69 – 3.61 (m, 4H), 2.06 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H), 1.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.5, 170.4, 170.0, 170.0, 169.6, 169.5, 169.5, 169.4, 169.4, 169.3, 169.2, 162.2, 161.4, 143.1, 143.0, 133.2, 133.2, 133.1, 132.1, 130.9, 130.8, 129.6, 129.4, 129.3, 129.1, 129.0, 128.7, 128.6, 128.5, 127.9, 125.6, 125.5, 125.5, 125.4, 125.2, 124.4, 122.4, 122.4, 119.2, 100.5, 95.4, 74.0, 73.1, 72.7, 72.6, 71.9, 71.4, 70.9, 70.8, 70.7, 70.4, 68.3, 68.0, 67.3, 67.0, 61.8, 61.8, 60.2, 20.5, 20.5, 20.5, 20.4, 20.3, 20.2. IR (film, cm^{-1}): ν = 2942, 1750, 1638, 1594, 1494, 1366, 1313, 1219, 1160, 1123. HRMS (ESI): calc. for $C_{40}H_{42}F_6N_2O_{16}Na$ (M+Na): 943.2336; found: 943.2333.

2,3,4,6-Tetra-*O*-Acetyl-α-D-Glucopyranosyl-(1→3)-4,6-Di-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl *N*-Phenyl Trifluoroacetimidate 159. A 100 mL RBF was charged with the disaccharide hemiacetal[35] (25 mg, 0.033 mmol, 1.0 equiv), 2,2,2-trifluoro-*N*-phenyl-ethanimidoyl chloride (69 mg, 0.33 mmol, 10.0 equiv.), K_2CO_3 (23 mg, 0.17 mmol, 5.0 equiv.) and anhydrous acetone (0.8 mL). The solution was stirred at room temperature overnight. When the reaction was complete as monitored by TLC (hexane/ethyl acetate = 3/1), the reaction mixture was filtered, evaporated, and purified by flash chromatography on silica gel (hexane/ethyl acetate = 3/1 → 3/2 with 1% Et_3N) to afford **159** (12 mg, 40%, α:β = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.71 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.74 –

7.70 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.57 (s, 2H), 6.30 (s, 1H), 5.33 (d, *J* = 2.8 Hz, 1H), 5.20 (t, *J* = 10.0 Hz, 1H), 5.00 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.83 (dd, *J* = 10.4, 3.2 Hz, 1H), 4.61 – 4.52 (m, 2H), 4.29 – 4.18 (m, 4H), 4.13 – 4.07 (m, 1H), 3.94 (t, *J* = 6.4 Hz, 1H), 3.81 (s, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 1.90 (s, 3H), 1.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7, 170.5, 170.2, 170.1, 169.3, 168.9, 162.1, 133.1, 132.4, 131.3, 129.5, 129.2, 128.6, 128.3, 125.9, 125.9, 100.2, 76.7, 73.0, 71.1, 70.8, 70.5, 69.1, 67.4, 66.8, 61.9, 61.0, 20.8, 20.6, 20.6, 20.5, 20.2. IR (film, cm^{-1}): ν = 2938, 1752, 1642, 1598, 1489, 1370, 1316, 1221, 1165, 1127. HRMS (ESI): calc. for $C_{40}H_{42}F_6N_2O_{16}Na$ (M+Na): 943.2336; found: 943.2334.

3,4,6-Tri-*O*-Benzoyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 160. A 10 mL oven-dried Schlenk flask was charged with donor **155** (46.0 mg, 0.056 mmol, 1.5 equiv), inositol acceptor **145** (20.0 mg, 0.037 mmol, 1.0 equiv), and CH_2Cl_2 (0.5 mL). Then 0.5 mL of preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from a reaction of $Ni(4\text{-F-PhCN})_4Cl_2$ (2.27 mg, 0.0037 mmol, 10 mol%) and AgOTf (1.90 mg, 0.0074 mmol, 20 mol%) in CH_2Cl_2 for 30 min, was added to the solution. The resulting mixture was stirred at 35 °C overnight. When the reaction was complete as monitored by TLC (toluene/acetonitrile = 4/1), the mixture was purified by silica gel flash chromatography (hexane/ethyl acetate = 5/1 → 3/1 → 3/2 → 1/1 with 1% Et_3N) to afford disaccharide **160** (24 mg, 55%, α:β = 13:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.62 (s, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 8.07 (d, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.61-7.18 (m, 32H), 5.99 (t, *J* = 10.0 Hz, 1H), 5.86 (t, *J* = 2.4

Hz, 1H), 5.68 (t, *J* = 10.0 Hz, 1H), 5.58 (t, *J* = 10.0 Hz, 1H), 5.16 (d, *J* = 3.6 Hz, 1H), 4.91 (d, *J* = 10.8 Hz, 1H), 4.85 – 4.69 (m, 5H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 2H), 4.01 (t, *J* = 9.6 Hz, 1H), 3.88 – 3.84 (m, 2H), 3.57 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.42 (t, *J* = 9.6 Hz, 1H), 2.40 (s, 3H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.8, 168.9, 166.2, 165.5, 165.1, 160.8, 138.3, 138.0, 137.4, 133.2, 133.1, 132.8, 132.7, 132.2, 130.7, 130.0, 129.8, 129.7, 129.4, 129.3, 129.1, 129.0, 128.7, 128.4, 128.4, 128.4, 128.4, 128.2, 128.2, 128.1, 127.9, 127.9, 127.7, 127.7, 127.6, 125.3, 125.3, 125.1, 125.0, 122.6, 100.4, 81.3, 80.6, 78.2, 77.2, 76.0, 75.5, 74.5, 72.9, 72.6, 72.5, 70.4, 69.6, 69.0, 68.9, 62.9, 29.7, 21.2, 20.5. IR (film, cm^{-1}): ν = 3088, 3064, 3031, 2924, 2868, 1728, 1640, 1601, 1582, 1495, 1452, 1366, 1314, 1268, 1248, 1221, 1166, 1094, 1068, 1025. HRMS (ESI): calc. for $C_{66}H_{60}NO_{15}F_3$ (M+Na): 1186.3813; found: 1186.3832.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Galactopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 161. A 10 mL oven-dried Schlenk flask was charged with donor **156**[36] (17.1 mg, 0.027 mmol, 1.5 equiv), inositol acceptor **145** (9.65 mg, 0.018 mmol, 1.0 equiv), and CH_2Cl_2 (0.5 mL). Then 0.5 mL of preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from a reaction of $Ni(4\text{-F-PhCN})_4Cl_2$ (1.11 mg, 0.0018 mmol, 10 mol%) and AgOTf (0.92 mg, 0.0036 mmol, 20 mol%) in CH_2Cl_2 for 30 min, was added to the solution. The resulting mixture was stirred at 35 °C overnight. When the reaction was complete as monitored by TLC (toluene/acetonitrile = 4/1), the mixture was purified by silica gel flash chromatography (hexane/ethyl acetate = 5/1 → 3/1 → 3/2 → 1/1 with 1% Et_3N) to afford disaccharide **161** (15 mg, 85%, α only). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.75 (s,

1H), 8.28 (d, *J* = 7.6 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.58 – 7.54 (m, 1H), 7.35 – 7.15 (m, 15H), 5.79 (t, *J* = 2.4 Hz, 1H), 5.55 – 5.50 (m, 2H), 5.37 (dd, *J* = 10.8, 3.2 Hz, 1H), 5.06 (d, *J* = 3.6 Hz, 1H), 4.92 – 4.57 (m, 7H), 4.26-4.10 (m, 2H), 3.97 (t, *J* = 9.6 Hz, 1H), 3.85 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.78 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.58 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.57 (dd, *J* = 10.2, 2.9Hz, 1H), 3.43 (t, *J* = 9.6 Hz, 1H), 2.25 (s, 3H), 2.19 (s, 3H), 2.08 (s, 3H), 1.84 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ =171.0, 170.8, 170.4, 169.7, 169.3, 160.9, 138.6, 138.3, 137.7, 133.3, 132.6, 131.1, 129.5, 129.3, 129.0 128.7, 128.6, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 125.8, 125.6, 125.5, 125.4, 101.0, 81.5, 80.9, 78.5, 77.5, 76.3, 75.8, 74.5, 72.9, 72.6, 69.1, 67.8, 67.7, 67.6, 67.5, 62.2, 21.3, 21.1, 21.1, 20.8, 20.6. IR (film, cm^{-1}): ν = 3103, 3089, 3068, 3031, 2884, 2853, 1748, 1642, 1497, 1455, 1433, 1373, 1315, 1279, 1224, 1167, 1124, 1097, 1072, 1049, 1027. HRMS (ESI): calc. for $C_{51}H_{55}NO_{15}F_3$ (M+H): 978.3524; found: 978.3536.

6-*O*-Acetyl-3,4-Di-*O*-Benzyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Galactopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 162. A 10 mL oven-dried Schlenk flask was charged with donor **157**[36] (25.4 mg, 0.035 mmol, 1.5 equiv), inositol acceptor **145** (12.4 mg, 0.023 mmol, 1.0 equiv), and CH_2Cl_2 (0.5 mL). Then 0.5 mL of 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$_2$ (1.41 mg, 0.0023 mmol, 10 mol%) and AgOTf (1.18 mg, 0.0046 mmol, 20 mol%) in CH_2Cl_2 for 30 min, was added to the solution. The resulting mixture was stirred at 35 °C overnight. When the reaction was complete as monitored by TLC (toluene/acetonitrile = 4/1), the mixture was purified by silica gel flash chromatography (hexane/ethyl acetate = 5/1 → 3/1 → 3/2 → 1/1 with 1% Et_3N) to

afford disaccharide **162** (14 mg, 56%, α only). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.73 (s, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 8.4 Hz, 1H), 7.36 – 7.19 (m, 25H), 5.76 (t, *J* = 2.8 Hz, 1H), 5.50 (t, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 3.6 Hz, 1H), 4.97 (d, *J* = 11.2 Hz, 1H), 4.89 (d, *J* = 10.4 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.77 (d, *J* = 10.8, 2H), 4.65 – 4.48 (m, 6H), 4.37 – 4.31 (m, 2H), 4.15 – 4.05 (m, 3H), 4.00 – 3.93 (m, 3H), 3.76 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.58 (dd, *J* = 10.0, 2.8 Hz, 1H), 3.42 (t, *J* = 9.6 Hz, 3H), 2.15 (s, 3H), 2.02 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = δ = 170.7, 170.5, 169.1, 160.2, 132.1, 130.4, 129.1, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 125.5, 125.3, 125.2, 122.8, 101.4, 95.3, 81.4, 80.7, 78.4, 77.2, 76.4, 76.0, 75.5, 74.6, 73.4, 73.2, 72.7, 72.2, 72.2, 70.1, 69.6, 69.4, 64.4, 63.8, 60.4, 30.6, 29.7, 21.2, 21.0, 20.5, 19.1, 13.7. IR (film, cm^{-1}): ν = 3088, 3064, 3030, 3007, 2921, 2871, 1742, 1666, 1638, 1602, 1577, 1509, 1496, 1454, 1365, 1314, 1277, 1223, 1162, 1123, 1095, 1057 1027. HRMS (ESI): calc. for $C_{61}H_{63}NO_{13}F_3$ (M+H): 1074.4252; found: 1074.4262.

2,3,4,6-Tetra-*O*-Acetyl-β-D-Glucopyranosyl-(1→6)-3,4-Di-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 163. A 10 mL oven-dried Schlenk flask was charged with donor **158** (10.91 mg, 0.0119 mmol, 1.5 equiv), inositol acceptor **145** (4.22 mg, 0.0079 mmol, 1.0 equiv), and CH_2Cl_2 (0.5 mL). Then 0.5 mL of preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from a reaction of $Ni(4\text{-F-PhCN})_4Cl_2$ (0.49 mg, 0.00079 mmol, 10 mol%) and AgOTf (0.41 mg, 0.00158 mmol, 20 mol%) in CH_2Cl_2 for 30 min, was added to the solution. The resulting mixture was stirred at 35 °C

overnight. When the reaction was complete as monitored by TLC (toluene/acetonitrile = 4/1), the mixture was purified by silica gel flash chromatography (hexane/ethyl acetate = 5/1 → 3/1 → 3/2 → 1/1 with 1% Et_3N) to afford the pseudotrisaccharide **163** (6.4 mg, 64%, α only) ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.56 (s, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.40 – 7.20 (m, 15H), 5.79 (t, *J* = 2.4 Hz, 1H), 5.53 (t, *J* = 10.0 Hz, 1H), 5.47 (t, *J* = 10.0 Hz, 1H), 5.09 (t, *J* = 10 Hz, 1H), 5.02 – 4.75 (m, 9H), 4.59 (t, *J* = 11.2 Hz, 2H), 4.47 (d, *J* = 10.0 Hz, 1H), 4.37 – 4.43 (m, 1H), 4.29 (dd, *J* = 12.4, 4.4 Hz, 1H), 3.97 (t, *J* = 9.6 Hz, 1H), 3.85 – 3.82 (m, 2H), 3.73 – 3.67 (m, 1H), 3.56 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.51 – 3.44 (m, 2H), 2.27 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.04 – 2.03 (m, 9H), 1.81 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.1, 170.9, 170.9, 170.5, 169.8, 169.7, 169.6, 169.2, 160.8, 138.7, 138.4, 138.0, 132.6, 129.7, 128.7, 128.6, 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 101.7, 101.2, 78.1, 76.2, 75.8, 72.7, 72.5, 72.4, 72.1, 71.2, 69.5, 69.2, 68.9, 68.5, 62.0, 53.7, 30.0, 21.4, 21.2, 21.1, 21.0, 20.9, 20.9, 20.9, 20.6, 14.4. IR (film, cm^{-1}): ν = 3063, 3030, 2956, 2925, 2855, 1747, 1640, 1602, 1578, 1496, 1455, 1431, 1367, 1314, 1278, 1219, 1168, 1096, 1035. HRMS (ESI): calc. for $C_{63}H_{70}NO_{23}F_3$ (M+Na): 1288.4188; found: 1288.4185.

2,3,4,6-Tetra-*O*-Acetyl-β-D-Glucopyranosyl-(1→3)-4,6-Di-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 164. A 10 mL oven-dried Schlenk flask was charged with donor **159** (13.94 mg, 0.0151 mmol, 1.5 equiv), inositol acceptor **145** (5.39 mg, 0.0101 mmol, 1.0 equiv), and CH_2Cl_2 (0.5 mL). Then 0.5 mL of preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from a reaction of $Ni(4\text{-F-PhCN})_4Cl_2$

(0.62 mg, 0.00101 mmol, 10 mol%) and AgOTf (0.52 mg, 0.00202 mmol, 20 mol%) in CH_2Cl_2 for 30 min, was added to the solution. The resulting mixture was stirred at 35 °C overnight. When the reaction was complete as monitored by TLC (toluene/acetonitrile = 4/1), the mixture was purified by silica gel flash chromatography (hexane/ethyl acetate = 5/1 → 3/1 → 3/2 → 1/1 with 1% Et_3N) to afford the pseudotrisaccharide **164** (4.6 mg, 36%, α only). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.31 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.36 – 7.31 (m, 15H), 5.80 – 5.79 (m, 1H), 5.75 (t, *J* = 2.8 Hz, 1H), 5.36 (bs, 1H), 5.22 (dd, *J* = 7.2, 4.0 Hz, 1H), 5.13 – 5.07 (m, 1H), 5.02 (d, *J* = 7.6 Hz, 1H), 4.96 (dd, *J* = 12.4, 11.2 Hz, 2H), 4.81 – 4.75 (m, 4H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.61 (d, *J* = 8 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.27 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.14 (dd, *J* = 12, 2 Hz, 1H), 4.08 – 3.86 (m, 4H), 3.75 – 3.61 (m, 3H), 3.44 – 3.36 (m, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 2.10 (s, 6H), 2.08 (s, 6H), 2.04 (s, 3H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 170.9, 170.6, 170.4, 170.1, 169.5, 169.4, 169.3, 168.5, 148.4, 138.4, 138.2, 137.4, 134.5, 131.9, 129.7, 128.7, 128.4, 128.4, 128.1, 128.0, 128.0, 127.9, 127.7, 127.2, 123.9, 100.7, 82.7, 81.1, 78.2, 75.9, 74.6, 72.6, 72.3, 72.0, 71.3, 71.0, 70.8, 68.3, 67.6, 67.0, 66.0, 62.6, 61.8, 53.4, 31.9, 29.7, 29.7, 29.4, 22.7, 20.9, 20.8, 20.7, 20.6, 20.5, 14.1. IR (film, cm^{-1}): ν = 2955, 2925, 2852, 1747, 1644, 1558, 1496, 1455, 1370, 1314, 1227, 1162, 1121, 1089, 1039. HRMS (ESI): calc. for $C_{63}H_{70}NO_{23}F_3$ (M+Na) 1288.4188; found: 1288.4204.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-Azido-α-D-Glucopyranosyl Trichloroacetimidate 165. A 100 mL oven-dried Schlenk was charged with hemiacetal[211] (672 mg, 2.03 mmol, 1 equiv) and dichloromethane (15 mL). The solution was cooled to 0 °C, and

trichloroacetonitrile (0.61 mL, 6.09 mmol, 3 equiv) was then added to the reaction mixture followed by DBU (0.15 mL, 1.02 mmol, 0.5 equiv). The resulting mixture was stirred at this temperature for 4 h and then concentrated in vacuo. The residue was purified by silica gel flash chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to provide trichloroacetimidate **165** (626 mg, 65%, α:β = 3:1) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.83 (s, 1H), 6.48 (d, *J* = 3.5 Hz, 1H), 5.50 (t, *J* = 9.8 Hz, 1H), 5.14 (t, *J* = 9.9 Hz, 1H), 4.28 – 4.21 (m, 2H), 4.08 (dd, *J* = 12.3, 1.7 Hz, 1H), 3.76 (dd, *J* = 10.5, 3.5 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 2.04 (s, 3H).

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-Azido-α-D-Glucopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 166. A 10 mL oven dried Schlenk flask was charged with imidate **165** (26.4 mg, 0.056 mmol, 1.0 equiv.), inositol **145** (35.9 mg, 0.067 mmol, 1.2 equiv.) and CH_2Cl_2 (0.5 mL). A preformed solution of $Ni(4\text{-}PhCN)_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-}F\text{-}PhCN)_4Cl_2$ (1.72 mg, 0.0028 mmol, 5 mol %) and AgOTf (1.44 mg, 0.0056 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 (3/1, hexane/ethyl acetate + 1% triethylamine → 1/1, hexane/ethyl acetate + 1% triethylamine) to give the desired pseudo-disaccharide **166** (8.5 mg, 18%, α:β = 12:1) ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 – 7.17 (m, 15H), 5.64 (t, *J* = 2.8 Hz, 1H), 5.58 (t, *J* = 10 Hz, 1H), 5.32 (dd, *J* = 10.8, 9.2 Hz, 1H), 5.09 (d, *J* = 3.6 Hz, 1H), 5.04 (t, *J* = 10.0 Hz, 1H), 4.89 (t, *J* = 11.2 Hz, 3H), 4.80 – 4.72 (m, 2H), 4.64 – 4.57 (m, 2H), 4.32 (dd, *J* = 12.8,

4.0 Hz, 1H), 4.20 (dt, *J* = 10.4, 2.4 Hz, 1H), 4.08 (dd, *J* = 12.4, 2.4 Hz, 1H), 3.97 (t, *J* = 9.6 Hz, 1H), 3.73 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.55 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.45 (t, *J* = 9.6 Hz, 1H), 3.23 (dd, *J* = 10.8, 4.0 Hz, 1H), 2.24 (s, 3H), 2.08 (s, 9H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.0, 170.8, 170.2, 169.9, 169.7, 138.5, 138.2, 137.5, 129.3, 128.8, 128.7, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.1, 125.6, 99.9, 81.6, 80.8, 78.1, 77.5, 76.4, 75.9, 75.1, 73.0, 72.8, 69.7, 69.2, 68.5, 68.4, 62.0, 60.9, 21.3, 21.0, 21.0, 21.0, 20.9. IR (film, cm^{-1}): ν = 3088, 3063, 3030, 3006, 2924, 2872, 2110, 1746, 1497, 1454, 1432, 1367, 1313, 1222, 1162, 1135, 1097, 1047, 1030. HRMS (ESI): calc. for $C_{43}H_{49}N_3O_{15}$ (M+Na) 870.3061; found: 870.3077.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-Amino-α-D-Glucopyranosyl-(1→1)-2,6-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-inositol 167. A 20 mL scintillation vial was charged with **153** (100.0 mg, 0.1024 mmol, 1 equiv), 5 N hydrochloric acid (0.1 mL, 0.512 mmol, 5 equiv), and acetone (1.0 mL). The resulting mixture was stirred at 65 °C for 5 min, then at room temperature for 30 min. The mixture was loaded onto a silica plug and purified (1/1, hexanes/ethyl acetate → 9/1 dichloromethane/methanol) to give the desired pseudodisaccharide **167** (81.7 mg, 98%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.33 (bs, 3H), 7.34 – 7.20 (m, 15H), 5.64 (t, *J* = 2 Hz, 1H), 5.30 (t, *J* = 10.0 1H), 5.23 (bs, 1H), 5.11 (bs, 1H), 4.93 (bs, 2H), 4.77 – 4.47 (m, 6H), 4.23 – 4.09 (m, 4H), 3.85 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.72 (t, *J* = 9.6 Hz, 2H), 3.58 (t, *J* = 9.2 Hz 1H), 2.17 (s, 3H), 2.01 (s, 9H), 1.98 (s, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 170.8, 170.7, 170.5, 170.5, 170.1, 139.2, 138.9, 138.6, 128.9, 128.9, 128.8, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 103.8, 81.4, 81.0, 78.4, 77.0, 75.5, 72.6, 72.0, 71.8, 70.3, 68.8, 68.5, 64.5, 64.0, 62.3, 62.1, 52.7,

46.2, 22.1, 21.6, 21.5, 21.3, 21.2. IR (film, cm^{-1}): ν = 3394, 3089, 3064, 3031, 2941, 2874, 2840, 1743, 1638, 1606, 1499, 1455, 1367, 1222, 1028, 908. HRMS (ESI): calc. for $C_{43}H_{52}NO_{15}$ (M+H) 822.3337; found: 822.3339.

2-Deoxy-2-Amino-α-D-Glucopyranosyl-(1→1)-*myo*-Inositol 168.[53] A 20 mL scintillation vial was charged with **167** (20.0 mg, 0.0245 mmol, 1 equiv.), Pearlman's catalyst (20 mol % $Pd(OH)_2$ on carbon, 87.9 mg), and *t*-BuOH (1.6 mL), pH 4 aqueous potassium acid phthalate buffer (0.4 mL). The unsealed scintillation vial was placed in a stainless steel high pressure reactor which was purged with hydrogen three times. The reactor was filled with hydrogen (190 psi) and stirred overnight at room temperature. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude product was flushed through silica (9/1 dichloromethane/methanol), concentrated, and used in the next step where it was charged in a 25 mL round bottom flask with sodium methoxide (6.6 mg, 0.122 mmol, 5 equiv.) and anhydrous methanol (0.5 mL). The reaction mixture was stirred for 3 h at room temperature. The reaction was quenched with glacial acetic acid and concentrated *in vacuo*. The crude product was passed through Sephadex G-10 column using water as the eluent to afford pure **168** (4.6 mg, 55%). ^{1}H NMR (D_2O, 400 MHz): δ = 5.34 (d, *J* = 3.6 Hz, 1H), 4.13 (t, *J* = 2.4 Hz, 1H), 3.85 (dd, *J* = 9.2, 10.4 Hz, 1H), 3.77 (m, 1H), 3.71 (m, 3H), 3.60 (dd, *J* = 10.0, 2.8 Hz, 1H), 3.55 (t, *J* = 10.4 Hz, 1H), 3.45 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.40 (m, 1H), 3.29 – 3.19 (m, 2H). ^{13}C NMR (D_2O, 100 MHz): δ = 97.3, 79.0, 74.1 72.8, 72.0, 71.9, 71.7, 71.0, 69.6, 69.4, 60.3, 54.2. IR (film, cm^{-1}): ν = 3370, 3003, 2933, 2854, 2782, 2697, 1744,

1658, 1564, 1408, 1345, 1244, 1089, 1043, 1013, 923. HRMS (ESI): calc. for $C_{12}H_{24}NO_{10}$ (M+H) 342.1400; found: 342.1399.

6-*O*-Allyl-3,4,5-Tri-*O*-Benzyl-*myo*-inositol 170.[58] A 50 mL oven-dried, Ar flushed Schlenk flask was charged with **141** (2.34 g, 4.8 mmol, 1 equiv.),[35] NaH (0.29 g, 7.2 mmol, 1.5 equiv.), and anhydrous DMF (25 mL). The solution was stirred at room temperature for 5 min followed by dropwise addition of allyl bromide (1.2 mL, 14.3 mmol, 3.0 equiv.). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with brine (2 x 50 mL), dried over Na_2SO_4, concentrated *in vacuo*. The resulting residue was added to a 250 mL RBF along with a solution of HCl (3.95 mL, 47.8 mmol, 10 equiv.) in MeOH (74 mL). The reaction mixture was stirred for 40 min at room temperature, followed by neutralization with 1 M NaOH. The reaction mixture was concentrated *in vacuo* and extracted with CH_2Cl_2 (5 x 100 mL). The organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield crude **170**. Crude **170** was purified by flash column chromatography (hexane/ethyl acetate = 1/1) to afford **170** (1.97 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40 – 7.37 (m, 15H), 6.08 – 5.95 (m, 1H), 5.33 (d, *J* = 22.8 Hz, 1H), 5.24 (d, *J* = 14 Hz, 1H), 4.95 – 4.85 (m, 4H), 4.78 (s, 2H), 4.48 (dd, *J* = 16.8, 7.2 Hz, 1H), 4.34 – 4.28 (m, 2H), 3.99 (t, *J* = 12.8 Hz, 1H), 3.77 (t, *J* = 12.8 Hz, 1H), 3.54 – 3.45 (m, 3H), 2.59 (s, 1H), 2.56 (s, 1H).

6-*O*-Allyl-1,2,3,4,5-Pent-*O*-Benzyl-*myo*-inositol 171.[212] A 250 mL oven-dried, Ar flushed RBF was charged with **170** (2.34 g, 4.8 mmol, 1 equiv.), and anhydrous DMF (72

mL). The solution was cooled to 0 ^{o}C after which NaH (0.77 g, 19.1 mmol, 4.0 equiv.) was added portion-wise over 30 min. The solution was stirred at 0 ^{o}C for another 30 min before BnBr (1.71 mL, 14.3 mmol, 3.0 equiv.) was added dropwise, followed by addition of TBAI (17.7 mg, 0.048 mmol, .01 equiv.). The reaction mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 ^{o}C followed by careful addition of MeOH (10 mL). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (5 x 100 mL). The combined extracts were washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to form crude **171**. Crude **171** was purified by flash column chromatography (hexane/ethyl acetate = 8/1) to afford **171** (2.83 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44 – 7.30 (m, 25H), 6.07 – 5.97 (m, 1H), 5.30 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.18 (dd, *J* = 10.4, 2 Hz, 1H), 4.96 – 4.85 (m, 6H), 4.75 – 4.62 (m, 4H), 4.40 (dd, *J* = 12.0, 5.6 Hz, 1H) 4.36 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.11 – 4.05 (m, 2H) 3.99 (t, *J* = 9.6 Hz, 1H), 3.46 (dd, *J* = 12.0, 9.2 Hz, 1H), 3.38 (dd, *J* = 9.6, 2.0 Hz, 1H) 3.33 (dd, *J* = 9.6, 2.0 Hz, 1H).

1,2,3,4,5-Penta-*O*-Benzyl-*myo*-inositol 172. A 100 mL oven-dried, Ar flushed Schlenk flask was charged with **171** (2.83 g, 4.2 mmol, 1.0 equiv.), NaOAc (1.1 g, 13.5 mmol, 3.2 equiv.), $PdCl_2$ (0.97 g, 5.5 mmol, 1.3 equiv.), AcOH (43 mL), and H_2O (2.3 mL). The reaction mixture was stirred overnight. The reaction mixture was diluted with EtOAc (150 mL) followed by careful addition of sat. aq. Na_2CO_3 (70 mL). The resulting solution was stirred for 30 min. The organic layer was separated, dried over Na_2SO_3, and concentrated *in vacuo* to give crude **172**. Crude **172** was purified by flash column chromatography (hexane/ethyl acetate = 5/1 $\rightarrow$ 1/1) to afford **172** (1.73 g, 65%) as a

colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24 – 7.30 (m, 25H), 4.96 – 4.80 (m, 6H), 4.66 (q, *J* = 12 Hz, 2H), 4.58 (d, *J* = 3.2 Hz, 2H), 4.51 – 4.36 (m, 2H), 4.11 – 4.04 (m, 2H), 3.90 (t, *J* = 9.6 Hz, 1H), 3.54 (t, 9.2 Hz, 1H), 3.43 – 3.37 (m, 2H), 2.39 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.9, 138.9, 138.9, 138.4, 138.0, 137.9, 129.1, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.4, 127.4, 125.4, 83.5, 81.5, 81.2, 80.2, 75.9, 75.4, 74.1, 73.8, 73.0, 72.9, 72.4. IR (film, cm^{-1}): ν = 3506, 3089, 3062, 3030, 3005, 2873, 1737, 1496, 1453, 1360, 1237, 1208, 1154, 1083, 1052, 1026. HRMS (ESI): calc. for $C_{41}H_{42}O_6$ (M+Na): 653.2879; found: 653.2886.

6-*O*-Allyl-3,4,5-Tri-*O*-Benzyl-1-*O*-(4-methoxybenzyl)-*myo*-inositol 173.[58] An oven dried 250 mL RBF was charged with **170** (0.76 g, 1.6 mmol, 1.0 equiv.), Bu_2SnO (0.43 g, 1.7 mmol, 1.1 equiv.), TBAI (0.63 g, 1.7 mmol, 1.1 equiv.), and anhydrous toluene (22 mL). The reaction mixture was fitted with a Dean-Stark trap and refluxed at 120 ^{o}C for 4 h. The reaction mixture was cooled to room temperature and PMBCl (0.85 mL, 6.2 mmol, 4.0 equiv.) and CsF (0.47 g, 3.1 mmol, 2.0 equiv.) were added. The reaction mixture was stirred overnight under reflux. The reaction mixture was then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to provide crude **173**. Crude **173** was purified by flash column chromatography (hexane/ethyl acetate = 3/1) to afford **173** (0.69 g, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51-7.24 (m, 10 H), 5.33 (d, *J* = 3.6 Hz, 1 H), 4.65-4.61 (m, 2 H), 4.59-4.52 (m, 2 H), 4.23-4.18 (m, 1 H), 4.11-4.02 (m, 2 H), 3.72-3.62 (m, 2 H), 3.57 (dd, *J* = 10.8, 3.6 Hz, 1 H).

6-*O*-Allyl-2,3,4,5-Tetra-*O*-Benzyl-1-*O*-(4-methoxybenzyl)-*myo*-inositol 174.[58] An oven dried, Ar flushed 25 mL Schlenk flask was charged with **173** (0.69 g, 1.1 mmol, 1.0 equiv.), and anhydrous DMF (4 mL). The solution was cooled to 0 ^{o}C after which NaH (0.14 g, 3.4 mmol, 3.0 equiv.) was added portion-wise over 30 min. The solution was stirred at 0 ^{o}C for another 30 min before BnBr (0.27 mL, 2.2 mmol, 2.0 equiv.) was added dropwise, followed by addition of TBAI (4.1 mg, 0.0112 mmol, .01 equiv.). The reaction mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 ^{o}C followed by careful addition of MeOH (1 mL). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to form crude **174**. Crude **174** was purified by flash column chromatography (hexane/ethyl acetate = 5/1) to afford **174** (0.69 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.41 – 7.26 (m, 22H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.05 – 5.95 (m, 1H), 5.28 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.16 (d, *J* = 10.4, 2.0 Hz, 1H), 4.92 – 4.82 (m, 6H), 4.64 – 4.55 (m, 4H), 4.41 (d, *J* = 12.4, 6.0 Hz, 1H), 4.32 (d, *J* = 12.0, 5.6 Hz, 1H), 4.05 (t, *J* = 9.6 Hz, 1H), 3.99 (t, *J* = 2.4 Hz, 1H), 3.93 (t, *J* = 9.2 Hz, 1H), 3.84 (s, 3H), 3.43 (t, *J* = 9.2 Hz, 1H), 3.34 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.28 (dd, *J* = 9.6, 2.4 Hz, 1H).

2,3,4,5-Tetra-*O*-Benzyl-1-*O*-(4-methoxybenzyl)-*myo*-inositol 175. A 50 mL oven-dried, Ar flushed Schlenk flask was charged with **174** (0.73 g, 1.0 mmol, 1.0 equiv.), NaOAc (0.27 g, 3.3 mmol, 3.2 equiv.), $PdCl_2$ (0.24 g, 1.3 mmol, 1.3 equiv.), AcOH (10 mL), and H_2O (0.6 mL). The reaction mixture was stirred overnight. The reaction mixture was diluted with EtOAc (40 mL) followed by careful addition of sat. aq. Na_2CO_3

(25 mL). The resulting solution was stirred for 30 min. The organic layer was separated, dried over Na_2SO_3, and concentrated *in vacuo* to give crude **175**. Crude **175** was purified by flash column chromatography (hexane/ethyl acetate = 4/1 → 1/1) to afford **175** (0.53 g, 78%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.43 – 7.23 (m, 22H), 6.89 (d, *J* = 11.2 Hz, 2H), 4.96 – 4.79 (m, 6H), 4.73 – 4.63 (m, 2H), 4.58 – 4.45 (m, 2H), 4.18 (t, *J* = 12.4 Hz, 1H), 4.11 – 4.05 (m, 2H), 3.84 (s, 3H), 3.43 – 3.37 (m, 2H), 3.19 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.51 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.9, 138.4, 130.0, 129.4, 128.4, 128.4, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.4, 114.0, 83.5, 81.5, 81.2, 79.8, 75.9, 75.4, 74.1, 73.7, 72.9, 72.0. IR (film, cm^{-1}): ν = 3575, 3062, 3030, 2877, 1611, 1512, 1454, 1360, 1302, 1247, 1111, 1053, 1026. HRMS (ESI): calc. for $C_{42}H_{44}O_7$ (M+Na): 683.2985; found: 683.2986.

3,4,5-Tri-*O*-Benzyl-6-*O*-(4-methoxybenzyl)-*myo*-inositol 176.[213] A 10 mL oven-dried, Ar flushed Schlenk flask was charged with **141** (0.36 g, 0.741 mmol, 1 equiv.),[35] and anhydrous DMF (1.12 mL). The solution was cooled to 0 °C after which NaH (59.3 mg, 1.48 mmol, 2.0 equiv.) was added. The solution was stirred at 0 °C for another 30 min before PMBCl (0.3 mL, 2.2 mmol, 3.0 equiv.) was added dropwise, followed by addition of TBAI (27.4 mg, 0.0741 mmol, 0.1 equiv.). The reaction mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C followed by careful addition of MeOH (1 mL). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was added to a 250 mL RBF along with a solution of HCl (0.31 mL, 3.71 mmol, 5 equiv.) in MeOH (15 mL). The

reaction mixture was stirred for 1 h at room temperature, followed by neutralization with 1 M NaOH. The reaction mixture was concentrated *in vacuo* and extracted with CH_2Cl_2 (5 x 40 mL). The organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield crude **177**. Crude **177** was purified by flash column chromatography (hexane/ethyl acetate = 2/1 → 1/1 → 1/3) to afford **177** (0.395 g, 95%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36 – 7.32 (m, 15H), 7.25 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.95 – 4.84 (m, 5H), 4.73 (d, *J* = 1.6 Hz, 2H), 4.68 (d, *J* = 10.8 Hz, 1H), 4.22 (t, *J* = 2.8 Hz, 1H), 3.98 (t, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 3.50 – 3.47 (m, 3H), 2.48 (s, 1H), 2.37 (d, *J* = 4.4 Hz, 1H).

1,2-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-6-*O*-(4-methoxybenzyl)-*myo*-inositol 177. An oven dried, Ar flushed 10 mL Schlenk flask was charged with **176** (240 mg, 0.421 mmol, 1.0 equiv.), anhydrous pyridine (1.5 mL), acetic anhydride (238.5 μL, 2.52 mmol, 6.0 equiv.), and DMAP (2.6 mg, 0.021 mmol, 0.05 equiv.). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated by azeotropic removal of pyridine with toluene (10 mL). The residue was redissolved in CH_2Cl_2 (10 mL) and washed with sat. aq. $CuSO_4$ (3 x 5 mL) and water (1 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to form pure **177** (223.3 mg, 81%) as an off white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40 – 7.33 (m, 17H), 6.91 (d, *J* = 11.6 Hz, 2H), 5.71 (t, *J* = 13.2 Hz, 1H), 5.02 – 4.69 (m, 10H), 4.25 – 4.15 (m, 2H), 3.84 (s, 3H), 3.61 – 3.55 (m, 2H), 2.04 (s, 3H), 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.4, 169.8, 159.2, 138.5, 138.3, 138.1, 130.3, 129.5, 128.5, 128.4, 128.4, 128.1, 127.8, 127.7, 127.6, 127.6, 127.5, 113.7, 81.4, 81.2, 80.6, 76.0, 75.5, 74.2, 73.9, 72.9,

72.0, 71.7, 55.3, 20.8. IR (film, cm^{-1}): ν = 3063, 2884, 1750, 1612, 1513, 1497, 1455, 1366, 1244, 1045. HRMS (ESI): calc. for $C_{39}H_{42}O_9$ (M+Na): 677.2727; found: 677.2731.

1,2-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-inositol 178. A 50 mL oven-dried RBF was charged with **177** (220.0 mg, 0.336 mmol, 1.0 equiv.), CH_2Cl_2 (5 mL), H_2O (0.25 mL), and DDQ (114.4 mg, 0.504 mmol, 1.5 equiv.). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture concentrated *in vacuo* and purified by silica gel flash chromatography (hexane/ethyl acetate = 1/1) to afford **178** (110.3 mg, 61%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36 – 7.27 (m, 15H), 5.64, (t, *J* = 10.0 Hz, 1H), 4.94 – 4.84 (m, 4H), 4.73 – 4.67 (m, 2H), 4.31 (bs, 1H), 4.08 (t, *J* = 9.6 Hz, 1H), 3.60 – 3.54 (m, 2H), 2.73 (bs, 1H), 2.11 (s, 3H), 1.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.4, 169.8, 138.4, 138.2, 137.5, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 81.0, 80.8, 79.7, 76.0, 75.6, 72.8, 71.4, 71.1, 67.8, 20.9, 20.8. IR (film, cm^{-1}): ν = 3488, 3088, 3063, 3030, 2877, 1746, 1496, 1454, 1365, 1223, 1146, 1128, 1044. HRMS (ESI): calc. for $C_{31}H_{34}O_8$ (M+Na): 557.2151; found: 557.2160.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Fluorobenzylideneamino-D-Glucopyranosyl Trichloroacetimidate 179.[36] A 50 mL oven dried Schlenk flask was charged with hemiacetal[36] (1.4 g, 3.403 mmol, 1.0 equiv.) and dichloromethane (17 mL). The solution was cooled to 0 °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 **179** (1.38 g, 73%). ^{1}H NMR (CDCl3, 400 MHz): δ = 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), 7.07 (t, *J* = 10.0 Hz, 1H), 6.45 (d, *J* = 3.6 Hz, 1H), 5.71 (t, *J* = 10.0 Hz, 1H), 5.25 (t, *J* = 10.0 Hz, 1H), 4.41 – 4.34 (m, 2H), 4.20 – 4.16 (m, 1H), 3.89 (dd, *J* = 10.0, 3.6 Hz, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 1.94 (s, 3H).

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Fluorobenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2,3,4,5-Penta-*O*-Benzyl-*myo*-Inositol 180. An oven dried, Ar flushed 10 mL Schlenk flask was charged with imidate **146** (83.4 mg, 0.15 mmol, 1.0 equiv), inositol **172** (123 mg, 0.195 mmol, 1.3 equiv), and dichloromethane (1 mL). The resulting mixture was cooled to 0 ^{o}C after which Ni(4-F-Ph-CN)$_4$(OTf)$_2$ (1.0 mL, 0.015 mmol, 10 mol %) was added. The reaction mixture was stirred at room temperature. When the reaction was complete as monitored by TLC (hexane/ethyl acetate = 3/1), the reaction mixture was filtered, evaporated, and purified by flash chromatography on silica gel (hexane/ethyl acetate = 3/1 → 3/2 with 1% Et$_3$N) to give **180** (104 mg, 78%, α:β = 11:1). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.93 (s, 1H), 7.78 – 7.74 (m, 0.2H), 7.55 – 7.52 (m, 2H), 7.43 – 7.27 (m, 16H), 7.23 – 7.13 (m, 9H), 7.03 (t, *J* = 11.0 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.72 – 5.68 (m, 2H), 5.24 (d, *J* = 14.5 Hz, 1H), 5.04 – 4.99 (m, 2H), 4.88 (dd, *J* = 14.5, 5.0 Hz, 2H), 4.80 (d, *J* = 8.5 Hz, 2H), 4.64 (d, *J* = 8.5 Hz, 2H), 4.46 (d, *J* = 13.0 Hz, 1H), 4.39 – 4.34 (m, 2H), 4.24 – 4.18 (m, 2H), 4.00 (t, *J* = 3.0 Hz, 1H), 3.65 – 3.59 (m, 3H), 3.51 – 3.42 (m, 4H), 2.04 (s, 3H), 1.90 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 170.6, 169.8, 169.7, 162.5, 138.7, 138.6, 138.5, 138.3, 137.8, 131.8,

131.8, 130.4, 130.3, 129.1, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 127.0, 126.0, 125.4, 125.3, 115.6, 115.4, 99.0, 82.1, 82.0, 81.2, 80.9, 77.4, 77.1, 76.8, 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, 20.7. IR (film, cm^{-1}): ν = 3063, 3030, 2869, 1744, 1644, 1601, 1508, 1454, 1363, 1227, 1125, 1048, 1021. HRMS (ESI): calc. for $C_{60}H_{63}NO_{13}F$ (M+H): 1024.4283; found: 1024.4290.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2,3,4,5-Penta-*O*-Benzyl-*myo*-Inositol 181. A 10 mL oven dried Schlenk flask was charged with imidate **93** (90.9 mg, 0.15 mmol, 1.0 equiv.), inositol **172** (123 mg, 0.195 mmol, 1.3 equiv.) and CH_2Cl_2 (1.1 mL). A preformed solution of $Ni(4\text{-}PhCN)_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-}F\text{-}PhCN)_4Cl_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.015 mmol, 10 mol %) in dichloromethane (1 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 °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 pseudo-disaccharide **181** (116 mg, 78%, α:β = 11:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.98 (s, 1H), 7.62 – 7.57 (m, 4H), 7.43 – 7.31 (m, 14H), 7.26 (s, 3H), 7.20 – 7.10 (m, 6H), 6.81 (d, *J* = 7.2 Hz, 1H), 5.75 – 5.71 (m, 2H), 5.24 (d, *J* = 11.2 Hz, 1H), 5.06 – 4.99 (m, 2H), 4.88 (d, *J* = 10.8 Hz, 2H), 4.83 – 4.75 (m, 2H), 4.68 – 4.60 (m, 2H), 4.46 (d, *J* = 10.4 Hz, 1H), 4.39 – 4.31 (m, 2H), 4.23 – 4.14 (m, 2H), 4.01 (t, *J* = 2.0 Hz, 1H), 3.65 – 3.59 (m, 3H), 3.54 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.43 (dd, *J* = 10.0, 2.0 Hz, 2H), 2.04 (s,

3H), 1.91 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.8, 170.1, 169.9, 162.8, 138.9, 138.8, 138.8, 138.7, 138.5, 137.9, 129.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.2, 127.1, 125.9, 125.6, 125.6, 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}): ν = 3063, 3030, 2872, 1747, 1645, 1497, 1455, 1364, 1322, 1223, 1167, 1125, 1019, 728. HRMS (ESI): calc. for $C_{61}H_{63}NO_{13}F_3$ (M+H): 1074.4252; found: 1074.4259.

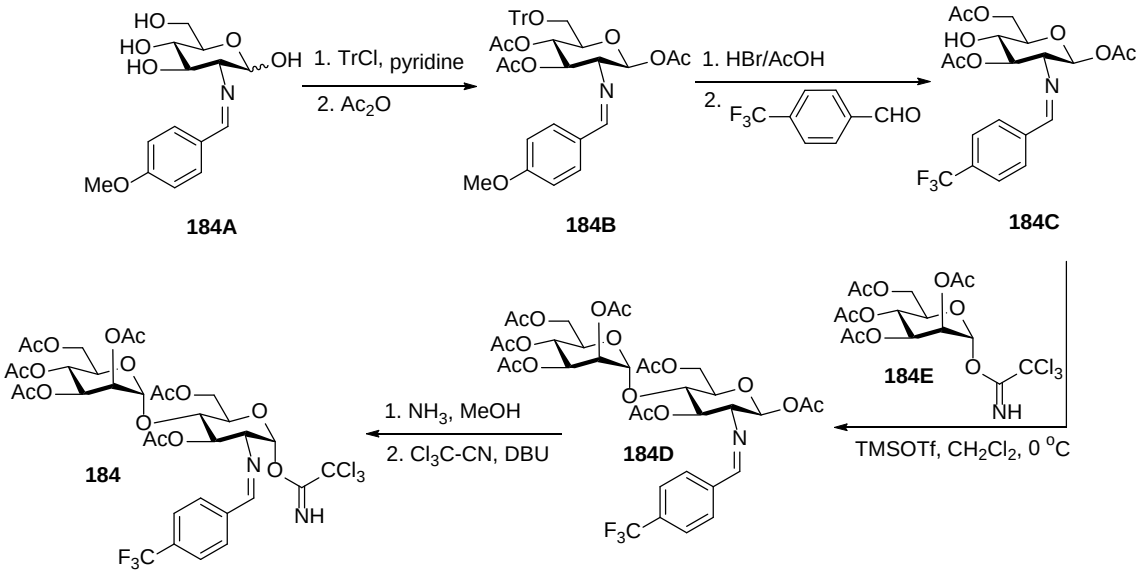
3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Fluorobenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2,3,4,5-Penta-*O*-Benzyl-*myo*-Inositol 182. A 10 mL oven dried Schlenk flask was charged with imidate **179** (83.4 mg, 0.15 mmol, 1.0 equiv.), inositol **172** (123 mg, 0.195 mmol, 1.3 equiv.) and CH_2Cl_2 (1.1 mL). A preformed solution of Ni(4-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, 0.015 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 (14/1, toluene/acetonitrile + 1% triethylamine) to give the desired pseudo-disaccharide **182** (101.3 mg, 66%, α:β = 15:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.32 (s, 1H), 8.04 (t, *J* = 5.6 Hz, 1H) 7.42 – 7.33 (m, 15H), 7.25 (s, 5H), 7.24 – 7.10 (m, 6H), 7.00 (t, *J* = 9.6 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 2H), 5.71 – 5.65 (m, 2H), 5.23 (d, *J* = 11.2 Hz, 1H), 5.06 – 4.98 (m, 2H), 4.88 (t, *J* = 10.8 Hz, 2H), 4.81 (d, *J* = 6.0 Hz, 2H), 4.78 – 4.66 (m, 1H), 4.63 (d, *J* = 6.8 Hz, 2H), 4.46 (d, *J* = 10.4 Hz, 1H), 4.37 (t, *J* = 10.0 Hz, 2H), 4.29 (d, *J* =

11.6 Hz, 1H), 4.20 (t, *J* = 9.6 Hz, 1H), 3.99 (t, *J* = 2.0 Hz, 1H), 3.70 – 3.59 (m, 3H), 3.53 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.47 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.43 (dd, *J* = 9.6, 2.0 Hz, 1H), 2.03 (s, 3H), 1.88 (s, 3H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.9, 170.0, 170.0, 157.6, 157.6, 139.0, 138.9, 138.8, 138.5, 137.9, 128.6, 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 127.6, 127.4, 127.2, 126.4, 116.1, 115.9, 99.0, 82.5, 82.3, 81.5, 81.2, 76.1, 75.8, 75.6, 74.6, 73.9, 73.6, 72.9, 72.2, 71.6, 68.6, 67.3, 61.7, 21.0, 20.9, 20.9. IR (film, cm^{-1}): ν = 3088, 3063, 3030, 2872, 1745, 1638, 1613, 1581, 1454, 1364, 1225, 1125, 1020, 909. HRMS (ESI): calc. for $C_{60}H_{63}NO_{13}F$ (M+H): 1024.4283; found: 1024.4285.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2,3,4,5-Penta-*O*-Benzyl-*myo*-Inositol 183. A 10 mL oven dried Schlenk flask was charged with imidate **99** (48.5 mg, 0.08 mmol, 1.5 equiv.), inositol **172** (33.6 mg, 0.053 mmol, 1.0 equiv.) and CH_2Cl_2 (0.7 mL). A preformed solution of $Ni(4\text{-}PhCN)_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-}F\text{-}PhCN)_4Cl_2$ (2.46 mg, 0.004 mmol, 5 mol %) and AgOTf (2.06 mg, 0.008 mmol, 10 mol %) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 °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 pseudo-disaccharide **183** (45.3 mg, 79%, α:β = 15:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.45 (d, *J* = 2.4 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.41 – 7.33 (m, 12H), 7.26 – 7.24

(m, 8H), 7.05 (t, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 6.8 Hz, 2H), 5.72 (d, *J* = 3.6 Hz, 1H), 5.64 (t, *J* = 9.6 Hz, 1H), 5.21 (d, *J* = 11.6 Hz, 1H), 5.07 – 4.97 (m, 2H), 4.91 – 4.81 (m, 4H), 4.67 – 4.60 (m, 2H), 4.47 (d, *J* = 10.4 Hz, 1H), 4.41 – 4.30 (m, 3H), 4.19 (t, *J* = 9.6 Hz, 1H), 3.99 (t, *J* = 2.4 Hz, 1H), 3.73 – 3.58 (m, 4H), 3.48 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.43 (dd, *J* = 10.0, 2.4 Hz, 1H), 2.03 (s, 3H), 1.86 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.9, 170.0, 170.0, 160.5, 139.0, 138.9, 138.8, 138.5, 137.7, 132.0, 130.8, 129.3, 128.6, 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.1, 126.7, 98.6, 82.5, 82.3, 81.6, 81.1, 77.5, 76.1, 75.6, 74.6, 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}): ν = 3064, 3031, 2883, 1747, 1640, 1602, 1497, 1454, 1277, 1364, 1314, 1226, 1164, 1124, 1025. HRMS (ESI): calc. for $C_{61}H_{63}NO_{13}F_3$ (M+H): 1074.4252; found: 1074.4254.

7.2. Synthesis of Trichloroimidate **184**



Scheme 7.2. Synthesis of 2,3,4,6-Tetra-*O*-Acetyl-α-D-Mannopyranosyl-(1→4)-3,6-Di-*O*-Acetyl-2-Deoxy-2-*ortho*-Trifluoro-methyl-benzylideneamino-α-D-Glucopyranosyl Trichloroacetimidate **184**.

1,3,4-Tri-*O*-Acetyl-6-*O*-(Triphenylmethyl)-2-Deoxy-2-*p*-Methoxybenzylideneamino-D-Glucopyranoside 184B. An oven dried 1 L round bottom flask was charged with *p*-methoxybenzylidene D-glucosamine **184A**[33, 35] (41.4 g, 139.25 mmol, 1.0 equiv), trityl chloride (116.5 g, 417.76 mmol, 3.0 equiv), triethylamine (97 mL, 696.25 mmol, 5.0 equiv), dimethylamino pyridine (849 mg, 6.95 mmol, 0.05 equiv), and anhydrous pyridine (464 mL). The reaction mixture was stirred at room temperature overnight. The mixture was cooled to 0 °C and acetic anhydride (79 mL, 835.5 mmol, 6.0 equiv) was added. The resulting mixture was stirred for 24 h at room temperature. The mixture was

then added to ice cold water in which a white precipitate formed. The white precipitate was filtered and dissolved in ethyl acetate (200 mL) and dried with anhydrous Na_2SO_4. The ethyl acetate solution was concentrated *in vacuo*. The residue was then purified by silica gel flash chromatography (hexane/ethyl acetate = 5/1 → 2/1 with 1% Et_3N) to afford **184B** (80.0 g, 86%) as a solid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.21 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 6H), 7.33 – 7.24 (m, 10H), 6.93 (d, *J* = 8.4 Hz, 2H), 5.96 (d, *J* = 8.1 Hz, 1H), 5.41 – 5.26 (m, 2H), 3.86 (s, 3H), 3.51 (t, *J* = 9.0 Hz, 1H), 3.41 (dd, *J* = 10.5, 2.1 Hz, 1H), 3.12 (dd, *J* = 10.8, 4.2 Hz, 1H), 2.08 (s, 3H), 1.89 (s, 3H), 1.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.7, 169.5, 168.8, 164.1, 162.3, 143.7, 130.3, 128.8, 128.5, 127.8, 127.0, 114.1, 93.4, 86.6, 74.1, 72.7, 73.3, 68.7, 62.0, 55.4. IR (film, cm^{-1}): ν = 3060, 2945, 2876, 1755, 1645, 1606, 1578, 1513, 1491, 1449, 1366, 1248, 1218, 1167, 1067, 1033. HRMS (ESI): calc. for $C_{39}H_{39}O_9$ (M+Na): 688.2523; found: 688.2520.

1,3,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Trifluoromethylbenzylideneamino-D-Glucopyranoside 184C. A 100 mL round bottom flask was charged with **184B** (2.0 g, 3.00 mmol, 1.0 equiv), acetic acid (12 mL), and a solution of HBr in acetic acid (0.6 mL, 33 wt. %). The reaction mixture was stirred for 1 min, filtered and concentrated to a brown oil. The oil was washed with a 1:1 mixture of hexanes/ethyl acetate (5 x 30 mL). A 100 mL round bottom flask was charged with the resulting brown oil, pyridine (2.4 mL, 30 mmol, 10.0 equiv), 4-trifluoromethylbenzaldehyde (1.2 mL, 6.0 mmol, 3.0 equiv), and dichloromethane (5 mL). The resulting mixture was refluxed at 50 °C overnight and then concentrated *in vacuo*. The residue was purified by silica gel flash

chromatography (hexane/ethyl acetate = 1/1 with 1% Et_3N) to afford **184C** (690 mg, 50%) as a solid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.30 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 8.1 Hz, 2H), 5.97 (d, *J* = 8.1 Hz, 1H), 5.30 (t, *J* = 9.6 Hz, 1H), 4.55 (dd, *J* = 12.6, 4.5 Hz, 1H), 4.35 (dd *J* = 12.3, 2.1 Hz, 1H), 3.85 – 3.79 (m, 1H), 3.64 (t, *J* = 9.6 Hz, 1H), 3.46 (dd, *J* = 9.6, 8.4 Hz, 1H), 3.20 (bs, 1H), 2.15 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.7, 171.2, 168.7, 163.4, 138.3, 133.2, 132.9, 129.9, 129.9, 128.8, 125.7, 124.8, 122.7, 93.0, 75.7, 75.3, 72.9, 68.7, 62.9, 20.9, 20.8, 20.7. IR (film, cm^{-1}): ν = 3501, 2925, 2880, 1745, 1648, 1367, 1322, 1217, 1166, 1126, 1091, 1063, 1033. HRMS (ESI): calc. for $C_{20}H_{22}NO_8F_3$ (M+Na): 484.1195; found: 484.1201.

2,3,4,6-Tetra-*O*-Acetyl-α-D-Mannopyranosyl-(1-4)-1,3,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Trifluoromethylbenzylideneamino-D-Glucopyranoside 184D. A 50 mL oven-dried Schlenk flask was charged with donor **184E** (409.3 mg, 0.831 mmol, 1.0 equiv), acceptor **184C** (500 mg, 1.08 mmol, 1.3 equiv), crushed 4 Å molecular sieves (50 mg), and CH_2Cl_2 (13 mL). The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was cooled to 0 °C and TMSOTf (30.1 μL, 0.166 mmol, 0.2 equiv.) was added. The reaction was stirred at 0 °C for 4 h. Triethylamine (0.5mL) was added to quench the reaction. The resulting mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate = 5/1 → 3/1 → 1/1 with 1% Et_3N) to afford disaccharide **184D** (421.0 mg, 64%) as a solid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.27 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.1 Hz, 2H), 5.55 (t, *J* = 9.0 Hz, 1H), 5.31 – 5.28 (m, 2H), 5.03 (s, 2H), 4.52 (d, *J* = 9.0 Hz, 1H), 4.28 (dd, *J* = 13.2, 4.2 Hz, 2H), 4.17 – 4.09 (m, 4H), 3.94 – 3.86 (m, 2H), 3.42 (t, *J*

= 9.6 Hz, 1H), 2.14 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.5, 169.9, 169.7, 169.5, 169.3, 163.2, 138.3, 133.2, 132.9, 129.9, 128.8, 125.7, 99.7, 92.7, 74.2, 73.8, 73.6, 70.1, 69.9, 68.3, 65.9, 62.8, 62.2, 60.4. IR (film, cm^{-1}): ν = 2952, 2877, 1748, 1648, 1581, 1432, 1371, 1324, 1221, 1167, 1129, 1064, 1042, 981, 913. HRMS (ESI): calc. for $C_{20}H_{22}NO_9F_3$ (M+H): 792.2327; found: 792.2325.

2,3,4,6-Tetra-*O*-Acetyl-α-D-Mannopyranosyl-(1→4)-3,6-Di-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl Trichloroacetimidate 184. A 25 mL rbf was charged with **184D** (167.8 mg, 0.212 mmol, 1 equiv) and anhydrous THF (1.4 mL). The solution was cooled to 0 °C. 7.0 M ammonia in methanol solution (0.45 mL, 3.18 mmol, 15.0 equiv) was added to the solution. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated to a yellow oil and used in the next step without further purification. A 25 mL oven-dried Schlenk was charged with the yellow oil and dichloromethane (30 mL). The solution was cooled to 0 °C, and trichloroacetonitrile (63.8 μL, 0.636 mmol, 3 equiv) was then added to the reaction mixture followed by DBU (15.8 μL, 0.106 mmol, 0.5 equiv). The resulting mixture was stirred at this temperature for 4 h and then concentrated in vacuo. The residue was purified by silica gel flash chromatography (2/1, hexane/ethyl acetate + 1% Et_3N) to provide trichloroacetimidate **184** as a white solid (108 mg, 57%). ^{1}H NMR (CDCl3, 500 MHz): δ = 8.57 (s, 1H), 8.37 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 6.40 (d, *J* = 4.5 Hz, 1H), 5.63 (t, *J* = 9.5 Hz, 1H), 5.52 (d, *J* = 2.0 Hz, 1H), 5.27 (t, *J* = 12.0 Hz, 2H), 5.17 – 5.13 (m, 2H), 4.69 – 4.67 (m, 1H), 4.53 (dd, *J* = 12.0,

2.0 Hz, 1H), 4.29 – 4.24 (m, 3H), 4.19 – 4.11 (m, 4H), 3.86 (t, *J* = 9.5 Hz, 2H), 3.69 – 3.66 (m, 2H), 3.40 – 3.36 (m, 1H), 3.34 – 3.27 (m, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.96 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.5, 169.4, 169.4, 169.3, 169.3, 169.2, 160.9, 138.5, 132.9, 132.7, 129.3, 128.0, 128.0, 126.3, 126.2, 124.9, 97.7, 96.3, 95.8, 94.4, 91.0, 78.0, 77.7, 77.6, 76.4, 71.6, 71.1, 70.9, 70.5, 70.1, 69.4, 65.7, 64.4, 64.0, 63.0, 62.8, 61.8, 21.3, 21.1, 21.0, 20.3, 20.2, 20.1. IR (film, cm^{-1}): ν = 3337, 2955, 2879, 1744, 1674, 1649, 1433, 1370, 1323, 1224, 1167, 1129, 1064, 1030. HRMS (ESI): calc. for $C_{34}H_{38}F_3N_2O_{16}Na$ (M+Na): 915.1137; found: 915.1130.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→6)-2,3,4,5-Tetra-*O*-Benzyl-1-*O*-(4-methoxybenzyl)-*myo*-Inositol

185. A 10 mL oven dried Schlenk flask was charged with imidate **93** (12.8 mg, 0.021 mmol, 1.5 equiv.), inositol **175** (9.3 mg, 0.014 mmol, 1.0 equiv.) and CH_2Cl_2 (0.5 mL). A preformed solution of $Ni(4\text{-}PhCN)_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-}F\text{-}PhCN)_4Cl_2$ (0.86 mg, 0.0014 mmol, 10 mol %) and AgOTf (0.72 mg, 0.0028 mmol, 20 mol %) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 °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 pseudo-disaccharide **185** (22 mg, 71%, α:β = 10:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.05 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.41 – 7.22 (m, 20H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.64 (d,

J = 8.5 Hz, 2H), 5.73 – 5.69 (m, 2H), 5.22 (d, *J* = 11.5 Hz, 1H), 5.03 – 4.98 (m, 3H), 4.89 – 4.85 (m, 3H), 4.82 – 4.75 (m, 2H), 4.66 – 4.59 (m, 2H), 4.45 (d, *J* = 10.5 Hz, 2H), 4.34 (t, *J* = 9.5 Hz, 1H), 4.26 (d, *J* = 11.5 Hz, 1H), 4.18 (t, *J* = 9.0 Hz, 2H), 4.10 (d, *J* = 11.5 Hz, 1H), 3.97 (s, 1H), 3.87 – 3.83 (m, 1H), 3.80 (s, 3H), 3.68 – 3.54 (m, 4H), 3.40 (t, *J* = 10.0 Hz, 3), 2.04 (s, 3H), 1.89 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.5, 158.6, 138.7, 138.6, 138.5, 138.2, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 127.8, 127.6, 127.3, 113.4, 98.8, 82.0, 81.2, 80.9, 75.9, 74.2, 73.3, 73.1, 72.7, 71.4, 68.3, 61.4, 55.3, 53.4. IR (film, cm^{-1}): ν = 3063, 3030, 2926, 2857, 1749, 1645, 1613, 1513, 1455, 1323, 1245, 1229, 1127, 1028. HRMS (ESI): calc. for $C_{62}H_{65}NO_{14}F_3$ (M+H): 1104.4357; found: 1104.4355.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*p*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 186. A 10 mL oven dried Schlenk flask was charged with imidate **93** (15.4 mg, 0.025 mmol, 1.5 equiv.), inositol **178** (9.1 mg, 0.017 mmol, 1.0 equiv.) and CH_2Cl_2 (0.5 mL). A preformed solution of $Ni(4\text{-}PhCN)_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-}F\text{-}PhCN)_4Cl_2$ (1.04 mg, 0.0017 mmol, 10 mol %) and AgOTf (0.87 mg, 0.0034 mmol, 20 mol %) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 °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 pseudo-disaccharide **186** (21 mg, 79%, α:β = 12:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.35 (s, 1H), 7.98 (d, *J* = 8.0

Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.30 (m, 15H), 5.72 (t, *J* = 10.0 Hz, 1H), 5.63 (t, *J* = 9.6 Hz, 1H), 5.16 (d, *J* = 3.6 Hz, 1H), 5.12 – 4.57 (m, 8H), 4.38 (t, *J* = 2.4 Hz, 1H), 4.29 (t, *J* = 9.6 Hz, 1H), 3.95 (dd, *J* = 12.4, 2.8 Hz, 1H), 3.67 – 3.53 (m, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.89 (s, 3H), 1.83 (s, 3H), 1.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.6, 171.2, 170.9, 170.6, 170.2, 164.0, 139.3, 139.2, 138.6, 130.4, 129.6, 129.6, 129.5, 129.3, 129.0, 128.9, 128.8, 128.4, 126.6, 126.6, 104.5, 100.4, 82.6, 81.9, 79.7, 78.3, 77.0, 76.7, 74.5, 74.4, 73.5, 73.1, 72.8, 72.0, 69.5, 68.8, 62.5, IR (film, cm^{-1}): ν = 3063, 3030, 2926, 2857, 1751, 1646, 1600, 1497, 1455, 1367, 1324, 1239, 1166, 1128, 1044. HRMS (ESI): calc. for $C_{51}H_{55}NO_{15}F_3$ (M+H): 978.3524; found: 978.3539.

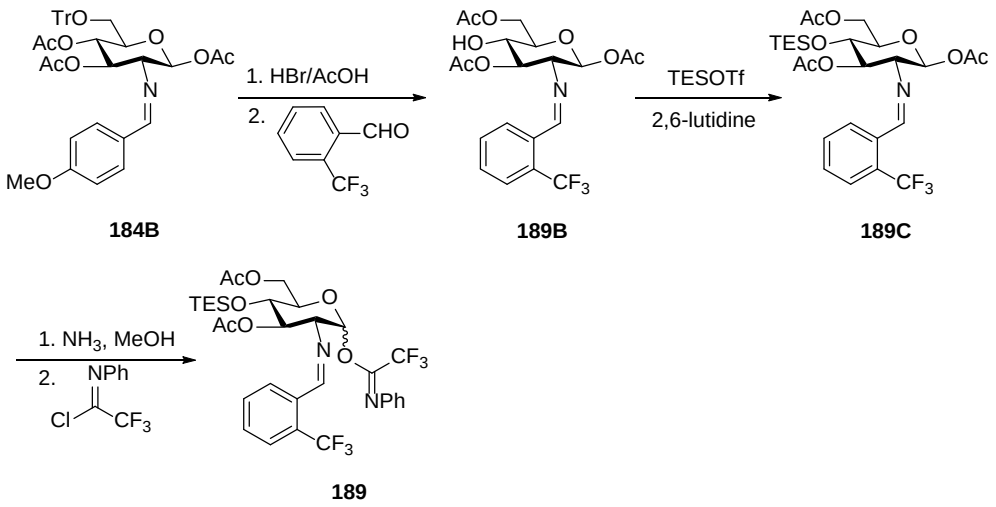
3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 187. A 10 mL oven-dried Schlenk flask was charged with donor **107** (16.8 mg, 0.027 mmol, 1.5 equiv), inositol acceptor **178** (9.44 mg, 0.018 mmol, 1.0 equiv), and CH_2Cl_2 (0.5 mL). Then 0.5 mL of preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from a reaction of $Ni(4\text{-F-PhCN})_4Cl_2$ (1.09 mg, 0.0018 mmol, 10 mol%) and AgOTf (0.91 mg, 0.0035 mmol, 20 mol%) in CH_2Cl_2 for 30 min, was added to the solution. The resulting mixture was stirred at 35 °C overnight. When the reaction was complete as monitored by TLC (toluene/acetonitrile = 4/1), the mixture was purified by silica gel flash chromatography (hexane/ethyl acetate = 5/1 → 3/1 → 3/2 → 1/1 with 1% Et_3N) to afford disaccharide **187** (24.0 mg, 72%, α:β = 10:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.69 (d, *J* = 2 Hz, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H) 7.40 – 7.30 (m, 15H), 5.75 (t, *J* = 10.0 Hz, 1H), 5.64 (t,

J = 10.0 Hz, 1H), 5.58 (t, *J* = 10.0 Hz, 0.1H), 5.16 – 5.11 (m, 2H), 5.04 (d, *J* = 11.0 Hz, 1H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.92-4.88 (m, 2H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 11.0, 1H), 4.63 (dt, *J* = 10.5, 2.5 Hz, 1H), 4.41 (t, *J* = 2.5 Hz, 1H), 4.30 (t, *J* = 10.0 Hz, 1H), 3.93 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.70 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.64 (dd, *J* = 12.5, 2.0 Hz, 1H), 3.57 (t, *J* = 9.5, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 1.91 (s, 3H), 1.86 (s, 3H), 1.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.6, 170.0, 169.9, 169.7, 169.1, 160.8, 132.7, 130.5, 130.2, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.7, 127.6, 127.4, 127.2, 125.1, 125.0, 99.5, 81.7, 80.7, 78.6, 75.9, 75.4, 73.6, 73.5, 72.8, 72.1, 72.0, 70.8, 68.6, 67.7, 46.0, 29.7, 20.8, 20.4. IR (film, cm^{-1}): ν = 3032, 2952, 2926, 2859, 1753, 1643, 1455, 1367, 1315, 1239, 1123, 1044. HRMS (ESI): calc. for $C_{51}H_{55}NO_{15}F_3$ (M+H): 978.3524; found: 978.3549.

2,3,4,6-Tetra-*O*-Acetyl-β-D-Mannopyranosyl-(1→4)-3,6-Di-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 188. A 10 mL oven dried Schlenk flask was charged with imidate **184** (29.1 mg, 0.033 mmol, 1.5 equiv.), inositol **178** (11.6 mg, 0.022 mmol, 1.0 equiv.) and CH_2Cl_2 (0.5 mL). A preformed solution of $Ni(4\text{-}PhCN)_4(OTf)_2$, which was generated *in situ* from $Ni(4\text{-}F\text{-}PhCN)_4Cl_2$ (1.35 mg, 0.0022 mmol, 10 mol %) and AgOTf (1.13 mg, 0.0044 mmol, 10 mol %) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 25 °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 pseudo-trisaccharide **188** (11 mg, 40%, α:β = 11:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.02 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.24 (m, 15H), 5.86 (s, 1H), 5.64 (d, *J* = 2.5 Hz, 1H), 5.32 – 5.26 (m, 2H), 5.19 (dd, *J* = 9.5, 4.0 Hz, 1H), 4.93 – 4.83 (m, 3H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.73 – 4.65 (m, 4H), 4.55 – 4.51 (m, 2H), 4.40 – 4.36 (m, 1H), 4.29 – 4.23 (m, 4H), 4.18 – 4.15 (m, 3H), 3.73 – 3.66 (m, 3H), 3.59 – 3.52 (m, 2H), 3.43 – 3.38 (m, 2H), 3.33 – 3.28 (m, 1H), 3.21 (t, *J* = 7.5 Hz, 1H), 2.17 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.7, 170.6, 170.5, 170.5, 170.4, 170.3, 169.8, 169.4, 149.4, 147.9, 139.9, 131.8, 131.5, 129.9, 128.6, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.8, 125.6, 124.9, 123.1, 97.4, 97.0, 81.3, 81.0, 80.8, 80.5, 79.6, 78.1, 76.1, 76.0, 75.8, 75.6, 75.0, 72.9, 72.3, 71.3, 71.0, 70.4, 70.2, 69.8, 67.8, 66.2, 65.4, 63.3, 62.2, 61.7, 50.1, 46.9, 43.2, 40.4, 29.7, 25.2, 20.9, 20.9, 20.8, 20.7, 20.7. IR (film, cm^{-1}): ν = 3065, 3030, 2928, 2856, 1744, 1644, 1555, 1498, 1455, 1437, 1370, 1323, 1225, 1168, 1034. HRMS (ESI): calc. for $C_{63}H_{71}NO_{23}F_3$ (M+H): 1266.4369; found: 1266.4382.

7.3. Synthesis of *N*-Phenyl Trifluoroimidate **189**



Scheme 7.3. Synthesis of 3,6-Di-*O*-Acetyl-4-*O*-(Triethylsylyl)-2-Deoxy-2-*o*-Trifluoromethyl-benzylideneamino-D-Glucopyranosyl *N*-Phenyl Trifluoroacetimidate **189**.

1,3,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-D-Glucopyranoside 189B. A 100 mL round bottom flask was charged with **184B** (2.0 g, 3.00 mmol, 1.0 equiv), acetic acid (12 mL), and a solution of HBr in acetic acid (0.6 mL, 33 wt. %). The reaction mixture was stirred for 1 minute. The reaction mixture was then filtered and concentrated to a brown oil. The oil was washed with a 1:1 mixture of hexanes/ethyl acetate (5 x 30 mL). A 100 mL round bottom flask was charged with the brown oil, pyridine (2.4 mL, 30 mmol, 10.0 equiv), 2-trifluoromethylbenzaldehyde (1.2 mL, 6.0 mmol, 3.0 equiv), and dichloromethane (5 mL). The resulting mixture was refluxed at 50 ^{o}C overnight and concentrated *in vacuo*. The residue was then purified by

silica gel flash chromatography (hexane/ethyl acetate = 1/1 with 1% Et_3N) to afford **189B** (690 mg, 50%) as a semisolid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.64 (d, *J* = 2.4 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.55 (m, 2H), 6.00 (d, *J* = 8.4 Hz, 1H), 5.34 (t, *J* = 9.6 Hz, 1H), 4.57 (dd, *J* = 12.4, 4.0 Hz, 1H), 4.34 (dd, *J* = 12.4, 2.0 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.66 (t, *J* = 9.6 Hz, 1H), 3.52 (dd, *J* = 9.6, 8.0 Hz, 1H), 2.16 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.5, 171.1, 168.7, 161.5, 133.4, 132.2, 130.7, 128.7, 127.7, 125.5, 125.4, 119.4, 92.8, 75.6, 75.1, 73.1, 68.4, 62.8. IR (film, cm^{-1}): ν = 3501, 2925, 2880, 1745, 1648, 1367, 1322, 1217, 1166, 1126, 1091, 1063, 1033. HRMS (ESI): calc. for $C_{20}H_{22}NO_8F_3$ (M+Na): 484.1195; found: 484.1200.

1,3,6-Tri-*O*-Acetyl-4-*O*-(Triethylsylyl)-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-D-Glucopyranoside 189C. A 25 mL Schlenk was charged with **189B** (300 mg, 0.65 mmol, 1.0 equiv), 2,6-lutidine (226.1 μL, 1.951 mmol, 3.0 equiv), CH_2Cl_2 (8 mL), and triethylsilyl trifluoromethanesulfonate (210.4 μL, 0.975 mmol, 1.5 equiv) and stirred at 0 °C. The reaction was monitored by TLC. After the starting material was consumed, the reaction mixture was concentrated and purified by silica gel flash chromatography (hexane/ethyl acetate = 10/1 → 2/1 with 1% Et_3N) to afford **189C** (249 mg, 67%) as a semisolid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.57 (d, *J* = 2.0 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.51 (m, 2H), 5.97 (d, *J* = 8.0 Hz, 1H), 5.41 (t, *J* = 9.2 Hz, 1H), 4.42 (dd, *J* = 12.4, 2.0 Hz, 1H), 4.19 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.92 (t, *J* = 9.2 Hz, 1H), 3.81 – 3.77 (m, 1H), 2.11 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.58 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR

($CDCl_3$, 100 MHz): δ = 170.6, 169.1, 168.6, 160.9, 133.5, 132.4, 130.7, 129.1, 128.9, 125.4, 103.6, 92.7, 75.6, 75.3, 74.4, 68.8, 62.8, 58.2, 20.9, 20.6, 8.2, 6.7, 5.0. IR (film, cm^{-1}): ν = 2956, 2914, 2879, 1753, 1645, 1455, 1367, 1315, 1285, 1217, 1169, 1122, 1034. HRMS (ESI): calc. for $C_{26}H_{36}NO_8F_3Si$ (M+Na): 598.2060; found: 598.2065.

3,6-Di-*O*-Acetyl-4-*O*-(Triethylsylyl)-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-D-Glucopyranosyl *N*-Phenyl Trifluoroacetimidate 189. A 25 mL round bottom flask was charged with **189D** (1.36 g, 2.36 mmol, 1 equiv) and anhydrous THF (6.4 mL). The solution was cooled to 0 ºC. 7.0 M ammonia in methanol solution (5.06 mL, 35.4 mmol, 15.0 equiv) was added to the solution. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated to a yellow oil and used in the next step without further purification. A 100 mL round bottom flask was charged with the yellow oil, 2,2,2-trifluoro-*N*-phenyl-ethanimidoyl chloride (1.47 g, 7.08 mmol, 3.0 equiv.), K_2CO_3 (652 mg, 4.72 mmol, 2.0 equiv.) and anhydrous acetone (14.0 mL). The solution was stirred at room temperature overnight. When the reaction mixture was complete as monitored by TLC (hexane/ethyl acetate = 3/1), the reaction mixture was filtered, evaporated, and purified by flash chromatography on silica gel (hexane/ethyl acetate = 5/1 → 3/1 with 1% Et_3N) to afford **189** as a white solid (1.40 g, 84%; α:β = 3:4). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.57 (s, 1H), 8.37 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 6.40 (d, *J* = 4.5 Hz, 1H), 5.63 (t, *J* = 9.5 Hz, 1H), 5.52 (d, *J* = 2.0 Hz, 1H), 5.27 (t, *J* = 12.0 Hz, 2H), 5.17 – 5.13 (m, 2H), 4.69 – 4.67 (m, 1H), 4.53 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.29 – 4.24 (m, 3H), 4.19 – 4.11 (m, 4H), 3.86 (t, *J* = 9.5 Hz, 2H), 3.69 – 3.66 (m, 2H), 3.40 – 3.36 (m, 1H), 3.34 – 3.27 (m, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.07 (s,

3H), 2.06 (s, 3H), 1.96 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.5, 169.4, 169.4, 169.3, 169.3, 169.2, 160.9, 138.5, 132.9, 132.7, 129.3, 128.0, 128.0, 126.3, 126.2, 124.9, 97.7, 96.3, 95.8, 94.4, 91.0, 78.0, 77.7, 77.6, 76.4, 71.6, 71.1, 70.9, 70.5, 70.1, 69.4, 65.7, 64.4, 64.0, 63.0, 62.8, 61.8, 21.3, 21.1, 21.0, 20.3, 20.2, 20.1. IR (film, cm^{-1}): ν = 3337, 2955, 2879, 1744, 1674, 1649, 1433, 1370, 1323, 1224, 1167, 1129, 1064, 1030. HRMS (ESI): calc. for $C_{34}H_{38}F_3N_2O_{16}Na$ (M+Na): 915.1137; found: 915.1130.

3,6-Di-*O*-Acetyl-4-*O*-(Triethylsilyl)-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 190. A 10 mL oven-dried Schlenk flask was charged with donor **189** (23.6 mg, 0.033 mmol, 1.5 equiv), inositol acceptor **178** (11.9 mg, 0.022 mmol, 1.0 equiv), and CH_2Cl_2 (0.5 mL). Then 0.5 mL of preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated *in situ* from a reaction of $Ni(4\text{-F-PhCN})_4Cl_2$ (1.37 mg, 0.0022 mmol, 10 mol%) and AgOTf (1.15 mg, 0.0045 mmol, 20 mol%) in CH_2Cl_2 for 30 min, was added to the solution. The resulting mixture was stirred at 35 ^{o}C overnight. When the reaction was complete as monitored by TLC (toluene/acetonitrile = 4/1), the mixture was purified by silica gel flash chromatography (hexane/ethyl acetate = 5/1 → 3/1 → 3/2 → 1/1 with 1% Et_3N) to afford disaccharide **190** (15 mg, 64%, α:β = 11:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.64 (d, *J* = 3.0 Hz, 1H), 8.56 (d, *J* = 9.0 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.49 (t, *J* = 6.0 Hz, 1H) 7.34-7.29 (m, 15H), 5.71 (t, *J* = 9.0, 1H), 5.61 (t, *J* = 9.9 Hz, 1H), 5.09 (d, *J* = 3.6 Hz, 1H), 5.02 (d, *J* = 10.8 Hz, 1H), 4.92 (d, *J* = 10.2 Hz, 1H), 4.88 (s, 1H), 4.76 (s, 2H), 4.62 (t, *J* = 11.4 Hz, 1H), 4.45 – 4.38 (m, 2H), 4.32 (t, *J* =

9.6 Hz, 1H), 4.00 (dd, *J* = 12.0, 1.8 Hz, 1H), 3.93 (d, *J* = 9.3 Hz, 1H), 3.84 (dd, *J* = 13.2, 3.9 Hz, 1H), 3.58 - 3.50 (m, 3H), 2.08 (s, 3H), 1.91 (s, 3H), 1.81 (s, 3H), 1.72 (s, 3H), 0.95 (t, *J* = 8.1, 9H), 0.59 (q, *J* = 7.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.6, 170.0, 169.0, 168.9, 159.6, 138.4, 138.3, 137.6, 133.2, 132.8, 130.3, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.6, 127.5, 127.3, 127.1, 124.9, 124.9, 123.3, 99.4, 81.6, 80.5, 78.9, 75.8, 75.0, 74.2, 73.5, 73.3, 73.2, 72.2, 72.0, 70.5, 69.4, 62.8, 29.7, 20.9, 20.8, 20.4, 6.9, 5.1. IR (film, cm^{-1}): ν = 3065, 3032, 2952, 2926, 2859, 1749, 1643, 1455, 1367, 1315, 1220, 1162, 1123, 1033. HRMS (ESI): calc. for $C_{55}H_{66}NO_{14}F_3Si$ (M+Na): 1072.4107; found: 1072.4102.

3,6-Di-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 191. A 25 mL oven-dried round bottom flask was charged with **190** (24 mg, 0.023 mmol, 1.0 equiv) and THF (0.5 mL). A solution of TBAF (1.0 M in THF), neutralized with AcOH (102 μL, 0.102 mmol, 4.4 equiv.), was then added. The reaction mixture was monitored by TLC until the reaction was complete. The mixture was diluted with ethyl acetate and washed with sat. aq. $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 2/1 → 1/2 with 1% Et_3N) to afford disaccharide **191** (18.1 mg, 84%) as a white semisolid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.70 (s, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H) 7.38 – 7.30 (m, 15H), 5.74 (t, *J* = 10.0 Hz, 1H), 5.43 (t, *J* = 9.5 Hz, 1H), 5.09 (d, *J* = 3.5 Hz, 1H), 5.04 – 4.90 (m, 3H), 4.87 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.82 – 4.76 (m, 2H), 4.66

(d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 10.0 Hz, 1H), 4.39 (t, *J* = 2.5 Hz, 1H), 4.24 (t, *J* = 10.0 Hz, 1H), 4.20 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.86 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.63 – 3.54 (m, 4H), 3.09 (bs, 1H), 2.09 (s, 3H), 2.01 (s, 3H), 1.87 (s, 3H), 1.73 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.3, 171.2, 169.9, 169.1, 160.6, 138.3, 137.5, 133.2, 132.7, 130.5, 130.2, 128.6, 128.4, 128.4, 128.2, 128.0, 127.9, 127.7, 127.6, 127.4, 125.1, 125.0, 99.7, 81.6, 80.7, 78.5, 75.8, 75.5, 74.0, 73.5, 73.3, 72.8, 72.1, 70.6, 69.5, 62.6, 20.9, 20.8, 20.7, 20.4. IR (film, cm^{-1}): ν = 3486, 3033, 2928, 2857, 1752, 1698, 1642, 1605, 1494, 1367, 1315, 1239, 1168, 1123, 1039. HRMS (ESI): calc. for $C_{49}H_{53}NO_{14}F_3$ (M+H) 936.3416; found: 936.3422.

2,3,4,6-Tetra-*O*-Benzyl-α-D-Mannopyranosyl-(1→4)-3,6-Di-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Glucopyranosyl-(1→6)-1,2-*O*-Di-Acetyl-3,4,5-Tri-*O*-Benzyl-*myo*-Inositol 193. A 10 mL oven-dried Schlenk flask was charged with 2,3,4,6-tetrakis-*O*-(phenylmethyl)-α-D-mannosyl trichloroacetimidate **192** (10.0 mg, 0.015 mmol, 2.0 equiv), acceptor **191** (7.0 mg, 0.0075 mmol, 1.0 equiv), crushed 4 Å molecular sieves (10 mg), and CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 1 h at room temperature. The mixture was cooled to 0 °C and TMSOTf (0.27 μL, 0.0075 mmol, 0.2 equiv.) was added. The reaction was stirred at 0 °C for 4 h. Triethylamine (0.5mL) was added to quench the reaction. The reaction mixture was filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate = 5/1 → 3/1 → 1/1 with 1% Et_3N) to afford trisaccharide **193** (6.1 mg, 56%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.64 (d, *J* = 2.5 Hz, 1H), 8.57 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.59 (t, 7.5 Hz, 1H), 7.51 (t, *J* = 8.0 Hz,

1H), 7.37 – 7.24 (m, 40H), 5.74 – 5.69 (m, 2H), 5.11 (d, *J* = 2.0 Hz, 1H), 5.08 (d, *J* = 4.0 Hz, 1H) 5.05 – 4.86 (m, 6H), 4.78 – 4.77 (m, 3H), 4.70 – 4.64 (m, 5H), 4.51 – 4.46 (m, 3H), 4.38 (t, *J* = 2.0 Hz, 1H), 4.30 (t, *J* = 9.5 Hz, 1H), 4.15 (t, *J* = 9.5 Hz, 1H), 4.02 (dd, *J* = 12.5, 2.0 Hz, 1H), 3.91 (t, *J* = 9.5 Hz, 1H), 3.87 – 3.85 (m, 2H), 3.65 (d, *J* = 7.5 Hz, 1H), 3.58 – 3.53 (m, 4H), 3.46 – 3.43 (m, 2H), 2.02 (s, 3H), 1.83 (s, 3H), 1.75 (s, 3H), 1.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.5, 169.9, 169.1, 169.0, 160.1, 138.6, 138.5, 138.5, 138.5, 138.4, 138.3, 137.4, 133.1, 132.8, 130.9, 130.5, 130.3, 128.8, 128.7, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 127.4, 127.3, 125.0, 125.0, 100.9, 99.4, 81.5, 80.6, 79.5, 78.6, 76.2, 75.9, 75.7, 75.3, 74.4, 73.5, 73.4, 73.2, 73.2, 73.0, 72.8, 72.1, 72.0, 71.9, 70.6, 68.7, 68.6, 68.2, 62.8, 38.7, 30.4, 29.7, 28.9, 26.5, 23.8, 23.0, 22.7, 20.9, 20.8, 20.6, 20.4. IR (film, cm^{-1}): ν = 3088, 3066, 3033, 2928, 2854, 1752, 1497, 1455, 1367, 1315, 1238, 1224, 1163, 1038. HRMS (ESI): calc. for $C_{83}H_{87}NO_{19}F_3$ (M+H) 1458.5824; found: 1458.5841.

2-Deoxy-2-Acetylamino-α-D-Galactopyranosyl-L-Threonine 197.[214] An oven dried 100 mL round bottom flask was charged with **215** (1.18 g, 1.67 mmol, 1 equiv), sodium hydroxide (0.2 M in methanol) (33.4 mL, 6.680 mmol, 4.00 equiv), and triethylamine (1.16 mL, 8.350 mmol, 5.00 equiv). The resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated to a yellow oil. The yellow oil was washed with dichloromethane (3 x 5 mL). The residue was redissolved in water and brought to neutral pH using Amberlyst 15 hydrogen form. The aqueous solution was decanted and lyophilized to a white solid **197** (0.51 g, 99%). ^{1}H NMR

($CDCl_3$, 300 MHz): δ = 4.85 (d, *J* = 3.9 Hz, 1H), 4.32 (dd, *J* = 6.9, 2.1 Hz, 1H), 4.02 (dd, *J* = 7.5, 3.6 Hz, 1H), 3.94 (t, *J* = 6.3 Hz, 1H), 3.87 (d, *J* = 2.7 Hz, 1H), 3.76 (dd, *J* = 8.1, 3.0 Hz, 1H), 3.66 – 3.61 (m, 3H) 1.95 (s, 3H), 1.30 (d, *J* = 6.6 Hz, 1H).

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-Acetylamino-α-D-Galactopyranosyl-*N*-Fmoc-L-Threonine 202. A 250 mL oven-dried round bottom flask was charged with glycosyl amino acid **215** (1.12 g, 1.576 mmol, 1 equiv) and anhydrous tetrahydrofuran (44 mL). The solution was cooled to 0 °C, *N*-methylaniline (838.8 µL, 7.75 mmol, 4.92 equiv) and tetrakis(triphenylphosphine)palladium (179 mg, 0.155 mmol, 0.098 equiv) were then added. The resulting mixture was stirred at room temperature while being monitored by TLC. After 1 h, the reaction mixture was concentrated to a dark oil and purified by silica gel flash chromatography (9/1, dichloromethane/methanol) to provide pure **202** (1.02 g, 97%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.78 – 7.31 (m, 10H), 5.40 (s, 1H), 5.31 – 5.26 (m, 1H), 5.15 (d, *J* = 7.5 Hz, 1H), 5.02 (d, *J* = 27 Hz, 1H), 4.59 – 4.42 (m, 4H), 4.29 – 4.25 (m, 3H), 4.20 (d, *J* = 5.0 Hz, 1H), 4.14 – 4.09 (m, 3H), 2.18 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.29 (d, *J* = 13 Hz, 3H). *The ^{1}H NMR spectrum of* **202** *matches the result obtained by Sigma-Aldrich website*.

***N*-Fmoc-L-Threonine Allyl Ester 206.**[215] A 100 mL oven-dried Schlenk flask was charged with Fmoc-Thr-OH (3 g, 8.788 mmol, 1.0 equiv), allyl bromide (1.50 mL, 17.577 mmol, 2.00 equiv), DIPEA (3.10 mL, 17.577 mmol, 2.00 equiv), and anhydrous DMF (35 mL). The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with brine (4 x 40

mL). The organic layer was dried with anhydrous sodium sulfate and concentrated to a white solid. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate = 2/1) to afford **206** as a white solid (2.70 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.79 – 7.30 (m, 8H), 5.99 – 5.86 (m, 2H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.26 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 5.7 Hz, 2H), 4.46 – 4.40 (m, 4H), 4.28 – 4.24 (m, 1H), 2.74 (bs, 1H), 1.28 (d, *J* = 6.3 Hz, 3H).

Large Scale Glycosylation Procedure Using Ni(4-F-PhCN)$_4$(OTf)$_2$ as the Catalyst: 3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Galactopyranosyl-*N*-Fmoc-L-Threonine Allyl Ester 208 (Scheme 4.6a and b). A 100 mL oven-dried Schlenk flask was charged with Ni(4-F-PhCN)$_4$Cl$_2$ (78.6 mg, 0.128 mmol, 10 mol%) and AgOTf (65.8 mg, 0.256 mmol, 20 mol%) in dichloromethane (4 mL). The resulting mixture was stirred at room temperature for 30 min. A solution of D-galactosamine *N*-phenyl trifluoroacetimidate donor **156** (808 mg, 1.278 mmol, 1.0 equiv), threonine acceptor **206** (585 mg, 1.534 mmol, 1.20 equiv), and CH_2Cl_2 (4.5 mL) was added. The resulting mixture was stirred under argon at 35 ^{o}C overnight. The reaction mixture was filtered through Celite and then purified by silica gel flash chromatography (3/1, hexanes/ethyl acetate + 1% triethylamine) to give the desired glycosyl amino acid **208** (783 mg, 74%, α only). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.68 (d, *J* = 2.1 Hz, 1H), 8.39 (d, *J* = 2.4 Hz, 1H), 7.79 – 7.60 (m, 9H), 7.49 – 7.30 (m, 10H), 6.21 (d, *J* = 9.0 Hz, 1H), 6.10 (s, 1H), 5.80 – 5.68 (m, 1H), 5.53 – 5.47 (m, 2H), 5.21 – 5.13 (m, 2H), 5.03 (d, *J* = 3.3 Hz, 1H), 4.53 – 4.40 (m, 6H), 4.34 – 4.24 (m, 2H), 4.19 (d, *J* = 6.6 Hz, 2H), 3.86 (dd, *J* = 10.5, 3.9 Hz, 1H), 2.21 (s, 3H), 2.10 (s, 3H), 1.91 (s, 3H), 1.44 (d, *J* = 6.3 Hz,

3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.4, 170.2, 170.2, 161.9, 156.8, 143.9, 143.8, 141.2, 132.2, 131.2, 130.7, 129.1, 128.7, 127.7, 127.1, 127.1, 125.3 (q, J_{C-F} = 5.4 Hz), 121.0, 119.9, 119.0, 100.0, 77.2, 75.3, 68.2, 68.0, 67.6, 67.2, 67.0, 66.0, 62.1, 58.8, 47.2, 20.8, 20.7, 20.4, 19.3. IR (film, cm^{-1}): ν = 3154, 2982, 2892, 1746, 1471, 1378, 1315, 1245, 1173, 1095, 911. HRMS (ESI): calc. for $C_{42}H_{44}N_2O_{12}F_3$ (M+H): 825.2846; found: 825.2850.

Large Scale Glycosylation Procedure Using Ni(4-F-PhCN)$_4$(OTf)$_2$ as the Catalyst: 3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Galactopyranosyl-*N*-Fmoc-L-Threonine Allyl Ester 208 (Scheme 4.6c). A 100 mL oven-dried Schlenk flask was charged with Ni(4-F-PhCN)$_4$Cl$_2$ (434.7 mg, 0.71 mmol, 10 mol%) and AgOTf (363.8 mg, 1.42 mmol, 20 mol%) in dichloromethane (23 mL). The resulting mixture was stirred at room temperature for 30 min. A solution of D-galactosamine *N*-phenyl trifluoroacetimidate donor **156** (5.73 g, 9.059 mmol, 1.28 equiv), threonine acceptor **206** (2.7 g, 7.078 mmol, 1.0 equiv), and CH_2Cl_2 (24 mL) was added. The resulting mixture was stirred under argon at 35 °C overnight. The reaction mixture was filtered through Celite and then purified by silica gel flash chromatography (3/1, hexanes/ethyl acetate + 1% triethylamine) to give the desired glycosyl amino acid **208** (3.77 g, 66%, α only).

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Galactopyranosyl-*N*-Fmoc-L-Threonine Benzyl Ester 210. A 10 mL oven-dried Schlenk flask was charged with D-galactosamine *N*-phenyl trifluoroacetimidate donor

156 (58.8 mg, 0.093 mmol, 1.0 equiv), *N*-Fmoc-L-Threonine Benzyl Ester **31** (48.1 mg, 0.112 mmol, 1.2 equiv), and CH_2Cl_2 (0.5 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated in situ from Ni(4-F-PhCN)$_4$Cl$_2$ (5.7 mg, 0.0093 mmol, 10 mol%) and AgOTf (4.8 mg, 0.0186 mmol, 20 mol%) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 35 ^oC overnight, and purified by silica gel flash chromatography (3/1, hexanes/ethyl acetate + 1% triethylamine) to give the desired glycoside **210** (70 mg, 86%, α:β = 14:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.60 (s, 1 H), 8.37-8.26 (m, 2 H), 7.82-7.18 (m, 15 H), 6.30 (d, *J* = 8.8 Hz, 1 H), 5.51-5.42 (m, 2 H), 5.00 (d, *J* = 12.0 Hz, 1 H), 4.91 (d, *J* = 12. Hz, 1 H), 4.87 (d, *J* = 2.4 Hz, 1 H), 4.55-4.37 (m, 4 H), 4.30 (t, *J* = 7.2 Hz, 1 H), 4.22 (d, *J* = 7.2 Hz, 1 H), 4.15 (d, *J* = 6.4 Hz, 2 H), 3.74 (dd, *J* = 3.2, 10.4 Hz, 1 H), 2.20 (s, 3 H), 2.06 (s, 3 H), 1.89 (s, 3 H), 1.40 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.5, 170.3, 170.2 170.0, 161.9, 156.9, 155.0, 143.81, 143.75, 141.2, 135.3, 130.7, 129.3, 128.5, 128.4, 128.3, 127.67, 127.66, 127.1, 126.2, 125.24, 125.19, 120.6, 119.9, 99.9, 75.3, 68.1, 67.9, 67.6, 67.2, 67.1, 66.9, 62.1, 58.8, 47.1, 20.7, 20.6, 20.3, 19.2. IR (film, cm^{-1}): ν = 3323, 1747, 1641, 1314. HRMS (ESI): calc. for $C_{46}H_{46}F_3N_2O_{12}$ (M+H): 875.3003; found: 875.3026.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Galactopyranosyl-*N*-Fmoc-L-Threonine Propargyl Ester 211. A 10 mL oven-dried Schlenk flask was charged with D-galactosamine *N*-phenyl trifluoroacetimidate donor **156** (51.2 mg, 0.081 mmol, 1.0 equiv), *N*-Fmoc-L-Threonine Propargyl Ester **209** (36.9 mg, 0.097 mmol, 1.2 equiv), and CH_2Cl_2 (0.5 mL). A preformed solution of Ni(4-F-

PhCN)$_4$(OTf)$_2$, which was generated in situ from Ni(4-F-PhCN)$_4$Cl$_2$ (5.0 mg, 0.0081 mmol, 10 mol%) and AgOTf (4.2 mg, 0.0162 mmol, 20 mol%) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 35 ^{o}C overnight, and purified by silica gel flash chromatography (3/1, hexanes/ethyl acetate + 1% triethylamine) to give the desired glycoside **211** (52 mg, 78%, α only). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.67 (s, 1 H), 8.36 (d, *J* = 7.6 Hz, 1 H), 7.82-7.27 (m, 11 H), 6.37 (d, *J* = 8.8 Hz, 1 H), 5.5-5.44 (m, 2 H), 5.07 (d, *J* = 2.4 Hz, 1 H), 4.58-4.40 (m, 6 H), 4.328-4.25 (m, 2 H), 4.19 (d, *J* = 6.4 Hz, 2 H), 3.85 (dd, *J* = 3.6, 10.4 Hz, 1 H), 2.40 (s, 1 H), 2.21 (s, 3 H), 2.09 (s, 3 H), 1.90 (s, 3 H), 1.45 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 170.4, 170.1, 169.9, 169.7, 162.1, 156.8, 143.8, 143.7, 141.1, 133.1, 132.2, 130.7, 129.0, 127.63, 127.61, 127.0, 125.5 (q, $J_{C\text{-}F}$ = 5.4 Hz), 125.22, 125.18, 119.9, 100.0, 75.5, 75.4, 68.0, 67.5, 67.1, 66.9, 62.1, 58.7, 52.6, 47.0, 20.73, 20.65, 20.3, 19.1. IR (film, cm^{-1}): ν = 3328, 1738, 1643, 1316. HRMS (ESI): calc. for $C_{42}H_{42}F_3N_2O_{12}$ (M+H): 823.2690; found: 823.2705.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Galactopyranosyl-*N*-Cbz-L-Threonine Benzyl Ester 212. A 10 mL oven-dried Schlenk flask was charged with D-galactosamine *N*-phenyl trifluoroacetimidate donor **156** (93.0 mg, 0.147 mmol, 1.0 equiv), Z-Thr-OBzl **73** (60.6 mg, 0.176 mmol, 1.2 equiv), and CH_2Cl_2 (0.5 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated in situ from Ni(4-F-PhCN)$_4$Cl$_2$ (9.0 mg, 0.0147 mmol, 10 mol%) and AgOTf (7.6 mg, 0.0294 mmol, 20 mol%) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 35 ^{o}C overnight, and purified

by silica gel flash chromatography (3/1, hexanes/ethyl acetate + 1% triethylamine) to give the desired glycoside **212** (76.0 mg, 67%, α only). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.56 (s, 1H), 8.25 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.15 (m, 10H), 6.09 (d, *J* = 9.0 Hz, 1H), 5.47 (d, *J* = 2.0 Hz, 1H), 5.38 (dd, *J* = 10.5, 3.0 Hz, 1H), 5.21 – 5.13 (m, 2H), 5.01 – 4.89 (m, 2H), 4.83 (d, *J* = 4.0 Hz, 1H), 4.51 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.40 (d, *J* = 7.0 Hz, 2H), 4.15 (d, *J* = 7.0 Hz, 2H), 3.70 (dd, *J* = 15.0, 3.5 Hz, 1H), 2.20 (s, 3H), 2.07 (s, 3H), 1.87 (s, 3H), 1.39 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.4, 170.1, 169.9, 161.7, 156.9, 136.3, 135.0, 133.1, 132.2, 130.6, 129.0, 129.0, 128.7, 128.5, 128.3, 128.2, 128.1, 125.5, 125.3 (q, $J_{C\text{-}F}$ = 5.4 Hz), 122.8, 99.6, 74.9, 68.1, 67.7, 67.2, 67.1, 66.9, 62.1, 58.7, 53.4, 20.7, 20.7, 20.3, 19.4. IR (film, cm^{-1}): ν = 3432, 3342, 3064, 3031, 2925, 2251, 1728, 1638, 1495, 1376, 1315, 1229, 1166, 1066, 1017. HRMS (ESI): calc. for $C_{39}H_{42}N_2O_{12}F_3$ (M+H): 787.2690; found: 787.2709.

6-*O*-Acetyl-3,4-Di-*O*-Benzyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Galactopyranosyl-*N*-Fmoc-L-Threonine Allyl Ester 213. A 10 mL oven-dried Schlenk flask was charged with D-galactosamine *N*-phenyl trifluoroacetimidate donor **157** (22.3 mg, 0.031 mmol, 1.0 equiv), *N*-Fmoc-L-Threonine Allyl Ester **206** (14.0 mg, 0.037 mmol, 1.2 equiv), and CH_2Cl_2 (0.5 mL). A preformed solution of $Ni(4\text{-F-PhCN})_4(OTf)_2$, which was generated in situ from $Ni(4\text{-F-PhCN})_4Cl_2$ (1.9 mg, 0.0031 mmol, 10 mol%) and AgOTf (1.6 mg, 0.0061 mmol, 20 mol%) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 35 °C overnight, and purified by silica gel flash chromatography (4/1, hexanes/ethyl acetate + 1% triethylamine) to give the desired glycoside **213** (22 mg, 78%, α only). (62%, α only) ^{1}H

NMR ($CDCl_3$, 400 MHz): δ = 8.78 (s, 1 H), 8.41 (d, *J* = 6.8 Hz, 1 H), 7.82-7.22 (m, 21 H), 6.38 (d, *J* = 8.8 Hz, 1 H), 5.76-5.66 (m, 1 H), 5.18-5.07 (m, 2 H), 4.99 (d, *J* = 11.6 Hz, 1 H), 4.93 (d, *J* = 3.2 Hz, 1 H), 4.69-4.55 (m, 3 H), 4.38-4.02 (m, 14 H), 3.96 (s, 1 H), 2.04 (s, 3 H), 1.39 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.6, 170.1, 161.3, 156.8, 143.8, 141.2, 138.1, 138.0, 132.0, 131.2, 130.4, 128.7, 128.40, 128.37, 128.2, 127.8, 127.7, 126, 127.4, 127.0, 125.5 (q, $J_{C\text{-}F}$ = 5.4 Hz), 125.2, 119.9, 118.9, 100.6, 75.1, 74.6, 73.2, 72.4, 70.8, 69.4, 67.3, 65.9, 63.9, 58.9, 47.2, 20.8, 19.2. IR (film, cm^{-1}): ν = 3341, 1727, 1313. HRMS (ESI): calc. for $C_{52}H_{52}F_3N_2O_{10}$ (M+H): 921.3574; found: 921.3590.

6-*O*-Acetyl-3,4-Di-*O*-Benzyl-2-Deoxy-2-*o*-Trifluoromethylbenzylideneamino-α-D-Galactopyranosyl-*N*-Fmoc-L-Threonine Benzyl Ester 214. A 10 mL oven-dried Schlenk flask was charged with D-galactosamine *N*-phenyl trifluoroacetimidate donor **157** (21.8 mg, 0.030 mmol, 1.0 equiv), *N*-Fmoc-L-Threonine Benzyl Ester **31** (15.4 mg, 0.036 mmol, 1.2 equiv), and CH_2Cl_2 (0.5 mL). A preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated in situ from Ni(4-F-PhCN)$_4Cl_2$ (1.8 mg, 0.0030 mmol, 10 mol%) and AgOTf (1.5 mg, 0.0060 mmol, 20 mol%) in dichloromethane (0.5 mL) was then added to the solution. The resulting mixture was stirred under argon at 35 ^oC overnight, and purified by silica gel flash chromatography (4/1, hexanes/ethyl acetate + 1% triethylamine) to give the desired glycoside **214** (20 mg, 69% α only). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.76 (d, *J* = 1.6 Hz, 1 H), 8.42 (d, *J* = 6.4 Hz, 1 H), 7.83-7.17 (m, 26 H), 6.39 (d, *J* = 7.2 Hz, 1 H), 5.05-4.85 (m, 4 H), 4.62-3.92 (m, 14 H), 2.04 (s, 3 H), 1.37 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.6, 170.2, 161.3, 156.8,

143.84, 143.77, 141.2, 138.1, 138.0, 134.9, 133.5, 131.9, 130.4, 128.8, 128.7, 128.6, 128.5, 128.40, 128.37, 128.24, 128.19, 127.8, 127.7, 127.6, 127.5, 127.4, 127.0, 125.5 (q, $J_{C\text{-}F}$ = 5.4 Hz), 119.9, 100.7, 75.2, 74.6, 73.1, 72.4, 70.6, 69.4, 67.3, 67.1, 65.9, 63.9, 59.0, 47.2, 20.8, 19.1. IR (film, cm^{-1}): ν = 3342, 1727, 1313. HRMS (ESI): calc. for $C_{56}H_{54}F_3N_2O_{10}$ (M+H): 971.3731; found: 971.3756.

3,4,6-Tri-*O*-Acetyl-2-Deoxy-2-Acetylamino-α-D-Galactopyranosyl-*N*-Fmoc-L-Threonine Allyl Ester 215. An oven dried 250 mL round bottom flask was charged with **208** (3.77 g, 4.57 mmol, 1 equiv), anhydrous methanol (57 mL), and acetyl chloride (520 µL, 7.32 mmol, 1.6 equiv). The resulting mixture was stirred at room temperature overnight. Pyridine (40 mL) was added, and the reaction mixture was concentrated to a yellow oil. The yellow oil was then placed under high vacuum for 2 h to remove trace methanol. The yellow oil was dissolved in anhydrous pyridine (46 mL). Acetic anhydride (3.5 mL, 36.56 mmol, 8.0 equiv) was added to the solution. The reaction mixture was stirred at room temperature overnight and then concentrated to afford crude **215**. The resulting residue was purified by silica gel flash chromatography (1/1 hexane/ethyl acetate → 1/2 hexane/ethyl acetate) to provide pure **215** (2.25 g, 70%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.79 (d, *J* = 7.2 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.44 – 7.33 (m, 4H), 5.94 – 5.84 (m, 1H), 5.77 (d, *J* = 10.4 Hz, 1H), 5.58 (d, *J* = 9.6 Hz, 1H), 5.41 – 5.30 (m, 4H), 5.10 (dd, *J* = 11.6, 3.2 Hz, 1H), 4.90 (d, *J* = 3.2 Hz, 1H), 4.69 (dd, *J* = 13.2, 7.2 Hz, 1H), 4.62 – 4.56 (m, 3H), 4.46 (dd, *J* = 7.6, 4.0 Hz, 2H), 4.31 – 4.22 (m, 3H), 4.16 – 4.07 (m, 3H), 2.18 (s, 3H), 2.06 (s, 3H), 2.02 (s, 6H), 1.35 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.9, 170.6, 170.3, 170.3, 156.5, 143.8, 143.6,

141.3, 130.8, 127.8, 127.1, 125.1, 125.1, 120.1, 120.0, 100.1, 68.4, 67.5, 67.3, 66.4, 62.1, 58.5, 53.4, 47.5, 47.1, 29.7, 23.2, 20.7, 20.6, 18.2. IR (film, cm^{-1}): ν = 3432, 3145, 2933, 2843, 2251, 1744, 1670, 1499, 1372, 1229, 1037. HRMS (ESI): calc. for $C_{36}H_{43}N_2O_{13}$ (M+H): 711.2765; found: 711.2771

Compound 219. An oven dried 250 mL round bottom flask was charged with **217**[199] (2.45 g, 14.85 mmol, 1 equiv.), anhydrous tetrahydrofuran (42 mL), triphenylphosphine (5.8 g, 22.27 mmol, 1.5 equiv), compound **218**[216] (4.26 g, 19.30 mmol, 1.3 equiv.) under nitrogen. The resulting mixture was stirred at 0 °C. After 1 h, DEAD (40% in toluene, 9.7 mL, 22.27 mmol, 1.5 equiv.) was added portionwise. The mixture was slowly brought to room temperature and stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified by silica gel flash chromatography (3/1 hexane/ethyl acetate $\rightarrow$ 1/1 hexane/ethyl acetate) to provide pure 219 (5.4 g, 98%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.51 (s, 1H), 5.26 (s, 1H), 3.75 – 3.60 (m, 3H), 3.50 (t, *J* = 5.2 Hz, 1H), 2.85 (s, 1H), 0.88 (s, 4H), 0.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.1, 137.5, 81.8, 78.6, 78.3, 78.0, 73.1, 68.1, 64.9, 63.7, 63.2, 48.4, 39.2, 26.9, 19.3, 15.4, 15.1, -4.4. HRMS (ESI): calc. for $C_{18}H_{30}NO_5Si$ (M+H): 368.1893; found: 368.1891.

Compound 220. A 100 mL oven-dried round bottom flask was charged with compound **219** (1.57 g, 4.30 mmol, 1 equiv.) and anhydrous tetrahydrofuran (20 mL) under nitrogen. The mixture was cooled to 0 °C, a solution of TBAF in tetrahydrofuran (1M, 8.5 mL, 8.50 mmol, 2 equiv.) was added. The resulting mixture was stirred at 0 °C for 45 min and

then concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (ethyl acetate → 10/1 dichloromethane/methanol) to provide pure **7** (883 mg, 82%) as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.53 (s, 2H), 5.31 (s, 2H), 3.74 (t, *J* = 5.3 Hz, 2H), 3.71 – 3.62 (m, 5H), 3.60 – 3.51 (m, 2H), 2.89 (s, 2H), 2.56 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 176.3, 136.5, 81.0, 72.3, 67.1, 61.6, 47.4, 38.6. IR (film, cm^{-1}): ν = 3480, 3090, 3007, 2947, 2874, 1773, 1694, 1429, 1400, 1336, 1130, 1066, 1021. HRMS (ESI): calc. for $C_{12}H_{15}NO_5Na$ (M+Na): 276.0848; found: 276.0852.

Monoantennary Monomer 222. A 10 mL oven-dried Schlenk flask was charged with D-mannose trichoroacetimidate donor **221** (278 mg, 0.38 mmol, 1 equiv.), acceptor **220** (142 mg, 0.56 mmol, 1.5 equiv.), activated 3Å molecular sieves and CH_2Cl_2 (13.7 mL). The resulting mixture was stirred under argon at room temperature for 30 min and then cooled to 0 °C. TMSOTf (13.7 μL, 0.08 mmol, 0.2 equiv.) was added to the slurry solution, and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with triethylamine and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography (1/1 hexanes/ethyl acetate) to afford α-mannose monoantennary monomer **222** (267 mg, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.13 (d, *J* = 7.1 Hz, 2H), 8.06 (d, *J* = 7.1 Hz, 2H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.84 (d, *J* = 7.1 Hz, 2H), 7.63 – 7.56 (m, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.47 – 7.36 (m, 8H), 7.32 – 7.25 (m, 2H), 6.43 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.39 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.14 (t, *J* = 9.8 Hz, 1H), 5.93 (dd, *J* = 10.1, 3.3 Hz, 1H), 5.73 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.23 (d, *J* = 1.5 Hz, 2H), 5.14 (d, *J* = 1.7 Hz, 1H), 4.79 – 4.69 (m, 1H), 4.51 (d, *J* = 10.0 Hz, 2H), 3.98 – 3.89 (m, 2H), 3.83 – 3.66 (m, 9H), 2.97 – 2.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ =

176.2, 166.2, 165.5, 165.4, 136.5, 136.4, 133.4, 133.1, 133.0, 130.0, 129.9, 129.8, 129.7, 129.5, 129.2, 129.1, 128.6, 128.5, 128.4, 128.3, 97.7, 81.0, 70.4, 70.2, 69.6, 68.8, 67.4, 67.2, 67.0, 62.9, 47.5, 38.2. IR (film, cm^{-1}): ν = 3068, 2944, 1744, 1723, 1700, 1602, 1451, 1398, 1057, 1024. HRMS (ESI): calc. for $C_{46}H_{41}NO_{14}K$ (M+K): 870.2164; found: 870.2192.

Glycopolymer 224. An oven dried 10 mL Schlenk flask was charged with **222** (50 mg, 0.06 mmol, 1.0 equiv.) and anhydrous degassed dichloroethane. Catalyst **223**, bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (2.5 mg, 0.003 mmol, 0.05 equiv.) was then added to the solution. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated *in vacuo* to a brown oil. The crude product was dissolved in a minimal amount of ethyl acetate and precipitated with an excess of petroleum ether. The solid was filtered and then re-dissolved in ethyl acetate. This process was repeated 2 more times to yield the protected glycopolymer **224P** as a white solid (41.5 mg, 83%) The protected glycopolymers were then injected onto a Waters Styragel HR 4 size exclusion column with THF as the eluent. Absolute polymer molecular weight and polydispersity measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.09 (d, *J* = 7.5 Hz, 2H), 8.02 (d, *J* = 5.4 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.55 – 7.23 (m, 12H), 6.14 (t, *J* = 9.6 Hz, 1H), 6.04 (bs, 1H), 5.91 (d, *J* = 18.9 Hz, 1H), 5.72 (bs, 1H), 5.12 (bs, 2H), 4.70 (d, *J* = 10.8 Hz, 1H), 4.47 (d, *J* = 9.0 Hz, 2H), 4.36 (bs, 1H), 3.90 (bs, 1H), 3.69 (bs, 6H), 3.28 (bs, 2H), 1.79 (bs, 2H). An oven dried 10 mL Schlenk flask was charged with the

protected glycopolymer of **224P** (40 mg, 0.00158 mmol, 1.0 equiv.), anhydrous dichloromethane (2 mL), anhydrous methanol (2 mL), and sodium methoxide (5 mg, 0.0926 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured off and the oily residue was washed with methanol (3 x 1 mL) and dichloromethane (3 x 1 mL). The resulting residue was dissolved in water (5 mL) and brought to neutral pH with Amberlyst 15. The aqueous solution was filtered and lyophilized to a yield the deprotected polymer **224** as a white solid (13.4 mg, 67%). The deprotected polymers were dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water before ITC experiments were performed. ^{1}H NMR (D_2O, 500 MHz): δ = 5.98 – 5.80 (m, 2H), 4.76 (bs, 1H), 3.84 (bs, 1H), 3.76 – 3.51 (m, 18H).

Glycopolymer 225. An oven dried 10 mL Schlenk flask was charged with **222** (50 mg, 0.06 mmol, 1.0 equiv.) and anhydrous degassed dichloroethane. Catalyst **223**, bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (1.5 mg, 0.0018 mmol, 0.03 equiv.) was then added to the solution. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated *in vacuo* to a brown oil. The crude product was dissolved in a minimal amount of ethyl acetate and precipitated with an excess of petroleum ether. The solid was filtered and then re-dissolved in ethyl acetate. This process was repeated 2 more times to yield the protected glycopolymer **225P** as a white solid (41.5 mg, 83%) The protected glycopolymers were then injected onto a Waters Styragel HR 4 size exclusion column with THF as the eluent. Absolute polymer molecular weight and polydispersity measurements were determined using a Wyatt Dawn Heleos-II light scattering detector.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.09 (d, *J* = 7.5 Hz, 2H), 8.02 (d, *J* = 5.4 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.55 – 7.23 (m, 12H), 6.14 (t, *J* = 9.6 Hz, 1H), 6.04 (bs, 1H), 5.91 (d, *J* = 18.9 Hz, 1H), 5.72 (bs, 1H), 5.12 (bs, 2H), 4.70 (d, *J* = 10.8 Hz, 1H), 4.47 (d, *J* = 9.0 Hz, 2H), 4.36 (bs, 1H), 3.90 (bs, 1H), 3.69 (bs, 6H), 3.28 (bs, 2H), 1.79 (bs, 2H). An oven dried 10 mL Schlenk flask was charged with the protected glycopolymer of **225P** (40 mg), anhydrous dichloromethane (2 mL), anhydrous methanol (2 mL), and sodium methoxide (5 mg, 0.0926 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured off and the oily residue was washed with methanol (3 x 1 mL) and dichloromethane (3 x 1 mL). The resulting residue was dissolved in water (5 mL) and brought to neutral pH with Amberlyst 15. The aqueous solution was filtered and lyophilized to a yield the deprotected polymer **225** as a white solid (13.0 mg, 65%). The deprotected polymers were dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water before ITC experiments were performed. ^{1}H NMR (D_2O, 500 MHz): δ = 5.98 – 5.80 (m, 2H), 4.76 (bs, 1H), 3.84 (bs, 1H), 3.76 – 3.51 (m, 18H).

Glycopolymer 226. An oven dried 10 mL Schlenk flask was charged with **222** (50 mg, 0.06 mmol, 1.0 equiv.) and anhydrous degassed dichloroethane. Catalyst **223**, bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (0.99 mg, 0.0012 mmol, 0.02 equiv.) was then added to the solution. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated *in vacuo* to a brown oil. The crude product was dissolved in a minimal amount of ethyl acetate and precipitated with an excess of petroleum ether. The

solid was filtered and then re-dissolved in ethyl acetate. This process was repeated 2 more times to yield the protected glycopolymer **226P** as a white solid (39.5 mg, 79%) The protected glycopolymers were then injected onto a Waters Styragel HR 4 size exclusion column with THF as the eluent. Absolute polymer molecular weight and polydispersity measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.09 (d, *J* = 7.5 Hz, 2H), 8.02 (d, *J* = 5.4 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.55 – 7.23 (m, 12H), 6.14 (t, *J* = 9.6 Hz, 1H), 6.04 (bs, 1H), 5.91 (d, *J* = 18.9 Hz, 1H), 5.72 (bs, 1H), 5.12 (bs, 2H), 4.70 (d, *J* = 10.8 Hz, 1H), 4.47 (d, *J* = 9.0 Hz, 2H), 4.36 (bs, 1H), 3.90 (bs, 1H), 3.69 (bs, 6H), 3.28 (bs, 2H), 1.79 (bs, 2H). An oven dried 10 mL Schlenk flask was charged with the protected glycopolymer of **226P** (20 mg), anhydrous dichloromethane (2 mL), anhydrous methanol (2 mL), and sodium methoxide (5 mg, 0.0926 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured off and the oily residue was washed with methanol (3 x 1 mL) and dichloromethane (3 x 1 mL). The resulting residue was dissolved in water (5 mL) and brought to neutral pH with Amberlyst 15. The aqueous solution was filtered and lyophilized to a yield the deprotected polymer **226** as a white solid (4.0 mg, 40%). The deprotected polymers were dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water before ITC experiments were performed. ^{1}H NMR (D_2O, 500 MHz): δ = 5.98 – 5.80 (m, 2H), 4.76 (bs, 1H), 3.84 (bs, 1H), 3.76 – 3.51 (m, 18H).

Glycopolymer 227. An oven dried 10 mL Schlenk flask was charged with **222** (50 mg, 0.06 mmol, 1.0 equiv.) and anhydrous degassed dichloroethane. Catalyst **223**,

bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (0.49 mg, 0.0006 mmol, 0.01 equiv.) was then added to the solution. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated *in vacuo* to a brown oil. The crude product was dissolved in a minimal amount of ethyl acetate and precipitated with an excess of petroleum ether. The solid was filtered and then re-dissolved in ethyl acetate. This process was repeated 2 more times to yield the protected glycopolymer **227P** as a white solid (39.0 mg, 79%) The protected glycopolymers were then injected onto a Waters Styragel HR 4 size exclusion column with THF as the eluent. Absolute polymer molecular weight and polydispersity measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.09 (d, J = 7.5 Hz, 2H), 8.02 (d, J = 5.4 Hz, 2H), 7.95 (d, J = 7.2 Hz, 2H), 7.82 (d, J = 7.2 Hz, 2H), 7.55 – 7.23 (m, 12H), 6.14 (t, J = 9.6 Hz, 1H), 6.04 (bs, 1H), 5.91 (d, J = 18.9 Hz, 1H), 5.72 (bs, 1H), 5.12 (bs, 2H), 4.70 (d, J = 10.8 Hz, 1H), 4.47 (d, J = 9.0 Hz, 2H), 4.36 (bs, 1H), 3.90 (bs, 1H), 3.69 (bs, 6H), 3.28 (bs, 2H), 1.79 (bs, 2H). An oven dried 10 mL Schlenk flask was charged with the protected glycopolymer of **227P** (20 mg), anhydrous dichloromethane (2 mL), anhydrous methanol (2 mL), and sodium methoxide (5 mg, 0.0926 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured off and the oily residue was washed with methanol (3 x 1 mL) and dichloromethane (3 x 1 mL). The resulting residue was dissolved in water (5 mL) and brought to neutral pH with Amberlyst 15. The aqueous solution was filtered and lyophilized to a yield the deprotected polymer **227** as a white solid (6.2 mg, 62%). The deprotected polymers were dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water before ITC

experiments were performed. ^{1}H NMR (D_2O, 500 MHz): δ = 5.98 – 5.80 (m, 2H), 4.76 (bs, 1H), 3.84 (bs, 1H), 3.76 – 3.51 (m, 18H).

Azide-Linked Mannoside 229. A 10 mL oven-dried Schlenk flask was charged with D-mannose trichoroacetimidate **221** (300 mg, 0.41 mmol, 1 equiv.), acceptor **228** (106 mg, 0.81 mmol, 2 equiv.), and CH_2Cl_2 (4 mL). $Pd(CH_3CN)_4(BF_4)_2$ (9 mg, 0.04 mmol, 10 mol %) was then added to the solution. The resulting mixture was stirred under argon at 25 °C without light for 3 h, concentrated *in vacuo*, and then purified by silica gel flash chromatography (2/1, hexane/ethyl acetate) to give the desired mannoside **229** (211 mg, 74%) as white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.11 (dd, *J* = 18.5, 7.1 Hz, 4H), 8.04 – 7.94 (m, 2H), 7.87 (d, *J* = 7.2 Hz, 2H), 7.68 – 7.54 (m, 3H), 7.54 – 7.22 (m, 12H), 6.18 (t, *J* = 9.9 Hz, 1H), 5.99 (dd, *J* = 10.1, 3.3 Hz, 1H), 5.78 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.19 (d, *J* = 1.6 Hz, 1H), 4.82 – 4.70 (m, 1H), 4.64 – 4.46 (m, 2H), 4.11 – 3.95 (m, 1H), 3.90 – 3.70 (m, 5H), 3.54 – 3.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.2, 166.6, 166.5, 134.5, 134.5, 134.2, 134.1, 131.0, 130.9, 130.8, 130.4, 130.2, 130.1, 129.6, 129.5, 129.4, 98.9, 71.5, 71.4, 71.2, 69.9, 68.7, 68.0, 63.9, 51.9. IR (film, cm^{-1}): ν = 3065, 2925, 2106, 1722, 1602, 1451, 1259, 1092, 1067, 1026. HRMS (ESI): calc. for $C_{38}H_{35}N_3O_{11}Na$ (M+Na): 732.2169; found: 732.2167.

Amine-linked mannoside 230. A 50 mL round bottom flask was charged with azide-linked mannoside **229** (270 mg, 0.38 mmol, 1 equiv.), tetrahydrofuran (15 mL) and water (1.5 mL). Triphenylphosphine (150 mg, 0.57 mmol, 1.5 equiv.) was then added to the solution. The resulting mixture was stirred overnight at 55 °C. The reaction mixture was

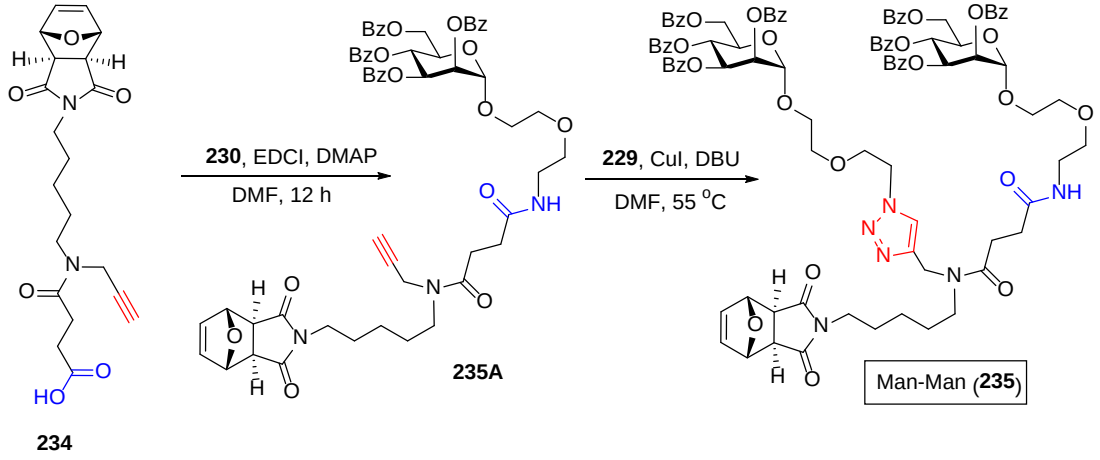
concentrated *in vacuo* and co-evaporated with toluene twice to remove water. The residue was purified by silica gel flash chromatography (ethyl acetate → 9/1 dichloromethane/methanol) to afford amine-linked mannoside **230** (158 mg, 61%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.12 (d, *J* = 7.6 Hz, 2H), 8.07 (d, *J* = 7.6 Hz, 2H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.59 (q, *J* = 7.1 Hz, 3H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.47 – 7.32 (m, 7H), 7.27 (t, *J* = 7.3 Hz, 2H), 6.16 (t, *J* = 9.9 Hz, 1H), 5.96 (dd, *J* = 10.1, 2.9 Hz, 1H), 5.75 (s, 1H), 5.21 (s, 1H), 4.75 (d, *J* = 10.1 Hz, 1H), 4.52 (m, 2H), 3.99 (d, *J* = 10.5 Hz, 2H), 3.79 (dd, *J* = 47.0, 19.5 Hz, 6H), 3.11 (bs, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 166.2, 165.5, 133.5, 133.2, 133.1, 129.9, 129.8, 129.7, 129.3, 129.1, 129.0, 128.6, 128.5, 128.3, 97.8, 70.5, 70.1, 70.0, 68.9, 67.5, 66.9, 62.9, 53.5. IR (film, cm^{-1}): ν = 2925, 2877, 1723, 1602, 1451, 1260, 1177, 1094, 1066, 1026. HRMS (ESI): calc. for $C_{38}H_{38}NO_{11}$ (M+H): 684.2445; found: 684.2457.

Azide-linked glucoside 232.[217] A 25 mL oven-dried Schlenk flask was charged with D-glucose trichoroacetimidate donor **231** (1.62 g, 2.19 mmol, 1 equiv.), acceptor **228** (345 mg, 2.63 mmol, 1.2 equiv.), and CH_2Cl_2 (10 mL). $Pd(CH_3CN)_4(BF_4)_2$ (49 mg, 0.11 mmol, 5 mol %) was then added to the solution. The resulting mixture was stirred under argon at 25 °C without light for 3 h, concentrated *in vacuo*, and then purified by silica gel flash chromatography (2/1, hexane/ethyl acetate) to give the desired glucoside **232** (1.2 g, 77%) as white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.09 – 7.82 (m, 8H), 7.62 – 7.28 (m, 12H), 5.93 (t, *J* = 9.6 Hz, 1H), 5.70 (t, *J* = 9.7 Hz, 1H), 5.55 (dd, *J* = 9.8, 7.9 Hz, 1H), 4.98 (d, *J* = 7.9 Hz, 1H), 4.66 (dd, *J* = 12.1, 3.2 Hz, 1H), 4.51 (dd, *J* = 12.1, 5.1 Hz,

1H), 4.23 – 4.15 (m, 1H), 4.03 (dt, *J* = 11.4, 3.8 Hz, 1H), 3.82 (ddd, *J* = 11.2, 6.9, 3.8 Hz, 1H), 3.67 – 3.58 (m, 2H), 3.48 (t, *J* = 5.1 Hz, 1H), 3.10 (q, *J* = 4.7 Hz, 2H).

Amine-linked glucoside 233. A 50 mL round bottom flask was charged with azide-linked glucoside **232** (415 mg, 0.59 mmol, 1 equiv.), tetrahydrofuran (20 mL), and water (2 mL). Triphenylphosphine (230 mg, 0.88 mmol, 1.5 equiv.) was then added to the solution. The resulting mixture was stirred overnight at 55 °C. The reaction mixture concentrated and co-evaporated with toluene twice to remove water. The residue was purified by silica gel flash chromatography (ethyl acetate → 9/1 dichloromethane/methanol) to afford the desired amine-linked glucoside **233** (280 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.09 – 7.76 (m, 8H), 7.57 – 7.17 (m, 12H), 5.95 (t, *J* = 9.6 Hz, 1H), 5.72 (t, *J* = 9.7 Hz, 1H), 5.49 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.98 (d, *J* = 7.8 Hz, 1H), 4.67 (d, *J* = 9.5 Hz, 1H), 4.51 (dd, *J* = 12.1, 4.8 Hz, 1H), 4.28 – 4.14 (m, 1H), 3.99 (d, *J* = 11.1 Hz, 1H), 3.85 – 3.70 (m, 1H), 3.55 (s, 2H), 3.38 (s, 2H), 2.73 (bs, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.5, 167.2, 166.8, 166.2, 134.5, 134.3, 134.2, 132.4, 130.9, 130.8, 130.7, 130.6, 129.9, 129.6, 129.5, 129.4, 129.0, 128.1, 102.3, 73.8, 73.3, 73.0, 71.0, 70.7, 70.5, 70.2, 64.1, 41.3, 40.7. IR (film, cm^{-1}): ν = 3352, 3065, 2925, 2855, 1726, 1451, 1261, 1092, 1068, 1026. HRMS (ESI): calc. for $C_{38}H_{38}NO_{11}$ (M+H): 684.2445; found: 684.2447.

7.4. Synthesis of Man-Man (**235**)



Scheme 7.4. Synthesis of Homofunctional Diantennary Glycomonomer (Man-Man) **235**.

Amide 235A. A 10 mL oven dried round bottom flask was charged with mannosyl amine **230** (153 mg, 0.22 mmol, 1 equiv.), scaffold **234**[206] (131 mg, 0.34 mmol, 1.5 equiv.) and dichloromethane (1 mL). EDCI (64 mg, 0.34 mmol, 1.5 equiv.) and DMAP (2.7 mg, 0.022 mmol, 0.10 equiv.) were sequentially added to the solution. The resulting mixture was stirred overnight at 25 °C under nitrogen. The reaction mixture was diluted with dichloromethane (25 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 X 15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel flash chromatography (ethyl acetate → 9/1 dichloromethane/methanol) to afford the desired mannose-containing amide linker **235A** (183 mg, 78%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.08 (dd, *J* = 15.5, 7.7 Hz, 4H), 7.96 (d, *J* = 7.3 Hz, 2H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.66 – 7.55 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.47 – 7.32 (m, 7H), 7.32 – 7.21 (m, 2H), 6.66 (t, *J* = 4.9 Hz, 0.5H), 6.57 (t, *J* = 5.2 Hz, 0.4H), 6.49 (td, *J* = 5.7, 2.8 Hz, 1H), 6.38 (dd, *J* = 5.8, 3.7 Hz, 1H), 6.14 (t, *J* =

10.0 Hz, 1H), 5.95 (dt, *J* = 10.2, 2.5 Hz, 1H), 5.72 (s, 1H), 5.28 – 5.17 (m, 2H), 5.14 (dd, *J* = 9.8, 1.7 Hz, 1H), 4.81 – 4.66 (m, 1H), 4.56 – 4.44 (m, 2H), 4.17 (t, *J* = 2.4 Hz, 1H), 4.04 (s, 1H), 4.00 – 3.90 (m, 1H), 3.90 – 3.80 (m, 1H), 3.80 – 3.65 (m, 2H), 3.60 (t, *J* = 5.4 Hz, 2H), 3.56 – 3.30 (m, 6H), 2.78 – 2.53 (m, 7H), 2.29 (s, 0.4H), 2.18 (t, *J* = 2.5 Hz, 0.5H), 1.61 (dq, *J* = 37.7, 7.2 Hz, 5H), 1.42 – 1.19 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.7, 172.5, 171.9, 171.7, 171.6, 171.2, 166.2, 165.6, 165.5, 165.5, 138.0, 135.5, 133.5, 133.4, 133.2, 133.1, 129.9, 129.8, 129.7, 129.3, 129.1, 129.0, 128.6, 128.5, 128.3, 97.8, 81.5, 81.4, 79.8, 79.3, 79.7, 78.7, 72.6, 71.6, 70.7, 70.2, 70.0, 68.9, 67.4, 67.0, 62.9, 53.5, 49.9, 46.7, 45.9, 41.5, 41.5, 39.9, 39.9, 39.5, 39.4, 37.4, 34.5, 31.2, 28.7, 28.5, 27.6, 27.2, 26.8, 26.7, 23.9. IR (film, cm^{-1}): ν = 3295, 2930, 1725, 1660, 1451, 1261, 1096, 1069, 1028. HRMS (ESI): calc. for $C_{58}H_{62}N_3O_{16}$ (M+H): 1056.4130; found: 1056.4139.

(Man-Man) 235. A 10 mL Schlenk flask was charged with mannose-containing amide linker **235A** (150 mg, 0.14 mmol, 1 equiv.), **229** (151 mg, 0.21, 1.5 equiv.) and DMF (1 mL). DBU (22 μL, 0.14 mmol, 1 equiv.) and copper iodide (8 mg, 0.04 mmol, 0.3 equiv.) were then sequentially added to the solution. The resulting mixture was stirred overnight at 55 °C. The reaction mixture was diluted with ethyl acetate (30 mL), washed with brine (2 X 20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (ethyl acetate → 9/1 dichloromethane/methanol) to afford the homofunctional diantennary glycomonomer (Man-Man) **235** (155 mg, 62%). ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.09 (dd, *J* = 20.8, 7.5 Hz, 12.5H), 8.03 – 7.93 (m, 7.5H), 7.85 (d, *J* = 7.8 Hz, 6.6H), 7.63 – 7.54 (m, 6.6H),

7.51 (t, *J* = 6.9 Hz, 3.6H), 7.47 – 7.31 (m, 23H), 7.31 – 7.21 (m, 7H), 6.74 – 6.58 (m, 1H), 6.52 – 6.42 (m, 1H), 6.41 – 6.32 (m, 1.5H), 6.15 (t, *J* = 10.0 Hz, 3H), 6.01 – 5.88 (m, 3H), 5.74 (s, 3H), 5.34 – 5.19 (m, 5H), 5.19 – 5.08 (m, 3H), 4.74 (d, *J* = 12.5 Hz, 3H), 4.64 – 4.43 (m, 11H), 4.05 – 3.88 (m, 7H), 3.88 – 3.80 (m, 2.4H), 3.80 – 3.64 (m, 9H), 3.64 – 3.57 (m, 3H), 3.52 (s, 1.7H), 3.50 – 3.24 (m, 7H), 3.22 – 3.04 (m, 2H), 2.59 (d, *J* = 9.7 Hz, 6.5H), 1.71 – 1.40 (m, 7H), 1.38 – 1.12 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.7, 171.8, 171.5, 166.2, 165.5, 137.8, 135.6, 133.5, 133.2, 133.1, 129.9, 129.8, 129.7, 129.3, 129.0, 128.6, 128.5, 128.3, 97.9, 97.8, 79.8, 79.0, 70.6, 70.5, 70.2, 70.1, 69.6, 69.0, 68.9, 67.5, 67.4, 67.0, 66.9, 62.9, 53.5, 50.2, 49.9, 41.6, 41.5, 39.8, 39.4, 31.1, 30.9, 29.7, 28.3, 26.7, 23.9, 23.7. IR (film, cm^{-1}): ν = 3064, 2931, 2877, 1724, 1651, 1451, 1265, 1096, 1068, 1027. HRMS (ESI): calc. for $C_{96}H_{97}N_6O_{27}$ (M+H): 1765.6402; found: 1765.6425.

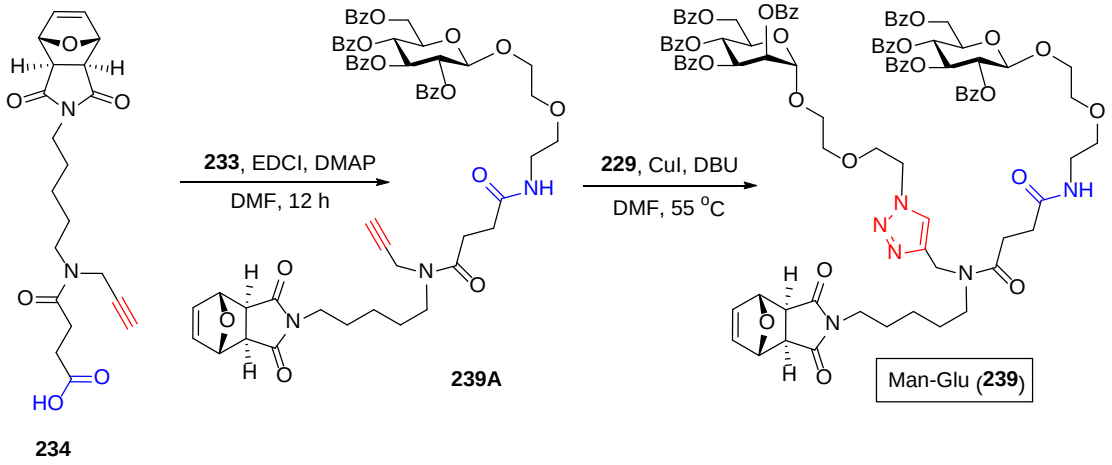
Compound 236. An oven dried 10 mL Schlenk flask was charged with the protected monomer **235** (80 mg, 0.0454 mmol, 1.0 equiv.), anhydrous methanol (0.5 mL), and sodium methoxide (5 mg, 0.0454 mmol, 1.0 equiv.). The resulting mixture was stirred overnight at room temperature. The reaction mixture brought to neutral pH with acidic Amberlyst 15. The solution was filtered, concentrated *in vacuo* and purified by C-18 reverse phase flash chromatography (0 → 80% acetonitrile in water) to yield the deprotected monomer **236** (29.5 mg, 70%). ^{1}H NMR (D_2O, 500 MHz): δ = 7.98 (s, 0.43H), 7.83 (s, 0.74H), 6.45 (s, 1.1H), 6.44 (s, 0.85H), 5.33 (d, *J* = 7.6 Hz, 0.66H), 5.27 (s, 0.65H), 5.12 – 4.96 (m, 2H), 4.80 (s, 1.7H), 4.53 (td, *J* = 10.1, 8.2, 5.5 Hz, 5.3H), 3.96 – 3.85 (m, 4.3H), 3.83 – 3.71 (m, 8H), 3.70 – 3.62 (m, 8H), 3.59 – 3.53 (m, 12H), 3.49

(dtd, *J* = 10.2, 7.5, 6.3, 3.7 Hz, 3H), 3.40 – 3.22 (m, 7.5H), 3.05 (dddd, *J* = 20.7, 12.2, 7.6, 3.8 Hz, 2.2H), 2.83 (d, *J* = 7.2 Hz, 0.77H), 2.73 (dp, *J* = 11.1, 5.4, 3.8 Hz, 1.89H), 2.67 (dq, *J* = 6.9, 4.5 Hz, 1.55H), 2.60 (t, *J* = 7.6 Hz, 0.84H), 2.52 – 2.38 (m, 3.5H), 2.28 (dd, *J* = 7.3, 1.6 Hz, 0.58H), 1.48 (dddd, *J* = 40.3, 24.0, 11.5, 4.7 Hz, 6.3H), 1.16 (dt, *J* = 29.7, 9.7 Hz, 3.3H). ^{13}C NMR (D_2O, 125 MHz): δ = 175.1, 174.5, 144.2, 136.8, 136.5, 135.8, 124.6, 99.9, 99.8, 82.4, 80.7, 80.4, 79.8, 79.0, 72.8, 72.7, 70.5, 70.0, 69.4, 68.9, 68.8, 66.8, 66.7, 66.4, 66.3, 60.9, 50.1, 50.0, 49.7, 48.7, 46.8, 41.1, 39.8, 39.0, 31.3, 30.7, 28.1, 25.9, 23.3. HRMS (ESI): calc. for $C_{40}H_{64}N_6O_{19}Na$ (M+Na): 955.4124; found: 955.4126.

Homobifunctional Diantennary Glycopolymer 238. An oven dried 10 mL Schlenk flask was charged with (Man-Man) **235** (20 mg, 0.017 mmol, 1.0 equiv.) and anhydrous degassed dichloroethane (500 µL). Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)bis(3-bromopyridine)ruthenium(II) (0.75 mg, 8.5 x 10^{-4} mmol, 0.03 equiv.) was then added. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated to a brown oil. The crude oil was dissolved in a minimal amount of ethyl acetate and precipitated with an excess of petroleum ether. The solid was filtered and then re-dissolved in ethyl acetate. This process was repeated 2 more times to yield the protected polymer **238P** as a white solid (19.9 mg, 99%). The protected polymers were injected onto a Waters Styragel HR 4 size exclusion column with THF as the eluent. Absolute polymer molecular weight (M_n) and polydispersity (PDI) measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^{1}H NMR ($CDCl_3$,

500 MHz): δ = 8.10 (bs, 2H), 8.06 (bs, 2H), 7.96 (bs, 2H), 7.85 (bs, 2H), 7.59 – 7.39 (m, 8H), 6.14 (t, *J* = 10.0 Hz, 1H), 5.94 (bs, 1H), 5.73 (bs, 1H), 5.22 – 5.14 (m, 1H), 4.72 (bs, 1H), 4.50 (bs, 3H), 3.92 (bs, 1H), 3.70 (bs, 2H), 3.58 (bs, 1H), 2.56 (bs, 2H), 1.63 (bs, 4H), 1.28 (bs, 2H). An oven dried 10 mL Schlenk flask was charged with the protected glycopolymer of **238P** (19 mg), anhydrous dichloromethane (2 mL), anhydrous methanol (2 mL), and sodium methoxide (5 mg, 0.0926 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured off and the oily residue was washed with methanol (3 x 1 mL) and dichloromethane (3 x 1 mL). The resulting residue was dissolved in water (5 mL) and brought to neutral pH with Amberlyst 15. The aqueous solution was filtered and lyophilized to a yield the deprotected polymer **238** as a white solid (5.3 mg, 53%). The deprotected polymers were dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water before ITC experiments were performed. ^{1}H NMR (D_2O, 500 MHz): δ = 5.93 – 5.71 (m, 2H), 5.04 (bs, 1H), 4.79 (bs, 1H), 4.53 (bs, 1H), 3.88 (bs, 1H), 3.80 – 3.49 (m, 8H), 3.30 (bs, 2H), 3.08 (bs, 1H), 2.67 (bs, 2H), 2.47 (bs, 2H), 1.51 (bs, 3H), 1.17 (bs, 2H).

7.5. Synthesis of Man-Glu (**239**)



Scheme 7.5. Synthesis of Heterobifunctional Diantennary Glycomonomer (Man-Glu) **239**.

Amide Compound 239A. A 10 mL oven dried round bottom flask was charged with glucosyl amine **233** (153 mg, 0.22 mmol, 1 equiv.), scaffold **234**[206] (131 mg, 0.34 mmol, 1.5 equiv.) and dichloromethane (1 mL). EDCI (64 mg, 0.34 mmol, 1.5 equiv.) and DMAP (2.7 mg, 0.022 mmol, 0.10 equiv.) were sequentially added to the solution. The resulting mixture was stirred overnight at 25 °C under nitrogen. The reaction mixture was diluted with dichloromethane (25 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 X 15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel flash chromatography (ethyl acetate → 9/1 dichloromethane/methanol) to afford the desired glucose-containing amide linker **239A** (176 mg, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.02 (d, *J* = 7.4 Hz, 2.4H), 7.96 (d, *J* = 7.6 Hz, 2.5H), 7.89 (d, *J* = 7.5 Hz, 2.4H), 7.83 (d, *J* = 7.4 Hz, 2.4H), 7.57 – 7.45 (m, 4H), 7.44 – 7.36 (m, 6.2H), 7.33 (t, *J* = 7.8 Hz, 2.5H), 7.27 (t, *J* = 7.8 Hz, 2.7H), 6.55

– 6.44 (m, 1H), 6.45 – 6.28 (m, 2.8H), 5.94 (td, *J* = 9.6, 3.6 Hz, 1.2H), 5.70 (t, *J* = 9.7 Hz, 1.6H), 5.53 (dd, *J* = 9.5, 7.9 Hz, 1.3H), 5.26 – 5.17 (m, 0.7H), 5.11 (dd, *J* = 17.6, 5.8 Hz, 1.4H), 5.05 – 4.90 (m, 2.5H), 4.66 (d, *J* = 11.5 Hz, 1.2H), 4.52 (dd, *J* = 12.1, 5.0 Hz, 1.3H), 4.30 – 4.10 (m, 3H), 4.10 – 3.96 (m, 2.3H), 3.83 – 3.71 (m, 1.5H), 3.55 (t, *J* = 4.5 Hz, 2.7H), 3.38 (dt, *J* = 22.8, 6.1 Hz, 6H), 3.30 – 3.11 (m, 3.8H), 2.79 – 2.45 (m, 7.6H), 2.26 (m, 2H), 1.74 – 1.45 (m, 5.5H), 1.30 (dq, *J* = 22.4, 6.9, 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.8, 172.5, 171.9, 171.8, 171.6, 171.3, 166.2, 165.6, 165.5, 138.0, 135.5, 133.2, 133.1, 129.9, 129.8, 129.7, 129.7, 129.3, 129.1, 129.0, 128.6, 128.5, 128.3, 97.8, 81.5, 79.8, 79.3, 79.0, 72.6, 71.2, 70.7, 70.2, 70.0, 68.9, 67.4, 67.0, 62.9, 50.0, 49.9, 46.7, 45.9, 41.5, 40.0, 39.5, 37.4, 34.3, 31.2, 28.7, 28.5, 27.6, 27.2, 26.8, 26.7, 23.9. IR (film, cm^{-1}): ν = 3065, 2930, 2869, 1730, 1654, 1452, 1266, 1095, 1069. HRMS (ESI): calc. for $C_{58}H_{62}N_3O_{16}$ (M+H): 1056.4130; found: 1056.4139.

Man-Glu 239. A 10 mL Schlenk flask was charged with glucose-containing amide linker **239A** (150 mg, 0.14 mmol, 1 equiv.), **229** (151 mg, 0.21, 1.5 equiv.) and DMF (1 mL). DBU (22 μL, 0.14 mmol, 1 equiv.) and copper iodide (8 mg, 0.04 mmol, 0.3 equiv.) were then sequentially added to the solution. The resulting mixture was stirred overnight at 55 °C. The reaction mixture was diluted with ethyl acetate (30 mL), washed with brine (2 X 20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (ethyl acetate → 9/1 dichloromethane/methanol) to afford the homofunctional diantennary glycomonomer Man-Man **239** (155 mg, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.19 – 7.77 (m, 17H), 7.68 – 7.49 (m, 6H), 7.49 – 7.33 (m, 15H), 6.49 – 6.32 (m, 2H), 6.15 (t, *J* = 9.6 Hz, 1H),

5.95 (d, *J* = 9.9 Hz, 2H), 5.73 (d, *J* = 9.9 Hz, 2H), 5.55 (t, *J* = 8.5 Hz, 1H), 5.15 (d, *J* = 14.0 Hz, 2H), 5.00 (s, 3H), 4.71 (dd, *J* = 28.8, 13.0 Hz, 3H), 4.59 – 4.44 (m, 4H), 4.29 – 4.17 (m, 2H), 4.13 – 3.87 (m, 5H), 3.74 (dd, *J* = 18.4, 12.6 Hz, 5H), 3.64 – 3.50 (m, 3H), 3.45 – 3.14 (m, 8H), 2.78 – 2.42 (m, 6H), 2.35 – 2.22 (m, 1H), 1.79 – 1.44 (m, 5H), 1.28 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.2, 165.8, 165.5, 165.4, 165.2, 136.6, 135.7, 133.5, 133.3, 133.2, 129.8, 129.7, 129.3, 129.0, 128.8, 128.6, 128.5, 128.4, 128.3, 101.3, 97.9, 82.3, 80.6, 72.8, 72.3, 72.0, 70.5, 70.2, 70.1, 69.7, 69.2, 68.9, 67.5, 66.9, 63.2, 62.9, 50.2, 49.1, 47.9, 29.7. IR (film, cm^{-1}): ν = 3065, 2925, 2871, 1726, 1451, 1263, 1095, 1069, 1027. HRMS (ESI): calc. for $C_{96}H_{97}N_6O_{27}$ (M+H): 1765.6402; found: 1765.6425.

Compound 240. An oven dried 10 mL Schlenk flask was charged with the protected monomer **239** (80 mg, 0.0454 mmol, 1.0 equiv.), anhydrous methanol (0.5 mL), and sodium methoxide (5 mg, 0.0454 mmol, 1.0 equiv.). The resulting mixture was stirred overnight at room temperature. The reaction mixture brought to neutral pH with acidic Amberlyst 15. The solution was filtered, concentrated *in vacuo* and purified by C-18 reverse phase flash chromatography (0 → 80% acetonitrile in water) to yield the deprotected monomer **240** (29.5 mg, 70%). ^{1}H NMR (D_2O, 500 MHz): δ = 7.97 (s, 0.4H), 7.82 (s, 0.6H), 6.45 (s, 1H), 6.44 (s, 1H), 5.33 (d, *J* = 7.6 Hz, 1H), 5.07 – 4.99 (m, 2H), 4.53 (d, *J* = 5.5 Hz, 4.6H), 4.40 (d, *J* = 10.0 Hz, 1.8H) 3.96 – 3.85 (m, 4.3H), 3.83 – 3.71 (m, 8H), 3.70 – 3.62 (m, 8H), 3.59 – 3.53 (m, 12H), 3.49 (dtd, *J* = 10.2, 7.5, 6.3, 3.7 Hz, 3H), 3.40 – 3.22 (m, 7.5H), 3.05 (dddd, *J* = 20.7, 12.2, 7.6, 3.8 Hz, 2.2H), 2.83 (d, *J* = 7.2 Hz, 0.36H), 2.73 – 2.46 (m, 5H), 1.48 (bs, 3.25H), 1.20 (bs, 4.2H). ^{13}C NMR

(D_2O, 125 MHz): δ = 175.2, 175.1, 174.5, 174.2, 174.1, 173.7, 160.6, 144.2, 143.9, 136.8, 136.5, 136.3, 135.8, 124.6, 124.4, 102.3, 99.8, 82.4, 80.7, 79.8, 79.0, 75.9, 75.7, 73.1, 72.8, 70.5, 70.0, 69.7, 69.5, 68.9, 68.8, 66.8, 66.7, 66.4, 66.3, 60.9, 60.8, 50.1, 50.0, 49.7, 46.8, 41.1, 38.9, 39.0, 30.7, 28.1, 25.9. HRMS (ESI): calc. for $C_{40}H_{64}N_6O_{19}Na$ (M+Na): 955.4124; found: 955.4114.

Heterobifunctional Diantennary Glycopolymer 241. An oven dried 10 mL Schlenk flask was charged with (Man-Glu) **239** (20 mg, 0.017 mmol, 1.0 equiv.) and anhydrous degassed dichloroethane (500 µL). Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)bis(3-bromopyridine)ruthenium(II) (0.75 mg, 8.5 x 10^{-4} mmol, 0.03 equiv.) was then added. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated to a brown oil. The crude oil was dissolved in a minimal amount of ethyl acetate and precipitated with an excess of petroleum ether. The solid was filtered and then re-dissolved in ethyl acetate. This process was repeated 2 more times to yield the protected polymer **241P** as a white solid (19.7 mg, 97%). The protected polymers were injected onto a Waters Styragel HR 4 size exclusion column with THF as the eluent. Absolute polymer molecular weight (M_n) and polydispersity (PDI) measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.10 – 7.83 (m, 11H), 7.58 – 7.34 (m, 15H), 6.14 (t, *J* = 11.0 Hz, 1H), 5.95 – 5.91 (m, 2H), 5.73 – 5.69 (m, 2H), 5.53 (bs, 1H), 5.13 – 5.09 (m, 2H), 4.98 – 4.93 (m, 2H), 4.73 – 4.65 (m, 2H), 4.50 (bs, 4H), 4.21 (bs, 1H), 3.98 (bs, 3H), 3.73 (bs, 4H), 3.56 (bs, 2H), 3.36 (bs, 3H), 3.19 (bs, 3H), 2.67 (bs, 2H), 2.53 (bs, 2.5H), 1.71 (bs, 6H),

1.27 (bs, 4H). An oven dried 10 mL Schlenk flask was charged with the protected glycopolymer of **241P** (19 mg), anhydrous dichloromethane (2 mL), anhydrous methanol (2 mL), and sodium methoxide (5 mg, 0.0926 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured off and the oily residue was washed with methanol (3 x 1 mL) and dichloromethane (3 x 1 mL). The resulting residue was dissolved in water (5 mL) and brought to neutral pH with Amberlyst 15. The aqueous solution was filtered and lyophilized to a yield the deprotected polymer **241** as a white solid (4.5 mg, 45%). The deprotected polymers were dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water before ITC experiments were performed. ^{1}H NMR (D_2O, 500 MHz): δ = 5.92 – 5.71 (m, 2H), 4.53 (bs, 7H), 4.39 (d, *J* = 7.5 Hz, 3H), 3.94 – 3.20 (m, 49H), 2.66 (bs, 6H), 2.47 (bs, 4H), 1.51 (bs, 7H), 1.18 (bs, 5H).

Glu-Glu 242. A 10 mL Schlenk flask was charged with glucose-containing amide linker **239A** (150 mg, 0.14 mmol, 1 equiv.), **232** (151 mg, 0.21, 1.5 equiv.) and DMF (1 mL). DBU (22 μL, 0.14 mmol, 1 equiv.) and copper iodide (8 mg, 0.04 mmol, 0.3 equiv.) were then sequentially added to the solution. The resulting mixture was stirred overnight at 55 °C. The reaction mixture was diluted with ethyl acetate (30 mL), washed with brine (2 X 20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (ethyl acetate → 9/1 dichloromethane/methanol) to afford the homofunctional diantennary glycomonomer Glu-Glu **242** (155 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.23 – 7.69 (m, 17H), 7.68 – 7.27 (m, 25H), 6.57 – 6.17 (m, 2H), 6.07 – 5.83 (m, 2H), 5.82 – 5.63 (m, 2H), 5.53 (t, *J* = 8.9 Hz, 2H), 5.38 – 5.07 (m, 2H), 4.92 (d, *J* = 7.5 Hz, 2H), 4.65 (d, *J* = 11.9 Hz,

3H), 4.57 – 4.39 (m, 3H), 4.32 – 4.06 (m, 4H), 4.06 – 3.91 (m, 2H), 3.86 – 2.99 (m, 17H), 2.88 – 2.43 (m, 5H), 1.97 – 1.39 (m, 6H), 1.39 – 1.09 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.2, 165.8, 165.2, 165.1, 133.5, 133.3, 133.2, 129.8, 129.7, 129.6, 129.3, 128.8, 128.4, 128.3, 101.4, 72.9, 72.3, 71.9, 70.2, 70.1, 70.0, 69.9, 69.8, 69.7, 69.6, 69.5, 69.4, 69.3, 69.2, 63.2, 63.1, 50.0, 39.7, 39.2, 31.2, 29.7. IR (film, cm^{-1}): ν = 3065, 2925, 2871, 1726, 1451, 1263, 1095, 1069, 1027. HRMS (ESI): calc. for $C_{96}H_{97}N_6O_{27}$ (M+H): 1765.6402; found: 1765.6425.

Homobifunctional Diantennary Glycopolymer 243. An oven dried 10 mL Schlenk flask was charged with (Glu-Glu) **242** (20 mg, 0.017 mmol, 1.0 equiv.) and anhydrous degassed dichloroethane (500 µL). Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)bis(3-bromopyridine)ruthenium(II) (0.30 mg, 3.4 x 10^{-4} mmol, 0.02 equiv.) was then added. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated to a brown oil. The crude oil was dissolved in a minimal amount of ethyl acetate and precipitated with an excess of petroleum ether. The solid was filtered and then re-dissolved in ethyl acetate. This process was repeated 2 more times to yield the protected polymer **243P** as a white solid (18.8 mg, 94%). The protected polymers were injected onto a Waters Styragel HR 4 size exclusion column with THF as the eluent. Absolute polymer molecular weight (M_n) and polydispersity (PDI) measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.04 – 7.85 (m, 6H), 7.56 – 7.30 (m, 9H), 5.94 (bs, 1H), 5.72 (bs, 1H), 5.50 (bs, 1H), 4.96 (bs, 1H), 4.66 (bs, 1H), 4.52 (bs, 1H), 4.22 (bs, 1H), 3.98 (bs, 1H),

3.74 (bs, 1H), 3.54 (bs, 2H), 3.33 (bs, 2H), 3.19 (bs, 2H), 2.56 (bs, 2H), 1.61 (bs, 2H), 1.28 (bs, 2H). An oven dried 10 mL Schlenk flask was charged with the protected glycopolymer of **243P** (18 mg), anhydrous dichloromethane (2 mL), anhydrous methanol (2 mL), and sodium methoxide (5 mg, 0.0926 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured off and the oily residue was washed with methanol (3 x 1 mL) and dichloromethane (3 x 1 mL). The resulting residue was dissolved in water (5 mL) and brought to neutral pH with Amberlyst 15. The aqueous solution was filtered and lyophilized to a yield the deprotected polymer **243** as a white solid (3.9 mg, 44%). The deprotected polymers were dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water before ITC experiments were performed. ^{1}H NMR (D_2O, 500 MHz): δ = 5.91 – 5.70 (m, 2H), 5.03 (bs, 1H), 4.78 (bs, 1H), 4.51 (bs, 2H), 3.86 (bs, 1H), 3.79 – 3.48 (m, 10H), 3.29 (bs, 3H), 3.07 (bs, 1H), 2.66 (bs, 2H), 2.46 (bs, 2H), 1.51 – 1.42 (m, 3H), 1.17 (m, 2H).

Alkyne 244. A 25 mL Schlenk flask was charged with **234**[206] (123 mg, 0.317 mmol, 1 equiv.), anhydrous dichloromethane (8 mL), and anhydrous methanol (1 mL). The Schlenk flask was cooled to 0 ^{o}C, and a solution of trimethylsilyldiazomethane (2 M, 792 µL, 1.58 mmol, 5.0 equiv.) in hexanes was then added. The resulting mixture was stirred at room temperature for 30 min and was monitored regularly by TLC until the reaction reached completion. The reaction mixture was quenched with silica until it turned colorless. The resulting was then concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (20/1, dichloromethane/methanol) to afford **244** (100.3 mg, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.41 (t, J = 5.7 Hz, 1H), 6.31 (d, J = 5.7

Hz, 1H), 5.18 – 5.14 (m, 2H), 5.04 (s, 1H), 4.09 (s, 1H), 3.97 (s, 1H), 3.59 (s, 1H), 3.33 (t, *J* = 7.5 Hz, 3H), 3.13 – 3.03 (m, 1H), 2.64 – 2.51 (m, 6H), 2.29 (s, 0.5H), 2.16 (s, 0.5H), 1.59 – 1.47 (m, 4H), 1.29 – 1.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 174.5, 171.8, 137.6, 136.8, 93.2, 83.3, 81.7, 73.9, 73.6, 72.7, 52.9, 52.8, 52.6, 51.0, 50.1, 48.1, 47.5, 44.5, 44.5, 42.5, 41.3, 41.1, 38.5, 35.5, 30.1, 29.2, 29.0, 28.9, 27.8, 27.3, 24.9, 24.8. IR (film, cm^{-1}): ν = 3076, 2933, 2856, 2117, 1733, 1647, 1436, 1369, 1218, 1168. HRMS (ESI): calc. for $C_{21}H_{28}N_2O_6Na$ (M+Na): 427.1845; found: 427.1855.

Man-OMe 245. A 10 mL Schlenk flask was charged with linker **244** (150 mg, 0.14 mmol, 1 equiv.), **229** (151 mg, 0.21, 1.5 equiv.) and DMF (1 mL). DBU (22 μL, 0.14 mmol, 1 equiv.) and copper iodide (8 mg, 0.04 mmol, 0.3 equiv.) were then sequentially added to the solution. The resulting mixture was stirred overnight at 55 °C. The reaction mixture was diluted with ethyl acetate (30 mL), washed with brine (2 X 20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (ethyl acetate → 9/1 dichloromethane/methanol) to afford the homofunctional diantennary glycomonomer (Man-OMe) **245** (125 mg, 50%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.11 – 7.96 (m, 14.5H), 7.86 – 7.81 (m, 5H), 7.73 (s, 1H), 7.61 – 7.35 (m, 24H), 6.50 (t, *J* = 5.7 Hz, 1H), 6.38 (d, *J* = 6.0 Hz, 1H), 6.14 (t, *J* = 9.9 Hz, 2.5H), 5.95 – 5.90 (m, 2.5H), 5.72 (s, 2H), 5.31 – 5.16 (m, 7.2H), 4.74 – 4.45 (m, 12H), 3.95 (t, *J* = 4.8 Hz, 7H), 3.80 – 3.65 (m, 14H), 3.47 – 3.22 (m, 6H), 3.17 – 3.12 (m, 2H), 2.82 – 2.78 (m, 2H), 2.67 – 2.60 (m, 7.5H), 1.65 – 1.51 (m, 9.5H), 1.31 – 1.27 (m, 11H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.1, 181.5, 180.2, 177.2, 130.9, 130.8, 130.8, 129.5, 129.5, 129.4, 119.7, 119.7, 106.0, 90.2, 89.5, 82.1, 78.3, 69.8, 63.5, 57.6, 51.5, 51.0, 42.9,

40.6, 33.3. IR (film, cm^{-1}): ν = 2942, 1729, 1683, 1636, 1602, 1452, 1373, 1266, 1094. HRMS (ESI): calc. for $C_{59}H_{63}N_5O_{17}Na$ (M+Na): 1136.4117; found: 1136.4149.

Homofunctional Monoantennary Glycopolymer 246. An oven dried 10 mL Schlenk flask was charged with (Man-OMe) **245** (20 mg, 0.017 mmol, 1.0 equiv.) and anhydrous degassed dichloroethane (500 µL). Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)bis(3-bromopyridine)ruthenium(II) (0.45 mg, 5.1×10^{-4} mmol, 0.03 equiv.) was then added. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated to a brown oil. The crude oil was dissolved in a minimal amount of ethyl acetate and precipitated with an excess of petroleum ether. The solid was filtered and then re-dissolved in ethyl acetate. This process was repeated 2 more times to yield the protected polymer **246P** as a white solid (19.0 mg, 99%). The protected polymers were injected onto a Waters Styragel HR 4 size exclusion column with THF as the eluent. Absolute polymer molecular weight (M_n) and polydispersity (PDI) measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.11 – 7.98 (m, 8H), 7.83 (bs, 3H), 7.58 (bs, 4H), 7.41 (bs, 10H), 6.14 (t, *J* = 9.3 Hz, 2H), 5.92 (bs, 2H), 5.73 (bs, 2H), 5.16 (bs, 2H), 4.74 – 4.47 (m, 8H), 3.93 (m, 4H), 3.71 (m, 4H), 3.63 (m, 4H), 2.61 (bs, 5H), 1.65 (bs, 8H), 1.27 (bs, 5H). An oven dried 10 mL Schlenk flask was charged with the protected glycopolymer of **246P** (19 mg), anhydrous dichloromethane (2 mL), anhydrous methanol (2 mL), and sodium methoxide (5 mg, 0.0926 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured off and the oily residue was washed with

methanol (3 x 1 mL) and dichloromethane (3 x 1 mL). The resulting residue was dissolved in water (5 mL) and brought to neutral pH with Amberlyst 15. The aqueous solution was filtered and lyophilized to a yield the deprotected polymer **246** as a white solid (11.2 mg, 75%). The deprotected polymers were dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water before ITC experiments were performed. ^{1}H NMR (D_2O, 500 MHz): δ = 5.93 (bs, 2H), 4.51 (bs, 10H), 3.86 – 3.45 (m, 77H), 3.29 (bs, 15H), 2.68 – 2.46 (m, 3H), 1.53 – 1.42 (m, 5H), 1.18 (bs, 10H).

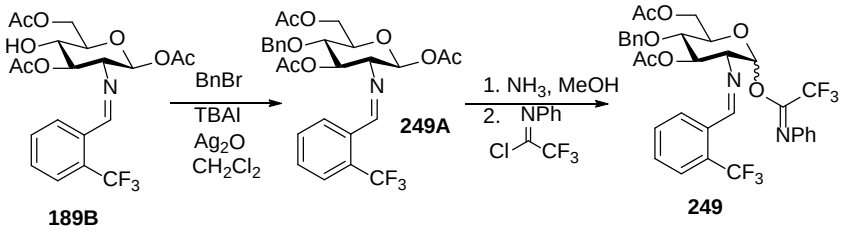
(Glu-OMe) 247. A 10 mL Schlenk flask was charged with linker **244** (150 mg, 0.14 mmol, 1 equiv.), **232** (151 mg, 0.21, 1.5 equiv.) and DMF (1 mL). DBU (22 μL, 0.14 mmol, 1 equiv.) and copper iodide (8 mg, 0.04 mmol, 0.3 equiv.) were then sequentially added to the solution. The resulting mixture was stirred overnight at 55 °C. The reaction mixture was diluted with ethyl acetate (30 mL), washed with brine (2 X 20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (ethyl acetate → 9/1 dichloromethane/methanol) to afford the homofunctional diantennary glycomonomer (Glu-OMe) **247** (125 mg, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.03 – 7.81 (m, 13H), 7.63 – 7.28 (m, 19H), 6.50 (t, *J* = 5.7 Hz, 1H), 6.40 – 6.37 (m, 1H), 5.98 – 5.90 (m, 2H), 5.71 (t, *J* = 9.6 Hz 2H), 5.57 – 5.51 (m, 2H), 5.13 (bs, 2H), 4.94 (q, *J* = 11.4 Hz, 2H), 4.70 – 4.48 (m, 6H), 4.21 – 4.13 (m, 4H), 4.02 – 3.97 (m, 2H), 3.76 – 3.73 (m, 2H), 3.67 (s, 7H), 3.67 (s, 5H), 3.63 – 3.53 (m, 7H), 3.42 – 3.33 (m, 5H), 2.68 – 2.60 (m, 6.5H), 1.64 – 1.51 (m, 6H), 1.33 – 1.26 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.7, 172.8, 172.0, 167.2, 166.8, 166.2, 166.1, 139.2, 136.4, 136.4, 134.5, 134.4, 134.3, 134.2, 130.9, 130.8, 130.3, 129.9, 129.8, 129.6, 129.5,

129.5, 129.4, 102.4, 82.6, 82.5, 80.8, 80.1, 73.9, 73.3, 73.0, 71.2, 71.1, 70.7, 70.5, 70.4, 64.1, 52.8, 51.0, 48.8, 42.6, 42.1, 40.9, 30.2, 28.9, 24.9. IR (film, cm^{-1}): ν = 2945, 1723, 1686, 1634, 1611, 1459, 1371, 1263, 1095. HRMS (ESI): calc. for $C_{59}H_{63}N_5O_{17}Na$ (M+Na): 1136.4117; found: 1136.4146.

Heterobifunctional Monoantennary Glycopolymer 248. An oven dried 10 mL Schlenk flask was charged with (Man-OMe) **245** (10 mg, 0.0085 mmol, 0.5 equiv.), (Glu-OMe) **247** (10 mg, 0.0085 mmol, 0.5 equiv.) and anhydrous degassed dichloroethane (500 μL). Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)bis(3-bromopyridine)ruthenium(II) (0.30 mg, 3.4 x 10^{-4} mmol, 0.02 equiv.) was then added. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated to a brown oil. The crude oil was dissolved in a minimal amount of ethyl acetate and precipitated with an excess of petroleum ether. The solid was filtered and then re-dissolved in ethyl acetate. This process was repeated 2 more times to yield the protected polymer **248P** as a white solid (19.6 mg, 98%). The protected polymers were injected onto a Waters Styragel HR 4 size exclusion column with THF as the eluent. Absolute polymer molecular weight (M_n) and polydispersity (PDI) measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.10 – 7.81 (m, 12H), 7.59 – 7.33 (m, 14H), 6.14 (t, *J* = 10.2 Hz, 1H), 5.95 – 5.90 (m, 2H), 5.72 (m, 2H), 5.54 (bs, 1H), 5.16 (bs, 1H), 4.96 – 4.91 (m, 1H), 4.74 – 4.48 (m, 8H), 4.21 (bs, 1H), 3.93 (bs, 3H), 3.63 (bs, 10H), 3.33 (bs, 3H), 2.61 (bs, 4H), 1.79 (bs, 6H), 1.60 (bs, 5H). An oven dried 10 mL Schlenk flask was charged with the

protected glycopolymer of **248P** (19 mg), anhydrous dichloromethane (2 mL), anhydrous methanol (2 mL), and sodium methoxide (5 mg, 0.0926 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured off and the oily residue was washed with methanol (3 x 1 mL) and dichloromethane (3 x 1 mL). The resulting residue was dissolved in water (5 mL) and brought to neutral pH with Amberlyst 15. The aqueous solution was filtered and lyophilized to a yield the deprotected polymer **248** as a white solid (6.1 mg, 61%). The deprotected polymers were dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water before ITC experiments were performed. ^{1}H NMR (D_2O, 500 MHz): δ = 5.91 – 5.68 (m, 2H), 5.03 (bs, 1H), 4.50 (bs, 3H), 4.33 (t, *J* = 7.5 Hz, 1H), 4.04 (bs, 1H), 3.87 – 3.73 (m, 3H), 3.66 – 3.47 (m, 6H), 3.40 – 3.18 (m, 4H), 3.06 (bs, 1H), 2.73 – 2.55 (m, 3H), 1.50 (bs, 3H), 1.18 (bs, 2H).

7.6. Synthesis of Donor (**249**)



Scheme 7.6. Synthesis of Glycosyl Donor **249**.

1,3,6-Tri-*O*-Acetyl-4-*O*-Benzyl-2-Deoxy-2-*p*-Trifluoromethylbenzylideneamino-D-Glucopyranoside 249A. A 250 mL Schlenk flask was charged with **189B** (7.26 g, 15.75 mmol, 1.0 equiv.), benzyl bromide (37.5 mL, 315.0 mmol, 20.0 equiv.), tetrabutylammonium iodide (1.16 g, 3.15 mmol, 0.2 equiv.), 4 Å molecular sieves (8 g),

and anhydrous dichloromethane (80 mL). The solution was stirred at room temperature without light for 1 h. Silver (I) oxide (3.65 g, 15.75 mmol, 1.0 equiv.) was added to the reaction mixture. The reaction mixture was stirred at 35 ^{o}C overnight, filtered through celite, and concentrated *in vacuo* to a yellow oil. The yellow oil was purified by silica gel flash chromatography (hexanes/ethyl acetate = 3/1 → 2/1 → 1/1 with 1% Et_3N) to afford **249A** (5.2 g, 57%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.61 (q, *J* = 2.5 Hz, 1H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.64 – 7.52 (m, 1H), 7.41 – 7.25 (m, 5H), 6.00 (d, *J* = 8.2 Hz, 1H), 5.60 (t, *J* = 9.5 Hz, 1H), 4.61 (q, *J* = 11.2 Hz, 2H), 4.39 (dd, *J* = 12.1, 2.2 Hz, 1H), 4.32 (dd, *J* = 12.1, 4.4 Hz, 1H), 3.91 (ddd, *J* = 9.9, 4.4, 2.2 Hz, 1H), 3.75 (t, *J* = 9.5 Hz, 1H), 3.50 (dd, *J* = 9.8, 8.2 Hz, 1H), 2.09 (s, 3H), 2.03 (s, 3H), 1.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.6, 169.3, 168.7, 161.2, 137.2, 133.4, 132.4, 130.8, 129.1, 128.9, 128.6, 128.2, 128.1, 125.5, 125.2, 123.0. HRMS (ESI): calc. for $C_{27}H_{29}NO_8F_3$ (M+H): 552.1845; found: 552.1841.

3,6-Di-*O*-Acetyl-4-*O*-Benzyl-2-Deoxy-2-*p*-Trifluoromethylbenzylideneamino-D-Glucopyranosyl-*N*-Phenyl-Trifluoroacetimidate 249. A 100 mL Schlenk flask was charged with the **249B** (3.52 g, 6.9 mmol, 1.0 equiv.), 2,2,2-trifluoro-*N*-phenyl-ethanimidoyl chloride (2.86 g, 13.8 mmol, 2.0 equiv.), oven-dried K_2CO_3 (1.90 g, 13.8 mmol, 2.0 equiv.), and anhydrous acetone (60 mL). The solution was stirred at room temperature overnight. When the reaction mixture was complete as monitored by TLC (hexanes/ethyl acetate = 2/1), the reaction mixture was filtered, evaporated, and purified by silca gel flash chromatography (hexanes/ethyl acetate = 5/1 → 1/1 with 1% Et_3N) to afford **249** (3.98 g, 85%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.67 (s, 1

H), 8.26 (d, *J* = 8.0 Hz, 1 H), 7.76-7.01 (m, 13 H), 6.73 (brs, 1 H), 5.79 (t, *J* = 9.6 Hz, 1 H), 4.65-4.27 (m, 4 H), 3.82-3.66 (m, 3 H), 2.11 (s, 3 H), 1.86 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.6, 169.4, 169.2, 161.8, 160.8, 143.3, 137.1, 133.4, 132.3, 131.0, 130.9, 129.3, 128.8, 128.7, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 126.2, 125.6, 125.6, 125.5, 124.4, 123.0, 120.6, 119.3, 95.8, 75.3, 75.0, 74.7, 74.6, 74.5, 74.2, 73.9, 72.3, 72.1, 71.7, 62.5, 20.8, 20.6. HRMS (ESI): calc. for $C_{33}H_{31}N_2O_7F_6$ (M+H): 681.2035; found: 681.2027.

Disaccharide 251. A 50 mL oven-dried Schlenk flask was charged with donor **249** (2.13 g, 3.13 mmol, 2.0 equiv), acceptor **250** (784 mg, 1.57 mmol, 1.0 equiv), and CH_2Cl_2 (15 mL). A preformed solution of $Ni(4\text{-}FPhCN)_4(OTf)_2$, which was generated in situ from a reaction of $Ni(4\text{-}FPhCN)_4Cl_2$ (96.1 mg, 0.16 mmol, 10 mol %) and AgOTf (80.4 mg, 0.31 mmol, 20 mol %) in dichloromethane (1.0 mL) for 30 min, was added to the solution. The resulting mixture was stirred under argon at 35 ^{o}C overnight, filtered through celite, concentrated *in vacuo*, and purified by silica gel flash chromatography (2/1 → 1/1 hexanes/ethyl acetate + 1% triethylamine) to give the desired disaccharide **251** (1.32 g, 85%, α only) as yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.48 (d, *J* = 2.5 Hz, 1H), 8.37 – 8.27 (m, 1H), 7.73 – 7.64 (m, 1H), 7.60 – 7.46 (m, 2H), 7.44 – 7.24 (m, 10H), 7.19 – 7.09 (m, 3H), 6.96 – 6.81 (m, 2H), 5.66 (dd, *J* = 10.3, 9.0 Hz, 1H), 5.56 (d, *J* = 3.6 Hz, 1H), 4.93 (d, *J* = 10.9 Hz, 1H), 4.84 (d, *J* = 11.4 Hz, 1H), 4.65 (dd, *J* = 11.2, 7.0 Hz, 2H), 4.62 – 4.54 (m, 3H), 4.38 – 4.33 (m, 2H), 4.24 (dd, *J* = 9.5, 8.6 Hz, 1H), 4.11 (d, *J* = 9.6 Hz, 1H), 4.09 – 4.04 (m, 1H), 3.91– 3.78 (m, 7H), 3.76 – 3.69 (m, 3H), 3.69 – 3.64 (m, 3H), 3.57 – 3.51 (m, 1H), 3.48 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.35 (td, *J*

= 4.8, 1.7 Hz, 2H), 2.13 (s, 3H), 1.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7, 169.3, 169.0, 160.1, 138.3, 138.1, 137.5, 133.0, 132.2, 130.7, 129.3, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 126.9, 126.3, 125.5, 103.9, 98.4, 83.9, 81.5, 75.5, 75.4, 74.6, 74.5, 74.3, 74.2, 73.3, 72.3, 70.4, 70.0, 69.3, 69.2, 62.6, 52.6, 50.7, 20.9, 20.6. HRMS (ESI): calc. for $C_{50}H_{56}N_4O_{14}F_3$ (M+H): 993.3745; found: 993.3739.

Disaccharide 252. A 25 mL oven-dried Schlenk flask was charged with disaccharide **251** (291 mg, 0.67 mmol, 1 equiv.) and anhydrous methanol (7 mL). Sodium methoxide (18 mg, 0.34 mmol, 0.5 equiv.) was then added and stirred at 25 °C for 2 hr and monitored by TLC. The reaction mixture was neutralized with Amberlyst® 15 hydrogen form, filtered, and concentrated to a yellow oil. The yellow oil was carried forward without any further purification. A 25 mL round bottom flask was charged with the yellow oil, aqueous hydrochloric acid (2 N, 3.1 mL, 6.1 mmol, 9 equiv.), and acetone (6 mL). The reaction mixture was stirred at 25 °C for 1 hr then quenched with Et_3N (2 mL) and concentrated *in vacuo*. The crude product was dissolved in dichloromethane (100 mL) and washed with water (2 x 40 mL). The aqueous layer was back extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel flash chromatography (1/1 hexanes/ethyl acetate → ethyl acetate → 9/1 dichloromethane/methanol) to afford **252** (306 mg, 57% over two steps) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 – 7.19 (m, 15H), 5.25 (d, *J* = 3.6 Hz, 1H), 5.08 (dd, *J* = 10.5, 8.9 Hz, 1H), 4.93 (d, *J* = 10.9 Hz, 2H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.66 (d, *J* = 11.1 Hz, 1H), 4.57 (s, 2H), 4.52 (d, *J* = 7.5 Hz, 1H), 4.06 (t, *J* = 9.1 Hz, 1H), 3.98 (ddd, *J* = 10.9, 4.8, 3.4 Hz, 1H), 3.89 (d, *J* =

9.4 Hz, 1H), 3.80 – 3.70 (m, 5H), 3.68 – 3.60 (m, 4H), 3.58 (t, *J* = 5.1 Hz, 2H), 3.54 – 3.41 (m, 3H), 3.26 (td, *J* = 4.9, 1.8 Hz, 2H), 2.65 (dd, *J* = 10.5, 3.7 Hz, 1H), 1.97 (s, 3H), 1.23 (bs, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.8, 168.9, 138.1, 137.9, 128.5, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 127.6, 103.9, 100.1, 83.1, 81.6, 75.8, 75.8, 75.1, 74.8, 74.5, 74.4, 72.1, 70.4, 69.9, 69.2, 61.5, 55.1, 52.8, 50.7, 21.1. HRMS (ESI): calc. for $C_{40}H_{51}N_4O_{13}$ (M+H): 795.3453; found: 795.3461.

Disaccharide 253. A 25 mL oven-dried Schlenk flask was sequentially charged with disaccharide **252** (291 mg, 0.37 mmol, 1 equiv.), DMF (6 mL), $SO_3.Me_3N$ (2.04 g, 14.64 mmol, 40 equiv.), and Et_3N (1.04 mL, 7.4 mmol, 20 equiv.). The reaction mixture stirred at 50 °C for 3 d. The reaction progress was monitored by negative mode mass spectrometry. MeOH (6 mL) and Et_3N (2 mL) were added to the reaction mixture and stirred for 30 min. The reaction mixture was concentrated *in vacuo*. The residue was purified using C-18 reverse phase silica gel flash chromatography (0 → 80% acetonitrile/water with 0.1% NH_4OH) to afford **253** (330 mg, 92%) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz): δ = 7.62 – 7.06 (m, 15H), 5.54 (d, *J* = 3.5 Hz, 1H), 5.17 (dd, *J* = 10.9, 9.0 Hz, 2H), 4.97 (dd, *J* = 11.1, 9.0 Hz, 2H), 4.81 (dd, *J* = 11.0, 6.1 Hz, 4H), 4.67 (d, *J* = 7.5 Hz, 1H), 4.62 (dd, *J* = 11.2, 1.8 Hz, 2H), 4.33 (dd, *J* = 10.7, 2.1 Hz, 1H), 4.21 (dd, *J* = 10.7, 1.5 Hz, 1H), 4.16 – 4.06 (m, 2H), 4.00 – 3.92 (m, 1H), 3.86 – 3.75 (m, 5H), 3.72 (d, *J* = 7.5 Hz, 2H), 3.69 – 3.65 (m, 2H), 3.62 (t, *J* = 5.0 Hz, 2H), 3.46 (t, *J* = 7.9 Hz, 1H), 3.40 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.27 (td, *J* = 4.8, 1.9 Hz, 2H), 2.77 (s, 1H), 2.00 (s, 3H). ^{13}C NMR (CD_3OD, 125 MHz): δ = 170.2, 168.0, 137.1, 136.8, 136.7, 126.8, 126.4, 126.3, 126.2, 125.8, 125.6, 125.5, 101.9, 96.7, 80.0, 79.8, 74.6, 74.1, 73.0,

72.8, 72.5, 72.2, 71.3, 68.8, 68.5, 68.1, 67.3, 63.8, 55.4, 50.5, 48.8, 45.0, 42.8, 18.5. HRMS (ESI): calc. for $C_{40}H_{49}N_4O_{19}S_2$ (M+H): 953.2432; found: 953.2427.

GlcN-GlcA Monomer 254. A 10 mL Schlenk flask was charged with linker **234** (22 mg, 0.055 mmol, 1.3 equiv.), **253** (40 mg, 0.42, 1.0 equiv.) and DMF (400 μL). DBU (4.2 μL, 0.042 mmol, 1.0 equiv.) and copper iodide (4.0 mg, 0.021 mmol, 0.5 equiv.) were then sequentially added to the solution. The resulting mixture was stirred overnight at 50 °C. The solution was filtered, concentrated *in vacuo* and purified by C-18 reverse phase flash chromatography (0 → 80% acetonitrile in water) to yield the monomer (GlcN-GlcA) **254** (34.1 mg, 60%). ^{1}H NMR (CD_3OD, 500 MHz): δ = 7.98 (s, 0.5H), 7.81 (s, 0.5H), 7.36 – 7.20 (m, 15H), 6.48 – 6.45 (m, 2H), 5.55 (bs, 1H), 5.35 – 5.32 (m, 2H), 5.20 (dd, *J* = 15, 10 Hz, 1H), 5.04 (s, 1H), 4.97 (t, *J* = 10 Hz, 1H), 4.91 – 4.77 (m, 19H), 4.68 – 4.54 (m, 5H), 4.50 (t, *J* = 5 Hz, 1H), 4.44 (dd, *J* = 10, 5 Hz, 1H), 4.35 – 4.33 (m, 1H), 4.23 (d, *J* = 10 Hz, 1H), 4.17 (t, *J* = 10 Hz, 1H), 4.14 – 4.10 (m, 1H), 3.93 – 3.86 (m, 3H), 3.82 (t, *J* = 5 Hz, 1H), 3.79 (s, 3H), 3.76 – 3.72 (m, 3H), 3.66 (s, 1.5H), 3.65 (s, 1.5H), 3.47 – 3.42 (m, 2H), 3.77 (s, 7H), 3.33 (s, 5H), 3.18 – 3.08 (m, 1H), 2.79 (t, *J* = 10 Hz, 1H), 2.68 – 2.60 (m, 4H), 2.53 (t, *J* = 7 Hz, 1H), 2.02 (s, 3H), 1.63 – 1.50 (m, 4H), 1.31 – 1.22 (s, 3H). ^{13}C NMR (CD_3OD, 125 MHz): δ = 173.8, 173.8, 173.0, 173.0, 172.4, 172.3, 171.8, 169.5, 138.6, 138.5, 138.4, 138.2, 138.2, 136.7, 136.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.3, 127.2, 127.2, 127.0, 127.0, 124.3, 123.8, 103.4, 103.2, 98.3, 98.2, 81.4, 81.3, 81.2, 81.2, 80.5, 80.5, 80.4, 79.7, 78.7, 76.2, 76.1, 75.7, 75.7, 74.6, 74.5, 74.4, 74.0, 73.9, 73.6, 73.5, 72.9, 70.3, 70.0, 68.9, 68.8, 65.3, 56.9, 52.0, 50.1, 50.0, 49.6, 48.5, 45.7, 42.5, 41.6,

40.7, 39.3, 39.3, 28.7, 28.7, 28.0, 27.7, 27.5, 26.6, 26.4, 26.3, 26.3, 26.3, 23.6, 20.0. HRMS (ESI): calc. for $C_{61}H_{77}N_6O_{25}S_2$ (M+H): 1357.4380; found: 1357.4382.

Glycopolymer 255. An oven dried 10 mL Schlenk flask was charged with (GlcN-GlcA) **254** (20 mg, 0.0148 mmol, 1.0 equiv.), Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)bis(3-bromopyridine)ruthenium(II) (3.3 mg, 0.0037 mmol, 0.25 equiv.), anhydrous degassed 2,2,2-trifluoroethanol (99 μL), and anhydrous degassed dichloroethane (493 μL). The resulting solution was stirred at 50 °C for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated to a brown oil. The crude oil was dissolved in a minimal amount of methanol and precipitated with an excess of diethyl ether. The solid was filtered and then re-dissolved in methanol. This process was repeated 2 more times to yield the protected polymer as a brown solid **255P** (19.6 mg, 98%). The protected polymers were injected onto a Waters Styragel HR 4 size exclusion column with 0.2 M LiBr in DMF as the eluent. Absolute polymer molecular weight (M_n) and polydispersity (PDI) measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^{1}H NMR (CD_3OD, 500 MHz): δ = 7.96 – 7.27 (m, 16H), 5.95 (bs, 1H), 5.54 (s, 1H), 5.17 (d, *J* = 11 Hz, 1H), 4.96 (s, 1H), 5.54 (bs, 1H), 4.63 – 4.47 (m, 5H), 4.33 (d, *J* = 8.5 Hz, 1H), 4.20 – 4.09 (m, 2H), 3.77 (s, 6H), 3.62 (s, 3H), 3.42 (d, *J* = 7.5 Hz, 1H), 2.60 (bs, 2H), 2.00 (s, 3H), 1.57 (bs, 3H), 1.30 – 1.16 (m, 3H). A 100 mL round bottom flask was charged with the protected glycopolymer of **255P** (19 mg), tetrahydrofuran (5.13 mL), water (19.4 mL), and lithium hydroxide (616 μL, 0.25 M in H_2O). The reaction mixture was stirred for 5 h at room temperature. The reaction mixture was lyophilized to a yield the partially deprotected

polymer **255PP** as a brown solid (14.9 mg, 83%). The partially deprotected polymer was dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water, lyophilized and carried forward to the next step. ^{1}H NMR (D_2O, 500 MHz): δ = 7.61 (bs, 1H), 7.40 – 7.08 (m, 15H), 5.81 (bs, 1H), 5.47 (bs, 1H), 4.44 – 4.31 (m, 10H), 4.11 (bs, 3H), 3.84 – 3.65 (m, 11H), 3.55 (bs, 4H), 3.36 (bs, 2H), 3.23 (bs, 3H), 3.02 (bs, 4H), 2.41 (bs, 3H), 1.29 (bs, 4H), 0.98 (bs, 2H). A 20 mL scintillation vial was charged with the partially deprotected polymer **255PP** (14.9 mg), Pearlman's catalyst (20 mol % $Pd(OH)_2$ on carbon, 89 mg, 6x the weight of the polymer), EtOH (0.5 mL), and 80 mM pH 7.2 aqueous phosphate buffer (0.5 mL). The unsealed scintillation vial was placed in a stainless steel high pressure reactor which was purged with hydrogen three times. The reactor was filled with hydrogen (150 psi) and stirred for 48 h at room temperature. The reaction mixture was filtered through a 0.2 μm PES membrane and lyophilized. The deprotected polymer was dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water. The aqueous solution was removed from the dialysis cassette and lyophilized to give **255** as a white solid (3 mg, 25%). ^{1}H NMR (D_2O, 500 MHz): δ = 5.57 (bs, 1H), 4.40 (d, *J* = 5.0 Hz, 4H), 4.27 (d, *J* = 10.0 Hz, 3H), 4.08 (d, *J* = 10.0 Hz, 2H), 4.09 – 4.01 (m, 3H), 3.89 (bs, 2H), 3.77 – 3.65 (m, 11H), 3.62 (bs, 7H), 3.51 – 3.45 (m, 5H), 3.38 – 3.27 (m, 5H), 3.22 – 3.18 (m, 4H), 2.37 (bs, 1H), 1.23 – 1.16 (m, 6H).

Glycopolymer 256. An oven dried 10 mL Schlenk flask was charged with (GlcN-GlcA) **254** (20 mg, 0.0148 mmol, 1.0 equiv.), Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)bis(3-bromopyridine)ruthenium(II) (2.2 mg, 0.0025 mmol, 0.17 equiv.), anhydrous degassed 2,2,2-trifluoroethanol (99 μL), and anhydrous

degassed dichloroethane (493 μL). The resulting solution was stirred at 50 °C for 1 h. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated to a brown oil. The crude oil was dissolved in a minimal amount of methanol and precipitated with an excess of diethyl ether. The solid was filtered and then re-dissolved in methanol. This process was repeated 2 more times to yield the protected polymer as a brown solid **256P** (19.0 mg, 95%). The protected polymers were injected onto a Waters Styragel HR 4 size exclusion column with 0.2 M LiBr in DMF as the eluent. Absolute polymer molecular weight (M_n) and polydispersity (PDI) measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^{1}H NMR (CD_3OD, 500 MHz): δ = 7.96 – 7.27 (m, 16H), 5.95 (bs, 1H), 5.54 (s, 1H), 5.17 (d, *J* = 11 Hz, 1H), 4.96 (s, 1H), 5.54 (bs, 1H), 4.63 – 4.47 (m, 5H), 4.33 (d, *J* = 8.5 Hz, 1H), 4.20 – 4.09 (m, 2H), 3.77 (s, 6H), 3.62 (s, 3H), 3.42 (d, *J* = 7.5 Hz, 1H), 2.60 (bs, 2H), 2.00 (s, 3H), 1.57 (bs, 3H), 1.30 – 1.16 (m, 3H). A 100 mL round bottom flask was charged with the protected glycopolymer of **256P** (19 mg), tetrahydrofuran (4.6 mL), water (17.6 mL), and lithium hydroxide (557 μL, 0.25 M in H_2O). The reaction mixture was stirred for 5 h at room temperature. The reaction mixture was lyophilized to a yield the partially deprotected polymer **256PP** as a brown solid (17 mg, 95%). The partially deprotected polymer was dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water, lyophilized and carried forward to the next step. ^{1}H NMR (D_2O, 500 MHz): δ = 7.61 (bs, 1H), 7.40 – 7.08 (m, 15H), 5.81 (bs, 1H), 5.47 (bs, 1H), 4.44 – 4.31 (m, 10H), 4.11 (bs, 3H), 3.84 – 3.65 (m, 11H), 3.55 (bs, 4H), 3.36 (bs, 2H), 3.23 (bs, 3H), 3.02 (bs, 4H), 2.41 (bs, 3H), 1.29 (bs, 4H), 0.98 (bs, 2H). A 20 mL scintillation vial was charged with the partially deprotected polymer **256PP** (17 mg), Pearlman's catalyst (20 mol % $Pd(OH)_2$ on carbon,

89 mg, 6x the weight of the polymer), EtOH (0.5 mL), and 80 mM pH 7.2 aqueous phosphate buffer (0.5 mL). The unsealed scintillation vial was placed in a stainless steel high pressure reactor which was purged with hydrogen three times. The reactor was filled with hydrogen (150 psi) and stirred for 48 h at room temperature. The reaction mixture was filtered through a 0.2 μm PES membrane and lyophilized. The deprotected polymer was dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water. The aqueous solution was removed from the dialysis cassette and lyophilized to give **256** as a white solid (3 mg, 22%). ^{1}H NMR (D_2O, 500 MHz): δ = 5.57 (bs, 1H), 4.40 (d, *J* = 5.0 Hz, 4H), 4.27 (d, *J* = 10.0 Hz, 3H), 4.08 (d, *J* = 10.0 Hz, 2H), 4.09 – 4.01 (m, 3H), 3.89 (bs, 2H), 3.77 – 3.65 (m, 11H), 3.62 (bs, 7H), 3.51 – 3.45 (m, 5H), 3.38 – 3.27 (m, 5H), 3.22 – 3.18 (m, 4H), 2.37 (bs, 1H), 1.23 – 1.16 (m, 6H).

Glycopolymer 257. An oven dried 10 mL Schlenk flask was charged with (GlcN-GlcA) **254** (17 mg, 0.0125 mmol, 1.0 equiv.), Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)bis(3-bromopyridine)ruthenium(II) (1.1 mg, 0.00125 mmol, 0.10 equiv.), anhydrous degassed 2,2,2-trifluoroethanol (83 μL), and anhydrous degassed dichloroethane (416 μL). The resulting solution was stirred at 50 °C for 4 h as complete by crude ^{1}H NMR. The reaction mixture was quenched with ethyl vinyl ether (0.1 mL) and concentrated to a brown oil. The crude oil was dissolved in a minimal amount of methanol and precipitated with an excess of diethyl ether. The solid was filtered and then re-dissolved in methanol. This process was repeated 2 more times to yield the protected polymer as a brown solid **257P** (13.8 mg, 81%). The protected polymers were injected onto a Waters Styragel HR 4 size exclusion column with 0.2 M

LiBr in DMF as the eluent. Absolute polymer molecular weight (M_n) and polydispersity (PDI) measurements were determined using a Wyatt Dawn Heleos-II light scattering detector. ^{1}H NMR (CD_3OD, 500 MHz): δ = 7.96 – 7.27 (m, 16H), 5.95 (bs, 1H), 5.54 (s, 1H), 5.17 (d, *J* = 11 Hz, 1H), 4.96 (s, 1H), 5.54 (bs, 1H), 4.63 – 4.47 (m, 5H), 4.33 (d, *J* = 8.5 Hz, 1H), 4.20 – 4.09 (m, 2H), 3.77 (s, 6H), 3.62 (s, 3H), 3.42 (d, *J* = 7.5 Hz, 1H), 2.60 (bs, 2H), 2.00 (s, 3H), 1.57 (bs, 3H), 1.30 – 1.16 (m, 3H). A 100 mL round bottom flask was charged with the protected glycopolymer of **257P** (13.5 mg), tetrahydrofuran (3.3 mL), water (12.5 mL), and lithium hydroxide (396 μL, 0.25 M in H_2O). The reaction mixture was stirred for 5 h at room temperature. The reaction mixture was lyophilized to a yield the partially deprotected polymer **257PP** as a brown solid (10 mg, 78%). The partially deprotected polymer was dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water, lyophilized and carried forward to the next step. ^{1}H NMR (D_2O, 500 MHz): δ = 7.61 (bs, 1H), 7.40 – 7.08 (m, 15H), 5.81 (bs, 1H), 5.47 (bs, 1H), 4.44 – 4.31 (m, 10H), 4.11 (bs, 3H), 3.84 – 3.65 (m, 11H), 3.55 (bs, 4H), 3.36 (bs, 2H), 3.23 (bs, 3H), 3.02 (bs, 4H), 2.41 (bs, 3H), 1.29 (bs, 4H), 0.98 (bs, 2H). A 20 mL scintillation vial was charged with the partially deprotected polymer **257PP** (10 mg), Pearlman's catalyst (20 mol % $Pd(OH)_2$ on carbon, 60 mg, 6x the weight of the polymer), EtOH (0.5 mL), and 80 mM pH 7.2 aqueous phosphate buffer (0.5 mL). The unsealed scintillation vial was placed in a stainless steel high pressure reactor which was purged with hydrogen three times. The reactor was filled with hydrogen (150 psi) and stirred for 48 h at room temperature. The reaction mixture was filtered through a 0.2 μm PES membrane and lyophilized. The deprotected polymer was dialyzed using Slide-A-Lyzer® dialysis cassette against milli Q water. The aqueous solution was removed from

the dialysis cassette and lyophilized to give **257** as a white solid (2 mg, 25%). ^{1}H NMR (D_2O, 500 MHz): δ = 5.57 (bs, 1H), 4.40 (d, *J* = 5.0 Hz, 4H), 4.27 (d, *J* = 10.0 Hz, 3H), 4.08 (d, *J* = 10.0 Hz, 2H), 4.09 – 4.01 (m, 3H), 3.89 (bs, 2H), 3.77 – 3.65 (m, 11H), 3.62 (bs, 7H), 3.51 – 3.45 (m, 5H), 3.38 – 3.27 (m, 5H), 3.22 – 3.18 (m, 4H), 2.37 (bs, 1H), 1.23 – 1.16 (m, 6H).

APPENDIX

NMR SPECTRA

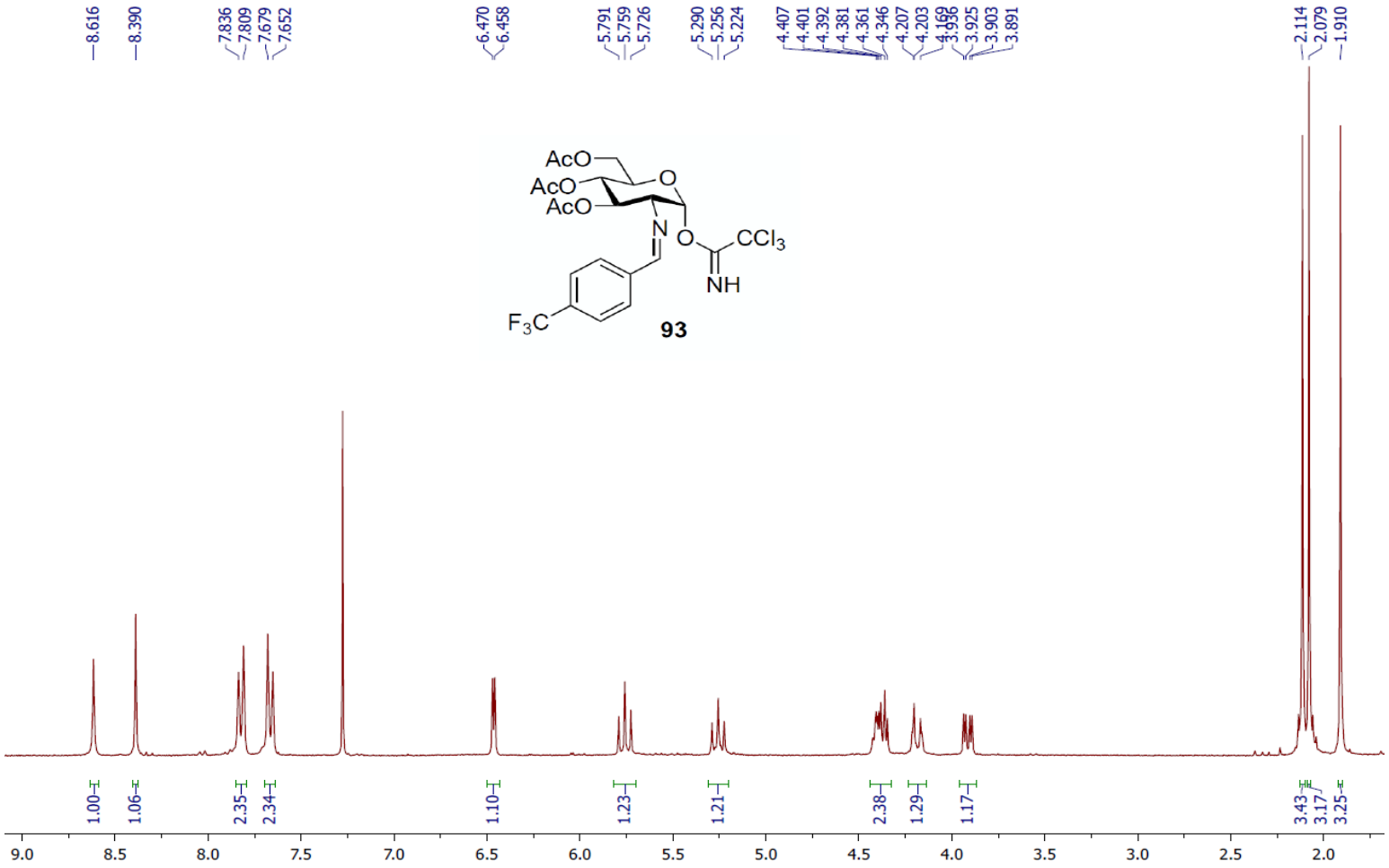


Figure A1. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trichloroimidate **93**

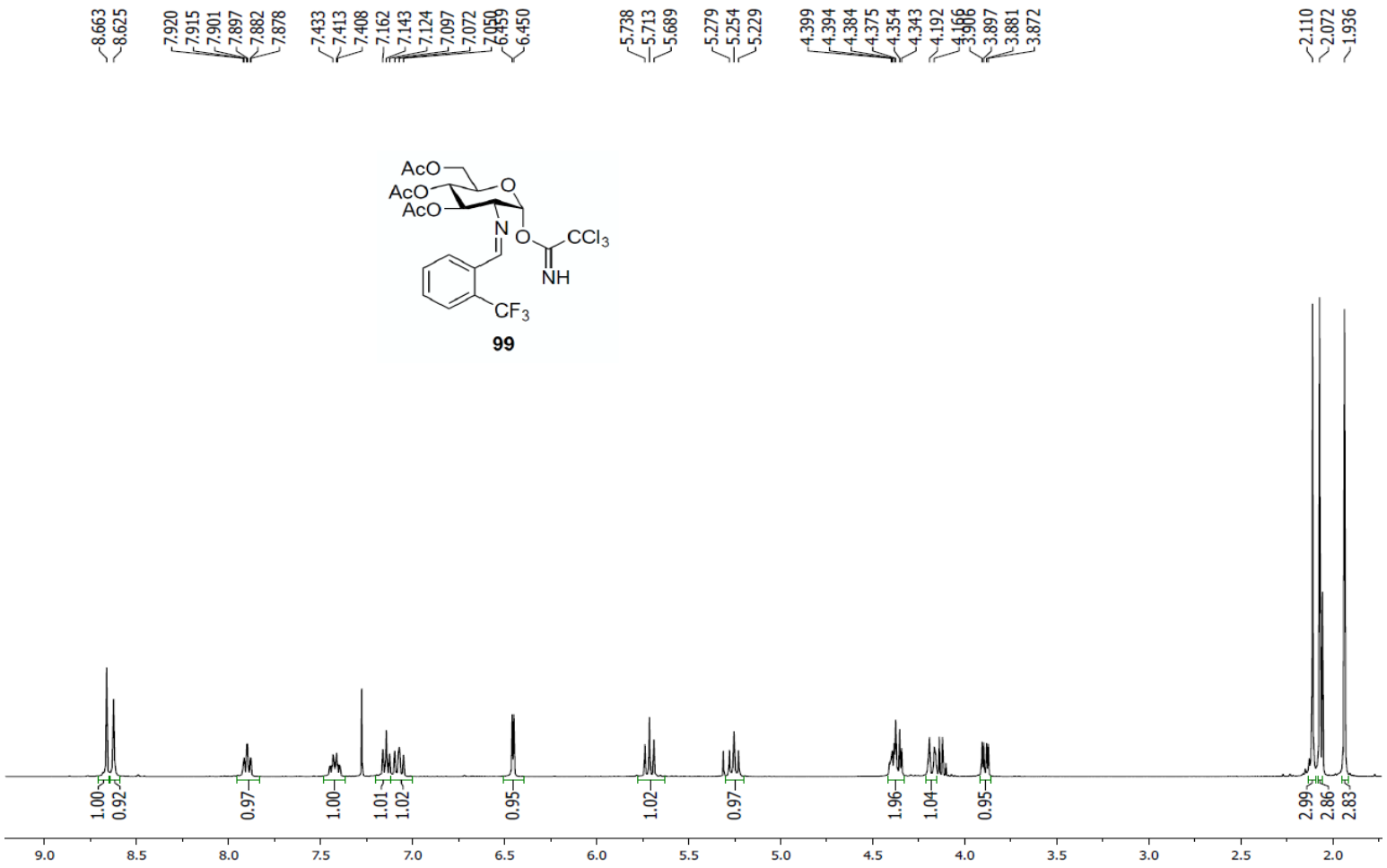


Figure A2. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trichloroimidate **99**

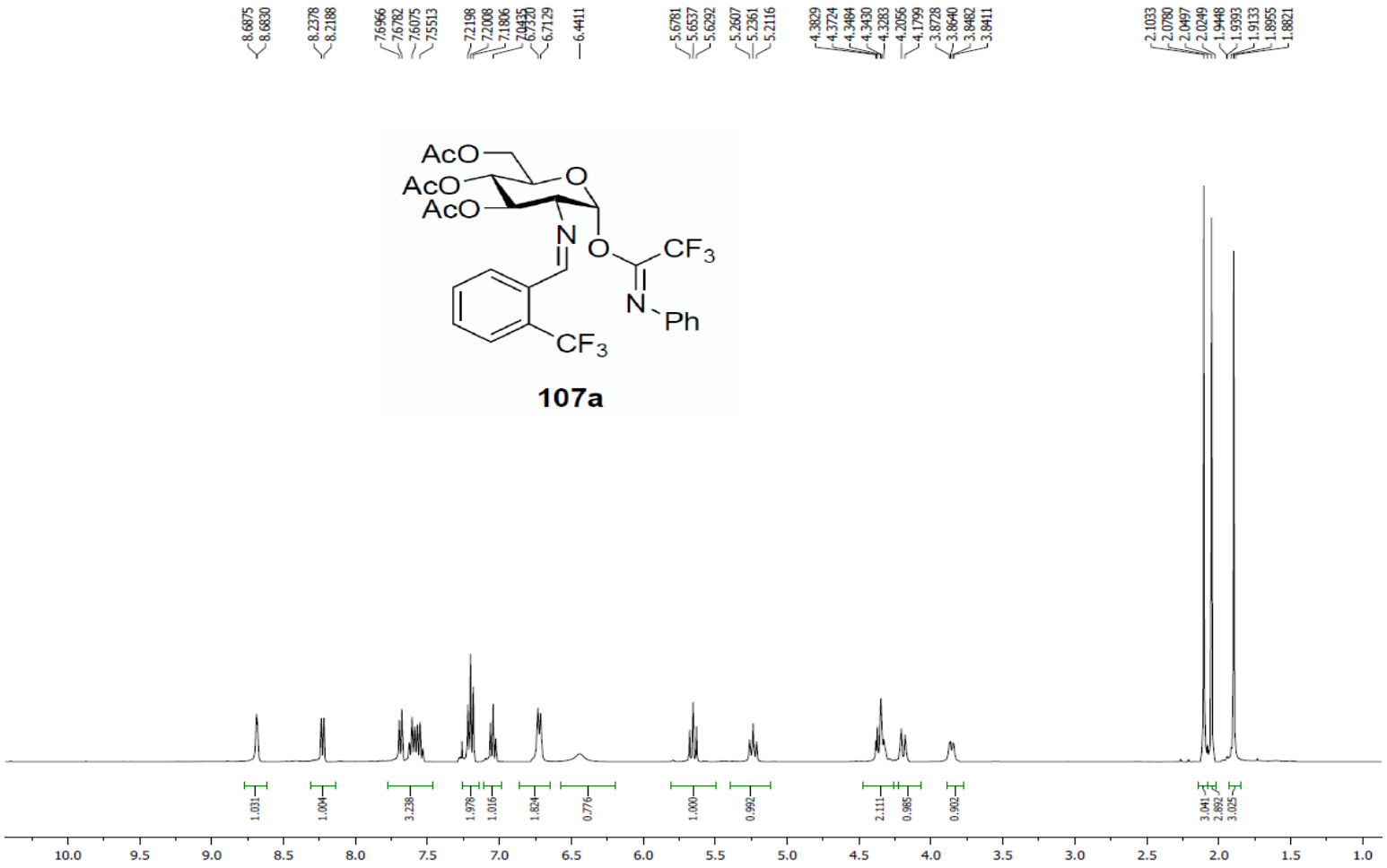


Figure A3. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **107a**

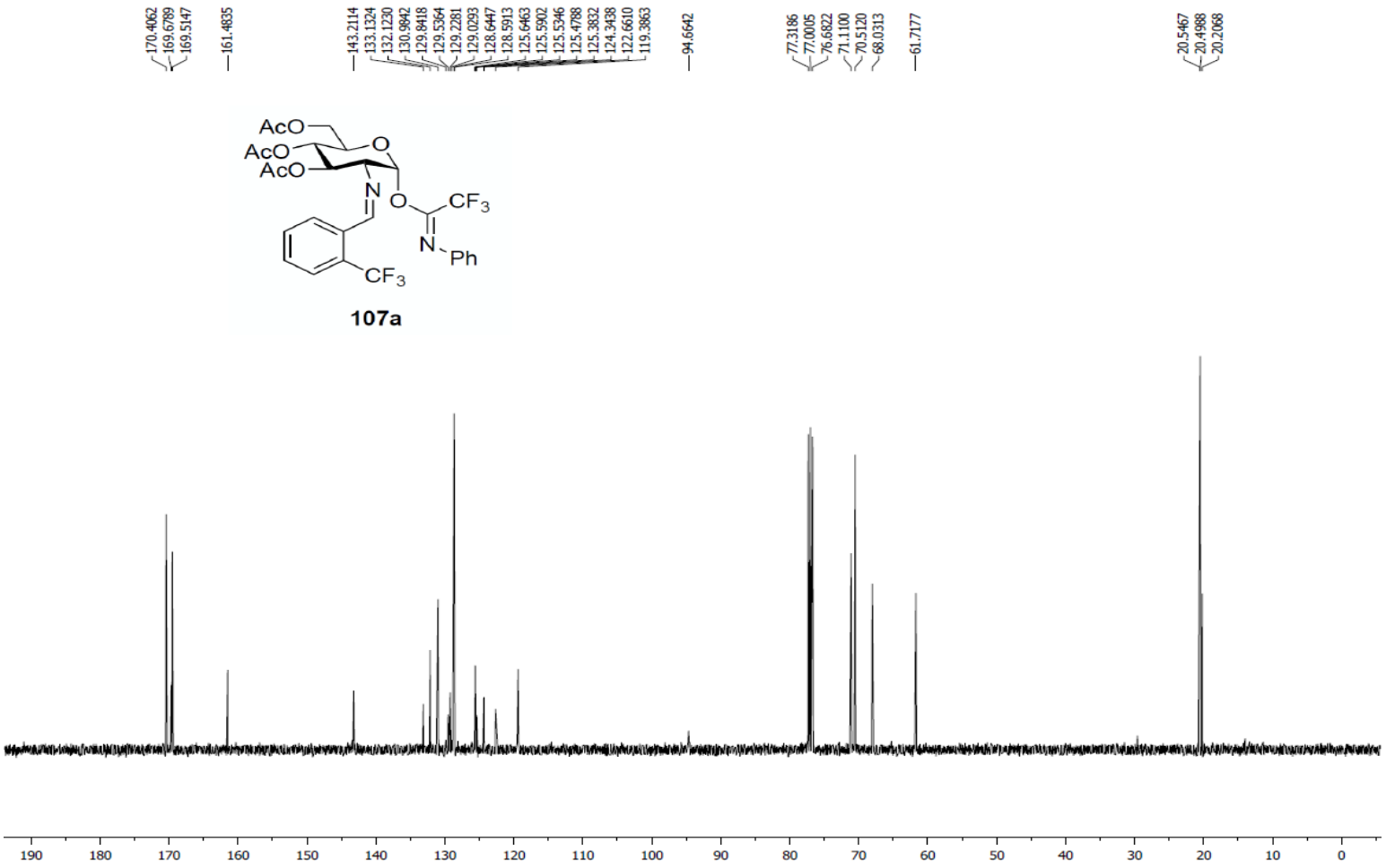


Figure A4. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **107a**

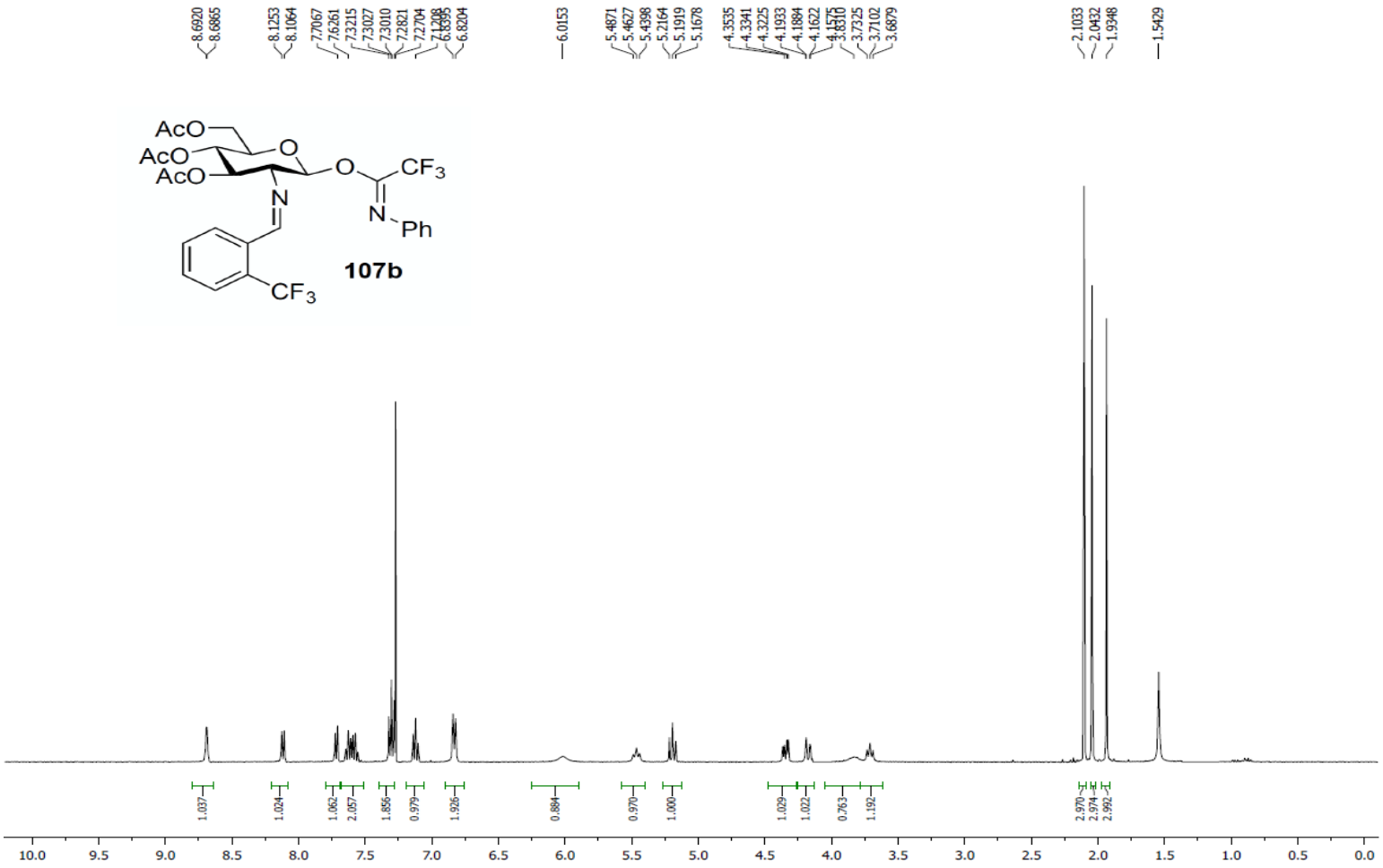


Figure A5. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **107b**

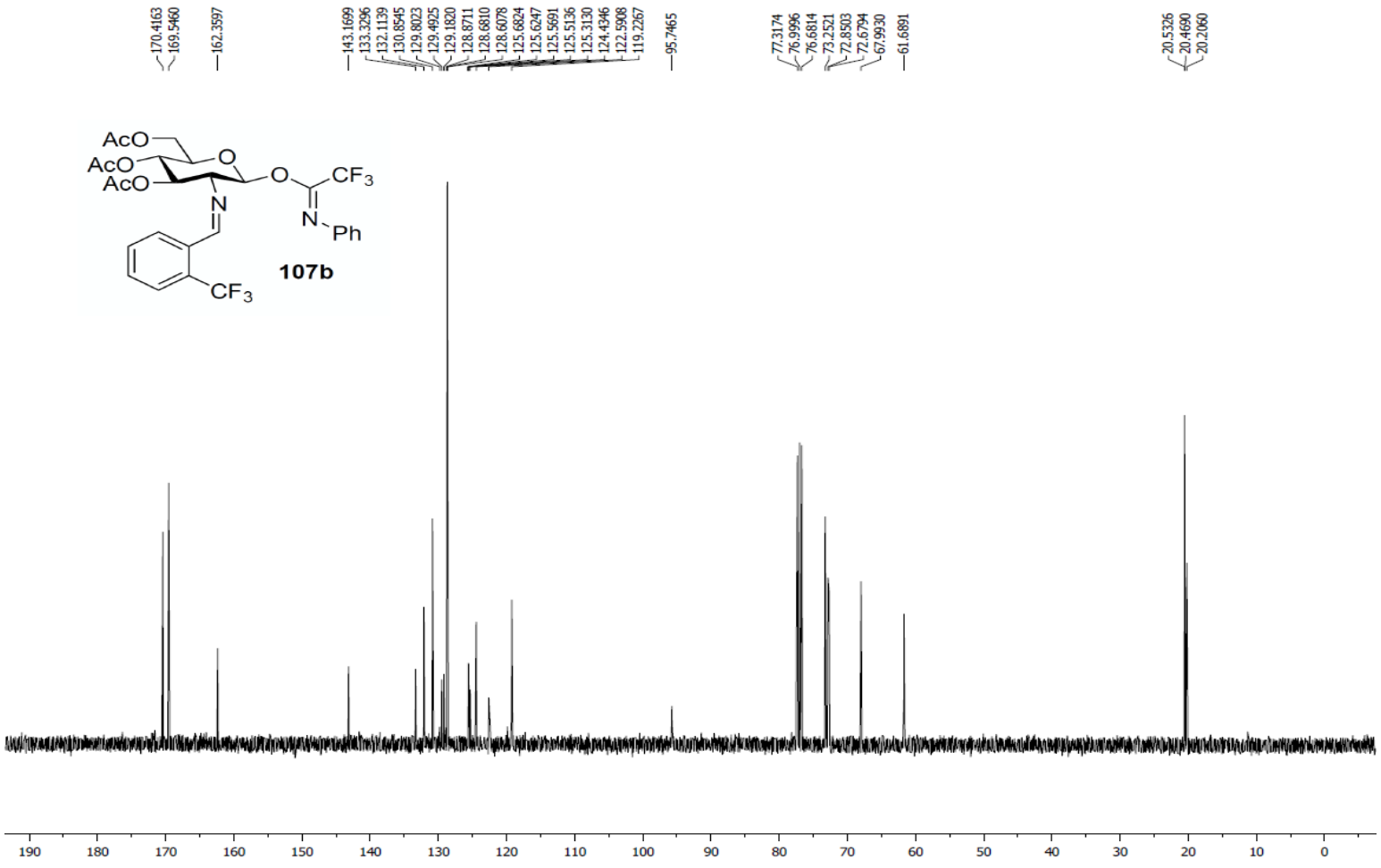


Figure A6. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **107b**

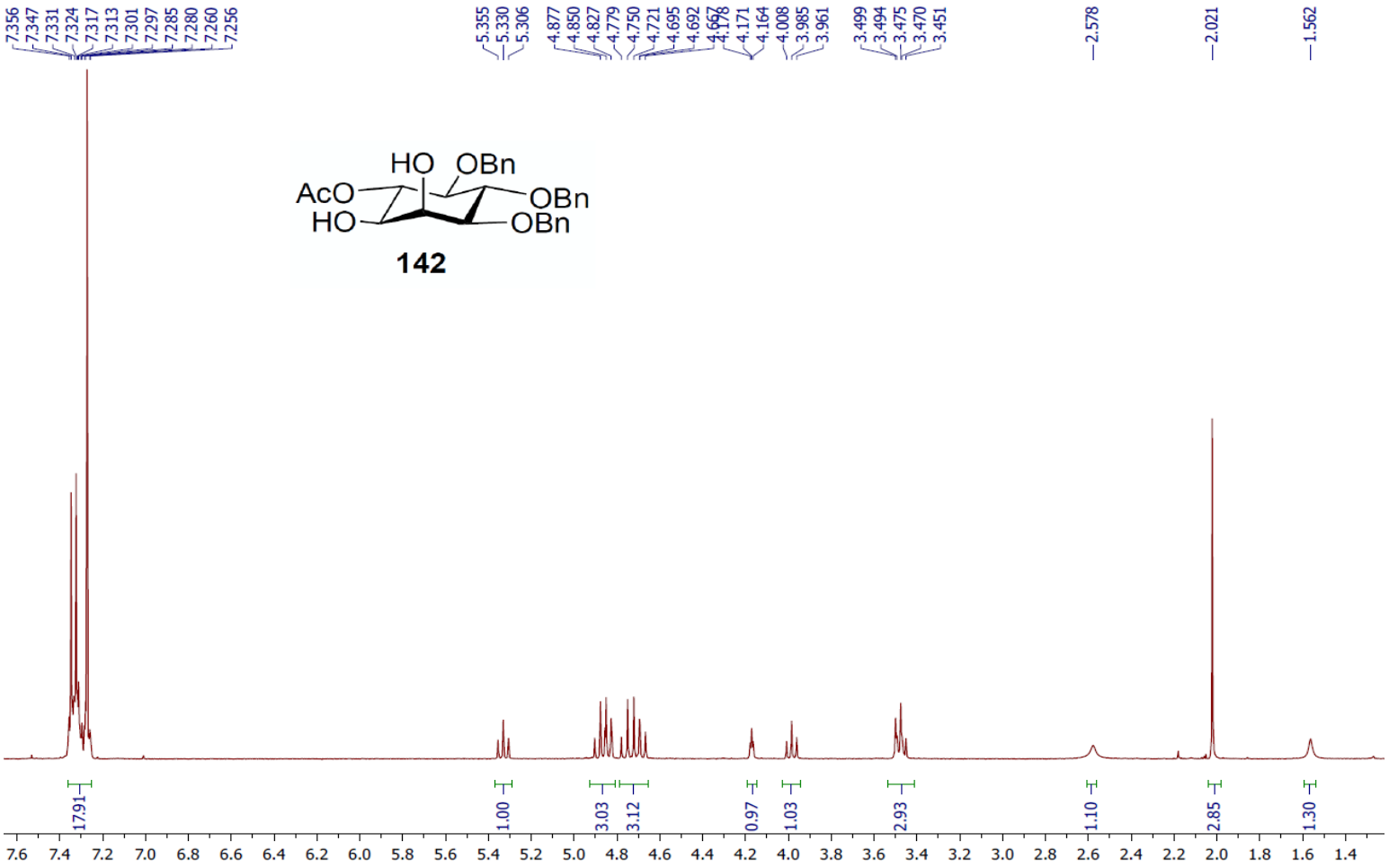


Figure A7. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **142**

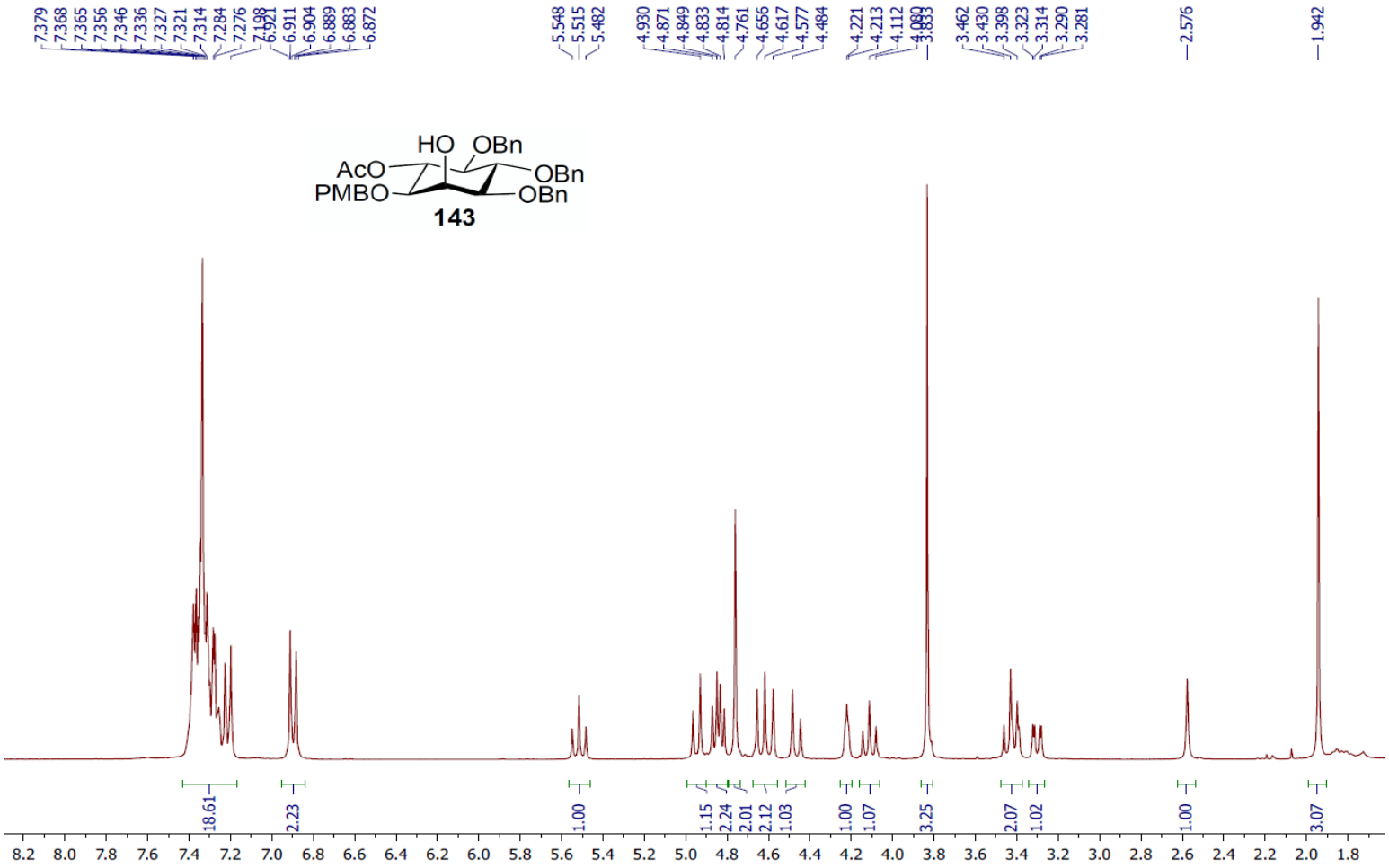


Figure A8. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **143**

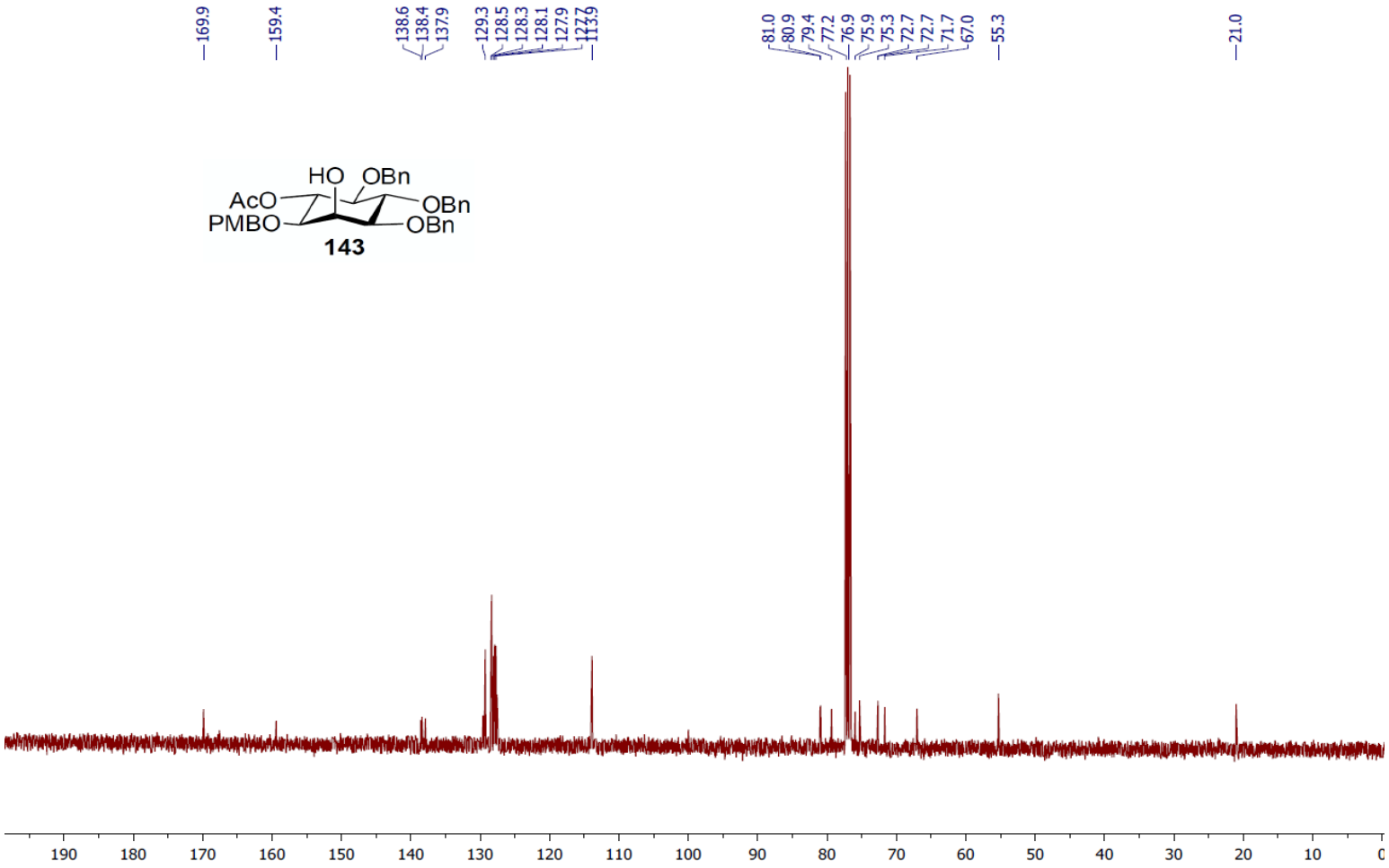


Figure A9. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Inositol **143**

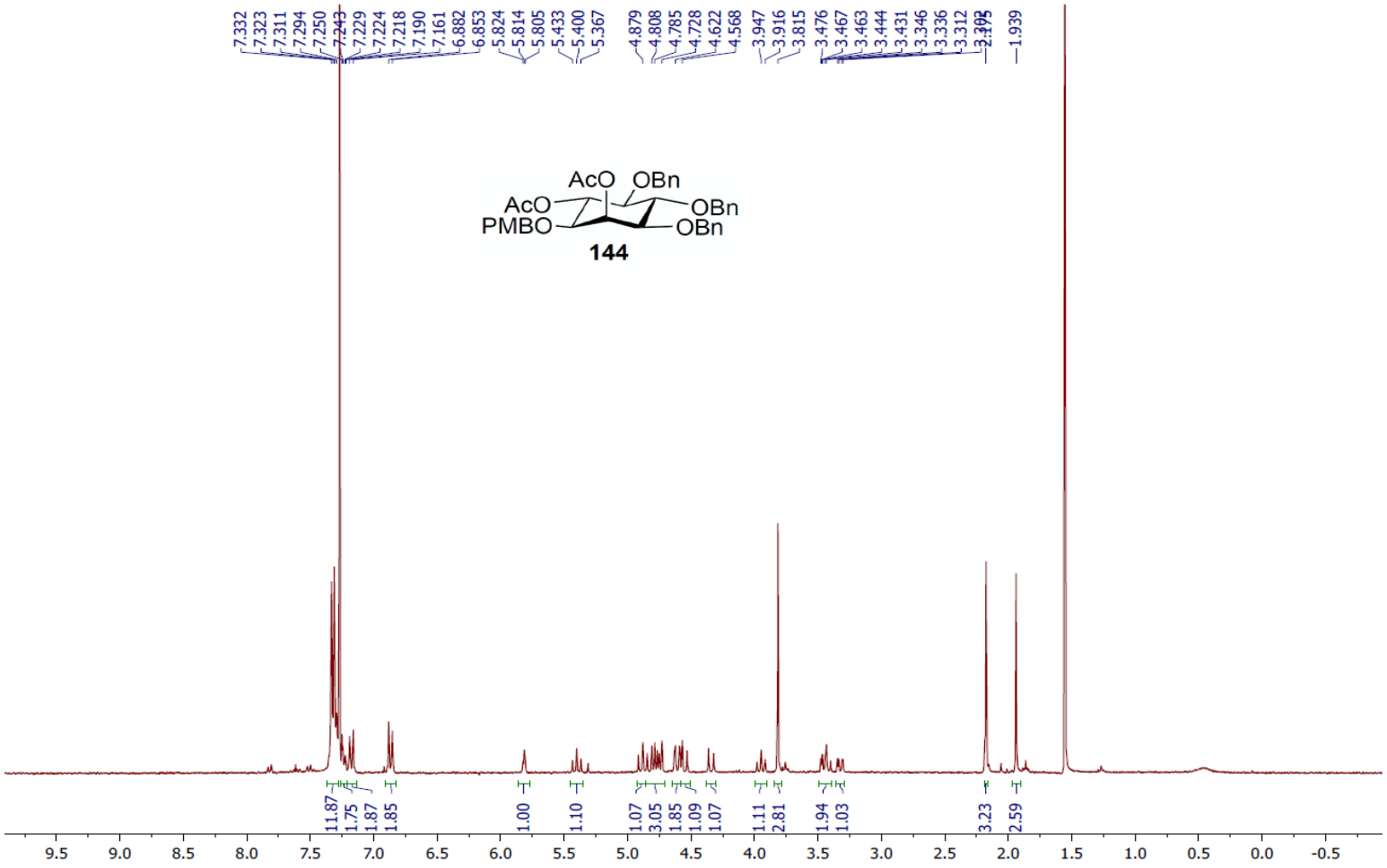


Figure A10. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **144**

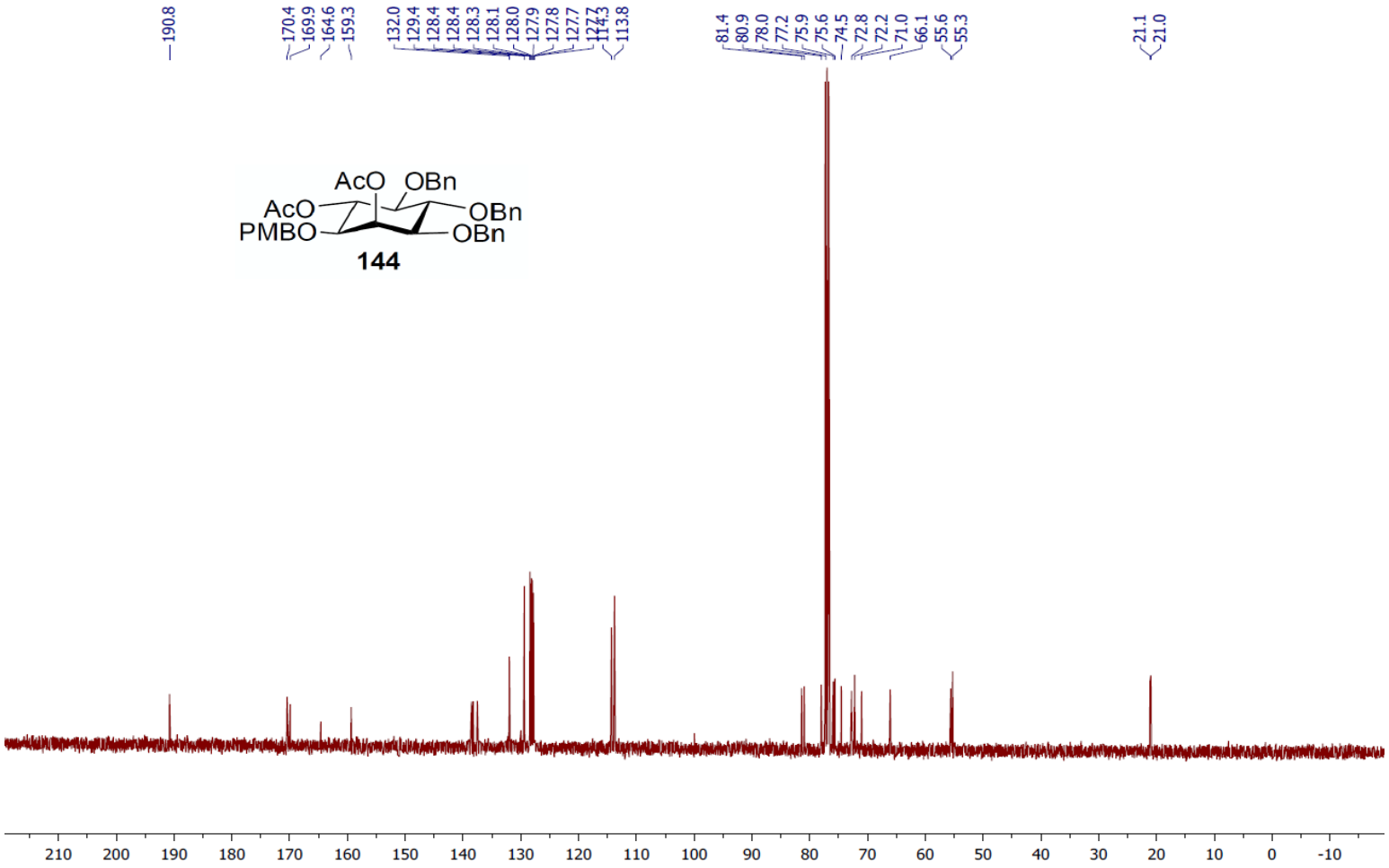


Figure A11. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Inositol **144**

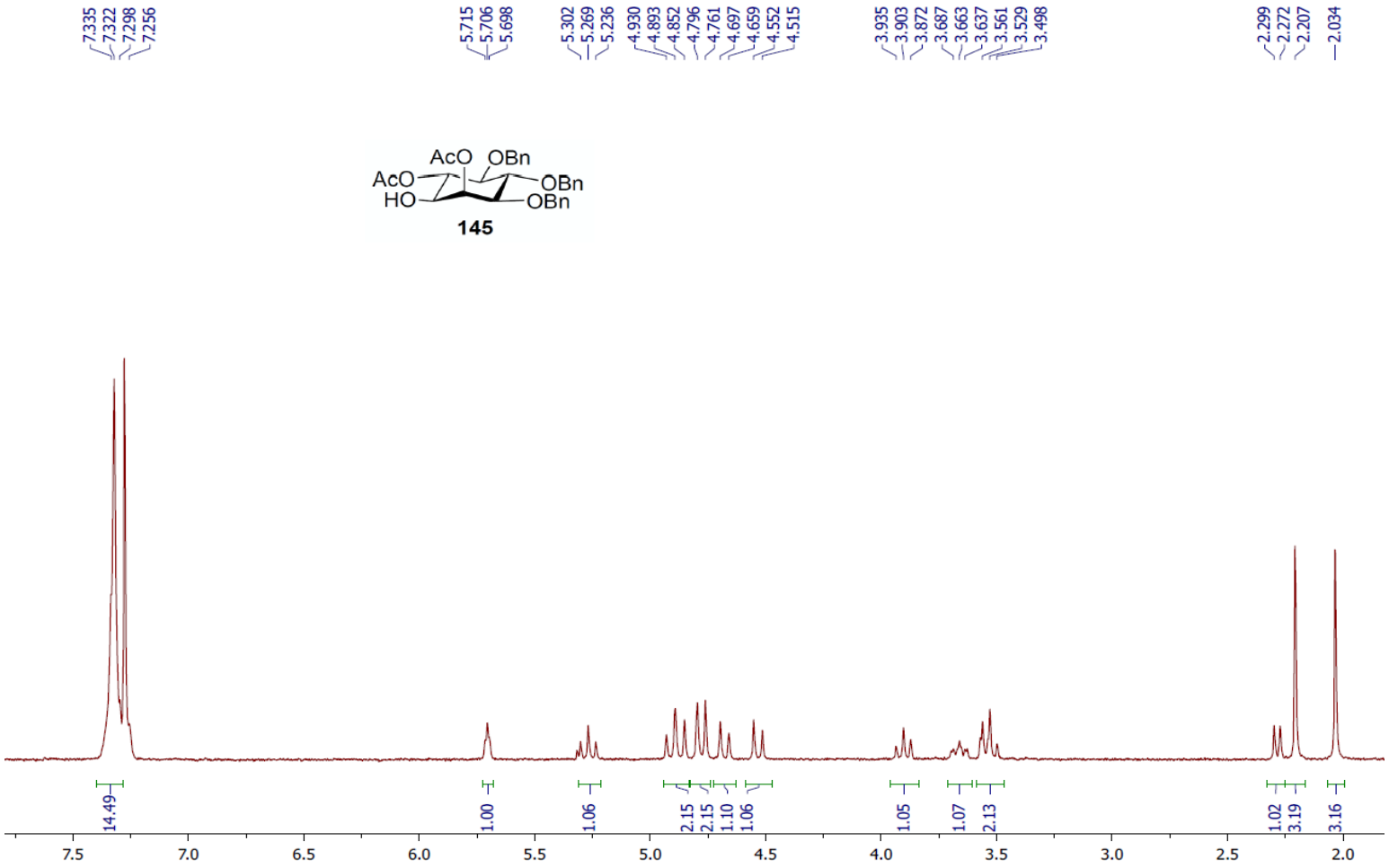


Figure A12. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **145**

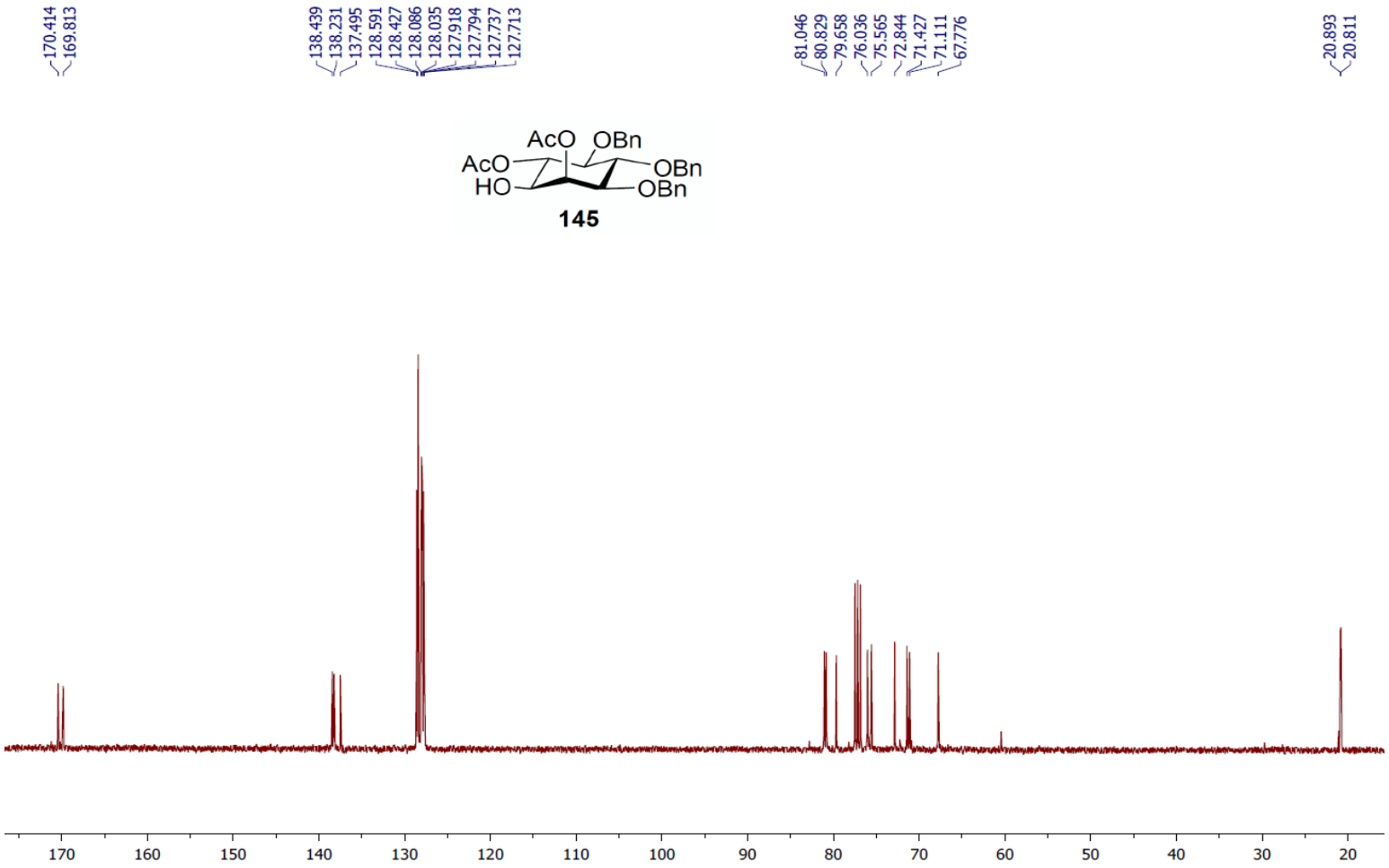


Figure A13. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Inositol **145**

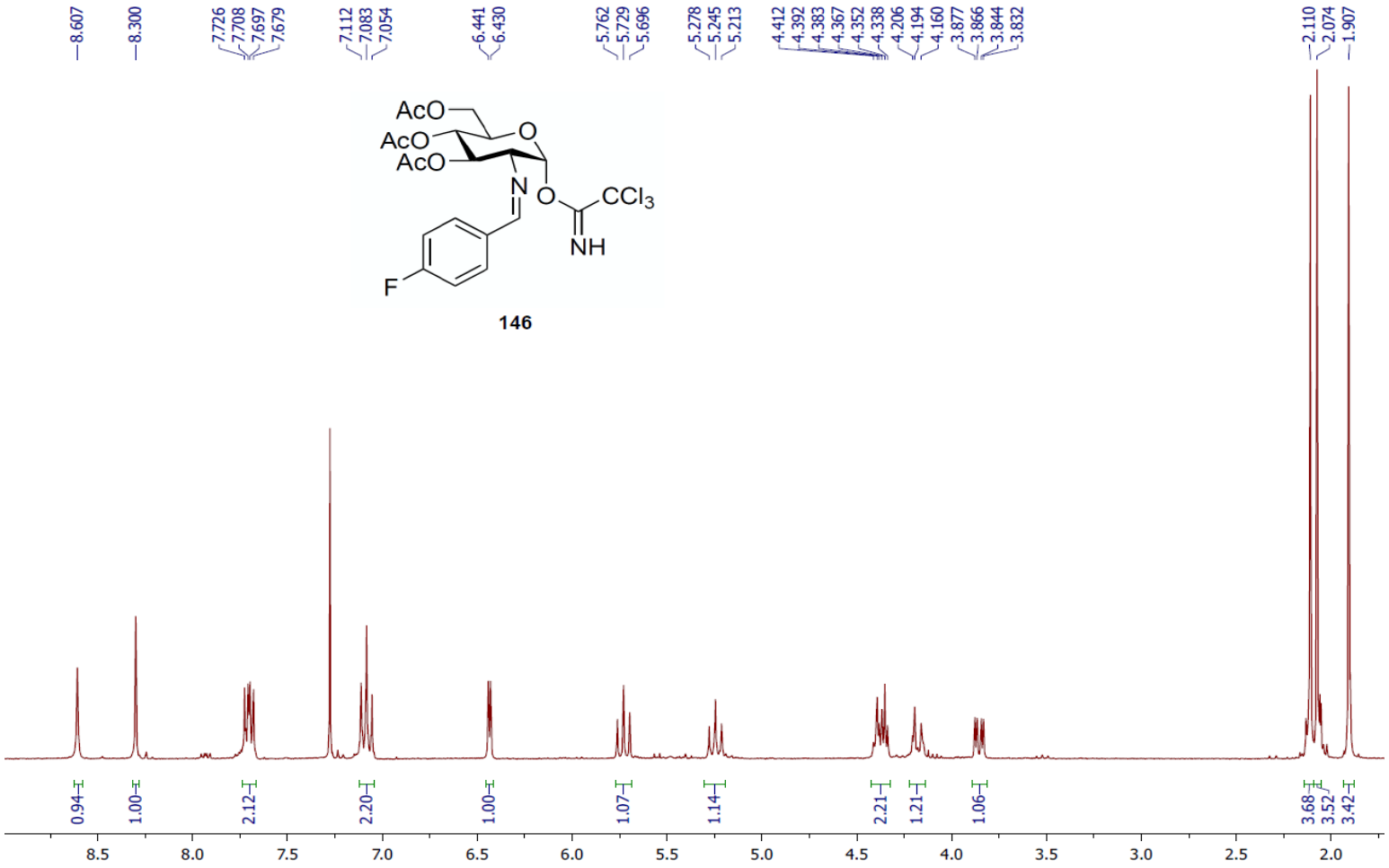


Figure A14. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **146**

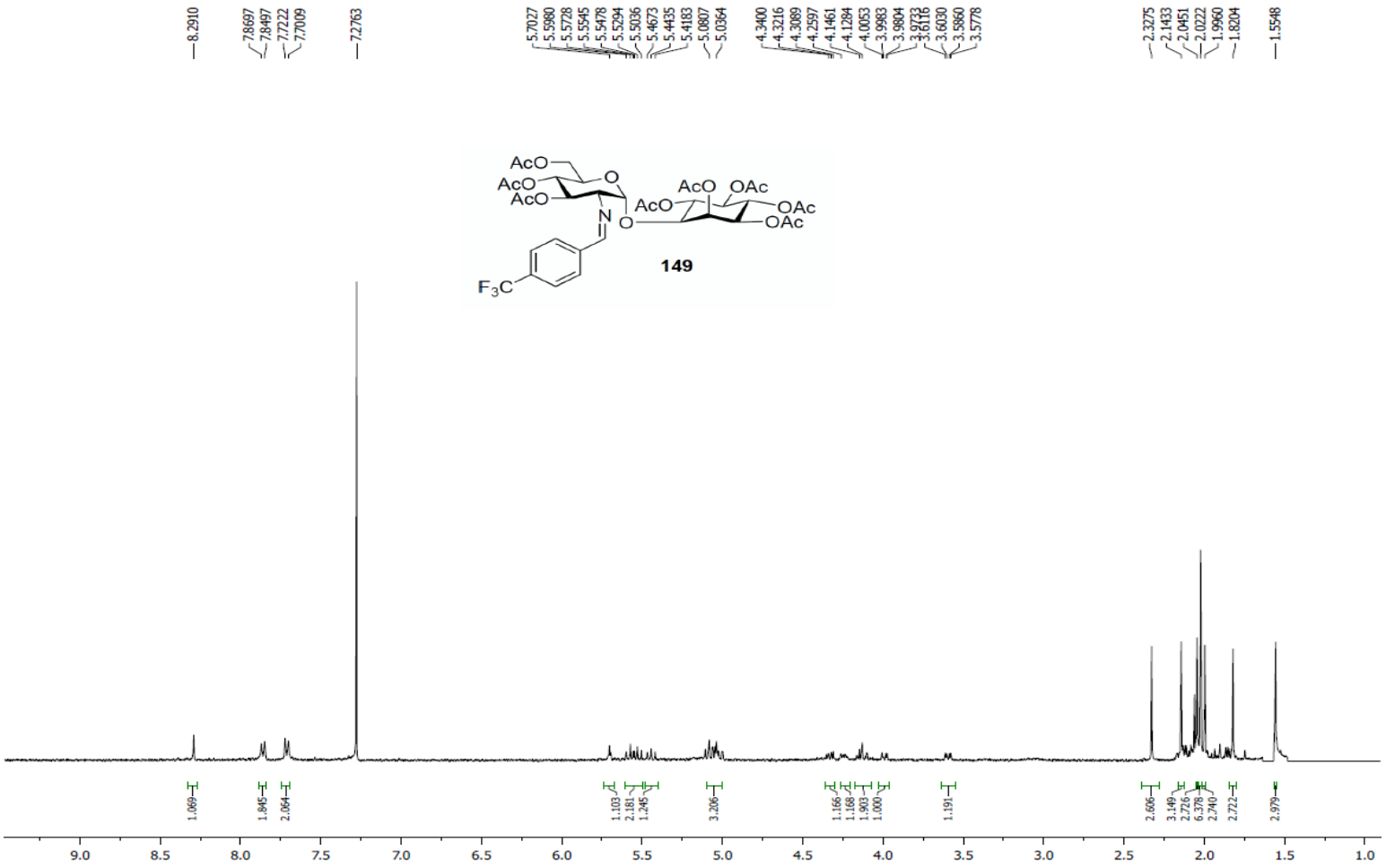


Figure A15. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **149**

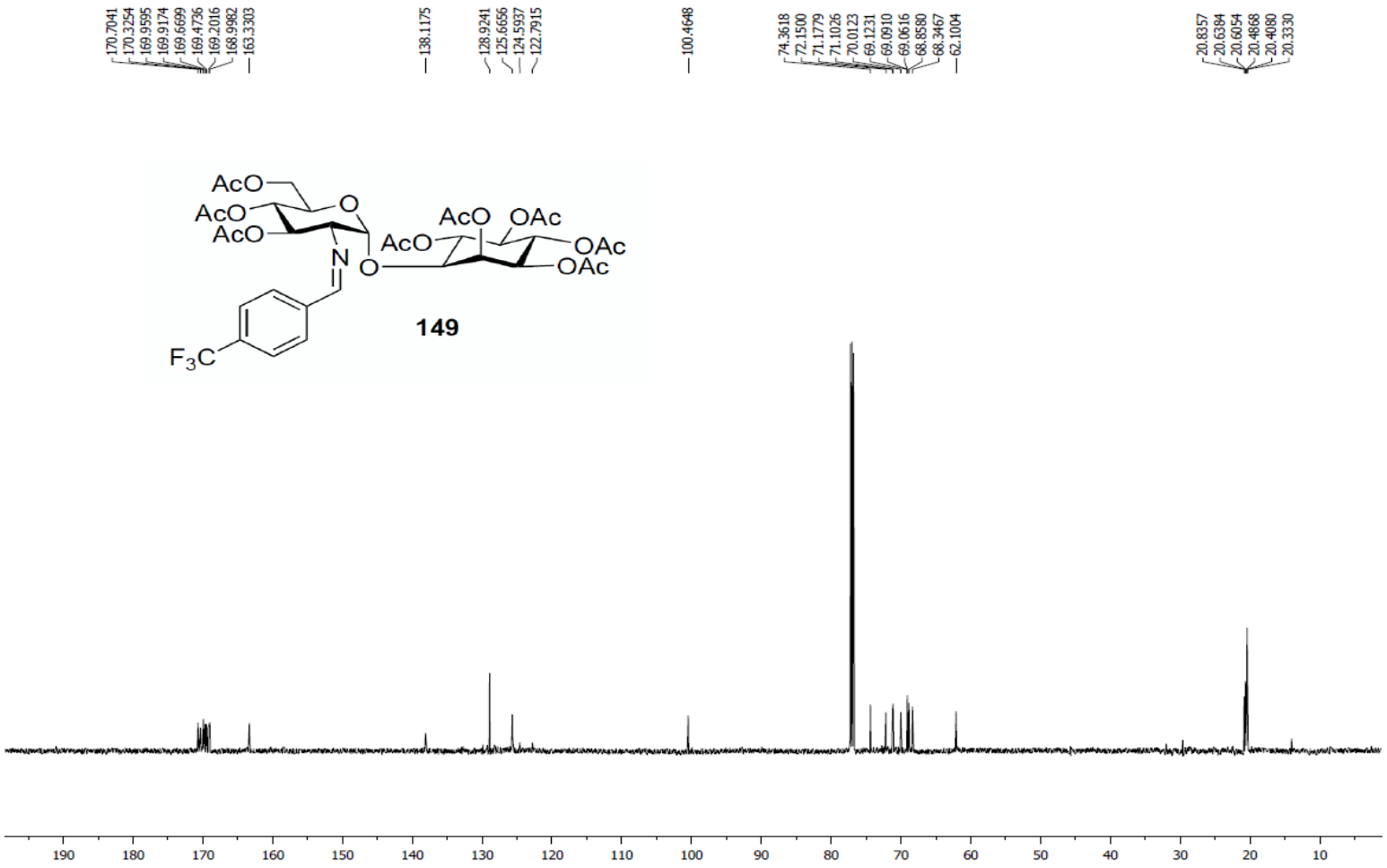


Figure A16. 150 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **149**

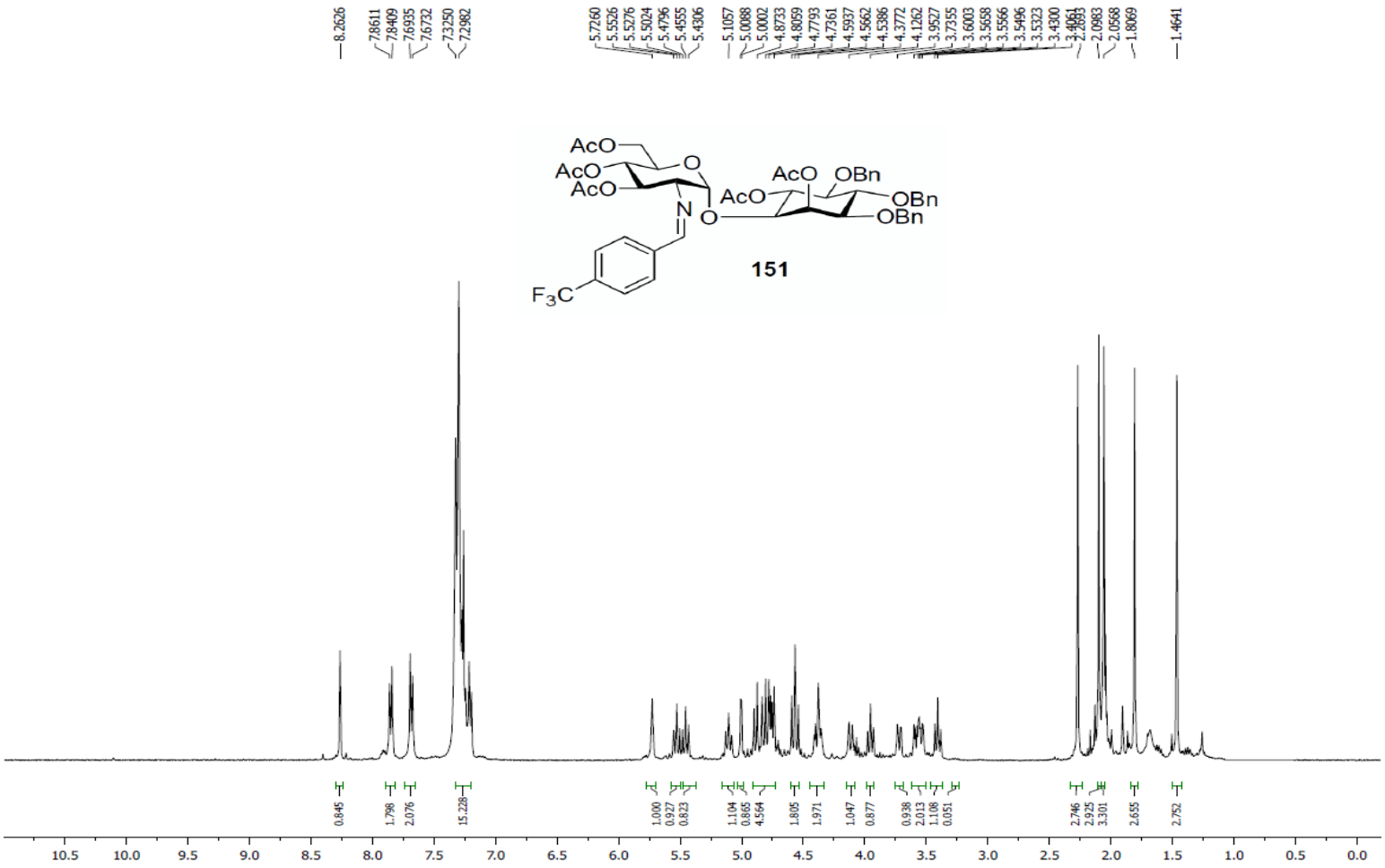


Figure A17. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **151**

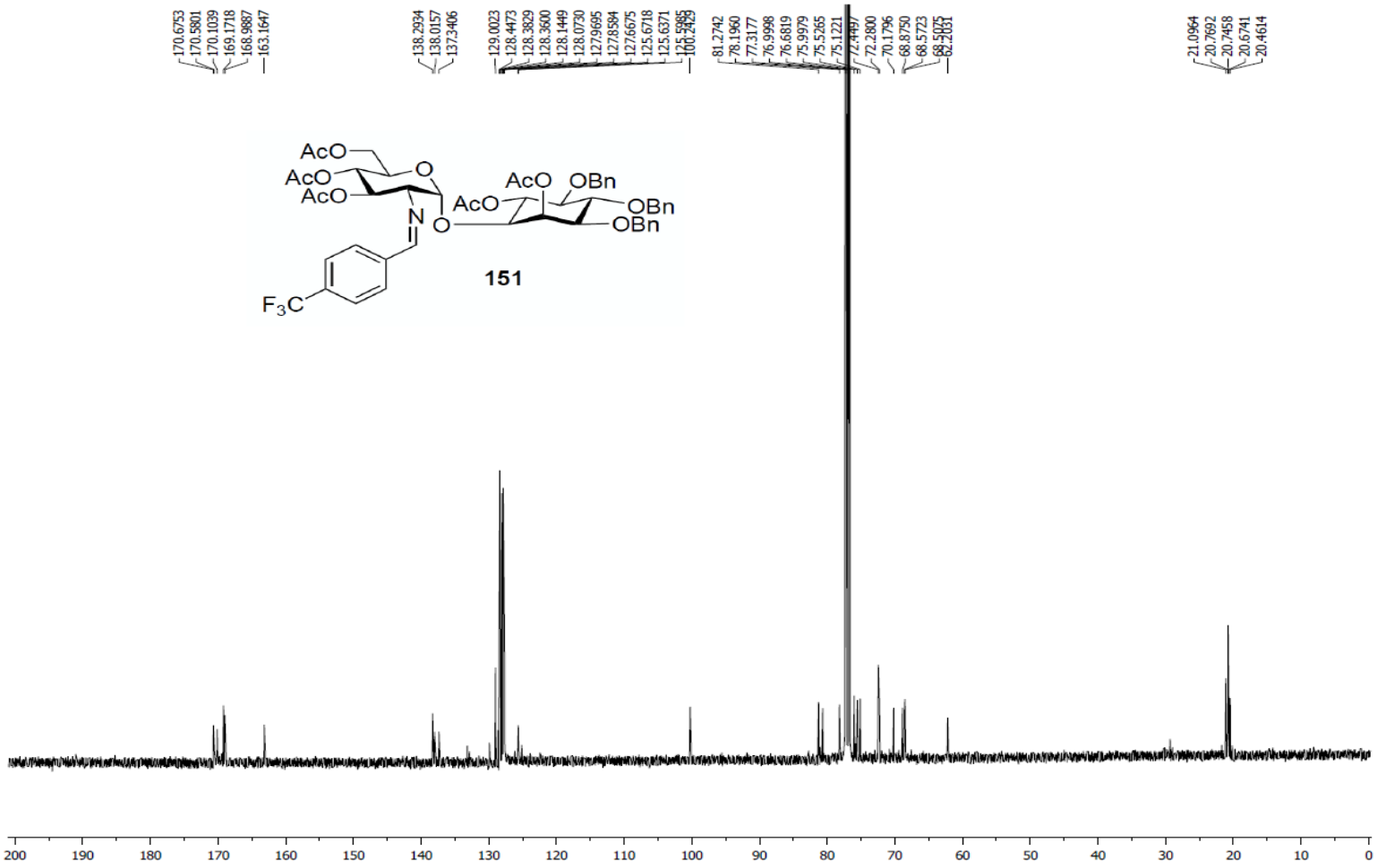


Figure A18. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **151**

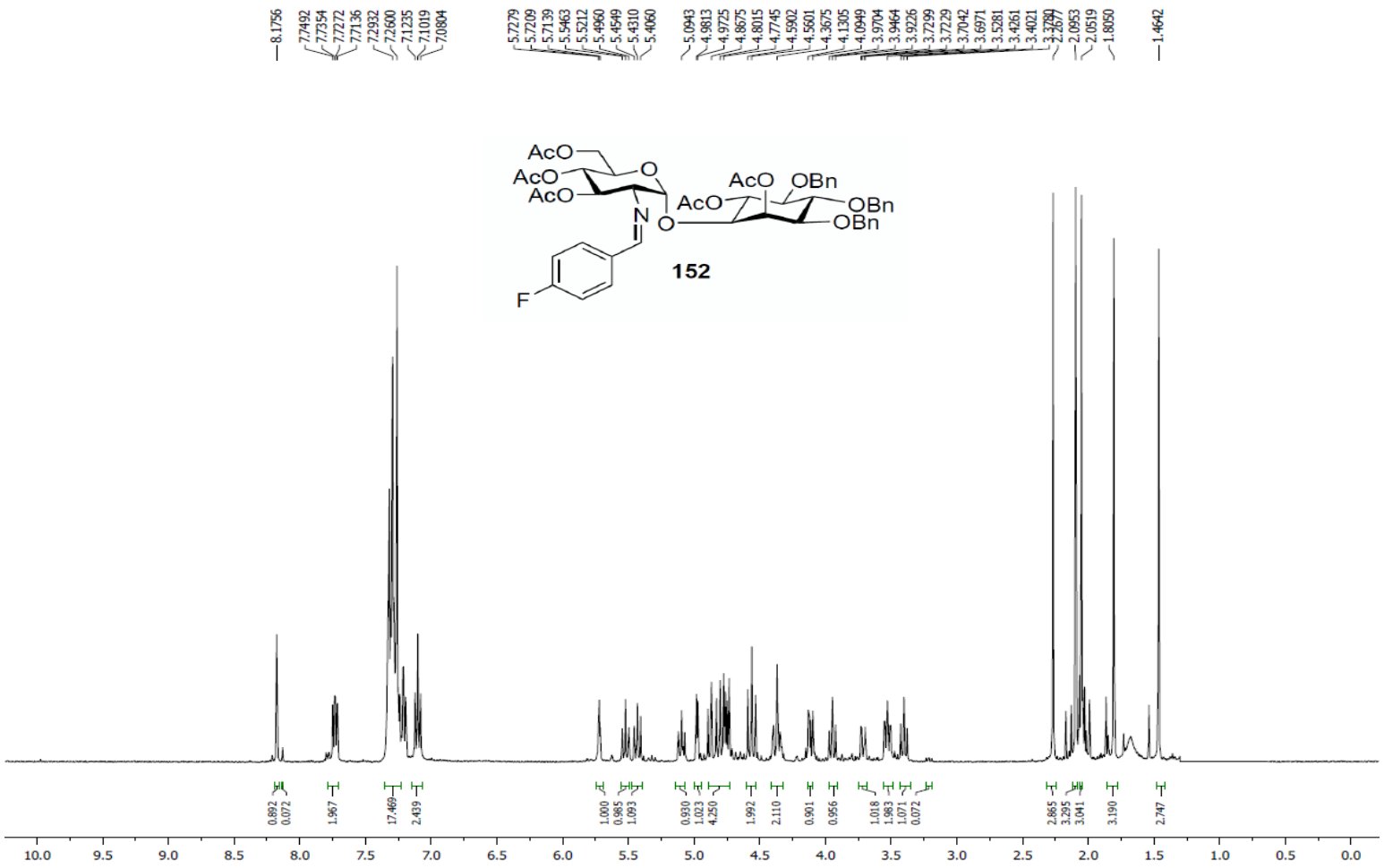


Figure A19. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **152**

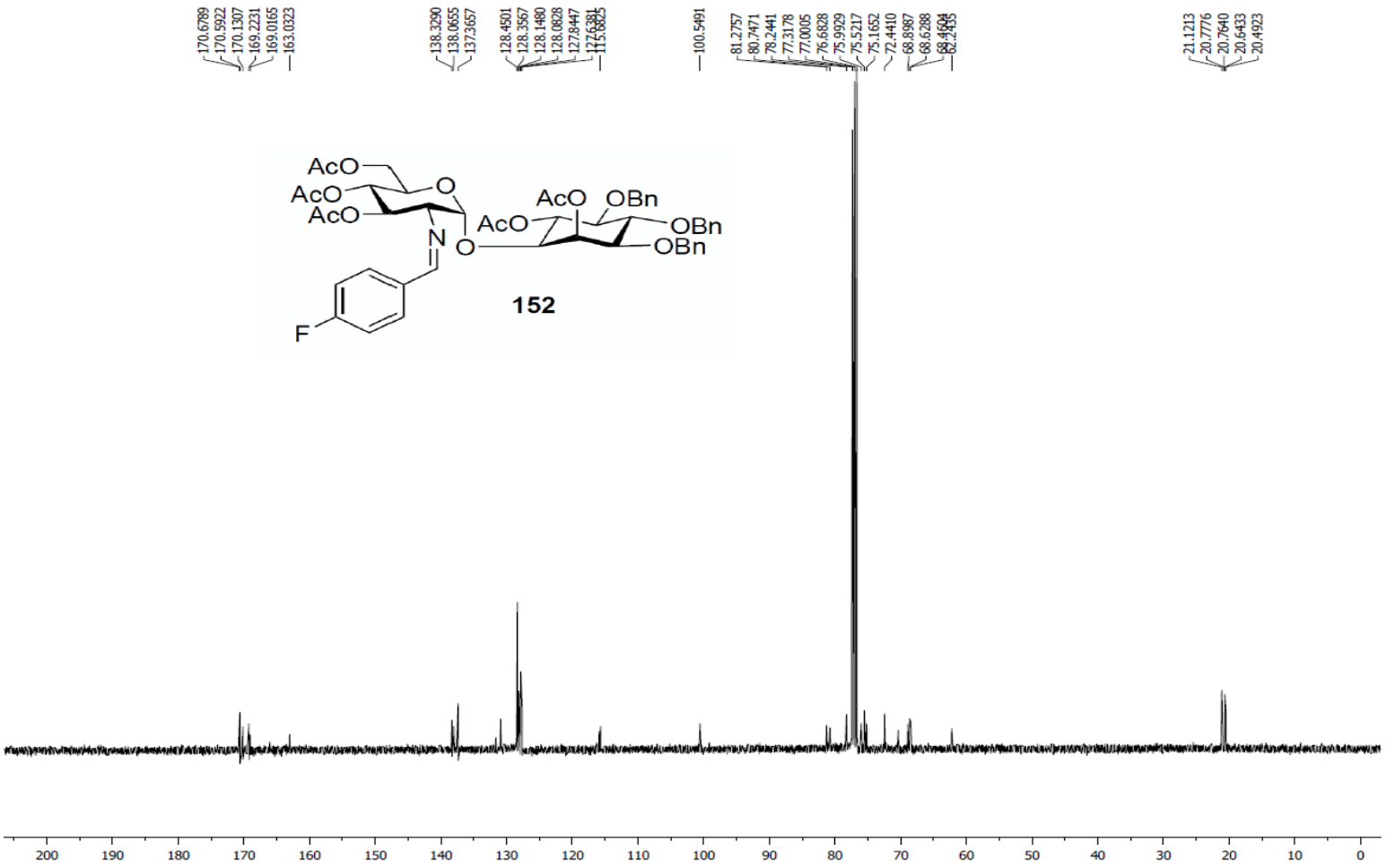


Figure A20. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **152**

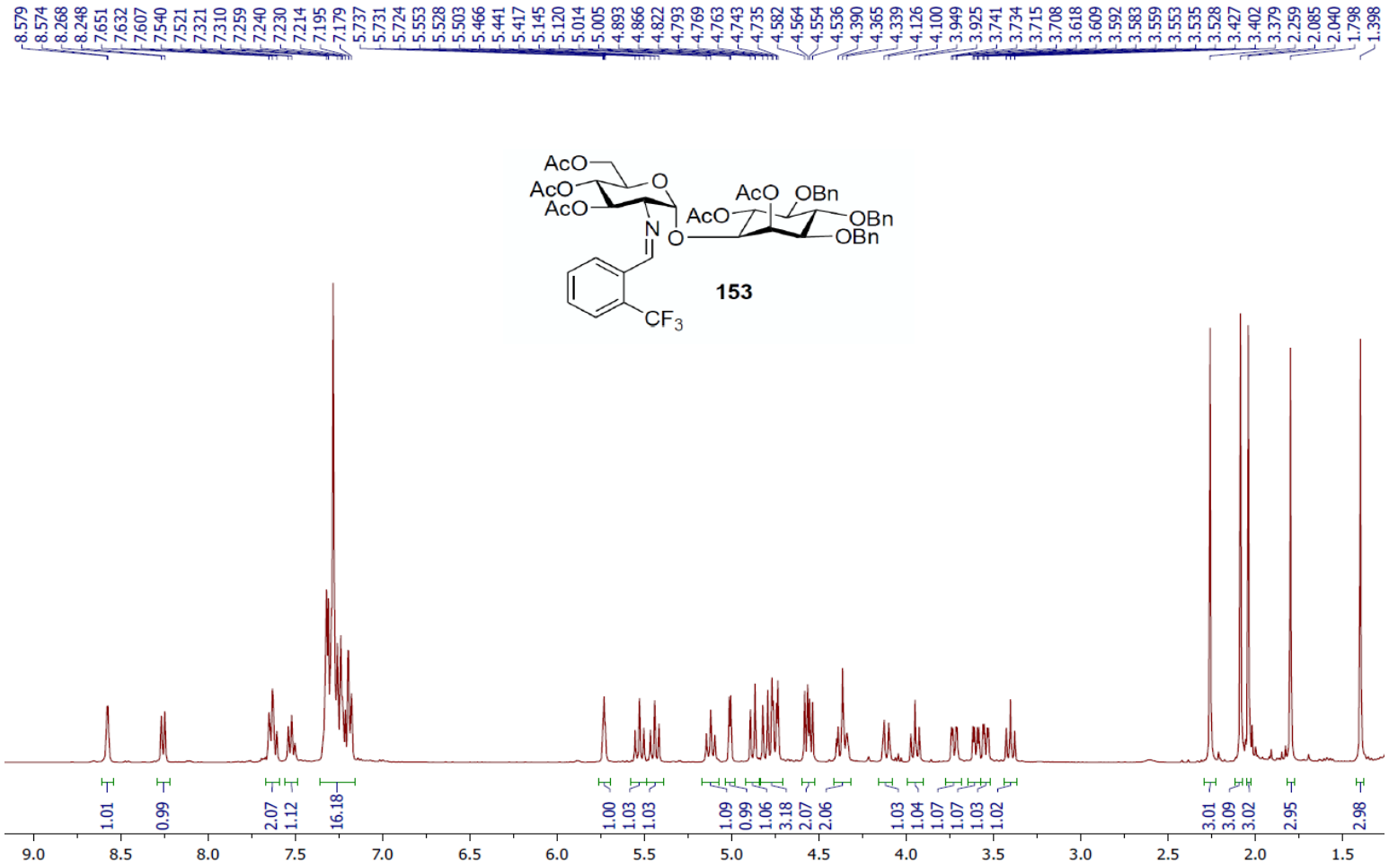


Figure A21. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **153**

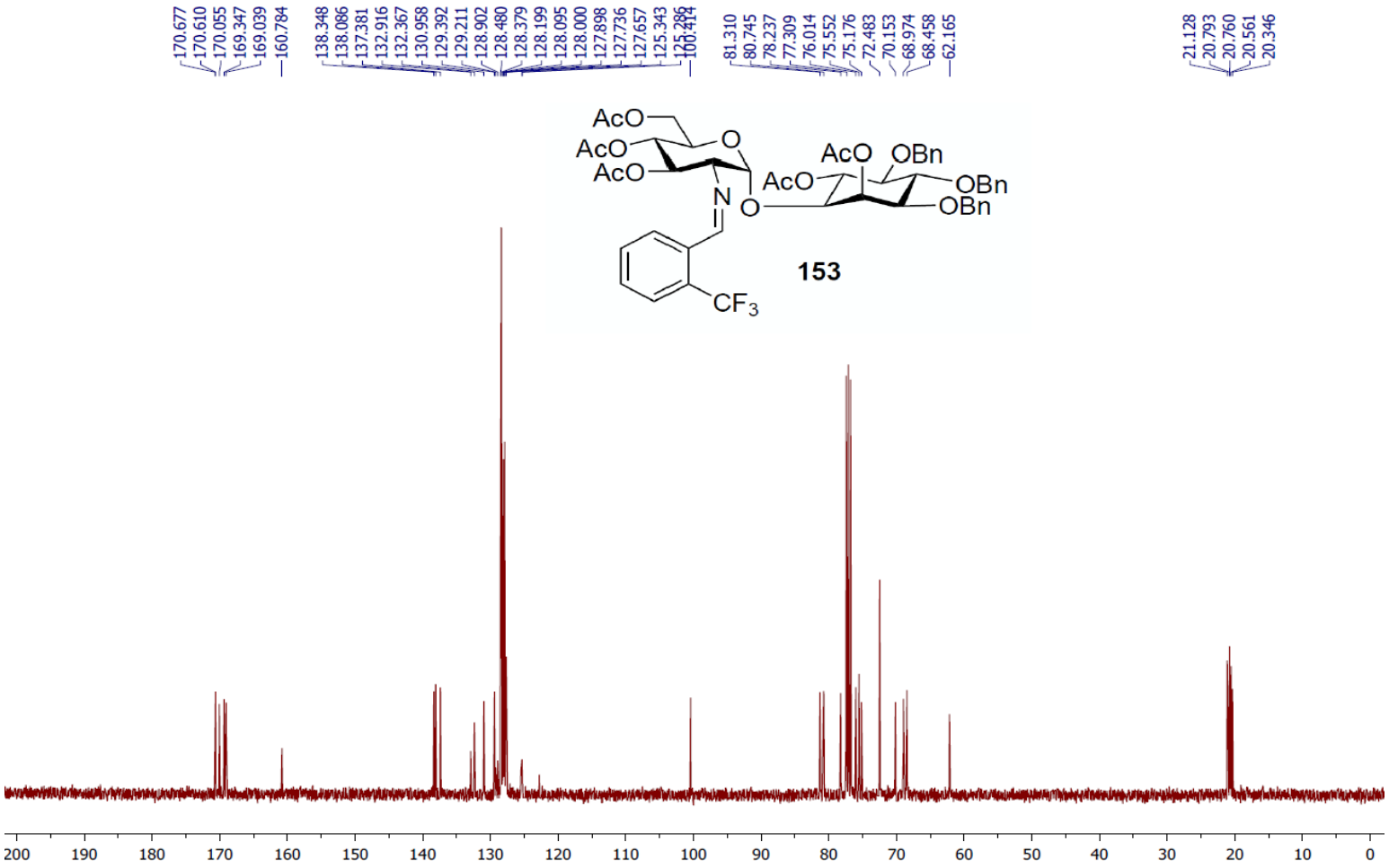


Figure A22. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **153**

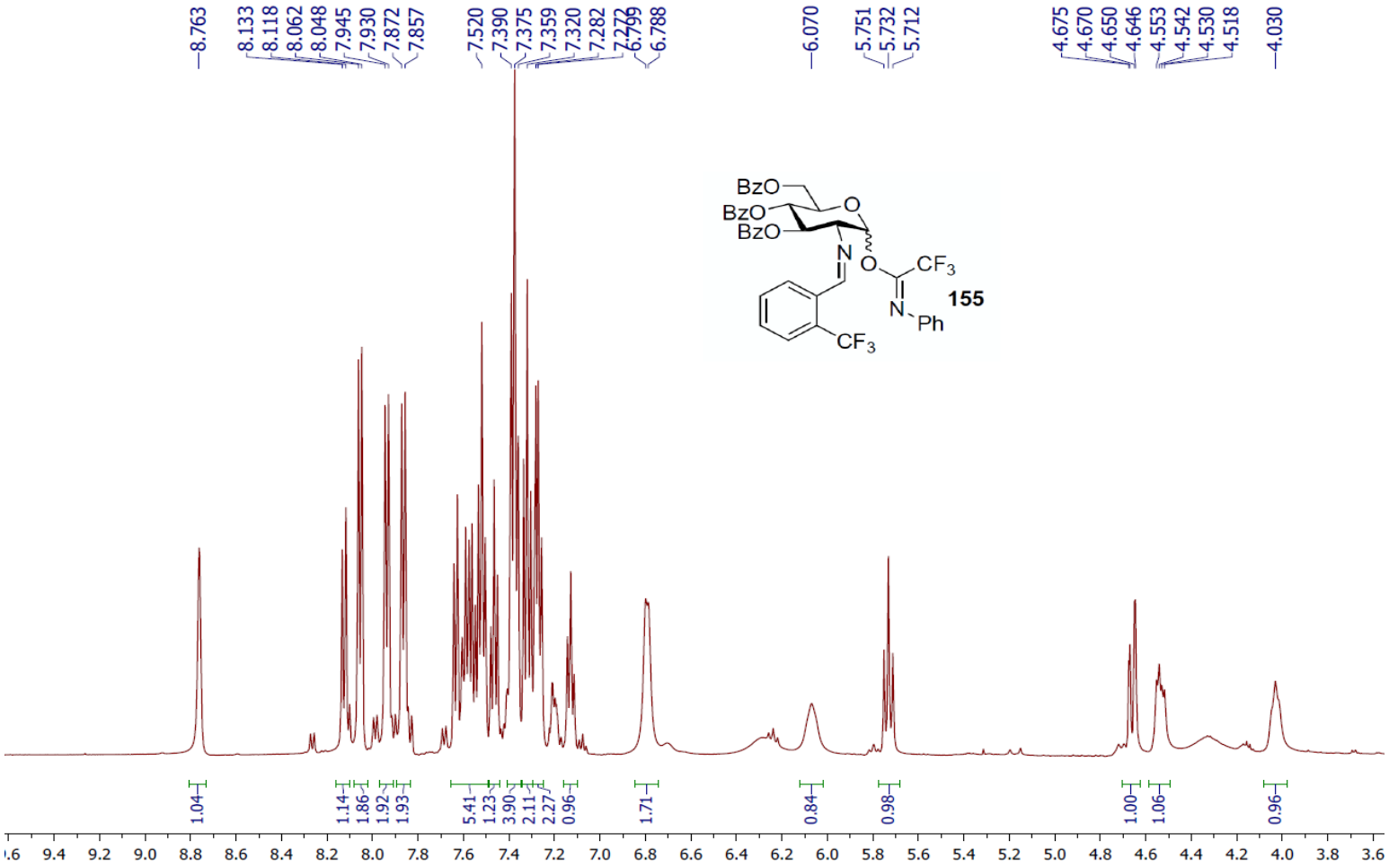


Figure A23. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **155**

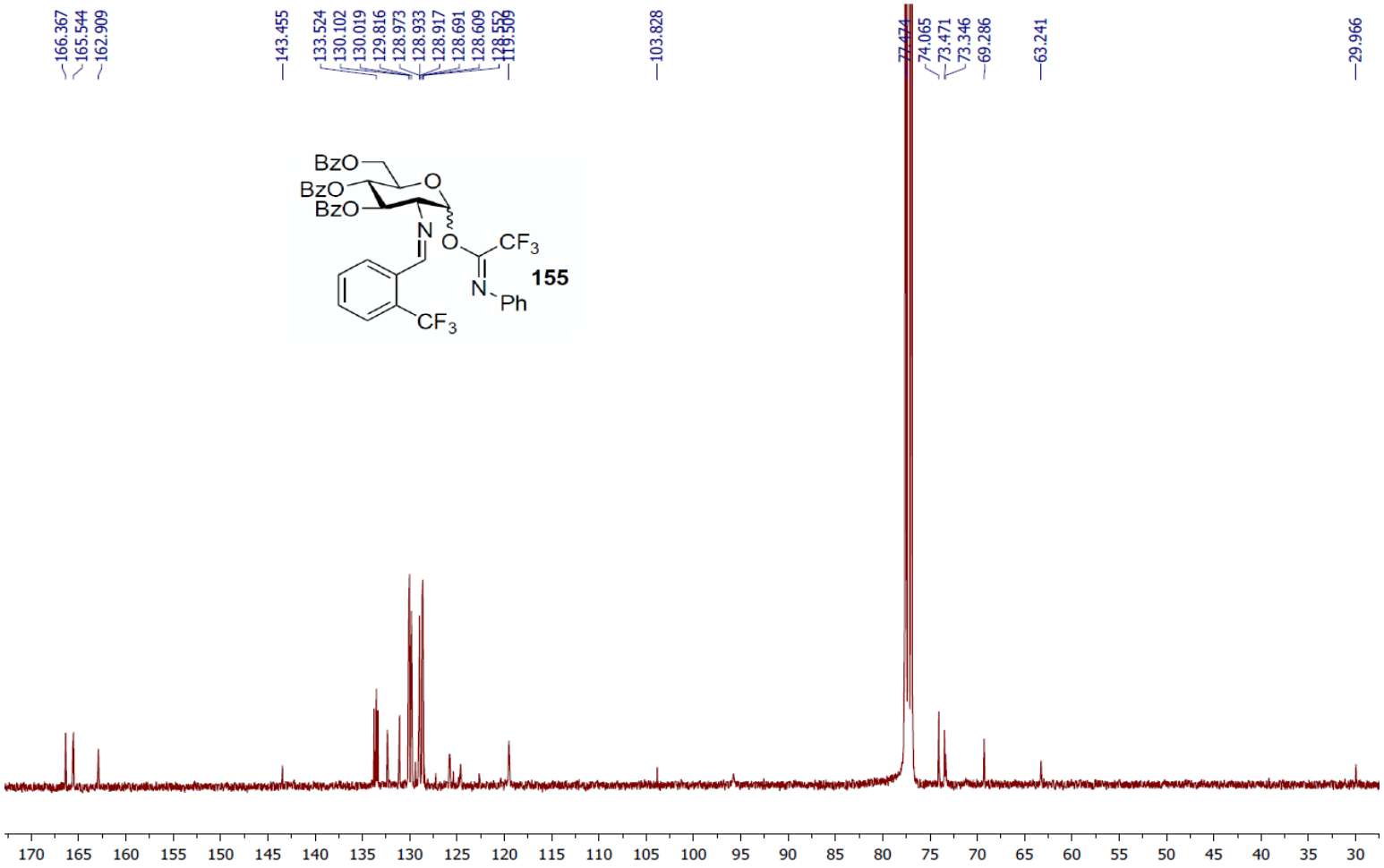


Figure A24. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **155**

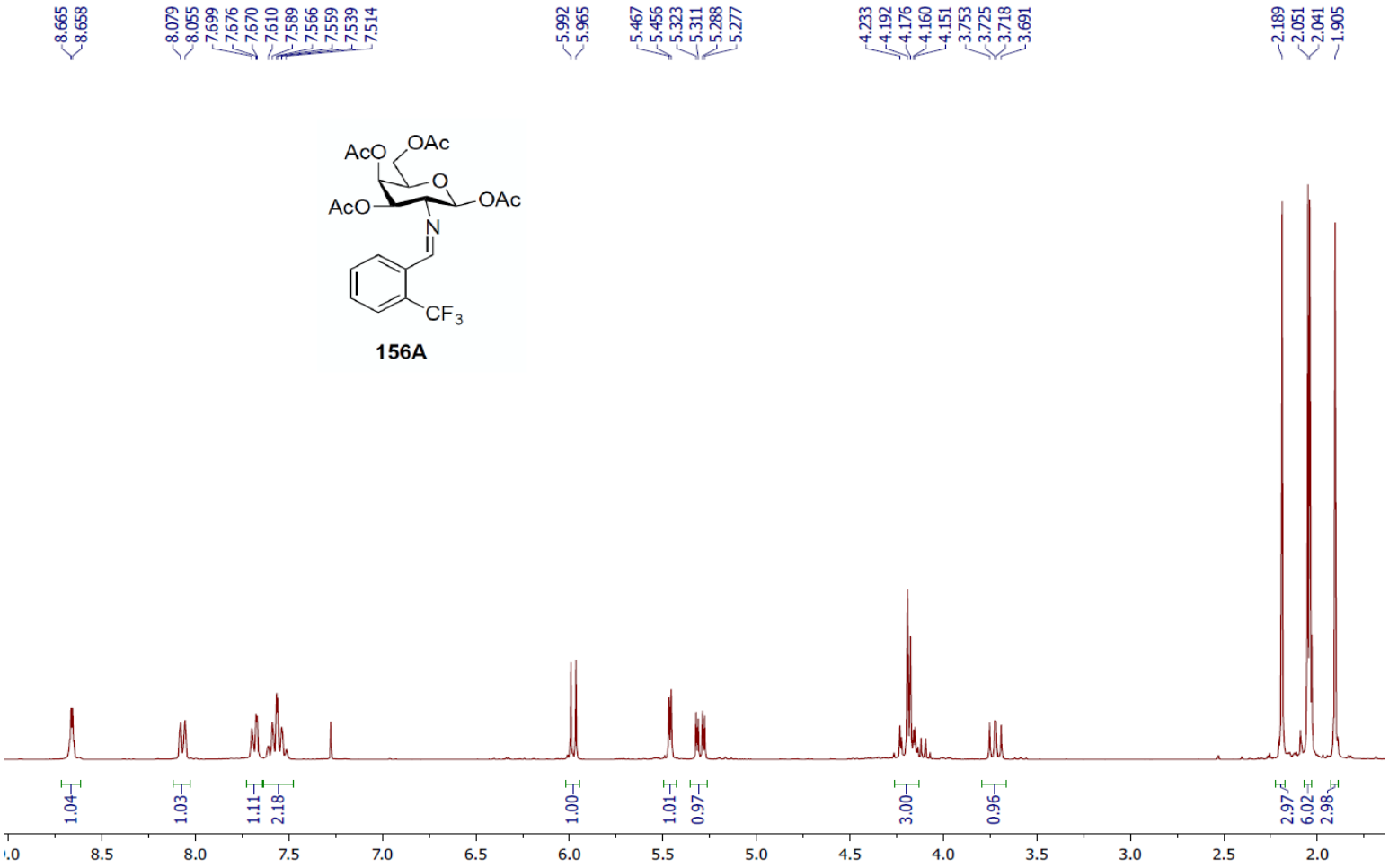


Figure A25. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Galactoside **156A**

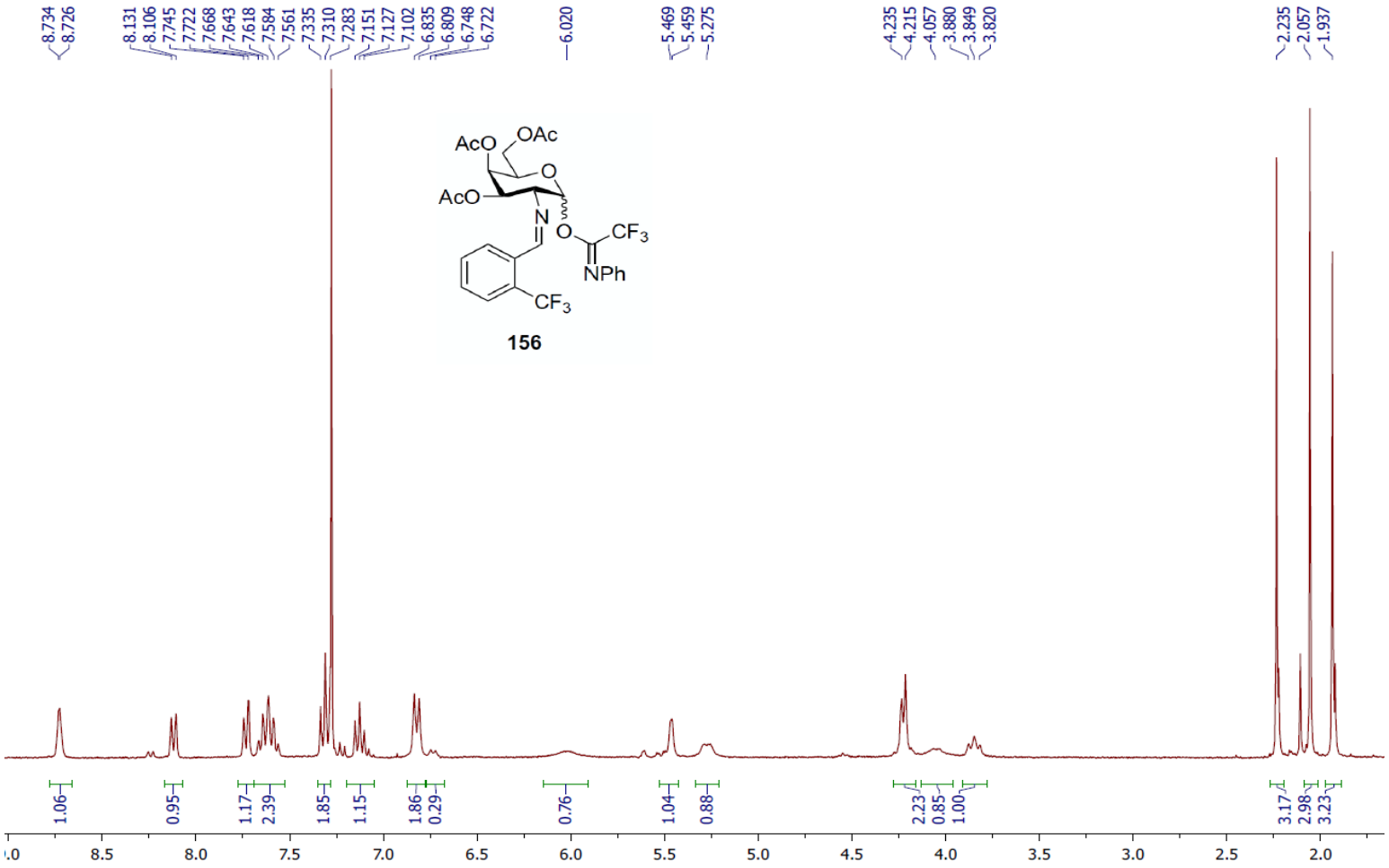


Figure A26. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **156**

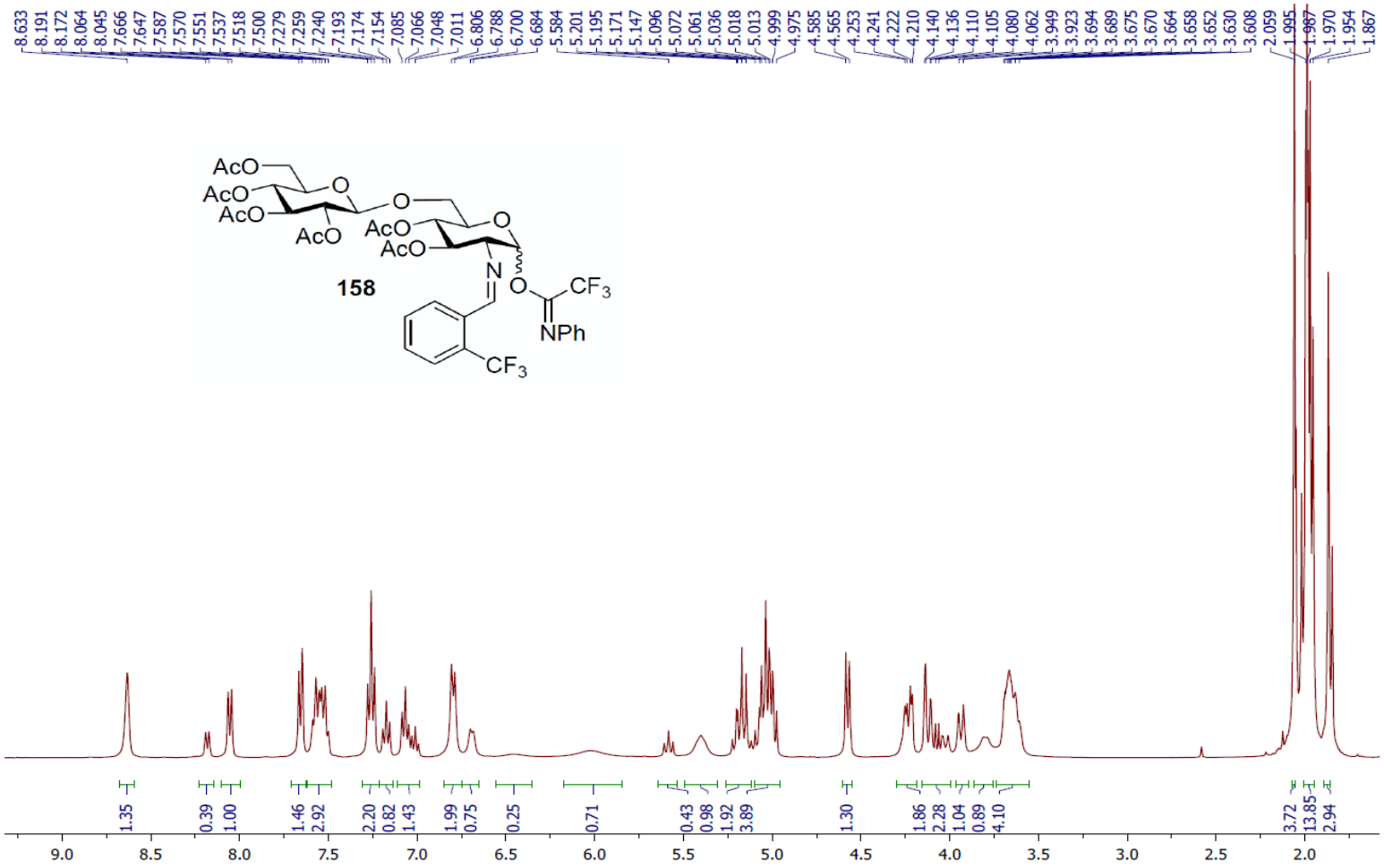


Figure A27. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **158**

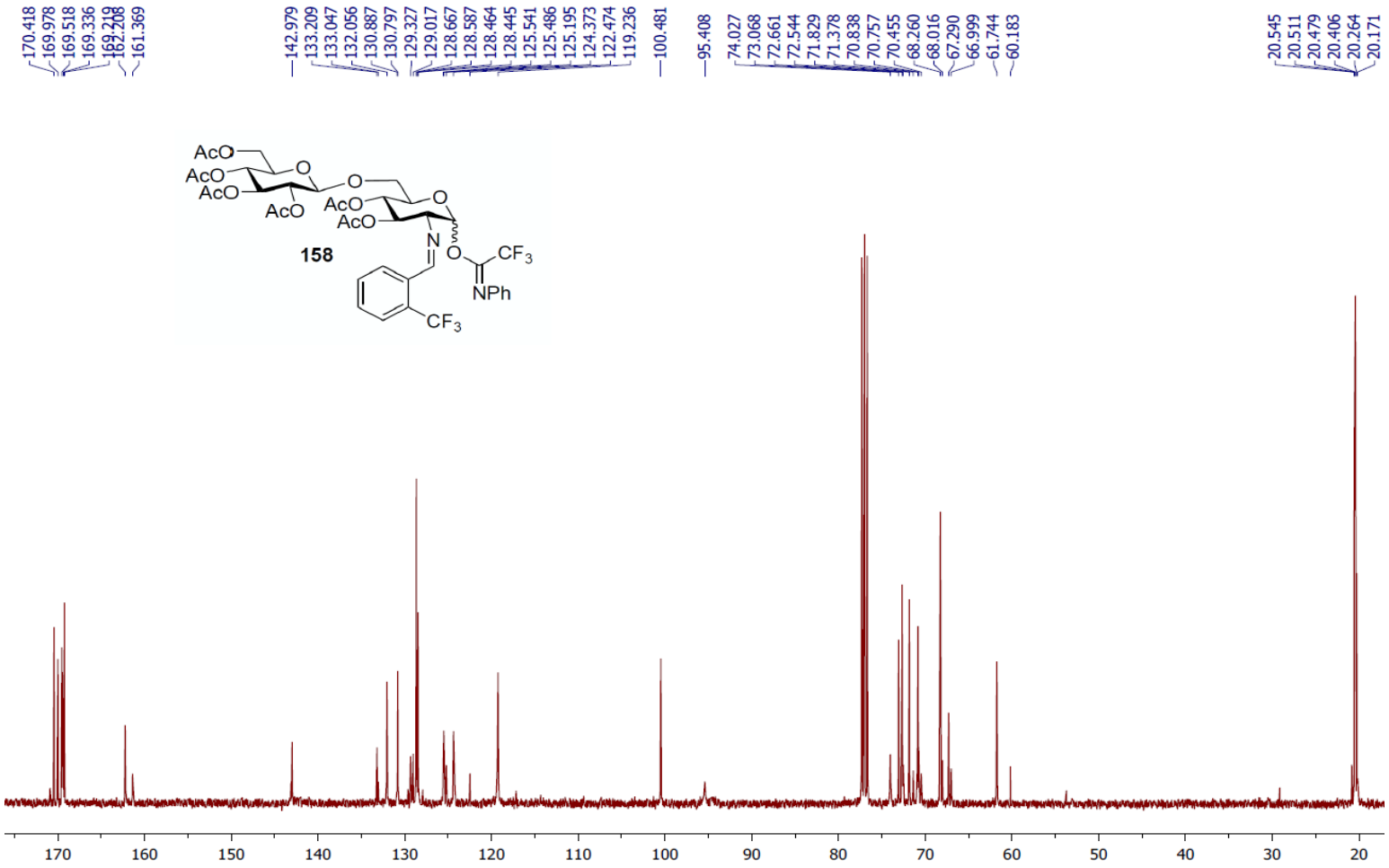


Figure A28. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **158**

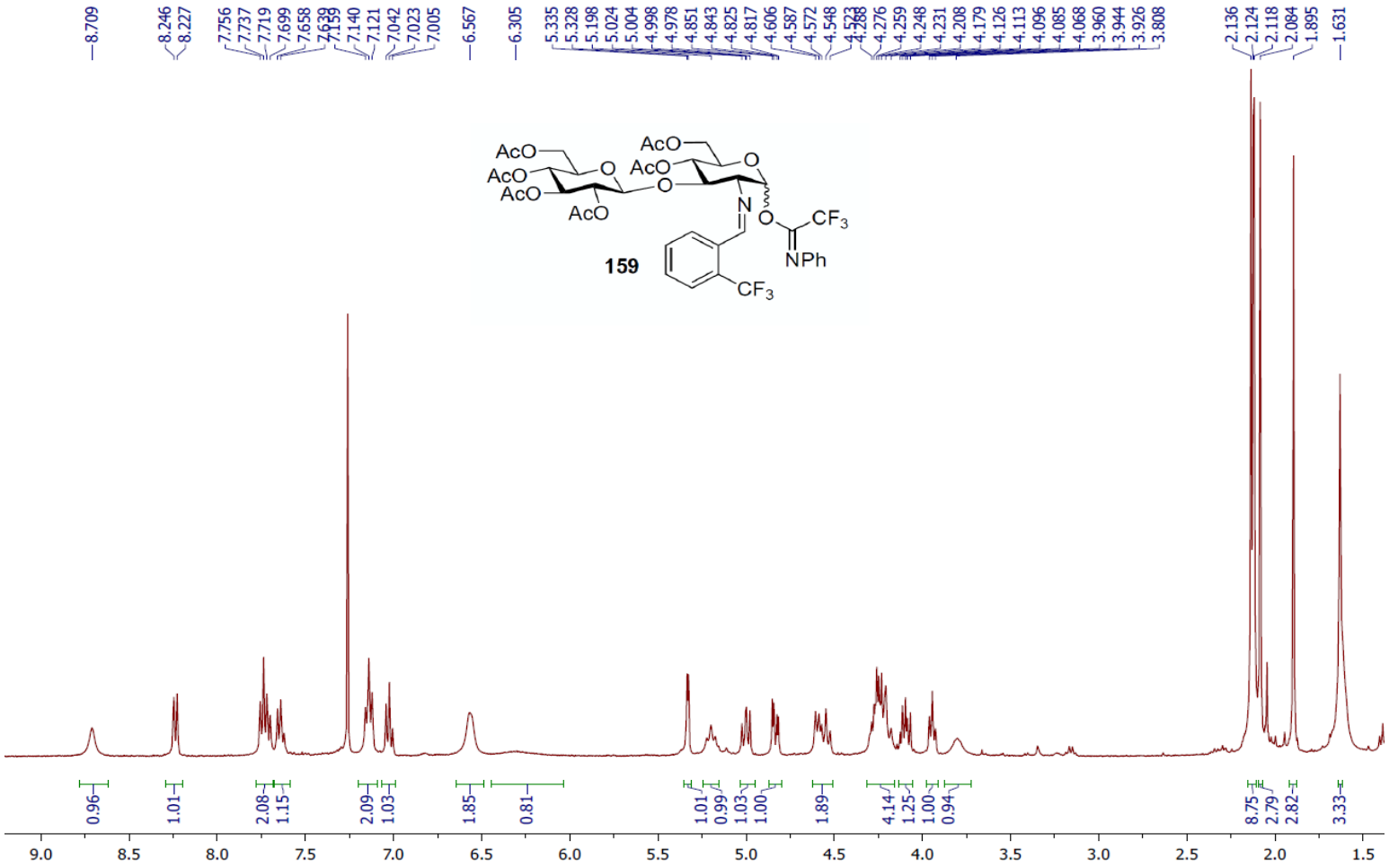


Figure A29. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **159**

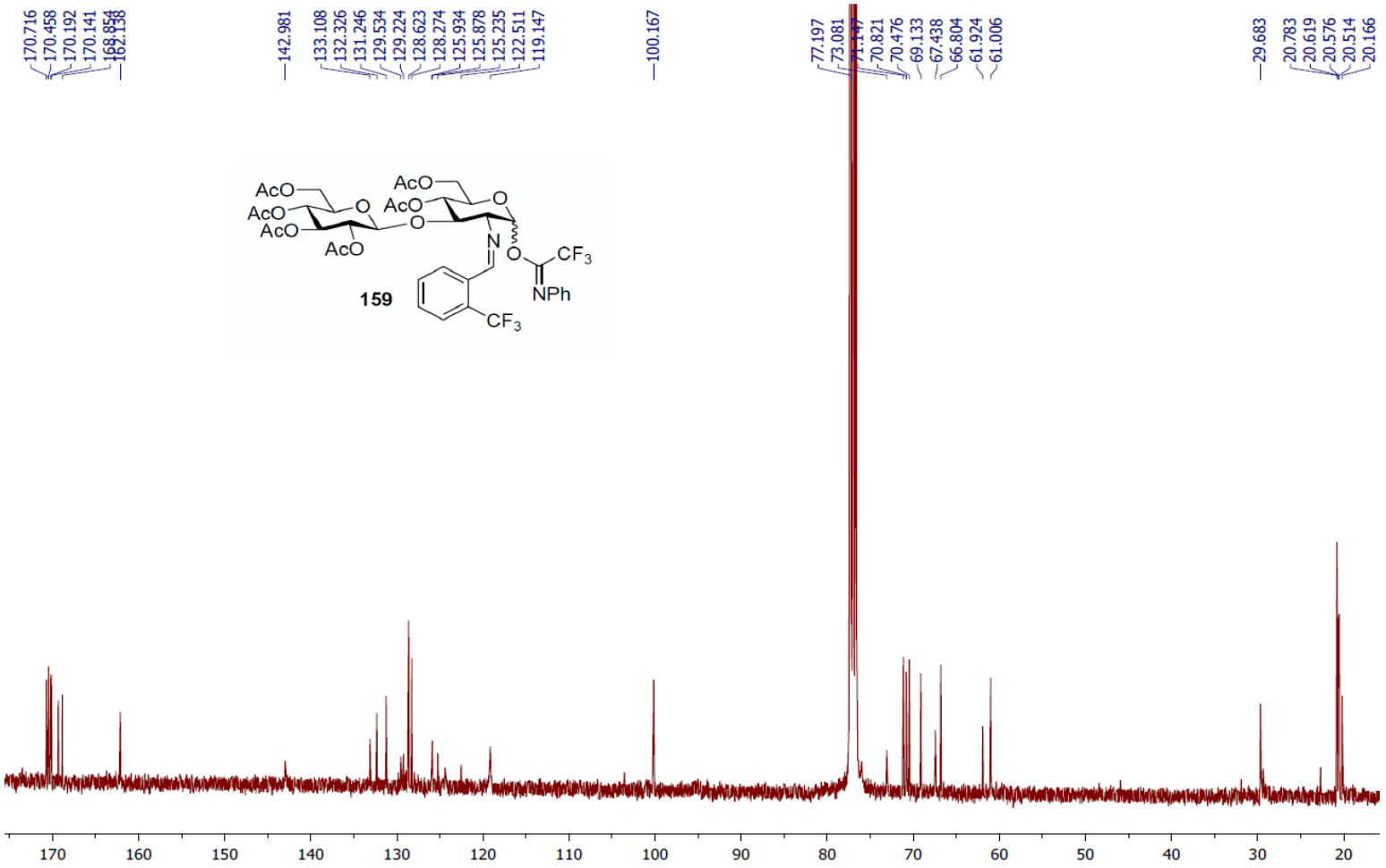


Figure A30. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **159**

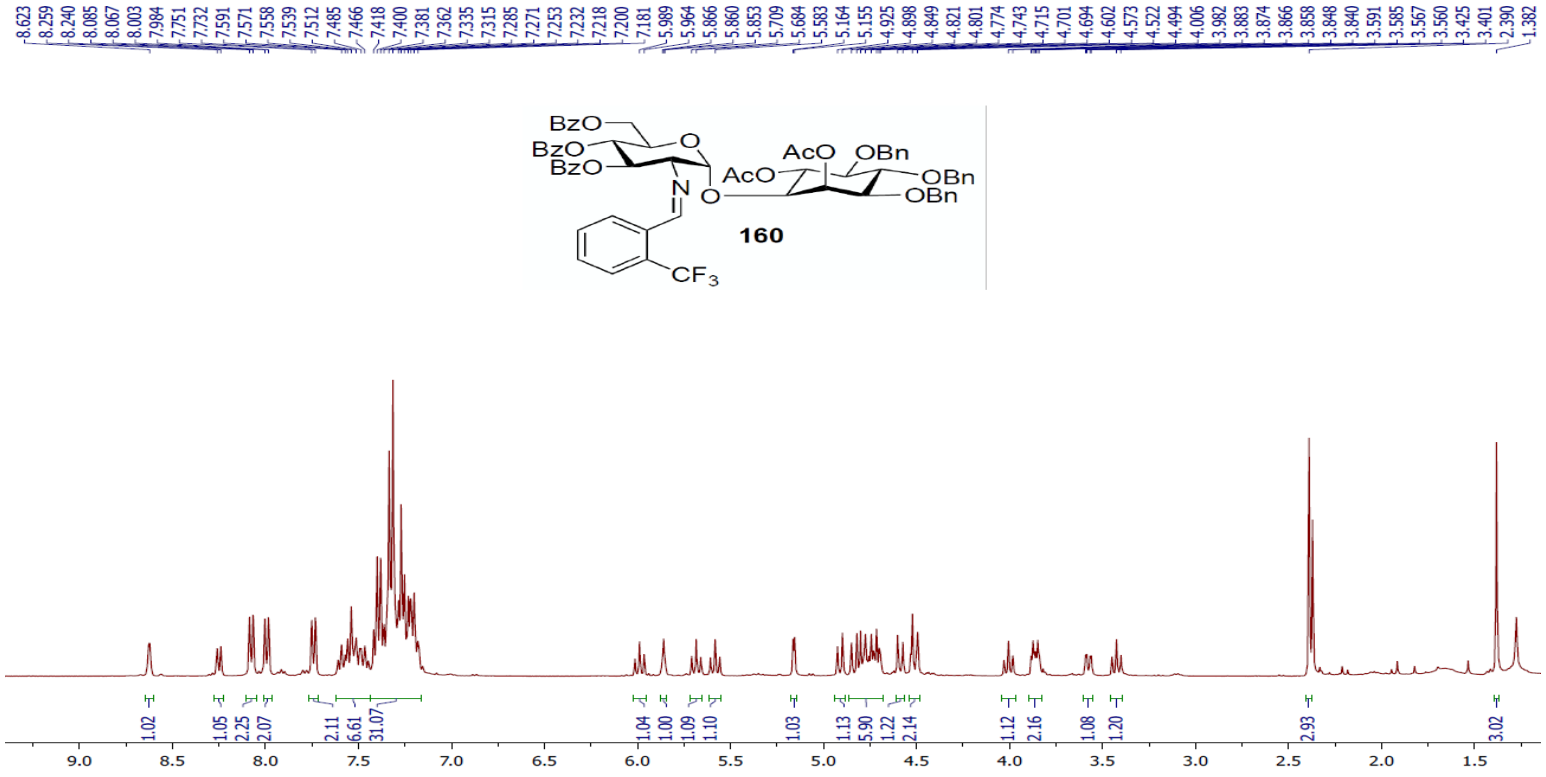


Figure A31. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **160**

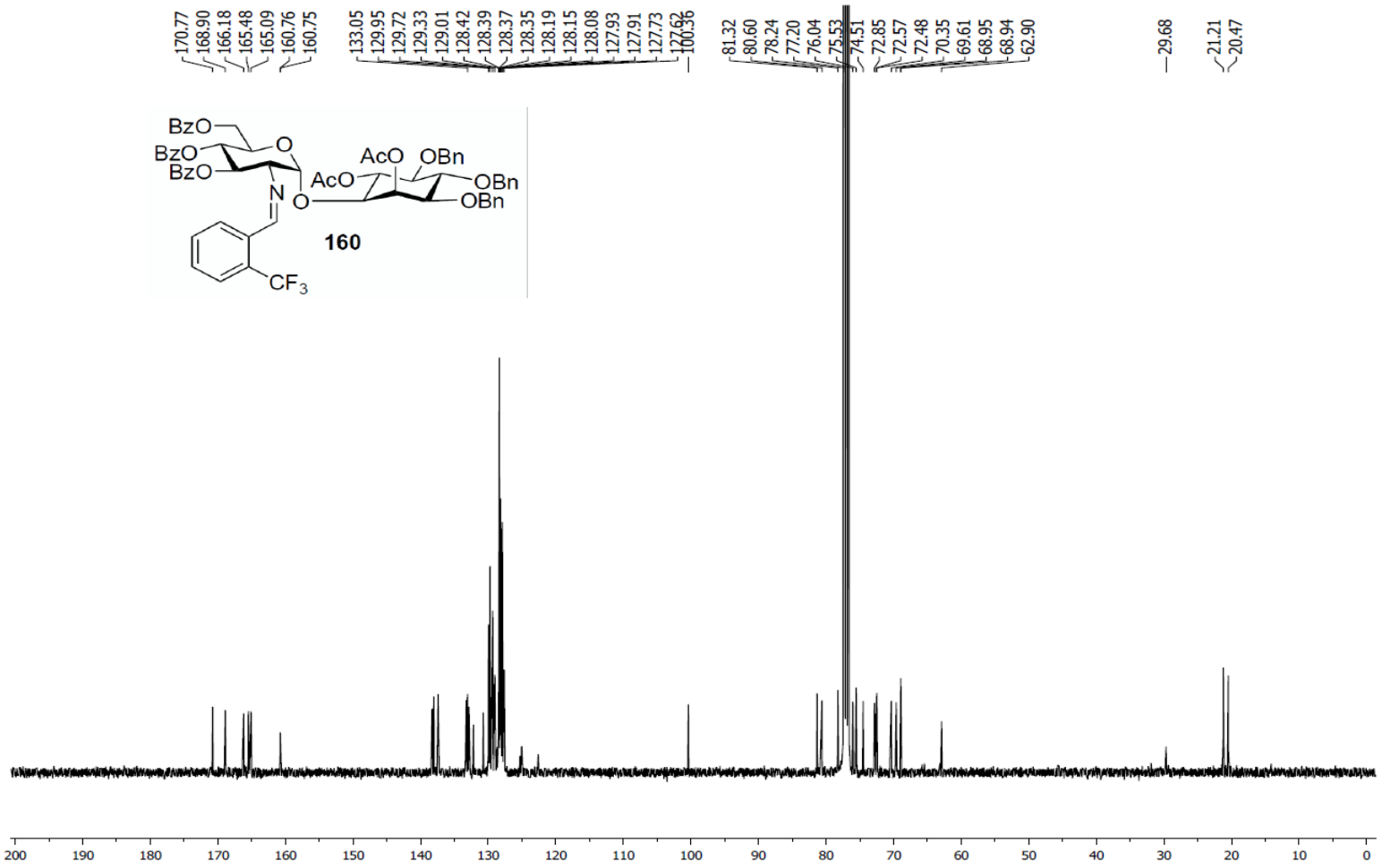


Figure A32. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **160**

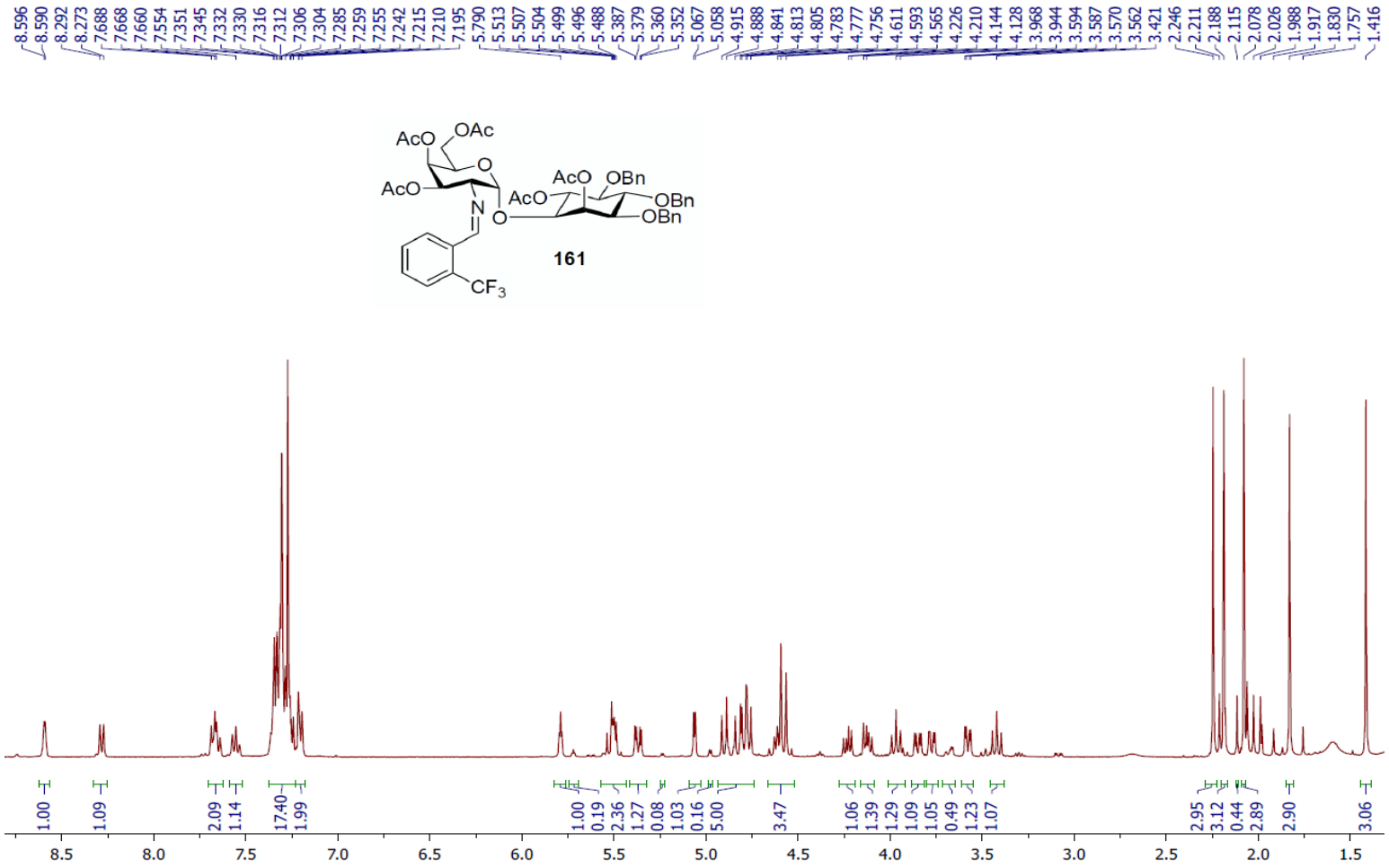


Figure A33. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **161**

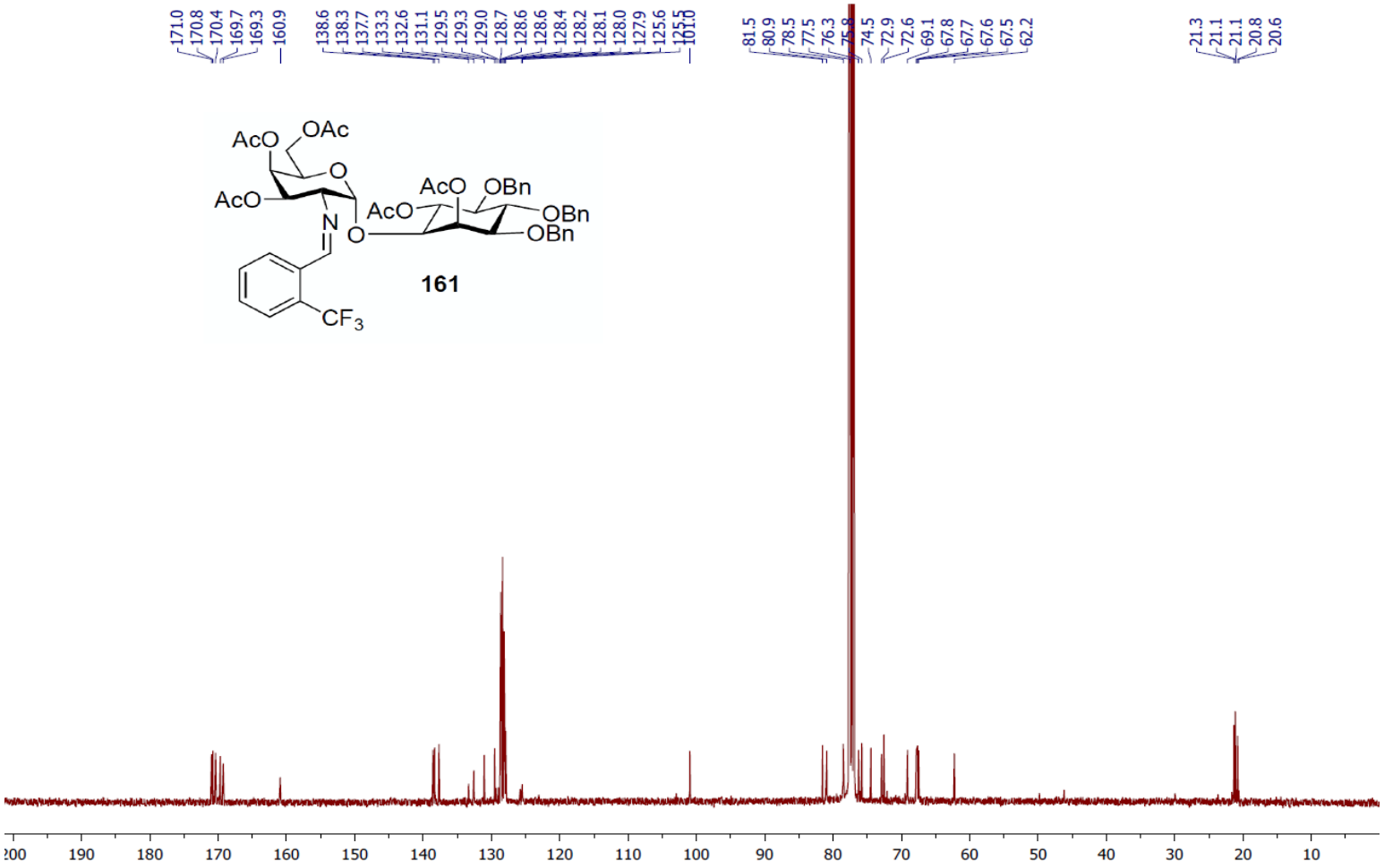


Figure A34. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **161**

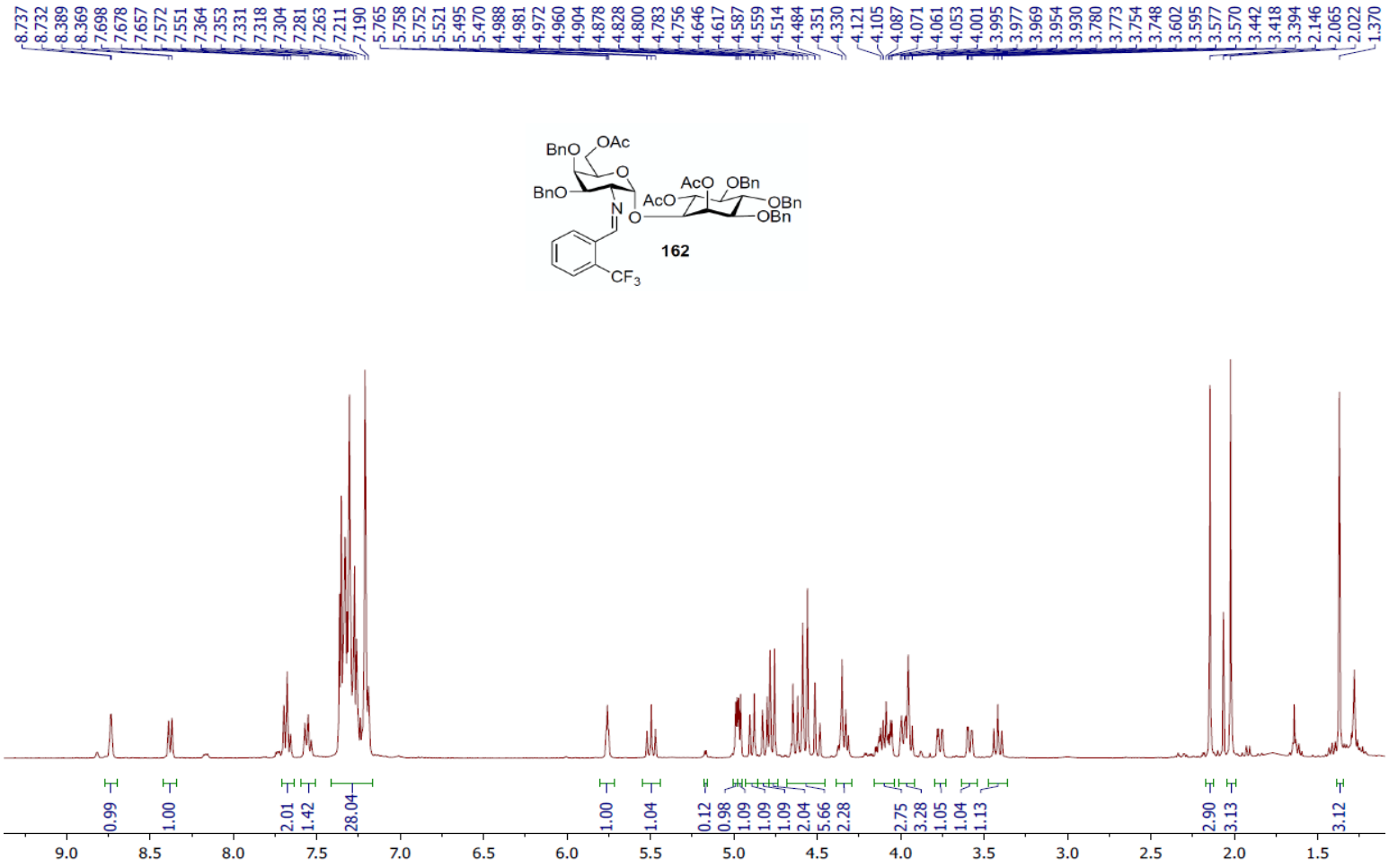


Figure A35. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **162**

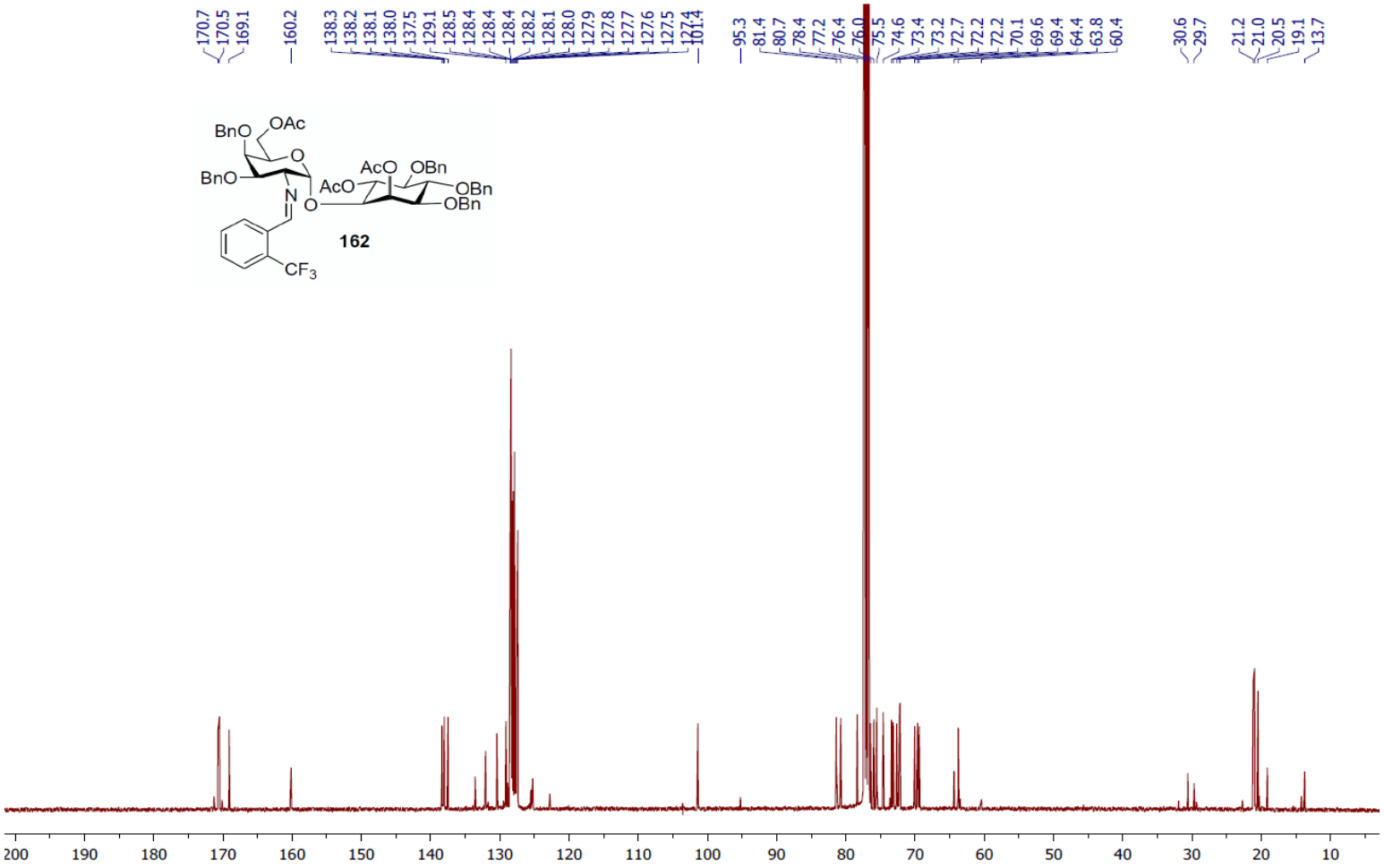


Figure A36. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **162**

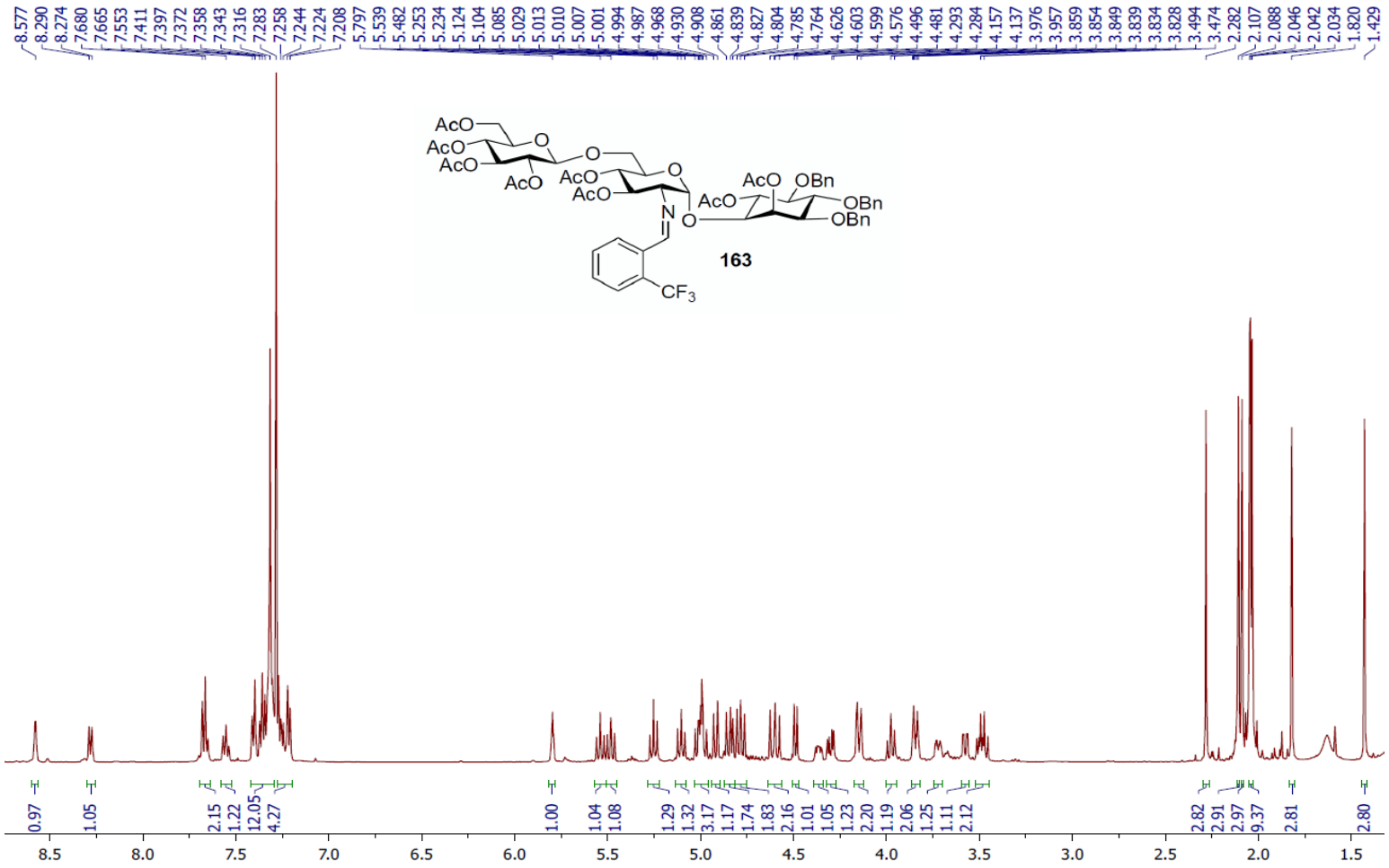


Figure A337. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **163**

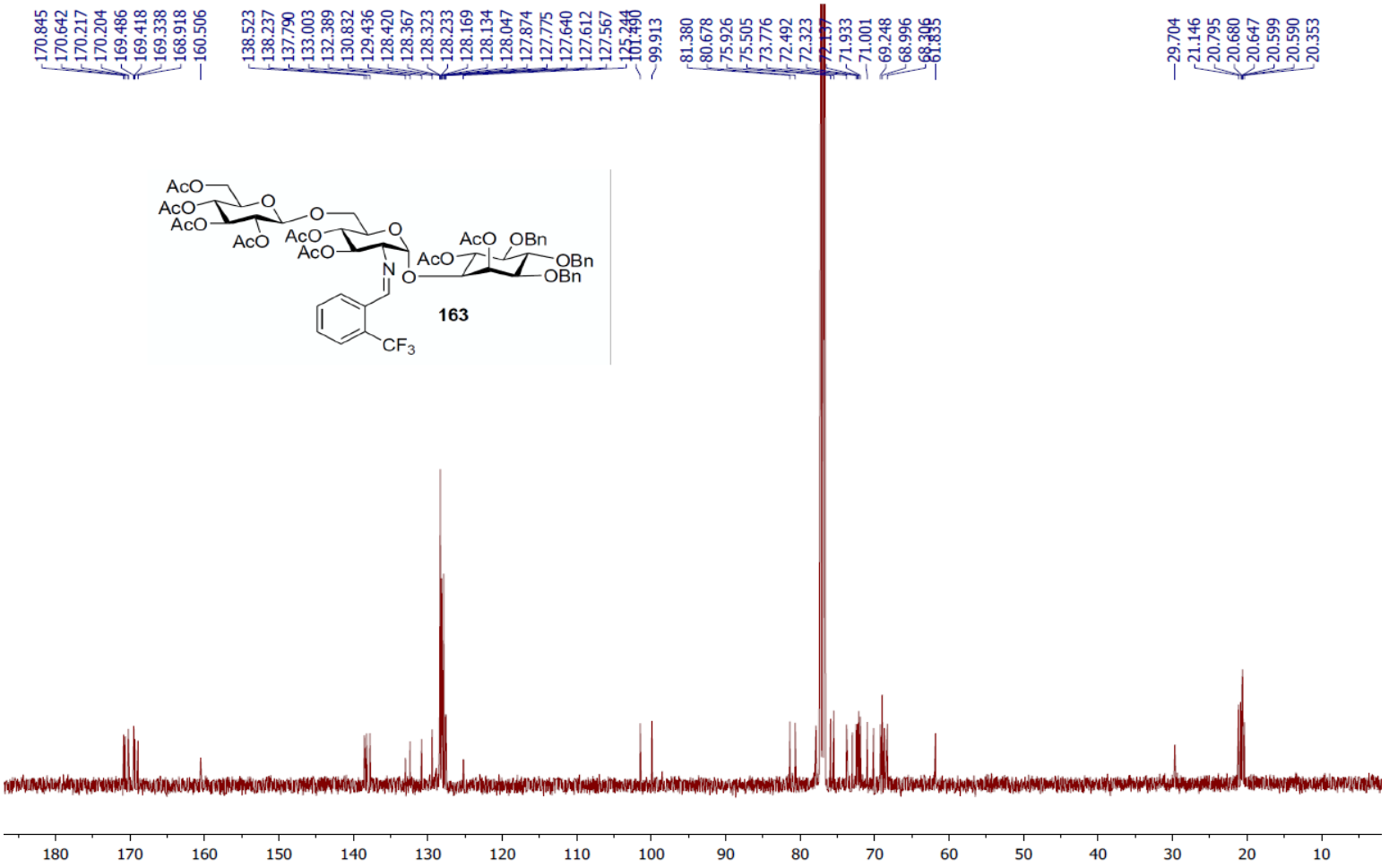


Figure A38. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **163**

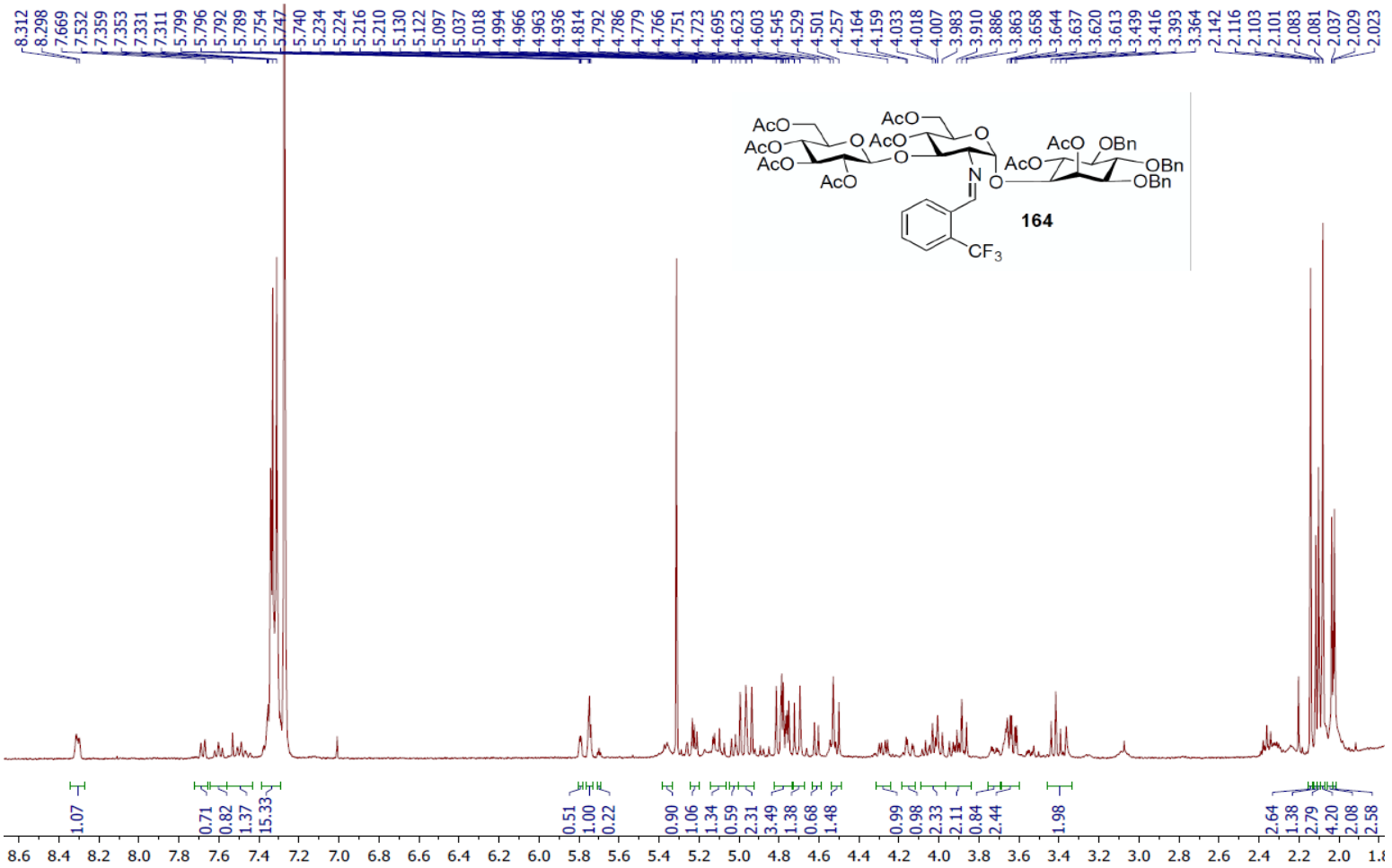


Figure A39. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **164**

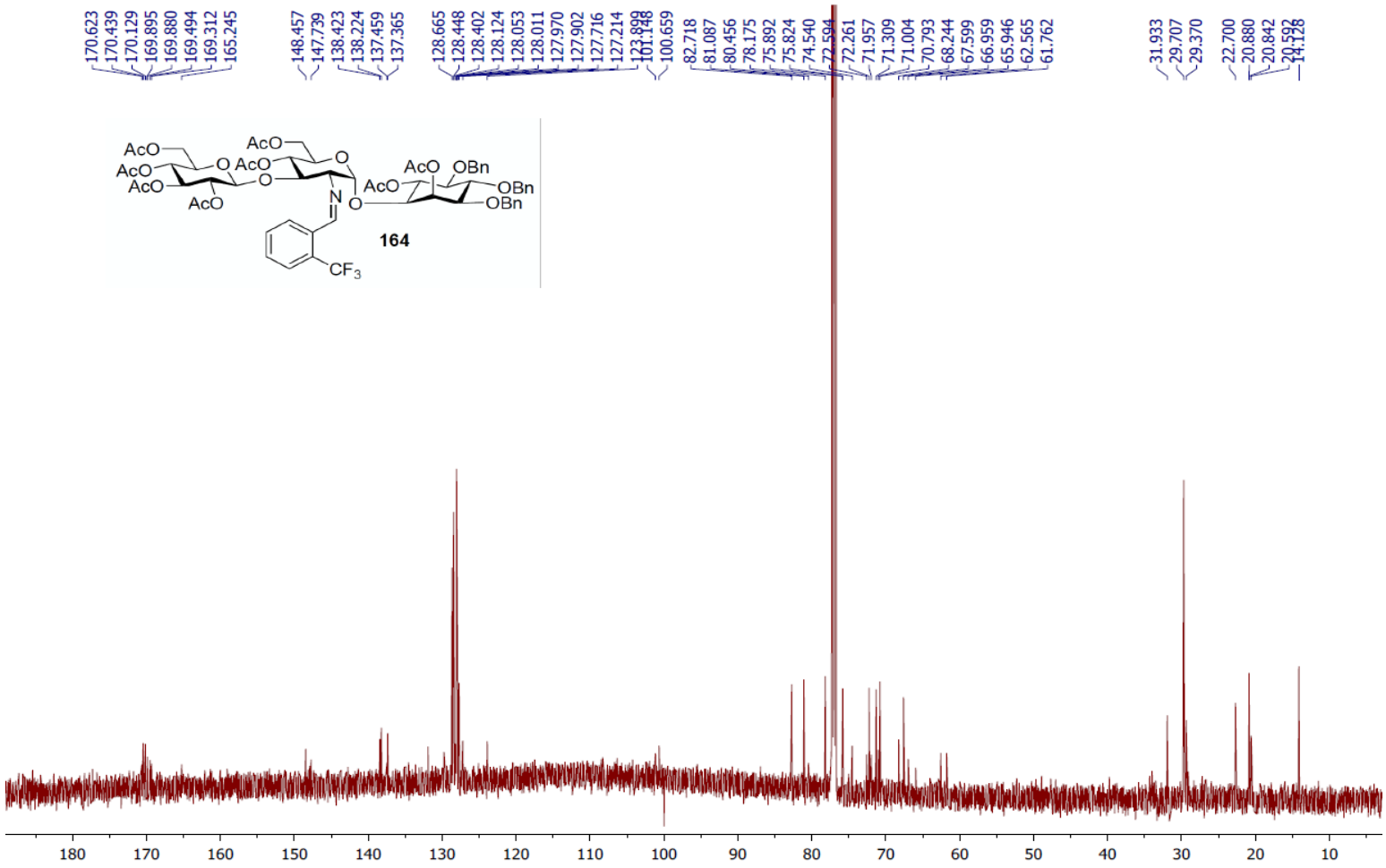


Figure A40. 150 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **164**

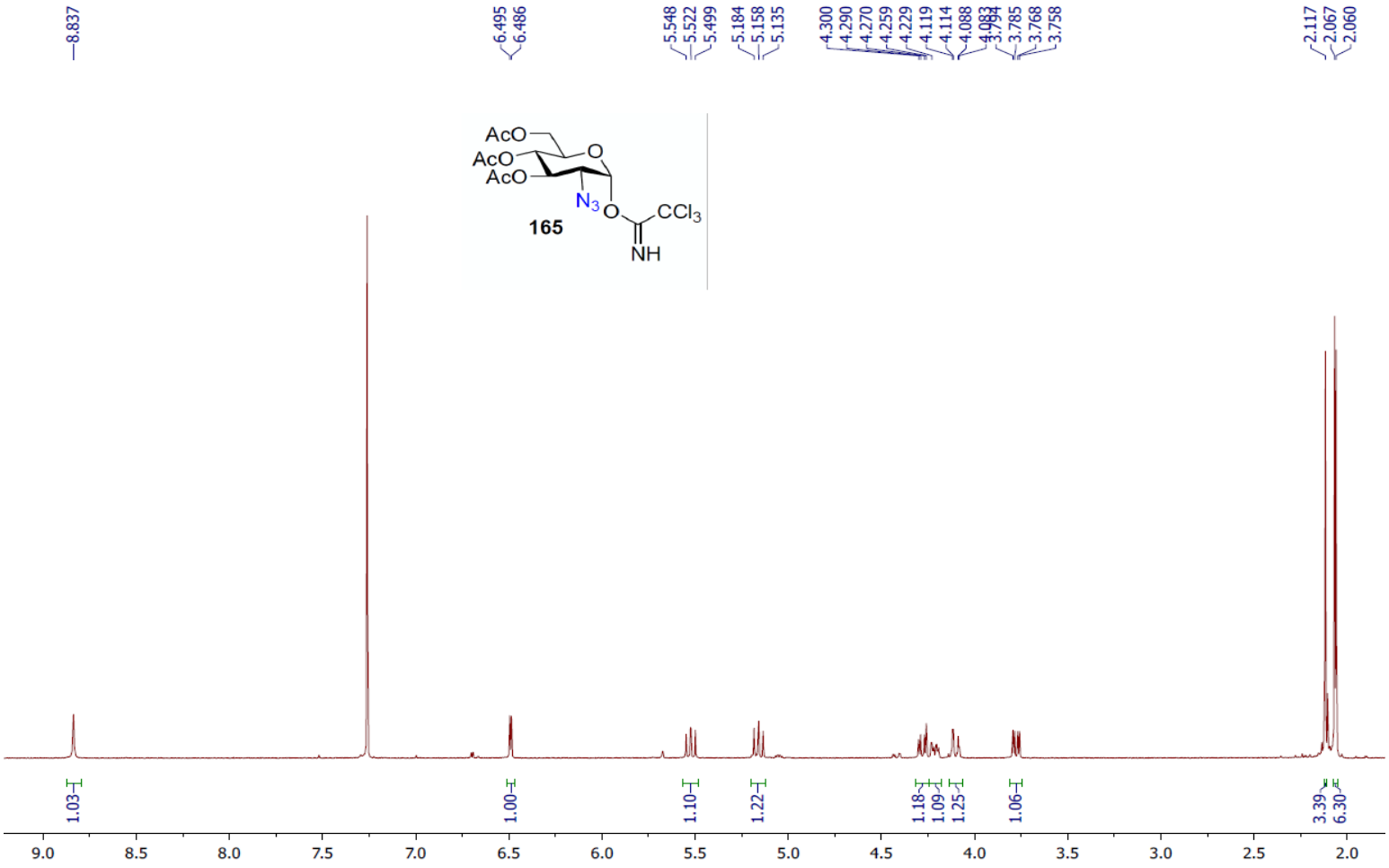


Figure A41. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **165**

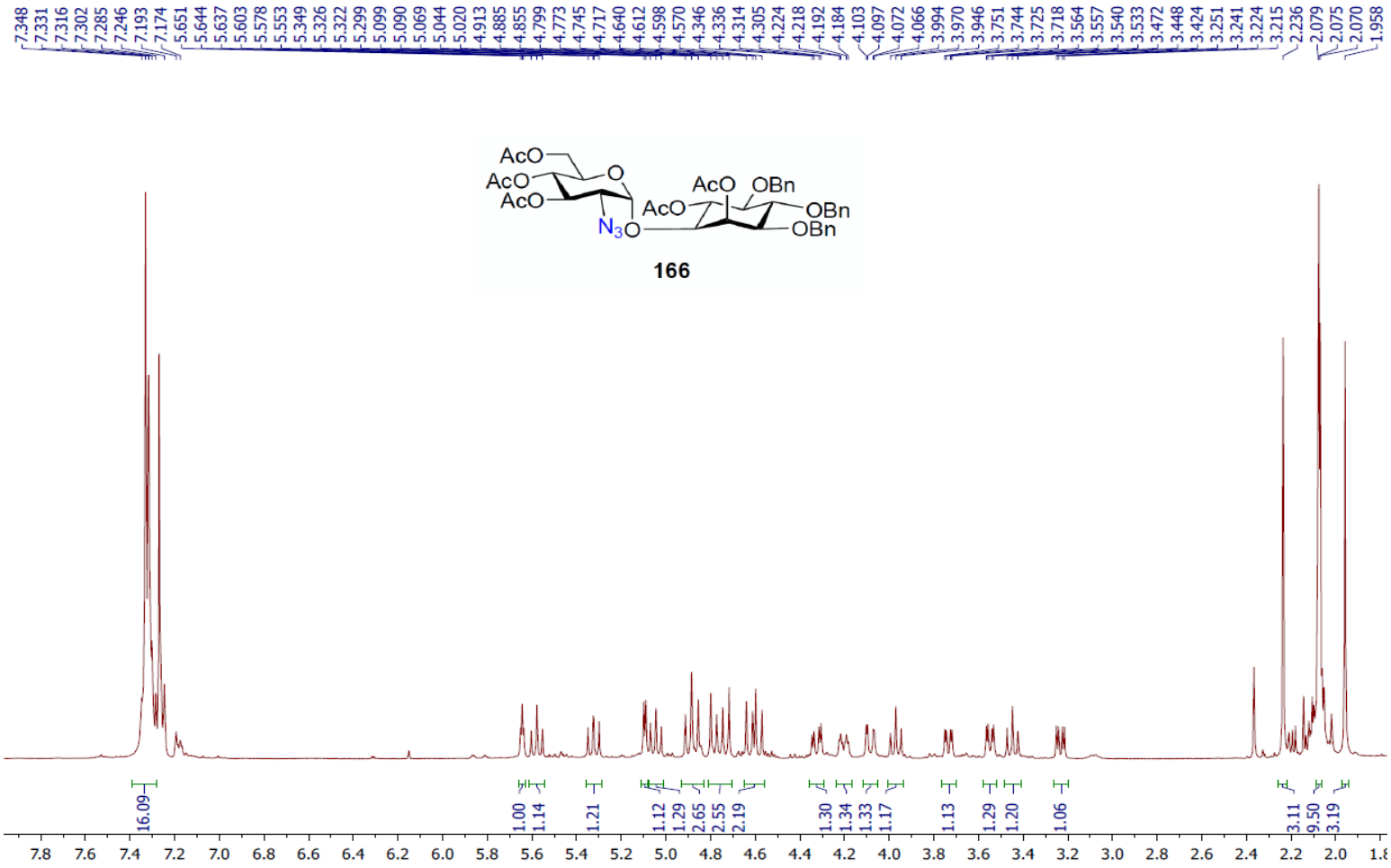


Figure A42. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **166**

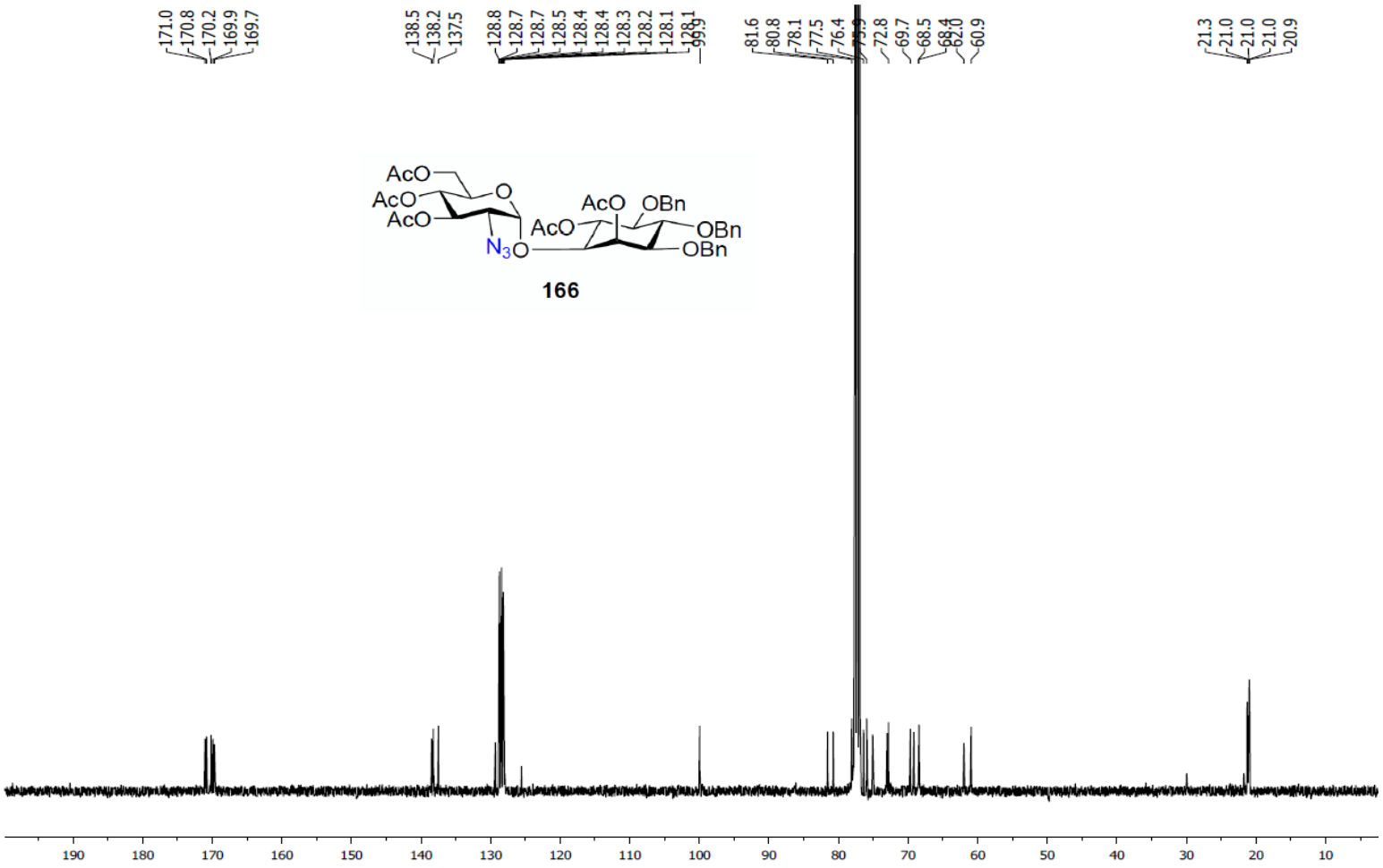


Figure A43. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **166**

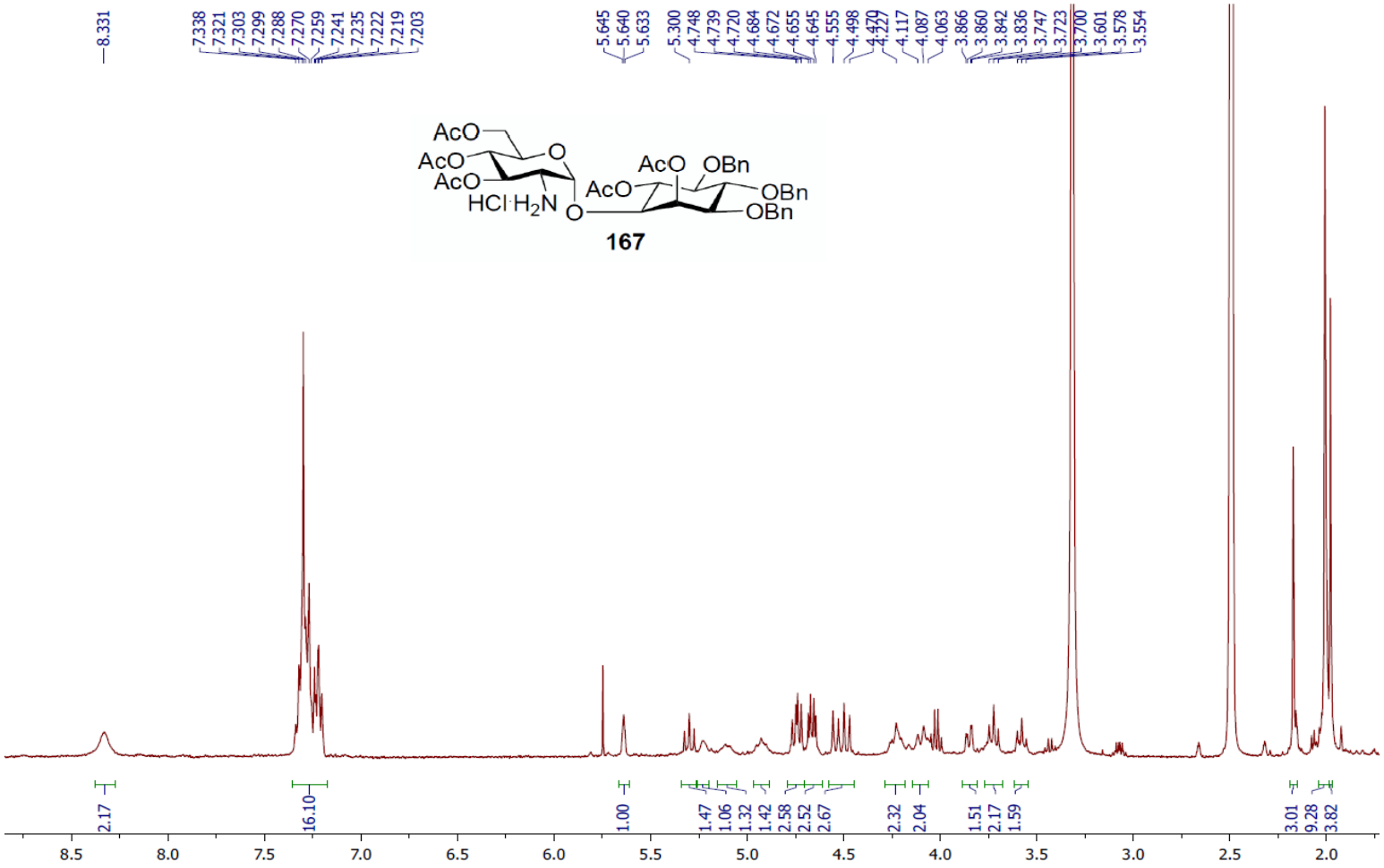


Figure A44. 400 MHz ^{1}H NMR Spectrum (DMSO-d_6) of Disaccharide **167**

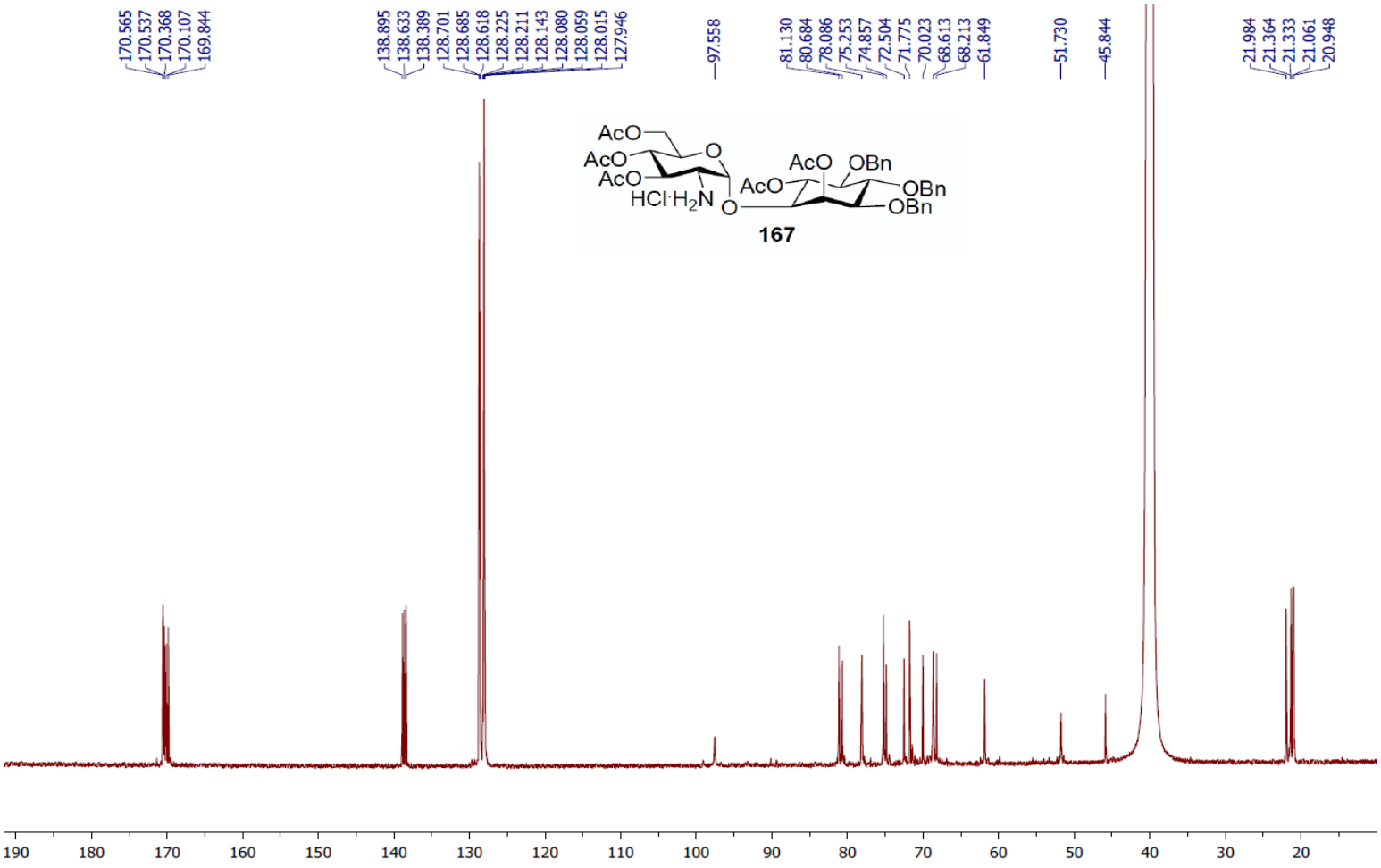


Figure A45. 125 MHz ^{13}C NMR Spectrum (DMSO-d_6) of Disaccharide **167**

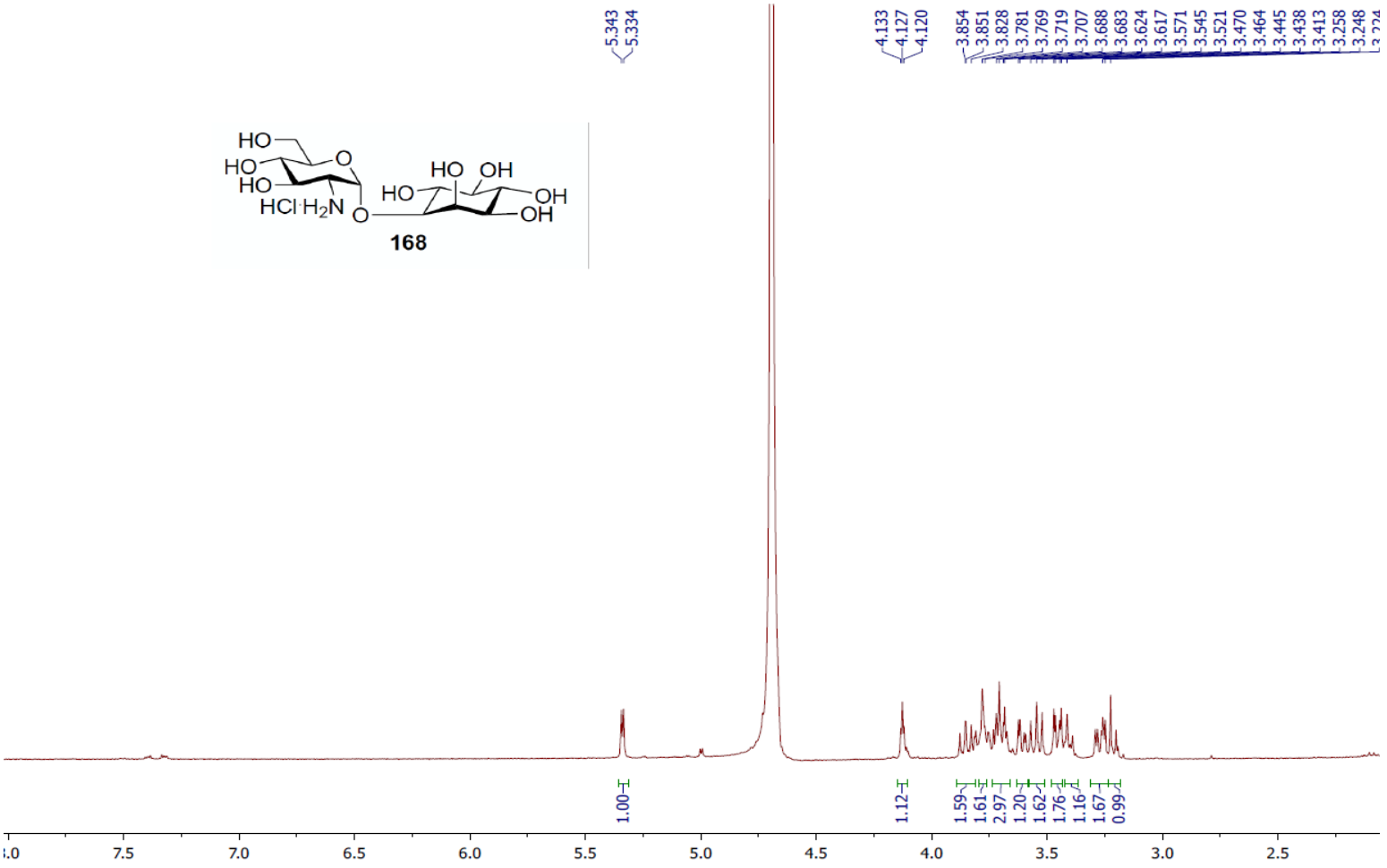


Figure A46. 400 MHz ^{1}H NMR Spectrum (D_2O) of Disaccharide **168**

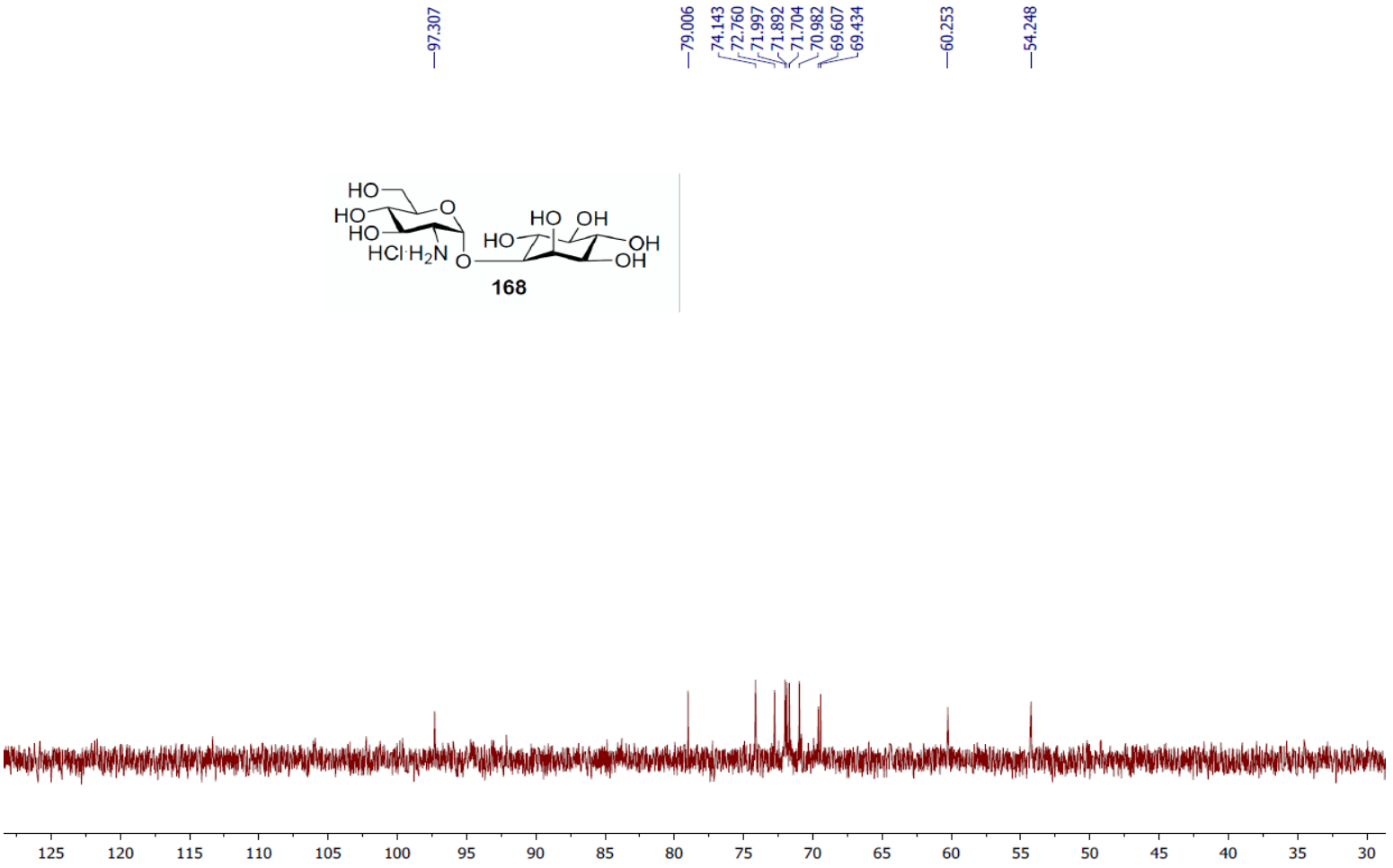


Figure A47. 125 MHz ^{13}C NMR Spectrum (D_2O) of Disaccharide **168**

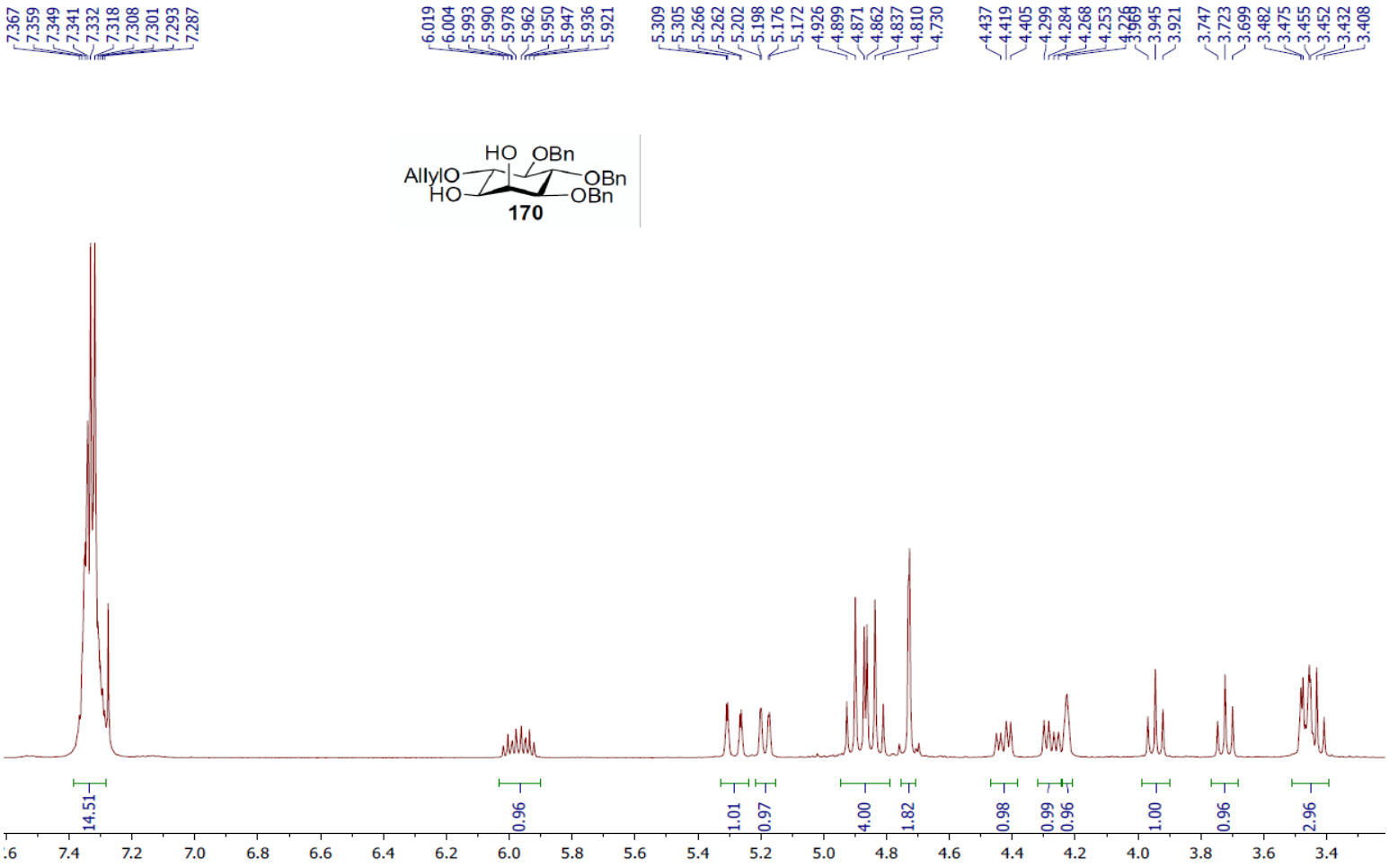


Figure A48. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **170**

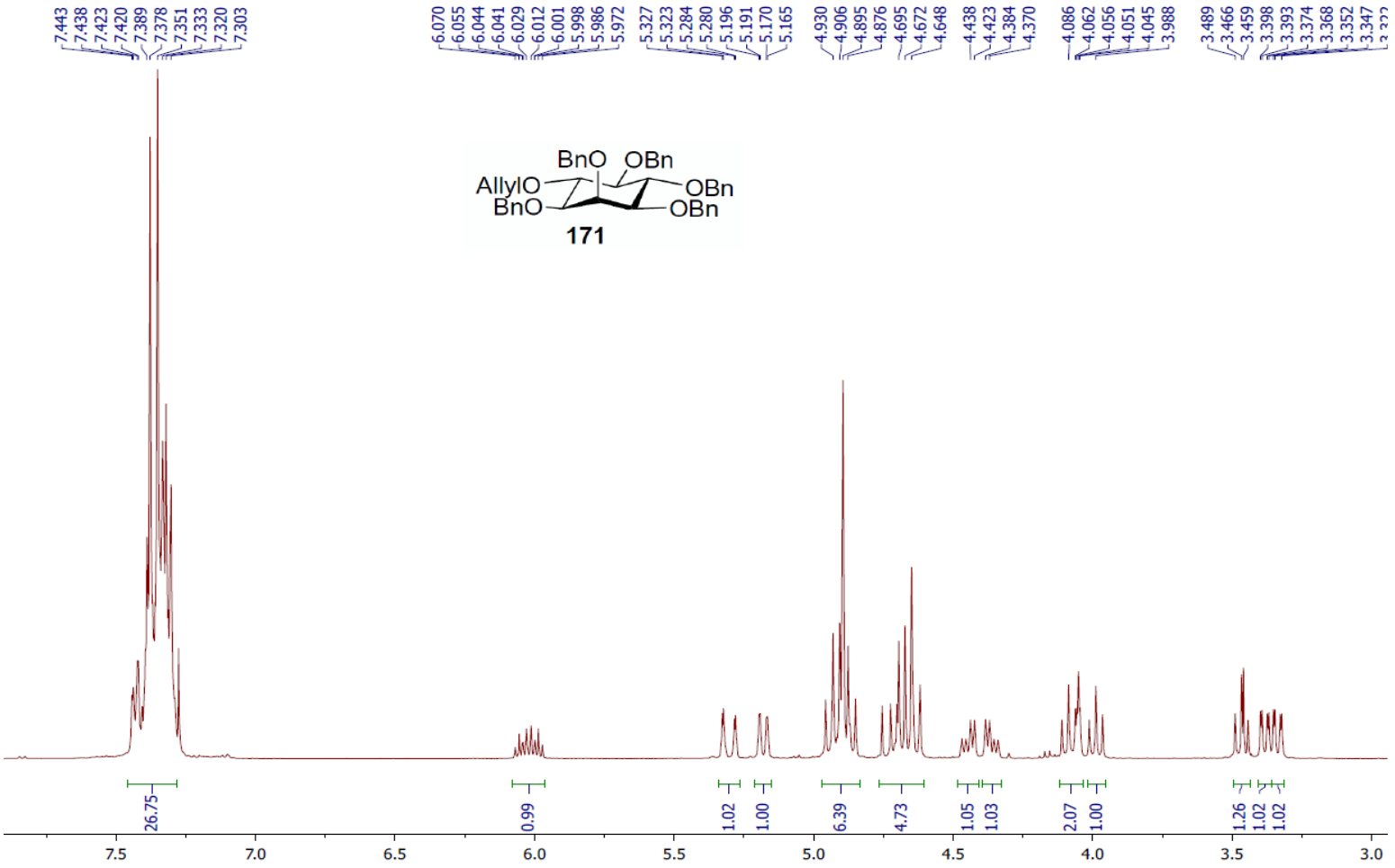


Figure A49. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **171**

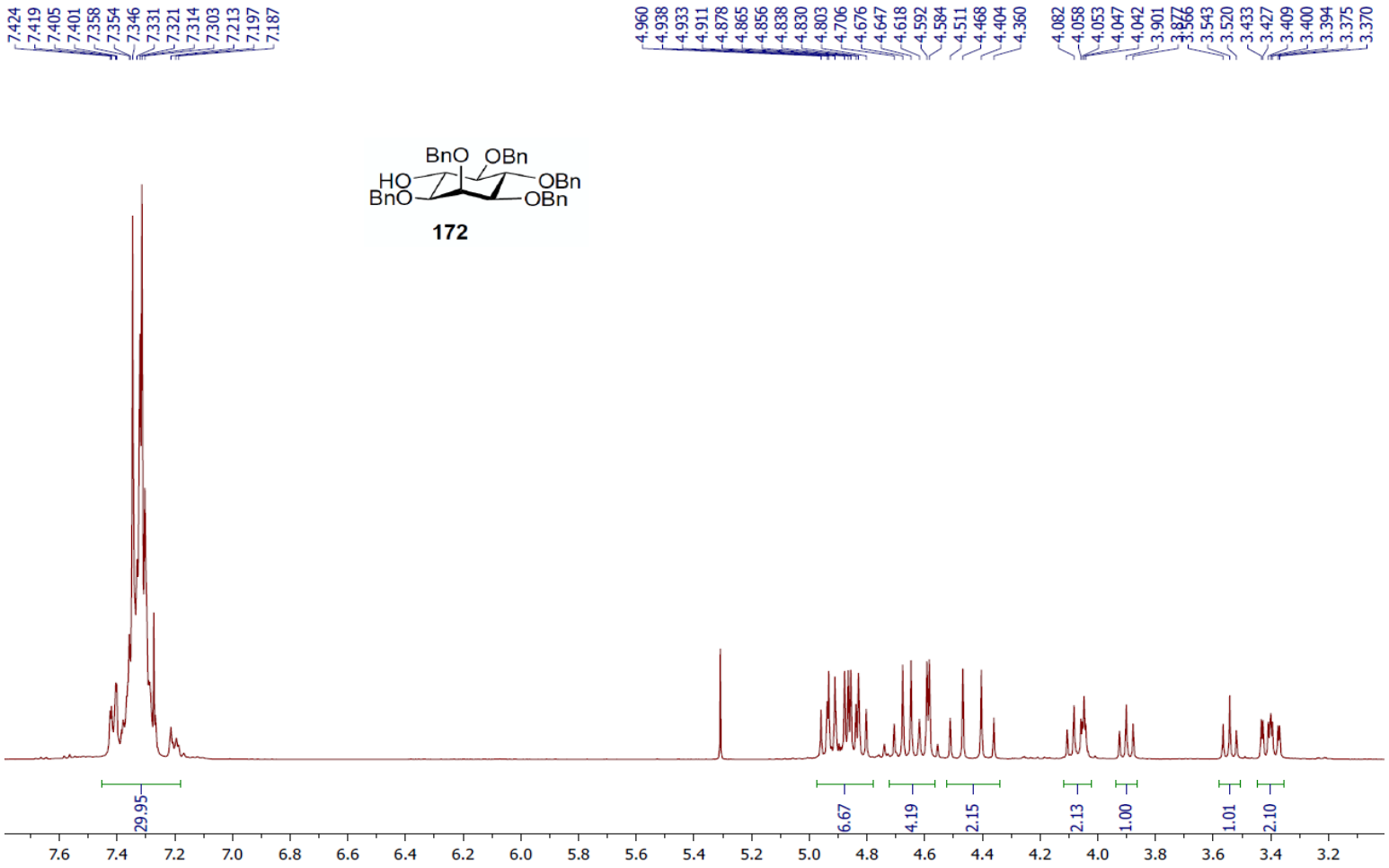


Figure A50. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **172**

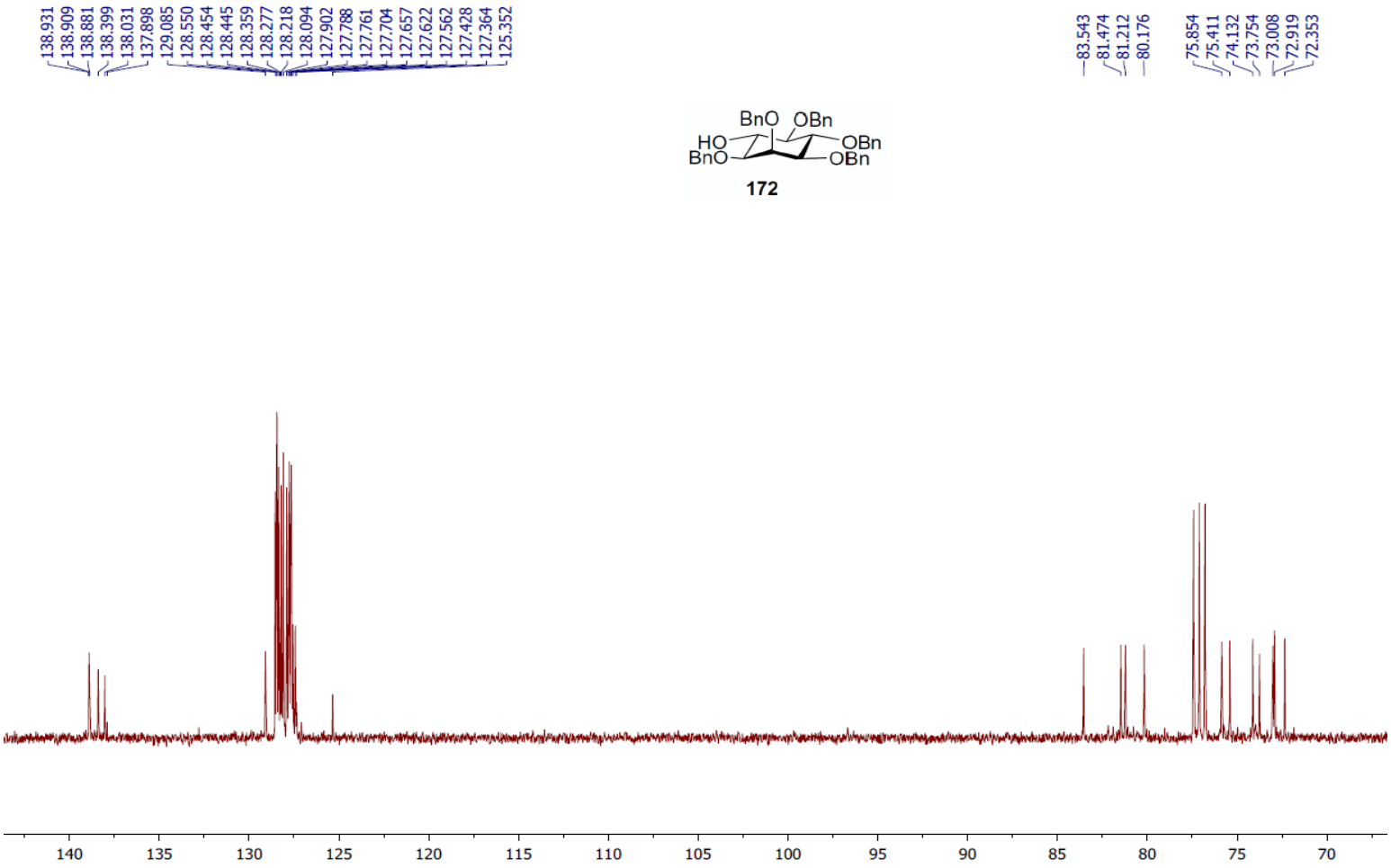


Figure A51. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Inositol **172**

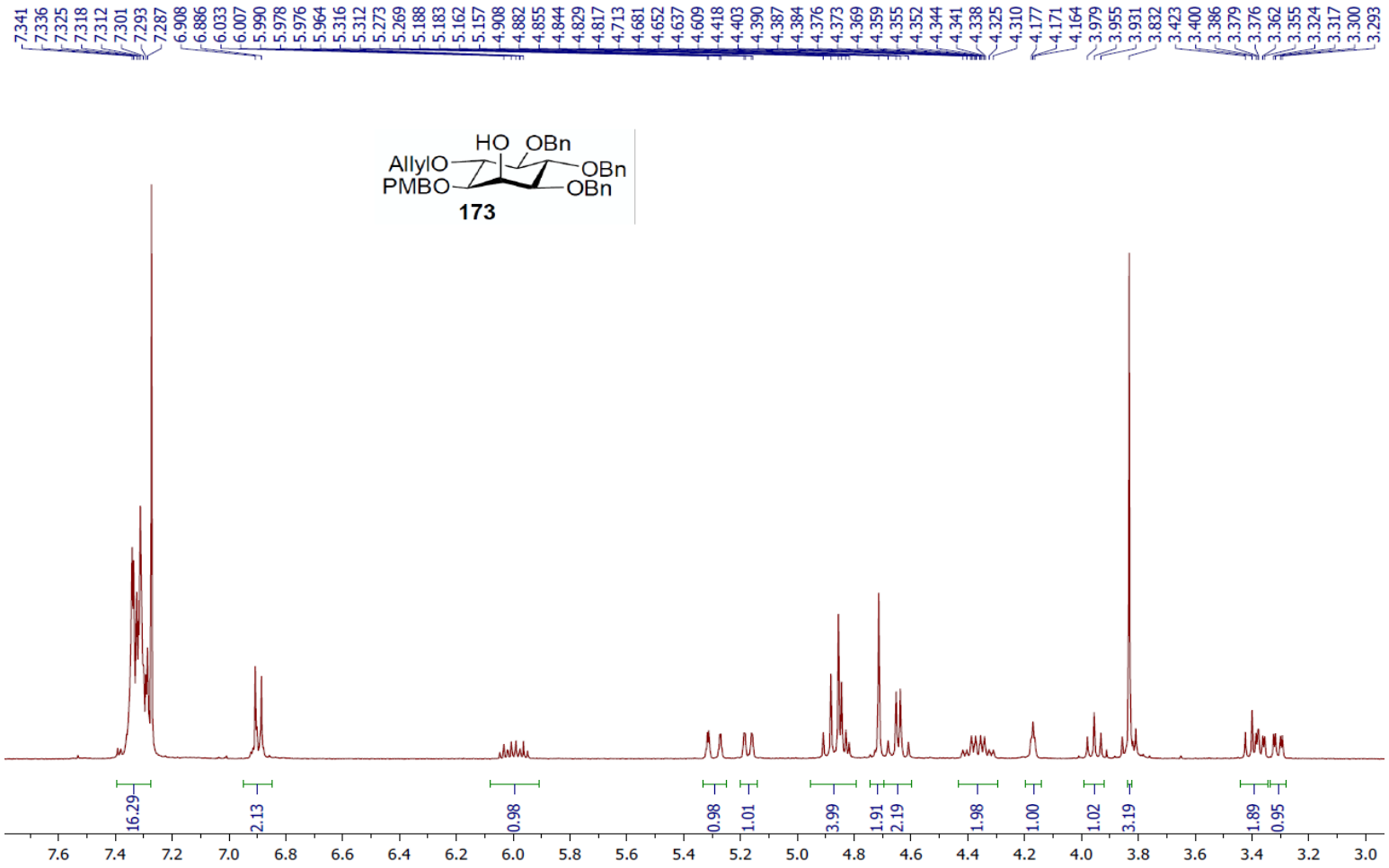


Figure A52. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **173**

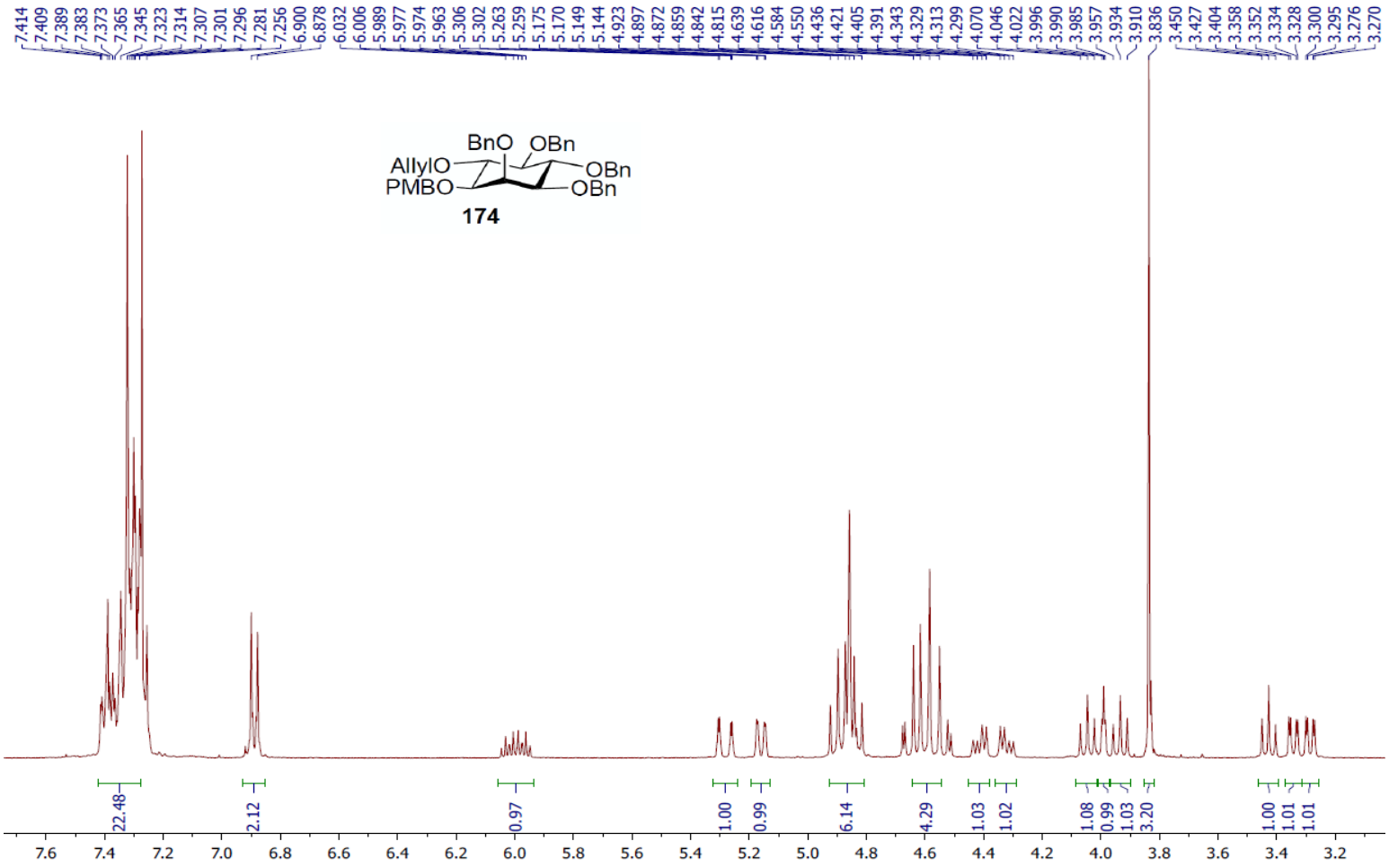


Figure A53. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **174**

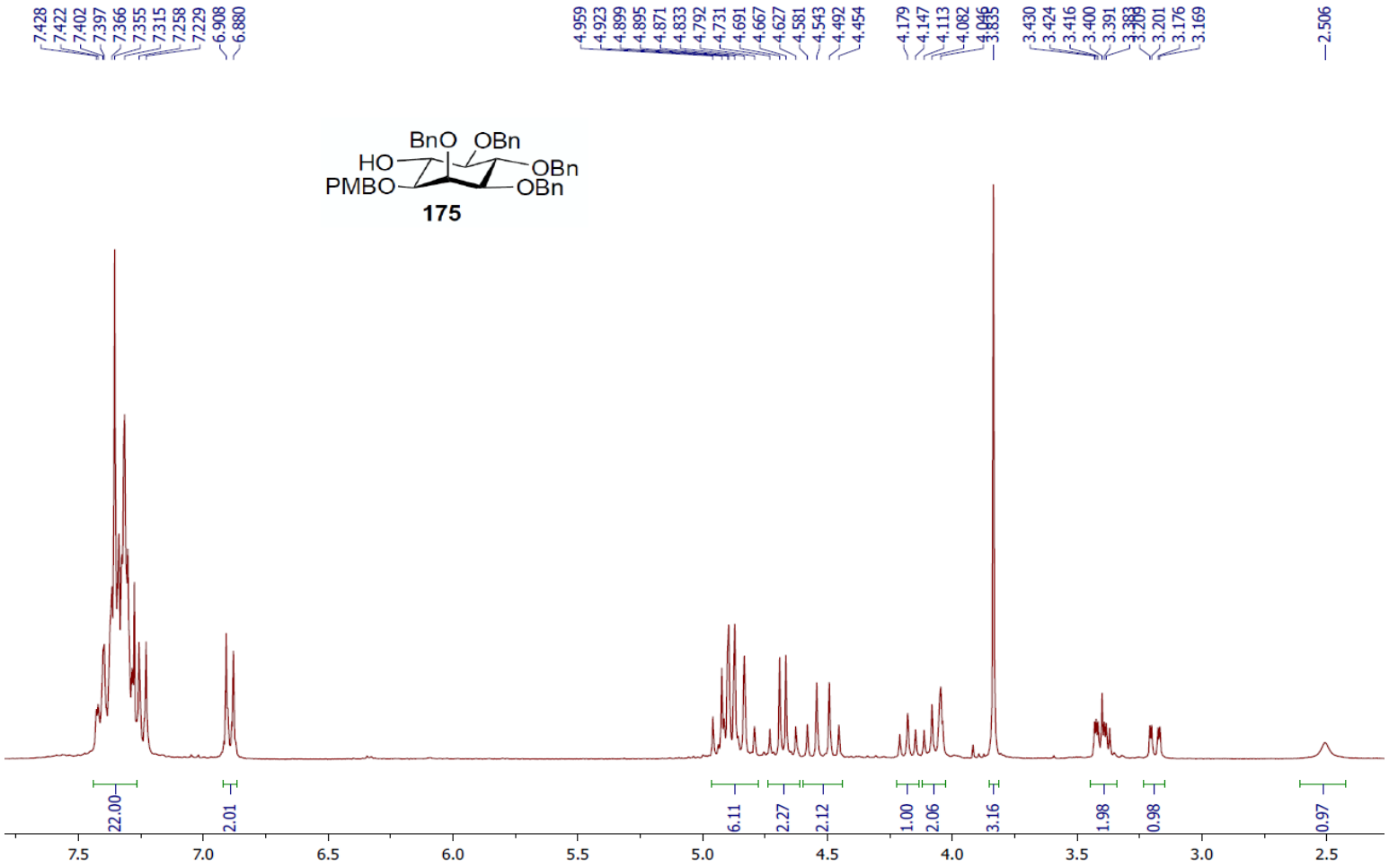


Figure A54. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **175**

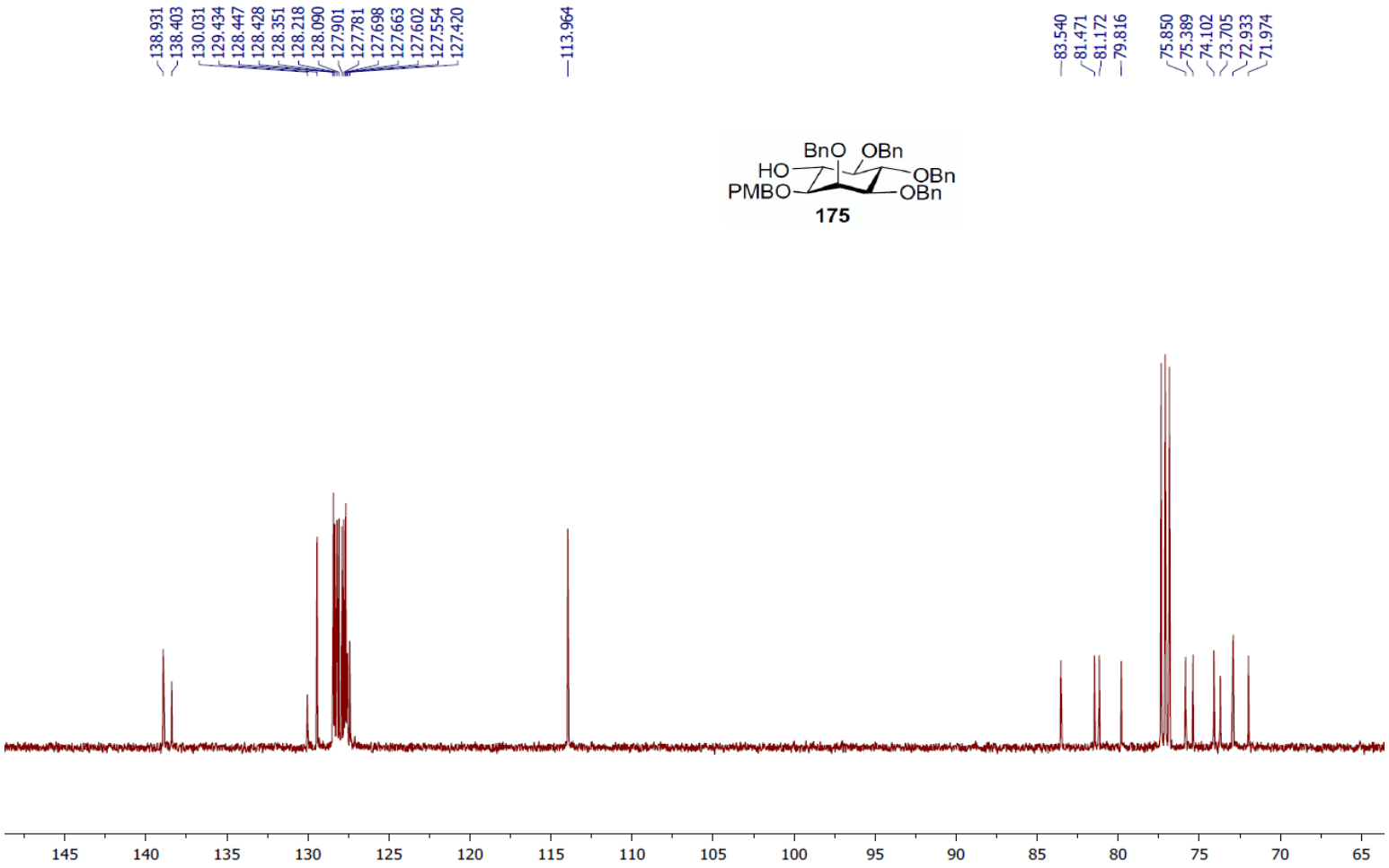


Figure A55. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Inositol **175**

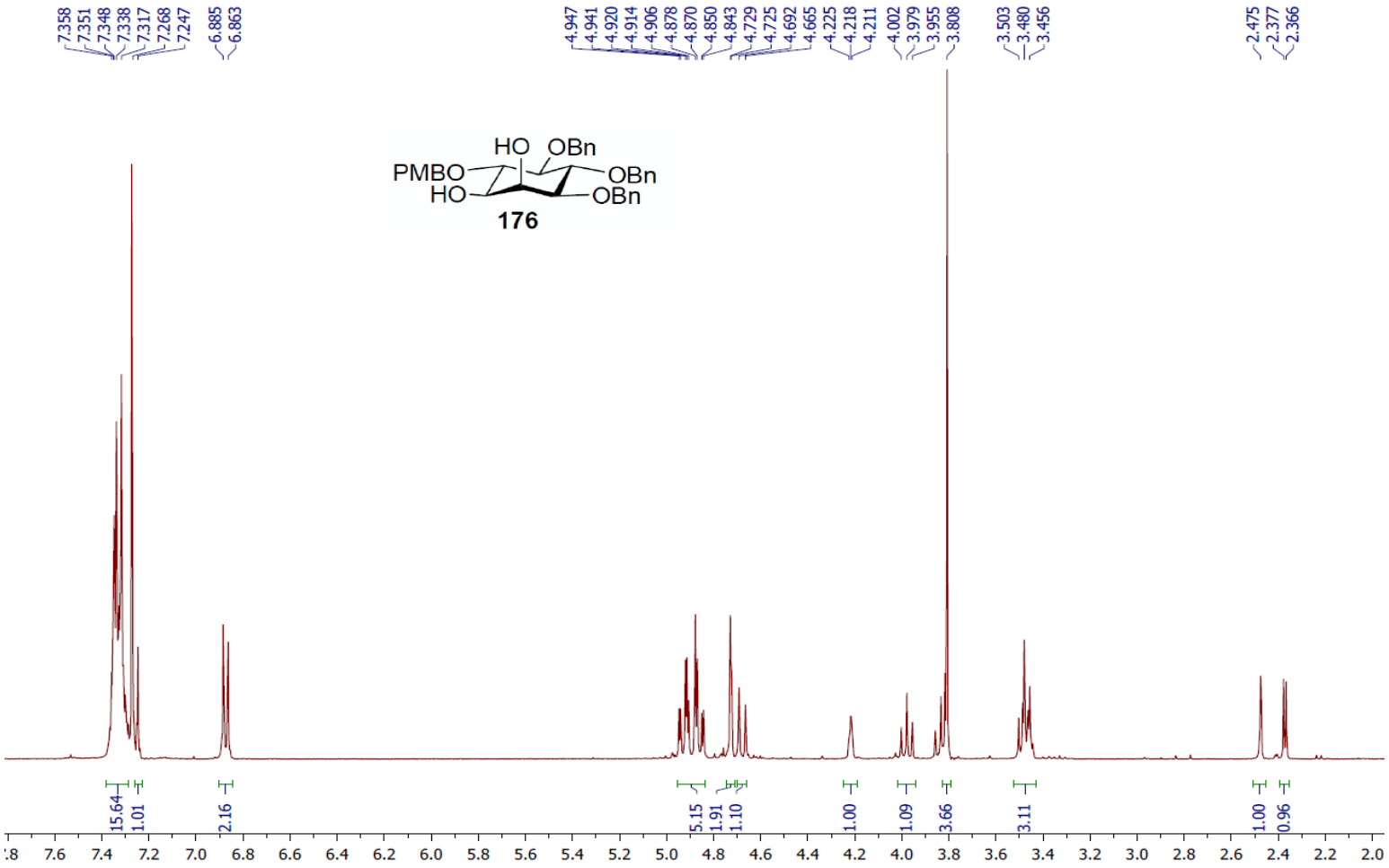


Figure A56. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **176**

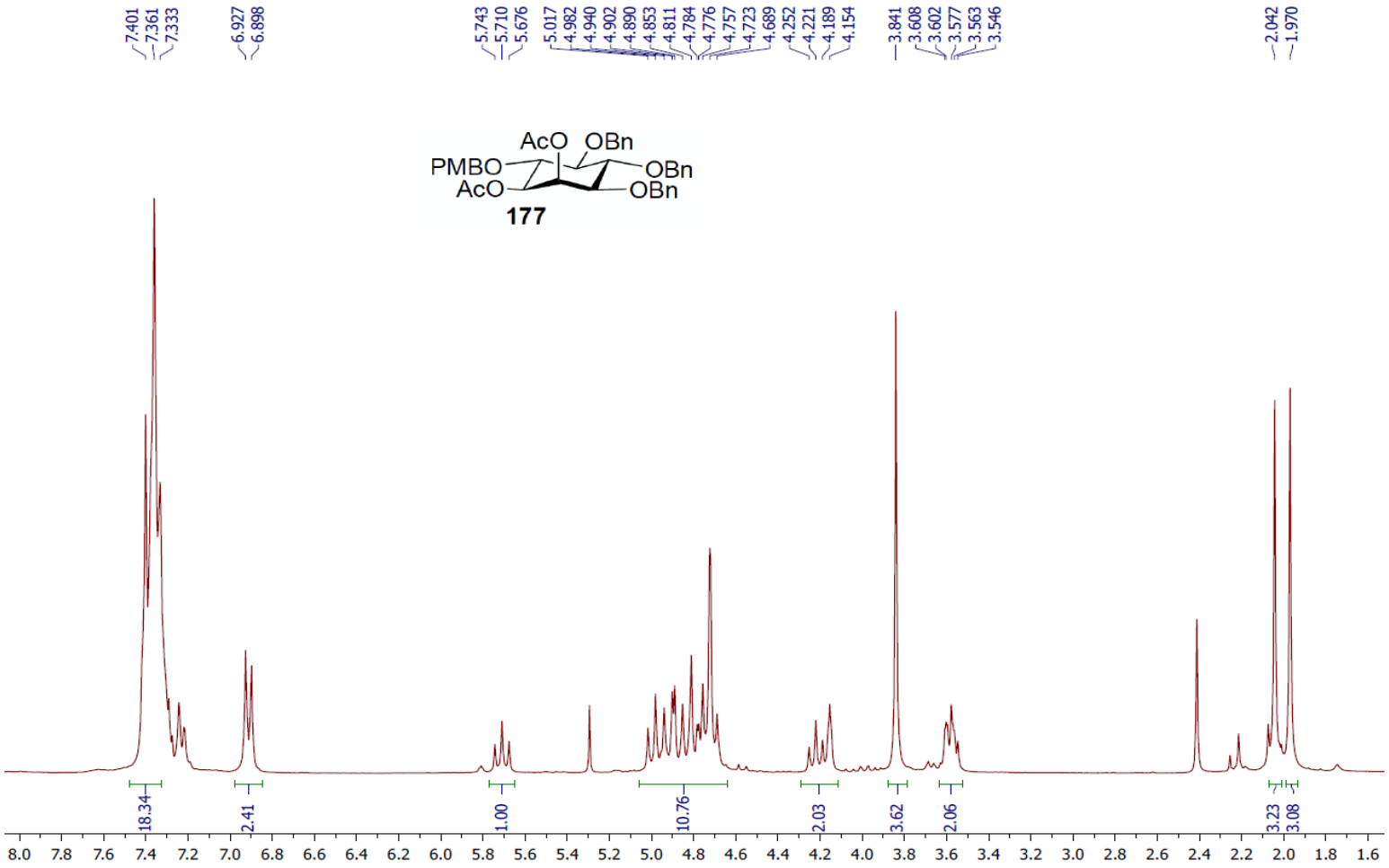


Figure A57. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **177**

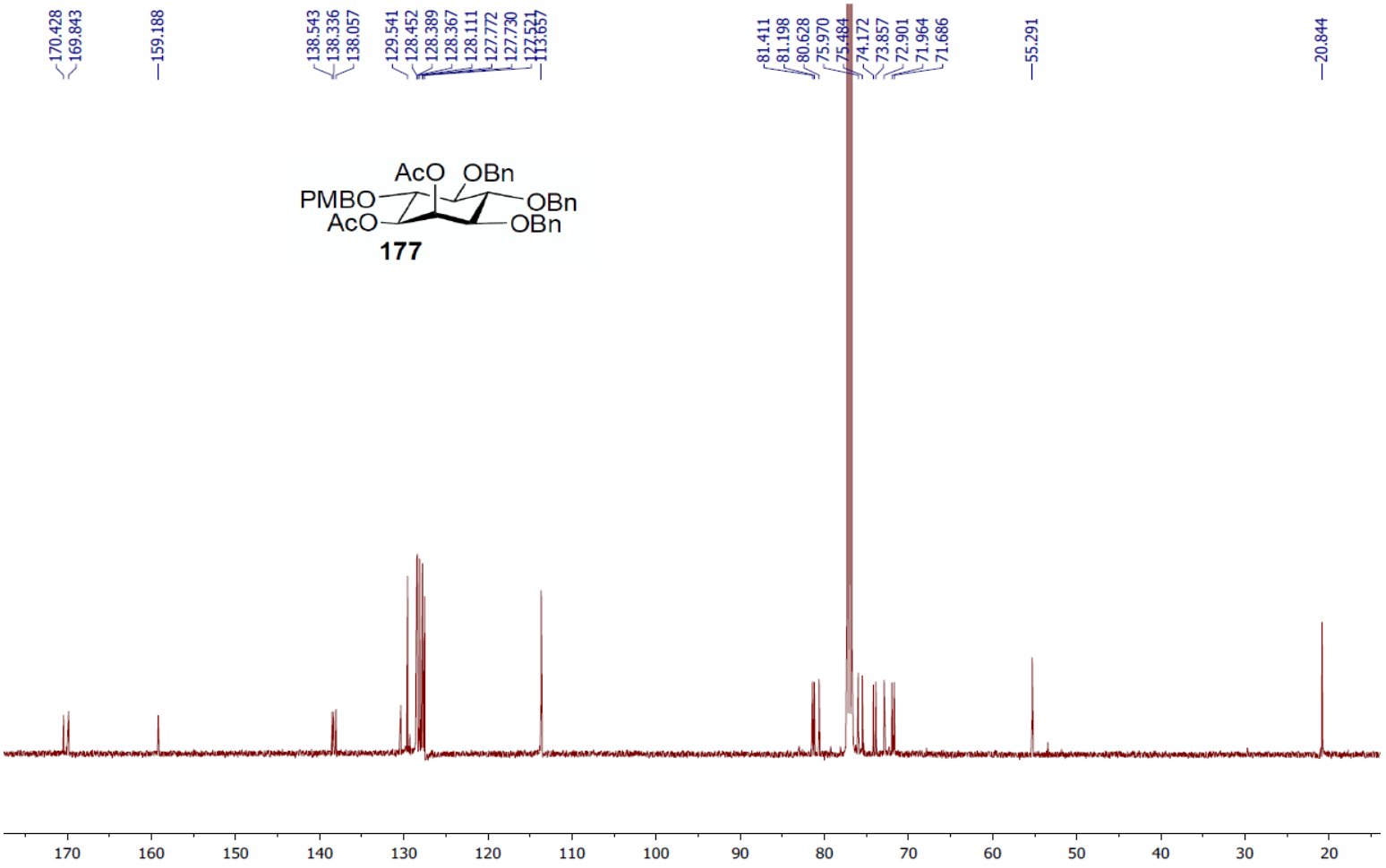


Figure A58. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Inositol **177**

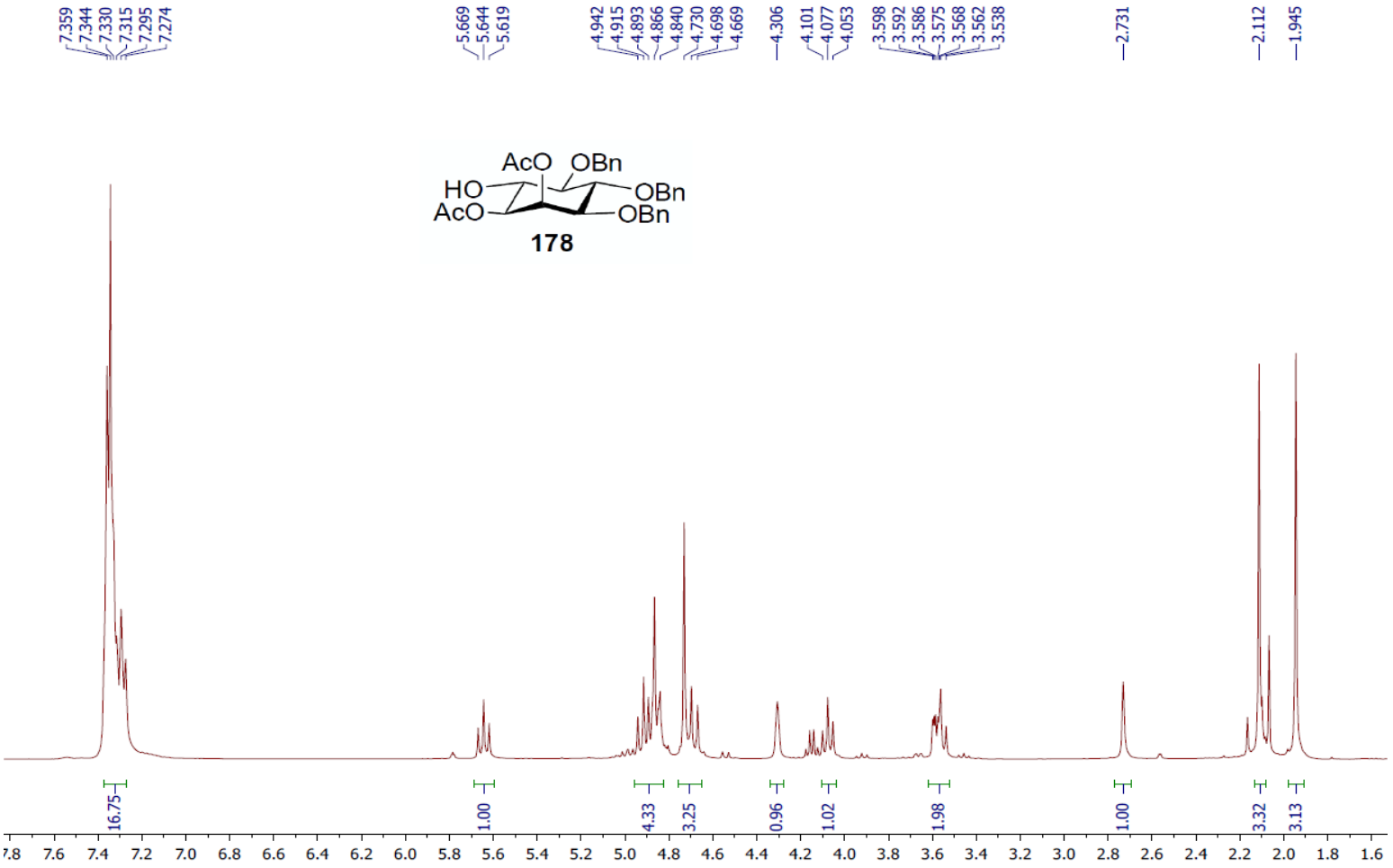


Figure A59. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Inositol **178**

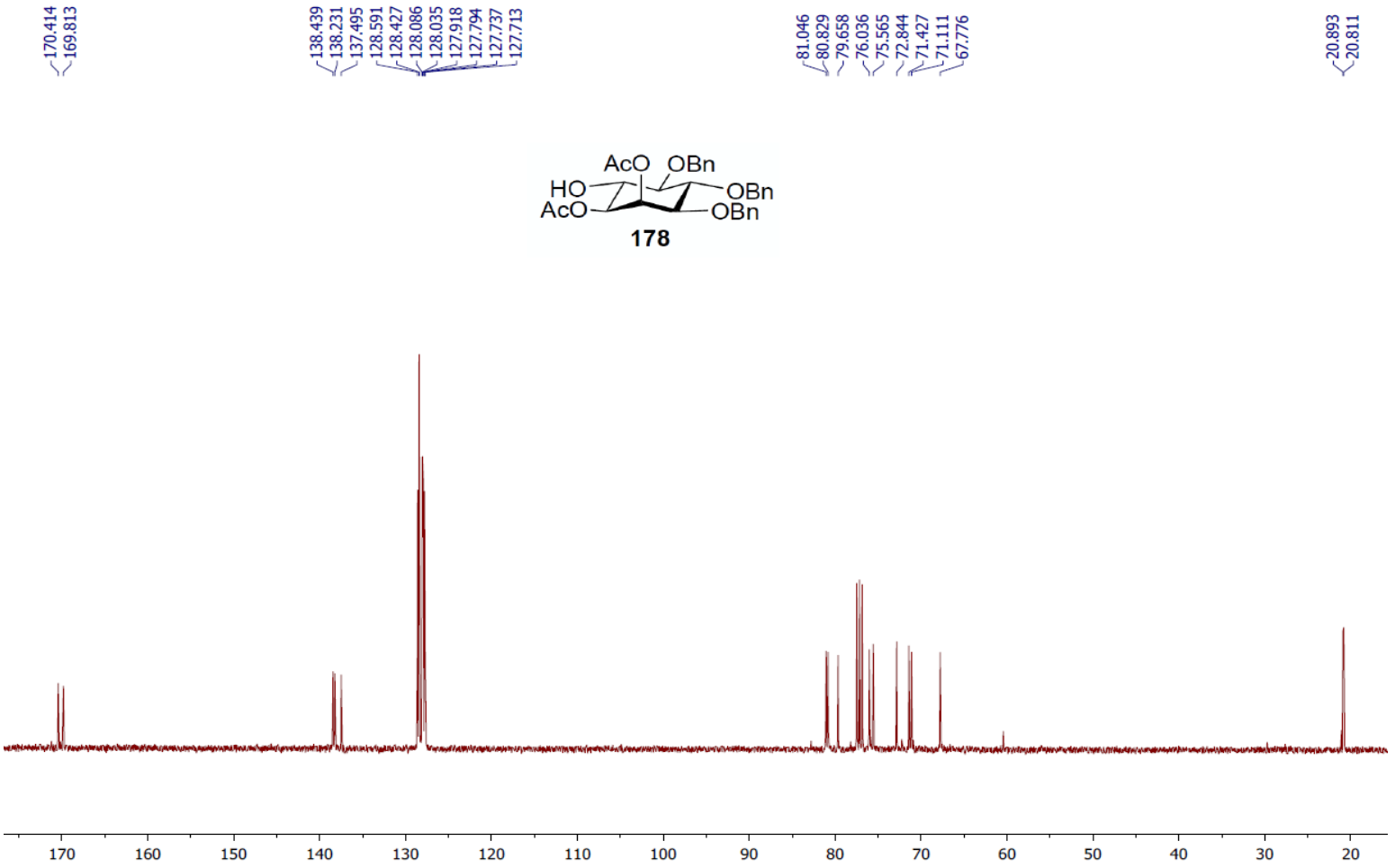


Figure A60. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Inositol **178**

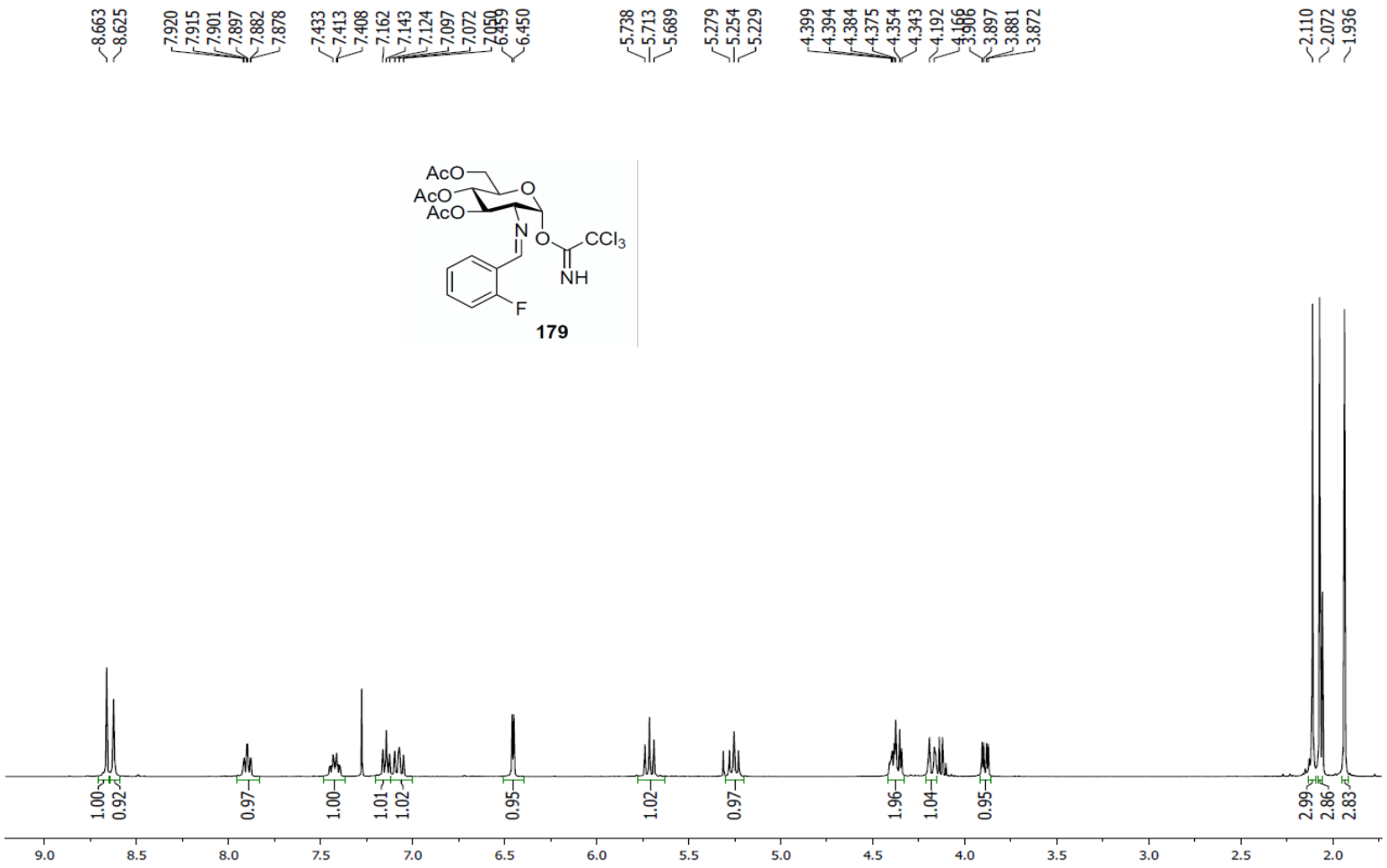


Figure A61. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **179**

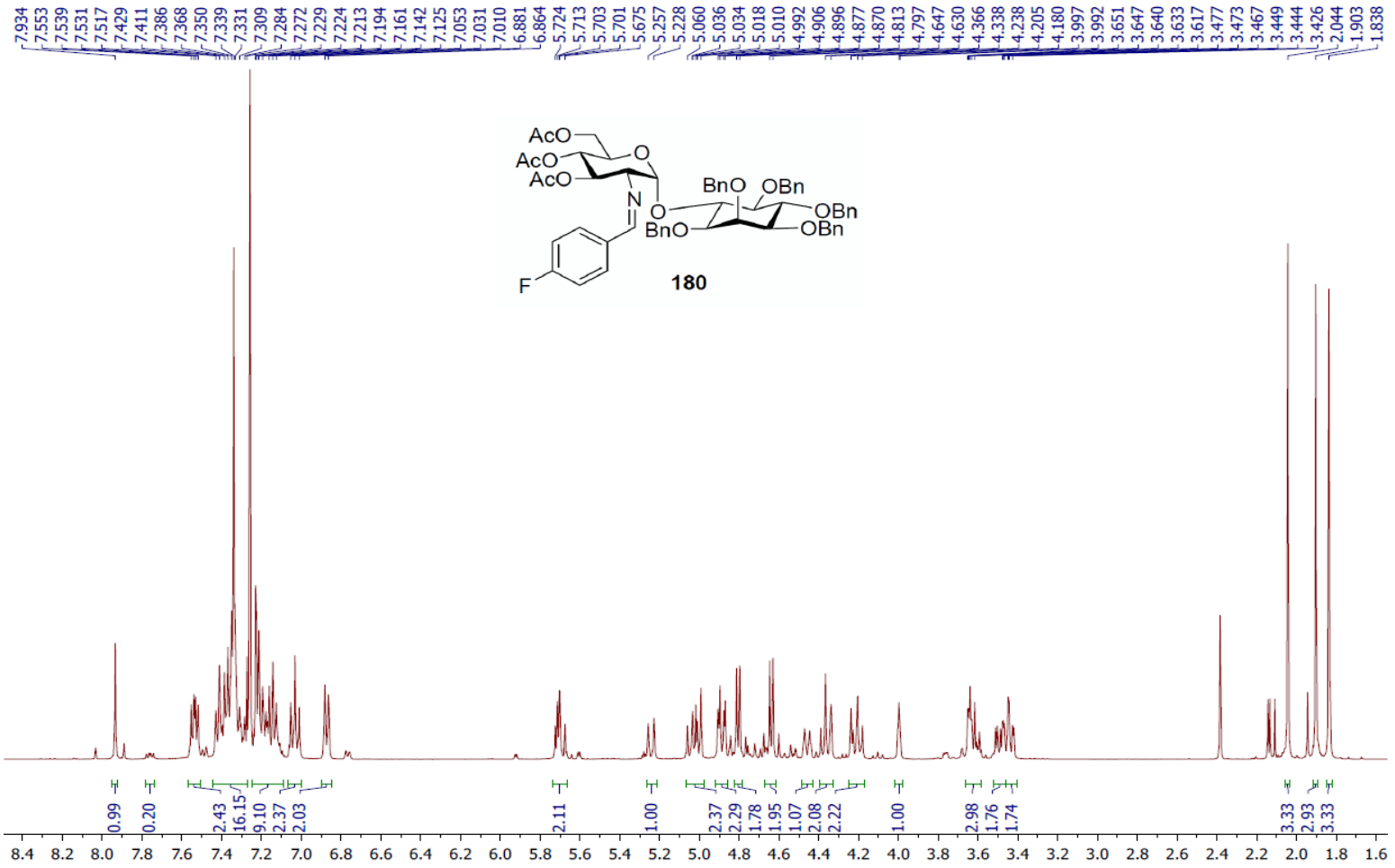


Figure A62. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **180**

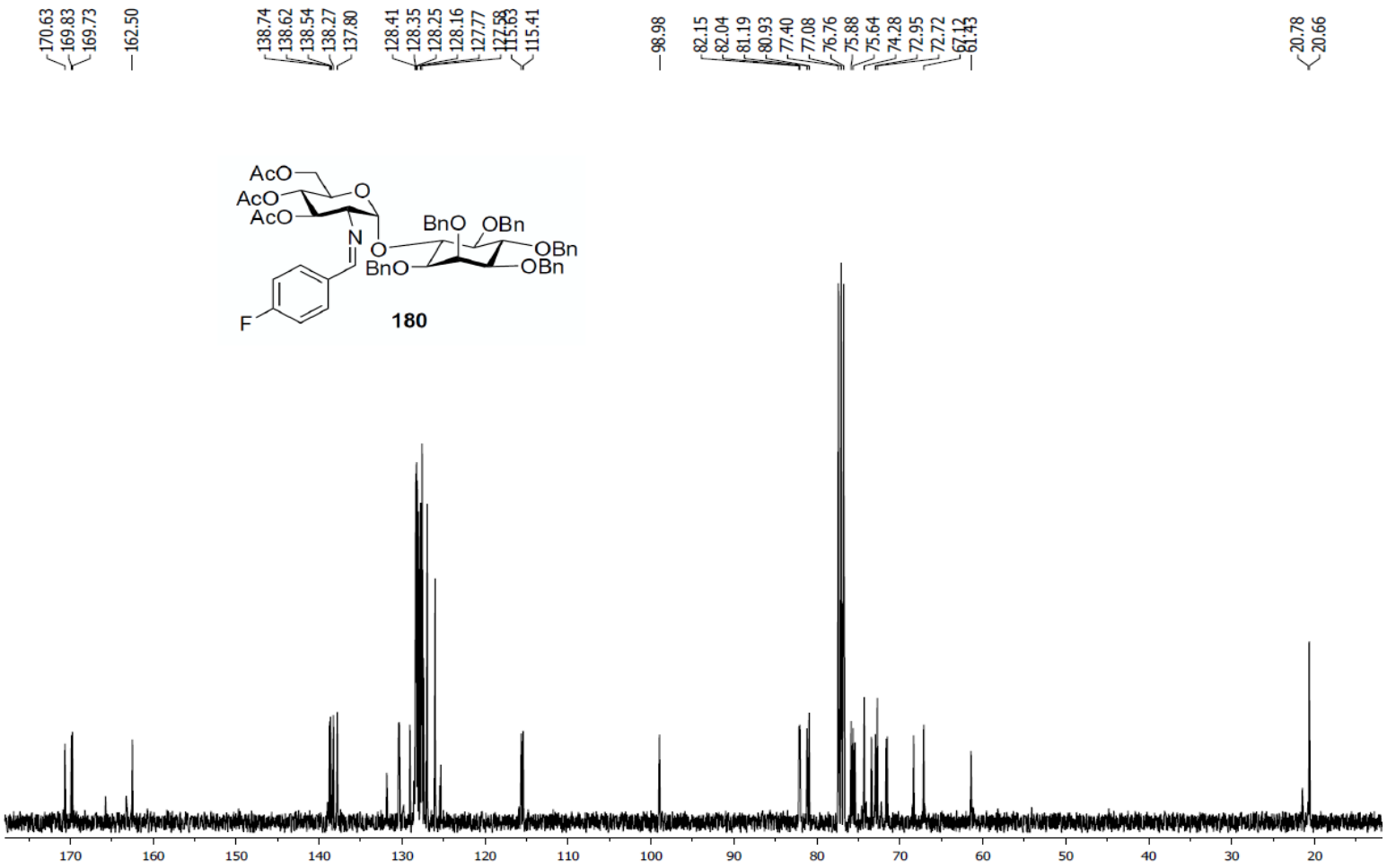


Figure A63. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **180**

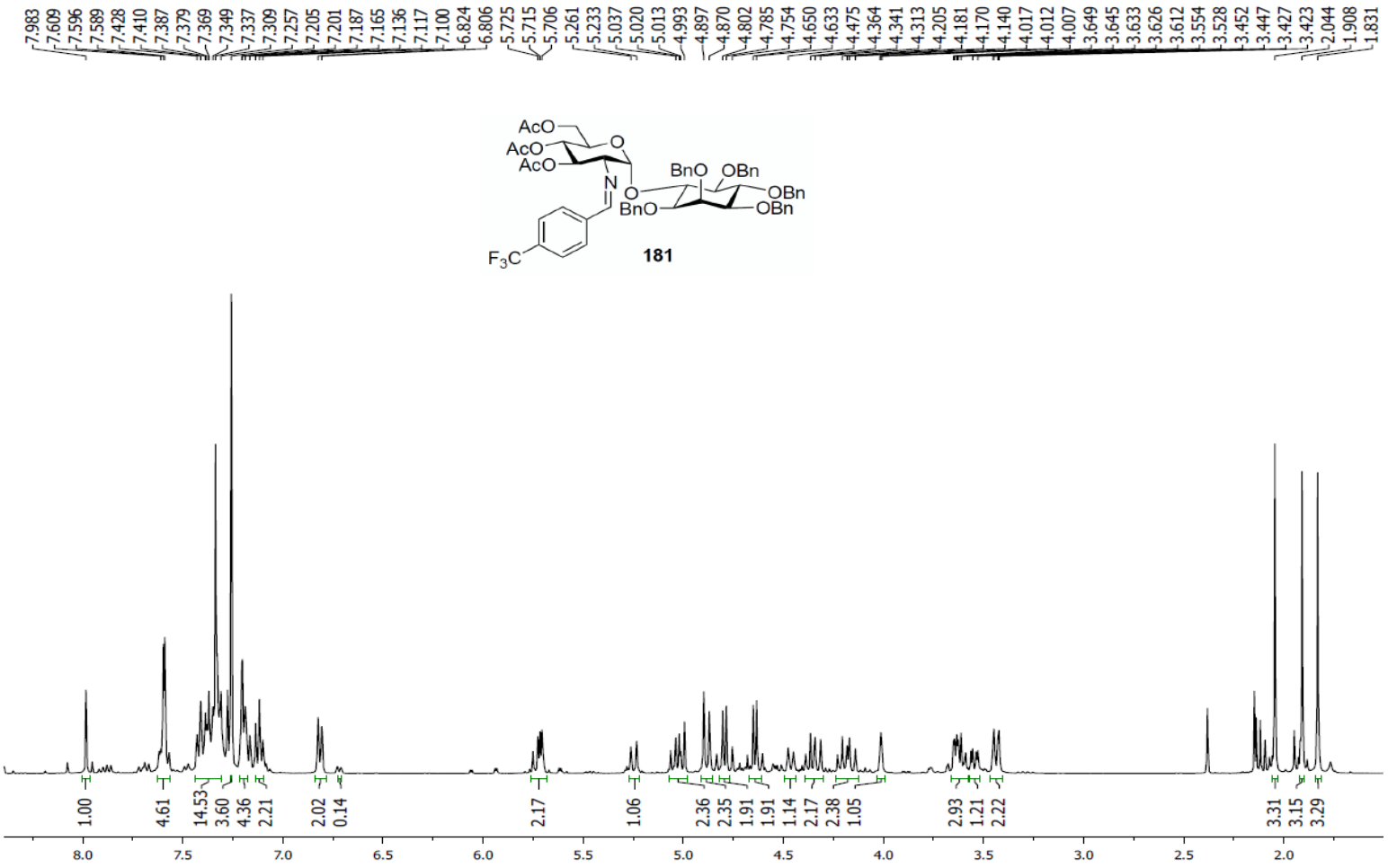


Figure A64. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **181**

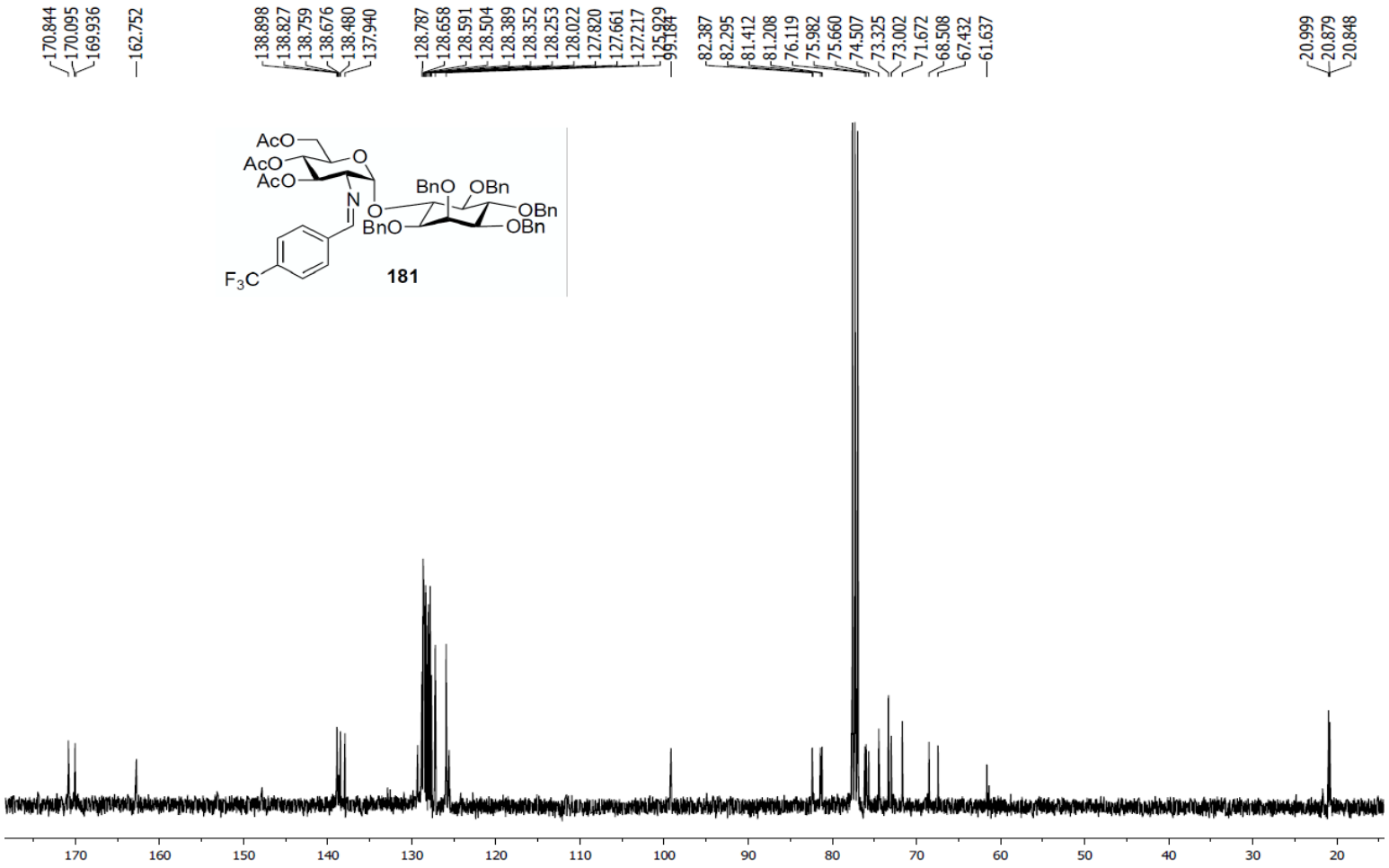


Figure A65. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **181**

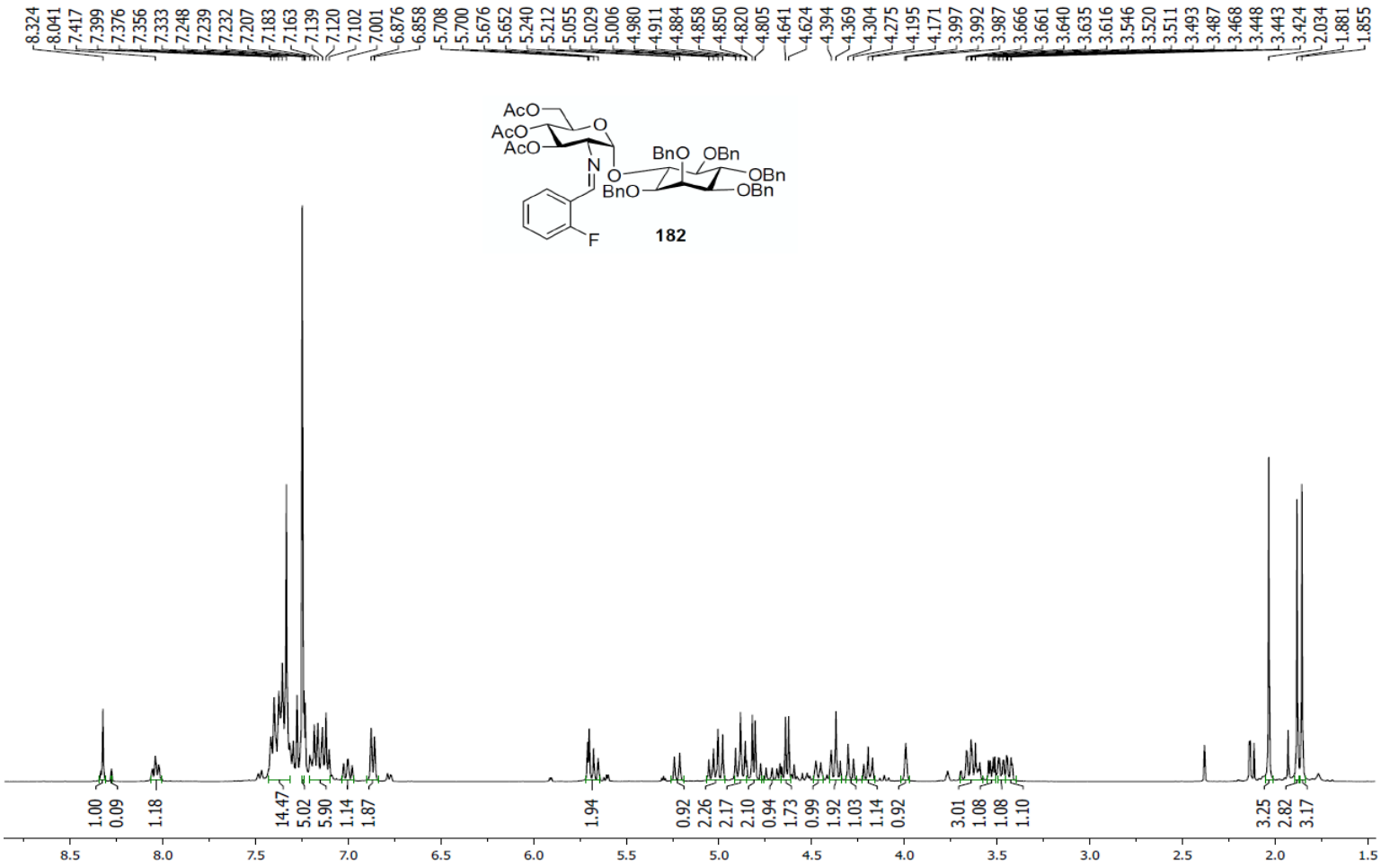


Figure A66. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **182**

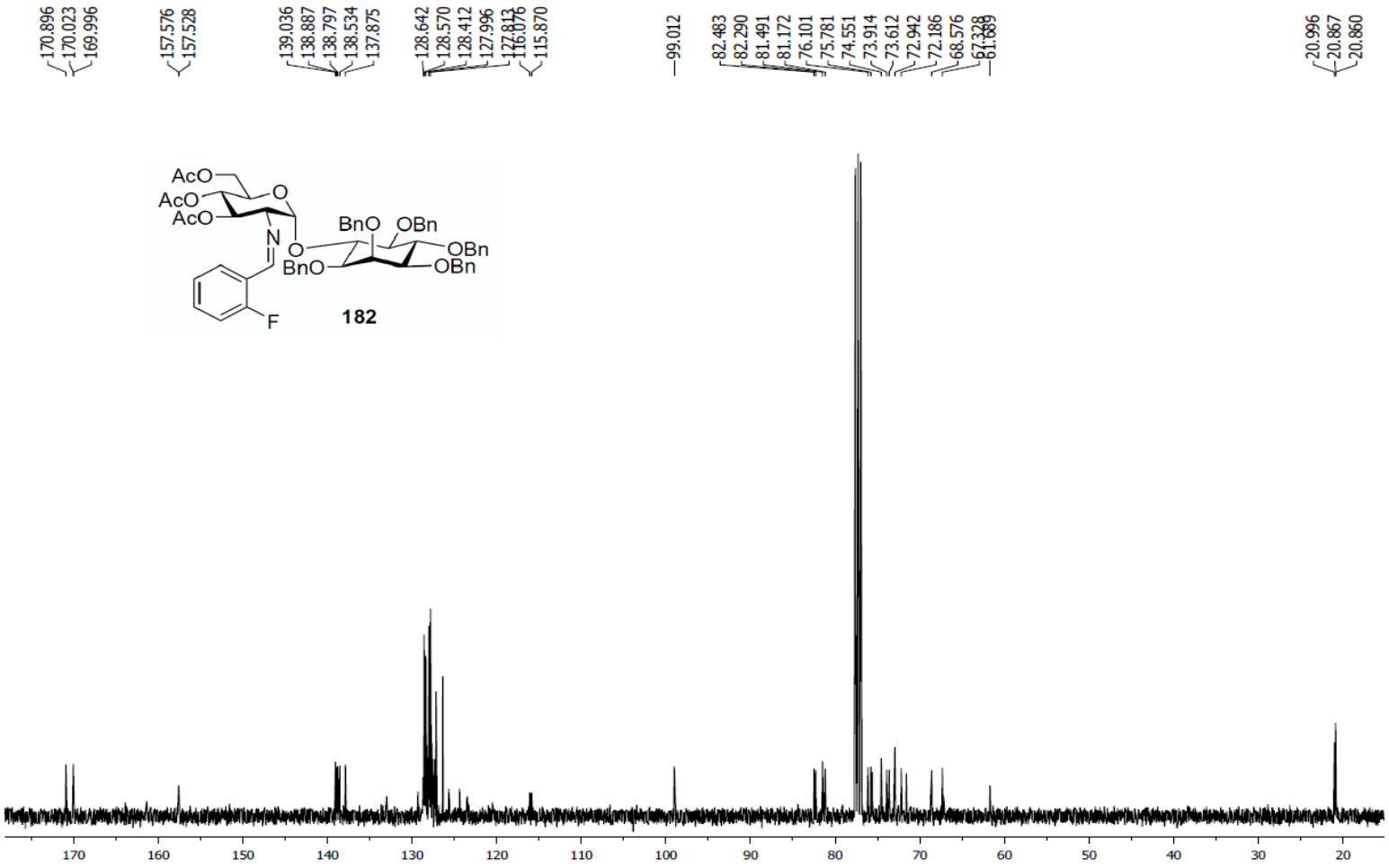


Figure A67. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **182**

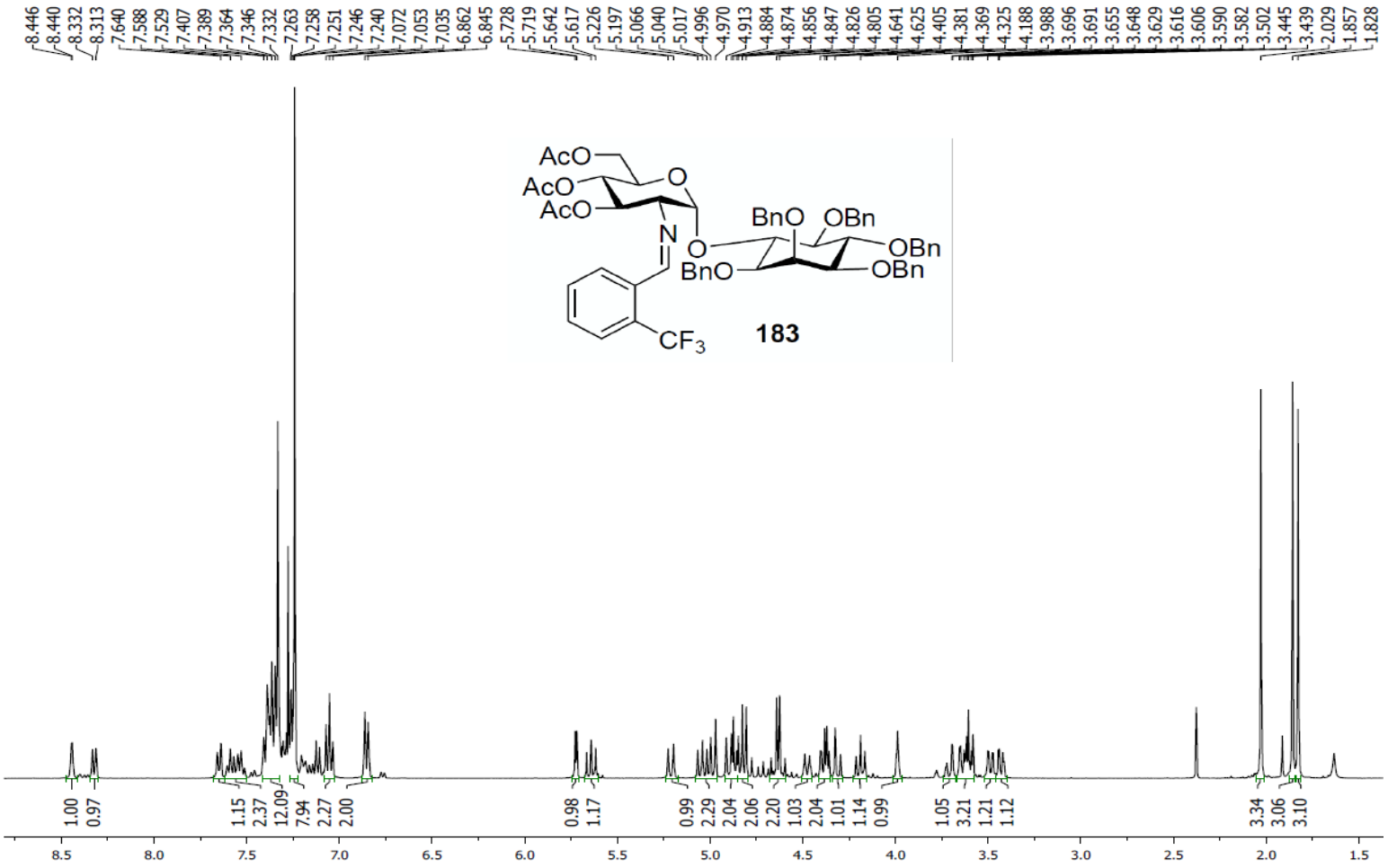


Figure A68. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **183**

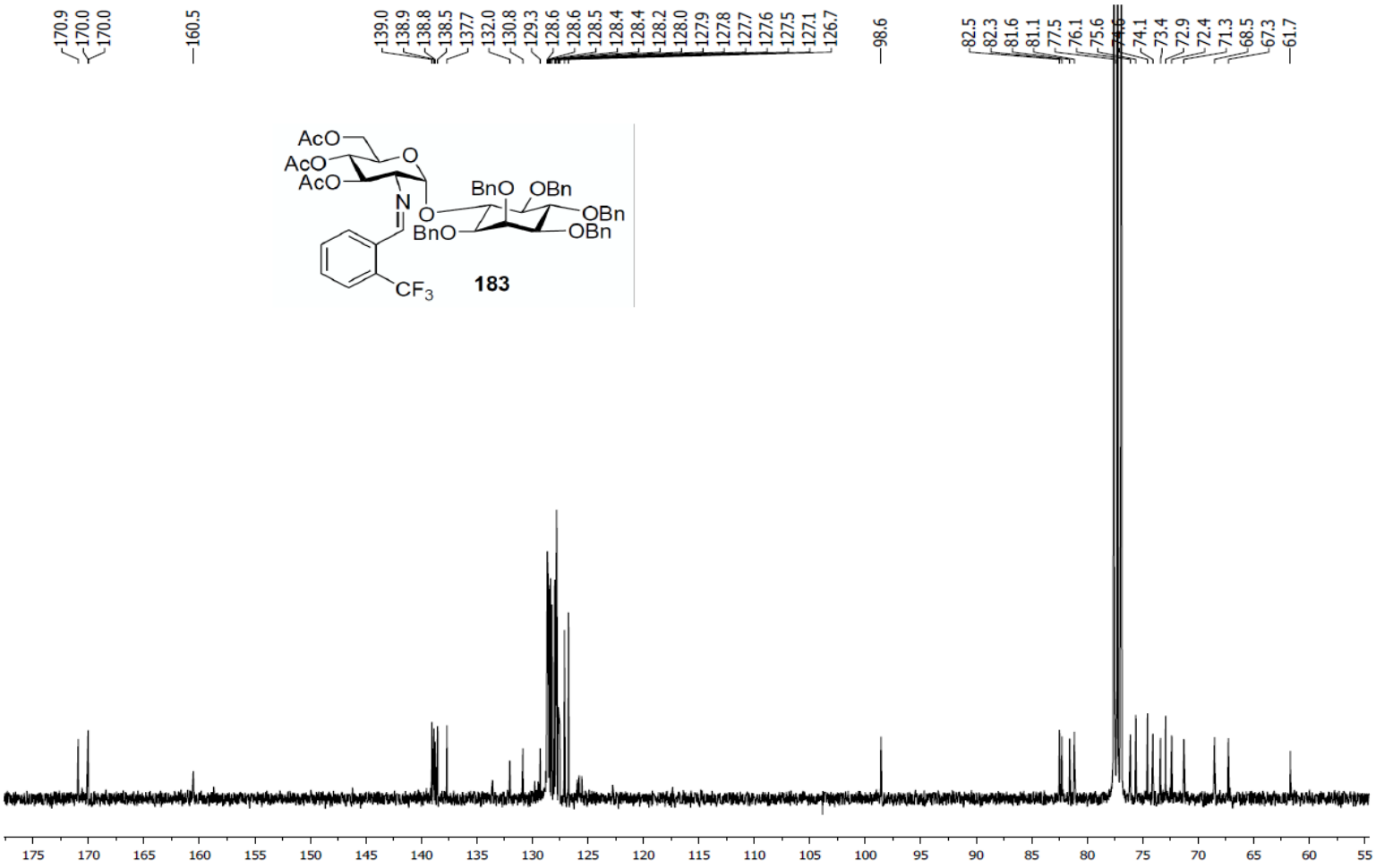


Figure A69. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **183**

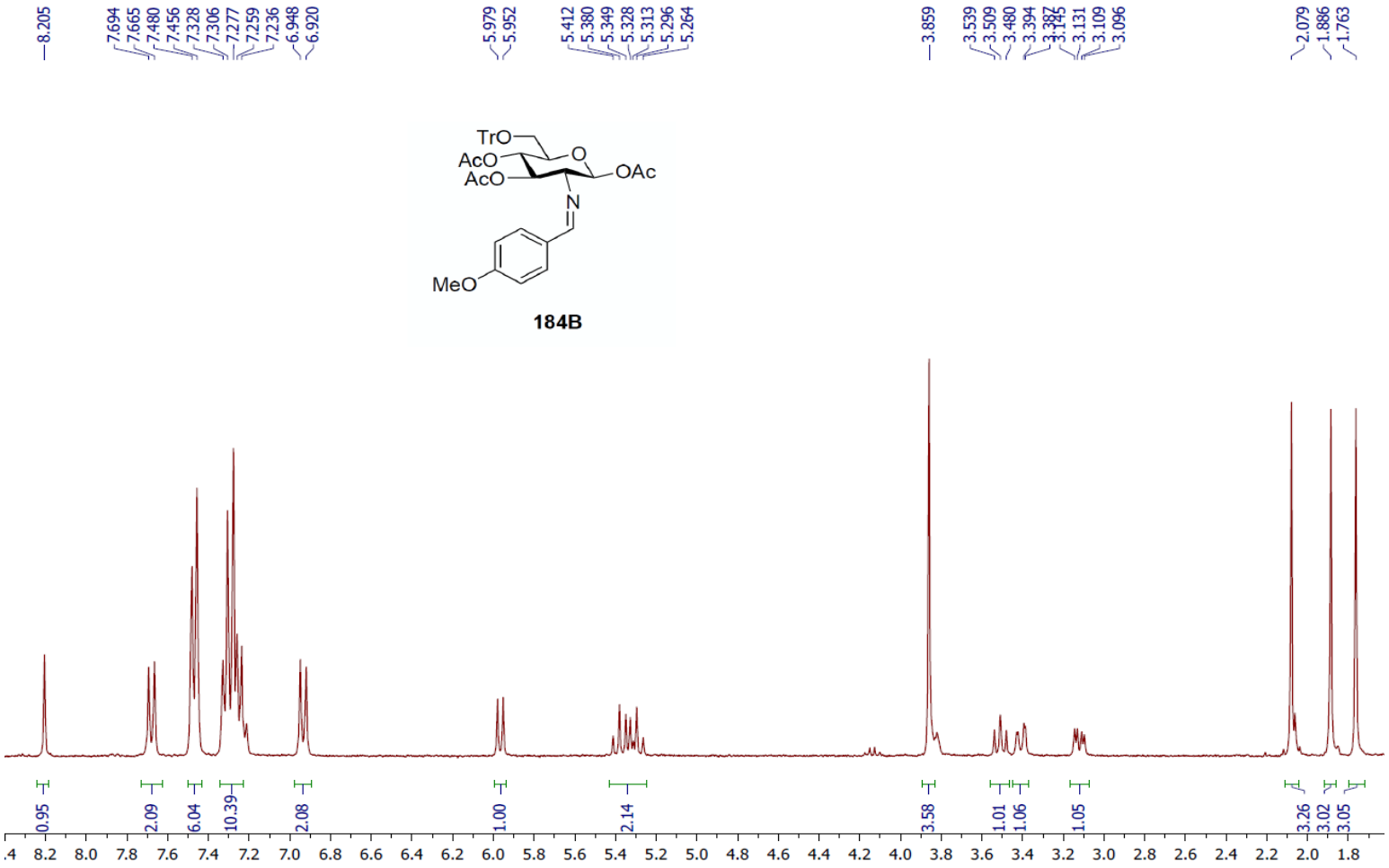


Figure A70. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **184B**

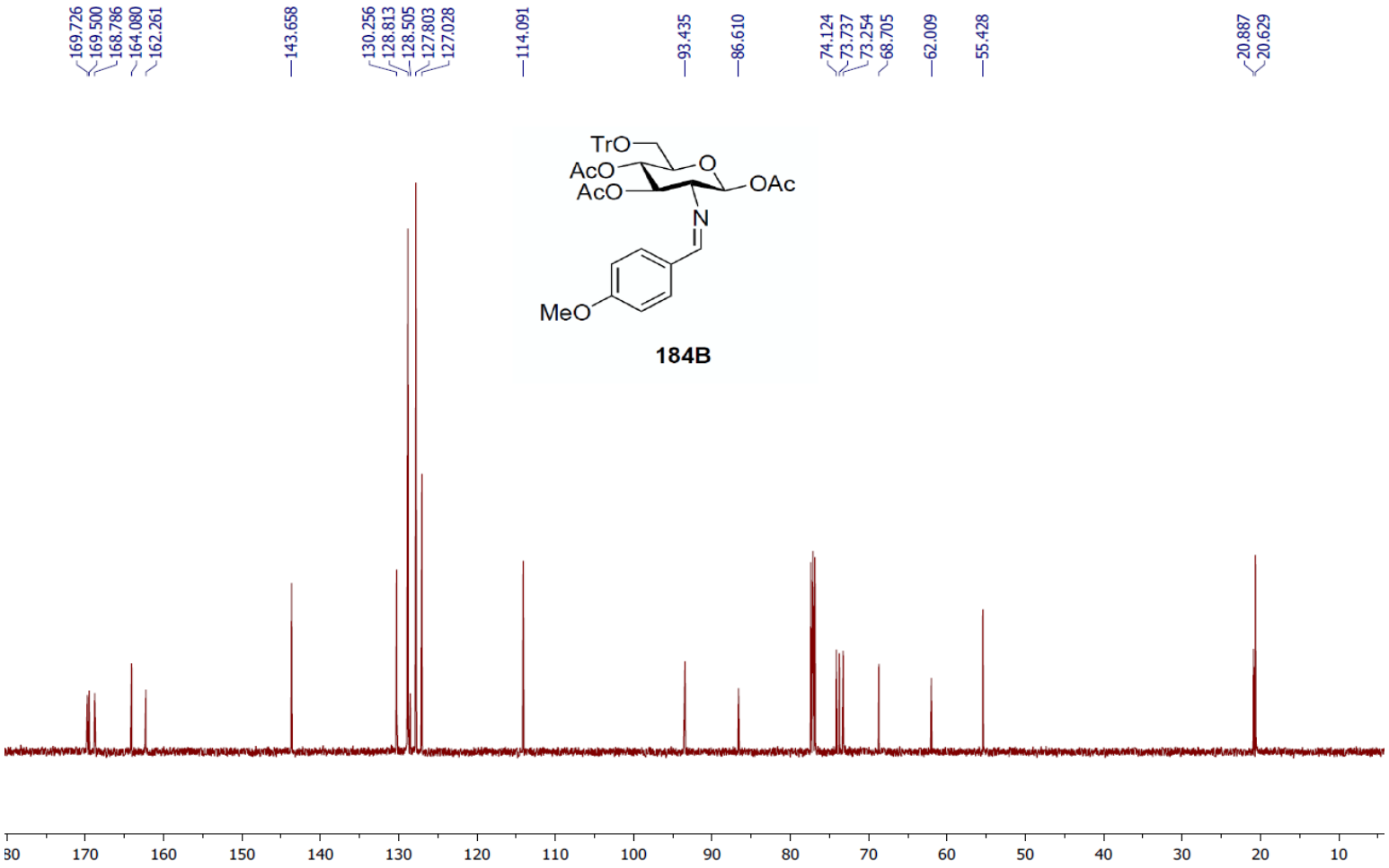


Figure A71. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glucoside **184B**

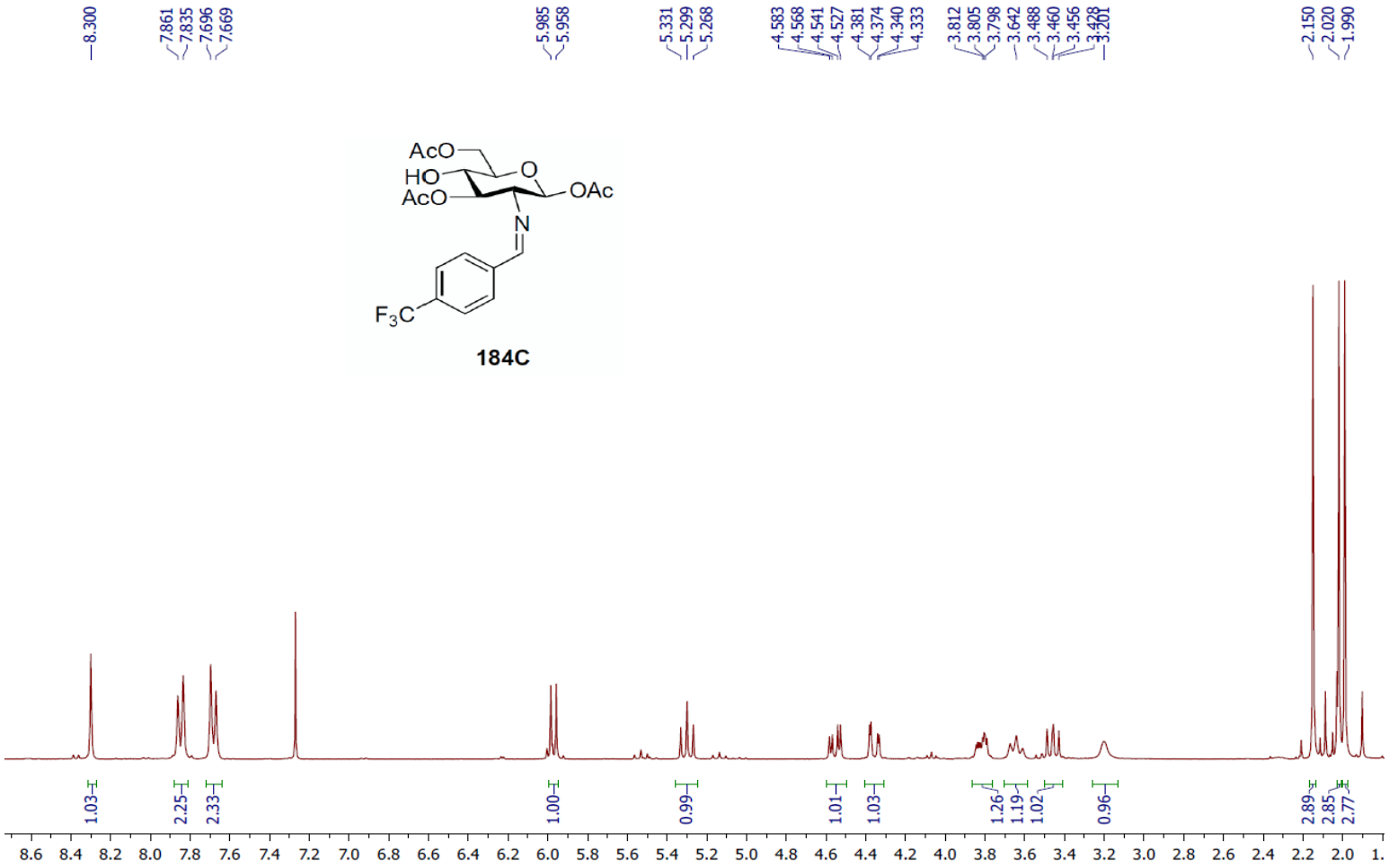


Figure A72. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **184C**

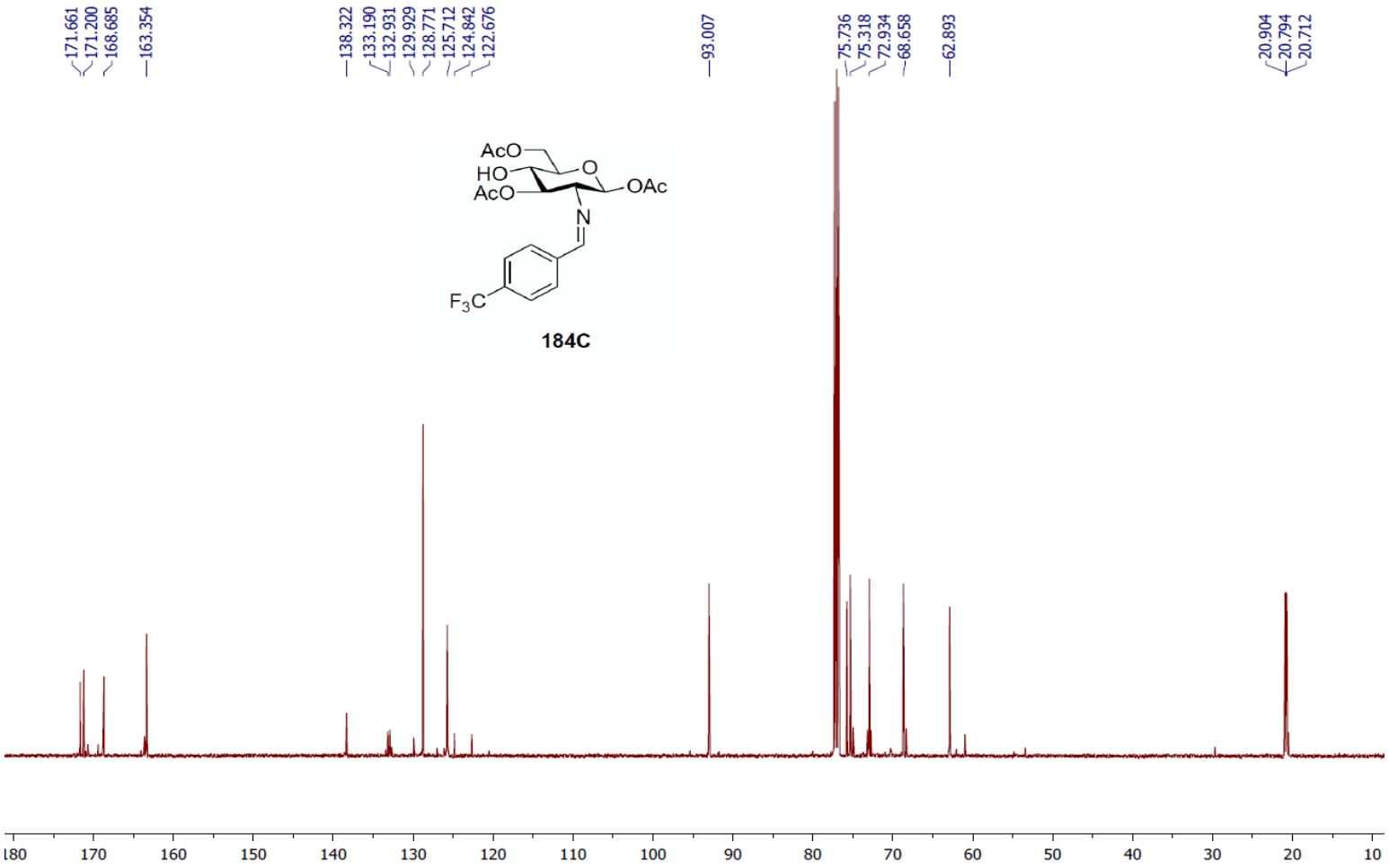


Figure A73. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glucoside **184C**

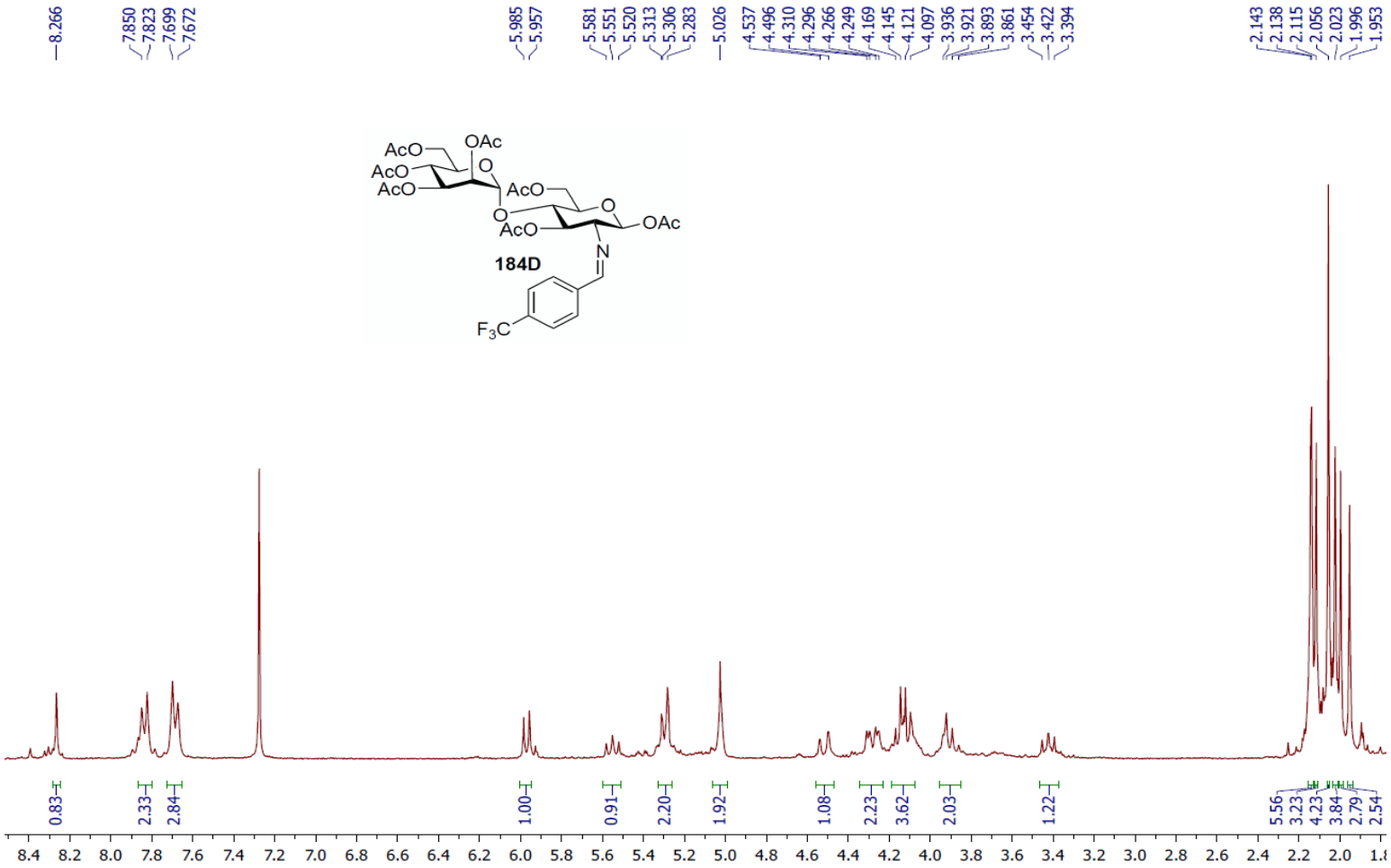


Figure A74. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **184D**

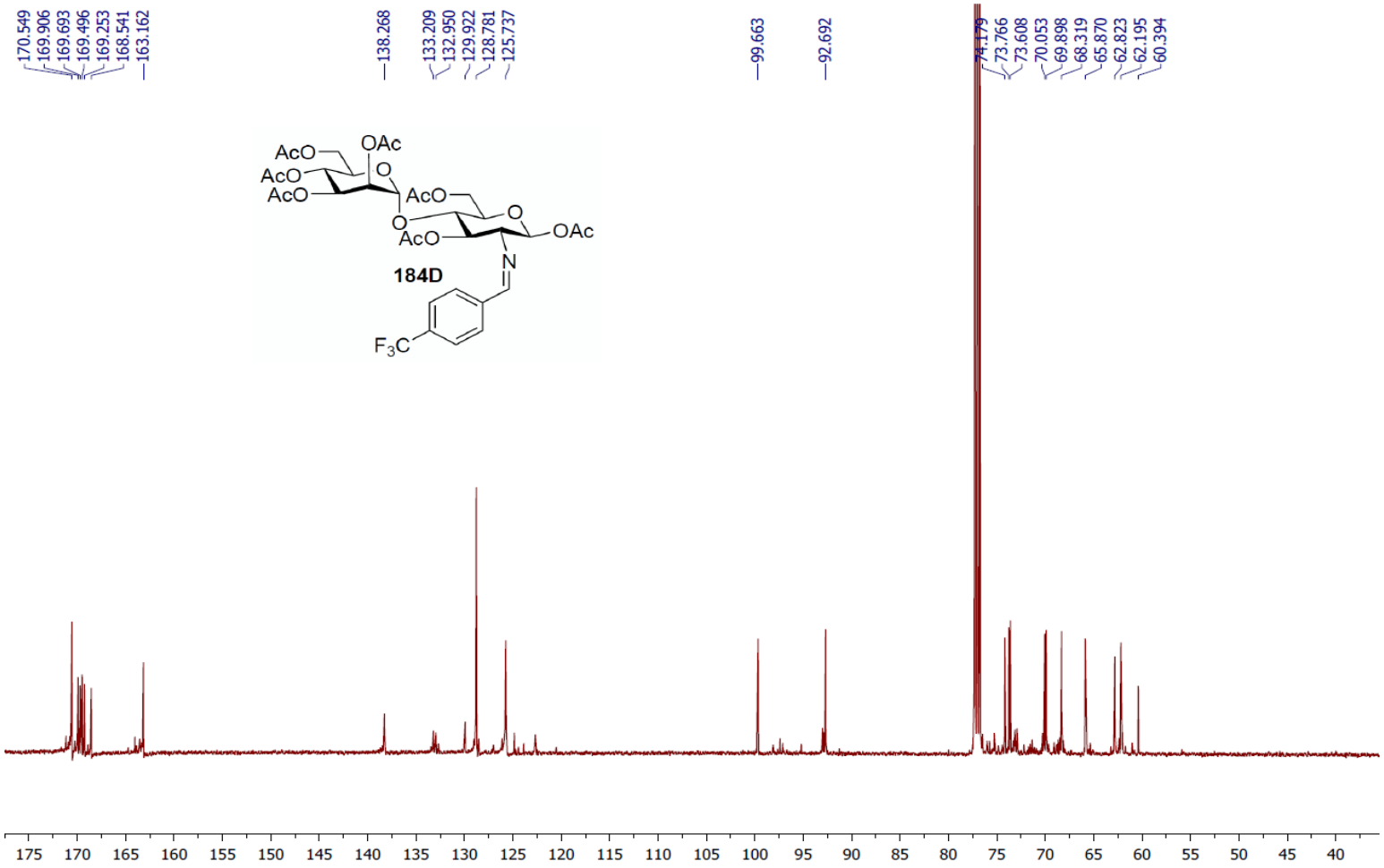


Figure A75. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glucoside **184D**

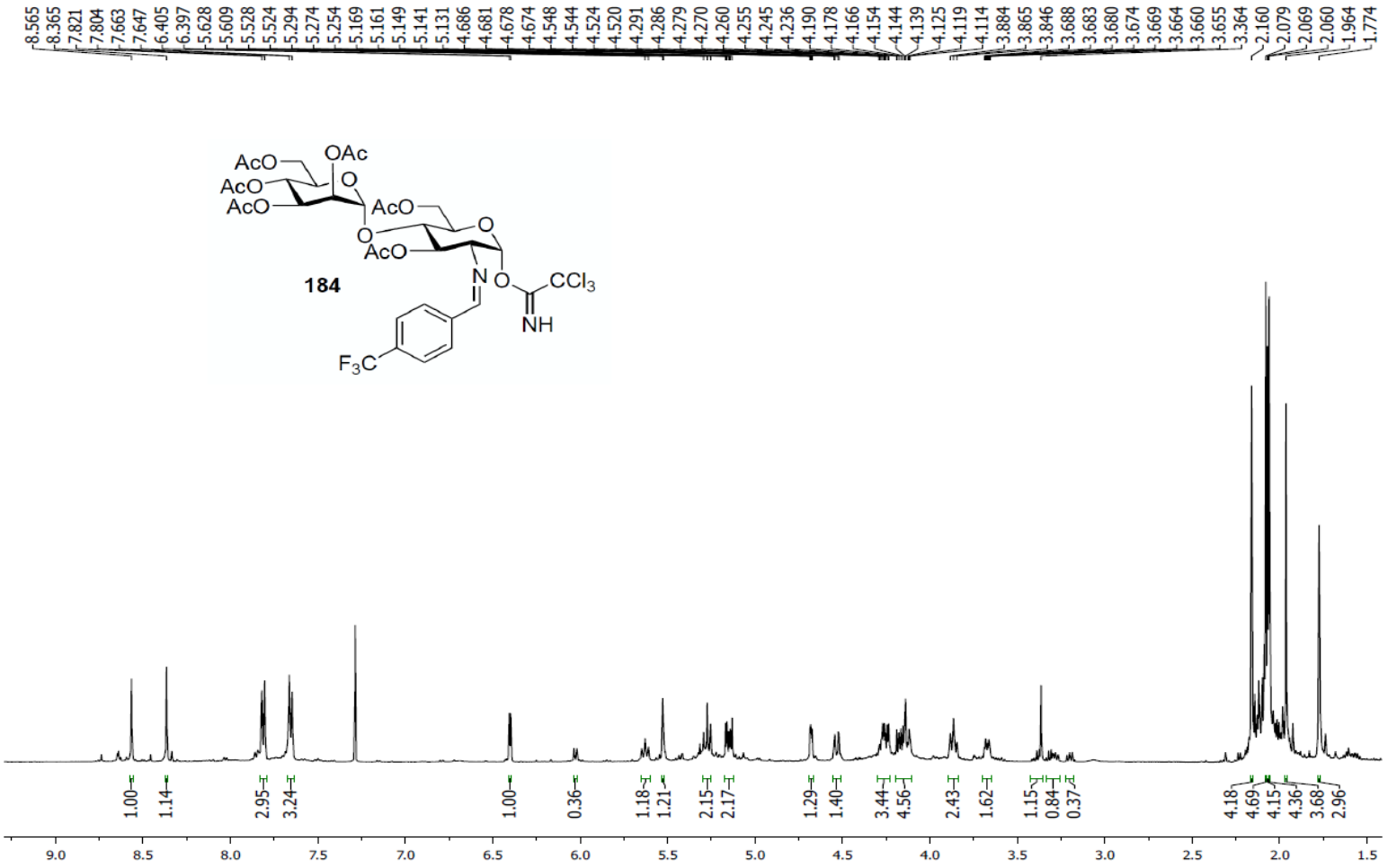


Figure A76. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **184**

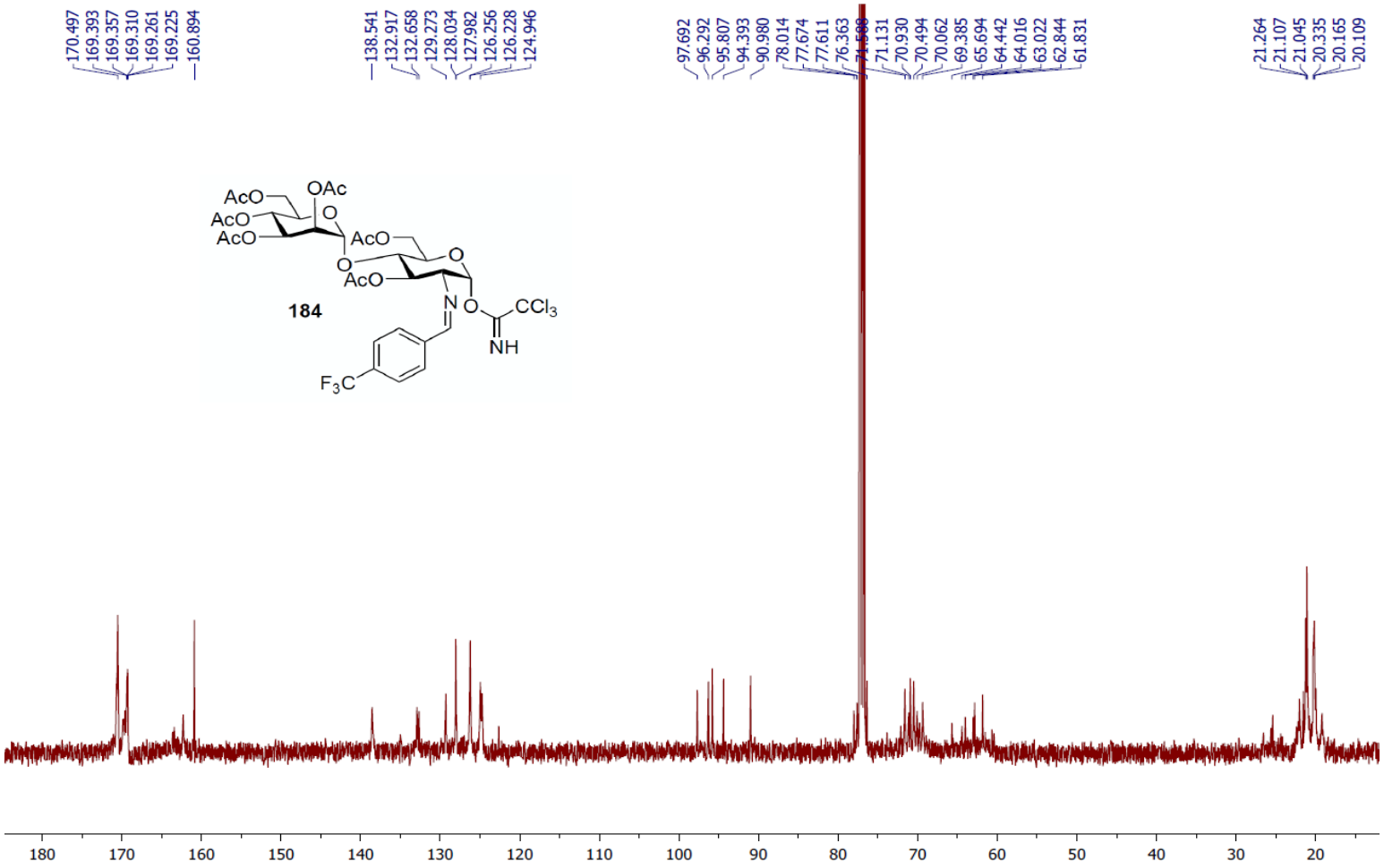


Figure A77. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **184**

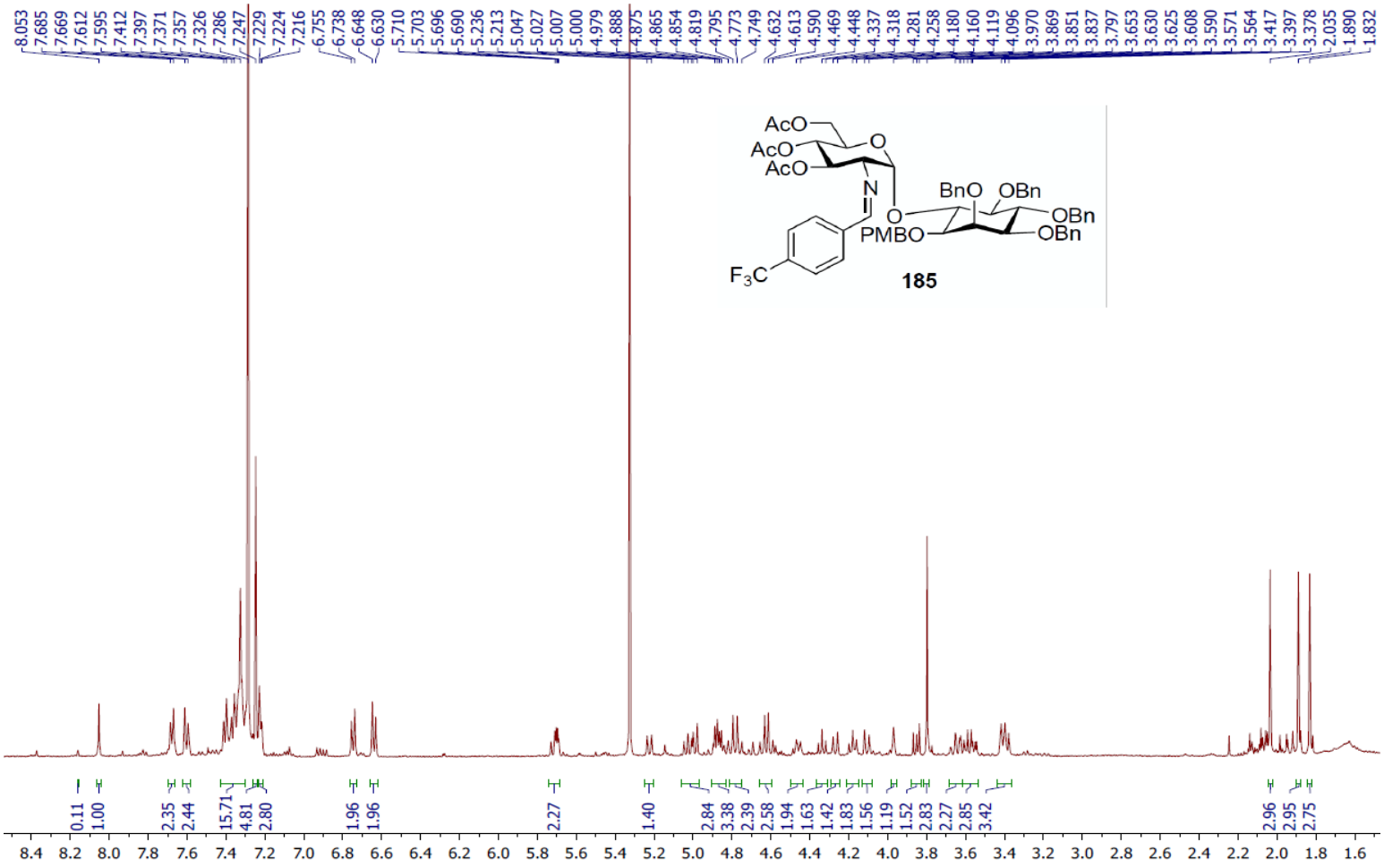


Figure A78. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **185**

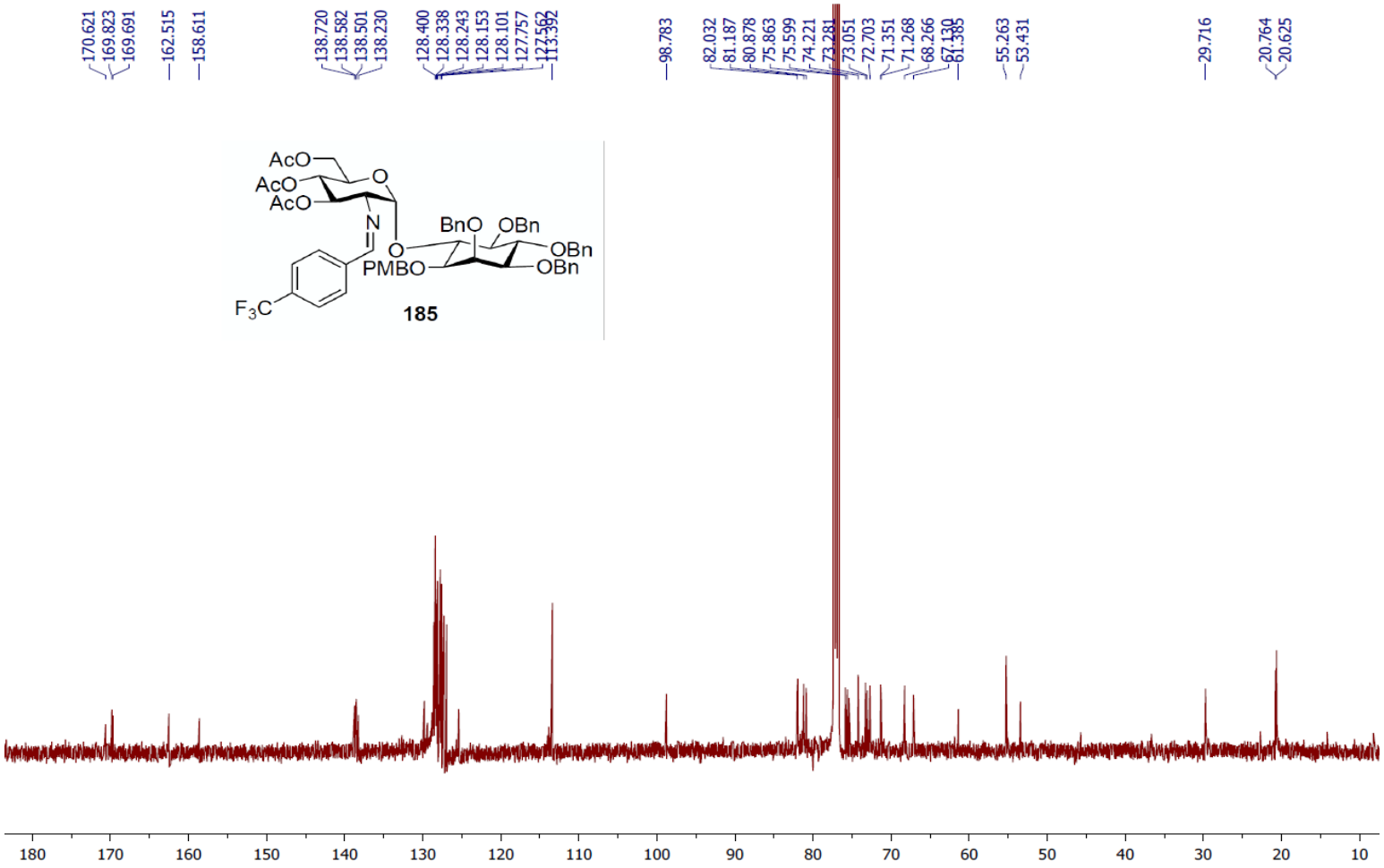


Figure A79. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **185**

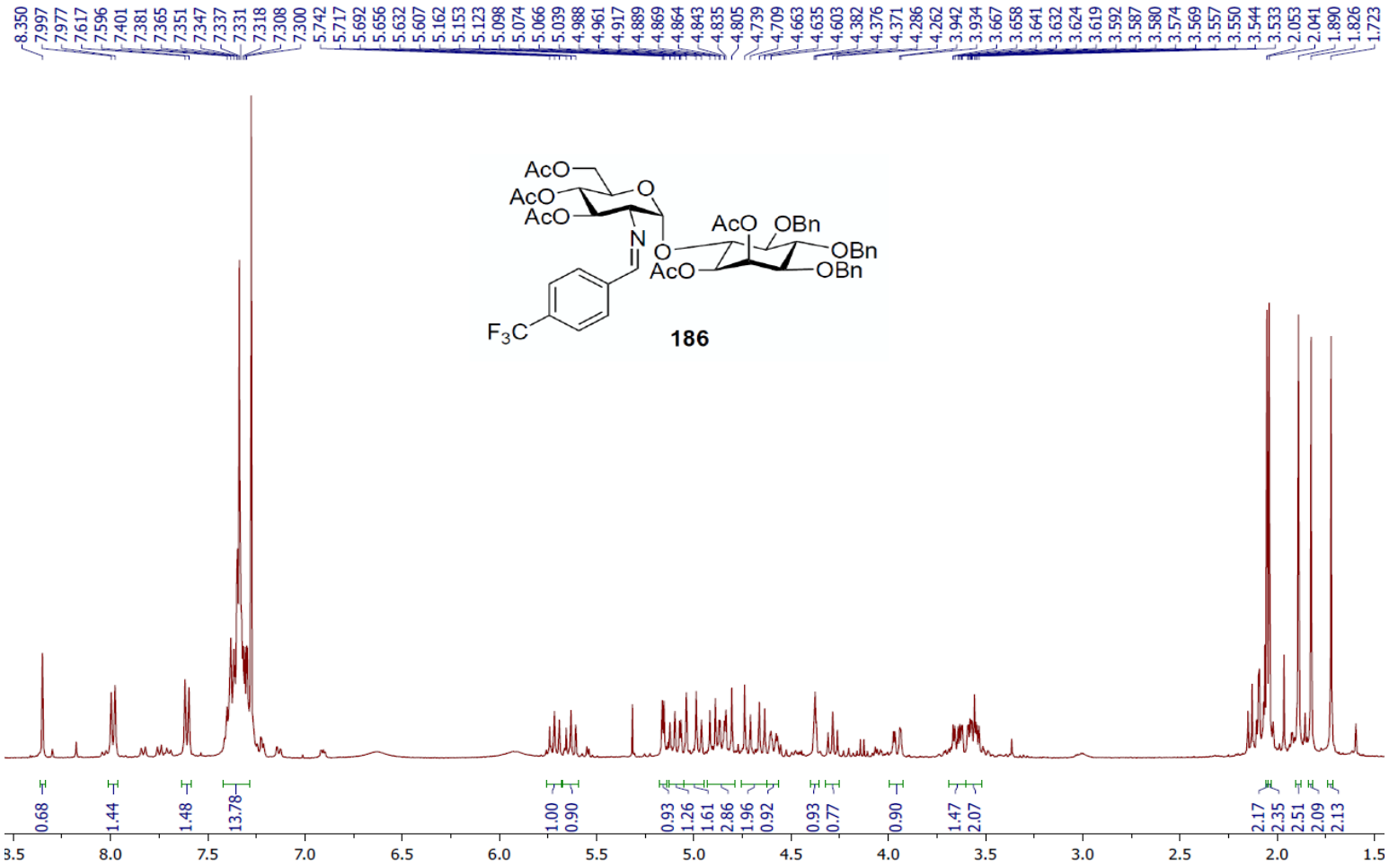


Figure A80. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **186**

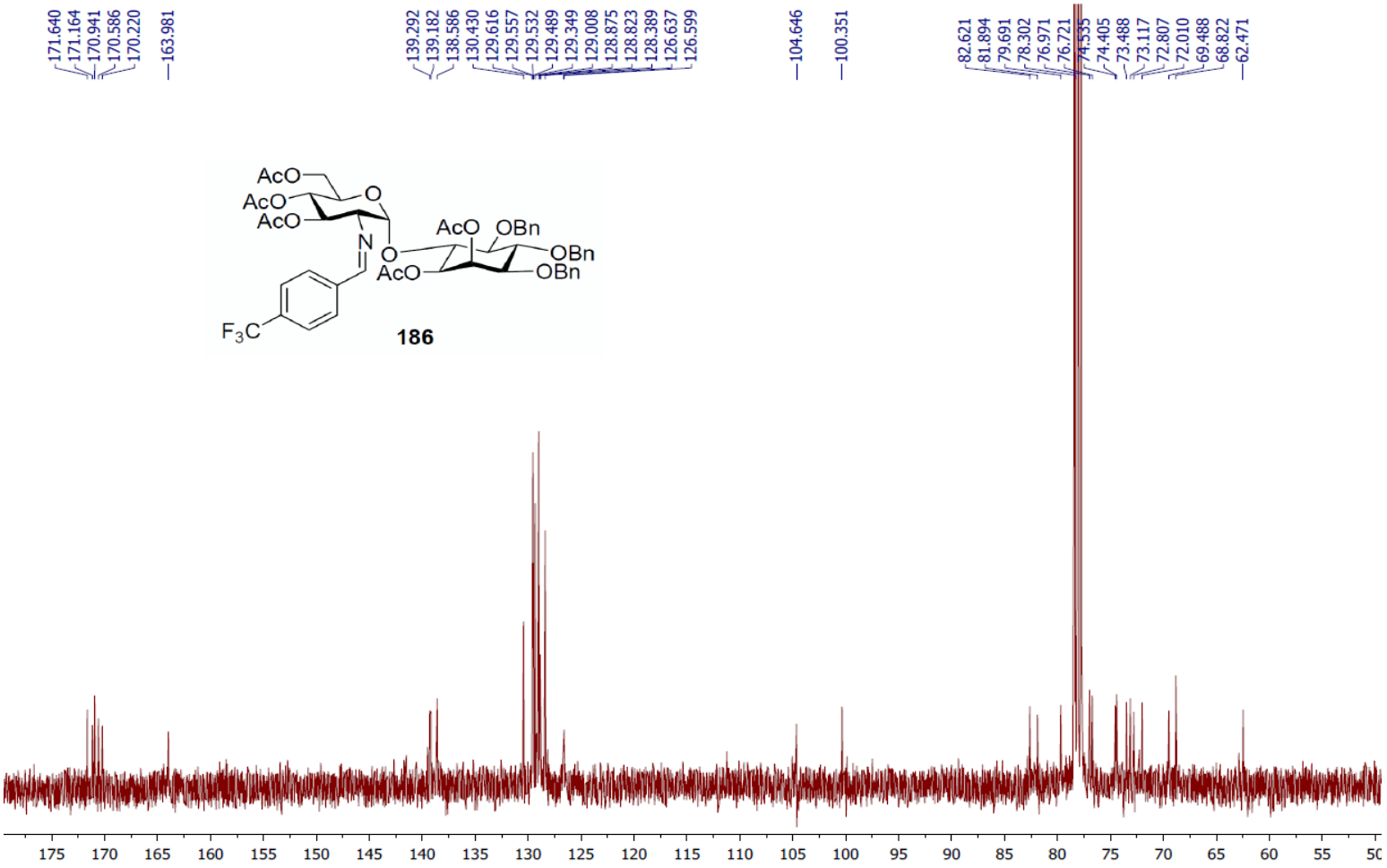


Figure A81. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **186**

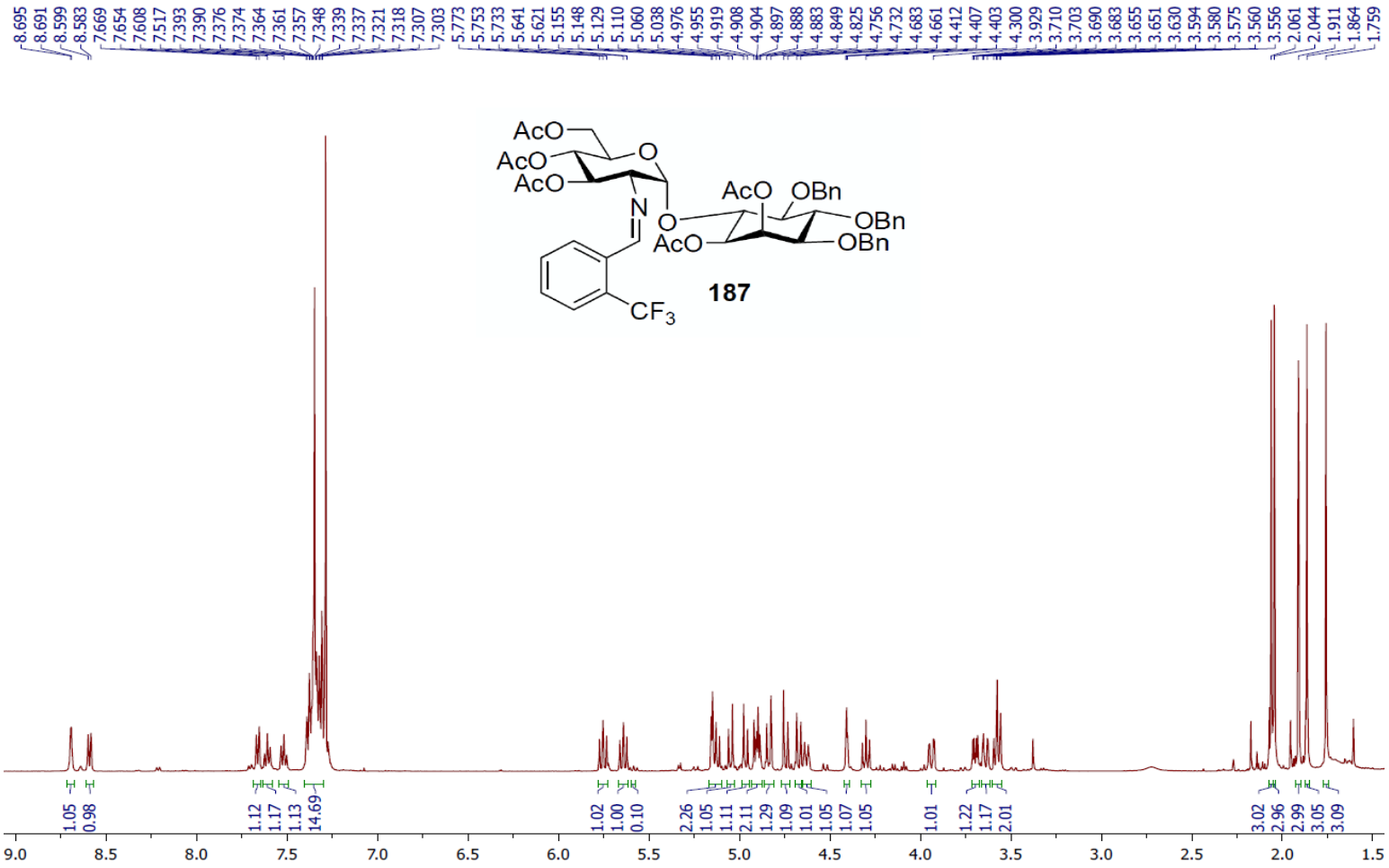


Figure A82. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **187**

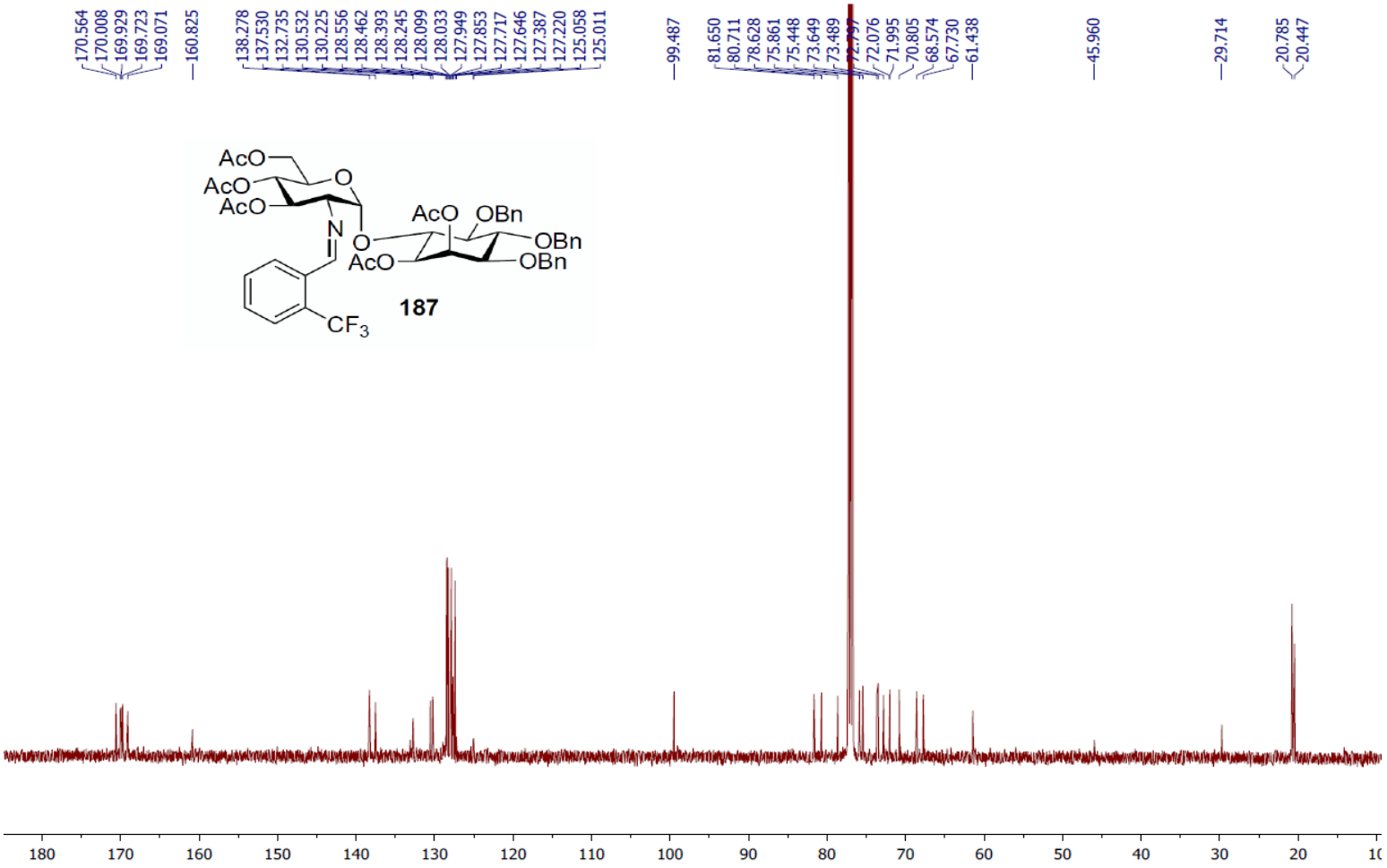


Figure A83. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **187**

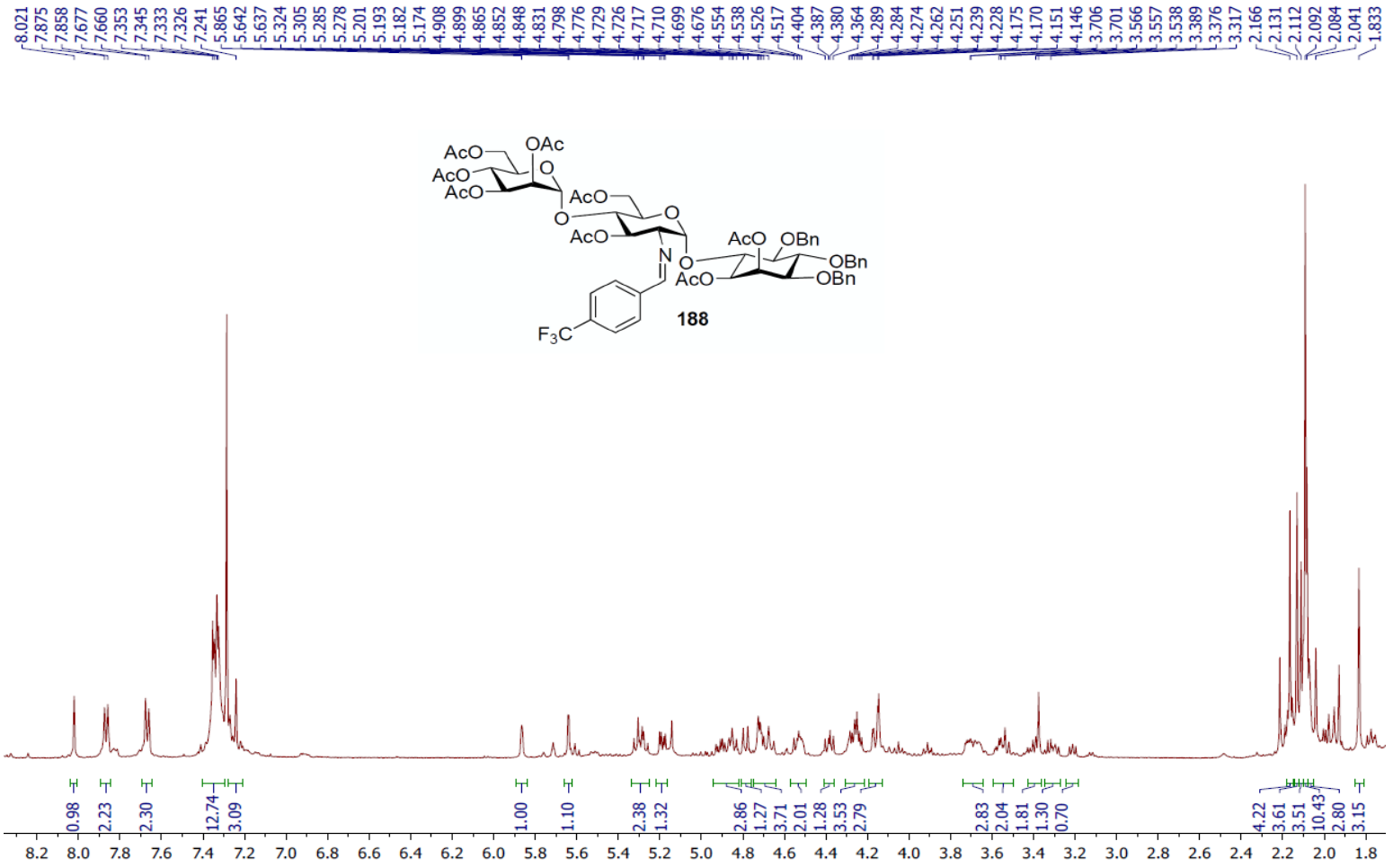


Figure A84. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **188**

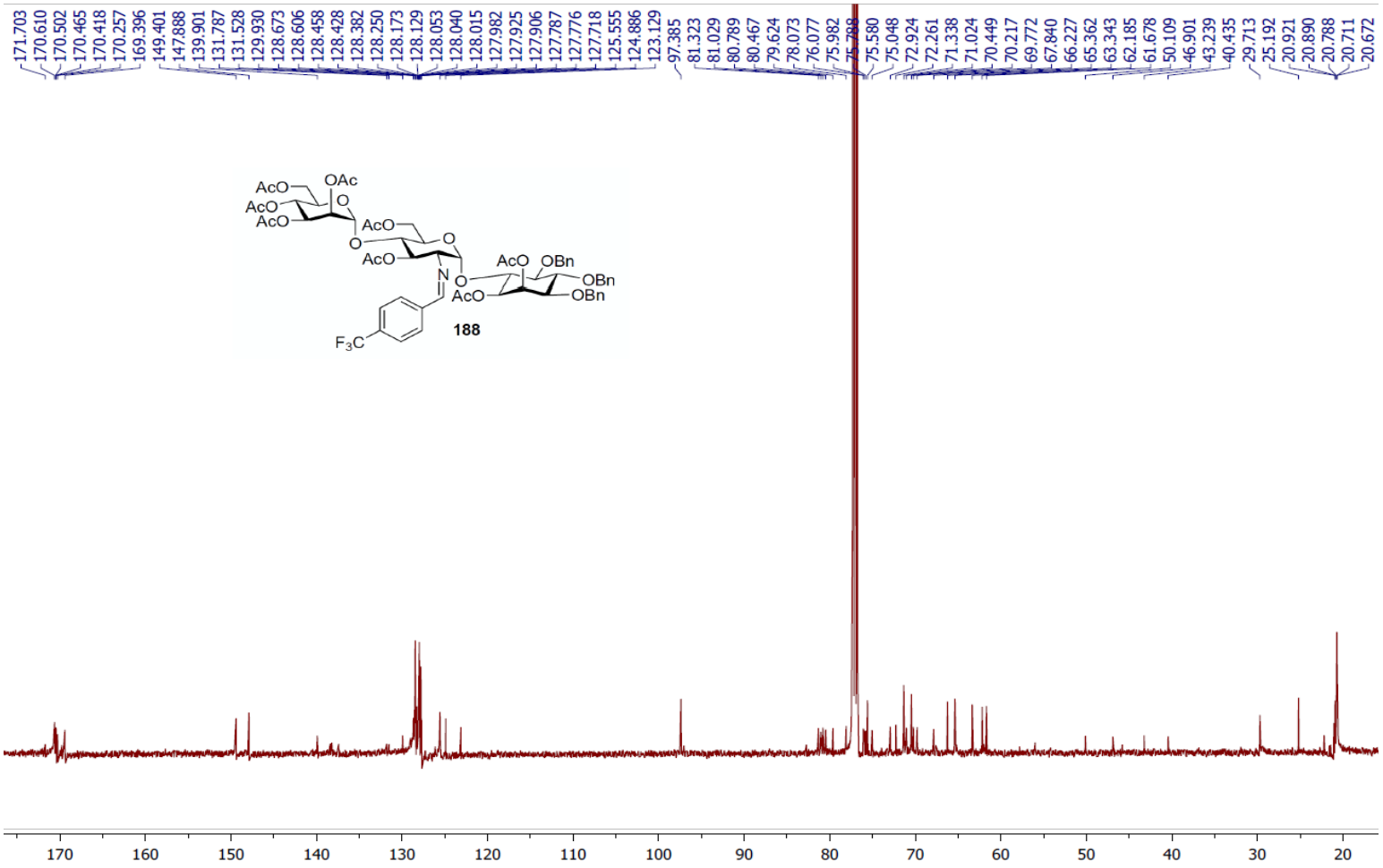


Figure A85. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **188**

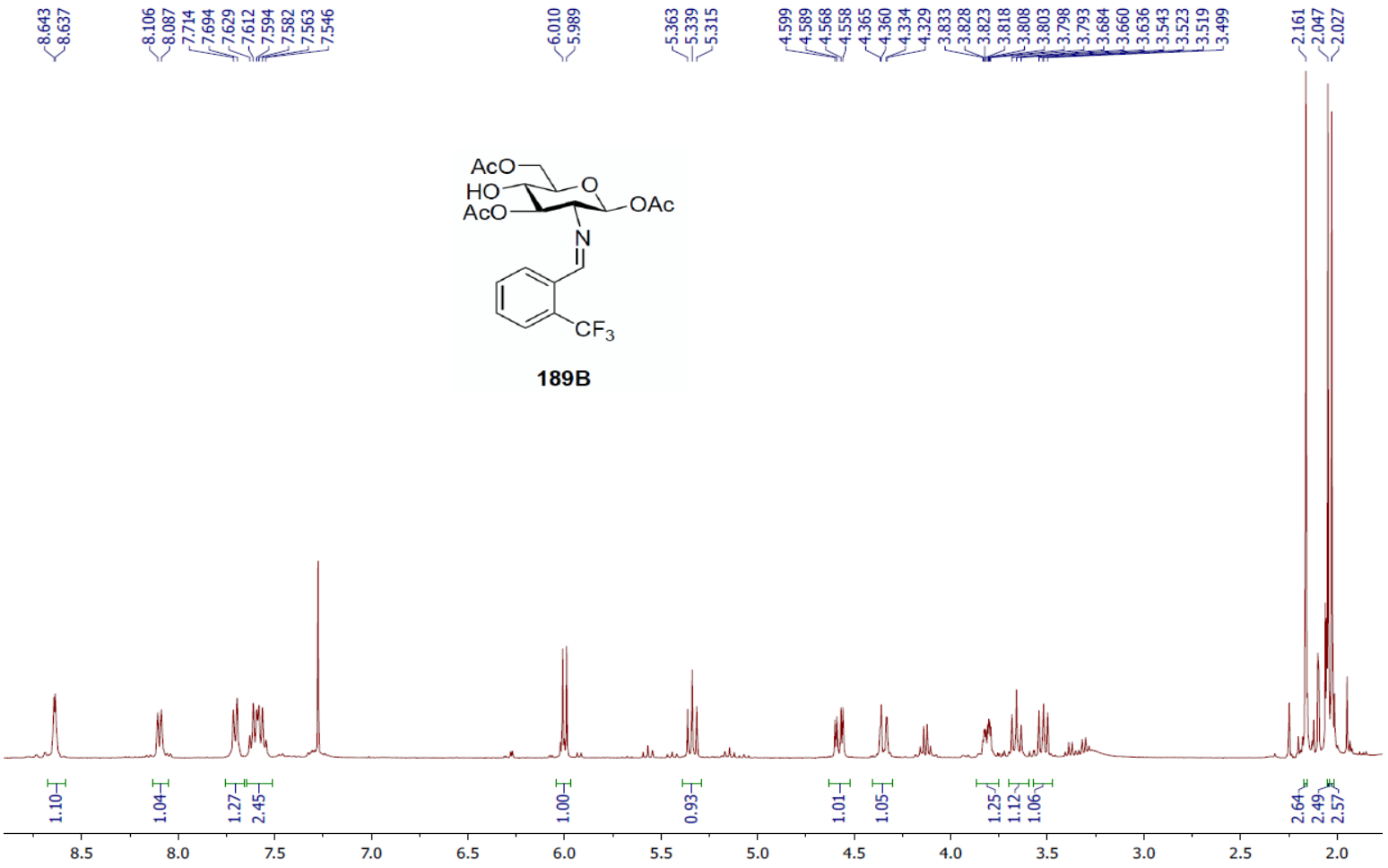


Figure A86. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **189B**

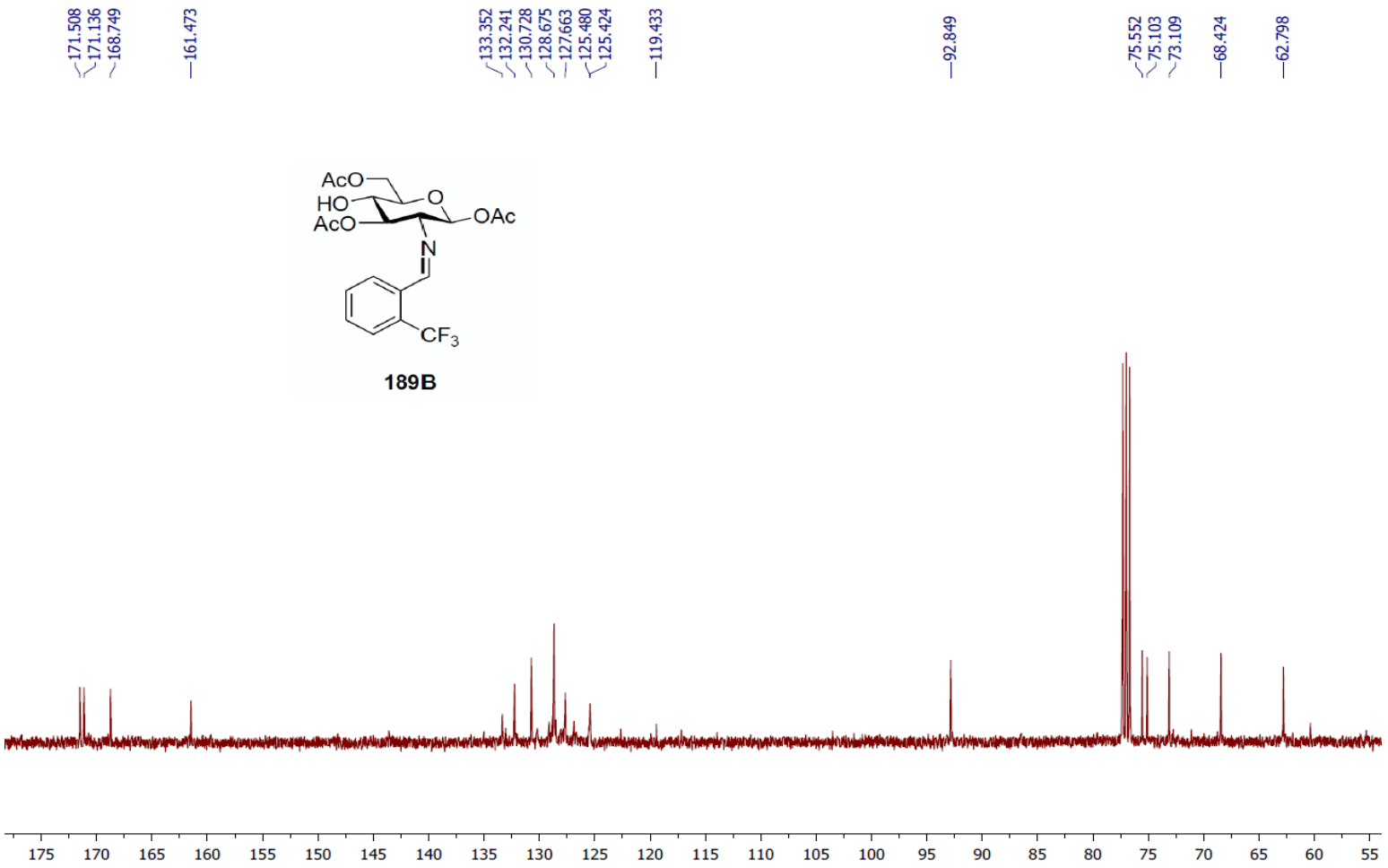


Figure A87. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glucoside **189B**

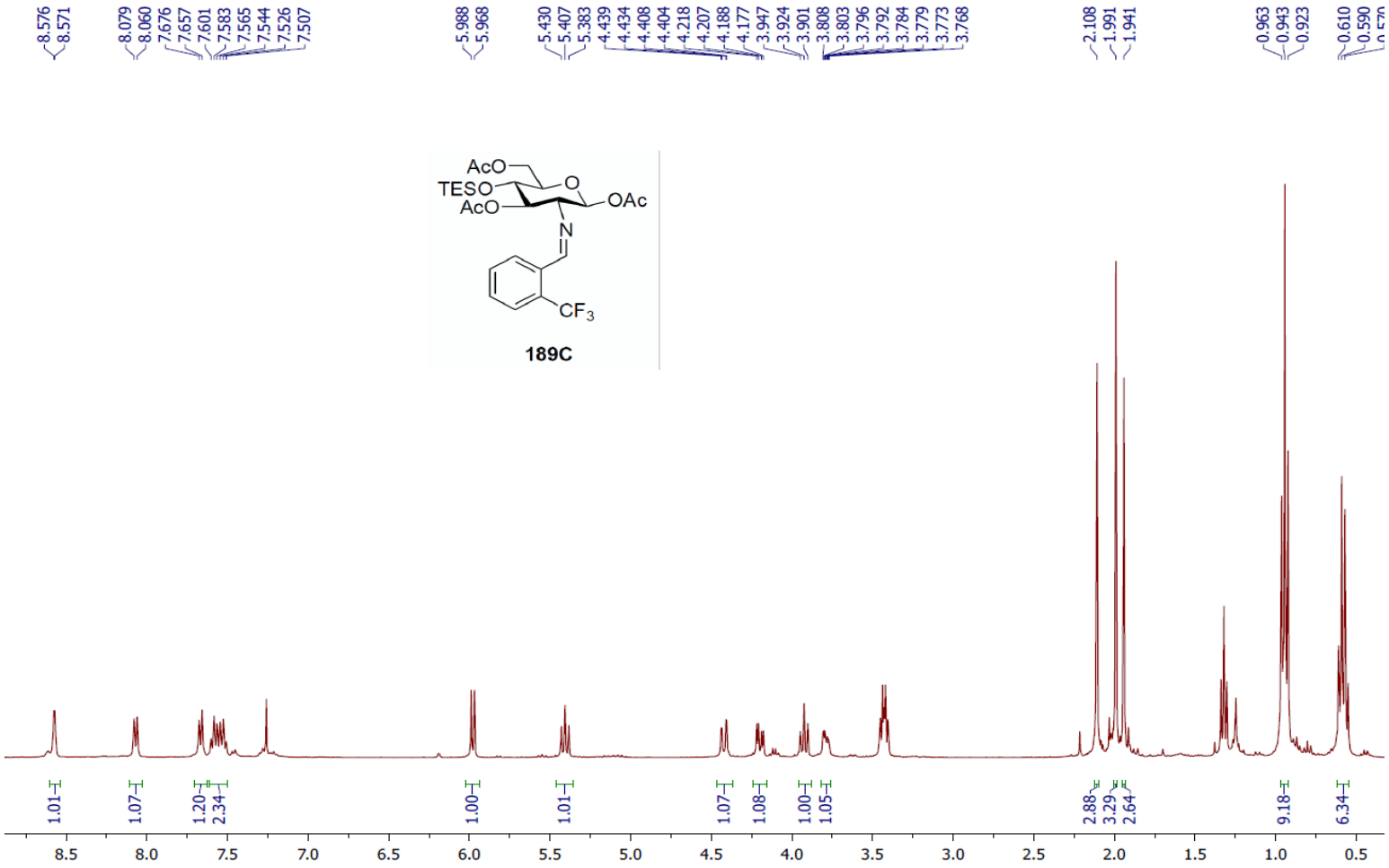


Figure A88. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **189C**

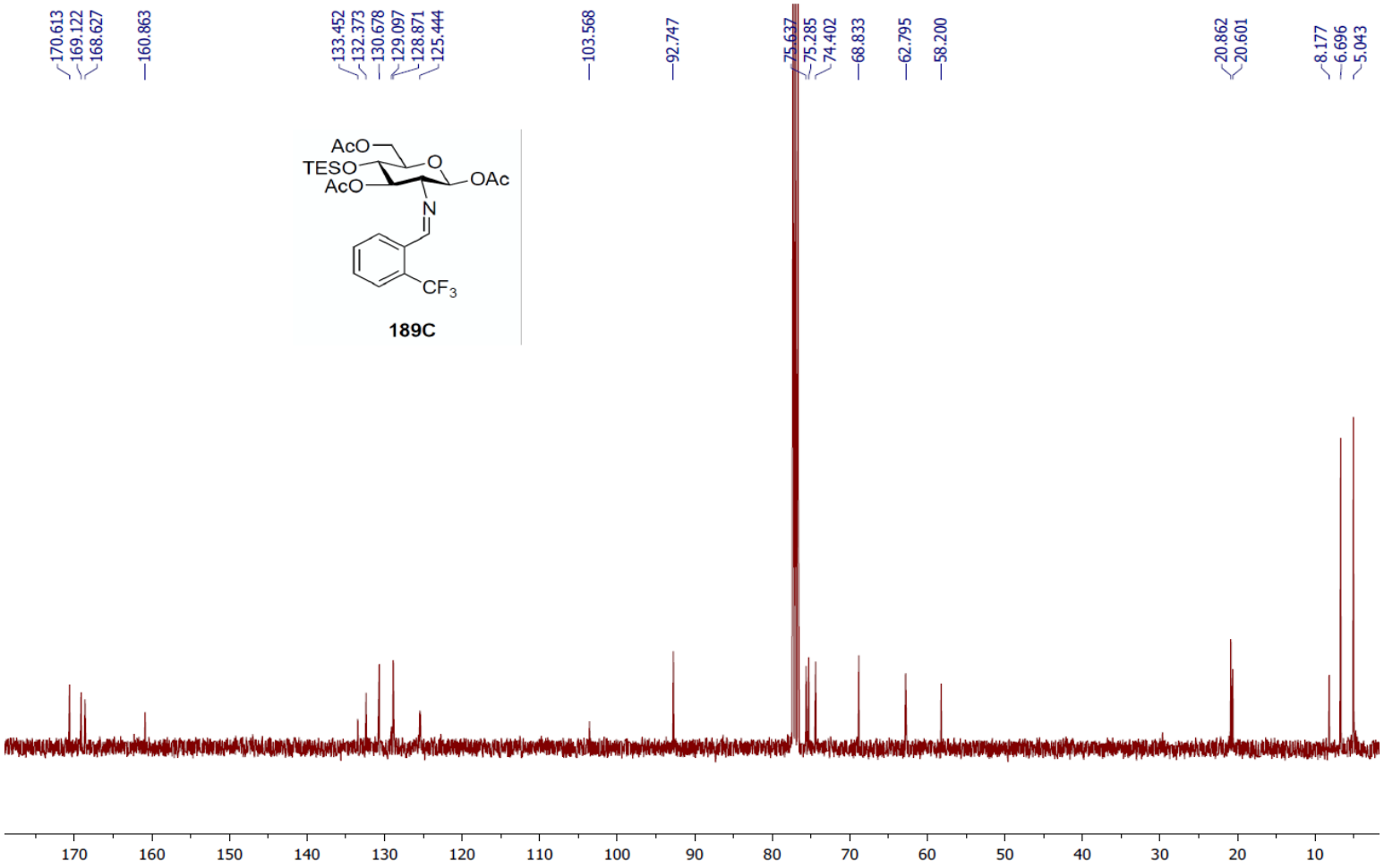


Figure A89. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glucoside **189C**

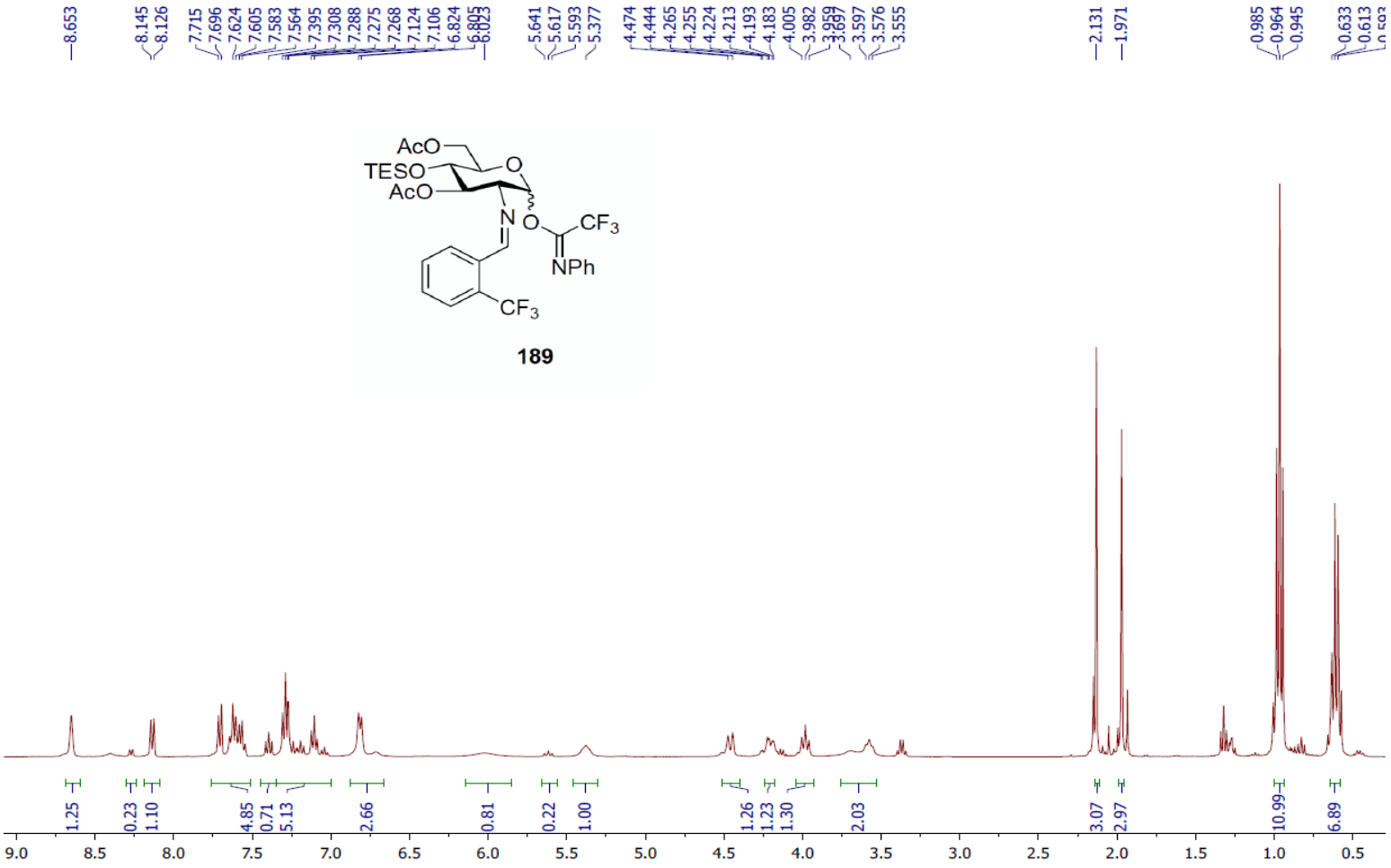


Figure A90. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **189**

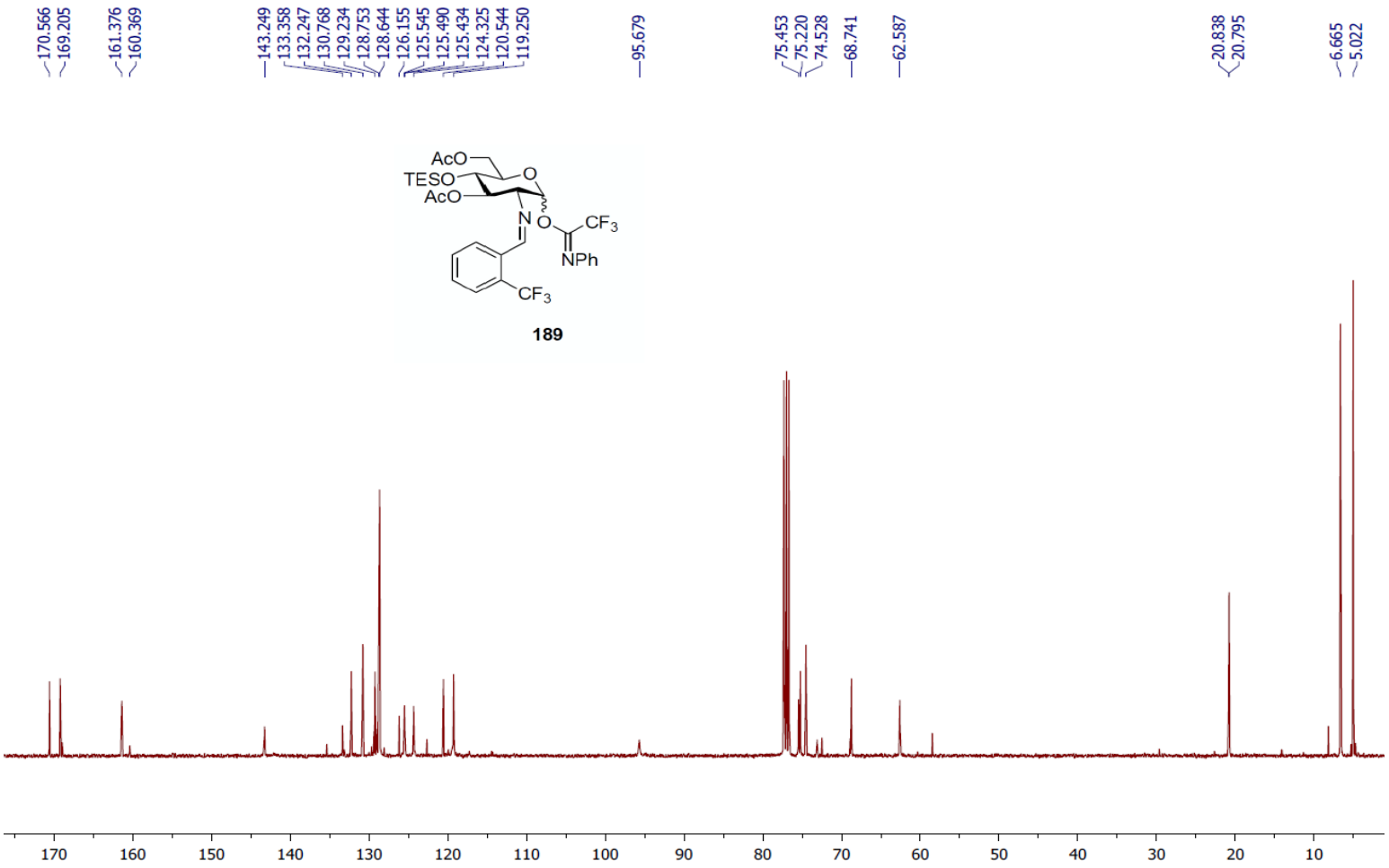


Figure A91. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **189**

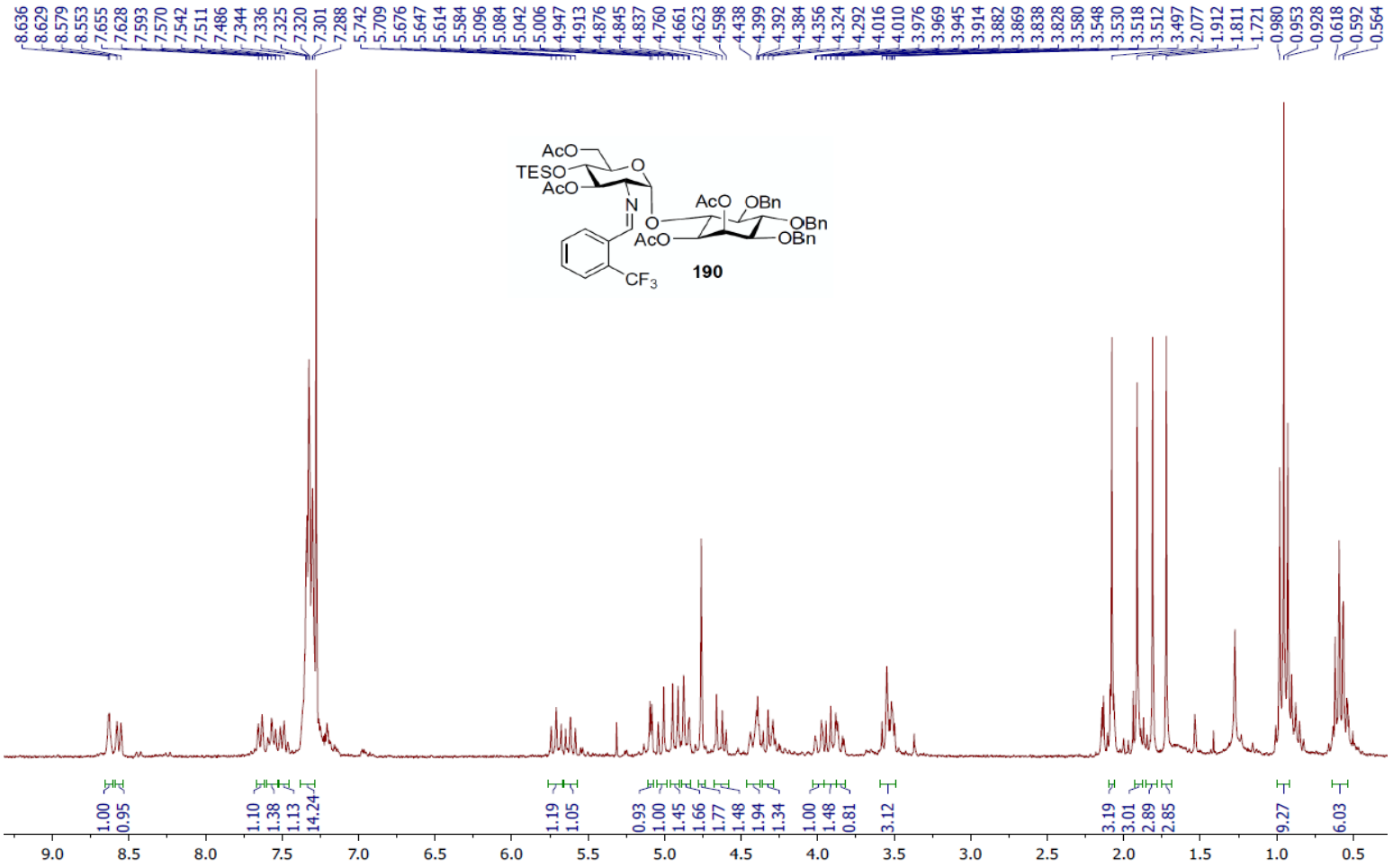


Figure A92. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **190**

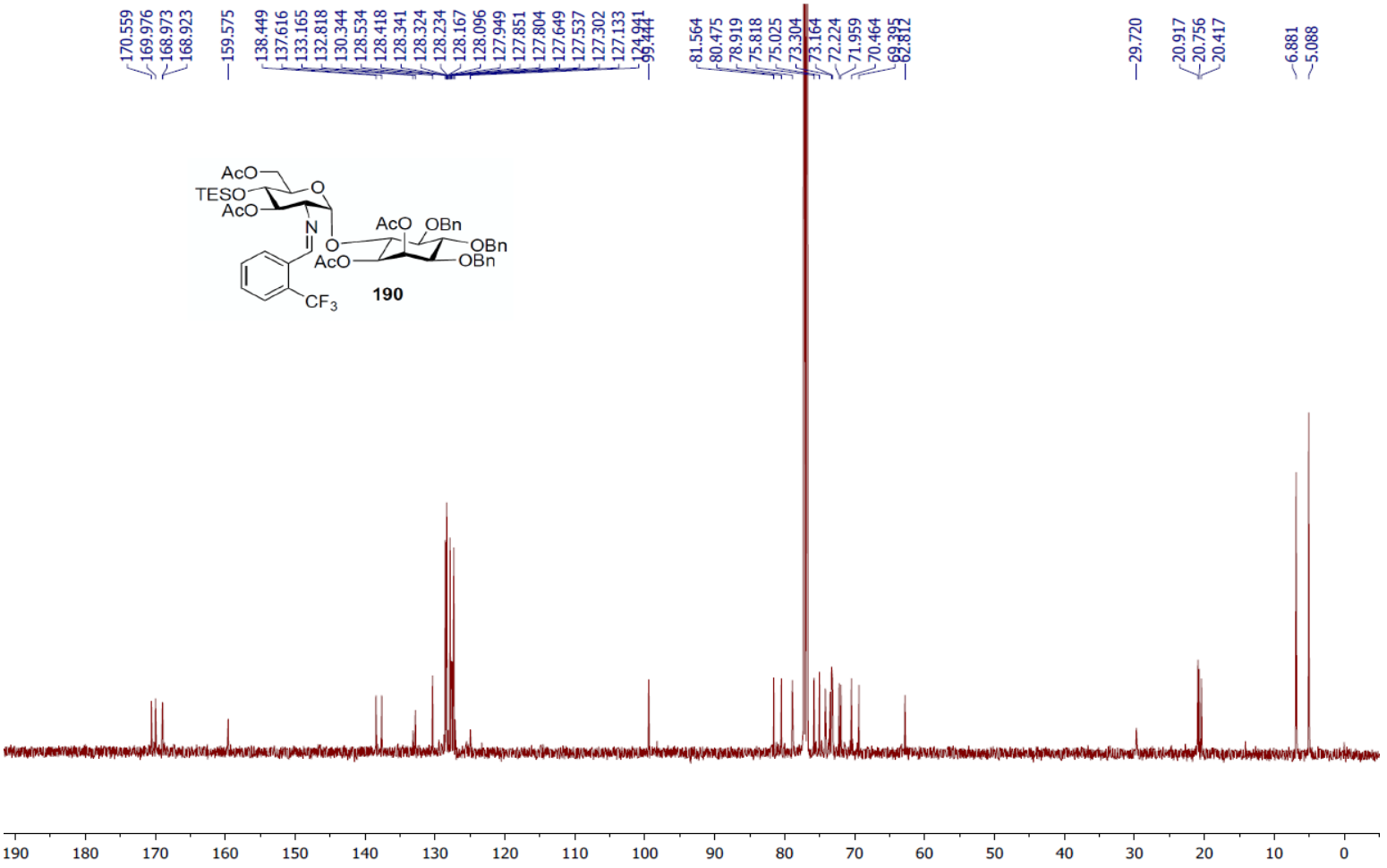


Figure A93. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **190**

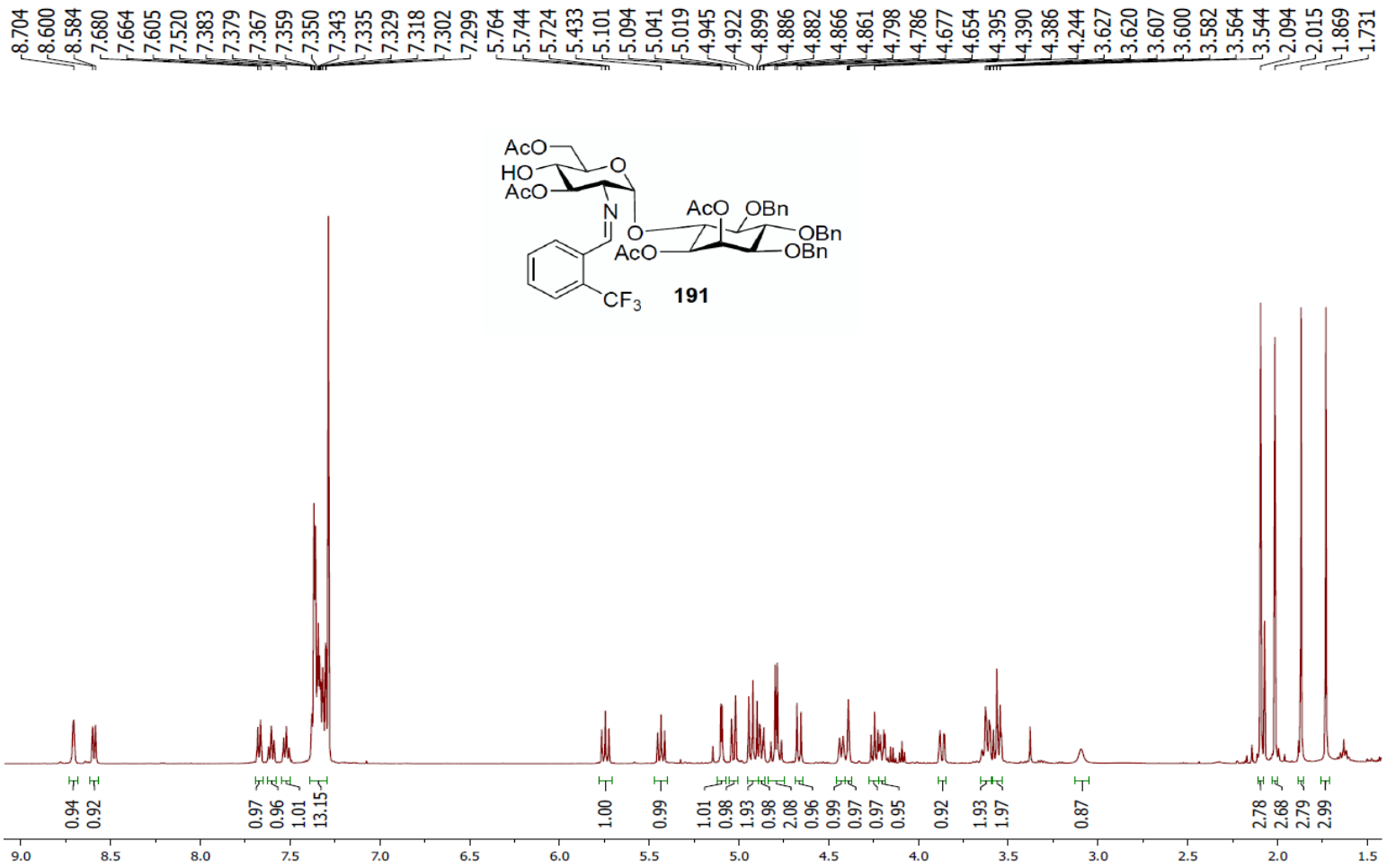


Figure A94. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **191**

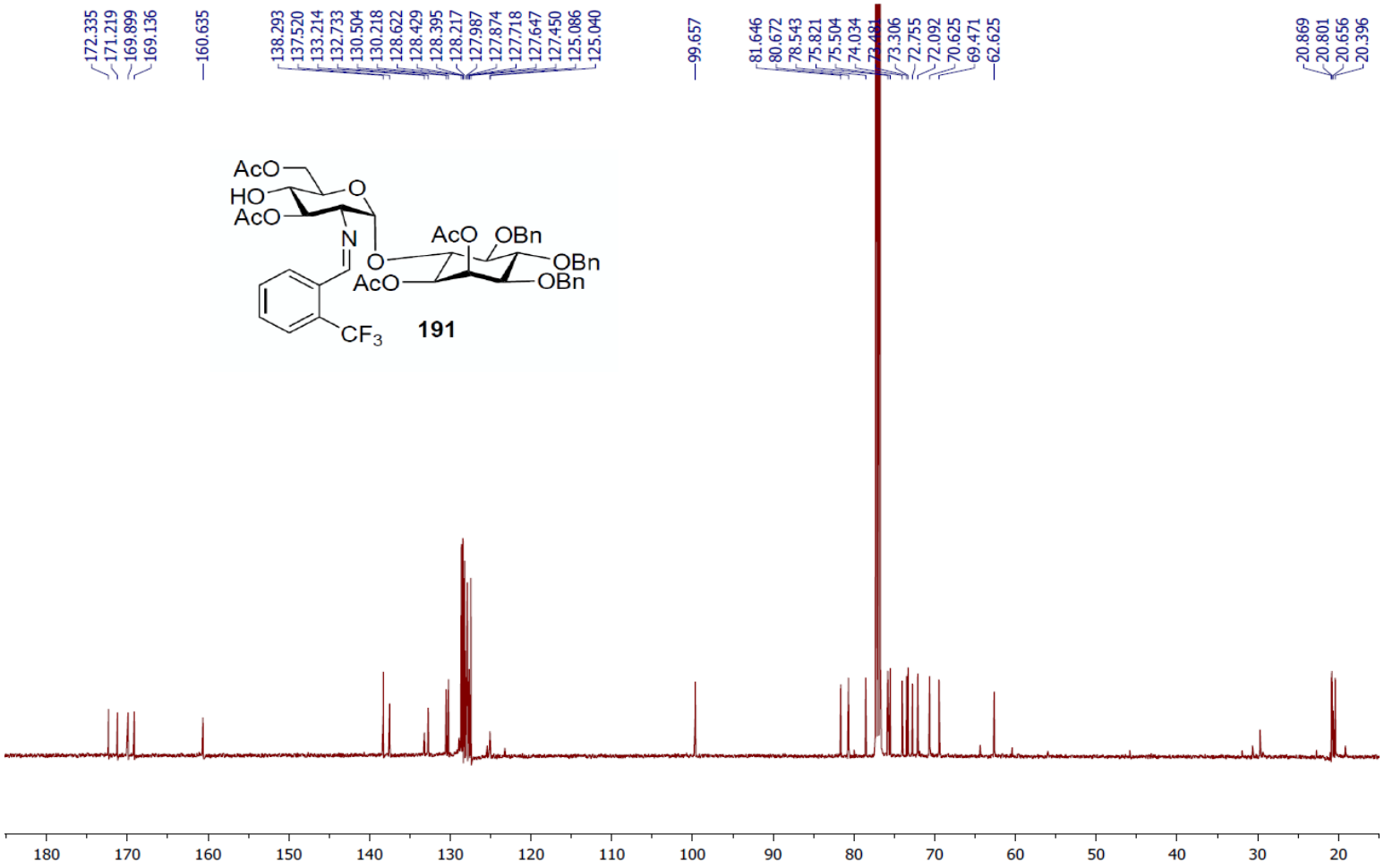


Figure A95. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **191**

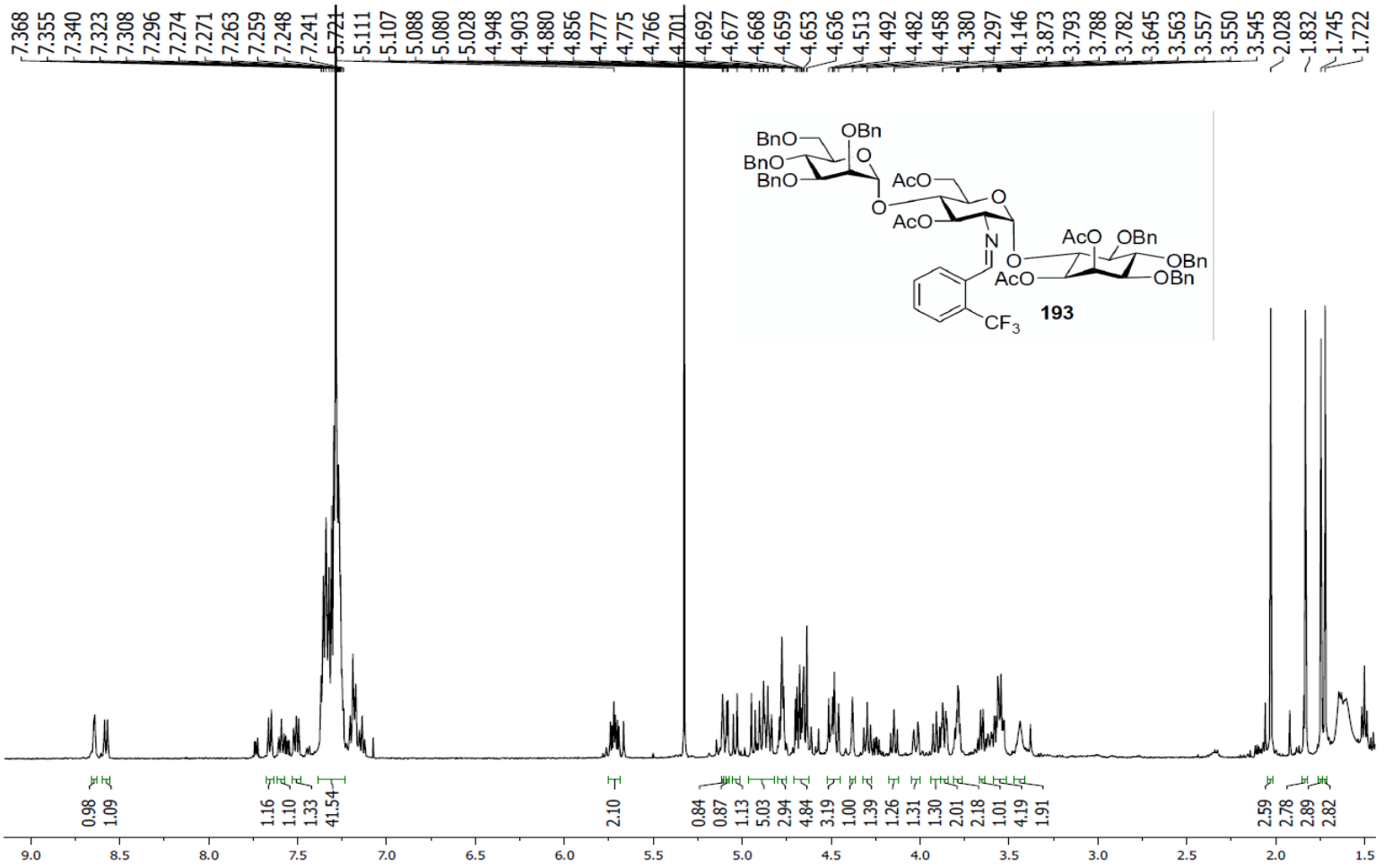


Figure A96. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trisaccharide **193**

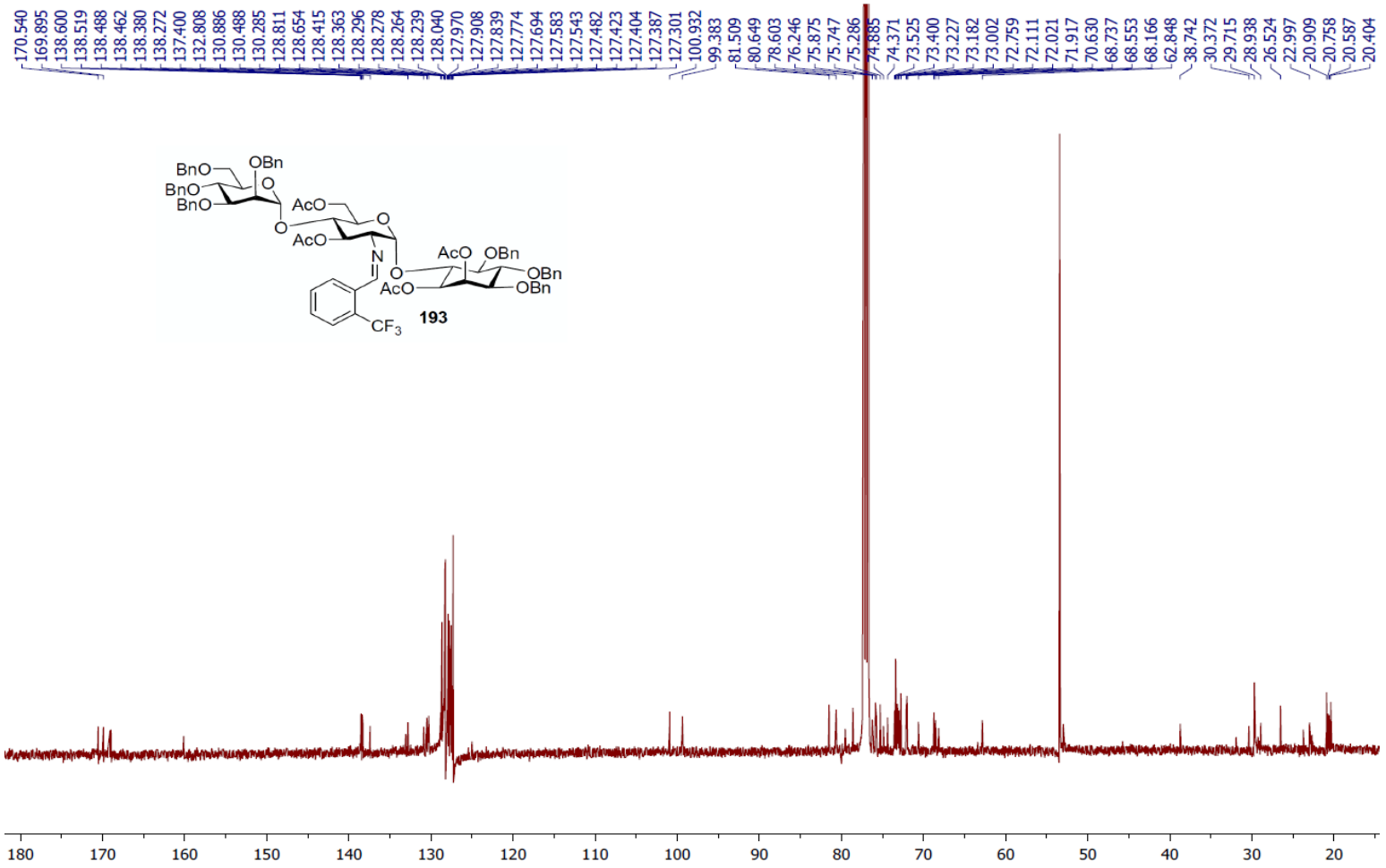


Figure A97. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trisaccharide **193**

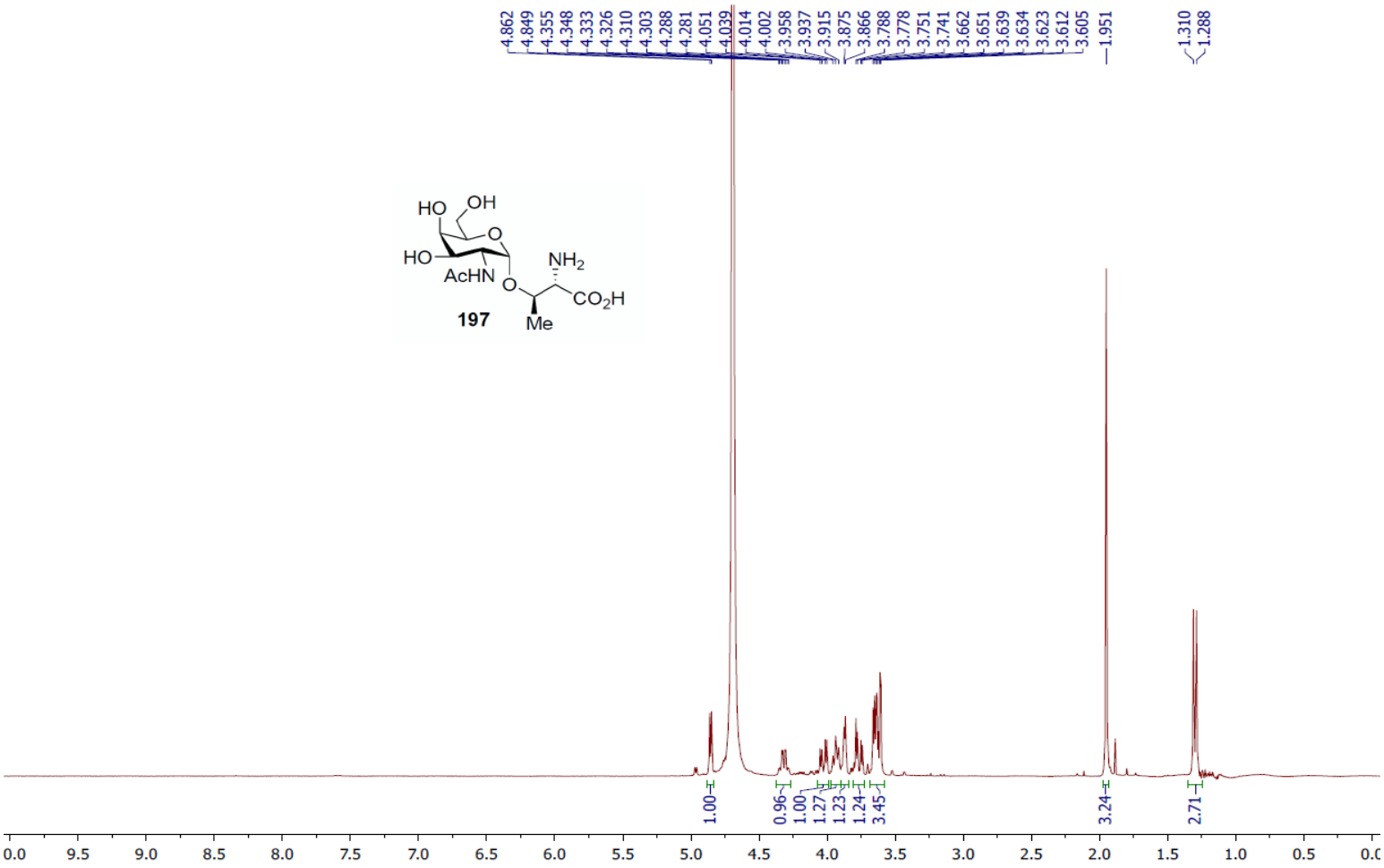


Figure A98. 300 MHz ^{1}H NMR Spectrum (D_2O) of Glycoconjugate **197**

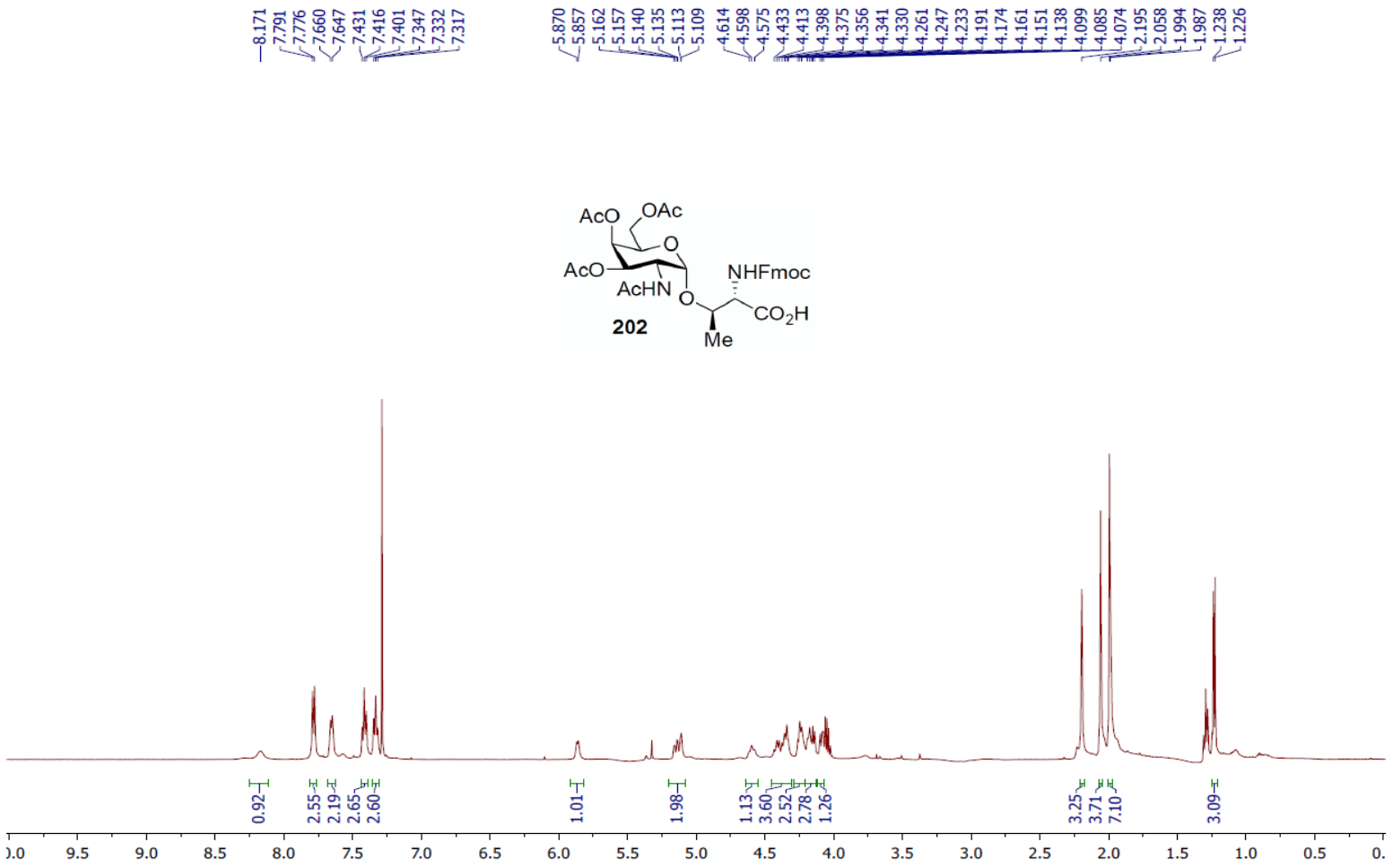


Figure A99. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **202**

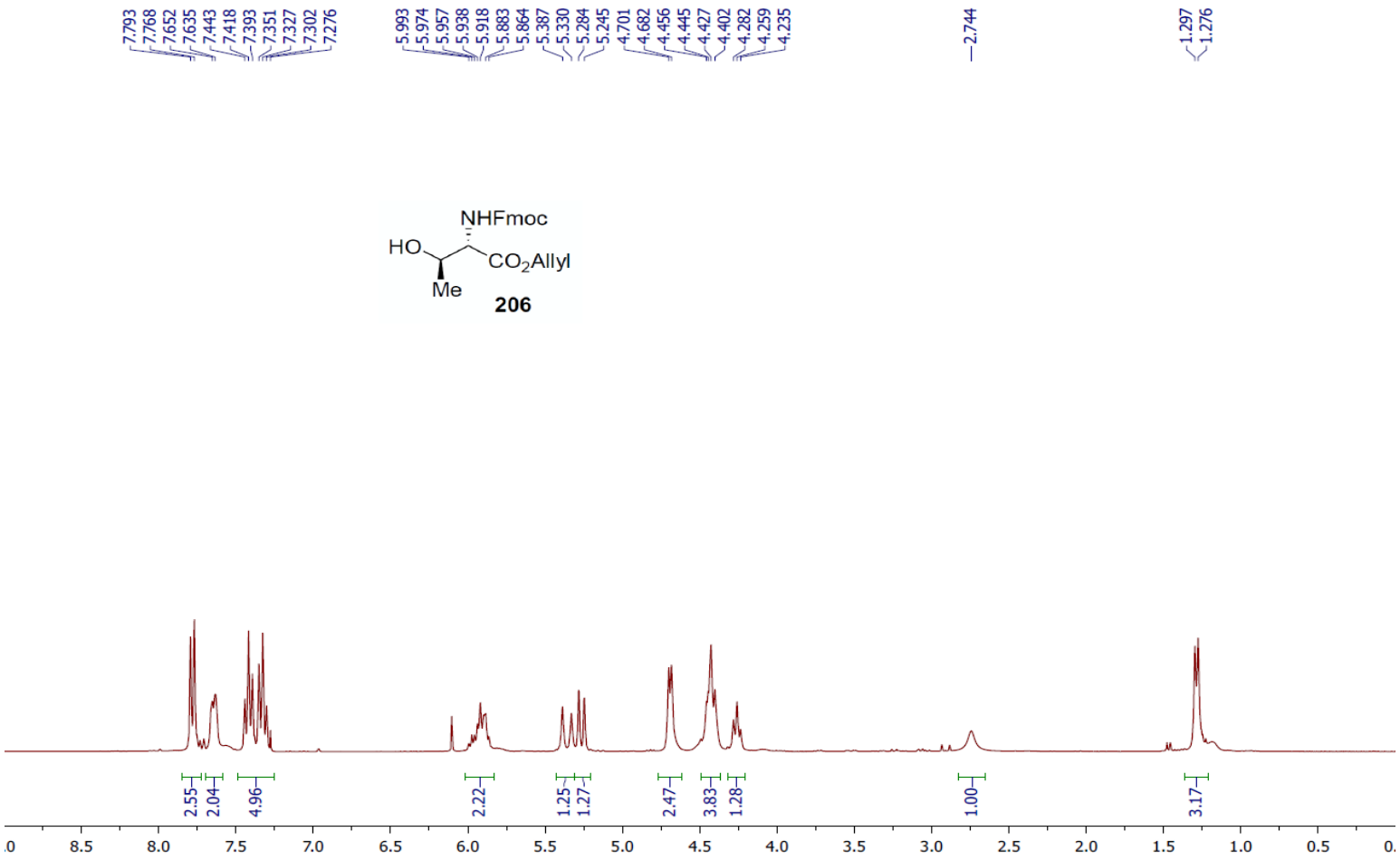


Figure A100. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Amino Acid **206**

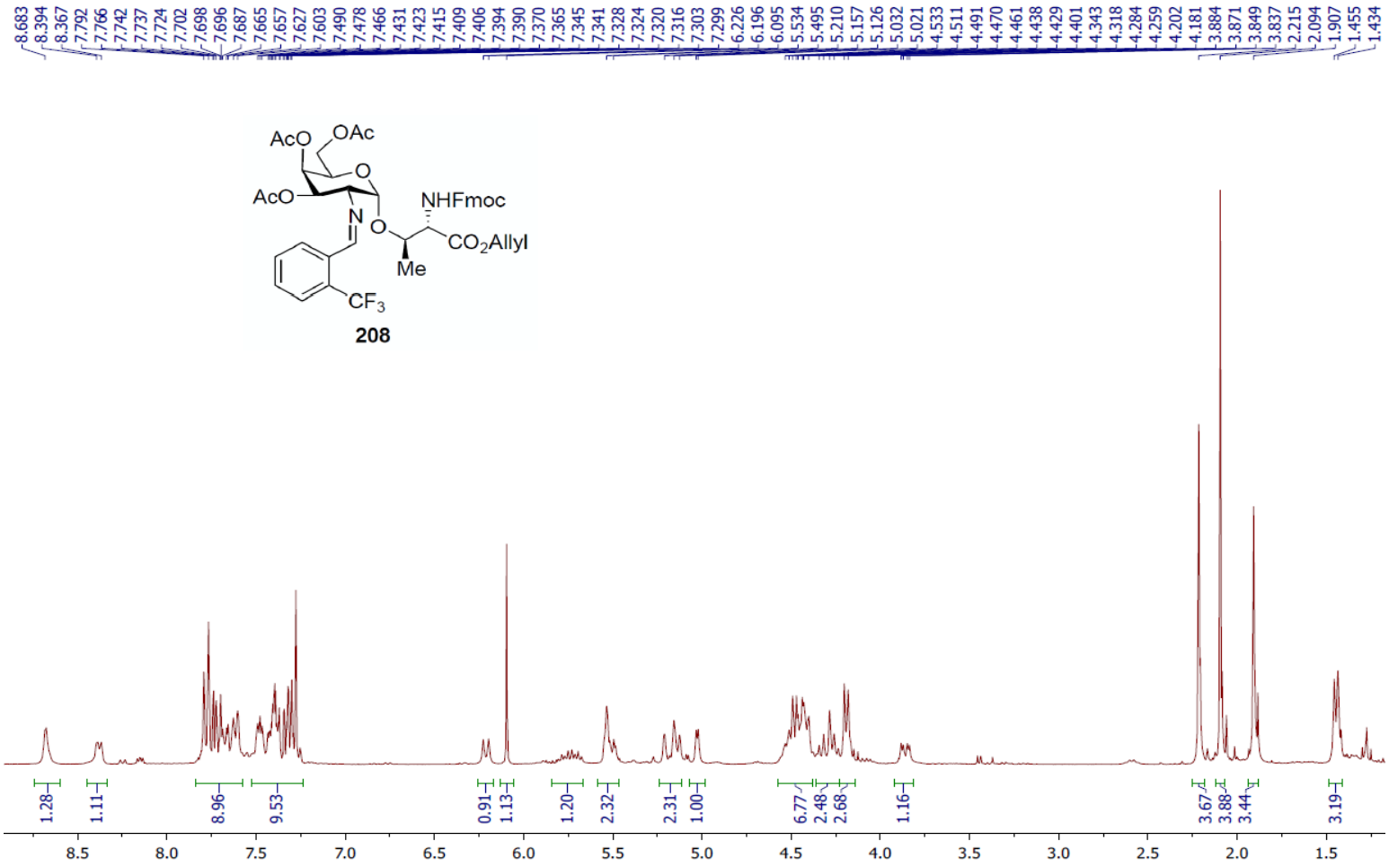


Figure A101. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **208**

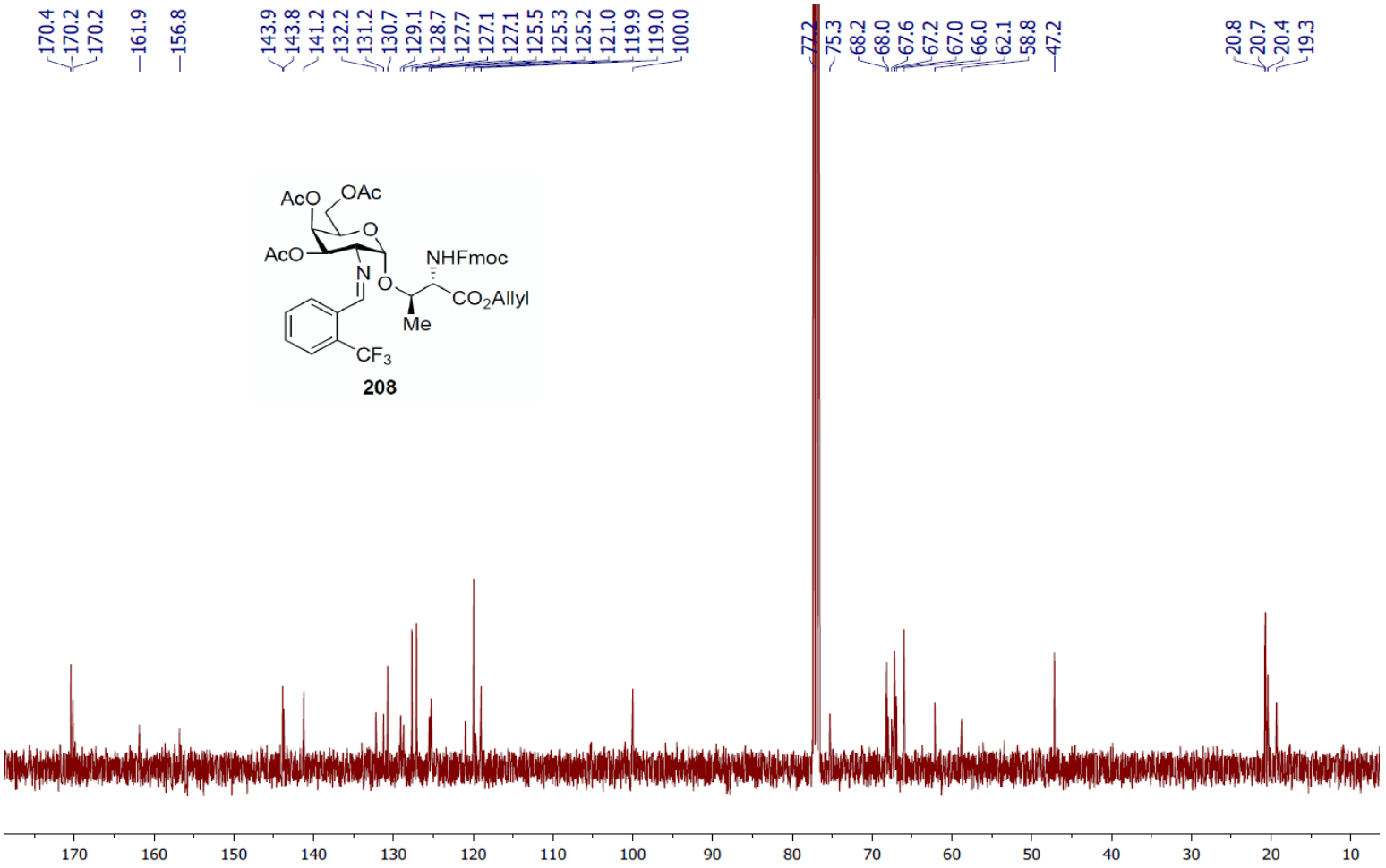


Figure A102. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **208**

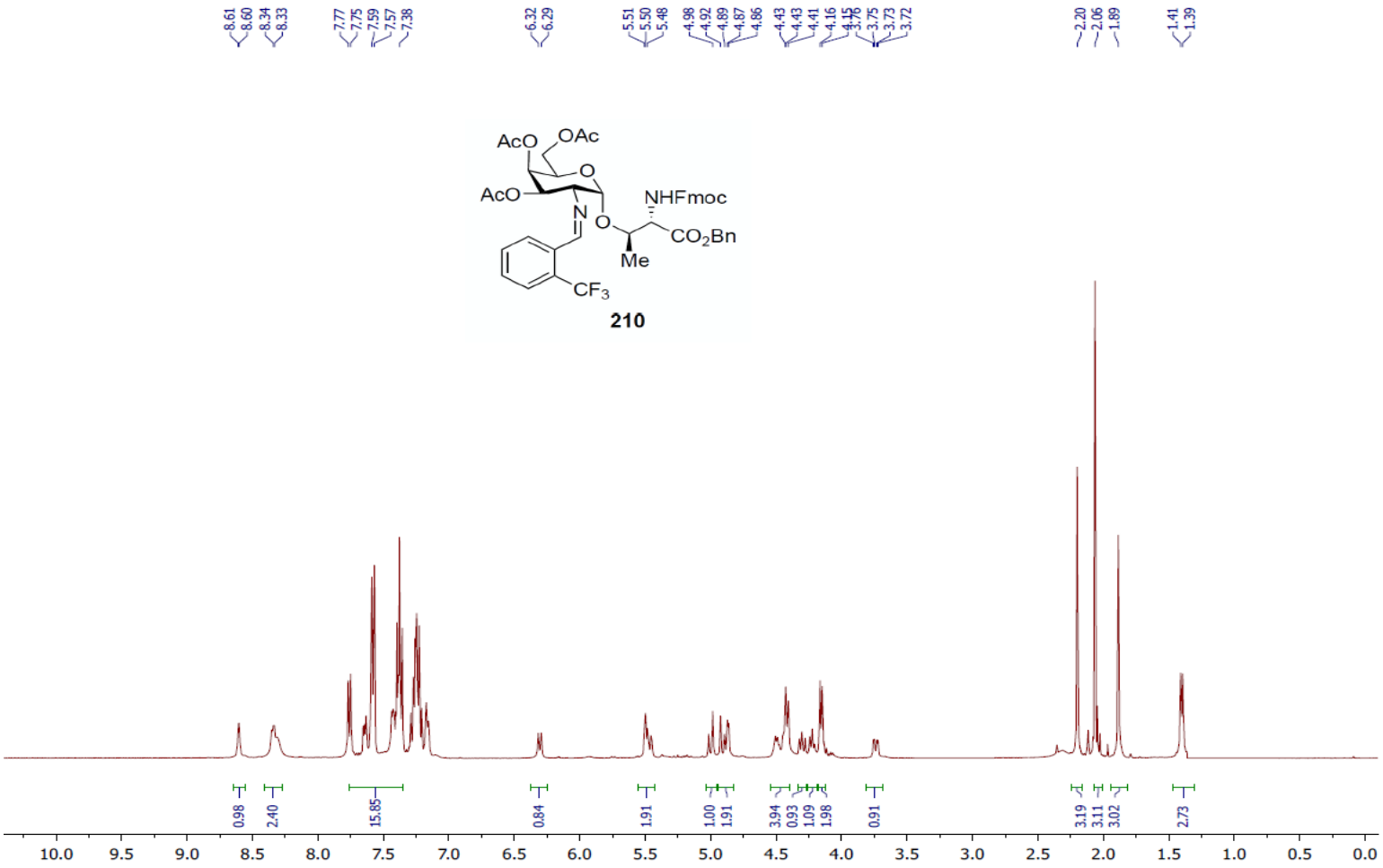


Figure A103. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **210**

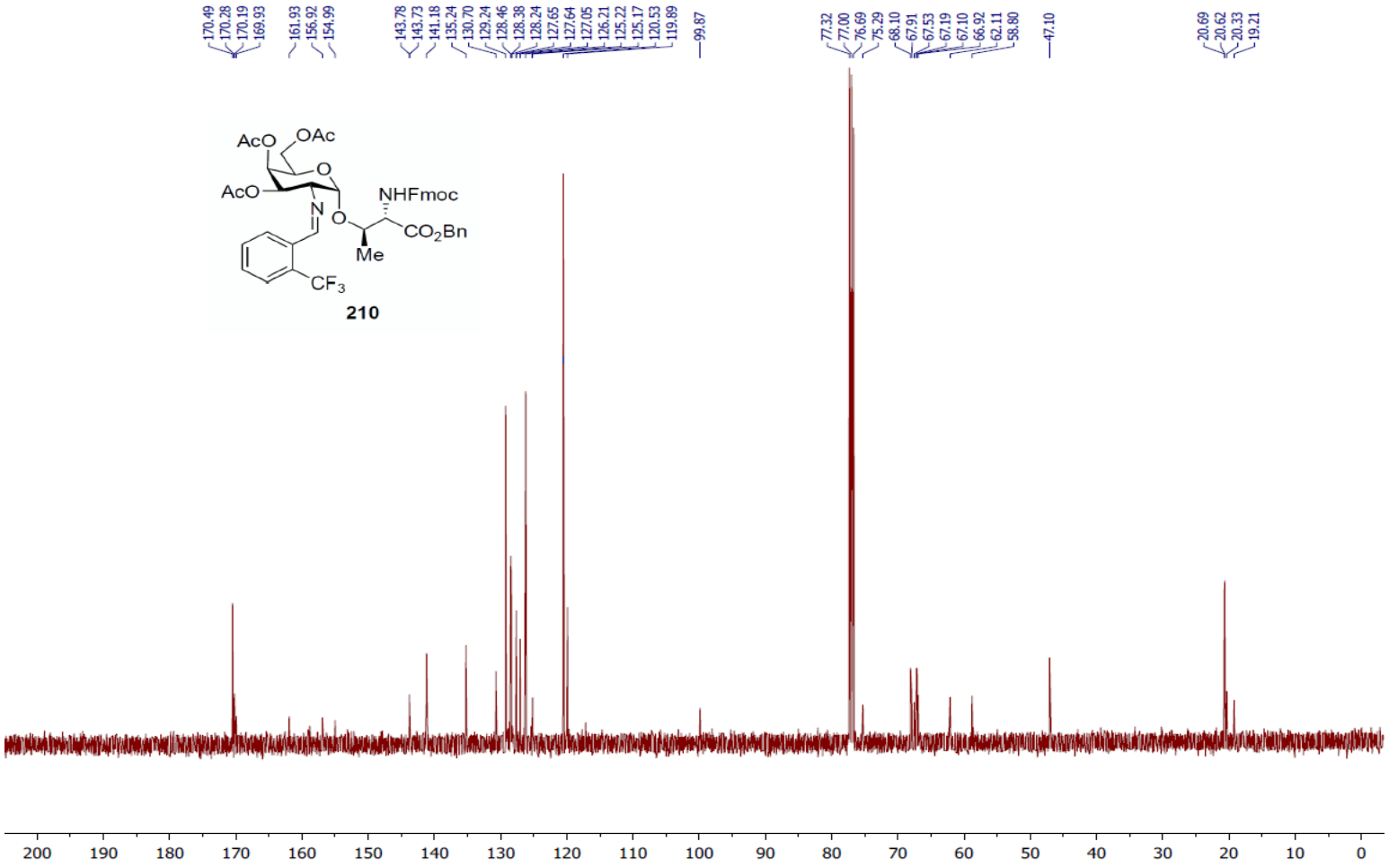


Figure A104. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **210**

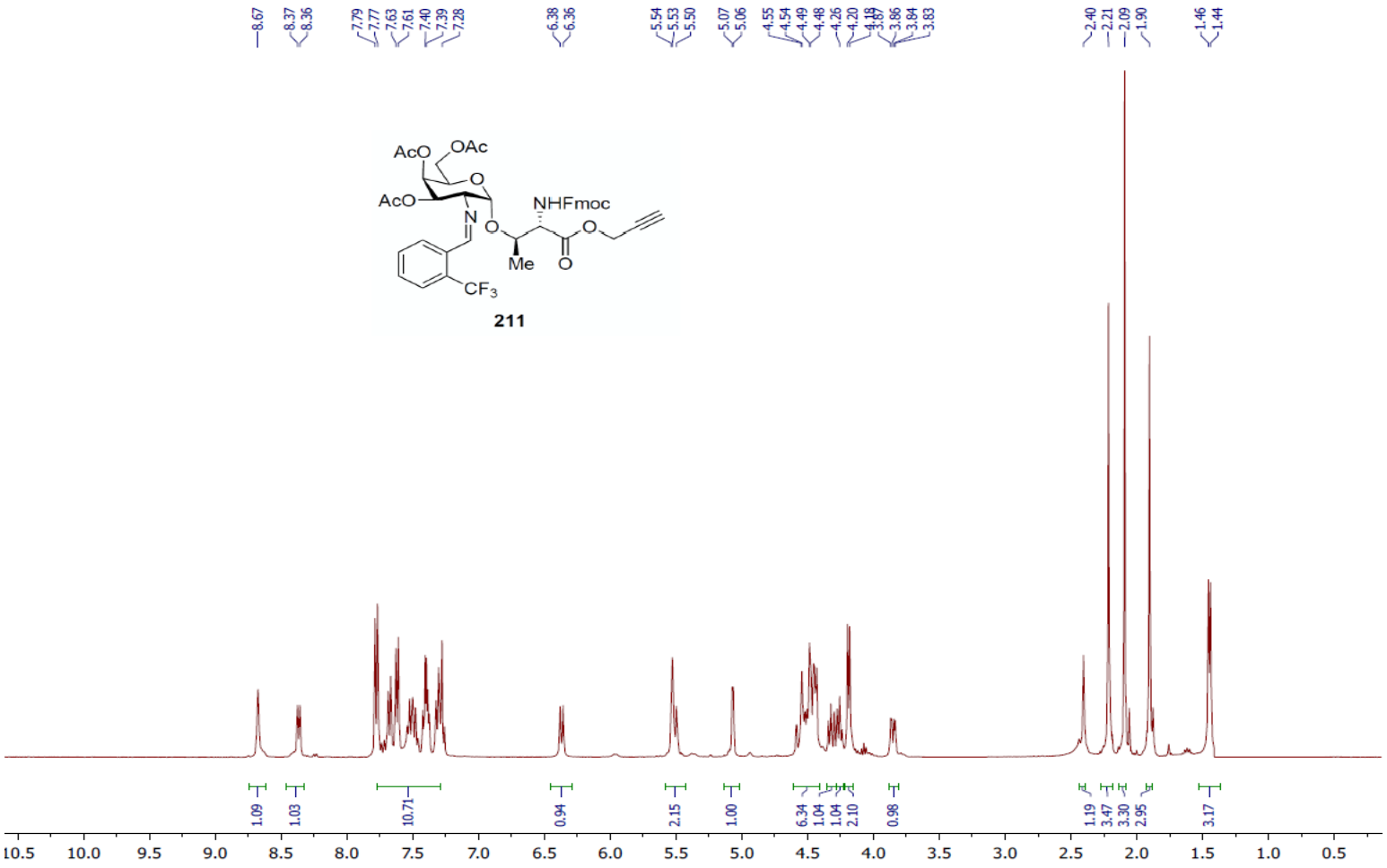


Figure A105. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **211**

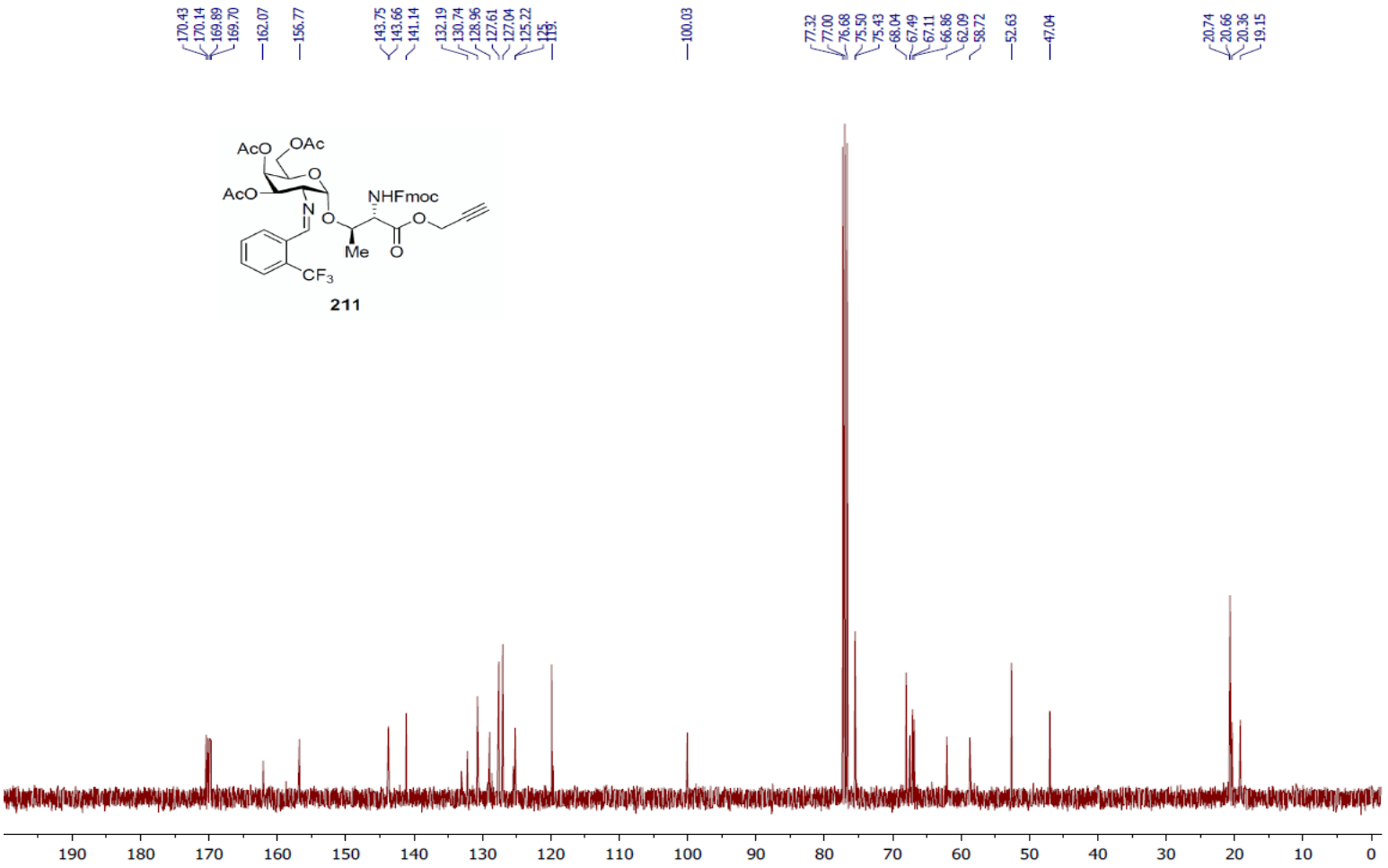


Figure A106. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **211**

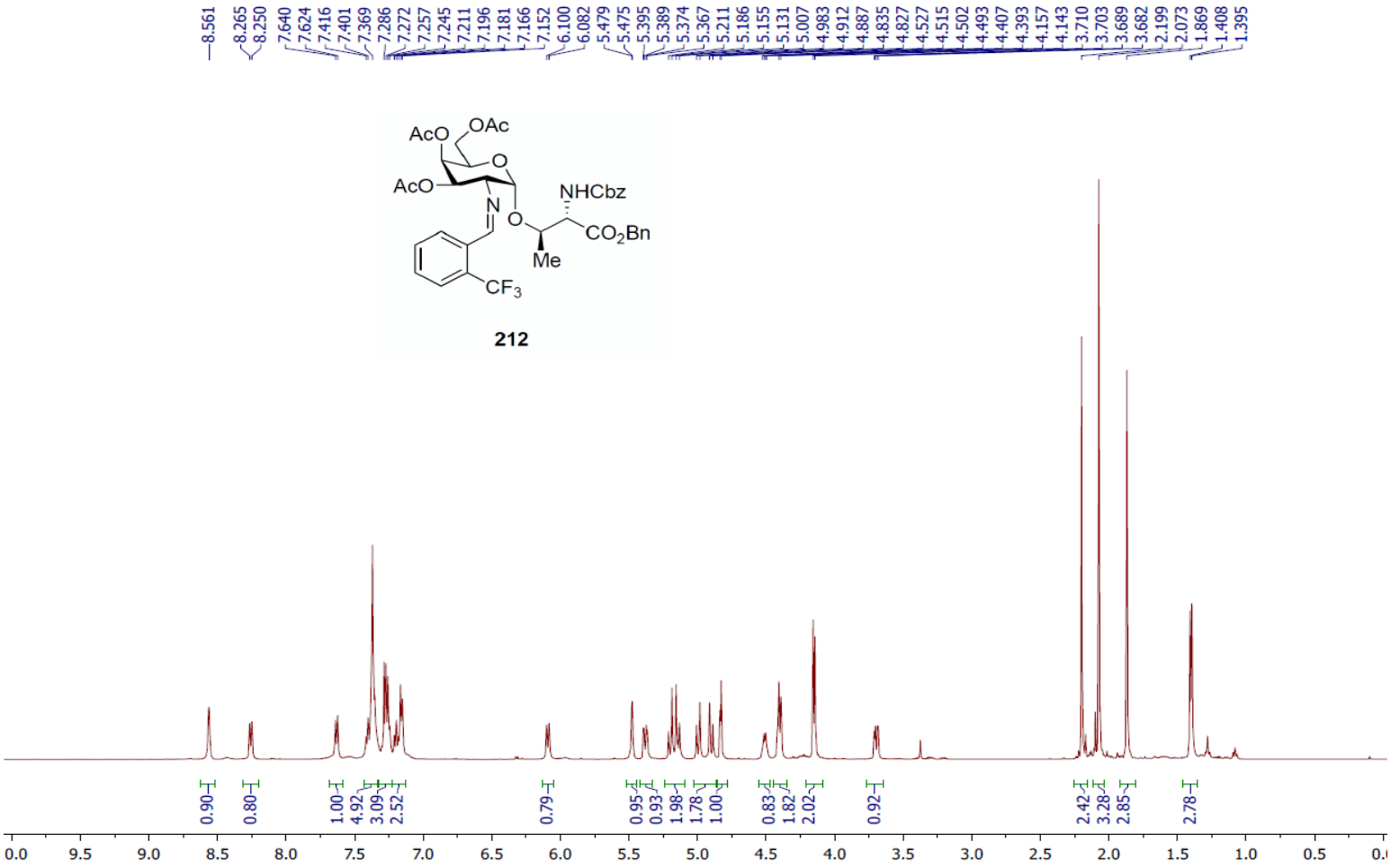


Figure A107. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **212**

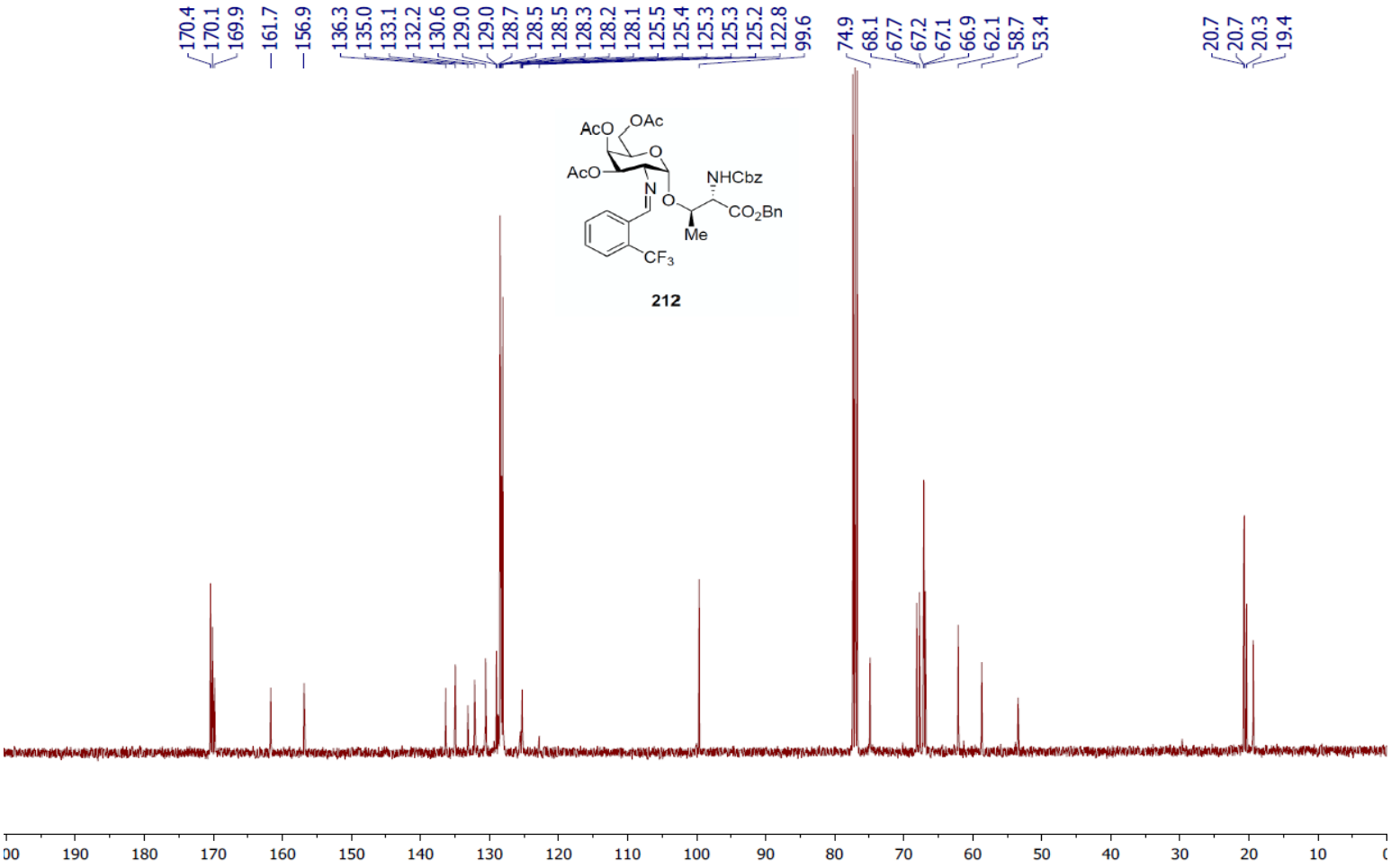


Figure A108. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **212**

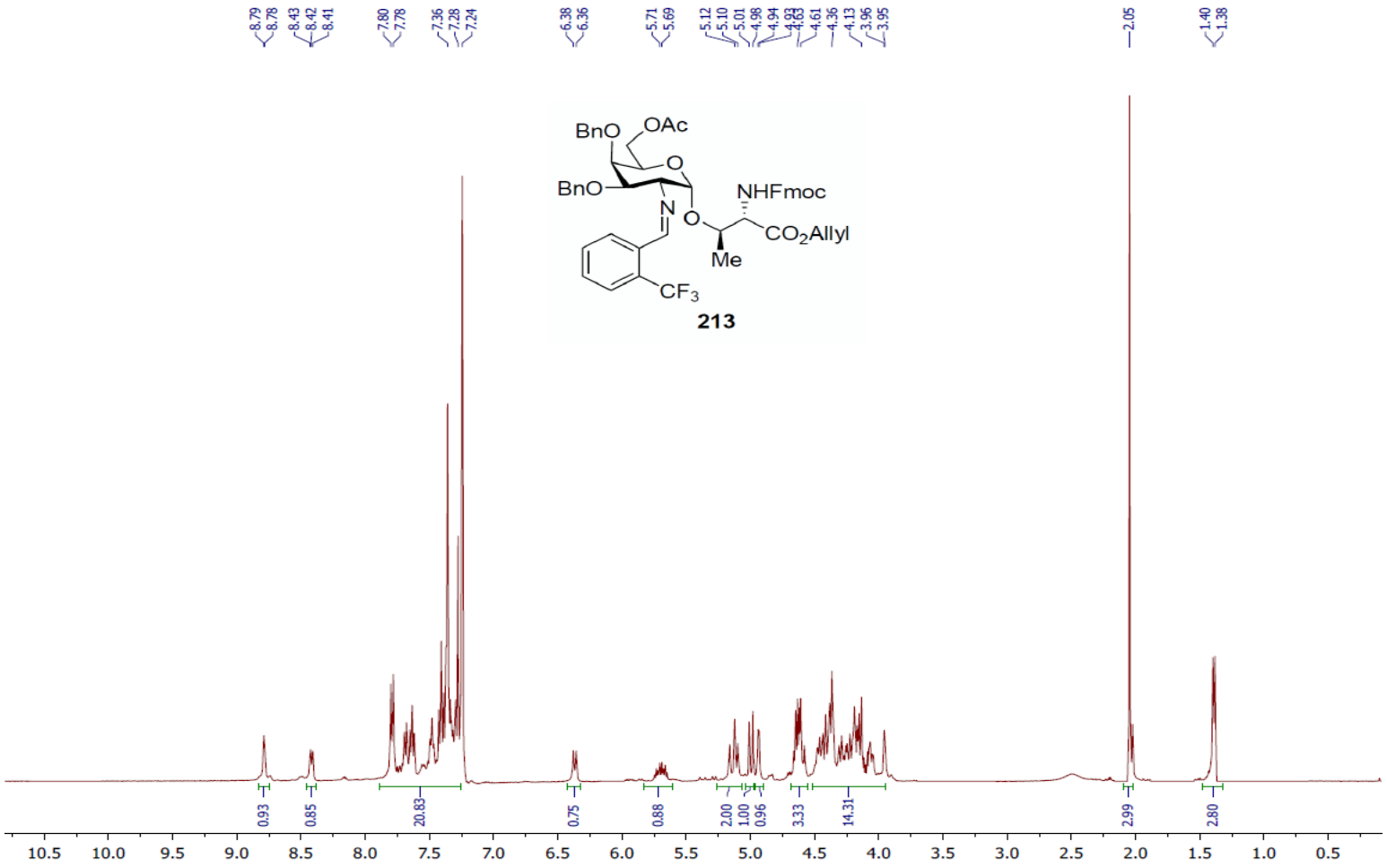


Figure A109. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **213**

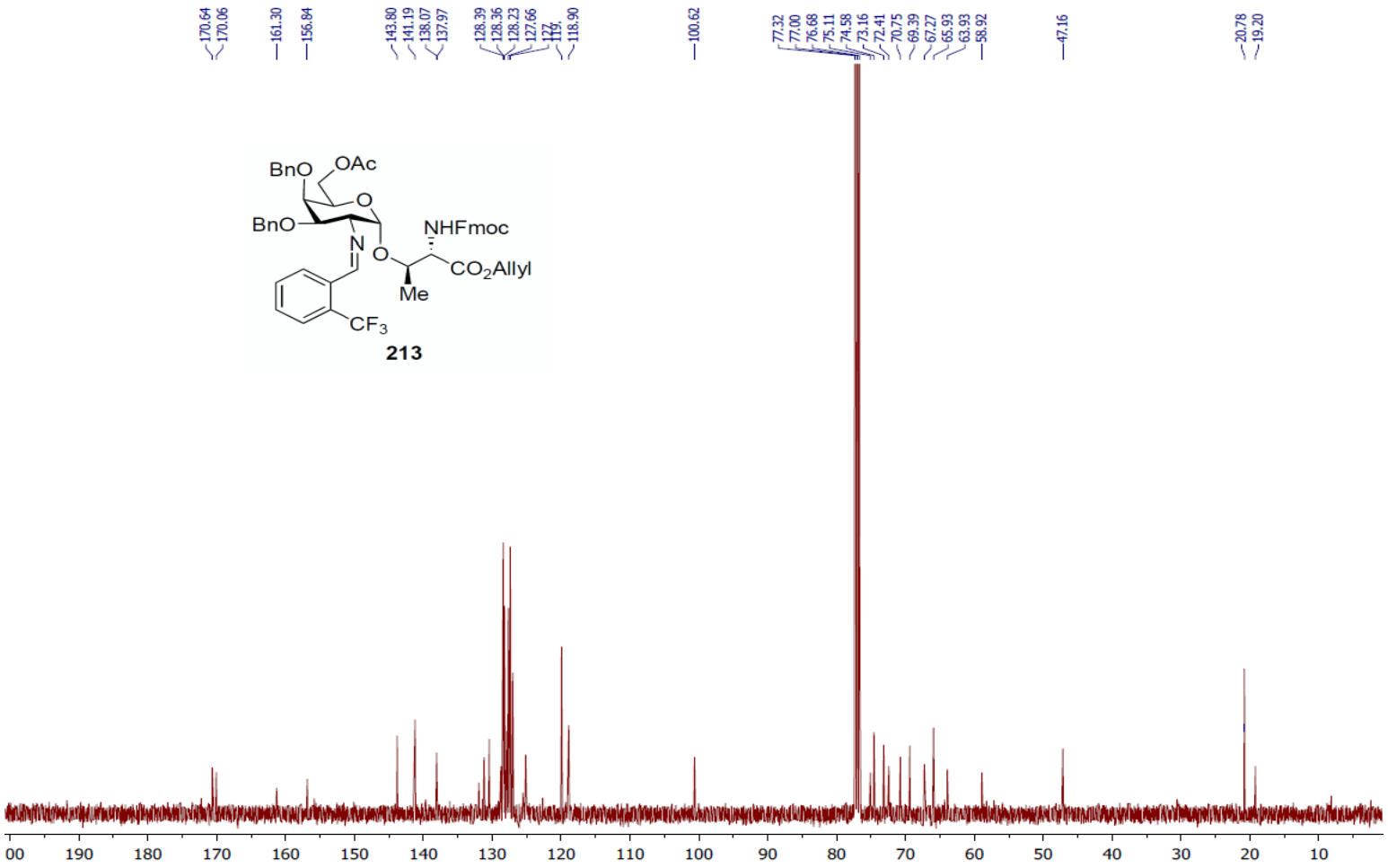


Figure A110. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **213**

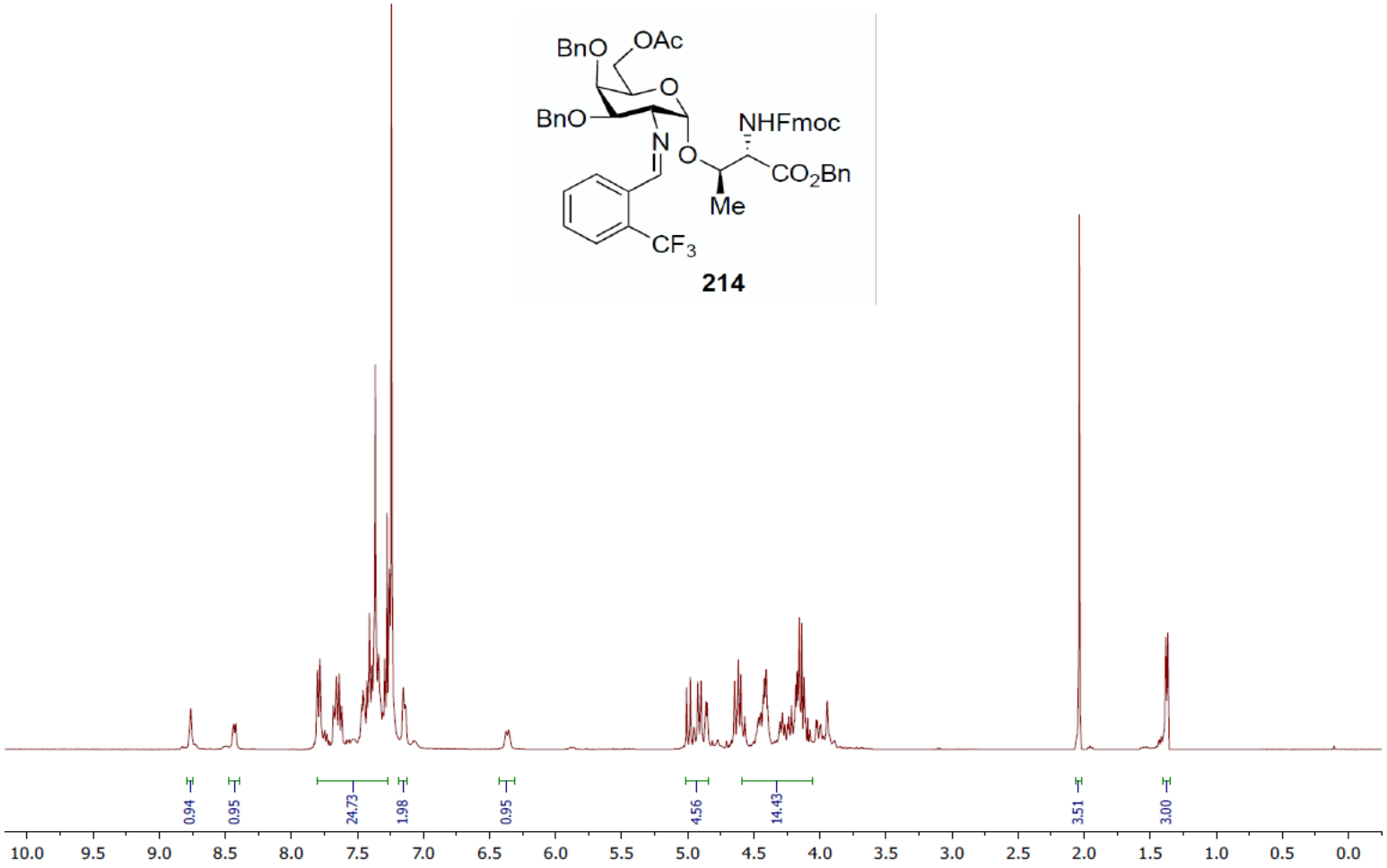


Figure A111. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **214**

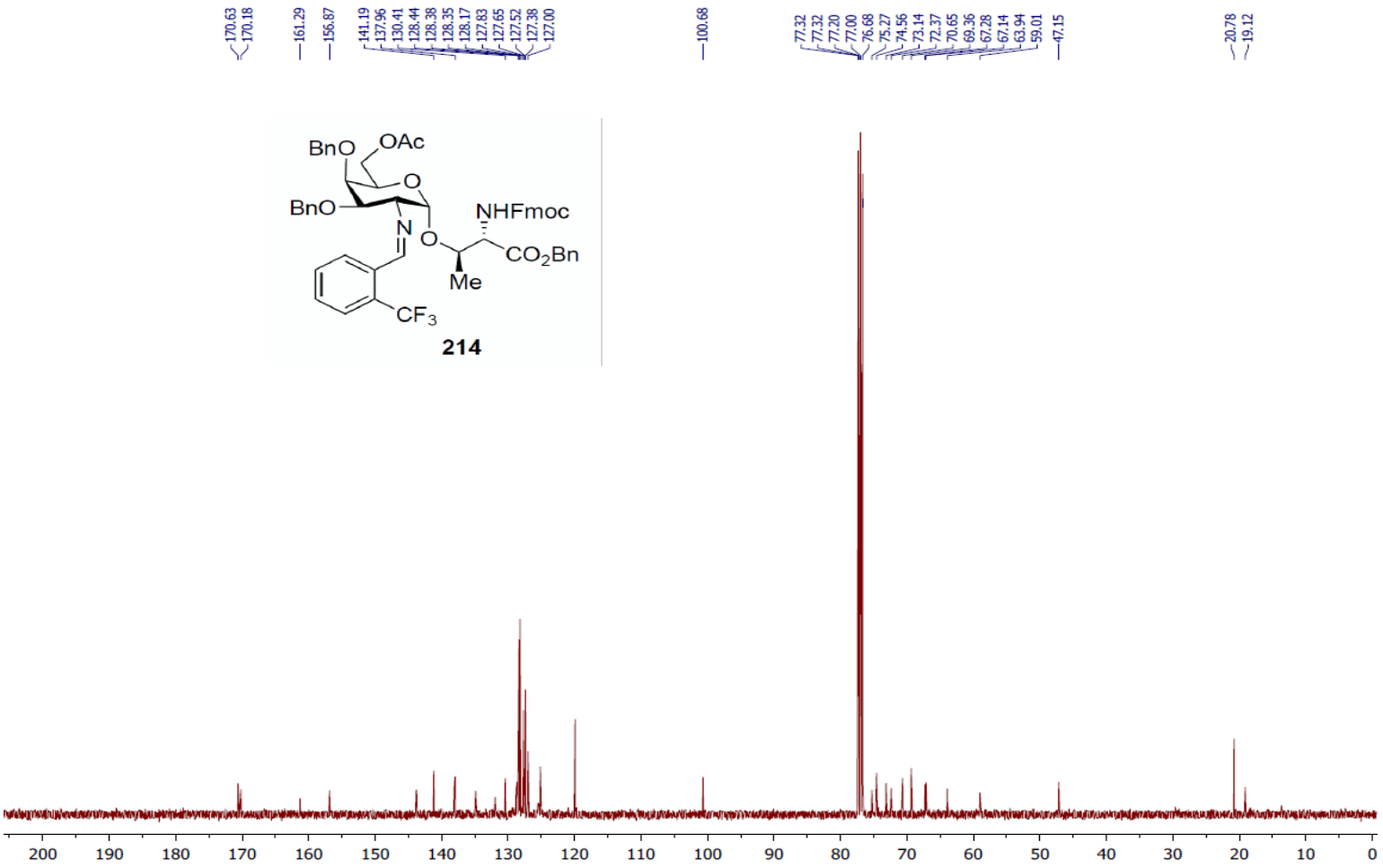


Figure A112. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **214**

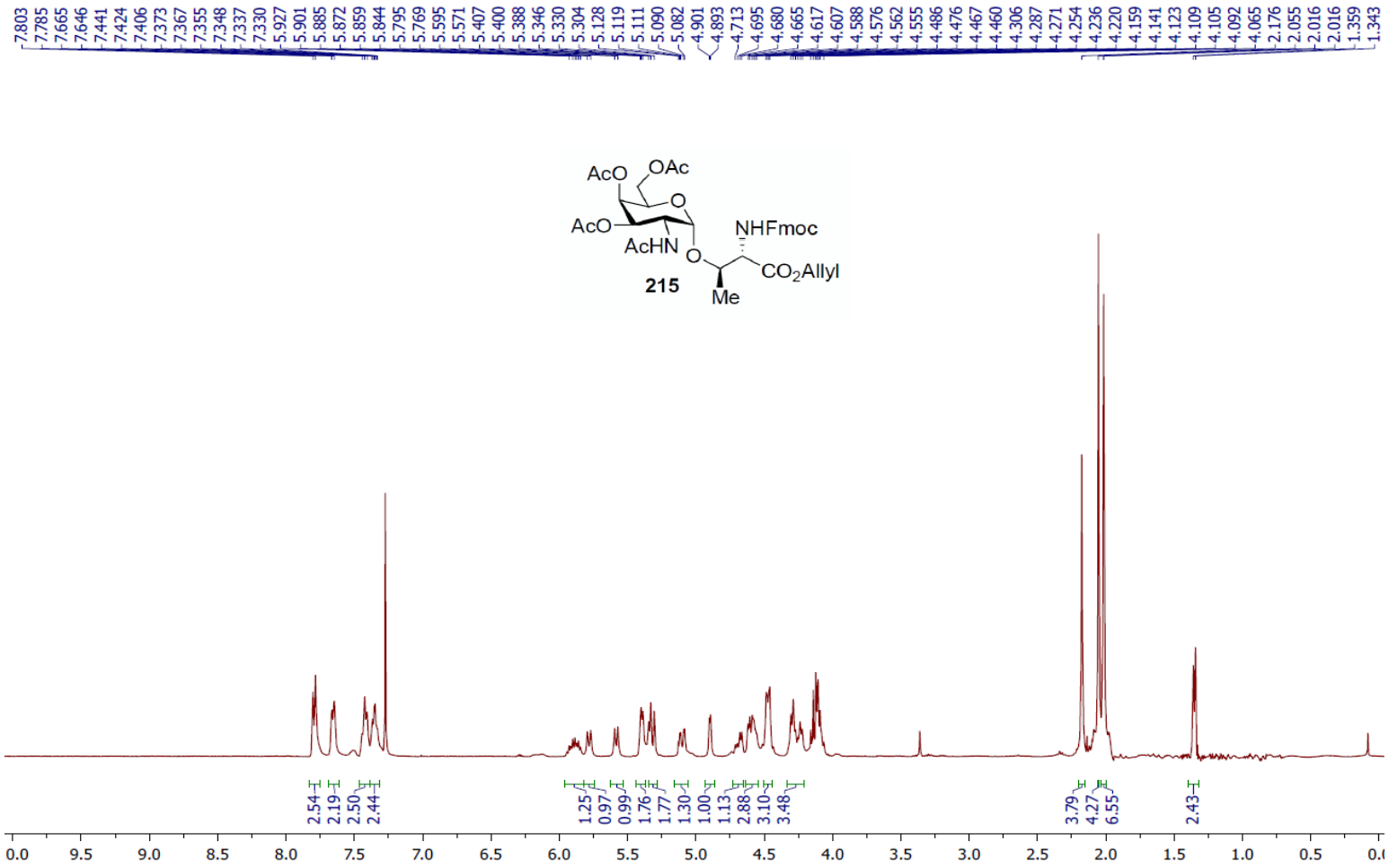


Figure A113. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **215**

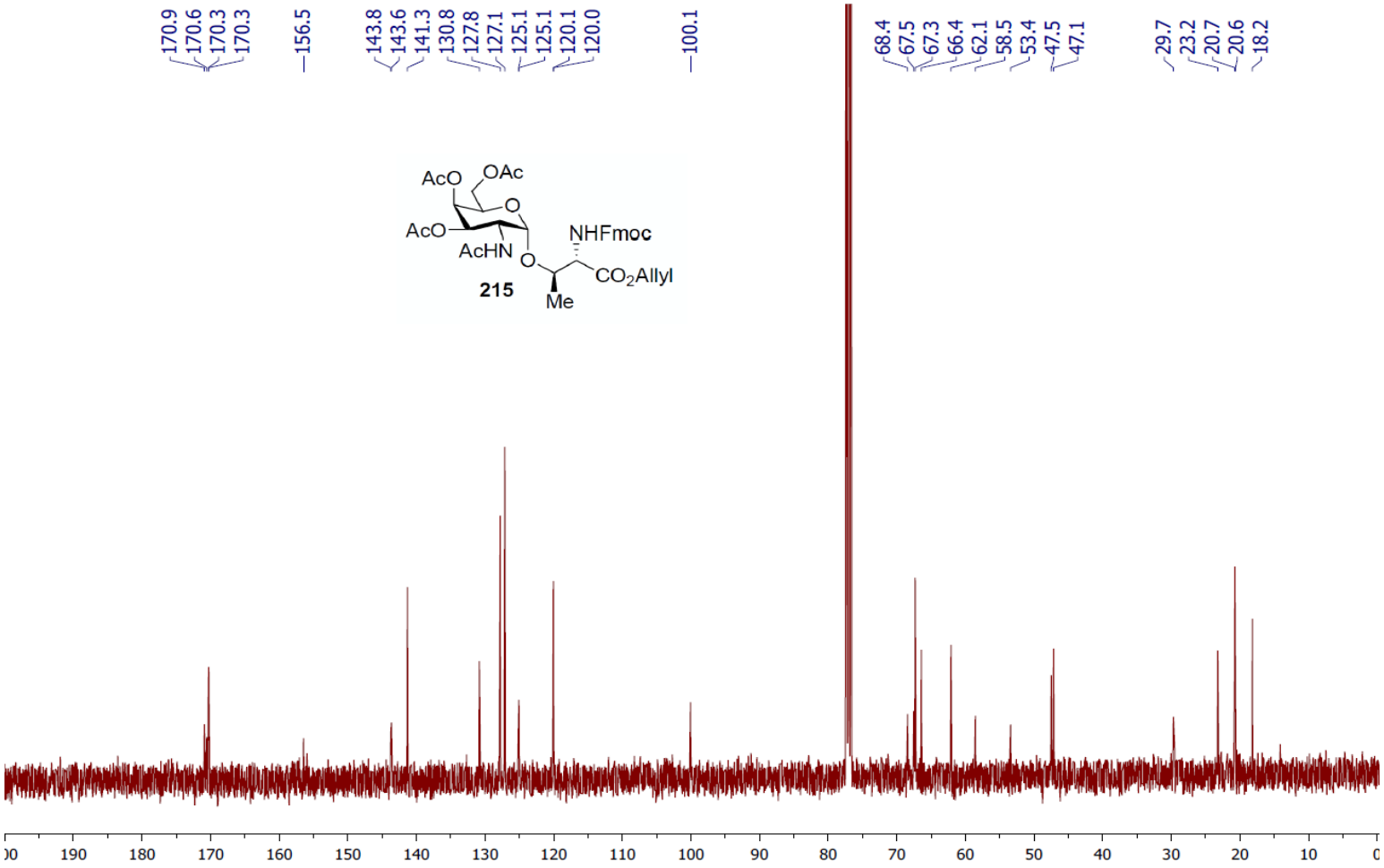


Figure A114. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glycoconjugate **215**

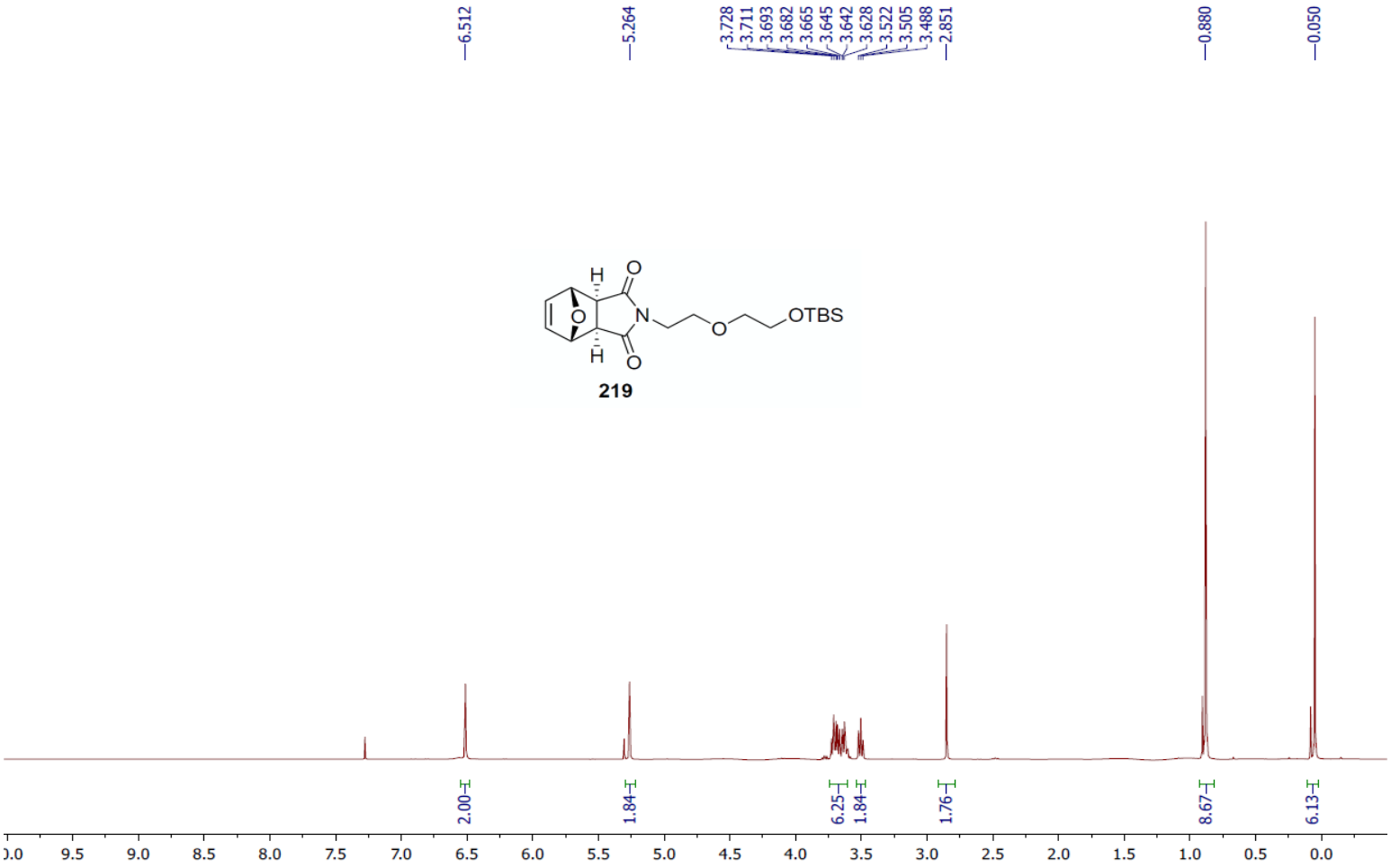


Figure A115. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **219**

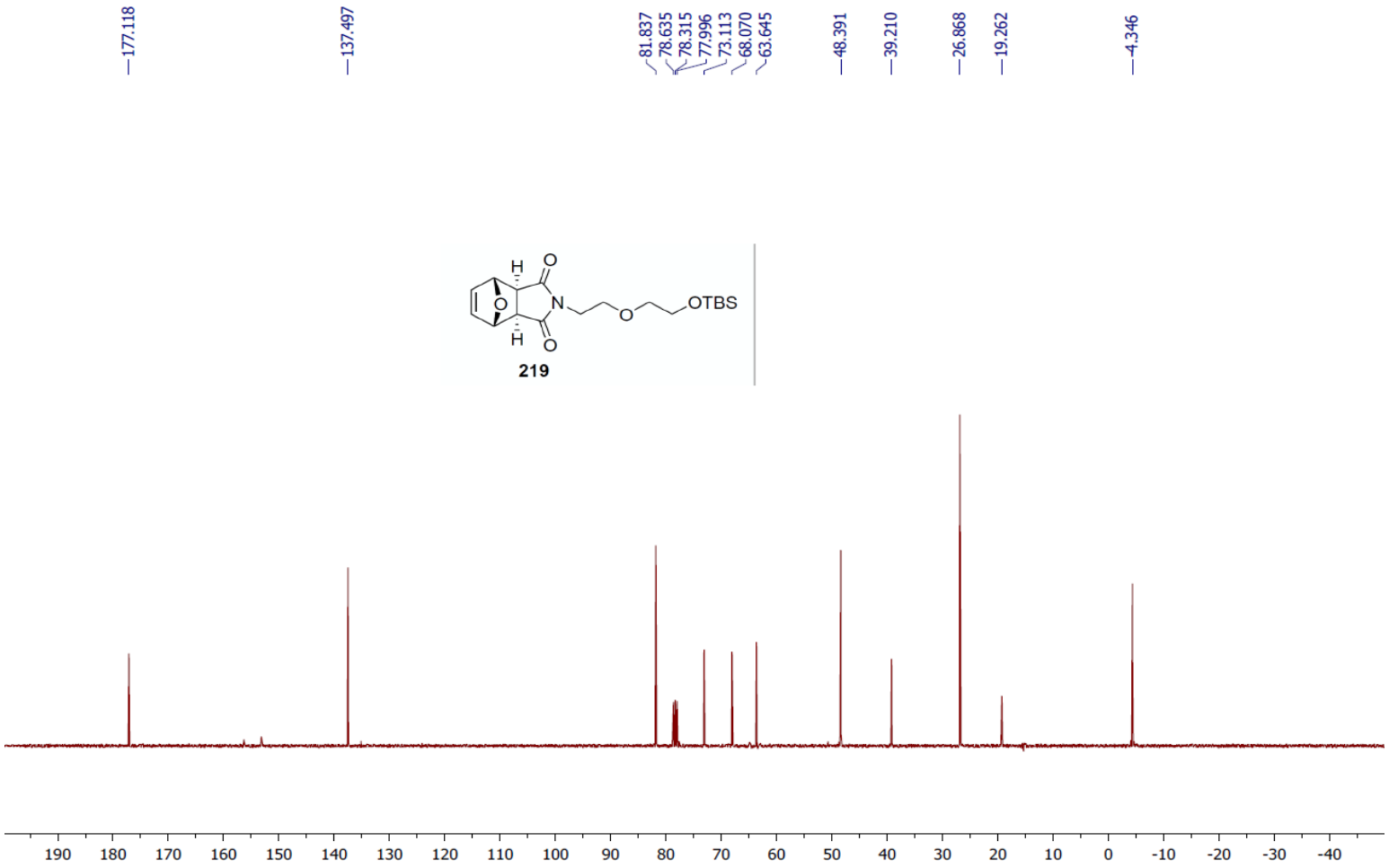


Figure A116. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **219**

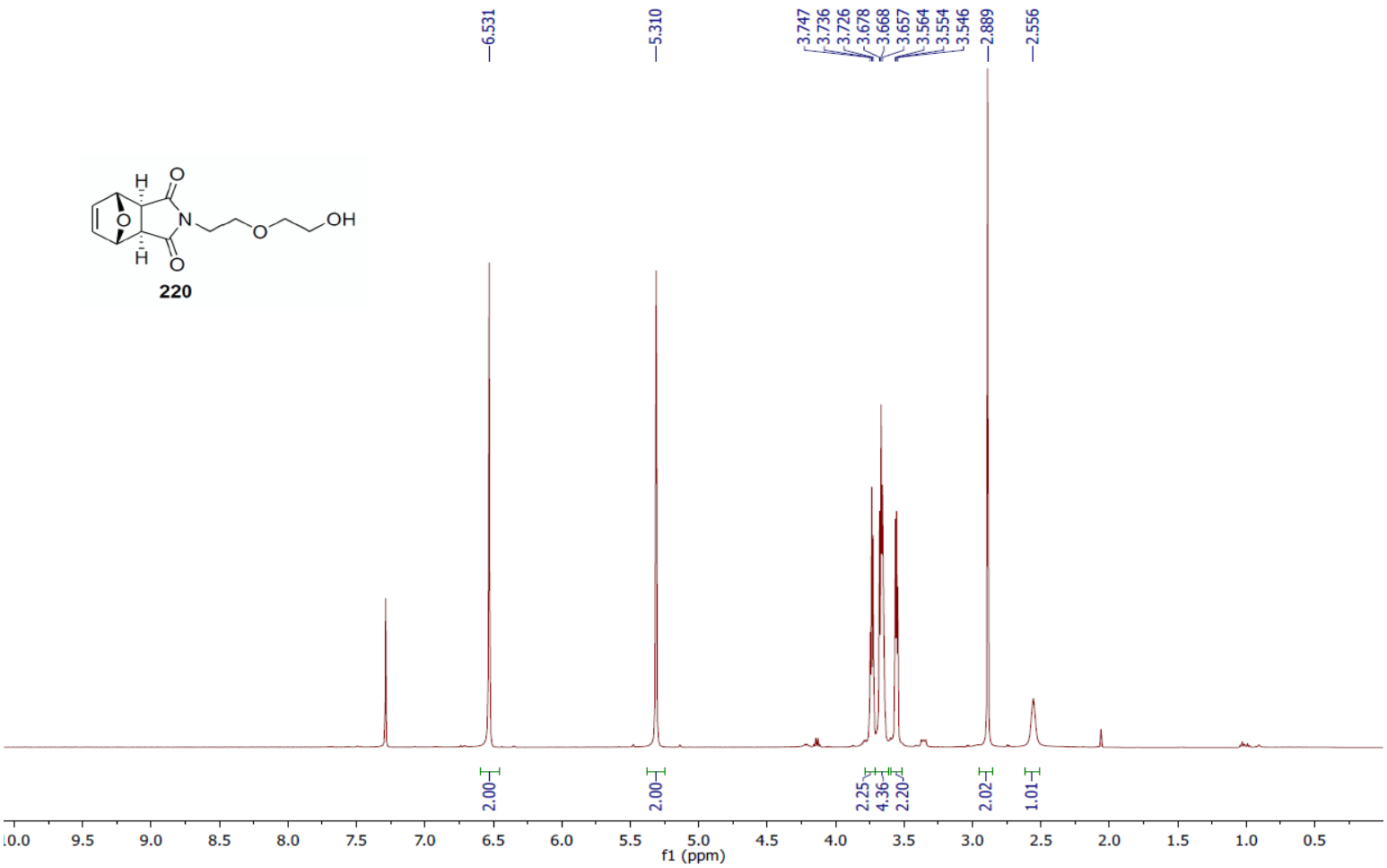


Figure A117. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glycoconjugate **220**

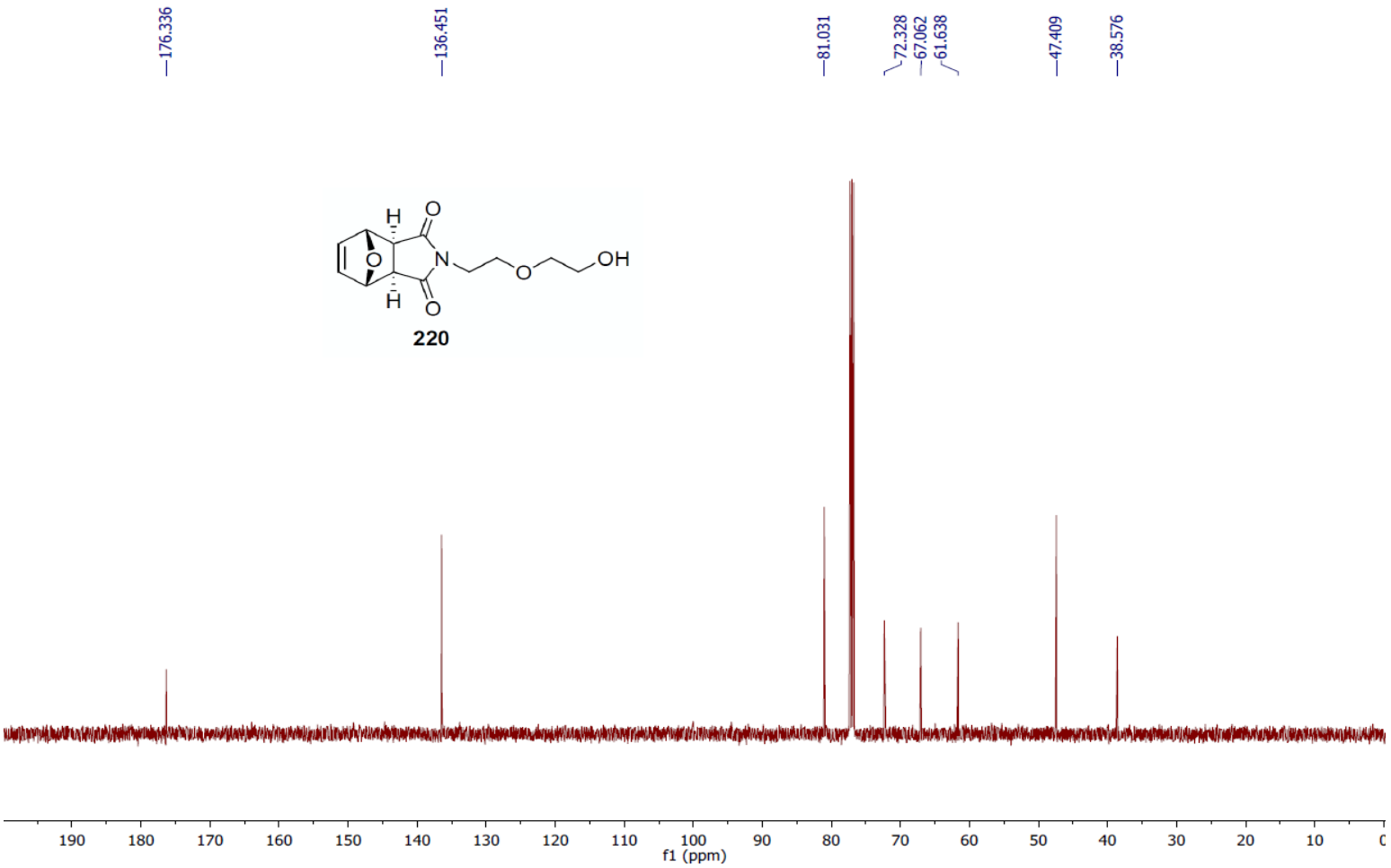


Figure A118. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **220**

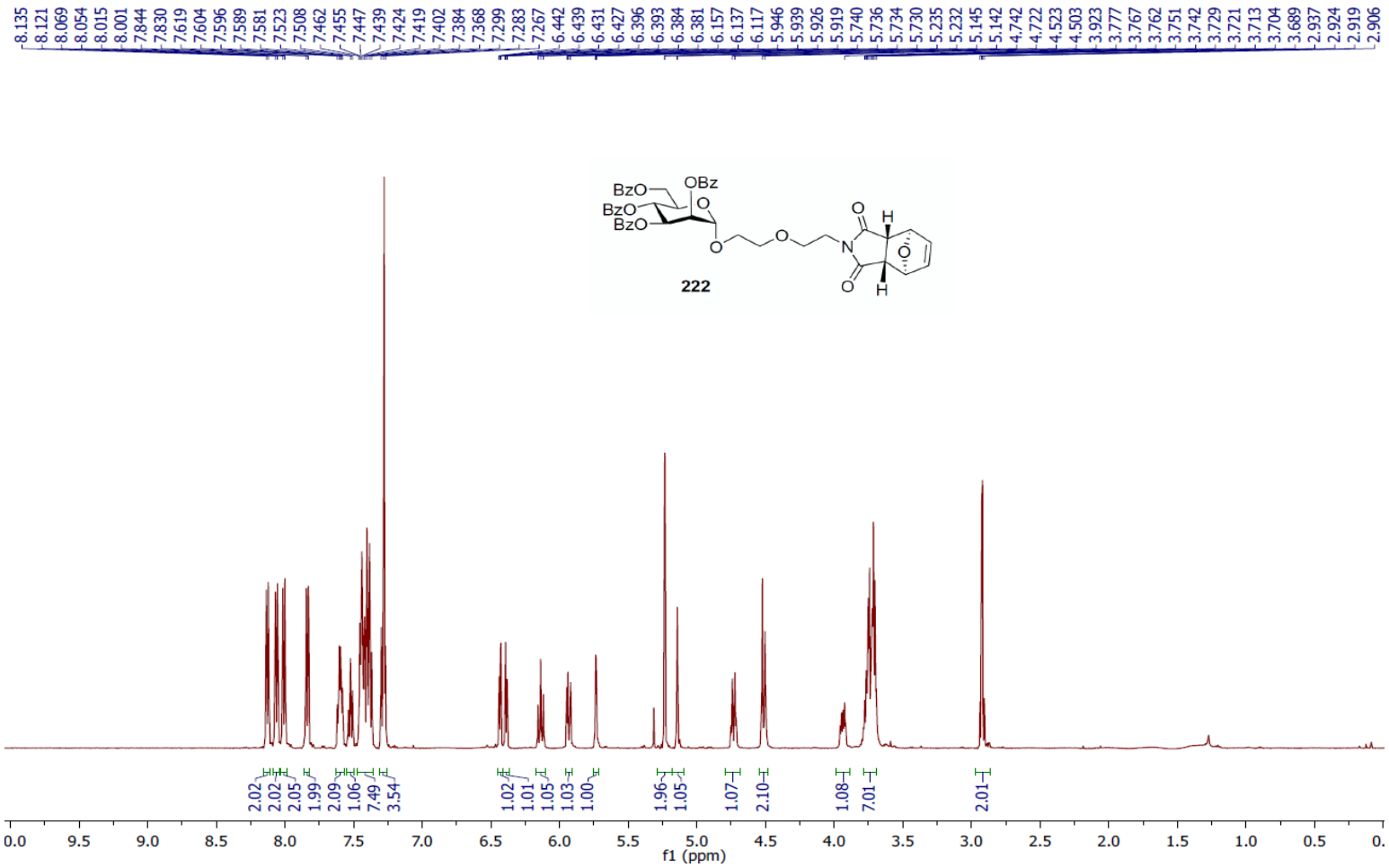


Figure A119. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Monomer **222**

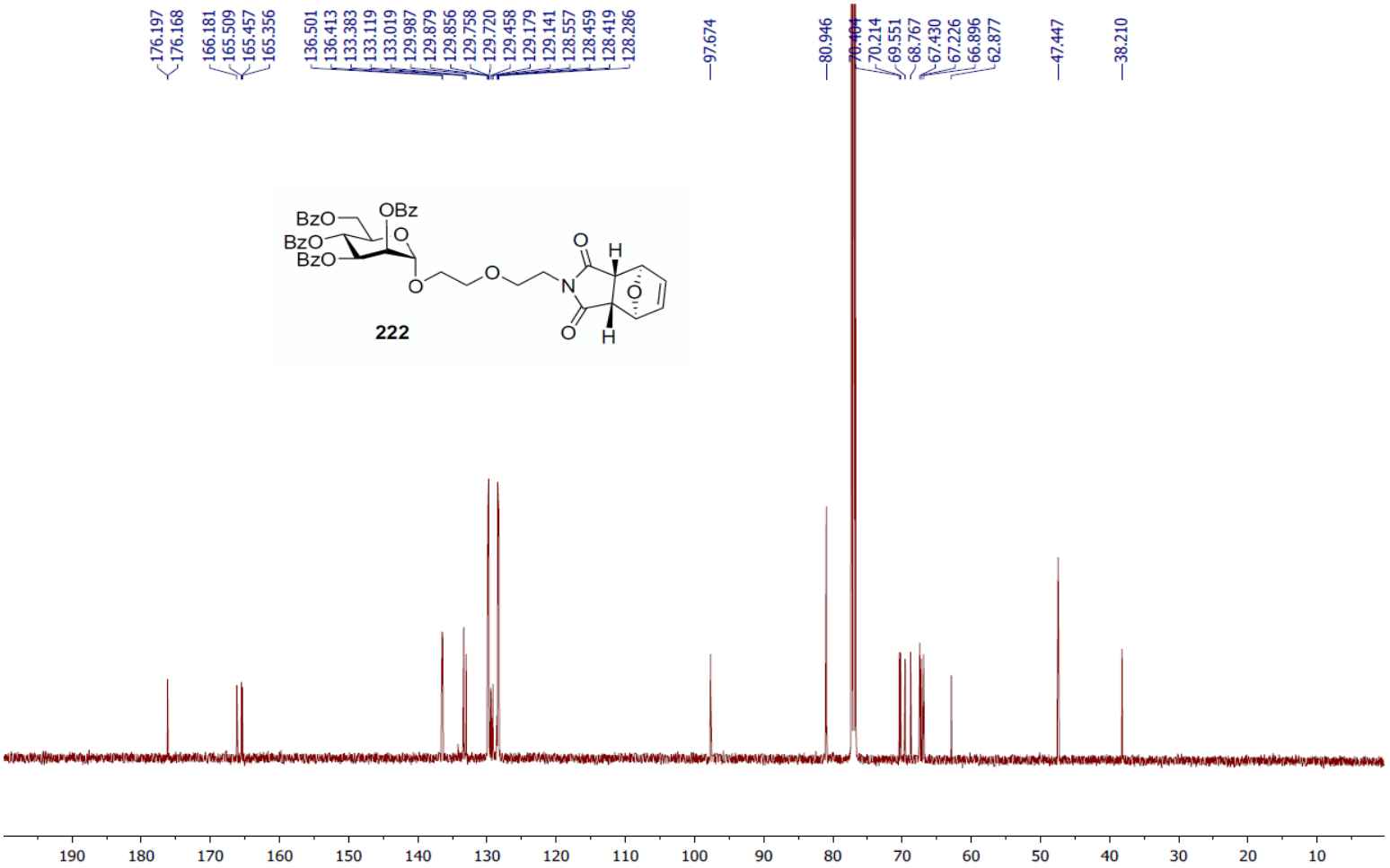


Figure A120. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Monomer **222**

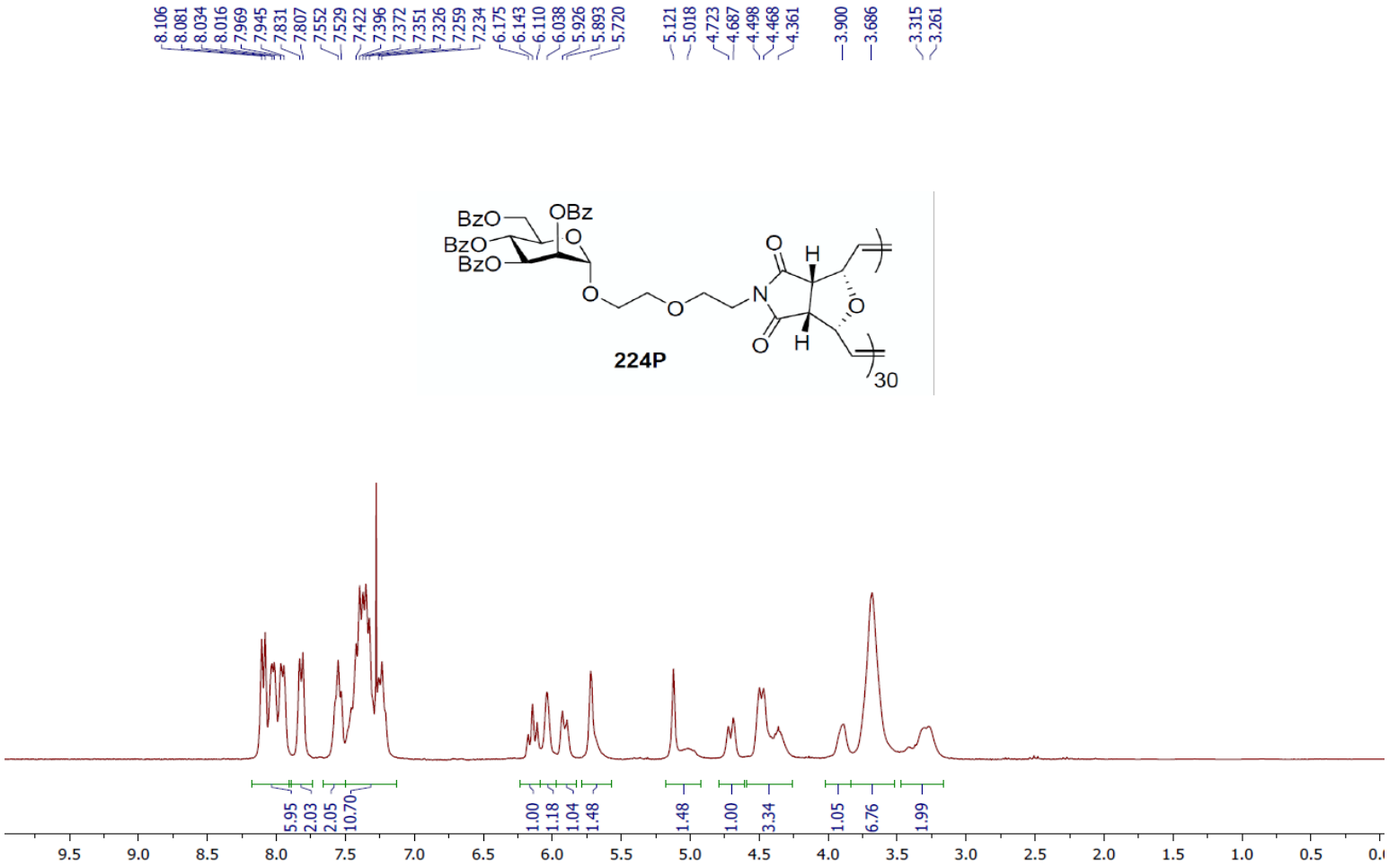


Figure A121. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Polymer **224P**

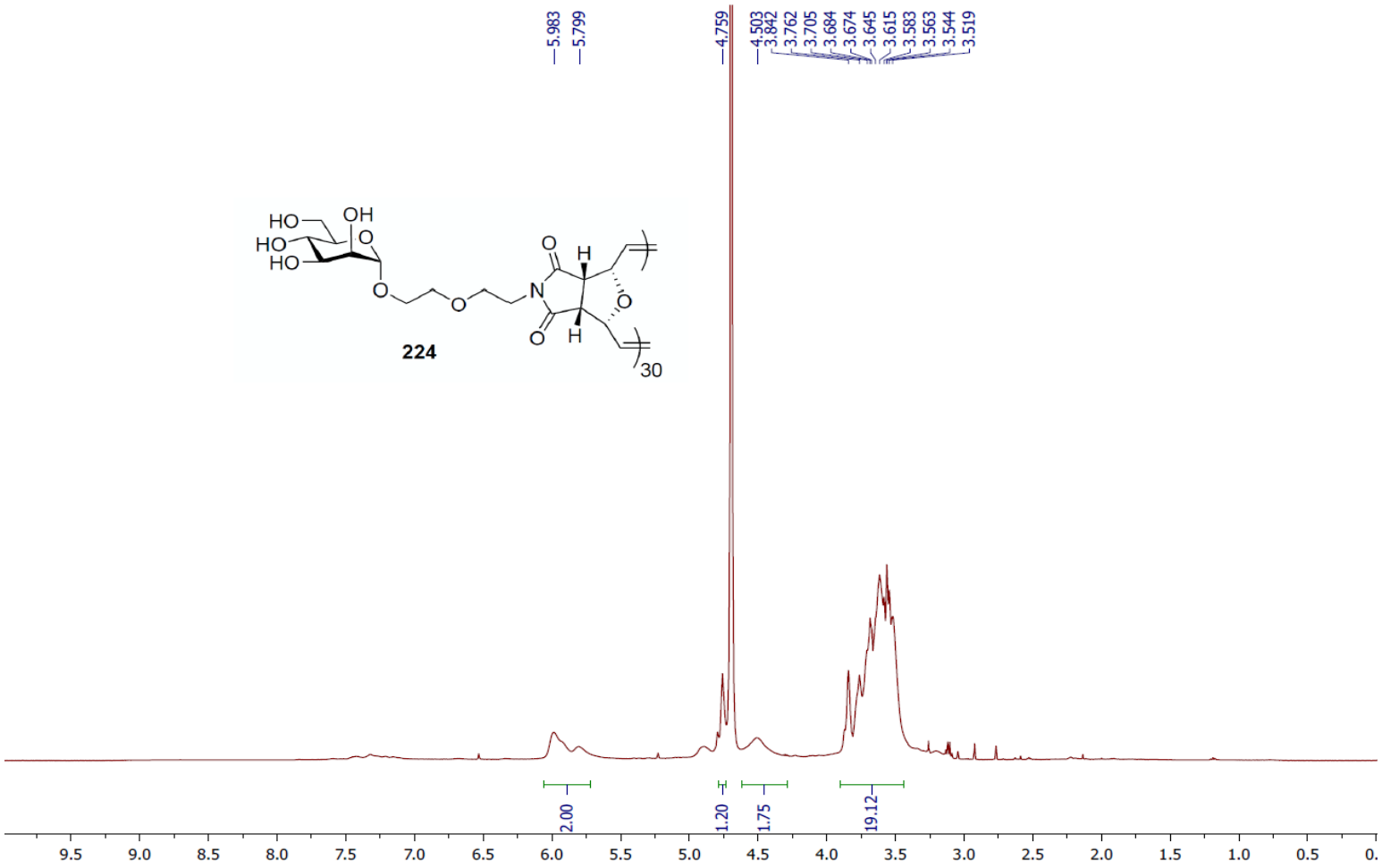


Figure A122. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **224**

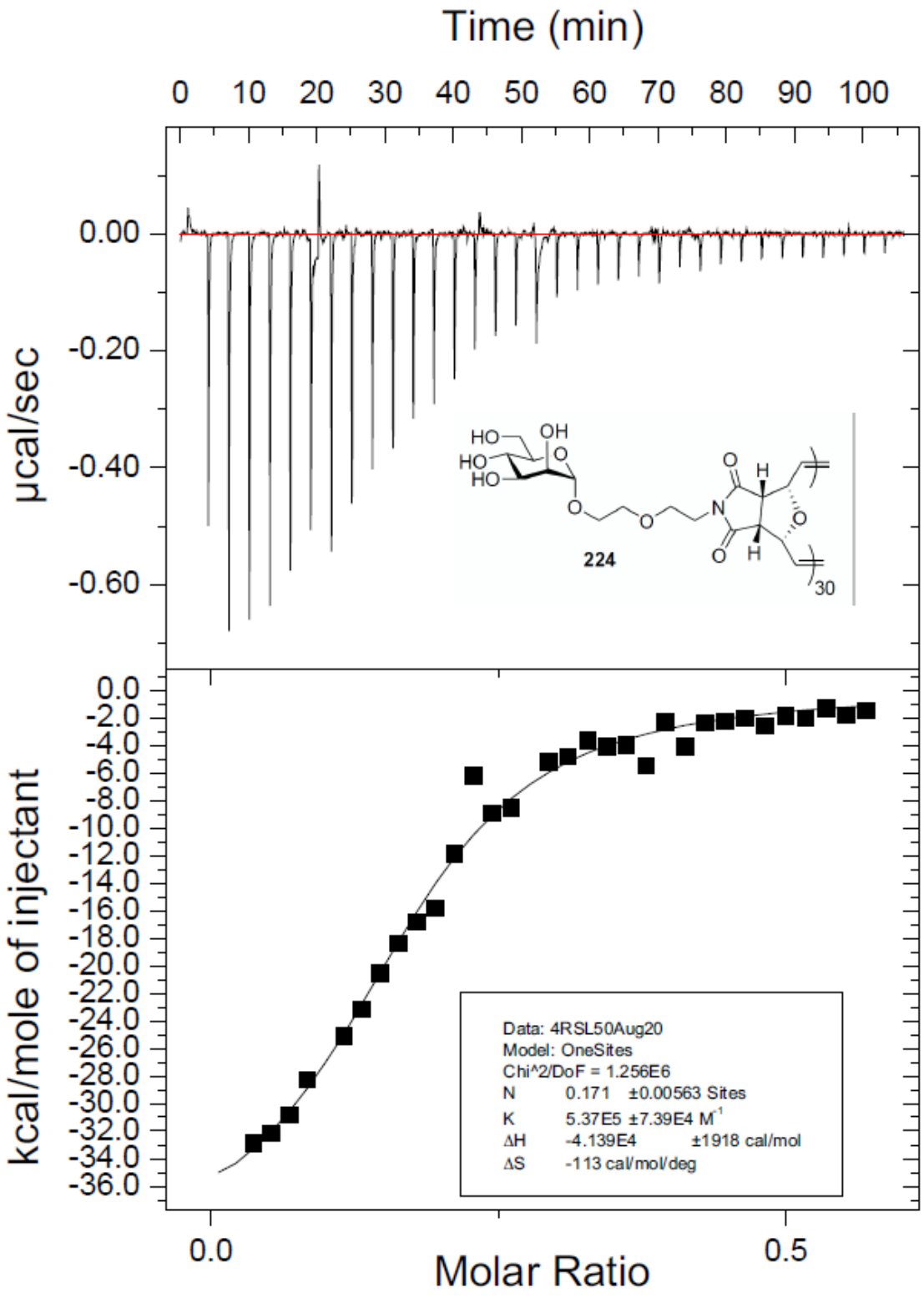


Figure A123. ITC Thermogram of Polymer **224**

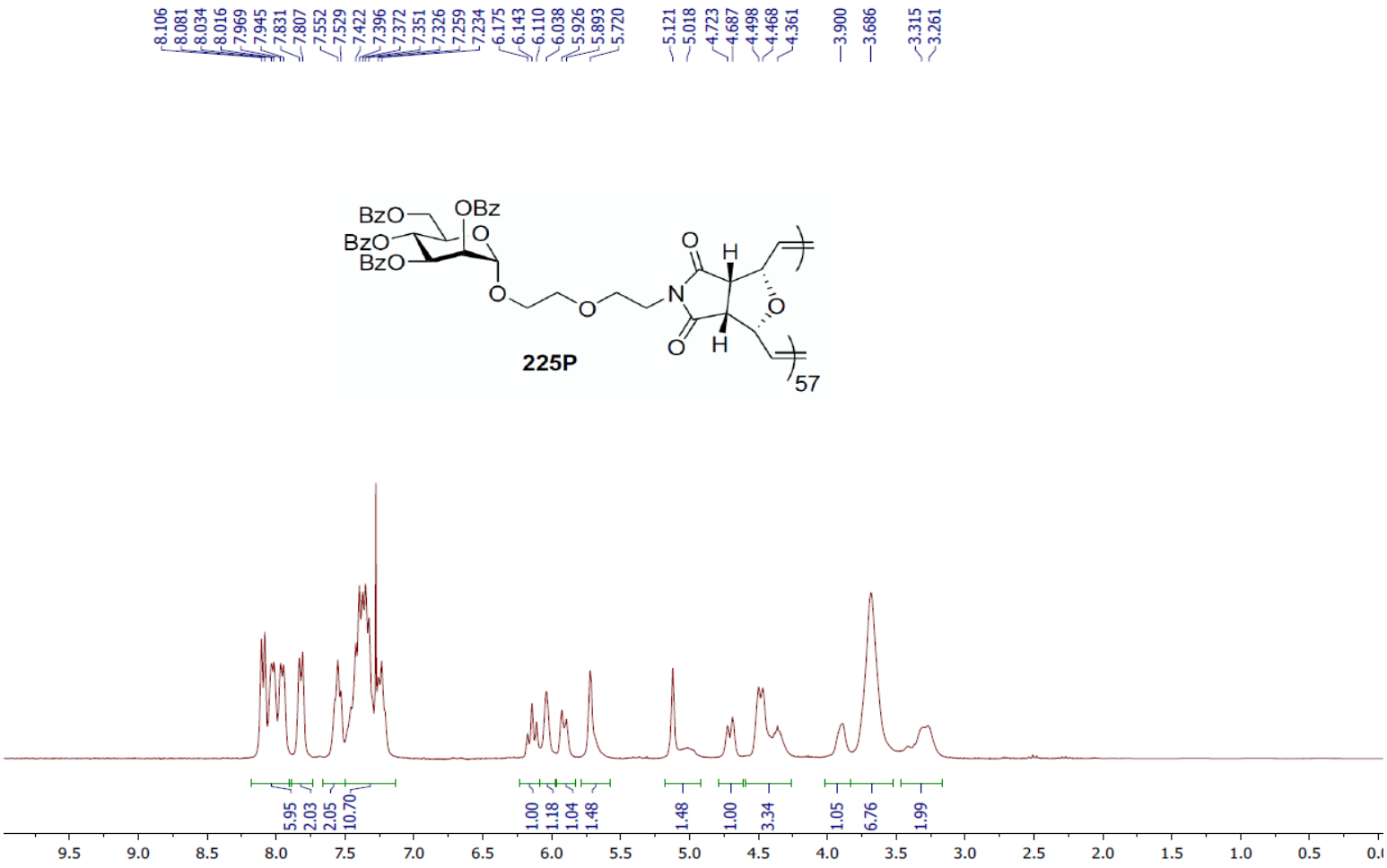


Figure A124. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Polymer **225P**

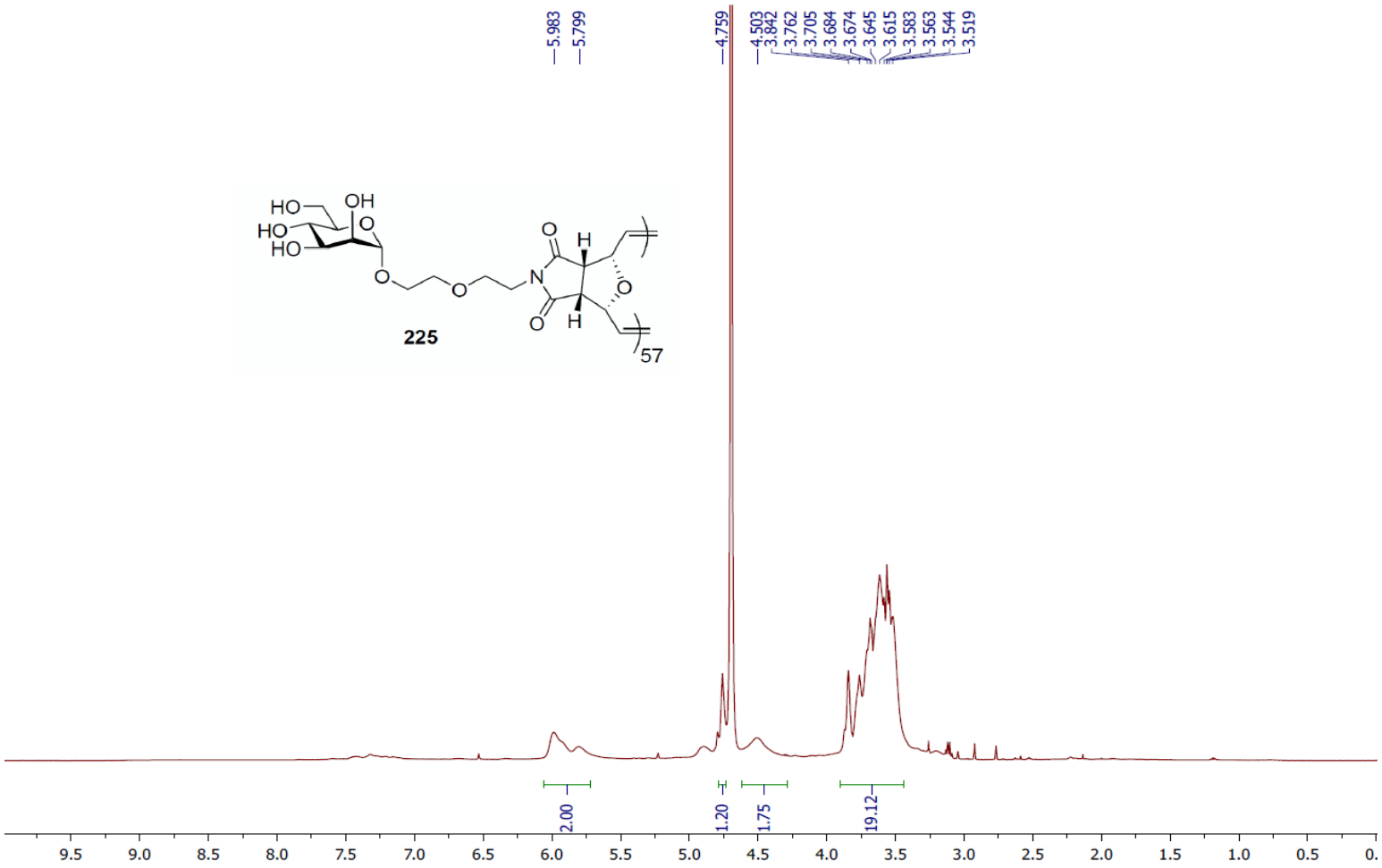


Figure A125. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **225**

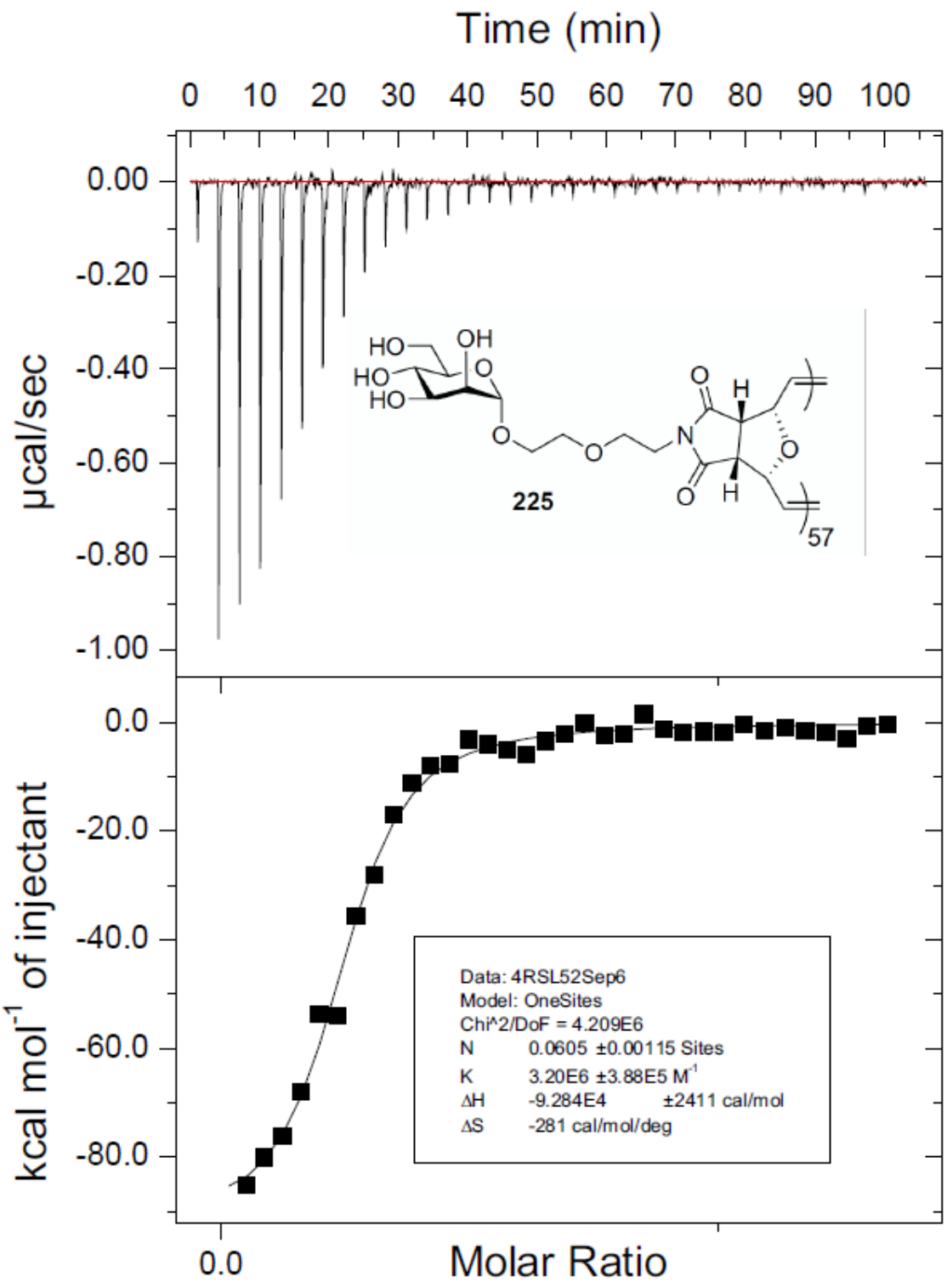


Figure A126. ITC Thermogram of Polymer **225**

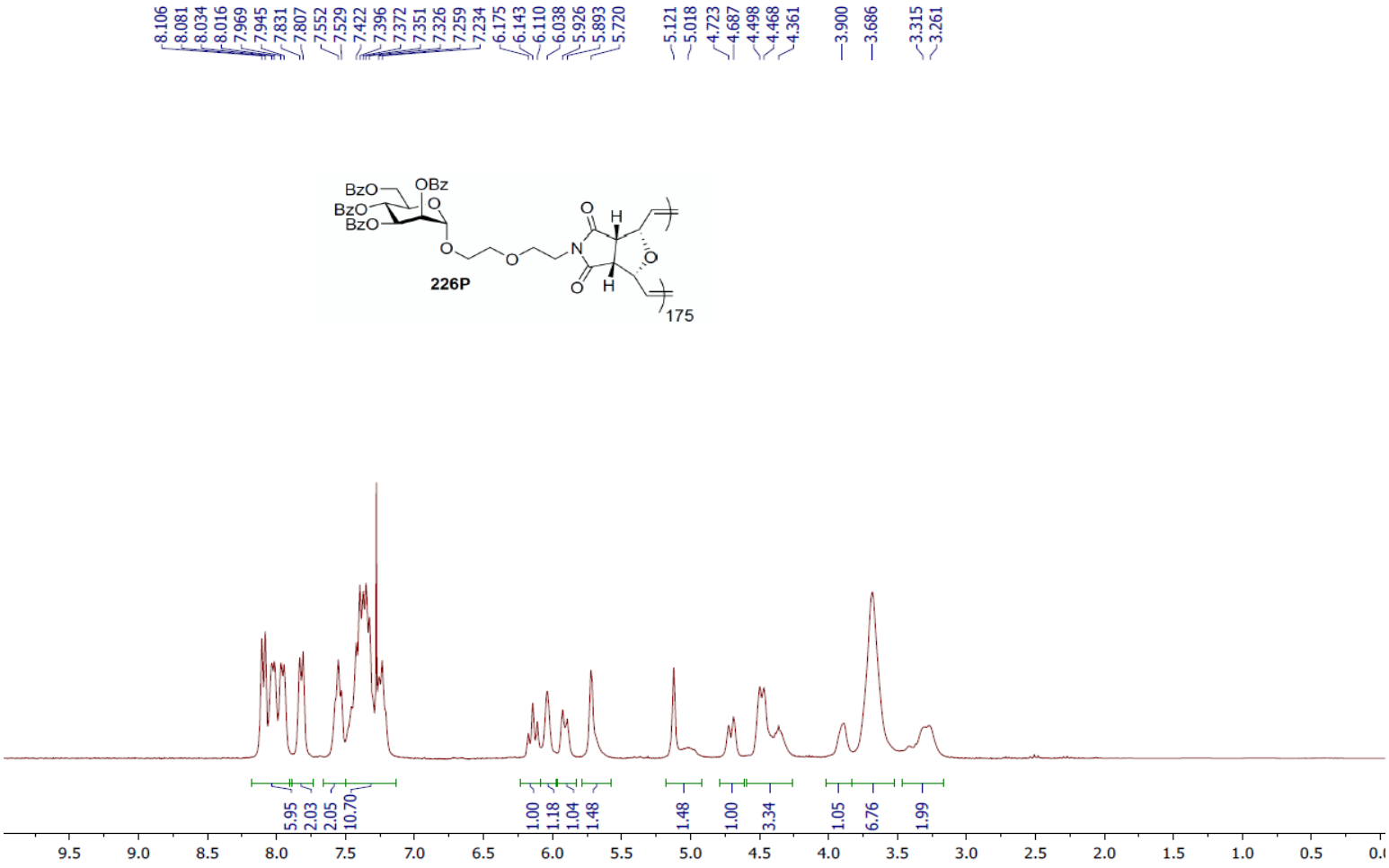


Figure A127. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Polymer **226P**

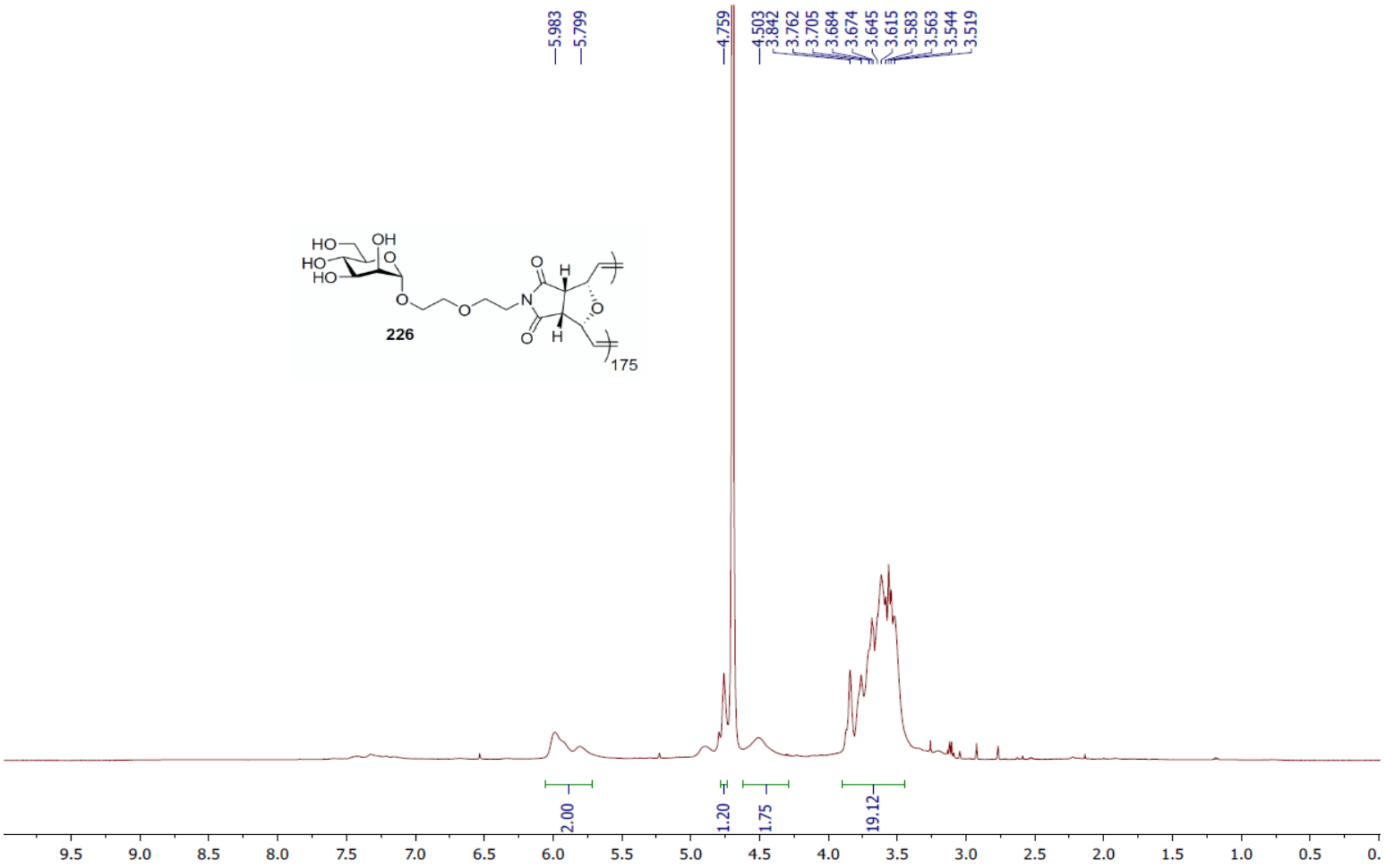


Figure A128. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **226**

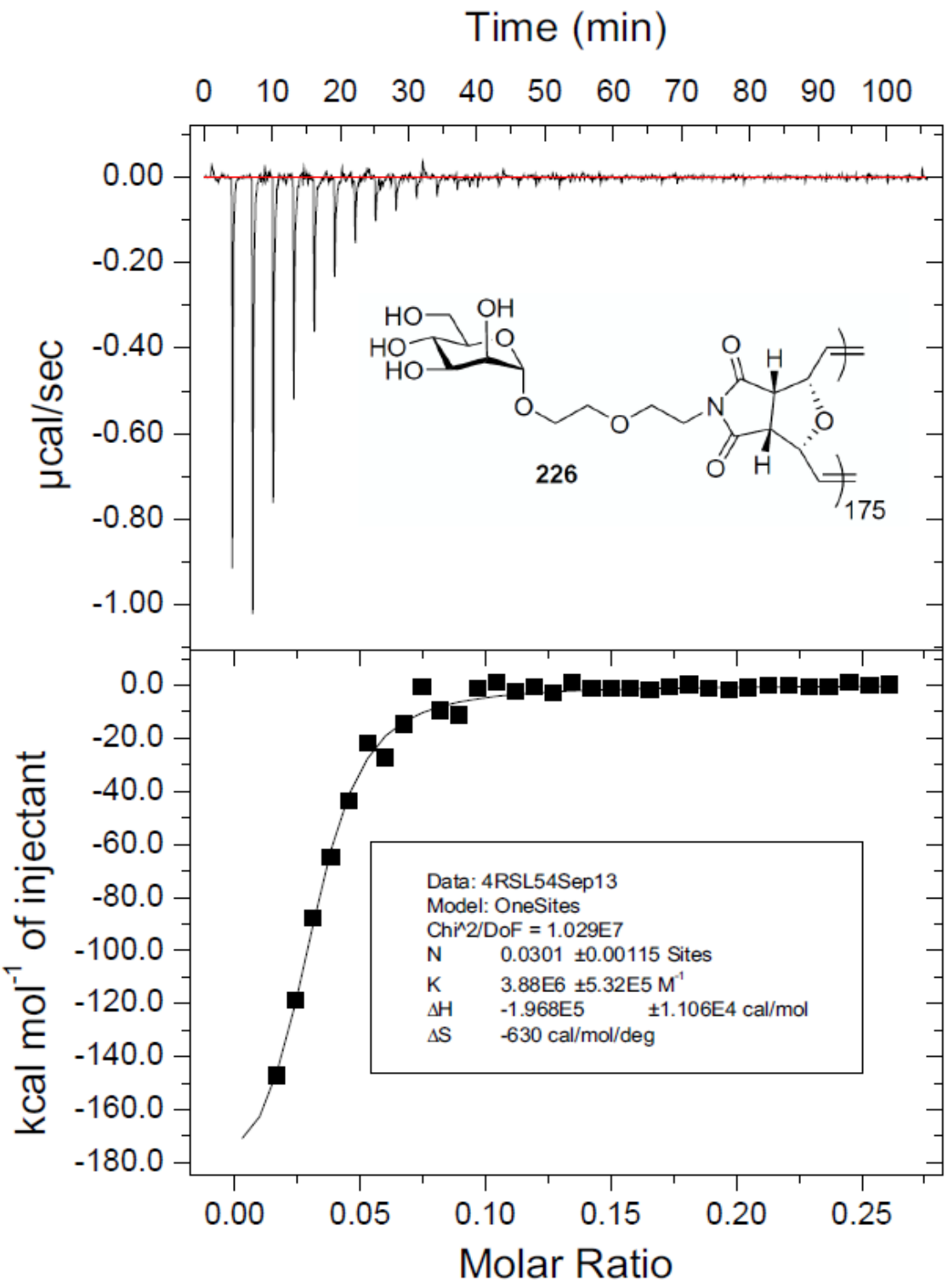


Figure A129. ITC Thermogram of Polymer **226**

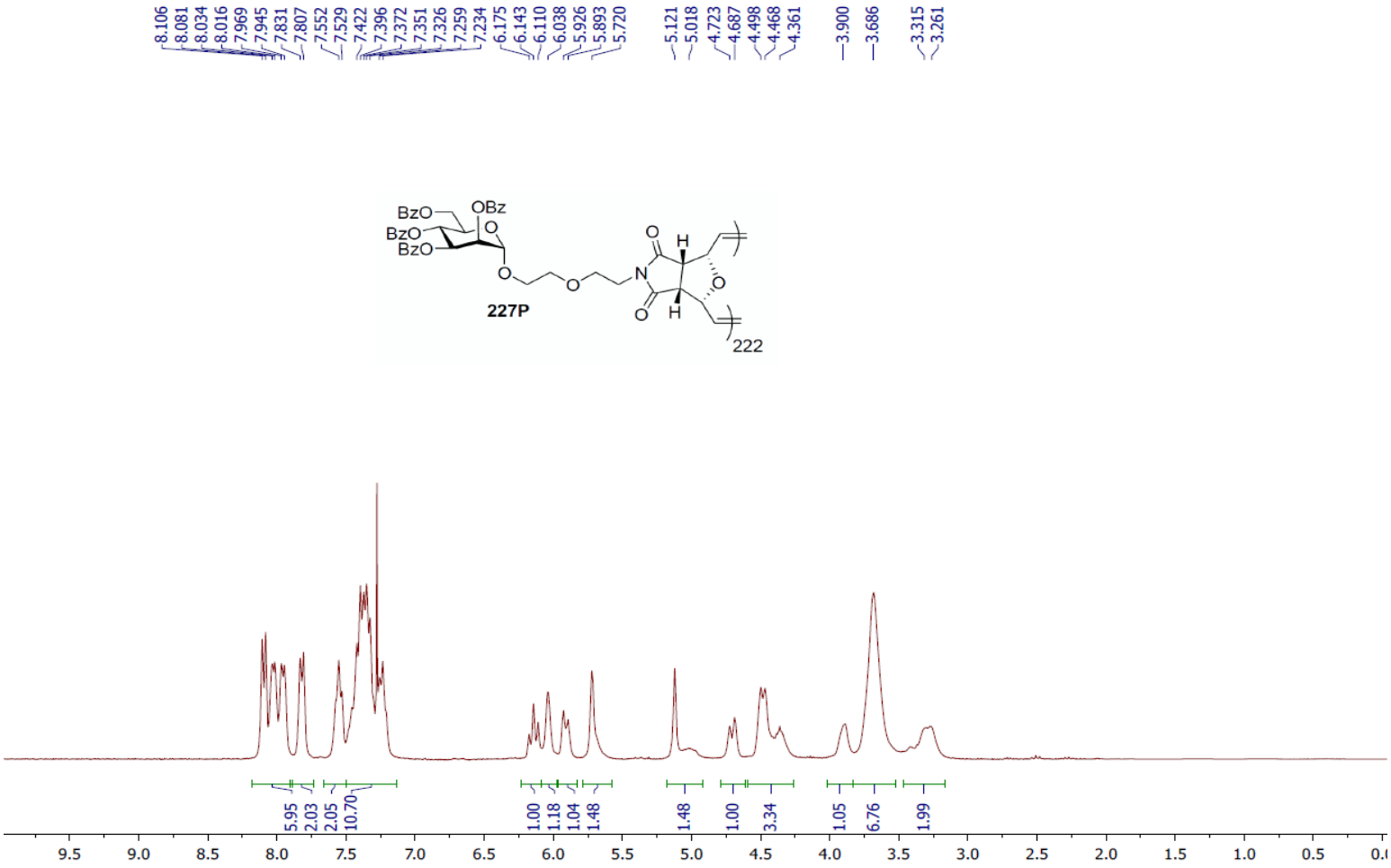


Figure A130. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Polymer **227P**

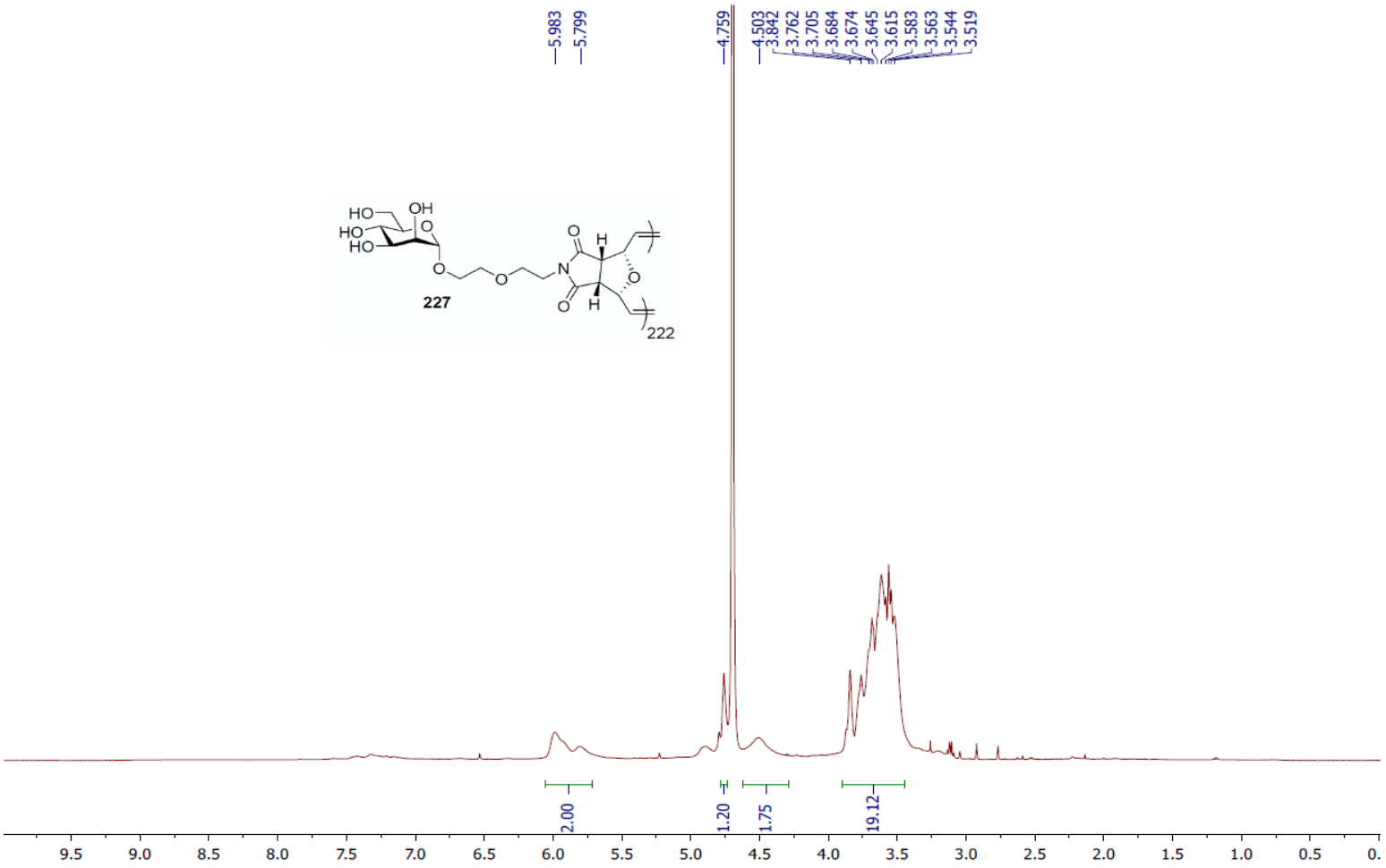


Figure A131. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **227**

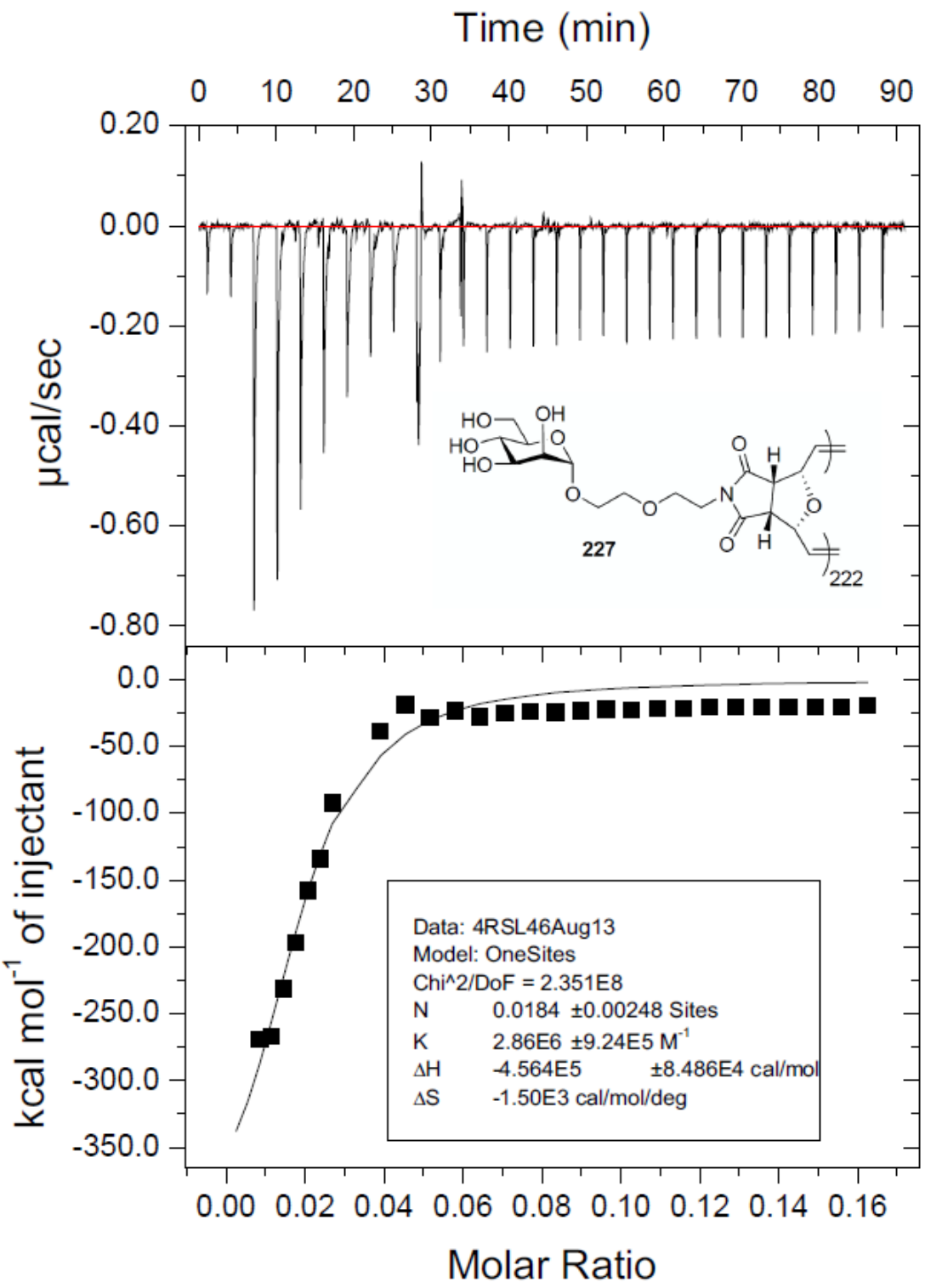


Figure A132. ITC Thermogram of Polymer **227**

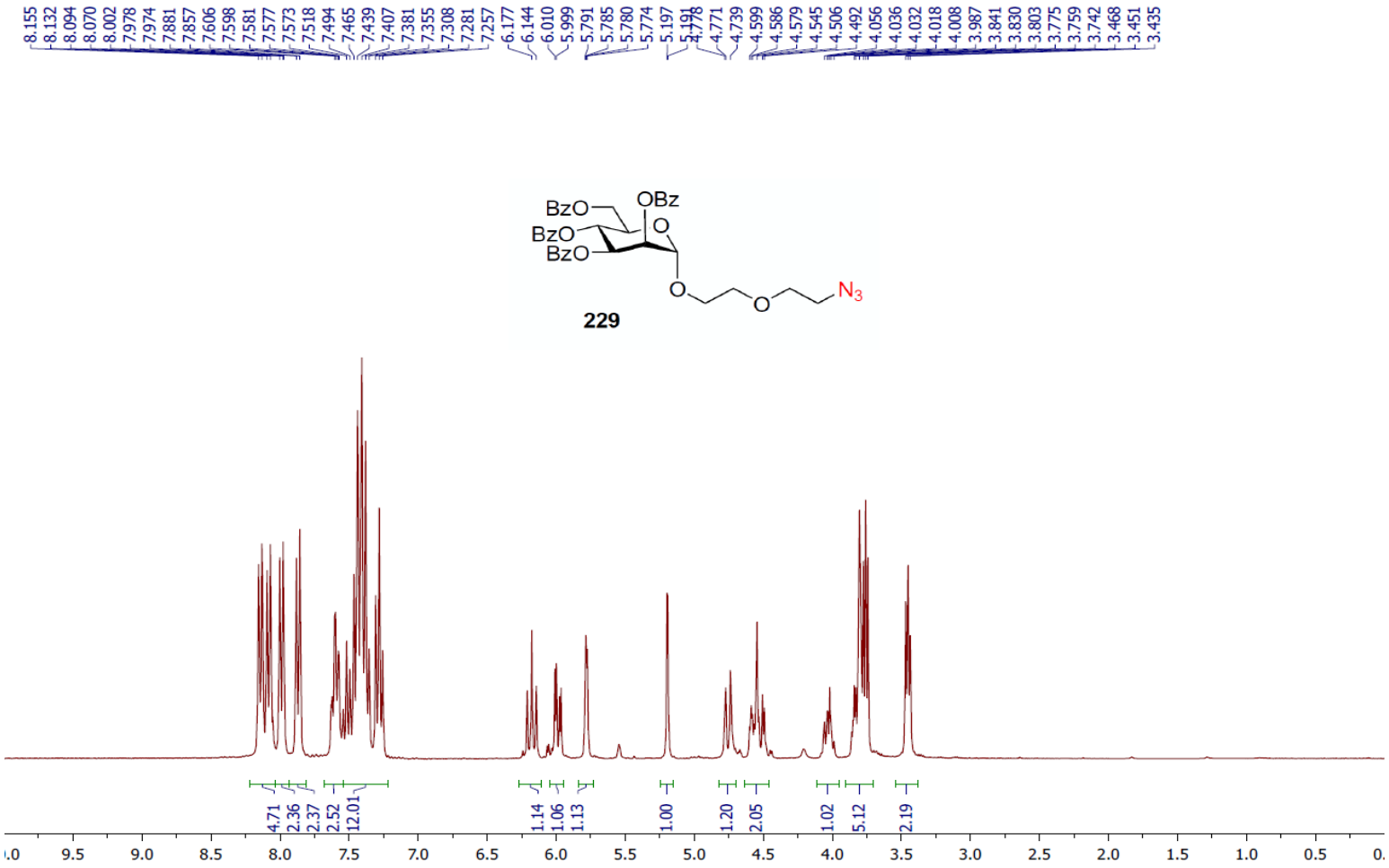


Figure A133. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Mannoside **229**

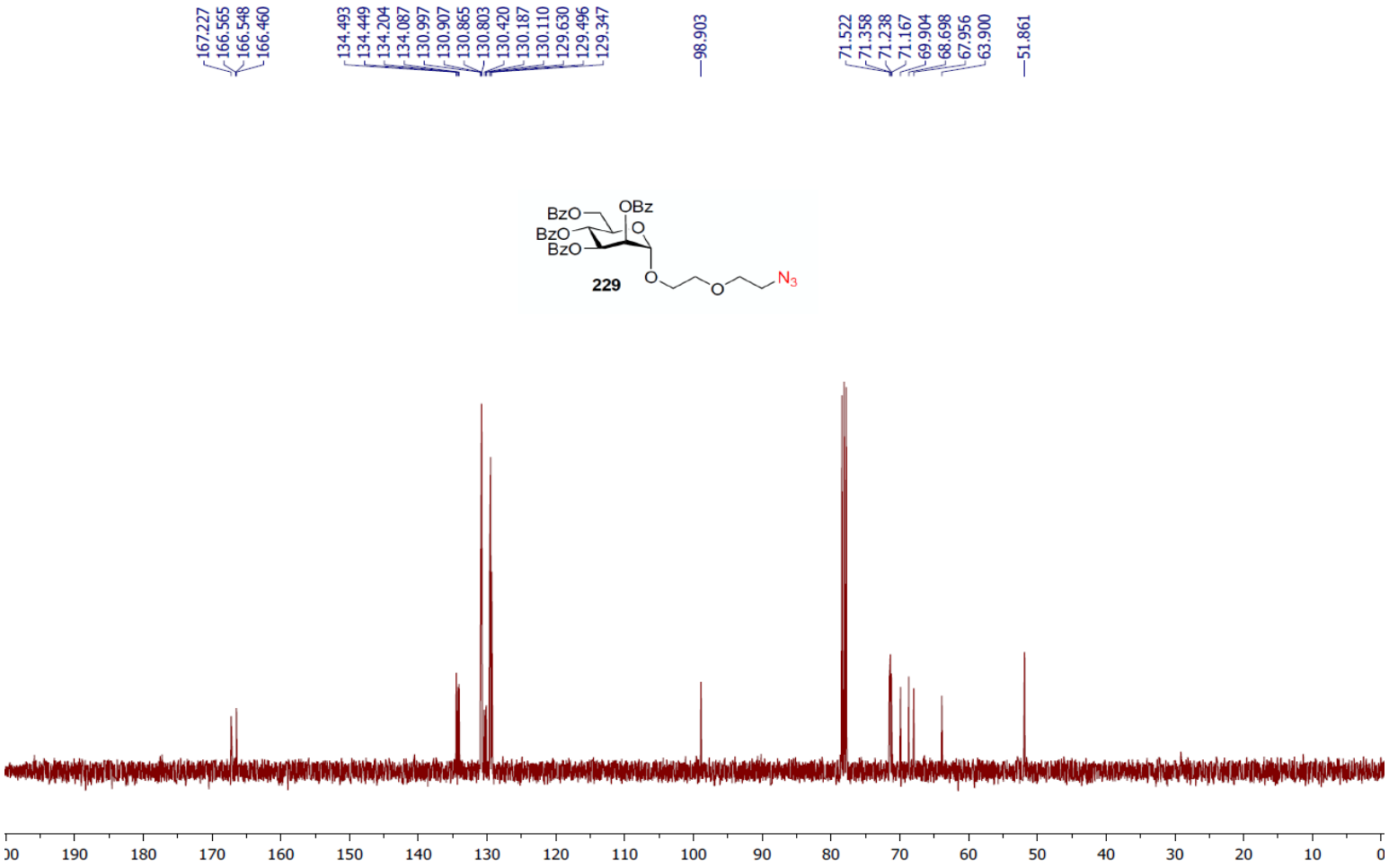


Figure A134. 100 MHz ^{13}CNMR Spectrum ($CDCl_3$) of Mannoside **229**

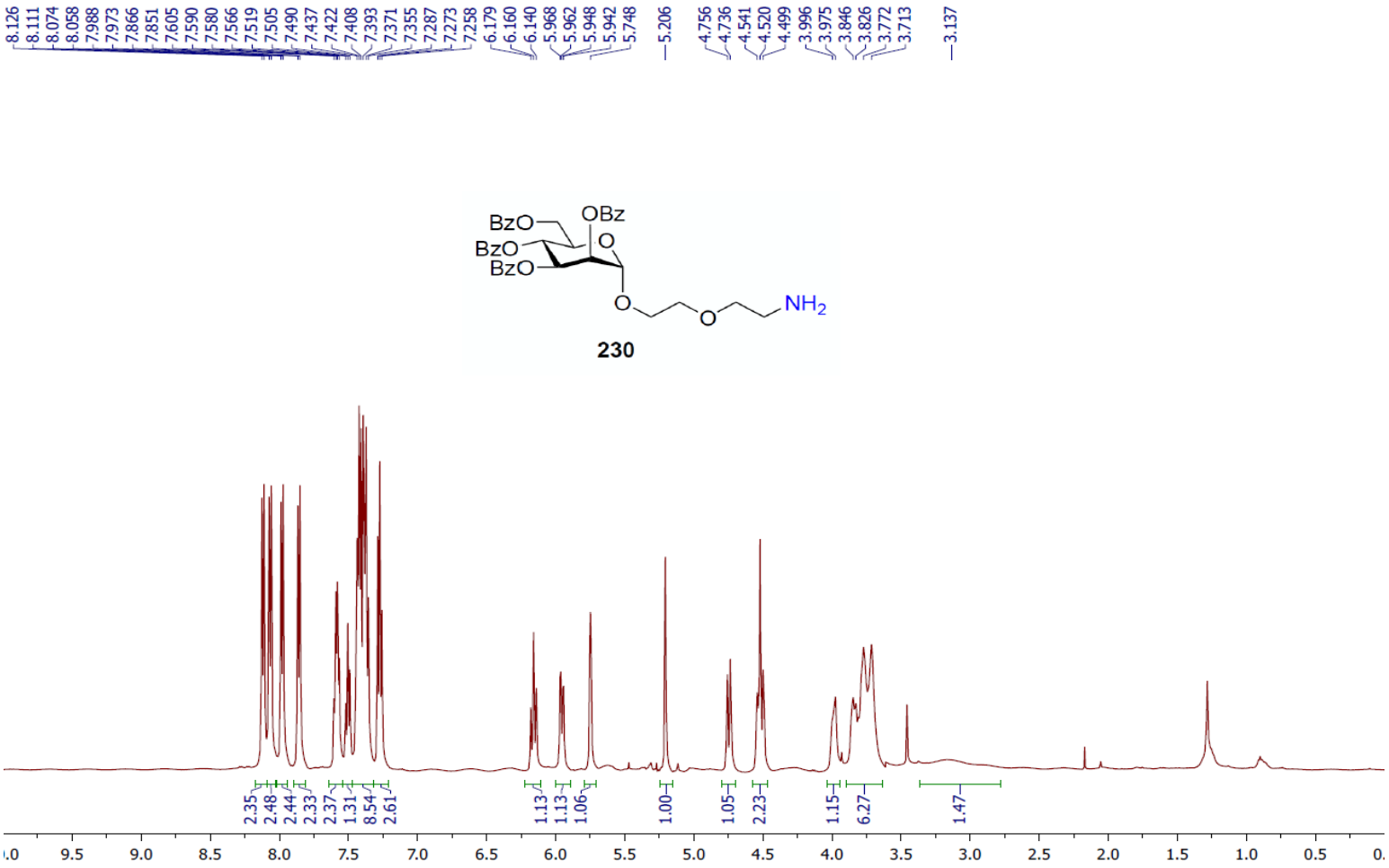


Figure A135. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Mannoside **230**

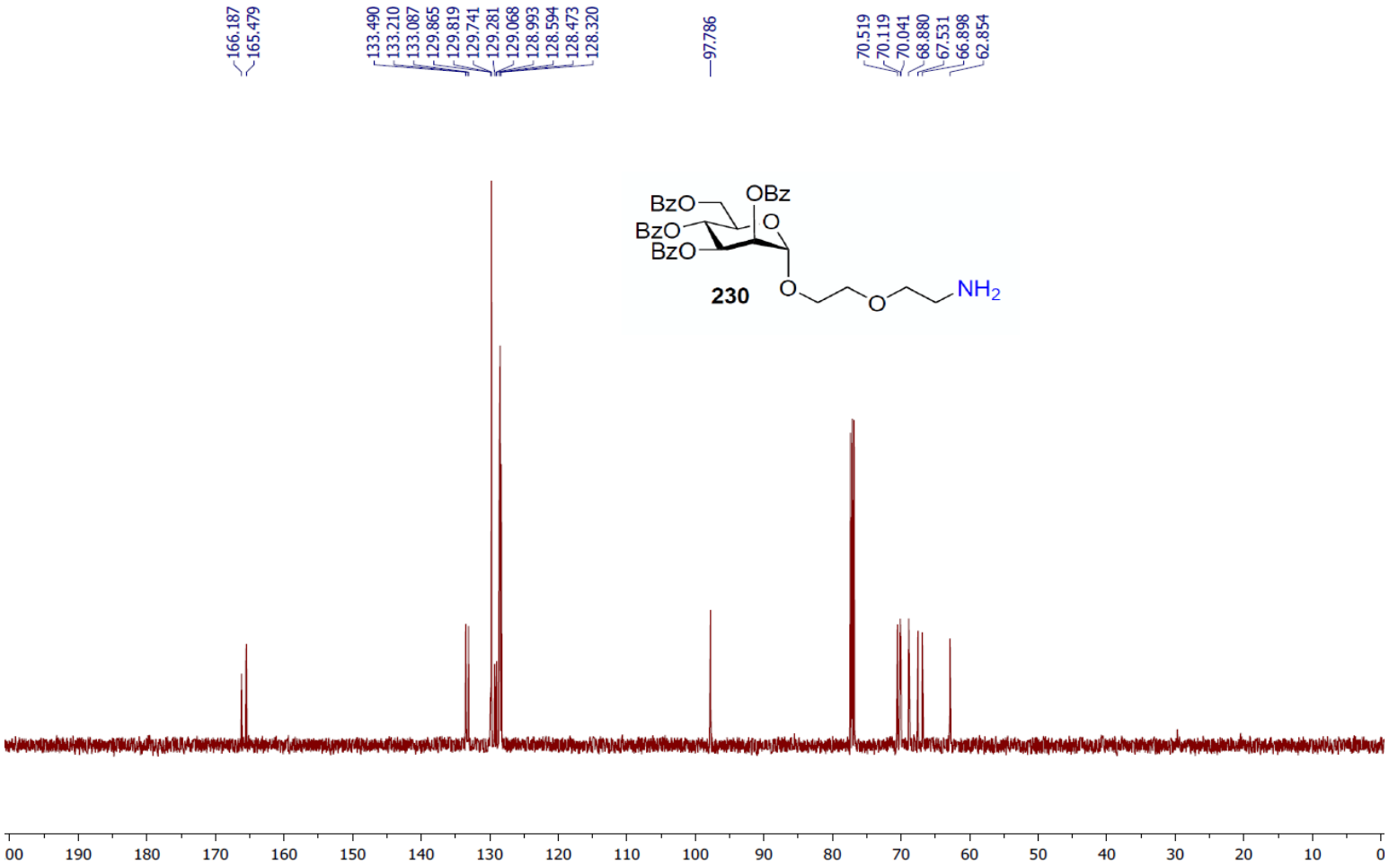


Figure A136. 150 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Mannoside **230**

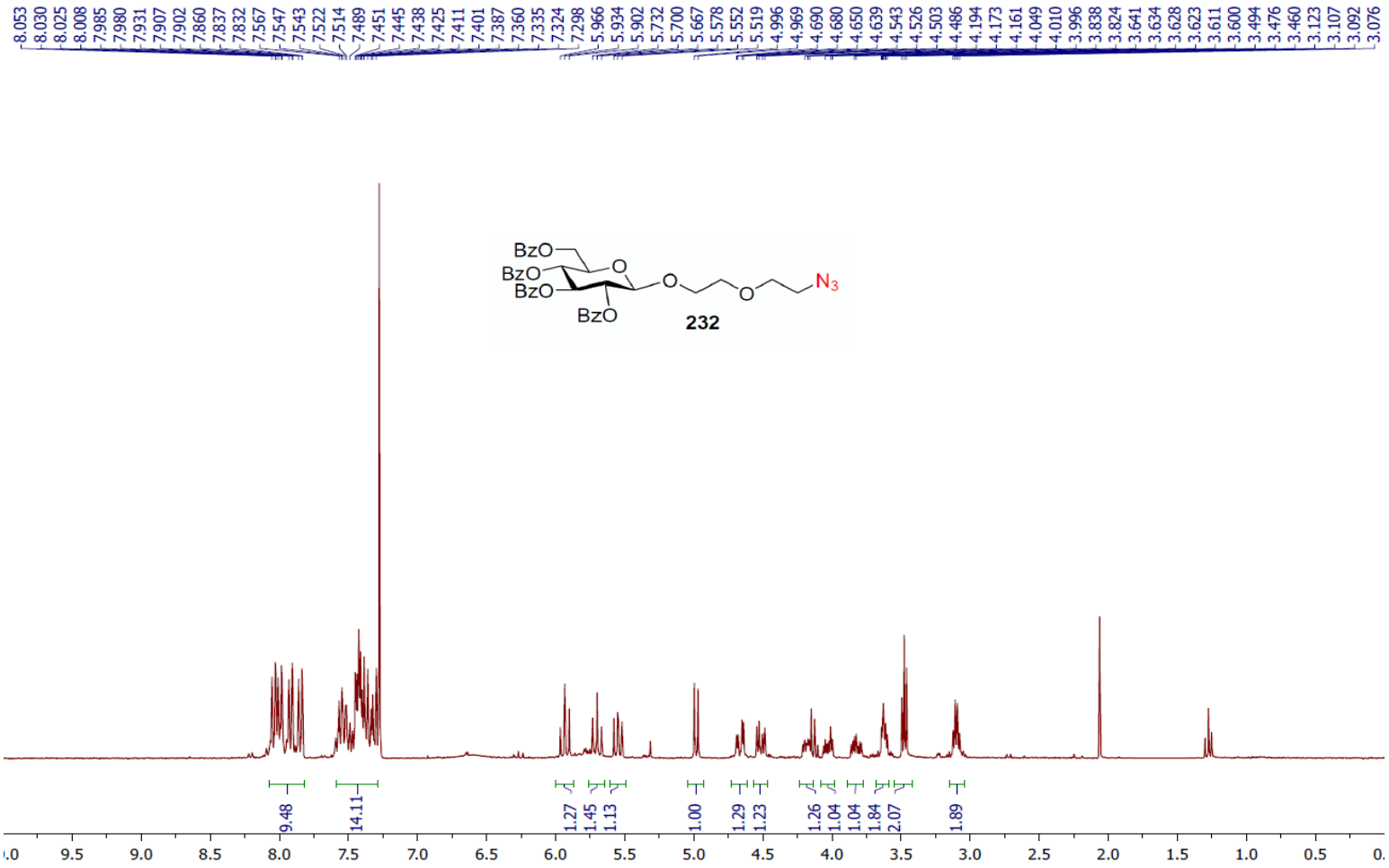


Figure A137. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **232**

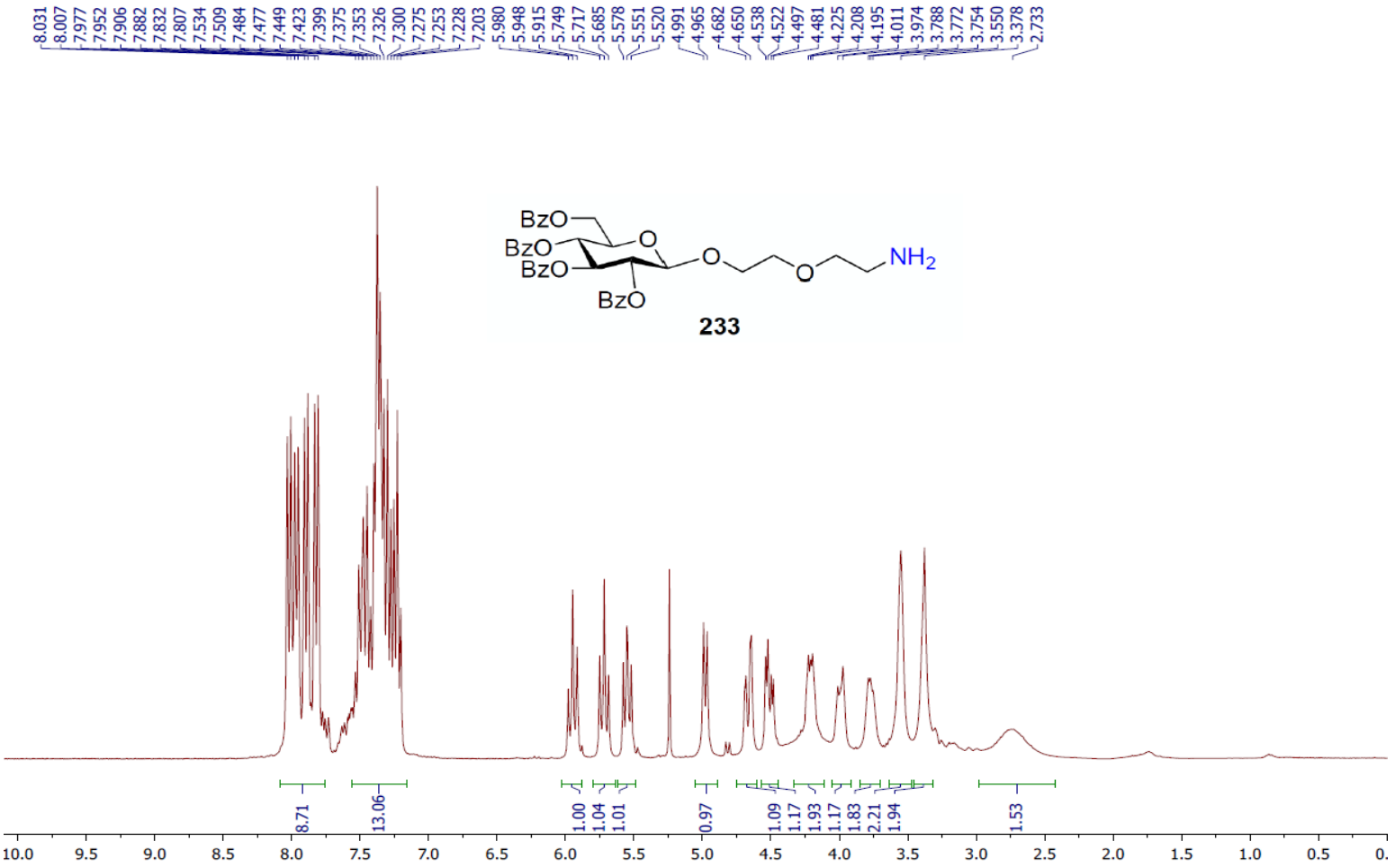


Figure A138. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **233**

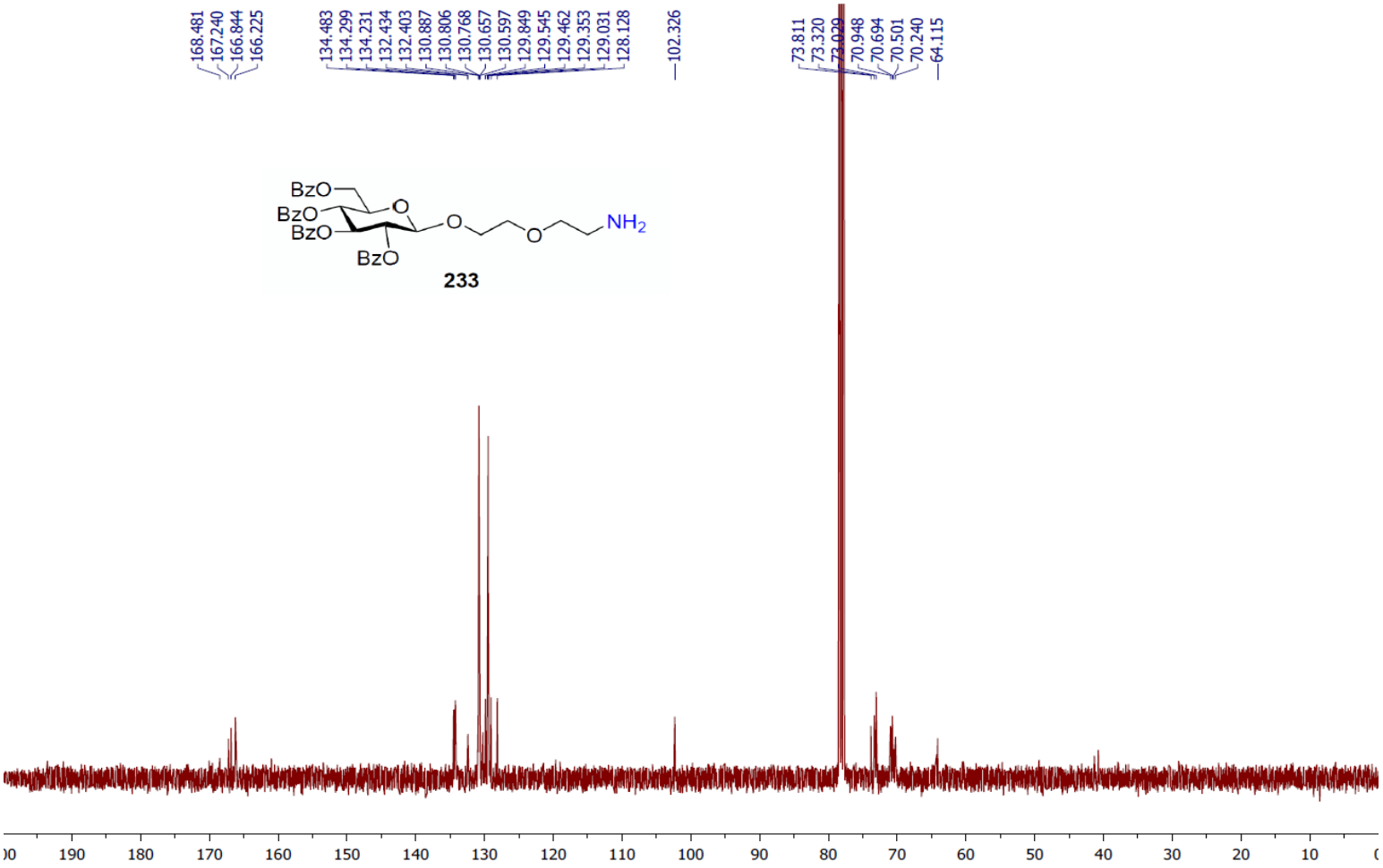


Figure A139. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glucoside **233**

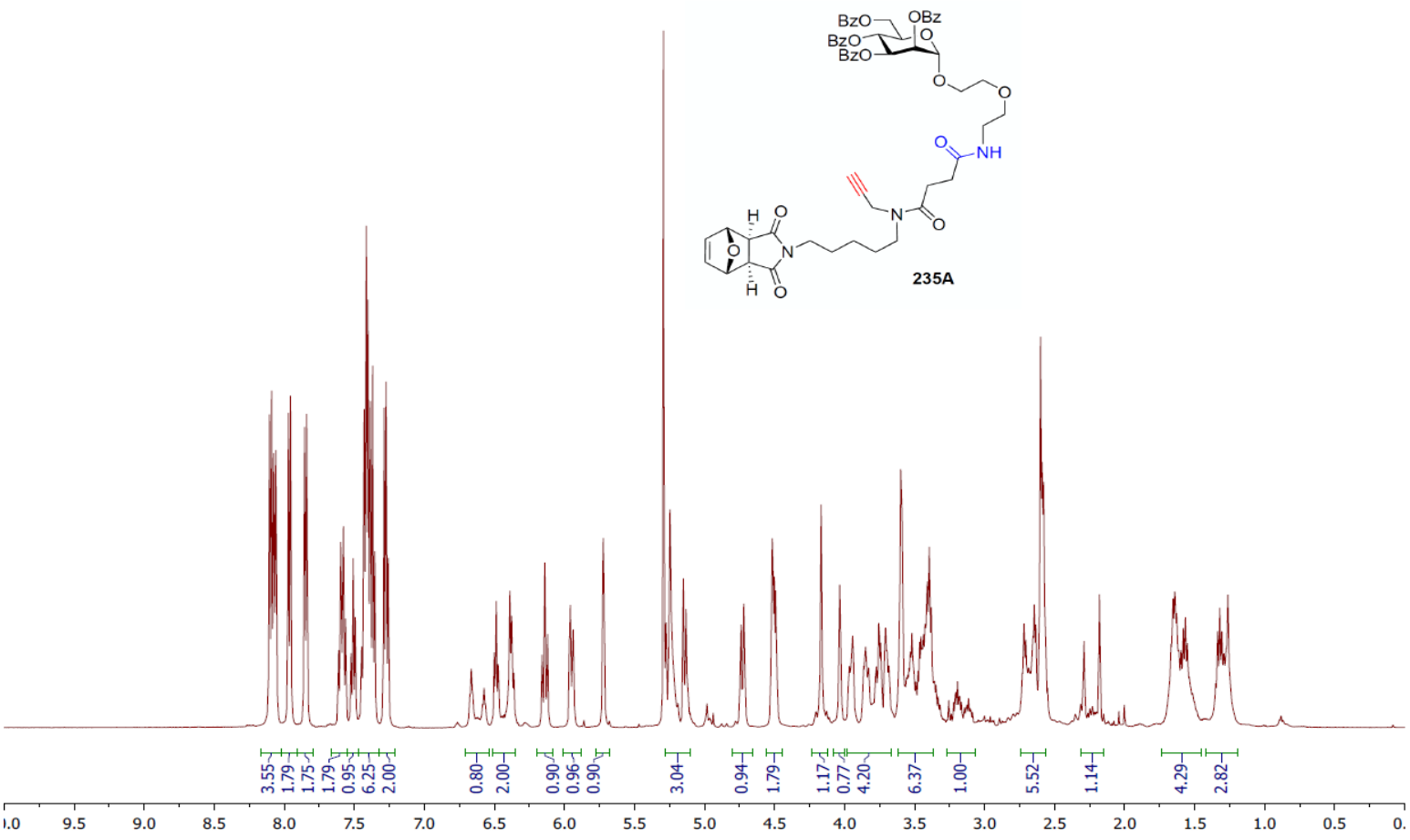


Figure A140. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Mannoside **235A**

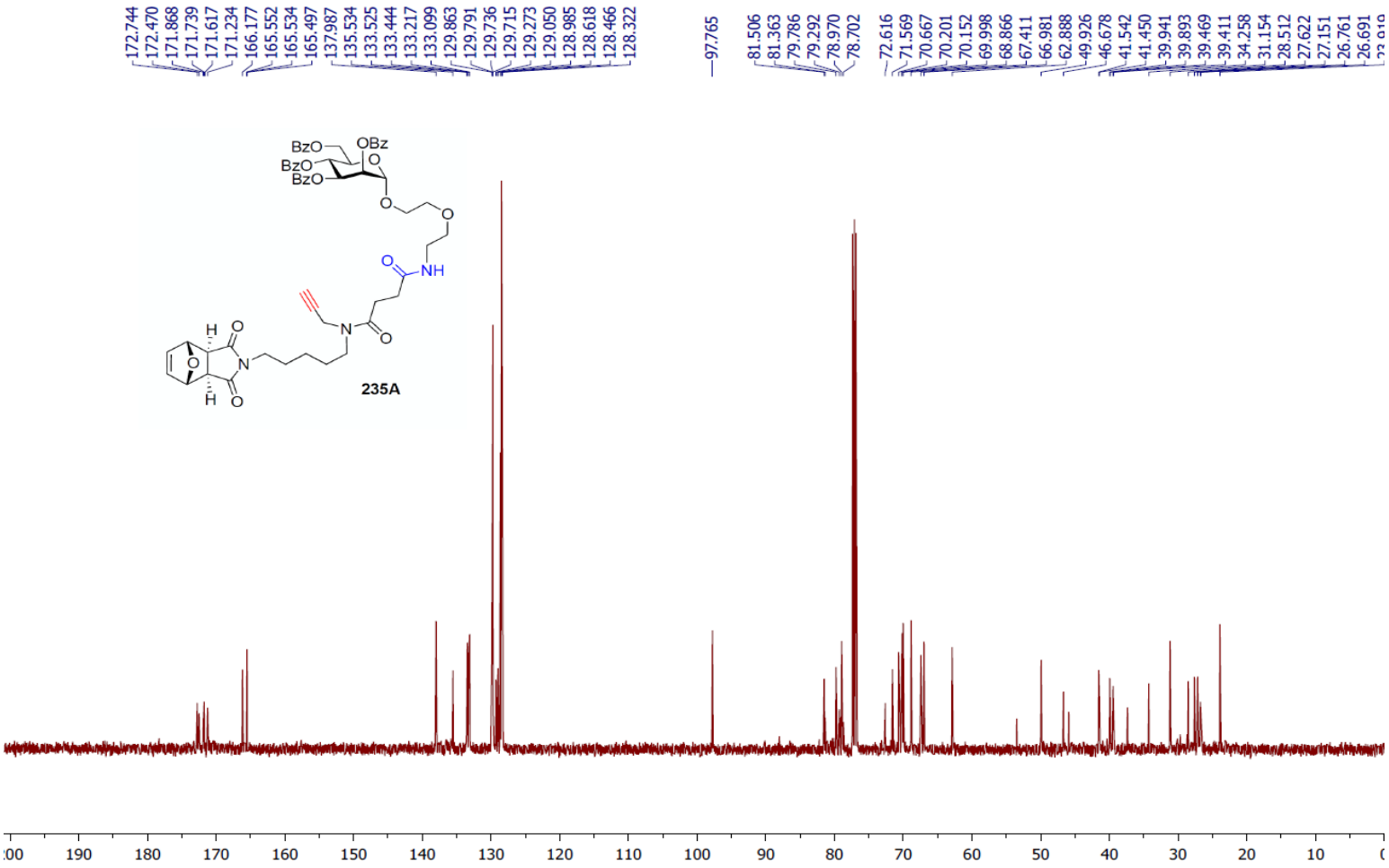


Figure A141. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Mannoside **235A**

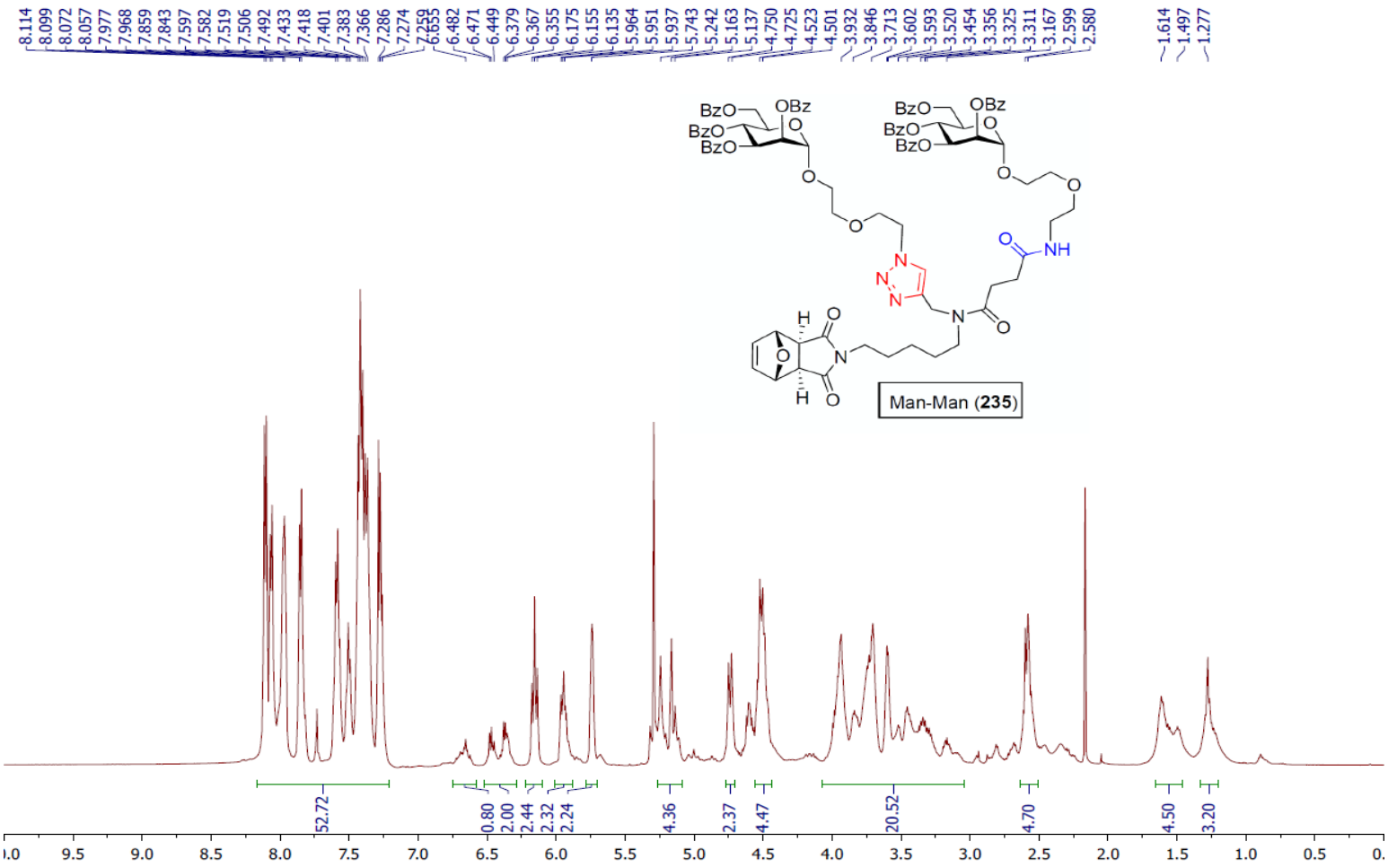


Figure A142. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Man-Man **235**

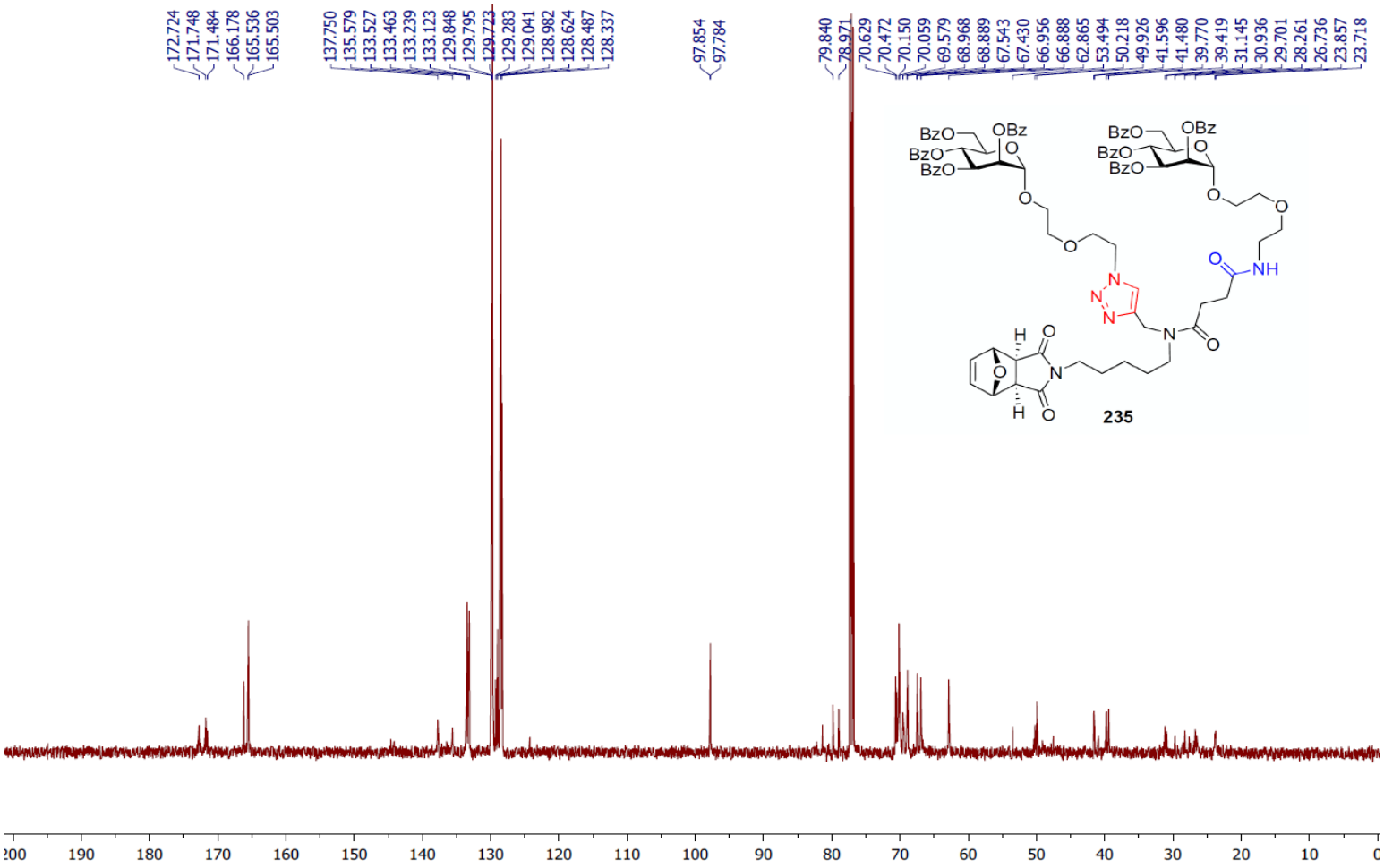


Figure A143. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Man-Man **235**

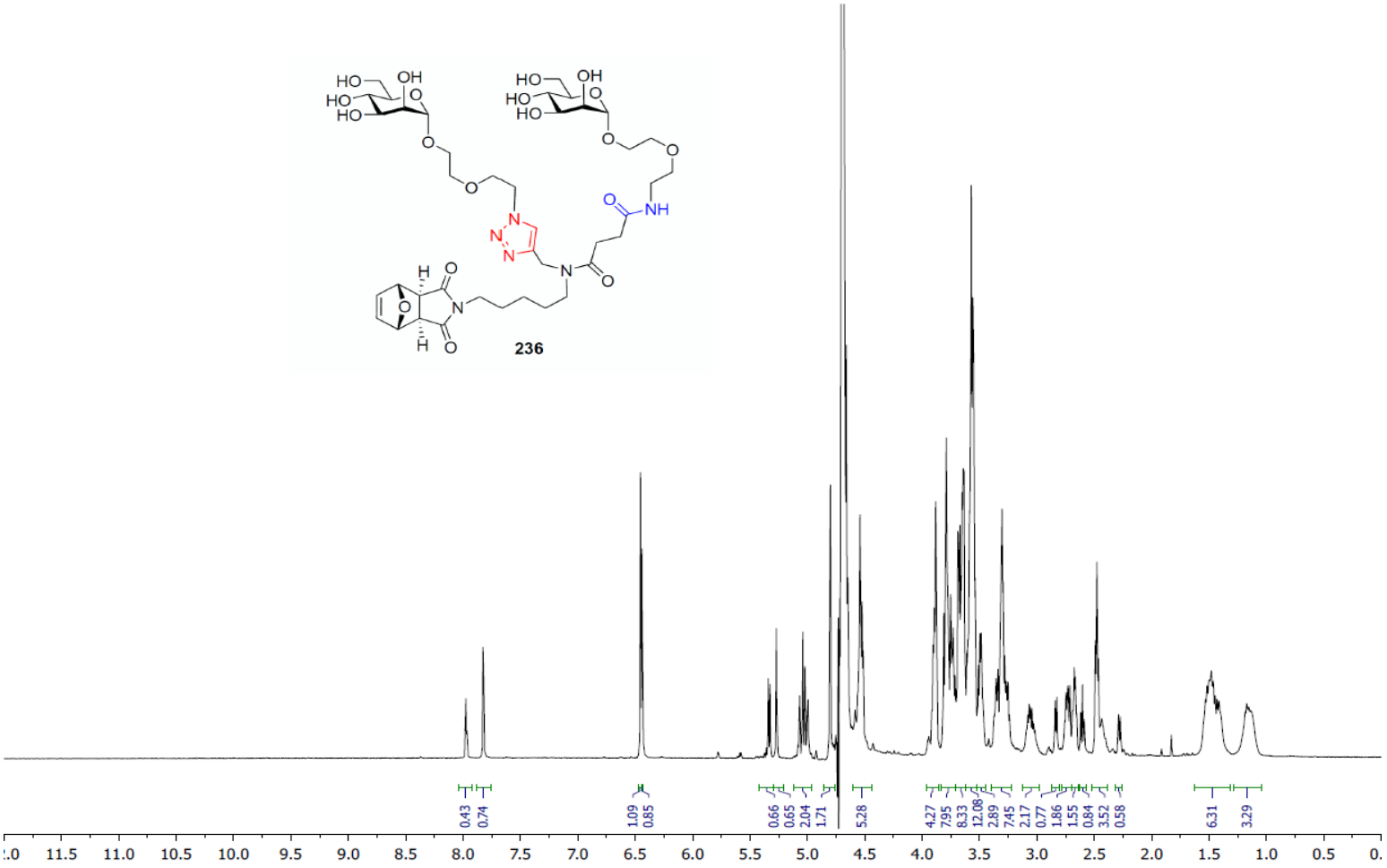


Figure A144. 500 MHz ^{1}H NMR Spectrum (D_2O) of Man-Man **236**

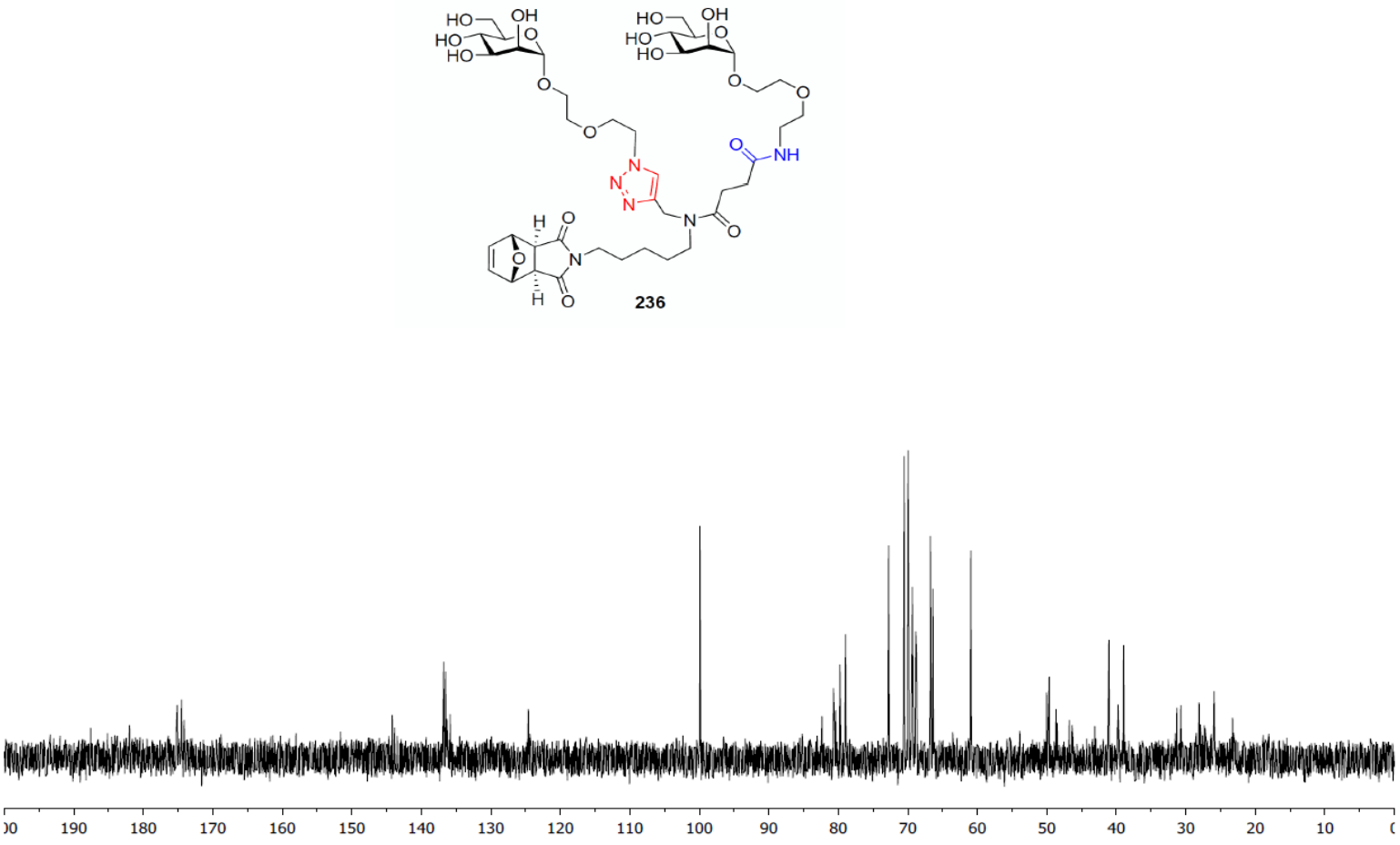


Figure A145. 125 MHz ^{13}C NMR Spectrum (D_2O) of Man-Man **236**

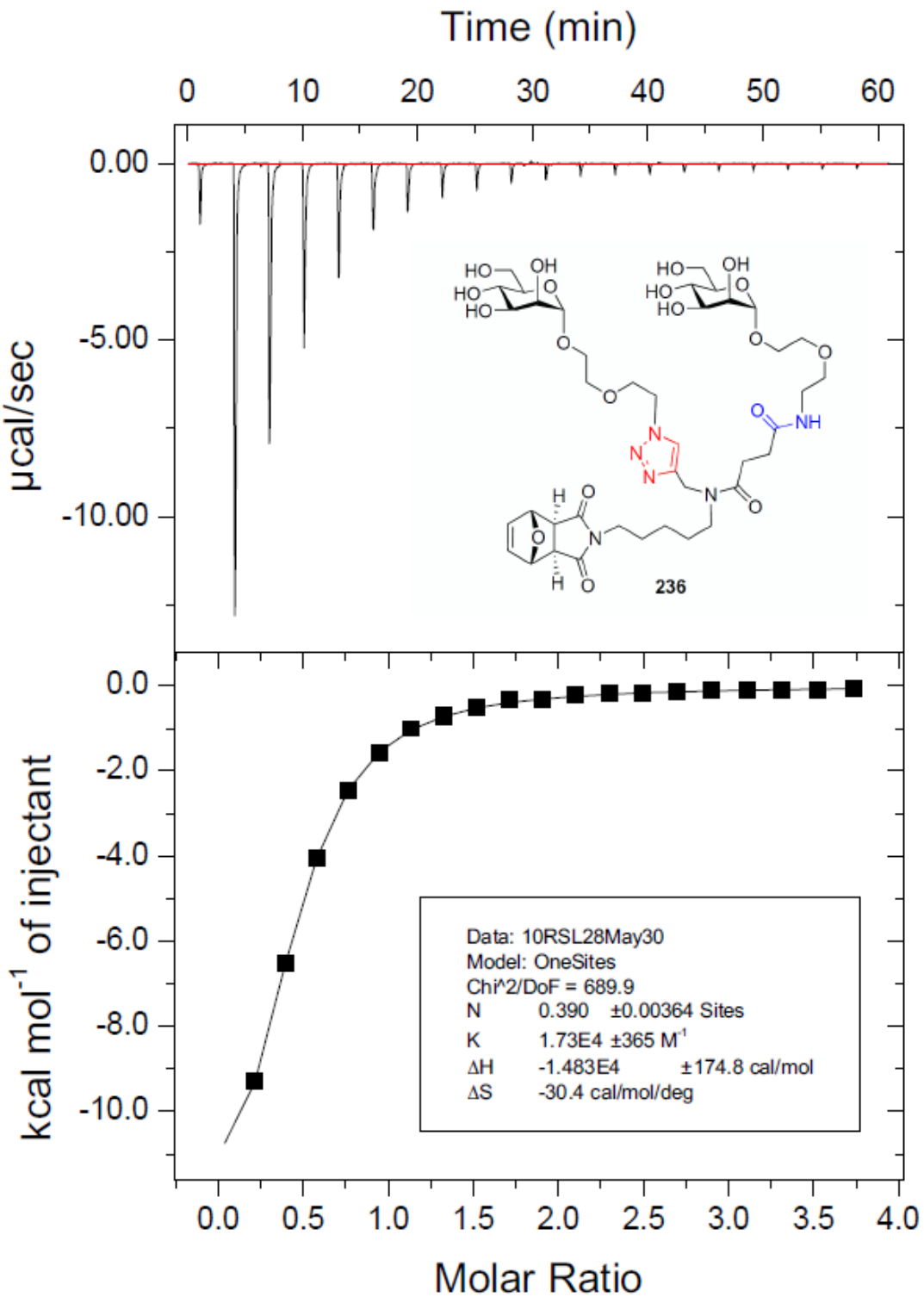


Figure A146. ITC Thermogram of Man-Man **236**

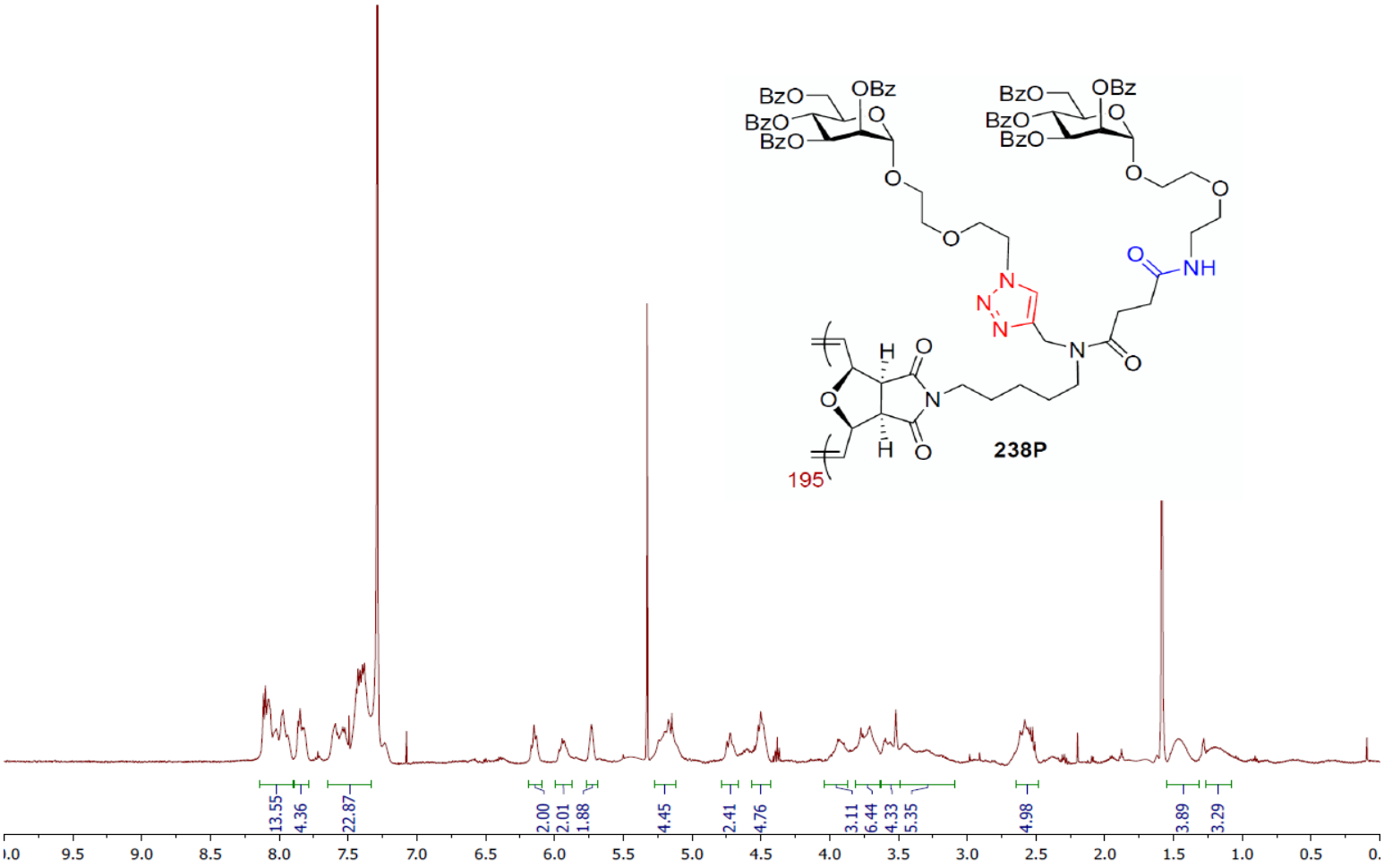


Figure A147. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Polymer **238P**

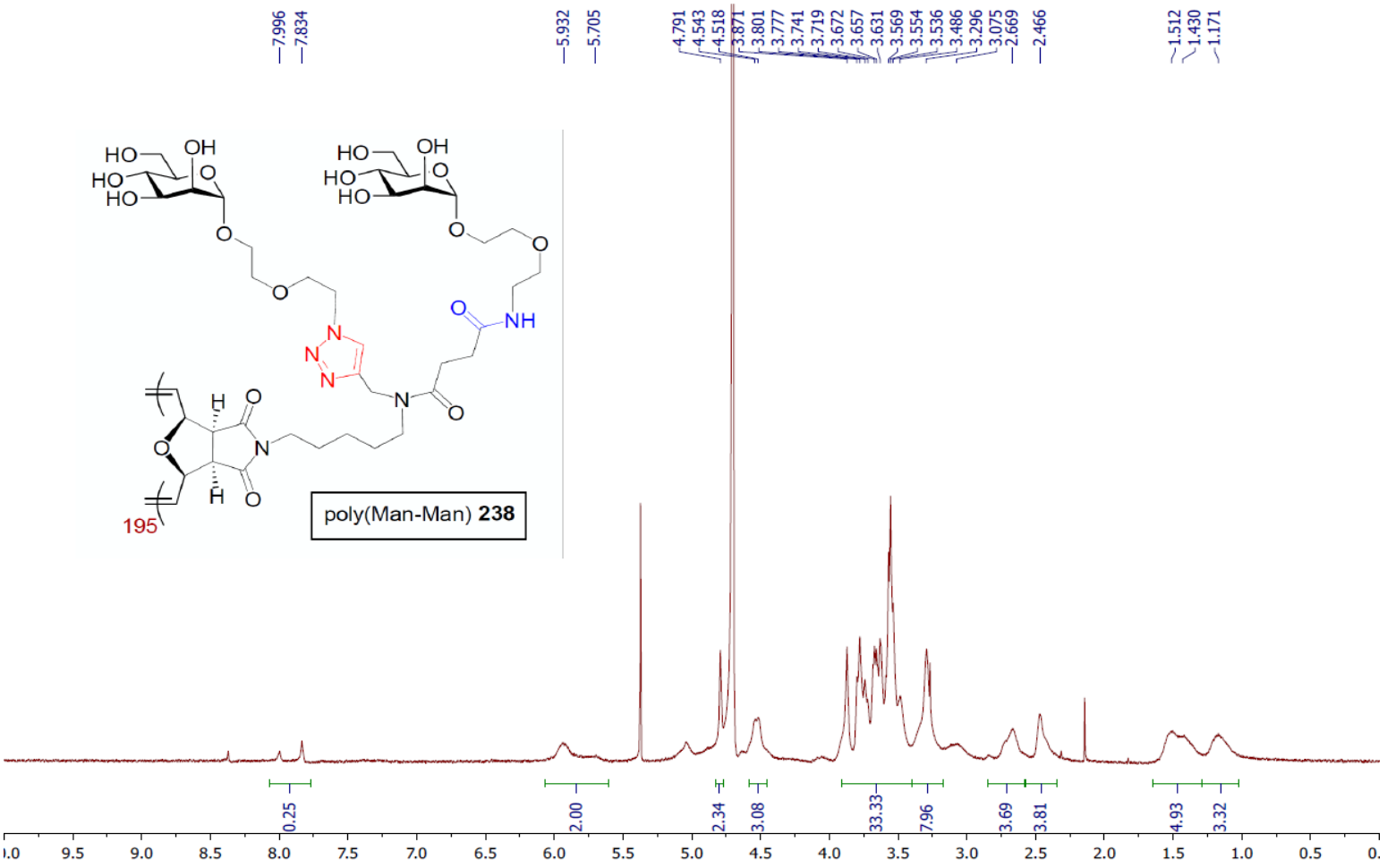


Figure A148. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **238**

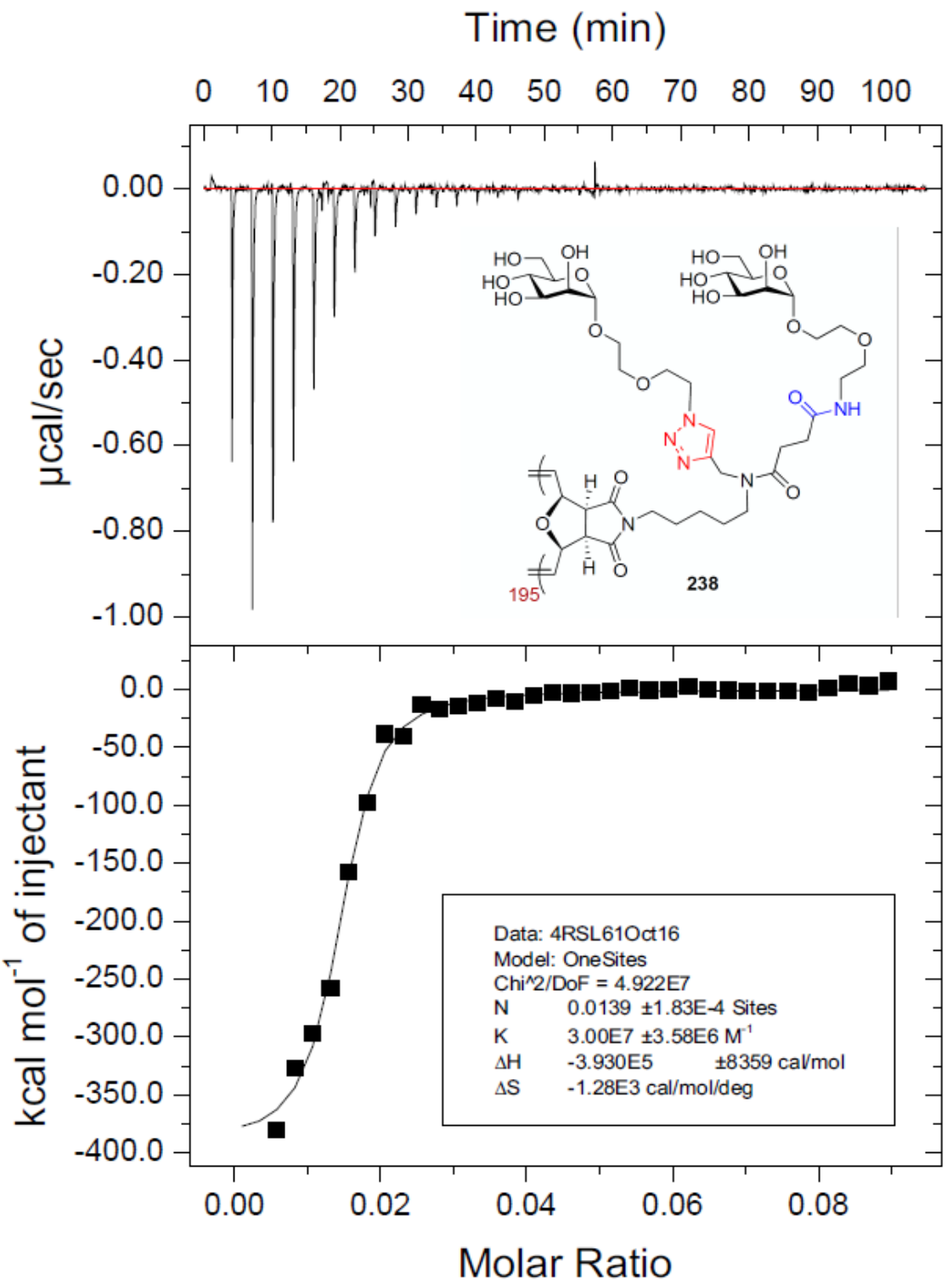


Figure A149. ITC Thermogram of Polymer **238**

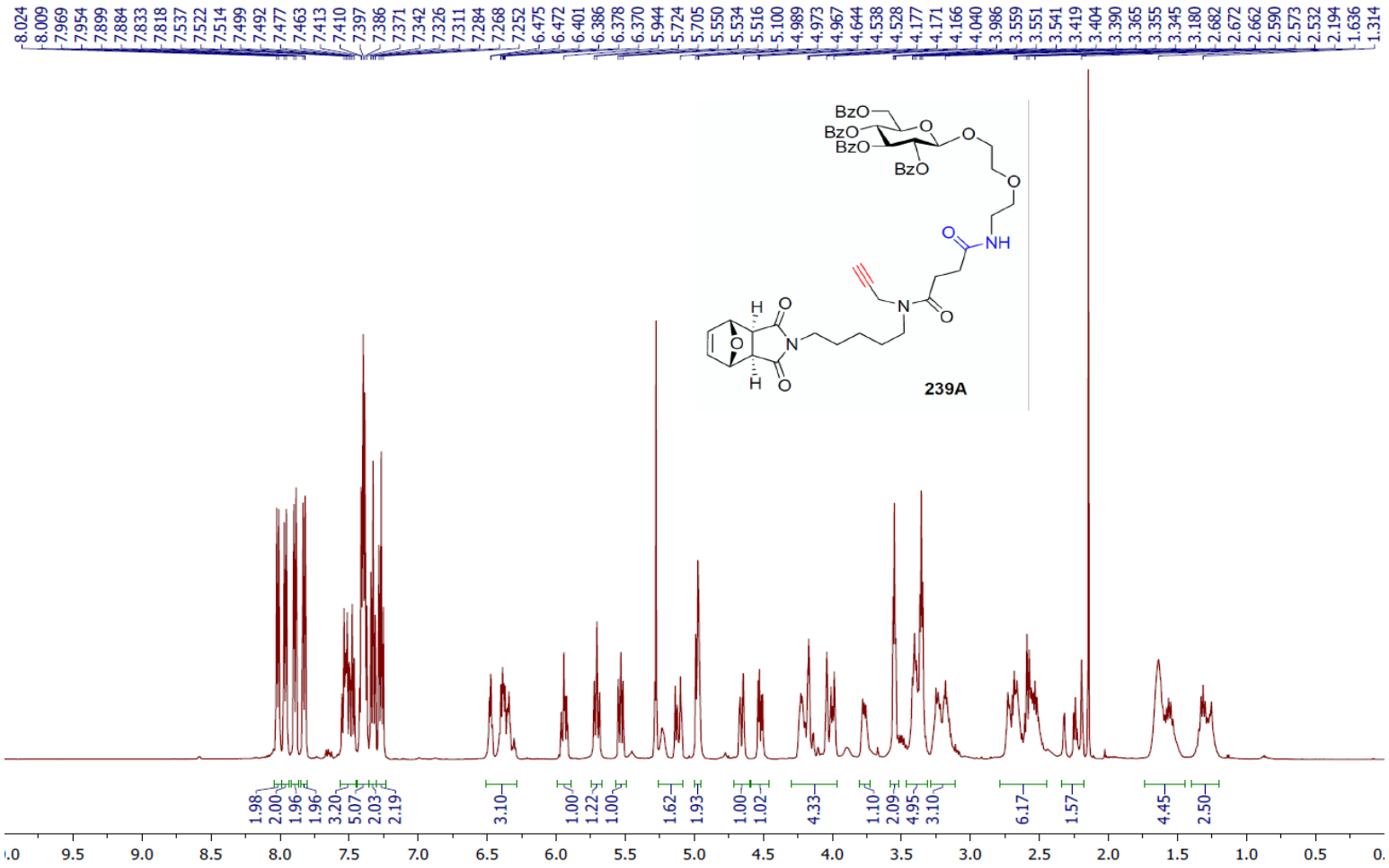


Figure A150. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **239A**

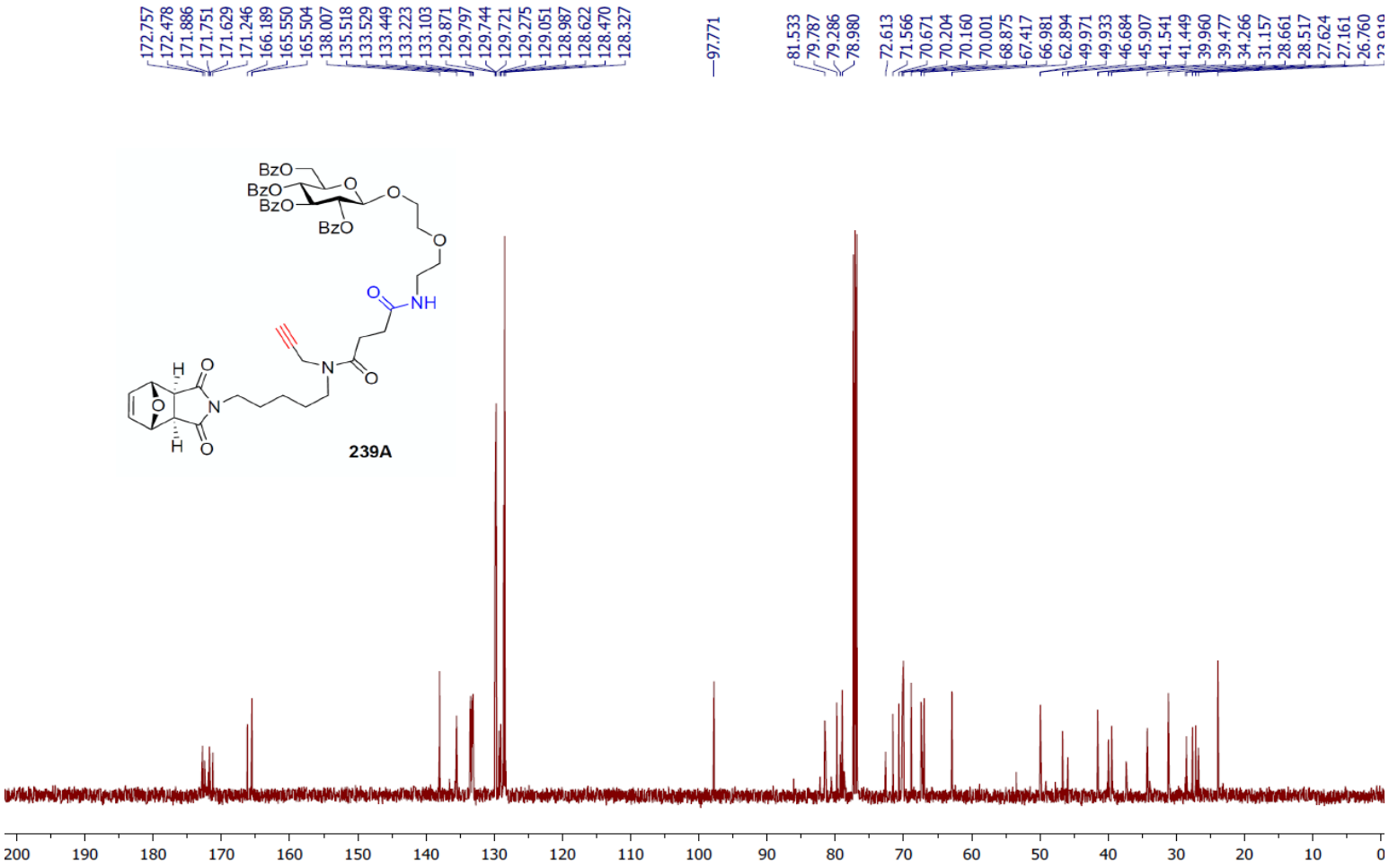


Figure A151. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glucoside **239A**

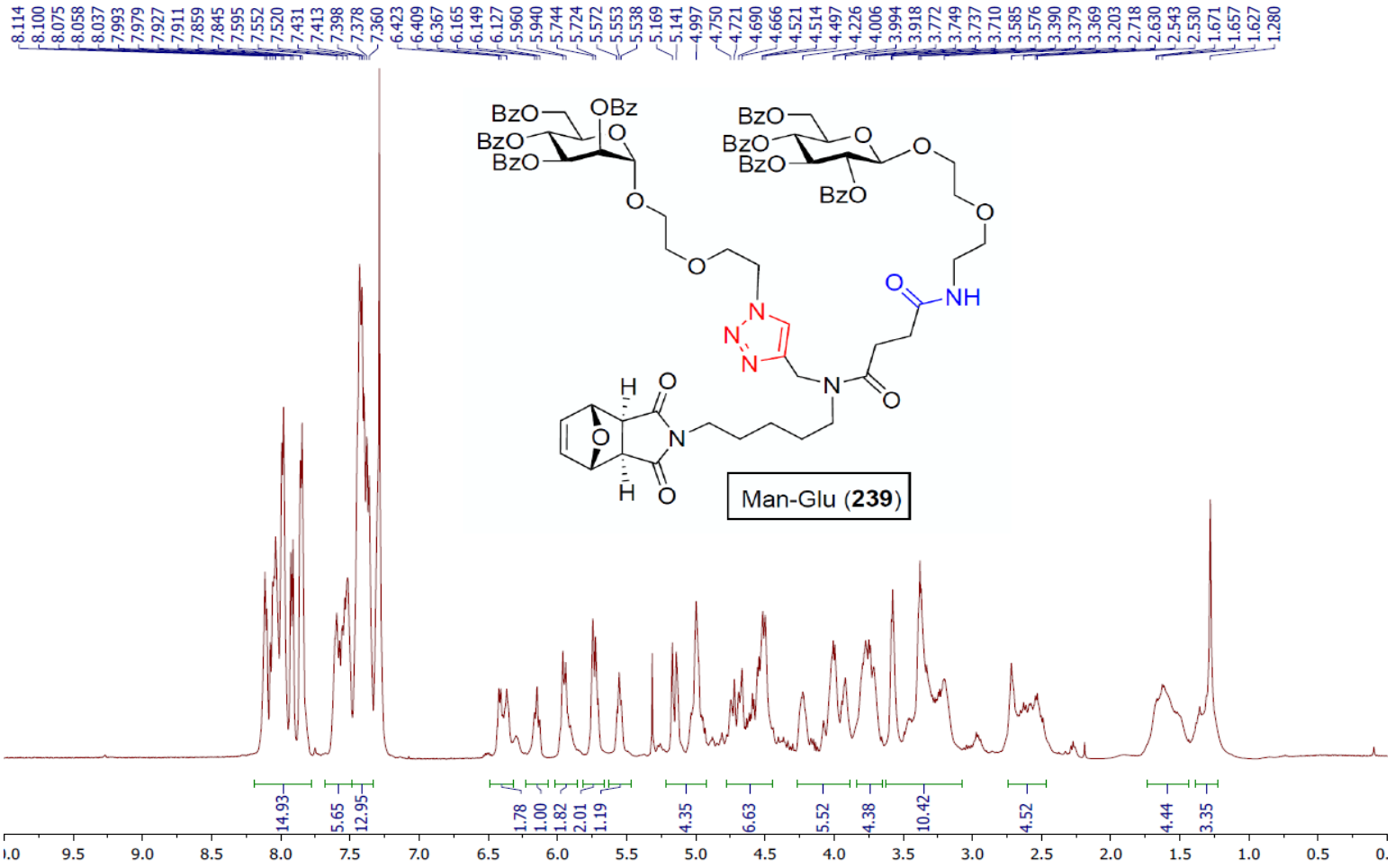


Figure A152. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Man-Glu **239**

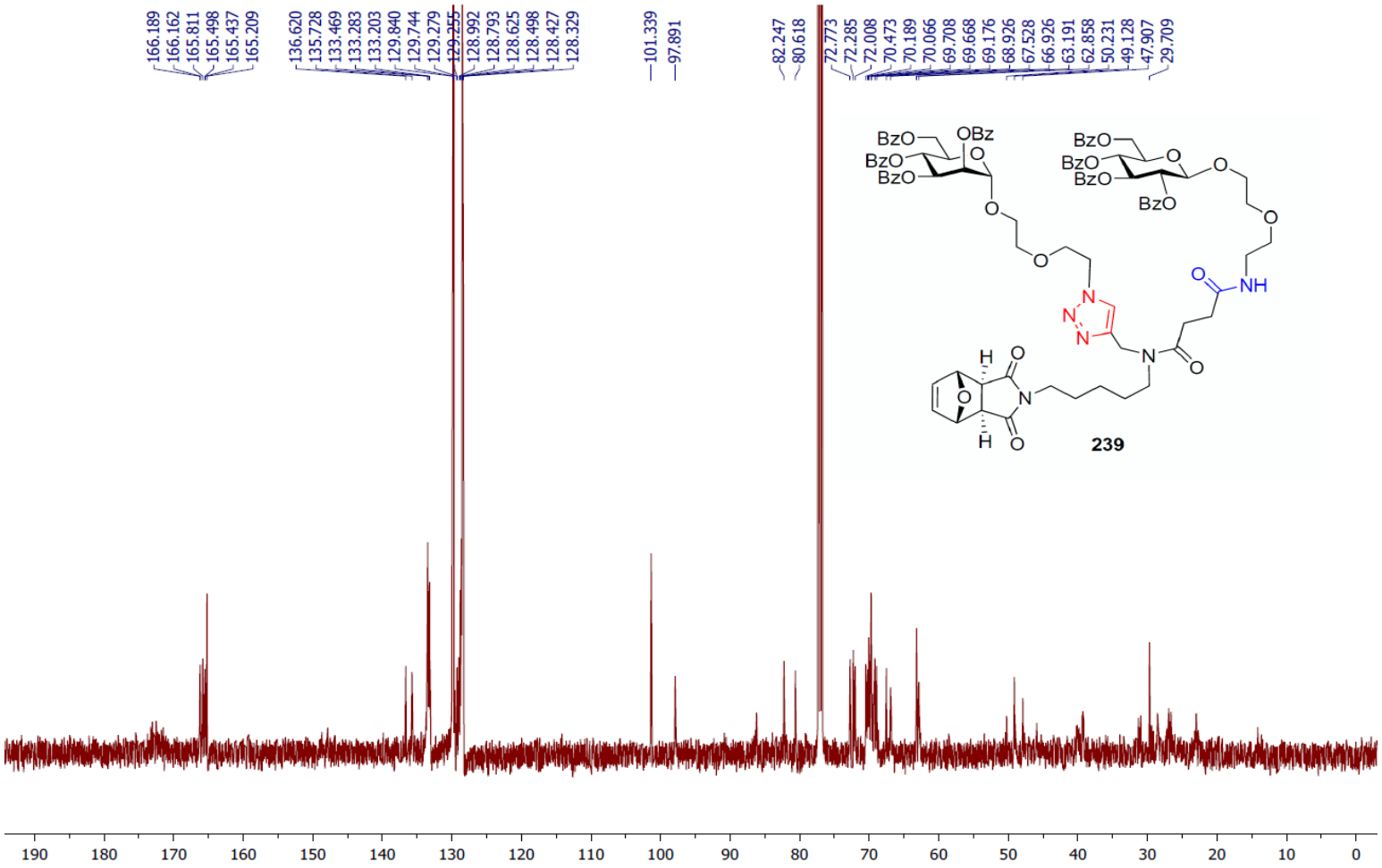


Figure A153. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Man-Glu **239**

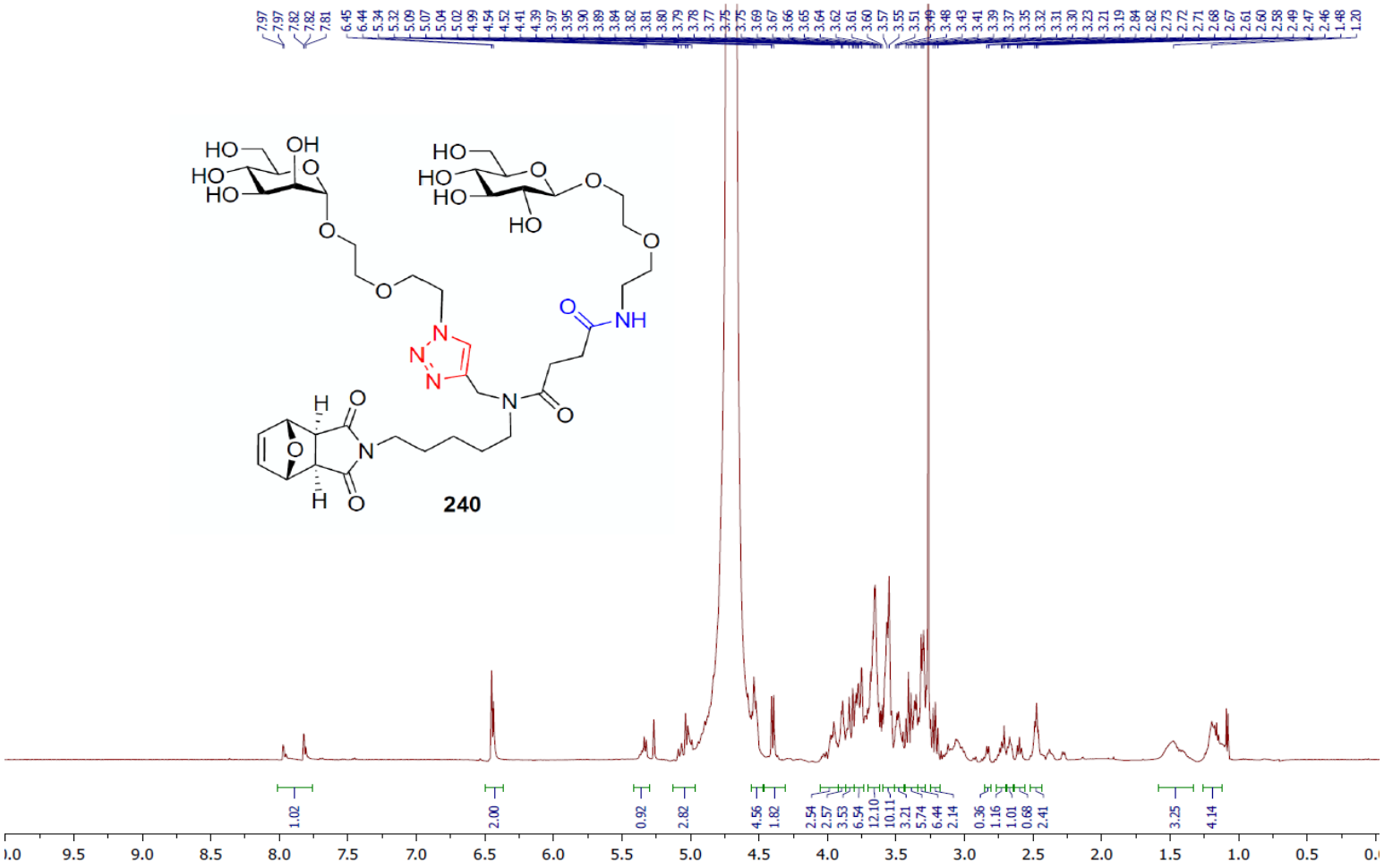


Figure A154. 500 MHz ^{1}H NMR Spectrum (D_2O) of Man-Glu **240**

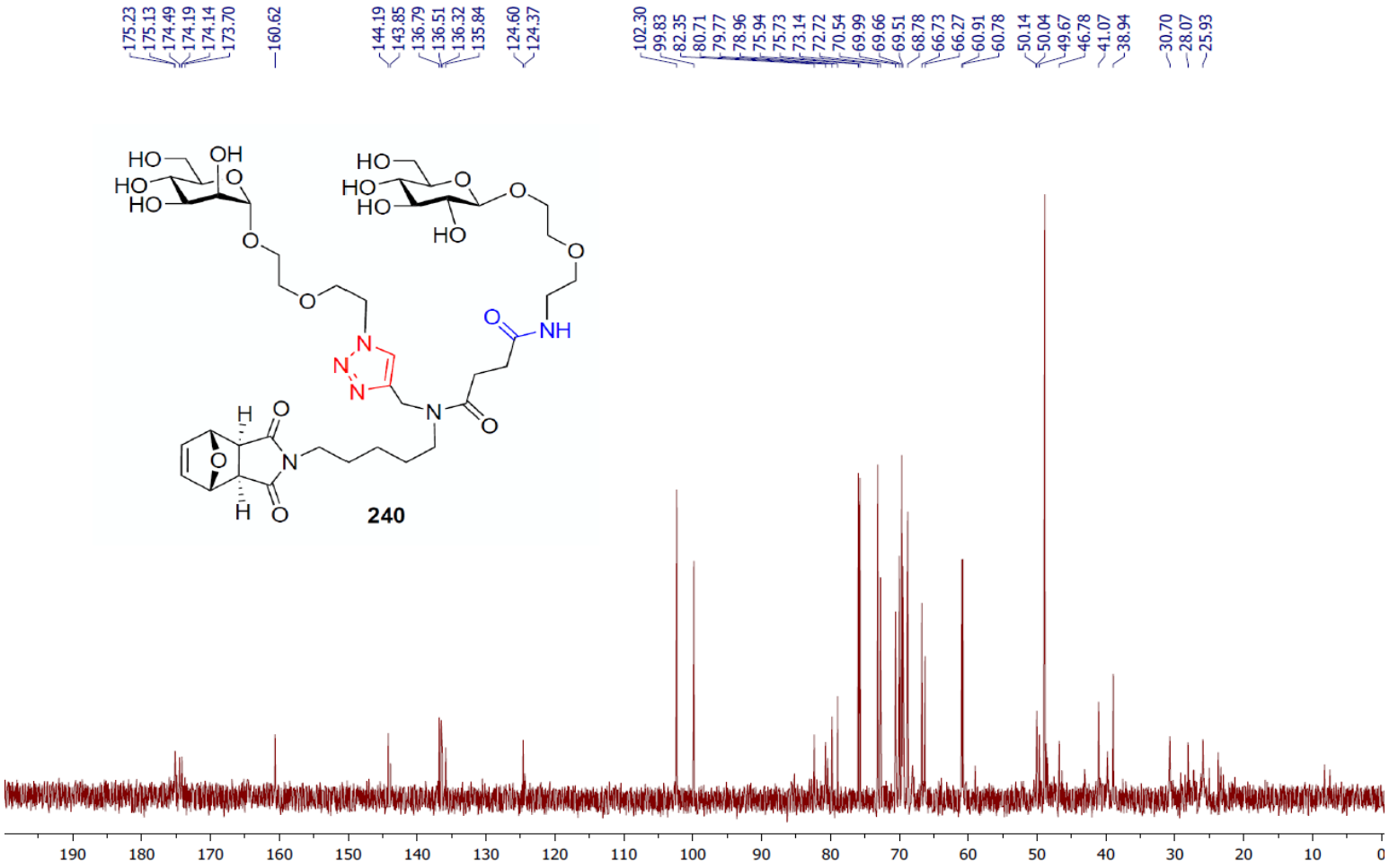


Figure A155. 125 MHz ^{13}C NMR Spectrum (D_2O) of Man-Glu **240**

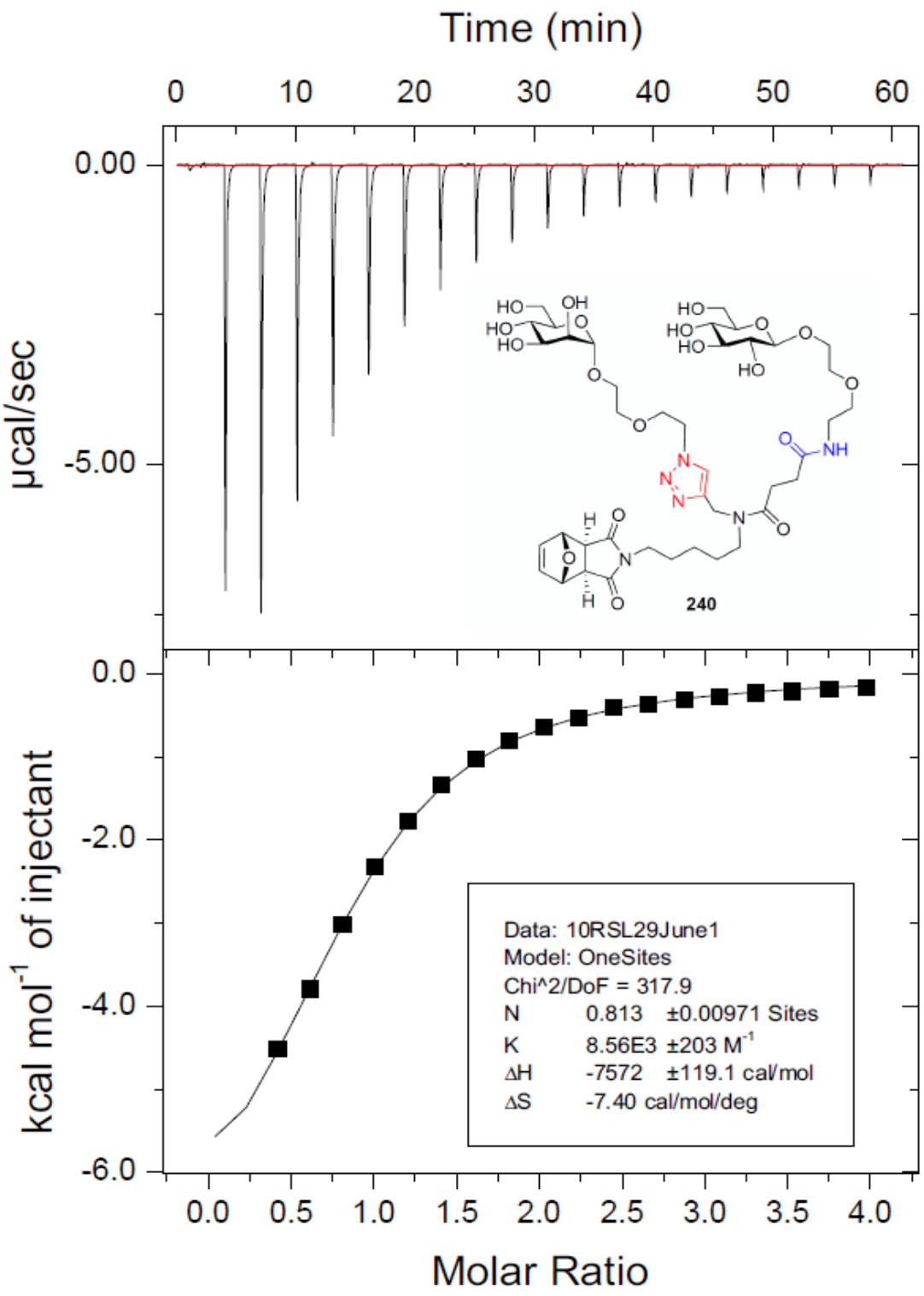


Figure A156. ITC Thermogram of Man-Glu **240**

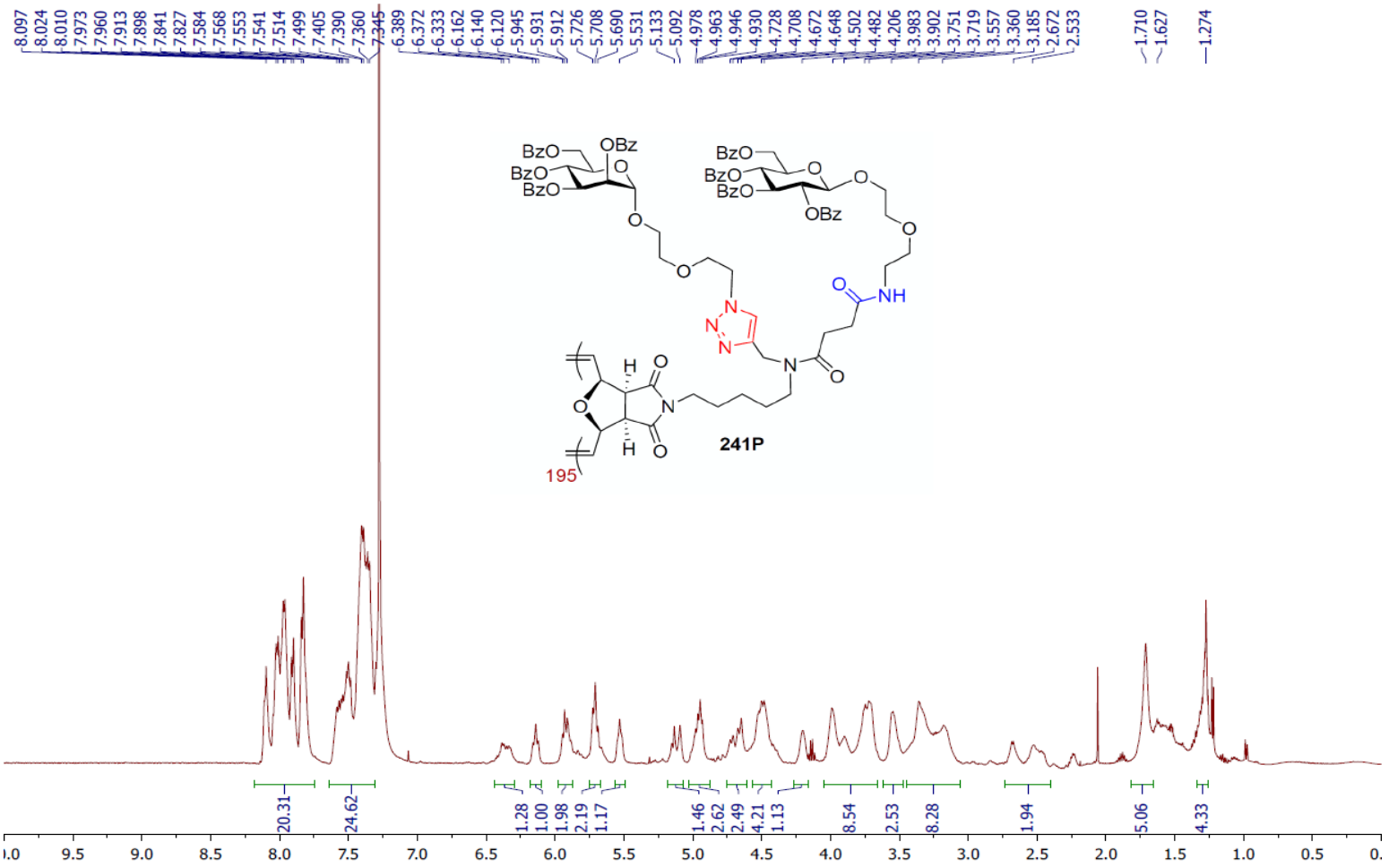


Figure A157. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Polymer **241P**

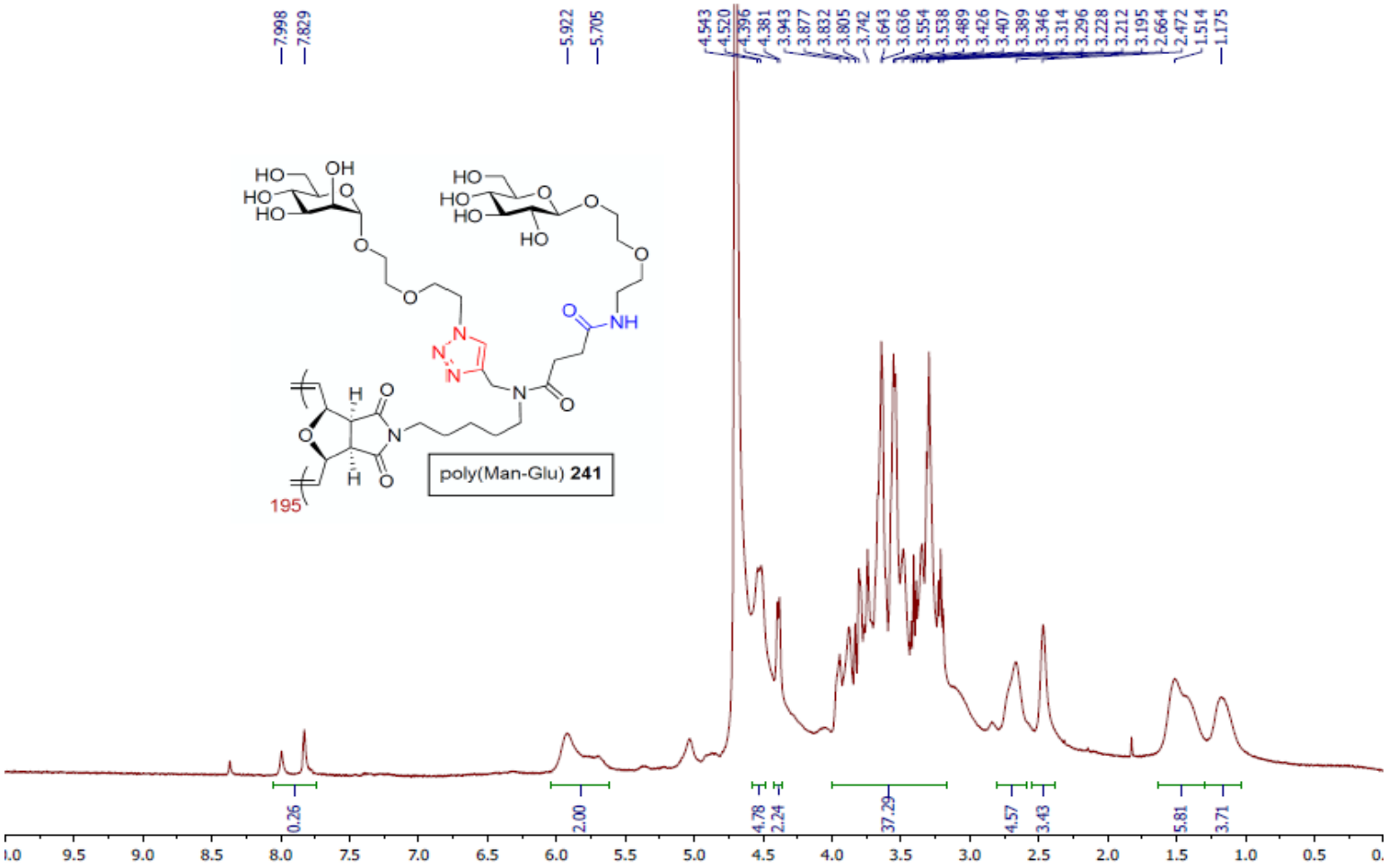


Figure A158. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **241**

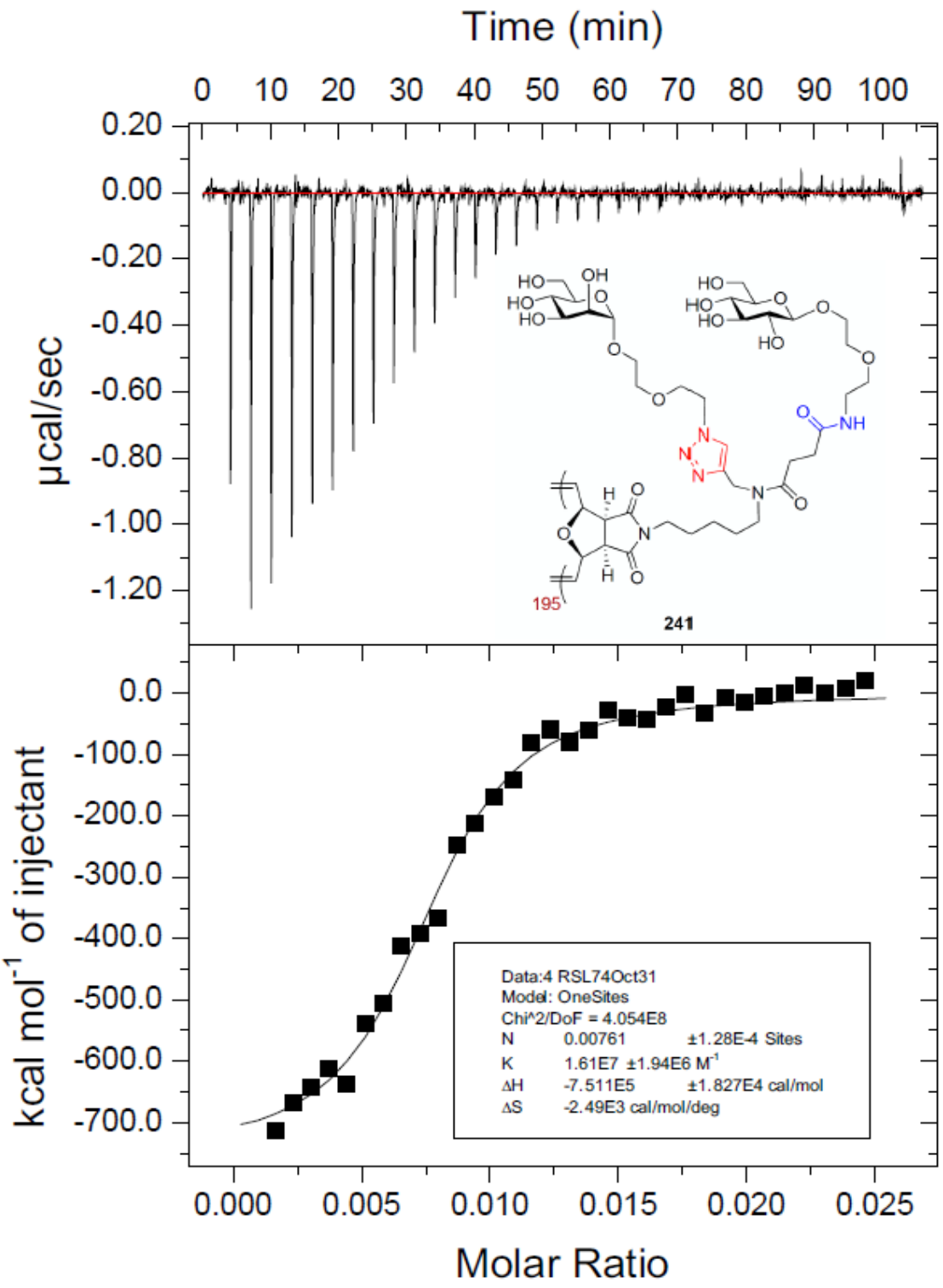


Figure A159. ITC Thermogram of Polymer **241**

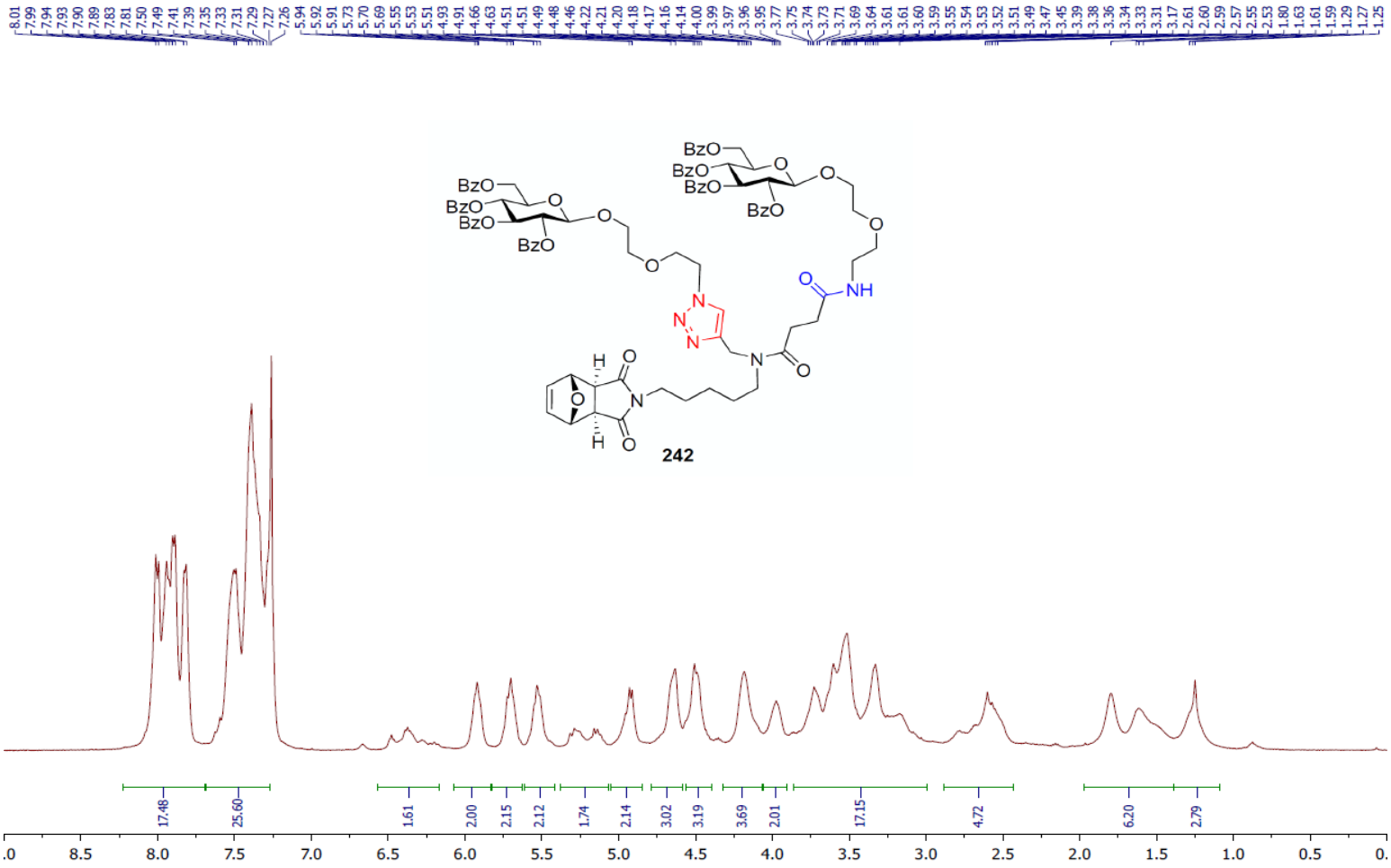


Figure A160. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glu-Glu **242**

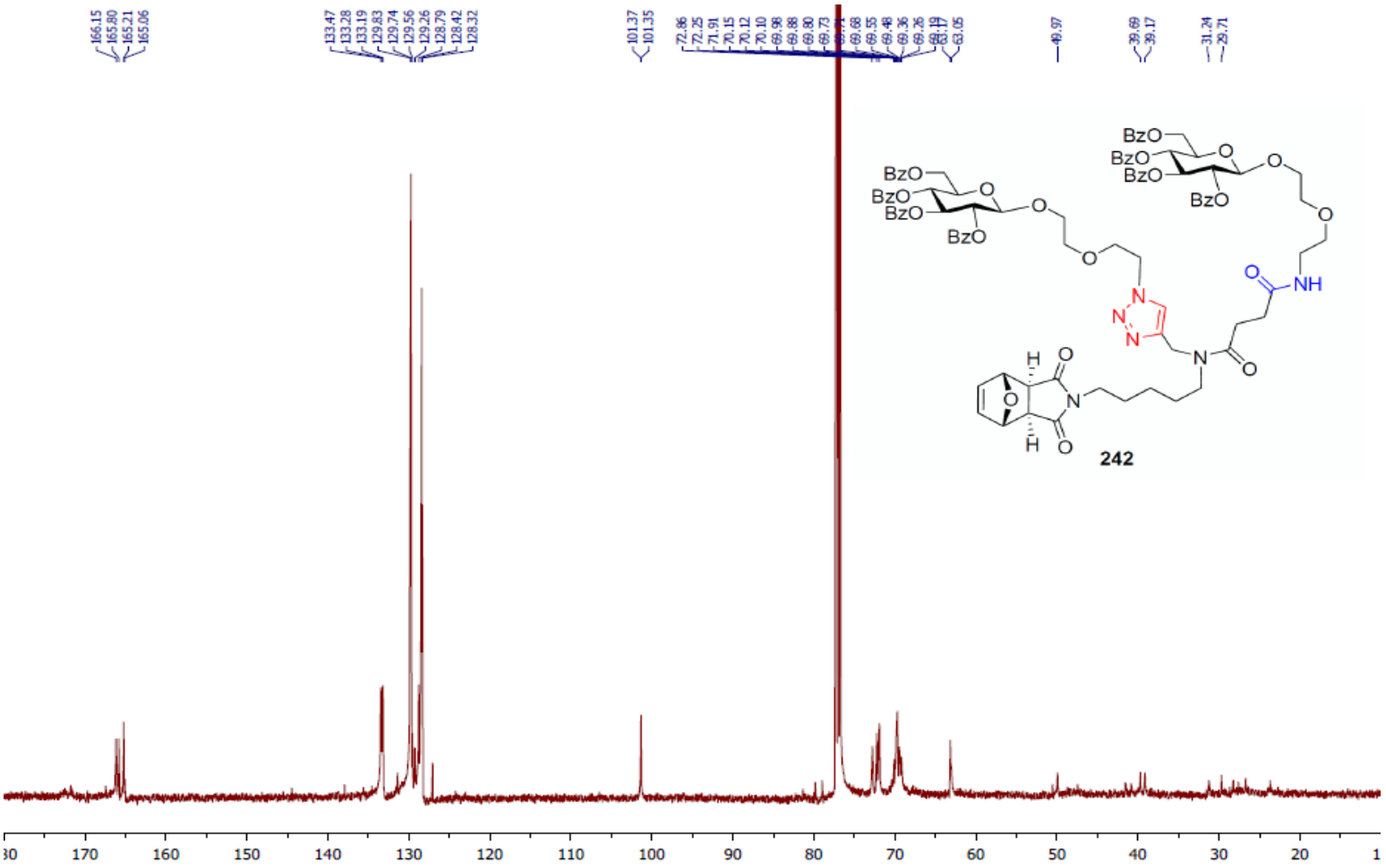


Figure A161. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glu-Glu **242**

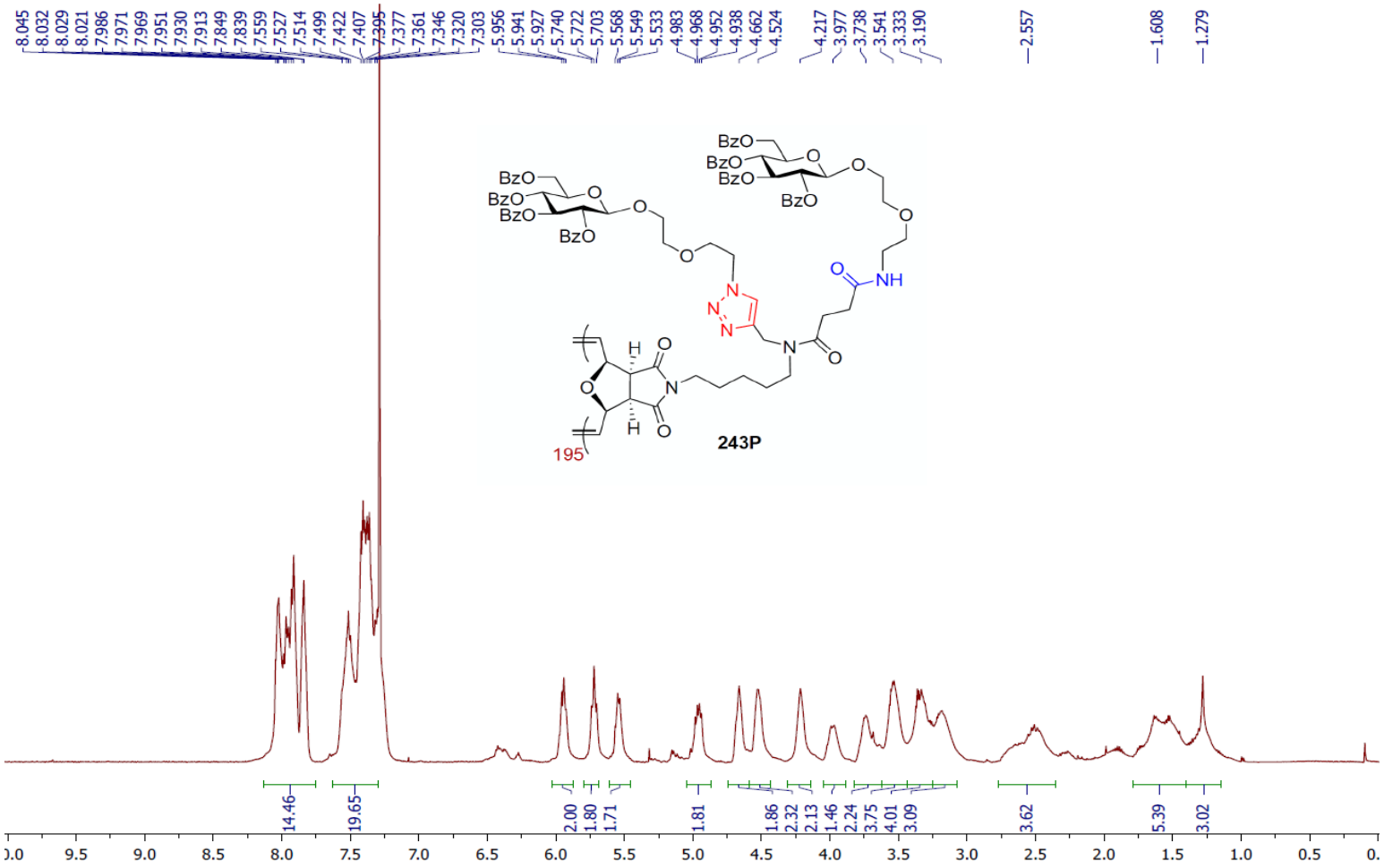


Figure A162. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Polymer **243P**

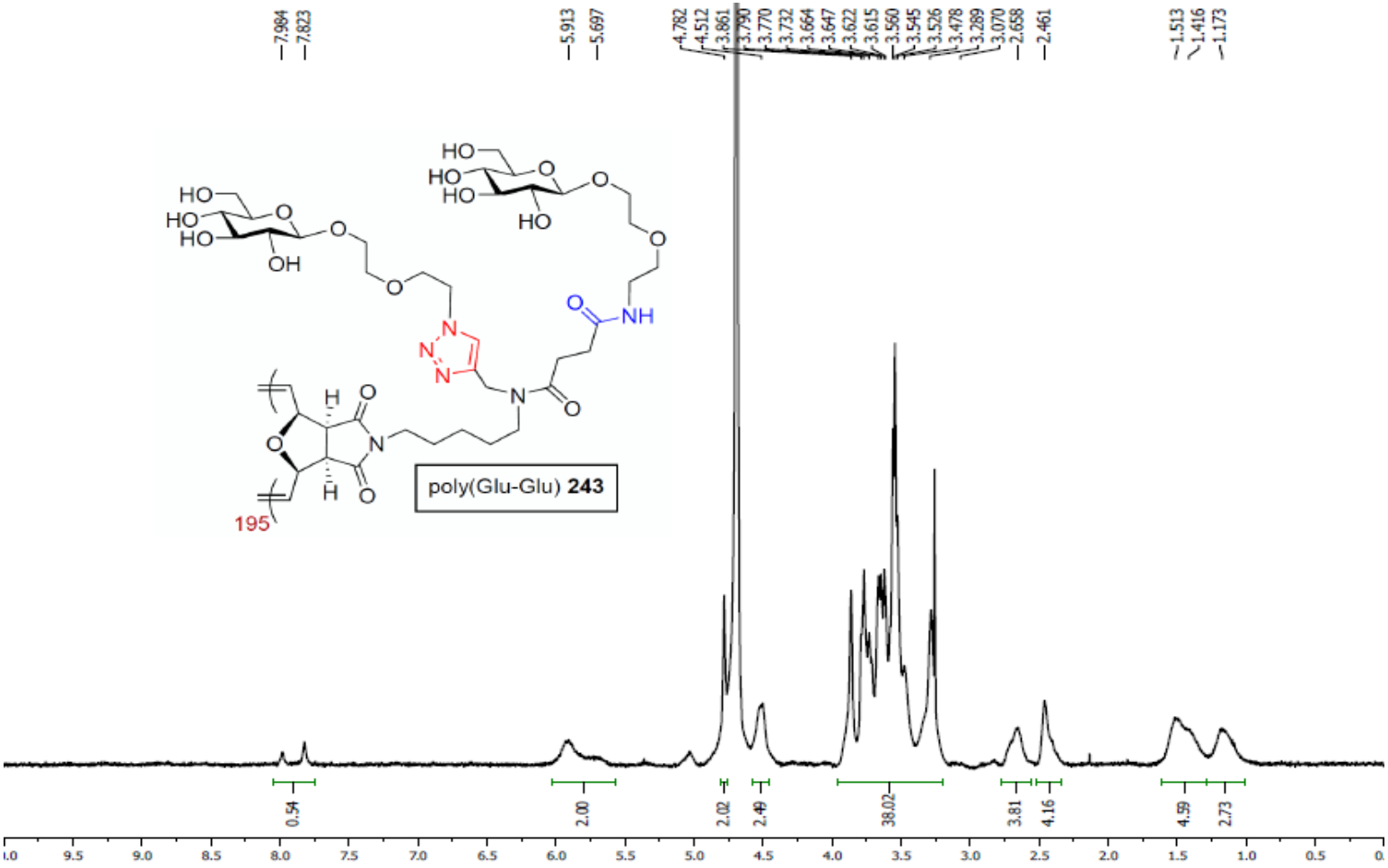


Figure A163. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **243**

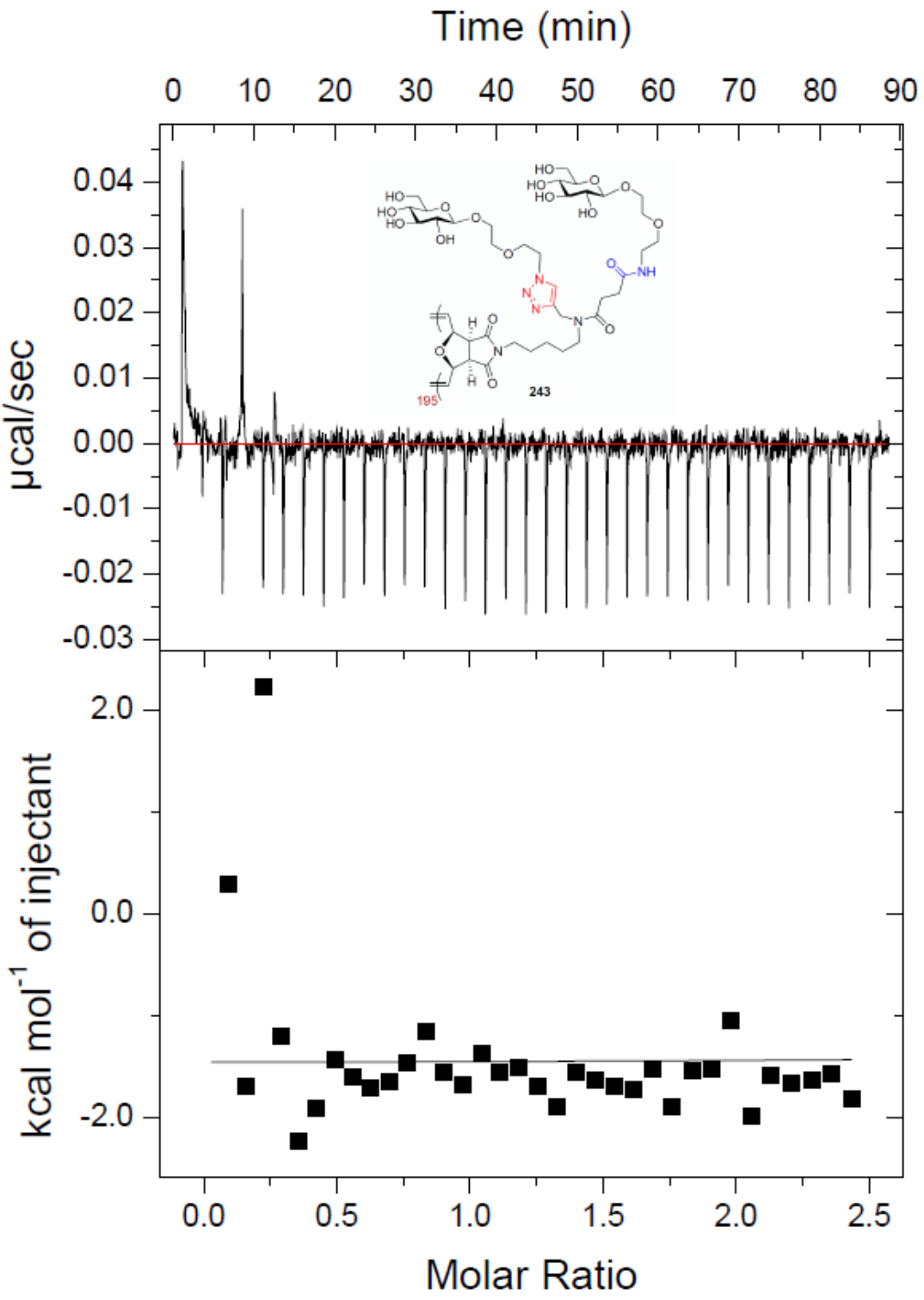


Figure A164. ITC Thermogram of Polymer **243**

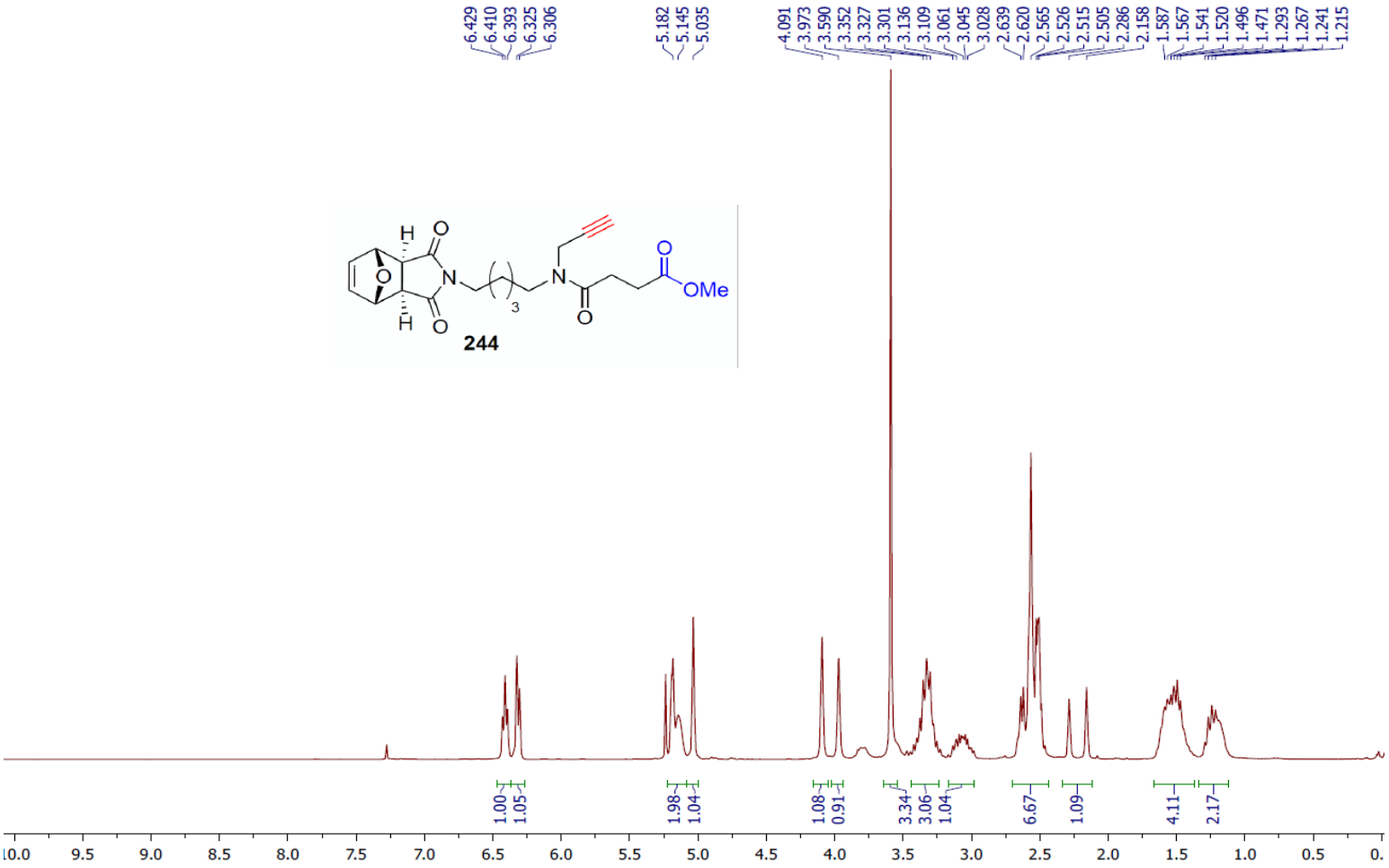


Figure A165. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **244**

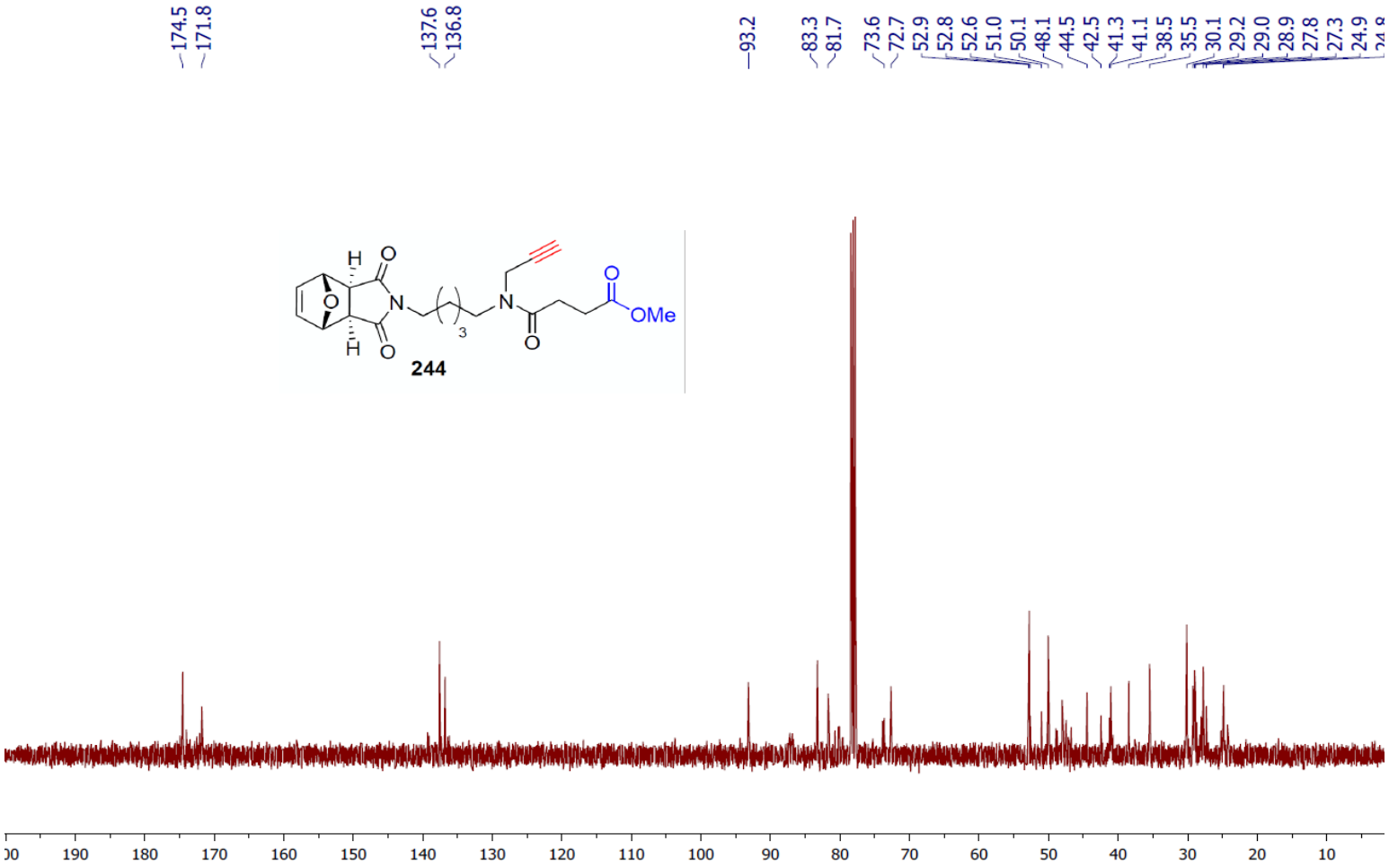


Figure A166. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **244**

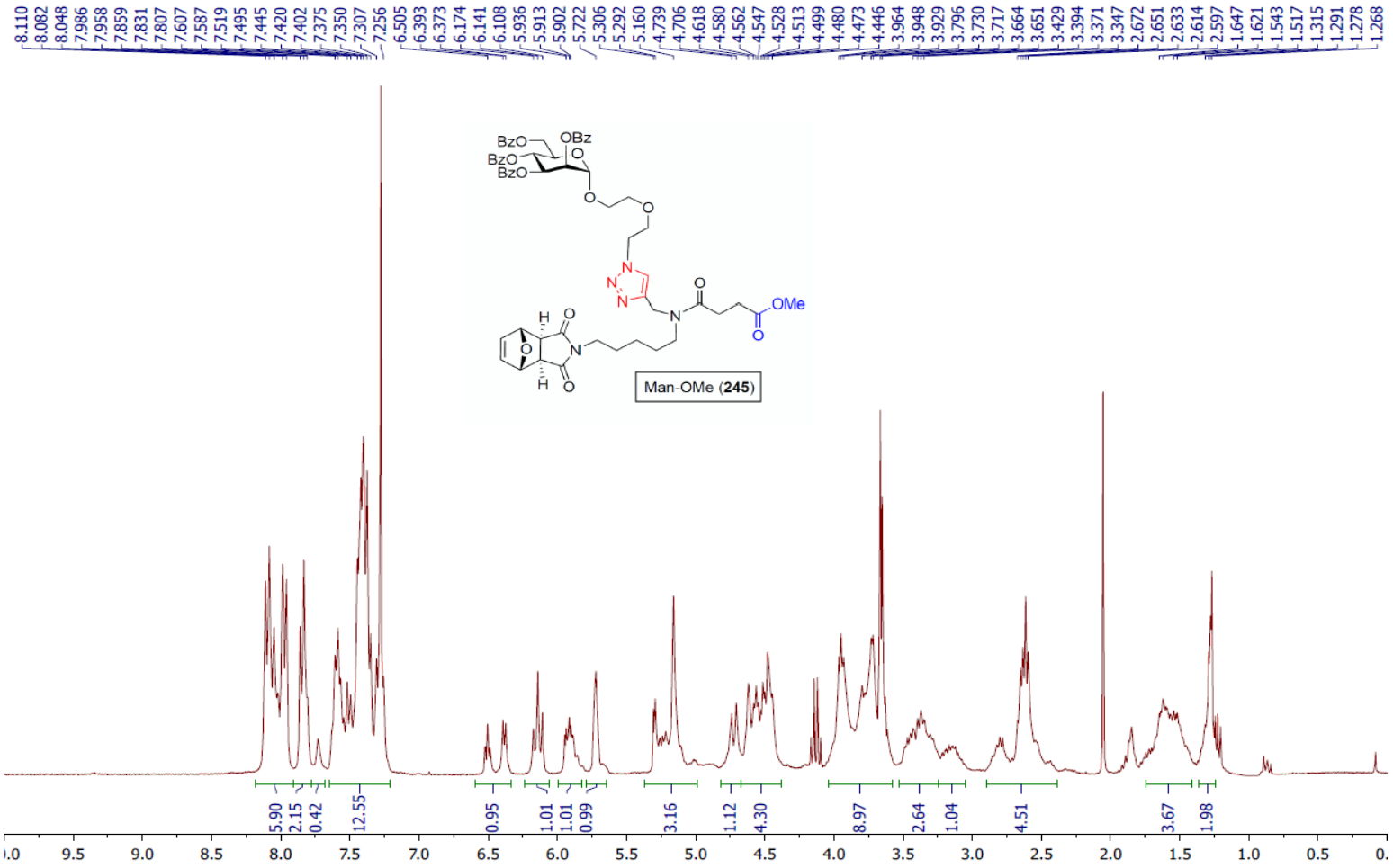


Figure A167. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Man-OMe **245**

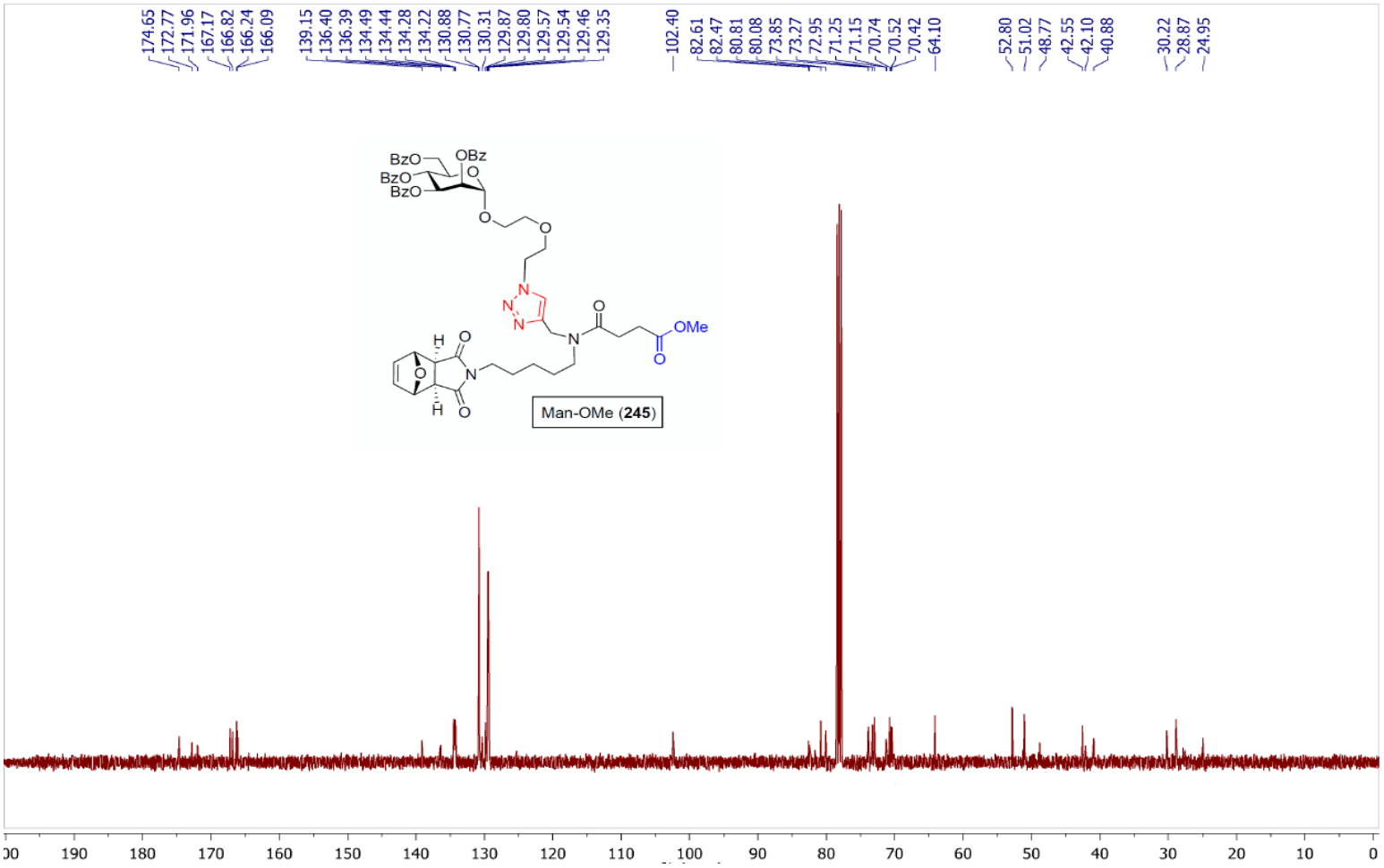


Figure A168. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Man-OMe **245**

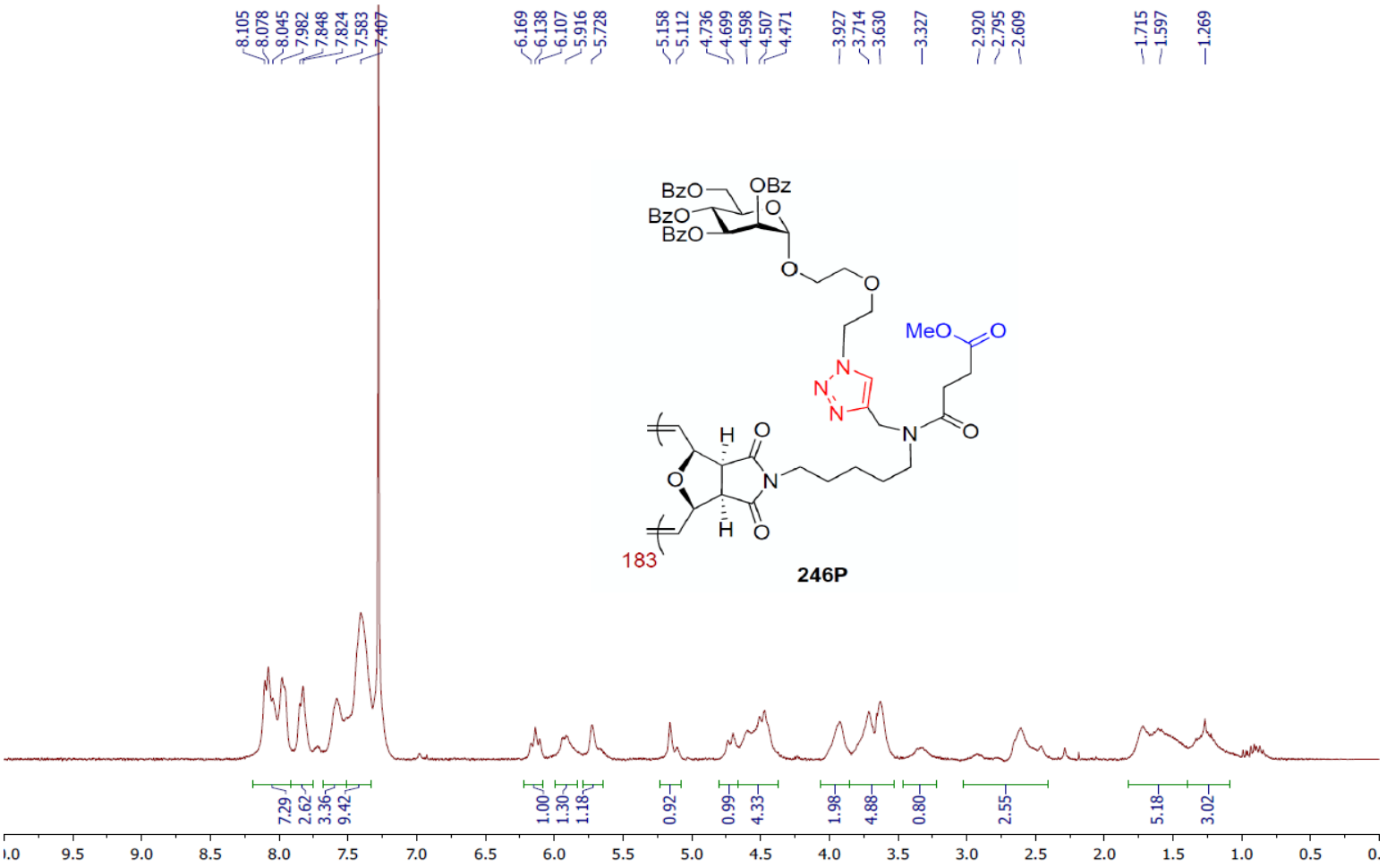


Figure A169. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Polymer **246P**

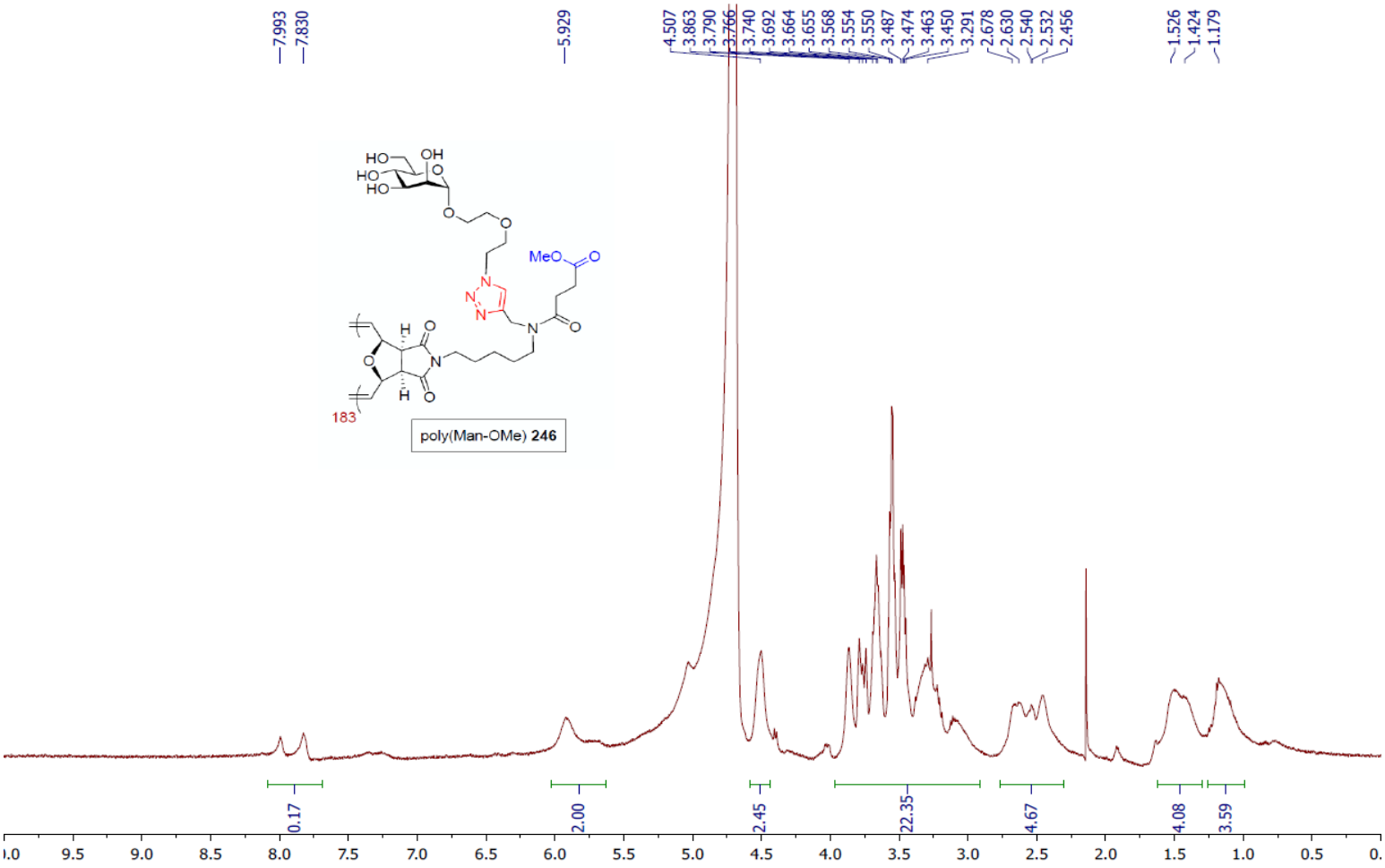


Figure A170. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **246**

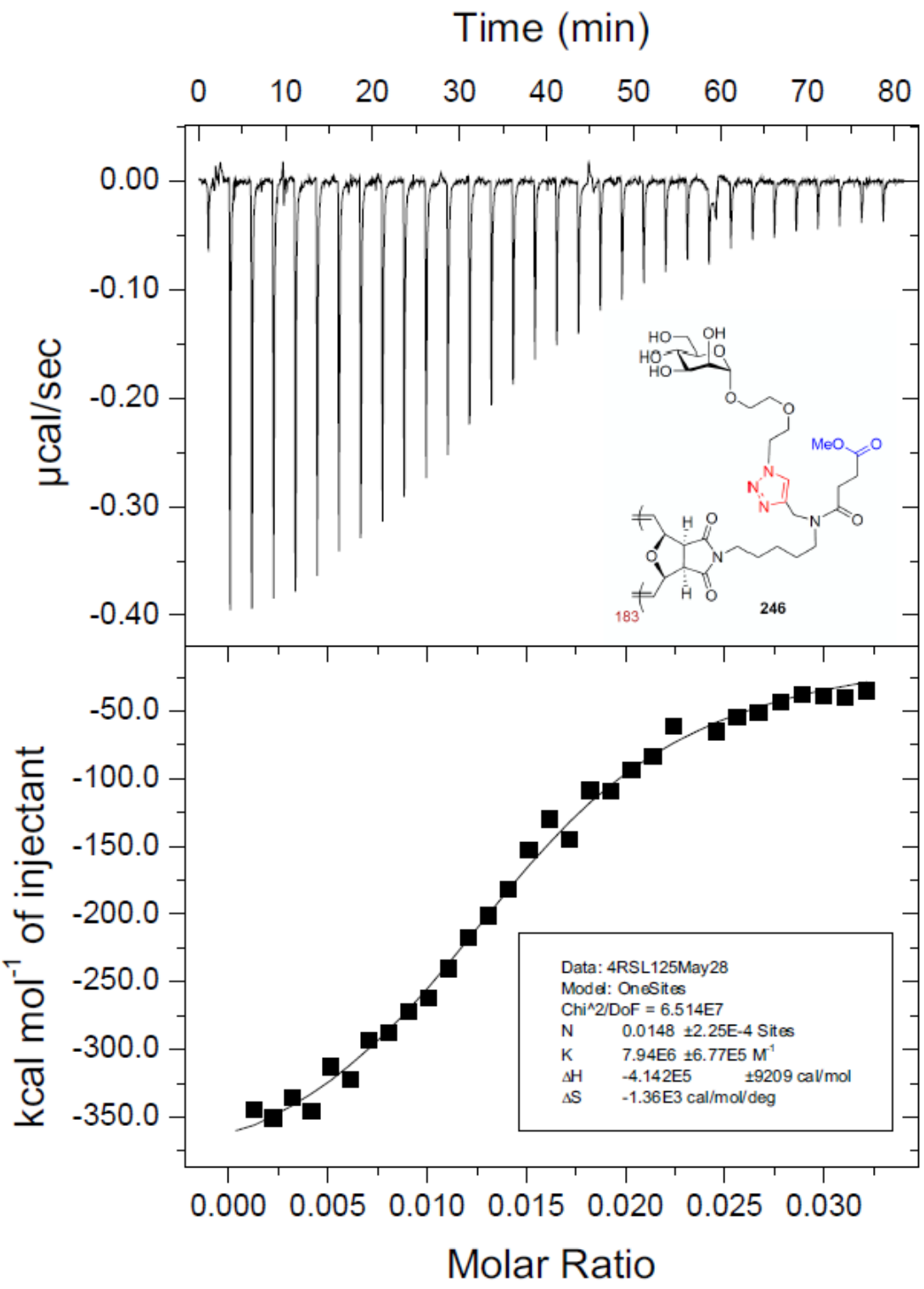


Figure A171. ITC Thermogram of Polymer **246**

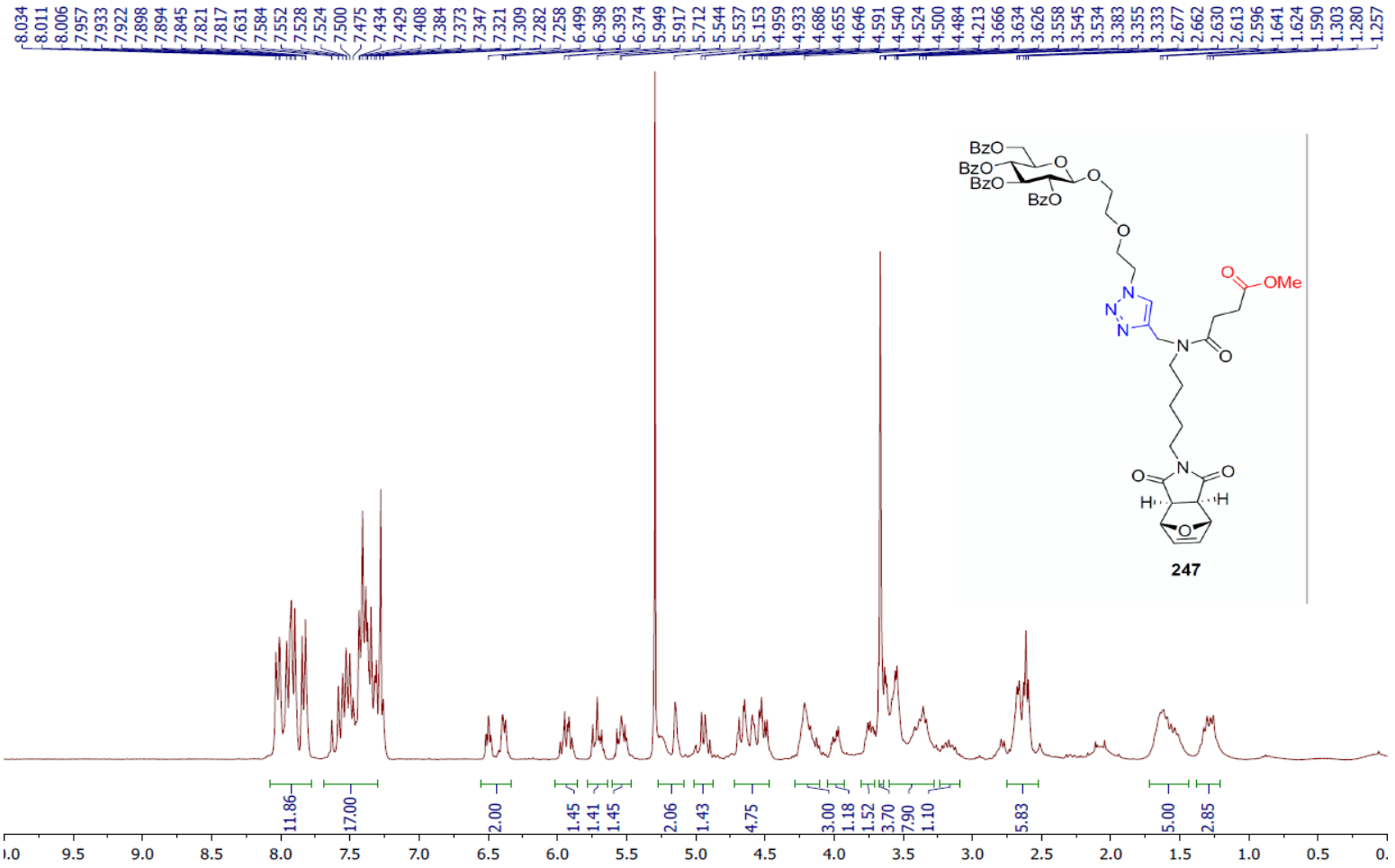


Figure A172. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **247**

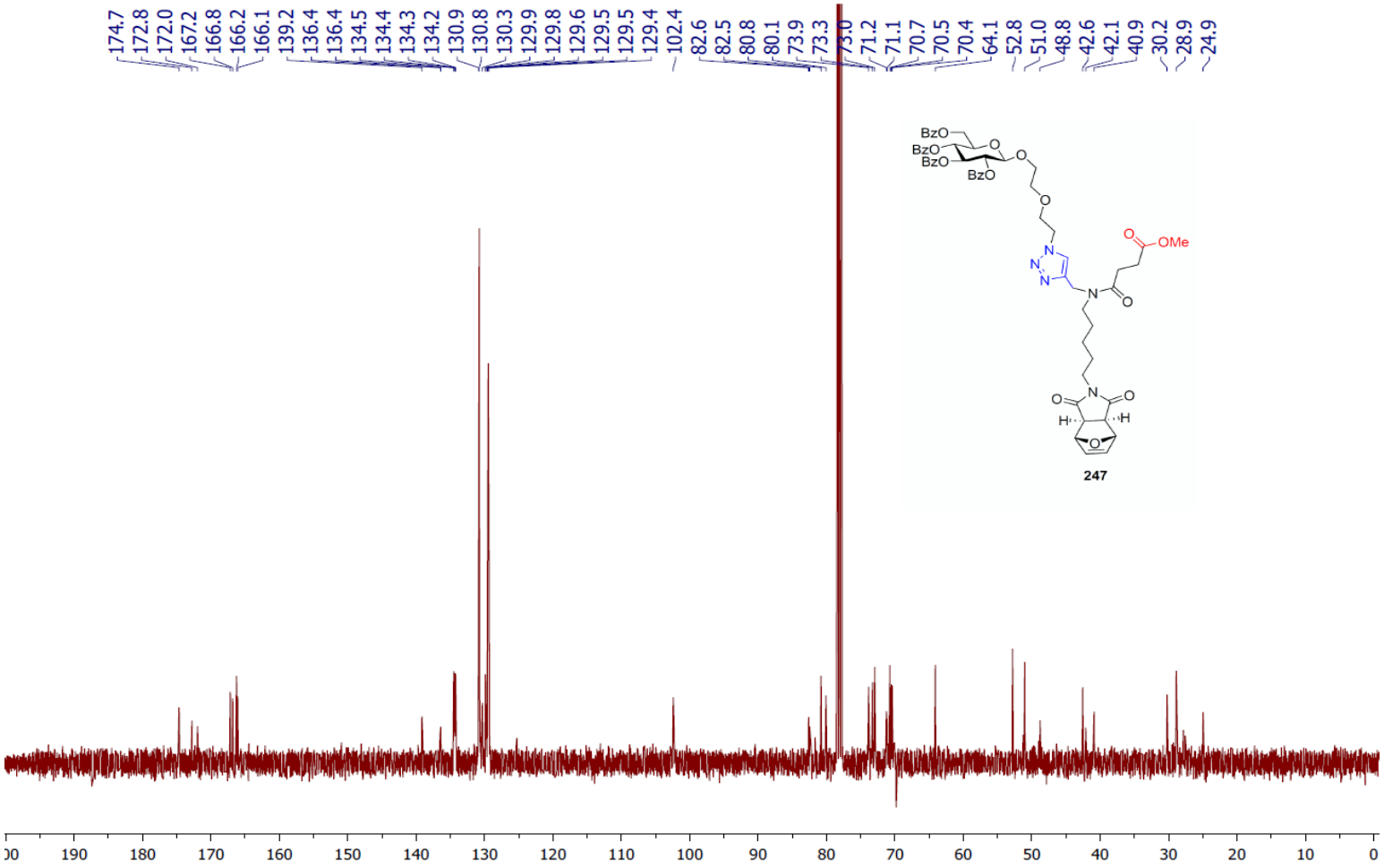


Figure A173. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glucoside **247**

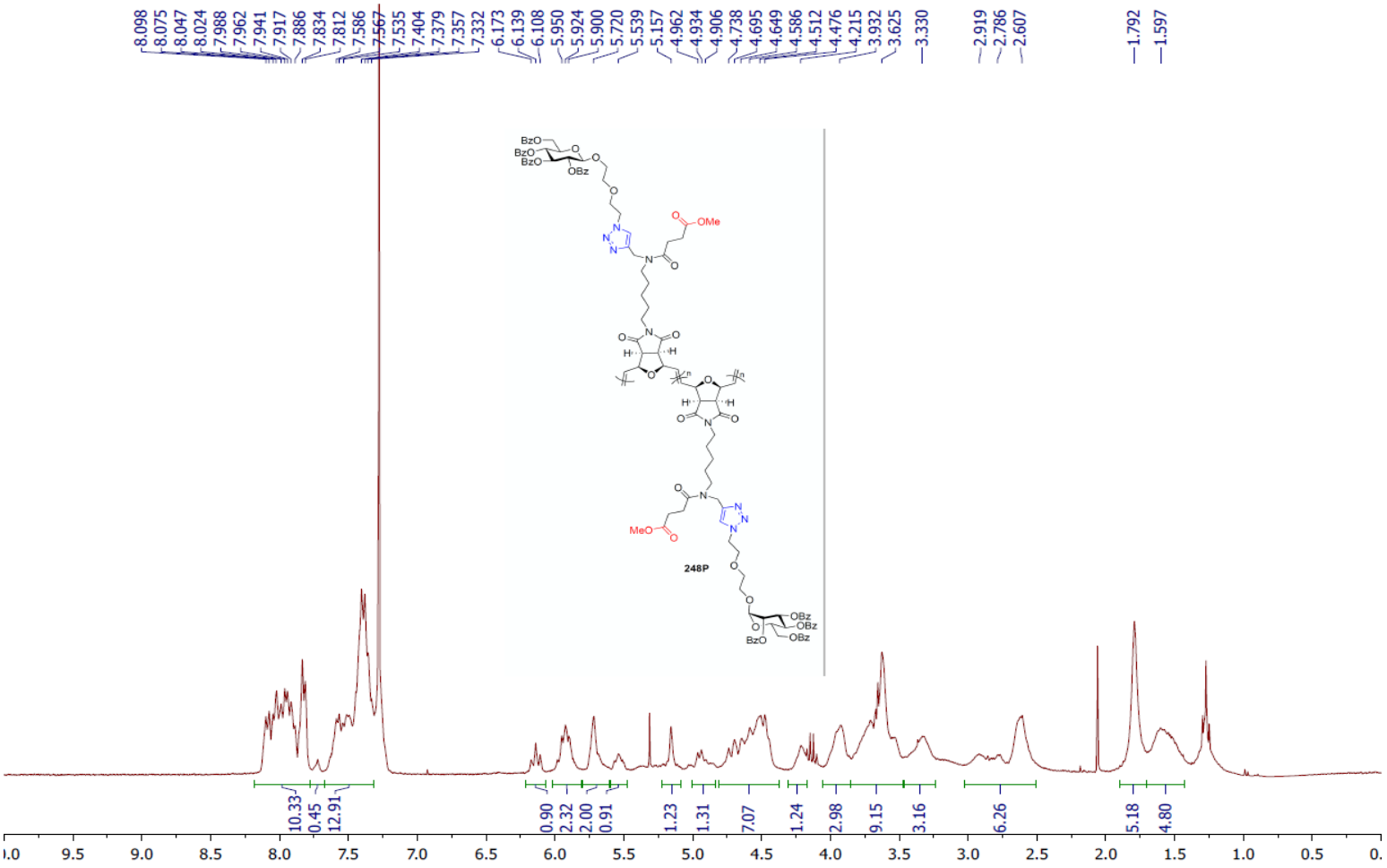


Figure A174. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Polymer **248P**

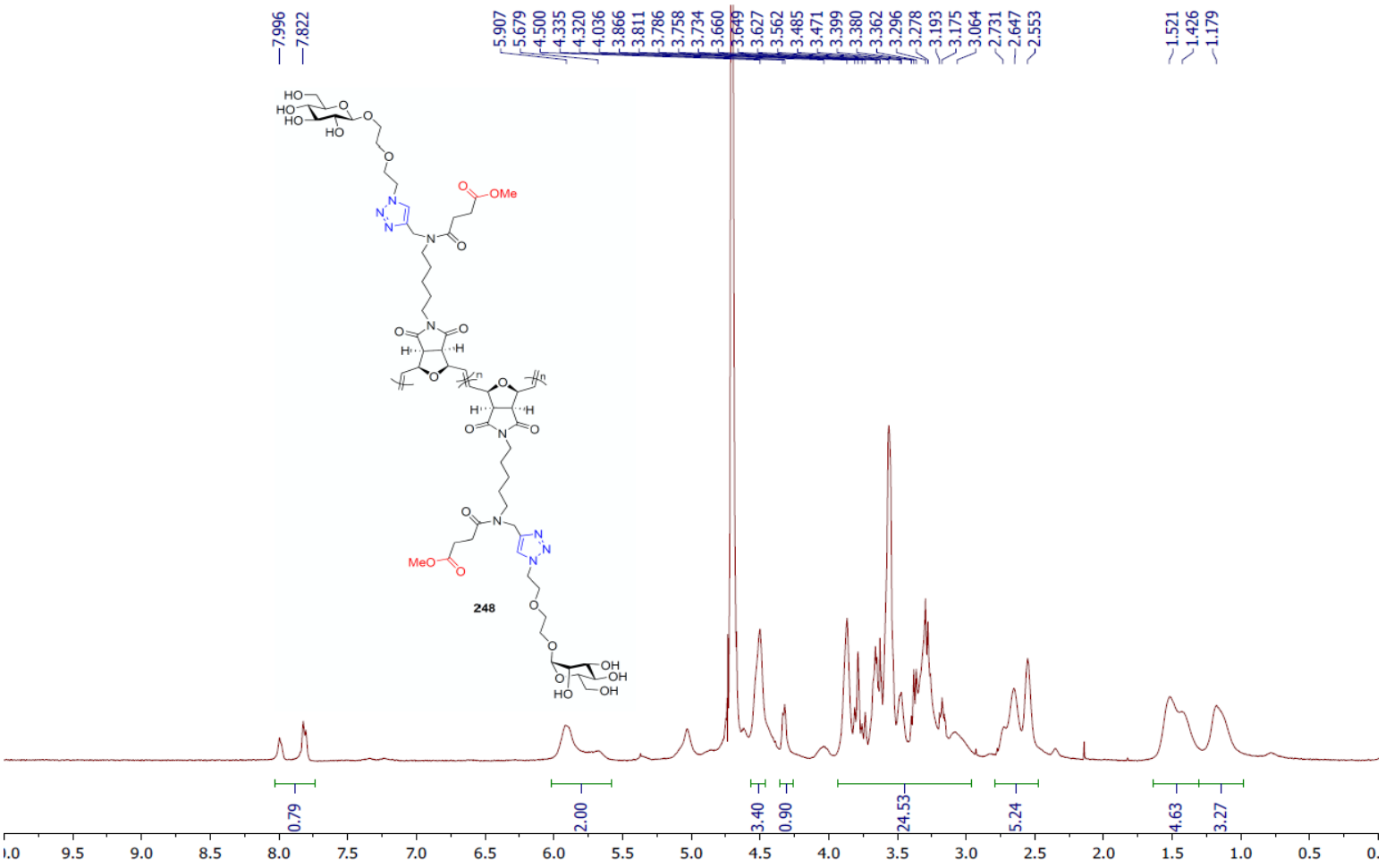


Figure A175. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **248**

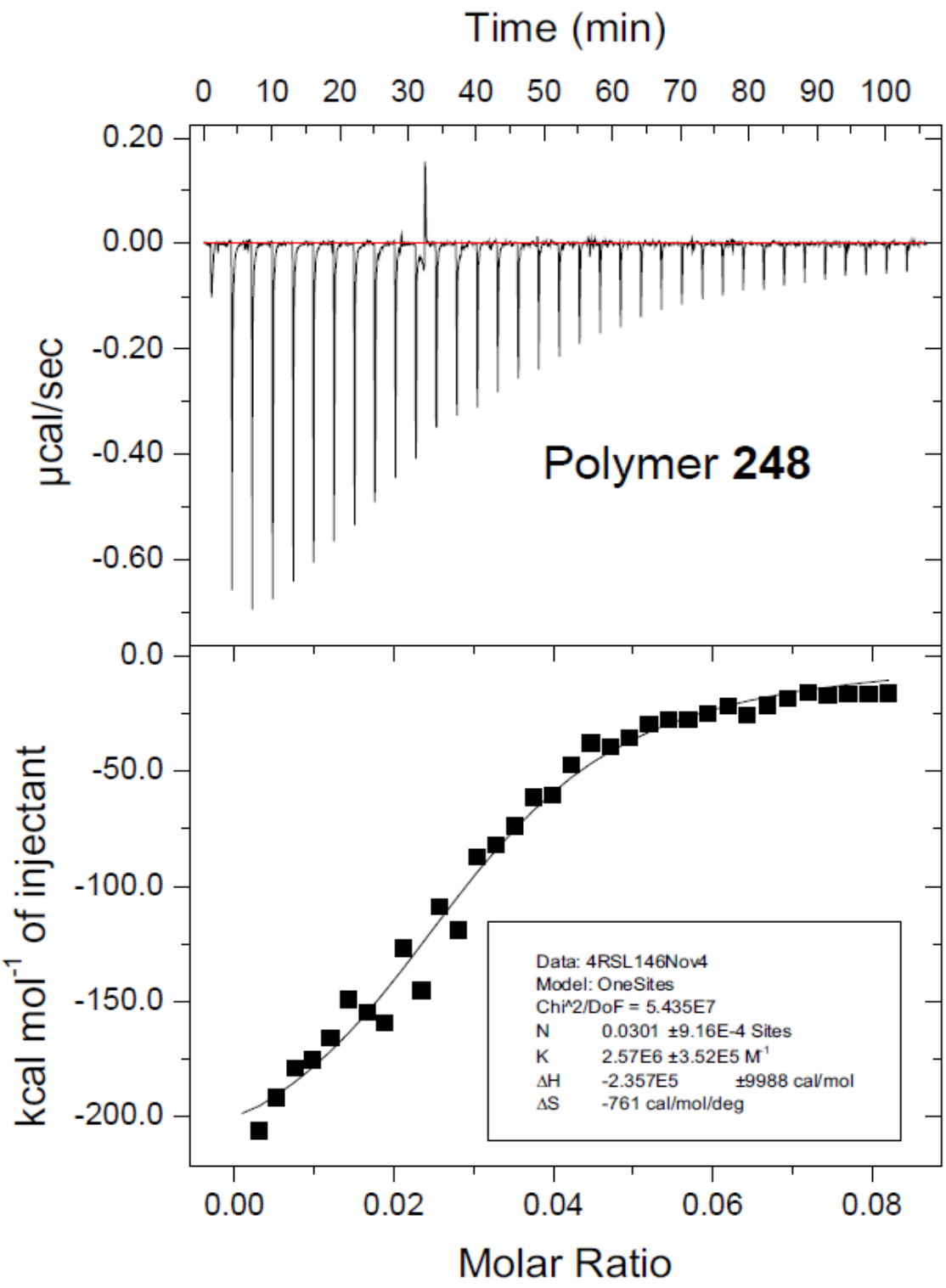


Figure A176. ITC Thermogram of Polymer **248**

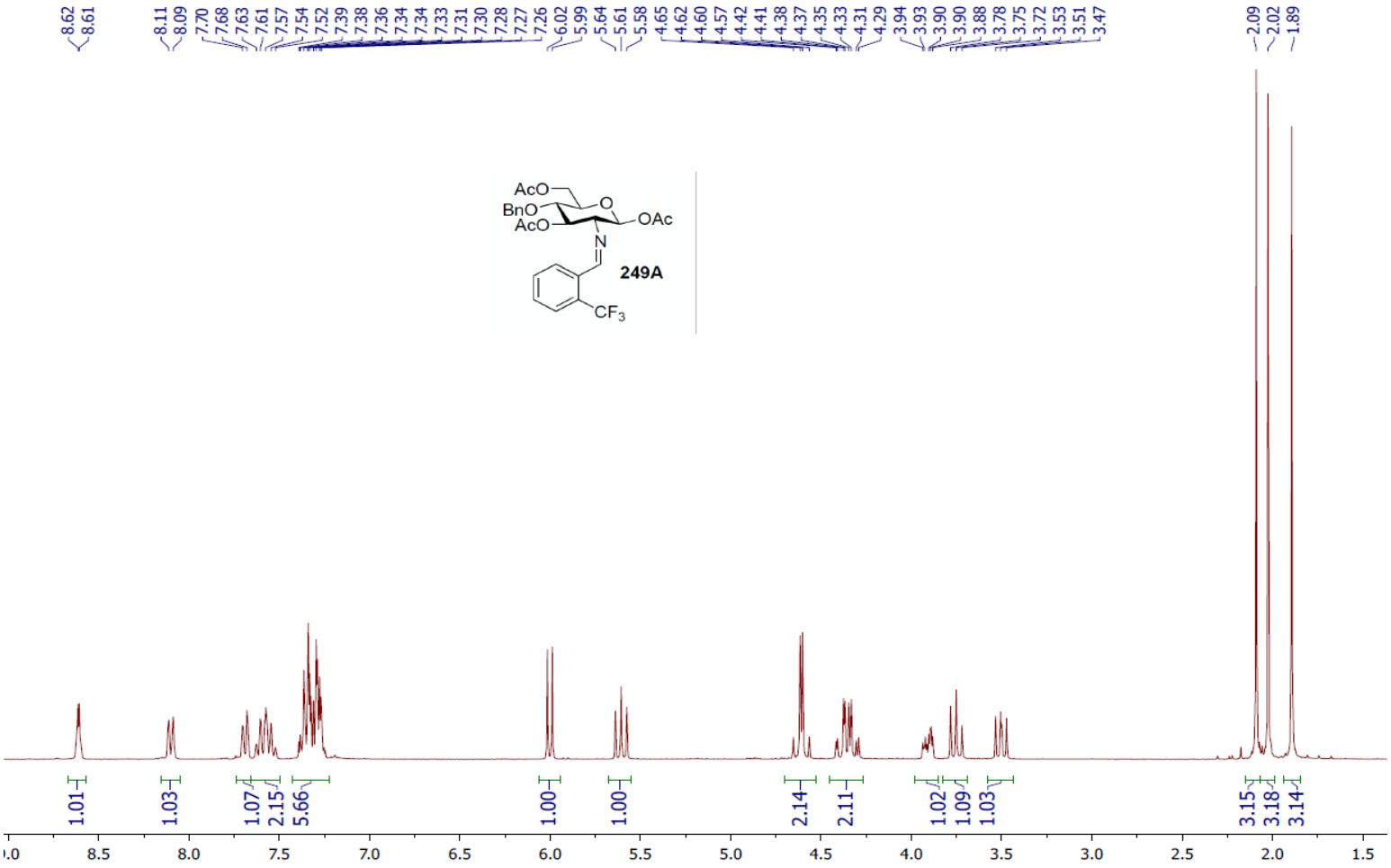


Figure A177. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Glucoside **249A**

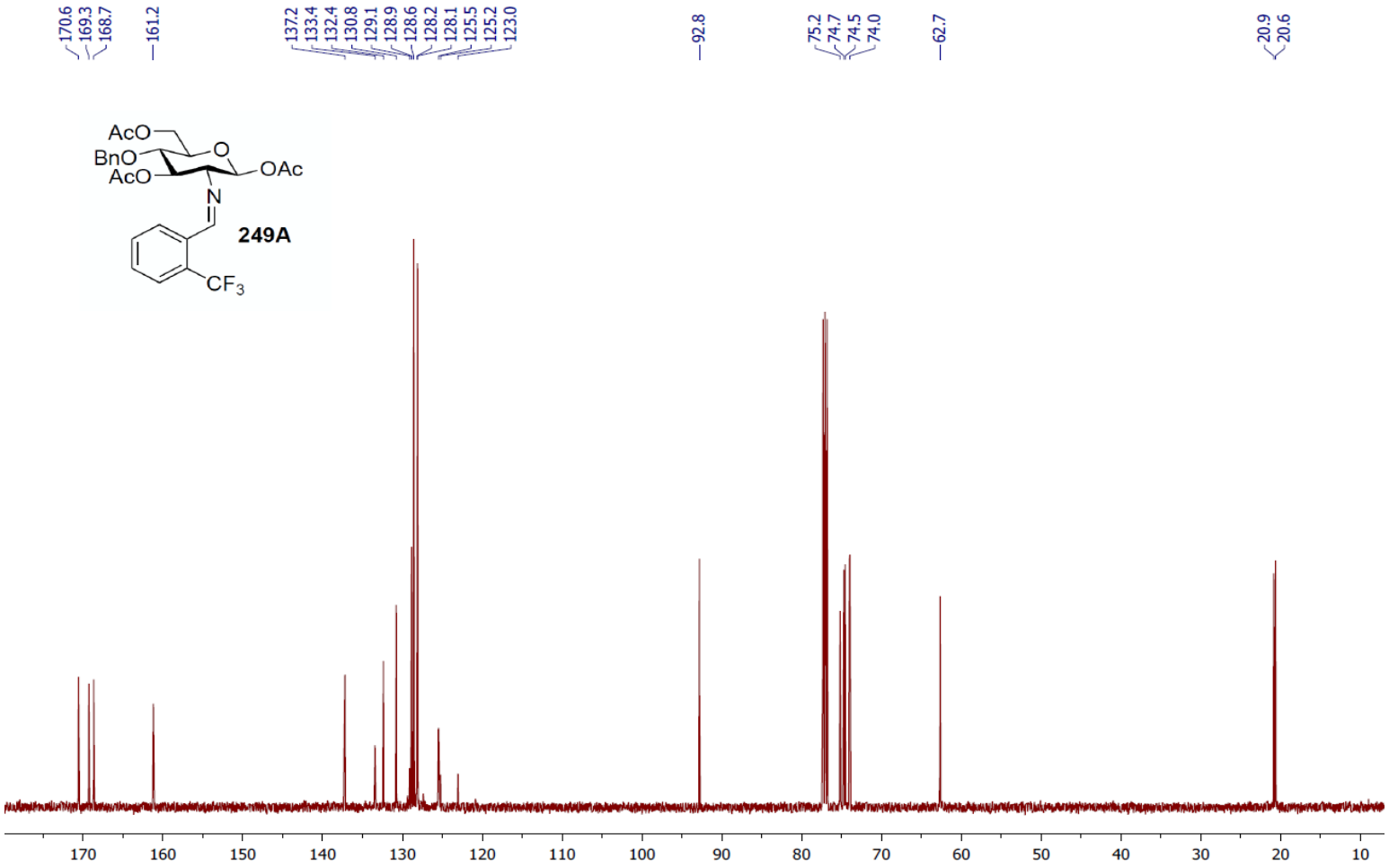


Figure A178. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Glucoside **249A**

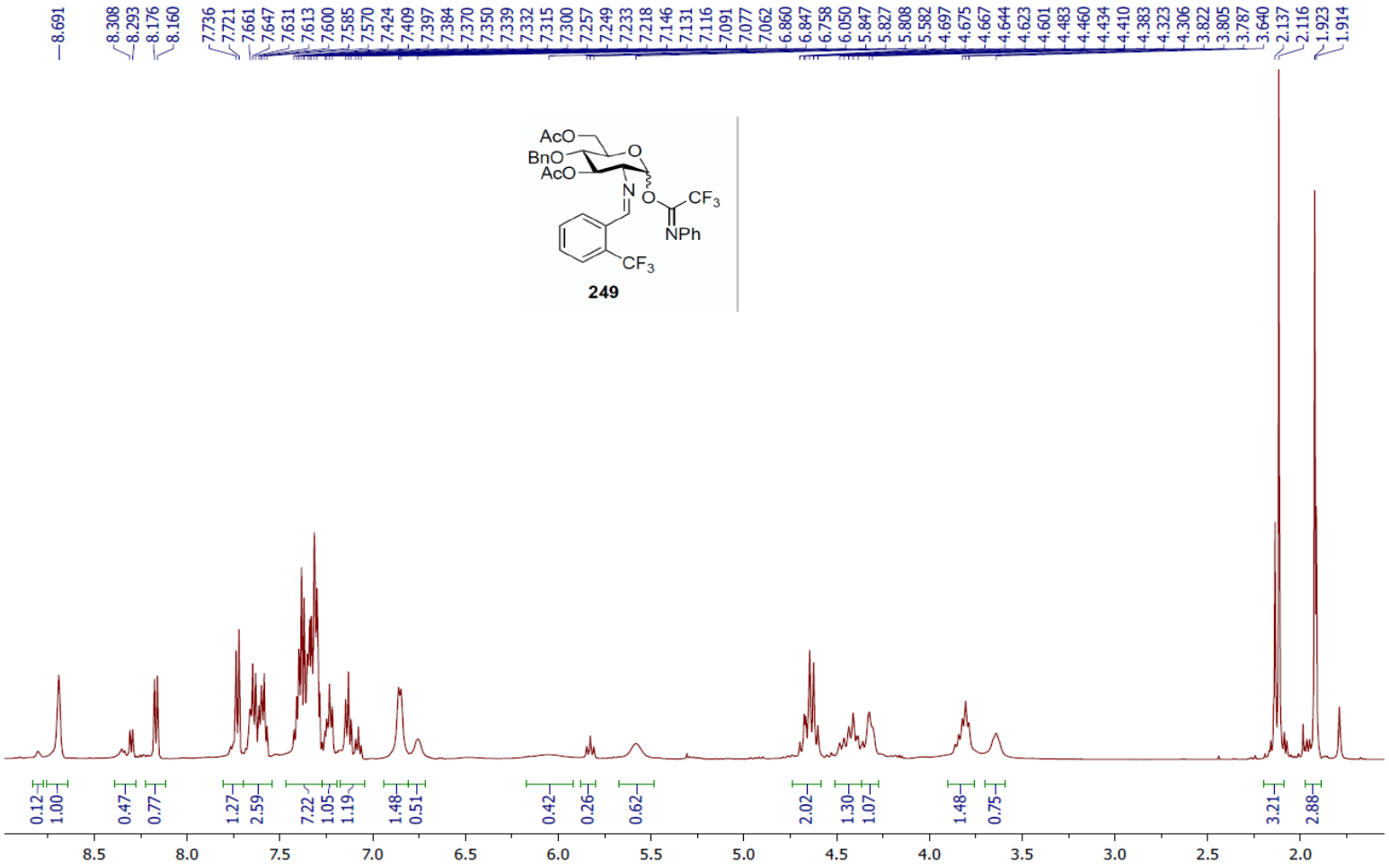


Figure A179. 500 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Imidate **249**

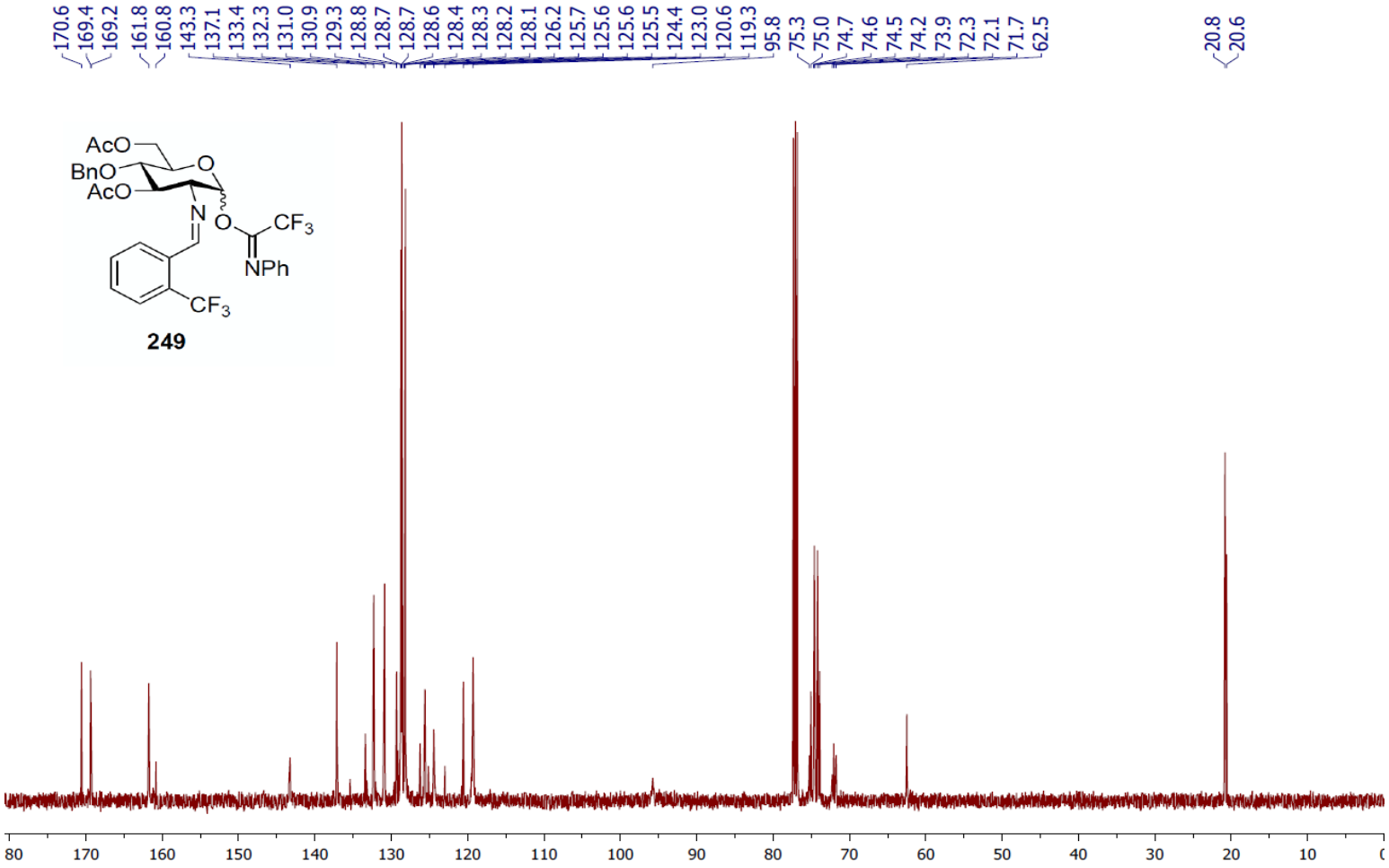


Figure A180. 125 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Imidate **249**

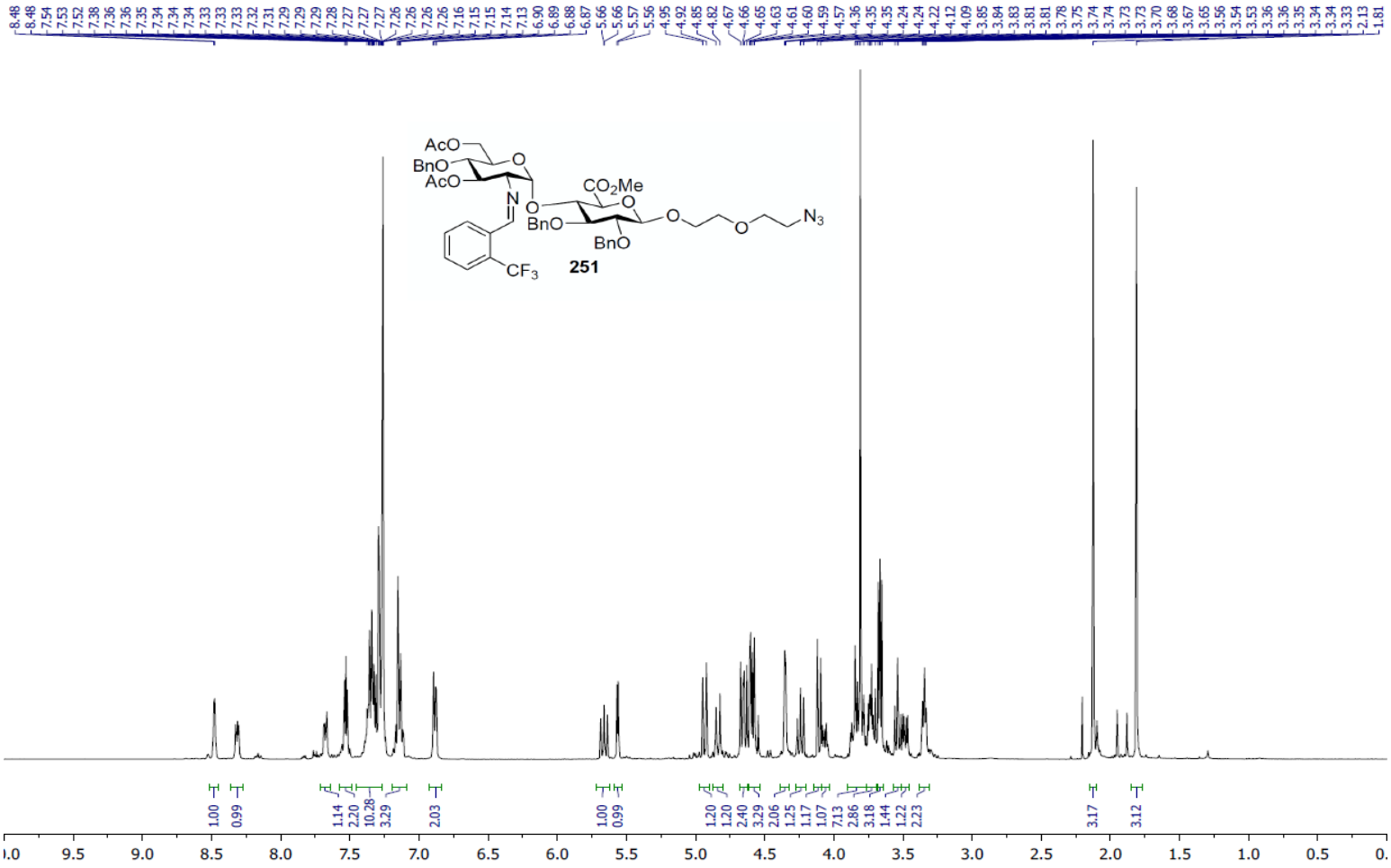


Figure A181. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **251**

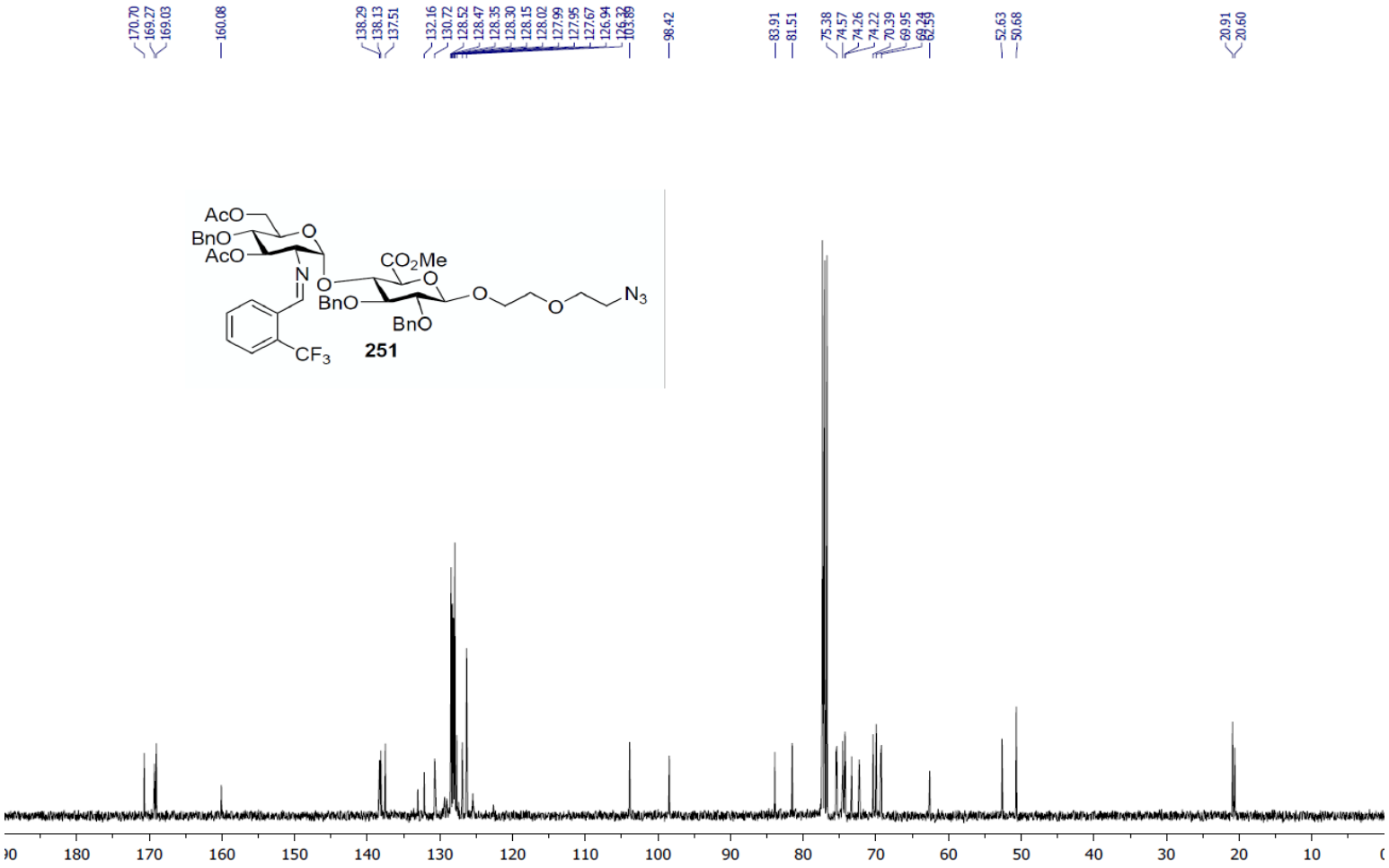


Figure A182. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **251**

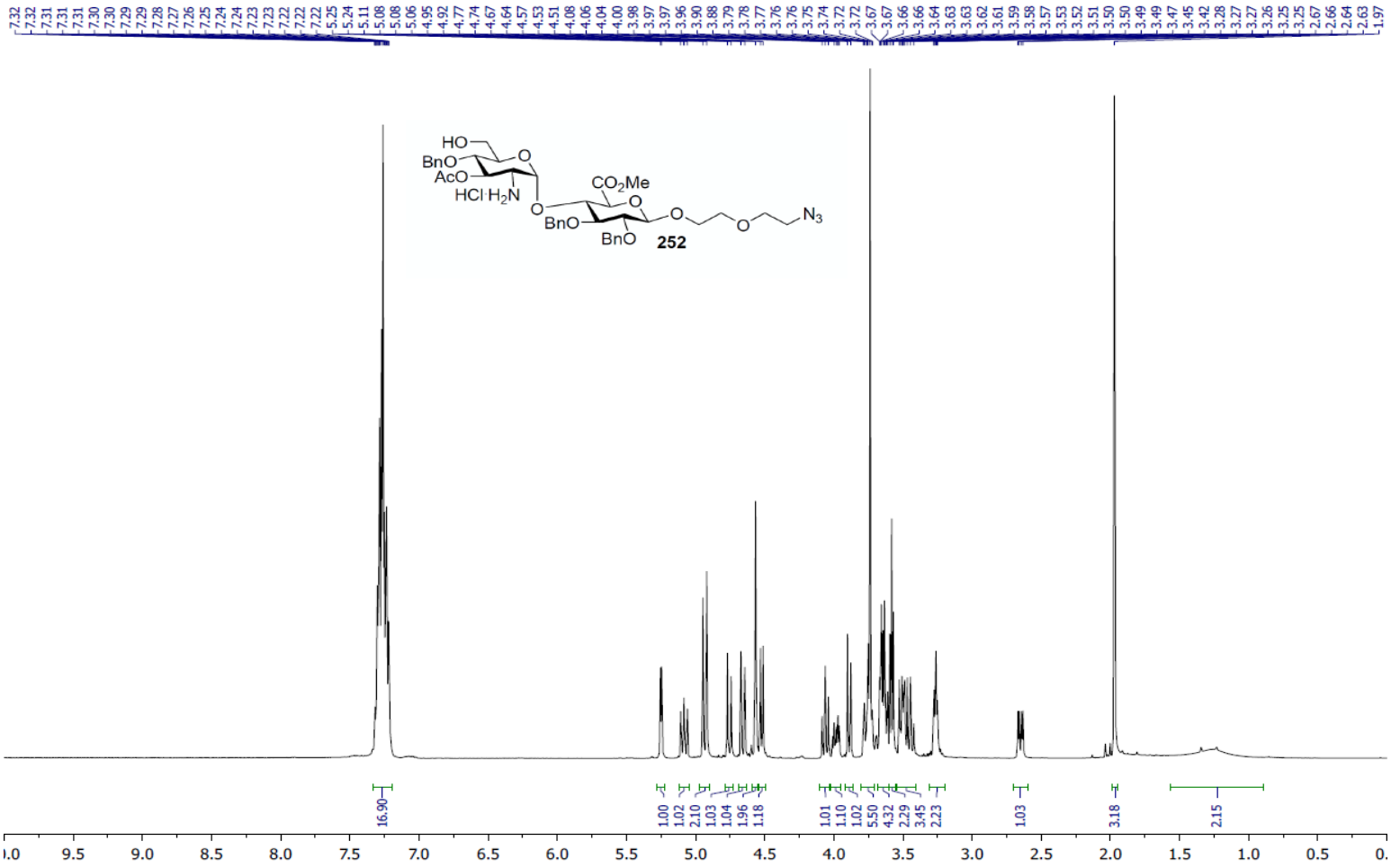


Figure A183. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Disaccharide **252**

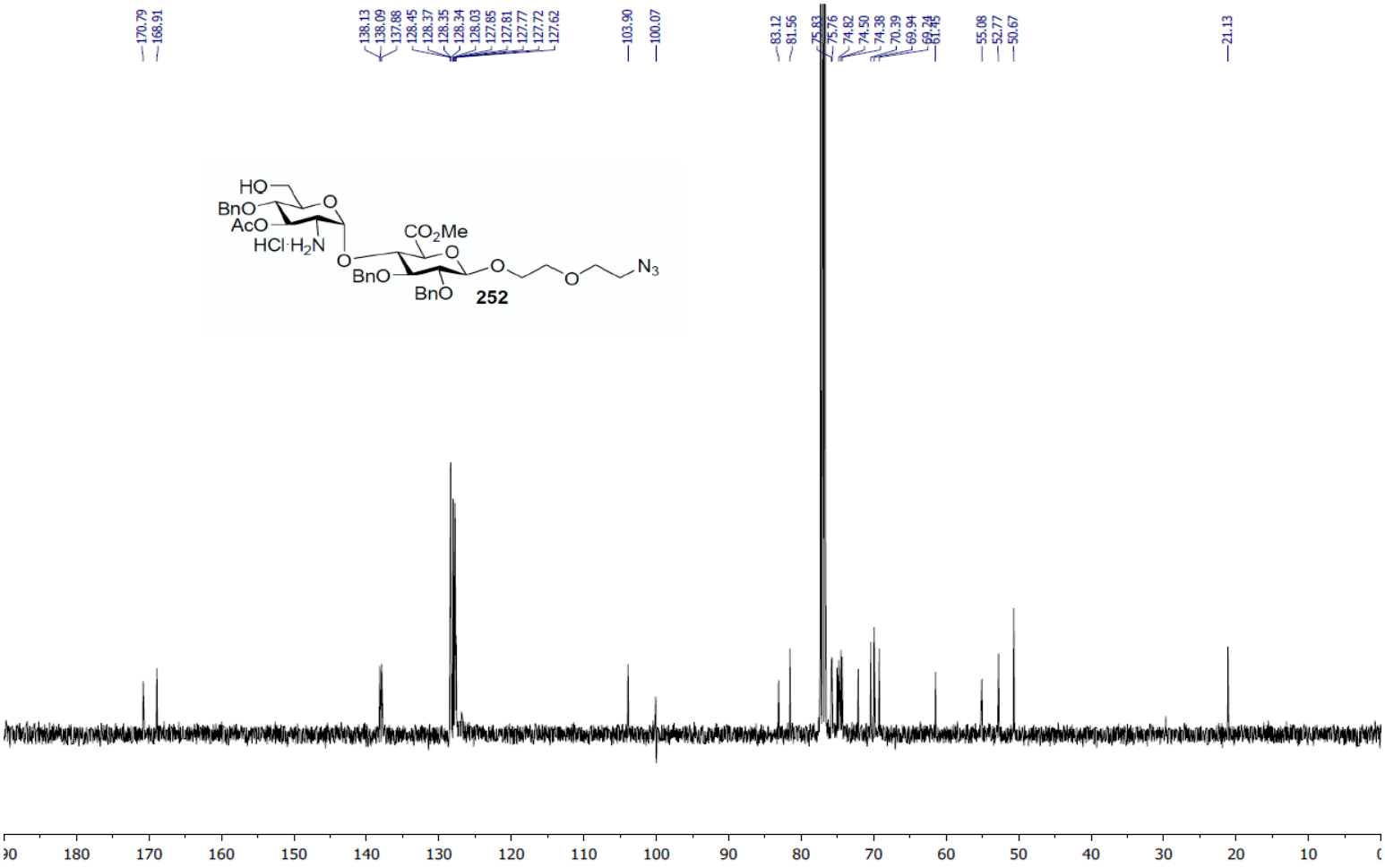


Figure A184. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Disaccharide **252**

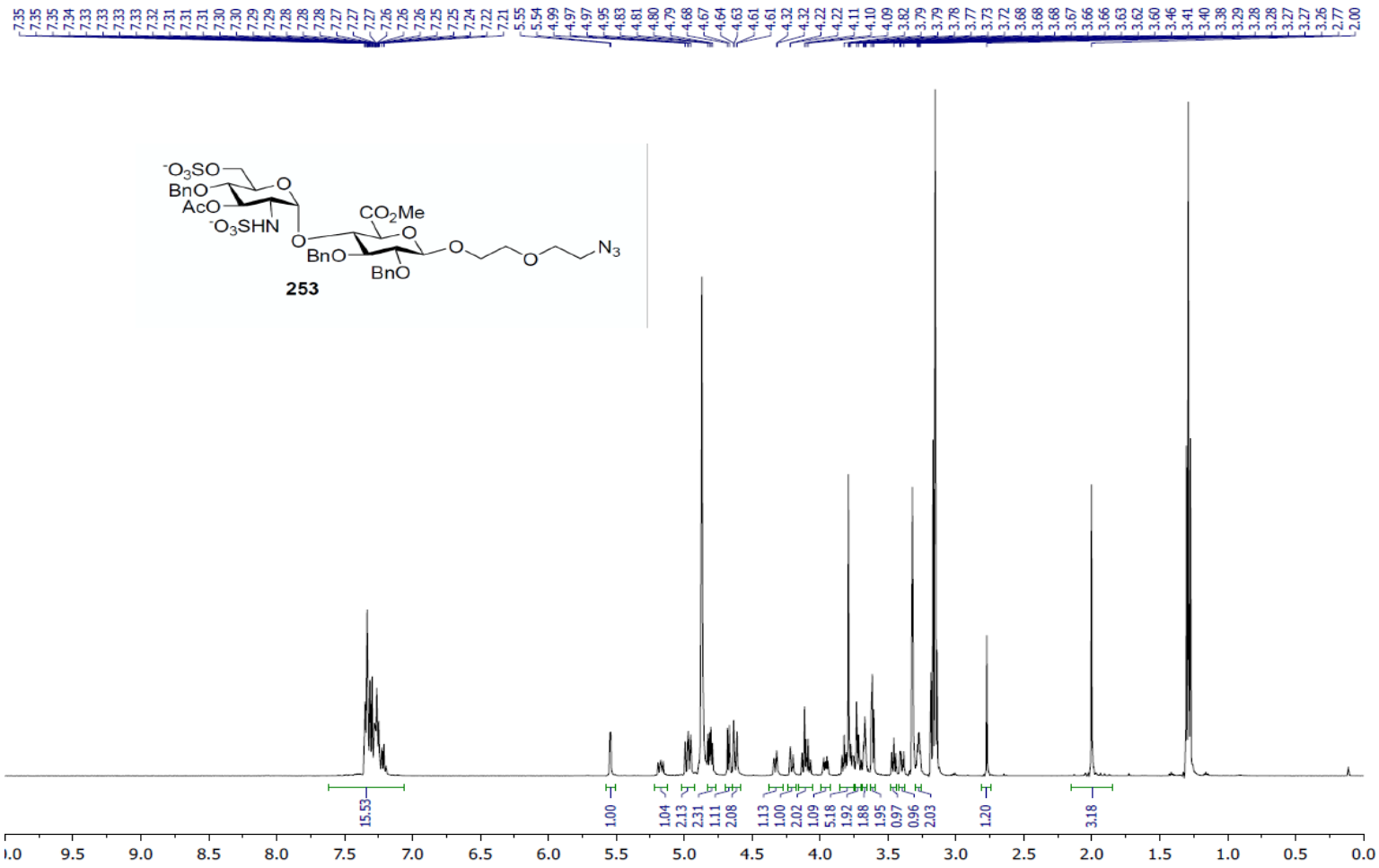


Figure A185. 500 MHz ^{1}H NMR Spectrum (CD_3OD) of Disaccharide **253**

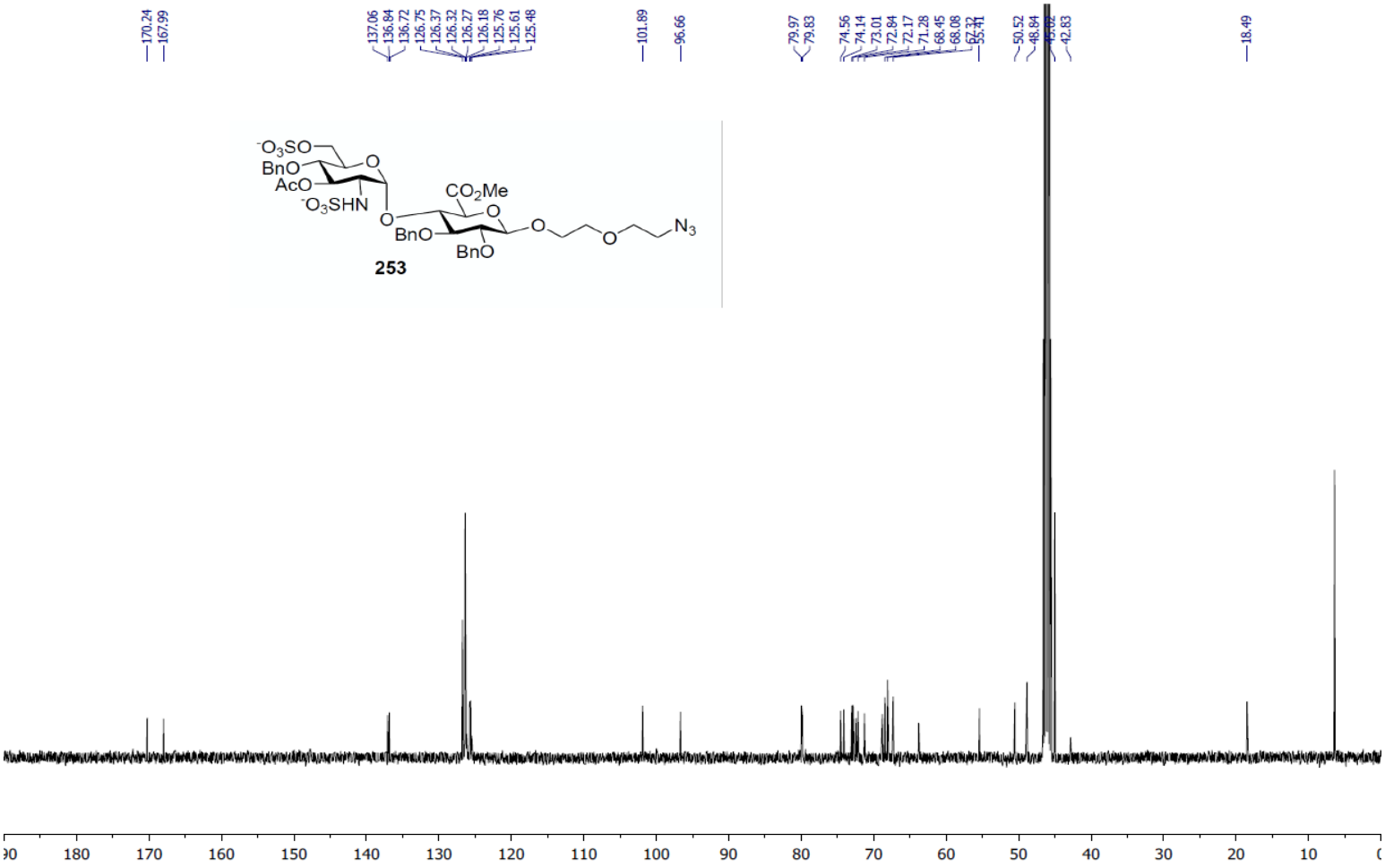


Figure A186. 125 MHz ^{13}C NMR Spectrum (CD_3OD) of Disaccharide **253**

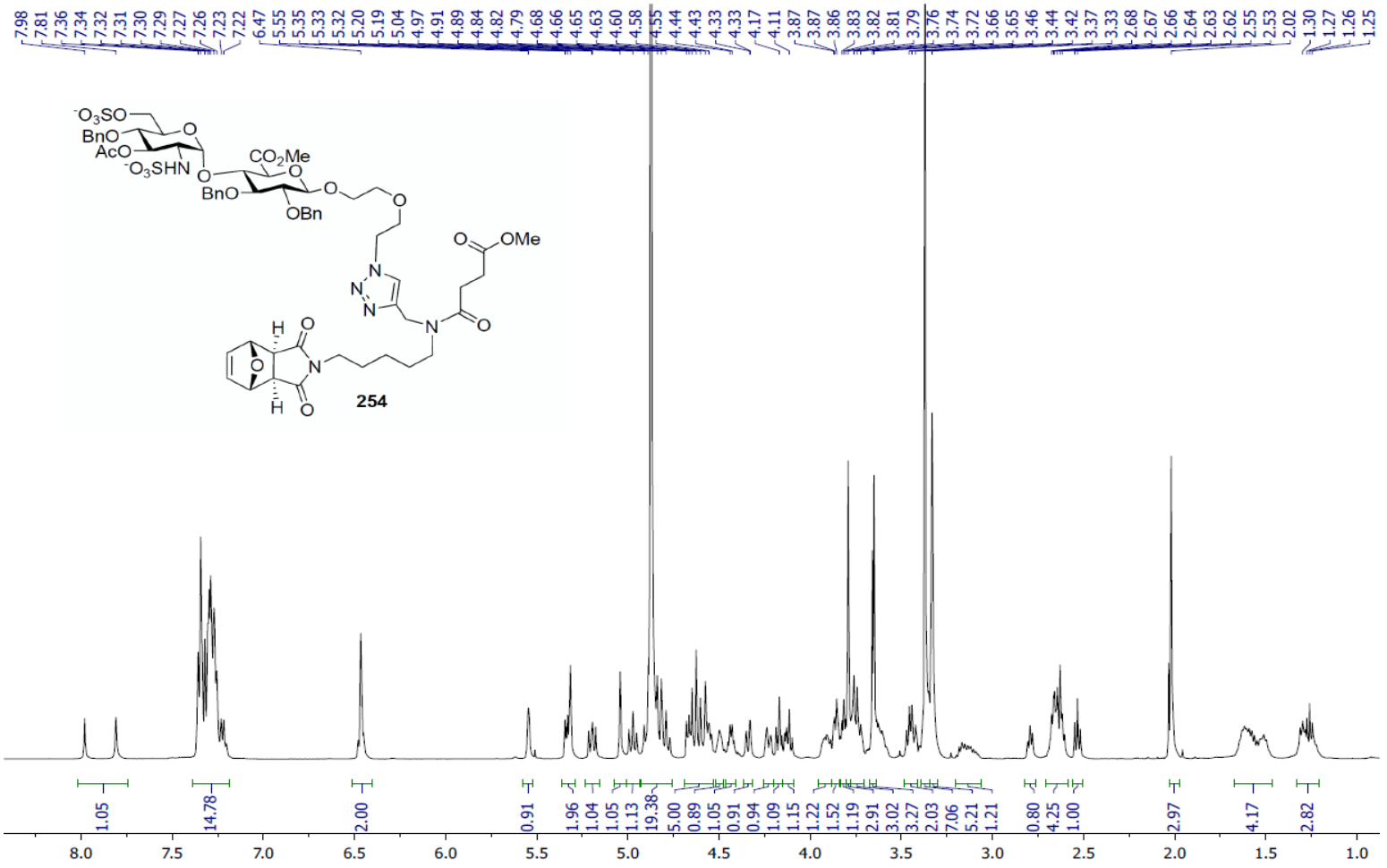


Figure A187. 500 MHz ^{1}H NMR Spectrum (CD_3OD) of Monomer **254**

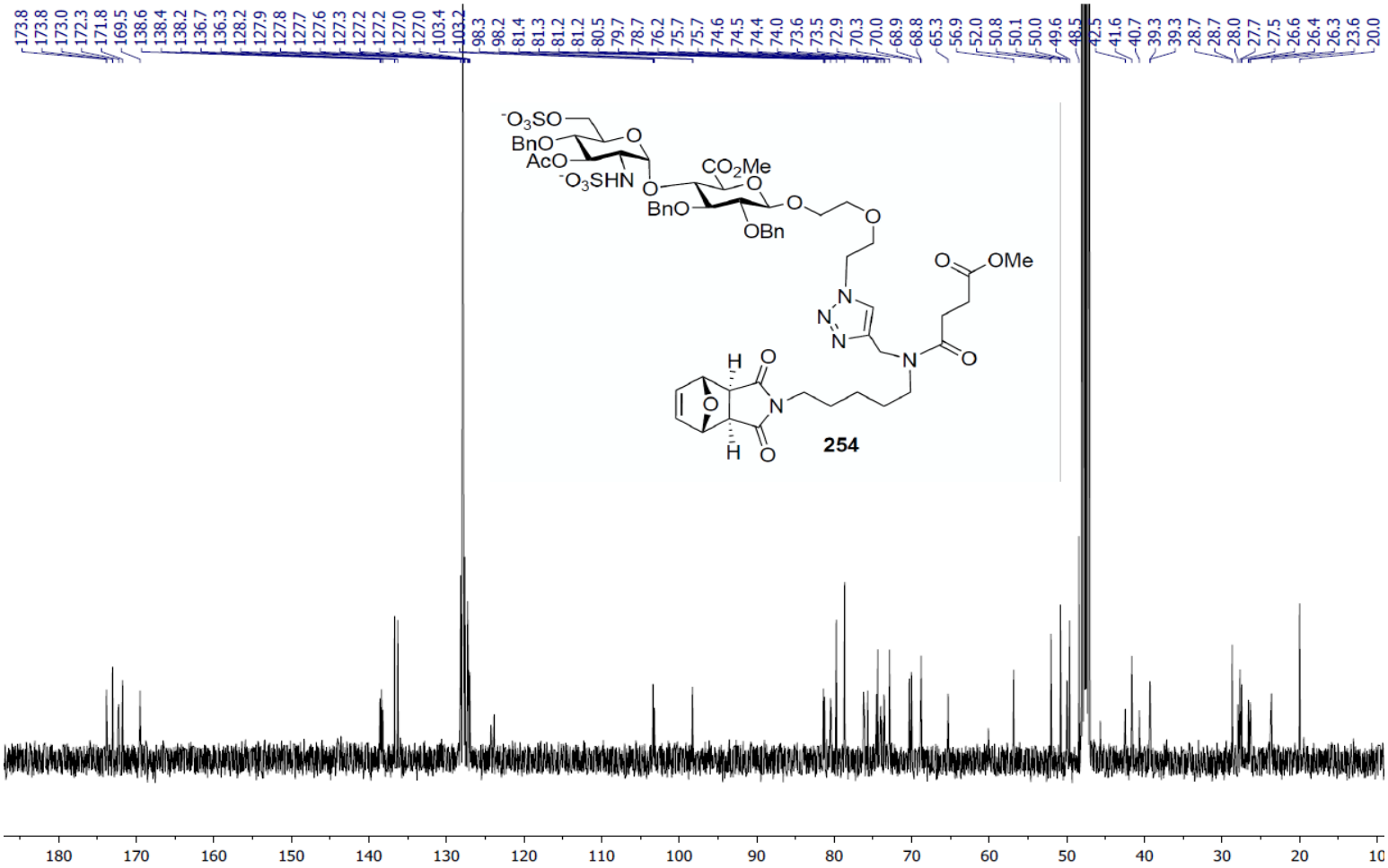


Figure A188. 125 MHz ^{13}C NMR Spectrum (CD_3OD) of Monomer **254**

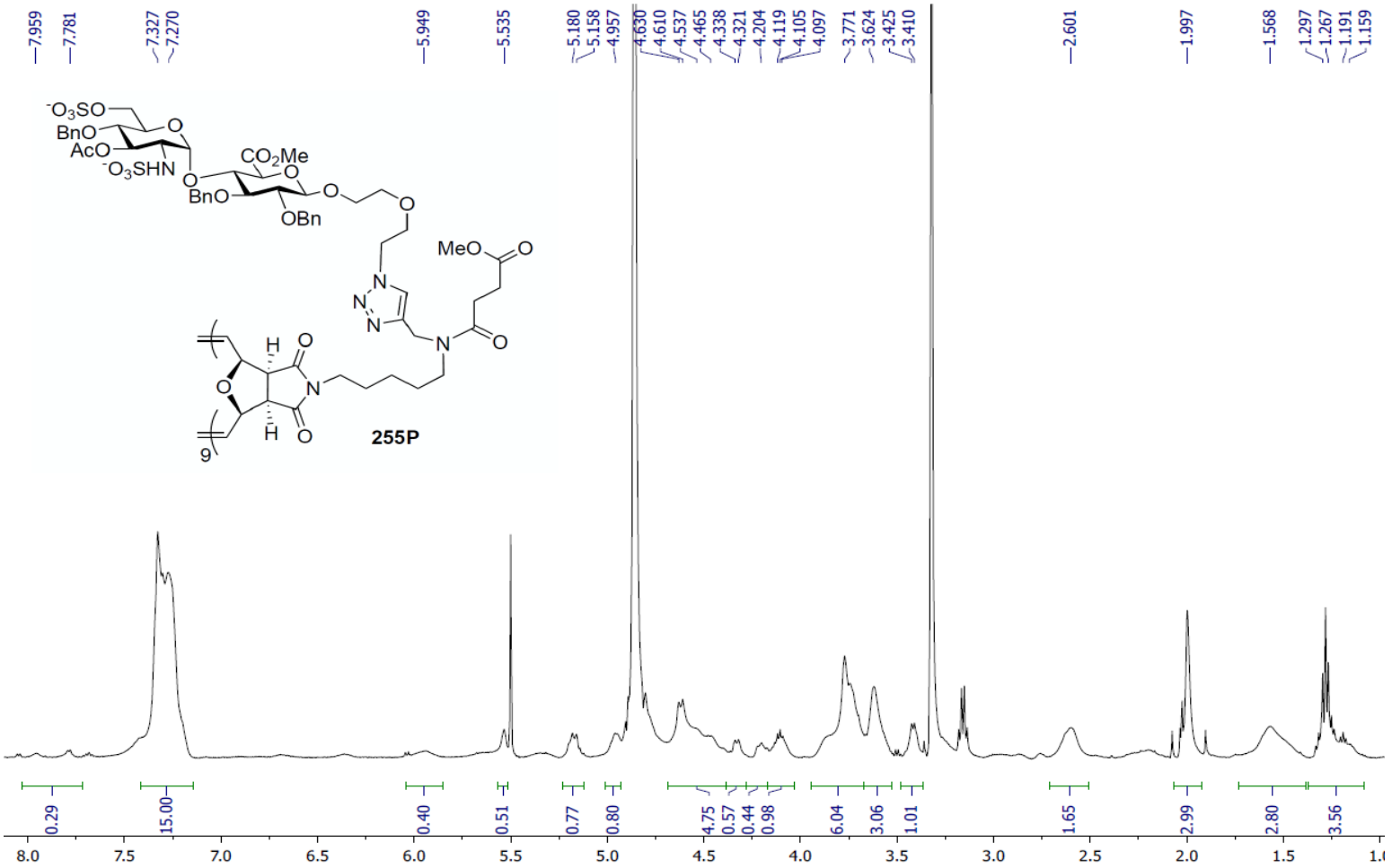


Figure A189. 500 MHz ^{1}H NMR Spectrum (CD_3OD) of Polymer **255P**

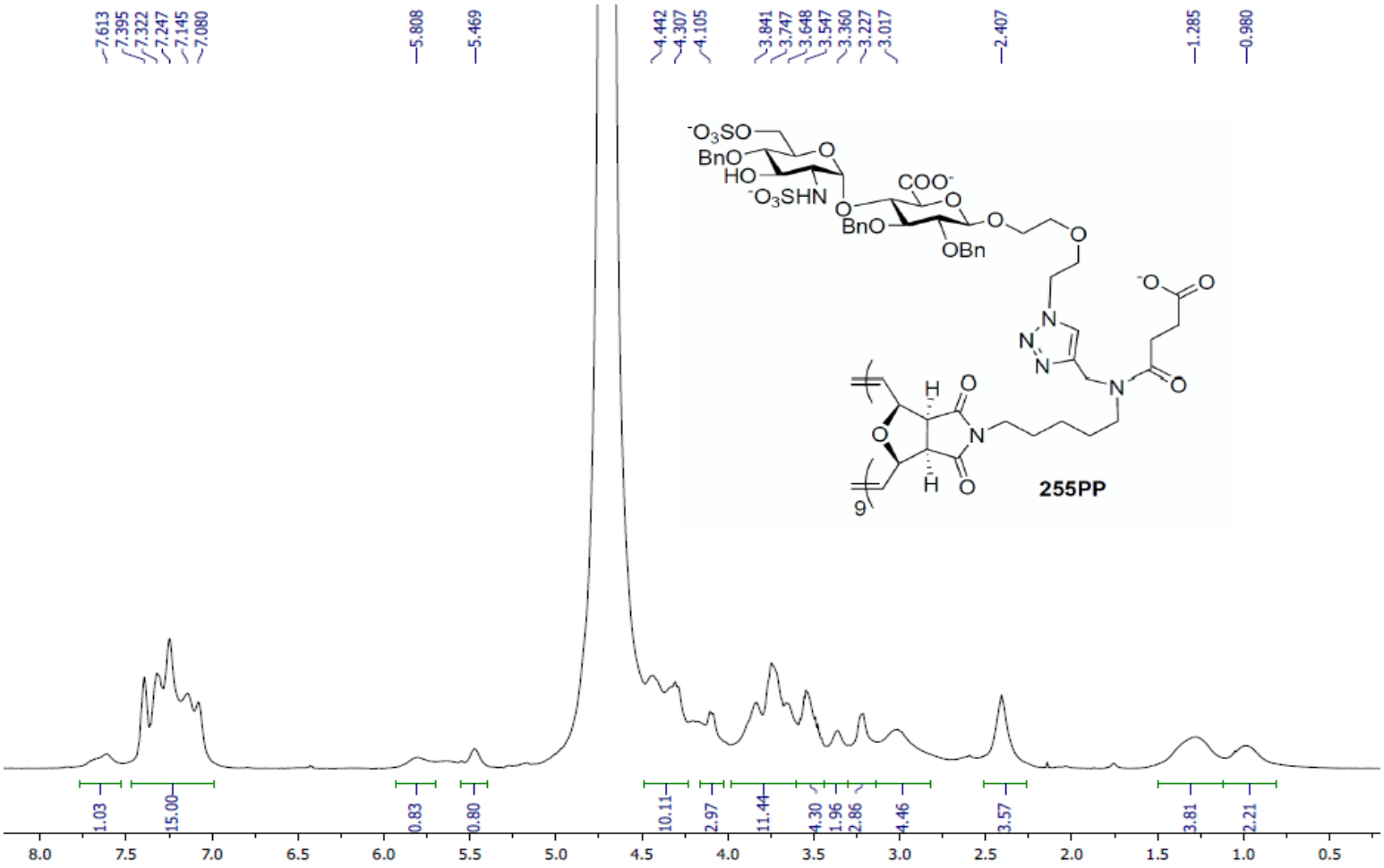


Figure A190. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **255PP**

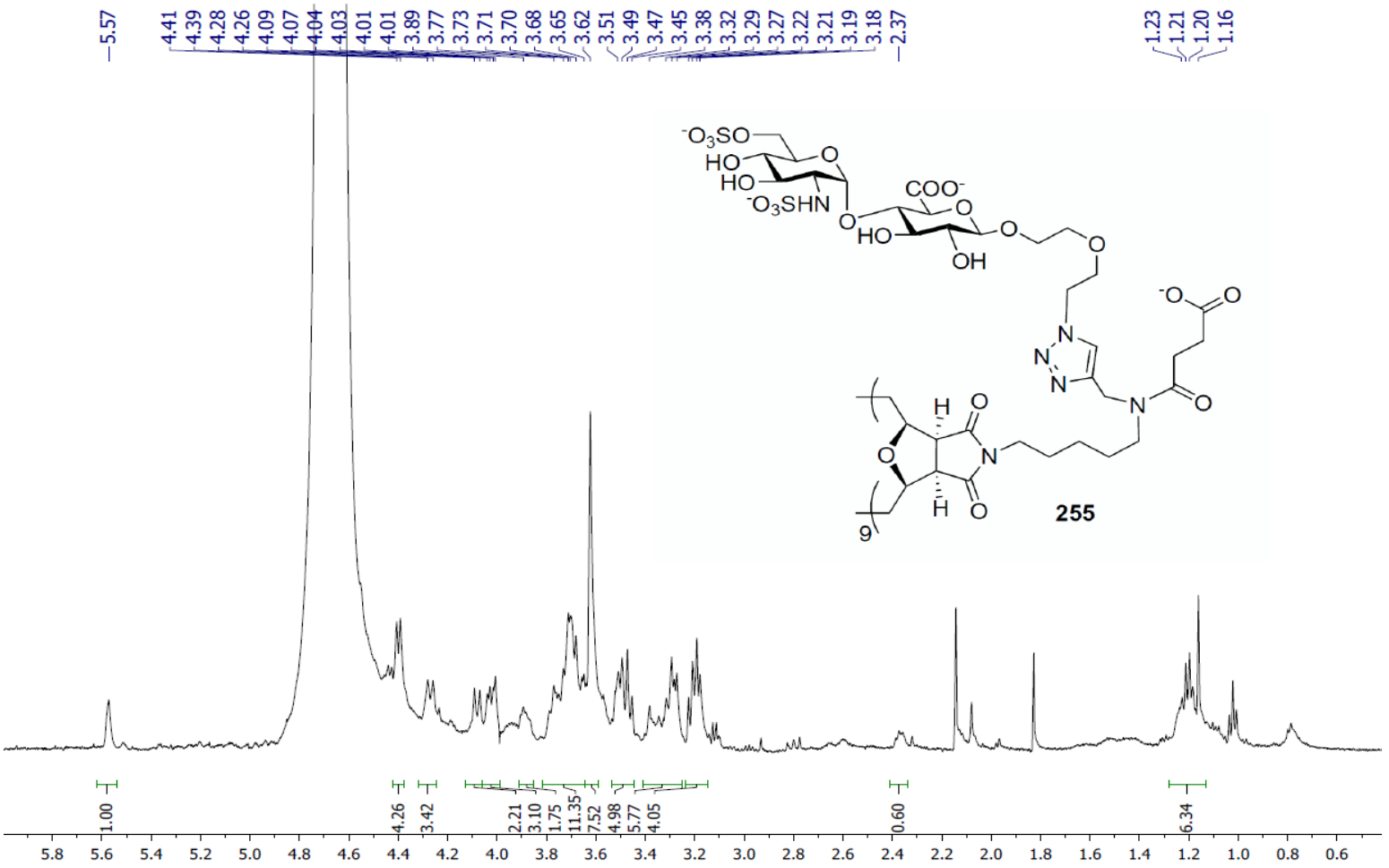


Figure A191. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **255**

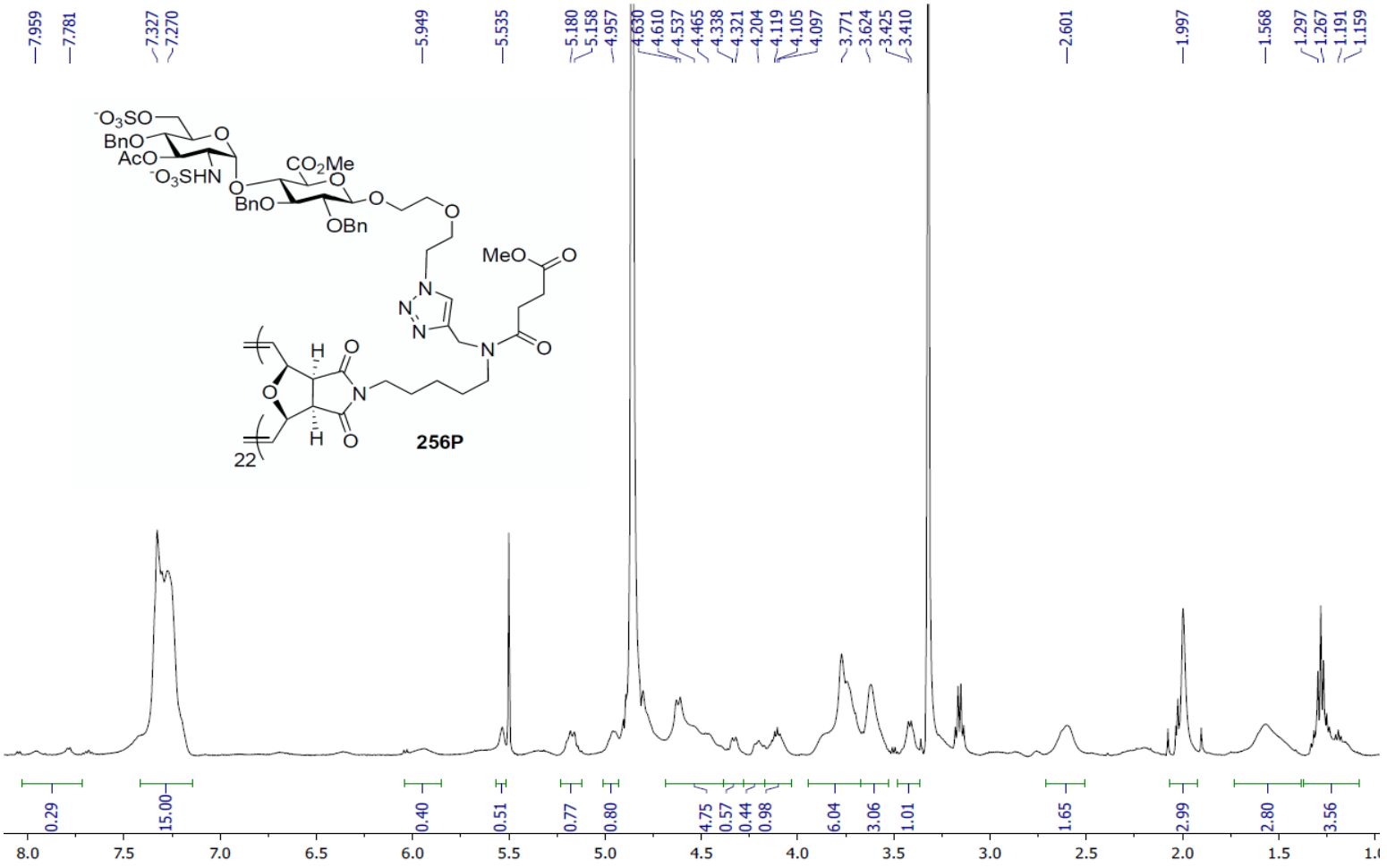


Figure A192. 500 MHz ^{1}H NMR Spectrum (CD_3OD) of Polymer **256P**

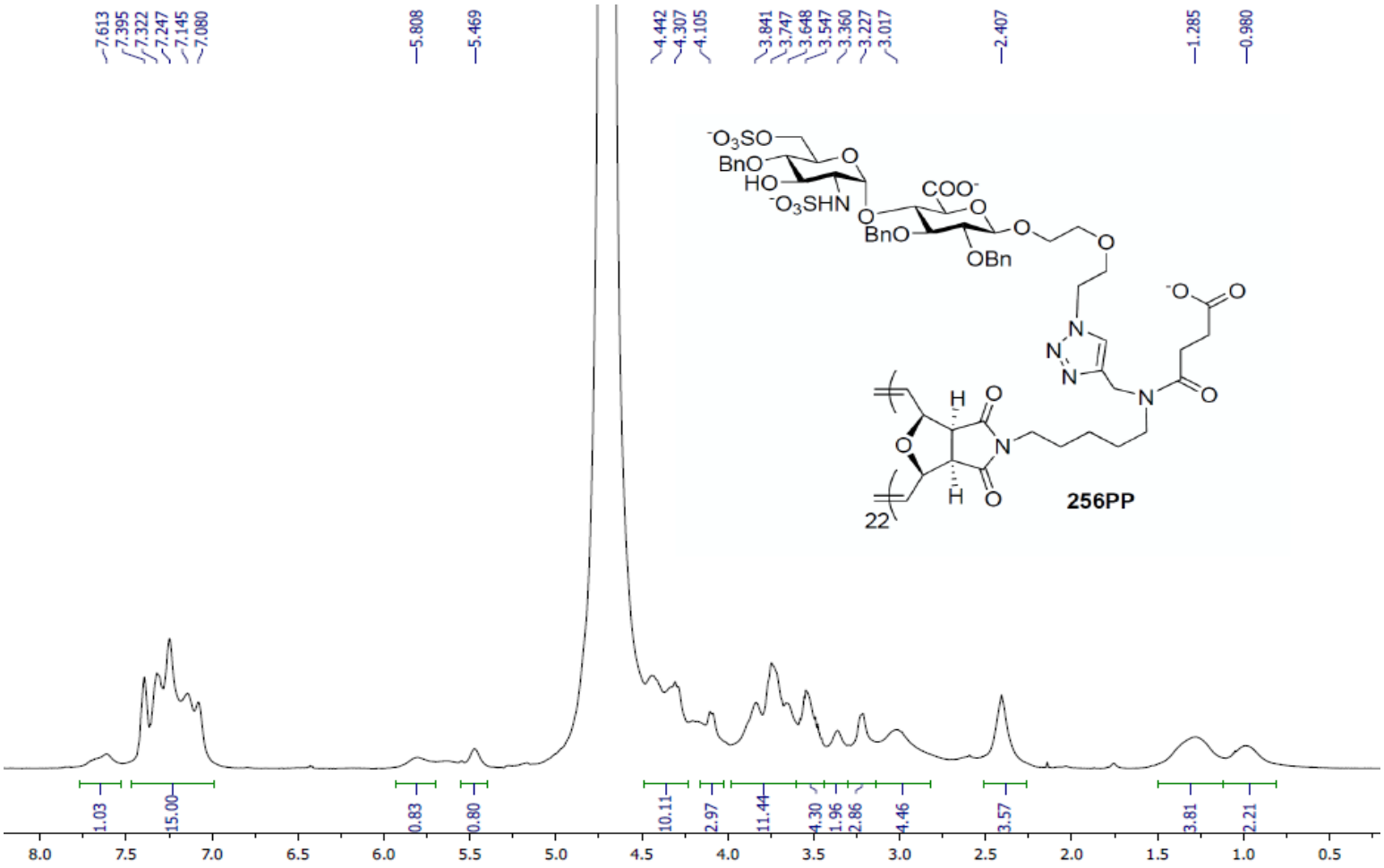


Figure A193. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **256PP**

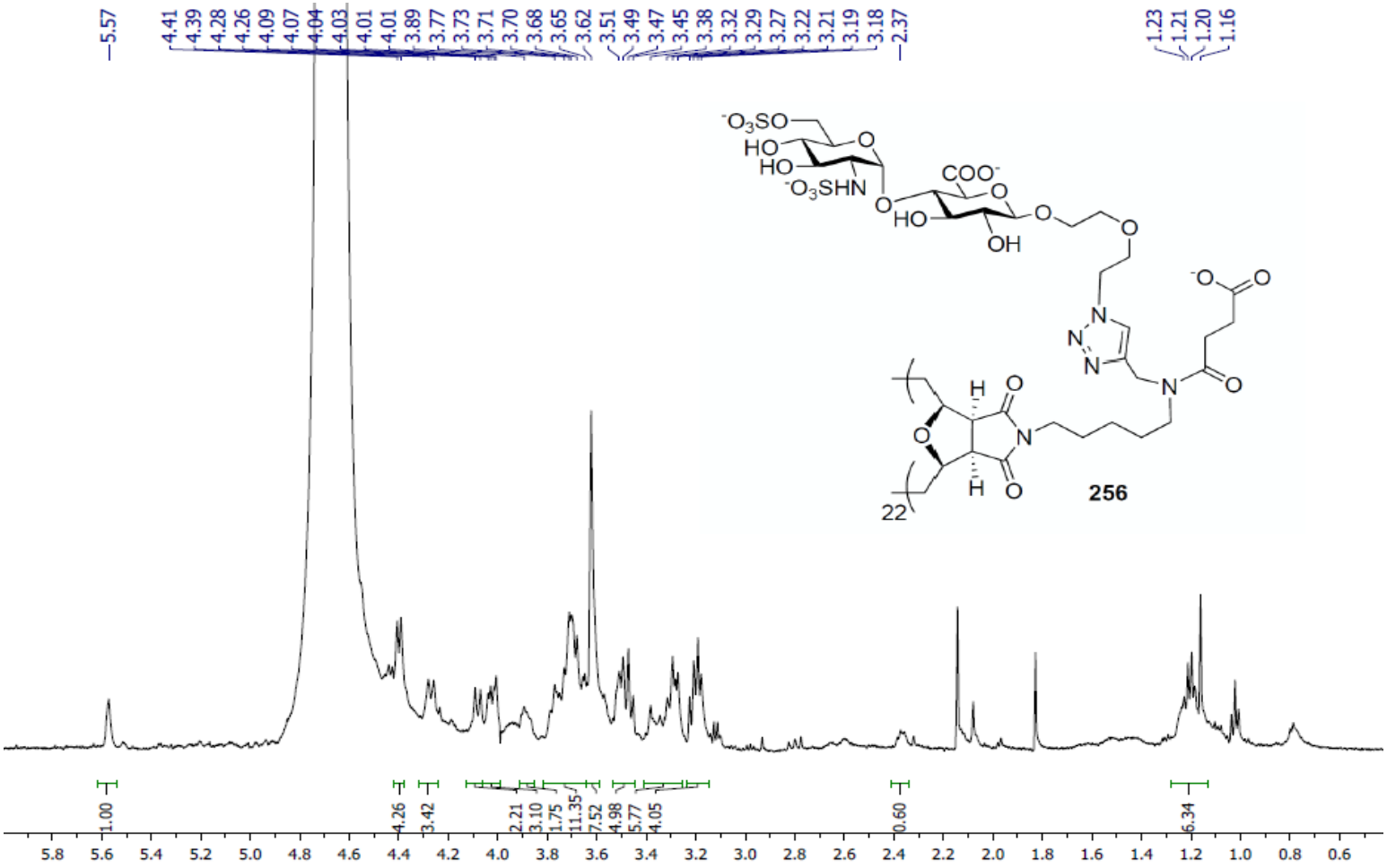


Figure A194. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **256**

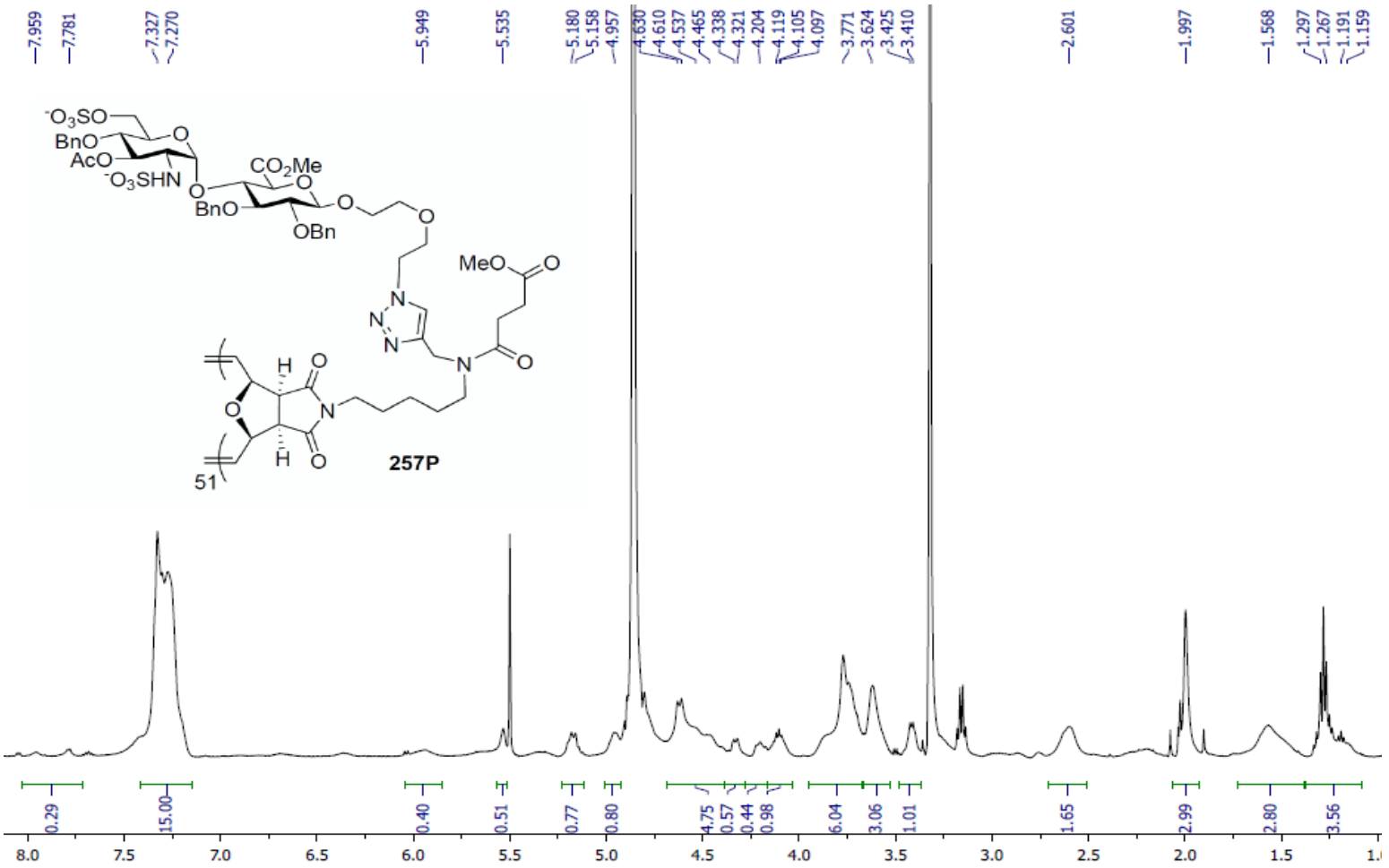


Figure A195. 500 MHz ^{1}H NMR Spectrum (CD_3OD) of Polymer **257P**

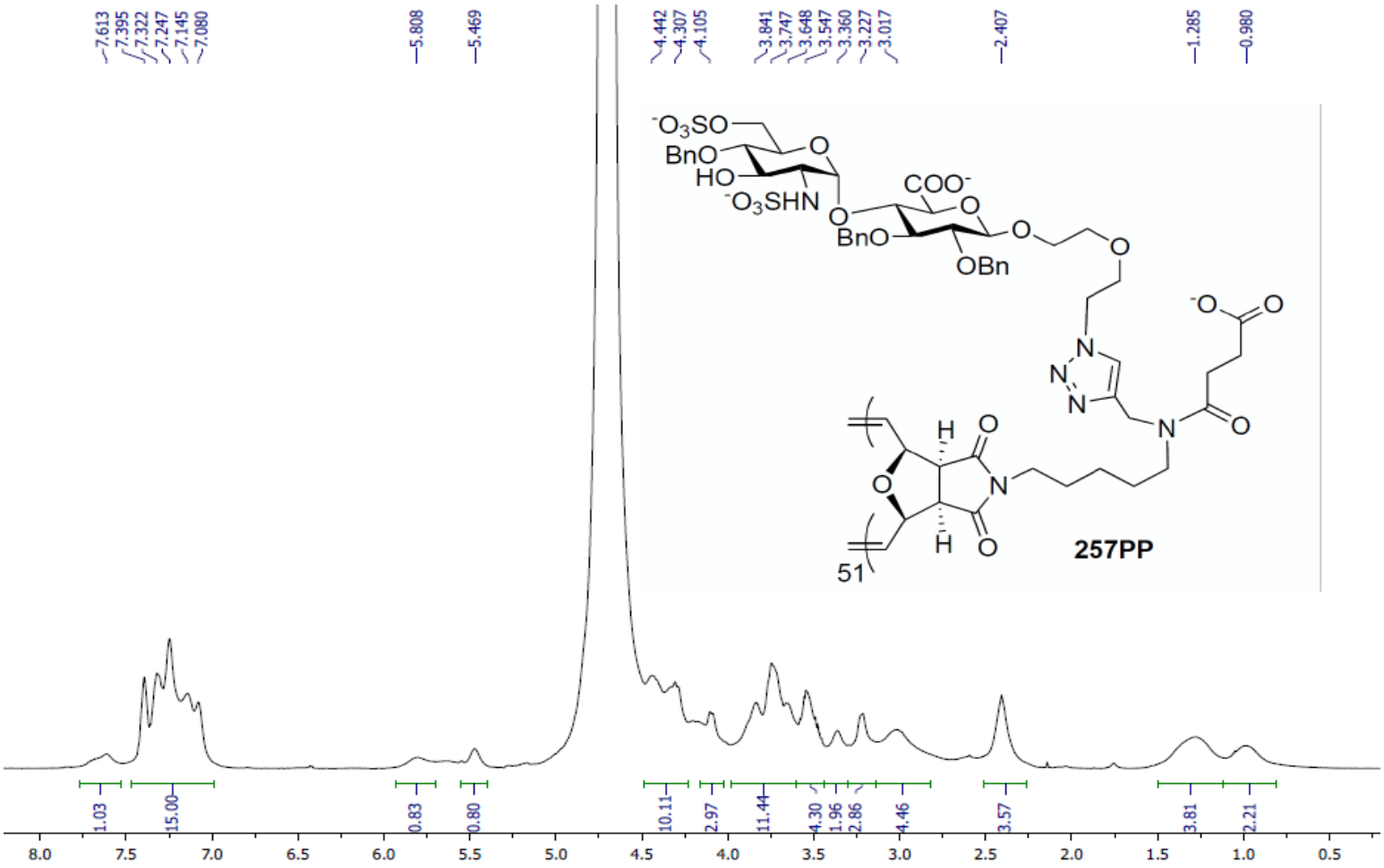


Figure A196. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **257PP**

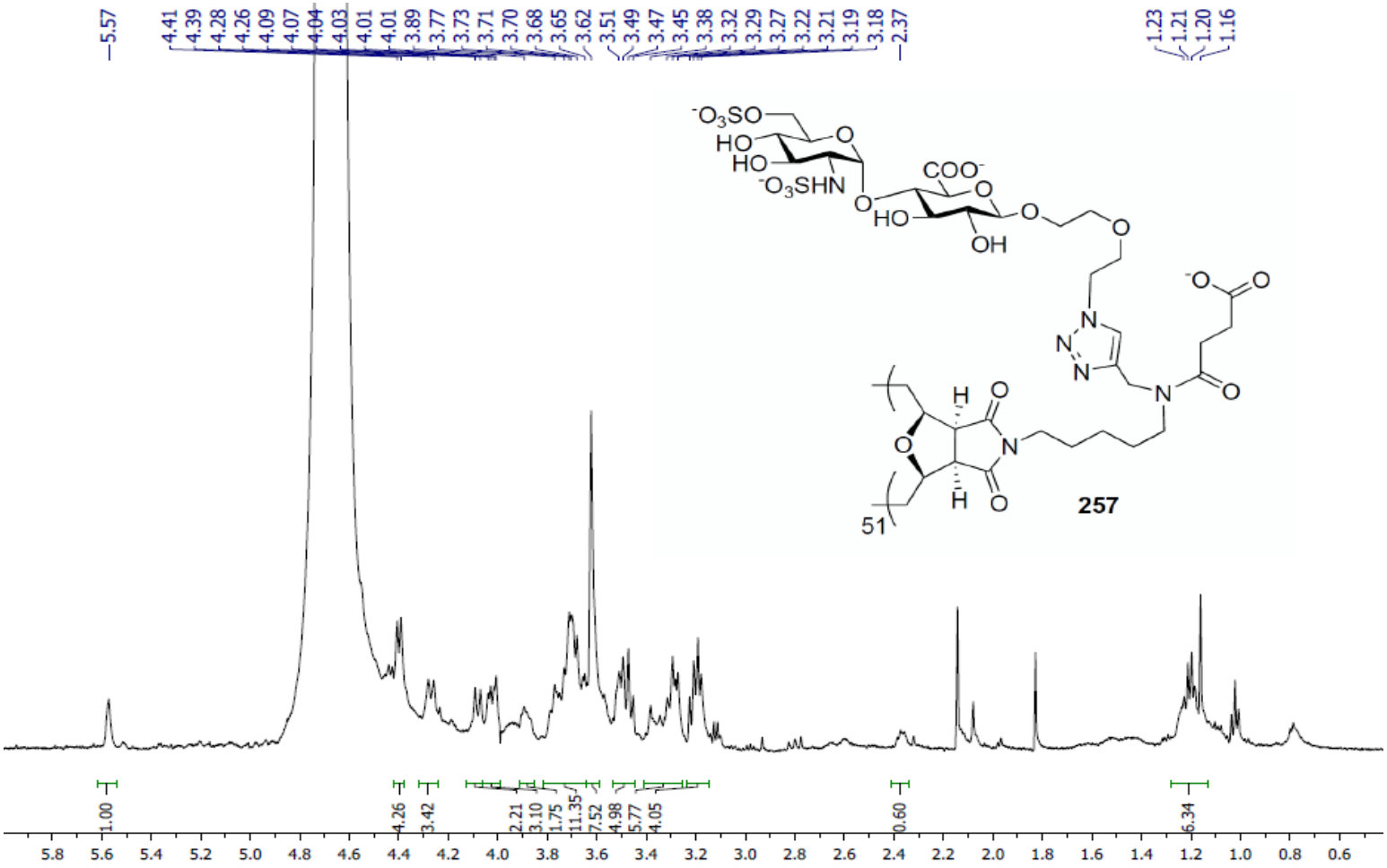


Figure A197. 500 MHz ^{1}H NMR Spectrum (D_2O) of Polymer **257**

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