Synthesis of oligosaccharides related to plant rhamnogalacturonan-II

Inaugural-Dissertation

to obtain the academic degree

Doctor rerum naturalium (Dr. rer. nat.)

submitted to the Department of Biology, Chemistry, Pharmacy

of Freie Universität Berlin

by

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2023

This work was conducted and written under the supervision of Prof. Fabian Pfrengle at the Max Planck Institute of Colloids and Interfaces in Potsdam (07.2018-02.2020) and the University of Natural Resources and Life Sciences in Vienna (03.2020-07.2023).

1st reviewer: Prof. Dr. Fabian Pfrengle

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Date of defense: 17.01.2024

Selbstständigkeitserklärung

Hereby I declare that my dissertation was draftet independently and I did not use other sources and means than the one stated. This dissertation has not been submitted before in a different examination procedure or at a different institution.

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28.07.2023, Vienna, Uwe Osswald

Acknowledgement

First and foremost, I'd like to express deep gratitude to my supervisor Prof. Dr. Fabian Pfrengle for outstanding supervision, for granting me tremendous freedom during my doctorate and for guidance through the hardships of both science and life.

I want to thank Prof. Dr. Peter Seeberger for providing a thriving and stimulating research environment at the Max Planck Institute of Colloids and Interfaces (MPIKG) and that he gave me the chance to participate.

Furthermore I would like to thank Prof. Dr. Beate Koksch for kindly agreeing to review this thesis.

Of course I would also like to thank Prof. Dr. Paul Kosma for welcoming us at BOKU so kindly and for reviewing NMR-assignments and names of tetra- and pentasaccharides with his great expertise.

Prof.Dr. J.D.C. Codee, thank you for hinting me towards the reactivity of Cbz carbamates.

Special thanks go to staff members from the MPIKG and BOKU: Eva Settels (MPIKG, support and introduction to HPLC-, mass spectrometry equipment), Olaf Niemeyer (MPIKG, NMR-facility), Felix Hentschel (MPIKG, employee organization). Dr. Markus Blaukopf (BOKU, NMR-facility, administration and general support with HPLC- and NMR equipment), Thomas Grasi (BOKU, purchase, maintainance and administration), and Ass.Prof. Dr. Andreas Hovinger-Horvath (BOKU, NMR-facility) for outstanding support and their relentless and indispensable efforts to improve scientific life.

This project was supported by EQ-BOKU VIBT GmbH and the BOKU Core Facility Mass Spectrometry.

For being such great lab mates I would like to thank my former and current colleagues:

From MPIKG: Deborah Senf, Max Bartetzko, Agata Baryzewska, Dr. Ignacio Álvarez, Dr. Sebastian Simonetti, Dr. Manish Chaube and Dr. Colin Ruprecht (now also at BOKU).

From BOKU: Irene Pasini, Charlie Lim, Alessandro Monti, Dr. Matteo Cattin, Katharina Obleser, Nivedia Ayinikkattuparambil Unmesh, Remya Kumbappilliyil Rajan, Sara Capellato, Dr. Duhwa Lee, Dr. Didier Ndeh, Tomás Vasícek, Daniele Zucchetta and Brian Sachini.

Many thanks to Dr. Manish Chaube for providing some peracetylated glucose thioglycoside and Dr. Nino Trattnig for providing Imidazole-1-sulfonyl azide hydrochloride.

I also gratefully acknowledge the contributions of my wonderfull hard working student interns who consented to contribute to this work:

Jonas Scholz synthesized fucose acceptor **81**, xylose thioglycoside **110** and galactose thioglycoside **96** as a student research assistant under my supervision.

Jakob Raffler has conducted research towards glucose building block **119** as a student research assistant under my supervision. He also synthesized the DMNPAA reagent and resynthesized intermediates of ABzOH and contributed in resynthesis of intermediates.

Karolina Dzedulionytė has resynthesized intermediates up to trisaccharide **146** and investigated alternative routes to access disaccharide acceptor **79** as an exchange PhD-student under my supervision.

Katharina Obleser took over the project as a new PhD-student one year ago. You are bearing the ring now. “I'm sorry I brought this upon you, my […] [girl]. I'm sorry that you must have to carry this burden. I'm sorry for everything.” *Bilbo Beutlin*

Finally, I want to thank my parents Doris and Uwe for their tremendous support and my sister Laura. Also I want to thank my parents in law Susanne and Jürgen for their tremendous support whenever we were in need. Of course I also want to express my deep love to my two kids Lars and Sven and my wife Xenia. Words cannot express my gratitude for the support and love she is sharing with me ever since we met.

Table of Contents

Abbreviations

%v	volume percent
%wt.	weight percent
2,2-DMP	2,2-dimethoxypropane
ABzOH	*o*-(hex-1-yn-1-yl)benzoic acid
Ac	acetyl
AGA	apiogalacturonan
Aka	Acceptor nucleophilic constant
Alloc	allyloxycarbonyl
anh.	anhydrous
api	apiose
aq.	aquatic
APT	attached proton test
Ar	aromatic ring
BA	brønsted acid
BAIB	bis(acetoxy)iodobenzene
BBA	2,3-dimethoxybutane-2,3-diyl
Bn	benzyl
BnA	benzylidene acetal
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCIP	close contact ion pair
CH	carbohydrate
CLIP HSQC	clean inphase heteronuclear single quantum coherence
CSA	camphorsulfonic acid
d	doublet
DCC	*N,N*'-Dicyclohexylcarbodiimide
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	3,4-dihydro-2*H*-pyran
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMNPA	2,2-dimethyl-2-(ortho-nitrophenyl)acetyl
DMNPAA	2,2-dimethyl-2-(ortho-nitrophenyl)acetic anhydride
DMP	Dess-Martin perjodinane
DMSO	dimethylsulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methyl pyridine
dt	doublet of triplets
E^+	electrophile
eq	equivalents
Et	ethyl
FA	formic acid
FC	flash chromatography
fuc	L-fucose
gal	D-galactose
galA	D-galacturonic acid
glc	D-glucose
glcA	D-glucuronic acid
hex	hexanes
HG	homogalacturonan
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HPTLC	high performance thin layer chromatography
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
imH	imidazole
*i*PrA	*iso*-propyl acetal
J	*coupling constant*
LA	lewis acid
LC/MS	liquid chromatography mass spectroscopy
LG	leaving group

L-gal	L-galactose
m	multiplet
MALDI-MS	matrix-assisted laser-desorption ionization-mass spectrometry
man	D-mannose
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
MS	molecular sieves
MTBE	*tert*-butyl methyl ether
NFM	*N*-formylmorpholine
NGP	neighbouring group participation
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
o. n.	over night
o. N s.	over N steps
OTf	triflate
p	pentet/quintet
PG	protective group
Ph	phenyl
Phth	phthalimidoyl
Pico	picolinoyl
PIDA	phenyliodine(III) diacetate
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
PP	polypropylene
ppm	parts per million
PTFAI	*N*-Phenyl-trifluoroacetimidate
PTFE	polytetrafluoroethylene
pyr	pyridine
q	quartet
quant.	quantitative
R	rest
Rf	retention factor
RG-I	rhamnogalacturonan-I
RG-II	rhamnogalacturonan-II
RGP	remote group participation
rha	L-rhamnose
RP	reversed phase
RRV	relative reactivity value
rt	room temperature
R_t	retention time
s	singlet
sat.	saturated
SSIP	solvent separated ion pair
t	triplet
TBACl	tetra-n-butylammonium chloride
TBAF	tetra-n-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
t-BuOH	*tert*-butylalcohol
td	triplet of doublets
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoracetic acid
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TLC	thin layer chromatography
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
tol	toluene
Tol	tolyl
TolSCl	4-toluoylsulfenyl chloride
Ts	tosyl
TTBP	2,4,6-tri-*tert*-butylpyrimidine
UV	ultraviolet light
X^-	counterion
XGA	xylogalacturonan
xyl	D-xylose

Abstract

Pectins are abundant polysaccharides in plant-derived biomass, with a plethora of possible applications such as usage as food preservative, formulation for cancer treatment and corrosion inhibitors for steels among many others. These acidic polysaccharides of high structural complexity have important biological functions in the plant cell wall. One domain of pectin, rhamnogalacturonan-II (RG-II) is the most complex oligosaccharide known to date. It is constructed from at least 13 different monosaccharides and at least 21 distinct glycosidic linkages. Despite its complexity, it is widely conserved in the plant kingdom. RG-II molecules form borate diesters with each other, an essential structure in the cell wall for plant growth. However, very little is known about the biosynthesis, the structure-function relationships and the three-dimensional structure of RG-II. Synthetic oligosaccharides that are well-defined and of high purity are very valuable tools to study RG-II. Here, a synthetic approach to a highly complex side chain A nonasaccharide equipped with an aminoalkyl linker for later immobilization on surfaces or fuctionalization with fluorescent dyes was developed. The main challenges were to design a retrosynthetic approach for the branched target nonasaccharide with a highly orthogonal protective group strategy, to find suitable glycosylation strategies to construct all nine glycosidic bonds, including four 1,2-*cis*-glycosidic bonds between monosaccharides, and the 1,2-*cis*-selective installation of an aminoalkyl linker at the reducing end. Using this strategy, small amounts of a protected version of the full side chain A analogue containing one backbone galacturonic acid were succesfully synthesized in 89 steps. Key transformation was a final [4+5]-glycosylation that requires further optimization. The results demonstrate that even the most complex oligosaccharides become synthetically accessible if modern synthetic glycochemistry methods are applied and further developed. Additionally, three linear side chain A fragments were synthesized. The obtained side chain A fragments are important tools for the investigation of RG-II biosynthesis. Furthermore, they may be useful to investigate structure-function relationships and the three-dimensional structure of the highly complex RG-II structure, which remain currently elusive. With the developed synthetic methods further RG-II fragments can be synthesized, expanding the molecular toolbox for studying RG-II biology.

Zusammenfassung

Pektine sind in pflanzlicher Biomasse reichlich vorhandene Polysaccharide, die eine Vielzahl von Anwendungsmöglichkeiten bieten, z. B. als Konservierungsmittel für Lebensmittel, in der Formulierung von Medikamenten für die Krebsbehandlung, als Korrosionsschutzmittel für Stähle und vieles mehr. Diese sauren Polysaccharide von hoher struktureller Komplexität haben wichtige biologische Funktionen in der pflanzlichen Zellwand. Eine Domäne des Pektins, Rhamnogalacturonan-II (RG-II), ist das komplexeste bisher bekannte Oligosaccharid. Es besteht aus mindestens 13 verschiedenen Monosacchariden und mindestens 21 verschiedenen glykosidischen Bindungen. Trotz seiner Komplexität ist es im Pflanzenreich weitgehend konserviert. RG-II-Moleküle bilden miteinander Boratdiester, eine für das Pflanzenwachstum unerlässliche Struktur in der Zellwand. Über die Biosynthese, die Struktur-Funktions-Beziehungen und die dreidimensionale Struktur von RG-II ist jedoch nur sehr wenig bekannt. Synthetische Oligosaccharide, die strukturell definiert und von hoher Reinheit sind, sind äußerst wertvolle Werkzeuge zur Untersuchung von RG-II. Hier wurde ein synthetischer Ansatz für ein hochkomplexes Nonasaccharid der Seitenkette A von RG-II entwickelt, das mit einem Aminoalkyl-Linker zur späteren Immobilisierung auf Oberflächen oder zur Funktionalisierung mit Fluoreszenzfarbstoffen ausgestattet ist. Die wichtigsten Herausforderungen bestanden darin, einen retrosynthetischen Ansatz für das verzweigte Ziel-Nonasaccharid mit einer hoch orthogonalen Schutzgruppenstrategie zu entwickeln, geeignete Glykosylierungsstrategien zu finden, um alle neun glykosidischen Bindungen, einschließlich vier 1,2-*cis*-glykosidischen Bindungen, zu konstruieren, und in der 1,2-*cis*-stereoselektiven Installation eines Aminoalkyl-Linkers. Mit der entwickelten Strategie wurden kleine Mengen eines geschützten Analogons der Seitenkette A, das eine Galakturonsäure aus dem Rückgrat der RG-II-Struktur enthält, in 89 Schritten erfolgreich synthetisiert. Die wichtigste Transformation war die abschließende [4+5]-Glykosylierung, die noch weiter optimiert werden muss. Außerdem wurden drei lineare Seitenkette-A-Fragmente synthetisiert. Die Ergebnisse zeigen, dass selbst die komplexesten Oligosaccharide synthetisch zugänglich sind, wenn moderne Methoden der synthetischen Glykochemie angewendet und weiterentwickelt werden. Die hergestellten Fragmente sind ein wichtiges Werkzeug für die Untersuchung der RG-II-Biosynthese. Darüber hinaus sind sie sehr nützlich, um Struktur-Funktionsbeziehungen und die dreidimensionale Struktur der hochkomplexen RG-II-Struktur zu untersuchen, die derzeit noch nicht bekannt sind. Mit den entwickelten Synthesemethoden können weitere RG-II-Fragmente synthetisiert werden, wodurch der molekulare Werkzeugkasten für die Forschung im Bereich der RG-II-Biologie deutlich erweitert werden kann.

1. Introduction

1.1 Biomass as sustainable resource

The combustion of fossil resources and associated emission of greenhouse gasses, such as CO_2, by humans is causing global climate change.[1] In addition, industrial products made from fossil resources are raising growing concerns, as they have been identified as major accumulating and poorly reversible pollutants[2] in the biosphere due to very slow biodegradation[3]. Fossil fuel derived plastic products decay in the environment to form plastic debris and among others microplastic particles, which have been widely found basically everywhere, e.g. in soils[4], the arctic[5], the marine environment[6] and even in human bodies[7]. Unfortunately, the problematic short-lifetime single use plastic packaging plays an important role in modern day society and a ban of these products could further increase greenhouse emissions and water- and energy consumption.[8] Due to the resulting long-term consequences of current plastic use and already existing plastic pollution, it becomes evident that more sustainable and renewable solutions must be found. Biomass is a sustainable, renewable and biodegradable resource, which does not produce the irreversible greenhouse emissions undisputably linked with fossil resources[9]. The by far most abundant component of biomass are carbohydrates derived from plants or algae. During photosynthesis these organisms use sunlight, water and CO_2 to synthesize the carbohydrates required for their growth. Carbohydrates have been used since ancient times as food and energy source, construction material and to create consumer products, such as fabric, vessels or paper. However, with a growing population in the Anthropocene, the human impact on the earth system has grown significantly[10]. The overall material output of humans likely already exceeded the amount of overall biomass on earth.[11] Carbohydrate-based biomass is therefore a renewable but also limited resource as it requires soil, space and water.[12] As a result, the available biomass must be used much more efficiently, to meet the growing demands, without affecting remaining ecosystems. To achieve this, a much more thorough and detailed understanding of carbohydrate-based biomass is required.

1.1.1 The plant cell wall

The plant cell wall makes up most of the dry plant material[13] and therefore plant derived biomass. It is a complex and strong fiber composite structure, defining the size and shape of plant cells and cumulatively determining the plant's mechanical properties. It withstands the high internal osmotic pressures of plant cells (0.1 to 3 MPa)[14] and is highly diverse in composition and setup, differing between plant species, cell types and even within a single cell.[15] The cell wall also allows biological signaling from one cell to another cell and can trigger defence responses to plant pathogens.

Plant cell walls can be categorized into two types, the primary and the secondary cell wall.

The primary cell wall is thin and flexible with a water content of around 70%. It is formed during cell growth and its dry mass consists of 10% proteins and 90% polysaccharides. The polysaccharide fraction consists of cellulose, hemicelluloses and pectins. In most plants the crystalline cellulose fibers make up 15-40% of the primary cell wall's dry mass. These fibers are crosslinked with hemicelluloses (20-30%) to strengthen the composite. The composite is intertwined with pectic polysaccharides that make up 30-50% of the dry mass and are vital for cell wall hydration.[16] As growth of certain cell types stops, the secondary cell wall is formed. It is much thicker, more stable, less hydrated and more hydrophobic. The secondary cell wall consists also of crystalline cellulose fibers crosslinked with hemicelluloses. Additionally, lignin is deposited to provide stiffness, which makes up up to 30% of the dry weight.[17]

1.1.2 Pectin - applications in research and industry

A sustainable approach to make more efficient use of the available biomass is by direct conversion of waste products to high value products, avoiding lengthy, energy- and waste-intensive multistep-preparations. Besides other major polysaccharide fractions commonly used on industrial scale, such as cellulose and hemicellulose, the pectin fraction, abundant in primary plant cells, represents a highly attractive renewable resource with low production costs and broad availability from agro-industrial residues. The properties of pectins, such as molecular weight and distribution, degree of esterification, methoxylation and acetylation and branching with neutral carbohydrate residues, can be controlled by the choice of agroindustrial residue used for extraction and the used extraction method. Pectic polysaccharides are easily extracted from biological waste products by hot aqueous acidic solutions and subsequently precipitated with alcohols or polyvalent metal ions.[18] Isolated pectin posesses outstanding properties that allow broad applications in the food-, pharmaceutical and biomedical industries and potentially other fields. In general, pectin tends to form gels in acidic media that are dissolved under basic conditions. In the food industry, pectin is used as a safe non-toxic ingredient, which can gel, thicken, stabilize, foam and emulsify products. Its antioxidant and metal-chelating capacities can reduce the need for synthetic preservatives. Additionally, pectin is a natural indispensable part of the human diet and its ingestion is known to have an important probiotic effect on the human intestine and helps to reduce glucose and LDL cholesterol levels in the blood. In form of films and coatings it may substitute some petrochemical-based food packagings, alleviating the associated pollution. Biomedical products derived from pectin, including novel drug delivery hydrogels, coatings, membrane production and healing-promoting wound dressings, are currently researched. It has also potential in cancer treatment as biocompatible, biodegradable drug delivery system with adjustable release properties. Furthermore, pectin can be used as a corrosion inhibitor for steels,

avoiding the use of commonly employed toxic chemical inhibitors.[18, 19] Given this vast field of applications, a deeper understanding of pectin biosynthesis and structure-function relationships is required to refine and improve applications and generate new application possibilities.

1.1.3 Pectin structure and function

Pectin is indispensable for plants, as it grants flexibility and mechanical strength to the cell wall[17] and supposedly controls cell wall porosity, adhesion to neighbouring cells and the ionic environment.[14] In addition to hydrating the plant cell wall, pectin may play a role in mitigating dehydration stress and the impact of attacks of fungal pathogens.[20] Pectin is the structurally most complex class of polysaccharides in nature, but relatively conserved between plant species and cell types. The major monosaccharide component is galacturonic acid, from which substantial parts of the backbone in pectin is constructed. Pectin contains four major domains named homogalacturonan (HG), rhamnogalacturonan-I (RG-I), xylogalacturonan (XGA) and rhamnogalacturonan-II (RG-II).

HG, often referred to as pectins 'smooth region', represents around 65% of the macromolecule. Structurally, it is made up of α1→4-linked galacturonic acid chains, with a degree of polymerization of up to 150 monosaccharide units and varying degrees of acetylations at C-2 and C-3 as well as methyl-esterifications. The degree of methyl-esterification determines, among other factors, the gelling ability, as the non-esterified regions of HG are known to complex calcium and cross-link with one another,[21] while the esterified regions aggregate through hydrophobic interactions.[22] These mechanisms are known to be involved in the regulation of mechanical strength and anisotropic growth of the plant (e. g. in leaf formation).[23] It was suggested that the initially methyl-esterified chain undergoes controlled deesterification *in vivo* by pectin methyl esterases to deposit the structure in the cell wall.[24, 25] In contrast to linear HG, other pectin domains are branched with various side chains. In aquatic plants the cell walls also contain apiogalacturonan (AGA)[21]. The structure of AGA resembles a HG backbone, with β1→2 and/or β1→3 linked apiose and apiobiose (Api-β1→3'-Api-1-) residues.

The most abundant structure of XGA is a HG backbone substituted with β1→3 linked xylose. The xyloses can bear also another β1→2 linked xylose. XGA is present in cell walls of reproductive plant tissues[25], fruits and seeds[26], and roots[27]. The function of XGA has not been identified yet, but it is hypothesized to improve resistance to pathogen attacks by increasing resistance to enzymatic digestion of pectins in root cells.[27, 28] It also may be associated with plant cell detachment.[26]

RG-I constitutes 20-35% of pectin[17, 21]. Its backbone is constructed from a α1→4-galacturonic acid-α1→2-rhamnose repeating unit and is predicted to adopt a threefold helical structure.[21] While the C-2 and C-3 positions of galacturonic acid may be acetylated, no esterification of C-6 occurs in RG-I.

Approximately 50% of the rhamnose moieties are substituted with side chains at the C-4 position. Those side chains include neutral carbohydrate chains such as arabinans, galactans-, and arabinogalactans, but possibly also possibly glucuronic acid.[25]

Finally, RG-II constitutes up to 10% of pectin, having a highly complex molecular structure that is discussed in the next paragraph.[17, 21] To date the connectivity of these domains is still under debate. Recent data suggest a model in which RG-I serves as a core structure ramified with neutral sugar side chains (arabinans, galactans, arabinogalactans) and XGA domains. The HG chains may be attached to the reducing and non-reducing ends of RG-I. RG-II (**1**) may be attached to the outer regions of HG, as it needs to be accessible for dimerization. Due to the lack of appropriate analytical tools the real *in muro* structure remains elusive.[29]

1.1.4 Rhamnogalacturonan-II

Structure and function of the rhamnogalacturonan-II (RG-II) domain (**1**) is of high interest to both biologists and chemists and poses long standing open questions. RG-II (**1**) is the most complex oligosaccharide structure known to date (Figure 1). The structure consists of six side chains (A to F), which are linked to a HG-type backbone, with the highly ramified side chains A and B being the largest substructures. RG-II (**1**) is constructed by at least 21 distinct glycosidic linkages and contains at least 13 different monosaccharides[30] including rare sugars such as 2-keto-3-deoxy-D-manno-octulosonic acid (KDO), 2-keto-3-deoxy-D-lyxo-heptulosaric acid (DHA), L-aceric acid, D-apiose, L-galactose, 2-O-methyl D-xylose and 2-O-methyl L-fucose.[17] Recent discoveries have led to a revised proposed structure of RG-II (**1**), as the originally described β1→3'-linked Rha-Api bond was discovered to be α1→3' instead.[30]

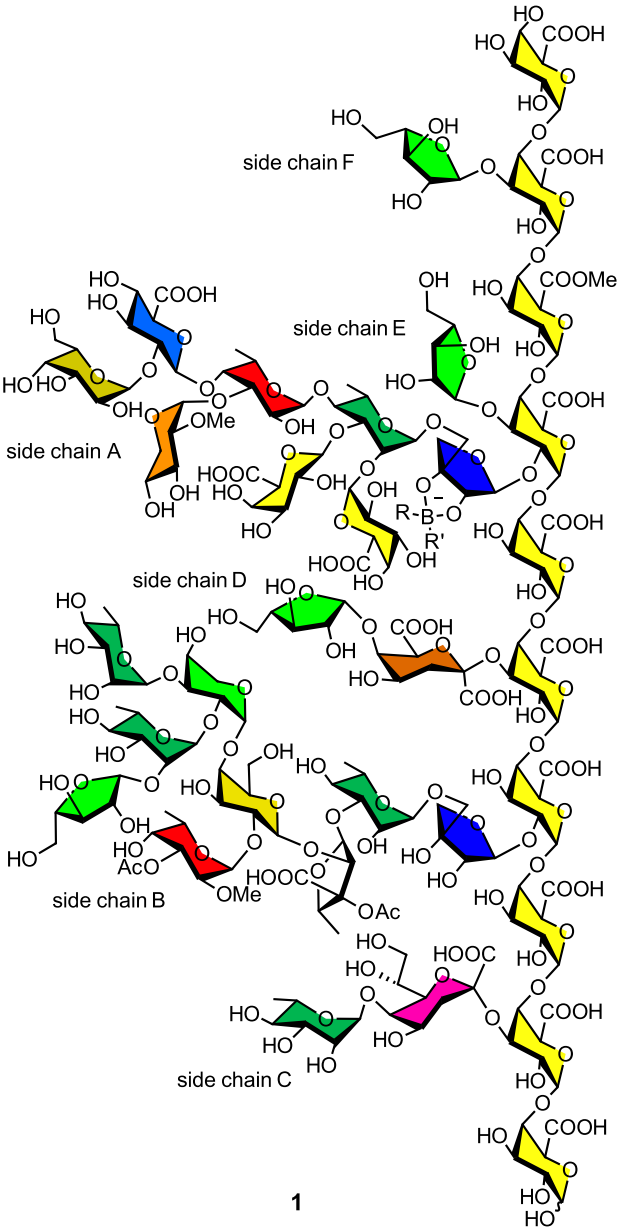


Figure 1: Most recent proposal of the rhamnogalacturonan-II structure based on the work of Ndeh et al.[30]

Plants and all other organisms achieve biosynthesis of oligosaccharides by a complex enzymatic machinery. Once glycosyl donors have been synthesized in the cell, they can undergo reaction with glycosyl acceptor substrates, catalyzed by highly selective enzymes called glycosyl transferases. Only very few glycosyl transferases involved in RG-II's biosynthesis are known to date.[31]

Despite its structural complexity and the resulting enormous biosynthetic effort plants have to expend, RG-II is widely conserved in the plant kingdom. All vascular plants produce RG-II (**1**).[32, 33] Only minor structural variations are reported, mostly limited to variations in methylation and acetylation patterns[34] and varying rhamnosylation patterns at the non-reducing ends of side chain B.[17, 35] About 45% of L-fucose is substituted for L-galactose in side chain A of *A. thaliana.*[36]

Once RG-II (**1**) is assembled, it forms a dimeric structure, as apiose moieties in the side chains A of two RG-II molecules (**1**) become esterified with boronic acid[21, 22, 33, 37] by a mechanism still under investigation.[14, 31, 38] More than 90% of RG-II (**1**) is dimerized with boronic acid in the plant cell wall.[31] The boron diester formation has been identified as crucial for plant growth and survival as alteration in the biosynthesis of RG-II by knockout experiments had detrimental effects on the mutants.[31, 39] RG-II (**1**) can be isolated from fermented beverages such as red wine, which has been exploited for research.[40] Despite enormous analytical efforts by scientists over the last decades,[17] RG-II (**1**) structure-function relationships and its biosynthesis remain currently elusive, making RG-II (**1**) one of the most intriguing open questions in vascular plant research.

To resolve some long standing questions regarding RG-II (**1**), synthetic fragments of defined structure represent important molecular tools.[41] For example, well defined synthetic fragments can serve as acceptor substrates for enzyme-catalyzed glycosylations from the biosynthetic pathway for RG-II (**1**) assembly *in vivo* or they may be used for the generation of fragment binding antibodies, that help to locate the precise antibody binding epitope *in vivo*. Recently described methods, such as a glycan array-based assay, allow identification and characterization of glycosyl transferases and help to provide an improved understanding of the biosynthetic pathways in plants.[42]

1.2 Oligosaccharides in synthesis

Carbohydrates are structurally highly diverse, with a plethora of elemental and stereochemical varieties. Carbohydrates possess a huge number of functionalities, making selective transformations an enormous synthetic challenge. This problem is solved in nature by selective enzymes, such as glycosyltransferases, designed to assemble oligosaccharides from monosaccharide donors. However, in many cases still highly heterogeneous polysaccharides are produced, particularly in the case of homooligomeric glycans, such as the hemicelluloses in plants or the glycosaminoglycans in the extracellular matrix of mammalian cells. But also, in RG-II (**1**) in *A. thaliana*, L-fucose can for example be substituted with L-galactose in side chain A, showing that even highly specific and selective enzymes can produce variations in naturally occurring oligosaccharides. This makes the isolation, purification and characterization of well-defined oligosaccharides from nature a challenging task. However, well-defined oligosaccharides can be obtained by synthetic chemistry. To achieve the chemical synthesis of oligosaccharides, a deep understanding of the chemical properties of the large number of functional groups and respective protective groups (PGs) is required.[43]

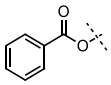
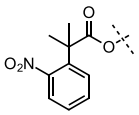
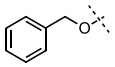
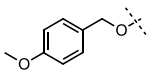
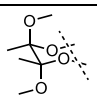
1.2.1 Protective groups

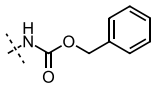
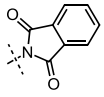
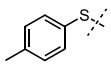
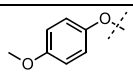
One of the most important tools for the chemical synthesis of oligosaccharides are protective groups (PGs). As carbohydrates bear several hydroxy functions, it is in most cases not possible to perform selective transformations at one specific position. To achieve regioselectivity in chemical reactions, PGs are a crucial tool. PGs are introduced to functional groups to prevent them from undergoing a certrain transformation. When this transformation has been carried out, the PGs are cleaved to restore the original functional group in a molecule. To successfully achieve this, many requirements must be fulfilled.

First of all, a PG's installation must be mild, selective and reproducible. The PG must be highly stable to as many reaction conditions as possible. After the desired transformation the PG must be cleavable under mild and selective conditions. As the introduction and cleavage of PGs are no productive steps in a synthetic pathway, the fewest possible of these transformations should be performed. Furthermore, they must be as high yielding as possible and the reagent used for introduction must be cheap, commercially available or easily accessible. The reagent for PG installation should neither be enantiotopic nor diastereotopic, as this would complicate NMR-analysis of the protected compound. Ideally, the NMR-signals of an installed PG should not overlap with other signals in the NMR-spectra. Oftentimes several functional groups must be protected and deprotected selectively over the course of a synthetic pathway. This requires the used PGs to be orthogonal, so that the cleavage conditions solely affect one type of PG and leave the others unaffected.

In case of complex carbohydrate synthesis not only a few but many functional groups must be addressed selectively, making it very challenging to fullfill all prerequisites. Furthermore, the nature of the PGs affects the reactivity and stereoselectivity of carbohydrate building blocks drastically, particularly concerning neighboring group participation (NPG) and remote group participation (RGP) effects or donor leaving groups (donor-LG), which will be discussed in the next paragraph. Because of these reasons, a well elaborated and robust PG-strategy is imperative for the synthesis of complex oligosaccharides. A usefull strategic consideration is the classification of PGs in two sets: permanent and transient. Permanent PGs are used to mask functional groups from the early beginning of a synthesis all the way to the last synthetic steps (final or global deprotections) and should therefore meet as many prerequisites as possible to obtain the highest possible orthogonality. Transient PGs are used to mask functional groups that have to be accessed at a later stage within the synthesis. For choosing transient PGs, the experimentator might select less restrictively. Less favourable properties, such as lability to certain conditions, migration tendency or the need for harsh conditions for removal may be tolerated to achieve the desired transformation, as long as side reactions can be minimized during the synthetic steps the temporary PG is intended for.

In the following table the introduction, cleavage and general properties of the PGs used in this work are summarized. Further information is provided in the literature.[44]

functional group to protect	protective group	abbr.	introduction	cleavage	properties	side reactions[44]	usage
alcohol, anomeric hemiacetal		AcO	1. Ac_2O, Pyridine, DMAP 2. Ac_2O, NEt_3 3. NaOAc, Ac_2O	1. NaOMe, MeOH 2. NaOMe, guanidinium nitrate, MeOH, CH_2Cl_2 (Ac > Bz selectivity)	very base labile, acid labile, NGP, RGP	migration, hydrolysis, orthoester formation	permanent, transient
alcohol		BzO	BzCl, NEt_3, CH_2Cl_2	NaOMe, MeOH	acid stable, base labile, RGP, NGP	migration, orthoester formation	permanent
alcohol		DMNPAO	DMNPAA, TMSOTf, CH_2Cl_2, MS 4Å[45]	Zn, AcOH, $CuSO_4$, Dioxane, H_2O[45]	very stable, strong RGP,[46] strong NGP, rapid cleavage (Thorbe-Ingold effect)[45]		transient
alcohol		BnO	1. NaH, BnBr, DMF 2. Ag_2O, BnBr, DMF	H_2, Pd/C	stable	oxidative cleavage	permanent
alcohol		PMBO	NaH, PMBCl, DMF	DDQ, CH_2Cl_2, phosphate buffer	slightly acid labile	acidic cleavage, oxidation to PMB acetals	transient
cis-diol		iPrA	DMP, CSA, acetone	AcOH 80% aq., 60°C	acid labile, base stable, cyclic PG	undesired acidic cleavage	permanent, transient
cis-diol, 4,6-diol		BnA	$PhC(OMe)_2$, *p*TsOH, Tol	1. H_2, Pd/C 2. BH_3·THF, $Cu(OTf)_2$ (selective reduction to Bn)	acid labile, base stable, cyclic PG, selective reduction to Bn possible	acidic cleavage	transient, permanent
trans-diol		BBA	diacetyl, TMOF, CSA, MeOH	90% TFA aq., CH_2Cl_2	very stable, cyclic PG, slightly acid labile	glycosidic bond cleavage upon BBA hydrolysis	transient

alcohol		TMSO	TMSCl, NEt_3, CH_2Cl_2	TBAF, THF, phosphate buffer	very base labile, very acid labile	migration, hydrolysis	transient
alcohol		TBDMSO	TBDMSCl, Im, CH_2Cl_2	TBAF, THF, phosphate buffer	slightly acid labile, slightly base labile	migration	transient
alcohol		OTFA	TFA_2O, NEt_3, CH_2Cl_2	buffer pH 7	acid stable, rapid hydrolysis, RGP, NGP	hydrolysis	transient
carboxylic acid		COOMe	$TMSCHN_2$ in hexanes, Tol, MeOH	LiOH, H_2O_2, MeOH	base labile	increased α-acidity, trans-esterfication	permanent
amine		NHCbz	CbzOSu, EtOAc CbzCl, NEt_3, CH_2Cl_2	1. H_2, Pd/C 2. H_2, Pd/C NH_4OAc (Cbz > Bn selectivity)	stable, slight acid sensitivity	*N*-alkylation during hydrogenation	permanent
amine		N_3	$ImSO_2N_3$·HCl, NEt_3, $CuSO_4$, MeOH	H_2, Pd/C	stable, sensitive against phosphine nucleophiles, slight sensitivity against electrophiles, slightly acid labile	1,3-dipolar cycloadditions	permanent
amine		NPhth	from OH: Phthalimide, PPh_3, DIAD, CH_2Cl_2	N_2H_4, MeOH	stable, possibly challenging to cleave	ring-opening with nucleophiles	transient
anomeric hemiacetal		-not required	H_2SO_4, propargyl alcohol	-not required	slightly acid labile	reaction with electrophiles	permanent
aldehyde, anomeric hemiacetal		STol	from Ac-ester: BF_3·Et_2O, TolSH	NIS, TFA, CH_2Cl_2/H_2O[47]	slight acid sensitivity, base stable, sensitive against soft electrophiles,	oxidation, aglycon transfer in glycosylation[48]	transient, donor-LG
anomeric hemiacetal		OPMP	from -STol: NIS, TfOH, *p*-MeO-PhOH	CAN, MeCN, H_2O	acid sensitive		permanent

1.2.2 The glycosylation reaction

In order to chemically synthesize complex oligosaccharides, chemists have developed ways to stereoselectively create glycosidic bonds between two carbohydrate building blocks. Usually the reducing end of one protected coupling partner is equipped with a suitable leaving group (LG) to form a glycosyl donor. A partially protected carbohydrate bearing one or more free hydroxy groups is referred to as the glycosyl acceptor. Upon activation with a promotor, the LG is expelled from the donor and in many cases liberates an oxocarbenium ion, which can be attacked by the acceptors hydroxy group to form a new glycosidic bond either in α- or β-configuration. While this theory sounds straight-forward the respective experiments can turn out extremely challenging, as usually mixtures of anomeric products are obtained and, in some cases, the α/β-product ratio does not favour the experimenter's desired anomeric product at all. To hurdle this major stereoselectivity issue, more in-depth understanding of the reaction mechanism is required. A plethora of studies have been undertaken in the past in order to understand more aspects of glycosylation reactions, and in recent years more and more general findings were made. In Scheme 1 the general reaction mechanism of a glycosylation reaction is depicted. The most commonly employed counterion X^- for the oxocarbenium ion is nucleophilic[49] TfO^-. Other frequently used counterions in glycosylation reactions include halides, other sulfonates or, less common, triflimides (Tf_2N^-) and non-coordination anions, all impacting the equilibria in the reaction mechanism.[50] For example, the OTf^- will favour the axial position when forming a covalent bond due to stabilization through the anomeric effect, while Tf_2N^- may favour the equatorial position.[51]

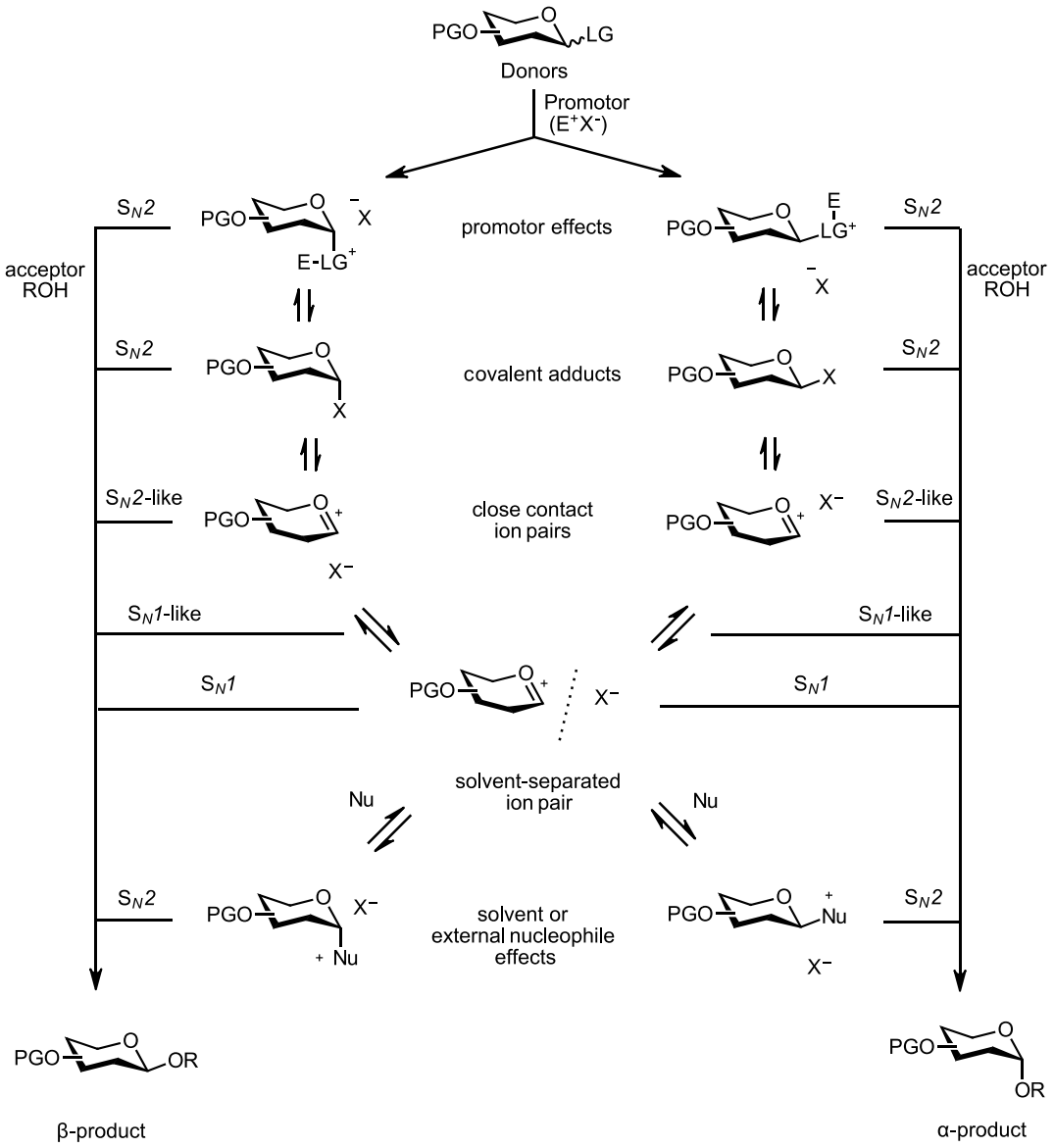
In the first step of the reaction, the LG attacks the promotor electrophile E^+ and the resulting adduct can expel a newly formed molecule E-LG, for example through attack by the counterion at the anomeric carbon atom to form covalent adducts. However, some E-LG molecules are sufficiently nucleophilic to reversibly attack the oxocarbenium ion or the covalent adducts (promotor effects). The covalent adducts between oxocarbenium ion and counter ion can dissociate and become solvated to form ionic close-contact-ion-pairs (CCIPs) or solvent-separated-ion-pairs (SSIPs) of oxocarbenium ion and counterion. Equilibria between covalent adducts, CCIPs and SSIP are strongly influenced by the solvents used. More polar solvent mixtures may allow the equilibria to shift towards solvated CCIPs and SSIPs, while more apolar solvent mixtures force the equilibria more towards covalent adducts.

A glycosylation reaction will therefore always be on a spectrum between a pure S_N2- and a pure S_N1-mechanism, and the mechanism can be influenced by solvent polarity. The reaction temperature will also strongly affect the glycosylation mechanism, as low temperatures rather favour S_N2-like reactions and higher temperatures favour S_N1-like reactions. The S_N1-like pathways to glycosidic bond formation are dependent on the conformation of the oxocarbenium ions which can either favor formation of the

α- or the β-product.[52] As oxocarbenium ions are highly reactive, solvents, such as Et_2O and MeCN, can form covalent solvent adducts (solvent effect).[53] Other externally added nucleophiles can impact the reaction in the same manner.[54, 55] The employed nucleophile concentrations strongly impact the reaction kinetics and they may change ones a nucleophile (e. g. acceptor) becomes depleted during the reaction.[56]

It is important to highlight that the stereoselectivity of a glycosylation is influenced by the sum of all factors (counterion, covalent adducts, promotor effects, solvent polarity, temperature, solvent adducts, external nucleophiles and concentrations) which poses a significant challenge for the experimenter to control the reaction.

Of course, the employed protective groups play an important role as well in modulating the reactivity of the formed oxocarbenium ions or covalent adducts, as will be discussed in the following paragraphs.



Scheme 1: The general mechanism of glycosylation reactions.

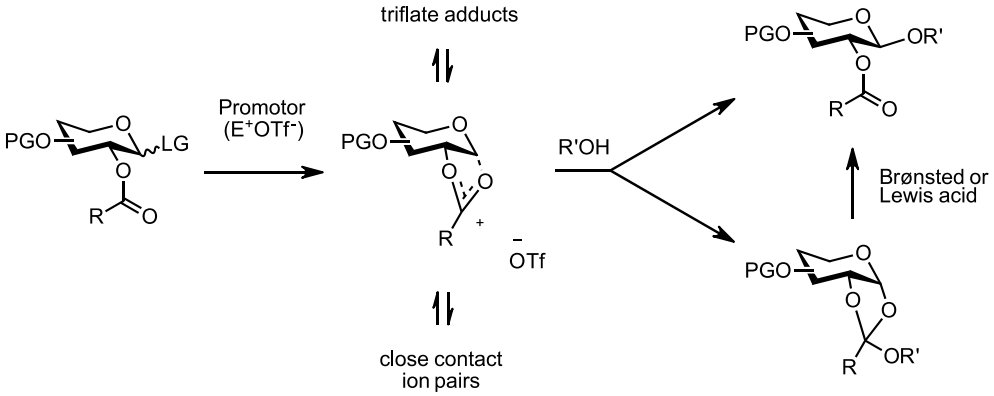
Donor reactivity

As in the case of other carbenium ions, the oxocarbenium ion's stability is greatly influenced by stereoelectronic effects. A decreased electron density in the carbohydrate ring leads to a less stabilized oxocarbenium ion, while increased electron density leads to a better stabilized oxocarbenium ion. This affects the equilibria shown in Scheme 1 and poses a factor in determining wether the glycosylation proceeds via S_N1- or S_N2-like mechanisms, or not at all if donor and acceptor missmatch.

The carbohydrate structure itsself already determines a great deal of oxocarbenium ion reactivity. Axial hydroxy groups are generally less electron withdrawing than equatorial hydroxy groups. Deoxy-positions in the carbohydrate moiety will not be electron withdrawing at all. The next determining factor is the proctective group pattern. Electron-withdrawing PGs, such as esters result in electron poor donors, referred to as "disarmed" donors, with the resulting oxocarbenium ion being less stabilized. On the other hand, electron-donating PGs, such as Bn-groups, result in rather electron rich donors, referred to as "armed" donors, with the resulting oxocarbenium ion being more stabilized.[57] It is important to note that the conformation of the oxocarbenium ion also plays a crucial role. For example, some donors bearing many sterically demanding silyl protective-groups are forced into conformations with many axial and pseudoaxial oxygens and thus become highly reactive, which is referred to as "conformationally superarmed".[58] Cyclic protective groups on the other hand lock the ring-conformation, which restricts conformational changes. This leads to intermediate reactitivity in most cases.[59] The effect of glycosyl substituents on a donor's reactivity is described as generally slightly disarming. The strength of the effect on the donor's reactivity depends on the PG-pattern at the glycosyl substituent and sterics. Relative reacitivity values (RRVs) have been established as a way to quantify the reactivity of various glycosyl donors.[60-62] RRVs can be accessed in competitive glycosylation reactions. Therefore, a reference donor and the donor to be determined are reacted with limiting amounts of a promotor and excess methanol. The product ratio is used for calculation of the RRV. It is also possible to predict the RRVs for certain carbohydrate building blocks.[62] However, RRVs of the unusual carbohydrate donors used in this work remain elusive. Moreover, functional groups within the same molecule can act as nucleophiles, such as ester moieties, also modulating the oxocarbenium ion, and therefore the product ratio.

Neighbouring group participation in glycosylation

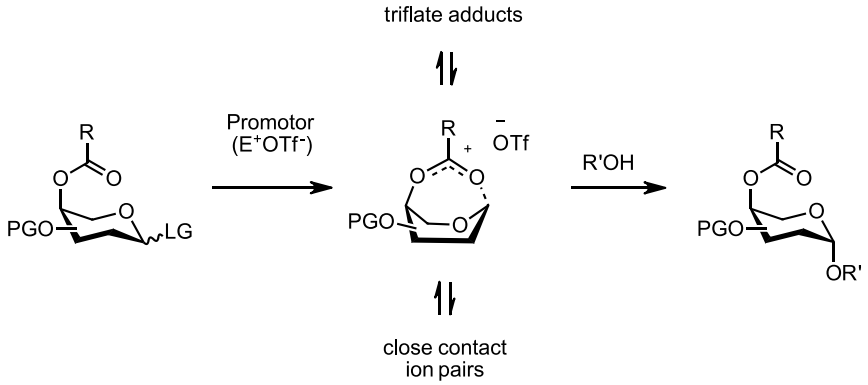
A well known and often employed strategy to achieve 1,2-*trans*-selective glycosylations is the use of ester-PGs in the 2-position of a glycosyl donor. After activation, the ester moiety can form a bicyclic C1,C2-dioxolenium ion intermediate. This can be attacked by the acceptor directly at the anomeric center to form the 1,2-*trans*-configured product in a stereospecific manner. This effect is called the neighbouring group participation (NGP) effect and is depicted in Scheme 2. Occasionally, the nucleophilic attack can occur at the former carbonyl position of the ester, leading to a bicyclic orthoester product. Under brønsted or lewis acid catalysis the orthoester can then undergo rearrangement to the more stable 1,2-*trans*-configured product. The orthoester formation is dependent on the constitution of the rest R and usually is increasingly suppressed with growing sterical demand of the group R. 1,2-*cis*-configured products are inaccessible by NGP, but remote group participation may be used to favor 1,2-*cis*-product formation.



Scheme 2: Neighbouring group participation (NGP) leading to 1,2-trans-products.

Remote group participation in glycosylation

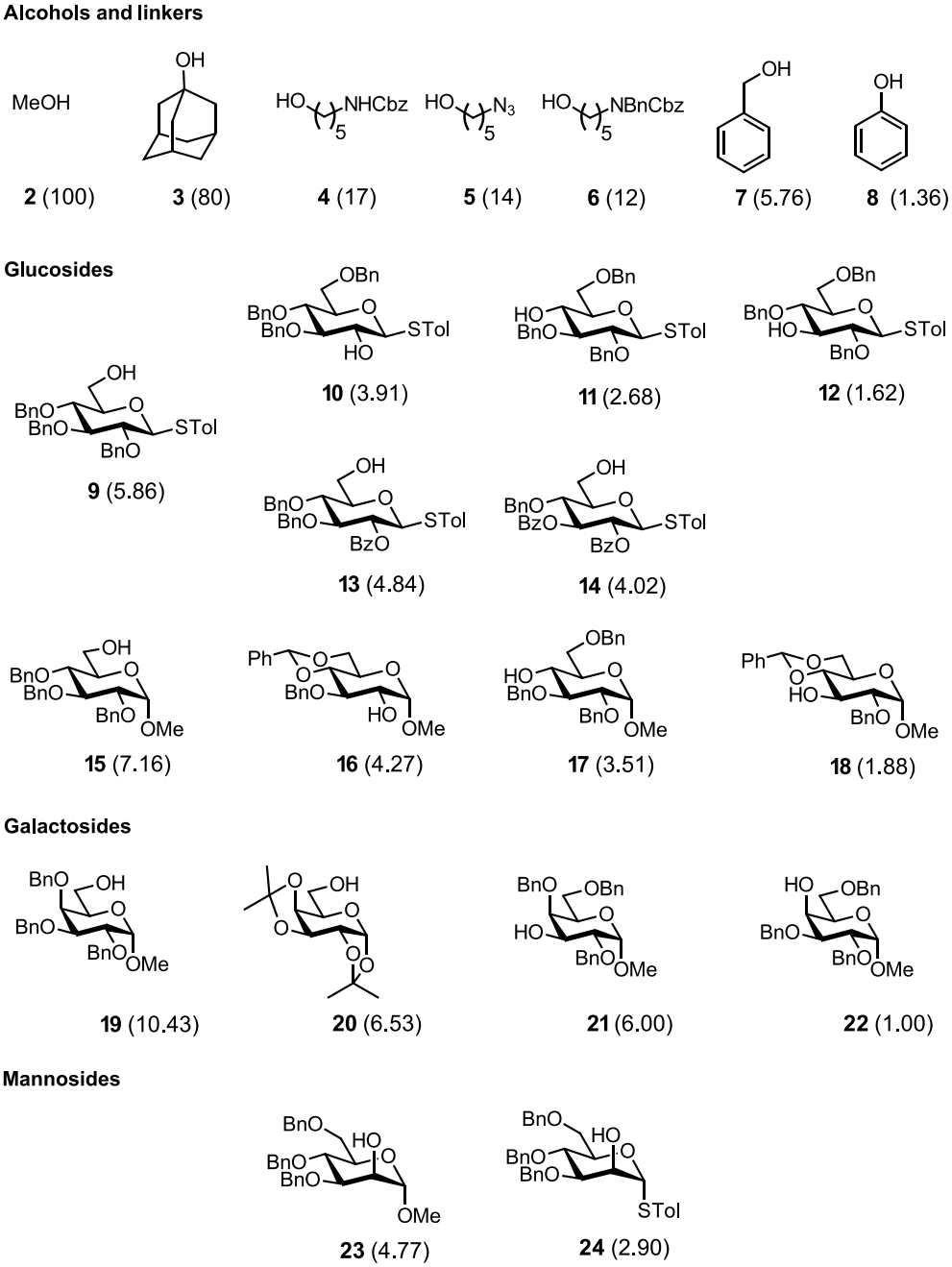
If ester-PGs are used at the C-3, C-4 or C-6 position of a glycosyl donor, they form dioxolenium ions in the gas phase, as has been shown using infrared ion spectroscopy.[63] This may play a role in solution as well and could facilitate the formation of 1,2-*cis*-products, although the effect in solution is currently debated and may not pose a main reaction pathway in glycosylation[64]. In Scheme 3 the remote group participation (RGP) of an axial C-4 ester PG is schematically depicted, as it is frequently mentioned as an explanation for the excellent α-selectivity of 4-ester-protected fucose donors. However, a favourable conformation of fucosyl oxocarbenium ions is also a likely explanation.[65] RGP in solution may have a stronger effect if further groups at the rest R of the PG are contributing to stabilize the dioxolenium ions as in the case of the DMNPA-protective group.[46, 66]



Scheme 3: Remote group participation of an axial C-4 ester PG.

Acceptor reactivity

The role of the acceptor in glycosylation has been poorly investigated in the past. Current works elucidate the importance of acceptor nucleophilicity. More nucleophilic acceptors drive the reaction mechanism towards S_N2-like reactions, while less nucleophilic acceptors favour an S_N1-like mechanism.[67] The nucleophilicity of hydroxy groups is influenced by the substitution, stereochemistry, position, and steric and electronic effects of adjacent and distant PGs as well as hydrogen bonding effects. Acceptor nucleophilic constants (Akas) have been recently determined by Chang *et al.* to gain a deeper understanding of acceptor nucleophilicity. To do so, competitive acidic THP-protection with a limiting amount of DHP, a reference acceptor and the acceptor under investigation is performed. The Akas are calculated from the obtained product ratio. Selected results of their work are shown in Scheme 4 to gain an oversight of the vast diversity of nucleophilicity of hydroxy groups. In general terms, the reactivity for hydroxy groups in carbohydrates ranks 6-OH > 2-OH > 4-OH > 3-OH and equatorial OH > axial OH. Ester-PGs reduce the nucleophilicity of alcohol groups in the same carbohydrate.[61]

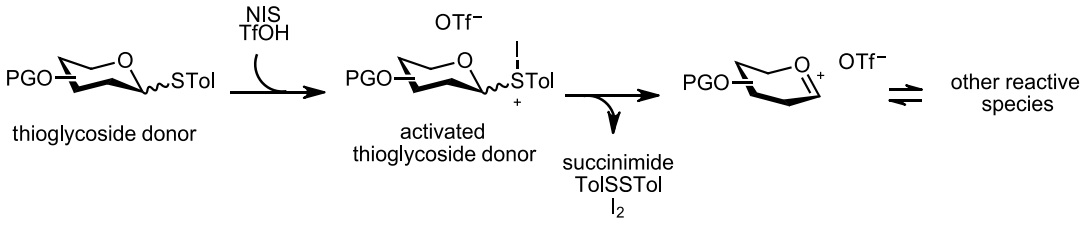


Scheme 4: Acceptor nucleophilic constants (Aka) for selected alcohols determined by Chang et al.[61]

Promotor systems for glycosylation reactions

Many chemical groups have been employed as donor-LGs in glycosylation, with a plethora of different promotors available for their activation.[68] In the following paragraphs, a selection of these LGs is described.

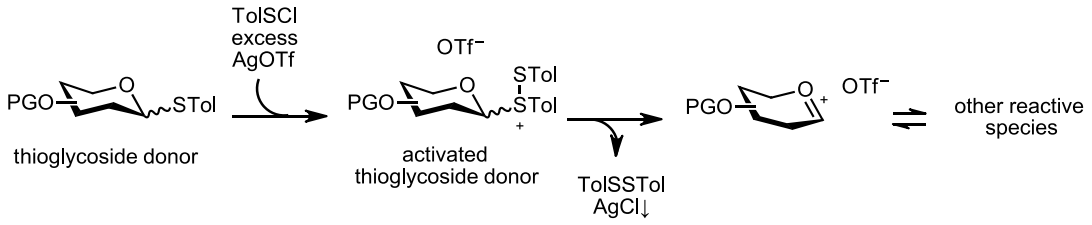
A very frequently used and versatile class of donors are the thioglycosides. The anomeric thioacetal also acts as robust PG under many reaction conditions. In the presence of soft nucleophiles (thiophiles), the sulfur reacts as an electrophile and becomes a LG, allowing to use thioglycosides as donors in glycosylations. Frequently employed for the activation of thioglycosides are combinations of NIS/AgOTf,[69] NIS/TMSOTf and NIS/TfOH (schematically represented in Scheme 5). These mixtures generate a thiophilic iodonium ion, which can attack the thioglycoside. After activation, the C-S-bond in the donor cleaves to liberate an oxocarbenium ion as well as a R-S-I molecule, which disproportionates to form a R-S-S-R disulfide and iodine. The formation of iodine can be observed visually and serves as an indicator for the reaction progress.[68] There are several acids and salts that can be employed in conjunction with NIS. NIS/AgOTf is a mild activator, as no acid is added. NIS/TMSOTf is often considered to be mild as well, but TMSOTf is a potent source of the pseudo-proton TMS^+, which can cause silyl ether migration and can also TMS-protect the acceptor, thereby liberating H^+ and lowering the pH-value. An activator system considered harsher is activation with NIS/TfOH. TfOH is insoluble in CH_2Cl_2, so it distributes over the surface of the commonly applied molecular sieves, which can be observed by the local formation of iodine on the MS after addition of TfOH. Although these reaction conditions are quite acidic, in our hands some acid-labile protective groups (TBDMS) were more stable when using TfOH compared to TMSOTf. A potential side reaction is the formation of glycosyl succinimides, as has been described in the literature.[60]



Scheme 5: Activation of thioglycoside donors with NIS/TfOH.

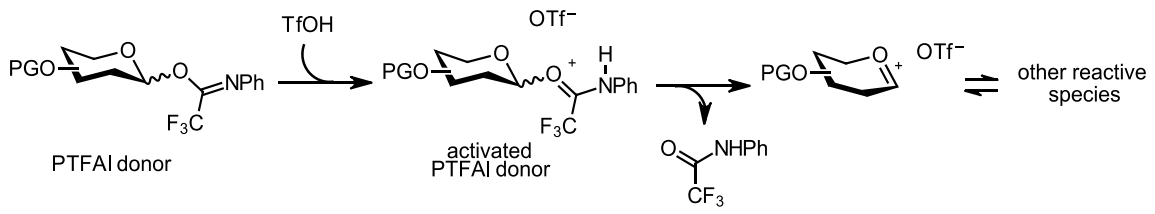
Another elegant activator system for thioglycosides is TolSCl/AgOTf as a precursor of $TolS^+OTf^-$, which is formed during the precipitation reaction between the halophilic Ag^+ and Cl^- (Scheme 6). The sulfenylium ion is a very strong thiophile, forming a symmetric non-participating disulfide after attacking the thioether and liberating the oxocarbenium ion species. As usually 3 eq of AgOTf are used, the triflate concentration is very high in this activator system, which impacts the reaction mechanism because the triflate competes as a nucleophile[49] with the acceptor.

Sterically hindered organo-bases such as TTBP or DTBMP are commonly used to buffer the liberated H^+ from the acceptor, thereby making the method very mild and applicable to acid-sensitive substrates. Key advantage of the method is that it enables preactivation of the donor thioglycosides to form metastable glycosyl triflates *in situ*, which can be reacted with a thioglycoside acceptor afterwards. This has been used in iterative one-pot glycosylations.[70, 71] The participation of Cl^- has been observed as well, forming powerful glycosyl chloride donors in specific cases.[72] In our hands this method also proved to be compatible with the use of external nucleophiles such as DMF. However, a drawback of using TolSCl is that TolSCl decomposes over time and has to be freshly prepared. *p*-Nitrophenylsulfenyl chloride[73] has been developed as a more stable alternative to TolSCl.[74]



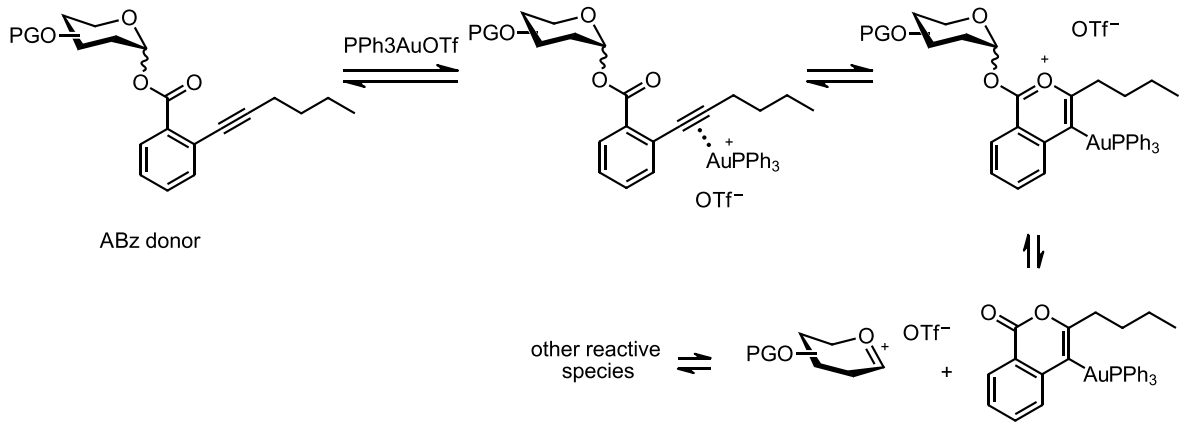
Scheme 6: Activation of thioglycoside donors with TolSOTf.

Schmidt and Michel developed 1980 the glycosyl trichloroacetimidate donor (Schmidt imidate)[75] which later became one of the most widely employed donor in chemical glycosylations.[68] Schmidt imidates are activated by Lewis acids, with typical examples being TMSOTf or $BF_3{\cdot}Et_2O$. Unfortunately, Schmidt-imidates can suffer from donor rearrangement to the unproductive trichloroacetylglycosyl amine as a side reaction.[48] It may have been this side reaction leading Biao Yu to develop the *N*-phenyl-trifluoroacetimidate donors (PTFAI-donors).[76] The additional Ph-substituent on the nitrogen decreases its nucleophilicity, making the PTFAI-donors more stable. In our hands, some donors remained stable at -18 °C for several years. Upon treatment with catalytic amounts of TfOH or TMSOTf the imidate is protonated or pseudo-protonated (Scheme 7). Upon rearrangement to the amide the LG departures liberating the oxocarbenium ion species. It is hypothesized that the amide can serve as a weak external nucleophile, forming another imidate species in the reaction (promotor effect), thereby altering the reaction mechanism, as this is known for methyl(phenyl)formamide and other formamides.[77]



Scheme 7: Schematic representation of PTFAI-activation with TfOH.

Orthoalkynylbenzoic acid esters have recently also attracted attention as donor-LGs, as many challenging glycosidic bonds with acid-sensitive substrates could be tackled employing this system.[78] Orthoalkinylbenzoic acid esters are isomerized to isocoumarines in the presence of the alkynophilic soft electrophile $LAu(I)^+$ (Scheme 8). The method typically employs PPh_3AuOTf as a strong promotor, but also the triflimide salt PPh_3AuNTf_2 can be used as a weaker promotor. It is important to note that the active catalyst undergoes a complex catalytic cycle with resting states and reactive intermediates that can form the glycosyl product. No acid is added and the protons released from the acceptor nucleophile are used in the catalytic cycle to produce the isocoumarine product, restoring the gold catalyst. The reaction is therefore pH-neutral and acid-labile groups remain uneffected. All activation steps are described as reversible, so the system exibits promotor effects, moderating the high reactivity of the oxocarbenium ion. These properties allow longer reaction times and higher temperatures, such as rt, compared to other activator systems, but controlling the stereoselectivity may be challenging.[78, 79]



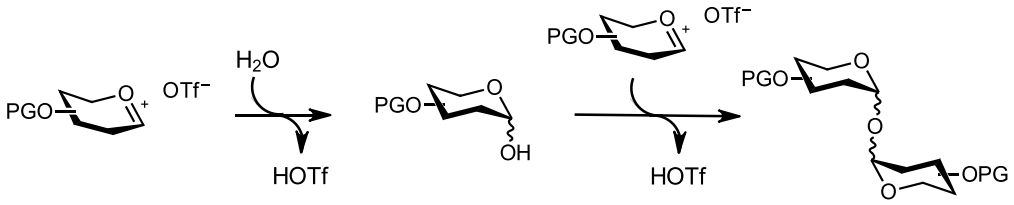
Scheme 8: Schematic activation of an ABz donor in presence of PPh3AuOTf.

Side reactions in glycosylations

A number of side reactions can occur during a glycosylation reaction. Prominent examples are hydrolysis, glycal formation and intermolecular aglycon transfer, which are relevant to this work and will be briefly described.

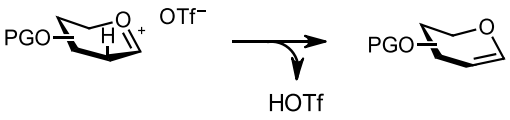
Hydrolysis is a common side reaction in glycosylations, as water can act as a nucleophile, attacking the reactive donor species and thereby forming a hemiacetal (Scheme 9). Hemiacetals can themselves occasionally act as nucleophiles and thus consume additional oxocarbenium ion to form trehalose-like side products. Fortunately, this can be suppressed by the strict exclusion of water, which is achieved by the use of super dry solvents with a water content <10 ppm. Additionally, the reactions must be performed under an argon atmosphere to avoid moisture migrating into the reaction mixture.

The reactions are usually also performed in the presence of suspended powdered MS with mesh sizes between 3-5 Å to scavange any residual moisture. As MS are fairly basic in nature, they influence the reaction by scavenging Brønsted/Lewis acid promotors. Cases are reported in which MS completely inhibited successful glycosylation. In those cases, reactions are simply performed without MS in super dry solvents, with the risk of an elevated rate of donor hydrolysis.



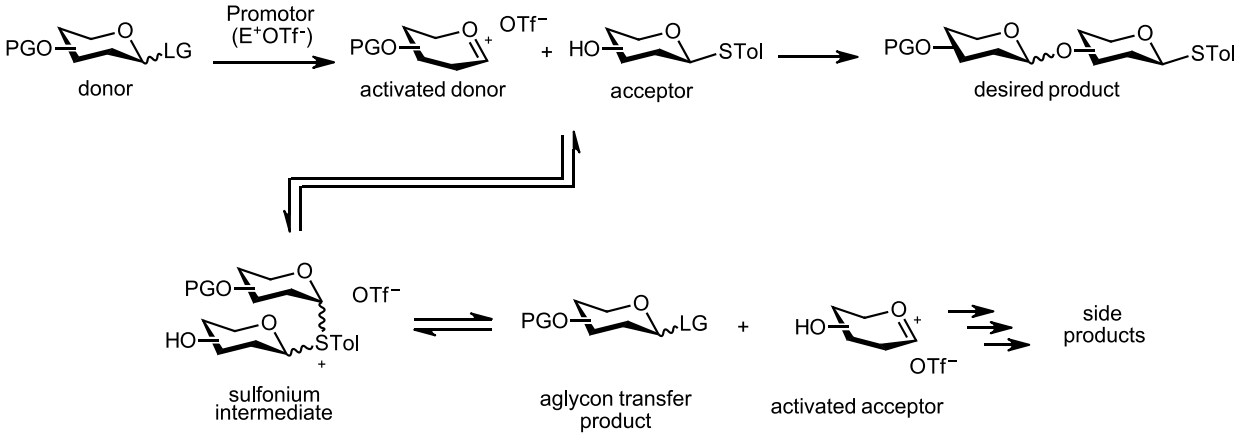
Scheme 9: Schematic representation of the hydrolysis of the reactive species after donor activation, forming a hemiacetal and occasional trehalose-type compounds.

Another common side product formed from activated donors are glycals. Reactive donor species can undergo β-elimination of a proton to form a glycal (Scheme 10). The probability for glycal formation is dependend on the donor's constitution and its protective groups, the LG, external nucleophiles and the reactivity of the acceptor as well as temperature and other reaction parameters. Highly problematic is an unforeseeable sterical mismatch of acceptor and donor, inhibiting product formation and thus only allowing the elimination pathway to the donor-glycal.



Scheme 10: Schematic representation of the elimination in the reactive species after donor activation forming a glycal.

After donor activation, the reactive oxocarbenium ion species is attacked by the nucleophilic acceptor. Unfortunately, in case of thioglycoside acceptors the nucleophilicity of the alcohol and the thioether are competing for the electrophile (Scheme 11). The activated donor can attack the thioether to form the donor thioglycoside as the aglycon transfer product and liberate activated acceptor (e.g. as oxocarbenium ion). The activated acceptor can then undergo glycosylation with other acceptors, leading to different destructive pathways and different side products. The reaction conditions regarding solvent, temperature and type of promotor and donor influence the probability of aglycon transfer. Particularly for less reactive acceptor alcohols, aglycon transfer becomes a significant side reaction. Aglycon transfer reactions are equilibrium reactions, so the most stable oxocarbenium ion will be formed in higher quantities. Thus, an electron poor donor in glycosylation with an electron rich thioglycoside readily provides the aglycon transfer product and the better stabilized oxocarbenium ion. Even after formation of the desired thioglycoside product, aglycon transfer can occur, further increasing the number of potential side products.[80]

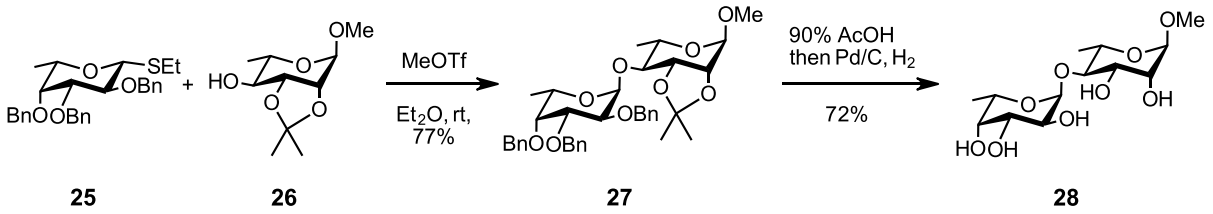


Scheme 11: Schematic representation of aglycon transfer reactions.

1.2.3 Chemical syntheses of RG-II side chain A fragments

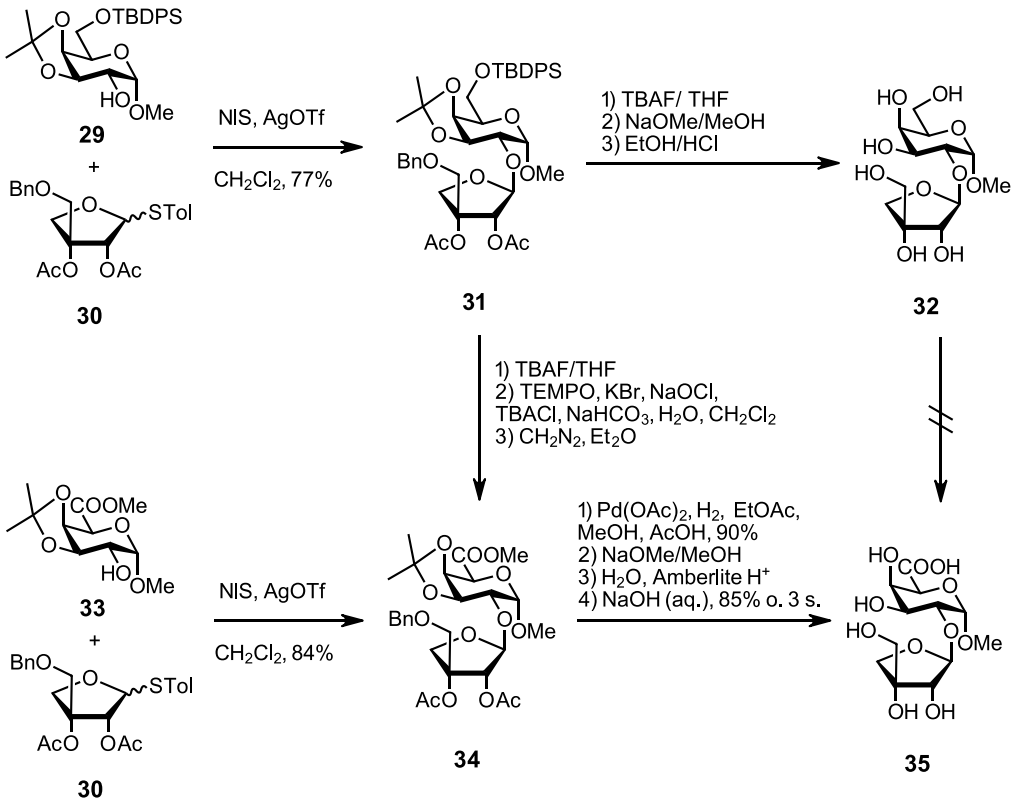
Due to the complexity of RG-II's ramified structure with 20 different glycosidic linkages previous works mainly focused on the development of synthetic methods to afford small fragments of the structure. Additionally, synthetic approaches to rare sugars like the monosaccharide apiose have been developed. From 1959 to 2002 numerous methods for the preparation of D-apiose and its derivatives starting from D-xylose[81], D-mannose[82], D-fructose[83] and L-arabinose[84, 85] and others[83] have been published.

In 1990 Backmann *et al.* synthesized a range of 1,4 linked disaccharides for conformational NMR studies.[86] This included the α-linked disaccharide **28** which was synthesized from fucose thioglycoside donor **25** and the *i*PrA-rhamnose acceptor **26** using MeOTf in Et_2O as activator, affording protected disaccharide **27** (Scheme 12). The reaction proceeded in good yields, indicating that the 4-hydroxyl of conformationally restricted rhamnose acceptors can be relatively reactive. Subsequent acidic hydrolysis and hydrogenolysis gave the deprotected disaccharide **28**.



*Scheme 12: Synthesis of disaccharide fragment **28** by Backman et al.[86]*

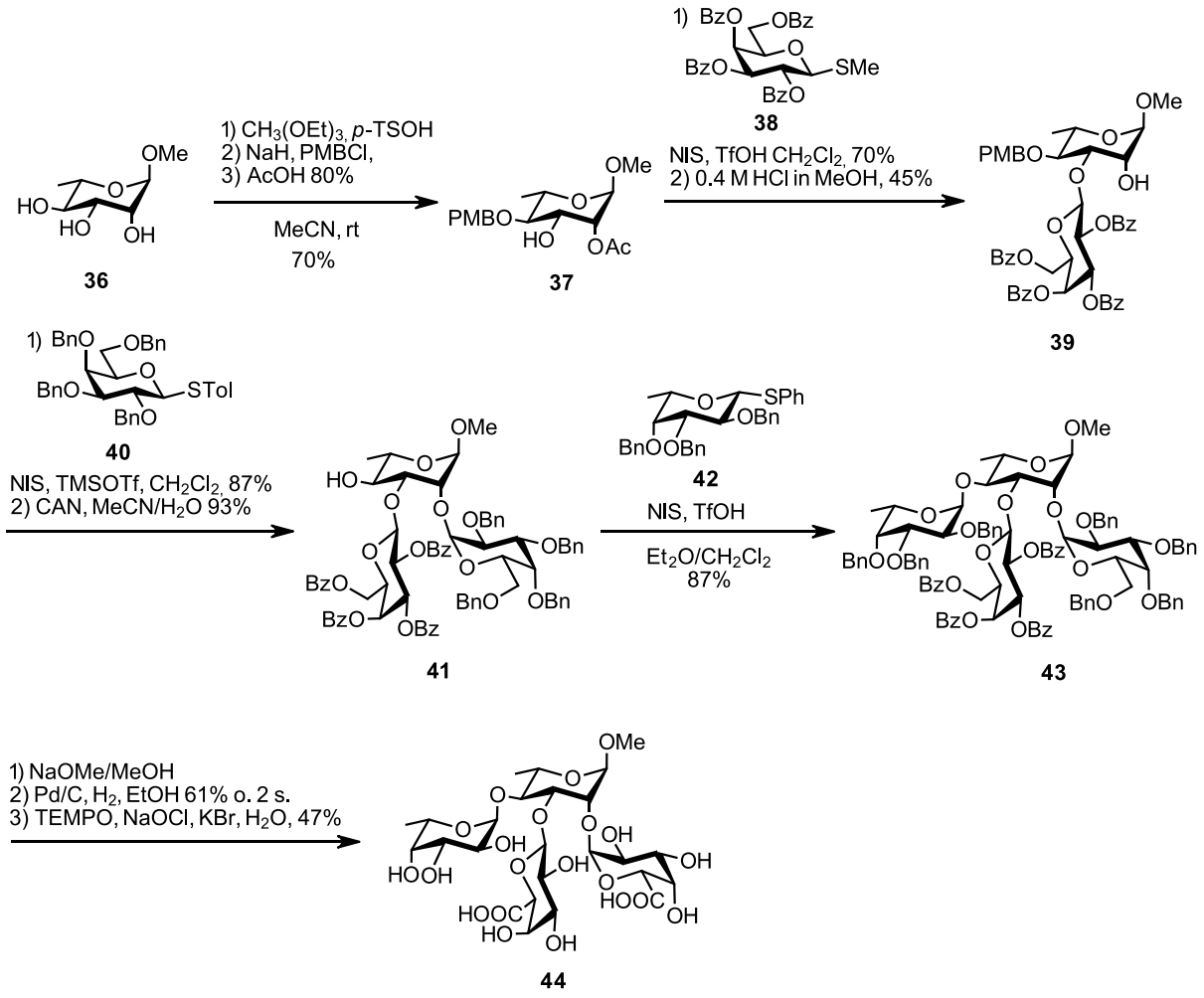
In 2004, Buffet *et al.* investigated the synthesis of the first apiose containing disaccharide **35** related to RG-II (**1**). The synthesis is depicted in Scheme 13.[87] Among four synthesized apiose donors, donor **30** was found most suitable for glycosylation with galactose acceptor **29** to afford protected disaccharide **31**. While the global deprotection of disaccharide **31** was possible, a late stage oxidation approach using variations of TEMPO, NaOCl, NaBr and base failed due to cleavage of the glycosidic bond. Instead, TBDPS cleavage in disaccharide **31** and subsequent oxidation of the primary hydroxyl group, followed by esterification, was performed, providing fully protected disaccharide **34**. Subsequent global deprotection was achieved by hydrogenolysis, followed by methanolysis, acidic acetal hydrolysis and ester hydrolysis in a mindful order to afford disaccharide **35** in high yields. However, it was found that the direct glycosylation of galacturonic acid acceptor **33** with apiose donor **30** is the more efficient way to prepare disaccharide **35**.



*Scheme 13: Synthesis of disaccharide **35** by Buffet et al.[87]*

In 2005, Chauvin *et al.* published a sophisticated synthesis of a 2,3,4-triglycosylated rhamnoside fragment, resembling the core structure of RG-II side chain A.[88] The synthetic approach is depicted in Scheme 14. Starting from rhamnose glycoside **36**, they introduced an orthoester in the 2,3-positions which allowed selective etherification with PMB at the 4-hydroxy group. Subsequent treatment with aqueous AcOH hydrolysed the orthoester and afforded the orthogonally protected rhamnose acceptor **37**. NGP-controlled glycosylation using per-benzoylated galactose thioglycoside **38** and subsequent acidic hydrolysis of the acetyl group afforded β-disaccharide alcohol **39**. Attempts to enhance the selectivity of the low yielding acetyl group hydrolysis were unsuccessfull. It was also not possible to use a 4-PMB-2,3-dihydroxy rhamnoside acceptor and differentiate the 2- and 3- positions by glycosylation. Instead a complex mixture was obtained, with no desired disaccharide **39** detectable. Disaccharide acceptor **39** was then 1,2-*cis*-selectively glycosylated with per-benzylated galactose thioglycoside **40** and subsequently deprotected with CAN to remove PMB and afford the desired trisaccharide alcohol **41**. An inversed glycosylation order using a 4-PMB-3-Ac-2-hydroxy rhamnoside acceptor was found to fully deteriorate the stereocontrol for the 1,2-*cis*-glycosylation. Finally, another 1,2-*cis*-selective glycosylation was performed using per-benzylated fucose thioglycoside donor **42** and trisaccharide acceptor **41** in Et_2O/CH_2Cl_2 to give protected tetrasaccharide **43**. By using a post-assembly-oxidation approach, the use of problematic galactopyranosyluronic acid donors was avoided, but now a late stage oxidation was required.

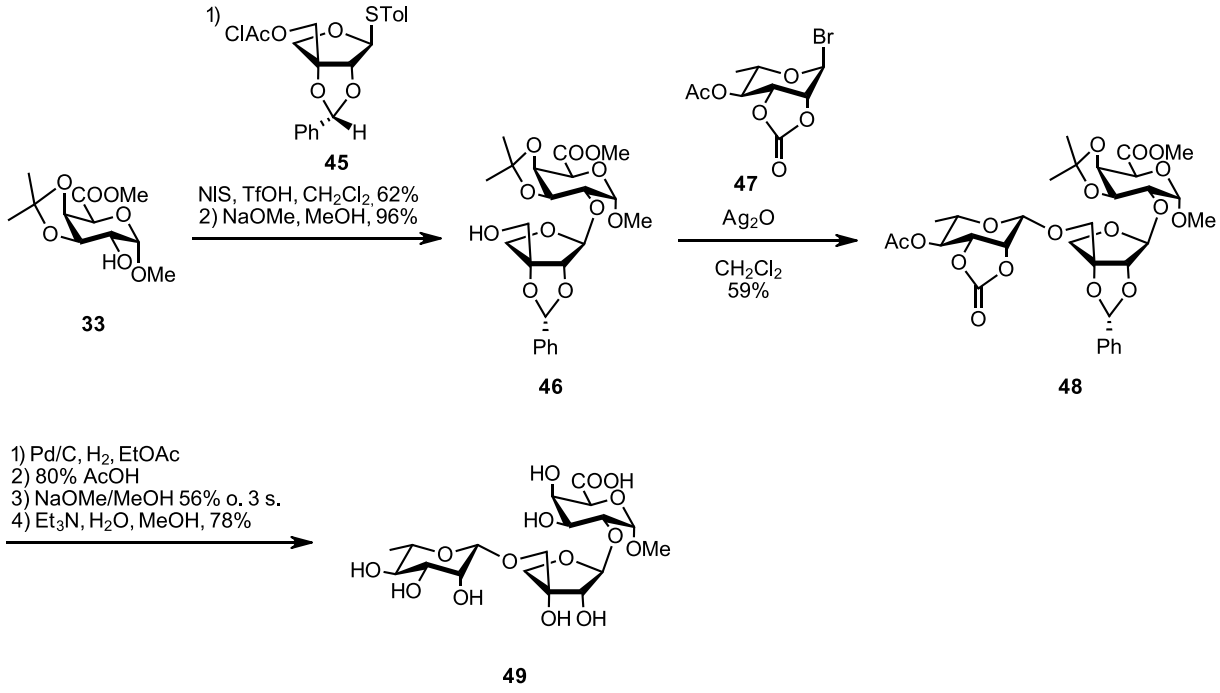
Global deprotection of tetrasaccharide **43** was achieved by ester removal using NaOMe/MeOH and hydrogenolysis in EtOH. Selective TEMPO mediated oxidation of the primary hydroxy groups finally afforded tetrasaccharide **44**. By comparing hydrogenolysis efficiencies in the deprotections of disaccharide **39**, trisaccharide **41** and tetrasaccharide **44**, they showed that the efficiency of hydrogenolysis decreased severly for the more ramnified structures, resulting in longer reaction times and lower yields. Also, the applied late stage TEMPO oxidation on fully deprotected structures became less efficient with the more ramnified structures.



*Scheme 14: Synthesis of 2,3,4-triglycosylated rhamnoside **44** by Chauvin et al.[88]*

In 2011, Nepogodiev *et al.* published the synthesis of apiose-containing oligosaccharide fragments of the plant cell wall.[89] During their investigations they improved the D-apiose thioglycoside synthesis from L-arabinose, that was originally developed by Kóóš *et al.*[85] and also published another synthetic route towards apiose-containing disaccharide **35**. Noteworthy is the synthesis of trisaccharide **49** which is depicted in Scheme 15. In this synthesis, galacturonic acid ester acceptor **33** was subjected to glycosylation with apiose thioglycoside donor **45**. Subsequently, the chloroacetyl group was removed to afford disaccharide acceptor **46**. Thereby it was found to be essential to protect the apiose with a

benzylidene- instead of an isopropylidene-acetal, as the latter acetal was unusually stable towards acidic hydrolysis, leading to cleavage of glycosidic bonds before acetal hydrolysis. The lack of participating PGs in thioglycoside donor **45** was reported to not compromise the stereoselectivity of the glycosylation reaction, as 1,2-*trans*-configured products are the preferred outcome with glycofuransyl donors. Graftifyingly, the methanolysis of ester groups with 0.1 M NaOMe/MeOH solution proceeded with high yields, which indicates that the 3,4-*i*PrA-PG on galacturonic acid esters suppresses β-elimination due to its cyclic structure. In this work a 1,2-*cis*-configured rhamnoside linkage was prepared, as it was assumed to be the natural occurring configuration at that time, but the linkage was later reassigned to be 1,2-*trans*.[30] Global deprotection of **48** by hydrogenolysis in EtOAc, treatment with AcOH 80%, subsequent methanolysis with NaOMe/MeOH followed by ester hydrolysis afforded the trisaccharide **49**. The yields were found to be rather moderate, which could be explained by the tendency of galacturonic acid esters for β-elimination under basic conditions.[90]

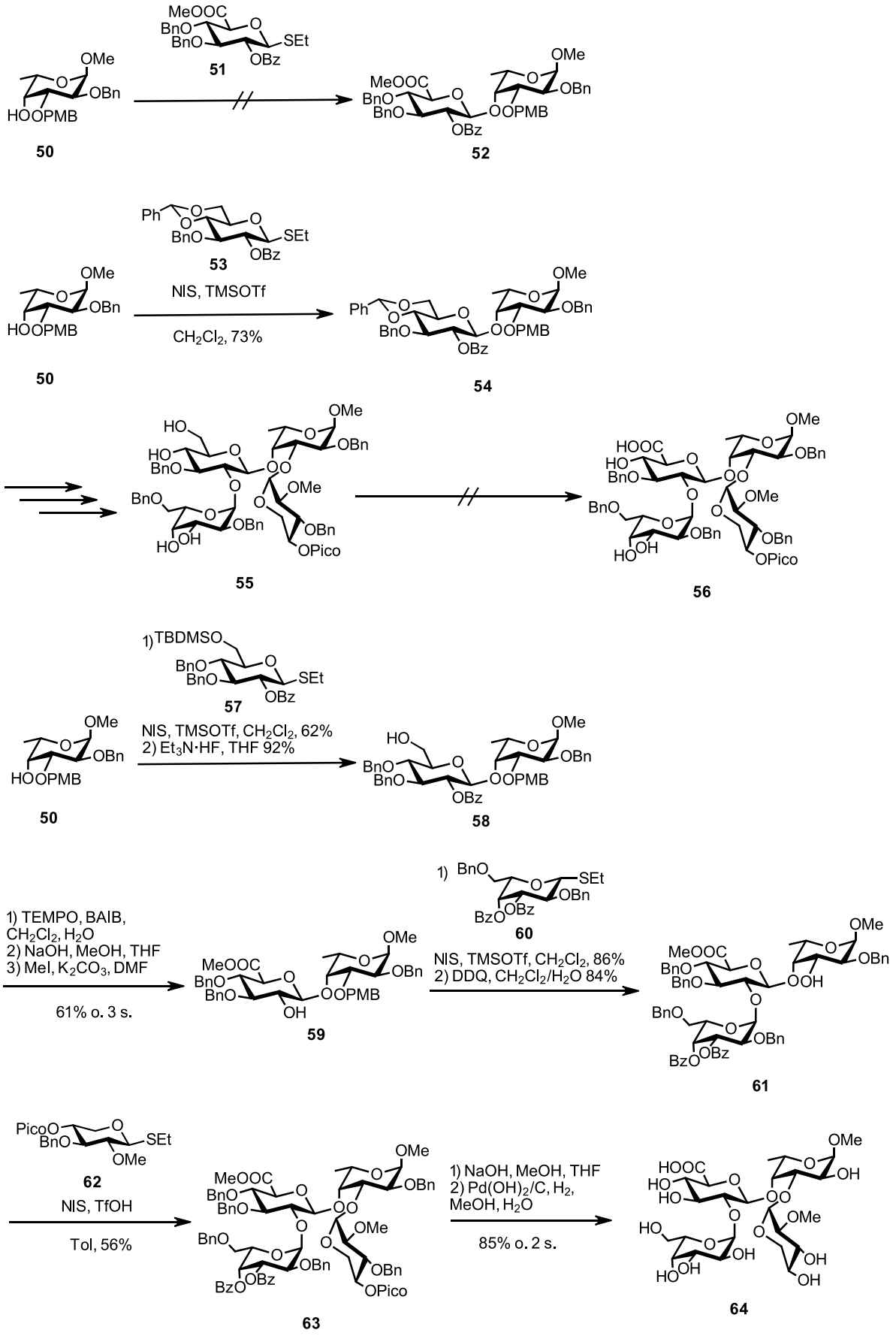


*Scheme 15: Synthesis of apiose-containing trisaccharide **49** by Nepogodiev et al.[89]*

In 2022, during the experimental work performed in this thesis, Lei *et al.* published an elegant synthesis of the branched tetrasaccharide **64**, resembling the outer structure of RG-II side chain A (depicted in Scheme 16).[91] By applying a counterclockwise approach, they glycosylated first the less reactive axial 4-hydroxy group of fucose acceptor **50**. Employing glucuronic acid donor **51** failed to provide disaccharide **52** in several trials, which was attributed to the incorrect[92] assumption of low donor reactivity. The use of 4,6-benzylidene-protected glucose donor **53** in the glycosylation with fucose acceptor **50** provided desired disaccharide **54**, maybe due to a better reactivity match of acceptor and donor.

Subsequent forward synthesis went smooth up to partially protected tetrasaccharide **55**, but all late stage oxidation protocols failed due to a lack of selectivity on this substrate and no tetrasaccharide **56** could be obtained. Alternatively, after employing glucose donor **57** in glycosylation with fucose acceptor **50**, subsequent removal of the TBDMS-PG gave disaccharide **58**. By applying a mindful order of oxidation, deprotection of the Bz-ester and subsequent esterification of the uronic acid, disaccharide **59** was obtained in fair yield. 1,2-*cis*-selective glycosylation of disaccharide **59** with L-galactose donor **60** followed by PMB-cleavage afforded then trisaccharide acceptor **61**. For the second challenging 1,2-*cis*-selective glycosylation, the 4-picolinoyl protected xylose thioglycoside **62** was employed as a donor in the reaction with acceptor **61** to afford the desired protected tetrasaccharide **63**. The notoriously difficult α-xylose glycosidic bond was formed by picolinoyl-assistance with full α-stereoselectivity, although tedious screenings had to be conducted first. Finally, the protected tetrasaccharide **63** was subjected to hydrolysis using NaOH, followed by hydrogenolysis to afford tetrasaccharide **64**. Overall Lei *et al.* managed to synthesize the tetrasaccharide in 45 total steps from L-fucose, D-glucose, D-xylose and L-galactose.

For a comprehensive review of the syntheses of other RG-II sidechains up to 2017 further reading is recommended.[17, 41]



*Scheme 16: Synthesis of tetrasaccharide **64** by Lei et al.[91]*

1.3 Aim of this work

Aim of this work was the synthesis of well defined and pure RG-II side chain A fragments. Due to the high structural complexity of the pectic oligosaccharide RG-II, which includes rare sugars, unusual carbohydrate building blocks as well as robust synthetic and chromatographic procedures for their preparation had to be developed. All target structures were designed to bear a sufficiently long aminoalkyl linker as a molecular handle to allow later functionalization with fluorescent dyes or immobilization on glycan microarray chips. The target structures may for example be used as acceptor substrates in screenings of putative biosynthetic enzymes. This may allow to identify novel glycosyl transferase activities and thus to elucidate the poorly understood biosynthetic pathway of RG-II in vascular plants.

To develop a total synthetic approach for the highly ramified side chain A and fragments thereof, an elegant retrosynthetic approach had to be developed. The following challenges, arising from the structural complexity of RG-II side chain A, had to be overcome: 1) The preparation of five challenging 1,2-*cis*-glycosidic bonds, 2) four different uronic acids and 3) nine different monosaccharide building blocks including three rare sugar moieties. The differentiation of 41 hydroxy functionalities in the starting materials requires a sophisticated and highly orthogonal PG-strategy, with sufficiently labile PGs to allow for global deprotection of the desired products in the end. Additionally, suitable strategies had to be developed for: 1) the challenging 1,2-*cis*-selective introduction of the aminoalkyl linker to galactose, 2) the stereoselective introduction of the uronic acid moieties and 3) the challenging introduction of the multiple branches in the highly ramified structure.

2. Results and discussion

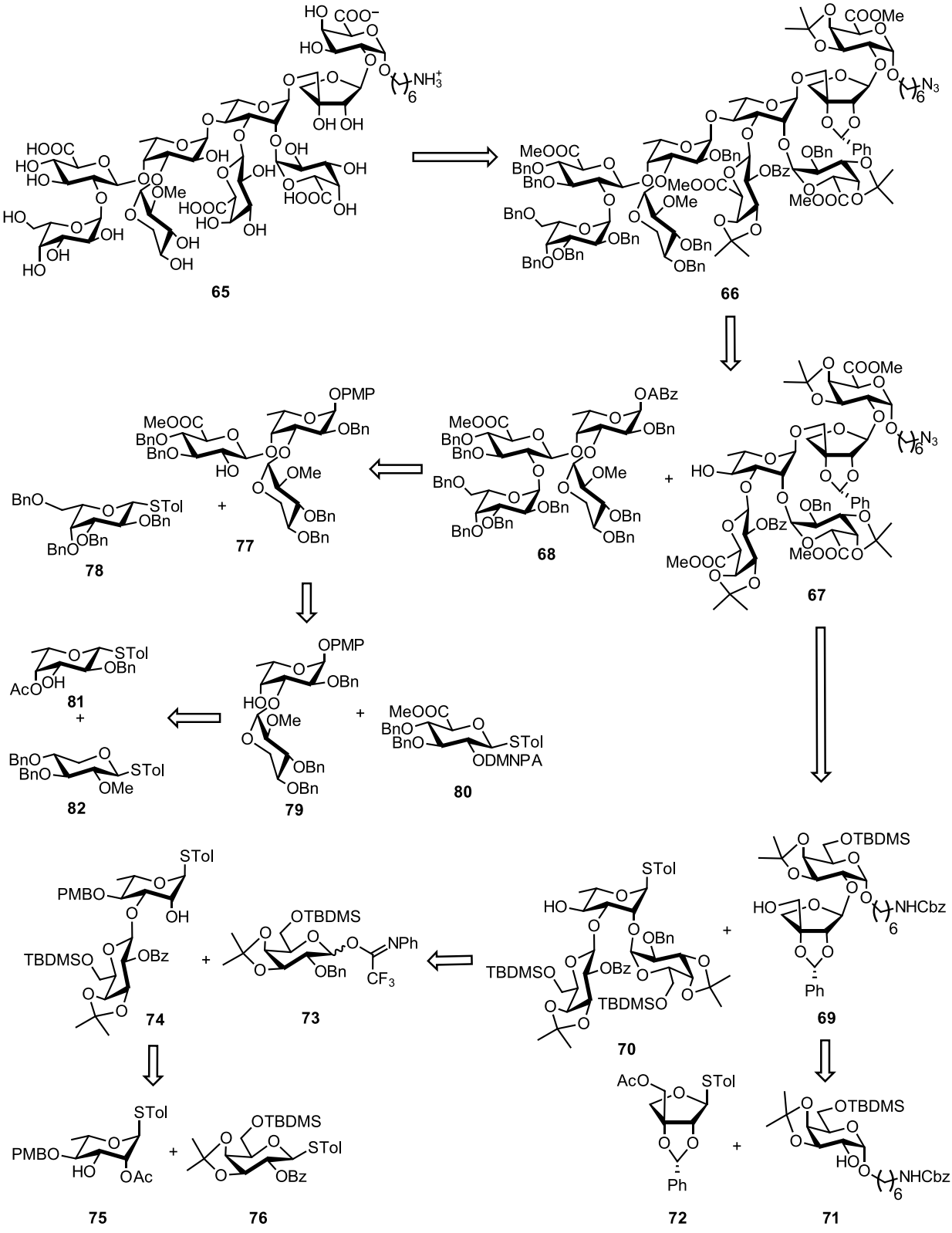
2.1 Retrosynthetic analysis

2.1.1 RG-II side chain A

Due to the complexity of the desired target nonasaccharide **65**, containing a linker-functionalized backbone galacturonic acid (Scheme 17), great care must be taken in the retrosynthetic analysis. Suitable PGs for all 19 alcohol groups, four carboxylic acid moieties and a primary amino group are required. The carboxylic acid groups were protected as methyl esters, as their easy and selective introduction was described in the literature[93]. The amino group of the linker needed to be permanently protected in a way that sufficiently suppresses its reactivity. This was achieved by using an azide moiety. The glycosylation reactions require participating PGs in the donor's 2-position for 1,2-*cis*-glycosidic bonds and non-participating PGs for 1,2-*trans*-glycosidic bonds, restraining the choice of alcohol PGs. Bn and Bz have proven to be a good choice for permanent protection of this position[45, 94]. For the *cis*-configured hydroxy goups at the 3- and 4-positions of the galacturonic acids, *iso*-propylidene acetal (*i*PrA) was shown to be a simple and selective to install PG which is easy to cleave as well.[89, 95] The 1,2-*cis*-configured hydroxyls in apiose needed special consideration, as the 3-OH is a tertiary alcohol with unique reactivity. Examples in the literature describe benzylidene acetal (BnA) as sufficiently labile to be removed by hydrogenolysis.[89] With these considerations in mind, protected nonasaccharide **66** was designed.

In order to avoid material losses and improve the overall efficiency of the synthesis, a convergent approach was favored over a linear approach. Therefore, the first retrosynthetic cut was set between rhamnose and fucose to give a tetrasaccharide donor **68** and a pentasaccharide acceptor **67**. The [4+5]-glycosylation reaction was expected to be highly challenging due to sterical demands of donor **68** and acceptor **67**. Therefore, a modern Au(I)-catalyzed glycosylation reaction approach using ABz as the leaving group was chosen to be explored first,[96] which is performed under neutral conditions and allows longer reaction times because no pH-dependent side reactions are expected to occur. Also, the reaction can be performed at room temperature, potentially allowing a larger variety of reactive conformations of acceptor and donor.

Retrosynthetic cleavage in tetrasaccharide donor **68** was conducted at the 1,2-*cis*-glycosidic linkage of the L-galactoside, leading to thioglycoside **78**, which is accessible from L-galactose. This decision was made to delay the notoriously difficult preparation of 1,2-*cis*-xylosides[97] in the synthetic scheme. By delaying this cleavage in the retrosynthesis more dispensable materials are used for this transformation of potentially low selectivity.



*Scheme 17: Retrosynthetic analysis of RG-II side chain A nonasaccharide **65** including a backbone galacturonic acid with an amino alkyl linker at the reducing end.*

The next retrosynthetic cut was set at the 1,2-*trans*-glycosidic bond between glucuronic acid and fucose in trisaccharide **77**, giving the glucuronic acid donor **80** accessible from 3-benzyl 4,6-benzylidene glucose thioglycoside **116**[98]. The recently developed DMNPA protective group was chosen as a participating PG in the 2-position of donor **80** to allow for deprotection under mild acidic conditions to avoid β-elimination at the 4-position[90]. The disaccharide acceptor **79** was protected with a sufficiently stable anomeric PG such as PMP to avoid aglycon transfer side reactions. The final retrosynthetic cut was set at the 1,2-*cis*-glycosidic linkage between xylose and fucose leading to the readily accessible fucose monosaccharide acceptor **81**[99] and xylose donor **82** accessible from xylose thioglycoside **110**[100].

For pentasaccharide acceptor **67** I decided to set a retrosynthetic cut at the 1,2-*trans*-configured rhamnose, giving disaccharide acceptor **69** and trisaccharide donor **70**, as 1,2-*trans*-configured rhamnosyl bonds can be readily formed. In this case, the stereoselectivity is aided by the sterical demand of the 2-glycoside substituent at the rhamnose. The 4-position of trisaccharide donor **70** can remain unprotected, as the reactivity of the primary alcohol in disaccharide acceptor **69** should outcompete the reactivity of the secondary and sterically hindered alcohol in trisaccharide donor **70**. A late stage oxidation of the galactose residues at the pentasaccharide stage was chosen, because the stereoselectivity of reactions with galacturonic acid donors is more difficult to control than when using galactose donors[101]. TBDMS-groups were employed as orthogonal temporary PGs for the 6-position of galactose, providing excellent selectivity for primary alcohols during introduction and enabling facile cleavage using fluoride sources[102].

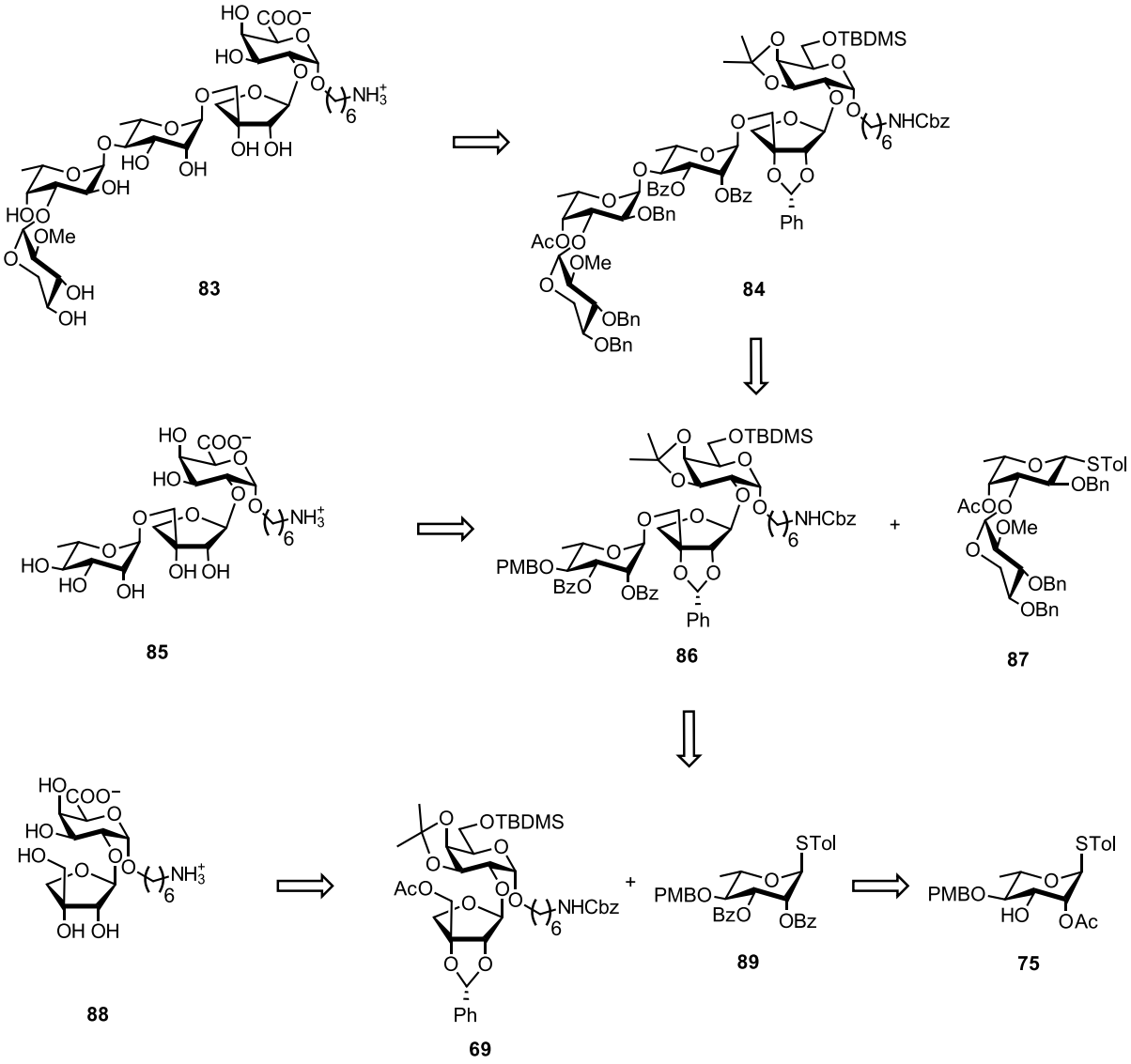
The next retrosynthetic cut in trisaccharide donor **70** was set at the 1,2-*cis*-glycosidic bond in the 2-position of rhamnose to give galactose donor **73** which can be accessed from 4-methylphenyl 1-thio-β-D-galactopyranoside **96**[103]. Disaccharide acceptor **74**, equipped with an orthogonal PMB PG in the 4-position was further dissected into the 2-Bz-protected galactose donor **76**, with similar PG-pattern as the 2-Bn protected galactose donor **73**, and the rhamnose acceptor **75** accessible from 4-methylphenyl 1-thio-α-L-rhamnopyranoside (**108**)[99, 104].

Disaccharide acceptor **69** is retrosynthetically cut into apiose donor **72**, which is accessible from L-arabinose (**103**) following literature procedures[89], and galactose acceptor **71** bearing the protected aminoalkyl-linker in a 1,2-*cis*-glycosidic linkage. Introduction of the linker in galactose acceptor **71** is challenging because reacting an electron-rich linker with a galactose donor provides a high excess of the 1,2-*trans*-product.[105] Therefore, I decided to dissect the linker further and start from readily available α-D-propargyl galactopyranoside (**90**), which can be prepared by Fischer-glycosylation.

2.1.2 Linear side chain A fragments

As this synthetic plan requires high commitment and includes many challenging glycosylation reactions, it is helpful to obtain as much information as possible by synthesizing smaller oligosaccharides. Therefore, a retrosynthetic plan for more accessible linear fragments of side chain A was designed in conjunction with the retrosynthesis of nonasaccharide **65** (Scheme 17). Linear pentasaccharide **83**, trisaccharide **85** and disaccharide **88** were chosen as target molecules (Scheme 18). The same PG strategy as implemented for nonasaccharide **65** was applied, with permanent PGs being Bz as participating group, Bn as non-participating group, *i*PrA as a protective group for 1,2-*cis*-diols and BnA for the diol in apiose. The Cbz group was chosen for permanent protection of the linker's primary amine. Ac was used as a permanent PG at fucose because it can be introduced early on in building block synthesis and adds stereo control in the glycosylation with the rhamnose acceptor towards the protected pentasaccharide **84** due to remote group participation.

As depicted in Scheme 18, the first cut in the retrosynthesis of pentasaccharide **84** is set at the 1,2-*cis*-glycosidic bond between fucose and rhamnose to give disaccharide **87** and trisaccharide **86**, conveniently resembling a protected surrogate of trisaccharide **85**. PMB was used as an orthogonal PG for the rhamnose 4-position. Disaccharide **87** is a useful intermediate in the synthesis of disaccharide acceptor **79**, shown in the retrosynthesis of nonasaccharide **65** (Scheme 17). It is directly accessible from fucose acceptor **81** and xylose donor **82**. Dissecting trisaccharide **85** further at the 1,2-*trans*-glycosidic bond between rhamnose and apiose leads to disaccharide acceptor **69**, shown in the retrosynthesis of nonasaccharide **65**, and the rhamnose donor **89**, which is conveniently accessed by protection of rhamnose acceptor **75**, also shown in the retrosynthesis of nonasaccharide **65**.



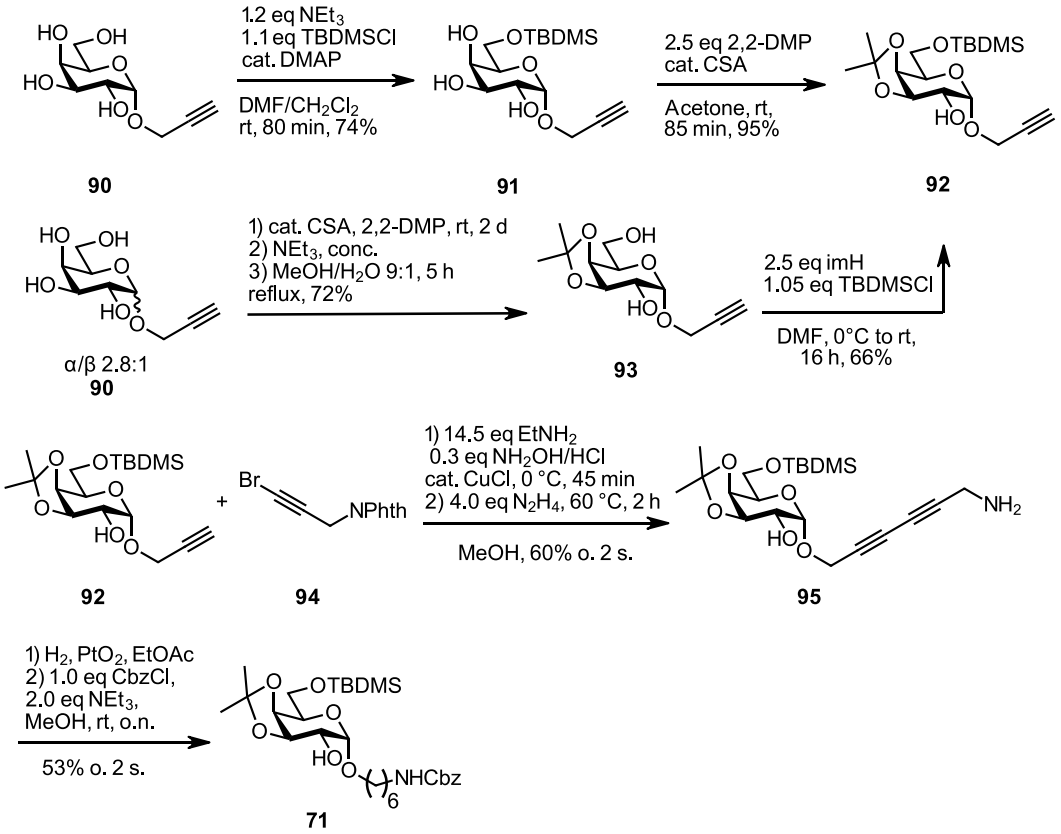
*Scheme 18: Retrosynthetic analysis of linear side chain A fragments **83, 85** and **88** bearing amino alkyl linkers.*

2.2 Synthesis of required building blocks

With a good strategy for the synthesis of both linear side chain A fragments and ramified nonasaccharide **65** at hand, I started to assemble the required carbohydrate building blocks for the desired oligosaccharide targets.

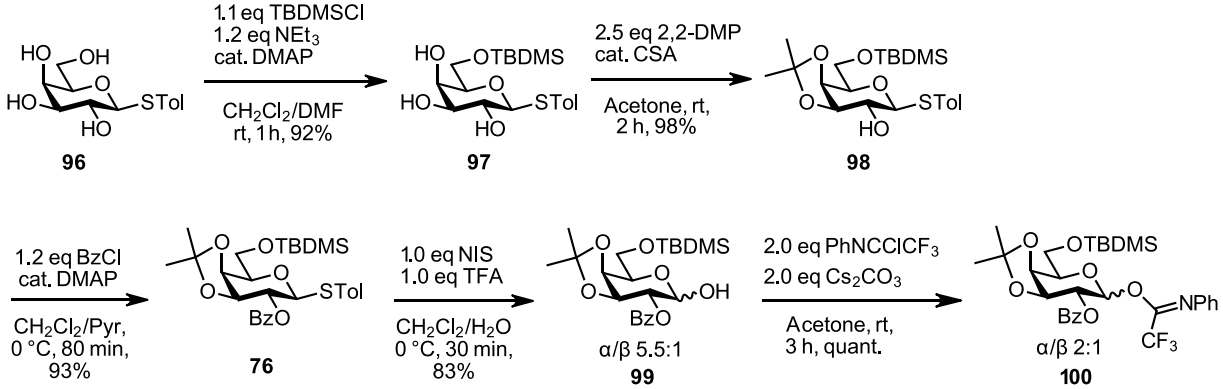
2.2.1 Galactose building blocks

To obtain galactose acceptor **71** I started with literature known α-D-propargyl galactopyranoside[106] which was protected at the primary alcohol with TBDMSCl following modified literature procedures[107, 108] to give triol **91**[109] in good yield, as shown in Scheme 19. Subsequent protection at the 3,4-*cis*-diol with 2,2-DMP[110] afforded alcohol **92** in excellent yield. An inverse order of events, first protection with 2,2-DMP to afford diol **93** and then protection with TBDMSCl, was found to be more challenging, as other acetals at the 2,3- and 4,6-positions were formed as side products and subsequent TBDMS protection was no longer selective for the primary hydroxy group at the 6-position. Alcohol **92** was cross-coupled with bromopropargyl phthalimide **94**[111] using a Cadiot-Chodkiewicz coupling[112], and the phthalimide group was subsequently cleaved by treatment with hydrazine to obtain amine **95** in fair yield over two steps. Unreacted alcohol **90** was reisolated. Hydrogenation at a platinum catalyst[113] and protection of the amino group with CbzCl afforded galactose acceptor **71** in fair yield over two steps. Further experiments suggested that by inverting the order of reactions and first protecting the amine with the Cbz-PG and then hydrogenating with platinum, the yield could be improved significantly, as the Cbz-PG is cleaved much slower than the diyne is hydrogenated under platinum catalysis.



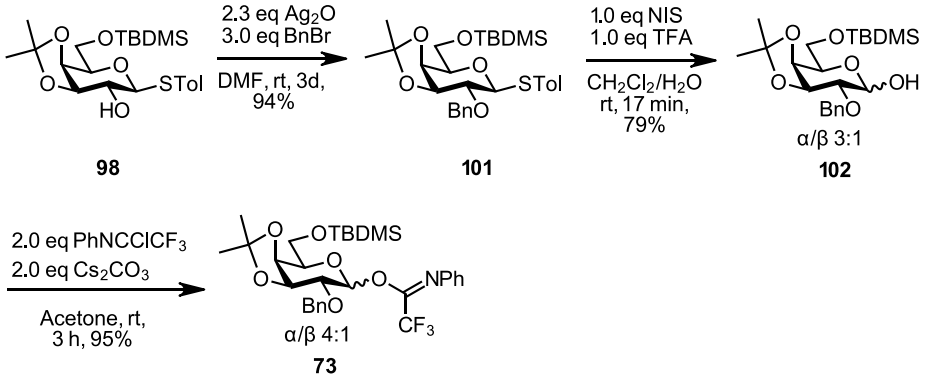
*Scheme 19: Synthesis of galactose acceptor **71** bearing a protected aminoalkyl linker.*

For preparation of thioglycoside donor **76** and PTFAI-donor **100** (Scheme 20), the thioglycoside tetraol **96** was synthesized in 3 steps following literature procedures[103, 114]. Using the same optimized order of reaction steps as in the synthesis of building block **71**, tetraol **96** was 6-TBDMS-protected to obtain triol **97** in excellent yield. Then the 3,4-*i*PrA group was installed to afford alcohol **98** again in excellent yield. Subsequent protection with BzCl gave thioglycoside donor **76**, with a participating Bz-group in the 2-position in excellent yield. By cleaving the STol group with NIS, TFA and water[47], hemiacetal **99** was obtained in very good yield. The hemiacetal was finally converted into the PTFAI-donor **100** quantitatively.



*Scheme 20: Synthesis of galactose thioglycoside **76** and imidate donor **100** with a participating PG in the 2-position.*

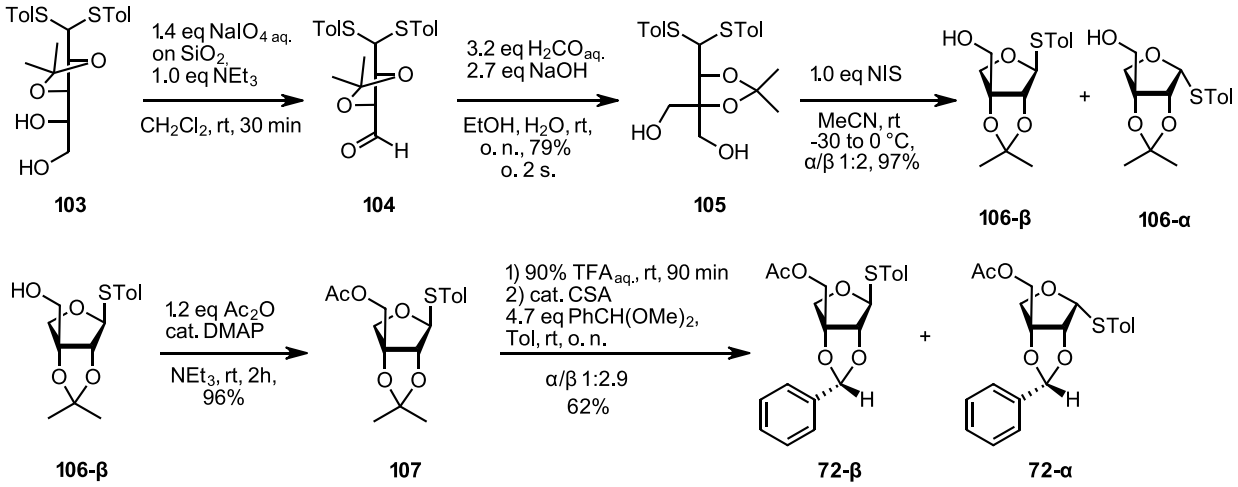
For the synthesis of imidate donor **73** with a non-participating Bn-PG in the 2-position (summarized in Scheme 21), alcohol **98** was subjected to mild benzylation with Ag_2O and BnBr[108] to yield the thioglycoside **101** in excellent yield. Subsequent hydrolysis of the thioglycoside using NIS, TFA and water[47] gave hemiacetal **102** and conversion to the *N*-phenyl trifluoroacetimidate provided PTFAI-donor **73** in excellent yield.



*Scheme 21: Synthesis of galactose thioglycoside and imidate donors **101** and **73** with a non-participating PG in the 2-position.*

2.2.2 Apiose building block

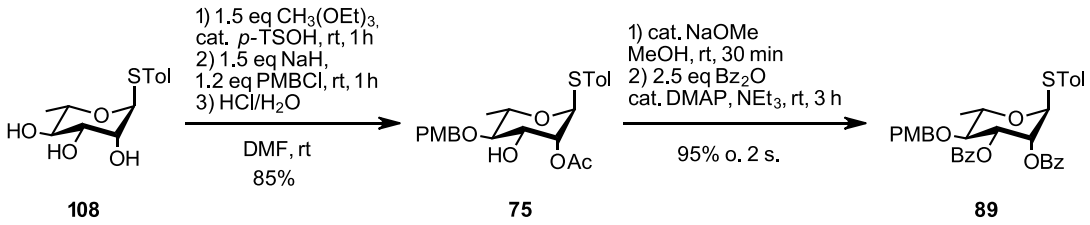
Apiose thioglycoside donor **72** was synthesized from L-arabinose in 8 steps following a literature procedure[89]. As depicted in Scheme 22, it was possible to significantly improve the overall yield by performing the Malaprade-reaction and subsequent Aldol-condensation with formaldehyde under a layer of argon instead of air to obtain diol **105**. The presence of oxygen from the air quickly oxidizes the aldehyde[115] which is avoided by an inert gas layer. Subsequent cyclization with NIS afforded alcohol **106** as an easily separable α/β-mixture in excellent yield, when the reaction was performed at the correct concentration range. If the reaction is performed in 10-fold higher concentration, as incorrectly stated in the literature[89], exclusive formation of apiose disaccharides is observed. The chloroacetyl-PG used in the literature proved to be too labile in my hands, so I have decided to deviate from the described methods and acetylate alcohol **106-β** with Ac_2O under basic conditions, affording thioglycoside **107**. As the 2,3-*i*PrA group was described to be unexpectedly stable in apiose systems[89], due to the presence of a tertiary alcohol, it was suggested in the literature to exchange the 2,3-*i*PrA for 2,3-BnA. Hydrolysis of thioglycoside **107** in 90% TFA_{aq} and subsequent protection with $PhCH(OMe)_2$ under acidic conditions afforded thermodynamically favoured *endo*-products **72-α** and **72-β** in good yield together with minor amounts of the *exo*-products. Prolonged storage of the *exo*-products under slightly acidic conditions resulted in full conversion into the *endo*-products **72-α** and **72-β**. Prolonging the reaction time might therefore give improved yields of the *endo*-products. Isomerization of the STol group can be explained by the very harsh reaction conditions required to cleave the *i*PrA group. Other procedures for preparation of thioglycosides **107** and **72-α/β** have been described in M. P. Bartetzko's PhD thesis[116].



*Scheme 22: Synthesis of apiose thioglycoside donor **72**.*

2.2.3 Rhamnose building blocks

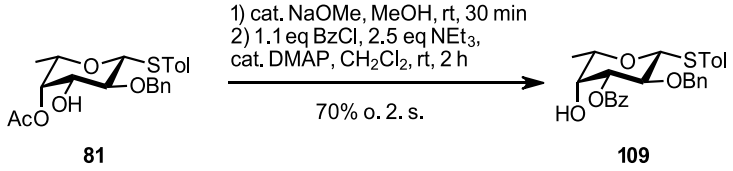
Rhamnose thioglycoside **108** was prepared in 3 steps according to literature procedures[104]. As summarized in Scheme 23, an ethyl orthoacetate was introduced in the 2,3-position under acidic conditions, and subsequently alkylation with PMBCl and NaH was performed in one pot, following a modified method[99]. Acidic workup then afforded rhamnose acceptor **75** in very good yield. Treatment of rhamnose acceptor **75** with NaOMe in MeOH and subsequent Bz protection afforded thioglycoside donor **89** in excellent yield.



*Scheme 23: Synthesis of rhamnose acceptor **75** and rhamnose donor **89**.*

2.2.4 Fucose building blocks

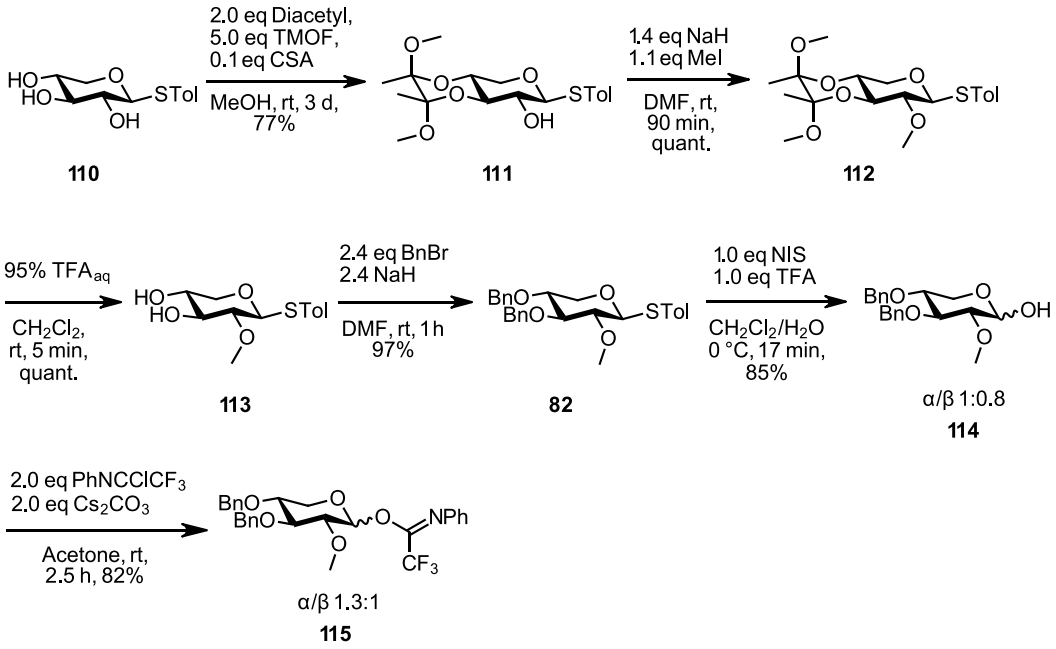
Fucose acceptor **81** was prepared in 6 steps according to literature procedures[99, 117]. To allow for introduction of the 4-glucoside prior to installation of the 3-xyloside, I also synthesized fucose acceptor **109** as shown in Scheme 24. Therefore, acceptor **81** was treated with NaOMe/MeOH and then selective introduction of a Bz group at the 3-position gave acceptor **109** in good yields.



*Scheme 24: Synthesis of fucose acceptor **109**.*

2.2.5 Xylose building blocks

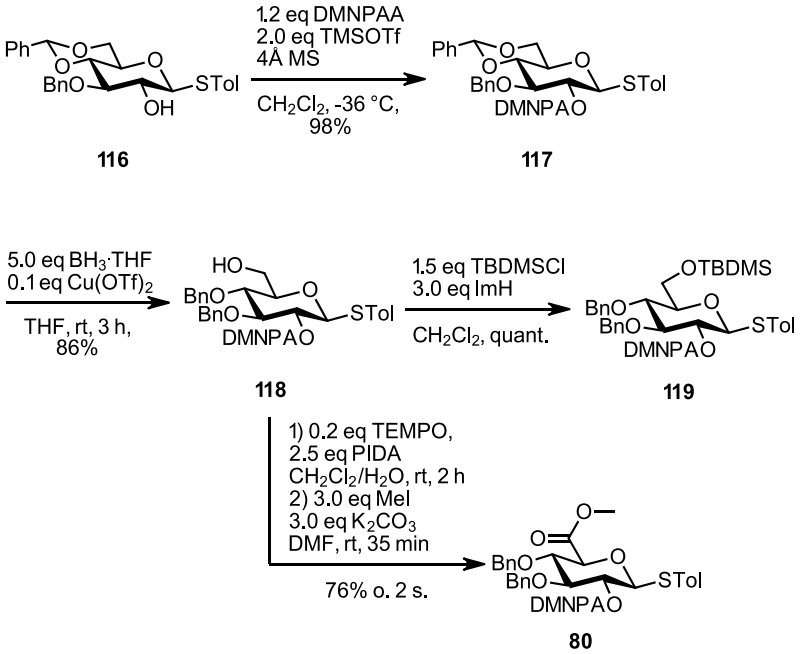
The approach to xylose donors **82** and **115** is summarized in Scheme 25. After preparation of triol thioglycoside **110**[118] in 3 steps, a literature procedure[100] was modified to introduce a BBA group selectively at the 3,4-*trans*-diol to afford alcohol **111** in good yields. Even though the reaction time was much longer, the use of cat. CSA instead of $BF_3{\cdot}Et_2O$ complex improved the yield of thermodynamic product **111** with the free hydroxy group in the 2-position, and smaller amounts of BBA-diastereomers were found along with the desired product. Alcohol **111** was then alkylated with MeI and NaH in DMF to give thioglycoside **112** in quantitative yield. Subsequent hydrolysis with 95% TFA_{aq} in CH_2Cl_2 gave pure diol **113**, which was alkylated with BnBr and NaH to afford thioglycoside donor **82** in excellent yield. Hydrolysis of the STol group with NIS, TFA and water[47] gave the hemiacetal **114** in very good yield. Subsequent imidate formation proceeded smoothly and afforded PTFAI-donor **115** in good yield. However, the product was found to be very sensitive to acid, with significant decomposition even during flash chromatography making purification challenging.



*Scheme 25: Synthesis of xylose thioglycoside donor **82** and imidate donor **115**.*

2.2.6 Glucose and glucuronic acid building blocks

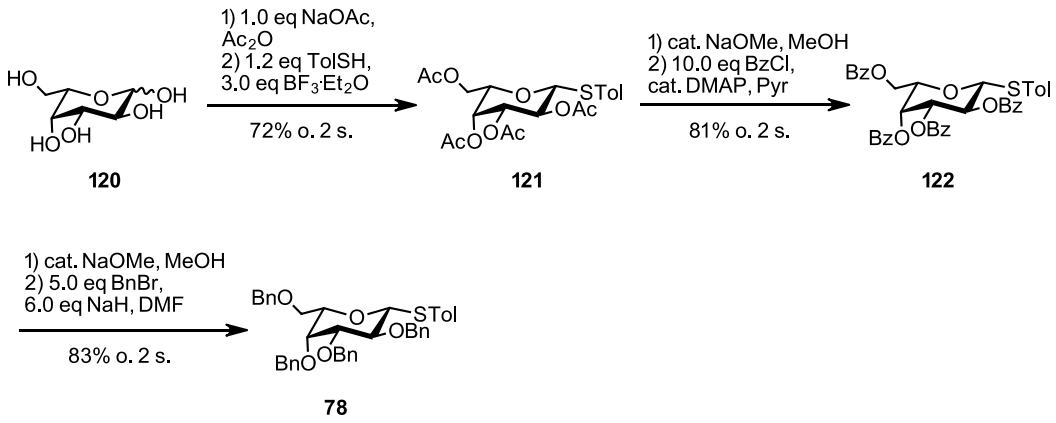
Alcohol **116** was prepared in 5 steps via a fully TMS-protected glucose thioglycoside following literature procedures[98, 119]. A facile one pot protection approach[120] was unsuccessfull in our hands, but a step-wise approach gave the product as described. As depicted in Scheme 26, DMNPA-protection of alcohol **116** according to a general procedure from the literature[45] worked well and gave thioglycoside **117** in very high to excellent yields, but occasionally it was challenging to remove DMNPA-related side products. By treating thioglycoside **117** with BH_3·THF complex and catalytic amounts of $Cu(OTf)_2$, the 4,6-BnA group was reduced with excellent chemoselectivity to afford alcohol **118** in very high to excellent yields. Subsequent purification also removed eventually remaining DMNPA-related side products. The outcome of the subsequent glycosylation of the 4-position of fucose acceptors, known to be of low reactivity, was challenging to predict. Also, it was unknown weather a post-assembly oxidation approach would be favourable, so I decided to prepare the glucuronic acid thioglycoside **80** as well as glucose thioglycoside **119** as donors for further synthesis. By treating alcohol **118** with TBDMSCl and imidazole, TBDMS-protected thioglycoside **119** was obtained quantitatively. Alternatively, alcohol **118** was oxidized using TEMPO in conjunction with PIDA and water, followed by basic esterification with MeI, to afford glucuronic acid thioglycoside **80** in good yields over two steps.



*Scheme 26: Synthesis of glucuronic acid thioglycoside **80** and glucose thioglycoside **119**.*

2.2.7 L-Galactose building blocks

The approach to L-galactose donor **78** is summarized in Scheme 27. L-Galactose **120** was peracetylated in Ac_2O using NaOAc as a base and subsequently the respective thioglycoside **121** was formed using TolSH and $BF_3{\cdot}Et_2O$ complex in good yields over two steps. Methanolysis using NaOMe/MeOH and esterification with BzCl gave thioglycoside **122** with a participating Bz-PG in the 2-position in very good yields over two steps. Saponification of thioglycoside **122** followed by benzylation under standard conditions then gave thioglycoside **78** in very good yields over two steps.

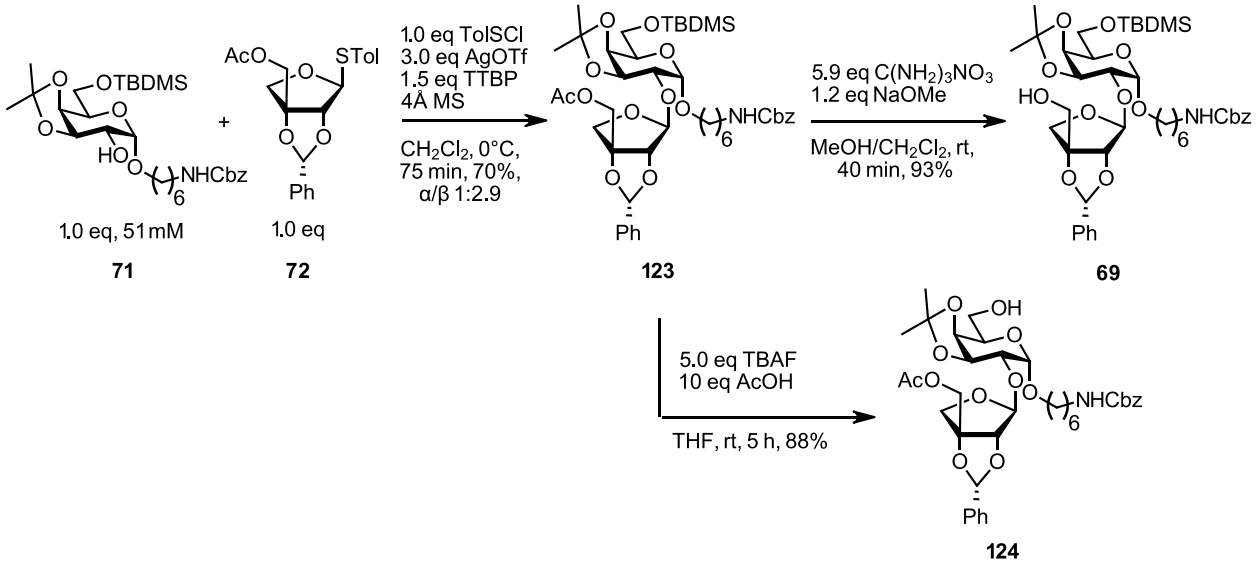


*Scheme 27: Synthesis of L-galactose donors **122** and **78**.*

2.3 Synthesis of linear RG-II side chain A fragments

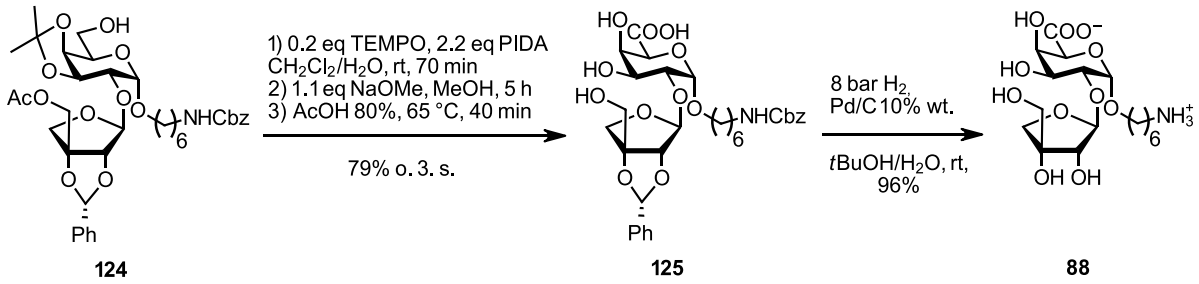
2.3.1 Disaccharide fragment 88

With the building blocks assembled, the investigation of glycosylation reactions for preparation of oligosaccharides was commenced. As shown in Scheme 28, galactose acceptor **71** was glycosylated with apiose donor **69** to obtain disaccharide **123**. Initial experiments with the NIS/TMSOTf promotor system were found to be sluggish, partly due to formation of TMS-protected acceptor side product. Using the NIS/TfOH-promotor system was more effective, however, the temperature range was limited due to insufficient activation of donor **72** at low temperatures and acid-mediated decomposition of materials at higher temperatures, not only leading to moderate yield, but also to an eratic anomeric ratio in the product. It was realized that high temperatures favoured the formation of the desired β-product. The same reaction with TolSCl and AgOTf as activator and TTBP as a base at 0°C afforded the products in an α/β-ratio of 1:2.9 in good yield, which were well separated in flash chromatography. However, the TolSCl should be added carefully, ideally substochiometrically, as rapid degradation was observed when excess was added. With disaccharide **123** in hand, the transient Ac-PG by was removed by methanolysis with NaOMe/MeOH, but initially silyl-migration negatively affected the yield and purity of alcohol **69**. This was avoided by the use of a mild guanidine/guanidinium nitrate solution described in the literature[121], affording alcohol **69** in excellent yield for later use as an acceptor in further glycosylations. For the synthesis of disaccharide fragment **88** (Scheme 18), the TBDMS-PG in disaccharide **123** had to be removed. This was achieved by treating the starting material with TBAF-solution in conjunction with acetic acid, which was necessary to counteract the basicity of TBAF[122], affording alcohol **124** in very good yield.



*Scheme 28: Synthesis of disaccharides **69** and **124**.*

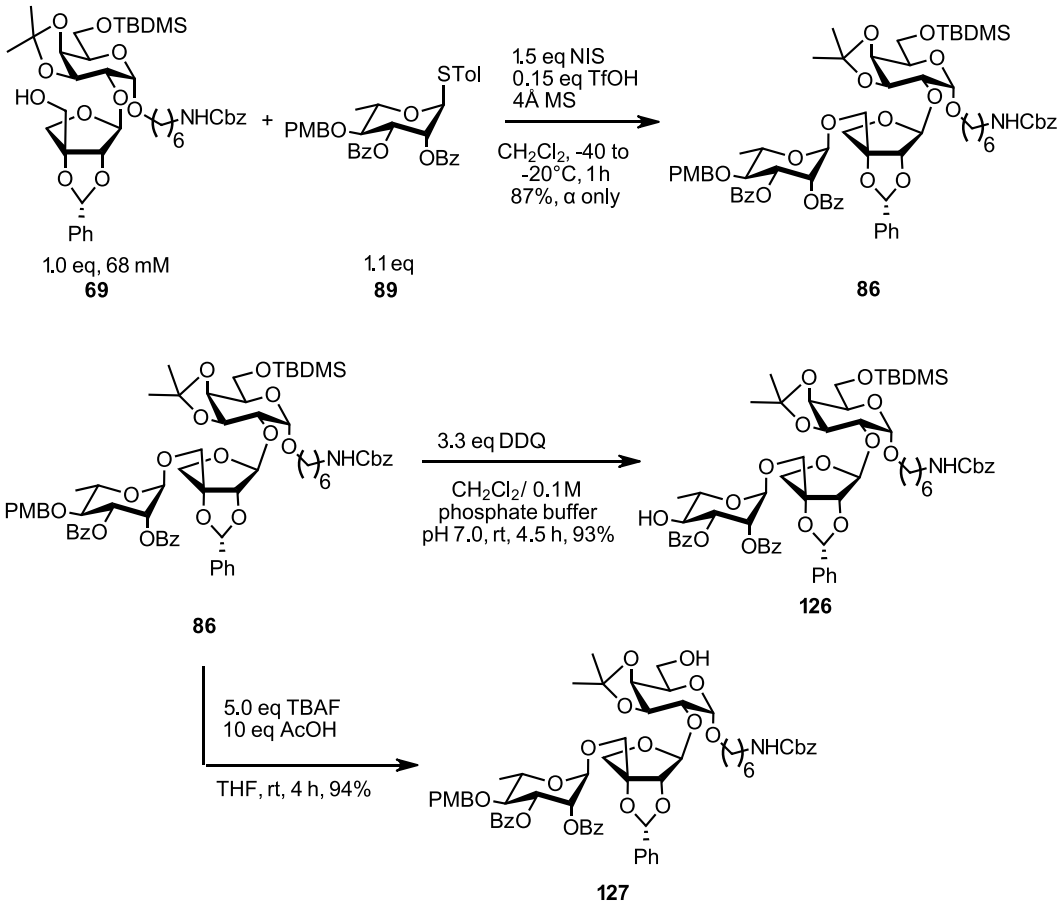
The free hydroxy group in the 6-position of disaccharide **124** was oxidized with PIDA and catalytic amounts of TEMPO in the presence of water[92] as shown in Scheme 29. The crude carboxylic acid was then treated with NaOMe/MeOH to remove the acetyl ester and afterwards treated with 80% AcOH to cleave the *i*PrA-PG[95], affording partially protected disaccharide **125** in good yield over 3 steps. This procedure was found more convenient compared to the two-step oxidation protocol with DMP as reagent and subsequent pinnick oxidation used in older literature[123]. Partially protected disaccharide **125** was then treated with H_2 in the presence of palladium on carbon catalyst to obtain fully deprotected disaccharide **88** in excellent yield. The use of *t*BuOH/water instead of solvent mixtures including MeOH was found crucial, as the prolonged reaction times necessary to achieve complete turnover led to alkylation of the amine when MeOH was used. Interestingly, this side reaction had been reported to only occur in the presence of oxygen when the experiment was not carefully performed[124], but in this case, methylation was observed despite application of accurate and repeated cycles of first argon addition and, after addition of the catalyst, hydrogen addition.



*Scheme 29: Oxidation and deprotection of alcohol **125** to afford disaccharide fragment **88**.*

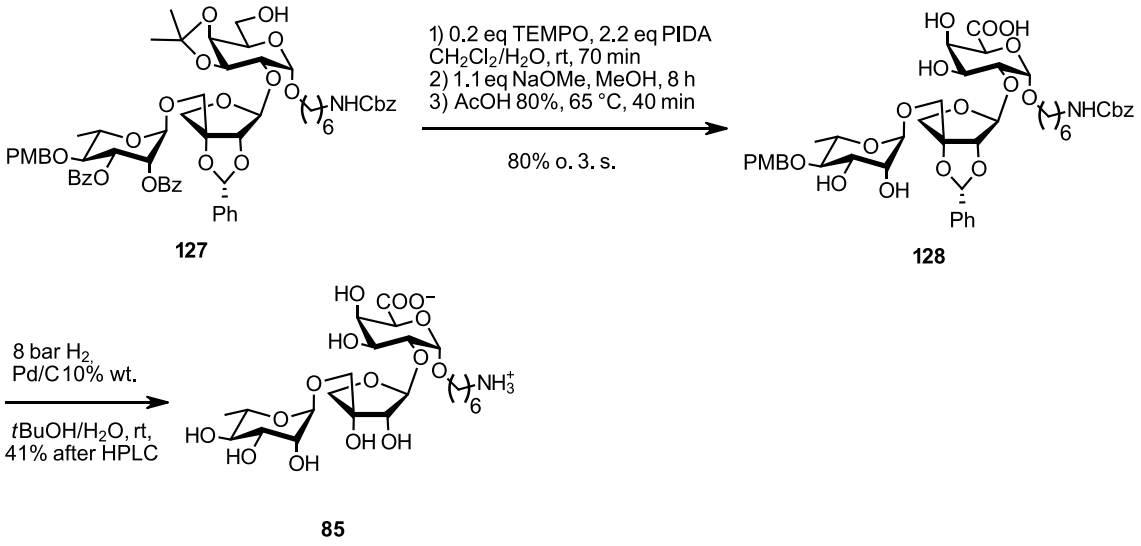
2.3.2 Trisaccharide fragment 85

Next, the trisaccharide intermediates **126** and **127** (Scheme 30) were prepared for further use. With disaccharide acceptor **69** and building block **89** in hand, a standard glycosylation with NIS/TfOH was performed to obtain trisaccharide **86** in very good yield and excellent stereoselectivity. The stereoselectivity was ensured by the neighboring group participation effect of the Bz-PG in 2-position. Removal of the PMB-PG by oxidation with DDQ in a buffered reaction media afforded acceptor **126** in excellent yield for further glycosylations. For the synthesis of the final linear trisaccharide fragment **88**, fully protected trisaccharide **86** was treated with AcOH and TBAF-solution to afford alcohol **127** in excellent yield.



*Scheme 30: Synthesis of trisaccharide intermediates **126** and **127**.*

To obtain the fully deprotected trisaccharide fragment **85** I employed the same reaction sequence as found suitable for the disaccharide, as shown in Scheme 31. Alcohol **127** was oxidized with TEMPO/PIDA in an aqueous environment, followed by methanolysis with NaOMe/MeOH and subsequent treatment with 80% AcOH to afford partially deprotected trisaccharide **128** in very good yield over three steps. Minor loss of the PMB-PG was observed during the *i*PrA cleavage in AcOH, which has been previously reported.[125] Hydrogenolysis of partially protected disaccharide **128** in the precence of palladium on carbon afforded trisaccharide fragment **85** in poor yield after RP-HPLC purification along with *N*-methylated and *N,N*-dimethylated side products. The formation of the methylated side products may be explained by the cleavage product *p*-methoxy toluene donating the methyl group in a reductive amination-type reaction during prolonged reaction times. This finding is in line with analogous reductive aminations when THF was used as the solvent for this hydrogenolysis reaction. Apparently, primary alcohols and ethers may eliminate β-hydrogen atoms in palladium on carbon-catalyzed reactions, leading to the formation of small amounts of aldehydes or other reactive species that can undergo Schiff-base formation with free amines before reduction. To the best of my knowledge these findings are not well documented in literature. The reductive amination can be avoided by first cleaving the PMB group in AcOH before performing the hydrogenolysis.

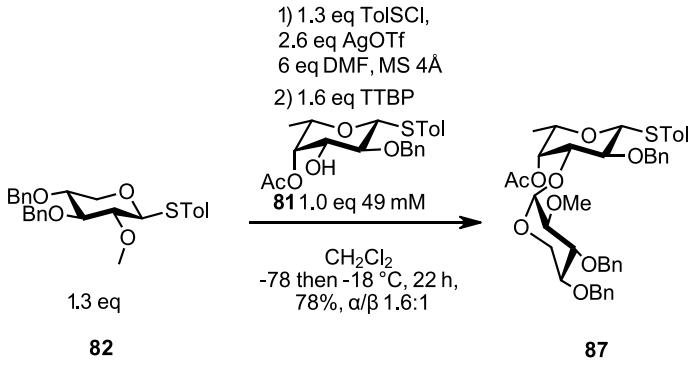


*Scheme 31: Oxidation and deprotection of alcohol **127** to provide trisaccharide fragment **85**.*

2.3.3 Pentasaccharide fragment

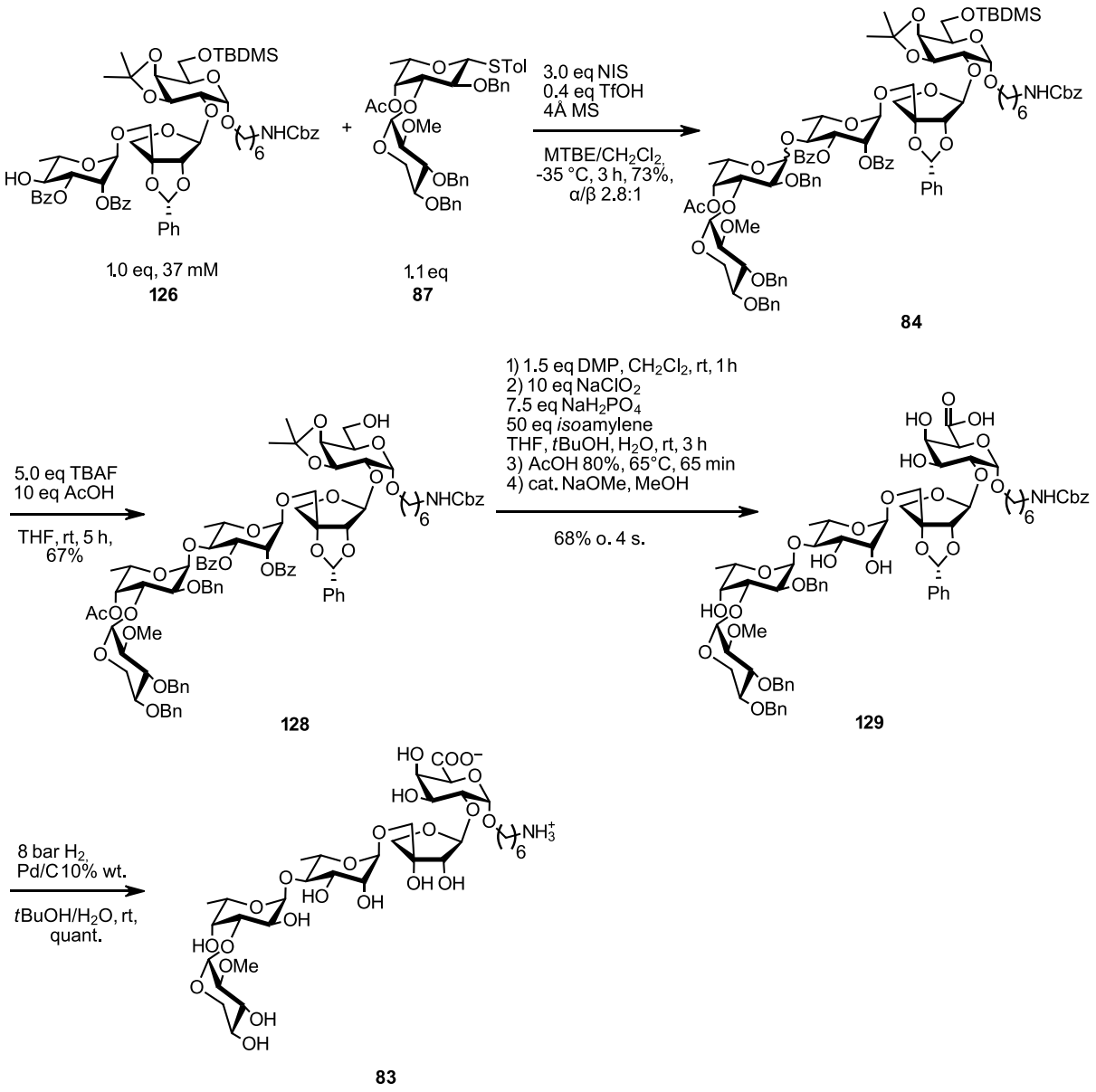
After successful preparation of di- and trisaccharide fragments **88** and **85**, pentasaccharide fragment **83** was prepared. With trisaccharide acceptor **128** already in hand, disaccharide donor **87** had to be synthesized. As the synthesis of 1,2-*cis*-xyloses is notoriously difficult[97] I decided to introduce this bond as early as possible in the synthesis. The only reported possibility for a highly stereoselective introduction of α-xylosides, a specific PG-pattern at the xylose, including the basic and nucleophilic picolinoyl group, is required that has to be introduced by a lengthy building block synthesis[91, 100].

Another possibility to increase the α-selectivity in this glycosylation is the addition of external nucleophiles[54] such as DMF[126, 127] and NFM[128] to form the imidate adduct as an intermediate. Therefore, a new methodology was developed consisting of preactivation of donor **82** with TolSCl/AgOTf at low temperature in the presence of DMF and then adding acceptor **81** and stirring the reaction mixture at -20 °C to afford disaccharide **87** in a modest α/β-ratio of 1.6:1 as depicted in Scheme 32. When PTFAI-donor **115** (Scheme 25) was activated with catalytic amounts of TfOH in the presence of DMF, a slightly further improved α/β-ratio was observed, probably due to a lower concentration of triflate nucleophile or due to a promotor effect from the *N*-phenyl-trifluoroacetimidate. Unfortunately, lower and inconsistent yields were observed due to the instability of PTFAI-donor **115**. Overall, the additional steps to afford PTFAI-donor **115** along with the reduced yield in the glycosylation reaction resulted in a less efficient synthesis of disaccharide **87**, so thioglycoside **82** was used in further syntheses. The equivalents of external nucleophile DMF used in the glycosylation influence the resulting α/β-ratio and provides an opportunity for reaction optimization. Also, the use of freshly prepared TolSCl is important to activate the donor quantitatively. To further improve the stereoselectivity in the synthesis of key intermediate disaccharide **87**, other methodologies may be explored. A recent paper of Hu *et al.* reports a 1,2-*cis*-xylosylation using a per benzylated xylose thioglycoside,[128] having a similar structure as thioglycoside **82**. By applying their flexible 1,2-cis α-glycosylation approach with the external nucleophile NFM in conjunction with TBAI, it might be possible to increase the α-selectivity in our synthetic approach and facilitate the synthesis of tetrasaccharide donor **149** (Scheme 17).



*Scheme 32: Synthesis of disaccharide donor **87**.*

The preparation of pentasaccharide **83** is shown in Scheme 33. Protected pentasaccharide **84** was synthesized from donor **87** and acceptor **128** using standard NIS/TfOH-activation in the presence of MTBE to give the product in good yield with an α/β-ratio of 2.8:1. Even though a remote-participating 4-acetyl group in the fucose donor and a solvent participation effect were used to support stereocontrol, only a modest excess of the α-anomer was formed. The two anomers were found inseperable by column chromatography, so the anomeric mixture of pentasaccharides **129** was employed in the next step. TBDMS-deprotection using AcOH/TBAF-solution and subsequent flash chromatography gave the pure desired α-anomer alcohol **128** in fair yield. A sequence of Dess-Martin oxidation, Pinnick oxidation, treatment with AcOH and methanolysis then gave partially protected pentasaccharide **129** in fair yields over four steps. To improve the yield of the oxidation, TEMPO/PIDA is recommended, as the method proved useful for the oxidation of the di- and trisaccharide fragments, which have been performed at a later time. Global deprotection of pentasaccharide **129** was achieved by hydrogenolysis in presence of palladium on carbon to afford pentasaccharide **83** in quantitative yield. In a test hydrogenolysis of pentasaccharide **129** using prolonged reaction time, traces of the *N*-methylation product (14 daltons more than the desired product) were observed, as well as very small amounts of a side product with a mass of 14 daltons less than the desired product. This finding is in line with the previous observations from the hydrogenolysis of the di- and trisaccharides. The methyl group might origin from the 2-OMe-xylose ether, with the liberated species undergoing subsequent reductive amination.

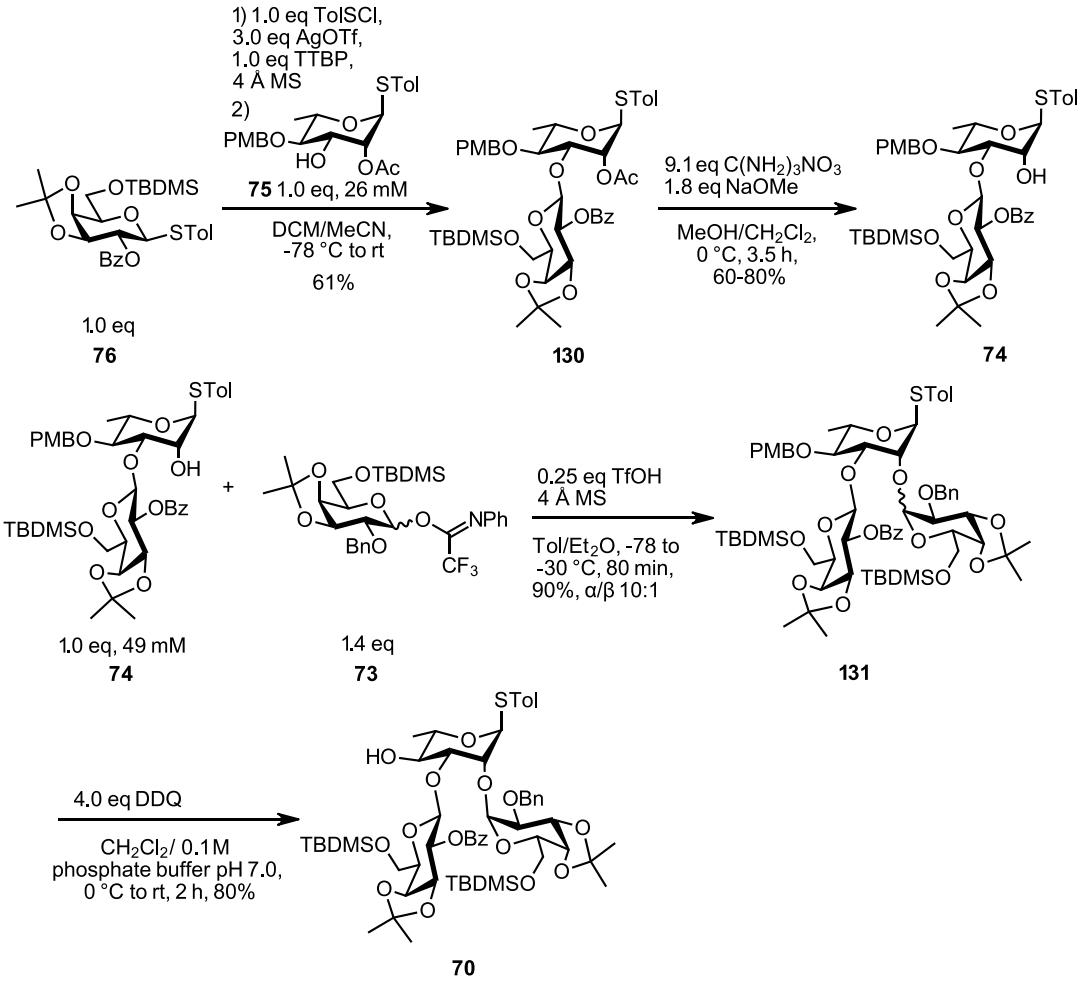


*Scheme 33: Synthesis of pentasaccharide **83**.*

2.4 Synthesis of RG-II side chain A nonasaccharide

2.4.1 The pentasaccharide acceptor 67

With the knowledge obtained from the synthesis of the linear side chain A fragments I moved on and tackled the branched rhamnose core region of target structure nonasaccharide **65** (Scheme 17). In line with the convergent retrosynthetic approach it was aimed for the preparation of the complex ramified pentasaccharide acceptor **67**. For that, trisaccharide donor **70** needed to be synthesized from the respective monosaccharide building blocks. To glycosylate the rhamnose core I decided to follow the order of substitution in the 3-, then 2-, and then 4-position, which has previously been described as successful[88] for a RG-II side chain A tetrasaccharide, as summarized in Scheme 34. Thioglycoside donor **76** was preactivated with TolSCl/AgOTf at low temperatures, then rhamnose acceptor **75** was added and the mixture warmed up to rt, affording disaccharide **130** in fair yield, presumably with the α-glycoside as a side product, which would be in line with the literature[71], but could not be isolated. This may be explained by a S_N2-reaction in β-triflate adducts, formed in equilibrium with the dioxolenium ion intermediate in the presence of high concentrations of nucleophilic triflate anions. The reaction between PTFAI-donor **100** (Scheme 20) and acceptor **75** catalyzed by TMSOTf was also investigated but substantial amounts of 1,6-anhydro galactose, TMS-protected acceptor and orthoester were formed. When the same glycosylation of PTFAI-donor **100** with acceptor **75** was catalyzed by TfOH in CH_2Cl_2 a good yield of **130** was obtained after rearrangement of initially formed galactose orthoester that had been isolated previously and can be monitored by TLC. However, the material loss due to the additional steps required to prepare PTFAI-donor **100** from the thioglycoside made this route less attractive compared to directly employing the thioglycoside. As expected no aglycon transfer was observed, as the equatorial hydroxy group in the 3-position clearly outcompetes the nucleophilicity of the sulfur atom in rhamnose acceptor **75.** Also, as rhamnose is a 6-deoxy sugar, rhamnose acceptor **75** would form upon aglycon transfer a less stabilized oxocarbenium ion compared to galactose donor **76**. To install the 2-glycoside in disaccharide **130**, a selective deacetylation was performed. This reaction was challenging as axial esters are more stable then equatorial esters[129] leading to a very small difference in reactivity between the Ac-PG in the rhamnose system and the Bz-PG in the galactose system. By treating disaccharide **130** with guanidine/guanidinium nitrate solution[121], the esters could be differentiated to afford acceptor **74** in fair to very good yields. The yield was found to depend on the water content as well as the time point of quenching, as too short reaction times gave insufficient turnover, while too long reaction times resulted in substantial saponification of both esters. As the Bz-PG can sometimes be selectively introduced in equatorial over axial positions[130], the fully saponified side product diol was reacted with BzCl and pyridine to convert the side product to the desired product **74**. Unexpectedly, not even traces of acceptor **74** were produced and esterification exclusively



*Scheme 34: Synthesis of branched trisaccharide donor **70**.*

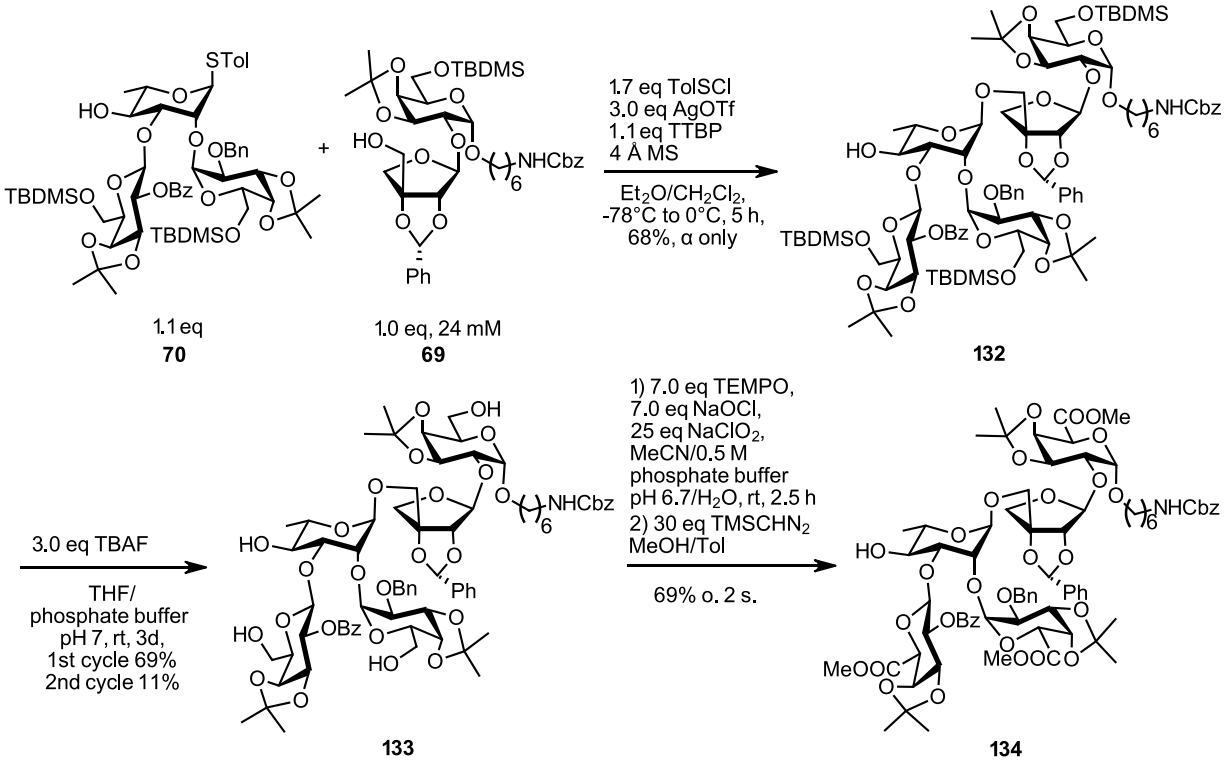
happened at the rhamnose 2-position, probably due to the rhamnose 2-alcohol being more electron rich in this case. Alcohol **74** was then reacted with PTFAI-donor **73** in toluene/Et_2O containing a catalytic amount of TfOH to afford a 10:1 mixture of α- and β-trisaccharides **131** in excellent yield. When thioglycoside **101** was preactivated with TolSCl/AgOTf in the presence of Et_2O/CH_2Cl_2 and TTBP before acceptor **74** was added, the α/β-stereoselectivity deteriorated to 1:1. Again, no aglycon transfer was observed, which can be explained by the same rationale as in the previous glycosylation. The difference in stereoselectivity for the preactivated and premixed glycosylations described above remain currently elusive, but may be explained either by a promotor effect and/or the different triflate concentrations employed. Unfortunately, effects of the slightly changed solvent mixture cannot be ruled out. To test the promotor effect-hypothesis further investigations must be conducted. *N*-phenyl-trifluoracetamide could be added to the TolSCl/AgOTf preactivated glycosylation to test for an altered anomeric ratio of products, testing its efficiency as modulating nucleophile. Separation of the anomeric mixture of trisaccharides **131** was found challenging using flash chromatography, so the anomeric mixture was treated with DDQ in a buffered environment to afford pure α-anomer alcohol **70** in very good yields after flash chromatography.

Trisaccharide **70** was found to have limited reactivity as an acceptor. In a test reaction preactivation of fucose disaccharide donor **87** (Scheme 32) and addition of trisaccharide **70** led to aglycon transfer followed by self glycosylation with unacceptably poor yields. Probably steric hindrance lowered the nucleophilicity of the hydroxy group in the 4-position of trisaccharide **70**. It was therefore decided to move on according to the retrosynthetic plan and pentasaccharide acceptor **132** was prepared. This initially was performed with 4-PMB-protected trisaccharide **131** (anomeric mixture), which provided the desired 4-PMB-protected pentasaccharide in fair yield and with high α-selectivity after glycosylation with disaccharide acceptor **69** both when NIS/AgOTf or TolSCl/AgOTf were used as activator system at temperatures around 0°C. Subsequent PMB-deprotection allowed purification of desired pentasaccharide acceptor **132** as a single diastereomer. As depicted in Scheme 35, alternatively the reaction of PMB-deprotected trisaccharide **70** and disaccharide acceptor **69** activated by TolSCl/AgOTf at lower temperature in presence of Et_2O was investigated. Gratifyingly, gradual warming resulted in significant conversion at 0°C, providing pentasaccharide **132** in fair yield as the α-anomer only. Self glycosylation of donor **70** was not prominent, as the nucleophilicity of the primary hydroxy group in disaccharide acceptor **69** outcompetes the sterically hindered 4-hydroxy group of trisaccharide donor **70** (Scheme 4). The high stereoselectvity may be explained by the sterical demand of the 2-glycoside efficiently shielding the β-face of rhamnose donor **70**. A conformational change at higher temperatures may be the reason for the comparably high temperature of 0 °C required for the reaction to proceed. However, further investigations are necessary.

Unfortunately, pentasaccharide **132** was found to be a bad acceptor in glycosylations with fucose disaccharide donor **87**, as no or sluggish reactions were observed. A possible explanation may be that the rotation cones of the TBDMS-protected C6-position of galactose are too big, thereby shielding the nucleophilic hydroxy group. Therefore, the TBDMS-PGs were cleaved and the resulting hydroxy groups oxidized in order to lower the sterical demand.

To remove the TBDMS groups in pentasaccharide **132,** a buffered TBAF-solution[102] was chosen, reducing the risk of undesired pH-induced protective group cleavages. Treating pentasaccharide **132** with this solution led to removal of the TBDMS-PGs in fair yield, affording tetraol **133**. After flash chromatography partially TBDMS-protected intermediates were isolated along with the product and converted under the same conditions to afford more fully deprotected product tetraol **133**. Facile purification of tetraol **133** fully removing TBAF-related contaminants was achieved by flash chromatography employing a toluene/acetone mixture. Even though acetone only forms small amounts of hemiacetal with primary alcohols[131], it was hypothesized that the hemiacetal formation between primary hydroxyls and excess acetone on acidic silica may alter polarity of primary alcohols significantly in chromatography, facilitating elution of highly polar tetraol **133**. Oxidation of tetraol **133** posed the challenge of differentiating the three primary alcohols from the secondary alcohol.

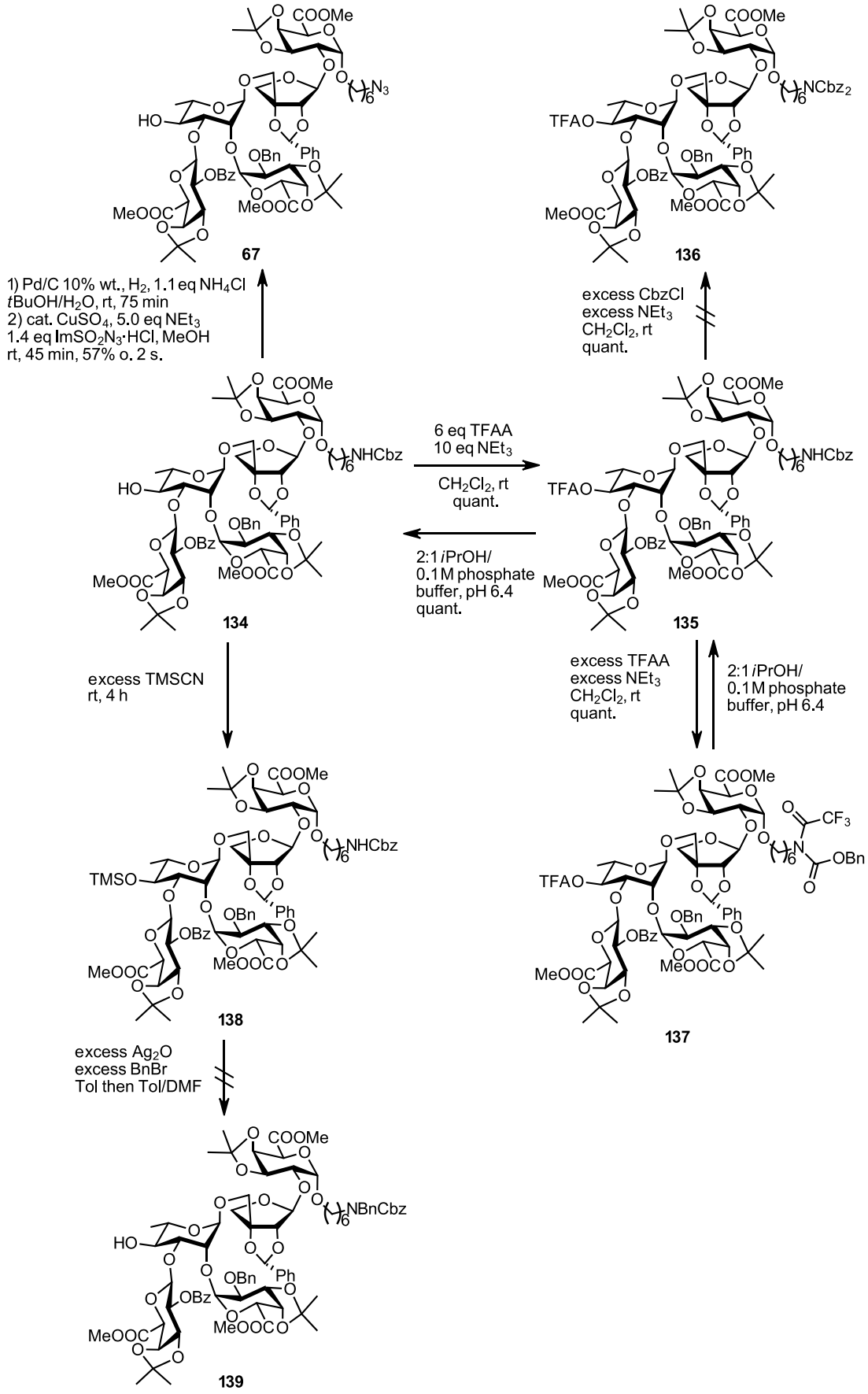
By treating the tetraol **133** with TEMPO in conjunction with buffered NaOCl and $NaClO_2$ solution[132] the three primary hydroxy groups were selectively oxidized and after esterification with TMS-diazomethane in toluene/MeOH[133], pentasaccharide acceptor **134** was obtained in fair yield over two steps. The incompletely oxidized pentasaccharide with one primary alcohol left was formed as the main side product. The ketone side product resulting from the oxidation of the rhamnose 4-hydroxy group was found only in traces. Further optimization of the reaction conditions may improve the yield significantly.



*Scheme 35: Synthesis of pentasaccharide acceptor **134**.*

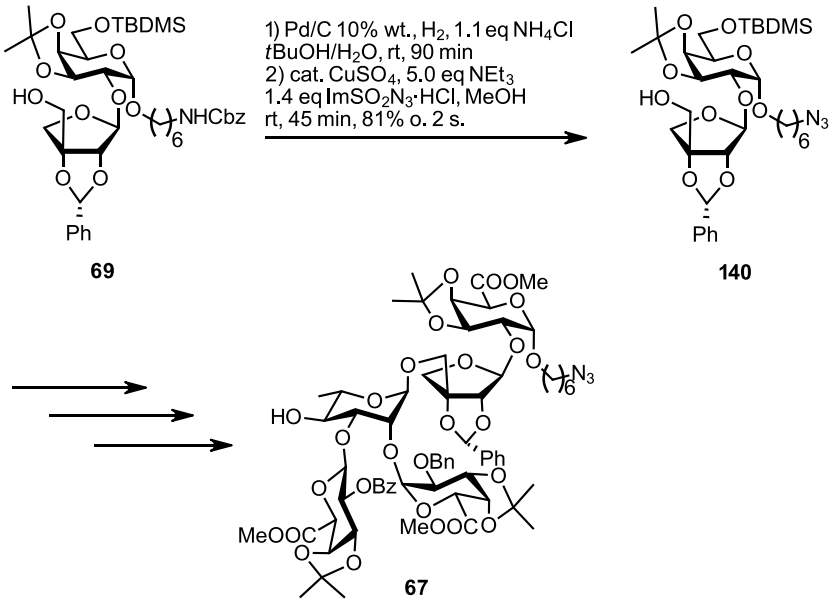
It was realized later that the aminolinker bearing a NHCbz-carbamate was insufficiently protected for further transformations. This will be covered in detail in the paragraph on the [4+5]-Glycosylation. To overcome this major road block, several detours were investigated based on changing the protection of the nitrogen, as summarized in Scheme 36. It was possible to introduce transient protective groups at the hydroxy group in the 4-position of the rhamnose of pentasaccharide **134**. For example, a TFA-ester was installed in quantitative yield by using TFA-anhydride/NEt_3 to afford pentasaccharide **135**. By treatment with excess reagents, it was also possible to convert the -NHCbz group to a -NTFACbz moiety. Unfortunately, this -NTFACbz amide bond in pentasaccharide **137** was found to be more labile than the TFA-ester bond, not allowing selective deprotection of the ester. An attempt to convert the -NHCbz moiety in pentasaccharide **138** to $-N(Cbz)_2$ by using excess CbzCl/NEt_3 was also unsuccessful. TMS-etherification of the hydroxy group in the rhamnose C-4 position with TMSCN proceeded smoothly to afford pentasaccharide **138**. However, subsequent introduction of a Bn-PG to

the -NHCbz moiety of pentasaccharide **138** with Ag_2O/BnBr failed. I therefore decided to cleave the Cbz-PG in pentasaccharide acceptor **134** by hydrogenolysis in the presence of NH_4Cl, avoiding removal of the Bn-PG[134] and obtaining a stable ammonium salt. Then, without purification a copper-catalyzed diazotransfer with potentially explosive (precautions!) imidazole-1-sulfonyl azide hydrochloride[135, 136] was performed to afford the azido-protected pentasaccharide **67** in fair yields over two steps. Unreacted starting material was obtained as well, as the hydrogenolysis did not reach completion. This synthetic sequence was not optimized.



*Scheme 36: Attemps to protect the NHCbz carbamate in pentasaccharide acceptor **67**.*

Performing the hydrogenolysis and diazotransfer sequence on disaccharide acceptor **69** (Scheme 37) gave the azido-protected acceptor **140** in very good to excellent yield, allowing the synthesis of the same pentasaccharide **67** by glycosylation of disaccharide **140** with trisaccharide donor **70** followed by a sequence of TBDMS-deprotection, oxidation and methyl-esterification with the described methods as above and in similar yields.



*Scheme 37: Resynthesis of pentasaccharide acceptor **67** with azido-protected disaccharide acceptor **140**.*

2.4.2 The tetrasaccharide donor 68

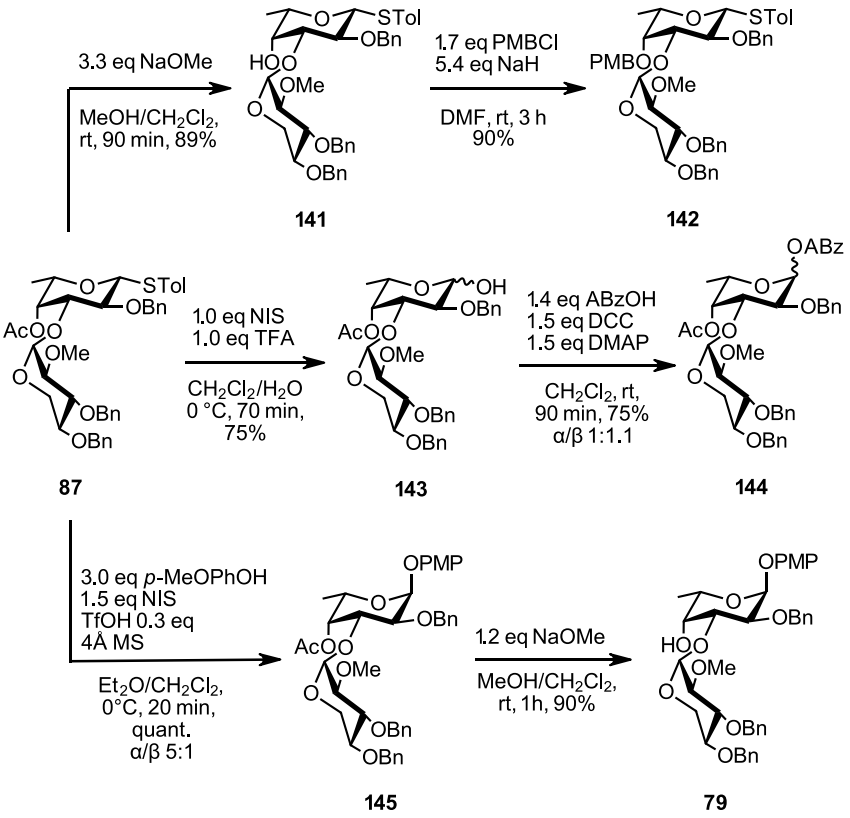
As shown in the retrosynthetic analysis (Scheme 17), the second major building block required for the synthesis of target nonasaccharide **65** was tetrasaccharide donor **68**, reacting with pentasaccharide acceptor **67** in the final [4+5]-glycosylation.

In the initial attempt for construction of tetrasaccharide donor **68** it was opted to keep the STol-PG at the anomeric fucose position for later use as a donor (Scheme 38). Therefore, disaccharide **87** was reacted with NaOMe to afford disaccharide alcohol **141** in very good yield. The Ac-PG proved to be unexpectedly stable, requiring excess of NaOMe in high concentration for methanolysis. The xyloside in the 3-position may pose a conformational restriction (ring lock), causing a significantly lower reaction rate for the axial ester[129]. Disaccharide alcohol **141** was found to have very low reactivity as an acceptor in preactivation glycosylations with glucose donor **119** or glucuronic acid donor **80**. Both reactions suffered from aglycon transfer and subsequent self-glycosylation. This may be explained by the much higher stability of the oxocarbenium ion formed from fucose disaccharide acceptor **141** compared to the glucosyl- and galactosyl-oxocarbenium ions. The deoxy-nature of the fucose acceptor **141** increases its reactivity as a donor. Furthermore, the nucleophilicity of the 4-postions in galactose and fucose systems is very low (Scheme 4). Conformational and/or steric effects exerted by the 3-xylosyl substituent may further lower acceptor nucleophilicity.

Discouraged by these findings, disaccharide **87** was modified in three different ways. First, it was protected in the 4-position of the rhamnose with a transient protecting group to test the possibility of performing a [2+2+5]-glycosylation approach.

An attempt to introduce the DMNPA-PG as a strong remote participating group to disaccharide acceptor **141** using TMSOTf and DMNPAA failed and gave the TMS-protected product, due to the low nucleophilicity of disaccharide acceptor **141**. Instead, the PMB-protected disaccharide donor **142** was obtained in excellent yields after treatment of acceptor **141** with PMBCl and NaH. However, glycosylation of pentasaccharide **132** with donor **142** did not afford any product, again due to the low nucleophilicity of acceptor **132**. To investigate if an Au^{+}-catalyzed glycosylation method would provide better results, an ABz-donor was synthesized from disaccharide **87**. Therefore, thioglycoside **87** was hydrolysed with NIS, TFA and water to afford hemiacetal **143** (Scheme 38). Subsequent Steglich-esterification using freshly prepared ABzOH, DCC and DMAP afforded ABz-donor **144** in excellent yield as an α/β-mixture of products. The results of the [2+5]-glycosylation with donor **144** will be covered in the next paragraph.

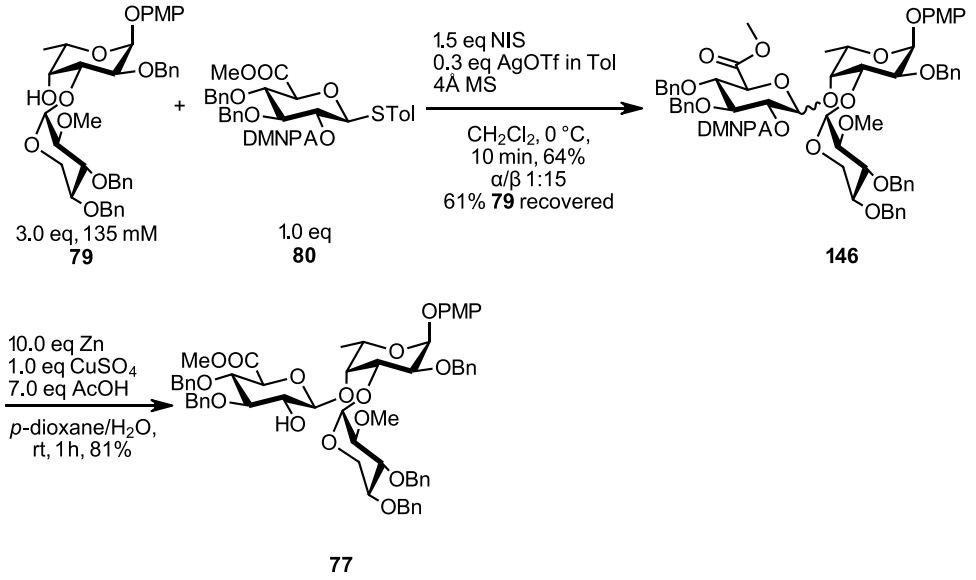
Due to the very low nucleophilicity of fucose disaccharide acceptor **141**, aglycon transfer was a major hurdle to overcome in glycosylation reactions. To avoid the aglycon transfer problem, a PMP-PG was introduced to the anomeric position of the fucose (Scheme 38). This was achieved by reacting thioglycoside **87** with *p*-methoxyphenol and NIS/TfOH as the promotor system in CH_2Cl_2/Et_2O, affording glycoside **145** quantitatively in an α/β-ratio of 5:1 (separable by flash chromatography). Treating glycoside **145** with NaOMe gave acceptor **79** in excellent yield.



*Scheme 38: Synthesis of disaccharide donors **142** and **144** as well as disaccharide acceptors **141** and **79**.*

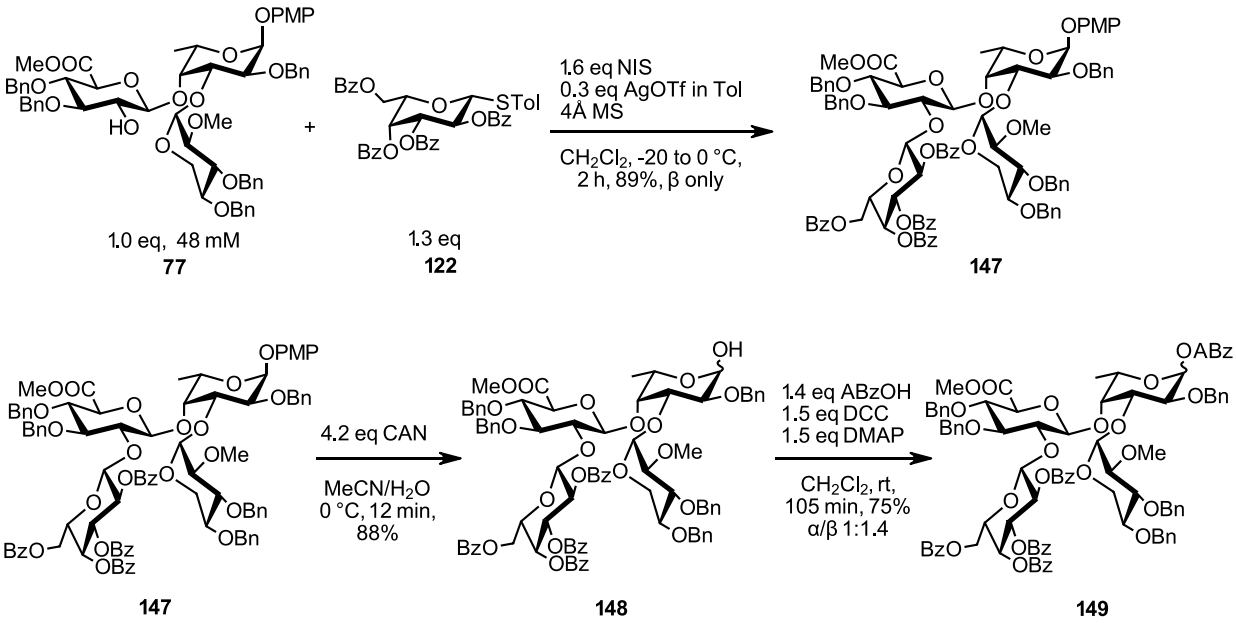
With acceptor **79** in hand, it was reacted with glucuronic acid donor **80** using NIS/AgOTf to afford trisaccharide **146** in fair yield and with high excess of the desired β- anomer. It is hypothesized that maybe the strong NGP of the DMNPA-PG played a beneficial role (Scheme 39) as a similar reported reaction with a Bz-PG at the donor failed (Scheme 16), but the reasons currently remain elusive. However, this reaction was found to be quite erratic, sometimes producing the desired product but many times producing a complex mixture of products while consuming both donor and acceptor. One reason was decomposition of reactive donor **80** during the reaction, which could be counteracted by raising the amount of acceptor **79** to three equivalents. Surprisingly xylosyl-migration was identified as a major side reaction (identified by Katharina Obleser). It was found that the pH-value under these reaction conditions played a crucial role as employing TfOH instead of AgOTf immediately decomposed all starting materials. This led to the assumption that reagent quality was an important factor.

It was hypothesized that AgOTf forms small quantities of TfOH in presence of moisture during long storage times and/or upon contact with light during handling, as the silver ions get reduced to metallic silver. This causes a lower pH-value in reactions involving AgOTf and causes phantom catalysis by TfOH. To circumvent this issue, I produced an AgOTf stock solution in anh. toluene that is stored over Ag_2O to neutralize any acid formed. In conjunction with fresh NIS the reaction became reproducible and allowed recovery of excess acceptor **79**. Further experiments are required to optimize this key reaction. As the reaction is believed to be highly sensitive to the pH-value, it is suggested to experiment with other promotor systems such as DMTSF[137] in conjunction with a sterically hindered organic base such as TTBP or 2,6-di-*tert*.-butyl-4-methyl-pyridine. Also, the activation temperature might be significantly lowered by employing this strong thiophile, which may help to avoid side reactions. Trisaccharide **146** was subsequently deprotected using Zn in conjunction with AcOH and $CuSO_4$ as a catalyst, affording alcohol **77** in very good yield.



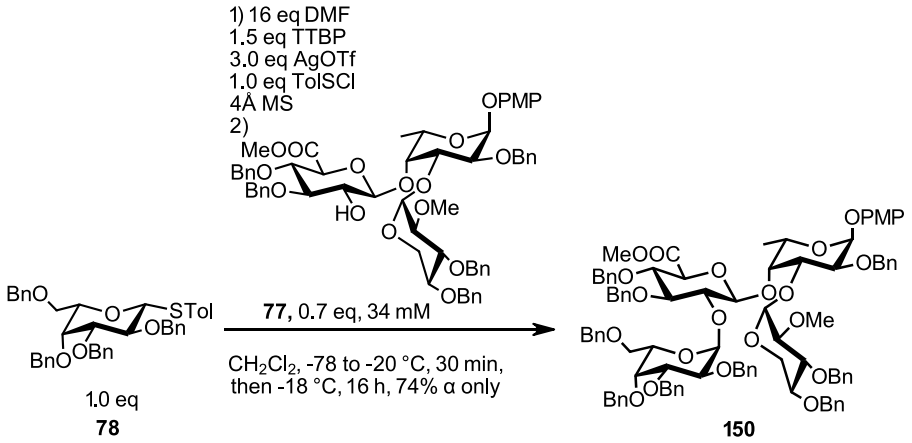
*Scheme 39: Synthesis of trisaccharide acceptor **77**.*

Trisaccharide acceptor **77** and L-galactose donor **122** were reacted in the presence of NIS/AgOTf to afford tetrasaccharide **147** in very good yield and excellent stereoselectivity due to neighboring group participation (Scheme 40). The PMP-PG was subsequently cleaved by oxidation with CAN to afford hemiacetal **148** in very good yield. Steglich esterification of hemiacetal **148** with ABzOH gave tetrasaccharide donor **149** in good yield. It was realized only later that the L-galactose glycoside had the wrong anomeric configuration. Nevertheless, tetrasaccharide donor **149** represented a valuable test substrate for the final glycosylation reaction.



*Scheme 40: Synthesis of tetrasaccharide donor **149**.*

To obtain tetrasaccharide donor **149** with the natural occurring anomeric configuration I opted for an external nucleophile moderated glycosylation approach to introduce yet one more 1,2-*cis*-glycosidic bond (Scheme 41). Using the newly developed DMF-mediated preactivation glycosylation for thioglycosides, donor **78** was preactivated with TolSCl/AgOTf in the presence of DMF to afford the imidate intermediate. Gratifyingly, the intermediate reacted with trisaccharide acceptor **77** to give the desired α-product tetrasaccharide **150** in good yield and excellent stereoselectivity.



*Scheme 41: Synthesis of tetrasaccharide **150** with 1,2-cis-L-galactoside.*

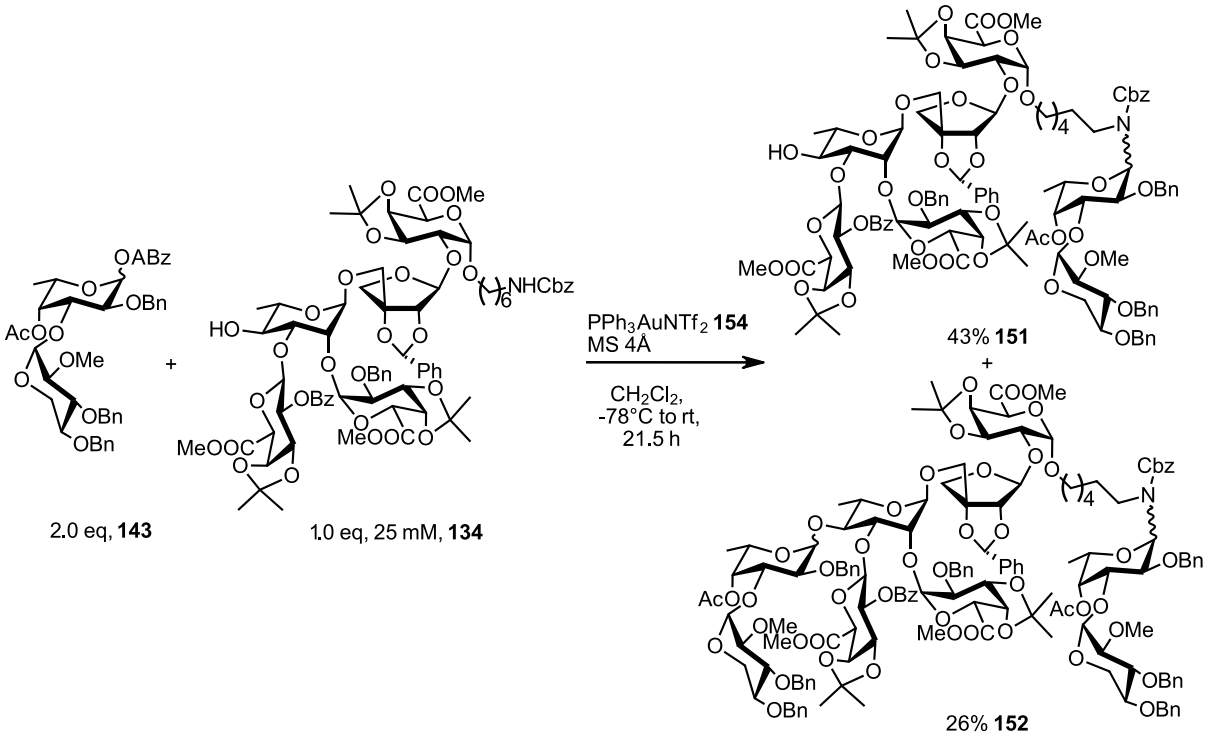
2.4.3 [4+5]-Glycosylation

As both building blocks, tetrasaccharide donor **149** and pentasaccharide acceptor **134** were successfully assembled, their coupling to afford a protected nonasaccharide was investigated next. At this point the amounts of high value building blocks available were generally around ~30 mg, which did not allow for broad screens or reactions in larger scales. Nevertheless, test glycosylations, typically on scales between 0.1-5 mg, were performed to gain information about the reactivities of tetrasaccharide donor **149** and pentasaccharide acceptor **134**.

First, a test glycosylation using disaccharide thioglycoside donor **87** (Scheme 38) and pentasaccharide acceptor **134** was performed. As activator system, TolSCl/AgOTf in conjunction with TTPB and Et_2O was chosen. Unfortunately, the reaction proceeded very sluggishly during warming up from -78°C to 0°C. Upon warming to rt a complex mixture was formed. Nevertheless, some product fraction could be isolated for MALDI-analysis, which indicated the desired mass adducts.

To avoid decomposition, the activator system was changed. The gold catalyzed ABz-glycosylation has proven to be a valuable method for challenging glycosylations[78, 79, 96] with sensitive substrates. The donor can be activated with PPh_3AuNTf_2 or PPh_3AuOTf as catalyst. It was decided in favour of PPh_3AuNTf_2 as it was commercially available, a stable solid material, considered to be the milder catalyst and was shown to give good α-selectivity in certain cases[79]. A test glycosylation with ABz donor **143** and pentasaccharide acceptor **134** was performed (Scheme 42). Unfortunately, the reaction behaved erratic, requiring multiple additions of catalyst. After the last addition, the reaction finished within 1.5 h at rt, giving a main product **151** and more apolar product **152**.

Unexpectedly, thorough investigation of the NMR-spectra of main product **151**, which formed in both the TolSCl/AgOTf- and ABz/PPh_3AuNTf_2-glycosylations (confirmed by stacked HSQC), revealed a shift of the linker -NCH_2- moiety in the HSQC-spectrum while the 4-position of the rhamnose moiety remained unaffected (Figure 2). This indicated that the linker carbamate had acted as the nucleophile. Thus, the amine was insufficiently protected for the desired transformations. Despite my best efforts, the definite connectivity (*O*- or *N*-glycoside) could not be determined by NMR. It was hypothezised that the lack of signal for the anomeric carbon of fucose is due to an altered relaxation time of the nucleus in the *N*-glycoside, but it cannot be ruled out that both *N*- and *O*-glycoside had formed. Further specialized NMR-experiments are required. Gratifyingly, the doubly glycosylated side product **152** was also found, indicating that the rhamnose 4-position of acceptor **134** can be accessed, despite the high steric hindrance.



*Scheme 42: [2+5]-Test glycosylation between ABz-donor **143** and acceptor **134**, providing main product **151** and side product **152**. Connectivity of the glycoside at the aminoalkyl-linker remains elusive.*

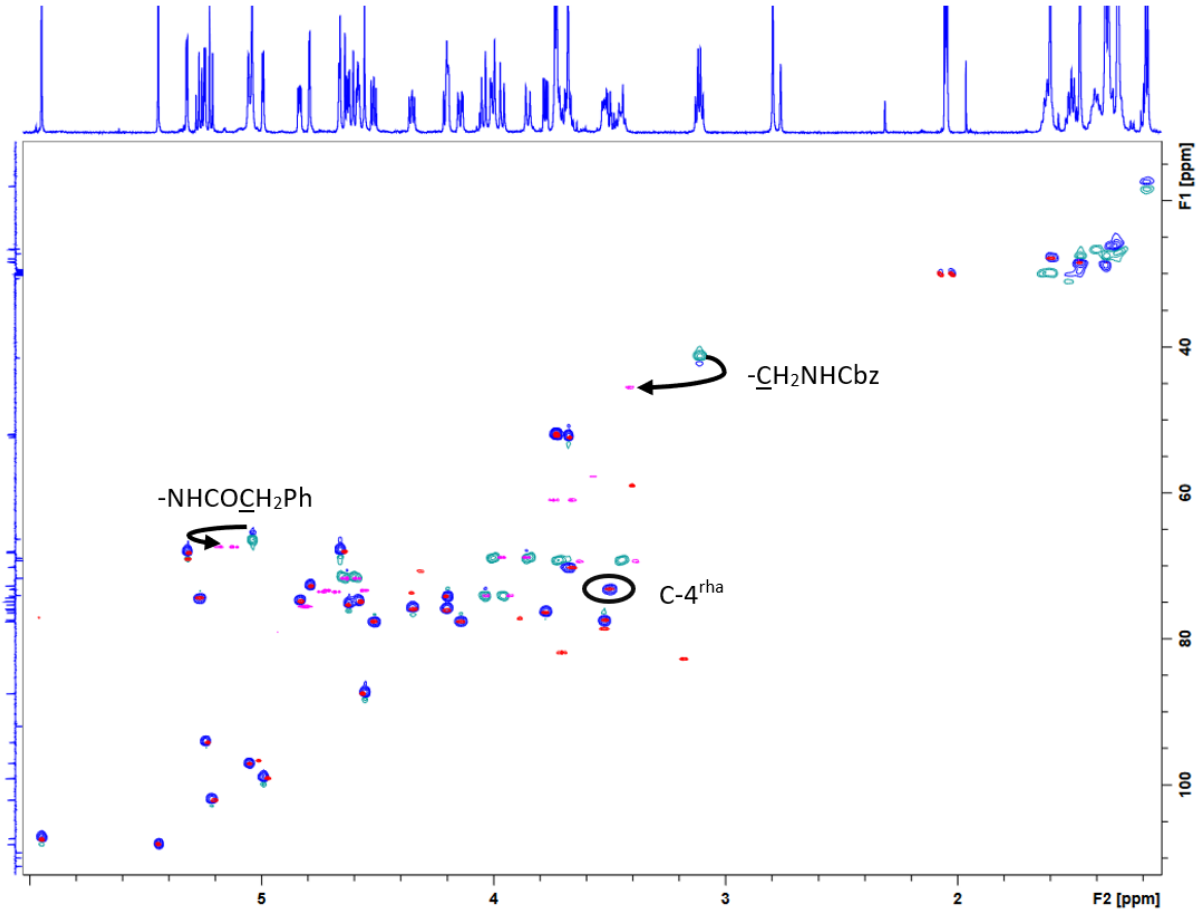
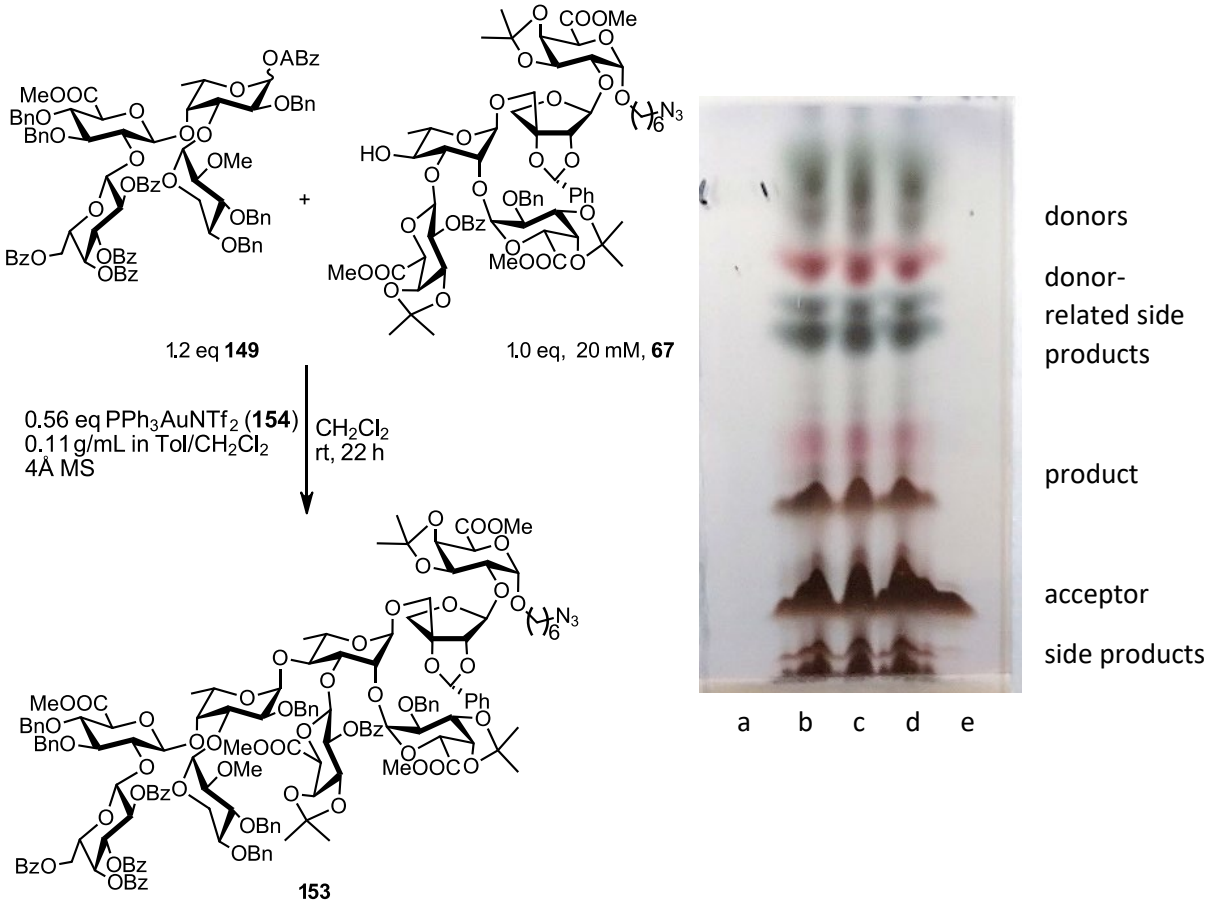


*Figure 2: Section of stacked ^{1}H-^{13}C decoupled HSQC-spectra of pentasaccharide acceptor **134** (blue and green) and product **151** (red and pink). Diagnostic signals are marked with black arrows and a circle.*

To circumvent this major roadblock, an azide-PG for the aminoalkyl linker was introduced as shown in Scheme 36. With azido-protected pentasaccharide acceptor **67**, the [4+5]-glycosylation with ABz-donor **149** was performed under argon atmosphere, employing super dry solvents (CH_2Cl_2 1.5 ppm H_2O, tol 3.5 ppm H_2O). As reaction vessel an HPLC-vial with 300 µL glas inlay was chosen to limit solvent losses by evaporation. An anhydrous catalyst stock solution was prepared and added to the charged reaction vessel under argon atmosphere.



*Scheme 43: Test glycosylation with tetrasaccharide donor **149** and pentasaccharide acceptor **67** (left) and corresponding HPTLC (right) in tol/EtOAc 71:29: a) tetrasaccharide donor **149**, b) donor **149** cospotted with product mix, c) product mix, d) acceptor **67** cospotted with product mix, e) pentasaccharide acceptor **67**.*

Gratifyingly, the formation of product was observed on HPTLC. After purification by chromatography, the product fractions were investigated with ^{1}H-NMR. Although the fraction was not pure, diagnostic peaks of OMe-esters, OMe-ether, -CH_2-N_3 and many others indicated that a nonasaccharide **153** may have formed. Also, the formation of polar side products was observed. It was hypothesized that the triphenylphosphine ligand could dissociate from its Gold(I)-complex and cause cleavage of the azide by Staudinger reduction which could lead to acceptor-, product- and catalyst decomposition.

To test this hypothesis, I decided to compare the catalyst with a commercial highly stable NHC-Au(I) complex, known to not dissociate[138]. Indeed, slight degradation of pentasaccharide acceptor **67** in presence of PPh_3AuNTf (**154**) was observed, while the NHCAuNTf **155** complex left acceptor **67** unaffected as depicted in Figure 3.

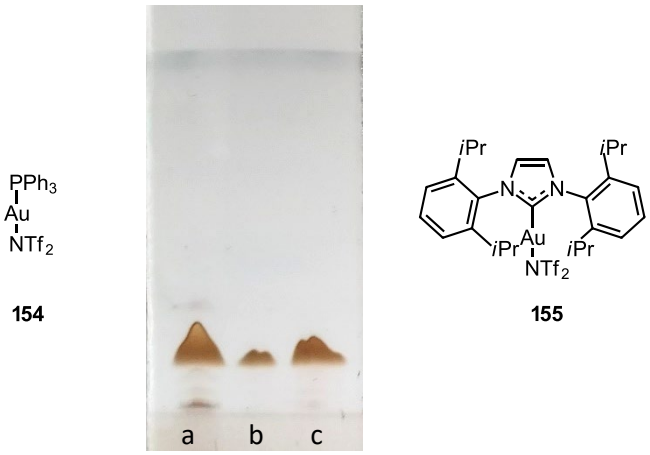
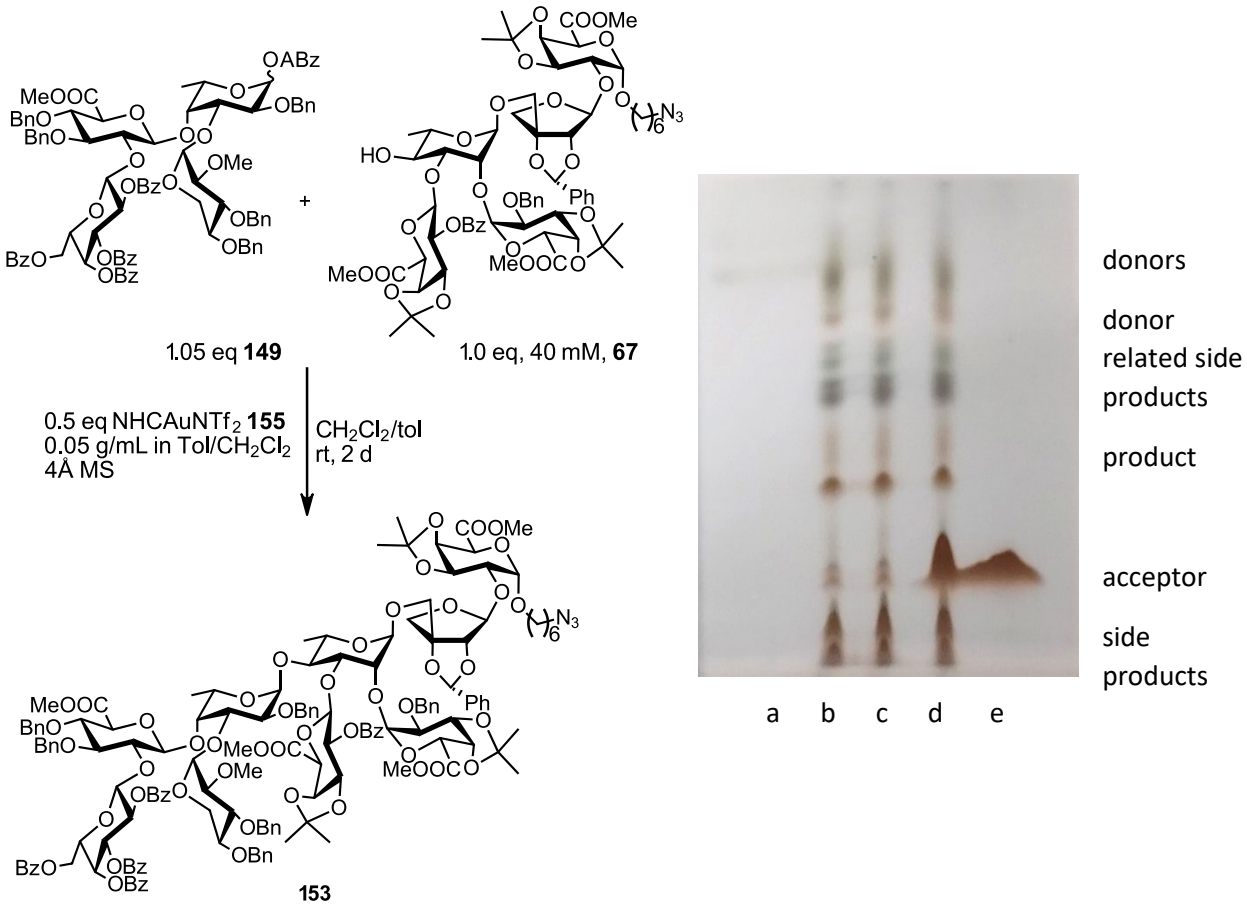


*Figure 3: HPTLC in Hex/EtOAc 60:40 of a) acceptor **67** with 0.25 eq of catalyst **154** b) acceptor **67** and c) acceptor **67** with 0.25 eq of catalyst **155** in anh. toluene/CH_2Cl_2 after 72 h at 4 °C under argon atmosphere.*

Encouraged by these findings, the NHC-$AuNTf_2$ catalyst **155** was employed in a test reaction between donor **149** and acceptor **67** (Scheme 44). This time toluene was used as a cosolvent with CH_2Cl_2 (50:50), as its volatility is much lower compared to CH_2Cl_2. This facilitated handling of the small-scale reaction with a total solvent volume of 50 µL. Initially only very little conversion was observed when only 0.1 eq of catalyst were employed and the reaction was allowed to stand overnight under argon. As the reaction was found to not progress after one night, additional 0.4 eq where added and the reaction was allowed to stand again overnight under argon atmosphere.



*Scheme 44: Test glycosylation with tetrasaccharide donor **149** and pentasaccharide acceptor **67** (left) and corresponding HPTLC (right) in tol/EtOAc 71:29. a) tetrasaccharide donor **149**, b) donor **149** cospotted with product mix, c) product mix, d) acceptor **67** cospotted with product mix, e) pentasaccharide acceptor **67**.*

Unexpectedly, the outcome of this reaction was not improved compared to the test reaction employing PPh_3AuNTf_2 (**154**), as indicated by HPTLC. More of the polar side products had formed employing the $NHCAuNTf_2$-catalyst **155**, indicating that other pathways than Staudinger reduction dominate in the formation of these side products during the glycosylation reaction. The enhanced side product formation could be related to a higher catalytic activity of NHC catalyst **155** compared to PPh_3AuNTf_2 (**154**) but effects of the more apolar solvent mixture cannot be ruled out. Analysis of the crude product mixture by MALDI-MS indeed indicated mass adducts of the desired product, of the glycal formed from the donor, of product with reduced azide, of acceptor with reduced azide and of acceptor with cleaved Bz-PG. The loss of Bz-PG is in line with an azide reduction, as free amines can undergo *N*-, *O*-, acyl transfer, forming the benzoic amide and liberating the formerly protected hydroxy function. It was concluded that neither -NHCbz nor the azide moiety are sufficiently unreactive under these glycosylation conditions. However, isolation of a small amount of product was possible. It was combined with the product fraction of the previous glycosylation and repurified to obtain 1 mg of fairly pure material which allowed analysis by ^{1}H-NMR spectroscopy. Significant shifts and line broadening in comparison with the starting materials were observed, indicating the formation of a sterically hindered product with limited rotation, which is in line with the presence of desired nonasaccharide

153 by MALDI-MS. Unfortunately, the amount and purity of isolated compound was found insufficient for further NMR studies. Further investigations are required.

3. Summary and Outlook

A synthetic route towards oligosaccharides related to the structure of RG-II side chain A was developed, starting from nine monosaccharide building blocks (Figure 4) which were efficiently synthesized from seven different monosaccharides.

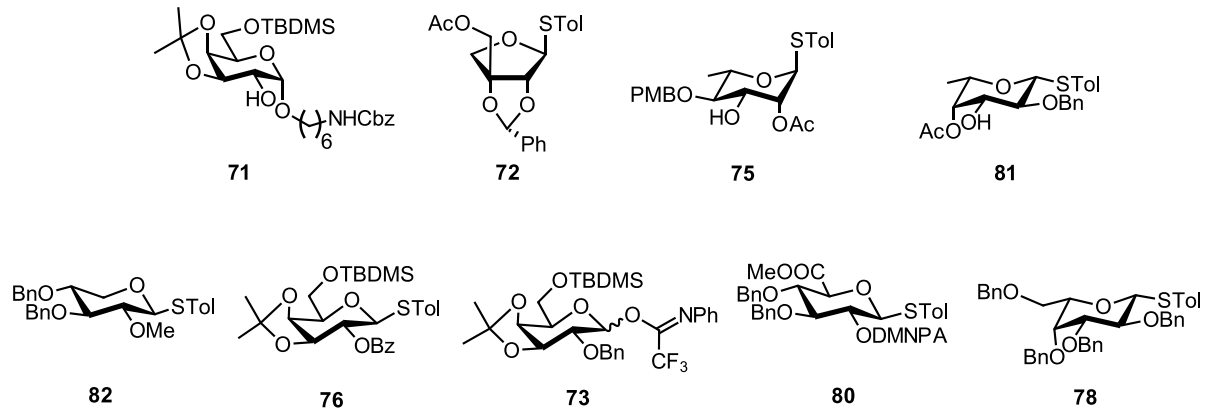
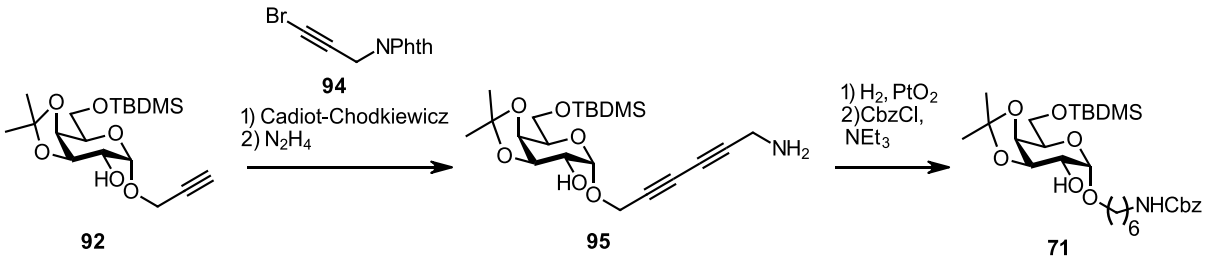


Figure 4: Building blocks used for the synthesis of RG-II side chain A oligosaccharides.

Therefore, a novel strategy for the 1,2-*cis*-selective introduction of aminoalkyl linkers to galactose was developed as well (Scheme 45). As the 1,2-*cis*-selective introduction of a linker using standard glycosylation chemistry is challenging, the problem was overcome by using an anomeric propargyl group, which was installed in a 1,2-*cis*-selective manner by Fischer-glycosylation. The facile elongation of alcohol **92** with a Cadiot-Chodkiewicz cross coupling and subsequent reduction and protection afforded acceptor building block **71**.



*Scheme 45: Introduction of the aminoalkyl linker to afford **71**.*

Three defined and highly pure linear fragments of RG-II (**88**, **85** and **83**) have been synthesized successfully (Figure 5), with many more fragments related to RG-II now accessible by the developed synthetic strategy.

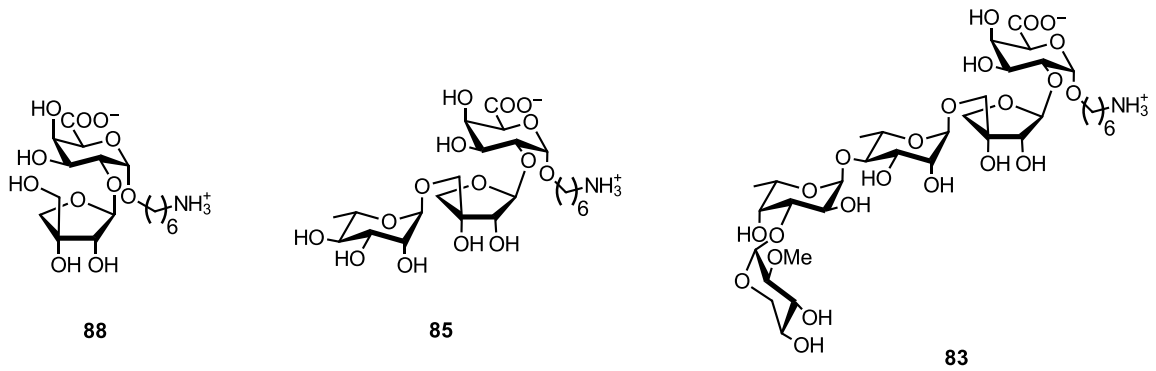
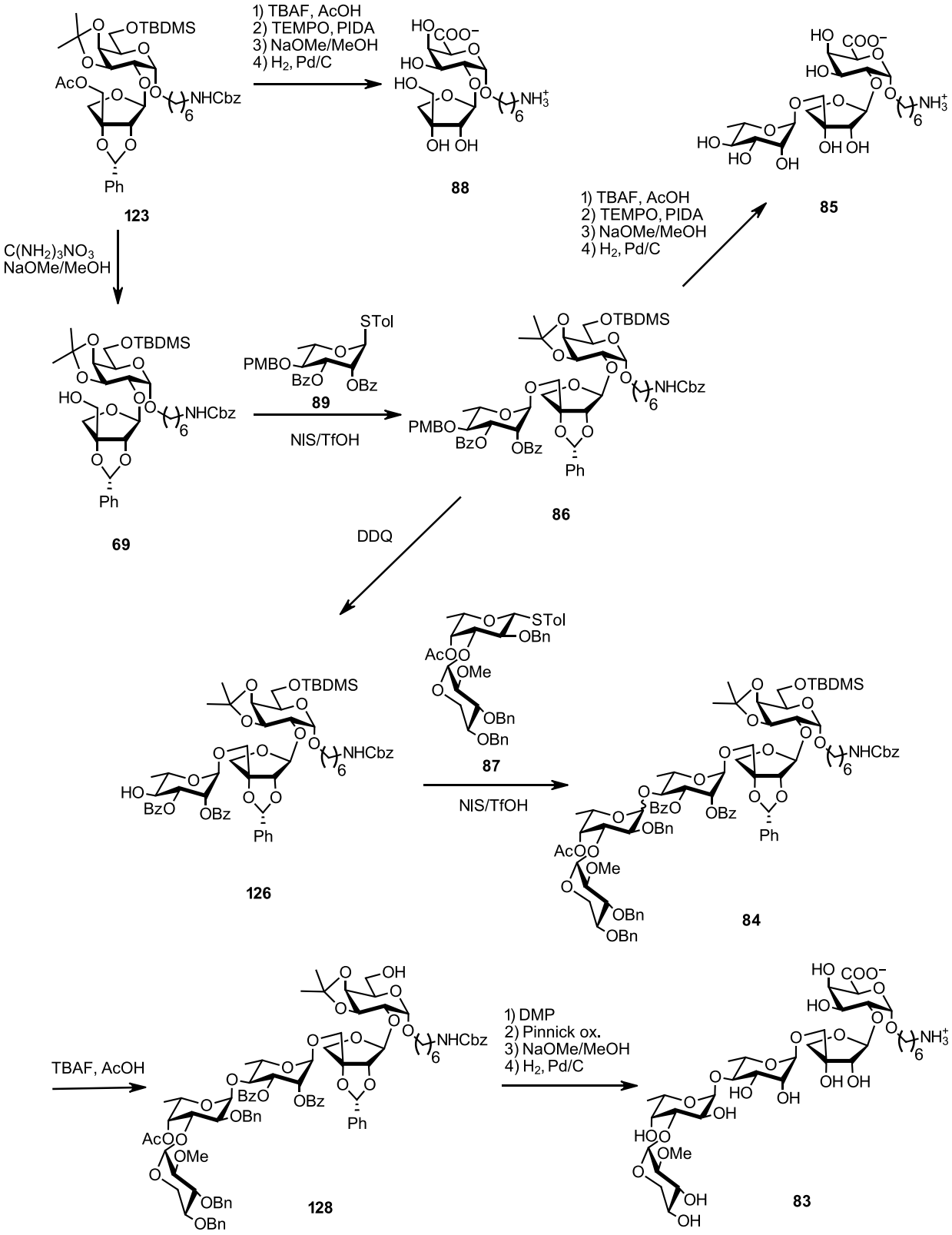


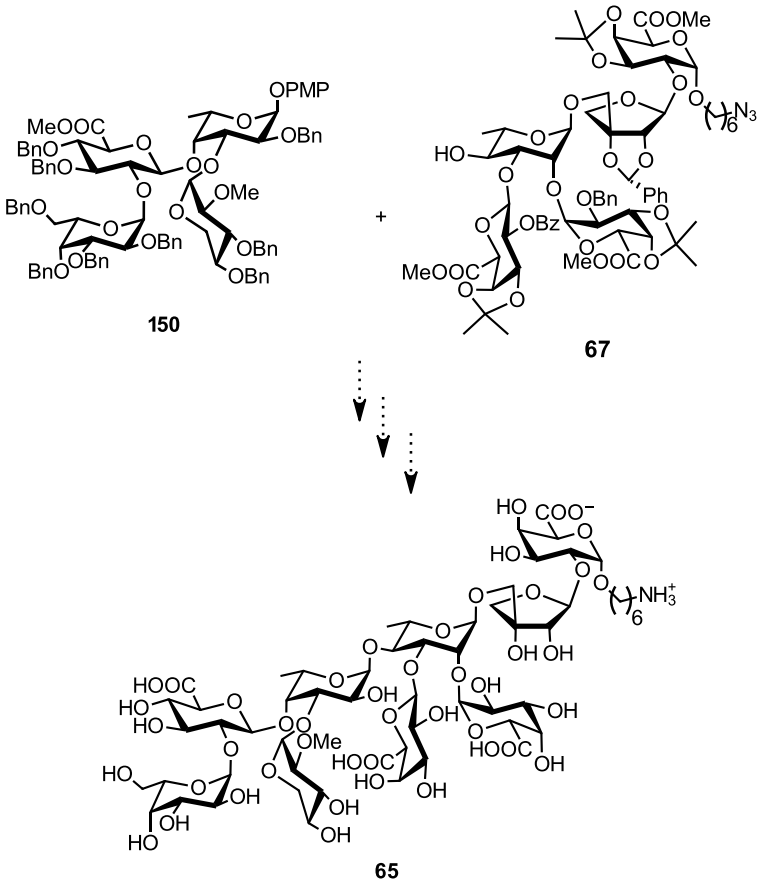
*Figure 5: Linear side chain A fragments **88**, **85** and **83**.*

The developed PG-strategy for synthesis of the RG-II fragments based on post-assembly oxidation of the galactose residue proved to be robust and highly orthogonal, and efficient deprotection and purification protocols have been established (Scheme 46). A number of transformations required particular attention: 1) Selective deacetylation of disaccharide **123** to afford key intermediate alcohol **69** was achieved with a guanidinium nitrate/guanidine solution, leaving the TBDMS group unaffected. 2) The purification of anomeric mixtures poses a notorious problem in glycochemistry. In case of the conversion of pentasaccharide mixture **84** to pentasaccharide alcohol **128** it was observed that strategic cleavage of PGs can enable facile separation of anomers by flash chromatography. 3) To identify the most robust post-assembly oxidation method for the galactose residues, two different procedures were employed. The TEMPO/PIDA-mediated oxidation in presence of water, as employed for the preparation of fragments **88** and **85**, was found to be more facile compared to the initially used oxidation with DMP and Pinnick-reaction. 4) During global deprotection of the three linear side chain A fragments, challenges arose from reductive amination of the aminoalkyl linker due to the long reaction times required. These challenges were overcome by avoiding the use of alcohols and ethers as solvents Furthermore, the PMB-PG was found to cause *N*-methylation under these reaction conditions.



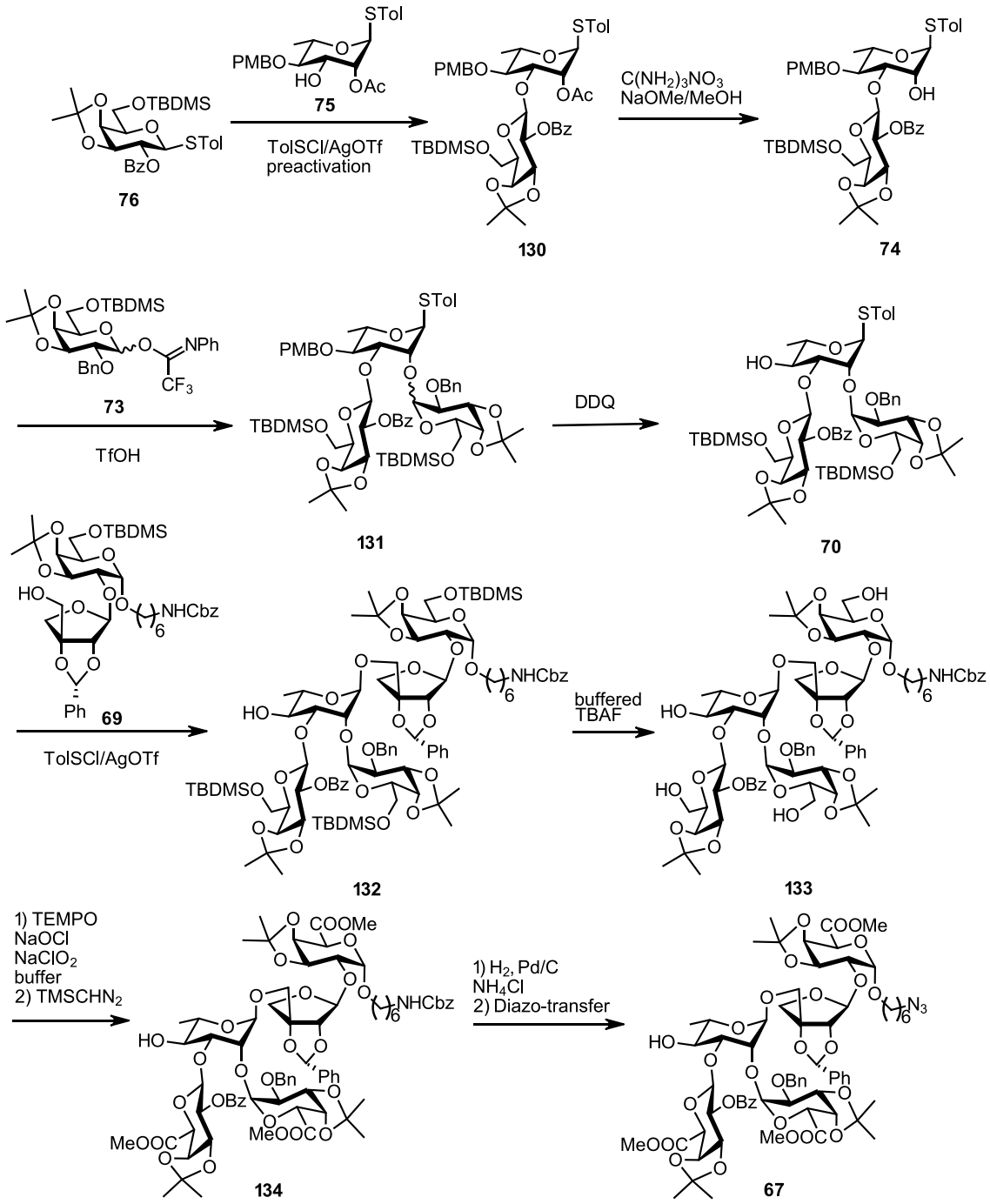
*Scheme 46: Synthesis of linear side chain A fragments **88**, **85** and **83**.*

Supported by the findings made during the synthesis of linear RG-II fragments, a synthetic strategy towards the synthesis of nonasaccharide **65**, respresenting the full side chain A, was developed. Pentasaccharide acceptor **67** and tetrasaccharide donor **150** were successfully synthesized as reactants for coupling to the protected form of nonasaccharide **65** (Scheme 47).



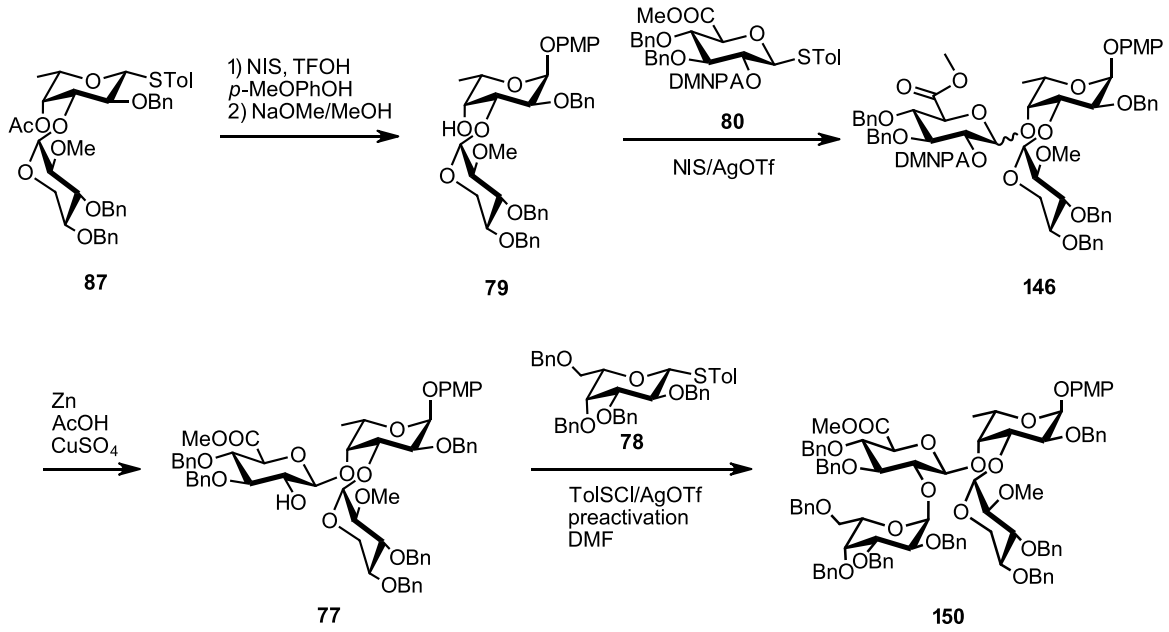
*Scheme 47: Nonasaccharide target molecule **67** and the tetrasaccharide **150** and pentasaccharide **67** precursors required for its synthesis.*

Pentasaccharide **67** was synthesized via a post-assembly oxidation approach, in which the galactose residues were oxized to galacturonic acids after pentasaccharide assembly, avoiding issues with the stereocontrol when using galacturonic acid donors (Scheme 48). The synthesis started by using a preactivation-based glycosylation protocol for coupling of thioglycoside donor **76** with thioglycoside acceptor **75**, affording disaccharide **130**. Subsequently, guanidinium nitrate/guanidine solution again proved to be a usefull reagent for selective deacetylation, in this case to convert disaccharide **130** into acceptor **74**. For the 1,2-*cis*-selective introduction of the next galactosyl-moiety, PTFAI-donor **73** was found to provide better results than the corresponding thioglycoside, affording trisaccharide mixture **131**. Again, the challenging separation of trisaccharide anomers **131** could be achieved by a strategic PG-cleavage. After removal of the PMB-group in donor **131**, pure trisaccharide **70** was obtained as a single anomer. Gratifyingly, deprotected donor **70** could be directly reacted with acceptor **69** for the synthesis of pentasaccharide **132**. Next, pentasaccharide **132** was TBDMS-deprotected for post-assembly oxidation. Orthogonality during prolonged reaction times was achieved by employing a buffered TBAF solution to afford tetraol **133**. Selective oxidation of the primary alcohols of tetraol **133** was then achieved in the presence of a secondary alcohol with a TEMPO-based protocol. Subsequent esterification of the carboxylic acids allowed facile purification of the Cbz-protected pentasaccharide acceptor **134**, which was transformed into the respective azido-protected pentasaccharide **67**.



*Scheme 48: Synthesis of pentasaccharide acceptor **67**.*

Tetrasaccharide donor **150** was prepared starting from disaccharide acceptor **87** (Scheme 49). Challenges arising from aglycon transfer when using the fucose-based thioglycoside acceptor in the following glycosylation reaction were overcome by the introduction of an anomeric OPMP-PG in thioglycoside **87** to afford acceptor **79**. The very low nucleophilicity of acceptor **79** resulted in problems in the glycosylation with glucuronic acid donor **80**, exacerbated by the pH-sensitivity of both substrates. Optimization of the glycosylation conditions by using a neutral AgOTf-stock solution for activation of the acid-sensitive reaction enabled the synthesis of trisaccharide **146**. Again, PG-cleavage in **146** alleviated purification problems and afforded acceptor **77** after zink-mediated DMNPA-cleavage and silica gel purification. The 1,2-*cis*-L-galactoside was successfully introduced with excellent stereoselectivity, using a newly developed protocol for DMF-mediated preactivation glycosylation of thioglycosides, enabling the coupling of L-galactose donor **78** with acceptor **77** to afford tetrasaccharide **150**, ready for conversion into a suitable glycosyl donor for the final [4+5]-glycosylation.

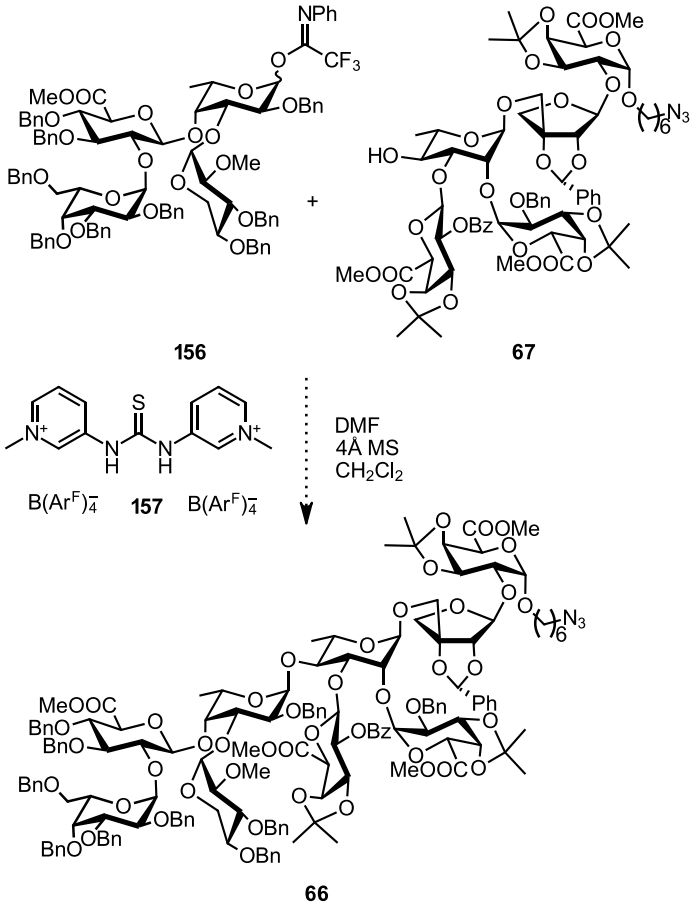


*Scheme 49: Synthesis of tetrasaccharide **150**.*

To assemble nonasaccharide **65** a very challenging [4+5]-glycosylation using a highly ramified pair of donor and acceptor must be conducted. Investigations were undertaken using disaccharide donors and acceptor **134**. Insufficient protection of the amine at the aminoalkyl linker by the Cbz-PG in **134** was found to be incompatible with the final [4+5]-glycosylation, as glycosylation of the linker -NHCbz group was found to be the major reaction path. After exchange of the Cbz-PG for an azide, acceptor **67** was glycosylated with a tetrasaccharide ABz-donor analogous to tetrasaccharide **150**. Two different Au(I)-complexes were tested as catalysts for donor activation. It was observed that the ABz/Au-complex activator system was not fully compatible with the azide-protected acceptor as well, as partial azide reduction and other side reactions were observed. However, limited success in the preparation of a nonasaccharide structure was indicated by HPTLC, MALDI-MS and ^{1}H-NMR. The developed strategy may allow the assembly of nonasaccharide **65** in a total of 93 transformations from commercialy available starting materials, including 29 literature known transformations and 11 transformations required to access commercially unavailable reagents.

In summary tetrasaccharide **150** and pentasaccharide acceptor **67** were successfully prepared in 83 synthetic transformations introducing four out of five 1,2-*cis*-glycosidic bonds while keeping full protective group orthogonality. Investigations into the final [4+5]-glycosylation provided important information to address the remaining challenges in the future.

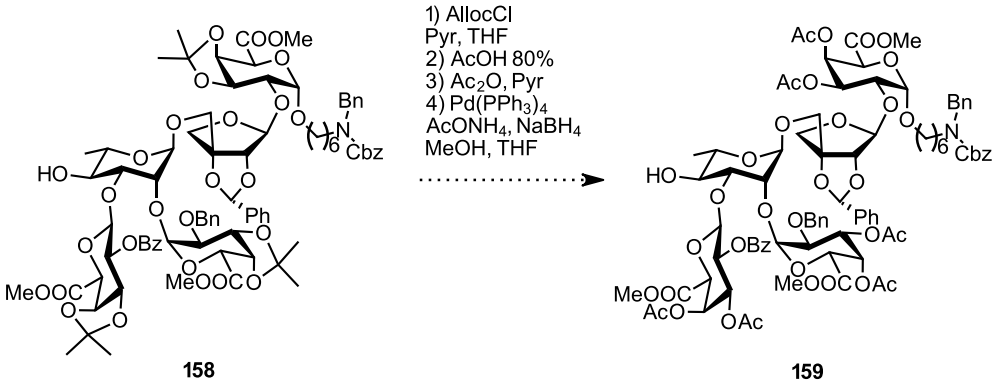
In the near future, the final 4 steps towards nonasaccharide **65** may be refined. As the azide-PG failed as a sufficiently stable PG for the aminoalkyl linker in conjunction with the ABz/Au(I)-complex activator system, other donors such as the PTFAI-donor **156** (accessible in 2 steps from tetrasaccharide **150**) may be tested. A recent publication highlights charged thiourea catalyst **157** as a promotor for activation of PTFAI-donors under very mild and neutral conditions. Gratifyingly, the use of DMF as an external nucleophile in conjunction with this catalyst affords excellent α-selectivity[139], potentially facilitating the desired [4+5]-glycosylation under neutral conditions at rt and with prolonged reaction times (Scheme 51). The use of imidates has been shown to be fully compatible with the azido-PG[77, 140] and also azido-alkyl linkers[77, 126].



*Scheme 50: Proposed [4+5]-glycosylation employing PTFAI-donor **156** and thiourea catalyst **157** to afford nonasaccharide **66**.*

To circumvent problems arising from the aminoalkyl linker other PG-patterns for the amino group may be used. It is hypothesized that the -NBnCbz protective group pattern may be superior for protection of the nitrogen. This protection can be achieved by resynthesizing the disaccharide acceptor with the respective linker, for which either the described linker-elongation approach must be adjusted (rebuilding bromopropargylimide **94**) or a suitable route to introduce the full linker by glycosylation must be found. After sufficient protection of the linker, acceptor **158** may be synthesized using the described methods (Scheme 50).

The nucleophilicity of acceptors **134** and **67** was found to be quite low, probably due to steric hindrance. The reactivity of the pentasaccharide acceptor may be enhanced by cleavage of the three *i*PrA-PGs and replacement by other PGs. Cyclic PGs cause severe conformational restrictions, making the pentasaccharide acceptors very rigid. More reactive or sterically less restricted conformations could therefore be inaccessible. By temporarily protecting the free hydroxy group in acceptor **158**, the *i*PrA-PGs can be cleaved and the resulting hydroxy groups protected by standard acetylation. Subsequent cleavage of the temporary PG may yield the more flexible and thus more reactive acceptor **159** that can be tested in the final [4+5]-glycosylation.



*Scheme 51: Proposed cleavage of iPrA-PGs and replacement with Ac-PGs to alleviate conformational restrictions and afford acceptor **159**.*

4. Experimental Section

4.1 General Methods

Chemicals used, if not stated otherwise, were purchased from Acros, Alfa Aesar, Molekula, Sigma-Aldrich, Thermo Fisher Scientific, TCI, Carbosynth, Roth, VWR or Apollo Scientific and were used as supplied without any further purification unless stated otherwise.

Activation of 4Å molecular sieves was performed by heating up to 500 °C at least three times in fine vacuum with a heat gun, or in a Kugelrohr apparatus (Büchi Glass Oven B-580) at 300°C in fine vacuum (typically 0.002 mbar) for at least 30 min before use and subsequently handled under an atmosphere of argon.

For reactions demanding anhydrous conditions, anhydrous solvents were produced by desiccation over freshly activated 4Å molecular sieves for at least 24 h prior to use, or taken from a dry solvent system (JC-Meyer Solvent Systems) under an atmosphere of argon. Anhydrous methanol was obtained by stirring spectroscopy grade MeOH with Mg shavings prior to distillation under an atmosphere of argon. Residual water content for solvents dried over molecular sieves or Mg was determined by coulombometric titration on a Mitsubishi CA-21 Karl Fischer apparatus and was well below 10 ppm.

Thin layer chromatography (TLC) was pre-coated TLC-plates SIL G-25/UV_{254} on glass support from Macherey-Nagel. High performance thin-layer chromatography was performed on silica gel 60 F254 HPTLC precoated glass plates with a 25 mm concentration zone supplied by Merck. Visualization was performed using an UV-lamp (254 nm) and subsequent *p*-anisaldehyde dipping stain (CH-stain) or other standard dipping stain reagents (ninhydrin, vanillin, cerium ammonium molybdate, potassium permanganate, iodine) if necessary, followed by heating to 250°C on a hot plate or by using a heat gun.

Amberlite IR-120 H^+-form was repeatedly suspended in MeOH and filtered off (six times) to remove residual impurities, then dried *in vacuo*, prior to use.

Normal-phase flash chromatography was performed on silica gel using Fluka Kieselgel 60 (230-400 mesh) or PuriFlash IR-50SI (40-60 µm) and pre-packed silica gel colums SI-S-2G/6 from Interchim. RP-chromatography was performed using 500 mg C18 Seppack cartridges from Waters. Size exclusion chromatography was performed using Biorad SX-20 resin. Filtrations were performed using 25 mm syringe filters (PTFE, 0.45 µm) from Fischer Brand. Celite aided filtrations employed celite 545 from Macherey-Nagel.

Organic solvents were removed in *vacuo* at 40 °C (unless stated otherwise) using rotary evaporators. Volatiles were removed from compounds in fine vacuum for several hours to overnight.

NMR spectra were recorded at 297 K in the solvent indicated, using a Bruker Avance III 600 (600.22 MHz for ^{1}H, 150.93 MHz for ^{13}C), a Bruker AVIII-HD (300 MHz), a Varian Premium Compact (400 MHz), a Bruker Ascend (400 MHz) or a Varian Premium Shielded (600 MHz) instrument, employing standard software provided by the manufacturer (e. g. Bruker TopSpin 3.5 pl 6). ^{1}H and ^{13}C spectra were referenced to the corresponding residual solvent peak chemical shift as internal standard ($CDCl_3$: 7.26 ppm ^{1}H, 77.16 ppm ^{13}C; CD_3COCD_3: 2.05 ppm ^{1}H, 29.84 ppm ^{13}C; CD_3OD: 3.31 ppm ^{1}H, 49.00 ppm ^{13}C; CD_3CN: 1.94 ppm ^{1}H, 1.32 ppm ^{13}C).[141] ^{1}H and ^{13}C spectra in D_2O were referenced *via* external calibration to sodium 3-(trimethylsilyl)propane-1-sulfonate (DSS)/dioxane (0.00 ppm ^{1}H, 67.19 ppm ^{13}C) in D_2O. Assignments were supported by ^{1}H-^{1}H-COSY, ^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC and if required CLIP-HSQC, ^{1}H-^{1}H-TOCSY and ^{1}H-^{29}Si-HMBC data. Anomeric configuration was verified by the ^{1}H-^{13}C coupling constant.[142] Data processing was performed using MestReNova v14.1.1-24571.

LC-MS analysis was performed on an Agilent 1200 series coupled to a quadrupole ESI LC/MS 6130 using a YMC-Pack DIOL-300-NP column (150 x 4.6 mm), or was performed on a Shimadzu LC10 system with Shimadzu 2020 mass spectrometer and Alltech ELSD 3300 (drift tube temperature: 60°C, receiver gain: 2) using a C_{18} (ZORBAX Eclipse XDB-C18, 4.6x150 mm, 5 µm) column.

Preparative HPLC separation was performed on an Interchim PuriFlash® 4/25 (Flash and preparative HPLC system) using a YMC-pack SIL-06 (250 x 10 mm, D. 5 µm, 6 nm).

Preparative RP-HPLC separation was performed on an Interchim PuriFlash® 4/25 (Flash and preparative HPLC system) using a YMC-Triart C18 column (150 x 10 mm, S-5 µm, 12 nm).

ESI-HRMS data was obtained using samples dissolved in MeCN/H_2O on an Agilent Technologies 6230B LCMS-TOF or a Waters Xevo G2-XS QTof instrument. Datasets were analysed by Mass Hunter Qualitative Navigator B.08.00 software or mass-adducts were calculated with Mass Hunter Isotope Distribution Calculator v. 8.0.8208.0 software and the ppm-differences calculated (< ±2.5 ppm).

MALDI-TOF MS was performed in positive-ion mode using a Bruker Autoflex Speed instrument with 6-aza-2-thiothymine or 2,5-dihydroxy acetophenone as the matrix.

4.2 Preparation of reagents

(*N*-Phthalimidoyl)-3-bromopropargyl amine (**94**)

(N-phthalimidoyl)-3-bromopropargyl amine (**94**) was prepared according to a published procedure in 2 steps. The analytical data is in full agreement with literature data.[111]

(*N*-Phenyl)-2,2,2-trifluoroacetimidate

$PhNCClCF_3$ was prepared according to a published procedure. The analytical data is in full agreement with literature data.[143]

p-Toluenesulfenylchloride

TolSCl was prepared according to a published procedure. The analytical data is in full agreement with literature data.[70] TolSCl was aliquoted under exclusion of moisture and air. Aliquots stored under Argon at -30 °C were stable for months.

2,2-Dimethyl-(*o*-nitrophenyl)acetic anhydride

DMNPAA was prepared in 4 steps by Jakob Raffler according to a published procedure. The analytical data is in full agreement with literature data.[45]

o-(Hex-1-yn-1-yl)benzoic acid

ABzOH was prepared in 3 steps according to published procedures. Described procedure proved unsuccessfull in our hands only yielding the isocoumarine-rearrangement product.[96] A different source was consulted which gave the desired product.[144] The analytical data is in full agreement with literature data.

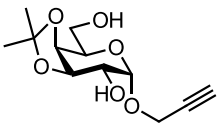
Imidazole-1-sulfonyl azide hydrochloride

Imidazole-1-sulfonyl azide hydrochloride was prepared by Nino Trattnig, according to literature procedure[135], and kindly provided. The analytical data is in full agreement with literature data.[135] Care must be taken as intermediates, liquors during preparation, and the reagent itsself have explosive properties.[136]

4.3 Preparation of carbohydrate building blocks

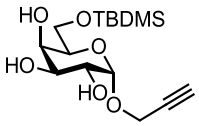
4.3.1 Synthesis of galactose donors

Prop-(2-ynyl) 3,4-*O*-isopropylidene-α-D-galactopyranoside (**93**)



Alkyne **90** (7.20 g, 33.0 mmol, 1.0 eq, α/β 2.8:1) was dissolved in 2,2-DMP (330 mL) and CSA (0.33 g, 1.42 mmol, 0.04 eq) was added. The mixture was stirred for 2 d at rt before it was quenched by the addition of NEt_3 (0.36 mL, 2.59 mmol, 0.08 eq) and concentrated *in vacuo*. Any excess NEt_3 was removed in fine vacuum overnight. The residue was dissolved in MeOH and water (90:10, 330 mL total) and it was refluxed for 5 h, at which point all intermediate spots vanished on TLC. After concentration the crude was purified by flash chromatography (hex:EtOAc 44:56, 0.1% of pyridine) yielding pure α-isomer of diol **93** (6.10 g, 72%) as a colorless syrup. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 5.10 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1 H, H-1), 4.34 (d, $J_{(OCH2)\text{-}(\equiv CH)}$ = 2.4 Hz, 2 H, OCH_2-), 4.27 (m, 2H, H-3 H-4), 4.13 (ddd, $J_{5\text{-}6a}$ = 6.4 Hz, $J_{5\text{-}6b}$ = 2.1 Hz, $J_{5\text{-}4}$ = 4.3 Hz, 1 H, H-5), 3.94 (ddd, J = 2.8 Hz, $J_{6a\text{-}5}$ = 6.3 Hz, $J_{6a\text{-}6b}$ = 11.9 Hz, 1 H, H-6a), 3.90-3.77 (m, 2 H, H-6b H-2), 2.48 (t, $J_{(\equiv CH)\text{-}(OCH2)}$ = 2.5 Hz, 1 H, ≡CH), 2.35 (d, 1 H, HOC-2), 2.25 (dd, 1 H, HOC-6), 1.50 (s, 3H, CH_3), 1.35 (s, 3H, CH_3'); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 110.1 ($OCMe_2O$), 96.6 (C-1), 78.8 (-C≡), 76.0 (C-3), 75.3 (≡CH), 74.0 (C-4), 69.2 (C-2), 68.8 (C-5), 62.9 (C-6), 55.3 (OCH_2-), 27.7 (CH_3), 26.0 (CH_3'); **HRMS**: calcd. for $C_{12}H_{18}O_6$: 281.0996 $[M+Na]^+$, found 281.0998; **TLC** (hex/EtOAc 40:60): R_f = 0.25 (CH stain).

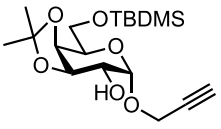
Prop-(2-ynyl) 6-*O*-*tert*-butyldimethylsilyl-α-D-galactopyranoside (**91**)



α-D-Propargyl galactopyranoside **90** (659 mg; 3.02 mmol; 1.0 eq) was dissolved in anh. DMF (2.5 mL) and anh. CH_2Cl_2 (7.5 mL) under a layer of argon. DMAP (15 mg; 0.12 mmol, 0.04 eq) and NEt_3 (0.50 mL; 3.62 mmol; 1.2 eq) were added followed by TBDMSCl (511 mg, 3.32 mmol, 1.1 eq). The mixture was stirred for 80 min, then diluted with EtOAc (25 mL) and the organic phase washed with water (2x 20 mL). The aqueous layer was extracted with EtOAc (3x 20 mL) and the organic phases were pooled. The combined organic phase was washed with brine (2x 20 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (tol/EtOAc 25:75 to EtOAc) gave pure triol **91** (740 mg, 74%) as colorless flaky crystals.

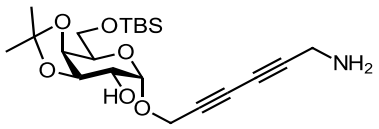
^{1}H NMR (CD_3OD, 600 MHz): δ = 5.01 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1 H, H-1), 4.30 (dd, $J_{(OCH2)a\text{-}(OCH2)b}$ = 15.8 Hz, $J_{(OCH2)\text{-}(\equiv CH)}$ = 2.3 Hz, 1 H, OCH_2a-), 4.27 (dd, $J_{(OCH2)a\text{-}(OCH2)b}$ = 15.8 Hz, $J_{(OCH2)\text{-}(\equiv CH)}$ = 2.3 Hz, 1 H, OCH_2b-), 3.90 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1H, H-4), 3.83-3.75 (m, 4 H, H-2 H-5 H-6a H-6b), 3.71 (dd, $J_{2\text{-}3}$ = 10.1 Hz, $J_{3\text{-}4}$ = 3.3 Hz, 1 H, H-3), 2.84 (t, $J_{(\equiv CH)\text{-}(OCH2)}$ = 2.4 Hz, 1 H, ≡CH), 0.92 (s, 9H, $C(CH_3)_3$), 0.01 (s, 6H, $Si(CH_3)_2$); **^{13}C NMR** (CD_3OD, 150 MHz): δ = 98.7 (C-1), 80.0 (-C≡), 76.0 (≡CH), 72.9 (C-5), 71.6 (C-3), 70.8 (C-4), 70.1 (C-2), 63.7 (C-6), 55.1 (OCH_2-), 26.3 ($C(\underline{C}H_3)_3$), 19.1 ($\underline{C}(CH_3)_3$), -5.2, -5.3 ($Si(CH_3)_2$); **HRMS**: calcd. for $C_{15}H_{28}O_6Si$: 350.1993 [M+NH_4]$^+$, found 350.1995; **TLC** (CH_2Cl_2/MeOH 88:12): R_f = 0.5 (CH stain).

Prop-(2-ynyl) 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**92**)



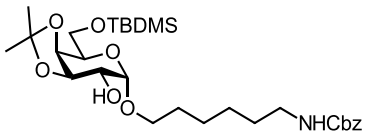
Starting from 91: Acetone was dried over $MgSO_4$ and the $MgSO_4$ was filtered off. Then triol **91** (549 mg, 1.65 mmol, 1.0 eq) was dissolved in the prepared acetone (7.0 mL) and 2,2-DMP (0.51 mL, 4.13 mmol, 2.5 eq) was added, followed by a catalytic amount of CSA (spatula tip). After 85 min the reaction had finished, so it was quenched by the addition of NEt_3 (until pH-value was >8) and concentrated *in vacuo*. The remaining crude was purified by flash chromatography (hex/EtOAc 80:20) to yield alcohol **92** (583 mg, 95%) as a crystalline solid; **Starting from 93:** Diol **93** (6.10 g, 23.6 mmol, 1.0 eq) was dissolved in anhydrous DMF (55 mL) under a layer of argon and the solution was cooled to 0 °C with an ice bath. Then, imidazole (4.02 g, 59.0 mmol, 2.5 eq) and TBDMSCl (3.77 g, 24.8 mmol, 1.05 eq) were added and the mixture was allowed to warm up to rt over the course of several hours, and stirring was continued overnight. At this point the mixture was concentrated *in vacuo*, the residue was dissolved in EtOAc (200 mL) and the resulting solution was washed with water (400 mL). The phases were separated and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over $MgSO_4$ and concentrated. The remaining crude was purified by flash chromatography (hex/EtOAc 75:25) to yield alcohol **92** (5.80 g, 66%) along with the 2,6-TBDMS-protected alkyne (1.70 g, 15%) both as crystalline solids. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 5.04 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1 H, H-1), 4.35, 4.28 (2 dd, $J_{(OCH2)\text{-}(\equiv CH)}$ = 2.5 Hz $J_{(OCH2)\text{-}(OCH2')}$= 15.5 Hz, 2 H, OCH_2-), 4.22 (m, 2H, H-3 H-4), 4.04 (ddd, $J_{5\text{-}6a}$ = 1.9 Hz, $J_{5\text{-}6b}$ = $J_{5\text{-}4}$ = 6.5 Hz, 1 H, H-5), 3.89-3.80 (m, 2 H, H-6a H-2), 3.77 (dd, $J_{6b\text{-}5}$ = 6.8 Hz $J_{6a\text{-}6b}$ = 10.1 Hz, 2 H, H-6b), 2.45 (t, $J_{(\equiv CH)\text{-}(OCH2)}$ = 2.4 Hz, 1 H, ≡CH), 1.49 (s, 3 H, CH_3^{iPrA}), 1.33 (s, 3 H, $CH_3^{iPrA\,\prime}$), 0.90 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ = 109.6 ($OCMe_2O$), 95.9 (C-1), 78.7 (-C≡), 76.0 (C-3), 75.2 (≡CH), 72.8 (C-4), 69.52 (C-2), 69.47 (C-5), 62.4 (C-6), 54.7 (OCH_2-), 27.9 (CH_3^{iPrA}), 26.00 ($CH_3^{iPrA\,\prime}$), 25.97 ($C(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}Me_3$), -5.2, -5.3 ($Si(CH_3)_2$); **HRMS**: calcd. for $C_{18}H_{32}O_6Si$: 395.1860 [M+Na]$^+$, found 395.1865; **TLC** (hex/EtOAc 67:33): R_f = 0.46 (CH stain).

6-Amino-(2,4-diynyl)-1-hexyl 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**95**)



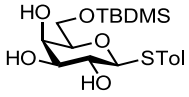
Under a layer of argon, copper-(I)-iodide (71.4 mg, 375 µmol, 0.06 eq) and hydroxylamine · HCl (153 mg, 2.21 mmol, 0.33 eq) were dissolved in 70% aqueous ethylamine solution (7.7 mL, 97.0 mmol, 14.5 eq) and MeOH (15 mL). The colorless solution was placed in an ice bath (0 °C) and a solution of alcohol **92** (2.74 g, 7.36 mmol, 1.1 eq) in MeOH (5 mL) was added. Then solid bromoalkyne **94** (1.77 g, 6.69 mmol, 1.0 eq) was added in one portion, the flask was immediately recapped and stirring was set to 800 rpm, so the solids dissolved quickly with a distinct color change of the solution from yellow to green. After 45 min the reaction was quenched by the addition of water and EtOAc (50 mL each). It was extracted with EtOAc (5 x 20 mL). The combined organic phase was washed with brine (2 x 25 mL) and concentrated *in vacuo*. The obtained crude product was dissolved in MeOH (20 mL) under a layer of argon, heated to 60 °C and hydrazine · H_2O (1.3 mL, 26.8 mmol, 4.0 eq) was added. After 2 h the intermediate was fully converted into the desired amine. The reaction mixture was cooled, diluted with CH_2Cl_2 (150 mL), celite (ca. 45 mL) was added and the mixture concentrated *in vacuo*. The obtained solid was loaded onto a silica gel column (CH_2Cl_2/MeOH 94:6) to obtain unreacted alcohol **92** and yield amine **95** (1.70 g, 60%) as colorless chunky crystals. **^{1}H NMR** (CD_3OD, 400 MHz): δ = 4.90 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1 H, H-1), 4.42-4.31 (m, 2 H, OCH_2), 4.27 (dd, $J_{4\text{-}3}$ = 5.5 Hz $J_{4\text{-}5}$ = 2.4 Hz, 1 H, H-4), 4.13 (dd, $J_{3\text{-}4}$ = 5.4 Hz $J_{3\text{-}2}$ = 7.7 Hz, 1 H, H-3), 4.03 (ddd, $J_{5\text{-}4}$ = 2.5 Hz $J_{5\text{-}6a}$ = $J_{5\text{-}6b}$ = 6.5 Hz, 1 H, H-5), 3.85 (dd, $J_{5\text{-}6a}$ = 6.3 Hz $J_{6a\text{-}6b}$ = 10.1 Hz, 1 H, H-6a), 3.78 (dd, $J_{5\text{-}6b}$ = 6.7 Hz $J_{6a\text{-}6b}$ = 10.1 Hz, 1 H, H-6b), 3.67 (dd, $J_{1\text{-}2}$ = 3.8 Hz $J_{2\text{-}3}$ = 7.8 Hz, 1 H, H-2), 3.46 (s, 2 H, CH_2N), 1.47 (s, 3 H, CH_3^{iPr}), 1.32 (s, 3 H, $CH_3^{iPr'}$), 0.92 (s, 9 H, $C(CH_3)_3$), 0.1 (s, 6 H, $Si(CH_3)_2$); **^{13}C NMR** (CD_3OD, 101 MHz): δ = 110.3 ($O\underline{C}Me_2O$), 98.6 (C-1), 80.8 (-C≡), 77.6 (C-3), 74.1, 71.6 (-C≡), 71.2 (C-2), 70.0 (C-5), 67.3 (-C≡), 63.5 (C-6), 55.9 (OCH_2), 31.8 (CH_2N), 28.5 (CH_3^{iPr}), 26.5 ($CH_3^{iPr'}$), 26.3 ($C(\underline{C}H_3)_3$), 19.2 ($\underline{C}(CH_3)_3$), -5.2, -5.3 ($Si(CH_3)_2$); **HRMS**: calcd. for $C_{21}H_{35}NO_6Si$: 448.2126 [*M*+Na]$^+$, found 448.2130; **TLC** (CH_2Cl_2/MeOH 94:6): R_f = 0.23 (ninhydrin stain)

(6-*N*-Benzyloxycarbonylamino)-1-hexyl 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**71**)



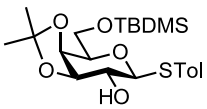
Under a layer of argon, amine **95** (566 mg, 1.33 mmol, 1.0 eq) was dissolved in EtOAc (56 mL) and Pt/C (10% wt., 57.0 mg) was added. Then hydrogen atmosphere was established by repeated brief degassing and flushing with a hydrogen balloon. The mixture was stirred for 4.5 h at which point the starting material has vanished on TLC and the mixture was filtered over a pad of celite, which was washed thoroughly with EtOAc. The obtained organic phase was then concentrated, and the light brown crude product immediately used for the next step by dissolving in anhydrous CH_2Cl_2 (24 mL) under argon atmosphere. After cooling down to 0 °C by placing the mixture in an ice bath, NEt_3 (0.37 mL, 2.66 mmol, 2.0 eq) was added followed by the dropwise addition of a solution of 95% Cbz-Cl (0.20 mL, 1.36 mmol, 1.02 eq) in anhydrous CH_2Cl_2 (6 mL) over the course of 10 min. The mixture was allowed to warm up to rt over the course of several hours and stirring was continued overnight. After 19 h in total the mixture was concentrated *in vacuo* and the light brown crude product subjected to flash chromatography (hex/EtOAc/MeOH 74:24:2) to afford acceptor **71** (401 mg, 53%) as a colorless oil. In some cases a second purification (75:25 tol:EtOAc) was performed. Compound decomposed slowly in $CHCl_3$. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.35 (m, 5 H, H^{Ph}), 5.09 (s, 2 H, OCH_2Ph), 4.81 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1 H, H-1), 4.78 (bs, 1 H, NH), 4.21 (dd, $J_{4\text{-}5}$ = 2.2 Hz $J_{4\text{-}3}$ = 5.9 Hz, 1 H, H-4), 4.17 (dd, $J_{3\text{-}4}$ = 6.0 Hz $J_{3\text{-}2}$ = 6.4 Hz, 1 H, H3), 4.00 (ddd, $J_{5\text{-}4}$ = 2.2 Hz, $J_{5\text{-}6a}$ = $J_{5\text{-}6b}$ = 6.5 Hz, 1 H, H-5), 3.84 (dd, $J_{6b\text{-}5}$ = 6.4 Hz, $J_{6b\text{-}6a}$ = 9.9 Hz, 1 H, H-6a), 3.80-3.70 (m, 3 H, H-6b H-2 OCH_2), 3.42 (dt, $J_{OCH2\text{-}OCH2'}$ = 9.7 Hz, $J_{OCH2\text{-}CH2}$ = 6.6 Hz, OCH_2'), 3.19 (m, 2 H, CH_2N), 2.21 (bs, 1 H, OH), 1.65-1.55 (m, 2 H, CH_2), 1.55-1.44 (m, 5 H, CH_2 $C(CH_3)_2$), 1.46-1.28 (m, 7 H, CH_2-CH_2 $C(CH_3)_2$'), 0.88 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 156.5 (N(C=O)O), 136.7, 128.68, 128.64, 128.26, 128.23 (C^{Ph}), 109.5 ($O\underline{C}Me_2O$), 97.5 (C-1), 76.5 (C-3), 72.9 (C-4), 70.1 (C-2), 68.8 (C-5), 68.0 (OCH_2-), 66.7 (OCH_2Ph), 62.5 (C-6), 41.0 (-CH_2N), 30.0 29.4 (CH_2), 28.0 (CH_3^{iPrA}), 26.6 (-CH_2-), 25.97 (CH_3^{iPrA} '), 25.85 (-CH_2-), 18.4 ($Si\underline{C}Me_3$), -5.18 ($SiCH_3$), -5.33 ($SiCH_3$'); **HRMS**: calcd. for $C_{29}H_{49}NO_8Si$: 590.3120 [M+Na]$^+$, found 590.3123; **TLC** (hex/EtOAc/MeOH 73:24:2): R_f = 0.28 (CH stain).

p-Tolyl 6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-galactopyranoside (**97**)



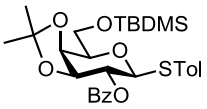
Silyl ether **97** was synthesized according to a modified literature procedure[109]. Thioglycoside **96** was suspended in an anhydrous mixture of CH_2Cl_2/DMF (3:1, 40 mL). Triethylamine (2.0 mL, 14.6 mmol, 1.2 eq) and a catalytic amount of DMAP (spatula tip) were added, followed by TBDMSCl (2.02 g, 13.4 mmol, 1.1 eq). The mixture was stirred for 1h at rt, diluted with EtOAc (100 mL) and washed with water (3 x 20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine (2 x 20 mL) and dried over $MgSO_4$. After concentration *in vacuo* the crude product was purified by flash chromatography (hex/EtOAc 60:40 to 50:50) to yield silyl ether **97** (4.50 g, 92%) as a colorless syrup. The analytical data is in full agreement with literature data.[109] **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.45 (m, 2 H, $H^{Ar, STol}$), 7.09 (m, 2 H, $H^{Ar, STol}$), 4.46 (d, $J_{1\text{-}2}$ = 9.5 Hz, 1 H, H-1), 4.06 (bs, 1 H, H-4), 3.95-3.83 (m, 2 H, H-6a H-6b), 3.68 (dd, $J_{2\text{-}1}$ = 9.5 Hz $J_{2\text{-}3}$ = 9.0 Hz, 1 H, H-2), 3.62-3.43 (m, 3 H, H-3 H-5 OH), 3.34 (bs, 1 H, OH), 3.23 (bs, 1 H, OH), 2.32 (s, 3 H, CH_3^{STol}), 0.89 (s, 9 H, CH_3^{tBu}), 0.09 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$').

p-Tolyl 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**98**)



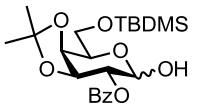
Silyl ether **97** (1.76 g, 4.39 mmol, 1.0 eq) was dissolved in acetone (17.6 mL) and DMP was added (1.4 mL, 11.0 mmol, 2.5 eq) followed by a catalytic amount of CSA (spatula tip). The reaction solution was stirred for 2 h, then quenched by the addition of NEt_3 (0.1 mL) and concentrated *in vacuo*. The crude product was purified by flash chromatography (hex/EtOAc 80:20) to yield alcohol **98** (1.90 g, 98%) as colorless crystals. **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 7.43 (m, 2 H, $H^{Ar, STol}$), 7.13 (m, 2 H, $H^{Ar, STol}$), 4.57 (d, $J_{1\text{-}2}$ = 10.0 Hz, 1 H, H-1), 4.48 (d, $J_{2\text{-}OH}$ = 5.0 Hz, 1 H, OH), 4.28 (dd, $J_{4\text{-}3}$ = 5.5 Hz $J_{4\text{-}5}$ = 2.1 Hz, 1 H, H-4), 4.09 (dd, $J_{3\text{-}4}$ = 5.5 Hz $J_{3\text{-}2}$ = 6.9 Hz, 1 H, H-3), 3.95 (ddd, $J_{5\text{-}4}$ = 2.0 Hz $J_{5\text{-}6a}$ = 5.6 Hz $J_{5\text{-}6b}$ = 6.9 Hz, 1 H, H-5), 3.83 (m, 2 H, H-6a H-6b), 3.52 (ddd, $J_{1\text{-}2}$ = 9.9 Hz $J_{2\text{-}3}$ = 6.8 Hz $J_{2\text{-}OH}$ = 5.0 Hz, 1 H, H-2), 2.30 (s, 3 H, CH_3^{STol}), 1.36 (s, 3 H, CH_3^{iPrA}), 1.28 (s, 3 H, CH_3^{iPrA} '), 0.90 (s, 9 H, CH_3^{tBu}), 0.10 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$'); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 137.7, 132.3, 131.7, 130.3 ($C^{Ar, STol}$), 109.9 ($O\underline{C}Me_2O$), 88.8 (C-1), 80.8 (C-3), 77.6 (C-5), 74.4 (C-4), 72.4 (C-2), 63.4 (C-6), 28.4 (CH_3^{iPrA}), 26.6 (CH_3^{iPrA} '), 26.2 (CH_3^{tBu}), 21.0 (CH_3^{STol}), 18.8 ($Si\underline{C}Me_3$), -5.1 ($SiCH_3$), -5.3 ($SiCH_3$'); **HRMS**: calcd. for $C_{22}H_{36}O_5SSi$: 463.1945 [*M*+Na]$^+$, found 463.1949;**TLC** (hex/EtOAc 67:33): R_f = 0.62 (UV, CH stain).

p-Tolyl 2-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**76**)



Alcohol **98** (498 mg, 1.13 mmol, 1.0 eq) and a catalytic amount of DMAP (spatula tip) were dissolved in anhydrous pyridine (15 mL) under a layer of argon. The stirred solution was placed in an ice bath (0 °C) and a solution of benzoyl chloride (0.16 mL, 1.36 mmol, 1.2 eq) in CH_2Cl_2 (10 mL) was added dropwise over the course of 10 min. After continued stirring for 80 min at 0 °C, the reaction was quenched by the addition of MeOH (0.5 mL). At this point the mixture was concentrated *in vacuo*, followed by purification using flash chromatography (hex/EtOAc 89:11) to yield thioglycoside **76** (573 mg, 93%) as a colorless solid. **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 8.07 (m, 2 H, $H^{Ar, Bz}$), 7.67 (m, 2 H, $H^{Ar, Bz}$), 7.55 (m, 2 H, $H^{Ar, Bz}$), 7.35 (m, 2 H, $H^{Ar, STol}$), 7.11 (m, 2 H, $H^{Ar, STol}$), 5.28 (dd, $J_{1\text{-}2}$ = 10.3 Hz $J_{2\text{-}3}$ = 7.3 Hz, 1 H, H-2), 4.97 (d, $J_{1\text{-}2}$ = 10.2 Hz, 1 H, H-1), 4.50 (dd, $J_{3\text{-}2}$ = 7.3 Hz $J_{3\text{-}4}$ = 5.2 Hz, 1 H, H-3), 4.42 (dd, $J_{4\text{-}3}$ = 5.2 Hz $J_{4\text{-}5}$ = 2.0 Hz, 1 H, H-4), 4.11 (ddd, $J_{5\text{-}4}$ = 2.1 Hz $J_{5\text{-}6a}$ = 5.7 Hz $J_{5\text{-}6b}$ = 7.8 Hz, 1 H, H-5), 3.91 (m, 2H, H-6a H-6b), 2.29 (s, 3 H, CH_3^{STol}), 1.51 (s, 3 H, CH_3^{iPrA}), 1.31 (s, 3 H, CH_3^{iPrA} ’), 0.92 (s, 9 H, CH_3^{tBu}), 0.12 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$’); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 165.9 (C=O), 138.1 ($C^{Ar, STol}$), 134.2 ($C^{Ar, Bz}$), 132.1, 131.6 ($C^{Ar, STol}$), 131.0, 130.46 ($C^{Ar, Bz}$), 130.43 ($C^{Ar, STol}$), 129.5 ($C^{Ar, Bz}$), 110.6 ($O\underline{C}Me_2O$), 86.6 (C-1), 78.0 (C-3), 77.8 (C-5), 74.6 (C-4), 73.1 (C-2), 63.3 (C-6), 28.2 (CH_3^{iPrA}), 26.6 (CH_3^{iPrA}‘), 26.2 (CH_3^{tBu}), 21.0 (CH_3^{STol}), 18.8 ($Si\underline{C}Me_3$), -5.1 ($SiCH_3$), -5.3 ($SiCH_3$’); **HRMS**: calcd. for $C_{29}H_{40}O_6SSi$: 567.2207 $[M+Na]^+$, found 567.2206; **TLC** (hex/EtOAc 80:20): R_f = 0.53 (UV, CH stain).

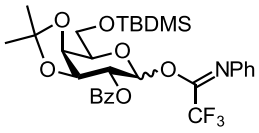
2-*O*-Benzoyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-galactopyranoside (**99**)



Thioglycoside **76** (300 mg, 551 µmol, 1.0 eq) was dissolved in CH_2Cl_2 (5.5 mL) and water (0.55 mL) was added. The emulsion was cooled to 0 °C using an ice bath and NIS (128 mg, 551 µmol, 1.0 eq) was added. After complete dissolution, TFA (42 µL, 551 mmol, 1.0 eq) was injected and the mixture stirred for 30 min. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$-solution (10 mL) and EtOAc (50 mL) was added. The phases were separated, the organic phase was washed with sat. aq. $NaHCO_3$ (3x 10 mL) and it was dried over $MgSO_4$. After concentration *in vacuo*, the crude was purified by flash chromatography (tol/EtOAc 91:9 to 83:17) to yield hemiacetal **99** (200 mg, α/β 5.5:1, 83%) as a colorless solid and the expected 2→1-benzoyl migrated side product as a colorless solid. **^{1}H NMR**

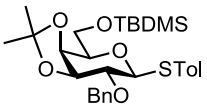
(CD_3COCD_3, 400 MHz): δ = 8.13-8.03 (m, 2 H, $H^{Ar\ Bz\ \alpha/\beta}$), 7.70-7.61 (m, 1 H, $H^{Ar\ Bz\ \alpha/\beta}$), 7.58-7.48 (m, 1 H, $H^{Ar\ Bz\ \alpha/\beta}$), 5.93-5.88 (m, 1 H, $OH^{\alpha\beta}$), 5.37 (dd, $J_{1\text{-}2}$ = 3.5 Hz, $J_{1\text{-}OH}$ = 4.7 Hz, H-1^{α}), 5.18 (dd, $J_{2\text{-}3}$ = 7.7 Hz, $J_{2\text{-}1}$ = 8.2 Hz, H-2^{β}), 5.09 (ddd, $J_{2\text{-}1}$ = 3.4 Hz, $J_{2\text{-}3}$ = 8.0 Hz, $J^{4}_{2\text{-}OH}$ = 1.2 Hz, 0.85 H, H-2^{α}), 4.83 (dd, $J_{1\text{-}2}$ = 8.3 Hz, $J_{1\text{-}OH}$ = 7.0 Hz, 0.15 H, H-1^{β}), 4.55 (dd, $J_{3\text{-}2}$ = 8.0 Hz, $J_{3\text{-}4}$ = 5.3 Hz, 0.86 H, H-3^{α}), 4.47-4.30 (m, 2 H, H-$4^{\alpha\beta}$ H-3^{β} H-5^{α}), 4.02 (ddd, $J_{5\text{-}4}$ = 2.1 Hz, $J_{5\text{-}6a}$ = 6.6 Hz $J_{5\text{-}6b}$ = 13.2 Hz, 0.18 H, H-5^{β}), 3.98-3.89 (m, 1 H, H-$6a^{\alpha\beta}$), 3.88-3.74 (m, 1 H, H-$6b^{\alpha\beta}$), 1.54 (s, 0.48 H, CH_3^{β}), 1.48 (s, 2.61 H, CH_3^{α}), 1.32 (s, 2.55 H, CH_3^{α}), 1.30 (s, 0.56 H, CH_3^{β}), 0.92 (m, 9 H, $C(CH_3)_3^{\alpha\beta}$), 0.11 (m, 6 H, $Si(CH_3)_2^{\alpha\beta}$); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 166.5 166.0 (C=O), 134.1, 133.9, 131.3, 130.9, 130.6, 130.4, 130.3, 129.4, 129.3 ($C^{Ar\ Bz\ \alpha}$ $C^{Ar\ Bz\ \beta}$), 110.4 ($O\underline{C}Me_2O^{\beta}$), 109.7 ($O\underline{C}Me_2O^{\alpha}$), 95.6 (C-$1^{\beta}$), 90.9 (C-$1_{OH}^{\alpha}$), 90.8 (C-$1_{OD}^{\alpha}$), 78.0 (C-$3^{\beta}$), 76.4 (C-$2^{\beta}$), 74.5 (C-$4^{\beta}$), 74.3 (C-$2^{\alpha}$), 74.2 (C-$3^{\alpha}$), 74.13 (C-$5^{\beta}$), 74.1 (C-$4^{\alpha}$), 68.5 (C-$5^{\alpha}$), 63.1 (C-$6^{\alpha}$), 63.0 (C-$6^{\beta}$), 28.4 ($CH_3^{i\text{PrA}\ \alpha}$), 28.3 ($CH_3^{i\text{PrA}\ \beta}$), 26.7 ($CH_3$'$^{i\text{PrA}\ \alpha}$), 26.6 ($CH_3$'$^{i\text{PrA}\ \beta}$), 26.2 ($CH_3^{t\text{Bu}\ \alpha/\beta}$), 18.8 ($Si\underline{C}Me_3^{\alpha/\beta}$), -5.1 ($SiCH_3^{\alpha/\beta}$), -5.3 ($SiCH_3$'); **HRMS**: calcd. for $C_{22}H_{34}O_7Si$: 461.1966 [M+Na]$^+$, found 461.1969. **TLC** (tol/EtOAc 83:17): R_f = 0.42 (UV, CH stain).

2-*O*-Benzoyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-galactopyranosyl *N*-Phenyl-trifluoroacetimidate (**100**)



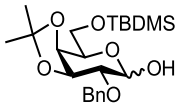
Hemiacetal **99** (300 mg, 684 µmol, 1.0 eq) was dissolved in acetone (3.5 mL, treated with $MgSO_4$ and filtrated) and Cs_2CO_3 (446 mg, 1.37 mmol, 2.0 eq), and subsequently trifluoro-N-phenylacetimidoyl chloride (0.22 mL, 1.37 mmol, 2.0 eq) was added. The mixture was stirred for 3 h at which point TLC indicated complete turnover, so the suspension was diluted with EtOAc (5 mL) and filtrated over a plug of celite. After washing with EtOAc the filtrate was concentrated and the residue purified by flash chromatography (hex/EtOAc 94:6). The two anomers of donor **100** (286 mg, 68%; 140 mg, 33%) were isolated separately as colorless crystalline solids. Due to instability of the compound in solution further characterization was not performed. **TLC** (hex/EtOAc 80:20): R_f = 0.77, 0.63 (UV, CH stain)

p-Tolyl 2-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**101**)



Alcohol **98** (500 mg, 1.13 mmol, 1.0 eq) and Ag_2O (615 mg, 2.66 mmol, 2.34 eq) were suspended in DMF (3 mL) under an atmosphere of argon and BnBr (0.40 mL, 3.40 mmol, 3.0 eq) was added. The mixture was protected from light and stirred for 3 d. After dilution with toluene (10 mL) it was filtered through a syringe filter (PTFE, 0.45 µm) and washed with toluene. The filtrate was washed with brine (3 x 5 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hex/EtOAc 94:6) to yield thioglycoside **101** (565 mg, 94%) as a colorless oil. **^{1}H NMR** (CD_3COCD_3, 300 MHz): δ = 7.43 (m, 4 H, $H^{Ar, STol}$ $H^{Ar, Bn}$), 7.39-7.24 (m, 3 H, $H^{Ar, Bn}$), 7.13 (m, 2 H, $H^{Ar, STol}$), 4.83 (d, $J_{1\text{-}2}$ = 11.7 Hz, 1 H, $PhCH_2$a), 4.72-4.65 (m, 2 H, H-1 $PhCH_2$b), 4.35-4.28 (m, 2 H, H-4 H-3), 3.95 (ddd, $J_{5\text{-}4}$ = 1.7 Hz $J_{5\text{-}6a}$ = 5.5 Hz $J_{5\text{-}6b}$ = 7.2 Hz, 1 H, H-5), 3.90-3.78 (m, 2H, H-6a H-6b), 3.47 (dd, $J_{2\text{-}3}$ = 6.0 Hz $J_{2\text{-}1}$ = 9.6 Hz, 1 H, H-2), 2.30 (s, 3 H, CH_3^{STol}), 1.39 (s, 3 H, CH_3^{iPrA}), 1.32 (s, 3 H, CH_3^{iPrA} '), 0.91 (s, 9 H, CH_3^{tBu}), 0.10 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$'); **^{13}C NMR** (CD_3COCD_3, 75 MHz): δ = 139.6, 137.8, 132.4, 131.8, 130.4, 128.9, 128.7, 128.3 ($C^{Ar, STol}$ $C^{Ar, Bn}$), 110.2 (O<u>C</u>Me_2O), 87.0 (C-1), 80.5 (C-3), 79.6 (C-2), 77.6 (C-5), 74.5 (C-4), 73.7 (Ph<u>C</u>H_2), 63.4 (C-6), 28.3 (CH_3^{iPrA}), 26.6 (CH_3^{iPrA} '), 26.3 (CH_3^{tBu}), 21.1 (CH_3^{STol}), 18.9 (Si<u>C</u>Me_3), -5.1 ($SiCH_3$), -5.3 ($SiCH_3$'); **HRMS**: calcd. for $C_{29}H_{42}O_5SSi$: 553.2414 [*M*+Na]$^+$, found 553.2405; **TLC** (hex/EtOAc 80:20): R_f = 0.59 (UV, CH stain).

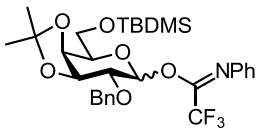
2-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-galactopyranoside (**102**)



Thioglycoside **101** (584 mg, 1.10 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (11 mL) and water (1.1) mL was added. The emulsion was cooled to 0 °C using an ice bath and NIS (255 mg, 97%, 1.10 mmol, 1.0 eq) was added. After complete dissolution, TFA (84 µL, 1.10 mmol, 1.0 eq) was injected and the mixture stirred for 17 min. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$-solution (11 mL) and EtOAc (50 mL) was added. The phases were separated, and the organic phase was washed with sat. aq. $NaHCO_3$-solution (3x 10 mL) and dried over $MgSO_4$. After concentration *in vacuo*, the crude product was purified by flash chromatography (hex/EtOAc 5:1) and the resulting mixed fractions by a second flash chromatography (tol/EtOAc 91:9) to yield hemiacetal **102** (371 mg, α/β 3:1, 79%) as a colorless crystalline solid. **^{1}H NMR** (CD_3COCD_3, 300 MHz): δ = 7.45-7.20 (m, 5 H, $H^{Ar\ Bn\ \alpha/\beta}$), 5.79 (d, $J_{OH\text{-}1}$ = 6.6 Hz,

0.25 H, OH^{β}), 5.35 (dd, J_{OH-1} = 5.1 Hz J_{OH-2} = 0.8 Hz, 0.75 H, OH^{α}), 5.22 (dd, J_{1-2} = 3.4 Hz J_{OH-1} = 5.0 Hz, 0.75 H, H-1^{α}), 4.86, 4.81 (2d, $J_{CH2-CH2'}$ = 12.2 Hz, 0.5 H, $PhCH_2^{\beta}$), 4.77, 4.72 (2d, $J_{CH2-CH2'}$ = 12.2 Hz, 1.5 H, $PhCH_2^{\alpha}$), 4.61 (dd, J_{1-OH} = 6.5 Hz J_{1-2} = 8.0 Hz, 0.25 H, H-1^{β}), 4.39-4.22 (m, 2.5 H, H-3^{α} H-4^{α} H-5^{α} H-5^{β}), 4.17 (dd, J_{3-2} = 7.0 Hz J_{3-4} = 5.6 Hz, 0.25 H, H-3^{β}), 3.90-3.75 (m, 1.5 H, H-$6a^{\alpha}$ H-$6a^{\beta}$ H-$6b^{\beta}$ H-4^{β}), 3.70 (dd, J_{6b-5} = 5.9 Hz J_{6a-6b} = 9.6 Hz, 0.75 H, H-$6b^{\alpha}$), 3.52 (ddd, J_{2-OH} = 0.7 Hz J_{2-1} = 3.4 Hz J_{2-3} = 7.0 Hz, 0.75 H, H-2^{α}), 3.32 (dd, J_{1-2} = 8.0 Hz J_{2-3} = 7.1 Hz, 0.25 H, H-2^{β}), 2.25 (s, 2.25 H, $CH_3^{i\text{PrA }\alpha}$), 1.36 (s, 0.75 H, $CH_3^{i\text{PrA }\beta}$), 1.30 (m, 3 H, $CH_3^{i\text{PrA }}$'), 0.90 (s, 9 H, $CH_3^{t\text{Bu}}$), 0.09 (s, 1.5 H, $Si(CH_3)_2^{\beta}$), 0.08 (s, 4.5 H, $Si(CH_3)_2^{\alpha}$); **^{13}C NMR** (CD_3COCD_3, 75 MHz): δ = 140.2, 140.0, 129.0, 128.8, 128.55, 128.50, 128.2, 128.0 ($C^{Ar\ Bn}$), 109.8 ($O\underline{C}Me_2O^{\beta}$), 109.2 ($O\underline{C}Me_2O^{\alpha}$), 97.7 (C-$1^{\beta}$), 91.6 (C-$1^{\alpha}$), 82.6 (C-$2^{\beta}$), 80.0 (C-$3^{\beta}$), 78.3 (C-$2^{\alpha}$), 76.3 (C-$3^{\alpha}$), 74.4 (C-$5^{\beta}$), 73.9 (C-4), 73.8 ($PhCH_2^{\beta}$), 72.5 ($PhCH_2^{\alpha}$), 68.7 (C-$5^{\alpha}$), 63.3 (C-$6^{\alpha}$), 63.1 (C-$6^{\beta}$), 28.4 ($CH_3^{i\text{PrA}}$), 26.7 ($CH_3^{i\text{PrA }\beta}$'), 26.5 ($CH_3^{i\text{PrA }\alpha}$'), 26.2 ($CH_3^{t\text{Bu}}$), 18.9 ($Si\underline{C}Me_3$), -5.1 ($SiCH_3$), -5.3 ($SiCH_3$'); **HRMS**: calcd. for $C_{22}H_{36}O_6Si$: 442.2619 $[M+NH_4]^+$, found 442.2621; **TLC** (hex/EtOAc 83:17): R_f = 0.25 (UV, CH stain).

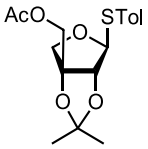
2-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-galactopyranosyl *N*-phenyl-trifluoroacetimidate (**73**)



Hemiacetal **73** (350 mg, 824 µmol, 1.0 eq) was dissolved in acetone (6 mL, treated with $MgSO_4$ and filtrated) and Cs_2CO_3 (537 mg, 1.65 mmol, 2.0 eq) followed by trifluoro-N-phenylacetimidoyl chloride (0.27 mL, 1.65 mmol, 2.0 eq) was added. The mixture was stirred for 2 h then the suspension was diluted with hexanes (6 mL), filtrated over a plug of celite and washed with hex/acetone (50:50). The filtrate was concentrated and the residue purified by flash chromatography (hex/EtOAc 95:5). The two anomers of donor **73** (412 mg, 84%; 103 mg, 21%) were isolated separately as colorless oils. Due to instability of the compound in solution further characterization was not performed. **TLC** (hex/EtOAc 89:11): R_f = 0.50, 0.38 (UV, CH stain)

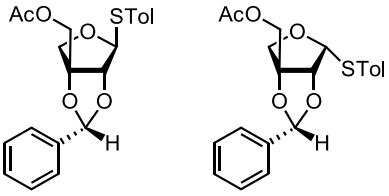
4.3.2 Synthesis of apiose building blocks

p-Tolyl 3'-*O*-acetyl-2,3-*O*-isopropylidene-1-thio-β-D-apiofuranoside (**107**)



The β-isomer of alcohol **106** (1.48 g, 5.00 mmol, 1.0 eq) was dissolved in NEt_3 (13.4 mL) followed by the addition of acetic anhydride (0.57 mL, 6.00 mmol, 1.2 eq) and a catalytic amount of DMAP (spatula tip). After stirring the mixture for 2 h it was concentrated *in vacuo*. The residue was taken up in EtOAc (50 mL) and the mixture was washed with 1 M HCl (2x 30 mL), followed by sat. aq. $NaHCO_3$ (2x 30 mL). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and the obtained crude product was purified by flash chromatography (hex/EtOAc 66:33) to yield the β-isomer of thioglycoside **107** as a colorless oil (1.63 g, 96%). The analytical data is in full agreement with literature data[89]. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.36 (m, 2 H, $H^{Ar, STol}$), 7.13 (m, 2 H, $H^{Ar, STol}$), 5.60 (s, 1 H, H-1), 4.54 (s, 1 H, H-2), 4.41 (d, $J_{3'a\text{-}3'b}$ = 11.7 Hz, 1 H, H-3'a), 4.29 (d, $J_{3'a\text{-}3'b}$ = 11.7 Hz, 1 H, H-3'b), 4.17 (d, $J_{4'a\text{-}4'b}$ = 10.5 Hz, 1 H, H-4'a), 4.04 (d, $J_{4'a\text{-}4'b}$ = 10.5 Hz, 1 H, H-4'b), 2.33 (s, 3 H, CH_3^{STol}), 2.15 (s, 3 H, CH_3^{Ac}), 1.48 (CH_3^{iPrA}), 1.41 ($CH_3^{iPrA'}$).

p-Tolyl 3'-*O*-acetyl-2,3-*O*-(*endo*)-benzylidene-1-thio-D-apiofuranoside (**72**)

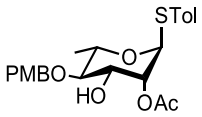


Thioglycoside **72** was prepared from the β-isomer of thioglycoside **107** in 2 steps according to a published procedure[89]. Thioglycoside **107** (1.63 g, 4.81 mmol, 1.0 eq) was dissolved in 90% $TFA_{aq.}$ (22 mL) and stirred at 20°C for 90 min, until TLC indicated almost complete consumption of starting material. Toluene (20 mL) was added and the volatiles were removed *in vacuo* at 20°C. The residue was redissolved in toluene and the $TFA_{aq.}$ removed by coevaporation (3x) *in vacuo* at 20°C to obtain a clear syrup. After removing all volatiles in fine vacuum, the syrup was dissolved in toluene (3.6 mL) and benzaldehyde dimethyl acetal (3.6 mL, 23.9 mmol, 5.0 eq) was added, followed by a catalytic amount (spatula tip) of CSA. The mixture was stirred at rt for 16 h, then quenched by the addition of NEt_3 until the pH-value was found to be around 8. The solution was concentrated *in vacuo,* and the residue was purified by column chromatography (83:17 hex/EtOAc) to yield *endo*-products **72-β** (860 mg, 46%) and **72-α** (294 mg, 16%) separated from the *exo*-products as colorless syrups that crystallized upon storage. For **72-β**: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.52 (m, 2 H, $H^{Ar, Ph}$), 7.38 (m, 5 H, $H^{Ar, Ph}$, $H^{Ar, STol}$), 7.14 (m, 2 H,

$H^{Ar, STol}$), 5.92 (s, 1 H, PhC<u>H</u>), 5.77 (s, 1 H, H-1), 4.60 (s, 1 H, H-2), 4.51 (d, $J_{3'a-3'b}$ = 12 Hz, 1 H, H-3'a), 4.42 (d, $J_{3'a-3'b}$ = 12 Hz, 1 H, H-3'b), 4.25 (d, $J_{4'a-4'b}$ = 10.5 Hz, 1 H, H-4'a), 4.21 (d, $J_{4'a-4'b}$ = 10.6 Hz, 1 H, H-4'b), 2.32 (s, 3 H, CH_3^{STol}), 2.18 (s, 3 H, CH_3^{Ac}); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 170.7 (CO), 138.3 ($C^{Ar, STol}$), 135.7 ($C^{Ar, Ph}$), 133.0 ($C^{Ar, STol}$), 130.3 ($C^{Ar, Ph}$), 130.1, 129.1 ($C^{Ar, STol}$), 128.6, 127.3 ($C^{Ar, Ph}$), 106.6 (Ph<u>C</u>H), 92.8 (C-1), 90.6 (C-3), 87.8 (C-2), 72.9 (C-4), 64.1 (C-3'), 21.3 (CH_3^{Ac}), 21.0 (CH_3^{STol}); **HRMS**: calcd. for $C_{21}H_{22}O_5S$: 387.1261 [*M*+H]$^+$, found 387.1268; **TLC** (hex/EtOAc = 5:1): R_f = 0.48 (UV, CH stain). For **72-α**: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.63 (m, 2 H, $H^{Ar, Ph}$), 7.45 (m, 2 H, $H^{Ar, STol}$), 7.42 (m, 3 H, $H^{Ar, Ph}$), 7.13 (m, 2 H, $H^{Ar, STol}$), 6.03 (s, 1 H, PhC<u>H</u>), 5.12 (d, J_{1-2} = 3.9 Hz, 1 H, H-1), 4.78 (d, J_{1-2} = 4.0 Hz, 1 H, H-2), 4.44 (d, $J_{3'a-3'b}$ = 12 Hz, 1 H, H-3'a), 4.31 (m, 2 H, H-3'b H-4a), 3.68 (d, 1 H, $J_{3'a-3'b}$ = 10.5 Hz, H-4b), 2.33 (s, 3 H, CH_3^{STol}), 2.13 (s, 3 H, CH_3^{Ac}); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 170.7 (CO), 137.7 ($C^{Ar, STol}$), 135.5 ($C^{Ar, Ph}$), 131.8, 131.4 ($C^{Ar, STol}$), 130.3 ($C^{Ar, Ph}$), 130.0 ($C^{Ar, STol}$), 128.6, 127.5 ($C^{Ar, Ph}$), 107.6 (Ph<u>C</u>H), 91.5 (C-1), 90.2 (C-3), 84.8 (C-2), 73.2 (C-4), 63.7 (C-3'), 21.3 (CH_3^{Ac}), 21.0 (CH_3^{STol}); **HRMS**: calcd. for $C_{21}H_{22}O_5S$: 387.1261 [*M*+H]$^+$, found 387.1268; **TLC** (hex/EtOAc 83:17): R_f = 0.25 (UV, CH stain).

4.3.3 Synthesis of rhamnose building blocks

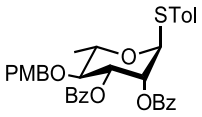
p-Tolyl 2-*O*-acetyl-4-*O*-*p*-methoxybenzyl-1-thio-α-L-rhamnopyranoside (**75**)



Alcohol **75** was prepared by a modified published procedure[99]. To a solution of thioglycoside **108** (0.54 g, 2.00 mmol, 1.0 eq) in anhydrous DMF (20 mL), triethyl orthoacetate (0.55 mL, 3.00 mmol, 1.5 eq) was added, followed by a catalytic amount of *p*-TsOH (spatula tip). After stirring the reaction mixture for 1 h, it was neutralized with NEt_3 (20 µL), and sodium hydride dispersion in mineral oil (60%, 120 mg, 3.00 mmol, 1.5 eq) and subsequently *p*-methoxybenzylchloride (0.32 mL, 2.40 mmol, 1.2 eq) were added. After stirring for 1 h, the reaction was complete, so it was quenched with MeOH (2 mL) and diluted with CH_2Cl_2 (40 mL). The organic phase was washed with 1 M HCl (3 x 30 mL) and sat. aq. $NaHCO_3$ (3x 30 mL), dried over $MgSO_4$ and concentrated. The residue was coevaporated with toluene (3x 5 mL) and purified by flash chromatography (hex/EtOAc 78:22 to 66:33) to yield alcohol **75** (0.73 g, 85%) as a colorless syrup. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.32 (m, 4 H, $H^{Ar\ STol}$ $H^{Ar\ PMB}$), 7.10 (m, 2 H, $H^{Ar\ STol}$), 6.90 (m, 2 H, $H^{Ar\ PMB}$), 5.38-5.32 (m, 2 H, H-1 H-2), 4.75, 4.68 (2d, $J_{OCH2-OCH2'}$ = 10.5 Hz, 2 H, OCH_2), 4.22 (dq, J_{4-5} = 9.5 Hz J_{5-6} = 6.2 Hz, 1 H, H-5), 4.08 (dd, J_{2-3} = 3.3 Hz J_{3-4} = 9.3 Hz, 1H, H-3), 3.81 (s, 3H, OCH_3), 3.41 (dd, J_{3-4} = J_{4-5} = 9.4 Hz, H-4), 2.32 (s, 3 H, CH_3^{STol}), 2.14 (s, 3 H, CH_3^{Ac}), 1.36 (d, J_{5-6} = 6.3 Hz, 3 H, H-6); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ = 170.8 (C=O), 159.6 ($C^{Ar\ PMB}$), 138.0 ($C^{Ar\ STol}$), 132.5 ($C^{Ar\ PMB}$), 130.4 ($C^{Ar\ STol}$), 130.2 ($C^{Ar\ PMB}$), 130.0 ($C^{Ar\ STol}$), 129.8 ($C^{Ar\ STol}$), 114.2 ($C^{Ar\ PMB}$), 86.4 (C-1), 81.8 (C-4), 75.1 (CH_2^{PMB}),

74.4 (C-2), 70.9 (C-3), 68.9 (C-5), 55.5 (OCH_3), 21.24 (CH_3^{STol}), 21.20 (CH_3^{Ac}), 18.1 (C-6); **TLC** (hex:EtOAc 67:33): R_f = 0.25 (CH stain, UV); **HRMS**: calcd. for $C_{23}H_{28}O_6S$: 455.1499 [*M*+Na]$^+$, found 455.1505.

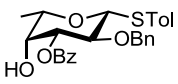
p-Tolyl 2,3-di-*O*-benzoyl-4-*O*-*p*-methoxybenzyl-1-thio-α-L-rhamnopyranoside (**89**)



Alcohol **75** (100 mg, 231 µmol, 1.0 eq) was dissolved in MeOH (1 mL) and a drop of 0.5 M sodium methoxide solution in MeOH was added. After 30 min TLC indicated complete deprotection and the reaction was quenched by the addition of prewashed Amberlite IR-120. After stirring for additional 5 min the liquid was decanted, the resin washed with MeOH and the combined solution concentrated *in vacuo*. The remaining colorless crystalline solid was then dissolved in NEt_3 (1.0 mL) and a catalytic amount of DMAP (spatula tip) followed by benzoic anhydride (131 mg, 578 µmol, 2.5 eq) was added. After 3 h the mixture was concentrated *in vacuo*. The crude was taken up in EtOAc (10 mL) and washed with 1 M HCl (3x10 mL) and sat. aq. $NaHCO_3$ (3x10 mL). After drying over $MgSO_4$ the organic phase was concentrated to yield a colorless crude. Flash chromatography (hex/EtOAc 88:12) yielded thioglycoside **89** (131 mg, 95%) as colorless crystals. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.02 (m, 2 H, $H^{Ar\ Bz}$), 7.92 (m, 2 H, $H^{Ar\ Bz}$), 7.61 (m, 1 H, $H^{Ar\ Bz}$), 7.53 (m, 1 H, $H^{Ar\ Bz}$), 7.47 (m, 2 H, $H^{Ar\ Bz}$), 7.44-7.33 (m, 4 H, $H^{Ar\ STol}$ $H^{Ar\ Bz}$), 7.13 (m, 4 H, $H^{Ar\ STol}$ $H^{Ar\ PMB}$), 6.75 (m, 2 H, $H^{Ar\ PMB}$), 5.84 (dd, $J_{2\text{-}1}$ = 1.7 Hz $J_{2\text{-}3}$ = 3.2 Hz, 1 H, H-2), 5.69 (dd, $J_{3\text{-}2}$ = 3.2 Hz $J_{3\text{-}4}$ = 9.6 Hz, 1 H, H-3), 5.50 (d, $J_{1\text{-}2}$ = 1.7 Hz, 1 H, H-1), 4.67, 4.60 (d, $J_{OCH2\text{-}OCH2'}$ = 10.5 Hz, 1 H, OCH_2 OCH_2'), 4.45 (dq, $J_{5\text{-}4}$ = 9.4 Hz $J_{5\text{-}6}$ = 6.2 Hz, 1 H, H-5), 3.85 (dd, $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 9.5 Hz, 1H, H-4), 3.74 (s, 3H, OCH_3), 2.33 (s, 3 H, CH_3^{STol}), 1.42 (d, $J_{5\text{-}6}$ = 6.2 Hz, 3 H, H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 165.49, 165.47 (C=O), 159.5 ($C^{Ar\ PMB}$), 138.2 ($C^{Ar\ STol}$), 133.5 133.3 ($C^{Ar\ Bz}$), 132.8, 130.0, 129.92, 129.90, 129.88, 129.82, 129.78, 129.77, 128.7, 128.5 ($C^{Ar\ Bz}$ $C^{Ar\ STol}$ $C^{Ar\ PMB}$), 113.9 ($C^{Ar\ PMB}$), 86.2 (C-1), 78.8 (C-4), 75.0 (OCH_2), 72.8 (C-3), 72.7 (C-2), 69.3 (C-5), 55.4 (OCH_3), 21.3 (CH_3^{STol}), 18.2 (C-6); **TLC** (hex:EtOAc 88:12): R_f = 0.3 (CH stain); **HRMS**: calcd. for $C_{35}H_{34}O_7S$: 621.1917 [*M*+Na]$^+$, found 621.1932.

4.3.4 Synthesis of fucose building blocks

p-Tolyl 2-*O*-benzyl-3-*O*-benzoyl-1-thio-β-L-fucopyranoside (**109**)

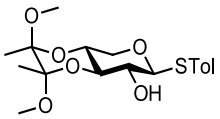


Alcohol **81** (52.0 mg, 129 µmol, 1.0 eq) was dissolved in MeOH (0.5 mL) and treated with catalytic amounts (one drop) of 0.5 M NaOMe in MeOH solution. After 30 min, Amberlite IR-120 was added and

the mixture stirred until the solution became neutral, then the amberlite was filtered off. After washing the amberlite with MeOH the combined solution was concentrated *in vacuo* and all volatile compounds were removed in fine vacuum. Under argon atmosphere, the crude was taken up in anh. CH_2Cl_2 (0.5 mL), a catalytic amount of DMAP (1.6 mg, 12.9 µmol, 0.1 eq) was added and the solution was cooled to -30 °C. A premixed solution of anh. CH_2Cl_2 (0.5 mL), NEt_3 (44.6 µL, 322 µmol, 2.5 eq) and BzCl (16.3 µL, 142 µmol, 1.1 eq) was added dropwise. After 2 h, the reaction was quenched by the addition of MeOH, warmed up to rt and concentrated *in vacuo*. The crude was purified by flash chromatography (tol to tol/EtOAc 95:5 to 91:9) to give alcohol **109** as a colorless crystalline solid (41.6 mg, 70% o. 2 s.). **^{1}H NMR** (CD_3COCD_3, 300 MHz): δ = 8.07 (m, 2 H, $H^{Ar, Bz}$), 7.64 (m, 1 H, $H^{Ar, Bz}$), 7.56-7.47 (m, 4 H, $H^{Ar, Bz}$ $H^{Ar, STol}$), 7.26-7.12 (m, 7 H, $H^{Ar, Bn}$ $H^{Ar, STol}$), 5.21 (dd, $J_{3\text{-}2}$ = 9.5 Hz, $J_{3\text{-}4}$ = 3.2 Hz 1 H, H-1), 4.88-4.80 (m, 2H, H-1 CH_2^{Bn}a), 4.66 (d, J_{CH2Ar} = 10.8 Hz, 1 H, CH_2^{Bn}b), 4.42 (d, $J_{2\text{-}OH}$ = 5.7 Hz, 1 H, OH), 4.07-3.98 (m, 2 H, H-2 H-4), 3.91 (dt, $J_{5\text{-}4}$ = $J_{5\text{-}6}$ = 6.4 Hz, 1 H, H-5), 2.33 (s, 3 H, CH_3^{STol}), 1.32 (d, $J_{6\text{-}5}$ = 6.4 Hz, 3 H, C-6); **^{13}C NMR** (CD_3COCD_3, 75 MHz): δ = 166.2 (C=O), 139.4, 137.9, 134.0, 132.4, 131.8, 131.3, 130.5, 129.3, 128.8, 128.6, 128.2 ($C^{Ar, STol}$ $C^{Ar, Bz}$ $C^{Ar, Bn}$), 88.2 (C-1), 79.1 (C-3), 76.2 (C-2), 75.7 (CH_2^{Bn}), 75.1 (C-5), 70.5 (C-4), 21.0 (CH_3^{STol}), 17.1 (C-6); **HPTLC** (hex:EtOAc 67:33): R_f = 0.64 (CH stain, UV); **HRMS**: calcd. for $C_{27}H_{28}O_5S$: 482.1996 $[M+NH_4]^+$, found 482.2005.

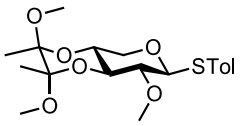
4.3.5 Synthesis of xylose building blocks

p-Tolyl 3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-1-thio-β-D-xylopyranoside (**111**)



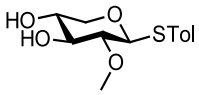
Alcohol **111** was prepared using a modified literature procedure.[100] Under a layer of argon, thioglycoside **110** (0.85 g, 3.32 mmol, 1.0 eq) was dissolved in anhydrous MeOH (11.6 mL) and trimethyl orthoformate (1.8 mL, 16.6 mmol, 5.0 eq) as well as diacetyl (0.58 mL, 6.63 mmol, 2.0 eq) were added. Then a catalytic amount of CSA (77 mg, 0.1 eq) was added in one portion. The mixture was stirred for 3 d at rt. After quenching the reaction with NEt_3 (1 mL) the solution was concentrated to a deep red crude which was purified by flash chromatography (hex/EtOAc 78:22) to yield alcohol **111** and trace amounts of other diastereomers (0.95 g, 77%) as a colorless solid. The analytical data is in full agreement with literature data.[100] **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.43 (m, 2 H, $H^{Ar, STol}$), 7.12 (m, 2 H, $H^{Ar, STol}$), 4.40 (d, $J_{1\text{-}2}$ = 9.3 Hz, 1 H, H-1), 3.96 (dd, $J_{6a\text{-}6b}$ = 10.7 Hz $J_{5\text{-}6a}$ = 4.4 Hz, 1 H, H-5a), 3.75-3.61 (m, 2 H, H-3 H-4), 3.48-3.38 (m, 2 H, H-5b H-2), 3.30 (s, 3 H, OCH_3^{BBA}), 3.24 (s, 3 H, $OCH_3^{BBA'}$), 2.46 (m, 1 H, OH), 2.35 (s, 3 H, CH_3^{STol}), 1.32 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3').

p-Tolyl 3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-2-*O*-methyl-1-thio-β-D-xylopyranoside (**112**)



Under a layer of argon, alcohol **111** (400 mg, 1.08 mmol, 1.0 eq) was dissolved in anhydrous DMF (3 mL) and 60% NaH dispersion in mineral oil (60.5 mg, 1.51 mmol, 1.4 eq) was added. After 3 min, MeI (74 µL, 1.19 mmol, 1.1 eq) was added and the reaction mixture was stirred for 90 min before it was quenched by the addition of MeOH (0.5 mL). It was stirred for 5 min, then sat. aq. $NaHCO_3$ (20 mL) and EtOAc (20 mL) were added, the phases were separated, and the aqueous layer extracted with EtOAc (3x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (hex/EtOAc 89:11) to yield thioglycoside **112** (411 mg, 99%) as a colorless crystalline solid. **^{1}H NMR** (CD_3COCD_3, 300 MHz): δ = 7.41 (m, 2 H, $H^{Ar, STol}$), 7.16 (m, 2 H, $H^{Ar, STol}$), 4.54 (d, $J_{1\text{-}2}$ = 9.3 Hz, 1 H, H-1), 3.81 (dd, $J_{6a\text{-}6b}$ = 10.5 Hz $J_{5\text{-}6a}$ = 4.6 Hz, 1 H, H-5a), 3.69-3.57 (m, 2 H, H-3 H-4), 3.54 (s, 3 H, OCH_3), 3.37-3.29 (m, 1 H, H-5b), 3.25 (s, 3 H, OCH_3^{BBA}), 3.21 (s, 3 H, OCH_3^{BBA}'), 2.97 (dd, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 9.1 Hz, 1 H, H-2), 2.32 (s, 3 H, CH_3^{STol}), 1.26 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3'); **^{13}C NMR** (CD_3COCD_3, 75 MHz): δ = 138.5, 133.5, 130.7, 130.4 ($C^{Ar, STol}$), 100.4, 100.1 ($C^{BBA\ Acetal}$), 88.6 (C-1), 79.8 (C-2), 76.0 (C-3), 67.8 (C-4), 66.6 (C-5), 60.7 (OCH_3), 48.0, 47.8 (OCH_3^{BBA}), 21.1 (CH_3^{STol}), 18.2, 17.9 (CH_3^{BBA}); **TLC** (hex:EtOAc 83:17): R_f = 0.5 (CH stain, UV); **HRMS**: calcd. for $C_{19}H_{28}O_6S$: 402.1945 $[M+NH_4]^+$, found 402.1963, calcd. for $C_{19}H_{28}O_6S$: 353.1417 $[M\text{-}OMe]^+$, found 353.1423.

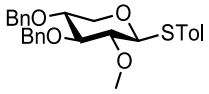
p-Tolyl 2-*O*-methyl-1-thio-β-D-xylopyranoside (**113**)



Thioglycoside **112** (400 mg, 1.04 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (10 mL) and 90% aqueous TFA (5.5 mL) was added. The mixture was stirred at rt for 5 min at which point TLC indicated complete turnover. Toluene (5 mL) was added and the solution was concentrated *in vacuo*, followed by repeated coevaporation of TFA with toluene (3 x 5 mL) to yield a colorless solid. The crude was purified by flash chromatography (EtOAc) to yield diol **113** as a crystalline colorless solid (271 mg, 96%). The crude may also be used without purification. **^{1}H NMR** (CD_3OD, 400 MHz): δ = 7.39 (m, 2 H, $H^{Ar, STol}$), 7.14 (m, 2 H, $H^{Ar, STol}$), 4.49 (d, $J_{1\text{-}2}$ = 9.4 Hz, 1 H, H-1), 3.91 (dd, $J_{5a\text{-}4}$ = 5.1 Hz , $J_{5a\text{-}5b}$ = 11.4 Hz, 1 H, H-5a), 3.58 (s, 3 H), 3.50-3.43 (m, 1 H, H-4), 3.39 (dd, $J_{3\text{-}2}$ = $J_{3\text{-}4}$ = 8.2 Hz, H-3), 3.16 (dd, $J_{5b\text{-}4}$ = 9.7 Hz $J_{5b\text{-}5a}$ = 11.3 Hz, 1 H, H-5b), 2.90 (dd, $J_{2\text{-}3}$ = 8.2 Hz $J_{1\text{-}2}$ = 9.3 Hz, 1 H, H-2), 2.32 (s, 3 H, CH_3^{STol}); **^{13}C NMR** (CD_3OD, 101 MHz): δ = 138.9, 133.4, 131.3, 130.6 ($C^{Ar, STol}$), 89.2 (C-1), 83.6 (C-2), 79.1 (C-3), 70.9 (C-4), 70.3 (C-3), 61.1

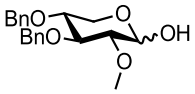
(OCH_3), 21.1 (CH_3^{STol}); **TLC** (tol/EtOAc 50:50): R_f = 0.13 (CH stain, UV); **HRMS**: calcd. for $C_{13}H_{18}O_4S$: 293.0818 [*M*+Na]$^+$, found 293.0827.

p-Tolyl 3,4-di-*O*-benzyl-2-*O*-methyl-1-thio-β-D-xylopyranoside (**82**)



Diol **113** (700 mg, 2.59 mmol, 1.0 eq) was dissolved in anh. DMF (27 mL) under a layer of argon. Then BnBr (0.74 mL, 6.21 mmol, 2.4 eq), freshly filtered over a plug of neutral aluminum oxide, was added followed by a NaH-dispersion in mineral oil (249 mg; 60%, 6.21 mmol, 2.4 eq). The mixture was stirred at rt for 1 h at which point TLC indicated complete turnover. The reaction was quenched with MeOH (2 mL) and as gas evolution faded the mixture was diluted with EtOAc (75 mL). The organic phase was washed with 2 M HCl (3x 20 mL), sat. aq. $NaHCO_3$ (3x 15 mL) and brine (3x 10 mL). The organic phase was dried over $MgSO_4$ filtered and concentrated *in vacuo* to obtain the crude product which was purified by flash chromatography (tol:EtOAc 98:2) yielding thioglycoside **82** (1.13 mg, 97%) as a pale yellow oil which turned into a crystalline solid upon storage. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.40-7.18 (m, 12 H, $H^{Ar, Bn}$ $H^{Ar, Bn'}$ $H^{Ar, STol}$), 7.05 (m, 2 H, $H^{Ar, STol}$), 4.84 (d, J_{CH2Ar} = 11.0 Hz, 1 H, CH_2^{Bn}a), 4.78 (d, J_{CH2Ar} = 11.0 Hz, 1 H, CH_2^{Bn}b), 4.66 (d, J_{CH2Ar} = 11.8 Hz, 1 H, $CH_2^{Bn'}$a), 4.56 (d, J_{CH2Ar} = 11.8 Hz, 1 H, $CH_2^{Bn'}$b), 4.44 (d, $J_{1\text{-}2}$ = 9.4 Hz , 1 H, H-1), 3.98 (dd, $J_{5a\text{-}4}$ = 4.5 Hz $J_{5a\text{-}5b}$ = 11.6 Hz, 1 H, H-5a), 3.57 (s, 3 H, OCH_3), 3.56-3.45 (m, 2 H, H-3 H-4), 3.21-3.02 (m, 2 H, H-5b H-2), 2.28 (s, 3 H, CH_3^{STol}); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ = 138.6, 138.2, 137.9, 132.8, 129.8, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8 ($C^{Ar, STol}$ $C^{Ar, Bn}$ $C^{Ar, Bn'}$), 88.6 (C-1), 85.5 (C-3), 82.4 (C-2), 77.7 (C-4), 75.7 (CH_2^{Bn}), 73.3 ($CH_2^{Bn'}$), 67.6 (C-5), 61.1 (OCH_3), 21.3 (CH_3^{STol}); **TLC** (tol/EtOAc 91:9): R_f = 0.44 (CH stain, UV); **HRMS**: calcd. for $C_{27}H_{30}O_4S$: 473.1757 [*M*+Na]$^+$, found 473.1761.

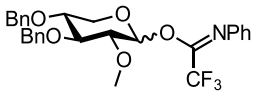
3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranoside (**114**)



Thioglycoside **82** (600 mg, 1.33 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (13 mL) and water (1.3 mL) was added. The emulsion was cooled to 0 °C using an ice bath and NIS (309 mg, 97%, 1.33 mmol, 1.0 eq) and subsequently TFA (102 µL, 1.33 mmol, 1.0 eq) were added. Then, the mixture was stirred for 17 min. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (10 mL) and stirred for 10 min. Then CH_2Cl_2 (20 mL) was added and the phases were separated. The organic phase was washed with

sat. aq. $NaHCO_3$ (3x 10 mL) and it was dried over $MgSO_4$. After filtration and concentration, the crude was purified by flash chromatography (tol/EtOAc 75:25) to yield hemiacetal **114** (382 mg, α/β 1:0.8, 85%) as a crystalline solid. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.40-7.24 (m, 10 H, $H^{Ar,\ Bn}$ $H^{Ar,\ Bn'}$), 5.24 (m, J_{CH2Ar} = 11.0 Hz, 0.57 H, H-1$^{\alpha}$), 4.83 (m, 1 H, $CH_2^{Bn\text{-}3\alpha/\beta}$ab), 4.75-4.67 (m, 1 H, $CH_2^{Bn\text{-}4\alpha/\beta}$a), 4.66-4.54 (m, 1.44 H, $CH_2^{Bn\text{-}4\alpha/\beta}$b, H-1$^{\beta}$), 3.93 (dd, $J_{5a\text{-}4}$ = 4.8 Hz $J_{5a\text{-}5b}$ = 11.4 Hz, 0.43 H, H-5a), 3.85-3.74 (m, 1.26 H, H-5a$^{\alpha}$ H-3$^{\alpha}$), 3.67 (dd, $J_{5b\text{-}4}$ = 5.4 Hz $J_{5a\text{-}5b}$ = 11.3 Hz, 0.68 H, H-5a$^{\beta}$), 3.63-3.47 (m, 4.62 H, $OCH_3^{\alpha/\beta}$ H-4$^{\alpha}$ H-4$^{\beta}$ H-3$^{\beta}$), 3.30-3.20 (m, 1.29 H, H-5b$^{\beta}$ H-2$^{\alpha}$), 3.04 (m, 0.42 H, H-2$^{\beta}$), 1.79-1.59 (m, 1 H, $OH^{\alpha/\beta}$); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ = 138.8, 138.7, 138.4, 138.2, 128.60, 128.56, 128.51, 128.49, 128.1, 128.0, 127.92, 127.89, 127.82, 127.76 ($C^{Ar,\ Bn\text{-}3\alpha/\beta}$ $C^{Ar,\ Bn\text{-}4\alpha/\beta}$), 97.7 (C-1$^{\beta}$), 91.1 (C-1$^{\alpha}$), 84.4 (C-2$^{\beta}$), 83.3 (C-3$^{\beta}$), 82.0 (C-2$^{\alpha}$), 80.5 (C-3$^{\alpha}$), 77.4 (C-4$^{\alpha}$), 75.46, 75.42 (C-4$^{\alpha/\beta}$), 73.4 ($CH_2^{Bn\text{-}4\alpha/\beta}$), 63.8 (C-5$^{\beta}$), 60.7 ($OCH_3^{\beta}$), 60.5 (C-5$^{\alpha}$), 59.3 ($OCH_3^{\alpha}$); **TLC** (tol/EtOAc 71:29): R_f = 0.29 (CH stain, UV); **HRMS**: calcd. for $C_{20}H_{24}O_5$: 367.1516 [*M*+Na]$^+$, found 367.1524.

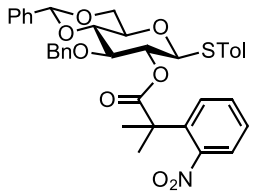
3,4-Di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl *N*-Phenyl-trifluoroacetimidate *(**115**)*



Under a layer of argon hemiacetal **114** (170 mg, 494 µmol, 1.0 eq) was dissolved in acetone (1.5 mL) and Cs_2CO_3 (322 mg, 988 µmol, 2.0 eq) followed by trifluoro-*N*-phenylacetimidoyl chloride (0.16 mL, 0.99 mmol, 2.0 eq) in acetone (1.0 mL) was added. The mixture was stirred for 3 h then the suspension was filtrated over a plug of celite and washed with hex/acetone (50:50). The filtrate was concentrated and the residue purified by flash chromatography (hex/EtOAc 86:14). The two anomers of donor **115** were isolated together as a pale-yellow oil (270 mg, quant.). The compound was found to be sensitive to silica gel during prolonged flash chromatography. Due to instability of the compound in solution further characterization was not performed. **TLC** (hex/EtOAc 83:17): R_f = 0.48, 0.38 (UV, CH stain)

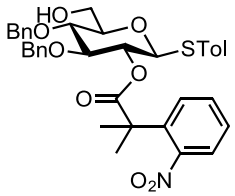
4.3.6 Synthesis of glucose and glucuronic acid building blocks

p-Tolyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-O-(2,2-dimethyl-2-(*o*-nitrophenyl)acetyl)-1-thio-β-D-glucopyranoside (**117**)



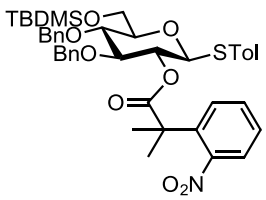
Under argon atmosphere, alcohol **116** (435 mg, 936 µmol, 1.0 eq), DMNPAA (440 mg, 1.12 mmol, 1.17 eq) and freshly activated molecular sieve powder 4Å (250 mg) were suspended in anh. CH_2Cl_2 (7.2 mL). The mixture was stirred for 1.5 h, then cooled to -40 °C and TMSOTf (0.34 mL, 1.87 mmol, 2.0 eq) was added slowly dropwise over the course of 10 min. The mixture was stirred for another 30 min at -40 to -36 °C, and then quenched by the addition of NEt_3 (1.5 mL). It was warmed up to rt, filtered over a plug of celite and washed with EtOAc. The organic phase was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated. The crude was purified by flash chromatography (tol/EtOAc 98:2) to obtain thioglycoside **117** as a glas like colorless compound that turned into a colorless foam upon repeated evaporation with CH_2Cl_2 (599 mg, 98%). The NMR data was measured by Katharina Obleser: **^{1}H NMR** ($CDCl_3$, 600 MHz): δ = 7.83 (m, 1 H, $H^{Ar,\ DMNPA}$), 7.56 (m, 1 H, $H^{Ar,\ DMNPA}$), 7.49 (m, 1 H, $H^{Ar,\ DMNPA}$), 7.42-7.32 (m, 8 H, $H^{Ar,\ DMNPA}$ $H^{Ar,\ BnA}$ $H^{Ar,\ STol}$), 7.30-7.19 (m, 5 H, $H^{Ar,\ Bn}$), 7.11 (m, 2 H, $H^{Ar,\ STol}$), 5.51 (s, 1 H, CH^{BnA}), 5.02 (dd, $J_{2\text{-}1}$ = 9.7 Hz $J_{2\text{-}3}$ = 8.2 Hz, 1 H, H-2), 4.83 (d, J_{CH2Ar} = 11.3 Hz, 1 H, $CH_2{}^{Bn}$a), 4.82 (m, 2 H, H-1 $CH_2{}^{Bn}$b), 4.35 (d, $J_{6a\text{-}5}$ = 5.1 Hz $J_{6a\text{-}6b}$ = 10.5 Hz, 1 H, H-6a), 3.81-3.72 (m, 3 H, H-3 H-6b H-4), 3.46 (ddd, $J_{5\text{-}4}$ = 9.3 Hz $J_{5\text{-}6a}$ = 5.1 Hz $J_{5\text{-}6b}$ = 9.9 Hz, 1 H, H-5), 2.34 (s, 3 H, $CH_3{}^{STol}$), 1.71 (s, 3 H, CH_3a^{DMNPA}), 1.69 (s, 3 H, CH_3b^{DMNPA}); **^{13}C NMR** ($CDCl_3$, 150 MHz): δ = 173.9 (C=O), 149.1, 138.52, 138.45, 138.3, 137.3, 133.4, 132.9, 129.8, 129.14, 129.06, 128.9, 128.4, 128.3, 128.0, 127.7, 127.5, 126.2, 125.6 ($C^{Ar,\ DMNPA}$ $C^{Ar,\ BnA}$ $C^{Ar,\ Bn}$ $C^{Ar,\ STol}$), 101.4 (CH^{BnA}), 86.9 (C-1), 81.5 (C-4), 80.1 (C-3), 73.9 ($CH_2{}^{Bn}$), 47.2 ($\underline{C}(CH_3)_2{}^{DMNPA}$), 27.1, 26.9 ($CH_3ab^{DMNPA}$), 21.3 ($CH_3{}^{STol}$); **TLC** (tol/EtOAc 94:6): R_f = 0.59 (CH stain, UV); **HRMS**: calcd. for $C_{37}H_{37}NO_8S$: 678.2132 [*M*+Na]$^+$, found 678.2138.

p-Tolyl 3,4-di-*O*-benzyl-2-*O*-(2,2-dimethyl-2-(*o*-nitrophenyl)acetyl)-1-thio-β-D-glucopyranoside (**118**)



Under argon-atmosphere, benzylidene acetal **117** (500 mg, 762 µmol, 1.00 eq) was dissolved in 1M BH_3·THF solution (3.8 mL, 3.8 mmol, 5.0 eq) at rt and $Cu(OTf)_2$ (27.6 mg, 7.62 µmol, 0.1 eq) was added. The black suspension was stirred for 3 h, then cooled to 0 °C and quenched by careful and slow addition of MeOH/NEt_3. After evaporation, the crude was purified by flash chromatography (100:1 SiO_2/compound, 91:9 tol/EtOAc) to obtain alcohol **118** as a colorless foam (433 mg, 86%). **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.80-7.72 (m, 2 H, $H^{Ar,\ DMNPA}$), 7.65 (m, 1 H, $H^{Ar,\ DMNPA}$), 7.50 (m, 1 H, $H^{Ar,\ DMNPA}$), 7.42 (m, 2 H, $H^{Ar,\ STol}$), 7.34-7.20 (m, 10 H, $H^{Ar,\ Bn}$ $H^{Ar,\ Bn'}$), 7.14 (m, 2 H, $H^{Ar,\ STol}$), 4.95 (dd, $J_{2\text{-}1}$ = 9.7 Hz, $J_{2\text{-}3}$ = 8.8 Hz, 1 H, H-2), 4.79 (d, $J_{1\text{-}2}$ = 9.8 Hz, 1 H, H-1), 4.73-4.64 (m, 4 H, CH_2^{Bn}ab $CH_2^{Bn'}$ab), 3.91 (dd, $J_{OH\text{-}6a}$ = 5.2 Hz, $J_{OH\text{-}6b}$ = 7.4 Hz, 1 H, OH), 3.86 (ddd, $J_{6a\text{-}5}$ = 2.1 Hz, $J_{6a\text{-}OH}$ = 5.1 Hz, $J_{6a\text{-}6b}$ = 12.0 Hz, 1 H, H-6a), 3.80 (dd, $J_{3\text{-}2} = J_{3\text{-}4}$ = 8.7 Hz, 1 H, H-3), 3.76-3.70 (m, 2 H, H-6b H-4), 3.51 (ddd, $J_{5\text{-}6a}$ = 2.2 Hz, $J_{5\text{-}6b}$ = 4.7 Hz , $J_{5\text{-}4}$ = 9.3 Hz, 1H, H-5), 2.31 (s, 3 H, CH_3^{STol}), 1.75 (s, 3 H, CH_3^{DMNPA}), 1.68 (s, 3 H, $CH_3^{DMNPA'}$); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 174.4 (C=O), 150.2 ($C^{Ar,\ DMNPA}$), 139.7, 139.5, 138.6, 138.2, 133.8, 132.5, 131.8, 130.4, 130.1, 129.0, 128.9, 128.6, 128.3, 128.0 ($C^{Ar,\ STol}$ $C^{Ar,\ Bn}$ $C^{Ar,\ Bn'}$ $C^{Ar,\ DMNPA}$), 126.0 ($C^{Ar,\ DMNPA}$), 87.2 (C-1), 84.2 (C-3), 81.0 (C-5), 78.6 (C-4), 75.1, 74.9 (CH_2^{Bn} $CH_2^{Bn'}$), 73.6 (C-2), 62.0 (C-6), 47.5 (Ar<u>C</u>$(CH_3)_2$), 27.5 (CH_3^{DMNPA}), 27.1 ($CH_3^{DMNPA'}$), 21.1 (CH_3^{STol}); **TLC** (tol/EtOAc 83:17): R_f = 0.47 (CH stain, UV); **HRMS**: calcd. for $C_{37}H_{39}NO_8S$: 675.2735 $[M+NH_4]^+$, found 675.2742.

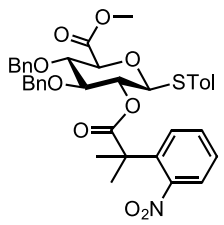
p-Tolyl 3,4-di-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-2-O-(2,2-dimethyl-2-(*o*-nitrophenyl)acetyl)-1-thio-β-D-glucopyranoside (**119**)



Under a layer of argon, alcohol **118** (116 mg, 176 µmol, 1.0 eq) was dissolved in anh. CH_2Cl_2 (1.0 mL) and imidazole (36.0 mg, 529 µmol, 3.0 eq) was added followed by TBDMSCl (39.9 mg, 265 µmol, 1.5 eq). After 10 min the reaction had finished, so the mixture was taken up in EtOAc and water. Phases were separated and the organic layer washed with water and brine. After drying over $MgSO_4$ the

organic phase was filtered and concentrated *in vacuo*. The obtained crude was purified by flash chromatography (2 g SiO_2 cartridge, tol to 98:2 tol/EtOAc) to obtain thioglycoside **119** as a colorless crystalline solid (136 mg, quant.). **^{1}H NMR** (CD_3COCD_3, 300 MHz): δ = 7.77 (m, 2 H, $H^{Ar, DMNPA}$), 7.64 (m, 1 H, $H^{Ar, DMNPA}$), 7.50 (m, 1 H, $H^{Ar, DMNPA}$), 7.44 (m, 2 H, $H^{Ar, STol}$), 7.35-7.19 (m, 10 H, $H^{Ar, Bn}$ $H^{Ar, Bn'}$), 7.14 (m, 2 H, $H^{Ar, STol}$), 4.95 (dd, $J_{2\text{-}1}$ = 9.9 Hz, $J_{2\text{-}3}$ = 8.4 Hz, 1 H, H-2), 4.79 (d, $J_{1\text{-}2}$ = 9.9 Hz, 1 H, H-1), 4.75 (m, 4 H, CH_2^{Bn}ab $CH_2^{Bn'}$ab), 3.92 (dd, $J_{6a\text{-}5}$ = 2.2 Hz, $J_{6a\text{-}6b}$ = 11.5 Hz, 1 H, H-6a), 3.88-3.76 (m, 2 H, H-6b H-3), 3.69 (dd, $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 9.1 Hz, 1H, H-4), 3.50 (ddd, $J_{5\text{-}6a}$ = 2.2 Hz, $J_{5\text{-}6b}$ = 4.3 Hz , $J_{5\text{-}4}$ = 9.2 Hz, 1H, H-5), 2.31 (s, 3 H, CH_3^{STol}), 1.76 (s, 3 H, CH_3^{DMNPA}), 1.69 (s, 3 H, $CH_3^{DMNPA'}$), 0.93 (s, 9 H, CH_3^{tBu}), 0.13 (s, 3 H, $SiCH_3$), 0.13 (s, 3 H, $SiCH_3$'); **^{13}C NMR** (CD_3COCD_3, 75 MHz): δ = 174.4 (C=O), 150.3 ($C^{Ar, DMNPA}$), 139.7, 139.5, 138.7, 138.3, 133.8, 132.7, 131.8, 130.4, 130.2, 129.1, 129.0, 128.9, 128.6, 128.4, 128.02, 127.98 ($C^{Ar, STol}$ $C^{Ar, Bn}$ $C^{Ar, Bn'}$ $C^{Ar, DMNPA}$), 126.0 ($C^{Ar, DMNPA}$), 87.3 (C-1), 84.2 (C-3), 80.8 (C-5), 78.5 (C-4), 75.2, 75.0 (CH_2^{Bn} $CH_2^{Bn'}$), 73.7 (C-2), 63.3 (C-6), 47.5 (Ar<u>C</u>$(CH_3)_2$), 27.5 (CH_3^{DMNPA}), 27.1 ($CH_3^{DMNPA'}$), 26.4 (C(<u>C</u>$H_3)_3$), 21.1 (CH_3^{STol}), 18.9 (Si<u>C</u>Me_3), -4.8 ($SiCH_3$), -5.1 ($SiCH_3$'); **TLC** (tol/EtOAc 83:17): R_f = 0.85 (CH stain, UV); **HRMS**: calcd. for $C_{43}H_{53}NO_8SSi$: 789.3599 $[M+NH_4]^+$, found 789.3608.

Methyl (*p*-Tolyl 3,4-di-*O*-benzyl-2-*O*-(2,2-dimethyl-2-(*o*-nitrophenyl)acetyl)-1-thio-β-D-glucopyranosyl)uronate (**80**)

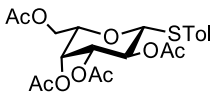


Alcohol **118** (150 mg, 227 µmol, 1.0 eq) and PIDA (184 mg, 568 µmol, 2.5 eq) were dissolved in CH_2Cl_2 (0.76 mL) and water (0.38 mL) was added. To the vigorously stirred emulsion, TEMPO (7.1 mg, 45 µmol, 0.2 eq) was added and stirring was continued for 2 h. Then, sat. aq. $Na_2S_2O_3$ and EtOAc were added, the phases were separated and the aqueous layer washed with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. All volatiles were removed from the pale-yellow crude in fine vacuum. Then it was dissolved in anh. DMF (1.14 mL) and MeI (42.5 µL, 682 µmol, 3.0 eq) and K_2CO_3 (94.2 mg, 682 µmol, 3.0 eq) were added. The mixture was stirred for 35 min and then quenched with MeOH (0.5 mL). It was diluted with EtOAc (20 mL) and washed with brine (4x) until the aqueous layer became pH-neutral. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (100:1 SiO_2/crude, dry loading, tol/EtOAc 97:3), followed by recrystallization from hot ethanol and washing the obtained crystals with MeOH gave the desired compound **80** as needle like crystals (119 mg, 76%). **^{1}H NMR** (CD_3COCD_3, 300 MHz): δ = 7.82

(m, 1 H, $H^{Ar, DMNPA}$), 7.76 (m, 1 H, $H^{Ar, DMNPA}$), 7.67 (m, 1 H, $H^{Ar, DMNPA}$), 7.52 (m, 1 H, $H^{Ar, DMNPA}$), 7.40 (m, 2 H, $H^{Ar, STol}$), 7.34-7.20 (m, 8 H, $H^{Ar, Bn}$ $H^{Ar, Bn'}$), 7.20-7.12 (m, 4 H, $H^{Ar, Bn}$ $H^{Ar, Bn'}$ $H^{Ar, STol}$), 5.05-4.95 (m, 2 H, H-1 H-2), 4.72-4.62 (m, 3 H, CH_2^{Bn}ab $CH_2^{Bn'}$a), 4.55 (d, $J_{CH2-CH2'}$ = 11.1 Hz 1 H, $CH_2^{Bn'}$b), 4.18 (d, J_{5-4} = 8.4 Hz, 1 H, H-5), 3.97-3.84 (m, 2 H, H-4 H-3), 3.71 (s, 3 H, OCH_3), 2.31 (s, 3 H, CH_3^{STol}), 1.75 (s, 3 H, CH_3^{DMNPA}), 1.69 (s, 3 H, $CH_3^{DMNPA'}$); **^{13}C NMR** (CD_3COCD_3, 75 MHz): δ = 174.4 (C=O), 169.4 (C-6), 139.5, 139.1, 138.69, 138.68, 134.0, 133.0, 130.8, 130.5, 130.1, 129.1, 129.0, 128.9, 128.6, 128.4, 128.08, 128.06 ($C^{Ar, STol}$ $C^{Ar, Bn}$ $C^{Ar, Bn'}$ $C^{Ar, DMNPA}$), 126.1 ($C^{Ar, DMNPA}$), 87.1 (C-1), 82.9 (C-3), 80.0 (C-4), 78.2 (C-5), 75.0 (CH_2^{Bn}), 74.7 ($CH_2^{Bn'}$), 73.1 (C-2), 52.7 (OCH_3), 47.5 (Ar<u>C</u>$(CH_3)_2$), 27.5 (CH_3^{DMNPA}), 27.2 ($CH_3^{DMNPA'}$), 21.1 (CH_3^{STol}); **HMBC**: 150.3 ($C^{Ar, DMNPA}$); **TLC** (tol/EtOAc 95:5): R_f = 0.42 (CH stain, UV); **HRMS**: calcd. for $C_{38}H_{39}NO_9S$: 703.2684 $[M+NH_4]^+$, found 703.2695.

4.3.7 Synthesis of L-galactose building blocks

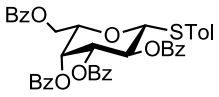
p-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-L-galactopyranoside (**121**)



L-Galactose (**120**) (100 mg, 555 µmol, 1.0 eq) was added to a refluxing mixture of Ac_2O (0.60 mL, 5.8 mmol, 10.4 eq) and NaOAc (50.0 mg, 555 µmol, 1.0 eq). The reaction mixture was refluxed for 30 min, ice (5 g) was added and the mixture was diluted with CH_2Cl_2. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3x 3 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product (0.23 g, α/β 1.66:1, quant.) was dissolved in anh. CH_2Cl_2 (2.5 mL) under a layer of argon and thiocresol (91.3 mg, 6.00 mmol, 1.2 eq) was added. After cooling the mixture to 0 °C, $BF_3{\cdot}Et_2O$ (0.40 mL, 1.5 mmol, 3.0 eq) was added dropwise. The ice bath was removed and the mixture stirred overnight. The reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ (5 mL) and stirring was continued for 30 min. As gas evolution ceased, it was diluted with CH_2Cl_2 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (4x 5 mL), and the combined organic phase dried over $MgSO_4$, filtered and concentrated. The crude was subjected to flash chromatography (tol/EtOAc 86:14 then 83:17) to obtain the desired product **121** as a colorless foam (163 mg, 72%). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ = 7.41 (m, 2 H, $H^{Ar\ STol}$), 7.13 (m, 2 H, $H^{Ar\ STol'}$), 5.40 (dd, J_{4-3} = 3.3 Hz, J_{4-5} = 0.8 Hz, 1 H, H-4), 5.76 (dd, J_{2-1} = J_{2-3} = 10.0 Hz, 1 H, H-2), 5.04 (dd, J_{3-2} = 10.0 Hz, J_{3-4} = 3.4 Hz, 1 H, H-3), 4.65 (d, J_{1-2}= 10.0 Hz, 1 H, H-1), 4.18 (dd, J_{6a-5} = 6.9 Hz, J_{6a-6b} = 11.4 Hz, 1 H, H-6a), 4.11 (dd, J_{6b-5} = 6.4 Hz, J_{6b-6a} = 11.4 Hz, 1 H, H-6b), 3.91 (ddd, J_{5-4} = 1.0 Hz, J_{5-6a} = 7.0 Hz, J_{5-6b} = 6.5 Hz, 1 H, H-5), 2.35 (s, 3 H, CH_3), 2.11 (s, 3H, CH_3^{Ac}), 2.10 (s, 3H, $CH_3^{Ac'}$), 2.04 (s, 3H, $CH_3^{Ac''}$), 1.97 (s, 3H, $CH_3^{Ac'''}$); **^{13}C NMR** ($CDCl_3$, 150 MHz): δ = 170.5, 170.3, 170.2, 169.6 (C=O C=O' C=O''

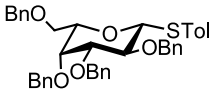
C=O’’’), 138.6, 133.3, 129.8, 128.8 ($C^{Ar, STol}$), 87.1 (C-1), 74.5 (C-5), 72.2 (C-3), 67.5 (C-2), 67.4 (C-4), 61.7 (C-6), 21.3 (CH_3^{STol}) 21.0, 20.80, 20.76, 20.72 (CH_3^{Ac} CH_3^{Ac}’ CH_3^{Ac}’’ CH_3^{Ac}’’’); **HRMS**: calcd. for $C_{21}H_{26}O_9S$: 472.1636 $[M+NH_4]^+$, found 472.1639; **TLC** (tol/EtOAc 83:17): R_f = 0.25 (CH stain, UV).

p-Tolyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-L-galactopyranoside (**122**)



Thioglycoside **121** (125 mg, 274 µmol, 1.0 eq), was dissolved in MeOH (2.2 mL) and a catalytic amount (one drop) of 0.5 M NaOMe was added. After 45 min of stirring, the reaction mixture was quenched by the addition of Amberlite IR-120, stirred until the pH was found neutral, filtered and concentrated. Under a layer of argon, the crude tetraol was dissolved in a premixed solution of BzCl (0.32 mL, 2.7 mmol, 10 eq) in anh. pyridine (2.21 mL). DMAP (1.7 mg, 14 µmol, 0.05 eq) was added and the mixture was stirred for 3 h. The reaction was quenched by the addition of MeOH, concentrated *in vacuo* and dried in fine vacuum. The obtained crude was purified by flash chromatography (98:2 tol/EtOAc) to yield the product **122** as a colorless foam (156 mg, 81%). **^{1}H NMR** (CD_3COCD_3, 300 MHz): δ = 8.01 (m, 4 H, H^{Ph} H^{Ph}’ H^{Ph}’’ H^{Ph}’’’), 7.93 (m, 2 H, H^{Ph} H^{Ph}’),7.76-7.43 (m, 14 H, H^{Ph} H^{Ph}’ H^{Ph}’’ H^{Ph}’’’ $H^{Ar, STol}$), 7.31 (m, 2 H, H^{Ph}’’ H^{Ph}’’’), 7.17 (m, 2 H, $H^{Ar, STol}$), 6.08 (dd, $J_{4\text{-}3}$ = 3.3 Hz, $J_{4\text{-}5}$ = 0.9 Hz, 1 H, H-4), 5.85 (dd, $J_{3\text{-}2}$ = 9.8 Hz, $J_{3\text{-}4}$ = 3.2 Hz, 1 H, H-3), 5.76 (dd, $J_{2\text{-}1}$ = $J_{2\text{-}3}$ = 9.7 Hz, 1 H, H-2), 5.43 (d, $J_{1\text{-}2}$= 9.6 Hz, 1 H, H-1), 4.79 (ddd, $J_{5\text{-}4}$ = 0.9 Hz, $J_{5\text{-}6a}$ = 6.9 Hz, $J_{5\text{-}6b}$ = 5.4 Hz, 1 H, H-5), 4.67 (dd, $J_{6a\text{-}5}$ = 6.9 Hz, $J_{6a\text{-}6b}$ = 11.3 Hz, 1 H, H-6a), 4.53 (dd, $J_{6b\text{-}5}$ = 5.4 Hz, $J_{6b\text{-}6a}$ = 11.3 Hz, 1 H, H-6b), 2.38 (s, 3 H, CH_3); **^{13}C NMR** (CD_3COCD_3, 75 MHz): δ = 166.3, 166.1, 165.73, 165.79 (C=O C=O’ C=O’’ C=O’’’), 139.3, 134.9, 134.6, 134.33, 134.25, 134.1, 130.7, 130.53, 130.46, 130.4, 130.2, 130.1, 129.6, 129.49, 129.43, 129.3, 128.4 (C^{Ph} C^{Ph}’ C^{Ph}’’ C^{Ph}’’’ $C^{Ar, STol}$), 85.6 (C-1), 75.6 (C-5), 74.0 (C-3), 69.9 (C-4), 69.0 (C-2), 63.5 (C-6), 21.3 (CH_3); **HRMS**: calcd. for $C_{41}H_{34}O_9S$: 720.2262 $[M+NH_4]^+$, found 720.2271; **HPTLC** (hex/EtOAc 91:9): R_f = 0.64 (CH stain, UV).

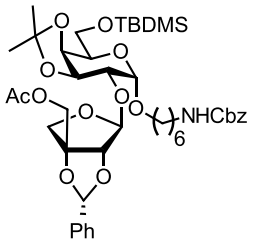
p-Tolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-L-galactopyranoside (**78**)



Thioglycoside **122** (60.0 mg, 85.4 µmol, 1.0 eq), was dissolved in CH_2Cl_2/MeOH (1:5, 0.60 mL) and a catalytic amount of 0.5 M NaOMe in MeOH (0.06 mL) was added. The mixture was stirred for 2.5 h until full conversion of the starting material was observed. The reaction was quenched by the addition of Amberlite IR-120, stirred until the pH was found neutral, filtered and concentrated *in vacuo*. The crude product was taken up in MeOH/MeCN (50:50) and the polar layer was washed with hexanes (3x) to remove methyl benzoate. After concentration of the polar lower layer *in vacuo* and removal of volatiles in fine vaccum crude tetraol was obtained. Under a layer of argon, the tetraol was taken up in anh. DMF (0.30 mL) and BnBr (51 µL, 0.43 mmol, 5.0 eq), freshly filtered over a plug of neutral aluminum oxide, was added followed by a NaH-dispersion in mineral oil (20.5 mg, 60%, 51.2 µmol, 6.0 eq). After 90 min, the reaction was quenched by the addition of MeOH (0.15 mL) and taken up in EtOAc. The organic phase was washed with sat. aq. $NaHCO_3$, water and brine. It was dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (prepacked 2g SiO_2 column, tol to tol/EtOAc 99:1 to 98:2) gave pure product **78** (46.0 mg, 83%) as colorless crystals. **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.49 (m, 2 H, $H^{Ar,\,STol}$), 7.41 (m, 4 H, H^{Ph} $H^{Ph\,\prime}$ $H^{Ph\,\prime\prime}$ $H^{Ph\,\prime\prime\prime}$),7.38-7.25 (m, 16 H, H^{Ph} $H^{Ph\,\prime}$ $H^{Ph\,\prime\prime}$ $H^{Ph\,\prime\prime\prime}$), 7.03 (m, 2 H, $H^{Ar,\,STol}$), 4.98 (m, 1 H, $PhCH_2a^{-4}$), 4.85 (m, 1 H, $PhCH_2a^{-3}$), 4.79-4.73 (m, 3 H, $PhCH_2ab^{-2}$ $PhCH_2b^{-3}$), 4.71 (m, 1 H, H-1), 4.64 (m, 1 H, $PhCH_2b^{-4}$), 4.55 (d, J_{CH2Ar} = 11.9 Hz, 1 H, $PhCH_2a^{-6}$), 4.50 (d, J_{CH2Ar} = 11.9 Hz, 1 H, $PhCH_2b^{-6}$), 4.15 (m, 1 H, H-4), 3.88-3.77 (m, 3 H, H-2 H-5 H-3), 3.72 (m, 1 H, H-6a), 3.68 (m, 1 H, H-6b) 2.27 (s, 3 H, CH_3); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 140.2, 139.9, 139.8, 139.6, 137.6, 132.4, 131.8, 130.4, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 128.31, 128.29, 128.2, 128.1 (C^{Ph} $C^{Ph\,\prime}$ $C^{Ph\,\prime\prime}$ $C^{Ph\,\prime\prime\prime}$), 88.2 (C-1), 85.0 (C-3), 78.3 (C-2), 77.9 (C-5), 75.8 ($PhCH_2^{-2}$), 75.3 ($PhCH_2^{-4}$), 75.2 (C-4), 73.8 ($PhCH_2^{-6}$), 73.0 ($PhCH_2^{-3}$), 70.0 (C-6), 21.1 (CH_3); **HRMS**: calcd. for $C_{41}H_{42}O_5S$: 664.3091 $[M+NH_4]^+$, found 664.3100; **TLC** (hex/EtOAc 96:4): R_f = 0.41 (CH stain, UV).

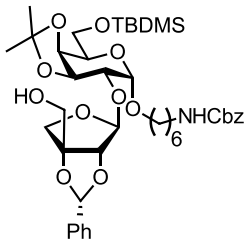
4.3.8 Synthesis of disaccharide fragments

(6-*N*-Benzyloxycarbonylamino)-1-hexyl 3'-O-acetyl-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**123**)



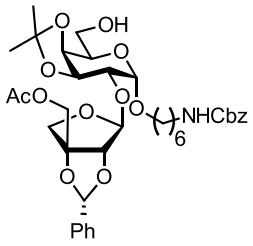
Donor thioglycoside **72** (114 mg, 294 µmol, 1.0 eq), acceptor alcohol **71** (167 mg, 294 mmol, 1.0 eq) and TTBP (110 mg, 441 µmol, 1.5 eq) were coevaporated with toluene and all volatile compounds removed in fine vacuum. Then, under a layer of argon, freshly activated powdered MS 4 Å (140 mg) was added and all compounds were suspended in anhydrous CH_2Cl_2 (5.7 mL). After stirring for 15 min, AgOTf (227 mg, 882 µmol, 3.0 eq) was added to the mixture and it was stirred for another 15 min before it was cooled down to 0 °C using an ice bath. Then, TolSCl (70 µL, 67%, 0.29 mmol, 1.0 eq) was added with a Hamilton syringe and the reaction mixture was stirred for 75 min at 0 °C. The reaction mixture was quenched by the addition of pyridine (0.5 mL), and it was filtered over a plug of celite and washed with EtOAc. The filtrate was washed with water, sat. aq. $Na_2S_2O_3$ solution and brine, then dried over $MgSO_4$ and the $MgSO_4$ was filtered off. The solution was concentrated *in vacuo* and the residue was purified by repeated flash chromatography (hex/EtOAc 78:22 then 71:29) to obtain the desired β-disaccharide **123** (126 mg, 52%) and the α-Isomer (43.3 mg, 18%) as pale-yellow oils. For **123-β**: **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 7.53 (m, 2 H, H^{Ph}), 7.44-7.25 (m, 8 H, H^{Ph} H^{Ph}'), 6.30 (bt, 1H, NH), 5.99 (s, 1H, PhCH), 5.43 (s, 1 H, H-1^{Api}), 5.05 (s, 2 H, OCH_2Ph), 4.89 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1 H, H-1^{Gal}), 4.56 (s, 1 H, H-2^{Api}), 4.42 (s, 2 H, H-3'^{Api}), 4.30 (dd, $J_{4\text{-}5}$ = 2.4 Hz $J_{4\text{-}3}$ = 5.5 Hz, 1 H, H-4), 4.22 (dd, $J_{4\text{-}3}$ = 5.4 Hz $J_{3\text{-}2}$ = 8.0 Hz, 1 H, H-3), 4.10-3.98 (m, 3 H, H-5^{Gal} H-4a^{Api} H-4b^{Api}), 3.88 (dd, $J_{5\text{-}6a}$ = 6.2 Hz $J_{6a\text{-}6b}$ = 10.1 Hz, 1 H, H-6a), 3.78 (dd, $J_{6b\text{-}5}$ = 6.7 Hz $J_{6a\text{-}6b}$ = 10.1 Hz, 1 H, H-6b), 3.75-3.66 (m, 2 H, OCH_2 H-2^{Gal}), 3.40 (dt, $J_{OCH2\text{-}OCH2'}$ = 9.5 Hz $J_{OCH2\text{-}CH2}$ = 6.6 Hz, 1 H, OCH_2'), 3.15 (dt, $J_{NCH2\text{-}CH2}$ = 6.7 Hz $J_{NCH2\text{-}NH}$ = 6.3 Hz, 2 H, CH_2N), 2.10 (s, 3 H, CH_3^{Ac}), 1.70-1.45 (m, 7 H, -CH_2- -CH_2- CH_3^{iPrA}), 1.45-1.25 (m, 7 H, -CH_2-CH_2- CH_3^{iPrA}'), 0.90 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 170.9 (O-C=O), 156.5 (N(C=O)O), 138.6, 137.7, 130.5, 129.2, 129.0, 128.6, 128.5, 128.1 (C^{Ph} C^{Ph}'), 109.5 ($O\underline{C}Me_2O$), 108.3 (C-1^{Api}), 106.7 (Ph$\underline{C}$H), 98.9 (C-1^{Gal}), 90.9 (C-3^{Api}), 87.7 (C-2^{Api}), 77.5 (C-2^{Gal}), 76.2 (C-3^{Gal}), 74.2 (C-4^{Gal}), 73.7 (C-4^{Api}), 68.8 (C-5^{Gal}), 68.6 (OCH_2-), 66.3 (OCH_2Ph), 64.9 (C-3'^{Api}), 63.3 (C-6^{Gal}), 41.5 (-CH_2N), 30.7, 30.2 (-CH_2-), 28.6 (CH_3^{iPrA}), 27.3 (-CH_2-), 26.72 (-CH_2-), 26.69 (CH_3^{iPrA}'), 26.2 ($C(\underline{C}H_3)_3$), 20.7 (CH_3^{Ac}), 18.8 ($Si\underline{C}Me_3$), -5.1 ($SiCH_3$), -5.3 ($SiCH_3$'); **HRMS**: calcd. for $C_{43}H_{63}NO_{13}Si$: 847.4407 [M+NH_4]$^+$, found 847.4407; **TLC** (hex/EtOAc 67:33): R_f = 0.48 (CH stain, UV).

(6-*N*-Benzyloxycarbonylamino)-1-hexyl 2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**69**)



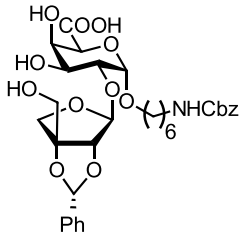
β-Disaccharide **123** (170 mg, 205 µmol, 1.0 eq) was dissolved in 12.3 mL of a stock solution containing guanidinium nitrate (937 mg) and NaOMe (3.0 mL, 0.5 M) in anh. MeOH (54 mL) and anh. CH_2Cl_2 (7.5 mL). The mixture was stirred for 40 min. At this point TLC indicated full conversion of the starting material, so the reaction was quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (4x). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (hex/EtOAc = 67:33) to yield alcohol **69** as a colorless oil (150 mg, 93%). **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 7.52 (m, 2 H, H^{Ph}), 7.43-7.24 (m, 8 H, H^{Ph} H^{Ph}'), 6.36 (bt, 1H, NH), 5.98 (s, 1H, PhCH), 5.40 (s, 1 H, H-1^{Api}), 5.05 (s, 2 H, OCH_2Ph), 4.86 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1 H, H-1^{Gal}), 4.53 (s, 1 H, H-2^{Api}), 4.39 (t, $J_{OH\text{-}3'}$ = 5.7 Hz, 1 H, OH), 4.30 (dd, $J_{4\text{-}5}$ = 2.6 Hz $J_{4\text{-}3}$ = 5.6 Hz, 1 H, H-4), 4.22 (dd, $J_{4\text{-}3}$ = 5.5 Hz $J_{3\text{-}2}$ = 8.1 Hz, 1 H, H-3), 4.04-3.92 (m, 3 H, H-5^{Gal} H-$4a^{Api}$ H-$4b^{Api}$), 3.92-3.83 (m, 3 H, H-$6a^{Gal}$ H-3'a^{Api} H-3'b^{Api}), 3.78 (dd, $J_{6b\text{-}5}$ = 6.8 Hz $J_{6a\text{-}6b}$ = 10.1 Hz, 1 H, H-6b), 3.75-3.68 (m, 2 H, OCH_2 H-2^{Gal}), 3.40 (dt, $J_{OCH2\text{-}OCH2'}$ = 9.6 Hz $J_{OCH2\text{-}CH2}$ = 6.7 Hz, 1 H, OCH_2'), 3.15 (dt, $J_{NCH2\text{-}CH2}$ = 6.9 Hz $J_{NCH2\text{-}NH}$ = 5.9 Hz, 2 H, CH_2N), 1.68-1.46 (m, 7 H, -CH_2- -CH_2- $CH_3{}^{iPrA}$), 1.46-1.25 (m, 7 H, -CH_2- -CH_2- $CH_3{}^{iPrA}$'), 0.90 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 157.2 (N(C=O)O), 138.5, 138.2, 130.3, 129.2, 129.0, 128.65, 128.56, 128.0 (C^{Ph} C^{Ph} '), 109.5 (O<u>C</u>Me_2O), 108.5 (C-1^{Api}), 106.8 (Ph<u>C</u>H), 99.0 (C-1^{Gal}), 93.7 (C-3^{Api}), 87.2 (C-2^{Api}), 77.3 (C-2^{Gal}), 76.2 (C-3^{Gal}), 74.2 (C-4^{Gal}), 73.8 (C-4^{Api}), 68.8 (C-5^{Gal}), 68.5 (OCH_2-), 66.3 (OCH_2Ph), 64.0 63.9 (C-3'$^{Api\ OH}$ C-3'$^{Api\ OD}$), 63.2 (C-6^{Gal}), 41.5 (-CH_2N), 30.7 30.2 (-CH_2-), 28.7 ($CH_3{}^{iPrA}$), 27.3 (-CH_2-), 26.72 (-CH_2-), 26.70 ($CH_3{}^{iPrA}$'), 26.2 ($C(\underline{C}H_3)_3$), 18.8 ($Si\underline{C}Me_3$), -5.1 ($SiCH_3$), -5.3 ($SiCH_3$'); **HRMS**: calcd. for $C_{41}H_{61}NO_{12}Si$: 810.3855 [*M*+Na]$^+$, found 810.3875; **TLC** (hex/EtOAc 60:40): R_f = 0.31 (CH stain, UV).

(6-*N*-Benzyloxycarbonylamino)-1-hexyl 3'-*O*-acetyl-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)- 3,4-*O*-isopropylidene-α-D-galactopyranoside (**124**)



Disaccharide **123** (83.0 mg, 100 µmol, 1.0 eq) was dissolved in THF (0.60 mL) and AcOH (57 µL, 1.00 mmol, 10 eq) followed by 1 M TBAF in THF (0.50 mL, 0.50 mmol, 5.0 eq) were added and it was stirred for 5 h. The solvent was removed *in vacuo* and the crystalline crude purified by flash chromatography (hex/EtOAc 50:50) to yield alcohol **124** (63.0 mg, 88%) as a colorless syrup. **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 7.53 (m, 2 H, H^{Ph}), 7.45-7.22 (m, 8 H, H^{Ph} H^{Ph}'), 6.33 (bt, 1H, NH), 5.98 (s, 1H, PhCH), 5.43 (s, 1 H, H-1^{Api}), 5.05 (s, 2 H, OCH_2Ph), 4.88 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1 H, H-1^{Gal}), 4.55 (s, 1 H, H-2^{Api}), 4.42 (s, 2 H, H-3'^{Api}), 4.31 (dd, $J_{4\text{-}5}$ = 2.5 Hz $J_{4\text{-}3}$ = 5.5 Hz, 1 H, H-4^{Gal}), 4.22 (dd, $J_{4\text{-}3}$ = 5.4 Hz $J_{3\text{-}2}$ = 8.1 Hz, 1 H, H-3), 4.10-3.98 (m, 3 H, H-5^{Gal} H-$4a^{Api}$ H-$4b^{Api}$), 3.81 (dd, $J_{5\text{-}6a}$ = 5.8 Hz $J_{6a\text{-}6b}$ = 11.8 Hz, 1 H, H-6a), 3.77-3.64 (m, 4 H, H-6b OCH_2 H-2^{Gal} OH), 3.39 (dt, $J_{OCH2\text{-}OCH2'}$ = 9.5 Hz $J_{OCH2\text{-}CH2}$ = 6.4 Hz, 1H, OCH_2'), 3.15 (dt, $J_{NCH2\text{-}CH2}$ = 7.0 Hz, $J_{NCH2\text{-}NH}$ = 6.3 Hz, 2 H, CH_2N), 2.10 (s, 3 H, CH_3^{Ac}), 1.68-1.45 (m, 7 H, $-CH_2-$ $-CH_2-$ CH_3^{iPrA}), 1.45-1.30 (m, 4 H, $-CH_2-$ $-CH_2-$), 1.28 (s, 3 H, CH_3^{iPrA}'); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 170.9 (O-C=O), 157.3 (N(C=O)O), 138.6, 137.6, 130.5, 129.2, 129.0, 128.64, 128.55, 128.1 (C^{Ph} C^{Ph}'), 109.5 ($O\underline{C}Me_2O$), 108.3 (C-1^{Api}), 106.7 (Ph$\underline{C}$H), 98.8 (C-1^{Gal}), 90.9 (C-3^{Api}), 87.7 (C-2^{Api}), 77.5 (C-2^{Gal}), 76.2 (C-3^{Gal}), 74.6 (C-4^{Gal}), 73.7 (C-4^{Api}), 69.1 (C-5^{Gal}), 68.5 (OCH_2-), 66.3 (OCH_2Ph), 64.9 (C-3'^{Api}), 62.3 (C-6^{Gal}), 41.5 ($-CH_2N$), 30.6, 30.3 ($-CH_2-$), 28.6 (CH_3^{iPrA}), 27.2 ($-CH_2-$), 26.66 (CH_2), 26.64 (CH_3^{iPrA}'), 20.7 (CH_3^{Ac}); **HRMS**: calcd. for $C_{37}H_{49}NO_{13}$: 738.3096 [*M*+Na]$^+$, found 738.3112; **TLC** (hex/EtOAc 50:50): R_f = 0.25 (CH stain, UV).

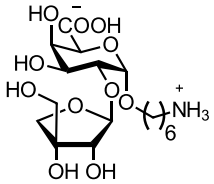
(6-*N*-Benzyloxycarbonylamino)-1-hexyl 2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-α-D-galactopyranosyluronic acid (**125**)



Under a layer of argon alcohol **124** (6.0 mg, 8.4 µmol, 1.0 eq) was dissolved in anh. CH_2Cl_2 (60 µL) and water (30 µL), then PIDA (6.0 mg, 18 µmol, 2.20 eq) and finally TEMPO (0.27 mg, 1.68 µmol, 0.2 eq) were added. After the mixture was stirred for 70 min, the starting material was fully consumed according to TLC (tol/acetone 2:1), so the reaction was quenched with sat. aq. $Na_2S_2O_3$ and diluted with sat. aq. NaH_2PO_4 solution and EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic phase was dried over $MgSO_4$ and concentrated to give the crude carboxylic acid (7.5 mg) which was directly used in the next step. **HPTLC** (CH_2Cl_2/MeOH 90:10 0.1% 2 M HCl): R_f = 0.27 (CH stain, UV). The crude carboxylic acid was dissolved in MeOH (120 µL) and 0.5 M NaOMe solution in MeOH (18.5 µL, 9.22 µmol, 1.1 eq) was added. The mixture was stirred for 5 h then MeOH washed Amberlite IR-120 ion exchange resin (H^+-form) was added and stirring was continued for 15 min. Filtration, thorough washing with MeOH and concentration *in vacuo* gave the crude disaccharide alcohol (6.4 mg) which was directly employed in the next step. **HPTLC** (CH_2Cl_2/MeOH 90:10 0.1% 2M HCl): R_f = 0.17 (CH stain, UV). The crude disaccharide alcohol was dissolved in 80% AcOH (300 µL) and heated to 65°C using a rotary evaporator. After 40 min of rotating, the reaction was finished, as confirmed by LCMS, so toluene was added and all volatiles coevaporated by repeated toluene addition. The crude was purified by RP-chromatography (Waters C18 Seppack 500 mg, MeCN/H_2O 25:75 to 45:55 + 0.1% AcOH) and the fractions were subsequently lyophilized to obtain partially protected disaccharide **125** (4.27 mg, 79% o. 3 s.) as a colorless powder. **HPTLC** (CH_2Cl_2/MeOH 90:10 + 0.1% 2M HCl): R_f = 0.06 (CH stain, UV), **^{1}H NMR** (CD_3CN + D_2O, 600 MHz): δ = 7.49 (m, 2 H, H^{Ph}), 7.43-7.27 (m, 8 H, H^{Ph} $H^{Ph'}$), 5.92 (s, 1 H, PhCH), 5.30 (s, 1 H, H-1^{Api}), 5.03 (s, 2 H, $PhCH_2$), 4.99 (d, $J_{1\text{-}2}$ = 3.5 Hz, 1 H, H-1^{GalA}), 4.50 (s, 1 H, H-2^{Api}), 4.29 (s, 1 H, H-5^{GalA}), 4.16 (d, $J_{4\text{-}3}$ = 3.0 Hz, 1 H, H-4^{GalA}), 3.98 (d, $J_{CH2a\text{-}CH2b}$ = 10.1 Hz, 1 H, H-$4a^{Api}$), 3.88 (d, $J_{CH2a\text{-}CH2b}$ = 10.2 Hz, 1 H, H-$4b^{Api}$), 3.85-3.72 (m, 4 H, H-3^{GalA} H-3'ab^{Api} H-2^{GalA}), 3.64 (dt, $J_{OCH2\text{-}CH2}$ = 6.4 Hz $J_{OCH2\text{-}OCH2'}$ = 9.6 Hz, 1 H, OCH_2a), 3.38 (dt, $J_{OCH2\text{-}CH2}$ = 6.4 Hz $J_{OCH2\text{-}OCH2'}$ = 9.6 Hz, 1 H, OCH_2b), 3.06 (t, $J_{NCH2\text{-}CH2}$ = 7.0 Hz, 2 H, CH_2N), 1.55 (p, J = 7.0 Hz 2 H, CH_2), 1.45 (p, J = 7.2 Hz 2 H, CH_2), 1.38-1.24 (m, 4 H, CH_2 CH_2); **^{13}C NMR** (CD_3CN + D_2O, 150 MHz): δ = 171.7* (C-6^{GalA}), 157.7* (N(C=O)O), 138.0, 130.7, 129.5, 129.4, 128.9, 128.7, 128.0 (C^{Ph} $C^{Ph'}$), 109.4 (C-1^{Api}), 106.7 (PhCH), 99.4 (C-1^{GalA}), 93.6 (C-3^{Api}), 87.4 (C-2^{Api}), 76.5 (C-2^{GalA}), 74.0 (C-4^{Api}), 71.3 (C-4^{GalA}), 71.1 (C-5^{GalA}), 69.19 (C-3^{GalA}), 69.17 (OCH_2), 66.8 ($PhCH_2$), 63.6 (C-3'^{Api}), 41.5 (NCH_2), 30.5 (CH_2), 30.2

(CH_2), 27.2 (CH_2), 26.6 (CH_2), *identified by ^{1}H-^{13}C HMBC; **^{1}H-^{13}C coupled HSQC:** 109.4 ($J_{C1\text{-}H1}$ = 175 Hz, C-1^{Api}), 99.4 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{GalA}); **HRMS**: calcd. for $C_{32}H_{41}NO_{13}$: 646.2505 [*M*-H]$^-$, found 646.2507; **HPLC** (5-100% MeCN + 0.1% AcOH in 15 min, column 1): R_t = 10.061 min.

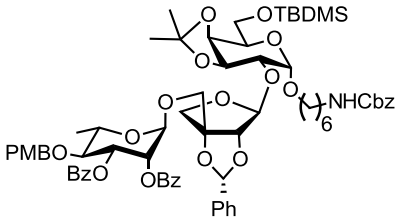
6-Amino-1-hexyl β-D-apiofuranosyl-(1→2)-α-D-galactopyranosyluronic acid (**88**)



Partially protected disaccharide **125** (3.40 mg, 5.25 µmol, 1.0 eq) was dissolved in *t*BuOH/H_2O (0.34 mL, 50:50). The stirred mixture was degassed in a pressure reactor and set under argon (6 cycles). Pd/C (3.4 mg, 10% wt. unreduced) was added and the stirred suspension degassed and set under hydrogen (6 cycles). The pressure was adjusted to 8 bar and stirring was continued for 72 h at rt. The reaction was found to be complete by LCMS and the crude mix was degassed and set under argon atmosphere and then filtered over a syringe filter (0.45 µm, PTFE). The filter was washed thoroughly with *t*BuOH/H_2O, H_2O, MeCN/H_2O, MeCN and then H_2O. The filtrate was concentrated *in vacuo*. The crude was purified by RP-chromatography (Waters C18 Seppack 500 mg, MeCN/H_2O 0:100 to 5:95 +0.1 % AcOH) and the fractions were subsequently lyophilized to obtain of disaccharide **88** (2.21 mg) partially as the AcO^- salt as colorless powder. Repeated RP-chromatography (Waters C18 Seppack 500 mg, MeCN/H_2O 0:100 to 5:95) and subsequent lyophilization gave disaccharide **88** (2.13 mg, 96%) as a colorless powder. **^{1}H NMR** (D_2O, 600 MHz): δ = 5.18 (d, $J_{1\text{-}2}$ = 2.8 Hz, 1 H, H-1^{Api}), 5.06 (d, $J_{1\text{-}2}$ = 4.0 Hz, 1 H, H-1^{GalA}), 4.28 (dd, $J_{4\text{-}3}$ = 3.6 Hz $J_{4\text{-}5}$ = 1.3 Hz, 1H, H-4^{GalA}), 4.20 (d, $J_{1\text{-}2}$ = 1.3 Hz, 1H, H-5^{GalA}), 4.04 (d, $J_{2\text{-}1}$ = 2.8 Hz, 1 H, H-2^{Api}), 4.01 (d, $J_{4a\text{-}4b}$ = 10.2 Hz, 1 H, H-4a^{Api}), 3.93 (dd, $J_{3\text{-}4}$ = 3.5 Hz $J_{3\text{-}2}$ = 10.3 Hz, 1 H, H-3^{GalA}), 3.89 (d, $J_{4a\text{-}4b}$ = 10.2 Hz, 1 H, H-4b^{Api}), 3.79 (dd, $J_{2\text{-}1}$ = 4.0 Hz $J_{2\text{-}3}$ = 10.3 Hz, 1 H, H-2^{GalA}), 3.72-3.67 (m, 2 H, OCH_2a H-3'a^{Api}), 3.66 (d, $J_{3a\text{-}3b}$ = 12.0 Hz, 1 H, H-3'b^{Api}), 3.58 (dt, $J_{OCH2\text{-}CH2}$ = 6.0 Hz $J_{OCH2\text{-}OCH2'}$ = 10.2 Hz, 1 H, OCH_2b), 2.96 (t, $J_{NCH2\text{-}CH2}$ = 7.6 Hz, 2 H, CH_2N), 1.70-1.55 (m, 4 H, CH_2 CH_2), 1.44-1.32 (m, 4 H, CH_2 CH_2); **^{13}C NMR** (D_2O, 150 MHz): δ = 176.1 (C-6^{GalA}), 111.0 (C-1^{Api}), 98.7 (C-1^{GalA}), 80.2 (C-3^{Api}), 77.8 (C-2^{Api}), 77.0 (C-2^{GalA}), 74.3 (C-4^{Api}), 71.9 (C-5^{GalA}), 71.3 (C-4^{GalA}), 69.4 (C-3^{GalA}), 69.0 (OCH_2), 64.3 (C-3'^{Api}), 40.1 (NCH_2), 28.9 (CH_2), 27.3 (CH_2), 25.7 (CH_2), 25.5 (CH_2); **^{1}H-^{13}C coupled HMBC:** 111.0 ($J_{C1\text{-}H1}$ = 173 Hz, C-1^{Api}), 98.7 ($J_{C1\text{-}H1}$ = 173 Hz, C-1^{Gal}); **HRMS**: calcd. for $C_{17}H_{31}NO_{11}$: 426.1970 [*M*+H]$^+$, found 426.1971; **HPLC** (0-10% MeCN + 0.1% AcOH in 15 min, column 1): R_t = 7.874 min.

4.3.9 Synthesis of trisaccharide fragments

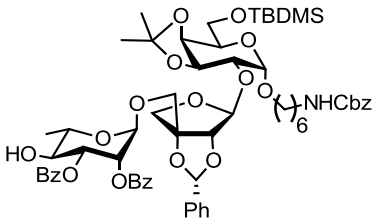
(6-*N*-Benzyloxycarbonylamino)-1-hexyl 2,3-di-*O*-benzoyl-4-*O*-*p*-methoxybenzyl-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**86**)



Acceptor alcohol **69** (102 mg, 129 µmol, 1.0 eq) and thioglycoside **89** (85.0 mg, 142 µmol, 1.1 eq) were coevaporated with toluene and all volatiles were removed in fine vacuum. Under a layer of argon atmosphere, freshly activated molecular sieve powder 4 Å (90 mg) was added and the mixture suspended in anhydrous CH_2Cl_2 (1.9 mL). After stirring for 15 min, NIS (43.5 mg, 194 µmol, 1.5 eq) was added and the mixture was cooled down to -40 °C. TfOH (1.7 µL, 19 µmol, 0.15 eq) was added and the mixture was allowed to warm up slowly to -20 °C over the course of 1 h at which point it was quenched by the addition of NEt_3 (0.05 mL) and filtrated over a plug of celite. After washing the celite with CH_2Cl_2, the filtrate was treated with sat. aq. $Na_2S_2O_3$ solution for 1 h until the organic phase remained colorless. The phases were separated and the organic phase was washed with sat. aq. $NaHCO_3$-solution. After drying over $MgSO_4$ the solution was concentrated and the residue purified by flash chromatography (hex/EtOAc 75:25) to yield trisaccharide **86** (132 mg, 81%) as a colorless foam. **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 8.07 (m, 2 H, $H^{Ar\ Bz}$), 7.94 (m, 2 H, $H^{Ar\ Bz}$), 7.70 (m, 1 H, $H^{Ar\ Bz}$), 7.64-7.52 (m, 5 H, $H^{Ar\ Bz}$), 7.47-7.24 (m, 10 H, $H^{Ar\ Ph}$ $H^{Ar\ Ph'}$), 7.14 (m, 2 H, $H^{Ar\ PMB}$), 6.74 (m, 2 H, $H^{Ar\ PMB}$), 6.25 (bt, 1H, NH), 6.12 (s, 1H, PhCH), 5.68 (m, 2 H, H-2^{Rha} H-3^{Rha}), 5.48 (s, 1 H, H-1^{Api}), 5.14 (s, 1 H, H-1^{Rha}), 5.01 (s, 2 H, OCH_2Ph), 4.92 (d, $J_{1\text{-}2}$ = 3.5 Hz, 1 H, H-1^{Gal}), 4.70, 4.67 (d, $J_{1\text{-}2}$ = 11.0 Hz, 1 H, CH_2^{PMB} $CH_2^{PMB'}$), 4.65 (s, 1 H, H-2^{Api}), 4.32-4.21 (m, 2 H, H-4^{Gal} H-3^{Gal}), 4.17 (d, $J_{4a\text{-}4b}$ = 10.9 Hz, 1 H, H-$4a^{Api}$), 4.14-3.94 (m, 6 H, H-$4b^{Api}$ H-3'a^{Api} H-3'b^{Api} H-5^{Gal} H-5^{Rha} H-4^{Rha}), 3.88 (dd, $J_{5\text{-}6a}$ = 6.2 Hz $J_{6a\text{-}6b}$ = 10.3 Hz, 1 H, H-6a), 3.81-3.68 (m, 6 H, H-$6b^{Gal}$ H-2^{Gal} OCH_2a OCH_3), 3.43 (dt, $J_{OCH2\text{-}OCH2'}$ = 9.5 Hz $J_{OCH2\text{-}CH2}$ = 6.6 Hz, 1 H, OCH_2b), 3.12 (dt, $J_{NCH2\text{-}CH2}$ = 7.1 Hz $J_{NCH2\text{-}NH}$ = 6.0 Hz, 2 H, CH_2N), 1.62 (m, 2 H, -CH_2-), 1.56-1.45 (m, 5 H, -CH_2- CH_3^{iPrA}), 1.45-1.31 (m, 7 H, -CH_2-CH_2- H-6^{Rha}), 1.28 (s, 3 H, $CH_3^{iPrA'}$), 0.91 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 166.04, 166.0 (C=O C=O'), 160.2 ($C^{Ar\ PMB}$), 157.1 (N(C=O)O), 138.5, 137.9 ($C^{Ar\ Ph}$ $C^{Ar\ Ph'}$), 134.5, 134.1 ($C^{Ar\ Bz}$ $C^{Ar\ Bz'}$), 131.3, 131.1, 130.73, 130.65, 130.51, 130.50, 130.47, 130.28, 129.6, 129.4, 129.1, 129.0, 128.6, 128.5, 128.2 ($C^{Ar\ PMB}$ $C^{Ar\ Bz}$ $C^{Ar\ Bz'}$ C^{Ph} C^{Ph} '), 114.3 ($C^{Ar\ PMB}$), 109.5 ($O\underline{C}Me_2O$), 108.2 (C-1^{Api}), 107.1 (Ph$\underline{C}$H), 98.8 (C-1^{Gal}), 98.6 (C-1^{Rha}), 91.9 (C-3^{Api}), 87.7 (C-2^{Api}), 78.9 (C-4^{Rha}), 77.4 (C-2^{Gal}), 76.2 (C-3^{Gal}), 75.3 (OCH_2^{PMB}), 74.2 (C-4^{Gal}), 73.8 (C-3'^{Api}), 73.5 (C-3^{Rha}), 71.6 (C-2^{Rha}), 69.3 (C-4^{Api}), 69.2 (C-5^{Rha}), 68.8 (C-5^{Gal}), 68.5 (OCH_2-), 66.3 (OCH_2Ph), 63.2 (C-6^{Gal}), 55.4 (OCH_3), 41.5

(-CH_2N), 30.7, 30.3 (-CH_2- -CH_2-), 28.6 (CH_3^{iPrA}), 27.3 (-CH_2-), 26.70 (-CH_2-), 26.67 ($CH_3^{iPrA'}$), 26.2 (C($\underline{C}H_3$)$_3$), 18.8 (Si$\underline{C}$Me$_3$), 18.5 (C-6^{Rha}), -5.1 (SiCH$_3$), -5.3 (SiCH$_3$'); **^{1}H coupled ^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 108.2 (d, $J_{C1\text{-}H1}$ = 178 Hz, C-1^{Api}), 98.8 (d, $J_{C1\text{-}H1}$ = 169 Hz, C-1^{Gal}), 98.6 (d, $J_{C1\text{-}H1}$ = 173 Hz, C-1^{Rha}). **HRMS**: calcd. for $C_{69}H_{87}NO_{19}Si$: 1284.5534 [*M*+Na]$^+$, found 1284.5532; **TLC** (hex/EtOAc 71:29): R_f = 0.35 (CH stain, UV).

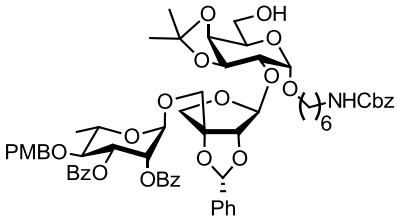
(6-*N*-Benzyloxycarbonylamino)-1-hexyl 2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**126**)



Trisaccharide **86** (72.0 mg, 57.0 µmol, 1.0 eq) was dissolved in CH_2Cl_2 (0.49 mL), 0.1 M phosphate buffer (pH 7, 55 µL) was added and the mixture was cooled to 0 °C. To the vigorously stirred emulsion, DDQ (14.2 mg, 62.7 µmol, 1.1 eq) was added in one portion. The ice bath was removed, and the reaction mixture was stirred for 1 h. At this point it was cooled again to 0°C and additional DDQ (6.5 mg, 29 µmol, 0.5 eq) was added. The mixture was again allowed to warm up to rt. After 2 h, the mixture was diluted with CH_2Cl_2 (10 mL) and the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$-solution (3 mL). Water was added (2 mL) and the phases were separated. The organic layer was washed with water (6 mL) and brine (6 mL). After drying over $MgSO_4$, the solution was concentrated and purified by flash chromatography (tol/EtOAc 86:14) to yield trisaccharide alcohol **126** (52.0 mg, 80%) as a faint yellow syrup. **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 8.06 (m, 2 H, H$^{Ar\ Bz}$), 7.92 (m, 2 H, H$^{Ar\ Bz}$), 7.68 (m, 1 H, H$^{Ar\ Bz}$), 7.61 (m, 2 H, H$^{Ar\ Bz}$), 7.58-7.50 (m, 3 H, H$^{Ar\ Bz}$), 7.45-7.22 (m, 10 H, H$^{Ar\ Ph}$ H$^{Ar\ Ph'}$), 6.26 (bt, 1H, NH), 6.14 (s, 1H, PhCH), 5.69 (dd, $J_{2\text{-}3}$ = 3.4 Hz $J_{2\text{-}1}$ = 1.7 Hz, 1 H, H-2^{Rha}), 5.57 (dd, $J_{3\text{-}2}$ = 3.4 Hz $J_{3\text{-}4}$ = 9.5 Hz, H-3^{Rha}), 5.49 (s, 1 H, H-1^{Api}), 5.14 (d, $J_{1\text{-}2}$ = 1.8 Hz, 1 H, H-1^{Rha}), 5.02 (s, 2 H, OCH_2Ph), 4.93 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1 H, H-1^{Gal}), 4.79 (d, $J_{OH\text{-}4}$ = 6.1 Hz, 1 H, OH), 4.67 (s, 1 H, H-2^{Api}), 4.33-4.23 (m, 2 H, H-4^{Gal} H-3^{Gal}), 4.18 (d, $J_{4a\text{-}4b}$ = 10.8 Hz, 1 H, H-4a^{Api}), 4.12 (d, $J_{4a\text{-}4b}$ = 10.2Hz, 1 H, H-3'a^{Api}), 4.09-3.94 (m, 5 H, H-3'b^{Api} H-4b^{Api} H-4^{Rha} H-5^{Gal} H-5^{Rha}), 3.98 (dd, $J_{5\text{-}6a}$ = 6.2 Hz $J_{6a\text{-}6b}$ = 10.3 Hz, 1 H, H-6a), 3.82-3.69 (m, 3 H, H-6b^{Gal} H-2^{Gal} OCH_2a), 3.43 (dt, $J_{OCH2\text{-}OCH2'}$ = 9.6 Hz $J_{OCH2\text{-}CH2}$ = 6.6 Hz, 1 H, OCH_2b), 3.12 (dt, $J_{NCH2\text{-}CH2}$ = 7.1 Hz $J_{NCH2\text{-}NH}$ = 6.0 Hz, 2 H, CH_2N), 1.64 (m, 2 H, -CH_2-), 1.57-1.48 (m, 5 H, -CH_2- CH_3^{iPrA}), 1.48-1.31 (m, 7 H, -CH_2-CH_2- H-6^{Rha}), 1.29 (s, 3 H, $CH_3^{iPrA'}$), 0.91 (s, 9 H, C(CH_3)$_3$), 0.10 (s, 6 H, Si(CH_3)$_2$); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 166.3, 166.0 (C=O C=O'), 157.1 (N(C=O)O), 138.5, 137.9 (C$^{Ar\ Ph}$

$C^{Ar\ Ph'}$), 134.4, 134.0 ($C^{Ar\ Bz}$ $C^{Ar\ Bz'}$), 131.0, 130.55, 130.49, 130.43, 130.3, 129.6, 129.2, 129.1, 129.0, 128.6, 128.5, 128.2 ($C^{Ar\ Bz}$ $C^{Ar\ Bz'}$ C^{Ph} C^{Ph} '), 109.5 (O<u>C</u>Me$_2$O), 108.2 (C-1^{Api}), 107.2 (Ph<u>C</u>H), 98.9 (C-1^{Gal}), 98.7 (C-1^{Rha}), 91.9 (C-3^{Api}), 87.7 (C-2^{Api}), 77.4 (C-2^{Gal}), 76.2 (C-3^{Gal}), 74.2 (C-4^{Gal}), 73.8 (C-3'^{Api}), 73.69, 73.65 (C-3$^{Rha,\ OH}$ C-3$^{Rha,\ OD}$), 71.4 (C-2^{Rha}), 71.3, 71.2 (C-4$^{Rha,\ OH}$ C-4$^{Rha,\ OD}$), 70.17, 70.14 (C-5$^{Rha,\ OH}$ C-5$^{Rha,\ OD}$), 69.4 (C-4^{Api}), 68.8 (C-5^{Gal}), 68.5 (OCH$_2$-), 66.3 (OCH$_2$Ph), 63.2 (C-6^{Gal}), 41.5 (-CH$_2$N), 30.7, 30.2 (-CH$_2$- -CH$_2$-), 28.6 (CH$_3$^{iPrA}), 27.3 (-CH$_2$-), 26.71 (-CH$_2$-), 26.68 (CH$_3$^{iPrA}'), 26.2 (C(<u>C</u>H$_3$)$_3$), 18.8 (Si<u>C</u>Me$_3$), 18.3 (C-6^{Rha}), -5.1 (SiCH$_3$), -5.3 (SiCH$_3$'); **HRMS**: calcd. for $C_{61}H_{79}NO_{18}Si$: 1159.5405 [*M*+NH$_4$]$^+$, found 1159.5389; **TLC** (tol/EtOAc 80:20): R_f = 0.45 (CH stain, UV).

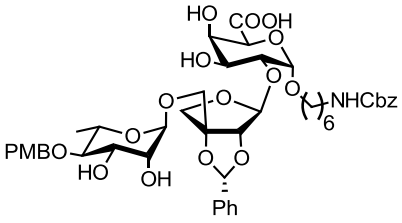
(6-*N*-Benzyloxycarbonylamino)-1-hexyl 2,3-di-*O*-benzoyl-4-*O*-*p*-methoxybenzyl-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-3,4-*O*-isopropylidene-α-D-galactopyranoside (**127**)



Trisaccharide **86** (55.0 mg, 43.6 µmol, 1.0 eq) was dissolved in THF (0.33 mL) and AcOH (25 µL, 0.44 mmol, 10 eq) and subsequently 1 M TBAF solution (0.22 mL, 0.22 mmol, 5.0 eq) were added. The mixture was stirred for 4 h, then concentrated and purified by flash chromatography (hex/EtOAc 50:50) to yield pure alcohol **127** (47.0 mg, 94%) as a colorless foam. **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 8.07 (m, 2 H, H$^{Ar\ Bz}$), 7.94 (m, 2 H, H$^{Ar\ Bz}$), 7.70 (m, 1 H, H$^{Ar\ Bz}$), 7.64-7.52 (m, 5 H, H$^{Ar\ Bz}$), 7.47-7.24 (m, 10 H, H$^{Ar\ Ph}$ H$^{Ar\ Ph'}$), 7.14 (m, 2 H, H$^{Ar\ PMB}$), 6.74 (m, 2 H, H$^{Ar\ PMB}$), 6.22 (bt, 1H, NH), 6.12 (s, 1H, PhCH), 5.68 (m, 2 H, H-2^{Rha} H-3^{Rha}), 5.47 (s, 1 H, H-1^{Api}), 5.14 (s, 1 H, H-1^{Rha}), 5.02 (s, 2 H, OCH$_2$Ph), 4.92 (d, $J_{1\text{-}2}$ = 3.5 Hz, 1 H, H-1^{Gal}), 4.70 4.67 (2 d, $J_{1\text{-}2}$ = 11.1 Hz, 1 H, CH$_2$^{PMB} CH$_2$$^{PMB'}$), 4.65 (s, 1 H, H-2^{Api}), 4.32-4.21 (m, 2 H, H-4^{Gal} H-3^{Gal}), 4.18 (d, $J_{4a\text{-}4b}$ = 10.9 Hz, 1 H, H-4a^{Api}), 4.14-3.92 (m, 6 H, H-4b^{Api} H-3'a^{Api} H-3'b^{Api} H-5^{Gal} H-5^{Rha} H-4^{Rha}), 3.80-3.66 (m, 8 H, H-6a^{Gal} H-6b^{Gal} H-2^{Gal} OH OCH$_2$a OCH$_3$), 3.43 (dt, $J_{OCH2\text{-}OCH2'}$ = 9.5 Hz $J_{OCH2\text{-}CH2}$ = 6.6 Hz, 1 H, OCH$_2$b), 3.12 (dt, $J_{NCH2\text{-}CH2}$ = 7.1 Hz $J_{NCH2\text{-}NH}$ = 6.0 Hz, 2 H, CH$_2$N), 1.62 (m, 2 H, -CH$_2$-), 1.56-1.45 (m, 5 H, -CH$_2$- CH$_3$^{iPrA}), 1.45-1.33 (m, 7 H, -CH$_2$-CH$_2$- H-6^{Rha}), 1.27 (s, 3 H, CH$_3$$^{iPrA'}$); **^{13}C NMR** ($CD_3COCD_3$, 150 MHz): δ = 166.13, 166.08 (C=O C=O'), 160.3 (C$^{Ar\ PMB}$), 157.2 (N(C=O)O), 138.6, 138.0 (C$^{Ar\ Ph}$ C$^{Ar\ Ph'}$), 134.5, 134.1 (C$^{Ar\ Bz}$ C$^{Ar\ Bz'}$), 131.2, 130.9, 130.65, 130.55, 130.53, 130.48, 130.34, 129.6, 129.4, 129.2, 129.0, 128.7, 128.5, 128.2 (C$^{Ar\ PMB}$ C$^{Ar\ Bz}$ C$^{Ar\ Bz'}$ C^{Ph} C^{Ph} '), 114.4 (C$^{Ar\ PMB}$), 109.6 (O<u>C</u>Me$_2$O), 108.3 (C-1^{Api}), 107.2 (Ph<u>C</u>H), 98.9 (C-1^{Gal}), 98.7 (C-1^{Rha}), 92.0 (C-3^{Api}), 87.8 (C-2^{Api}), 79.0 (C-4^{Rha}), 77.5 (C-2^{Gal}), 76.3 (C-3^{Gal}), 75.3 (OCH$_2$^{PMB}), 74.7 (C-4^{Gal}), 73.9 (C-3'^{Api}), 73.5 (C-3^{Rha}), 71.7 (C-2^{Rha}), 69.5 (C-4^{Api}),

69.3 (C-5^{Rha}), 69.2 (C-5^{Gal}), 68.6 (OCH_2-), 66.3 (OCH_2Ph), 62.4 (C-6^{Gal}), 55.5 (OCH_3), 41.6 (-CH_2N), 30.7, 30.2 (-CH_2- -CH_2-), 28.6 (CH_3^{iPrA}), 27.3 (-CH_2-), 26.75 (-CH_2-), 26.69 (CH_3^{iPrA}'), 18.5 (C-6^{Rha}); **HRMS**: calcd. for $C_{63}H_{73}NO_{19}$: 1170.4669 [*M*+Na]$^+$, found 1170.4633; **TLC** (hex/EtOAc 50:50): R_f = 0.38 (CH stain, UV).

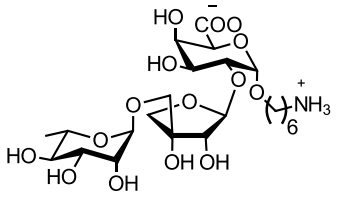
(6-*N*-Benzyloxycarbonylamino)-1-hexyl 4-*O*-*p*-methoxybenzyl-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-α-D-galactopyranosyluronic acid (**128**)



Under a layer of argon, alcohol **127** (5.0 mg, 4.4 µmol, 1.0 eq) was dissolved in anh. CH_2Cl_2 (30 µL) and water (13 µL). Then PIDA (3.2 mg, 9.7 µmol, 2.2 eq) and subsequently TEMPO (0.14 mg, 0.88 µmol, 0.2 eq) were added. After the mixture was stirred for 70 min the starting material was fully converted according to TLC (tol/acetone 2:1), so the reaction was quenched with a drop of MeOH and stirred for another 10 min. The mixture was then coevaporated with MeOH and concentrated *in vacuo* to give the crude carboxylic acid which was directly used in the next step. **HPTLC** (CH_2Cl_2/MeOH 90:10 0.1% 2M HCl): R_f = 0.36 (CH stain, UV). Crude carboxylic acid was dissolved in MeOH (100 µL) and 0.5 M NaOMe solution in MeOH (10 µL, 5.0 µmol, 1.13 eq) was added. The mixture was stirred for 8 h, then washed Amberlite IR-120 ion exchange resin (H^+) form was added and stirring continued for 15 min. Filtration, thorough washing with MeOH and concentration gave the crude diol trisaccharide which was directly employed in the next step. **HPTLC** (CH_2Cl_2/MeOH 90:10 0.1% 2M HCl): R_f = 0.21 (CH stain, UV). Crude diol disaccharide was dissolved in 80% AcOH (200 µL) and heated to 65°C using a rotary evaporator. After 40 min of rotation the reaction had finished, as confirmed by LCMS, so toluene was added and all volatiles coevaporated by repeated toluene addition. The crude was purified by RP-chromatography (Waters C18 Seppack 500 mg, MeCN/H_2O 30:70 to 55:45 + 0.1% AcOH) and the fractions were subsequently lyophilized to obtain partially protected trisaccharide **128** (3.18 mg, 80% o. 3 s.) as colorless powder. **^{1}H NMR** (CD_3CN + D_2O, 600 MHz): δ = 7.47 (m, 2 H, H$^{Ar\ Ph}$ H$^{Ar\ Ph}$'), 7.43-7.28 (m, 8 H, H$^{Ar\ Ph}$ H$^{Ar\ Ph}$'), 7.27 (m, 2 H, H$^{Ar\ PMB}$), 6.87 (m, 2 H, H$^{Ar\ PMB}$), 5.87 (s, 1H, PhCH), 5.30 (s, 1 H, H-1^{Api}), 5.03 (bs, 2 H, OCH_2Ph), 5.00 (d, $J_{1\text{-}2}$ = 3.5 Hz, 1 H, H-1^{GalA}), 4.75-4.71 (m, 2 H, H-1^{Rha} CH_2a^{PMB}), 4.53 (d, $J_{CH2a\text{-}CH2b}$ = 10.9 Hz, 1 H, CH_2b^{PMB}), 4.49 (s, 1 H, H-2^{Api}), 4.27 (d, $J_{5\text{-}4}$ = 0.8 Hz, 1 H, H-5^{GalA}), 4.15 (dd, $J_{4\text{-}3}$ = 2.2 Hz $J_{4\text{-}5}$ = 0.8 Hz, 1 H, H-4^{GalA}), 4.01 (d, $J_{4a\text{-}4b}$ = 10.2 Hz, 1 H, H-4a^{Api}), 3.97 (d, $J_{3'a\text{-}3'b}$ = 10.8 Hz, 1 H, H-3'a^{Api}), 3.91 (d, $J_{3'a\text{-}3'b}$ = 10.8 Hz, 1 H, H-3'b^{Api}), 3.85-3.79 (m, 2 H, H-3^{GalA} H-2^{Rha}), 3.78-3.72 (m, 5 H, H-3^{Rha} OCH_3^{PMB} H-2^{GalA}), 3.70 (d, $J_{4a\text{-}4b}$ = 10.8 Hz, 1 H, H-4b^{Api}), 3.67-3.60 (m, 2 H, H-5^{GalA} OCH_2a), 3.37 (dt,

$J_{OCH2\text{-}CH2}$ = 6.4 Hz $J_{OCH2a\text{-}OCH2b}$ = 9.6 Hz, 1 H, OCH_2b), 3.27 (dd, $J_{4\text{-}3}$= $J_{4\text{-}5}$ = 9.4 Hz, 1 H, OCH_2b), 3.12 (bt, $J_{NCH2\text{-}CH2}$ = 6.9 Hz, 2 H, CH_2N), 1.54 (bp, J = 6.8 Hz, 2 H, CH_2), 1.43 (p, J = 7.2 Hz, 2 H, CH_2), 1.36-1.22 (m, 4 H, CH_2 CH_2), 1.20 (d, J = 6.2 Hz, 3 H, H-6^{Rha}); **^{13}C NMR** (CD_3CN + D_2O, 150 MHz): δ = 172.0* (C-6^{GalA}), 160.3 (C^{PMB}), 157.8* (N(C=O)O), 138.7*, 137.7, 132.2, 130.9, 130.8, 129.5, 129.4, 128.9, 128.7, 128.1, 114.6 ($C^{Ar\ PMB}$ C^{Ph} $C^{Ph\prime}$), 109.2 (C-1^{Api}), 106.7 (PhCH), 101.2 (C-1^{Rha}), 99.4 (C-1^{GalA}), 92.0 (C-3^{Api}), 87.7 (C-2^{Api}), 81.8 (C-4^{Rha}), 76.8 (C-2^{GalA}), 75.2 ($OCH_2{}^{PMB}$), 74.2 (C-4^{Api}), 72.3 (C-3^{Rha}), 72.0 (C-2^{Rha}), 71.4 (C-4^{GalA}), 71.2 (C-5^{GalA}), 69.22 (OCH_2), 69.16 (C-3^{GalA}), 68.69 (C-3'^{Api}), 68.65 (C-5^{Rha}), 66.9 (PhCH_2), 63.6 (C-3'^{Api}), 56.0 ($OCH_3{}^{PMB}$), 41.5 (NCH_2), 30.5 (CH_2), 30.2 (CH_2), 27.3 (CH_2), 26.7 (CH_2), 18.4 (C-6^{Rha}), *identified by ^{1}H-^{13}C HMBC; **^{1}H-^{13}C coupled HSQC:** 109.2 ($J_{C1\text{-}H1}$ = 175 Hz, C-1^{Api}), 101.2 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{Rha}), 99.4 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{GalA}); **HRMS**: calcd. for $C_{46}H_{59}NO_{18}$: 912.3659 [*M*-H]$^-$, found 912.3662; **HPLC** (5-100% MeCN + 0.1% AcOH in 15 min, column 1): R_t = 11.078 min.

6-Amino-1-hexyl α-L-rhamnopyranosyl-(1→3')-β-D-apiofuranosyl-(1→2)-α-D-galactopyranosyluronic acid (**85**)

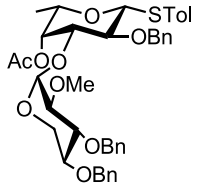


Partially protected trisaccharide **128** (2.80 mg, 3.06 µmol, 1.0 eq) was dissolved in *t*BuOH/H_2O (0.56 mL, 50:50). The stirred mixture was degassed in a pressure reactor and set under argon (6 cycles). Pd/C (2.8 mg, 10% wt. unreduced) was added and the stirred suspension degassed and set under hydrogen atmosphere (6 cycles). Pressure was adjusted to 8 bar and stirring was continued for 5 d at rt. The reaction was found complete by LCMS and the crude mix was degassed and set under argon atmosphere and then filtered over a syringe filter (0.45 µm, PTFE). The filter was washed thoroughly with *t*BuOH/H_2O, H_2O, MeCN/H_2O, MeCN and then H_2O. The filtrate was concentrated *in vacuo*. The crude was purified by RP-HPLC-chromatography (YMC-Triart C18 column 150x10, MeCN/H_2O 0:100 to 7:95) and fractions subsequently lyophilized to obtain pure trisaccharide **85** (0.71 mg, 41%) and *N*-methylated as well as *N,N*-dimethylated side products as colorless powders. **^{1}H NMR** (D_2O, 600 MHz): δ = 5.19 (d, $J_{1\text{-}2}$ = 2.5 Hz, 1 H, H-1^{Api}), 5.06 (d, $J_{1\text{-}2}$ = 4.0 Hz, 1 H, H-1^{GalA}), 4.78 (d, 1 H, H-1^{Rha}), 4.28 (dd, $J_{4\text{-}3}$ = 3.5 Hz $J_{4\text{-}5}$ = 1.3 Hz, 1H, H-4^{GalA}), 4.21 (d, $J_{1\text{-}2}$ = 1.3 Hz, 1H, H-5^{GalA}), 4.12 (d, $J_{2\text{-}1}$ = 2.5 Hz, 1 H, H-2^{Api}), 4.00 (d, $J_{4a\text{-}4b}$ = 10.3 Hz, 1 H, H-4a^{Api}), 3.98 (dd, $J_{2\text{-}1}$ = 1.8 Hz $J_{2\text{-}3}$ = 3.4 Hz, 1 H, H-2^{Rha}), 3.93 (dd, $J_{3\text{-}4}$ = 3.5 Hz $J_{3\text{-}2}$ = 10.3 Hz, 1 H, H-3^{GalA}), 3.91 (d, $J_{4a\text{-}4b}$ = 10.2 Hz, 1 H, H-4b^{Api}), 3.89 (d, $J_{3'a\text{-}3'b}$ = 10.2 Hz, 1 H, H-3'a^{Api}), 3.80 (dd, $J_{3\text{-}2}$ = 3.5 Hz $J_{3\text{-}4}$ = 9.8 Hz, 1 H, H-3^{Rha}), 3.78 (dd, $J_{3\text{-}2}$ = 3.9 Hz $J_{3\text{-}4}$ = 10.3 Hz, 1 H, H-2^{GalA}), 3.72-3.66 (m, 2 H, OCH_2a H-5^{Rha}), 3.57 (dt, $J_{OCH2\text{-}CH2}$ = 5.8 Hz $J_{OCH2\text{-}OCH2'}$ = 10.2 Hz, 1 H, OCH_2b),

3.54 (d, $J_{3a\text{-}3b}$ = 10.3 Hz, 1 H, H-3'b^{Api}), 3.43 (dd, Hz $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 9.7 Hz, H-4^{Rha}), 2.96 (t, $J_{NCH2\text{-}CH2}$ = 7.6 Hz, 2 H, CH_2N), 1.70-1.55 (m, 4 H, CH_2 CH_2), 1.44-1.32 (m, 4 H, CH_2 CH_2), 1.29 (d, $J_{6\text{-}5}$ = 6.3 Hz, 1 H, H-6^{Rha}); **^{13}C NMR** (D_2O, 150 MHz): δ = 176.2 (C-6^{GalA}), 111.0 (C-1^{Api}), 100.8 (C-1^{Rha}), 98.8 (C-1^{GalA}), 79.2 (C-3^{Api}), 77.6 (C-2^{Api}), 77.1 (C-2^{GalA}), 74.3 (C-4^{Api}), 72.7 (C-4^{Rha}), 71.9 (C-5^{GalA}), 71.4 (C-4^{GalA}), 70.9 (C-3^{Rha}), 70.6 (C-2^{Rha}), 70.1 (C-3'^{Api}), 69.4 (C-5^{Rha}), 69.3 (C-3^{GalA}), 68.9 (OCH_2), 40.1 (NCH_2), 29.0 (CH_2), 27.3 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 17.3 (C-6^{Rha}); **^{1}H-^{13}C coupled HMBC:** 111.0 ($J_{C1\text{-}H1}$ = 174 Hz, C-1^{Api}), 100.8 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Rha}), 98.8 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{GalA}); **HRMS**: calcd. for $C_{23}H_{41}NO_{15}$: 570.2403 [*M*-H]$^-$, found 570.2401; **HPLC** (0-10% MeCN + 0.1% AcOH in 15 min, column 1): R_t = 9.625 min.

4.3.10 Synthesis of pentasaccharide fragments

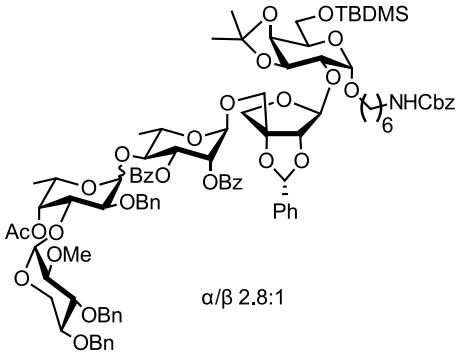
p-Tolyl 3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)-4-*O*-acetyl-2-*O*-benzyl-1-thio-β-L-fucopyranoside (**87**)



The synthetic procedure was conducted by visiting PhD-student Karolina Dzedulionyté under my direct supervision. Donor thioglycoside **82** (1.19 g, 2.63 mmol, 1.3 eq) was coevaporated with toluene and all volatile compounds were removed in fine vacuum. Then, under a layer of argon, freshly activated MS 4Å (1.00 g) was added followed by anh. CH_2Cl_2 (35 mL) and anh. DMF (0.94 mL, 12.1 mmol, 6.0 eq). The suspension was stirred for 30 min and AgOTf (1.35 g, 5.25 mmol, 2.6 eq) was added, before it was cooled to -78 °C. TolSCl (0.8 mL, 5.26 mmol, 2.6 eq, old/low quality batch containing <50% TolSCl) was added dropwise to the mixture and it was stirred for 3 h. As the donor was converted to the intermediate, indicated by TLC, a solution of acceptor alcohol **81** (815 mg, 2.02 mmol, 1.0 eq) and TTBP (805 mg, 3.23 mmol, 1.6 eq) in anh. CH_2Cl_2 (5 mL) was added and the mixture was placed in the freezer at -18 °C. After stirring for 20 h the reaction mixture was warmed to -2 °C and stirred for another 2 h, but no changes were observed by TLC. At this point it was quenched by the addition of Pyr (0.5 mL), filtered over a plug of celite and washed with CH_2Cl_2. The organic phase was washed with water (3x), sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$, filtrated and concentrated *in vacuo*. The obtained crude was purified by flash chromatography (tol then tol/EtOAc 94:6 to 89:11) to yield the desired product as an α/β-mixture (α/β 1.6/1) alongside with unreacted donor (243 mg, 20%) and acceptor (130 mg, 16%). Flash chromatography (tol then tol/EtOAc 94:6) gave α-isomer **87** (699 mg, 48%) and the corresponding β-isomer (437 mg, 30%) as separate fractions. For α-isomer **87**: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.53-7.43 (m, 4 H, H$^{Ar\ Ph}$ H$^{Ar\ Ph'}$ H$^{Ar\ STol}$), 7.39-7.27 (m, 13 H, H$^{Ar\ Ph}$ H$^{Ar\ Ph'}$ H$^{Ar\ Ph''}$) 7.11 (m,

2 H, $H^{Ar\ STol}$), 5.28 (d, $J_{4\text{-}3}$ = 3.0 Hz, 1 H, H-4^{Fuc}), 5.16 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1 H, H-1^{Xyl}), 4.95 (d, $J_{CH2\text{-}CH2'}$ = 10.3 Hz, 1 H, $PhCH_2^{Fuc}$), 4.88 (d, $J_{CH2\text{-}CH2'}$ = 11.0 Hz, 1 H, $PhCH_2^{Xyl\text{-}3}$), 4.85-4.78 (m, 2 H, $PhCH_2'^{Fuc}$ $PhCH_2'^{Xyl\text{-}3}$), 4.71 (d, $J_{CH2\text{-}CH2'}$ = 12.0 Hz, 1 H, $PhCH_2^{Xyl\text{-}4}$), 4.63 (d, $J_{CH2\text{-}CH2'}$ = 11.9 Hz, 1 H, $PhCH_2'^{Xyl\text{-}4}$), 4.59 (d, $J_{1\text{-}2}$ = 9.5 Hz, 1 H, H-1^{Fuc}), 3.85 (dd, $J_{3\text{-}4}$ = 3.1 Hz, $J_{3\text{-}2}$ = 9.4 Hz, 1 H, H-3^{Fuc}), 3.81-3.69 (m, 3 H, H-2^{Fuc} H-3^{Xyl} H-5^{Fuc}), 3.65 (d, $J_{5a\text{-}5b}$ = 10.7 Hz, 1 H, H-$5a^{Xyl}$), 3.62-3.47 (m, 2 H, H-$5b^{Xyl}$ H-4^{Xyl}), 3.41 (s, 3H, OCH_3), 3.17 (dd, $J_{1\text{-}2}$ = 3.7 Hz, $J_{2\text{-}3}$ = 9.6 Hz, H-2^{Xyl}), 2.35 (s, 3 H, CH_3^{STol}), 2.21 (s, 3 H, CH_3^{Ac}), 1.22 (d, $J_{6\text{-}5}$ = 6.4 Hz, 3 H, H-6^{Fuc}); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 170.8 (C=O), 138.9, 138.8, 138.6, 137.8, 132.7, 130.1, 129.7, 128.5, 128.47, 128.43, 128.1, 127.9, 127.8, 127.74, 127.68 ($C^{Ar\ Ph}$ $C^{Ar\ Ph'}$ $C^{Ar\ Ph''}$ $C^{Ar\ STol}$), 99.5 (C-1^{Xyl}), 88.1 (C-1^{Fuc}), 81.9 (C-2^{Xyl}), 81.4 (C-3^{Xyl}), 80.1 (C-3^{Fuc}), 78.1 (C-4^{Xyl}), 76.8 (C-2^{Fuc}), 75.6 ($PhCH_2^{Xyl\text{-}3}$), 75.0 ($PhCH_2^{Fuc}$), 73.6 (C-5^{Fuc}), 73.2 ($PhCH_2^{Xyl\text{-}4}$), 73.0 (C-4^{Fuc}), 60.8 (C-5^{Xyl}), 60.5 (OCH_3), 21.3 (CH_3^{STol}), 21.2 (CH_3^{Ac}), 17.1 (C-6^{Fuc}); **TLC** (tol:EtOAc 80:20): R_f = 0.63 (UV, CH stain); **HRMS**: calcd. for $C_{42}H_{48}O_9S$: 746.3357 $[M+NH_4]^+$, found 746.3364.

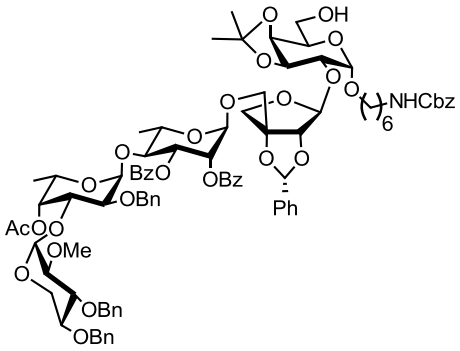
(6-*N*-Benzyloxycarbonylamino)-1-hexyl 3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)-4-*O*-acetyl-2-*O*-benzyl-L-fucopyranosyl-(1→4)-2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-6-*O*-*tert*-butyldimethylsilyl-3,4-O-isopropylidene-α-D-galactopyranoside (**84**)



Acceptor alcohol **126** (50.0 mg, 43.8 µmol, 1.0 eq) and thioglycoside **87** (35.0 mg, 48.2 mmol, 1.1 eq) were coevaporated with toluene and all volatiles were removed in fine vacuum. Under a layer of argon, freshly activated molecular sieve powder 4 Å (44 mg) was added and the mixture was suspended in anhydrous MTBE and anhydrous CH_2Cl_2 (10:2, 1.2 mL). After stirring for 40 min, NIS (30.0 mg, 131 µmol, 3.0 eq) was added and the mixture was cooled down to -35 °C. TfOH (1.6 µL, 18 µmol, 0.4 eq) was added and the mixture was stirred for 1 h, at which point the reaction was quenched by NEt_3 (40 µL) and filtrated over a plug of celite. After washing with CH_2Cl_2, the filtrate was stirred with sat. aq. $Na_2S_2O_3$ solution until the organic phase remained colorless. The phases were separated and the organic phase was washed with sat. aq. $NaHCO_3$ solution. After drying over $MgSO_4$, the solution was concentrated and the remaining residue was purified by flash chromatography (tol/EtOAc 86:14) to

yield pentasaccharide **84** (56.0 mg, α/β 2.75:1, 73%) as a colorless foam. The α/β ratio was determined by integration of UV traces (254 nm) after performing performing LC-MS analysis using a YMC-Pack DIOL-300-NP column (150 x 4.6 mm). **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 8.09 (m, 2 H, $H^{Ar\ Bz}$), 7.85 (m, 2 H, $H^{Ar\ Bz}$), 7.70 (m, 1 H, $H^{Ar\ Bz}$), 7.64-7.50 (m, 5 H, $H^{Ar\ Bz}$), 7.47-7.21 7.20-7.06 (2 m, 20 H 5 H, $H^{Ar\ Ph\ 1-5}$), 6.28 (bt, 1H, NH), 6.15 (s, 1H, PhCH), 5.79-5.68 (m, 2 H, H-2^{Rha} H-3^{Rha}), 5.49 (s, 1 H, H-1^{Api}), 5.28 (dd, J = 1.1 Hz J = 3.3 Hz, 1 H, H-4^{Fuc}), 5.21 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1H, H-1^{Fuc}), 5.18 (d, $J_{1\text{-}2}$ = 1.4 Hz, 1 H, H-1^{Rha}), 5.10-5.01 (m, 3 H, H-1^{Xyl} $PhCH_2$), 4.93 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1 H, H-1^{Gal}), 4.77, 4.74 (2 d, $J_{OCH2\text{-}OCH2'}$ = 11.5 Hz, 1 H, $PhCH_2^{Xyl\text{-}3}$), 4.71-4.66 (m, 2 H, H-2^{Api} $PhCH_2^{Xyl\text{-}4}$), 4.64 (d, $J_{OCH2\text{-}OCH2'}$ = 12.0 Hz, 1 H, $PhCH_2$'$^{Xyl\text{-}4}$), 4.35 (d, $J_{OCH2\text{-}OCH2'}$ = 12.0 Hz, 1 H, $PhCH_2^{Fuc}$), 4.32-4.09 (m, 9 H, H-4^{Gal} $PhCH_2$'^{Fuc} H-5^{Fuc} H-3^{Gal} H-4a^{Api} H-5^{Rha} H-3'a^{Api} H-4^{Rha} H-3^{Fuc}), 4.09-3.98 (m, 3 H, H-3'b^{Api} H-4b^{Api} H-5^{Gal}), 3.89 (dd, $J_{6\text{-}5}$ = 6.1 Hz $J_{6a\text{-}6b}$ = 10.1 Hz, 1 H, H-6a^{Gal}), 3.83-3.70 (m, 3 H, H-6b^{Gal} H-2^{Gal} OCH_2), 3.68 (dd, $J_{1\text{-}2}$ = 3.7 Hz, $J_{1\text{-}2}$ = 10.3 Hz, 1 H, H-2^{Fuc}), 3.65-3.53 (m, 3 H, H-5a^{Xyl} H-5b^{Xyl} H-3^{Xyl}), 3.50-3.37 (m, 2 H, H-4^{Xyl} OCH_2'), 3.19-3.07 (m, 5 H, OCH_3 CH_2N), 3.01 (dd, $J_{1\text{-}2}$ = 3.7 Hz, $J_{2\text{-}3}$ = 9.6 Hz, 1 H, H-2^{Xyl}), 2.05 (s, 3 H, CH_3^{Ac}), 1.68-1.58 (m, 2 H, -CH_2-), 1.58-1.46 (m, 8 H, -CH_2- H-6^{Rha} $CH_3^{i PrA}$), 1.46-1.33 (m, 4 H, -CH_2- -CH_2-), 1.30 (s, 3 H, $CH_3^{i PrA'}$), 1.03 (d, $J_{6\text{-}5}$ = 6.5 Hz, 3 H, H-6^{Fuc}), 0.91 (s, 9 H, $C(CH_3)_3$), 0.10 (s, 6 H, $Si(CH_3)_2$); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 170.7, 166.0, 165.8 (C=O^{Ac} C=O^{Bz} C=O^{Bz}), 157.1 (N(C=O)O), 140.4, 140.0, 139.5, 138.5, 137.9 ($C^{Ar\ Ph1\text{-}5}$), 134.5, 133.9 ($C^{Ar\ Bz}$ $C^{Ar\ Bz'}$), 130.8, 130.50, 130.48, 130.40, 130.36, 130.30, 129.63, 129.59, 129.22, 129.15, 129.03, 129.01, 128.87, 128.8, 128.6, 128.5, 128.43, 128.38, 128.23, 128.19, 128.0, 127.95, 127.86 ($C^{Ar\ Bz}$ $C^{Ar\ Bz'}$ $C^{Ph1\text{-}5}$), 109.5 (O<u>C</u>Me_2O), 108.3 (C-1^{Api}), 107.2 (Ph<u>C</u>H), 99.2 (C-1^{Fuc}) 98.87 (C-1^{Xyl}), 98.84 (C-1^{Gal}), 98.6 (C-1^{Rha}), 92.0 (C-3^{Api}), 87.7 (C-2^{Api}), 82.8 (C-2^{Xyl}), 81.5 (C-3^{Xyl}) 78.9 (C-4^{Xyl}), 78.2 (C-4^{Rha}), 77.4 (C-2^{Gal}), 76.4 (C-3^{Gal}), 76.2 (C-2^{Fuc}), 75.4 ($PhCH_2^{Xyl\text{-}3}$), 74.21 (C-4^{Gal}), 74.16 (C-4^{Fuc}), 73.8 (C-3'^{Api}), 73.7 (C-3^{Fuc}), 73.25 ($PhCH_2^{Xyl\text{-}4}$), 73.20 (C-3^{Rha}) 73.0 ($PhCH_2^{Fuc}$), 71.4 (C-2^{Rha}), 69.7 (C-4^{Api}), 68.8 (C-5^{Gal}), 68.7 (OCH_2-), 68.5 (C-5^{Rha}), 66.7 (C-5^{Fuc}), 66.3 (OCH_2Ph), 63.2 (C-6^{Gal}), 61.0 (C-5^{Xyl}), 59.4 (OCH_3), 41.5 (-CH_2N), 30.7 30.2 (-CH_2- -CH_2-), 28.7 ($CH_3^{i PrA}$), 27.3 (-CH_2-), 26.72 (-CH_2-), 26.7 ($CH_3^{i PrA'}$), 26.2 ($C(\underline{C}H_3)_3$), 20.8 (CH_3^{Ac}), 19.0 (C-6^{Rha}), 18.8 ($\underline{C}(CH_3)_3$), 16.4 (C-6^{Fuc}), -5.1, -5.3 ($Si(CH_3)_2$); **^{1}H-^{13}C coupled HSQC:** 108.3 ($J_{C1\text{-}H1}$ = 182 Hz, C-1^{Api}), 99.2 ($J_{C1\text{-}H1}$ = 172 Hz, C-1^{Fuc}) 98.87 ($J_{C1\text{-}H1}$ = 175 Hz, C-1^{Xyl}), 98.84 ($J_{C1\text{-}H1}$ = 175 Hz, C-1^{Gal}), 98.6 ($J_{C1\text{-}H1}$ = 176 Hz, C-1^{Rha}), **HRMS:** calcd. for $C_{96}H_{119}NO_{27}Si$: 1763.8077 [M+NH_4]$^+$, found 1763.8090; **TLC** (tol/EtOAc 83:17): R_f = 0.32 (CH stain, UV).

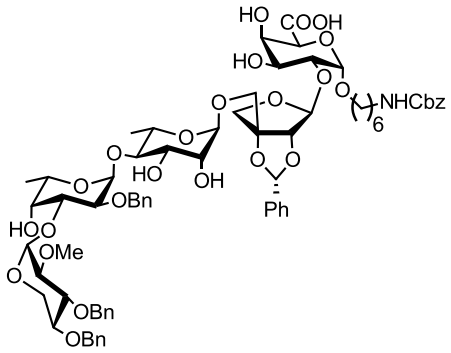
(6-*N*-Benzyloxycarbonylamino)-1-hexyl 3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)-4-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl-(1→4)-2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-3,4-*O*-isopropylidene-α-D-galactopyranoside (**128**)



The anomeric mixture of pentasaccharides **84** (66.9 mg, 38.3 µmol, 1.0 eq) was dissolved in THF (0.32 mL), and AcOH (22.0 µL, 383 µmol, 10 eq) and subsequently 1 M TBAF solution in THF (0.19 µL, 0.19 mmol, 5.0 eq) were added at rt under stirring. After 5 h of stirring, the starting material was fully converted as analyzed by TLC, so the reaction mixture was concentrated and the resulting residue purified by flash chromatography (hex/EtOAc 50:50) to yield alcohol **128** as the pure α anomer (42.0 mg, 67%) and β-anomer alcohol (15.4 mg, 25%) as colorless foams. **For 128-α: ^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 8.09 (m, 2 H, $H^{Ar\ Bz}$), 7.82 (m, 2 H, $H^{Ar\ Bz}$), 7.70 (m, 1 H, $H^{Ar\ Bz}$), 7.64-7.50 (m, 5 H, $H^{Ar\ Bz}$), 7.47-7.21 7.20-7.06 (2 m, 20 H 5 H, $H^{Ar\ Ph\ 1-5}$), 6.28 (bt, 1H, NH), 6.15 (s, 1H, PhCH), 5.80-5.68 (m, 2 H, H-2^{Rha} H-3^{Rha}), 5.49 (s, 1 H, H-1^{Api}), 5.28 (dd, J = 1.3 Hz J = 3.4 Hz, 1 H, H-4^{Fuc}), 5.21 (d, J_{1-2} = 3.6 Hz, 1H, H-1^{Fuc}), 5.18 (d, J_{1-2} = 1.6 Hz, 1 H, H-1^{Rha}), 5.05-5.01 (m, 3 H, H-1^{Xyl} $PhCH_2$), 4.93 (d, J_{1-2} = 3.3 Hz, 1 H, H-1^{Gal}), 4.77, 4.74 (2 d, $J_{OCH2\text{-}OCH2'}$ = 11.5 Hz, 1 H, $PhCH_2{}^{Xyl\text{-}3}$), 4.71-4.66 (m, 2 H, H-2^{Api} $PhCH_2{}^{Xyl\text{-}4}$), 4.64 (d, $J_{OCH2\text{-}OCH2'}$ = 11.5 Hz, 1 H, $PhCH_2{}'^{Xyl\text{-}4}$), 4.35 (d, $J_{OCH2\text{-}OCH2'}$ = 12.1 Hz, 1 H, $PhCH_2{}^{Fuc}$), 4.32-4.09 (m, 9 H, H-4^{Gal} $PhCH_2{}'^{Fuc}$ H-5^{Fuc} H 3^{Gal} H-4a^{Api} H-5^{Rha} H-3'a^{Api} H-4^{Rha} H-3^{Fuc}), 4.09-3.98 (m, 3 H, H-3'b^{Api} H-4b^{Api} H-5^{Gal}), 3.83 (t, $J_{OH\text{-}6}$ = 5.9 Hz, 1 H, OH), 3.78-3.70 (m, 4 H, H-2^{Gal} OCH_2 H-6a^{Gal} H-6b^{Gal}), 3.68 (dd, J_{1-2} = 3.7 Hz, J_{1-2} = 10.3 Hz, 1 H, H-2^{Fuc}), 3.64-3.53 (m, 3 H, H-5a^{Xyl} H-5b^{Xyl} H-3^{Xyl}), 3.50-3.37 (m, 2 H, H-4^{Xyl} OCH_2'), 3.18-3.09 (m, 5 H, OCH_3 CH_2N), 3.01 (dd, J_{1-2} = 3.5 Hz, J_{2-3} = 9.8 Hz, 1 H, H-2^{Xyl}), 2.05 (s, 3 H, $CH_3{}^{Ac}$), 1.68-1.58 (m, 2 H, -CH_2-), 1.58-1.47 (m, 8 H, -CH_2- H-6^{Rha} $CH_3{}^{iPrA}$), 1.46-1.32 (m, 4 H, -CH_2- -CH_2-), 1.29 (s, 3 H, $CH_3{}^{iPrA'}$), 1.03 (d, $J_{6\text{-}5}$ = 6.5 Hz, 3 H, H-6^{Fuc}); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 170.7, 166.0, 165.6 ($C{=}O^{Ac}$ $C{=}O^{Bz}$ $C{=}O^{Bz}$), 157.1 (N(C=O)O), 140.4, 140.0, 139.5, 138.5, 137.9 ($C^{Ar\ Ph1\text{-}5}$), 134.5, 133.9 ($C^{Ar\ Bz}$ $C^{Ar\ Bz'}$), 130.8, 130.51, 130.48, 130.4, 129.6, 129.23, 129.16, 129.03, 129.01, 128.9, 128.8, 128.6, 128.5, 128.43, 128.39, 128.24, 128.20, 128.0, 127.95, 127.86 ($C^{Ar\ Bz}$ $C^{Ar\ Bz'}$ $C^{Ph1\text{-}5}$), 109.5 (O<u>C</u>Me_2O), 108.2 (C-1^{Api}), 107.2 (Ph<u>C</u>H), 99.2 (C-1^{Fuc}) 98.8 (C-1^{Xyl} C-1^{Gal}), 98.6 (C-1^{Rha}), 92.0 (C-3^{Api}), 87.7 (C-2^{Api}), 82.8 (C-2^{Xyl}), 81.5 (C-3^{Xyl}) 78.9 (C-4^{Xyl}), 78.2 (C-4^{Rha}), 77.4 (C-2^{Gal}), 76.4 (C-3^{Gal}), 76.2 (C-2^{Fuc}), 75.4 ($PhCH_2{}^{Xyl\text{-}3}$), 74.6 (C-4^{Gal}), 74.2 (C-4^{Fuc}), 73.8 (C-$3'^{Api}$), 73.7 (C-3^{Fuc}), 73.3 ($PhCH_2{}^{Xyl\text{-}4}$), 73.2 (C-3^{Rha})

73.0 ($PhCH_2^{Fuc}$), 71.4 (C-2^{Rha}), 69.7 (C-4^{Api}), 69.1 (C-5^{Gal}), 68.7 (OCH_2-), 68.4 (C-5^{Rha}), 66.7 (C-5^{Fuc}), 66.3 (OCH_2Ph), 62.3 (C-6^{Gal}), 61.0 (C-5^{Xyl}), 59.4 (OCH_3), 41.5 (-CH_2N), 30.7, 30.2 (-CH_2- -CH_2-), 28.6 (CH_3^{iPrA}), 27.2 (-CH_2-), 26.70 (-CH_2-), 26.64 ($CH_3^{iPrA\,'}$), 20.8 (CH_3^{Ac}), 19.0 (C-6^{Rha}), 16.4 (C-6^{Fuc}); **HRMS**: calcd. for $C_{90}H_{105}NO_{27}$: 1654.6766 $[M+Na]^+$, found 1654.6755; **TLC** (hex/EtOAc 50:50): R_f = 0.27 (CH stain, UV).

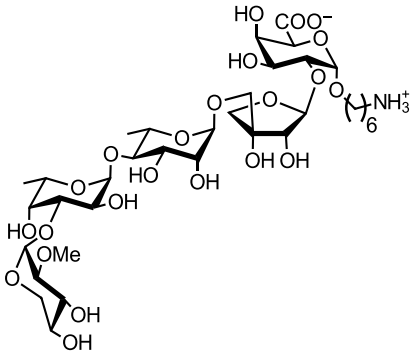
(6-*N*-Benzyloxycarbonylamino)-1-hexyl 3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)-2-*O*-benzyl-α-L-fucopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-α-D-galactopyranosyluronic acid (**129**)



Pentasaccharide **128** (41.0 mg, 25.1 µmol, 1.0 eq) was dissolved in anh. CH_2Cl_2 (1.0 mL) under a layer of argon, and DMP (16.0 mg, 37.7 µmol, 1.5 eq) was added. The solution was stirred for 1 h at rt and quenched by the addition of sat. aq. $Na_2S_2O_3$ solution and diluted with Et_2O. After stirring the mixture for 30 min, the phases were separated and the organic layer was washed with sat. aq. $NaHCO_3$ solution. The combined aqueous phase was extracted with Et_2O and the phases were separated. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude aldehyde (50.5 mg) was directly used without further purification. The crude aldehyde was dissolved in *t*BuOH (1.30 mL) and THF (0.56 mL) and 2-methyl-2-butene (0.11 mL, 1.3 mmol, 50 eq) were added. In separate Eppendorf tubes, NaH_2PO_4 (29.4 mg, 188 µmol, 7.5 eq) was dissolved in H_2O (0.23 mL) and $NaClO_2$ (28.4 mg, 80%, 251 µmol, 10 eq) was dissolved in H_2O (0.23 mL). The two solutions were mixed and added to the reaction vessel. The slightly green solution was stirred for 3 h at rt, and then diluted with sat. aq. NaH_2PO_4 solution and EtOAc. The aqueous phase was extracted with EtOAc (6x), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to obtain the crude carboxylic acid which was directly employed in the next step. **TLC** (CH_2Cl_2/MeOH 96:4 + 0.1% TFA): R_f = 0.43 (CH stain, UV). The crude carboxylic acid was dissolved in AcOH (2.5 mL) and water was added (0.6 mL). The obtained suspension was attached to a rotary evaporator and rotated for 55 min at 65 °C and ambient pressure, resulting in a clear solution. Toluene (3 mL) was added and the mixture was concentrated *in vacuo* followed by coevaporation with toluene (2x 2 mL) to obtain the crude pentasaccharide diol. **TLC** (CH_2Cl_2/MeOH 96:4 + 0.1% TFA): R_f = 0.33 (CH stain, UV). The crude pentasaccharide diol was dissolved

in CH_2Cl_2/tol (5:1, 0.6 mL) and 0.5 M NaOMe solution in MeOH (1.00 mL, 502 µmol, 20.0 eq) was added. The mixture was stirred for 80 min at rt, at which point TLC and analysis by mass spectrometry indicated full conversion. The reaction was quenched by the addition of washed Amberlite IR 120 resin (H^+-form) and stirring was continued until a pH-value between 4-5 was reached. The mixture was filtrated and the resin thoroughly washed with MeOH (5x 1 mL). The combined filtrate was concentrated *in vacuo* and the crude residue subjected to flash chromatography (CH_2Cl_2/MeOH 96:4 + 0.1% TFA). The combined fractions were diluted with toluene prior to concentration *in vacuo* to coevaporate TFA. The partially protected pentasaccharide **129** (23.2 mg, 68%, o. 4 s.) was obtained as a colorless crystalline powder. Trace impurities can be removed by another flash chromatography using a different solvent mixture (CH_2Cl_2/MeOH 90:10 + 0.1% AcOH). **^{1}H NMR** (CD_3CN + D_2O, 600 MHz): δ = 7.54-7.14 (m, 25 H, $H^{Ar\ Ph\ 1-5}$), 5.88 (s, 1H, PhCH), 5.32 (s, 1 H, H-1^{Api}), 5.20 (d, J = 3.4 Hz, 1 H, H-1^{Xyl}), 5.11-4.97 (m, 4 H, $PhCH_2{}^{Cbz}$ H-1^{Rha} H-1^{Fuc}), 4.95 (d, J = 11.6 Hz, 1 H, $PhCH_2a^{Fuc-2}$), 4.83-4.70 (m, 4 H, $PhCH_2b^{Fuc-2}$ $PhCH_2ab^{Xyl-3}$ H-1^{GalA}), 4.66 4.62 (2d, J = 11.6 Hz, $PhCH_2{}^{Xyl-4}$), 4.51 (s, 1 H, H-2^{Api}), 4.33 (s, 1 H, H-5^{GalA}), 4.18 (s, 1 H, H-4^{GalA}), 4.06-3.90 (m, 5 H, H-3'ab^{Api} H-4a^{Api} H-3^{Fuc} H-5^{Fuc}), 3.88-3.80 (m, 4 H, H-3^{GalA} H-2^{GalA} H-2^{Fuc} H-3^{Xyl}), 3.80-3.72 (m, 3 H, H-2^{Rha} H-3^{Rha} H-4^{Fuc}), 3.72-3.60 (m, 5 H, H-4b^{Api} OCH_2a H-5^{Rha} H-5ab^{Xyl}), 3.53 (dt, J = 9.1 Hz J = 6.5 Hz, 1 H, H-4^{Xyl}), 3.45-3.31 (m, 5 H, H-4^{Rha} OCH_2b OCH_3), 3.20 (dd, J = 9.6 Hz J = 3.5 Hz, 1 H, H-2^{Xyl}), 3.05 (t, J = 7.0 Hz, 2 H, CH_2N), 1.61-1.49 (m, 2 H, -CH_2-), 1.49-1.39 (m, 2 H, -CH_2-), 1.38-1.21 (m, 7 H, -CH_2- -CH_2- H-6^{Rha}), 1.11 (d, J_{6-5} = 6.4 Hz, 3 H, H-6^{Fuc}); **^{13}C APT NMR** (CD_3CN, 150 MHz): δ = 170.5 (CO_2H^{GalA}), 157.4 (N(C=O)O), 140.4, 139.8, 139.2, 138.5, 137.7, 130.7, 129.4, 129.35, 129.32, 129.30, 129.2, 128.9, 128.80, 128.78, 128.7, 128.6, 128.3, 128.0 ($C^{Ar\ Ph1-5}$), 109.1 (C-1^{Api}), 106.6 (Ph<u>C</u>H), 101.7 (C-1^{Fuc}), 101.0 (C-1^{GalA}), 99.6 (C-1^{Xyl}), 99.4 (C-1^{Rha}), 91.9 (C-3^{Api}), 87.7 (C-2^{Api}), 84.4 (C-4^{Fuc}), 82.8 (C-2^{Xyl}), 81.7 (C-3^{Xyl}), 79.1 (C-4^{Xyl}), 78.6 (C-3^{Fuc}), 76.9 (C-2^{Fuc} C-2^{Rha}), 75.6 (Ph<u>C</u>$H_2{}^{Xyl-3}$), 74.5 (Ph<u>C</u>$H_2{}^{Fuc-2}$), 74.2 (C-3'^{Api}), 73.7 (Ph<u>C</u>$H_2{}^{Xyl-4}$), 72.9 (C-4^{Fuc}), 72.5 (C-3^{Rha}), 71.2 (C-2^{GalA}), 71.1 (C-4^{GalA}), 70.7 (C-5^{GalA}), 69.13 (OCH_2-), 69.05 (C-3^{GalA}), 68.7 (C-4^{Api}), 68.1 (C-5^{Rha}), 67.6 (C-5^{Fuc}), 66.7 ($PhCH_2{}^{Cbz}$), 61.3 (C-5^{Xyl}), 59.7 (OCH_3), 41.6 (-CH_2N), 30.5, 30.1 (-CH_2- -CH_2-), 27.2 (-CH_2-), 26.6 (-CH_2-), 18.3 (C-6^{Rha}), 16.5 (C-6^{Fuc}); **^{1}H-^{13}C coupled HMBC:** 101.7 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{Fuc}), 101.0 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{GalA}), 99.6 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Xyl}), 99.4 ($J_{C1\text{-}H1}$ = 171 Hz, C-1^{Rha}), **HRMS**: calcd. For $C_{71}H_{89}NO_{25}$: 1354.5651 [M-H]$^-$, found 1354.5655; **HPLC** (5-100% MeCN + 0.1% AcOH in 15 min, column 1): R_t = 13.462 min. **TLC** (CH_2Cl_2/MeOH 96:4 + 0.1% TFA): R_f = 0.26 (CH stain, UV).

6-Amino-1-hexyl 2-*O*-methyl-D-xylopyranosyl-(1→3)-α-L-fucopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3')-β-D-apiofuranosyl-(1→2)-α-D-galactopyranosyluronic acid (**83**)

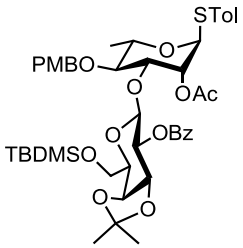


Partially protected pentasaccharide **129** (7.45 mg, 5.49 µmol, 1.0 eq) was dissolved in *t*BuOH/H_2O (0.55 mL, 50:50). The stirred mixture was degassed in a pressure reactor and set under argon atmosphere (6 cycles). Pd/C (7.6 mg, 10% wt. unreduced) was added and the stirred suspension degassed and set under hydrogen (6 cycles). Pressure was adjusted to 8 bar and stirring was continued for 63 h at rt. The reaction was found complete by LCMS and the crude mix was degassed and set under argon atmosphere and then filtered over a syringe filter (0.45 µm, PTFE). The filter was washed thoroughly with *t*BuOH/H_2O, H_2O, MeCN/H_2O, MeCN and then H_2O. The filtrate was concentrated *in vacuo*. The crude was purified by RP-chromatography (Waters C18 Seppack 500 mg, MeCN/H_2O 0:100 to 20:80) and the fractions were subsequently lyophilized to obtain pentasaccharide **83** (5.10 mg, quant.) as colorless powder. **^{1}H NMR** (D_2O, 600 MHz): δ = 5.43 (d, J = 3.7 Hz, 1 H, H-1^{Xyl}), 5.31 (d, J = 4.3 Hz, 1 H, H-1^{Fuc}), 5.21 (d, J = 2.2 Hz, 1 H, H-1^{Api}), 5.08 (d, J = 4.0 Hz, 1 H, H-1^{GalA}), 4.81 (d, J = 1.5 Hz, 1 H, H-1^{Rha}), 4.30 (dd, 1 H, J = 3.3 Hz J = 1.0 Hz, H-4^{GalA}), 4.23 (d, 1 H, J = 1.0 Hz, H-5^{GalA}), 4.20 (dq, 1 H, J = 6.6 Hz J = 0.7 Hz, H-5^{Fuc}), 4.16 (d, 1 H, J = 2.2 Hz, H-2^{Api}), 4.07 (dd, 1 H, J = 3.3 Hz J = 9.4 Hz, H-3^{Rha}), 4.05-3.99 (m, 3 H, H-2^{Fuc} H-4a^{Api} H-2^{Rha}), 3.97 (dd, J = 0.7 Hz J = 3.2 Hz, 1 H, H-4^{Fuc}), 3.96-3.89 (m, 4 H, H-3^{GalA} H-4b^{Api} H-3'a^{Api} H-3^{Fuc}), 3.84 (dq, 1 H, J = 6.2 Hz J = 9.6 Hz, H-5^{Rha}), 3.79 (dd, J = 4.0 Hz J = 10.2 Hz, 1 H, H-2^{GalA}), 3.78-3.69 (m, 3 H, H-3^{Xyl} H-6a^{Xyl} OCH_2a), 3.68-3.63 (m, 2 H, H-5^{Xyl} H-6b^{Xyl}), 3.63-3.54 (m, 3 H, OCH_2b H-3'b^{Api}), 3.52 (s, 3 H, OCH_3), 3.31 (dd, J = 9.8 Hz J = 3.7 Hz, 1 H, H-2^{Xyl}), 2.98 (t, J = 7.6 Hz, 2 H, CH_2N), 1.73-1.57 (m, 4 H, -CH_2- -CH_2-), 1.48-1.30 (m, 7 H, -CH_2-CH_2- H-6^{Rha}), 1.23 (d, J = 6.6 Hz, 3 H, H-6^{Fuc}); **^{13}C APT NMR** (D_2O, 150 MHz): δ = 176.2 (CO_2H^{GalA}), 111.0 (C-1^{Api}), 101.1 (C-1^{Fuc}), 100.6 (C-1^{Rha}), 98.8 (C-1^{GalA}), 98.3 (C-1^{Xyl}), 81.6 (C-4^{Rha}), 81.2 (C-2^{Xyl}), 79.1 (C-3^{Api}), 77.9 (C-3^{Fuc}), 77.5 (C-2^{Api}), 77.2 (C-2^{GalA}), 74.3 (C-4^{Api}), 72.6 (C-3^{Xyl}), 72.4 (C-4^{Fuc}), 71.9 (C-4^{GalA}), 71.6 (C-3^{Rha}), 71.3 (C-4^{GalA}), 70.6 (C-2^{Rha}), 70.3 (C-3'^{Api}), 70.1 (C-4^{Xyl}), 69.5 (C-3^{GalA}), 68.9 (OCH_2), 68.3 (C-2^{Fuc}), 67.9 (C-5^{Fuc}), 67.8 (C-5^{Rha}), 62.0 (C-5^{Xyl}), 58.3 (OCH_3), 40.1 (-CH_2N), 29.1 27.4 (-CH_2- -CH_2-), 25.7 (-CH_2-), 25.6 (-CH_2-), 17.8 (C-6^{Rha}), 15.8 (C-6^{Fuc}); **^{1}H-^{13}C coupled HSQC:** 111.0 ($J_{C1\text{-}H1}$ = 175 Hz, C-1^{Api}), 101.1 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{Fuc}), 100.6 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Rha}), 98.8 ($J_{C1\text{-}H1}$ = 174 Hz, C-1^{GalA}), 98.3 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Xyl}); **HRMS**: calcd. For $C_{35}H_{61}NO_{23}$:

862.3562 [*M*-H]$^-$, found 862.3570; **HPLC** (0-35% MeCN + 0.1% AcOH in 15 min, column 1): R_t = 8.539 min.

4.3.11 Synthesis of pentasaccharide acceptors

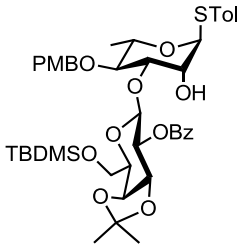
p-Tolyl 2-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→3)-2-*O*-acetyl-4-*O*-*p*-methoxybenzyl-1-thio-α-L-rhamnopyranoside (**130**)



Under argon atmosphere, thioglycoside donor **76** (550 mg, 1.01 mmol, 1.00 eq) and freshly activated molecular sieve powder 4 Å (3.40 g) were suspended in anh. CH_2Cl_2 (34 mL) and TTBP (251 mg, 1.01 mmol, 1.0 eq) was added. The mixture was stirred for 30 min at rt and then cooled to -78 °C. After stirring for another 10 min, a stock solution of AgOTf (779.0 mg, 3.03 mmol, 3.0 eq) in anh. MeCN (1.7 mL) was added directly into the cooled slurry and stirring was continued for another 10 min. Then, TolSCl (145 µL, 1.01 mmol, 1.0 eq) was added dropwise with a Hamilton syringe directly into the slurry. The yellow color of the reaction mixture vanished quickly while forming anomeric triflate intermediates. In a separate vial, under argon atmosphere acceptor alcohol **75** (437 mg, 1.01 mmol, 1.0 eq) was dissolved in anh. CH_2Cl_2 (1.40 mL) and the resulting solution was added dropwise along the walls of the flasks and the vial was washed with anh. CH_2Cl_2 (2x 1.00 mL). The mixture was stirred for 2 h while allowed to warm up to 0 °C. It was stirred for additional 30 min at 0 °C and then quenched with pyridine (1.0 mL) and filtered over a plug of celite. After extensive washing with CH_2Cl_2, the filtrate was washed with water, $NaHCO_3$ and brine (1x each). Drying over $MgSO_4$, filtration and concentration of the solution gave the crude product which was purified by flash chromatography (crude/SiO_2 100:1, tol/EtOAc 98:2 to 95:5 to 94:6) to yield the desired β-disaccharide **130** (527 mg, 61%) as a colorless foam. **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 8.00 (m, 2 H, $H^{Ar\ Bz}$), 7.59 (m, 1 H, $H^{Ar\ Bz}$), 7.42 (m, 2 H, $H^{Ar\ Bz}$), 7.36 (m, 2 H, $H^{Ar\ STol}$), 7.17 (m, 2 H, $H^{Ar\ STol}$), 7.07 (m, 2 H, $H^{Ar\ PMB}$), 6.81 (m, 2 H, $H^{Ar\ PMB}$), 5.40 (dd, $J_{2\text{-}1}$ = 1.8 Hz $J_{2\text{-}3}$ = 3.5 Hz, 1 H, H-2^{Rha}), 5.32-5.26 (m, 2 H, H-1^{Rha} H-2^{Gal}), 5.05 (d, $J_{1\text{-}2}$ = 8.2 Hz, 1 H, H-1^{Gal}), 4.57 (d, $J_{CH2\text{-}CH2'}$ = 11.0 Hz, 1 H, CH_2^{PMB}), 4.48 (dd, $J_{3\text{-}2}$ = 7.6 Hz $J_{3\text{-}4}$ = 5.3 Hz, 1 H, H-3^{Gal}), 4.40 (dd, $J_{4\text{-}3}$ = 5.3 Hz $J_{4\text{-}5}$ = 2.1 Hz, 1 H, H-4^{Gal}), 4.29 (d, $J_{CH2\text{-}CH2'}$ = 11.0 Hz, 1 H, $CH_2^{PMB'}$), 4.14-4.07 (m, 2 H, H-3^{Rha} H-5^{Gal}), 4.04 (dq, 1 H, H-5^{Rha}), 3.96-3.85 (m, 2 H, H-6a H-6b), 3.78 (s, 3 H, OCH_3), 3.38 (dd, $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 9.4 Hz, 1 H, H-4^{Rha}), 2.30 (s, 3 H, CH_3^{STol}), 2.05 (s, 3 H, CH_3^{Ac}), 1.54 (s, 3 H, CH_3^{iPrA}), 1.31 (s, 3 H, $CH_3^{iPrA'}$), 1.10 (d, $J_{4\text{-}5}$ = 9.4 Hz, 3 H, H-6^{Rha}), 0.94 (s, 9 H, $C(CH_3)_3$), 0.15 (s, 6 H, $Si(CH_3)_2$); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ =

170.4, 165.8 (C=O C=O'), 160.1 ($C^{Ar\ PMB}$), 138.7, 134.0, 133.1, 131.3, 131.0, 130.9, 130.7, 130.4, 130.2, 129.4 ($C^{Ar\ PMB}$ $C^{Ar\ Bz}$ $C^{Ar\ STol}$), 114.3 ($C^{Ar\ PMB}$), 110.5 ($O\underline{C}Me_2O$), 101.7 (C-1^{Gal}), 86.6 (C-1^{Rha}), 80.6 (C-4^{Rha}), 78.4 (C-3^{Rha}), 77.8 (C-3^{Gal}), 75.1 (OCH_2^{PMB}), 74.7 (C-2^{Gal}), 74.4 (C-2^{Rha}), 74.3 (C-4^{Gal}), 74.1 (C-5^{Gal}), 69.5 (C-5^{Rha}), 62.5 (C-6^{Gal}), 55.5 (OCH_3), 28.2 (CH_3^{iPrA}), 26.6 ($CH_3^{iPrA\ '}$), 26.3 ($C(\underline{C}H_3)_3$), 21.0 (CH_3^{STol}), 20.9 (CH_3^{Ac}), 18.9 ($Si\underline{C}Me_3$), 18.0 (C-6^{Rha}), -5.1 ($SiCH_3$), -5.3 ($SiCH_3$'); **^{1}H-^{13}C coupled HSQC:** 101.7 ($J_{C1\text{-}H1}$ = 163 Hz, C-1^{Gal}), 86.6 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Rha}); **HRMS**: calcd. for $C_{45}H_{60}O_{12}SSi$: 875.3467 $[M+Na]^+$, found 875.3474; **TLC** (tol/EtOAc 94:6): R_f = 0.41 (CH stain, UV).

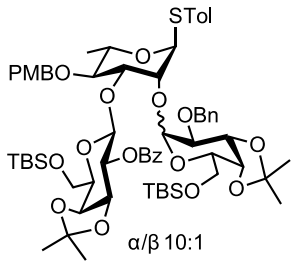
p-Tolyl 2-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→3)-4-*O*-*p*-methoxybenzyl-1-thio-α-L-rhamnopyranoside (**74**)



Under argon atmosphere, a stock solution of anh. CH_2Cl_2 (7.5 mL), anh. MeOH (54 mL), 0.5 M NaOMe solution in MeOH (3.0 mL) and guanidinium nitrate (937 mg) was prepared in a separate flask.[121] Disaccharide **130** (640 mg, 750 µmol, 1.0 eq) was dissolved in the stock solution (45 mL) at 0 °C under argon atmosphere. After stirring for 80 min, additional amounts of the stock solution (23 mL) were added and stirring was continued at 0 °C for a total of 3.5 h. TLC indicated that starting material and the diol side product had the same intensity, so the reaction was quenched with sat. aq. NH_4Cl and diluted with CH_2Cl_2. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x). The organic layers where pooled, dried over $MgSO_4$ and concentrated. The obtained crude residue was purified by flash chromatography (crude/SiO_2 100:1, tol/EtOAc 92:8 then 86:14 then 67:33) to yield alcohol **74** (420 mg, 69%) as a colorless foam as well as starting material (76.8 mg, 12%) and a diol side product (63.6 mg, 12%). **^{1}H NMR** (CD_3COCD_3, 400 MHz): δ = 8.00 (m, 2 H, $H^{Ar\ Bz}$), 7.59 (m, 1 H, $H^{Ar\ Bz}$), 7.42 (m, 2 H, $H^{Ar\ Bz}$), 7.36 (m, 2 H, $H^{Ar\ STol}$), 7.16 (m, 2 H, $H^{Ar\ STol}$), 6.99 (m, 2 H, $H^{Ar\ PMB}$), 6.75 (m, 2 H, $H^{Ar\ PMB}$), 5.39-5.32 (m, 2 H, H-2^{Gal} H-1^{Rha}), 5.07 (d, $J_{1\text{-}2}$ = 8.0 Hz, 1 H, H-1^{Gal}), 4.54 (d, $J_{CH2\text{-}CH2'}$ = 11.0 Hz, 1 H, CH_2^{PMB}), 4.50 (dd, $J_{3\text{-}2}$ = 7.3 Hz $J_{3\text{-}4}$ = 5.4 Hz, 1 H, H-3^{Gal}), 4.42 (dd, $J_{4\text{-}3}$ = 5.5 Hz $J_{4\text{-}5}$ = 2.0 Hz, 1 H, H-4^{Gal}), 4.35 (m, 1 H, H-2^{Gal}), 4.27 (d, $J_{CH2\text{-}CH2'}$ = 11.0 Hz, 1 H, $CH_2^{PMB'}$), 4.21 (ddd, $J_{5\text{-}4}$ = 2.1 Hz $J_{5\text{-}6a}$ = 5.7 Hz $J_{5\text{-}6b}$ = 8.9 Hz, 1 H, H-5^{Gal}), 4.02 (dq, $J_{5\text{-}6}$ = 6.2 Hz $J_{5\text{-}4}$ = 9.4 Hz, 1 H, H-5^{Rha}), 3.98 (dd, $J_{6a\text{-}6b}$ = 10.2 Hz $J_{5\text{-}6a}$ = 5.7 Hz, 1 H, H-6a), 3.95 (dd, $J_{3\text{-}2}$ = 3.2 Hz $J_{3\text{-}4}$ = 9.0 Hz, 1 H, H-3^{Rha}), 3.94-3.90 (m, 2 H, H-6b OH), 3.76 (s, 3 H, OCH_3), 3.44 (dd, $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 9.1 Hz, 1 H, H-4^{Rha}), 2.30 (s, 3 H, CH_3^{STol}), 1.57 (s, 3 H, CH_3^{iPrA}), 1.32 (s, 3 H, $CH_3^{iPrA'}$), 1.06 (d, $J_{4\text{-}5}$ = 6.2 Hz, 3 H, H-6^{Rha}), 0.94 (s, 9 H, $C(CH_3)_3$), 0.15 (2 s, 6 H, $Si(CH_3)_2$); **^{13}C NMR**

(CD_3COCD_3, 101 MHz): δ = 166.0 (C=O), 160.0 ($C^{Ar\ PMB}$), 138.3, 134.0, 133.1, 131.7, 131.6, 131.0, 130.6, 130.5, 130.2, 129.4 ($C^{Ar\ PMB}$ $C^{Ar\ Bz}$ $C^{Ar\ STol}$), 114.3 ($C^{Ar\ PMB}$), 110.8 (O<u>C</u>Me$_2$O), 101.7 (C-1^{Gal}), 88.9 (C-1^{Rha}), 83.2 (C-3^{Rha}), 79.9 (C-4^{Rha}), 78.1 (C-3^{Gal}), 75.0 (OCH_2^{PMB}), 74.6 (C-5^{Gal}), 74.55 (C-4^{Gal}), 74.47 (C-2^{Gal}), 72.5 (C-2^{Rha}), 69.3 (C-5^{Rha}), 63.2 (C-6^{Gal}), 55.5 (OCH_3^{PMB}), 28.1 ($CH_3^{i PrA}$), 26.6 ($CH_3^{i PrA}$'), 26.3 (C(<u>C</u>H$_3$)$_3$), 21.0 (CH_3^{STol}), 18.9 (Si<u>C</u>Me$_3$), 18.1 (C-6^{Rha}), -5.1 (SiCH$_3$), -5.3 (SiCH$_3$'); **HRMS**: calcd. for $C_{43}H_{58}O_{11}SSi$: 828.3807 $[M+NH_4]^+$, found 828.3802; **TLC** (tol/EtOAc 91:9): R_f = 0.25 (CH stain, UV).

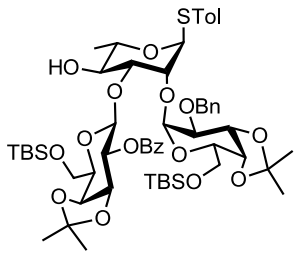
p-Tolyl 2-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→3)-[2-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-galactopyranosyl-(1→2)]-4-*O*-*p*-methoxybenzyl-1-thio-α-L-rhamnopyranoside (**131**)



Alcohol **74** (350 mg, 432 µmol, 1.0 eq) and *N*-phenyl trifluoracetimidate donor **73** (360 mg, 604 µmol, 1.4 eq) were coevaporated with toluene and dried in fine vacuum. Under argon atmosphere, freshly activated molecular sieve powder 4 Å (340 mg) was added and the mixture suspended in anh. toluene and anh. Et_2O (8.8 mL tol/Et_2O 50:50). It was stirred for 30 min at rt, and then cooled to -78 °C. After stirring for another 10 min, TfOH (9.5 µL, 0.11 mmol, 0.25 eq) was added dropwise with a Hamilton syringe and stirring continued for another 80 min while the mixture was allowed to warm up to -30 °C. The reaction was quenched with pyridine (0.5 mL) and filtered over a plug of celite. After washing with toluene, the filtrate was concentrated *in vacuo*. The obtained crude residue was purified by flash chromatography (crude/SiO_2 100:1, tol to tol/EtOAc 95:5) to yield desired trisaccharide **131** (475 mg, α/β 10:1, 90%) as a colorless foam. A sample was purified by HPLC chromatography (YMC pack SIL-06 250x10 mm, 7.0 mL/min, tol/EtOAc 96:4) for NMR characterization. For **131-α**: **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 8.03 (m, 2 H, $H^{Ar\ Bz}$), 7.59 (m, 1 H, $H^{Ar\ Bz}$), 7.42 (m, 2 H, $H^{Ar\ Bz}$), 7.35 (m, 2 H, $H^{Ar\ STol}$), 7.32 (m, 2 H, $H^{Ar\ Bn}$), 7.25-7.12 (m, 7 H, $H^{Ar\ Bn}$ $H^{Ar\ PMB}$ $H^{Ar\ STol}$), 6.89 (m, 2 H, $H^{Ar\ PMB}$), 5.59 (d, $J_{1\text{-}2}$ = 1.5 Hz, 1 H, H-1^{Rha}), 5.36 (dd, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 8.1 Hz, 1 H, H-2^{Gal}), 5.19 (d, $J_{1\text{-}2}$ = 3.3 Hz, 1 H, H-1$^{Gal'}$), 5.14 (d, $J_{1\text{-}2}$ = 8.4 Hz, 1 H, H-1^{Gal}), 4.66-4.60 (m, 2 H, CH_2^{PMB}a CH_2^{Bn}ab), 4.54 (dd, $J_{4\text{-}5}$ = 2.8 Hz $J_{3\text{-}4}$ = 5.5 Hz, 1 H, H-4$^{Gal'}$), 4.48 (ddd, $J_{5\text{-}4}$ = 2.8 Hz $J_{5\text{-}6a}$ = $J_{5\text{-}6a}$ = 6.5 Hz, 1 H, H-5$^{Gal'}$), 4.45 (dd, $J_{3\text{-}2}$ = 8.0 Hz $J_{3\text{-}4}$ = 5.2 Hz, 1 H, H-3^{Gal}), 4.39 (dd, $J_{4\text{-}3}$ = 5.3 Hz, $J_{4\text{-}3}$ = 1.8 Hz, 1 H, H-4^{Gal}), 4.35 (dd, $J_{2\text{-}1}$ = 1.6 Hz, $J_{2\text{-}3}$ = 2.9 Hz, 1 H, H-2^{Rha}), 4.33 (d, $J_{CH2a\text{-}CH2b}$ = 10.9 Hz, 1 H, CH_2^{PMB}b), 4.20 (dd, $J_{3\text{-}2}$ = 2.9 Hz, $J_{3\text{-}4}$ = 9.5 Hz, 1 H, H-3^{Rha}), 4.15 (dd, $J_{3\text{-}2}$ = 8.0 Hz,

$J_{3\text{-}4}$ = 5.4 Hz, 1 H, H-3$^{Gal'}$), 4.07-4.01 (m, 3 H, H-5^{Rha} H-5^{Gal} H-6a^{Gal}), 3.97-3.90 (m, 3 H, H-6b^{Gal} H-6ab$^{Gal'}$), 3.79 (s, 3 H, OCH_3), 3.53-3.48 (m, 2 H, H-4^{Rha} H-2$^{Gal'}$), 2.30 (s, 3 H, $CH_3{}^{STol}$), 1.58 (s, 3 H, $CH_3{}^{iPrA\ Gal}$), 1.41 (s, 3 H, $CH_3{}^{iPrA\ Gal'}$), 1.39 (s, 3 H, $CH_3{}^{iPrA\ Gal'}$), 1.32 (s, 3 H, $CH_3{}^{iPrA\ Gal}$), 1.09 (d, $J_{6\text{-}5}$ = 6.3 Hz, 3 H, H-6^{Rha}), 0.98 (s, 9 H, $C(CH_3)_3$'), 0.94 (s, 9 H, $C(CH_3)_3$), 0.16-0.15 (4 s, 12 H, $Si(CH_3)_2$ $Si(CH_3)_2$'); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 166.0 (C=O), 160.3 (C$^{Ar\ PMB}$), 140.1, 138.3, 134.1, 133.0, 131.8, 131.4, 131.0, 130.6, 130.4, 130.3, 129.5, 128.9, 128.4, 128.0 (C$^{Ar\ PMB}$ C$^{Ar\ Bz}$ C$^{Ar\ STol}$), 114.5 (C$^{Ar\ PMB}$), 110.6 (O<u>C</u>Me$_2$O^{Gal}), 109.4 (O<u>C</u>Me$_2$O$^{Gal'}$), 101.5 (C-1^{Gal}), 93.3 (C-1$^{Gal'}$), 84.9 (C-1^{Rha}), 81.5 (C-3^{Rha}), 78.3 (C-2$^{Gal'}$), 78.0 (C-3^{Gal}), 76.8 (C-3^{Rha}), 76.4 (C-3$^{Gal'}$), 75.9 (C-2^{Rha}), 75.2 (C-2^{Gal}), 75.0 ($OCH_2{}^{PMB}$), 74.74 (C-4^{Gal}), 74.66 (C-4$^{Gal'}$), 71.8 ($OCH_2{}^{Bn}$), 69.9 (C-5^{Rha}), 69.2 (C-5$^{Gal'}$), 63.8 (C-6$^{Gal'}$), 63.0 (C-6$^{Gal'}$), 55.6 (OCH_3), 28.7 ($CH_3{}^{iPrA\ Gal}$), 28.6 ($CH_3{}^{iPrA\ Gal'}$), 26.9 ($CH_3{}^{iPrA\ Gal'}$) 26.8 ($CH_3{}^{iPrA\ Gal}$), 26.7, 26.4 (C(<u>C</u>H$_3$)$_3$), 21.0 ($CH_3{}^{STol}$), 19.1 (Si<u>C</u>Me$_3{}^{Gal'}$), 18.9 (Si<u>C</u>Me$_3{}^{Gal}$), 18.1 (C-6^{Rha}), -4.6, -4.8, -4.9, -5.1 ($Si(CH_3)_2{}^{Gal}$, $Si(CH_3)_2{}^{Gal'}$); **^{1}H-^{13}C coupled HSQC:** 101.7 ($J_{C1\text{-}H1}$ = 161 Hz, C-1^{Gal}), 93.3 ($J_{C1\text{-}H1}$ = 169 Hz, C-1$^{Gal'}$), 84.9 ($J_{C1\text{-}H1}$ = 165 Hz, C-1^{Rha}); **HRMS**: calcd. for $C_{65}H_{92}O_{16}SSi_2$: 1234.5983 [M+NH_4]$^+$, found 1234.6009; **HPTLC** (tol/EtOAc 91:9): α R_f = 0.59, β R_f = 0.52 (CH stain, UV).

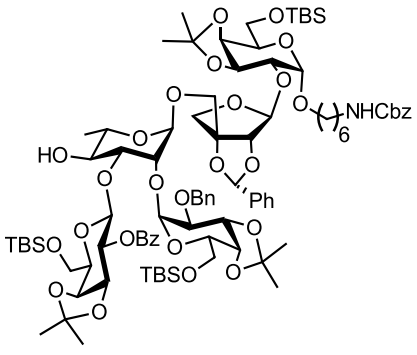
p-Tolyl 2-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→3)-[2-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranosyl-(1→2)]-1-thio-α-L-rhamnopyranoside (**70**)



Trisaccharide **131** (138 mg, α/β 10:1, 113 µmol, 1.0 eq) was dissolved in CH_2Cl_2 (7.5 mL) and phosphate buffer (0.75 mL, 0.1 M, pH 7.0) was added. The vigorously stirred emulsion was cooled to 0 °C and DDQ (103 mg, 453 µmol, 4.0 eq) was added in one portion. The ice bath was removed and stirring was continued for 2h. The reaction was quenched by the addition of a mixture of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ (8 mL, 50:50) and diluted with EtOAc. The phases were separated and the organic layer washed with sat. aq. $NaHCO_3$ and brine. The solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (tol/EtOAc 96:4 to 91:9) to obtain desired alcohol **70** as the α-anomer (99.0 mg, 80%) along with the corresponding β-isomer, which was not isolated. **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 8.09 (m, 2 H, H$^{Ar\ Bz}$), 7.62 (m, 1 H, H$^{Ar\ Bz}$), 7.49 (m, 2 H, H$^{Ar\ Bz}$), 7.36 (m, 2 H, H$^{Ar\ STol}$), 7.29 (m, 2 H, H$^{Ar\ Bn}$), 7.25-7.11 (m, 5 H, H$^{Ar\ Bn}$ H$^{Ar\ STol}$), 5.60 (d, $J_{1\text{-}2}$ = 1.3 Hz, 1 H, H-1^{Rha}), 5.30 (d, $J_{1\text{-}2}$ = 8.4 Hz, 1 H, H-1^{Gal}), 5.26 (dd, $J_{2\text{-}1}$ = 8.4 Hz, $J_{2\text{-}3}$ = 7.4 Hz, 1 H, H-2^{Gal}), 5.13 (d, $J_{1\text{-}2}$ = 3.4 Hz,

1 H, H-1$^{Gal'}$), 4.57, 4.54 (2d, $J_{CH2a-CH2b}$ = 12.6 Hz, 2 H, CH_2^{Bn}ab), 4.44-4.36 (m, 4 H, H-3^{Gal} H-4^{Gal} H-4$^{Gal'}$ H-5$^{Gal'}$), 4.30 (dd, J_{2-1} = 1.4 Hz J_{2-3} = 3.1 Hz, 1 H, H-2^{Rha}), 4.27 (d, J_{OH-4} = 6.4 Hz, 1 H, OH), 4.11 (dd, J_{3-2} = 3.2 Hz, J_{3-4} = 9.5 Hz, 1 H, H-3^{Rha}), 4.07-3.98 (m, 3 H, H-5^{Rha} H-5^{Gal} H-6a^{Gal}), 3.96-3.89 (m, 2 H, H-6b^{Gal} H-3$^{Gal'}$), 3.86 (dd, J_{6a-5} = 4.8 Hz J_{6a-6b} = 10.4 Hz, 1 H, H-6a$^{Gal'}$), 3.82 (dd, J_{6b-5} = 7.3 Hz J_{6a-6b} = 10.5 Hz, 1 H, H-6b$^{Gal'}$), 3.66 (ddd, J_{OH-4} = 6.5 Hz, J_{4-3} = J_{4-5} = 9.5 Hz, 1 H, H-4^{Rha}), 3.42 (dd, J_{4-3} = 8.1 Hz, J_{4-5} = 3.4 Hz, 1 H, H-4$^{Gal'}$), 2.30 (s, 3 H, CH_3^{STol}), 1.58 (s, 3 H, CH_3 ^{i}PrA Gal), 1.36 (s, 3 H, CH_3 ^{i}PrA Gal'), 1.34 (s, 3 H, CH_3 ^{i}PrA Gal'), 1.31 (s, 3 H, CH_3 ^{i}PrA Gal), 1.17 (d, J_{6-5} = 6.3 Hz, 3 H, H-6^{Rha}), 0.97 (s, 9 H, C(CH_3)$_3$'), 0.95 (s, 9 H, C(CH_3)$_3$), 0.16-0.13 (4 s, 12 H, Si(CH_3)$_2$ Si(CH_3)$_2$'); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 166.4 (C=O), 140.2, 138.3, 134.0, 133.0, 132.1, 131.6, 130.7, 130.5, 129.4, 128.9, 128.4, 128.0 (C$^{Ar\ PMB}$ C$^{Ar\ Bz}$ C$^{Ar\ STol}$), 110.6 (O<u>C</u>Me$_2$O^{Gal}), 109.0 (O<u>C</u>Me$_2$O$^{Gal'}$), 101.5 (C-1^{Gal}), 93.5 (C-1$^{Gal'}$), 85.3 (C-1^{Rha}), 81.5 (C-3^{Rha}), 78.4 (C-2$^{Gal'}$), 78.3 (C-3^{Gal}), 76.3 (C-3$^{Gal'}$), 75.7 (C-3^{Rha}), 75.4 (C-2^{Gal}), 74.76 (C-5^{Gal}), 74.69 (C-4^{Gal}), 74.62 (C-4$^{Gal'}$), 74.2 (C-4^{Rha}), 71.8 (OCH_2^{Bn}), 71.1 (C-5^{Rha}), 69.2 (C-5$^{Gal'}$), 63.7 (C-6$^{Gal'}$), 63.1 (C-6^{Gal}), 28.7 (CH_3 ^{i}PrA Gal), 28.6 (CH_3 ^{i}PrA Gal'), 26.9 (CH_3 ^{i}PrA Gal') 26.8 (CH_3 ^{i}PrA Gal), 26.7, 26.4 (C(<u>C</u>H$_3$)$_3$), 21.1 (CH_3^{STol}), 19.0 (Si<u>C</u>Me$_3^{Gal'}$), 18.9 (Si<u>C</u>Me$_3^{Gal}$), 17.8 (C-6^{Rha}), -4.7, -4.8, -4.9, -5.1 (Si(CH_3)$_2^{Gal}$, Si(CH_3)$_2^{Gal'}$); **^{1}H-^{13}C coupled HSQC:** 101.5 (J_{C1-H1} = 164 Hz, C-1^{Gal}), 93.5 (J_{C1-H1} = 170 Hz, C-1$^{Gal'}$), 85.3 (J_{C1-H1} = 165 Hz, C-1^{Rha}); **HRMS**: calcd. for $C_{57}H_{84}O_{15}SSi_2$: 1114.5408 [M+NH_4]$^+$, found 1114.5410; **HPTLC** (tol/EtOAc 91:9): α R_f = 0.1, β R_f = 0.24 (CH stain, UV).

(6-*N*-Benzyloxycarbonylamino)-1-hexyl 2-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→3)-[2-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranosyl-(1→2)]-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**132**)

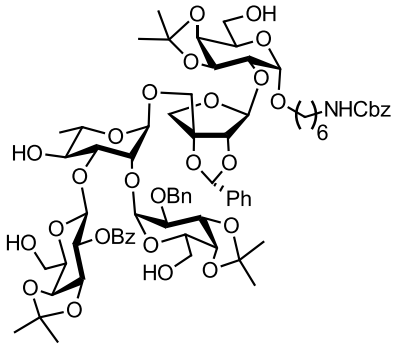


Trisaccharide donor **70** (25.0 mg, 22.7 µmol, 1.05 eq) and disaccharide acceptor **69** (17.1 mg, 21.7 µmol, 1.0 eq) were premixed and coevaporated with toluene, before all volatiles were removed in fine vacuum. Under argon atmosphere, TTBP (6.0 mg, 24 µmol, 1.1 eq) was added along with freshly activated molecular sieve powder 4 Å (75 mg), and the mixture was suspended in anh. CH_2Cl_2 (0.1 mL) and anh. Et_2O (0.8 mL). AgOTf (16.7 mg, 65.0 µmol, 3.0 eq) was added and the mixture was stirred

under the exclusion of light for 30 min. After cooling the mixture to -78 °C, TolSCl (5.4 µL, 36 µmol, 1.66 eq) was added with a Hamilton syringe directly into the solution. Over the course of 5 h the reaction was warmed up to 0 °C. At this temperature full conversion was observed by TLC within 10 min, so the reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ (0.1 mL) and diluted with CH_2Cl_2. Filtration over a plug of celite, washing with CH_2Cl_2 and concentration of the solution *in vacuo* gave the crude product which was purified by flash chromatography (2 g SiO_2 prepacked column, tol/EtOAc 20:1 to 5:1) to obtain desired pentasaccharide **132** as the α-anomer (26.0 mg, 68%) as a colorless foam. **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 8.09 (m, 2 H, $H^{Ar\ Bz}$), 7.61 (m, 1 H, $H^{Ar\ Bz}$), 7.56 (m, 2 H, $H^{Ar\ BnA}$), 7.49 (m, 2 H, $H^{Ar\ Bz}$), 7.45-7.39 (m, 3 H, $H^{Ar\ BnA}$), 7.38-7.23 (m, 9 H, $H^{Ar\ Bn}$ $H^{Ar\ CBz}$), 7.20 (m, 1 H, $H^{Ar\ Bn}$), 6.26 (t, $J_{CH2\text{-}NH}$ = 6.0 Hz, 1 H, NH), 5.97 (s, 1 H, CH^{BnA}), 5.45 (s, 1 H, H-1^{Api}), 5.34 (d, $J_{1\text{-}2}$ = 8.4 Hz, 1 H, H-1^{Gal}), 5.28 (dd, $J_{2\text{-}1}$ = 8.4 Hz, $J_{2\text{-}3}$ = 7.4 Hz, 1 H, H-2^{Gal}), 5.13 (d, $J_{1\text{-}2}$ = 3.2 Hz, 1 H, H-$1^{Gal'}$), 5.08 (d, $J_{1\text{-}2}$ = 1.6 Hz, H-1^{Rha}), 5.04 (s, 2 H, CH_2^{CBz}), 4.87 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1 H, H-$1^{Gal''}$), 4.62 (s, 1 H, H-2^{Api}), 4.59, 4.53 (2d, $J_{CH2a\text{-}CH2b}$ = 12.0 Hz, 2 H, CH_2^{Bn}ab), 4.47 (ddd, $J_{5\text{-}4}$ = 2.7 Hz $J_{5\text{-}6a}$ = 4.6 Hz $J_{5\text{-}6b}$ = 7.4 Hz, 1 H, H-$5^{Gal'}$), 4.41-4.35 (m, 3 H, H-3^{Gal} H-4^{Gal} H-$4^{Gal'}$), 4.31 (dd, Hz $J_{4\text{-}3}$ = 2.4 Hz $J_{4\text{-}5}$ = 5.3, 1 H, H-$4^{Gal''}$), 4.28 (dd, $J_{3\text{-}2}$ = 3.2 Hz $J_{3\text{-}4}$ = 9.5 Hz, 1 H, H-3^{Rha}), 4.24 (dd, $J_{3\text{-}2}$ = 8.1 Hz, $J_{3\text{-}4}$ = 5.4 Hz, 1 H, H-$3^{Gal''}$), 4.20 (d, $J_{OH\text{-}4}$ = 7.0 Hz, 1 H, OH), 4.13 (dd, $J_{2\text{-}1}$ = 1.6 Hz, $J_{2\text{-}3}$ = 3.0 Hz, 1 H, H-2^{Rha}), 4.05-3.97 (m, 4 H, H-$5^{Gal''}$ H-$4a^{Api}$ H-5^{Gal} H-$6a^{Gal}$), 3.96 (d, $J_{3'a\text{-}3'b}$ = 11.0 Hz, 1 H, H-3'a^{Api}), 3.92-3.81 (m, 7 H, H-$3^{Gal'}$ H-$6a^{Gal''}$ H-$4b^{Api}$ H-$6ab^{Gal'}$ H-$6b^{Gal}$ H-3'a^{Api}), 3.79 (dd, $J_{6a\text{-}5}$ = 6.7 Hz $J_{6a\text{-}6b}$ = 10.1 Hz, 1 H, H-$6b^{Gal''}$), 3.75-3.70 (m, 2 H, H-$2^{Gal''}$ OCH_2a), 3.66 (dq, $J_{4\text{-}5}$ = 3.4 Hz $J_{5\text{-}6}$ = 6.1 Hz, 1 H, H-5^{Rha}), 3.60 (ddd, $J_{OH\text{-}4}$ = 7.0 Hz, $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 9.4 Hz, 1 H, H-4^{Rha}), 3.43-3.37 (m, 2 H, H-$2^{Gal'}$ OCH_2b), 3.11 (dt, $J_{CH2\text{-}CH2}$ = 7.0 Hz $J_{CH2\text{-}NH}$ = 6.1 Hz , 2 H, CH_2N), 1.65-1.56 (m, 5 H, CH_2 $CH_3a^{i\text{PrA Gal}}$), 1.55-1.46 (m, 5 H, CH_2 $CH_3a^{i\text{PrA Gal''}}$), 1.45-1.29 (m, 16 H, CH_2-CH_2 $CH_3ab^{i\text{PrA Gal'}}$ $CH_3b^{i\text{PrA Gal''}}$ $CH_3b^{i\text{PrA Gal}}$), 1.21 (d, $J_{6\text{-}5}$ = 6.1 Hz, 3 H, H-6^{Rha}), 0.94, 0.91, 0.88 (3 s, 27 H, $C(CH_3)_3$ $C(CH_3)_3$' $C(CH_3)_3$''), 0.14, 0.13, 0.10, 0.05, 0.03 (5 s, 18 H, $Si(CH_3)_2$ $Si(CH_3)_2$' $Si(CH_3)_2$''); NMR data measured by Jakob Raffler: **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 166.4 (C=O), 157.2 (N(C=O)O), 140.0, 138.6, 138.1, 133.9, 131.5, 130.44, 130.39, 129.4, 129.2, 129.0, 128.8, 128.7, 128.6, 128.4, 128.2, 128.0 ($C^{Ar\ Bz}$ $C^{Ar\ BnA}$ $C^{Ar\ Bn}$ $C^{Ar\ CBz}$), 110.4 ($O\underline{C}Me_2O^{Gal}$), 109.5 ($O\underline{C}Me_2O^{Gal''}$), 108.9 ($O\underline{C}Me_2O^{Gal'}$), 108.7 (C-$1^{Api}$), 107.5 ($CH^{BnA}$), 101.3 (C-$1^{Gal}$), 99.0 (C-$1^{Gal''}$), 96.9 (C-$1^{Rha}$), 93.8 (C-$1^{Gal'}$), 92.1 (C-$3^{Api}$), 87.5 (C-$2^{Api}$), 78.12 (C-$3^{Gal}$), 78.08 (C-$2^{Gal'}$), 77.4 (C-$2^{Gal''}$), 76.3 (C-$3^{Gal''}$), 76.1 (C-$3^{Gal'}$), 75.27 (C-$2^{Gal}$), 75.19 (C-$3^{Rha}$), 74.5 (C-$4^{Gal'}$), 74.4 (C-$4^{Gal}$ C-$4^{Gal''}$), 74.3, 74.16 (C-4^{Rha} C-5^{Gal}), 74.11 (C-2^{Rha}), 74.0 (C-4^{Api}), 71.4 (OCH_2^{Bn}), 70.4 (C-5^{Rha}), 69.1 (C-$5^{Gal'}$), 68.9 (C-$5^{Gal''}$), 68.7 (C-3'^{Api}), 68.6 (OCH_2), 66.4 (OCH_2^{CBz}), 63.8 (C-$6^{Gal'}$), 63.1 (C-$6^{Gal''}$), 62.6 (C-6^{Gal}), 41.6 (CH_2N), 30.7 (CH_2), 30.3 (CH_2), 28.7 ($CH_3a^{i\text{PrA Gal}}$ $CH_3a^{i\text{PrA Gal'}}$), 28.6 ($CH_3a^{i\text{PrA Gal''}}$), 27.3 ($CH_2$), 26.9 ($CH_3b^{i\text{PrA Gal'}}$), 26.79 ($CH_2$), 26.76, 26.6 ($CH_3b^{i\text{PrA Gal}}$ $CH_3b^{i\text{PrA Gal''}}$), 26.2 ($C(\underline{C}H_3)_3$ $C(\underline{C}H_3)_3$' $C(\underline{C}H_3)_3$''), 19.0, 18.8 (3 $Si\underline{C}Me_3$), 18.0 (C-6^{Rha}), -4.7, -4.8, -5.1, -5.24, -5.27 (3 $Si(CH_3)_2$); **^{1}H-^{13}C coupled HSQC:** 108.7 ($J_{C1\text{-}H1}$ = 173 Hz, C-1^{Api}), 101.3 ($J_{C1\text{-}H1}$ = 163 Hz, C-1^{Gal}), 99.0 ($J_{C1\text{-}H1}$ = 169 Hz, C-$1^{Gal''}$), 96.9 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{Rha}), 93.8 ($J_{C1\text{-}H1}$ =

165 Hz, C-1$^{Gal'}$); **HRMS**: calcd. for $C_{91}H_{137}NO_{27}Si_3$: 1760.8759 [*M*+H]$^+$, found 1760.8746; **HPTLC** (tol/EtOAc 75:25): R_f = 0.33 (CH stain, UV).

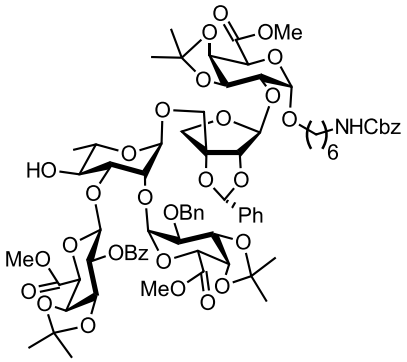
(6-*N*-Benzyloxycarbonylamino)-1-hexyl 2-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→3)-[2-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranosyl-(1→2)]-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-3,4-*O*-isopropylidene-α-D-galactopyranoside (**133**)



In a Falcon tube, a stock solution of TBAF was prepared. TBAF·H_2O (480 mg) was dissolved in anh. THF (180 µL) and sonicated in an ultrasound bath for 10 min. Then, phosphate buffer (360 µL, 0.1 M, pH 7) was added and the mixture was again sonicated for 3 min to obtain a pH 7 buffered 3.3 M stock solution of TBAF.[102] Pentasaccharide alcohol **132** (54.0 mg, 30.7 µmol, 1.0 eq) was dissolved in CH_2Cl_2, transferred in a save-lock Eppendorf tube (PP) and dried in fine vacuum. The colorless foam was dissolved in anhydrous THF (330 µL) and buffered TBAF stock solution (28.0 µL, 3.3 M, 92.0 µmol, 3.0 eq) was added. Under a layer of argon, the vessel was closed and the solution was stirred for 72 h. The solution was directly applied to a column (2 g SiO_2 prepacked column preconditioned with toluene) and the save lock Eppendorf tube was washed with small amounts of 80:20 tol/acetone, and the solution was also transferred to the column. Column chromatography (2 g SiO_2 prepacked column, tol then 80:20 to 66:33 tol/acetone). Pure tetraol **133** (30.0 mg, 69%) was obtained along with less polar partially protected intermediates. The intermediates were combined, concentrated *in vacuo* and transferred to a save lock Eppendorf tube (PP), as described. After dissolving in anh. THF (140 µL), it was treated with buffered TBAF stock solution (14 µL) and stirred for another 72 h. Workup was performed in same manner as before to give additional tetraol **133** (5.0 mg, 11% based on starting material **132**). **^{1}H NMR** (CD_3OD, 600 MHz): δ = 8.08 (m, 2 H, H$^{Ar\ Bz}$), 7.59 (m, 1 H, H$^{Ar\ Bz}$), 7.55 (m, 2 H, H$^{Ar\ BnA}$), 7.48 (m, 2 H, H$^{Ar\ Bz}$), 7.43-7.35 (m, 3 H, H$^{Ar\ BnA}$), 7.35-7.28 (m, 8 H, H$^{Ar\ Bn}$ H$^{Ar\ CBz}$), 7.21 (m, 1 H, H$^{Ar\ Bn}$), 5.95 (s, 1 H, CH^{BnA}), 5.44 (m, 1 H, H-1^{Api}), 5.21 (dd, $J_{2\text{-}1}$ = $J_{2\text{-}3}$ = 8.3 Hz, 1 H, H-2^{Gal}), 5.10 (d, $J_{1\text{-}2}$ = 8.4 Hz, 1 H, H-1^{Gal}), 5.06 (d, $J_{1\text{-}2}$ = 3.3 Hz, H-1$^{Gal'}$), 5.04 (s, 2 H, CH_2^{CBz}), 4.94-4.89 (m, 2 H, H-1^{Rha} H-1$^{Gal''}$), 4.67 (m, 1 H, H-5$^{Gal'}$), 4.61 (bs, 1 H, H-2^{Api}), 4.58, 4.54 (2d, $J_{CH2a\text{-}CH2b}$ = 12.0 Hz, 2 H, CH_2^{Bn}ab), 4.40 (dd,

$J_{4\text{-}5}$ = 2.7 Hz $J_{4\text{-}5}$ = 5.2 Hz, 1 H, H-4$^{Gal'}$), 4.34 (dd, $J_{3\text{-}2}$ = 7.3 Hz $J_{3\text{-}4}$ = 5.4 Hz, 1 H, H-3^{Gal}), 4.27-4.17 (m, 4 H, H-3$^{Gal''}$ H-4$^{Gal''}$ H-4^{Gal} H-2^{Rha}), 4.11-4.04 (m, 3 H, H-3^{Rha} H-4a^{Api} H-3$^{Gal'}$), 4.04-3.96 (m, 3 H, H-5$^{Gal''}$ H-5$^{Gal''}$ H-3'a^{Api}), 3.90 (d, $J_{4b\text{-}4a}$ = 10.2 Hz, 1 H, H-4b^{Api}), 3.88-3.77 (m, 5 H, H-6ab$^{Gal'}$ H-6ab^{Gal} H-3'b^{Api}), 3.77-3.73 (m, 3 H, H-6ab$^{Gal''}$ OCH_2a), 3.71-3.64 (m, 2 H, H-2$^{Gal''}$ H-5^{Rha}), 3.50-3.43 (m, 2 H, H-2$^{Gal'}$ H-4^{Rha}), 3.40 (dt, $J_{CH2a\text{-}CH2b}$= 9.5 Hz $J_{CH2\text{-}CH2}$= 6.5 Hz, 1 H, OCH_2b), 3.60 (t, $J_{NCH2\text{-}CH2}$ = 7.0 Hz, 1 H, NCH_2), 1.65-1.56 (m, 5 H, CH_2 CH_3a$^{i PrA Gal}$), 1.52-1.44 (m, 5 H, CH_2 CH_3a$^{i PrA Gal''}$), 1.44-1.28 (m, 16 H, CH_2-CH_2 CH_3ab $^{i PrA Gal'}$ CH_3b $^{i PrA Gal''}$ CH_3b $^{i PrA Gal}$), 1.21 (d, $J_{6\text{-}5}$ = 6.2 Hz, 3 H, H-6^{Rha}); **^{13}C NMR** (CD_3OD, 150 MHz): δ = 167.6 (C=O), 158.8 (N(C=O)O), 139.6, 138.5, 138.1, 134.4, 131.4, 130.8, 130.39, 129.6, 129.5, 129.29, 129.26, 129.1, 128.9, 128.8, 128.6, 128.5 (C$^{Ar\ Bz}$ C$^{Ar\ BnA}$ C$^{Ar\ Bn}$ C$^{Ar\ CBz}$), 111.5 (O<u>C</u>Me$_2$O^{Gal}), 110.5 (O<u>C</u>Me$_2$O$^{Gal''}$), 110.1 (O<u>C</u>Me$_2$O$^{Gal'}$), 109.0 (C-1^{Api}), 107.9 (CH^{BnA}), 102.5 (C-1^{Gal}), 99.4 (C-1$^{Gal''}$), 98.0 (C-1^{Rha}), 94.9 (C-1$^{Gal'}$), 92.5 (C-3^{Api}), 87.8 (C-2^{Api}), 78.5 (C-3^{Gal}), 78.3 (C-2$^{Gal'}$), 78.1 (C-2$^{Gal''}$), 77.2 (C-3^{Rha}), 76.8, 76.6 (C-3$^{Gal'}$C-3$^{Gal''}$), 75.6, 75.42, 73.36 (C-2^{Gal} C-3$^{Gal'}$ C-4^{Gal}), 75.1, 75.0 (C-4$^{Gal''}$ C-5^{Gal}), 74.9 (C-2^{Rha}), 74.6 (C-4^{Api}), 73.7 (C-3^{Rha}), 72.4 (OCH_2^{Bn}), 70.7 (C-5^{Rha}), 69.5 (C-5$^{Gal''}$), 69.4 (C-3'^{Api}), 69.1 (OCH_2), 68.9 (C-5$^{Gal'}$), 67.3 (OCH_2^{CBz}), 63.2 (C-6$^{Gal'}$), 62.6 (C-6$^{Gal''}$), 62.2 (C-6^{Gal}), 41.8 (CH_2N), 30.8 (CH_2), 30.5 (CH_2), 28.6, 28.5 (CH_3a$^{i PrA Gal}$ CH_3a$^{i PrA Gal''}$), 28.3 (CH_3a$^{i PrA Gal'}$), 27.6 (CH_2), 27.1 (CH_2), 26.70, 26.6 (CH_3b$^{i PrA Gal}$ CH_3b$^{i PrA Gal'}$ CH_3b$^{i PrA Gal''}$), 18.0 (C-6^{Rha}); **^{1}H-^{13}C coupled HSQC:** 109.0 ($J_{C1\text{-}H1}$ = 172 Hz, C-1^{Api}), 102.5 ($J_{C1\text{-}H1}$ = 160 Hz, C-1^{Gal}), 99.4 ($J_{C1\text{-}H1}$ = 170 Hz, C-1$^{Gal''}$), 98.0 ($J_{C1\text{-}H1}$ = 171 Hz, C-1^{Rha}), 94.9 ($J_{C1\text{-}H1}$ = 170 Hz, C-1$^{Gal'}$); **HRMS**: calcd. for $C_{73}H_{95}NO_{27}$: 1440.5984 [*M*+Na]$^+$, found 1440.5988; **HPTLC** (tol/EtOAc 63:33): R_f = 0.25 (CH stain, UV).

(6-*N*-Benzyloxycarbonylamino)-1-hexyl [methyl (2-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)uronate]-(1→3)-[[methyl (2-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranosyl)uronate]-(1→2)]-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-[methyl (3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate] (**134**)

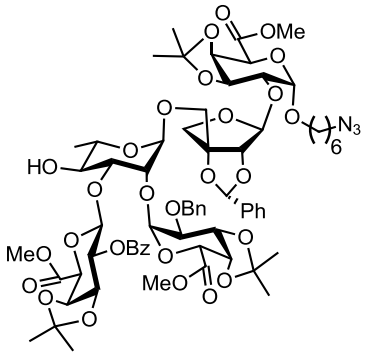


Tetraol **133** (31.0 mg, 21.9 µmol, 1.0 eq) was dissolved in MeCN (1.3 mL) and phosphate buffer (1.3 ml, 0.5 M, pH 6.7) was added. $NaClO_2$ (61.8 mg, 80%, 546 µmol, 25 eq) was dissolved in water (0.5 mL) and transferred to the previously prepared emulsion, and TEMPO (23.9 mg, 153 µmol, 7.0 eq) was added. Using a syringe pump, a solution of NaOCl (77.8 µL, 12% aq. technical grade, 153 µmol, 7.0 eq) in water

(0.50 mL) was added slowly (0.25 mL/h). The dark red solution was stirred for another 30 min at which point TLC (tol/acetone 50:50 +0.1% AcOH) indicated full conversion of the starting material. The reaction was quenched by the addition of a few drops of sat. aq. $Na_2S_2O_3$ and the colorless solution was saturated with solid $NaH_2PO_4{\cdot}2H_2O$. EtOAc was added and the phases were separated. The aqueous phase was washed with EtOAc (2 x) and the combined organic layers were dried over $MgSO_4$. Concentration gave a crude colorless syrup, which was dissolved in MeOH/tol (66:33, 4.9 mL). Under stirring, 2 M $TMSCHN_2$ solution in hexanes (0.33 mL, 0.66 mmol, 30 eq) was added. Vivid gas evolution set on and ceased quickly. After 30 min the reaction was quenched with one drop of AcOH and the yellow color vanished. After another 30 min of stirring, the reaction mixture was concentrated *in vacuo*. The obtained crude residue was taken up in tol and loaded onto a column (2 g SiO_2 prepacked column preconditioned with tol, then 50:50 hex/EtOAc) to give desired acceptor **134** (22.5 mg, 69%) as a colorless glassy solid. **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 8.08 (m, 2 H, $H^{Ar\ Bz}$), 7.63 (m, 1 H, $H^{Ar\ Bz}$), 7.57 (m, 2 H, $H^{Ar\ BnA}$), 7.50 (m, 2 H, $H^{Ar\ Bz}$), 7.43-7.39 (m, 3 H, $H^{Ar\ BnA}$), 7.39-7.31 (m, 6 H, $H^{Ar\ Bn}$ $H^{Ar\ CBz}$), 7.31-7.25 (m, 3 H, $H^{Ar\ Bn}$ $H^{Ar\ CBz}$), 7.22 (m, 1 H, $H^{Ar\ Bn}$), 6.23 (t, $J_{CH2\text{-}NH}$ = 6.2 Hz, 1 H, NH), 5.95 (s, 1 H, CH^{BnA}), 5.45 (s, 1 H, H-1^{Api}), 5.32 (d, $J_{5\text{-}4}$ = 3.0 Hz, 1 H, H-5^{GalA}), 5.27 (dd, $J_{2\text{-}1}$ = 7.9 Hz $J_{2\text{-}3}$ = 7.5 Hz, 1 H, H-$2^{GalA'}$), 5.24 (d, $J_{1\text{-}2}$ = 3.3 Hz, 1 H, H-$1^{GalA'}$), 5.22 (d, $J_{1\text{-}2}$ = 8.0 Hz, H-1^{GalA}), 5.07-5.02 (m, 2 H, H-1^{Rha} $CH_2{}^{CBz}$), 4.99 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1 H, H-$1^{GalA''}$), 4.84 (dd, $J_{4\text{-}5}$ = 3.1 Hz $J_{4\text{-}5}$ = 5.4 Hz, 1 H, H-4^{GalA}), 4.79 (d, $J_{4\text{-}5}$ = 2.6 Hz, 1 H, H-$5^{GalA'}$), 4.68-4.61 (m, 3 H, H-$5^{GalA''}$ H-$4^{GalA'}$ CH_2a^{Bn}), 4.61-4.57 (m, 2 H, $CH_2{}^{Bn}$b H-$4^{GalA''}$), 4.56 (s, 1 H, H-2^{Api}), 4.52 (dd, $J_{3\text{-}2}$ = 7.3 Hz $J_{3\text{-}4}$ = 5.4 Hz, 1 H, H-$3^{GalA'}$), 4.35 (dd, $J_{3\text{-}2}$ = 7.9 Hz $J_{3\text{-}4}$ = 5.6 Hz, 1 H, H-$3^{GalA''}$), 4.22-4.18 (m, 2 H, H-3^{GalA} H-2^{Rha}), 4.14 (dd, $J_{3\text{-}2}$ = 3.6 Hz $J_{3\text{-}4}$ = 9.5 Hz, 1 H, H-3^{Rha}), 4.04 (d, $J_{4a\text{-}4}$ = 10.2 Hz, 1 H, H-4a^{Api}), 4.01 (m, 2 H, OH H-3'a^{Api}), 3.96 (d, $J_{4b\text{-}4a}$ = 10.2 Hz, 1 H, H-4b^{Api}), 3.85 (d, $J_{4b\text{-}4a}$ = 10.9 Hz, 1 H, H-3'b^{Api}), 3.78 (dd, $J_{2\text{-}1}$ = 3.5 Hz $J_{2\text{-}3}$ = 7.9 Hz, 1 H, H-$2^{GalA''}$), 3.75-3.70 (m, 7 H, COOMe COOMe'' OCH_2a), 3.70-3.65 (m, 4 H, C-5^{Rha} COOMe'), 3.55-3.47 (m, 2 H, H-2^{GalA} H-4^{Rha}), 3.45 (dt, $J_{CH2a\text{-}Ch2b}$ = 9.5 Hz $J_{OCH2\text{-}CH2}$ = 6.5 Hz, 1 H, OCH_2b), 3.11 (t, $J_{CH2\text{-}NH}$ = 6.3 Hz $J_{NCH2\text{-}CH2}$ = 6.9 Hz, 1 H, NCH_2), 1.65-1.56 (m, 5 H, CH_2 $CH_3a^{i\text{PrA Gal}A'}$), 1.55-1.44 (m, 5 H, CH_2 $CH_3a^{i\text{PrA Gal}A''}$), 1.44-1.28 (m, 16 H, CH_2-CH_2 CH_3ab $^{i\text{PrA Gal}A}$ CH_3b $^{i\text{PrA Gal}A''}$ CH_3b $^{i\text{PrA Gal}A'}$), 1.19 (d, $J_{6\text{-}5}$ = 6.1 Hz, 3 H, H-6^{Rha}); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 169.0 (C-6^{GalA}), 168.7 (C-$6^{GalA''}$), 168.0 (C-$6^{GalA'}$), 166.2 (C=O^{Bz}), 157.2 (N(C=O)O), 139.9, 138.6, 138.0, 134.0, 131.2, 130.8, 130.5, 129.6, 129.4, 129.2, 129.0, 128.9, 128.7, 128.56, 128.54, 128.3, 128.1 ($C^{Ar\ Bz}$ $C^{Ar\ BnA}$ $C^{Ar\ Bn}$ $C^{Ar\ CBz}$), 111.2 (O<u>C</u>$Me_2O^{GalA'}$), 110.0 (O<u>C</u>$Me_2O^{GalA''}$), 109.3 (O<u>C</u>Me_2O^{GalA}), 108.2 (C-1^{Api}), 107.4 (CH^{BnA}), 102.1 (C-$1^{GalA'}$), 99.1 (C-$1^{GalA''}$), 97.1 (C-1^{Rha}), 94.2 (C-1^{GalA}), 92.0 (C-3^{Api}), 87.5 (C-2^{Api}), 77.65 (C-$3^{GalA'}$), 77.59 (C-3^{Rha}), 77.4 (C-2^{GalA}), 76.4 (C-$2^{GalA''}$), 76.1 (C-3^{GalA}), 75.9 (C-$3^{GalA''}$), 75.4 (C-$4^{GalA'}$), 75.94, 74.88 (C-4^{GalA} C-$4^{GalA''}$), 74.4 (C-$2^{GalA'}$), 74.14 (C-2^{Rha}), 74.08 (C-4^{Api}), 73.2 (C_{OH}-4^{Rha}), 73.1 (C_{OD}-4^{Rha}), 72.8 (C-$5^{GalA'}$), 71.7 ($OCH_2{}^{Bn}$), 70.2 (C-5^{Rha}), 69.3 (OCH_2), 68.9 (C-3'^{Api}), 68.2 (C-5^{Gal}), 68.1 (C-$5^{Gal''}$), 66.4 ($OCH_2{}^{Cbz}$), 52.4 (OMe), 52.1, 52.0 (OMe' OMe''), 41.5 (CH_2N), 30.7 (CH_2), 30.2 (CH_2), 28.5, 28.4 ($CH_3a^{i\text{PrA Gal}}$ $CH_3a^{i\text{PrA Gal''}}$), 27.9 ($CH_3a^{i\text{PrA Gal'}}$), 27.3 ($CH_2$), 26.73, 26.67, 26.63 ($CH_3b^{i\text{PrA Gal}}$ $CH_3b^{i\text{PrA Gal'}}$ $CH_3b^{i\text{PrA Gal''}}$), 26.6 ($CH_2$), 18.0

(C-6^{Rha}); **^{1}H-^{13}C coupled HMBC:** 108.2 ($J_{C1\text{-}H1}$ = 175 Hz, C-1^{Api}), 102.1 ($J_{C1\text{-}H1}$ = 163 Hz, C-1$^{GalA'}$), 99.1 ($J_{C1\text{-}H1}$ = 170 Hz, C-1$^{GalA''}$), 97.1 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Rha}), 94.2 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{GalA}); **HRMS**: calcd. for $C_{76}H_{95}NO_{30}$: 1519.6277 [*M*+NH_4]$^+$, found 1519.6292; **HPTLC** (Hex/EtOAc 50:50): R_f = 0.52 (CH stain, UV).

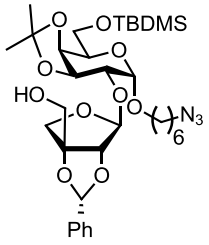
6-Azido-1-hexyl [methyl (2-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)uronate]-(1→3)-[[methyl (2-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranosyl)uronate]-(1→2)]-α-L-rhamnopyranosyl-(1→3')-2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-[methyl (3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate] (**67**)



Under argon atmosphere, pentasaccharide alcohol **134** (13.3 mg, 8.85 µmol, 1.0 eq) was dissolved in *t*BuOH/H_2O (66:33, 0.4 mL), and NH_4Cl (5.2 mg, 9.7 µmol, 1.1 eq) was added. Palladium on carbon (10% wt. unreduced, 6.5 mg) was added and a hydrogen atmosphere was established using a rubber balloon and repeated application of reduced pressure (6x). After 75 min of stirring at rt, the reaction mixture was set under argon atmosphere, and the suspension was filtered over a syringe filter (PTFE, 0.45 µL) and was washed with MeOH. The filtrate was concentrated *in vacuo* to obtain the crude pentasaccharide amine·HCl. Under a layer of argon, $CuSO_4 \cdot 5H_2O$ (0.1 mg, 0.4 µmol, 0.05 eq) and imidazole-1-sulfonyl azide·HCl (2.6 mg, 12 µmol, 1.4 eq) were added and the mixture was dissolved in a solution of NEt_3 (6.2 µL, 44 µmol, 5.0 eq) in MeOH (44 µL). Full conversion was reached quickly in 45 min as indicated by TLC, so the reaction was quenched by the addition of sat. aq. NH_4Cl and EtOAc. The phases were separated and the org. layer washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (2 g SiO_2 prepacked column preconditioned with tol, then 50:50 hex/EtOAc) gave the desired product as well as unreacted starting material. Further purification by size exclusion chromatography (Biorad SX-20, CH_2Cl_2/tol 66:33) gave pure azide **67** as a colorless solid (7.0 mg, 57% o. 2 s.). **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 8.08 (m, 2 H, H$^{Ar\ Bz}$), 7.63 (m, 1 H, H$^{Ar\ Bz}$), 7.57 (m, 2 H, H$^{Ar\ BnA}$), 7.50 (m, 2 H, H$^{Ar\ Bz}$), 7.43-7.39 (m, 3 H, H$^{Ar\ BnA}$), 7.39-7.35 (m, 2 H, H$^{Ar\ Bn}$), 7.31-7.25 (m, 2 H, H$^{Ar\ Bn}$), 7.23 (m, 1 H, H$^{Ar\ Bn}$), 5.95 (s, 1 H, CH^{BnA}), 5.45 (s, 1 H, H-1^{Api}), 5.32 (d, $J_{5\text{-}4}$ = 3.0 Hz, 1 H, H-5^{GalA}), 5.27 (dd, $J_{2\text{-}1}$ = 8.0 Hz $J_{2\text{-}3}$ = 7.5 Hz, 1 H, H-2$^{GalA'}$), 5.24-5.21 (m, 2-H, H-1$^{GalA'}$ H-1^{GalA}), 5.05 (d, $J_{1\text{-}2}$ = 1.6 Hz, 1 H, H-1^{Rha}), 5.00 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1 H, H-1$^{GalA''}$), 4.84 (dd, $J_{4\text{-}5}$ = 3.1 Hz $J_{4\text{-}5}$ = 5.4 Hz, 1 H, H-4^{GalA}), 4.79 (d,

$J_{4\text{-}5}$ = 2.6 Hz, 1 H, H-5$^{GalA'}$), 4.68-4.65 (m, 3 H, H-5$^{GalA''}$ CH_2a^{Bn}), 4.61-4.57 (m, 2 H, H-4$^{GalA'}$ $CH_2{}^{Bn}$b), 4.58 (d, $J_{4\text{-}3}$ = 5.4 Hz $J_{4\text{-}5}$ = 2.9 Hz, 1 H, H-4$^{GalA''}$), 4.55 (s, 1 H, H-2^{Api}), 4.52 (dd, $J_{3\text{-}2}$ = 7.3 Hz $J_{3\text{-}4}$ = 5.4 Hz, 1 H, H-3$^{GalA'}$), 4.35 (dd, $J_{3\text{-}2}$ = 7.9 Hz $J_{3\text{-}4}$ = 5.6 Hz, 1 H, H-3$^{GalA''}$), 4.21-4.18 (m, 2 H, H-3^{GalA} H-2^{Rha}), 4.14 (dd, $J_{3\text{-}2}$ = 3.5 Hz $J_{3\text{-}4}$ = 9.5 Hz, 1 H, H-3^{Rha}), 4.06-4.02 (m, 2 H, H-4a^{Api} OH), 4.00 (d, $J_{4b\text{-}4a}$ = 10.8 Hz, 1 H, H-3'a^{Api}), 3.96 (d, $J_{4b\text{-}4a}$ = 10.2 Hz, 1 H, H-4b^{Api}), 3.85 (d, $J_{4b\text{-}4a}$ = 10.8 Hz, 1 H, H-3'b^{Api}), 3.78 (dd, $J_{2\text{-}1}$ = 3.6 Hz $J_{2\text{-}3}$ = 8.0 Hz, 1 H, H-2$^{GalA''}$), 3.75-3.70 (m, 7 H, COOMe COOMe'' OCH_2a), 3.70-3.64 (m, 4 H, C-5^{Rha} COOMe'), 3.54-3.43 (m, 3 H, H-2^{GalA} H-4^{Rha} OCH_2b), 3.30 (t, $J_{NCH2\text{-}CH2}$ = 6.9 Hz, 1 H, NCH_2), 1.67-1.56 (m, 7 H, CH_2 CH_2 $CH_3a^{iPrA\ GalA'}$), 1.47 (s, 3 H, $CH_3a^{iPrA\ GalA''}$), 1.46-1.29 (m, 16 H, CH_2-CH_2 $CH_3ab^{iPrA\ GalA}$ $CH_3b^{iPrA\ GalA''}$ $CH_3b^{iPrA\ GalA'}$), 1.19 (d, $J_{6\text{-}5}$ = 6.2 Hz, 3 H, H-6^{Rha}); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 169.0 (C-6^{GalA}), 168.7 (C-6$^{GalA''}$), 168.0 (C-6$^{GalA'}$), 166.2 (C=O^{Bz}), 139.8, 138.0, 134.0, 132.1, 131.2, 130.5, 129.4, 129.0, 128.9, 128.5, 128.3, 128.1 ($C^{Ar\ Bz}$ $C^{Ar\ BnA}$ $C^{Ar\ Bn}$ $C^{Ar\ CBz}$), 111.2 (O<u>C</u>$Me_2O^{GalA'}$), 110.0 (O<u>C</u>$Me_2O^{GalA''}$), 109.3 (O<u>C</u>Me_2O^{GalA}), 108.2 (C-1^{Api}), 107.4 (CH^{BnA}), 102.1 (C-1$^{GalA'}$), 99.1 (C-1$^{GalA''}$), 97.1 (C-1^{Rha}), 94.2 (C-1^{GalA}), 92.0 (C-3^{Api}), 87.5 (C-2^{Api}), 77.6 (C-3$^{GalA'}$), 77.5 (C-3^{Rha}), 77.4 (C-2^{GalA}), 76.4 (C-2$^{GalA''}$), 76.1 (C-3^{GalA}), 75.9 (C-3$^{GalA''}$), 75.3 (C-4$^{GalA'}$), 74.92 (C-4$^{GalA''}$), 74.88 (C-4^{GalA}), 74.4 (C-2$^{GalA'}$), 74.2 (C-2^{Rha}), 74.1 (C-4^{Api}), 73.2 (C_{OH}-4^{Rha}), 72.8 (C-5$^{GalA'}$), 71.7 ($OCH_2{}^{Bn}$), 70.2 (C-5^{Rha}), 69.3 (OCH_2), 69.0 (C-3'^{Api}), 68.2 (C-5^{Gal}), 68.1 (C-5$^{Gal''}$), 67.3 ($OCH_2{}^{CBz}$), 52.4 (OMe), 52.1 (OMe''), 51.98 (OMe'), 51.97 (CH_2N), 30.1 (CH_2), 29.4 (CH_2), 28.44, 28.35 ($CH_3a^{iPrA\ Gal}$ $CH_3a^{iPrA\ Gal''}$), 27.9 ($CH_3a^{iPrA\ Gal'}$), 27.2 (CH_2), 26.72, 26.66, 26.61 ($CH_3b^{iPrA\ Gal}$ $CH_3b^{iPrA\ Gal'}$ $CH_3b^{iPrA\ Gal''}$), 26.4 (CH_2), 18.0 (C-6^{Rha}); **^{1}H-^{13}C coupled HMBC:** 108.2 ($J_{C1\text{-}H1}$ = 174 Hz, C-1^{Api}), 102.1 ($J_{C1\text{-}H1}$ = 165 Hz, C-1$^{GalA'}$), 99.1 ($J_{C1\text{-}H1}$ = 171 Hz, C-1$^{GalA''}$), 97.1 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{Rha}), 94.2 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{GalA}); **HRMS**: calcd. for $C_{68}H_{87}N_3O_{28}$: 1411.5814 [M+NH_4]$^+$, found 1411.5830; **HPTLC** (hex/EtOAc 62:38): R_f = 0.44 (CH stain, UV).

6-Azido-1-hexyl 2,3-*O*-(*endo*)-benzylidene-β-D-apiofuranosyl-(1→2)-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**140**)

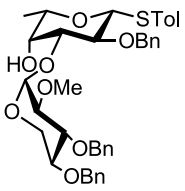


Alcohol **69** (15.0 mg, 18.7 µmol, 1.0 eq) was dissolved in *t*BuOH/H_2O (2:1, 0.33 mL), and NH_4Cl (1.1 mg, 21 µmol, 1.1 eq) was added. The mixture was placed under argon atmosphere and Pd/C (15 mg, 10% wt. unreduced) was added. By repeated degassing and flushing with H_2 (6x) a hydrogen atmosphere was established and the suspension was stirred vigorously for 90 min. After establishing an argon atmosphere to the flask, the mixture was filtered through a PTFE syringe filter (0.2 µm) and

it was washed with MeOH. Concentration *in vacuo* and removal of volatiles in fine vacuum gave a waxy colorless crude disaccharide amine·HCl, to which was added imidazole-1 sulfonyl azide · HCl (5.5 mg, 26 µmol, 1.4 eq), a catalytic amount of $CuSO_4 \cdot 5H_2O$ (0.1 mg, 0.04 µmol, 0.02 eq) and a solution of NEt_3 (13 µL, 93 µmol, 5.0 eq) in MeOH (0.10 mL). After stirring the azure mixture for 45 min, EtOAc was added followed by careful addition of sat. aq. NH_4Cl solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (2 g SiO_2 prepacked column, tol to hex/EtOAc = 80:20) gave the desired azide **140** (10.3 mg, 81% o. 2 s.) as colorless crystals. **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.52 (m, 2 H, H^{Ph}), 7.39 (m, 3 H, H^{Ph}), 5.99 (s, 1H, PhCH), 5.41 (s, 1 H, H-1^{Api}), 4.87 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1 H, H-1^{Gal}), 4.53 (s, 1 H, H-2^{Api}), 4.31-4.27 (m, 2 H, H-4^{Gal} OH), 4.22 (dd, $J_{4\text{-}3}$ = 5.5 Hz, $J_{3\text{-}2}$ = 8.1 Hz, 1 H, H-3), 4.03 (ddd, $J_{5\text{-}4}$ = 2.6 Hz, $J_{5\text{-}6a}$ = 6.6 Hz, $J_{5\text{-}6b}$ = 9.0 Hz, 1 H, H-5^{Gal}), 4.00 (d, $J_{4a\text{-}4b}$ = 10.0 Hz, 1 H, H-4a^{Api}), 3.96 (d, $J_{4b\text{-}4a}$ = 10.0 Hz, 1 H, H-4b^{Api}), 3.91-3.86 (m, 3 H, H-6a^{Gal} H-3'a^{Api} H-3'b^{Api}), 3.78 (dd, $J_{6b\text{-}5}$ = 6.7 Hz $J_{6a\text{-}6b}$ = 10.1 Hz, 1 H, H-6b^{Gal}), 3.76-3.70 (m, 2 H, OCH_2 H-2^{Gal}), 3.43 (dt, $J_{OCH2\text{-}OCH2'}$ = 9.7 Hz $J_{OCH2\text{-}CH2}$ = 6.5 Hz, 1 H, OCH_2'), 3.35 (t, $J_{NCH2\text{-}CH2}$ = 7.0 Hz, 2 H, CH_2N_3), 1.68-1.60 (m, 4 H, -CH_2- -CH_2-), 1.50-1.41 (m, 7 H, -CH_2- -CH_2- CH_3^{iPrA}), 1.30 (s, 3 H, CH_3^{iPrA}'), 0.92 (s, 9 H, $C(CH_3)_3$), 0.1 (s, 6 H, $Si(CH_3)_2$); **^{13}C NMR** (CD_3COCD_3, 101 MHz): δ = 138.4, 130.3, 129.0, 128.0 (C^{Ph}), 109.5 (O<u>C</u>Me_2O), 108.5 (C-1^{Api}), 106.9 (Ph<u>C</u>H), 99.1 (C-1^{Gal}), 93.7 (C-3^{Api}), 87.3 (C-2^{Api}), 77.3 (C-2^{Gal}), 76.3 (C-3^{Gal}), 74.3 (C-4^{Gal}), 73.9 (C-4^{Api}), 68.9 (C-5^{Gal}), 68.6 (OCH_2-), 64.1, 64.0 (C-3'$^{Api\ OH}$ C-3'$^{Api\ OD}$), 63.3 (C-6^{Gal}), 52.0 (-CH_2N_3), 30.1 (-CH_2-), 29.5 (-CH_2-), 28.7 (CH_3^{iPrA}), 27.3 (-CH_2-), 26.7 (CH_3^{iPrA}'), 26.6 (-CH_2-), 26.2 ($C(\underline{C}H_3)_3$), 18.8 (Si<u>C</u>Me_3), -5.1 ($SiCH_3$), -5.3 ($SiCH_3$'); **HRMS**: calcd. for $C_{33}H_{53}N_3O_{10}Si$: 702.3392 [*M*+Na]$^+$, found 702.3403; **TLC** (tol/EtOAc 67:33): R_f = 0.6 (CH stain, UV).

4.3.12 Synthesis of tetrasaccharide donors

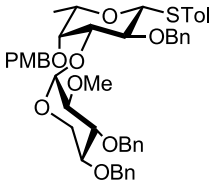
p-Tolyl 3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)-2-*O*-benzyl-1-thio-β-L-fucopyranoside (**141**)



Thioglycoside **87** (56.0 mg, 76.8 µmol, 1.0 eq), was dissolved in NaOMe solution (0.5 mL, 0.5 M in MeOH) and anh. CH_2Cl_2 (0.1 mL) was added to enhance solubility. After 90 min, TLC indicated full conversion of the starting material, so the reaction was quenched by the addition of sat. aq. NH_4Cl solution and EtOAc. The phases were separated and the organic phase was washed with brine until the pH-value of the aq. phase was found neutral. After drying the organic phase over $MgSO_4$, filtration and concentration *in vacuo*, the crude residue was purified by flash chromatography (2 g SiO_2

prepacked column, tol to tol/EtOAc 80:20) to give acceptor **141** (47.0 mg, 89%). **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.50-7.44 (m, 4 H, $H^{Ar\ Ph}$ $H^{Ar\ Ph'}$ $H^{Ar\ STol}$), 7.42-7.22 (m, 13 H, $H^{Ar\ Ph}$ $H^{Ar\ Ph'}$ $H^{Ar\ Ph''}$) 7.13 (m, 2 H, $H^{Ar\ STol}$), 5.22 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1 H, H-1^{Xyl}), 5.07 (d, $J_{CH2a,CH2b}$ = 10.7 Hz, 1 H, $PhCH_2a^{Fuc}$), 4.86, 4.84 (2 d, $J_{CH2a,CH2b}$ = 11.4 Hz, 2 H, $PhCH_2ab^{Xyl\text{-}3}$), 4.73 (d, $J_{CH2a,CH2b}$ = 11.7 Hz, 1 H, $PhCH_2a^{Xyl\text{-}4}$), 4.71-4.64 (m, 3 H, $PhCH_2b^{Fuc}$ $PhCH_2a^{Xyl\text{-}4}$ H-1^{Fuc}), 3.95 (d, $J_{OH,4}$ = 5.3 Hz, 1 H, OH), 3.93-3.87 (m, 2 H, H-3^{Xyl} H-4^{Fuc}), 3.83 (dd, $J_{5a,5b}$ = $J_{4,5a}$ = 10.9 Hz, 1 H, H-$5a^{Xyl}$), 3.79-3.72 (m, 3 H, H-2^{Fuc} H-3^{Fuc} H-5^{Fuc}), 3.68 (d, $J_{5b,4}$ =5.7 Hz, $J_{5a\text{-}5b}$ = 10.7 Hz, 1 H, H-$5b^{Xyl}$), 3.53 (ddd, 1 H, $J_{4\text{-}3}$ = 10.9 Hz, $J_{4\text{-}5a}$ = 8.9 Hz, $J_{4,5b}$ =5.7 Hz, H-4^{Xyl}), 3.35 (s, 3H, OCH_3), 3.18 (dd, $J_{1\text{-}2}$ = 3.6 Hz, $J_{2\text{-}3}$ = 9.7 Hz, H-2^{Xyl}), 2.30 (s, 3 H, CH_3^{STol}), 1.27 (d, $J_{6\text{-}5}$ = 6.4 Hz, 3 H, H-6^{Fuc}); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 140.6, 140.5, 140.0, 137.8, 132.4, 132.3, 130.4, 129.1, 129.0, 128.8, 128.6, 128.5, 128.43, 128.35, 128.04, 127.95 ($C^{Ar\ Ph}$ $C^{Ar\ Ph'}$ $C^{Ar\ Ph''}$ $C^{Ar\ STol}$), 100.1 (C-1^{Xyl}), 88.5 (C-1^{Fuc}), 84.7 (C-3^{Fuc}), 83.2 (C-2^{Xyl}), 82.1 (C-3^{Xyl}), 79.3 (C-4^{Xyl}), 77.4 (C-2^{Fuc}), 75.6 ($PhCH_2^{Xyl\text{-}3}$), 75.3 ($PhCH_2^{Fuc}$), 75.2 (C-5^{Fuc}), 73.7 ($PhCH_2^{Xyl\text{-}4}$), 72.6 (C-4^{Fuc}), 61.2 (C-5^{Xyl}), 59.8 (OCH_3), 21.1 (CH_3^{STol}), 17.2 (C-6^{Fuc}); **HRMS**: calcd. for $C_{40}H_{46}O_8S$: 704.3252 $[M+NH_4]^+$, found 704.3259; **TLC** (tol/EtOAc 83:17): R_f = 0.37 (CH stain, UV).

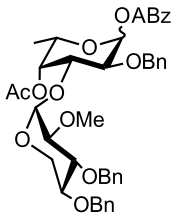
p-Tolyl 3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)-2-*O*-benzyl-4-*O*-*p*-methoxybenzyl-1-thio-β-L-fucopyranoside (**142**)



Under argon atmosphere, alcohol **141** (15.0 mg, 21.8 µmol, 1.0 eq) was dissolved in anh. DMF (0.2 mL). PMBCl (5.1 µL, 37 µmol, 1.7 eq) and NaH-dispersion (4.7 mg, 60% in mineral oil, 0.12 mmol, 5.4 eq) were added portion wise over the course of 2 h and stirring was continued for 1 h at rt. The reaction was quenched with MeOH and diluted with EtOAc and water. The phases were separated and the organic phase was washed with water and sat. aq. $NaHCO_3$ (2 x), dried over $MgSO_4$ filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (2 g SiO_2 prepacked column, tol/EtOAc 95:5) to give thioglycoside **142** (15.8 mg, 90%). **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.49-7.41 (m, 6 H, $H^{Ar\ Ph}$ $H^{Ar\ Ph'}$ $H^{Ar\ STol}$ $H^{Ar\ PMB}$), 7.38-7.21 (m, 13 H, $H^{Ar\ Ph}$ $H^{Ar\ Ph'}$ $H^{Ar\ Ph''}$), 7.05 (m, 2 H, $H^{Ar\ STol}$), 6.91 (m, 2 H, $H^{Ar\ PMB}$), 5.33 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1 H, H-1^{Xyl}), 4.96-4.93 (m, 2 H, $PhCH_2a^{Fuc\text{-}2}$ $ArCH_2a^{Fuc\text{-}4}$), 4.83, 4.80 (2 d, $J_{CH2a,CH2b}$ = 11.4 Hz, 2 H, $PhCH_2ab^{Xyl\text{-}3}$), 4.77-4.70 (m, 3 H, $PhCH_2a^{Xyl\text{-}4}$ $PhCH_2b^{Fuc\text{-}2}$ $ArCH_2b^{Fuc\text{-}4}$), 4.68 (d, $J_{CH2a,CH2b}$ = 11.8 Hz, 1 H, $PhCH_2b^{Xyl\text{-}4}$), 4.65 (d, $J_{1,2}$ = 9.5 Hz, 1 H, H-1^{Fuc}), 3.95 (d, $J_{3,2}$ = 9.4 Hz, $J_{3,4}$ = 2.9 Hz, 1 H, H-3^{Fuc}), 3.91-3.83 (m, 2 H, H-3^{Xyl} H-2^{Fuc}), 3.81-3.72 (m, 7 H, H-4^{Fuc} H-5^{Fuc} OCH_3^{PMB} H-$5ab^{Xyl}$), 3.59 (ddd, 1 H, $J_{4\text{-}3}$ = 10.0 Hz, $J_{4\text{-}5a}$ = 8.9 Hz, $J_{4,5b}$ =6.3 Hz, H-4^{Xyl}), 3.40 (s, 3H, OCH_3), 3.19 (dd,

$J_{1\text{-}2}$ = 3.6 Hz, $J_{2\text{-}3}$ = 9.8 Hz, H-2^{Xyl}), 2.28 (s, 3 H, CH_3^{STol}), 1.27 (d, $J_{6\text{-}5}$ = 6.4 Hz, 3 H, H-6^{Fuc}); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 160.3, 140.30, 140.26, 139.9, 137.6, 132.2, 132.0, 130.4, 130.3, 129.1, 129.0, 128.9, 128.55, 128.52, 128.3, 128.2, 128.1, 128.0, 114.5 (C$^{Ar\ Ph}$ C$^{Ar\ Ph'}$ C$^{Ar\ Ph''}$ C$^{Ar\ STol}$ C$^{Ar\ PMB}$), 99.4 (C-1^{Xyl}), 88.0 (C-1^{Fuc}), 82.9 (C-2^{Xyl}), 82.2 (C-3^{Xyl}), 81.5 (C-3^{Fuc}), 80.1 (C-4^{Fuc}), 79.2 (C-4^{Xyl}), 78.4 (C-2^{Fuc}), 75.7 ($PhCH_2^{Xyl\text{-}3}$), 75.33 ($ArCH_2^{Fuc\text{-}4}$), 75.30 (C-5^{Fuc}), 74.9 ($ArCH_2^{Fuc\text{-}4}$), 73.6 ($PhCH_2^{Xyl\text{-}4}$), 61.8 (C-5^{Xyl}), 60.4 (OCH_3), 55.6 (OCH_3^{PMB}), 21.1 (CH_3^{STol}), 17.7 (C-6^{Fuc}); **HRMS**: calcd. for $C_{48}H_{54}O_9S$: 824.3827 [M+NH_4]$^+$, found 824.3830; **TLC** (hex/EtOAc 67:33): R_f = 0.37 (CH stain, UV).

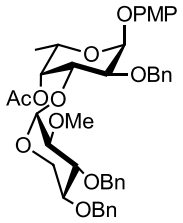
3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)-4-*O*-acetyl-2-*O*-benzyl-1-*O*-*o*-(Hex-1-yn-1-yl)-benzoyl-L-fucopyranose (**144**)



Thioglycoside **87** (34.5 mg, 47.1 µmol, 1.0 eq), was dissolved in CH_2Cl_2 (0.48 mL), and water (50 µL) was added. The stirred suspension was cooled to 0 °C and NIS (10.6 mg, 47.1 µmol, 1.0 eq), followed by TFA (3.1 µL, 47 µmol, 1.0 eq) was added. After 70 min the reaction was quenched by the addition of a mixture of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ (1:1). EtOAc was added, the phases separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (2 g SiO_2 prepacked column, tol to hex/EtOAc 91:9 to 50:50). The obtained mixed fractions were purified once again by flash chromatography (2 g SiO_2 prepacked column, tol to tol/EtOAc 66:33) to give hemiacetal **143** (22.0 mg, 75%) as a colorless solid, which was directly employed in the next step. **TLC** (hex/EtOAc 83:17): R_f = 0.13 (CH stain, UV). Hemiacetal **143** was dissolved in anh. CH_2Cl_2 (0.2 mL) and DMAP (6.5 mg, 53 µmol, 1.5 eq) and DCC (11 mg, 53 µmol, 1.5 eq) followed by freshly prepared ABzOH (11 mg, 90%, 50 µmol, 1.4 eq) were added. The mixture was stirred for 1.5 h, at which point it was found to be complete by TLC analysis. It was filtered over a plug of celite and the solids were washed with CH_2Cl_2. The filtrate was then washed with sat. aq. $NaHCO_3$, the phases were separated and the organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by column chromatography (2 g SiO_2 prepacked column, tol then tol/EtOAc 91:9) to obtain an α/β-mixture of ester **144** (26.1 mg, α/β 1:1.1, 91%) as a colorless syrup. Anomerically pure column fractions were used to characterize the anomers separately by NMR spectroscopy. For **144-α**: **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 8.01 (m, 1 H, H$^{Ar\ ABz}$), 7.60-7.54 (m, 2 H, H$^{Ar\ ABz}$), 7.46-7.20 (m, 16 H, H$^{Ar\ Ph}$ H$^{Ar\ Ph'}$ H$^{Ar\ Ph''}$ H$^{Ar\ ABz}$), 6.67 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1 H, H-1^{fuc}), 5.41 (dd, $J_{4\text{-}3}$ =

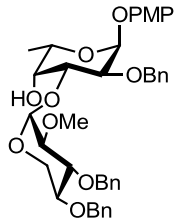
3.5 Hz, $J_{4\text{-}5}$ = 1.1 Hz, 1 H, H-4^{fuc}), 5.26 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1 H, H-1^{xyl}), 4.87-4.79 (m, 4 H, PhCH_2ab^{fuc} PhCH_2ab$^{xyl\text{-}3}$), 4.73 4.67 (2 d, $J_{CH2a,CH2b}$ = 12.0 Hz, 2 H, PhCH_2ab$^{Xyl\text{-}4}$), 4.52 (dq, $J_{5\text{-}4}$ = 1.0 Hz, $J_{5\text{-}6}$ = 6.5 Hz, 1 H, H-5^{fuc}), 4.36 (dd, $J_{3\text{-}2}$ = 10.1 Hz, $J_{3\text{-}4}$ = 3.5 Hz, 1 H, H-3^{fuc}), 4.12 (dd, $J_{1\text{-}2}$ = 3.7 Hz, $J_{2\text{-}3}$ = 10.1 Hz, 1 H, H-2^{fuc}), 3.72-3.66 (m, 2 H, H-3^{Xyl} H-5a^{Xyl}), 3.61 (dd, $J_{5a,5b}$ = 10.9 Hz, $J_{4,5a}$ = 5.7 Hz, 1 H, H-5b^{Xyl}), 3.49 (ddd, 1 H, $J_{4\text{-}3}$ = 10.8 Hz, $J_{4\text{-}5a}$ = 8.9 Hz, $J_{4,5b}$ =5.6 Hz, H-4^{Xyl}), 3.36 (s, 3H, OCH_3), 3.14 (dd, $J_{1\text{-}2}$ = 3.7 Hz, $J_{2\text{-}3}$ = 9.7 Hz, H-2^{Xyl}), 2.48 (m, 2 H, C≡C-CH_2), 2.16 (s, 3 H, CH_3^{Ac}), 1.60 (m, 2 H, $CH_2C\underline{H_2}CH_2$), 1.51 (m, 2 H, $CH_2C\underline{H_2}$Me), 1.12 (d, $J_{6\text{-}5}$ = 6.6 Hz, 3 H, H-6^{fuc}), 0.93 (t, J= 7.3 Hz, 3 H, $CH_2C\underline{H_3}$); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 170.9 (C=O^{Ac}), 165.4 (C=O^{ABz}), 140.6, 140.1, 139.5, 135.6, 133.0, 132.4, 131.6, 129.07, 129.06, 129.0, 128.50, 128.48, 128.45, 128.30, 128.26, 128.0, 125.5 (C$^{Ar\ Ph}$ C$^{Ar\ Ph'}$ C$^{Ar\ Ph''}$ C$^{Ar\ ABz}$), 99.0 (C-1^{xyl}), 96.9 (Ar-C≡$\underline{C}$-), 92.2 (C-1^{fuc}), 82.9 (C-2^{xyl}), 81.6 (C-3^{xyl}), 80.6 (Ar-$\underline{C}$≡C-), 79.0 (C-4^{xyl}), 76.6 (C-2^{fuc}), 75.5 (PhC$H_2^{xyl\text{-}3}$), 73.9 (C-3^{fuc}), 73.8 (C-4^{fuc}), 73.45 73.43 (PhC$H_2^{xyl\text{-}4}$ PhCH_2^{fuc}), 69.0 (C-5^{Fuc}), 61.3 (C-5^{Xyl}), 59.3 (OCH_3), 31.5 ($CH_2\underline{C}H_2CH_2$), 22.7 ($CH_2\underline{C}H_2CH_3$), 20.9 (CH_3^{Ac}), 20.0 (C≡C-$\underline{C}H_2$), 16.6 (C-6^{Fuc}), 14.0 ($CH_2\underline{C}H_3$); For **144-β**: **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.94 (m, 1 H, H$^{Ar\ ABz}$), 7.60-7.54 (m, 2 H, H$^{Ar\ ABz}$), 7.46-7.14 (m, 16 H, H$^{Ar\ Ph}$ H$^{Ar\ Ph'}$ H$^{Ar\ Ph''}$ H$^{Ar\ ABz}$), 5.92 (d, $J_{1\text{-}2}$ = 8.2 Hz, 1 H, H-1^{fuc}), 5.36 (dd, $J_{4\text{-}3}$ = 3.6 Hz, $J_{4\text{-}5}$ = 0.9 Hz, 1 H, H-4^{fuc}), 5.28 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1 H, H-1^{xyl}), 5.02 (d, $J_{CH2a,CH2b}$ = 11.2 Hz, 1 H, PhCH_2a^{fuc}) 4.87-4.80 (m, 3 H, PhCH_2b^{fuc} PhCH_2ab$^{xyl\text{-}3}$), 4.73 4.69 (2 d, $J_{CH2a,CH2b}$ = 12.0 Hz, 2 H, PhCH_2ab$^{Xyl\text{-}4}$), 4.17-4.11 (m, 2 H, H-3^{fuc} H-5^{fuc}), 3.93 (dd, $J_{1\text{-}2}$ = 8.2 Hz, $J_{2\text{-}3}$ = 9.7 Hz, 1 H, H-2^{fuc}), 3.74 (dd, $J_{3\text{-}2}$ = $J_{3\text{-}4}$ = 9.2 Hz, 1 H, H-3^{xyl}), 3.68-3.61 (m, 2 H, H-5ab^{Xyl}), 3.52 (ddd, 1 H, $J_{4\text{-}3}$ = 9.0 Hz, $J_{4\text{-}5a}$ = 10.1 Hz, $J_{4,5b}$ =6.3 Hz, H-4^{Xyl}), 3.40 (s, 3H, OCH_3), 3.19 (dd, $J_{1\text{-}2}$ = 3.7 Hz, $J_{2\text{-}3}$ = 9.7 Hz, H-2^{Xyl}), 2.49 (t, J = 7.1 Hz, 2 H, C≡C-CH_2), 2.17 (s, 3 H, CH_3^{Ac}), 1.63 (m, 2 H, $CH_2C\underline{H_2}CH_2$), 1.53 (m, 2 H, $CH_2C\underline{H_2}$Me), 1.16 (d, $J_{6\text{-}5}$ = 6.5 Hz, 3 H, H-6^{fuc}), 0.93 (t, J= 7.3 Hz, 3 H, $CH_2C\underline{H_3}$); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 170.8 (C=O^{Ac}), 164.8 (C=O^{ABz}), 140.5, 140.1, 139.8, 135.1, 133.2, 132.0, 131.3, 129.1, 129.0, 128.9, 128.52 128.50, 128.4, 128.3, 128.1, 128.0, 125.9 (C$^{Ar\ Ph}$ C$^{Ar\ Ph'}$ C$^{Ar\ Ph''}$ C$^{Ar\ ABz}$), 99.6 (C-1^{xyl}), 97.3 (Ar-C≡$\underline{C}$-), 95.4 (C-1^{fuc}), 82.9 (C-2^{xyl}), 81.8 (C-3^{xyl}), 80.0 (Ar-$\underline{C}$≡C-), 79.1 (C-4^{xyl} C-2^{fuc}), 78.8 (C-3^{fuc}), 75.6 (PhC$H_2^{xyl\text{-}3}$), 75.4 (PhCH_2^{fuc}), 73.43 (PhC$H_2^{xyl\text{-}4}$), 73.38 (C-4^{fuc}), 71.1 (C-5^{Fuc}), 61.4 (C-5^{Xyl}), 59.6 (OCH_3), 31.4 ($CH_2\underline{C}H_2CH_2$), 22.7 ($CH_2\underline{C}H_2CH_3$), 21.0 (CH_3^{Ac}), 20.0 (C≡C-$\underline{C}H_2$), 16.7 (C-6^{Fuc}), 14.0 ($CH_2\underline{C}H_3$); **HRMS**: calcd. for $C_{48}H_{54}O_{11}$: 824.4004 $[M+NH_4]^+$, found 824.4014; **HPTLC** (tol/EtOAc 88:12): α R_f = 0.51, β R_f = 0.40 (CH stain, UV).

p-Methoxyphenyl 3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)-4-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranoside (**145**)



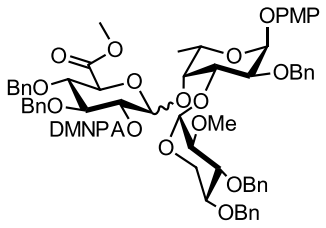
Under argon atmosphere, thioglycoside donor **87** (26.0 mg, 35.7 µmol, 1.0 eq), freshly activated molecular sieve powder 4 Å (20 mg) and *p*-methoxyphenol (13.5 mg, 107 µmol, 3.0 eq) were suspended in anh. CH_2Cl_2 and anh. Et_2O (1.62 mL, 50/50). After 1 h of stirring, the mixture was cooled to 0 °C, and then NIS (12.2 mg, 53.5 µmol, 1.5 eq) and subsequently TfOH (1.0 µL, 11 µmol, 0.3 eq) were added. The reaction was complete within 20 min as indicated by TLC, so it was quenched with pyridine (50 µL) and the mixture was filtered over a plug of celite. After washing with EtOAc, the filtrate was stirred over sat. aq. $Na_2S_2O_3$ until the color vanished. The phases were separated and the organic layer was washed with sat. aq. $NaHCO_3$ (2x) and brine. After drying over $MgSO_4$ and filtration, the organic layer was concentrated *in vacuo* and the crude residue was purified by flash chromatography (2 g SiO_2 prepacked column, tol to tol/EtOAc 94:6 to 91:9) to yield desired disaccharide **145** (26.0 mg, α/β 5:1, quant.) as a colorless foam. Another flash chromatography (2 g SiO_2 prepacked column, tol to hex/EtOAc 80:20) gave separated anomers **145-α** (22.0 mg, 80%) and **145-β** (4.0 mg, 20%) as colorless foams. For **145-α**: **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.44-7.35 (m, 6 H, $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$ $H^{Ar\ Bn''}$), 7.34-7.29 (m, 6 H, $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$ $H^{Ar\ Bn''}$), 7.29-7.23 (m, 3 H, $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$ $H^{Ar\ Bn''}$), 7.03 (m, 2 H, $H^{Ar\ PMP}$), 6.86 (m, 2 H, $H^{Ar\ PMP}$), 5.53 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1^{Fuc}), 5.38 (dd, $J_{4,3}$ = 3.6 Hz, $J_{4,5}$ = 1.3 Hz, 1 H, H-4^{Fuc}), 5.34 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1^{Xyl}), 4.87-4.80 (m, 3 H, $PhCH_2ab^{Xyl\text{-}3}$, $PhCH_2a^{Fuc}$), 4.78 (d; $J_{CH2a,CH2b}$ = 11.9 Hz, 1 H, $PhCH_2b^{Fuc}$), 4.73 (d; $J_{CH2a\text{-}CH2b}$ = 12.0 Hz, 1 H, $PhCH_2a^{Xyl\text{-}4}$), 4.68 (d; $J_{CH2a,CH2b}$ = 12.0 Hz, 1 H, $PhCH_2b^{Xyl\text{-}4}$), 4.38 (dd, $J_{3,4}$ = 3.7 Hz, $J_{3,2}$ = 10.3 Hz, 1 H, H-3^{Fuc}), 4.33 (dq, $J_{5,4}$= 1.2 Hz, $J_{5,6}$ = 6.6 Hz, 1 H, H-5^{Fuc}), 4.02 (dd, $J_{2,1}$= 3.6 Hz, $J_{2,3}$ = 10.3 Hz, 1 H, H-2^{Fuc}), 3.76 (s, 3 H, OCH_3^{PMP}), 3.73-3.67 (m, 2H, H-3^{Xyl} H-$5a^{Xyl}$), 3.63 (dd, $J_{5b,4}$= 5.7 Hz, $J_{5b,5a}$ = 10.9 Hz, H-$5b^{Xyl}$), 3.51 (ddd, $J_{4,3}$ = 10.8 Hz, $J_{4,5a}$ = 8.9 Hz, $J_{4,5b}$= 5.7 Hz, H-4^{Xyl}), 3.39 (s, 3 H, OCH_3), 3.17 (dd, $J_{2\text{-}1}$ = 3.7 Hz, $J_{2\text{-}3}$ = 9.7 Hz, 1 H, H-2^{Xyl}), 2.13 (s, 3 H, CH_3^{Ac}), 1.06 (d, $J_{6,5}$ = 6.6 Hz); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 170.9 (C=O), 156.2, 152.3 ($C^{Ar\ PMP}$), 140.6, 140.1, 139.9, 129.08, 129.06, 128.9, 128.49, 128.47, 128.45, 128.25, 128.23, 128.0 ($C^{Ar\ Bn}$, $C^{Ar\ Bn'}$, $C^{Ar\ Bn''}$), 119.3, 115.4 ($C^{Ar\ PMP}$), 98.8 (C-1^{Xyl}), 98.0 (C-1^{Fuc}), 83.0 (C-2^{Xyl}), 81.6 (C-3^{Xyl}), 79.0 (C-4^{Xyl}), 77.4 (C-2^{Fuc}), 75.5 ($CH_2^{Bn,\ Xyl\text{-}3}$), 74.0 (C-4^{Fuc}), 73.5 (C-3^{Fuc}), 73.4 ($CH_2^{Bn,\ Xyl\text{-}4}$), 73.1 ($CH_2^{Bn,\ Fuc}$), 66.6 (C-5^{Fuc}), 61.2 (C-5^{Xyl}), 59.1 (OCH_3), 55.8 (OCH_3^{PMP}), 20.9 (CH_3^{Ac}), 16.4 (C-6^{Fuc}); **^{1}H-^{13}C coupled HSQC:** 98.8 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Xyl}), 98.0 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{Fuc}); **HRMS**: calcd. for $C_{42}H_{48}O_{11}$: 746.3535 $[M+NH_4]^+$, found 746.3542; **HPTLC** (tol/EtOAc 88:12): α R_f = 0.37, β R_f = 0.31 (CH stain, UV).

p-Methoxyphenyl 3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)-2-*O*-benzyl-α-L-fucopyranoside (**79**)



Ester **145** (31.0 mg, 42.5 µmol, 1.0 eq), was dissolved in NaOMe solution (0.11 mL, 0.5 M in MeOH, 51 µmol, 1.2 eq) and anh. CH_2Cl_2 (0.11 mL) was added to enhance solubility. After 1 h, the reaction mixture was quenched by the addition of sat. aq. NH_4Cl solution and EtOAc. The phases were separated and the organic phase was washed with brine until the pH-value of the aq. layer was found neutral. After drying the organic phase over $MgSO_4$, filtration and concentration *in vacuo* gave a crude off-white solid. Flash chromatography (2 g SiO_2 prepacked column, tol to tol/EtOAc 80:20) gave alcohol **79** (26.4 mg, 90%) as a colorless solid. **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.45-7.40 (m, 4 H, $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$ $H^{Ar\ Bn''}$), 7.38-7.21 (m, 11 H, $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$ $H^{Ar\ Bn''}$), 7.03 (m, 2 H, $H^{Ar\ OPMP}$), 6.86 (m, 2 H, $H^{Ar\ OPMP}$), 5.43 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1^{Fuc}), 5.37 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1^{Xyl}), 4.90-4.83 (m, 3 H, $PhCH_2ab^{Xyl-3}$, $PhCH_2a^{Fuc}$), 4.75 (m; 2 H, $PhCH_2b^{Fuc}$ $PhCH_2a^{Xyl-4}$), 4.69 (d; $J_{CH2a-CH2b}$ = 11.7 Hz, 1 H, $PhCH_2b^{Xyl-4}$), 4.20 (dd, $J_{3,4}$ = 3.2 Hz, $J_{3,2}$ = 10.2 Hz, 1 H, H-3^{Fuc}), 4.14 (dq, $J_{5,4}$= 1.0 Hz, $J_{5,6}$ = 6.5 Hz, 1 H, H-5^{Fuc}), 4.09 (dd, $J_{2,1}$= 3.6 Hz, $J_{2,3}$ = 10.2 Hz, 1 H, H-2^{Fuc}), 4.06 (dd, $J_{OH,4}$= 4.34 Hz, J = 0.6 Hz, 1 H, OH), 3.97-3.91 (m, 2 H, H-4^{Fuc} H-3^{Xyl}), 3.79-3.73 (m, 4 H, H-$5a^{Xyl}$ OCH_3^{OPMP}), 3.71 (dd, $J_{5b,4}$= 5.8 Hz, $J_{5b,5a}$ = 10.9 Hz, 1H, H-$5b^{Xyl}$), 3.55 (ddd, $J_{4,3}$ = 10.8 Hz, $J_{4,5a}$ = 8.9 Hz, $J_{4,5b}$= 5.8 Hz, H-4^{Xyl}), 3.41 (s, 3 H, OCH_3), 3.22 (dd, $J_{2\text{-}1}$ = 3.6 Hz, $J_{2\text{-}3}$ = 9.6 Hz, 1 H, H-2^{Xyl}), 1.19 (d, $J_{6,5}$ = 6.6 Hz); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 156.1, 152.5 ($C^{Ar\ OPMP}$), 140.7, 140.2, 139.9, 129.1, 129.02, 128.95, 128.7, 128.5, 128.39, 128.34, 128.1, 128.0 ($C^{Ar\ Bn}$, $C^{Ar\ Bn'}$, $C^{Ar\ Bn''}$), 119.3, 115.3 ($C^{Ar\ OPMP}$), 99.3 (C-1^{Xyl}), 98.3 (C-1^{Fuc}), 83.2 (C-2^{Xyl}), 81.8 (C-3^{Xyl}), 79.2 (C-4^{Xyl}), 77.4 (C-3^{Fuc}), 76.4 (C-4^{Fuc}), 75.6 ($CH_2^{Bn,\ Xyl-3}$), 73.7 ($CH_2^{Bn,\ Xyl-4}$), 73.2 ($CH_2^{Bn,\ Fuc}$), 72.8 (C-4^{Fuc}), 67.8 (C-5^{Fuc}), 61.0 (C-5^{Xyl}), 59.0 (OCH_3), 55.8 (OCH_3^{OPMP}), 16.6 (C-6^{Fuc}); **HRMS**: calcd. for $C_{40}H_{46}O_{10}$: 709.2983 [*M*+Na]$^+$, found 709.2991; **HPTLC** (tol/EtOAc 83:17): R_f = 0.26 (CH stain, UV).

p-Methoxyphenyl [Methyl (3,4-di-*O*-benzyl-2-*O*-(2,2-dimethyl-2-(*o*-nitrophenyl)acetyl)-β-D-glucopyranosyl)uronate]-(1→4)-[3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)]-2-*O*-benzyl-α-L-fucopyranoside (**146**)

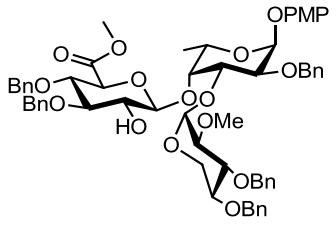


α/β 1:15

Under argon atmosphere, a saturated stock solution of AgOTf was prepared in a septum capped brown glas vial by dissolving AgOTf (1.29 g) in anh. toluene (5 mL) followed by addition of Ag_2O (100 mg). After stirring the mixture for 30 min, an aliquot was taken, all volatile compounds were evaporated in fine vacuum and the resulting residue weighed to determine the concentration (486 mM) of the saturated solution. In a separate flask thioglycoside donor **80** (80 mg, 116 µmol, 1.0 eq) and alcohol **79** (240 mg, 349 µmol, 3.0 eq) were coevaporated with toluene. After drying the residue in fine vacuum, freshly activated powdered molecular sieve 4Å (300 mg) was added under argon atmosphere and all solids were suspended in anh. CH_2Cl_2 (2.6 mL). The suspension was stirred for 30 min and then cooled to 0 °C using an ice bath. NIS (39.3 mg, 175 µmol, 1.5 eq) was added, followed by the addition of the AgOTf stock solution (7.2 µL, 486 mM, 35 µmol, 0.3 eq) with a Hamilton syringe. After 10 min, the reaction was quenched by the addition of pyridine, filtered over a plug of celite and washed with EtOAc. The organic layer was stirred over sat. aq. $Na_2S_2O_3$ until it became colorless. The phases were separated and the organic phase was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained crude was purified by flash chromatography (SiO_2/crude 100:1 tol to 91:9 to 83:17) to give the desired product **146** (92.7 mg, α/β 1:15, 64%) as a colorless foam as well as recovered acceptor (165 mg, 61%) as a colorless solid. For **146-β**: **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.82 (m, 1 H, $H^{Ar\ DMNPA}$), 7.67 (m, 1 H, $H^{Ar\ DMNPA}$), 7.60 (m, 1 H, $H^{Ar\ DMNPA}$), 7.45 (m, 1 H, $H^{Ar\ DMNPA}$), 7.42-7.37 (m, 5 H, $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$ $H^{Ar\ Bn''}$ $H^{Ar\ Bn'''}$ $H^{Ar\ Bn''''}$), 7.34-7.15 (m, 20 H, $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$ $H^{Ar\ Bn''}$ $H^{Ar\ Bn'''}$ $H^{Ar\ Bn''''}$), 6.99 (m, 2 H, $H^{Ar\ PMP}$), 6.86 (m, 2 H, $H^{Ar\ PMP}$), 5.40 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1^{Xyl}), 5.39 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1^{Fuc}), 5.20 (d, $J_{1,2}$ = 6.9 Hz, 1 H, H-1^{GlcA}), 5.12 (d, $J_{2,1}$ = $J_{2,3}$ = 6.8 Hz, 1 H, H-2^{GlcA}), 4.92, 4.89 (2 d, $J_{CH2a-CH2b}$ = 11.6 Hz, 2 H, $PhCH_2ab^{Xyl-3}$), 4.83 (d, $J_{CH2a-CH2b}$ = 11.8 Hz, 1 H, $PhCH_2a^{Fuc}$), 4.75 (d, $J_{CH2a-CH2b}$ = 11.8 Hz, 1 H, $PhCH_2a^{Xyl-4}$), 4.73-4.64 (m, 5 H, $PhCH_2b^{Fuc}$ $PhCH_2b^{Xyl-4}$ $PhCH_2ab^{GlcA-3}$ $PhCH_2a^{GlcA-4}$), 4.54 (d; $J_{CH2a-CH2b}$ = 11.2 Hz, 1 H, $PhCH_2b^{GlcA-4}$), 4.41 (dd; $J_{2,1}$ = 3.5 Hz, $J_{2,3}$ = 10.5 Hz, 1 H, H-2^{Fuc}), 4.37 (d, $J_{5,4}$ = 8.1 Hz, 1 H, H-5^{GlcA}), 4.33 (dd, $J_{3,2}$ = 10.5 Hz, $J_{3,4}$ = 2.6 Hz, 1 H, H-3^{Fuc}), 4.18-4.12 (m, 2 H-4^{Fuc} H-5^{Fuc}), 4.10 (dd, $J_{4,3}$ = $J_{4,5}$ = 10.5 Hz, 1 H, H-4^{GlcA}), 3.95 (dd, $J_{3,2}$ = $J_{3,4}$ = 9.4 Hz, 1 H, H-3^{Xyl}), 3.79 (dd, $J_{3,2}$ = 6.7 Hz, $J_{3,4}$ = 7.8 Hz, 1 H, H-3^{GlcA}), 3.76 (s, 3 H, OCH_3^{PMP}), 3.70-3.66 (m, 2 H, H-5ab^{Xyl}), 3.65 (s, 3 H, $COOCH_3$), 3.51

(ddd, $J_{4,3}$ = 9.3 Hz, $J_{4,5a}$ = 7.0 Hz, $J_{4,5b}$ = 5.3 Hz, 1 H, H-4^{Xyl}), 3.17 (dd, $J_{2,1}$ = 3.7 Hz, $J_{2,3}$ = 9.6 Hz, 1 H, H-2^{Xyl}), 3.35 (s, 3 H, OCH_3), 1.63 (s, 3 H, CH_3^{DMNPA}), 1.60 (s, 3 H, CH_3^{DMNPA}), 1.10 (d, $J_{6,5}$ = 6.7 Hz, 3 H, H-6^{Fuc}); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 174.6 (C=O^{DMNPA}), 170.1 (C-6^{GlcA}) 156.1, 152.6 (C$^{Ar\ PMP}$), 140.9, 140.3, 140.0, 139.5, 139.14, 139.07, 134.1, 129.8, 129.1, 129.0, 128.96, 128.93, 128.8, 128.5, 128.4, 128.37, 128.34, 128.14, 128.1, 127.9, 126.5 (C$^{Ar\ DMNPA}$ C$^{Ar\ Bn}$ C$^{Ar\ Bn'}$ C$^{Ar\ Bn''}$ C$^{Ar\ Bn'''}$ C$^{Ar\ Bn''''}$), 119.4, 115.4 (C$^{Ar\ PMP}$), 100.8 (C-1^{GlcA}), 98.7 (C-1^{Xyl}), 98.4 (C-1^{Fuc}), 83.3 (C-2^{Xyl}), 82.1 (C-3^{GlcA}), 81.9 (C-3^{Xyl}), 80.1 (C-4^{Fuc}), 79.8 (C-4^{GlcA}), 79.3 (C-4^{Xyl}), 77.6 (C-2^{Fuc}), 75.6 ($CH_2^{Bn\ Xyl-3}$), 75.4 (C-5^{GlcA}), 75.2 (C-2^{GlcA}), 74.4 ($CH_2^{Bn\ GlcA-4}$), 73.8 ($CH_2^{Bn\ Xyl-4}$ $CH_2^{Bn\ GlcA-3}$), 73.5 (C-3^{Fuc}), 73.4 ($CH_2^{Bn\ Fuc}$), 68.6 (C-5^{Fuc}), 61.3 (C-5^{Xyl}), 59.2 (OCH_3), 55.8 (OCH_3^{PMP}), 52.7 (COO<u>C</u>H$_3$), 47.3 (Ar<u>C</u>(CH$_3$)$_2$), 27.6 (CH_3^{DMNPA}), 27.3 ($CH_3^{DMNPA'}$), 17.1 (C-6^{Fuc}); **^{1}H-^{13}C coupled HMBC:** 100.8 ($J_{C1\text{-}H1}$ = 163 Hz, C-1^{GlcA}), 98.7 ($J_{C1\text{-}H1}$ = 164 Hz, C-1^{Xyl}), 98.3 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Fuc}); **HRMS**: calcd. for $C_{71}H_{77}NO_{19}$: 1265.5428 [M+NH_4]$^+$, found 1265.5431; **HPTLC** (tol/EtOAc 83:17): R_f = 0.54 (CH stain, UV).

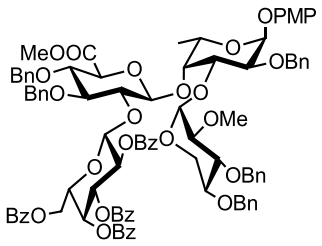
p-Methoxyphenyl [methyl (3,4-di-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-[3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)]-2-*O*-benzyl-α-L-fucopyranoside (**77**)



Trisaccharide **146** (90.0 mg, 71.9 µmol, 1.0 eq) was taken up in dioxane (90 µL) and a solution of $CuSO_4 \cdot 5\ H_2O$ (18.3 mg, 71.9 µmol, 1.0 eq) in H_2O (90 µL) and subsequently Zn dust (47.0 mg, 719 µmol, 10 eq) were added. To the stirred suspension was added acetic acid (28.8 µL, 360 µmol, 7.0 eq) and the mixture was stirred for 1 h. After dilution with EtOAc, it was filtered over a plug of celite and washed extensively with EtOAc. The filtrate was washed with sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Two step flash chromatography (2 g SiO_2 prepacked column, 90:10 tol/EtOAc, then 2 g SiO_2 prepacked column, 71:29 hex/EtOAc) gave pure alcohol **77** (61.6 mg, 81%) as a colorless syrup. **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.43-7.36 (m, 6 H, H$^{Ar\ Bn}$ H$^{Ar\ Bn'}$ H$^{Ar\ Bn''}$ H$^{Ar\ Bn'''}$ H$^{Ar\ Bn''''}$), 7.33-7.15 (m, 19 H, H$^{Ar\ Bn}$ H$^{Ar\ Bn'}$ H$^{Ar\ Bn''}$ H$^{Ar\ Bn'''}$ H$^{Ar\ Bn''''}$), 7.02 (m, 2 H, H$^{Ar\ PMP}$), 6.86 (m, 2 H, H$^{Ar\ PMP}$), 5.59 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H-1^{Xyl}), 5.39 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1^{Fuc}), 5.07 (d, $J_{CH2a\text{-}CH2b}$ = 12.0 Hz, 1 H, PhCH_2a^{GlcA-3}), 4.90-4.86 (m, 2 H, H-1^{GlcA} PhCH_2a^{Xyl-3}), 4.85-4.80 (m, 2 H, PhCH_2b^{GlcA-3} PhCH_2b^{Xyl-3}), 4.80-4.71 (m, 5 H, PhCH_2ab^{Xyl-4} PhCH_2a^{GlcA-4} PhCH_2ab^{Fuc}), 4.57 (m, 1 H, OH), 4.53 (d, $J_{CH2a\text{-}CH2b}$ = 11.0 Hz, 1 H, PhCH_2b^{GlcA-4}), 4.45 (dd, $J_{2,1}$ = 2.5 Hz, $J_{2,3}$ = 10.4 Hz, 1 H, H-3^{Fuc}), 4.32-4.27 (m, 2 H, H-2^{Fuc} H-4^{Fuc}), 4.24-4.16 (m, 2 H, H-5^{Fuc} H-5^{GlcA}), 3.98 (dd, $J_{3,2}$ = $J_{3,4}$ = 9.2 Hz, 1 H, H-3^{Xyl}), 3.78-3.70 (m,

6 H, H-4^{GlcA} OCH$_3$^{PMP} H-5a^{Xyl} H-2^{GlcA}), 3.70-3.63 (m, 5 H, COOCH$_3$ H-3^{GlcA} H-5b^{Xyl}), 3.56 (ddd, $J_{4,3}$ = 10.7 Hz, $J_{4,5a}$ = 8.9 Hz, $J_{4,5b}$ = 5.6 Hz, 1 H, H-4^{Xyl}), 3.40 (s, 3 H, OCH$_3$), 3.24 (dd, $J_{2,1}$ = 4.0 Hz, $J_{2,3}$ = 9.5 Hz, 1 H, H-2^{Xyl}), 1.24 (d, $J_{6,5}$ = 6.6 Hz, 3 H, H-6^{Fuc}); **^{13}C NMR** (CD$_3$COCD$_3$, 150 MHz): δ = 170.1 (C-6^{GlcA}) 156.1, 152.5 (C$^{Ar\ PMP}$), 140.7, 140.3, 140.1, 139.9, 139.4, 129.13, 129.10, 129.0, 128.9, 128.8, 128.6, 128.50, 128.48, 128.35, 128.29, 128.26, 128.2, 127.9, 127.8 (C$^{Ar\ Bn}$ C$^{Ar\ Bn'}$ C$^{Ar\ Bn''}$ C$^{Ar\ Bn'''}$ C$^{Ar\ Bn''''}$), 119.5, 115.4 (C$^{Ar\ PMP}$), 103.0 (C-1^{GlcA}), 98.23, 98.17 (C-1^{Xyl} C-1^{Fuc}), 85.2 (C-3^{GlcA}), 83.0 (C-2^{Xyl}), 82.1 (C-3^{Xyl}), 80.6 (C-4^{GlcA}), 78.9 (C-4^{Xyl}), 77.9 (C-2^{Fuc}), 77.6 (C-4^{Fuc}), 75.7 (CH$_2$$^{Bn\ GlcA-3}$), 75.6 (C-5^{GlcA}), 75.5 (CH$_2$$^{Bn\ Xyl-3}$), 75.3 (CH$_2$$^{Bn\ GlcA-4}$), 74.5 (C-2^{GlcA}), 73.5 (CH$_2$$^{Bn\ Xyl-4}$), 73.0 (CH$_2$$^{Bn\ Fuc}$), 72.9 (C-3^{Fuc}), 68.8 (C-5^{Fuc}), 61.3 (C-5^{Xyl}), 59.3 (OCH$_3$), 55.8 (OCH$_3$^{PMP}), 52.6 (COOCH$_3$), 17.4 (C-6^{Fuc}); **^{1}H-^{13}C coupled HMBC:** 103.0 ($J_{C1\text{-}H1}$ = 162 Hz, C-1^{GlcA}), 98.17 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{Xyl}, $J_{C1\text{-}H1}$ = 172 Hz, C-1^{Fuc}); **HRMS**: calcd. for $C_{61}H_{68}O_{16}$: 1079.4400 [M+Na]$^+$, found 1079.4412; **HPTLC** (tol/EtOAc 83:17): R_f = 0.37 (CH stain, UV).

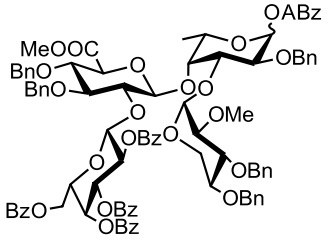
p-Methoxyphenyl 2,3,4,6-tetra-*O*-benzoyl-β-L-galactopyranosyl-(1→2)-[methyl (3,4-di-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-[3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)]-2-*O*-benzyl-α-L-fucopyranoside (**147**)



Acceptor alcohol **77** (61.0 mg, 57.7 µmol, 1.0 eq) and donor thioglycoside **122** (52.8 mg, 75.0 µmol, 1.3 eq) were coevaporated with toluene and all volatiles were removed in fine vacuum. Under argon atmosphere, freshly activated powdered molecular sieves 4 Å (120 mg) was added and the reaction mixture was suspended in anh. CH_2Cl_2 (1.2 mL). After stirring for 45 min, it was cooled down to -20 °C and NIS (21.0 mg, 97%, 92.3 µmol, 1.6 eq) and subsequently neutral AgOTf stock solution (35.8 µL, 486 mM in anh. tol, 17.3 µmol, 0.3 eq) were added. The mixture was warmed up over the course of 2 h to 0°C, then quenched with pyridine (50 µL) and filtered over a plug of celite. After washing with EtOAc, the filtrate was stirred over sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ (1:1) until the color vanished. The phases were separated, and the organic layer was washed with brine, then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (SiO_2:crude 100:1, tol/EtOAc 95:5 to 91:9 to 83:17) to give product **147** (83.7 mg, 89%) as a colorless foam. **^{1}H NMR** (CD$_3$COCD$_3$, 600 MHz): δ = 8.06-7.96 (m, 6 H, H$^{Ar\ Bz}$ H$^{Ar\ Bz'}$ H$^{Ar\ Bz''}$), 7.73 (m, 2H, H$^{Ar\ Bz'''}$), 7.66-7.16 (m, 37 H, H$^{Ar\ Bz}$ H$^{Ar\ Bz'}$ H$^{Ar\ Bz''}$ H$^{Ar\ Bz'''}$ H$^{Ar\ Bn}$ H$^{Ar\ Bn'}$ H$^{Ar\ Bn''}$ H$^{Ar\ Bn'''}$ H$^{Ar\ Bn''''}$), 7.13 (m, 2 H, H$^{Ar\ PMP}$), 6.92 (m, 2 H, H$^{Ar\ PMP}$), 6.10 (dd, $J_{4,3}$ = 3.5 Hz $J_{4,5}$ = 0.8 Hz, 1H, H-4$^{L\text{-}Gal}$), 5.95 (dd, $J_{2,1}$ = 8.0 Hz $J_{2,3}$ = 10.2 Hz, 1 H,

H-2$^{L\text{-}Gal}$), 5.90 (d, $J_{1,2}$ = 8.0 Hz, 1 H, H-1$^{L\text{-}Gal}$), 5.80 (dd, $J_{3,2}$ = 10.2 Hz $J_{3,4}$ = 3.5 Hz, 1 H, H-3$^{L\text{-}Gal}$), 5.70 (d, $J_{1,2}$ = 3.6 Hz, 1 H H-1^{Fuc}), 5.36-5.33 (m, 2 H, PhCH$_2$a$^{GlcA\text{-}3}$ H-1^{Xyl}), 5.07 (d, $J_{1,2}$ = 8.0 Hz, 1 H, H-1^{GlcA}), 4.95-4.90 (m, 3 H, PhCH$_2$ab$^{Xyl\text{-}3}$ PhCH$_2$a^{Fuc}), 4.84-4.66 (m, 7 H, PhCH$_2$b^{Fuc} PhCH$_2$b$^{GlcA\text{-}3}$ PhCH$_2$a$^{GlcA\text{-}4}$ H-6a$^{L\text{-}Gal}$ H-5$^{L\text{-}Gal}$ PhCH$_2$ab$^{Xyl\text{-}4}$), 4.58 (dd, $J_{6b,5}$ = 7.0 Hz $J_{6b,6a}$ = 10.4 Hz, 1 H, H-6b$^{L\text{-}Gal}$), 4.47-4.43 (m, 2 H, H-2^{Fuc} PhCH$_2$b$^{GlcA\text{-}4}$), 4.34-4.21 (m, 5 H, H-2^{GlcA} H-3^{Fuc} H-5^{Fuc} H-4^{Fuc}), 4.23 (d, $J_{5,4}$ = 9.3 Hz, 1H, H-5^{GlcA}), 3.86 (dd, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 8.5 Hz, 1 H, H-3^{Xyl}), 3.82-3.75 (m, 5 H, H-4^{GlcA} OCH$_3^{PMP}$ H-3^{GlcA}), 3.65 (s, 3 H, COOCH$_3$), 3.50-3.40 (m, 3 H, H-4^{Xyl} H-5ab^{Xyl}), 3.33 (s, 3 H, OCH$_3$), 3.17 (dd, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 9.8 Hz, 1 H, H-2^{Xyl}), 1.33 (d, $J_{6,5}$ = 6.7 Hz, 3 H, H-6^{Fuc}); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 169.9 (C-6^{GlcA}), 166.3, 166.2, 166.0, 165.8 (C=O), 156.2, 152.5, (C$^{Ar\ PMP}$), 140.8, 140.22, 140.20, 139.9, 139.5, 134.4, 134.27, 134.1, 131.4, 130.8, 130.47, 130.45, 130.42, 130.37, 130.2, 130.1, 129.63, 129.55, 129.4, 129.3, 129.09, 129.07, 129.0, 128.93, 128.89, 128.8, 128.49, 128.47, 128.34, 128.30, 128.19, 128.17, 127.9 (C$^{Ar\ Bn}$ C$^{Ar\ Bn}$’ C$^{Ar\ Bn}$’’ C$^{Ar\ Bn}$’’’ C$^{Ar\ Bn}$’’’’ C$^{Ar\ Bz}$ C$^{Ar\ Bz}$’ C$^{Ar\ Bz}$’’ C$^{Ar\ Bz}$’’’), 119.5, 115.4 (C$^{Ar\ PMP}$), 102.3 (C-1^{GlcA}), 100.4 (C-1$^{L\text{-}Gal}$), 99.1 (C-1^{Xyl}), 98.3 (C-1^{Fuc}), 83.2 (C-3^{GlcA}), 83.1 (C-2^{Xyl}), 82.1 (C-3^{Xyl}), 80.3 (C-4^{GlcA}), 79.5 (C-2^{GlcA}), 79.2 (C-4^{Xyl}), 79.0 (C-4^{Fuc}), 77.7 (C-2^{Fuc}), 75.8 (CH$_2^{Bn\ Xyl\text{-}3}$), 75.7 (CH$_2^{Bn\ GlcA\text{-}3}$), 75.3 (CH$_2^{Bn\ GlcA\text{-}4}$), 75.1 (C-5^{GlcA}), 74.2 (C-3^{Fuc}), 73.6 (CH$_2^{Bn\ Xyl\text{-}4}$ CH$_2^{Bn\ Fuc}$), 73.1 (C-3$^{L\text{-}Gal}$), 72.1 (C-5$^{L\text{-}Gal}$), 71.7 (C-2$^{L\text{-}Gal}$), 69.7 (C-4$^{L\text{-}Gal}$), 68.9 (C-5^{Fuc}), 62.4 (C-6$^{L\text{-}Gal}$), 61.2 (C-5^{Xyl}), 59.4 (OCH$_3$), 55.9 (OCH$_3^{PMP}$), 52.7 (COOCH$_3$), 17.9 (C-6^{Fuc}); **^{1}H-^{13}C coupled HSQC:** 102.3 ($J_{C1\text{-}H1}$ = 164 Hz, C-1^{GlcA}), 100.4 ($J_{C1\text{-}H1}$ = 165 Hz, C-1$^{L\text{-}Gal}$), 99.1 ($J_{C1\text{-}H1}$ = 171 Hz, C-1^{Xyl}), 98.3 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{Fuc}); **HRMS**: calcd. for $C_{95}H_{94}O_{25}$: 1652.6422 [M+NH_4]$^+$, found 1652.6448; **HPTLC** (tol/EtOAc 83:17): R_f = 0.55 (CH stain, UV).

2,3,4,6-tetra-*O*-benzoyl-β-L-galactopyranosyl-(1→2)-[methyl (3,4-di-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-[3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)]-2-*O*-benzyl-1-*O*-*o*-(Hex-1-yn-1-yl)-benzoyl-L-fucopyranose (**148**)

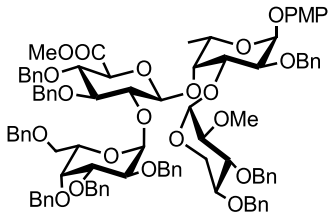


Tetrasaccharide acetal **147** (81.0 mg, 49.5 µmol, 1.0 eq) was dissolved in MeCN (4.0 mL) and the solution was cooled to 0 °C. Under vigorous stirring, a solution of CAN (149 mg, 208 µmol, 4.2 eq) in water (1.0 mL) was added dropwise over the course of 8 min. After 12 min the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ (10:1, 11 mL) and then EtOAc. The phases were separated and the organic layer was washed with brine (2x), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (tol to tol/EtOAc 91:9

to 50:50) to obtain hemiacetal **148** (66.8 mg, 88%) as colorless crystalline solid which was directly employed in the next step. **HRMS**: calcd. for $C_{88}H_{88}O_{24}$: 1567.5297 $[M+K]^+$, found 1567.5324; **HPTLC** (tol/EtOAc 80:20): R_f = 0.24 0.15 (CH stain, UV). To hemiacetal **148** (66.0 mg, 43.0 µmol, 1.0 eq) was added DCC (13.9 mg, 64.5 µmol, 1.5 eq), DMAP (8.0 mg, 64.5 µmol, 1.5 eq) and a solution of freshly prepared ABzOH (12.5 mg, 60.2 µmol, 1.4 eq) in anh. CH_2Cl_2 (0.24 mL). The mixture was stirred for 105 min, then filtered over a plug of celite, washed with CH_2Cl_2 and concentrated. The crude residue was purified by repeated flash chromatography (1st: 2 g SiO_2 prepacked column, hex/acetone 83:17; 2nd: 2 g SiO_2 prepacked column, tol to tol/EtOAc 97:3 to 91:9) to obtain a pure α/β-mixture of ester **149** (55.2 mg, α/β 1:1.4, 75%). Pure fractions of anomers were used for NMR characterization. For **149-α**: **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 8.07-7.94 (m, 7 H, $H^{Ar\ Bz}$ $H^{Ar\ Bz'}$ $H^{Ar\ Bz''}$ $H^{Ar\ ABz}$), 7.73 (m, 2 H, $H^{Ar\ Bz'''}$), 7.66-7.10 (m, 40 H, $H^{Ar\ Bz}$ $H^{Ar\ Bz'}$ $H^{Ar\ Bz''}$ $H^{Ar\ Bz'''}$ $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$ $H^{Ar\ Bn''}$ $H^{Ar\ Bn'''}$ $H^{Ar\ Bn''''}$ $H^{Ar\ ABz}$), 6.85 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1^{Fuc}), 6.13 (dd, $J_{4,3}$ = 3.6 Hz $J_{4,5}$ = 0.5 Hz, 1H, H-$4^{L\text{-}Gal}$), 5.96 (dd, $J_{2,1}$ = 8.1 Hz $J_{2,3}$ = 10.4 Hz, 1 H, H-$2^{L\text{-}Gal}$), 5.88 (d, $J_{1,2}$ = 8.1 Hz, 1 H, H-$1^{L\text{-}Gal}$), 5.82 (dd, $J_{3,2}$ = 10.4 Hz $J_{3,4}$ = 3.5 Hz, 1 H, H-$3^{L\text{-}Gal}$), 5.37 (d, $J_{CH2,CH2'}$ = 11.0 Hz, 1 H, $PhCH_2a^{GlcA\text{-}3}$), 5.26 (d, $J_{1,2}$ = 3.9 Hz, H-1^{Xyl}), 5.06 (d, $J_{1,2}$ = 8.0 Hz, 1 H, H-1^{GlcA}), 4.97-4.79 (m, 7 H, $PhCH_2ab^{Xyl\text{-}3}$ $PhCH_2b^{GlcA\text{-}3}$ $PhCH_2ab^{Fuc}$ H-$6a^{L\text{-}Gal}$ H-$5^{L\text{-}Gal}$), 4.74-4.66 (m, 3 H, $PhCH_2a^{GlcA\text{-}4}$ $PhCH_2ab^{Xyl\text{-}4}$), 4.60 (dd, $J_{6b,5}$ = 5.6 Hz $J_{6b,6a}$ = 9.7 Hz, 1 H, H-$6b^{L\text{-}Gal}$), 4.53 (dd, $J_{6b,5}$ = 3.6 Hz $J_{6b,6a}$ = 10.4 Hz, 1 H, H-2^{Fuc}), 4.45-4.40 (m, 2 H, H-5^{Fuc} $PhCH_2b^{GlcA\text{-}4}$), 4.36-4.29 (m, 3 H, H-2^{GlcA} H-3^{Fuc} H-4^{Fuc}), 4.20 (d, $J_{5,4}$ = 9.3 Hz, 1H, H-5^{GlcA}), 3.88 (dd, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 8.3 Hz, 1 H, H-3^{Xyl}), 3.84-3.77 (m, 2 H, H-4^{GlcA} H-3^{GlcA}), 3.66 (s, 3 H, $COOCH_3$), 3.53 (dd, $J_{5a,5b}$ = $J_{5a,6}$ = 12.2 Hz, 1 H, H-$5a^{Xyl}$), 3.49-3.42 (m, 2 H, H-4^{Xyl} H-$5b^{Xyl}$), 3.29 (s, 3 H, OCH_3), 3.14 (dd, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 9.7 Hz, 1 H, H-2^{Xyl}), 2.45 (m, 2 H, C≡C-CH_2), 1.59 (m, 2 H, $CH_2\underline{CH_2}CH_2$), 1.50 (m, 2 H, $CH_2\underline{CH_2}Me$), 1.36 (d, $J_{6,5}$ = 6.7 Hz, 3 H, H-6^{Fuc}), 0.93 (t, J= 7.4 Hz 3 H, $CH_2\underline{CH_3}$); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 169.8 (C-6^{GlcA}), 166.3, 166.1, 165.8, 165.4 (C=O), 140.8, 140.3, 139.9, 139.8, 139.6, 135.5, 134.4, 134.25, 134.23, 134.1, 132.9, 132.8, 131.4, 130.84, 130.81, 130.48, 130.45, 130.41, 130.22, 130.1, 129.63, 129.59, 129.5, 129.3, 129.09, 129.05, 129.02, 128.94, 128.89, 128.8, 128.51, 128.50, 128.44, 128.36, 128.25, 128.21, 128.18, 128.16, 127.9, 125.5 ($C^{Ar\ Bn}$ $C^{Ar\ Bn'}$ $C^{Ar\ Bn''}$ $C^{Ar\ Bn'''}$ $C^{Ar\ Bn''''}$ $C^{Ar\ Bz}$ $C^{Ar\ Bz'}$ $C^{Ar\ Bz''}$ $C^{Ar\ Bz'''}$ $C^{Ar\ ABz}$), 102.4 (C-1^{GlcA}), 100.4 (C-$1^{L\text{-}Gal}$), 99.3 (C-1^{Xyl}), 96.9 (Ar-C≡C-), 92.7 (C-1^{Fuc}), 83.2 (C-3^{GlcA}), 83.0 (C-2^{Xyl}), 82.0 (C-3^{Xyl}), 80.5 (Ar-C≡C-), 80.3 (C-4^{GlcA}), 79.5 (C-2^{GlcA}), 79.3 (C-4^{Xyl}), 78.4 (C-4^{Fuc}), 77.1 (C-2^{Fuc}), 75.8 ($CH_2^{Bn\ Xyl\text{-}3}$), 75.7 ($CH_2^{Bn\ GlcA\text{-}3}$), 75.3 ($CH_2^{Bn\ GlcA\text{-}4}$), 75.1 (C-5^{GlcA}), 74.5 (C-3^{Fuc}), 73.9 ($CH_2^{Bn\ Xyl\text{-}4}$), 73.7 ($CH_2^{Bn\ Fuc}$), 73.2 (C-$3^{L\text{-}Gal}$), 72.1 (C-$5^{L\text{-}Gal}$), 71.7 (C-$2^{L\text{-}Gal}$), 71.3 (C-5^{Fuc}), 69.6 (C-$4^{L\text{-}Gal}$), 62.4 (C-$6^{L\text{-}Gal}$), 61.3 (C-5^{Xyl}), 59.5 (OCH_3), 52.7 ($COO\underline{C}H_3$), 31.5 ($CH_2\underline{C}H_2CH_2$), 22.7 ($CH_2\underline{C}H_2CH_3$), 20.0 (C≡C-$\underline{C}H_2$), 17.9 (C-6^{Fuc}), 14.0 ($CH_2\underline{C}H_3$); **^{1}H-^{13}C coupled HSQC:** 102.4 ($J_{C1\text{-}H1}$ = 163 Hz, C-1^{GlcA}), 100.4 ($J_{C1\text{-}H1}$ = 167 Hz, C-$1^{L\text{-}Gal}$), 99.3 ($J_{C1\text{-}H1}$ = Hz 170 Hz, C-1^{Xyl}), 92.7 ($J_{C1\text{-}H1}$ = 173 Hz, C-1^{Fuc}); For **149-β**: **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 8.07 (m, 2 H, $H^{Ar\ Bz}$), 8.01-7.97 (m, 4 H, $H^{Ar\ Bz'}$ $H^{Ar\ Bz''}$), 7.88 (m, 1 H, $H^{Ar\ ABz}$), 7.72 (m, 2 H, $H^{Ar\ Bz'''}$), 7.66-7.56 (m, 4 H, $H^{Ar\ Bz'}$ $H^{Ar\ Bz''}$ $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$), 7.54-7.45 (m, 5 H, $H^{Ar\ Bz}$ $H^{Ar\ Bz'}$ $H^{Ar\ Bz'''}$ $H^{Ar\ ABz}$), 7.43-7.36 (m, 7 H, $H^{Ar\ Bz}$ $H^{Ar\ Bz''}$ $H^{Ar\ Bn''}$ $H^{Ar\ Bn'''}$ $H^{Ar\ ABz}$), 7.33-7.10 (m,

24 H, $H^{Ar\ Bz'''}$ $H^{Ar\ Bn}$ $H^{Ar\ Bn'}$ $H^{Ar\ Bn''}$ $H^{Ar\ Bn'''}$ $H^{Ar\ Bn''''}$ $H^{Ar\ ABz}$), 6.05 (dd, $J_{4,3}$ = 3.5 Hz $J_{4,5}$ = 0.8 Hz, 1H, H-$4^{L\text{-}Gal}$), 6.01 (d, $J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Fuc}), 5.99-5.94 (m, 2 H, H-$1^{L\text{-}Gal}$ H-$2^{L\text{-}Gal}$), 5.79 (m, 1 H, H-$3^{L\text{-}Gal}$), 5.34 (d, $J_{CH2,CH2'}$ = 10.7 Hz, 1 H, $PhCH_2a^{GlcA\text{-}3}$), 5.29 (d, $J_{1,2}$ = 3.8 Hz, H-1^{Xyl}), 5.09 (d, $J_{1,2}$ = 7.9 Hz, 1 H, H-1^{GlcA}), 5.06 (d, $J_{CH2,CH2'}$ = 11.3 Hz, 1 H, $PhCH_2a^{Fuc}$), 4.97-4.87 (m, 3 H, $PhCH_2ab^{Xyl\text{-}3}$ $PhCH_2b^{Fuc}$), 4.85-4.80 (m, 2 H, $PhCH_2b^{GlcA\text{-}3}$ H-$5^{L\text{-}Gal}$), 4.76-4.66 (m, 4 H, $PhCH_2a^{GlcA\text{-}4}$ H-$6a^{L\text{-}Gal}$ $PhCH_2ab^{Xyl\text{-}4}$), 4.61 (dd, $J_{6b,5}$ = 7.9 Hz $J_{6b,6a}$ = 11.1 Hz, 1 H, H-$6b^{L\text{-}Gal}$), 4.42 (d, $J_{CH2,CH2'}$ = 11.2 Hz, 1 H, $PhCH_2b^{GlcA\text{-}4}$), 4.36-4.28 (m, 3 H, H-2^{Fuc} H-4^{Fuc} H-2^{GlcA}), 4.25 (d, $J_{5,4}$ = 9.8 Hz, 1H, H-5^{GlcA}), 4.13 (dq, $J_{5,4}$ = 0.9 Hz $J_{5,6}$ = 6.6 Hz, 1H, H-5^{Fuc}), 4.08 (dd, $J_{3,2}$ = 9.7 Hz $J_{3,4}$ = 2.6 Hz, 1 H, H-3^{Fuc}), 3.91 (dd, $J_{3,2}$ = 9.3 Hz, $J_{3,4}$ = 8.4 Hz, 1 H, H-3^{Xyl}), 3.85 (dd, $J_{4,3}$ = 9.0 Hz, $J_{4,5}$ = 9.8 Hz, 1 H, H-4^{GlcA}), 3.79 (dd, $J_{3,2}$ = $J_{3,4}$ = 8.9 Hz, 1 H, H-3^{GlcA}), 3.69 (s, 3 H, $COOCH_3$), 3.60-3.46 (m, 2 H, H-4^{Xyl} H-$5ab^{Xyl}$), 3.35 (s, 3 H, OCH_3), 3.18 (dd, $J_{2,1}$ = 3.7 Hz, $J_{2,3}$ = 9.6 Hz, 1 H, H-2^{Xyl}), 2.47 (m, 2 H, $C{\equiv}C\text{-}CH_2$), 1.60 (m, 2 H, $CH_2C\underline{H_2}CH_2$), 1.53 (m, 2 H, $CH_2C\underline{H_2}Me$), 1.46 (d, $J_{6,5}$ = 6.5 Hz, 3 H, H-6^{Fuc}), 0.93 (t, J= 7.4 Hz 3 H, $CH_2C\underline{H_3}$); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 169.9 (C-6^{GlcA}), 166.3, 166.2, 166.1, 165.7, 164.5 (C=O), 140.5, 140.2, 139.9, 139.8, 139.5, 135.1, 134.4, 134.3, 134.2, 134.1, 132.9, 131.8, 131.0, 130.8, 130.7, 130.46, 130.44, 130.42, 130.26, 130.0, 129.65, 129.53, 129.48, 129.3, 129.1, 129.0, 128.98, 128.94, 128.89, 128.7, 128.52, 128.47, 128.35, 128.26, 128.20, 128.19, 128.0, 127.9, 126.1 ($C^{Ar\ Bn}$ $C^{Ar\ Bn'}$ $C^{Ar\ Bn''}$ $C^{Ar\ Bn'''}$ $C^{Ar\ Bn''''}$ $C^{Ar\ Bz}$ $C^{Ar\ Bz'}$ $C^{Ar\ Bz''}$ $C^{Ar\ Bz'''}$ $C^{Ar\ ABz}$), 102.1 (C-1^{GlcA}), 100.6 (C-$1^{L\text{-}Gal}$), 99.9 (C-1^{Xyl}), 97.3 (Ar-C≡$\underline{C}$-), 95.8 (C-1^{Fuc}), 83.2 (C-3^{GlcA}), 82.9 (C-2^{Xyl}), 82.3 (C-3^{Xyl}), 80.2 (C-4^{GlcA}), 80.1 (C-2^{GlcA}), 80.0 (Ar-$\underline{C}$≡C-), 79.45 (C-2^{Fuc}), 79.3 (C-4^{Xyl}), 78.4 (C-3^{Fuc}), 75.9 ($CH_2^{Bn\ Xyl\text{-}3}$), 75.8 ($CH_2^{Bn\ GlcA\text{-}3}$), 73.6 ($CH_2^{Bn\ Fuc}$), 75.3 ($CH_2^{Bn\ GlcA\text{-}4}$), 75.1 (C-5^{GlcA}), 73.5 ($CH_2^{Bn\ Xyl\text{-}4}$), 73.2 (C-$3^{L\text{-}Gal}$), 72.6 (C-5^{Fuc}), 72.1 (C-$5^{L\text{-}Gal}$), 71.5 (C-$2^{L\text{-}Gal}$), 69.5 (C-$4^{L\text{-}Gal}$), 62.4 (C-$6^{L\text{-}Gal}$), 61.5 (C-5^{Xyl}), 60.3 (OCH_3), 52.7 ($COO\underline{C}H_3$), 31.5 ($CH_2\underline{C}H_2CH_2$), 22.7 ($CH_2\underline{C}H_2CH_3$), 19.9 (C≡C-$\underline{C}H_2$), 18.0 (C-6^{Fuc}), 14.0 ($CH_2\underline{C}H_3$); **^{1}H-^{13}C coupled HSQC:** 102.1 ($J_{C1\text{-}H1}$ = 166 Hz, C-1^{GlcA}), 100.6 ($J_{C1\text{-}H1}$ = 166 Hz, C-$1^{L\text{-}Gal}$), 99.9 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Xyl}), 95.8 ($J_{C1\text{-}H1}$ = 168 Hz, C-1^{Fuc}); **HRMS**: calcd. for $C_{101}H_{100}O_{25}$: 1730.6892 $[M{+}NH_4]^+$, found 1730.6926; **HPTLC** (tol/EtOAc 83:17): α R_f = 0.85, β R_f = 0.75 (CH stain, UV).

p-Methoxyphenyl 2,3,4,6-tetra-*O*-benzyl-α-L-galactopyranosyl-(1→2)-[methyl (3,4-di-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-[3,4-di-*O*-benzyl-2-*O*-methyl-D-xylopyranosyl-(1→3)]-2-*O*-benzyl-α-L-fucopyranoside (**150**)



Donor thioglycoside **78** (13.2 mg, 20.2 µmol, 1.0 eq) was coevaporated with toluene and all volatiles were removed in fine vacuum. Under argon atmosphere, freshly activated powdered molecular sieve 4 Å (55 mg) and TTBP (7.5 mg, 30 µmol, 1.5 eq) were added and the resulting reaction mixture was suspended in anh. CH_2Cl_2 (0.30 mL) and anh. DMF (25.0 µL, 323 µmol, 16 eq). After stirring for 1 h, AgOTf (15.6 mg, 60.7 µmol, 3.0 eq) was added as a solid, which dissolved within 5 min. The mixture was cooled to -78 °C within 15 min, TolSCl (3.1 µL, 95%, 20 µmol, 1.0 eq) was added directly into the suspension and the mixture was allowed to warm up to -20 °C within 30 min. In a separate vial acceptor alcohol **77** (15.0 mg, 14.2 µmol, 0.7 eq) was coevaporated with toluene and all volatiles were removed in fine vacuum. After preactivation of the donor was confirmed by TLC, under argon atmosphere the acceptor alcohol **77** was dissolved in anh. CH_2Cl_2 and transferred into the reaction mixture using a syringe (3x 30 µL). The reaction mixture was stirred at -18 °C for 16 h, then the reaction was quenched with pyridine (50 µL), filtered over a plug of celite and the solids washed with EtOAc. The filtrate was washed with water, sat. aq. $NaHCO_3$ and brine, and then dried over $MgSO_4$, filtered and concentrated. The obtained crude residue was purified by repeated flash chromatography (1st: 2 g SiO_2 prepacked column, tol to tol/EtOAc 91:9; 2nd: 2 g SiO_2 prepacked column, tol to hex/EtOAc 80:20) to give the tetrasaccharide acetal **150** (16.5 mg, 74%) as a colorless foam. **^{1}H NMR** (CD_3COCD_3, 600 MHz): δ = 7.45-7.12 (m, 45 H, $H^{Ar\ Bn1}$-$H^{Ar\ Bn9}$), 7.01 (m, 2 H, $H^{Ar\ PMP}$), 6.84 (m, 2 H, $H^{Ar\ PMP}$), 5.72 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1$^{L\text{-}Gal}$), 5.68 (d, $J_{2,1}$ = 3.1 Hz, 1 H, H-1^{Fuc}), 5.32 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H-1^{Xyl}), 5.02 (d, $J_{1,2}$ = 8.0 Hz, 1 H, H-1$^{L\text{-}Gal}$), 5.02-4.95 (m, 2 H, $PhCH_2a^{Xyl\text{-}3}$ $PhCH_2a^{L\text{-}Gal\text{-}4}$), 4.92 (d, $J_{CH2,CH2'}$ = 11.6 Hz, $PhCH_2b^{Xyl\text{-}3}$), 4.89 (d, $J_{CH2,CH2'}$ = 11.5 Hz, $PhCH_2a^{GlcA\text{-}3}$), 4.86-4.80 (m, 3 H, $PhCH_2b^{GlcA\text{-}3}$ $PhCH_2ab^{L\text{-}Gal\text{-}3}$), 4.80-4.76 (m, 2 H, $PhCH_2a^{L\text{-}Gal\text{-}2}$ H-5$^{L\text{-}Gal}$), 4.73 (d, $J_{CH2,CH2'}$ = 11.4 Hz, 1 H, $PhCH_2a^{Fuc}$), 4.71-4.65 (m, 5 H, $PhCH_2b^{L\text{-}Gal\text{-}2}$ $PhCH_2a^{GlcA\text{-}4}$ $PhCH_2a^{L\text{-}Gal\text{-}6}$ $PhCH_2ab^{Xyl\text{-}4}$), 4.63 (d, $J_{CH2,CH2'}$ = 12.0 Hz, 1 H, $PhCH_2b^{L\text{-}Gal\text{-}6}$), 4.56 (d, $J_{CH2,CH2'}$ = 11.1 Hz, 1 H, $PhCH_2b^{L\text{-}Gal\text{-}4}$), 4.52-4.48 (m, 2 H, $PhCH_2b^{L\text{-}Gal\text{-}4}$ $PhCH_2b^{Fuc}$), 4.44 (d, $J_{3,2}$ = 10.4 Hz $J_{3,4}$ = 2.9 Hz, 1 H, H-3$^{L\text{-}Gal}$), 4.30-4.16 (m, 6 H, H-3^{Fuc} H-2^{Fuc} H-4$^{L\text{-}Gal}$ H-5^{Fuc} H-5^{GlcA} H-4^{Fuc}), 4.06-3.99 (m, 2 H, H-2$^{L\text{-}Gal}$ H-2^{GlcA}), 3.94-3.83 (m, 4 H, H-3^{Xyl} H-4^{GlcA} H-3^{GlcA} H-6a$^{L\text{-}Gal}$), 3.77 (dd, $J_{6b,6a}$ = $J_{6b,5}$ = 8.6 Hz, 1 H, H-6b$^{L\text{-}Gal}$), 3.75 (s, 3 H, OCH_3^{PMP}), 3.70 (dd, $J_{5a,5b}$ = 10.6 Hz $J_{5,4}$ = 8.7 Hz, 1 H, H-5a^{Xyl}), 3.58 (dd, $J_{5a,5b}$ = 10.6 Hz $J_{5,4}$ = 5.3 Hz, 1 H, H-5b^{Xyl}), 3.54 (s, 3 H, $COOCH_3$), 3.44 (ddd, $J_{4,5a}$ = 8.8 Hz $J_{4,5b}$ = 5.3 Hz $J_{4,3}$ = 10.7 Hz, 1 H, H-4^{Xyl}),

3.23 (s, 3 H, OCH_3), 3.11 (dd, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 9.7 Hz, 1 H, H-2^{Xyl}), 1.45 (d, $J_{6,5}$ = 6.8 Hz, 3 H, H-6^{Fuc}); **^{13}C NMR** (CD_3COCD_3, 150 MHz): δ = 170.2 (C-6^{GlcA}), 156.1, 152.5 ($C^{Ar\ PMP}$), 141.2, 140.35, 140.33, 140.1, 140.00, 139.96, 139.5, 139.4, 139.1, 129.22, 129.17, 129.09, 129.07, 129.04, 128.97, 128.9, 128.8, 128.6, 128.5, 128.41, 128.37, 128.24, 128.15, 128.08, 128.06, 127.9, 127.84, 127.8 ($C^{Ar\ Bn1}$-$C^{Ar\ Bn9}$), 119.7, 115.4 ($C^{Ar\ PMP}$), 103.1 (C-1^{GlcA}), 99.0 (C-1^{Xyl}), 98.4 (C-1^{Fuc}), 97.7 (C-$1^{L\text{-}Gal}$), 85.9 (C-3^{GlcA}), 83.3 (C-2^{Xyl}), 81.5 (C-3^{Xyl}), 81.3 (C-4^{GlcA}), 80.7 (C-4^{Fuc}), 79.9 (C-$3^{L\text{-}Gal}$), 79.5 (C-4^{Xyl}), 77.7 (C-2^{Fuc}), 77.0 (C-$2^{L\text{-}Gal}$), 76.5 (C-$4^{L\text{-}Gal}$), 75.54 ($CH_2^{Bn\ L\text{-}Gal\text{-}4}$), 75.45 ($CH_2^{Bn\ Xyl\text{-}3}$), 75.2 (C-$5^{GlcA}$), 75.0 ($CH_2^{Bn\ GlcA\text{-}4}$), 74.7 (C-$2^{GlcA}$), 74.6 ($CH_2^{Bn\ GlcA\text{-}3}$), 74.2 ($CH_2^{Bn\ L\text{-}Gal\text{-}6}$), 73.7 ($CH_2^{Bn\ L\text{-}Gal\text{-}2}$), 73.6 ($CH_2^{Bn\ Xyl\text{-}4}$), 73.5 (C-$3^{Fuc}$), 73.1 ($CH_2^{Bn\ L\text{-}Gal\text{-}3}$), 72.8 ($CH_2^{Bn\ Fuc\text{-}2}$), 70.1 (C-$5^{L\text{-}Gal}$), 70.0 (C-$6^{L\text{-}Gal}$), 69.0 (C-$5^{Fuc}$), 61.0 (C-$5^{Xyl}$), 59.0 ($OCH_3$), 55.9 ($OCH_3^{PMP}$), 52.8 ($COO\underline{C}H_3$), 17.4 (C-$6^{Fuc}$); **^{1}H-^{13}C coupled HSQC:** 103.1 ($J_{C1\text{-}H1}$ = 162 Hz, C-1^{GlcA}), 99.0 ($J_{C1\text{-}H1}$ = 170 Hz, C-1^{Xyl}), 98.4 ($J_{C1\text{-}H1}$ = 169 Hz, C-1^{Fuc}), 97.7 ($J_{C1\text{-}H1}$ = 174 Hz, C-$1^{L\text{-}Gal}$); **HRMS**: calcd. for $C_{95}H_{102}O_{21}$: 1596.7252 $[M+NH_4]^+$, found 1596.7283; **HPTLC** (hex/EtOAc 71:29): R_f = 0.41 (CH stain, UV).

5. Literature sources

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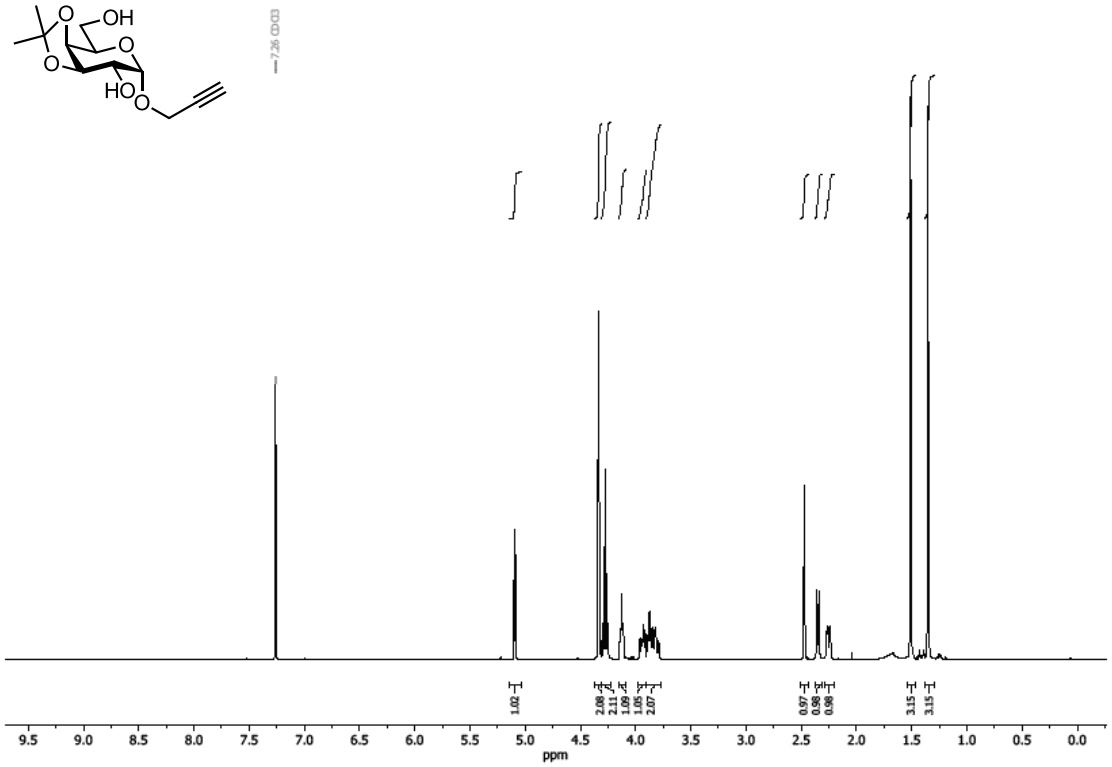
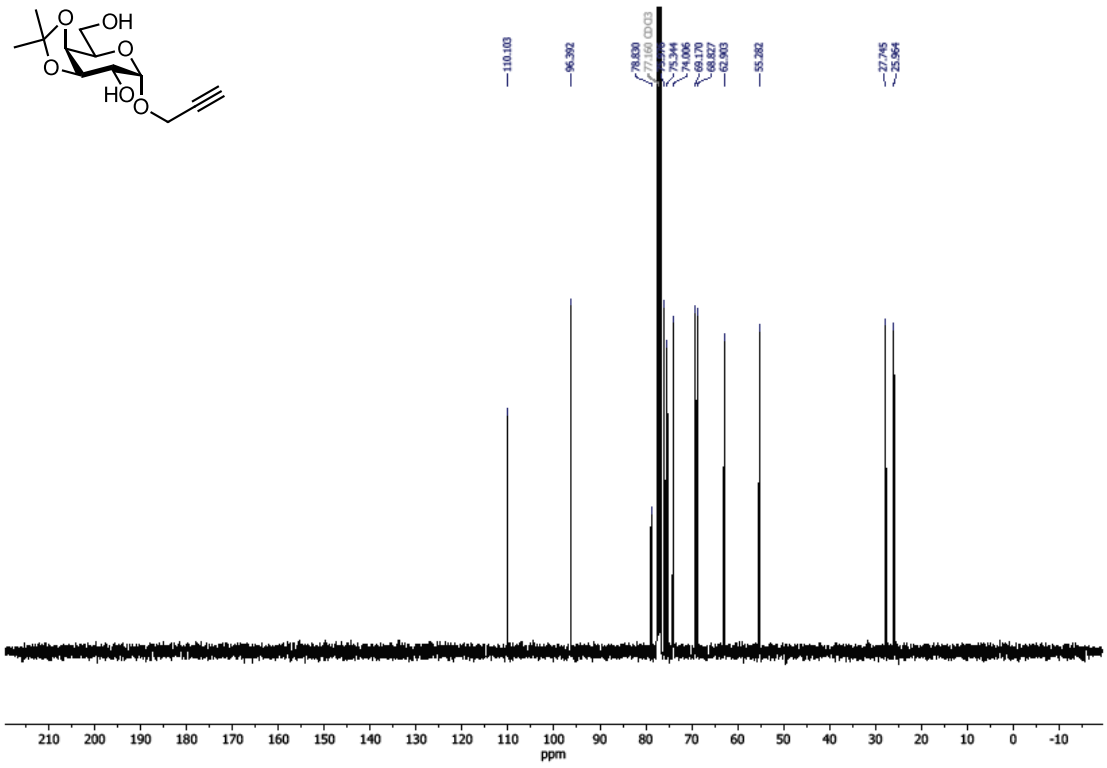
6. Appendix

6.1 NMR Data



^{1}H NMR of **93** ($CDCl_3$, 400 MHz, 297 K)



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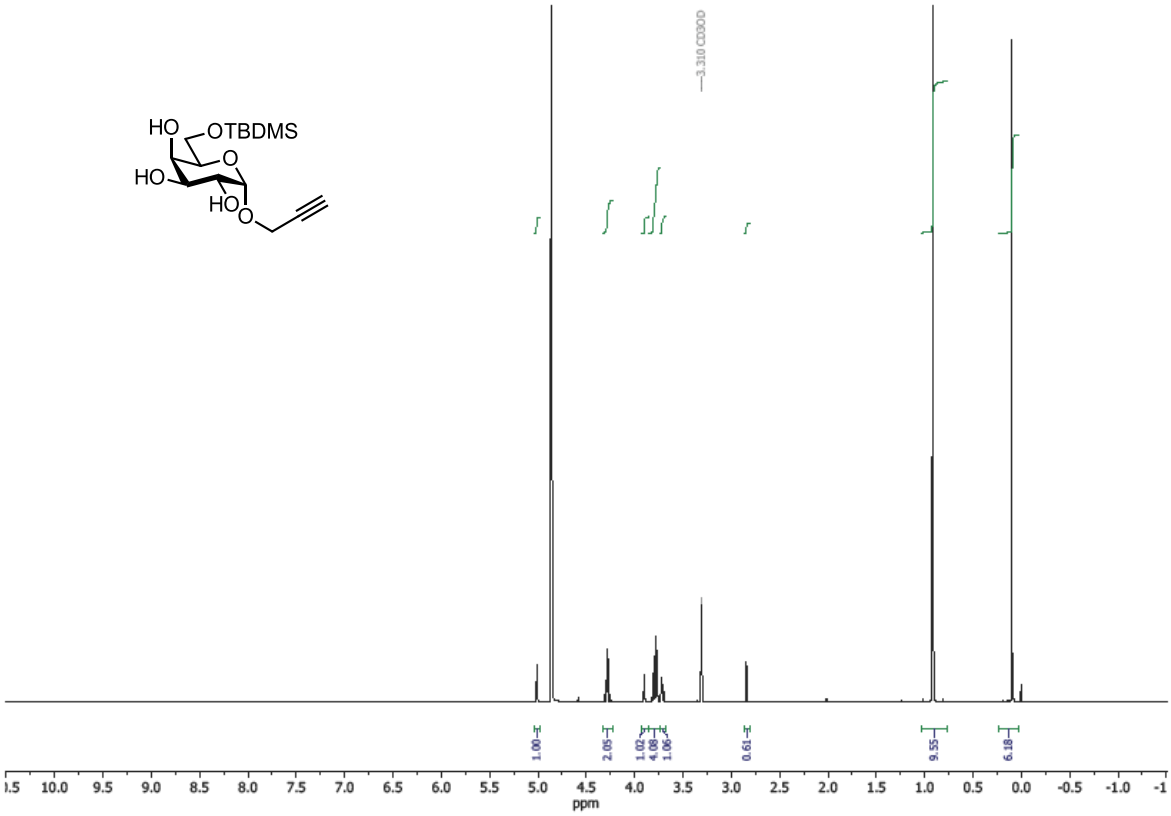

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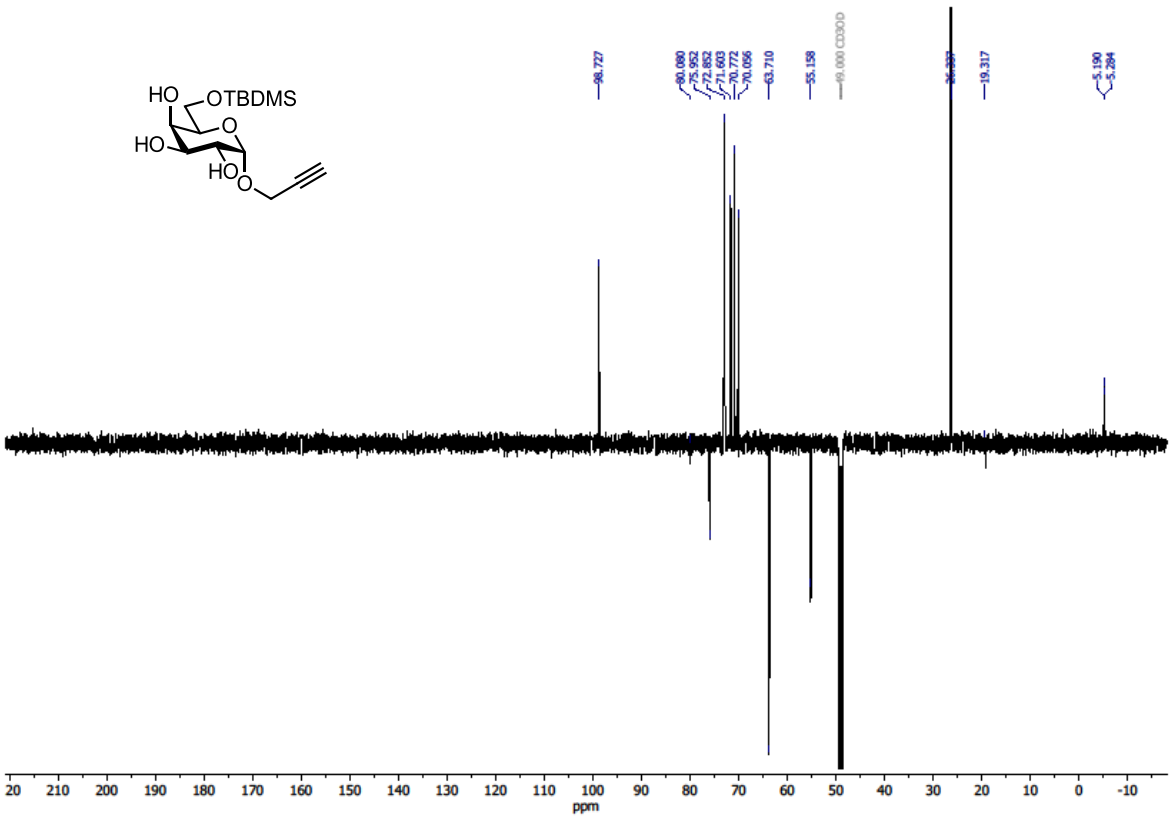

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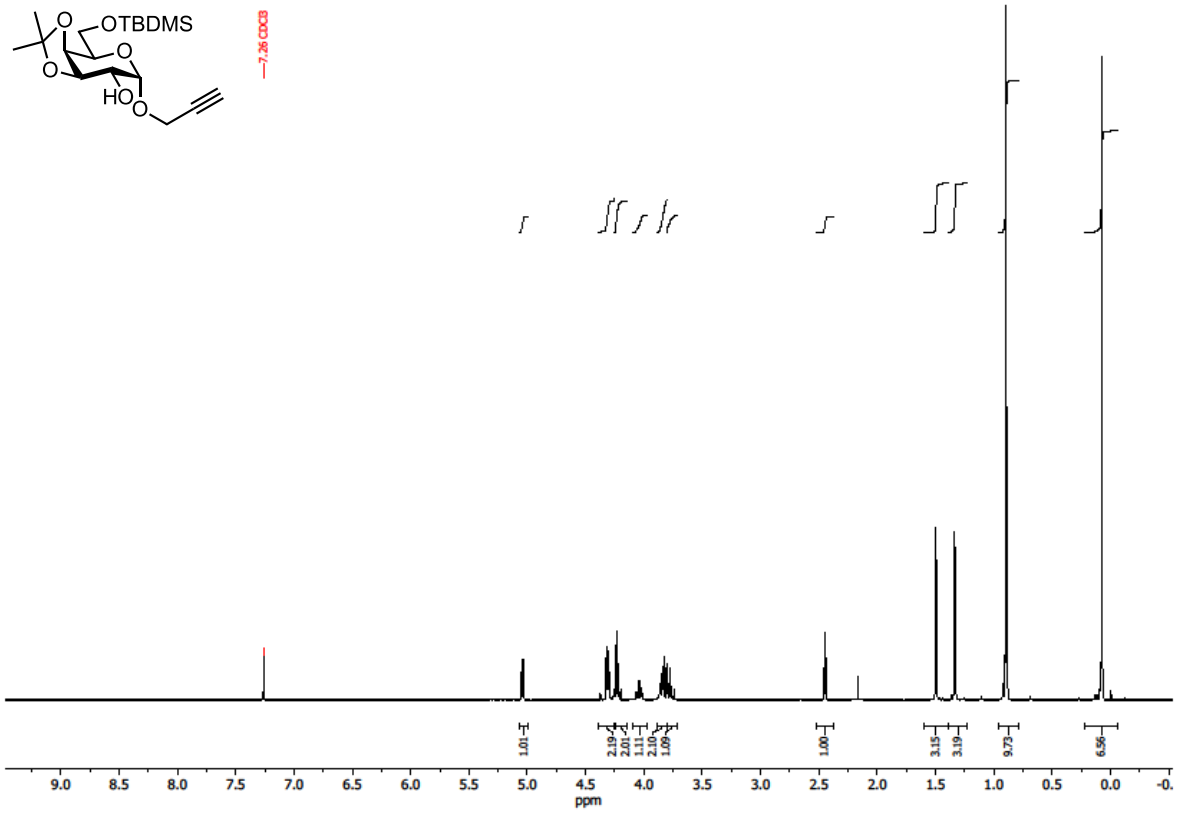

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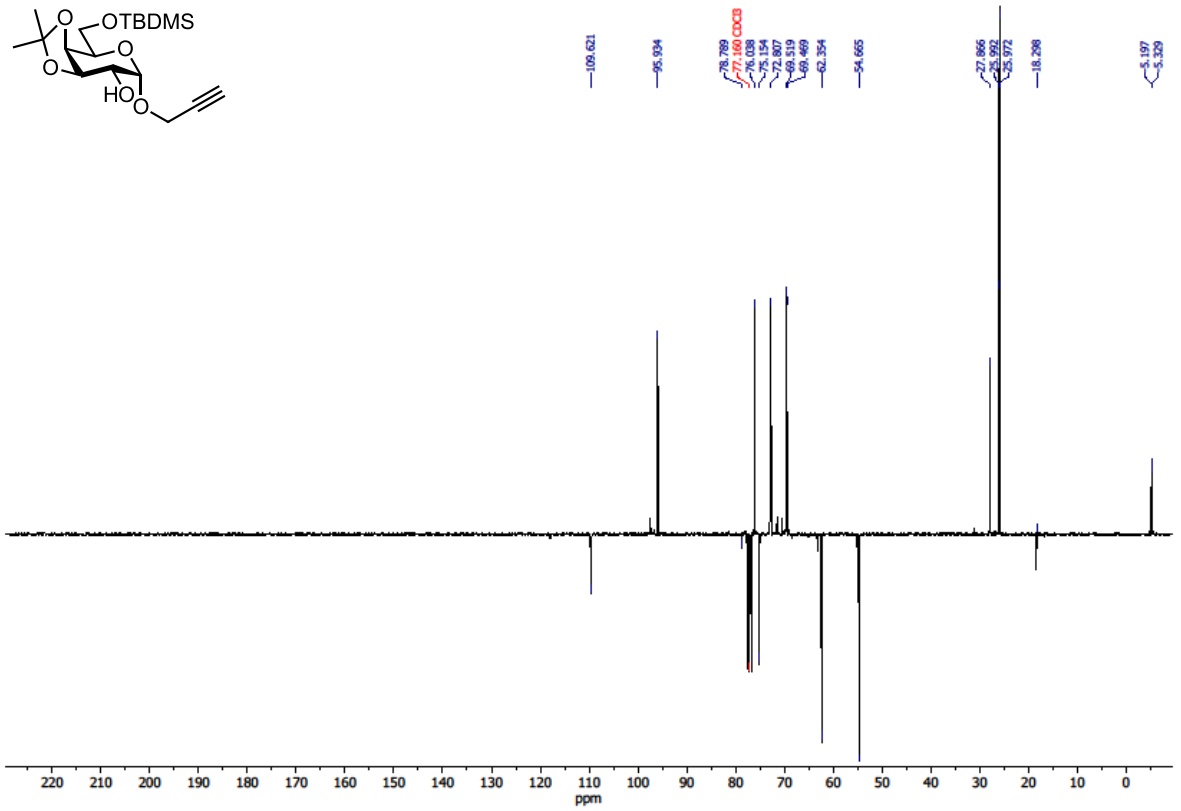
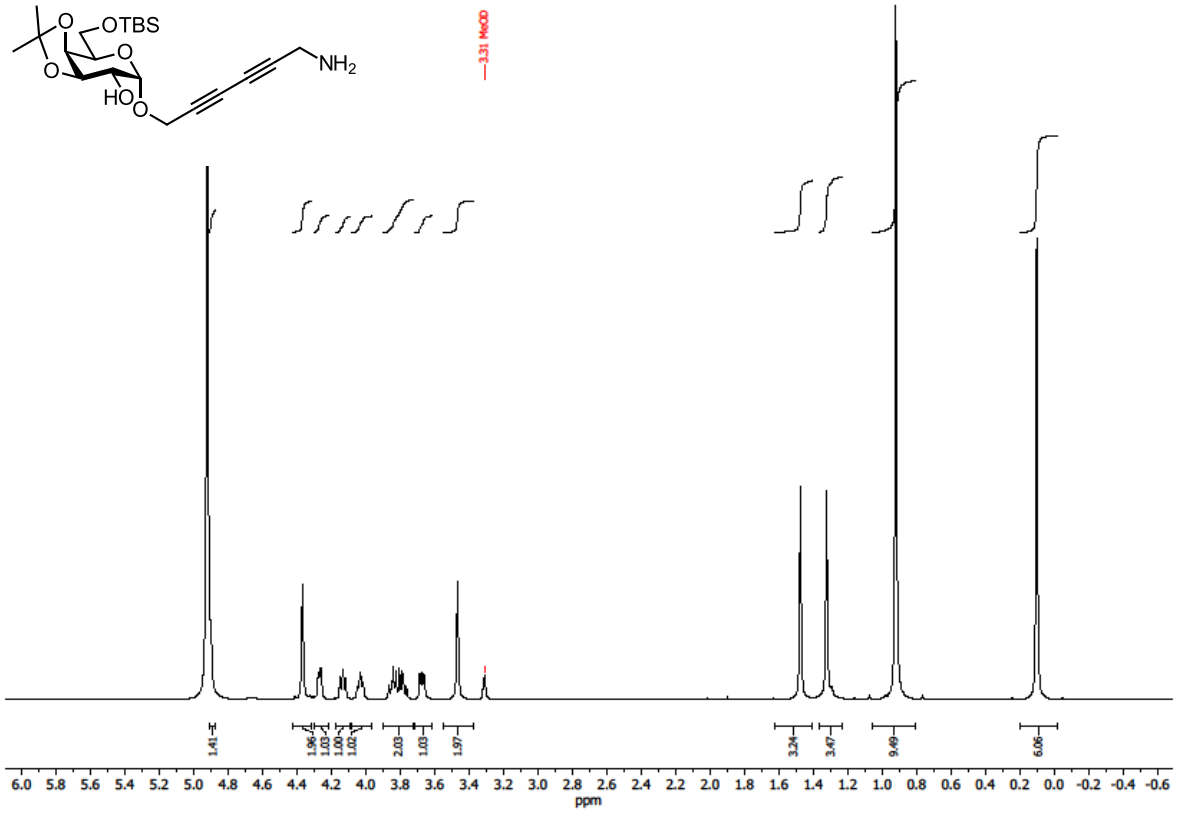
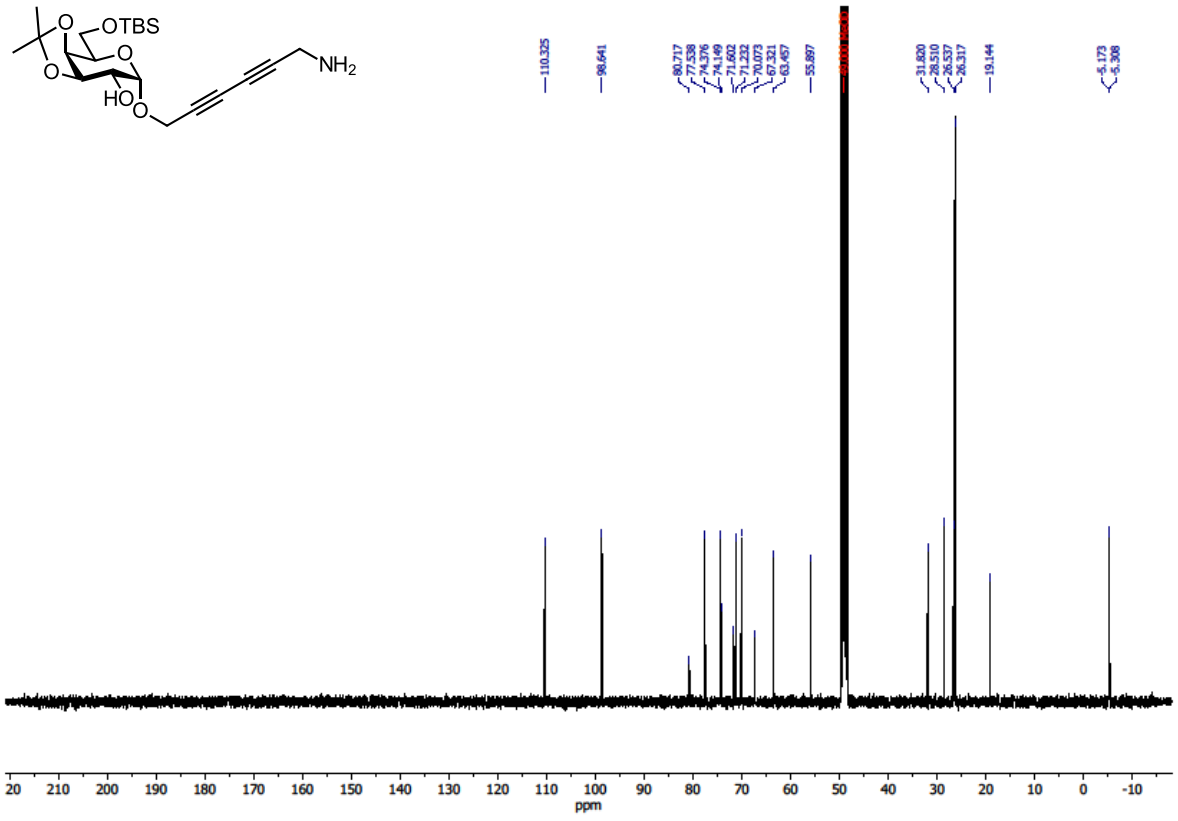


^{13}C APT NMR of **92** ($CDCl_3$, 75 MHz, 297 K)



^{1}H NMR of **95** (CD_3OD, 400 MHz, 297 K)



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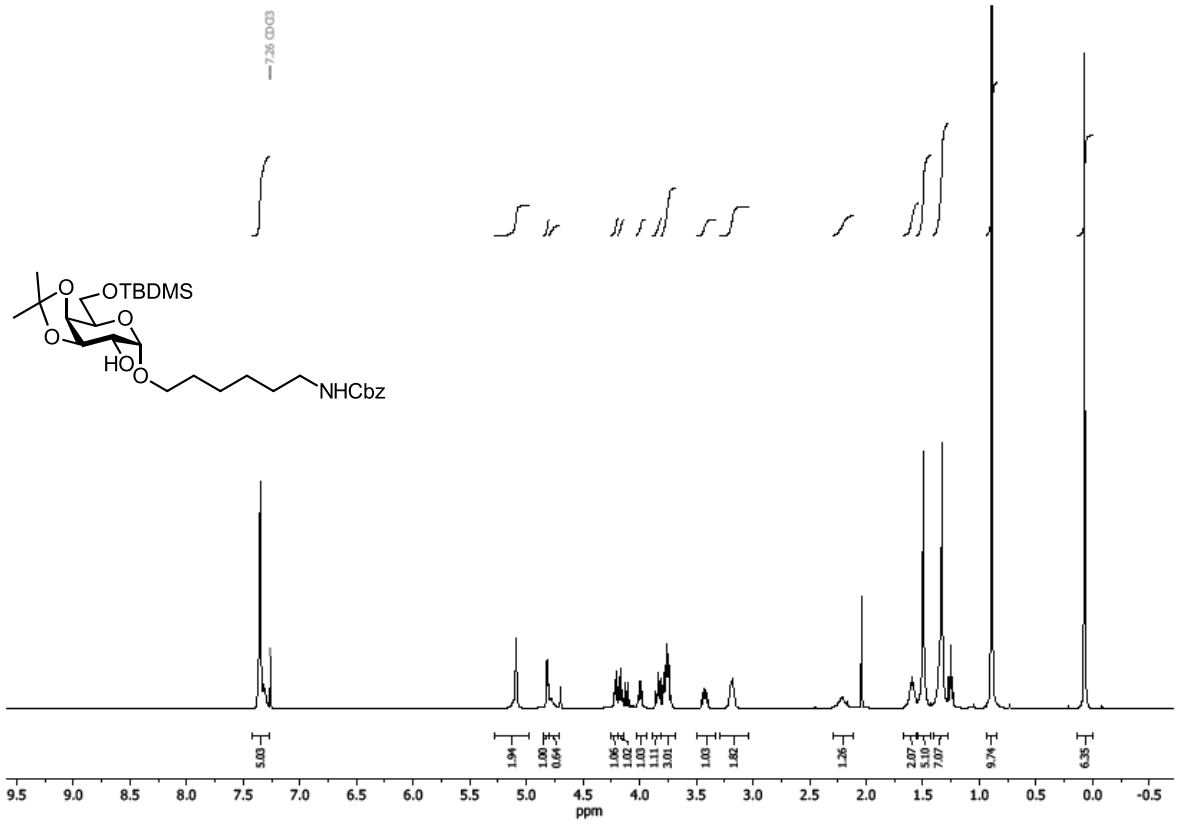

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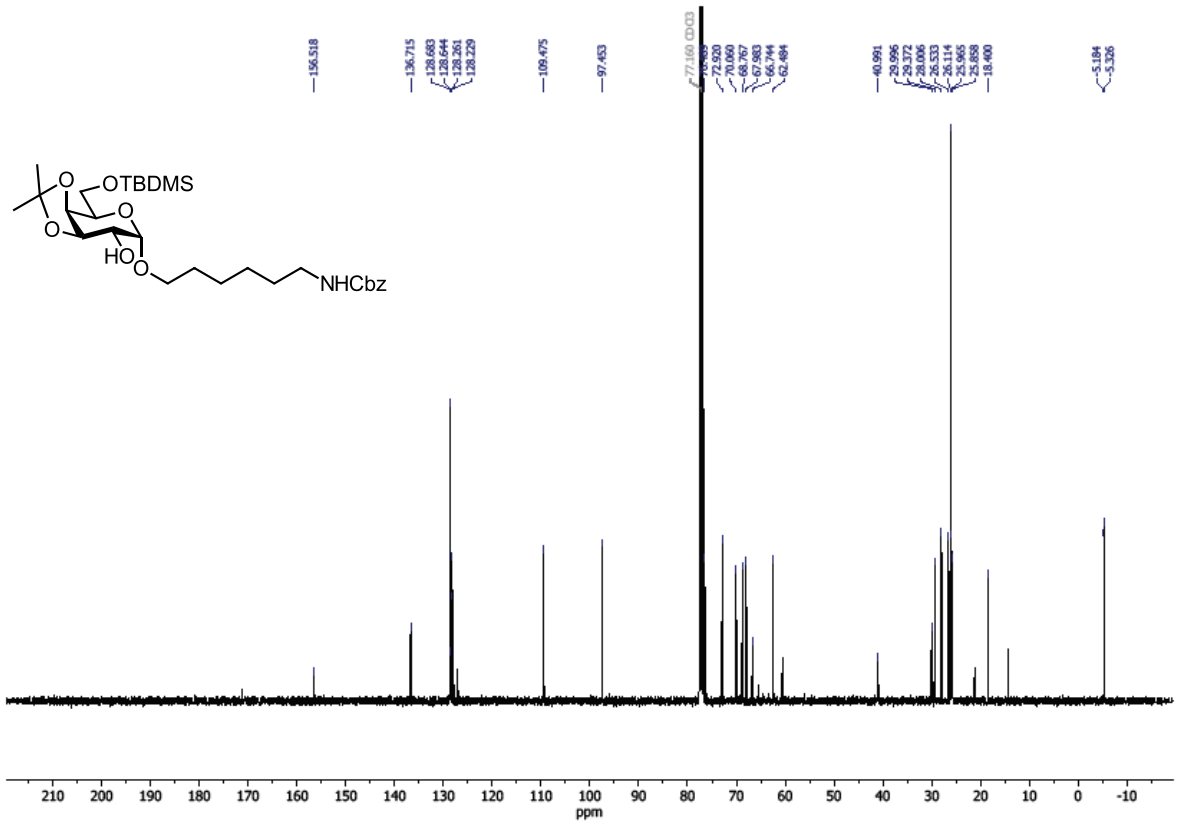
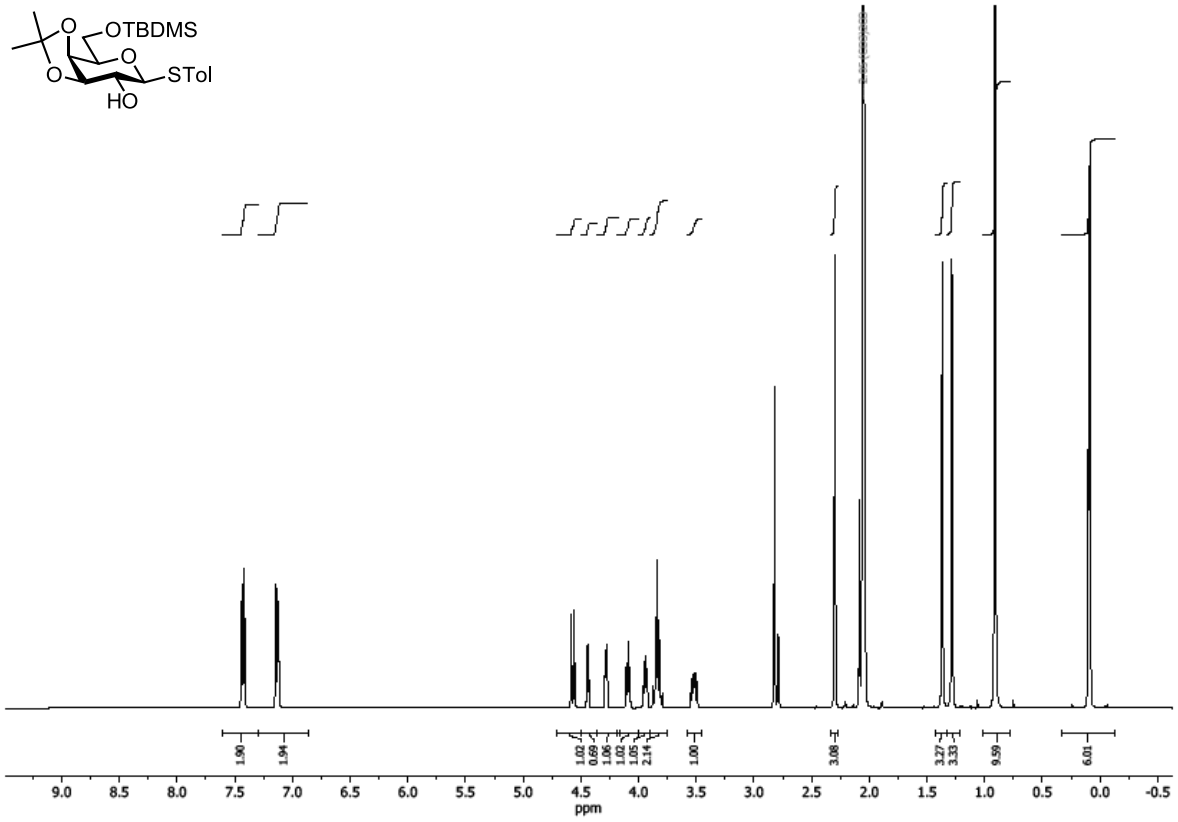
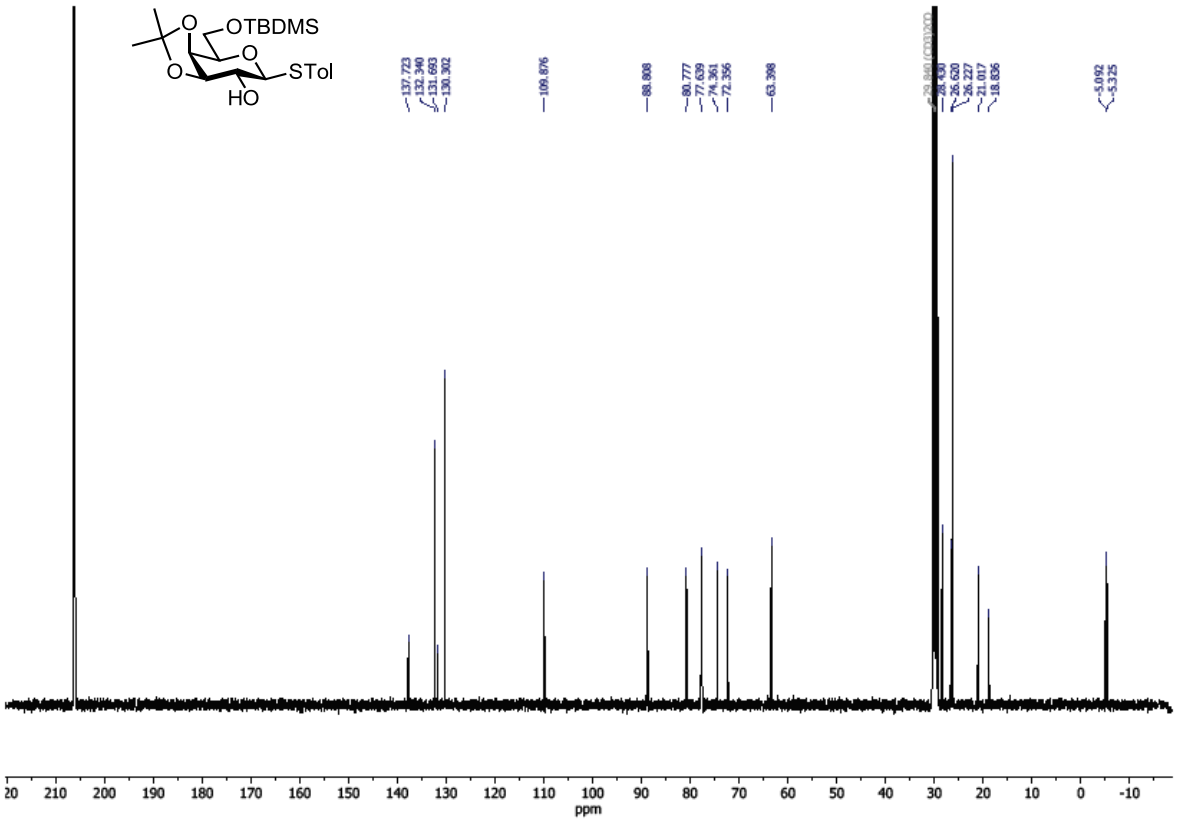


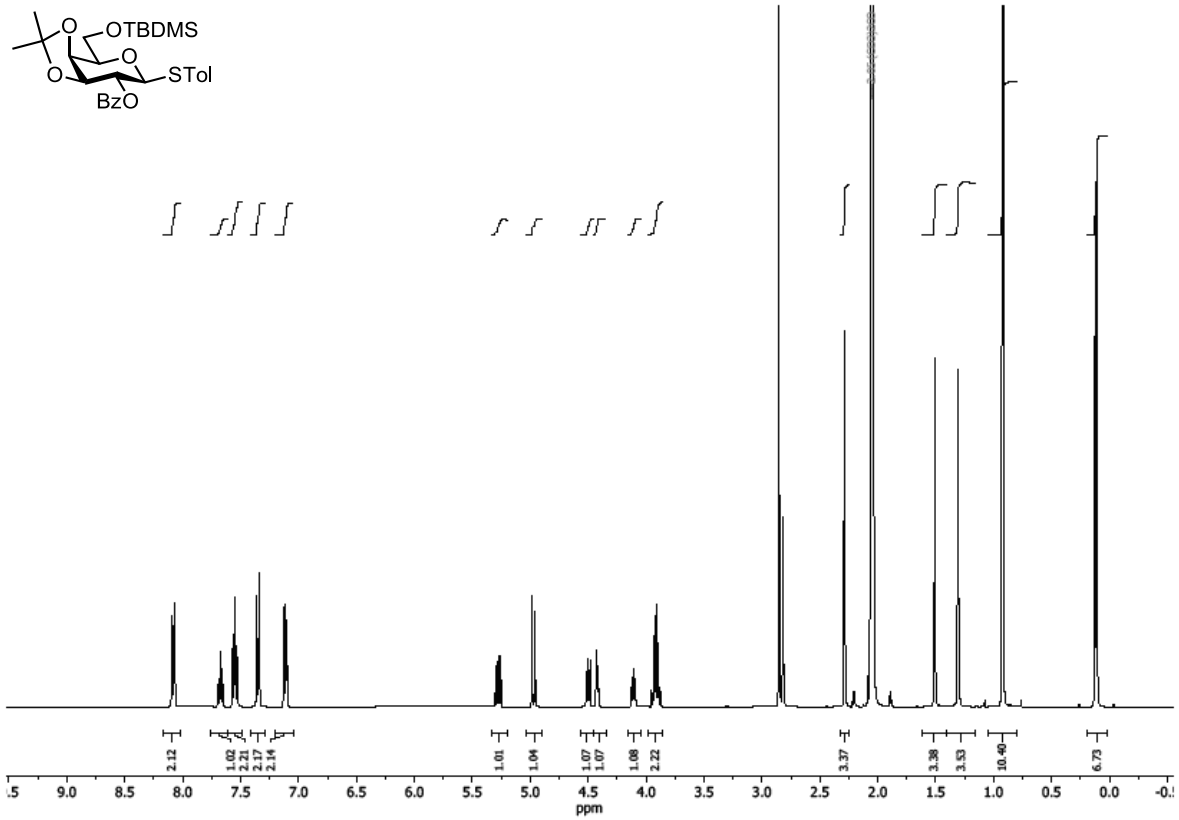
^{13}C NMR of **71** ($CDCl_3$, 100 MHz, 297 K, 171.3 60.5 21.2 14.3 EtOAc)



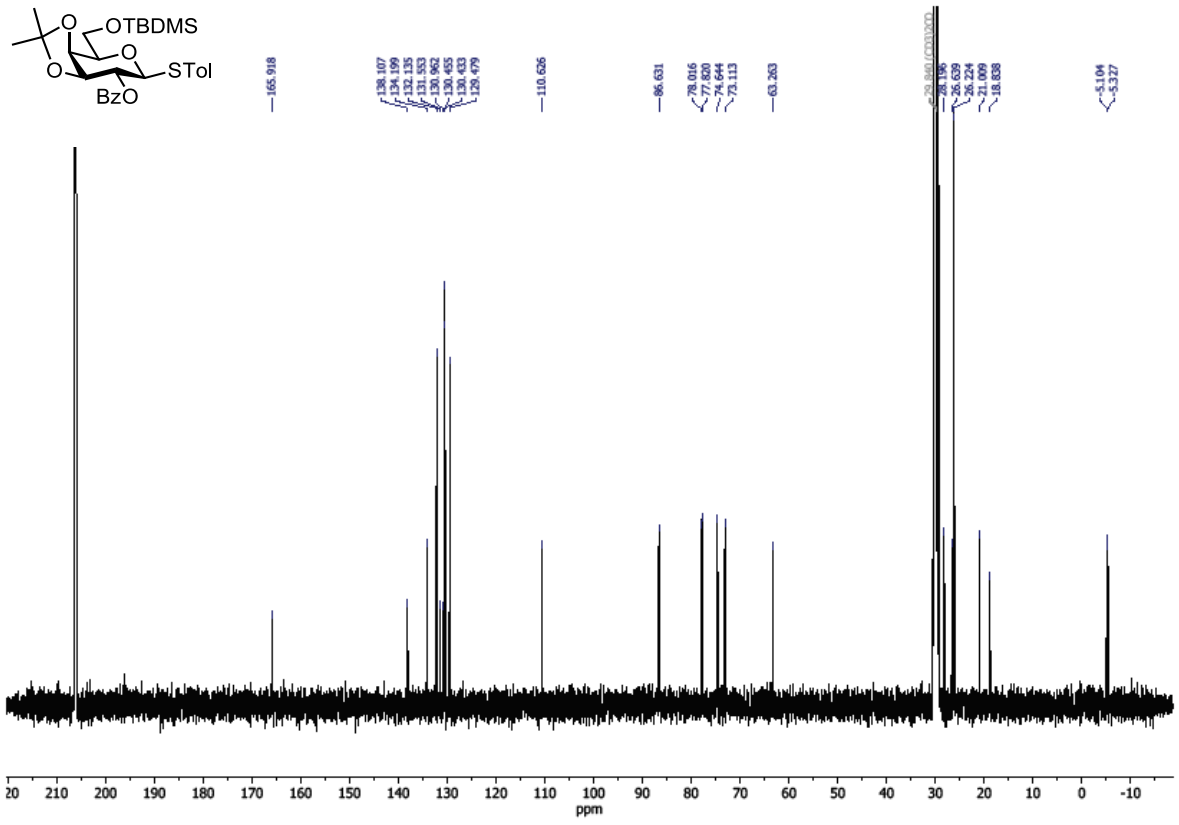
^{1}H NMR of **98** (CD_3COCD_3, 400 MHz, 297 K, 2.84 H_2O 2.81 HDO, 2.09 CH_3COCH_3)



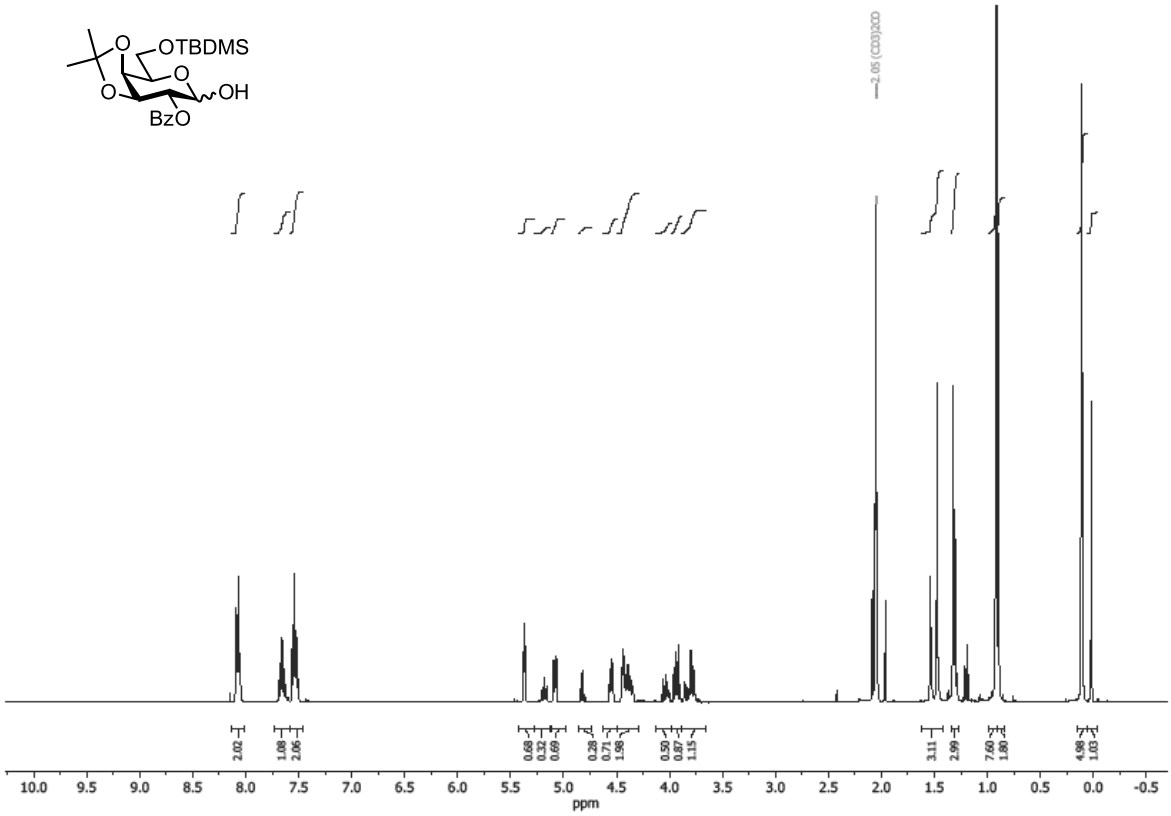
^{13}C NMR of **98** (CD_3COCD_3, 100 MHz, 297 K)



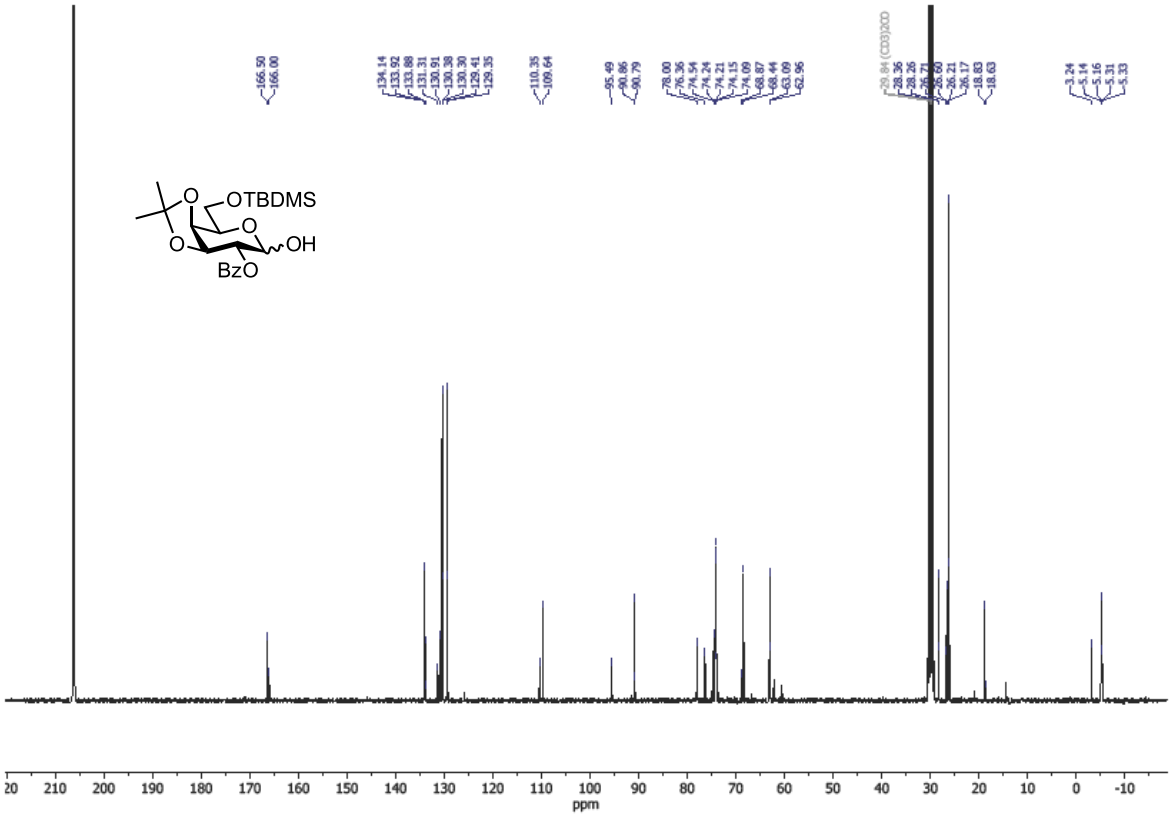
^{1}H NMR of **76** (CD_3COCD_3, 400 MHz, 297 K, 2.84 H_2O 2.81 HDO)



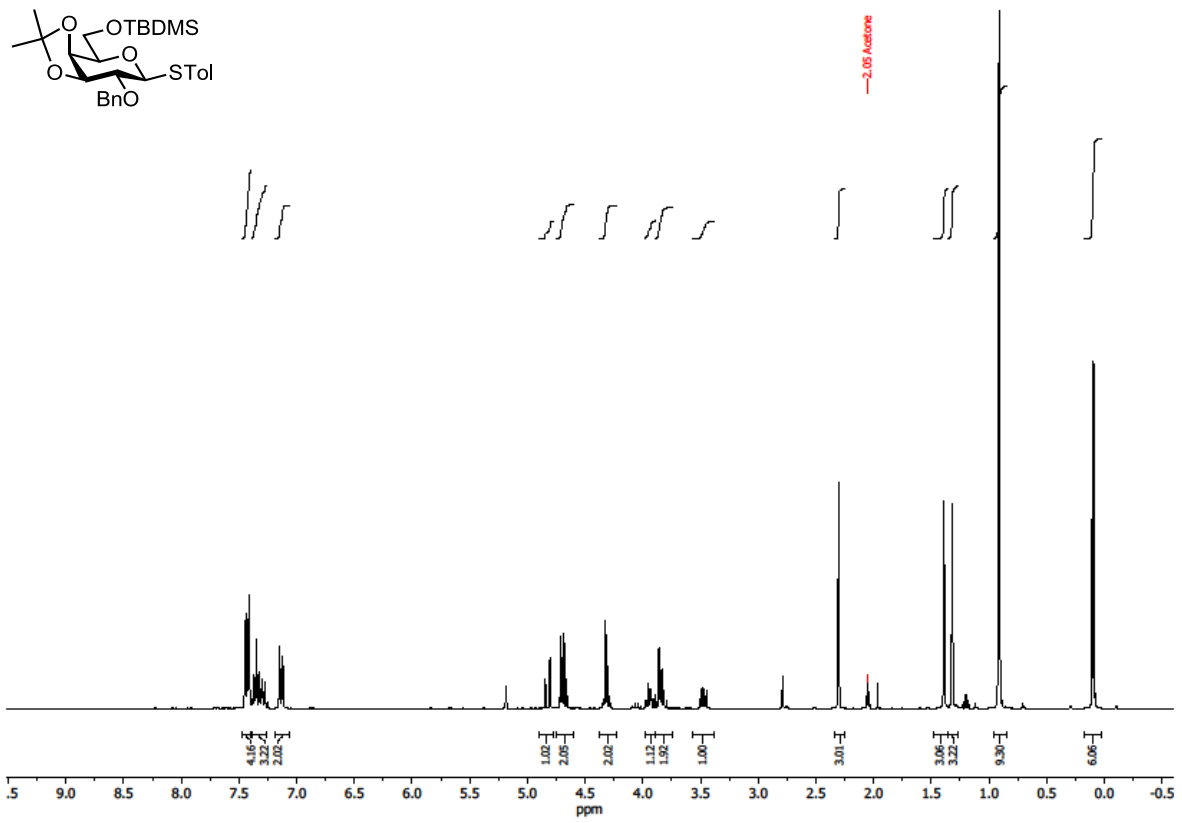
^{13}C NMR of **76** (CD_3COCD_3, 100 MHz, 297 K)



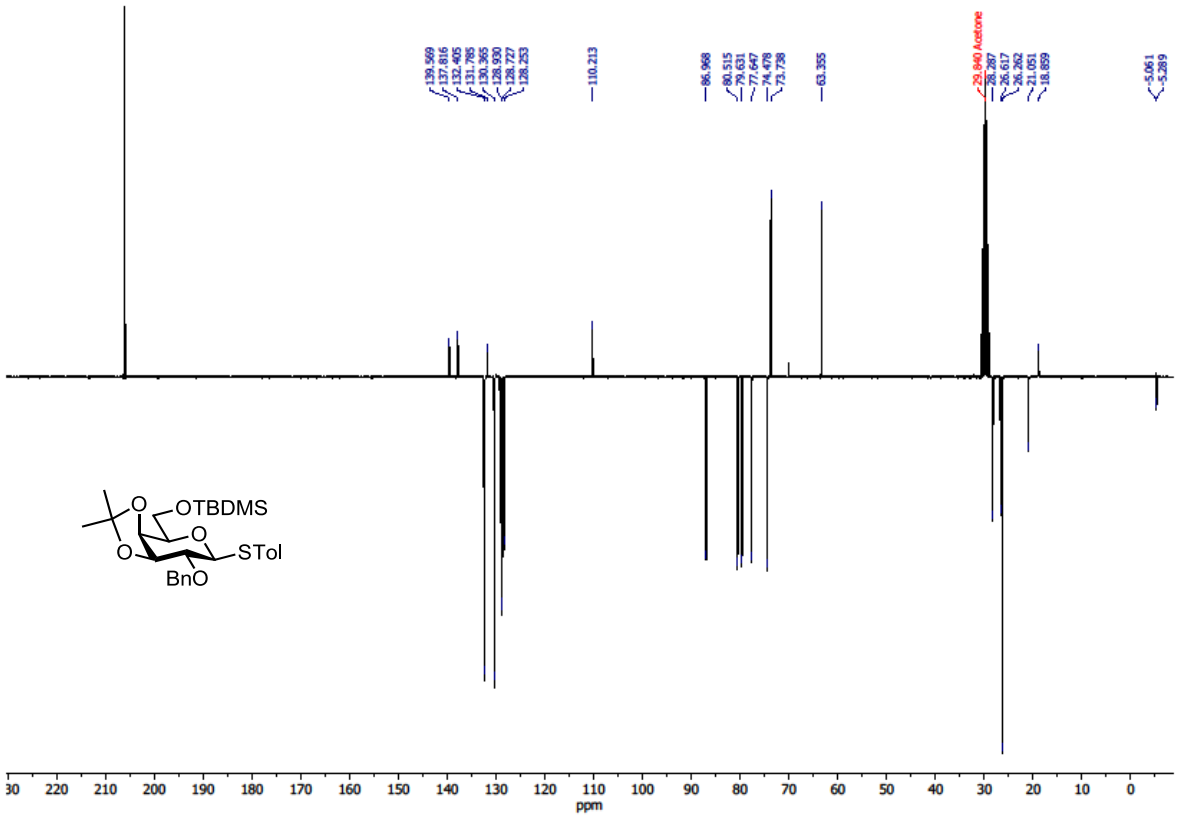
^{1}H NMR of **99** (CD_3COCD_3, 400 MHz, 297 K, 2.84 H_2O 2.81 HDO, 4.05 1.97 1.20 EtOAc)



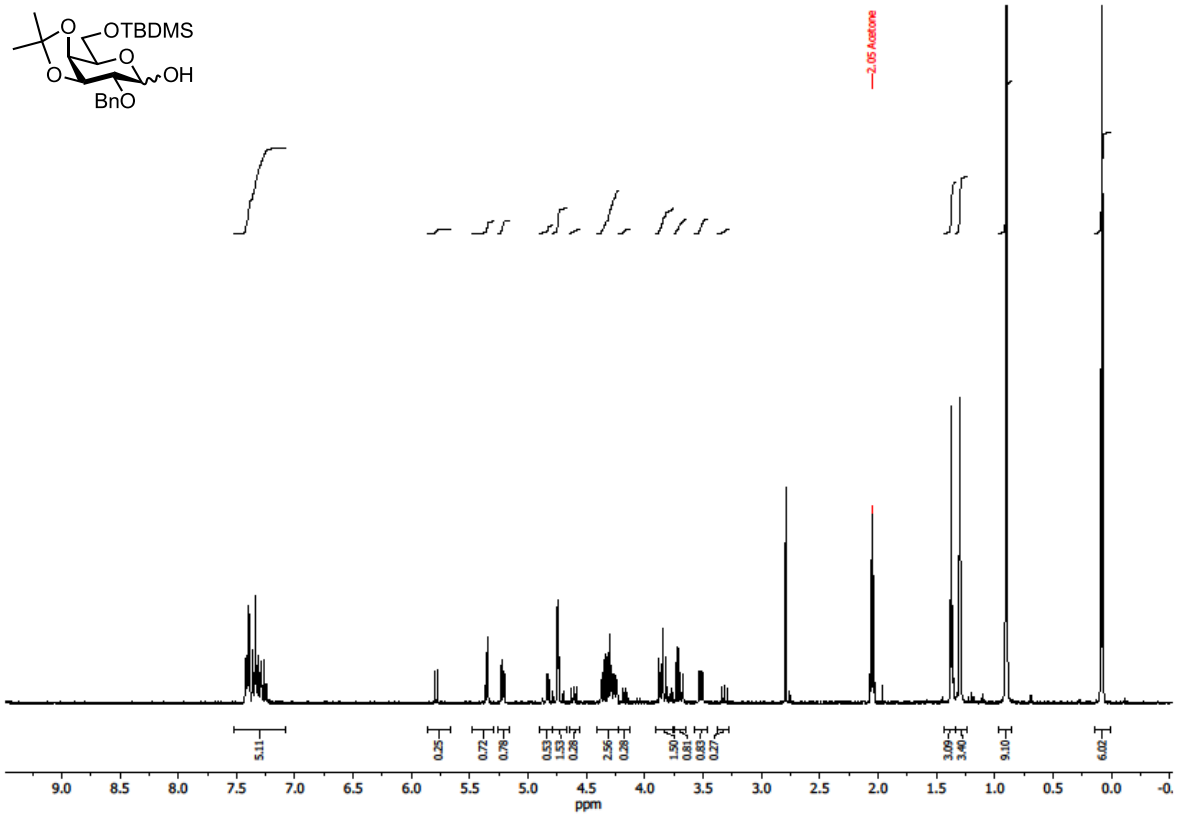
^{13}C NMR of **99** (CD_3COCD_3, 100 MHz, 297 K)



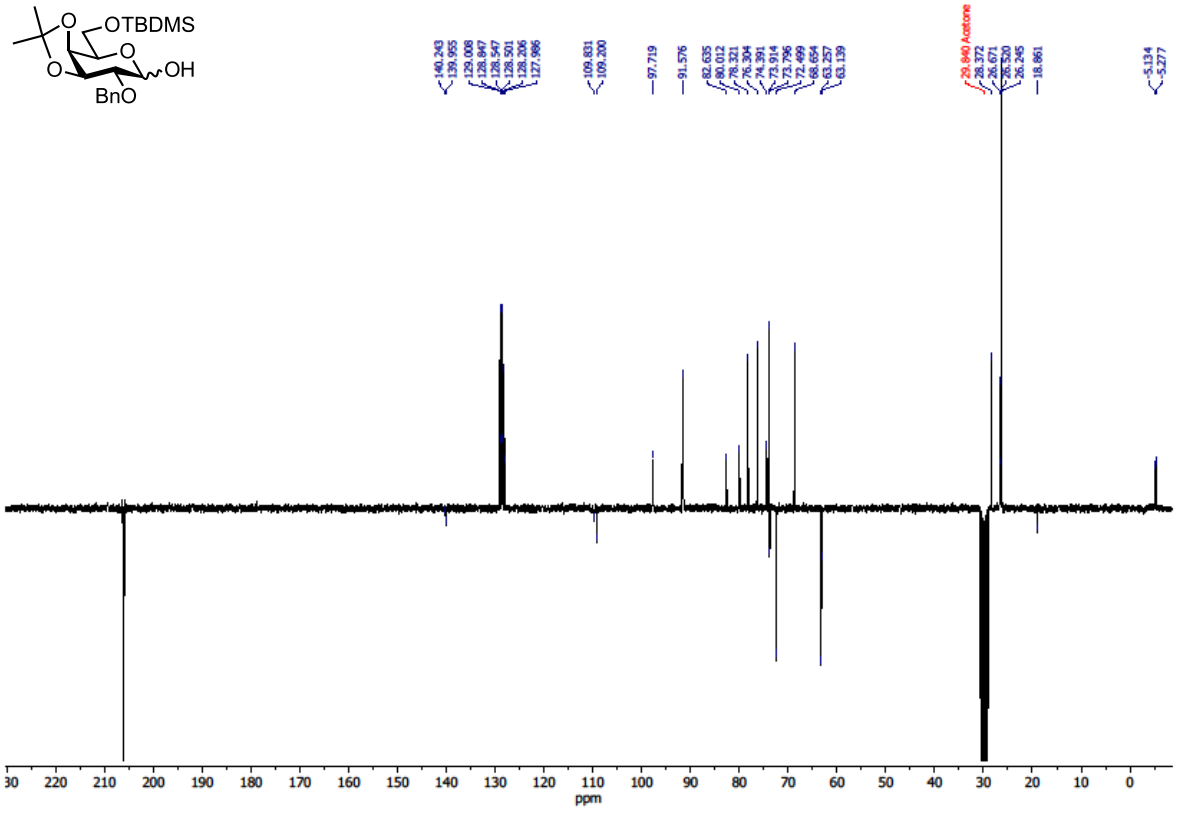
^{1}H NMR of **101** (CD_3COCD_3, 300 MHz, 297 K, 4.05 1.97 1.20 EtOAc, 2.84 H_2O 2.81 HDO, 5.19 Impurity)



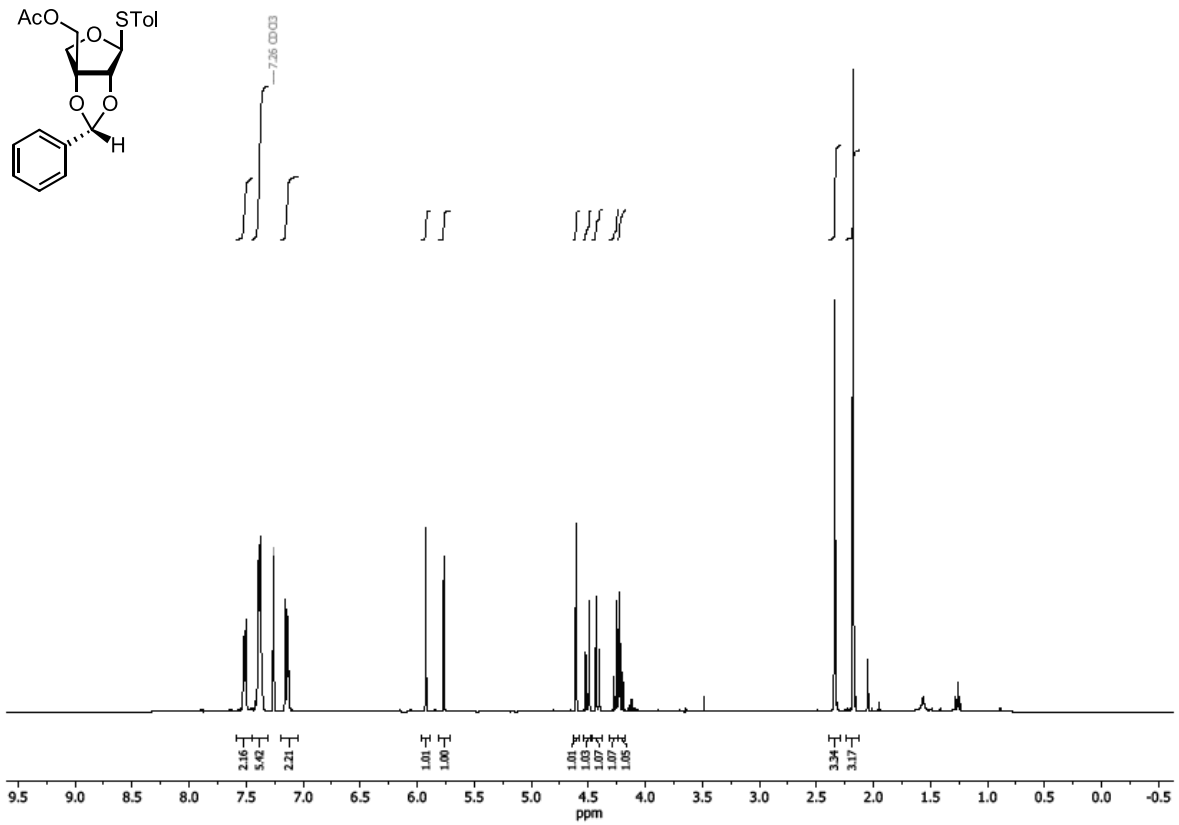
^{13}C APT NMR of **101** (CD_3COCD_3, 75 MHz, 297 K, 70.0 Impurity)



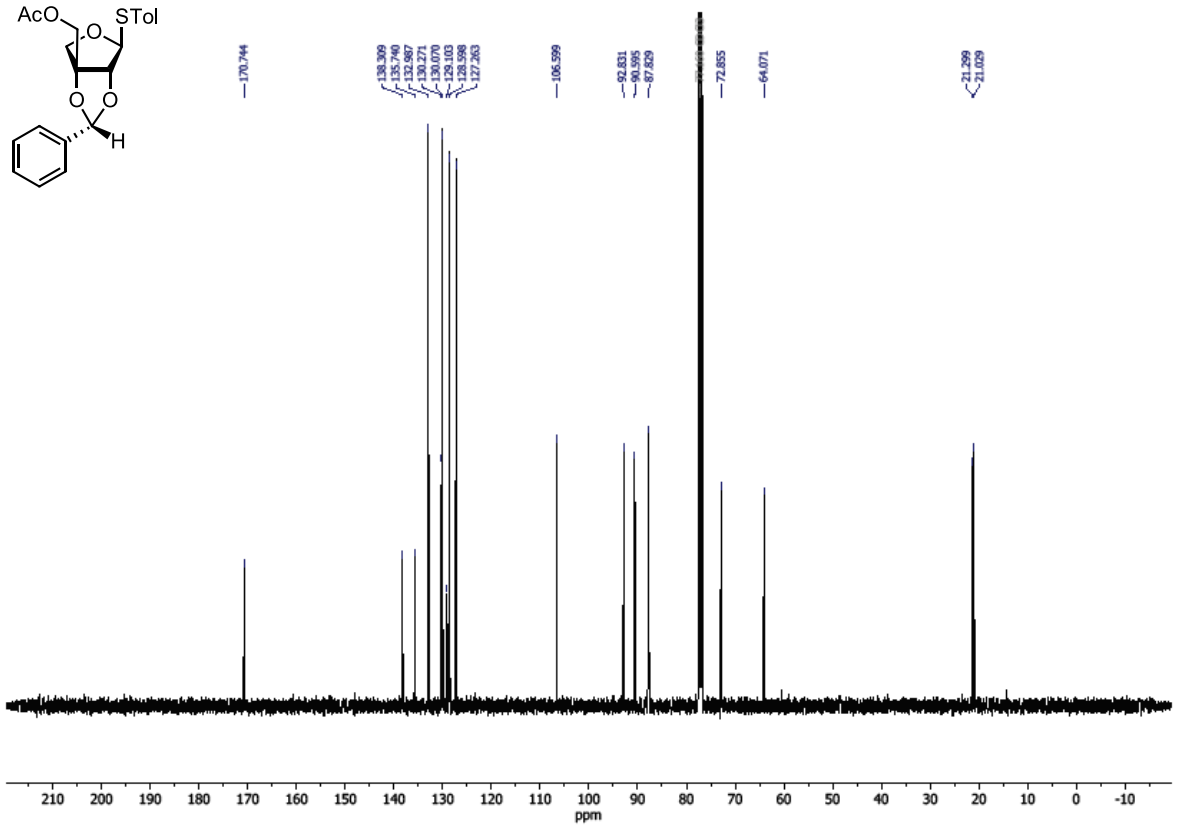
^{1}H NMR of **102** (CD_3COCD_3, 300 MHz, 297 K, 4.05 1.97 1.20 EtOAc, 2.84 H_2O 2.81 HDO)



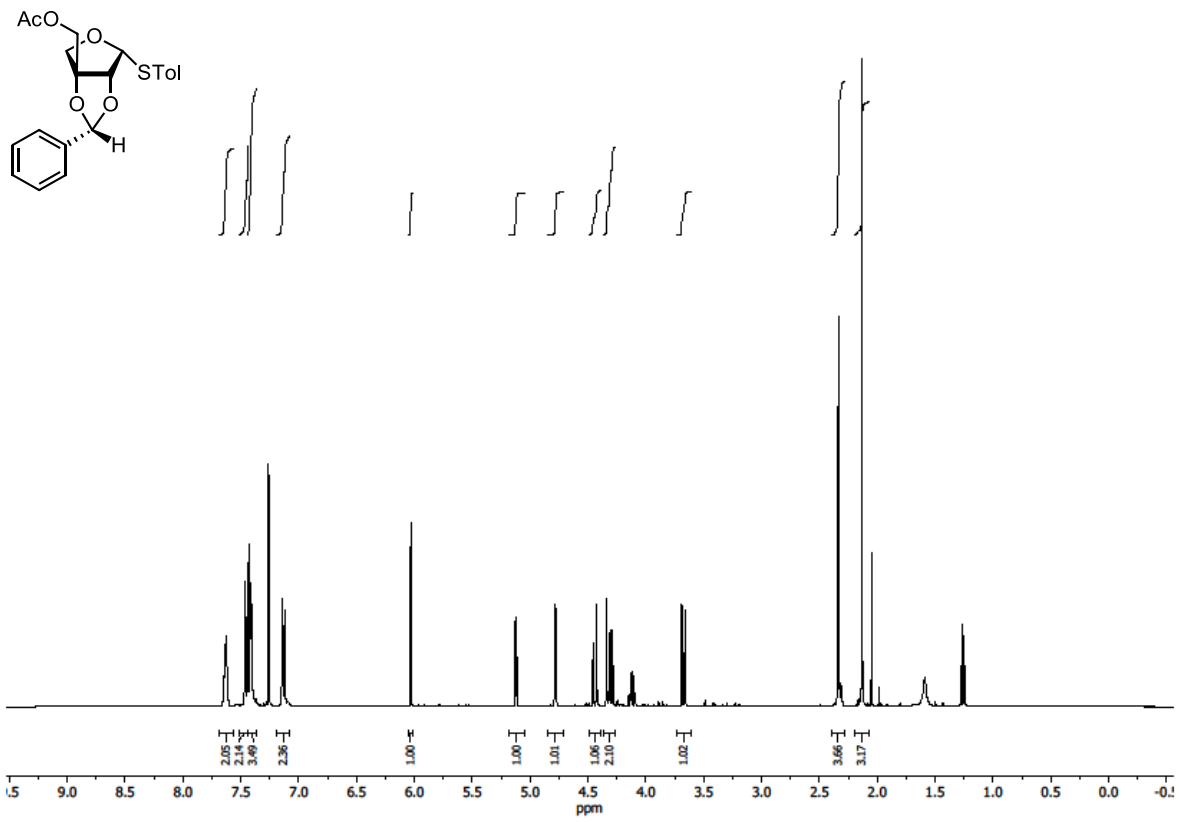
^{13}C APT NMR of **102** (CD_3COCD_3, 75 MHz, 297 K)



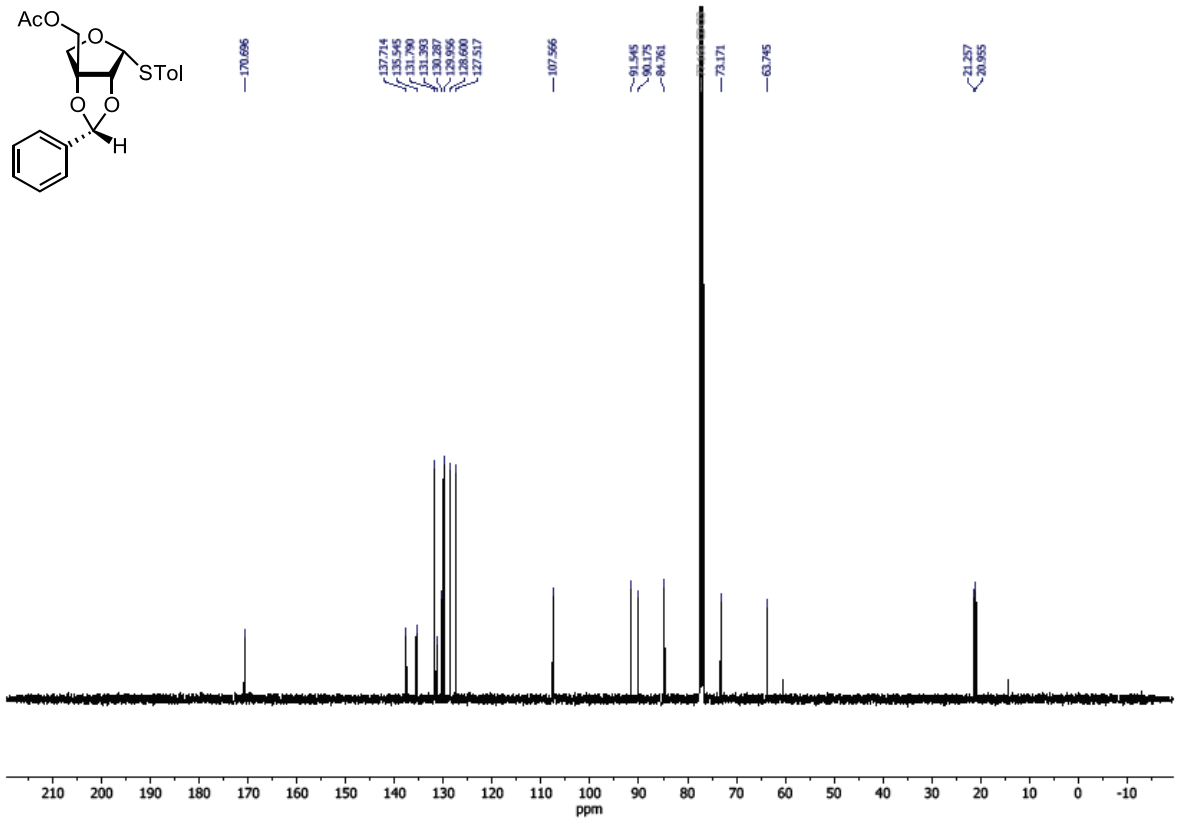
^{1}H NMR of **72-β** ($CDCl_3$, 400 MHz, 297 K, 4.12 2.05 1.26 EtOAc)



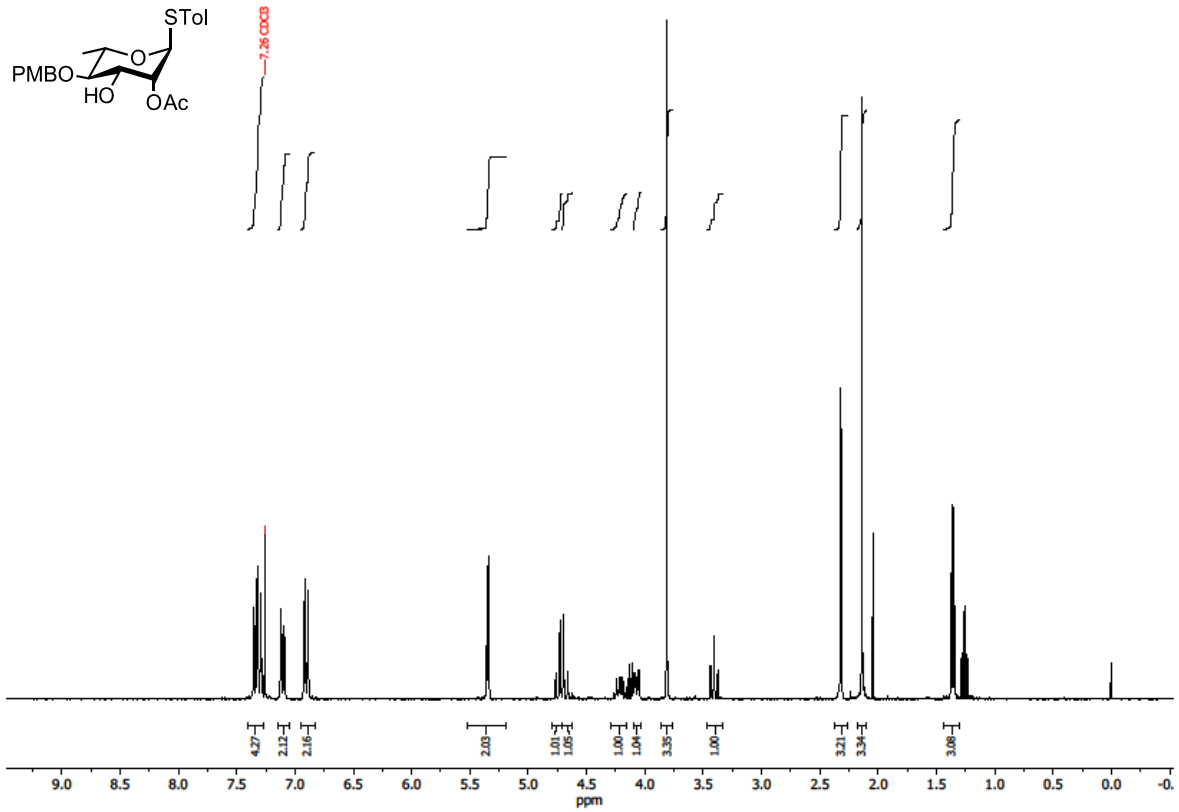
^{13}C NMR of **72-β** ($CDCl_3$, 100 MHz, 297 K)



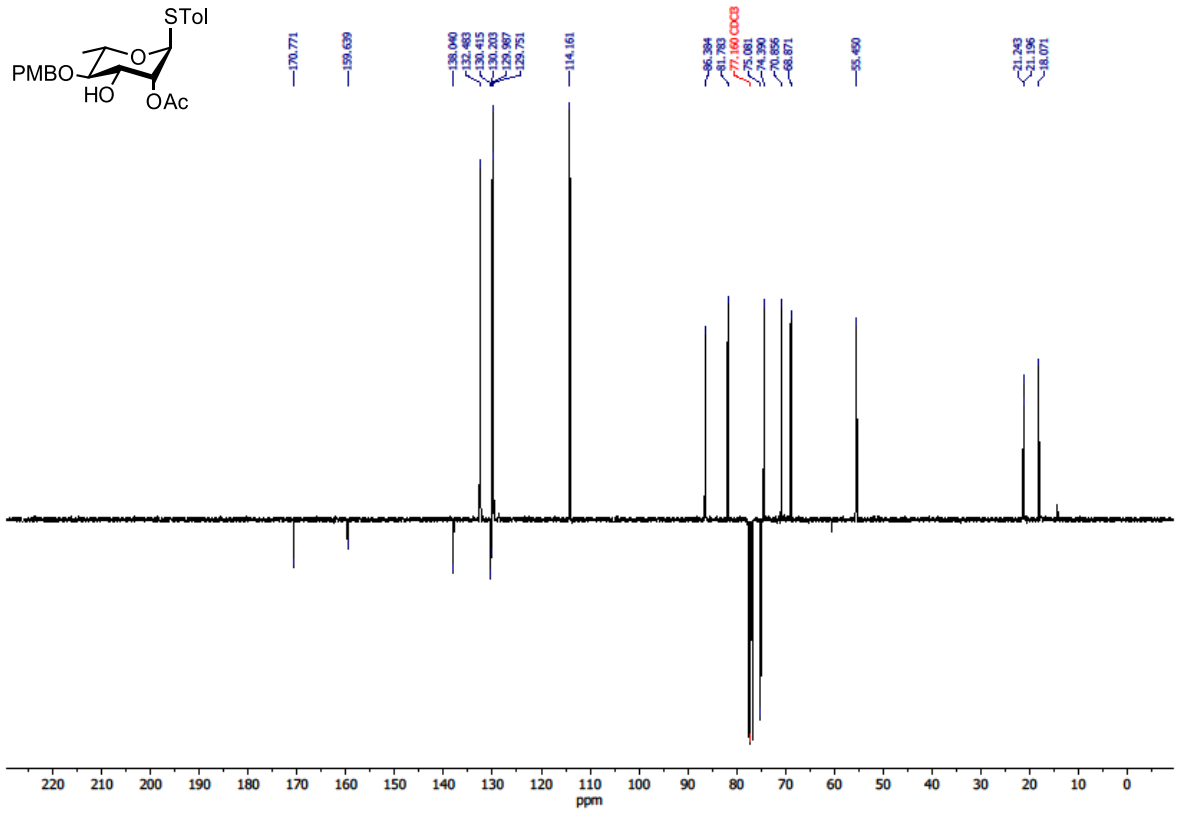
^{1}H NMR of **72-α** ($CDCl_3$, 400 MHz, 297 K, 4.12 2.05 1.26 EtOAc)



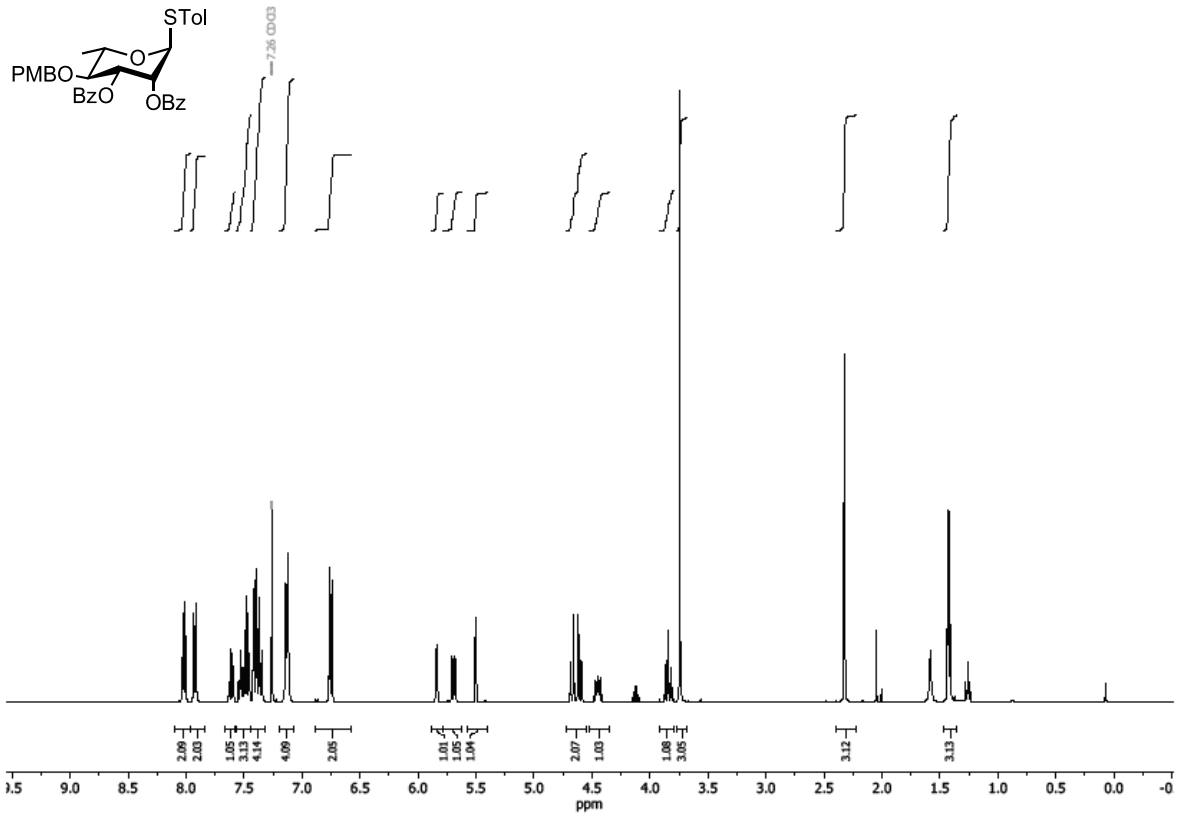
^{13}C NMR of **72-α** ($CDCl_3$, 100 MHz, 297 K, 171.3 60.5 21.2 14.3 EtOAc)



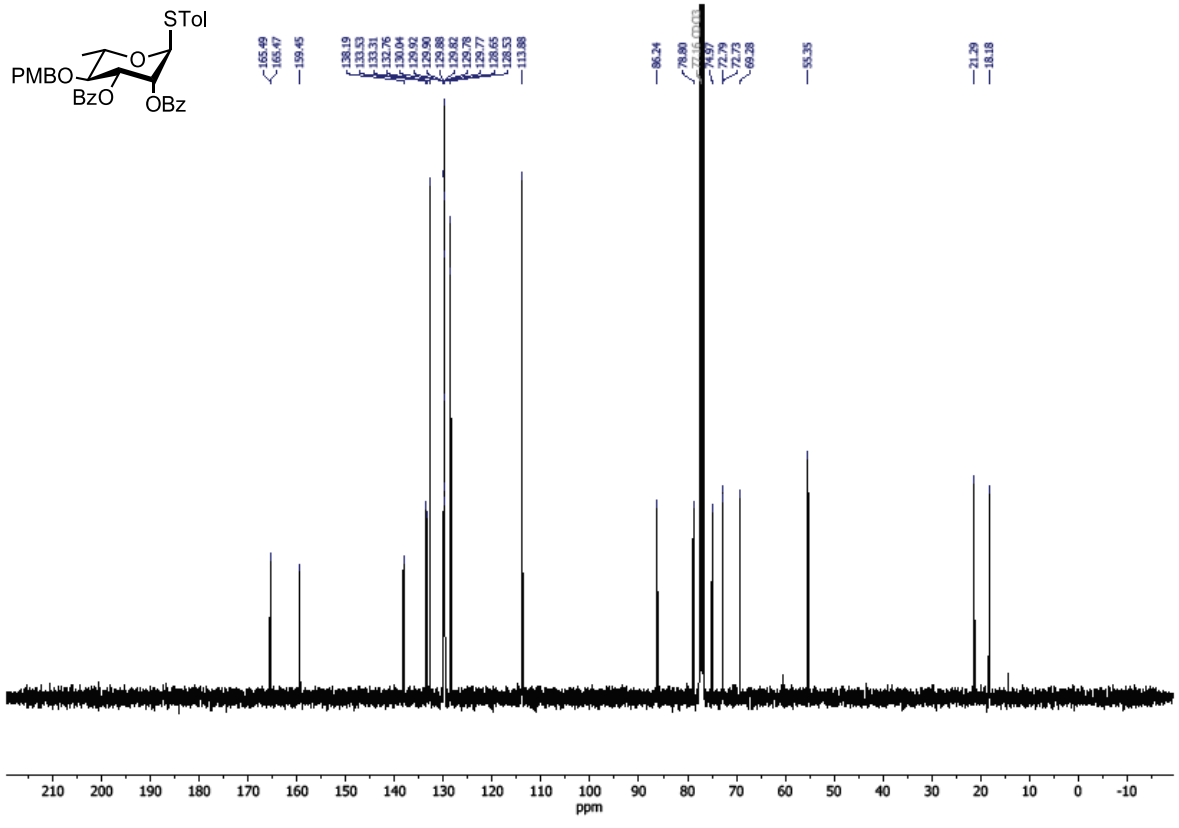
^{1}H NMR of **75** ($CDCl_3$, 300 MHz, 297 K, 4.12 2.05 1.26 EtOAc)



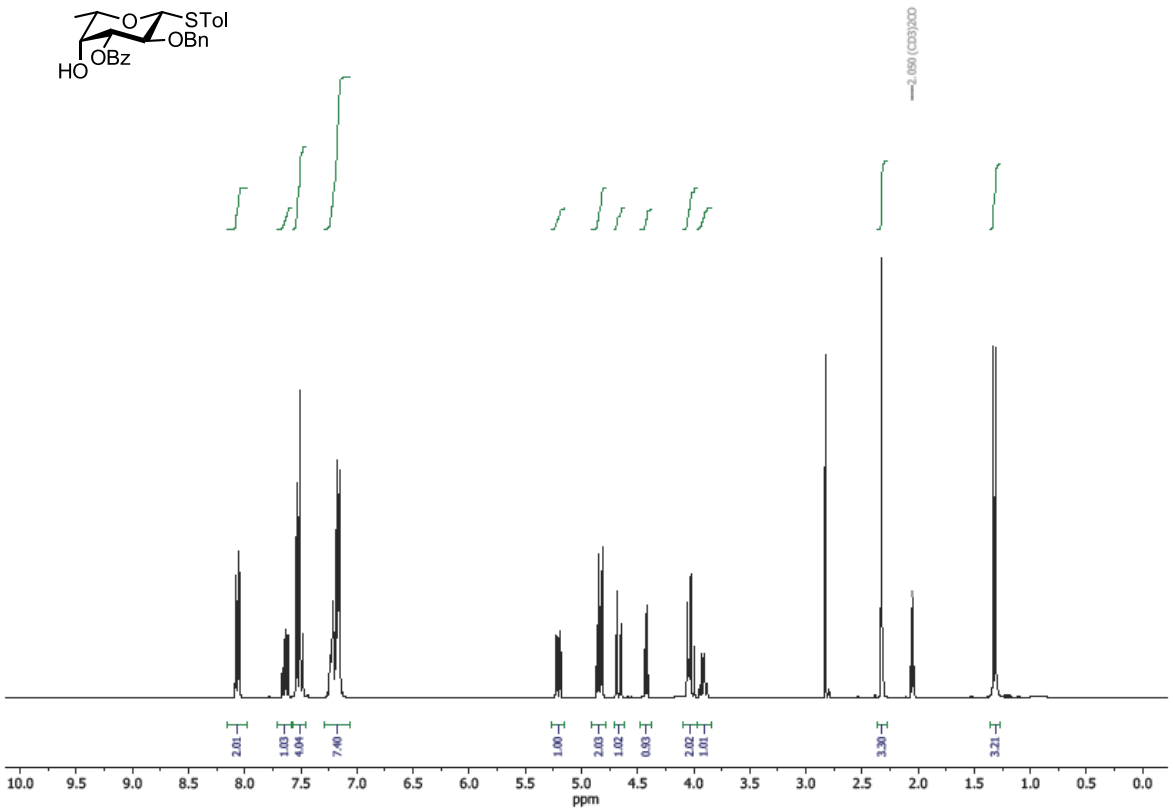
^{13}C APT NMR of **75** ($CDCl_3$, 75 MHz, 297 K, 171.4 60.5 21.0 14.2 EtOAc)



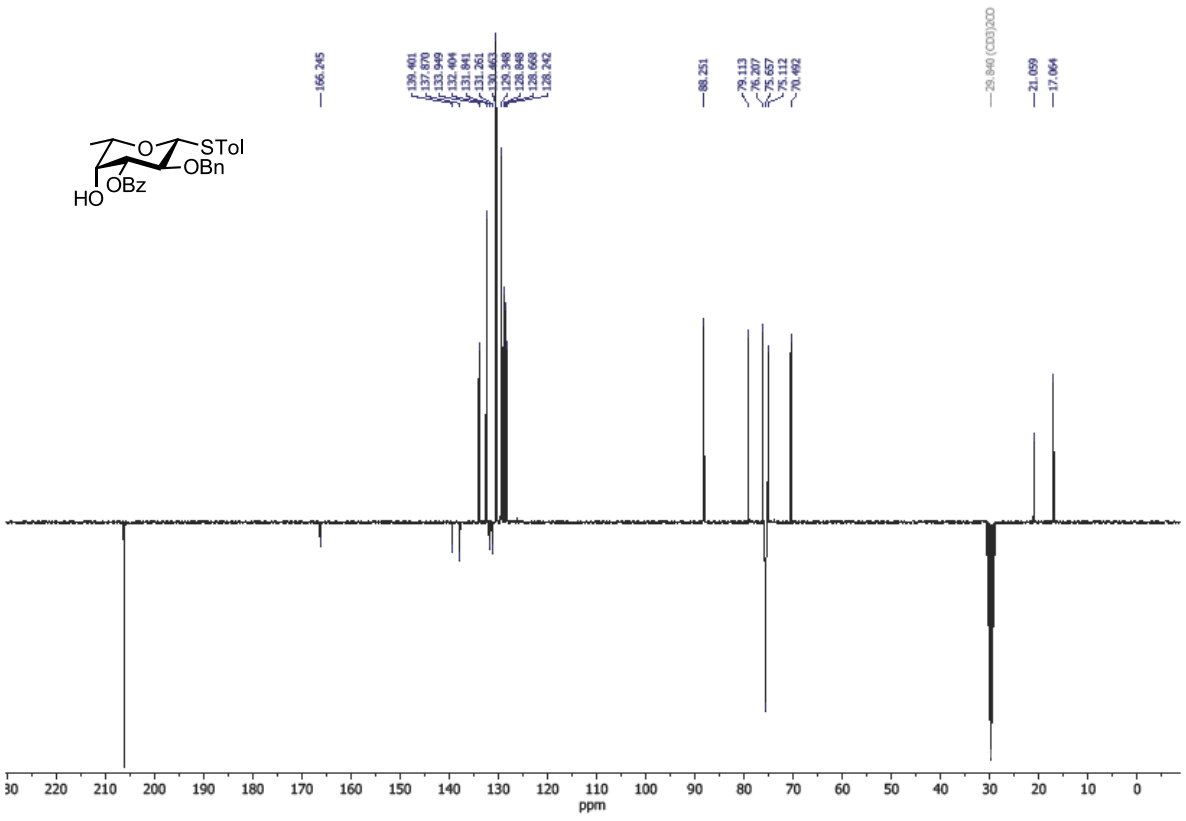
^{1}H NMR of **89** ($CDCl_3$, 400 MHz, 297 K, 4.12 2.05 1.26 EtOAc, 1.56 H_2O)



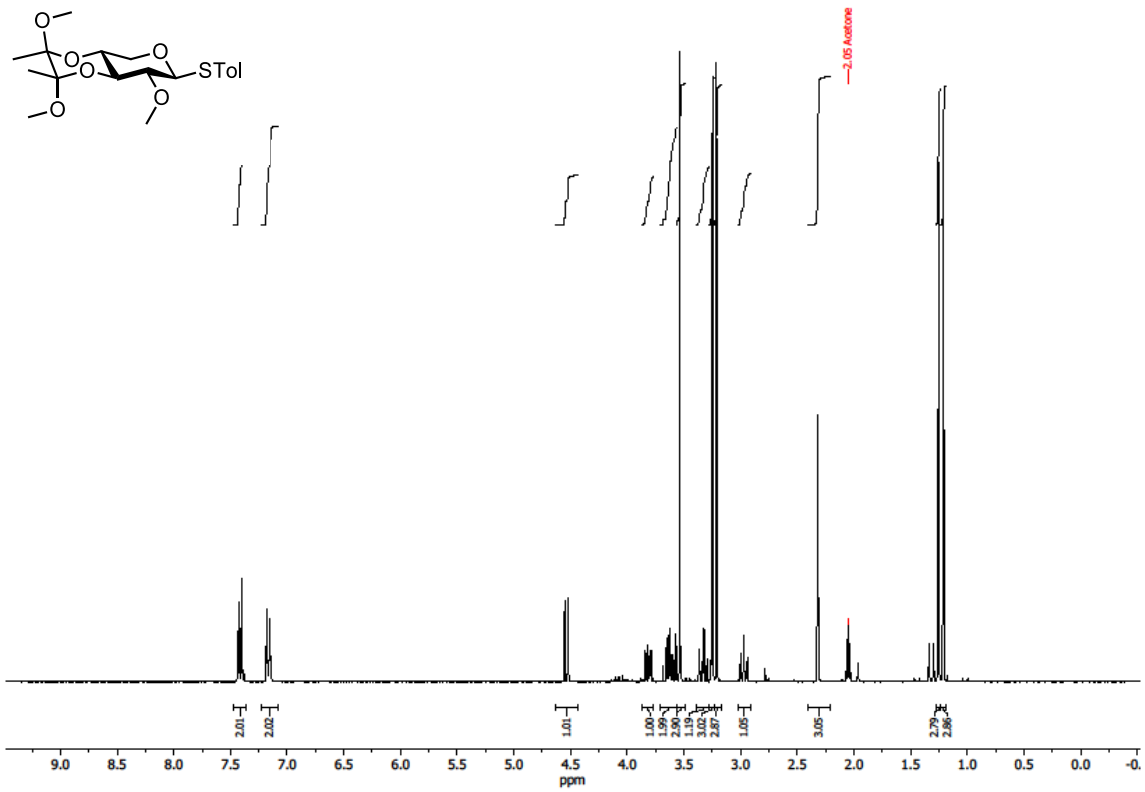
^{13}C NMR of **89** ($CDCl_3$, 100 MHz, 297 K)



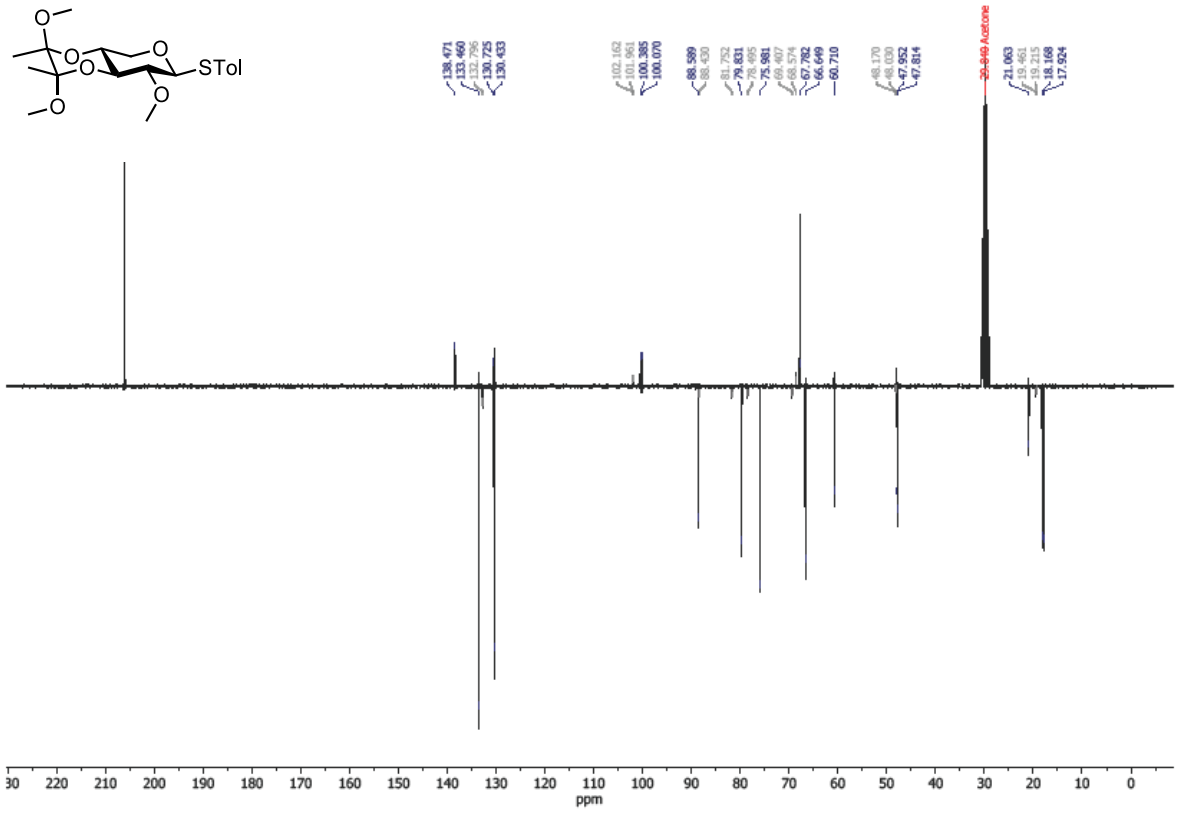
^{1}H NMR of **109** (CD_3COCD_3, 300 MHz, 297 K)



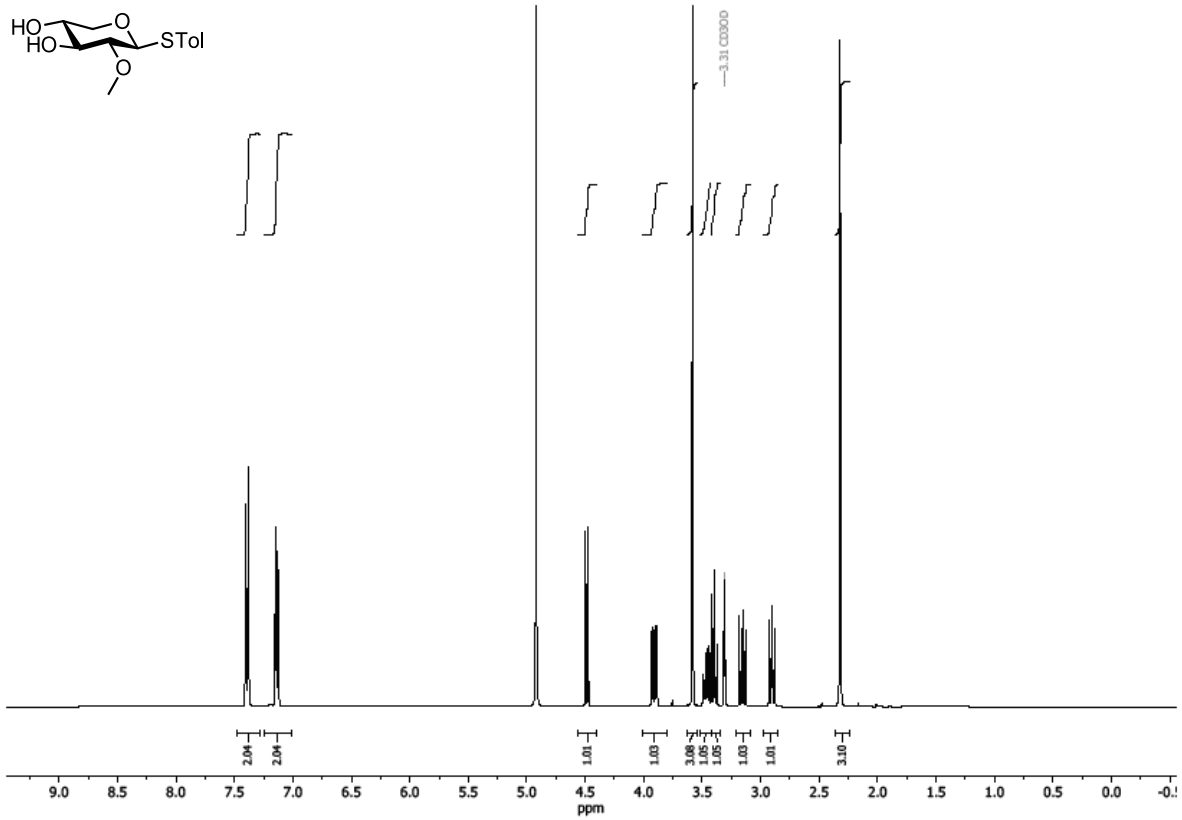
^{13}C APT NMR of **109** (CD_3COCD_3, 75 MHz, 297 K)



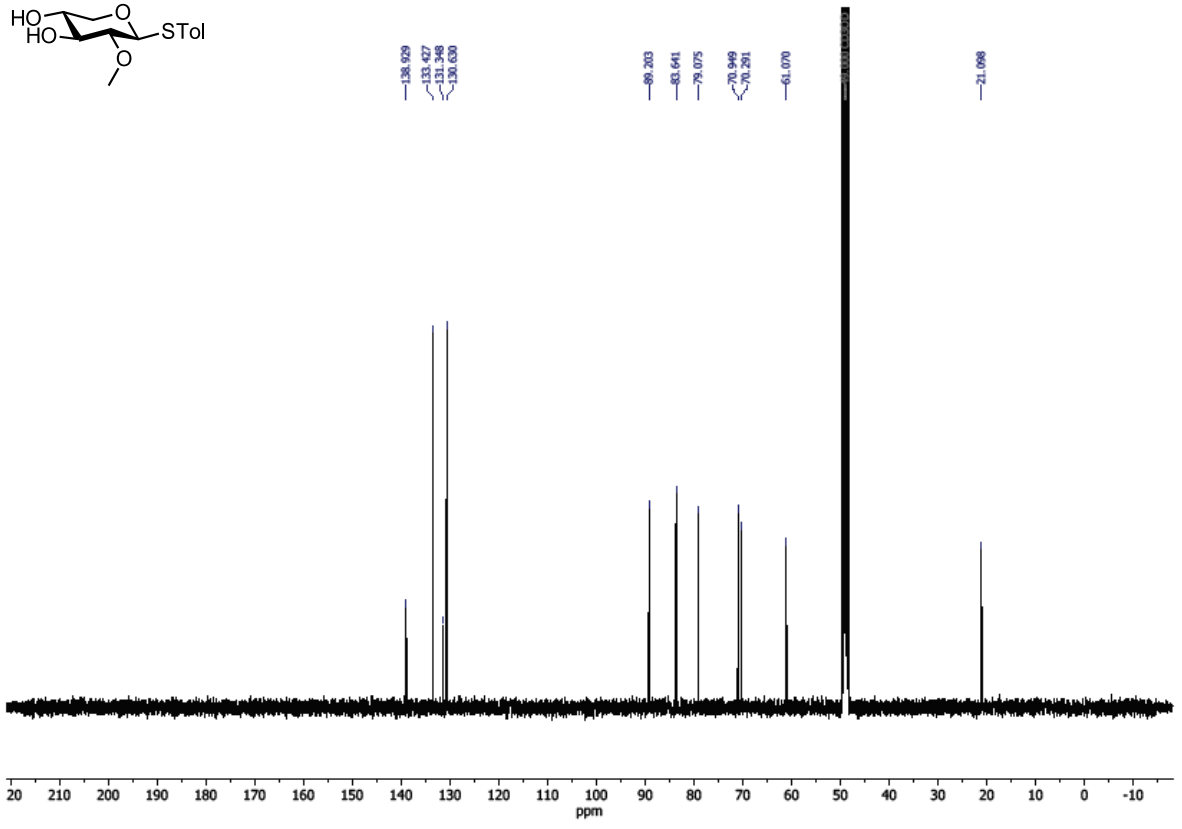
^{1}H NMR of **112** (CD_3COCD_3, 300 MHz, 297 K, 4.05 1.97 1.20 EtOAc, 2.84 H_2O 2.81 HDO, 3.32 3.26 1.34 1.30 BBA diastereomers)



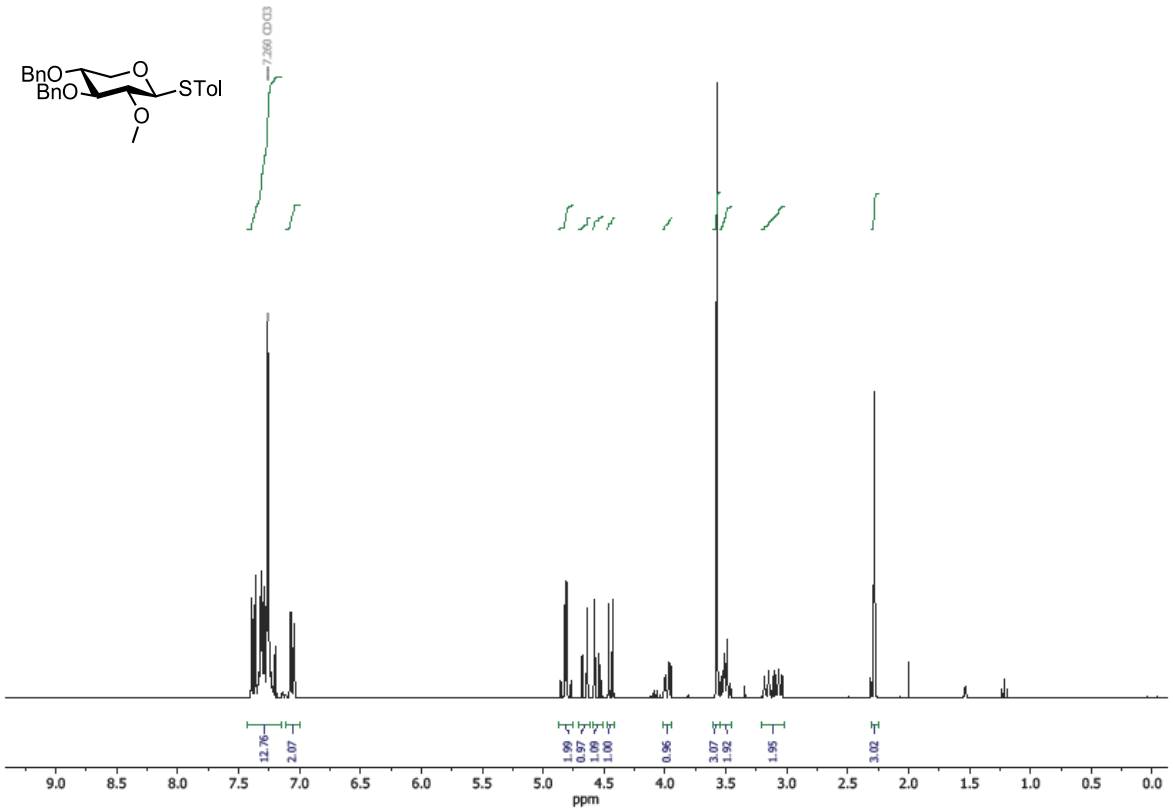
^{13}C APT NMR of **112** (CD_3COCD_3, 75 MHz, 297 K, grey: BBA diastereomers)



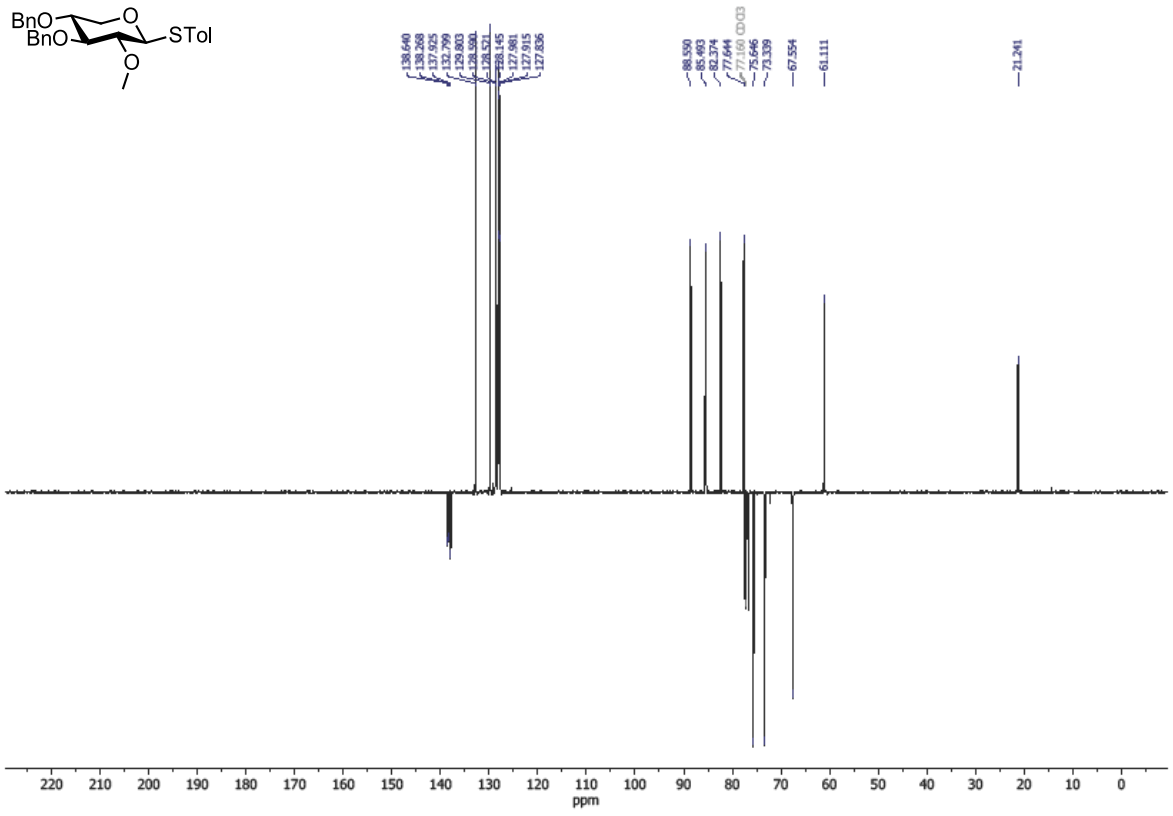
^{1}H NMR of **113** (CD_3OD, 400 MHz, 297 K, 4.87 H_2O)



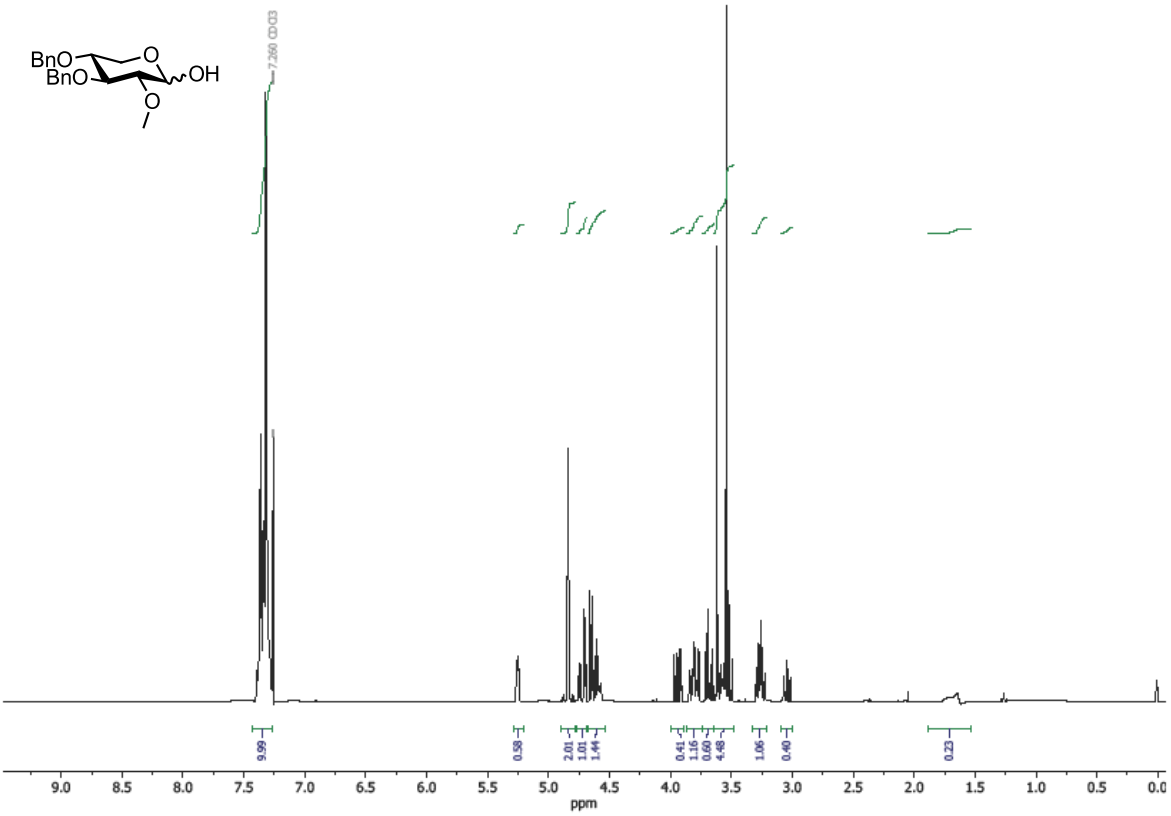
^{13}C NMR of **113** (CD_3OD, 100 MHz, 297 K)



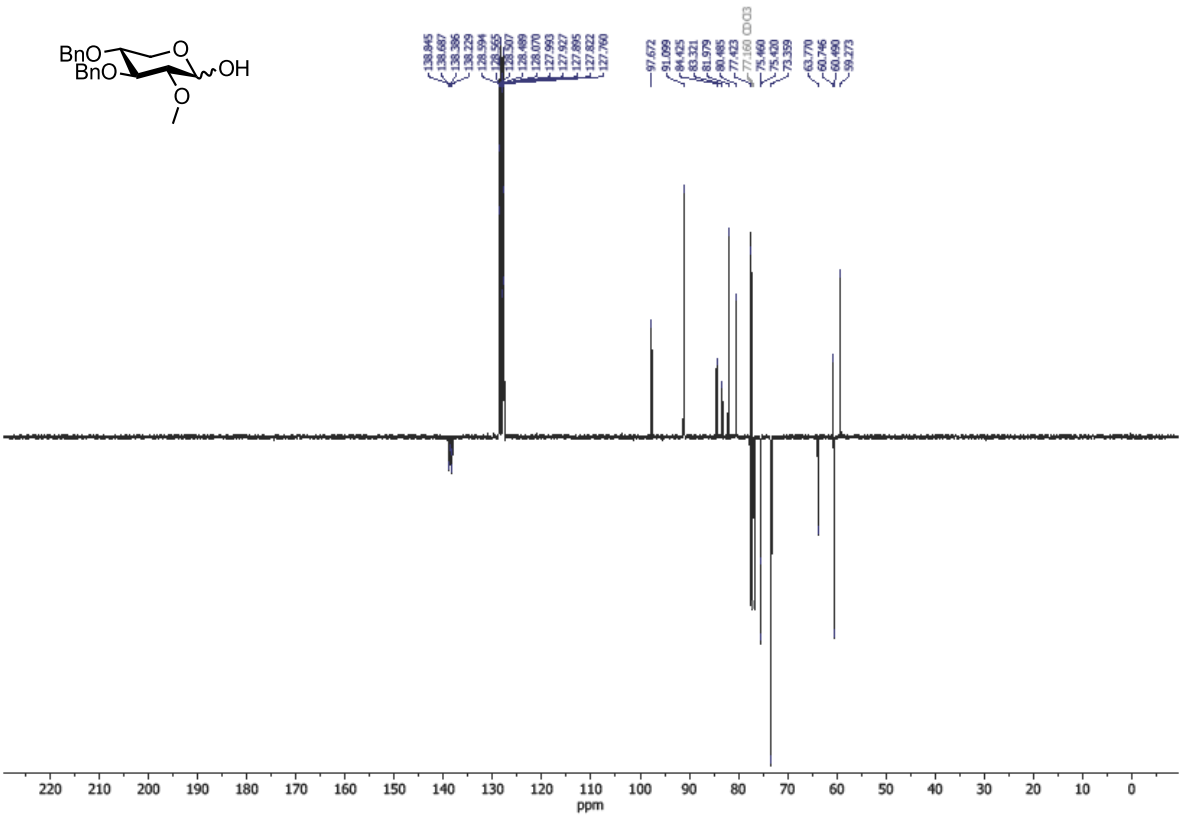
^{1}H NMR of **82** ($CDCl_3$, 300 MHz, 297 K, 4.12 2.05 1.26 EtOAc, 1.56 H_2O)



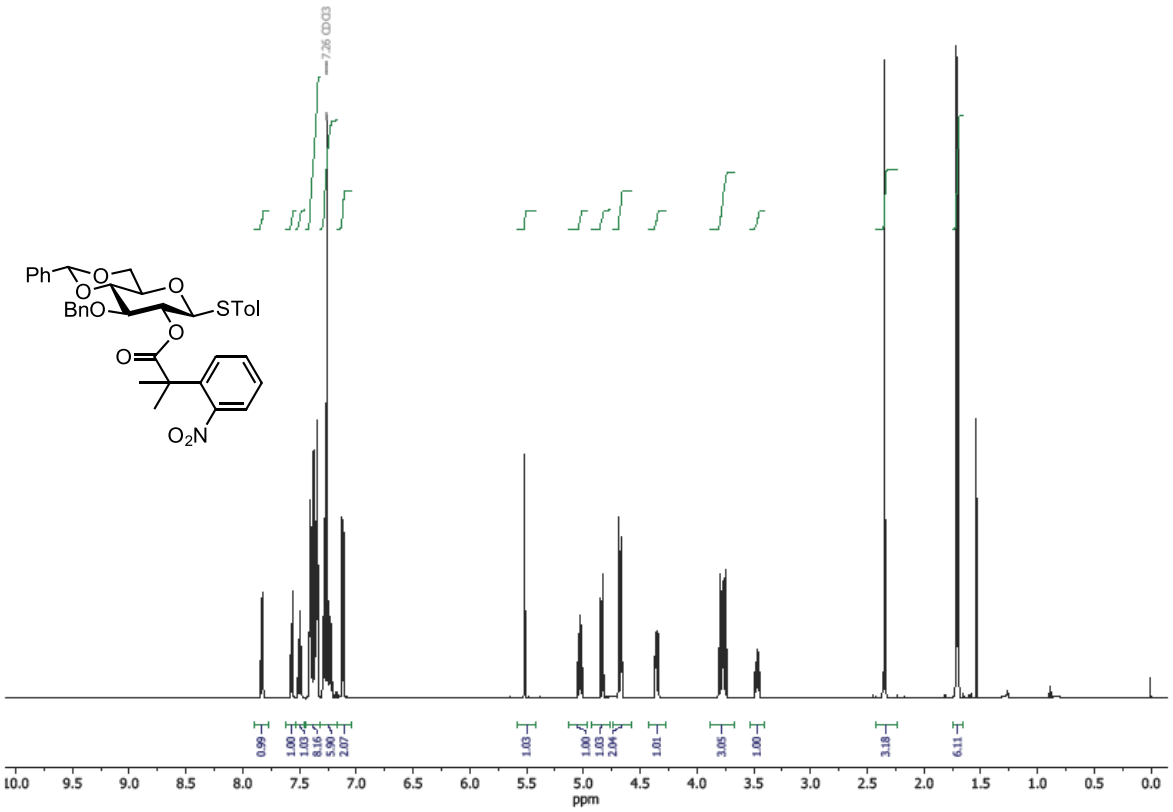
^{13}C APT NMR of **82** ($CDCl_3$, 75 MHz, 297 K)



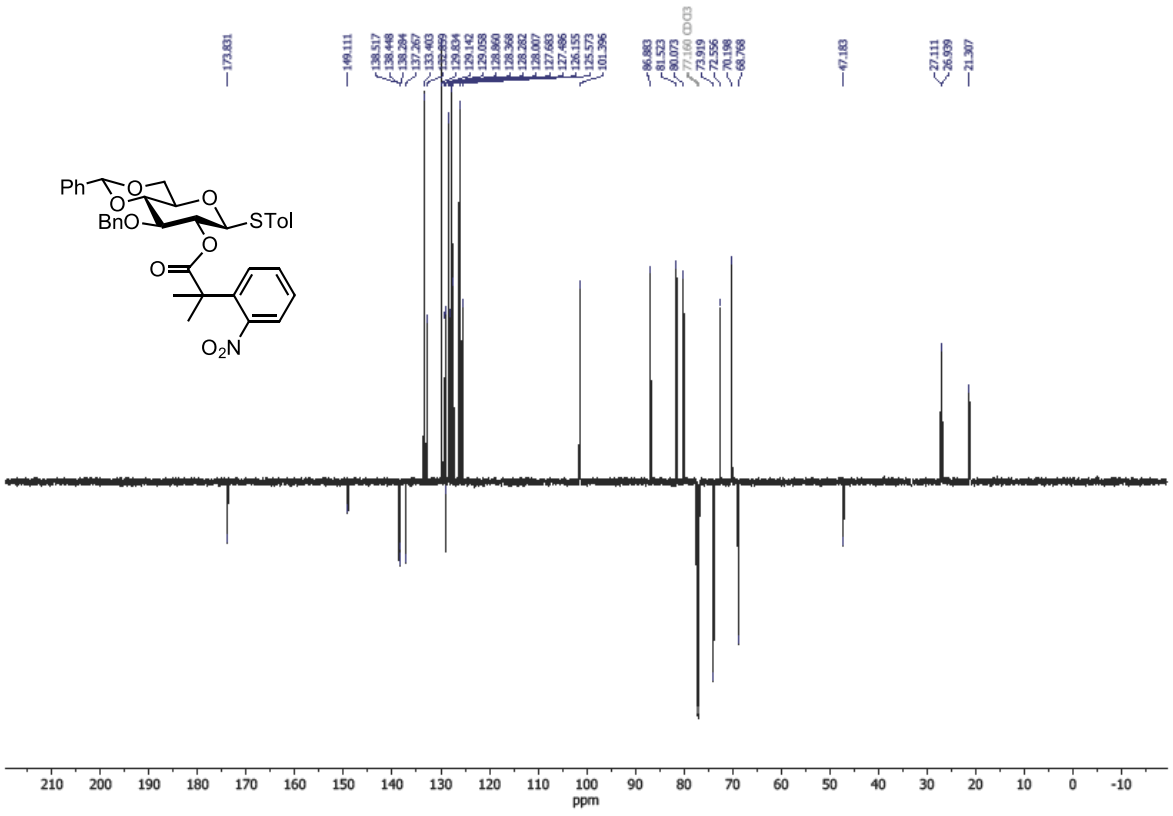
^{1}H NMR of **114** ($CDCl_3$, 300 MHz, 297 K)



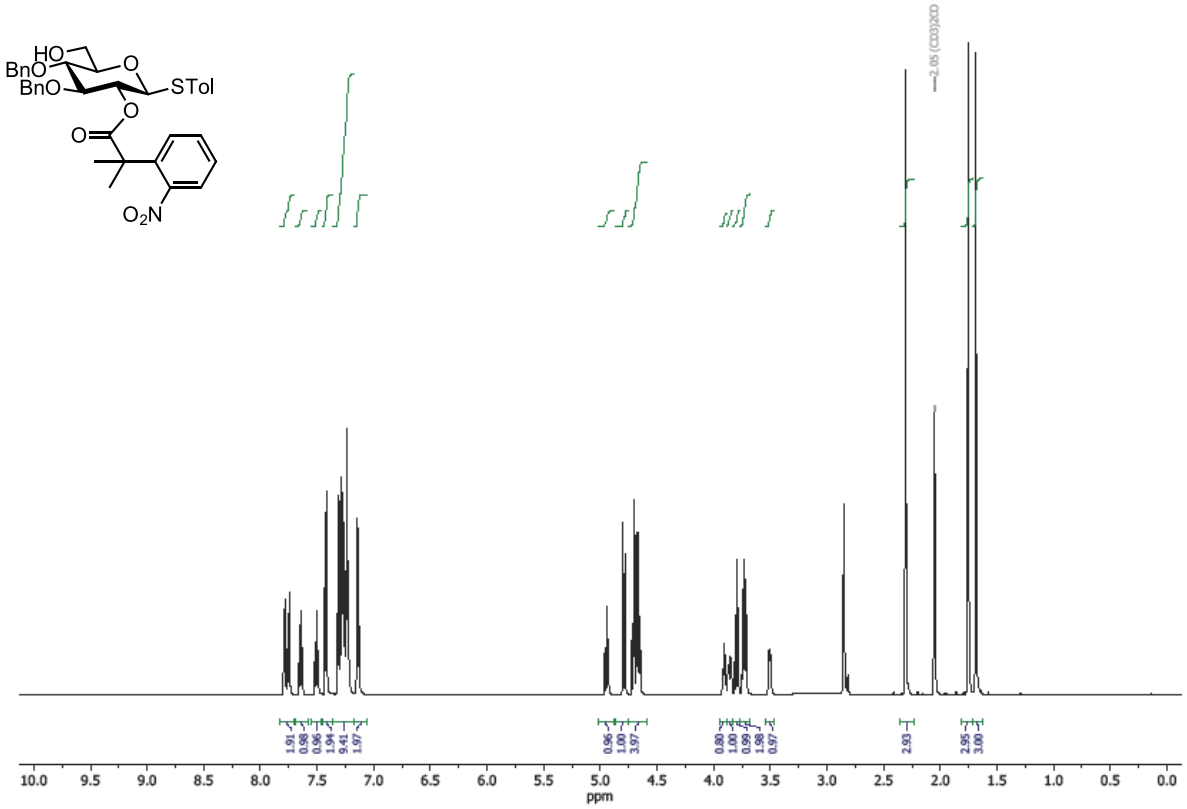
^{13}C APT NMR of **114** ($CDCl_3$, 75 MHz, 297 K)



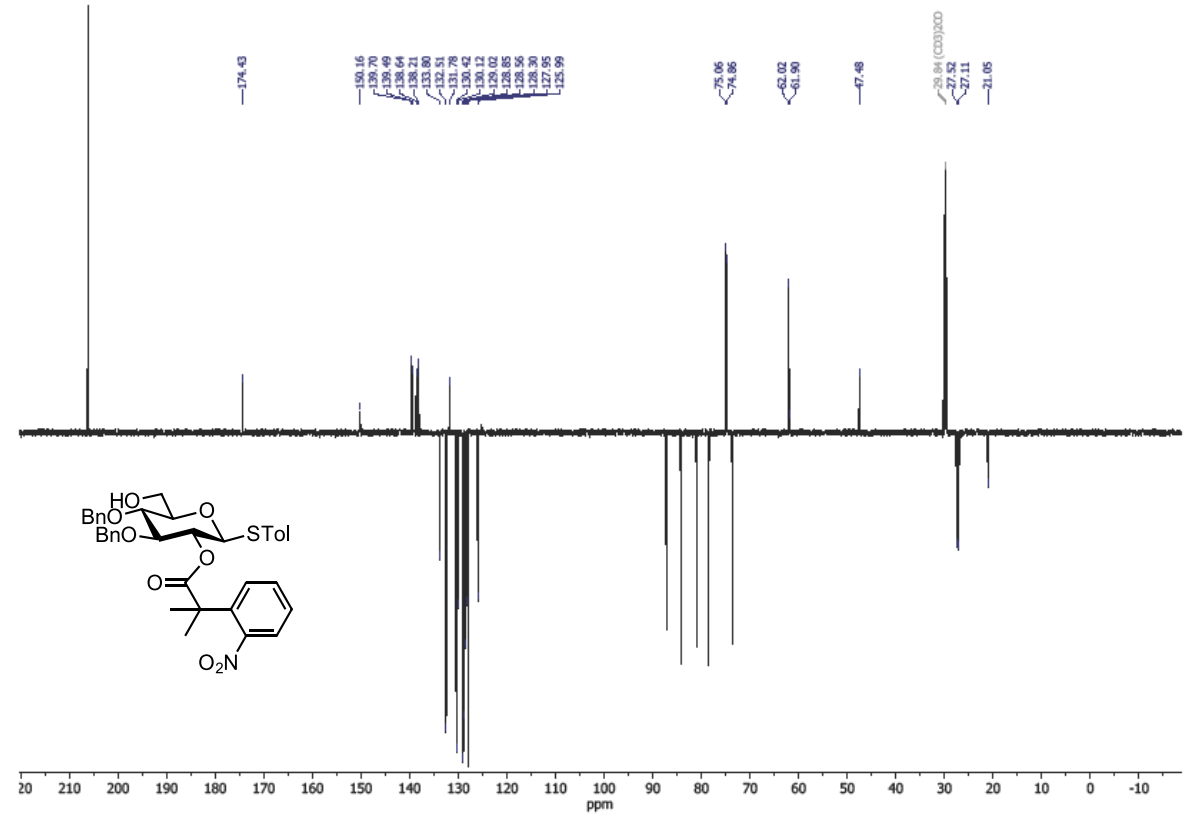
^{1}H NMR of **117** ($CDCl_3$, 600 MHz, 297 K, 1,56 H_2O)



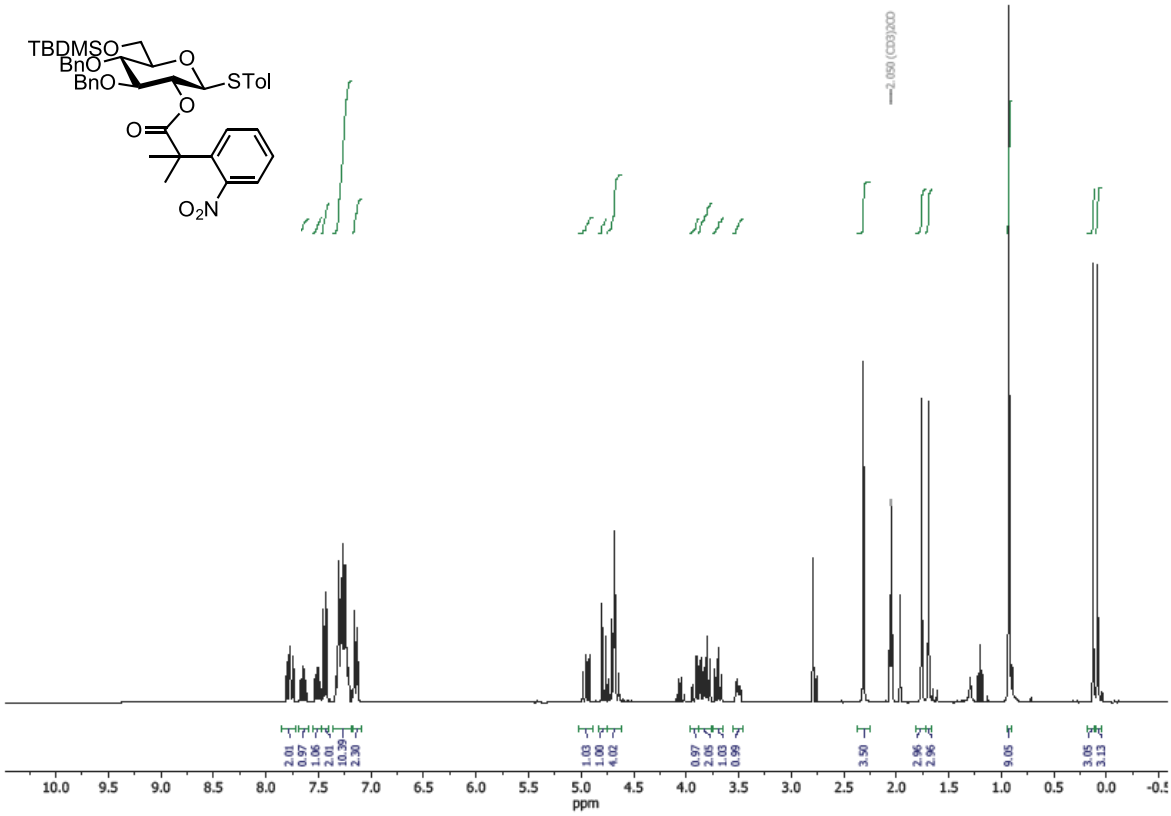
^{13}C APT NMR of **117** ($CDCl_3$, 150 MHz, 297 K)



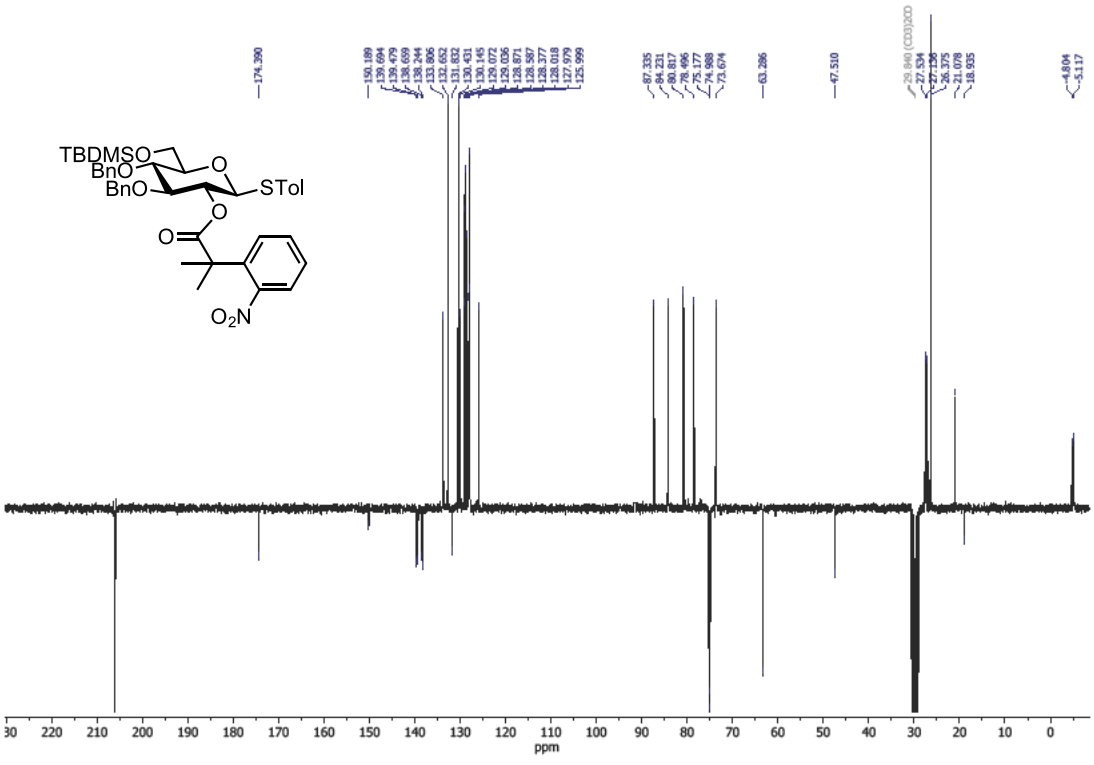
^{1}H NMR of **118** (CD_3COCD_3, 600 MHz, 297 K, 2.84 H_2O 2.81 HDO)



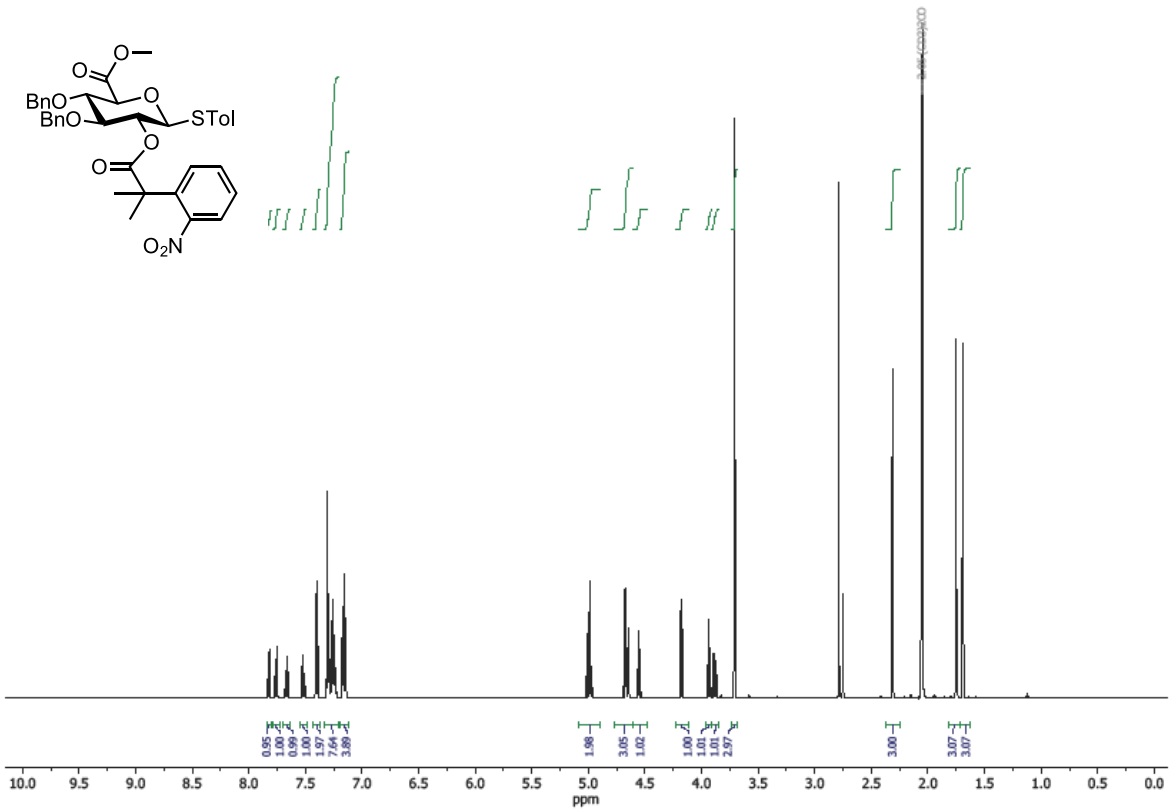
^{13}C APT NMR of **118** (CD_3COCD_3, 150 MHz, 297 K)



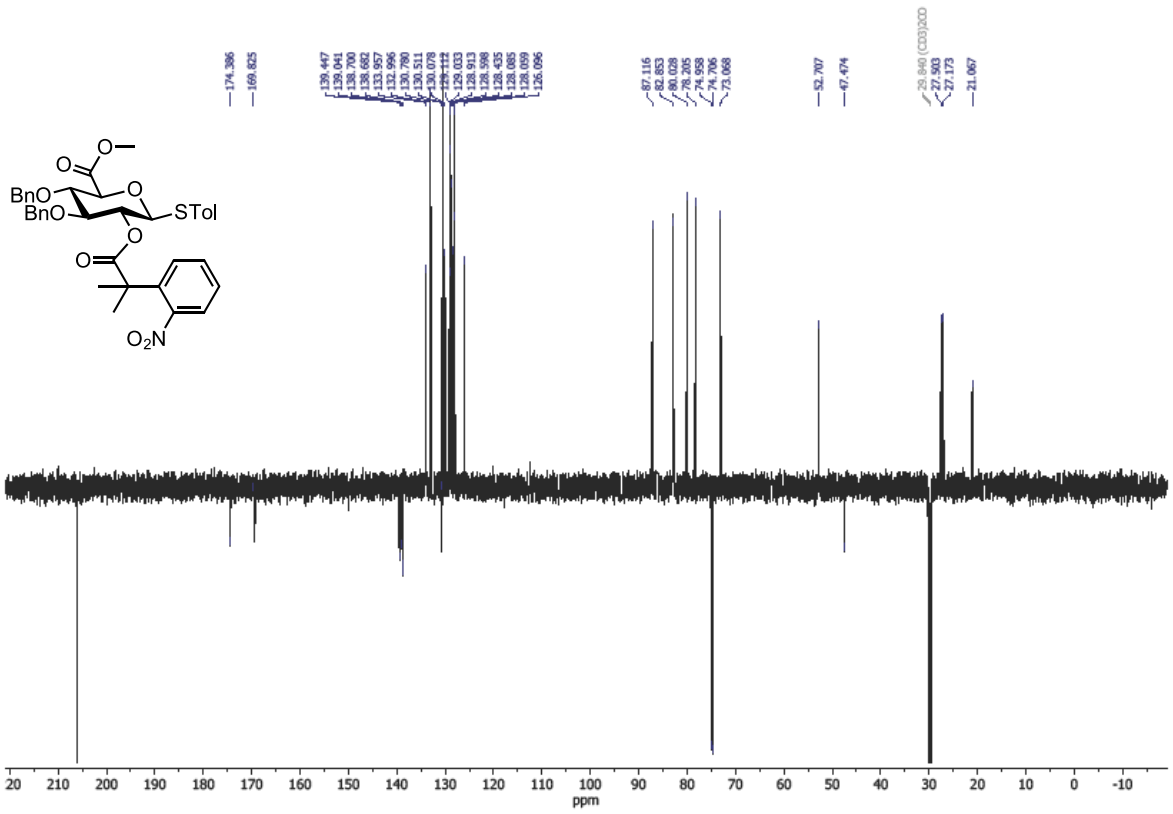
^{1}H NMR of **119** (CD_3COCD_3, 300 MHz, 297 K, 4.05 1.97 1.20 EtOAc, 2.84 H_2O 2.81 HDO)



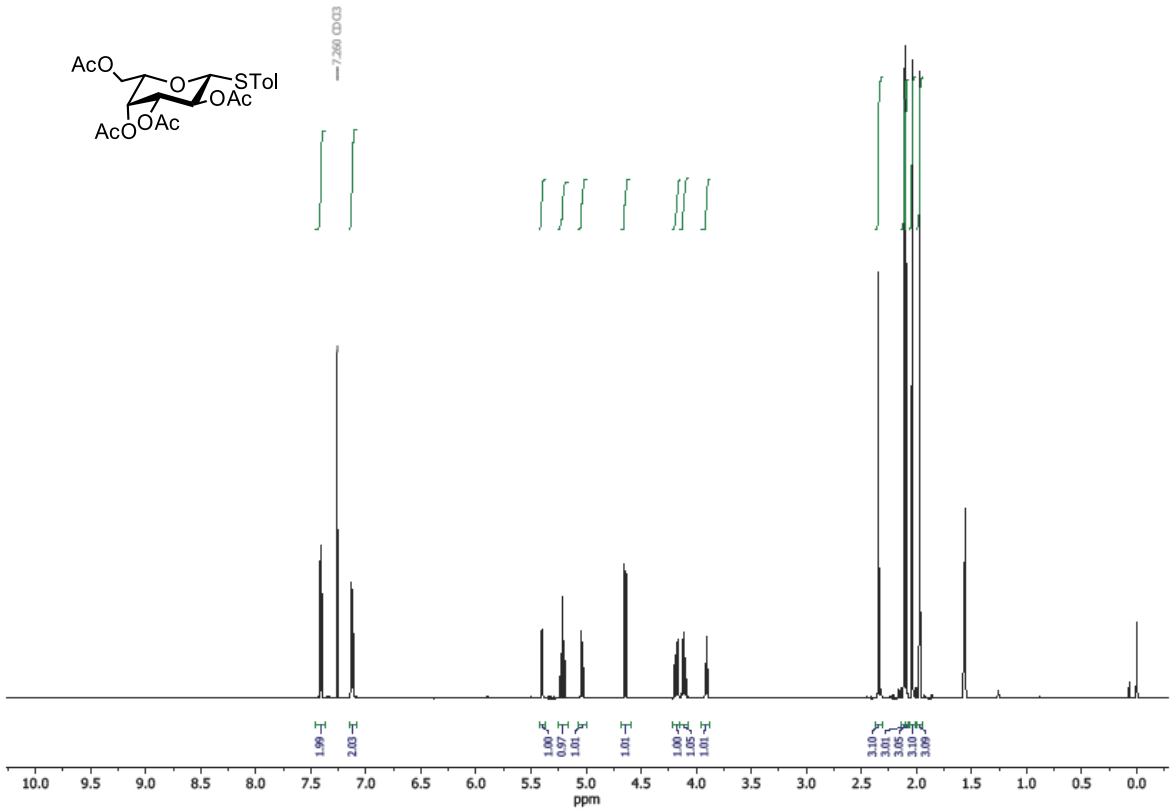
^{13}C APT NMR of **119** (CD_3COCD_3, 75 MHz, 297 K)



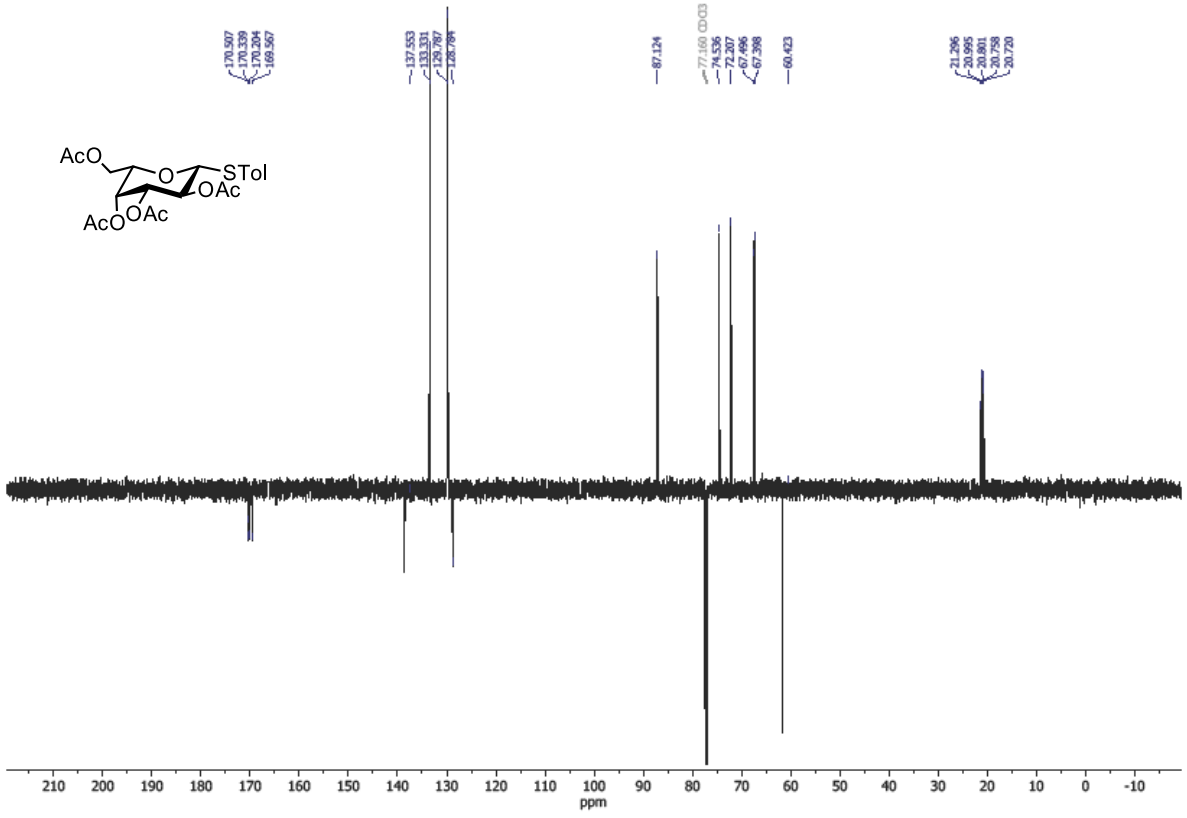
^{1}H NMR of **80** (CD_3COCD_3, 300 MHz, 297 K, 2.84 H_2O 2.81 HDO)



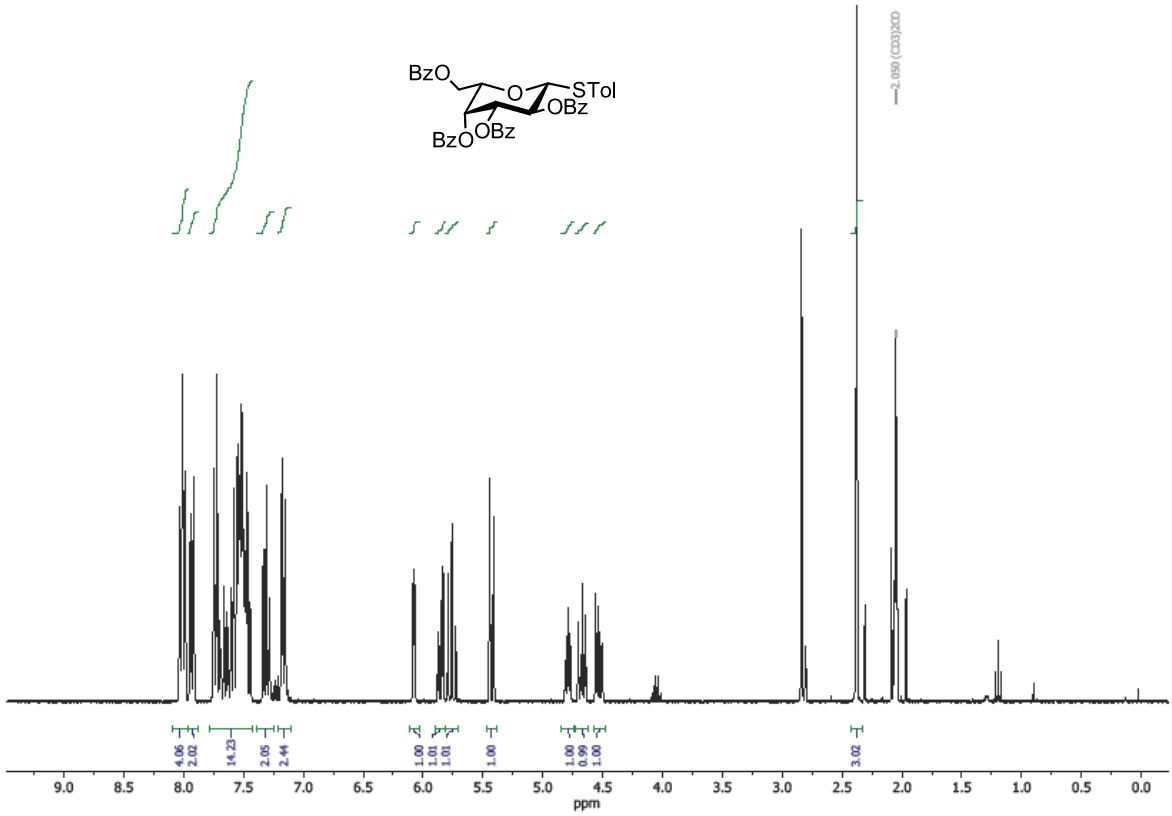
^{13}C APT NMR of **80** (CD_3COCD_3, 75 MHz, 297 K)



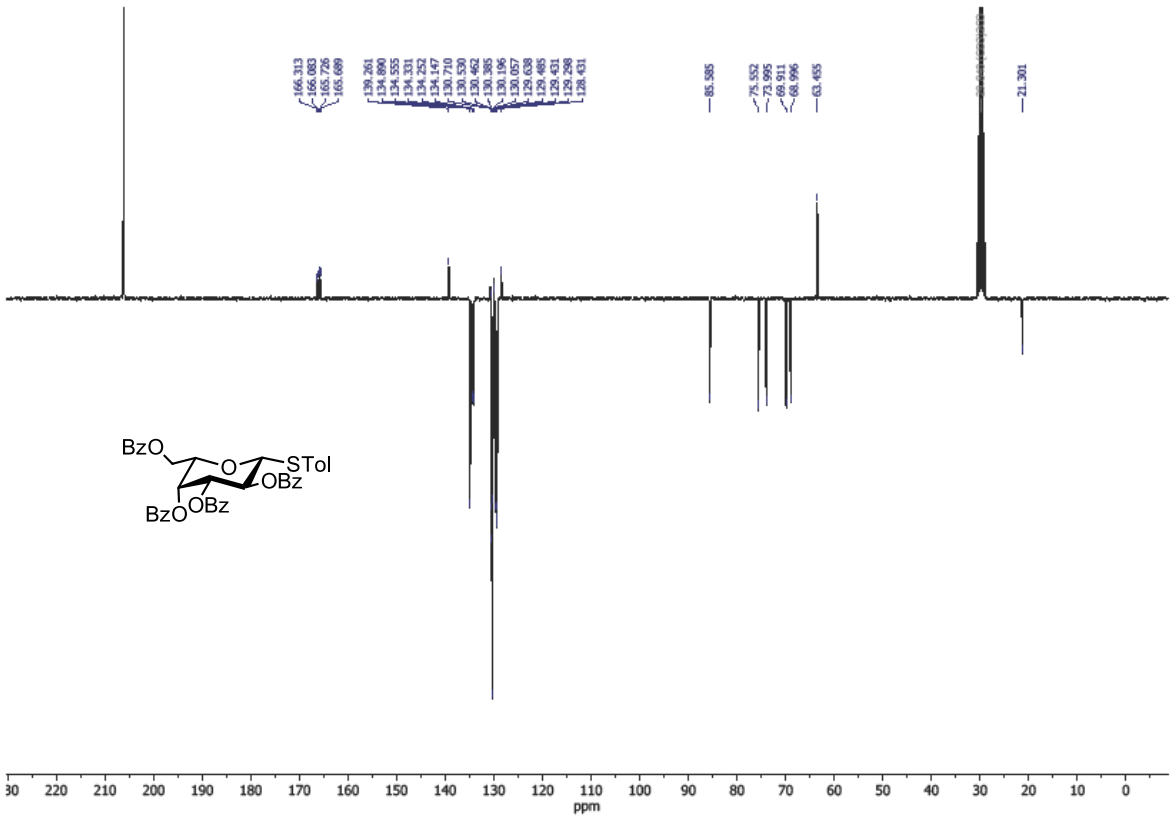
^{1}H NMR of **121** ($CDCl_3$, 600 MHz, 297 K, 1,56 H_2O)



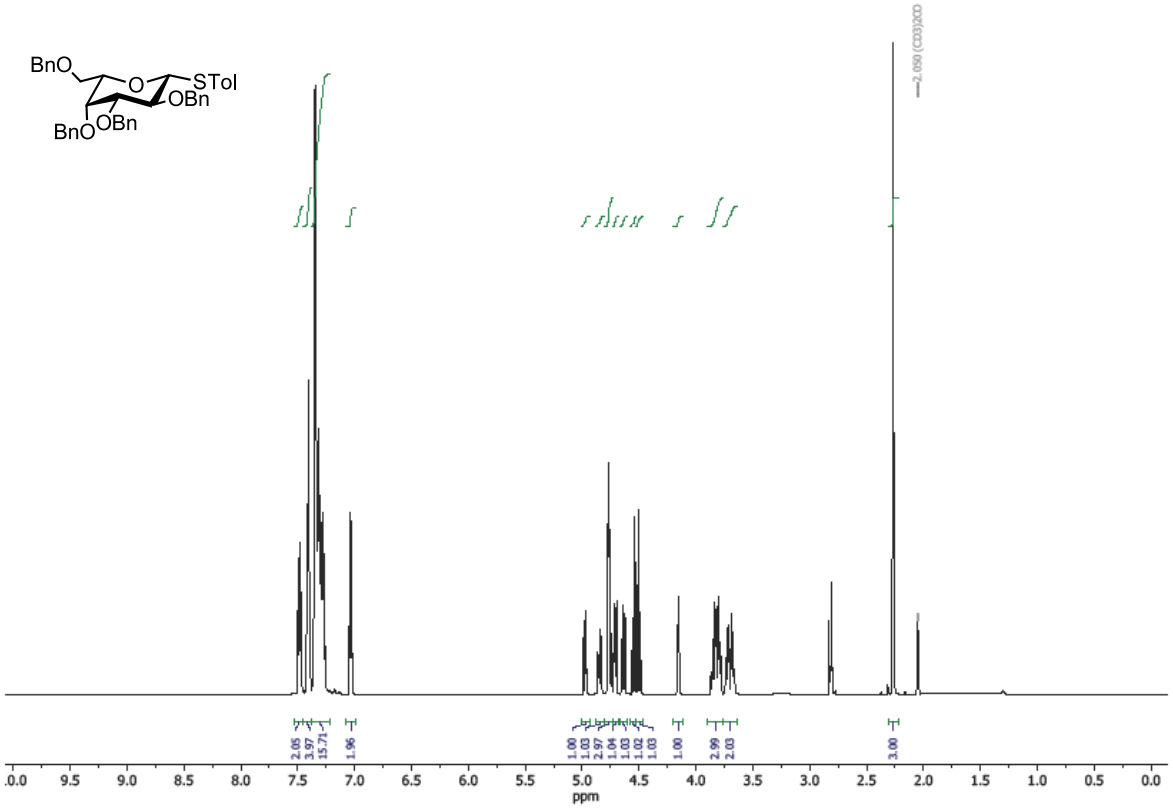
^{13}C APT NMR of **121** ($CDCl_3$, 150 MHz, 297 K)



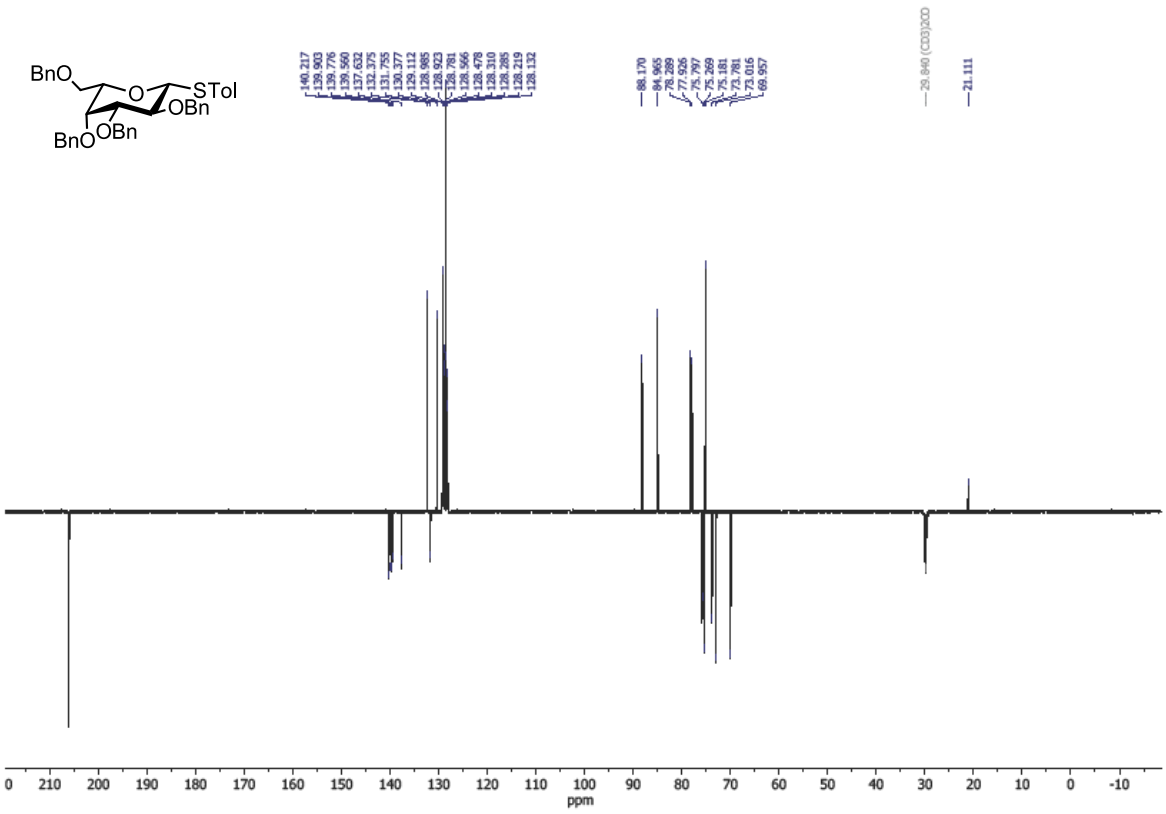
^{1}H NMR of **122** (CD_3COCD_3, 300 MHz, 297 K, 4.05 1.97 1.20 EtOAc, 2.84 H_2O 2.81 HDO)



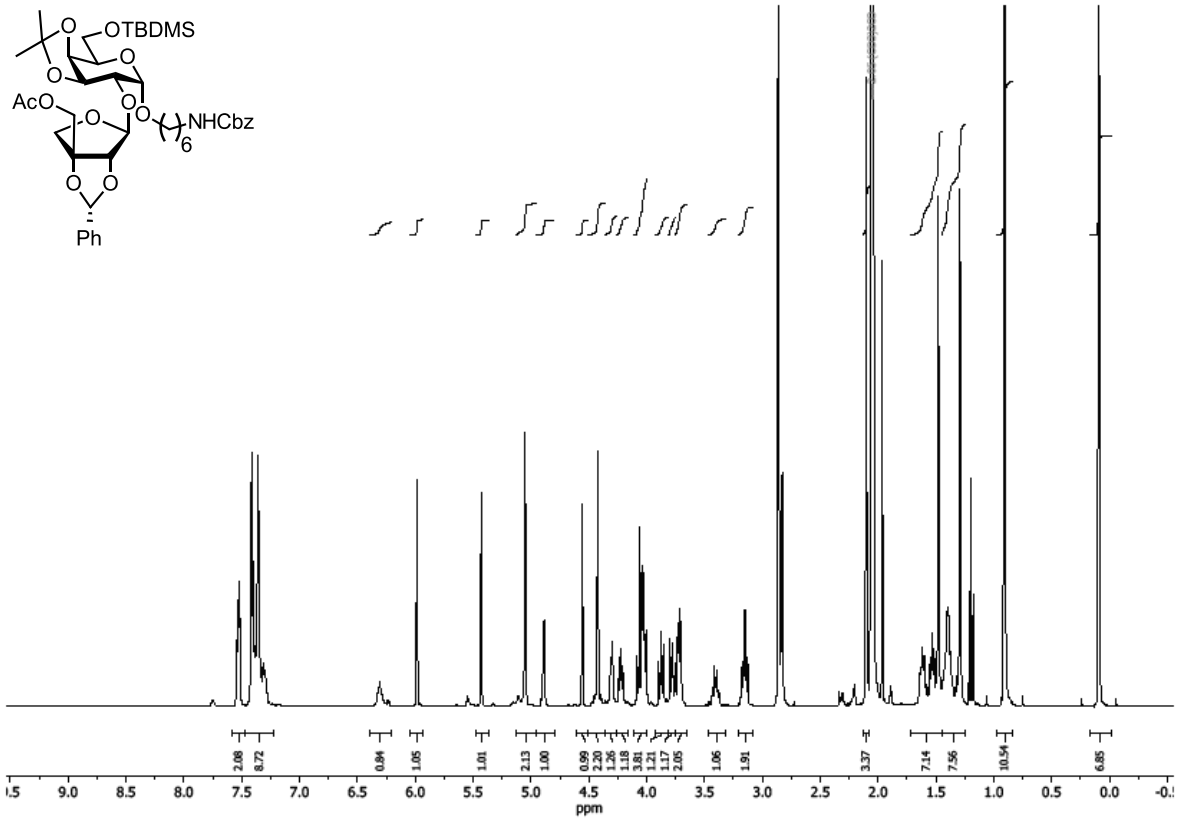
^{13}C APT NMR of **122** (CD_3COCD_3, 75 MHz, 297 K)



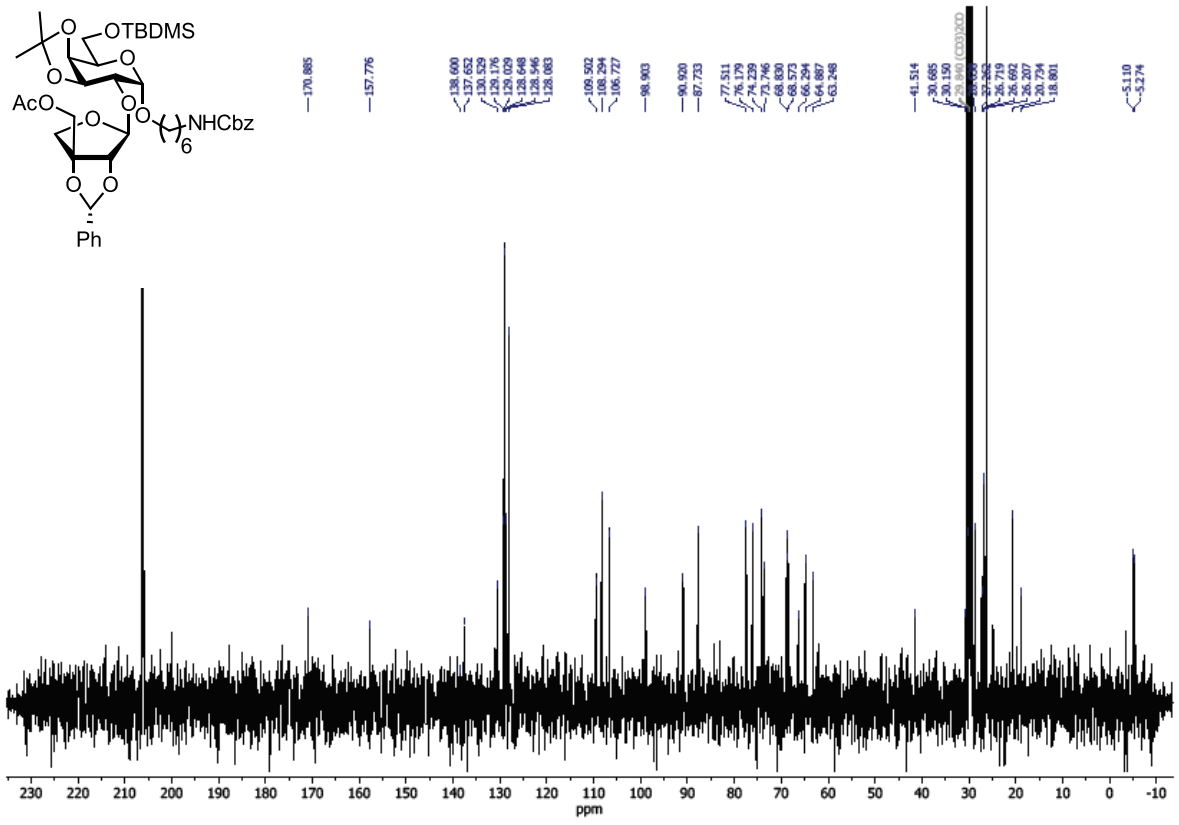
^{1}H NMR of **78** (CD_3COCD_3, 600 MHz, 297 K)



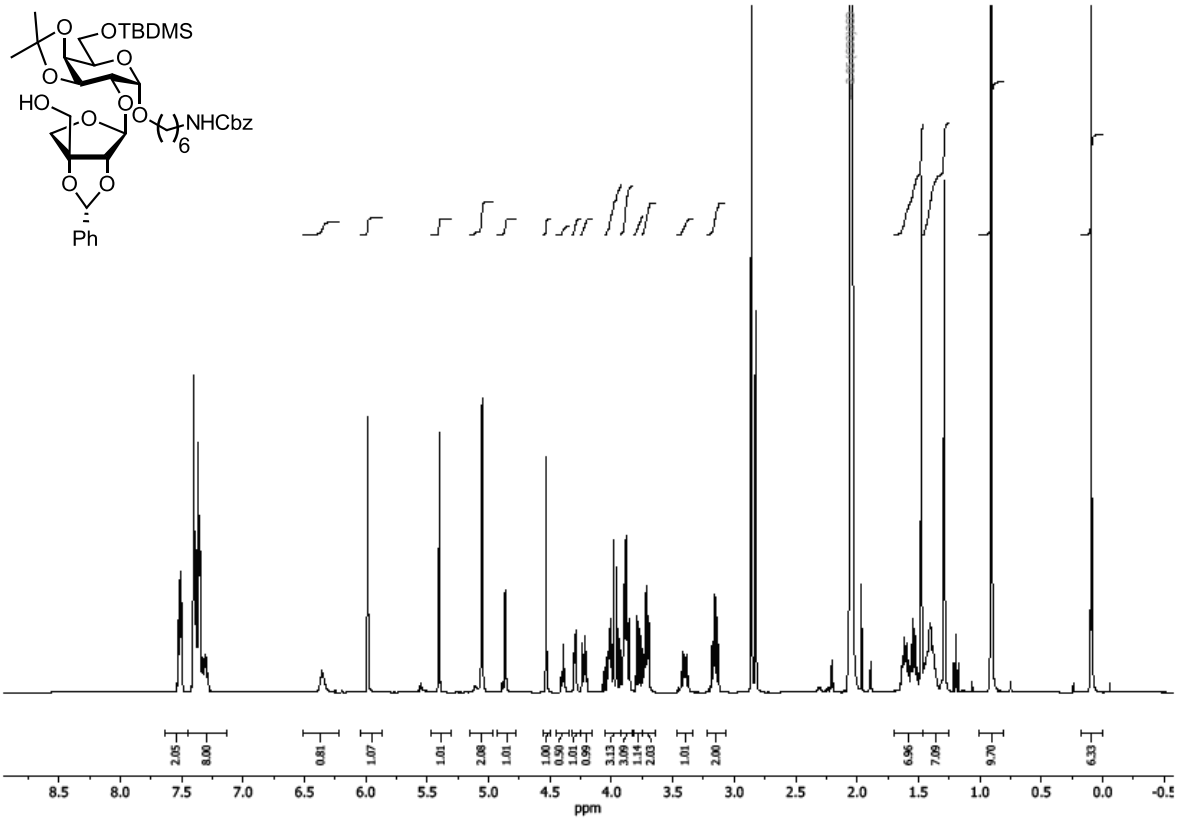
^{13}C APT NMR of **78** (CD_3COCD_3, 150 MHz, 297 K)



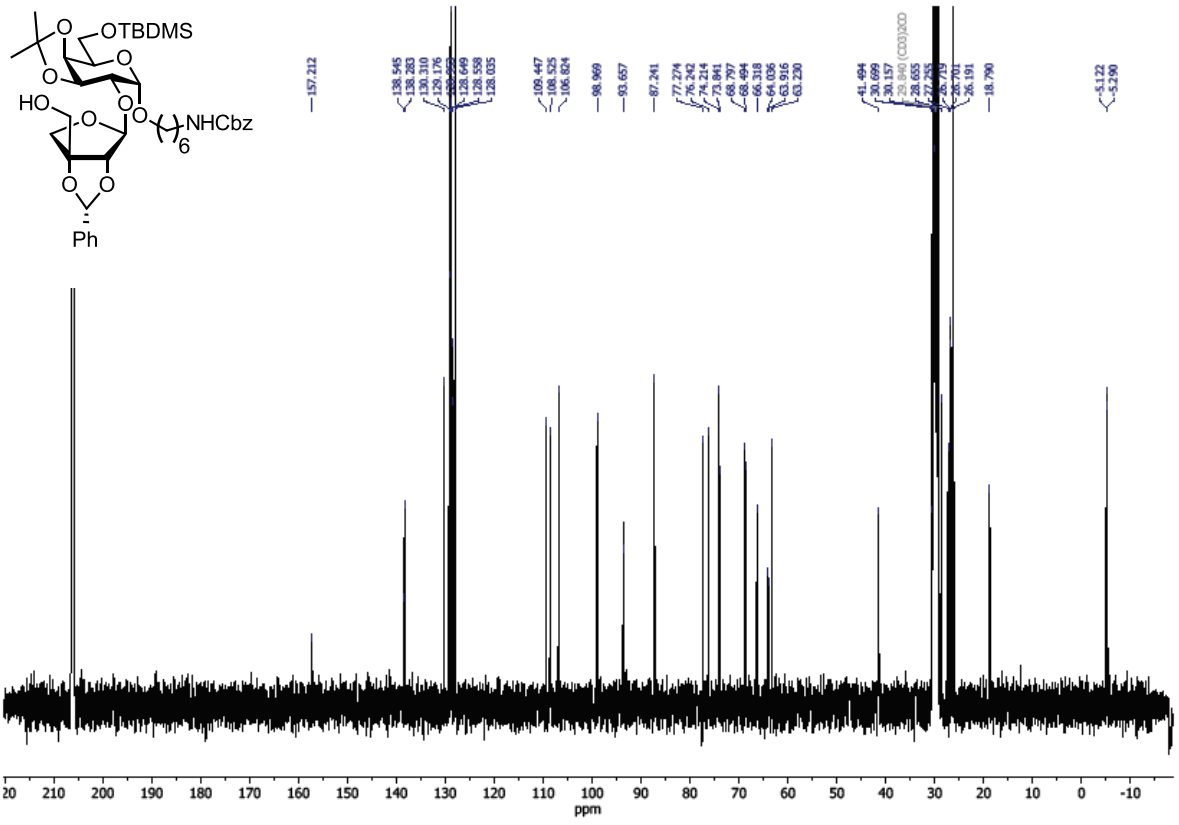
^{1}H NMR of **123** (CD_3COCD_3, 400 MHz, 297 K, 4.05 1.97 1.20 EtOAc, 2.84 H_2O 2.81 HDO)



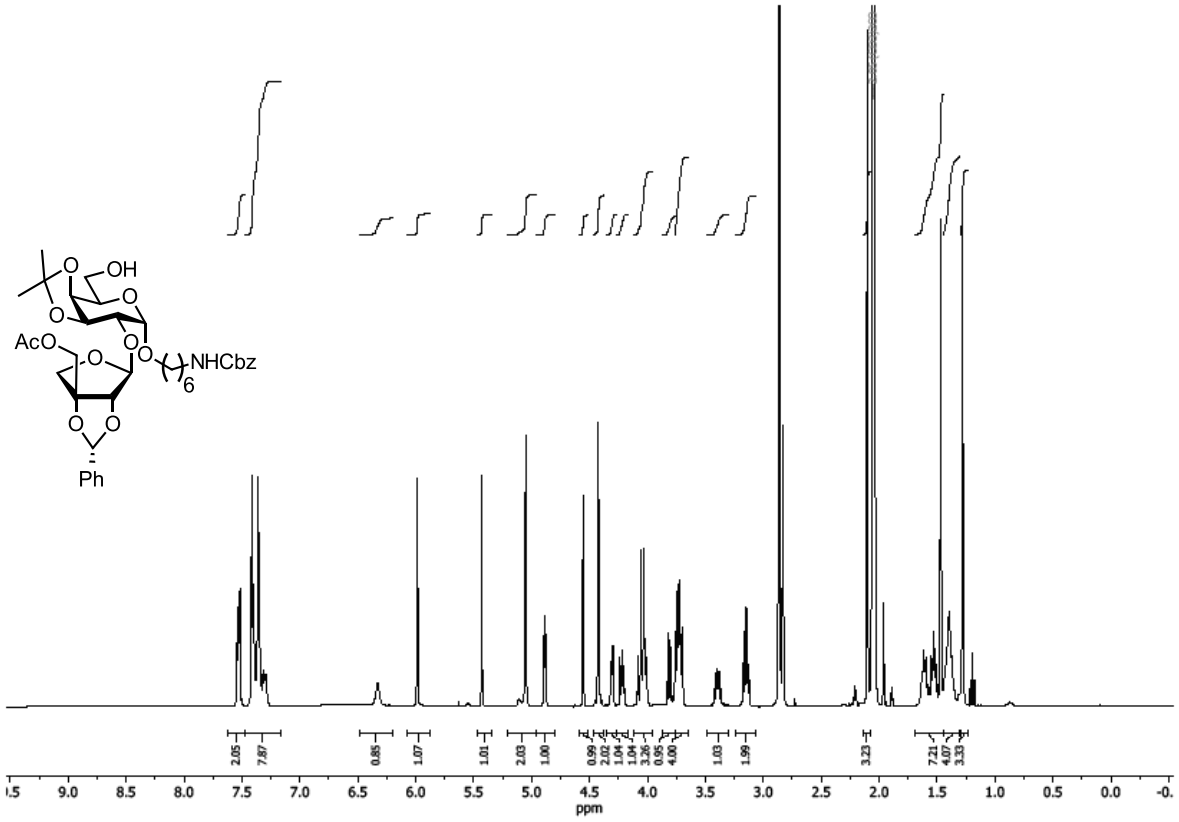
^{13}C NMR of **123** (CD_3COCD_3, 100 MHz, 297 K)



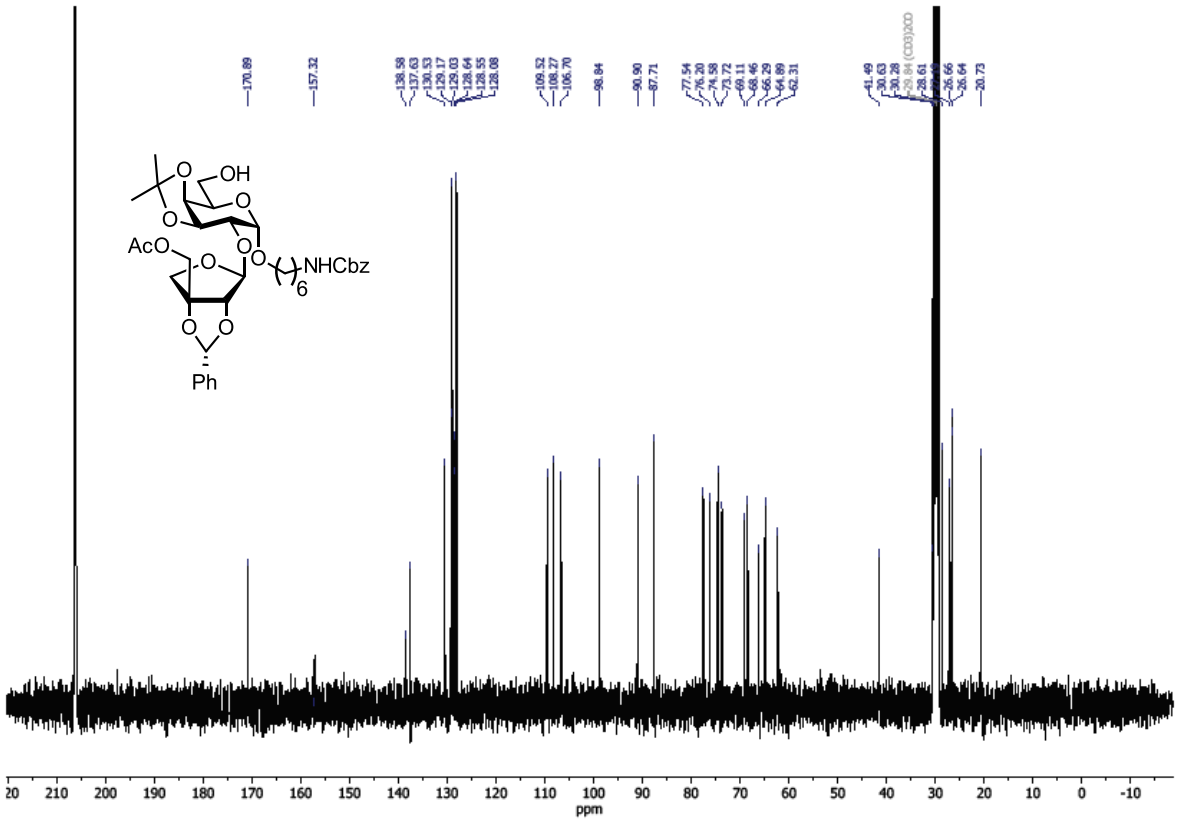
^{1}H NMR of **69** (CD_3COCD_3, 400 MHz, 297 K, 4.05 1.97 1.20 EtOAc, 2.84 H_2O 2.81 HDO)



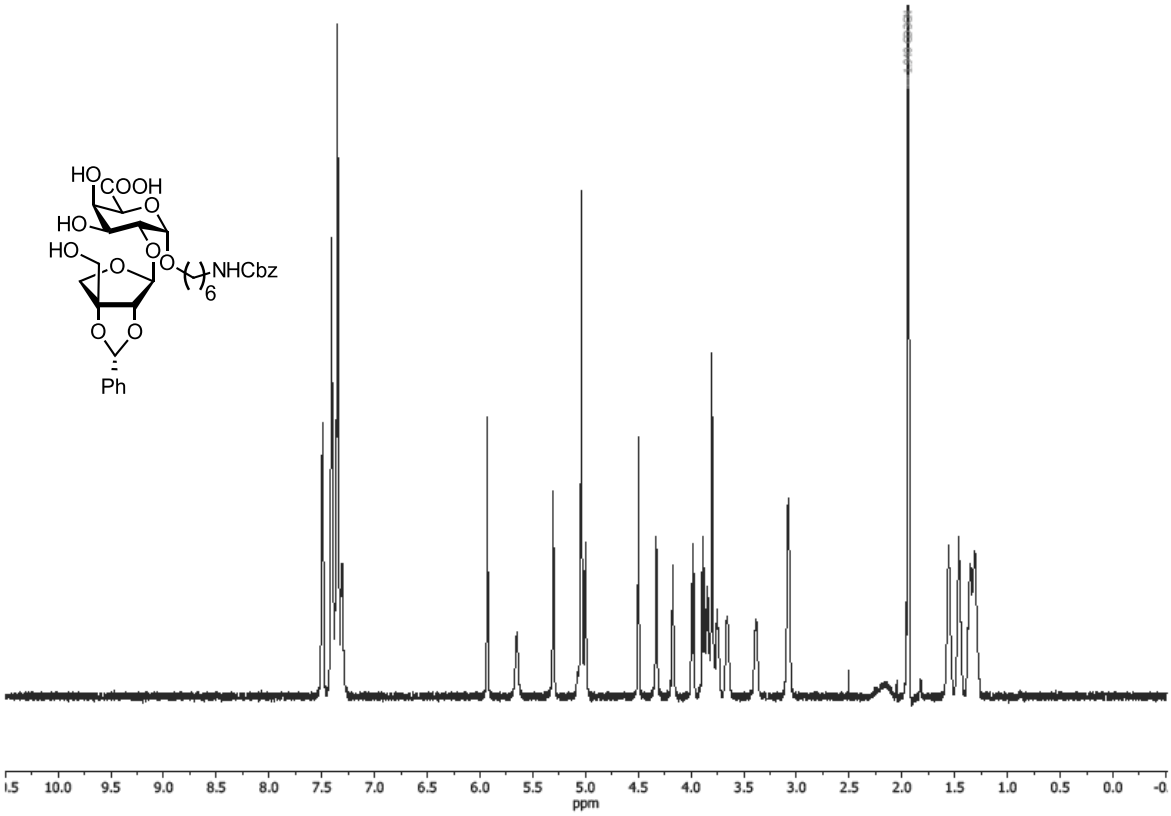
^{13}C NMR of **69** (CD_3COCD_3, 100 MHz, 297 K)



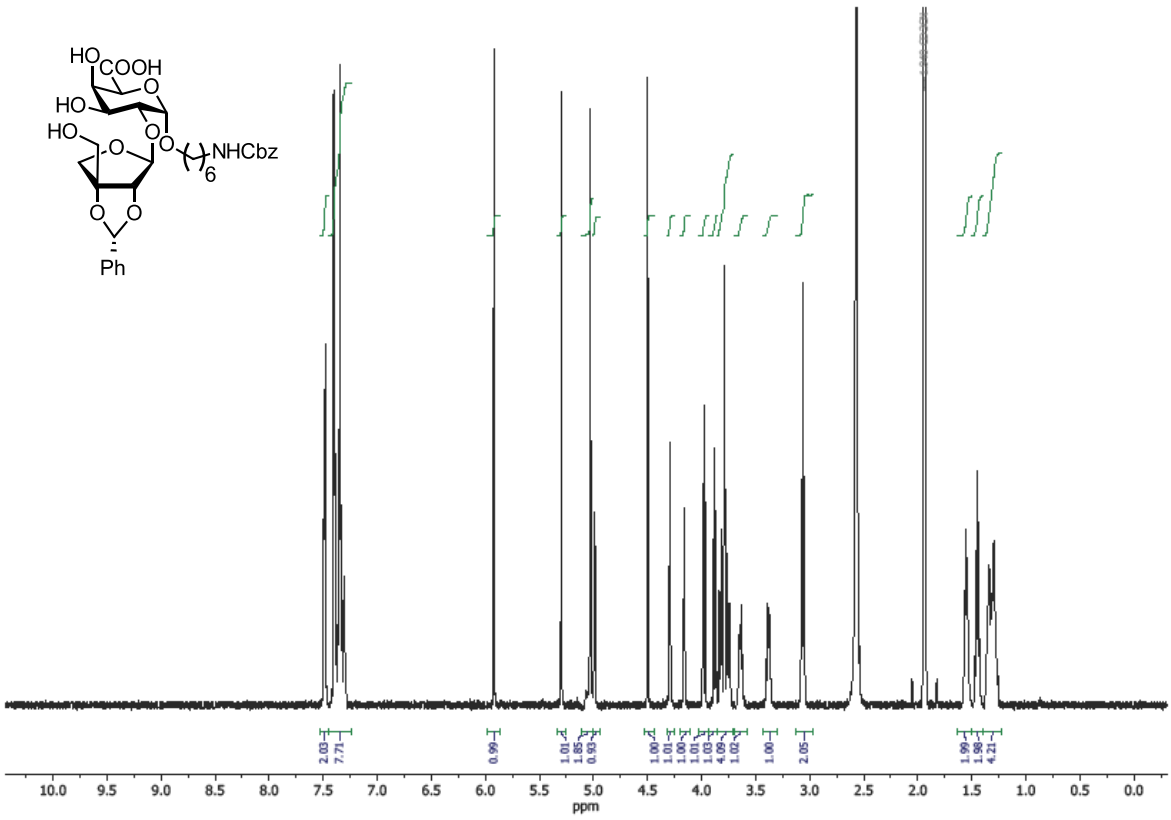
^{1}H NMR of **124** (CD_3COCD_3, 400 MHz, 297 K, 4.05 1.97 1.20 EtOAc, 2.84 H_2O 2.81 HDO)



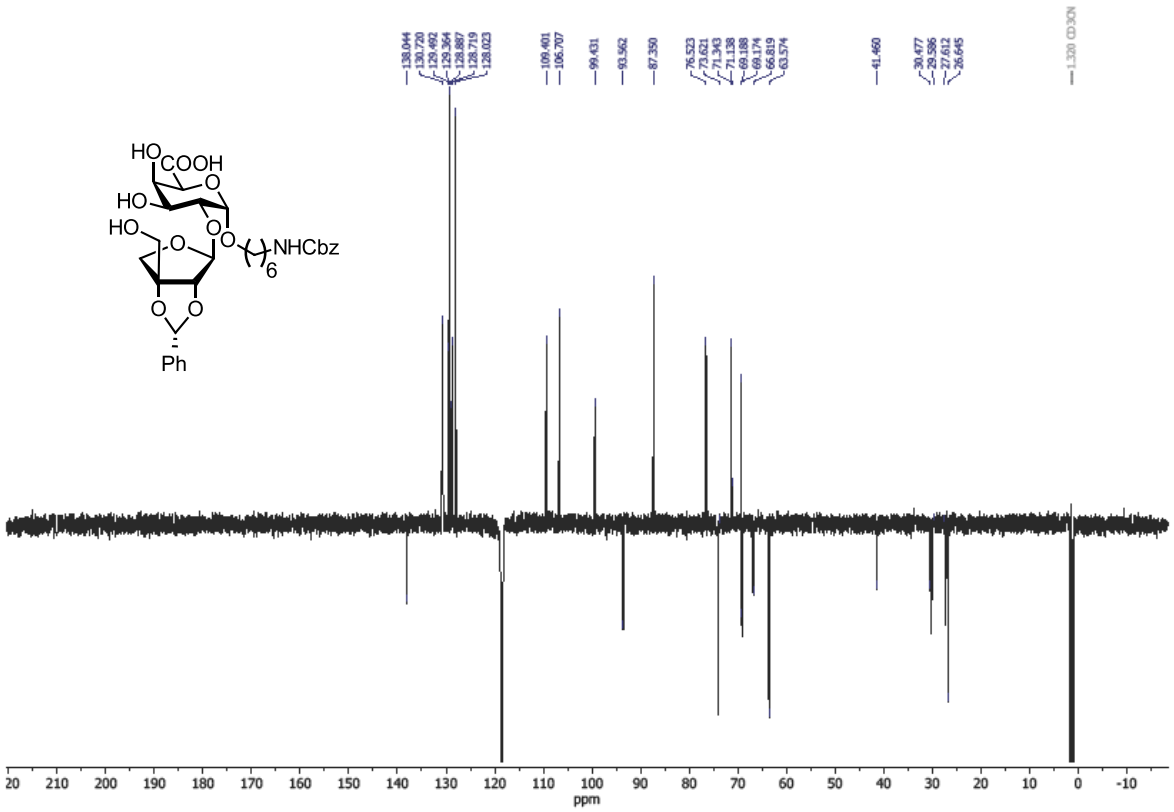
^{13}C NMR of **124** (CD_3COCD_3, 100 MHz, 297 K)



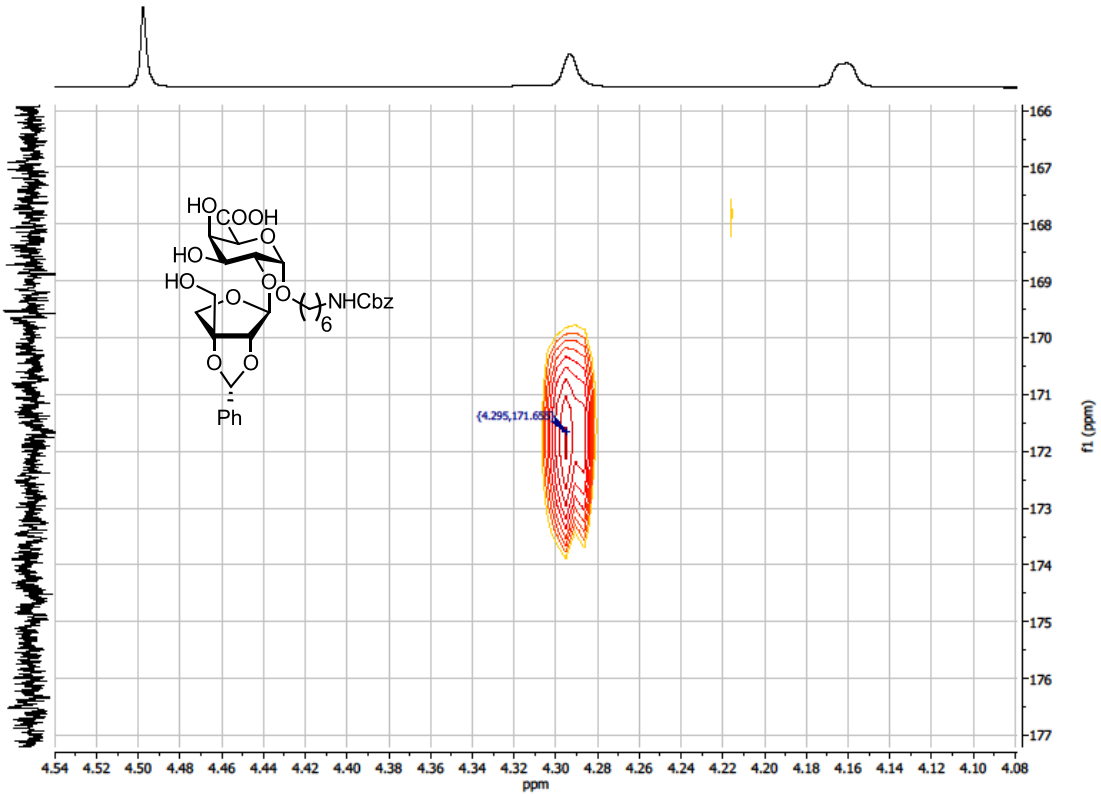
^{1}H NMR of **125** (CD_3CN, 600 MHz, 297 K)



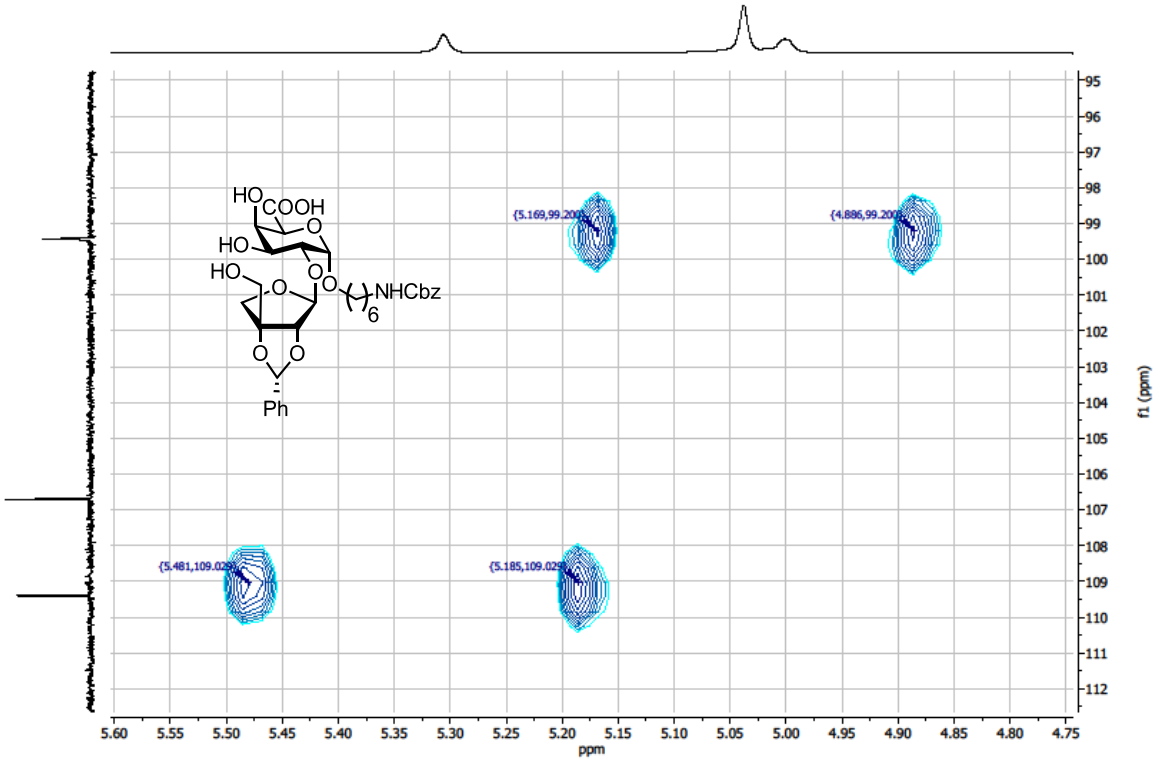
^{1}H NMR of **125** (CD_3CN + D_2O, 600 MHz, 297 K)



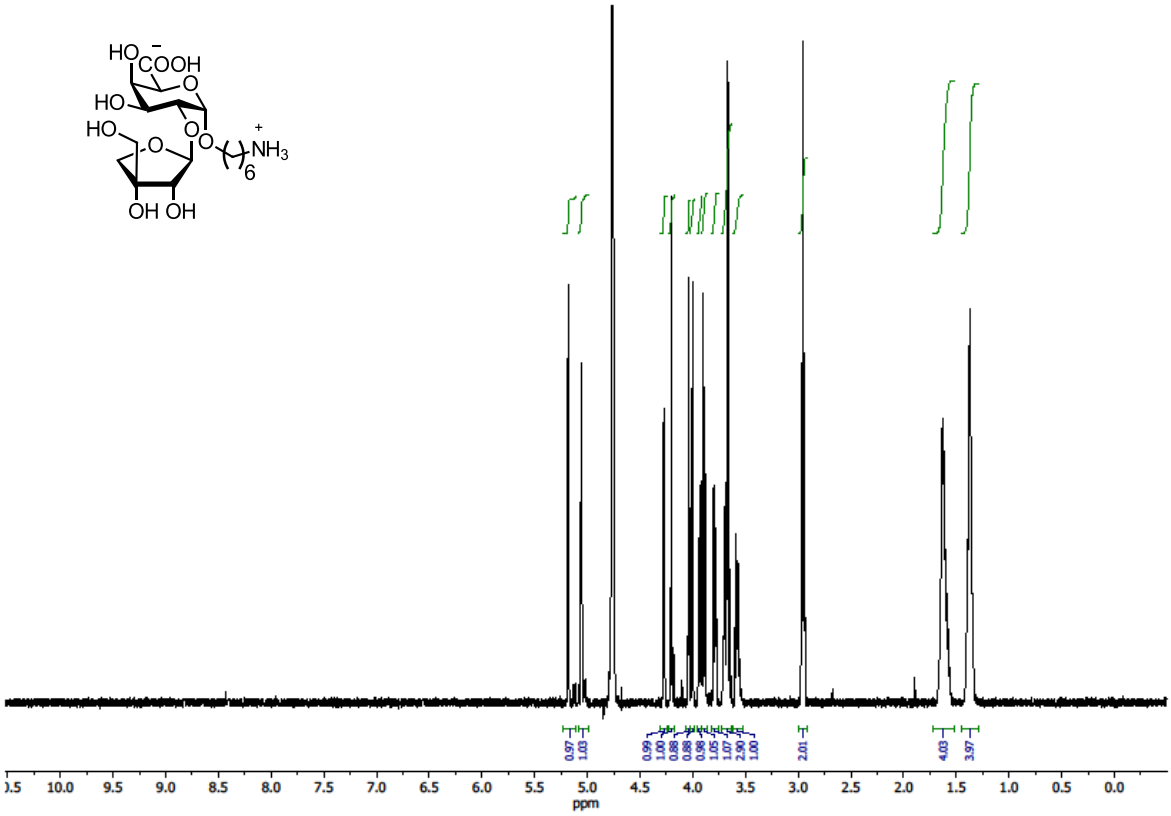
^{13}C APT NMR of **125** (CD_3CN, 600 MHz, 297 K)



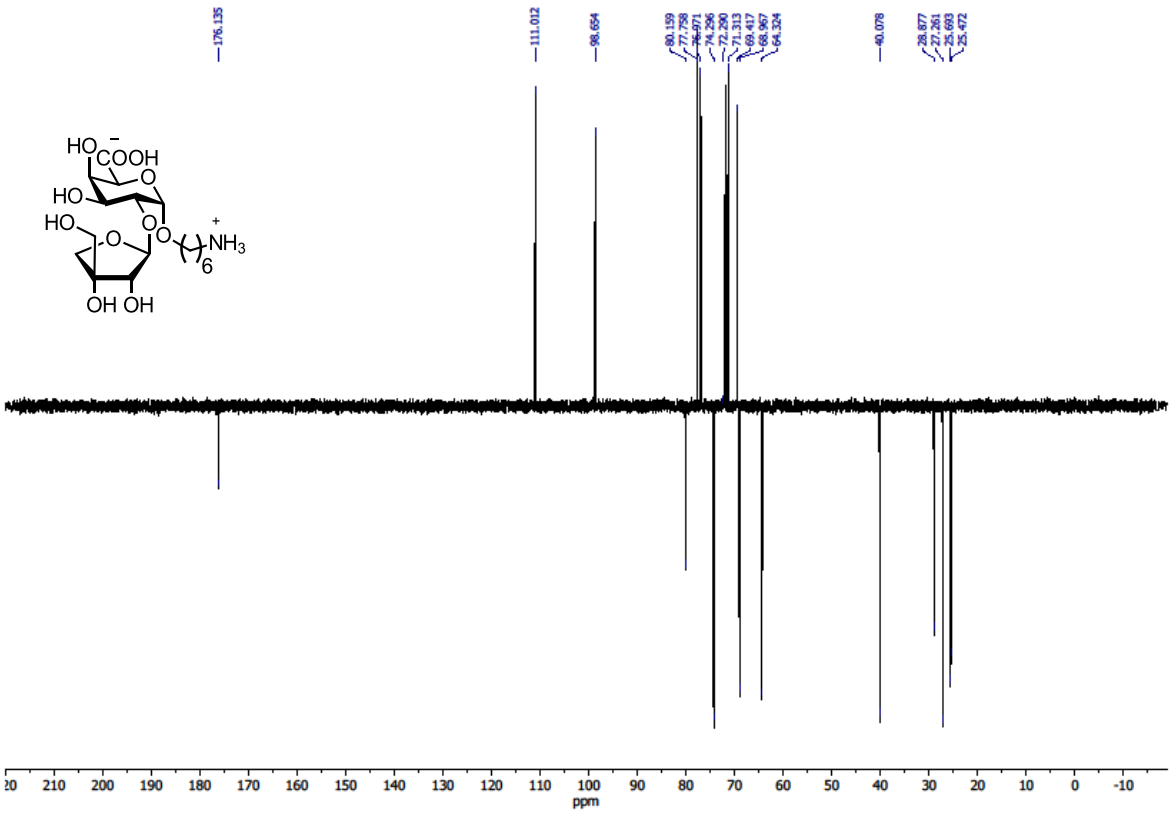
^{1}H-^{13}C HMBC NMR of **125** (CD_3CN, 600 MHz, 297 K)



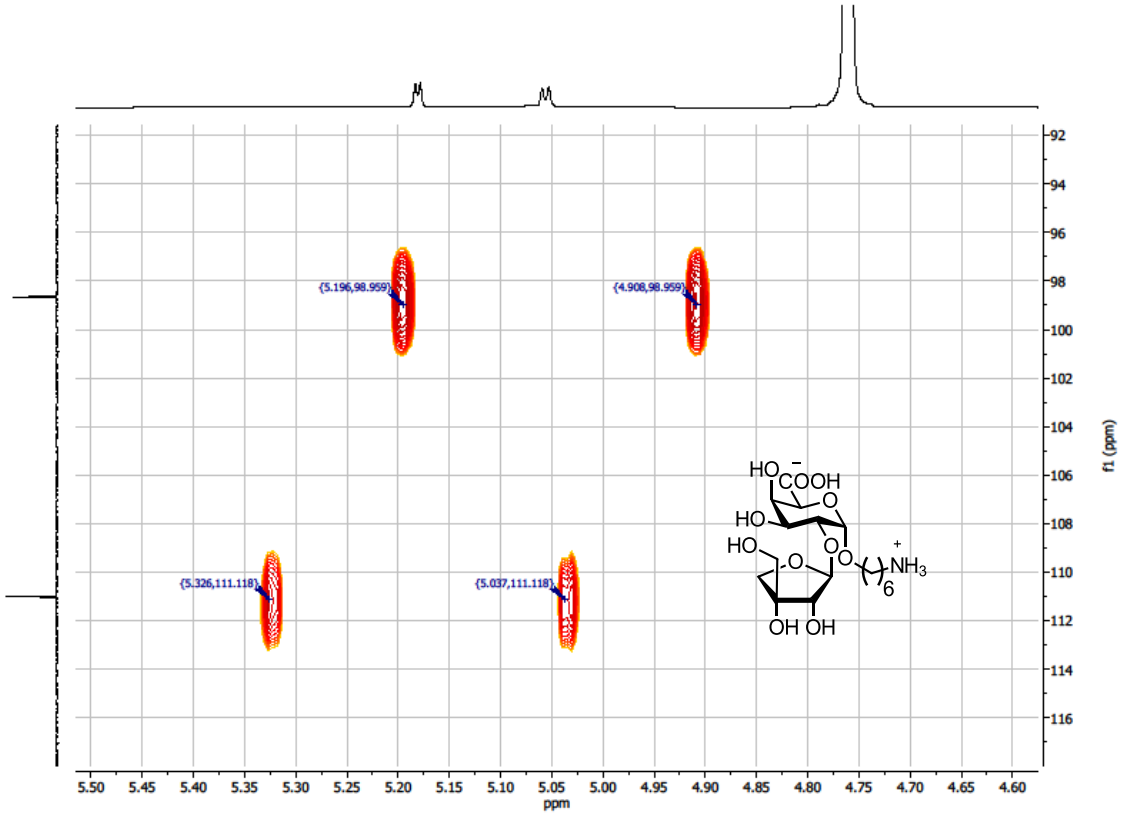
^{1}H-^{13}C CLIP HSQC NMR of **125** (CD_3CN, 600 MHz, 297 K)



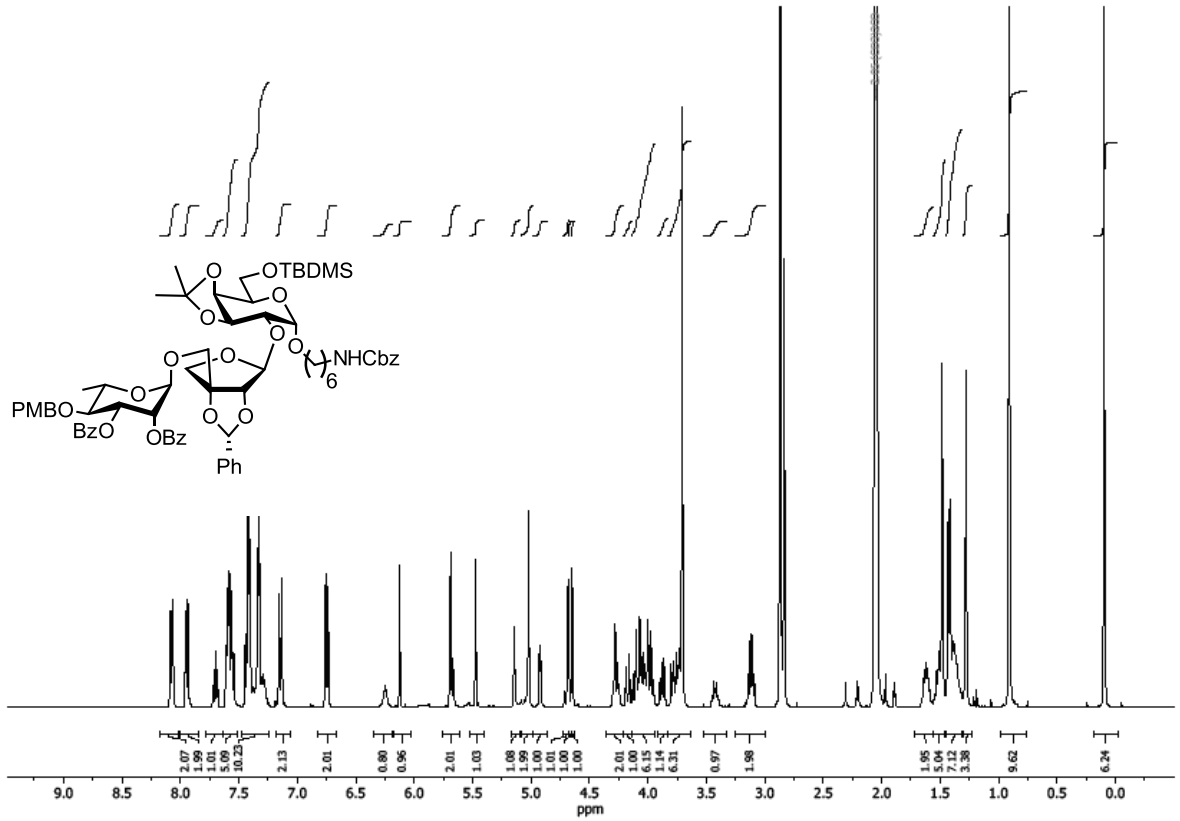
^{1}H NMR of **88** (D_2O, 600 MHz, 297 K)



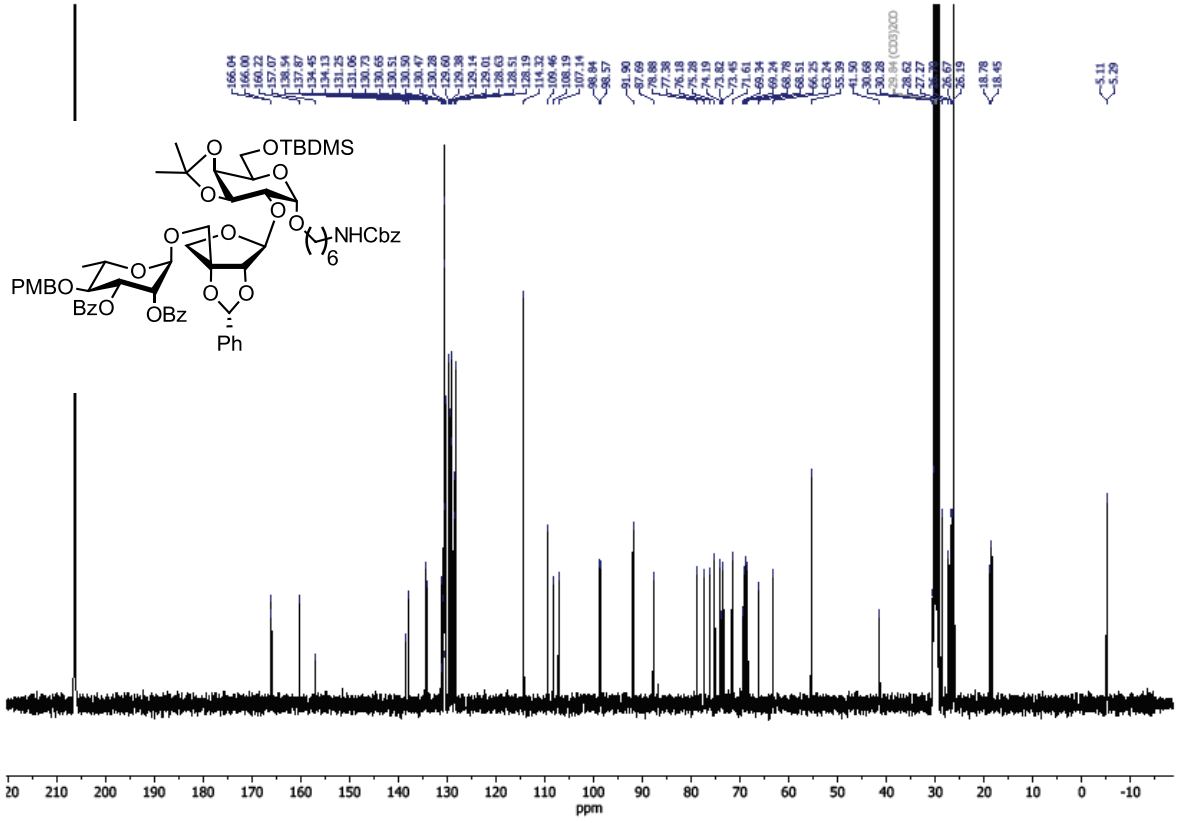
^{13}C APT NMR of **88** (D_2O, 150 MHz, 297 K)



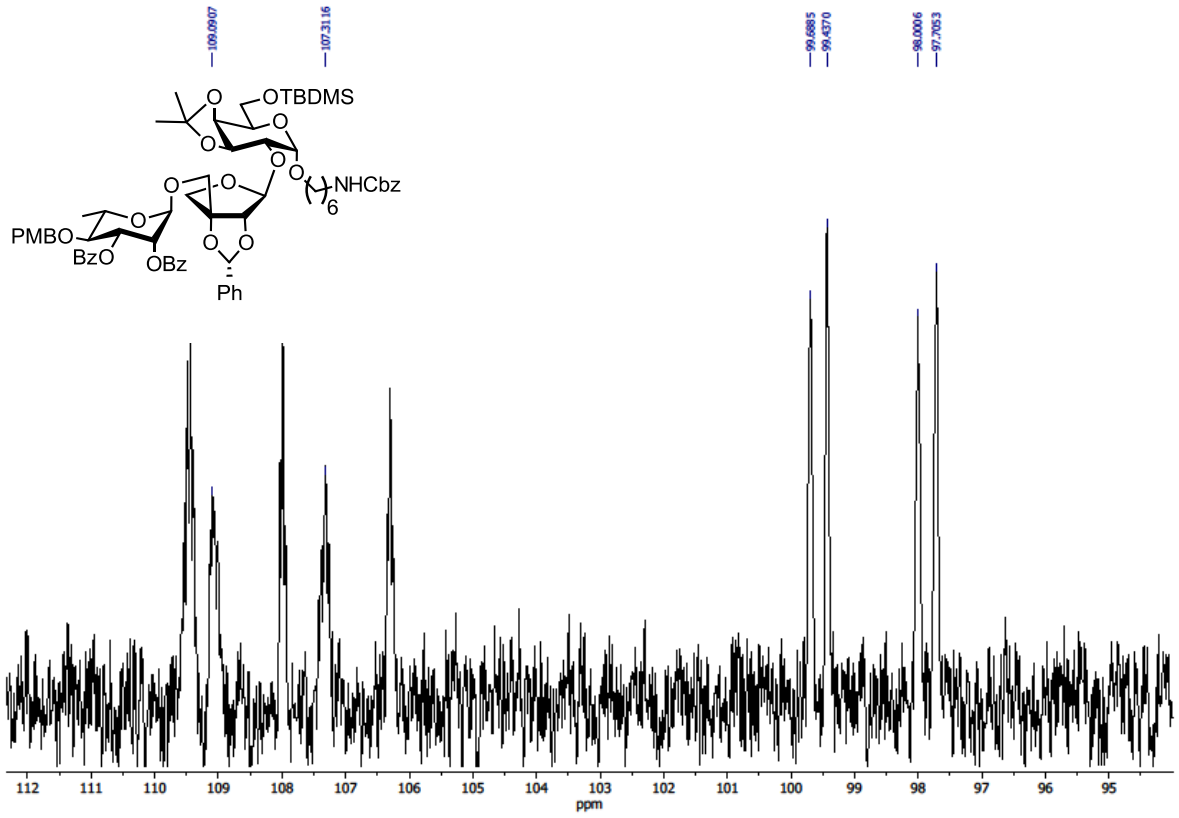
^{1}H-^{13}C coupled HMBC NMR of **88** (D_2O, 600 MHz, 297 K)



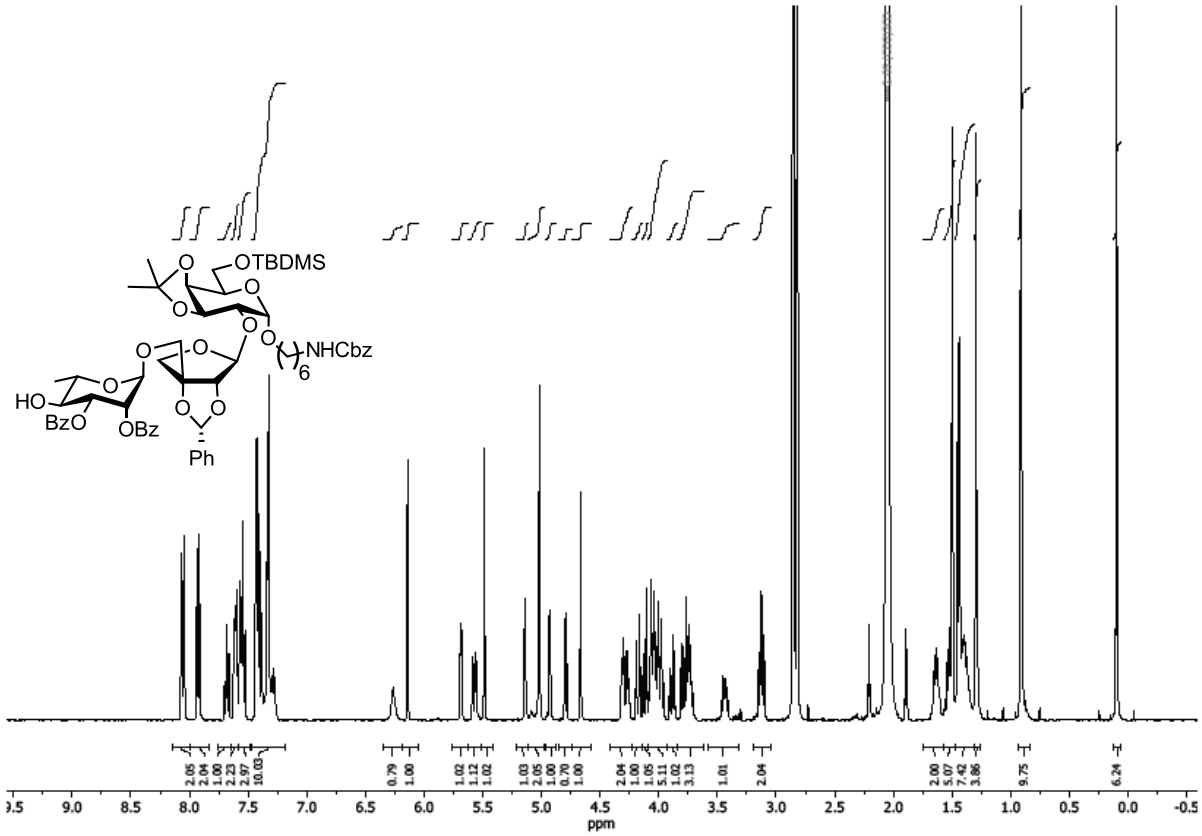
^{1}H NMR of **86** (CD_3COCD_3, 400 MHz, 297 K, 2.84 H_2O 2.81 HDO)



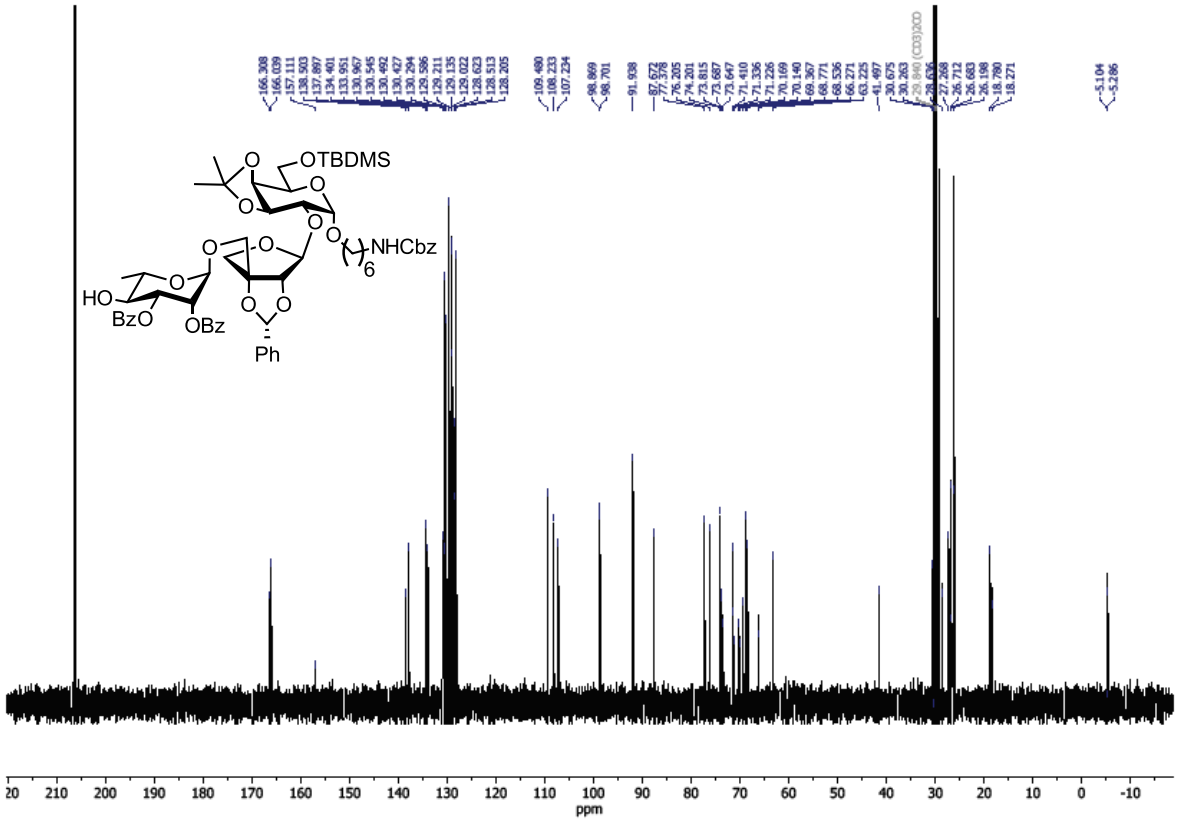
^{13}C NMR of **86** (CD_3COCD_3, 100 MHz, 297 K)



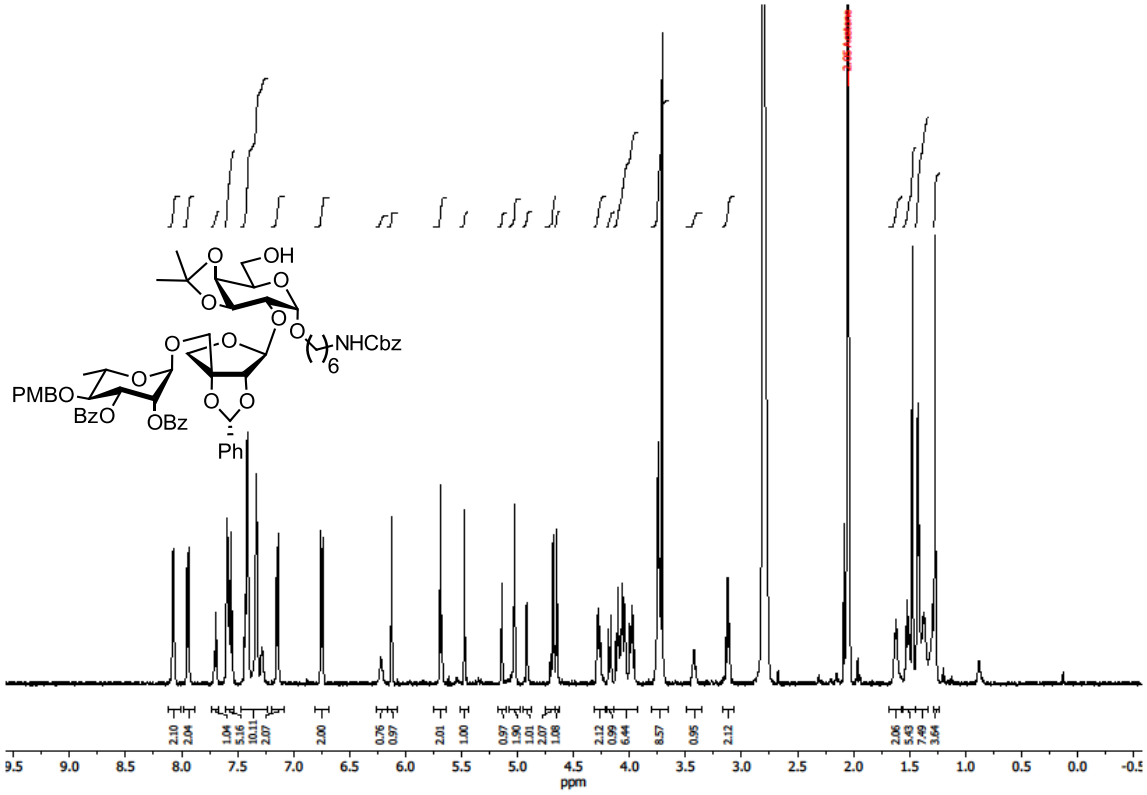
^{1}H coupled ^{13}C NMR of **86** (CD_3COCD_3, 100 MHz, 297 K)



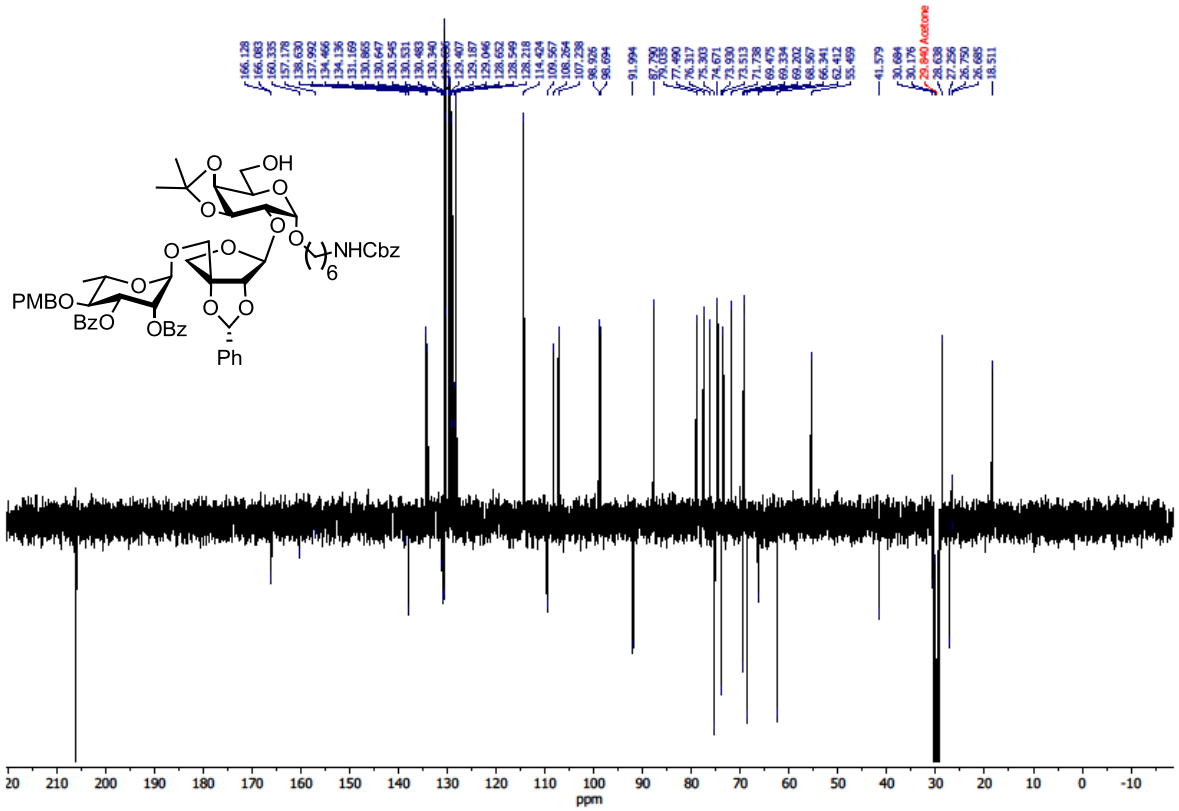
^{1}H NMR of **126** (CD_3COCD_3, 400 MHz, 297 K, 2.84 H_2O 2.81 HDO)



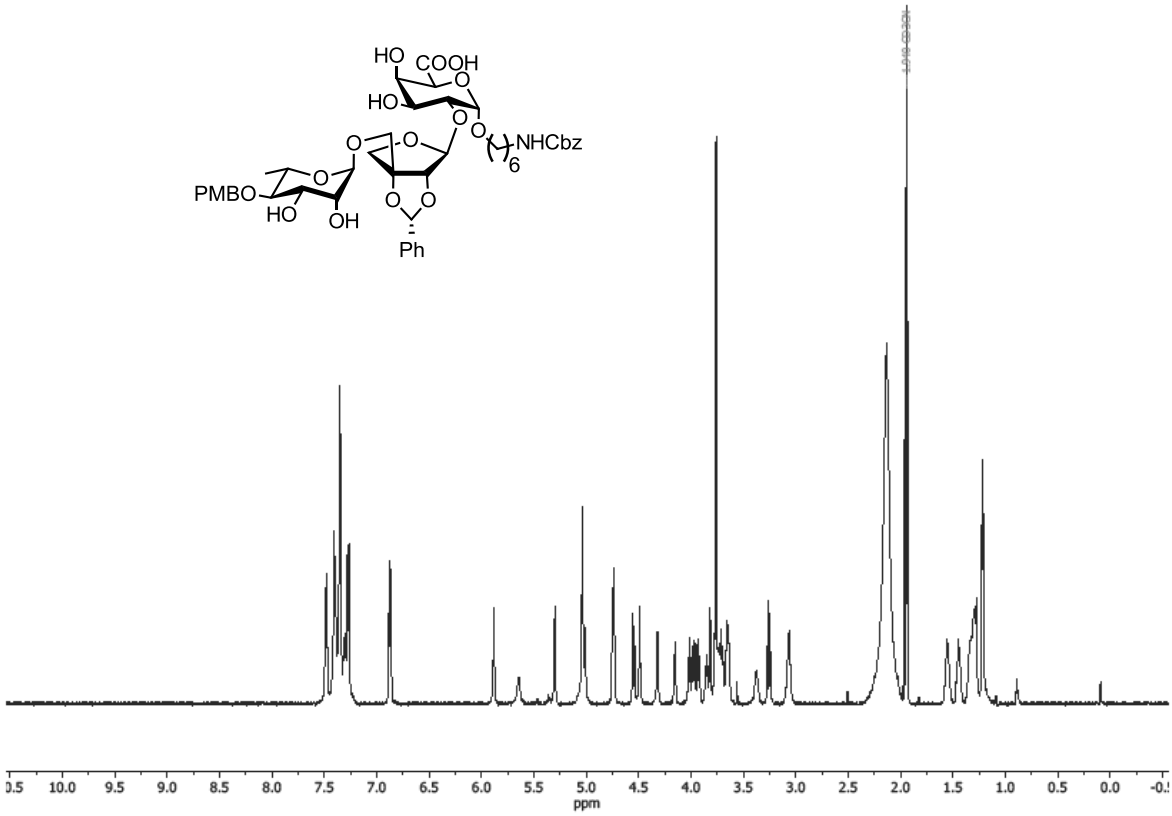
^{13}C NMR of **126** (CD_3COCD_3, 100 MHz, 297 K)



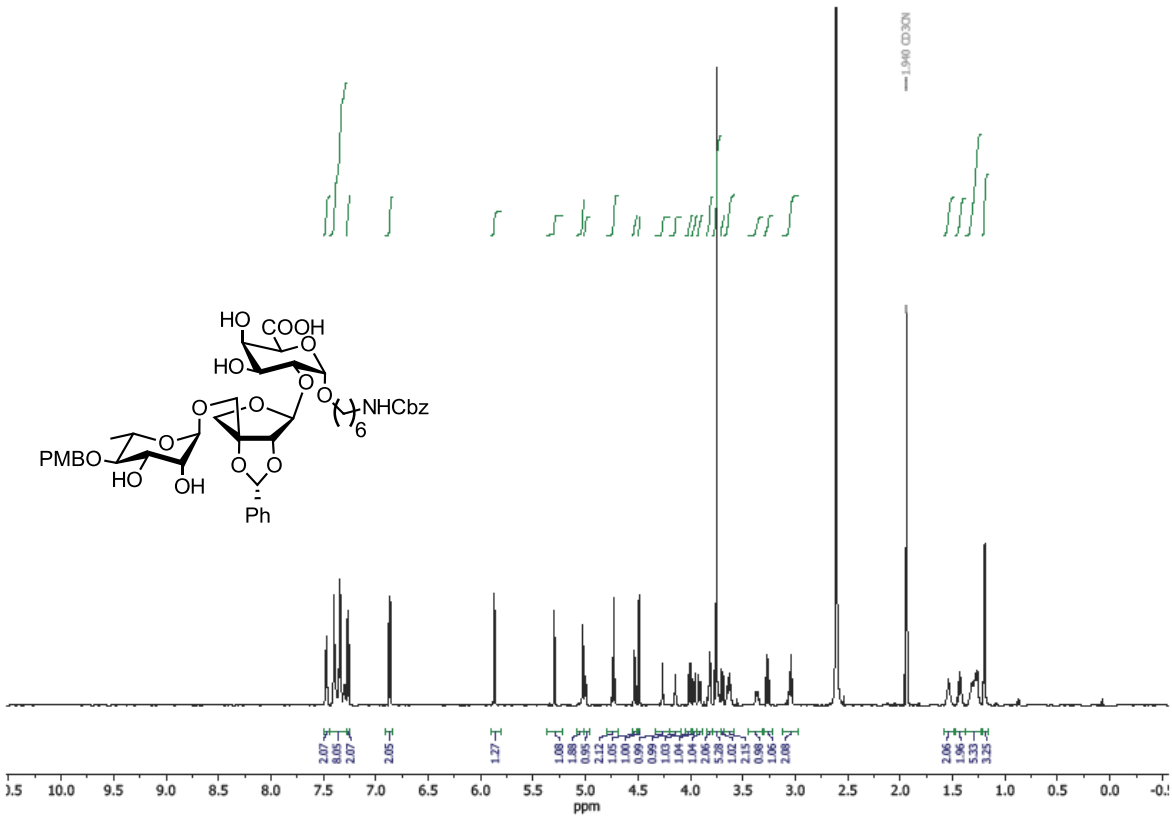
^{1}H NMR of **127** (CD_3COCD_3, 600 MHz, 297 K, 2.84 H_2O 2.81 HDO, 4.05 1.97 1.20 EtOAc, 2.05 Acetone)



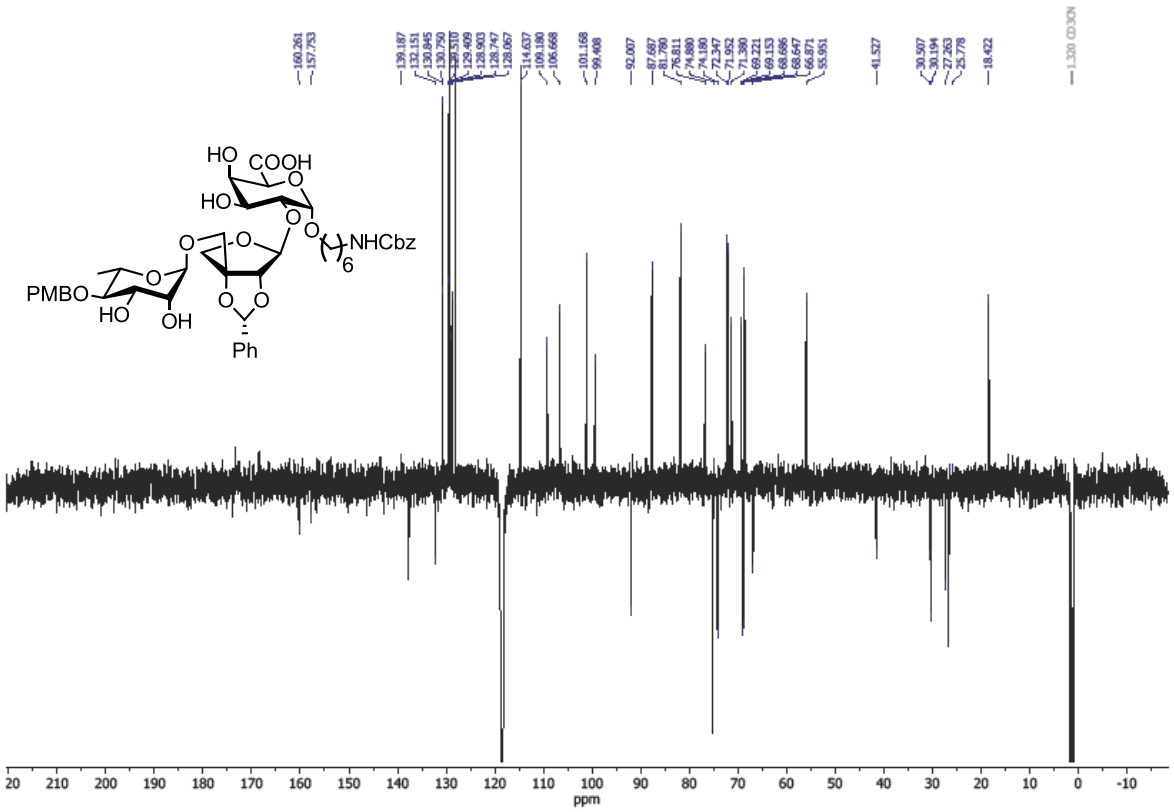
^{13}C APT NMR of **127** (CD_3COCD_3, 150 MHz, 297 K)



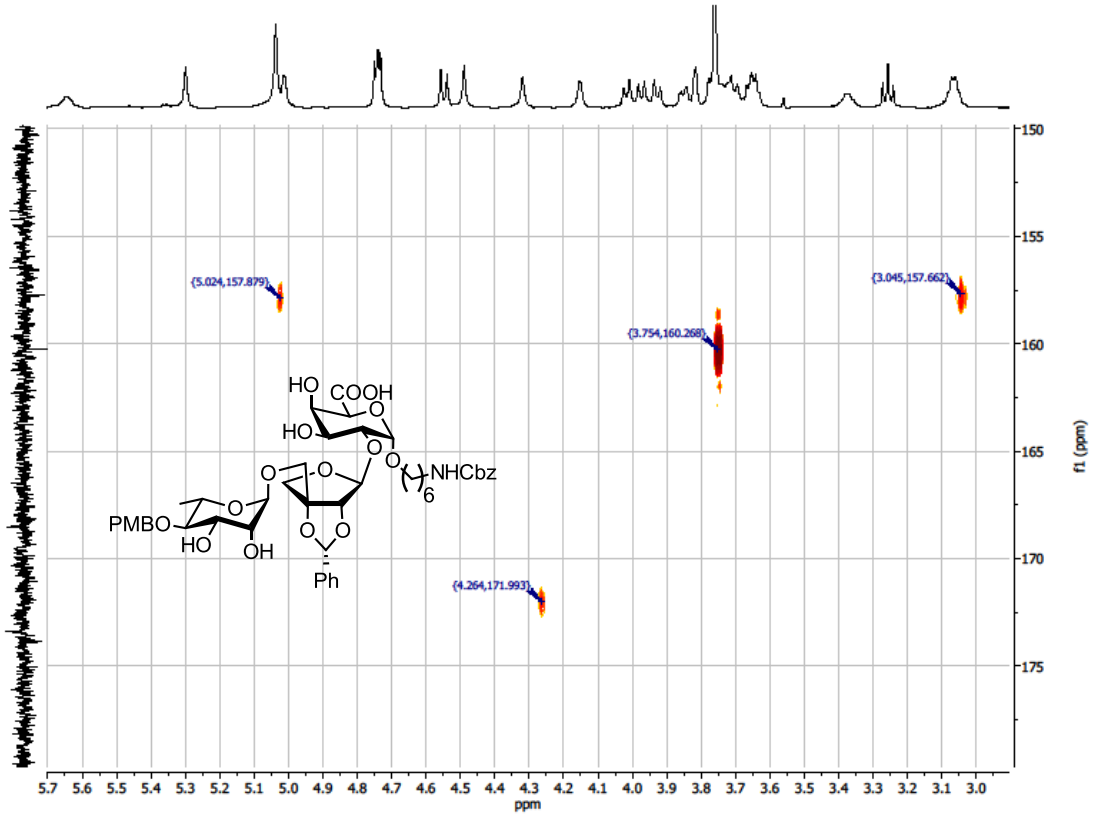
^{1}H NMR of **128** (CD_3CN_3, 600 MHz, 297 K)



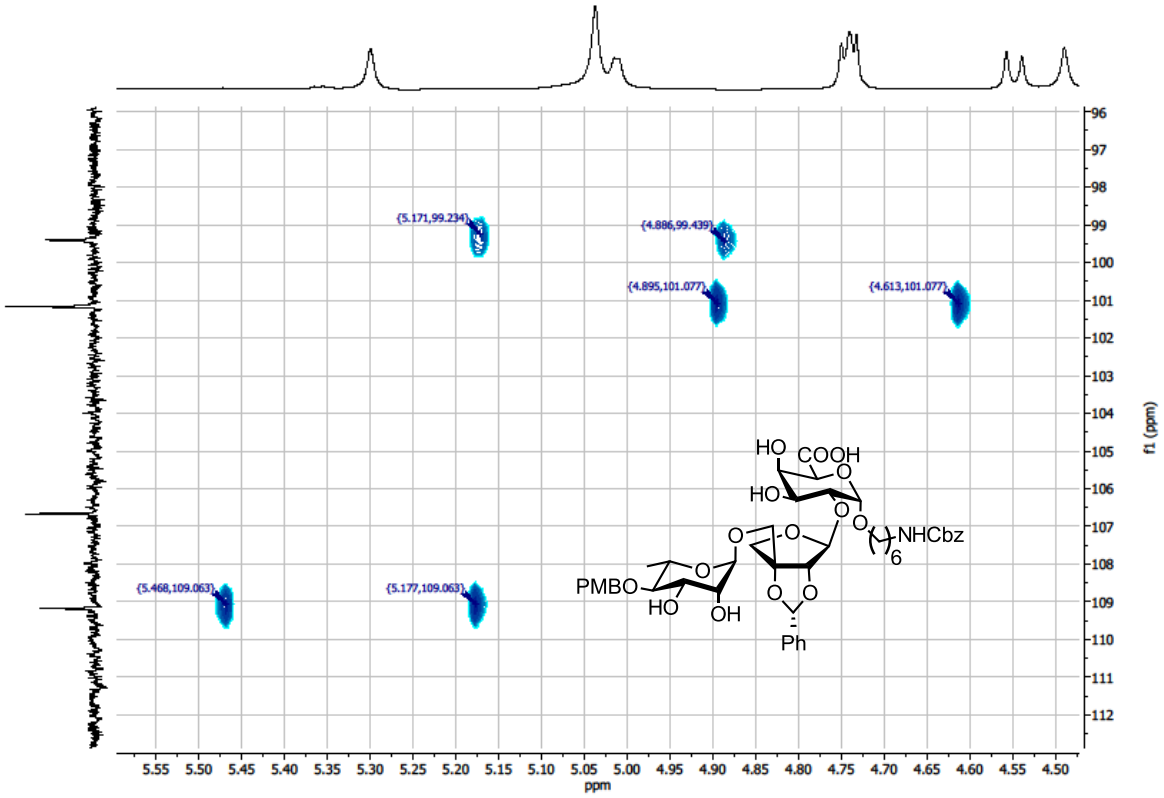
^{1}H NMR of **128** (CD_3CN_3 + D_2O, 600 MHz, 297 K)



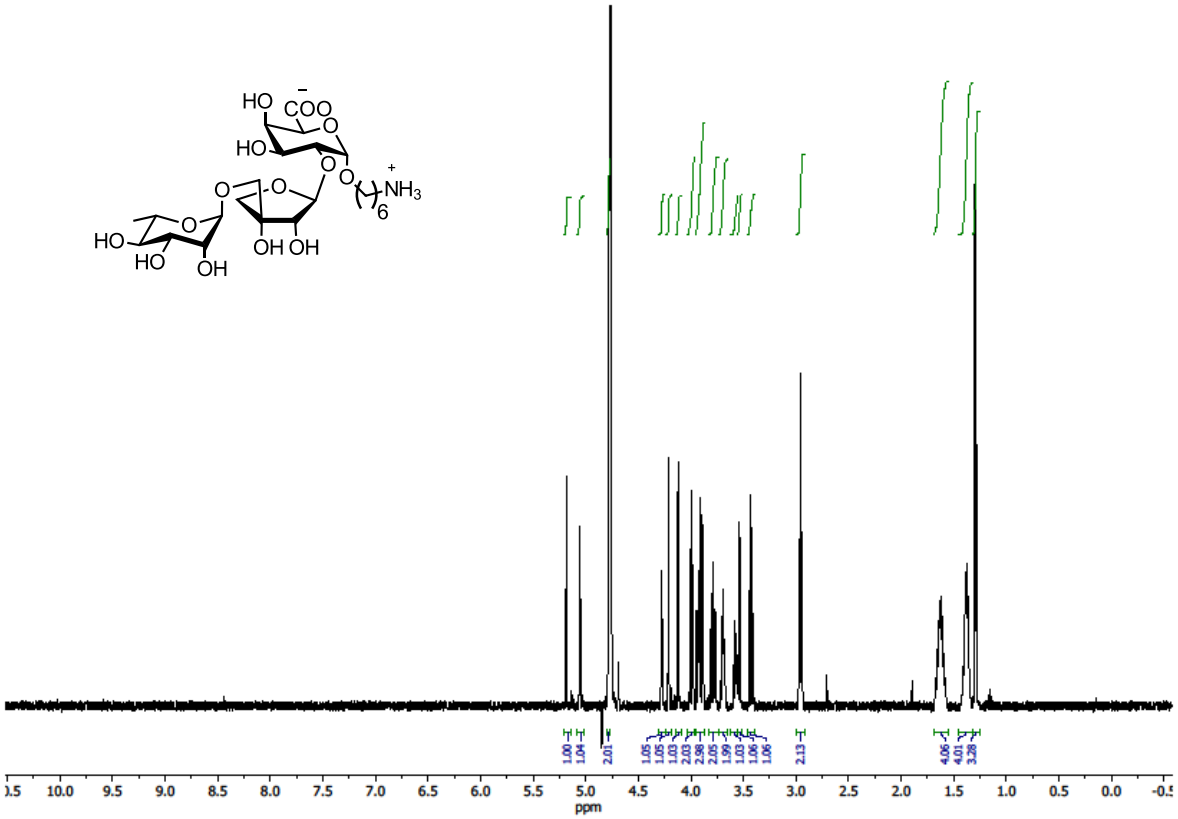
^{13}C APT NMR of **128** (CD_3CN, 150 MHz, 297 K)



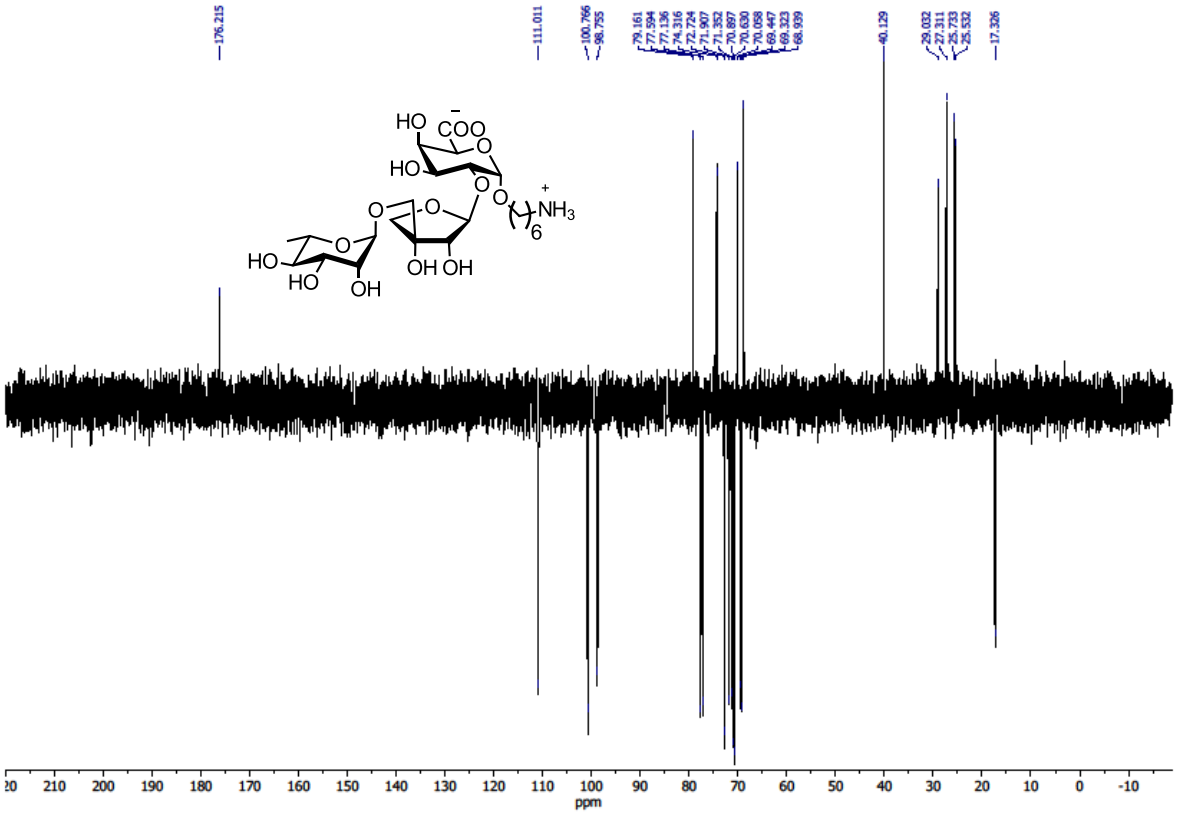
^{1}H-^{13}C HMBC NMR of **128** (CD_3CN, 150 MHz, 297 K)



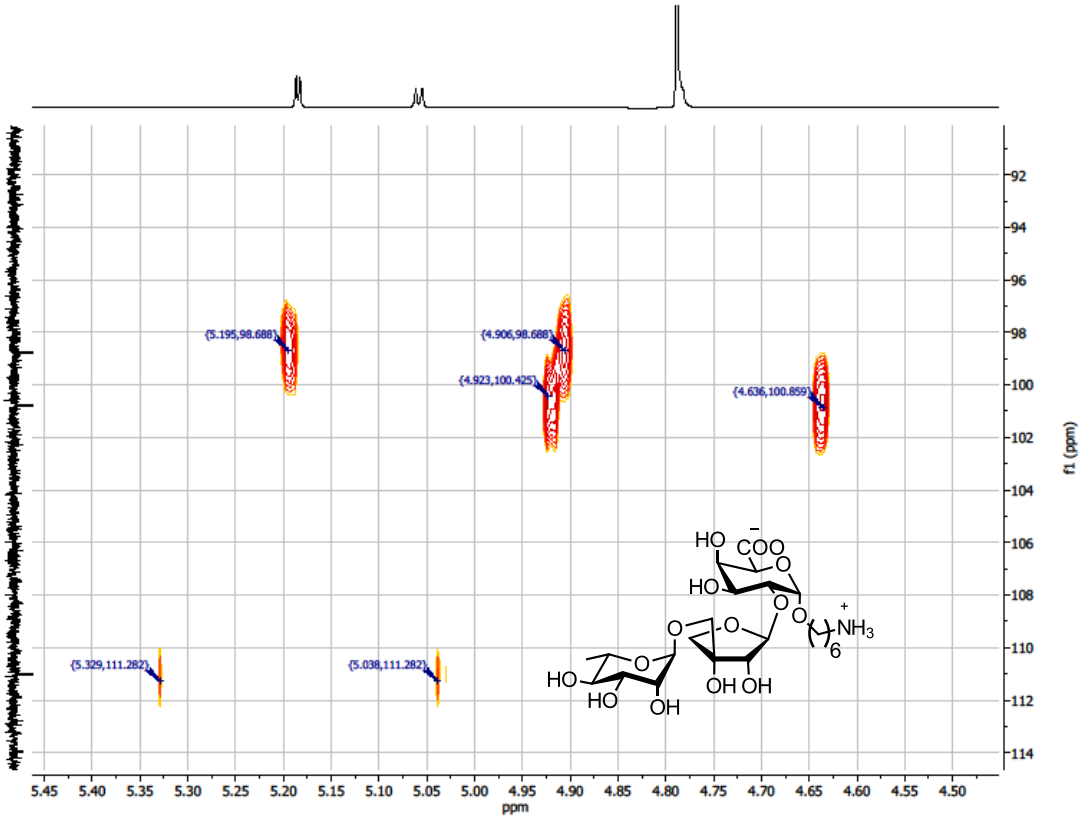
^{1}H-^{13}C CLIP HSQC NMR of **128** (CD_3CN, 600 MHz, 297 K)



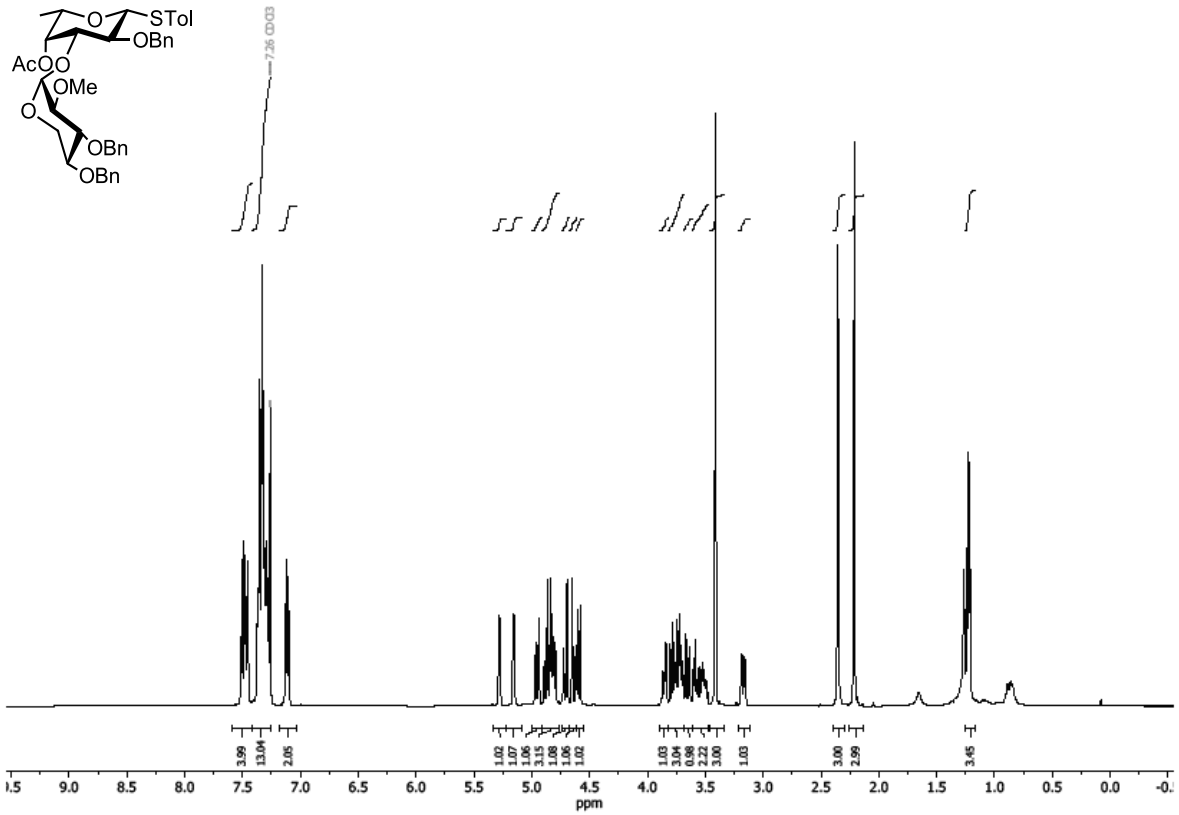
^{1}H NMR of **85** (D_2O, 600 MHz, 297 K)



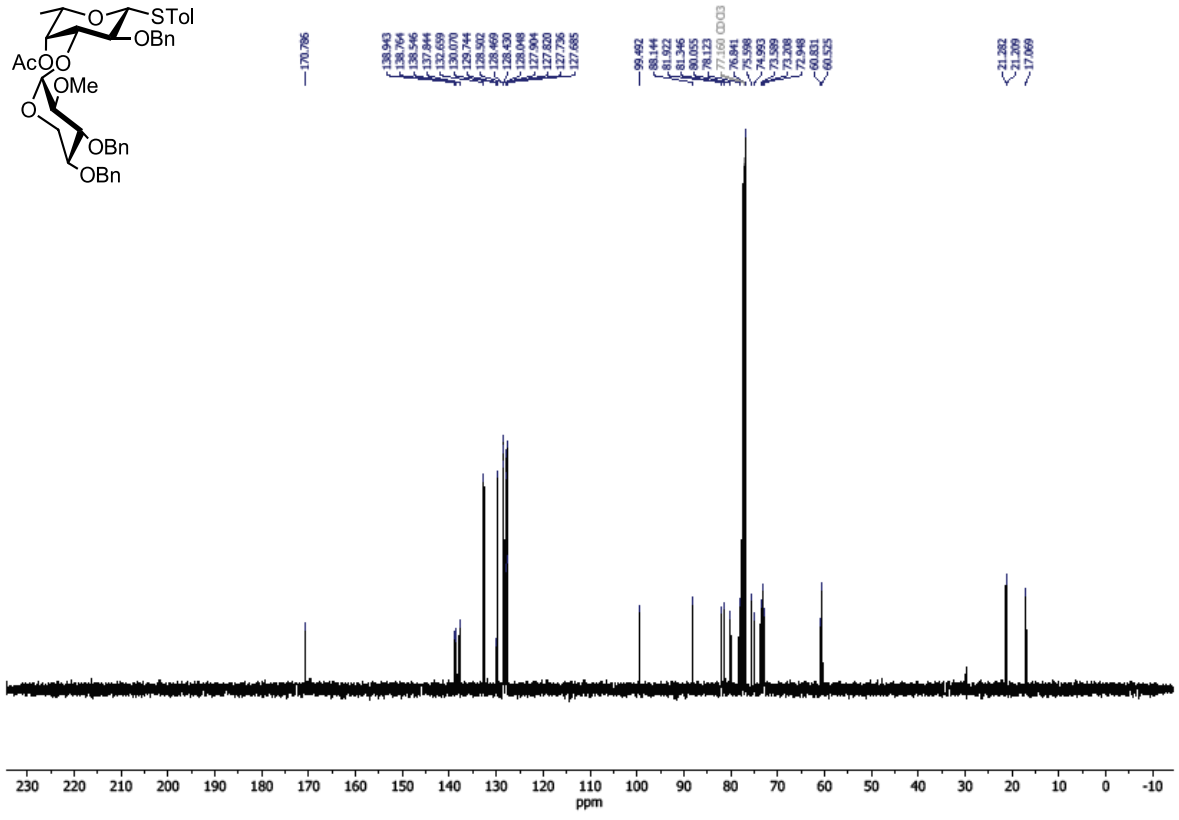
^{13}C APT NMR of **85** (D_2O, 150 MHz, 297 K)



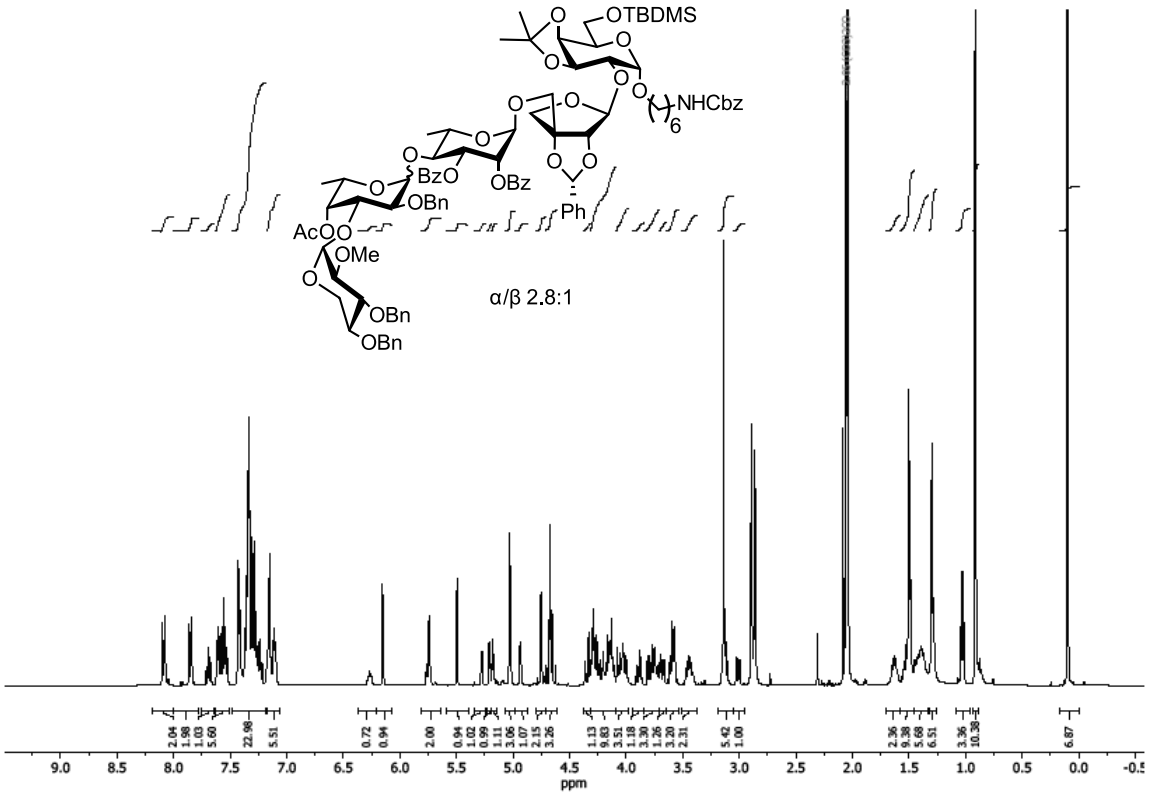
^{1}H-^{13}C coupled HMBC NMR of **85** (D_2O, 600 MHz, 297 K)



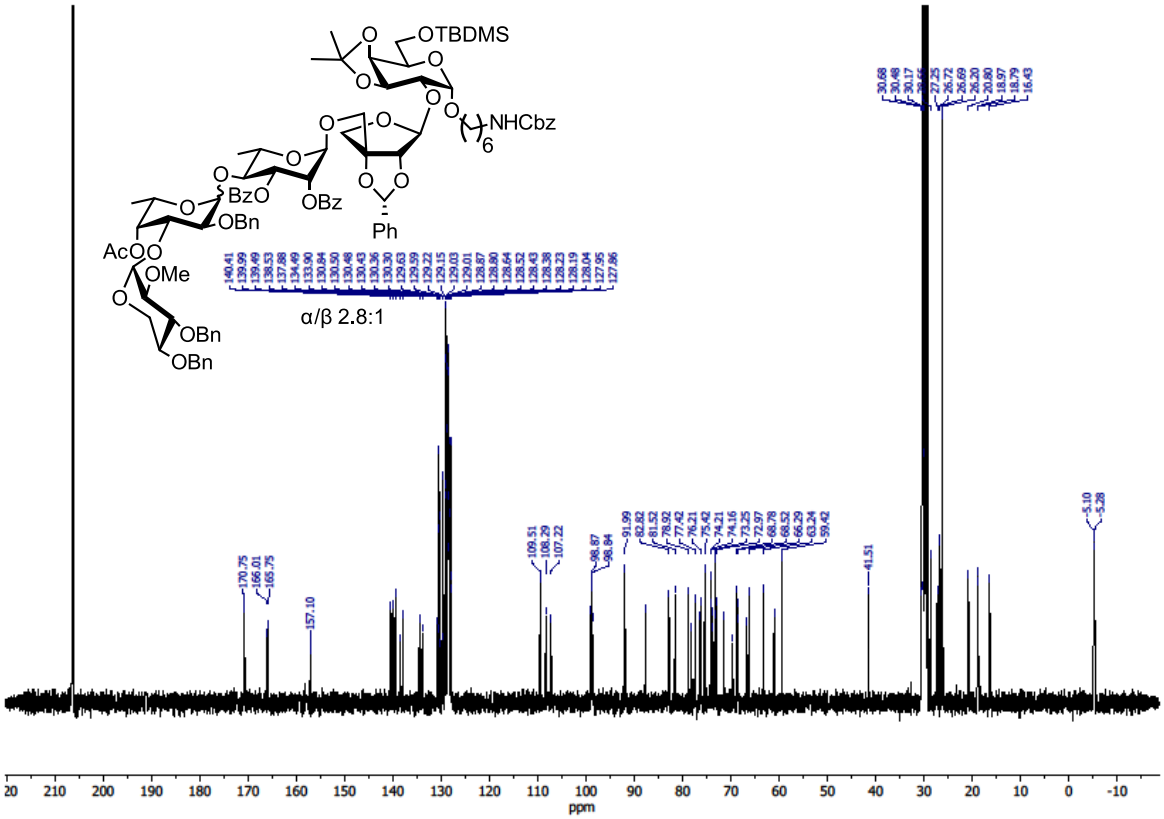
^{1}H NMR of **87** ($CDCl_3$, 400 MHz, 297 K, 1.56 H_2O)



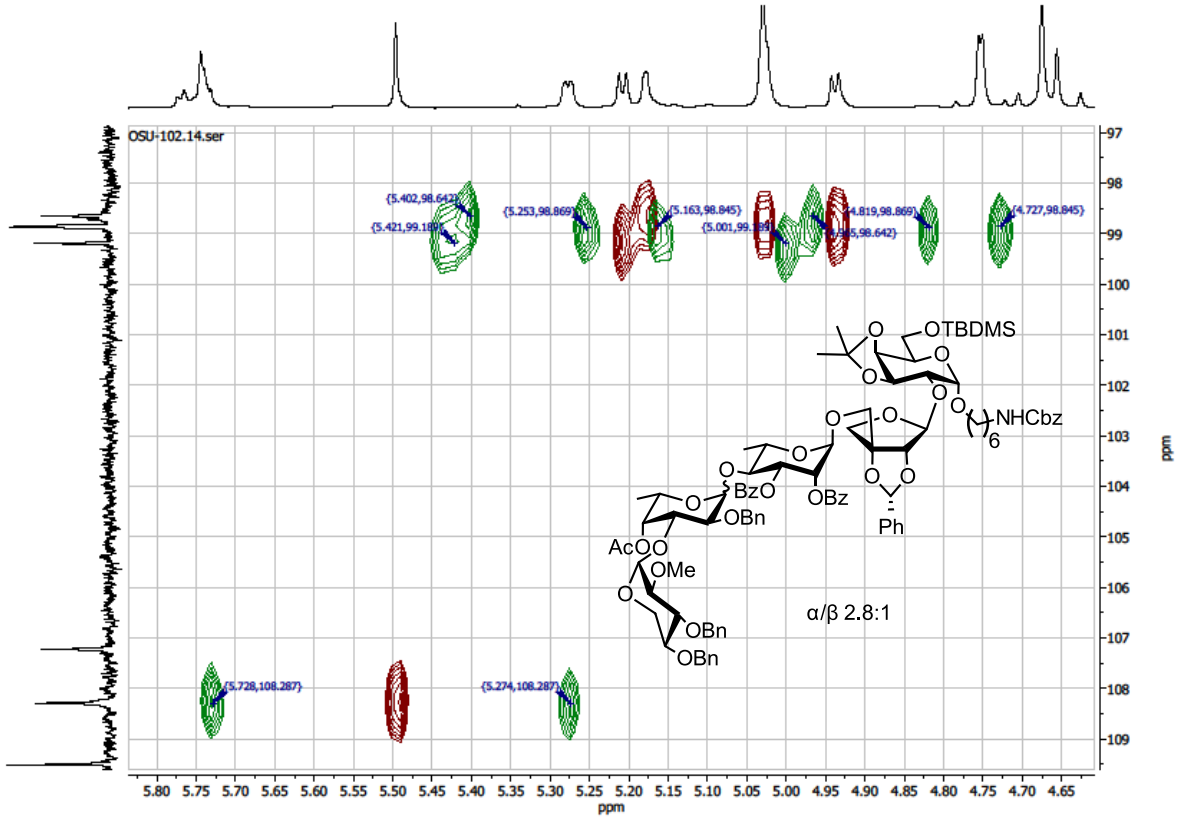
^{13}C NMR of **87** ($CDCl_3$, 100 MHz, 297 K)



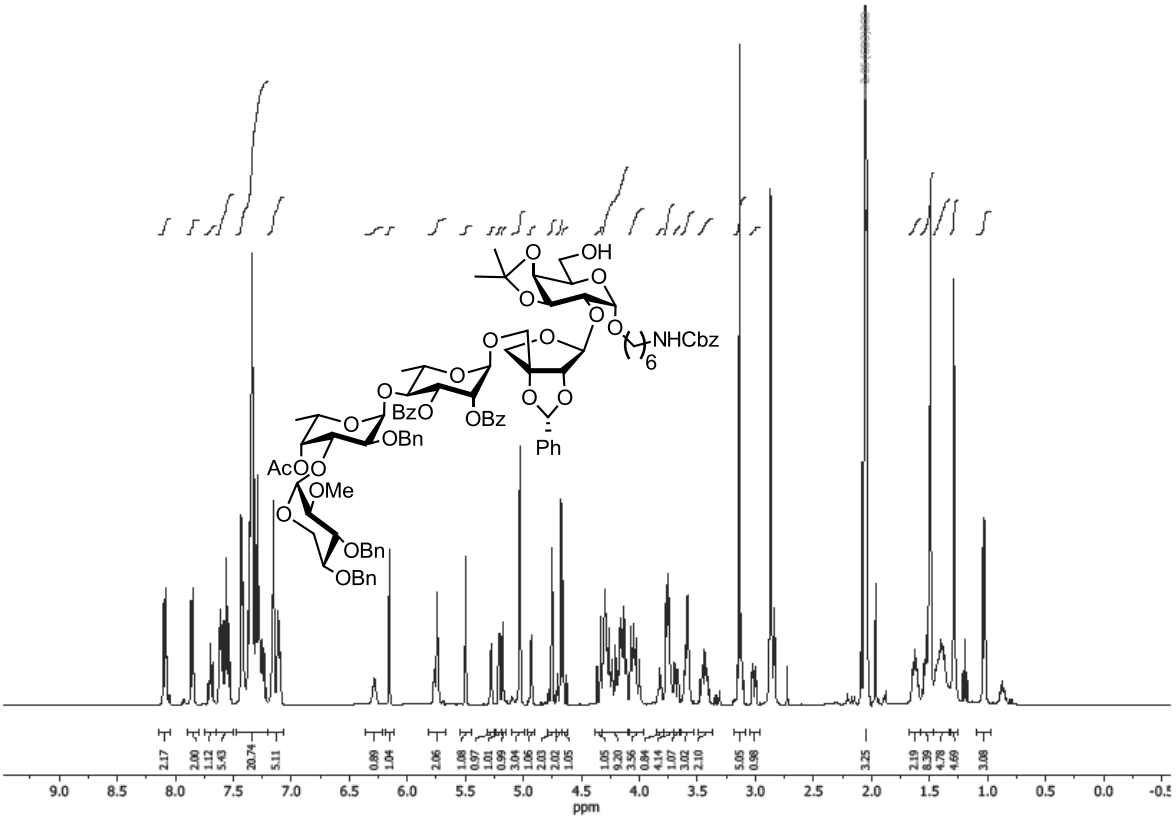
^{1}H NMR of **84** (CD_3COCD_3, 400 MHz, 297 K, 7.20-7.10 2.32 Toluene, 2.84 H_2O 2.81 HDO, 2.05 Acetone)



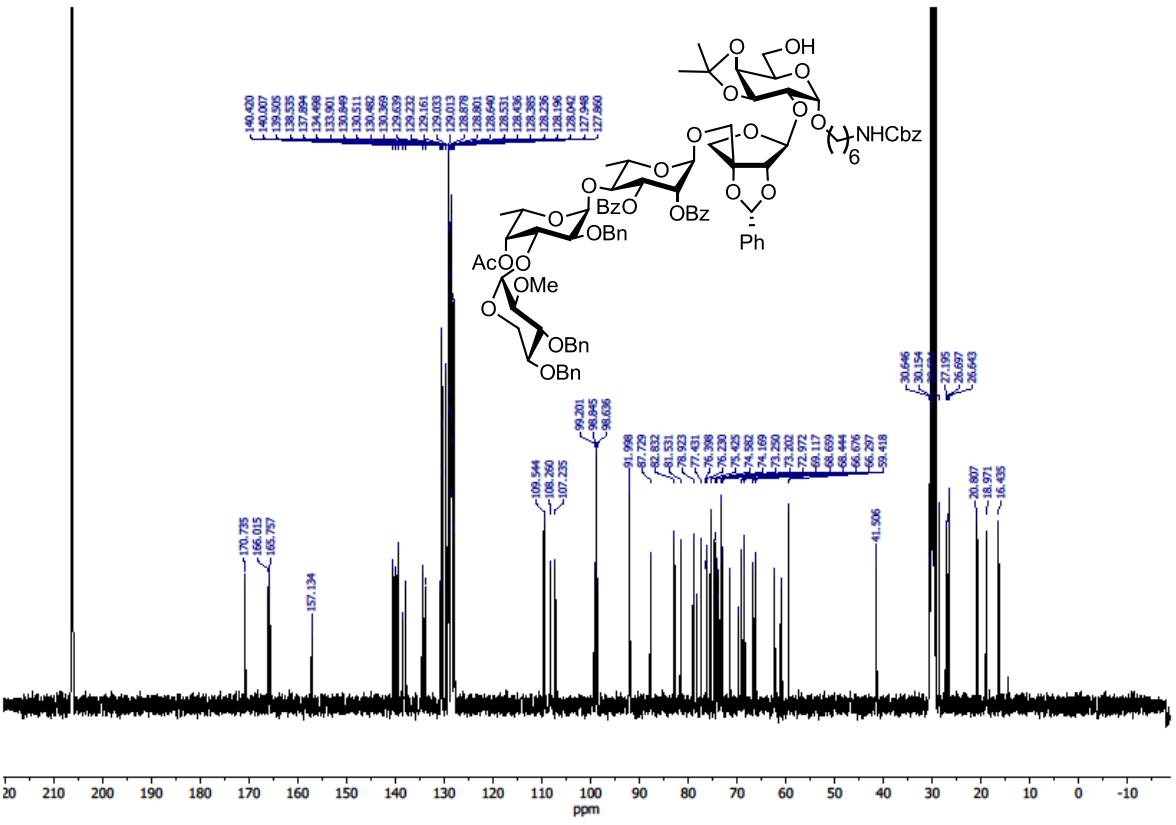
^{13}C NMR of **84** (CD_3COCD_3, 100 MHz, 297 K)



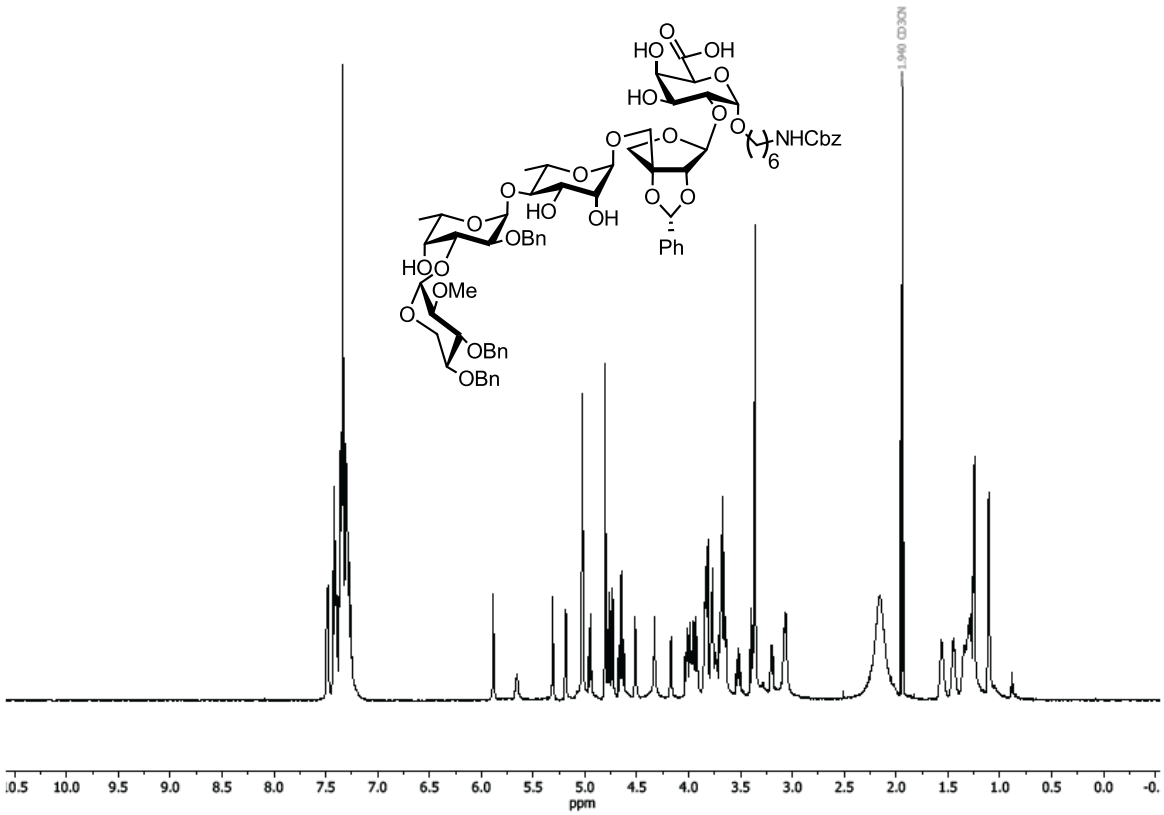
^{1}H-^{13}C CLIP HSQC/HSQC of **84** (stacked presentation, CD_3COCD_3, 400 MHz, 297 K)



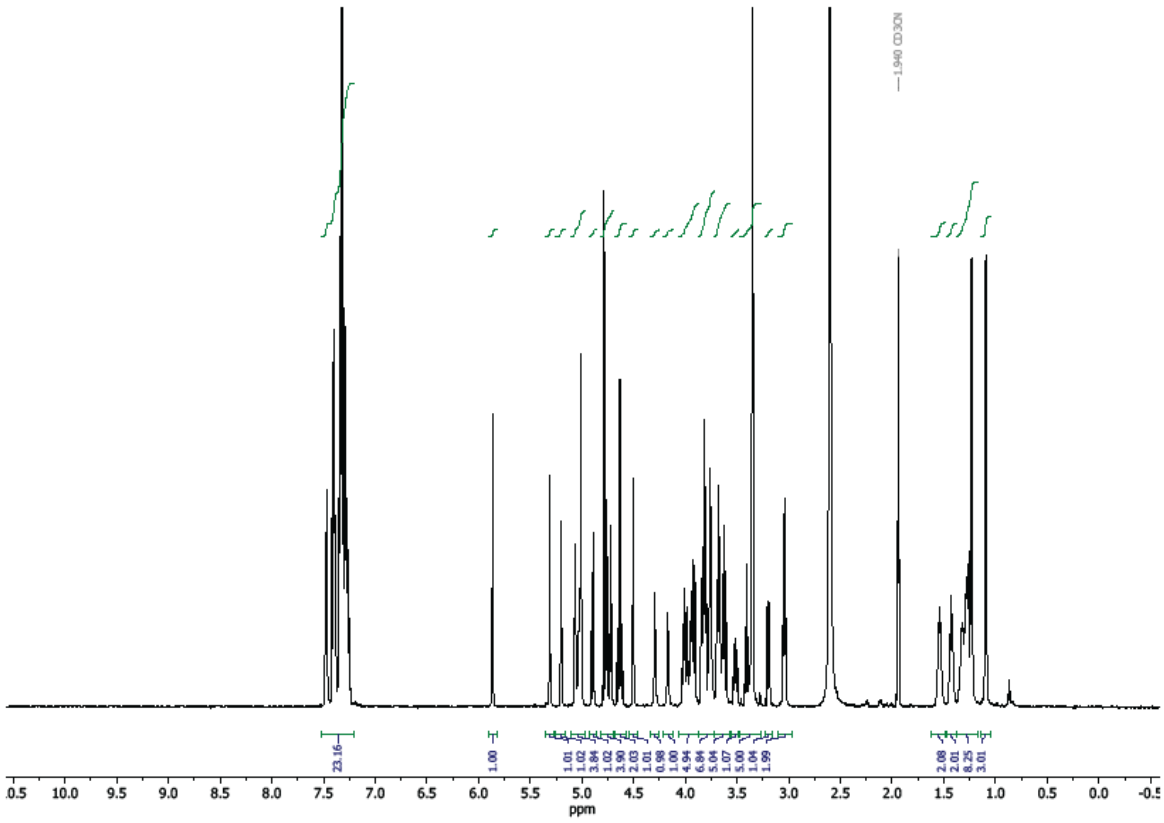
^{1}H NMR of **128** (CD_3COCD_3, 400 MHz, 297 K, 2.05 1.26 EtOAc, 2.84 H_2O 2.81 HDO)



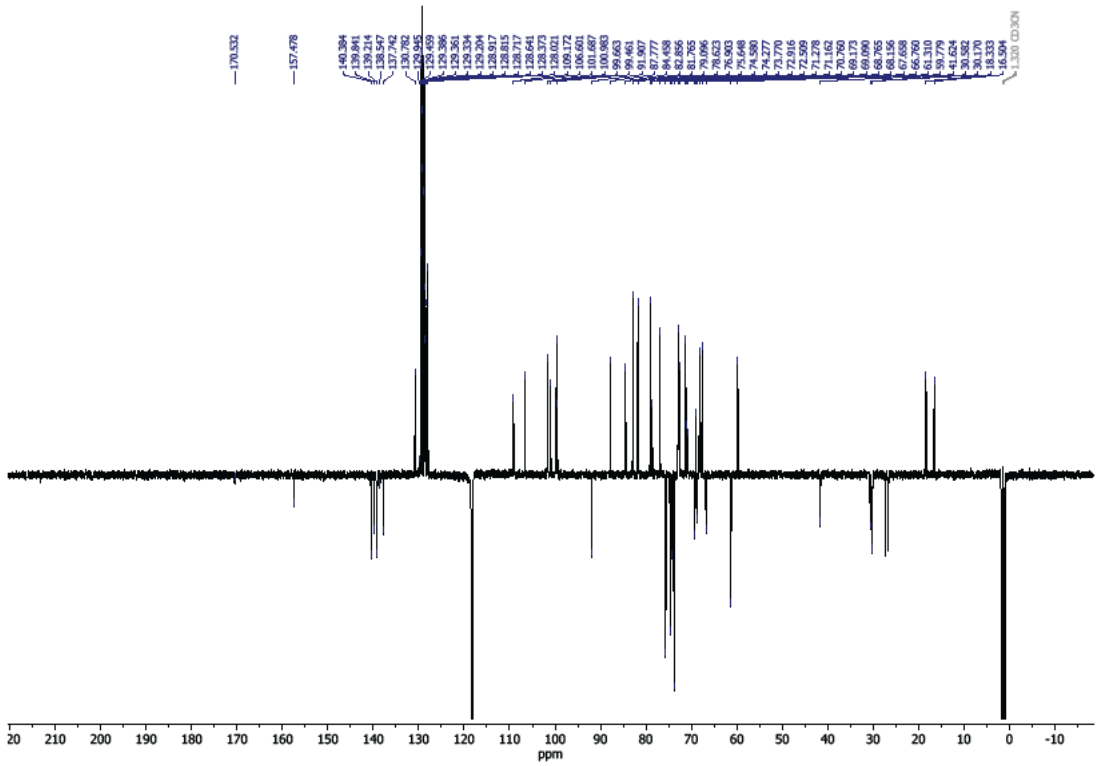
^{13}C NMR of **128** (CD_3COCD_3, 100 MHz, 297 K)



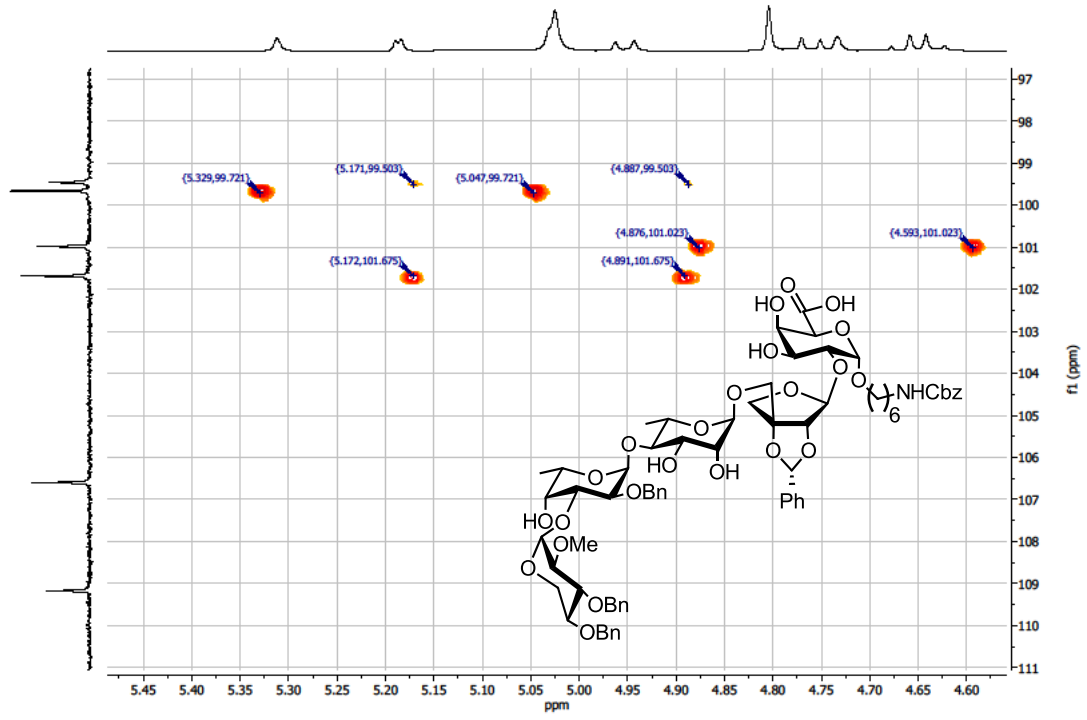
^{1}H NMR of **129** (CD_3CN, 600 MHz, 297 K)



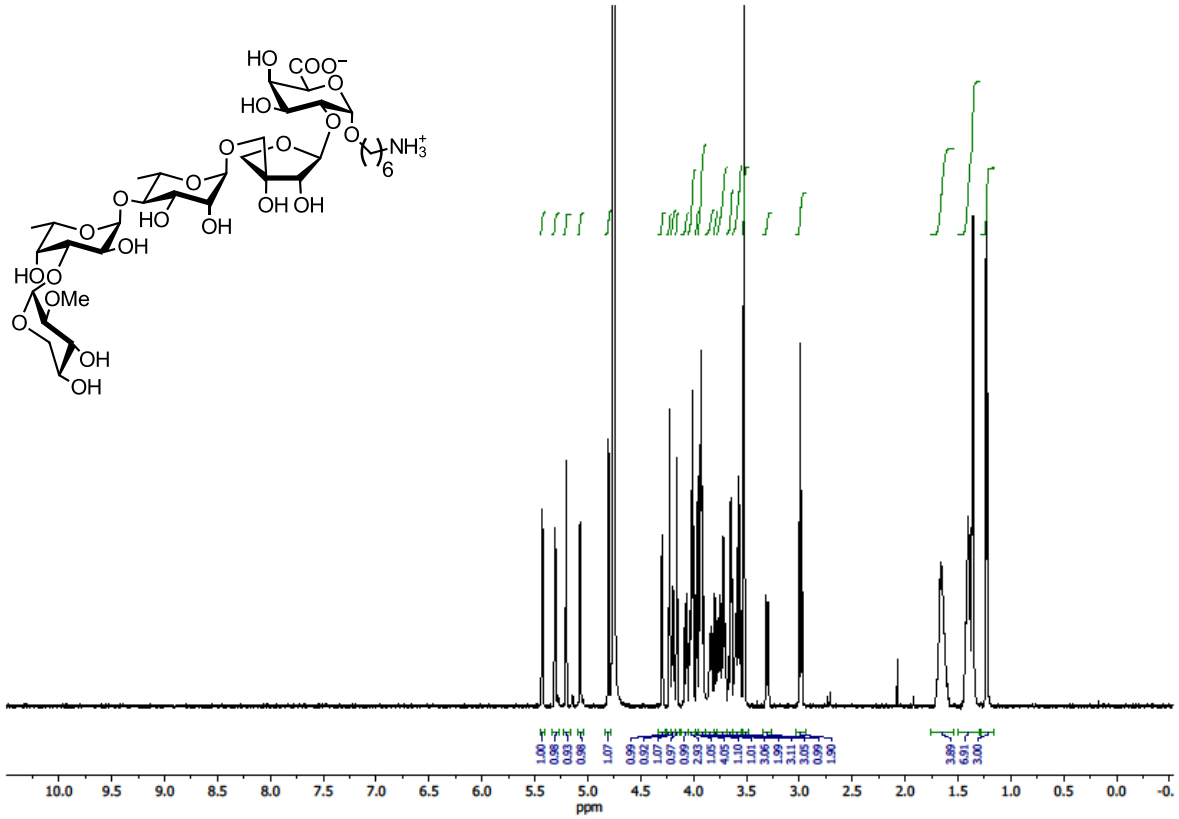
^{1}H NMR of **129** (CD_3CN+ D_2O, 600 MHz, 297 K)



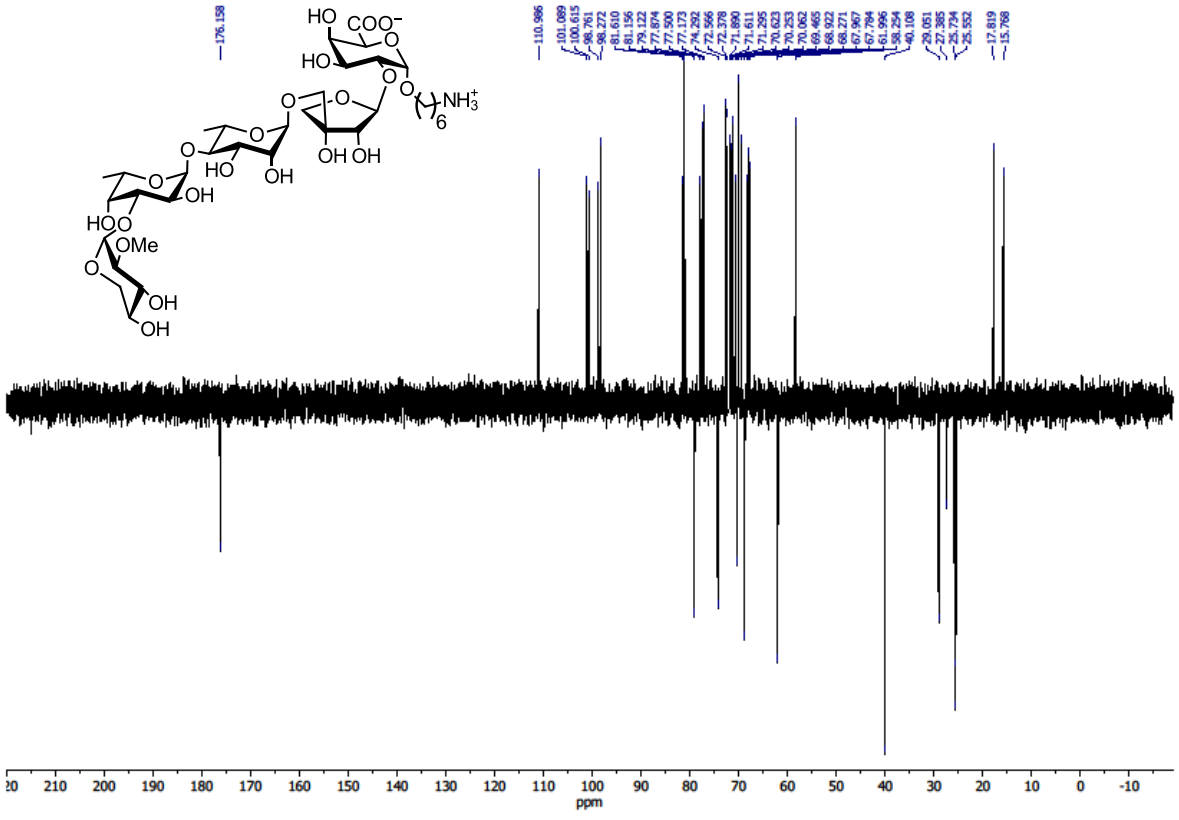
^{13}C APT NMR of **129** (CD_3CN, 150 MHz, 297 K)



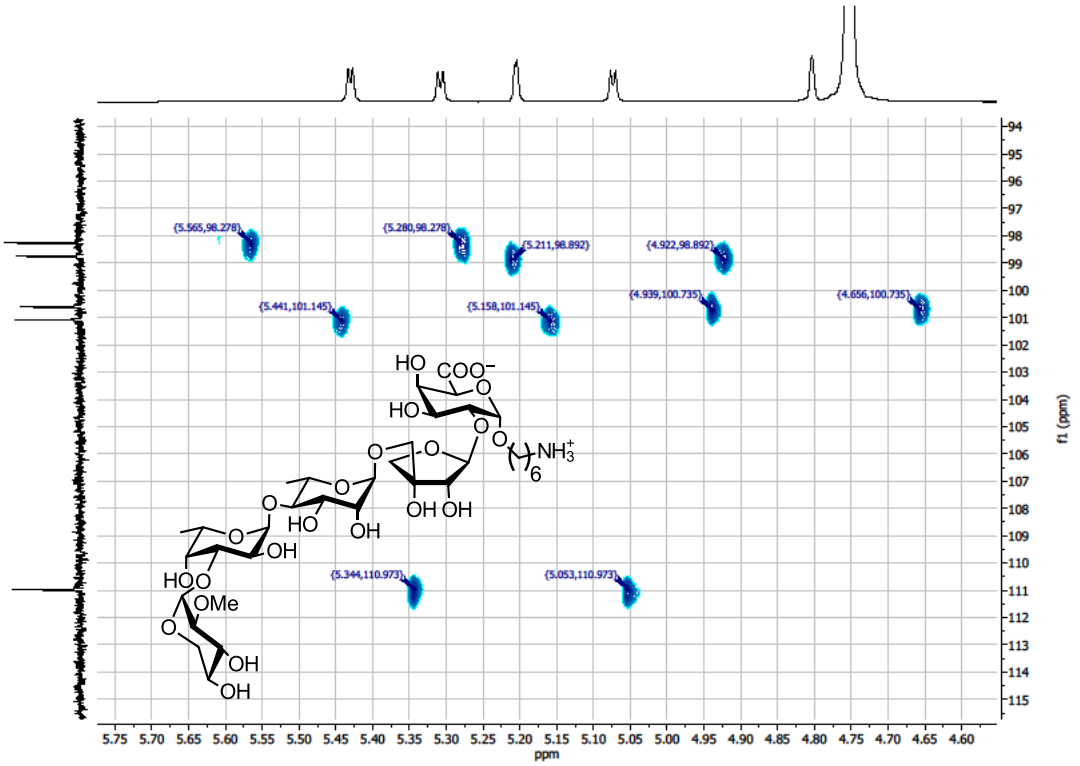
^{1}H-^{13}C HMBC NMR of **129** (CD_3CN, 600 MHz, 297 K)



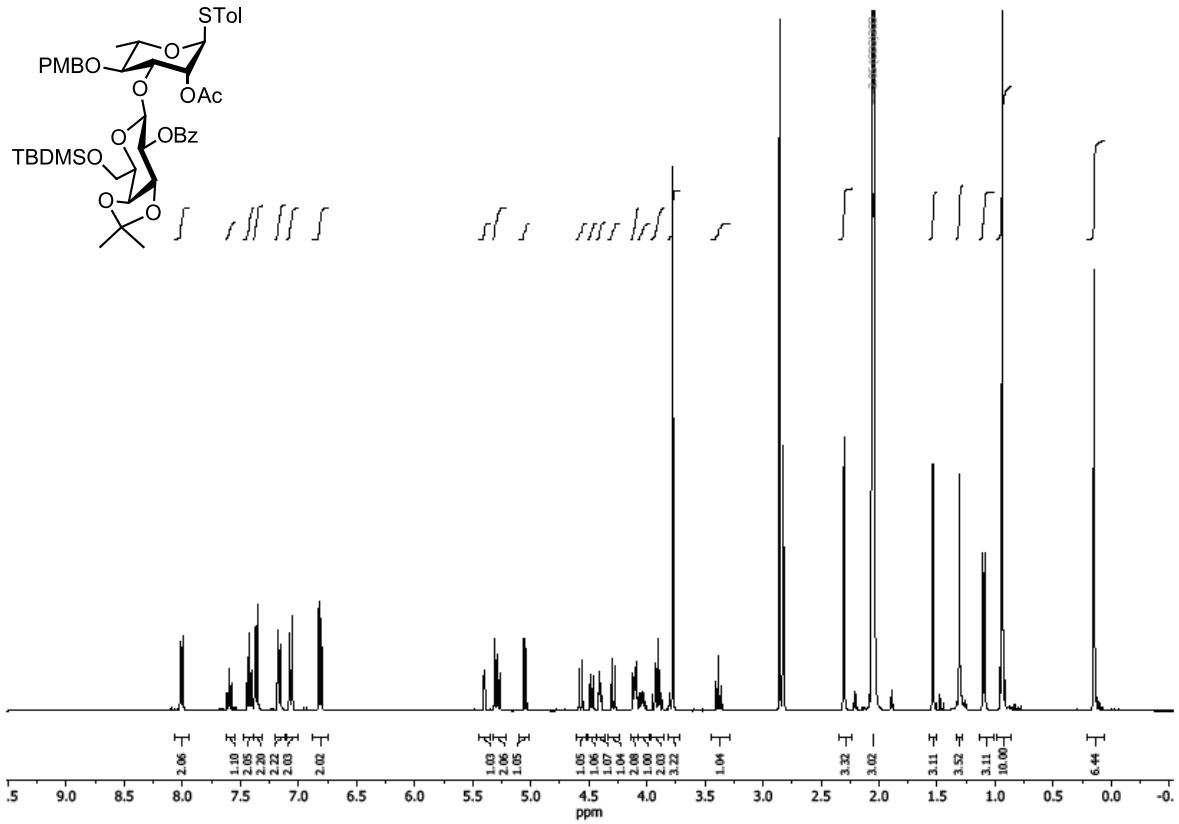
^{1}H NMR of **83** (D_2O, 600 MHz, 297 K)



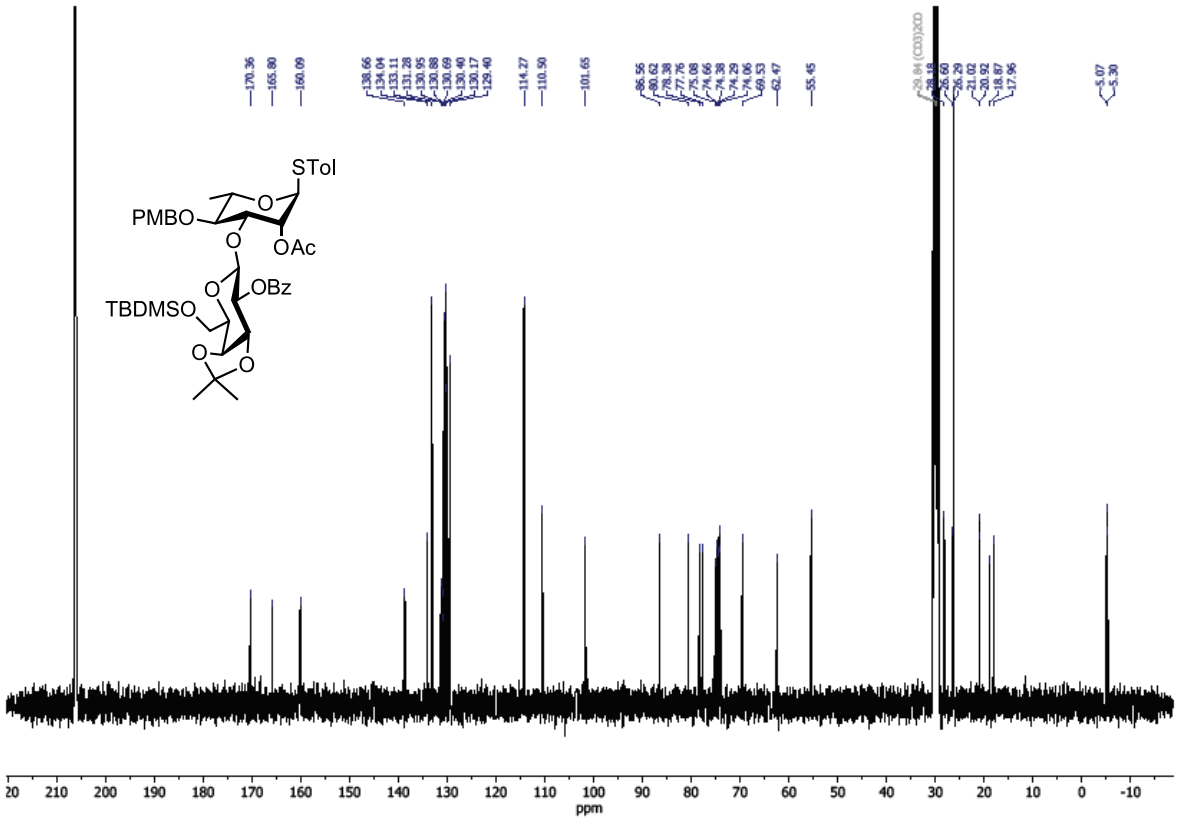
^{13}C APT NMR of **83** (D_2O, 150 MHz, 297 K)



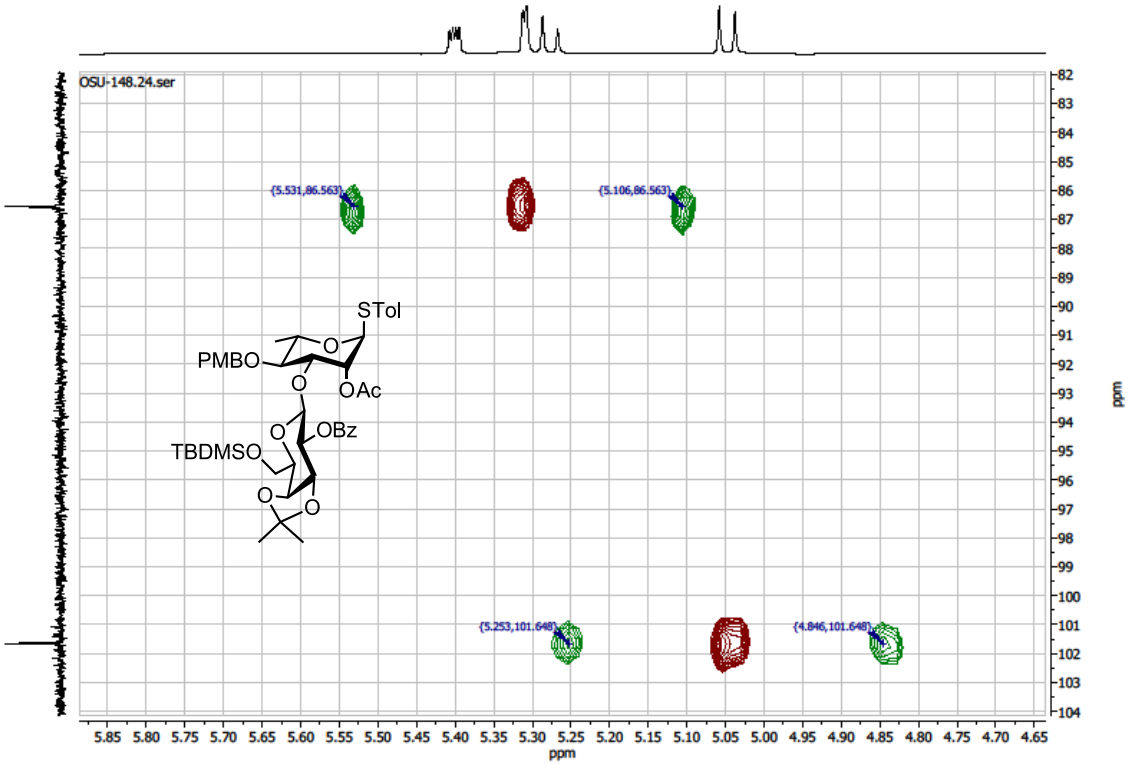
^{1}H-^{13}C coupled HMBC NMR of **83** (D_2O, 600 MHz, 297 K)



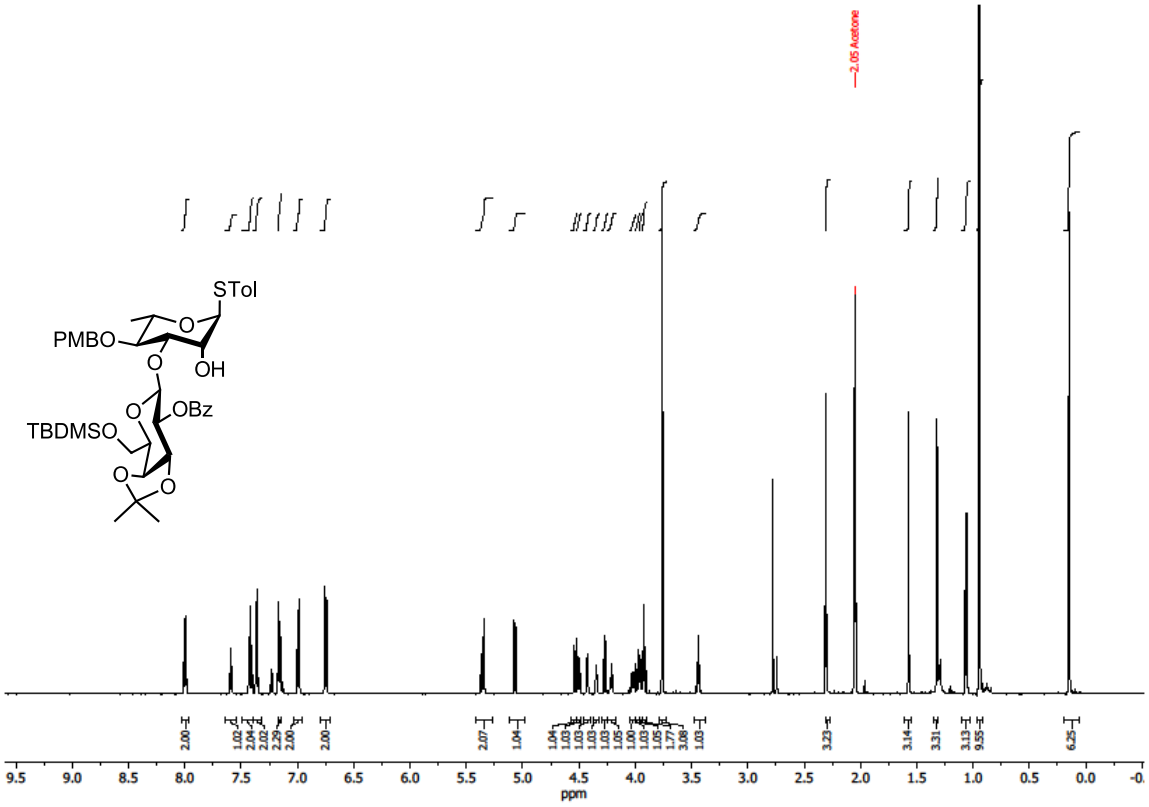
^{1}H NMR of **130** (CD_3COCD_3, 400 MHz, 297 K, H_2O 2.84 HDO 2.81)



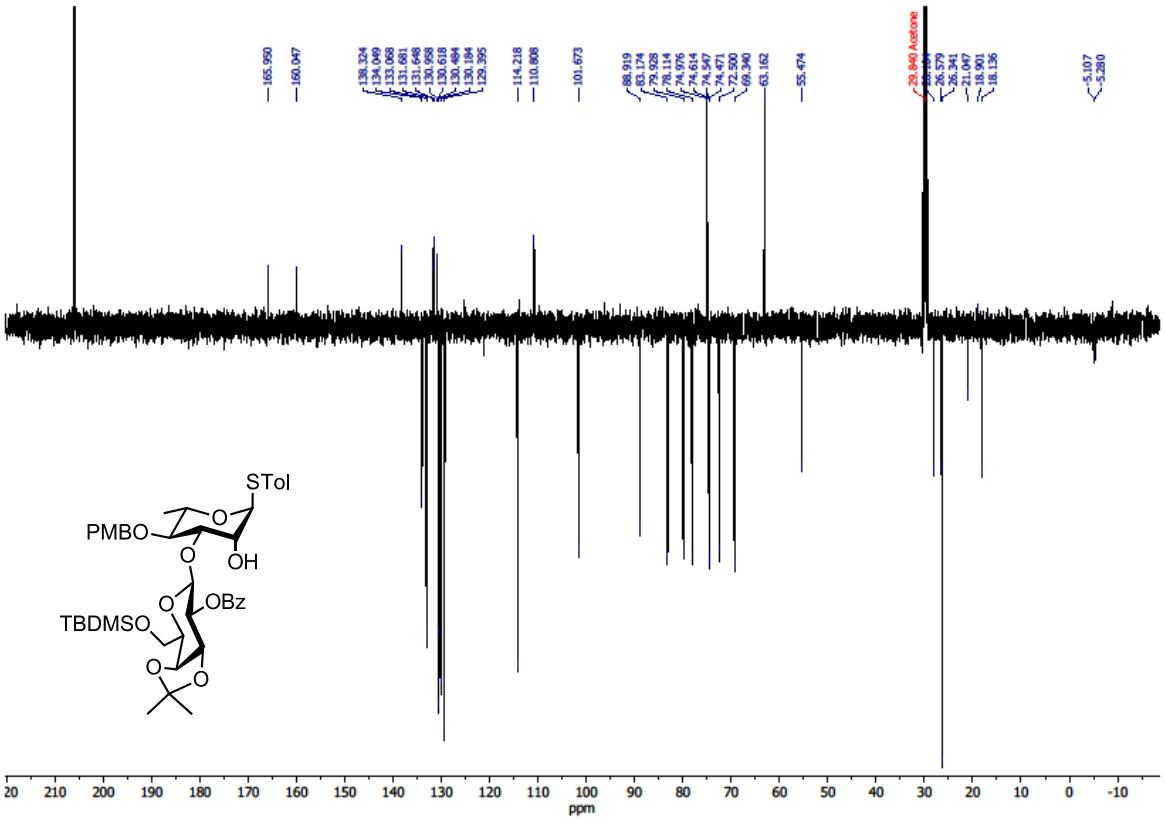
^{13}C NMR of **130** (CD_3COCD_3, 100 MHz, 297 K)



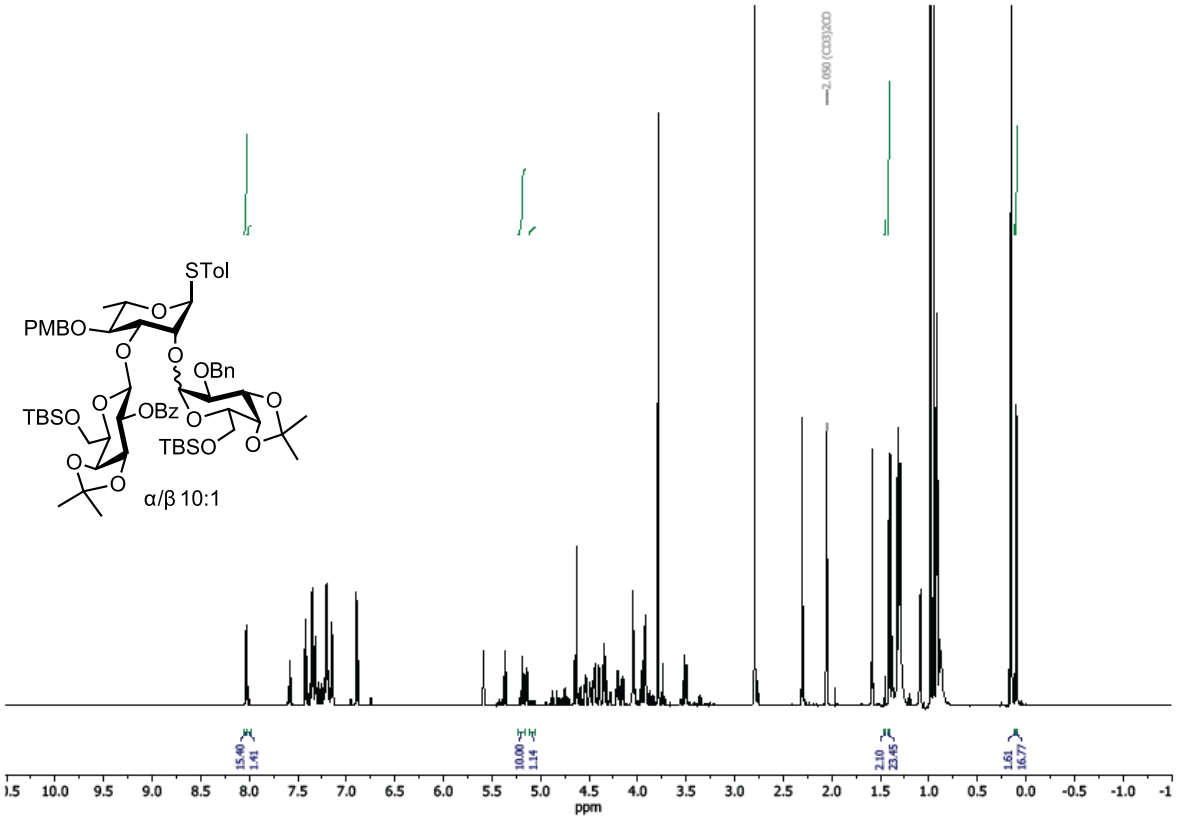
^{1}H-^{13}C CLIP HSQC/HSQC of **130** (stacked presentation, CD_3COCD_3, 400 MHz, 297 K)



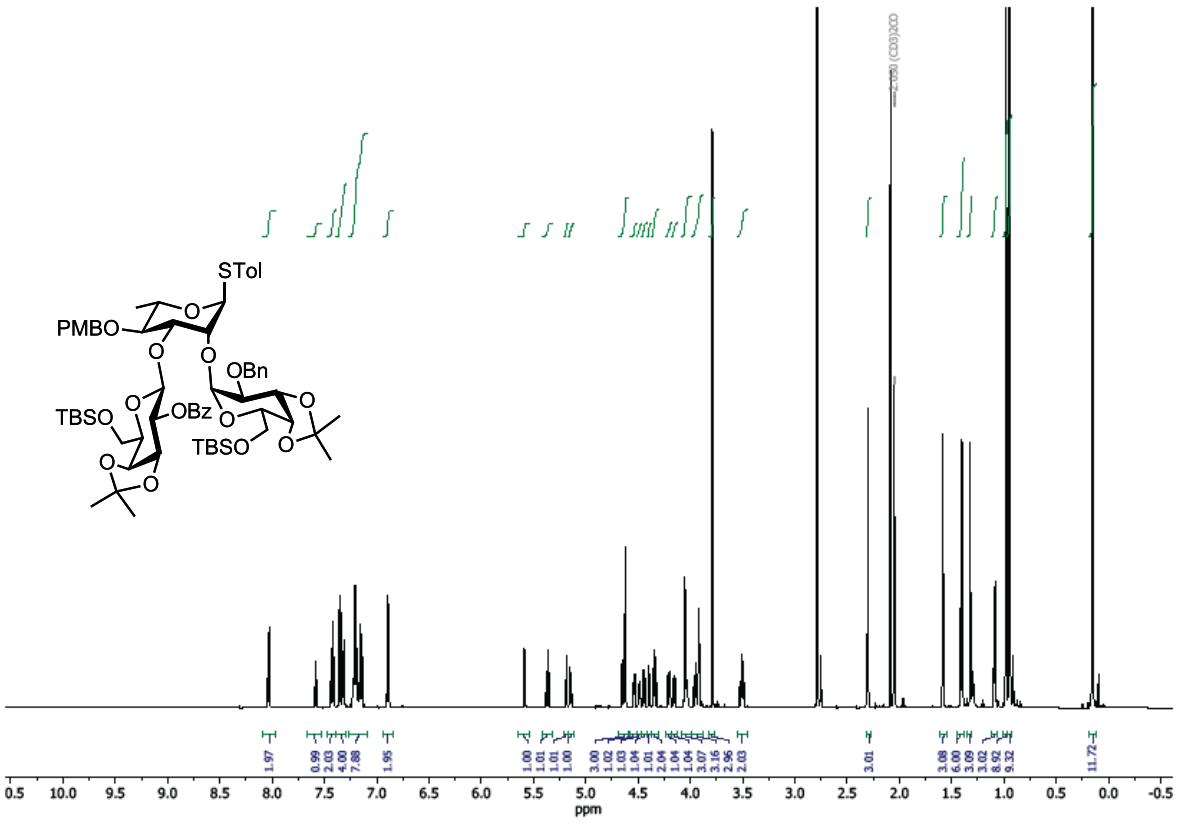
^{1}H NMR of **74** (CD_3COCD_3, 600 MHz, 297 K, 7.20-7.10 and 2.32 toluene, 2.84 H_2O 2.81 HDO, 2.05 acetone)



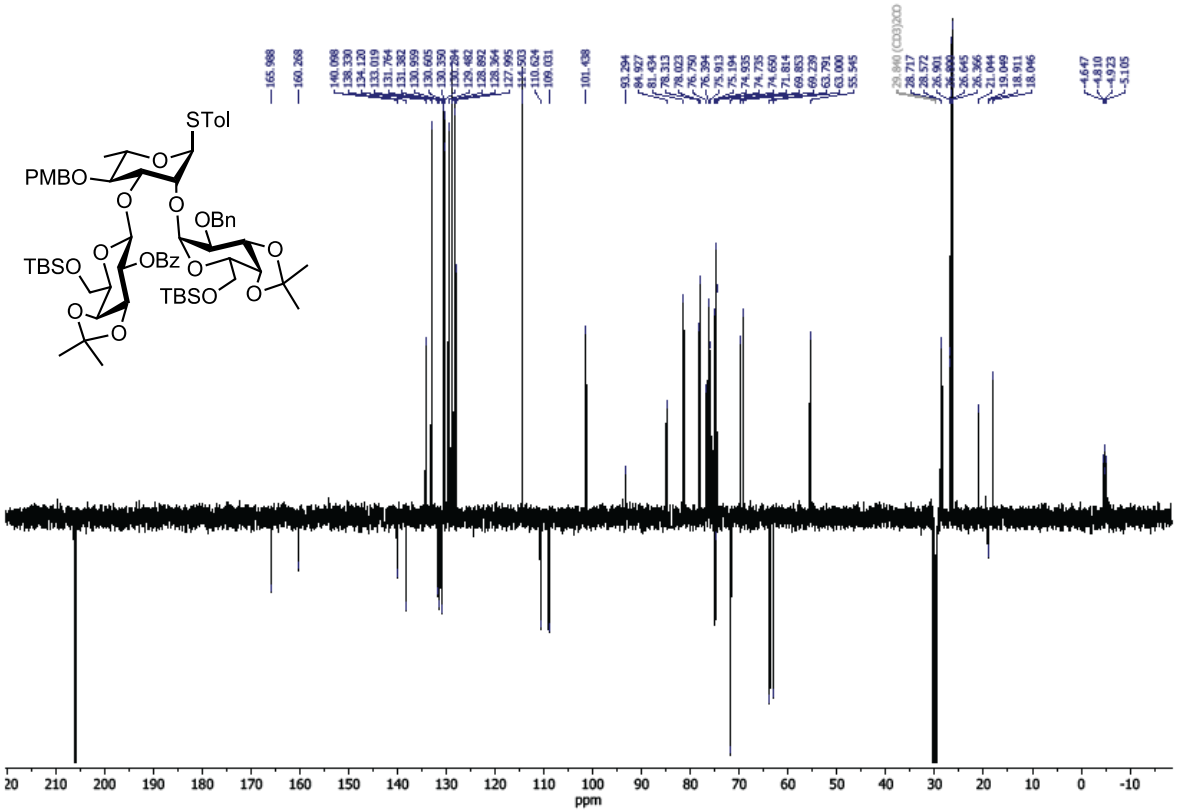
^{13}C APT NMR of **74** (CD_3COCD_3, 150 MHz, 297 K)



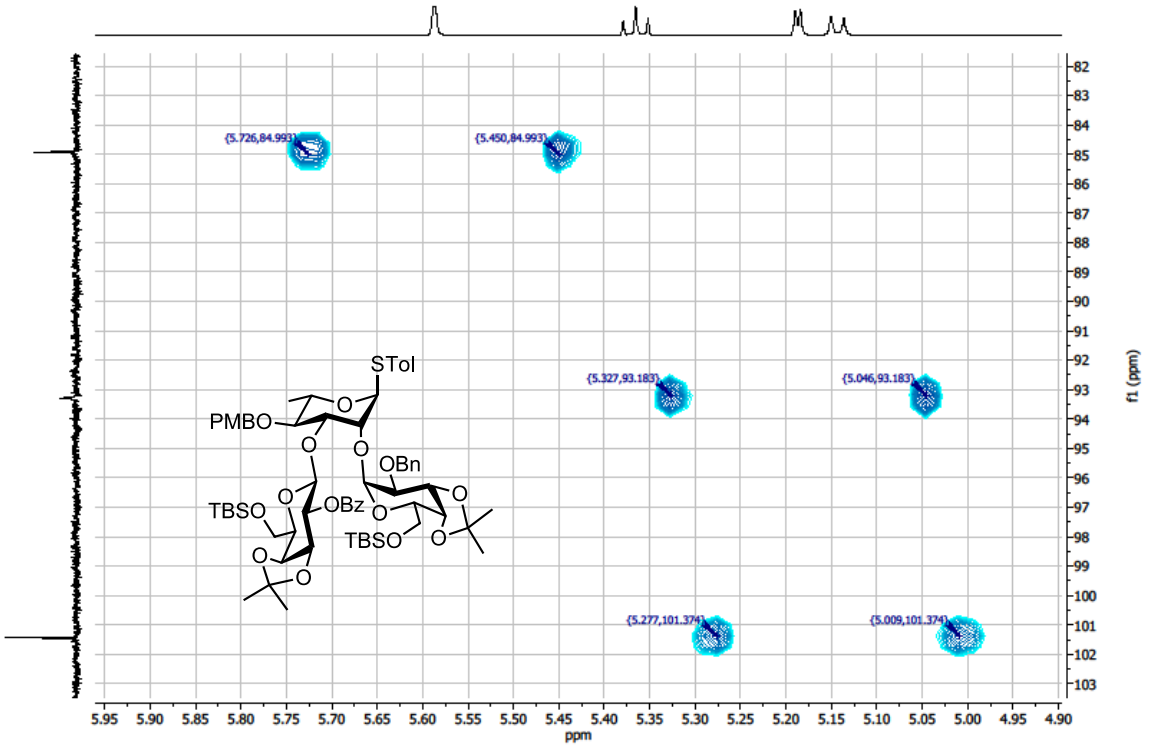
^{1}H NMR of **131-α/β** (CD_3COCD_3, 600 MHz, 297 K)



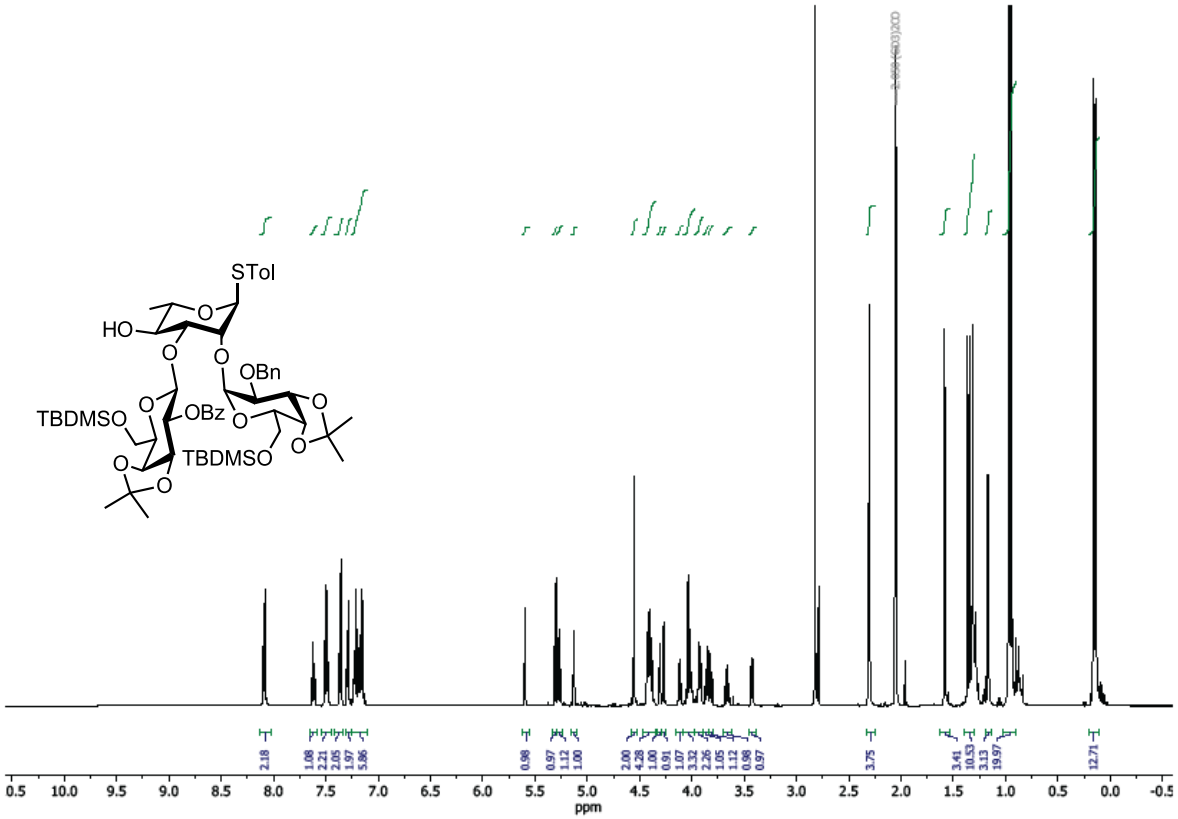
^{1}H NMR of **131-α** (CD_3COCD_3, 600 MHz, 297 K)



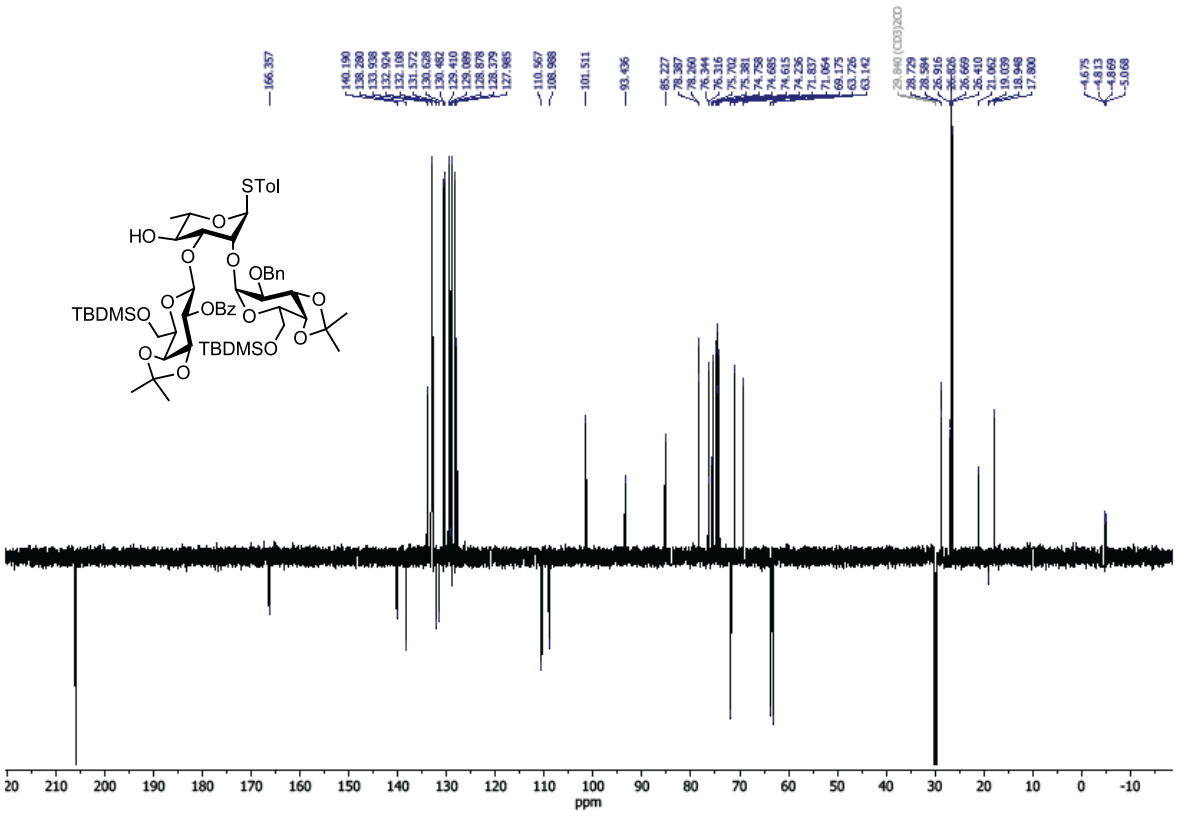
^{13}C APT NMR of **131-α** (CD_3COCD_3, 150 MHz, 297 K)



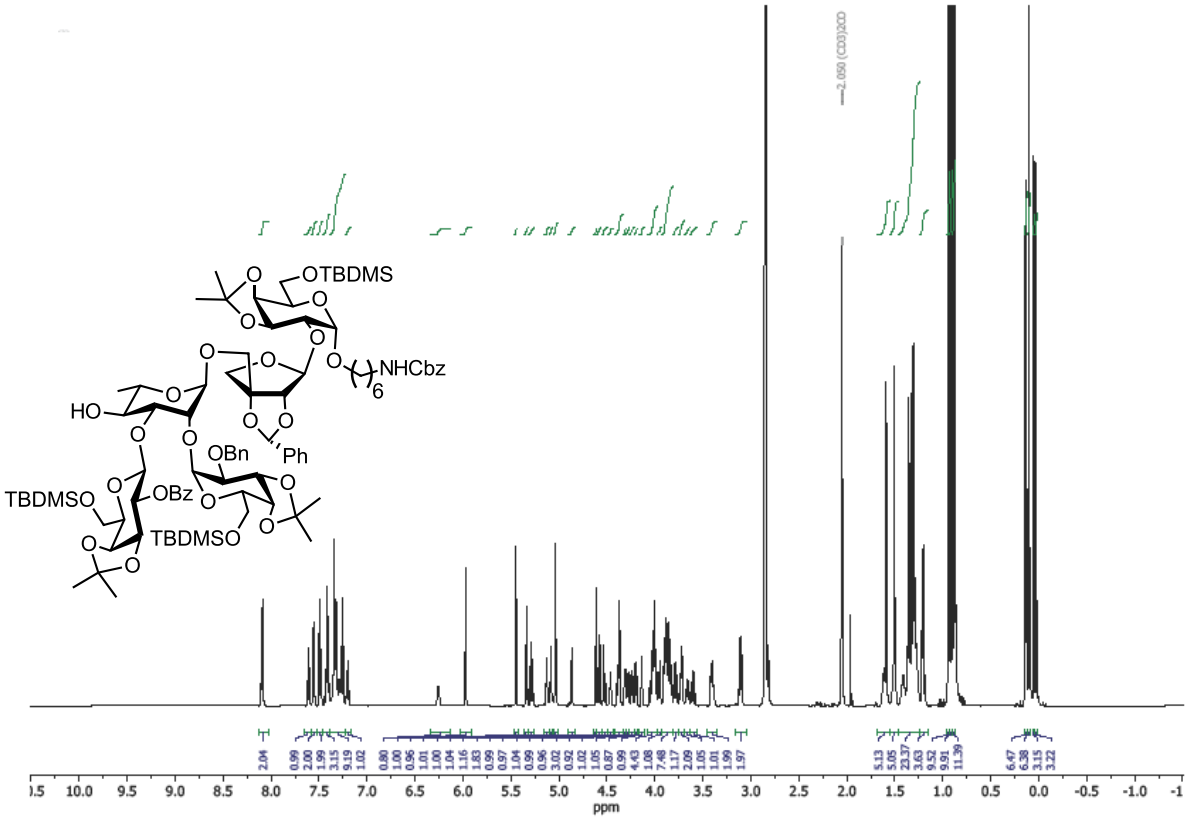
^{1}H-^{13}C CLIP HSQC NMR of **131-α** (CD_3COCD_3, 600 MHz, 297 K)



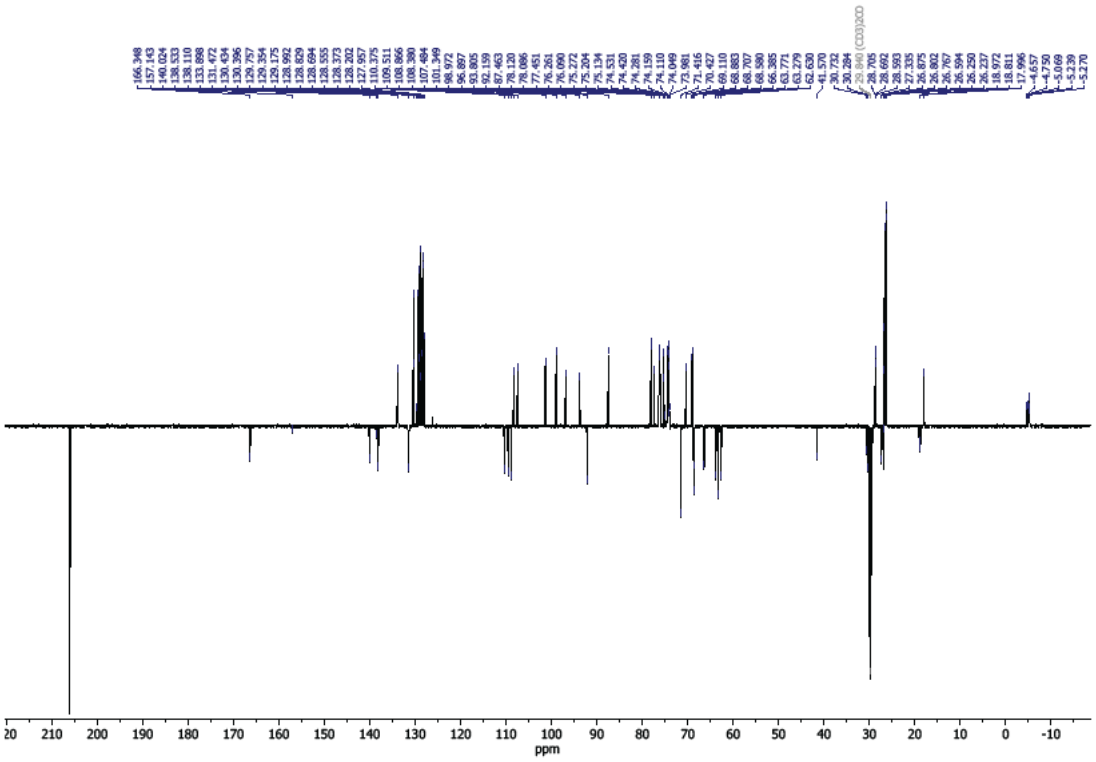
^{1}H NMR of **70** (CD_3COCD_3, 600 MHz, 297 K, 7.10-7.20 and 2.32 toluene)



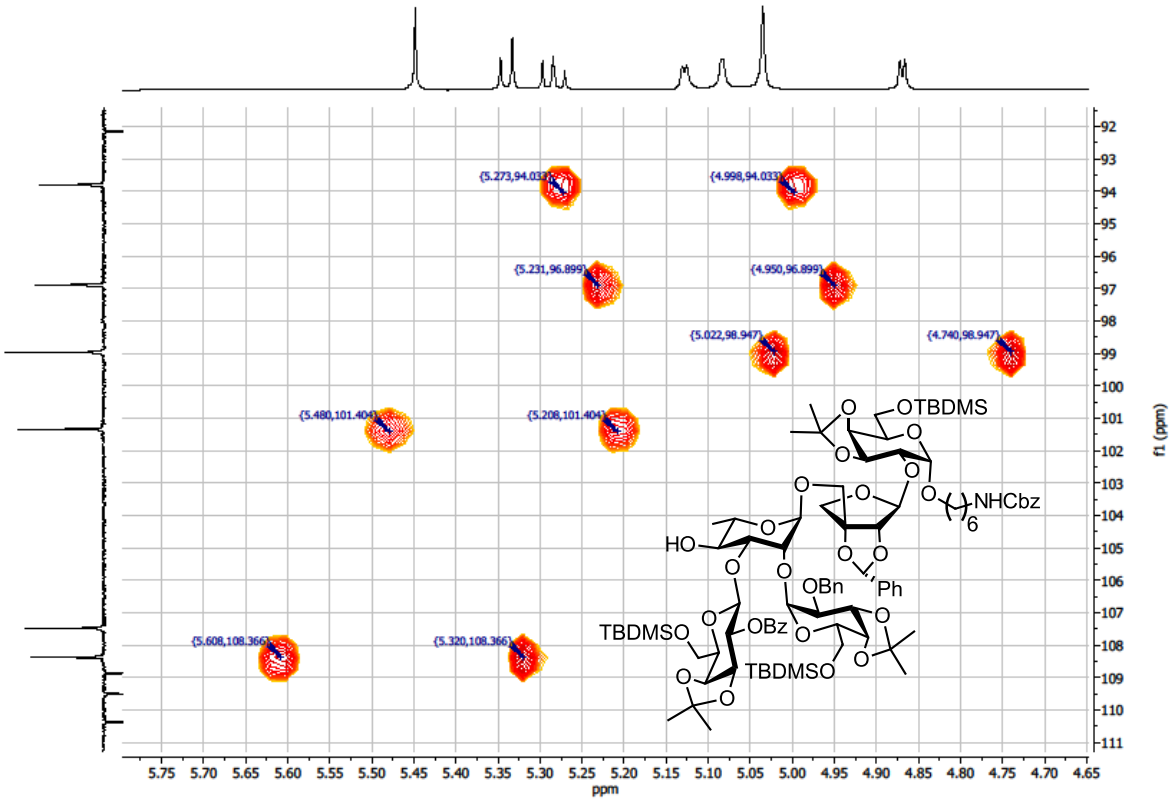
^{13}C APT NMR of **70** (CD_3COCD_3, 150 MHz, 297 K)



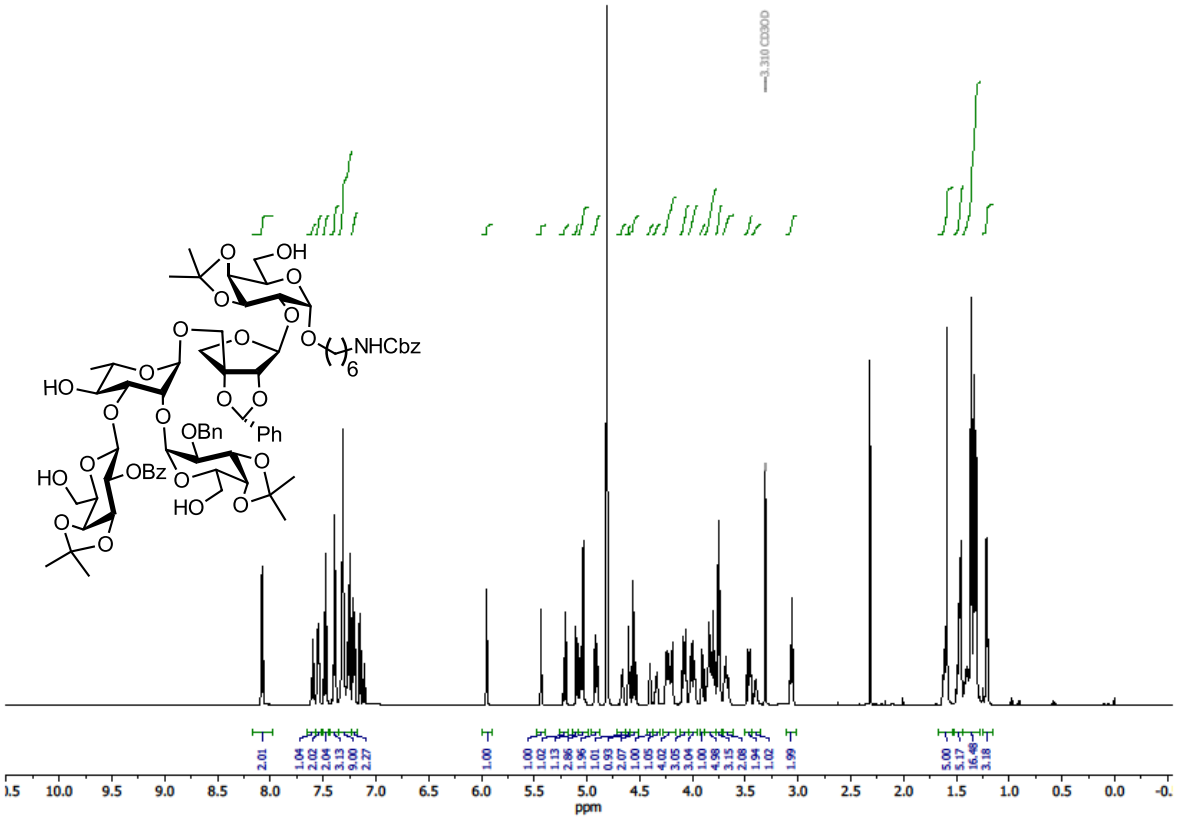
^{1}H NMR of **132** (CD_3COCD_3, 600 MHz, 297 K, 4.05 1.97 and 1.20 EtOAc)



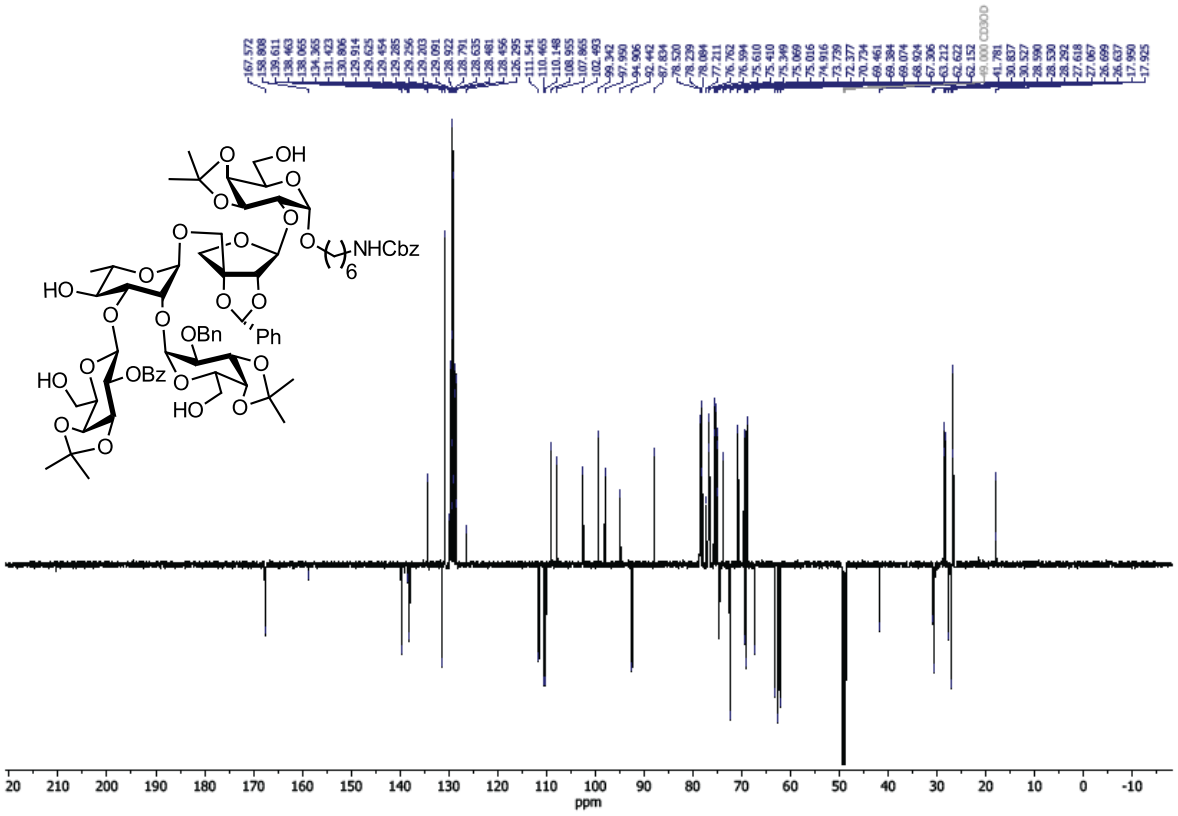
^{13}C APT NMR of **132** (CD_3COCD_3, 150 MHz, 297 K)



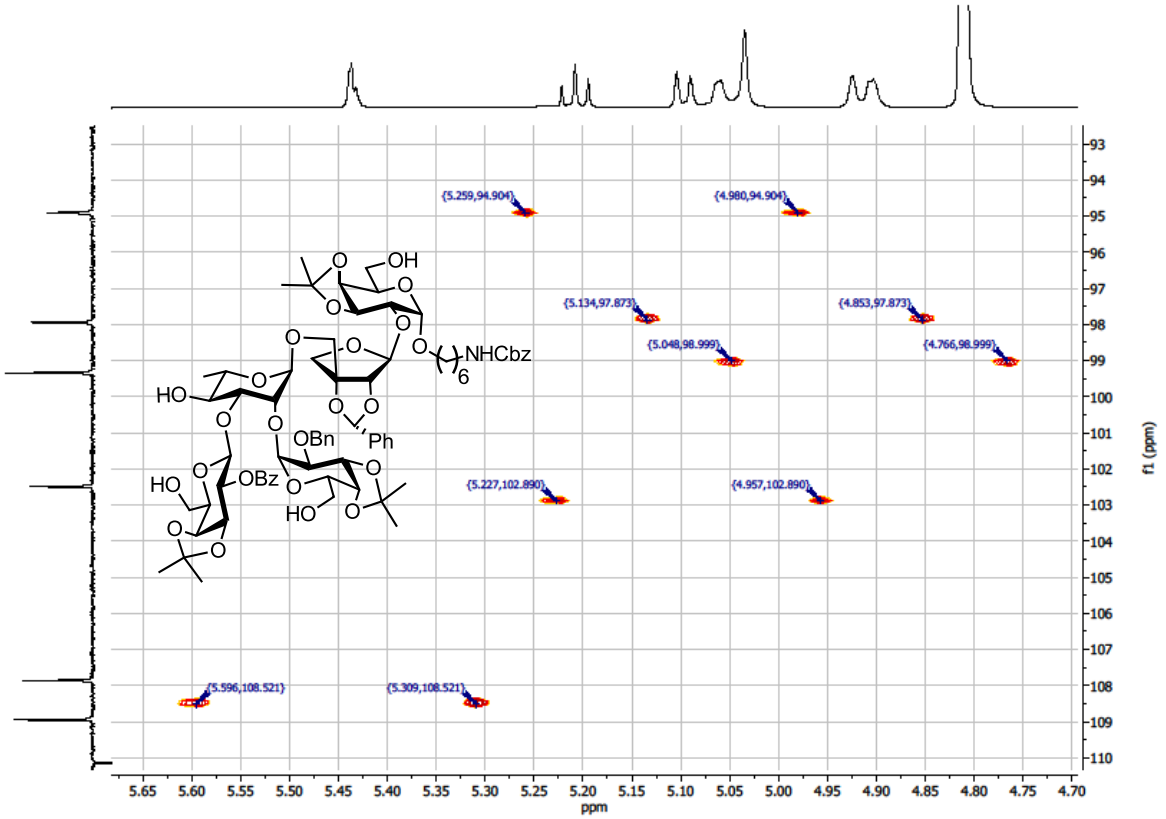
^{1}H-^{13}C CLIP HSQC NMR of **132** (CD_3COCD_3, 600 MHz, 297 K)



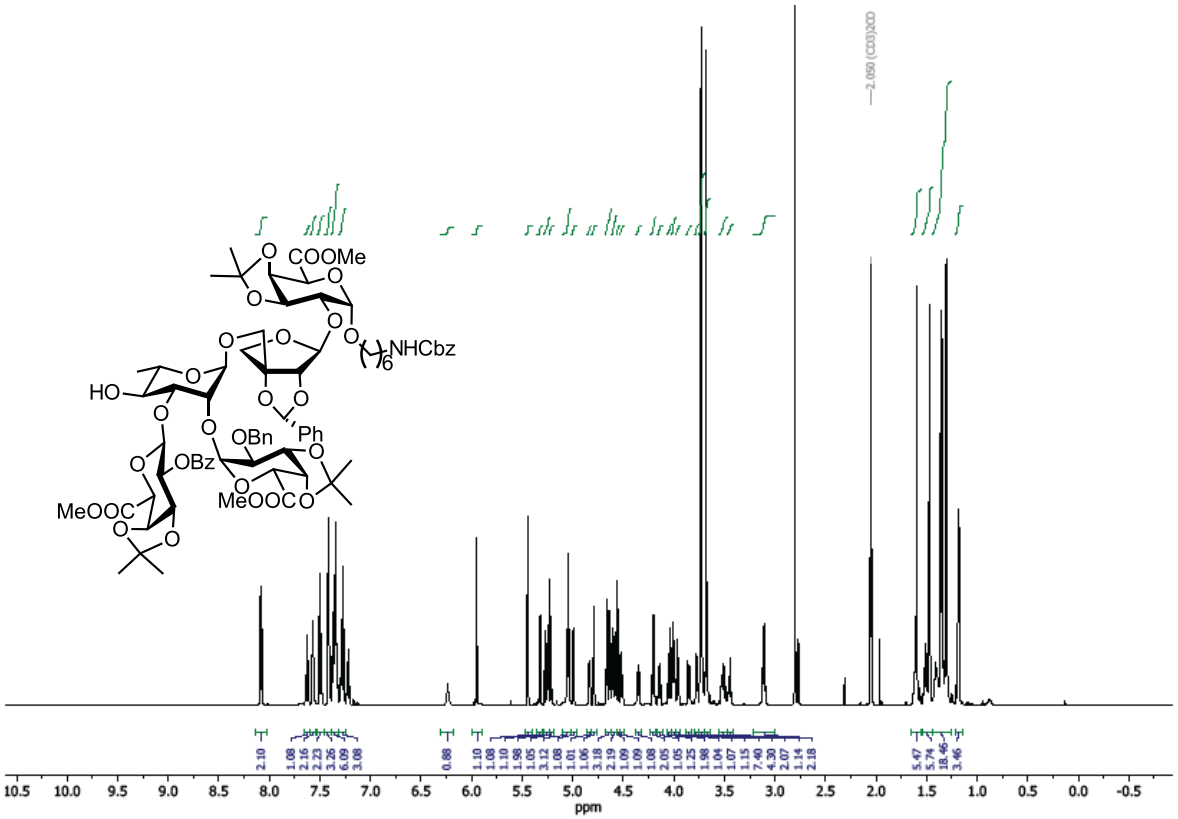
^{1}H NMR of **133** (CD_3OD, 600 MHz, 297 K, 7.16 and 2.32 toluene)



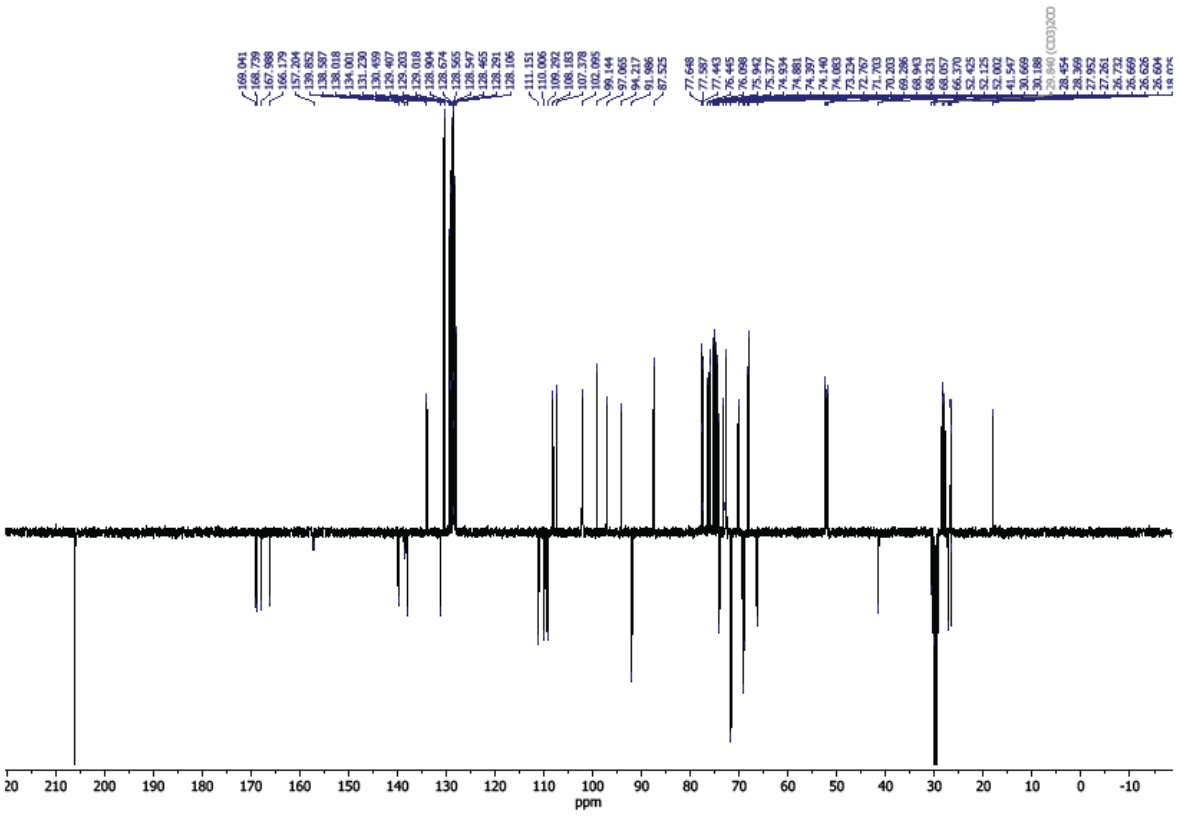
^{13}C APT NMR of **133** (CD_3OD, 150 MHz, 297 K)



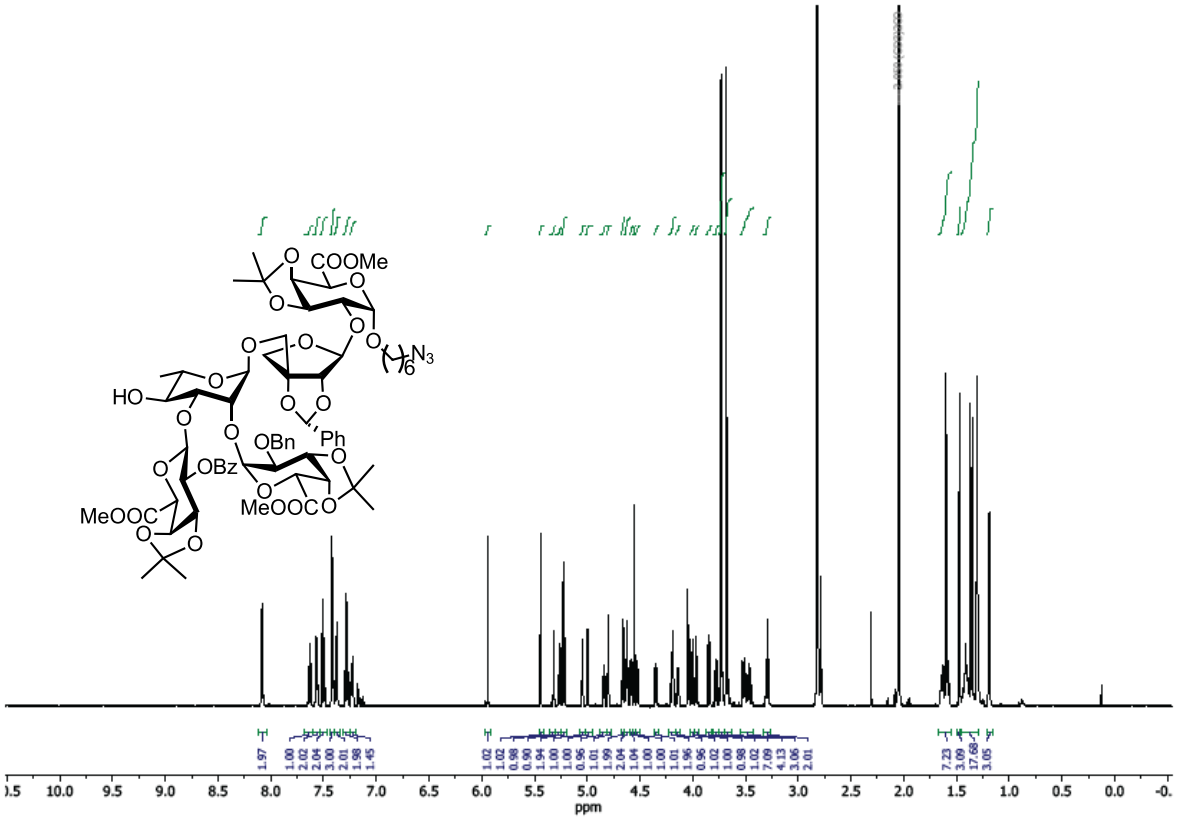
^{1}H-^{13}C CLIP HSQC NMR of **133** (CD_3OD, 600 MHz, 297 K)



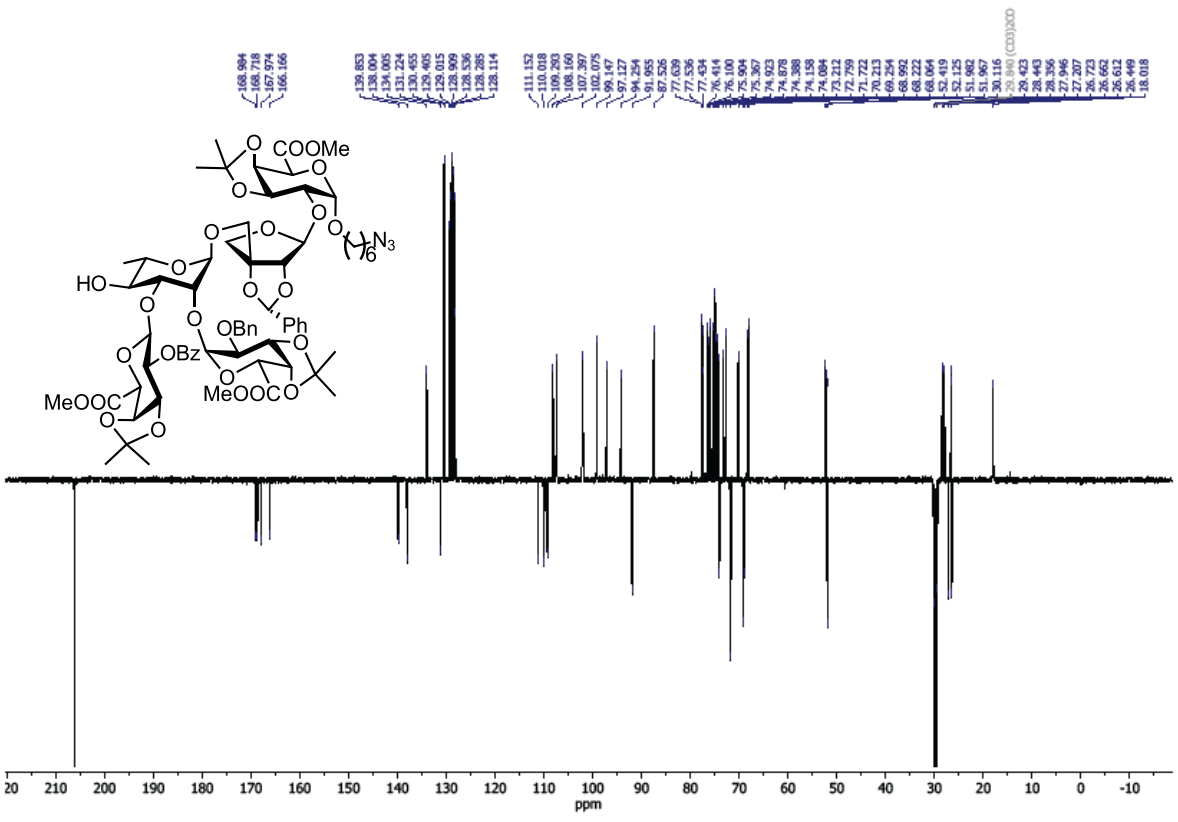
^{1}H NMR of **134** (CD_3COCD_3, 600 MHz, 297 K, 7.10-7.20 and 2.32 toluene, 4.05 1.97 and 1.20 EtOAc)



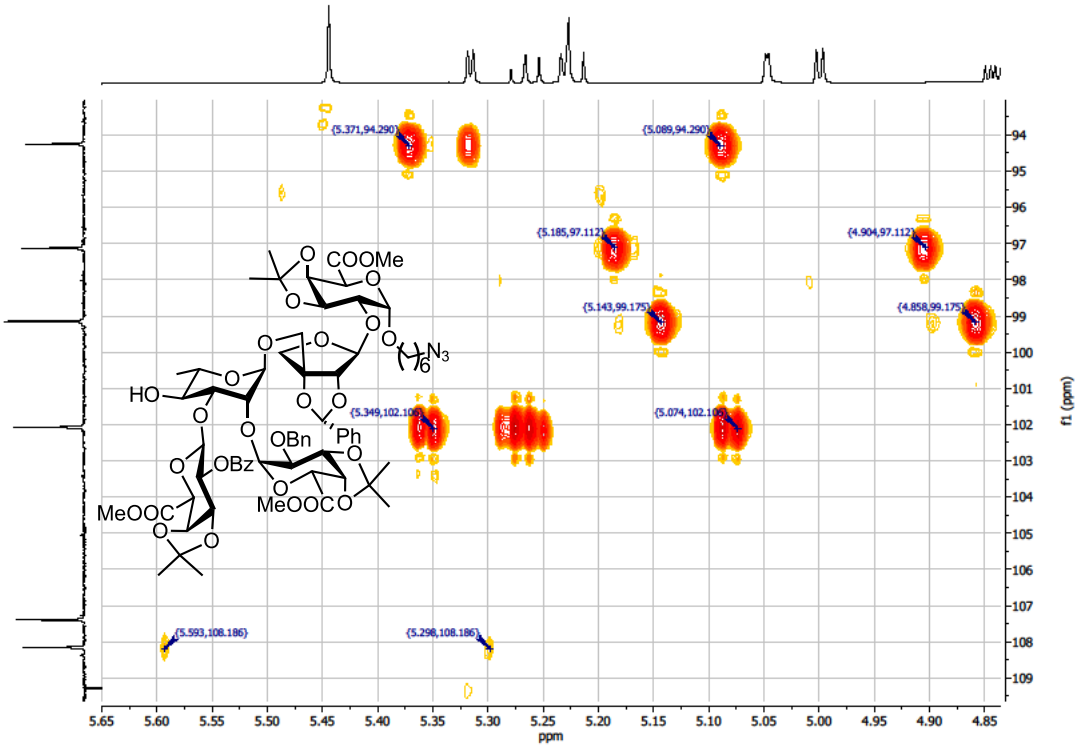
^{13}C APT NMR of **134** (CD_3COCD_3, 150 MHz, 297 K)



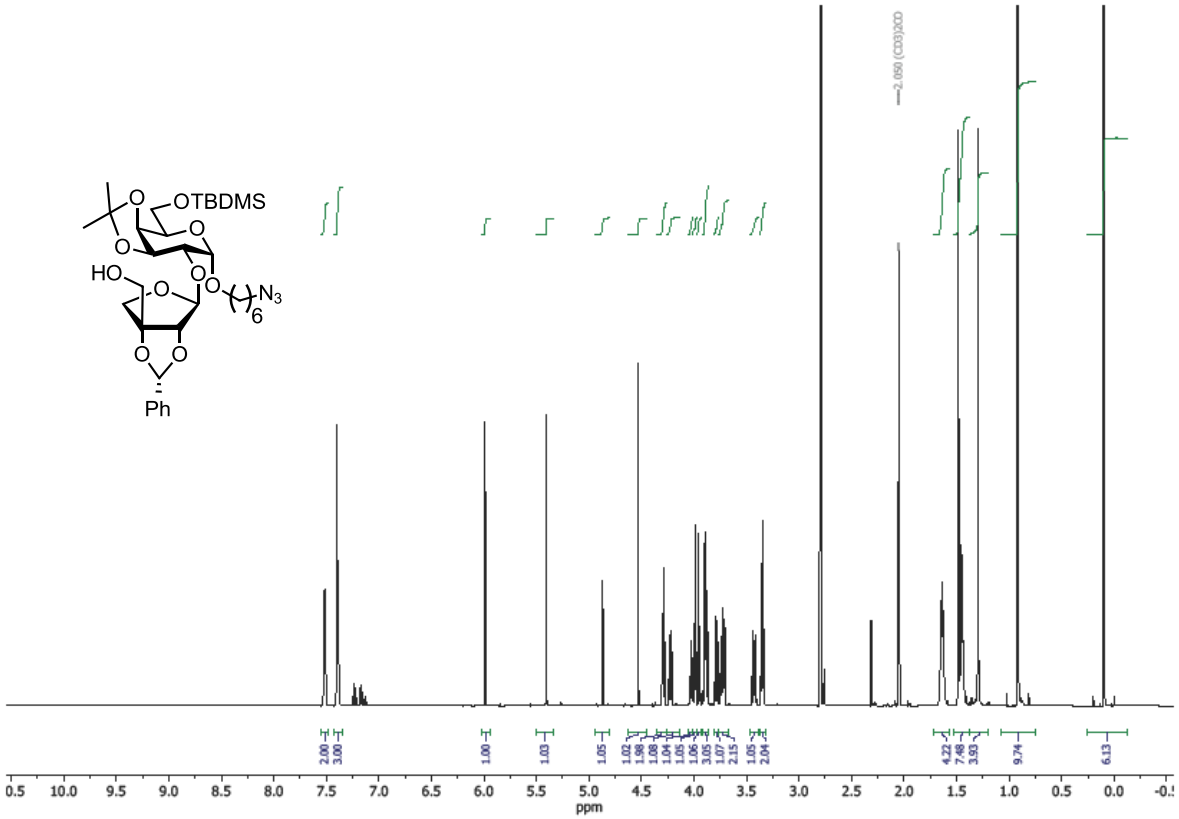
^{1}H NMR of **67** (CD_3COCD_3, 600 MHz, 297 K, 7.10-7.20 and 2.32 toluene)



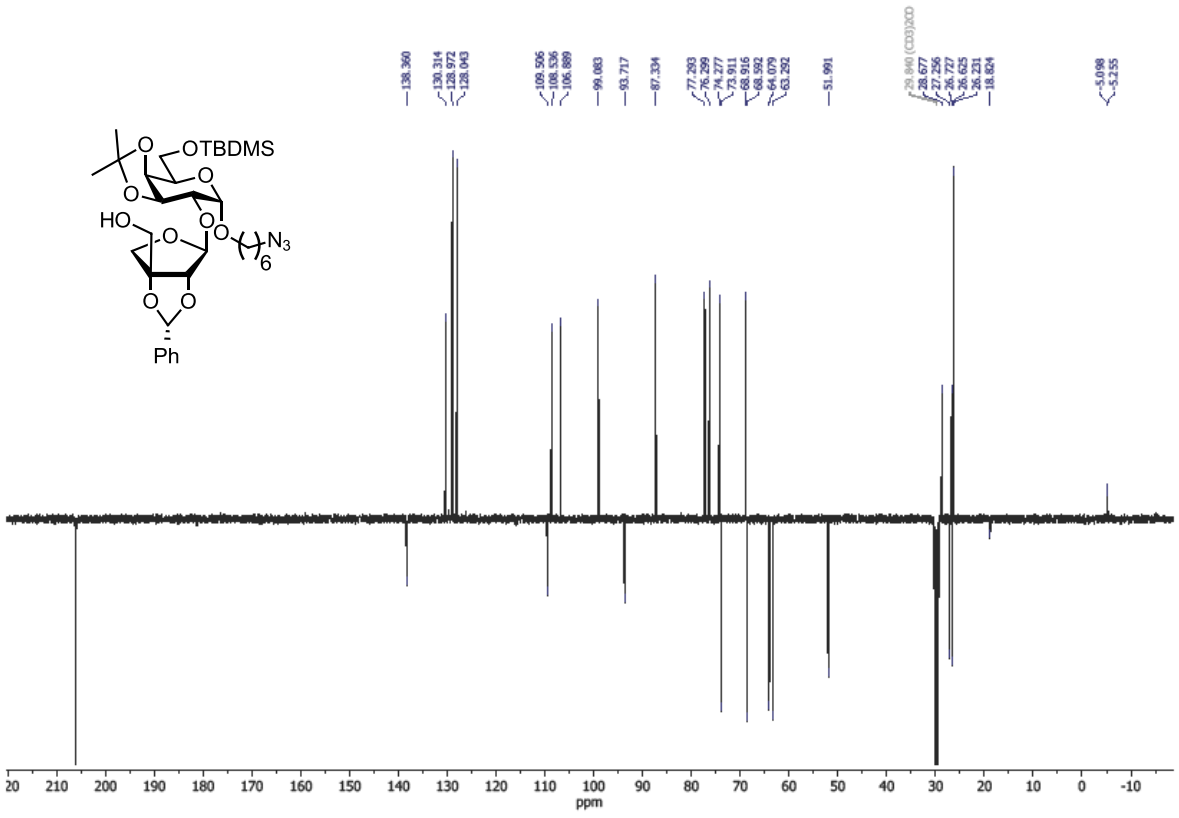
^{13}C APT NMR of **67** (CD_3COCD_3, 150 MHz, 297 K)



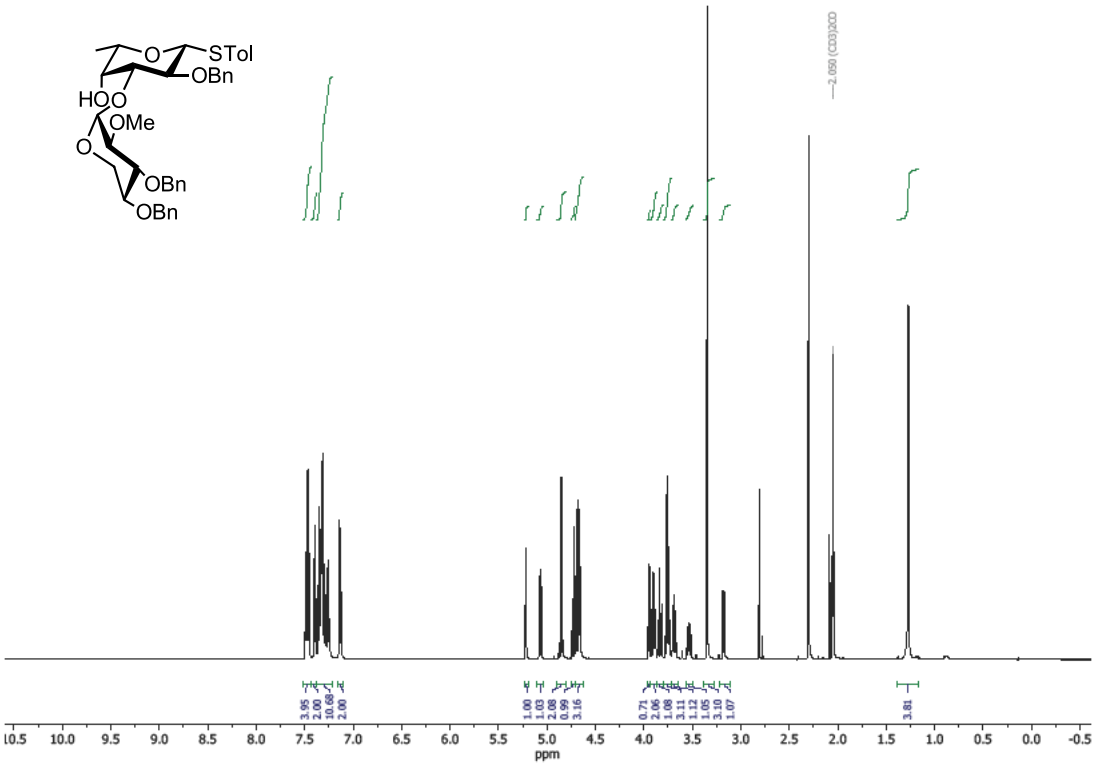
^{1}H-^{13}C coupled HMBC NMR of **67** (CD_3COCD_3, 600 MHz, 297 K)



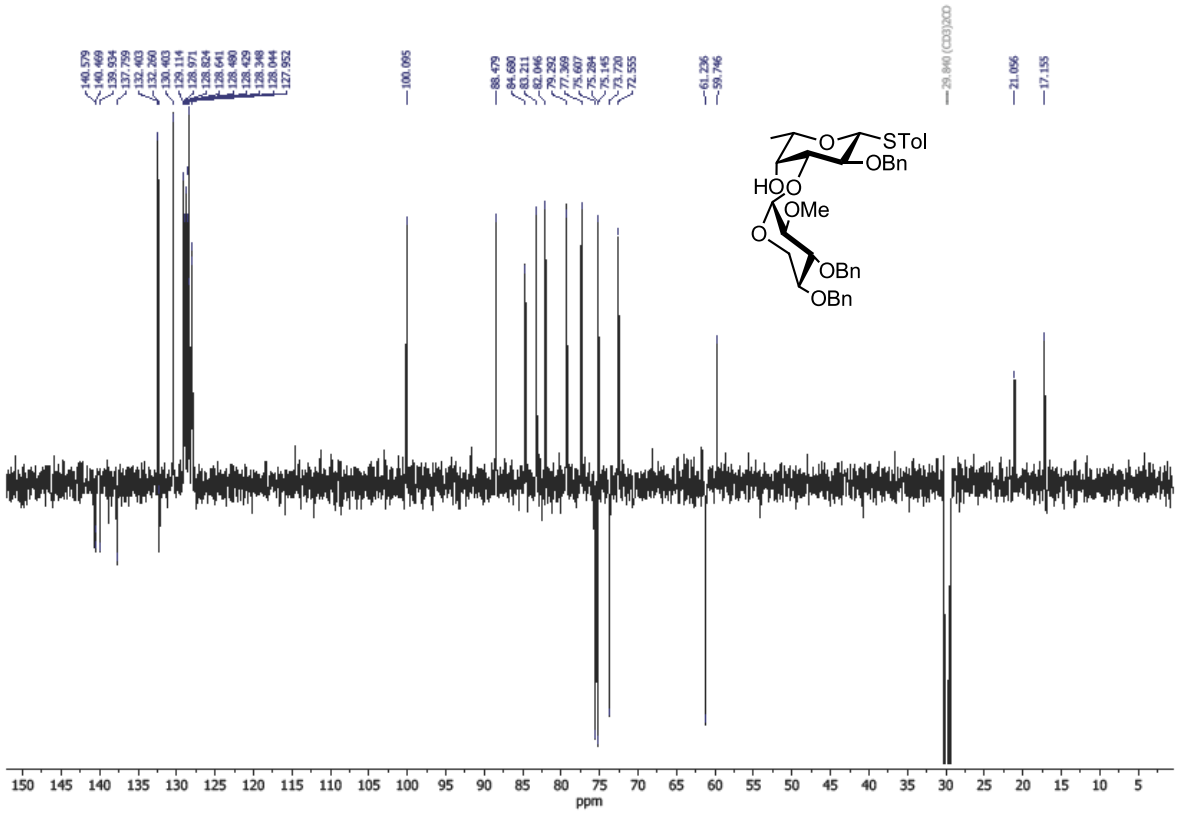
^{1}H NMR of **140** (CD_3COCD_3, 600 MHz, 297 K, 7.20-7.10 and 2.32 toluene)



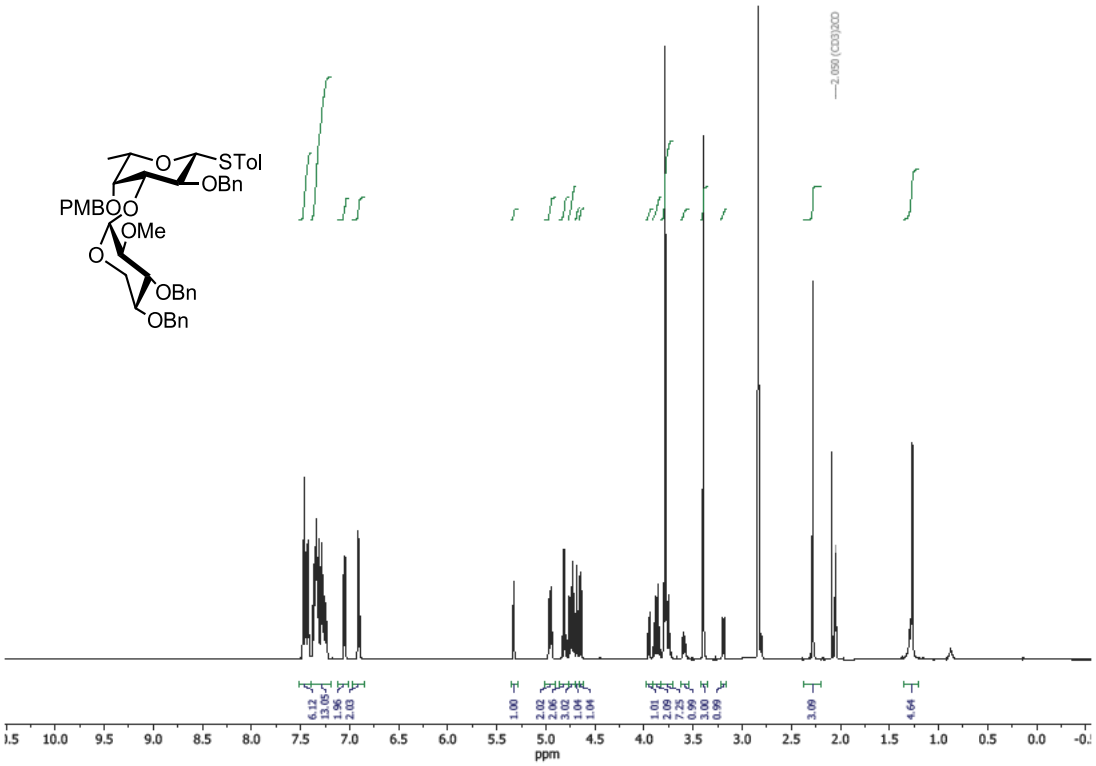
^{13}C APT NMR of **140** (CD_3COCD_3, 150 MHz, 297 K)



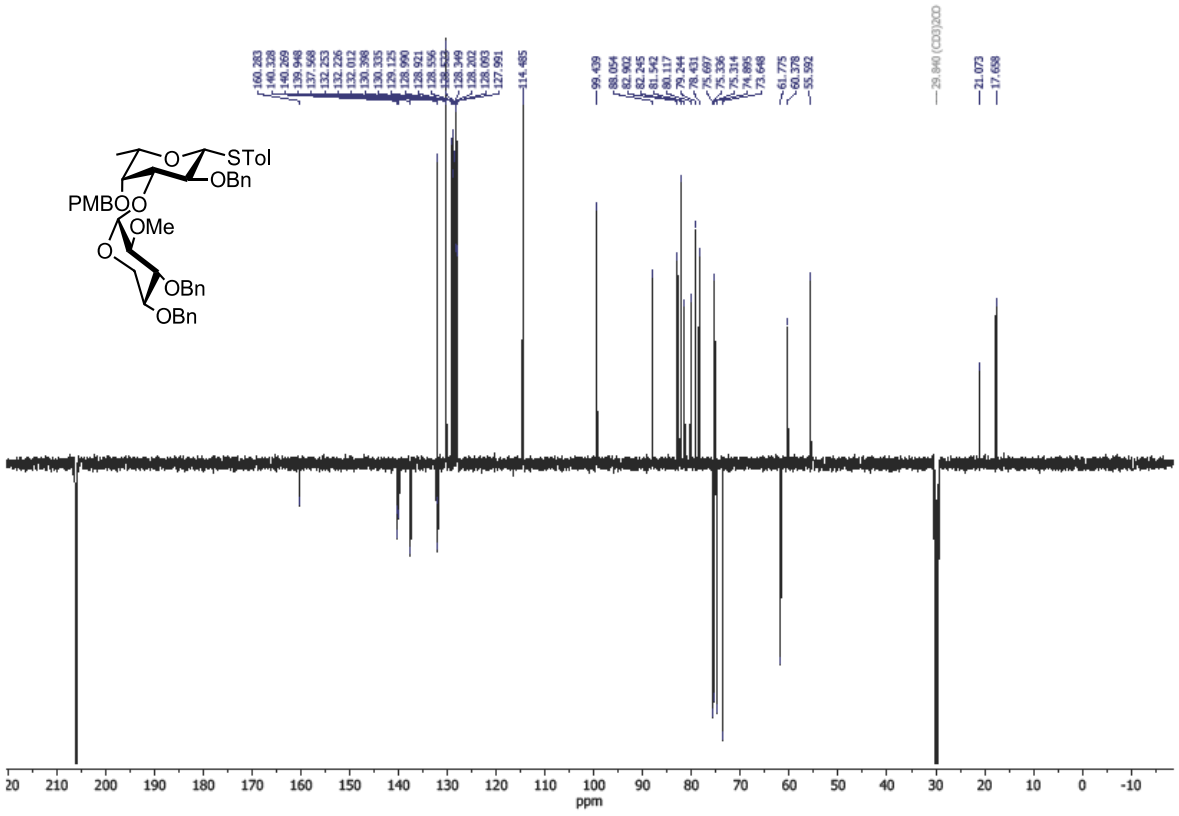
^{1}H NMR of **141** (CD_3COCD_3, 600 MHz, 297 K)



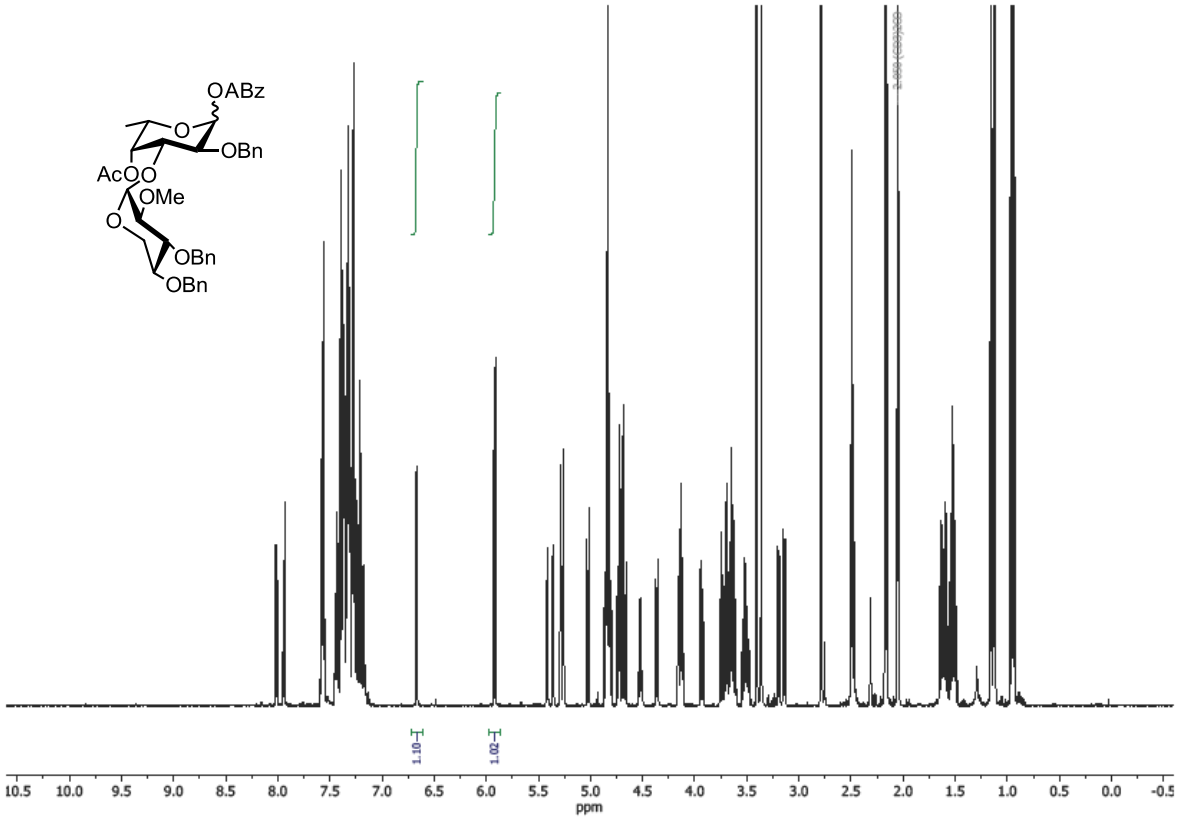
^{13}C APT NMR of **141** (CD_3COCD_3, 150 MHz, 297 K)



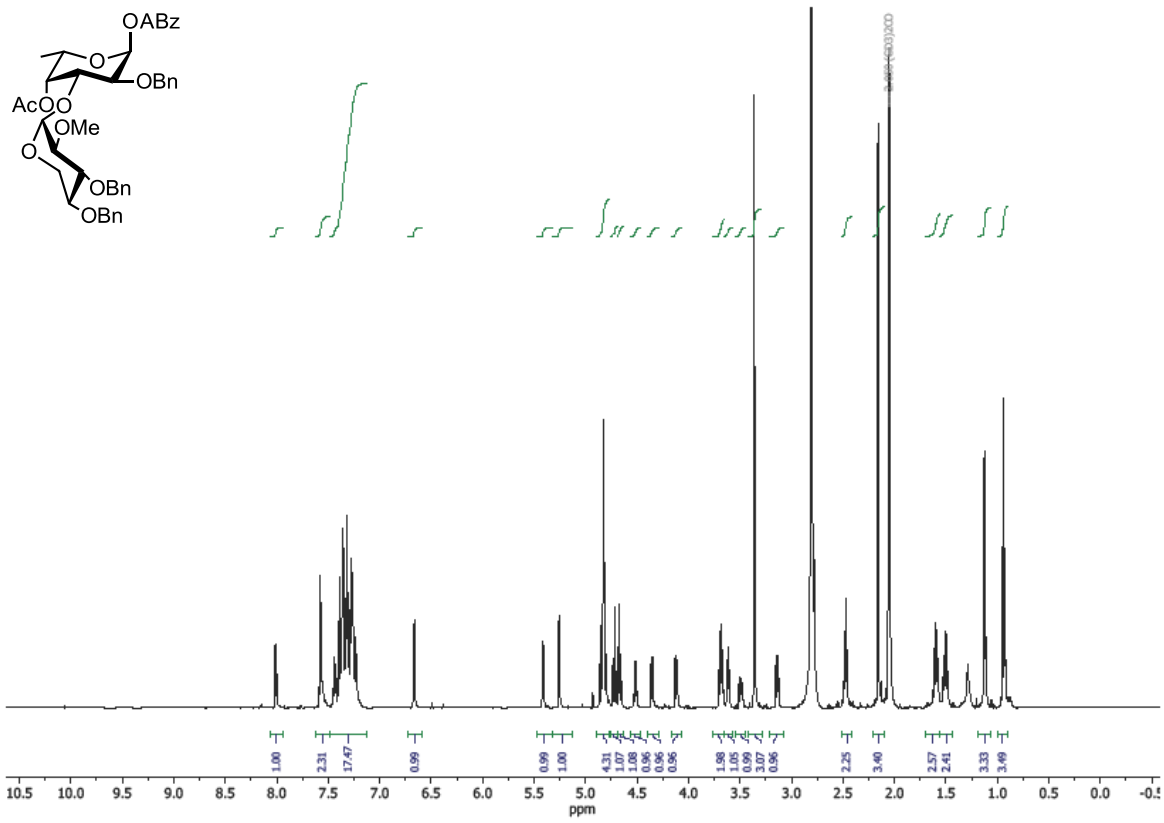
^{1}H NMR of **142** (CD_3COCD_3, 600 MHz, 297 K, 2.09 acetone)



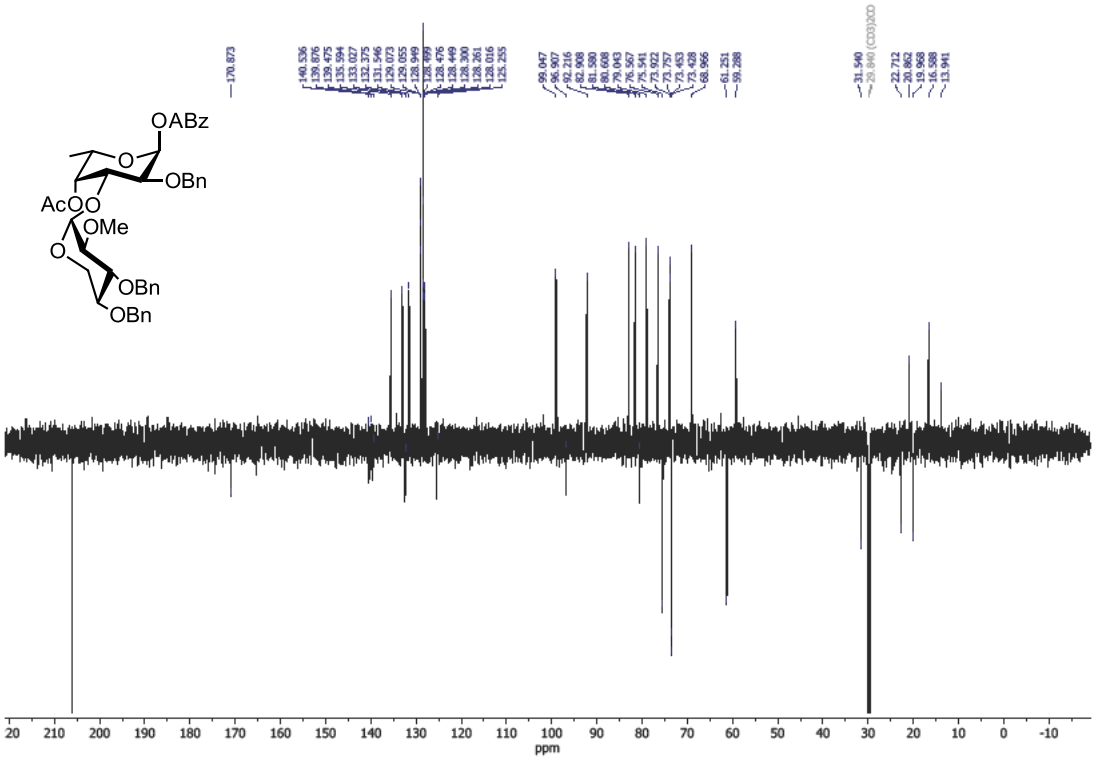
^{13}C APT NMR of **142** (CD_3COCD_3, 150 MHz, 297 K)



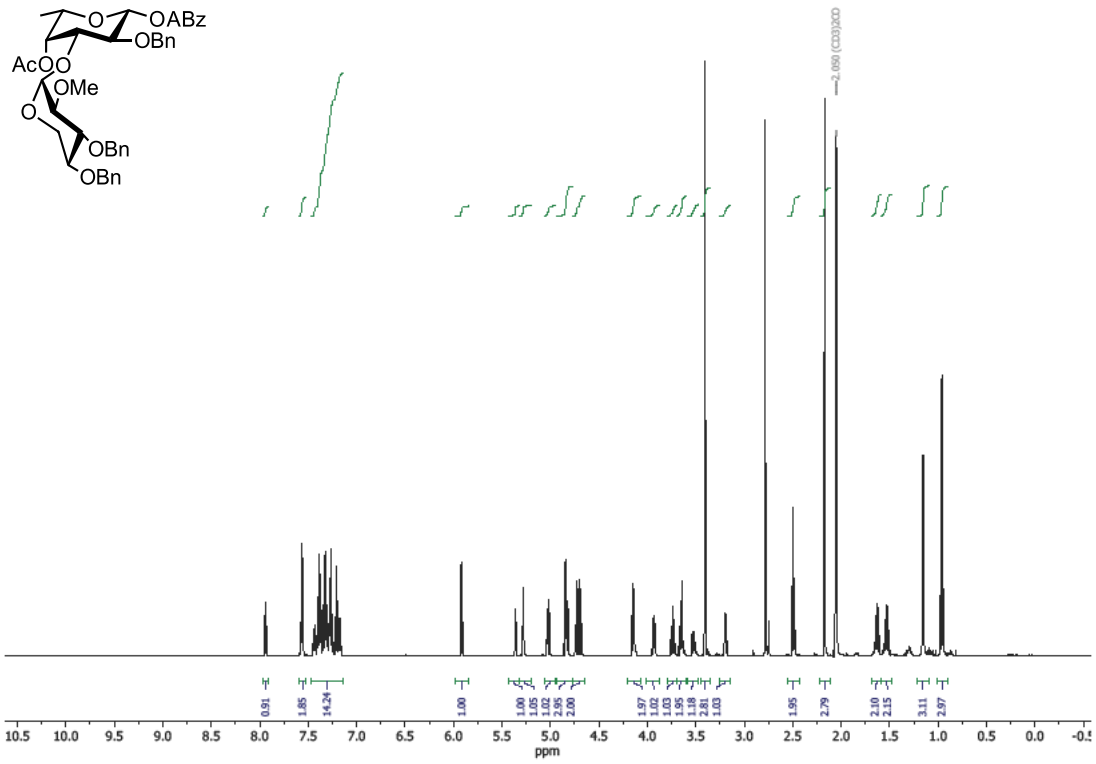
^{1}H NMR of **144-α/β** (CD_3COCD_3, 600 MHz, 297 K)



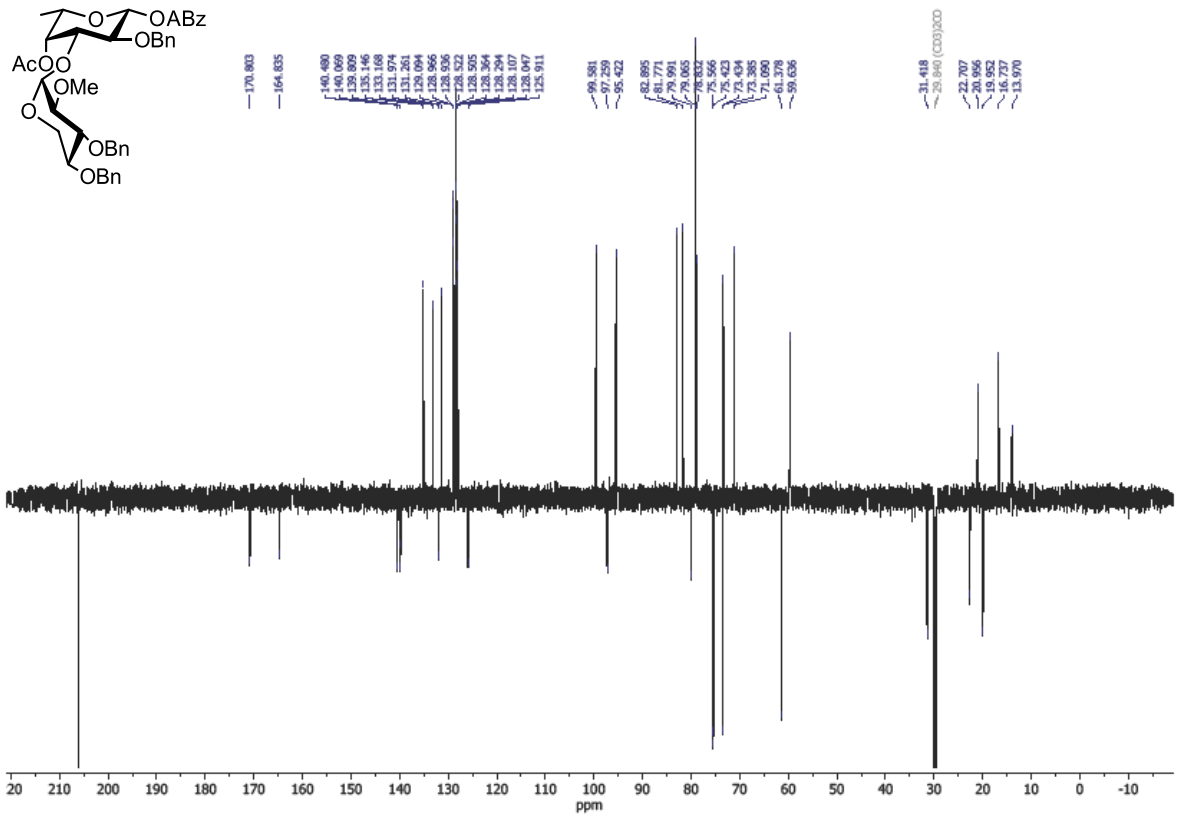
^{1}H NMR of **144-α** (CD_3COCD_3, 600 MHz, 297 K)



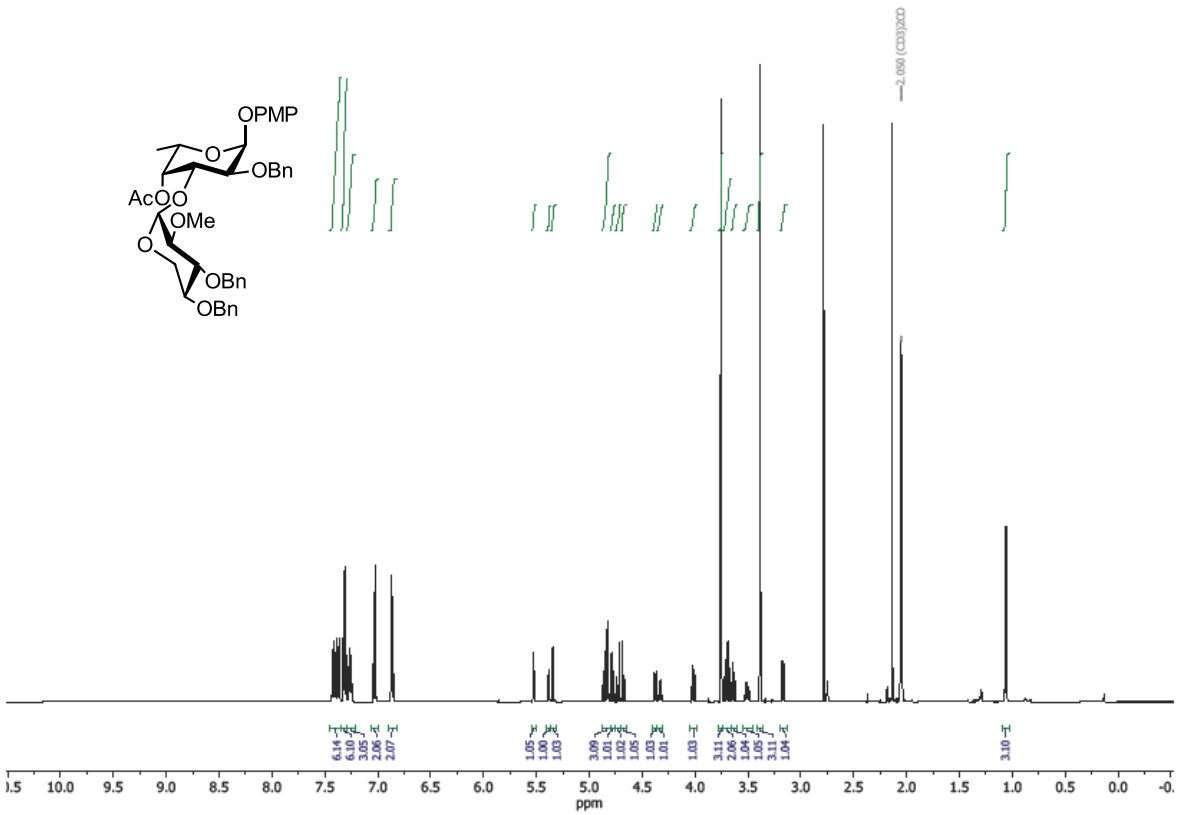
^{13}C APT NMR of **144-α** (CD_3COCD_3, 150 MHz, 297 K)



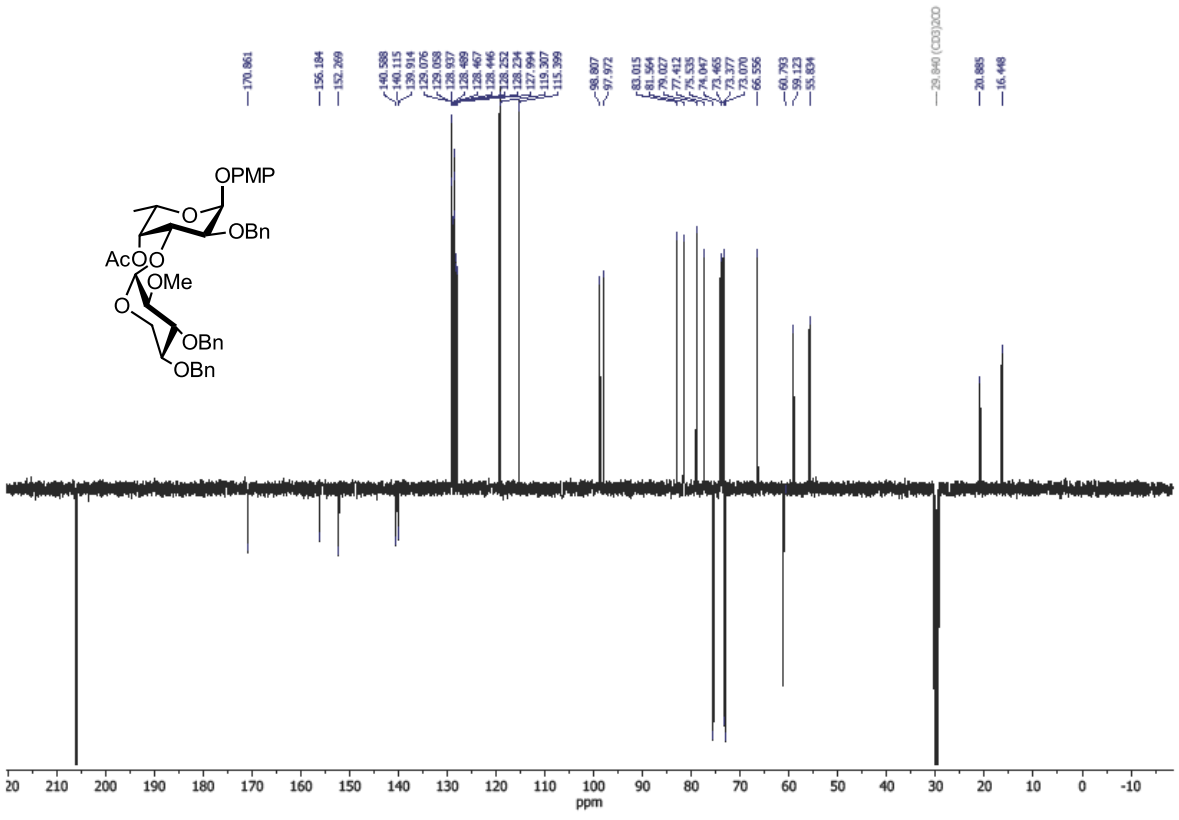
^{1}H NMR of **144-β** (CD_3COCD_3, 600 MHz, 297 K)



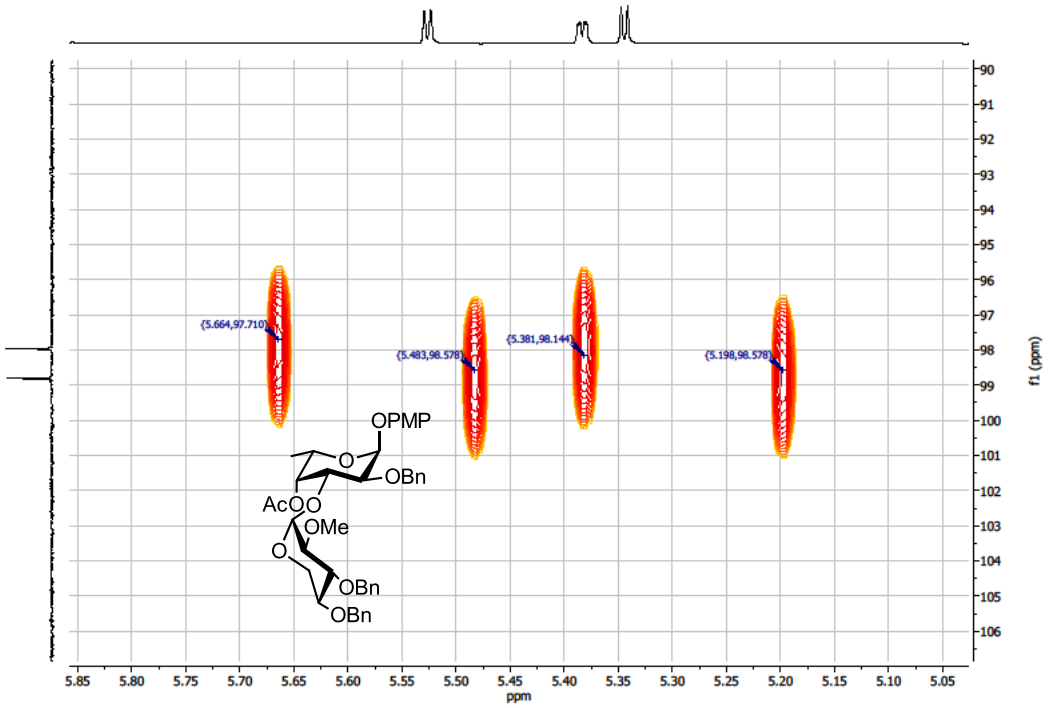
^{13}C APT NMR of **144-β** (CD_3COCD_3, 150 MHz, 297 K)



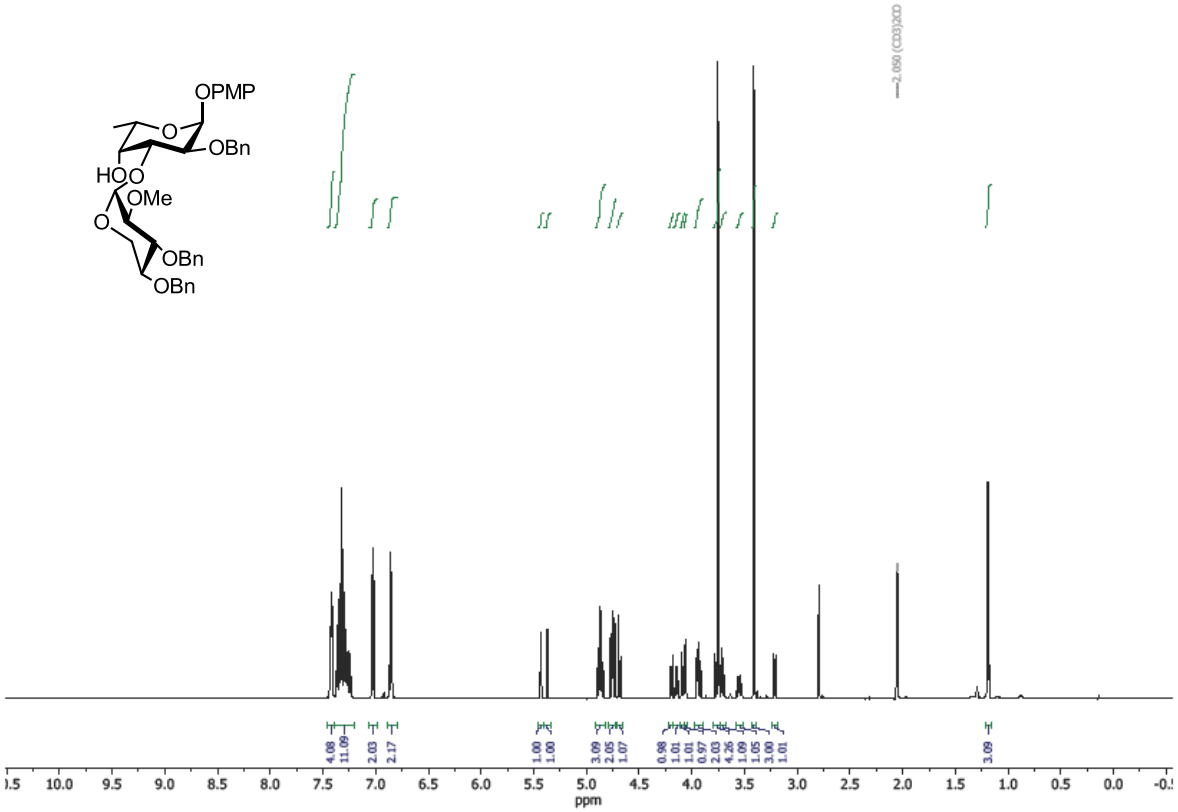
^{1}H NMR of **145** (CD_3COCD_3, 600 MHz, 297 K)



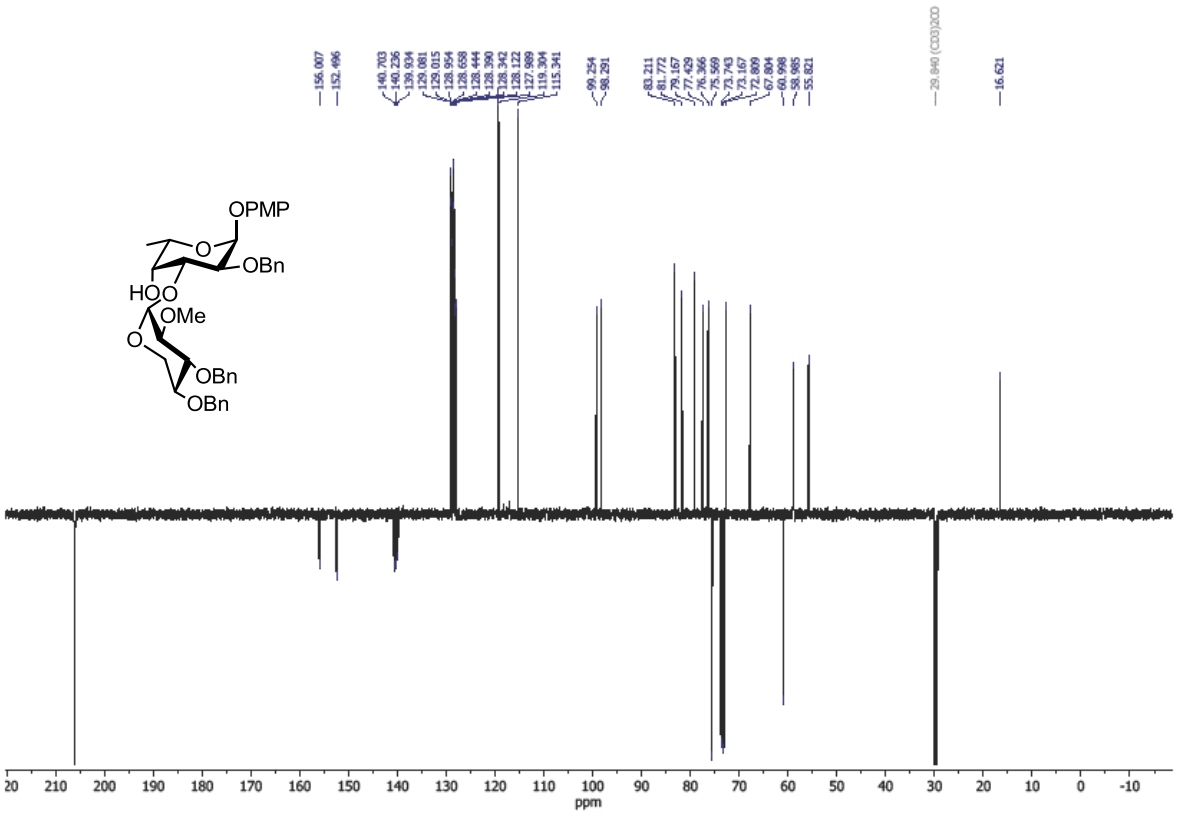
^{13}C APT NMR of **145** (CD_3COCD_3, 150 MHz, 297 K)



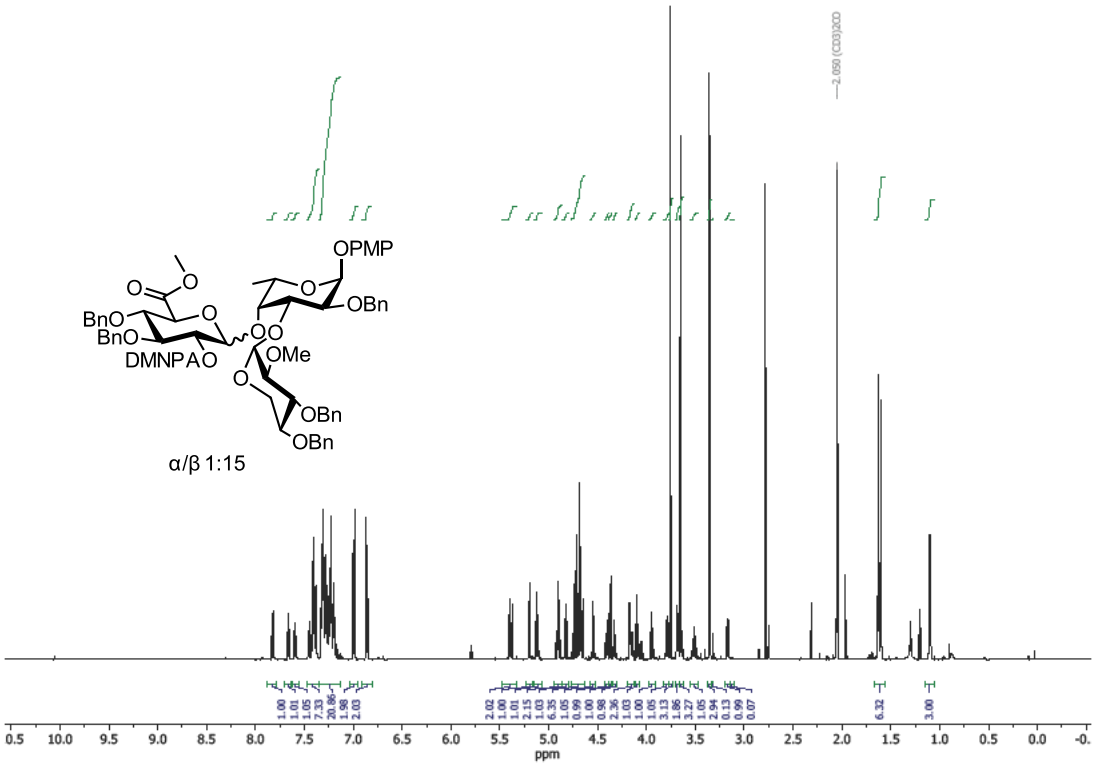
^{1}H-^{13}C decoupled HMBC NMR of **145** (CD_3COCD_3, 600 MHz, 297 K)



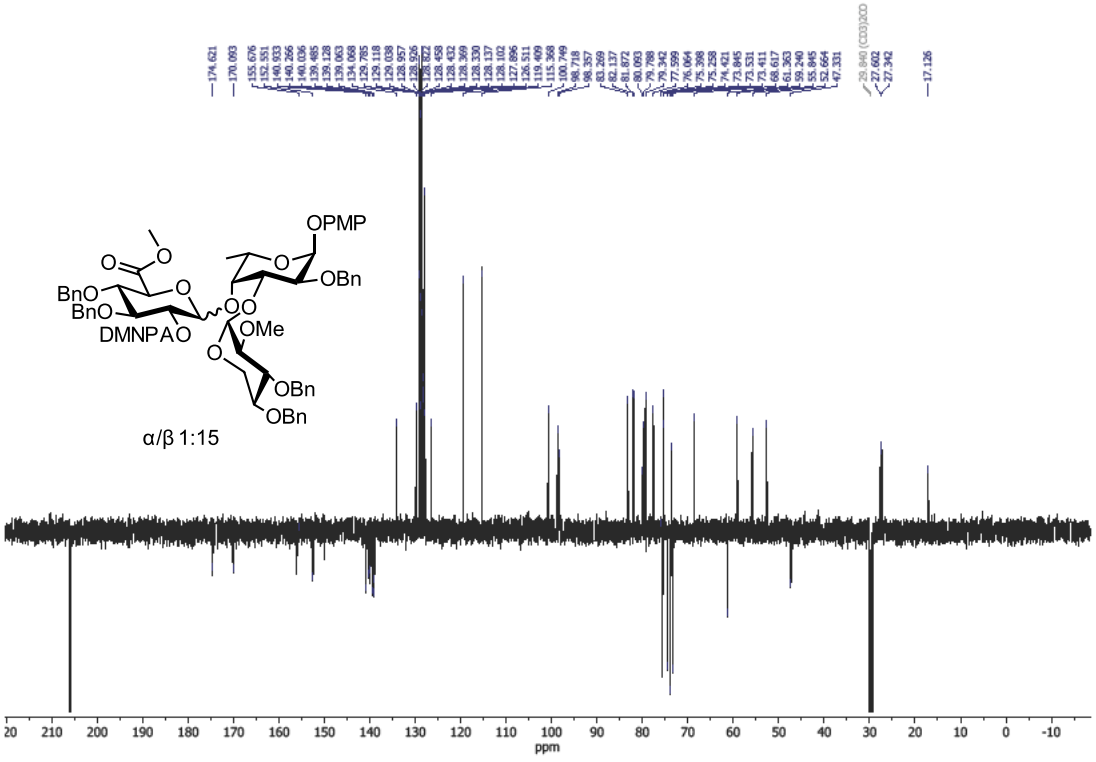
^{1}H NMR of **79** (CD_3COCD_3, 600 MHz, 297 K)



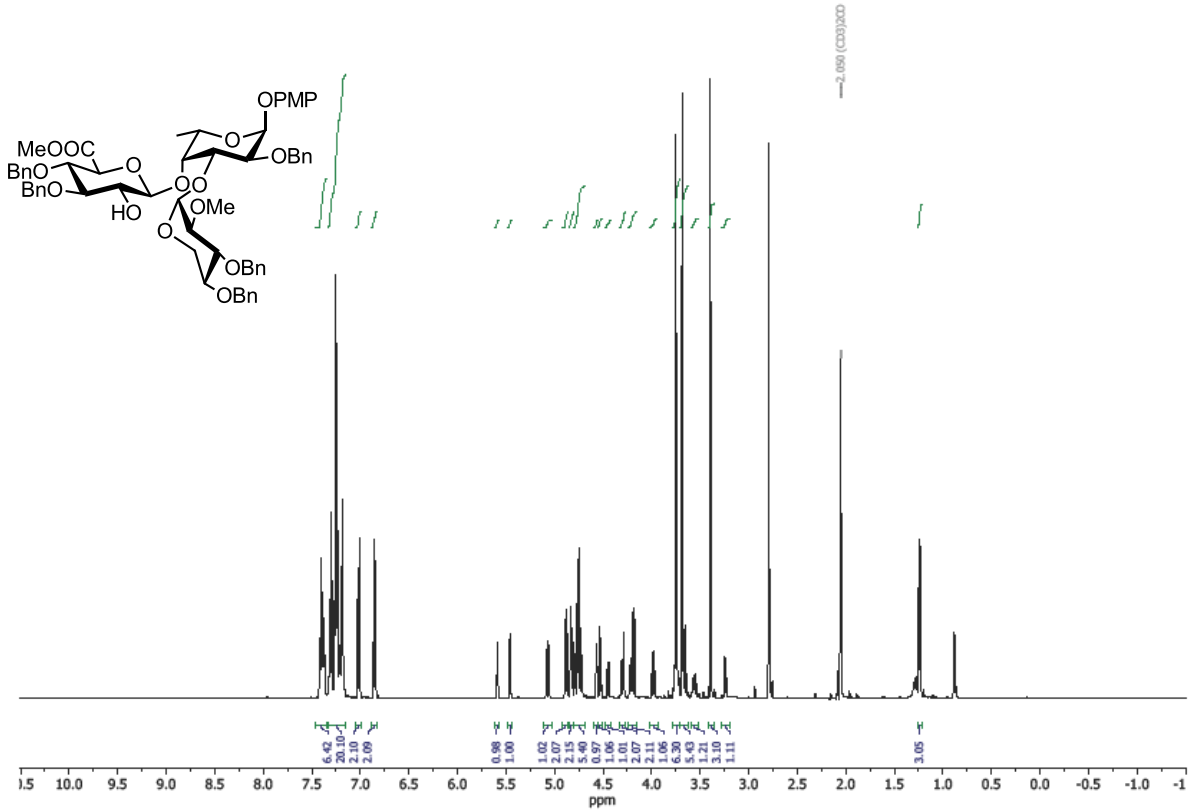
^{13}C APT NMR of **79** (CD_3COCD_3, 150 MHz, 297 K)



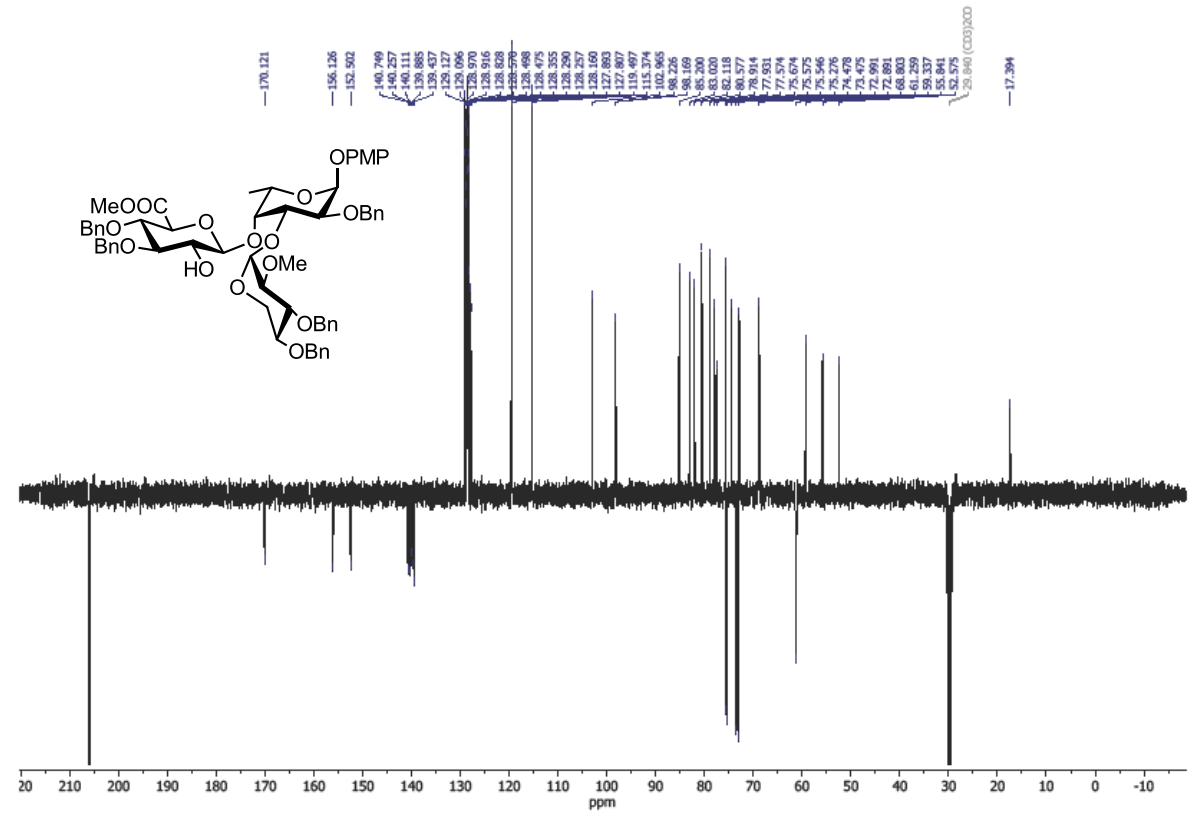
^{1}H NMR of **146** (CD_3COCD_3, 600 MHz, 297 K, 7.10-7.20 and 2.32 toluene, 4.05 1.97 and 1.20 EtOAc)



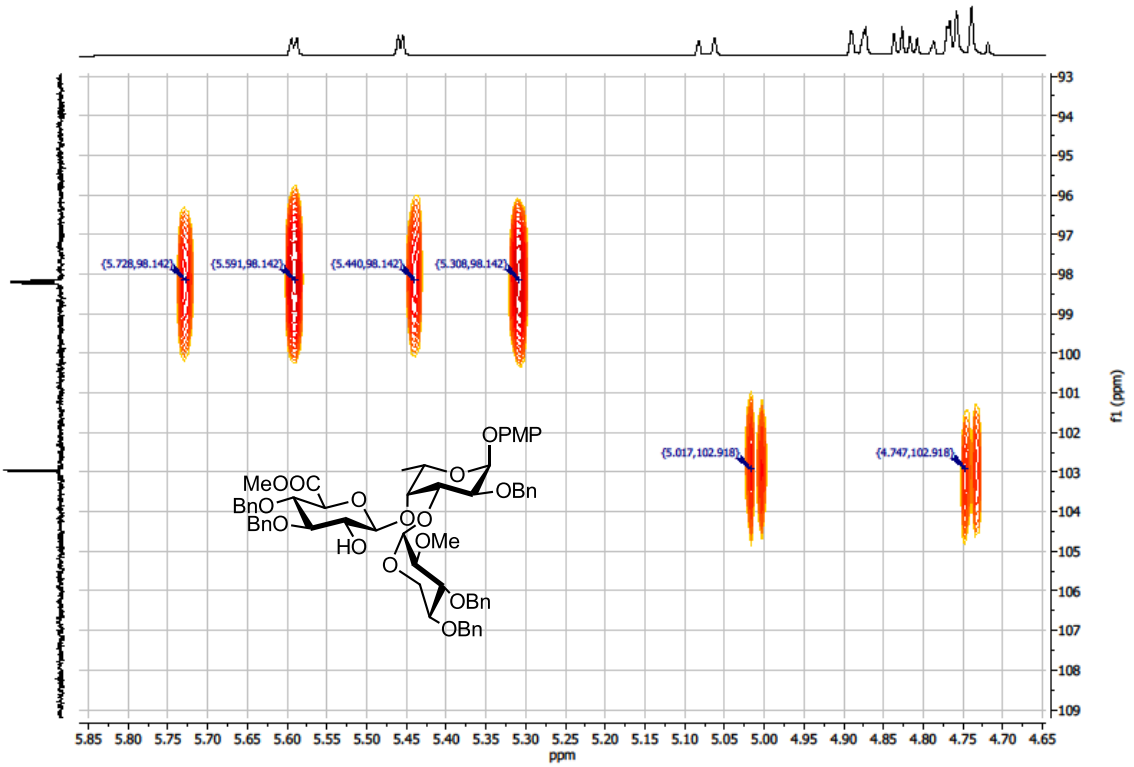
^{13}C APT NMR of **146** (CD_3COCD_3, 150 MHz, 297 K)



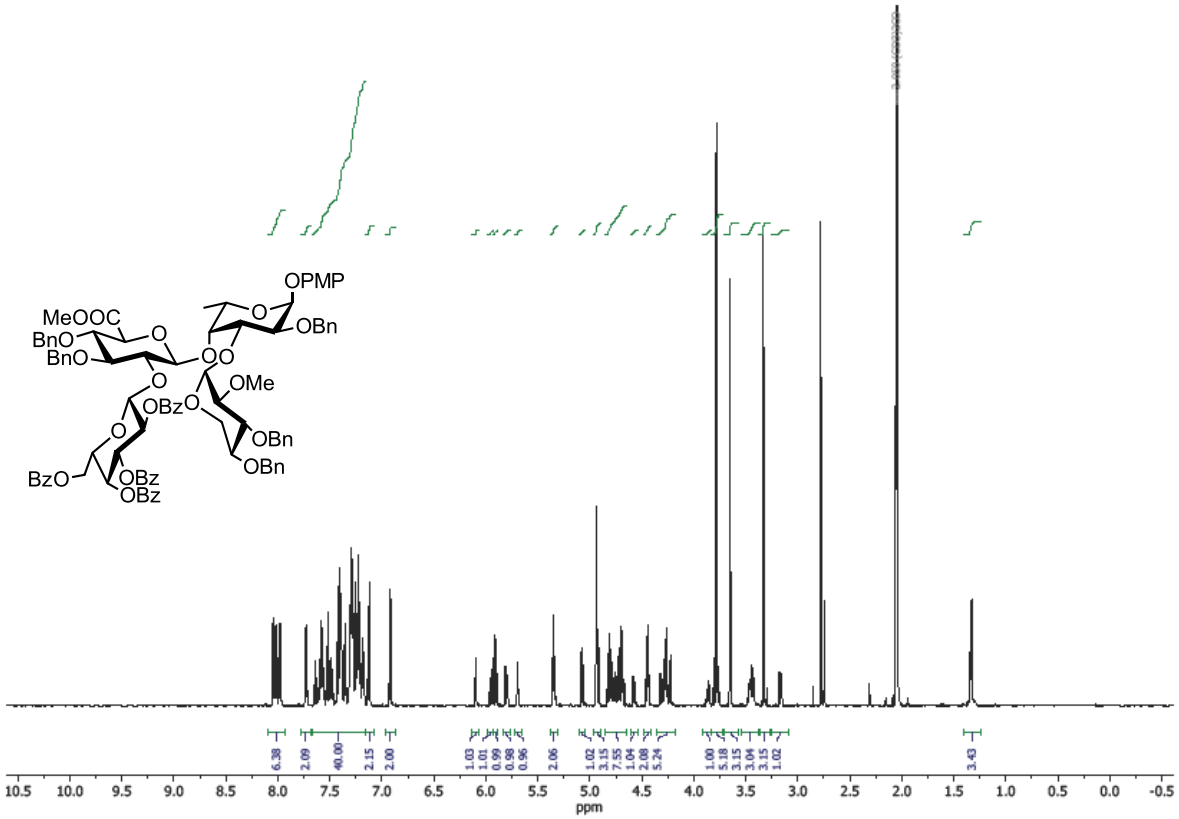
^{1}H NMR of **77** (CD_3COCD_3, 600 MHz, 297 K)



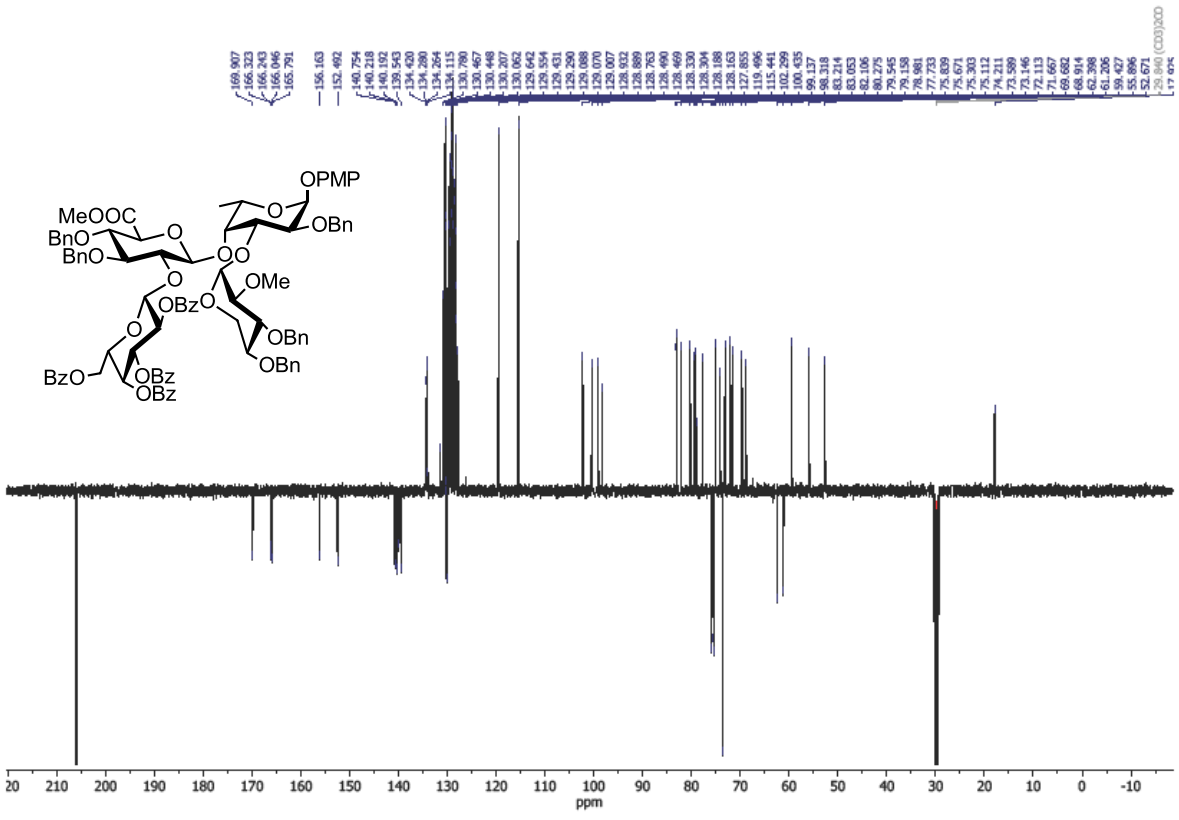
^{13}C APT NMR of **77** (CD_3COCD_3, 150 MHz, 297 K)



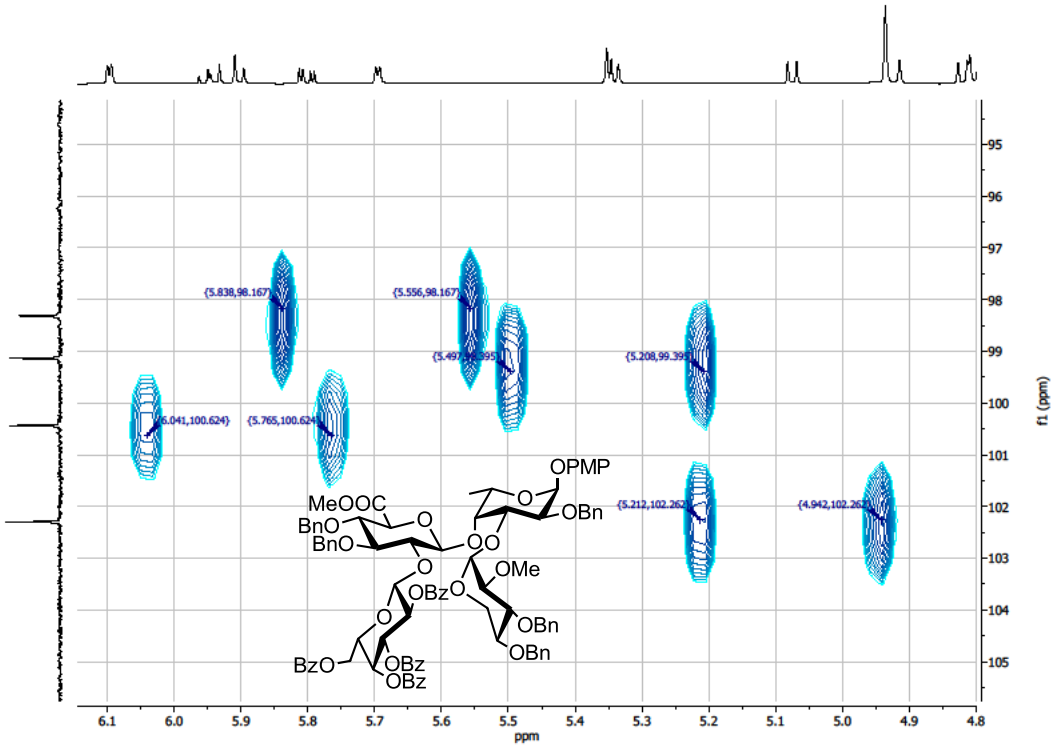
^{1}H-^{13}C coupled HMBC NMR of **77** (CD_3COCD_3, 600 MHz, 297 K)



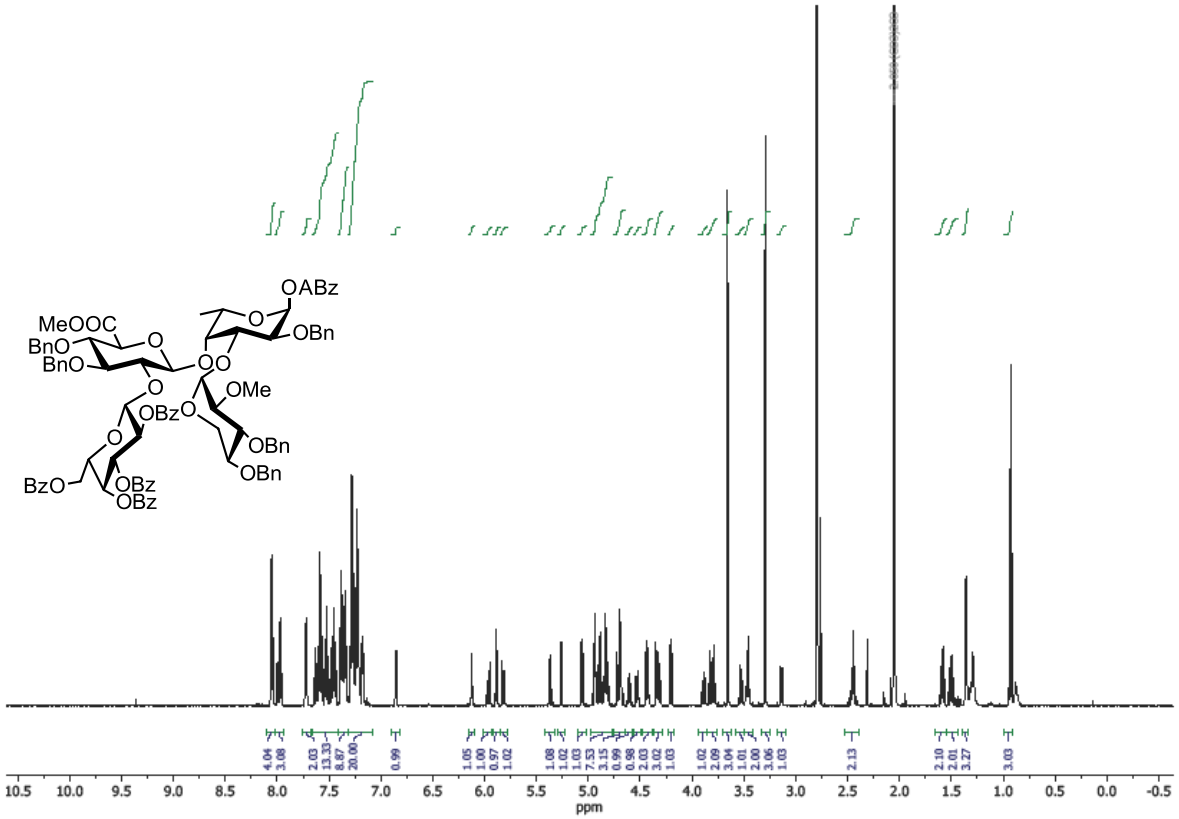
^{1}H NMR of **147** (CD_3COCD_3, 600 MHz, 297 K)



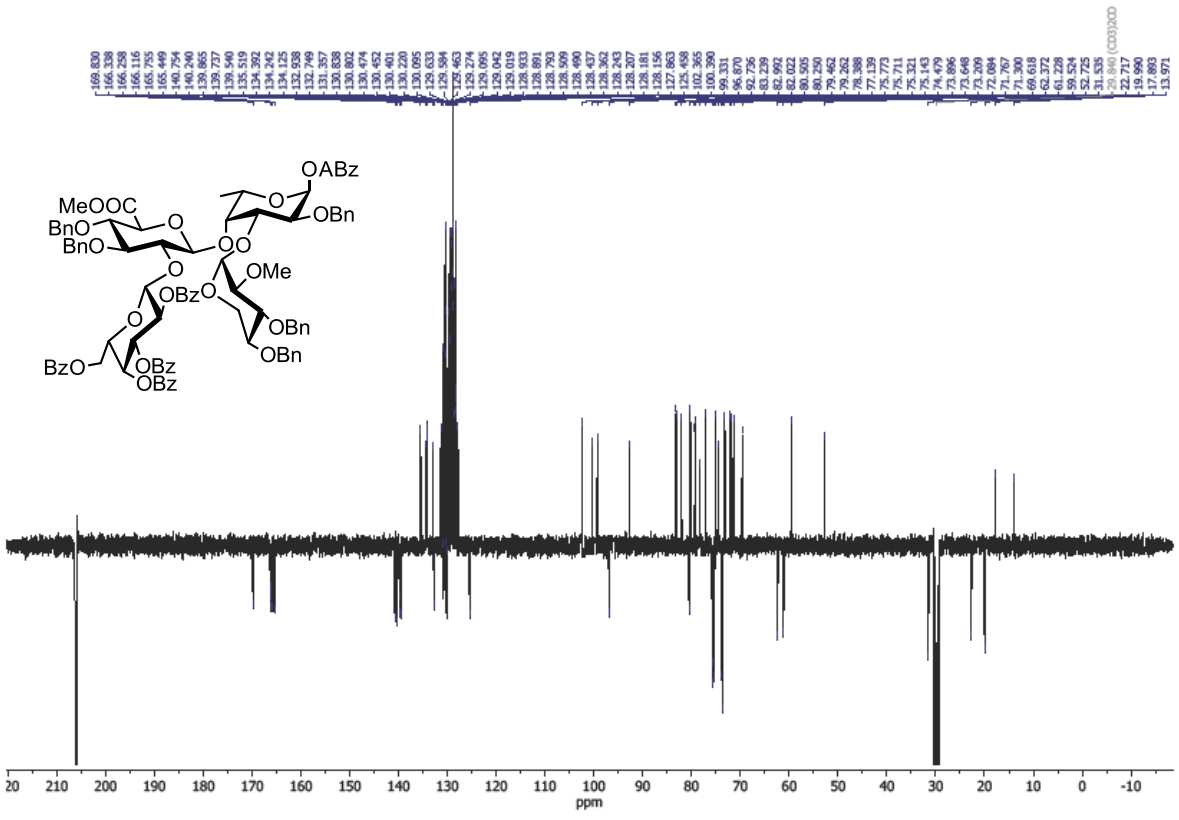
^{13}C APT NMR of **147** (CD_3COCD_3, 150 MHz, 297 K)



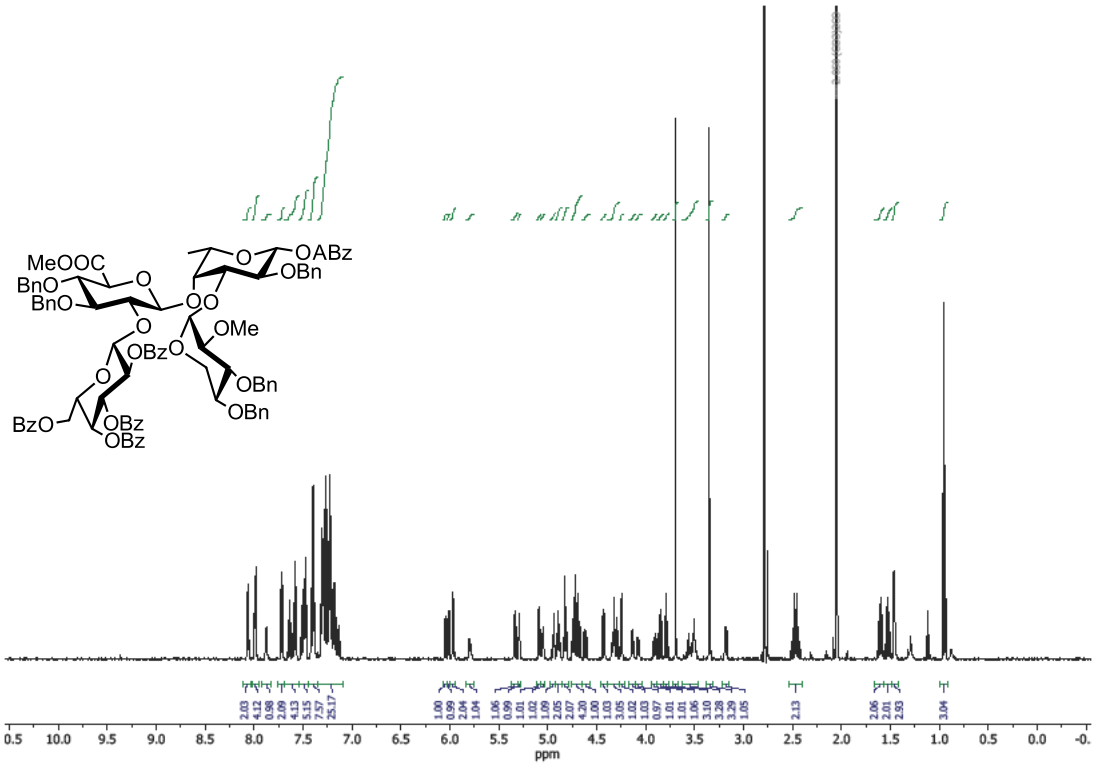
^{1}H-^{13}C CLIP HSQC NMR of **147** (CD_3COCD_3, 600 MHz, 297 K)



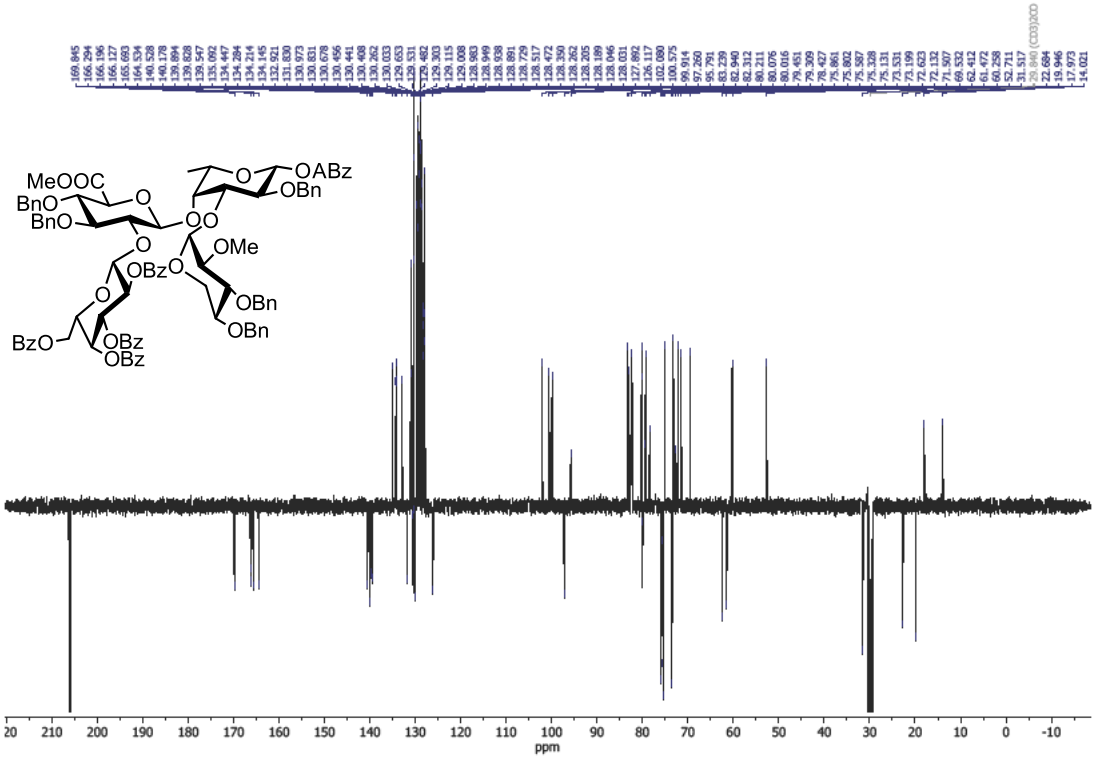
^{1}H NMR of **149-α** (CD_3COCD_3, 600 MHz, 297 K)



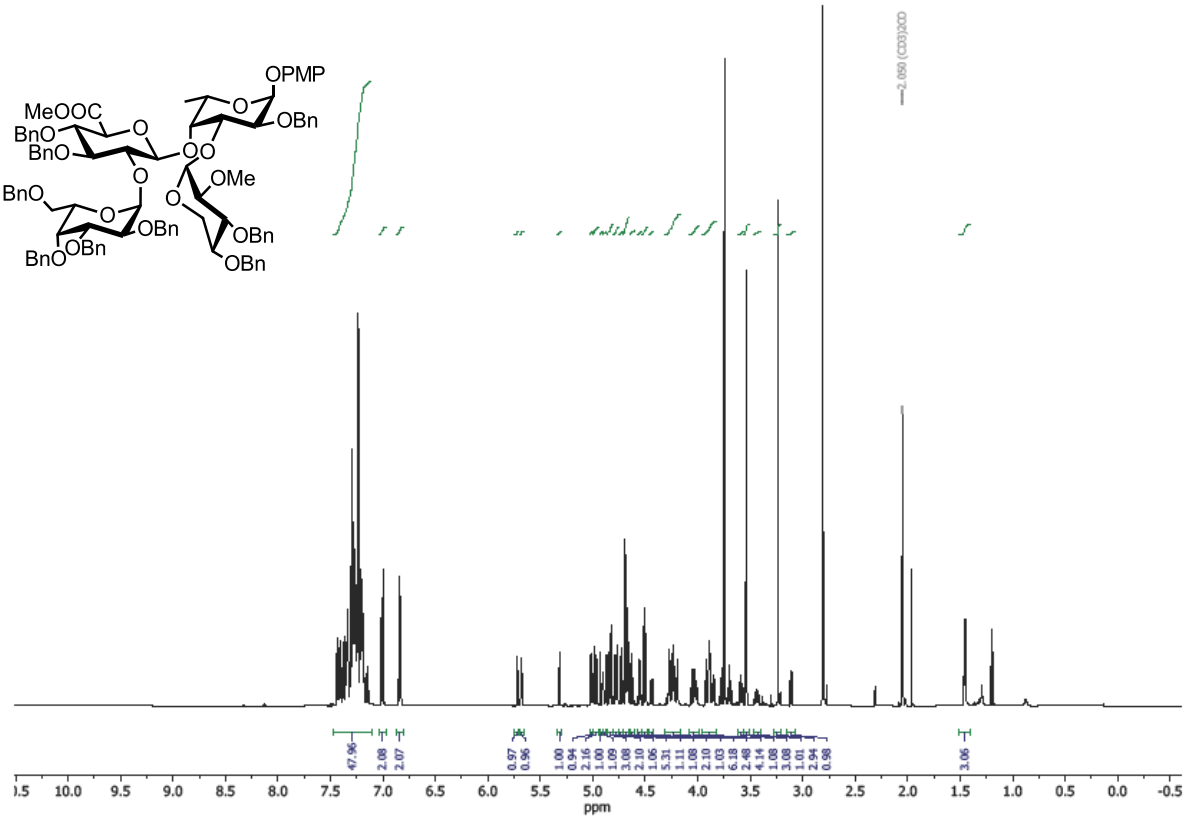
^{13}C APT NMR of **149-α** (CD_3COCD_3, 150 MHz, 297 K)



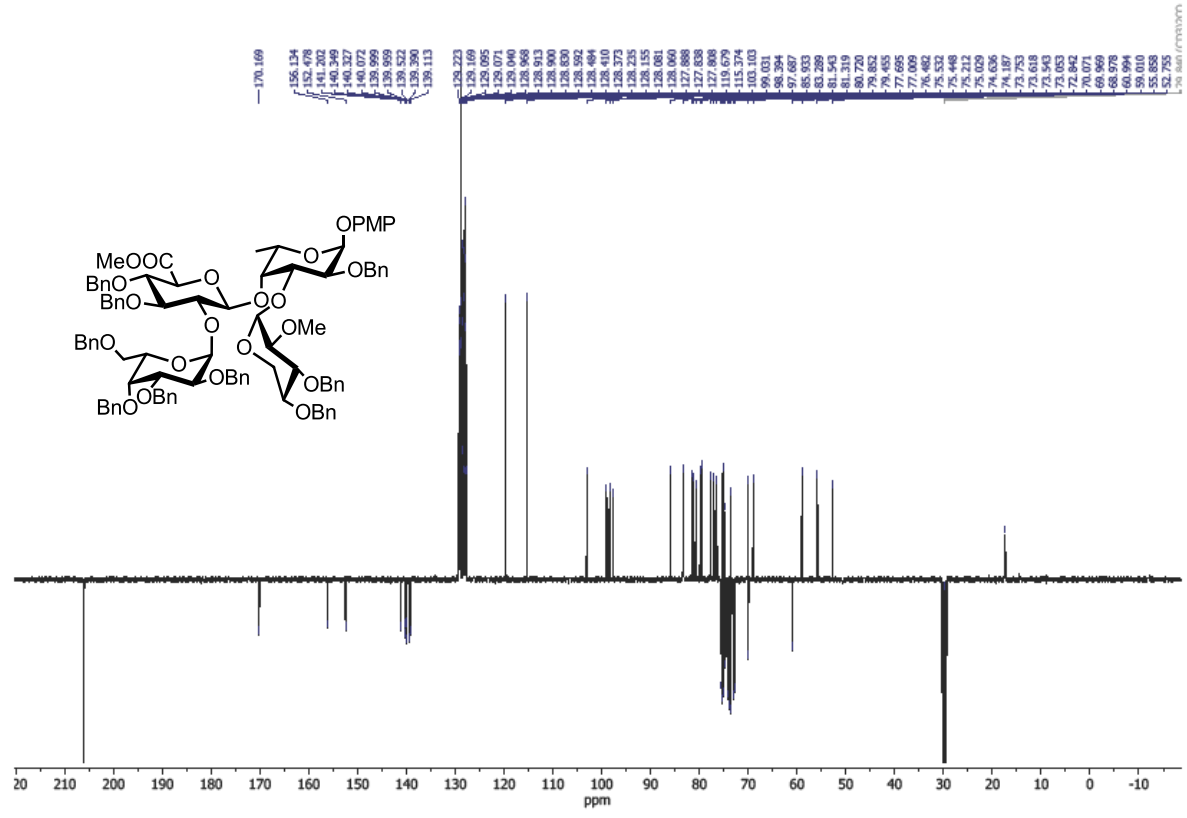
^{1}H NMR of **149-β** (CD_3COCD_3, 600 MHz, 297 K)



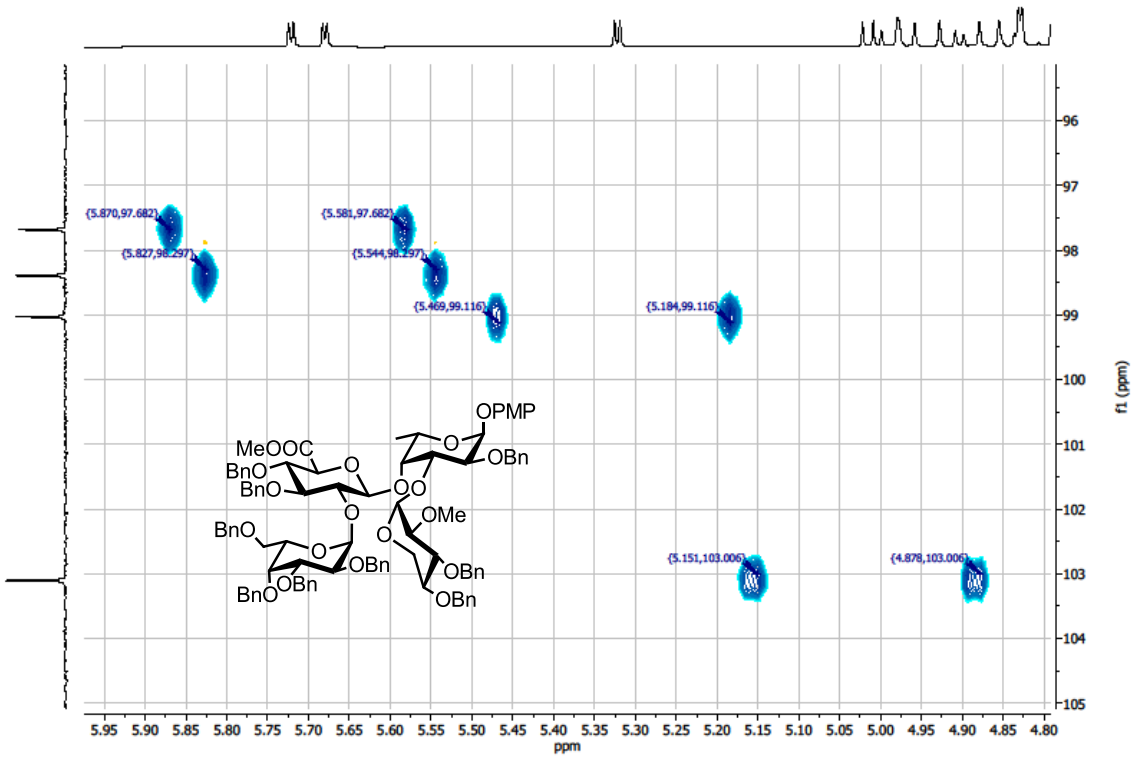
^{13}C APT NMR of **149-β** (CD_3COCD_3, 150 MHz, 297 K)



^{1}H NMR of **150** (CD_3COCD_3, 600 MHz, 297 K, 7.10-7.20 and 2.32 toluene, 4.05 1.97 and 1.20 EtOAc)

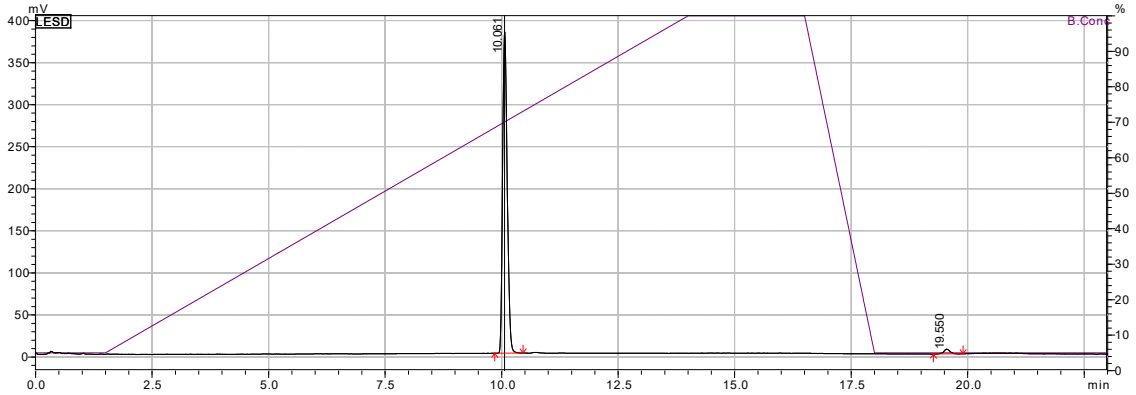


^{13}C APT NMR of **150** (CD_3COCD_3, 150 MHz, 297 K)

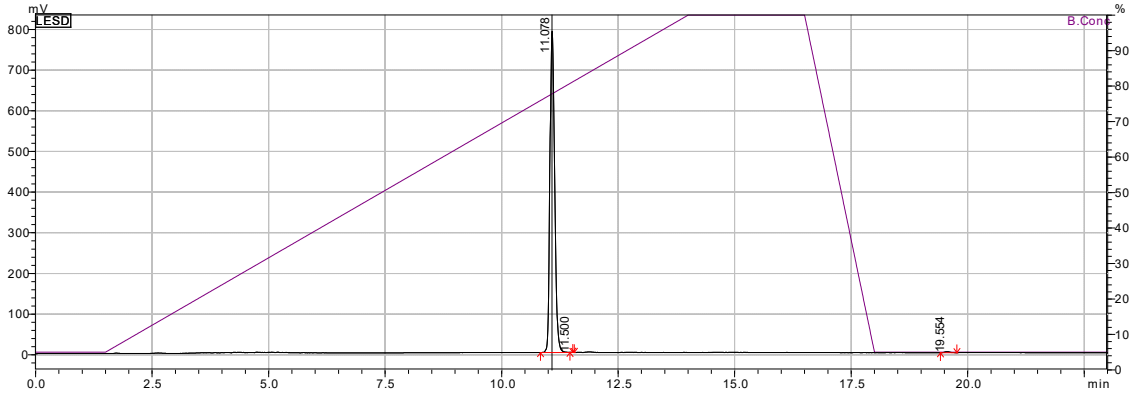


^{1}H-^{13}C CLIP HSQC NMR of **150** (CD_3COCD_3, 600 MHz, 297 K)

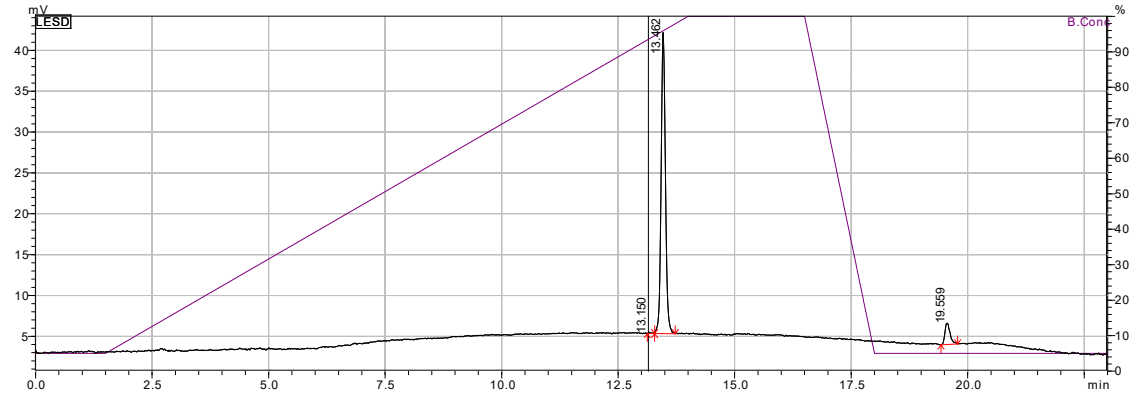
6.2 Selected HPLC chromatograms



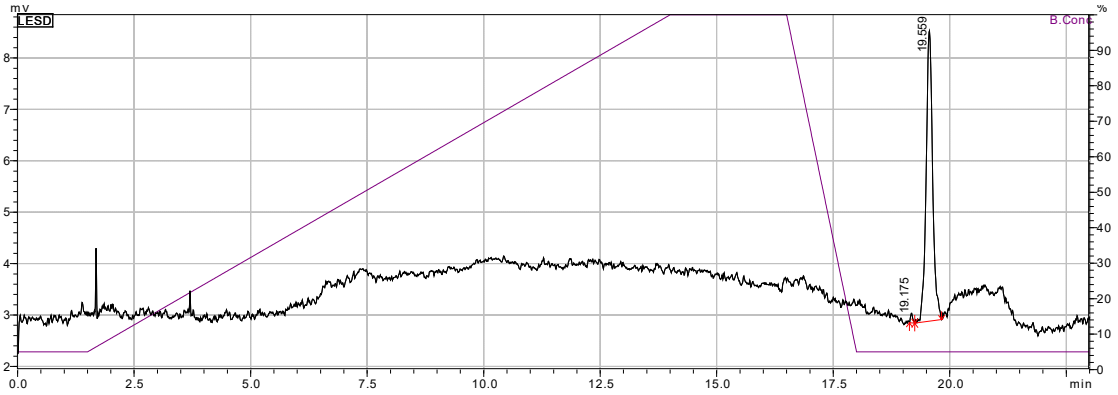
HPLC profile of partially protected disaccharide **125** (5-100% MeCN + 0.1% AcOH in 15 min, Eclipse XDB C18 150x46mm, 1 mL/min)



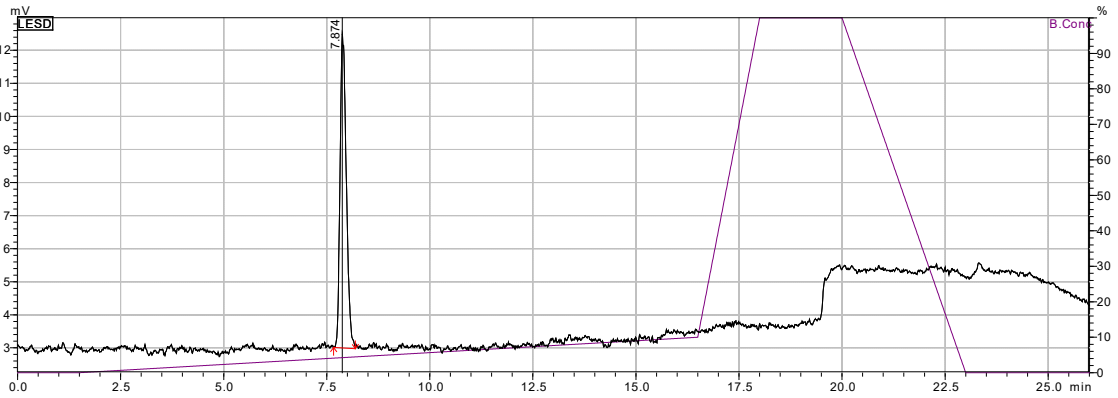
HPLC profile of partially protected trisaccharide **128** (5-100% MeCN + 0.1% AcOH in 15 min, Eclipse XDB C18 150x46mm, 1 mL/min)



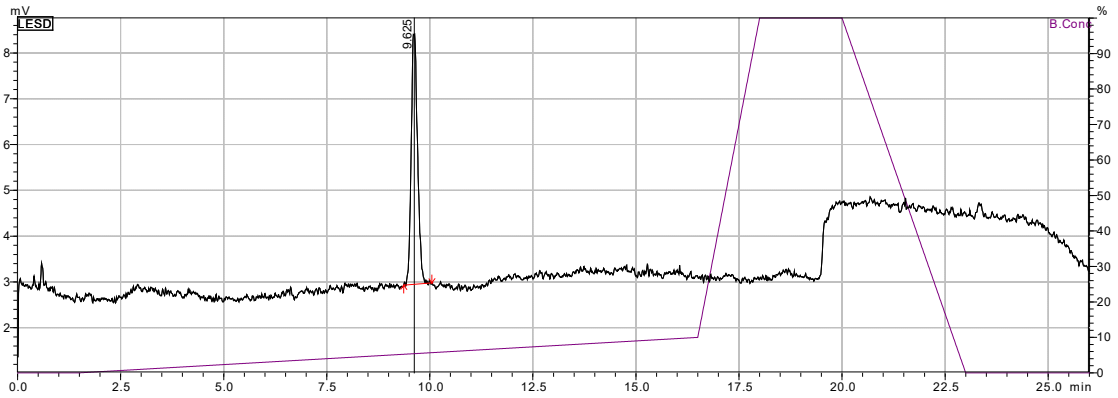
HPLC profile of partially protected pentasaccharide **129** (5-100% MeCN + 0.1% AcOH in 15 min, Eclipse XDB C18 150x46mm, 1 mL/min)



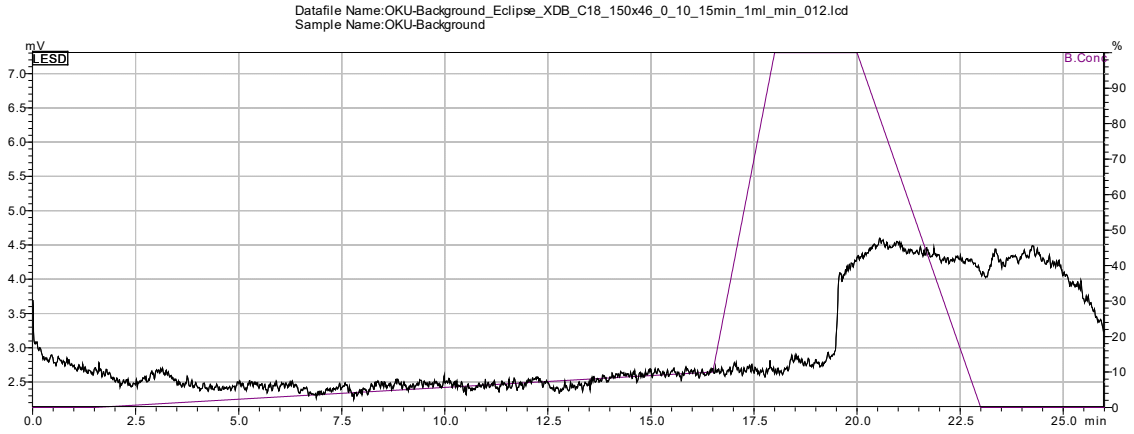
HPLC background profile (5-100% MeCN + 0.1% AcOH in 15 min, Eclipse XDB C18 150x46mm, 1 mL/min)



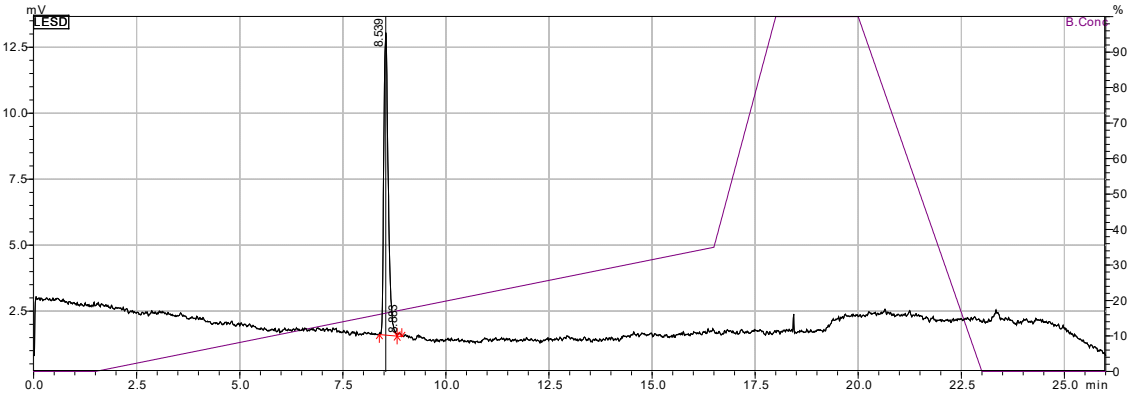
HPLC profile of disaccharide **88** (0-10% MeCN + 0.1% AcOH in 15 min, Eclipse XDB C18 150x46mm, 1 mL/min)



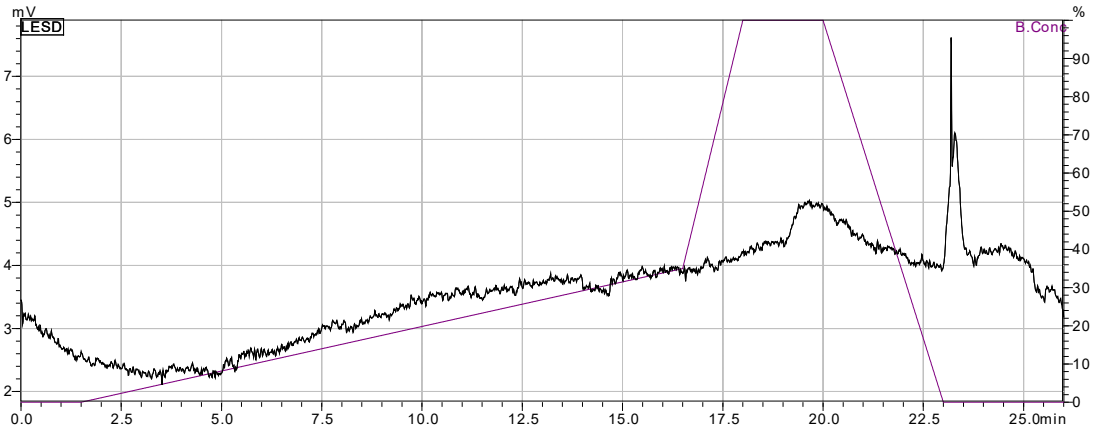
HPLC profile of trisaccharide **85** (0-10% MeCN + 0.1% AcOH in 15 min, Eclipse XDB C18 150x46mm, 1 mL/min)



HPLC background profile (0-10% MeCN + 0.1% AcOH in 15 min, Eclipse XDB C18 150x46mm, 1 mL/min)



HPLC profile of pentasaccharide **83** (0-35% MeCN + 0.1% AcOH in 15 min, Eclipse XDB C18 150x46mm, 1 mL/min)



HPLC background profile (0-35% MeCN + 0.1% AcOH in 15 min, Eclipse XDB C18 150x46mm, 1 mL/min)