# *Synthesis of Heptamannoside, Lactam Glycoconjugates and Spirocyclic Glycooxazolines*

**A Thesis submitted in partial fulfillment of the requirements of the degree of Doctor of Philosophy**

**By**

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**January 2023**

*Dedicated to...*

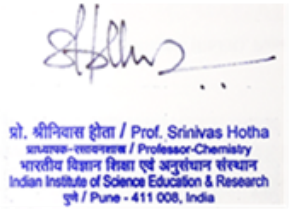
**Akka Dada**

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# CERTIFICATE

Certified that the work incorporated in the thesis entitled "***Synthesis of Heptamannoside, Lactam Glycoconjugates and Spirocyclic Glycooxazolines"*** submitted by **Mr. Ganesh Punjaram Shinde** was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.




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I declare that, this written submission represents my ideas in my own words and where ideas of others have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/ source in my submission. I understand that violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.



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# Acknowledgement

*"The price of success is hard work, dedication to the job at hand, and the determination that whether we win or lose, we have applied the best of ourselves to the task at hand"*

The sincere assistance and support of many people led to the completion of this thesis. I want to take this opportunity to express how much I appreciate each and every one of these people. I want to start by expressing my gratitude to Dr. Srinivas Hotha, my PhD supervisor, for allowing me to work in his lab. His persistent direction, regular recommendations, support, and patience made this work possible. When I needed assistance with the experiments, he was always there. He has always given me the resources I need to explore my concepts and encouraged me to come up with new ones. His deep understanding of carbohydrate chemistry was immensely beneficial to me throughout this project. Additionally, I want to thank him for consistently motivating me to conference participation and presenting my work to the scientific community

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***Ganesh Shinde***

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# General remarks

- $^{1}H$ NMR spectra were recorded on AV 200, AV 400, DRX-500 MHz, JEOL ECX 400 or Bruker Avance 500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in ppm units downfield to TMS.
- $^{13}C$ NMR spectra were recorded on AV 50, AV 100, DRX-125 MHz, JEOL ECX 100 or Bruker Avance 125 MHz spectrometer.
- High resolution mass spectroscopy (HRMS) was performed on Waters Synapt G2 or Applied Biosystems MALDI-ToF-ToF spectrometer.
- IR spectra were recorded on Perkin-Elmer 1310 or Perkin-Elmer 1600 FT-IR spectrometers with sodium chloride optics and are measured in $cm^{-1}$.
- Specific rotations were measured on a JASCO P-1020 and measured in degrees.
- All reactions were monitored by Thin-Layer Chromatography carried out on pre-coated Merck silica plates ($F_{254}$, 0.25 mm thickness); compounds were visualized by UV light or by staining with anisaldehyde spray.
- All reactions were carried out under nitrogen or argon atmosphere with freshly prepared anhydrous solvents under anhydrous conditions, and yields refer to chromatographically homogenous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Büchi and Heidolph rotary evaporators below 45 °C unless otherwise specified.
- Silica gel (100-200) and (230-400) mesh were used for column chromatography.
- All gold and transition metal salts were purchased from multinational commercial vendors.
- Materials were obtained from commercial suppliers and were used without further purification.
- Scheme, Figure, and Compound numbers in abstract and individual chapters are different.

# Abbreviations

Å – Angstrom
Ac – Acetate
$Ac_2O$ – Acetic anhydride
AcBr – Acetyl bromide
AcCl – Acetyl chloride
AcOH – Acetic acid
AG – Arabinogalactan
AGA- automated glycan assembly
AgOTf- silver trifluoromethane sulphonate
Ara*f* – arabinofuranosyl/arabinofuranoside
$AuBr_3$- gold tribromide
$AuCl_3$- gold trichloride
BB: Building Block
$BF_3.OEt_2$- Boron trifluoride diethyl etherate
Bu: Butyl
Bz – Benzoyl
BzCl – Benzoyl chloride
Calcd – Calculated
cat. – catalytic
Cbz – Carbobenzoxy
$CDCl_3$ – Chloroform-D
$CHCl_3$ – Chloroform
d – days
$D_2O$ – Deuterium oxide
DBU – 1,8-Diazabicycloundec-7-ene
DBN –1,5-Diazabicyclo[4.3.0]non-5-ene
DCC- Dicyclohexylcarbodiimide
DEPT – Distortion less Enhancement by Polarization Transfer
DIC – *N,N′*-Diisopropylcarbodiimide
DIPEA – *N,N′*-Diisopropylethylamine
DMAP – *N,N′*-Dimethylaminopyridine
DMDO- Dimethyldioxirane
DMF – *N,N′*-Dimethyl formamide
DMSO-$d_6$ – Dimethyl sulfoxide (deuterated)
DMTST- Dimethyl(methylthio)-sulfonium triflate
DTBP- di-*tert*-butylpyridine
eq. – equivalents
$Et_3N$ – Triethyl amine
$Et_3SiH$ – Triethylsilane
Fmoc: Fluorenylmethyloxycarbonyl
g – gram
Gal*f* – galactofuranosyl / galactofuranoside
h – hour
HF- Hydrogen flouride

# Abbreviations

HPLC: High Performance Liquid Chromatography
HRMS – High-Resolution Mass Spectrometry
HSQC: Heteronuclear single quantum coherence spectroscopy
Hz – Hertz
hν : photocleavage
IR – Infrared
*J* – coupling constant
LAM – Lipoarabinomannan.
LC: Liquid Chromatography
Lev – Levulinoate
LevOH: Levulinic acid
LG: Leaving Group
M – Molar
m/z: mass-to-charge ratio
MALDI-TOF: Matrix-Assisted Laser Desorption/Ionization-Time of Flight
MeOD – Methanol-D4
MeOTf- Methyl trifluoromethane sulphonate
mg – milligram
MHz – Megahertz
min. – minutes
mL – milliliter
mmol – millimolar
MS – Molecular sieves
MS: Mass Spectrometry
Mtb – Mycobacterium tuberculosis
NaH – Sodium hydride
NaOMe- Sodium methoxide
NGP – Neighbouring group participation
NIS – N-Iodosuccinimide
NMR – Nuclear Magnetic Resonance
NNGP – Non-neighbouring group participation
NPG – n-Pentenyl glycoside
PDA- Photodiode Array
Ph: Phenyl
ppm – parts per million
Py – Pyridine
RP: Reversed Phase
rt – room temperature
sat. – saturated
SPOS- Solid-Phase Oligosaccharide Synthesis
Tb – Tuberculosis
TBAI – tetra-n-Butyl ammonium iodide
TBDPS – *t*-Butyldiphenylsilyl
TBDPSCl – *t*-Butyldiphenylsilylchloride

# Abbreviations

TCA – Trichloroacetimidate
TESOTf- Triethylsilyl trifluoromethanesulfonate
TFA – Triflouroacetic acid
TfOH – trifluoromethanesulfonic acid
THF – Tetrahydrofuran
TIPDSCl– 1,3-dichlorotetraisopropyldisiloxane chloride
TLC – Thin Layer Chromatography
TMSOTf – Trimethylsilyl trifluoromethanesulfonate
UPLC: Ultra Performance Liquid Chromatography
UV: Ultraviolet
$ZnCl_2$- Zinc dichloride
δ – delta (in ppm)
μL – microliter

# Synopsis

The thesis titled, "**Synthesis of Heptamannoside, Lactam Glycoconjugates and Spirocyclic Glycooxazolines**" is divided into three chapters. Chapter one describes about the importance of carbohydrates, glycoconjugates and types of glycosylations, factors governing the stereochemical outcome during glycosylation events, account of glycosyl donors and their utilisation for glycosylation reaction. Chapter two delineates the use of glycosyl alkynyl carbonate donor activation under [Au]/[Ag]-catalytic combination in heptamannoside synthesis. Chapter three is subdivided into two sections. Section-3A describes the utility amidine bases DBU and DBN in the ring-opening reactions with *p*-nitrophenyl carbonates to afford the lactam glycoconjugates and in section-3B shown the development of a facile protocol for spirocyclic glycooxazolines from D-fructose.

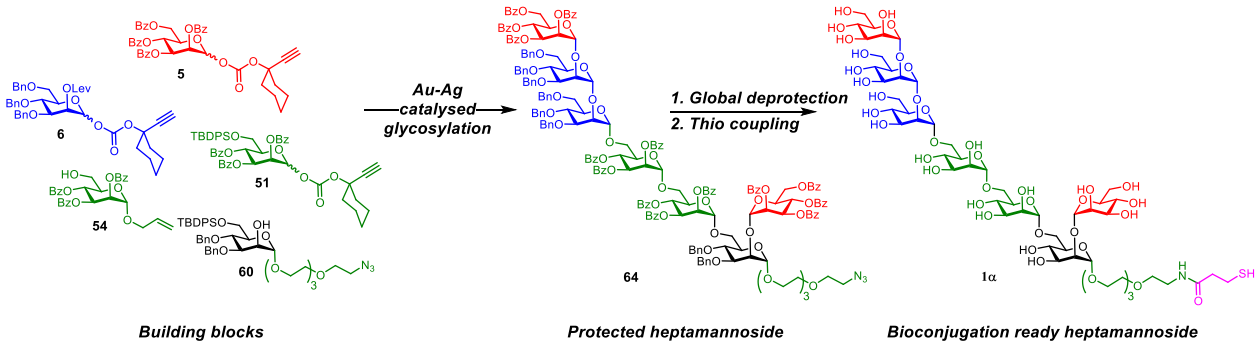
**Chapter 1: Introduction to Carbohydrate and Glycoconjugates**

Carbohydrates as well as glycoconjugates are ubiquitous, decoding their significant influence on a variety of biological processes including virus replication, immunological response, cell-cell communication, fertilization, and cell proliferation requires a pure form of glycoconjugates. Naturally occurring oligosaccharides and glycoconjugates are particularly difficult to isolate due to their availability of micro heterogeneous nature. Hence the chemical synthesis of such organic compounds resolves the challenges associated with such synthesis and is required to attain purity and abundance. Therefore, it is obvious that having access to trustworthy and highly productive glycosylation methodologies is necessary for the chemical synthesis of this kind of complicated structure as well as new methods to build interglycosidic bonds in a remarkably stereo- and regioselective manner in the laboratory. So far, synthetic chemists developed various glycosyl donors and protocols for glycosylation to address the above issues among them: thiophenyl, n-pentenyl, trichloroacetamidate and alkynyl glycosyl donors are noted. However, the need for new glycosyl donors and glycosylation protocols to form the regiodefined glycans and glycoconjugates is still challenging and demanding.

**Chapter 2: Synthesis of Conjugation Ready Heptamannopyranoside Immunogenic Epitope**

More than two million people die from tuberculosis (TB) each year in the world, a disease that has afflicted people for ages. *Mycobacterium tuberculosis* (Mtb) is the causal agent. The prevalence of multidrug-resistant (MDR) and extensively drug-resistant of bacteria is steadily increasing

(XDR) TB because of the compositional and structurally complexity of Mtb cell wall. Pioneering microbiologist Brennan unraveled the chemical structure of the Mtb cellular envelope which composed of: the outer membrane, the core cell wall and inner plasma membrane. The outer membrane of Mtb cell wall consists of proteins and glycolipids which are non-covalently connected. The core cell wall having two major carbohydrate segments: a) The mycolyl-arabinogalactan-peptidoglycan complex having heteropolysaccharide arabinogalactan (AG) which is covalently linked to long chain mycolic acid while the peptidoglycan (PG) at reducing end; and b) lipoglycans, consists of lipoarabinomannan (LAM) and lipomannan (LM). ManLAM is a significant immune-modulating motif having significant impact on the host's immunological network. So, the synthesis of an heptamannopyranoside caping of ManLAM has been planned.



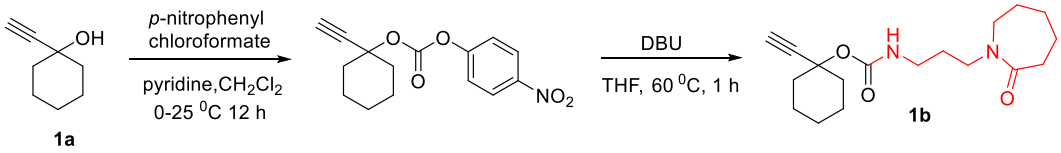

Scheme 2. Schematic representation of heptamannoside motif synthesis.

An elegant in-house developed glycosylation protocol composed of stable alkynyl glycosyl carbonate donor has been utilized for a linear as the well convergent approach for the stereoselective synthesis of heptamannoside using Au/Ag catalysts. In due course of comparative study, both the methods found to be fruitful to synthesize target oligosaccharides, however convergent synthesis supersede the linear synthesis in terms of overall yields and efficiency. Finally, the coupling of linker with the 3-mercaptopropanyl-*N*-hydroxysuccinimide ester at the reducing end of the oligomannose domain was accomplished to study the various biological and immunological response in collaboration with Prof. Beston Hamasur, Karolinksa University, Sweden.

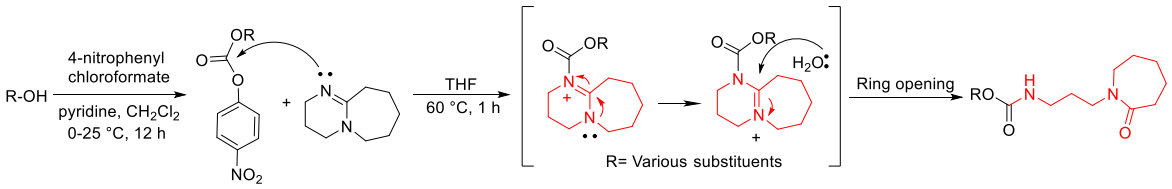
## Chapter 3A: *p*-Nitrophenyl Carbonates Promote the Nucleophilic Ring Opening of DBU and DBN Affording Lactam Carbamates

The amidines e.g DBN (1,5-diazabicyclo[4,3,0]non-5-ene and DBU (1,8-diazobicyclo[5,4,0]undec-7-ene) are known for long as strong neutral bases and are synthetically useful to catalyse various organic reactions. 4-nitrophenyl carbonates which are electrophilic and highly reactive compounds that upon treatment with the nucleophiles such alcohols or amines to form either a new carbonate or a carbamate-linked compound. During the course of reaction, the *p*-nitrophenyl carbonate of 1-ethynylcyclohexanol treated with 2 equivalents of DBU in THF in absence of nucleophile, we noticed exclusive formation of the ε-caprolactam **1b**.

Scheme 3A.1. Reaction of DBU with *p*-nitrophenyl carbonate

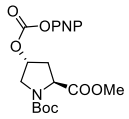
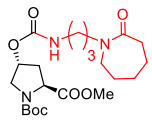
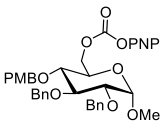
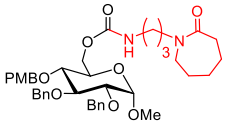
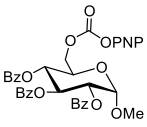
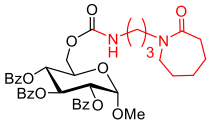



Mechanistically, we postulated that the imine nitrogen atom of DBU makes a nucleophilic attack on the carbonyl carbon, which is followed by the elimination of a *p*-nitrophenoxide ion. Following that, water molecules present in the solvent attack the imine carbon of DBU, causing the ring to open and afford the caprolactam carbamates.

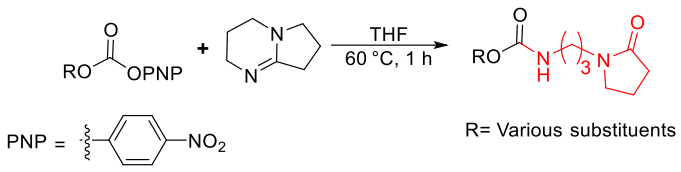



Scheme 3A.2. General mechanistic pathway for caprolactam carbamate synthesis

Table 3A.1. Representative example of ε-caprolactam carbamates

| Carbonate | Product | Yield |
|---|---|---|
|  **5a** |  **5b** | 71% |
|  **6a** |  **6b** | 82% |
|  **7a** |  **7b** | 87% |

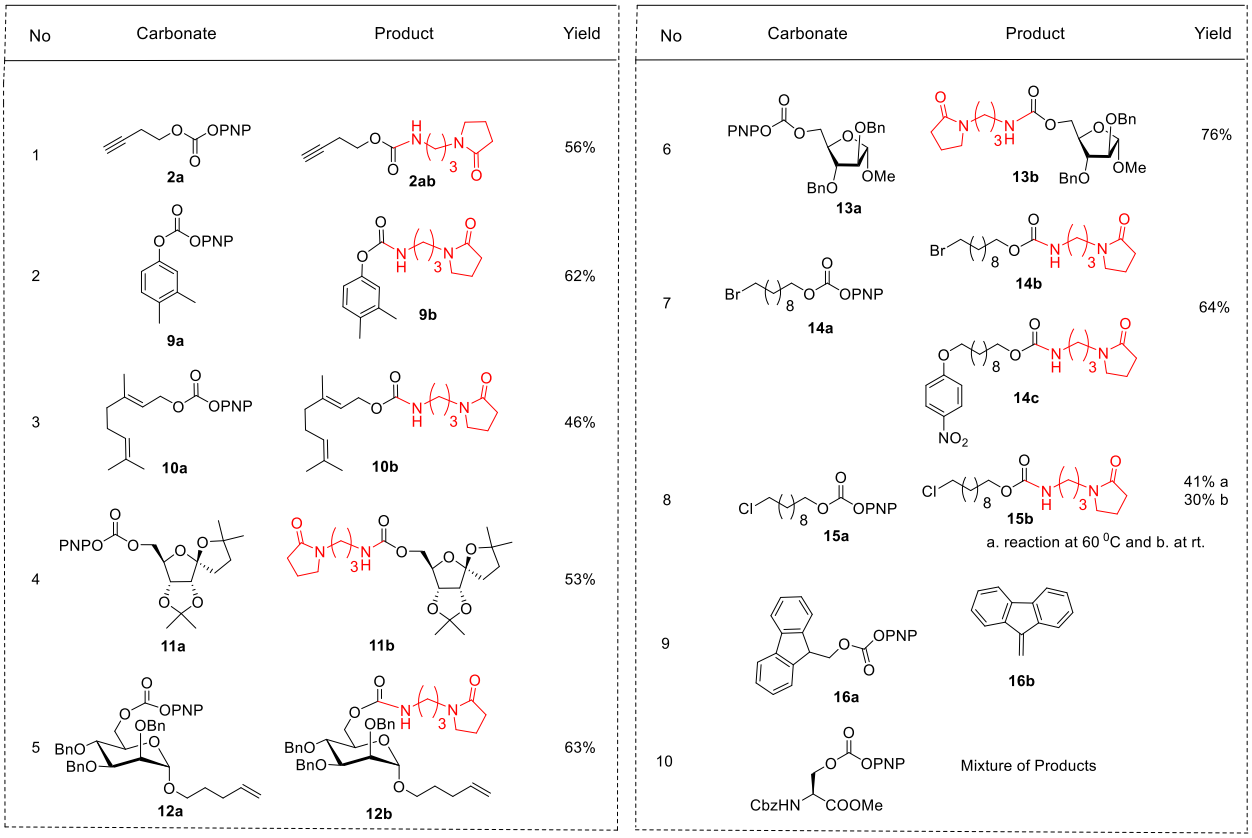
Further, the attention was shifted to another non-nucleophilic base DBN. Both DBU as well DBN are very similar in nature except that the DBU has the bicyclic [5.4.0] systems whereas the DBN has [4.3.0] bicyclic systems.




Scheme 3A.3. Reaction of DBN with *p*-nitrophenyl carbonates

Initially, homopropargyl alcohol was treated with *p*-nitrophenyl chloroformate in $CH_2Cl_2$ at 0-25 ºC to observe *p*-nitrophenyl carbonate **2a** in 90% within 1 h. Subsequent heating of the reaction mixture of carbonate **2a** to 60 ºC for 1 h resulted in the formation of γ-lactam carbamate **2ab** in 56% yield. We performed the reaction of 3,4-dimethylphenyl *p*-nitrophenyl carbonate **9a** afforded corresponding γ-lactam **9b** having 62% yield. Interestingly, geranyl carbonate **10a** also underwent this ring opening reaction yielding 46% of γ-lactam **10b**. The γ-lactam-carbamate hybrid **11b** was obtained in 53% from the *p*-nitrophenyl carbonate of D-psicofuranose whereas in case of armed *p*-nitrophenyl carbonate of *n*-pentenyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **12a** and methyl 2,3-di-*O*-benzyl-α-D-arabinofuranoside **13a** afforded γ-lactam carbamates in 63% and 67% yields respectively.

Table 3A.2. Synthesis of γ-caprolactam-derived **2ab,9b-16b**.

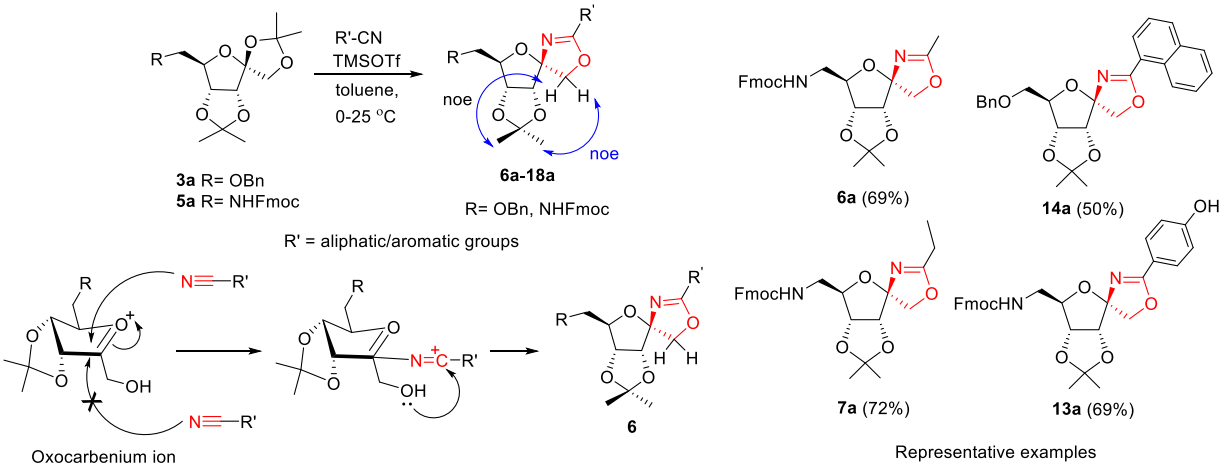



As DBU and DBN are known to induce dehydrohalogenation reactions, we focused on halogenated alcohols. So, when *p*-nitrophenyl carbonate of 10-bromo-1-decanol **14a** was treated with DBN at 60 ºC for one hour afforded single spot on TLC; however, the $^{1}$H NMR spectrum revealed the presence of two compounds **14b** and **14c** with the carbamate NH showing a multiplet rather than a triplet and an extra signal for the *p*-nitrophenyl group much to our surprise. From this NMR analysis its noticed that DBN underwent $S_N2$ displacement with the *p*-nitrophenoxide ion to afford compound **14c**. Accordingly, the 2-(2-chloroethoxyl) ethanol carbonate **15a** was treated with DBN at 25 ºC and at 60 ºC to afford the ring opened γ-lactam carbamate **15b** in 30% and 41% yield. This can be attributed to the poor leaving ability of chloride ion in comparison to the bromide ion. In this direction, *p*-nitrophenyl carbonates of 9-fluorenemethanol **16a** and *N*-Cbz-L-serine methyl ester **17a** were treated with DBN to note the formation of dibenzofulvene **16b** as the lone product. This has unequivocally demonstrated that the DBN functions as a base in molecules with functional methylene groups. In order to check the nucleophilicity of DBN and DBU with different carbonate substrate, we demonstrate three distinct carbonates of 1-ethynylclyclohexanol

using phenyl, benzyl, and ethyl chloroformate, respectively with DBU. The phenyl carbonate was treated with DBU at 60 °C for 20 hours, yielding ε-caprolactam **1b** in 12% yield whereas no trace of lactam **1b** was generated in the reaction of benzyl and ethyl carbonates with DBU. This has been attributed to the poor leaving character of alkoxides in comparison to phenolates.

**Chapter 3B: Synthesis of Spirocyclic 2-Substituted-2-Oxazoline Ribofuranosides from D-Fructose**

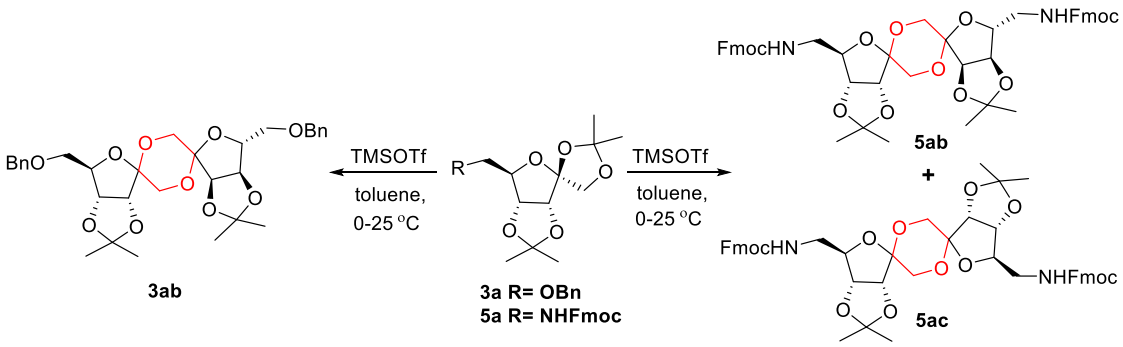
The majority of biologically significant ingredients, including many pharmaceuticals, natural products, and natural products like small molecule inhibitors having heterocycles composition in their core structure. Many times, the unique biological roles of hetero atoms in heterocyclic systems are claimed. The pharmaceuticals, natural products, foods, medicines, polymers, and agriculture often seen to include oxazolines. One such significant, privileged heterocyclic moiety that attracted a significant amount of interest is oxazoline. The oxazoline moiety needs to be synthesized with stereo as well as regiochemical control as 2-oxazoline moiety has its own unique properties and also act as the synthetic precursor or an intermediate to various chemical processes.




Scheme 3B.1. Synthesis of spirooxazolines via Ritter like reaction

The present chapter describes trimethylsilyl trifluoromethanesulfonate (TMSOTf) mediated synthesis of β-configured spirocyclic 2-substituted-2-oxazoline ribosides (**6**). In this course of study "Ritter-like" reactions were explored in toluene through nucleophilic addition of electron-rich nitriles to the oxocarbenium ion intermediate of 1,2:3,4-di-*O*-isopropylidene-*β*-D-psicofuranose derivatives with concomitant intramolecular trapping of the C2 hydroxymethyl group on the electrophilic nitrilium carbon. The synthesized carbohydrate-derived spirocyclic

oxazolines has a high shelf life. Furthermore, the generality of the present method was explored by synthesizing various spirocyclic oxazolines in good to excellent yields. We hypothesize that the stereochemical outcome of the reaction is governed by the conformational rigidity imparted by the 3,4-isopropylidene group (Scheme 3A.1). The oxocarbenium ion intermediate resulting from the D-psicofuranose underwent spiroketalization in the absence of nucleophiles producing the di-D-fructose dianhydride (Scheme 3A.2).




Scheme 3B.2. Synthesis of spiroketals from **3a** and **5a**

# Chapter 1

## Introduction of Carbohydrate and Glycoconjugates

# Chapter-1

## 1.1 Introduction of Carbohydrates

The majority of living cells are rich in carbohydrates. Polysaccharides, commonly known as carbohydrates are macromolecules. It is an end product of most of the metabolic processes such as glucose is a product of photosynthesis. Polysaccharides are made up of monosaccharide units (sugar molecules) and depend on number of units can be monosaccharide, disaccharide, trisaccharide, and polysaccharide. Carbohydrates are macronutrients and are the major sources through which our body will get energy. Name itself indicates carbohydrates have carbon, hydrogen and oxygen at their chemical level. Monosaccharide has single sugar unit; a disaccharide also called as a double sugar contain two monomers of sugar units and in oligosaccharides, 2-9 sugar monomers linked together through a glycosidic bond. Polysaccharides (complex carbohydrates) have two or more sugar units and have low rate of digestion and conversion as compared to simple carbohydrates. The lentils, beans, potatoes, peas, corn etc. are having abundant amount of complex carbohydrates. The starch, glycogen, cellulose exhibit extensive branching in their structures and are homopolymers.

## 1.2 Nomenclature, Structural Diversity and Properties of Sugars

The 'International Union of Pure and Applied Chemistry' i.e. IUPAC, officially defines that glycan is the synonymous to polysaccharides considering more numbers of monosaccharides through glycosidic linkage to each other. Most of the simple sugars have an empirical formula of $C_n(H_2O)_m$. Depending on chemical structure and degree of polymerisation, they are further split in to two categories: monosaccharides (simple sugar) and complex saccharides such as oligosaccharides and polysaccharides. Monosaccharides and complex saccharides depend on their size exhibits different physical and chemical properties. Stable secondary and tertiary structures will form by polysaccharides and further hydrolysed into simple subunit upon aqueous acid hydrolysis. While simple sugar units are found in variety of forms including linear as well as cyclic structures. The oligosaccharides and polysaccharides make up from monosaccharides building blocks. These building blocks are polyhydroxyaldehydes (aldoses) and polyhydroxyketones (ketoses) and can perform further reaction on carbonyl functionality, via oxidation to form carboxylic acids, or replacement hydroxyl group by one or more numbers with amino, thiol, hydrogen or any other functional groups (figure 1.1).

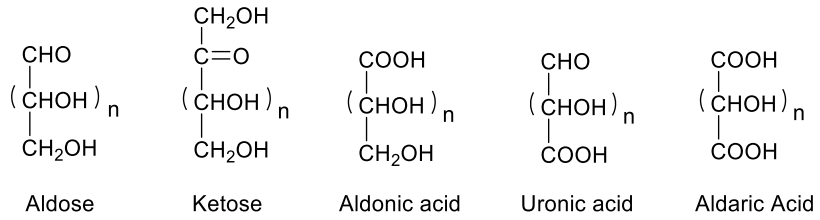



Figure 1.1 Representative sugars with different oxidation levels

According to IUPAC recommendations classification of monosaccharides depends on number of carbons in their skeleton.[1] The suffix *–ose* indicates an aldose, while *–ulose* a ketose. The trioses, tetraoses, pentoses, hexoses are the common aldoses in ascending manner. Depending on their natural sources carbohydrates named like fructose for fruit sugar, lactose in milk or cane sugar gets sucrose and the physical properties like dextrose rotates plane-polarized light in a clockwise (dextrorotation) for glucose, while laevorotatory nature for fructose is levulose.

### 1.2.1 Monosaccharides in Linear Forms

The D-glyceraldehyde as the reference molecule for stereochemical relation with monosaccharides, this deduced by Emil Fischer. He applied this proof to generate the D-aldose family and still using today's also (figure 1.2). The abbreviation for aldopentoses as well as aldohexoses considering the first three letters from their footling names, except for "glc" which designate for glucose. The epimers of carbohydrates change in configuration at only one stereo center. For example, glucose and mannose are *C2* epimer to each other. Aldoses have footling names from configurational prefixes such as *glycerol*, *arabino*, *xylo*, *manno*, *erythro*, and *gluco*, along with the "D" or "L" notation.[1] The figure 1.3, D-ketoses are depicted in Fischer projections with structure, derived and trivial names.

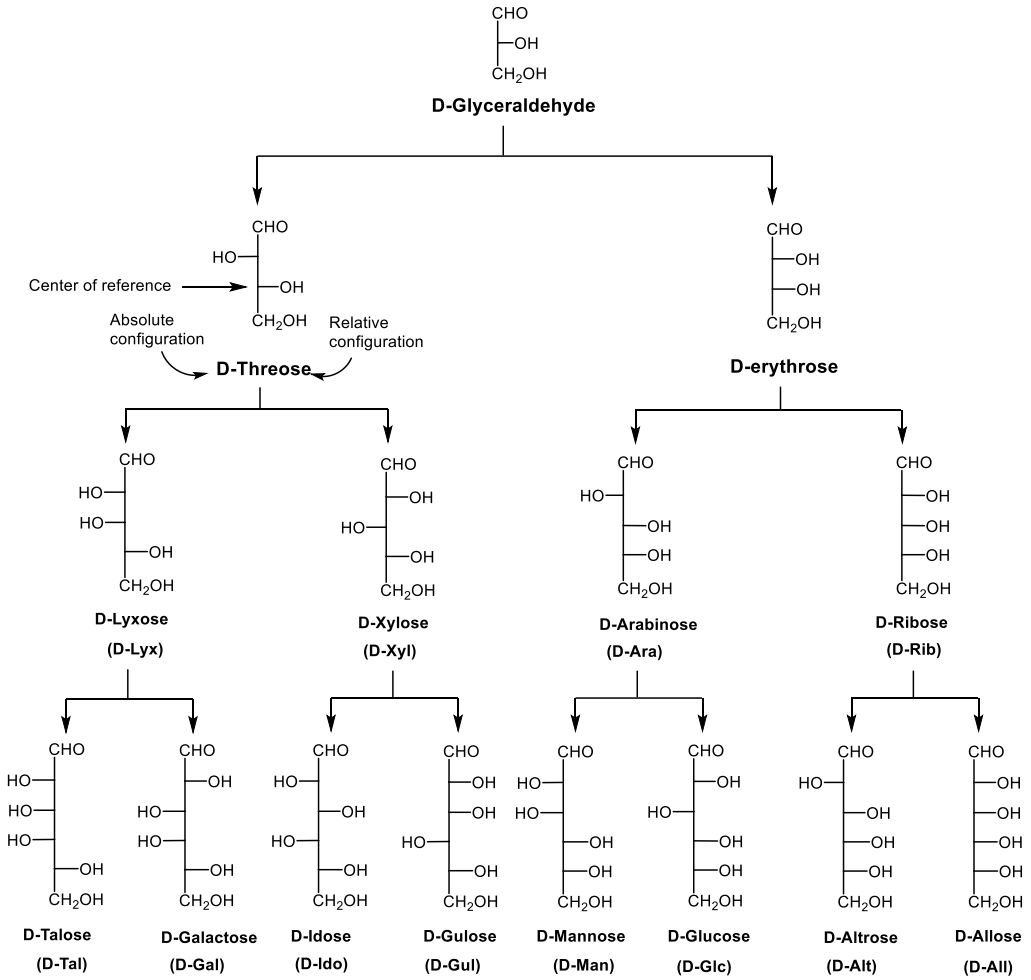



Figure 1.2 The D-Aldoses-family tree with the trivial and abbreviated names

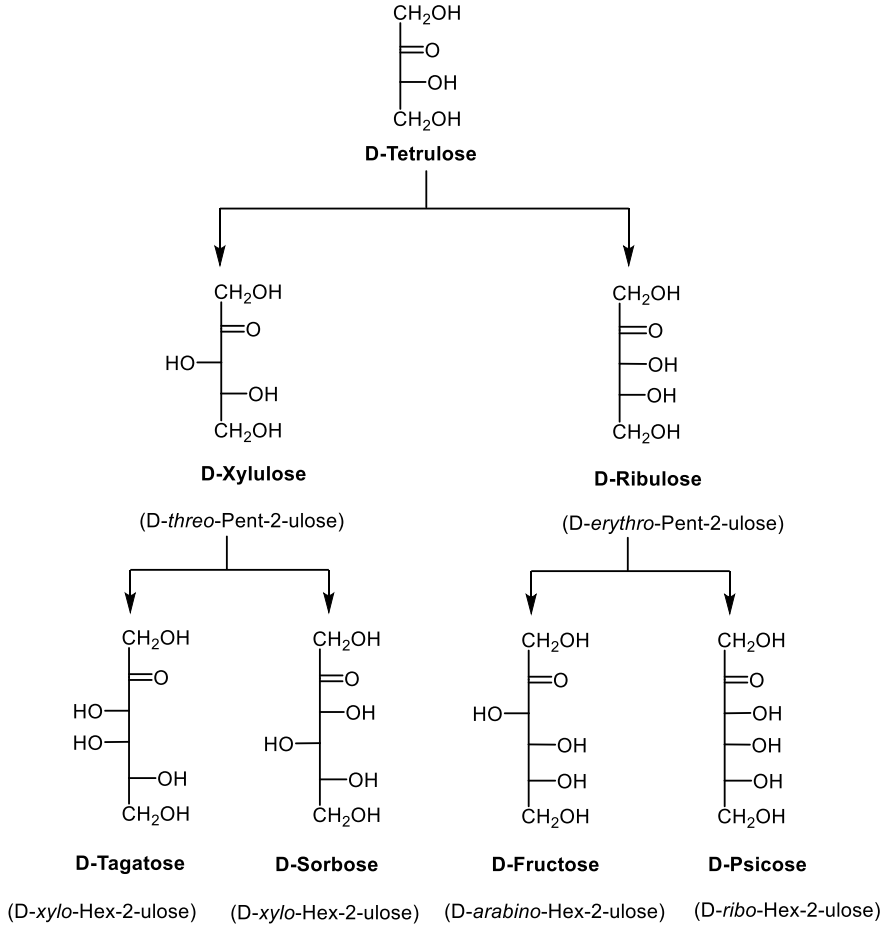



Figure 1.3 The D-ketoses family tree with the trivial and derived names

### 1.2.2 Monosaccharides in Cyclic Forms

The carbonyl group is the electrophilic centre and is readily available to interact with nucleophiles like water or alcohols; formation of hemiacetals or hydrates is a reversible process. In case of carbohydrates, the electrophilic carbonyl and nucleophilic hydroxyl group are present within the same molecule. The intramolecular cyclization can afford six membered pyranoses or five membered furanoses. This cyclization is entropically favoured over the intermolecular attack; further stability of this product is associated with the small amount of torsional strain.[2] Cyclic structure of sugars can be drawn by using Fischer projections. This is simply involvement of drawing a loop in between hydroxyl group involved and former electrophilic carbonyl carbon. Importantly, the bond formation is the continuation with the carbon skeleton and finally this action leads to the formation of stereogenic centre called as the anomeric position and the two diastereomers are assigned as $\alpha$ and $\beta$.

### 1.2.3 Mills and Haworth Projections

Haworth in 1929 depicted a representation to draw cyclic monosaccharides having 3-D perspective. The below process permits a Fischer projection conversion to Haworth representation:

1. Identification of Hydroxyl group that can react with electrophilic carbonyl carbon, like 5-OH in aldopyranose.

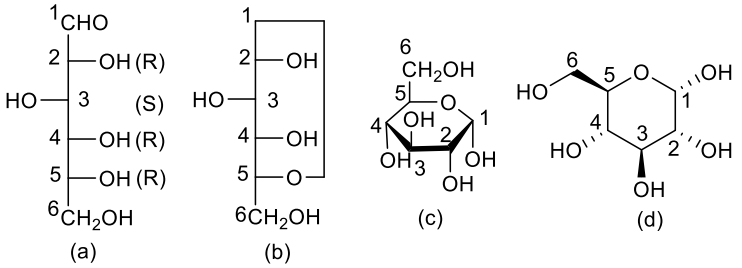



Figure 1.4 The (a) Fisher projection of D-glucose in linear form, (b) Cyclic Fischer, (c) Haworth, (d) Mills projections of α-D-glucopyranose

2. The manipulation in Fischer projection such a way that hydroxyl group is the bottom when exchange with the terminal (C6) functional group.
3. Draw the sugar skeleton such way the ring is drawn on its side. The viewer has closest face drawn at lower side, having a thicker line than the upper more distant side. On the upper right-side corner, the ring oxygen pinpointed in pyranoses and in furanoses it located at top.
4. Those substituents are right side in the Fischer projection is at bottom face in the Haworth projection while left side substituents are on top face of the ring. Just for clarity hydrogen atoms are omitted typically.

In the Haworth projections the ring atoms are arranged perpendicular to plane of paper while Mills chose to represent the sugar carbon skeleton in the plane of paper (figure 1.4). So, these Fischer, Haworth and Mills projections are needful tools to illustrate the carbohydrate structures.[3]

### 1.2.4 Reeves Projection

Reeves in 1949, redesigned the Haworth projection by employing the cyclohexane ring conformations to illustrate the pyranoses structure in solution.[4] The important edge of this convention is that close similarity to the actual geometry of molecules. It allows measuring of the dihedral angles and distances in between substituents by using the Karplus equation.[5,6]

Figure 1.5 shows furanose and pyranose structures in Reeves projections associated with α-D-pentoses and α-D-hexoses.

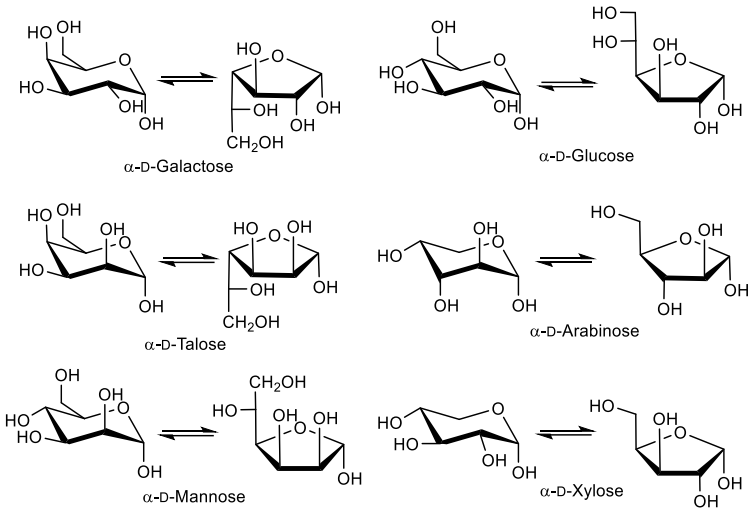



Figure 1.5 Convention of α-D-pentoses and β-D-hexoses in Reeves projections

### 1.2.5 Disaccharides, Oligosaccharides and Polysaccharides

Disaccharides are formed through the condensation of two monomer sugar units. These are connected to each other through anomeric carbons; the newly formed bond is known as a glycosidic bond. Typically, there is an involvement of anomeric carbon of one sugar unit and the nucleophilic non-anomeric hydroxyl group of another monomer to form a reducing disaccharide. The sugar unit may be in either furanose or pyranose form and in addition it could be a mixture of α and β-anomers. To do the nomenclature of saccharides it includes the abbreviation name of, monosaccharides, ring form- pyranose (*p*) or furanose (*f*), the anomeric centers configuration and site of glycosidic linkage. The "oligosaccharide" term is not exactly defined; it is used to report complex saccharides composed of 2 to 10 monomer sugar units. It can be a branched or linear sequence. Whenever branched structures are there, consider long arm assigned as the parent one. All the links exactly are stated within brackets. Whenever two or more than those branches are present and if they are in equal length, give the priority from there to the branching point. The polysaccharides are the biopolymers made up of more than 10 monomer units. These polysaccharide structures are present in homo or heteropolysaccharide forms. The physical properties of polysaccharides depend on chain conformation, intra- and intermolecular bonding, and which solvent it dissolves.

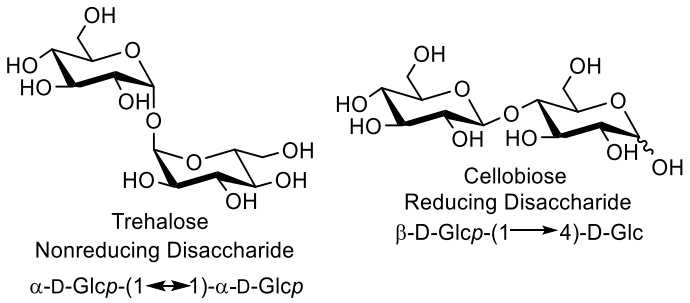



Figure 1.6 Structure and nomenclatures for selected disaccharides

### 1.2.6 Anomeric Effect

It is well known equatorial substituents impart less steric hindrance in six membered cyclohexane and it's energetically in favour of their axial analogues. When substituents are at axial position, the adverse 1,3-diaxial interaction associated with these substituents. However, the pyranose rings in contrast to the cyclohexane holds an endocyclic oxygen atom which is adjacent to the anomeric carbon (C1). John Edward in 1955 identified the axial bias of anomeric substituents in sugars[7] and later on, Lemieux explain this unusual behaviour as the "anomeric effect".[8] Subsequently, many hypotheses were proposed for ascribing the combination of hyperconjugation and electrostatic effects.[9] The C1 anomeric position is the electron deficient cause of the combination of the electronegative species X (Where X may be O, S, N, F, Cl, Br, or I) at anomeric having nonbonding electrons and the adjacent ring oxygen. When these X species is in axial direction, a nonbonding electron from endocyclic oxygen oriented antiperiplanar to the σ* C1-X) antibonding orbital and these electrons delocalization stabilize the electron deficient anomeric centre through a hyperconjugation. When substituent X is at equatorial position such stabilizing *n*-σ* interaction not possible (figure 1.7) and this also shows the dominance of anomeric effect when electronegativity of substituent X is increases.

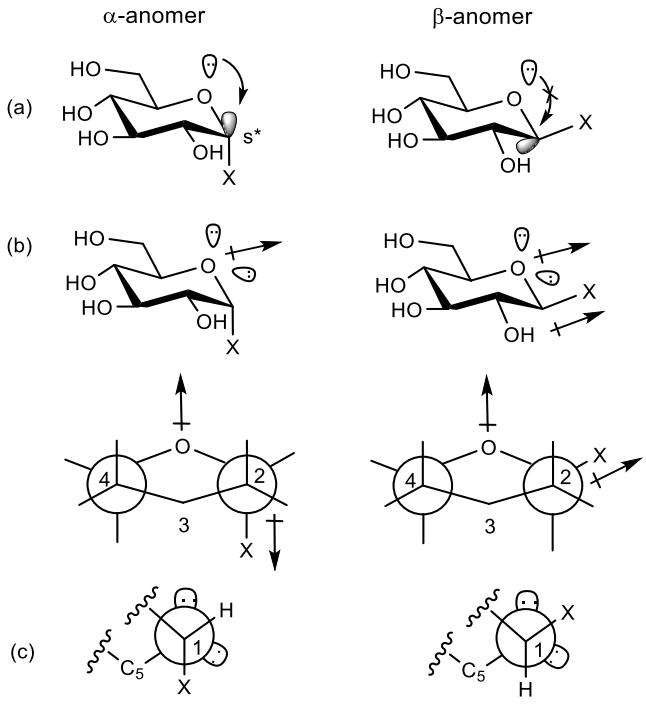



Figure 1.7 (a) The n-σ* interplay which stabilizes the α-anomer. (b) The β-anomer encounters adverse dipole-dipole interaction which is minimising in α-anomer. (c) Stronger electrostatic force of repulsion between nonbonding electron lone pairs of endocyclic oxygen and the electronegative anomeric species in β-anomer

When an electronegative substituent X is in the equatorial orientation, the exocyclic nonbonding electron lone pairs show the strong repulsion of electrostatic interactions with endocyclic O5 electron lone pairs and these repulsions drastically are reduced when the substituent is in the axial orientation (figure 1.7b). To get more stabilization, conformations that show anomeric effect prefer the synclinal (*gauche*) conformation over the antiperiplanar conformation in the system C5-O5-C1-X (figure 1.7c) looking the strong electrostatic force of repulsion in between two nonbonding electron pairs of electronegative heteroatoms along the C1-O5 bond in *anti*-conformer. The other factor that can also contribute to the anomeric preference of a specific sugar includes solvent effects and steric hindrance.

### 1.2.7 Mutarotation

The changes in optical rotation because of epimerization are called as a mutarotation.[10] Cyclic forms of sugars have α- and β- anomeric forms. These diastereomers show changes in specific rotation in aqueous sugar solution with the time. For example, pure crystalline sample of α-D-glucose is soluble in water at pH 7 showing the optical rotation at initial about +112°; but after 3 h optical rotation value decreased to +52.7°. If on starts with β-D-glucopyranose aqueous

sample, its optical rotation value is +18.7°; over time, β-D-glucopyranose will become α-D-glucopyranose through mutarotation. But in solution, ring opening, closing and hydrolysis gives the equilibrium establishment (figure 1.8), along with the trace amount of furanose and open chain form.

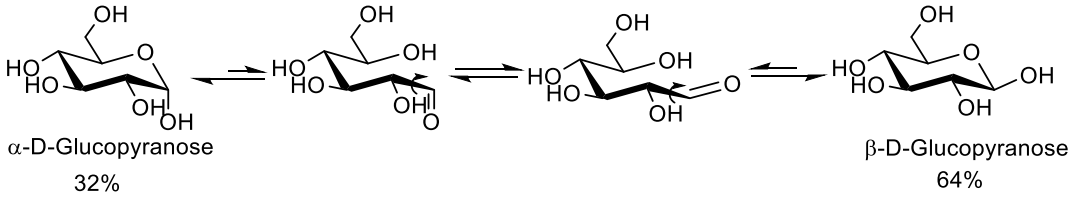


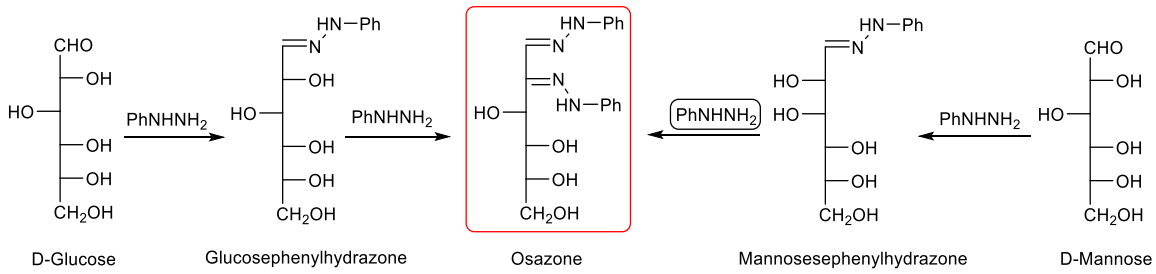

Figure 1.8 Interconversion of α and β- anomer of D-glucose showing mutarotation

### 1.3 Historical Root

### 1.3.1 Emil Fischer (1852-1919): The Father of Carbohydrate Chemistry [11-14]

In previous sections, structures and properties are described and would not be appropriate if we do not recollect "father of carbohydrate chemistry" - Emil Fischer. Fischer and his students worked on the relative configurations and structural characterization of monosaccharides by using the chemical and analytical (polarimetry) techniques.

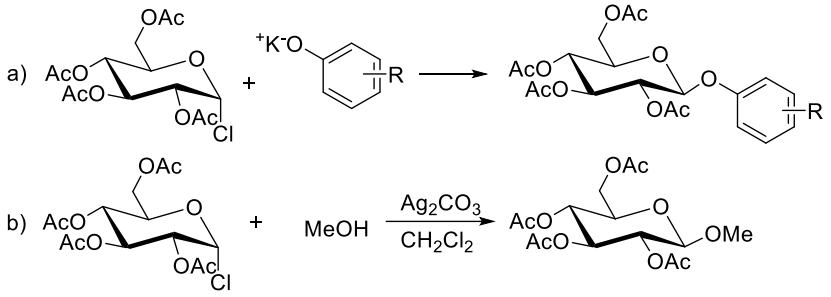
In 1870, only glucose and galactose were familiar; later, lactose, maltose and sucrose were identified as disaccharides. But the milestone on this path was led by Fischer who won the Nobel Prize in 1902 for the discovery of the reagent phenyl hydrazine in 1857. He found that rapid reactivity of phenylhydrazine with aldehydes resulting to the formation of phenylhydrazones. Phenylhydrazones are crystalline in nature; Fischer used this property to demonstrate the glucose and fructose osazones and identified that they have same configuration at C3, C4, and C5. He reported phenylhydrazones intermediate identification and isolation at reduced temperature and came to conclusion that mannose and glucose are C2 epimers (Scheme 1.1).




Scheme 1.1. Osazones formation from glucose and mannose

### 1.3.2 Koenings-Knorr Reaction

In the early twentieth century, with limited resources, Arthur Michael conducted the first chemical glycosylation was performed in 1879 using potassium phenolates using anomeric halide (Scheme 1.2a). [15,16] Later on, Koenings-Knorr conducted a reaction in the presence of silver salts that became a landmark glycosylation (Scheme 1.2b). [17,18] Later on, the reaction was widely used to synthesize alkyl and aryl *O*-glycosides and also *O*-linked oligosaccharides.




Scheme 1.2 a) The first chemical glycosylation method. b) The Koenings-Knorr reaction

### 1.3.3 Karl Freudenberg (1886-1983)

Karl Freudenberg explored cyclic acetals of monosaccharides and furnished the di-*O*-isopropylidene derivatives of mannose, glucose, galactose and xylose.[19] Freudenberg also reported the synthesis of 3-*O*-tosyl-D-glucose and 6-*O*-tosyl-D-galactose which are valuable intermediates to construct the complex glycans as well as modified carbohydrate substrates.[20] He postulated in 1939 that macromolecules like starch and proteins form helical structures due to the intramolecular hydrogen bonding.[21]

### 1.3.4 Horace Isbell (1898-1992)

In a seminal study, he showed the effect of neighbouring groups during the reactions[22] and developed the systems to describe pyranoid sugar conformation[23] which built up on Haworth's pioneering work.[24,25] He investigated the conformational effects on the substrate reactivity. The major breakthrough of his contribution was that for the first time, he reported a practical approach for the synthesis of $^{3}H$ and $^{14}C$- radiolabelled sugars.[26] This revolutionary work enabled visualization of complex biological processes.

### 1.3.5 Raymond Lemieux (1920-2000)

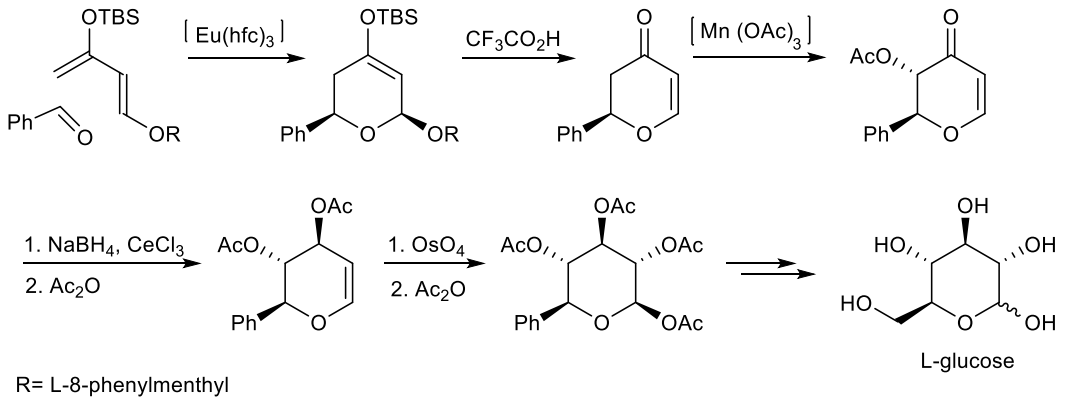
Lemieux has developed tools to study carbohydrates by NMR including their stereochemistry and biological implications.[27] He has synthesized sucrose for the first time in the lab.[28] He showed for the first time, the correlation between protons in local environment and its chemical

shift through the $^{1}H$-$^{1}H$ couplings to determine the favoured conformation of per *O*-acetylated sugars in solution. He explored the reverse anomeric[29] and *exo*-anomeric effect[30-32] by conformational analysis of glycosides. A long-lasting problem associated with all carbohydrate chemists is to achieve 1,2-*cis*-glycosides formation. In an outstanding work, Lemieux accomplished stereoselectively 1,2-*cis*-glycosides synthesis by equilibration of α- halide anomer to more stable β-halide anomer.[33,34] And for the first time, his studies have depicted the clear picture of complex interactions between glycans and protein receptors

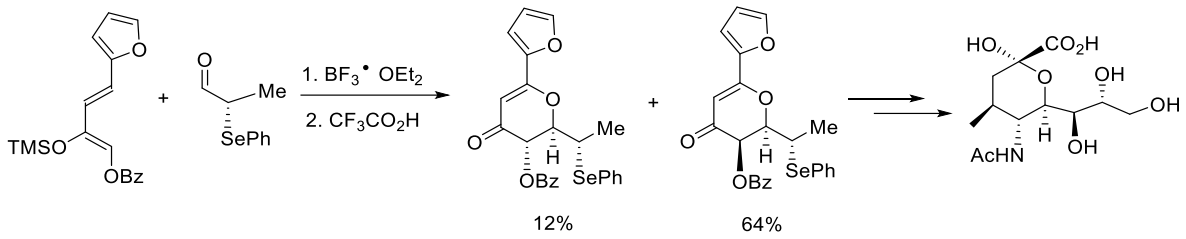
### 1.4 Sugars by De Nova Synthesis

In the middle of 20$^{th}$ century, organic synthesis rapidly expanded across the globe, a large number of synthetic chemists focused on total synthesis of natural products including carbohydrates. Organic chemists used carbenes,[35] carbocations,[36] carbanions,[37] organometallics[38] to synthesize sugars and its derivatives using the existing toolkit. In most of these reactions, they have obtained mixture of products but with new characterisation methodology, novel purification techniques were utilized to synthesize branched, longer, C-linked glycosides as well as nucleosides. The elegant example to the *de nova* approach is the utility of Danishefsky's diene to the synthesis of sugar derivatives.[39] It is known that electron rich dienes and activated aldehydes will undergo cycloaddition. To this reaction major breakthrough came after the utility of Lewis acid to catalysed the cyclocondensation reaction. This provided new synthetic strategy for sugars and other natural polyoxygenated products synthesis (Scheme 1.3).[40]

Use of aldehydes which are optically pure undergo Lewis catalysed cyclocondensation reaction afforded the synthesis of enantiomerically pure glycans. Synthesis of various complex monosaccharides is accomplished through *de novo* synthesis of sialic acid-type *N*-acetylneuraminic acid (Neu5Ac) (Scheme 1.4). [41,42]



Scheme 1.3 Enantioselective L-glucose synthesis via Lewis acid catalysed reaction. Hfc: 3-(heptafluropropylhydroxylmethylen)-D-camphoro; TBS: *tert*-butyldimethylsily.

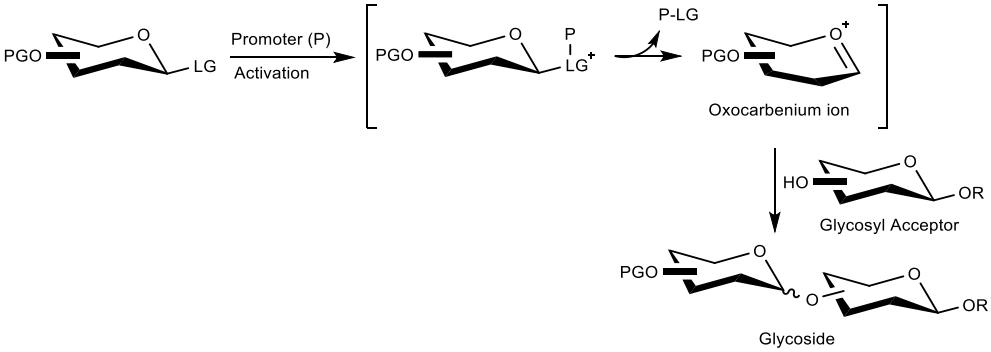



Scheme 1.4 Via Lewis acid catalysed cyclocondensation reaction synthesis of Neu5Ac. Bz, benzoyl; TMS, trimethylsilyl

## 1.5 Carbohydrate Chemistry in the 21st Century

### 1.5.1 Glycosylation System and Glycosyl Donors

In late 20th century the development and design of glycosylation methods have become major focus. In this traditional process two components are involved: glycosyl donor and glycosyl acceptor. The glycosyl donor is an electrophilic species which contributes anomeric centre to form a glycoside and acceptors are nucleophilic species in glycosylation reactions. For *O*-glycosides, glycosylation reaction begins with donor activation by promoter. Here the leaving group departs from the anomeric center of the donor and forms a highly reactive oxocarbenium ion. Subsequently the nucleophilic hydroxyl group of aglycone or glycosyl acceptor will attack and form glycosidic linkage (Scheme 1.5). There are a number of factors that influence the selectivity and reactivity of the glycosylation event and have broad range of mechanisms through which reaction proceeds.[43]




Scheme 1.5 The general mechanistic pathway of chemical glycosylation reaction

#### 1.5.1.1 Types of Linkages[43]

Commonly two types of linkages in respect to C2 substitution are envisage viz. α and β or 1,2-*cis* and 1,2-*trans* glycosides. Here are some common examples of α-glycosides; these are D-glucose, D-mannose, D-galactose and L-fucose showing 1,2-*cis* glycosyl residues and the β-D-glucopyranoside, 2-acetamido-2-deoxy-β-D-glucopyranoside and β-D-xylopyranoside are showing β-glycosidic linkage i. e 1,2-*trans* glycosides (figure 1.9).

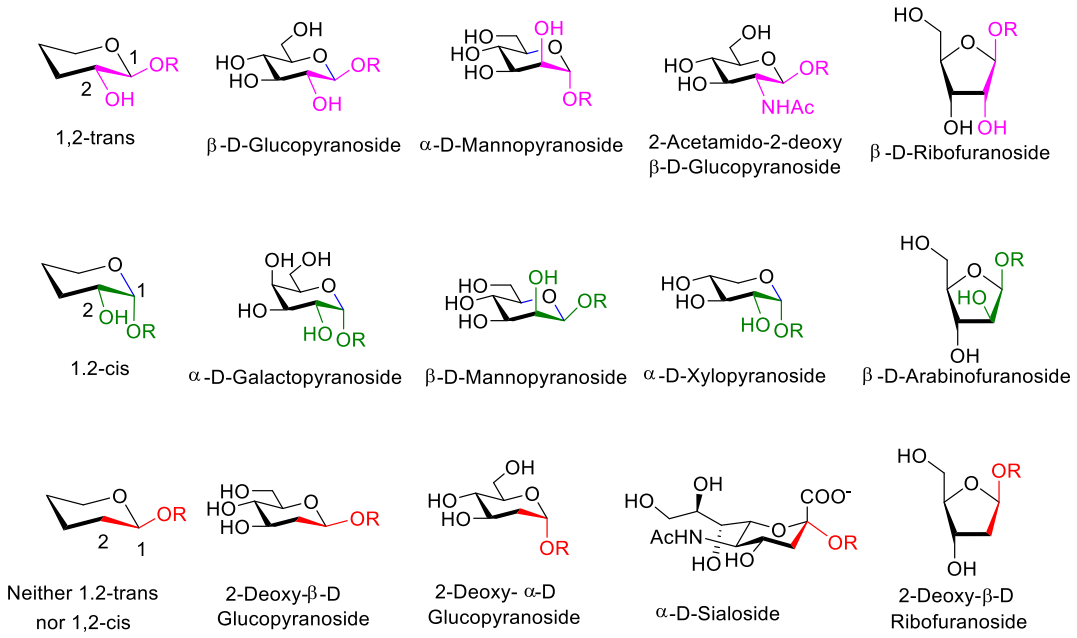
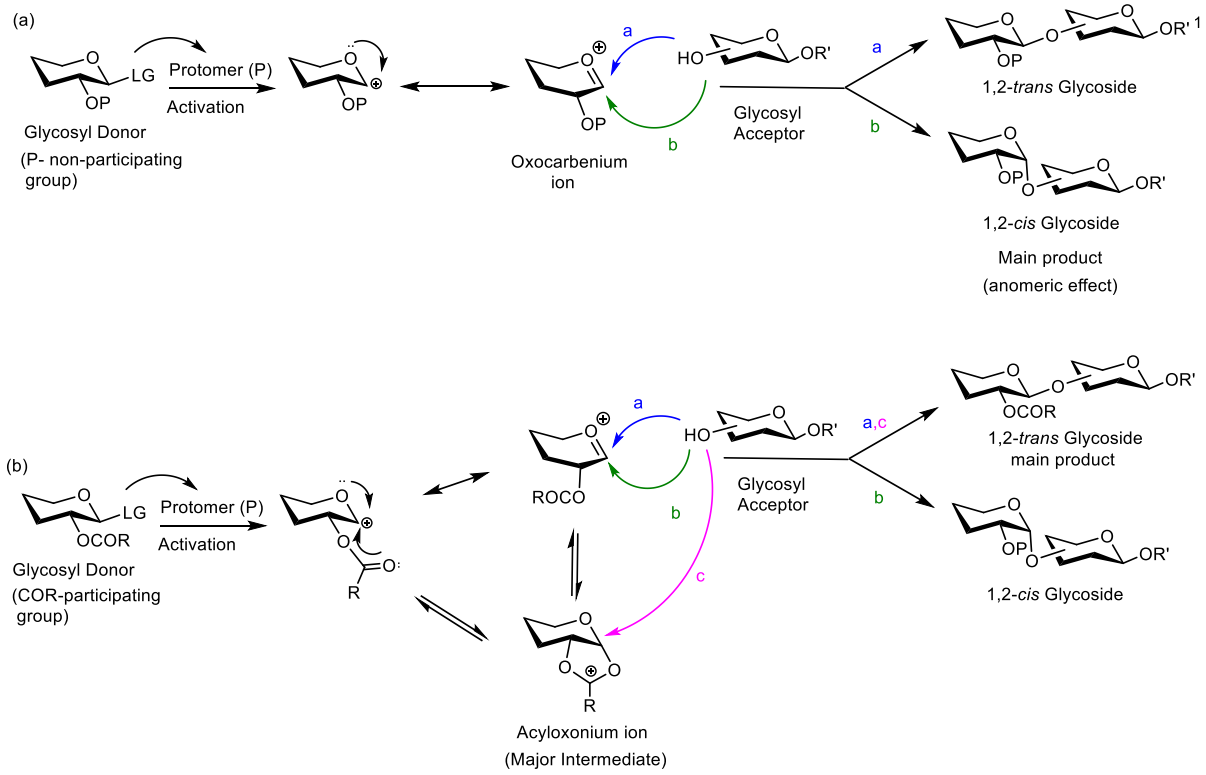



Figure 1.9 Representative example for different glycosidic linkage

### 1.5.1.2 Mechanism for Stereoselective Glycosylation Event

The common and accepted way of glycosylation events is shown in scheme 1.6a, 1.6b. The nucleophilic displacement takes place at the anomeric carbon if the nucleophiles are weak in nature (glycosyl acceptor) and the reaction follows $S_N1$ mechanism. The donor having participating and non-participating group will be discussed separately (scheme 1.6a and 1.6b). In glycosylation event, the promoter or catalyst will active the donor and facilitate the departure of the leaving group from the anomeric center to form oxocarbenium ion. When the glycosyl donors bear the non-participating group, this cation will be stabilized intramolecularly by the endocyclic oxygen O-5 resulting in the formation of oxocarbenium ion formation (scheme 1.6a). Frequently the benzyl (OBn), azide ($N_3$) are used as non-participating groups. The anomeric carbon possesses $sp^2$ hybridisation once leaving group departs, the incoming nucleophile attack axial (cis, α-) or equatorial (*trans*, β-) fashion. The α-anomer will favour thermodynamically because of the anomeric effect; minor amount of β-glycoside is the kinetic product.



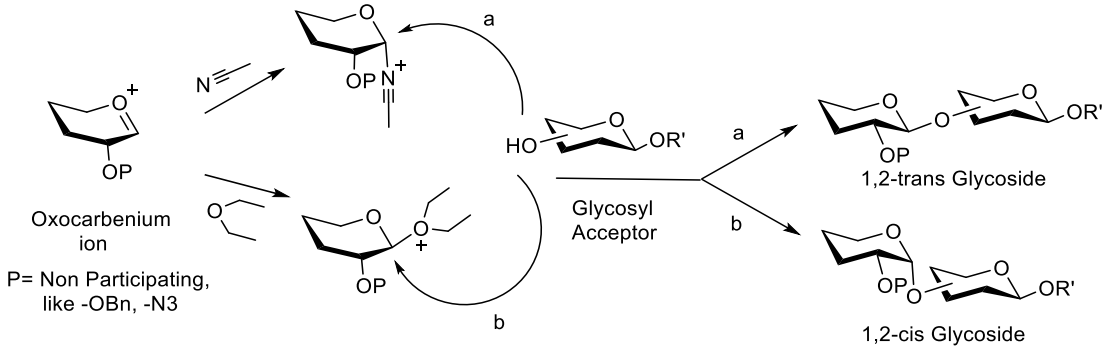

Scheme 1.6 The mechanistic pathway for stereoselective glycosylation reaction.

The stereoselective 1,2-*trans* glycosidic bond formation was accomplished through the anchimeric assistance or neighbouring group participation (NGP) via *O*-benzoyl (Bz), *O*-acetyl (Ac), 2-phthalimido (NPhth).[44-46] This type of glycosylation reaction proceeds through a bicyclic intermediate called as acyloxonium ion (Scheme 1.6b), which is formed intramolecularly by stabilising the glycosyl cation through NGP. In this case nucleophile (alcohol, glycosyl acceptor) will attack in an equatorial fashion (top face, path c) to result into formation of stereoselective 1,2-*trans* glycoside.

### 1.5.1.3 Factors Influencing the Glycosylation Event

#### 1.5.1.3a Solvent Effect

The rate of formation of β-glucoside products increases in polar solvents. The non-nucleophilic solvents such as $CH_2Cl_2$, $ClCH_2CH_2Cl$ or toluene are suitable solvents for α-glucosides. In participating solvents such as diethyl ether and acetonitrile, the β-glycosidic adduct is predominant (Scheme 1.7).




Scheme 1.7 Participating solvent influences stereochemistry at anomeric centre

### 1.5.1.3b Activators and Additives

Slow and milder reaction conditions generally favour 1,2-*cis* glycosidic bond formation as noticed in the glycosylation with glycosyl halide donors.[47-49] Trichloroacetimidates are activated in presence of triflouromethanesulfonic acid (TfOH) or trimethylsilyl trifluoromethanesulfonate (TMS-OTf) along various additives that influence the outcome (e.g. perchlorates) to favour 1,2-*cis* glycosylation.[50]

### 1.5.1.3c Reactivity of Glycosyl Acceptor

The glycosyl acceptor (nucleophile) is a vital constituent in the glycosylation. Its structural and functional reactivity decides the outcome of the stereochemistry at the anomeric center. Generally, reactivity depends on the spatial arrangement of the hydroxyl group in the sugar moiety. The *axially* oriented hydroxyls are less reactive than those which are *equatorial*. The reactivity order in glycosylation for glucose is 6-OH>> 3-OH>>2-OH>>4-OH.[51]

### 1.5.1.3d Reactivity of Glycosyl Donor

It is an electrophilic component of glycosylation reaction.

### 1.5.1.3e Protecting Group

Regio- and stereo-selectivity during the glycosylation is strongly influenced by the protecting groups present in the glycosyl donor. Less reactivity was noticed when glycosyl donors have electron-withdrawing groups such as -OAc or -OBz and they are termed as *disarmed* by Fraser-Reid in his pioneering studies; whereas, glycosyl donor which has ether functionality impart electron donating effect and stabilise the oxocarbenium ion and are termed as *armed donors* by Fraser Reid (figure 1.10).[52]

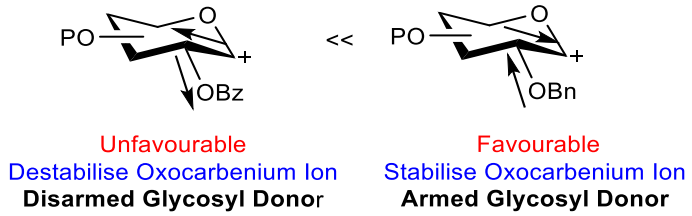



Figure 1.10 Disarm and arm glycosyl donor

### 1.5.1.3f Leaving Group

A wide range of substituents at the anomeric position has been reported as leaving groups in the glycosylation. The spatial arrangement of leaving group at *C*1 has lesser importance to stereochemical outcome.

### 1.5.1.4 Account of Glycosyl Donor

### 1.5.1.4a Glycosyl Halides

Historically, glycosyl chlorides and glycosyl bromides as glycosyl donors were introduced independently by Koenings-Knorr, Fischer and Armstrong wherein heavy metal silver salts such as $Ag_2O$, $AgCO_3$ and AgOTf are used as promoter with various alcohols. Zemplén *et al.*[53] and Helferich *et al.*[54] subsequently introduced organic soluble mercury(II) salts ($HgBr_2$, HgCN, and HgO) to enhance yield during the glycosylation in a significant manner. The Per-*O*-acetyl glycosyl iodides were discovered by Emil Fischer in early 20$^{th}$ century.[55] This donor has very limited shelf-life compared to the other halide donors. Gervay-Hague and co-workers demonstrated the ether protected glycosyl iodide is very reactive to render β-glycosides at very low temperature.[56-58] The glycosyl fluorides are known since 1923 and utilised as glycosyl donors by Mukaiyama in 1981.[59] There are various fluorophilic reagents developed to activate glycosyl fluorides such as $SnCl_2$-$AgClO_4$ (Mukaiyama *et al.*), $BF_3$•$OEt_2$ (Nicolaou *et al.*) and $SiF_4$ (Noyori *et al.*). Glycosyl fluorides are thermally more stable compared to other glycosyl halides.

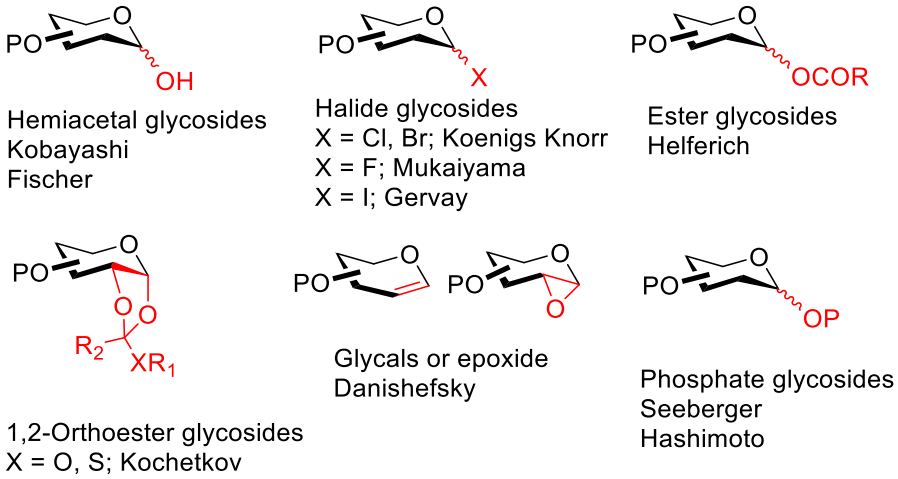



Figure 1.11 Early evolution of glycosyl donors

### 1.5.1.4b Thioglycosides

Introduced by Fisher[60] in 1909, the thiol functionality at the anomeric position is very stable towards broad range of protection-deprotection. Thioglycosides can be activated under mild reaction conditions often in an orthogonal fashion to other glycosyl donors. The per-*O*-acetate sugar substrate and thiols in presence of Lewis acids easily produce thioglycosides. Thioglycosides are activated by NIS-AgOTf/TfOH[61] and they can also be converted to other glycosyl donors viz. hemiacetals, sulfoxides, halides and imidates. Subsequently, many promoters are reported for the activation of thioglycosides e.g. $NOBF_4$, NBS/TfOH, $Br_2$/AgOTf, IDCP (iodoniumdicollidine perchlorate), $I_2$ or PhIO/$Tf_2O$.

### 1.5.1.4c Glycosyl Imidates

Pierre Sinäy in 1977 introduced novel *O*-imidate leaving group[62] and was further refinements led to trichloroacetimidate by Richard Schmidt.[63] The TCA donor can be easily synthesized from lactols and trichloroacetonitrile in presence of bases like $K_2CO_3$, DBU or NaH. To perform glycosylation, TCA donor can be activated by $BF_3$•$OEt_2$, TMSOTf or $Tf_2O$. The armed imidate donors are slightly less stable compared to their disarmed ones. Later on, Yu *et al.* brought *N*-phenyltrifluoroacetimidate donors which can be stored for longer time and activated by catalytic amounts of Lewis acid.[64]

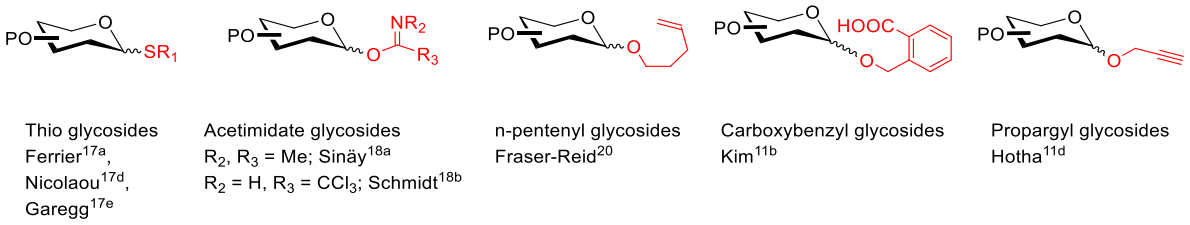
### 1.5.1.4d Glycals

Glycals are the important constituents in sugar chemistry and are utilised effectively in the synthesis of 2,3-unsaturated glycosides. Glycals are transformed into unsaturated glycosides in the presence of Lewis acids and the reaction is called as Ferrier reaction.[65] Substantial

modifications in electrophiles (e.g. NIS, PhSeCl, PhSCl, NBS and $I(col)_2ClO_4$) are reported to carry out the Ferrier reaction. Recently Wong and co-workers introduced a protocol for the synthesis of 2-fluorosugars from glycals by exposing them to Selectfluor.[66] Halcomb and Danishefsky achieved 1,2-anhydro sugar intermediate by treating glycals with DMDO, which is further utilised to assemble oligosaccharides and glycoconjuagtes using $ZnCl_2$.[67]

### 1.5.1.4e Glycosyl esters and 1,2-Orthoesters

Glycosyl esters act as donors and are activated by stoichiometric Lewis/Brønsted acids to afford glycosides.[68] The resultant stereoselectivity of glycosyl adducts is influenced by the promoter and solvents. The sugar orthoesters are first noticed by Pascu in 1945,[69] as side products during the Koenings-Knorr reaction.[70] Kochetkov *et al*. explored 1,2-*O*-alkyl orthoesters as donors using catalytic amount of $HgBr_2$ and *p*TsOH to furnish 1,2-*trans* glycosides in polar solvents like nitromethane and acetonitrile.[71] Wong group employed mannose 1,2,5-*O*-orthoester and demonstrated for α-mannosylation using $BF_3$•$OEt_2$.[72] Later on, replacement of the nucleophilic alcohol with various others were reported such as oximate orthoesters,[73] phosphate orthoesters,[74] fluoro orthoesters[75] and cyanoethylidene orthoesters.[76]




Thio glycosides
Ferrier[17a],
Nicolaou[17d],
Garegg[17e]

Acetimidate glycosides
$R_2$, $R_3$ = Me; Sinäy[18a]
$R_2$ = H, $R_3$ = $CCl_3$; Schmidt[18b]

n-pentenyl glycosides
Fraser-Reid[20]

Carboxybenzyl glycosides
Kim[11b]

Propargyl glycosides
Hotha[11d]

Figure 1.12 Second generation glycosyl donors

### 1.5.1.4f *n*-Pentenyl glycosides

*n*-Pentenyl glycosides were accidentally discovered by Bert Fraser-Reid[77] in late 1980s. During the activation by NBS or NIS of alkenyl alcohols led to the cyclization giving way to tetrahydrofuranyl oxonium moiety which upon nucleophilic attack by acceptor furnished desired glycosylated product. Hemiacetals and 4-penten-1-ol at elevated temperature in presence of Lewis acids afford *n*-pentenyl glycosyl donor. The electrophilic source for activation can be NBS, NIS, $I_2$, IDCP, NIS/TfOH or NIS/$Yb(OTf)_3$ etc. 4-Penten-1-ol can be also utilised for the synthesis of *n*-pentenyl orthoesters; another diverse donor system that can be further activated by above mentioned activators.

### 1.5.1.4g Glycosyl Phosphates and Phosphites

Over decades, several phosphorous based leaving groups were developed and they are classified based on the oxidation state of central phosphorus atom - phosphite glycosyl donors where oxidation state of phosphorous is +3 oxidation state whereas in phosphate glycosyl donors have +5 oxidation state. Phosphite donors are more reactive in comparison to phosphate glycosyl donors. Inazu group in 1985 introduced novel dimethylphosphinothioate glycosyl donors which were efficiently activated by stoichiometric amount of silver perchlorate.[78] Various trityl salts were also explored as catalysts to activate dimethylphosphinothioate donors such as $TrClO_4$, $TrBF_4$, and $TrSnCl_5$ and found to be suitable for the synthesis of oligosaccharides and glycoconjugates synthesis.

Schmidt and Wong groups concurrently introduced phosphite glycosyl donors in the early 1990's.[79] Wong group reported dibenzyl phosphite, whereas Schmidt group utilised diethyl phosphite and in both the cases phosphite leaving group departs in presence of TMSOTf. Schmidt group reported various *p*-derived phosphite donors included cyclic variants as well. Various promoters have been used to activate phosphite glycosyl donors such as TMSOTf, $BF_3$•$OEt_2$, $Sn(OTf)_2$, $ZnCl_2$, $HBF_4$, HOTf, $HNTf_2$ and $AgClO_4$.

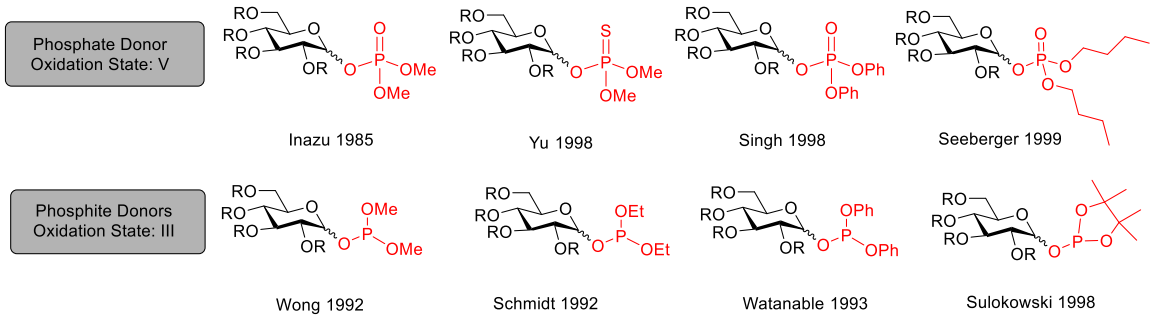



Figure 1.13 Example for phosphorous based glycosyl donors

### 1.5.1.4h Alkyne Glycosides

Activation of alkyne functionality using catalytic amounts started a new era in glycochemistry. From Hotha group, propargyl glycosides were activated in presence of 3-5 mol% of $AuCl_3$.[80] In this seminal report, benzylated donors were activated under catalytic conditions to afford disaccharides whereas donors containing benzoates did not react at all. Before that, propargyl ether functionality at C3 got catalysed Ferrier reaction in Au(III) condition to afford highly α-selective 2,3-unsaturated *O*-glycosides.[81]

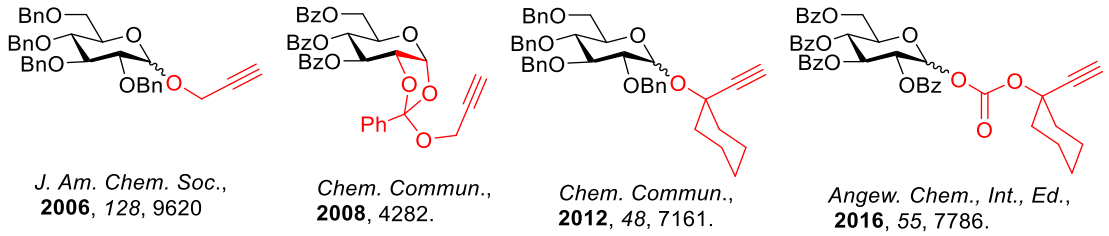



Figure 1.14 Alkyne based donors reported by Hotha group's

Shortly after this initial disclosure by Hotha and Kashyap, Yu and co-workers introduced *ortho*-alkynylbenzoates glycosyl donors[82] using $PPh_3AuOTf$ and demonstrated in synthesis N,N,N-trimethyl-D-glucosamine-chitotriomycin. In 2007, Hotha and co-workers developed propargyl 1,2-*O*-orthoesters as glycosyl donors and demonstrated high 1,2-*trans* selective disaccharides synthesis[83] $AuBr_3$ was found to be the efficient for higher yield of glycosyl adduct. In consideration of all effects in glycosylation events like solvents, temperature and protecting group, Hotha and co-workers found ethynylcyclohexyl glycosides are more reactive than propargyl glycosides by activating in the presence of silver salts like AgOTf or $AgSbF_6$ along with gold(III) halides at room temperature. In an exploration of the alkynophilicity of gold, the Hotha group in dominance to glycosylation reactions using alkynes systems showed a combination of ethynylcyclohexyl moiety and introduced alkynyl glycosyl carbonates[84] as stable glycosyl donors; catalytically activated them using 8 mol% each of Au-phosphite and AgOTf to afford disaccharide to oligosaccharides.

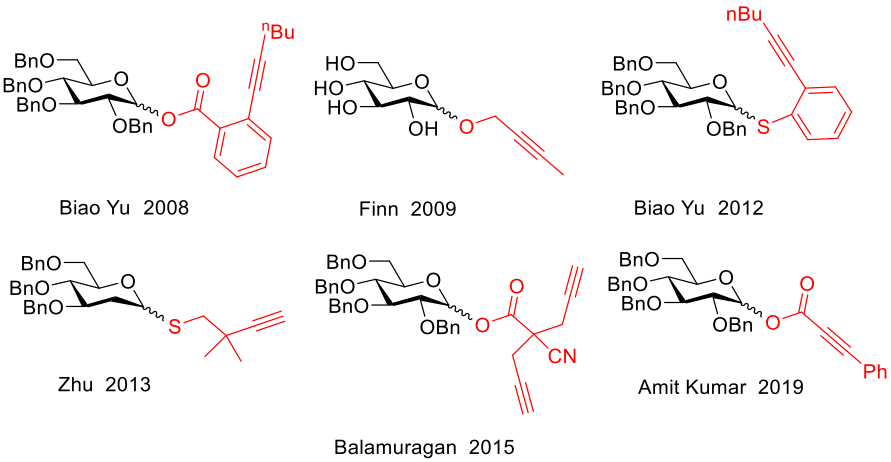



Figure 1.15 Alkyne system based glycosyl donor

### 1.6 Glycoconjugates and Its Biological Relevance

Glycoconjugates play important role in myriad of biological events between cells and other governing factors of biological phenomena.[85] As these glycoconjugates are structurally very

complex and hence, are encoded with biological messages on a single sugar unit. In 1965, Eylar proposed a hypothesis that carbohydrate portion in proteins acts as a "chemical passport" that receives signal for protein molecule for further biological actions.[86] These glycan components decide the fate of molecules. Generally, glycoconjugates are post-translational modifications; the biosynthesis happens in the cytoplasm of the cell. Mainly *N*-linked glycosylation occurs in the endoplasmic reticulum of eukaryotes and *O*-linked glycosylation in the Golgi apparatus.[87] Better understanding of their biological role requires synthetically defined scaffolds.[85] The non-sugar moieties are covalently attached to saccharides through various linkages like *O*-, *N*-,*S*-,C-, *P*- and rarely such as *O*-*N*, *N*-*O*.

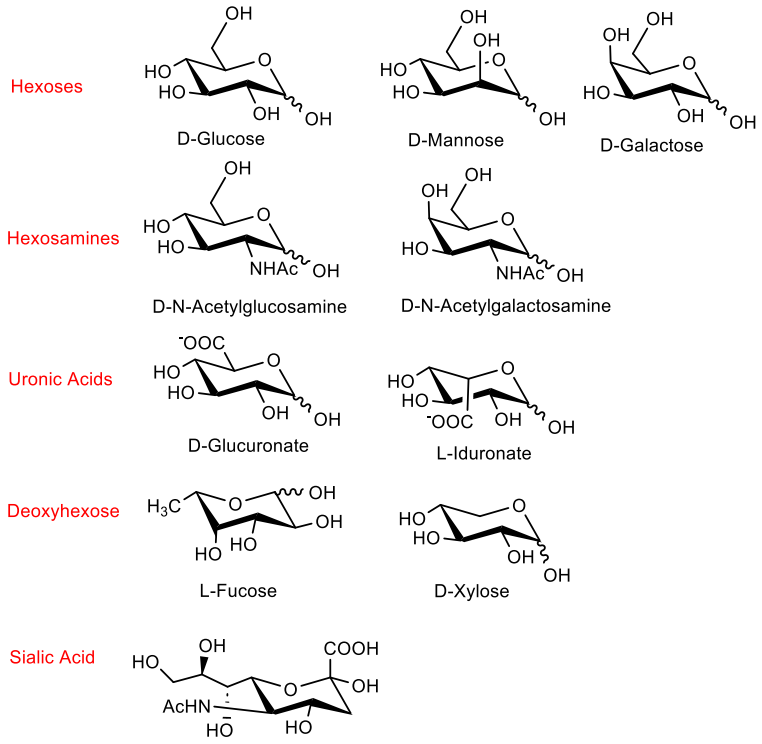



Figure 1.16 Common monosaccharides in human glycans

### 1.6.1 Proteoglycans[88]

Proteoglycans are constituents of extracellular matrices expressed by cells. These are the family of macromolecules which consist of protein at the core and to which various high molecular weight anionic glycosaminoglycan (GAG) chains are covalently attached. GAG chains consist of repeating disaccharide units along with sulfate groups to definite monosaccharides such as chondroitin sulfate (CS), heparin/heparan sulfate, dermatan sulfate (DS) and keratan sulfate (KS). The variable core protein structure and highly charged polyanionic GAG are widespread among numerous families of proteoglycans. These are essential for biological processes like

morphogenesis, inflammation, wound healing and in response to disease in multicellular organisms. PGs play important role in structural organization, cellular signalling, storage depots for cytokines and growth factors, skin and tendons tensile strength maintenance.

### 1.6.1.1 Glycosaminoglycans- Element of Proteoglycans (PGs)

Glycosaminoglycans (GAGs) are the repeating disaccharide units, which are negatively charged heteropolysaccharides. These repeating disaccharide units are composed of chemical linkages between amino sugar and uronic acid. Most of the GAGs form long unbranched chains containing 50-150 disaccharide units. Further these components are attached to a protein core in a very sequence specific manner via a carbohydrate-protein linkage through a tetrasaccharide (GlcA-Gal-Gal-Xyl) attached to the serine residue or glycoprotein like structure via a glycosidic bond. The

| Cellular Compartment | Proteoglycan | GAG | Biological Functions |
|---|---|---|---|
| **Extracellular** | Agrin<br>Testican-1 | HS | Act as lubricant agent<br>Major component of ECM<br><br>Biophysical role in tissue hydration<br><br>Modulation of growth factor-chemokine, cytokines<br><br>Creation of mesh network in between blood vessels, lymphatics, immune cell, pericytes and endothelial cells<br><br>GAGs as diagnostic tools and therapeutic agents<br><br>Co-receptors for growth factor signaling<br><br>Implicated in cell-cell and cell-matrix interactions |
| | Aggrecan<br>Brevican | CS | |
| | Biglyan<br>Decorin | DS | |
| | Fibromodulin<br>Keratocan | KS | |
| **Pericellular** | Perlecan<br>Collagen XV<br>Collagen XVIII | HS/CS/KS<br>CS/HS<br>HS | |
| **Intracellular** | Serglycin | HP, CS, DS | |
| **Cell Surface** | Glypican 1-6<br>Syndecan 1-4<br>Neuropilin 1<br>Phosphacan | HS<br>HS<br>CS<br>CS | |

Figure 1.17 Partial list of PGs, classification based on their location, GAGs element of PGs and various biological as well as biomedical applications

number of disaccharide units, their compositions and the sulfation patterns define GAGs classification. Five major classes of GAGs were recognized. These are mainly hyaluronic acid (HA), chondroitin sulfates (CSs), dermatan sulfate (DS), heparin (HP)/ heparan sulfate (HS) and keratan sulfate (KS). Among these GAGs, CSs has more abundance in body.

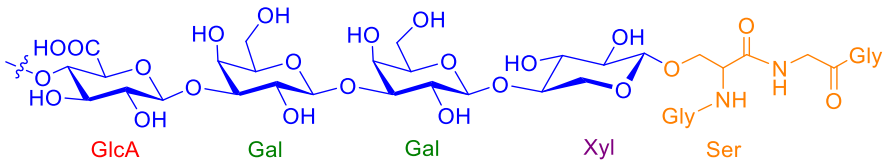



Figure 1.18 Tetrasaccharide common linker linked to proteins via serine residue[89]

The biosynthesis of GAGs is non-template driven and is a complex process that is initiated at Golgi apparatus. There is an addition of xylose residue through serine hydroxyl functionality on the protein core catalysed by xylosyltransferase XylT1 and XylT2 and for this process (UDP)-Xyl (uridinediphosphate) as a donor is utilised.

### 1.6.1.1a Hyaluronic Acid (HA)[90]

Karl Meyer and his assistant John palmer in 1934 isolated an unknown substance from cows' eye. Hyaluronic acid, specifically is a high molecular weight mucopolysaccharide. Natural biopolymer presents within all living things, mainly at extracellular, pericellular and intracellular matrix. HA shows biological activity in maintenance elastoviscosity of connective tissues like eye vitreous fluid and joint synovial fluid, balancing of tissue hydration and water transport, numerous receptor-based roles in mitosis, metastasis, migration, tumour development and inflammation. Remarkable amount of HA was found in kidney, muscles tissues, brain and lung as well. The disaccharide consists two sugar substrates - one is amino sugar *N*-acetyl-D-glucosamine and another uronic acid component is D-glucuronic acid. Both having an alternating β-(1→4) and β-(1→3) glycosidic linkages. HA is a polyanion, having linear repeating disaccharide structural linkage as $[(1\rightarrow3)\text{-}\beta\text{-D-GlcNAc-}(1\rightarrow4)\text{-}\beta\text{-D-GlcA-}]_n$.

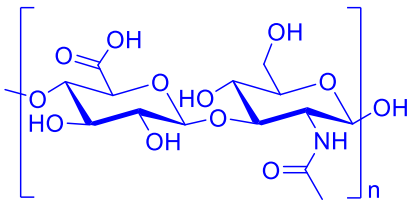
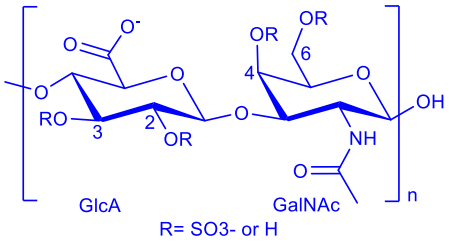



Figure 1.19 Chemical structure of HA

HA was isolated from many sources to study the biomedical and physicochemical properties and to understand the biological role of this polysaccharides. As HA having viscoelastic nature, non-immunogenicity and biocompatibility led its many clinical applications such as ministration in eye surgery, regeneration and healing of surgical wounds, joint fluid supplementation in arthritis. Hyaluronic acid is synthesized by hyaluronan synthases which are integral membrane proteins, in vertebrates there are three different types of enzymes - HAS1, HAS2 and HAS3. The activated (UDP=glucuronic acid, UDP-*N*-acetylglucosamine) nucleotide are used as substrates by hyaluronan synthase enzymes to synthesize unbranched polymers of aforementioned disaccharide (figure 1.19). The natural degradation of HA in mammals involves three types of enzymes as hyaluronidase(hylase), β-D-glucuronidase and β-*N*-acetyl-hexosaminidase. After catabolism of HA the degradation products shows pro-angiogenic properties i.e., high tissue permeability. Notably other GAG types show sulfate groups but HA doesn't show any other modifications.

### 1.6.1.1b Chondroitin Sulfate (CS)[91]

Chondroitin sulfates are polyanionic, unbranched polysaccharides and yet is another class of GAGs family. These glycoconjugates consist of repeating disaccharide unit, further disaccharide composed of D-glucuronic acid (GlcA) (uronic acid unit) and 2-acetamido-2-*deoxy*-D-galactose (amino sugar unit). Both units are arranged in an alternating sequential manner consisting of β-(1→4) and β-(1→3) glycosidic bonds. The structural polysaccharide pattern of CS is [(1→3)-β-D-GalNAc-(1→4)-β-D-GlcA-]$_n$.




A- GlcA-GalNAc(4SO3-)
C- GlcA-GalNAc(6SO3-)
D- GlcA(2SO3-)-GalNAc(4SO3-)
E- GlcA-GalNAc(4, 6SO3-)
K- GlcA(3SO3-)-GalNAc(4SO3-)
L- GlcA(3SO3-)-GalNAc(6SO3-)
M- GlcA(3SO3-)-GalNAc(4, 6SO3-)
R- GlcA(2, 3SO3-)-GalNAc

Figure 1.20 Chemical structure of CS & major subtypes

The polymerization of (1→3)-β-D-GalNAc-(1→4)-β-D-GlcA- disaccharide repeating unit gets unbranched during the lengthening of CS chains. The CS modified with sulfate groups often at *O*-2 and *O*-3 of GlcA and 4-O and 6-O positions of GalNAc. As a component of proteoglycan covalently attachment to single or more chains of CS to serine remnant of core protein via (D-GlcA-β-D-(1→3)-galactose (Gal)-β-D-(1→3)-Gal-β-D-(1→4)-xylose (Xyl)) a tetrasaccharide

linker and such macromolecules are referred as CSPGs, which are present in all animal cells in extracellular matrices. There are numerous enzymes involved to the biosynthesize CSPGs which occur at Golgi compartments. Here, UDP-GlcA and UDP-GalNAc are utilized as active donors for polymerization. So overall pathway makes more diverse structures of CS and having eight different combinations of modified disaccharides (figure 1.20). CSPGs and CSs are involved in many biological events as cell behaviour regulation, intercellular signalling, inflammation and amyloid plaque formation. The various sulfation patterns also have importance in biological functions such as neuronal stimulations.

**1.6.1.1c Dermatan Sulfate (DS)**

Dermatan sulfate (DS) is another family member of GAGs which is structurally very complex having variant sulfate patterns and unbranched polysaccharides. Both CS and dermatan sulfate (DS) have structural similarity to subfamily called galactosaminoglycans. Such glycosaminoglycans attached to protein core form a macromolecule called as proteoglycan. These PGs are localized at extracellular matrix as well as on cell surfaces.[92a] DS is also designated as chondroitin sulfate B (CS-B), which is composed of unbranched biopolymers of disaccharide units having a hexosamine, GalNAc and uronic acid, glucuronic acid (GlcA) linked by β-1,4 or -1,3 glycosidic bonds. The presence of GalNAc residue in DS is referred as chondroitin sulfate. IdoA has special role for site selection and high amount of IdoA containing GAGs responsible to inhabit the normal fibroblasts proliferation than the GAGs have higher GlcA content.[92b] Variable percentage of IdoA residues within polysaccharide chain of DS instead of GlcA, in which the unmodified portions[(1→3)-β-D-GalNAc-(1→4)-β-D-GlcA-] cause the microheterogeneity in DS polysaccharide chain. The carbohydrate sulfotransferases transfer the sulfate group at C-4, C-6 position of GalNAc as well as to a lesser extent to C-2 of IdoA.[92c]

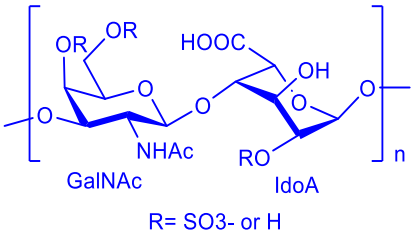



Figure 1.21 Major disaccharide unit in DS chain

Dermatan sulfate is found in connective tissues like tendon, skin, blood vessels, muscle, cartilage and bone. These biomolecules have active role for lipid metabolism, acceleration of heparin cofactor II to inhibition of thrombin, regulate the enzyme activity, molecular signalling

response to wounding, infection and tumorigenesis, and show biological response with respect to growth factors chemokines and cytokines.[92d]

### 1.6.1.1d Heparan (HP) & Heparin Sulfate (HS)[93]

Heparin sulfate (HS) is generally found in extracellular matrix as well as on the cell surfaces of animal cells playing key role in various biological functions like lipid metabolism, controlling angiogenesis, blood coagulation, inflammatory responses and tumour metastasis. HS is composed of repeating disaccharide unit with 1→4 alternating linkage of α-D-glucosamine with α-L-iduronic acid or with β-D-glucuronic acid. Also, per disaccharide unit of HP, 2.6 sulfate groups are present in an average where as in HS 0.6% sulfo group per disaccharide unit. The positions of IdoA, GlcA and sulfation patterns within chains of HS and HP have profound role in biological activity.

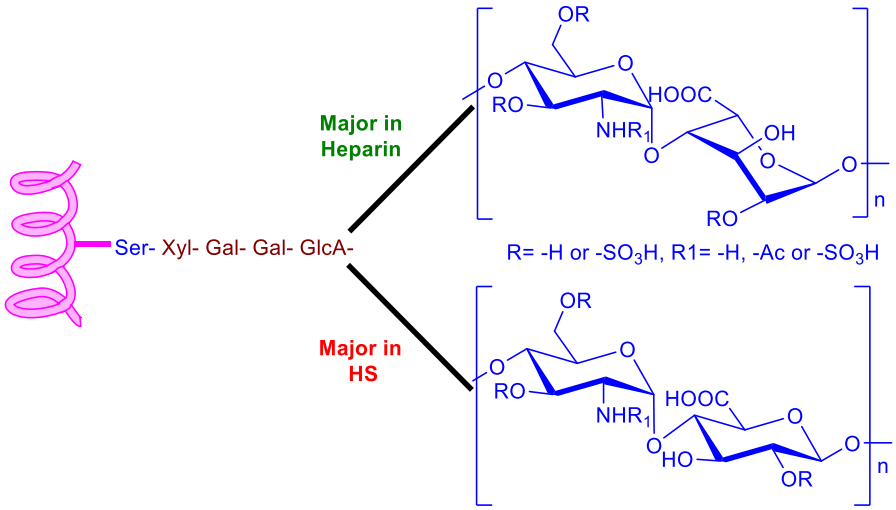



Figure 1.22 The disaccharide repeating units in heparin and HS with common tetrasaccharide linker

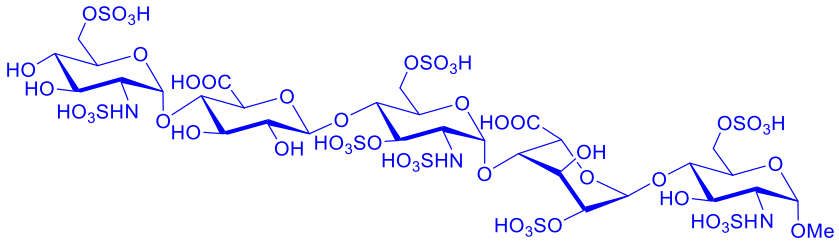


Figure 1.23 The chemical structure of ULMWH, pentasaccharide, fondaparinux with sulfated group

Over the century, heparin has become the first choice for controlling blood coagulation and in the treatment of arterial thrombotic disorders. The pentasaccharide sequence in heparin chain binds to Serpin AT, there is a formation of AT-heparin complex which prevents blood clotting.

Heparins are further classified into three types: (1) unfractionated heparin (UFH, average molecular weight 17000 Da, (2) low molecular weight heparin (LMWH, average molecular weight 3500-6000 Da, (3) ultralow molecular weight heparin (ULMWH, $MW_{avg}$ higher than 2000 Da). The UFH is further depolymerisation to prepared the LMWH, having longer half-life, and is used in the treatment of heparin-induced thrombocytopenia (HIT). ULMW heparins are synthetic products, showing high reduction risks to HIT and have five to ten saccharide moieties and one of the clinically approved ULMW heparin is the fondaparinux (figure 1.23) which is a pentasaccharide.

### 1.6.1.1e Keratan Sulfate (KS)[94]

Keratan sulfate is composed of unbranched polymer of lactosamine consisting of a repeating disaccharide unit having linkage as -3Galβ1→4GlcNAc6Sβ1- and both hexoses at the C6 position are functionalized with sulfates by galactose 6-*O*-sulphotranferase and *N*-acetyl glucosamine 6-*O*-sulfotransferase. Such sulfated glycosaminoglycans are found specially in bone, cartilage and cornea. KS chains present within proteoglycans are attached to core protein as in lumican, mimecan, keratocan, fibromodulin and aggrecan.

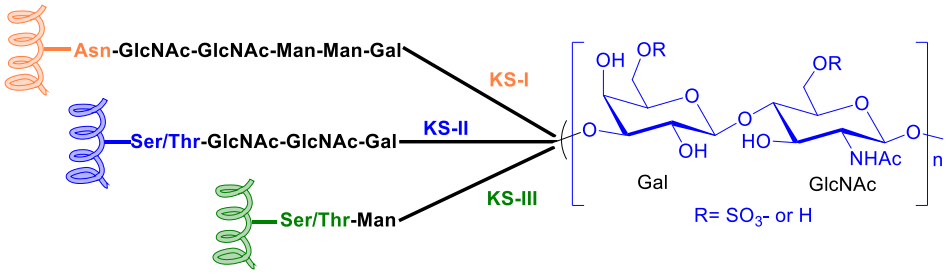



Figure 1.24 Chemical structure of KSI, KSII, KSIII

The designations as KS-I and KS-II are originally based on kind of tissue source from which KSs are isolated viz. KS-I from cornea whereas KS-II from cartilage. Corneal keratan sulfate found in embryonic lung, liver as well as in cornea, which is *N*-linked to core protein through Asn residue whereas KS-II consists *O*-linkage to core protein through Ser- or Thr- residues. So currently the class designations not on tissue types but the associated structural linkage (figure 1.24) and the third type KS-III is mainly found in brain tissue. All such variant KSs are important to maintain the hydration level of various tissues and have applications as lubricant agent in treatment of arthritis.

## 1.7 Glycopeptides/Glycoproteins[95]

Glycoproteins and glycopeptides are a class of biomolecules where the amino acid residue of the protein chain covalently links to oligosaccharides. These are the co-translational or posttranslational modifications. Most of the secretory proteins are often glycosylated such as toxins, hormones, and enzymes belonging to such a class of biomolecules. It's recognized that such biomolecules have been playing various vital roles in biological events. They have a key role in the immune system, inflammation, endocrine system, brain development, hormonal activities and fertilization. Such glycoconjugates which are present on cells' surfaces their glycan moiety of host cells are employing the pathogen entry i.e.in response to pathogen invasion. The correct glycosylation pattern is important for protein folding if not then the process of protein expulsion will fail. However, glycans are also important for tertiary structure and prevent proteolysis.

As aforementioned glycoproteins and glycopeptides are fundamental for various biological events. Their expression with cell envelope as heterogeneous mixtures. During the biological events tracking the actual biosynthetic pathway is quite challenging. However, the biosynthesis of proteins is genetic control but for the glycan portion biosynthesis is not templet driven. Such glycan residue synthesis is subjected to glycosyltransferase, glycosidase and other enzymes. The overall posttranslational process forms a mature glycan structure called 'glycoforms'. The glycoprotein or glycopeptide has the same protein backbone but various sites of glycosylation and different oligosaccharide units, which lead to mixtures of glycoforms. So, it's a hard job to know the structural and functional relationships of such biomolecules. Therefore, need to develop alternative sources for homogenous glycoconjugates.

### 1.7.1 Assembly of Glycopeptides/Glycoproteins[96]

Broadly speaking, glycopeptide and glycoprotein are synthesized in nature by covalently attaching peptide chains mostly through asparagine for *N*-linkage or the *O*-linkage via serine or threonine amino acid residues of the chains. Rarely, glycans are attached as *P*-glycosylation through phosphorus, *S*-glycosylation via cysteine amino acid residue and in *C*-glycosidic linkage by direct carbon addition of tryptophan to sugar unit.

#### 1.7.1.1 Strategies to Form Glycosidic Linkage

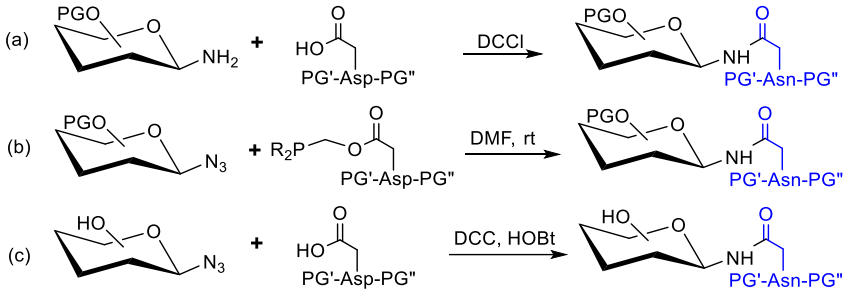
In Nature, mostly *N*-(Asn) and *O*-(Ser/Thr) glycosidic linkages are prevalent for the conjugation of glycan to the protein. For *N*-linkage majority motifs are GlcNAcβ-Asn and for

*O*-linkages GlcNAcβ-Ser/Thr or GalNAcα-Ser/Thr, though there are some unusual linkage such as GlcNAc-α-Asn,[97a] Glc-Asn,[97b] Rha-Asn,[97c] GalNAc-Asn[97d] and Man-α-Ser/Thr.[97e]

### 1.7.1.1.1 Formation of Natural Linkages

#### 1.7.1.1.1a N-Linked Glycans

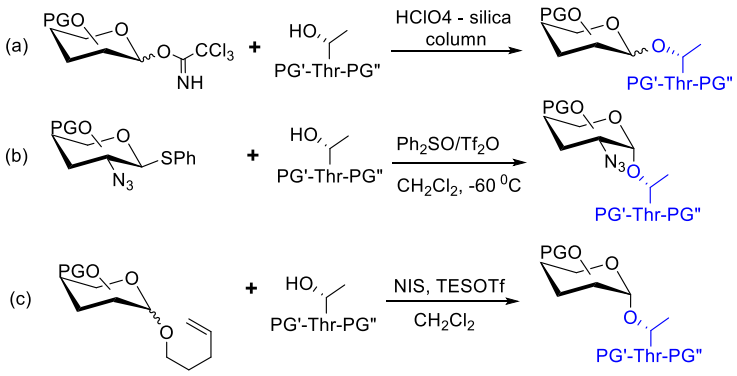
The most common synthetic route for *N*-glycosylation is the reaction of protected or deprotected glucosamine with suitably protected Asp derivatives (Scheme 1.8a) via an amidation reaction.[98] Staudinger reaction is yet another choice for the asparagylation wherein Asp side chain carboxyl derivative are coupled to glycosyl azides in the presence of $PPh_3$ to afford β-Asn *N*-glycosides (Scheme 1.8b). Recently, Kiessling group reported Staudinger ligation to get *N*-glycosides using glycosyl azides and asaparagine derived phosphinothioesters.[99] The deprotected sugars utility for expanded Staudinger reaction has been reported by the Davis and co-workers (Scheme 1.8c).[96]




Scheme 1.8 Methods for N-Linked Glycopeptide Synthesis

#### 1.7.1.1.1b *O*-Linked Glycans

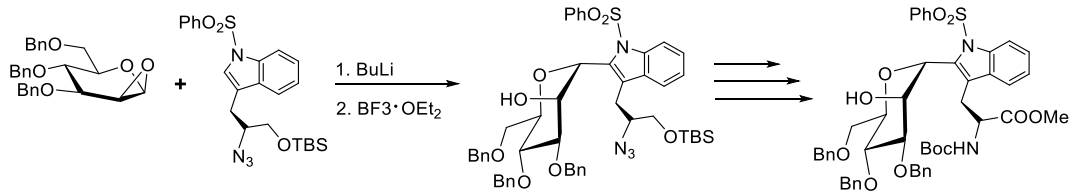
Installation of desired protected Ser- or Thr- through hydroxyl group was accomplished by using various glycosyl donors.[100,101] The Lewis acid catalysed activation of TCA has been done by Field and co-workers to afford *O*-glycosides (Scheme 1.9a).[102] Thioglycosides are also explored using a promoter $Ph_2SO/Tf_2O$ by Boons group in stereospecific antigen preparation (Scheme 1.9b).[103] For *O*-glycopeptide synthesis use of *n*-pentenyl glycosides are also reported (Scheme 1.9c).[104]



Scheme 1.9 Methods for O-Linked glycopeptide synthesis

### 1.7.1.1.1c C-Linked Glycans

The incorporation of *C*-glycosylated amino acids to different glycoproteins has been reported. Ito and co-workers showed such incorporation to afford *C*-glycoside using a 1,2-anhydromannosyl donor and tryptophan substrate (Scheme 1.10).[105]

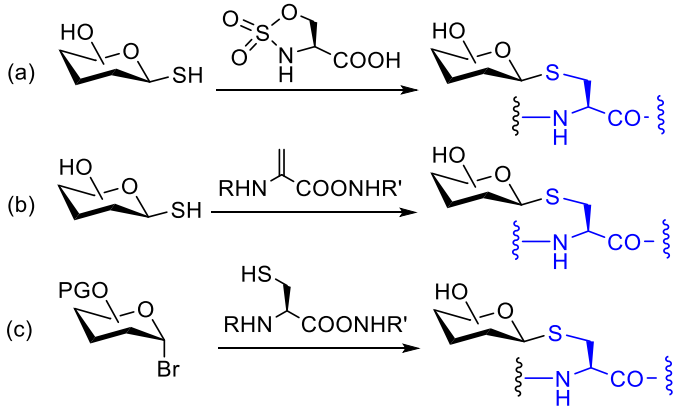



Scheme 1.10 Ito's C-mannosyl tryptophan synthesis

### 1.7.1.2 Synthetic Unnatural Linkage Approaches

### 1.7.1.2a Methods for Thioester Glycans

There are many methods for the synthesis of the unnatural glycan peptide linkages. Some of them are restricted to peptide systems only and few allow attachment of longer protein systems as well. The reaction of thiohexoses with serine-derived sulfamidate for *S*-linked glycans in an aqueous medium is a good example in this direction (Scheme 1.11a).[106] In another method, the peptide mimics by Michael addition of differently protected as well as unprotected thiosugars to dehydroalanine in a small peptide system has been reported recently (Scheme 1.11b).[107] The glycosyl bromides utilisation for *S*-glycan attachment to peptides has been reported by Schmidt and co-workers (Scheme 1.11c).[108]

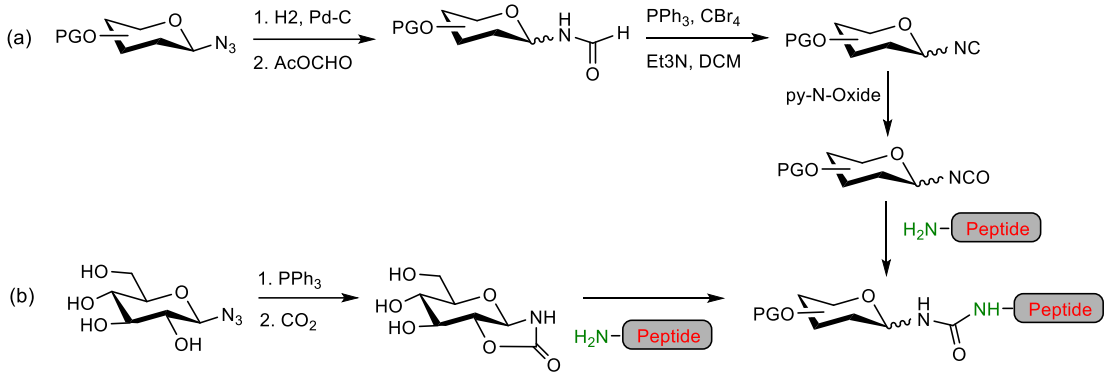



Scheme 1.11 Methods for thioester linked glycopeptide synthesis

### 1.7.1.2b Methods for Unnatural *N*-linked Glycopeptide

The oxidation of isocyanides to anomeric formamides to afford the glycosylisocyanates which can further react with amines to give urea is yet another method for the conjugation of glycosyl amino acids to peptides (Scheme 1.12a).[109,110] Another method in which Steyermark's

glucopyranosyl oxazolidinone was used successfully to get amino acid conjugates in water (Scheme 1.12b).[111] Oxazolidinone synthesized from glycosyl azide in presence of $PPh_3$, $CO_2$ and further treated with cysteine or lysine containing peptides to afford urea-tethered glycopeptides.




Scheme 1.12 Synthesis of unnatural N-linked glycopeptide

### 1.7.2 Assembly Tactics

#### 1.7.2.1 Linear Assembly

These strategies mostly are concerned with the SPPS methodology - best example is the synthesis of HIV-1 V3 domain having two GlcNAc residues.[112] Kajihara and co-workers employed this strategy for the preparation of sialylglycopeptide CTLA-4, **(**figure 1.25).[113]

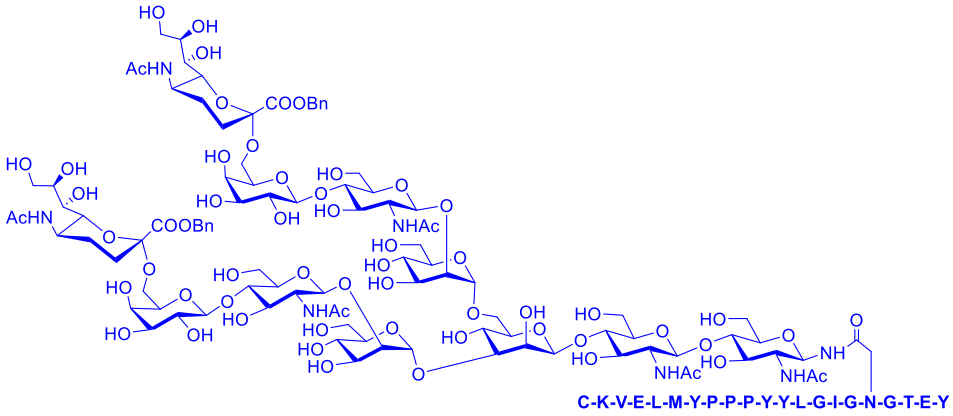
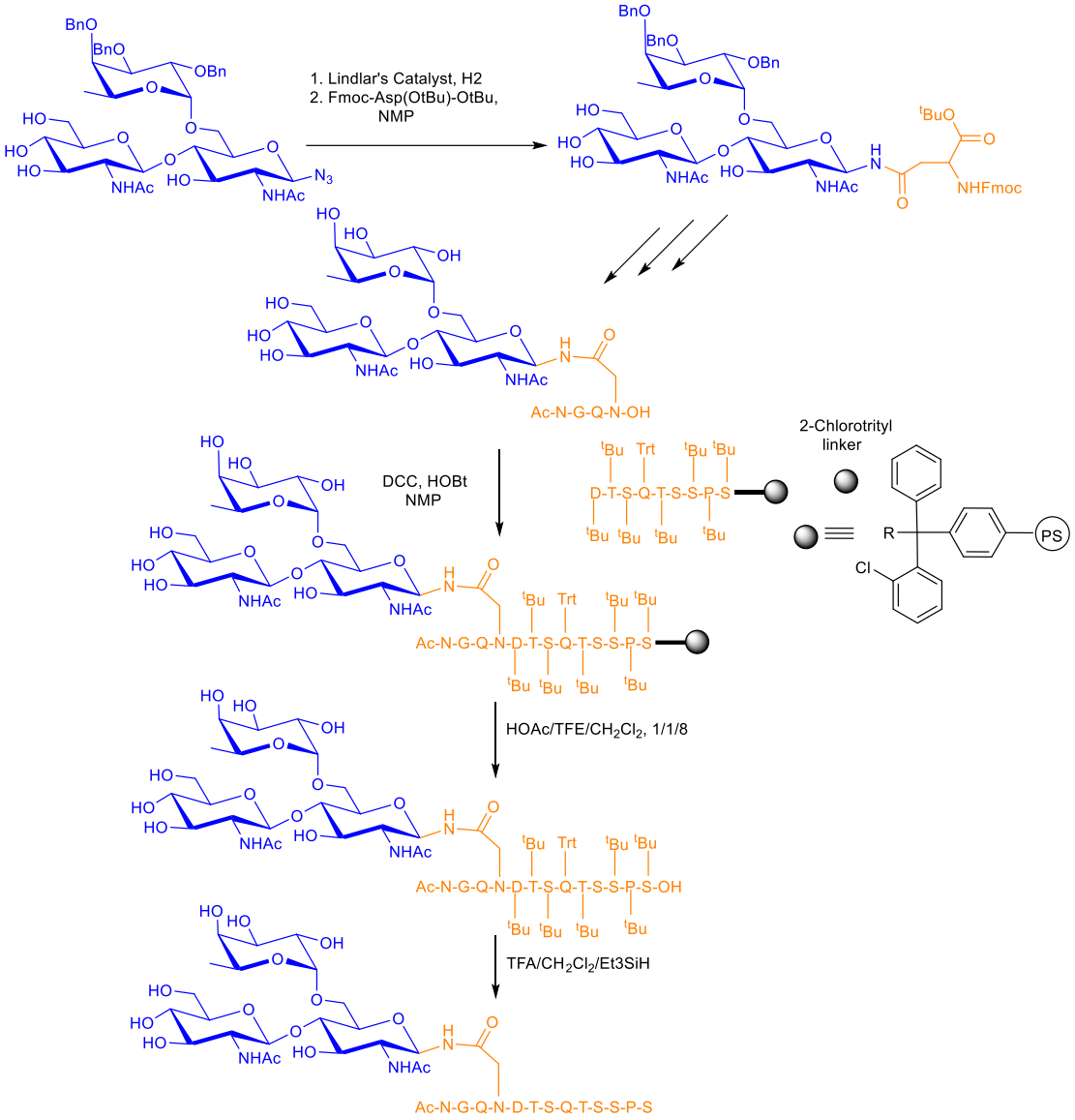



Figure 1.25 Intermediate for synthesis of CTLA-4 [113]

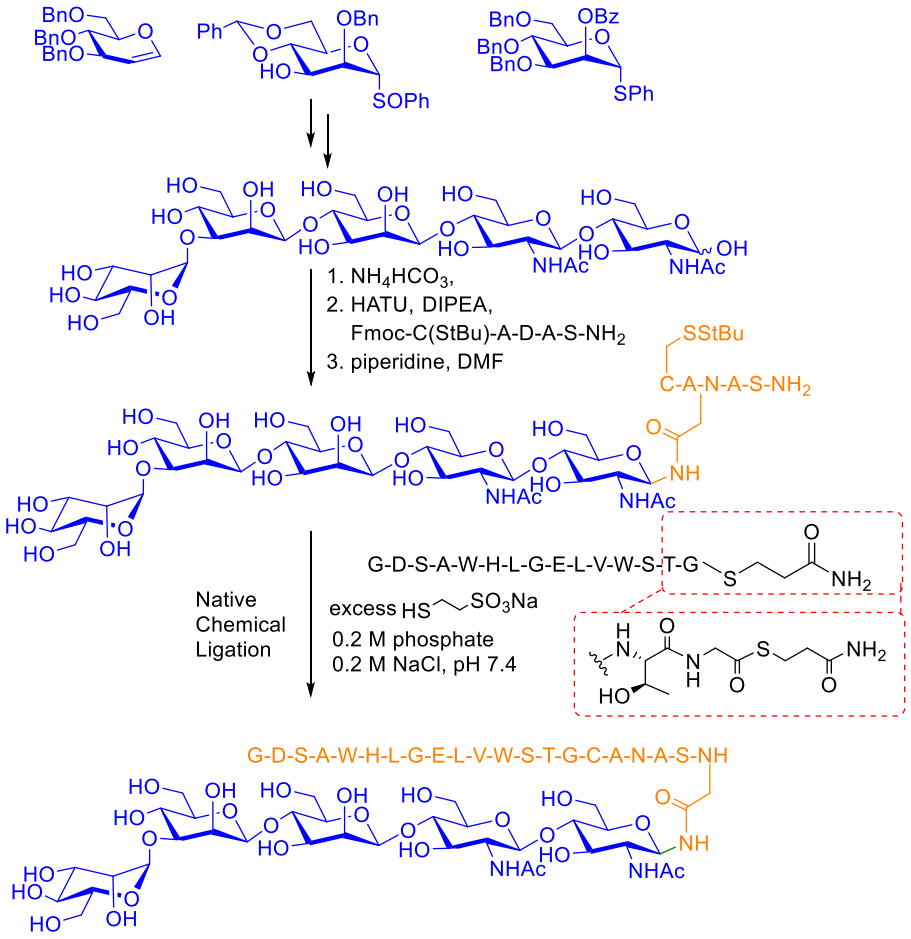
One more report by Guo and co-workers is concerned with the synthesis of a GPI anchor CD-52 glycopeptide which is expressed mostly on human lymphocytes and sperm cells (Scheme 1.13).[114] The coupling of Asp residue of peptide chain with oligosaccharide amine in the presence of coupling reagent DCC/HOBT formed *N*-glycan. The HBTU-mediated coupling by convergent strategy has been reported by Lansbury and co-workers to prepare GlcNAc glycosylamine[115] or $Man_5(GlcNAc)_2$[116] to synthesize CD-52.




Scheme 1.13 Synthesis of a CD-52 Glycopeptide by Guo et al[114]

### 1.7.2.2 Convergent Assembly

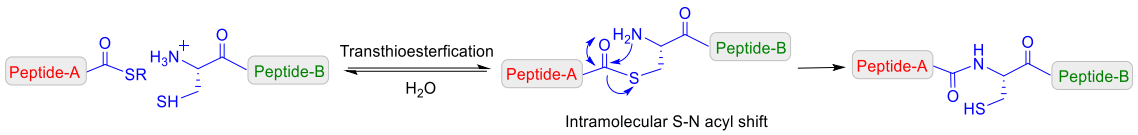
In the convergent approach for glycopeptide synthesis, direct peptide glycosylations showed low yields in comparison to the linear strategy; but with this limitation, aspartate carboxylate residue of pentapeptide was utilized to prepare Asn-linked *N*-glycan glycopeptide. Danishefsky and co-workers developed this strategy to synthesize prostate-specific antigen (Scheme 1.14).[117]




Scheme 1.14 Danishefsky's 'Universal' Approach for Synthesis of N-Linked Complex Glycopeptides

### 1.7.2.2a Native Chemical Ligation Assembly

Native Chemical Ligation is a heavily investigated technique for the glycopeptide synthesis.[118] In an SPPS strategy, peptide chains up to 50 amino acid residues can be synthesized easily; and it is not a sufficient technology for the glycoprotein syntheses. In 'Native Chemical Ligation' coupling of *N*-terminal cysteine residue of one peptide fragment is treated with *C*-terminal thioester of another peptide fragment (Scheme 1.15). This ligation proceeds through transthioesterification followed by intramolecular S→N acyl migration. This migration is an irreversible and spontaneous process to form the new native peptide bond. Kent and co-workers in 1990s introduced this methodology for protein synthesis.[119] The ligation proceeds with unprotected fragments in aqueous medium thereby growing its application for the glycoprotein synthesis.




Scheme 1.15 Mechanistic Way of Native Chemical Ligation (NCL)

This NCL approach has been utilised by many groups to synthesize their glycoprotein. Of them, Danishefsky's efforts to synthesize the highly mannosylated fragment of HIV viral protein gp120 (figure 1.26) is noteworthy.[120]

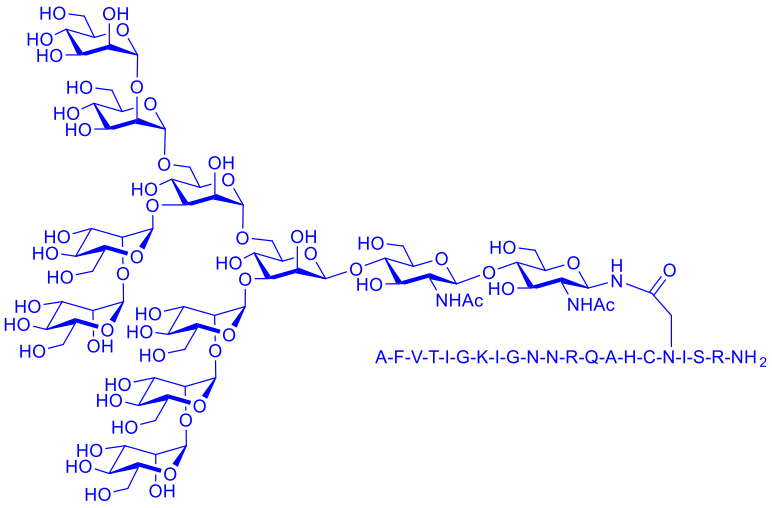


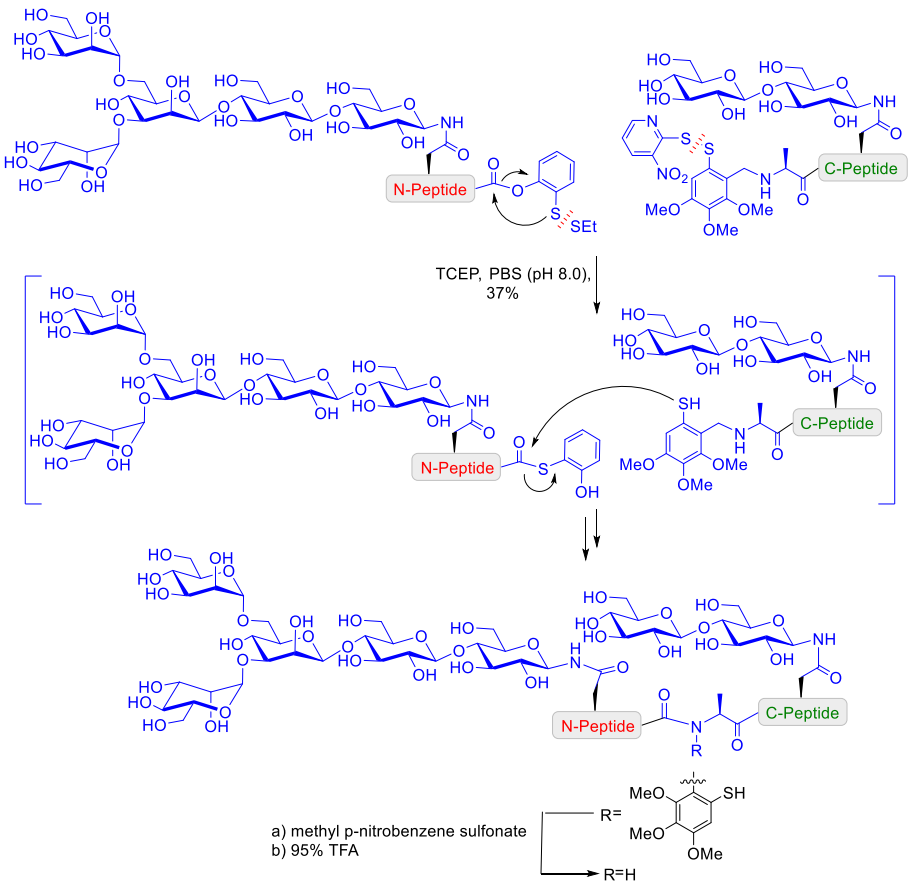

Figure 1.26 Highly mannosylated fragment of HIV viral protein gp120

### 1.7.2.2b Auxiliary Assisted Ligation

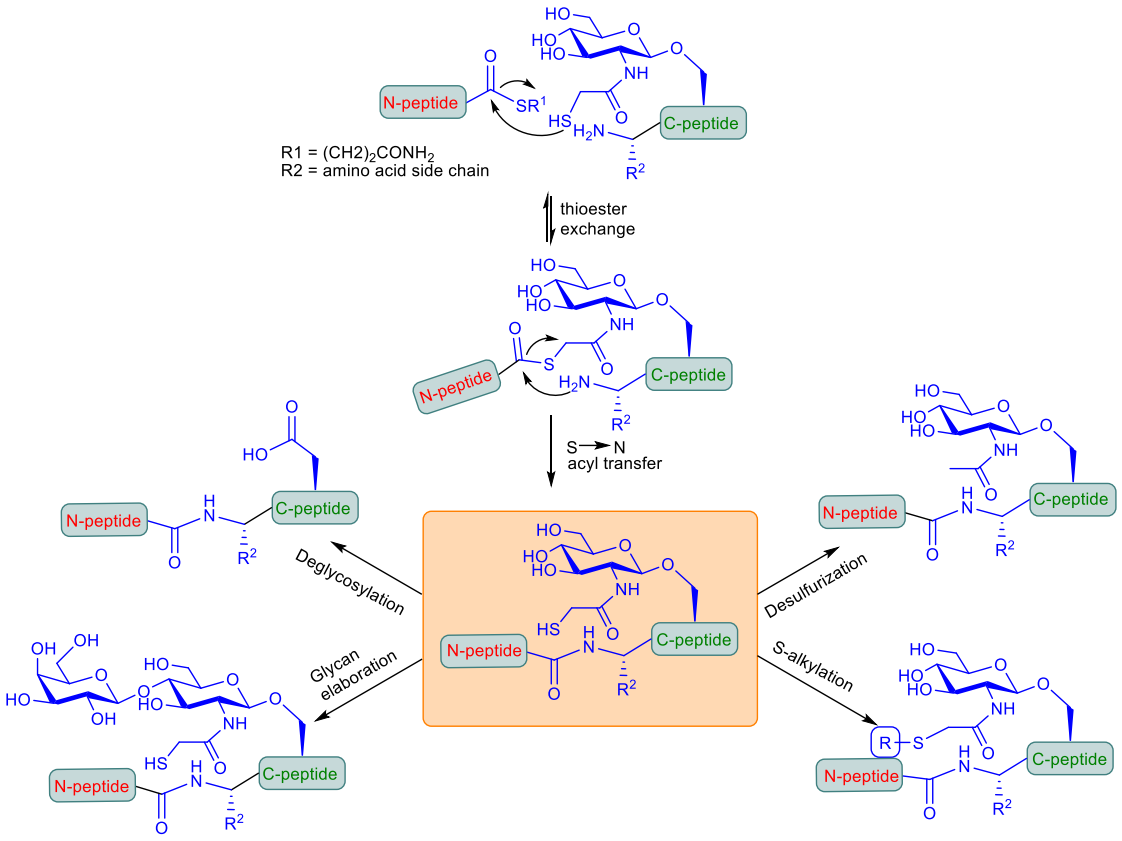
The NCL-based strategy has broad applications in glycoprotein synthesis but the major drawback is the necessity of the N-terminal cysteine residue. To overcome this limitation various methods have been developed by recruiting the thiol auxiliaries which can be removed after NCL.[121] In this method, cysteines are used first for NCL and then desulfurized to afford the alanine.[122] Various methods have been developed for the incorporation of thio-amino acids into the NCL-based strategy[123] for example thiovaline, thiolysine and thiophenylalanine are explored. Some of the nonamino acid auxiliaries are also demonstrated for glycopeptide synthesis. For example, Danishefsky group developed a thiol-based auxiliary-assisted strategy while synthesizing the glycopeptide (Scheme.1.16)[121f] using 4,5,6-trimethoxy-2-mercaptobenzyl auxiliary for the synthesis of bifunctional glycopeptide.

In one more example of auxiliary assisted ligation, thiol auxiliary is attached to the sugar moiety. Such sugar-assisted ligation (SAL) was demonstrated by Wong and co-workers in the

synthesis of glycopeptides. A glycosyl amino acid containing thiol auxiliary has been synthesized by SSPS in such way that it is near to the ligation site, where the formation of amide bond with proximate peptide ester (scheme 1.17).[121g] After completion of ligation, thio sugar can be removed in presence of PNGase or further can be reduced to the natural unit.




Scheme 1.16 Auxiliary-Assisted Ligation[121f]



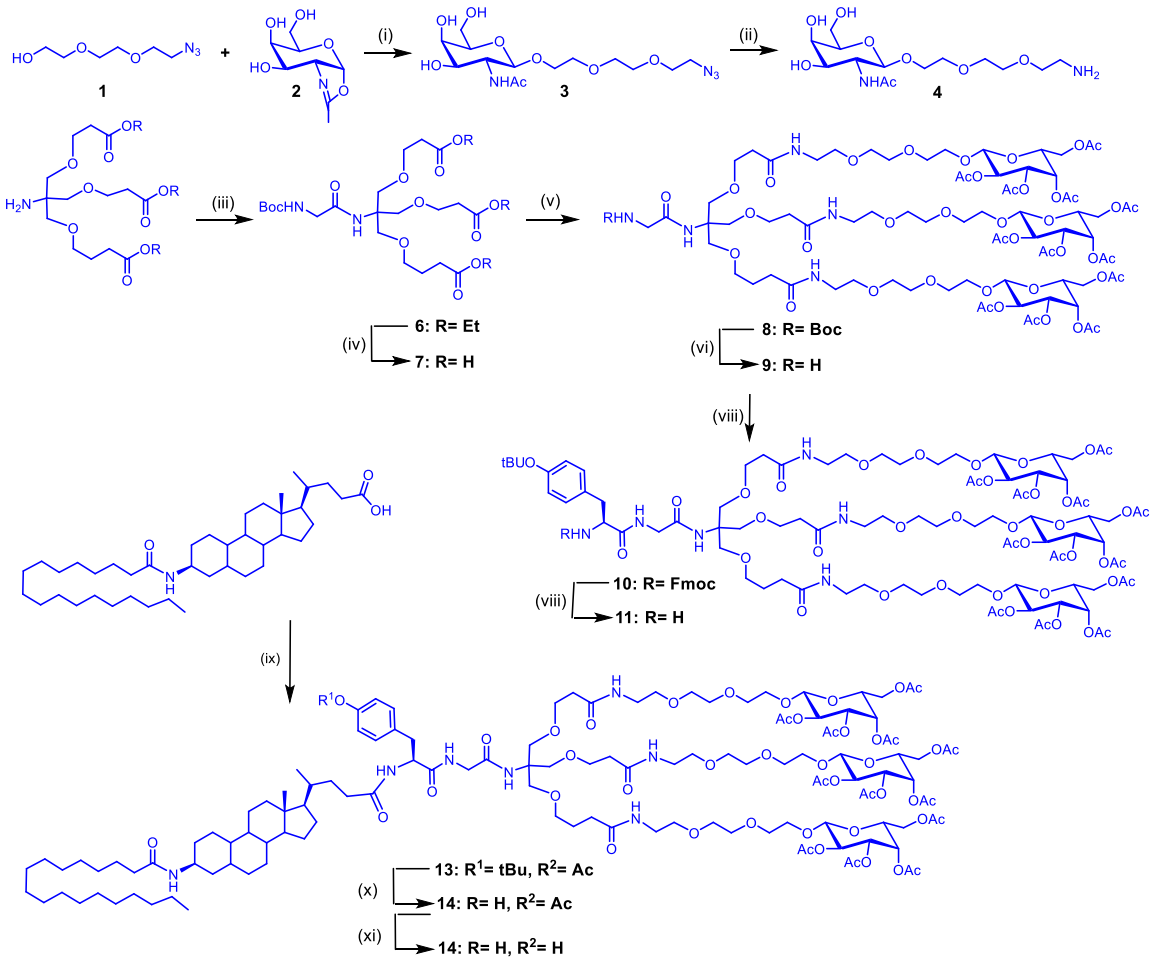

Scheme 1.17 Sugar-Assisted Ligation (SAL)[121g]

## 1.8 Glycolipids

These are the glycoconjugates which containing covalent bonds between sugar units and lipids. They are amphiphilic in nature and self-insert to cell membrane. As a constitutional part of the cell membrane, they impart stability to the cell membrane. Such glycoconjugates are associated with many cellular functions such as intracellular trafficking, signal transduction and cellular interactions. The glycolipids containing one or more monosaccharides with hydrophobic membrane anchoring compounds are known as acylglycerol, a sphingoid, or a ceramide. So primary classification of glycolipids depends on the aglycone part. The glycoglycerolipid is a glycolipid that contains one or more glycerol residues. Most of the plant and bacterial glycolipids have glycerol-containing glycolipids. Glycosphingolipids (GSLs) contain a sphingoid or a ceramide and they are mostly abundant in animal cells. One more glycolipid family is the glycophosphatidylinositols (GPIs) which contain saccharides that have covalently linkages with the inositol moiety of phosphatidylinositol. As many techniques that are developed for the synthesis of glycoprotein/glycopeptide are also useful for the synthesis of glycolipids as well.[124]

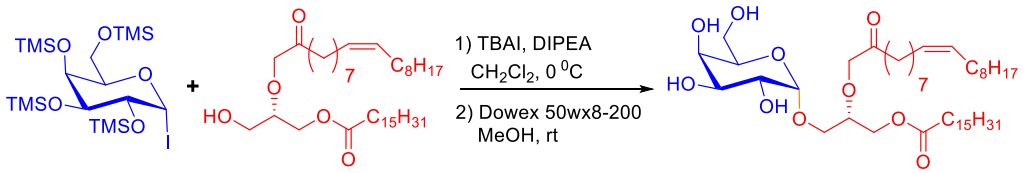
Recently, cholesteryl 6-*O*-acyl-β-D-galactopyranoside (ACGal) has been synthesized chemoenzymatically by Stubs and co-workers.[125] For such β-glycoside synthesis, TCA donor has been used. The regioselective coupling of primary hydroxyl group of galactose with palmitic acid in the presence of coupling reagent failed. However, enzymatic coupling of acyl transfer reagent (acetone oxime esters) with 6-hydroxyl group of galactose afforded moderate to low yields. Rensen and co-workers have reported a novel route for the synthesis of *N*-acetylgalactosamine based glycolipid that has affinity towards asialoglycoprotein receptor (ASGPr).[126] Utilization of sugar oxazoline donor chemistry for the glycosylation and using TBTU/HOBt as a coupling reagent demonstrated glycolipid synthesis (Scheme 1.18).

Glycosphingolipids (GSL) are prevalent very widely from bacteria to man cell membranes. There are ten different types of ceramide molecules which linked to glycans thereby making them structurally diverse compounds and have different specific biological functions as well. The main hurdle in this synthesis is the stereochemistry at the anomeric position of the aglycone moiety. Extensive protection and deprotection are invoked to afford desired stereo and chemo selectivity but they minimise synthetic efficiency. Few common glycosyl[127] donors are used for GSL synthesis such as trichloroacetimidates, fluorides, Phosphites, bromides and thioglycosides. Along with all these efforts Du and co-workers[128] utilized per-*O*-silylated galactosyl iodide to demonstrate the stereospecific α-glycosylation with lipid components with no extra functional group manipulations (Scheme 1.19). This method is further used to synthesize α-galactosylceramide analogues and other biologically important glycoconjugates.



Reagents: (i) TMSOTf,58%; (ii) $PPh_3$, THF, 49%; (iii) BocGlyOH, BOP, DiPEA, 93%; (iv) aq NaOH, dioxane, 100%; (v) 4, HOBt, PyBOP, DiPEA, DMF; (vi) TFA/$CH_2Cl_2$ 1:4, 100% (vii) FmocTyr(tBu)OH, TBTU, HOBt, DiPEA, DMF, 70%; (viii) 20% piperidine/DMF, 75% (ix) TBTU, HOBt,. DiPEA, DMF, 80%; (x) $CH_2Cl_2$/TFA, 100% and (xi) NaOMe, MEOH, 90%

Scheme 1.18 Rensen and co-workers synthesized a glycolipid (3β-(oleoylamino)-5β-cholanoyl)-Tyr-Gly-tris $(GalNAc)_3$ p[126]



Scheme 1.19 Du and co-workers synthesized α-galactosylceramide analogues[128]

## 1.9 Conclusions and Outlook

Peptide chemistry and carbohydrate chemistry have received significant attention for more than a century. However, the total synthesis of bioactive glycoconjugates and their analogues is still a difficult challenge and is not routine. Extensive protection and deprotection steps are necessary in spite of several elegant methods for glycosylation. The structurally complex targeted molecules have opened new opportunities for synthetic chemists to develop new

glycosylations as well as new synthetic strategies. Stereochemical incorporation of an acceptor or an aglycone at the anomeric position still is challenging. Functional group interconversions, reagents for protection and deprotection are still very expensive. Chemoenzymatic strategy addresses some of the lacunae, but their availability, low yields under high dilutions makes them cumbersome. Hence, the chemical approaches give more flexibility to researchers in comparison to biological models. The microwave assisted reactions have shortened reaction times and improved reaction yields. Still there is scope and need to develop a new synthetic strategy for the synthesis of glycoconjugates in large scales.

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# Chapter 2

## Synthesis of Conjugation Ready Heptamannopyranoside Immunogenic Epitope

# Chapter-2

## 2.1 Introduction

Tuberculosis (TB) has been around for more than a millennium and is still a significant health issue worldwide; with the entry of human immunodeficiency virus (HIV), Tb was identified as the top ten major causes of fatalities caused by a single infectious agent. According to the World Health Organization's Tuberculosis Report 2018, TB killed an estimated 1.3 million HIV-negative humans in 2017 and killed an additional 300,000 HIV-positive patients. India is the top country among the top 30 countries with the highest TB case load with 64 percent of all new TB cases (Figure 2.1).

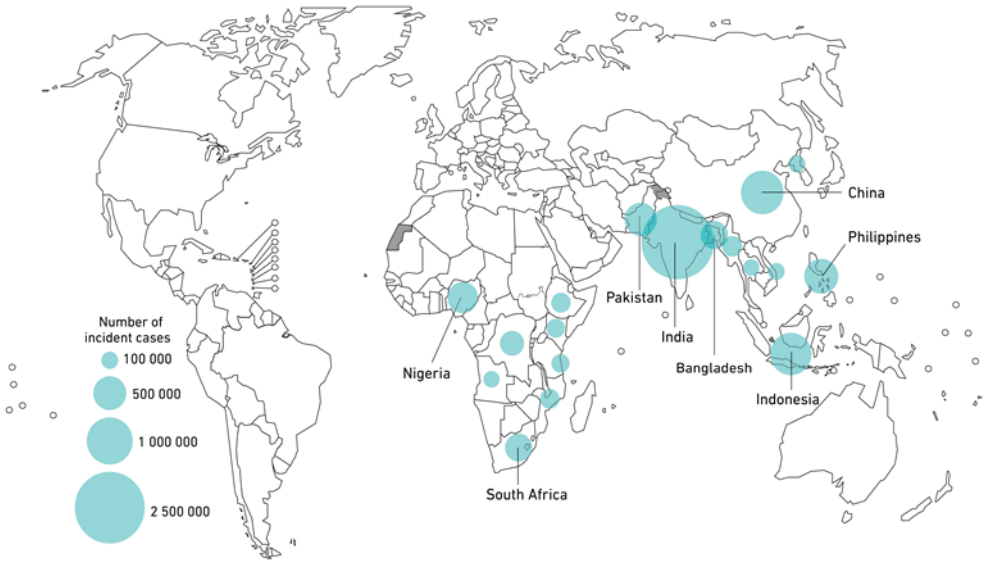



Figure 2.1 Incidence of tuberculosis (TB) in nations with at least 10,000 incident cases in 2017 (*Source: Worldwide Tuberculosis Report 2018 by World Health Organization*)

## 2.2 Fundamentals about Tuberculosis (TB)

The main cause for the TB was unknown until Koch's discovery on March 24, 1882 who has identified that the TB occurs due to the bacillus *Mycobacterium tuberculosis*; tubercle bacilli were identified even in fossilized ancient human skeletons. TB usually affects the lungs and transmits through the air when pulmonary TB infected patients exhale bacteria while coughing. HIV-infected people are more prone to get TB as their immunity is compromised. People who suffer from malnutrition, diabetes, smoking, or excessive alcohol consumption are at an increased risk of contracting tuberculosis.

## 2.3 Mtb Pathogenesis

Mtb infection is typically disseminated through the aerosols while coughing, sneezing as well as talking to someone who has pulmonary TB. Mtb bypasses the mucociliary clearance, it enters the alveolar spaces via inhalation and it reaches to lungs where multiplication takes place over a period of 2-3 days. Thereafter, Mtb is engulfed by macrophages and produce cytokines and proteolytic enzymes to destroy Mtb bacteria; such immune responses form defensive granulomas to control the replication as well as more infection of Mtb. But granuloma having low oxygen and low pH under such environment phagocytic cells get destroyed and Mtb gets adapted to survive. In case of poor immunity system, there are chances of tuberculosis infection e.g., primary progressive disease, latent infection, extrapulmonary disease.[1]

## 2.4 Tuberculosis (TB) diagnostics[2]

- *Sputum Smear Microscopy* - one of the oldest and most common method to diagnose TB in which sputum samples are inspected under a microscope for tubercular bacilli
- *Culture-based methods* - more advanced and can take 12 weeks to get results
- *Rapid Molecular Tests* - WHO recommended the Xpert®MTB/RIF assay is the only fast (within 2 h) diagnostic test for TB.

Currently available BCG vaccine for TB is discovered in 1923 and is used all over the world. BCG vaccine is highly effective in childhood TB and insufficient in case of mature pulmonary TB. The development of new, more potent TB vaccines is thus one of the main priorities in TB research.

## 2.5 Structural Details of *Mycobacterium tuberculosis* Cell Wall

The prevalence of multidrug-resistant (MDR) and extensively drug-resistant of bacteria is steadily increasing (XDR) TB because of the architectural as well as compositional complexity of Mtb cell wall. The cell wall of Mtb differs significantly from that of Gram-positive and Gram-negative bacteria. The Mtb cell wall has high glycolipid composition acting as a permeability barrier for foreign chemotherapeutic agents as well as antibiotics.[3] Taking these factors into account, intensive attempts have been made to determine the appropriate structure of the Mtb cell wall and its biosynthesis to get better understanding of biochemistry with an overarching goal of

discovering of new drugs. The best model of the cell wall of Mtb is hypothesized by Brenan by in-depth analysis of mass spectroscopic data.[4]

The cell wall membrane of Mtb is made up of three major components: the outer membrane, the core cell wall and inner plasma membrane. The outer membrane of Mtb cell wall consists of proteins and glycolipids which are non-covalently connected. There are two major segments in the core cell wall: a) The mycolyl-arabinogalactan-peptidoglycan complex having heteropolysaccharide arabinogalactan (AG) which is covalently linked to long chain mycolic acid (MA) ($C_{70}$-$C_{90}$) at non-reducing end while the peptidoglycan (PG) at reducing end; and b) lipoglycans, consists of lipoarabinomannan (LAM) and lipomannan (LM) (Figure 2.2).[5]

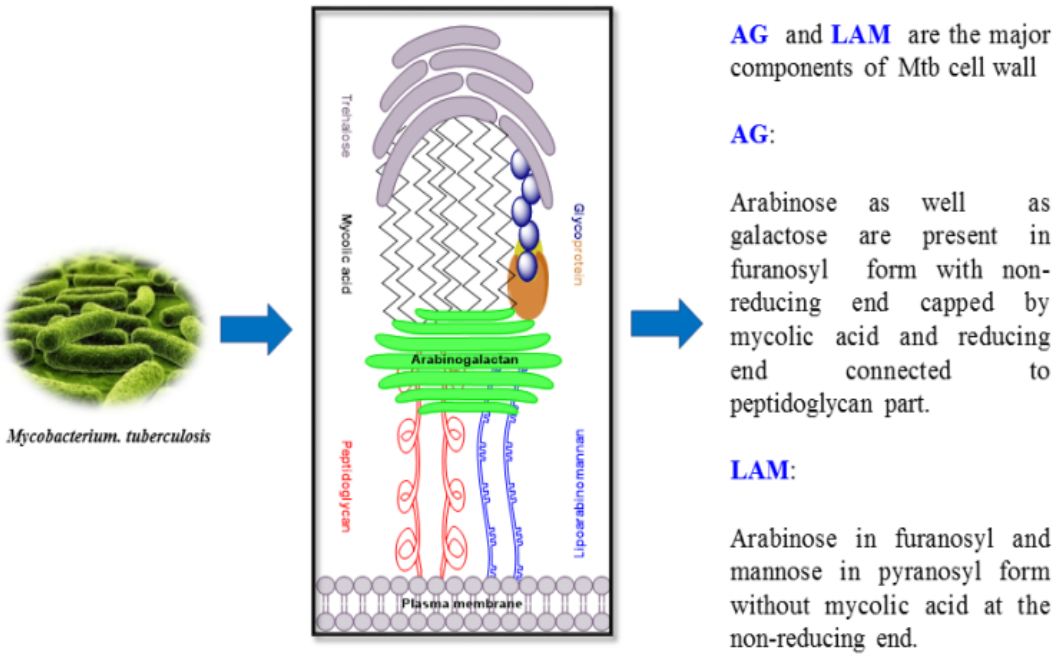



Figure 2.2 Representative structure of Mtb cell wall

### 2.6.1 Mycolic acids

Nearly 60% of the mycobacterial cell wall is made up of lipids, which are long-chain fatty acids with 60-90 carbons known as mycolic acids. It aids the cell wall in controlling fluidity as well as permeability.[6] These mycolic acids linked covalently to the polysaccharides. They are classified into three types, mainly as: α-mycolic acid having *cis*-cyclopropane configuration, whereas methoxy and keto mycolic acids having cyclopropane rings in either a *cis*- or *trans*-position with an adjacent methyl group. (Figure 2.3)[7]

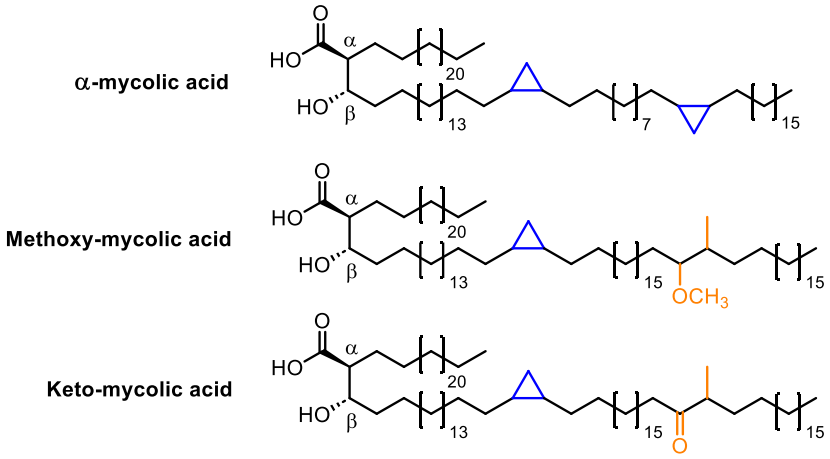



Figure 2.3 Structures of Mycolic Acids in Mtb cell wall

### 2.6.2 Lipoglycans (Lipoarabinomannan (LAM) and Lipomannan (LM)

The lipomannan (LM), lipoarabinomannan (LAM) and phosphatidyl-*myo*-inositol mannosides (PIMs) are the lipoglycans present in mycobacterium tuberculosis cell wall. LM and LAM are composed of three structural units: i) capping moieties ii) a mannan backbone and iii) a mannosyl phosphate inositol anchor. The mannan backbone in LM as well as LAM having 21–34 Man*p* residues, linked via α-Man*p*(1→6)Man*p* in a linear fashion having side chain with 5-10 units of α(1→2)Man*p*.[8] However, the mannan backbone in LAM has additionally an arabinan domain containing 55–70 Ara*f* residues linked linearly via α-Ara*f*(1→5)Ara*f* linkages.[9] Mainly two types of arabinan motifs have been observed in arabinan domain: i) linear tetraarabinofuranoside, β-D-Ara*f*(1→2)-α-D-Ara*f*(1→5)-α-D-Ara*f*(1→5)-α-D-Ara*f* and ii) branched pentaarabinofuranosyl motif, [β-D-Ara*f*(1→2)-α-D-Ara*f*]$_2$-3,5-α-D-Ara*f*(1→5).

Both LAM and AG have β-D-Ara*f*(1→2)-α-D-Ara*f*- as a unique disaccharide unit as a common motif.[10] There are three common capping fragments *viz*. i) mannose capped LAM (ManLAM), in most pathogenic bacteria which are slow growing such as M. leprae, M. bovis BCG, M. avium, M. marinum, M. tuberculosis and M. xenopi, ii) phosphoinositol capped LAM (PI LAM) present in non-pathogenic fast-growing bacteria as M. smegmatis, M fortuitum, iii) uncapped LAM which is known as AraLAM in M. chelonae.[11] The dimannoside α (1→2) Man*p* unit along with that mono and tri-α(1→2)-D-Man*p* saccharide units also exist within mycobacterium species (Figure 2.4).[12]

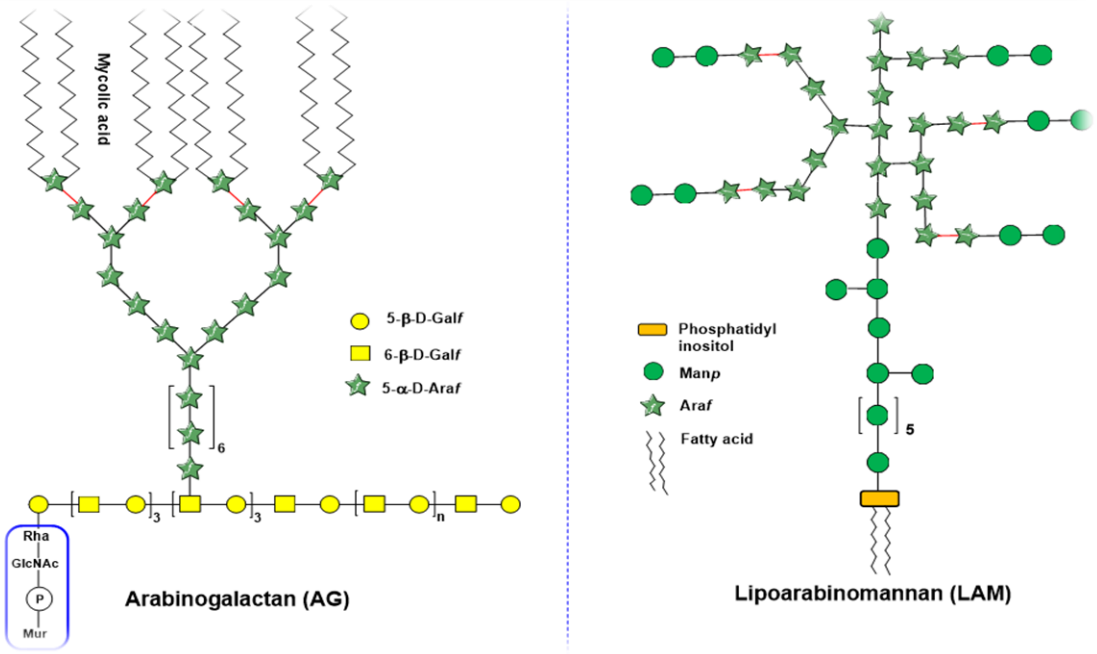



Figure 2.4 Structures of Arabinogalactan (AG) and Lipomannan (LAM) in Mtb cell wall

### 2.6.3 Arabinogalactan (AG)

Mycolyl–arabinogalactan–peptidoglycan (mAGP) complex is another major constituent of Mtb cell wall in which AG is the important structural component.[13] One of the distinguishing features is that all the sugar residues are in furanosyl form or in other words no routinely occurring pyranosyl forms. The utilization of advanced techniques such as NMR, GC-MS and FABMS for the detailed analysis of per-*O*-alkylated AG residues unraveled the complete structure of arabinogalactan.[14] Through a diglycosylphosphoryl connection, α-L-Rha*p*-(1→3)-α-D-GlcNAc-(1→P), the galactan part of the arabinogalactan is linked to the C-6 of muramyl residues of peptidoglycan.[15] The linear galactan chain is made up of approximately 30 galactofuranose (Gal*f*) residues that are linked in a linear fashion by an alternating β(1→5) and β(1→6) fashion.[16] Further linear galactan chain has extensions at the 8$^{th}$, the 10$^{th}$ and the 12$^{th}$ positions at the branched arabinan C-5 of β(1→6) Gal*f* residues.[17] Each component of an arabinan is made up of linearly placed α(1→5) linked Ara*f* residues and further branching at *C*-3 position build 3,5-Ara*f*-linked residues. There are four 1,2-*cis* and twenty-six 1,2-*trans* glycosidic linkages within arabinan component. The distinctive linkage i.e. [β-D-Ara*f*-(1→2)-α-D-Ara*f*]$_2$-3,5-α-D-Ara*f*-(1→5)-α-D-Ara*f*] at the non-reducing end, wherein the mycolic acids are anchored to the terminal β-Ara*f* unit.[18]

## 2.7 Biosynthesis of LM and LAM

The linear α(1→6)Man*p* backbone is built up by two different enzymes MptA (*Rv2174*) and MptB (*Rv149c*). The MptB is responsible for the priming of $Ac_1/Ac_2$-$PIM_4$ in case of C. glutamicium and also for the installation of approximately 12-15 Man*p* units. Whereas MptA responsible for construction of distal Man*p* residues. Further, there is an extention of α(1→2) Man*p* units to the linear α(1→6) mannan chain by MptC (Rv2181).[19-23] The lipoarabinomannan synthesis begins with an installation of 50-70 Ara*f* units to the mannan core back bone. The insertion of Ara*f* units to the mannan core is facilitated by the arabinofuranosyl transferase (Ara*f*T) and the role of AftC (*Rv2673*), AftD (*Rv0236c*) and EmbC (*Rv3793*) was well-known and the most important Ethambutol acts by inhibition of some of these enzymes.[24-25] Although, the initial installation of Ara*f* units of arabinan domain to the lipomannan incorporated by arabinofuranosyltransferase and subsequently 12-16 α(1→5) Ara*f* residues installation is exclusively mediated by EmbC. In both LAM and AG, the α(1→3) arabinan branching is controlled by AftC and further lengthening of these branched arabinofuranosides by an unknown α(1→5) arabinofuranosyltransferases. The Skovierova hypothesized that the Ara*f*T is responsible for the α(1→3) incorporation and the linear α(1→5) acceptor during the branching of arabinan component. As a result, AftD is identified as a second branching enzyme. At the end of arabinan biosynthesis, the AtfB (*Rv3805c*) installs terminal β(1→2) Ara*f* unit in both AG and LAM.[26-27] The synthesis of mannose caps is started in a two-step sequence that is catalyzed by two different mannopyranosyltransferases viz. MptC (*Rv2181*) and CapA (*Rv1635c*). The CapA catalyzes the first step, introduction of Man*p* unit to the non-reducing end of arabinan domain; and, further lengthening of mannose caps by the incorporation of second α(1→2) Man*p* unit is catalyzed by MptC in the second step.[27]

## 2.8 Biological importance of Man-LAM

ManLAM is a significant immune-modulating motif that has a significant impact on the host's immunological network. The LAM isolated from M. leprae and M. tuberculosis impacts host immune system and it has also been demonstrated to reduce T-cell proliferation.[28-31] Additionally, spin trapping and ESR spectroscopic techniques demonstrated that LAM inhibits protein kinase activity by acting as a free radical scavenger and also interleukin-2 (IL2) mRNA synthesis in human T-cells.[32] furthermore, ManLAM demonstrated to inhibit human dendritic cell production of TNF-α and IL-12. Indirect evidence suggests that ManLAM helps the bacteria survive in the

host macrophages.[33-34] So, the synthesis of an oligosaccharide having mannose residues has been planned in order to study it as diagnostic tool or for new vaccine development.

### 2.9 Account of Chemical Way to Synthesis Major Fragments of Mtb Cell Wall

The first chemical approach to synthesis the immunogenical pentaarabinofuranosyl epitope of Mtb cell wall was reported by Gurjar group employing thiopyridyl and *n*-pentenyl arabinofuranosyl donors.[35] Various LM and AG fragments of Mtb cell wall were synthesized by Seeberger group using of automated solid phase syntheser.[36] The synthesis of dodecasaccharide arabinomannan motif by using phosphate glycosyl donor was carried-out by the coupling of six α-D-Man*p* and α-D-Ara*f* residues *via* 6+6 coupling strategy.[37] In 2006, Fraser-Reid group reported the synthesis of 28-mer heterooligosaccharide motif by coupling arabinomannan-imidate donor with mannosylated inositol acceptor *via* 12+16 coupling strategy.[38] Lowary group in 2007, reported the highly convergent [(2x5) +7+5] approach for the synthesis of docasanyl arabinofuranoside employing thiotolyl and trichloroacetimidate glycosyl donors.[39] Later, Ito group demonstrated the intramolecular aglycon delivery (IAD) approach for the synthesis of the same arabinan motif through [(2x7)+8)] coupling strategy.[40] The utilization of propargyl 1,2-orthoester glycosyl donors and its Au-catalyzed activation in the synthesis branched hexaarbinofuranoside which is common domain in both LAM and AG fragments of mycobacterium cell wall has been reported by Hotha group.[41] Subsequently using single glycosylation strategy they have reported a 21-mer arabinogalactan motif by employing highly convergent [(2x4)+7+6] coupling strategy.[42] Subsequently, the alkynyl carbonate glycosyl donor was employed for the synthesis of branched tridecasaccharide[43] and nonadecaarabinofuanoside[44] motif of Mtb cell wall. Apart from this, Hotha group successfully employed the single strategic Au/Ag-catalyzed glycosylation method to the synthesis of pentacosafuranoside motif[45] and heneicosasaccharyl mannose capped arabinomannan[46] of Mtb cell wall.

Xin-Shan Ye group in 2017, assembled the 92-mer of mycobacterial cell wall in well-defined manner by employing the pre-activation based one-pot glycosylation protocol.[47] More recently, Xin-Shan Ye group used the automated multiplicative synthetic approach to assemble the 1080-arabinan units.[48]

### 2.10 Present Work

# Chapter-2

The Mtb cell wall is composed of two major structural components i.e., arabinogalactan (AG) and Lipoarabinomannan (LAM) out of which LAM is the structurally more diversified one with a phospholipid and further linkage of arabinomannan with myo-inositol.[49] The phosphatidyl inositol motif to its non-reducing end having mannose backbone with α(1→6) and α(1→2) Man*p* residues. The arabinan domain consists of α(1→5) arabinofuranoside backbone having two different linkages viz. i) α(1→5), α(1→3) and β(1→2) hexaarbinofuranoside motif and ii) α(1→5) and β(1→2) linked tetraarabinofuranoside motifs. In continuation, the β-linked Ara*f* at the non-reducing end are capped with mannopyranosyl units. It is well known that the non-reducing end of ManLAM has a role in mycobacterial infection and a number of immunomodulatory processes and any changes to this motif reduces the immunogenicity of the oligosaccharide.[55] Additionally, a quick point-of-care diagnostic test and carbohydrate-based vaccine were created recently harnessing the Man-LAM antigenicity.[50] Despite the fact that multiple groups have put forth a lot of effort to successfully synthesize various AG and LAM motifs, the biggest stumbling block in chemical carbohydrate synthesis is forming glycosidic connections with suitable stereo- and regiochemical orientation.

Of the various glycosyl donors reported till date (Chapter 1), the alkynyl carbonate glycosyl donor from Hotha group was demonstrated to be superior for the synthesis of tridecasaccharide and heneicosasaccharyl mannose capped arabinomannan motifs of Mtb cell wall.[46,51] As part of our continued interest in the synthesis and biochemical/biophysical investigations of Mtb cell wall motifs we have identified heptamannoside as potential target for the development of a diagnostic tool or as a novel vaccine candidate (Figure 2.5). All the biochemical experiments will be carried out by Prof. Beston Hamasur Biopromic AB and Karolinska Institute in Sweden.

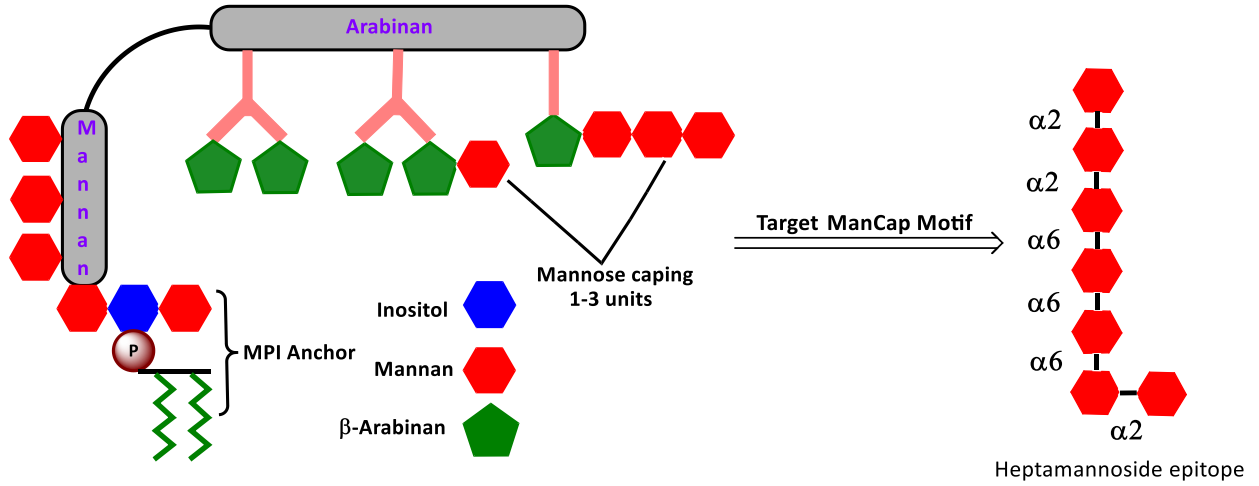
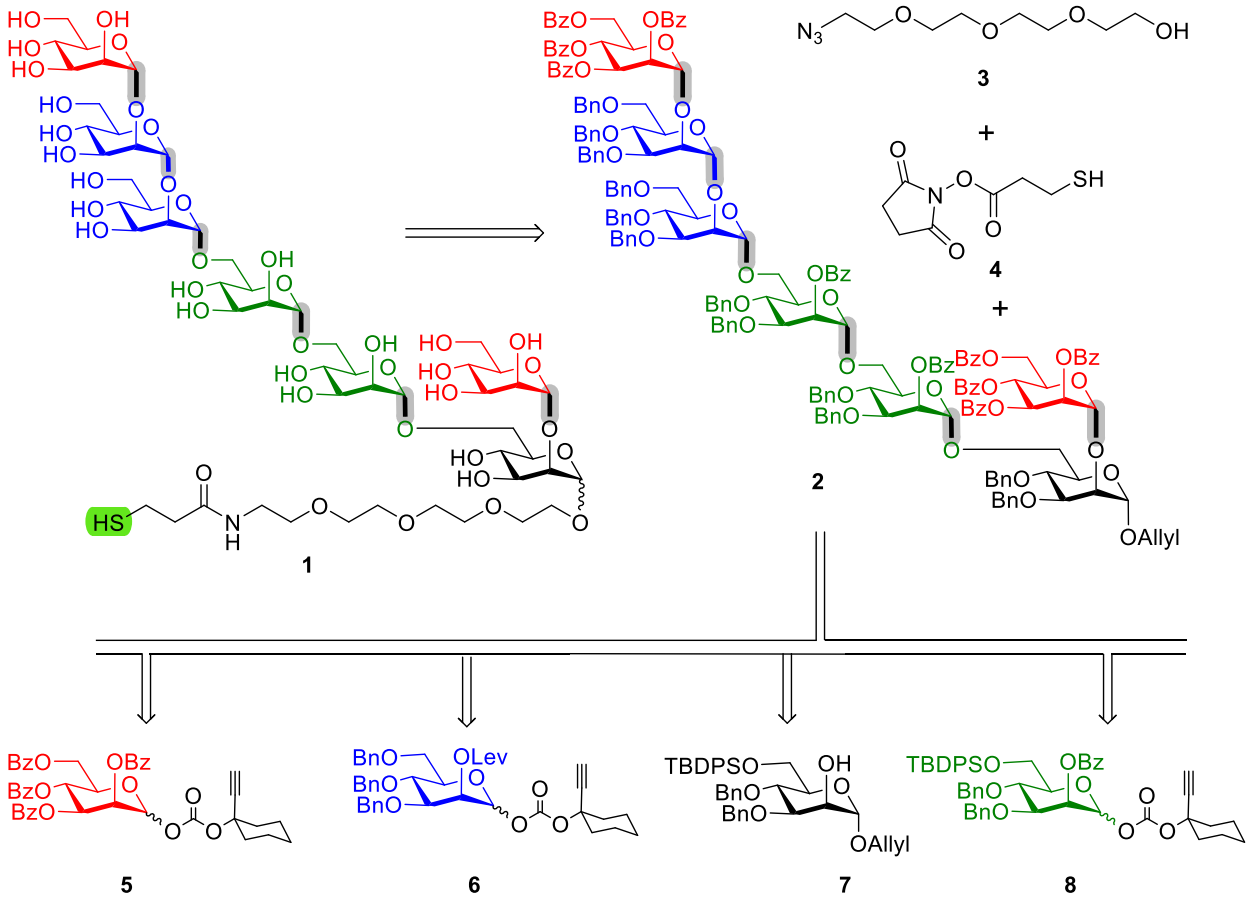



Figure 2.5 General representation of Mannose-capped heptamannoside motif

### 2.10.1 Retrosynthetic Disconnection of Heptamannoside (1)

Regarding the stereoselective linkages and branching at α(1→2) Man*p* residue in heptamannoside **1** enough complexity and quite challenge to synthesis. To synthesis heptamannoside **1** having i) α-selective glycosidic linkages ii) installation of α(1→2) Man*p* unit to C2-O at reducing end and iii) Additionally, an TEG-amino group linker with thiol functionality is stitched to the reducing end of the mannan domain to permit conjugation with a carrier protein for the evaluation of various biological and immunological processes. Given all of these difficulties, Planning a detailed retrosynthetic analysis that suggested heptamannoside motif can envisioned from three different fragements heptamannosyl **44**, TEG-azido spacer and commercially available 3-mercaptopropanyl-*N*-hydroxysuccinimide ester. The heptamannoside **44** composed of 1,2-*trans*(α) interglycosidic linkages and allylic functionality at reducing end. The installation of 1,2-trans connections has been done by the neighboring group participation of C2-benzoate protecting group of glycosyl donor. Consequently, additional retrosynthesis of **44** was carried out while bearing in mind the significant features of recently reported alkynyl glycosyl carbonate donor activation in presence of Au(I) and AgOTf catalysts. The preliminary phase of our synthetic quest began with 7-mer carbonate **46** *en route* to mannan motif **1**. As a means of achieving the hepta carbonate **46**, we have approached through linear as well convergent coupling strategy where glycosyl acceptor and donor are prepared from identical sources. Futher, these precursor can be divided into two fragements and each of fragements separetely with proper reagents converted to the glycosyl

donor and acceptor, which on coupling afford glycoside. Such overall synthetic platform, reduction in number of steps significanlty.




Scheme 2.1. Retrosynthetic analysis of heptamannoside **1**

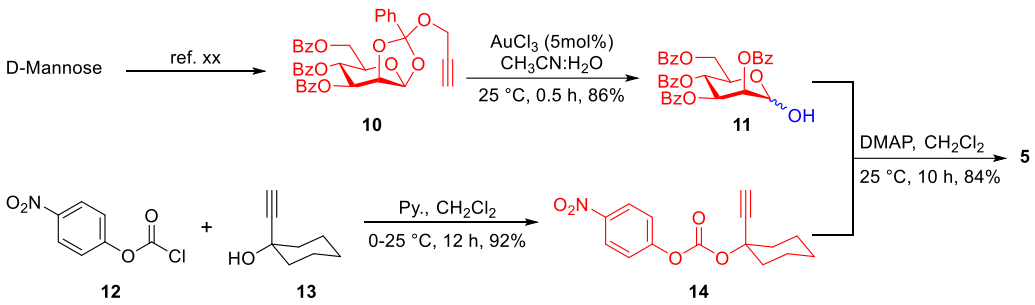
Targetted conjugation ready heptamannoside **1** can be assembled from the oligosaccharide **2** and the spacer molecules **3** and **4** out of which spacer **3** can be easily synthesized by following reported procedures whereas the molecule **4** is commercially available. Further, heptasaccharide **2** is envisioned from four monosaccharide building blocks **5-8** (Scheme 2.1). The allyl functionality at reducing end serves the dual role: (i) initially as the anomeric protection and (ii) hydrolysis to corresponding hemiacetal when required for further extrapolation to the carbonate donor prepartion. Identificatino of benzyl, benzoate, Lev and TBDPS protecting groups is strategic as they are known to be orthogonal to each other. The presence of the ester linkages in building blocks **5**,**6** and **8** enables the preparation of required 1,2-*trans* mannopyrosidic linkages through the neighbouring group participation.

### 2.10.2 Synthesis of heptasaccharide 2

In accordance with the retrosynthetic plan delineated in the Scheme 2.1, the synthesis plan commenced with the preparation of building blocks **5**-**8** from commercially available D-mannose.

#### 2.10.2.1 Synthesis of mannopyranoside building block 5

Synthesis of the building block **5** started with the conversion of the D-mannose to its propargyl 1,2-*O*-orthoester **10** by adopting a procedure that was well established in our group.[52] Further, the orthoester **10** was uneventfully tranformed to its corresponding hemiacetal **11** under gold catalyzed conditions in 86% yield. In parallel, *p*-nitrophenylchloroformate (**12**) in $CH_2Cl_2$ was stirred in the presence of ethynylcyclohexanol **(13)** and pyridine to produce the desired carbonate **14** that in turn was treated with the hemiacetal **11** prepared *vide supra* to obtain the required building block **5** in 84% yield (Scheme 2.2).



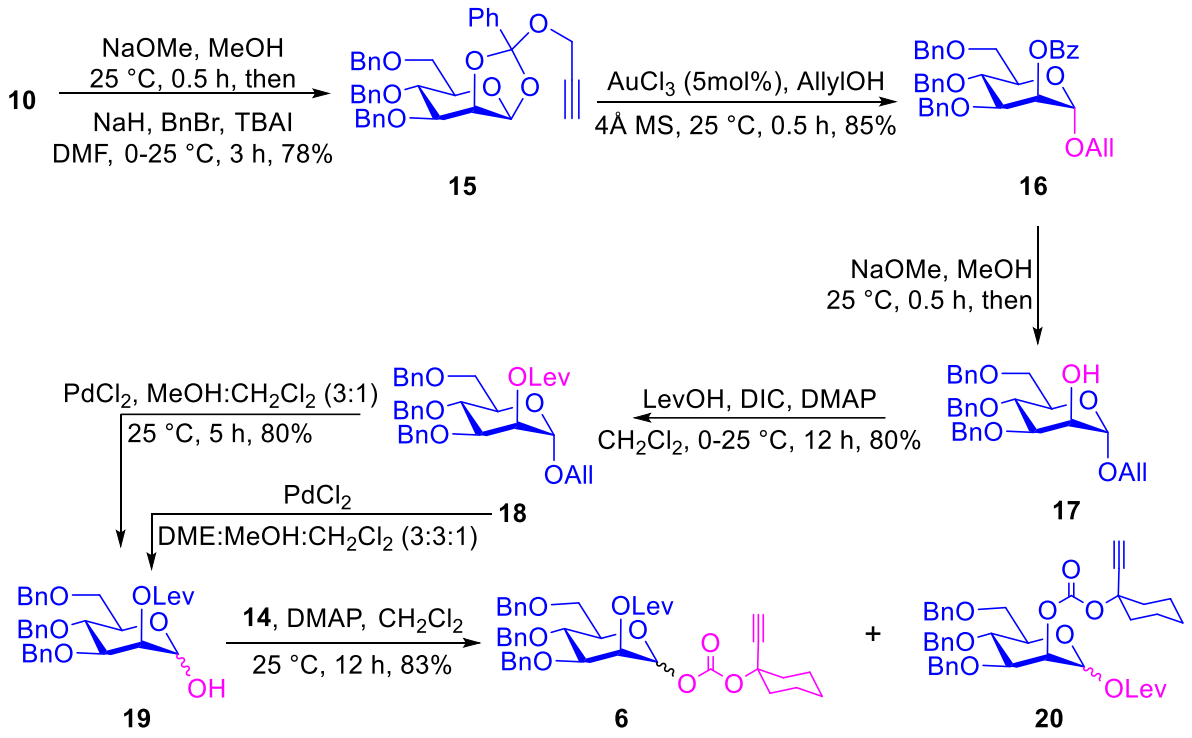

Scheme 2.2. Synthesis of mannopyranosyl carbonate donor **5**

#### 2.10.2.2 Synthesis of mannopyranoside building block 6

Synthesis of building block **6** started with the saponification under Zemplén deacylation conditions to obtain a triol that was immediately converted to the corresponding tri-*O*-benzyl ether **15** in 78% over two steps. Subsequently, compound **15** was subjected to the gold-catalyzed glycosidation using 5mol% of $AuCl_3$ for 0.5 h to obtain the allyl mannopyranoside **16**. Debenzoylation using NaOMe, MeOH at room temperature afforded alcohol **17** which was transformed to its levulinoate **18** using LevOH, DIC, DMAP. Further, the allyl glycoside was released by utilizing PdCl2, MeOH-$CH_2Cl_2$ (3:1) for 5 h at room temperature to afford the hemiacetals **19** in 80% yield. Hemiacetals **19** were treated with the carbonate reagent **14** and DMAP in $CH_2Cl_2$ to notice the

fomation of the desired compound **6** and the Lev-migrated product **20** as an inseparable mixture as shown in Scheme 2.3.

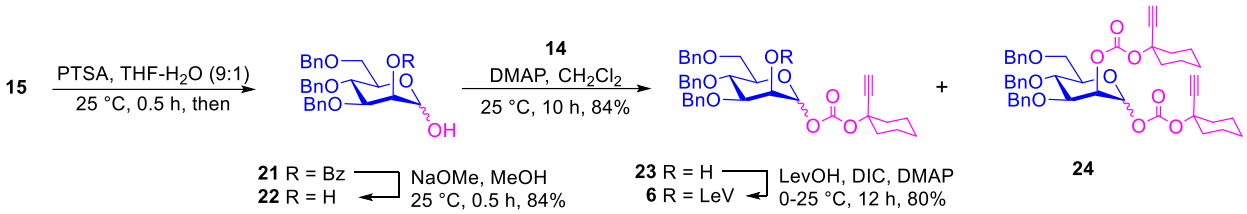
However, the unwarranted formation of the compound **20** and loss of material encouraged us to look at literature for the right conditions to avoid the migration and enable us to prepare the desired donor **6** in a facile manner. After a lot of trials, we noticed that the switching the solvent system from MeOH:$CH_2Cl_2$ (3:1) to dimethoxyethane:MeOH:$CH_2Cl_2$ (3:3:1) suppressed the migration and afforded the donor **6** in an exclusive manner.




Scheme 2.3. Synthesis of building block **6**

Alternatively, hydrolysis of the orthester to obtain the lactol **21**, followed by it's conversion to the diol **22** was carried out. Further diol **22** was treated with the carbonate reagent **14** to notice formation of the two compounds which are found to be the desired carbonate **23** (55%) and the unwanted di-carbonate derivative **24** (35%). Separation of these two compounds was affected by flash silica gel column chromatography. The lone hydroxyl group of the major isomer **23** was protected as its levulinoate to obtain compound **6** (Scheme 2.4). Of these two routes, compound

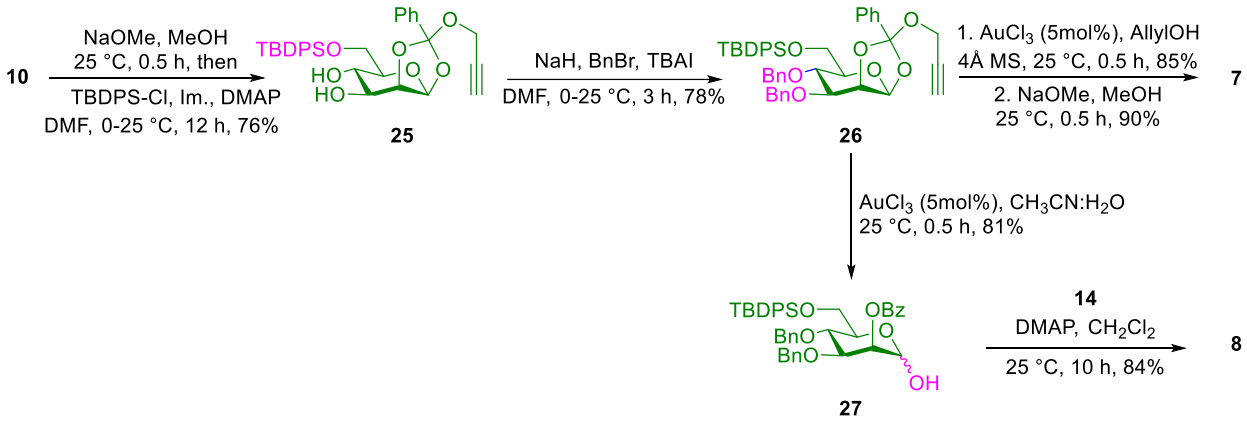
**6** can be easily prepared by adopting the route described in Scheme 2.4 due to the feasibility and scalability.




Scheme 2.4. Alternate route for the synthesis of donor **6**

### 2.10.2.3 Synthesis of mannopyranoside building block 7 and 8

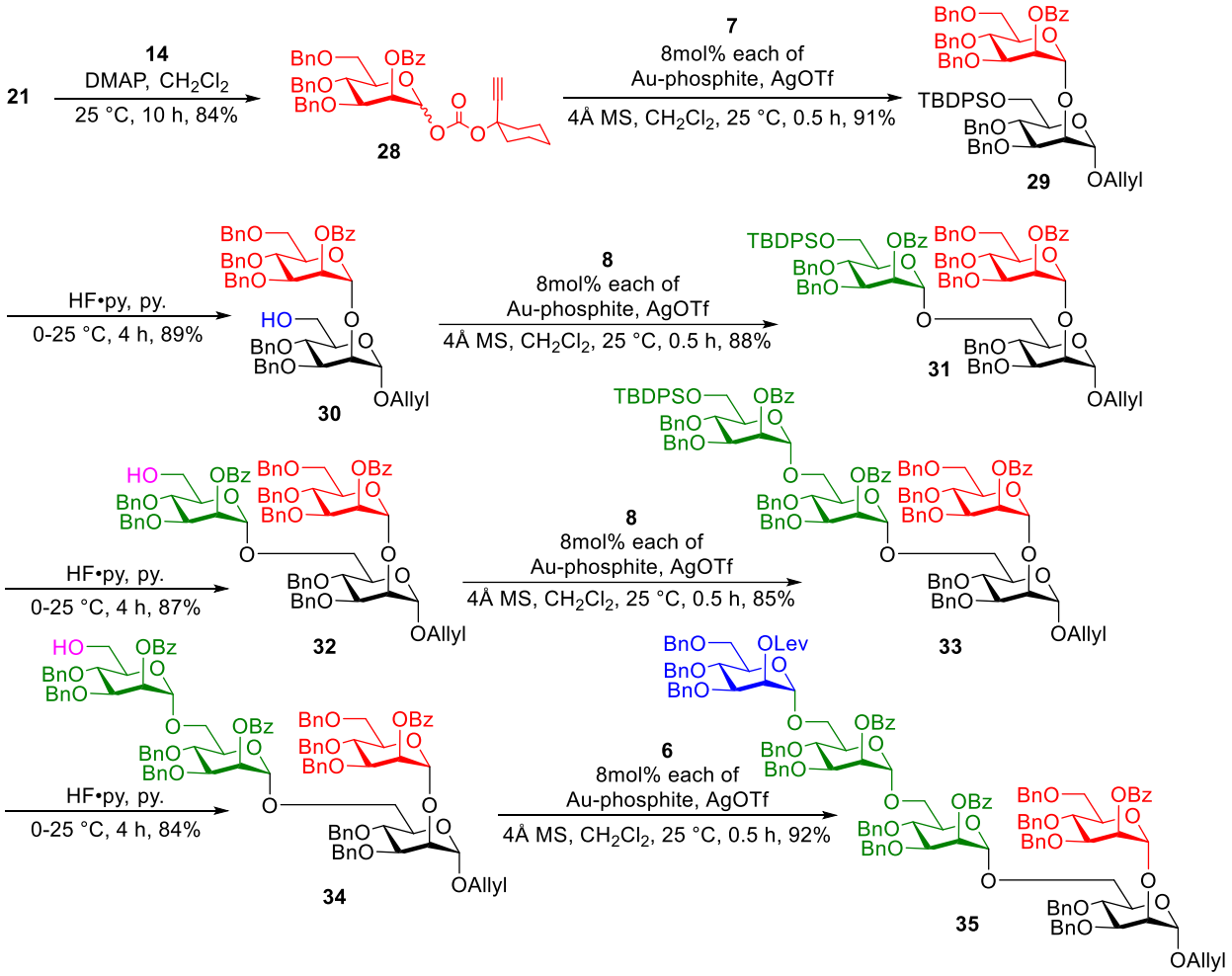
In parallel, synthesis of building blocks **7** and **8** was initiated by the Zemplén deacylation of orthoester **10** in the presence of NaOMe in MeOH followed by the protection of the primary hydroxyl group as its O-TBDPS ether happened effortlessly to afford compound **25** in 76% yield. The remaining two hydroxyl groups of silyl ether **25** were protected as benzyl ethers and the resulting di-*O*-benzyl ether **26** was split into two portions. The first portion was subjected to gold-catalyzed hydrolysis of the propargyl orthoester to afford the hemiacetal **27**. Hemiacetals **27** were converted to the desired carbonate donor **8** by treating with the carbonate reagent **14** in the presence of the DMAP at room temperature. The second portion was treated with allyl alcohol, $AuCl_3$ (5mol%) and 4Å MS powder to get the allyl mannopyranoside **7** in 85% yield (Scheme 2.5).




Scheme 2.5. Synthesis of building block **7** and **8**

### 2.10.2.4 Synthesis of Pentamannopyranoside

Identification of scalable routes for the synthesis of building blocks and the preparation of good quantities of all the building blocks encouraged us to advance the synthesis of a pentamannopyranoside as the first milestone (Scheme 2.6).




Scheme 2.6 Synthesis of pentamannopyranoside **35**

The synthesis of pentamannoside **35** was initiated with the preparation of the carbonate glycosyl donor **28** by aforementioned conditions. Further, the first silver-gold catalyzed glycosidation reaction between donor **28** and the aglycon **7** was carried out in the presence of 8mol% each of chloro[2,4-di-$^t$butylphenyl) phosphite]gold [abbreviated as Au-phosphite] and AgOTf catalysts and 4Å molecular sieves powder to obtain the disaccharide **29** in 91% yield. In the $^1$H NMR spectrum of compound **29**, two anomeric protons were identified as doublets at δ 4.98 (d, $J$ = 1.8 Hz) and 5.21 (d, $J$ = 2 Hz) ppm, methylene and olefinic methine protons were observed at δ 5.20

(dq, *J* = 10.5, 1.4 Hz) and 5.89 (m) ppm respectively. In the $^{13}$C NMR spectrum, two anomeric carbons were found at δ 99.9 and 97.9 ppm and the signal at δ 117.4 ppm was attributed to the allylic methylene carbon. Further signals at δ 165.2 ppm for carbonyl of benzoate group were noticed. The silyl ether of disaccharide **29** was hydrolyzed by HF•py./py. to afford the disaccharide acceptor **30** and this acceptor was subjected to the glycosylation with donor **8** in presence of [Au/Ag]-catalytic condition to produce the trisaccharide **31** in very good yields. The $^{1}$H NMR spectrum showed three anomeric protons at δ 5.22 (d, *J* = 2 Hz), 5.05 (d, *J* = 1.8 Hz) and 4.87 (s) ppm respectively. The signal at δ1.09 ppm for nine hydrogens was observed for the $^{t}$butyl moiety of TBDPS protecting group. Where as in the $^{13}$C NMR spectrum, three distinguishable anomeric carbons were noticed at δ 99.6, 97.8 and 97.7 ppm for the three 1,2-*trans* linked mannopyranosides. The signals at δ 165.9, 165,6 and 165.4 ppm confirmed presence of three benzoate esters. The $^{t}$butyl was confirmed due to the presence of resonances at δ 26.9 (3C) and 19.4 ppm for TBDPS of trisaccharide **31**.

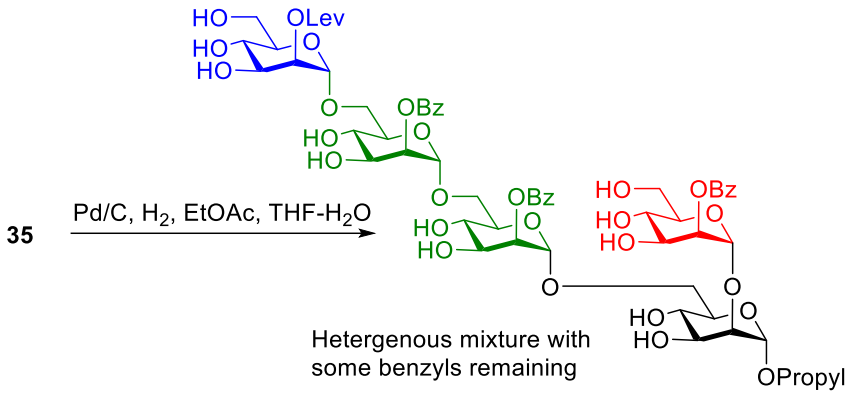
| **Entry** | **$^{1}$H NMR (δ ppm)** | **$^{13}$C NMR (δ ppm)** |
|---|---|---|
| Anomeric | 5.24 (d, *J* = 2 Hz, 1H), 5.06 (d, *J* = 1.9 Hz, 1H), 5.04 (d, *J* = 1.9 Hz, 1H), 4.93 (d, *J* = 1.9 Hz, 1H), 4.91 (s,1H) | 99.7, 98.2, 98.4, 97.9 (2C) |
| Benzoates | 8.10-7.23 (m, 15H) | 165.6, 165.5 and165.5 |
| Levulinoate | 2.69 (d, *J* = 2.4 Hz, 4H) and 2.06 (s, 3H) | 28.3, 29.8, 38.1, 171.8 206.3 |

Table 2.1 Characteristic $^{1}$H NMR and $^{13}$C NMR signals of Pentasaccharide **33**

Further C5-O-TBDPS ether was cleaved of in presence HF•py./py. to furnish trisaccharide acceptor **32** in excellent yields that was subjected to [Au/Ag]-assisted glycosidation with donor **8** to get the tetrasaccharide **33**. The $^{1}$H NMR analysis showed that four anomeric protons resonated at δ 5.23 (d, *J* = 1.9 Hz), 5.09 (d, *J* = 1.9 Hz), 5.03(d, *J* = 1.9 Hz), and 4.90 (d, *J* = 1.9 Hz) ppm. Whilst $^{13}$C NMR spectrum revealed four 1,2-*trans* Man*p* anomeric carbons at δ 99.7, 98.4, 97.9 and 97.8 ppm. Further, $^{1}J_{C\text{-}H}$ coupling constants verified 171 Hz and 175 Hz confirmed the established interglycosidic bonds as 1,2-*trans* linkages. In the MALDI (TOF) spectrum of compound **33**, *m/z* value for $C_{127}H_{130}O_{24}SiNa$, $(M+Na)^{+}$: 2090.7640 (calcd *m/z* = 2090.8653). The *O*-TBDPS group of compound **33** was deprotected again under the HF•py./py. conditions to provide excellent yield of the tetrasaccharide acceptor **34** that was glycosylated with donor **6** under

silver assisted gold catalyzed glycosylation conditions to furnish the pentasaccharide **35**. The 1,2-*trans* selectivity was guided by the presence of C2-O-Lev moiety of the donor **6** through NGP. The compound (**35**) confirmed by thorough NMR spectral analysis (Table 2.1).

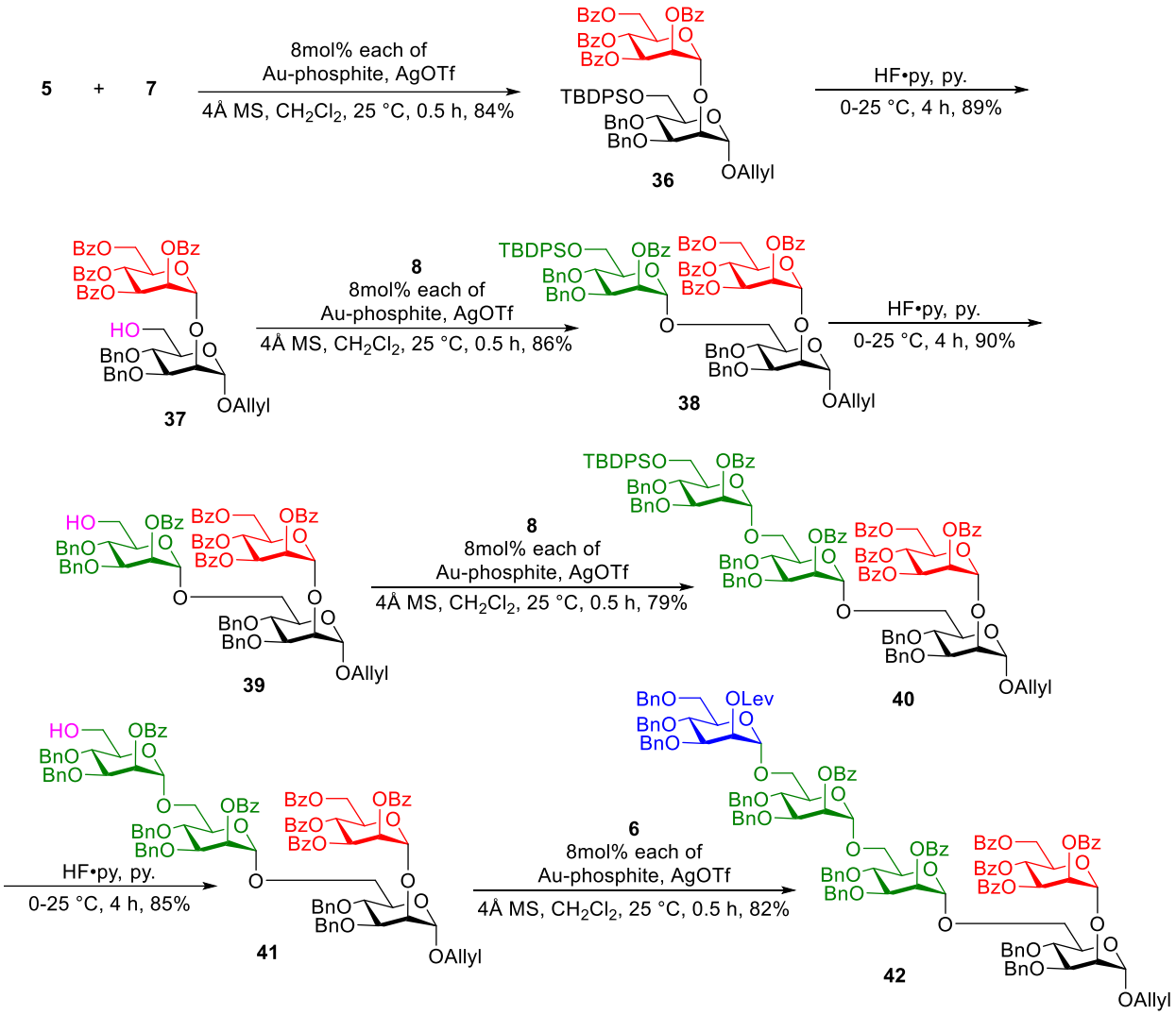
Our experience with the deprotection of benzyl groups in larger oligosaccharides of arabinofuranosyl systems was not very encouraging with the increased number of sugar residues. Often, we find that some of the benzyl groups will not be deprotected easily. In view of this, we thought of checking the feasibility of deprotection at this stage in order to avoid problems after the complete the synthesis of heptasaccharide (Scheme 2.7). As expected, the hydrogenolysis did not go to completion and it has given us a heterogenous mixture of pentasaccharides that are partially debenzylated and the separation became a herculean task. However, we realized that the removal of the benzyl groups attached to the C-2 mannopyranosyl unit are the ones which were difficult to unmask. Hence, revision of the plan was necessitated in order to produce the target heptasaccharide **2**.




Scheme 2.7. Hydrogenolysis of the pentasaccharide **35**

### 2.10.2.2 Synthesis of Heptasaccharide 2

Glycosyl donor **5** and acceptor **7** were glycosylated in the presence of 8mol% each of Au-phosphite and AgOTf at room temperature to get disaccharide **36** in 84% yield. The 1,2-*trans* stereoselectivity was accomplished through the neighboring group participation of C2-OBz of the donor **5**. Two singlets for the two anomeric protons were noticed at δ 5.25 and 5.07 ppm respectively in the $^{1}$H NMR spectrum of compound **36**. Methylene and olefinic methine protons appeared at δ 5.22 (dq, $J$ = 10.5, 1.4 Hz) and 5.88 (m) ppm respectively.




Scheme 2.8. Synthesis of the pentasaccharide

Whereas, $^{13}$C NMR spectrum of compound **36** showed resonances at δ 100.0 and 97.9 ppm for two anomeric carbons, at δ 117.4 ppm for olefinic carbon. The four benzoate carbonyls were noticed at δ 166.3, 165.6, 165.2 and 165.1 ppm. The resonating signals at δ 26.9(3C) and 19.4 ppm for *tert*-butyl component of TBDPS protecting group were also identified. The deprotection of TBDPS was performed in presence of HF•py./py. to get the disaccharide acceptor **37**. Subsequently, acceptor **37** subjected to the silver-assisted gold-catalysed glycosylation with the donor **8** to furnish trimannoside **38**. In the $^{1}$H NMR spectrum of trisaccharide **38**, three anomeric protons appeared at δ 5.31 (d, $J$ = 1.8 Hz), 5.13 (d, $J$ = 1.8 Hz) and 5.00 (s) ppm whilst $^{13}$C NMR spectrum revealed three anomeric carbons at δ 99.7, 98.1 and 97.9 ppm respectively and the five

benzoate carbonyl carbons appeared at δ 166.2, 165.7, 165.6, 165.3 and 165.0 ppm thereby confirming the structural homogeneity of the trisaccharide **38**.

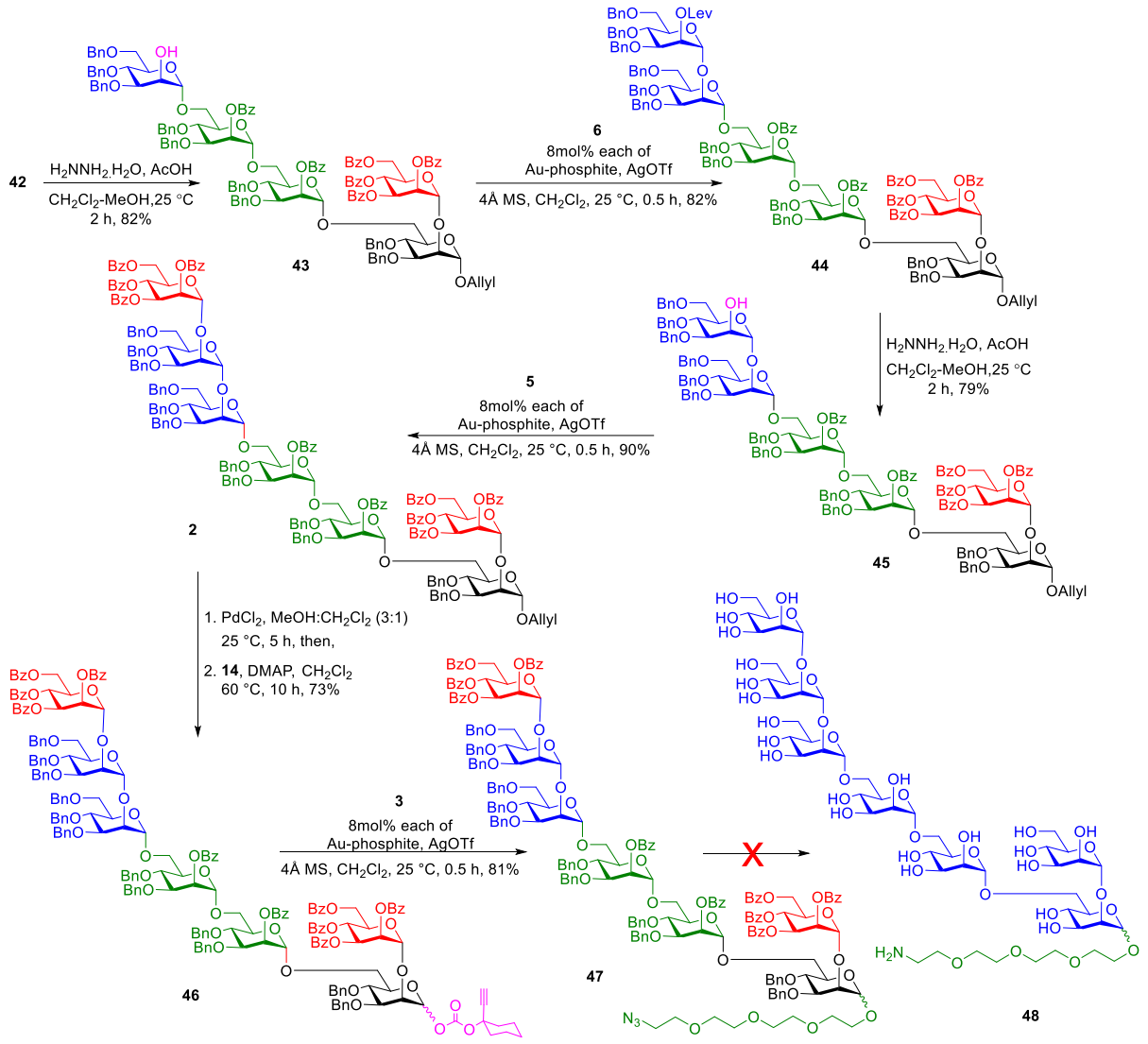
Further, the unmasking of TBDPS group was performed using the HF•py./py. to obtain the trisaccharide acceptor **39** in an excellent yield and thereafter the gold/silver mediated glycosylation was performed with the donor **8** to furnish tetramannopyranoside **40** in 79% yield. In the $^{1}$H NMR spectrum of compound **40**, four anomeric protons were identified at δ 5.24, 5.14, 5.09 and 5.02 ppm respectively where as in the $^{13}$C NMR spectrum, four anomeric carbon resonances were at δ 99.8, 98.5, 98.3 and 98.2 ppm.

In continuation, TBDPS group was deprotected from the tetrasaccharide **40** by HF•py./py. To afford the tetrasaccharide acceptor **41** in 85% yield. The glycosylation of glycosyl donor **6** with the glycosyl acceptor **41** under the [Au]/[Ag]-catalysed conditions provided pentasaccharide **42** effortlessly (Scheme 2.8). In the $^{1}$H NMR spectrum of compound **42**, five anomeric protons were perceived at δ 5.33, 5.13, 5.04, 5.01 and 4.95 ppm. The methylene and methyl moiety of levulinoate protection displayed resonances at δ 2.70 (d, *J* = 3.0 Hz, 4H) and 2.10 (s, 3H) ppm. In the $^{13}$C NMR spectrum of pentasaccharide **42**, five anomeric carbons were noticed at δ 99.7, 98.1, 98.3, 98.2 and 98.2 ppm. The levulinoate moiety having ketone and ester carbonyl signals appeared at δ 206.3 and 171.8 ppm respectively. Rest of the resonances were in accordance with that of the assigned structure. Furthermore, the 1,2-*trans* selectivity was established by $^{1}J_{C\text{-}H}$ coupling constants of 180 to 172 Hz.

| **Entry** | **$^{1}$H NMR (δ ppm)** | **$^{13}$C NMR (δ ppm)** |
|---|---|---|
| Anomeric | 5.33 (s, 1H), 5.13 (d, *J* = 1.8 Hz, 1H) 5.11 (d, *J* = 1.9 Hz, 1H), 5.02 (d, *J* = 2.3 Hz, 1H), 4.97 (t, *J* = 2.2 Hz, 2H) | 99.7, 99.5, 98.3 (2C), 98.2 (2C) |
| Benzoates | 8.14-7.20 (m, 30H) | 166.2, 165.6 (2C),165.5 165.3, 165.0 |
| Levulinoate | 2.67 (s, 4H), 2.10 (s, 3H) | 38.1, 29.8, 28.3, 171.8, 206.3 |

Table 2.2 Characteristic $^{1}$H NMR and $^{13}$C NMR resonance values of hexasaccharide **44**

In continuation, the hydrolysis of levulinoyl ester was performed in the presence hydrazine hydrate/AcOH/$CH_2Cl_2$-MeOH to furnish acceptor **43** (82%) that was taken forward to the silver




Scheme 2.9. Synthesis of Heptasaccharide **2**

assisted gold catalyzed glycosylation with donor **6** to get the hexasaccharide **44** in 82% yield. The structural integrity of the hexasaccharide **44** was established by NMR spectroscopic analysis (Table 1.2) and MS spectroscopy. The *m/z* for hexasaccharide **44** showed $[M+Na]^+$ at 2856.9629 in MALDI (TOF){calcd for $[M+Na]^+$ 2856.9631}. The levulinoate deprotection of hexasaccharide **44** was performed under aforementioned conditions to obtain the aglycon **45** in good yield and subsequently coupled with the monosaccharyl donor **5** under silver-assisted gold-catalyzed glycosidation protocol to obtain the desired heptasaccharide **2** in 90% yield. Successful synthesis of heptasaccharide **2** was confirmed by $^{1}H$ and $^{13}C$ NMR spectroscopy (Table 2.3) along with MALDI (TOF) analysis [Calcd for $C_{199}H_{188}O_{46}Na$, $[M+Na]^+$: 3326.2372, found 3326.2379].

| Entry | $^{1}$H NMR (δ ppm) | $^{13}$C NMR (δ ppm) |
|---|---|---|
| Anomeric | 5.41 (s, 1H), 5.33 (s, 1H) 5.14 (s, 1H), 5.06 (s, 1H), 5.04 (s, 1H), 5.01 (s, 1H), 4.98 (s, 1H) | 100.4, 99.7, 99.3, 99.2, 98.4, 98.3, 98.2 |
| Benzoates | 8.12-7.22 (m, 50H) | 166.2, 165.9, 165.6, 165.6, 165.5, 165.5, 165.3, 165.3, 165.1, 165.0 |

Table 2.3 Characteristic $^{1}$H NMR and $^{13}$C NMR resonance values of hexasaccharide **2**

We planned to check the immunogenicity of heptasaccharide **2** for which we need to attach this to a carrier protein that in turn requires us to attach a linker moiety **3**. Linker moiety can be attached to the heptasaccharide after converting it into a glycosyl donor that is accomplished in two steps. First, we have hydrolysed the allyl glycosides to obtain hemiacetals which were quickly treated with the carbonate reagent **14** to obtain the heptasaccharide-carbonate-donor **46** that was subjected to the glycosidation under [Au]/[Ag]-catalysis to get the linker-equipped heptasaccharide **47** in 81% yield as α:β (10:3) mixture of glycosides in 81% yield. In the $^{13}$C NMR spectrum of compound **47**, the presence of the azide moiety was apparent with the appearance of resonances at δ 50.6 ppm for the lone $\underline{C}$-$N_3$ bond. Additionally, azide functional group was confirmed through the asymmetric vibration frequency in the IR spectrum at 2100 cm$^{-1}$. The MALDI (TOF) analysis showed *m/z* value of **47** for $C_{204}H_{199}O_{49}N_3Na$ at 3499.3109 which agrees with that of the calculated *m/z* 3499.3137.

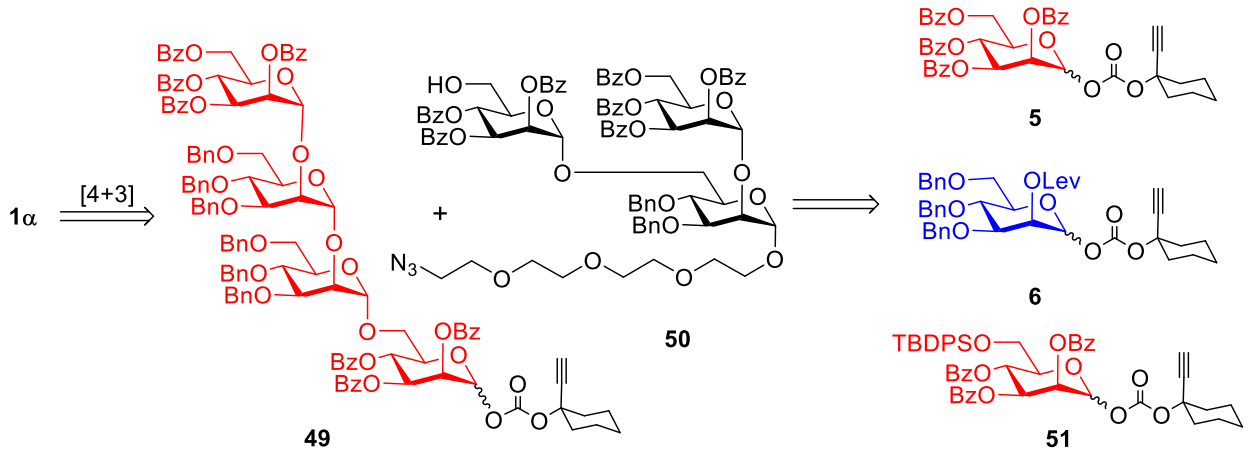
To our dismay, the deprotection steps did not produce the desired globally deprotected heptasaccharide **48** under saponification using the NaOMe/$CH_2Cl_2$/MeOH followed by the Pd-catalyzed hydrogenolysis to afford the bio-conjugation ready motif (Scheme 2.9). Earlier problem of partially deprotected compounds was evident even in the deprotection of this compound. Also, lack of enough quantities of the heptasaccharide **47** compounded the problem as standardization of reaction conditions for the global deprotection was necessary that required us to relook at the entire synthesis plan without much variation in the building blocks. It is well known that convergent approaches are superior to the more traditionally followed linear strategies for the assembly oligosaccharides. Hence, fresh synthesis plan has been charted out; accordingly, which, we would require one more building block in addition to already optimized synthetic route.

### 2.10.3 Convergent Approach to Synthesis Immunogenic Epitope (1α)

The linear assembly of building blocks was noticed to be cumbersome for the synthesis of conjugation ready heptasaccharide **1** as it required us to prepare in large quantities to perform the global deprotection for further biochemical experiments. In addition, we thought of synthesizing the single isomer of the heptasaccharide since (i) decreases the complexity of the molecule to be evaluated (ii) increase the number of benzoates (iii) decrease the number of benzyl groups and (iv) increased convergence so that the molecule can be assembled in a facile manner.

### 2.10.3.1 Retrosynthetic Analysis of Immunogenic Epitope

Change of strategy forced us to revisit the synthesis route. The heptasaccharide **1α** can be accomplished in a convergent manner by the glycosylation between a tetrasaccharide donor **49** and the trisaccharide acceptor **50** which in turn are envisioned from donors **5** and **6** whose route was identified. In addition, another building block **51** would be required that can be easily obtained following some of the optimized procedures (Scheme 3.10).

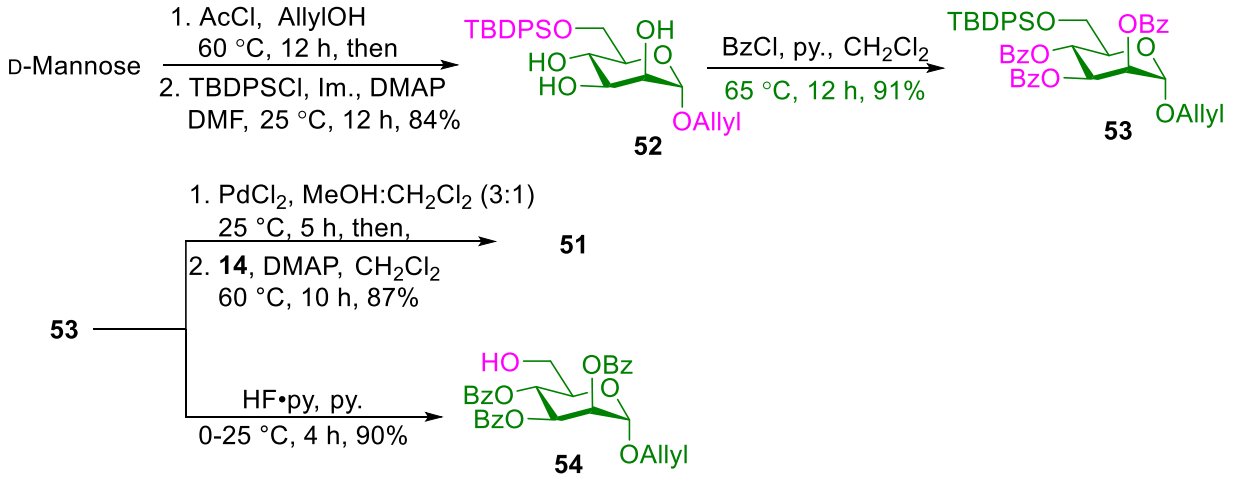



Scheme 2.10. Revised retrosynthetic plan

### 2.10.3.2 Synthesis of mannopyranosyl donor 51

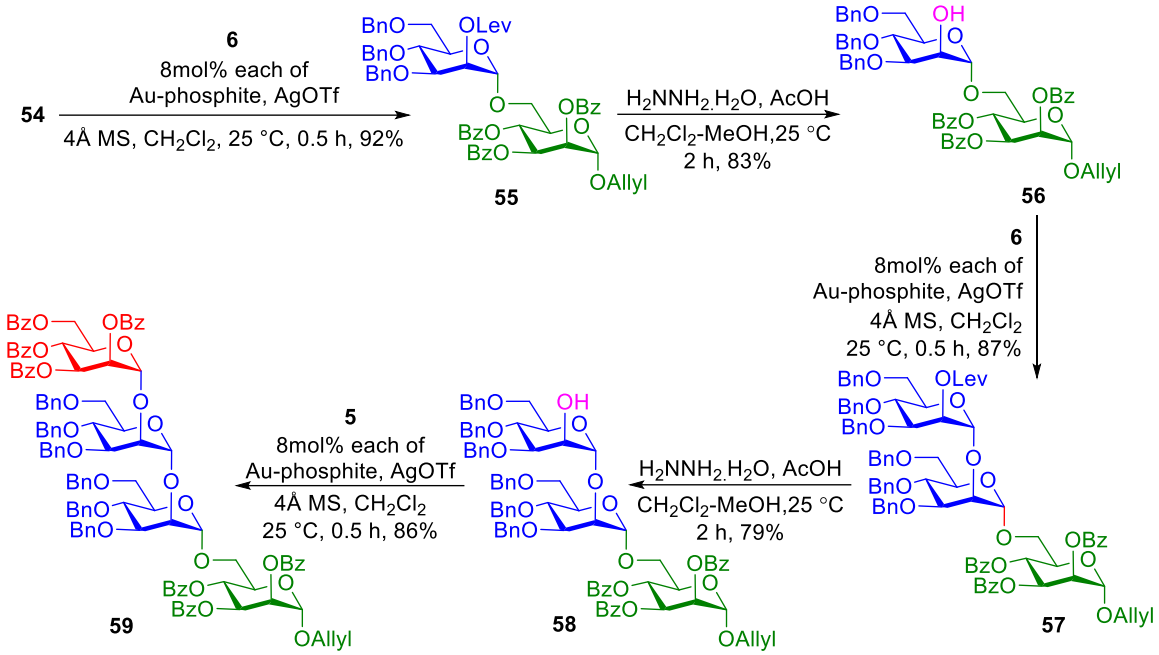
Commercially available D-mannose was suspended in allyl alcohol and heated to 60 °C in the presence of catalytic amount of acetyl chloride for 12 h and then, the reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3x) and the resulting result residue was treated with TBDPS-Cl, Imidazole, DMAP in DMF to obtain the silyl ether **52** in 84% yield. Remaining three hydroxyl groups were esterified using BzCl in py. at 65 °C for 12 h to get tri-*O*-benzoate **53**. Compound **53** was split into two portions; the first portion was subjected to the Pd-

catalyzed hydrolysis to obtain hemiacetals which were quickly converted to the corresponding alkynyl carbonate **51** adopting a procedure that was already well optimized. The second portion was treated with HF•py. in pyridine to unblock the C6-hydroxy group which can be utilized further in the synthesis of the tetrasaccharide **49** (Scheme 2.11).




Scheme 2.11. Synthesis of donor **51** and acceptor **54**

The assembly of heptasaccharide **1α** commenced with the glycosylation of the acceptor **54** and donor **6** under [Au]/[Ag]-catalyzed glycosylation conditions to afford the disaccharide **55** in 92% yield. In the $^{1}$H NMR spectrum of disaccharide **55**, two anomeric protons were noticed to resonate at δ 4.92 and 5.13 ppm as singlets, whereas the methylene and methyl moieties of the levulinoate group appeared at δ 2.75 – 2.66 (m, 4H) and 2.13 (s, 3H). In $^{13}$C NMR spectrum of compound **55** showed two anomeric carbons at δ 97.8 and 96.5 ppm, the three benzoate ester carbonyls at δ 165.6, 165.5 (2C) ppm whilst signals at δ 206.4 and 171.9 ppm were attributed to the corresponding ketone and ester portions of the levulinoate group. The =$\underline{C}$H$_2$ of **55** appeared at δ 118.6 ppm. Saponification of the levulinoate functionality was performed using hydrazine hydrate to get C2-OH containing compound **56** that was treated with the mannopyranosyl donor **6** under aforementioned gold/silver-catalyzed glycosidation conditions to afford the trisaccharide **57** in 87% (Scheme 2.12). In the $^{1}$H NMR spectrum of trisaccharide **57**, three anomeric protons resonated at δ 5.16, 5.08 and 5.03 ppm as singlets, the levulinoate group having methylene and methyl moiety appeared




Scheme 2.12. Synthesis of the tetrasaccharide **59**

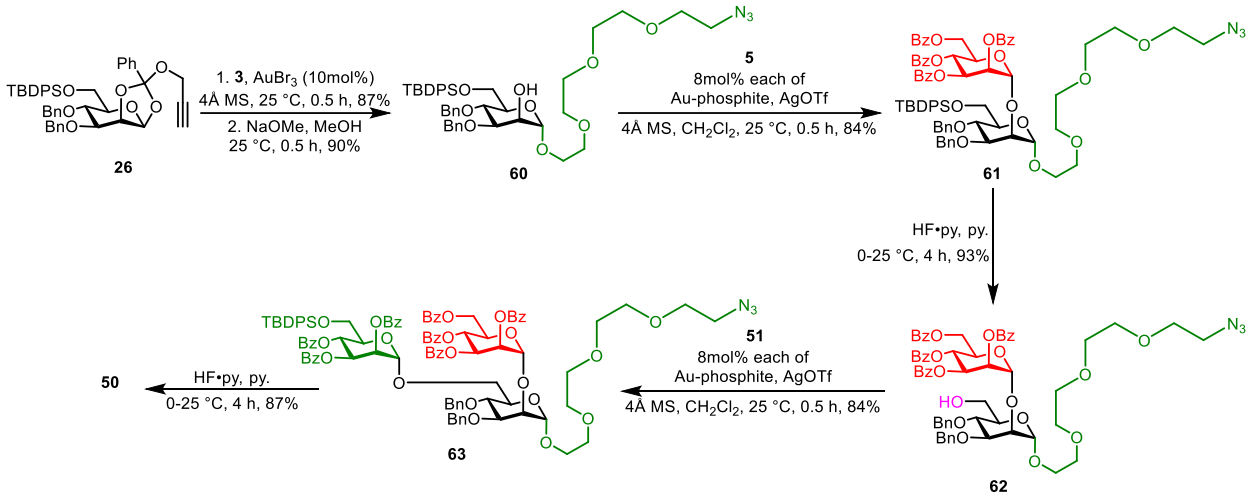
at δ 2.76 (s, 4H) and 2.19 (s, 3H) ppm respectively. The distinguishable anomeric carbons in the $^{13}$C NMR spectrum of **57** were noticed at δ 99.6, 98.9 and 96.5 ppm. The ketone and ester carbonyl carbons of lev protecting group were identified at δ 206.4 and 171.8 ppm whereas three benzoate carbonyl carbons resonanced at δ 165.6 (2C) and 165.5 ppm respectively. Once again, the deprotection of the levulinoate produced the aglycon **58** that was subjected to the glycosidation with glycosyl donor **5** under aforementioned conditions to obtain the tetrasaccharide **59** in 86% yield. The structural homogeneity of tetrasaccharide **59** was established through the $^{1}$H and $^{13}$C NMR spectral analysis (Table 1.4) along with the MALDI (TOF) analysis *m/z* value for **59** [calculated for $C_{118}H_{110}O_{28}Na$, $[M+Na]^+$: 1998.7115, found 1998.7109].

| **Entry** | **$^{1}$H NMR (δ ppm)** | **$^{13}$C NMR (δ ppm)** |
|---|---|---|
| Anomeric | 5.31 (s, 1H), 5.09 (s, 1H) 5.05 (s, 1H), 4.96 (s, 1H) | 100.5, 99.3, 99.0, 96.4 |
| Benzoates | 8.12-7.22 (m, 35H) | 166.1, 165.6(2C), 165.5, 165.4(2C) 165.1 |

Table 2.4 Characteristic $^{1}$H NMR and $^{13}$C NMR spectral values of tetrasaccharide **59**

### 2.10.3.3 Synthesis of trisaccharide Acceptor 50

1,2-*O*-orthoester **26** was treated with the readily available azide-acceptor **3** in presence of 10mol% of $AuBr_3$ to afford glycoside in 87% yield that was saponified under Zemplén debenzoylation conditions to afford the aglycon **60** in 90% yield. Aglycon **60** was taken forward for the glycosylation with the donor **5** to furnish the disaccharide **61** in 84% yield (Scheme 2.13).




Scheme 2.13. Synthesis of the trisaccharide acceptor **50**

In the $^{1}$H NMR spectrum of disaccharide **61**, two anomeric singlets were noticed at δ 5.26 and 5.05 ppm, the presence of a triplet at δ 3.32 (*J* = 5.1 Hz) ppm for two protons established the presence of the tetraethylene glycol unit. Further, $^{13}$C NMR spectrum revealed two anomeric carbons at δ 100.0 and 98.8 ppm for the two 1,2-*trans* mannopyranosides and the -$H_2$C-$N_3$ at δ 50.6 ppm respectively. The silyl ether of **61** was hydrolyzed by HF•py./py. to give the disaccharide acceptor **62** in 93% yield and the catalytic [Au]/[Ag]-glycosylation was employed with the glycosyl donor **51** to offer trisaccharide **63** in 84% yield. In the $^{1}$H NMR spectrum of compound **63**, three distinguishable anomeric protons were identified at δ 5.36, 5.29 and 5.11 ppm singlets at δ 99.8, 99.1 and 98.0 ppm in the $^{13}$C NMR spectrum. Further The $^{1}J_{C\text{-}H}$ coupling constant showed 176-172 establishing the occurrence of the 1,2-*trans* glycosidic linkages. Subsequently, the C6-silyl ether was cleaved off under HF•py./py. conditions to afford the aglycone **50** in 87% yield.

### 2.10.3.4 Synthesis of heptasaccharide 1α

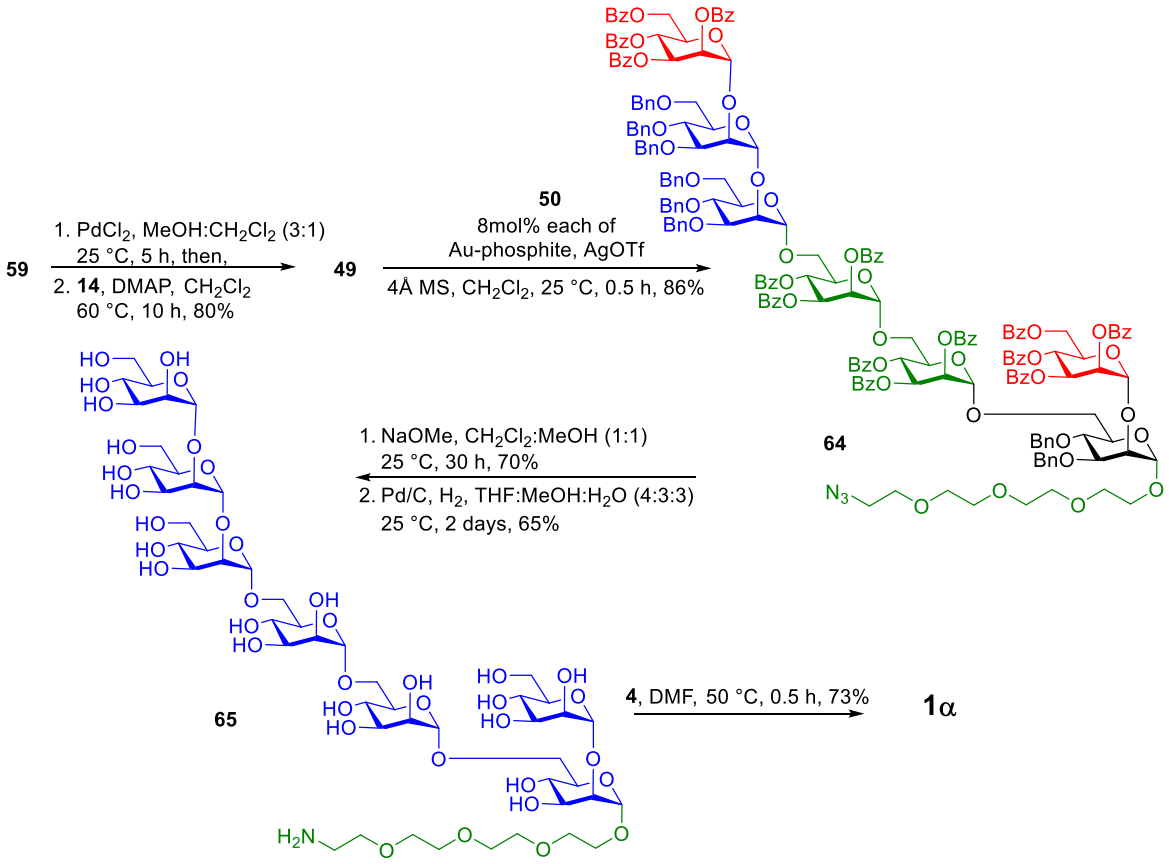
Tetrasaccharide **59** was converted to the donor **49** in two steps (80%) adopting above delineated procedure of Pd-catalyzed hydrolysis of the allyl glycoside followed by the hemiacetal conversion to the corresponding carbonate using the reagent **14** (Scheme 2.14). The donor was allowed to react with the acceptor **50** in the presence of Au-phosphite and AgOTf to afford the heptasaccharide **64** whose structural integrity was established unequivocally by various spectroscopic techniques (Table 2.5) and additional MALDI (TOF) analysis *m/z* for **64** [calcd for $C_{204}H_{191}N_3O_{53}Na$, $[M+Na]^+$: 3555.2308, found 3555.2311].

| **Entry** | **$^1$H NMR (δ ppm)** | **$^{13}$C NMR (δ ppm)** |
|---|---|---|
| Anomeric | 5.37 (s, 1H), 5.34 (s, 1H) 5.31 (s, 1H), 5.12 (s, 1H), 5.09 (s, 1H), 5.01 (s, 1H), 4.81 (s, 1H) | 100.3, 99.8, 99.3, 99.2, 99.0, 98.2, 98.1 |
| Benzoates | 8.15-7.23 (m, 70H) | 166.3, 166.0, 165.8, 165.6, 165.5,165.4,165.3(3C),165.2(3C), 165.0, 164.9, |

Table 2.5 Characteristic $^1$H NMR and $^{13}$C NMR signals of heptasaccharide **64**

Thereafter, heptasaccharide **64** subjected to the Zemplén saponification using NaOMe/MeOH/$CH_2Cl_2$ conditions to afford a polyol which was directly taken forward for the hydrogenolysis using Pd/C/$H_2$ to afford the globally deprotected conjugation ready heptasaccharide **65.** In the $^1$H NMR spectrum of compound **65**, seven anomeric protons were identified at δ 5.20, 5.02, 5.02, 4.95, 4.93, 4.81, 4.80 ppm as singlets whereas distinguishable anomeric carbons resonances appeared at δ 102.3, 102.2, 100.6, 99.6, 99.5, 98.5, 98.1 ppm in the $^{13}$C NMR spectrum. Furthermore, MALDI(TOF) spectrum showed *m/z* for heptasaccharide **65** at 1350.4988 [calculated for $C_{50}H_{89}NO_{39}Na$, $[M+Na]^+$: 1350.4909].

Further the globally deprotected heptasaccharide **65** was coupled with 3-mercaptopropanyl-*N*-hydroxysuccinimide ester to furnish final immunogenic epitope **1α** in 73% yield (Scheme 2.14). In the $^1$H NMR spectrum of conjugate **1α**, seven anomeric protons were noticed at δ 5.21, 5.03, 5.03, 4.95, 4.95, 4.81, 4.81 ppm as singlets whereas, anomeric carbons were identified at δ 102.3, 102.2, 100.6, 99.6, 99.5, 98.5, 98.1 ppm in the $^{13}$C NMR spectrum of conjugate **1α**. The MALDI (TOF) analysis showed *m/z* for **1α** as 1454.4619 [calcd for $C_{53}H_{93}NO_{40}SK$, $[M+K]^+$: 1454.4632].




Scheme 2.14 Synthesis of target molecule **1α**

In summary, a conjugation ready heptasaccharide motif was synthesized by employing silver-assisted gold-catalyzed glycosidation protocol. A liner and convergent routes were developed due to problems with the deprotection of some of the protecting groups. The efficiency of the convergent approach was found to be superior for synthesizing large quantities of the heptasaccharide motif. We have employed split-react-couple strategy propounded in our group as many times as possible while executing this synthesis. The 1,2-*trans*- glycosidic linkages are accomplished through the neighboring group participation while employing the alkynyl glycosyl carbonate donors. The amino functionality was transformed to the corresponding mercaptan for further conjugation to the immunogenic protein. The immunogenicity studies are currently underway in our collaborator's (Prof. Beston Hamasur laboratory) group at Karolinska University, Sweden.

## 2.11 Experimental Section

**Synthesis of 1-ethynylcyclohexyl 4-nitrophenyl carbonate 14:** Commercially available 1-ethynylcyclohexanol (5.00 g, 40.26 mmol) was dissolved in anhydrous $CH_2Cl_2$ (60 mL), pyridine (20 mL) was added and stirred for 20 min at 0 °C. *p*-Nitrophenyl chloroformate (9.74 g, 48.32 mmol) was added drop-wise and stirred for 30 minutes at 0 °C. The reaction mixture was then stirred at 25 °C for 5 hours, quenched by adding 2N aq. HCl (20 mL) and extracted with $CH_2Cl_2$ (2x50 mL). The combined organic layers were washed with sat. aq. sodium bicarbonate solution followed by the brine solution, dried over $Na_2SO_4$ and concentrated under diminished pressure. The crude pale-yellow residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford the title carbonate reagent as a white solid (13 g, 85%).

**General procedure for the synthesis of ethynylcyclohexyl glycosyl carbonate donors (5, 6, 8, 24, 28, 46):** To a solution of hemiacetals (1 mmol) in anhydrous $CH_2Cl_2$ (15 mL), DMAP (1.5 mmol) was added at 25 °C and stirred for 15 min, ethynylcyclohexyl(4-nitrophenyl) carbonate (**14**) (1.2 mmol) was added portion wise (3x) in 25 min intervals. Stirred the the reaction mixture for 8-10 h at 25 °C, the progress of the reaction was monitored by the TLC analysis and after consumption of starting material, reaction mixture was concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (EtOAc/*n*-hexane). Eluents along with alkynyl carbonate donor along with trace amount of 4-nitrophenol were concentrated *in vacuo*. Further, the resulting residue was redissolved in $CH_2Cl_2$ (30 mL) and washed with saturated solution of $NaHCO_3$ (3x15 mL) followed by brine solution. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo* to obtain the desired alkynyl glycosyl carbonate donors in 82-90% yield.

**General procedure for the synthesis of benzyl ethers (15, 26):**

To a solution of alcohol (1 mmol) in anhydrous DMF (15 mL) was added NaH (60% oil dispersion, 2.5 mmol per alcohol) at 0 °C and stirred for 15 minutes. BnBr (1.1 mmol per alcohol) was added dropwise to the resulting reddish-brown cake under $N_2$ atmosphere. The reaction mixture gradually warmed to 25 °C and stirred for 1 h. At the end of reaction, the reaction mixture was quenched by adding ice-cold water (50 mL) and diluted with ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (2x50 mL). The combined ethyl acetate layers were washed with cold water and brine solution, the organic layers were dried over anhydrous sodium sulfate, filtered and

the filtrate was concentrated *in vacuo* to obtain a crude residue that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford desired compounds in 75-82% yield.

**Synthesis of 1,2-*O*-propargyl orthoester (10):** To a solution of 2,3,4,6-tetra-*O*-benzoylglucopyranosyl bromide (2.00 g, 3.03 mmol) in 15 mL anhydrous $CH_2Cl_2$, propargyl alcohol (874.61 μL, 15.16 mmol) and 2,6-lutidine (2.46 mL, 21.23 mmol) were added. Subsequently catalytic amount of tetra *n*-butyl ammonium iodide was added to the reaction mixture and refluxed for 24 h at 65 °C. After completion of the reaction (as adjudged by TLC analysis), the reaction mixture was cooled to room temperature, diluted with water (20 mL) and extracted with $CH_2Cl_2$ (2x30 mL). The combined $CH_2Cl_2$ layers were washed with saturated aqueous solution of oxalic acid, brine solution, dried over anhydrous sodium sulphate, filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (EtOAc/*n*-hexane) to afford corresponding propargyl 1,2-*O*-orthoester in 82% yield.

**Synthesis of hemiacetals from orthoester (21**, **27):** To a solution of orthoester (1.00 g, 1.69 mmol) in $CH_3CN$ (9 mL) and water (560 μL, 30.50 mmol) was added a catalytic amount of $AuBr_3$ (36.84 mg, 84.36 μmol) and stirred the reaction mixture for 30 min at room temperature. After completion, the reaction mixture was quenched by adding $Et_3N$ (0.5 mL) and concentrated under diminished pressure to obtain crude residue that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain desired hemiacetals in 80-83%yield.

**Opening of orthoester using $AuBr_3$ (7**, **16):** To a solution of orthoester (1 mmol) and allyl alcohol (6 mmol) in anhydrous $CH_2Cl_2$ (5 mL) was added freshly activated 4Å MS powder (0.5 g) at 25 °C and stirred for 20 minutes. After this, catalytic amount of $AuBr_3$ was added and stirred the reaction mixture for 30 min. After completion, the reaction mixture was neutralized by the addition of $Et_3N$ (1 mL), filtered off through a pad of Celite® and concentrated *in vacuo*. The resulting crude thick gum was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain allyl mannopyranosides in 84-86% yield.

**Synthesis of 53:** To a solution of alcohol (2.00 g, 4.36 mmol) and a catalytic amount of DMAP (266.38 mg, 2.18 mmol) in pyridine (10 mL), benzoyl chloride (1.77 mL, 15.26 mmol) was added drop wise at 0 °C. Gradually warmed the reaction mixture to room temperature and stirred for 3 h at 60 °C. After completion, the reaction mixture was cooled to room temperature and quenched

by addition 2N aq. HCl solution (15 mL), extracted with $CH_2Cl_2$ (3x10 mL) and $CH_2Cl_2$ layers were washed with saturated solution of sodium bicarbonate followed by brine solution and dried over $Na_2SO_4$. The organic layers were concentrated under diminished pressure and resultant crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford the desired benzoate in 83% yield.

**General procedure for the deprotection of benzoates (7**, **17**, **22**, **60):** To a solution of 0.5 M NaOMe in methanol was added a solution of the benzoate compound (1 mmol) in MeOH-$CH_2Cl_2$ (3:1) (10 mL) and stirred at reaction mixture at 25 °C. After 10 h, the reaction mixture was neutralised by adding Amberlite® IR 120 ($H^+$) resin and filtered; filtrate was concentrated under diminished pressure, the crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain the desired compound.

**General procedure for the deprotection of allyl glycosides (2**, **18**, **53**, **59):** $PdCl_2$ (0.2 mmol) in methanol (10 mL) was added drop-wise to a solution of allyl glycosides (1mmol) in $CH_2Cl_2$ (12 mL) at 25 °C and stirred the reaction mixture for 5-7 h. At end of reaction confirmed by checking the TLC, the reaction was arrested by the addition of excess of $Et_3N$ and filtered through a pad of Celite®, filtrate was concentrated under diminished pressure. The crude material was purified by silica gel column chromatography (*n*-hexane/EtOAc) to furnish desired hemiacetals in good yields. In case of compounds **18**, **53** (to stop the migration of Lev), 12 mL of DME:MeOH:$CH_2Cl_2$ (4:3:3) was used as the solvent system instead of methanol and $CH_2Cl_2$ system as per the reported procedure.[50]

**General procedure for the protection of silyl ether (25**, **52):** To a solution of alcohol (1 mmol) in anhydrous DMF (15 mL), imidazole (1.3 mmol) and a catalytic amount of DMAP (0.5 mmol) were added and stirred it for 10 minutes. After this, TBDPSCl (1.2 mmol) was added dropwise at 0 °C and gradually warmed the reaction mixture to room temperature and stirred at 25 °C for 5 h. At the end, the reaction mixture was diluted with EtOAc (20 mL) and water (20 mL), extracted with EtOAc (2x15 mL), combined organic layers were washed with brine solution and dried over $Na_2SO_4$, concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain desired product in 86% yield.

**General procedure for the deprotection of silyl ethers (30**, **32**, **34**, **37**, **39**, **41**, **54):** HF•py (3 mmol) was added dropwise under $N_2$ atmosphere to a solution of silyl ether (1 mmol) in pyridine

(3 times to the volume of HF•py) at 0 °C and gradually warmed to 25 °C. Stirred the reaction mixture for 6 h at 25 °C, the reaction was quenched by adding 2N aq. solution of HCl at 0 °C and diluted with EtOAc (30 mL), washed with ice cold water (2x10 mL), sat. solution of sodium bicarbonate, and brine solution. The organic layers were dried over anhydrous $Na_2SO_4$, concentrated *in vacuo*. The obtained crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes) to afford the alcohols in 84-90% yield.

**Levulinoate ester protection (for 18):** A catalytic amount of DMAP (124 mg, 1.02 mmol), Levulinic acid (237.30 μl, 2.65 mmol) and *N*,*N*′-Diisopropylcarbodiimide (410.33 μL, 2.65 mmol) were sequentially added to a solution of alcohol **19** (1.00 g, 2.05 mmol) in anhydrous $CH_2Cl_2$ (5 mL) at 0 °C under $N_2$ atmosphere and gradually warmed to 25 °C and stirred for 5 h. After completion, the reaction mixture was concentrated under diminished pressure, the resultant crude material was purified by silica gel column chromatography (*n*-hexane/EtOAc) to get desired levulinoate ester in 80% yield.

**General procedure for the deprotection of levulinoate ester (for 42**, **44**, **55**, **57):** To a solution of levulinoate ester (1.0 mmol) in $CH_2Cl_2$ (7 mL), a buffer solution of py./AcOH (27:22 mmol) and 70% hydrazine hydrate (6 mmol) were added and stirred the reaction mixture at 25 °C for 3-4 h. After completion (by examining TLC), the excess hydrazine was quenched by the addition of acetone (2 mL) and extracted with ethyl acetate (2x10 mL). The combined organic layers were washed with 1N aq. solution of HCl (15 mL), sat. solution of sodium bicarbonate followed by brine solution, the organic layers were dried over anhydrous $Na_2SO_4$ and concentrated under diminished pressure. The crude residue was purified by silica gel column chromatography to furnish the desired product in 85-90% yield.

**General protocol for glycosylation (21**, **29**, **31**, **33**, **35**, **36**, **38**, **40**, **42**, **44**, **47**, **55**, **57**, **59**, **63**, **64):** Freshly activated 4Å MS powder (0.100 g) was added to a solution of glycosyl acceptor (1.0 mmol) and alkynyl glycosyl carbonate donor (1.0 mmol) in anhydrous $CH_2Cl_2$ (10 mL) at 25 °C and stirred for 10 min. After this, chloro[tris(2,4-di-*tert*-butylphenyl)phosphite]gold(I) (8mol%) and AgOTf (8mol%) were added to the reaction mixture and stirred for 20-30 minutes. After completion, the reaction was quenched by adding $Et_3N$ and filtered off through a bed of Celite®. The filtrate was concentrated under diminished pressure and the resultant crude residue was

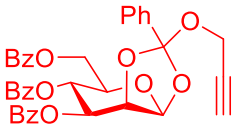
purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford desired glycosides in 80-92% yield.

**General procedure of hydrogenolysis of benzyl groups:** 10% Pd/C (50 mg per benzyl ether) was added to the starting material containing benzyl ethers (1 mmol) in equimolar mixture MeOH:THF:$H_2O$ and stirred the reaction mixture vigorously under $H_2$ atmosphere (balloon pressure). After 48 h, the reaction mixture was filtered off through a pad of Celite® and concentrated under reduced pressure. The residue was purified using bond elute C18-prepacked columns using acetonitrile and water as mobile phase. The collected fractions were lyophilized to obtain the desired compound.

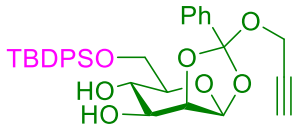
**Synthesis of compound 1*α*:** To a solution of 65 (1 mmol) in anhydrous DMF (4 mL), 3-mercaptopropanyl-*N*-hydroxysuccinimide ester (1.1 mmol) were added and stirred it for 30 minutes at 50 °C. After completion (by examining TLC), co-evaporation with toluene (2x 3 mL), the residue was purified using bond elute C18-prepacked columns with acetonitrile and water as mobile phase. The collected fractions were lyophilized to obtain the desired compound.

## 2.12 Compound Characterization Data

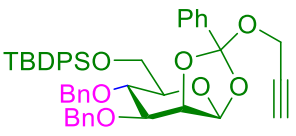
**3,4,6-tri-*O*-benzoyl-β-D-mannopyranoside (prop-2-ynyl)-1,2-orthobenzoate (10):** Yield: (85%); Sticky syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -29.5°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.10 – 8.06 (m, 2H),8.04 – 7.96 (m, 4H), 7.87 – 7.80 (m, 2H), 7.58 – 7.45 (m, 3H),7.43 – 7.32 (m, 9H), 6.13 – 6.02 (m, 1H), 5.94 (d, *J* = 2.9 Hz, 1H),5.91 – 5.82 (m, 1H), 5.28 (t, *J*= 3.5 Hz, 1H), 4.68 (dd, *J* = 12.1, 3.2 Hz, 1H), 4.48 (dd, *J* = 12.2, 4.3 Hz, 1H), 4.28 – 4.19 (m, 1H), 4.20 – 4.06 (m, 2H), 2.37 (t, *J* = 2.4 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.1, 166.0, 165.3, 135.5, 133.6, 133.5, 133.1, 130.0(2C), 129.8(2C), 129.8(2C), 129.8, 129.7, 129.0, 129.0, 128.5(4C), 128.4(4C), 126.8(2C), 122.9, 98.1, 79.4, 76.6, 74.2, 72.1, 71.0, 66.5, 63.0, 52.6; HRMS (ESI-MS): m/z calcd for$[C_{37}H_{30}O_{10}Na]^+$ : 657.1737; Found: 657.1729.



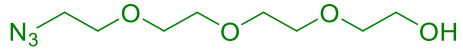

**6-*O*-tert-Butyldiphenylsilyl-β-D-mannopyranoside (prop-2-ynyl)-1,2-orthobenzoate (25):** Yield: (76%); Sticky syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -20.6°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.65 (ddt, *J* = 6.9, 4.6, 2.7 Hz, 5H), 7.47 – 7.43 (m, 2H), 7.38 (t, *J* = 7.3 Hz, 5H), 7.34 – 7.28 (m, 3H), 5.60 (d, *J* = 3.0 Hz, 1H), 4.83 (t, *J* = 3.3 Hz, 1H), 4.11 (d, *J* = 2.4 Hz, 2H), 3.92 (d, *J* = 7.1 Hz, 2H), 3.88 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.81 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.42 (dt, *J* = 8.9, 4.8 Hz, 1H), 3.00 (s, 1H), 2.64 (s, 1H), 2.42 (t, *J* = 2.4 Hz, 1H), 1.04 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 135.6(2C)), 135.6(2C), 135.5, 132.8, 132.7, 129.9, 129.9, 129.6, 128.3(2C), 127.9(2C), 127.8(2C), 126.6(2C), 122.1, 98.1, 79.4, 77.7, 74.6, 73.9, 71.9, 69.5, 64.7, 52.4, 26.8(3C), 19.2. HRMS (ESI-MS): m/z calcd for$[C_{32}H_{36}O_7Na]^+$ : 583.2123; Found: 583.2113.




**2,3-di-*O*-benzyl-6-*O*-tert-Butyldiphenylsilyl-β-D-mannopyranoside prop-2-ynyl-1,2-orthobenzoate (26):** Yield: (78%); Sticky; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -15.6°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.78 – 7.75 (m, 2H), 7.66 (ddd, *J* = 6.6, 4.4, 2.2 Hz, 4H), 7.49 – 7.46 (m, 2H), 7.41 (ddt, *J* = 10.6, 4.2, 2.2 Hz, 4H), 7.36 (q, *J* = 1.9 Hz, 1H), 7.32 (td, *J* = 6.9, 2.6 Hz, 8H), 7.27 (d, *J* = 3.2 Hz, 1H), 7.25 – 7.23 (m, 3H), 5.53 (d, *J* = 2.9 Hz, 1H), 4.97 (dd, *J* = 19.7, 11.3 Hz, 2H), 4.87 – 4.82 (m, 2H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.13 (d, *J* = 2.3 Hz, 3H), 3.96 – 3.92 (m, 2H), 3.82 (dd, *J* = 11.1, 2.3 Hz, 1H), 3.40 (ddd, *J* = 9.0, 3.8, 2.3 Hz, 1H), 2.45 (t, *J* = 2.4 Hz, 1H), 1.01 (s, 9H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 138.4, 137.8, 135.8(2C), 135.7(2C), 135.5, 133.3, 133.1, 129.6, 129.5, 129.4,

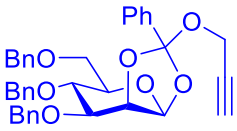


128.6(2C), 128.4(2C), 128.2(2C), 128.1(2C), 128.0, 127.9(2C), 127.7(3C), 127.6(2C), 126.9(2C), 122.3, 98.1, 79.9, 78.6, 76.2, 75.6, 75.1, 74.1, 73.7, 72.0, 62.9, 52.4, 26.9(3C), 19.2; HRMS (ESI-MS): m/z calcd for$[C_{46}H_{48}O_7Na]^+$ : 763.3067; Found: 763.3047.

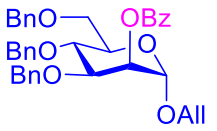
**2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-ol (3):** Yield: (70%); Oil; $^1$H NMR (400 MHz, $CDCl_3$): δ 3.74 (t, *J* = 4.7 Hz, 2H), 3.68 (d, *J* = 5.2 Hz, 10H), 

3.64 – 3.61 (m, 2H), 3.41 (t, *J* = 5.3 Hz, 2H), 2.69 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 72.6, 70.8, 70.7, 70.6, 70.4, 70.1, 61.8, 50.7.

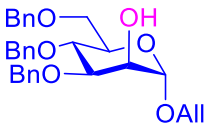
**3,4,6-tri-*O*-benzyl-β-D-mannopyranoside prop-2-ynyl-1,2-orthobenzoate (15)**: Yield: (85%); Sticky; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +13.7°; Yield: (78%); mp (°C): 73.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -13.5°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 7.1, 1.9 Hz, 2H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.42 – 7.38 (m, 3H), 7.34 (dt, *J* = 7.8, 2.4 Hz, 9H), 7.30 – 7.27 (m, 4H), 5.59 (d, *J* = 3.0 Hz, 1H), 4.94 (d, *J* = 11.5 Hz, 2H), 4.86 – 4.82 (m, 2H), 4.68 (d, *J* = 10.9 Hz, 1H), 4.51 – 4.43 (m, 2H), 4.15 (t, *J* = 1.9 Hz, 2H), 4.03 – 3.97 (m, 1H), 3.92 (dd, *J* = 9.3, 3.8 Hz, 1H), 3.72 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.64 – 3.56 (m, 2H), 2.45 (q, *J* = 2.0 Hz, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 138.4, 138.3, 137.9, 135.7, 129.5, 128.6(2C), 128.4(2C), 128.3(2C), 128.2(2C), 128.1(2C), 128.1(2C), 128.0, 127.8, 127.5(2C), 127.5, 126.9(2C), 122.3, 98.1, 79.8, 78.2, 76.1, 75.3, 75.1, 74.3, 73.8, 73.3, 72.0, 69.2, 52.4; HRMS (ESI-MS): m/z calcd for $[C_{37}H_{36}O_7Na]^+$ : 615.2359; Found: 615.2345.



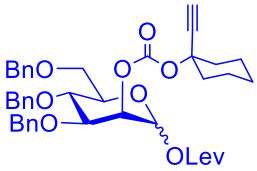

**Allyl 2-*O*-benzoyl-3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (16):** Yield: (70%); Sticky syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -14.6°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.56 – 7.51 (m, 1H), 7.40 – 7.32 (m, 6H), 7.31 – 7.26 (m, 6H), 7.25 – 7.21 (m, 3H), 7.20 – 7.17 (m, 2H), 5.90 (m, 1H), 5.64 (dd, *J* = 2.9, 1.9 Hz, 1H), 5.31 – 5.24 (m, 1H), 5.20 (m, 1H), 5.02 (d, *J* = 1.9 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.60 – 4.54 (m, 2H), 4.52 (d, *J* = 3.3 Hz, 1H), 4.20 (ddt, *J* = 12.9, 5.2, 1.5 Hz, 1H), 4.16 – 4.07 (m, 2H), 4.02 (m, 1H), 3.93 – 3.89 (m, 1H), 3.89 – 3.87 (m, 1H), 3.81 – 3.75 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.8, 138.5, 138.4, 138.1, 133.5, 133.2, 130.0(2C), 129.9, 128.4(2C), 128.4(2C), 128.4(3C), 128.3(2C), 128.1(3C), 127.7, 127.7, 127.6(2C), 127.6, 117.9, 97.0, 78.3, 75.4, 74.4, 73.5, 71.7, 71.6, 69.1(2C), 68.3; HRMS (ESI-MS): m/z calcd for$[C_{37}H_{38}O_7Na]^+$ : 617.2515; Found: 617.2508.



**Allyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (17):** Yield: (84%); Sticky syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -10.6°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 10H), 7.28 (m, 3H), 7.20 – 7.16 (m, 2H), 5.89 (m, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.18 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.96 (d, *J* = 1.7 Hz, 1H), 4.83 (d, *J* = 10.8 Hz, 1H), 4.70 (d, *J* = 3.4 Hz, 2H), 4.66 (d, *J* = 12.2 Hz, 1H), 4.52 (t, *J* = 11.3 Hz, 2H), 4.24 – 4.15 (m, 1H), 4.07 (dt, *J* = 3.5, 1.7 Hz, 1H), 3.99 (ddt, *J* = 12.9, 6.2, 1.4 Hz, 1H), 3.92 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.87 (t, *J* = 9.0 Hz, 1H), 3.82 – 3.78 (m, 1H), 3.76 (d, *J* = 4.2 Hz, 1H), 3.73 – 3.69 (m, 1H), 2.55 (s, *J* = 2.7 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 138.3, 138.2, 138.0, 133.7, 128.6(2C), 128.4(2C), 128.4(2C), 128.0(2C), 127.9(2C), 127.9(2C), 127.9, 127.7, 127.6, 117.5, 98.4, 80.3, 75.2, 74.3, 73.5, 72.0, 71.1, 68.9, 68.4, 68.0; HRMS (ESI-MS): m/z calcd for$[C_{30}H_{34}O_6Na]^+$ : 513.2213; Found: 513.2219.



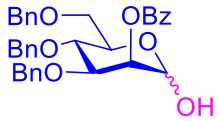

**Allyl 2-*O*-levolinoate-3,4,6-tri-*O*-benzyl- α-D-mannopyranoside (18):** Yield: (80%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +1.6°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.34 (m, 3H), 7.33 – 7.30 (m, 5H), 7.29 – 7.25 (m, 5H), 7.19 – 7.15 (m, 2H), 5.87 (m, 1H), 5.39 (dd, *J* = 3.4, 1.9 Hz, 1H), 5.26 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.18 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.88 (d, *J* = 1.9 Hz, 1H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.70 (d, *J* = 5.7 Hz, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 4.54 (d, *J* = 1.1 Hz, 1H), 4.50 (d, *J* = 10.8 Hz, 2H), 4.16 (ddt, *J* = 12.8, 5.2, 1.5 Hz, 1H), 4.04 – 4.00 (m, 1H), 4.00 – 3.95 (m, 1H), 3.87 (t, *J* = 9.2 Hz, 1H), 3.83 (d, *J* = 4.4 Hz, 1H), 3.80 (t, *J* = 3.0 Hz, 1H), 3.74 – 3.68 (m, 1H), 2.73 – 2.67 (m, 4H), 2.12 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 206.4,172.1, 138.4, 138.3, 138.1, 133.5, 128.4(6C), 128.1(2C), 128.0(2C), 127.8(2C), 127.7, 127.7, 127.7, 117.8, 96.9, 78.2, 75.3, 74.3, 73.5, 71.7, 71.4, 68.9, 68.9, 68.2, 38.0, 29.8, 28.2; HRMS (ESI-MS): m/z calcd for$[C_{35}H_{40}O_8Na]^+$: 611.2621; Found: 617.2615.



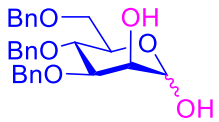

**Compound 20:** Yield: (82%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +2.8°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.26 (m, 13H), 7.19 – 7.14 (m, 2H), 5.39 – 5.34 (m, 1H), 4.86 (dd, *J* = 5.4, 1.6 Hz, 1H), 4.85 – 4.81 (m, 1H), 4.71 – 4.67 (m, 1H), 4.67 – 4.64 (m, 1H), 4.56 – 4.50 (m, 2H), 4.49 – 4.47 (m, 1H), 4.41 – 4.36 (m, 1H), 4.00 – 3.94 (m, 1H), 3.93 – 3.88 (m, 1H), 3.87 – 3.84 (m, 1H), 3.83 – 3.76 (m, 2H), 3.71 – 3.67 (m, 1H), 3.57 – 3.45 (m, 1H), 2.74 – 2.66 (m, 4H), 2.64 – 2.61 (m, 1H), 2.21 – 2.13 (m, 2H), 2.12 (s, 3H), 1.92 – 1.80 (m, 2H), 1.71 – 1.62 (m, 4H), 1.56 – 1.49

(m, 1H), 1.37 – 1.29 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 206.4, 206.4, 172.0, 172.0, 152.2, 152.2, 151.9, 151.9, 138.3, 138.2, 137.9, 137.9, 128.4, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 98.2, 98.2, 97.9, 97.8, 82.7, 82.7, 82.6, 78.4, 78.3, 78.2, 78.1, 78.0, 77.9, 77.3, 75.3, 75.2, 74.3, 74.2, 74.1, 74.0, 73.5, 73.4, 71.9, 71.9, 71.8, 71.8, 71.8, 68.8, 68.7, 68.7, 68.6, 68.6, 68.2, 67.2, 67.2, 66.7, 66.3, 46.1, 46.1, 38.0, 36.8, 36.8, 36.7, 29.7, 29.6, 29.4, 28.2, 24.9, 24.9, 24.9, 22.6; HRMS (ESI-MS): m/z calcd for$[C_{41}H_{46}O_{10}Na]^+$: 721.2989; Found: 721.2980.

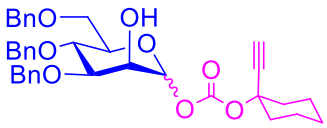
**2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α/β-D-mannopyranoside (21):** Yield: (82%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +10.6°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.55 – 7.51 (m, 1H), 7.39 – 7.36 (m, 2H), 7.35 – 7.34 (m, 2H), 7.32 (d, *J* = 0.9 Hz, 1H), 7.31 – 7.24 (m, 8H), 7.23 – 7.21 (m, 2H), 7.16 (dd, *J* = 7.2, 2.4 Hz, 2H), 5.59 (dd, *J* = 3.2, 2.0 Hz, 1H), 5.30 (dd, *J* = 3.6, 1.9 Hz, 1H), 4.85 (d, *J* = 10.9 Hz, 1H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.56 – 4.52 (m, 2H), 4.50 (d, *J* = 5.3 Hz, 1H), 4.13 (td, *J* = 11.1, 10.3, 3.4 Hz, 2H), 4.03 (d, *J* = 3.8 Hz, 1H), 3.90 (t, *J* = 9.6 Hz, 1H), 3.74 (d, *J* = 3.7 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.8, 138.3, 138.1, 133.2, 130.0, 130.0, 128.5, 128.4, 128.1, 127.9, 127.7, 127.7, 92.5, 77.8, 75.2, 74.6, 73.4, 71.6, 71.3, 69.5; HRMS (ESI-MS): m/z calcd for$[C_{34}H_{34}O_7Na]^+$: 577.2202; Found: 577.2112.



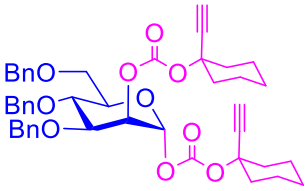

**3,4,6-tri-*O*-benzyl-α/β-D-mannopyranoside (22):** Yield: (83%); Sticky; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -1.6°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.32 (m, 5H), 7.32 – 7.29 (m, 10H), 7.28 – 7.26 (m, 6H), 7.17 – 7.15 (m, 3H), 5.25 (d, *J* = 1.5 Hz, 1H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.67 – 4.65 (m, 2H), 4.62 (d, *J* = 3.2 Hz, 1H), 4.60 – 4.56 (m, 1H), 4.54 (s, 1H), 4.49 (d, *J* = 4.4 Hz, 2H), 4.46 (d, *J* = 3.4 Hz, 1H), 4.07 – 4.02 (m, 1H), 3.99 (dd, *J* = 3.3, 1.8 Hz, 1H), 3.92 (dd, *J* = 9.1, 3.3 Hz, 2H), 3.74 – 3.70 (m, 2H), 3.66 – 3.63 (m, 2H), 2.68 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 138.3, 138.2, 138.0, 137.9, 137.8, 137.8, 128.6(2C), 128.5, 128.4(2C), 128.4(2C), 128.2, 128.1(2C), 128.0, 128.0(2C), 127.9, 127.9, 127.8(2C), 127.7, 94.4, 93.9, 81.6, 79.7, 75.1, 75.1, 74.6, 74.6, 73.8, 73.6, 73.4, 72.0, 71.5, 70.7, 69.4, 68.9, 68.8, 68.6; HRMS (ESI-MS): m/z calcd for$[C_{27}H_{30}O_6Na]^+$: 473.1940; Found: 473.1933.



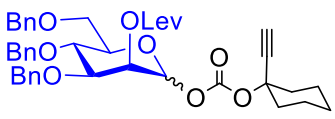
**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-3,4,6-tri-*O*-benzyl-α/β-D-mannopyranoside (23):** Yield: (84%); Sticky; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -9.5°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 2.2 Hz, 3H), 7.33 (s, 1H), 7.33 (s, 3H), 7.30 (d, *J* = 3.1 Hz, 2H), 7.29 – 7.24 (m, 4H), 7.18 (dd, *J* = 7.4, 2.1 Hz, 2H), 6.08 (d, *J* = 1.9 Hz, 1H), 4.83 (d, *J* = 10.8 Hz, 1H), 4.70 (s, 2H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.52 (t, *J* = 11.0 Hz, 2H), 4.07 (t, *J* = 2.5 Hz, 1H), 3.99 – 3.93 (m, 2H), 3.90 (dt, *J* = 10.1, 2.2 Hz, 1H), 3.77 (dd, *J* = 11.1, 3.8 Hz, 1H), 3.70 (dd, *J* = 11.1, 1.8 Hz, 1H), 2.72 (d, *J* = 9.4 Hz, 1H), 2.60 (s, 1H), 2.14 (dq, *J* = 19.5, 5.5, 5.0 Hz, 2H), 1.86 (dp, *J* = 13.4, 4.1 Hz, 2H), 1.62 (ddd, *J* = 13.0, 8.7, 4.0 Hz, 4H), 1.54 – 1.48 (m, 1H), 1.35 – 1.29 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 150.7, 138.3, 138.3, 137.8, 128.7(2C), 128.5(2C), 128.4(2C), 128.1, 128.0(2C), 128.0(2C), 127.9(2C), 127.8, 127.7, 96.1, 82.7, 79.6, 78.3, 75.3, 73.7, 73.6, 73.6, 72.3, 68.5, 67.5, 37.0, 36.6, 25.0, 22.6(2C); HRMS (ESI-MS): m/z calcd for$[C_{36}H_{40}O_8Na]^+$: 623.2621; Found: 623.2611.




**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (24):** Yield: (40%); mp (°C): 65.4; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +8.6°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.35 (dt, *J* = 7.6, 1.7 Hz, 4H), 7.33 – 7.30 (m, 2H), 7.29 – 7.28 (m, 2H), 7.26 (ddd, *J* = 4.2, 2.8, 1.1 Hz, 5H), 7.18 – 7.14 (m, 2H), 6.11 (d, *J* = 2.0 Hz, 1H), 5.31 (dd, *J* = 3.3, 2.1 Hz, 1H), 4.87 (d, *J* = 10.7 Hz, 1H), 4.79 (d, *J* = 11.0 Hz, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.53 (d, *J* = 2.0 Hz, 1H), 4.50 (d, *J* = 3.2 Hz, 1H), 4.06 – 4.01 (m, 1H), 3.99 – 3.93 (m, 2H), 3.83 – 3.78 (m, 1H), 3.73 (dd, *J* = 11.2, 1.4 Hz, 1H), 2.61 (s, 1H), 2.57 (s, 1H), 2.15 (dt, *J* = 13.1, 7.6 Hz, 4H), 1.92 – 1.83 (m, 4H), 1.63 (dtd, *J* = 13.2, 9.6, 8.5, 4.2 Hz, 8H), 1.51 (dd, *J* = 6.2, 3.6 Hz, 2H), 1.33 (dt, *J* = 5.9, 3.0 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 152.3, 150.3, 138.3, 138.2, 137.9, 128.3(2C), 128.3(2C), 128.3(2C), 128.0(2C), 128.0(2C), 127.9(2C), 127.7, 127.7, 127.6, 94.2, 82.9, 82.5, 78.5, 78.2, 77.9, 75.3, 75.3, 75.0, 73.9, 73.6, 73.5, 72.1, 70.5, 68.6, 37.0, 36.9, 36.5, 36.5, 25.0, 24.9, 22.5(2C), 22.5(2C); HRMS (ESI-MS): m/z calcd for$[C_{45}H_{50}O_{10}Na]^+$: 773.3302; Found: 773.3299.

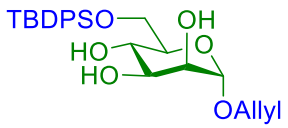



**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-levolinoate-3,4,6-tri-*O*-benzyl-α/β-D-mannopyranoside (6):** Yield: (80%); Sticky syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -9.5°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.7 Hz, 3H), 7.35 – 7.26 (m, 28H), 7.19 – 7.14 (m, 4H), 6.87 – 6.83 (m, 3H), 5.98 (d, *J* = 2.0 Hz, 1H), 5.45 (dd,

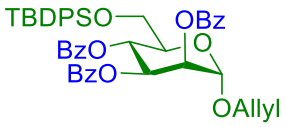


*J* = 3.3, 2.1 Hz, 1H), 4.88 – 4.82 (m, 2H), 4.75 – 4.62 (m, 4H), 4.56 – 4.47 (m, 6H), 4.06 – 4.00 (m, 2H), 3.96 – 3.91 (m, 3H), 3.86 – 3.78 (m, 3H), 3.75 – 3.70 (m, 2H), 2.77 (s, 2H), 2.74 – 2.68 (m, 5H), 2.62 (d, *J* = 4.6 Hz, 2H), 2.17 – 2.09 (m, 10H), 1.91 – 1.81 (m, 4H), 1.69 – 1.52 (m, 10H), 1.35 – 1.28 (m, 2H),1.32 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 207.3, 207.2, 172.2, 171.9, 150.9, 150.4, 141.1, 138.1, 137.9, 137.8, 137.7, 137.3, 128.5, 128.4, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 126.2, 115.7, 94.2, 93.8, 82.4, 79.7, 78.9, 78.7, 77.6, 77.4, 77.3, 77.1, 76.8, 76.2, 75.5, 75.4, 75.3, 73.6, 73.6, 73.5, 72.0, 71.6, 68.4, 67.7, 67.5, 38.2, 38.0, 36.8, 36.7, 36.6, 36.6, 29.8, 29.8, 28.3, 28.1, 24.9, 22.5; HRMS (ESI-MS): m/z calcd for$[C_{42}H_{50}O_{10}Na]^+$: 737.3296; Found: 737.3305.

**Allyl 6-*O*-$^t$butyldiphenylsilyl-α-D-mannopyranoside (52):** Yield: (84%); Sticky syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -7.8°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.68 (ddd, *J* = 7.8, 4.5, 1.7 Hz, 4H), 7.43 – 7.34 (m, 6H), 5.84 (m, 1H), 5.23 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.15 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.80 (d, *J* = 1.5 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.98 – 3.90 (m, 2H), 3.90 – 3.84 (m, 2H), 3.83 – 3.79 (m, 1H), 3.75 (td, *J* = 9.2, 1.9 Hz, 1H), 3.67 (td, *J* = 9.5, 4.7 Hz, 2H), 3.48 (s, 1H), 3.13 (s, 1H), 1.05 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 135.6(4C), 133.7, 133.0, 133.0, 129.9(2C), 127.8(4C), 117.6, 98.7, 71.8, 71.3, 70.5, 70.0, 67.9, 65.1, 26.8(3C), 19.2; HRMS (ESI-MS): m/z calcd for$[C_{34}H_{34}O_7Na]^+$: 577.2202; Found: 577.2112.

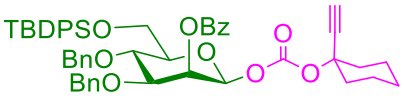



**Allyl 2,3,4-tri-*O*-benzoyl-6-*O*-$^t$butyldiphenylsilyl-α-D-mannopyranoside (53):** Yield: (90%); Sticky syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +9.3°; IR ($cm^{-1}$, $CHCl_3$): 3067, 2930, 2861, 1724, 1600, 1454, 1356, 1266, 1106, 1065, 1027, 968, 706; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.10 (m, 2H), 7.88 (ddd, *J* = 21.2, 8.3, 1.3 Hz, 4H), 7.73 – 7.68 (m, 2H), 7.61 – 7.49 (m, 4H), 7.46 – 7.32 (m, 6H), 7.30 – 7.23 (m, 5H), 7.16 (t, *J* = 7.4 Hz, 2H), 6.13 (t, *J* = 10.1 Hz, 1H), 5.98 (m, 1H), 5.88 (dd, *J* = 10.2, 3.3 Hz, 1H), 5.72 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.37 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.27 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.16 (d, *J* = 1.8 Hz, 1H), 4.31 (dd, *J* = 12.8, 5.2 Hz, 1H), 4.21 – 4.16 (m, 1H), 4.16 – 4.09 (m, 1H), 3.92 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.85 (dd, *J* = 11.5, 2.1 Hz, 1H), 1.06 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.7, 165.6, 165.3, 135.7(2C), 135.6(2C), 133.4, 133.4, 133.2,133.1, 133.1, 133.0, 130.0(2C), 129.8(2C), 129.8(2C), 129.6, 129.6, 129.5, 129.5, 129.3, 128.6(2C), 128.4(2C),

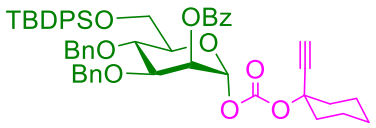


128.3(2C), 127.6(2C), 127.6(2C), 118.2, 96.7, 71.6, 70.9, 70.7, 68.5, 66.7, 62.7, 26.7(3C), 19.2; HRMS (ESI-MS): m/z calcd for$[C_{46}H_{46}O_9SiNa]^+$: 793.2809; Found: 793.2803.

**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-tert-butyldiphenylsilyl-β-D-mannopyranoside (8β):** Yield: (84%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -7.5°; ; IR ($cm^{-1}$, $CHCl_3$): 3068, 2929, 2857, 1762, 1729, 1598, 1454, 1240, 1108, 1071, 1018, 945, 910, 849, 706; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.77 – 7.74 (m, 2H), 7.71 (dt, *J* = 6.9, 1.4 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.40 – 7.35 (m, 6H), 7.32 (dd, *J* = 7.7, 1.8 Hz, 4H), 7.29 – 7.25 (m, 5H), 7.24 (s, 1H), 7.18 – 7.15 (m, 2H), 6.16 (d, *J* = 2.0 Hz, 1H), 5.75 (dd, *J* = 3.3, 2.1 Hz, 1H), 4.94 (d, *J* = 10.6 Hz, 1H), 4.83 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 10.7 Hz, 1H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.30 (t, *J* = 9.7 Hz, 1H), 4.16 (dd, *J* = 9.5, 3.3 Hz, 1H), 4.05 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.93 (dd, *J* = 11.3, 1.7 Hz, 1H), 3.91 – 3.87 (m, 1H), 2.61 (s, 1H), 2.14 (q, *J* = 7.2, 6.3 Hz, 2H), 1.86 (t, *J* = 10.3 Hz, 2H), 1.63 (ddd, *J* = 18.1, 8.3, 4.0 Hz, 4H), 1.54 – 1.49 (m, 1H), 1.35 – 1.29 (m, 1H), 1.10 (s, 9H); $^{13}C$ NMR (101 MHz, $CDCl_3$): δ 165.5, 150.4, 138.4, 137.9, 135.9(2C), 135.7(2C), 134.8, 133.5, 133.3, 133.0, 130.1(2C), 129.7, 129.7, 129.6, 129.6, 128.4(2C), 128.4(3C), 128.1(2C), 127.8(2C), 127.8(2C), 127.7(2C), 127.6, 94.7, 82.5, 78.4, 78.1, 75.4, 75.3, 74.5, 73.4, 71.9, 68.0, 62.4, 36.9, 36.6, 26.9(3C), 24.9, 22.5(2C), 19.4; HRMS (ESI-MS): m/z calcd for$[C_{52}H_{56}O_9SiNa]^+$: 875.3591; Found: 875.3590.

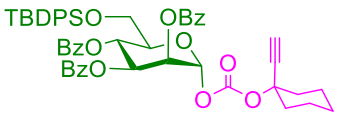



**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-tert-butyldiphenylsilyl-α-D-mannopyranoside (8α):** Yield: (84%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -7.2°; IR ($cm^{-1}$, $CHCl_3$): 3066, 2929, 2857, 1763, 1729, 1598, 1454, 1240, 1108, 1071, 1018, 945, 910, 849, 705; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 6.8 Hz, 2H), 7.86 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.79 (d, *J* = 6.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.49 – 7.38 (m, 10H), 7.38 – 7.29 (m, 7H), 7.25 (dd, *J* = 6.7, 2.6 Hz, 2H), 6.02 (dd, *J* = 3.0, 1.2 Hz, 1H), 5.79 (d, *J* = 1.2 Hz, 1H), 5.00 (d, *J* = 10.6 Hz, 1H), 4.92 (d, *J* = 11.3 Hz, 1H), 4.75 (d, *J* = 10.6 Hz, 1H), 4.64 (d, *J* = 11.3 Hz, 1H), 4.33 (t, *J* = 9.5 Hz, 1H), 4.12 (dd, *J* = 11.5, 2.9 Hz, 1H), 4.06 (dd, *J* = 11.4, 1.9 Hz, 1H), 3.90 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.57 (d, *J* = 9.6 Hz, 1H), 2.65 (s, 1H), 2.27 – 2.17 (m, 2H), 1.99 – 1.88 (m, 2H), 1.77 – 1.63 (m, 4H), 1.61 – 1.55 (m, 1H), 1.40 – 1.34 (m, 1H), 1.19 (s, 9H); $^{13}C$ NMR (101 MHz, $CDCl_3$): δ 165.9, 151.2, 138.3, 137.5, 136.0(2C), 135.7(2C), 133.5, 133.1, 133.0,

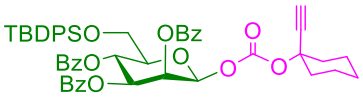


130.2(2C), 130.0, 129.7, 129.6, 128.5(2C), 128.4(2C), 128.4(2C), 128.3(2C), 128.0(2C), 127.9, 127.8(2C), 127.8, 127.7(2C), 94.1, 82.6, 80.1, 78.6, 76.9, 75.5, 75.3, 73.4, 71.6, 67.9, 62.4, 36.8, 36.7, 26.9(3C), 25.0, 22.5(2C), 19.4; HRMS (ESI-MS): m/z calcd for$[C_{52}H_{56}O_9SiNa]^+$: 875.3591; Found: 875.3590.

**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl) 2,3,4-tri-*O*-benzoyl-6-*O*-$^t$butyldiphenylsilyl-α-D-mannopyranoside (51α):** Yield: (85%); mp (°C): 65.9; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -7.5°; IR ($cm^{-1}$, $CHCl_3$): 3067, 2929, 2857, 1763, 1729, 1598, 1455, 1240, 1108, 1071, 1018, 945, 910, 849, 708; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.10 (m, 2H), 7.94 – 7.91 (m, 2H), 7.86 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.77 – 7.74 (m, 2H), 7.58 (dd, *J* = 6.8, 1.3 Hz, 2H), 7.55 – 7.52 (m, 1H), 7.47 – 7.41 (m, 3H), 7.40 – 7.37 (m, 4H), 7.36 – 7.32 (m, 2H), 7.30 – 7.26 (m, 3H), 7.16 (d, *J* = 7.6 Hz, 2H), 6.19 (t, *J* = 9.4 Hz, 1H), 6.05 (d, *J* = 1.3 Hz, 1H), 6.03 (dd, *J* = 3.2, 1.3 Hz, 1H), 5.62 (dd, *J* = 9.8, 3.1 Hz, 1H), 3.99 (dd, *J* = 11.1, 2.3 Hz, 1H), 3.96 – 3.93 (m, 1H), 3.89 (dd, *J* = 11.1, 3.6 Hz, 1H), 2.60 (s, 1H), 2.16 (d, *J* = 8.6 Hz, 2H), 1.87 (t, *J* = 10.8 Hz, 2H), 1.67 (s, 1H), 1.61 – 1.49 (m, 4H), 1.34 – 1.29 (m, 1H), 1.09 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.7, 165.6, 165.1, 151.0, 135.9(2C), 135.7(2C), 133.4, 133.4(2C), 133.0, 130.3(2C), 130.0(2C), 129.9(2C), 129.7(2C), 129.5, 129.4, 129.0, 128.6(5C), 128.4(2C), 127.8(2C), 127.7(2C), 93.5, 82.5, 78.9, 76.0, 75.5, 72.0, 68.8, 65.9, 62.2, 36.8, 36.7, 26.7(3C), 25.0, 22.6(2C), 19.3; HRMS (ESI-MS): m/z calcd for$[C_{52}H_{52}O_{11}SiNa]^+$: 903.3177; Found: 903.3169.

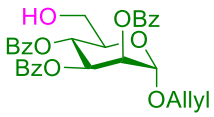



**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl) 2,3,4-tri-*O*-benzoyl-6-*O*-$^t$butyldiphenylsilyl-β-D-mannopyranoside (51β):** An analytical sample was prepared by silica gel column chromatography for characterization purposes. IR ($cm^{-1}$, $CHCl_3$): 3066, 2929, 2857, 1763, 1729, 1598, 1454, 1240, 1108, 1071, 1018, 945, 910, 849, 705 $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.96 – 7.89 (m, 2H), 7.89 – 7.82 (m, 2H), 7.71 (dt, *J* = 6.6, 1.6 Hz, 2H), 7.56 (m, 4H), 7.48 – 7.37 (m, 5H), 7.40 – 7.25 (m, 6H), 7.12 (t, *J* = 7.6 Hz, 2H), 6.30 (d, *J* = 7.0 Hz, 1 H), 6.26 (s, 1H), 5.88 (dd, *J* = 10.2, 3.4 Hz, 1H), 5.81 (dd, *J* = 3.4, 2.0 Hz, 1H), 4.29 (dt, *J* = 10.2, 2.7 Hz, 1H), 3.87 (d, *J* = 2.7 Hz, 2H), 2.66 (s, 1H), 2.29 – 2.21 (m, 2H), 1.98 – 1.86 (m, 2H), 1.80 – 1.62 (m, 4H), 1.66 – 1.60 (m, 1H), 1.36 (dq, *J* = 9.3, 3.7, 2.5 Hz, 1H), 1.07 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.6, 165.3, 165.1, 150.3, 135.8(2C), 135.6(2C), 133.6, 133.3, 133.2, 132.9, 132.8, 130.1(2C),

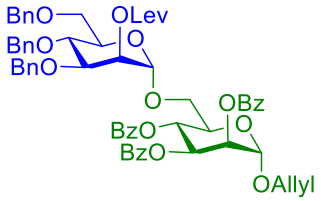


129.8(2C), 129.8(2C), 129.6, 129.5, 129.4, 129.1(2C), 128.6(2C), 128.4(2C), 128.3(2C), 127.7(2C), 127.6(2C), 94.1, 82.4, 78.9, 75.6, 73.5, 70.3, 69.4, 65.8, 62.0, 36.9, 36.8, 26.7(3C), 25.0, 22.7(2C), 19.2; HRMS (ESI-MS): m/z calcd for$[C_{52}H_{52}O_{11}SiNa]^+$: 903.3177; Found: 903.3176.

**Allyl 2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (54):** Yield: (90%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +4.5°; IR ($cm^{-1}$, $CHCl_3$): 3488, 3068, 2927, 1724, 1603, 1453, 1268, 1112, 1067, 1033, 982, 710; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.08 (m, 2H), 7.99 – 7.96 (m, 2H), 7.84 – 7.81 (m, 2H), 7.62 – 7.57 (m, 1H), 7.53 – 7.46 (m, 3H), 7.43 – 7.35 (m, 3H), 7.26 – 7.22 (m, 2H), 6.04 – 6.00 (m, 1H), 6.00 – 5.91 (m, 1H), 5.85 (t, *J* = 10.1 Hz, 1H), 5.70 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.38 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.28 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.16 (d, *J* = 1.8 Hz, 1H), 4.33 – 4.28 (m, 1H), 4.16 – 4.11 (m, 1H), 4.11 – 4.07 (m, 1H), 3.88 – 3.81 (m, 1H), 3.77 (d, *J* = 12.7 Hz, 1H), 2.73 (t, *J* = 6.9 Hz, 1H); $^{13}C$ NMR (101 MHz, $CDCl_3$): δ 166.6, 165.7, 165.6, 133.8, 133.7, 133.3, 133.2, 130.0(4C), 129.8(2C), 129.4, 129.2, 128.8, 128.7(2C), 128.6(2C), 128.4(2C), 118.5, 96.9, 71.2, 70.8, 69.8, 68.9, 67.4, 61.4; HRMS (ESI-MS): m/z calcd for$[C_{30}H_{28}O_9Na]^+$: 555.1631; Found: 555.1626.

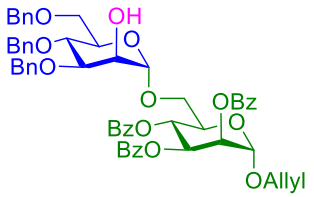



**Allyl 2,3,4-tri-O-benzoyl-6-O-[3,4,6-tri-O-benzyl-2-*O*-(4-oxopentanoyl)-α-mannopyranosyl]-α-D-mannopyranoside (55) :** Yield: (91%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +9.5°; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 7.1, 2.2 Hz, 2H), 7.99 (dd, *J* = 7.3, 2.1 Hz, 2H), 7.86 (dd, *J* = 7.1, 1.9 Hz, 2H), 7.60 – 7.54 (m, 1H), 7.52 – 7.42 (m, 4H), 7.38 – 7.32 (m, 7H), 7.31 (d, *J* = 2.0 Hz, 7H), 7.28 (d, *J* = 7.7 Hz, 3H), 7.19 (dq, *J* = 6.4, 2.0 Hz, 2H), 6.05 – 5.89 (m, 3H), 5.71 (q, *J* = 2.0 Hz, 1H), 5.44 – 5.36 (m, 2H), 5.28 (dd, *J* = 10.4, 2.2 Hz, 1H), 5.13 (d, *J* = 2.3 Hz, 1H), 4.91 (d, *J* = 3.2 Hz, 1H), 4.87 (dt, *J* = 10.9, 2.2 Hz, 1H), 4.60 (dd, *J* = 12.1, 2.2 Hz, 1H), 4.56 – 4.46 (m, 2H), 4.39 (ddt, *J* = 16.0, 11.0, 2.2 Hz, 2H), 4.33 – 4.27 (m, 2H), 4.16 – 4.09 (m, 1H), 3.98 (ddt, *J* = 10.0, 7.6, 3.7 Hz, 2H), 3.87 (ddd, *J* = 11.8, 8.5, 2.6 Hz, 1H), 3.80 (t, *J* = 7.1 Hz, 1H), 3.71 (dd, *J* = 10.9, 3.0 Hz, 2H), 3.57 (dd, *J* = 10.9, 2.4 Hz, 1H), 2.75 – 2.66 (m, 4H), 2.13 (d, *J* = 1.3 Hz, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$): δ 206.4, 171.9, 165.6, 165.5, 165.5, 138.6, 138.2, 138.0, 133.5, 133.4, 133.1, 133.1(2C), 129.9(2C), 129.9(2C), 129.8(2C), 129.4, 129.2, 129.1, 128.6(2C), 128.5(2C), 128.3(2C), 128.3(4C), 128.2(2C), 128.0(2C), 127.9(2C), 127.8(2C), 127.7, 127.6, 127.6, 118.6, 97.8, 96.5, 78.3, 75.1, 74.1, 73.3,

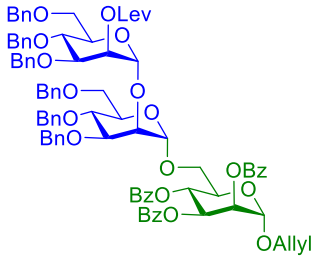


71.6, 71.4, 70.7, 70.2, 69.4, 68.7, 68.7, 67.4, 66.6, 38.0, 29.8, 28.2; HRMS (ESI-MS): m/z calcd for$[C_{62}H_{60}O_{16}Na]^+$: 1085.3936; Found: 1085.3935.

**Allyl 2,3,4-tri-O-benzoyl-6-O-[3,4,6-tri-O-benzyl-α-D-mannopyranosyl]-α-D-mannopyranoside (56):** Yield: (84%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +10.7°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 7.8 Hz, 2H), 8.02 (d, *J* = 7.9 Hz, 2H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.53 – 7.44 (m, 4H), 7.38 (d, *J* = 5.8 Hz, 7H), 7.33 (t, *J* = 4.1 Hz, 8H), 7.29 (s, 2H), 7.25 – 7.18 (m, 2H), 6.06 – 5.94 (m, 3H), 5.74 (d, *J* = 2.2 Hz, 1H), 5.43 (dd, *J* = 17.6, 1.8 Hz, 1H), 5.31 (d, *J* = 10.3 Hz, 1H), 5.16 (d, *J* = 1.8 Hz, 1H), 5.06 (s, 1H), 4.86 (dd, *J* = 10.9, 2.4 Hz, 1H), 4.62 – 4.56 (m, 3H), 4.52 (dd, *J* = 10.9, 2.1 Hz, 1H), 4.44 (dd, *J* = 12.2, 1.8 Hz, 1H), 4.37 – 4.30 (m, 2H), 4.16 (dd, *J* = 12.8, 6.3 Hz, 1H), 4.07 (s, 1H), 4.01 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.89 (d, *J* = 6.9 Hz, 2H), 3.83 – 3.76 (m, 2H), 3.69 (dd, *J* = 10.7, 4.3 Hz, 1H), 3.58 (dd, *J* = 10.8, 2.1 Hz, 1H), 2.54 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.6(2C), 165.4, 138.5, 138.2, 138.0, 133.5, 133.4, 133.2, 133.1, 129.9(2C), 129.9(2C), 129.8(2C), 129.5, 129.2, 129.2, 128.6(2C), 128.5(2C), 128.5(2C), 128.3(4C), 128.3(2C), 127.9(3C), 127.9(2C), 127.8(2C), 127.6, 127.6, 118.6, 99.4, 96.6, 80.2, 75.1, 74.1, 73.4, 71.8, 71.2, 70.8, 70.2, 69.6, 68.8, 68.7, 68.2, 67.6, 66.4; HRMS (ESI-MS): m/z calcd for$[C_{57}H_{56}O_{14}Na]^+$: 987.3568; Found: 987.3357.

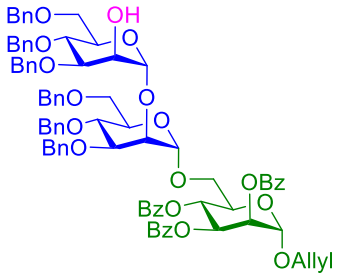



**Allyl 2,3,4-tri-O-benzoyl-6-O-[3,4,6-tri-O-benzyl-2-*O*-[3,4,6-tri-O-benzyl-2-*O*-(4-oxopentanoyl)-α-D-mannopyranosyl]-α-D-mannopyranosyl]-α-D-mannopyranoside (57):** Yield: (87%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +34.2°; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.1 Hz, 2H), 8.04 (d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* = 7.0 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.53 – 7.45 (m, 6H), 7.38 (d, *J* = 7.2 Hz, 9H), 7.35 (d, *J* = 5.3 Hz, 7H), 7.33 (s, 9H), 7.29 (d, *J* = 2.8 Hz, 4H), 7.25 – 7.22 (m, 2H), 6.08 – 5.97 (m, 3H), 5.77 (d, *J* = 5.9 Hz, 1H), 5.58 (s, 1H), 5.45 (d, *J* = 17.1 Hz, 1H), 5.33 (d, *J* = 10.3 Hz, 1H), 5.16 (s, 1H), 5.08 (s, 1H), 5.03 (s, 1H), 4.92 (d, *J* = 10.6 Hz, 2H), 4.71 (s, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.65 – 4.60 (m, 2H), 4.59 (d, *J* = 4.5 Hz, 1H), 4.56 (d, *J* = 5.5 Hz, 1H), 4.52 (d, *J* = 7.0 Hz, 1H), 4.46 (dq, *J* = 13.2, 6.8 Hz, 3H), 4.34 (d, *J* = 12.6 Hz, 2H), 4.18 – 4.12 (m, 1H), 4.04 (d, *J* = 8.2 Hz, 2H), 4.00 (d, *J* = 12.1 Hz, 3H), 3.93 (dd, *J* = 13.0, 9.2 Hz, 2H), 3.86 (d, *J* = 11.0 Hz, 1H), 3.82 (s,

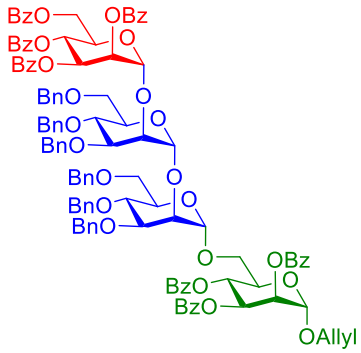


1H), 3.76 (d, *J* = 9.0 Hz, 1H), 3.70 (d, *J* = 10.9 Hz, 2H), 3.63 (s, 1H), 2.76 (s, 4H), 2.19 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 206.4, 171.8, 165.6, 165.6, 165.5, 138.7, 138.6, 138.5, 138.5, 138.3, 138.2, 133.6, 133.4, 133.2, 133.1, 129.9(3C), 129.8(2C), 129.5, 129.2, 129.2, 128.7(2C), 128.5(2C), 128.5(2C), 128.4(4C), 128.3(6C), 128.3(4C), 128.2(2C), 128.1(2C), 127.9(2C), 127.9(2C), 127.7(2C), 127.6, 127.6(2C), 127.6, 127.5(2C), 127.4, 118.7, 99.6, 98.9, 96.5, 79.8, 78.0, 75.2, 75.1, 75.1, 74.5, 74.3, 73.4, 73.2, 72.0, 71.9, 71.9, 71.8, 70.8, 70.3, 69.5, 69.0, 69.0, 68.9, 68.7, 67.6, 66.7, 38.1, 29.9, 28.3; HRMS (ESI-MS): m/z calcd for$[C_{89}H_{90}O_{21}Na]^+$: 1517.5872; Found: 1517.5868.

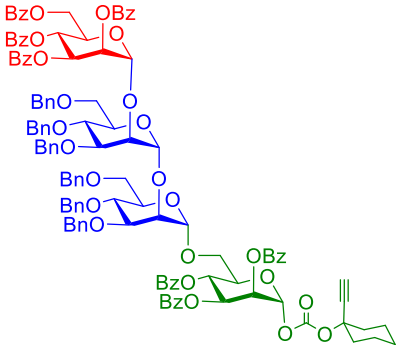
**Allyl 2,3,4-tri-*O*-benzoyl-6-*O*-[3,4,6-tri-*O*-benzyl-2-*O*-[3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl]-α-D-mannopyranosyl]-α-D-mannopyranoside (58):** Yield: (79%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -14.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.10 – 8.07 (m, 2H), 7.96 – 7.93 (m, 2H), 7.84 – 7.81 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.38 (m, 5H), 7.30 (s, 2H), 7.28 (s, 4H), 7.28 (s, 4H), 7.27 (d, *J* = 2.2 Hz, 6H), 7.25 – 7.24 (m, 7H), 7.22 (dd, *J* = 4.5, 3.1 Hz, 4H), 7.20 – 7.17 (m, 3H), 7.16 – 7.13 (m, 3H), 5.98 – 5.89 (m, 3H), 5.66 (s, 1H), 5.35 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.06 (s, 2H), 4.96 (d, *J* = 1.5 Hz, 1H), 4.81 (d, *J* = 9.2 Hz, 1H), 4.79 (d, *J* = 9.2 Hz, 1H), 4.60 (d, *J* = 2.2 Hz, 1H), 4.56 (s, 1H), 4.53 (d, *J* = 3.3 Hz, 1H), 4.52 – 4.49 (m, 2H), 4.47 (s, 2H), 4.43 (d, *J* = 12.3 Hz, 1H), 4.39 (d, *J* = 12.2 Hz, 1H), 4.25 (dd, *J* = 12.8, 5.1 Hz, 2H), 4.08 (s, 1H), 4.07 – 4.02 (m, 1H), 3.98 (s, 1H), 3.91 (d, *J* = 3.2 Hz, 2H), 3.88 (d, *J* = 2.8 Hz, 2H), 3.84 (d, *J* = 6.6 Hz, 2H), 3.81 (d, *J* = 9.4 Hz, 1H), 3.75 – 3.71 (m, 2H), 3.69 (d, *J* = 10.3 Hz, 1H), 3.66 (d, *J* = 8.9 Hz, 1H), 3.60 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.53 (d, *J* = 9.7 Hz, 1H), 2.43 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.6, 165.6, 165.4, 138.7, 138.6, 138.5, 138.3, 138.2, 138.1, 133.5, 133.3, 133.2, 133.1, 129.9(4C), 129.8(2C), 129.5, 129.2, 129.2, 128.7(2C), 128.5(2C), 128.5(4C), 128.3(7C), 128.3(5C), 128.0(2C), 127.9(2C), 127.9(2C), 127.9(4C), 127.6(4C), 127.4(2C), 118.7, 101.2, 99.0, 96.4, 80.0, 79.9, 75.1, 75.0, 74.9, 74.6, 74.3, 73.4, 73.2, 72.2(2C), 72.0, 71.6, 70.8, 70.2, 69.5, 69.1, 68.9, 68.6, 68.6, 67.6, 66.6; HRMS (ESI-MS): m/z calcd for$[C_{84}H_{84}O_{19}Na]^+$: 1419.5505; Found: 1419.5503.



**Allyl 2,3,4-tri-*O*-benzoyl-6-*O*-[3,4,6-tri-*O*-benzyl-2-*O*-[3,4,6-tri-O-benzyl-2-*O*-[2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl]-α-D-mannopyranosyl]-α-D-mannopyranosyl]-α-D-mannopyranoside (59):** Yield: (86%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +13.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.08 (dt, *J* = 14.8, 7.5 Hz, 6H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.91 – 7.80 (m, 6H), 7.64 – 7.45 (m, 4H), 7.44 – 7.35 (m, 12H), 7.26 (s, 18H), 7.23 (d, *J* = 6.3 Hz, 12H), 7.17 – 7.13 (m, 3H), 7.09 (t, *J* = 7.8 Hz, 2H), 6.14 (t, *J* = 10.0 Hz, 1H), 6.00 – 5.86 (m, 5H), 5.68 (s, 1H), 5.42 – 5.29 (m, 2H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.09 (s, 1H), 5.07 (s, 1H), 4.96 (s, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 10.9 Hz, 1H), 4.66 – 4.59 (m, 3H), 4.58 – 4.55 (m, 2H), 4.54 – 4.51 (m, 2H), 4.51 – 4.46 (m, 3H), 4.41 (d, *J* = 12.3 Hz, 1H), 4.29 – 4.20 (m, 3H), 4.11 – 4.03 (m, 4H), 3.99 – 3.91 (m, 3H), 3.88 (d, *J* = 8.9 Hz, 1H), 3.81 (d, *J* = 9.4 Hz, 1H), 3.79 – 3.71 (m, 3H), 3.68 (d, *J* = 11.3 Hz, 1H), 3.60 (d, *J* = 10.7 Hz, 1H), 3.53 (d, *J* = 11.0 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.1, 165.6, 165.6, 165.5, 165.4, 165.4, 165.1, 138.7, 138.6, 138.5, 138.5, 138.4, 138.2, 133.6, 133.4, 133.4, 133.3, 133.2, 133.1, 133.1, 133.0, 130.1, 129.9(3C), 129.9(3C), 129.8(4C), 129.8(4C), 129.6, 129.4, 129.3, 129.2, 129.1, 128.7(2C), 128.6(2C), 128.5(4C), 128.4(2C), 128.4(2C), 128.4(2C), 128.3(10C), 128.3(2C), 128.2(2C), 127.9(2C), 127.8(2C), 127.7(2C), 127.5(8C), 127.5(2C), 127.4, 118.7, 100.5, 99.3, 99.0, 96.4, 80.0, 79.3, 77.3, 75.2(2C), 75.1, 74.9, 74.6, 73.2, 73.2, 72.5, 72.5, 72.3, 71.9, 70.8, 70.5, 70.3, 70.2, 69.5, 69.2, 69.0(2C), 68.6, 67.5, 66.8, 66.6, 62.5; HRMS (ESI-MS): m/z calcd for$[C_{118}H_{110}O_{28}Na]^+$: 1998.7115; Found: 1998.7109.

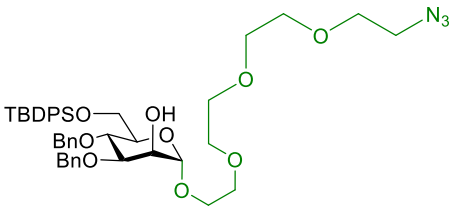



**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-((6-*O*-((2-*O*-((2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl))-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl))3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)))-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (49):** Yield: (80%); Sticky; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +6.3°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.2 Hz, 2H), 8.05 (d, *J* = 8.2 Hz, 4H), 7.91 (dd, *J* = 18.1, 7.2 Hz, 4H), 7.86 – 7.80 (m, 4H), 7.59 (dt, *J* = 24.0, 7.5 Hz, 2H), 7.48 – 7.36 (m, 14H), 7.28 (dd, *J* = 7.2, 2.9 Hz, 8H), 7.26 (s, 8H), 7.23 (s, 5H), 7.22 – 7.19 (m, 6H), 7.15 (ddd, *J* = 14.1, 7.5, 4.5 Hz,

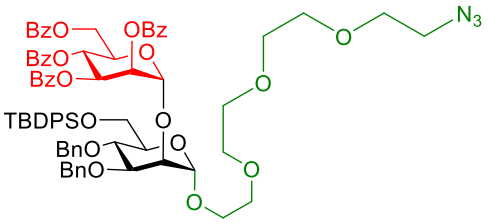


5H), 7.11 – 7.04 (m, 3H), 6.25 (d, *J* = 1.7 Hz, 1H), 6.12 (t, *J* = 10.1 Hz, 1H), 6.06 (t, *J* = 10.1 Hz, 1H), 5.97 (dd, *J* = 10.1, 3.2 Hz, 1H), 5.90 (dd, *J* = 10.3, 3.3 Hz, 1H), 5.87 – 5.84 (m, 1H), 5.78 (dd, *J* = 3.1, 2.0 Hz, 1H), 5.29 (s, 1H), 5.03 (d, *J* = 1.5 Hz, 1H), 4.93 (s, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 11.0 Hz, 1H), 4.63 (d, *J* = 12.3 Hz, 1H), 4.61 (s, 1H), 4.57 (d, *J* = 4.3 Hz, 2H), 4.53 (dd, *J* = 6.5, 4.3 Hz, 3H), 4.51 – 4.48 (m, 2H), 4.46 (s, 1H), 4.43 (s, 1H), 4.37 (s, 1H), 4.34 (s, 1H), 4.23 (dd, *J* = 12.3, 3.0 Hz, 1H), 4.11 – 4.03 (m, 3H), 3.95 (dd, *J* = 9.1, 2.9 Hz, 2H), 3.91 – 3.87 (m, 2H), 3.81 – 3.75 (m, 2H), 3.73 (d, *J* = 9.2 Hz, 1H), 3.62 (d, *J* = 8.8 Hz, 2H), 3.58 (d, *J* = 8.3 Hz, 1H), 3.45 (d, *J* = 9.0 Hz, 1H), 2.67 (s, 1H), 2.26 (d, *J* = 11.5 Hz, 2H), 2.00 – 1.89 (m, 2H), 1.72 – 1.53 (m, 5H), 1.34 (s, 1H; $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.0, 165.6, 165.5, 165.4, 165.3, 165.1, 165.1, 150.2, 138.8, 138.6, 138.6, 138.5, 138.4, 138.2, 133.7, 133.4(2C), 133.3, 133.3, 133.1, 133.0, 130.1, 129.9(6C), 129.8(6C), 129.8(2C), 129.8, 129.6, 129.4, 129.1, 129.0, 129.0, 128.7(2C), 128.6(2C), 128.5(2C), 128.5(2C), 128.4(4C), 128.4(2C), 128.3(2C), 128.3(3C), 128.3(5C), 128.2(2C), 128.1(2C), 127.9(4C), 127.7(2C), 127.5, 127.5, 127.5(4C), 127.4(4C), 127.3, 100.5, 99.3, 99.2, 93.8, 82.3, 80.0, 79.4, 79.2, 77.3, 75.8, 75.3, 75.2, 75.0, 74.9, 74.5, 73.3, 73.2, 72.5, 72.5, 72.3, 72.0, 71.5, 70.5, 70.2, 69.9, 69.4, 69.3, 69.1, 69.0, 66.8, 66.5, 66.3, 62.5, 36.9, 36.7, 25.0, 22.7(2C); MALDI-TOF (ESI-MS): m/z calcd for$[C_{124}H_{116}O_{30}Na]^+$: 2108.7483; Found: 2108.7480.

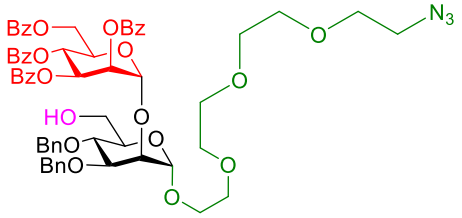
**1-*O*-2-{2-[2-(2-Azidoethoxy)ethoxy]ethoxy}ethyl-6-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-benzyl-α-D-mannopyranoside (60):** Yield: (90%); Sticky; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +24.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.71 (ddd, *J* = 14.1, 8.0, 1.5 Hz, 4H), 7.45 – 7.38 (m, 3H), 7.36 (m, 4H), 7.34 (m, 2H), 7.31 (m, 2H), 7.26 – 7.24 (m, 3H), 7.16 (dd, *J* = 6.6, 3.0 Hz, 2H), 4.95 (d, *J* = 1.7 Hz, 1H), 4.85 (d, *J* = 10.8 Hz, 1H), 4.75 – 4.66 (m, 2H), 4.58 (d, *J* = 10.8 Hz, 1H), 4.11 (d, *J* = 2.4 Hz, 1H), 3.95 – 3.90 (m, 3H), 3.86 (d, *J* = 9.2 Hz, 1H), 3.82 – 3.77 (m, 1H), 3.73 (ddd, *J* = 9.3, 4.4, 2.3 Hz, 1H), 3.64 – 3.59 (m, 13H), 3.34 (t, *J* = 5.1 Hz, 2H), 2.47 (s, 1H), 1.05 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 138.4, 138.1, 135.9(2C), 135.7(2C), 133.7, 133.3, 129.6(2C), 128.6(2C), 128.4(2C), 128.0(2C), 127.9, 127.9(2C), 127.7(3C), 127.6(2C), 99.2, 80.3, 75.2, 74.3, 72.5, 72.0, 70.7(2C), 70.7, 70.7, 70.2, 70.0, 68.4, 66.3, 63.2, 50.7, 26.8(3C), 19.3; HRMS (ESI-MS): m/z calcd for$[C_{44}H_{57}N_3O_9SiNa]^+$: 822.3762; Found: 822.3758.



**1-*O*-2-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}ethyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-benzyl-α-D-mannopyranoside (61):** Yield: (84%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -20.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.1 Hz, 2H), 8.04 (d, *J* = 8.1 Hz, 2H), 7.84 (t, *J* = 7.8 Hz, 4H), 7.81 – 7.77 (m, 2H), 7.73 (d, *J* = 6.8 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.1 Hz, 4H), 7.39 – 7.37 (m, 5H), 7.35 (d, *J* = 8.3 Hz, 4H), 7.29 – 7.26 (m, 4H), 7.25 (d, *J* = 4.0 Hz, 3H), 7.19 (m, 4H), 7.11 (t, *J* = 7.3 Hz, 1H), 6.10 (t, *J* = 10.5 Hz, 1H), 5.92 (d, *J* = 4.3 Hz, 2H), 5.26 (s, 1H), 5.05 (s, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.77 – 4.66 (m, 4H), 4.62 (d, *J* = 14.5 Hz, 1H), 4.53 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.10 (s, 1H), 4.08 (d, *J* = 9.7 Hz, 1H), 4.01 – 3.95 (m, 3H), 3.79 – 3.74 (m, 2H), 3.63 – 3.54 (m, 14H), 3.49 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.32 (t, *J* = 5.1 Hz, 2H), 1.11 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.6, 165.1(2C), 138.5, 138.4, 135.9(2C), 135.6(2C), 133.8, 133.4, 133.4, 133.3, 133.1, 133.0, 129.9(4C), 129.8(2C), 129.7(2C), 129.7, 129.6, 129.5, 129.3, 129.0, 128.6(2C), 128.5(2C), 128.4(4C), 128.3(2C), 128.3(2C), 128.2(2C), 127.7(2C), 127.7(2C), 127.7(2C), 127.6(2C), 127.6, 100.0, 98.8, 79.7, 77.5, 75.3, 74.6, 73.1, 72.5, 70.7(3C), 70.6, 70.4, 70.1, 70.1, 70.0, 69.3, 67.0, 66.5, 63.3, 63.1, 50.6, 26.9(3C), 19.3; HRMS (ESI-MS): m/z calcd for$[C_{78}H_{83}N_3O_{18}SiNa]^+$: 1400.5339; Found: 1400.5335.

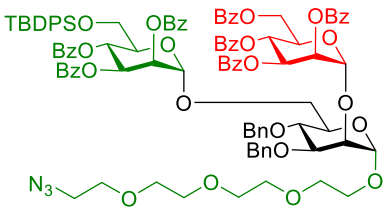



**1-*O*-2-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}ethyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-3,4-di-*O*-benzyl-α-D-mannopyranoside (62):** Yield: (92%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -4.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 7.9, 1.5 Hz, 2H), 8.09 – 8.06 (m, 2H), 8.04 – 8.00 (m, 2H), 7.90 – 7.86 (m, 2H), 7.66 – 7.57 (m, 2H), 7.57 – 7.52 (m, 1H), 7.45 (m, 7H), 7.40 – 7.36 (m, 6H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.29 (s, 1H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 6.04 (t, *J* = 9.8 Hz, 1H), 5.98 (dd, *J* = 10.0, 3.0 Hz, 1H), 5.89 (t, *J* = 2.3 Hz, 1H), 5.33 (d, *J* = 1.9 Hz, 1H), 5.03 (d, *J* = 1.9 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.80 – 4.75 (m, 3H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.68 – 4.62 (m, 1H), 4.45 (dd, *J* = 12.1, 5.5 Hz, 1H), 4.14 (s, 1H), 4.08 – 4.00 (m, 2H), 3.88 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.83 (dd, *J* = 12.0, 4.6 Hz, 1H), 3.71 (dd, *J* = 8.6, 4.0 Hz, 1H), 3.65 (m, 9H), 3.62 – 3.57 (m, 2H), 3.55 – 3.53 (m, 2H), 3.44 – 3.39 (m, 1H), 3.39 –

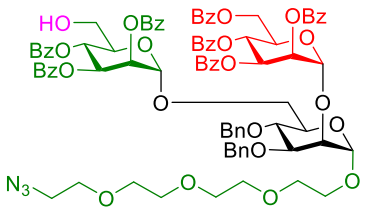


3.35 (m, 2H), 2.43 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.5, 165.7, 165.4, 165.2, 138.4, 138.3, 133.5, 133.4, 133.2, 133.2, 129.9(2C), 129.9(2C), 129.9, 129.8, 129.8(2C), 129.4, 129.2, 128.9, 128.6(2C), 128.5(5C), 128.5(2C), 128.4(2C), 128.4(2C), 128.3(2C), 127.8, 127.5(2C), 127.5, 99.2, 98.7, 79.5, 76.4, 75.3, 74.4, 72.5, 72.3, 70.7, 70.7, 70.6(2C), 70.4, 70.1, 70.0, 69.9, 69.3, 67.2, 66.8, 63.5, 62.3, 50.7; HRMS (ESI-MS): m/z calcd for$[C_{62}H_{65}N_3O_{18}SiNa]^+$: 1162.4161; Found: 1162.4155.

**1-*O*-2-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}ethyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(6-*O*-*tert*-butyldiphenylsilyl-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl)-3,4-di-*O*-benzyl-α-D-mannopyranoside (63):** Yield: (84%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +23.4°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.0 Hz, 2H), 8.11 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.97 – 7.92 (m, 4H), 7.73 (dd, *J* = 6.1, 1.9 Hz, 2H), 7.63 – 7.55 (m, 6H), 7.52 – 7.49 (m, 3H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.32 (m, 11H), 7.32 – 7.24 (m, 6H), 7.19 – 7.12 (m, 8H), 7.12 – 7.03 (m, 3H), 6.92 (t, *J* = 7.7 Hz, 4H), 6.31 (t, *J* = 10.2 Hz, 1H), 6.19 (t, *J* = 9.9 Hz, 1H), 6.11 (s, 1H), 6.00 (dd, *J* = 10.1, 3.6 Hz, 1H), 5.90 (q, *J* = 7.9, 5.7 Hz, 2H), 5.36 (s, 1H), 5.29 (s, 1H), 5.10 (d, *J* = 10.1 Hz, 2H), 4.85 (d, *J* = 11.7 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.74 (d, *J* = 4.8 Hz, 3H), 4.54 (dd, *J* = 12.1, 4.3 Hz, 1H), 4.24 (s, 1H), 4.22 – 4.16 (m, 2H), 4.14 – 4.08 (m, 1H), 4.07 – 4.03 (m, 1H), 3.93 (td, *J* = 10.3, 8.1, 4.6 Hz, 2H), 3.82 (d, *J* = 19.3 Hz, 3H), 3.72 – 3.69 (m, 2H), 3.67 – 3.63 (m, 7H), 3.61 – 3.57 (m, 4H), 3.31 (t, *J* = 4.9 Hz, 2H), 1.06 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.3, 165.8, 165.5, 165.3, 165.2, 165.2, 165.0, 138.5, 138.1, 135.8(2C), 135.6(2C), 133.2, 133.2, 133.1(2C), 133.1, 132.5, 132.4, 130.1, 130.0, 129.9(7C), 129.8, 129.7, 129.7, 129.6, 129.6, 129.5(3C), 129.4, 129.2, 129.1, 128.6(3C), 128.5(4C), 128.4(5C), 128.4(3C), 128.3, 127.9, 127.8, 127.8(3C), 127.7(3C), 127.7(3C), 127.6(3C), 127.6(3C), 99.8, 99.1, 98.0, 80.3, 76.6, 75.3, 74.5, 72.7, 71.3, 71.3, 71.1, 70.9, 70.7(2C), 70.7(2C), 70.6, 70.4, 70.2, 70.0, 69.5, 66.9, 66.8, 66.7, 66.5, 63.0, 62.4, 50.7, 26.7(3C), 19.3; HRMS (ESI-MS): m/z calcd for $[C_{105}H_{105}N_3O_{26}SiNa]^+$: 1875.6687; Found: 1875.6678.

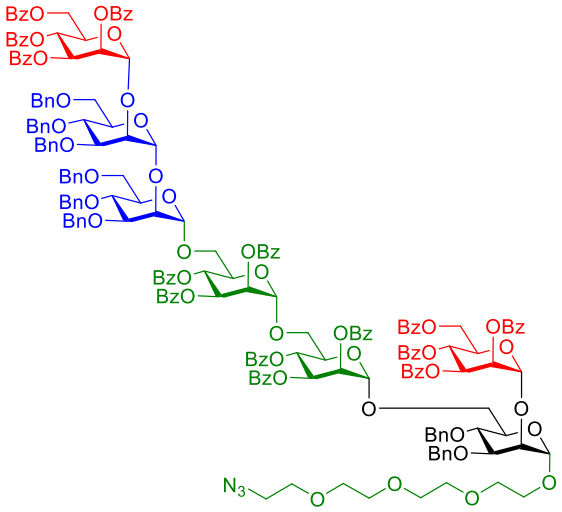



**1-*O*-2-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}ethyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl)-3,4-di-*O*-benzyl-α-D-mannopyranoside (50):** Yield: (87%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -14.5°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.2, 1.4 Hz, 2H), 8.12 (dd, *J* = 8.2, 1.4 Hz, 2H), 8.04 (ddd, *J* = 9.8,



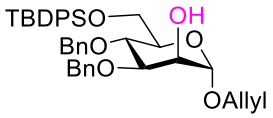
8.3, 1.4 Hz, 4H), 8.00 – 7.96 (m, 2H), 7.73 – 7.69 (m, 2H), 7.63 – 7.57 (m, 5H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.47 (m, 5H), 7.43 – 7.35 (m, 11H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.27 – 7.17 (m, 5H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 2H), 7.01 (t, *J* = 7.8 Hz, 2H), 6.20 (t, *J* = 10.1 Hz, 1H), 6.11 – 6.09 (m, 1H), 6.08 – 6.05 (m, 1H), 6.05 – 6.01 (m, 1H), 5.93 (t, *J* = 10.1 Hz, 1H), 5.88 (dd, *J* = 3.1, 1.6 Hz, 1H), 5.40 (d, *J* = 1.8 Hz, 1H), 5.33 (d, *J* = 1.8 Hz, 1H), 5.15 – 5.10 (m, 2H), 4.86 (d, *J* = 11.5 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 2H), 4.78 (s, 1H), 4.76 – 4.71 (m, 1H), 4.57 (dd, *J* = 12.2, 4.1 Hz, 1H), 4.29 – 4.25 (m, 1H), 4.20 (ddd, *J* = 10.5, 4.0, 2.3 Hz, 1H), 4.14 (dd, *J* = 9.6, 1.5 Hz, 1H), 4.12 – 4.06 (m, 2H), 4.05 – 4.00 (m, 1H), 3.98 – 3.91 (m, 2H), 3.84 (dd, *J* = 12.6, 5.2 Hz, 1H), 3.73 (dd, *J* = 7.2, 3.6 Hz, 3H), 3.68 (s, 6H), 3.67 – 3.64 (m, 3H), 3.63 (d, *J* = 5.3 Hz, 2H), 3.36 (t, *J* = 5.1 Hz, 2H), 2.72 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.5, 166.3, 165.7, 165.4, 165.3, 165.1, 165.0, 138.4, 138.0, 133.6, 133.4, 133.3, 133.2, 133.1, 132.7, 130.0, 129.9(5C), 129.9, 129.9, 129.8(2C), 129.6(3C), 129.5, 129.5(3C), 129.3, 129.2, 129.0, 128.9, 128.6(2C), 128.5(5C), 128.5(3C), 128.5, 128.4(2C), 128.3, 128.0(4C), 128.0(2C), 127.7, 127.7(2C), 127.6, 99.7, 98.9, 97.6, 80.2, 76.3, 75.3, 74.6, 72.7, 71.0(2C), 70.8, 70.7(3C), 70.7, 70.6, 70.4(2C), 70.2, 70.0, 69.9, 69.5, 67.4, 67.0, 66.8, 66.8, 63.0, 61.4, 50.7; HRMS (ESI-MS): m/z calcd for$[C_{89}H_{87}N_3O_{26}SiNa]^+$: 1636.5470; Found: 1636.5466.

**1-*O*-2-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}ethyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(6-*O*-((6-*O*-((2-*O*-((2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl))-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl))-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl))-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl)-3,4-di-*O*-benzyl-α-D-mannopyranoside (64):** Yield: (86%); Sticky; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -40.3°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.9 Hz, 4H), 8.10 (d, *J* = 7.9 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 3H), 8.00 (d, *J* = 7.8 Hz, 7H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.85 (m, 5H), 7.60 (m, 3H), 7.55 (d, *J* = 8.1 Hz, 3H), 7.50 (d, *J* = 7.7 Hz, 2H), 7.46 – 7.43 (m, 5H), 7.39 (dd, *J* = 15.7, 7.7 Hz, 14H), 7.33 (d, *J* = 7.0 Hz, 8H), 7.25 (m, 22H), 7.23 – 7.18 (m, 11H), 7.16 – 7.11 (m, 10H),

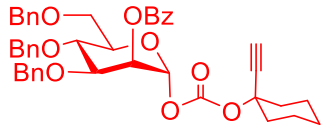


7.06 (t, *J* = 7.2 Hz, 4H), 6.90 (d, *J* = 3.3 Hz, 4H), 6.82 – 6.73 (m, 1H), 6.23 (t, *J* = 10.1 Hz, 1H), 6.16 (d, *J* = 9.5 Hz, 1H), 6.09 (q, *J* = 10.0, 9.2 Hz, 3H), 6.03 (d, *J* = 10.1 Hz, 1H), 5.97 (d, *J* = 9.3 Hz, 4H), 5.83 (d, *J* = 17.9 Hz, 2H), 5.37 (s, 1H), 5.35 (s, 1H), 5.32 (s, 1H), 5.14 (s, 1H), 5.12 (s, 1H), 5.09 (s, 1H), 5.01 (s, 1H), 4.90 (d, *J* = 11.5 Hz, 2H)**,** 4.83 (s, 1H), 4.81 (s, 1H), 4.79 (d, *J*= 4.6 Hz, 1H), 4.75 (m, 3H), 4.61 (d, *J* = 12.1 Hz, 2H), 4.56 (d, *J* = 4.8 Hz, 2H), 4.51 (m, 4H), 4.49 – 4.42 (m, 4H), 4.35 (d, *J* = 10.0 Hz, 1H), 4.30 – 4.24 (m, 3H), 4.18 (d, *J* = 9.3 Hz, 2H), 4.11 (d, *J* = 9.4 Hz, 1H), 4.09 – 4.03 (m, 4H), 4.02 – 3.96 (m, 2H), 3.90 (d, *J* = 9.3 Hz, 5H), 3.81 – 3.73 (m, 2H), 3.70 – 3.66 (m, 3H), 3.63 (m, 9H), 3.61 – 3.57 (m, 5H), 3.47 (t, *J* = 6.7 Hz, 2H), 3.32 – 3.29 (m, 2H), 3.26 (d, *J* = 8.4 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.3, 166.0, 165.8, 165.6, 165.5, 165.4, 165.3, 165.3, 165.3, 165.2, 165.2(2C), 165.0, 164.9, 138.9, 138.7, 138.7, 138.5, 138.5, 138.4, 138.3, 138.1, 133.5, 133.4, 133.4, 133.3, 133.2, 133.2, 133.1(2C), 133.1, 133.0, 132.9, 132.4, 132.4, 130.1, 130.1, 130.0, 130.0, 129.9(3C), 129.9(6C), 129.8(6C), 129.8(4C), 129.7, 129.6, 129.6, 129.5(4C), 129.4, 129.3, 129.3, 129.2, 129.1, 129.1, 128.8, 128.6(5C), 128.5(2C), 128.5(3C), 128.5(4C), 128.4(8C), 128.3(4C), 128.3(14C), 128.2(2C), 128.1(2C), 127.9(3C), 127.9(4C), 127.8(2C), 127.7(2C), 127.7(6C), 127.5(2C), 127.5, 127.4(8C), 127.4(2C), 100.3, 99.8, 99.3, 99.2, 99.0, 98.2, 98.1, 80.3, 80.2, 79.4, 77.3(3C), 76.6, 75.2(2C), 75.0, 74.9, 74.5, 73.2, 73.1, 72.8, 72.7, 72.4, 72.3, 71.9, 71.3, 70.7, 70.7(4C), 70.7(2C), 70.6(2C), 70.6(2C), 70.4(3C), 70.2(2C), 70.0, 69.5, 69.4, 69.2, 68.9, 68.9, 66.9, 66.8, 66.7, 66.3, 66.3, 65.6, 63.0, 62.3, 50.6; MALDI-TOF (ESI-MS): m/z calcd for$[C_{204}H_{191}N_3O_{53}SiNa]^+$: 3555.230; Found: 3554.304.

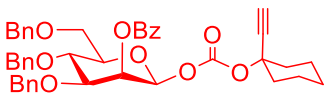
**Allyl 3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside (7):** Yield: (90%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -17.2; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.69 (m, 4H), 7.44 – 7.39 (m, 2H), 7.39 – 7.34 (m, 6H), 7.34 – 7.29 (m, 3H), 7.27 – 7.23 (m, 3H), 7.15 (dd, *J* = 6.3, 3.0 Hz, 2H), 5.88 (ddt, *J* = 16.8, 11.4, 5.7 Hz, 1H), 5.25 (d, *J* = 17.1 Hz, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 4.95 (s, 1H), 4.85 (d, *J* = 10.8 Hz, 1H), 4.75 – 4.66 (m, 2H), 4.57 (d, *J* = 10.8 Hz, 1H), 4.18 (dd, *J* = 12.8, 5.1 Hz, 1H), 4.08 (s, 1H), 3.98 (dd, *J* = 12.9, 6.3 Hz, 1H), 3.95 – 3.90 (m, 3H), 3.85 (t, *J* = 9.4 Hz, 1H), 3.74 (d, *J* = 9.7 Hz, 1H), 2.45 (s, 1H), 1.06 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 138.3, 138.0, 135.9, 135.7, 133.8, 133.8, 133.4, 129.6(2C), 128.6(2C), 128.4(2C), 128.0(4C), 127.9(2C), 127.7(4C), 127.6(2C), 117.6, 98.1, 80.4, 75.3, 74.3, 72.5, 72.1, 68.6, 67.7, 63.2, 26.8(3C), 19.3; HRMS (ESI-MS): m/z calcd for$[C_{39}H_{46}O_6SiNa]^+$: 661.2961; Found: 661.2955.



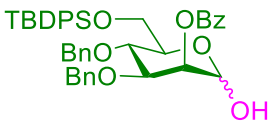
**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (28α):** Yield: (84%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +2.7; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.63 – 7.57 (m, 1H), 7.45 – 7.29 (m, 15H), 7.23 (dd, *J* = 7.5, 2.2 Hz, 2H), 5.98 (d, *J* = 2.9 Hz, 1H), 5.77 (s, 1H), 4.91 (d, *J* = 5.9 Hz, 1H), 4.89 (d, *J* = 6.5 Hz, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.61 (dd, *J* = 11.6, 4.1 Hz, 3H), 4.15 (t, *J* = 9.4 Hz, 1H), 3.96 (dd, *J* = 11.2, 3.7 Hz, 1H), 3.92 (d, *J* = 1.9 Hz, 1H), 3.88 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.71 (ddd, *J* = 9.7, 3.9, 1.9 Hz, 1H), 2.66 (s, 1H), 2.18 (m, 2H), 1.94 – 1.82 (m, 2H), 1.74 (m, 1H), 1.67 – 1.49 (m, 4H), 1.38 – 1.33 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.7, 151.1, 138.5, 138.1, 137.4, 133.2, 130.2(2C), 129.9, 128.4(2C), 128.4(2C), 128.4(2C), 128.4(2C), 128.2(2C), 128.1(2C), 127.9, 127.8, 127.6(2C), 127.5, 94.1, 82.5, 80.0, 78.7, 76.4, 75.4, 75.3, 73.6, 73.5, 71.5, 68.6, 67.7, 36.8, 36.6, 24.9, 22.5(2C); HRMS (ESI-MS): m/z calcd for$[C_{43}H_{44}O_9Na]^+$: 727.2883; Found: 727.2878.




**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (28β):** Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +2.6°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.44 – 7.35 (m, 6H), 7.35 – 7.27 (m, 9H), 7.25 – 7.21 (m, 2H), 6.16 (d, *J* = 2.1 Hz, 1H), 5.75 (t, *J* = 2.4 Hz, 1H), 4.91 (d, *J* = 10.7 Hz, 1H), 4.85 (d, *J* = 11.2 Hz, 1H), 4.77 (d, *J* = 11.9 Hz, 1H), 4.65 – 4.56 (m, 3H), 4.20 (dd, *J* = 5.5, 2.0 Hz, 2H), 4.07 – 4.01 (m, 1H), 3.95 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.83 (dd, *J* = 11.2, 1.8 Hz, 1H), 2.66 (s, 1H), 2.20 (m, 2H), 1.92 (m, 2H), 1.69 (m, 4H), 1.57 m, 1H), 1.40 – 1.34 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.4, 150.4, 138.5, 138.3, 137.8, 133.3, 130.1(2C), 129.5, 128.5(2C), 128.4(6C), 128.0(2C), 128.0(2C), 127.7(2C), 127.5(2C), 127.5, 94.4, 82.5, 78.5, 77.8, 75.4, 75.4, 73.9, 73.7, 73.5, 71.8, 68.7, 67.7, 36.9, 36.6, 24.9, 22.5(2C); HRMS (ESI-MS): m/z calcd for$[C_{43}H_{44}O_9Na]^+$: 727.2883; Found: 727.2878.

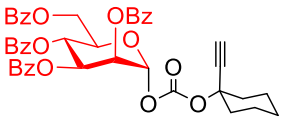



**2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α/β-D-mannopyranoside (27):** Yield: (81%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +5.2°; IR ($cm^{-1}$, $CHCl_3$): 3013, 2935, 2860, 1727, 1603, 1455, 1366, 1267, 1107, 952, 704; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.20 – 8.16 (m, 2H), 7.78 (m, 5H), 7.61 – 7.56 (m, 1H), 7.46 – 7.27 (m, 21H), 7.23 (dd, *J* = 6.7, 2.9 Hz, 2H), 5.70 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.39 (d, *J* = 1.9 Hz, 1H), 5.00 (d, *J* = 10.7 Hz, 1H), 4.84 (d, *J* = 11.4 Hz, 1H), 4.72 (d, *J* = 10.6 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.30 (t, *J* = 9.4 Hz, 1H), 4.20 (dd, *J* = 9.5, 3.1 Hz, 1H), 4.14 (dd, *J* = 11.3,

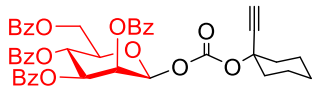


3.3 Hz, 1H), 4.04 – 3.99 (m, 1H), 3.94 (d, *J* = 11.3 Hz, 1H), 2.99 (s, 1H), 1.18 (s, 1H), 1.15 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.0, 138.6, 138.1, 136.0, 135.9, 135.7, 133.7, 133.2, 133.2, 130.2, 130.1(2C), 129.9, 129.7, 129.6, 128.4(2C), 128.4(4C), 128.3, 128.2, 128.1(2C), 127.9(2C), 127.8(2C), 127.7, 127.6(2C), 127.6, 127.6, 92.8, 77.9, 75.3, 74.2, 72.5, 71.7, 69.6, 62.9, 26.9(3C), 19.4; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{46}O_7Na]^+$: 725.2911; Found: 725.2909.

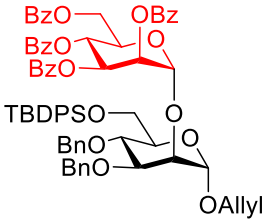
**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (5α):** mp (°C): 75.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): - 64.3°; IR ($cm^{-1}$, $CHCl_3$): 3290, 2941, 1731, 1516, 1452, 1237, 1163, 1102, 908, 707; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.09 (ddd, *J* = 15.5, 8.3, 1.4 Hz, 4H), 7.93 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.84 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.63 – 7.46 (m, 4H), 7.46 – 7.33 (m, 8H), 7.30 – 7.26 (m, 2H), 6.10 (d, *J* = 1.3 Hz, 1H), 6.08 (d, *J* = 9.5 Hz, 1H), 6.05 – 6.04 (m, 1H), 5.71 (dd, *J* = 9.7, 3.1 Hz, 1H), 4.75 (dd, *J* = 12.2, 3.0 Hz, 1H), 4.56 (dd, *J* = 12.2, 4.6 Hz, 1H), 4.28 (ddd, *J* = 9.4, 4.6, 3.0 Hz, 1H), 2.61 (s, 1H), 2.18 – 2.12 (m, 2H), 1.83 (m, 2H), 1.64 (m, 1H), 1.58 – 1.45 (m, 4H), 1.36 – 1.30 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.1, 165.5, 165.4, 165.2, 150.7, 133.6, 133.5, 133.4, 133.1, 130.1(2C), 129.9(5C), 129.8(2C), 129.3, 128.7, 128.7, 128.5(2C), 128.5(2C), 128.4(2C), 128.4(2C), 93.4, 82.2, 79.1, 75.5, 73.3, 71.4, 68.6, 66.3, 62.7, 36.7, 36.6, 24.9, 22.5(2C). HRMS (ESI-MS): m/z calcd for$[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2267.



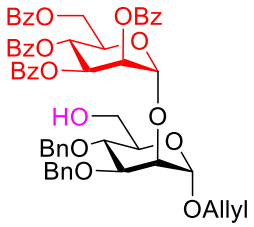

**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranoside (5β):** mp (°C): 76.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -64.4°; IR ($cm^{-1}$, $CHCl_3$): 3290, 2941, 1730, 1516, 1451, 1237, 1161, 1102, 908, 708; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.08 (ddd, *J* = 15.5, 8.4, 1.3 Hz, 4H), 7.95 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.83 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.64 – 7.45 (m, 4H), 7.44 – 7.31 (m, 8H), 7.29 – 7.24 (m, 2H), 6.27 (d, *J* = 2.0 Hz, 1H), 6.17 (t, *J* = 10.2 Hz, 1H), 5.97 (dd, *J* = 10.2, 3.3 Hz, 1H), 5.83 (dd, *J* = 3.4, 2.0 Hz, 1H), 4.73 (dd, *J* = 12.2, 2.5 Hz, 1H), 4.59 (ddd, *J* = 10.1, 4.3, 2.4 Hz, 1H), 4.49 (dd, *J* = 12.3, 4.4 Hz, 1H), 2.65 (s, 1H), 2.28 – 2.21 (m, 2H), 1.93 (m, 2H), 1.75 – 1.64 (m, 4H), 1.60 – 1.55 (m, 1H), 1.36 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.1, 165.5, 165.3, 165.1, 150.1, 133.7, 133.6, 133.3, 133.1, 130.0(2C), 129.8(2C), 129.8(2C), 129.8(2C), 129.0, 128.9, 128.8, 128.7(2C), 128.5(2C), 128.4(2C), 128.4(2C), 93.6, 82.2, 79.2, 75.7, 70.9, 69.7, 69.2, 66.3, 62.5, 36.7(2C), 24.9, 22.7(2C); HRMS (ESI-MS): m/z calcd for$[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2266.



**Allyl 3,4-di-*O*-benzyl-6-*O*-$^{tert}$-butyldiphenylsilyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside (36):** Yield: (84%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +15.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.11 (m, 2H), 8.07 – 8.03 (m, 2H), 7.89 – 7.83 (m, 4H), 7.81 – 7.73 (m, 4H), 7.58 (dt, *J* = 11.8, 7.5 Hz, 2H), 7.49 – 7.42 (m, 3H), 7.41 – 7.34 (m, 12H), 7.29 – 7.24 (m, 7H), 7.22 – 7.17 (m, 4H), 6.10 (t, *J* = 9.9 Hz, 1H), 5.93 (dt, *J* = 5.2, 2.2 Hz, 2H), 5.88 – 5.78 (m, 1H), 5.25 (s, 1H), 5.24 – 5.18 (m, 1H), 5.16 (d, *J* = 10.6 Hz, 1H), 5.07 (s, 1H), 4.93 (d, *J* = 10.9 Hz, 1H), 4.76 (d, *J* = 11.3 Hz, 1H), 4.70 (d, *J* = 7.4 Hz, 1H), 4.67 (d, *J* = 7.4 Hz, 1H), 4.66 – 4.60 (m, 2H), 4.53 (dd, *J* = 12.0, 4.3 Hz, 1H), 4.16 (ddd, *J* = 12.9, 5.2, 1.6 Hz, 1H), 4.09 – 4.03 (m, 2H), 4.02 – 3.97 (m, 3H), 3.86 (dd, *J* = 12.9, 6.0 Hz, 1H), 3.78 (dd, *J* = 7.2, 2.5 Hz, 1H), 1.12 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.3, 165.6, 165.2, 165.1, 138.5, 138.4, 135.9(2C), 135.7(2C), 133.9, 133.8, 133.5, 133.4(2C), 133.1, 133.1, 129.9(5C), 129.9(2C), 129.8(2C), 129.7, 129.7, 129.5, 129.3, 129.0, 128.6(2C), 128.5(2C), 128.4(2C), 128.4(4C), 128.3(2C), 128.2(2C), 127.8(4C), 127.7(2C), 127.6, 127.6, 117.4, 100.0, 97.9, 79.8, 77.5, 75.3, 74.7, 73.3, 72.7, 70.4, 70.1, 69.4, 67.7, 67.0, 63.4, 63.1, 26.9(3C), 19.4; HRMS (ESI-MS): m/z calcd for$[C_{73}H_{72}O_{15}Na]^+$: 1239.4538; Found: 1239.4527.

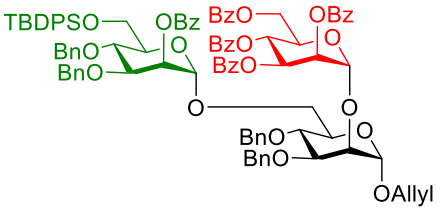



**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside (37):** Yield: (89%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -14.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.07 (ddd, *J* = 14.5, 8.4, 1.4 Hz, 4H), 7.99 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.85 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.63 – 7.49 (m, 3H), 7.45 – 7.40 (m, 5H), 7.39 – 7.33 (m, 8H), 7.30 – 7.25 (m, 3H), 7.23 – 7.18 (m, 2H), 7.15 – 7.10 (m, 1H), 6.03 – 5.97 (m, 1H), 5.96 (dd, *J* = 9.4, 2.8 Hz, 1H), 5.87 (dd, *J* = 2.8, 1.9 Hz, 1H), 5.75 (ddt, *J* = 17.2, 10.7, 5.5 Hz, 1H), 5.30 (d, *J* = 1.9 Hz, 1H), 5.19 – 5.11 (m, 2H), 5.00 (d, *J* = 1.9 Hz, 1H), 4.95 (d, *J* = 11.0 Hz, 1H), 4.77 – 4.75 (m, 1H), 4.75 – 4.71 (m, 2H), 4.69 (d, *J* = 11.8 Hz, 1H), 4.62 (ddd, *J* = 8.9, 5.7, 2.4 Hz, 1H), 4.43 (dd, *J* = 12.1, 5.7 Hz, 1H), 4.08 (dd, *J* = 4.9, 2.4 Hz, 1H), 4.05 (d, *J* = 9.4 Hz, 1H), 4.00 (dd, *J* = 9.3, 2.8 Hz, 1H), 3.90 (dd, *J* = 12.9, 5.2 Hz, 1H), 3.84 (t, *J* = 2.8 Hz, 2H), 3.70 (dd, *J* = 12.9, 5.8 Hz, 1H), 3.64 (d, *J* = 9.4 Hz, 1H), 2.31 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.5, 165.7, 165.5, 165.2, 138.3, 138.2, 133.6, 133.5, 133.5, 133.2, 133.2, 129.9(2C), 129.9(2C), 129.8(2C), 129.8(2C), 129.8, 129.4, 129.2, 128.9, 128.6(2C), 128.5(3C), 128.5(3C), 128.4(2C), 128.4(2C), 128.3(2C), 127.8, 127.6(3C), 117.2, 99.2, 97.9, 79.5, 76.4, 75.4, 74.2, 72.5, 72.4, 70.4,

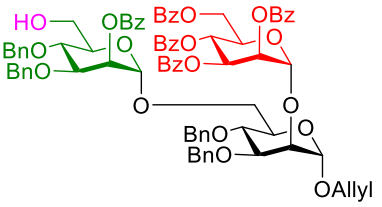


69.9, 69.3, 67.9, 67.3, 63.5, 62.2; HRMS (ESI-MS): m/z calcd for$[C_{57}H_{54}O_{15}Na]^+$: 1001.3360; Found: 1001.3354.

**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-α-D-mannopyranoside (38):** Yield: (86%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +25.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.4, 1.4 Hz, 4H), 8.00 (d, *J* = 7.0 Hz, 2H), 7.95 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.80 – 7.76 (m, 2H), 7.74 – 7.69 (m, 4H), 7.59 – 7.54 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.36 (m, 7H), 7.36 – 7.29 (m, 9H), 7.28 – 7.23 (m, 9H), 7.21 – 7.14 (m, 9H), 7.13 – 7.10 (m, 4H), 6.11 (t, *J* = 9.9 Hz, 1H), 6.00 – 5.93 (m, 2H), 5.91 – 5.80 (m, 2H), 5.31 (d, *J* = 1.8 Hz, 1H), 5.27 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.18 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.13 (d, *J* = 1.8 Hz, 1H), 5.00 (s, 1H), 4.98 (d, *J* = 9.2 Hz, 1H), 4.93 (d, *J* = 11.4 Hz, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.74 – 4.71 (m, 1H), 4.69 (d, *J* = 5.3 Hz, 2H), 4.67 (s, 1H), 4.62 (s, 1H), 4.62 – 4.58 (m, 2H), 4.50 (dd, *J* = 12.1, 4.4 Hz, 1H), 4.30 (t, *J* = 9.6 Hz, 1H), 4.21 (dd, *J* = 9.5, 3.2 Hz, 1H), 4.19 – 4.13 (m, 2H), 4.01 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.96 (dd, *J* = 9.2, 2.0 Hz, 2H), 3.94 – 3.91 (m, 1H), 3.90 – 3.88 (m, 1H), 3.88 – 3.82 (m, 2H), 3.80 – 3.72 (m, 2H), 1.10 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.7, 165.6, 165.3, 165.0, 138.9, 138.2, 138.2, 138.0, 136.0(2C), 135.7(2C), 133.8, 133.6, 133.4, 133.3, 133.3, 133.1(2C), 133.0, 132.9, 130.1, 130.1, 130.0, 129.9(2C), 129.9(2C), 129.8(2C), 129.8(2C), 129.6, 129.6, 129.5, 129.2, 129.0, 128.5(5C), 128.4(2C), 128.4(3C), 128.4(2C), 128.4, 128.3(2C), 128.2(2C), 128.2, 128.1(2C), 127.9(2C), 127.8(2C), 127.7(2C), 127.7(2C), 127.6(3C), 127.6, 127.4, 127.4, 117.7, 99.7, 98.1, 97.9, 80.1, 78.6, 76.2, 75.3, 75.1, 74.7, 74.2, 72.8, 72.4, 71.6, 71.2, 70.2, 70.2, 69.5, 69.3, 68.0, 66.9, 66.2, 63.0, 62.8, 26.9(3C), 19.4; HRMS (ESI-MS): m/z calcd for $[C_{100}H_{98}O_{21}SiNa]^+$: 1686.6301; Found: 1686.6299.

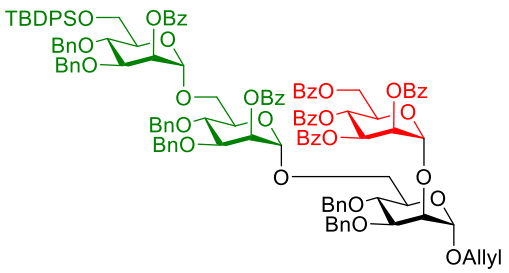



**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (39):** Yield: (90%); Sticky syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -20.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.6 Hz, 2H), 8.06 (d, *J* = 7.5 Hz, 2H), 7.99 (dd, *J* = 16.7, 7.7 Hz, 4H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.60 – 7.54 (m, 3H), 7.45 – 7.35 (m, 9H), 7.31 (d, *J* = 4.7 Hz, 6H), 7.30 – 7.26 (m,



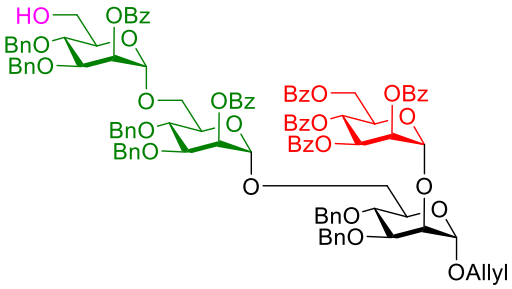
8H), 7.21 – 7.10 (m, 10H), 6.12 (t, *J* = 10.0 Hz, 1H), 5.97 (d, *J* = 7.8 Hz, 2H), 5.89 – 5.79 (m, 1H), 5.74 (s, 1H), 5.32 (s, 1H), 5.26 (dd, *J* = 17.6, 1.8 Hz, 1H), 5.17 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.08 (s, 1H), 4.99 (s, 1H), 4.97 (d, *J* = 8.7 Hz, 1H), 4.94 (d, *J* = 8.5 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.75 – 4.70 (m, 2H), 4.70 – 4.66 (m, 2H), 4.64 (d, *J* = 2.0 Hz, 1H), 4.62 – 4.57 (m, 2H), 4.51 (dd, *J* = 12.1, 4.5 Hz, 1H), 4.19 (dd, *J* = 9.3, 3.2 Hz, 1H), 4.17 – 4.12 (m, 2H), 4.03 – 3.98 (m, 2H), 3.92 (td, *J* = 7.7, 6.6, 4.9 Hz, 3H), 3.88 – 3.83 (m, 3H), 3.82 – 3.77 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.6, 165.6, 165.4, 165.0, 138.5, 138.3, 138.0, 137.9, 133.6, 133.4, 133.4, 133.2, 133.1, 133.0, 130.0, 129.9, 129.0, 129.9(4C), 129.8(2C), 129.8(2C), 129.5, 129.2, 129.0, 128.5(2C), 128.5(2C), 128.5(2C ), 128.5(4C), 128.4(3C), 128.4(2C), 128.2(2C), 128.2, 128.1(2C), 128.0(2C), 128.0(2C), 127.7(4C), 127.7, 127.7, 127.4, 117.8, 99.6, 98.0, 97.6, 80.1, 78.2, 76.0, 75.3, 75.2, 74.8, 74.1, 72.7, 71.9, 71.4, 71.0, 70.3, 70.2, 69.5, 69.1, 68.0, 66.9, 66.6, 63.0, 62.1; HRMS (ESI-MS): m/z calcd for$[C_{84}H_{80}O_{21}Na]^+$: 1447.5090; Found: 1447.5094.

**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranoside (40):** Yield: (79%); Sticky syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +40.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 7.4 Hz, 4H), 7.99 (dd, *J* = 18.5, 7.6 Hz, 4H), 7.78 – 7.73 (m, 3H), 7.72 – 7.66 (m, 3H), 7.60 – 7.53 (m, 3H), 7.45 – 7.40 (m, 6H), 7.37 (d, *J* = 7.9 Hz, 5H), 7.35 – 7.28 (m, 10H), 7.26 – 7.21 (m, 10H), 7.15 – 7.07 (m, 20H), 6.13 (t, *J* = 9.9 Hz, 1H), 6.04 – 6.02 (m, 1H), 6.01 – 5.98 (m, 1H), 5.94 – 5.77 (m, 4H), 5.34 (s, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.0 Hz, 1H), 5.14 (s, 1H), 5.09 (s, 1H), 5.02 (s, 1H), 4.97 (d, *J* = 13.8 Hz, 1H), 4.92 (d, *J* = 7.6 Hz, 1H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.81 (d, *J* = 10.1 Hz, 1H), 4.77 – 4.74 (m, 1H), 4.73 – 4.71 (m, 1H), 4.69 (d, *J* = 11.5 Hz, 2H), 4.63 (d, *J* = 10.8 Hz, 2H), 4.55 (d, *J* = 10.6 Hz, 1H), 4.50 (t, *J* = 10.9 Hz, 2H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.26 (t, *J* = 9.7 Hz, 1H), 4.21 (dd, *J* = 9.3, 3.3 Hz, 1H), 4.16 (dd, *J* = 13.6, 3.9 Hz, 2H), 4.08 (dd, *J* = 9.3, 3.0 Hz, 1H), 4.04 (d, *J* = 5.7 Hz, 1H), 4.02 (d, *J* = 2.7 Hz, 1H), 4.01 (s, 1H), 3.98 (d, *J* = 4.4 Hz, 1H), 3.94 (dd, *J* = 13.0, 6.1 Hz, 1H), 3.89 – 3.86 (m, 1H), 3.85 (s, 2H), 3.82 (d, *J* = 2.4 Hz, 1H), 3.76 (d, *J* = 10.4 Hz, 1H), 3.72 (d, *J* = 11.0 Hz, 1H), 3.63 – 3.58 (m, 2H), 1.11 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ

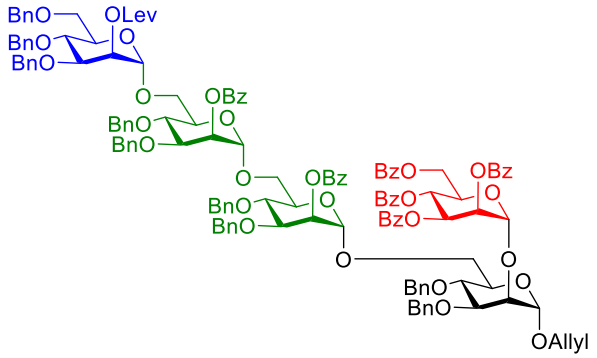


166.3, 165.7(3C), 165.4, 165.1, 138.9, 138.7, 138.4, 138.1, 138.0, 137.9, 136.0(2C), 135.8(2C), 133.7, 133.7, 133.5, 133.4, 133.3, 133.2, 133.0, 130.2(2C), 130.1, 130.0, 129.9(4C), 129.9(2C), 129.8(2C), 129.7, 129.7, 129.6, 129.3, 129.0, 128.7, 128.6(5C), 128.5, 128.5(8C), 128.4(2C), 128.4(2C), 128.3(2C), 128.3(5C), 128.2(5C), 127.8, 127.8(5C), 127.7, 127.7(7C), 127.5, 127.4, 127.3(3C), 117.8, 99.8, 98.5, 98.3, 98.2, 80.3, 78.8, 78.4, 76.2, 75.3, 75.3, 75.1, 74.6, 74.1, 74.0, 72.9, 72.6, 71.6, 71.5, 71.3, 70.8, 70.3, 70.3, 69.5, 68.9(2C), 68.1, 66.9, 66.3, 65.9, 63.1, 62.6, 27.0(3C), 19.4; MALDI-TOF (ESI-MS): m/z calcd for $[C_{127}H_{124}O_{27}SiNa]^+$: 2132.8030; Found: 2132.8025.

**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl- α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (41):** Yield: (85%); Sticky syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -4.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.07 (m, 6H), 7.98 (dd, *J* = 18.8, 8.3 Hz, 4H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.61 – 7.53 (m, 4H), 7.46 (q, *J* = 8.1 Hz, 6H), 7.42 – 7.34 (m, 6H), 7.30 – 7.26 (m, 11H), 7.24 – 7.21 (m, 6H), 7.20 – 7.18 (m, 5H), 7.12 – 7.10(m, 9H), 7.09 – 7.05 (m, 2H), 6.11 (t, *J* = 9.8 Hz, 1H), 5.98 (d, *J* = 8.8 Hz, 2H), 5.88 – 5.81 (m, 2H), 5.77 (s, 1H), 5.33 (s, 1H), 5.26 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 5.11 (s, 1H), 5.04 (s, 1H), 5.00 (s, 1H), 4.95 (d, *J* = 14.3 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 2H), 4.84 (d, *J* = 10.9 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 2H), 4.68 (d, *J* = 6.2 Hz, 3H), 4.63 (d, *J* = 13.9 Hz, 2H), 4.57 (d, *J* = 11.9 Hz, 2H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.47 (s, 1H), 4.41 (s, 1H), 4.21 (d, *J* = 9.0 Hz, 1H), 4.16 (s, 2H), 4.07 (d, *J* = 9.8 Hz, 1H), 4.00 (d, *J* = 14.2 Hz, 4H), 3.95 (s, 2H), 3.89 (d, *J* = 7.7 Hz, 3H), 3.76 (d, *J* = 11.0 Hz, 1H), 3.67 (d, *J* = 9.8 Hz, 3H), 3.62 (d, *J* = 10.3 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.6, 165.6, 165.4, 165.4, 165.0, 138.6, 138.4, 138.3, 138.0, 137.9, 137.7, 133.6, 133.4, 133.3, 133.3, 133.2, 133.1, 132.9, 130.1, 130.0(2C), 129.9(4C), 129.9, 129.9, 129.8(2C), 129.7, 129.5, 129.2, 128.9, 128.6(2C), 128.5(7C), 128.5, 128.4(5C), 128.3(2C), 128.3(2C), 128.3(2C), 128.2(2C), 128.2(5C), 128.1(2C), 128.0(2C), 127.8(2C), 127.7(4C), 127.6(2C), 127.6, 127.5(2C), 127.4, 127.4, 117.8, 99.6, 98.1, 98.1(2C), 80.2, 78.6, 77.8, 76.0, 75.2, 75.2, 75.1, 74.6, 74.1, 73.8, 72.8, 72.1, 71.5, 71.3, 71.2, 70.6, 70.2, 70.2, 69.5, 68.9, 68.6, 68.0, 66.9, 66.4, 65.8, 63.0, 61.9; HRMS (ESI-MS): m/z calcd for $[C_{111}H_{106}O_{27}Na]^+$: 1894.6853; Found: 1894.6842.

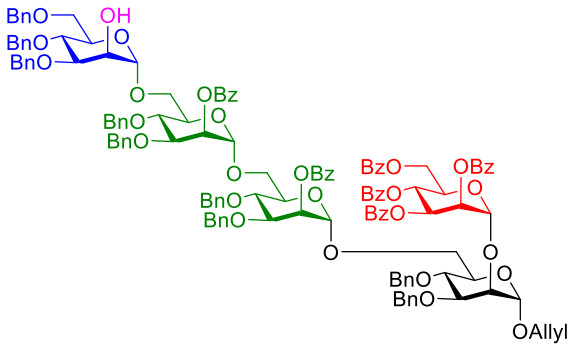


**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl)-6-*O*-(2-*O*-(4-oxopentanoyl-3,4,5-tri-*O*-benzyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranoside (42):** Yield: (82%); Sticky syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +13.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.10 (m, 6H), 7.98 (dd, *J* = 17.9, 7.7 Hz, 4H), 7.71 (d, *J* = 7.7 Hz, 2H), 7.61 – 7.55 (m, 2H), 7.47 – 7.41 (m, 9H), 7.36 (dd, *J* = 15.7, 7.8 Hz, 4H), 7.28 (q, *J* = 3.4 Hz, 12H), 7.24 – 7.21 (m, 4H), 7.16 (td, *J* = 12.3, 11.5, 6.0 Hz, 20H), 7.09 (p, *J* = 4.7, 3.9 Hz, 12H), 6.12 (t, *J* = 9.9 Hz, 1H), 6.03 – 5.96 (m, 2H), 5.90 – 5.79 (m, 3H), 5.54 (s, 1H), 5.33 (s, 1H), 5.26 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 10.4 Hz, 1H),



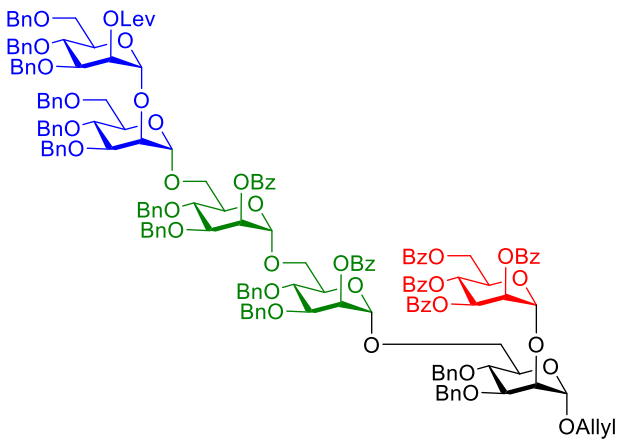

5.13 (s, 1H), 5.04 (s, 1H), 5.01 (s, 1H), 4.97 (s, 1H), 4.95 (s, 1H), 4.93 (s, 1H), 4.84 (t, *J* = 5.4 Hz, 2H), 4.81 – 4.77 (m, 2H), 4.74 – 4.70 (m, 2H), 4.69 (s, 1H), 4.65 (d, *J* = 8.9 Hz, 2H), 4.62 – 4.56 (m, 3H), 4.55 – 4.49 (m, 2H), 4.42 (d, *J* = 11.3 Hz, 3H), 4.37 (d, *J* = 11.6 Hz, 2H), 4.32 (d, *J* = 11.4 Hz, 1H), 4.22 (dd, *J* = 9.4, 3.2 Hz, 1H), 4.15 (dd, *J* = 14.4, 2.9 Hz, 2H), 4.03 (d, *J* = 8.9 Hz, 3H), 4.00 – 3.96 (m, 2H), 3.94 (d, *J* = 8.7 Hz, 1H), 3.92 – 3.89 (m, 2H), 3.86 (d, *J* = 9.3 Hz, 3H), 3.75 (d, *J* = 11.4 Hz, 2H), 3.68 – 3.61 (m, 2H), 3.58 (dd, *J* = 10.8, 3.9 Hz, 2H), 3.46 (t, *J* = 10.3 Hz, 2H), 2.70 (d, *J* = 3.0 Hz, 4H), 2.10 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 206.3, 171.8, 166.2, 165.6, 165.6, 165.5, 165.3, 165.0, 138.7, 138.6, 138.6, 138.3, 138.2, 138.0, 137.9, 137.7, 137.7, 133.6, 133.4, 133.3, 133.2, 133.2, 133.1, 132.9, 130.1, 130.1, 129.9(2C), 129.9(2C), 129.8(2C), 129.7(2C), 129.5, 129.2, 129.0, 128.6, 128.6, 128.5(5C), 128.5, 128.4(3C), 128.4(7C), 128.4(7C), 128.3(5C), 128.2(2C), 128.2(2C), 128.1(6C), 128.1(2C), 127.8(2C), 127.8(2C), 127.8, 127.7(5C), 127.6, 127.6, 127.5, 127.4, 127.3(2C), 127.3(2C), 127.3, 127.2, 117.7, 99.7, 98.3, 98.2, 98.2, 98.1, 80.2, 78.7, 78.3, 77.7, 76.0, 75.2, 75.1, 75.0, 75.0, 74.5, 74.1, 74.0, 73.8, 73.4, 72.8, 71.6, 71.5, 71.3, 71.3, 71.2, 70.9, 70.8, 70.2, 70.2, 69.5, 68.9, 68.5, 68.4, 68.4, 68.0, 66.9, 66.2, 65.9, 65.8, 63.0, 38.1, 29.8, 28.3; MALDI-TOF (ESI-MS): m/z calcd for $[C_{143}H_{140}O_{34}Na]^+$: 2424.9157; Found: 2424.9150.

**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl)-6-*O*-(3,4,5-tri-*O*-benzyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranoside**




**(43):** Yield: (82%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +33.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.08 (m, 6H), 8.01 – 7.94 (m, 4H), 7.73 – 7.69 (m, 2H), 7.59 – 7.54 (m, 2H), 7.45 – 7.33 (m, 14H), 7.29 – 7.27 (m, 9H), 7.26 – 7.23 (m, 11H), 7.21 (d, *J* = 7.4 Hz, 11H), 7.15 – 7.08 (m, 16H), 6.11 (t, *J* = 9.9 Hz, 1H), 6.02 – 5.96 (m, 2H), 5.89 – 5.80 (m, 2H), 5.78 – 5.75 (m, 1H), 5.33 (s, 1H), 5.25 (d, *J* = 17.0 Hz, 1H), 5.17 (d, *J* = 10.5 Hz, 1H), 5.14 (s, 1H), 5.12 (s, 1H), 5.03 (s, 1H), 5.00 (s, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.93 (d, *J* = 11.4 Hz, 1H), 4.85 (d, *J* = 6.0 Hz, 1H), 4.83 (d, *J* = 5.7 Hz, 1H), 4.81 – 4.73 (m, 3H), 4.71 – 4.67 (m, 3H), 4.64 (d, *J* = 11.7 Hz, 2H), 4.60 (d, *J* = 3.0 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 3H), 4.52 (d, *J* = 4.5 Hz, 1H), 4.49 (d, *J* = 5.5 Hz, 1H), 4.45 (d, *J* = 3.5 Hz, 1H), 4.44 – 4.40 (m, 3H), 4.22 (dd, *J* = 9.2, 3.2 Hz, 1H), 4.17 – 4.12 (m, 3H), 4.07 – 4.02 (m, 2H), 3.99 (dd, *J* = 8.4, 5.3 Hz, 3H), 3.94 (d, *J* = 9.0 Hz, 2H), 3.90 – 3.86 (m, 3H), 3.83 (dd, *J* = 9.1, 3.1 Hz, 2H), 3.78 – 3.73 (m, 2H), 3.69 – 3.65 (m, 2H), 3.61 (d, *J* = 11.1 Hz, 3H), 3.51 (d, *J* = 10.6 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.6, 165.6, 165.4, 165.3, 165.0, 138.7, 138.6, 138.5, 138.3, 138.2, 138.0, 137.9, 137.7, 137.7, 133.6, 133.4, 133.3, 133.2, 133.1, 132.9, 130.1, 129.9(4C), 129.9(3C), 129.9(3C), 129.8, 129.7, 129.5, 129.2, 129.0, 129.0, 128.6, 128.5(6C), 128.5(3C), 128.5, 128.4(2C), 128.4(3C), 128.3(3C), 128.3(2C), 128.3(7C), 128.2(2C), 128.2(2C), 128.2, 128.1(2C), 127.9(2C), 127.9(3C), 127.8(5C), 127.7(4C), 127.6(2C), 127.6, 127.5(2C), 127.4, 127.4, 127.4, 127.3(2C), 117.7, 99.7, 99.6, 98.2(2C), 98.1, 80.2, 79.8, 78.6, 78.1, 76.0, 75.2, 75.1, 75.1(2C), 74.5, 74.2, 74.1, 73.9, 73.4, 72.8, 71.8, 71.5(2C), 71.3, 71.2, 71.2, 70.8, 70.2, 70.2, 69.5, 68.9, 68.6, 68.5, 68.3, 68.0, 66.9, 66.3, 66.0, 65.2, 63.0; MALDI-TOF (ESI-MS): m/z calcd for $[C_{138}H_{134}O_{32}Na]^+$: 2326.8789; Found: 2326.8777.

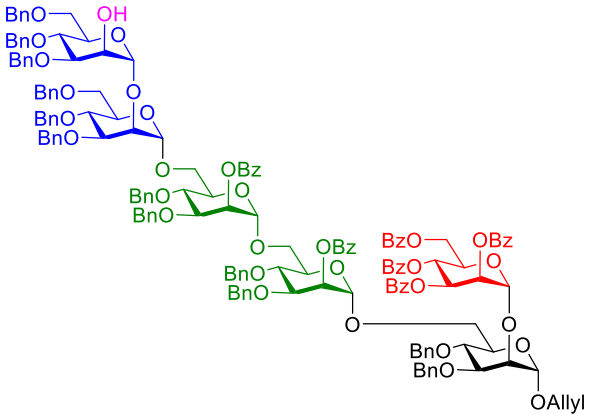
**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl)-2-*O*-(3,4,5-tri-*O*-benzyl)-2-*O*-(4-oxopentanoyl-3,4,6-tri-*O*-benzyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranoside (44):** Yield: (83%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -16.2; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.08 (m, 6H), 8.02 – 7.98 (m, 2H), 7.97 – 7.93 (m, 2H), 7.74 – 7.67 (m, 2H), 7.60 – 7.55 (m, 2H), 7.41 (m, 11H), 7.35 – 7.28 (m, 11H), 7.27 – 7.22 (m, 22H), 7.19 – 7.16 (m, 12H), 7.13 (m, 10H), 7.11 – 7.07 (m, 10H),




6.12 (dd, *J* = 11.1, 8.8 Hz, 1H), 6.02 (t, *J* = 2.5 Hz, 1H), 5.99 (dd, *J* = 9.9, 3.2 Hz, 1H), 5.89 – 5.80 (m, 2H), 5.77 (s, 1H), 5.52 (t, *J* = 2.4 Hz, 1H), 5.33 (s, 1H), 5.28 – 5.22 (m, 1H), 5.17 (dd, *J* = 10.5, 1.6 Hz, 1H), 5.13 (d, *J* = 1.8 Hz, 1H), 5.11 (d, *J* = 1.9 Hz, 1H), 5.02 (d, *J* = 2.3 Hz, 1H), 5.00 (d, *J* = 4.6 Hz, 1H), 4.97 (t, *J* = 2.2 Hz, 2H), 4.93 (d, *J* = 11.6 Hz, 1H), 4.86 (d, *J* = 4.0 Hz, 1H), 4.83 (d, *J* = 4.0 Hz, 2H), 4.80 (d, *J* = 4.6 Hz, 1H), 4.77 – 4.72 (m, 2H), 4.72 – 4.67 (m, 3H), 4.66 (s, 1H), 4.60 (d, *J* = 5.3 Hz, 1H), 4.59 – 4.56 (m, 3H), 4.55 (s, 1H), 4.53 (d, *J* = 1.9 Hz, 2H), 4.50 (s, 1H), 4.47 (d, *J* = 10.3 Hz, 2H), 4.42 (d, *J* = 4.5 Hz, 1H), 4.38 (dd, *J* = 7.4, 3.9 Hz, 2H), 4.36 (d, *J* = 2.5 Hz, 1H), 4.34 (d, *J* = 3.4 Hz, 1H), 4.23 (dd, *J* = 9.2, 3.2 Hz, 1H), 4.17 (t, *J* = 2.3 Hz, 1H), 4.16 – 4.11 (m, 2H), 4.05 (d, *J* = 3.7 Hz, 1H), 4.02 (d, *J* = 3.7 Hz, 1H), 4.01 (d, *J* = 3.2 Hz, 1H), 4.00 – 3.97 (m, 2H), 3.96 (d, *J* = 2.9 Hz, 1H), 3.95 (s, 1H), 3.93 (d, *J* = 3.4 Hz, 1H), 3.90 (d, *J* = 2.4 Hz, 1H), 3.88 (d, *J* = 2.2 Hz, 2H), 3.86 (d, *J* = 4.3 Hz, 2H), 3.80 (d, *J* = 3.7 Hz, 1H), 3.77 (d, *J* = 3.9 Hz, 1H), 3.76 – 3.72 (m, 1H), 3.71 – 3.67 (m, 1H), 3.64 (d, *J* = 8.9 Hz, 2H), 3.60 (s, 1H), 3.56 (s, 1H), 3.52 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.45 – 3.36 (m, 2H), 2.67 (s, 4H), 2.10 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 206.3, 171.8, 166.2, 165.6, 165.6, 165.5, 165.3, 165.0, 138.7, 138.6, 138.6, 138.6, 138.5, 138.4, 138.2, 138.1, 138.0, 138.0, 137.9, 137.6, 133.6, 133.4, 133.3, 133.2, 133.1, 132.9, 130.2, 130.1, 129.9, 129.9, 129.8(3C), 129.8, 129.7, 129.5, 129.2, 129.0, 128.6(2C), 128.5(4C), 128.5(2C), 128.4(5C), 128.4(8C), 128.4(4C), 128.3(2C), 128.3(2C), 128.3(7C), 128.2(2C), 128.2(5C), 128.1(6C), 128.1(2C), 128.0, 127.9(2C), 127.9(2C), 127.8(2C), 127.8, 127.7(2C), 127.7, 127.7, 127.6(2C), 127.6(6C), 127.5(2C), 127.5, 127.4, 127.4, 127.3, 127.2, 127.2, 117.7, 99.7, 99.5, 99.2, 98.3, 98.3, 98.2, 79.4, 78.6, 78.3, 78.1, 77.3(2C), 76.0, 75.2, 75.1, 75.1, 74.9, 74.7, 74.5, 74.5, 74.4, 74.2, 74.1, 73.7, 73.4, 73.2, 72.8, 72.1, 71.9, 71.8, 71.7, 71.5, 71.3, 71.2, 71.0, 70.8, 70.2, 69.5, 69.0, 68.9, 68.8, 68.7, 68.5, 68.0, 66.9, 66.2, 66.1, 65.9, 63.0, 38.1, 29.8, 28.3; MALDI-TOF (ESI-MS): m/z calcd for $[C_{170}H_{168}O_{39}Na]^+$: 2857.1094; Found: 2857.1090.

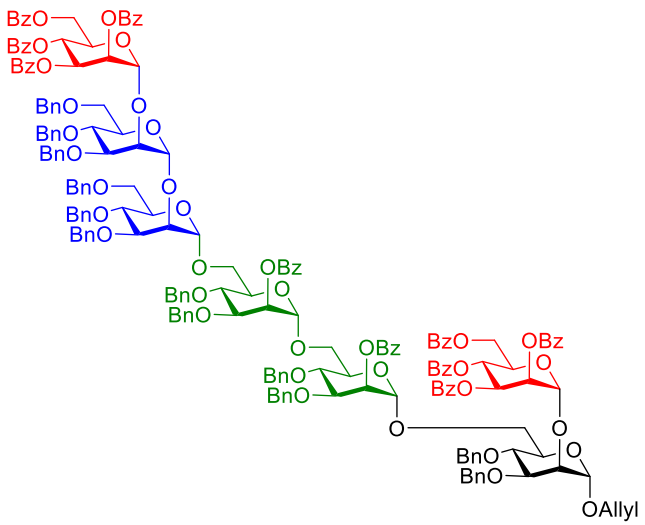
**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl)-2-*O*-(3,4,5-tri-*O*-benzyl)-2-*O*-(3,4,6-tri-*O*-benzyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-**

**mannopyranosyl)-α-D-mannopyranoside**




**(45):** Yield: (79%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -13.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.9 Hz, 6H), 7.97 (dd, *J* = 19.5, 7.8 Hz, 4H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.57 (dt, *J* = 7.3, 3.7 Hz, 2H), 7.41 (m, 11H), 7.31 – 7.25 (m, 18H), 7.21 (m, 11H), 7.18 – 7.12 (m, 26H), 7.11 – 7.06 (m, 10H), 6.12 (t, *J* = 10.0 Hz, 1H), 6.02 (t, *J* = 2.4 Hz, 1H), 5.99 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.88 – 5.80 (m, 2H), 5.76 (t, *J* = 2.5 Hz, 1H), 5.33 (s, 1H), 5.25 (d, *J* = 17.0 Hz, 1H), 5.19 (s, 1H), 5.16 (s, 1H), 5.13 (s, 1H), 5.00 (d, *J* = 4.8 Hz, 3H), 4.97 (s, 1H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 4.1 Hz, 1H), 4.82 (d, *J* = 5.7 Hz, 2H), 4.78 (s, 1H), 4.74 (d, *J* = 4.3 Hz, 1H), 4.70 (d, *J* = 8.4 Hz, 3H), 4.66 (s, 1H), 4.62 (s, 1H), 4.58 (d, *J* = 5.6 Hz, 2H), 4.56 (d, *J* = 5.2 Hz, 2H), 4.53 (d, *J* = 6.4 Hz, 2H), 4.50 (d, *J* = 2.2 Hz, 2H), 4.48 (t, *J* = 3.2 Hz, 2H), 4.42 (d, *J* = 4.4 Hz, 1H), 4.39 (t, *J* = 5.4 Hz, 2H), 4.35 (s, 1H), 4.33 (d, *J* = 7.6 Hz, 1H), 4.23 (dd, *J* = 9.2, 3.3 Hz, 1H), 4.18 (dd, *J* = 5.1, 2.4 Hz, 2H), 4.15 – 4.11 (m, 2H), 4.06 – 4.01 (m, 3H), 3.98 (dd, *J* = 11.9, 4.5 Hz, 3H), 3.93 (dd, *J* = 6.6, 2.4 Hz, 3H), 3.90 (s, 1H), 3.88 (d, *J* = 3.1 Hz, 3H), 3.84 (d, *J* = 8.1 Hz, 3H), 3.79 (d, *J* = 2.8 Hz, 1H), 3.76 (d, *J* = 4.1 Hz, 1H), 3.73 (t, *J* = 3.3 Hz, 1H), 3.66 (d, *J* = 11.5 Hz, 1H), 3.62 (d, *J* = 10.0 Hz, 2H), 3.58 (s, 1H), 3.55 (d, *J* = 4.6 Hz, 1H), 3.41 (dd, *J* = 20.2, 10.4 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.7, 165.6, 165.5, 165.3, 165.0, 138.7, 138.7, 138.6, 138.6, 138.5, 138.4, 138.2, 138.1, 138.0, 137.9, 137.9, 137.6, 133.6, 133.4, 133.3, 133.2, 133.1, 132.9, 130.2, 130.1, 129.9, 129.9(2C), 129.9(5C), 129.8(2C), 129.7(2C), 129.5, 129.5, 129.2, 129.0, 128.6(3C), 128.5(3C), 128.5(3C), 128.4(3C), 128.4(7C), 128.3(2C), 128.3(4C), 128.3(2C), 128.3(4C), 128.3, 128.2(2C), 128.2(2C), 128.2(2C), 128.1(2C), 128.1(2C), 127.9(2C), 127.9(2C), 127.8(4C), 127.8(2C), 127.8(2C), 127.7(5C), 127.6(2C), 127.6, 127.5, 127.4(4C), 127.4, 127.4, 127.3(2C), 127.2(2C), 117.7, 101.1, 99.7, 99.3, 98.3, 98.3, 98.2, 80.0, 79.4, 78.6, 78.3, 76.1, 75.2, 75.0(2C), 74.9, 74.5, 74.5(2C), 74.3, 74.3, 74.1, 73.9, 73.8, 73.7, 73.3, 73.3, 72.8, 72.2, 71.8, 71.6, 71.5, 71.3, 71.2(2C), 71.0, 70.8, 70.2, 70.2, 69.5, 68.9, 68.9, 68.8, 68.6, 68.5, 68.0, 66.9, 66.1, 63.0, 63.0; MALDI-TOF (ESI-MS): m/z calcd for $[C_{165}H_{162}O_{37}Na]^+$: 2759.0726; Found: 2759.0720.

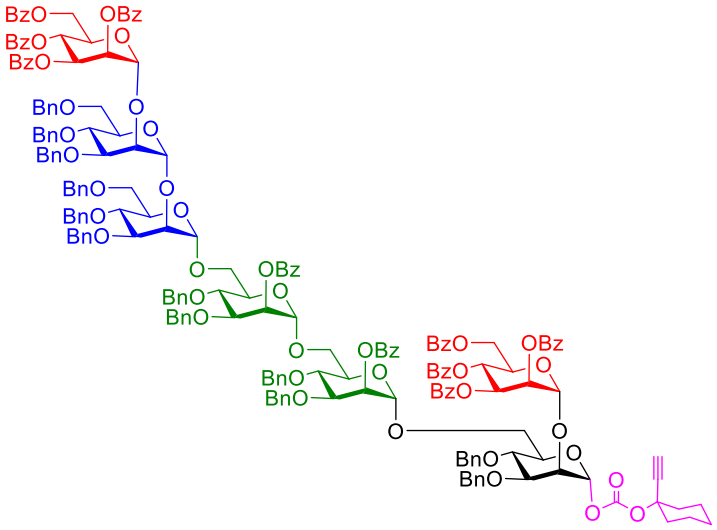
**Allyl 3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-**




**benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranoside (2):** Yield: (89%); Sticky syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +17.4°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.08 (m, 9H), 8.04 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.87 – 7.84 (m, 5H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.64 – 7.48 (m, 8H), 7.42 (d, *J* = 7.3 Hz, 10H), 7.40 – 7.37 (m, 8H), 7.35 – 7.32 (m, 8H), 7.27 (d, *J* = 7.7 Hz, 11H), 7.23 – 7.20 (m, 12H), 7.18 (d, *J* = 2.9 Hz, 6H), 7.17 (s, 5H), 7.14 (d, *J* = 3.1 Hz, 8H), 7.12 (s, 4H), 7.09 (d, *J* = 4.3 Hz, 8H), 6.13 (q, *J* = 9.6 Hz, 3H), 6.02 (s, 1H), 6.00 (s, 1H), 5.98 (s, 1H), 5.90 – 5.85 (m, 3H), 5.85 – 5.76 (m, 3H), 5.41 (s, 1H), 5.33 (s, 1H), 5.25 (d, *J* = 17.1 Hz, 1H), 5.16 (d, *J* = 10.6 Hz, 1H), 5.14 (s, 1H), 5.06 (s, 1H), 5.04 (s, 1H), 5.01 (s, 1H), 4.98 (s, 1H), 4.97 (s, 1H), 4.94 (s, 1H), 4.92 – 4.91 (m, 1H), 4.89 (s, 1H), 4.86 (d, *J* = 4.5 Hz, 1H), 4.82 (d, *J* = 9.9 Hz, 1H), 4.77 (d, *J* = 6.5 Hz, 1H), 4.73 (s, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 4.65 (s, 1H), 4.63 (s, 1H), 4.62 – 4.61 (m, 1H), 4.60 (s, 1H), 4.58 (s, 1H), 4.57 (s, 1H), 4.55 (s, 1H), 4.52 (s, 1H), 4.51 (s, 1H), 4.48 (s, 1H), 4.46 (d, *J* = 5.0 Hz, 1H), 4.44 (s, 1H), 4.41 (d, *J* = 5.6 Hz, 2H), 4.38 (d, *J* = 3.7 Hz, 2H), 4.35 (s, 1H), 4.23 (s, 2H), 4.21 (s, 1H), 4.16 (d, *J* = 7.2 Hz, 2H), 4.13 (s, 1H), 4.10 (s, 1H), 4.06 (s, 1H), 4.03 (s, 1H), 4.01 (s, 1H), 3.99 (s, 1H), 3.97 (d, *J* = 4.1 Hz, 1H), 3.94 (s, 1H), 3.92 (d, *J* = 5.1 Hz, 1H), 3.90 (s, 1H), 3.85 (s, 3H), 3.83 (s, 2H), 3.80 (d, *J* = 5.4 Hz, 1H), 3.77 (s, 1H), 3.72 (s, 1H), 3.69 (s, 1H), 3.67 – 3.64 (m, 1H), 3.59 (s, 1H), 3.57 (s, 1H), 3.51 (d, *J* = 10.8 Hz, 1H), 3.39 (d, *J* = 11.1 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.9, 165.6, 165.6, 165.5, 165.5, 165.3, 165.3, 165.1, 165.0, 138.7(2C), 138.6, 138.5(2C), 138.5, 138.4, 138.0, 137.9, 137.8, 137.6, 137.5, 133.6, 133.4, 133.3(2C), 133.2, 133.1, 133.0, 133.0, 133.0, 132.9, 130.2, 130.1, 130.0, 129.9(4C), 129.9, 129.8(2C), 129.8(7C), 129.8(2C), 129.7(2C), 129.6, 129.5, 129.4, 129.2, 128.9, 128.6(4C), 128.5(4C), 128.5(6C), 128.5, 128.4(6C), 128.4(4C), 128.3(4C), 128.3(10C), 128.2(4C), 128.2(4C), 128.1(4C), 128.1(4C), 127.8(4C), 127.7(4C), 127.7(3C), 127.7(2C), 127.6, 127.5(2C), 127.5(2C), 127.5, 127.4(2C), 127.4(4C), 127.3(2C), 127.2, 127.1(2C), 117.7, 100.4, 99.7, 99.3, 99.2, 98.4, 98.3, 98.2, 80.2, 79.8, 79.4, 78.6, 78.3, 76.1,

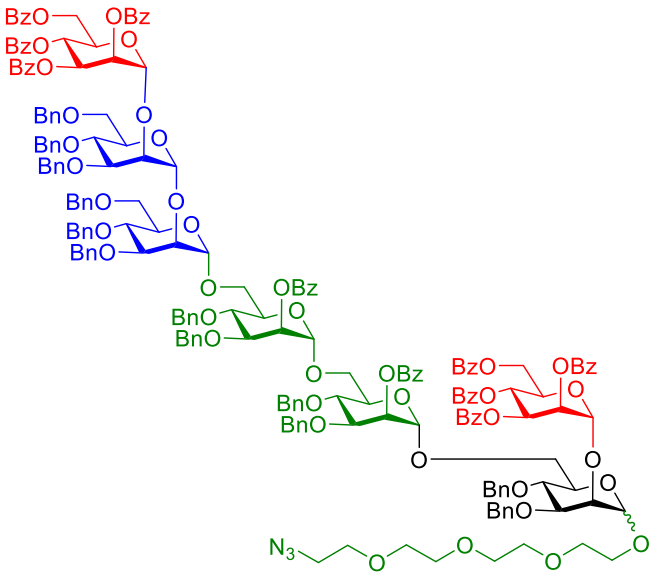
75.2(2C), 75.2, 75.1, 74.8(2C), 74.5, 74.5, 74.1, 73.3, 73.2, 72.8, 72.8, 72.5, 72.4, 72.3, 72.1, 71.5, 71.2(2C), 70.9, 70.8, 70.5, 70.2, 70.2, 70.2, 69.5, 69.3, 69.2, 68.9(3C), 68.5, 68.0, 66.9, 66.9, 66.8, 66.1, 66.1, 66.0, 63.0, 62.3; MALDI-TOF (ESI-MS): m/z calcd for $[C_{199}H_{188}O_{46}Na]^+$: 3338.2337; Found: 3338.8921.

**1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(6-*O*-((6-*O*((2-*O*-((2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl))-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl))-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl))-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl)-3,4-di-*O*-benzyl-α-D-mannopyranoside (46):** Yield: (73%); Sticky; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +14.2°; $^1$H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, *J* = 7.7 Hz, 2H), 8.14 – 8.10 (m, 6H), 8.08 (d, *J* = 7.7 Hz, 2H), 8.00 (t, *J* = 8.5 Hz, 4H), 7.90 (dt, *J* = 16.0, 7.9 Hz, 6H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.66 (dt, *J* = 12.1, 7.5 Hz, 2H), 7.61 – 7.56 (m, 5H), 7.46 – 7.37 (m, 25H), 7.31 – 7.28 (m, 18H), 7.25 – 7.23 (m, 13H), 7.17 – 7.09 (m, 25H), 6.25 (t, *J* = 10.2 Hz, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 6.17 (t, *J* = 10.1 Hz, 1H), 6.09 (s, 1H), 6.02 (dt, *J* = 10.2, 3.7 Hz, 2H), 5.91 (s, 2H), 5.80 – 5.77 (m, 1H), 5.47 – 5.41 (m, 2H), 5.17 (s, 1H), 5.09 (d, *J* = 1.9 Hz, 1H), 5.05 (d, *J* = 1.8 Hz, 1H), 5.03 (d, *J* = 11.1 Hz, 1H), 5.00 (s, 1H), 4.95 (d, *J* = 5.3 Hz, 1H), 4.94 – 4.90 (m, 2H), 4.86 (d, *J* = 10.7 Hz, 1H), 4.82 (d, *J* = 11.3 Hz, 2H), 4.79 (d, *J* = 6.5 Hz, 1H), 4.77 (d, *J* = 6.0 Hz, 1H), 4.73 (dd, *J* = 10.2, 3.2 Hz, 4H), 4.66 (d, *J* = 12.7 Hz, 2H), 4.63 (s, 1H), 4.61 (d, *J* = 4.1 Hz, 1H), 4.59 (s, 1H), 4.58 (d, *J* = 4.0 Hz, 2H), 4.57 – 4.56 (m, 2H), 4.54 (d, *J* = 4.6 Hz, 1H), 4.51 (t, *J* = 4.7 Hz, 2H), 4.49 (d, *J* = 5.2 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 2H), 4.39 (d, *J* = 12.3 Hz, 2H), 4.30 (t, *J* = 2.5 Hz, 1H), 4.26 (dt, *J* = 9.2, 2.6 Hz, 3H), 4.22 (d, *J* = 10.5 Hz, 1H), 4.19 (d, *J* = 11.7 Hz, 1H), 4.15 (d, *J* = 9.9 Hz, 1H), 4.13 (d, *J* = 2.5 Hz, 1H), 4.06 (d, *J* = 3.0 Hz, 1H), 4.05 (d, *J* = 2.8 Hz, 2H), 4.02 (d, *J* = 10.1 Hz, 2H), 4.00 – 3.98 (m, 2H), 3.96 (d, *J* = 9.7 Hz, 1H), 3.89 – 3.88 (m, 1H), 3.87 – 3.84 (m, 2H), 3.83 (d, *J* = 3.8 Hz, 1H), 3.81 (d, *J* = 4.2 Hz, 1H), 3.78 – 3.75 (m, 1H), 3.71 (dd, *J* = 10.8, 2.1 Hz, 1H), 3.69 – 3.66 (m, 1H),



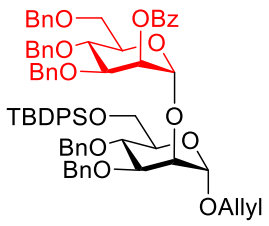
3.62 – 3.57 (m, 2H), 3.53 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.41 (t, *J* = 10.6 Hz, 1H), 2.68 (s, 1H), 2.25 – 2.20 (m, 2H), 2.19 – 2.14 (m, 2H), 1.96 – 1.89 (m, 3H), 1.87 (d, *J* = 7.0 Hz, 2H), 1.31(s, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 166.2, 166.0, 165.6, 165.6, 165.5, 165.5, 165.4, 165.4, 165.1, 164.9, 150.5, 138.7, 138.6(2C), 138.6, 138.5, 138.4, 138.3, 138.2, 138.0, 137.8, 137.6, 137.5, 133.4, 133.3(2C), 133.3(2C), 133.1, 133.1, 133.0(2C), 132.9, 130.1, 130.1, 130.0, 129.9(11C), 129.9, 129.9, 129.8(6C), 129.8(2C), 129.7(2C), 129.6, 129.4, 129.3, 129.1, 129.1, 129.0, 128.9, 128.6(2C), 128.5(2C), 128.5(3C), 128.5(2C), 128.5(2C), 128.4(2C), 128.4(3C), 128.4(6C), 128.3(2C), 128.3(3C), 128.3(13C), 128.2(2C), 128.2(2C), 128.1(4C), 128.1, 128.1, 127.8(2C), 127.7(2C), 127.7(2C), 127.7(2C), 127.7(3C), 127.6, 127.6(2C), 127.5(2C), 127.5, 127.5, 127.5, 127.4, 127.3, 127.3, 127.3, 127.2(2C), 127.1, 127.1, 100.3, 99.6, 99.3, 99.2, 98.5, 98.3, 95.8, 82.4, 78.6, 78.6, 78.3, 75.6, 75.2, 75.1, 75.0, 74.8, 74.8, 74.7, 74.5, 74.4, 74.1, 73.8, 73.7, 73.7, 73.3(2C), 73.2, 73.1(2C), 72.6, 72.3, 72.3, 72.1, 71.5, 71.2, 70.8, 70.7, 70.4, 70.3, 70.2, 70.1, 69.7, 69.2, 68.8, 68.8, 68.8, 68.5, 68.2, 66.7, 66.3, 66.2, 66.0, 65.8, 62.6, 62.3, 62.0, 36.6(2C), 24.7, 22.7(2C); MALDI-TOF (ESI-MS): m/z calcd for $[C_{205}H_{194}O_{48}Na]^+$: 3448.2704; Found: 3448.2611.

**1-*O*-2-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}ethyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(6-*O*-((6-*O*-((2-*O*-((2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl))3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl))3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl))-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl)-3,4-di-*O*-benzyl-α/β-D-mannopyranoside (47): (α:β): (10:3)** Yield: (81%); Sticky; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -50.3°; $^1$H NMR (600 MHz, $CDCl_3$): δ 8.16 – 8.11 (m, 12H), 8.08 (d, *J* = 7.5 Hz, 2H), 8.04 (m, 4H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.89 (m, 6H), 7.74 (m, 3H), 7.61 (m, 7H), 7.48 – 7.38 (m, 21H), 7.31 (m, 17H), 7.25 – 7.19 (m, 38H), 7.17 – 7.11 (m, 34H), 6.20 – 6.16 (m, 2H), 6.07 (d, *J* = 10.6 Hz, 2H), 6.02 (d, *J* = 7.9 Hz, 2H), 5.92 – 5.89 (m, 2H), 5.85 – 5.80



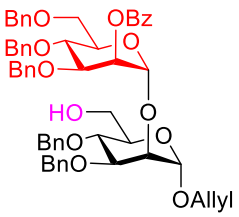
(m, 2H), 5.45 (s, 2H), 5.38 (s, 1H), 5.20 (s, 1H), 5.13 (s, 1H), 5.10 – 5.08 (m, 2H), 5.06 (d, *J* = 7.0 Hz, 1H), 5.02 – 5.00 (m, 2H), 4.95 (s, 1H), 4.93 (s, 1H), 4.91 (s, 1H), 4.87 (d, *J* = 10.6 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.79 – 4.78 (m, 1H), 4.77 (d, *J* = 5.7 Hz, 2H), 4.75 – 4.74 (m, 1H), 4.73 (s, 1H), 4.71 (s, 1H), 4.67 (s, 1H), 4.65 (s, 2H), 4.63 (m, 1H), 4.61 – 4.60 (m, 1H), 4.59 (s, 1H), 4.57 (s, 2H), 4.55 – 4.53 (m, 2H), 4.52 (s, 2H), 4.50 (d, *J* = 4.7 Hz, 1H), 4.48 (s, 1H), 4.45 (s, 1H), 4.43 (s, 1H), 4.41 (s, 2H), 4.39 (s, 1H), 4.27 – 4.24 (m, 4H), 4.18 – 4.15 (m, 2H), 4.15 – 4.12 (m, 3H), 4.08 (s, 1H), 4.07 (d, *J* = 2.6 Hz, 3H), 4.06 (s, 2H), 4.04 (s, 1H), 4.03 (s, 5H), 4.01 (s, 5H), 3.99 (s, 1H), 3.98 (s, 1H), 3.96 (s, 1H), 3.91 – 3.90 (m, 1H), 3.89 – 3.88 (m, 2H), 3.86 (d, *J* = 9.6 Hz, 2H), 3.83 (s, 1H), 3.82 – 3.80 (m, 2H), 3.78 (d, *J* = 4.4 Hz, 1H), 3.73 – 3.70 (m, 2H), 3.69 (d, *J* = 3.8 Hz, 1H), 3.63 – 3.59 (m, 18H), 3.43 – 3.40 (m, 2H), 3.34 – 3.32 (m, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 166.3, 166.2, 166.0, 165.6, 165.6, 165.6, 165.5, 165.5, 165.3, 165.3, 165.1, 165.0, 164.9, 138.7, 138.6, 138.6, 138.5, 138.5, 138.4, 138.3, 138.2, 138.1, 138.0, 137.9, 137.8, 137.6, 137.5, 137.5, 133.4, 133.4, 133.3(4C), 133.2, 133.1, 133.1, 133.0, 132.9, 130.3, 130.2, 130.1, 130.1, 130.0, 129.9(7C), 129.9, 129.9, 129.8(5C), 129.8(4C), 129.8(4C), 129.7(3C), 129.7, 129.6, 129.5, 129.3, 129.3, 129.2, 129.1, 128.9, 128.6(8C), 128.5(2C), 128.5(2C), 128.5(2C), 128.5(2C), 128.4(2C), 128.4(3C), 128.4, 128.4(12C), 128.3(2C), 128.3(9C), 128.3(3C), 128.2(2C), 128.2, 128.2, 128.1(4C), 128.1(2C), 128.1(2C), 128.1, 128.1, 127.8(2C), 127.8(4C), 127.7(3C), 127.7(5C), 127.7, 127.6(2C), 127.6, 127.6, 127.6, 127.6, 127.5(8C), 127.5(2C), 127.5(4C), 127.5, 127.4(3C), 127.4, 127.3, 127.3, 127.2(2C), 127.1(2C), 127.1, 127.1, 100.3, 100.1, 99.8, 99.3, 99.3, 99.2, 99.1, 98.8, 98.4, 98.3, 98.2, 98.1, 82.6, 79.8, 79.4, 78.6, 78.4, 78.3, 76.1, 75.2(2C), 75.1(3C), 75.1, 74.8(3C), 74.6, 74.5, 74.5, 74.4, 74.1, 74.0, 73.7, 73.3(2C), 73.2, 72.8, 72.5, 72.4, 72.3, 72.3, 72.1, 71.5, 71.4, 71.2, 70.9, 70.9, 70.8, 70.8, 70.7, 70.7(2C), 70.7(3C), 70.6, 70.6, 70.5, 70.4, 70.4, 70.2, 70.1, 70.0, 70.0, 69.5, 69.2, 68.9, 68.9, 68.8, 68.7, 68.6, 68.5, 68.4, 66.8, 66.7, 66.7, 66.6, 66.3, 66.2, 66.1, 66.0, 66.0, 63.0, 62.6, 62.3, 61.3, 50.6; MALDI-TOF (ESI-MS): m/z calcd for $[C_{204}H_{199}O_{49}Na]^+$: 3499.3137; Found: 3499.3104.

**Allyl 3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (29):** Yield: (90%); Sticky syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +11.9°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.09 – 8.06 (m, 2H), 7.77 – 7.69 (m, 4H), 7.58 – 7.53 (m, 1H), 7.40 – 7.30 (m, 16H), 7.26 – 7.22 (m, 10H), 7.16 (m, 7H), 5.86 – 5.76 (m, 2H), 5.21 (d, *J* = 2.0 Hz, 1H), 5.18 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.11 (dd, *J* = 10.4, 1.6 Hz,

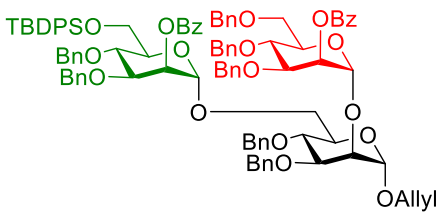


1H), 4.98 (d, *J* = 1.8 Hz, 1H), 4.89 (d, *J* = 10.7 Hz, 1H), 4.85 (d, *J* = 10.9 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.73 (d, *J* = 11.9 Hz, 1H), 4.69 (d, *J* = 2.4 Hz, 2H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.53 (dd, *J* = 12.7, 11.4 Hz, 2H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.13 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.11 – 4.05 (m, 2H), 4.03 (d, *J* = 7.6 Hz, 2H), 3.96 – 3.94 (m, 1H), 3.90 (ddd, *J* = 9.3, 5.3, 2.8 Hz, 4H), 3.85 (dt, *J* = 6.1, 1.4 Hz, 1H), 3.82 – 3.79 (m, 1H), 3.70 (ddd, *J* = 9.1, 4.2, 2.3 Hz, 1H), 1.05 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.5, 138.5, 138.4, 138.4, 138.1, 135.9(2C), 135.7(2C), 133.9, 133.8, 133.3, 133.1, 130.1, 130.0(2C), 129.6, 129.6, 128.4(3C), 128.4(4C), 128.4(2C), 128.3(2C), 128.2(2C), 128.0(2C), 128.0(2C), 127.9(2C), 127.7(2C), 127.6(4C), 127.6(2C), 127.6(2C), 127.5(2C), 127.5, 117.2, 99.9, 97.9, 80.1, 78.4, 75.5, 75.2(2C), 74.6, 74.5, 73.5, 72.9, 72.4, 72.0, 71.8, 69.3, 69.2, 67.6, 63.2, 26.9(3C), 19.3; HRMS (ESI-MS): m/z calcd for $[C_{73}H_{78}O_{12}SiNa]^+$: 1197.5160 ; Found: 1197.5154.

**Allyl 3,4-di-*O*-benzyl-2-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (30):** Yield: (89%); Sticky syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -15.4°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.45 – 7.33 (m, 15H), 7.33 – 7.29 (m, 5H), 7.28 – 7.16 (m, 7H), 5.89 – 5.78 (m, 2H), 5.23 (d, *J* = 17.3 Hz, 1H), 5.20 (s, 1H), 5.17 (dd, *J* = 10.4, 1.7 Hz, 1H), 4.96 (s, 1H), 4.93 (s, 1H), 4.88 (t, *J* = 10.7 Hz, 2H), 4.76 – 4.68 (m, 4H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.55 (t, *J* = 10.7 Hz, 2H), 4.12 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.10 – 4.04 (m, 2H), 4.02 (d, *J* = 9.1 Hz, 1H), 3.99 (dd, *J* = 9.1, 2.6 Hz, 2H), 3.89 (d, *J* = 9.6 Hz, 2H), 3.86 – 3.82 (m, 2H), 3.81 – 3.73 (m, 2H), 3.69 – 3.64 (m, 1H), 2.03 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.4, 138.3, 138.3, 138.2, 138.2, 137.9, 133.6, 133.1, 130.0(2C), 128.5(2C), 128.4(2C), 128.4(2C), 128.4(5C), 128.4(2C), 128.3(2C), 128.2(2C), 128.2(2C), 127.8, 127.8, 127.7, 127.6(2C), 127.6(2C), 127.6(2C), 117.4, 99.6, 98.0, 79.6, 77.8, 75.4, 75.3, 75.3, 74.4(2C), 73.5, 72.2, 72.1, 72.0, 71.6, 69.3, 68.9, 68.0, 62.3; HRMS (ESI-MS): m/z calcd for $[C_{57}H_{60}O_{12}Na]^+$: 959.3982 ; Found: 959.3971.

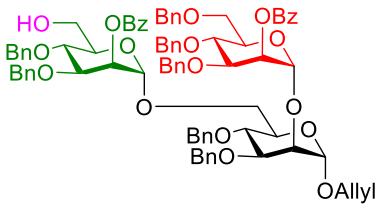



**Allyl 3,4-di-*O*-benzyl-2-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-α-D-mannopyranoside (31):** Yield: (89%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +15.7°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.3, 1.4 Hz, 2H), 8.05 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.77 (dd, *J* = 7.9, 1.6 Hz,



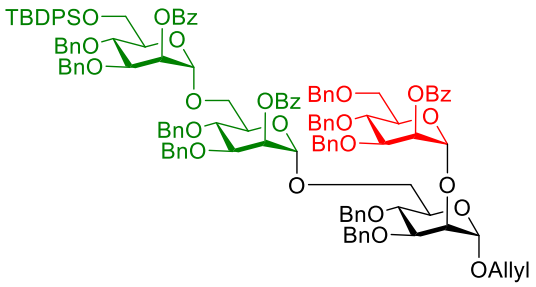
2H), 7.72 – 7.68 (m, 2H), 7.58 – 7.47 (m, 3H), 7.38 – 7.30 (m, 14H), 7.29 – 7.24 (m, 9H), 7.23 – 7.19 (m, 11H), 7.16 (dq, *J* = 7.5, 1.8 Hz, 11H), 5.86 – 5.76 (m, 2H), 5.69 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.24 – 5.19 (m, 2H), 5.12 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.05 (d, *J* = 1.8 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.87 (s, 1H), 4.86 (d, *J* = 9.2 Hz, 1H), 4.82 (d, *J* = 7.7 Hz, 1H), 4.79 (d, *J* = 7.7 Hz, 1H), 4.73 (d, *J* = 11.4 Hz, 1H), 4.71 – 4.63 (m, 5H), 4.56 – 4.53 (m, 2H), 4.52 – 4.50 (m, 2H), 4.48 (d, *J* = 6.8 Hz, 1H), 4.27 (t, *J* = 9.6 Hz, 1H), 4.16 – 4.13 (m, 1H), 4.12 – 4.10 (m, 1H), 4.09 (dd, *J* = 3.3, 1.7 Hz, 1H), 4.07 – 4.05 (m, 1H), 4.03 (dd, *J* = 8.7, 3.5 Hz, 2H), 3.98 – 3.95 (m, 1H), 3.93 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.89 – 3.86 (m, 2H), 3.85 – 3.83 (m, 1H), 3.81 – 3.76 (m, 2H), 3.74 (t, *J* = 2.1 Hz, 1H), 3.71 (d, *J* = 4.2 Hz, 1H), 3.64 (t, *J* = 9.4 Hz, 1H), 1.09 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.7, 165.4, 138.8, 138.5, 138.4, 138.2, 138.1, 138.1, 138.0, 136.0(2C), 135.7(2C), 133.7, 133.7, 133.3, 133.0, 130.1(2C), 130.0, 130.0, 129.6, 129.6, 128.4(3C), 128.4(6C), 128.4(3C), 128.3(2C), 128.3(2C), 128.3(2C), 128.2(2C), 128.2(2C), 128.2(2C), 128.1(3C), 127.8(2C), 127.8(2C), 127.7(2C), 127.6(3C), 127.6(2C), 127.6(3C), 127.6(2C), 127.5, 127.5, 127.4, 117.6, 99.6, 97.8, 97.7, 80.1, 78.3, 78.1, 75.3(2C), 75.0, 74.7, 74.6, 74.4, 74.1, 73.4, 72.4, 72.3, 72.1, 71.7, 71.5, 70.9, 69.2(2C), 69.1, 67.8, 66.6, 62.8, 26.9(3C), 19.4; HRMS (ESI-MS): m/z calcd for $[C_{100}H_{104}O_{18}SiNa]^+$: 1644.6923 ; Found: 1644.6911.

**Allyl 3,4-di-*O*-benzyl-2-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (32):** Yield: (87%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +111.2°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.06 (m, 4H), 7.60 – 7.53 (m, 2H), 7.46 – 7.42 (m, 2H), 7.40 – 7.32 (m, 8H), 7.31 – 7.24 (m, 21H), 7.22 – 7.18 (m, 8H), 5.84 – 5.75 (m, 2H), 5.62 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.20 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.16 (d, *J* = 2.0 Hz, 1H), 5.10 (dd, *J* = 10.4, 1.5 Hz, 1H), 4.98 (d, *J* = 1.8 Hz, 1H), 4.92 (s, 1H), 4.90 (s, 1H), 4.88 (d, *J* = 3.7 Hz, 1H), 4.85 (d, *J* = 4.8 Hz, 1H), 4.83 (d, *J* = 5.1 Hz, 1H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 10.8 Hz, 3H), 4.62 (d, *J* = 7.1 Hz, 1H), 4.59 (d, *J* = 7.1 Hz, 1H), 4.54 – 4.50 (m, 2H), 4.50 (d, *J* = 1.6 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.14 (dd, *J* = 9.2, 3.1 Hz, 1H), 4.09 (dd, *J* = 6.0, 3.2 Hz, 1H), 4.07 (d, *J* = 3.2 Hz, 1H), 4.04 (dq, *J* = 3.1, 1.6 Hz, 1H), 4.01 (dd, *J* = 3.2, 1.8 Hz, 1H), 3.97 (ddd, *J* = 9.7, 3.9, 2.0 Hz, 2H), 3.93 (d, *J* = 2.5 Hz, 1H), 3.91 – 3.84 (m, 2H), 3.83 – 3.79 (m, 2H), 3.79 (s, 1H), 3.77 – 3.73 (m, 3H), 3.71 (d, *J* = 1.9 Hz, 1H), 3.60 (t, *J* = 9.3 Hz, 1H), 2.02 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.6, 165.5, 138.5, 138.4, 138.2, 138.2, 138.1, 137.9, 133.6, 133.2, 133.1, 130.0, 130.0(2C), 129.9, 129.9, 128.5(2C),

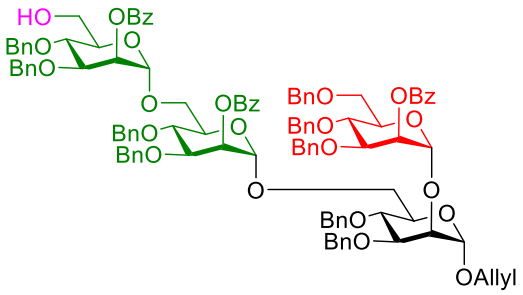


128.5(2C), 128.4(2C), 128.4(2C), 128.4(2C), 128.3(6C), 128.3(4C), 128.2(2C), 128.0(5C), 127.9(2C), 127.7(2C), 127.7(5C), 127.6, 127.6, 127.5(2C), 127.5, 117.8, 99.9, 97.5, 97.2, 79.9, 78.1, 78.0, 75.5, 75.3, 75.2, 75.1, 74.9, 74.4, 74.1, 73.4, 72.2, 72.0, 71.9, 71.8, 71.4, 70.6, 69.1(2C), 69.0, 67.8, 66.7, 61.9; HRMS (ESI-MS): m/z calcd for $[C_{84}H_{86}O_{18}Na]^+$: 1405.5701 ; Found: 1405.5701.

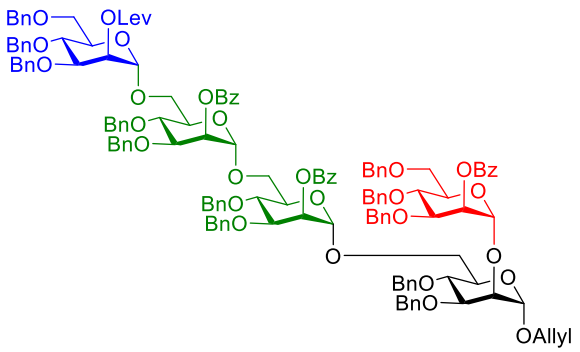
**Allyl 3,4-di-*O*-benzyl-2-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranoside (33):** Yield: (85%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +54.3°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.16 – 8.10 (m, 4H), 8.06 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.75 – 7.72 (m, 2H), 7.66 – 7.63 (m, 2H), 7.57 – 7.51 (m, 2H), 7.43 – 7.42 (m, 2H), 7.36 (m, 10H), 7.32 – 7.27 (m, 8H), 7.25 – 7.22 (m, 11H), 7.21 – 7.16 (m, 15H), 7.15 – 7.05 (m, 12H), 5.85 – 5.77 (m, 3H), 5.70 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.24 – 5.18 (m, 2H), 5.11 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.09 (d, *J* = 1.9 Hz, 1H), 5.03 (d, *J* = 1.8 Hz, 1H), 4.92 (d, *J* = 9.4 Hz, 1H), 4.90 (d, *J* = 1.8 Hz, 1H), 4.89 (d, *J* = 6.0 Hz, 1H), 4.84 (d, *J* = 6.1 Hz, 1H), 4.83 (d, *J* = 3.7 Hz, 1H), 4.81 (d, *J* = 1.7 Hz, 1H), 4.75 (dd, *J* = 11.1, 2.1 Hz, 2H), 4.70 – 4.66 (m, 3H), 4.61 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 10.9 Hz, 1H), 4.53 (d, *J* = 8.2 Hz, 1H), 4.51 (d, *J* = 2.6 Hz, 1H), 4.48 (t, *J* = 5.4 Hz, 2H), 4.45 (d, *J* = 5.3 Hz, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.25 (t, *J* = 9.6 Hz, 1H), 4.17 (dd, *J* = 9.0, 3.2 Hz, 1H), 4.10 – 4.08 (m, 2H), 4.07 – 4.04 (m, 2H), 4.02 – 3.97 (m, 2H), 3.96 – 3.92 (m, 2H), 3.90 – 3.86 (m, 2H), 3.86 – 3.83 (m, 1H), 3.82 – 3.77 (m, 4H), 3.76 – 3.66 (m, 4H), 3.64 – 3.58 (m, 2H), 1.08 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.6, 165.6, 165.5, 138.8, 138.5, 138.5, 138.3, 138.2, 138.1, 138.1, 137.8, 137.8, 135.9(2C), 135.7(2C), 133.6, 133.6, 133.2, 133.2, 133.1, 130.1(2C), 130.0(2C), 130.0, 129.9, 129.6, 129.5, 128.6, 128.4(3C), 128.4(2C), 128.4(6C), 128.3(2C), 128.3(7C), 128.2(2C), 128.2(2C), 128.2(2C), 128.1(5C), 128.1(2C), 127.8(3C), 127.7(6C), 127.6(6C), 127.6, 127.5(3C), 127.5, 127.5, 127.3, 127.2(3C), 117.7, 99.7, 98.4, 97.9, 97.8, 80.1, 78.4, 78.3, 78.2, 75.3, 75.2, 75.0, 75.0, 74.8, 74.6, 74.4, 73.9, 73.9, 73.4, 72.6, 72.3, 72.1, 71.7, 71.4, 71.4, 70.9, 70.8, 69.2, 69.1, 68.9, 68.7, 67.9, 66.7, 65.9, 62.6, 26.9(3C), 19.4; HRMS (ESI-MS): m/z calcd for $[C_{127}H_{130}O_{24}SiNa]^+$: 2090.8653 ; Found: 2090.8640.



**Allyl 3,4-di-*O*-benzyl-2-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranoside (34):** Yield: (84%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +34.3°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 6.8, 3.0 Hz, 2H), 8.09 – 8.05 (m, 4H), 7.56 (m, 2H), 7.48 – 7.44 (m, 5H), 7.39 – 7.30 (m, 9H), 7.28 – 7.21 (m, 25H), 7.19 – 7.17 (m, 9H), 7.14 – 7.07 (m, 4H), 5.86 – 5.79 (m, 2H), 5.78 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.71 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.25 – 5.19 (m, 2H), 5.12 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.07 (d, *J* = 1.8 Hz, 1H), 5.03 (d, *J* = 1.8 Hz, 1H), 4.91 (s, 1H), 4.90 (s, 1H), 4.88 (d, *J* = 5.2 Hz, 1H), 4.85 – 4.77 (m, 3H), 4.75 (d, *J* = 7.1 Hz, 1H), 4.71 (d, *J* = 1.2 Hz, 1H), 4.68 – 4.67 (m, 2H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.58 (d, *J* = 6.4 Hz, 1H), 4.55 – 4.52 (m, 2H), 4.50 (dd, *J* = 8.4, 2.6 Hz, 2H), 4.43 (dd, *J* = 13.1, 11.4 Hz, 2H), 4.17 (dd, *J* = 9.0, 3.2 Hz, 1H), 4.12 – 4.10 (m, 1H), 4.08 (dd, *J* = 4.7, 3.1 Hz, 2H), 4.06 – 4.03 (m, 2H), 4.01 – 3.96 (m, 3H), 3.96 – 3.90 (m, 3H), 3.90 – 3.87 (m, 2H), 3.85 (dd, *J* = 4.8, 1.5 Hz, 1H), 3.83 – 3.77 (m, 3H), 3.76 – 3.70 (m, 2H), 3.67 (d, *J* = 9.9 Hz, 3H), 3.61 (dd, *J* = 9.6, 3.0 Hz, 1H), 1.77 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 165.7, 165.5, 165.5, 138.6, 138.5, 138.4, 138.3, 138.3, 138.1, 138.1, 137.8, 137.7, 133.6, 133.3, 133.3, 133.1, 130.1, 130.1, 130.0(2C), 130.0, 130.0, 129.9, 128.6(2C), 128.5(2C), 128.5(2C), 128.4(2C), 128.4(3C), 128.4(8C), 128.3(3C), 128.3(2C), 128.2(2C), 128.2(2C), 128.2(2C), 128.1(2C), 128.1(2C), 127.8(3C), 127.7(2C), 127.7, 127.7, 127.7, 127.7, 127.6(2C), 127.6(4C), 127.5(2C), 127.5, 127.4, 117.7, 99.8, 98.2, 97.8, 97.8, 80.1, 78.4, 78.2, 77.8, 75.4, 75.2, 75.1, 75.1, 74.9, 74.7, 74.4, 74.0, 73.8, 73.4, 72.3, 72.2, 72.1, 71.8, 71.5, 71.3, 70.9, 70.7, 69.2, 69.1, 68.7, 68.7, 67.9, 66.8, 66.0, 61.9; ; HRMS (ESI-MS): m/z calcd for $[C_{111}H_{112}O_{24}Na]^+$: 1852.7475 ; Found: 1852.7467.

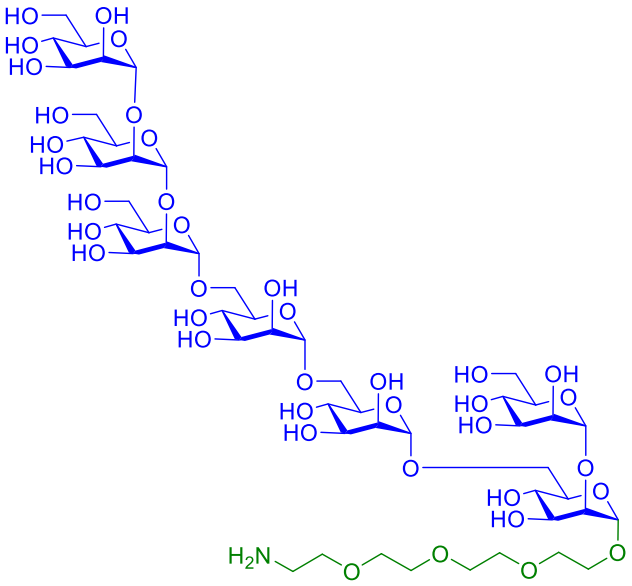



**Allyl 3,4-di-*O*-benzyl-2-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(2-*O*-(4-oxopentanoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranoside (35):** Yield: (90%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -54.3°; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.11 (m, 4H), 8.08 – 8.04 (m, 2H), 7.47 – 7.43 (m, 6H), 7.40 – 7.30 (m, 9H), 7.29 – 7.23 (m, 19H), 7.21 – 7.14 (m, 28H), 7.09 (td, *J* = 6.6, 6.1, 4.2 Hz, 7H), 5.85 – 5.77

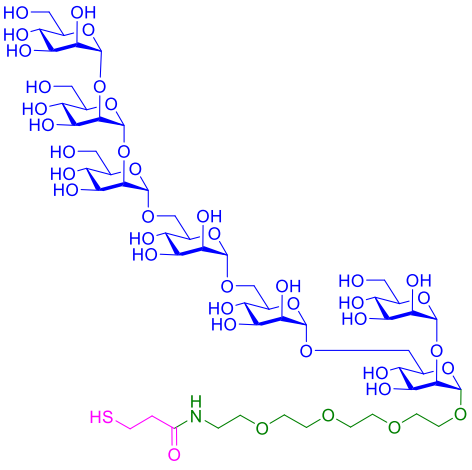



(m, 3H), 5.72 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.52 (dd, *J* = 3.0, 1.8 Hz, 1H), 5.25 – 5.19 (m, 2H), 5.12 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.06 (d, *J* = 1.9 Hz, 1H), 5.04 (d, *J* = 1.8 Hz, 1H), 4.93 (d, *J* = 1.9 Hz, 1H), 4.92 (d, *J* = 4.3 Hz, 1H), 4.91 (s, 1H), 4.89 (d, *J* = 4.3 Hz, 1H), 4.82 (dd, *J* = 11.2, 3.2 Hz, 4H), 4.77 (dd, *J* = 11.0, 2.5 Hz, 2H), 4.72 – 4.67 (m, 3H), 4.61 (d, *J* = 8.7 Hz, 1H), 4.60 – 4.56 (m, 2H), 4.54 (d, *J* = 7.8 Hz, 1H), 4.53 – 4.50 (m, 2H), 4.49 (d, *J* = 5.9 Hz, 1H), 4.42 (dd, *J* = 11.1, 5.2 Hz, 3H), 4.38 (d, *J* = 3.4 Hz, 1H), 4.35 – 4.30 (m, 2H), 4.18 (dd, *J* = 8.9, 3.2 Hz, 1H), 4.15 – 4.08 (m, 3H), 4.08 – 4.02 (m, 3H), 4.01 – 3.97 (m, 2H), 3.94 (dd, *J* = 9.3, 2.7 Hz, 3H), 3.91 (d, *J* = 2.0 Hz, 1H), 3.89 (d, *J* = 6.3 Hz, 2H), 3.87 – 3.84 (m, 2H), 3.82 (s, 1H), 3.80 – 3.77 (m, 2H), 3.75 (dd, *J* = 5.2, 2.2 Hz, 2H), 3.72 (d, *J* = 2.7 Hz, 1H), 3.65 (d, *J* = 1.8 Hz, 2H), 3.62 – 3.58 (m, 1H), 3.58 – 3.54 (m, 1H), 3.45 (ddd, *J* = 10.9, 7.8, 2.0 Hz, 2H), 2.69 (d, *J* = 2.4 Hz, 4H), 2.09 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 206.3, 171.8, 165.6, 165.5, 165.5, 138.6, 138.6, 138.6, 138.5, 138.4, 138.3, 138.2, 138.1, 138.1, 137.8, 137.7, 137.7, 133.7, 133.2, 133.1, 130.1, 130.0, 129.9(4C), 128.6(3C), 128.4(7C), 128.4(4C), 128.4(10C), 128.3(3C), 128.3(5C), 128.2(2C), 128.2(7C), 128.1(2C), 127.8(7C), 127.7(4C), 127.7, 127.6(3C), 127.6(2C), 127.6, 127.5, 127.5, 127.5, 127.4, 127.3(2C), 127.3(2C), 127.3, 117.7, 99.7, 98.4, 98.2, 97.9(2C), 80.1, 78.4, 78.3, 78.2, 77.7, 75.3, 75.1, 75.1, 75.0(2C), 74.8, 74.6, 74.4, 74.0, 74.0, 73.8, 73.4(3C), 72.3, 72.1, 71.8, 71.6, 71.5, 71.3, 71.3, 70.9, 70.8, 69.2, 69.1, 68.7, 68.5, 68.5, 68.4, 67.9, 66.7, 66.0, 65.8, 38.1, 29.8, 28.3; MALDI-TOF (ESI-MS): m/z calcd for $[C_{143}H_{146}O_{31}Na]^+$: 2383.6998 ; Found: 2383.6998.

**2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethanyl 2-*O*-(α-D-mannopyranosyl)-6-*O*-(6-*O*-(6-*O*-(2-*O*-(2-*O*-α-D-mannopyranosyl α -D-mannopyranosyl)- α-D-mannopyranosyl)- α-D-mannopyranosyl)- α-D-mannopyranosyl)- α-D-mannopyranoside (65):** Yield: (65%); Thick syrup; $[\alpha]^{25}_{D}$ ($H_2O$, *c* 1.0): -15.8°; $^1$H NMR (600 MHz, $D_2O$): δ 5.20 (s, 1H), 5.02 (d, *J* = 4.6 Hz, 2H), 4.95 (s, 1H), 4.93 (s, 1H), 4.81 (s, 1H), 4.80 (s, 1H), 4.03 – 3.99 (m, 2H), 3.99 – 3.96 (m, 2H), 3.91 – 3.85 (m, 12H), 3.84 – 3.77 (m, 9H), 3.76 – 3.69 (m, 15H), 3.67 – 3.59 (m, 32H), 3.58 – 3.52 (m, 8H), 2.82 (t, *J* = 10.6 Hz, 2H); $^{13}$C NMR (151 MHz, $D_2O$): δ 102.3, 102.2, 100.6, 99.6, 99.5, 98.5, 98.1, 78.8, 78.8, 78.5, 73.3, 73.2, 72.7, 71.1, 71.0, 70.8, 70.7, 70.4, 70.4, 70.3, 70.3, 70.2, 70.0, 69.9, 69.9(2C), 69.6, 69.6, 69.5, 69.5, 69.5, 69.4, 67.0, 66.9, 66.8, 66.7(2C), 66.5, 66.5, 66.4, 65.9, 65.4, 65.3, 65.0, 63.8, 61.1, 61.0, 60.9, 60.8, 60.8; HRMS (ESI-MS): m/z calcd for $[C_{50}H_{89}NO_{39}Na]^+$: 1350.4909; Found: 1350.4887.

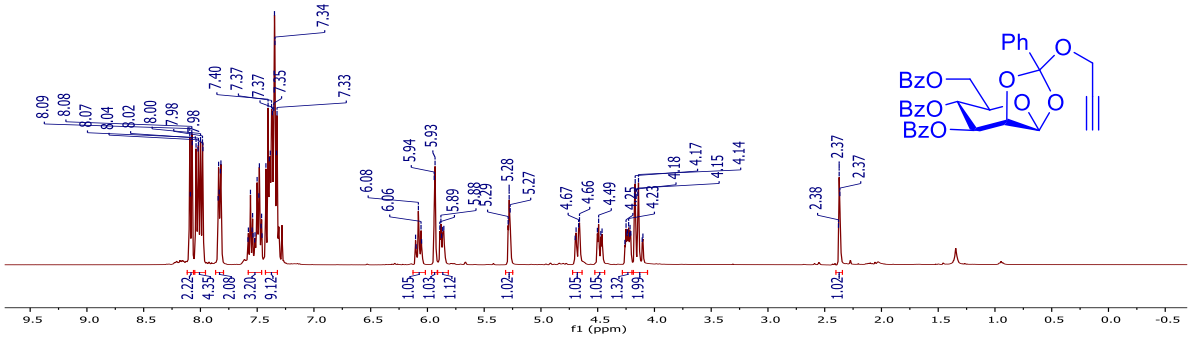


**3-mercapto-*N*-(2-(2-(2-(2-((2-*O*-(α-D-mannopyranosyl)-6-*O*-(6-*O*-(6-*O*-(2-*O*-(2-*O*-α-D-mannopyranosyl α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)oxy)ethoxy)ethoxy)ethyl)propanamide (1α):** Yield: (73%); Thick syrup; $[\alpha]^{25}_{D}$ ($H_2O$, *c* 1.0): 23.5°; $^1$H NMR (400 MHz, $D_2O$): δ 5.21 (s, 1H), 5.03 (d, *J* = 3.0 Hz, 2H), 4.95 (d, *J* = 7.6 Hz, 2H), 4.81 (d, *J* = 5.2 Hz, 2H), 4.04 – 3.86 (m, 16H), 3.81 – 3.52 (m, 65H), 2.86 (t, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 6.9 Hz, 2H); $^{13}$C NMR (151 MHz, $D_2O$): δ 102.3, 102.2, 100.6, 99.6, 99.5, 98.5, 98.1, 78.8, 78.8, 78.5, 73.3, 73.2, 72.7, 71.1, 71.0, 70.8, 70.7, 70.4, 70.3, 70.2, 70.0, 69.9, 69.9, 69.9, 69.6, 69.6, 69.6, 69.5, 69.5, 69.5, 69.5, 69.4, 67.0, 66.9, 66.8, 66.7, 66.5, 66.5, 66.3, 65.9, 65.4, 65.0, 63.8, 63.8, 61.1, 61.0, 61.0, 61.0, 60.9, 60.7, 28.2, 20.2; HRMS (ESI-MS): m/z calcd for $[C_{53}H_{93}NO_{49}K]^+$: 1454.4632; Found: 1454.4619.

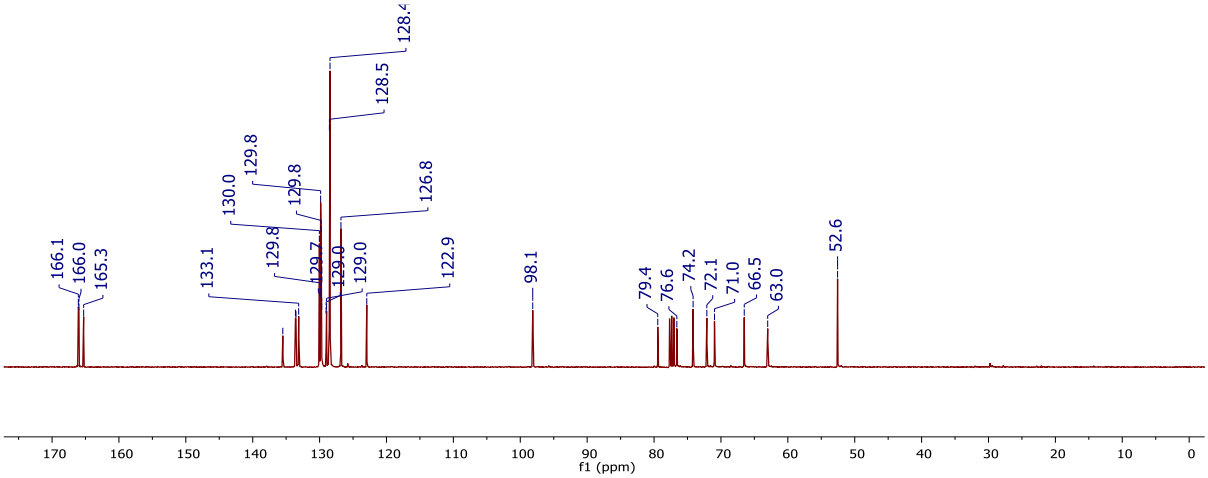


## 2.13 Spectral charts

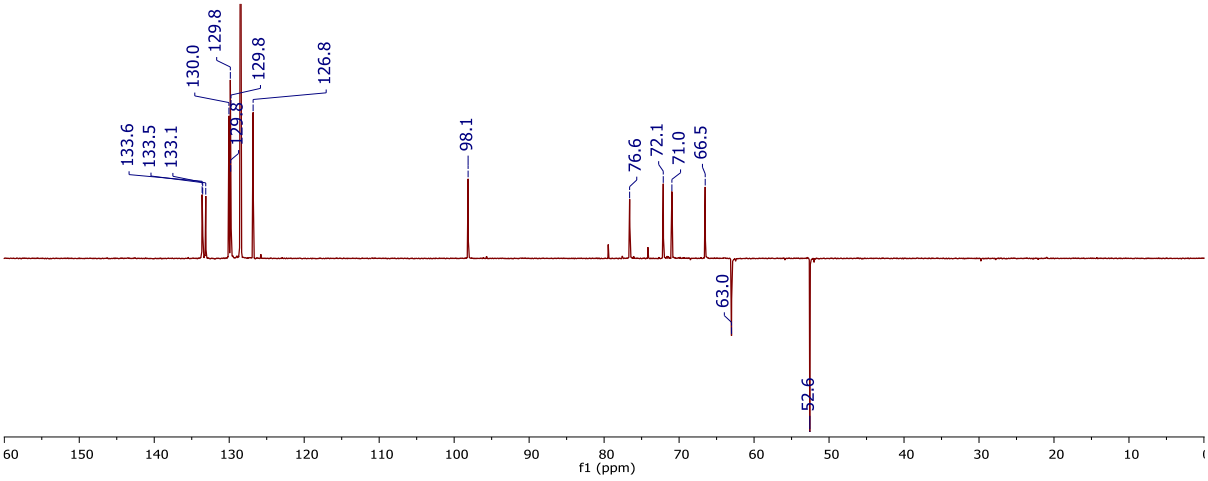
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 10**



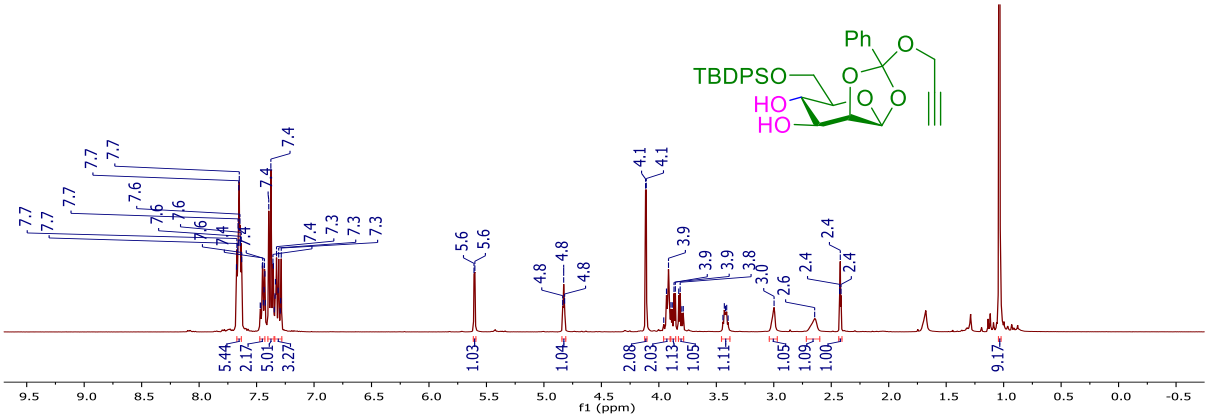

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 10**



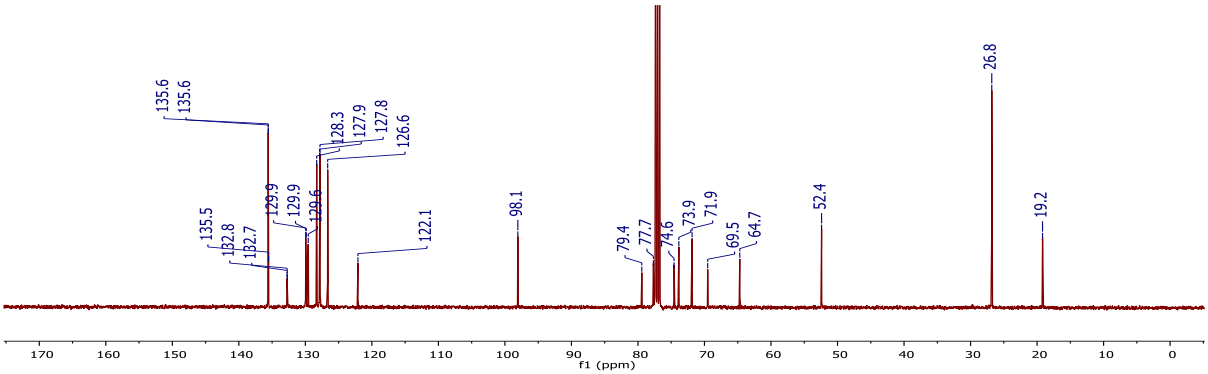

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 10**



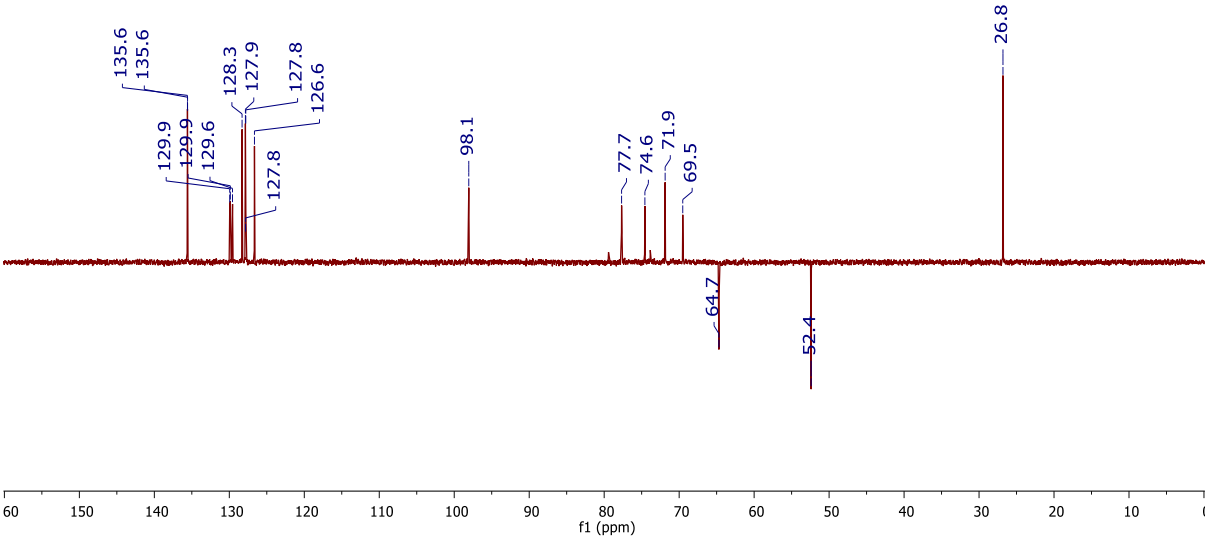
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 25**



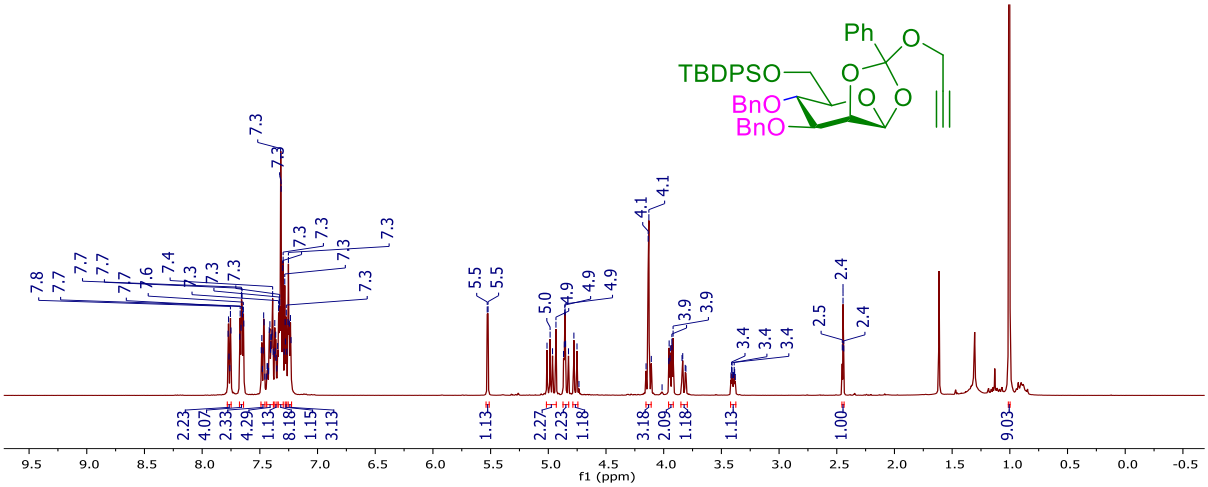

**$^{13}$C NMR Spectrum (100.67 Hz, $CDCl_3$) of compound 25**



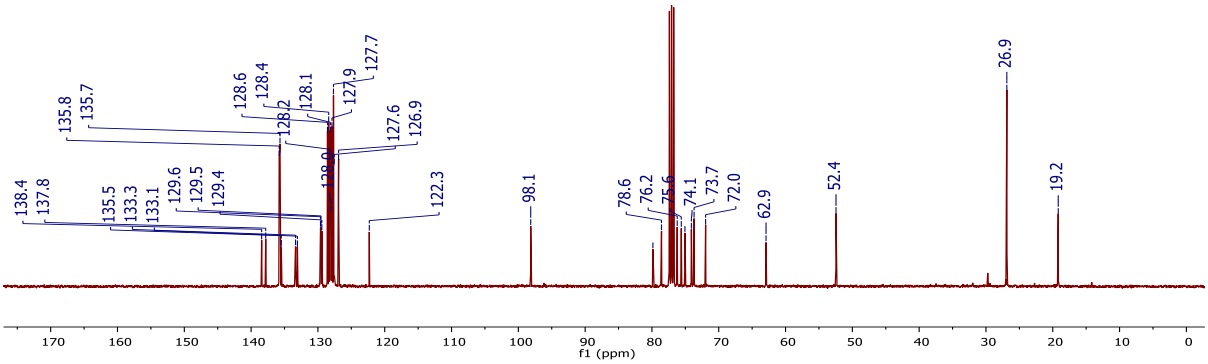

**DEPT NMR Spectrum (100.67 Hz, $CDCl_3$) of compound 25**



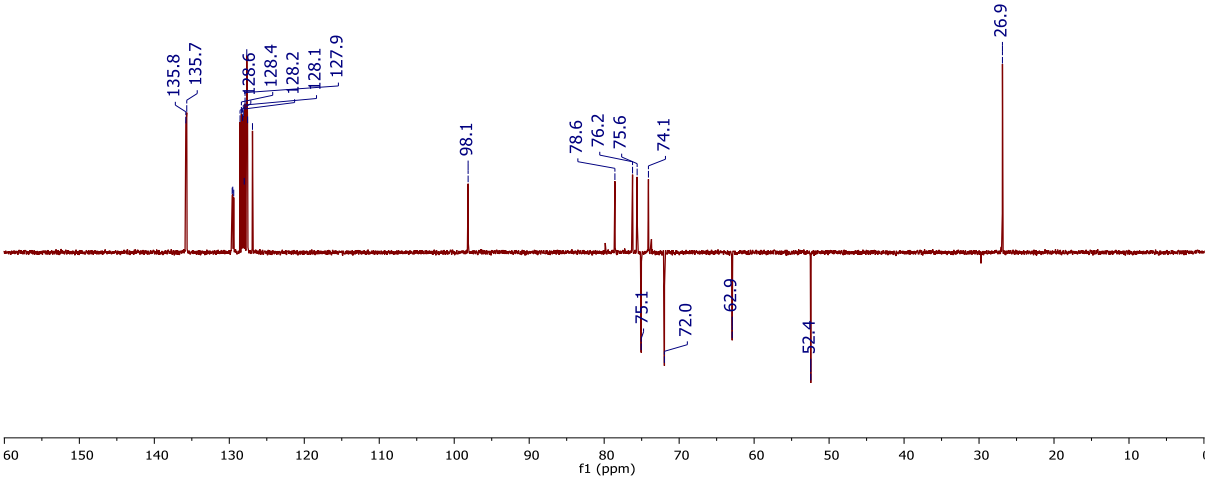
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 26**



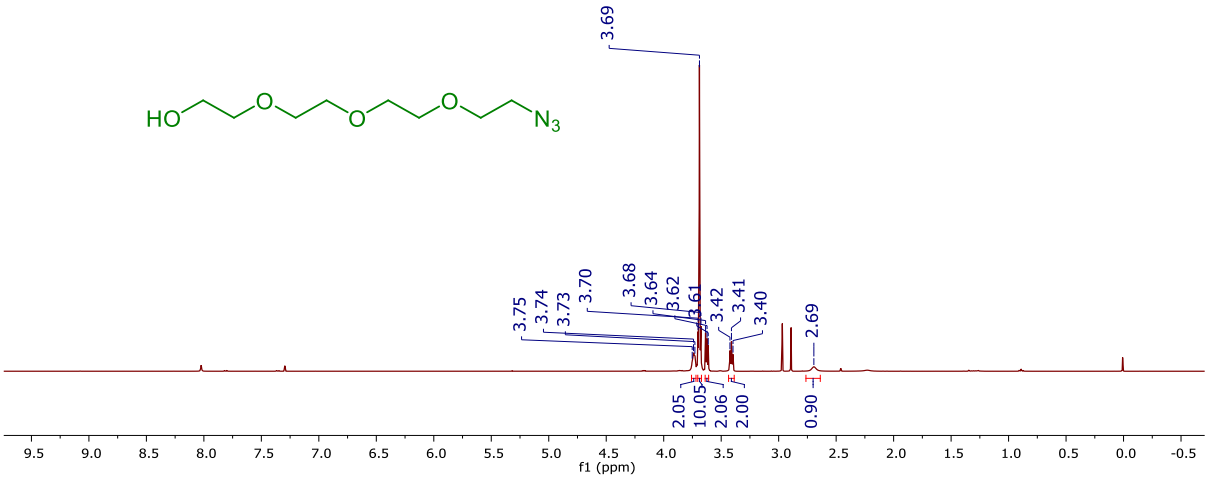

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 26**



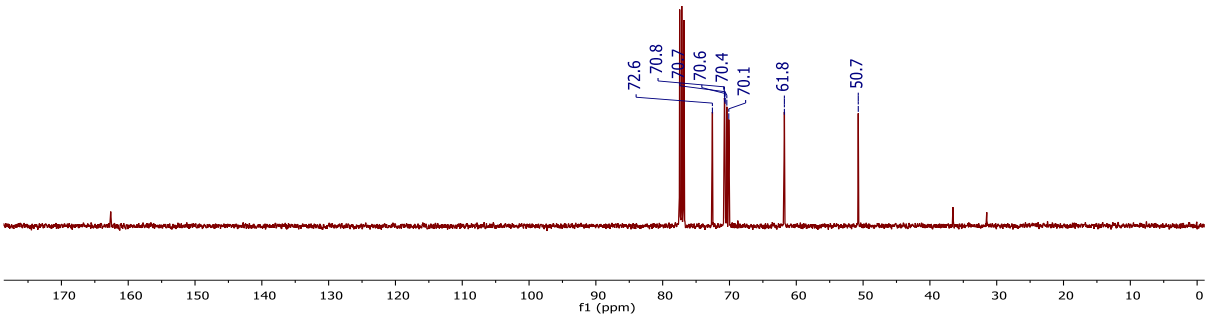

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 26**



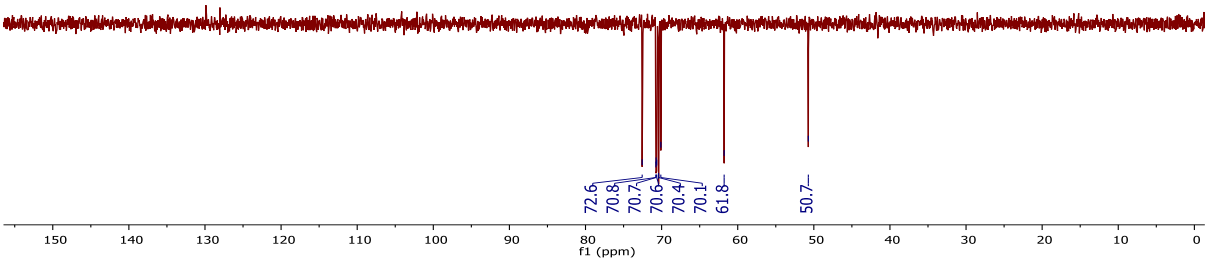
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 3**



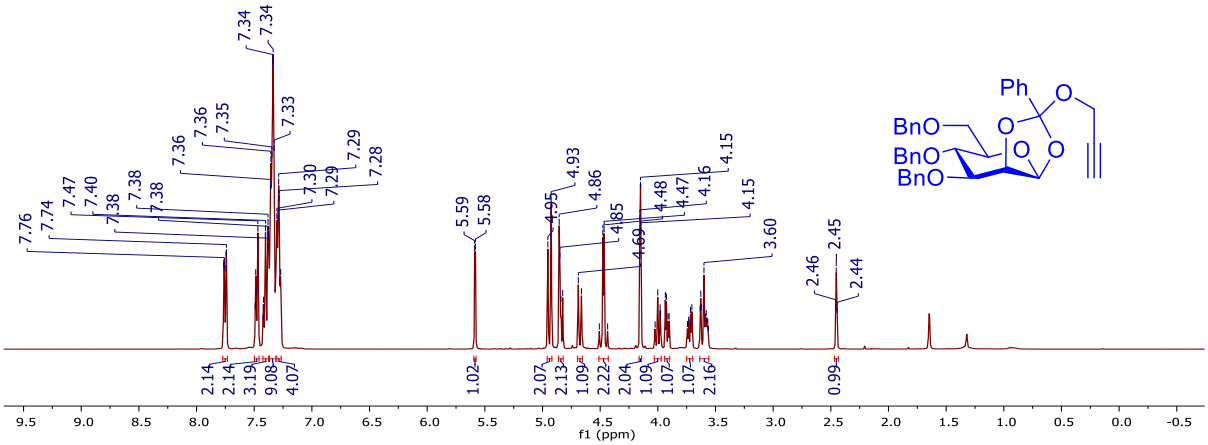

**$^{13}$CNMR Spectrum (100.67Hz, $CDCl_3$) of compound 3**



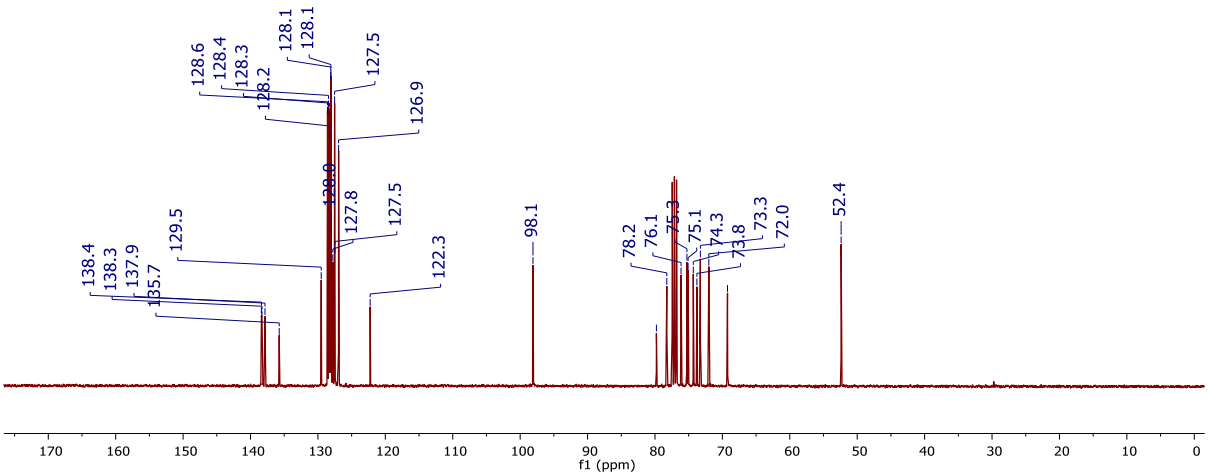

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 3**



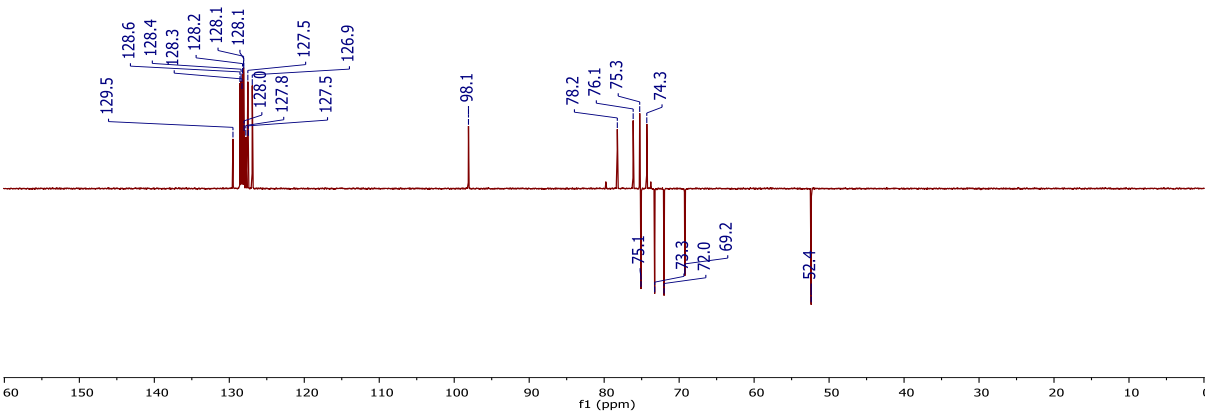
**$^{1}$HNMR Spectrum (400.31Hz, $CDCl_3$) of compound 15**



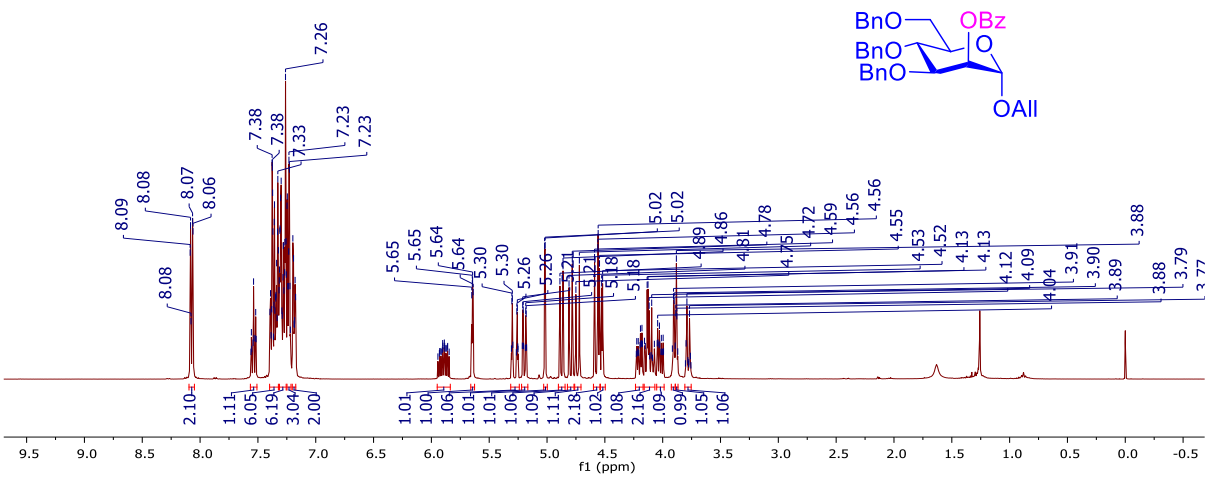

**$^{13}$CNMR Spectrum (100.67Hz, $CDCl_3$) of compound 15**



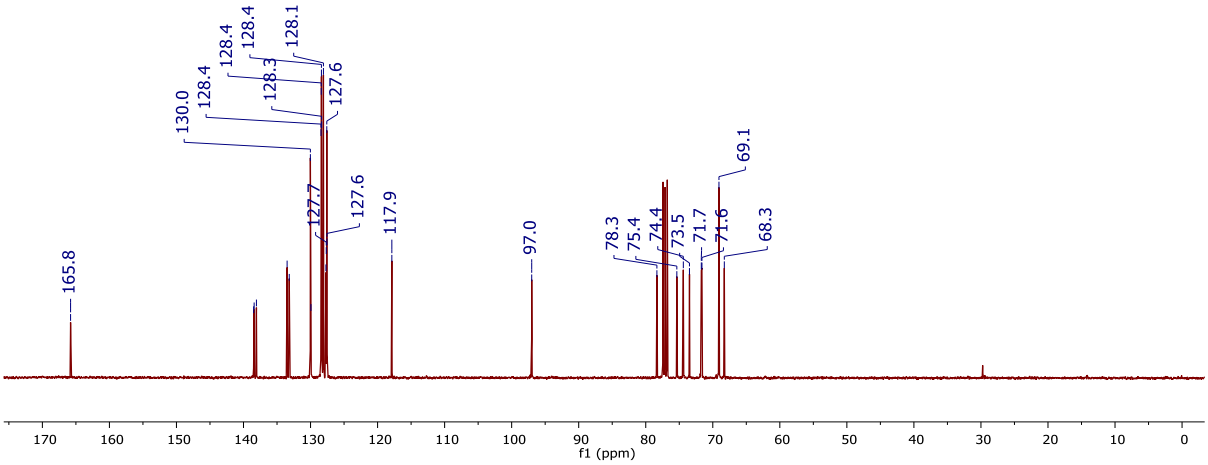

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 15**



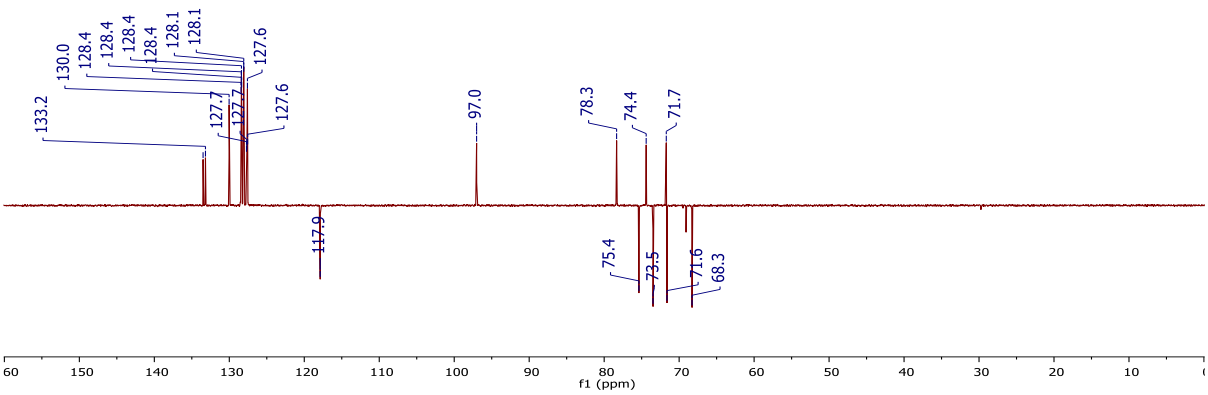
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 16**



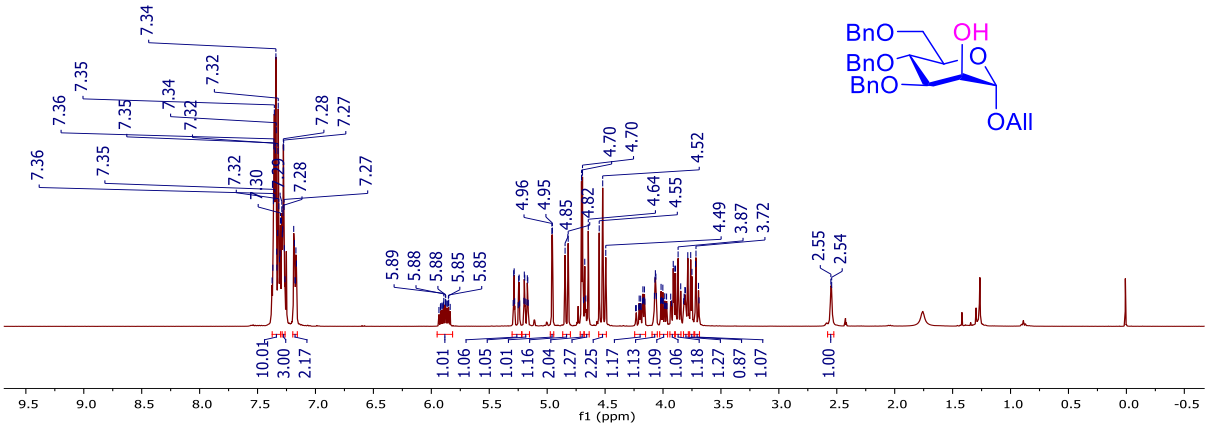

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 16**



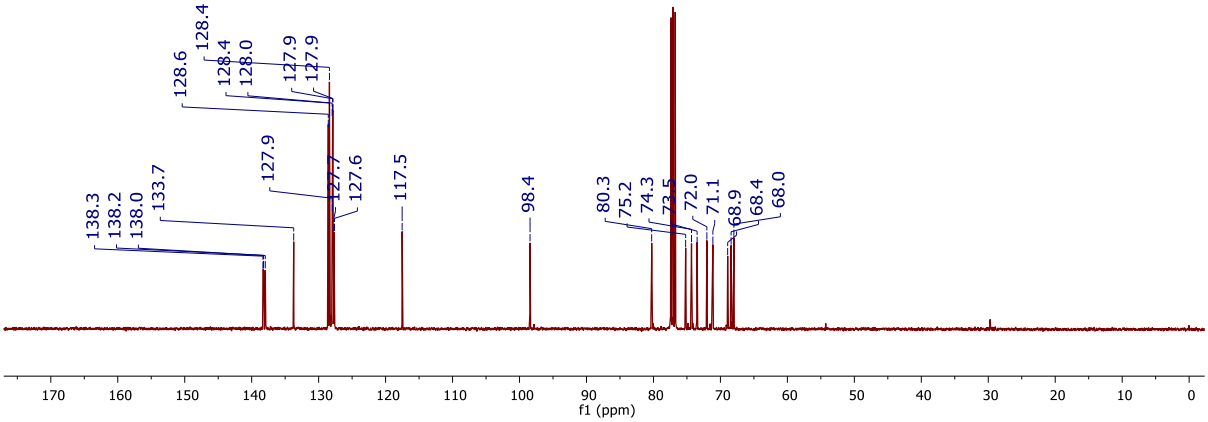

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 16**



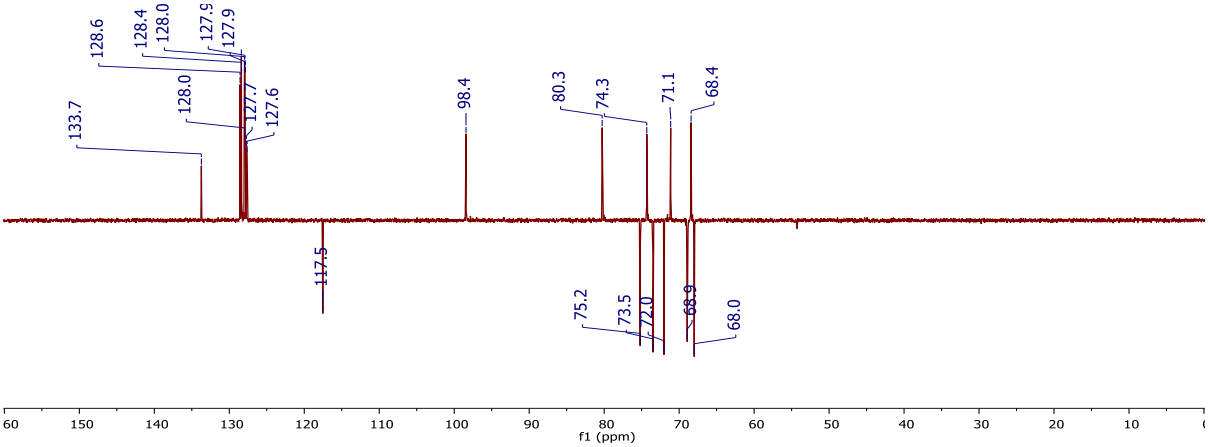
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 17**



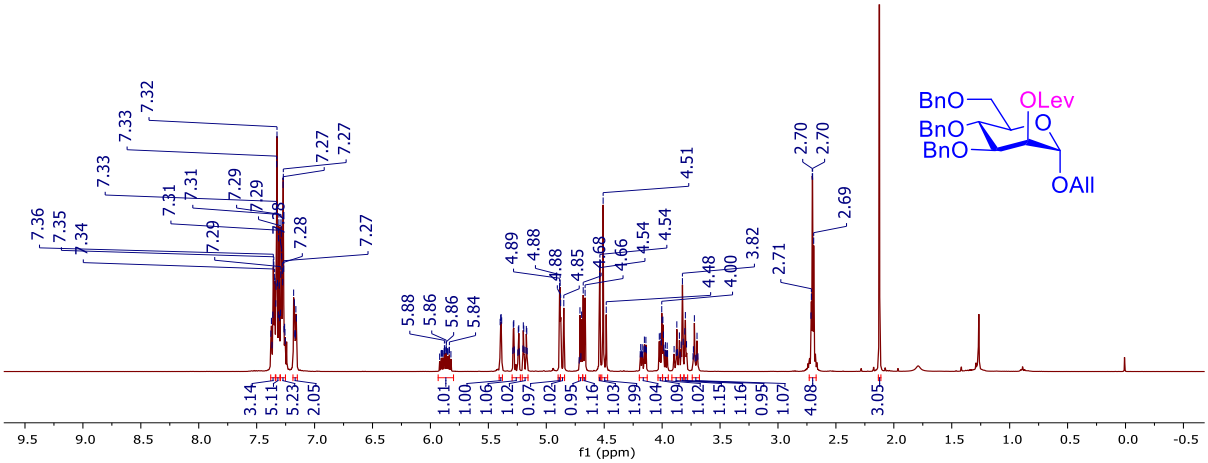

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 17**



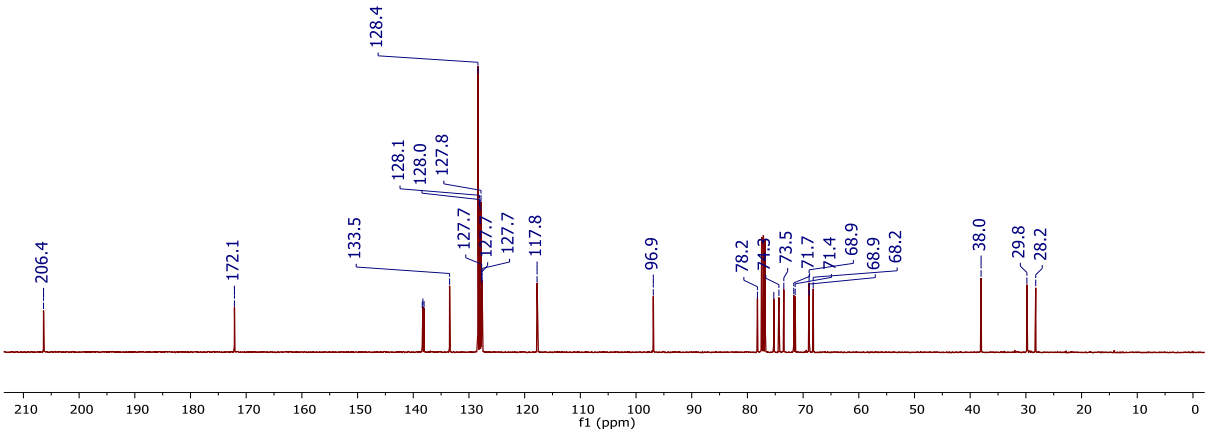

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 17**



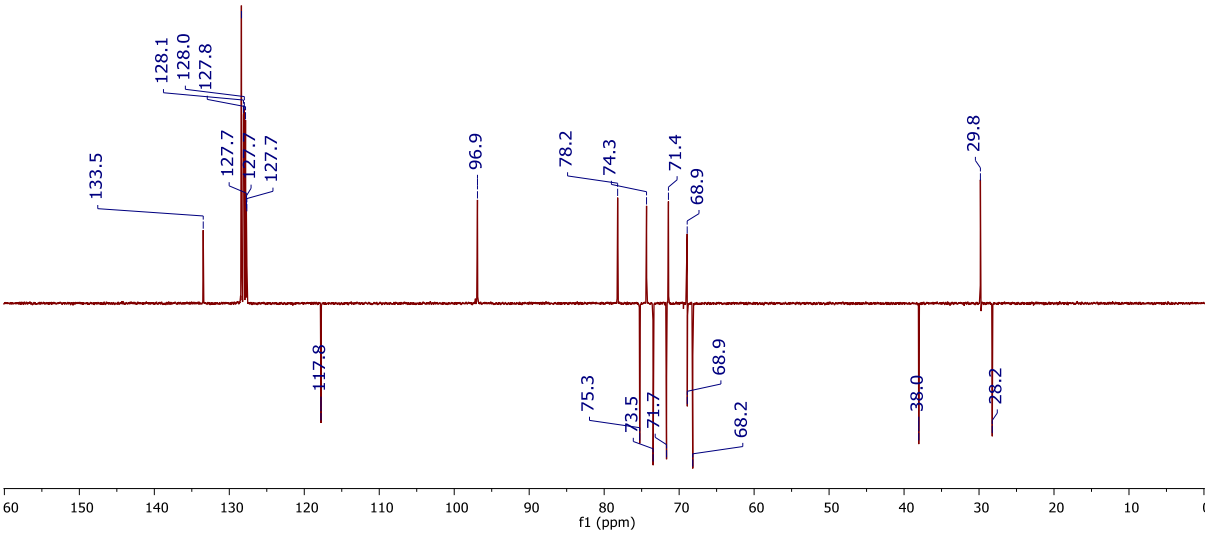
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 18**



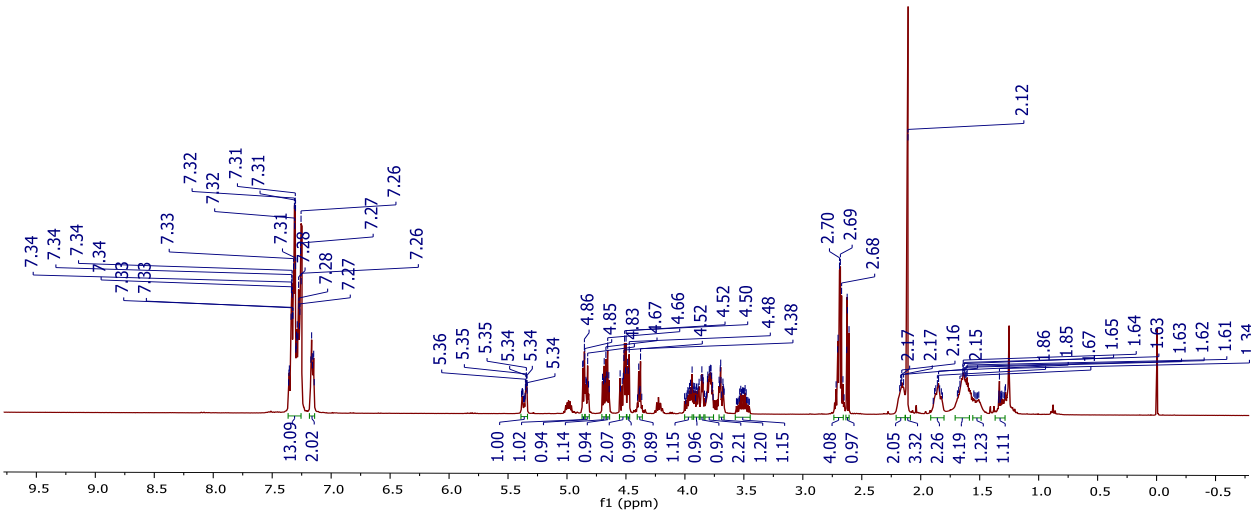

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 18**



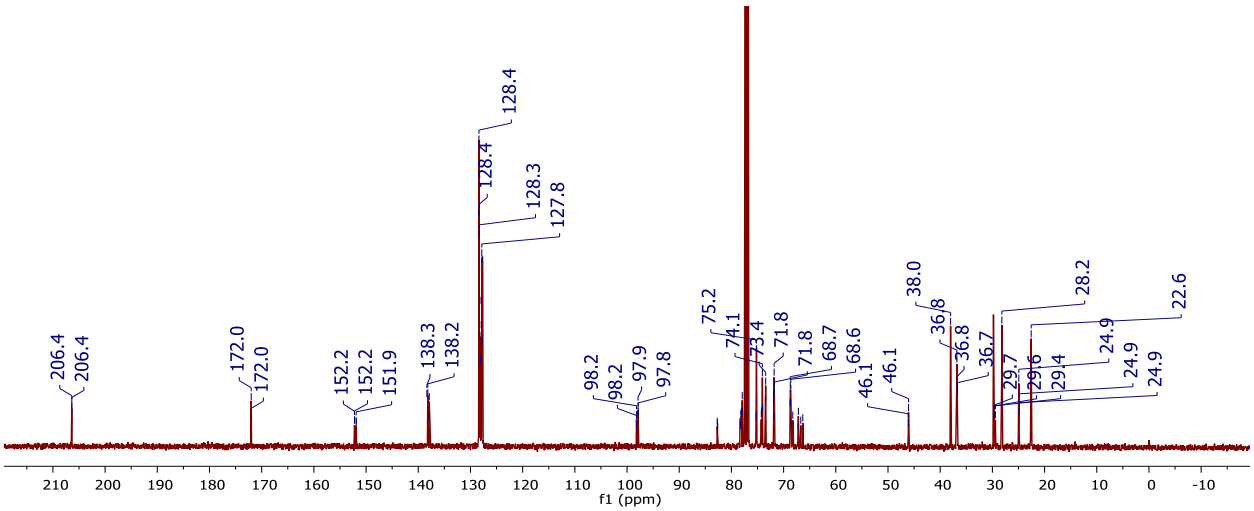

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 18**



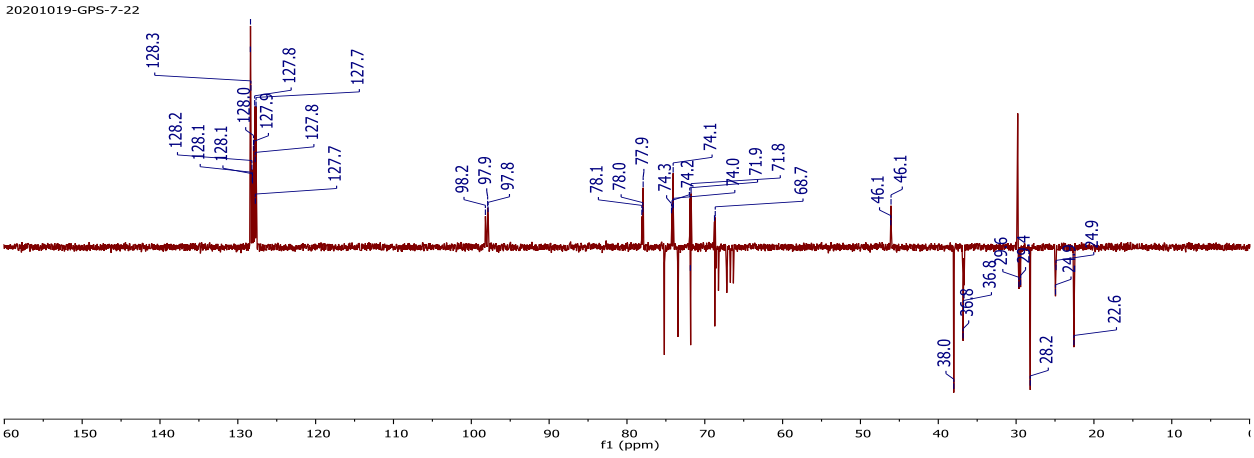
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 20**



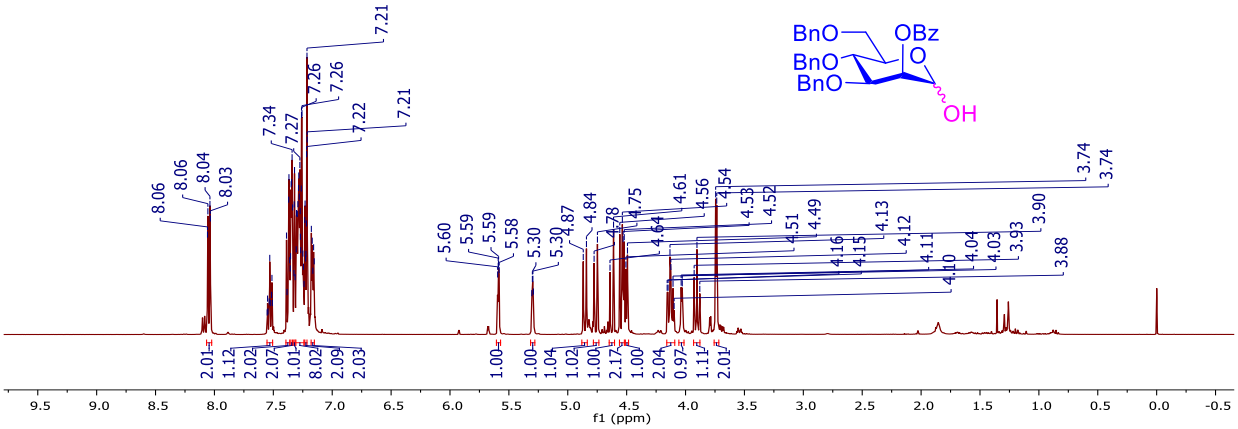
**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 20**



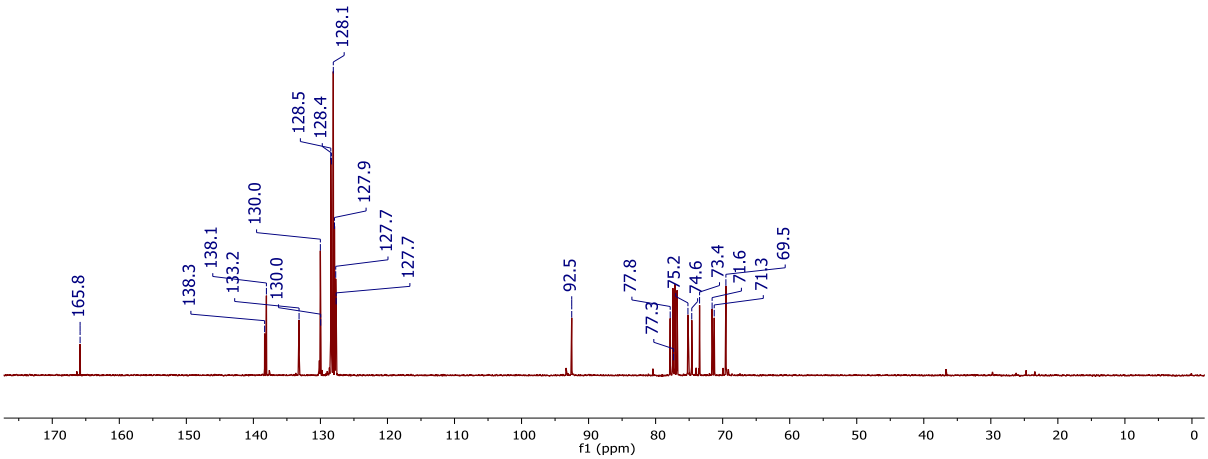
**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 20**



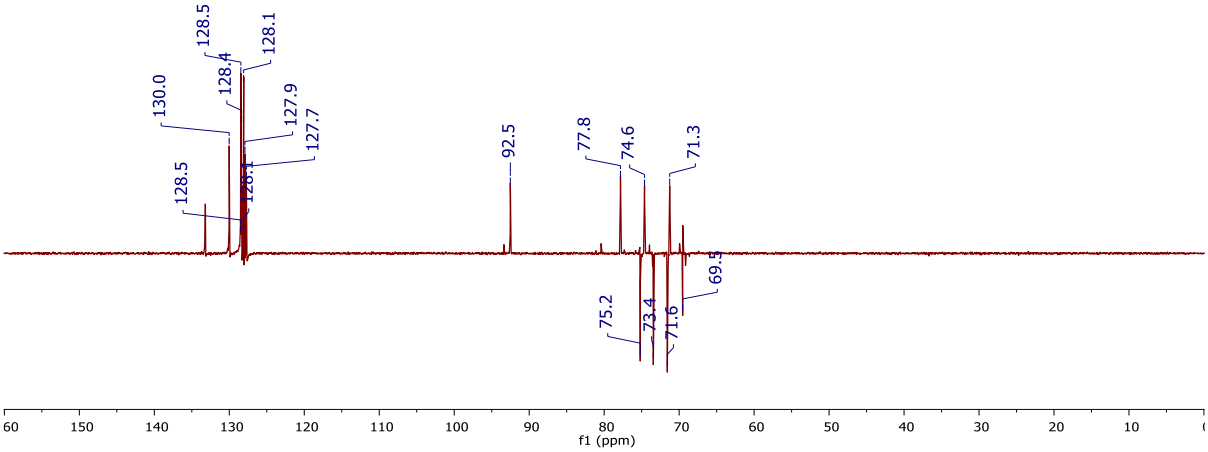
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 21**



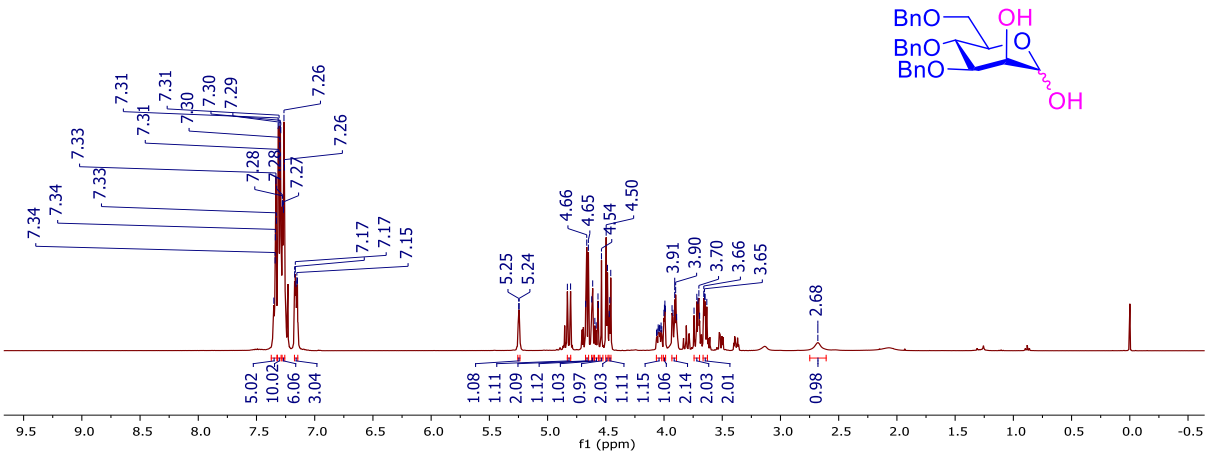

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 21**



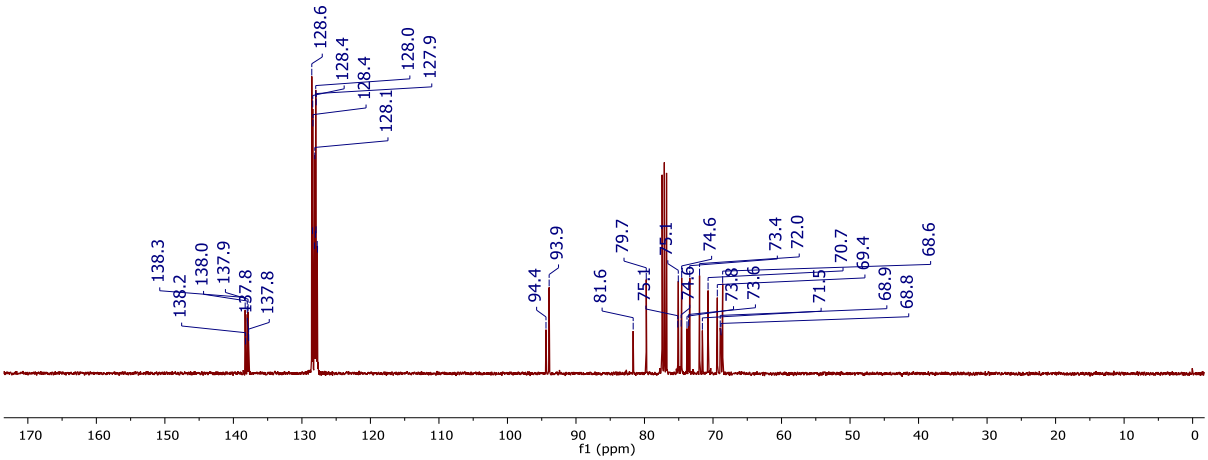

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 21**



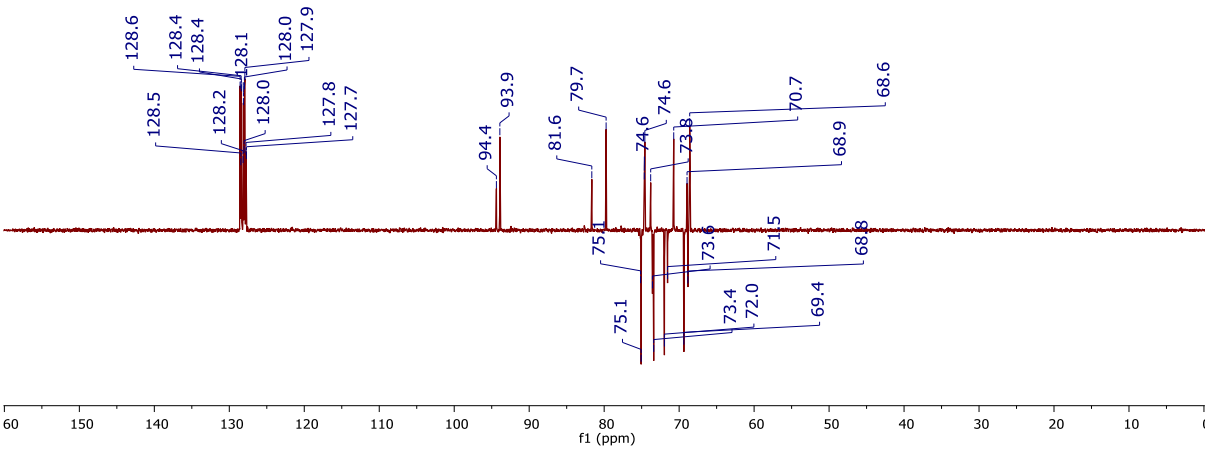
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 22**



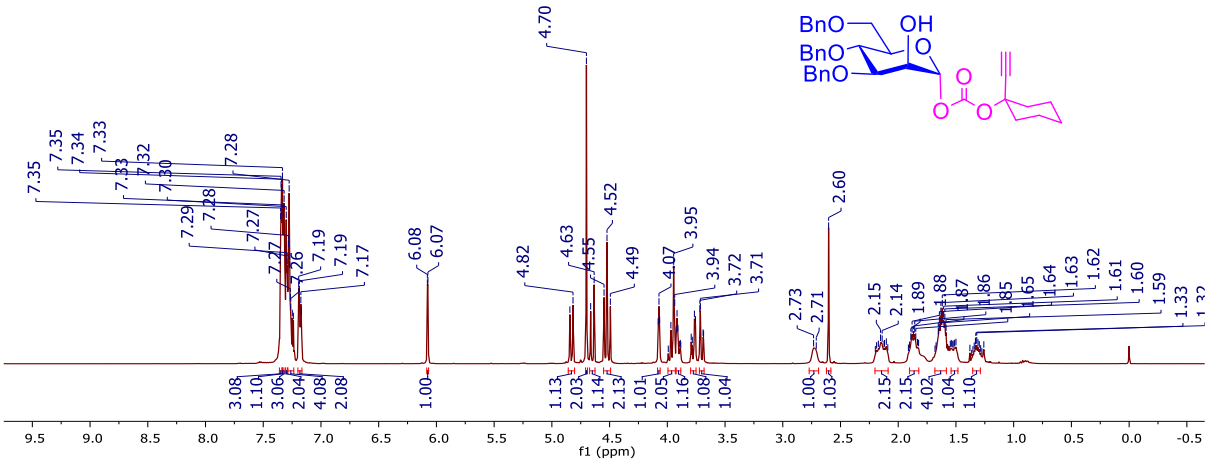

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 22**



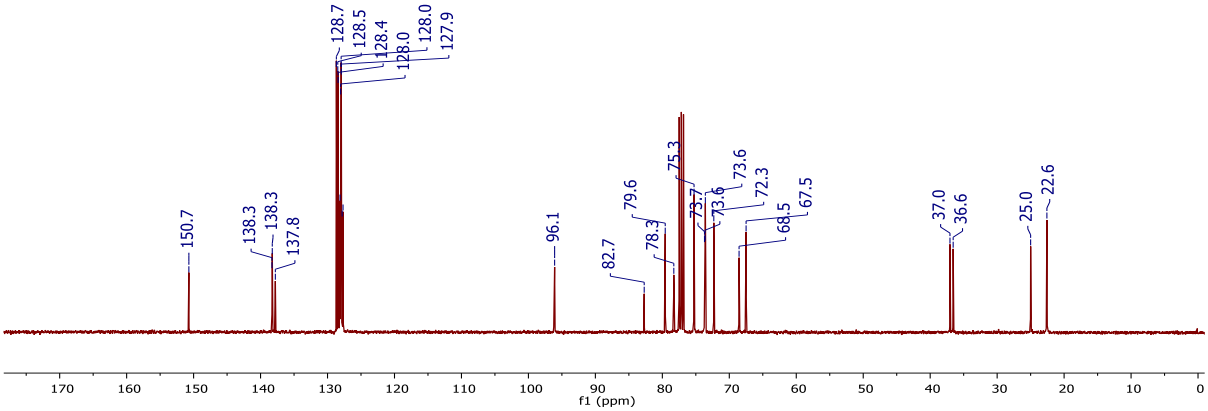

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 22**



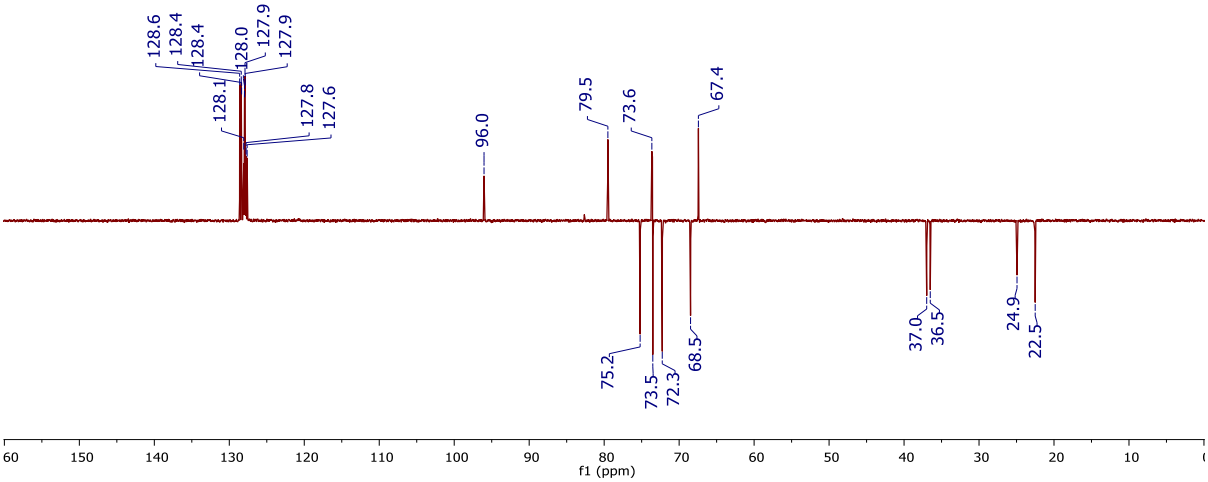
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 23**



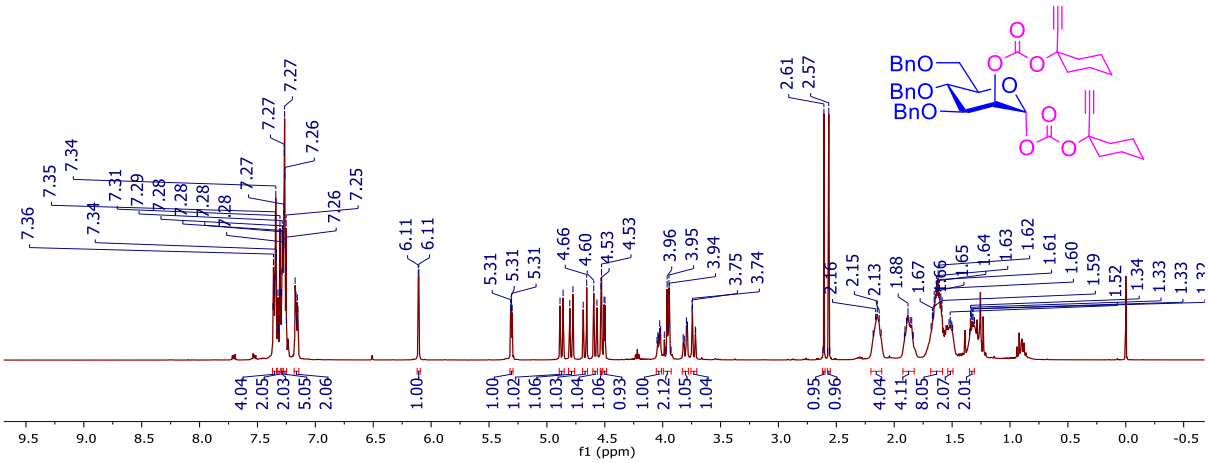

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 23**



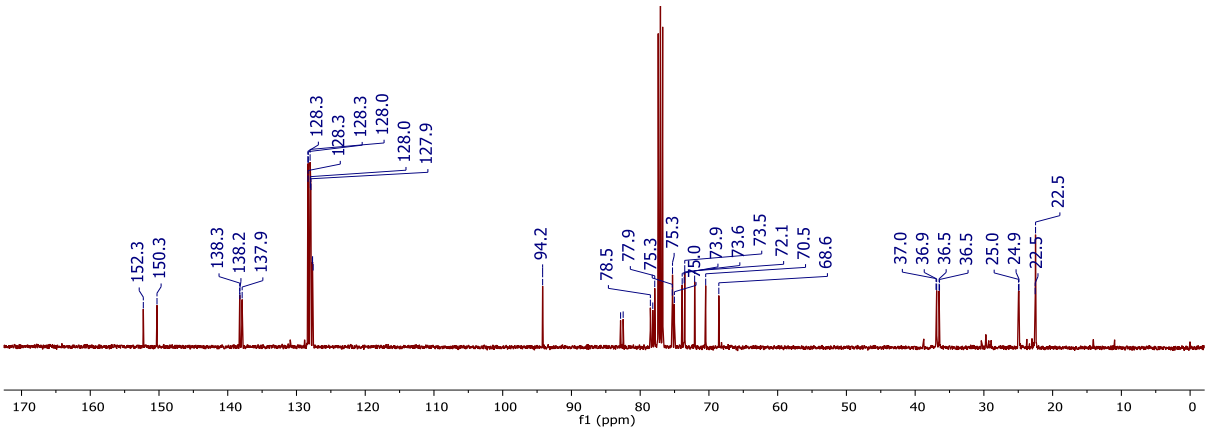

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 23**



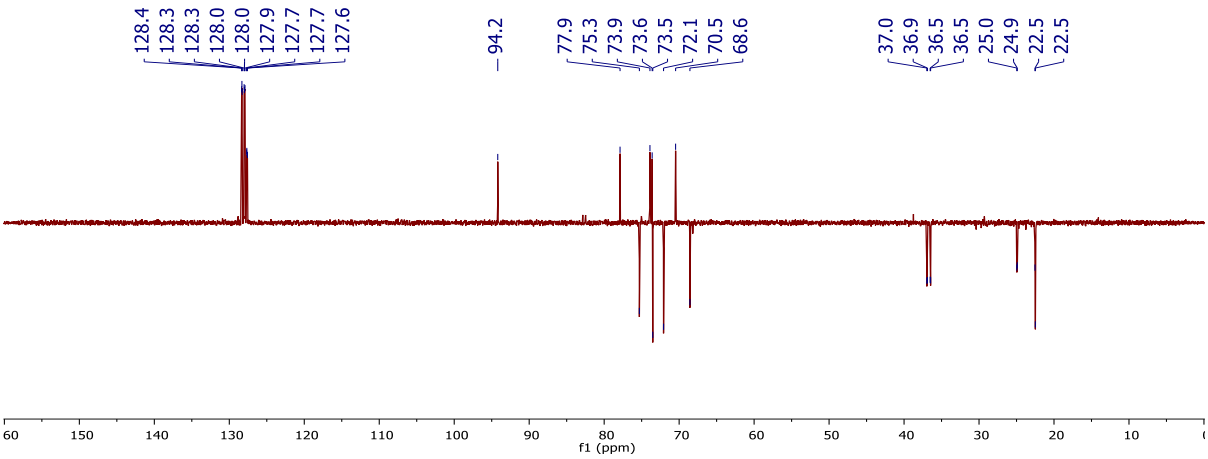
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 24**



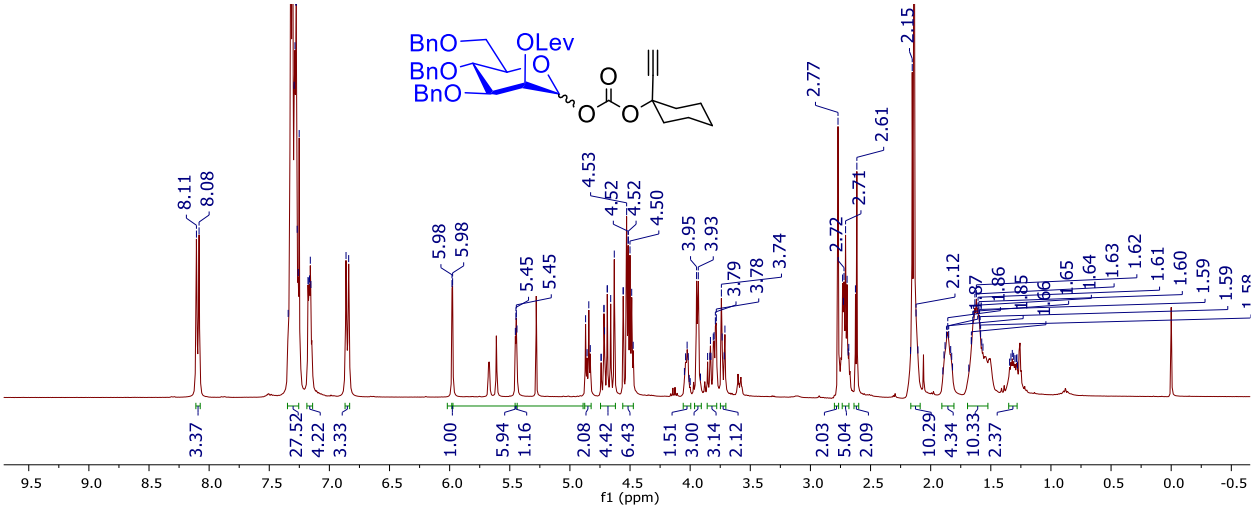

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 24**



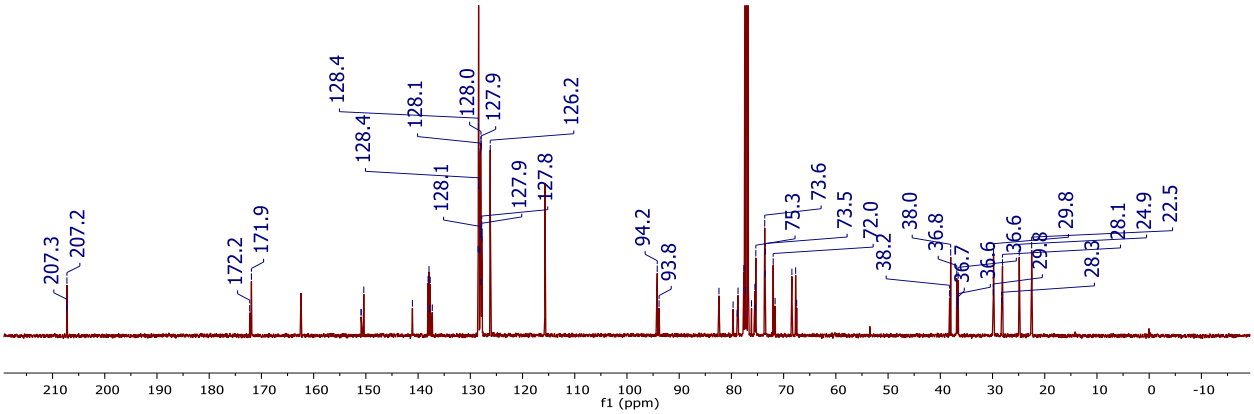

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 24**



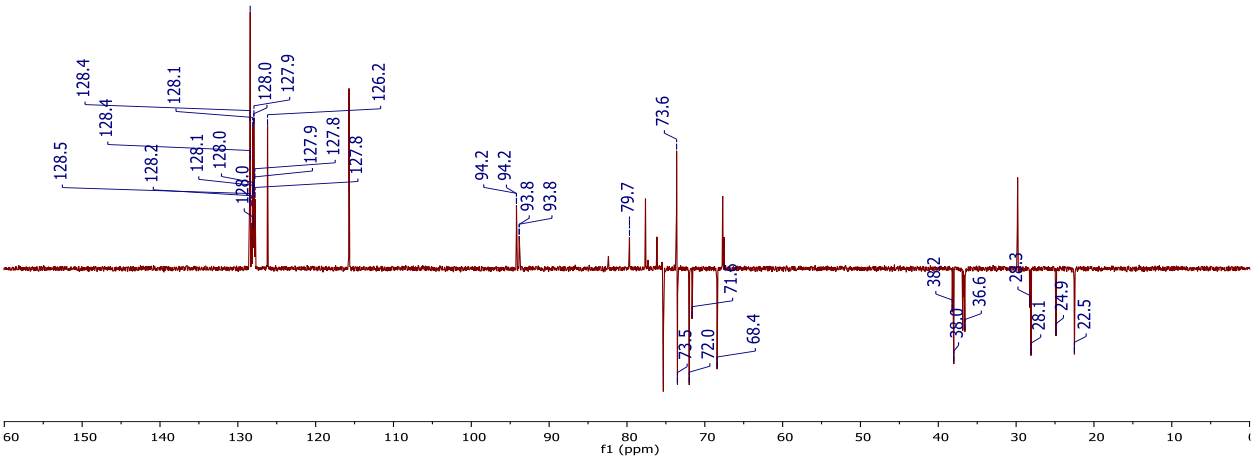
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 6**



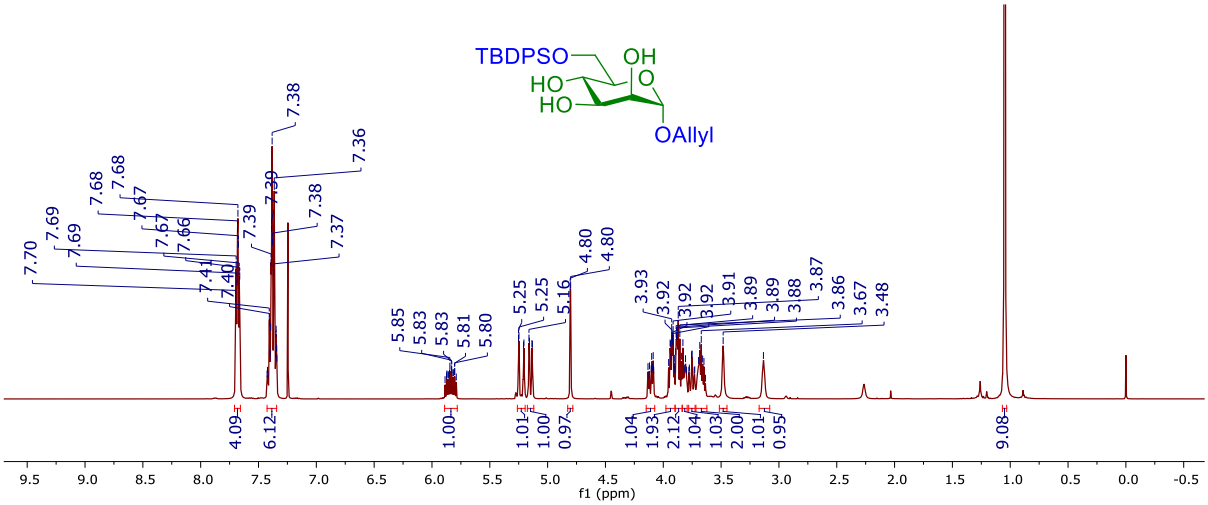

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 6**



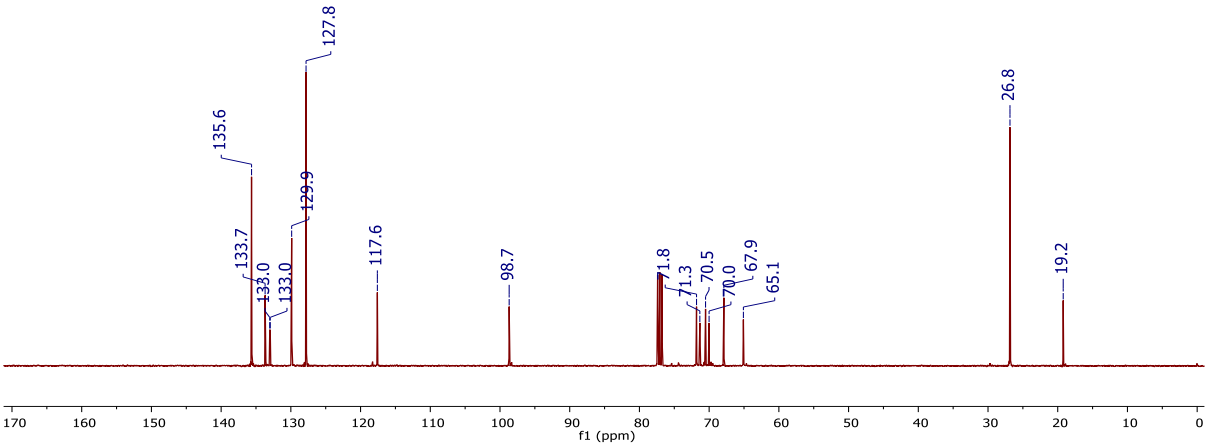

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 6**



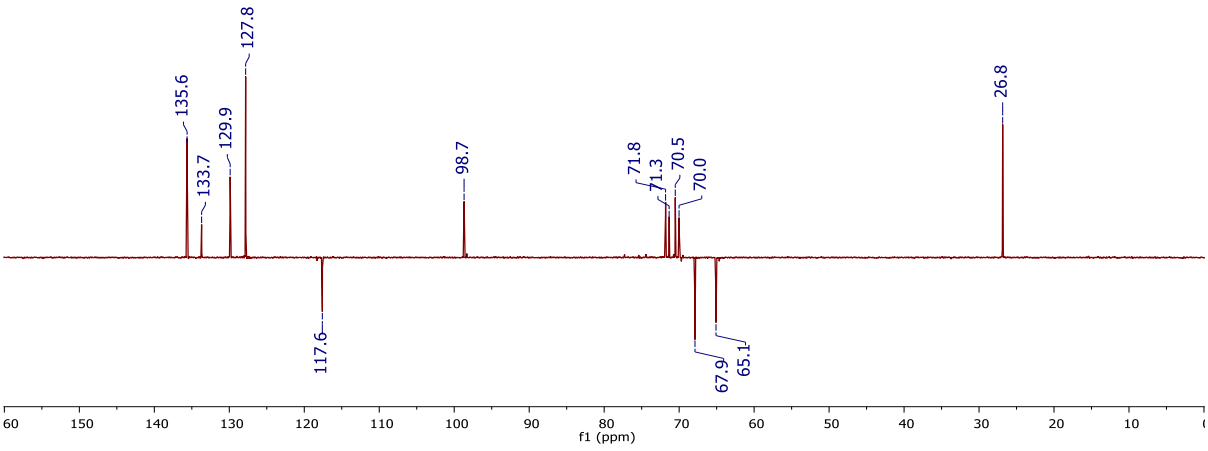
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 52**



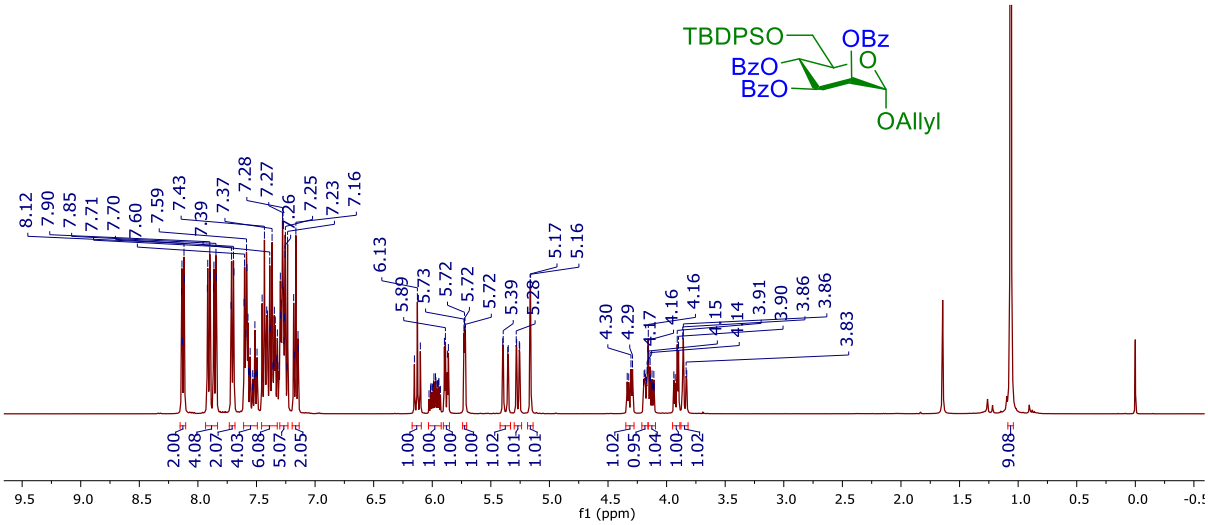

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 52**



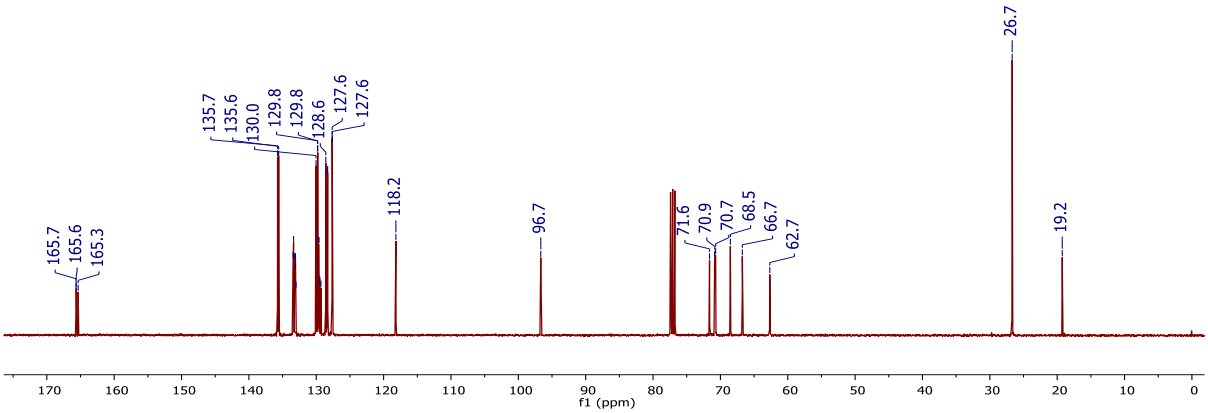

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 52**



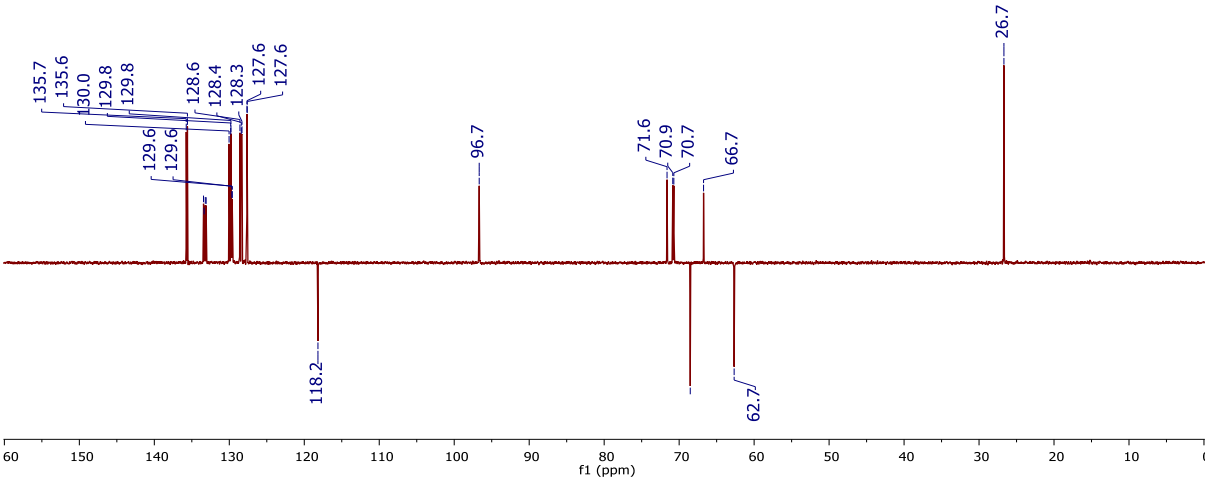
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 53**



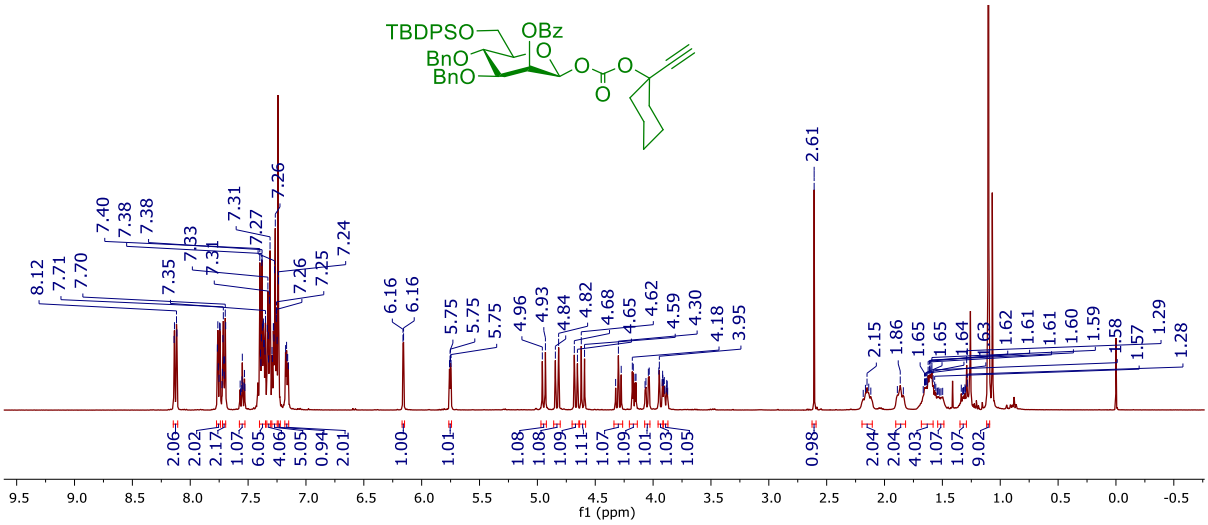

**$^{13}$CNMR Spectrum (100.66Hz, $CDCl_3$) of compound 53**



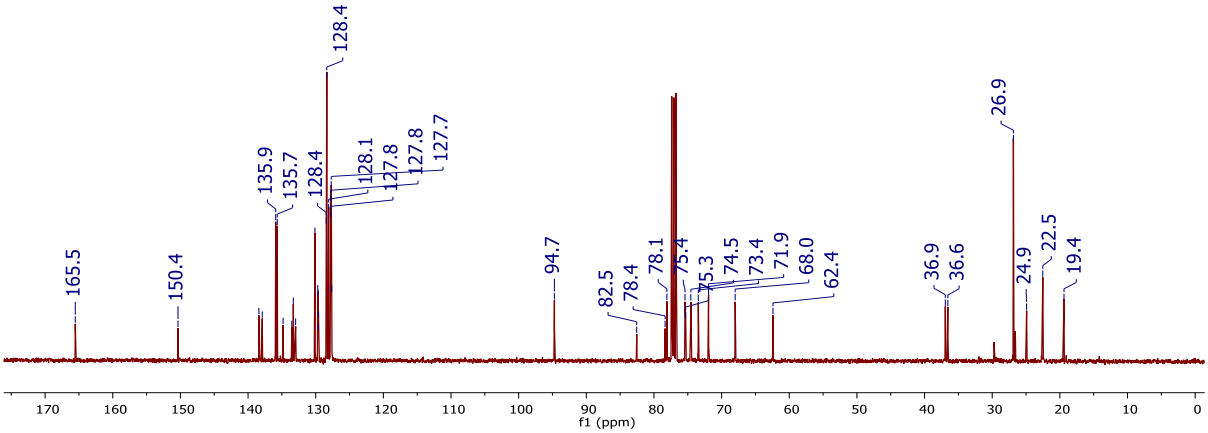

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 53**



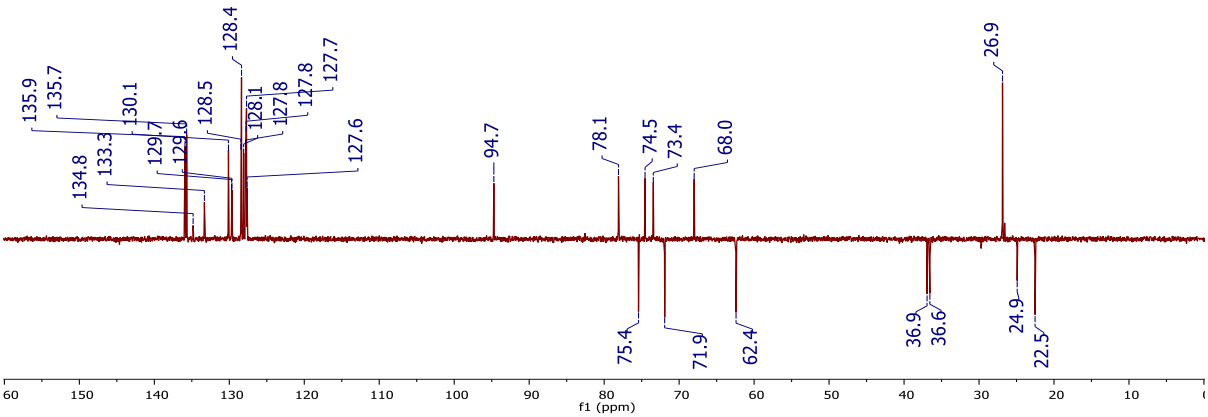
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 8β**



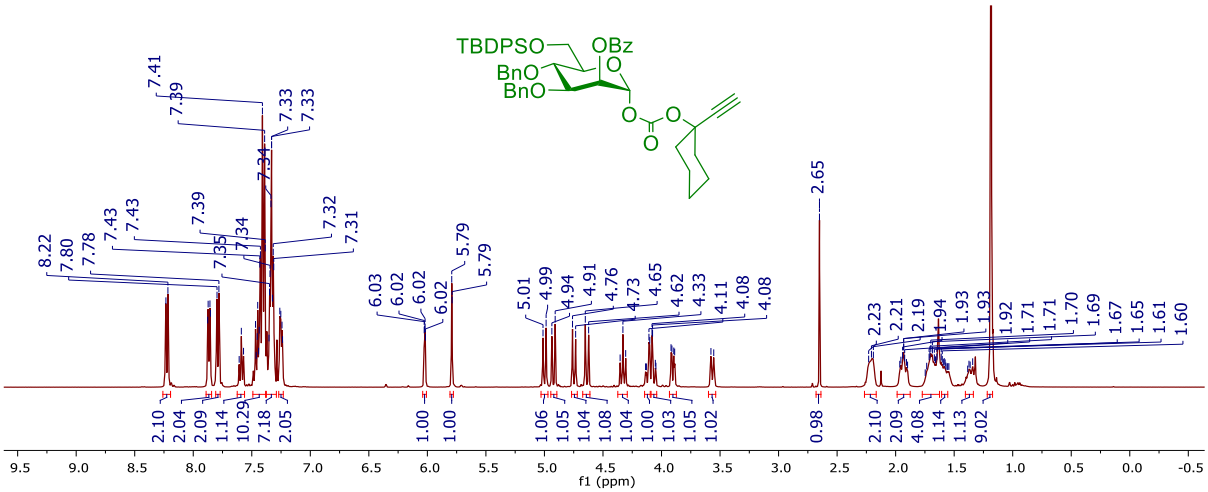

**$^{13}$C NMR Spectrum (100.66Hz, $CDCl_3$) of compound 8β**



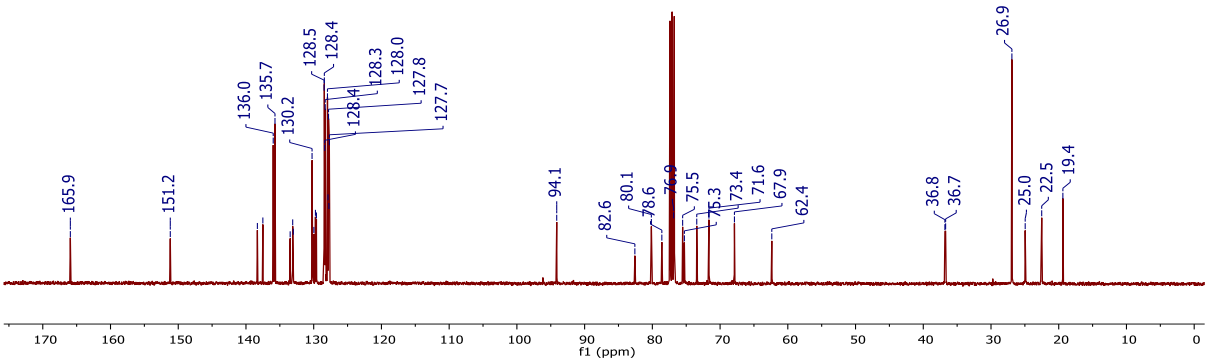

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 8β**



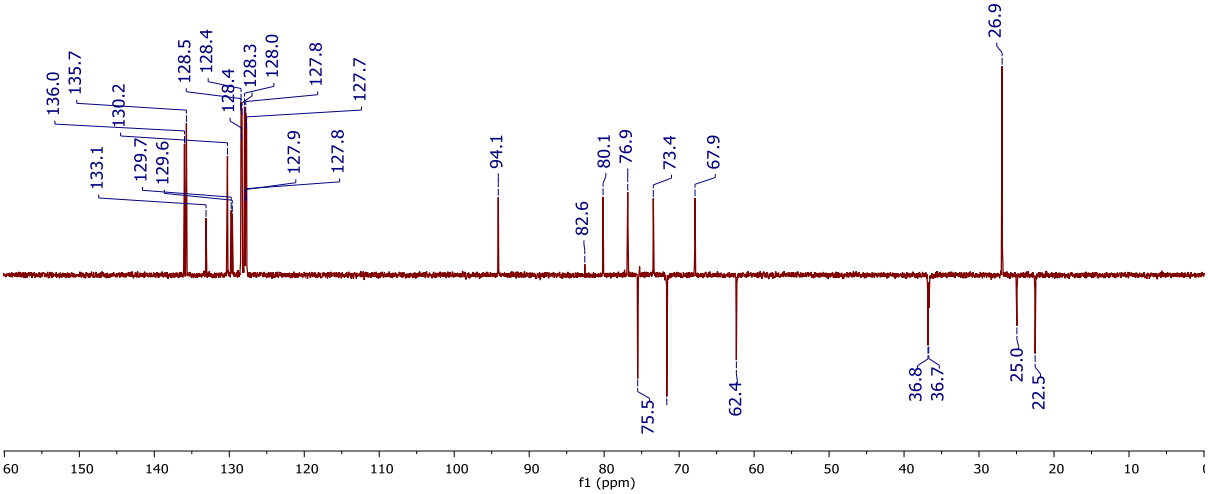
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 8α**



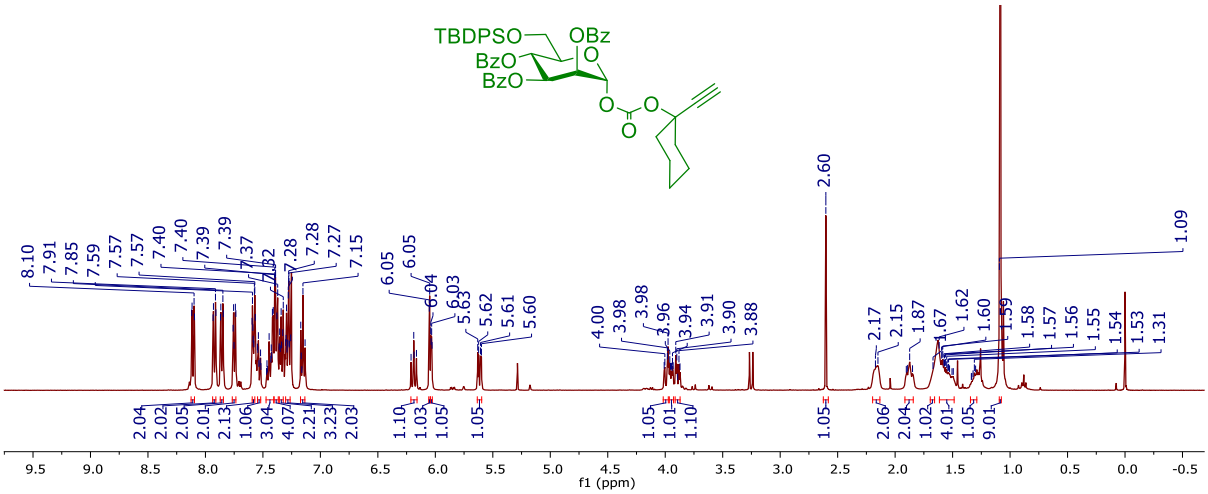

**$^{13}$C NMR Spectrum (100.66Hz, $CDCl_3$) of compound 8α**



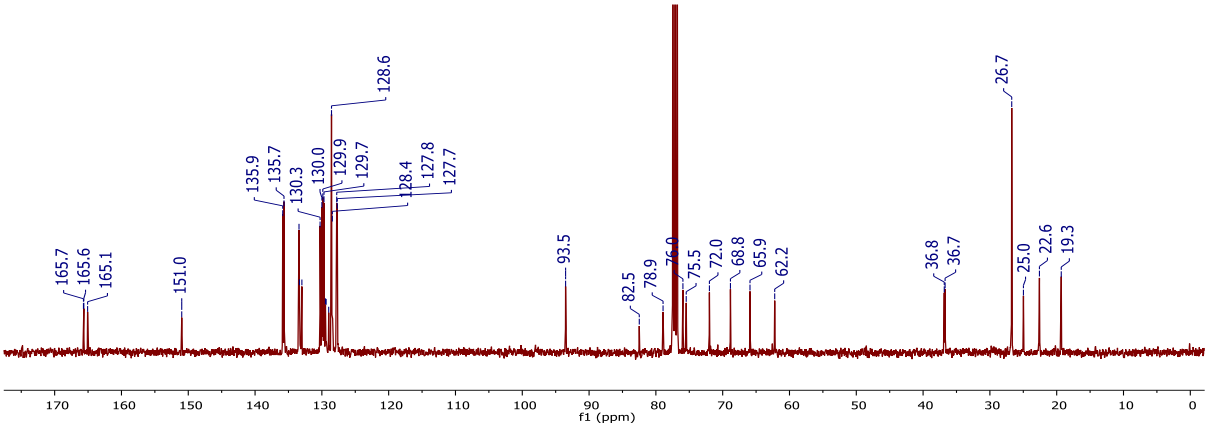

**DEPT NMR Spectrum (100.66Hz, $CDCl_3$) of compound 8α**



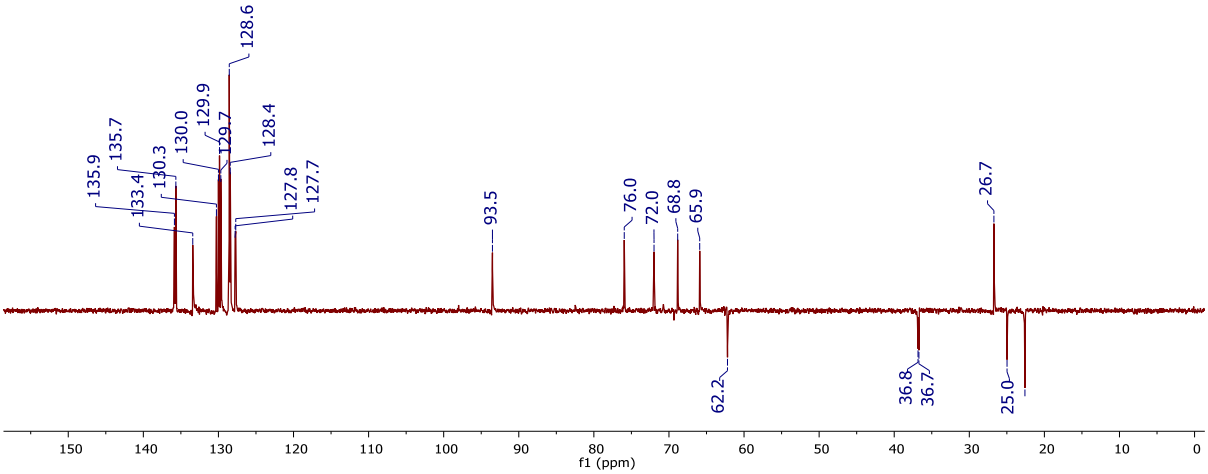
**$^{1}$H NMR Spectrum (399.78Hz, $CDCl_3$) of compound 51α**



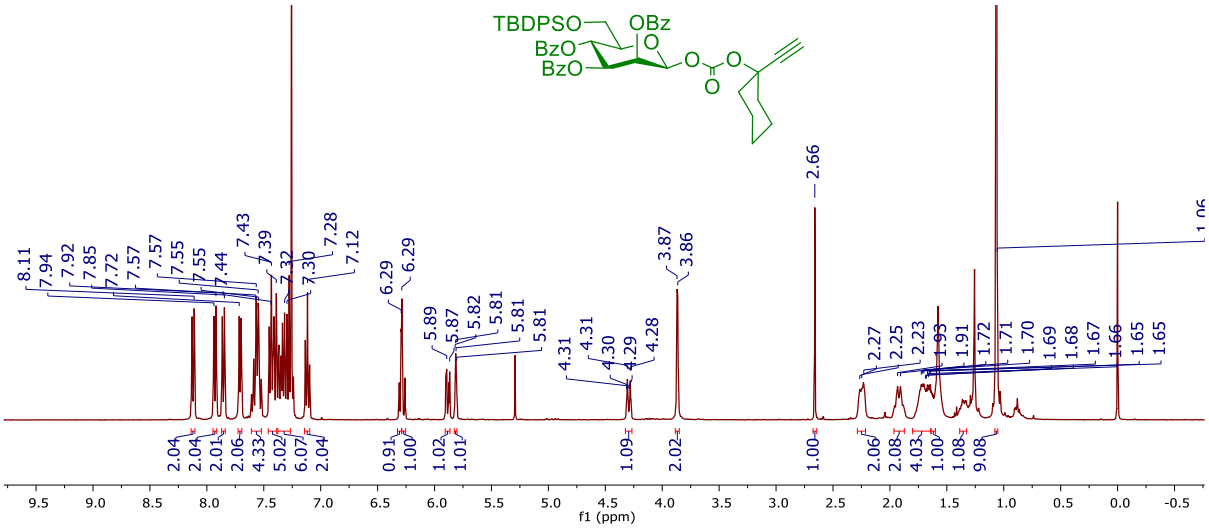

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 51α**



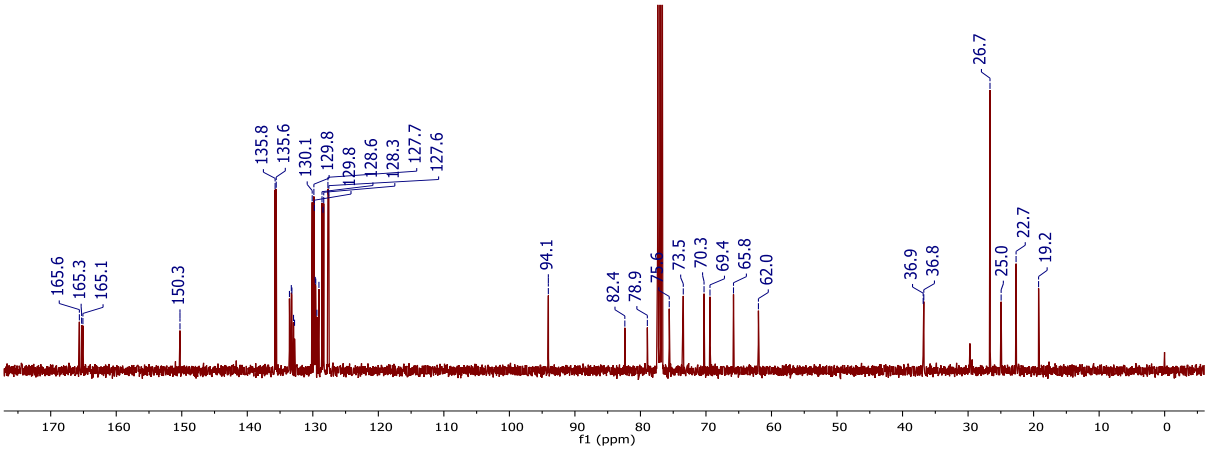

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 51α**



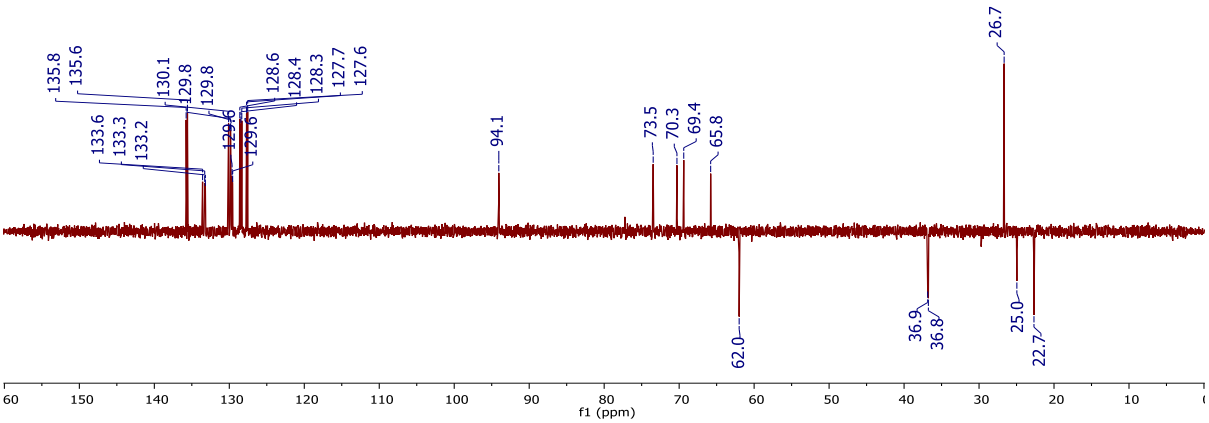
**$^{1}$H NMR Spectrum (399.78Hz, $CDCl_3$) of compound 51β**



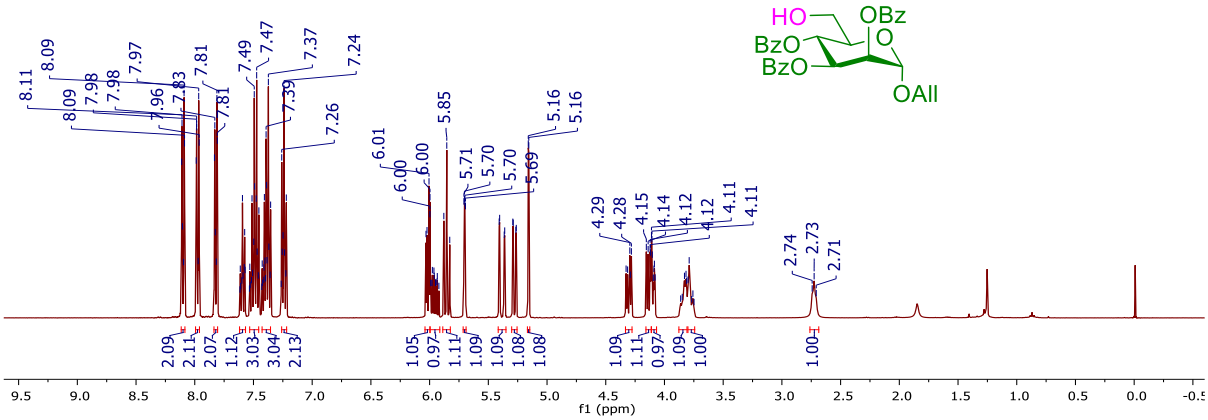

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 51β**



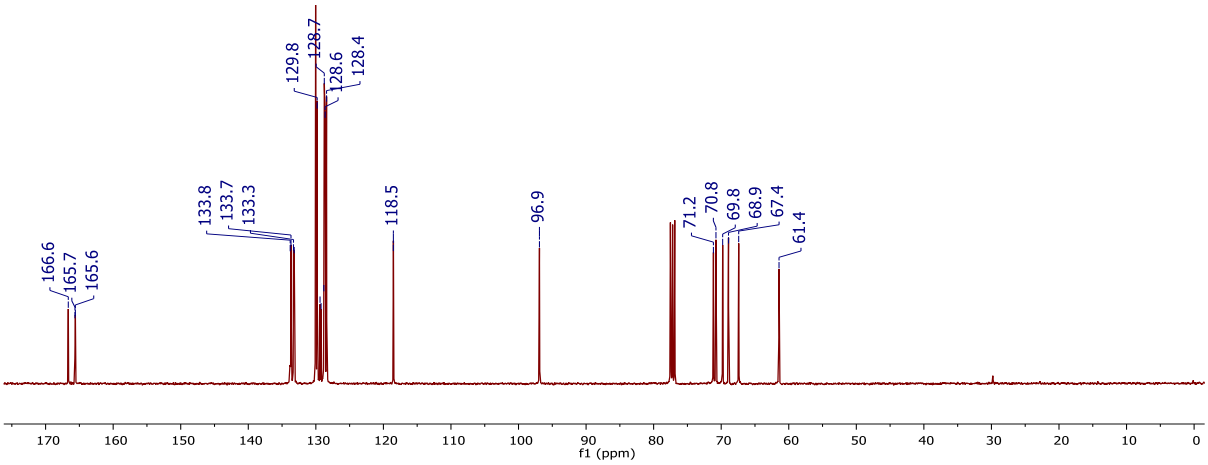

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 51β**



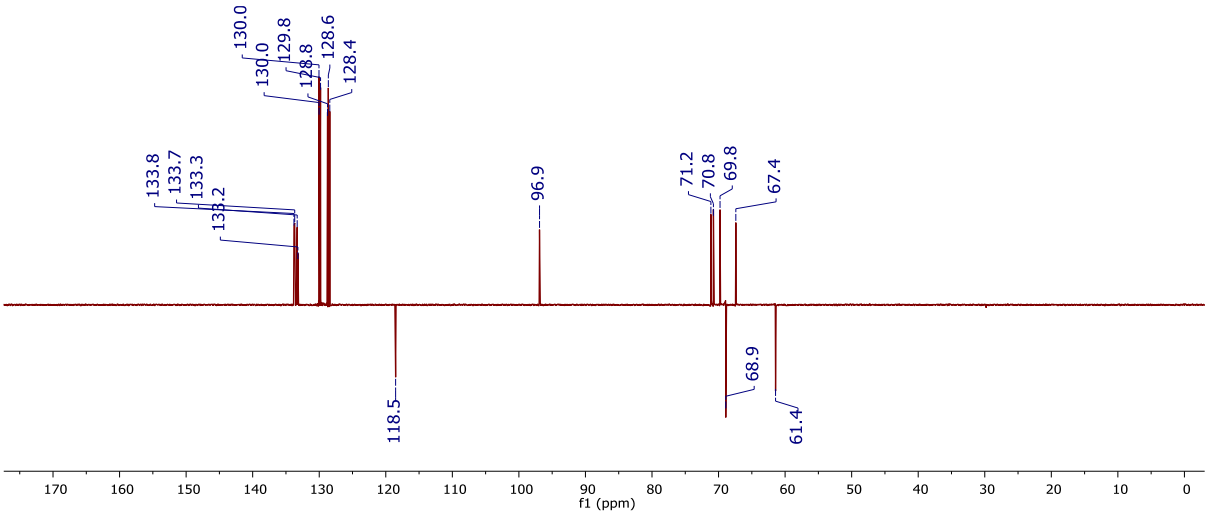
**$^{1}$H NMR Spectrum (399.78Hz, $CDCl_3$) of compound 54**



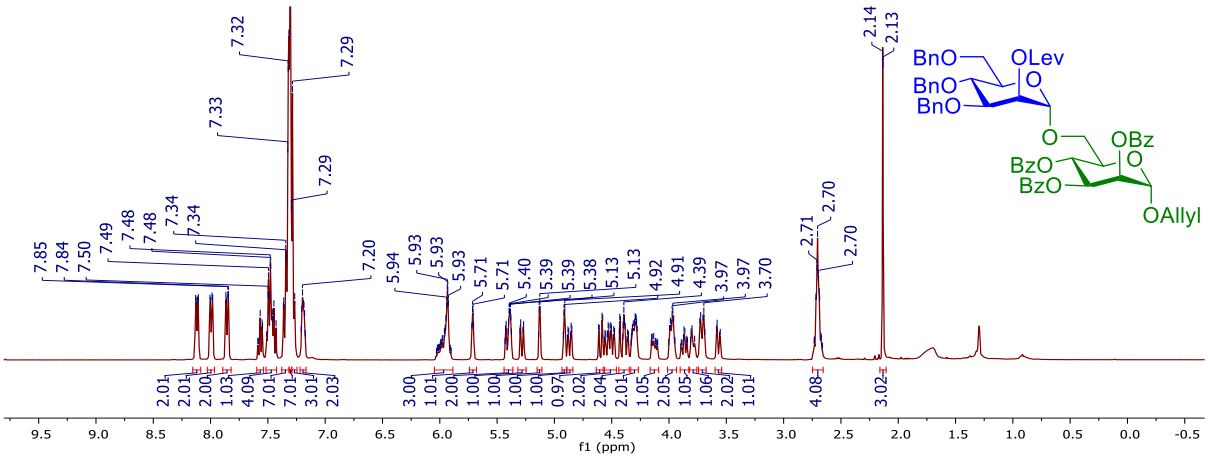

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 54**



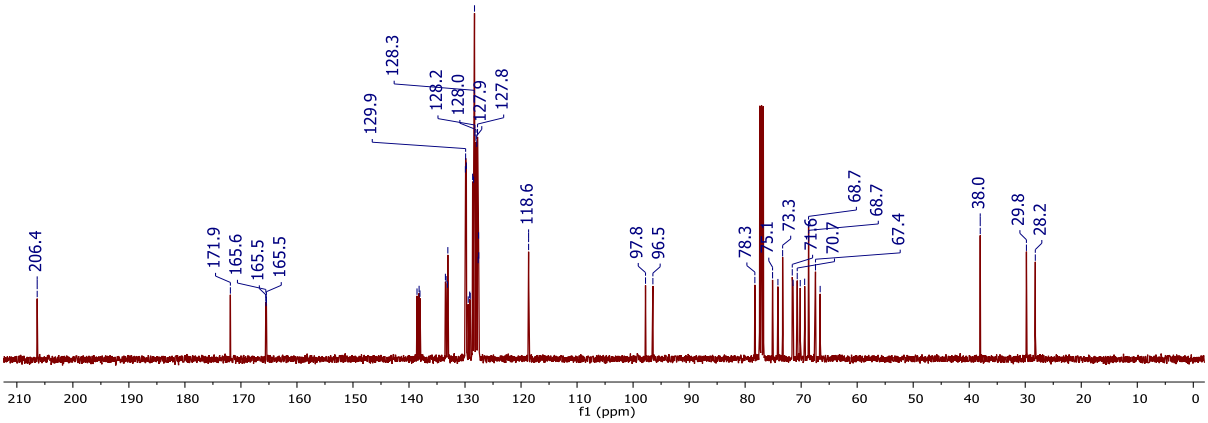

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 54**



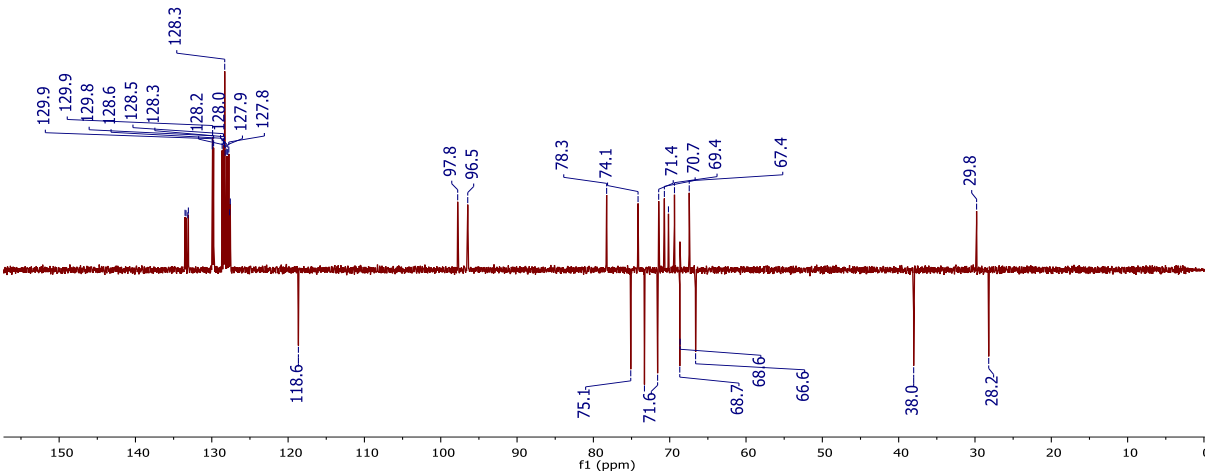
**$^{1}$H NMR Spectrum (399.78Hz, $CDCl_3$) of compound 55**



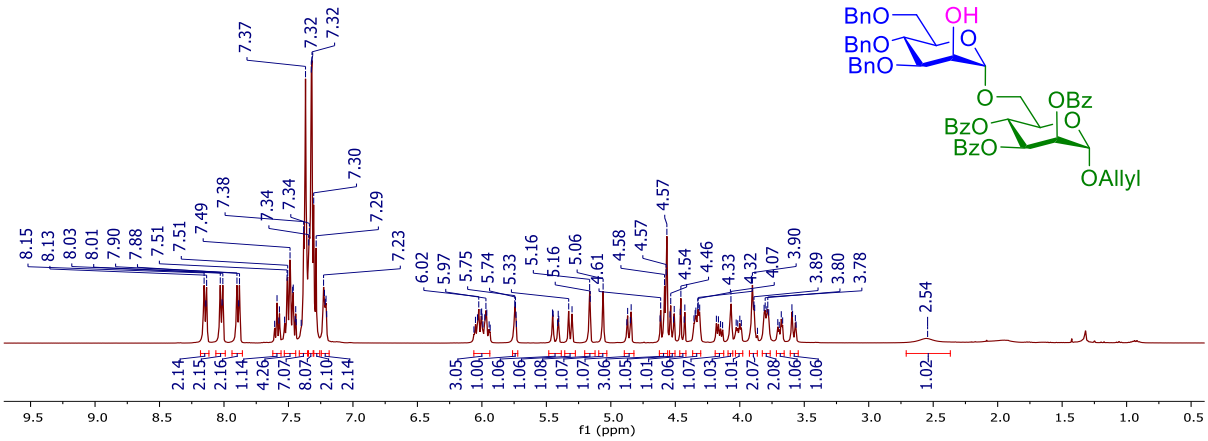

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 55**



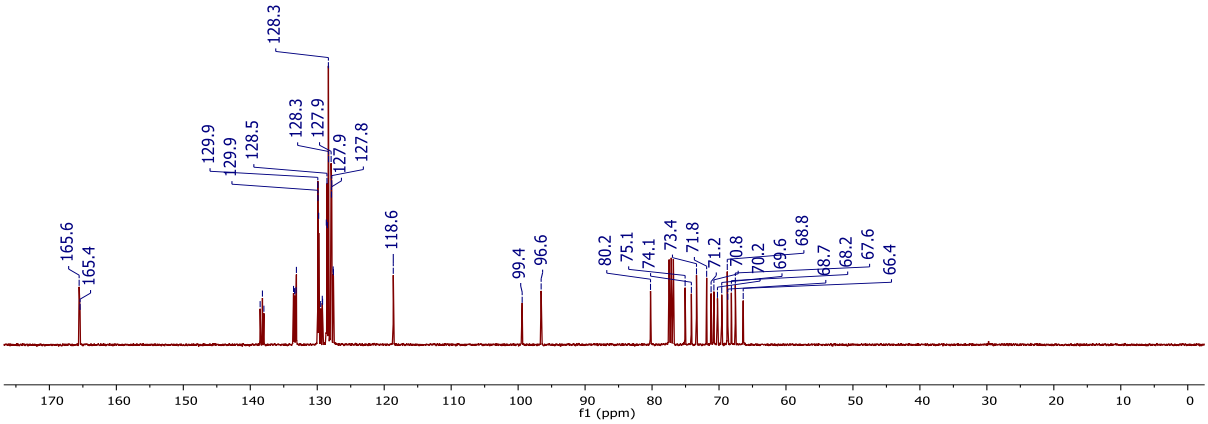

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 55**



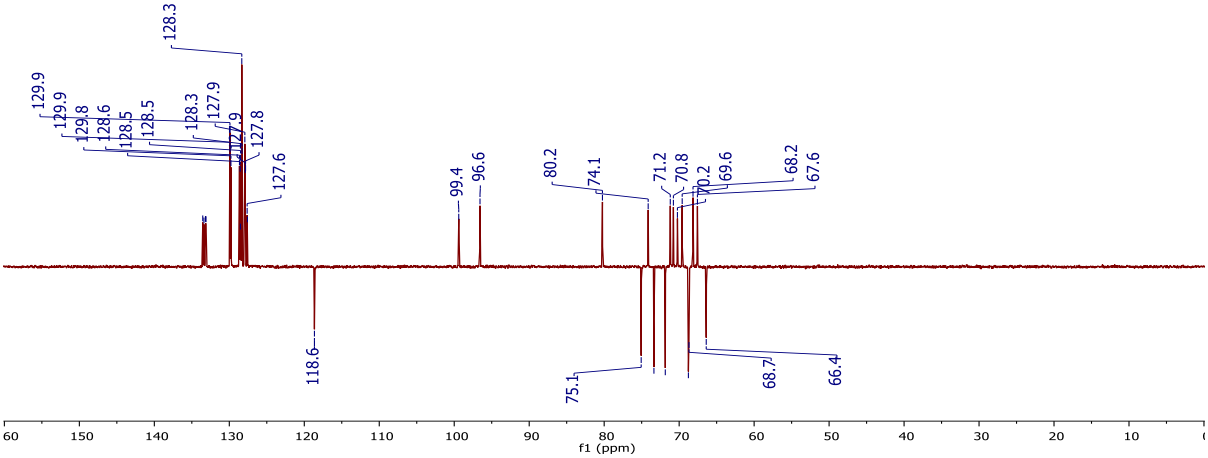
**$^{1}$H NMR Spectrum (399.78Hz, $CDCl_3$) of compound 56**



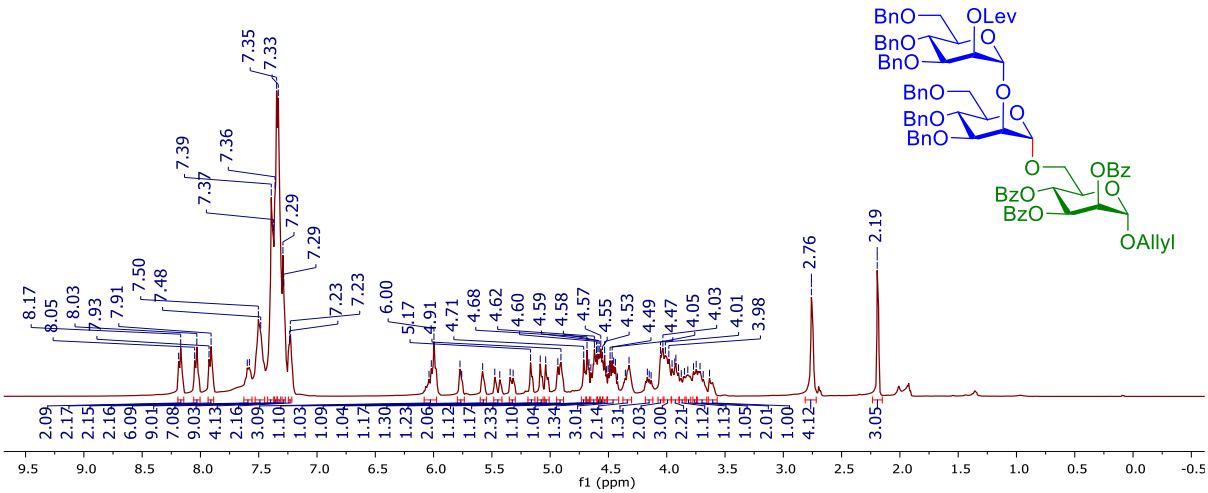

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 56**



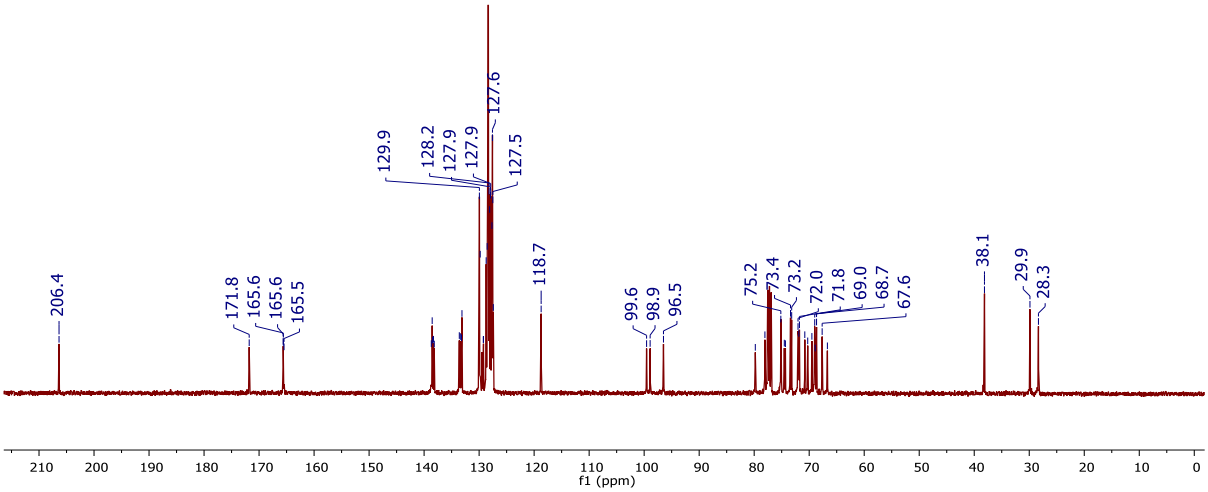

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 56**



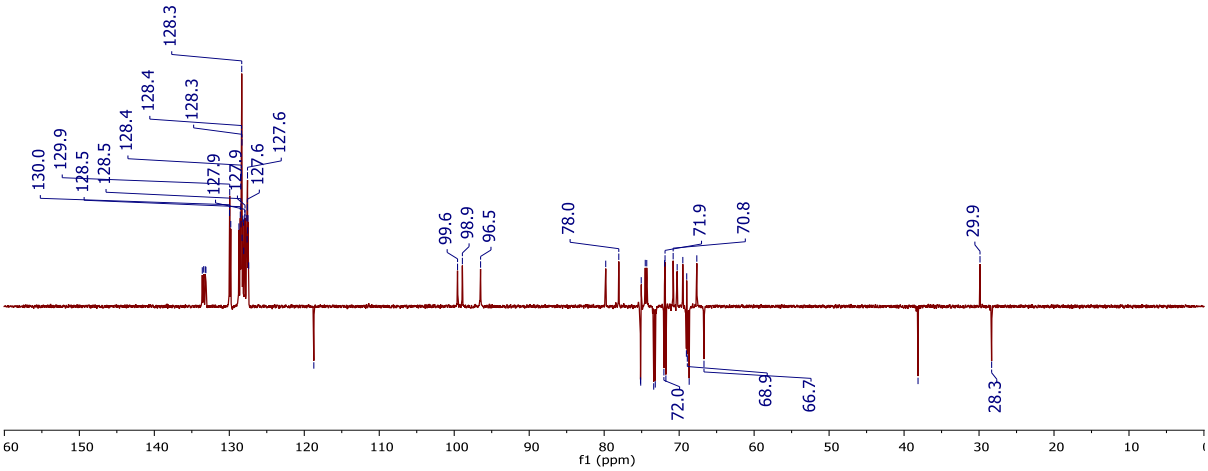
**$^{1}$H NMR Spectrum (399.78Hz, $CDCl_3$) of compound 57**



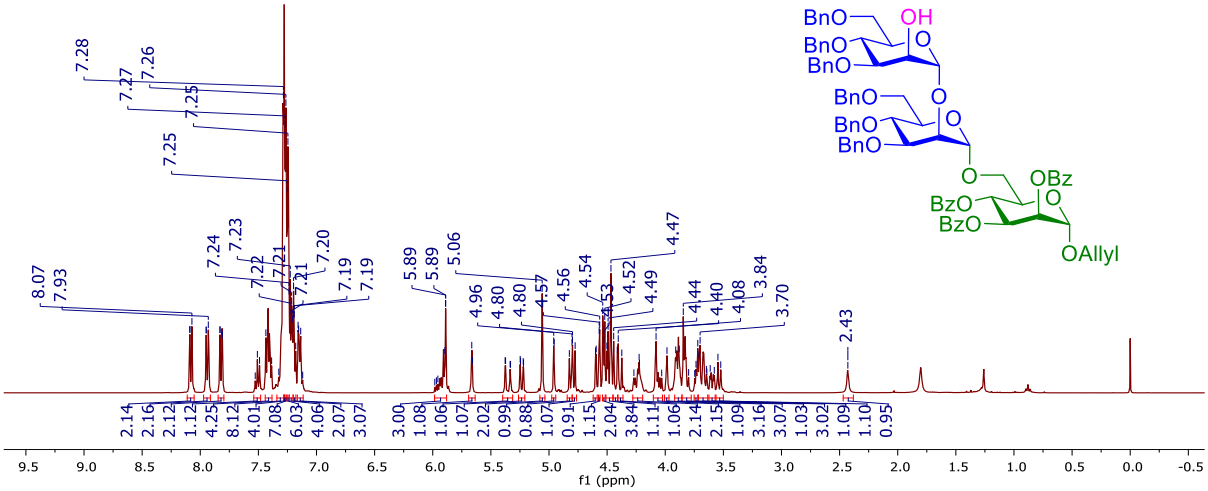

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 57**



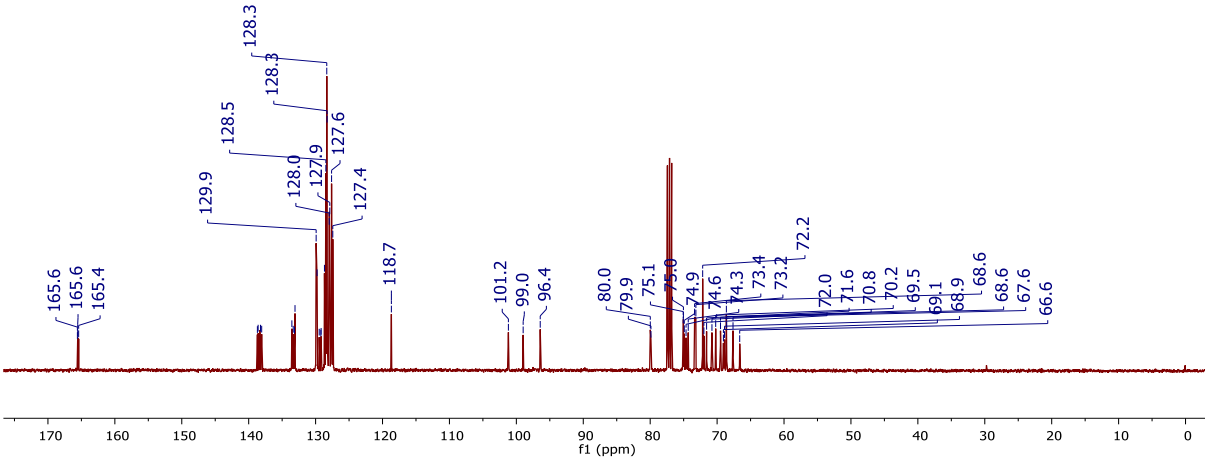

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 57**



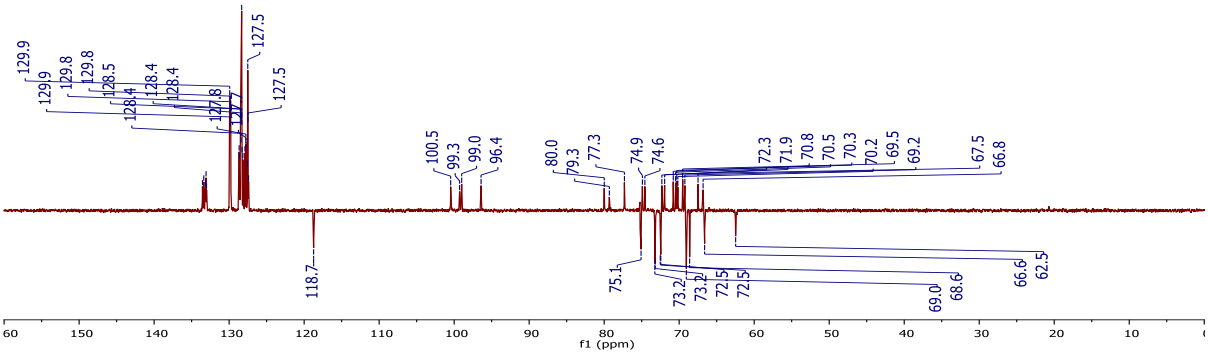
**$^{1}$H NMR Spectrum (399.78Hz, $CDCl_3$) of compound 58**



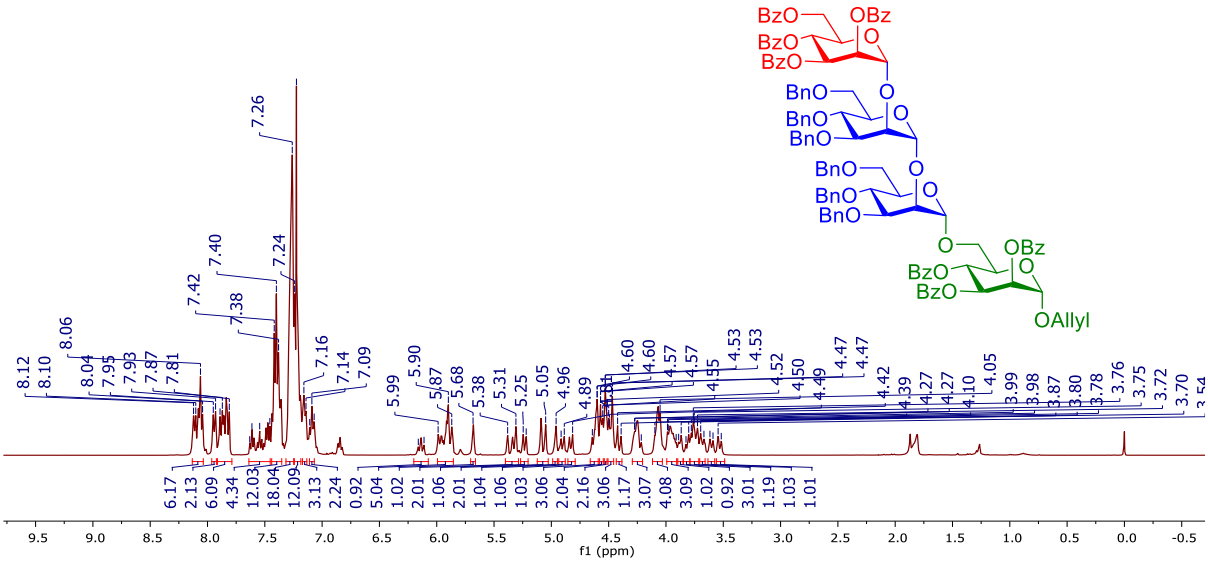

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 58**



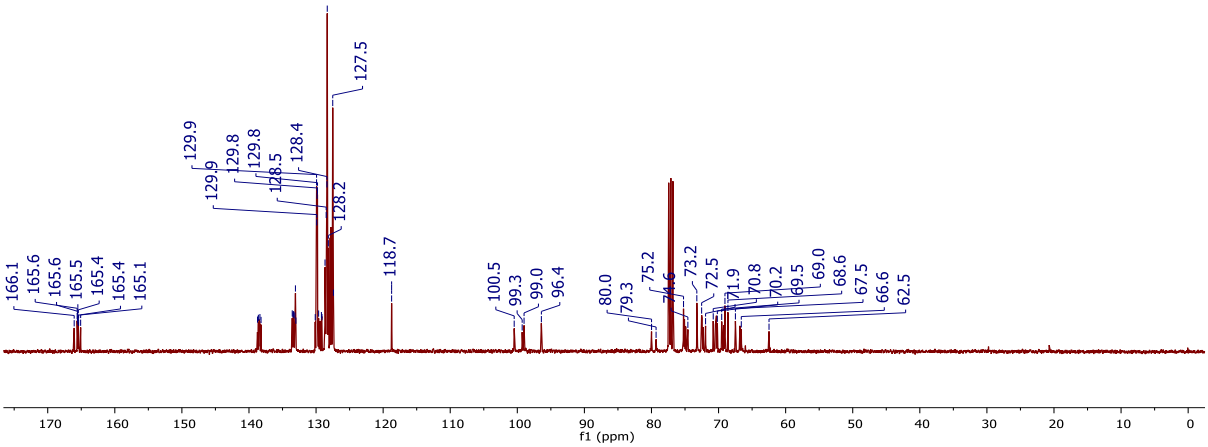

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 58**



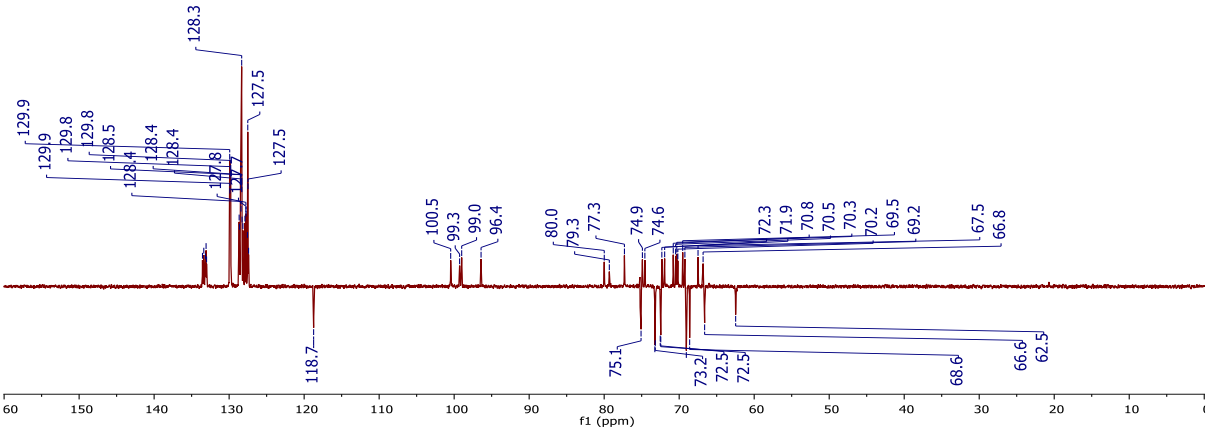
**$^{1}$H NMR Spectrum (399.78Hz, $CDCl_3$) of compound 59**



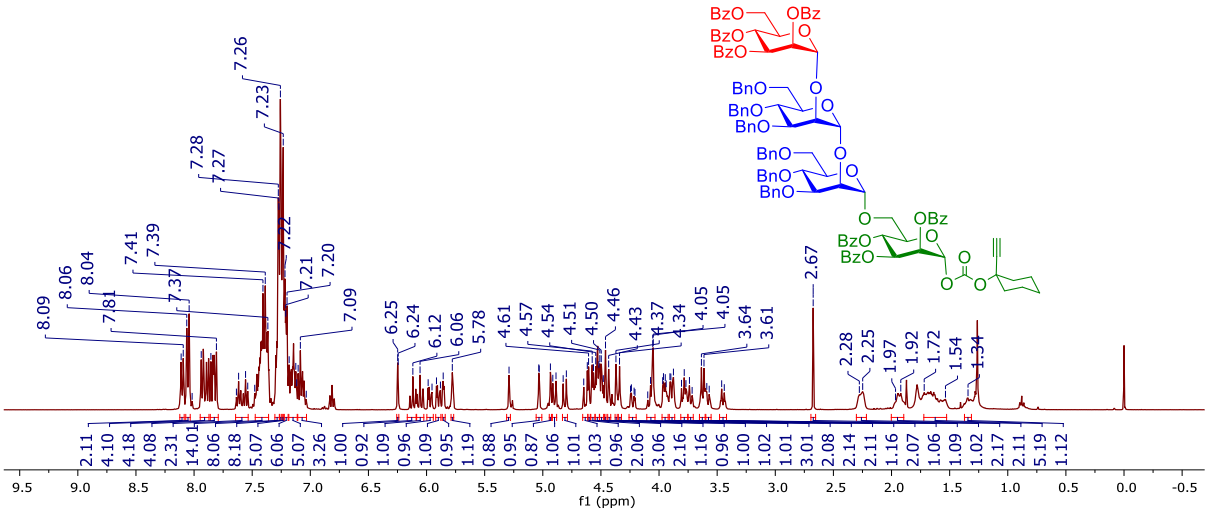

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 59**



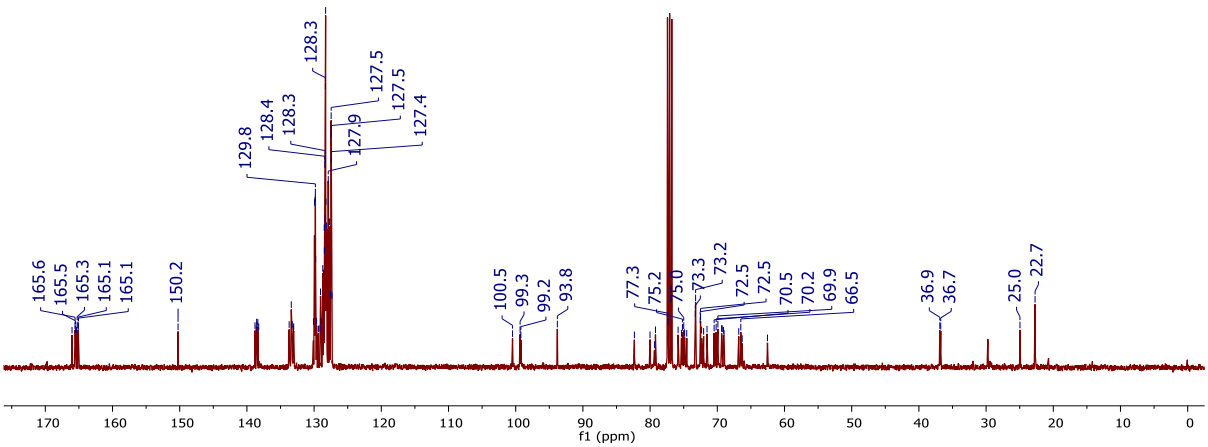

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 59**



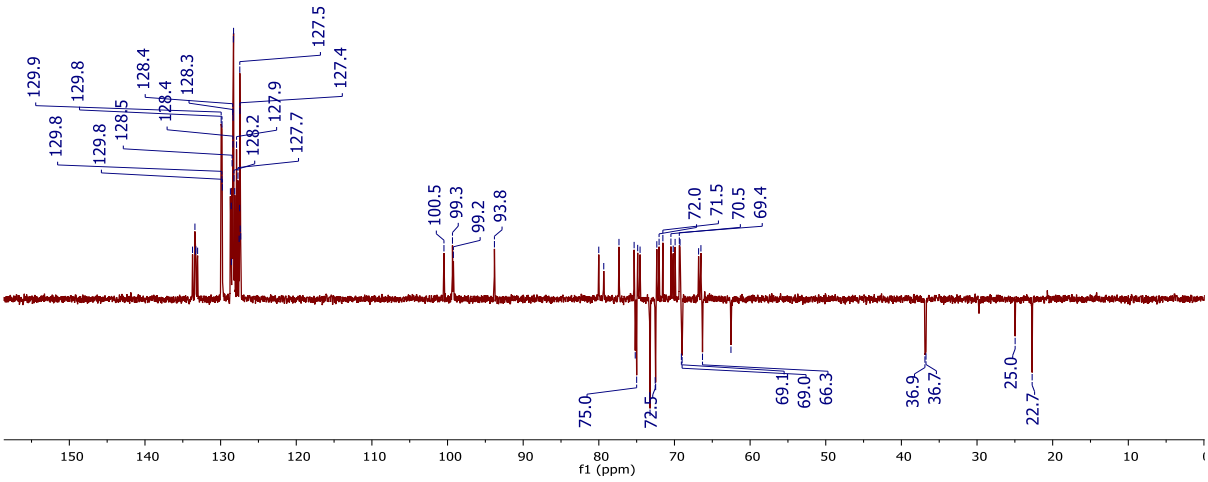
**$^{1}$H NMR Spectrum (399.78Hz, $CDCl_3$) of compound 49**



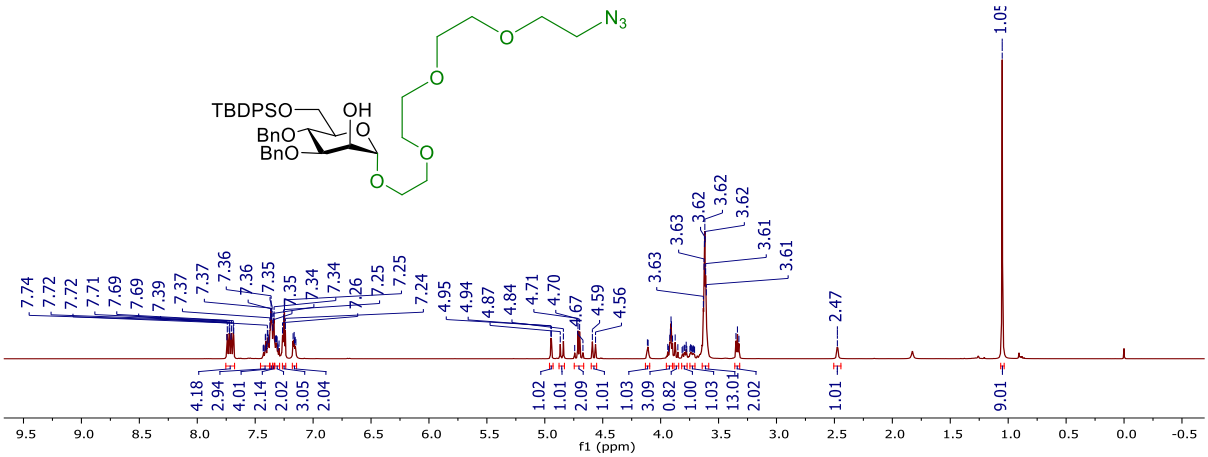

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 49**



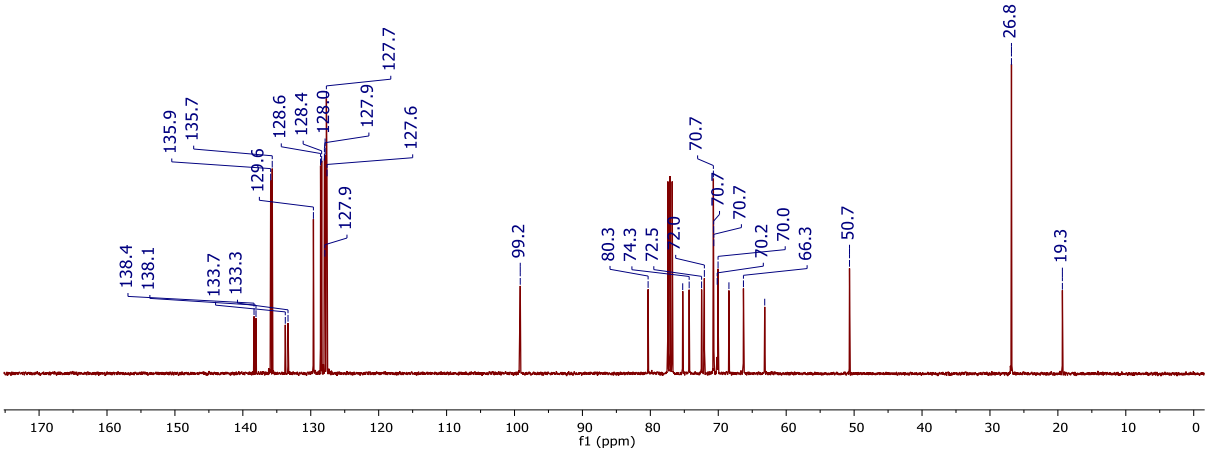

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 49**



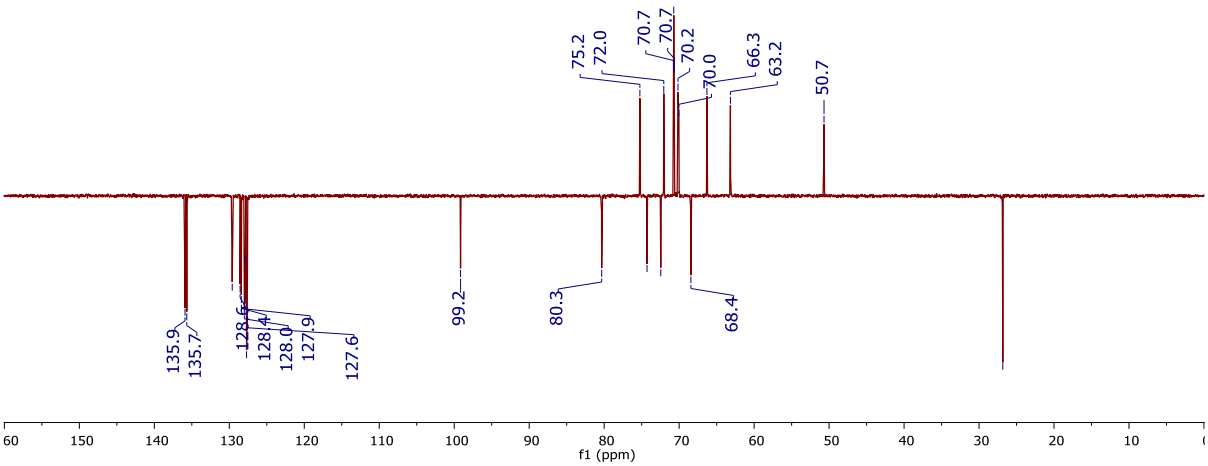
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 60**



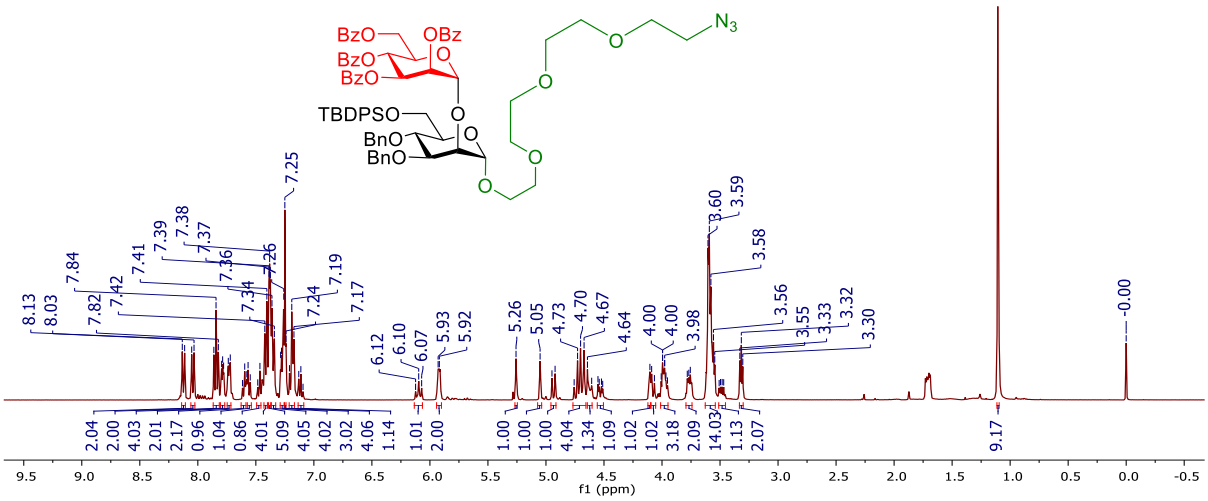

**$^{13}$C NMR Spectrum (100.53Hz, $CDCl_3$) of compound 60**



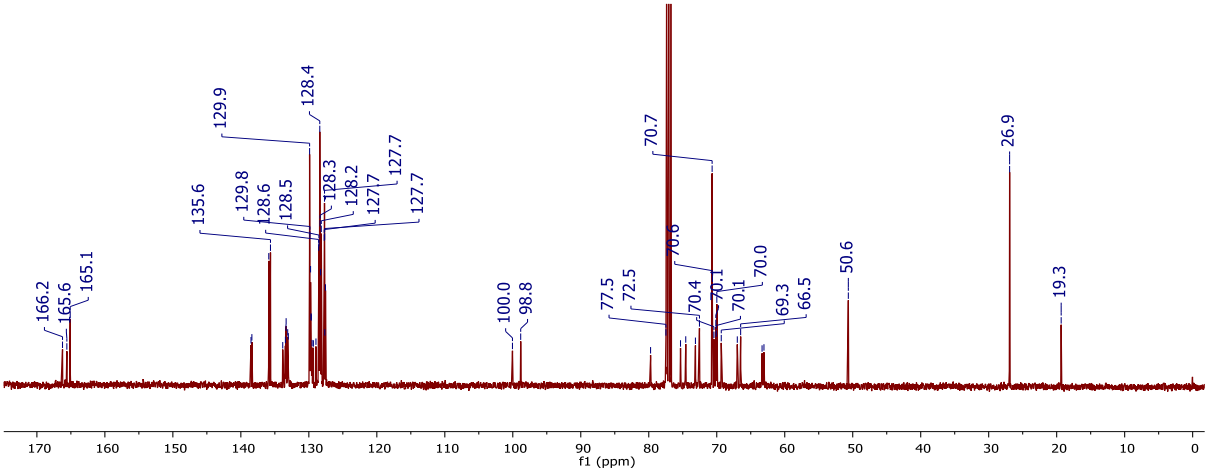

**DEPT NMR Spectrum (100.53Hz, $CDCl_3$) of compound 60**



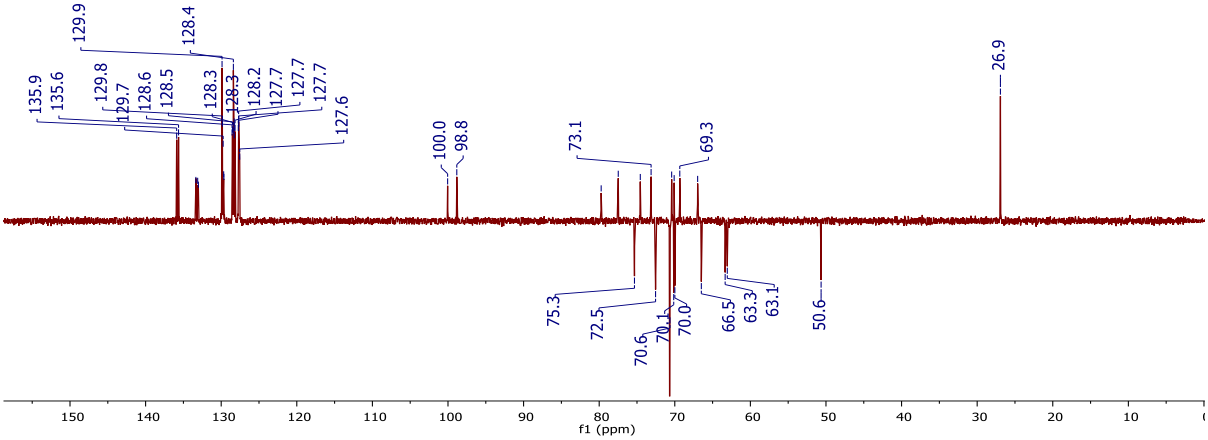
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 61**



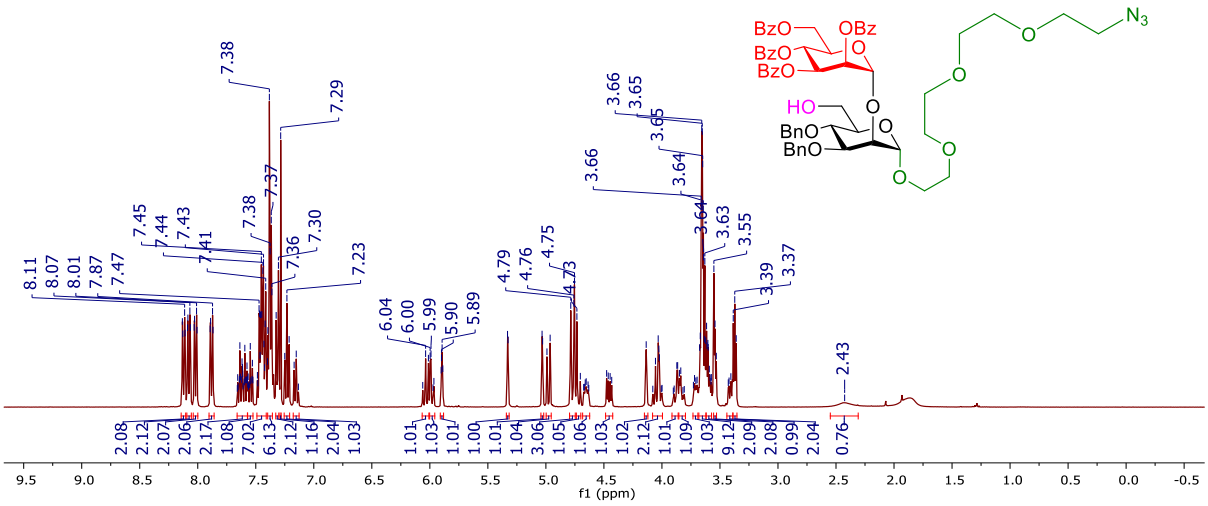

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 61**



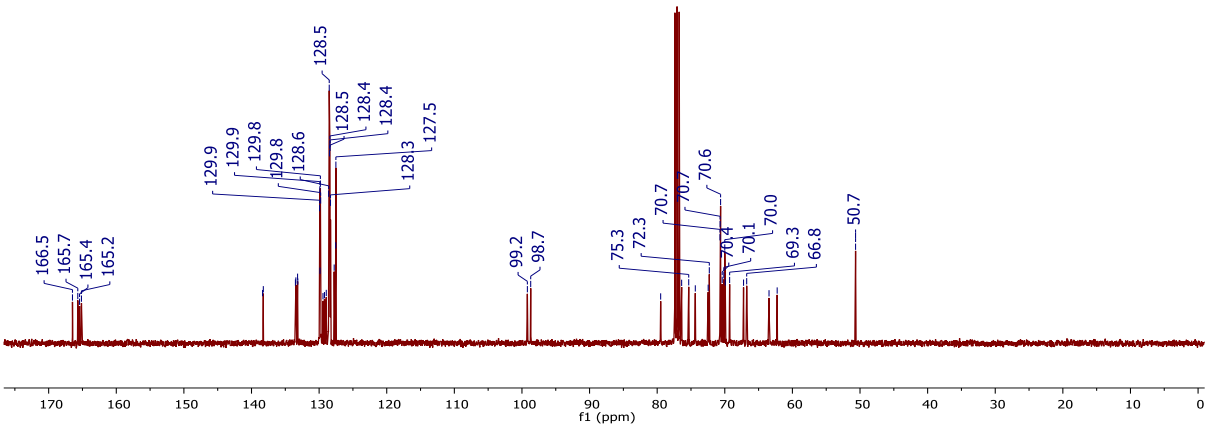

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 61**



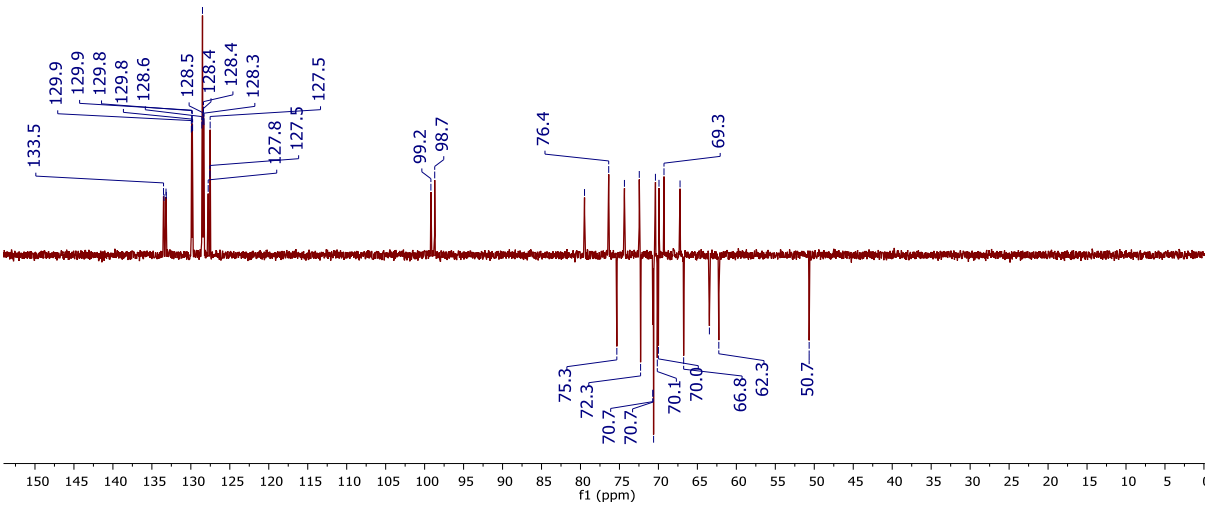
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 62**



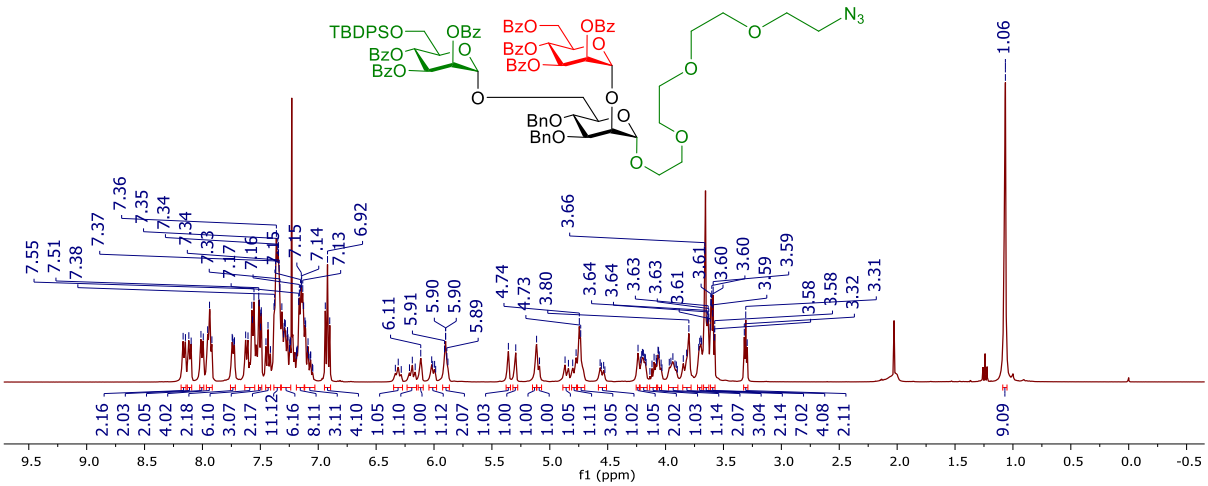

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 62**



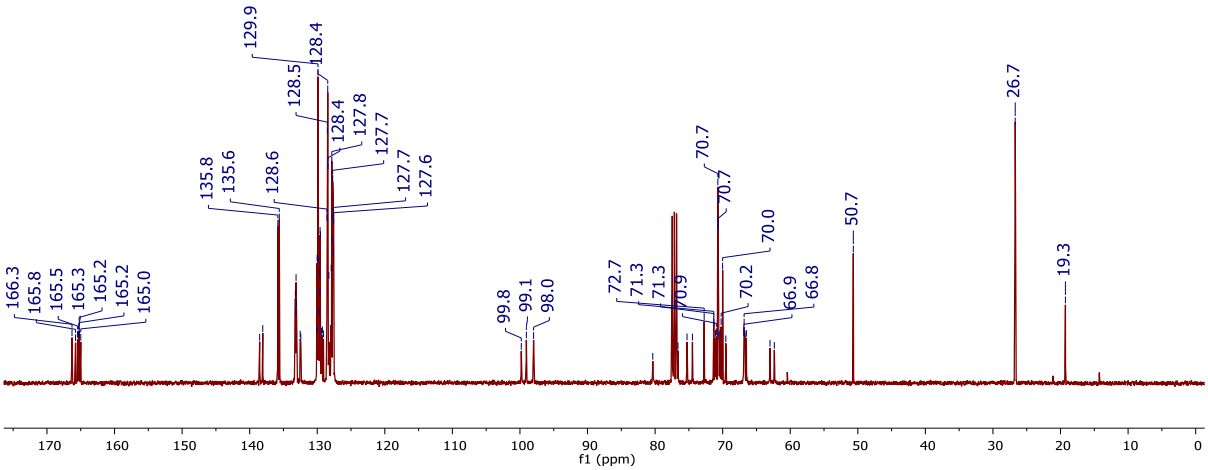

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 62**



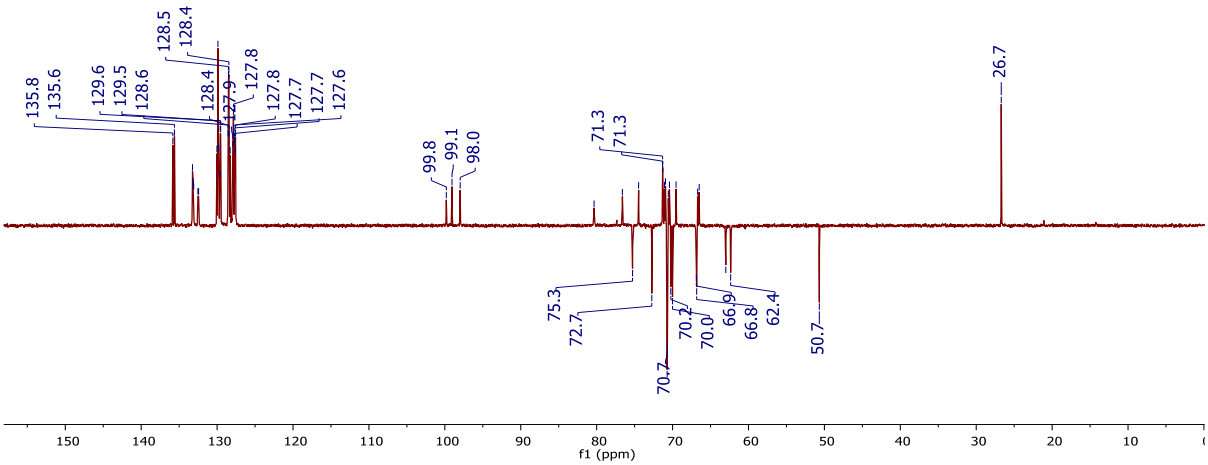
## $^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 63



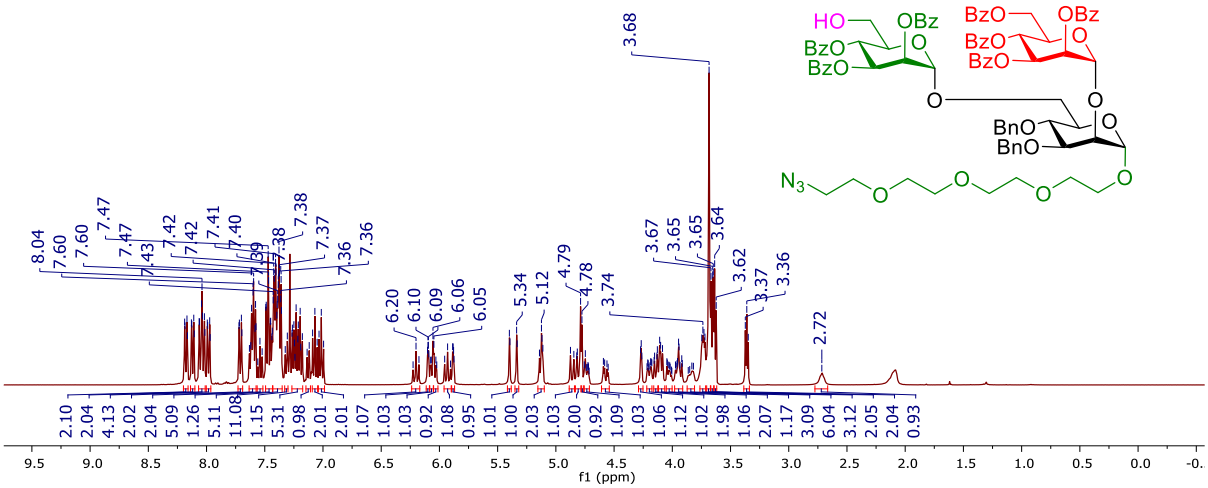

## $^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 63



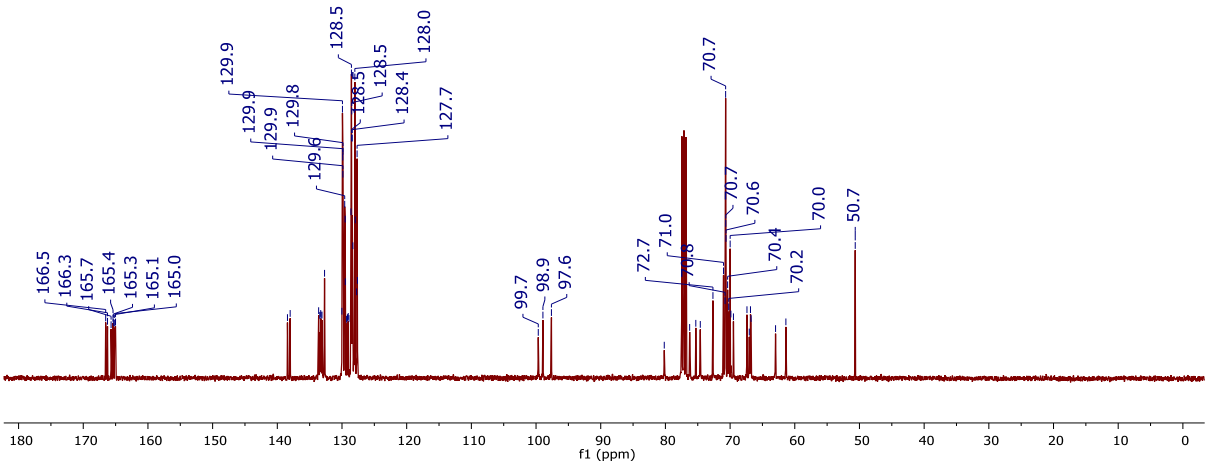

## DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 63



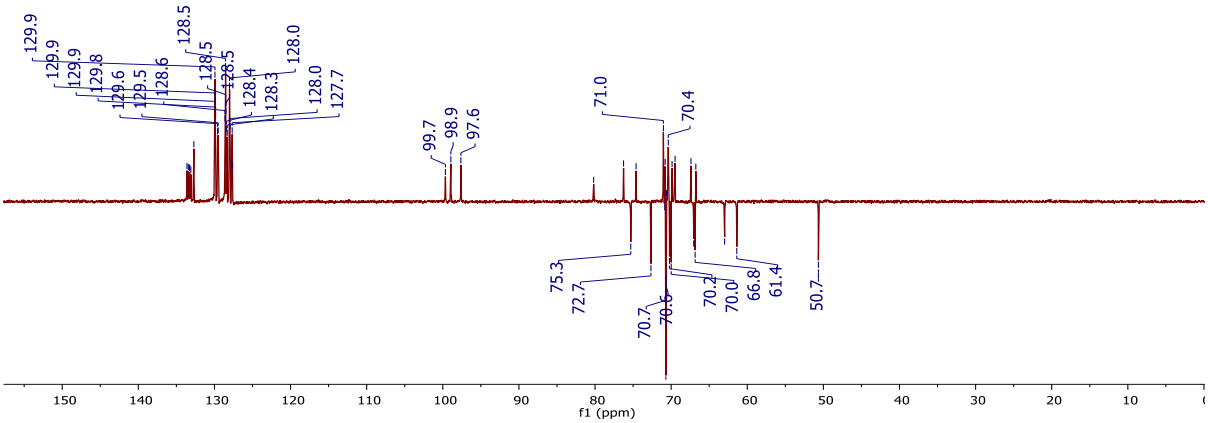
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 50**



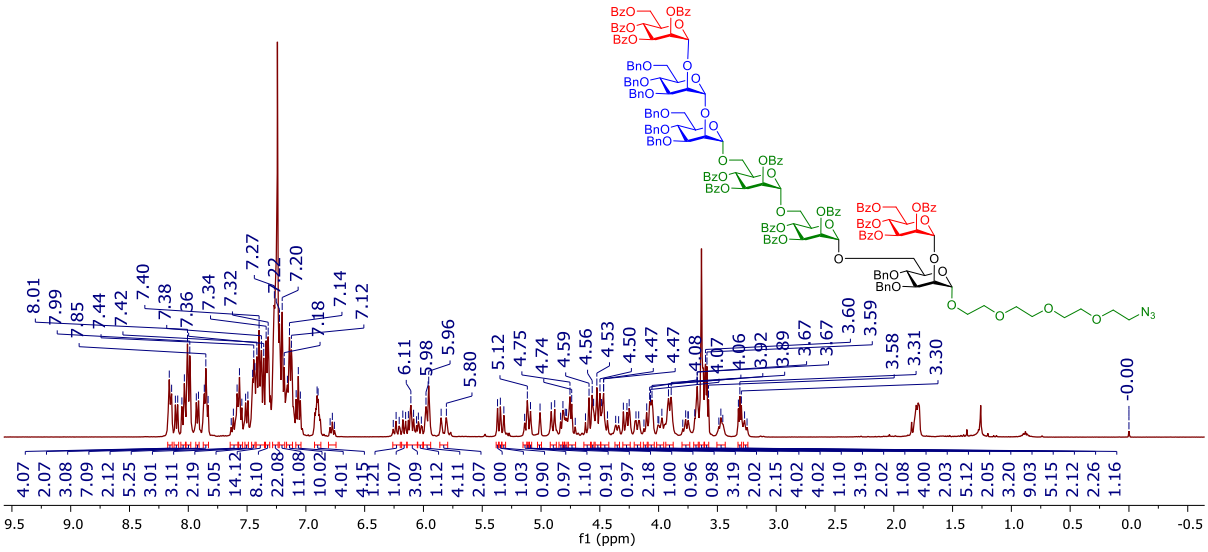

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 50**



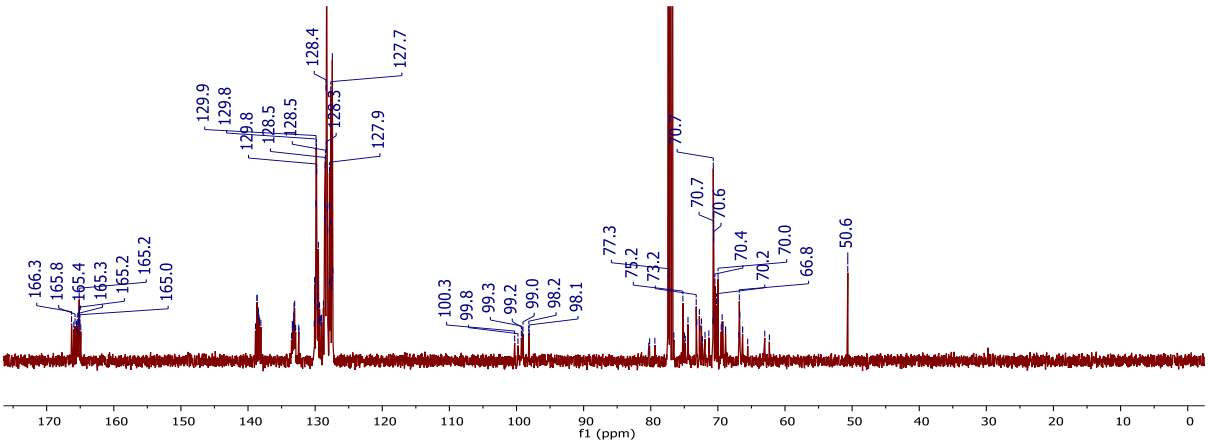

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 50**



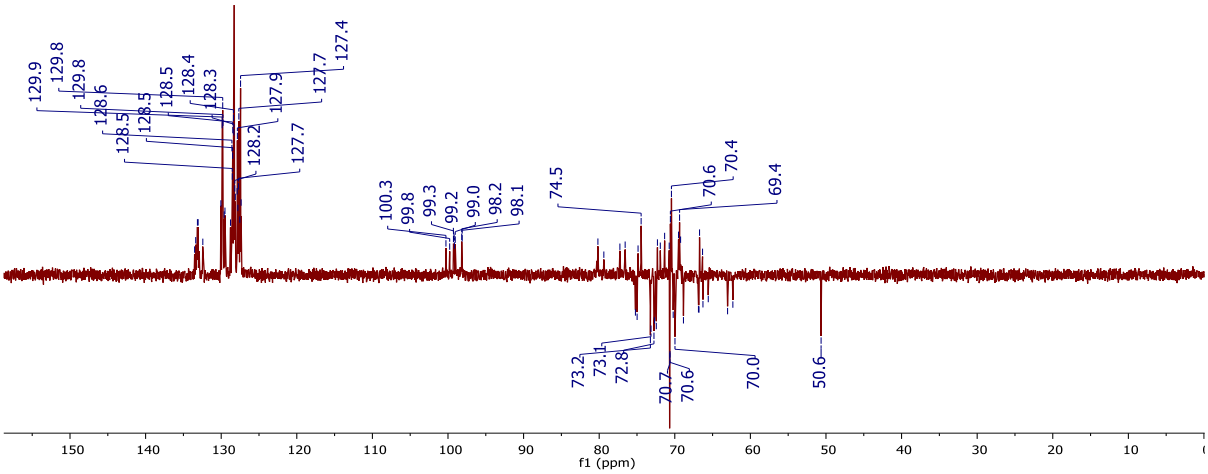
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 64**



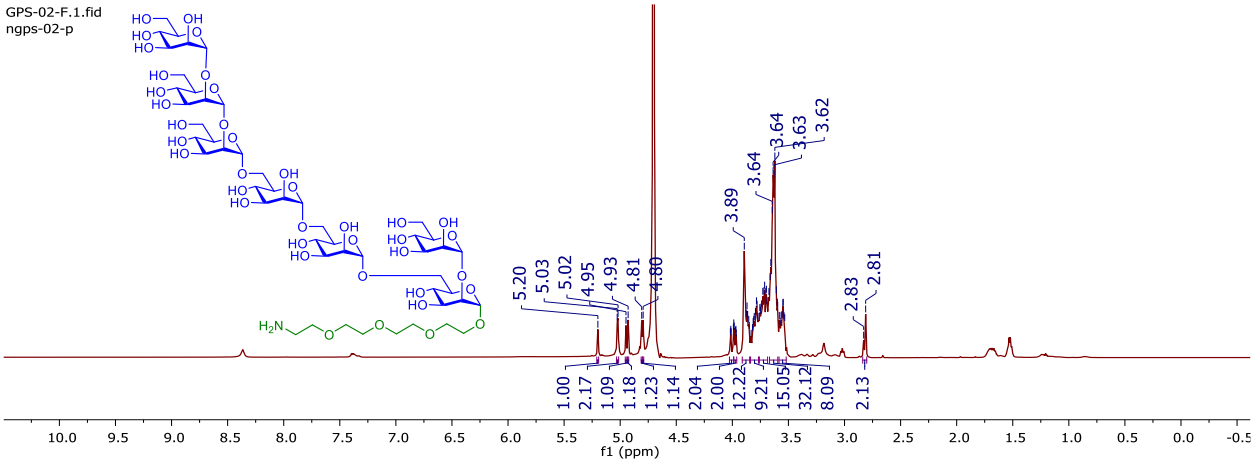

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 64**



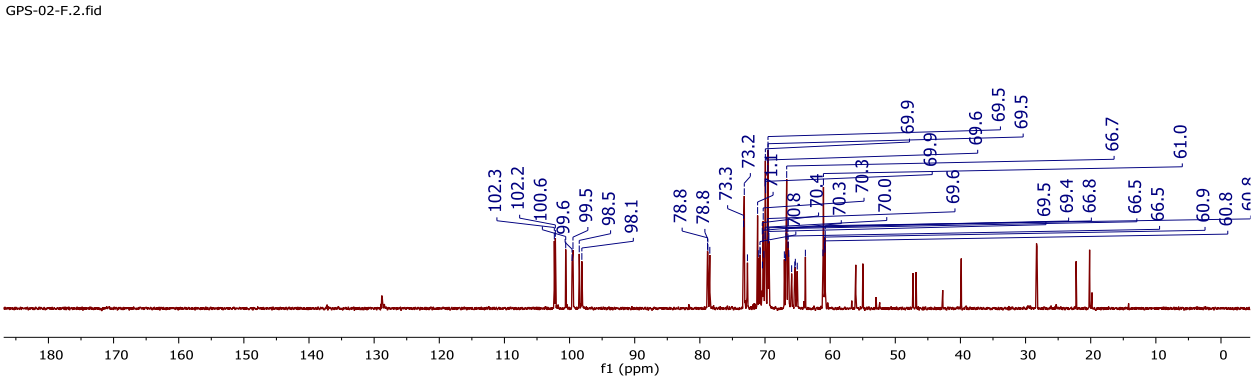

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 64**



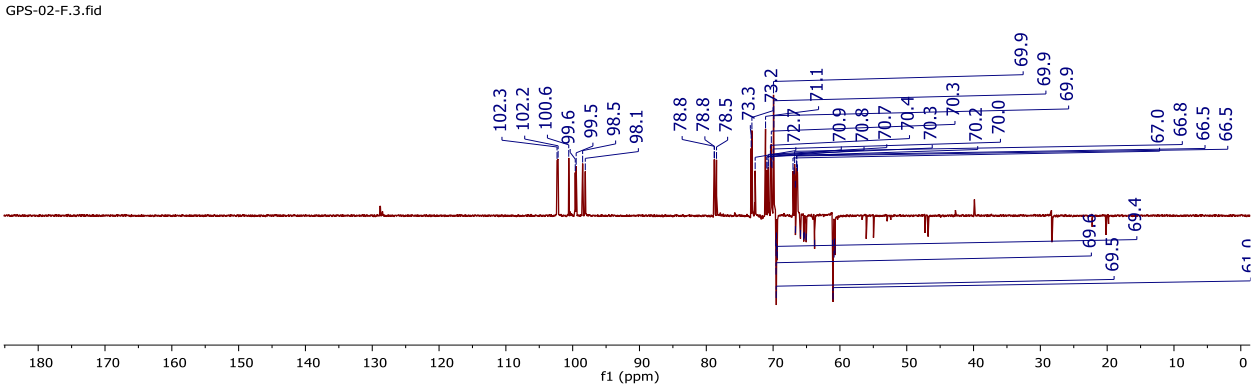
## $^{1}$H NMR (600 MHz, MeOD$_4$) of Compound 65



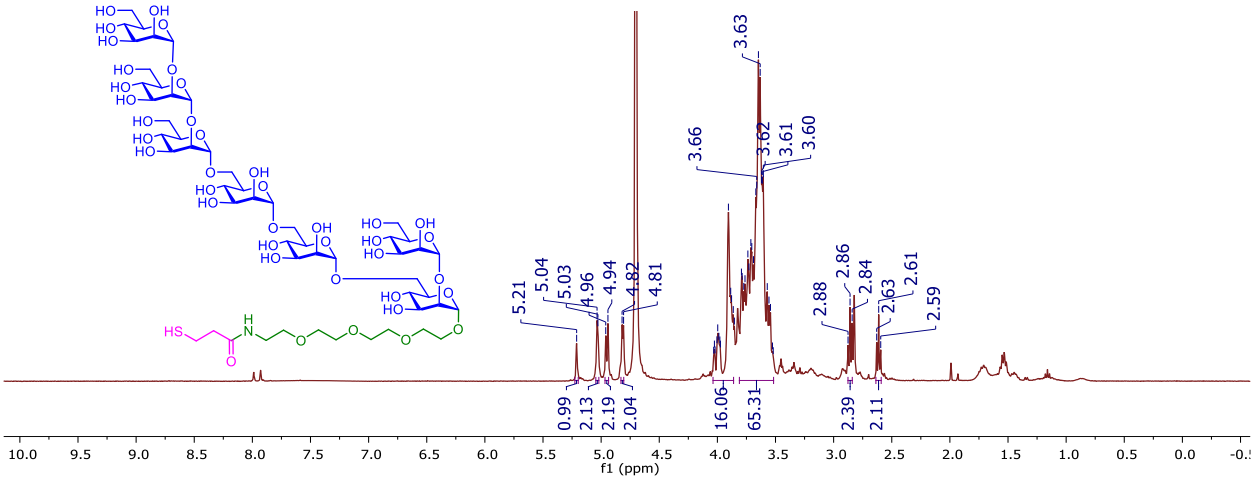

## $^{13}$C NMR (150 MHz, MeOD$_4$) of Compound 65



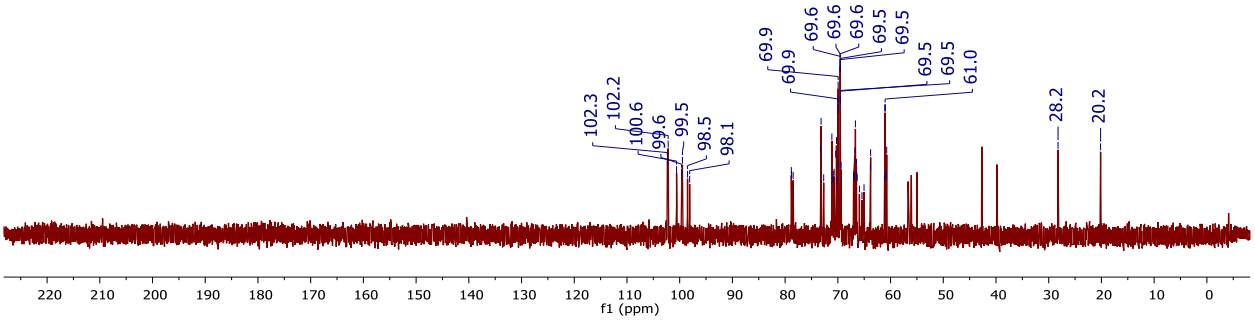

## $^{13}$C-DEPT NMR (150 MHz, MeOD$_4$) of Compound 65



## $^{1}$H NMR (600 MHz, $D_2O$) of Compound 1α

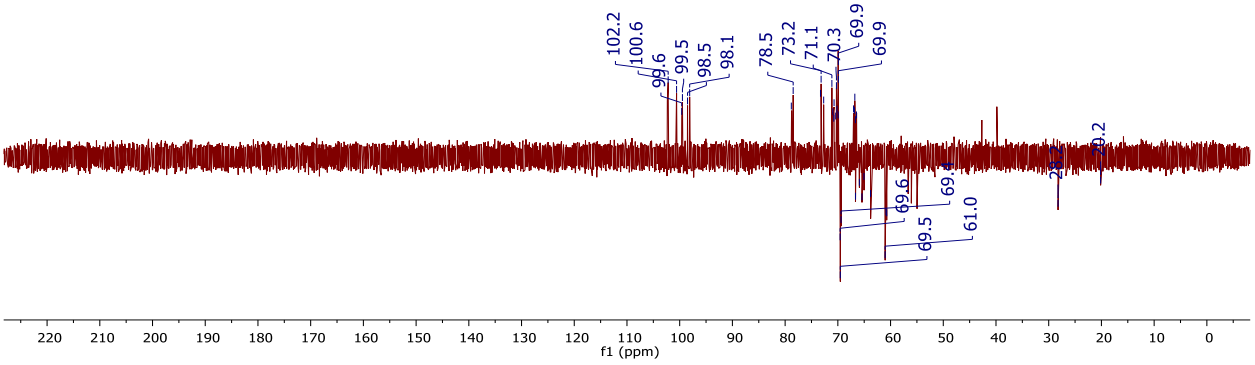



## $^{13}$C NMR (150 MHz, $D_2O$) of Compound 1α

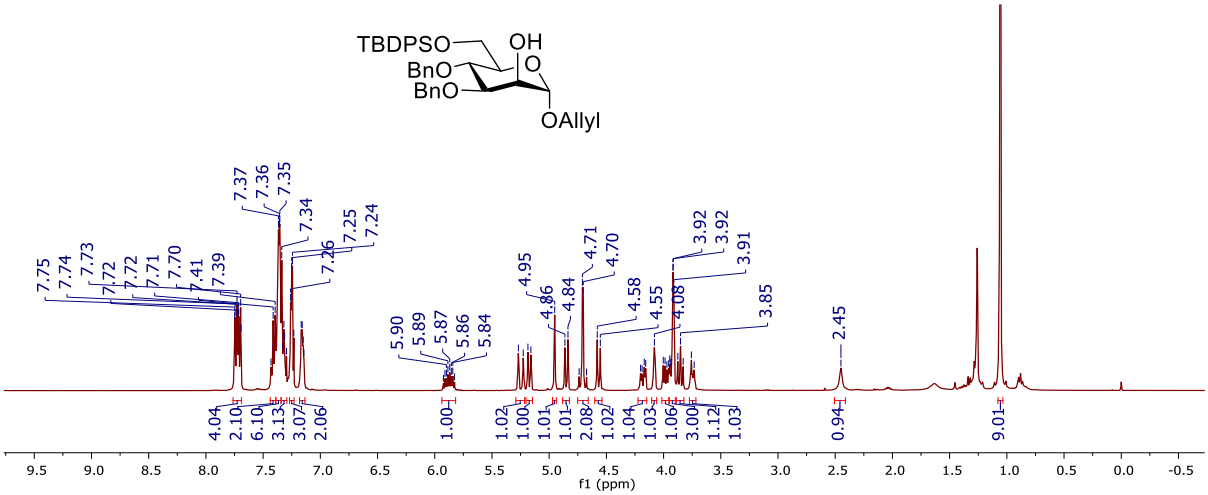



## DEPT NMR (150 MHz, $D_2O$) of Compound 1α

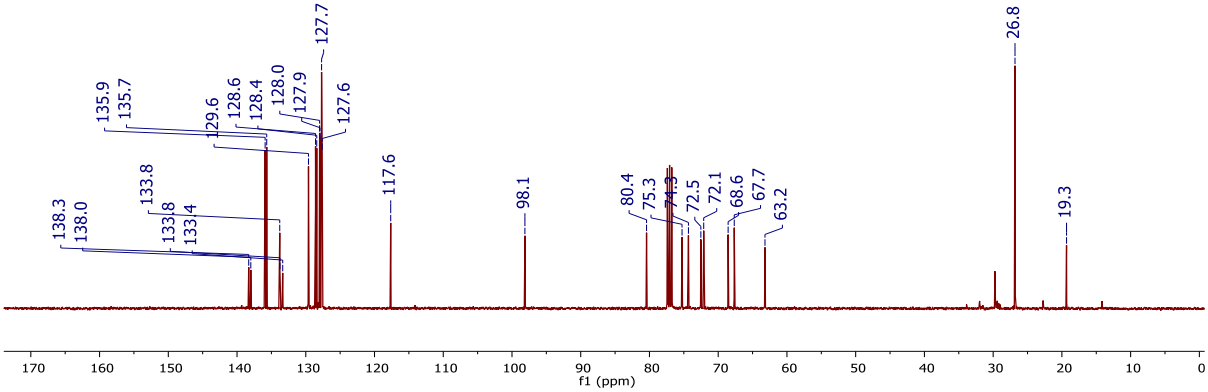
N-GPS-F-2D.7.fid



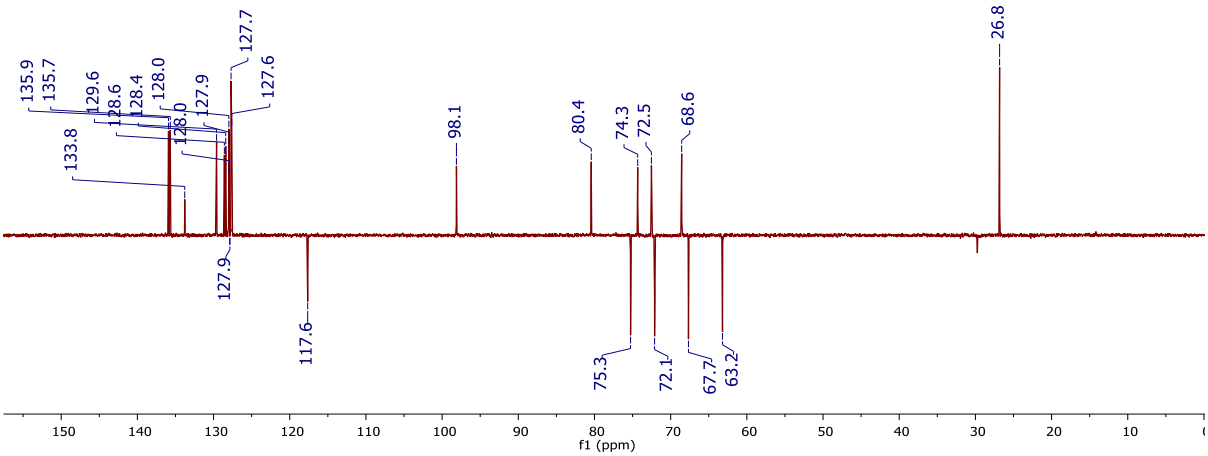
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 7**



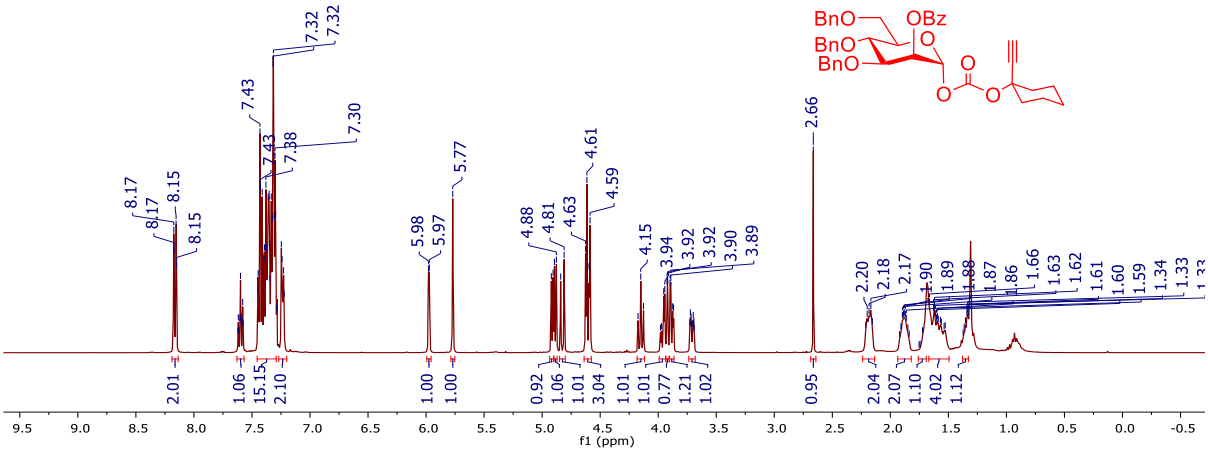

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 7**



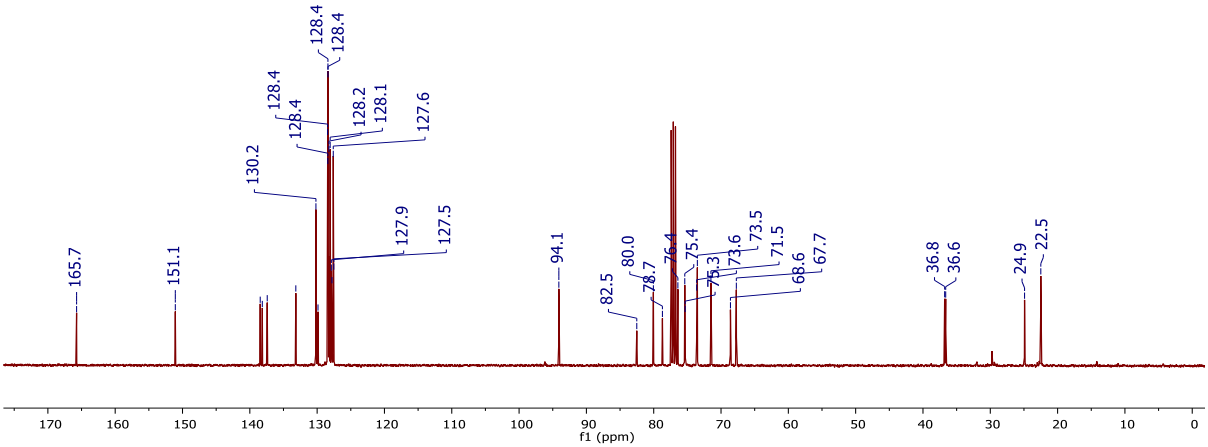

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 7**



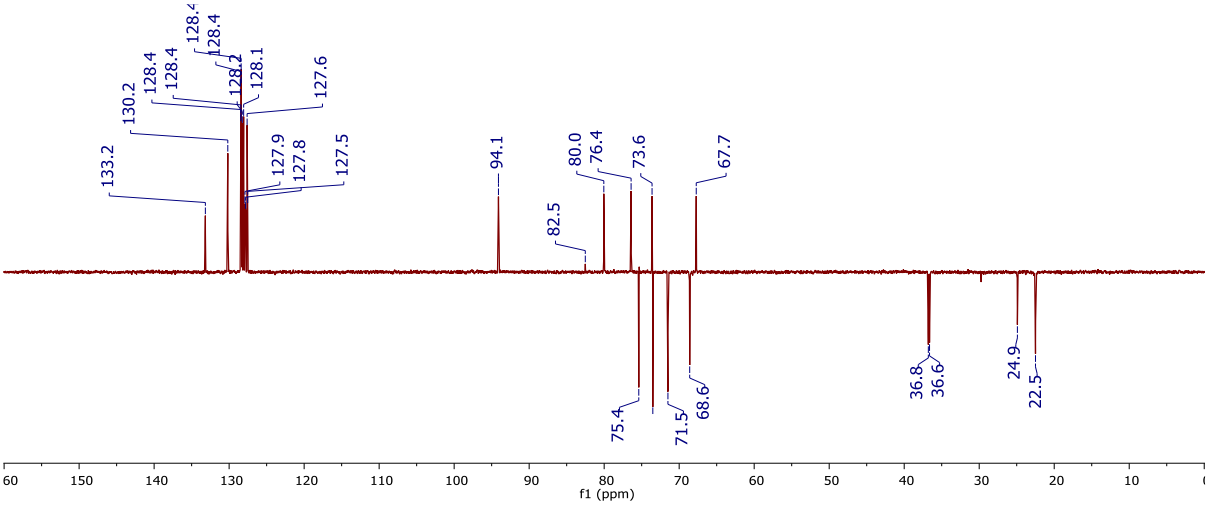
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 28α**



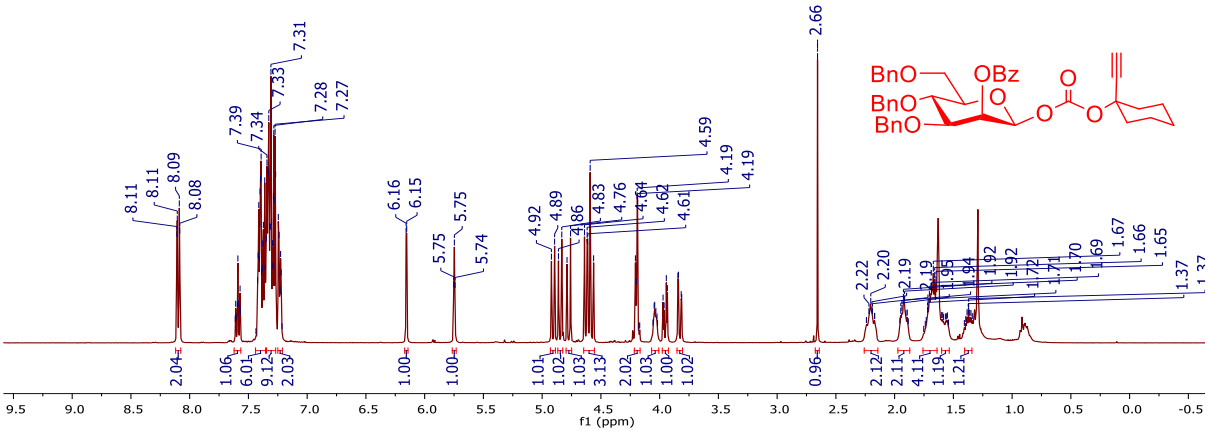

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 28α**



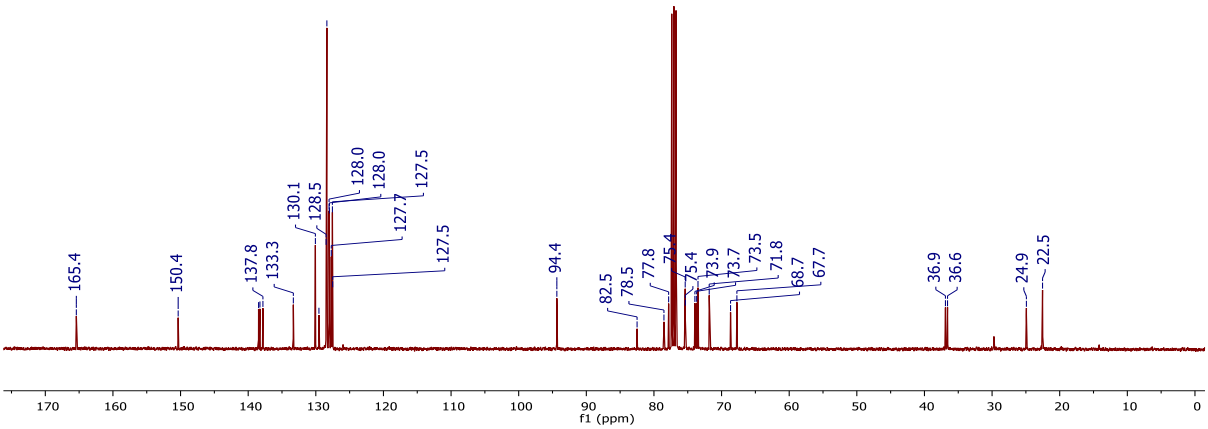

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 28α**



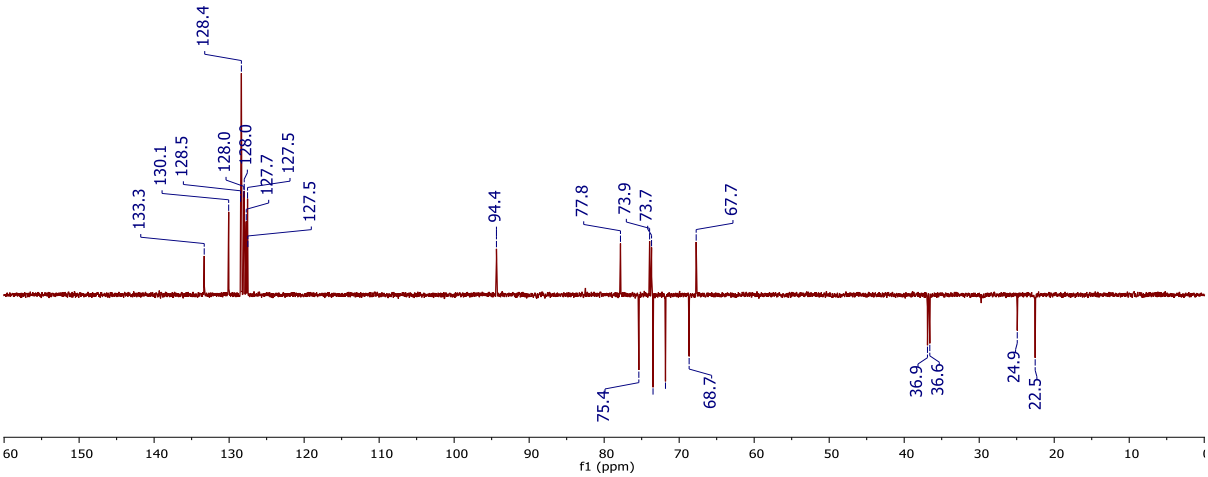
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 28β**



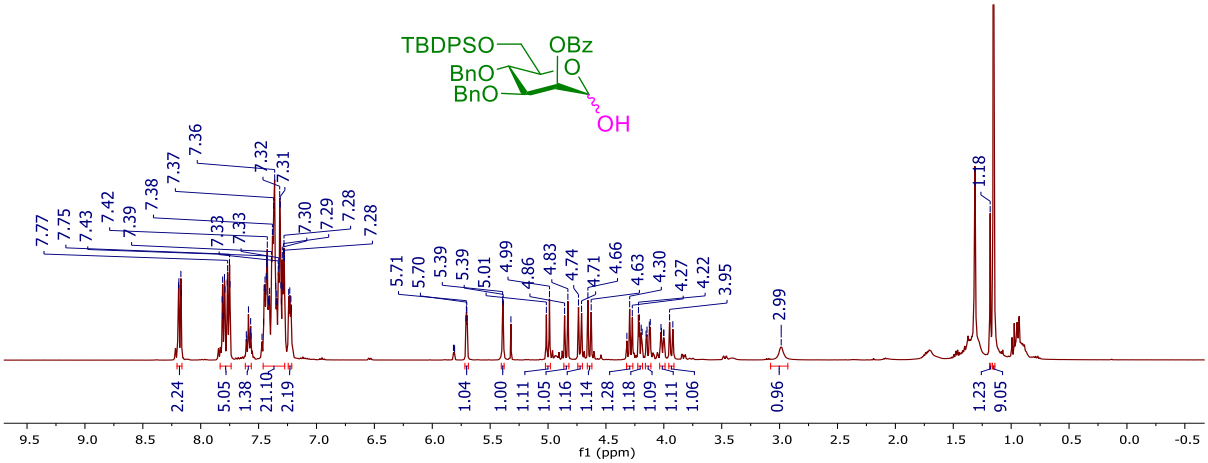

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 28β**



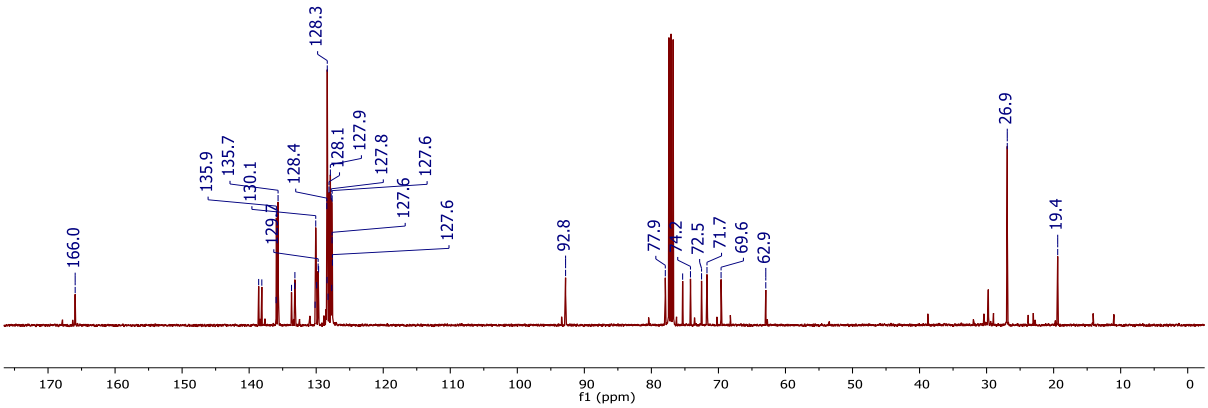

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 28β**



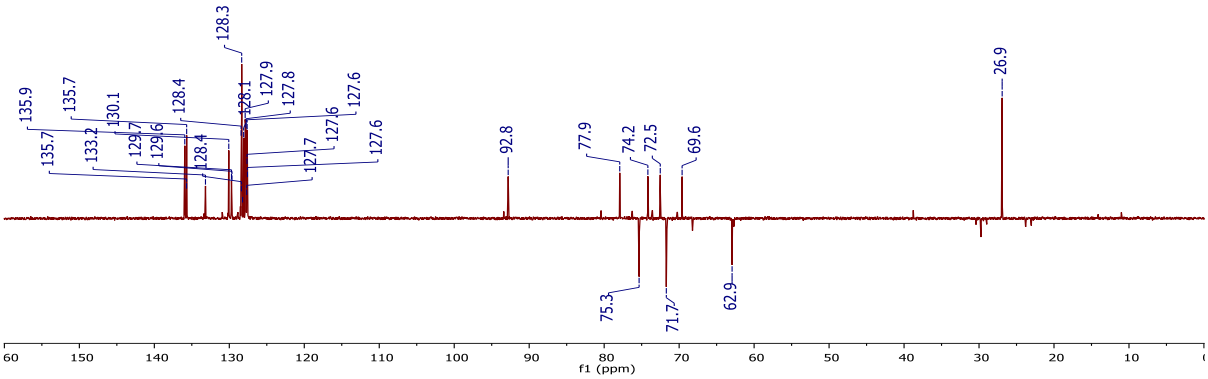
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 27**



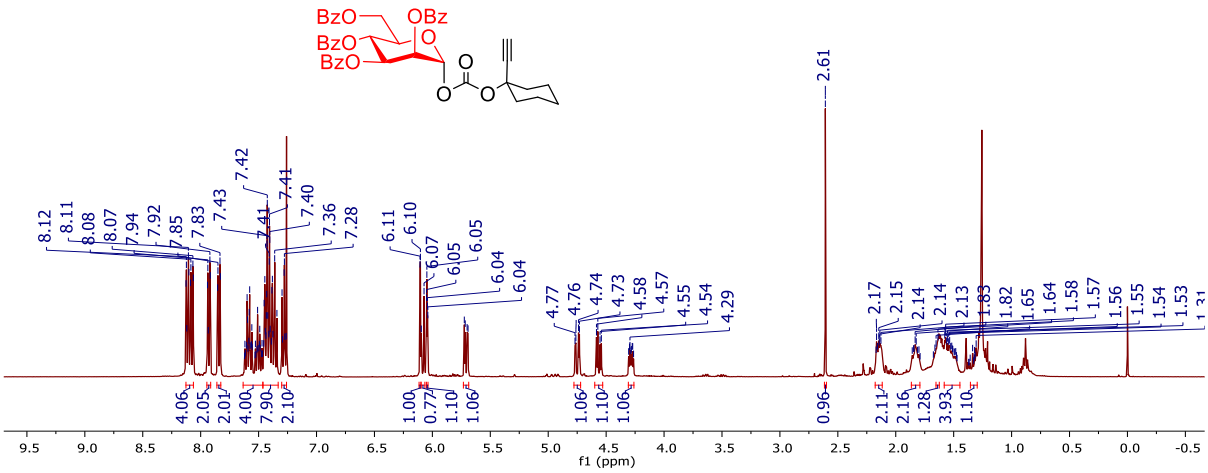

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 27**



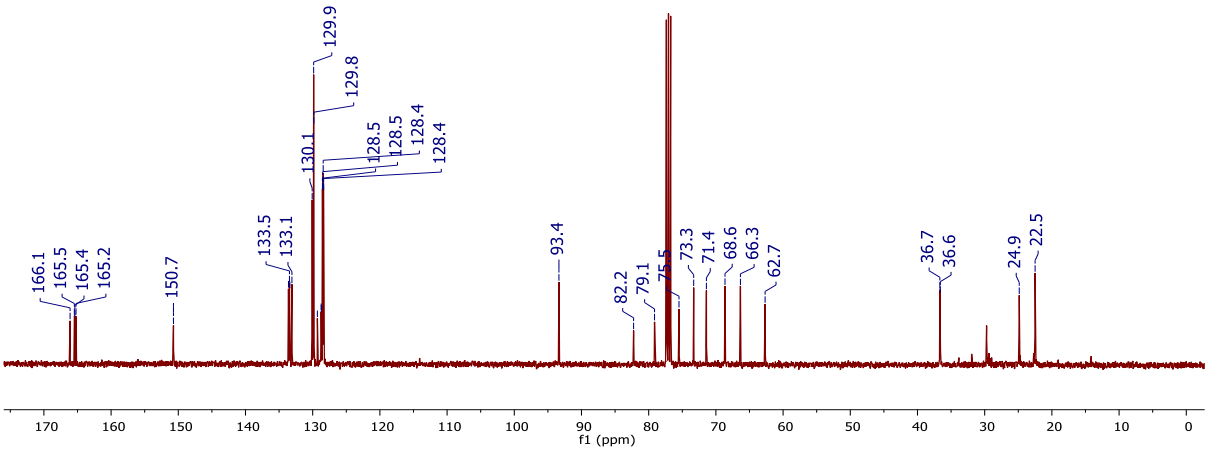

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 27**



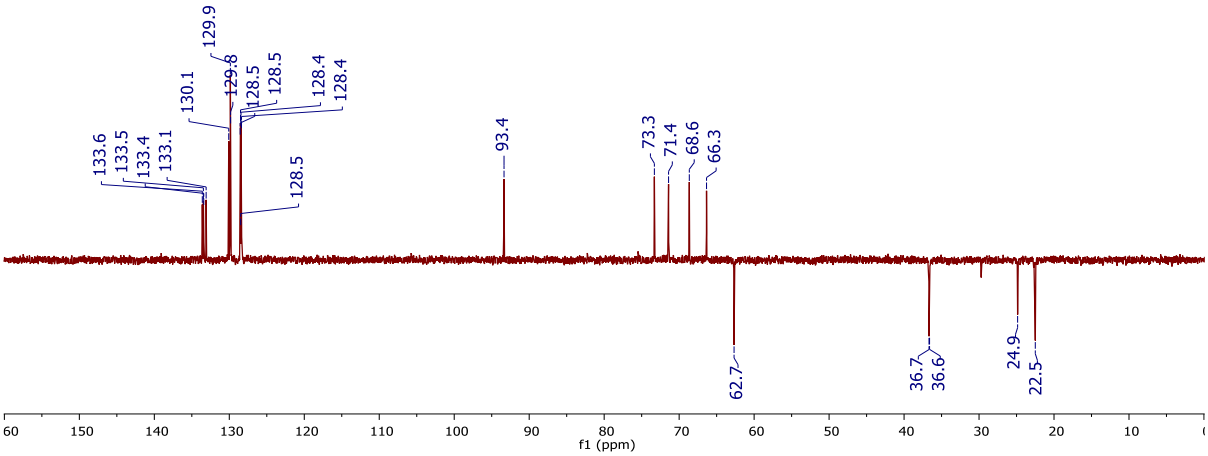
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 5α**



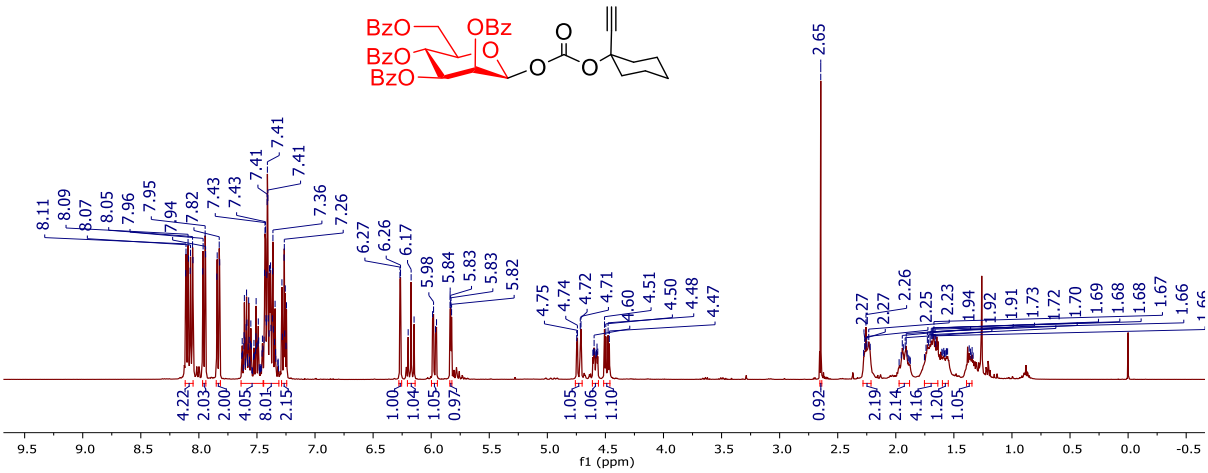

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 5α**



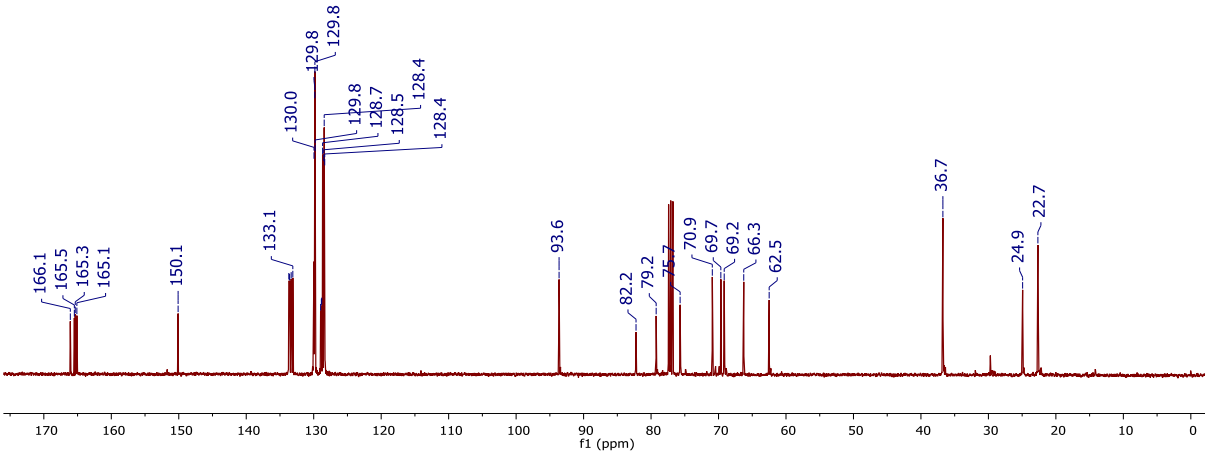

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 5α**



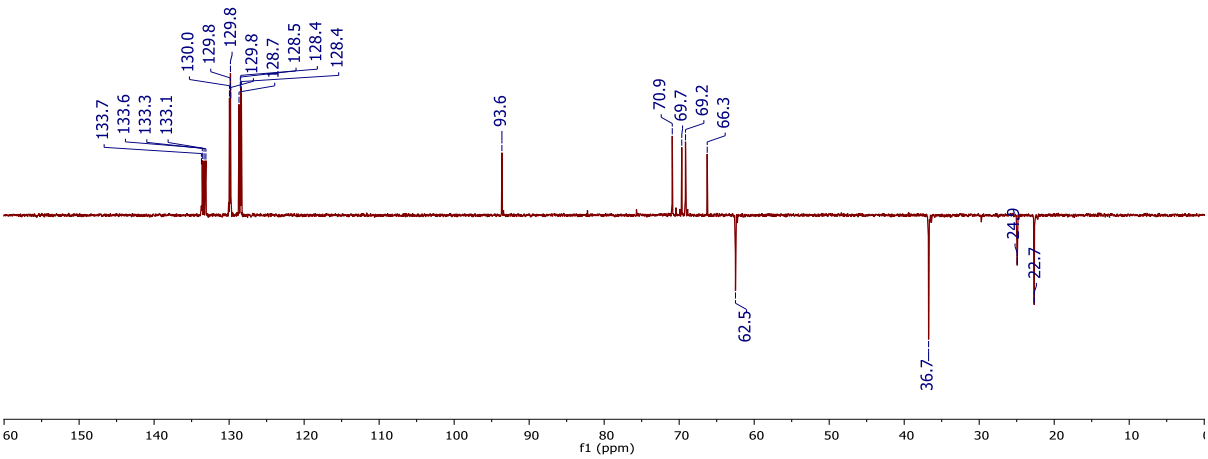
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 5β**



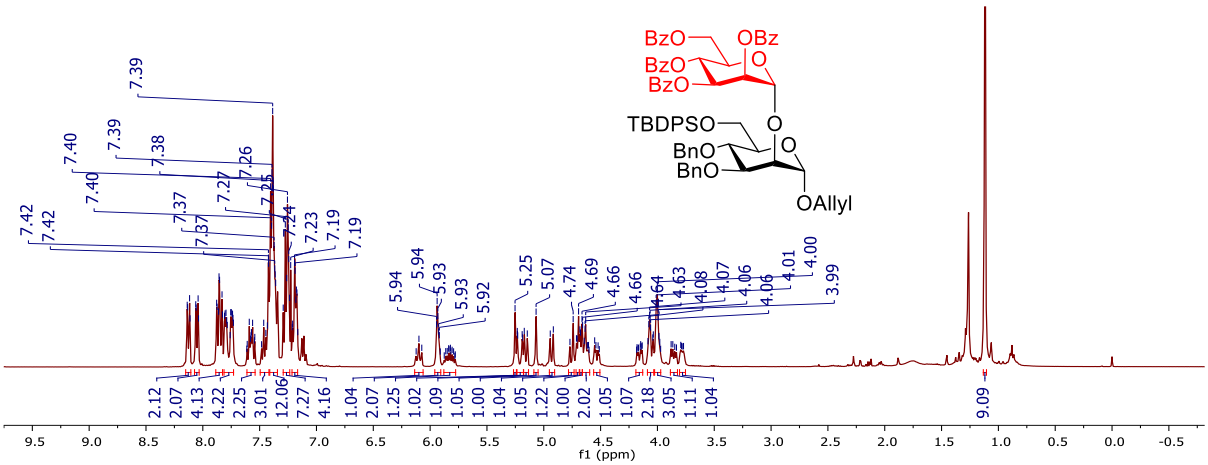

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 5β**



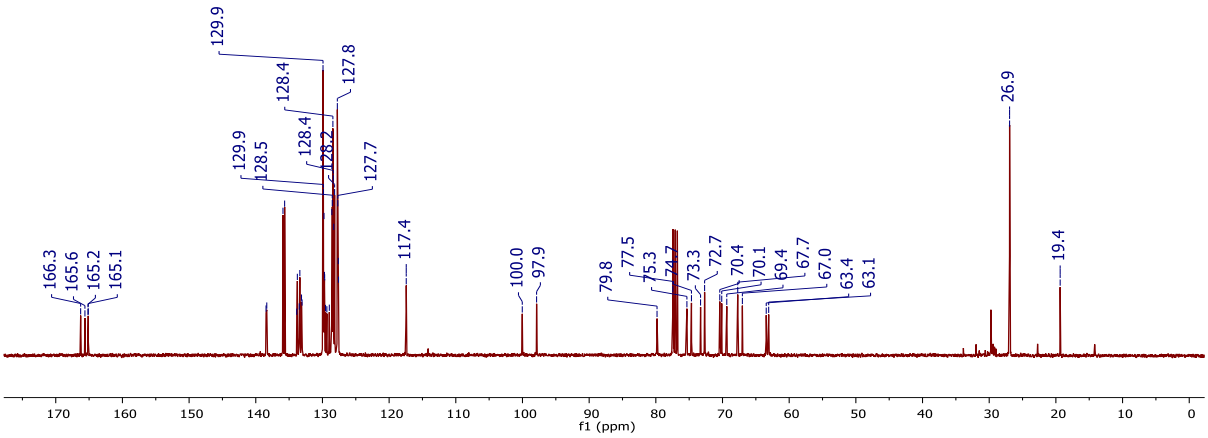

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 5β**



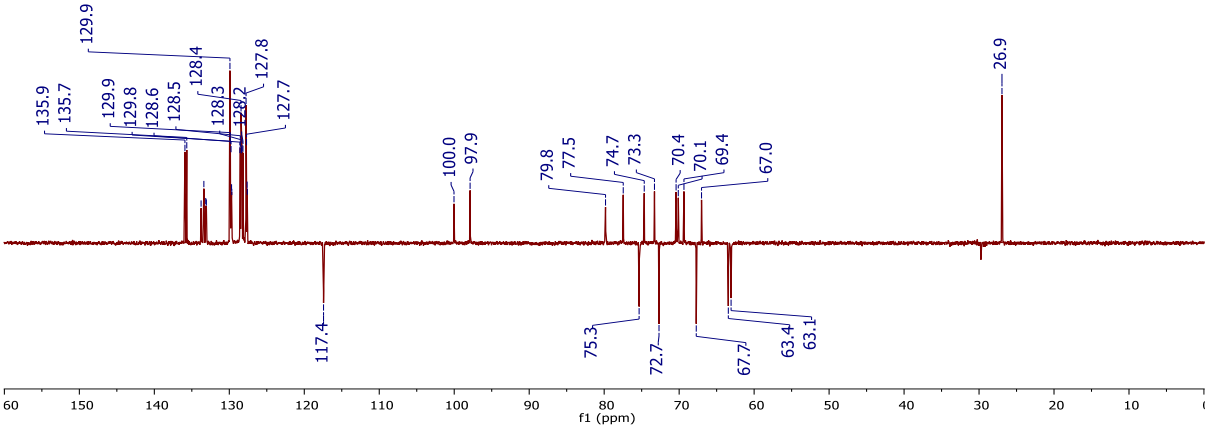
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 36**



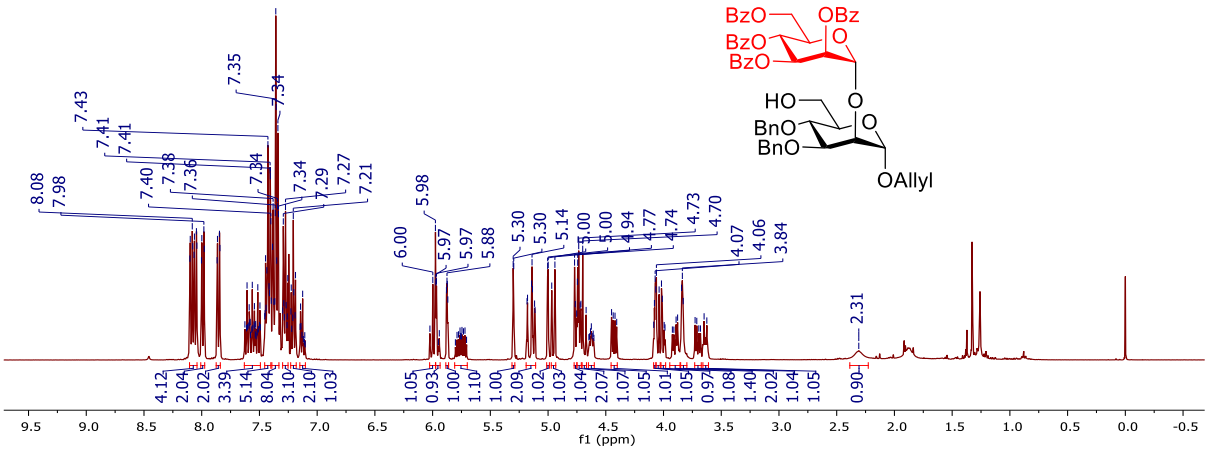

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 36**



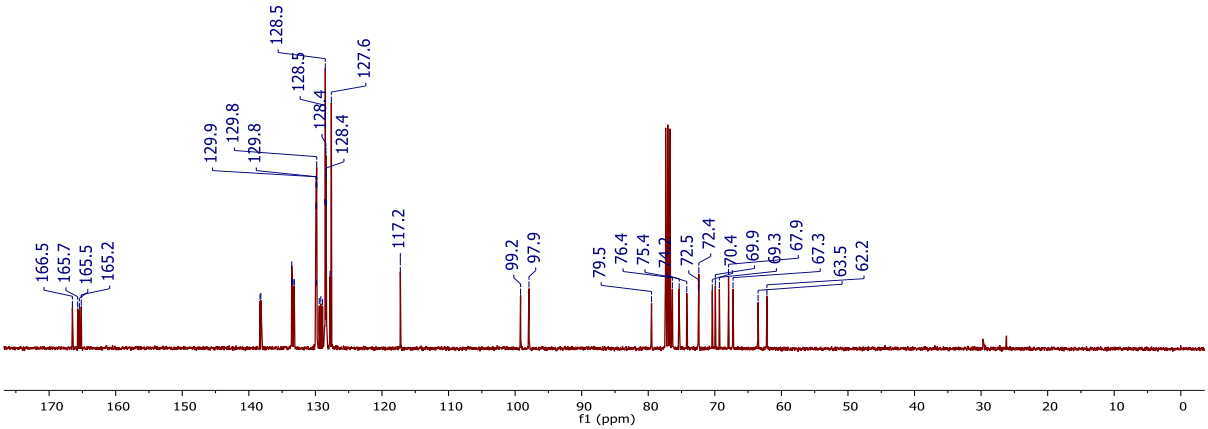

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 36**



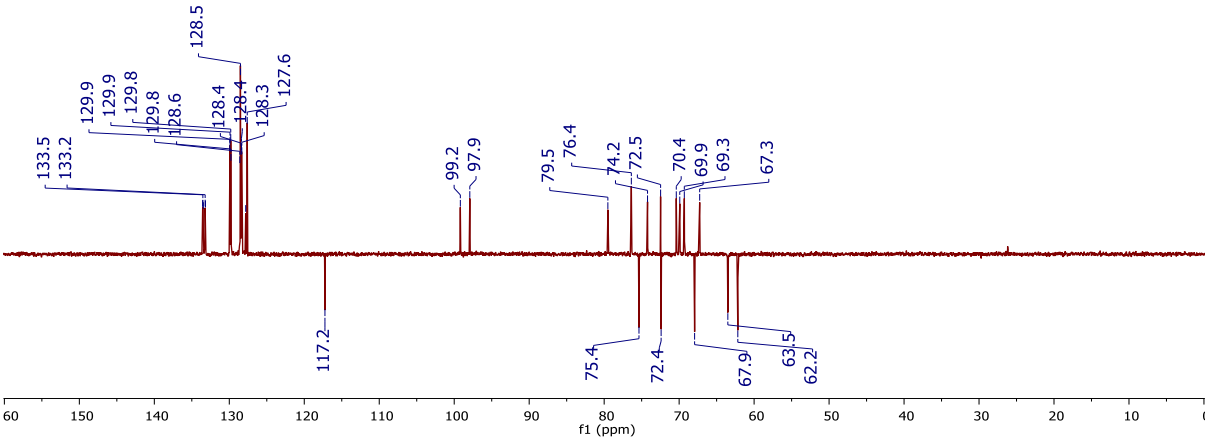
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 37**



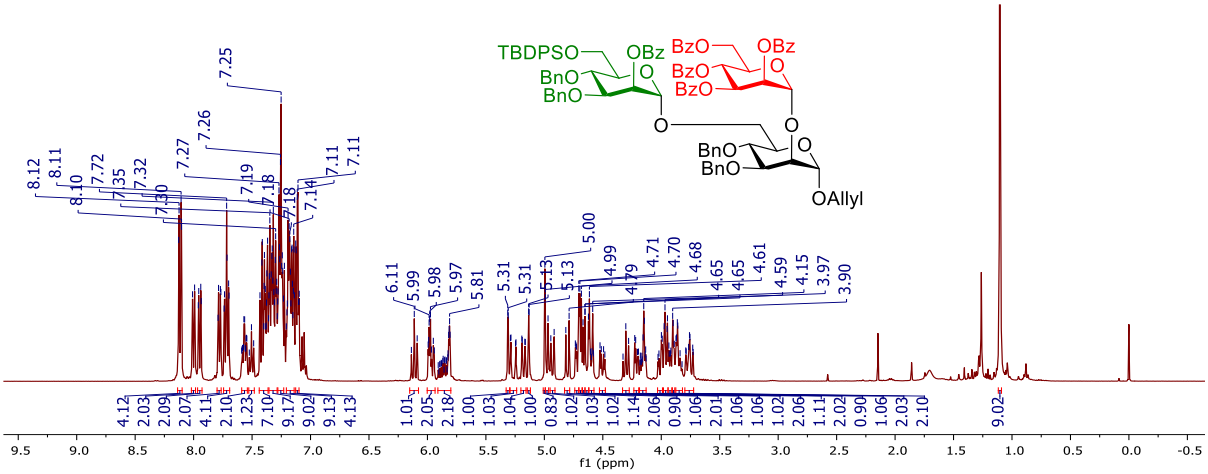

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 37**



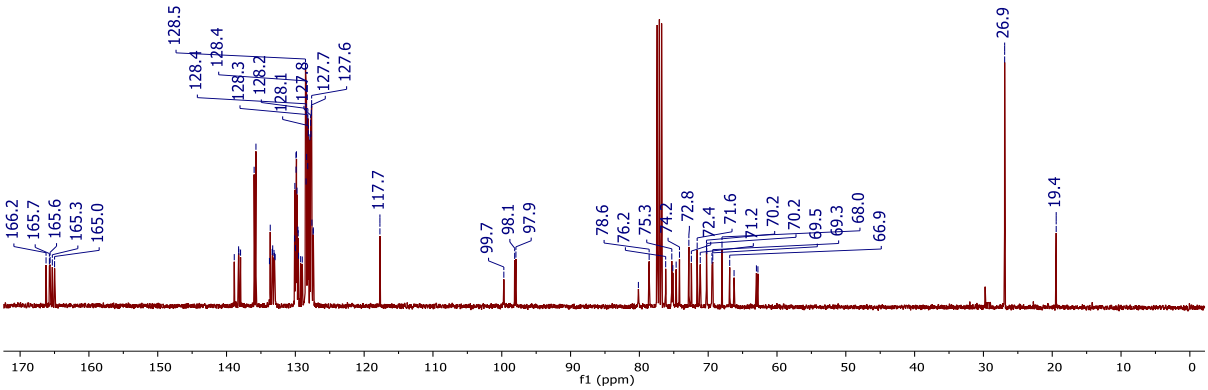

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 37**



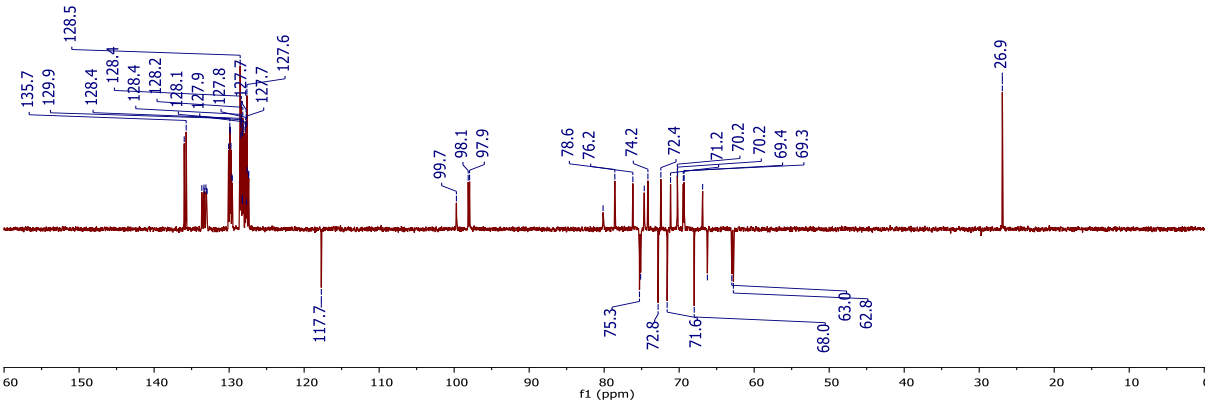
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 38**



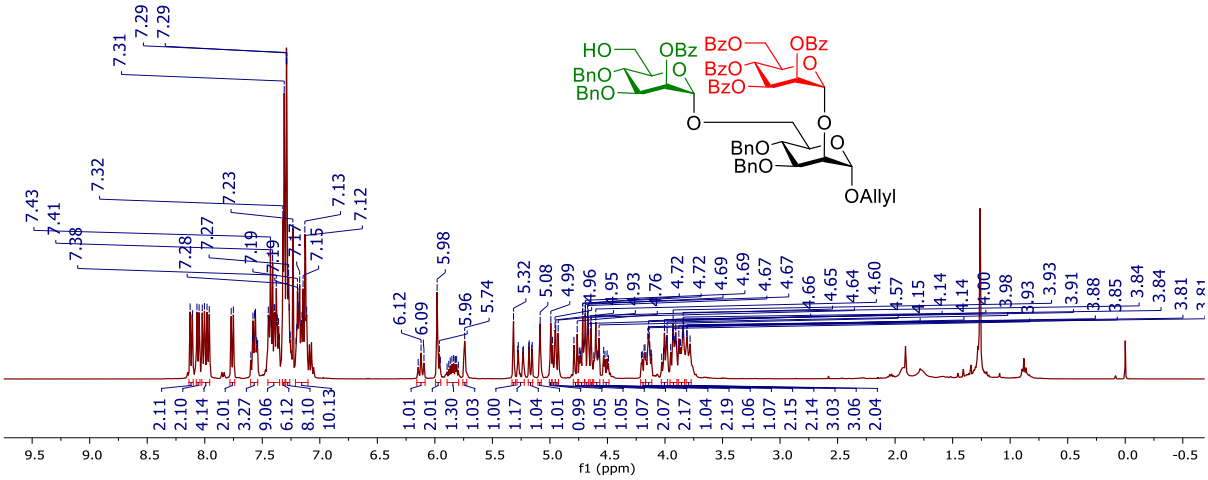

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 38**



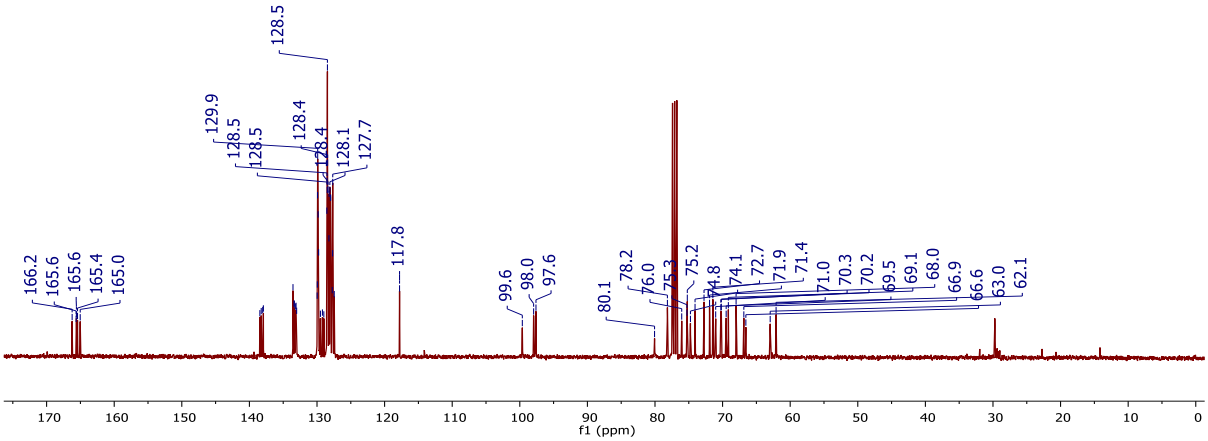

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 38**



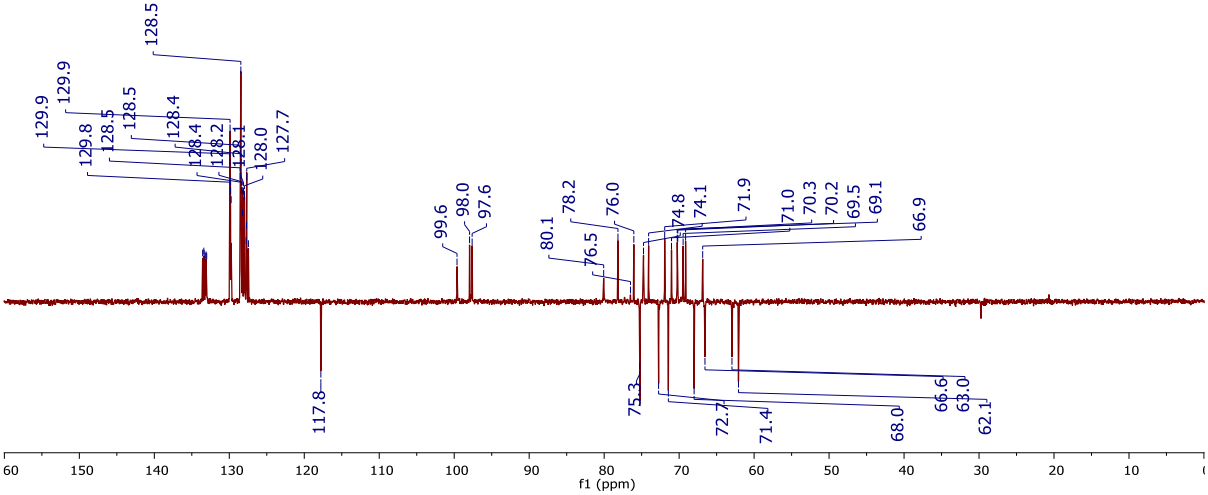
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 39**



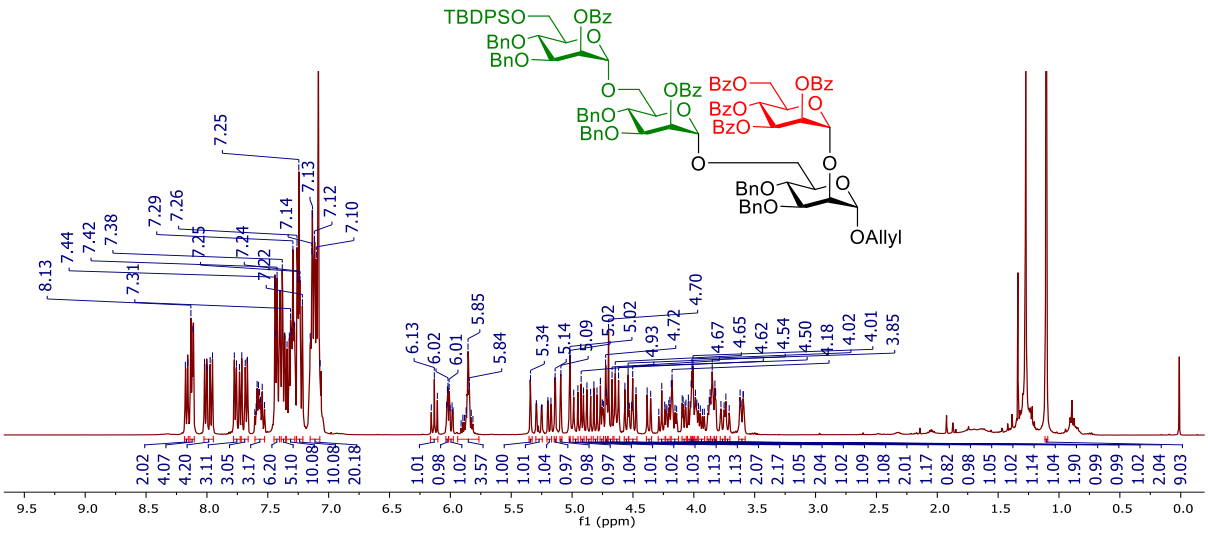

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 39**



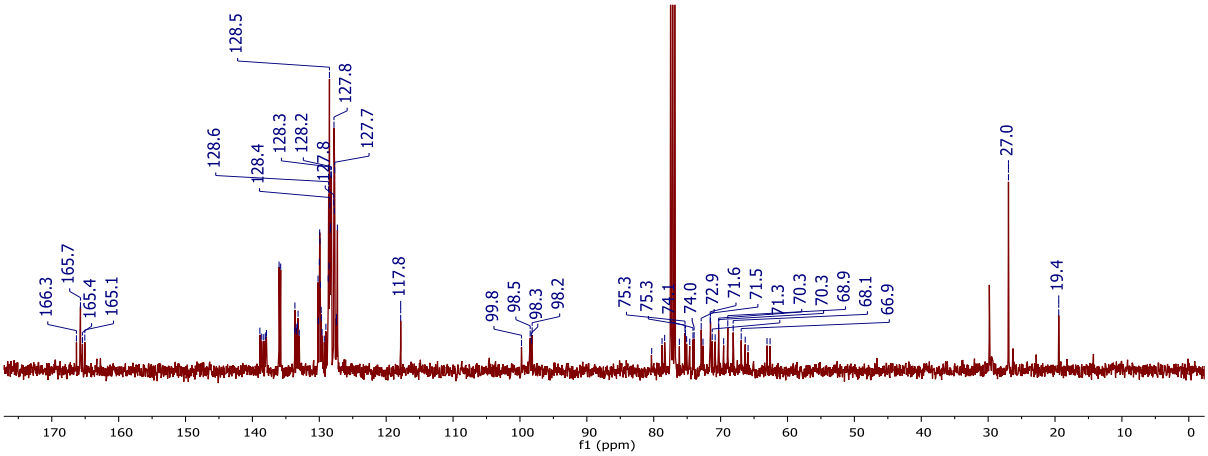

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 39**



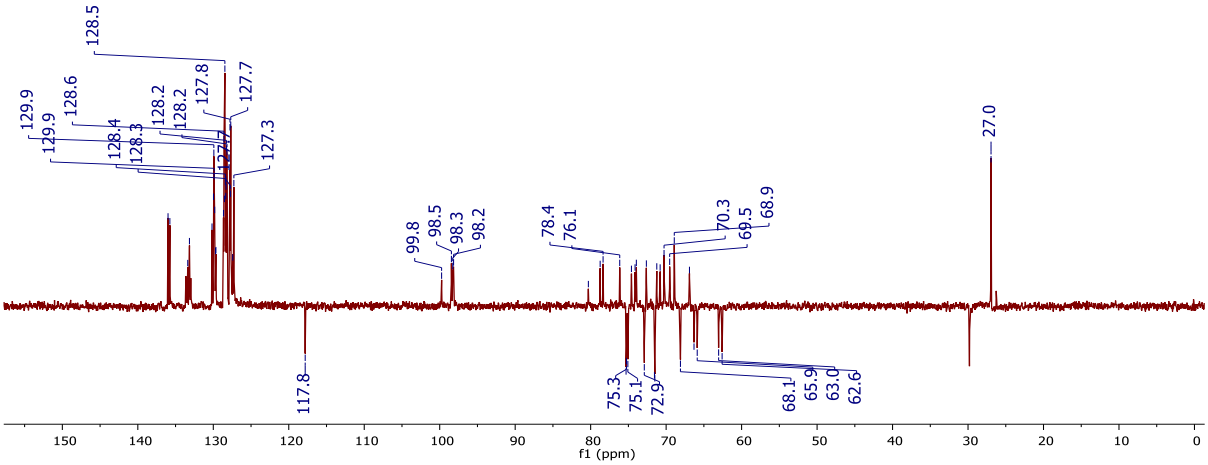
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 40**



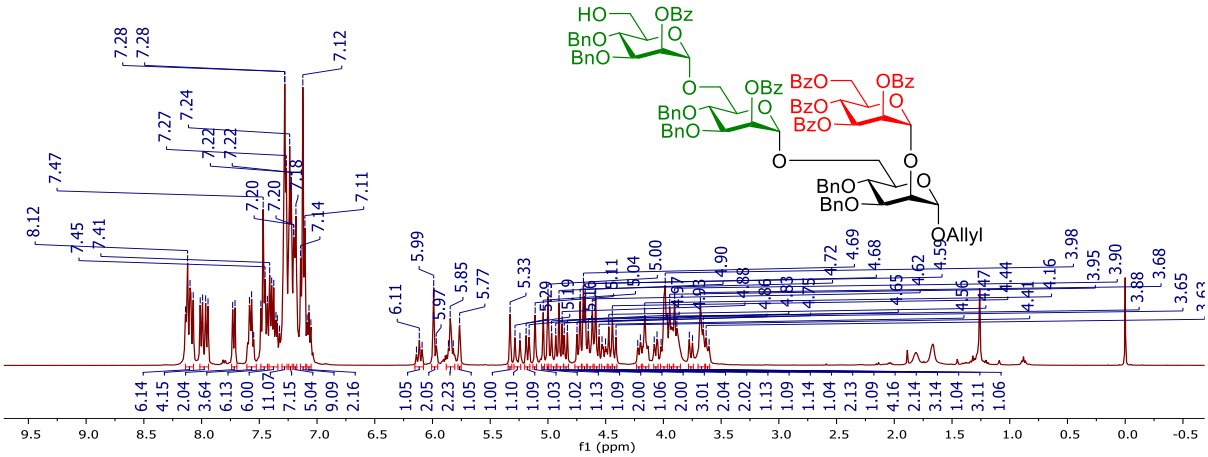

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 40**



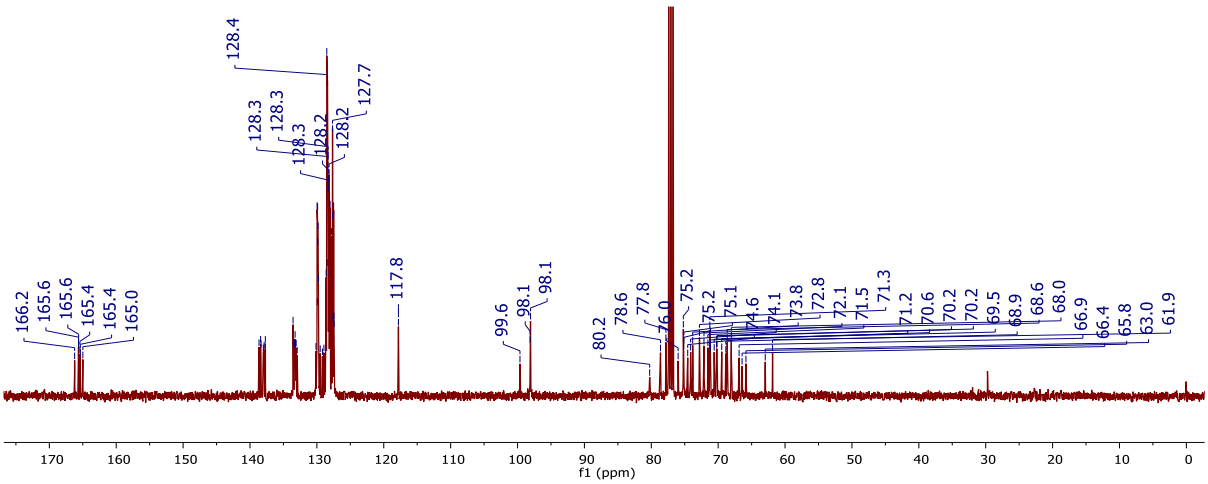

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 40**



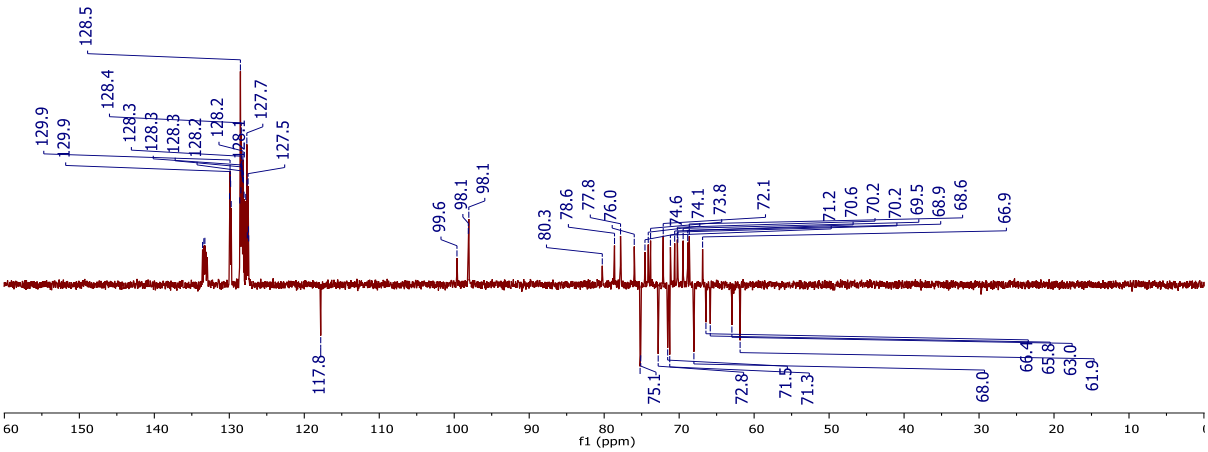
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 41**



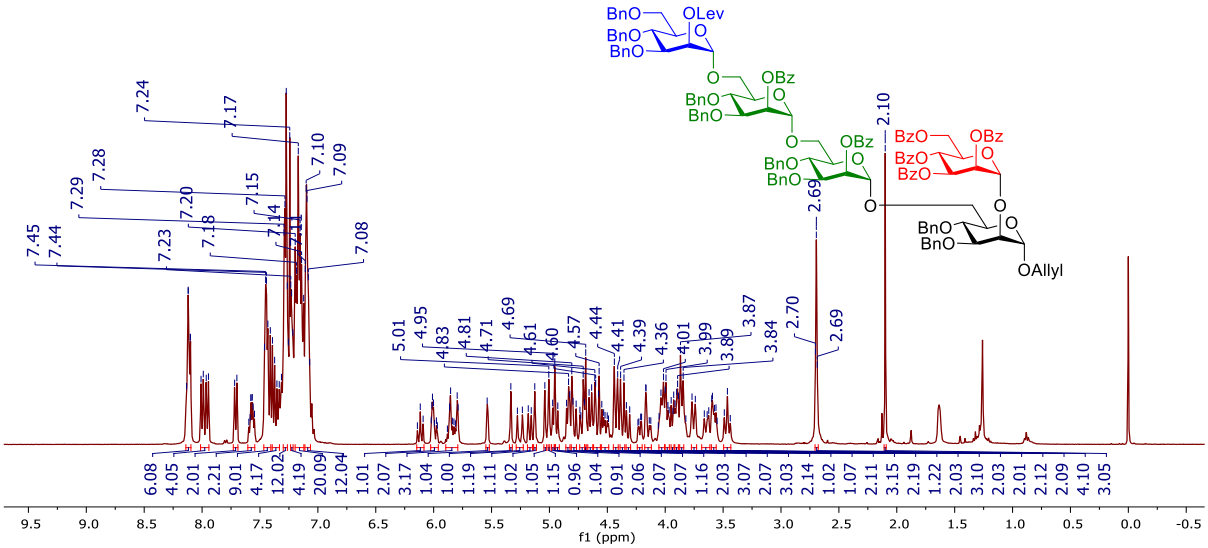

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 41**



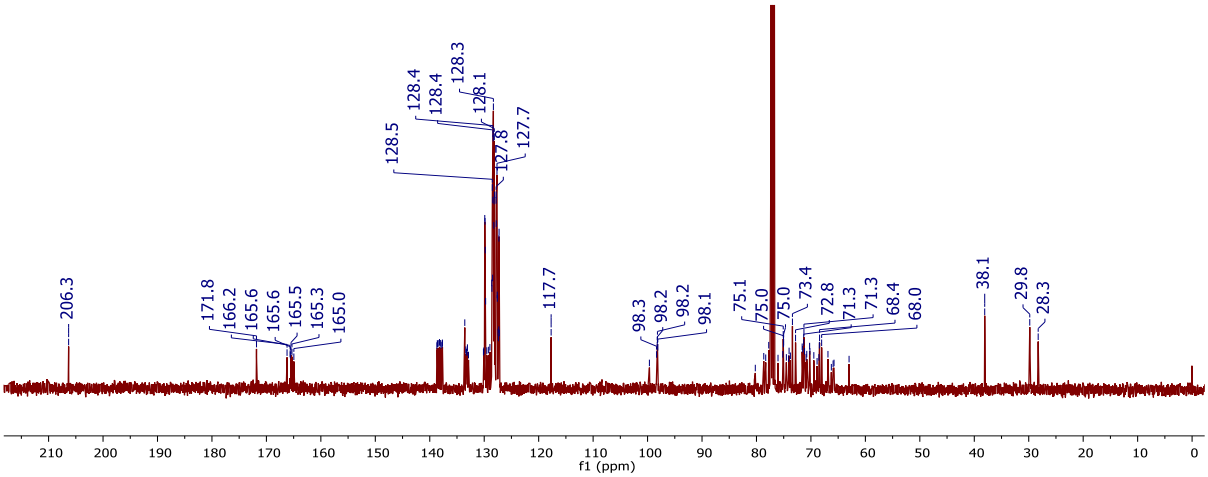

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 41**



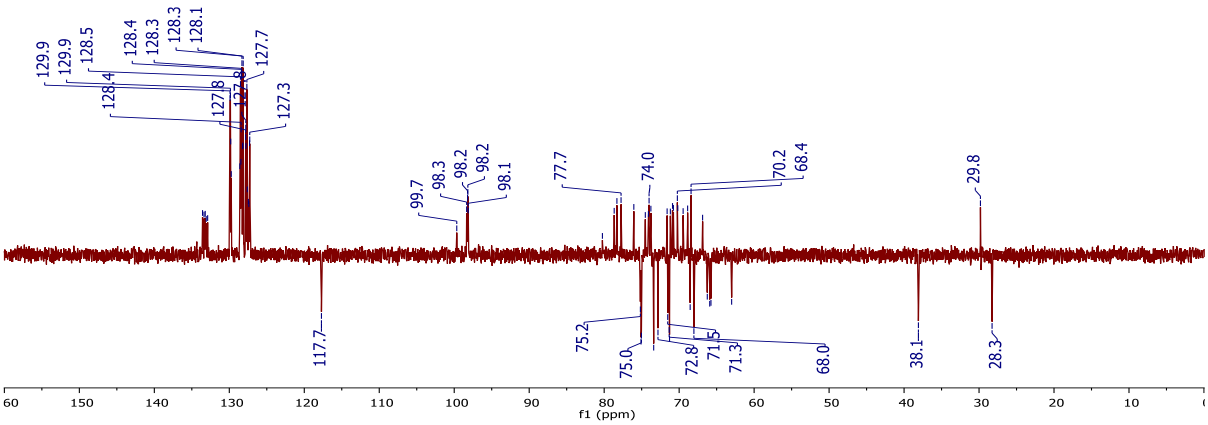
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 42**



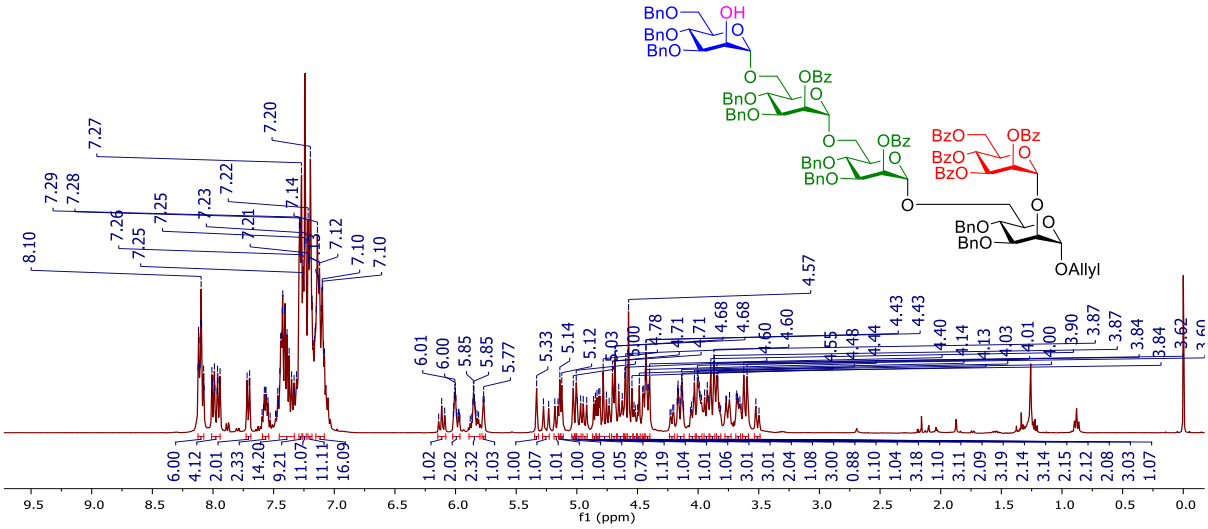

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 42**



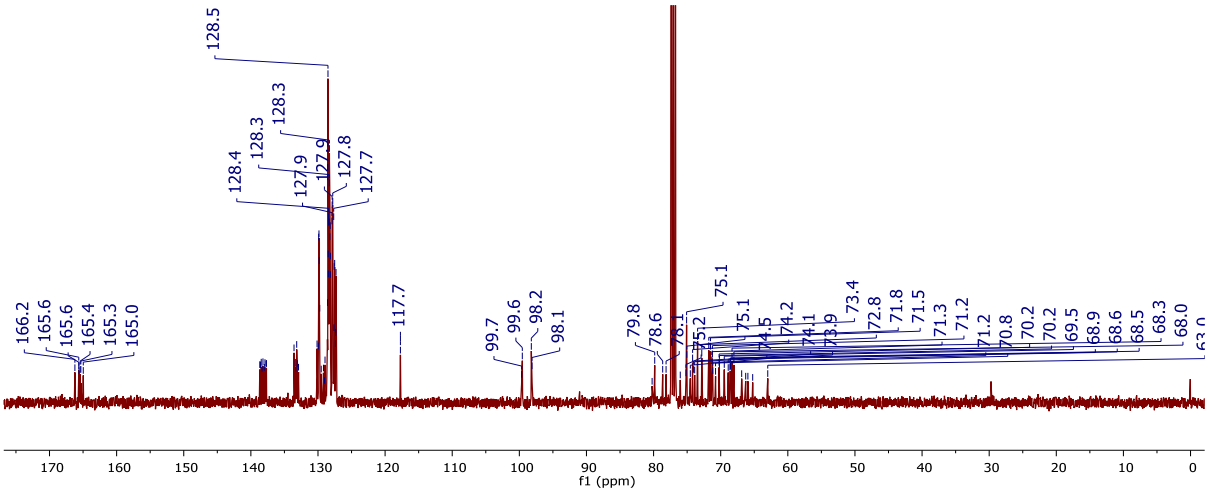

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 42**



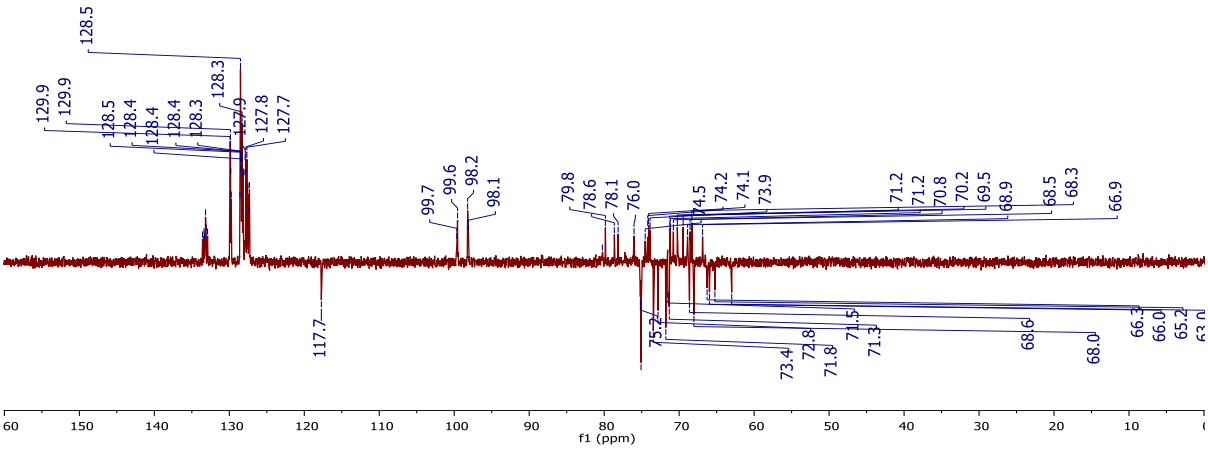
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 43**



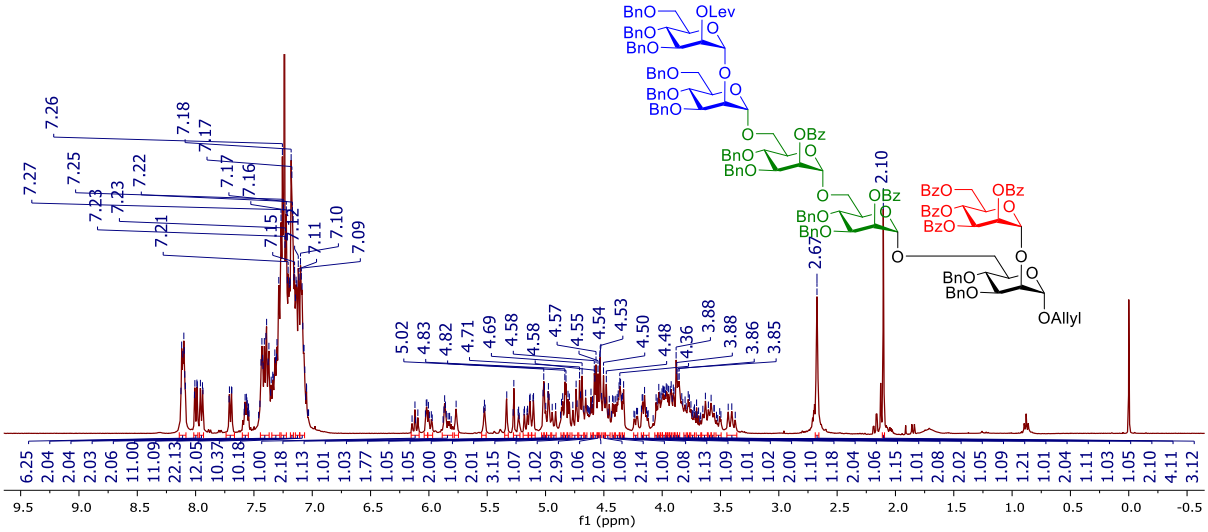

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 43**



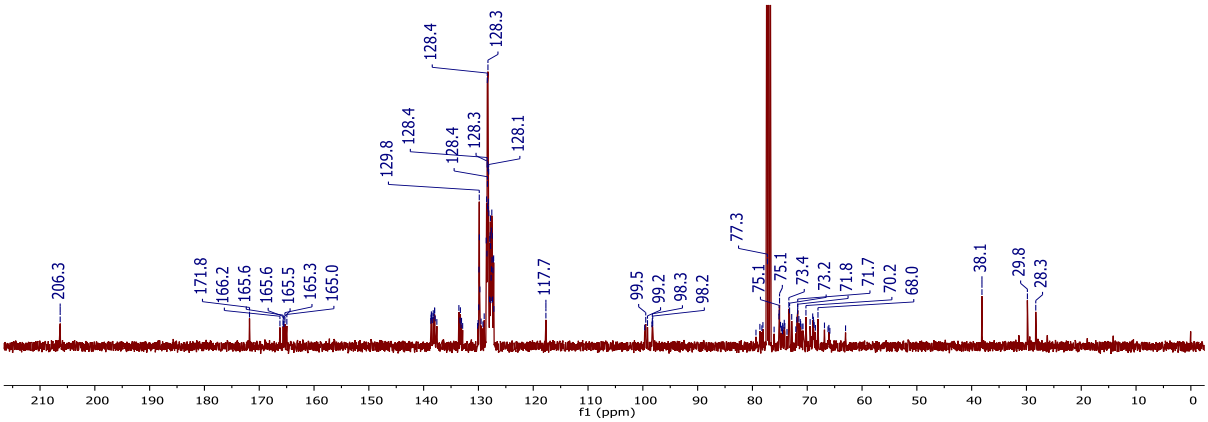

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 43**



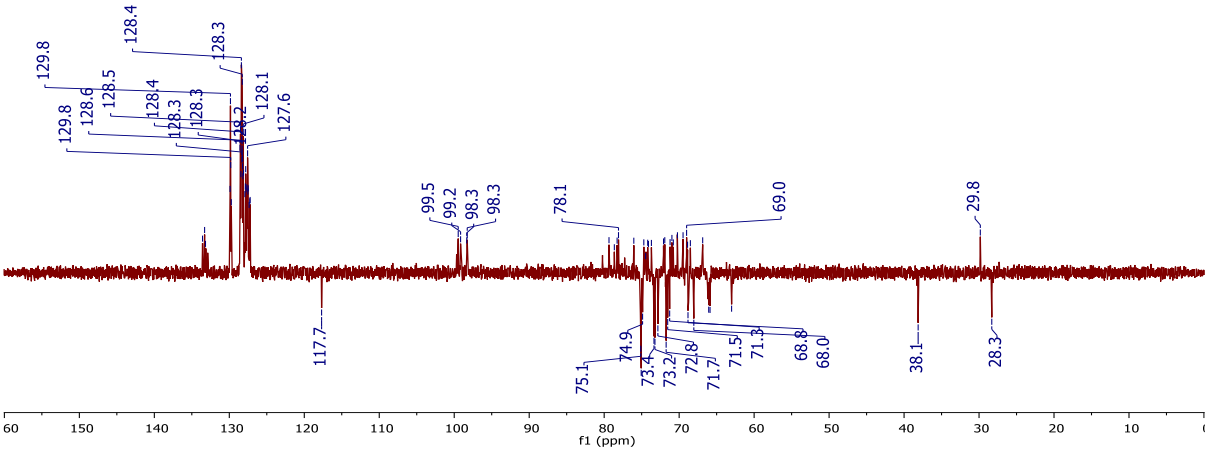
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 44**



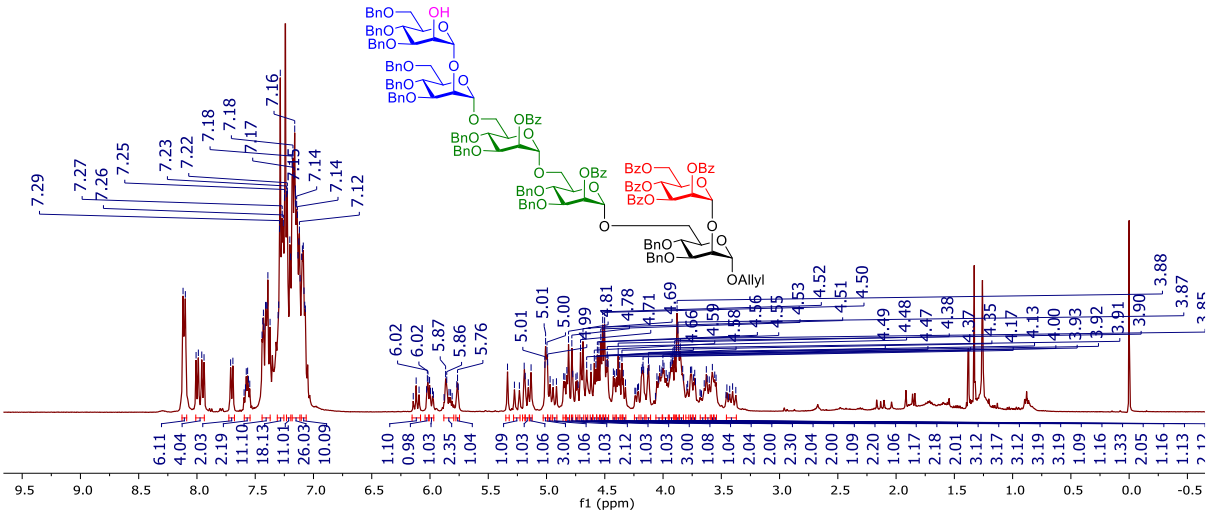

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 44**



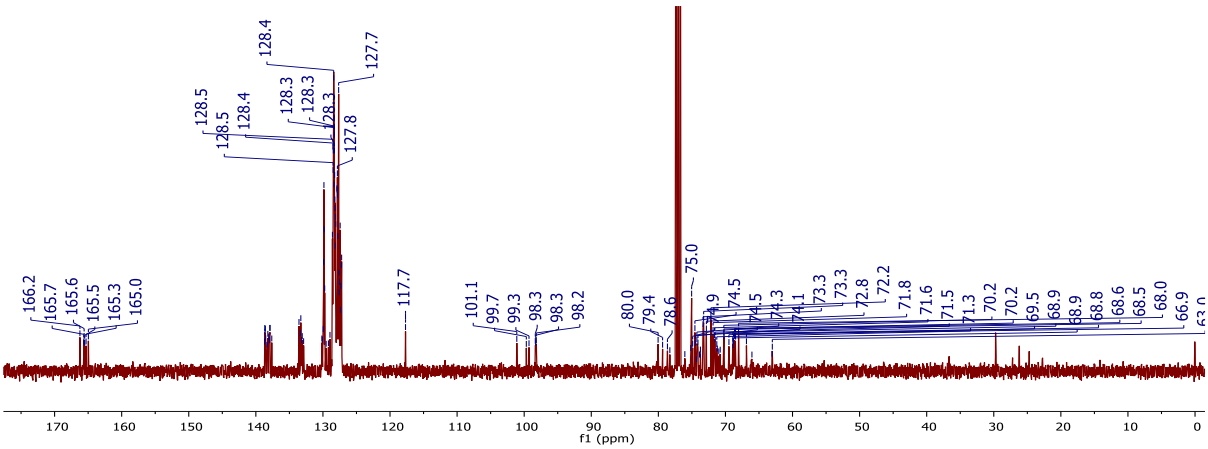

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 44**



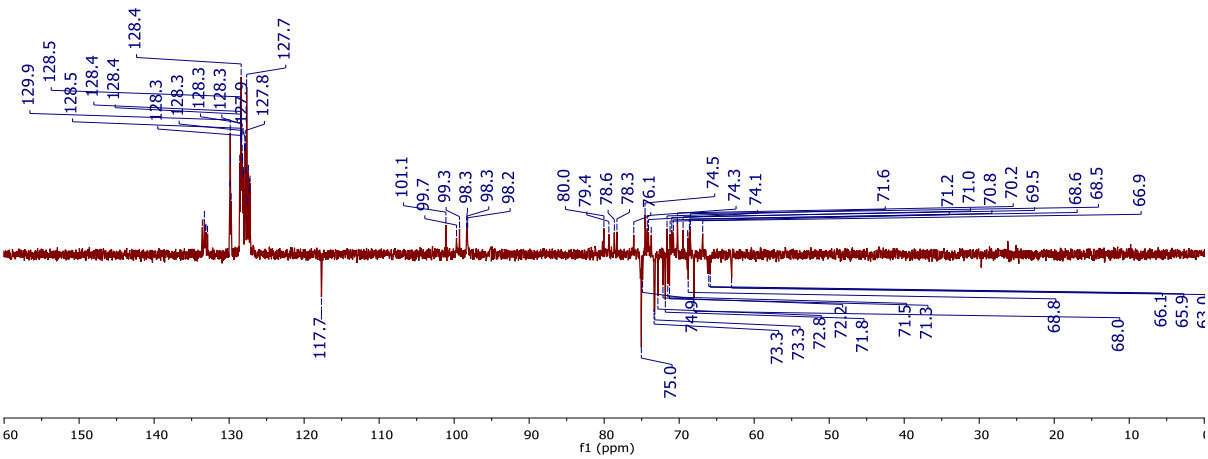
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 45**



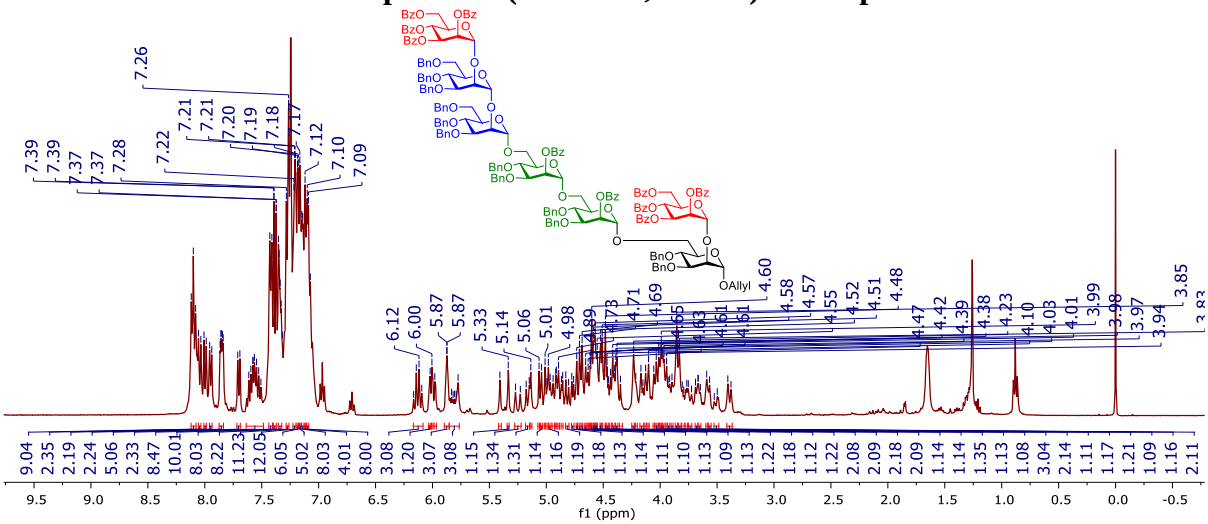

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 45**



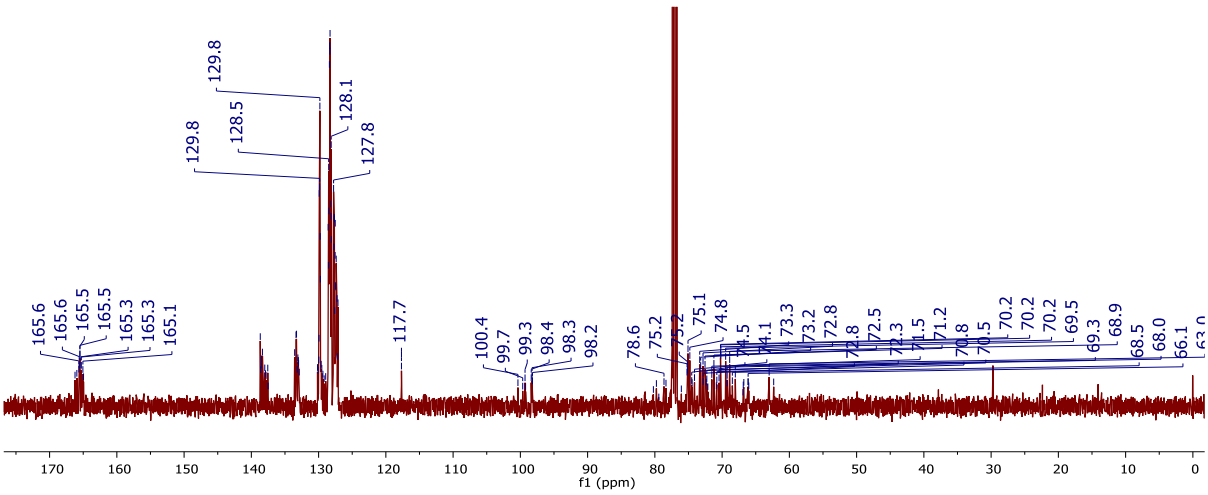

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 45**



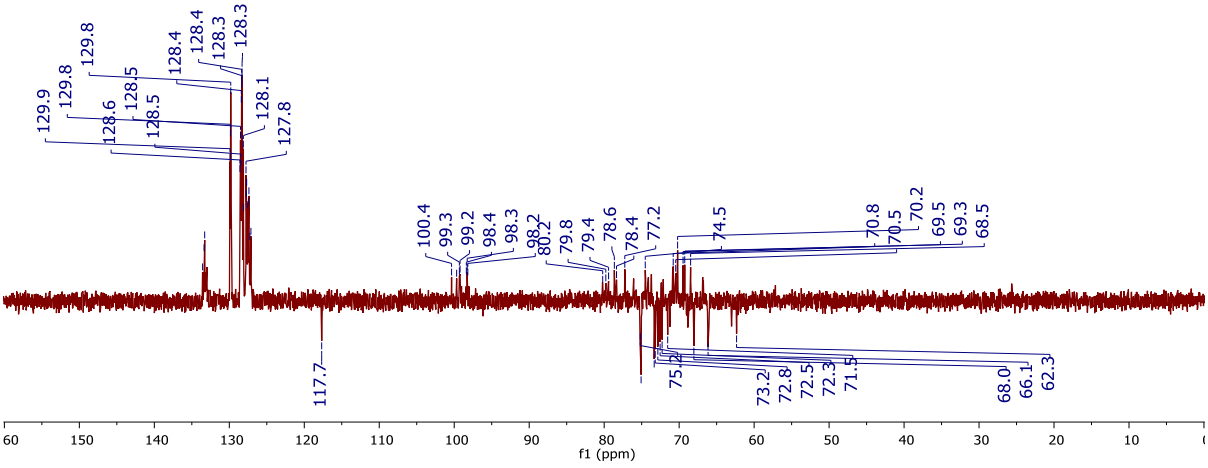
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 2**



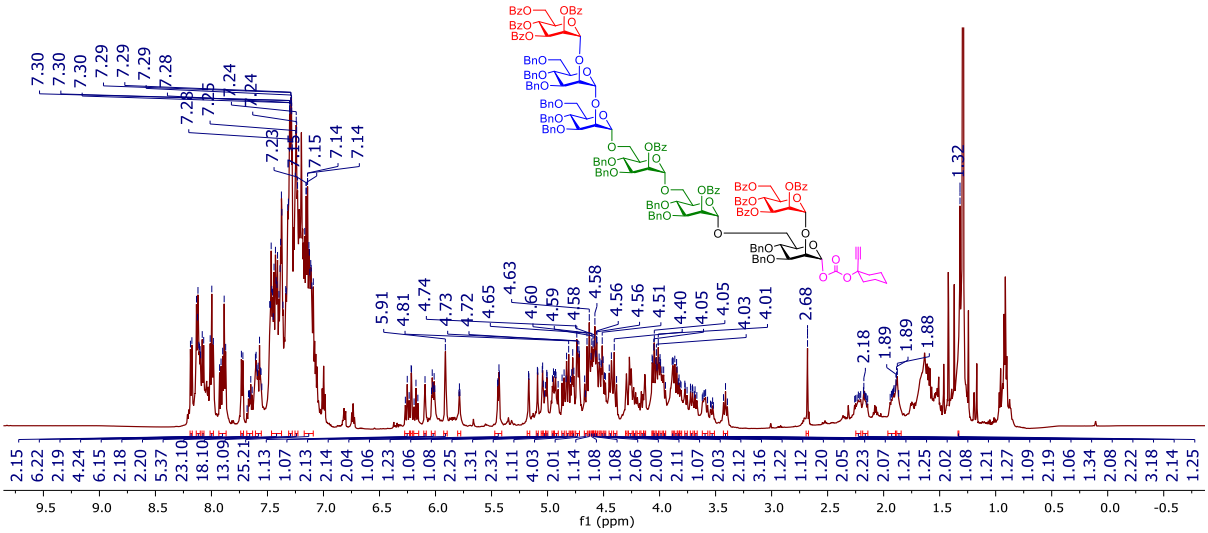

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 2**



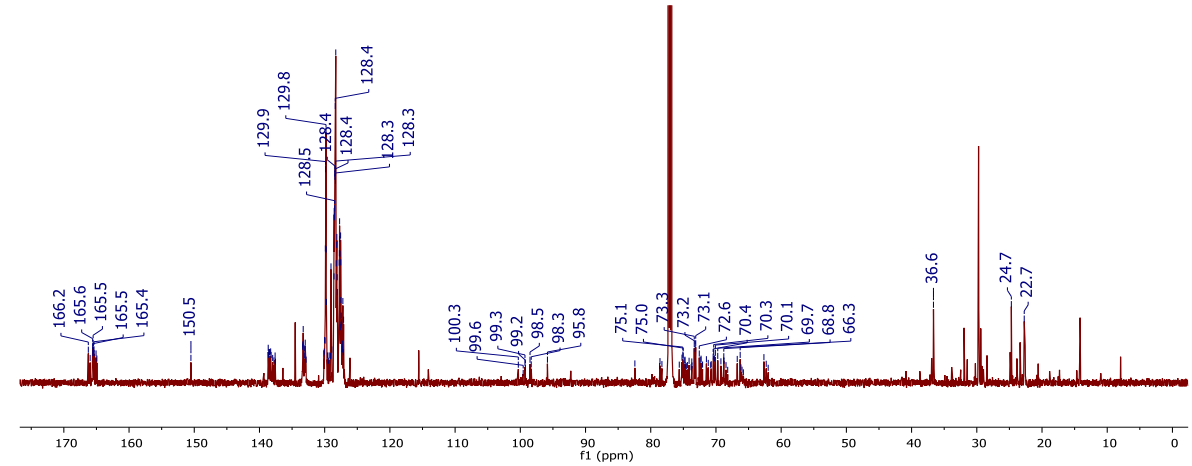

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 2**



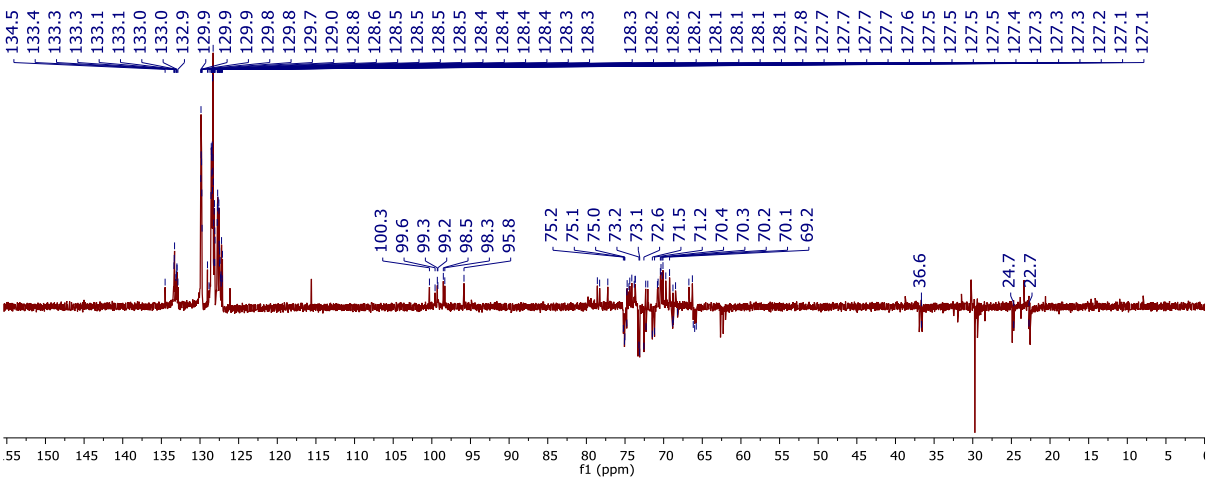
**$^{1}$H NMR Spectrum (600.40Hz, $CDCl_3$) of compound 46**



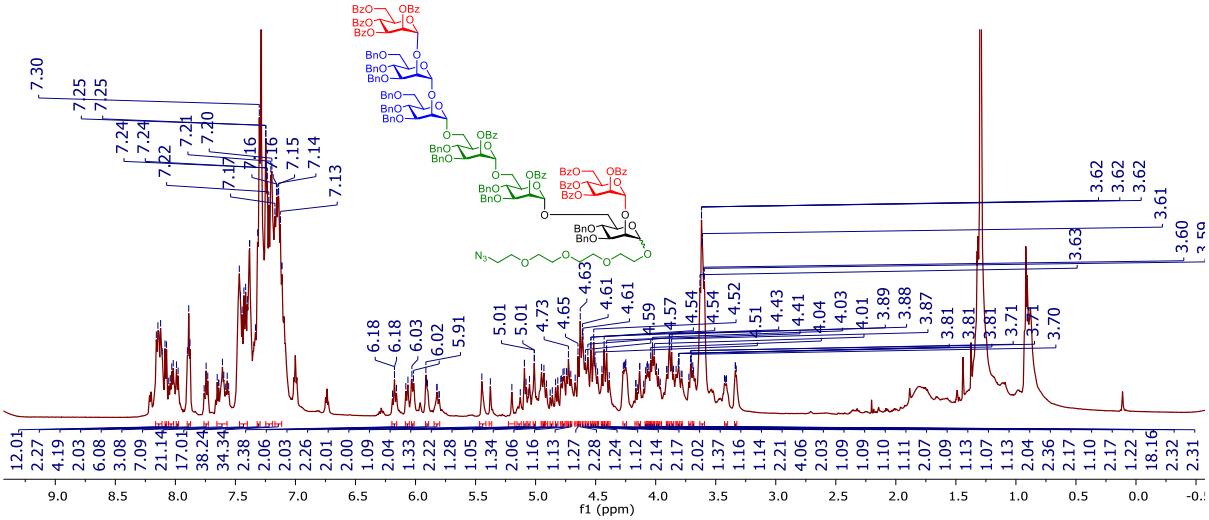

**$^{13}$C NMR Spectrum (150.99Hz, $CDCl_3$) of compound 46**



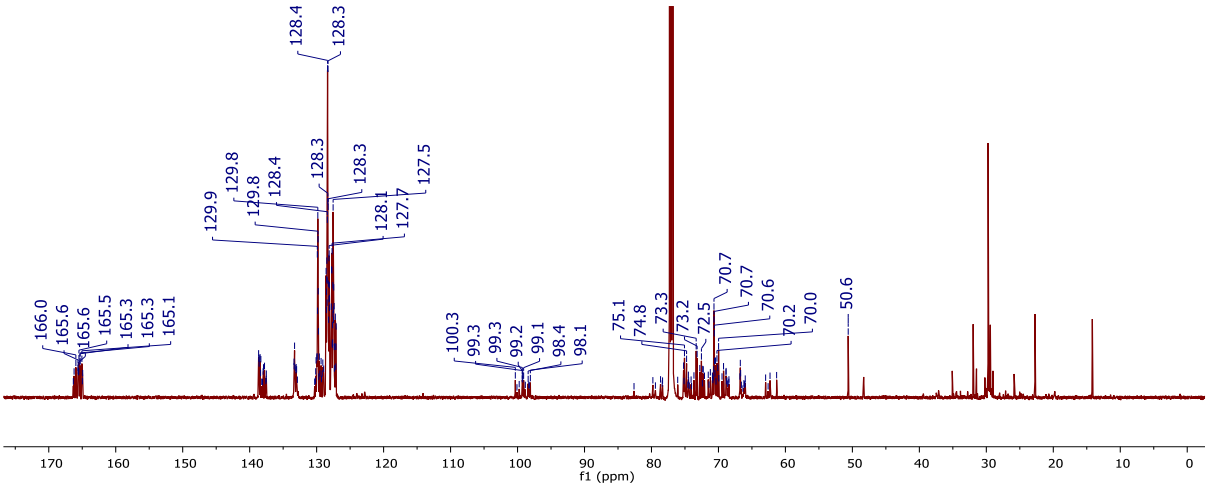

**DEPT NMR Spectrum (150.99Hz, $CDCl_3$) of compound 46**



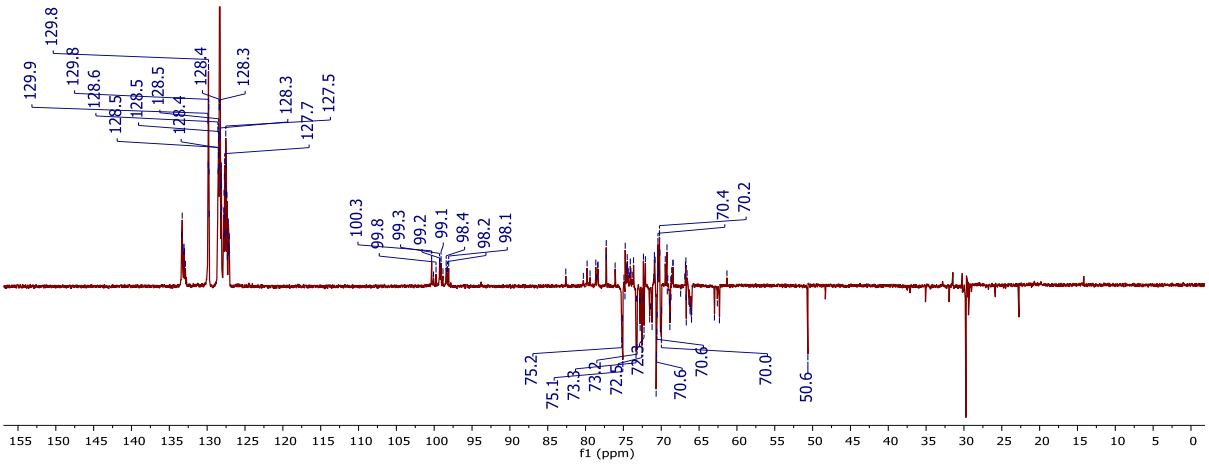
**$^{1}$H NMR Spectrum (600.40Hz, $CDCl_3$) of compound 47**



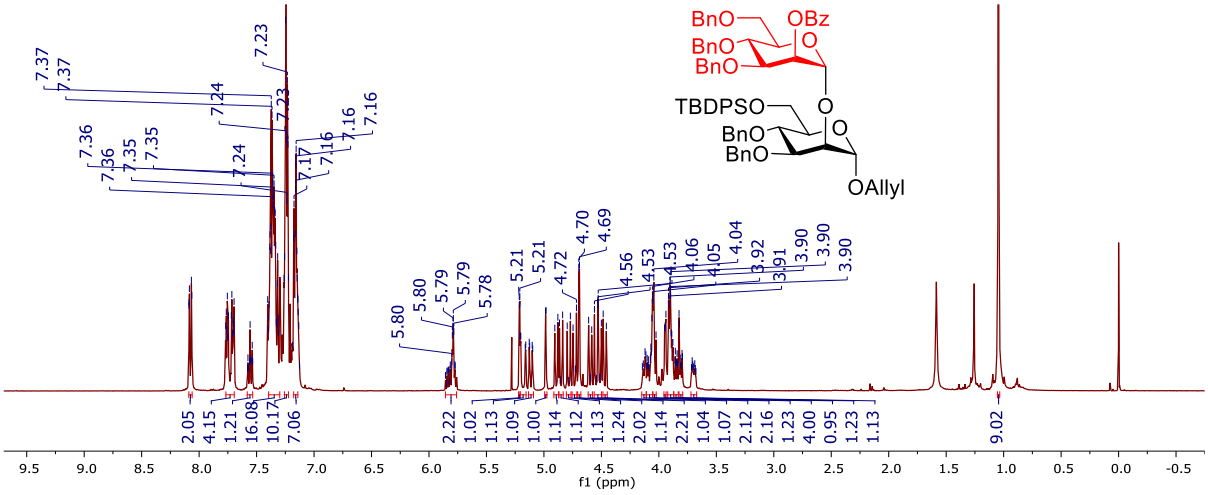
**$^{13}$C NMR Spectrum (150.99Hz, $CDCl_3$) of compound 47**



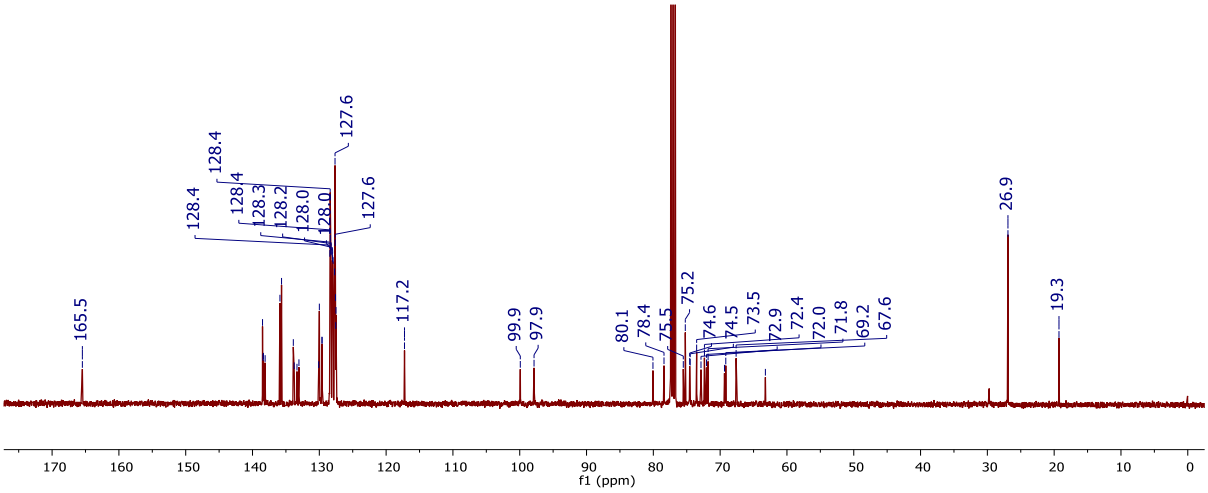
**DEPT NMR Spectrum (150.99Hz, $CDCl_3$) of compound 47**



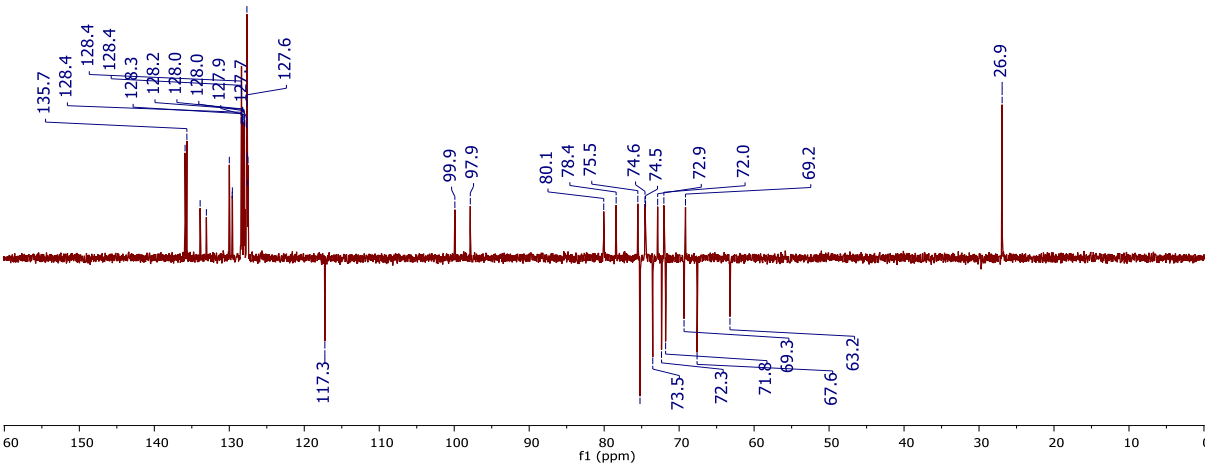
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 29**



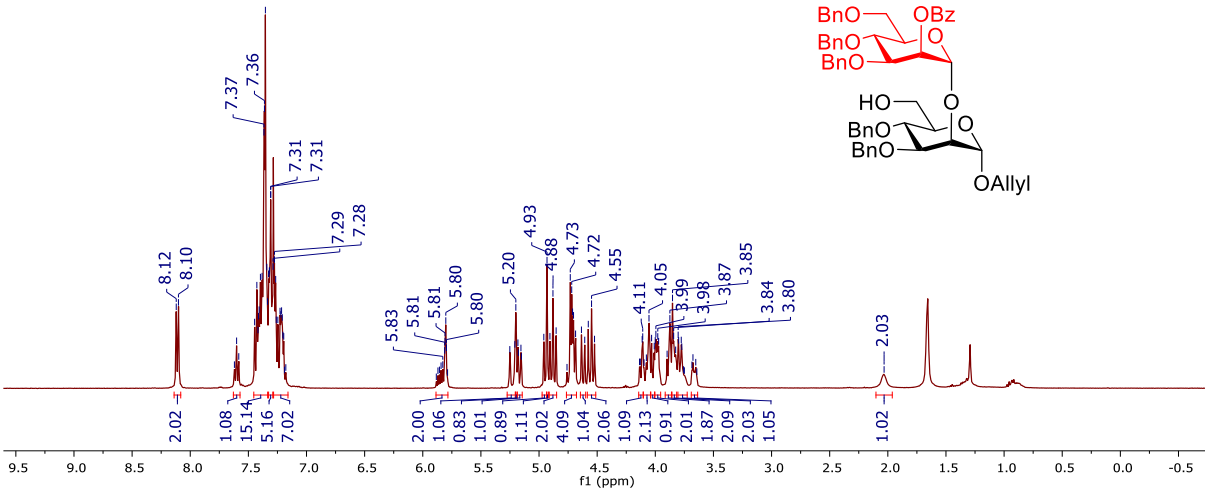

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 29**



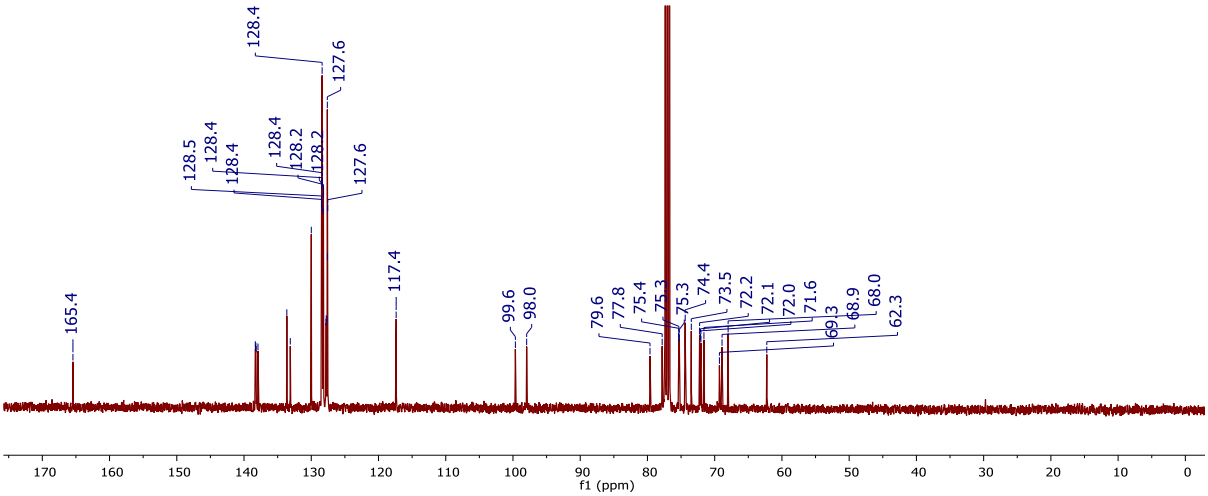

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 29**



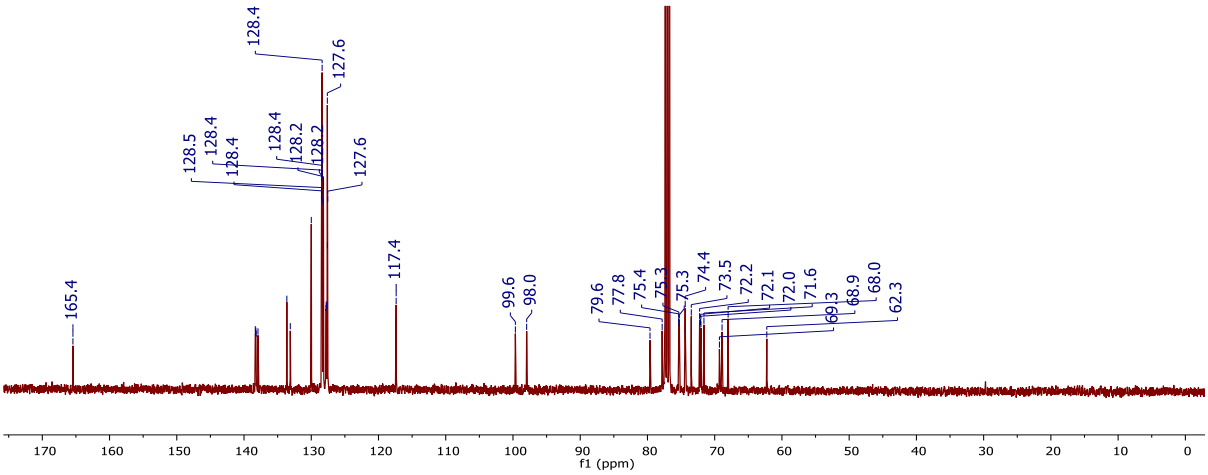
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 30**



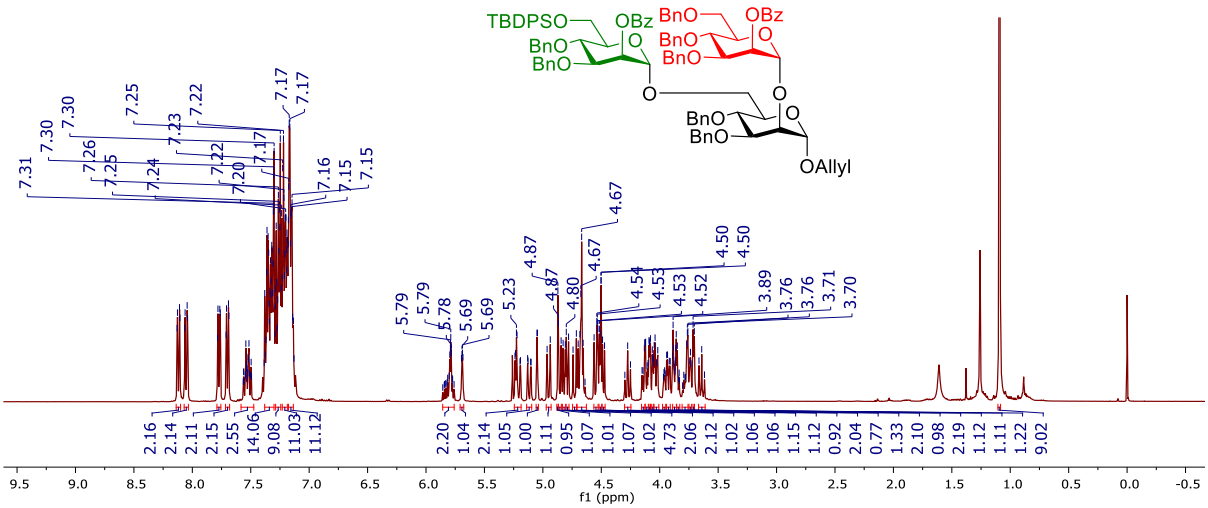

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 30**



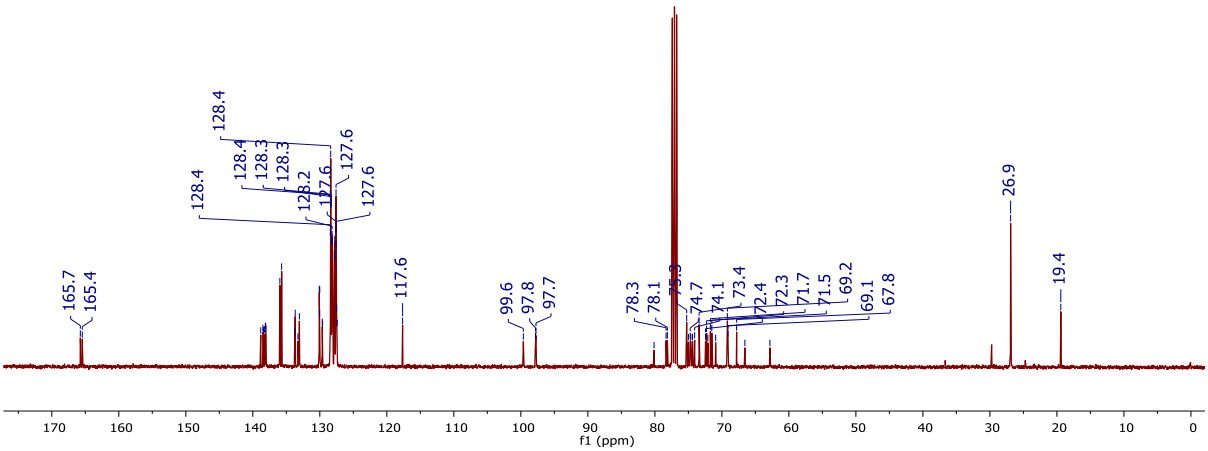

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 30**



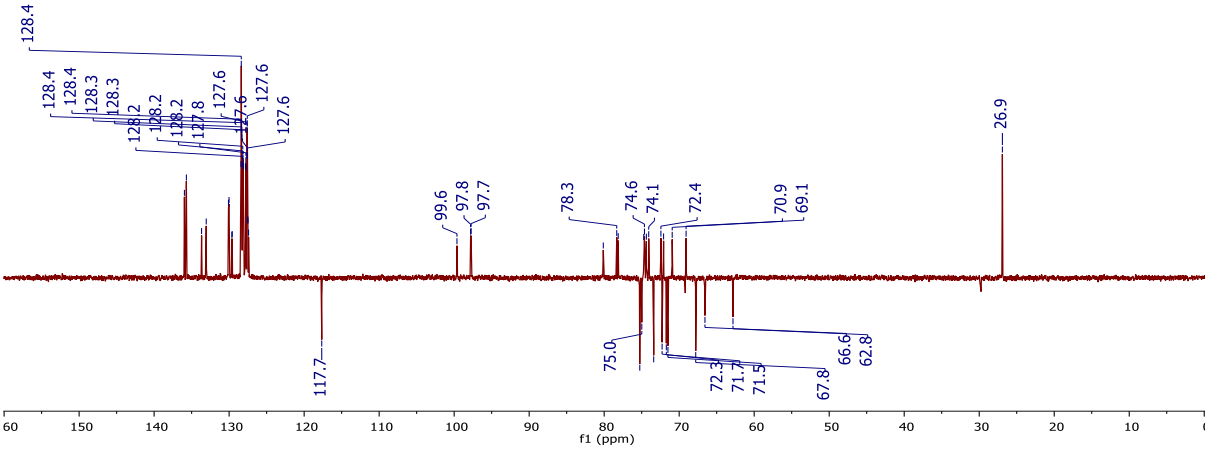
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 31**



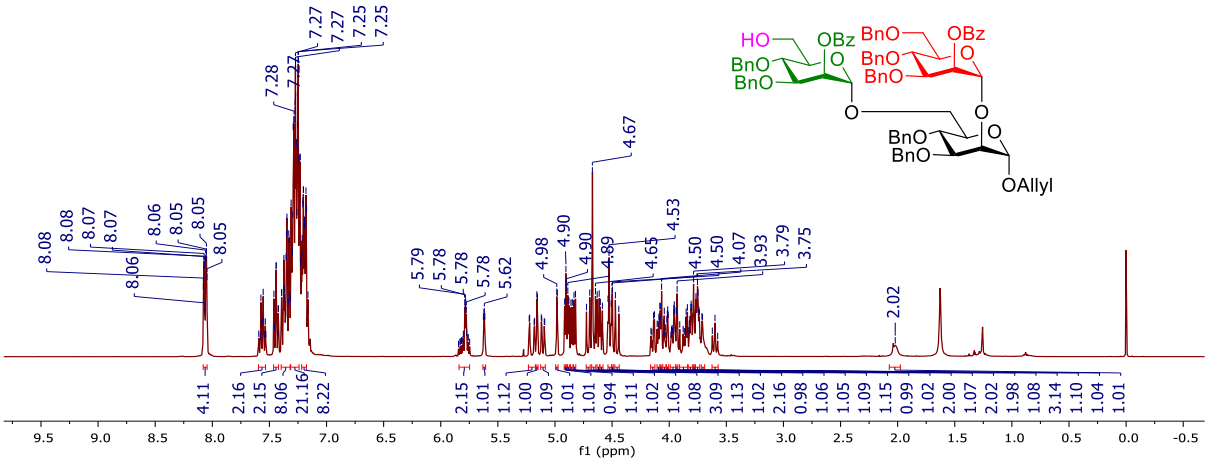

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 31**



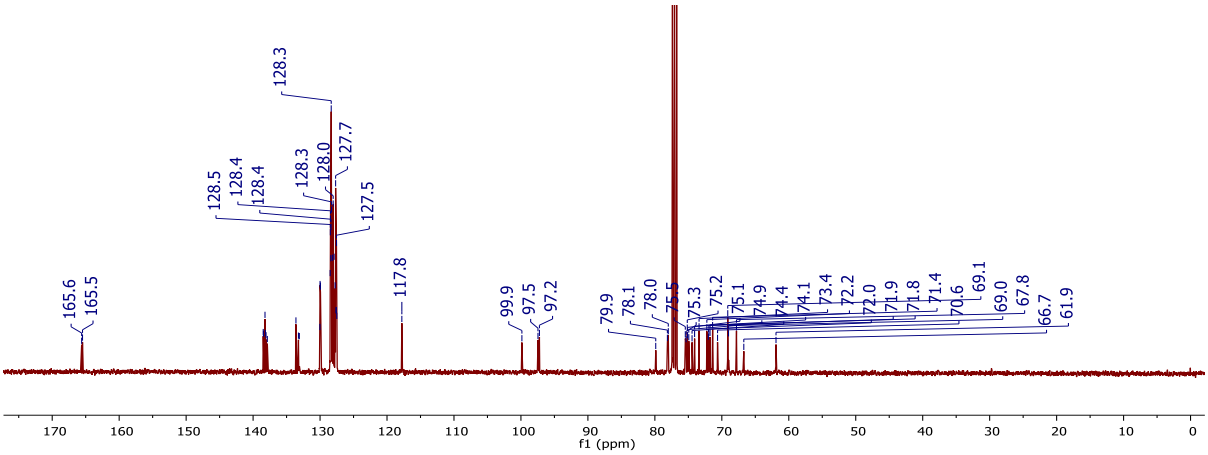

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 31**



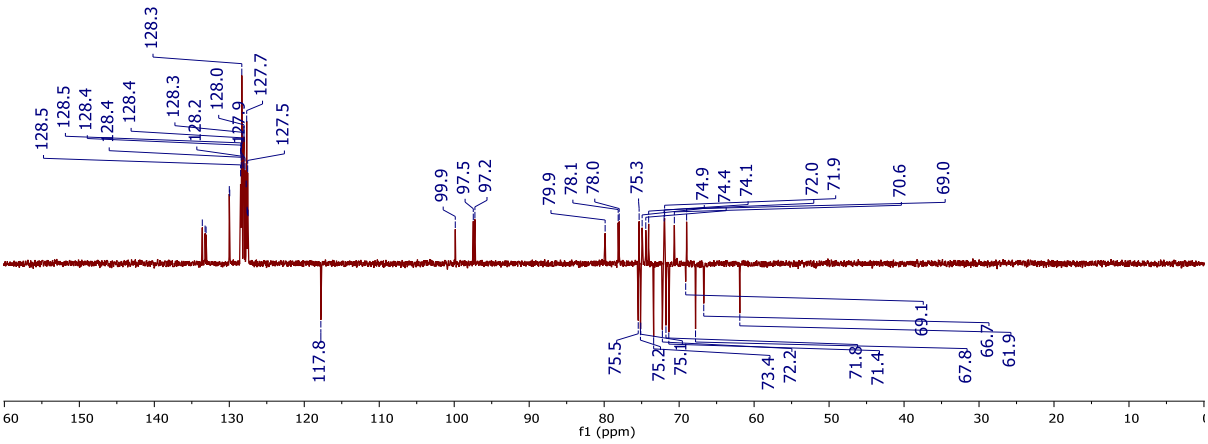
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 32**



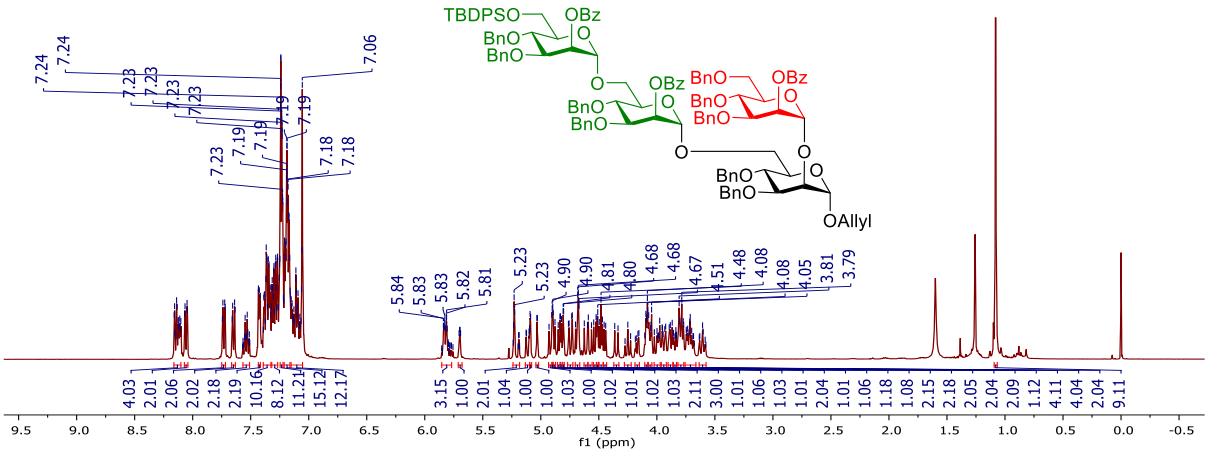

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 32**



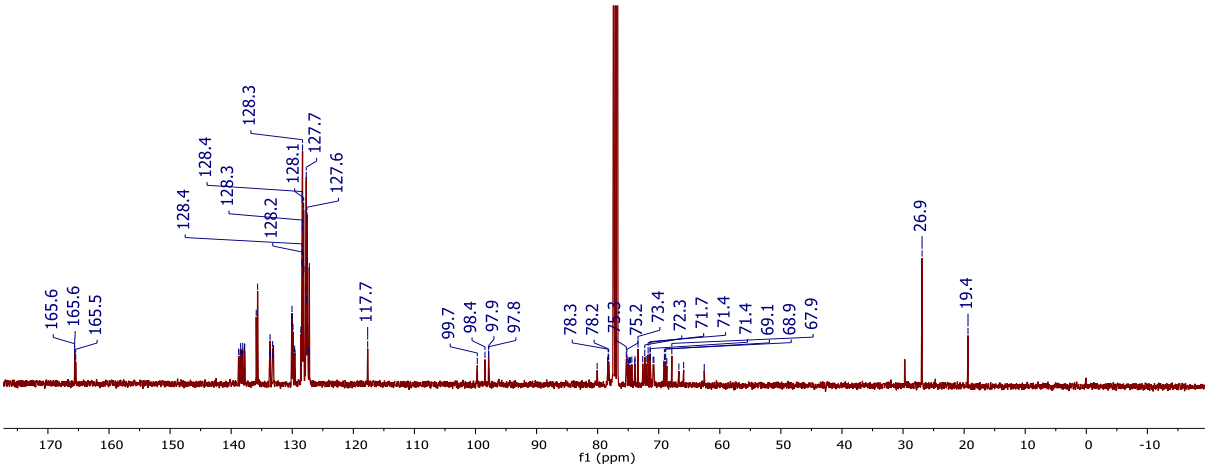

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 32**



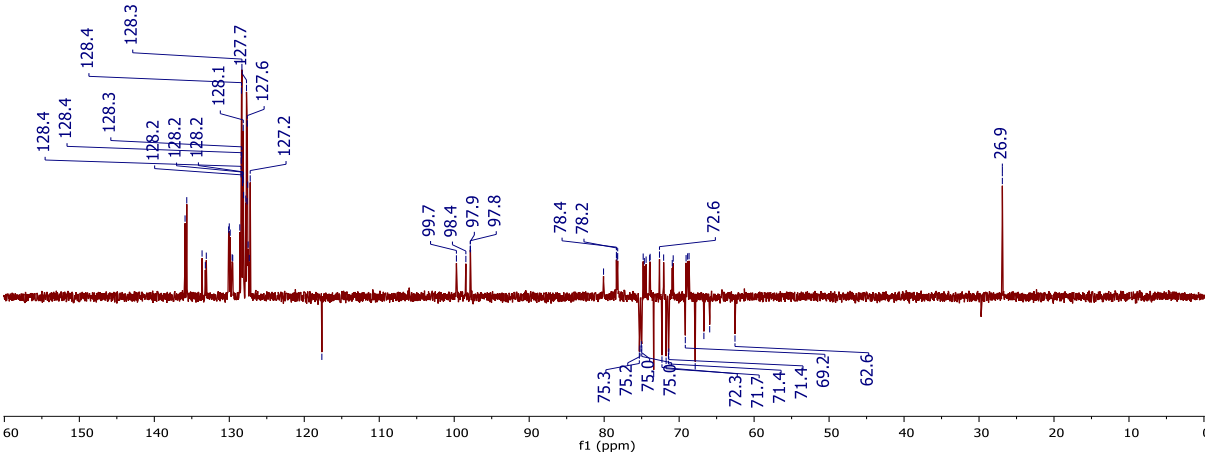
**$^{1}$H NMR Spectrum (400.31Hz, $CDCl_3$) of compound 33**



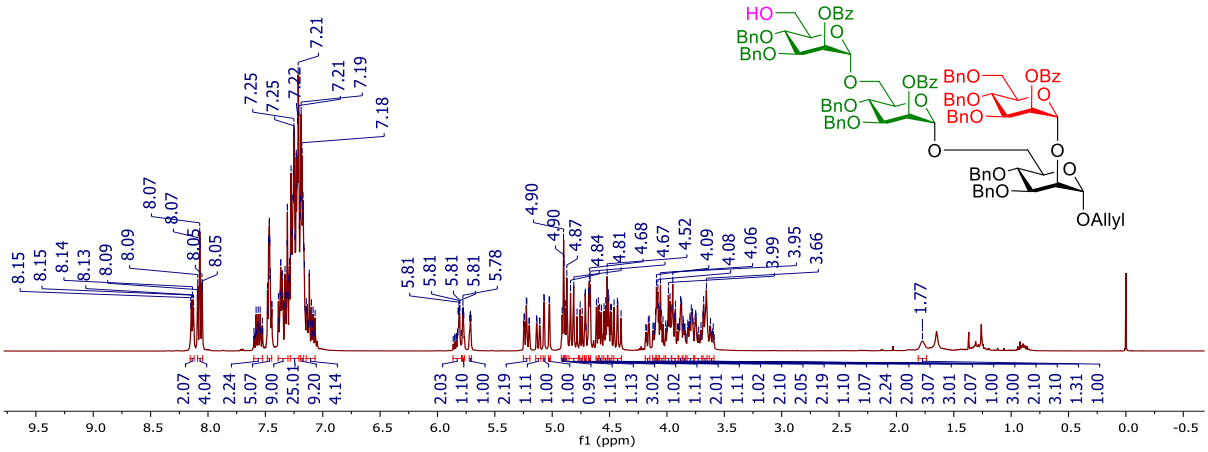

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 33**



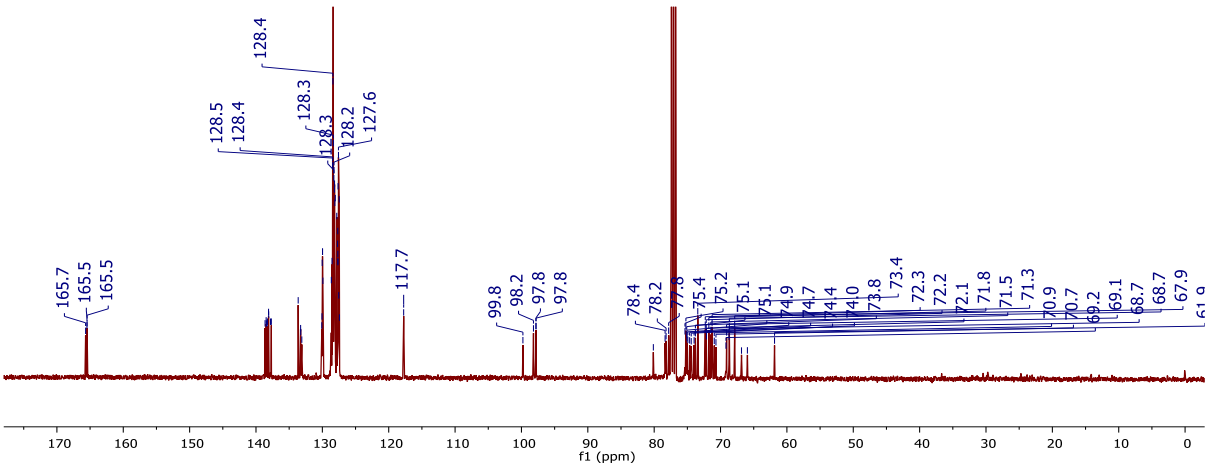

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 33**



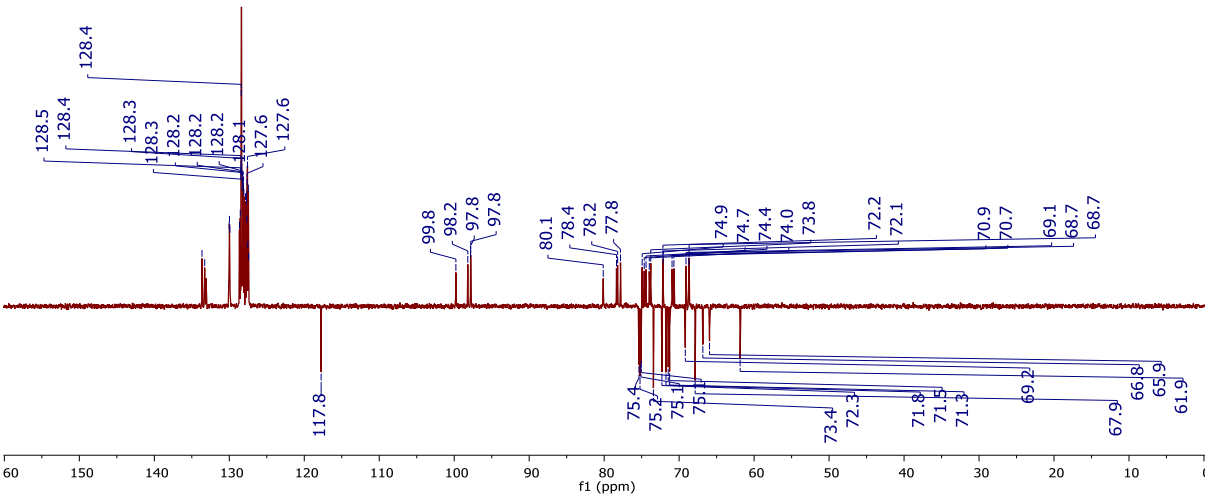

**$^{1}$H NMR Spectrum (400.31 Hz, $CDCl_3$) of compound 34**



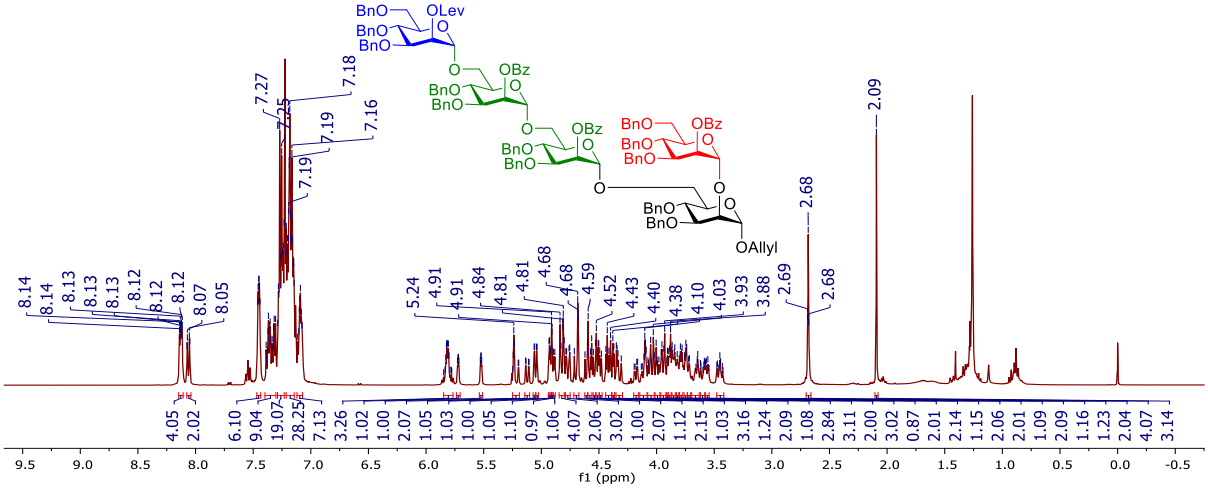

**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 34**



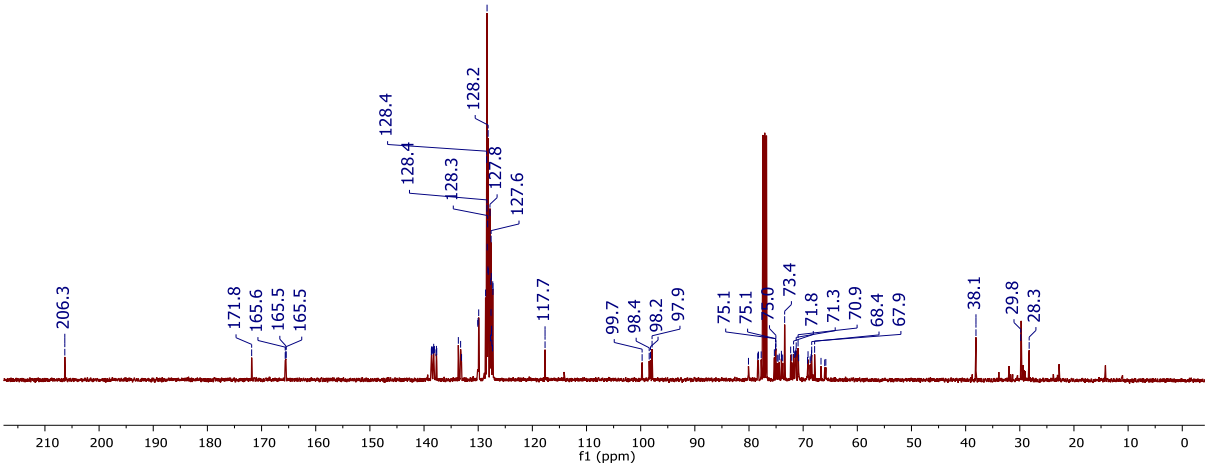

**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 34**



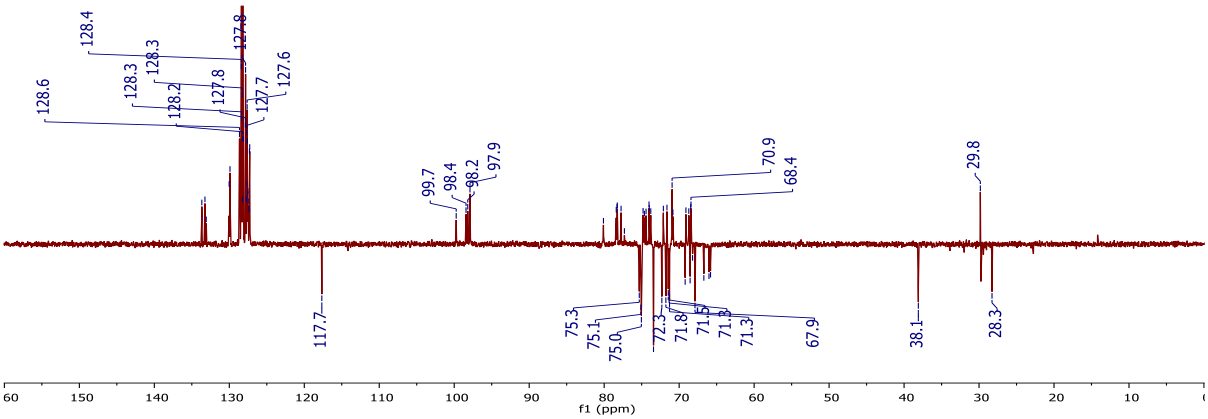
**$^{1}$H NMR Spectrum (400.31 Hz, $CDCl_3$) of compound 35**




**$^{13}$C NMR Spectrum (100.67Hz, $CDCl_3$) of compound 35**




**DEPT NMR Spectrum (100.67Hz, $CDCl_3$) of compound 35**



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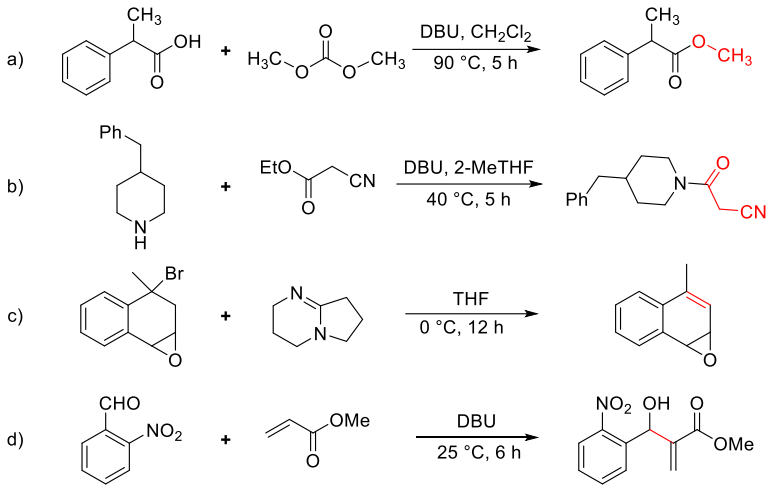
# Chapter 3A

## *p*-Nitrophenyl Carbonates Promote the Nucleophilic Ring Opening of DBU and DBN Affording Lactam Carbamates

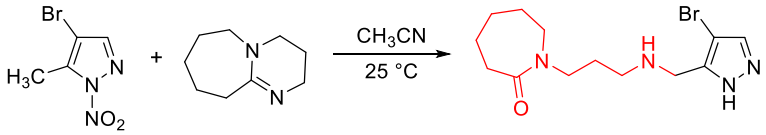
# Chapter-3A

## 3A.1 Introduction

There are various organic bases, among them amidines e.g DBN (1,5-diazabicyclo[4,3,0]non-5-ene and DBU (1,8-diazobicyclo[5,4,0]undec-7-ene) contain an imino group that is attached to the α-carbon of the amines. These are synthetically useful as well as strong neutral bases and are shown to catalyse various organic reactions such as carbonylation (Scheme 3.1a)[1], amidations (Scheme 3.1b)[2], dehydrohalogenations (Scheme 3.1c)[3] and Baylis-Hillman reactions (Scheme 3.1d).[4] Numerous example that these bicyclic amidines shows the potential to act as C and N nucleophiles as these amidines (DBU & DBN) are thought to be non-nucleophilic bases in nature,[5-8] (Scheme 3.2).

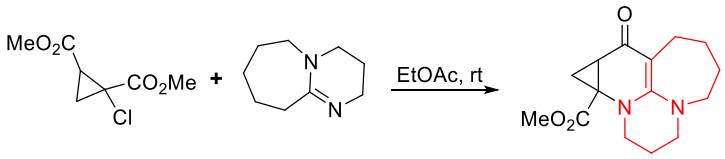



Scheme 3.1. DBU and DBU catalysed organic transformations



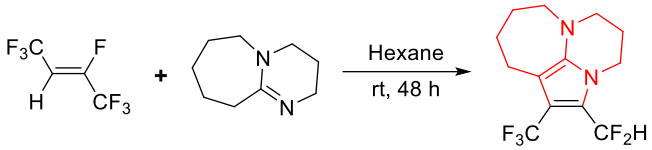

Scheme 3.2. Nucleophilic addition of DBN to pyrrole substrate

McCoy and MaI in 1981 reported for the first time the formation of unusual tetracyclic dihydropyridin-4-one using excess DBU during dehydrohalogenation of dimethyl 1-chloro-3-methyl cyclopropane-1,2-dicarboxylate (Scheme 3.3).[9]



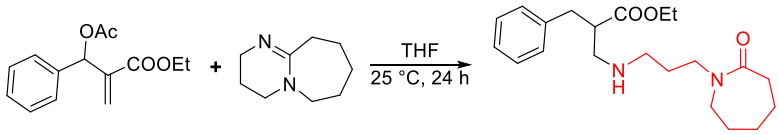

Scheme 3.3. Formation of tetracyclic dihydropyridine-4-one structure

Bertrand and co-workers in 1993, reported the nucleophilic nature towards halo derivatives of main group elements with DBN and DBU wherein bicyclic rings of DBN and DBU remain unaffected (Scheme 3.4).[10,11]



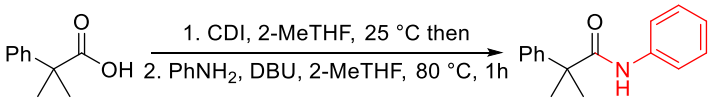

Scheme 3.4. Nucleophilicity of DBU towards halo derivative to form fused pyrrole derivative

Lammers et al. identified the nucleophilicity of amidine bases with 4-halo-3,5-dimethyl-1-nitro-1H-pyrazole in 1994, as well as their subsequent ring opening and lactam derivatives.[12] Following that, Ma and Dolphin isolated chlorin-$\varepsilon_6$ lactams from methyl pheophorbide reaction with DBU and DBN that were aided by trialkyl triflates.[13] In addition to this 1,4-addition of DBU to diarylpyrone gave caprolactam.[14] The Baylis-Hillman acetates also afforded similar caprolactam products with reaction of DBU (Scheme 3.5).[15]



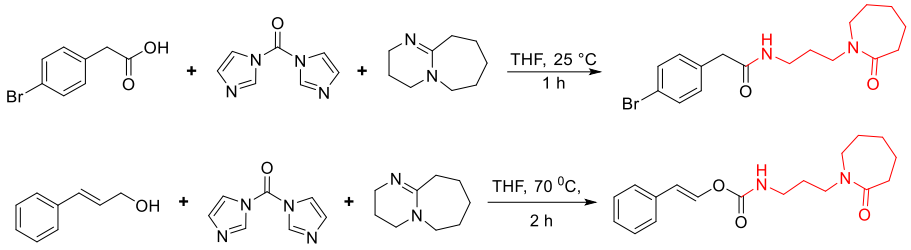

Scheme 3.5. Reaction of DBU with Baylis-Hillman acetates

A detailed examination of these results revealed the nucleophilic nature of the DBU with respect to those specific substrates. Vaidyanathan and co-workers reported amide bond formation between acyl imidazole and amine in presence of DBU (Scheme 3.6).[16]




Scheme 3.6. Amidation catalyzed by DBU

Rajagopal et al. found nucleophilic nature of DBU towards imidazolides, giving ε-caprolactam-derived carbamates and amides, using stoichiometric quantity of DBU (Scheme 3.7).[17]




Scheme 3.7. ε-caprolactam-derived amide synthesis

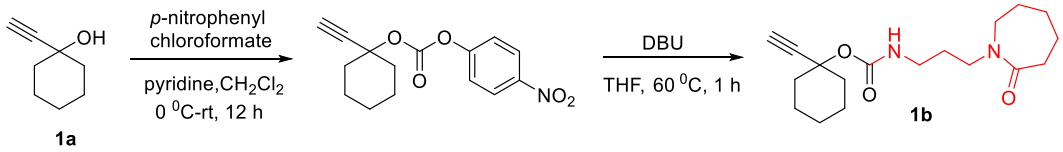
### 3A.2 Present Work

*p*-Nitrophenyl carbonates are electrophilic and highly reactive compounds that, depending on the nucleophile, i.e., treated with alcohols or amines to yield either a new carbonate or a carbamate-linked compound. In one of previous reports, Madhuri et al. showed synthesis of polycarbamate nucleic acids from *p*-nitrophenyl carbonates and amines of nucleic acid derivatives.[18] Hotha group recently identified alkynyl glycosyl carbonates as glycosyl donors from hemiacetals using 1-ethynylcyclohexyl *p*-nitrophenyl carbonate.[19] There are few other reports, where the synthesis of glycocarbamates from glycosyl *p*-nitrophenyl carbonates,[20-24] and explored in studies of ligation, surfactant properties and carbohydrate-protein interactions.[25-27] Despite the widespread use of *p*-nitrophenyl carbonates in these processes, the nucleophilicity of amidine bases towards such carbonates is under explored. In keeping view of our interest in the chemistry of carbohydrates[28,29] and the syntheses of carbamate-linked compounds from *p*-nitrophenyl carbonates, we present here our findings from nucleophilic ring opening reactions of DBU and DBN with *p*-nitrophenyl carbonates.

#### 3A.2.1 Nucleophilicity and Reaction of DBU with 1-ethynylcyclohexyl *p*-nitrophenyl carbonate

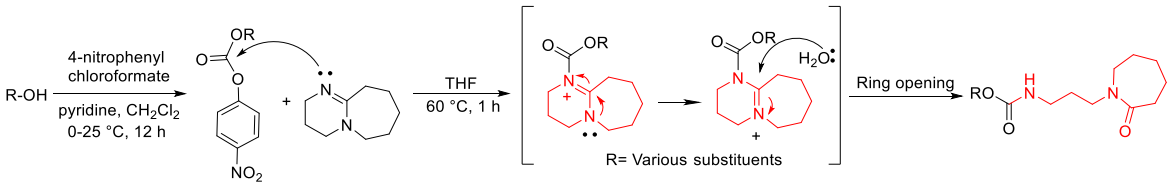
During the study of reaction, the *p*-nitrophenyl carbonate of 1-ethylcyclohexanol treated with 2 equivalents of DBU in THF in absence of nucleophile, we observed exclusive formation of the ε-caprolactam **1b**. The reaction at room temperature after 1 h TLC analysis showed starting material been almost consumed (90% TLC) and starting material got completely consumed at 60 ºC within in 1 h to afford lactam **1b**. Mechanistically, one can hypothesize that the imine nitrogen atom of DBU makes a nucleophilic attack on the carbonyl carbon, which is followed by the elimination of a *p*-nitrophenoxide ion. Following that, water molecules present in the solvent attack the imine

carbon of DBU, causing the ring to open and afford the caprolactam carbamates (Scheme 3.8 & 3.9).




Scheme 3.8. Reaction of DBU with p-nitrophenyl carbonate

The structure of ε-caprolactam **1b** was confirmed by $^{1}H$ and $^{13}C$ spectroscopy, which revealed the distinctive carbamate NH triplet at δ 5.80 ppm in the $^{1}H$ NMR spectrum and the corresponding resonances for the caprolactam and carbamate carbonyl carbons were identified at δ 176.6 and 155.0 ppm in the $^{13}C$ NMR spectrum. The ring opening of DBU was further confirmed by satisfactory matching in the HRMS (ESI): *m/z* $[M + Na]^{+}$: 343.1996; [calcd for compound **1a** $C_{18}H_{28}N_2NaO_3$]: 343.1997 and IR absorptions of the carbonyl groups at 1713, 1624, and carbamate NH at 3301 $cm^{-1}$.

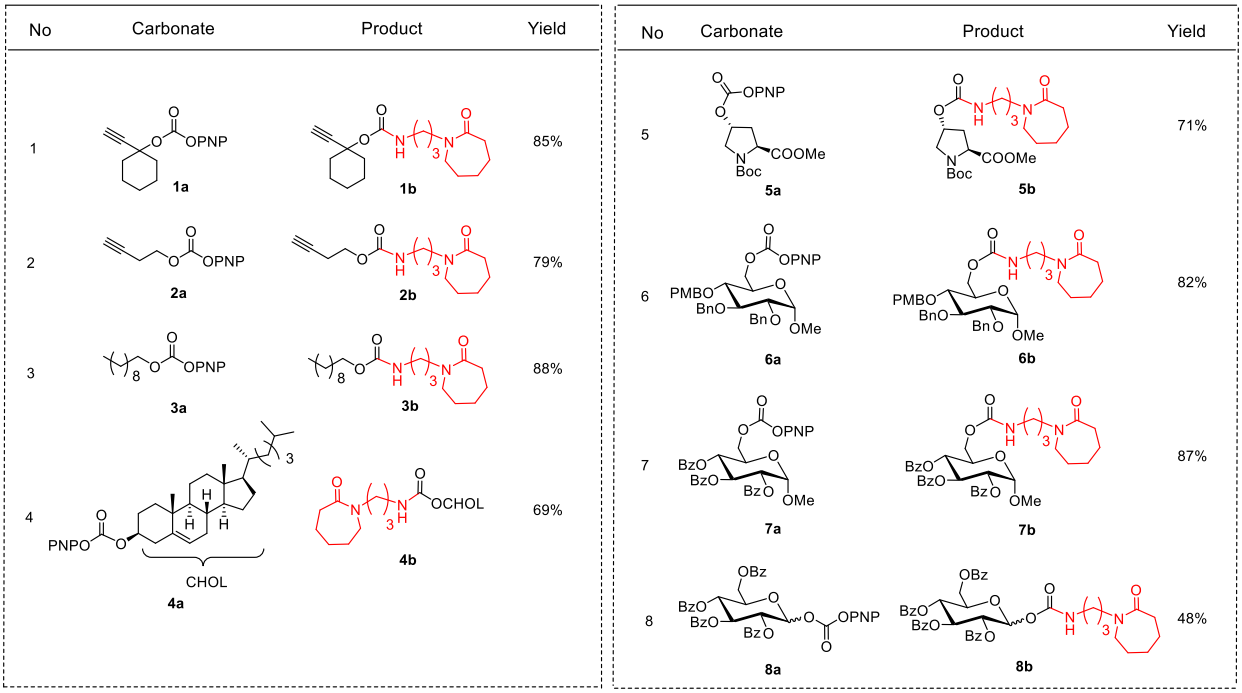



Scheme 3.9. General mechanistic pathway for caprolactam carbamate synthesis

The surprising formation of the ε-caprolactam from the *p*-nitrophenyl carbonate derivative in the presence of DBU has encouraged us to explore the utility of this novel procedure for the synthesis of other substituted carbamate caprolactams. Needless to say, that the ε-caprolactams are very important synthons for the polymerizations. Accordingly, we have synthesized structural diverse set of *p*-nitrophenyl carbonates by treating alcohols with *p*-nitrophenyl chloroformate in $CH_2Cl_2$ with pyridine as a base. Thus, cholesterol, decanol, *N*-Boc-*trans*-4-hydroxyl-L-proline methyl ester and homopropargyl alcohol resulted in the isolation of good to excellent yields of corresponding carbonates (Table 3.1, **2a**-**5a**). Subsequently, purified carbonates (**2a**-**5a**) were treated with 2 equiv of DBU in THF at 60 °C for 1 h to afford the ε-caprolactam carbamates **2b**-**5b** in very high yields along with the *p*-nitrophenol as the sole byproduct that could be easily removed by simple acid-base work up or silica gel column chromatography. The ε-caprolactam

formation from *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester **5b** showed rotamers due to the conformational flexibility of the *N*-Boc group.[30] Furthermore, we have investigated the synthesis of glycosyl caprolactams as the later can be polymerized in order to obtain glycopolymers easily with good polydispersity.[31] Thus, we have prepared the *p*-nitrophenyl carbonates **6a** and **7a** in good yields from methyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-α-D-glucopyranoside and methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside.[32,33] These carbonates **6a** and **7a** were reacted with DBU under aforementioned reaction conditions to yield gluco-caprolactam hybrids **6b** and **7b** in 82% and 87% yields respectively. However, per-*O*-benzoyl glucopyranose **8a** produced modest yield of the carbamate **8b** during the DBU reaction (48% yield); the major product being the hemiacetals.

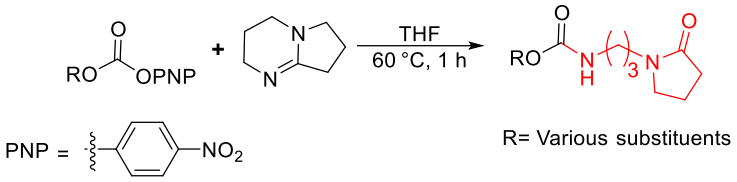
Table 3.1. Synthesis of ε-caprolactam-derived **1b-8b**.




### 3A.2.2 Nucleophilicity and Reaction of DBN with *p*-nitrophenyl carbonate

Having successfully developed the protocol for the synthesis of ε-caprolactam carbamates in good yields, we have turned our attention to yet another commercially available non-nucleophilic base DBN. DBU and DBN are very similar in nature except that the DBU has the bicyclic [5.4.0] systems whereas the DBN has [4.3.0] which might change the course of the reactivity (Scheme

3.10). The [5.4.0] system can undergo ring opening easily compared to the [4.3.0] bicyclic system which might alter the reactivity pattern or diminish the yield or increase the reaction time.



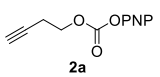
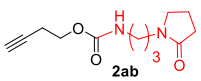
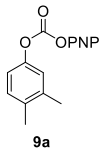
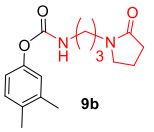
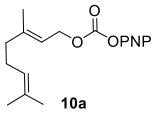
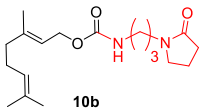
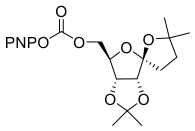
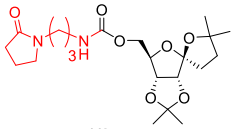
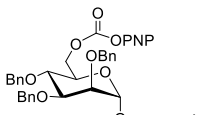
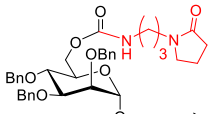
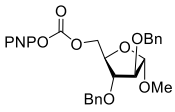
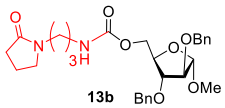
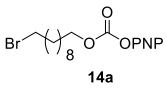
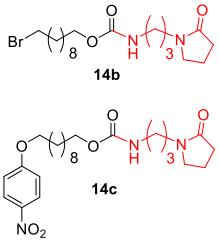
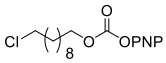
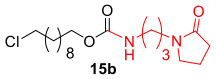
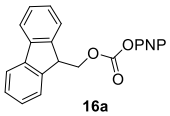
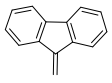
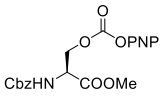

Scheme 3.10. Reaction of DBN with *p*-nitrophenyl carbonates

To begin our investigation, homopropargyl alcohol was treated with *p*-nitrophenyl chloroformate in $CH_2Cl_2$ at 0-25 ºC to observe *p*-nitrophenyl carbonate **2a** in 90% within 1 h. Subsequent heating of the reaction mixture of carbonate **2a** to 60 ºC for 1 h resulted in the formation of γ-lactam carbamate **2ab** in 56% yield only (Table 3.2). In the $^1$H NMR spectrum of product **2ab** carbamate NH broad singlet at δ 5.70 ppm and corresponding signals at δ 175.6 ppm, 156.3ppm for lactam amide and carbamate carbonyl respectively were observed which clearly indicate the ring opening of DBN. The general applicability of this method was evaluated by performing the reaction with a phenol, an allylic alcohol and three carbohydrate derived alcohols. The 3,4-dimethylphenyl *p*-nitrophenyl carbonate **9a** afforded corresponding γ-lactam **9b** having 62% yield. Interestingly, geranyl carbonate **10a** also underwent this ring opening reaction yielding 46% of γ-lactam **10b**. The γ-lactam-carbamate hybrid **11b** was obtained in 53% from the *p*-nitrophenyl carbonate of D-psicofuranose[28] whereas in case of armed *p*-nitrophenyl carbonate of *n*-pentenyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **12a**[34-36] and methyl 2,3-di-*O*-benzyl-α-D-arabinofuranoside **13a**[37] afforded γ-lactam carbamates in 63% and 67% yields respectively.

As DBU and DBN are known to induce dehydrohalogenation reactions, we turned out our focus on halogenated alcohols. So, when *p*-nitrophenyl carbonate of 10-bromo-1-decanol **14a** was treated with DBN at 60 ºC for one hour afforded single spot on TLC; however, the $^1$H NMR spectrum revealed the presence of two compounds with the carbamate NH showing a multiplet rather than a triplet and an extra signal for the *p*-nitrophenyl group much to our surprise. The ring opening of DBN was confirmed by peaks at δ 175.7 and 157.0 ppm for the cyclic amide and carbamate carbon in the $^{13}$C NMR spectrum. The appearance of new signals in the $^{13}$C NMR at δ 164.3, 141.2, and 126.0 ppm as well as the upfield shift of the C2-carbon of the *p*-nitrophenyl

substituent from δ 122 to 114.4 ppm indicated that the DBN underwent $S_N2$ displacement with the *p*-nitrophenoxide ion to afford compound **14c**. The *ipso*- and *ortho*- carbons of the *p*-nitrophenyl substituent in compound **14c** can thus be ascribed to the peaks at δ 164.3 and 114.4 ppm. This finding was particularly intriguing as substitution took priority over the *N*-alkylation of DBN.[38] Similar reaction with chloride leaving group was next envisaged. Accordingly, the 2-(2-chloroethoxyl) ethanol carbonate **15a** was treated with DBN at 25 ºC and at 60 ºC to afford the ring opened γ-lactam carbamate **15b** in 30% and 41% yield. This can be ascribed to the poor leaving ability of chloride ion in comparison to the bromide ion.

Table 3.2 Synthesis of γ-caprolactam-derived **2ab,9b-16b**.

| No | Carbonate | Product | Yield |
|---|---|---|---|
| 1 |  **2a** |  **2ab** | 56% |
| 2 |  **9a** |  **9b** | 62% |
| 3 |  **10a** |  **10b** | 46% |
| 4 |  **11a** |  **11b** | 53% |
| 5 |  **12a** |  **12b** | 63% |
| 6 |  **13a** |  **13b** | 76% |
| 7 |  **14a** |  **14b** **14c** | 64% |
| 8 |  **15a** |  **15b** | 41% a 30% b |
| 9 |  **16a** |  **16b** | |
| 10 |  | Mixture of Products | |

a. reaction at 60 $^0$C and b. at rt.

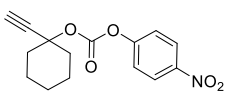
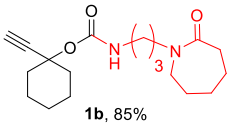
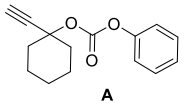
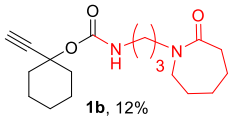
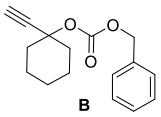
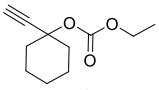
We then turned our attention to the substrates that contain active methylene groups in order to check the nucleophilicity vs the basicity of DBN. In this direction, *p*-nitrophenyl carbonates of 9-fluorenemethanol **16a** and *N*-Cbz-L-serine methyl ester **17a** were treated with DBN to notice the formation of dibenzofulvene **16b** as the sole product. This has clearly proved that the DBN acts as a based in the molecules that have active methylene groups. Finally, when 3.5 g of substrates

**3a** and **7a** were reacted with DBU at 60 °C for 1 h, lactams **3b** and **7b** were produced in 90% and 94% yield, respectively which means that method is suitable for large-scale transformations too.

### 3A.2.3 Nucleophilicity towards alkoxide carbonate.

The foregoing reactions clearly prove that DBN and DBU have nucleophilicity specific to highly electrophilic *p*-nitrophenyl carbonate. To check the nucleophilicity with different carbonate substrate, we have been synthesized a set of three distinct carbonates of 1-ethylclyclohexanol using phenyl, benzyl, and ethyl chloroformate, respectively. The phenyl carbonate (Table 3.3, A) was treated with DBU at 60 °C for 20 hours, yielding ε-caprolactam **1b** in 12% yield whereas no trace of lactam **1b** was generated in the reaction of benzyl and ethyl carbonates (**B**, **C**) with DBU. This is due to the poor leaving character of alkoxides in comparison to phenolates.

Table 3.3. Reactivity of alkoxide carbonates with DBU

| No | Carbonate | Product |
|---|---|---|
| 1 |  **1b** |  **1b**, 85% 60 °C, 1 h |
| 2 |  **A** |  **1b**, 12% 60 °C, 20 h |
| 3 |  **B** | No Reaction 60 °C, 20 h |
| 4 |  **C** | No Reaction 60 °C, 20 h |

### 3A.4 Conclusion

Finally, using the nucleophilicity of DBU/DBN and highly electrophile *p*-nitrophenyl carbonate derivatives, we demonstrated an operationally simple synthesis of carbamate-derived ε-caprolactam and γ-lactam molecules. All the reactions progressed and showed nucleophilic addition and substitution with the *p*-nitrophenyl carbonate derivative of 10-bromodecanol. Caprolactam derivatives could be find usefulness in polymer chemistry.

### 3A.5 Experimental Section

**General procedure for the synthesis of *p*-nitrophenyl carbonate derivatives**

The alcohol (0.5 g) was dissolved in dry $CH_2Cl_2$ (6 mL) and cooled to 0 $^oC$ in an ice bath. Dry pyridine (2 equiv) was added and the mixture was allowed to stir for 10 min. *p*-Nitrophenyl chloroformate (1.2 equiv) dissolved in $CH_2Cl_2$ (2 mL) was added stirring continued for 1.5 h at room temperature. After completion, the reaction mixture was extracted with $CH_2Cl_2$ (2 × 30 mL), the organic layer washed with water, brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude compound was purified by column chromatography using hexane/ethylacetate.

**General procedure for the synthesis of ε-caprolactam and γ-lactam derived compounds**

The *p*-nitrophenyl carbonate derivative (0.3 g) was dissolved in AR grade THF (5 mL) at room temperature and DBU or DBN (2 equiv) was added. The temperature of the reaction mixture was raised to 60 $^oC$ and stirring was continued for 1 h. After completion, the reaction mixture was extracted with ethyl acetate (2 × 30 mL), the organic layer washed with saturated $NaHCO_3$ solution, water, brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude compound was purified by column chromatography.

**General procedure for the synthesis of carbonates A, B, C**

**A**. To an ice-cooled solution of 1-ethynylcyclohexanol (1 g) in anhydrous $CH_2Cl_2$ (15 mL) was added pyridine (2 equiv) and stirred for 10 min. Phenyl chloroformate (1.5 equiv) was added, and the reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was extracted with DCM (2 × 25 mL), the organic layer washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous $Na_2SO_4$. The concentrated crude mixture was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford compound **A**.

**B**. To an ice-cooled solution of 1-ethynylcyclohexanol (1 g) in anhydrous DMF (15 mL) was added NaH (2 equiv) in portions and stirred for 10 min. Subsequently, benzyl chloroformate or ethyl chloroformate (1.5 equiv) was added. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was extracted with $CH_2Cl_2$ (2 × 25 mL), the organic layer washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous $Na_2SO_4$. The concentrated crude mixture was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford compound **B** or **C**.

### 3A.6.1 Structural data of p-nitrophenyl carbonates 1a-7a, 9a-17a

*Compound* **1a:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.30 – 8.26 (m, 2H), 7.44 – 7.40 (m, 2H), 2.72 (s, 1H), 2.34-2.17 (m, 2H), 2.04-1.91 (m, 2H), 1.80-1.64 (m, 4H), 1.63-1.54 (m, 1H), 1.41-1.32 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.5, 150.0, 145.2, 125.2, 121.8, 82.0, 79.7, 75.9, 36.8, 25.0, 22.6.

*Compound* **2a:** $R_f$ = 0.5 (hexane/EtOAc, 80:20); white solid (86% yield), mp 73-74 °C; IR ($CHCl_3$) : *v* 3290, 1774, 1589, 1493, 1272, 1216, 773 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.34 – 8.22 (m, 2H), 7.45 – 7.35 (m, 2H), 4.39 (t, *J* = 6.8 Hz, 2H), 2.70 – 2.65 (m, 2H), 2.08 (t, *J* = 2.7 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.5, 152.4, 145.6, 125.5, 121.9, 79.1, 70.8, 66.8, 19.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_9NNaO_5$:258.0378; Found: 258.0372.

*Compound* **3a:** $R_f$ = 0.7 (hexane/EtOAc, 80:20); thick liquid (90% yield); IR ($CHCl_3$): *v* 1768, 1528, 1349, 1218 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.28 – 8.22 (m, 2H), 7.40 – 7.34 (m, 2H), 4.27 (t, *J* = 6.7 Hz, 2H), 1.78 – 1.70 (m, 2H), 1.45 – 1.23 (m, 14H), 0.86 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.7, 152.6, 145.4, 125.3, 121.8, 69.7, 32.0, 29.6, 29.5, 29.4, 29.2, 28.6, 25.7, 22.7, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{26}NO_5$:324.1811, Found: 324.1822.

*Compound* **4a:** $R_f$ = 0.5 (hexane/EtOAc, 85:15); white solid (80% yield), mp 160-162 °C; $[\alpha]_D^{25}$ = -28.4 (*c* 0.42, $CH_2Cl_2$); IR ($CHCl_3$): *v* 1760, 1521, 1350, 1257 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.36 (d, *J* = 9.1 Hz, 2H), 5.40 (d, *J* = 3.7 Hz, 1H), 4.66 – 4.50 (m, 1H), 2.51 – 2.38 (m, 2H), 2.05 – 1.87 (m, 4H), 1.85 – 1.65 (m, 2H), 1.60 – 1.41 (m, 6H), 1.39 – 1.21 (m, 5H), 1.20 – 1.05 (m, 7H), 1.02 (s, 3H), 0.99 – 0.92 (m, 2H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.84 (dd, *J* = 6.6, 1.4 Hz, 6H), 0.66 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.7, 151.8, 145.3, 138.9, 125.3, 123.6, 121.8, 79.8, 56.7, 56.2, 50.0, 42.4, 39.8, 39.6, 37.9, 36.9, 36.6, 36.3, 35.9, 32.0, 31.9, 28.3, 28.1, 27.6, 24.4, 23.9, 22.9, 22.7, 21.1, 19.3, 18.8, 11.9; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{49}NNaO_5$:574.3508, Found: 574.3512.

*Compound* **5a:** $R_f$ = 0.4 (hexane/EtOAc, 75:25); thick liquid (79% yield); $[\alpha]_D^{25}$ = -24.62 (*c* 0.46, $CH_2Cl_2$); IR ($CHCl_3$): *v* 1757, 1698, 1526, 1201, 758 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.25 (m, 2H), 7.41 – 7.34 (m, 2H), 5.36 – 5.28 (m, 1H), 4.53 – 4.39 (m, 1H), 3.91 – 3.71 (m, 2H), 3.75 (s, 3H), 2.64 – 2.50 (m, 1H), 2.35 – 2.23 (m, 1H), 1.43 (d, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$):

δ 172.9, 172.7, 155.3, 154.1, 153.6, 151.9, 145.7, 125.5, 121.8, 81.0, 78.0, 77.3, 57.8, 57.4, 52.6, 52.4, 52.1, 52.0, 36.5, 35.6, 28.5, 28.3; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{22}N_2NaO_6$:433.1222, Found: 433.1227.

*Compound* **6a:** $R_f$ = 0.4 (hexane/EtOAc, 75:25); white solid (88% yield), mp 94-95 °C; $[\alpha]_D^{25}$ = +64.80 (*c* 0.38, $CH_2Cl_2$); IR ($CHCl_3$): *v* 1768, 1609, 1520, 1211, 1036, 740; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.24 (m, 2H), 7.44 – 7.30 (m, 12H), 7.25 – 7.19 (m, 2H), 6.89 – 6.83 (m, 2H), 5.04 (d, *J* = 10.8 Hz, 1H), 4.91 – 4.79 (m, 3H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 4.57 (d, *J* = 10.8 Hz, 1H), 4.43 (dd, *J* = 11.4, 2.4 Hz, 1H), 4.37 (dd, *J* = 11.5, 4.4 Hz, 1H), 4.04 (t, *J* = 9.2 Hz, 1H), 3.90 – 3.83 (m, 1H), 3.75 (s, 3H), 3.61 – 3.49 (m, 2H), 3.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.5, 155.5, 152.3, 145.4, 138.7, 138.0, 129.9, 128.6, 128.6, 128.2, 128.1, 128.0, 127.8, 125.3, 121.7, 114.0, 113.8, 98.2, 82.1, 79.8, 76.4, 75.8, 74.7, 73.5, 68.4, 67.7, 55.5, 55.3; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{36}H_{37}NNaO_{11}$:682.2264, Found: 682.2271.

*Compound* **7a:** $R_f$ = 0.5 (hexane/EtOAc, 80:20); thick liquid (89% yield); $[\alpha]_D^{25}$ = +76.05 (*c* 0.65, $CH_2Cl_2$); IR ($CHCl_3$) *v* 1771, 1725, 1526, 1252, 1097, 701 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.28 – 8.22 (m, 2H), 8.01 – 7.93 (m, 4H), 7.90 – 7.85 (m, 2H), 7.53 – 7.45 (m, 2H), 7.43 – 7.33 (m, 7H), 7.29 – 7.23 (m, 2H), 6.23 (t, *J* = 9.8 Hz, 1H), 5.69 (t, *J* = 9.9 Hz, 1H), 5.33 (dt, *J* = 9.9, 3.6 Hz, 2H), 4.57 (dd, *J* = 12.0, 4.6 Hz, 1H), 4.49 (dd, *J* = 12.0, 2.5 Hz, 1H), 4.38 (ddd, *J* = 10.2, 4.4, 2.6 Hz, 1H), 3.50 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 165.9, 165.8, 165.5, 155.5, 152.4, 145.5, 133.7, 133.5, 133.3, 129.9, 129.9, 129.7, 129.1, 128.9, 128.7, 128.5, 128.5, 128.4, 125.3, 121.9, 97.2, 71.9, 70.2, 69.0, 67.4, 66.8, 55.9; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{35}H_{29}NNaO_{13}$:694.1536, Found: 694.1531.

*Compound* **9a:** $R_f$ = 0.5 (hexane/EtOAc, 85:15); white solid (82% yield), mp 119-121 °C; IR ($CHCl_3$) *v* 1770, 1600, 1523, 1247 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.34 – 8.27 (m, 2H), 7.50 – 7.45 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.5 Hz, 1H), 2.29 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.5, 151.4, 148.8, 145.7, 138.5, 135.3, 130.7, 125.5, 121.9, 121.7, 117.8, 20.0, 19.3; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{14}NO_5$:288.0872, Found: 288.0901.

*Compound* **10a:** $R_f$ = 0.6 (hexane/EtOAc, 85:15); thick liquid (77% yield); IR ($CHCl_3$): *v* 1763, 1525, 1447, 1200 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.31 – 8.23 (m, 2H), 7.42 – 7.35 (m, 2H),

5.48 – 5.41 (m, 1H), 5.12 – 5.05 (m, 1H), 4.80 (d, *J* = 7.3 Hz, 2H), 2.19 – 2.05 (m, 4H), 1.77 (d, *J* = 0.8 Hz, 3H), 1.68 (s, 3H), 1.61 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.8, 152.7, 145.4, 145.0, 132.2, 125.4, 123.6, 121.9, 116.8, 66.2, 39.7, 26.3, 25.8, 17.8, 16.7; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{22}NO_5$:320.1498, Found: 320.1502.

*Compound* **11a:** $R_f$ = 0.5 (hexane/EtOAc, 70:30); thick liquid (77% yield); $[\alpha]_D^{25}$ = -37.27 (*c* 0.44, $CH_2Cl_2$); IR ($CHCl_3$) *v* 1770, 1526, 1213, 1069, 858 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.31 – 8.26 (m, 2H), 7.41 – 7.36 (m, 2H), 4.79 (d, *J* = 5.6 Hz, 1H), 4.66 (d, *J* = 5.8 Hz, 1H), 4.44 – 4.35 (m, 3H), 4.31 (d, *J* = 9.8 Hz, 1H), 4.09 (d, *J* = 9.8 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.6, 152.4, 145.6, 125.5, 121.8, 113.9, 113.2, 112.1, 85.2, 82.4, 82.0, 69.9, 68.9, 26.5, 26.4, 25.2; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{23}NNaO_{10}$:448.1219, Found: 448.1227.

*Compound* **12a:** $R_f$ = 0.5 (hexane/EtOAc, 70:30; thick liquid (84% yield); $[\alpha]_D^{25}$ = +36.63 (*c* 1.09, $CH_2Cl_2$); IR ($CHCl_3$) *v* 1769, 1525, 1215, 1094, 741 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 5.9 Hz, 2H), 7.48 – 7.27 (m, 17H), 5.90 – 5.75 (m, 1H), 5.10 – 4.96 (m, 3H), 4.93 – 4.86 (m, 1H), 4.84 – 4.75 (m, 2H), 4.72 – 4.65 (m, 3H), 4.62 – 4.55 (m, 1H), 4.53 – 4.46 (m, 1H), 4.06 – 3.96 (m, 2H), 3.95 – 3.82 (m, 2H), 3.76 – 3.66 (m, 1H), 3.49 – 3.37 (m, 1H), 2.17 – 2.06 (m, 2H), 1.74 – 1.61 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.6, 152.4, 145.4, 138.3, 138.2, 138.0, 128.6, 128.5, 128.5, 128.2, 127.9, 127.9, 127.8, 125.3, 121.9, 115.1, 98.1, 80.2, 75.3, 74.7, 74.4, 72.9, 72.2, 69.9, 68.3, 67.3, 30.3, 28.6; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{39}H_{41}NNaO_{10}$:706.2627, Found: 706.2631.

*Compound* **13a:** $R_f$ = 0.4 (hexane/EtOAc, 80:20); thick liquid (82% yield); $[\alpha]_D^{25}$ = +55.64 (*c* 0.61, $CH_2Cl_2$); IR ($CHCl_3$) *v* 1768, 1596, 1524, 1213 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.28 – 8.23 (m, 2H), 7.39 – 7.28 (m, 12H), 4.99 (s, 1H), 4.66 – 4.44 (m, 5H), 4.38 – 4.28 (m, 2H), 4.04 (dd, *J* = 2.8, 0.8 Hz, 1H), 3.91 (dd, *J* = 6.2, 2.7 Hz, 1H), 3.42 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.5, 152.4, 145.5, 137.5, 137.3, 128.6, 128.2, 128.1, 128.1, 128.0, 125.4, 121.8, 107.6, 87.8, 83.3, 79.0, 72.5, 72.3, 68.3, 55.3; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{27}H_{27}NNaO_9$:532.1583, Found: 532.1577.

*Compound* **14a:** $R_f$ = 0.5 (hexane/EtOAc, 85:15); thick liquid (86% yield); IR ($CHCl_3$): *v* 1764, 1525, 1252, 858 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.31 – 8.22 (m, 2H), 7.42 – 7.33 (m, 2H),

4.27 (t, *J* = 6.7 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 1.89 – 1.80 (m, 2H), 1.79 – 1.70 (m, 2H), 1.46 – 1.37 (m, 4H), 1.30 (s, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.7, 152.6, 145.4, 125.4, 121.9, 69.8, 34.1, 32.9, 29.4, 29.2, 28.8, 28.6, 28.2, 25.7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{24}BrNNaO_5$:424.0736, Found: 424.0737.

*Compound* **15a:** $R_f$ = 0.5 (hexane/EtOAc, 80:20); thick liquid (83% yield); IR ($CHCl_3$): *v* 1765, 1593, 1520, 1339, 1206, 812 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.29 – 8.23 (m, 2H), 7.41 – 7.34 (m, 2H), 4.47 – 4.42 (m, 2H), 3.85 – 3.77 (m, 4H), 3.65 (t, *J* = 5.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.6, 152.5, 145.5, 125.4, 121.9, 71.4, 68.7, 68.1, 42.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{13}ClNO_6$:290.0431, Found: 290.0440.

*Compound* **16a:** $R_f$ = 0.4 (hexane/EtOAc, 80:20); light yellow solid (81% yield), mp 87-88 °C; IR ($CHCl_3$) *v* 1766, 1528, 1453, 1225, 913 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 9.0 Hz, 2H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.32 (d, *J* = 9.1 Hz, 2H), 4.62 (d, *J* = 7.0 Hz, 2H), 4.34 (t, *J* = 7.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.4, 152.3, 145.3, 142.8, 141.3, 128.1, 127.2, 125.2, 125.0, 121.7, 120.2, 70.8, 46.5; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{15}NNaO_5$:384.0848, Found: 384.0842.

*Compound* **17a:** $R_f$ = 0.4 (hexane/EtOAc, 70:30); white solid (68% yield), mp 87-88 °C; $[\alpha]_D^{25}$ = +16.02 (*c* 0.26, $CH_2Cl_2$); IR ($CHCl_3$): *v* 3368, 1762, 1714, 1520, 1203, 858 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.1 Hz, 2H), 7.36 – 7.24 (m, 7H), 5.91 (d, *J* = 8.0 Hz, 1H), 5.17 – 5.05 (m, 2H), 4.77 – 4.71 (m, 1H), 4.65 – 4.54 (m, 2H), 3.77 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 169.3, 155.8, 155.2, 152.1, 145.4, 135.9, 128.5, 128.2, 128.1, 125.2, 121.6, 68.2, 67.3, 53.1, 53.1; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{18}N_2NaO_9$:441.0909, Found: 441.0909.

### 3A.6.2 Structural data of lactam compounds 1b-7b, 2ab and 9b-15b

*Compound* **1b:** $R_f$ = 0.5 (EtOAc); thick liquid (85% yield); IR ($CHCl_3$): *v* 3301, 1713, 1624, 1497, 1237 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 5.76 (br s, 1H), 3.41 (t, *J* = 6.3 Hz, 2H), 3.33 – 3.26 (m, 2H), 3.10 (dd, *J* = 12.2, 6.2 Hz, 2H), 2.53 (s, 1H), 2.52 – 2.45 (m, 2H), 2.12 – 2.02 (m, 2H), 1.87 – 1.76 (m, 2H), 1.74 – 1.53 (m, 12H), 1.50 – 1.40 (m, 1H), 1.33 – 1.23 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 176.7, 155.0, 84.7, 74.4, 73.6, 49.6, 45.3, 37.4, 37.2, 37.1, 30.0, 28.6, 27.8, 25.2, 23.5, 22.5; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{28}N_2NaO_3$:343.1997, Found: 343.1996.

*Compound* **2b:** $R_f$ = 0.2 (EtOAc); thick liquid (79% yield); IR ($CHCl_3$): *v* 3294, 1708, 1620, 1525, 1440, 1244 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.05 (t, *J* = 7.0 Hz, 2H), 3.35 (t, *J* = 6.3 Hz, 2H), 3.28 – 3.22 (m, 2H), 3.05 (dd, *J* = 12.2, 6.2 Hz, 2H), 2.48 – 2.38 (m, 4H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.70 – 1.51 (m, 8H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 176.6, 156.2, 80.4, 69.7, 62.2, 49.5, 45.0, 37.2, 37.1, 29.9, 28.5, 27.7, 23.3, 19.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{23}N_2O_3$:267.1709, Found: 267.1718.

*Compound* **3b:** $R_f$ = 0.2 (EtOAc); white solid (88% yield), mp 68-70 °C; IR ($CHCl_3$) *v* 3322, 1709, 1629, 1520, 1246, 731 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.80 – 5.72 (m, 1H), 3.96 (t, *J* = 6.7 Hz, 2H), 3.39 (t, *J* = 6.3 Hz, 2H), 3.31 – 3.24 (m, 2H), 3.08 (dd, *J* = 12.2, 6.2 Hz, 2H), 2.52 – 2.44 (m, 2H), 1.75 – 1.47 (m, 10H), 1.33 – 1.14 (m, 14H), 0.83 (t, *J* = 6.9 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 176.6, 157.1, 64.8, 49.6, 45.2, 37.3, 37.2, 31.9, 30.0, 29.6, 29.4, 29.3, 29.1, 28.6, 27.9, 25.9, 23.5, 22.7, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{29}N_2O_3$:355.296, Found: 355.2967.

*Compound* **4b:** $R_f$ = 0.3 (EtOAc); white solid (69% yield), mp 162-164 °C; $[\alpha]_D^{25}$ = -16.1 (*c* 0.52, $CH_2Cl_2$); IR ($CHCl_3$): *v* 3355, 1708, 1629, 1512, 1247, 733 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.74 (t, *J* = 6.1 Hz, 1H), 5.29 (d, *J* = 4.9 Hz, 1H), 4.46 – 4.34 (m, 1H), 3.38 (t, *J* = 6.2 Hz, 2H), 3.30 – 3.24 (m, 2H), 3.07 (dd, *J* = 12.0, 6.1 Hz, 2H), 2.49 – 2.44 (m, 2H), 2.32 – 2.16 (m, 2H), 1.91 (ddd, *J* = 12.0, 9.9, 2.7 Hz, 2H), 1.77 (dd, *J* = 9.8, 3.7 Hz, 3H), 1.63 (ddd, *J* = 18.5, 11.0, 5.4 Hz, 8H), 1.52 – 1.35 (m, 7H), 1.25 (ddd, *J* = 23.8, 18.3, 11.0 Hz, 4H), 1.05 (ddd, *J* = 24.7, 12.1, 6.6 Hz, 7H), 0.94 (s, 3H), 0.97 – 0.88 (m, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.80 (dd, *J* = 6.7, 1.7 Hz, 6H), 0.61 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 176.5, 156.3, 140.0, 122.2, 73.9, 56.7, 56.1, 50.0, 49.5, 45.1, 42.3, 39.7, 39.5, 38.6, 37.2, 37.0, 36.5, 36.2, 35.8, 31.9, 31.8, 30.0, 28.6, 28.2, 28.1, 28.0, 27.8, 24.3, 23.8, 23.4, 22.8, 22.6, 21.0, 19.3, 18.7, 11.8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{37}H_{62}N_2NaO_3$:605.4658, Found: 605.4670.

*Compound* **5b:** $R_f$ = 0.2 (EtOAc); thick liquid (71% yield); $[\alpha]_D^{25}$ = -30.9 (*c* 0.61, $CH_2Cl_2$); IR ($CHCl_3$): *v* 3328, 1699, 1626, 1400, 1158, 1074 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.02 – 5.94 (m, 1H), 5.10 (br s, 1H), 4.30 – 4.18 (m, 1H), 3.62 (s, 3H), 3.60 – 3.40 (m, 2H), 3.38 – 3.29 (m, 2H), 3.27 – 3.19 (m, 2H), 3.08 – 2.95 (m, 2H), 2.47 – 2.38 (m, 2H), 2.33 – 2.21 (m, 1H), 2.09 – 1.97 (m, 1H), 1.69 – 1.48 (m, 8H), 1.33 (d, *J* = 14.9 Hz, 9H rotamer); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ (rotamers) 176.7, 173.2, 172.9, 155.7, 155.5, 154.1, 153.4, 80.2, 72.6, 71.9, 57.9, 57.5, 52.4,

52.3, 52.1, 51.9, 49.5, 44.9, 37.0, 36.7, 35.7, 29.8, 28.4, 28.3, 28.1, 27.6, 27.6, 23.3; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{35}N_3NaO_7$:464.2372, Found: 464.2375.

*Compound* **6b:** $R_f$ = 0.2 (EtOAc); thick liquid (82% yield); $[\alpha]_D^{25}$ = +37.8 (*c* 0.29, $CH_2Cl_2$); IR ($CHCl_3$): *v* 3351, 1717, 1625, 1513, 1067, 732 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.27 (m, 10H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.79 (t, *J* = 6.1 Hz, 1H), 4.99 (d, *J* = 11.0 Hz, 1H), 4.86 – 4.74 (m, 3H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.58 (d, *J* = 3.5 Hz, 1H), 4.50 (d, *J* = 10.3 Hz, 1H), 4.31 (dd, *J* = 11.7, 4.4 Hz, 1H), 4.24 (dd, *J* = 11.6, 1.6 Hz, 1H), 3.97 (t, *J* = 9.3 Hz, 1H), 3.77 (s, 3H), 3.76 – 3.72 (m, 1H), 3.55 – 3.51 (m, 1H), 3.47 (t, *J* = 9.5 Hz, 1H), 3.43 – 3.37 (m, 2H), 3.35 (s, 3H), 3.32 – 3.27 (m, 2H), 3.17 – 3.08 (m, 2H), 2.54 – 2.47 (m, 2H), 1.75 – 1.58 (m, 8H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 176.7, 159.4, 156.4, 138.9, 138.2, 130.3, 129.9, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6, 113.9, 98.1, 82.1, 79.9, 75.7, 74.9, 73.5, 69.1, 63.3, 55.4, 55.3, 49.6, 45.1, 37.5, 37.2, 30.0, 28.6, 28.0, 23.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{51}N_2O_9$:691.3594, Found: 691.3602.

*Compound* **7b:** $R_f$ = 0.2 (EtOAc); white solid (87% yield), mp 70-72 °C; $[\alpha]_D^{25}$ = +61.7 (*c* 0.32, $CH_2Cl_2$); IR ($CHCl_3$): *v* 3397, 1722, 1628, 1447, 1250, 1096, 704 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.90 (m, 4H), 7.89 – 7.84 (m, 2H), 7.53 – 7.46 (m, 2H), 7.44 – 7.33 (m, 5H), 7.31 – 7.25 (m, 2H), 6.13 (t, *J* = 9.7 Hz, 1H), 5.82 (t, *J* = 6.2 Hz, 1H), 5.60 – 5.51 (m, 1H), 5.25 (dt, *J* = 10.6, 3.6 Hz, 2H), 4.31 – 4.22 (m, 3H), 3.47 (s, 3H), 3.41 (dd, *J* = 10.9, 6.2 Hz, 2H), 3.34 – 3.28 (m, 2H), 3.15 – 3.08 (m, 2H), 2.54 – 2.50 (m, 2H), 1.75 – 1.58 (m, 8H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 176.7, 165.9, 165.9, 165.3, 156.2, 133.4, 133.2, 130.0, 130.0, 129.8, 129.3, 129.2, 129.1, 128.5, 128.4, 97.0, 72.2, 70.6, 69.4, 68.0, 63.0, 55.7, 49.7, 45.2, 37.6, 37.3, 30.1, 28.7, 27.9, 23.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{43}N_2O_{11}$:703.2867, Found: 703.2888.

*Compound* **8b:** $R_f$ = 0.2-0.3 (EtOAc); thick liquid (48% yield); IR ($CHCl_3$): *v* 3364, 1727, 1627, 1448, 1251, 1096, 700 $cm^{-1}$; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{44}H_{44}N_2NaO_{12}$:815.2972, Found: 815.294.

*Compound* **2ab:** $R_f$ = 0.2 (EtOAc); thick liquid (56% yield); IR ($CHCl_3$): *v* 3289, 1705, 1657, 1532, 1251 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.69 (br s, 1H), 4.09 (t, *J* = 6.9 Hz, 2H), 3.31 (dt, *J* = 13.0, 6.7 Hz, 4H), 3.08 (q, *J* = 6.3 Hz, 2H), 2.51 – 2.41 (m, 2H), 2.34 (t, *J* = 8.1 Hz, 2H), 2.03 – 1.96 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.64 (p, *J* = 6.4 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ

175.7, 156.3, 80.4, 69.8, 62.4, 47.3, 39.6, 37.6, 30.9, 27.0, 19.4, 18.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{18}N_2NaO_3$:261.1214, Found: 261.1220.

*Compound* **9b:** $R_f$ = 0.2 (EtOAc); white solid (62% yield), mp 85-87 °C; IR ($CHCl_3$): *v* 3306, 1727, 1660, 1533, 1492, 1232 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.1 Hz, 1H), 6.88 (s, 1H), 6.82 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.10 (br s, 1H), 3.41 – 3.33 (m, 4H), 3.22 – 3.14 (m, 2H), 2.43 – 2.35 (m, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 2.07 – 1.97 (m, 2H), 1.77 – 1.68 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 175.9, 155.2, 149.1, 137.6, 133.4, 130.1, 122.7, 118.8, 47.3, 39.5, 37.7, 30.9, 26.9, 19.9, 19.2, 18.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{22}N_2NaO_3$:313.1528, Found: 313.1535.

*Compound* **10b:** $R_f$ = 0.2 (EtOAc); thick liquid (46% yield); IR ($CHCl_3$): *v* 3322, 1669 (br), 1524, 1441, 1249 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.53 (br s, 1H), 5.35 – 5.27 (m, 1H), 5.09 – 5.03 (m, 1H), 4.54 (d, *J* = 6.9 Hz, 2H), 3.38 – 3.29 (m, 4H), 3.11 (q, *J* = 6.3 Hz, 2H), 2.37 (t, *J* = 8.0 Hz, 2H), 2.11 – 1.97 (m, 6H), 1.71 – 1.62 (m, 8H), 1.57 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 175.7, 156.9, 141.5, 131.8, 123.9, 123.9, 119.1, 61.7, 47.3, 39.6, 37.6, 31.0, 29.8, 27.1, 26.4, 25.8, 18.0, 17.8, 16.5; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{30}N_2NaO_3$:345.2153, Found: 345.2154.

*Compound* **11b:** $R_f$ = 0.2 (EtOAc); thick liquid (53% yield); $[\alpha]_D^{25}$ = -48.0 (*c* 1.7, $CH_2Cl_2$); IR ($CHCl_3$): *v* 3325, 1715, 1666, 1528, 1376, 1250, 1060, 856 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.69 (t, *J* = 5.9 Hz, 1H), 4.70 (d, *J* = 5.8 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 1H), 4.21 (t, *J* = 7.3 Hz, 2H), 4.08 (d, *J* = 7.3 Hz, 2H), 4.00 (d, *J* = 9.7 Hz, 1H), 3.34 (d, *J* = 8.7 Hz, 2H), 3.30 (dd, *J* = 7.0, 6.2 Hz, 2H), 3.09 (dd, *J* = 7.5, 6.1 Hz, 2H), 2.35 (t, *J* = 8.1 Hz, 2H), 2.06 – 1.94 (m, 2H), 1.69 – 1.60 (m, 2H), 1.39 (s, 6H), 1.32 (s, 3H), 1.27 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 175.7, 156.2, 113.6, 112.7, 111.8, 85.1, 83.1, 82.3, 69.8, 64.6, 47.3, 39.6, 37.7, 30.9, 27.0, 26.5, 26.5, 26.3, 25.2, 18.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{32}N_2NaO_8$:451.2056, Found: 451.2054.

*Compound* **12b:** $R_f$ = 0.2 (EtOAc); thick liquid (63% yield); $[\alpha]_D^{25}$ = +19.2 (*c* 0.39, $CH_2Cl_2$); IR ($CHCl_3$): *v* 3328, 1716, 1670, 1522, 1249, 1090, 742 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 15H), 5.84 – 5.71 (m, 1H), 5.52 – 5.44 (m, 1H), 5.03 – 4.94 (m, 2H), 4.92 (d, *J* = 10.6 Hz, 1H), 4.81 (s, 1H), 4.73 (d, *J* = 3.1 Hz, 2H), 4.64 – 4.58 (m, 3H), 4.38 – 4.31 (m, 2H), 3.91 (d, *J* = 5.8 Hz, 2H), 3.80 – 3.74 (m, 2H), 3.65 (dt, *J* = 9.7, 6.6 Hz, 1H), 3.39 – 3.28 (m, 5H), 3.18 –

3.09 (m, 2H), 2.37 (t, *J* = 8.1 Hz, 2H), 2.10 – 1.96 (m, 4H), 1.72 – 1.57 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.6, 156.5, 138.5, 138.4, 138.3, 138.1, 128.5, 128.4, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 115.0, 98.0, 80.2, 75.3, 74.7, 72.7, 72.2, 70.5, 67.1, 64.0, 47.3, 39.8, 38.0, 31.0, 30.3, 28.6, 27.3, 18.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{40}H_{50}N_2NaO_8$:709.3464, Found: 709.3459.

*Compound* **13b:** $R_f$ = 0.2 (EtOAc); thick liquid (67% yield); $[\alpha]_D^{25}$ = +41.8 (*c* 1.48, $CH_2Cl_2$); IR ($CHCl_3$): *v* 3340, 1718, 1669, 1455, 1257, 1106, 746 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.23 (m, 10H), 5.52 (t, *J* = 6.1 Hz, 1H), 4.91 (s, 1H), 4.55 – 4.41 (m, 4H), 4.25 (dd, *J* = 11.1, 3.1 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.96 (dd, *J* = 2.7, 0.7 Hz, 1H), 3.81 (dd, *J* = 6.2, 2.7 Hz, 1H), 3.36 (s, 3H), 3.35 – 3.25 (m, 4H), 3.09 (q, *J* = 6.3 Hz, 2H), 2.36 (t, *J* = 8.1 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.68 – 1.59 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.7, 156.3, 137.7, 137.5, 128.5, 128.4, 127.9, 127.9, 127.8, 107.4, 87.9, 83.5, 79.9, 72.3, 72.0, 64.4, 55.0, 47.3, 39.6, 37.8, 30.9, 27.1, 18.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{28}H_{36}N_2NaO_7$:535.242, Found: 535.2417.

*Compound* **14b** *and* **14c** (reaction at 60 °C)**:** $R_f$ = 0.2 (EtOAc); thick liquid (64% yield); IR ($CHCl_3$): *v* 3321, 1668 (br), 1594, 1252, 850 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.20 – 8.11 (m, 2H), 6.96 – 6.85 (m, 2H), 5.62 – 5.49 (m, 2H), 4.06 – 3.93 (m, 6H), 3.41 – 3.27 (m, 10H), 3.14 – 3.03 (m, 4H), 2.41 – 2.31 (m, 4H), 2.01 (qd, *J* = 7.5, 3.9 Hz, 4H), 1.87 – 1.72 (m, 4H), 1.70 – 1.61 (m, 4H), 1.55 (s, 4H), 1.47 – 1.34 (m, 4H), 1.35 – 1.19 (m, 20H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.7, 164.3, 157.0, 141.3, 126.0, 114.5, 68.9, 64.9, 47.3, 39.6, 37.5, 34.2, 32.9, 31.0, 29.7, 29.5, 29.4, 29.3, 29.1, 29.0, 28.8, 28.2, 27.0, 25.9, 18.0; HRMS (ESI) for **14b**: *m/z* $[M + H]^+$ calcd for $C_{18}H_{34}BrN_2O_3$:405.1753, Found: 405.1756. HRMS (ESI) for **14c**: *m/z* $[M + H]^+$calcd for $C_{24}H_{38}N_3O_6$:464.2761, Found: 464.2770.

*Compound* **14b** *and* **14c** (reaction at rt)**:** Thick liquid, (60% yield); $^1$H NMR (400 MHz, $CDCl_3$): δ 8.22 – 8.10 (m, 1H), 6.91 (dd, *J* = 7.3, 5.1 Hz, 1H), 5.52 (br s, 2H), 4.06 – 3.94 (m, 5H), 3.41 – 3.27 (m, 11H), 3.10 (dd, *J* = 12.4, 6.2 Hz, 4H), 2.37 (t, *J* = 8.1 Hz, 4H), 2.06 – 1.96 (m, 4H), 1.87 – 1.77 (m, 4H), 1.70 – 1.62 (m, 4H), 1.61 – 1.52 (m, 4H), 1.44 – 1.36 (m, 4H), 1.26 (s, 20H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.7, 164.3, 157.0, 141.4, 126.0, 114.5, 69.0, 64.9, 47.3, 39.6, 37.5, 34.1, 32.9, 31.0, 29.5, 29.4, 29.3, 29.1, 28.8, 28.2, 27.1, 25.9, 18.0;

*Compound* **15b:** $R_f$ = 0.2 (EtOAc); thick liquid (41% yield); IR ($CHCl_3$): *v* 3340, 1671, 1592, 1522, 1210, 816 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.63 (br s, 1H), 4.22 – 4.15 (m, 2H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.70 – 3.66 (m, 2H), 3.60 (t, *J* = 5.7 Hz, 2H), 3.38 – 3.29 (m, 4H), 3.11 (q, *J* = 6.3 Hz, 2H), 2.37 (t, *J* = 8.0 Hz, 2H), 2.06 – 1.97 (m, 2H), 1.70 – 1.63 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 175.7, 156.5, 71.3, 69.7, 63.8, 47.3, 42.8, 39.6, 37.7, 31.0, 27.1, 18.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{21}ClN_2NaO_4$:315.1087, Found: 315.1093.

### 3A.6.3 Structural data of carbonates A, B, C

*Compound* **(*A*):** $R_f$ = 0.5 (hexane/EtOAc, 85:15); white solid (82% yield), mp 53-54 °C; IR ($CHCl_3$): *v* 3292, 1766, 1595, 1491, 1233, 1016 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 2H), 7.29 – 7.15 (m, 3H), 2.64 (s, 1H), 2.26 – 2.16 (m, 2H), 2.00 – 1.89 (m, 2H), 1.76 – 1.60 (m, 4H), 1.58 – 1.50 (m, 1H), 1.42 – 1.29 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 151.2, 151.1, 129.5, 126.0, 121.3, 82.6, 78.7, 75.4, 36.9, 25.1, 22.7.

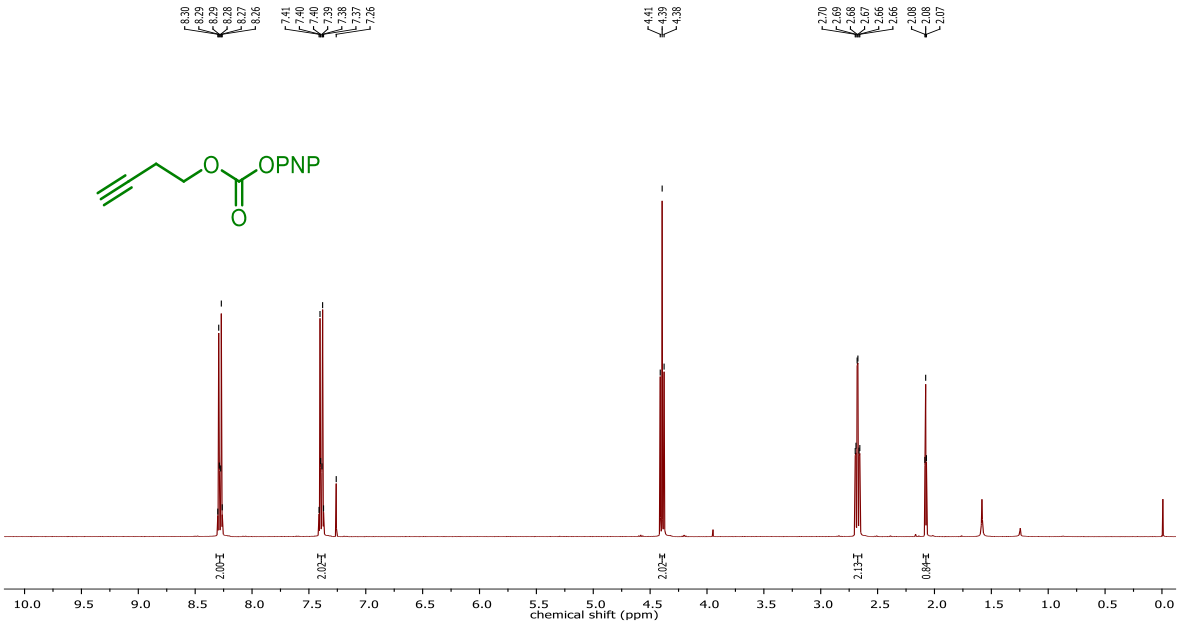
*Compound* **(*B*):** $R_f$ = 0.5 (hexane/EtOAc, 85:15); thick liquid; IR ($CHCl_3$): *v* 3289, 1744, 1452, 1225, 912 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.31 (m, 5H), 5.16 (s, 2H), 2.64 (s, 1H), 2.24 – 2.15 (m, 2H), 1.92 – 1.83 (m, 2H), 1.73 – 1.60 (m, 4H), 1.58 – 1.49 (m, 1H), 1.38 – 1.26 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 155.1, 135.3, 128.6, 128.5, 128.5, 83.0, 77.7, 74.9, 69.3, 36.8, 25.0, 22.6.

*Compound* **(C):** $R_f$ = 0.5 (hexane/EtOAc, 85:15); thick liquid; IR ($CHCl_3$): *v* 3285, 1747, 1369, 1271, 1231, 1014; $^1H$ NMR (400 MHz, $CDCl_3$): δ 4.19 (t, *J* = 10.7 Hz, 2H), 2.62 (s, 1H), 2.23 – 2.12 (m, 2H), 1.92 – 1.80 (m, 2H), 1.72 – 1.59 (m, 4H), 1.58 – 1.48 (m, 1H), 1.38 – 1.26 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 153.0, 83.2, 77.4, 74.8, 63.7, 37.0, 25.1, 22.7, 14.4.

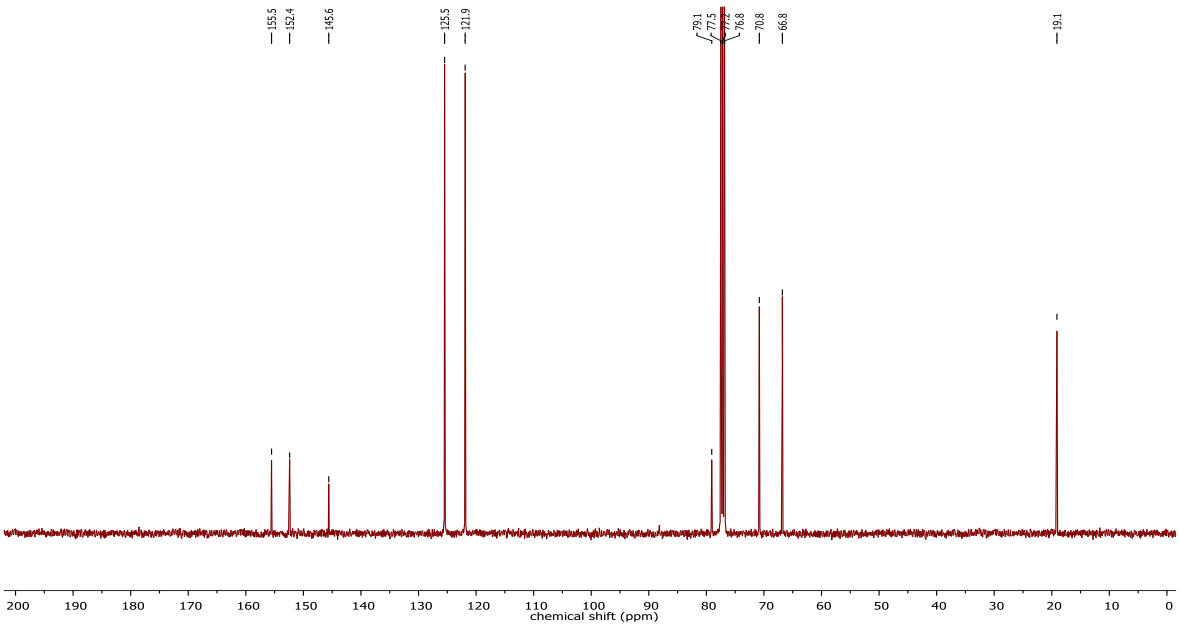
### 3A.7 Representative Spectral Charts

Kindly see the supporting documents file in *Beilstein J. Org. Chem.* **2016,** *12*, 2086–2092. https://doi.org/10.3762/bjoc.12.197 for spectral charts of compounds (**10a, 15a, 16a and 17a**).

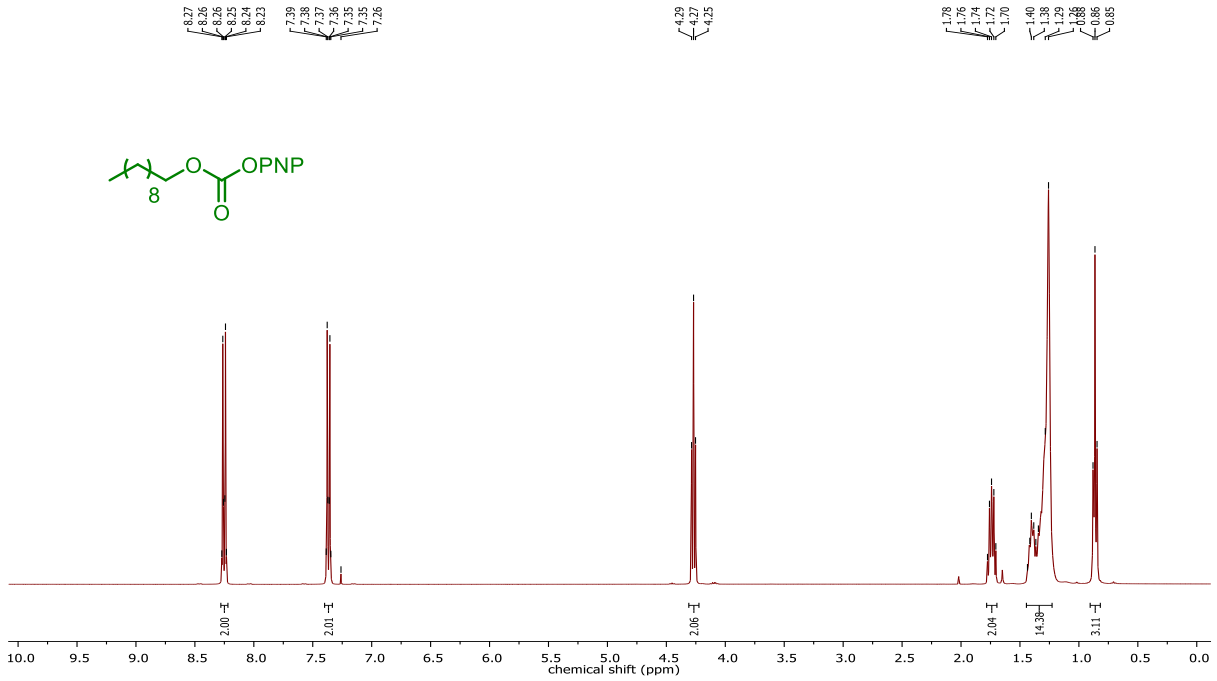
## $^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 2a



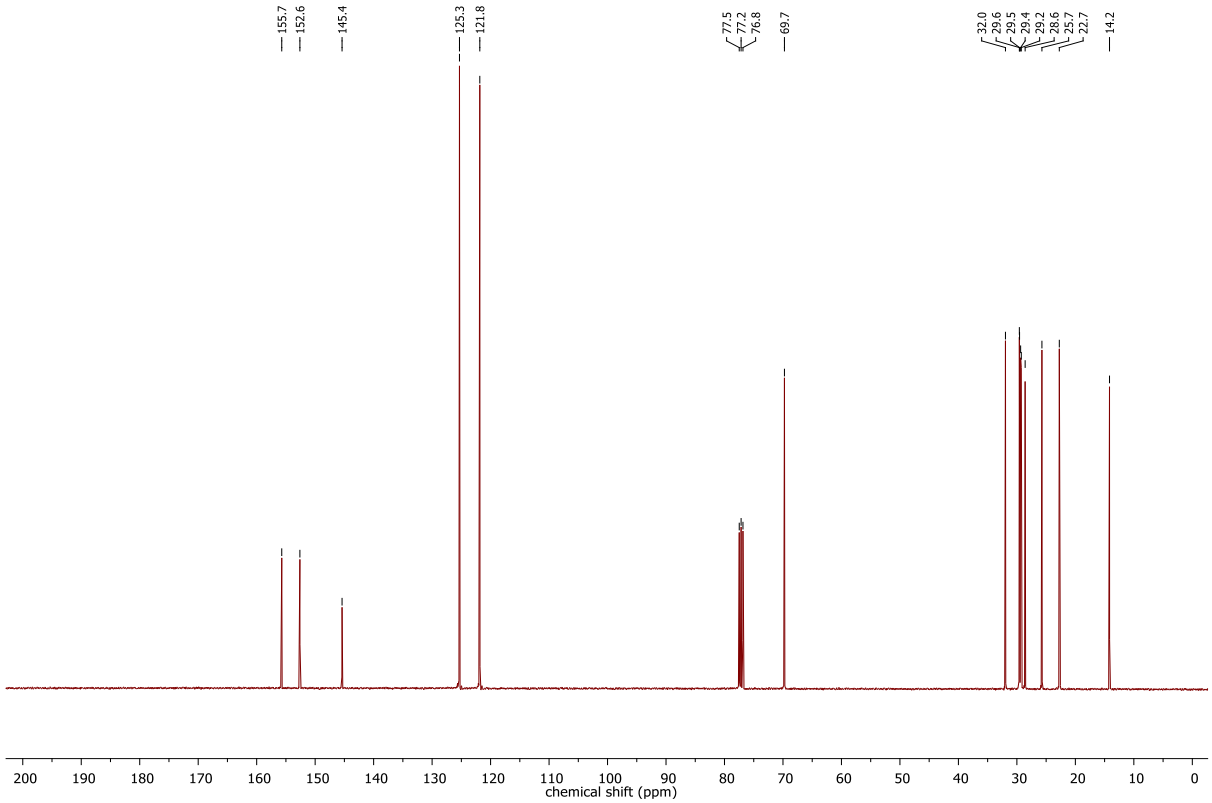

## $^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 2a



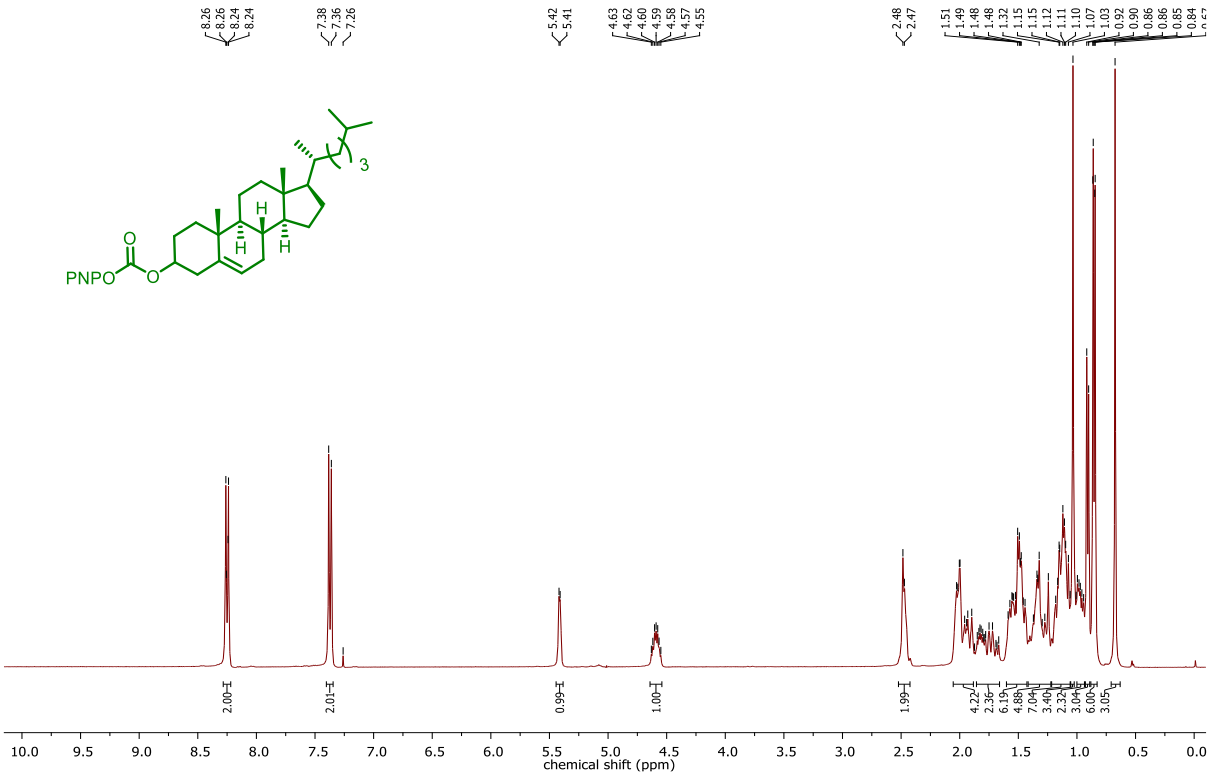
## $^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 3a



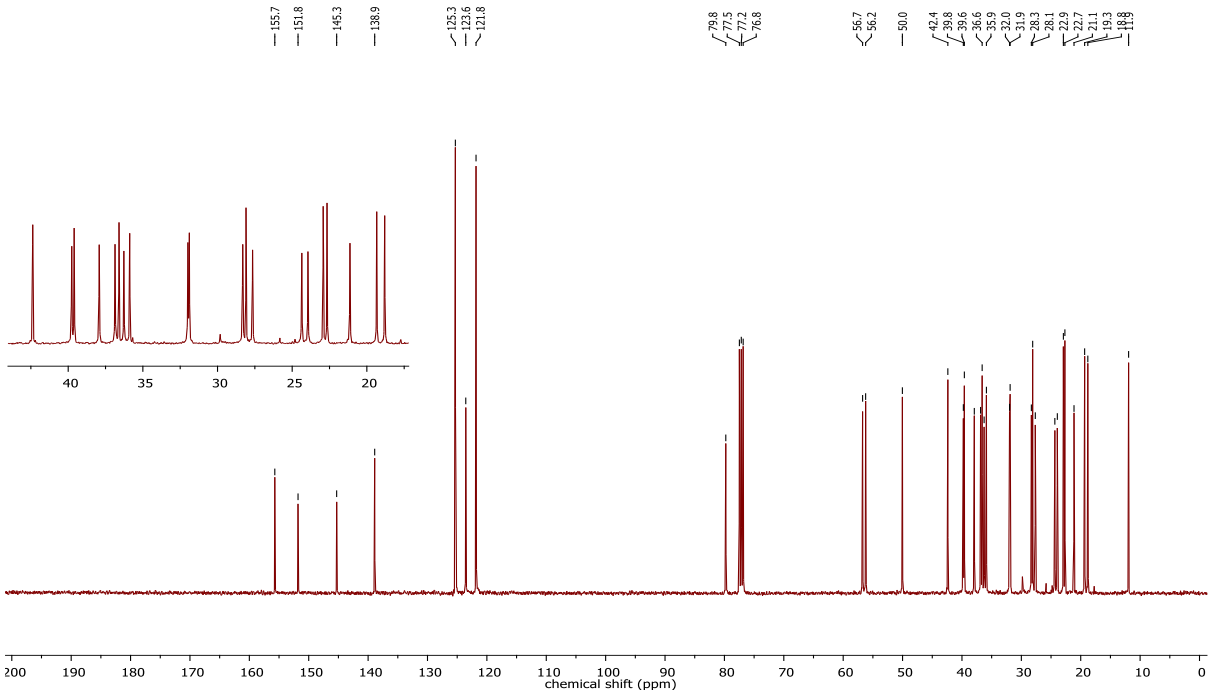

## $^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 3a



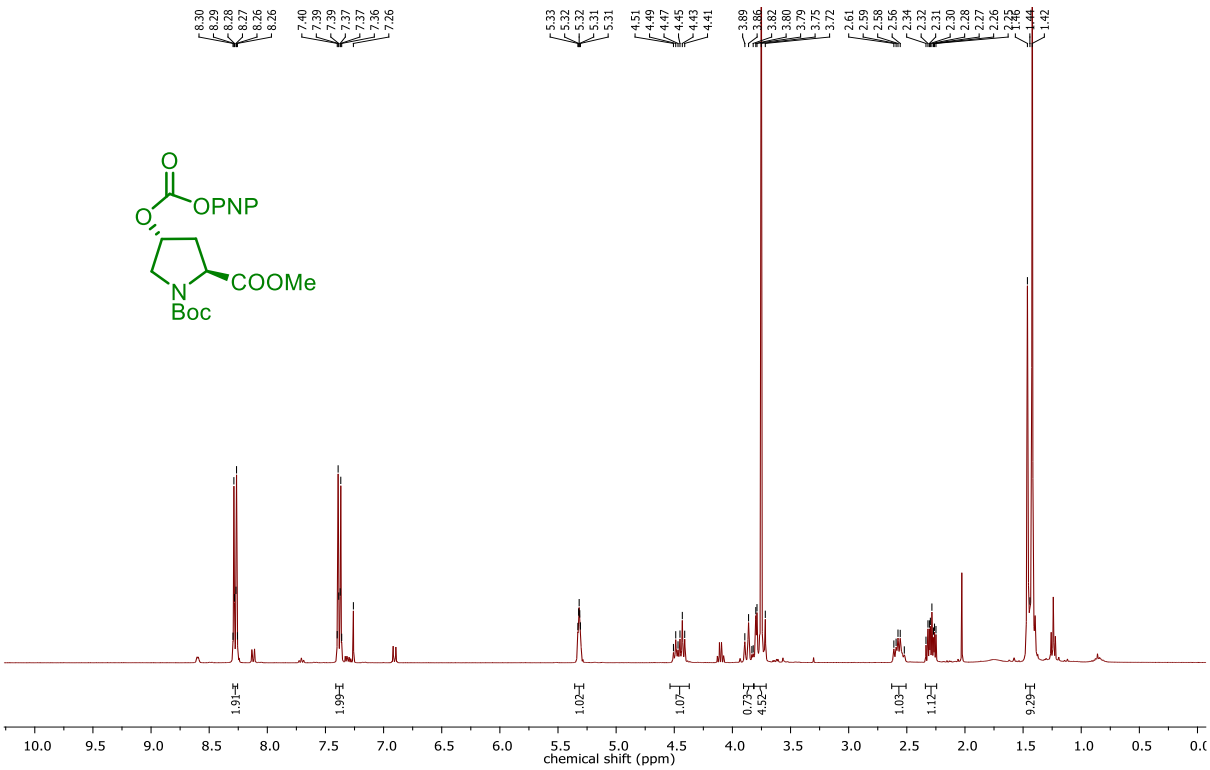
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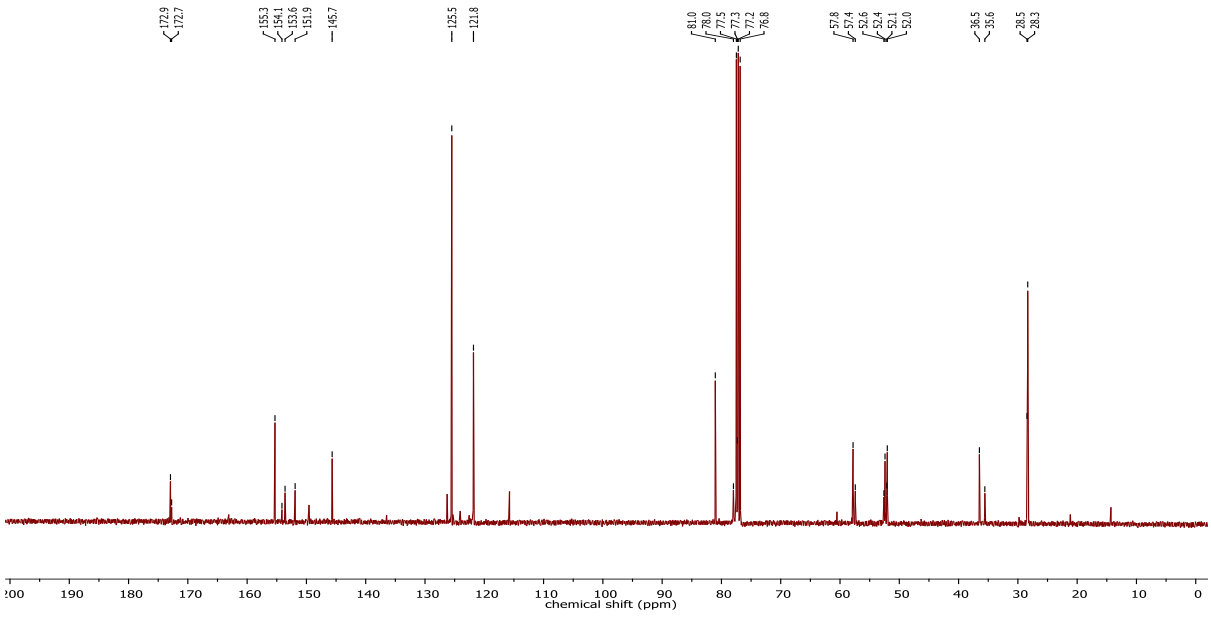

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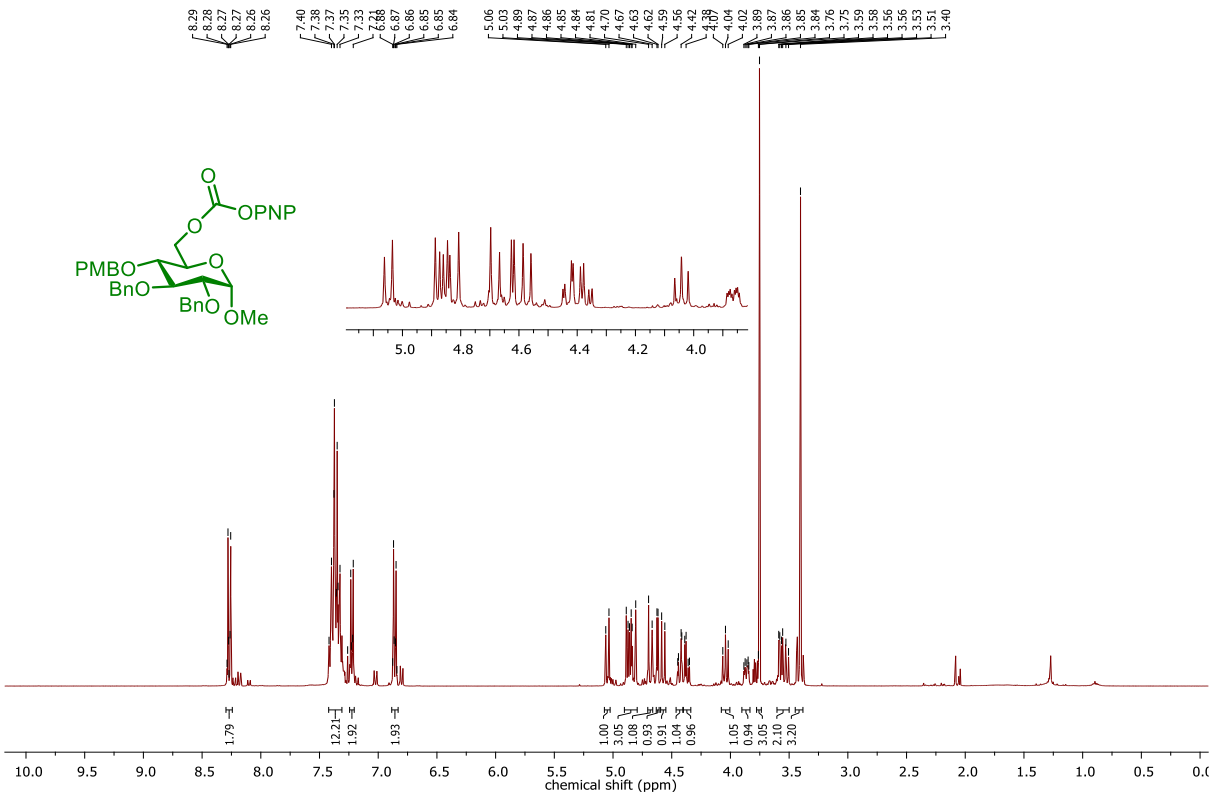
**$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 5a**



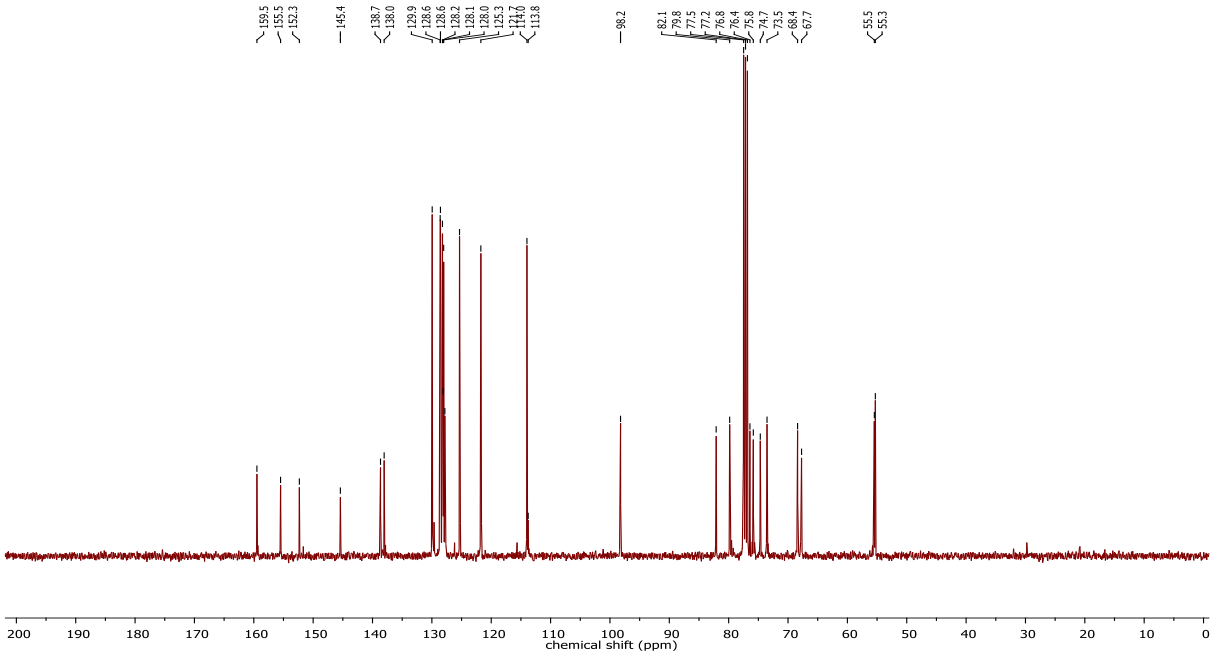

**$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 5a**



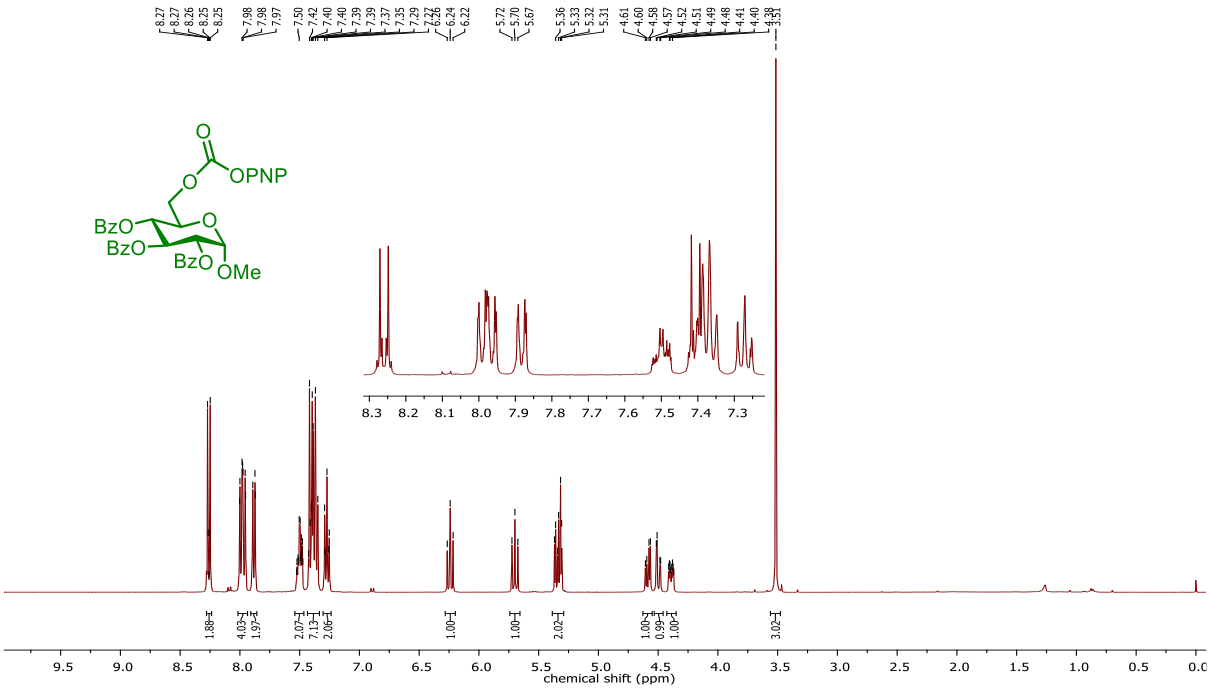
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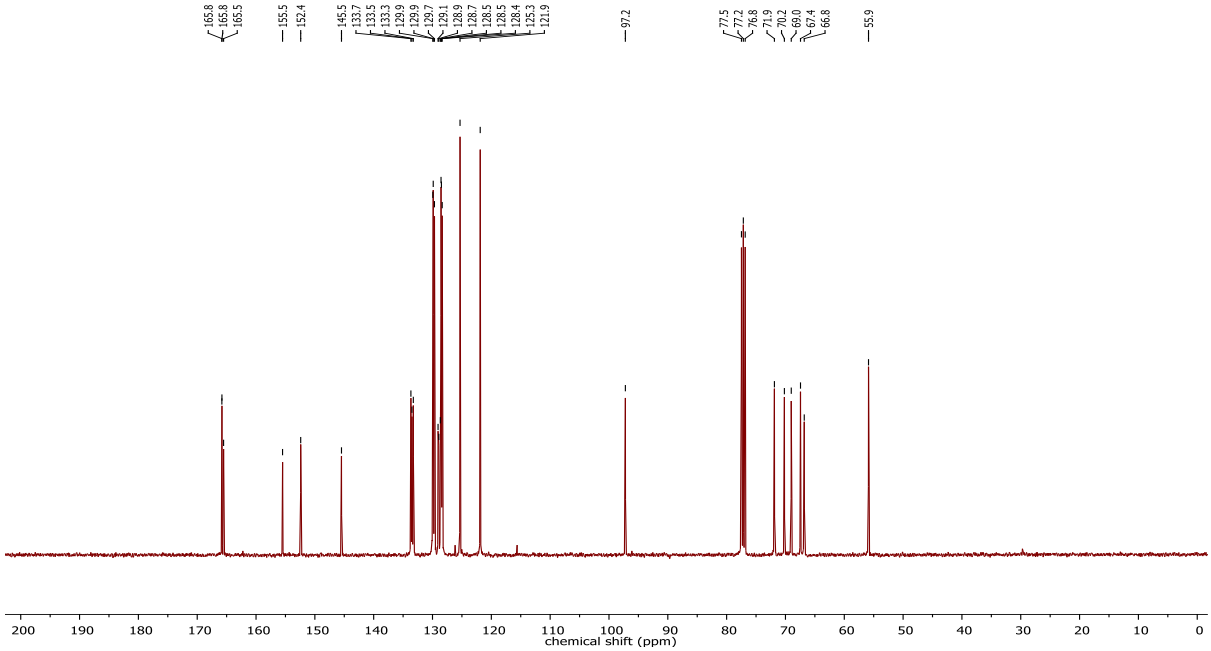

**$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 6a**



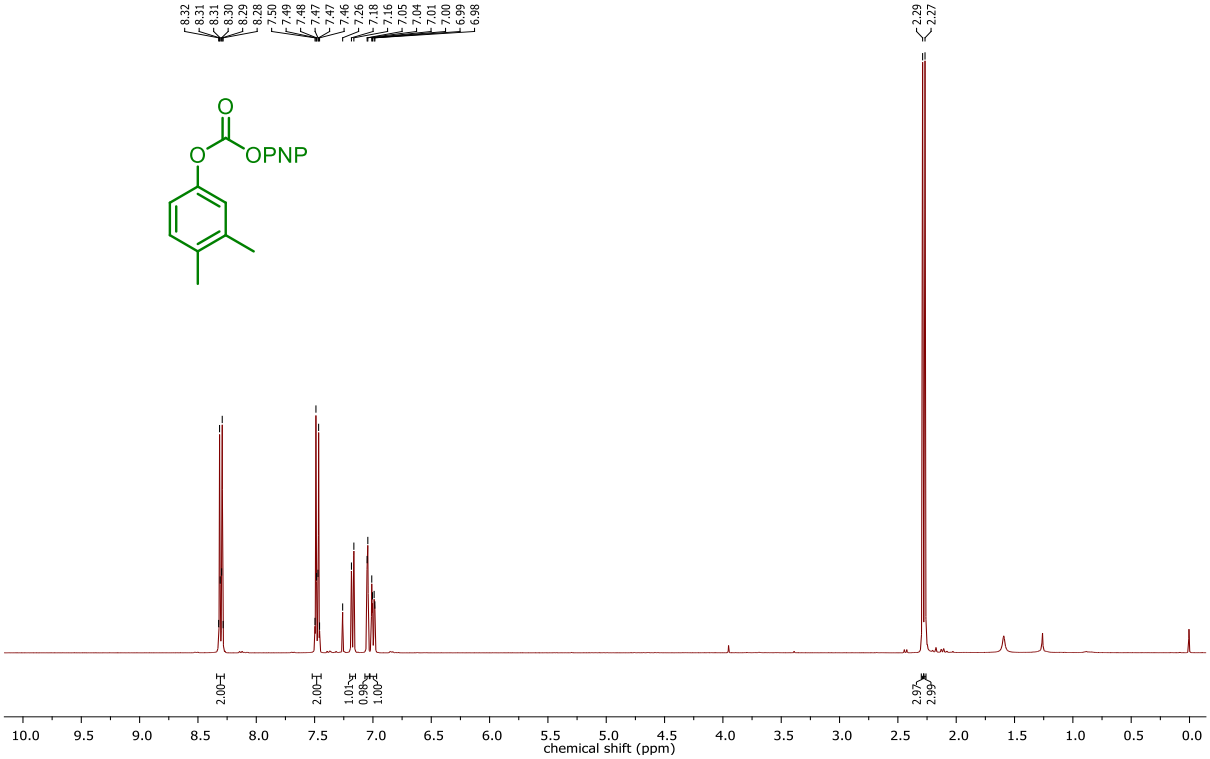
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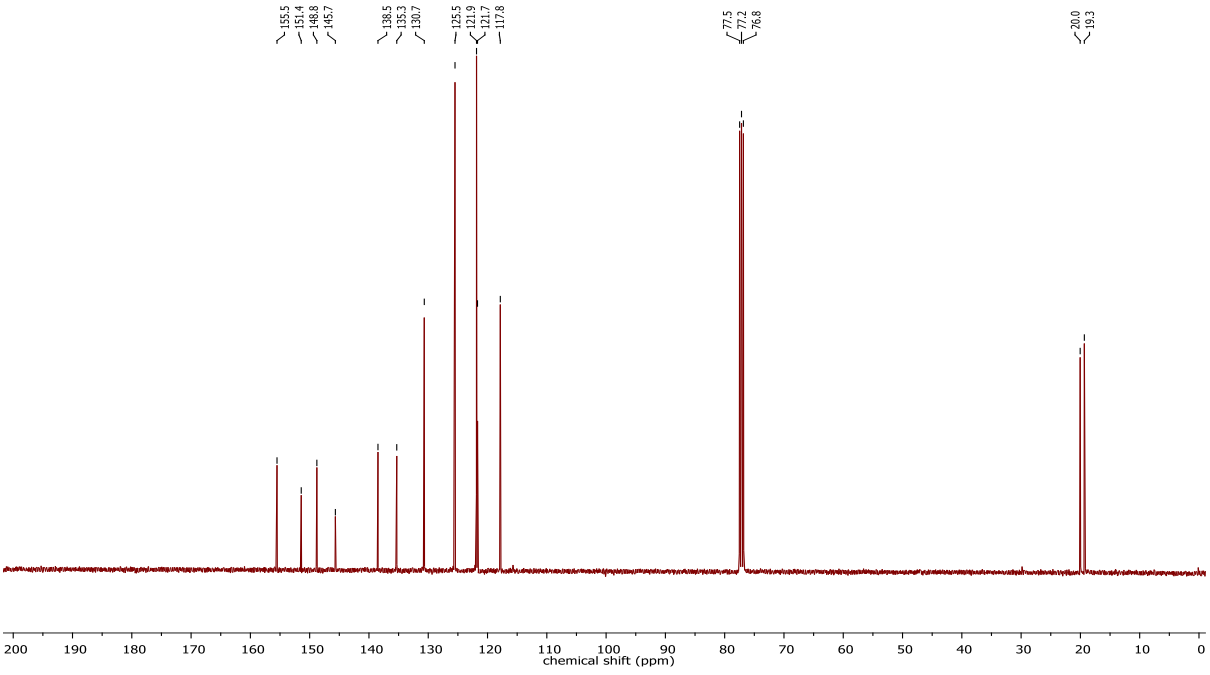

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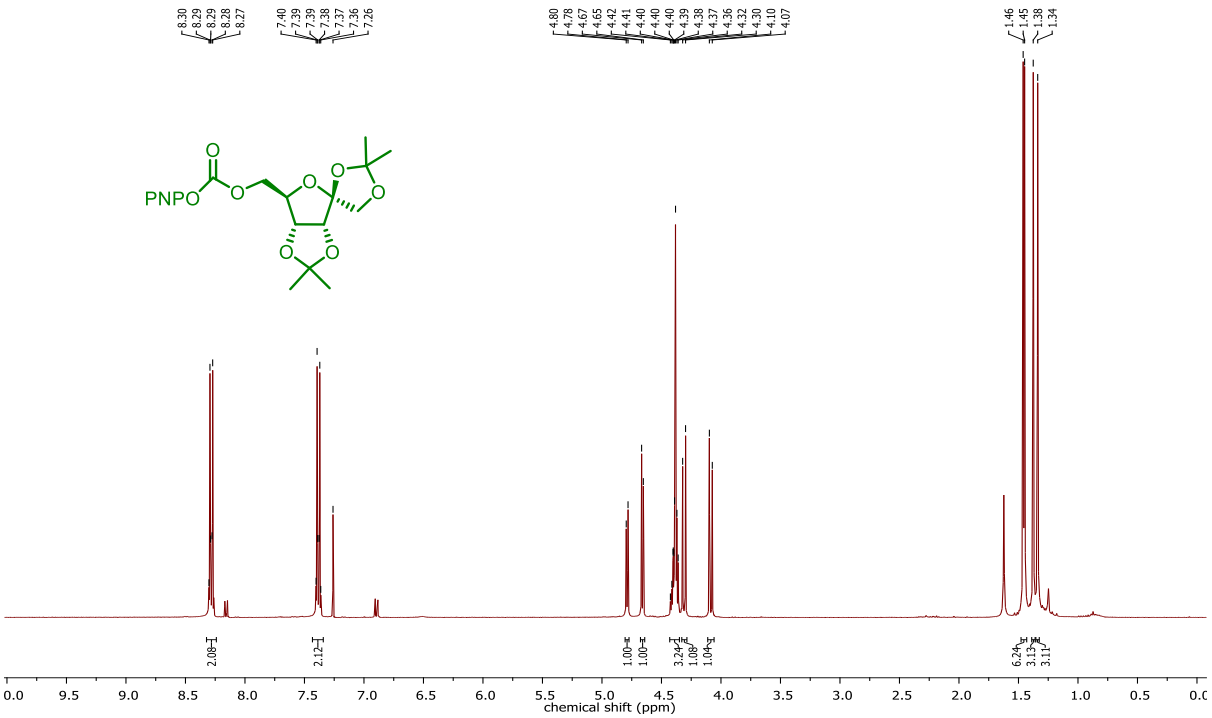
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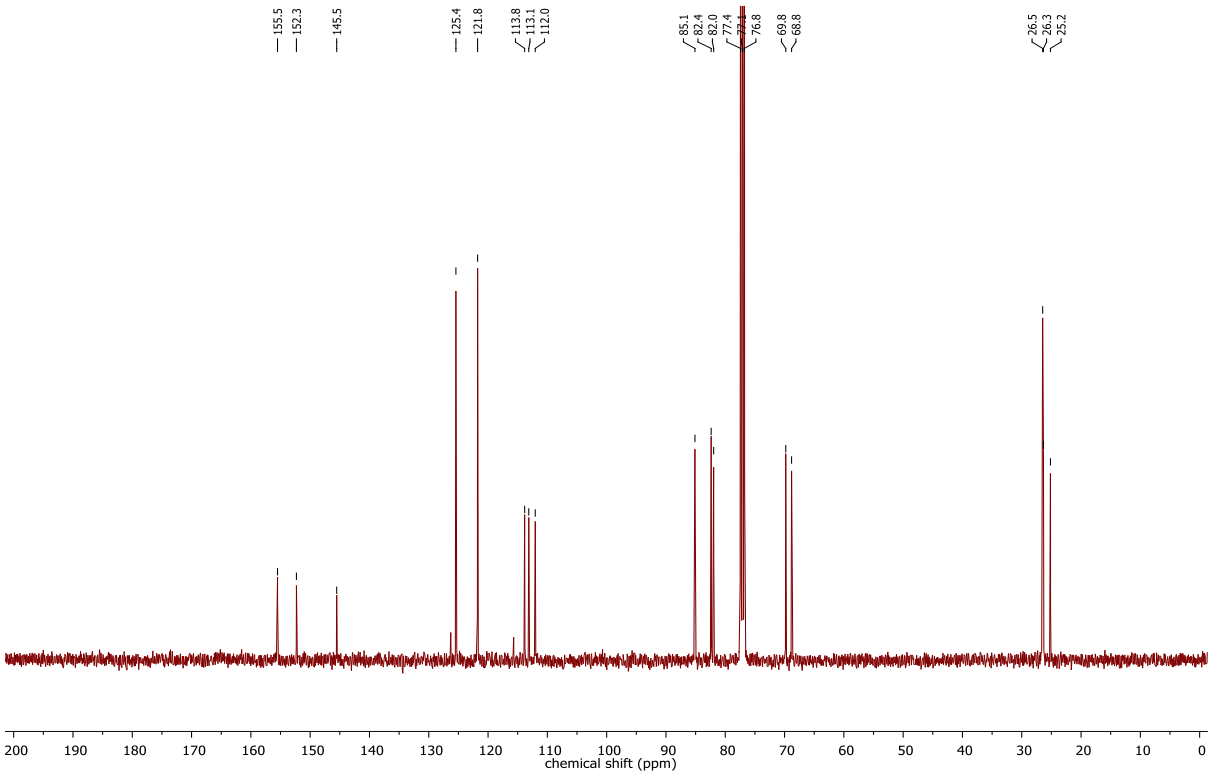

**$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 9a**



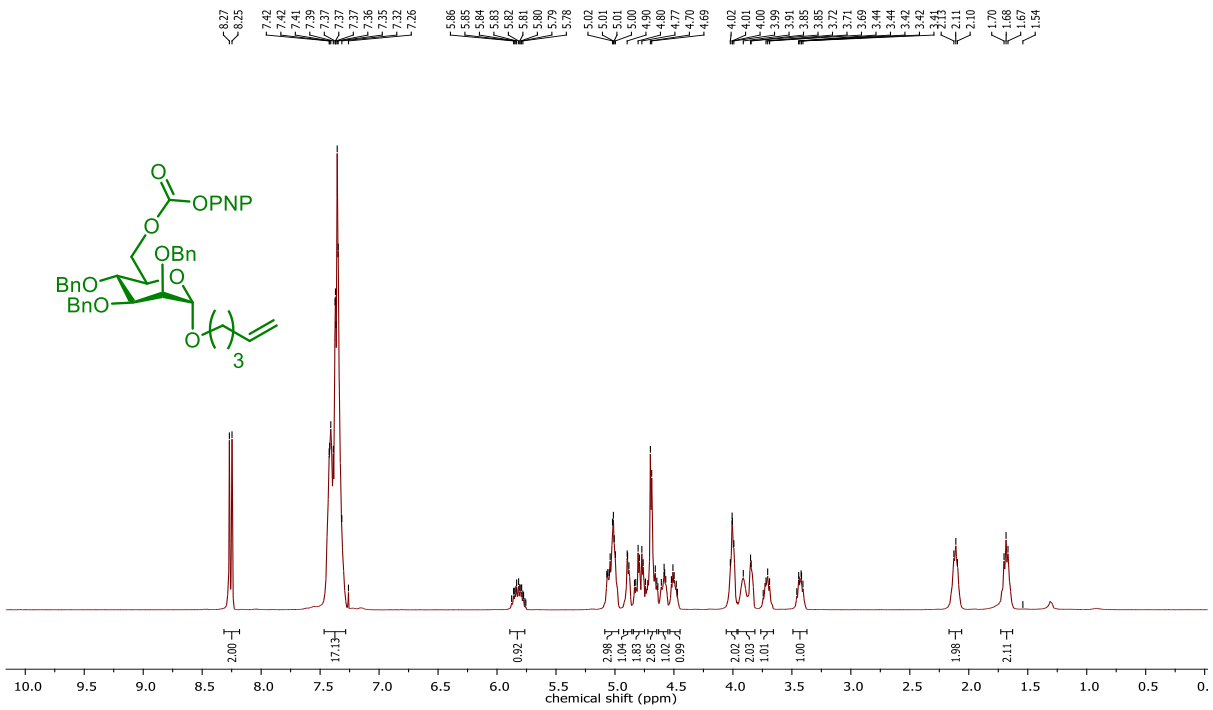
**$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 11a**



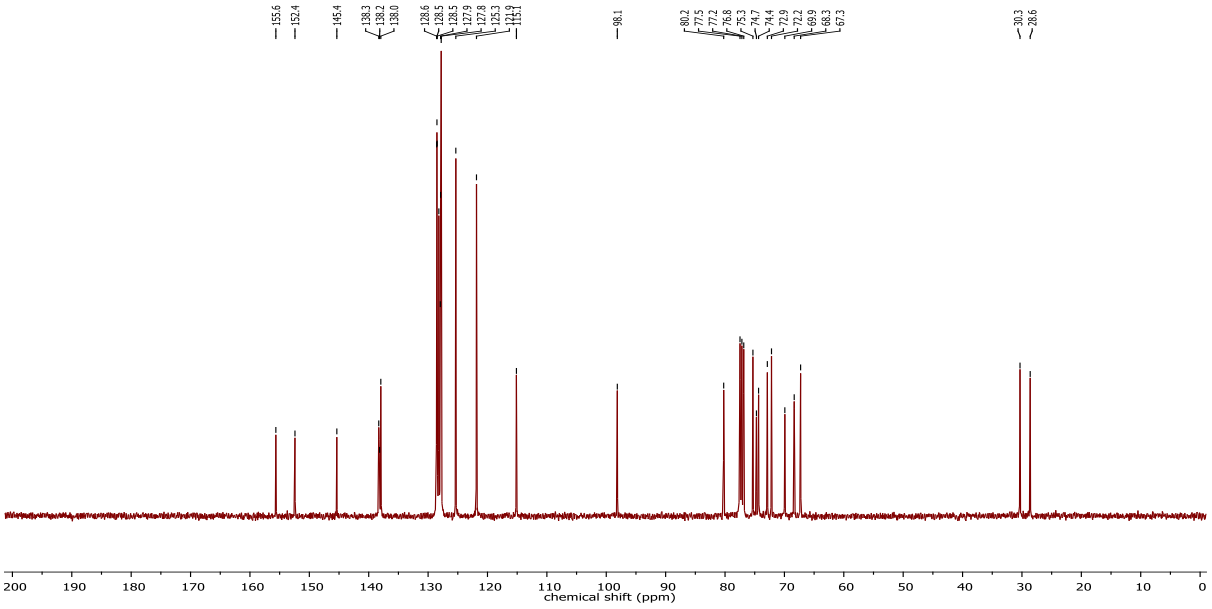

**$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 11a**



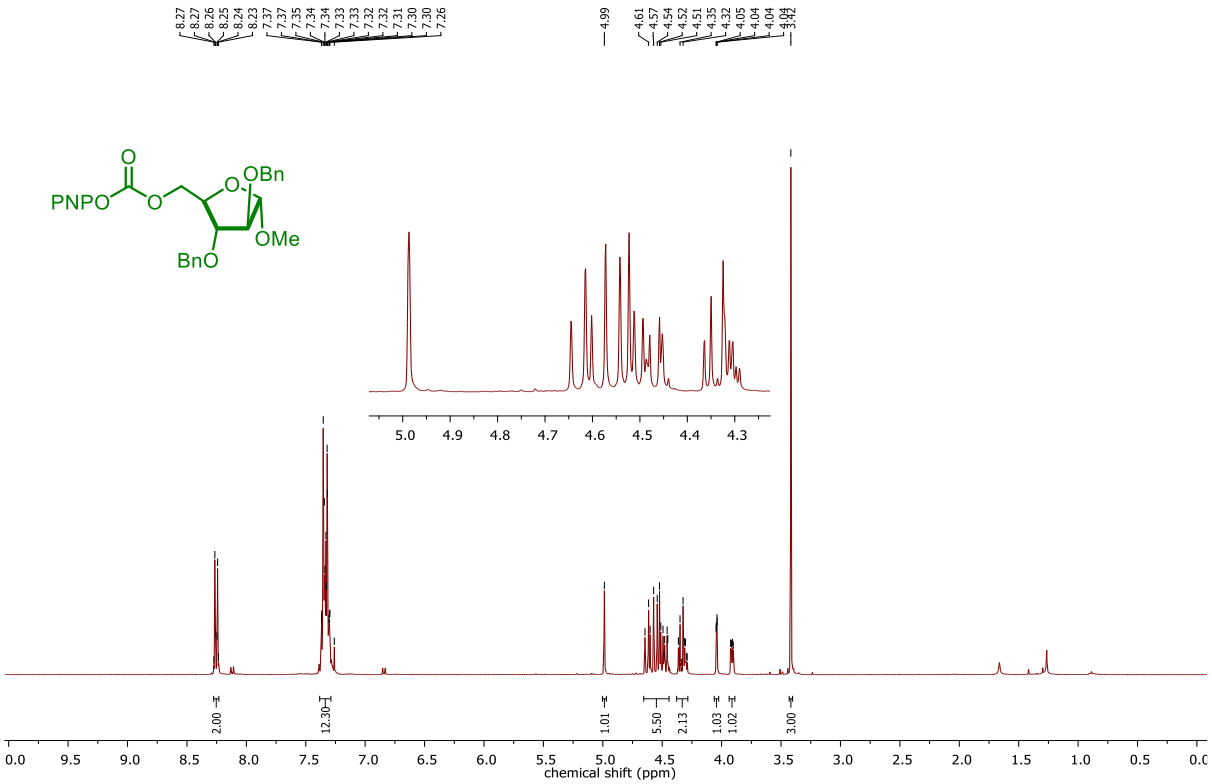
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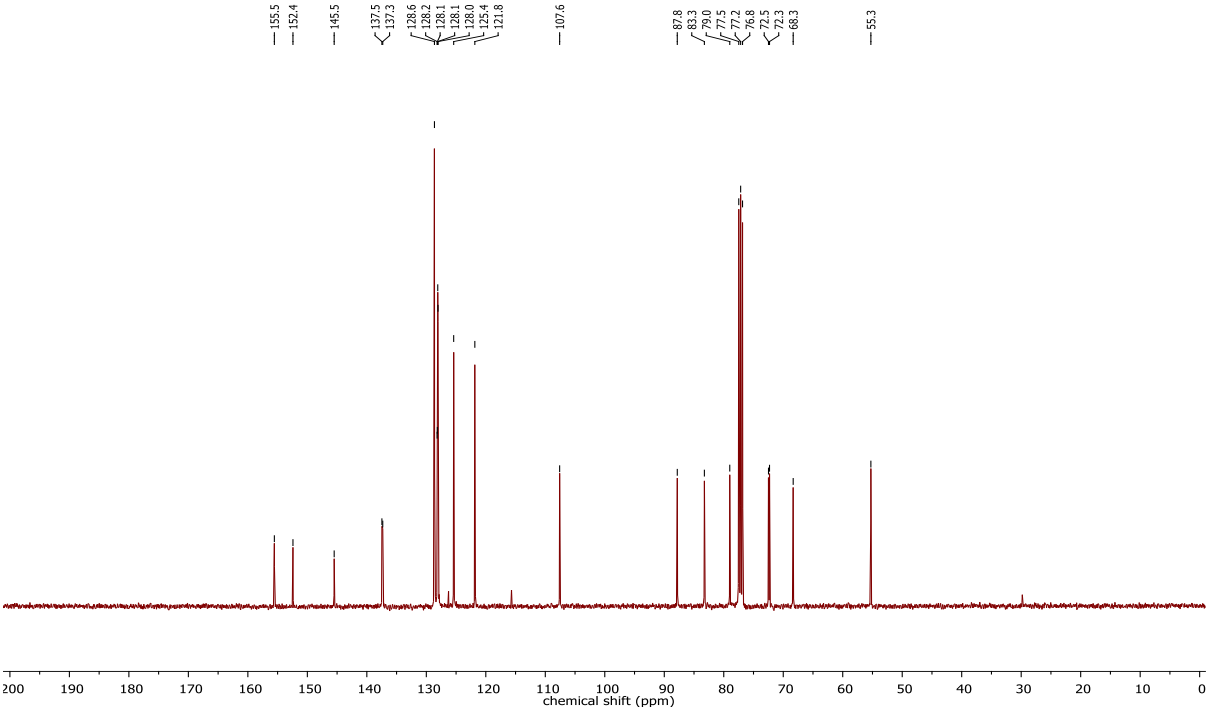

## $^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 12a



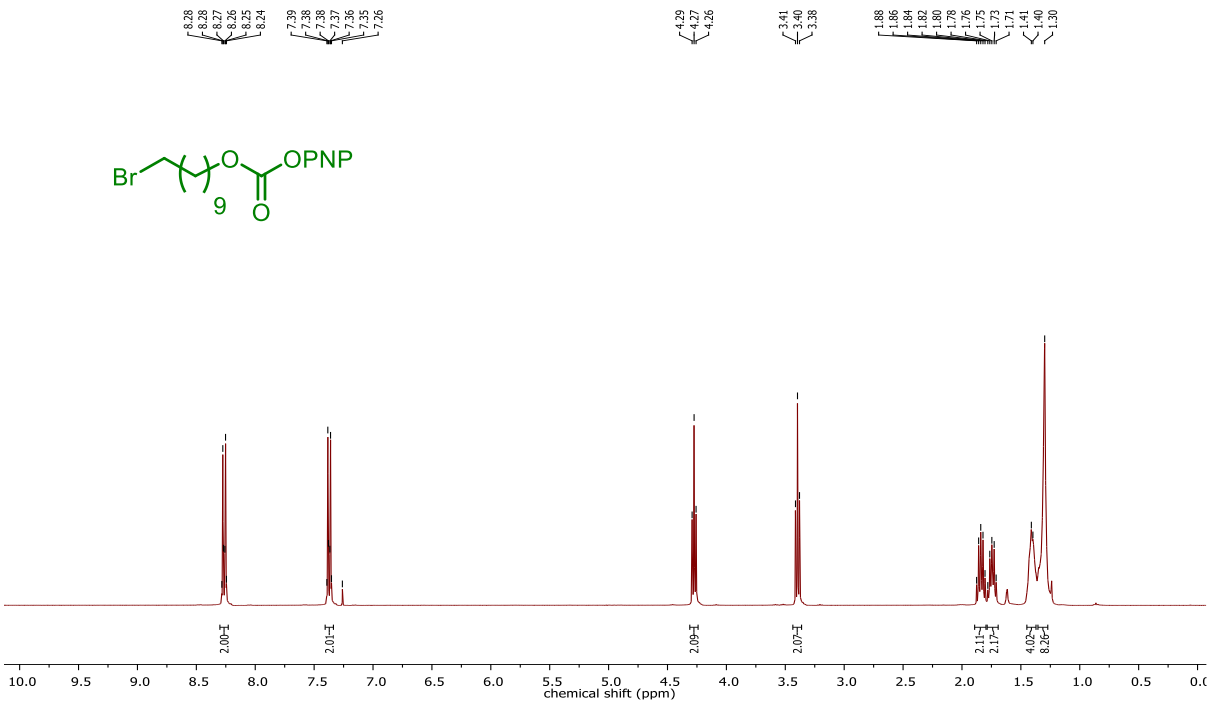
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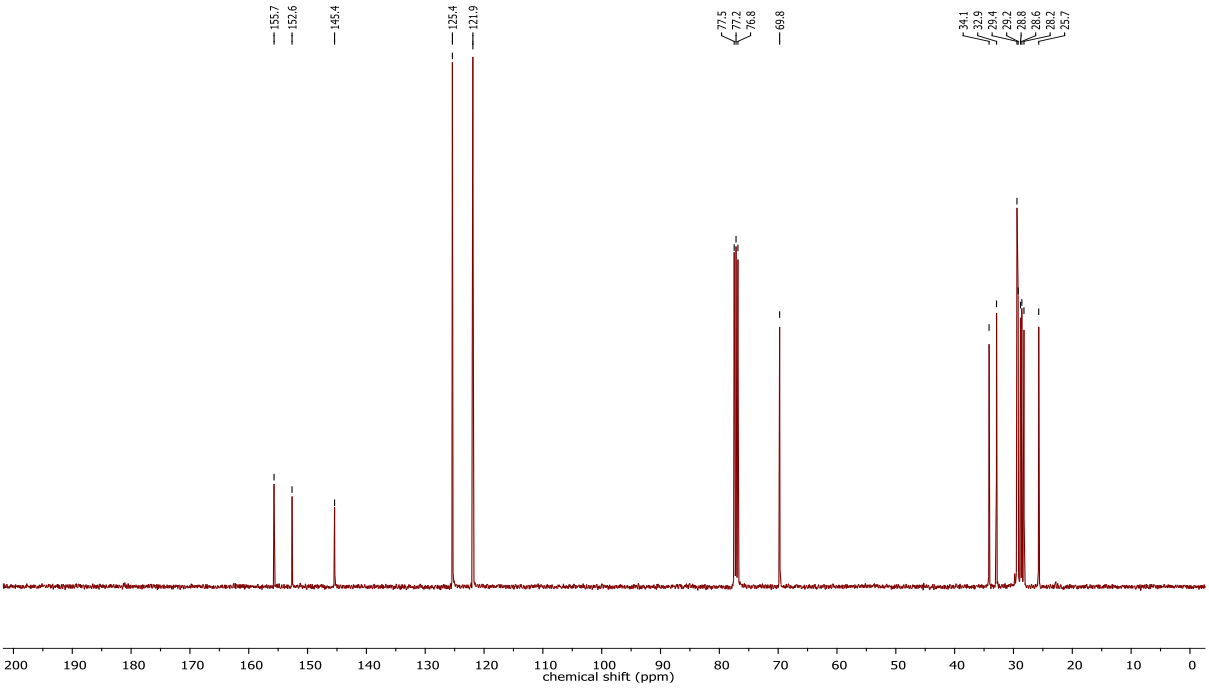

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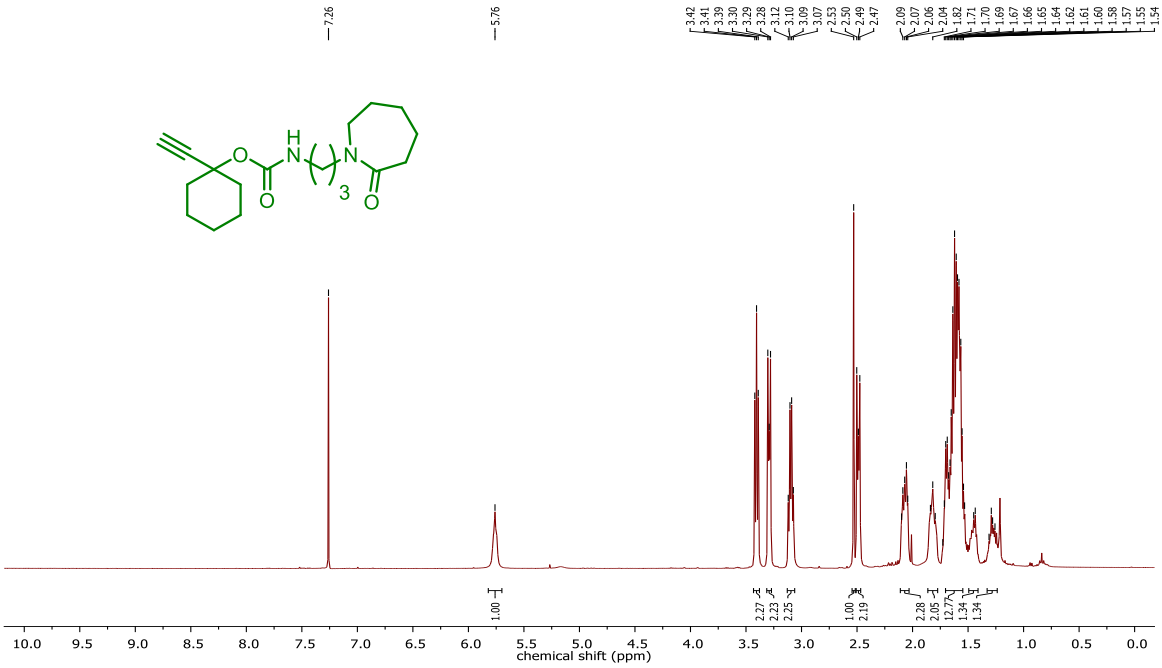
## $^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 14a



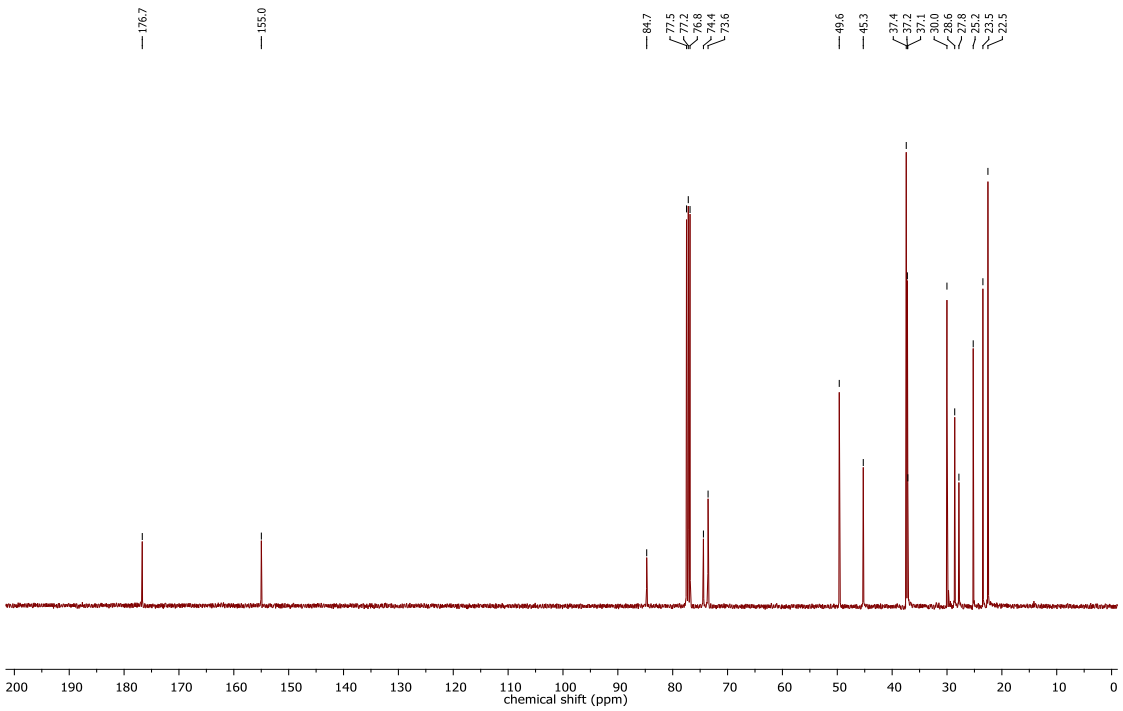

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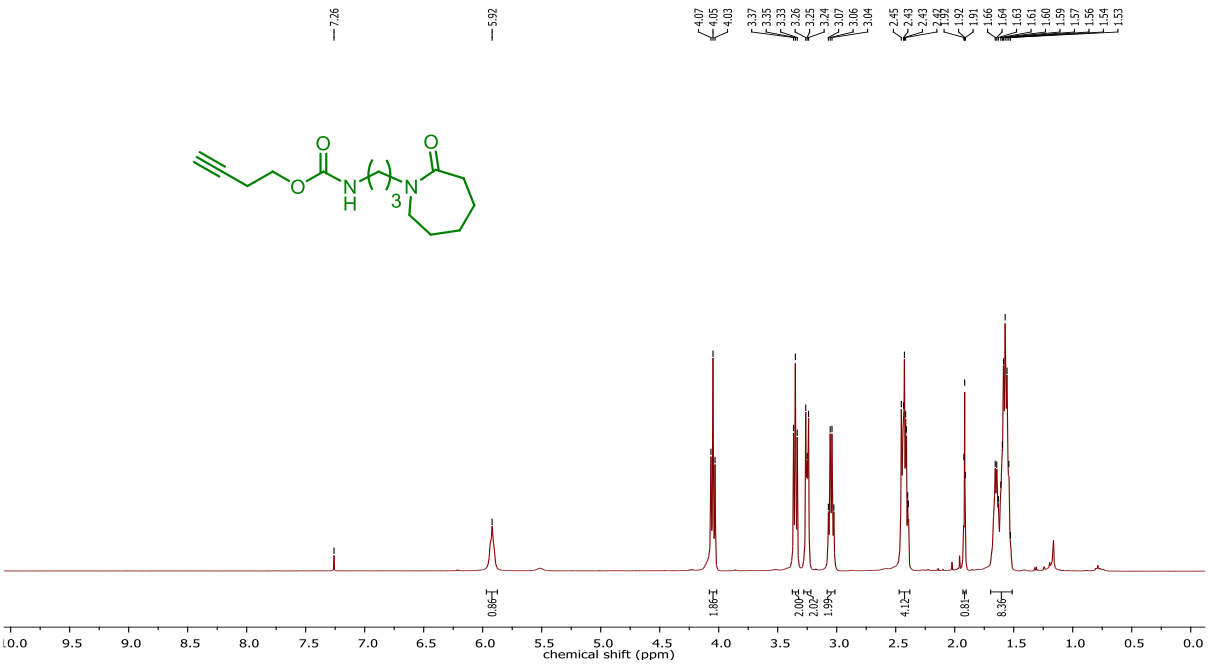
**$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 1b**



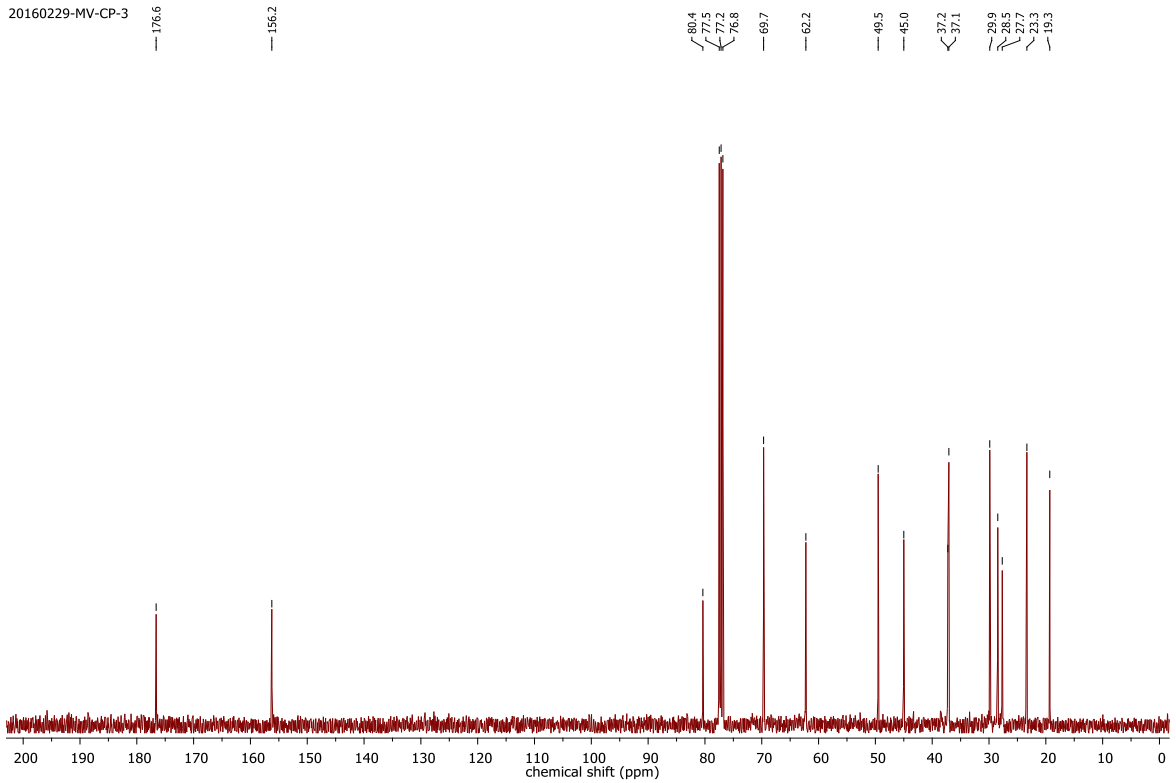

**$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 1b**



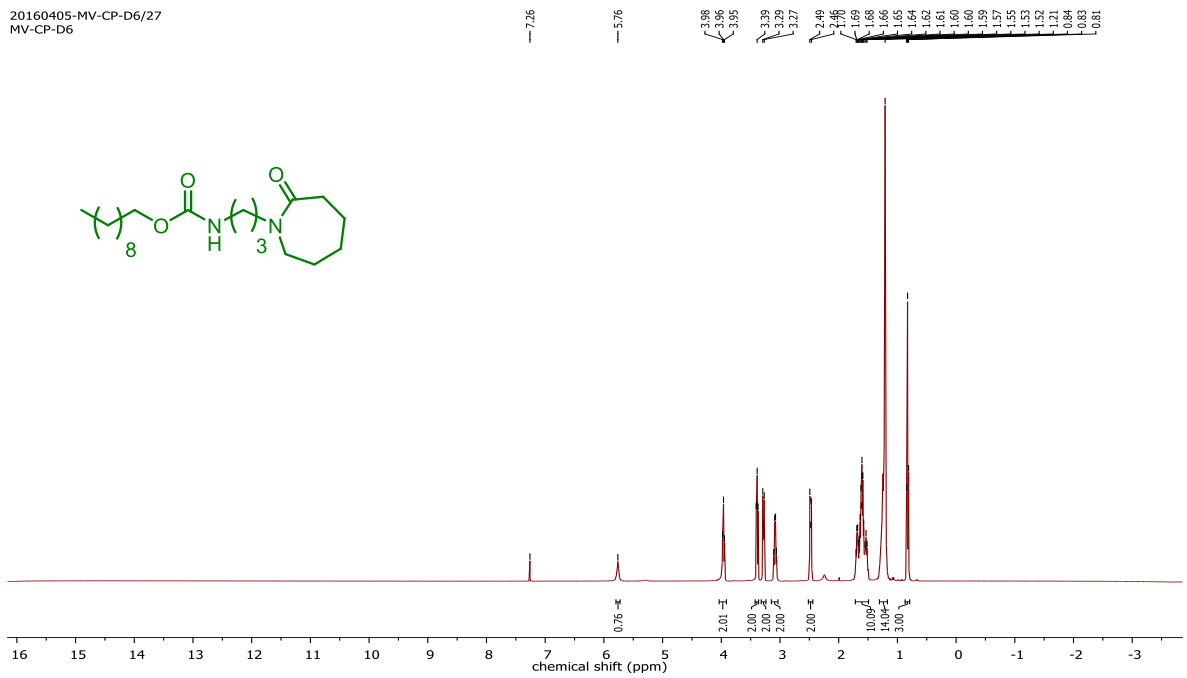
## $^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 2b



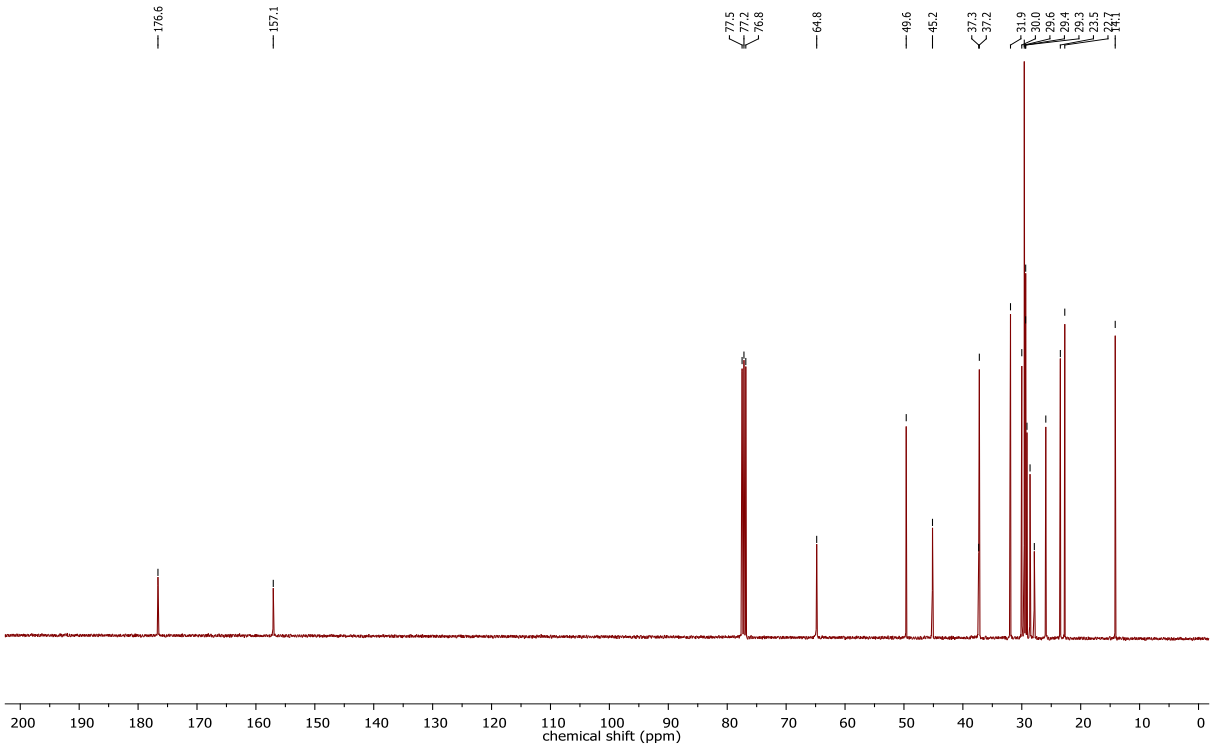

## $^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 2b



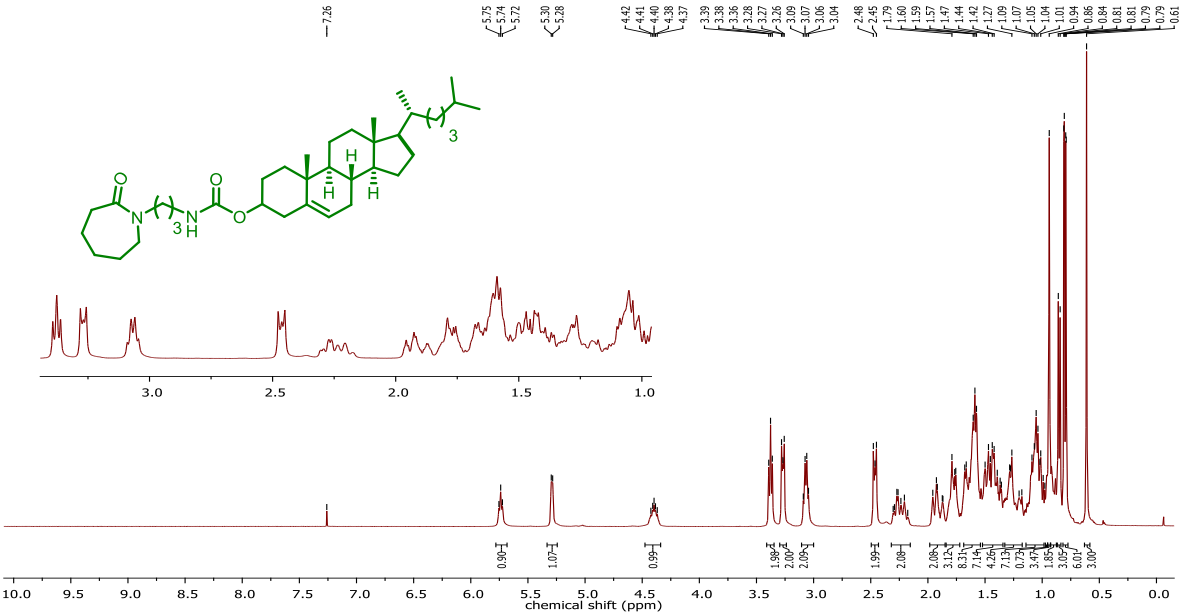
## $^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 3b



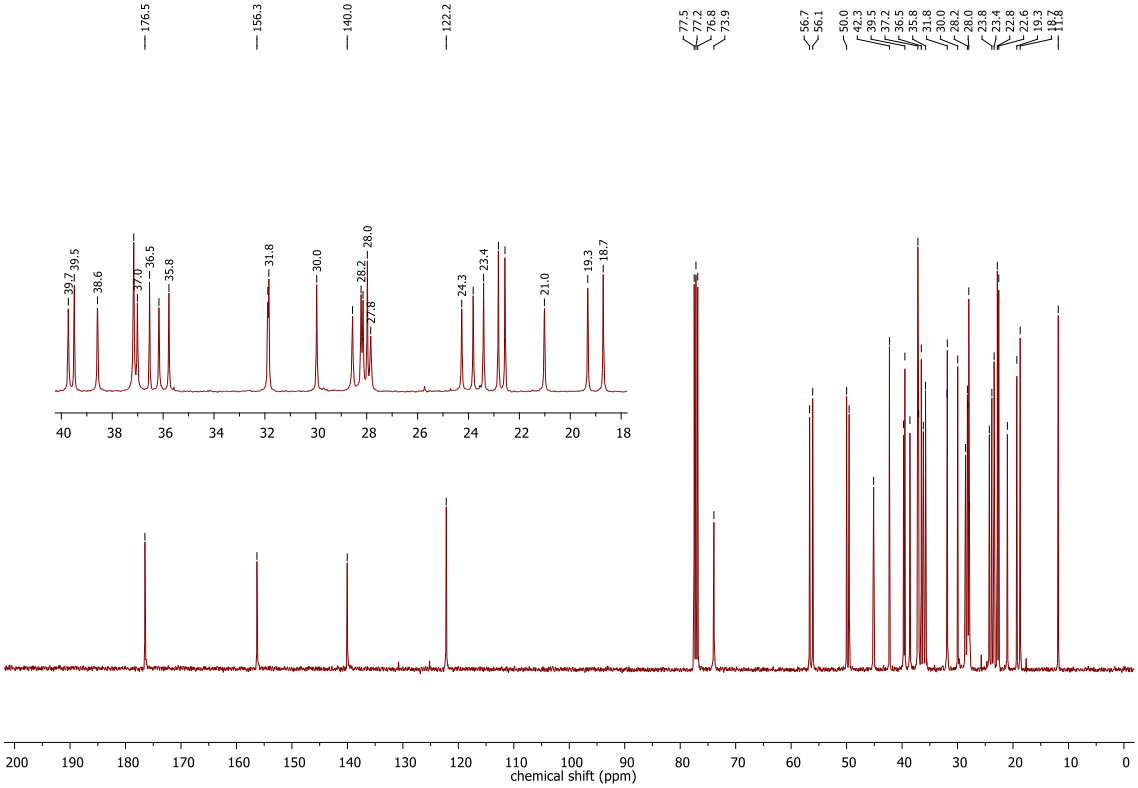

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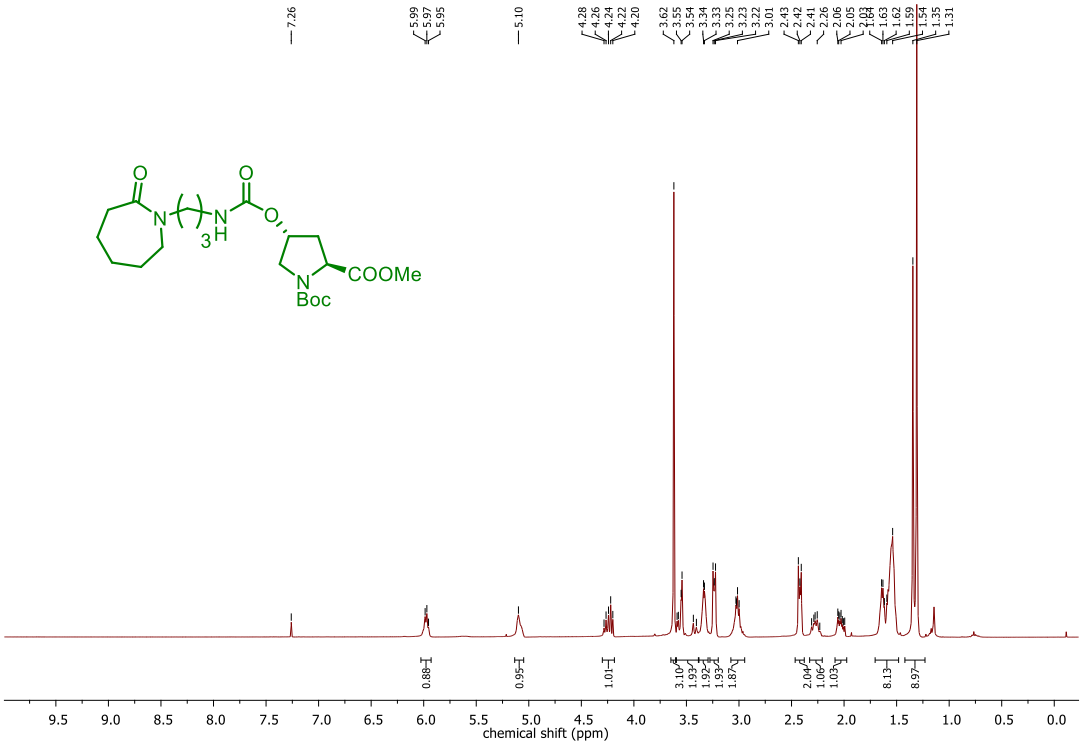
## $^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 4b



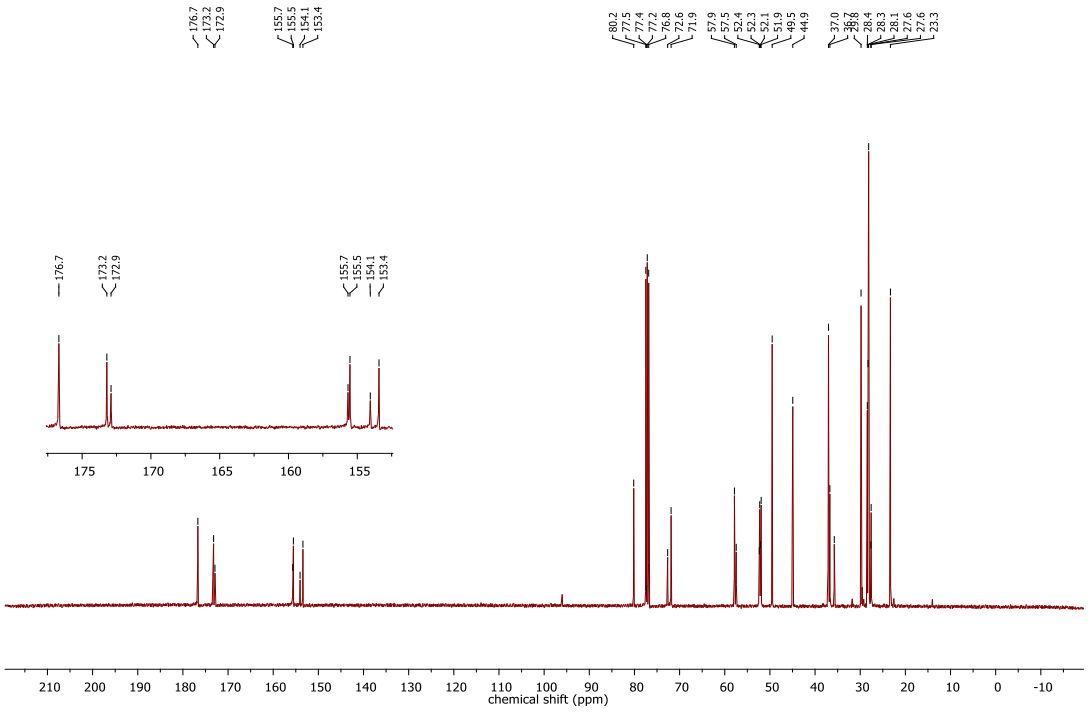

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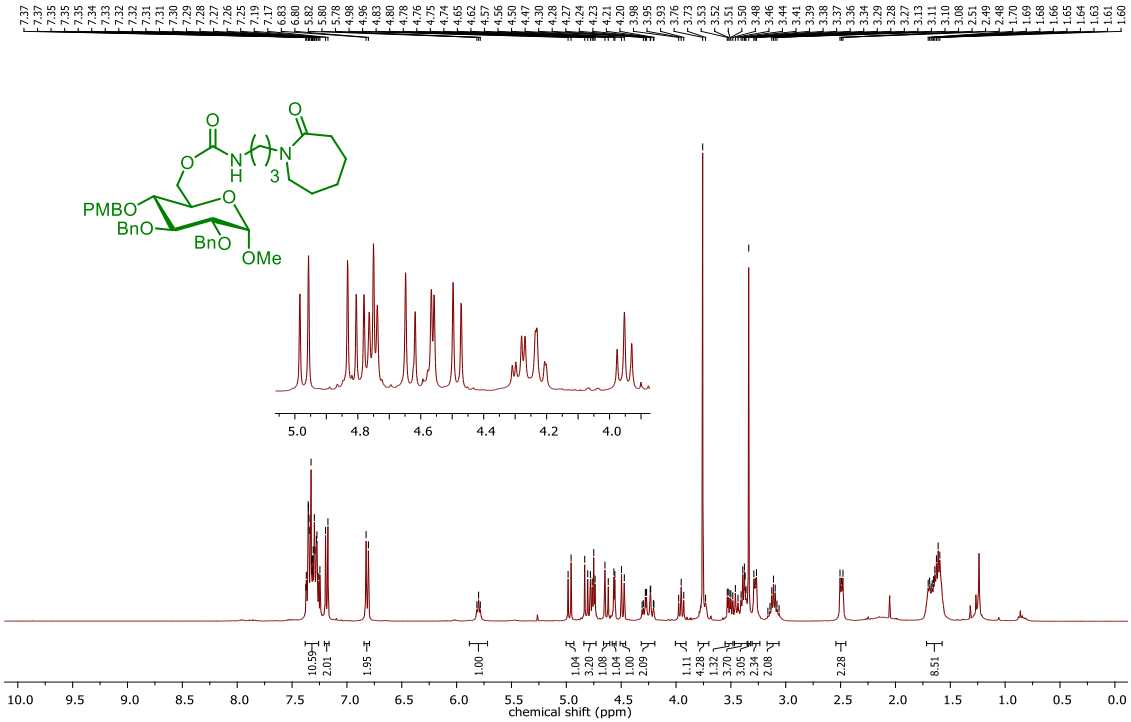
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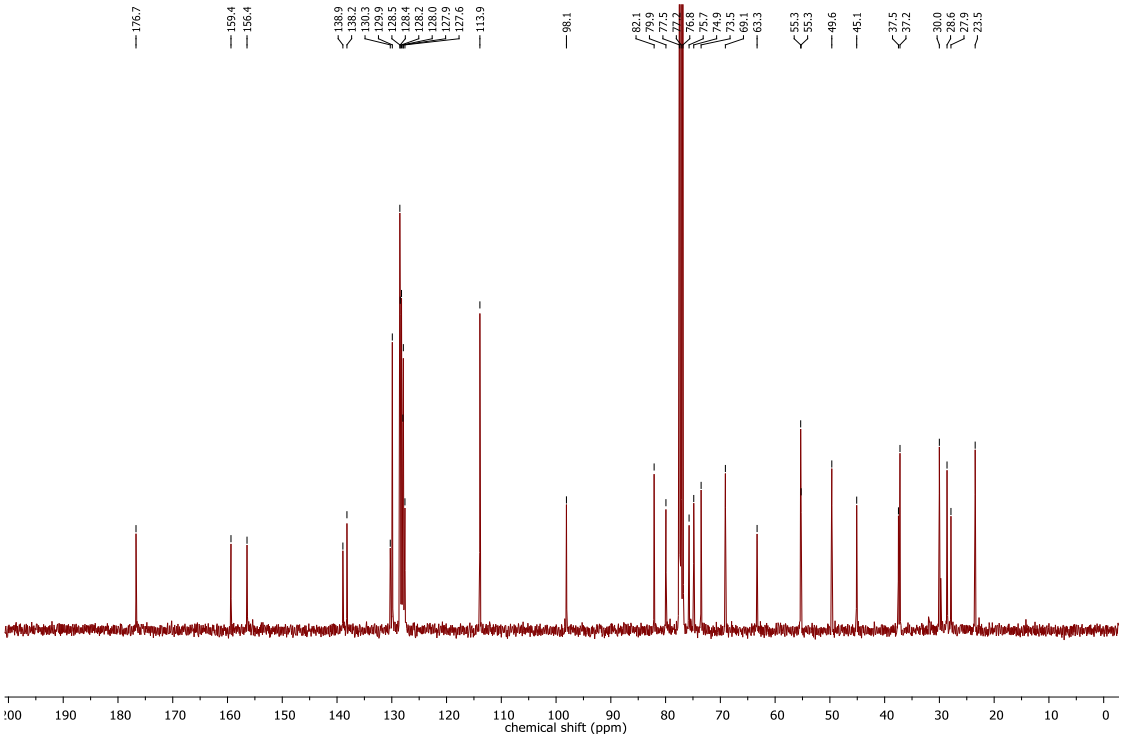

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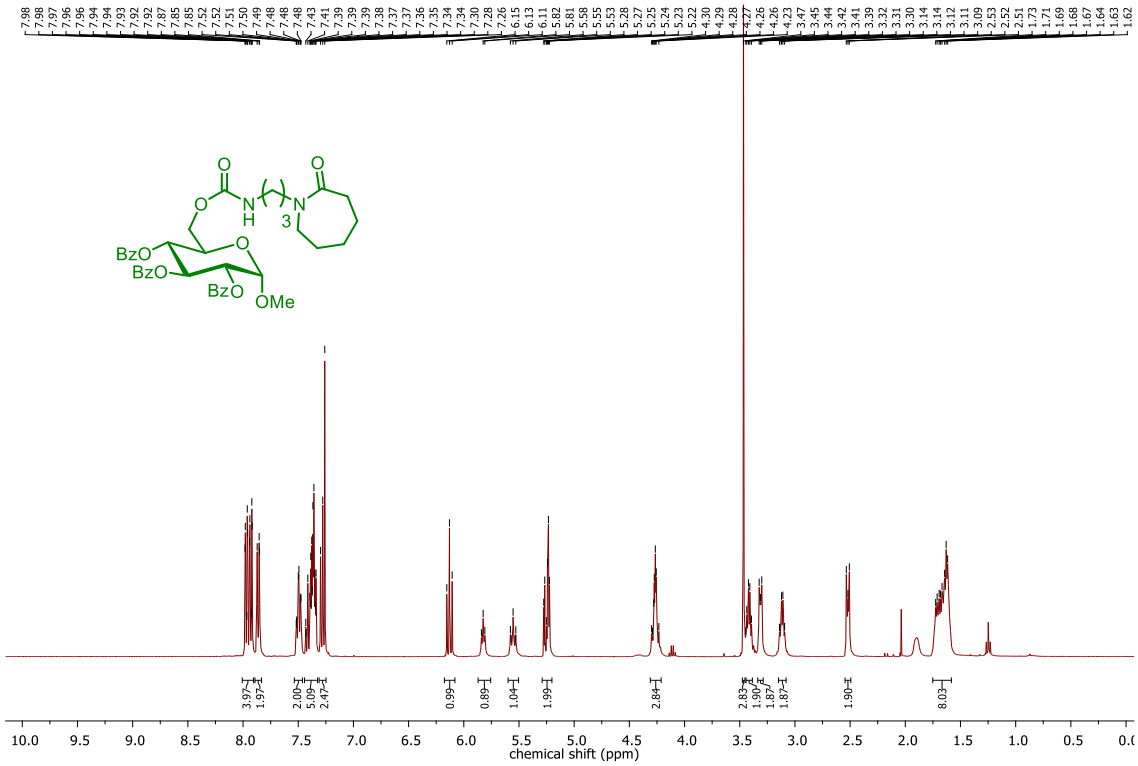
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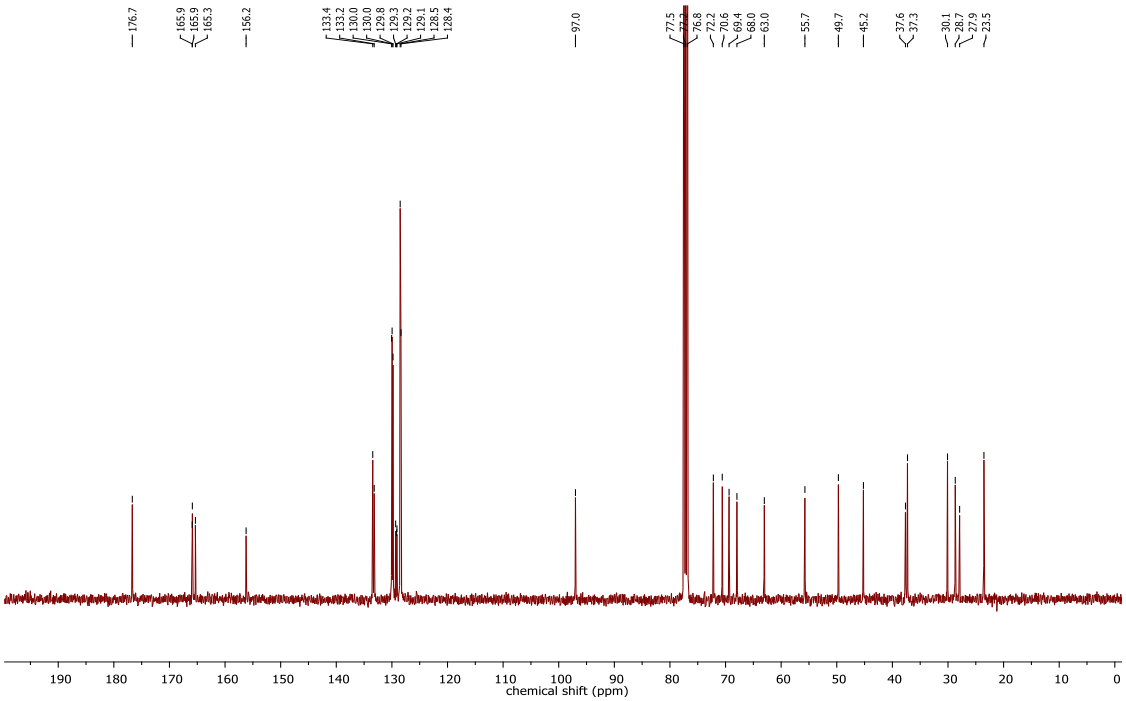

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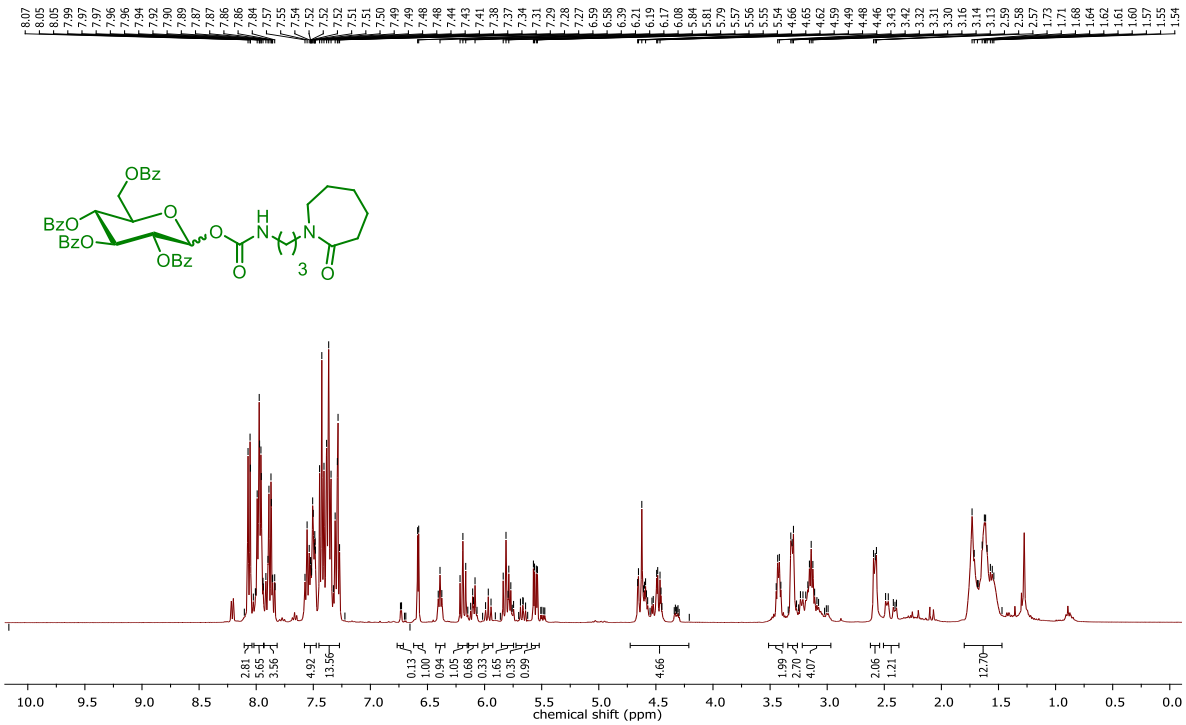
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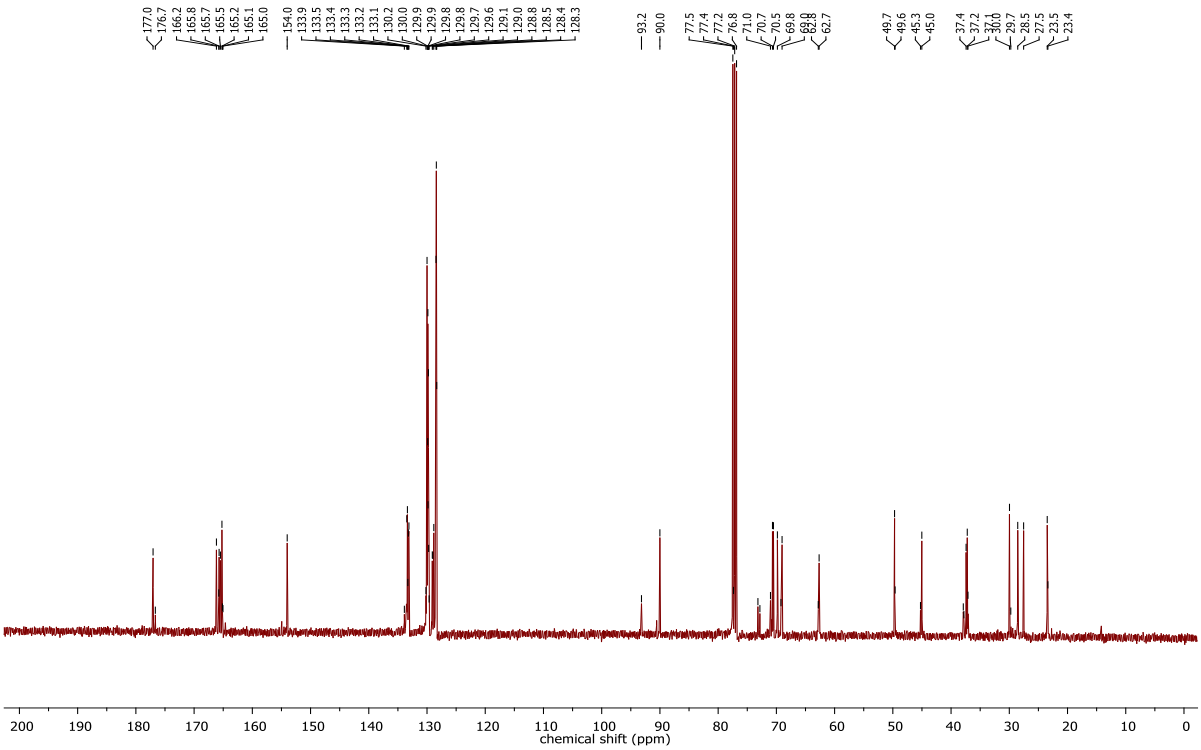

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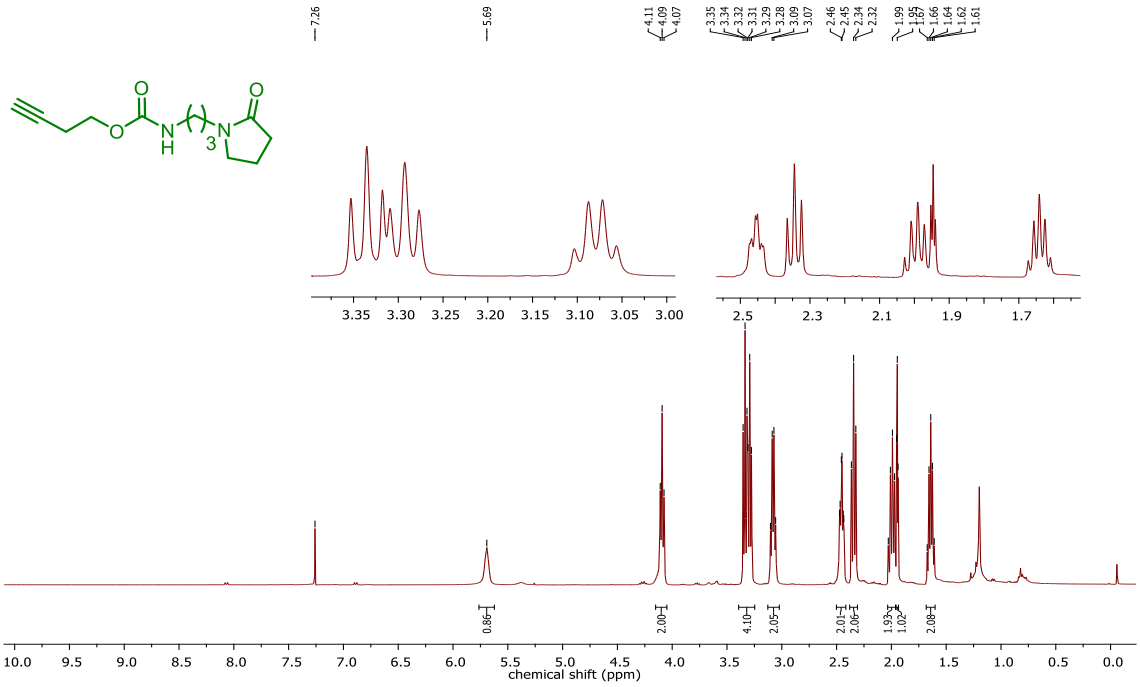
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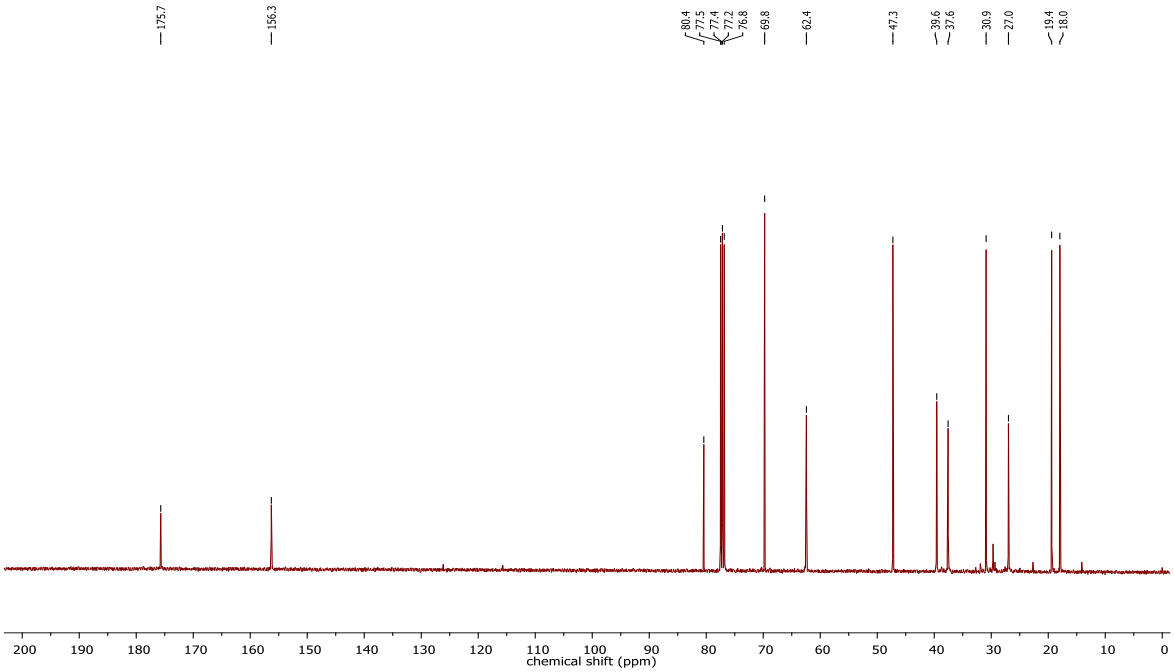

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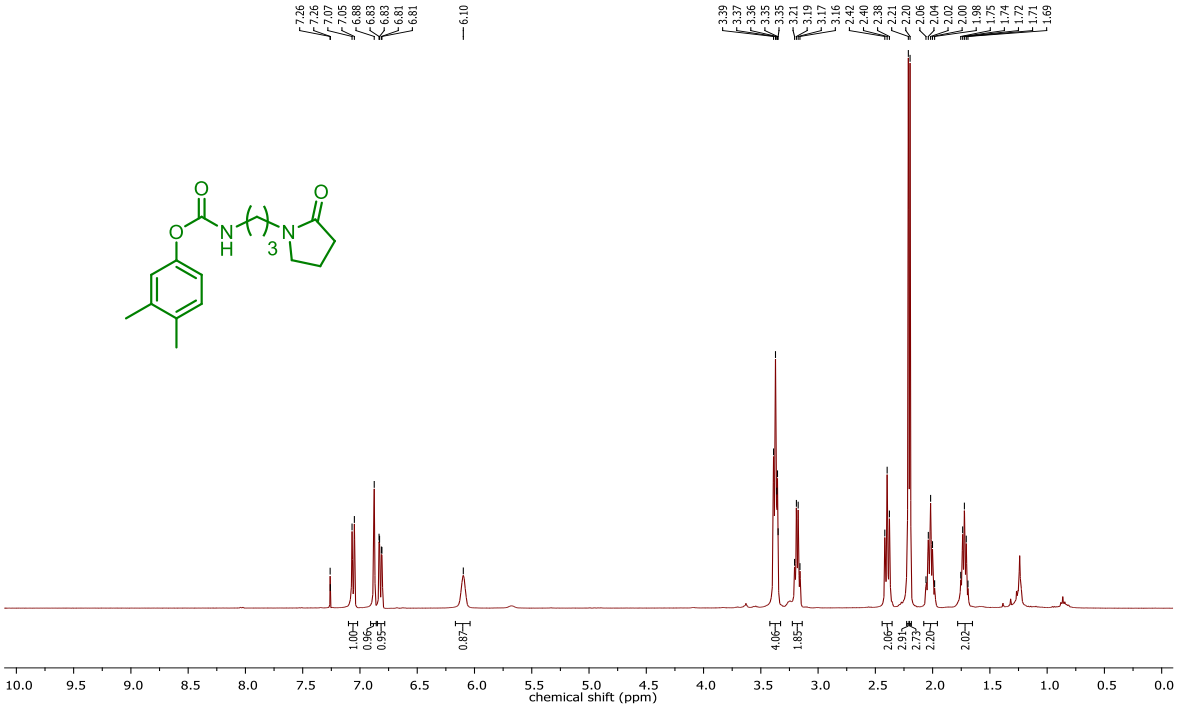
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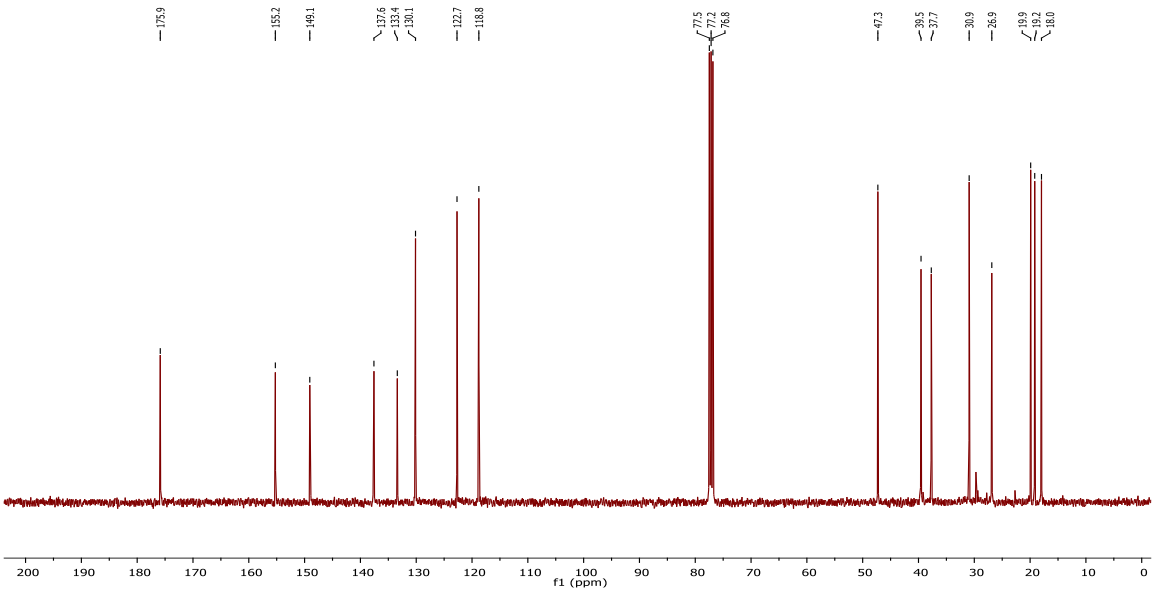

## $^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 2ab



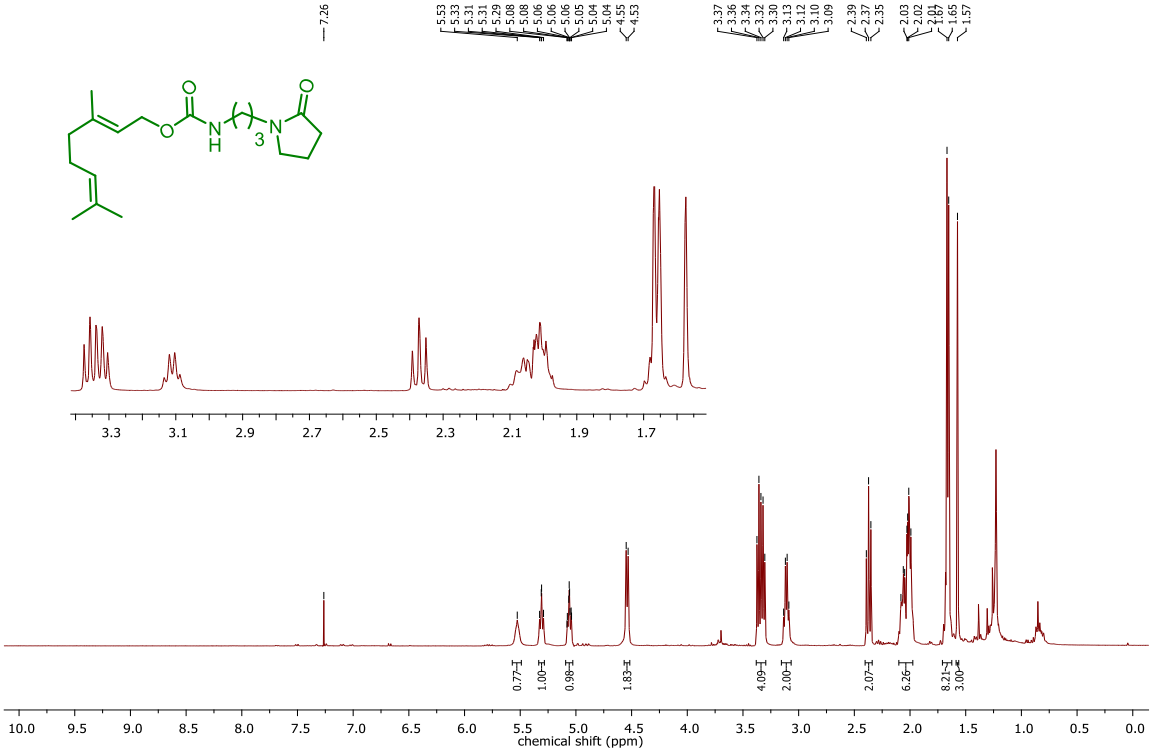
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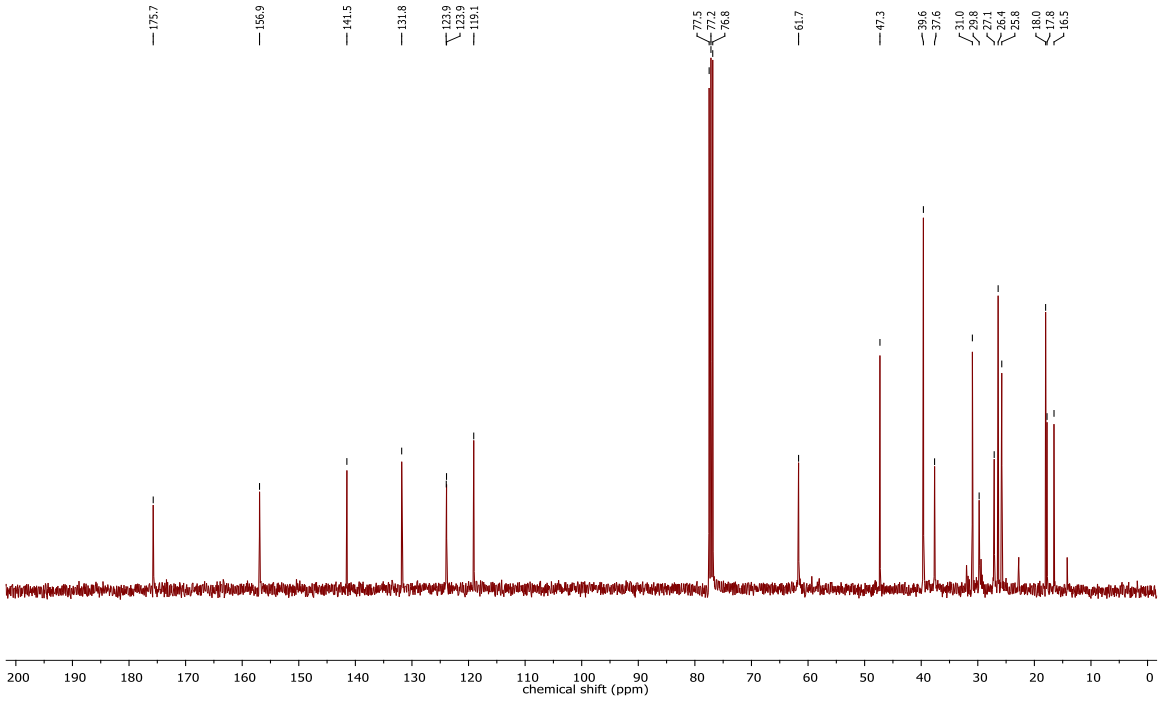

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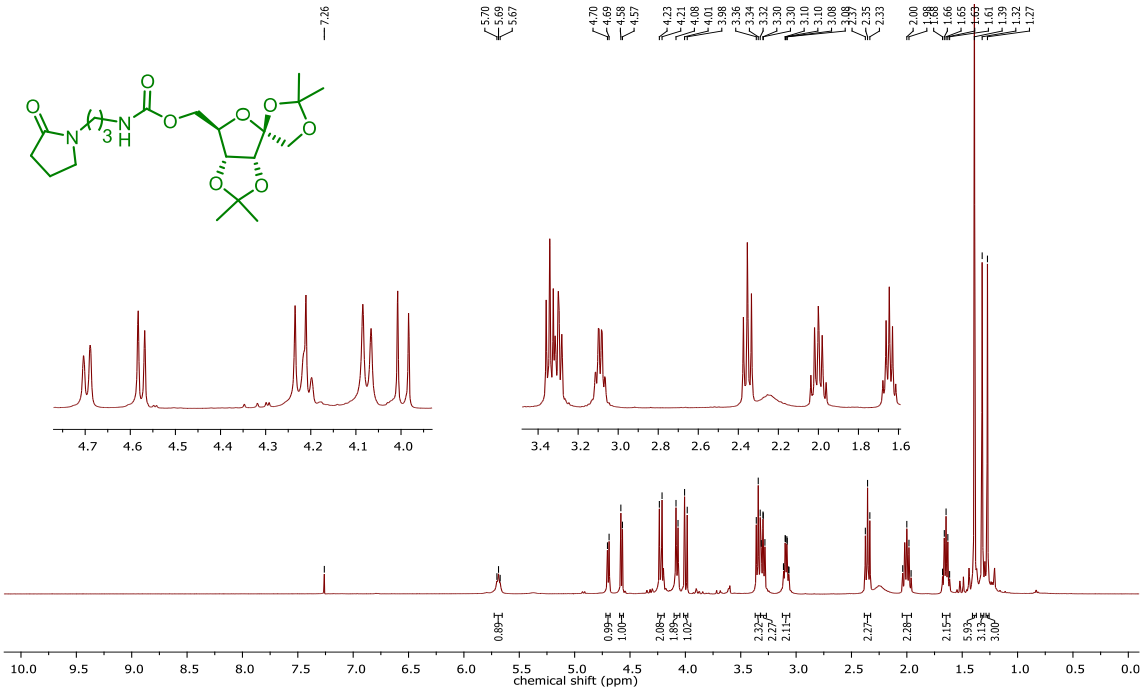
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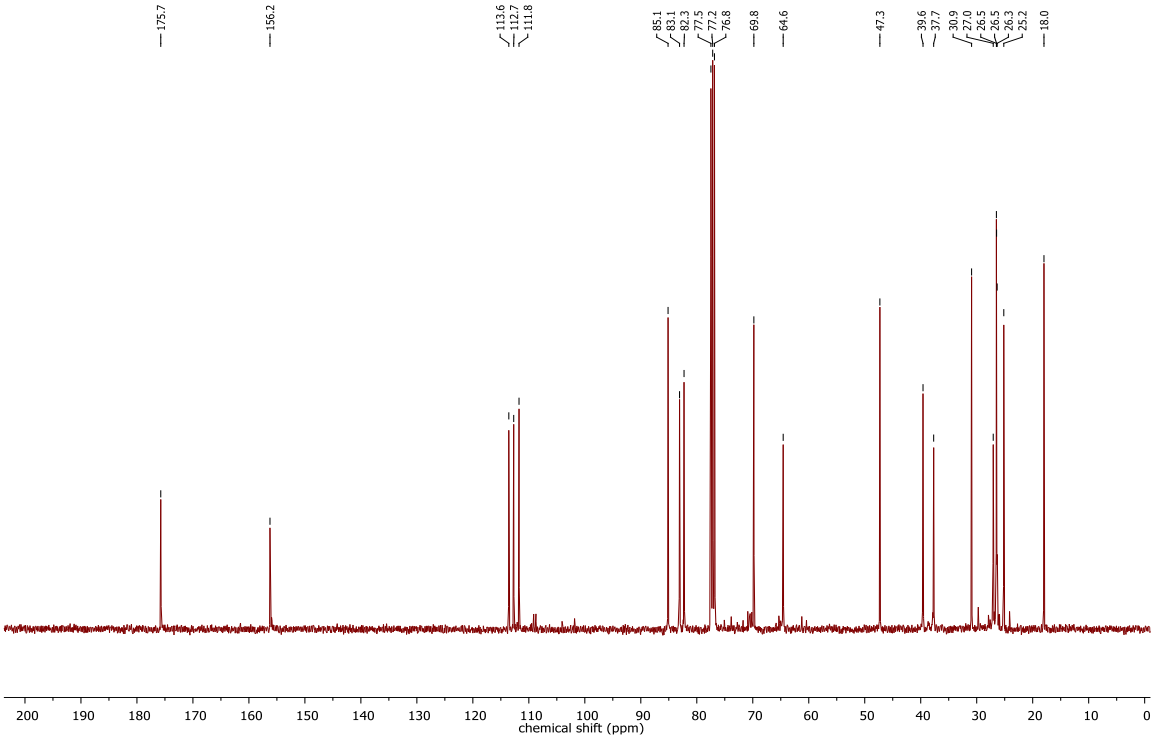

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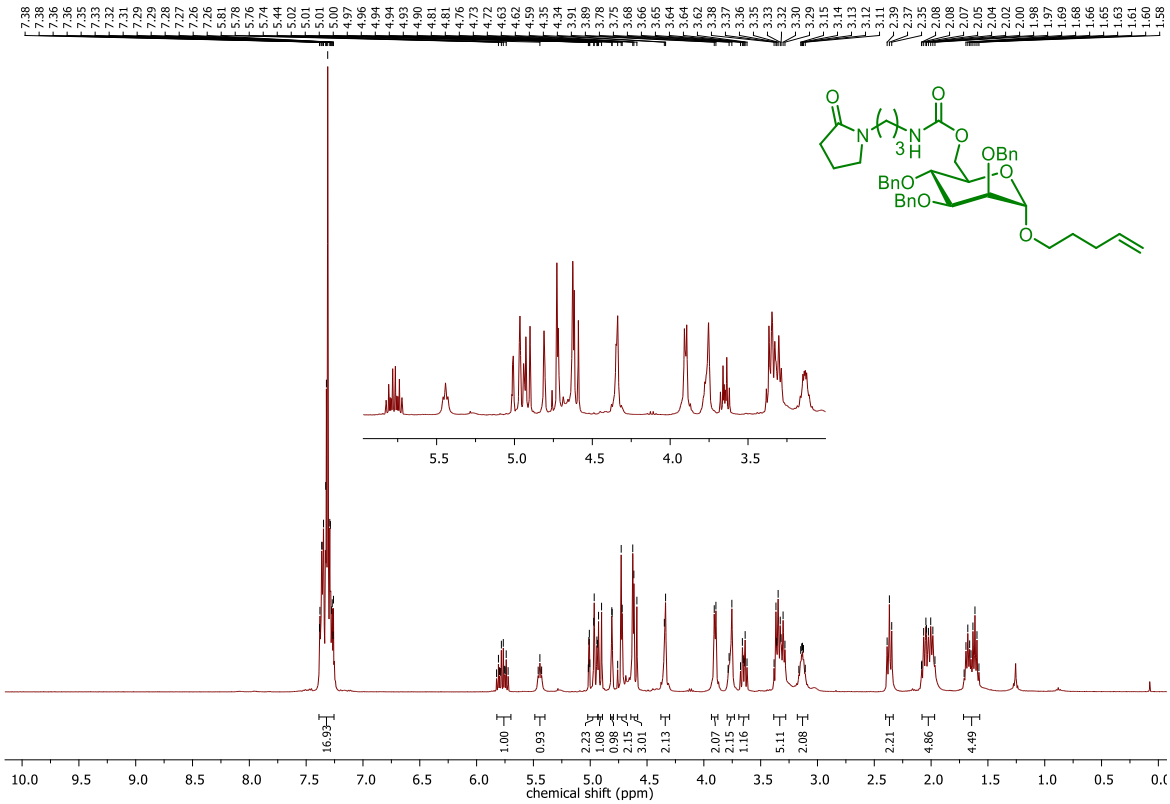
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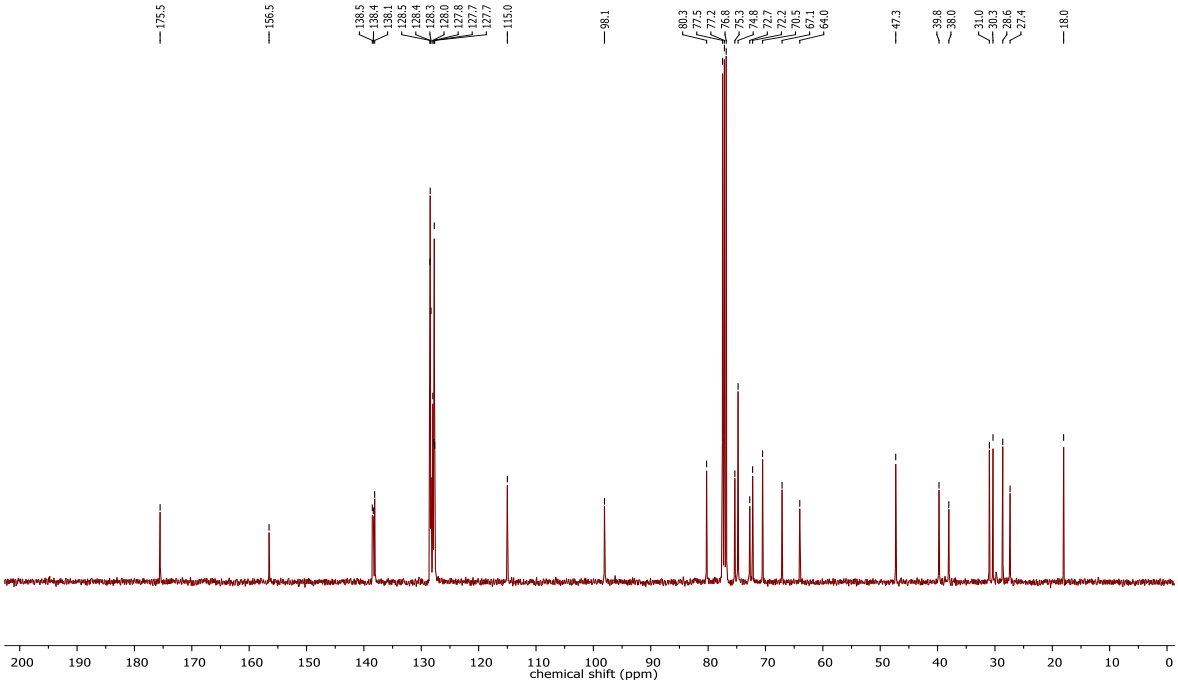

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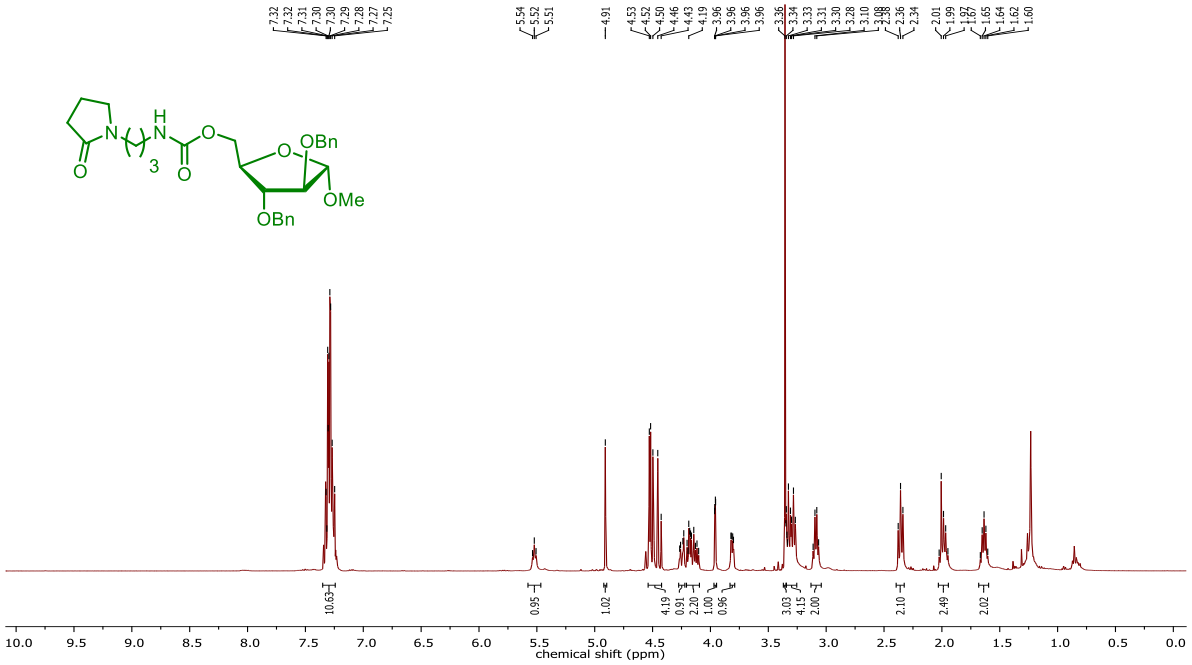
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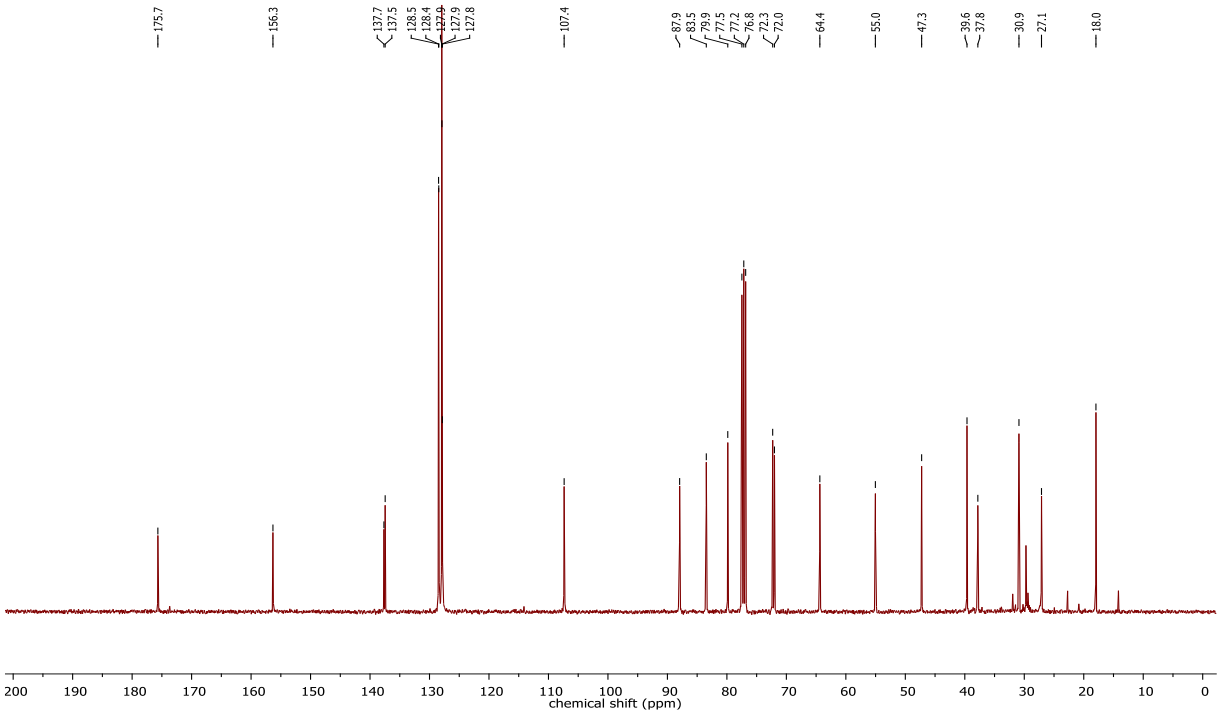

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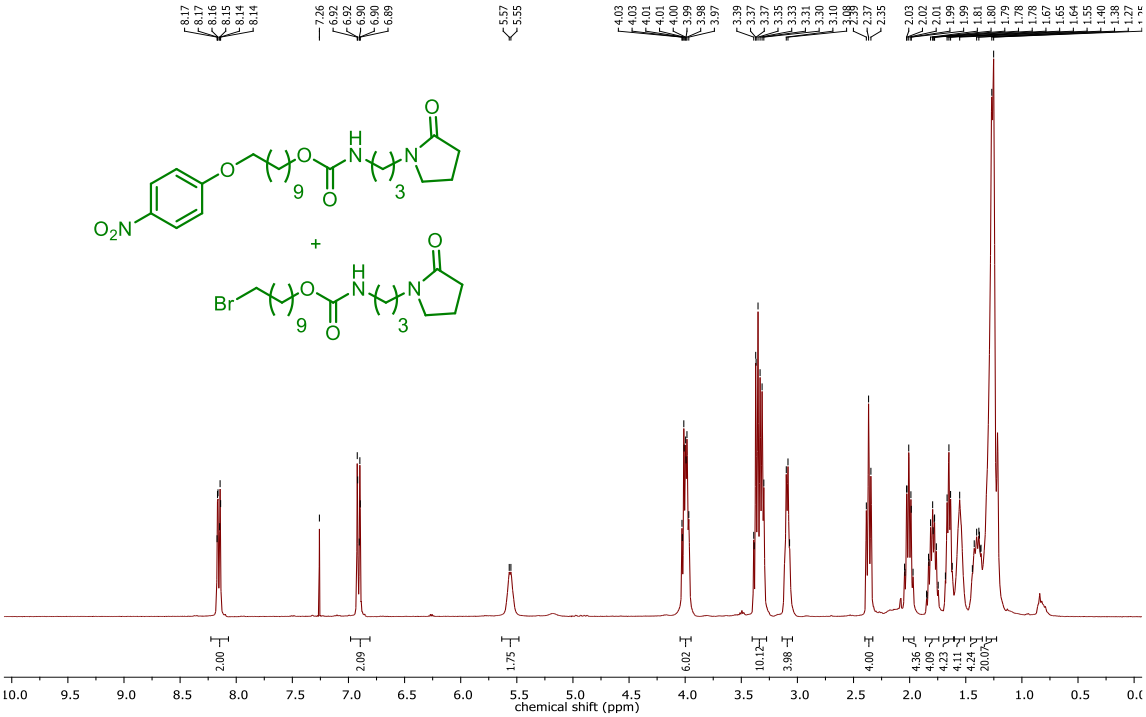
## $^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 13b



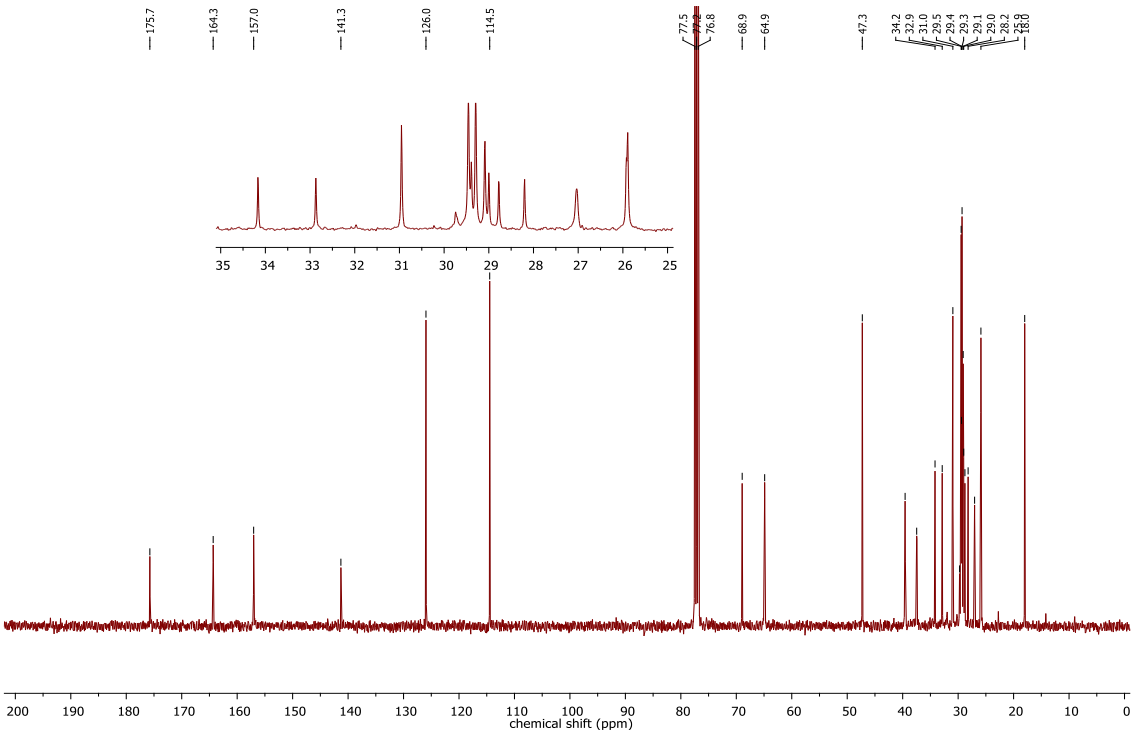

## $^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 13b



## $^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound 14b, 14c




## $^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound 14b, 14c



**3A.8 References**


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# Chapter 3B

## Synthesis of Spirocyclic 2-Substituted-2-Oxazoline Ribofuranosides from D-Fructose

### 3B.1 Introduction

Heterocycles are the most important constituents with a lot of biological relevance as many drugs, natural products and natural product-like small molecule inhibitors, materials have heterocycles. Many a times, hetero atoms in heterocyclic systems are attributed to their special biological functions and oxazoline is one such important privileged heterocyclic moiety that received great attention. Oxazolines are routinely noticed in pharmaceuticals, natural products, foods, medicines, polymers and in agriculture too. Oxazolines were synthesized for the first time in the middle of the 19$^{th}$ century. The bioactive natural products with oxazole as a core structure oxazoline have vital role in medicinal chemistry as oxazolines are found to possess potent biological roles such as antifungal, antibacterial, antimicrobial, antiseptic, antioxidant, anti-malarial, antitumor, anti-inflammatory, and some as anti-HIV as well (Figure 3.1).[1] So oxazoline containing molecules have wide range of biological activities which generate a lot of interest among synthetic chemists for more than five decades. In fact, the very first oxazoline was synthesized by Andreasch in 1884 and later by Gabriel five years later.[2]

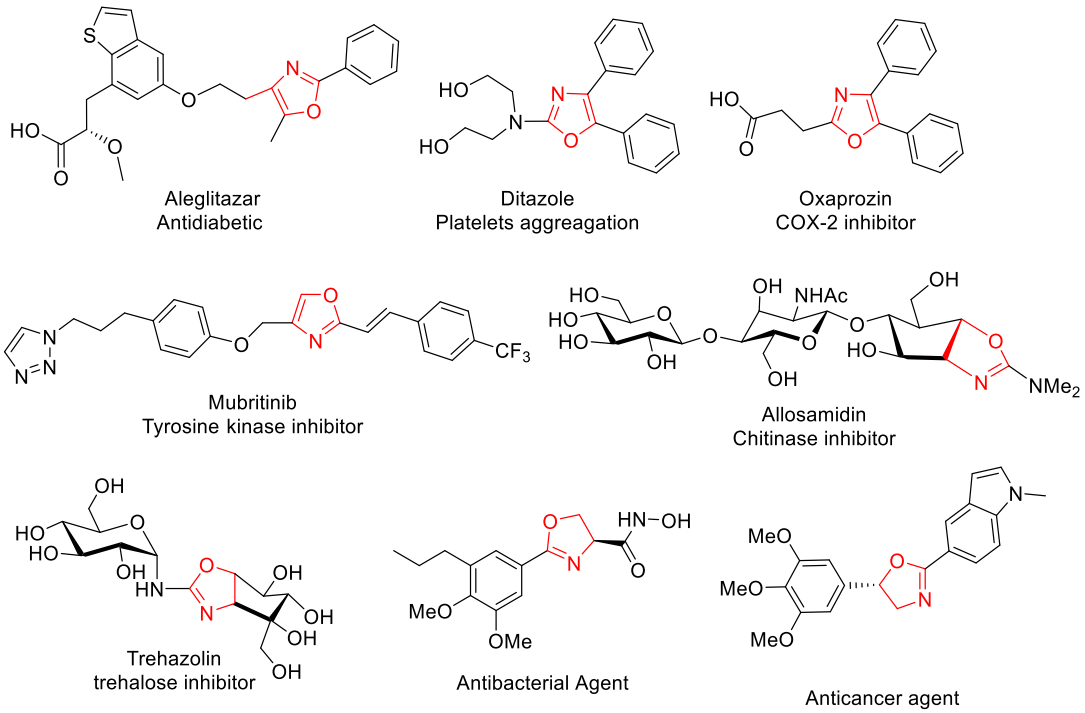



Figure 3.1. Some APIs with oxazoline moiety in their core structure

Oxazolines belong to the unique class of five-membered heterocycles having oxygen at the C-1 position and nitrogen atom at the third position and in between them a carbon. The cyclic system has one double bond, which can have different positions within the ring. Therefore, existence of

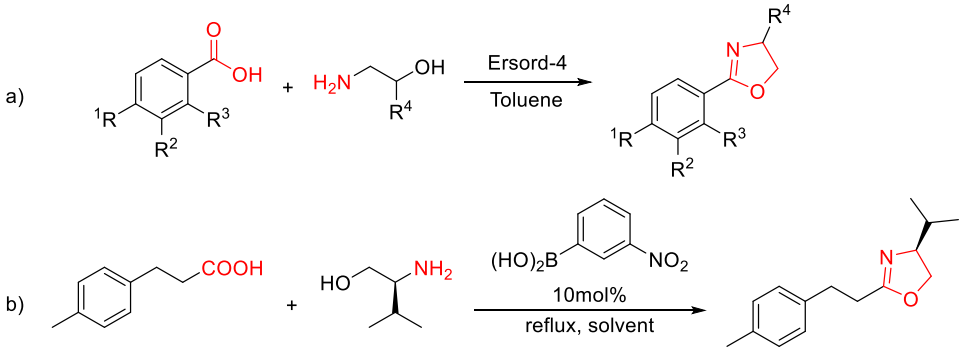
three different possibilities for oxazoline rings (Figure 3.2) depending on the number of atoms between the oxygen and the nitrogen. 2-oxazoline is the common in many natural products and drugs, while 3-oxazoline and 4-oxazoline are also synthesized.




Figure 3.2. Three different types of oxazolines

The oxazoline moiety needs to be synthesized with stereo as well as regiochemical control as 2-oxazoline moiety has its own unique properties and also act as an intermediate or the synthetic precursor to various chemical processes.[3] Such diverse biologically active as well as pharmacologically important moieties have been targeted by various synthetic chemists for the development of new chemical entities in response to medicinal chemistry. Oxazolines can be synthesized from aromatic substituents such as aldehydes, nitriles, acids and azides. Several methods have been reported in literature to construct 2-oxazoline functionality from carboxylic acid derivatives, alkenes, nitriles, etc.[4]

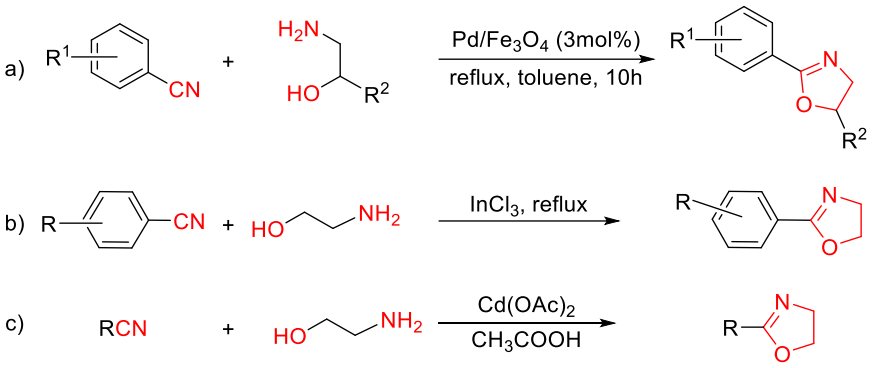
One of the most inexpensive and simplest methods is the condensation of the carboxylic acid and an amino alcohol to afford 2-oxazoline derivatives. The amino alcohol in which $NH_2$ and OH groups are adjacent to each other, while acid can be aromatic or aliphatic in nature. The reaction in between benzoic acid and 2-amino ethanol at elevated temperature in the presence of Ersorb-4 afforded 2-substituted oxazolines in good amount of yield (Scheme 3.1a).[5]




Scheme 3.1. Synthesis of 2-substituted oxazolines by condensation

In another example, direct condensation of aromatic acids with amino alcohols in presence of a 3-nitrophenylboronic acid for dehydration has produced 2-substituted oxazoline in good yields (Scheme 3.1b).[5] The reaction of aromatic/aliphatic nitriles with amino alcohols afforded the

oxazolines - for example, heating of a solution containing benzonitrile and amino alcohol at 100 ºC in presence of $Pd/Fe_3O_4$ catalyst afforded oxazolines (Scheme 3.2a).[6] This reaction can also be performed by using 12-tungstophosphoric acid (TPA), activated carbon and poly (4-styryl methyl) pyridinium chloride (PMP).[7] In yet another important development, α-amino alcohols were refluxed with aromatic nitriles in presence of $InCl_3$ to notice formation of oxazolines (Scheme 3. 2b**)**.[8] Witte *et al*. reported the synthesis of 2-oxazolines by using Cadmium acetate (Scheme 3.2c**)**.[9]

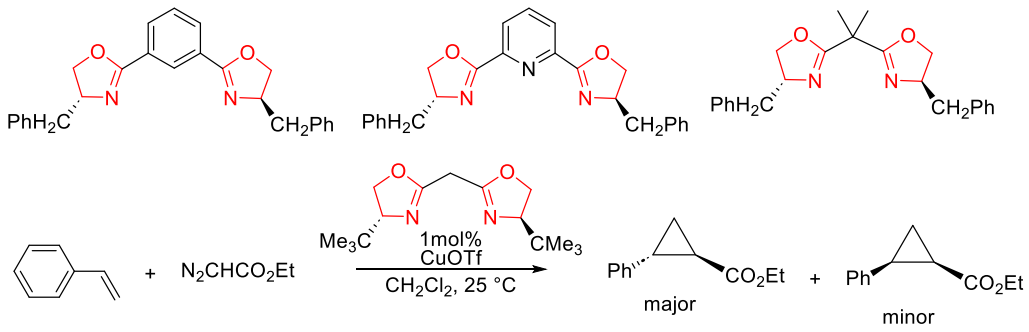



Scheme 3.2. Synthesis of 2-substituted oxazoline using nitriles

### 3B.2. Application of 2-oxazoline

#### 3B.2.1 Asymmetric Transformations

Asymmetric transformations have great ramifications for polymer syntheses, agrochemicals, pharmaceuticals as well as many industrial applications. The synthesis of enantiomerically pure molecules is accomplished by using chiral catalysts, chiral reagents or by conducting reactions in chiral media or by co-crystallization. During the last decade, utilization of chiral oxazolines as unique chiral ligands for such asymmetric transformations has emerged.[10] The chiral bis-oxazolines possessing $C_2$-symmetry have broad range of applications in different asymmetric reactions (Scheme 3.3).



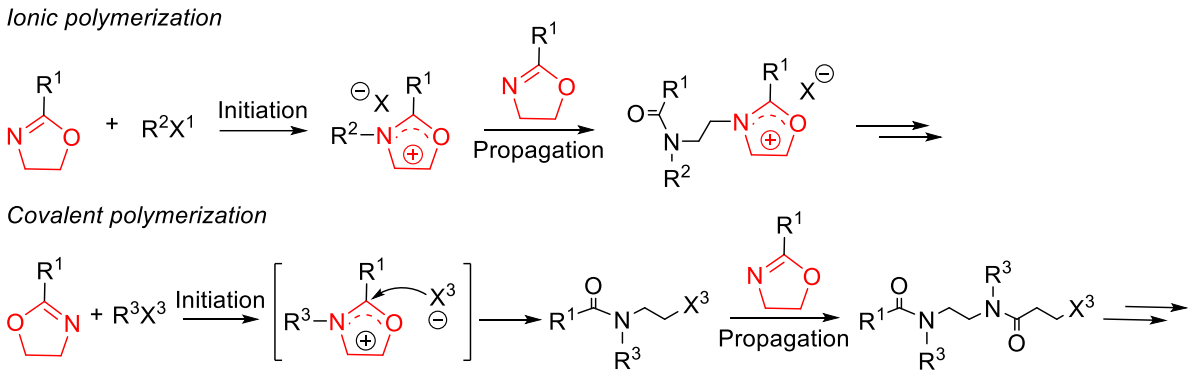

Scheme 3.3. Representative example of bis(isoxazoline) ligands and cyclopropanation

Evans[11] has reported the reaction of styrene and ethyl diazoacetate for cyclopropanation in presence of bisoxazoline and copper(I) triflate with high diastereoselectivity (Scheme 3.3). Recently new bis(oxazoline) carbohydrate-based ligands also have been reported for such asymmetric cyclopropanations.[18] So oxazolines having nitrogen atom have strong affinity towards metals which makes them suitable for deriving chiral derivatives which can be magnificent as catalysts for asymmetric transformations.

### 3B.2.2 Biocompatibility

The polymerization of 2-oxazolines gives biocompatible, amphiphilic, water-soluble polymers that have wide spread applications in drug delivery, materials, coatings as well as pigment dispersants and utilized as biomaterials. The interest in this poly(oxazolines) increased ever since the first report in 1960s.[13] The 2-substituted oxazolines are polymerized and demonstrated by various groups.[14] The polymerization of oxazolines with substitutions at 4 or 5-position are quite difficult because of steric hindrance.[11] The cationic ring opening polymerization gives rise to good and well-defined polymers (Scheme 3.4).[13]

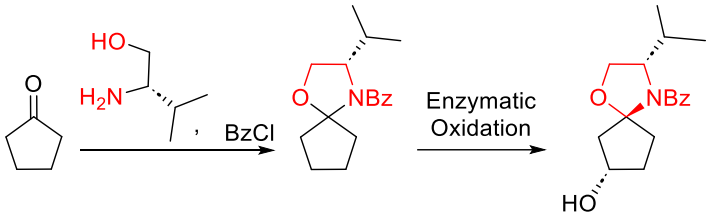
The small functionality such as methyl, ethyl, phenyl groups at the 2-position of the oxazole demonstrated good results and are commercially available. The principal application of such polymers are in biology as the gene and drug delivery agents.[15] The conjugation of drug molecules with polymers has shown advantages with increased solubility of drugs, improvement in pharmacogenetics, less chances of drug degradation during circulation or transportation.[16] So far, many poly-(oxazoline) polymers such as poly(*N*-2-hydroxylpropyl methacrylamide),[17] poly(ethylene oxide),[18] on the other hand amphiphilic block copolymers,[19] star shaped polymers,[20] dendrimers,[21] and lipopolymers[22] have been investigated in this context (Scheme 3.4).




Scheme 3.4. Mechanistic pathway for cationic ring opening polymerization of 2-oxazoline

### 3B.2.3 Oxazolines act as protecting group:

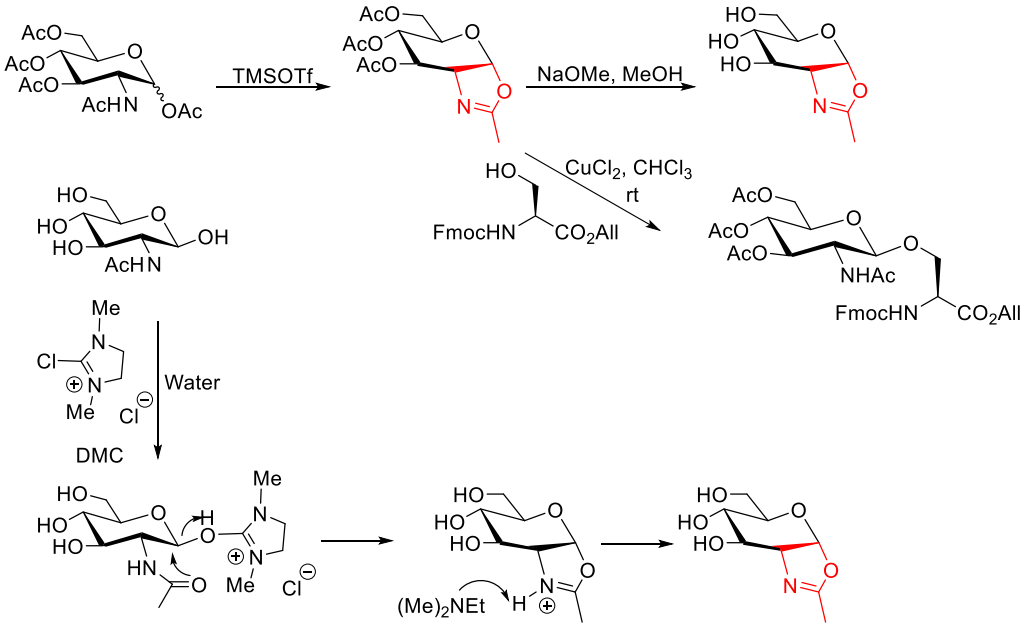
In yet another effort, cyclopentanone was reacted with a valine derived amino alcohol to form oxazoline ring to mask the ketone and impart chiral induction so that the molecule can further undergo enzymatic oxidation to afford desired compound (Scheme 3.5).[23]




Scheme 3.5. Oxazoles as protecting group to induce chirality

### 3B.2.4 Intermediate for *N*-linked Glycoprotein Synthesis

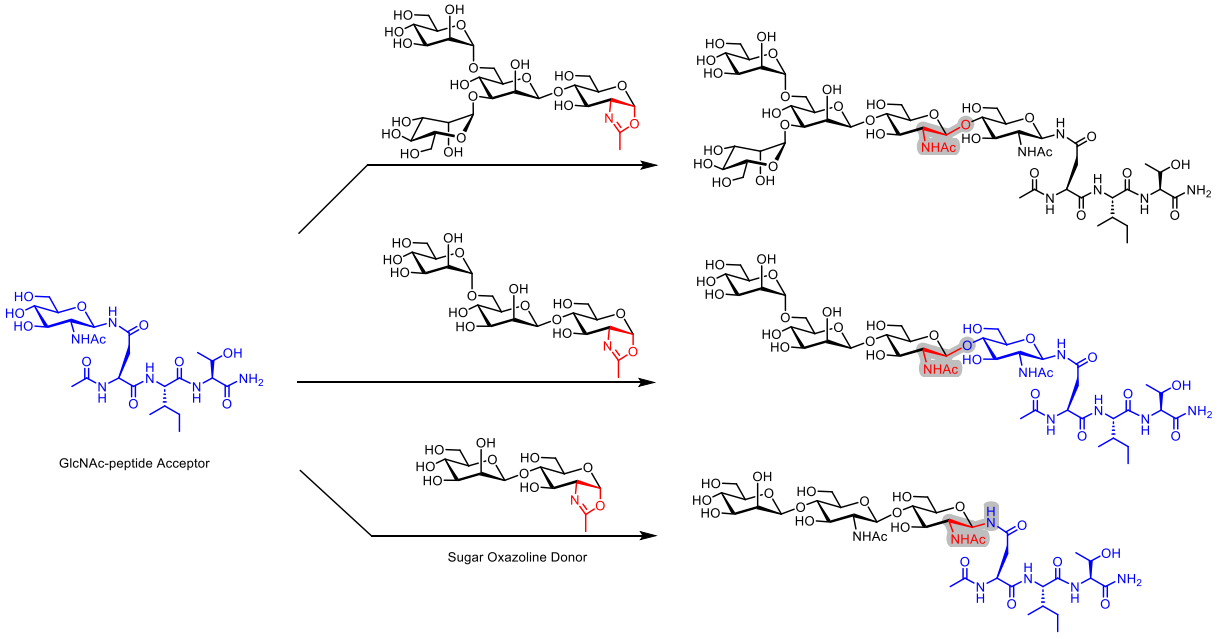
The sugar oxazoline derivatives are utilized as glycosyl donors and further demonstrated for *N*-linked glycoprotein syntheses.[24] The glycosidase-based chemo-enzymatic glycosylation is a powerful tool for the stereoselective glycosidic bond formation.[25] In case of chemo-enzymatic method: glycosyl donor with a leaving group at anomeric position such as *p*-nitrophenyl or fluorine undergo enzymatic transglycosylation with the acceptor.[26] Such trans glycosylations are performed with unprotected substrates in aqueous media. Unprotected sugar oxazoline was prepared in multiple steps (Scheme 3.6).




Scheme 3.6. 1,2-Oxazolines as glycosyl donors

per-*O*-Acetylated 2-*deoxy*-2-acetamido-sugars are treated with Lewis acids such as tin(IV) chloride, ferric(III) chloride, boron trifluoride and other promoters like triflic acid, TMSOTf followed by saponification resulted in the corresponding sugar oxazolines (Scheme 3.6).[27] Shin-ichiro Shoda *et al* reported an efficient method for the direct synthesis of sugar oxazoline by reaction of *N*-acetyl-2-amino sugars with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) in aqueous medium (Scheme 3.6).[28] Thus synthesized sugar oxazolines were used as glycosyl donors for both chemical as well as chemo-enzymatic glycosylations.[29]

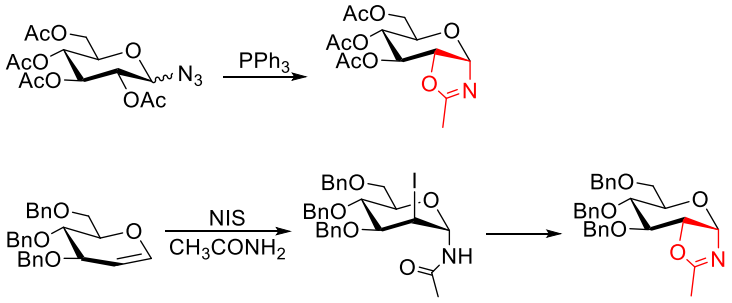
Further, Fujita and co-workers have demonstrated enzymatic transglycosylation of disaccharide oxazoline of Man-(1→4)β-GlcNAc.[30] Taking into account of all preliminary studies in consideration, Wang and co-workers utilised di-, tri- and tetrasaccharide oxazoline substrates as glycosyl donors and efficiently demonstrated chemoenzymatic glycosylation in *N*-glycopeptide synthesis (Scheme 3.7).[31] In this phenomenally convergent effort, Endo-β-*N*-acetylglucosaminidase (ENGase) specially Endo-M from *Mucor hiemalis*[32] and Endo-A from *Arthrobacter protophormiae*[33] catalysed transglycosylation allowing large oligosaccharide attachment to an unprotected GlcNAc-peptide/protein chain in a stereo- and regio-specific manner.[34] Such highly efficient chemoenzymatic demonstration of sugar oxazolines enhanced synthetic efficiency for large *N*-glycopeptide as well as for glycoprotein remodelling.




Scheme 3.7. Chemoenzymatic glycosylation of sugar oxazoline catalysed by Endo-A[35]

### 3B.3 Synthesis of regioisomer of glycooxazoline

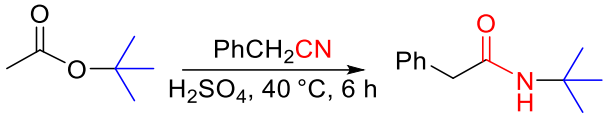
Owing to the bicyclic nature, two different regioisomers of glycooxazolines are possible viz. C1 *O*-linked 1,2-glycooxazoline and C2 *N*-linked 1,2-glycooxazolines between C1 and C2 positions of the pyranoside ring. The formation of *O*-linked 1,2-glycooxazolines by vicinal participation of acylamino group (Scheme 3.6) can accomplished by an intramolecular nucleophilic substitution of acylamino group at the anomeric centre. These sugar oxazolines are highly reactive and favour the formation of 1,2-*trans* glycosides.[36] The C1 *N*-linked 1,2-glycooxazolines can be synthesized from glycosyl azides having a vicinal ester group in presence of triphenylphosphine[37] (Scheme 3.8) by intramolecular condensation or by the reaction of D-glucals with *N*-iodosuccinimide and amides[38] (Scheme 3.6b).




Scheme 3.8. Synthesis of C1 *N*-linked 1,2-glycooxazoline

### 3B.4 Ritter like Reaction

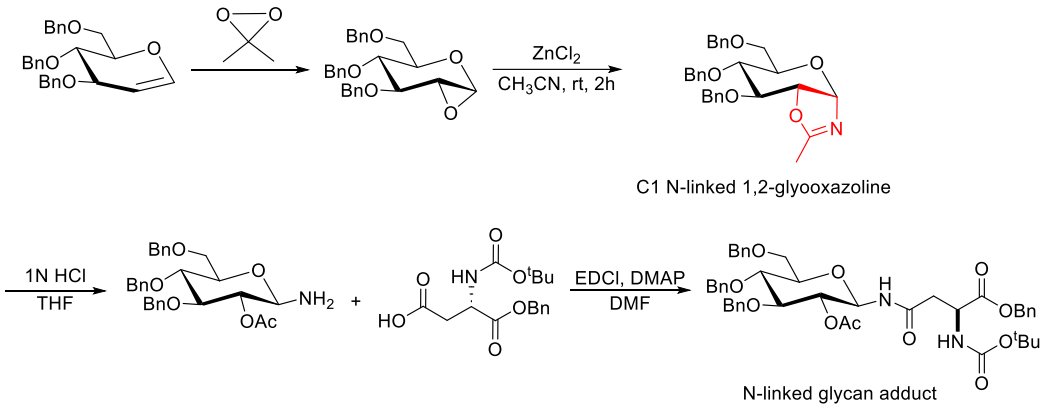
Ritter reaction can be defined as an acid involved addition of nitrile moiety to the carbenium ion that results into the nitrilinium ion which hydrolyses to give rise to an amide (Scheme 3.9).[39]




Scheme 3.9. Synthesis of N-*tert*-butyl amide through a modified Ritter reaction[39]

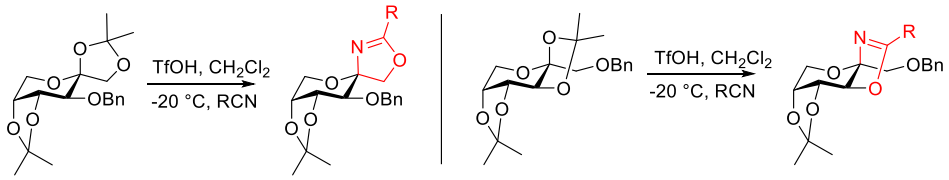
Alternatively, nitrilinium ion can be trapped to get 1,2-glycooxazolines via Ritter-like reaction.[40] It was demonstrated that glycooxazolines can be obtained by trapping of the nitrilinium ion resulting from the nitrile by the oxocarbenium ion intermediate and subsequently intramolecular nucleophilic attack of a free hydroxyl group of the vicinal C2 ether.[41] Such glycooxazolines are further utilised for the *N*-glycan synthesis.[42] During the *O*-glycosylation reactions, there is formation of an oxocarbenium intermediate which interacts with nitrile solvents to form a transient α/β–glycosyl nitrilium moiety. Subsequently, participation of vicinal oxygen atom produces oxazolinium intermediate. Pavia and co-workers in 1981 proposed such uncharacterized

oxazolium formation from glycosyl hemiacetal upon the acid hydrolysis in acetonitrile.[43] Danishefsky and co-workers, in 1991 reported the synthesis of a C1 *N*-linked 1,2-glycooxazoline from a 1,2-anhydropyranose glycosyl system using zinc chloride as Lewis acid in dry acetonitrile (Scheme 3.10).[41]




Scheme 3.10. Synthesis of C1 *N*-linked 1,2-glycooxazoline with *N*-linked glycan[41]

Garcia Fernandez and co-workers in 2004 synthesized fused and spiroglycooxazolines from a substituted D-fructose (Scheme 3.11).[44]




Scheme 3.11. Synthesis of spiro- and fused-oxazolines from D-fructose precursors

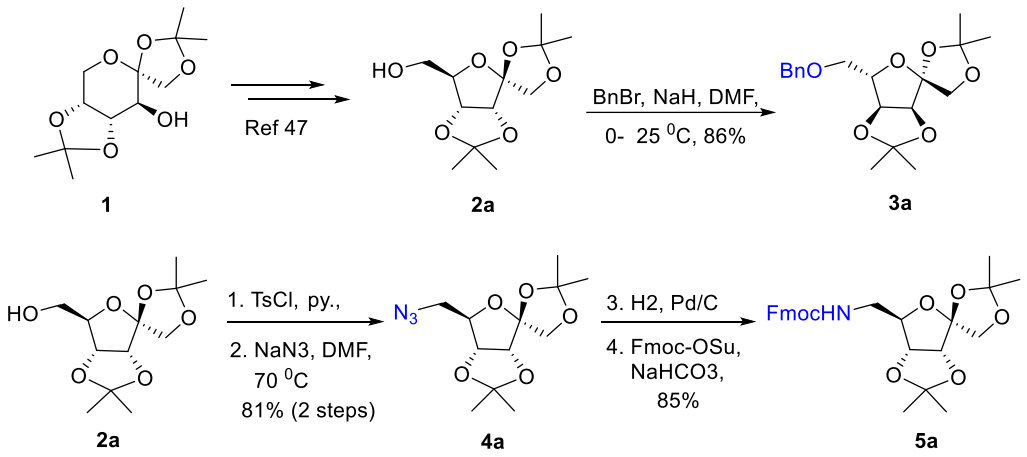
Mong and co-workers reported fused glucopyranose oxazolines in the presence of nitrile solvents using thioglycoside donors and utilized for the preparation of α(1→5)-arabinan.[45] These carbohydrate-based oxazolines can serve as glycosyl donors or in some cases act as intermediates for the *N*-glycan synthesis.[46] A few more pyranose based glycooxazoline frameworks are known and a limited number of furanoids such as spiro 2-oxazolines are reported.[47] In this section of the thesis, synthesis of spiroribofuranosyl oxazoles are investigated so that thus synthesized compounds can be utilized for biological screening of small molecule inhibitors.[48]

### 3B.5 Present Work

Garcia Fernandez *et al*. reported (Scheme 3.11) a reaction 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose and 3,4,6-tri-*O*-benzoyl or *O*-benzyl-protected 1,2-*O*-isopropylidene-β-D-fructofuranose derivatives with triflic acid (1.5 eq.) in presence of nitriles (10 eq.) at -20 °C to rt in dichloromethane to afford the fused and spiroglycooxazolines.[44] The fructopyranoses showed reaction with benzonitrile, propionitrile and acetonitrile but there is only one example for fructofuranose with acetonitrile. Thus, formed spirooxazolines were noticed to be unstable in comparison to fused oxazolines.[44]

So, we have explored the TMSOTf mediated activation of β-D-psicofuranose derivative **5a** in acetonitrile exclusively to afford spirooxazoline **6a**. The spirooxazoline compounds formed are noticed to be quite stable and thus, inspired us for exploring their synthesis and isolation. To begin with the key intermediate D-psicofuranose **2a** was synthesized from readily available D-fructose. D-Fructose was treated with 2,2-dimethoxypropane in presence of perchloric acid in dry acetone at 55 °C to obtain 1,2:3,4-di-*O*-isopropylidene-β-D-fructose followed by oxidation with PDC/$Ac_2O$/$CH_2Cl_2$ at 50 °C to obtain the 3-ulose derivative. Further reduction of the ketone was carried out with $NaBH_4$ in methanol at 0 °C and subsequently the alcohol was treated with 2,2-dimethoxypropane and perchloric acid in dry acetone at 0 °C to produce **2a** in 65% overall yield.[49] In the $^1$H NMR spectrum of compound **2a**, the four methyl moieties of isopropylidene were noticed at δ 1.49, 1.43, 1.39 and 1.31 ppm as four singlets whereas in the $^{13}$C NMR spectrum, the anomeric carbon appeared at δ 111.8 ppm and quaternary carbons of isopropylidene resonated at δ 113.5 and 112.4 ppm respectively. Further HRMS (TOF) analysis of **2a** showed m/z of 283.1159 [Calcd for $C_{12}H_{20}O_6Na$, $[M+Na]^+$: 283.1158] confirmed the compound **2a**. Further, the benzylation of C6-OH group of D-psicofuranose **2a** was carried out by using BnBr and NaH in DMF to afford benzyl ether **3a** in 86% yield (Scheme 3.12). In the $^1$H NMR spectrum of compound **3a**, four singlets were noticed for four $CH_3$s of isopropylidene at δ 1.45, 1.44, 1.38 and 1.33 ppm as four singlets and $^{13}$C NMR spectrum of benzyl ether **3a** displayed the anomeric carbon at δ 111.5 ppm. The additional confirmation was obtained through HRMS (TOF) analysis of **3a** wherein m/z was found at 373.1631 [Calcd for $C_{19}H_{20}O_6Na$, $[M+Na]^+$ : 373.1627]. Thereafter, nucleophilic displacement of C6-tosyl intermediate using $NaN_3$ in DMF at 70 °C afforded the formation of 6-*deoxy*-6-azido-1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose **4a**. The formation of the desired **4a** was confirmed through $^1$H NMR spectrum in which, four methyl singlets were identified at δ

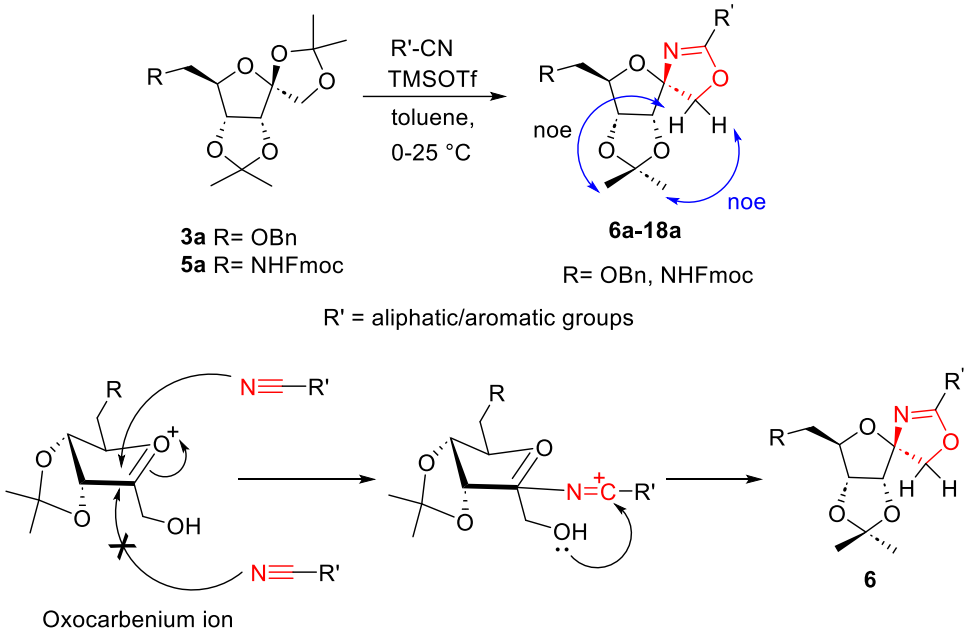
1.46, 1.43, 1.37 and 1.30 ppm. The protons corresponding to the $\underline{CH_2}$-$N_3$ were noticed at δ 3.51 (dd, *J*= 12.6, 7.6 Hz) and 3.28 (dd, *J*= 12.6, 6.8 Hz) ppm. Whereas in the $^{13}C$ NMR spectrum of compound **4a**, anomeric carbon appeared at δ 112.0 ppm and the quaternary carbons of isopropylidene were noticed at δ 113.9 and 113.0 ppm respectively. The presence of the azide was evident with the appearance of resonances at δ 53.3 ppm for the lone $\underline{C}$-$N_3$ bond. Additionally, azide functional group was confirmed through the asymmetric vibration frequency in IR spectrum at 2099 $cm^{-1}$. The HRMS (TOF) analysis showed *m/z* value of **4a** for $C_1H_{19}O_5N_3Na$ at 308.1219 which agrees with that of the calculated *m/z* 308.1222. Further, the specific rotation of **4a** $[\alpha]_D^{25}$ = -53.0º which was in accordance with the previously reports.[47,49,50] Subsequently, hydrogenation of the azide moiety was carried out with 10% Pd/C in ethyl acetate to afford the primary amine, which is further reacted with Fmoc-OSu/$NaHCO_3$ in THF to get the Fmoc-amine derivative **5a.** Finally, the C6-NHFmoc and C6-OBn-protected compounds **5a** and **3a** were studied for the substrate feasibility to synthesize the spirooxazolines (Scheme 3.12).




Scheme 3.12. Synthesis of **3a** and **5a**

Accordingly, the compound **5a** was treated with TMSOTf in the presence of nucleophilic participating solvent acetonitrile at 0 °C and warmed to room temperature and stirred for 1 h. In our observations, the complete consumption of starting material was noticed affording the spiro 2-substituted-2-oxazoline **6a** around 69% yield. The formation of the spirocyclic oxazoline can be rationalized by a Ritter-like reaction that be visualized through TMSOTf-mediated *in situ* cleavage of the 1,2-*O*-isopropylidene group generating an oxocarbenium ion and subsequently nucleophilic addition of nitrile to generate nitrilinium ion (Scheme 3.13). Upon the intramolecular trapping of

the C2 hydroxyl group on this electrophilic nitrilinium carbon gives rise to spiro 2-substituted-2-oxazoline **6** (Scheme 3.13).



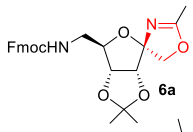
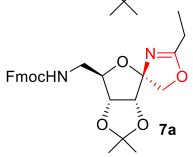
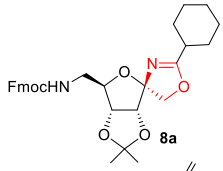
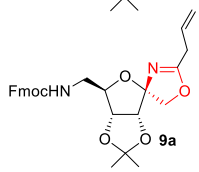
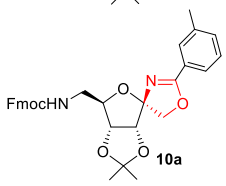
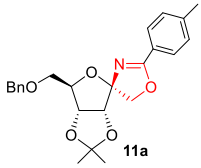
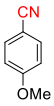
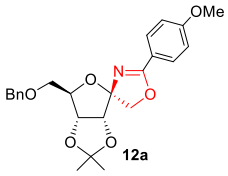
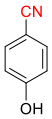
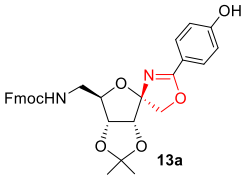
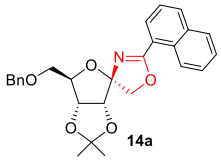
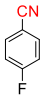
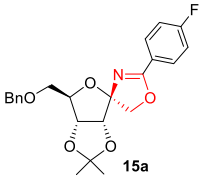
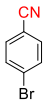
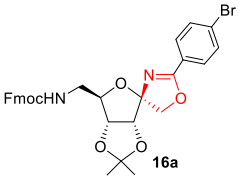
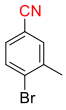
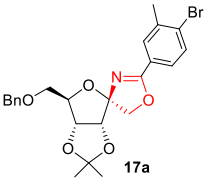
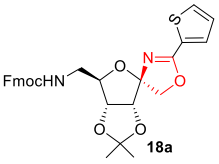

Scheme 3.13. Synthesis of spirooxazolines via Ritter like reaction

Importantly, 3,4-*O*-isopropylidene group was intact under these reaction conditions that further proves the stability of the *cis*-fused 5-membered ring systems and secondary isopropylidenes. The conformation of spirooxazoline product was done by $^{13}C$ NMR spectra which showed signals at δ 110 ppm for the anomeric position (C2 carbon) and at δ 168 ppm for the N=C carbon. The IR absorption at 1657 $cm^{-1}$ for C=N and no IR stretch for OH group proved the presence of oxazoline. In similar reaction conditions, the compound **5a** treated with propionitrile afforded product **7a** in 72% yield (Table 1, entry 2). The reaction of **5a** (0.2 g, 0.415 mmol) at optimized reaction conditions for nitrile reagents at different concentrations (2.5, 5, 10, 15 equiv) of cyclohexane carbonitrile (Table 1, entry 3) in dry toluene using TMSOTf (1 equiv) at 0 ºC to room temperature in an inert atmosphere was performed. Mixture of products was formed with 2.5 equiv and 5 equiv of nitrile and trace amount of desired product has been obtained. When 10 equiv of cyclohexane carbonitrile has been used, moderate yield of product **8a** along with formation of spiroketals[51] **5ab** or di-D-fructose dianhydride **5ac** as the side product was noticed. Finally, it was optimized that 15 equiv of nitrile serves best for this transformation to obtain spirooxazoline **8a** in 65% yield. This result makes a conclusion that in the absence of a nucleophilic nitrogen, or a lower concentration

of the nitrile, the oxocarbenium-ion intermediate of D-fructose undergoes spiroketalization, which gives rise spirocyclic disaccharides[51] along with other unknown products.

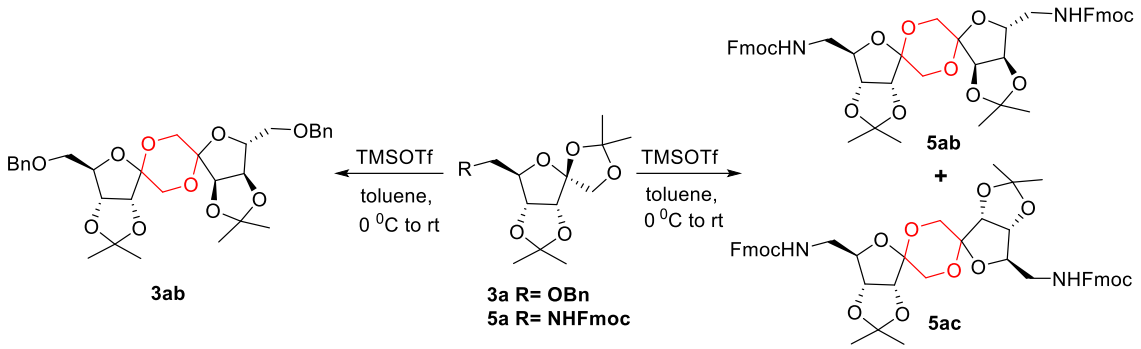
With this optimization in hand, we explored the utility of this reaction with various aromatic as well as aliphatic nitriles bearing electron-withdrawing and electron donating substituents. Accordingly, the compound **5a** reacted with allyl cyanide to obtain **9a** in 53% yield in a stereoselective fashion (table 1, entry 4). Next, the reaction was performed with electron-withdrawing groups accommodated aliphatic nitriles such as trichloroacetonitrile, bromoacetonitrile and malonitrile. However, in all the reactions, there is no product formation but instead of that reaction mixture gave spiroketals. With this observation, we turned our attention to check the possibility of the reaction with various substituted aromatic nitriles. In this perspective, electron-rich aromatic nitriles such as 3-methyl, 4-methyl, 4-methoxybenzonitrile (Table 1, entries 5-7) and 1-naphthonitrile (Table 1, entry 9) were treated with **3a** and **5a** to afford products **10a**-**12a** and **14a**, in 61%, 52%, 72% and 50% yields respectively. The reaction with 4-hydroxybenzonitrile (Table 1, entry 8) reaction was performed in 10:1 DCM: THF instead of toluene due to the poor solubility. The important things in this reaction were that hydroxyl groups need be protected to obtain the desired oxazoline product **13a** as the major product. The reaction tolerates even halogen containing benzonitriles such as a 4-fluorobenzonitrile (Table 1, entry 10) as well to afford compound **15a** in 66% yield. Whereas, in case of 4-bromo and 4-bromo-3-methylbenzonitriles (Table 1, entries 11 and 12) gave moderate yield for corresponding products **16a** and **17a**. Finally, when 2-cyanopyridine (Table 1, entry 13) was treated with **5a** to afford **18a** in 45% yield. Further, electron-withdrawing group containing 2-cyanopyridine and 4-nitrobenzonitrile did not give desired product may be due to the less nucleophilic nature of nitrile group. In such low yielding reactions 15-20% yield of spiroketals is observed.

Table 1: Synthesis of spiro 2-substituted-2-oxazoline **6a-18a.**

| Entry | Substrate | Nitrile | Product | Yield[a] (%) |
|---|---|---|---|---|
| 1 | **5a** | $CH_3CN$ |  **6a** | 69% |
| 2 | **5a** | $CH_3CH_2CN$ |  **7a** | 72% |
| 3 | **5a** |  |  **8a** | 65% |
| 4 | **5a** |  |  **9a** | 53% |
| 5 | **5a** |  |  **10a** | 61% |
| 6 | **3a** |  |  **11a** | 52% |
| 7 | **3a** |  |  **12a** | 72% |
| 8 | **5a**[b] |  |  **13a** | 69% |
| 9 | **3a** |  |  **14a** | 50% |
| 10 | **3a** |  |  **15a** | 66% |
| 11 | **5a** |  |  **16a** | 44% |
| 12 | **3a** |  |  **17a** | 45% |
| 13 | **5a** |  |  **18a** | 45% |

a) conditions: All reactions are performed with 0.2 g of substrate, 1 eq TMSOTf, 15 eq. nitrile in toluene.(Except entries 1, 2) at 0°C to rt for 1-1.5 h.
b) As 4-hydroxybenzonitrile is insoluble in toluene, the reaction was carried out in 10:1 DCM/THF.

The evidence for the formation of spiroketals has been collected by the activation of compound **3a** and **5a** using TMSOTf (1equiv) in absence of nucleophile in toluene. So, in case of compound **3a**, a symmetric **3ab** in 75% yield was obtained as inseparable mixture (Scheme 3.13) whereas compound **5a** afforded a separable 1:1 mixture of symmetric **5ab** as well as unsymmetrical **5ac** spiroketals in 74% yield (Scheme 3.13).




Scheme 3.13. Synthesis of spiroketals from **3a** and **5a**

Contrary to Garcia's observation of unstable nature of sugar-oxazolines, we noticed all the psicofuranose derived ribosyl spiro 2-substituted-2-oxazolines were stable and synthesized as single diastereomers. The compound **11a** and **17a** are subjected to 2D NMR analysis to interpret the stereochemistry at the anomeric position, The NOESY spectra showed cross peak between $CH_3$ groups of acetonide and C1-H, C1-H' which confirmed $CH_2$-O group has α-orientation and N-substituent has β-orientation (experimental section). The stereochemical outcome at the anomeric position is confirmed based on the presence of 3,4-acetonide group in α-orientation, therefore incoming nucleophile attack from the β-orientation leading to high diastereoselectivity. In order to check the applicability of this method for the synthesis of multi gram level owing to the wide spread applications of chiral oxazolines, we examined synthesis of multigram scale of fructose-derived spirooxazolines. For example, the compound **5a** (1.2 g, 2.49 mmol) was treated with cyclohexane carbonitrile (15 equiv) in the presence of TMSOTf (1 equiv) at 0 ºC to rt in toluene for 1.5 h afforded compound **8a** in 61% yield.

**3B.6 Conclusion**

In conclusion, spiro 2-substituted 2-oxazoline ribofuranosides are diastereoselectively synthesized from D-psicofuranose in the presence of TMSOTf and electron-rich nitriles in good yields. The oxocarbenium ion intermediate resulting from the D-psicofuranose underwent spiroketalization in the absence of nucleophiles producing the di-D-fructose dianhydride. We envisage that these conformationally restricted, stable spiro glyco-oxazolines find applications in medicinal chemistry as drug delivery agents after covalently cross-linking with polymers. Such cross-linked glycopolymers might be suitable for material research and in nanomedicine as well.

### 3B.7 Experimental Section

Experimental data for, **2a**, **3a**, **4a**, **5a**, **3ab**, **5ab**, **5ac**

**1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (2a).** Thick liquid: $[\alpha]_D^{25}$ = -80.3° (*c* 1.02, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.90 (dd, 1H, *J* = 5.9, 0.8 Hz), 4.63 (d, 1H, *J* = 5.9 Hz), 4.32 (d, 1H, *J* = 9.7 Hz), 4.28 (t, 1H, *J* = 2.8 Hz), 4.06 (d, 1H, *J* = 5.9 Hz), 3.74 (dt, 1H, *J* = 12.6, 2.8 Hz), 3.67 – 3.59 (m, 1H), 3.20 (dd, 1H, *J* = 10.5, 3.0 Hz), 1.49 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 113.5, 112.4, 111.8, 86.9, 85.9, 81.7, 70.0, 64.0, 26.6, 26.4, 26.2; 24.9; IR ($CHCl_3$) *v* 3495, 2988, 1376, 1205, 1015, 852 $cm^{-1}$; HRMS (ESI-MS): m/z calcd for $[C_{12}H_{20}NO_6Na]^+$:283.1158; found: 283.1159.

**1,2:3,4-di-*O*-isopropylidene-6-*O*-benzyl-β-D-psicofuranose (3a).** To a stirring solution of **2a** (2 g, 7.6 mmol) in DMF at 0 °C, NaH (0.4 g, 10.0 mmol) was added under $N_2$ atmosphere and stirred for 10 min. To this, benzyl bromide (1 mL, 8.4 mmol) was added drop-wise. The resulting mixture was slowly allowed to warm to room temperature and stirred overnight. After completion of starting material saturated aq. $NaHCO_3$ is added and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over $Na_2SO_4$ filtered and concentrated *in vacuo*. Purification of the crude product by column chromatography using petroleum ether/EtOAc gave the title compound **3a**. Thick liquid; $R_f$ = 0.5 (petroleum ether/EtOAc, 85:15); Yield: (2.4 g, 92%); $[\alpha]_D^{25}$ = -65.6 (*c* 0.67, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40 – 7.25 (m, 5H,), 4.76 (d, 1H, *J* = 5.9 Hz), 4.61 (d, 1H, *J* = 5.7 Hz), 4.57 (d, 2H, *J* = 4.9 Hz), 4.34-4.27 (m, 2H), 4.06 (d, 1H, *J* = 9.6 Hz), 3.62 – 3.50 (m, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.1, 128.4, 127.6, 113.5, 112.6, 111.5, 85.1, 83.9, 82.5, 73.3, 70.9, 69.8, 26.6, 26.5, 26.4, 25.2; IR ($CHCl_3$) *v* 3495, 2988, 1376, 1205, 1015, 852 $cm^{-1}$; HRMS (ESI-MS): m/z calcd for $[C_{19}H_{20}NO_6Na]^+$: 373.1627; found: 373.1631.

**6-Azido-6-deoxy-1,2;3,4-di-*O*-isopropylidene-β-D-psicofuranose (4a):** Thick liquid: $[\alpha]_D^{25}$ = -53.0° (*c* 1.06, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.63 (dd, 1H, *J* = 5.9, 1.0 Hz), 4.59 (d, 1H, *J* = 5.8 Hz), 4.30 (d, 1H, *J* = 9.7 Hz), 4.21 – 4.15 (1H, m), 4.04 (d, 1H, *J* = 9.9 Hz), 3.51 (dd, 1H, *J* = 12.6, 7.6 Hz), 3.28 (dd, 1H, *J* = 12.6, 6.8 Hz), 1.46 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 113.9, 113.0, 112.0, 85.3, 84.2, 82.5, 69.7, 53.3, 26.5, 26.5, 26.3, 25.2; IR ($CHCl_3$) *v* 2989, 2099, 1376, 1205, 1065, 1020, 853 $cm^{-1}$; HRMS (ESI-MS): m/z calcd for $[C_{12}H_{19}N_3O_5Na]^+$: 308.1222; found: 308.1219.

**6-deoxy-6-((9H-fluoren-9-yl)methylcarbamate)-1,2;3,4-di-*O*-isopropylidene-β-D psicofuranose (5a):** To a solution of compound **4a** (3.5 g, 12.2 mmol) in EtOAc (15 mL) in a RB flask was added 10% Pd–C 0.5 g. The mixture was hydrogenated using $H_2$ balloon at room temperature for 3 h. After completion of reaction the slurry was filtered through celite and concentrated *in vacuo* to give amine quantitatively. This crude amine was dissolved in THF and 10% $NaHCO_3$ sol$^n$ (7.5 mL) added. The resulting solution was cooled to 0 °C and Fmoc-OSu 1.1 eq (4.5 g, 13.5 mmol) with respect to amine was added slowly as a solution in THF. The resulting mixture was allowed to warm to room temperature overnight. Water was then added and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with water, brine and dried over $Na_2SO_4$ and concentrated to dryness. The dry residue was chromatographed on a column of silica gel using petroleum ether/EtOAc to get **5a**. White solid: $R_f$ = 0.5 (petroleum ether/EtOAc, 75:25); Yield: (5.0 g, 85%); $[\alpha]_D^{25}$ = -53.0 (*c* 0.7, $CHCl_3$); mp- 102-104 ºC; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.77 (d, 2H, *J* = 7.5 Hz), 7.62 – 7.57 (m, 2H), 7.40 (t, 2H, *J* = 7.4 Hz), 7.31 (t, 2H, *J* = 7.4 Hz), 5.54 (t, 1H, *J* = 5.4 Hz), 4.66 (d, 1H, *J* = 5.8 Hz), 4.59 (d, 1H, *J* = 5.7 Hz), 4.48 – 4.37 (m, 2H), 4.34 (d, 1H, *J* = 9.8 Hz), 4.25 (dt, 2H, *J* = 13.9, 6.2 Hz), 4.06 (d, 1H, *J* = 9.9 Hz), 3.42 (t, 2H, *J* = 5.7 Hz), 1.49 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 156.6, 144.1, 144.0, 141.5, 141.4, 127.8, 127.1, 125.1, 120.1, 113.7, 112.8, 111.8, 85.7, 84.6, 82.3, 70.0, 66.8, 47.3, 43.6, 26.5, 26.5, 26.4, 25.2; IR ($CHCl_3$) *v* 3356, 2988, 1718, 1519, 1243, 1064, 855, 733 cm$^{-1}$; HRMS (ESI-MS): m/z calcd for $[C_{27}H_{31}NO_7Na]^+$:504.1998; found: 504.1998.

Compound **(3ab)**: To a solution of **3a** (0.2 g, 0.57 mmol) in toluene at 0 °C, was added TMSOTf (0.103 mL, 0.57 mmol). After addition ice bath was removed and reaction stirred at room temperature. After 45 min complete consumption of starting material was observed and reaction quenched by adding $Et_3N$. Toluene removed on rota evaporator. Water was added and extracted into EtOAc. The combined organic layers were washed with water, brine and dried over $Na_2SO_4$ and concentrated to dryness. The dry residue was chromatographed on a column of silica gel using petroleum ether/EtOAc to get **3ab**. Thick liquid: $R_f$ = 0.4 (petroleum ether/EtOAc, 85:15); Yield: (125 mg, 75%); $[\alpha]_D^{25}$ = -74.2° (*c* 0.73, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.38 – 7.27 (m, 5H), 4.73 (dd, 1H, *J* = 6.0, 1.1 Hz), 4.59 (d, 1H, *J* = 6.0 Hz), 4.54 (d, 2H, *J* = 2.1 Hz), 4.34 – 4.27 (m, 1H), 3.95 (d, 1H, *J* = 12.5 Hz), 3.78 (d, 1H, *J* = 12.5 Hz), 3.59 – 3.46 (m, 2H), 1.46 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 138.1, 128.5, 127.9, 113.1, 106.4, 84.2, 83.7, 83.0,

73.4, 71.0, 60.1, 26.5, 25.2; IR ($CHCl_3$) *v* 2925, 1375, 1212, 1093 $cm^{-1}$; HRMS (ESI-MS): m/z calcd for $[C_{32}H_{40}NaO_{10}Na]^+$: 607.2519; found: 607.2515.

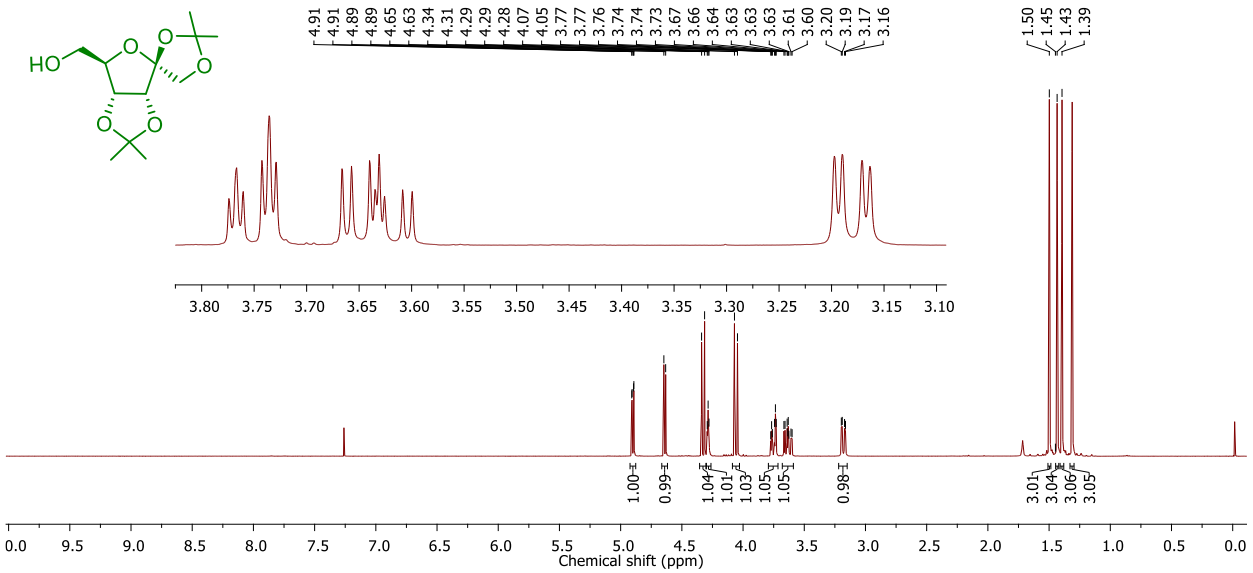
Compound **(5ab)**: This compound was prepared following the above procedure for **3ab** using **5a** (0.2 g, 0.57 mmol) of the starting material to obtain **5ab**, **5ac** as 1:1 in 74% yield. White solid: $R_f$ = 0.3 (petroleum ether/EtOAc, 60:40); Yield: (70 mg, 40%); $[\alpha]_D^{25}$ = -48.8° (*c* 0.44, $CHCl_3$); mp-101-103 ºC; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.77 (d, 2H, *J* = 7.5 Hz), 7.60 (d, 2H, *J* = 7.4 Hz), 7.40 (t, 2H, *J* = 7.5 Hz), 7.32 (td, 2H, *J* = 7.4, 0.9 Hz), 5.36 (t, 1H, *J* = 5.5 Hz), 4.67 (dd, 2H, *J* 1= 8.2, 5.8 Hz), 4.50 – 4.35 (m, 2H), 4.30 (t, 1H, *J* = 5.1 Hz), 4.22 (t, 1H, *J* = 6.9 Hz), 4.07 (d, 1H, *J* = 12.4 Hz), 3.88 (d, 1H, *J* = 12.3 Hz), 3.53 – 3.33 (m, 2H), 1.49 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 156.6, 144.1, 144.0, 141.5, 127.8, 127.2, 125.2, 120.1, 113.4, 106.0, 85.4, 83.9, 82.6, 66.9, 61.3, 47.4, 44.1, 26.6, 25.1; IR ($CHCl_3$) *v* 3345, 2940, 1708, 1519, 1245, 1074, 739 $cm^{-1}$; HRMS (ESI-MS): m/z calcd for $[C_{48}H_{51}N_2O_{12}Na]^+$: 847.3442; found: 847.3442.

Compound **(5ac)**: Thick liquid: $R_f$ = 0.25 (petroleum ether/EtOAc, 60:40); Yield: (60 mg, 34%); $[\alpha]_D^{25}$ = -12.8° (*c* 0.83, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.76 (d, 4H, *J* = 7.5 Hz), 7.64 – 7.55 (m, 4H), 7.40 (t, 4H, *J* = 7.5 Hz), 7.35 – 7.28 (m, 4H), 5.35 (br t, 1H), 5.03 (t, 1H, *J* = 5.9 Hz), 4.70 (d, 1H, *J* = 5.9 Hz), 4.59 (d, 1H, *J* = 5.8 Hz), 4.53 – 4.32 (m, 6H), 4.28 – 4.07 (m, 6H), 3.81 (d, 1H, *J* = 12.2 Hz), 3.58 – 3.44 (m, 3H), 3.43 – 3.31 (m, 2H), 1.58 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 156.6, 144.0, 141.4, 127.8, 127.2, 125.2, 125.1, 120.1, 117.1, 113.2, 104.1, 99.3, 85.9, 85.7, 82.5, 82.0, 81.0, 67.0, 66.8, 63.9, 62.8, 47.3, 44.1, 42.5, 26.4, 26.3, 26.1, 25.0; IR ($CHCl_3$): *v* 3017, 1712, 1517, 1214, 1086, 741 $cm^{-1}$; HRMS (ESI-MS): m/z calcd for $[C_{48}H_{51}N_2O_{12}Na]^+$ :847.3442; found: 847.3448.

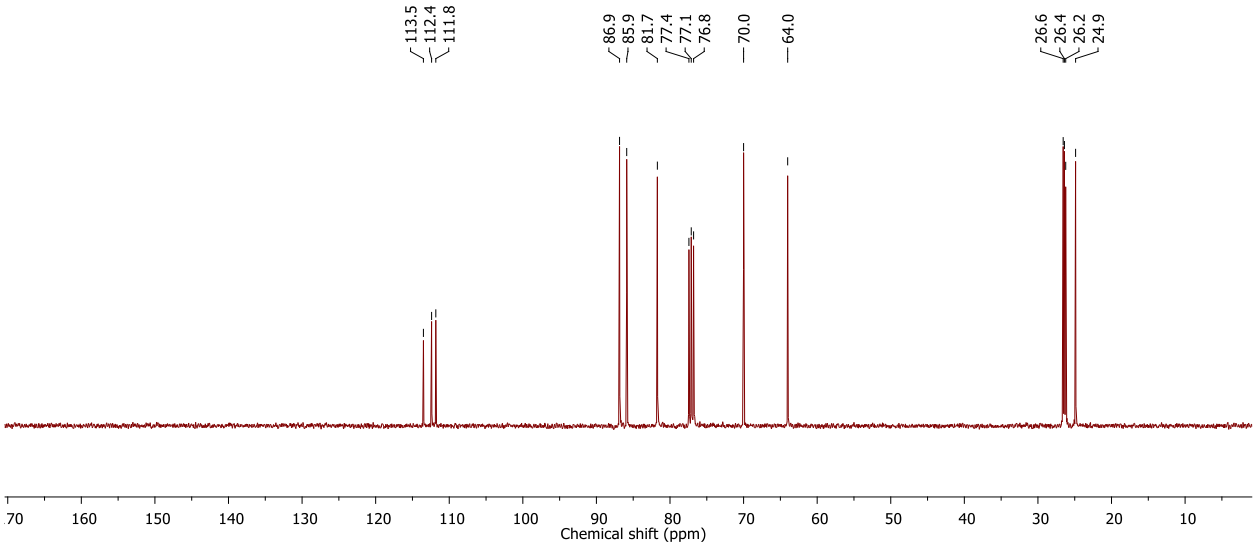
### 3B.8 Representative Spectral Charts

Kindly see the supporting documents file in *Beilstein J. Org. Chem.* **2015,** *11,* 2289–2296. doi:10.3762/bjoc.11.249 for spectral charts of compounds (**6a-17a**).

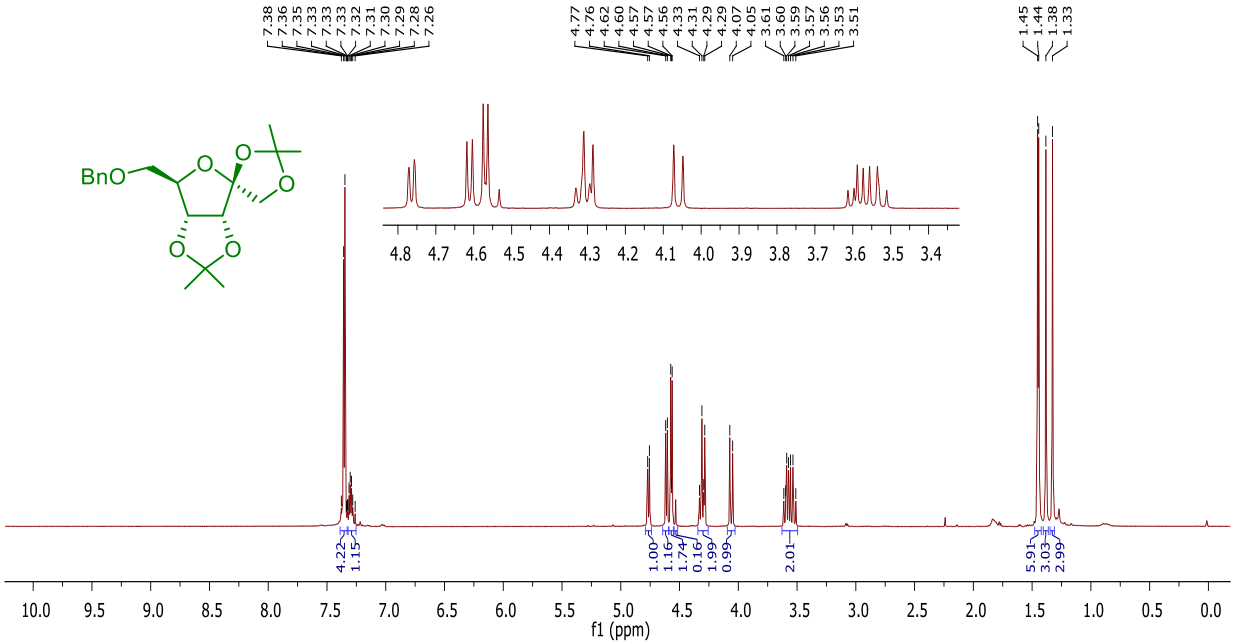
$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound **2a**



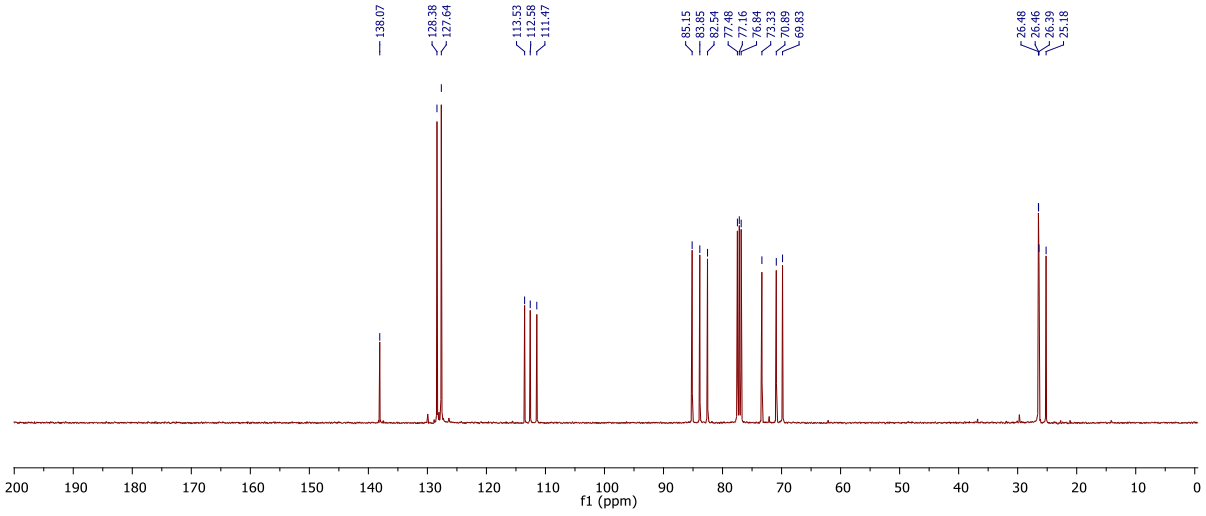

$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound **2a**



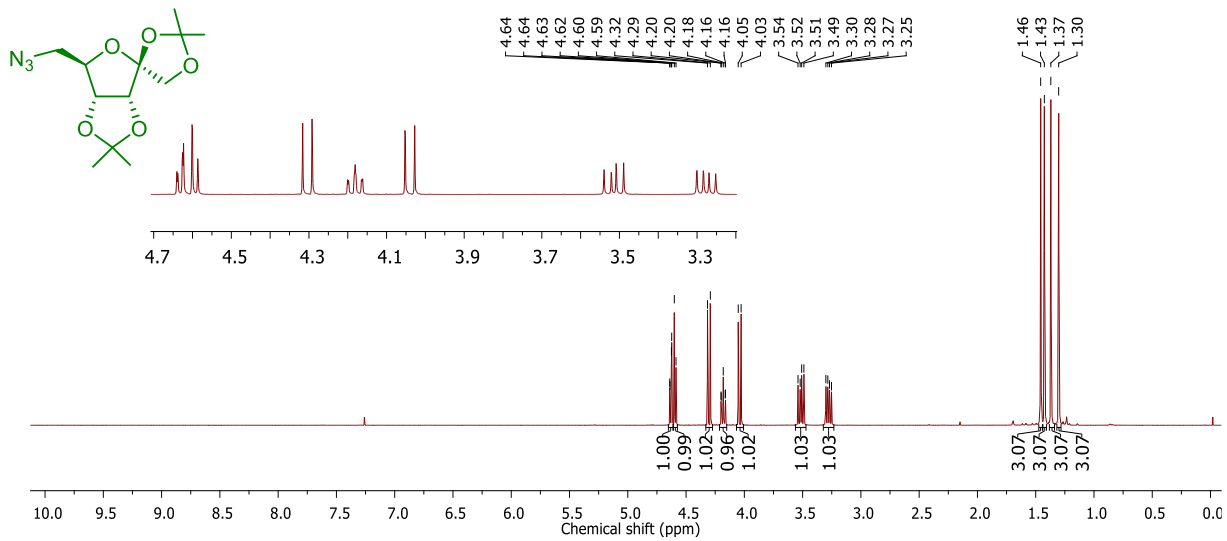
$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound **3a**



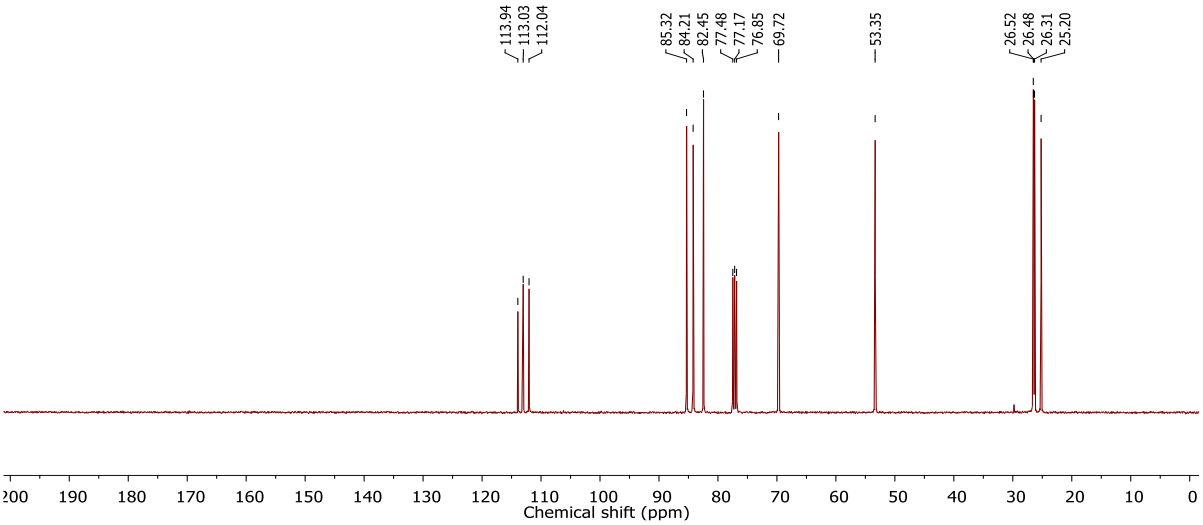

$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound **3a**



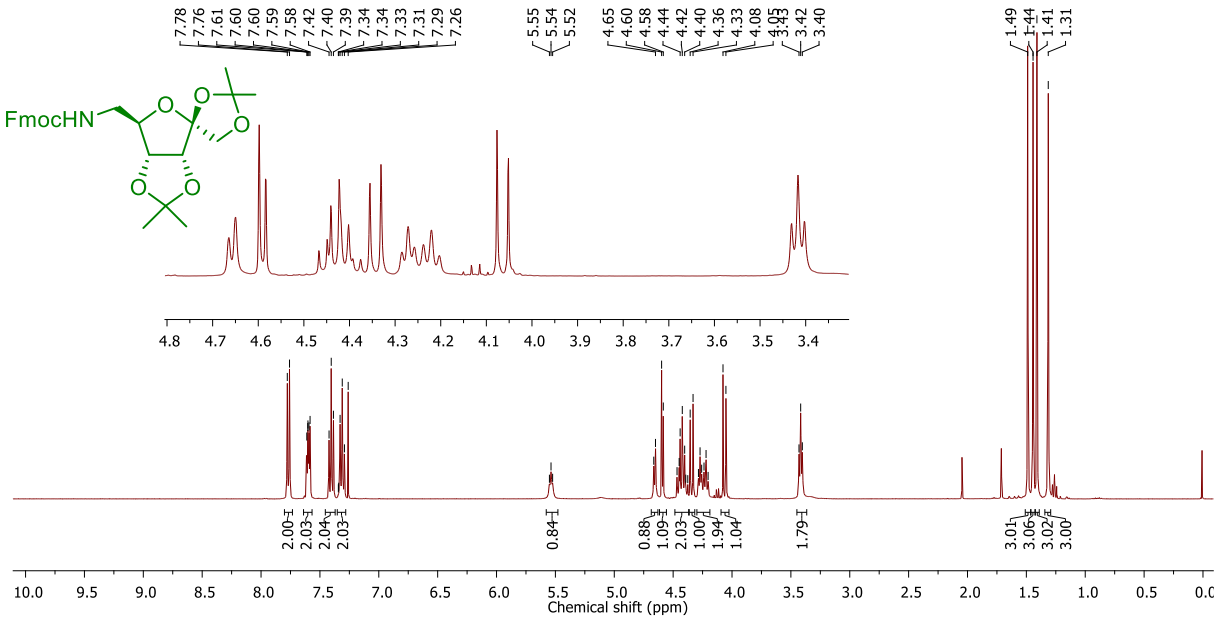
$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound **4a**



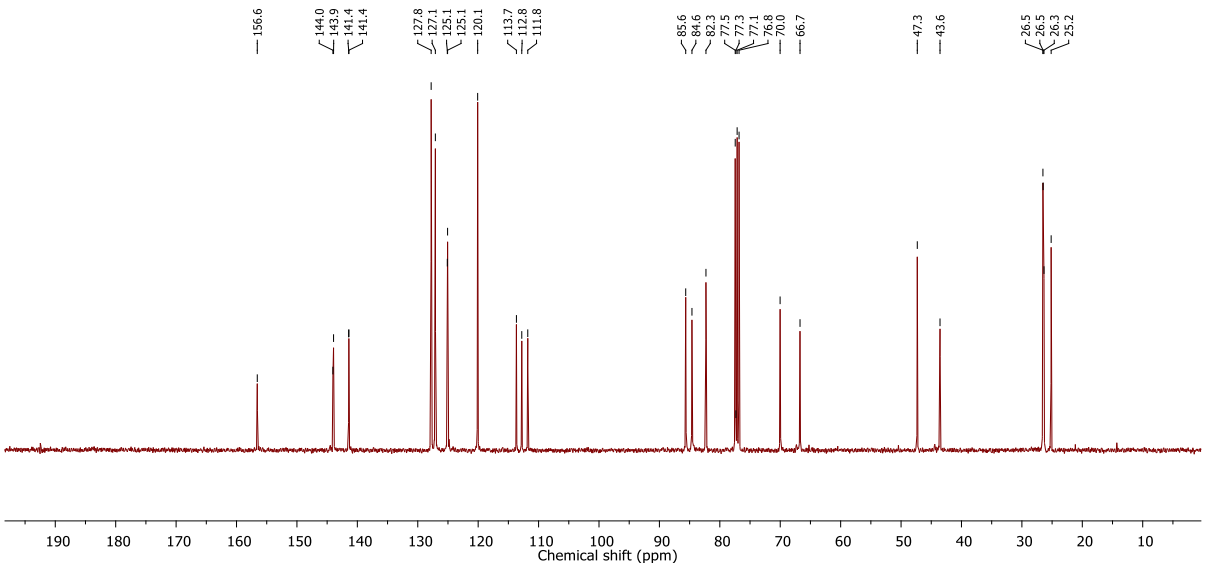

$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound **4a**



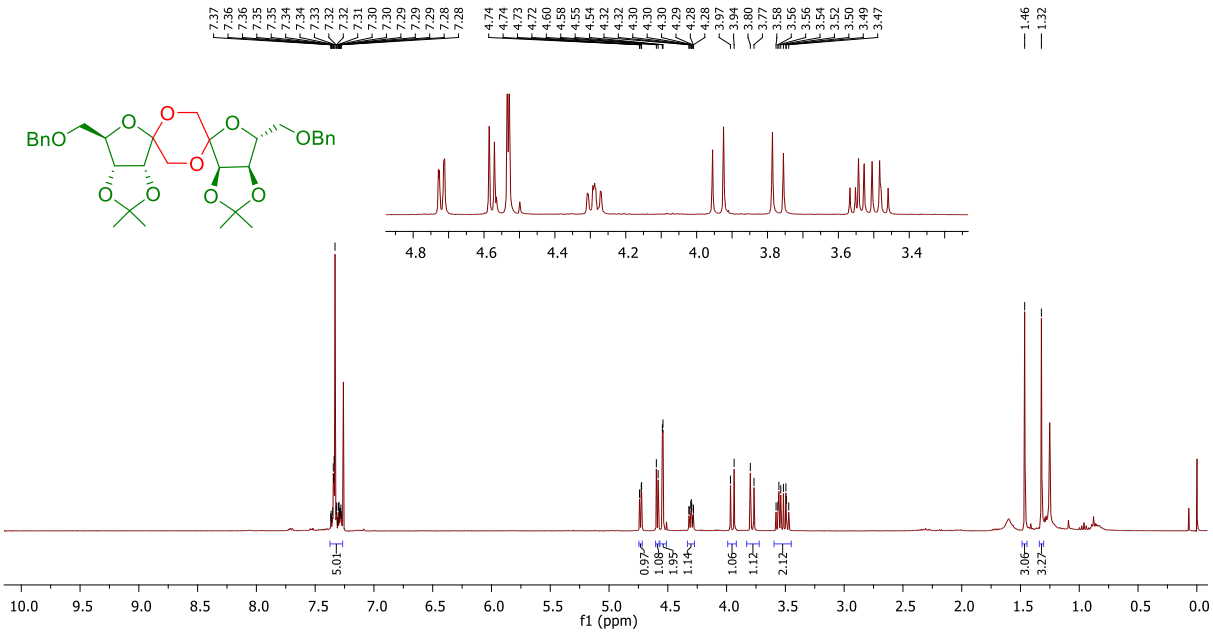
$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound **5a**



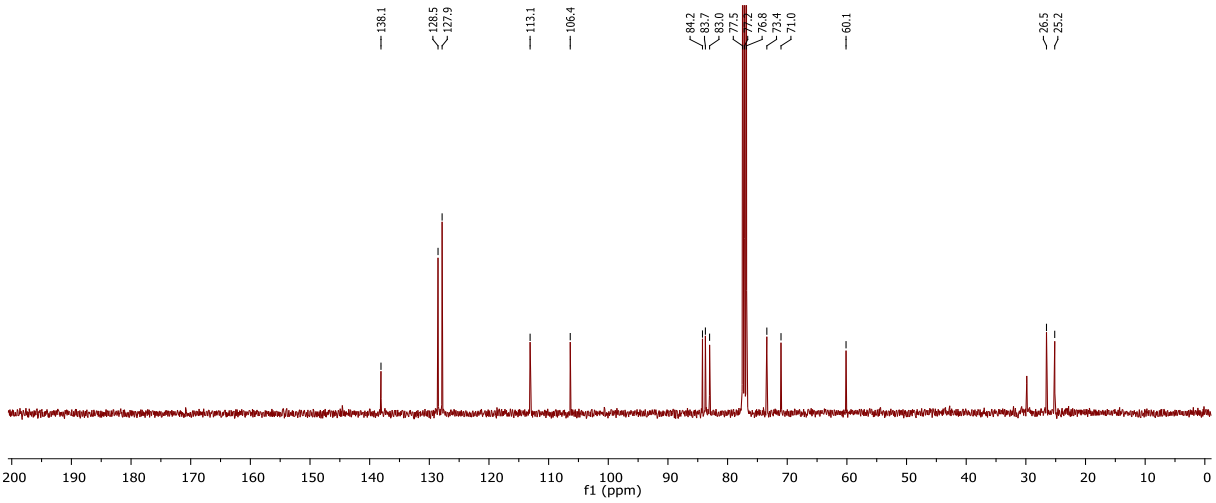

$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound **5a**



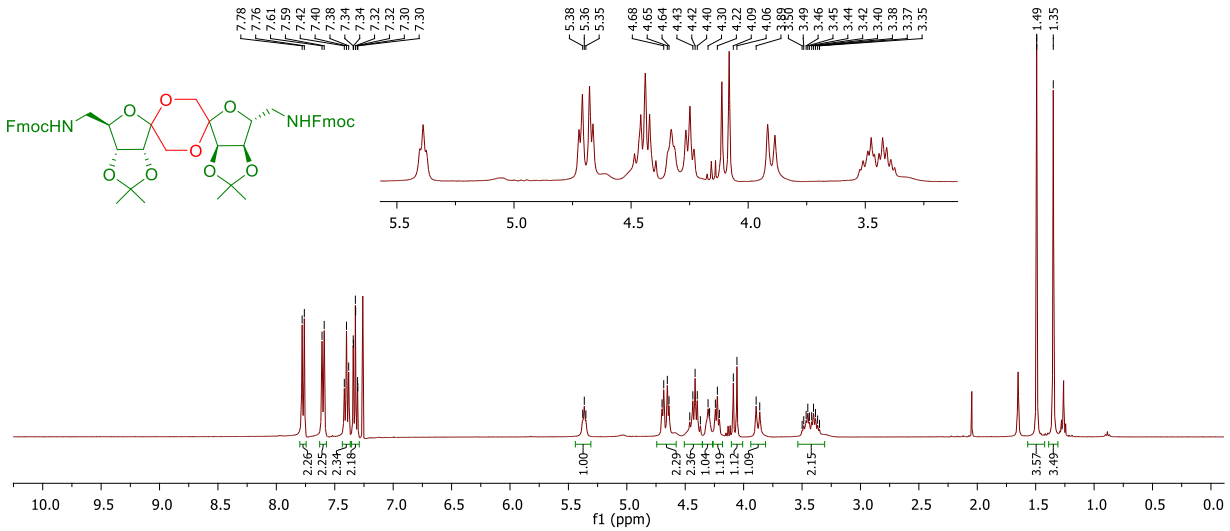
$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound **3ab (Symmetric)**



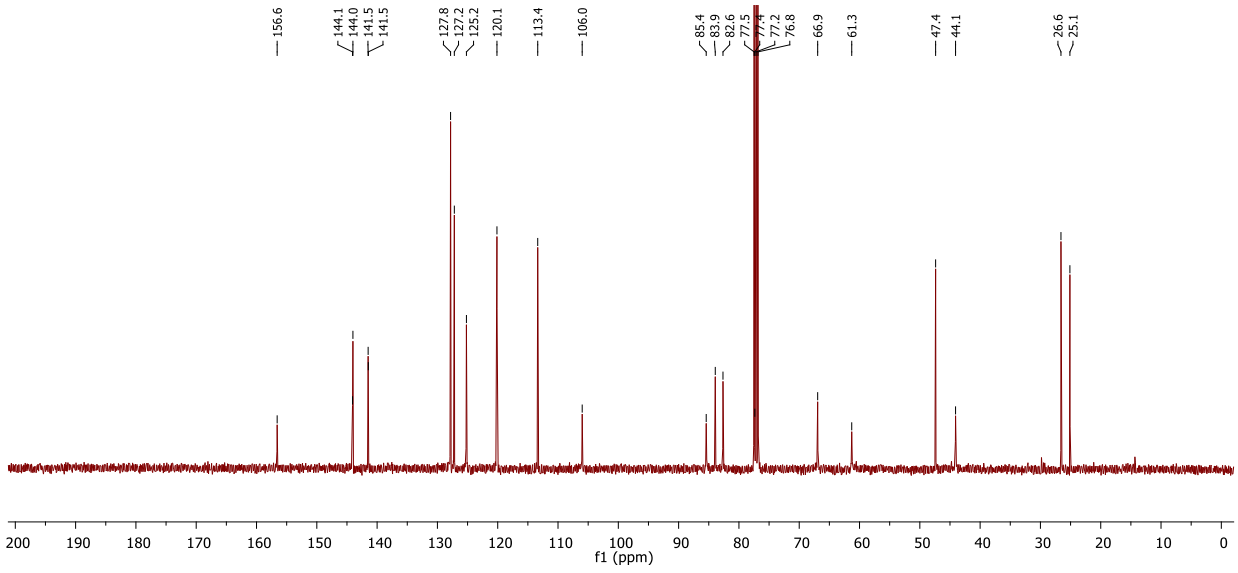

$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound **3ab**



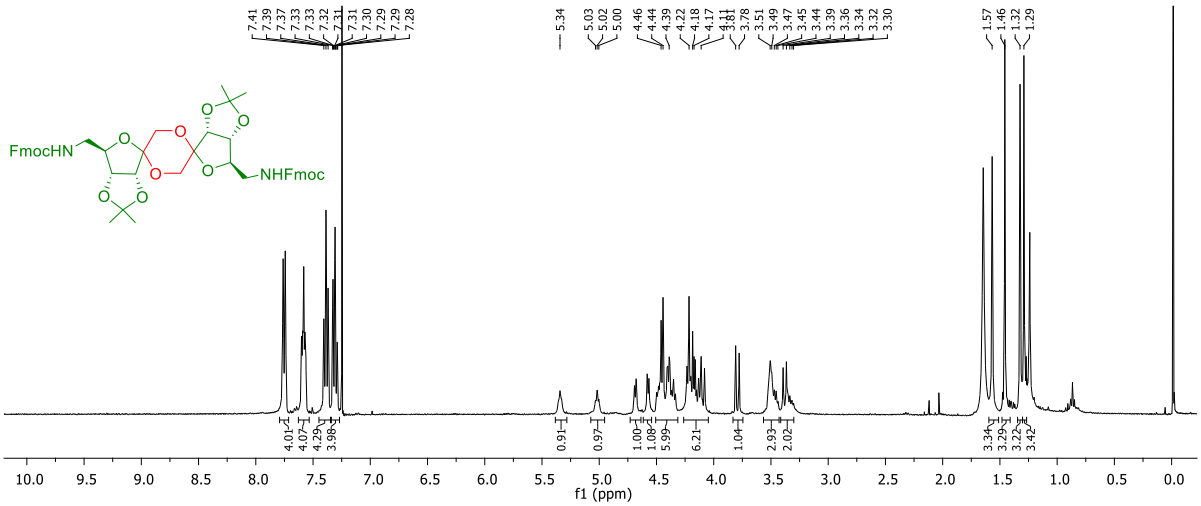
$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound **5ab (Symmetric)**



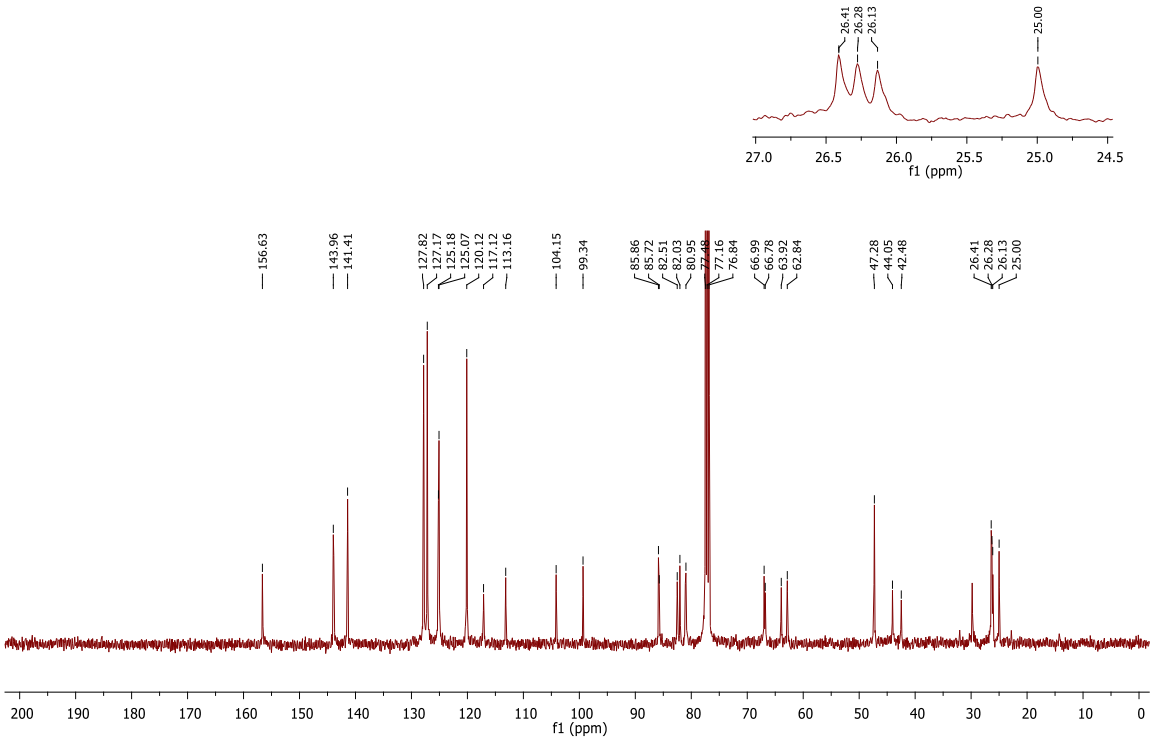

$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound **5ab**



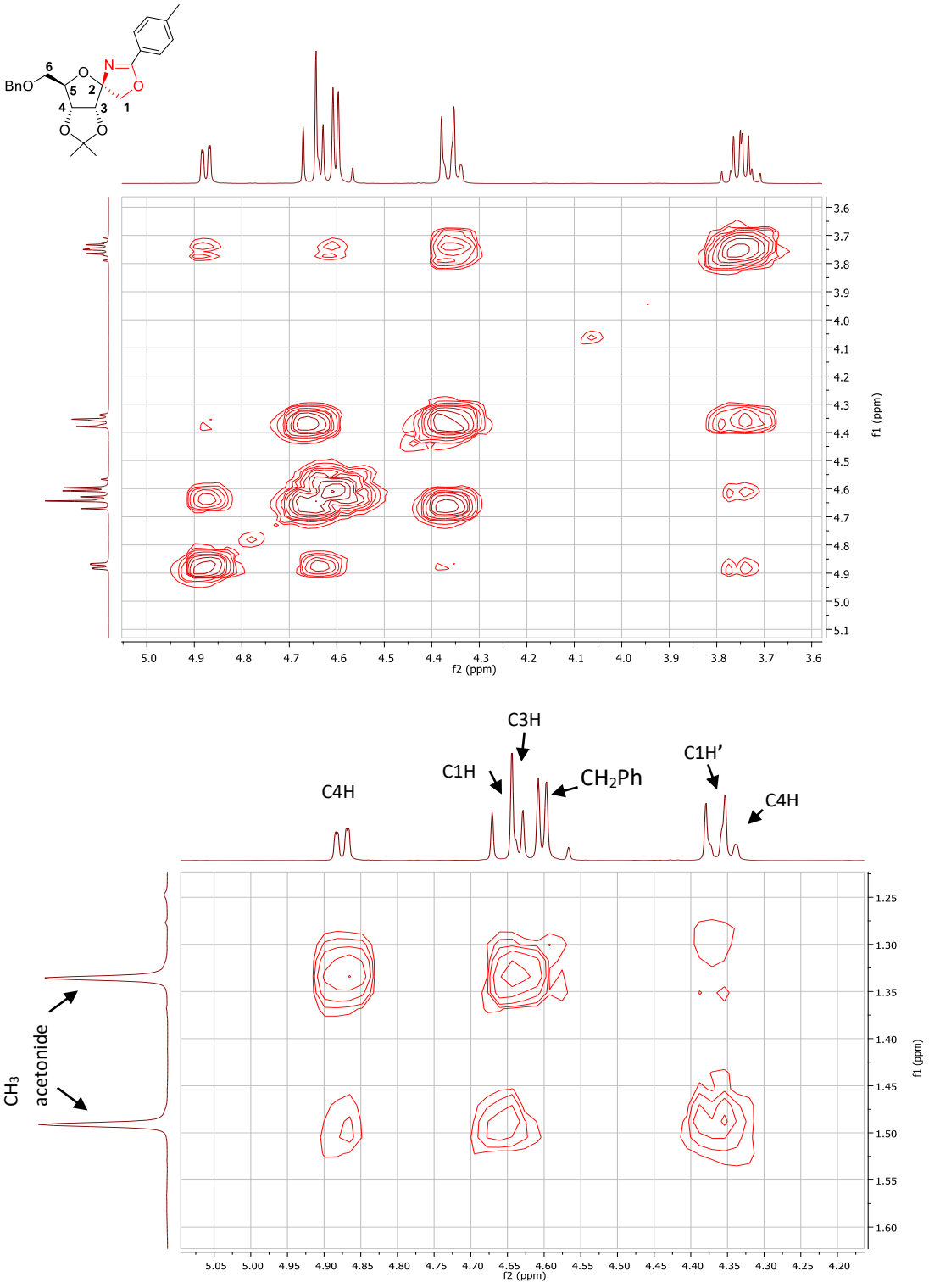
$^{1}$H NMR Spectrum (399.78 MHz, $CDCl_3$) of Compound **5ac (Asymmetric)**



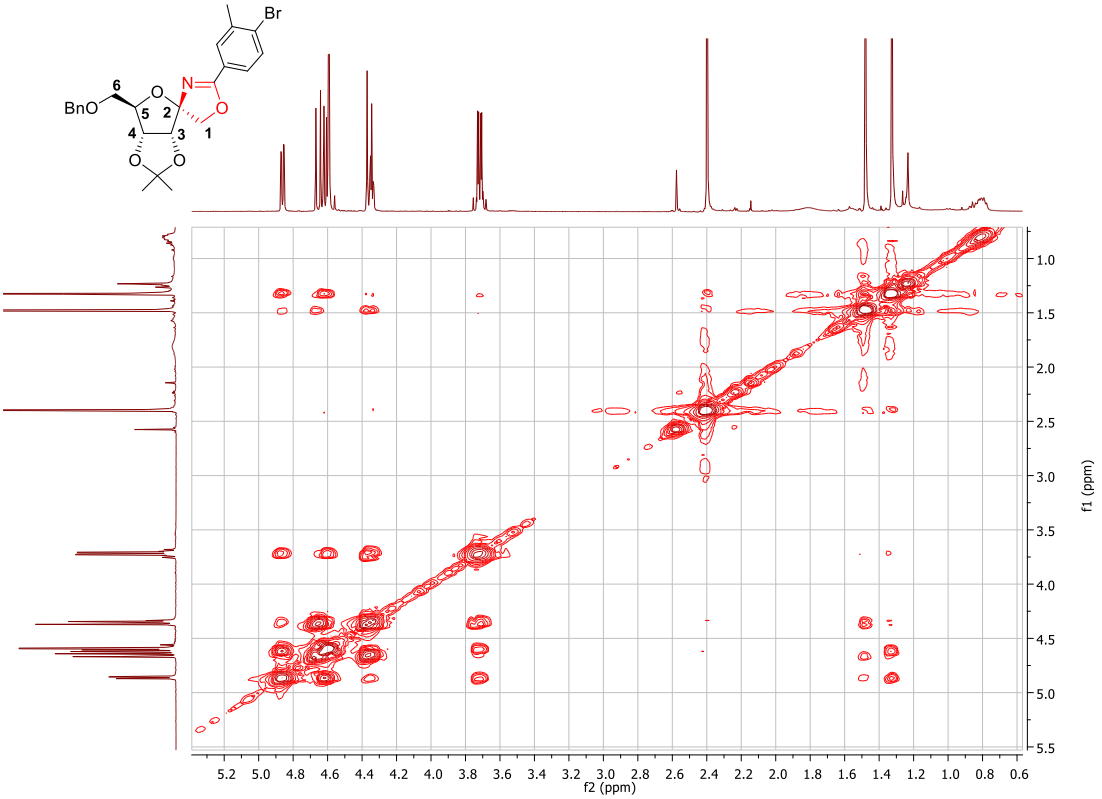

$^{13}$C NMR Spectrum (100.53 MHz, $CDCl_3$) of Compound **5ac**

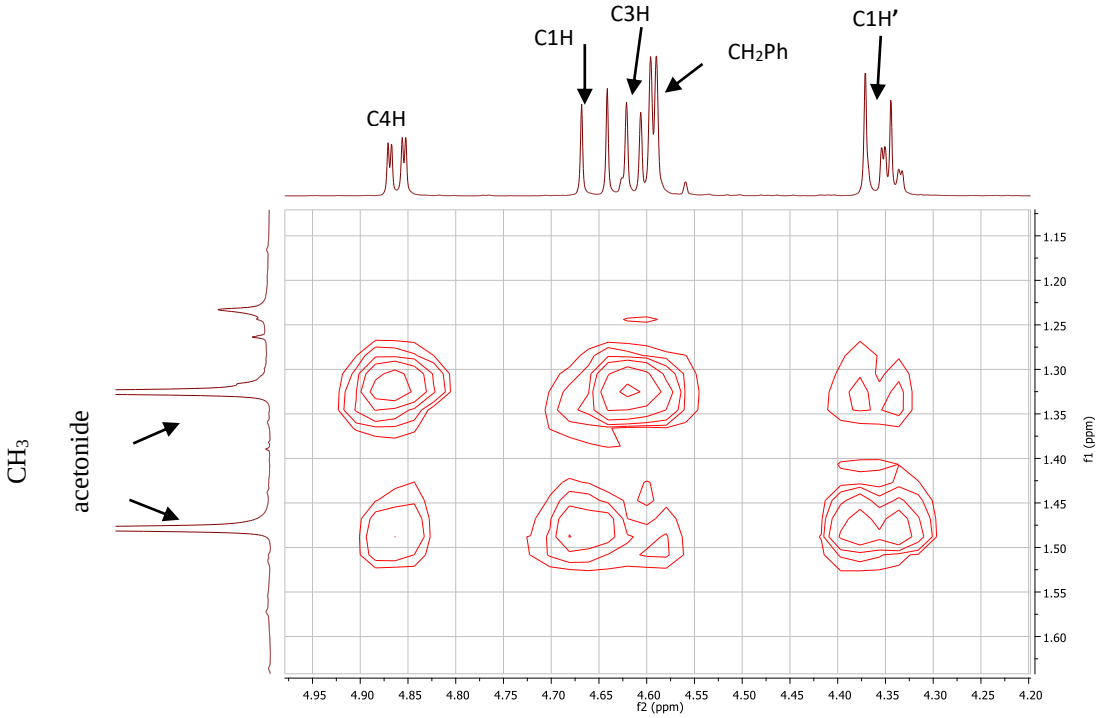


NOESY Spectrum (399.78 MHz, $CDCl_3$) of Compound **11a**



NOESY Spectrum (399.78 MHz, $CDCl_3$) of Compound **17a**



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# List of Publications

1. Expedient synthesis of the heneicosasaccharyl mannose capped arabinomannan of the *Mycobacterium tuberculosis* cellular envelope by glycosyl carbonate donors. Islam, M.; **Shinde, G. P**.; Hotha, S. *Chem. Sci.* **2017**, *8*, 2033.
2. [Au]/[Ag]-catalysed expedient synthesis of branched heneicosafuranosyl arabinogalactan motif of *Mycobacterium tuberculosis* cell wall. Thadke, S. A.; Mishra, B.; Islam, M.; Pasari, S.; Manmode, S.; Rao, B. V.; Neralkar, M.; **Shinde, G. P**.; Walke, G.; Hotha, S. *Nat. Commun*. **2017**, *8*, 14019.
3. *p*-Nitrophenyl carbonate promoted ring-opening reactions of DBU and DBN affording lactam carbamates. Vangala, M.; **Shinde, G. P.** *Beilstein J. Org. Chem.* **2016,** *12*, 2086–2092.
4. Synthesis of D-fructose-derived spirocyclic 2-substituted-2-oxazoline ribosides. Vangala, M.; **Shinde, G. P.** *Beilstein J. Org. Chem.* **2015,** *11*, 2289–2296.
5. Synthesis of conjugation ready heptamannopyranoside immunogenic epitope. **Shinde, G. P**.; Sutar, Y.; Kasdekar, N.; Hotha, S. (*Manuscripts under preparation*)

# Synthesis of D-fructose-derived spirocyclic 2-substituted-2-oxazoline ribosides

Madhuri Vangala* and Ganesh P. Shinde

Full Research Paper

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## Abstract

The TMSOTf-mediated synthesis of β-configured spirocyclic 2-substituted-2-oxazoline ribosides was achieved using a "Ritter-like" reaction in toluene through nucleophilic addition of electron-rich nitriles to the oxacarbenium ion intermediate of 1,2;3,4-di-*O*-isopropylidene-β-D-psicofuranose derivatives with concomitant intramolecular trapping of the C2 hydroxymethyl group on the electrophilic nitrilium carbon. These carbohydrate-derived spirooxazolines are stable and were obtained in good yield with high stereoselectivity due to the conformational rigidity imparted by the 3,4-isopropylidene group.

## Introduction

2-Oxazolines represent a unique class of 5-membered heterocyclic compounds with a wide range of applications spanning different chemistry disciplines. 2-Oxazoline derivatives are extensively studied due to their presence in numerous bioactive natural products [1-3] and synthetic drugs with anticancer, antibiotic, antidiabetic, and antifungal properties (Figure 1, **1**–**4**) [4-6]. The strong affinity of the nitrogen in oxazoline towards metal makes the chiral derivatives excellent catalysts for asymmetrical transformations [7-10]. The amphiphilicity and biocompatibility of poly-2-substituted-2-oxazolines gained them recognition as biomaterials for polymer therapeutics [11-13]. Traditionally, oxazolines are used as protecting groups in organic synthesis [14]. Several efficient methods for the construction of the 2-oxazoline functionality are reported in the literature from alkenes, carboxylic acid derivatives, nitriles [15-19], etc. In carbohydrate chemistry, they are versatile intermediates in the synthesis of *N*-linked glycoproteins [20-22].

In the context of carbohydrate chemistry, there are two possible regioisomers for glycooxazolines. Firstly, the C1 *O*-linked 1,2-glycooxazolines (Figure 1, **5**) are formed by intramolecular nucleophilic substitution at the anomeric center by vicinal participation of the C2 acylamino group. These are highly reactive and favor the formation of 1,2-*trans*-glycosides in a diastereoselective fashion [23-26]. Secondly, the C1 *N*-linked 1,2-glycooxazolines (Figure 1, **5**) are derived from either glycosyl azides

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

# *p*-Nitrophenyl carbonate promoted ring-opening reactions of DBU and DBN affording lactam carbamates

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Full Research Paper

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## Abstract

The amidine bases DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) display nucleophilic behaviour towards highly electrophilic *p*-nitrophenyl carbonate derivatives with ring opening of the bicyclic ring to form corresponding substituted ε-caprolactam and γ-lactam derived carbamates. This simple method presents a unified strategy to synthesize structurally diverse ε-caprolactam and γ-lactam compounds with a large substrate scope.

## Introduction

Among various organic bases, amidines such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) having an imino group attached to the α-carbon of the amine are synthetically useful and strong neutral bases. Besides, DBU and DBN catalyze various organic reactions such as dehydrohalogenations [1], carbonylations [2], amidations [3] and Baylis–Hillman reactions [4]. These bicyclic amidines have been thought to be non-nucleophilic bases, but meanwhile numerous examples unveiled their ability to act as C and N nucleophiles [5-8]. In 1981, McCoy and Mal first isolated an adduct of DBU with dimethyl 1-chloro-3-methyl cyclopropane-1,2-dicarboxylate during the dehydrohalogenation of halocyclopropanes [9]. In 1993, Bertrand and co-workers, showed that DBU and DBN act as nucleophiles towards halo derivatives of main group elements where the DBU and DBN bicyclic rings remained unaffected [10,11]. Later in 1994, Lammers et al. observed the nucleophilicity of amidine bases with 4-halo-3,5-dimethyl-1-nitro-1*H*-pyrazole and their subsequent ring opening leading to the lactam products [12]. Subsequently, Ma and Dolphin isolated chlorin-$e_6$ lactams from the reaction of methyl pheophorbide with DBU and DBN promoted by trialkyl triflates [13]. Additionally, the conjugate addition reaction of DBU to diarylpyrone [14] and Baylis–Hillman acetates [15] also gave caprolactam products. A closer look at these results suggested that the nucleophilic behavior of DBU highly depends on specific substrates. Vaidyanathan and co-workers reported the DBU-catalyzed addition of amines to acyl imidazoles [16], however, using a stoichiometric amount of

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# [Au]/[Ag]-catalysed expedient synthesis of branched heneicosafuranosyl arabinogalactan motif of *Mycobacterium tuberculosis* cell wall

Shivaji A. Thadke[1,*], Bijoyananda Mishra[1,*], Maidul Islam[1], Sandip Pasari[1], Sujit Manmode[1], Boddu Venkateswara Rao[1], Mahesh Neralkar[1], Ganesh P. Shinde[1], Gulab Walke[1] & Srinivas Hotha[1]

Emergence of multidrug-resistant and extreme-drug-resistant strains of *Mycobacterium tuberculosis* (MTb) can cause serious socioeconomic burdens. Arabinogalactan present on the cellular envelope of MTb is unique and is required for its survival; access to arabinogalactan is essential for understanding the biosynthetic machinery that assembles it. Isolation from Nature is a herculean task and, as a result, chemical synthesis is the most sought after technique. Here we report a convergent synthesis of branched heneicosafuranosyl arabinogalactan (HAG) of MTb. Key furanosylations are performed using [Au]/[Ag] catalysts. The synthesis of HAG is achieved by the repetitive use of three reactions namely 1,2-*trans* furanoside synthesis by propargyl 1,2-orthoester donors, unmasking of silyl ether, and conversion of *n*-pentenyl furanosides into 1,2-orthoesters. Synthesis of HAG is achieved in 47 steps (with an overall yield of 0.09%) of which 21 are installation of furanosidic linkages in a stereoselective manner.

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# Expedient synthesis of the heneicosasaccharyl mannose capped arabinomannan of the *Mycobacterium tuberculosis* cellular envelope by glycosyl carbonate donors†

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The global incidence of tuberculosis is increasing at an alarming rate, and *Mycobacterium tuberculosis* (Mtb) is the causative agent for tuberculosis, a disease with high mortality. Lipoarabinomannan (LAM) is one of the major components of the Mtb cellular envelope and is an attractive scaffold for developing anti-tubercular drugs, vaccines and diagnostics. Herein, a highly convergent strategy is developed to synthesize heneicosasaccharyl arabinomannan for the first time. The arabinomannan synthesized in this endeavour has several 1,2-*trans* or α-Ara*f* linkages and three 1,2-*cis* or β-Ara*f* linkages end capped with 1,2-*trans* or α-Man*p* linkages. All the key glycosidations were performed with alkynyl carbonate glycosyl donors under [Au]/[Ag] catalysis conditions, which gave excellent yields and stereoselectivity even for the reactions between complex and branched oligosaccharides. The resultant allyl oligosaccharide was globally deprotected to obtain the heneicosasaccharyl arabinomannan as a propyl glycoside. In summary, heneicosasaccharyl mannose capped arabinomannan synthesis was achieved in 56 steps with 0.016% overall yield.

## Introduction

The world-wide resurgence of mycobacterial infections coupled with the emergence of multi- and extreme drug resistance have placed tuberculosis (TB) as a major public health concern.[1–3] The only available protection against tuberculosis is the BCG vaccine; however, multi-centered clinical trials demonstrated variable efficacy.[4] Tuberculosis infections are caused by *Mycobacterium tuberculosis* (Mtb), which has a thick waxy cell wall making it impervious to drugs.[5,6] As a consequence, patients suffering from TB are prescribed a long regimen of multiple drugs. Therefore, TB is an ever growing challenge, and novel strategies to diagnose, control or eradicate it are in great demand.

The chemical structure of the waxy cellular envelope has been identified as a unique glycocalyx comprising mycolic acids, Ara*f*, Gal*f*, Man*p*, Rha*p* and inositols.[7–10]‡ Further investigations revealed that the glycocalyx contains trehalose lipids, lipoarabinomannan (LAM), arabinogalactan (AG) and peptidoglycan.[7–10] Of these, the structure of LAM was noticed to have a key C-3 branched arabinan domain with many α-1 → 5-linked D-Ara*f*s, and a few β-1 → 2-linked D-Ara*f*s capped with α-1 → 2 linked D-Man*p*s at the non-reducing end.[7–10,13] It has been well established that mannose capped LAM (ManLAM) is prevalent in more pathogenic mycobacterial species such as *M. tuberculosis*, *M. leprae*, *M. bovis*.[11–13] ManLAM has been shown to inhibit the production of tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12) by human dendritic cells and macrophages *in vitro* to modulate *M. tuberculosis* induced macrophage apoptosis.[14,15] Quite recently, a rapid point of care diagnostic kit was developed exploiting the antigenic properties of ManLAM.[16–18] In another study LAM was investigated as a candidate vaccine for mycobacterial diseases. Thus, the non-reducing end portion of LAM is beneficial to various immunological studies, diagnostics and the development of carbohydrate-based tuberculosis vaccines.

Owing to the significance of ManLAM, the synthesis of ManLAM and arabinan fragments has been attempted over the last two decades.[19–27,44] A recent investigation by Guo's group verified the synthetic and immunological potential of protein conjugated ManLAM fragments.[28] However, far too little attention has been paid to synthesizing the large oligomers in ManLAM. The main aim of the current research has therefore been to synthesize naturally occurring large oligosaccharide portions of ManLAM such as arabinomannan **1** (Fig. 1) to facilitate vaccine and diagnostic development.

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