[Au]/[Ag]-Catalyzed Activation of Glycosyl Alkynyl Carbonates and Their Application to the Syntheses of Various Glycoconjugates

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

By

Bijoyananda Mishra

ID: 20123170

Indian Institute of Science Education and Research, Pune

Thesis Supervisor

Prof. Srinivas Hotha, PhD
Department of Chemistry
Indian Institute of Science Education and Research, Pune

January 2019

Dedicated to…

All those who crave to do research but unfortunately could not do so….

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान पुणे
INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH PUNE
डॉ. होमी भाभा मार्ग, पुणे 411008, महाराष्ट्र, भारत | Dr. Homi Bhabha Road, Pune 411008, Maharashtra, India
T +91 20 2590 8001 W www.iiserpune.ac.in

IISER PUNE

Prof. Srinivas Hotha, PhD
Department of Chemistry

CERTIFICATE

Certified that the work incorporated in the thesis entitled "***[Au]/[Ag]-catalysed Activation of Glycosyl Alkynyl Carbonates and Their Application to the Syntheses of Various Glycoconjugates***" submitted by **Mr. Bijoyananda Mishra** 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.

Date: December 2018, Pune

Prof. Srinivas Hotha
(Research Supervisor)

DECLARATION

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.

Date: January 15, 2019
Pune (MH), India

Bijoyananda Mishra
ID: 20123170
Department of Chemistry
IISER Pune – 411008, India

Acknowledgement

The hardest thing in life is having feelings in your heart that you can't put into words……

*First and foremost, I would like to express my most sincere gratitude to my mentor and research supervisor Prof. Srinivas Hotha. He is a man of ethics, compassion, forgiveness, encouragement and motivation. Whatever I have achieved during my entire PhD expedition has been possible because of his limitless encouragement, outstanding guidance and kind supports. He not only always listens and provides solutions for our research problems but our personal problems too. He is a constant source of inspiration for me and without this I might lost myself in the cloud phase of PhD life. His motivational speech and cool perspective about life always has been a ray of hope for us during our difficult and frustrating times. He always wants that we not only just become a skilful labor but an independent innovative thinker, a creative investigator, a good speaker, a good narrator and above all of this a good human being. His famous quotes about research is "**Research is not just barely mixing of few chemicals. There are so many things before and after of it**". It will remain as a guideline for all of his students during their independent endeavor. I am really fortunate to have him as my PhD supervisor and it was a great pleasure to working with him. I am grateful to him for making my PhD journey so easy and full of excitement through the up and down terrain of life.*

I am ardently indebted to my research advisory committee members, Dr. Hosahudya N. Gopi from IISER Pune and Dr. Dilip D. Dhavale from Shavitribai Phule Pune University for their insight suggestions during my RAC meetings. Personally I want to thank Prof. M. Jayakannan, Dr. H. Chakrapani, Dr. N. Ballav, Dr. R. Kikkeri, Dr. R. G. Bhat and all faculty members of chemistry department for their valuable discussions.

For a successful PhD, after research supervisor if anything matters most that is our lab environment and relation with our lab colleagues. I am really lucky in this matter. I am extremely thankful to my lab seniors (Dr. A. sheikh, Dr. A. Kayastha, Dr. S. Thadke, Dr. B. V. Rao, Dr. M. Islam), my juniors (Mahesh, Sujit, Saptashwa, Jyoti, Ganesh, Gulab, Jayashri, Nitesh) and other lab members (Dr. Madhuri, Dr. Sandip, Harsha, Raviraja, Nishant) for their constant supports, sharing of knowledge and maintaining a healthy lab environment. I am especially thankful to Mahesh and Saptashwa for their significant contribution in many of my research projects. I also want to express my thanks to Chenna Reddy, Rahul, Arun, Dhrubojyoti Da, Rajkumar,

Rahi, Sanjit, Kundan, Kavita, Rajesh, Tushar, Trimbak, Chetan and Bala for their kind helps regarding various matters.

We succeed not only because of our capability, but the sacrifices that our family made for it. I don't have enough words to express my gratitude to my family members. I just feel proud for having the privilege of such a nice family. I am extremely grateful to my Maa (Smt. Bhagyalaxmi Mishra), Baba (Sri. Pradip Mishra), Wife (Aparna), Kaka (Late Billamngal Mishra), Nitu (Somnath), Didi (Minakshi Acharjee), Jamaibabu (Astik Acharjee), Dadu (Shri. Subhas Mishra), Bou (Smt. Namita Mishra), Mithu (Devarshi), Indira, Mother-in-law (Smt. Doli Chatterjee), Father-in-law (Late Uttam Chatterjee) Pisi (Aparupa, Rinku and Juthika), Piso (Shri. Ajay Mishra), Kitu kaku (Shri. Kiriti Mukherjee), Laxmipada, Fucha, Pranab, Sukanta Da (Adra) and all other family members for encouraging me all the times without any expectations. Their patience and sacrifice always remains a source of inspiration to get success in my life. I am thankful to my friends with whom I have enjoyed my journey of life. I sincerely thankful to Somnath (Arrah), Jagatjyoti (Adra), Somnath (Anara), BHU friends (Arpan, Subhodip, Sujit, Pathak, Mona Da, Shankha, Late Agnimitra, Azmeera), BARC friends (Dilip, Debashish) and all others.

Apart from my family and close friends, if from anywhere I have been supported to follow my dream and passion for science, these are my colleagues from RAPS, NPCIL (DAE). I would like to express my deep and sincere gratitude to Dr. Puraram Ji, Pandey Ji, Tiwari Ji, Neel Bhaiya, Mahesh Ji, Rajiv Ji, Suryajyoti Dai, Paras Da, Trivedi Ji, Sony Ji, Sudhir Ji, Gourav Ji and all health physics division. I am also grateful to my beloved teachers (Dr. Niranjan Kole, Dr. Suman das, Mantu Master, Prabir Mishra, Pankaj Dubey and Goutam Chakraborty) for their support.

I sincerely thank our former Director Prof. K. N. Ganesh and Director Prof. Jayant B. Udgaonkar for providing a world class research facility in IISER-Pune. I wholeheartedly thank and give acknowledgements to the entire academic, technical and non-technical staff of IISER Pune.

I am grateful to University Grant Commission, Government of India, for awarding the Junior and Senior research fellowships.

Finally, I bow down to the almighty Lord Vishnu, the only ultimate truth above all as per the scriptures.

Bijoyananda Mishra

Contents

- ^{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.

Å – Angstrom
Ac – Acetate
AcBr – Acetyl bromide
AcCl – Acetyl chloride
AcOH – Acetic acid
Ac_2O – Acetic anhydride
AG – Arabinogalactan
Ara*f* – arabinofuranosyl/arabinofuranoside
Bn – Benzyl
BnBr – Benzyl bromide
Boc – *t*-butylcarbonyl
BSA – Bis(trimethylsilyl)acetamide
Bu_2SnO – Dibutyltin oxide
Bz – Benzoyl
BzCl – Benzoyl chloride
Calcd – Calculated
Cbz – Carbobenzoxy
cat. – catalytic
$CDCl_3$ – Chloroform-D
$CHCl_3$ – Chloroform
d – days
DBU – 1,8-Diazabicycloundec-7-ene
DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DCM – Dichloromethane
DCE – Dichloroethane
DEPT – Distortion less Enhancement by Polarization Transfer
DIPEA – *N*,*N*′-Diisopropylethylamine
DIC – *N,N*′-Diisopropylcarbodiimide
DMAP – *N*,*N*′-Dimethylaminopyridine
DMF – *N*,*N*′-Dimethyl formamide
DMSO-d_6 – Dimethyl sulfoxide (deuterated)
D_2O – Deuterium oxide
δ – delta (in ppm)
eq. – equivalents
Et_3N – Triethyl amine
Et_2O – Diethylether
EDC– 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc – Ethyl acetate
Et_3SiH – Triethylsilane
g – gram
Gal*f* – galactofuranosyl / galactofuranoside
h – hour
HOAt – 1-Hydroxy-7-azabenzotriazole
HRMS – High-Resolution Mass Spectrometry
Hz – Hertz
Im. – Imidazole
IR – Infrared
J – coupling constant
Kg – Kilogram
LAM – Lipoarabinomannan.
Lev – Levulinoate
M – Molar
Man*p* – mannopyranosyl / mannopyranoside
MeI – Methyl Iodide
MeOD – Methanol-D4
mg – milligram
min. – minutes
MHz – Megahertz
mL – millilitre
mmol – millimolar
MS – Molecular sieves
Mtb – Mycobacterium tuberculosis
NaH – Sodium hydride
NAP – N-bromomethyl naphthalene
NGP – Neighbouring group participation
NIS – N-Iodosuccinimide
NMR – Nuclear Magnetic Resonance
NNGP – Non-neighbouring group participation
NPG – n-Pentenyl glycoside
PMB – p-Methoxy benzyl
PMBCl – p-Methoxy benzyl chloride
Py – Pyridine
PTSA, TsOH – *p*-Toluene sulfonic acid
ppm – parts per million
Rib*f* – ribofuranoside / ribofuranosyl
rt – room temperature
sat. – saturated
Tb – tuberculosis
TBAI – tetra-n-Butyl ammonium iodide
TBDMS – *t*-Butyldimethylsilyl
TBDMSCl – *t*-Butyldimethylchloride
TBDPS – *t*-Butyldiphenylsilyl
TBDPSCl – *t*-Butyldiphenylsilylchloride
TCA – Trichloroacetimidate
TfOH – trifluoromethanesulfonic acid
TFA – Triflouroacetic acid
THF – Tetrahydrofuran
TLC – Thin Layer Chromatography
TMSOTf – Trimethylsilyl trifluoromethanesulfonate
µg – microgram
µmol – micromolar
µL – microliter

The thesis titled, "***[Au]/[Ag]-Catalyzed Activation of Glycosyl Alkynyl Carbonates and Their Application to the Syntheses of Various Glycoconjugates***" is divided into four chapters. Chapter one delineates the importance of glycoconjugates and glycosylation, types of glycosylations, factors affecting the stereochemical outcome of any glycosylation, various types of glycosyl donors and their glycosylation methods along with existing Au-catalysed glycosylation protocols available in the literature. Chapter two describes the discovery of glycosyl alkynyl carbonate donors, activation by synergistic combination of [Au]/[Ag]-catalysis and their application for syntheses of various *O*-, *C*- and *N*-glycosides. Chapter three describes excellent features of the developed glycosyl alkynyl carbonate donor chemistry through the syntheses of linear nonadecaarabinofuranoside of Arabinogalactan (AG) as well as the highly branched tridecasaccharide reminiscent of Lipoarabinomannan (LAM) part of *Mycobacterium tuberculosis* cell wall. Chapter four describes the total synthesis of a unique, highly complex and hyper-branched *N*-linked core hexasaccharide from chloroviruses along with the optimization of [Au]/[Ag]-catalysed glycosylation conditions for the exclusive synthesis of 1,2-*cis* glycosidic bond in case of D-galactose and L-fucose sugar residues.

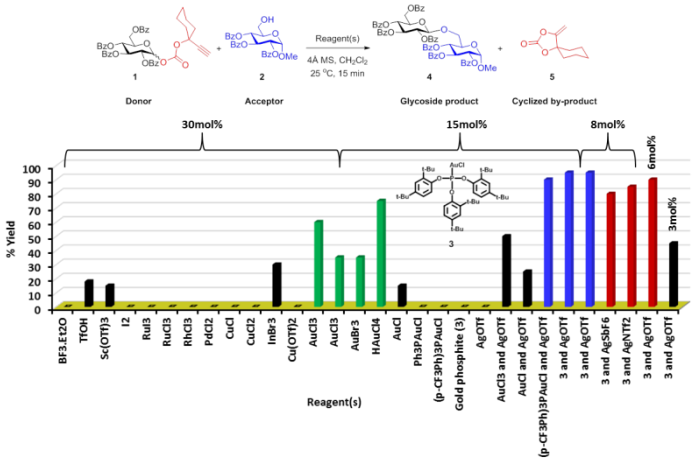
Chapter 1: Gold-Catalysed Glycosylation

Glycoconjugates are highly essential for all living organisms and are widely distributed on cell surfaces and secreted fluids in the form of polysaccharides, glycoproteins, proteoglycans and/or glycolipids. They regulate many biological processes such as viral and bacterial infection, tumour metastasis, angiogenesis, inflammation, cell-cell communication, hormone balance and metabolism. Medicinal uses of glycoconjugates are also well recognized and many carbohydrate-based drugs/vaccines are currently in clinical trials. However, due to the micro-heterogeneous nature of these naturally occurring glycoconjugates, accessibility of pure and structurally well-defined glycoconjugates is very limited. In this context, chemical synthesis of complex glycoconjugates with higher glycosylation yields and excellent stereoselectivity is of great importance. As a result, in the last few decades, a number of glycosyl donors and glycosylation protocols have emerged. Starting from highly acidic (i.e. BF_3•Et_2O/TMSOTf/TfOH) to very mild (i.e. Au/Ag/Pd/Cu/Zn catalysis) glycosylation conditions, a large number of activators or promotors have been developed. Use of Au-catalysts in the glycosylation reaction not only widened the

substrate scope in a significant manner but also improved the overall yields due to mild reaction conditions. However, necessity of a novel glycosyl donor chemistry that can be utilised for any type of glycoconjugates syntheses is still highly demanding and courageous.

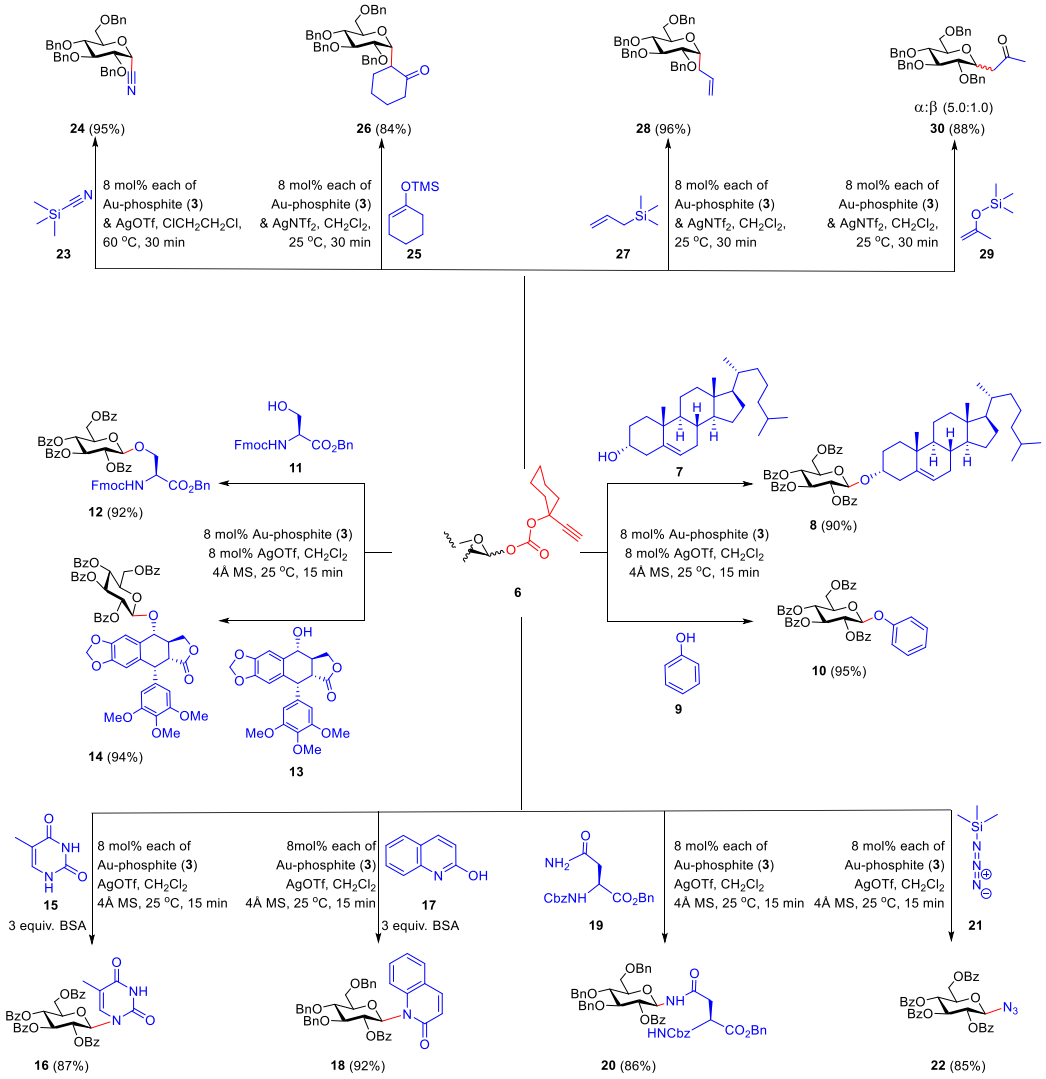
Chapter 2: Synthesis of *O*-, *C*- and *N*-Glycosides by [Au]/[Ag]-Catalysed Glycosylation

Even after several decades of the first glycosylation method developed by Fischer, glycosylation protocols based on the stable glycosyl donors and mild reaction conditions are very limited. Identification of stable propargyl glycosides as glycosyl donors under mild condition employing catalytic amount of $AuCl_3$ by our group has been a transformative advance in the Glycoscience. However, few limitations associated with this glycosylation protocol are: (i) not suitable for glycosyl donors possesing ester functional groups at *C*-2 position, (ii) formation of glycoside products as α/β mixture and (iii) cleavage of the inter-glycosidic bonds in some instances, restricted its application to oligosaccharides and glycocojugates synthesis. These inherent drawbacks associated with the propargyl glycoside donors motivated us to develop a new kind of alkyne based glycosyl donor which will not only be capable of overcoming existing limitations but also possesses all the salient features of Au-catalysed glycosylations. Therefore, conformationally rigid glucosyl ethynylcyclohexyl carbonate donor (**1**) was first synthesized from easily accessible per-*O*-benzoyl glucopyranose and screened with various alkynophilic or oxophilic Lewis and Brønsted acids or metal catalysts in presence of acceptor **2**.



Scheme 2.1: Identification of the [Au]/[Ag]-catalysed glycosylation using ethynylcyclohexyl carbonate donor

The tedious screening process finally revealed the optimised reaction condition as 8mol% each of Au-phosphite **3** and AgOTf in CH_2Cl_2 at 25 ^{0}C with reaction time 15min that resulted in the desired disaccharide in ~95% yield with the extrusion of non-competitive cyclised product (**5**). Further, to check the importance of alkyne moiety and the strain in the leaving group, different types of glycosyl carbonate donors have been synthesized and screened under optimized [Au]/[Ag]-catalysed glycosylation conditions. The results not only confirmed the importance of alkyne moiety and the conformational restriction in the system but also the superiority of ethynylcyclohexyl carbonate donor (**1**) over others.



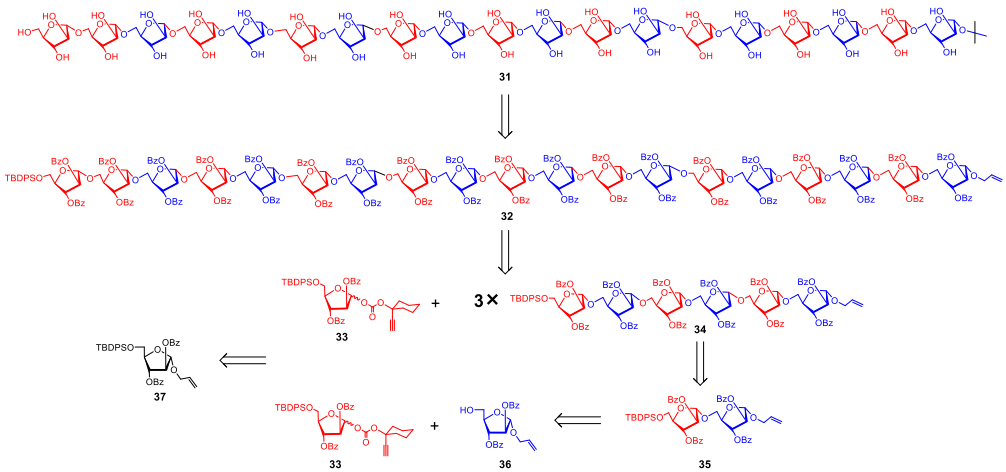
Scheme 2.2: Syntheses of biologically important *O*-, *N*-, *C*- glycosides

The generality of the developed protocol was further explored with various glycosyl carbonate donors (**6**) and acceptors (**7**, **9**, **11**, **13**, **15**, **17**, **19**, **21**) under optimized glycosylation condition. The outstanding protocol was proven excellent even

for the synthesis of tri- and tetrasaccharide synthesis with more than 90% yield. Furthermore, various armed, disarmed and superarmed glucosyl carbonates donors (**6**) were been employed for the synthesis of different *O*-glycosides (**8**, **10**, **12**, **14**), *N*-glycosides (**16**, **18**, **20**, **22**) and *C*-glycosides (**24**, **26**, **28**, **30**) under [Au]/[Ag]-catalysed conditions.

Chapter 3: Expedient Syntheses of Linear as well as Branched Oligosaccharides of M. tuberculosis Cell Wall

Arabinogalactan (AG) and Lipoarabinomannan (LAM) are the two major structural components of *Mycobacterium tuberculosis* cell wall and access to various natural and their mimics of these components are highly demanding due to their immense significance in the overall disease management. Increasing number of TB infections due to multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR- TB) stains continues as a major public health crisis and urged immediate action on finding out new drug or vaccine candidate where the use of synthetic AG and LAM fragments are also of great importance for high-throughput screening.

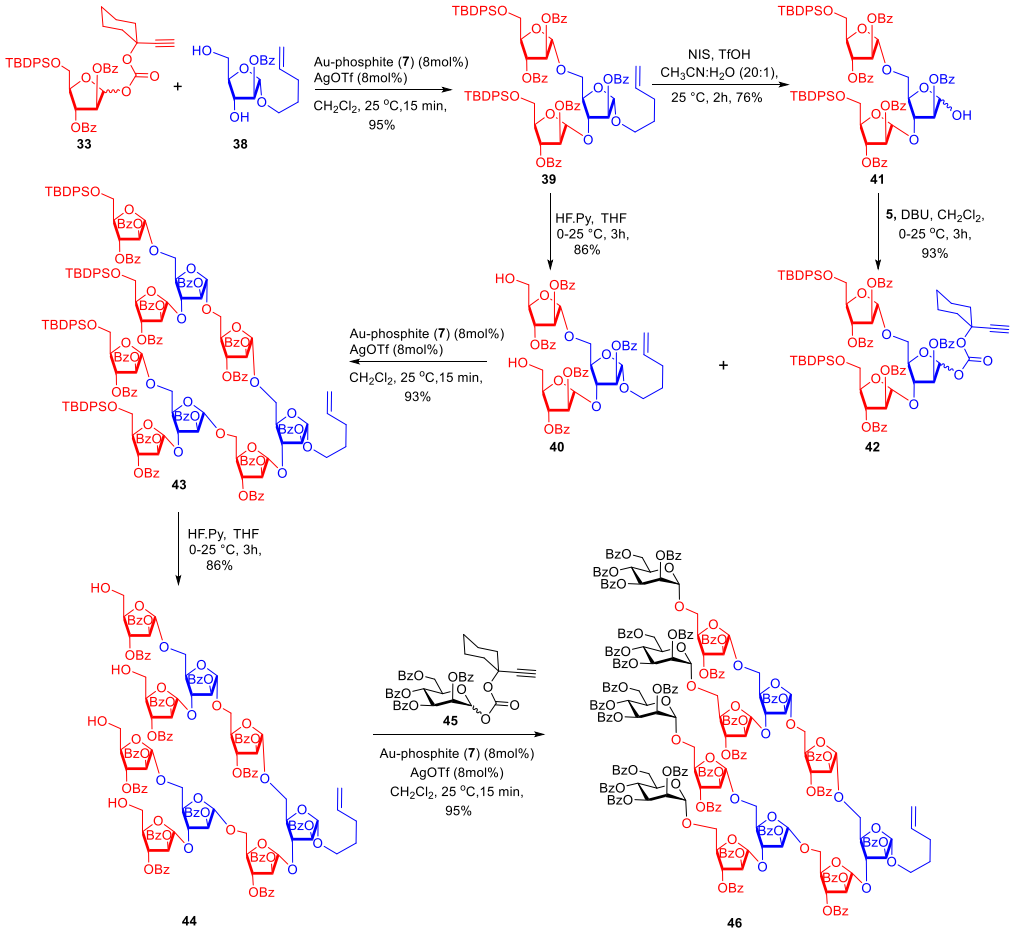


Scheme 3.1: Synthesis of linear nonadecaarabinofuranoside motif

Hence, synthesis of different AG and LAM motifs has received considerable attention. Although successful attempts for different AG and LAM motifs have been made by several groups, the use of less efficient glycosyl donor chemistry resulted in poor glycosylation yields and restricted their accessibility in large scales. In this premise, we envisioned that use of the recently developed [Au]/[Ag]-catalysed glycosylation protocol could be of great significance for the synthesis of linear

nonadecaarabinofuranoside motif of AG fragment and branched tridecasaccharide reminiscent of LAM fragments from *Mycobacterium tuberculosis* cell wall.

A *Split-React-Couple* strategy has been incorporated in both the oligosaccharides syntheses in such a way that both glycosyl donor and acceptor can be easily prepared from the same precursor resulting in a very significant reduction in the total number of steps involved in the synthesis. Our synthetic endeavour of linear nonadecaarabinofuranoside motif (**31**) was started with the preparation of arabinofuranosyl donor (**33**) and acceptor (**36**) from the key arabinofuranosyl building block (**37**) through a number of steps. The disaccharide arabinofuranosyl motif (**35**) was then synthesized from the donor (**33**) and acceptor (**36**) employing [Au]/[Ag]-catalysed glycosylation protocol.



Scheme 3.2: Synthesis of Tridecasaccharide Reminiscent of the Mycobacterial Cell wall

Next, the disaccharide motif (**35**) was *split* into two fractions, *reacted* with respective reagents for conversion into the corresponding disaccharide arabinofuranosyl donor and acceptor and finally *coupled* under standard [Au]/[Ag]-catalysed

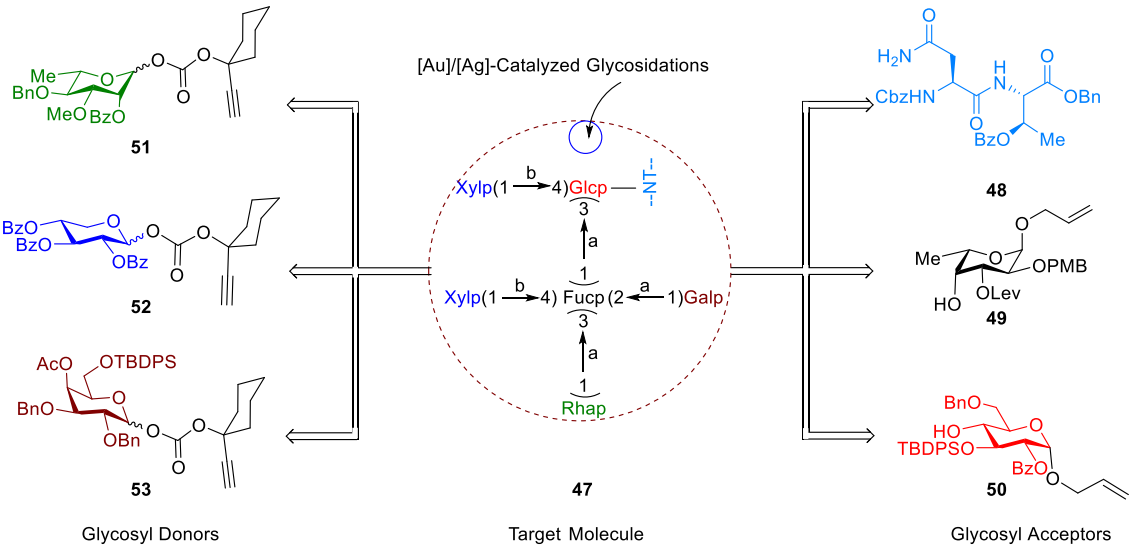
glycosylation conditions to afford the desired hexaarabinofuranosyl motif (**34**). The iterative procedure was repeated until the octadecasaccharide and then added one unit of the glycosyl donor **33** to realize the nonadecaarabinofuranoside (**32**) in fully protected form. Final global deprotection of the (**32**) afforded the target molecule (**31**) over 23 steps in 6.4% overall yield.

Similarly, synthesis of the branched tridecasaccharide arabinomannan motif was initiated with the preparation of arabinofuranosyl donor (**33**), acceptor (**38**) and mannopyranosyl donor (**45**). Arabinofuranosyl donor and acceptor were first subjected to [Au]/[Ag]-catalysed glycosylation to afford the desired trisaccharide (**39**) which was further converted into the nonaarabinofuranoside (**43**) using the *Split-React-Couple* strategy. Final attachment of four mannose residues with nonasaccharide alcohol **44** under [Au]/[Ag]-catalysed conditions led to the formation of the target tridecasacharyl arabinomannan (**46**).

Chapter 4: Synthesis of Hyper-branched *N*-linked Semi-conserved Core Hexasaccharide Motif of Chloroviruses

Chlorella viruses, mostly known as chloroviruses (CV) are present in freshwater throughout the world and infect certain unicellular, eukaryotic, chlorella like green algae. They are from the Phycodnaviridae family and probably share a common ancestor with the poxviruses, iridoviruses, African swine fever virus, and Mimivirus. One of the most important features these chloroviruses possess is the ability to use their own glycosylation machinery to encode most, if not all, of the components involved in manipulating carbohydrates. Furthermore, the presence of chlorovirus ATCV-1 in human oropharyngeal virome and its association with a modest but statistically significant decline in the performance of cognitive assessments in humans as well in mouse models as independently reported by Yolken and Petro placed the chlorovirus in news lime light and people started to call it as ‘stupid virus’. Analysis of the glycan structures of major capsid glycoproteins from various chloroviruses has revealed that all of them possess a highly branched *N*-linked semi-conserved hexasaccharide core motif in common. Some unique features such as: (i) having five different sugar residues in pyranose form; (ii) presence of hyper branched central L-Fucose unit connected with four different sugar residues; (iii) presence of four 1,2-*trans* and two synthetically challenging 1,2-*cis* glycosidic linkages; (iv) existence of glycosidic amide bond

[glycan–NHCOR] at the reducing end of glucose unit instead of commonly observed *N*-acetylglucosamine or *N*-acetylgalactosamine unit; and (v) attachment of asparagine residue from N-T instead of N-X-T sequence, associated with the *N*-linked hexasaccharide provoked us to choose the *N*-linked hexasaccharide (**47**) from chlorovirus ATCV-1 as model synthetic target.



Scheme 4.1: Retrosynthesis of the conserved hyper-branched hexasaccharide motif of chloroviruses

In this premise, three different glycosyl acceptors (**48**, **49**, **50**) and three different glycosyl donors (**51**, **52**, **53**) were first synthesized following reported procedures. Installation of 1,2-*trans* glycosidic linkages were achieved through standard [Au]/[Ag]-catalysed glycosylation conditions. However, installation of challenging 1,2-*cis* glycosidic linkages was not easy. A large number of factors such as solvents, temperature, catalyst loading, counter anions, Au-complexes, catalyst addition times, addition sequences, solvent concentrations and finally acceptor's concentrations were screened with variety of different galactosyl carbonates as donor and glucosyl primary alcohol (**2**) as acceptor in order to get 1,2-*cis* galactopyranoside. For better α-selectivity, a number of protecting group modifications were conducted at *C*-4 and *C*-6 positions of galactose residue and glycosylation reactions were performed under optimized α-selective glycosylation condition (10 mol% each of Au-phosphite and AgOTf, chlorobenzene solvent, 4Å MS powder, 25 ^{o}C and reaction time 1 h) and 100% α-

selectivity was achieved. Similar optimization strategy was adopted for accomplishing the 100% α-selectivity for installation of the L-fucose.

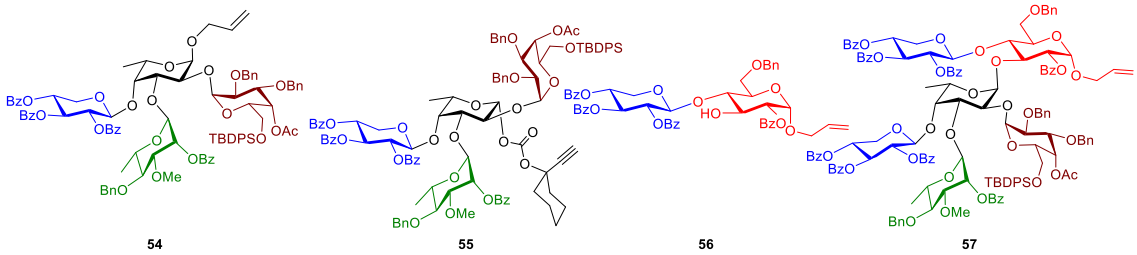


Figure 4.1: Some of the key milestone compounds *en route* to the synthesis of hyper-branched *N*-linked hexasaccharide

A [4+2] coupling strategy was envisioned for the synthesis of the hexasaccharide motif. Hence, the hyper-branched tetrasaccharide motif (**54**) was first synthesized in exclusively stereoselective manner via two different pathways whereas another disaccharide was prepared from xylose carbonate donor and glucose acceptor. However, the coupling between tetrasaccharide carbonate donor (**55**) and disaccharide acceptor (**56**) proceeded with very poor yield. As a result, full characterization of the desired hexasaccharide could not be completed. Preparation of the core hexasaccharide in large scale is currently under progress. Once we have the hexasaccharide (**57**) in sufficient amount, another few steps are to be carried out in order to get the final core hexasaccharide linked with Asn-Thr dipeptide residue at the reducing end (**47**).

*****

Chapter 1

Gold-Catalysed Glycosylation

1.1 – Introduction[1]

Carbohydrates are one of the most abundant and extensively disseminated organic compounds on our planet. These are belonging to some of the first few organic compounds whose structures are well determined. Carbohydrates establish a bridge between organic chemistry, biochemistry and contributed significantly to the development of principles of stereochemistry.

In the prebiotic era, when life started to evolve on earth, carbohydrates played a crucial role to make a direct link between light energy (Sun) and chemical energy through photosynthesis. During the photosynthesis process, carbon dioxide combines with water in presence of sunlight to produce carbohydrates and oxygen (**Fig.1.1**). Carbohydrates are used by plants and some microorganisms as source of chemical energy and storage. Other non-photosynthesizing organisms utilize this chemical energy

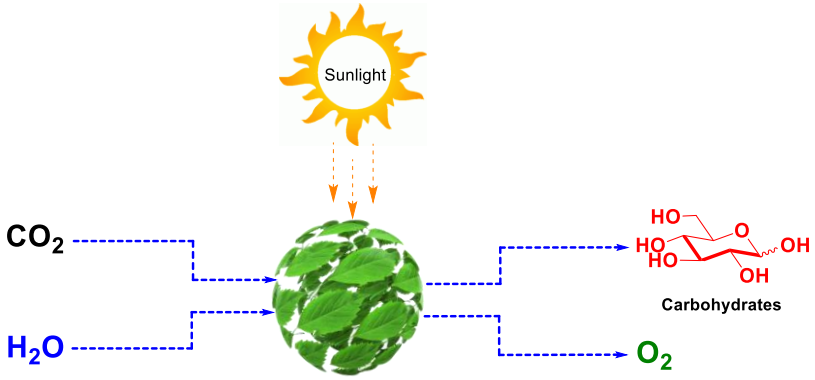


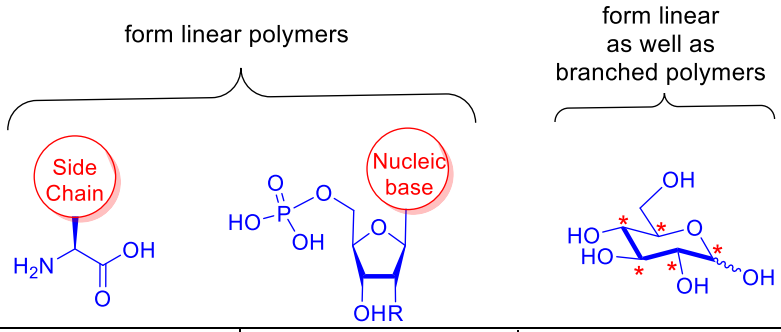
Figure 1.1: **Photosynthesis**

via glycolysis and respiration for their survival and evolution. Apart from this, carbohydrates are also widely utilized as structural materials in arthropods, plants and as a part of cell walls ranging from unicellular to highly complex multicellular organisms.

1.2 – Diversity in Carbohydrates[2]

Carbohydrates in Nature possess a unique kind of diversity, which allows them to form more complex oligomeric and polymeric structures as compared to other biomacromolecules such as proteins, nucleic acids and lipids.[2a,2b] In case of amino acids and nucleic acids, only head to tail polymerization is possible, which confined their polymeric diversity into very limited chemical space. On the other hand, carbohydrates

are not only having more than two ends for oligomerization but also possesses so many variations such as (i) anomeric status, (ii) linkage positions, (iii) ring size, (iv) branching and (v) introduction of site-specific substitutions etc. (**Fig.1.2**).[2c] It is very interesting that in evolution, only four monomeric building blocks have been used for RNA or DNA which carry out genetic information. In a similar fashion, twenty two natural amino acids have been utilized for the entire proteome. But in case of carbohydrates, the glycome database is very huge with multitude of possibilities due to the presence of many sugars, many possibilities for branching and post-translational modifications. It is still to be answered that why nature has chosen such diversity in carbohydrates.



Pentamer	Amino acids	Nucleotides	Carbohydrates
Homooligomeric	1	1	17872
Heterooligomeric	120	120	2144640

Figure 1.2: **Constitutional stereoisomers of Amino acids, Nucleotides & Carbohydrates**

1.3 – Early studies on carbohydrates[1,3]

The first carbohydrate was isolated from honey in the late eighteenth century (1792). Subsequently, within two decades, three other carbohydrates were isolated from different sources (grapes, starch and cellulose) and found that all were identical to the sugar present in the parent honey but was different from sucrose. In 1838, that unknown sugar was named as glucose by Dumans. In 1866, because of its unique nature of rotating the plane polarized light to the right, the German chemist August Kekule changed the name to Dextrose. In 1888, the German chemist Emil Fischer, for the first time, determined the structure of Dextrose based on the observation, arguments and deduction after performing a number of experiments. In 1890, he changed the name of

dextrose back to glucose. The actual configuration of *C*-5 had to wait sixty years before it was determined by X-ray crystallography.[1] In the meantime, Heinz and Heidi proposed that in aqueous solution, cyclic structure of glucose can be present with two different optical rotations (α- and β). In 1926, Haworth definitively demonstrated the size of carbohydrate rings to be primarily six-membered pyranoses and proposed a six-membered hexagon to represent the carbohydrates. He also suggested that, cyclic six membered rings can adopt several conformations. Later, Hassel and Barton demonstrated that the pyranose ring is of non-planar shape. From the conformational study of glucose molecule, Edward observed that the energy difference between the two conformers is about 1.5 $KJmol^{-1}$ in favour of β-isomer which has three times lesser value (3.5 $KJmole^{-1}$) for an equatorial over an axial hydroxyl group which favours the formation of α-isomer. Later, Lemieux named this phenomenon as "anomeric effect" (explained in **1.5.3**).[3]

1.4 – Glycobiology and Glycoconjugates[4]

In 1988, Dwek from Oxford Glycosciences Institute has first introduced the term 'Glycobiology' which can be defined as "study of the structure, biosynthesis, and biology of saccharides (sugar chains or glycans) that are widely distributed in Nature." Glycobiology made a bridge between traditional carbohydrate chemistry and biochemistry for greater understanding of the cellular and molecular biology of glycans.

In nature, glycans are covalently linked to many other types including biological molecules such as proteins, lipids, organic molecules, natural products, other sugar residues, and peptides. These are commonly known as glycoconjugates and are widely distributed on cell surfaces and secreted fluids. Glycoproteins, proteoglycans and glycolipids are the major types of glycoconjugates found in mammalian cells. Glycoconjugates plays crucial role in so many biological processes such as viral and bacterial infection, tumour metastasis, angiogenesis, inflammation, immunological response, cell–cell communication, hormone balance and metabolism in living organisms (**Fig.1.3**). The human blood antigens are one such phenomenon. Based on the types of sugar residues present on the red blood cell surface, four different types of blood groups (A, B, AB and O) have been evolved in human beings.[4a] Medicinal use of glycoconjugates are also well recognized. Fondaparinux (trade name Arixtra®) is a commercially available anti-coagulant. It is a low molecular weight heparin, use for the

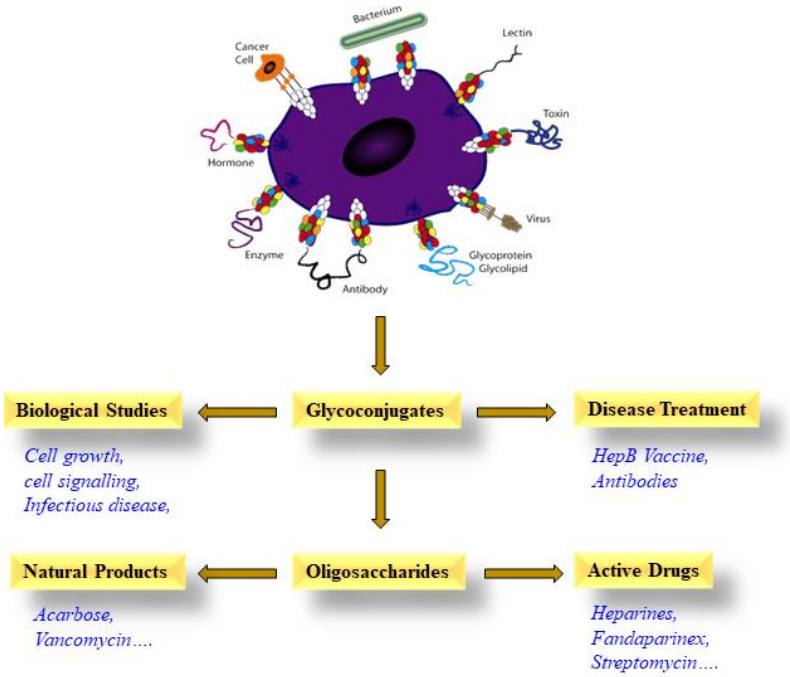


Figure 1.3: **Biological significance of glycoconjugates**

prevention of deep vein thrombosis in patients during surgeries. It is also being used for the treatment of pulmonary embolism.[4b,4c] Many glycopeptide-based vaccines are currently under investigation for many diseases. A recent advancement in this area encompasses the development of a synthetic conjugate vaccine against Haemophilus influenza type b (Hib), the causative agent of pneumonia and meningitis.[4d] Furthermore, glycoconjugates are also routinely used in other areas such as in chromatography, diagnostic kits, sensing, polymer chemistry, etc.

1.5 – Synthesis of glycoconjugates[5-15]

Glycoconjugate structures are mostly very complex and encode specific biological information. Therefore, synthetic methods for the preparation of well-defined scaffolds are necessary to understand the role of natural glycoconjugates in different biological processes. Further, molecular design and synthesis of glycoconjugates via biomimetic approaches are of tremendous practical importance for the development of new polymeric materials possessing unique properties with superior functions. Saccharides are joined together by various types of linkages such as *O*-, *N*-, *C*-, *S*-, *P*- and rarely with *N*-*O*-, *O*-*N*.

Glycoconjugate synthesis is challenging due to the presence of multiple functional groups, conformational forms (pyranose and furanose), configurational (α-

and β- form) and constitutional isomers (epimers) in a simple monomeric unit. In addition, the complexity is further compounded by functionalization on any of the hydroxyl groups (methylation, sulfation, phosphorylation, or acylation). Several physio-chemical factors are involved in the synthesis of glycosides or glycoconjugates. Proper understanding of these factors is highly important for the synthesis of glycoside or glycoconjugates.

1.5.1 – Glycosylation[5]

The term glycosylation can be defined as, "the nucleophilic displacement of the leaving group attached to anomeric carbon of a sugar residue by a nucleophile." Glycosylation reaction occurs between a glycosyl donor which is invariably a sugar residue and a glycosyl acceptor which frequently possesses a lone hydroxyl group. In glycosylation reaction, glycosyl donor is the one which donates the glycosyl moiety and a glycosyl acceptor accepts that glycosyl moiety. The glycosyl acceptor/nucleophile can be a thiol, amine, amide or a carbon nucleophile. The availability of enormous number of glycosyl donors and glycosyl acceptors in Nature envisages a large collection of biologically relevant glycosides or glycoconjugates through glycosylation. All the known glycosylation methods can be broadly classified into two types *viz.* enzymatic glycosylation and chemical glycosylation.

1.5.1.1 – Enzymatic glycosylation[5a,b]

In biological systems, glycosidic bond formation occurs by the action of one of more enzymes. A large number of enzymes are involved for the enzymatic synthesis of saccharides and glycoconjugates. Because of their highly stereospecific and regioselective nature, enzymatic glycosylations provide an attractive alternate to chemical glycosylation for complex saccharides and glycoconjugate synthesis. In conventional chemical synthesis of complex glycoconjugates, regio- and stereochemical control over the glycosidic bond invokes multiple protection and deprotection steps, resulting in diminished yield. Whereas, enzymes will be able form specific glycosidic linkages under mild reaction conditions without any protection or deprotection of functional groups. Enzymes, responsible for oligosaccharide biosynthesis are known as 'Leloir enzymes', after the name of the scientist who discovered their proper mechanism in action. Glycosylsynthases and glycosyltransferases are two major classes of enzymes.

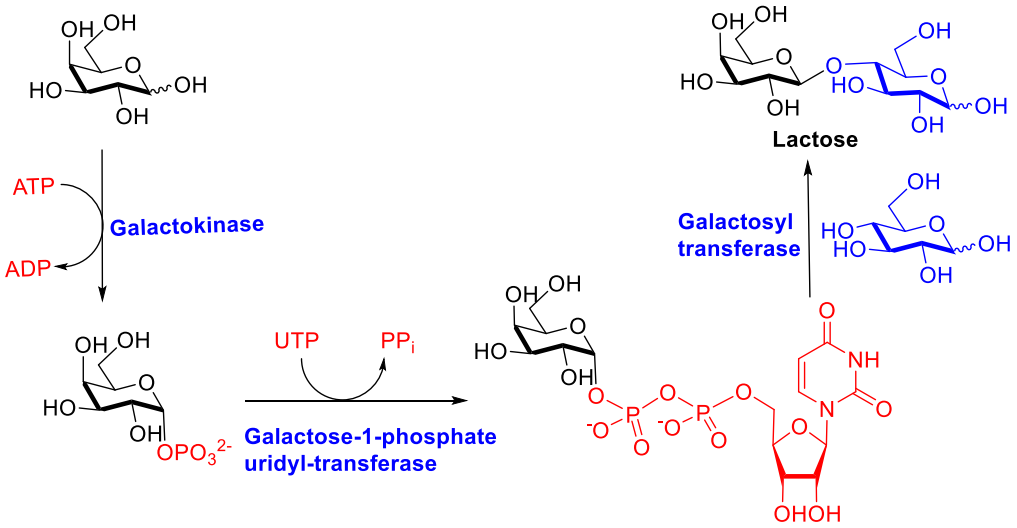


Figure 1.4: **Enzymatic synthesis of oligosaccharides**

On the downside, only a handful of enzymes are available for the synthesis of complex glycans. Another limitation associated with the enzymatic reactions is that enzymes in their natural form are rarely suitable for industrial scale glycoconjugate syntheses.

Glycosyl Donor + Acceptor $\xrightarrow{\text{Enzymes}}$ Glycoconjugates

Enzymes	Glycosyl donor	Advantages	Disadvantages
Leloir glycosyltransferase	Glycosyl necleotide	• High stereo & regioselctivity • High yield • Essential for important sugar sequences	• High cost
Non-Leloir glycosyltransferase	Glycosyl phosphate	• High stereo & regioselctivity • High yield	• Not essential for important sugar sequences
Glycosynthase	Glycosyl fluoride	• High yield	• Low avilability • Poor regioselctivity
Glycosidase	Nitrophenyl glycoside	• Low cost • Easy to perform	• Low yield • Poor regioselctivity

Table 1.1: **Few enzymes in glycosylation**

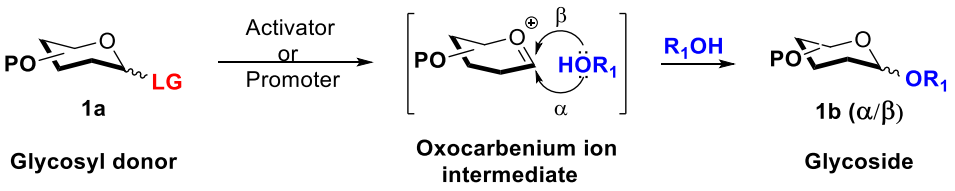
However, the discovery of new biocatalysts with improved catalytic activity, higher stability and compatibility in organic solvents through the genetic engineering of

existing enzymes or genomic and metagenomic approaches or rational design and directed evolution offers great promise. responsible for polysaccharides and complex oligosaccharides. Conversely, glycosidases are a class of enzymes which trim the polysaccharides/oligosaccharides into monosaccharides building blocks.

Leloir-enzymes use nucleoside monophosphates or diphosphates as substrates for the stereo- and regio- selective transfer of respective monosaccharides on to an acceptor sugar (**Figure 1.4**). The transfer of sugar residue from a sugar nucleotide donor to a hydroxyl group of an acceptor is energetically more favored. The union of glycosyl acceptor and the donor-nucleotide takes unique path and as a result, each glycosylation requires a unique glycosyl transferase. Other enzymes, such as glycosynthase, glycosidase and non-Leloir glycosyltransferases are deployed sometimes (**Table 1.1**).

1.5.1.2 – Chemical glycosylation [5c]

Chemical glycosylations are the most suitable ones to circumvent the above delineated limitations associated with the enzymatic glycosylations. In chemical glycosylations, the functional group attached to the anomeric position of a glycosyl donor (leaving group) will be activated by means of an activator or promoter (acidic/basic/neutral

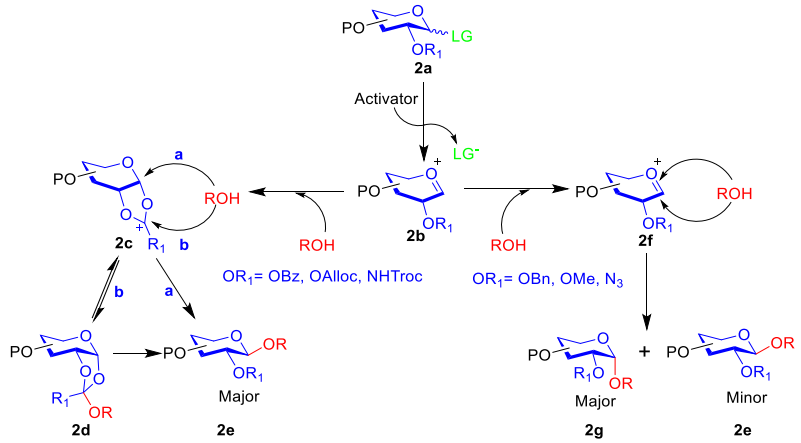


Scheme 1.1: **General glycosylation reaction**

reagent) to generate an oxocarbenium ion intermediate. This short lived and highly energetic oxocarbenium ion intermediate gets stabilized or destabilized depending on the nature of the other protecting groups present on the glycosyl donor residue. Further trapping of the oxocarbenium ion by a nucleophile or glycosyl acceptor results in the formation of a glycoside bond either in axial (α-) or equatorial (β-) fashion (**Scheme 1.1**).

Two major obstacles are associated with the chemical syntheses to obtain complete regio- and stereo- selectivity of the newly formed glycosidic bond. Issues

related to the regioselectivity can be addressed by keeping a lone hydroxyl group for the reaction by inviting the protecting group strategy on the glycosyl acceptor. But the stereospecificity is comparatively much more complex as it is governed by many stereoelectronic considerations. In general, nature of the functional group at *C*-2 position of the glycosyl donor controls the stereochemical outcome either 1,2-*cis* and/or 1,2- *trans* glycoside formation. A carbonyl moiety at *C*-2 position in the form of an



Scheme 1.2: General mechanism for glycosidic bond formation

ester, a carbonate or a carbamate results in the 1,2-*trans* glycoside formation due to the anchimeric assistance which is also known as neighboring group participation to form corresponding more stable acycloxonium ion (**2c**) (**Scheme 1.2**). The generation of (**2c**) intermediate restricts the approach of the incoming nucleophile from one side to form 1,2-*trans* glycoside predominantly. On the other hand, ethers at *C*-2 position in the form of benzyl, methyl, azide, etc. afford a mixture of 1,2- *trans* and 1,2-*cis* glycosides as the acceptor will have equal opportunity to attack the oxocarbenium ion (**2f**) from either axial or equatorial side. The exact ratio of 1,2- *trans* and 1,2-*cis* will be dependent on the stereoelectronic effects. In majority of cases axial glycosides are formed as major products in spite of steric crowding due to the well documented anomeric effect. Many factors including solvent, temperature, conformation, protecting groups, promoter and leaving groups influence the outcome of glycosylation reaction.

1.5.2 – Types of glycosidic linkages[5d,e,f,g]

Two types of glycosidic linkages are possible based on the relative orientation of functional groups connected at the *C*-1 and *C*-2 positions. If both the groups at *C*-1 and *C*-2 position are co-planar to each other then it can be classified as 1,2-*cis* linkage

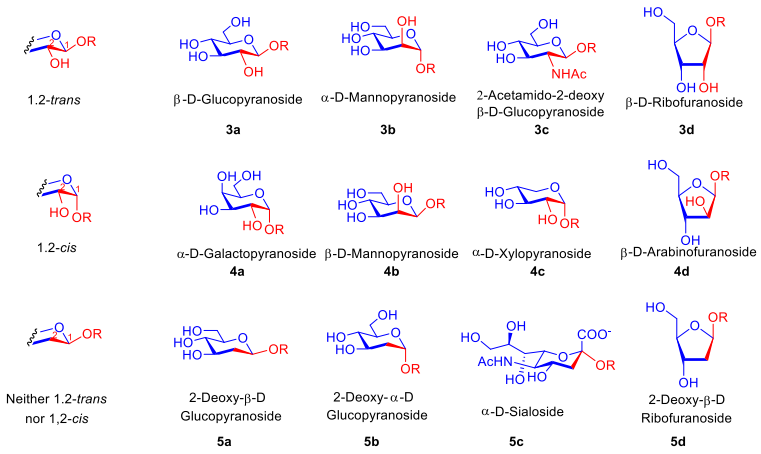


Figure 1.5: Types of 1,2-linkages

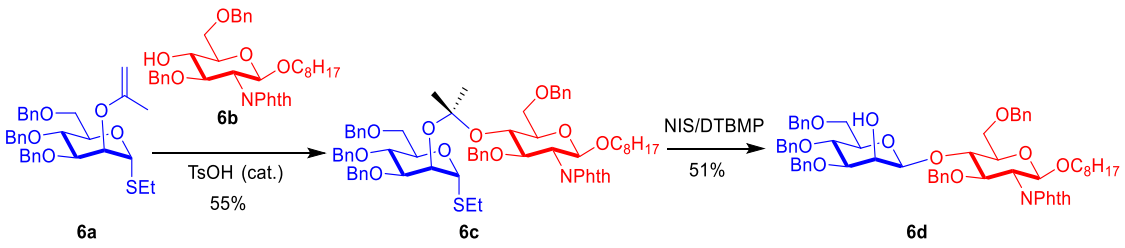
whereas, if both the groups are non-coplanar then it is known as 1,2-*trans* linkage. In the absence any functional group at *C*-2 (e.g. 2-*deoxy* sugars), assignment of 1,2-*cis* and 1,2-*trans* linkages are purely based on the orientation of functional groups at *C*-1 position.

1.5.2.1 – 1,2-*trans* glycosides[5d]

Synthesis of 1,2-*trans* glycosides is relatively less challenging as one can invoke the neighboring group participation strategy in the form of a carbonyl functional group at the *C*-2 position as delineated above in (**Scheme 1.2**).

1.5.2.2 – 1,2-*cis* glycosides[5e-g]

Synthesis of 1,2-*cis* glycosides is more demanding compared to the 1,2-*trans* glycosides. Presence of a non-participation group at the *C*-2 position generally leads to the 1,2-*cis* glycoside as a major product but not the sole product. A number of methods



Scheme 1.3: Synthesis of β- mannosides through Intramolecular Aglycon Delivery

are developed over the last several decades for the stereoselctive 1,2-*cis* glycoside syntheses. In one of the early efforts, Hindsgaul introduced the intramolecular aglycon delivery (IAD) between glycosyl donor and glycosyl acceptor for the synthesis of 1,2-mannopyranosides (**Scheme 1.3**).[5e] Other methods such as installation of a neighboring protecting group at *C*-2 position by Boon *et al.*,[5f] use of remote protecting group at *C*-3 or *C*-4 position by Kim *et al.*,[5g] epimerization at *C*-2 position using oxidation reduction strategy are commonly used for 1,2-*cis* glycoside synthesis by Garegg are some of the pioneering efforts.

1.5.3 – Factors influencing the stereochemical outcome of any glycosylation reaction

1.5.3.1 – Anomeric effect[6a-d]

The unusual preference of sterically or energetically unfavored axial position over the equatorial position at the anomeric center of any saccharide has been termed as 'anomeric effect'. This phenomenon was first observed by Edward[6a] and later named as 'anomeric effect' by Lemieux.[6b] Along with the nature of anomeric group, the substituent on *C*-2 position also strongly influences the anomeric effect.

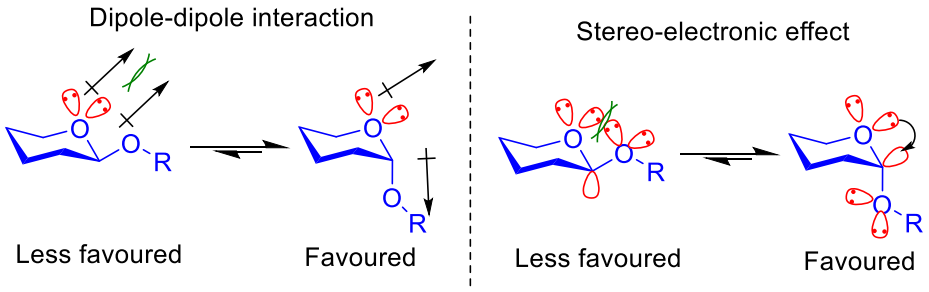


Figure 1.6: Anomeric effect

The anomeric effect can be explained based on two main factors namely, (i) the dipole-dipole interaction and (ii) the stereoelectronic effect. Anomeric configuration where two dipoles, one from non-bonding electron pairs on the ring oxygen and the other from polarised bond between the anomeric carbon and exocyclic heteroatom are parallel (β-conformation) is less stable as compare to the perpendicular one (α-conformation). In the first case the dipoles work in the same direction that causes more repulsion than the second one where the dipoles partially neutralize each other. According to the stereoelectronic interpretation, when the substituent at anomeric

position is in α-conformation, then, the non-bonding electrons of the ring oxygen atom are *syn*-periplanar to the *anti*-bonding orbital of the anomeric substituent. As a result, the two orbitals can overlap, allowing an n→σ* sp interaction, which stabilizes the α-anomer over β-anomer. Anomeric effect also gets affected by solvent polarity. In general, solvent polarity and extent of anomeric effect are inversely proportional. Another interesting phenomenon, widely known as 'reverse anomeric effect' is just opposite to the normal anomeric effect. This effect is mostly observed when the anomeric substituent is an electropositive group. In this case the population of β-anomer (**7b**) dramatically increases over α-anomer (**7a**).[6c-d]

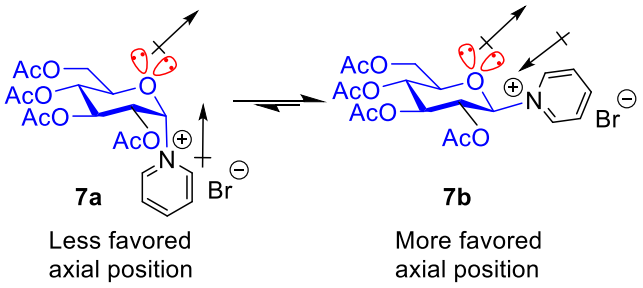


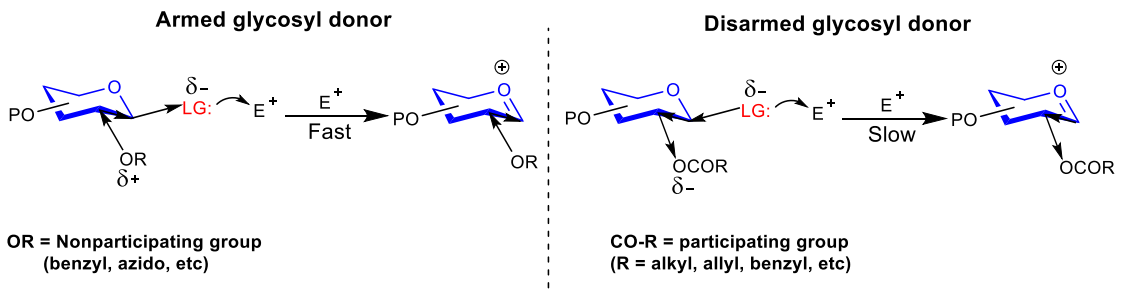
Figure 1.7: Reverse anomeric effect

1.5.3.2 – Reactivity of glycosyl donors

Reactivity of any glycosyl donors also depends on the various factors, such as:

1.5.3.2.1 – Armed and disarmed nature[7a-f]

The reactivity of a glycosyl donor mostly depends on the choice of the protecting groups at the *C*-2 position of the donor. Glycosyl donors have been categorized into two main groups: armed donors having an ether group on *C*-2, and disarmed donors with



Scheme 1.4: Armed and disarmed glycosyl donor

esters, amides on *C*-2. A general rationalization for armed and disarmed effect was first recognized in *n*-pentenyl glycosides by Bert Fraser-Reid.[7a-c] Later, this concept has been extended to a variety of glycosyl donors.[7d-f] Although it is not easy to choose the best glycosyl donor for a particular glycosylation reaction, however, some factors effecting the glycosyl donor's reactivity shall be taken into account at the designing stage. Generally armed donors are more reactive than disarmed donors as the positively charged oxocarbenium ion will get destabilized by the presence of electron withdrawing groups (e.g esters) whereas electron donating groups (i.e. ethers) the *C*-2 position stabilize (**Scheme 1.4**).

1.5.3.2.2 –Protecting groups at remote positions[5d]

Though less significant, the outcome of the glycosylation is sometimes dependent on the protecting groups at remote positions other than *C*-2 as well. It has been documented that an ester or an ether substituent at C-6 position can significantly control the stereochemical outcome of a glycosylation reaction. Although there is lack of concrete experimental proof for to support it, still preferential formation of α-glucosides due to the long-range 6-*O*-ester or carbonate group assistance cannot be ruled over. A strong electron-withdrawing or sterically bulky substituents at C-6 position is beneficial for 1,2-*cis* glucoside formation. It may be because of shielding the equatorial face of the anomeric center either by sterics or stereoelectronics favoring the acceptor approach from axial face. Protecting groups at the other positions of sugar ring also influence the selectivity. For example, a strong remote participation effect from *C*-4 position for D-galacto series and *C*-3 position for L-fucose, L-rhamnose, D-mannose and D-glucose series are also observed.

1.5.3.2.3 – Leaving group[2a,5c, 8a-c]

The glycosylation reactions mostly proceed *via* unimolecular S_N1 mechanism. So, the stereochemical outcome rarely depends on the orientation of the leaving group at the anomeric centre but rarely through a bimolecular S_N2 mechanism with the inversion of the anomeric configuration. The former mechanism is postulated for the glycosyl bromide donors with Ag_2O[2a] and imidates donors with BF_3•Et_2O at low temperatures.[8a] Highly reactive β-glucosyl halides[8b] and *in situ* generated anomeric triflates by Crich are well known examples for the bimolecular S_N2 mechanism.[8c]

1.5.3.3 – Reactivity of Glycosyl acceptor[9a-d]

The stereochemical outcome of any glycosylation depends not only on the glycosyl donor but also on glycosyl acceptor as well. The least reactive nucleophiles give more stereoselectivity and *vice versa*.[9a] In case of a sugar or aliphatic alcohol, the less reactive tertiary alcohol provides more 1,2-*cis* selectivity than the secondary one, which in turn is more selective for 1,2-*cis* selectivity than the primary alcohol. Similar trend has also been observed for amino acid acceptors as well.[9b]

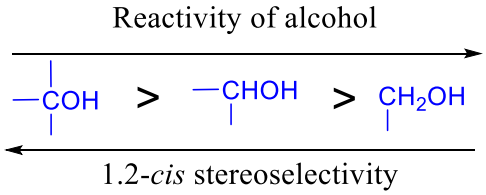


Figure 1.8: Reactivity and selectivity order of alcohol

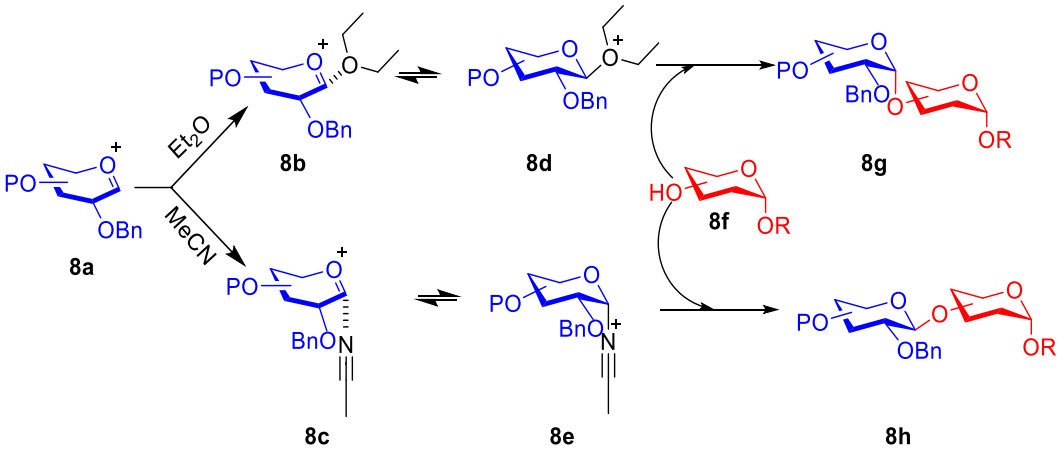
The reactivity of glycosyl acceptor also gets affected by the spatial orientation of the hydroxyl groups. Generally, *equatorial* hydroxyl groups are more reactive as compared to the *axia*l one. In an aldo-hexopyanoside if all the hydroxyl groups at *C*-2, *C*-3, *C*-4 and *C*-6 are positioned in an equatorial orientation, then, the general order of reactivity for glycosidic bond formation is: 6-OH >> 3-OH >>2-OH >>4-OH.

The presence of electron-withdrawing groups and bulky substituents also decrease the reactivity of an acceptor. Whenever any electron withdrawing groups (i.e.-OAc, -OBz) are present in an acceptor specially in sugar aglycon, it generally decreases the reactivity of the alcohol resulting in an overall increase in the 1,2-*cis* selectivity and vice-versa. The presence of trityl-, silyl- protecting groups can also decrease the 1,2-*cis* selectivity due to the increased reactivity of the acceptor.[9c,d]

1.5.3.4 – Reaction conditions (solvents, promoters and temperature)[10a-f]

1.5.3.4.1 – Solvent effect[10a-b]

Influence of reaction solvents on the stereochemical outcome of a glycosylation reaction has been extensively studied. In general, polar solvents such as acetonitrile, DMF etc. increase the ratio of 1,2-*trans* glycoside due to the charge separation between *O*-5 and β-*O*-1. But if the desired product is 1,2-*cis* glycoside, then non-polar solvents like DCM, 1,2-dichloroethane or toluene would be ideal. A large number of experimen-



Scheme 1.5: Solvent effects on glycosylation

tal results demonstrated that ethereal solvents increase the α-glycoside, whereas nitrile solvents drive the glycosylation towards formation of β-glycoside. If the glycosylation reaction proceeds through unimolecular S_N1 pathway, then, ethereal solvents preferentially result in equatorial intermediate (**8d**) thereby affording the β-glycoside (**8g**) stereoselectively. On the other hand, if the reaction solvent is acetonitrile, axially oriented nitrilium cation intermediate (**8e**) forms exclusively leading to the formation of β-glycoside product (**8h**) (**Scheme 1.5**).

1.5.3.4.2 – Temperature and pressure[10c-d]

In general, glycosylation at low temperature favour the β-glycoside formation through kinetic control[10c] though rare exceptions exist.[10d] Contrary to this, due to the anomeric effect, higher temperatures favour α-glycoside is formed preferentially due to thermodynamic control. It has also been noted that when high pressure was applied to a glycosylation reaction with non-participating glycosyl donor, the yield has significantly increased with negligible change in selectivity.

1.5.3.4.3 – Promoters[10e-f]

For an ideal glycosylation reaction, there should be a delicate balance between the reactivity and stereoselectivity. It has been found that faster the glycosylation reaction, lower the stereoselectivity and vice versa.[10e] Milder activating conditions are usually beneficial for 1,2-*cis* glycosylation. For example, thioglycosides often give better selectivity when triggered through a mild agent, such as iodonium dicollidine

perchlorate (IDCP) or molecular bromine.[10f] Similarly, best outcome for the glycosyl halides donor was found when it is activated with halide-ion promoter.

1.5.4 – A treatise on glycosyl donors[11-16]

Considering all the factors which could influence the stereochemical outcome of a glycosylation reaction; starting from Fisher's first glycosylation[11a] of an aldose or ketose with methanol in presence of an acid catalyst, to date a large number of glycosylation methods have been developed in the last 100 years. Currently a number of glycosylation methods are available for the synthesis of glycoconjugates. However, it is difficult to choose the best one for a particular glycoconjugate synthesis. In this regard, Paulsen's famous quote is most justified: "Each oligosaccharide synthesis remains an independent problem whose resolution requires considerable systemic research and a good deal of know-how. There are no universal reaction conditions for oligosaccharide synthesis."

1.5.4.1 – Koenigs-Knorr method[11b-d]

The oldest and still the most widely used method for the synthesis of 1,2-*trans* glycosides in a highly stereospecific manner. Koenigs-Knorr method used glycosyl halide (chloride/bromide) as a glycosyl donor and insoluble silver salts, Ag_2O and Ag_2CO_3 as promoters.[11b] Later, Helferich-Weiss modified this method by using soluble heavy metals salts ($HgBr_2$, HgCN, and HgO). Another modification of this method was carried out by Hanessian-Banoub, using less toxic and less hazardous AgOTf catalyst. Sometimes, use of tetramethyl urea as a co-catalyst is necessary to increase the yield of glycosylated products. The presence of participating groups at *C*-2 position in glycosyl halide donor normally leads to 1,2-*trans* glycosides. Very unreactive glycosyl fluoride (Mukaiyama, 1981) and Highly reactive glycosyl iodide (J. Gervay, 1998) donors have also been identified and utilized for the glycoconjugate synthesis.[11c-d] Nevertheless, the Koenigs-Knorr method suffers from two main disadvantages: (i) the highly labile nature of glycosyl bromides, mostly used for selective glycosylation. (ii) Use of toxic and heavy metal salts in equimolar amount.

1.5.4.2 – Glycosyl trichloroacetimidate[12]

Sinaÿ and coworkers first time used the imidate glycosyl donor for the glycoside synthesis. Schmidt extended this methodology incorporating trichloroacetimidate group

at anomeric position and nurtured it as an excellent glycosyl donor as compared to many other donors. The trichloroacetimidate donor can be prepared from hemiacetals using trichloroacetonitrile in presence of a base (DBU, K_2CO_3 or NaH). Further activation of the donor using catalytic amount of Lewis acids (BF_3•Et_2O or TMSOTf) or Brønsted acid (TfOH) leads to the glycoside. Glycosyl trichloroacetimidate method provides good yield in small as well as large scales. In general, trichloroacetimidate donors are quite stable than respective glycosyl bromides and some of the donors can be stored at -20 ^{0}C for months. Although trichloroacetimidate method is the most utilized method till date, few drawbacks are of great concerns. For example, glycosylation should be carried out at low temperature when ether protecting groups are present in order to avoid unwanted trichloroacetamide rearrangement product or decomposition of the starting material.

1.5.4.3 – Thio glycosides[13]

In 1980, Lonn and co-worker introduced thioglycosides as glycosyl donors. Since that time, thioglycosides donors have been proven as the donor of choice for oligosaccharides syntheses. Thioglycosides donors are easily prepared from thiols and per-acetylated sugars in the presence of Lewis acids (BF_3•Et_2O, TMSOTf, and $SnCl_4$). It can also be prepared from glycosyl halides/trichloroacetimidates donors using thiols as acceptors. A wide range of activators such as MeOTf, DMTST, IDCP, NIS-TfOH or NIS-AgOTf etc. have been explored to tune the reactivity of thioglycosyl donors. The major advantage of thioglycoside donors is that they can tolerate diverse range of chemical modifications and are inert under several glycosylation conditions. But the use of thioglycoside donors has been limited because of their unpleasant odor and deterministic effect on human health.

1.5.4.4– *n*-Pentenyl glycosides[14]

Bert Fraser-Reid and co-workers introduced the *n*-pentenyl glycosides as glycosyl donors in late 1980s. The *n*-pentenyl glycosyl donor gets activated by an electrophilic addition of the iodinium/bromonium ion to the double bond followed by the removal of a five membered cyclized tetrahydrofurfuryl iodide to afford an oxocarbenium ion which can be further attacked by the acceptor. Commonly used activators for *n*-pentenyl glycosyl donors are NBS, NIS, I_2, IDCP, NIS/TfOH or NIS/$Yb(OTf)_3$ etc. Later, *n*-pentenyl 1,2-*O*-orthoesters were also developed as glycosyl donors and

successfully applied for the synthesis of various oligosaccharides. Excess use of activator (2-3 eq. of NIS), cost of the 4-penten-1-ol, and purification are the major disadvantages of this glycosylation method.

1.5.4.5 – 1,2-anhydro sugars[15]

Lemieux and co-workers first time used 1,2-anhydro sugars as glycosyl donors for the chemical synthesis of sucrose. But considerable credit shall go to Danishefsky as well for the extensive work on the application of 1,2-anhydro sugars for complex glycoconjugate syntheses. Danishefsky and co-workers have developed an effective method to prepare 1,2-anhydro sugars from glycals using dimethyldioxirane (DMDO) as an oxidant, followed by activation with $ZnCl_2$ to get the 1,2-*trans* glycosides stereoselectively.

1.5.4.6 –1,2-Orthoesters[16]

Various types of 1,2-orthoesters were prepared and their application for the stereoselective 1,2-*trans* glycoside syntheses has been systematically studied by Kochetkov and co-workers. In 1964, for the first time, Kochetkov reported a preparative method for the methyl 1,2-*O*-orthoester and utilized it as a glycosyl donor. A number of different 1,2-orthoesters such as ethyl, isopropyl, *tert*-butyl, mercapto and cyano 1,2-orthoesters were studied for their leaving ability to be a suitable glycosyl donor. The alkyl 1,2-orthoacetate donors get activated in presence of catalytic amounts of $HgBr_2$ and pTsOH, followed by the nucleophilic attack by the alcohol furnishing acetylated 1,2-*trans* glycoside or isomeric orthoesters depending on the reaction conditions. Use of polar solvents (nitromethane, acetonitrile) and large amounts of catalyst favoured direct 1,2-*trans* glycosides formation, whereas less polar solvent (dichloroethane) and less catalyst loading favoured transorthoesterification. Later, Fraser-Reid and co-workers introduced the *n*-pentenyl 1,2-orthoester donor using NIS/$Yb(OTf)_3$ as a promoter and implemented for oligosaccharide syntheses. Other types of orthoesters such as arabinofuranose 1,2,5-orthoesters and mannopyranose 1,2,6-orthoesters have also been developed as glycosyl donors but with very limited utility. Recently, Sureshkumar and Hotha extended the orthoester chemistry using their gold-catalysis as described in **Section 1.5.5.5**.

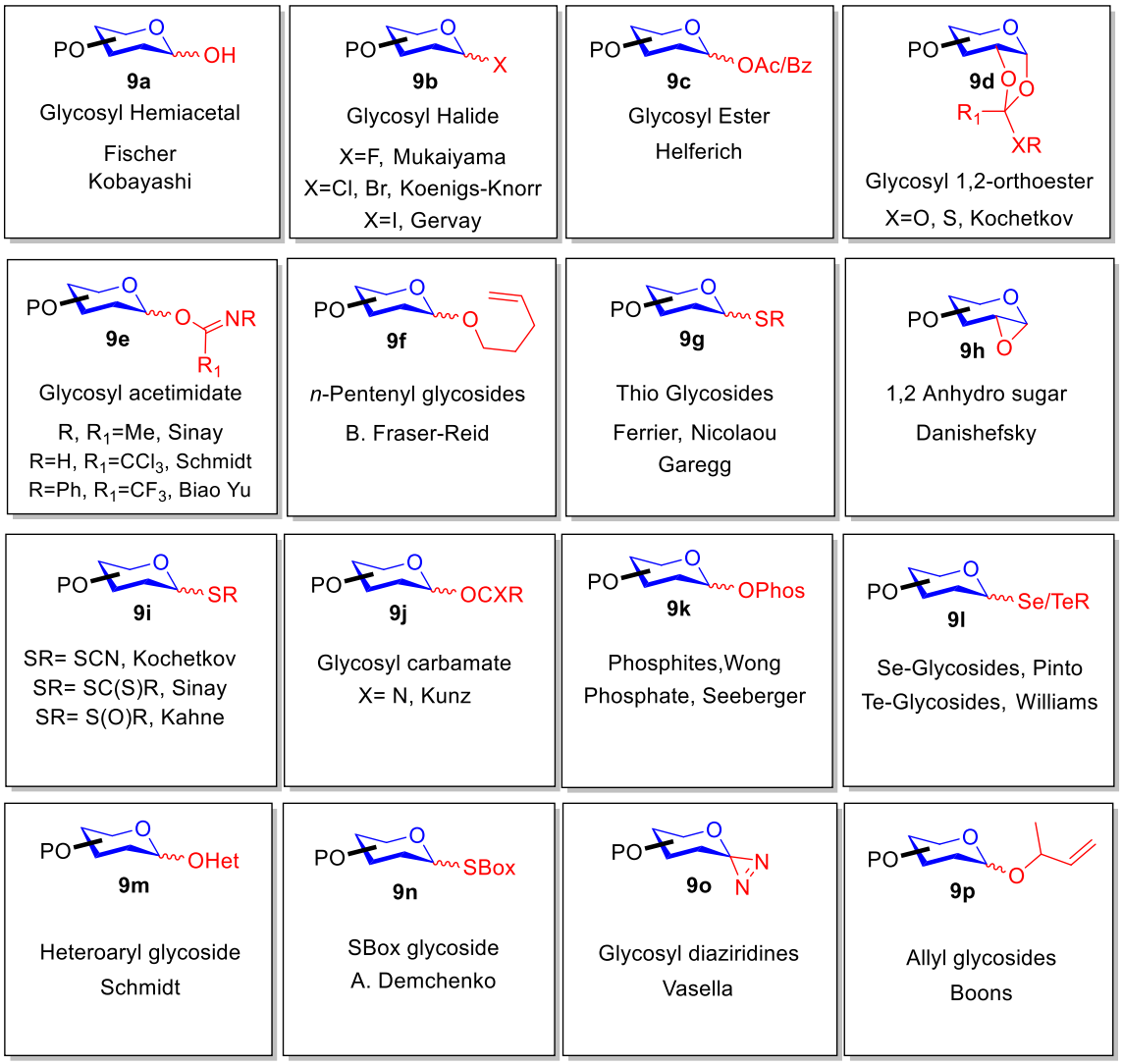


Figure 1.9: Account of glycosyl donors

1.5.4.7 – Other glycosyl donors[17-18]

Time to time there are several other glycosyl donors have been developed and the count is still on. Unfortunately, very few of these found wide spread utility for complex glycoconjugate syntheses.

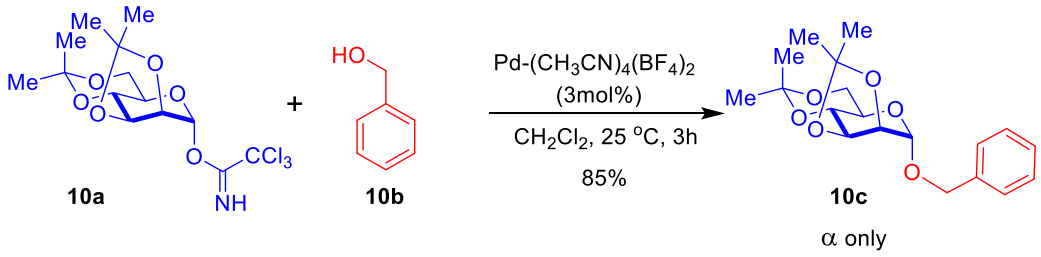
1.5.5 – Transition metals catalysis in glycosylation[19-22]

Transition metals catalysis in glycosylation reaction is comparatively a new area in carbohydrate chemistry, which has gained much popularity in the last two decades. In general, most of the conventional glycosylation protocols require stoichiometric amount of activators to fully activate the glycosyl donors, resulting in production of excess

waste. Furthermore, requirement of strictly anhydrous and very low temperature condition is very common for these air and moisture sensitive promoters. Sometimes, presence of acid labile group either in glycosyl donors or acceptor makes the situation much more complicated. On the other hand, continuous development in automated solid phase carbohydrate synthesis, developed by Seeberger or fluorous-based carbohydrate microarrays developed by Pohl severely demands the use of activators in catalytic amount under less anhydrous and mild reaction conditions. The use of transition metal catalysts not only permitted the glycosylation to be performed under ambient reaction conditions, but also increased the synthetic efficiency through minimization of side products. A brief summary on the application of few transition metals as an activator in glycosylation reactions discussed below.

1.5.5.1 – Palladium (Pd) catalysis[19a-g]

In 2008, Nguyen *et al*. reported the activation of glycosyl trichloroacetimidate donor (**10a**) using cationic Pd-$(CH_3CN)_4(BF_4)_2$ catalyst and demonstrated the synthesis of exclusive α-D-mannopyranoside (**10c**) without a participating group at the *C*-2 position on the donor by reacting with benzyl alcohol (**10b**) as an acceptor (**Scheme1.6**).[19b-c] Later, the same group showed the use of cationic Pd-$(PhCN)_2(OTf)_2$ catalyst instead of Pd-$(CH_3CN)_4(BF_4)_2$ catalyst to improve the β-selectivity significantly for galactosyl trichloroacitamidate donor.[19d] Application of Pd-catalysis has also been explored both for Ferrier-type and non-Ferrier-type glycosylations. In Ferrier-type glycosylation, 1,2-



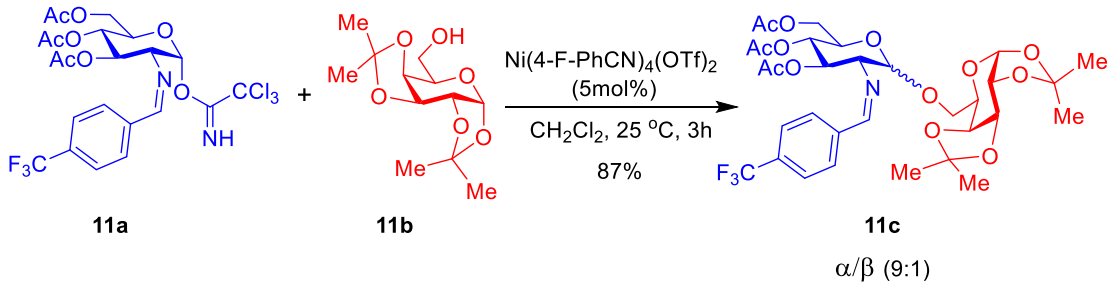
Scheme 1.6: Glycosylation with cationic Pd-catalyst

unsaturated glycals are subjected to the S_N2' addition by Pd-catalyst to generate a Pd-π-allyl metal intermediate followed by the nucleophilic addition to afford glycosides. An important example in this regard was Pd-catalysed *O*-glycosylation protocol of glycal donors by Lee[19e] whereas, non-Ferrier-type glycosylations 2,3-unsaturated pyranone

donors containing leaving group at *C*-1 position act as synthons to access Pd-π-allyl metal complexes. Doherty and co-workers have explored the synthetic utility of such reactions for complex glycoconjugate syntheses extensively.[19f] The Pd-catalysed Ferrier-type reaction is not only explored for selective *O*-glycosylation but also for *C*-glycosylation. Rajan Babu *et al.* reported a *C*-*C* bond formation at anomeric position using Pd(0) catalyst.[19g]

1.5.5.2 – Nickel (Ni) catalysis[20]

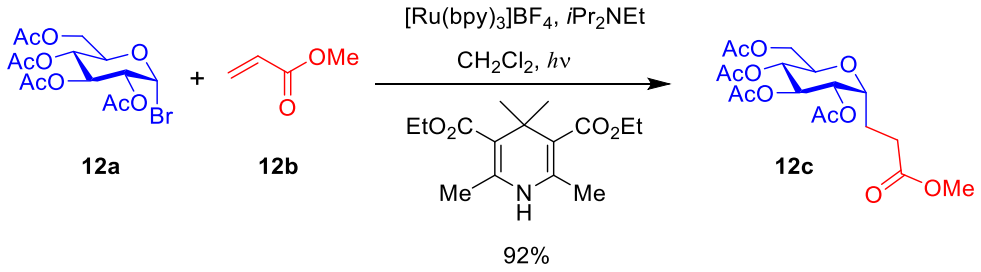
The utility of Ni(II) catalyst in glycosylation was investigated by Nguyen *et al*. in 2009. Nguyen group reported the use of Ni(II) catalyst for the selective formation of the 1,2-*cis*-2-amino glycosides from glycosyl donors (**11a**) having nonparticipating groups at *C*-2 position (**Scheme1.7**).[20a] The developed protocol has also been utilised for oligosaccharide syntheses containing 1,2-*cis* 2-*deoxy*-2-amino linkages.[20b] In addition, Fu *et al*. has reported an effective coupling of various α-bromo glycosyl donors with alkyl zinc reagents using ^{i}Pr-PyBox/Ni(II) complex for stereoselective formation α- or β-glycoside based on the nature of glycosyl donors.[20c] Subsequently, Gagne′ group extended the application of the developed protocol for *C*-aryl glycosides.[20d]



Scheme 1.7: Ni-catalysed 1,2-*cis*-2-amino glycosylation

1.5.5.3 – Ruthenium (Ru), Rhodium (Rh) and Rhenium (Re) catalysis[21]

In 2010, Gagne′ reported the coupling of glycosyl halides to electron-deficient alkenes in presence of $[Ru^{II}(bpy)_3](BF_4)_2$ photo-redox catalytic system for the preparation of fully saturated α-*C*-alkyl glycosides (**Scheme1.8**).[21a] The maximum yield (92%) of *C*-glycoside (**12c**) was obtained at high concentration of glycosyl bromide donor (**12a**) in CH_2Cl_2 as solvent and in presence of methyl acrylate (**12b**). In parallel, Ernst and co-workers mentioned the use of Rhodium(III)-triphos catalyst to prepare protected glucos-

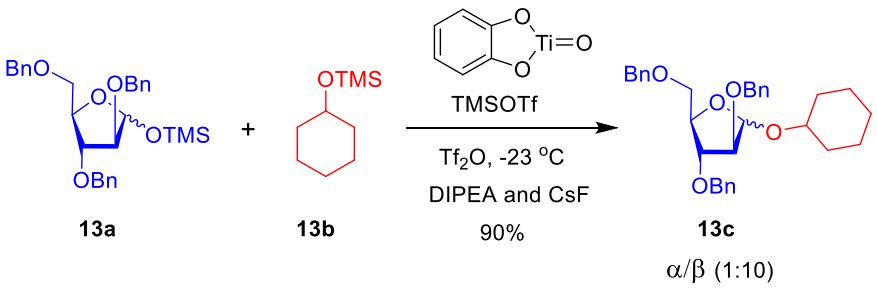


Scheme 1.8: Ru-catalysed *C*-glycoside preparation

ide derivatives with various acceptors.[21b] Major drawback of this protocol was the limited donor scopes (i.e. highly reactive donors only). In 2004, Toste *et al.* published a report on glycosylation of glycal donors with variety of glycosyl acceptors activated by a Re(V)-oxo complex, $ReOCl_3(Sme_2)(Ph_3PO)$ as a catalyst with further application for iterative α-2-*deoxy* oligosaccharide.[21c]

1.5.5.4 – Titanium(Ti), Copper (Cu) and Zinc (Zn) catalysis[22]

In 1991, Mukaiyama *et al.* reported a unique glycosylation strategy where 1-hydroxy sugar donors and alcohol or trimethylsilylated nucleophiles were coupled using catalytic amount of Titanium(IV)oxides to construct stereoselective glycosidic bonds at anomeric position.[22a] Later, Kobayashi and Mukaiyama converted the glycosylation protocol to a catalytic one by using trimethylsilyl sugar (**13a**) and the trimethylsilyl ether (**13b**) to generate the corresponding *O*-glycoside (**13c**) (**Scheme1.7**).[22b] Subsequently, Mahrwald and co-workers found that fully unprotected carbohydrates also could be activated with 10 mol% of $Ti(O^tBu)_4$ and 4 mol% of mandelic acid to prepare various glycosides.[22c]



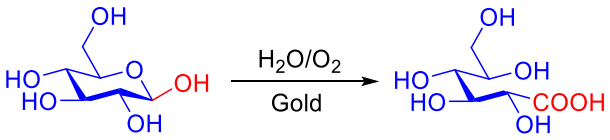
Scheme 1.9: Ti-catalysed synthesis of 1,2-*cis*-arabinofuranoside

The use of Cu and Zn catalysts in glycosylation reaction has also been explored by several groups. The major advantages associated with the use of Cu and Zn catalyst is their low cost and easy availability as compare to the other transition metal catalysts

such as Au, Ag, Pd, Ru, Rh etc. In most of the cases, $Cu(OTf)_2$ and $Zn(OTf)_2$ catalysts were used as a Lewis acid for glycosylations. In 2013, Miller *et al.* published a report on glycosylation of partially protected carbohydrates using chiral Cu(II)-complex as a catalyst for the stereoselective glycosidic bond formation.[22d] Further applications of Cu(II)-complexes for stereoselective synthesis of α- or β-glycosides of N-acetylglucosamine has been proven by various groups.[22e-f]

1.5.5.5 – Gold Catalysis in glycosylation[23-25]

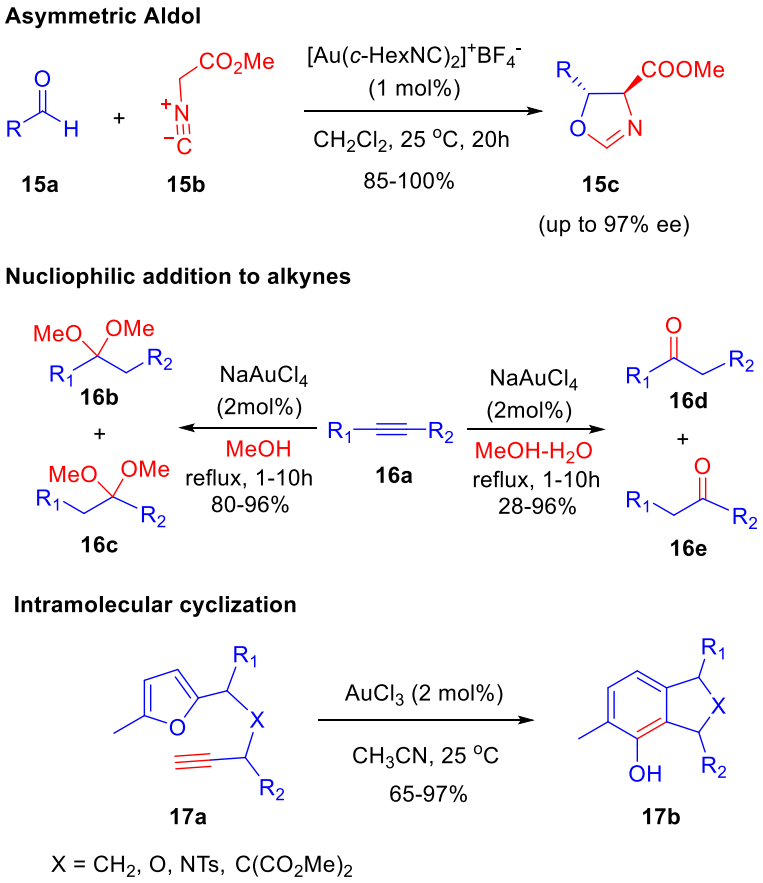
Gold, a symbol of 'power and prosperity' is an element that has captivated mankind for millennia. It has played a key role in the evolution of many civilizations, influencing economics, politics, arts, religion, and technology. Although, in early days, due to its complete chemical inertness in the bulk form, the catalytic properties of gold have been a source of debate. But over the last decade, the interest in gold catalysis has increased phenomenally due to its some unique properties regarding efficiency, selectivity, robustness, and versatility. While Gold can exist in various oxidation states ranging from -1 to +5; the most prevalent are Au(0), Au(I), and Au(III) species.[23a] In 1973 Bond *et al.* reported the use of supported gold as a heterogeneous catalyst for the hydrogenation of olefins.[23b] After a decade, Haruta and Hutchings simultaneously and



14a **14b**

Scheme 1.10: Oxidation of glucose by gold catalysis

independently reported the low-temperature oxidation of CO and the hydrochlorination of ethyne to vinyl chloride utilizing extraordinary catalytic properties of gold.[23c-d] Later, Michele Rossi *et al.* published a report on the position-selective oxidation of different alcohols using supported gold as a heterogeneous catalyst and implemented the oxidation strategy to the carbohydrates, referring the selective oxidation of glucose (**14a**) into gluconate (**14b**) with molecular oxygen (**Scheme 1.10**).[23e] In 1986, Ito, Hayashi and coworkers published a report on the asymmetric addition of an isocyanate (**15b**) onto aldehyde (**15a**) to produce oxazolines (**15c**) in presence of chiral ferrocenyl diphospine gold(I) complex **(Scheme 1.11**).[23f]



Scheme 1.11: Homogeneous gold-catalysed reactions

In 1991, a major breakthrough in the field of homogeneous gold catalysis was made when Fukuda and Utimoto demonstrated the gold(III) salt mediated nucleophilic addition of alcohol and water onto alkyne to convert into ketals (**16b**, **16c**) and ketones (**16d**, **16e**) respectively **(Scheme 1.11**).[23g] A few years later in 1998, Teles *et al.* reported that a phosphine, phosphite or arsine ligand bearing cationic gold(I) complexes could be better choice for nucleophilic addition on alkynes with turnover numbers up to 10^5.[23h] The intramolecular addition of oxygen nucleophiles to alkynes (**17a**) and the synthesis of fused bicyclic phenol compounds (**17b**) through cycloisomerization of furan-ynes in presence of catalytic $AuCl_3$ is a major discovery made in 2000 by Hashmi and co-workers (**Scheme 1.11**).[23i] Later in 2002, Krause and co-workers firstly demonstrated the application of gold catalysis in the total synthesis of citreoviral.[23j]

Application of homogeneous gold catalysis in glycosylation reactions were completely unknown, until the first report by Hotha *et al.* in 2006; in which they have demonstrated the utility of catalytic amount of gold(III) salt for a Ferrier-type glycosylation of 3-*O*- propargyl glycals (**18a**).[24b] Shortly thereafter they reported that

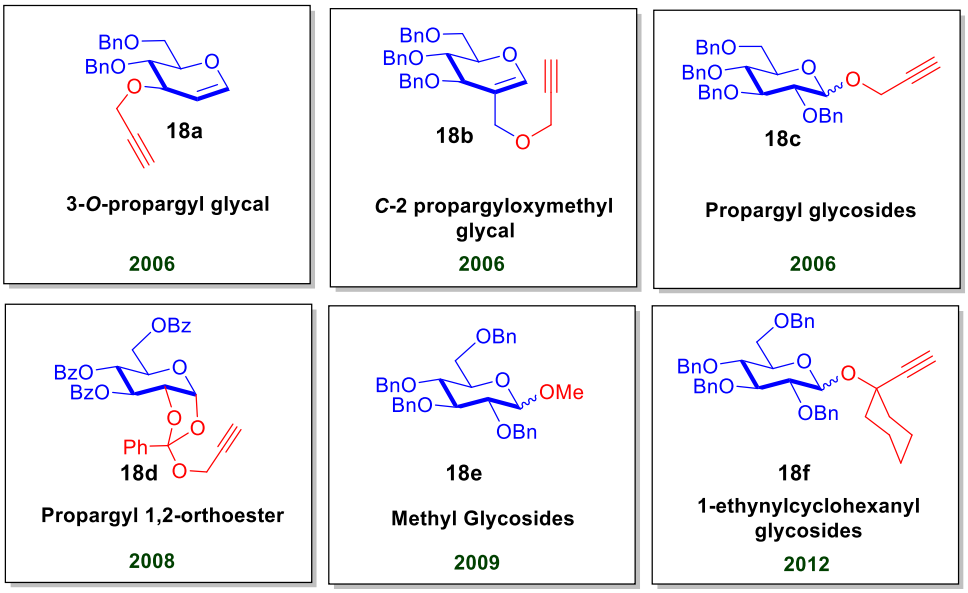
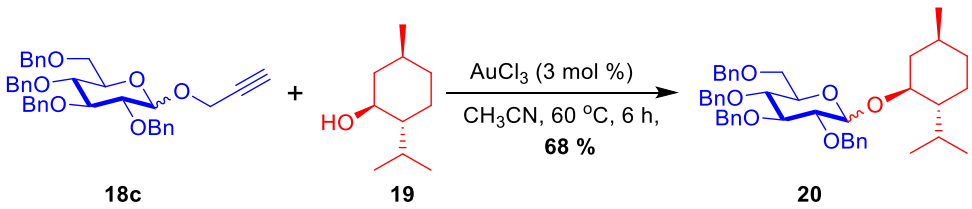


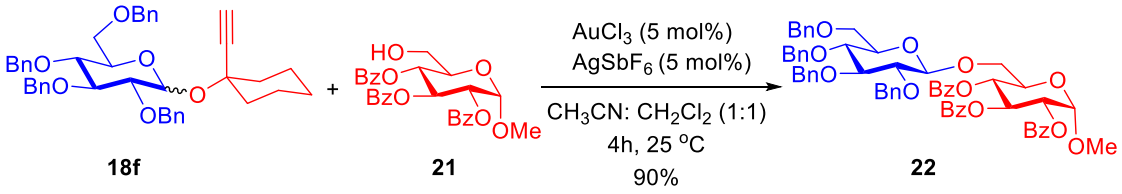
Figure 1.10: Various gold catalysed glycosyl donors identified by Hotha *et al.*

propargyl glycosides (**18c**) could be used as glycosylation donors under the catalysis of $AuCl_3$ (**Scheme 1.12**).[24c] The salient features of this protocol, such as stability of the donors, good reaction yields and use of catalytic amount of the $AuCl_3$ as promoter was inspiring. However, relatively strong reaction conditions (CH_3CN, 60 ^{0}C) and limited substrate scope were major hurdle which were addressed subsequently over the last one



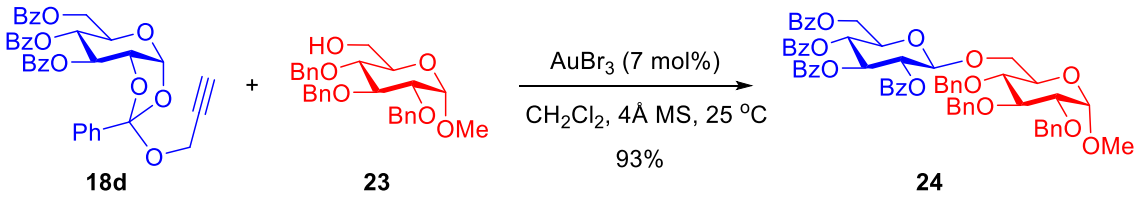
Scheme 1.12: Gold-catalysed glycosylation reaction

decade. Later it was observed that under similar conditions, methyl glycosides (**18e**) could also act as a glycosyl donor for effective glycosylation.[24d] These results clearly indicated that it was not only the alkynophilicity but also the Lewis acidity or the oxophilic nature of the gold(III) catalyst that contributed in the activation of these glycosyl donors. Another report by Hotha *et al.* mentioned the conversion of *C*-2 propargyloxymethylene glycals (**18b**) to *C*-2 methylene glycosides using catalytic $AuCl_3$.[24e]



Scheme 1.13: 1-ethynylcyclohexanyl glycoside donor as glycosyl donors

Later in 2012, after an extensive study on various parameters influencing the glycosylation reaction such as the leaving capability of various substituted propargyl glycosides donors, solvents, addition of co-catalysts Kayastha and Hotha found that 1-ethynylcyclohexanyl glycoside donor (**18f**) are much reactive than simple propargyl glycosides as the former could be activated at room temperature using $AgSbF_6$ or AgOTf as a co-catalyst in CH_2Cl_2:CH_3CN (1:1) solvent mixture (**Scheme 1.13**).[24f] Mamidyala and Finn showed that even unprotected propargyl glycosides could also be utilized for glycosylations in presence of $AuCl_3$ catalytic system.[24g]



Scheme 1.14: Propargyl 1,2-orthoesters as glycosyl donors

In 2007, Hotha et al. further emphasized the importance of gold-alkyne system in 1,2-orthoester donor development. They have shown that propargyl 1,2-orthoesters (**18d**) could act as excellent glycosyl donors for glycoconjugate syntheses in the presence of $AuBr_3$ conditions (**Scheme 1.14**).[24h] One major advantage in the utilization of these propargyl 1,2-orthoesters donors for oligosaccharides synthesis is that these donors can be activated selectively in the presence of other glycosyl donors such as propargyl and *n*-pentenyl glycosides.Since, the gold-catalysis protocol provided good yields of various glycosides in a stereoselective 1,2-*trans* fashion under mild reaction conditions, it was further utilized for the synthesis of furanosides, pyrimidine nucleosides, aminooxy glycosides, glycosyl carbamates, thioglycosides, as well as glycopeptides and glycopolymers.[24a]

Following the cue, several other groups also utilized gold(I) /gold(III) catalytic

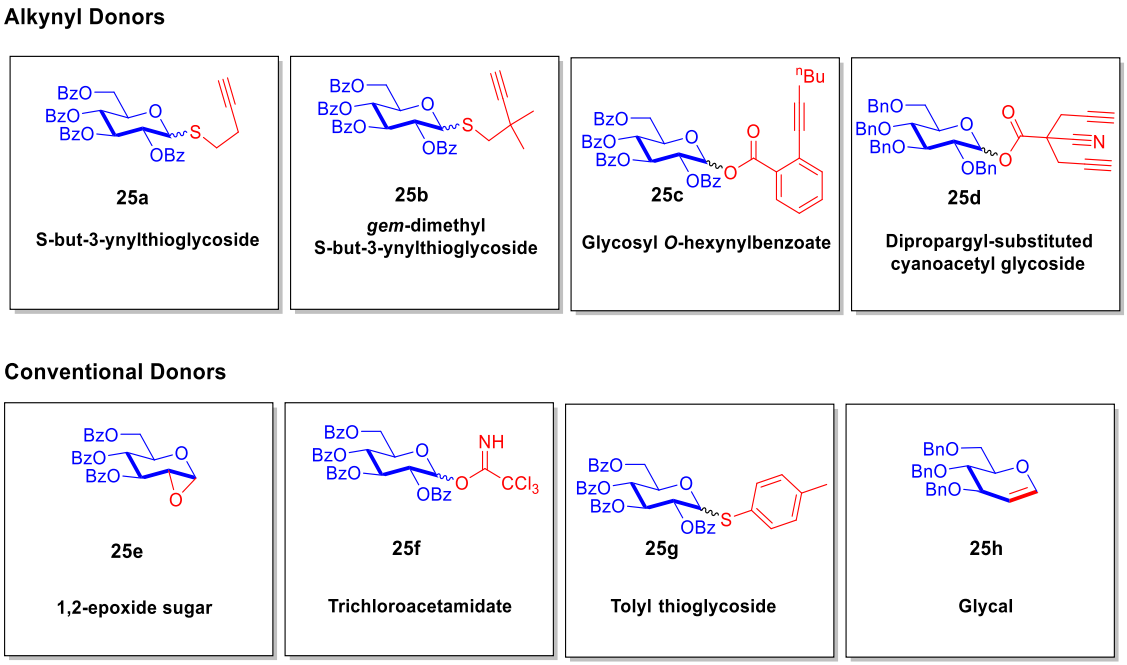


Figure 1.10: Various glycosyl donors activated by gold catalyst

system for the activation of various leaving groups at the anomeric position and tried to develop newer glycosylation method. Few of them employed gold catalysis to activate the already existed conventional glycosyl donors. For example, in 2015, Vankar *et al.* reported the activation of trichloroacetimidates (**25f**) donors in presence of catalytic $AuCl_3$.[24i] The yield of the glycosylation reaction improved significantly when phenylacetylene was added along with $AuCl_3$. Another report by Schmidt and co-workers revealed that at a very low temperature (-60 ^{0}C to -70 ^{0}C), $AuCl_3$ facilitated the trichloroacetimidates donor activation via intramolecular hydrogen bonding in association with the acceptor and prompted to a S_N2-type glycosylation in a stereospecific manner.[24j] Similarly, In 2016, Sureshan *et al.* claimed that 8mol% $AuCl_3$, instead of excess NIS/AgOTf reagents could be a better choice for tolyl thioglycosides (**25g**) activation intended for effective glycosylation;[24k] Although it was later found that for effective glycosylation as mentioned, stoichiometric amount of $AuCl_3$ was required in actual.

In early 2008, Biao Yu group reported the activation of *O* -hexynylbenzoates glycosyl donors (**25c**) in presence of $Ph_3PAuOTf$ or $Ph_3PAuNTf_2$ to provide a wide range of glycoconjugates.[24l] Extensive studies on the glycosylation related issues such as improvement of catalytic systems, modification of *O*-alkynylbenzoyl leaving groups and proper understanding of glycosylation reaction mechanism by Biao Yu and co-workers improved the glycosylation protocol. Various types of glycosides have been

synthesized employing this *O*-alkynylbenzoyl glycosylation protocol including *C*-glycosides, *N*- glycosides, Purine and pyrimidine nucleosides, oxime, phosphate or carboxylate glycosides. This protocol has also been utilized to address few synthetic challenges such as stereoselective *1,2-cis* glycoside preparation in case of glucose, galactose, mannose, rhamnose, sialic acid and synthesis of saponins, digitoxin and Tunicamycins. Biao Yu *et al.* also reported that $Ph_3PAuOTf$ catalyst could be a better choice for sugar 1,2-epoxides donor (**25e**) than the conventional $ZnCl_2$ promoter, as noted by Denishefsky.[24m] In 2013, Zhu *et al.* published a report on the development of *S*-but-3-ynyl and *gem*-dimethyl *S*-but-3-ynyl thioglycosides as glycosyl donors (**25a** and **25b**) under the activation of $AuCl_3$/AgOTf catalytic system.[24n] Recently, Galan demonstrated that glycals (**25h**) could undergo α-selective glycosylation Under the catalysis of (p-$CF_3Ph)_3PAuCl$/AgOTf catalytic system.[24o]

1.5.6 – Requires another glycosyl donor for glycoconjugates?

Over the last 100 years, various groups have developed numerous numbers of glycosyl donors. Each of these has its own merits and demerits over the other glycosyl donors (**Figure 1.11**). For example, the hemiacetal glycosyl donor used in Fisher type glycosylation is stable and easily accessible but not useful for the synthesis of oligosaccharides as aglycons are mostly used as solvents. Similarly, highly unstable nature of glycosyl halide donors (Cl, Br, I) and use of toxic heavy metal salts restricted the widespread applications of the Koneing-Knorr type glycosylation. Similarly, glycosyl donors such as 1,2-anhydro sugars, diaziridines, phosphate and phosphite etc. are not explored much for oligosaccharide synthesis due to their unstable nature along with the problem of interglycosidic bond cleavage and poor functional group compatibility. On the other hand, stable glycosyl donors such as thio-, pentenyl-, acetate-, carbamate- or modified thio- glycosides require stoichiometric or sub-stoichiometric activators and difficulties in isolation of desired glycoside products from side products limited their scope in glycoconjugate syntheses.

Likewise, the 1,2-*O*-orthoester glycosyl donors are quite stable and excellent for stereoselective 1,2-*trans* glycosides preparation. However, not much explored due to its propensity to form direct glycosylation product which resulted in low glycosylation yields. Ease in the preparation of glycosyl donors is also a very crucial factor for the overall glycoconjugate synthesis. There are a many glycosyl donors which are

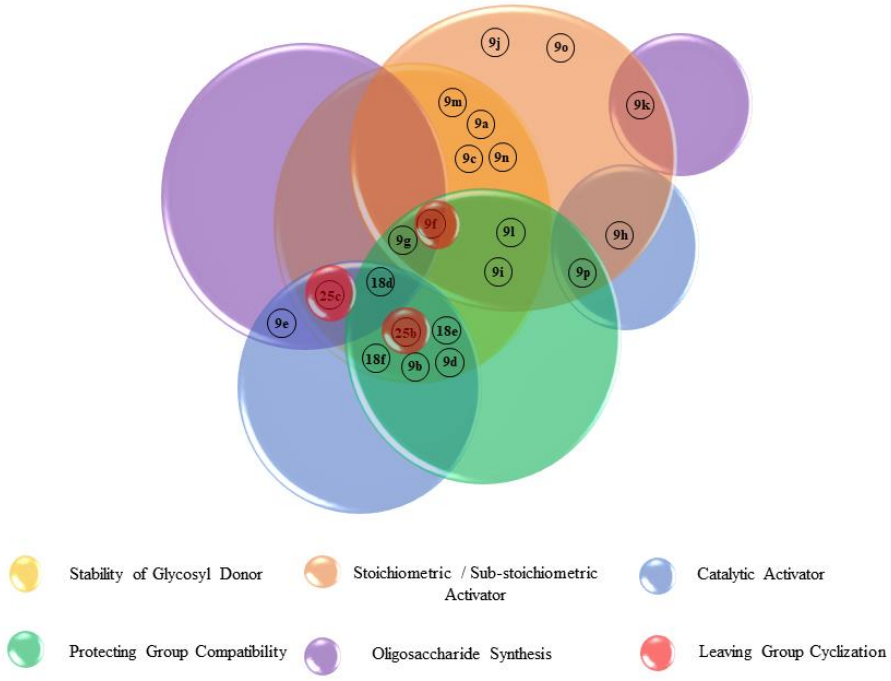


Figure 1.11: Glycosyl donors utility and numbers indicate reference number

providing excellent glycosylation yields, but not get proper attention due to complicated preparation procedures. Apart from that compatibility of a glycosyl donor towards various protection and deprotection steps is also a major concern regarding donor development.

Another major drawback for most of the existing glycosyl donors is that for a single glycosyl donor, glycosylation yields for all types of aglycons vary significantly. Till date, glycosyl trichloroacetimidate/*N*-phenyl trifluoroacetimidate donor and thioglycosyl donors are the only options for the synthesis of oligosaccharides or glycoconjugates. Although it is worthy to mention that not all glycosyl trichloroacetimidate donors are stable enough to be stored for longer time. Hence, development of a novel glycosyl donor which can be used for any type of glycoconjugate synthesis is highly demanding and is an open area for further investigations.

*****

1.6 – References

1. Robyt, J. F. *Essentials of Carbohydrate Chemistry*. Springer press, New York, **1998**, pp.1–47.
2. (a) Paulsen, H. *Angew. Chem. Int. Ed.* **1982**, *21*, 155–173; (b) Sharon, N. *Chem. Eng. News*, **1981**, *59*, 21; (c) Laine, R.A. *Glycobiology* **1994**, *4*, 759–762.
3. Stick, R. V. *Carbohydrates: The Sweet Molecules of Life.* Academic press, New York, **2001**, pp.1–150.
4. (a) Dwek, R. A. *Chem. Rev*. **1996**, *96*, 683–720; (b) Conrad, H. E. *Heparin-binding Proteins;* Academic Press, **1998**; (c) Awad, L.; Demange, R.; Zhud, Y. H.; Vogel, P. *Carbohydr*. *Res*. **2006**, *341*, 1235–1252; (d) Verez-Bencomo, V.; Fernández-Santana, V.; Diaz, M.; Roy, R. *Science* **2004**, *305*, 522–525.
5. (a) Davis, G. J.; Charnock, S. J.; Henrissat, B. *Trends Glycosci. Glycotechnol*. **2001**, *13*, 105–120; (b) Kobayashi, S.; Uyama, H.; Kimura, S. *Chem. Rev.* **2001**, *101*, 3793–3818; (c) Demchenko, A. V. *Handbook of Chemical Glycosylation,* Wiley-VCH press, New York, **2008**; (d) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687–2704; (e) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc*. **1991**, *113*, 9376–9377; (f) Kim, J. H.; Yang, H.; Boons, G. J.; *Angew. Chem., Int. Ed.* **2005**, *44*, 947–949; (g) Baek, J. Y.; Lee, B. Y.; Jo, M. G.; Kim, K. S.; *J. Am. Chem. Soc*. 2009, *131*, 17705–17713.
6. (a) Edward, J.T. *Chem & Ind.* **1955**, 1102–1104; (b) Lemieux, R.U. *Pure and Appl. Chem.* **1971**, *25*, 527–548; (c) Schmidt, R. R.; Riicker, E. *Tetrahedron Lett.* **1980**, *21*, 1421–1424; (d) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205–2213.
7. (a) Lu, J.; Jayaprakash, K. N.; Schlueter, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **2004**, *126*, 7540–7547 (b) Roberts, C.; Madsen, R.; Fraser-Reid, B. *J. Am. Chem. Soc*. **1995**, *117*, 1546–1553 (c) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem*. **1990**, *55*, 6068–6070; (d) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275–278; (e) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656–6660; (f) Ley, S. V.; Pietruszka, J.; Osborn, H. M. I.; Priepke, H. W. M.; Warriner, S. L. *Chem. Eur. J.* **1997**, *3*, 431–440.
8. (a) Hanessian, S. *Preparative Carbohydrate Chemistry*, Marcel Dekker Inc., New York, **1997**, pp. 283–312. (b) Lemieux, R.U.; Hendriks, K.B.; Stick, R.V.; James,

K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062; (c) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506–4507.

9. (a) Chen, Q.; Kong, F. *Carbohydr. Res.* **1995**, *272*, 149–157; (b) Sames, D.; Chen, X. T.; Danishefsky, S. J. *Nature* **1997,** *389*, 587–591; (c) Ernst, B.; Hart, G. W.; Sinay, P. *Carbohydrates in Chemistry and Biology*, Wiley-VCH press, New York, **2000**, pp. 427–448; (d) Tsvetkov, Y. E.; Kitov, P. I.; Backinowsky, L. V.; Kochetkov, N. K. *J. Carbohydr. Chem.* **1996**, *15*, 1027–1050,
10. (a) Uchiro, H.; Mukaiyama, T. *Chemistry Lett.* **1996**, 271–272; (b) Boons, G. J. *Contemp. Org. Synth.* **1996**, *3*, 173–200; (c) Andersson, F.; Fugedi, P.; Garegg, P. J.; Nashed, M. *Tetrahedron Lett.* **1986**, *27*, 3919–3922; (d) Schmidt, R. R.; Rucker, E. *Tetrahedron Lett.* **1980**, *21*, 1421–1424; (e) Conrow, R. B.; Bernstein, S. *J. Org. Chem.* **1971**, *36*, 863–870; (f) Kaeothip, S.; Yasomanee, J. P.; Demchenko, A. V. *J. Org. Chem.* **2012**, *77*, 291–299.
11. (a) Fischer, E. *Chem. Ber.* **1893**, *26*, 2400–2412; (b) Koenigs, W.; Knorr, E. *Chem. Ber.* **1901**, *34*, 957–981; (c) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431–432; (d) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961–6967.
12. (a) Pougny, J. R.; Jacquinet, J. C.; Nassr, M.; Duchet, D.; Milat, M. L.; Sinaÿ, P. *J. Am. Chem. Soc.* **1977**, *99*, 6762–6763; (b) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Eng.* **1980**, *19*, 731–732; (c) Mukaiyama, T.; Nakatsuka, T.; Shoda, S. I., *Chem. Lett.* **1979**, 487–490.
13. (a) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Carbohydr. Res.* **1973,** *27*, 55–61; (b) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430–2434; (c) Garegg, P. J.; Henrichson, C.; Norberg, T. *Carbohydr. Res.* **1983**, *116*, 162–165.
14. Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc.: Chem. Commun.* **1988**, 823–825.
15. (a) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656–6660; (b) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666.
16. (a) Bochkov, A. F.; Kochetkov, N. K. *Carbohydr. Res.* **1975**, *39*, 355–357; (b) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron lett.* **1964**, *5*, 289–293; (c) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron Lett.*

1967, 23, 693–707; (d) Kochetkov, N. K.; Bochkov, A. F.; Sokolavskaya, T. A.; Snyatkova, V. J. *Carbohydr*. *Res*. **1971**, *16*, 17–27; (e) Jayaprakash, K. N.; Radhakrishnan, K. V.; Fraser-Reid, B. *Tetrahedron lett*. **2002**, *43*, 6953–6955.

17. (a) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N., *Tetrahedron Lett*. **1989**, *30*, 5459–5462; (b) Marra, A.; Sinaÿ, P. *Carbohydr*. *Res*. **1990**, *195*, 303–308; (c) Kahne, D.; Walker, S.; Cheng, Y.; van Engen, D. *J. Am. Chem. Soc*. **1989,** *111*, 6881–6882; (d) Kunz, H.; Zimmer, J., *Tetrahedron Lett*. **1993**, *34*, 2907–2910; (e) Kondo, H.; Ichikawa, Y.; Wong, C. H. *J. Am. Chem. Soc*. **1992**, *114*, 8748–8750; (f) Plante, O. J.; Andrade, R. B.; Seeberger, P. H. *Org*. *Lett*. **1999**, *1*, 211–214; (g) Mehta, S.; Pinto, B. M. *Tetrahedron Lett*. **1991**, *32*, 4435–4438; (h) Stick, R.V.; Tilbrook, D. M. G.; Williams, S. J. *Aus*. *J. Chem*. **1997**, *50*, 237–240.

18. (a) Huchel, U.; Schmidt, C.; Schmidt, R. R. *Eur. J. Org. Chem*. **1998**, 1353–1360; (b) Demchenko, A. V., Malysheva, N. N.; De Meo, C. *Org. Lett.* **2003**, *5*, 455–458 (c) Briner, K.; Vasella, A., *Hel. Chim. Acta.* **1989**, *72*, 1371–1382; (d) Boons, G. J.; Isles, S. *Tetrahedron Lett*. **1994**, *35*, 3593–3596.

19. (a) McKay, M. J.; Nguyen, H. M. *ACS Catal*. **2012**, *2*, 1563−1595; (b) Yang, J.; Cooper-Vanosdell, C.; Mensah, E. A.; Nguyen, H. M. *J. Org. Chem*. **2008**, *73*, 794–800; (c) Reed, C. A. *Acc. Chem. Res.* **1998**, *31*, 133–139; (d) Mensah, E. A.; Azzarelli, J. M.; Nguyen, H. M. *J. Org. Chem.* **2009**, *74*, 1650–1657; (e) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc*. **2004**, *126*, 1336–1337; (f) Babu, R. S.; O′ Doherty, G. A. *J. Am. Chem. Soc*. **2003**, *125*, 12406–12407; (g) RajanBabu, T. V. *J. Org. Chem*. **1985**, *50*, 3642–3644.

20. (a) Mensah, E. A.; Nguyen, H. M. *J. Am. Chem. Soc*. **2009**, *131*, 8778–8780; (b) Mensah, E. A.; Yu, F.; Nguyen, H. M. *J. Am. Chem. Soc*. **2010**, 132, 14288–14302; (c) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 10482–10483; (d) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc*. **2008**, *130*, 12177–12183.

21. (a) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed*. **2010**, *49*, 7274–7276; (b) Wagner, B.; Heneghan, M.; Schnabel, G.; Ernst, B. *Synlett* **2003**, 1303−1306; (c) Sherry, B. D.; Loy, R. N.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4510-4511.

22. (a) Mukaiyama, T.; Yamada, M.; Suda, S.; Yokomizo, Y.; Kobayashi, S. *Chem. Lett.* **1992**, 1401−1404; (b) Pfaffe, M.; Mahrwald, R. *Org. Lett.* **2012**, *14*, 792−795; (c) Sanki, A. K.; Boucau, J.; Srivastava, P.; Adams, S. S.; Ronning, D. R.; Sucheck, S. J. *Bioorg. Med. Chem*. **2008**, *16*, 5672−5682; (d) Allen, C. L.; Miller, S. J. *Org. Lett.* **2013**, *15*, 6178−6181; (e) Frem, D.; Urban, D.; Norsikian, S.; Beau, J.-M. *Eur. J. Org. Chem*. **2017**, 5094−5101; (f) Sommer, R.; Hauck, D.; Titz, A. *Chemistry Select* **2017**, *2*, 4187−4192.

23. (a) Toste, F. D.; Michelet, V. *Gold Catalysis: An Homogeneous Approach*, Imperial College Press, **2014**, pp. 1-44; (b) Bond, G. C.; Sermon, P. A.; Webb, G.; Buchanan, D. A.; Wells, P. B. *J. Chem. Soc. Chem. Commun.* **1973**, 444–445; (c) Haruta, M.; Kobayashi, T.; Sano, H.; Yamada, N. *Chem. Lett.* **1987**, *16*, 405–408; (d) Hutchings, G. J. *J. Catal.* **1985**, *96*, 292–295; (e) Prati, L.; Rossi, M. *J. Catal.* **1998**, *176*, 552–560; (f) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406; (g) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729–3731; (h) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418; (i) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; (j) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1759–1774.

24. (a) Li, W.; Yu, B. *Chem. Soc. Rev. DOI: 10.1039/c8cs00209f* and references therein; (b) Kashyap, S.; Hotha, S. *Tetrahedron Lett*. **2006**, *47*, 2021–2023; (c) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc*. **2006**, *128*, 9620–9621; (d) Vidadala, S. R.; Hotha, S. *Chem. Commun.*, **2009**, 2505–2507; (e) Kashyap, S.; Vidadala, S. R.; Hotha, S. *Tetrahedron Lett*. **2007**, *48*, 8960–8962; (f) Kayastha, A. K.; Hotha, S. *Chem. Commun*. **2012**, *48*, 7161–7163; (g) Mamidyala, S. K.; Finn, M. G. *J. Org. Chem.* **2009**, *74*, 8417–8420; (h) Sureshkumar, G.; Hotha, S. *Tetrahedron Lett*. **2007**, *48*, 6564–6568; (i) Roy, R.; Palanivel, A. K.; Mallick, A.; Vankar, Y. D. *Eur. J. Org. Chem*. **2015**, 4000–4005; (j) Peng, P.; Schmidt, R. R. *J. Am. Chem. Soc*. **2015**, *137*, 12653–12659; (k) Vibhute, A. M.; Dhaka, A.; Athiyarath, V.; Sureshan, K. M. *Chem. Sc*i. **2016**, *7*, 4259–4263; (l) Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett*. **2008**, *49*, 3604–3608; (m) Li, Y.; Tang, P.; Chen, Y.; Yu, B. *J. Org. Chem*. **2008**, *73*, 4323–4325; (n) Adhikari, S.; Li, X.; Zhu, J. *J. Carbohydr. Chem.* **2013**, *32*, 336–359; (o) Palo-Nieto, C.; Sau, A.; Galan, M. C. *J. Am. Chem. Soc*. **2017**, *139*, 14041–14044.

Chapter 2

Synthesis of O-, C- and N-Glycosides by [Au]/[Ag]-Catalysed Glycosylation

2.1 – Introduction

Very first report on the utility of homogeneous gold catalyst in glycosylation reactions set a bench mark in the glycosylation method development.[1a] The perfect amalgamation by employing propargyl alcohol as a leaving group at the anomeric position and a gold(III) catalyst with synergistic Lewis/BrØnsted acid properties as an activator promoted the gold catalysed glycosylation protocol to achieve a new height.[1b] In 2006, the journey of gold catalysed glycosylation in our lab commenced when per-*O*-benzylated propargyl glucoside donor (**1**) in presence of catalytic amount $AuCl_3$ has been successfully activated to synthesize a variety of glucosides (**2**) (**Fig. 2.1**). In spite of having several advantages as compared to the then existing glycosyl donors, the newly developed glycosylation protocol did not get much attention from the synthetic carbohydrate community may be due to its high temperature (60–70 ^{0}C) reaction condition and unreactive nature of per-*O*-benzoylated propargyl glycosyl donors toward Au-catalysed glycosylation.

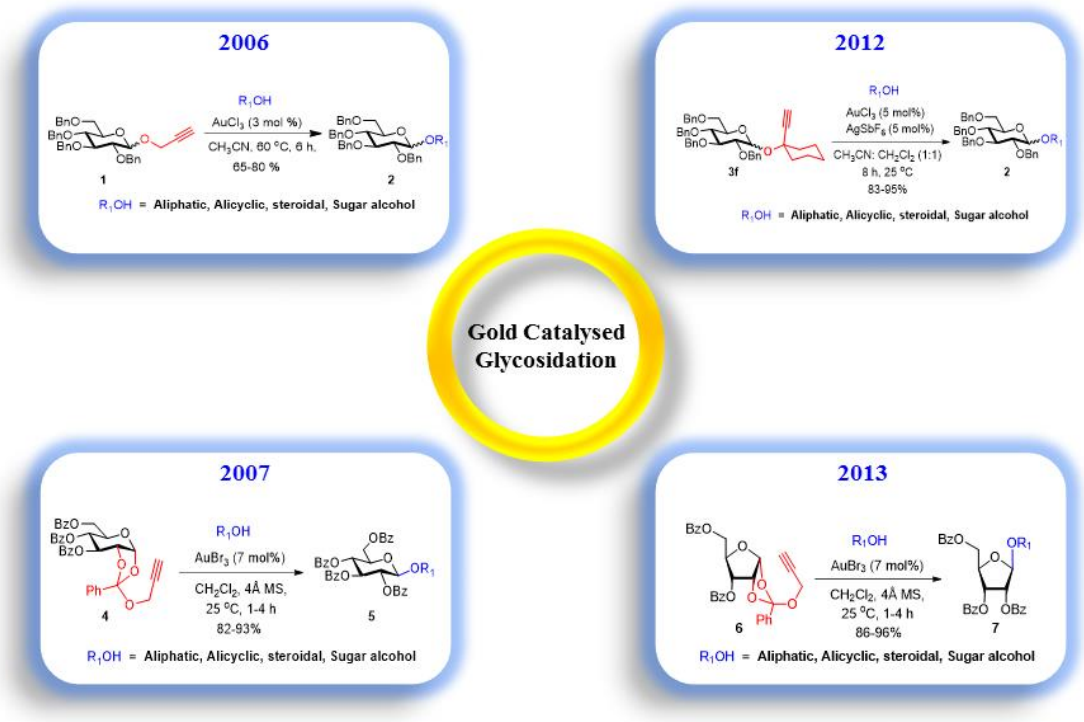


Figure 2.1: Development of gold-catalysed glycosylation by Hotha group

Later in 2012, a systematic investigation on various alkyne bearing leaving groups was carried out in search of a room temperature version of the gold-catalysed glycosylation.[1c] In-depth study of various leaving groups revealed that the use of simple

propargyl moiety (**3a**) under catalytic $AuCl_3$ condition at room temperature resulted in very poor glycosylation yield (18%) even after 12 h reaction time. Further it was found that *gem*-dialkyl substituted propargyl moieties (**3d** and **3e**) are superior to the mono methyl (**3b**) or phenyl substituted version (**3c**). However, placing the cyclohexyl moiety (**3f**) in place of *gem*-dimethyl group was noticed to be the most beneficial for techno commercial reasons (**Fig. 2.2**). Increased reactivity of the *gem*-disubstituted donors has been explained based on reported Thorpe–Ingold like effect.

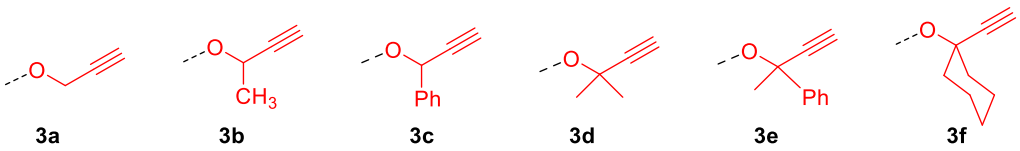
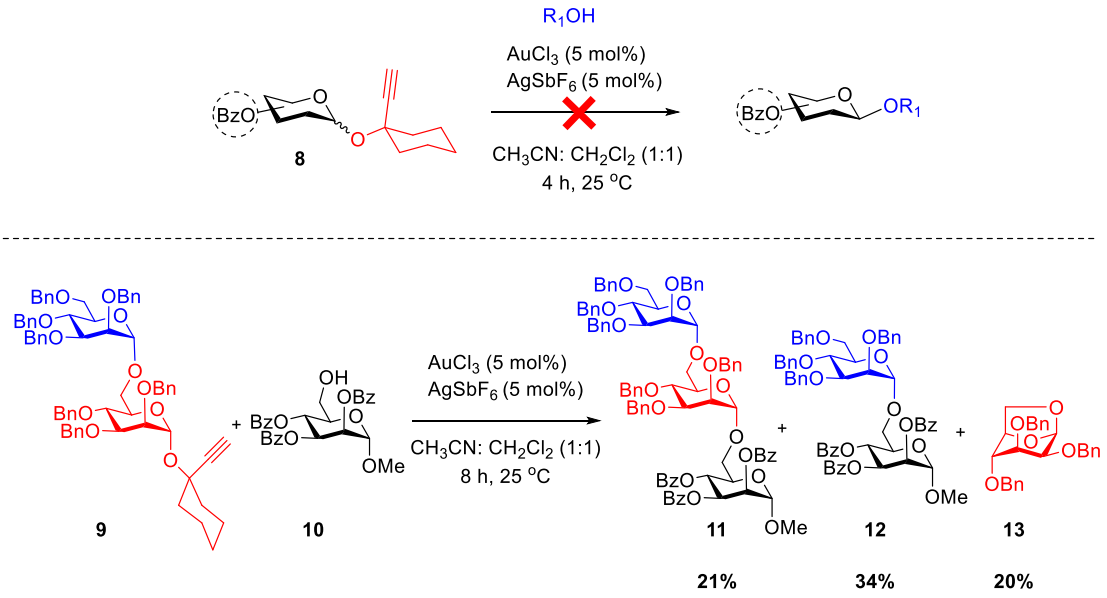


Figure 2.2: Screening of leaving groups for gold-catalysed transglycosylation

Moreover, use of 5 mol% $AgSbF_6$ along with 5 mol% $AuCl_3$ as a co-catalyst resulted in higher glycosylation yield (>90%) at room temperature (25 ^{o}C). The use of 1-ethynylcyclohexanyl glycosyl donors (**3f**) and $AgSbF_6$ co-catalyst widened the substrates (**2**) scope significantly (**Fig. 2.1**). However, major drawbacks associated with the Au-catalysed glycosylation method remained unsolved. The modified Au-catalysed gycosylation protocol still had to overcome few limitations, such as (i) not suitable for glycosyl donors (**9**) possesing ester functional groups at *C*-2 position, (ii) formation of glycoside products as α/β mixture and (iii) cleavage of the inter-glycosidic bonds in some instances due to the high oxophilicity of the Au(III)-salts (**Scheme 2.1**).[1d,e]

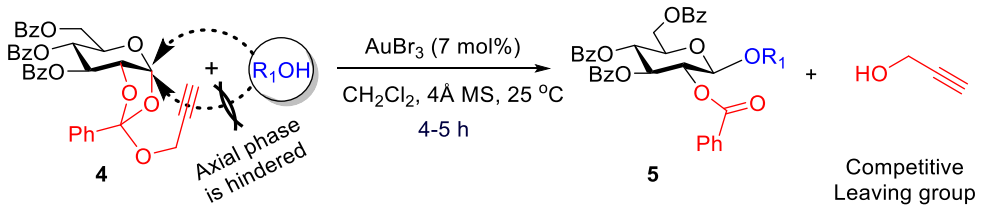
Some of the above mentioned limitations were addressed by switching the glycosyl donor from propargyl glycosides to propargyl 1,2-*O*-orthoesters. In 2007, propargyl 1,2-orthoester chemistry was explored for the first time in pyranose sugars (**4**) (**Fig. 2.1**).[1f] Modified protocol was found to be an excellent alternative to propargyl glycoside donors with good to excellent yields and in addition giving exclusive 1,2-*trans* glycosylation products (**5**). In 2013, propargyl 1,2-*O*-orthoester strategy was further extrapolated to more challenging furanosides (**6**) with the synthesis of a highly complex branched hexasaccharide from *Mycobacterium tuberculosis* cell wall (**Fig. 2.1**).[1g]

In parallel, the propargyl 1,2-orthoesters were successfully shown to be superior for the synthesis of various oligosaccharides/glycoconjugates synthesis, glycopeptides,



Scheme 2.1: Limitations of 1-ethynylcyclohexanyl glycoside donor

polymers, nucleosides and thioglycosides etc.[2a-c] One major advantage of the propargyl 1,2-orthoester glycosyl donors was that they can be orthogonally activated by catalytic $AuCl_3$ in presence of propargyl glycosides and *n*-pentenyl glycoside/orthoester donors.[2d,e] Another unique feature of propargyl 1,2-orthoester protocol was the ease in the interconversion of propargyl 1,2-orthoester and *n*-pentenyl glycoside donors, which allowed it to become a very useful protocol for the convergent synthesis of highly complex glycoconjugate.[2f] It is beyond doubt that propargyl 1,2-orthoester strategy



Scheme 2.2: Major drawbacks of propargyl 1,2-orthoester donor

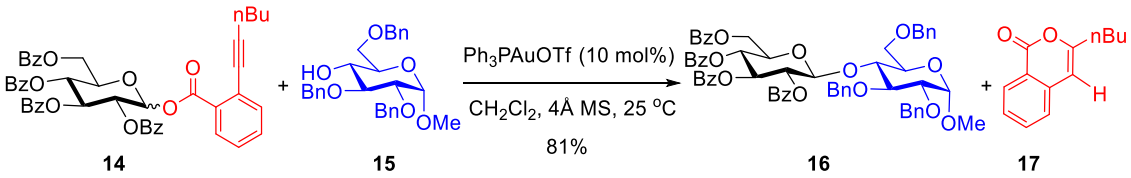
contributed significantly in the advancement of gold catalysed glycosylation. Still, there were some inherent downsides associated with the protocol such as (i) 1,2-*cis* glycosidic bond formation was not possible *via* 1,2-orthoester strategy (ii) average reaction time was long (iii) preparation of glycosyl donors at higher oligosaccharides level was very cumbersome, (iv) sterically demanding aglycons resulted in low glycosylation yields, (v) glycosylation of *C*-2 deoxy sugars were beyond the scope and most importantly (vi) generation of propargyl alcohol during the glycosylation reaction

that compete with the upcoming nucleophile resulted in unwanted side product (**Scheme 2.2**). In spite of these, propargyl 1,2-orthoesters offered tremendous lift to the gold-catalysed glycosylation efforts.

So, the search for a versatile and stable glycosyl donor that can be activated in a catalytic fashion persisted. Either replacement of the leaving group or change in the catalytic system/promoter were the chosen alternatives to enhance the glycosylation. However, improvements to the catalytic system/promoter did not provide encouraging results due to the availability of limited number of gold-catalysts from commercial sources. Alternatively, modifying the leaving group in such a way that the leaving group gets transformed to another product that does not interfere with the glycosylation or the purification looked to be more promising.

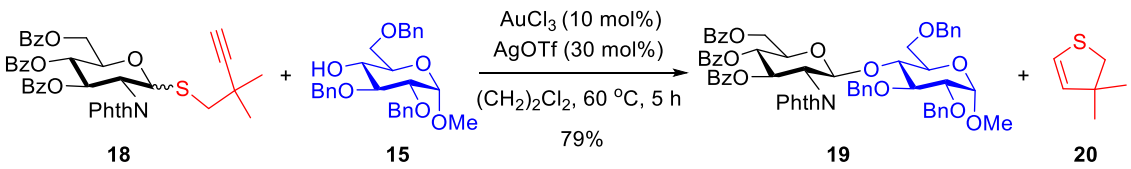
2.2 – Gold catalysed glycosylation using leaving group cyclization strategy

In the meantime, alkyne bearing leaving groups using Au(I)/Au(III) catalysis has caught the attention of several others. Biao Yu group from China reported one such kind of glycosylation through the activation of *O*-hexynylbenzoates as glycosyl donors in the



Scheme 2.3: Activation of *O*-hexynylbenzoate glycosyl donor with $Ph_3PAuOTf$

presence of $Ph_3PAuOTf$. The leaving group underwent an intramolecular cyclization resulting in the formation of benzopyrenone derivative (**17**) which has been subsequently isolated and characterized by Yu (**Scheme 2.3**).[3a]



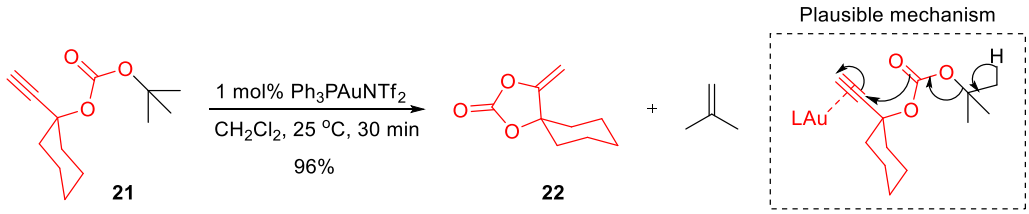
Scheme 2.4: Activation of gem-dimethyl S-but-3-ynyl glycosyl donor

Similarly, Zhu group implemented the cyclization ability of *gem*-dimethyl *S*-but-3-ynyl

leaving group for the glycosylation in presence of $AuCl_3$/AgOTf catalytic system (**Scheme 2.4**).[3b] These reports suggest that alkyne bearing modifications that result into a cyclized product and the Au-catalytic systems would be a far better choice than other combinations.

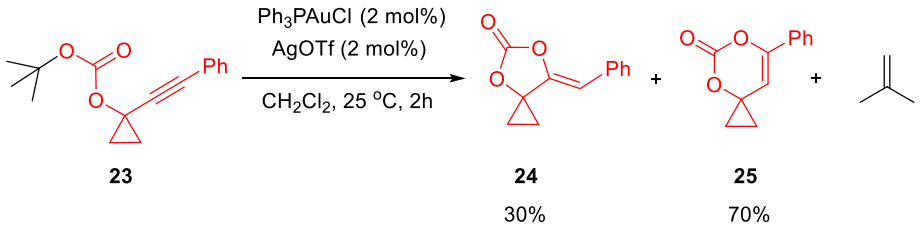
2.3 – Gold catalysed cyclization of carbonates

Around the same time, gold-catalysed cyclization of cyclohexyl alkynyl *tert*-butyl carbonate (**21**) to construct spirocyclic alkylidene (**22**) was demonstrated by Gagosz group[3c] (**Scheme 2.5**) and cyclization of 1-alkynyl cyclopropyl *tert*-butyl carbonate (**23**)



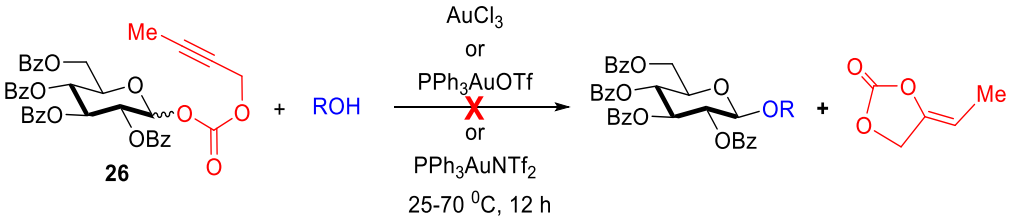
Scheme 2.5: Cyclization of cyclohexyl alkynyl carbonates to spirocyclic alkylidenes

into multi-functionalized vinyl cyclopropane derivatives (**24** and **25**) was explored by Chen group[3d] (**Scheme 2.6**). Formation of isobutylene through the formation of a ^{t}butyl carbocation inspired us to study the activation of alkynyl carbonates for the glycosylation.



Scheme 2.6: Cyclization of 1-alkynyl cyclopropyl carbonate into vinyl cyclopropane

However, Yu noticed that the *O* -alkynyl ester as 2-butynyl carbonate glycosyl donor (**26**) was unreactive under gold-catalyzed glycosylation conditions (e.g. $AuCl_3$, PPh_3AuOTf and PPh_3AuNTf_2) even at elevated temperature as well (**Scheme 2.7**).[3e] The unsuccessful attempts to activate 2-butynyl carbonate donor (**26**) were not postulated by Yu *et al.* However, they can be attributed to the possible higher degree of



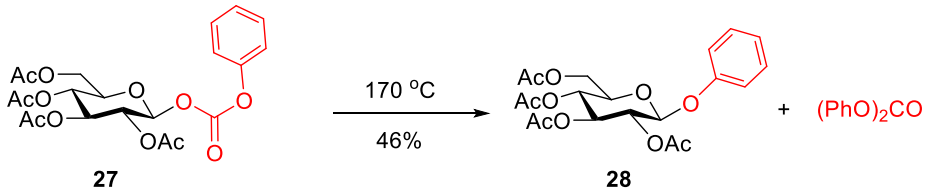
Scheme 2.7: Inertness of glycosyl alkynyl carbonate donor towards gold catalysis

freedom of the leaving group as compared to the *gem*-dimethyl alkynyl system, which diminishes the likelihood of Au-alkyne coordination which is essential for successful activation.

Initially, similar kind of results were noticed from our laboratory as well. Glycosylation yields were noticed to improve tremendously after replacement of propargyl glycosides with ethynylcyclohexyl glycosides due to the well documented Thorpe-Ingold effect.[1c] These results suggested that exchange of the propargyl unit to the *gem*-dialkyl alkynyl glycosyl carbonates might enhance its reactivity to a considerable extent.

2.4 – Developments of various glycosyl carbonates donors

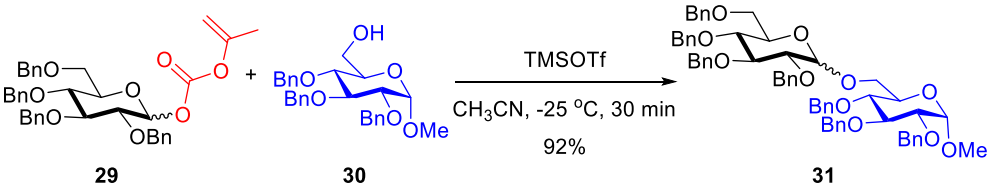
Glycosyl carbonates as glycosyl donors are well known in the literature. In 1973, Ishido first time utilized 1-*O*-aryloxycarbonyl sugar derivatives for the synthesis of various glycosides.[4a] Synthesis of phenyl 2,3,4,6-tetra-*O*-acetyl-β-glucopyranoside (**28**) was carried out through pyrolysis of the 2,3,4,6-tetra-*O*-acetyl-l-*O*-phenoxycarbonyl-β-D-glucopyranose (**27**) at 170 ^{0}C with 46 % product yield (**Scheme 2.8**). Further application of this protocol was demonstrated by treating the 2,3,4,6-tetra-*O*-acetyl-l-*O*-phenoxycarbonyl-β-D-glucopyranose (**27**) with 6-chloropurine**,** 2,6-dichloropurine**,** theophylline**,** 4-methoxy-2(1H)-pyrimidone and 2(1H)-pyridone under pyrolytic conditions to prepare the corresponding glycosides. Harsh reaction condition i.e. very



Scheme 2.8: Pyrolytic glycosylation method developed by Ishido *et al.*

high temperature (140–160 ^{0}C) under reduced pressure, removal of co-produced phenol throughout the reaction, low glycosylation yields and very limited substrate scope were the major drawbacks associated with this pyrolytic glycosylation protocol.

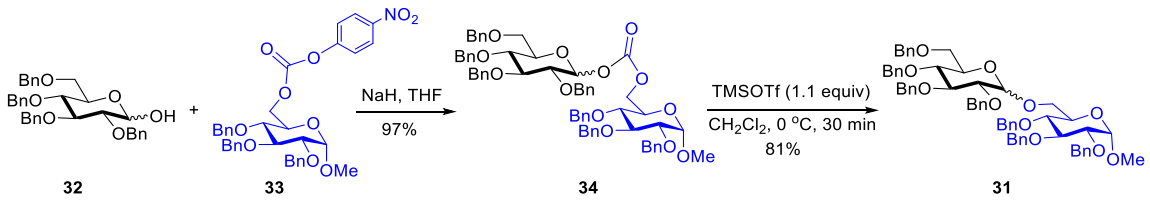
Later, Sinäy *et al*. provided an useful glycosylation method where isopropenyl carbonate glycosyl donor (**29**) was activated in presence of TMSOTf promoter in acetonitrile solvent at -25^{o}C (**Scheme 2.9**).[4b] Although, reaction of primary sugar alcohol (**30**) with isopropenyl carbonate donor (**29**) delivered disaccharide in excellent



Scheme 2.9: Activation of isopropenyl carbonate glycosyl donor for glycosylation

yield with good stereoselectivity, however failed to work well with secondary carbohydrate-based acceptors. Use of stoichiometric amount TMSOTf was another downside of this glycosylation procedure which limited its application for oligosaccharide synthesis.

Further, a two-step intramolecular decarboxylative glycosylation procedure was developed by Ikegami *et al*.[4c] The first step of this procedure involved linking of two sugar residues (**32** and **33**) by using carbonate as a connector. Whereas, the second step was the Lewis acid mediated interconversion of disaccharide carbonate (**34**) to the desired disaccharide product (**31**) through removal of carbon dioxide (**Scheme 2.10**).

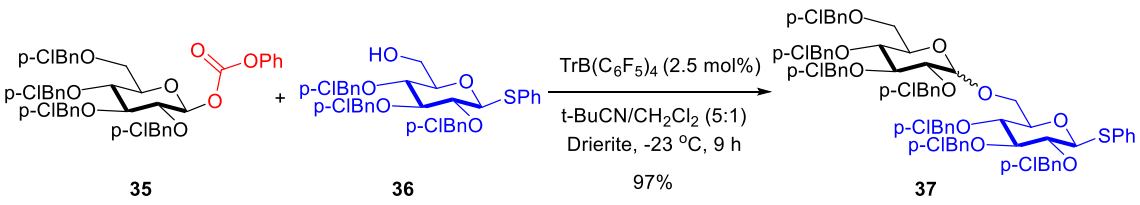


Scheme 2.10: Intramolecular decarboxylative glycosylation reported by Ikegami *et al*.

One very interesting fact about this glycosylation protocol was the opposite mode of connection, where a glycosyl acceptor is getting activated to make a glycosidic bond with the glycosyl donors. Though the intramolecular decarboxylative glycosylation

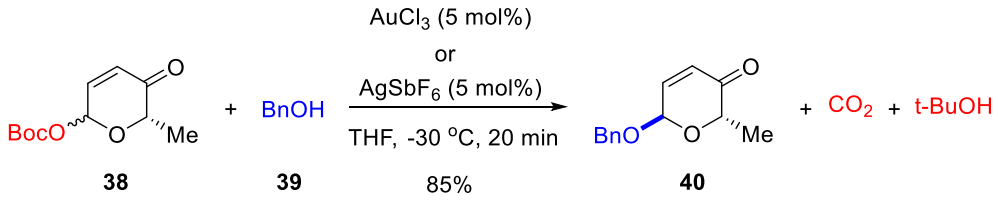
procedure could not succeed in synthesizing complex oligosaccharides but provided a new synthetic avenue for the oligosaccharide synthesis.

In 1998, Mukaiyama *et al.* reported a glycosylation method using glycosyl phenyl carbonate (**35**) as glycosyl donor in presence of 10 mol% of $TrB(C_6F_5)_4$ as an activator (**Scheme 2.11**).[4d] The respective yield of the glycosylation product (**37**) was



Scheme 2.11: Glycosylation using the phenyl carbonate as a glycosyl donor

found to be excellent with good diastereoselectivity. This method was also successfully employed in one-pot synthesis of a trisaccharide and a mucin-related antigen. The effects of protecting groups (armed/disarmed effect) on the glycosyl donor reactivity have also been thoroughly studied. It was also noticed that the use of 4-chlorobenzyl protecting groups increases the glycosylation yield significantly; whereas, per-*O*-benzoylated phenyl carbonate donors are too unreactive with $TrB(C_6F_5)_4$ even up to 30 mol% catalyst loading at -40 °C. The unreactive nature of the disarmed glycosyl donor limited its scope for the synthesis of higher oligosaccharides.



Scheme 2.12: Au- and Ag-catalysed glycosylation with pyrenone glycosyl donors

In 2015, O'Doherty group developed a mild, efficient and diastereoselective glycosylation protocol under 5mol% of Au(III)- or Ag(I)-catalyst using pyrenones (**38**) bearing ^{t}butoxycarbonyl(Boc) group at the anomeric position (**Scheme 2.12**).[4e] There were many advantages associated with this protocol such as: (i) good reaction yields, (ii) good diastereoselectivity, (iii) use of catalytic promoter, and (iv) mild reaction condition. The major limitation was the limited substrates scope.

So, development of a novel glycosyl carbonate donor that can be activated catalytically under mild reaction conditions with excellent yields and high diastereoselectivity is still highly demanding and useful for the synthesis of complex glycoconjugates.

2.5 – Present work

As delineated in section **2.1.3**, our hypothesis of shifting from conformationally flexible propargyl moiety to conformationally rigid cyclohexyl propargyl moiety at the anomeric position of a glycosyl carbonate donor (**Figure 2.3**) was explored. In this regard, the conformationally rigid glucosyl ethynylcyclohexyl carbonate bearing a tactfully positioned alkyne functionality was first designed to bring the Thorpe–Ingold effect into the alkynyl carbonate donor chemistry.

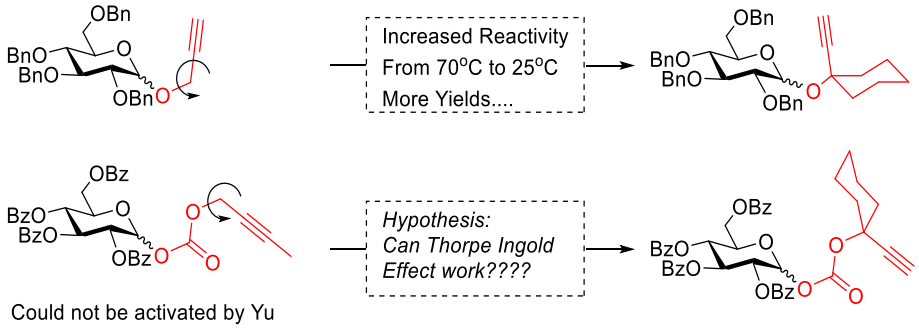
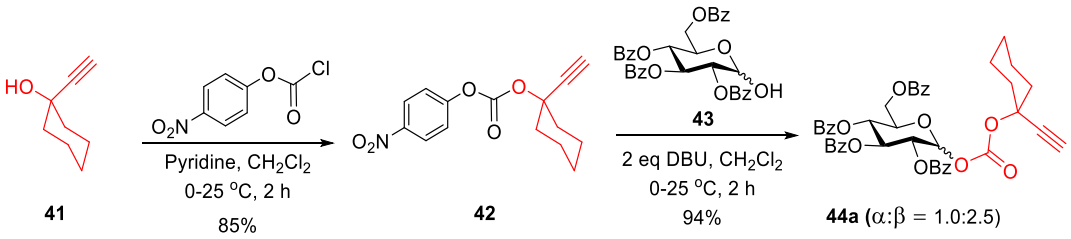


Figure 2.3: Thorpe–Ingold effect on glycosyl carbonates

2.5.1 – Preparation of glucosyl ethynylcyclohexyl carbonate donor

The key alkynyl glucosyl carbonate **44a** was synthesized in two simple steps. Commercially available 1-ethynylcyclohexanol (**41**) was first treated with *p*-nitro phenyl chloroformate using pyridine as base in CH_2Cl_2 to convert alcohol **41** into the corresponding carbonate **42** in 85% yield which was further treated with readily accesi-



Scheme 2.13: Synthesis of glucosyl ethynylcyclohexyl carbonate donor 44a

ble per-*O*-benzoyl glucopyranose (**43**)[5] in the presence of DBU as a base to give glucosyl ethynylcyclohexyl carbonate **44a** as α/β mixture (1.0:2.5) in 94% yield (**Scheme 2.13**). The α-anomer (**44aα**) and β-anomer (**44aβ**) were separated by silica gel column chromatography.

In the ^{1}H NMR spectrum of (**44aα**), a doublet (*J*=3.7 Hz) was observed at δ 6.51 ppm which is characteristic of pure α-isomer at *C*-1 and other six pyranoside ring protons were noticed between δ 4.46 – 6.24 ppm. The resonances due to the -CH_2 protons of cyclohexyl moiety were identified as multiplets between δ 1.26–2.22 ppm. Characteristic resonances of C≡CH were found at δ 2.38 ppm as a singlet. The aromatic protons of four benzoates were noticed as multiplets in the aromatic region at δ 7.25 ppm to 7.22 ppm integrating for twenty protons. In the ^{13}C NMR spectrum, the *C*-1 carbon was observed at δ 92.6 ppm and rest of the pyranoside ring carbons were noticed between δ 62.5 and 70.5 ppm. Appearance of two quaternary carbons at δ 78.9 and 88.2 ppm, one carbon at δ 78.9 ppm and five carbons between δ 22.5–36.7 ppm confirmed the presence of ethynylcyclohexyl moiety attached to the *C*-1 carbon. The characteristic quaternary resonances of carbonate at δ 155.6 ppm assured the presence of carbonate linkage at anomeric position. Signals due to the eight quaternary carbons between δ 128.7–129.6 ppm and δ 165.1–166.1 ppm along with four carbons at δ 133.5 ppm and sixteen carbons around δ 128.4–130.1 ppm in the aromatic region indicated the presence of four benzoyl groups. The ^{1}H NMR and ^{13}C NMR spectrum of **44aβ** are similar to that of **44aα** except that the *H*-1 proton resonated at δ 6.03 ppm as a doublet

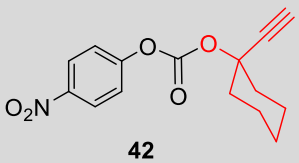
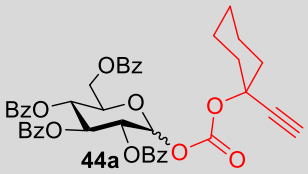
Base	 **42**	 **44a**
	% Yield	% Yield
Et_3N	20	No reaction
$(i\text{-}Pr)_2NEt$	25	No reaction
Imidazole	28	40
2,6-lutidine	30	No reaction
Pyridine	85	No reaction
DBU	No reaction	95

Table 2.1: Screening of various bases for glucosyl carbonate donor preparation

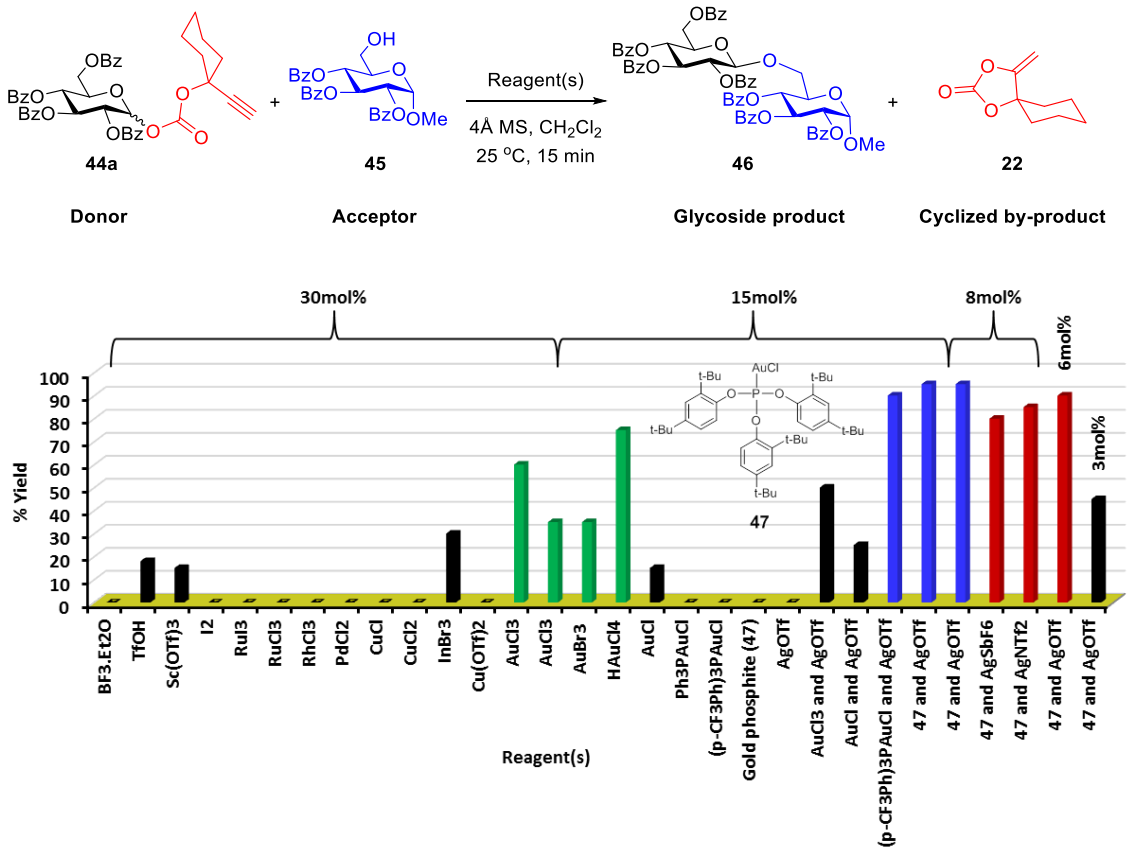
similar to that of **44aα** except that the *H*-1 proton resonated at δ 6.03 ppm as a doublet (*J* = 8.0 Hz) and *C*-1 carbon at δ 95.2 ppm indicating the β-conformer. Efforts to synthesize the glucosyl carbonate in one pot by the use of other bases resulted in discouraging results. Imidazole was the only base that afforded both compounds **42** and

44a albeit in poor yields (**Table 2.1**). However, one can prepare stable reagent **42** and treat with hemiacetals when required for the synthesis of glycosyl carbonates.

2.5.2 – Optimization of glycosylation reaction condition

Once we have glucosyl ethynylcyclohexyl carbonate donor **44a** in our hand, we started our glycosidation studies by treating carbonate **44a** and glucosyl acceptor **45**[1c] with several Lewis acids, Brønsted acids and metal salts which are known to be either alkynophilic or carbonate activators (**Scheme 2.14**). It was observed that glycosyl carbonate donor **44a** did not undergo glycosylation reaction in presence of 30 mol% of the known alkyne activators, such as I_2, $Cu(OTf)_2$, CuCl, $CuCl_2$, $RuCl_3$, $RhCl_3$, $PdCl_2$, or $BF_3{\bullet}Et_2O$ and reacted poorly with TfOH, $Sc(OTf)_3$ and $InBr_3$ even at elevated temperature (25-60 ^{o}C) and prolong reaction time (12h). However, the desired disaccharide **46** was observed (60%) along with formation of the by-product **22** when 30mol% of alkynophilic $AuCl_3$ or $AuBr_3$ salts were used. Surprisingly, reduction in the amount of AuX_3 (X = Cl, Br) from 30 mol% to 15 mol% resulted in the dropping of the disaccharide product; however, use of 15 mol% of $HAuCl_4$ raised the yield up to 72%. Discouraging results were noticed with a range of Au(I) complexes such as 15 mol% of AuCl, [Ph_3PAuCl], [(*p*-$CF_3C_6H_4)_3AuCl$] and even highly alkynophilic gold phosphite complex (**47**)[6]. Use of AgOTf also failed to yield the desired disaccharide. Nevertheless, the addition of 15 mol% each of the gold phosphite **47** and AgOTf dramatically improved the performance of the reaction to near-quantitative yield within 15min. It was quite surprising that AgOTf and the gold phosphite complex individually were ineffective to activate the alkynyl carbonate donor but a combination of them was observed to be an effective catalytic system. Hence, based on the previous reports on the reactions catalysed by a mixed catalytic system, the glycosylation by complex **47** and AgOTf falls under the recently propounded category of a Type II Au-Ag bimetallic reaction.[6a] Gold phosphite complex **47** in combination with other silver salts, such as $AgNTf_2$ and $AgSbF_6$ provided the disaccharide **46** in 80-90% yield. Reduction of the amount of the gold phosphite complex **47** and AgOTf to 8 mol% compromised the overall yield of the disaccharide. Therefore, optimized glycosylation conditions were 8 mol% of gold phosphite complex **47** and AgOTf each in CH_2Cl_2 at 25 ^{0}C for 15min.

Formation of the desired disaccharide **46** was confirmed by the NMR, HRMS and other spectroscopic tools. In the ^{1}H NMR spectrum of **46**, the characteristic resonances

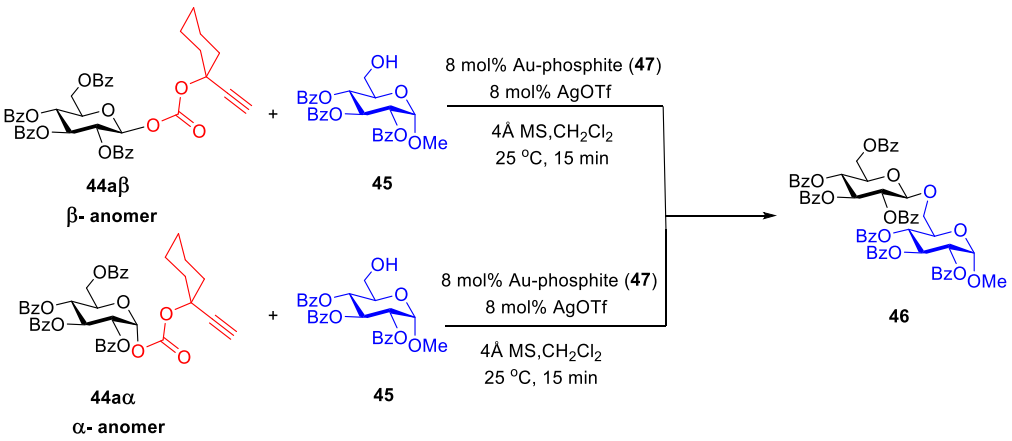


Scheme 2.14: **Screening of reagents for the glycosylation reaction between glycosyl alkynyl carbonate donor 44a and sugar acceptor 45**

corresponding to -OC<u>H</u>$_3$ were observed as a singlet at δ 3.11 ppm. Two anomers were identified at δ 4.95 (d, *J* = 3.6 Hz) and 4.99 (d, *J* = 7.8 Hz) ppm. The coupling constant values of the anomeric protons revealed the presence of one α- as well as one β- anomer in the disaccharide. Twelve pyranoside ring protons of the two sugar residues were noticed between δ 3.80 - 6.08 ppm. Thirty five aromatic protons from seven benzoyl protecting groups (-Bz) were also observed as multiplets in the aromatic region between δ 7.22–8.04 ppm inferring the presence of two sugar residues. In the ^{13}C NMR spectrum, two anomeric carbons were identified at δ 96.5 and 101.8 ppm confirming the presence of one α- and one β- configuration. Rest of the ten pyranoside ring carbons were noticed between δ 63.1 and 72.9 ppm. Characteristic resonances of one -O<u>C</u>H$_3$ and seven carbonyls due to seven benzoates were noticed at δ 55.1 ppm and between δ 165.2–166.1 ppm respectively. The attachment of -OCH$_3$ group in α- fashion of the acceptor **45** indicated that the glycosylation reaction occurred in β-stereoselective fashion exclusively.

In the ^{1}H NMR spectrum of by-product **22**, ten -C<u>H</u>$_2$ protons of cyclohexyl moiety were observed as multiplets between δ 1.27–2.07 ppm. Exocyclic methylene protons appeared as doublets at δ 4.30 (J = 3.8 Hz) and 4.76 (J = 3.8 Hz) ppm. In the ^{13}C NMR spectrum, presence of one quaternary carbon at δ 86.4 ppm and five carbons between δ 21.6–36.5 ppm indicated the presence of cyclohexyl moiety. Characteristic resonances of carbonate were found at δ 151.5 ppm; whereas, other two observable signals at δ 85.5 ppm and δ 158.5 ppm were attributed to the quaternary carbon and terminal carbon of exocyclic methylene group.

2.5.3 – Influence of glycosyl donor's stereochemistry on reactivity



Scheme 2.15: **Glycosylation reactions of α- and β- anomers of donor 44a**

Anomers **44aα** and **44aβ** were separated in order to investigate the influence of stereochemistry (α/β) of glycosyl donor on the reactivity of glycosylation reaction. Both isomers **44aα** and **44aβ** were subjected to the glycosylation with acceptor **45** under the same conditions. In both the cases, the resulting disaccharide was noticed to be having a 1,2-*trans* linkage. The reaction time, the yield of the glycosylation were found to be independent of the anomeric configuration of the initial glycosyl donor **44a** thereby signifying the intermediacy of most celebrated oxocarbenium ion intermediate during the glycosylation. (**Scheme 2.15**).

2.5.4 – Importance of alkyne functionality and Thorpe-Ingold effect

The necessity of alkyne functionality and importance of Thorpe–Ingold effect on the reactivity of glycosyl carbonate donors for gold catalyzed glycosylation reaction was investigated with a number of glycosyl carbonate donors (**44b-44i**) (**Chart 2.1**).

Various commercially available alcohols were first converted into corresponding *p*-nitrophenyl carbonates and subsequently treated with per-*O*-benzoyl α/β-D-glucopyranose to obtain various donors (**44b**-**44i**). All thus synthesized donors were

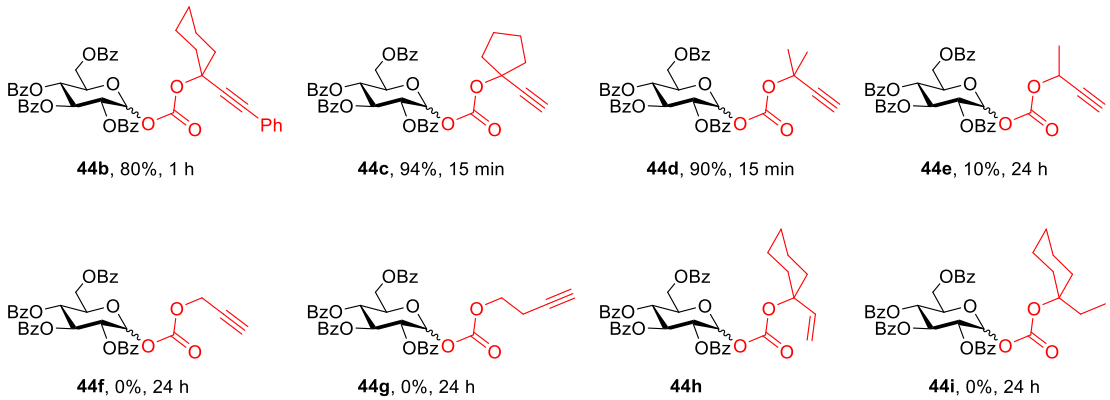


Chart 2.1: Screening of various glycosyl carbonate donors (44b-44i) for Au/Ag-catalysed glycosylation

treated with glucosyl acceptor **45** in presence of 8 mol% Au-catalyst **47** and AgOTf in CH_2Cl_2 at 25 ^{o}C. It was observed that the use of substituted alkyne donor as in **44b** resulted in the reduction of the glycosylation yield may be because of the steric crowding created by the phenyl group which potentially can reduce the coordination. The performance of the glycosylation remained as it is among the other dialkyl substituent bearing carbonate donors (**44c** and **44d**) (**Chart 2.1**). On the other hand, mono-methyl substituted donor (**44e**) diminished the reaction yield drastically. It was also observed that the propargyl carbonate donor **44f** or homopropargyl carbonate donor **44g** could not get activated under glycosylation reaction conditions even after 24h, which is in accordance with the observation reported by Yu group.[3e] All these control experiments indicate the significance of Thorpe-Ingold effect on the reactivity of carbonate donors as previously postulated.[1c] Several attempts to prepare the vinyl carbonate donor **44 h** *via* various routes miserably failed due to the unstable nature.[7] Furthermore, total inertness of the carbonate donors **44i** and **44j** towards glycosyl acceptor **45** under aforementioned standard glycosylation conditions showed the importance of the alkyne moiety during the Au-Ag catalysed glycosylation (**Chart 2.1**).

2.5.5 – Plausible reaction mechanism

Though a thorough mechanistic investigation is currently underway, a plausible mecha-

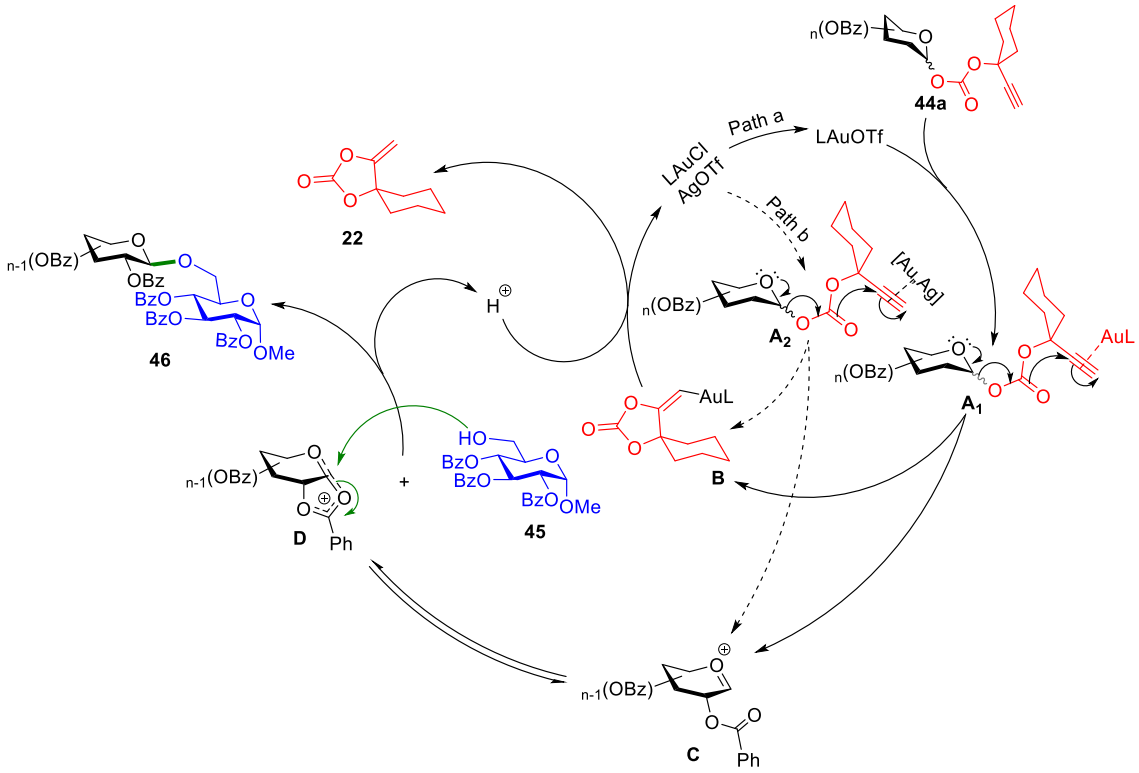


Figure 2.4: Plausible mechanism for the alkynyl carbonate glycosylation

nism can be postulated based on the control experiments and the recent literature reports on the effect of silver salts in gold catalysed reactions known as *Silver effect*.[6] Glycosylation did not undergo in presence of either Au-phosphite complex **47** or AgOTf separately, but provided quantitative glycosylation yield while using them together. So, the role of silver or the "silver effect" can be attributed to: (i) the ability of silver ion (Ag^+) to act as a chloride ion scavenger to form the active Au-catalyst [LAuOTf], where L stands for ligand and/or (ii) the capability of Ag-salts to prevent the formation of chloride-bridged dinuclear species $[LAuClAuL]^+$ which is highly unreactive in nature. As of now it is considered that the glycosylation reaction may proceed through two pathways:

Path a: Au-catalyst **47** first reacts with AgOTf to form the active [LAuOTf] complex through precipitation of AgCl thereby facilitating the coordination of [LAuOTf] active complex with the alkyne group of the donor **44a** to afford a gold–alkyne complex **A1**;

Path b: Both [Au] and [Ag] together as a bimetallic system coordinate with alkyne group to form Au/Ag–alkyne complex **A2** by arresting the formation of undesired dinuclear species $[LAuClAuL]^+$.

In either case, the triple bond gets activated to promote the cyclization of 1-ethynylcyclohexyl carbonate to release the *spiro*-cyclic vinylgold cyclic carbonate **B** and the oxocarbenium ion **C**. The intermediate **C** further gets stabilized through neighboring-group participation from *C*-2 benzoyl ester group to form the trioxolenium ion **D**. Further reaction of the glucosyl acceptor **45** as a nucleophile with the trioxolenium ion **D** intermediate results in the disaccharide product **46** through the generation of a proton (H^+) which will captured by the vinyl-gold cyclic carbonate **B** to undergo protodeauration resulting in *spiro*-cyclic compound **22** as by-product and thus regenerating the reactive catalyst for the next cycle.

2.5.6 – Substrates scope

2.5.6.1 – Synthesis of various *O*-glycosides

The excellent disaccharide product yield in case of glucosyl ethynylcyclohexyl carbonate donor **44a** inspired us to extend the scope of this productive methodology to other pyranosyl donors as well for which a number of glycosyl carbonate donors (compounds **44j**-**44q**) have been synthesized utilizing the optimized carbonate donor preparation procedure. Scope of the current developed methodology was initially explored with various monosaccharide glycosyl carbonates (**44a, 44j**-**44q**) and aglycons (**15**[1f], **39**, **45**, **48**[8a] and **49**) under the optimized glycosylation conditions (**Scheme 2.16**). Gratifyingly, disaccharides **50** and **51** in high yields were isolated when glucosyl carbonate **44a** was treated with glycosyl acceptors bearing a secondary -OH group (**15** and **48**).

Furthermore, Carbonate donor **44a** was allowed to react with alicyclic alcohol **49** and benzylic alcohol **39** to produce the desired glucosides **52** (94%) and **53** (93%) respectively with exclusive 1, 2-*trans* stereoselectivity. Similar set of reactions were performed using galactose, mannose and rhamnose carbonate donors **44j**-**44l** with primary or secondary -OH group bearing glycosyl acceptors (**15**, **45** and **48**) to afford corresponding disaccharide products (**54**-**61**) with more than 90% yields in all cases (**Scheme 2.16**). Successful synthesis of all the glycoside products (**50**-**65**) was confirmed by ^{1}H, ^{13}C and DEPT NMR along with HRMS analysis. Exclusive formation of 1, 2-*trans* glycosides for all *C*-2-OBz protected glycosyl carbonate donors showed neighboring group participation. On the other hand, treatment of per-*O*-benzyl protected

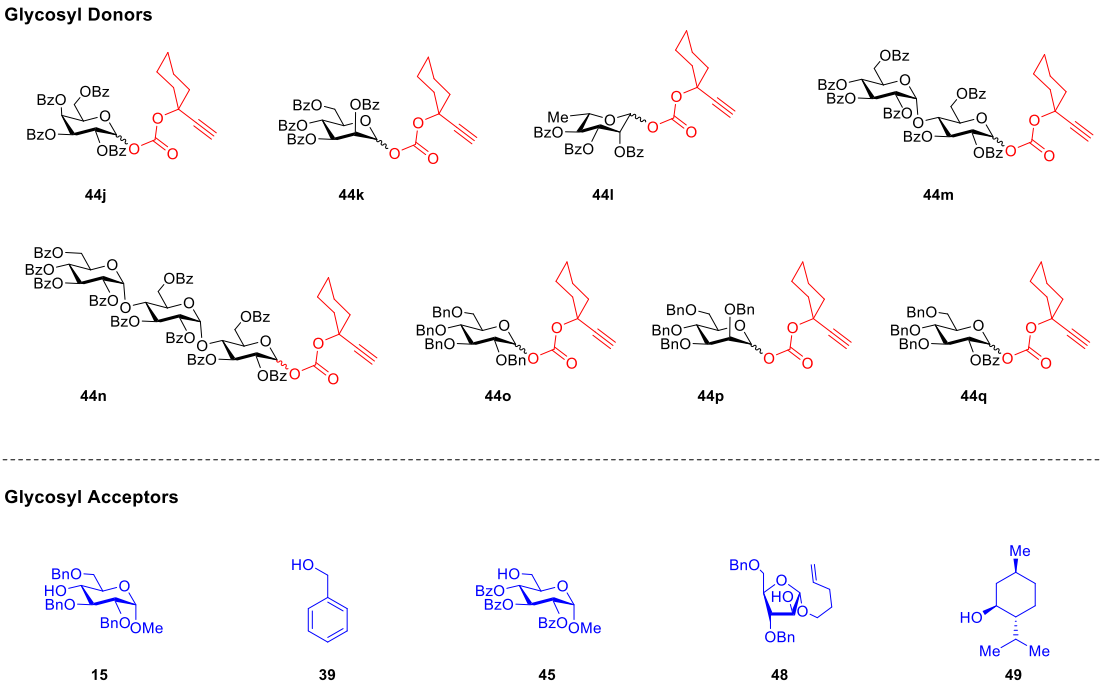
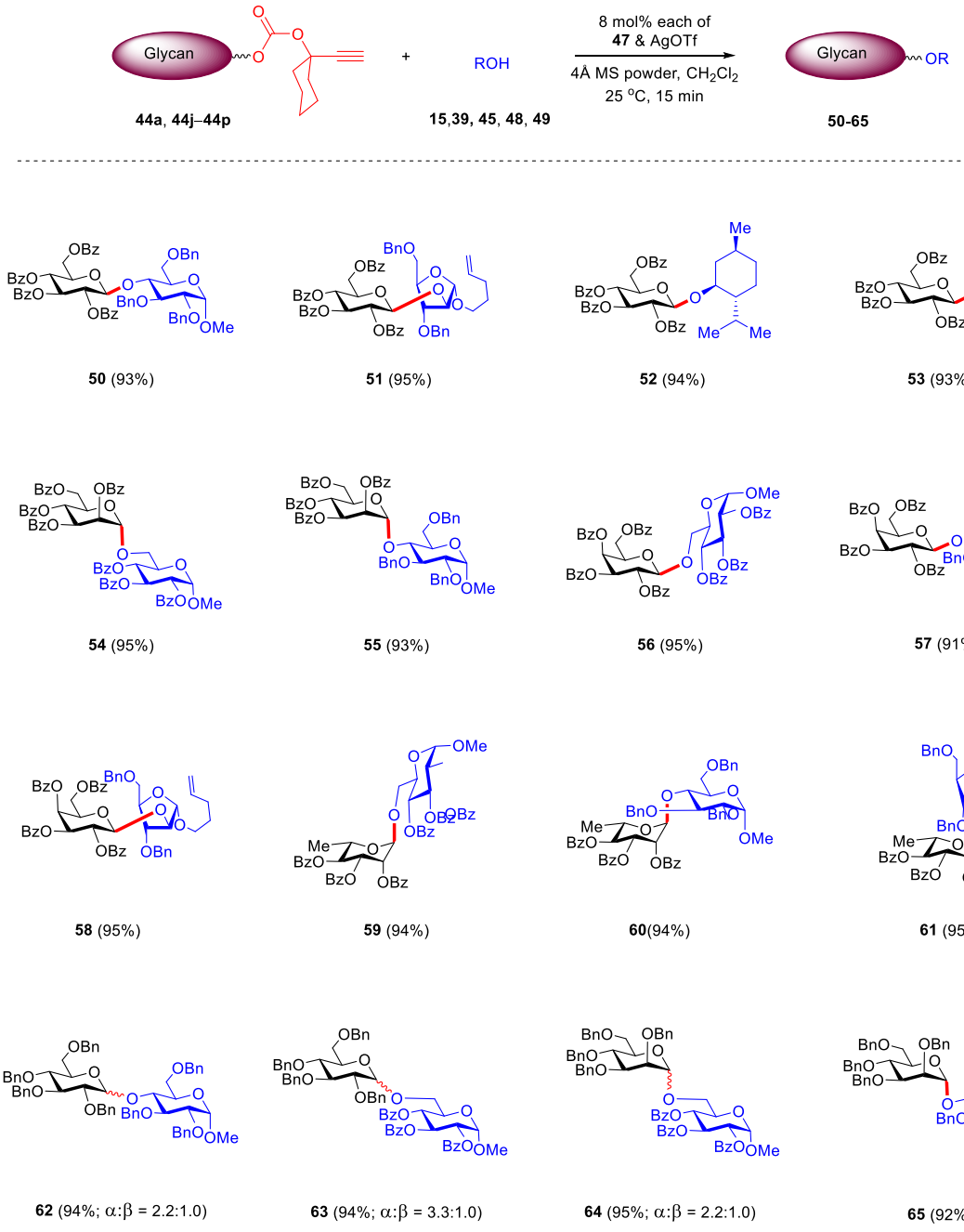


Chart 2.2: List of glycosyl donors and aglycons

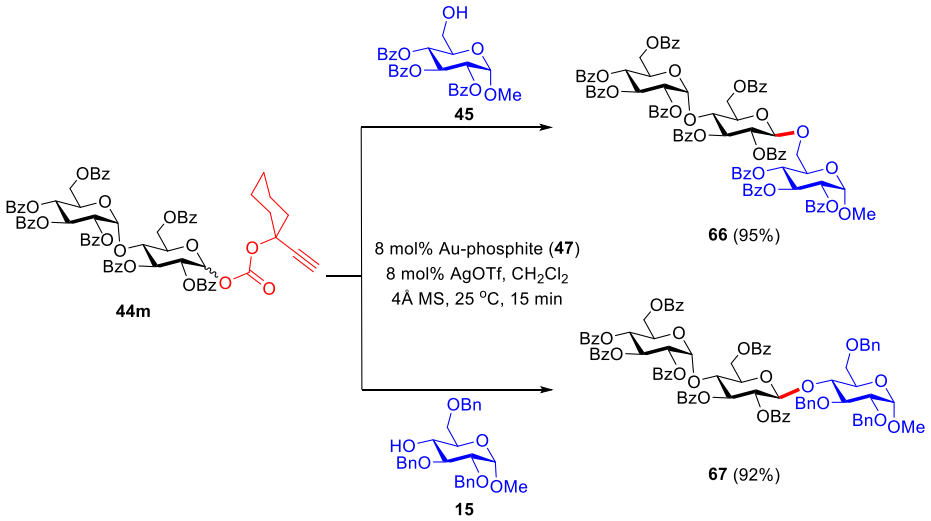
glucosyl carbonate donor **44o** with acceptor **15** under optimized Au-Ag catalysed glycosylation conditions provided disaccharide **62** as α/β (2.2:1.0) mixture with 94% yield. Similar reaction between donor **44o** and acceptor **45** resulted in the formation of disaccharide **63** as a α/β (3.3:1.0) mixture in favor of α-selectivity. Likewise, per-*O*-benzyl protected mannosyl carbonate donor **44p** on reaction with acceptor **45** produced glycoside **64** as α/β (2.2:1.0) mixture whereas acceptor **15** resulted in α-disaccharide **65** exclusively.

The versatility of the newly developed glycosylation protocol was explored for the synthesis of disaccharide and trisaccharide donor levels as well. For this purpose, maltose carbonate donor **44m** was reacted with primary sugar alcohol **45** as well as secondary sugar alcohol **15** as acceptors in the presence of 8 mol% each of Au-catalyst **47** and AgOTf each in CH_2Cl_2 at 25 ^{0}C. By our surprise, we found that the trisaccharide products (**66** and **67**) yields are also more than 90% (95% and 92% respectively) in both the cases and the TLC of these reaction mixtures clearly showed that the glycosylation reaction time is only 15 minutes (**Scheme 2.17**). The formation of the trisaccharide compounds **66** and **67** were confirmed by the NMR and mass-spectroscopy tools.



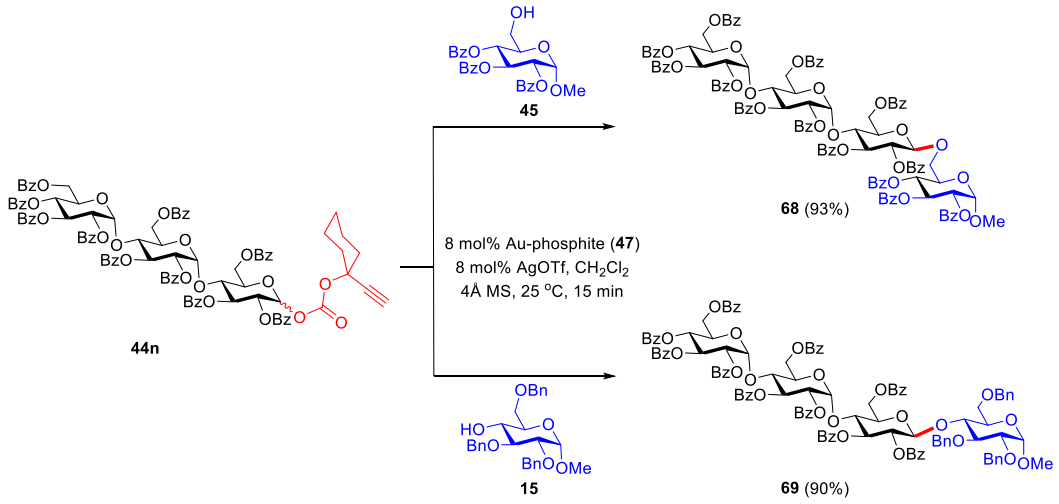
Scheme 2.16: Synthesis of various *O*-glycosides using carbonate donor chemistry

In the ^{1}H NMR of compound **66**, three anomeric protons were found to resonate at δ 4.92 (d, *J* = 2.4 Hz), 4.94 (d, *J* = 1.5 Hz) and 5.73 (d, *J* = 3.9 Hz) ppm. Whereas in the ^{13}C NMR spectrum, two anomeric carbons were noticed at δ 96.5 ppm and one anomeric carbon at δ 101.4 ppm. The coupling constant values of anomeric protons in ^{1}H NMR along with the position of anomeric carbons in ^{13}C NMR clearly showed the presence of two α- and one β- glycosidic linkage in the trisaccharide compound.



Scheme 2.17: Synthesis of trisaccharides under [Au]/[Ag] catalysed glycosylation

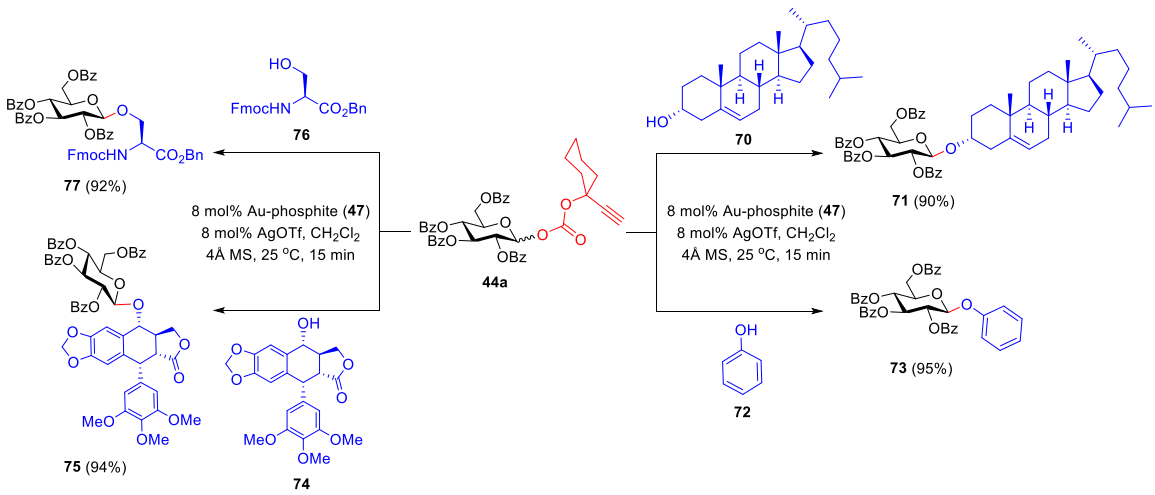
Occurrences of characteristic carbon peaks for one -O<u>C</u>H$_3$ at δ 55.1 ppm and for ten -OBz protecting groups between δ 128.3–162.2 ppm along with the fifteen carbon peaks from three sugar rings betweenδ 62.6–75.0 ppm are in accordance with the assigned trisaccharide structure. The ^{1}H, ^{13}C and DEPT NMR spectral analysis also strongly confirmed the formation of a single trisaccharide diastereomer during the course of the glycosylation. Similarly, in the ^{13}C NMR spectrum of compound **67**, presence of three anomeric carbons at δ 96.0, 98.5 and 100.2 ppm along with other residual corresponding peaks confirmed the formation of trisaccharide compound **67**.



Scheme 2.18: Synthesis of tetrasaccharides under [Au]/[Ag] catalysed glycosylation

Motivated by this result, we also performed the glycosylation reaction of maltotriose carbonate donor **44n**, a trisaccharide donor with the sugar acceptors **45** and **15**, previously used for trisaccharides preparation under Au-Ag catalysis and the results were quite inspiring. Gratifyingly, the desired tetrasaccharides **68** and **69** were produced in 93% and 90% respectively with excellent diastereoselectivity (**Scheme 2.18**). Both the tetrasaccharides **68** and **69** were confirmed by NMR and mass spectrometric analysis. Presence of four anomeric protons resonances at δ 4.90 (J = 7.6 Hz), 4.94 (J = 3.6 Hz), 5.59 (J = 3.9 Hz) and 5.76 (d, J = 3.7 Hz) ppm as doublets in the ^{1}H NMR spectrum andcharacteristic four anomeric carbon signals at δ 96.5, 96.5, 96.8 and 101.2 ppm in the ^{13}C NMR spectrum along with other remaining signals suggested that the tetrasaccharide **68** has three α- and one β- glycosidic linkages which perfectly matched with the assigned structure. In addition to the NMR spectroscopic analysis, successful synthesis of tetrasaccharide **68** was also confirmed by HRMS analysis, *m*/*z* calculated for $C_{116}H_{96}O_{34}Na^{+}$, [M+$Na^{+}$]: 2055.5681; Found: 2055.5711. In a similar way, successful preparation of tetrasaccharide **69** was confirmed by ^{1}H, ^{13}C and DEPT NMR spectral analysis along with HRMS analysis, *m*/*z* calculated for $C_{116}H_{102}O_{31}Na^{+}$, [M+$Na^{+}$]: 2013.6303; Found: 2013.6343.

The utility of the newly developed alkynyl carbonate donor has been explored for the syntheses of various other *O*-glycosides (**71**, **73**, **75** and **77**) under optimized Au-Ag catalyzed glycosylation reaction conditions. Per-*O*-benzoyl carbonate glucoside **44a** was found to be an excellent donor for the synthesis of cholesteryl glucoside **71** and phenolic glucoside **73** in presence of cholesterol and phenol as acceptors respectively (**Scheme 2.19**). Formation of the cholesteryl glucoside **71** and phenolic glucoside **73** was confirmed by NMR and mass spectrometric analysis. Presence of anomeric carbon resonances at δ 99.7 ppm and characteristic signals of aromatic carbons between δ 117.3 and 123.4 ppm in the ^{13}C NMR spectrum along with anomeric proton resonances at δ 5.46 (J = 7.7 Hz) ppm as a doublet in the ^{1}H NMR spectrum clearly showed the formation of phenolic glucoside **73**. In a similar way, the *epi*-podophyllotoxin 4-*O*-glucoside **75** and serinyl glucoside **77** were conveniently synthesized from carbonate **44a** in 15 min at 25 ^{0}C by using corresponding alcohols (**74** and **76**[2a]) and 8 mol% each of catalyst **47** and AgOTf with 92% and 94% yield respectively (**Scheme 2.19**). Formation of the *epi*-podophyllotoxin 4-*O*-glucoside **75**[8b] was confirmed from the ^{1}H, ^{13}C and DEPT NMR spectral and HRMS analysis which



Scheme 2.19: Synthesis of biologically important *O*-glycosides

was in perfectly matching with the reported one. In the ^{1}H NMR of compound **77**, the aromatic protons for -Fmoc and -OBn protecting group of serine amino acid moiety were found to resonate between δ 7.21–7.86 ppm as multiplets along with residual -OBz protecting groups. Whereas in the ^{13}C NMR spectrum, characteristic aromatic carbons for -Fmoc protecting group found to resonate at δ 120.1, 141.4 ppm and between δ 139.8–144.0 ppm along with characteristic peak for carbamate at δ 156.0 ppm. Likewise, characteristic carbon of benzyl ester from serine moiety was also noticed to resonate at δ 169.4 ppm along with four benzoyl ester protecting group between δ 165.2–166.2 ppm and anomeric carbon at δ 101.4 ppm from the sugar residue. All this data clearly confirmed the successful formation of the serenyl glucoside **77**.

2.5.6.2 – Synthesis of various *C*-glycosides

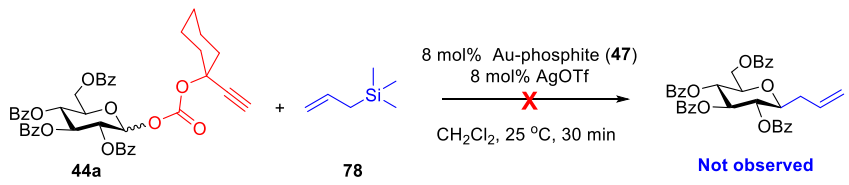
Wide availability of *C*-glycosides as natural metabolites with great structural diversity and versatile biological activities inspired the synthetic carbohydrate chemists to develop various strategies for replacement of the glycosidic *C*-*O* acetal linkage with a *C*-*C* linkage.[9] The synthesis *C*-glycosides as a mimic of *O*-glycosides not only provide metabolically stable carbohydrate mimics but are also of great therapeutic promises.[10] Few decades of research culminated in the development of a large number of glycosylation protocols but use of harsh reaction conditions or poor yields or tedious work-up process limited their application beyond monosaccharide level.[9,11] Whereas, a

versatile protocol for the *C*-glycoside synthesis by the modification of the *O*-glycosylation protocols using conventional glycosyl donors and *C*-nucleophiles instead of *O*-nucleophiles is of high importance.[9,10]

In 2015, a gold (III)-catalysed glycosylation with allyl trimethylsilane to afford the allyl *C*-glycoside was reported by Balamurugan *et al*. in moderate yield.[12a] Recently, Biao Yu *et al.* showed the development of a *C*-glycosylation protocol using glycosyl *ortho*-hexynylbenzoates as donors and allyl trimethylsilane or silyl enol ethers as *C*-nucleophiles in presence of $Ph_3PAuNTf_2$ catalyst with high yields and stereoselectivity. In-depth study on the reaction mechanism of the *C*-glycosylation protocol has also revealed the crucial role of moisture sequestered by the molecular sieves in the catalytic cycle.[12b]

After successful implementation of the newly developed glycosylation protocol for the synthesis of various types of *O*-glycosides, we got interested in exploring the utility of our current protocol for *C*-glycosides synthesis using alkynyl glycosyl carbonates donors with allyl trimethylsilane or silyl enol ethers.

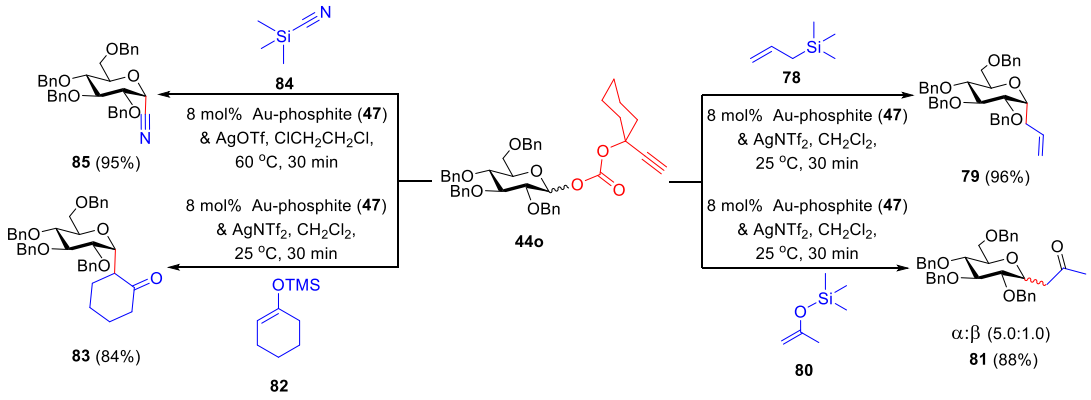
At first, glucosyl carbonate donor **44a** was used to performed the *C*-glycosylation with allyl trimethylsilane (**78**) (2 equiv.) in the presence of 8 mol% each of Au-phosphite complex **47** and AgOTf and 4Å MS in CH_2Cl_2 at 25 ^oC. The reaction yielded a complex mixture of products with none of the compounds matched with that of desired allyl *C*-glucoside (**Scheme 2.20**). Replacement of co-catalyst from AgOTf to $AgNTf_2$ did not improve the outcome. So, we moved to the more reactive per *O*-benzyl glucosyl alkynyl carbonate donor **44o** and carried out the glycosylation reaction with allyl trimethylsilane **78**; gratifyingly, expected allyl *C*-glucoside **79** was formed with



Scheme 2.20: Glycosylation of carbonate donor 44a and allyl trimethylsilane 78

complete α-selectivity albeit in very low yield (20%).[11,12b] However, increasing the amount of allyl trimethylsilane up to 6 equivalents provided the allyl *C*-glycoside **79** in quantitative yield. Interestingly, use of 8 mol% $AgNTf_2$ instead of 8 mol% AgOTf

greatly enhanced the glycosylation yield up to 80% without the addition of **78** in excess. Further optimization of the number of equivalents of nucleophile revealed that 3 equivalents of **78** is enough for the maximum yield (96%). Decomposition of allyl trimethylsilane **78** within very short period of time in presence of AgOTf might be the reason for low glycosylation product yield.[12b] Presence of characteristic resonances of allyl carbons (–$\underline{C}H_2$–$\underline{C}H$=$\underline{C}H_2$) at δ 29.9, 117.0 and 134.8 ppm respectively in the ^{13}C NMR spectrum and anomeric proton resonances at δ 4.14 (dt, *J* = 10.2, 5.1, 1H) ppm along with characteristic allylic proton (–CH_2–$C\underline{H}$=CH_2) at δ 5.82 (ddt, *J* = 17.2, 10.2, 6.8 Hz, 1H) ppm in the ^1H NMR spectrum clearly showed the formation of allylic *C*-glucoside **79** with complete α-selectivity.



Scheme 2.21: Synthesis of various *C*-glycosides

Next, we explored the Au-Ag catalysed *C*-glycosylation protocol with commercially available silyl enol ethers (**80** and **82**) and cyano trimethylsilane (**84**) as *C*-nucleophiles (**Scheme 2.21**). On treatment of carbonate donor **44o** with silyl enol ether **80** and **82** under previously optimized reaction condition (i.e. 8 mol% each of Au-phoshphite **47** and $AgNTf_2$, 4 Å MS powder, CH_2Cl_2, 25 °C, 30 min) afforded the desired *C*-glycoside **81** as α/β (5.0:1.0) mixture with 88% yield and *C*-glycoside **83** in 84% yield with complete α-selectivity. In the ^{13}C NMR spectrum of compound **81**, characteristic resonances corresponding to the 2-propanone moiety were noticed around at δ 30.1 and 41.1 ppm whereas anomeric carbon was observed to resonate at δ 87.3 ppm. Observation of other characteristic resonances were also in complete agreement with the assigned structure of compound **81**. Similarly in the ^{13}C NMR spectrum of compound **83**, presence of characteristic resonance at δ 211.8 ppm corresponding to the

carbonyl carbon of cyclohexanone moiety along with anomeric carbon observed at δ 79.9 ppm confirmed the formation of compound **83**.

Under similar condition, glycosylation between cyanotrimethylsilane (**84**) and carbonate donor **44o** did not proceed at all. The carbonate donor **44o** was recovered as such. However, raising temperature of the reaction up to 40 ^{o}C led to the desired cyanoglucoside **85** in moderate yield (40%) with complete α-selectivity. Nevertheless, switching the solvent from CH_2Cl_2 to $ClCH_2CH_2Cl$ and heating the reaction mixture to 60 ^{o}C with 3 equivalents of **84** resulted in the isolation of desired compound **85** in excellent yield (95%) with exclusive α-selectivity. Formation of cyanoglucoside **85** was confirmed by the ^{1}H, ^{13}C and DEPT NMR spectrum along with HRMS analysis.

2.5.6.3 – Synthesis of various *N*-glycosides

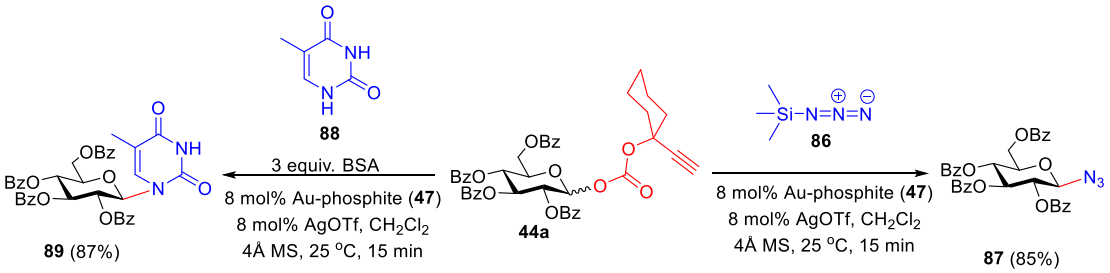
N-glycosides are the second most abundant glycosides in nature after *O*-glycosides. When anomeric carbon of a sugar residue is connected to an aglycon through a nitrogen atom then these kinds of glycosides are produced. Nucleosides and glycosyl amides are among the most celebrated *N*-glycosides in Nature. Nucleosides are the basic building blocks of DNA/RNA involved in the genetic storage of information and transfer it from one generation to the next. These are also indispensable constituents of co-factors which play key roles in enzyme mediated biochemical transformation and a variety of antiviral and antitumor drugs. Synthesis of modified nucleosides have also gained much attention due to its wide spread applications as therapeutic potential.[13] Similarly in recent years, the synthetic 1-aminosugar moiety caught considerable attention in pharmaceutical industry because of its unique physical, chemical and biochemical properties which arise due to the presence of sugar moiety connected to the biologically active quinolin-2-one core.[14]

Glycosyl amides are widely available in *N*-linked glycoproteins and proteoglycans which play crucial role in many biological processes such as immune defence, viral replication, cell-cell adhesion, inflammation and cell growth *etc*.[15a] Along with this, synthetic glycopeptides are having enormous potential for the development of new vaccines against various life threatening diseases.[15b] In the *N*-linked glycoproteins, sugar residues are usually connected to the nitrogen atom present on the amide side-chain of asparagine or glutamine. This glycosyl amide bond can be prepared either by

direct coupling of amide group of amino acids and amide functional group containing moieties or through azido glycoside intermediate. The azido glycosides are another important class of *N*-glycosides which act as very useful intermediates for the synthesis of various glycosyl amides, *N*-glycosyl triazole and glycoconjugates.[16]

Over a period of time, several glycosyl donors and glycosylation methods have been developed for various azido glycosides,[17] nucleosides,[18] 1-amidosugars[19] and glycosyl amides[20] synthesis. However, very poor yields of the desired *N*-glycosides and limited substrates scope restricted their use for further explorations. One of the main reasons for the limited synthetic access of *N*-glycosides (except azido glycosides) may be due to the very poor solubility and poorly nucleophilic nature of *N*-nucleophiles and competitive glycosylation reaction with other nucleophiles that generated from the leaving groups or promoters.

These considerations provoked us to try our glycosyl alkynyl carbonate donors for *N*-glycoside synthesis as well as these donors have already proven to be beneficial for the *C*-glycoside synthesis as the extruded by-product is non-competitive in the glycosylation. Initially, glucosyl carbonate donor **44a** was treated with azido trimethylsilane **86** under 8 mol% each of Au-phosphite complex **47** and AgOTf and 4 Å MS powder in CH_2Cl_2 at 25 ^{o}C resulted in the corresponding azido glucoside **87** with

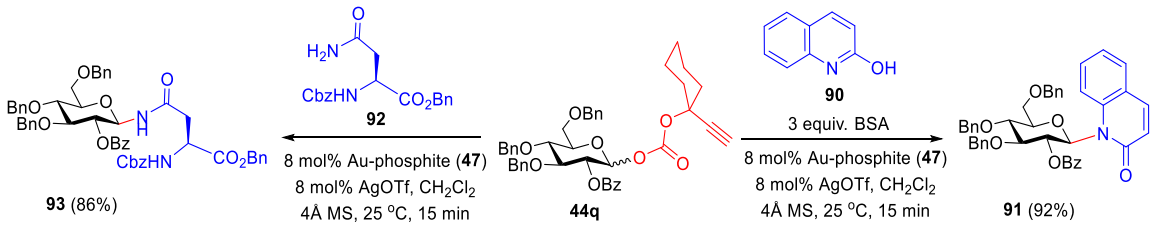


Scheme 2.22: Synthesis of *N*-glycosides using carbonate donor 44a

85% yield (**Scheme 2.22**). Later, the same protocol was applied for the synthesis of thiamine glucoside **89**, but failed to produce the desired product miserably.This was because of the poor solubility of thiamine nucleobase **88** in CH_2Cl_2. So, to solubilize the nucleobase 3 equivalents of BSTFA was added to thiamine nucleobase **88** in CH_2Cl_2 first and refluxed in a sealed pressure tube at 60 ^{o}C for 6 h. Further, sequential addition of glucosyl carbonate donor **44a**, 4 Å MS and 8 mol% each of Au-phosphite complex **47** and AgOTf led to the thiamine nucleoside **89** within 15 minutes in 87% yield

(**Scheme 2.22**). Formations of both the *N*-glycosides (**87** and **89**) were confirmed by the ^{1}H, ^{13}C NMR spectrum along with HRMS analysis.

Further, the super armed glucosyl carbonate donor **44q** was utilized for the synthesis of 1-amidosugar such as *N*-glucosyl quinolin-2-one **91** in 92% yield (**Scheme 2.23**). Preparation of the glucosyl amide **93** was also achieved by reacting carbonate donor **44q** with protected asparagine moiety **92** under the same Au-Ag catalysed glycosylation condition. Use of super armed glycosyl donor **44q** permitted the glycosylated product in excellent yield (80%) with complete 1,2-*trans* selectivity (**Scheme 2.23**). Addition of BSTFA or heating the reaction mixture or even both did not



Scheme 2.23: Synthesis of *N*-glycosides using carbonate donor 44q

improved the yield further. Formations of both the *N*-glycosides (**91** and **93**) were confirmed by the ^{1}H, ^{13}C NMR spectrum along with HRMS analysis. In the ^{13}C NMR spectrum of compound **91**, presence of characteristic anomeric carbon at δ 83.9 ppm along with resonance at δ 162.6 ppm corresponding to the *N*-quinoline-2-one moiety confirmed the formation of *N*-glycoside **91**. In addition, compound **91** was further confirmed by HRMS analysis, *m/z* calculated for $C_{43}H_{39}NO_7Na^+$, [M+Na^+]: 704.2624; Found: 704.2620. Similarly in the ^{13}C NMR spectrum of compound **93**, characteristic anomeric carbon was noticed at δ 81.1 ppm. Presence of three carbonyl carbons at δ 156.4, 169.9 and 170.9 ppm corresponding to asparagine moiety along with carbonyl carbon of –Bz group at δ 155.9 ppm revealed the formation of *N*-glycoside **93**. Furthermore, HRMS analysis (*m/z* calculated for $C_{53}H_{52}N_2O_{11}Na^+$, [M+$Na^+$]: 915.3469; Found: 915.3468) of compound **93** also confirmed its synthesis.

2.6 – Conclusions

In conclusion, we have identified alkynyl glycosyl carbonates as glycosyl donors that are: (1) easy to prepare from very cheap starting materials; (2) stable solid compounds,

can be stored for several months at room temperature; (3) get activated in catalytic amounts (8 mol%) of Au & Ag catalyst; (4) produce glycosides with excellent yields in just 15 minutes; (4) proven to be excellent for the synthesis of various *O*-, *C*- and *N*-glycosides which are otherwise cumbersome to synthesize; and hence (6) highly suitable for oligosaccharide synthesis in very short period of time.

This newly developed glycosylation protocol not only provides stereoselective 1,2-*trans* glycoside products exclusively for carbonate donors bearing NGP protecting group (e.g. esters) at *C*-2 position but also allowed to synthesize some 1,2-*cis* glycosides in case of carbonate donors with ethers at *C*-2 position.

This simple, easy, scalable and stereoselective methodology can overcome some of the the drawbacks of the existing glycosyl donors.

Note: Characterization data and full spectral charts for all compounds excluding compound no **44q**, **75**, **79**, **81**, **83**, **85**, **91** and **93** can also be found in *Angew. Chem. Int. Ed.* **2016**, *128*, 7917–7922. Characterization data for **44q**, **75**, **79**, **81**, **83**, **85**, **91** and **93** is provided herein.

2.7 – Experimental section

Synthesis of 1-Ethynylcyclohexyl 4-nitrophenyl carbonate (**42**): To an ice cold solution of commercially available 1-ethynylcyclohexanol **41** (10 g, 80.50 mmol) in anhydrous CH_2Cl_2 (80 mL) was added pyridine (40 mL, 0.50 mol) and stirred for 15 min. A solution of *p*-nitrophenyl chloroformate (21.10 g, 0.10 mol) in anhydrous CH_2Cl_2 (50 mL) was added drop-wise and stirred at 0 ^oC for 20 min. Subsequently, the reaction mixture was stirred at 25 ^0C for 2.5 h. The reaction was stopped by the addition of 2N HCl (500 mL) and extracted into CH_2Cl_2 (2x200mL), the combined CH_2Cl_2 layers was washed with saturated $NaHCO_3$ solution (50mL) followed by brine solution. CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain a pale yellow coloured solid that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford compound **5** (19.8 g, 85%) as a white solid.

General procedure for synthesis of ethynylcyclohexylglycosyl carbonate donors (44a-44o): To a rapidly stirring ice cold solution of hemiacetal (1 mmol) in anhydrous CH_2Cl_2 was added DBU (2 mmol) and stirred for 20 min. A solution of above prepared compound **42** (1 mmol) in anhydrous CH_2Cl_2 was added drop-wise and stirred at 0 ^oC for 30 min. Subsequently, the reaction mixture was stirred at 25 ^0C for another 2 h. After complete consumption of the hemiacetal, the reaction was concentrated *in vacuo* to obtain an oily residue that was partially purified by silica gel column chromatography (*n*-hexane/EtOAc). Fractions containing ethynylcyclohexylglycosyl carbonate donor along with trace quantities of *p*-nitro phenol were concentrated *in vacuo*. The crude residue was redissolved in CH_2Cl_2 and washed with an aqueous saturated $NaHCO_3$ solution to remove *p*-nitro phenol and obtain pure glycosyl alkynyl carbonate donor **44a-44o** in 90-96% yield.

General glycosylation procedure for synthesis of *O*-glycosides (46, 55-69, 71, 73, 75, 77): To a solution of glycosyl donor (1.0 mmol) and acceptor (1.0 mmol) in anhydrous CH_2Cl_2 was added freshly activated 4Å MS powder (50 mg/mL) and stirred for 10 min at 25 ^0C. Au-phosphite **47** (8 mol%) and AgOTf (8 mol%) were added to the reaction mixture and stirred for 15 min at 25 °C. After completion of the reaction, Et_3N was added and filtered through a bed of Celite®. The filtrate was concentrated *in vacuo* and

the resulting residue was purified by column chromatography (*n*-hexane/EtOAc) to afford the desired *O*-glycoside in 92-98% yield.

General glycosylation procedure for synthesis of *C*-glycosides (79, **81**, **83):** To a solution of glycosyl donor **44o** (1.0 mmol) in anhydrous CH_2Cl_2 was added freshly activated 4Å MS powder (50 mg/mL) and stirred for 10 min at 25 ^{0}C. Subsequently, acceptor (2.0-3.0 mmol) was added and stirred for another 5 min. Au-phosphite **47** (8 mol%) and $AgNTf_2$ (8 mol%) were added to the reaction mixture and stirred at 25 °C for 30 min. After completion of the reaction, Et_3N was added and filtered through a bed of Celite®. The filtrate was concentrated *in vacuo* and the resulting residue was purified by column chromatography (*n*-hexane/EtOAc) to afford the desired *C*-glycoside in 84-96% yield.

Synthesis of 1-*deoxy*-1-Cyano 2,3,4,6-tetra-*O*-benzoyl α-D-glucopyranoside (85): To a solution of glycosyl donor **44o** (200 mg, 0.29 mmol) in anhydrous $ClCH_2CH_2Cl$ (4 mL) was added freshly activated 4Å MS powder (200 mg) and stirred for 10 min at 25 ^{0}C. Subsequently, Cyanotrimethylsilane (**84**) (110 μL, 0.87 mmol) was added and stirred for another 5 min. Au-phosphite **47** (20 mg, 23.2 μmol) and AgOTf (6 mg, 23.2 μmol) were added to the reaction mixture and stirred at 60 °C for 30 min. After completion of the reaction, Et_3N was added and filtered through a bed of Celite®. The filtrate was concentrated *in vacuo* and the resulting residue was purified by column chromatography (*n*-hexane/EtOAc) to afford the cyanoglucoside (152 mg, 95%) as colourless syrup.

Synthesis of 1-*deoxy*-1-Azido 2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranoside (**87**): AgOTf (5.5 mg, 21.4 μmol) and Au-phosphite (**47**) (18.8 mg, 21.4 μmol) were added to a solution of donor **44a** (200 mg, 0.27 mmol) and Azidotrimethylsilane (**86**) (285 μL, 2.2 mmol) in anhydrous CH_2Cl_2 (4mL) containing 4Å MS powder (200 mg) and stirred at 25 ^{0}C for 15min, concentrated *in vacuo*, and resulting residue was purified by column chromatography (*n*-hexane/EtOAc) to afford azido glucoside **87** (142 mg, 85%) as a white solid.

The same procedure was repeated for the synthesis of compounds **93**.

Synthesis of 1-*deoxy*-1-Thymine-2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranoside (89): Commercially available Bis(trimethylsilyl) acetamide (197 μL, 0.80 mmol) and

Thymine (**88**) (34 mg, 0.27 mmol) in CH_2Cl_2 (7 mL) were stirred at 25 ^{0}C until a clear solution is obtained (~30min). Subsequently, 4Å MS powder (150 mg) and donor **44a** (200 mg, 0.27 mmol) were added to this solution. AgOTf (5.5 mg, 21.4 μmol) and Au-phosphite (**47**) (18.8 mg, 21.4 μmol) were added and stirred at 25 ^{0}C for 15min, concentrated *in vacuo*, and resulting residue was purified by column chromatography (*n*-hexane/EtOAc) to afford thymine glucoside **89** (164 mg, 87%).

The same procedure was repeated for the synthesis of compounds **91**.

Compound **39**, **41**, **47**, **49**, **70**, **72**, **74**, **76**, **78**, **80**, **82**, **84**, **86**, **88**, **90** and **92** were purchased from Sigma-Aldrich.

1-Ethynylcyclohexyl 4-nitrophenyl carbonate (**42**): mp (^{0}C): 82.3; IR (cm^{-1}, $CHCl_3$): 3290, 2940, 2863, 1770, 1593, 1493, 1268, 1206, 1008, 771; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.39 (dtt, *J* = 13.7, 9.3, 4.3 Hz, 1H), 1.54 – 1.63 (m, 1H), 1.64 – 1.80 (m, 4H), 1.91 – 2.04 (m, 2H), 2.17 – 2.34 (m, 2H), 2.72 (s, 1H), 7.44 – 7.40 (m, 2H), 8.30 – 8.26 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.6, 22.6, 24.9, 36.8, 36.8, 75.9, 79.7, 82.0, 121.8, 121.8, 125.2, 125.2, 145.2, 149.8, 155.5; HRMS (ESI-MS): m/z calcd for $[C_{15}H_{15}NO_5Na]^+$: 312.0848; Found: 312.0846.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α-D-glucopyranoside (**44aα**): mp (^{0}C): 62.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +41.6; IR (cm^{-1}, $CHCl_3$): 2939, 1729, 1451, 1362, 1264, 1100, 899, 756, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.26 – 1.35 (m, 1H), 1.46 – 1.68 (m, 5H), 1.71 – 1.91 (m, 2H), 2.00 – 2.10 (m, 1H), 2.14 – 2.22 (m, 1H), 2.38 (s, 1H), 4.46 (dd, *J* = 12.1, 4.3 Hz, 1H), 4.58 – 4.70 (m, 2H), 5.56 (ddd, *J* = 10.2, 3.7, 0.8 Hz, 1H), 5.79 (t, *J* = 9.8 Hz, 1H), 6.24 (t, *J* = 10.0 Hz, 1H), 6.51 (d, *J* = 3.7 Hz, 1H), 7.25 – 7.32 (m, 2H), 7.33 – 7.39 (m, 4H), 7.39 – 7.46 (m, 3H), 7.47 – 7.59 (m, 3H), 7.84 – 7.90 (m, 2H), 7.91 – 7.99 (m, 4H), 8.03 – 8.10 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.5, 22.6, 24.9, 36.6, 36.7, 62.5, 68.8, 70.2, 70.4, 70.5, 75.3, 78.9, 82.2, 92.6, 128.3, 128.3, 128.3, 128.4, 128.4, 128.4, 128.6, 128.6, 128.7, 128.7, 128.9, 129.6, 129.7, 129.7, 129.8, 129.8, 129.9, 129.9, 130.1, 130.1, 133.2, 133.3, 133.4, 133.5, 150.6, 165.1, 165.3, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2263.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranoside (**44aβ**): mp (^{0}C): 66.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +41.5; IR (cm^{-1},

$CHCl_3$): 3294, 2941, 1731, 1453, 1369, 1267, 1099, 1023, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.15 – 1.30 (m, 1H), 1.38 – 1.64 (m, 5H), 1.66 – 1.78 (m, 1H), 1.83 (ddd, *J* = 13.2, 9.4, 3.8 Hz, 1H), 1.95 – 2.05 (m, 1H), 2.05 – 2.17 (m, 1H), 2.47 (s, 1H), 4.31 (ddd, *J* = 9.7, 5.0, 3.1 Hz, 1H), 4.52 (dd, *J* = 12.3, 5.0 Hz, 1H), 4.64 (dd, *J* = 12.3, 3.1 Hz, 1H), 5.68 (dd, *J* = 9.5, 8.1 Hz, 1H), 5.75 (t, *J* = 9.6 Hz, 1H), 5.95 (t, *J* = 9.5 Hz, 1H), 6.03 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.33 (m, 3H), 7.33 – 7.39 (m, 3H), 7.39 – 7.45 (m, 3H), 7.46 – 7.58 (m, 3H), 7.81 – 7.87 (m, 2H), 7.88 – 7.93 (m, 2H), 7.92 – 8.00 (m, 2H), 8.01 – 8.10 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.3, 22.4, 24.8, 36.5, 36.5, 62.7, 69.0, 70.9, 72.8, 73.2, 75.3, 78.9, 82.2, 95.2, 128.3, 128.3, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.7, 128.7, 128.9, 129.6, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 130.0, 130.0, 133.1, 133.3, 133.4, 133.5, 150.9, 164.9, 165.1, 165.7, 166.1; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2264.

1-*O*-(((1-(phenethynyl)cyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α/β-D-glucopyranoside [α:β (1:1.5)] (44b): mp(^{0}C): 58.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +58.5; IR (cm^{-1}, $CHCl_3$): 3065, 2927, 1725, 1610, 1452, 1260, 1107, 1027, 962, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.28 – 1.40 (m, 2H), 1.43 – 1.57 (m, 5H), 1.58 – 1.66 (m, 5H), 1.75 – 1.99 (m, 4H), 2.16 – 2.35 (m, 4H), 4.27 – 4.36 (m, 1H), 4.42 – 4.48 (dd, J = 12.3, 4.6 Hz, 1H), 4.51 (dd, J = 12.3, 4.6 Hz, 1H), 4.59 – 4.69 (m, 3H), 5.60 (dd, J = 10.0, 3.1 Hz, 1H), 5.71 (t, J = 8.5 Hz, 1H), 5.74 – 5.87 (m, 2H), 5.96 (t, J = 9.5 Hz, 1H), 6.07 (d, J = 7.3 Hz, 1H), 6.26 (t, J = 10.0 Hz, 1H), 6.55 (d, J = 3.0 Hz, 1H), 7.20 – 7.44 (m, 29H), 7.44 – 7.54 (m, 5H), 7.81 – 7.98 (m, 12H), 8.01 – 8.09 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.6, 22.7, 22.9, 22.9, 24.9, 25.1, 36.8, 36.8, 36.8, 37.0, 62.4, 62.7, 68.7, 69.0, 70.3, 70.4, 70.5, 70.9, 72.9, 73.2, 79.8, 79.9, 87.2, 87.3, 87.7, 87.7, 92.5, 95.1, 122.3, 122.4, 128.2, 128.2, 128.2, 128.2, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.6, 128.7, 128.7, 128.7, 128.9, 128.9, 129.5, 129.6, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 131.9, 131.9, 131.9, 131.9, 133.1, 133.2, 133.3, 133.4, 133.4, 133.5, 133.5, 133.5, 150.6, 150.9, 165.0, 165.1, 165.1, 165.4, 165.7, 165.8, 166.1, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{49}H_{42}O_{12}Na]^+$: 845.2574; Found: 845.2569.

1-*O*-(((1-ethynylcyclopentyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α/β D-glucopyranoside [α:β (1:1.3)] (44c): mp(^{0}C): 65.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +41.1; IR

(cm^{-1}, $CHCl_3$): 3294, 2959, 1766, 1728, 1601, 1452, 1258, 1098, 1027, 756, 709; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.62 (m, 8H), 1.89 – 2.22 (m, 8H), 2.26 (s, 1H), 2.34 (s, 1H), 4.19 – 4.26 (m, 1H), 4.33 – 4.47 (m, 2H), 4.49 – 4.62 (m, 3H), 5.48 (ddd, J = 10.3, 3.8, 1.4 Hz, 1H), 5.59 (ddd, J = 9.8, 8.0, 1.6 Hz, 1H), 5.63 – 5.75 (m, 2H), 5.83 – 5.91 (m, 1H), 5.95 (dd, J = 8.1, 1.8 Hz, 1H), 6.09 – 6.20 (m, 1H), 6.43-6.46(m, 1H), 7.15 – 7.38 (m, 18H), 7.39 – 7.53 (m, 6H), 7.71 – 8.03 (m, 16H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 23.1, 23.2, 23.2, 23.2, 40.0, 40.1, 40.2, 40.2, 62.4, 62.7, 68.7, 69.0, 70.1, 70.4, 70.6, 70.9, 72.8, 73.3, 73.9, 74.0, 82.6, 82.7, 83.9, 84.1, 92.7, 95.3, 128.3 –128.7 (16C), 128.7, 128.7, 128.7, 128.9, 128.9, 129.6, 129.6, 129.7, 129.7 – 130.0 (16C), 133.1, 133.1, 133.3, 133.3, 133.4, 133.4, 133.5, 133.5, 151.2, 151.4, 164.9, 165.1, 165.1, 165.3, 165.7, 165.8, 166.1, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{42}H_{36}O_{12}Na]^+$: 755.2104; Found: 755.2104.

1-*O*-(((2-methylbut-3-yn-2-yl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α/β D-glucopyranoside [α:β (1:3.3)] (**44d**): mp (^0C): 72.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +43.3; IR (cm^{-1}, $CHCl_3$): 3294, 3067, 2926, 1767,1726, 1452, 1256, 1176, 1076, 707; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.67 (m, 12H), 2.35 – 2.36 (m, 1H), 2.45 (d, *J* = 1.5 Hz, 1H), 4.30 – 4.72 (m, 6H), 5.55 – 5.86 (m, 4H), 5.93 – 6.08 (m, 3H), 6.19 – 6.61 (m, 1H), 7.27 – 7.49 (m, 18H), 7.49 – 7.61 (m, 6H), 7.84 – 8.12 (m, 16H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 28.4, 28.5, 28.5, 28.5, 62.4, 62.7, 68.7, 69.0, 70.1, 70.4, 70.6, 70.8, 72.8, 73.2, 73.4, 73.4, 75.3, 75.4, 83.2, 83.3, 92.6, 95.2, 128.3 – 128.5 (14C), 128.6, 128.7, 128.7, 128.9, 128.9, 129.6, 129.6, 129.6, 129.7, 129.7, 129.8 – 130.0 (14C), 130.1, 130.1, 133.1, 133.2, 133.3, 133.3, 133.4, 133.5, 133.5, 133.5, 150.8, 151.0, 164.9, 165.1, 165.1, 165.3, 165.7, 165.7, 166.1, 166.1.; HRMS (ESI-MS): m/z calcd for $[C_{40}H_{34}O_{12}Na]^+$: 729.1948; Found: 729.1937.

1-*O*-(((but-3-yn-2-yl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α/β D-glucopyranoside [α:β (1:1.4)] (**44e**): mp (^0C): 66.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +51.3; IR (cm^{-1}, $CHCl_3$): 3295, 2927, 1727, 1600, 1452, 1253, 1096, 1020, 707; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.48 (d, *J* = 6.6 Hz, 3H), 1.51 – 1.57 (m, 6H), 1.60 (d, *J* = 6.6 Hz, 3H), 2.35 (d, *J* = 2.0 Hz, 1H), 2.39 (d, *J* = 2.0 Hz, 1H), 2.48 (d, *J* = 2.0 Hz, 1H), 2.51 (d, *J* = 2.0 Hz, 1H), 4.32 – 4.68 (m, 11H), 4.68 – 5.34 (m, 6H), 5.54 – 5.66 (m, 2H), 5.69 – 5.86 (m, 5H), 5.86 – 6.10 (m, 4H), 6.21 – 6.31 (m, 2H), 6.56 (s, 2H), 7.27 – 7.49 (m, 36H), 7.49 – 7.63 (m, 12H), 7.80 – 8.13 (m, 32H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 21.0, 21.0,

21.0, 21.1, 62.4, 62.4, 62.6, 62.7, 65.1, 65.1, 65.2, 65.2, 68.6, 68.7, 68.9, 68.9, 70.0, 70.1, 70.3, 70.4, 70.6, 70.6, 70.7, 70.8, 72.7, 72.7, 73.2, 73.2, 74.3, 74.4, 74.5, 74.5, 80.5, 80.6, 80.6, 80.7, 93.3, 93.3, 95.6, 95.7, 128.3- 128.5(28C), 128.6 – 129.6 (20C), 129.7 – 130.0 (32C), 130.1 – 133.6 (16C), 152.2, 152.2, 152.4, 152.5, 164.8, 164.9, 165.1, 165.1, 165.1, 165.1, 165.3, 165.4, 165.6, 165.6, 165.7, 165.7, 166.0, 166.1, 166.1, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{39}H_{32}O_{12}Na]^+$: 715.1791; Found: 715.1789.

1-*O*-(((prop-2-yn-1-yl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α-D-glucopyranoside (**44f**): mp (^{0}C): 56.6; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +61.2; IR (cm^{-1}, $CHCl_3$): 3293, 2961, 2923, 1728, 1601, 1451, 1253, 1097, 965, 706; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.39 (t,*J*=2.3Hz, 1H), 4.38 (dd, *J* = 12.0, 3.9 Hz, 1H), 4.48 – 4.60 (m, 2H), 4.63 (s, 2H), 5.48 (dd, *J* = 10.2, 3.4 Hz, 1H), 5.72 (t, *J* = 9.9 Hz, 1H), 6.13 (t, *J* = 10.0 Hz, 1H), 6.43 (d, *J* = 3.4 Hz, 1H), 7.28 (m, 9H), 7.44 (m, 3H), 7.77 – 7.79 (m, 2H), 7.84 – 7.89 (m, 4H), 7.97 – 7.99 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.0, 61.3, 67.6, 68.9, 69.3, 69.6, 75.2, 75.3, 92.5, 127.2, 127.3, 127.3, 127.3, 127.4, 127.4, 127.4, 127.4, 127.5, 127.6, 127.8, 128.5, 128.7, 128.7, 128.8, 128.8, 128.9, 128.9, 129.0, 129.0, 132.1, 132.3, 132.5, 132.6, 151.6, 164.0, 164.3, 164.6, 165.0; HRMS (ESI-MS): m/z calcd for $[C_{38}H_{30}O_{12}Na]^+$: 701.1634; Found: 701.1624.

1-*O*-(((but-3-yn-1-yl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α/β D-glucopyranoside [α:β (1:1.2)] (**44g**): mp (^{0}C): 60.7; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +58.0; IR (cm^{-1}, $CHCl_3$): 3294, 2961, 1729,1601, 1453, 1260, 1100, 1027, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.91 (t, *J* = 2.6 Hz, 1H), 2.01 (t, *J* = 2.3 Hz, 1H), 2.44 – 2.61 (m, 4H), 4.17 – 4.28 (m, 4H), 4.35 (ddd, *J* = 10.2, 4.7, 2.3 Hz, 1H), 4.50 (td, *J* = 12.6, 4.6 Hz, 2H), 4.58 – 4.69 (m, 3H), 5.57 (ddd, *J* = 10.3, 3.8, 1.9 Hz, 1H), 5.66 – 5.86 (m, 3H), 5.93 – 6.03 (m, 2H), 6.24 (td, *J* = 10.0, 1.7 Hz, 1H), 6.52 (dd, *J* = 3.9, 1.8 Hz, 1H), 7.23 – 7.47 (m, 18H), 7.47 – 7.60 (m, 6H), 7.81 – 8.00 (m, 12H), 8.03 – 8.09 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 18.8, 18.9, 62.4, 62.6, 66.1, 66.2, 68.7, 68.9, 70.0, 70.4, 70.5, 70.5, 70.6, 70.7, 72.7, 73.2, 78.8, 79.0, 93.1, 95.6, 128.3, 128.3, 128.3, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.7, 128.8, 128.8, 128.9, 129.5, 129.6, 129.7, 129.7, 129.7, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 130.0, 130.0, 133.2, 133.2, 133.3, 133.4, 133.5, 133.5, 133.5, 133.6, 153.0, 153.1, 164.8, 165.1, 165.1, 165.4,

165.7, 165.7, 166.1, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{39}H_{32}O_{12}Na]^+$: 715.1791; Found: 715.1791.

1-*O*-(((1-ethylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α/β D-glucopyranoside [α:β (1:1.4)] (**44i)**: mp (^{0}C): 59.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +58.6; IR (cm^{-1}, $CHCl_3$): 2963, 2921, 1734, 1611, 1451, 1254, 1100, 965, 702; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.69 (t, *J* = 7.5 Hz, 3H), 0.77 (t, *J* = 7.5 Hz, 3H), 1.09 – 1.24 (m, 3H), 1.30 – 1.61 (m, 13H), 1.71 – 1.90 (m, 4H), 1.99 – 2.24 (m, 4H), 4.28 – 4.38 (m, 1H), 4.45 – 4.57 (m, 2H), 4.60 – 4.72 (m, 3H), 5.57 (dd, *J* = 10.2, 3.7 Hz, 1H), 5.69 (t, *J* = 8.9 Hz, 1H), 5.72 – 5.83 (m, 2H), 5.95 (d, *J* = 9.5 Hz, 1H), 6.00 (d, *J* = 8.1 Hz, 1H), 6.27 (t, *J* = 9.9 Hz, 1H), 6.49 (d, *J* = 3.7 Hz, 1H), 7.16 – 7.66 (m, 24H), 7.73 – 8.15 (m, 16H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 7.1, 7.2, 21.5, 21.6, 21.8, 21.8, 25.3, 25.4, 29.6, 29.7, 33.5, 33.6, 33.8, 33.8, 62.6, 62.8, 68.9, 69.2, 70.2, 70.3, 70.5, 70.9, 72.9, 73.1, 87.7, 88.0, 91.8, 94.8, 128.3 – 128.4 (16C), 128.7, 128.7, 128.8, 128.8, 129.0, 129.0, 129.6, 129.6, 129.7 – 129.9 (16C), 133.1, 133.1, 133.2, 133.3, 133.4, 133.4, 133.5, 133.5, 150.9, 151.1, 164.9, 165.1, 165.2, 165.4, 165.7, 165.7, 166.1, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{43}H_{42}O_{12}Na]^+$: 773.2574; Found: 773.2570.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α-D-galactopyranoside (44jα): mp (^{0}C): 72.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +79.5; IR (cm^{-1}, $CHCl_3$): 3294, 2939, 2861, 1727, 1602, 1519, 1452, 1268, 1102, 899, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.27 – 1.39 (m, 1H), 1.50 – 1.68 (m, 5H), 1.74 – 1.97 (m, 2H), 2.01 – 2.13 (m, 1H), 2.14 – 2.25 (m, 1H), 2.43 (s, 1H), 4.46 (dd, *J* = 11.4, 6.4 Hz, 1H), 4.65 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.85 (t, *J* = 6.5 Hz, 1H), 5.95 (dd, *J* = 10.6, 3.4 Hz, 1H), 6.08 (dd, *J* = 10.7, 3.0 Hz, 1H), 6.15 (d, *J* = 2.9 Hz, 1H), 6.64 (d, *J* = 3.4 Hz, 1H), 7.24 – 7.32 (m, 2H), 7.35-7.68 (m, 9H), 7.62 – 7.70 (m, 1H), 7.79 – 7.86 (m, 2H), 7.96 – 8.01 (m, 2H), 8.01 – 8.07 (m, 2H), 8.08 – 8.16 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.5, 22.5, 24.9, 36.6, 36.7, 62.0, 67.7, 68.2, 68.6, 69.6, 75.2, 78.7, 82.3, 93.3, 128.3, 128.3, 128.3, 128.3, 128.4, 128.4, 128.7, 128.7, 128.9, 128.9, 129.0, 129.4, 129.7, 129.8, 129.8, 129.8, 130.0, 130.0, 130.0, 130.0, 133.2, 133.3, 133.4, 133.7, 150.8, 165.5, 165.5, 165.6, 165.9; HRMS (ESI-MS): m/z calcd for $[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2257.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl β-D-galactopyranoside (**44jβ**): mp (^{0}C): 74.9; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +92.1; IR (cm^{-1},

$CHCl_3$): 3277, 2939, 2862, 1727, 1600, 1451, 1263, 1096, 908, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.22 – 1.34 (m, 1H), 1.44 – 1.73 (m, 5H), 1.73 – 1.84 (m, 1H), 1.83 – 1.96 (m, 1H), 1.99 – 2.11 (m, 1H), 2.11 – 2.21 (m, 1H), 2.50 (s, 1H), 4.41 – 4.57 (m, 2H), 4.71 (dd, *J* = 11.0, 6.1 Hz, 1H), 5.69 (dt, *J* = 10.2, 2.4 Hz, 1H), 5.98 (ddd, *J* = 9.8, 8.2, 1.4 Hz, 1H), 6.02 – 6.10 (m, 2H), 7.24 – 7.33 (m, 2H), 7.35 – 7.68 (m, 10H), 7.78 – 7.90 (m, 2H), 7.95 – 8.01 (m, 2H), 8.01 – 8.07 (m, 2H), 8.07 – 8.16 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.3, 22.4, 24.8, 36.5, 36.6, 61.8, 67.8, 68.9, 71.8, 72.4, 75.2, 79.0, 82.2, 95.5, 128.3, 128.3, 128.4, 128.4, 128.4, 128.4, 128.7, 128.7, 128.7, 128.9, 129.0, 129.4, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 130.0, 130.0, 133.2, 133.4, 133.4, 133.7, 150.9, 165.0, 165.4, 165.5, 165.9; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2262.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4-tri-*O*-benzoyl α-L-rhamnopyranoside (**44kα**): mp (^{0}C): 76.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +85.7; IR (cm^{-1}, $CHCl_3$): 3293, 2939, 1730, 1598, 1452, 1241, 1101, 908, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.35 – 1.42 (m, 1H), 1.43 (d, *J* = 6.2 Hz, 3H), 1.55 – 1.82 (m, 5H), 1.92 – 2.05 (m, 2H), 2.20 – 2.37 (m, 2H), 2.73 (s, 1H), 4.37 (dt, *J* = 12.3, 6.1 Hz, 1H), 5.75 (t, *J* = 10.0 Hz, 1H), 5.81 (dt, *J* = 3.2, 1.4 Hz, 1H), 5.92 (dd, *J* = 10.2, 3.5 Hz, 1H), 6.21 (s, 1H), 7.23 – 7.34 (m, 2H), 7.38 – 7.48 (m, 3H), 7.49 – 7.59 (m, 3H), 7.60 – 7.69 (m, 1H), 7.82 – 7.87 (m, 2H), 7.96 – 8.05 (m, 2H), 8.13 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 17.7, 22.7, 22.7, 25.0, 36.7, 36.9, 69.1, 69.5, 69.6, 71.3, 75.6, 79.0, 82.4, 93.8, 128.3, 128.3, 128.5, 128.5, 128.6, 128.6, 129.0, 129.1, 129.2, 129.7, 129.7, 129.7, 129.8, 130.0, 130.0, 133.2, 133.4, 133.6, 150.3, 165.3, 165.5, 165.7; HRMS (ESI-MS): m/z calcd for$[C_{36}H_{34}O_{10}Na]^+$: 649.2050; Found: 649.2054.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4-tri-*O*-benzoyl β-L-rhamnopyranoside (**44kβ**): mp (^{0}C): 72.1; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +131.7; IR (cm^{-1}, $CHCl_3$): 3290, 2941, 1732, 1515, 1453, 1264, 1096, 1027, 915, 711; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.29 – 1.37 (m, 1H), 1.48 – 1.52 (m, 3H), 1.53 – 1.73 (m, 5H), 1.80 – 1.95 (m, 2H), 2.11 – 2.23 (m, 2H), 2.68 (s, 1H), 3.97 – 4.09 (m, 1H), 5.59 – 5.73 (m, 2H), 5.94 – 6.14 (m, 2H), 7.20 – 7.34 (m, 2H), 7.35 – 7.59 (m, 6H), 7.59 – 7.71 (m, 1H), 7.79 – 7.89 (m, 2H), 7.94 – 8.03 (m, 2H), 8.05 – 8.19 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 17.8, 22.5, 22.5, 24.9, 36.5, 36.8, 69.0, 71.1, 71.4, 71.83, 75.4, 78.9, 82.4, 93.4, 128.3, 128.3, 128.5, 128.5, 128.5, 128.5, 128.9, 129.1, 129.4, 129.7, 129.7,

129.8, 129.8, 130.1, 130.1, 133.3, 133.4, 133.5, 150.8, 165.4, 165.5, 165.8; HRMS (ESI-MS): m/z calcd for$[C_{36}H_{34}O_{10}Na]^+$: 649.2050; Found: 649.2053.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α-D-mannopyranoside (**44lα**): mp (^{0}C): 74.9; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): - 28.9; IR (cm^{-1}, $CHCl_3$): 3291, 2941, 1730, 1516, 1451, 1237, 1161, 1102, 908, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.32 – 1.47 (m, 1H), 1.56 – 1.82 (m, 5H), 1.86 – 2.05 (m, 2H), 2.20 – 2.36 (m, 2H), 2.68 (s, 1H), 4.51 (dd, *J* = 12.3, 4.3 Hz, 1H), 4.62 (ddd, *J* = 10.1, 4.3, 2.4 Hz, 1H), 4.76 (dd, *J* = 12.3, 2.5 Hz, 1H), 5.86 (dd, *J* = 3.4, 2.0 Hz, 1H), 6.00 (dd, *J* = 10.2, 3.3 Hz, 1H), 6.20 (t, *J* = 10.1 Hz, 1H), 6.30 (d, *J* = 2.0 Hz, 1H), 7.25 – 7.34 (m, 2H), 7.36 – 7.48 (m, 7H), 7.50 – 7.68 (m, 3H), 7.84 – 7.90 (m, 2H), 7.96 – 8.02 (m, 2H), 8.07 – 8.11 (m, 2H), 8.11 – 8.17 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.7, 22.7, 24.9, 36.8, 36.8, 62.5, 66.3, 69.2, 69.7, 70.9, 77.4, 79.2, 82.2, 93.7, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 128.7, 128.7, 128.7, 128.8, 128.9, 129.0, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9, 133.1, 133.3, 133.5, 133.7, 150.1, 165.1, 165.3, 165.5, 166.0; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2260.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl β-D-mannopyranoside (**44lβ**): mp (^{0}C): 75.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): - 65.4; IR (cm^{-1}, $CHCl_3$): 3292, 2940, 1730, 1603, 1510, 1452, 1265, 1176, 1099, 912, 712; ^{1}H NMR (400.31 MHz, $CDCl_3$) :δ 1.26 – 1.35 (m, 1H), 1.49 – 1.71 (m, 5H), 1.85 (dq, *J* = 13.2, 4.4 Hz, 2H), 2.12 – 2.22 (m, 2H), 2.65 (s, 1H), 4.27 – 4.43 (m, 1H), 4.60 (dd, *J* = 12.3, 4.5 Hz, 1H), 4.79 (dd, *J* = 12.2, 2.9 Hz, 1H), 5.76 (ddd, *J* = 9.9, 3.8, 2.0 Hz, 1H), 6.07 – 6.18 (m, 3H), 7.27 – 7.34 (m, 2H), 7.35 – 7.56 (m, 8H), 7.57 – 7.67 (m, 2H), 7.82 – 7.92 (m, 2H), 7.94 – 8.00 (m, 2H), 8.09 – 8.13 (m, 2H), 8.13 – 8.19 (m, 2H); ^{13}C NMR (101.67 MHz, $CDCl_3$): δ 22.5, 22.5, 24.9, 36.6, 36.7, 62.7, 66.4, 68.7, 71.4, 73.3, 75.5, 79.1, 82.3, 93.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.7, 128.8, 129.3, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 130.1, 130.1, 133.1, 133.4, 133.4, 133.6, 150.7, 165.2, 165.4, 165.4, 166.1; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2261.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl α-D-glucopyranosyl) α/β D-glucopyranoside [α:β (1:2.5)] (**44m**): mp (^{0}C): 101.9; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +57.3; IR (cm^{-1}, $CHCl_3$): 3290, 2940, 1729, 1601, 1452,

1267, 1172, 1099, 1028, 906, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.16 – 1.38 (m, 2H), 1.42 – 1.70 (m, 10H), 1.71 – 1.93 (m, 5H), 1.97 – 2.16 (m, 3H), 2.49 (s, 1H), 2.50 (s, 1H), 4.23 – 4.38 (m, 3H), 4.38 – 4.68 (m, 7H), 4.73 – 5.01 (m, 4H), 5.24 – 5.56 (m, 4H), 5.62 – 5.91 (m, 6H), 6.03 (d, *J* = 7.3 Hz, 1H), 6.06 – 6.26 (m, 2H), 6.45 (s, 1H), 7.19 – 7.61 (m, 42H), 7.68 – 8.20 (m, 28H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.3, 22.4, 22.6, 22.6, 24.8, 24.9, 36.5, 36.6, 36.6, 36.8, 62.5, 62.5, 63.1, 63.2, 69.1, 69.1, 69.2, 69.4, 69.8, 69.9, 70.8, 70.9, 70.9, 71.0, 71.1, 71.2, 72.1, 72.8, 73.8, 74.7, 75.2, 75.4, 78.8, 78.9, 82.2, 82.4, 92.4, 94.8, 96.6, 96.7, 128.1 – 128.6 (28C), 128.6 – 129.5 (14C), 129.6 –130.1 (28C), 133.0, 133.0, 133.1 (3C), 133.3 (5C), 133.4 (3C), 133.5, 150.6, 150.7, 164.9, 164.9, 165.0, 165.1, 165.1, 165.4, 165.5, 165.5, 165.6, 165.7, 165.8, 165.8, 166.1, 166.1; HRMS (ESI-MS): m/z calcd for$[C_{70}H_{60}O_{20}Na]^+$: 1243.3576; Found: 1243.3579.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,6-tri-*O*-benzoyl -4-*O*-(2,3,6-tri-O-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl α-D-glucopyranosyl) α-D-glucopyranosyl) α/β D-glucopyranoside [α:β (1:2.2)] (**44n**): mp (^{0}C): 116.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +86.2; IR (cm^{-1}, $CHCl_3$): 3067, 2940, 1728, 1601, 1496, 1451, 1265, 1097, 1028, 906, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.17 – 1.37 (m, 2H), 1.40 – 1.64 (m, 10H), 1.71 – 1.90 (m, 4H), 2.05 (m, 4H), 2.50 (s, 1H), 2.50 (s, 1H), 4.08 – 4.82 (m, 21H), 4.91 – 5.08 (m, 2H), 5.09 – 5.19 (m, 2H), 5.27 – 5.52 (m, 4H), 5.59 – 5.78 (m, 6H), 5.77 – 6.05 (m, 4H), 6.07 – 6.48 (m, 3H), 7.11 – 7.57 (m, 60H), 7.58 – 8.29 (m, 40H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.3, 22.4, 22.5, 22.5, 24.8, 24.9, 36.5, 36.6, 36.6, 36.9, 62.3, 62.3, 62.7, 63.0, 63.0, 63.0, 69.1, 69.1, 69.2, 69.2, 70.0, 70.0, 70.2, 70.3, 70.7, 70.8, 70.9, 70.9, 71.2, 71.3, 71.7, 71.7, 72.1, 73.1, 73.3, 73.6, 73.6, 73.7, 74.8, 74.8, 75.2, 75.4, 78.8, 78.8, 82.3, 82.5, 92.4, 94.7, 96.7, 96.8, 96.8, 96.8, 127.9 – 128.6 (40C), 128.7 – 129.5 (20C), 129.5 – 130.1 (40C), 133.0 – 133.4 (20C), 150.7, 150.7, 164.7 – 166.1 (20C); HRMS (ESI-MS): m/z calcd for$[C_{97}H_{82}O_{28}Na]^+$: 1717.4890; Found: 1717.4885.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzyl α/β D-glucopyranoside [α:β (1:2.3)] (**44o**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +29.6; IR (cm^{-1}, $CHCl_3$): 3291, 3031, 2934, 1762, 1496, 1453, 1270, 1238, 1081, 905, 739; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.30 – 1.48 (m, 2H), 1.53 – 1.80 (m, 10H), 1.87 – 2.07 (m, 4H), 2.13 – 2.32 (m, 4H), 2.65 (s, 1H), 2.67 (s, 1H), 3.59 – 3.72 (m, 3H), 3.73 – 4.11

(m, 9H), 4.44 – 5.07 (m, 16H), 5.58 (d, *J* = 8.1 Hz, 1H), 6.29 (s, 1H), 7.18 – 7.41 (m, 40H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.5 (4C), 25.0, 25.0, 36.7, 36.8 (3C), 68.2, 68.2, 73.0, 73.2, 73.5, 73.5, 75.1, 75.1, 75.2, 75.7, 75.8, 76.8, 76.9, 77.1, 77.3, 77.4, 77.9, 78.3, 79.0, 81.1, 81.6, 82.7, 82.9, 84.6, 93.6, 97.6, 127.6 – 127.9 (20C), 128.0 – 128.4 (20C), 137.8 – 138.7 (8C), 151.3, 151.5; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{46}O_8Na]^+$: 713.3090; Found: 713.3093.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzyl α/β D-mannopyranoside [α:β (1.0:1.0)] (**44p**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +1.3; IR (cm^{-1}, $CHCl_3$): 3284, 3031, 2935, 2863, 1759, 1496, 1453, 1270, 1238, 1091, 1016, 906, 739; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.30 – 1.46 (m, 2H), 1.53 – 1.82 (m, 10H), 1.86 – 2.04 (m, 4H), 2.12 – 2.32 (m, 4H), 2.66 (s, 1H), 2.68 (s, 1H), 3.60 – 3.69 (m, 2H), 3.77 – 3.95 (m, 5H), 3.95 – 4.04 (m, 2H), 4.03 – 4.12 (m, 2H), 4.16 (td, *J* = 9.6, 2.7 Hz, 1H), 4.54 – 4.68 (m, 8H), 4.69 – 4.76 (m, 2H), 4.77 – 5.03 (m, 6H), 5.58 (d, *J* = 2.4 Hz, 1H), 6.18 (s, 1H), 7.21 – 7.55 (m, 40H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.5 (4C), 25.0, 25.0, 36.5, 36.6, 37.0, 37.1, 68.9, 69.0, 72.0, 72.3, 72.7, 73.4, 73.5, 73.5, 73.7, 74.1, 74.3, 74.3, 74.4, 75.1, 75.2, 76.6, 76.8, 76.8, 78.1, 78.2, 79.4, 81.8, 82.8, 82.8, 94.9, 96.1, 127.5 – 128.0 (16C), 128.1 – 128.4 (24C), 137.9 – 138.4 (8C), 150.8, 151.3; HRMS (ESI-MS): m/z calcd for $[C_{43}H_{46}O_8Na]^+$: 713.3090; Found: 713.3089.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,4,6-tri-*O*-benzoyl α/β-D-mannopyranoside [α:β (1.0:3.0)] (**44q**): mp (^{0}C): 69.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +13.8; IR (cm^{-1}, $CHCl_3$): 3250, 2935, 1730, 1625, 1455, 1260, 1130, 1080, 915, 705; ^{1}H NMR (400.31 MHz, $CDCl_3$) :δ 1.21 – 1.30 (m, 2H), 1.42 – 1.50 (m, 4H), 1.56 – 1.63 (m, 6H), 1.70 – 1.80 (m, 2H), 1.82 – 1.93 (m, 2H), 1.95 – 2.05 (m, 2H), 2.06 – 2.22 (m, 2H), 2.43 (s, 1H), 2.46 (s, 1H), 3.71– 3.79 (m, 2H), 3.81 – 3.98 (m, 7H), 4.07 – 4.32 (m, 1H), 4.54 – 4.80 (m, 9H), 4.80 – 5.41 (m, 4H), 5.44 – 6.40 (m, 3H), 7.14 – 7.26 (m, 14H), 7.30 – 7.42 (m, 16H), 7.42 – 7.49 (m, 4H), 7.56 – 7.63 (m, 2H), 8.05 – 8.07 (m, 4H); ^{13}C NMR (101.67 MHz, $CDCl_3$): δ 22.2, 22.2, 22.3, 22.5, 24.8, 24.9, 36.4, 36.4, 36.6, 36.7, 68.1, 68.2, 72.5, 72.7, 73.4, 73.6, 73.6, 74.9, 75.1, 75.1, 75.2, 75.2, 75.6, 76.2, 76.2, 77.2, 77.4, 78.2, 78.3, 79.8, 82.5, 82.5, 93.5, 95.4, 127.7 – 128.1 (12C), 128.3 – 128.5 (22C), 129.5, 129.6, 130.0 (4C), 133.2 (2C), 137.6, 137.8, 137.9, 138.0 (3C), 150.9, 151.3, 165.0, 165.4; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{44}O_9Na]^+$: 727.2883; Found: 727.2878.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranosyl) α-D-glucopyranoside (**46**): mp (^{0}C): 64.6; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +27.3; IR (cm^{-1}, $CHCl_3$): 3065, 2926, 2856, 1728, 1601, 1452, 1368, 1264, 1099, 1029, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.11 (s, 3H), 3.80 (dd, *J* = 11.3, 7.6 Hz, 1H), 4.06 – 4.19 (m, 2H), 4.20 – 4.27 (m, 1H), 4.46 (dd, *J* = 12.1, 5.1 Hz, 1H), 4.62 (dd, *J* = 12.2, 3.1 Hz, 1H), 4.95 (d, *J* = 3.6 Hz, 1H), 4.99 (d, *J* = 7.8 Hz, 1H), 5.11 (dd, *J* = 10.2, 3.6 Hz, 1H), 5.33 (t, *J* = 9.9 Hz, 1H), 5.58 (dd, *J* = 9.6, 8.1 Hz, 1H), 5.67 (t, *J* = 9.7 Hz, 1H), 5.94 (t, *J* = 9.7 Hz, 1H), 6.08 (t, *J* = 9.8 Hz, 1H), 7.22 – 7.29 (m, 4H), 7.29 – 7.43 (m, 12H), 7.44 – 7.56 (m, 5H), 7.75 – 7.83 (m, 3H), 7.83 – 7.86 (m, 2H), 7.86 – 7.91 (m, 3H), 7.92 – 7.95 (m, 2H), 7.96 – 8.04 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.1, 63.1, 68.8, 68.9, 69.7, 69.7, 70.4, 71.9, 72.0, 72.3, 72.9, 96.5, 101.8, 128.2 – 128.4 (14C), 128.8, 128.8, 128.8, 129.1, 129.2, 129.4, 129.6, 129.6 – 129.9 (14C), 133.0, 133.1, 133.2, 133.2, 133.3, 133.4, 133.4, 165.2, 165.2, 165.4, 165.7, 165.7, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{52}O_{18}Na]^+$: 1107.3051; Found: 1107.3062.

4-methylene-1,3-dioxaspiro[4.5]decan-2-one (**22**): Colourless liquid; IR (cm^{-1}, $CHCl_3$): 2941, 2865, 1837, 1816, 1684, 1313, 1268, 1201, 1060, 1026, 941, 769; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.27 – 1.38 (m, 2H), 1.60 – 1.68 (m, 3H), 1.68 – 1.76 (m, 3H), 1.89 – 2.07 (m, 2H), 4.30 (d, *J* = 3.8 Hz, 1H), 4.76 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 21.6, 21.6, 24.3, 36.5, 36.5, 85.5, 86.4, 151.5, 158.7.

Methyl-2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranosyl) α-D-glucopyranoside (**50**): mp (^{0}C): 55.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -31.0; IR (cm^{-1}, $CHCl_3$): 3293, 3067, 2926, 1726, 1600, 1452, 1256, 1076, 1025, 859, 707; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.27 (s, 3H), 3.47 (m, 3H), 3.66 – 3.79 (m, 2H), 3.89 (t, *J* = 9.2 Hz, 1H), 3.98 (t, *J* = 9.4 Hz, 1H), 4.27 (dd, *J* = 12.1, 4.9 Hz, 1H), 4.35 (d, *J* = 12.1 Hz, 1H), 4.41 (dd, *J* = 12.1, 3.1 Hz, 1H), 4.52 – 4.64 (m, 2H), 4.70 – 4.86 (m, 4H), 5.08 (d, *J* = 11.2 Hz, 1H), 5.47 (t, *J* = 8.8 Hz, 1H), 5.56 (t, *J* = 9.5 Hz, 1H), 5.63 (t, *J* = 9.5 Hz, 1H), 7.13 – 7.30 (m, 10H), 7.31– 7.54 (m, 17H), 7.78 – 7.80 (m, 2H), 7.87 – 7.89 (m, 4H), 7.96 – 7.98(m,2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.5, 63.2, 67.7, 69.6, 70.0, 71.9, 72.3, 73.3, 73.7, 73.7, 75.5, 77.4, 78.9, 80.1, 98.6, 100.5, 127.3 – 128.6 (25C), 129.0 – 129.9 (10C), 133.1, 133.3, 133.4, 133.5, 138.0, 138.4, 139.4, 164.9, 165.2, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{58}O_{15}Na]^+$: 1065.3673; Found: 1065.3674.

Pent-4-enyl 3,5-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranosyl) α-D-arabinofuranoside (51): Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +44.8; IR (cm^{-1}, $CHCl_3$): 3071, 2926, 1733, 1604, 1509, 1453, 1264, 1217, 1028, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.64 (p, *J* = 7.1 Hz, 2H), 2.08 (p, *J* = 7.2 Hz, 2H), 3.28 (q, *J* = 7.0 Hz, 1H), 3.46 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.54 (dd, *J* = 10.7, 2.3 Hz, 1H), 3.58 – 3.68 (m, 1H), 3.95 (dd, *J* = 6.5, 3.1 Hz, 1H), 4.09 – 4.20 (m, 2H), 4.38 – 4.44 (m, 1H), 4.44 – 4.56 (m, 4H), 4.63 (t, *J* = 11.5 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.84 (s, 1H), 4.93 – 5.06 (m, 3H), 5.55 (td, *J* = 8.8, 8.1, 1.3 Hz, 1H), 5.72 (td, *J* = 8.8, 8.1, 1.3 Hz, 1H), 5.81 (ddt, *J* = 16.9, 10.5, 6.7 Hz, 1H), 5.90 (td, *J* = 9.7, 1.3 Hz, 1H), 7.20 – 7.45 (m, 19H), 7.46 – 7.56 (m, 3H), 7.75 – 8.04 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 28.7, 30.3, 62.8, 67.1, 69.5, 69.6, 71.9, 72.0, 72.5, 73.0, 73.3, 80.5, 82.6, 88.3, 100.8, 106.4, 114.9, 127.6 – 128.4 (20C), 128.6 – 129.8 (10C), 133.1, 133.3, 133.4, 133.5, 137.9, 138.1, 138.1, 165.0, 165.2, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{58}H_{56}O_{14}Na]^+$: 999.3568; Found: 999.3569.

Menthyl 2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranoside (**52**): mp (^{0}C): 63.8; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -23.4; IR (cm^{-1}, $CHCl_3$): 2925, 2864, 1729, 1602, 1452, 1262, 1100, 1028, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.72 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 7.1 Hz, 3H), 0.86 – 0.97 (m, 2H), 1.22 (m, 3H), 1.50 – 1.62 (m, 2H), 1.94 (d, *J* = 12.2 Hz, 1H), 2.26 (td, *J* = 6.8, 2.4 Hz, 1H), 3.48 (td, *J* = 10.7, 4.2 Hz, 1H), 4.14 (ddd, *J* = 9.3, 5.5, 3.3 Hz, 1H), 4.49 (dd, *J* = 12.0, 5.7 Hz, 1H), 4.63 (dd, *J* = 12.0, 3.3 Hz, 1H), 4.94 (d, *J* = 8.0 Hz, 1H), 5.50 (dd, *J* = 9.7, 8.0 Hz, 1H), 5.64 (t, *J* = 9.7 Hz, 1H), 5.90 (t, *J* = 9.7 Hz, 1H), 7.22 – 7.30 (m, 2H), 7.30 – 7.44 (m, 7H), 7.44 – 7.56 (m, 3H), 7.80 – 7.86 (m, 2H), 7.88 – 7.93 (m, 2H), 7.94 – 8.03 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 15.7, 20.9, 22.1, 23.1, 25.2, 31.5, 34.2, 40.9, 47.4, 63.6, 70.3, 72.1, 72.2, 73.3, 79.2, 99.1, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.9, 129.0, 129.6, 129.7, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 133.2, 133.2, 133.3, 133.5, 165.2, 165.4, 166.0, 166.2; HRMS (ESI-MS): m/z calcd for $[C_{44}H_{46}O_{10}Na]^+$: 757.2989; Found: 757.2987.

Benzyl 2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranoside (**53**): mp (^{0}C): 55.8; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -31.0; IR (cm^{-1}, $CHCl_3$): 2927, 1728, 1602, 1452, 1367, 1264, 1104, 1027, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 4.44 (ddd, *J* = 9.3, 5.5, 3.3 Hz, 1H), 4.49 (dd, *J* = 12.0, 3.3 Hz, 1H), 4.66 (d, *J* = 15.4 Hz, 1H), 4.79 ((ABq, *J* = 12.0 Hz, 2H)),

5.18 (d, *J* = 8.0 Hz, 1H), 5.76 (m, 1H), 5.95 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.12 (t, *J* = 9.8 Hz, 1H), 7.21 – 7.28 (m, 2H), 7.31 – 7.46 (m, 12H), 7.45 – 7.62 (m, 3H), 7.79 – 7.86 (m, 2H), 7.89 – 7.98 (m, 2H), 8.00 – 8.07 (m, 2H), 8.07 – 8.14 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 62.9, 67.0, 69.2, 70.1, 70.3, 70.6, 97.0, 128.3, 128.3, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 128.6, 128.7, 128.7, 128.7, 128.8, 129.0, 129.2, 129.4, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 130.0, 133.2, 133.3, 133.5, 133.6, 136.4, 165.5, 165.6, 165.6, 166.3; HRMS (ESI-MS): m/z calcd for $[C_{41}H_{34}O_{10}Na]^+$: 709.2050; Found: 709.2048.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl α-D-mannopyranosyl) α-D-glucopyranoside (**54**): mp (^{0}C): 70.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +2.4; IR (cm^{-1}, $CHCl_3$): 3068, 2927, 1726, 1603, 1452, 1261, 1099, 1029, 974, 754, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.59 (s, 3H), 3.76 (d, *J* = 10.7 Hz, 1H), 4.07 (dd, *J* = 10.7, 6.1 Hz, 1H), 4.35 (dt, *J* = 12.1, 5.5 Hz, 2H), 4.45 – 4.56 (m, 1H), 4.60 (d, *J* = 12.2 Hz, 1H), 5.13 (s, 1H), 5.24 (dd, *J* = 10.2, 3.7 Hz, 1H), 5.31 (d, *J* = 3.6 Hz, 1H), 5.56 (t, *J* = 10.0 Hz, 1H), 5.69 – 5.82 (m, 1H), 5.97 (dd, *J* = 10.1, 3.2 Hz, 1H), 6.07 (t, *J* = 10.1 Hz, 1H), 6.19 (t, *J* = 9.9 Hz, 1H), 7.23 – 7.35 (m, 6H), 7.35 – 7.49 (m, 11H), 7.49 – 7.65 (m, 4H), 7.81 – 8.13 (m, 14H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.7, 62.8, 66.5, 66.9, 68.3, 69.0, 69.4, 70.0, 70.4, 70.6, 72.1, 97.0, 97.5, 128.3 – 128.6 (14C), 128.8, 129.1, 129.2, 129.2, 129.2, 129.3, 129.3, 129.7 – 130.0 (14C), 133.0, 133.1, 133.1, 133.3, 133.4, 133.4, 133.5, 165.3, 165.4, 165.4, 165.5, 165.7, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{52}O_{18}Na]^+$: 1107.3051; Found: 1107.3066.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl α-D-mannopyranosyl) α-D-glucopyranoside (**55**): mp (^{0}C): 56.1; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -25.4; IR (cm^{-1}, $CHCl_3$): 3012, 2967, 1735, 1514, 1454, 1367, 1268, 1102, 907, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.50 (s, 3H), 3.63 (dd, *J* = 9.5, 3.4 Hz, 1H), 3.84 (d, *J* = 10.2 Hz, 1H), 3.90 – 4.06 (m, 3H), 4.16 (t, *J* = 8.7 Hz, 1H), 4.30 (dd, *J* = 12.2, 3.4 Hz, 1H), 4.42 (d, *J* = 9.9 Hz, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.59 – 4.72 (m, 4H), 4.80 (d, *J* = 12.1 Hz, 1H), 4.92 (d, *J* = 11.0 Hz, 1H), 5.13 (d, *J* = 11.0 Hz, 1H), 5.67 (s, 1H), 5.80 (s, 1H), 5.93 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.10 (t, *J* = 10.1 Hz, 1H), 6.98 – 7.22 (m, 4H), 7.24 – 7.50 (m, 20H), 7.51 – 7.67 (m, 3H), 7.79 – 7.90 (m, 2H), 7.92 – 8.04 (m, 4H), 8.08 – 8.18 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.4, 62.8, 66.8, 69.3, 69.6, 69.7, 70.0, 70.5, 73.3, 73.6, 75.4, 76.3, 80.3, 81.4, 98.0, 99.0, 127.2 – 128.5 (24C), 129.1 – 130.0 (11C), 133.0,

133.1, 133.3, 133.4, 137.9, 138.0, 138.3, 164.9, 165.4, 165.6, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{58}O_{15}Na]^+$: 1065.3673; Found: 1065.3689.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl β-D-galactopyranosyl) α-D-glucopyranoside (**56**): mp (^{0}C): 89.7; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +69.4; IR (cm^{-1}, $CHCl_3$): 2928, 2854, 1728, 1601, 1452, 1366, 1266, 1101, 917, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.11 (s, 3H), 3.80 (dd, *J* = 11.3, 7.7 Hz, 1H), 4.18 (d, *J* = 11.2 Hz, 1H), 4.22 – 4.29 (m, 1H), 4.32 (t, *J* = 6.5 Hz, 1H), 4.37 – 4.45 (m, 1H), 4.61 (dd, *J* = 11.2, 6.4 Hz, 1H), 4.92 (d, *J* = 3.4 Hz, 1H), 4.95 (d, *J* = 8.0 Hz, 1H), 5.03 – 5.11 (m, 1H), 5.34 (t, *J* = 9.9 Hz, 1H), 5.64 (dd, *J* = 10.4, 3.4 Hz, 1H), 5.85 (dd, *J* = 10.2, 8.1 Hz, 1H), 6.00 (d, *J* = 3.0 Hz, 1H), 6.09 (t, *J* = 9.8 Hz, 1H), 7.19 – 7.30 (m, 4H), 7.31 – 7.51 (m, 15H), 7.52 – 7.63 (m, 2H), 7.75 – 7.83 (m, 4H), 7.86 – 7.96 (m, 4H), 7.97 – 8.03 (m, 4H), 8.04 – 8.11 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.1, 61.9, 68.1, 68.8, 69.3, 69.7, 69.8, 70.4, 71.5, 71.7, 72.1, 96.5, 102.3, 128.3 – 128.7 (14C), 128.8, 129.1, 129.1, 129.3, 129.5, 129.5, 129.7, 129.7 – 130.1 (14C), 133.2, 133.4, 133.4, 133.4, 133.4, 133.6, 133.7, 165.5, 165.6, 165.6, 165.7, 165.8, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{52}O_{18}Na]^+$: 1107.3051; Found: 1107.3062.

Methyl 2,3,6-tri-*O*-benzyl-4-O-(2,3,4,6-tetra-*O*-benzoyl β-D-galactopyranosyl) α-D-glucopyranoside (**57**): mp(^{0}C): 62.8; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +4.82; IR(cm^{-1}, $CHCl_3$): 3023, 2932, 1731, 1604, 1511, 1453, 1265, 1097, 910, 707; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.31 (s, 3H), 3.45 (d, *J* = 10.7 Hz, 1H), 3.50 – 3.58 (m, 2H), 3.67 – 3.76 (m, 1H), 3.93 (td, *J* = 9.1, 2.6 Hz, 2H), 4.04 (td, *J* = 9.6, 3.0 Hz, 1H), 4.15 – 4.26 (m, 1H), 4.33 (dd, *J* = 12.2, 2.3 Hz, 1H), 4.41 (ddd, *J* = 10.3, 6.0, 2.7 Hz, 1H), 4.59 (t, *J* = 3.0 Hz, 1H), 4.66 (dd, *J* = 12.3, 2.3 Hz, 1H), 4.73 – 4.85 (m, 3H), 4.92 (dd, *J* = 11.1, 2.2 Hz, 1H), 5.19 (dd, *J* = 11.1, 2.5 Hz, 1H), 5.31 (dt, *J* = 10.4, 3.2 Hz, 1H), 5.63 – 5.77 (m, 1H), 5.87 (t, *J* = 2.7 Hz, 1H), 7.15 – 7.33 (m, 10H), 7.34 – 7.60 (m, 17H), 7.72 – 7.80 (m, 2H), 7.82 – 7.89 (m, 2H), 7.91 – 7.98 (m, 2H), 8.00 – 8.06 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.5, 61.5, 67.6, 67.9, 69.6, 70.4, 71.1, 72.0, 73.7, 73.8, 75.4, 76.8, 78.7, 79.9, 98.7, 100.5, 127.3 – 128.9 (25C), 129.2 – 130.0 (10C), 133.3, 133.3, 133.5, 133.6, 137.9, 138.4, 139.5, 165.0, 165.6, 165.6, 166.0; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{58}O_{15}Na]^+$: 1065.3673; Found: 1065.3684.

Pent-4-enyl 3,5-di-O-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl β-D-galactopyranosyl) α-D-arabinofuranoside (**58**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +43.2; IR (cm^{-1}, $CHCl_3$):

3071, 2926, 2865, 1731, 1603, 1453, 1366, 1265, 1101, 911, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.67 (q, *J* = 7.0 Hz, 2H), 2.12 (q, *J* = 7.1 Hz, 2H), 3.32 (dt, *J* = 9.6, 6.6 Hz, 1H), 3.51 – 3.59 (m, 1H), 3.59 – 3.73 (m, 2H), 4.08 (dd, *J* = 6.9, 3.6 Hz, 1H), 4.17 – 4.26 (m, 1H), 4.36 (t, *J* = 6.4 Hz, 1H), 4.43 – 4.56 (m, 4H), 4.59 – 4.71 (m, 2H), 4.79 (d, *J* = 11.9 Hz, 1H), 4.93 (s, 1H), 4.96 – 5.11 (m, 3H), 5.64 (dd, *J* = 10.4, 3.3 Hz, 1H), 5.77 – 5.84 (m, 1H), 5.85 – 5.90 (m, 1H), 6.05 (d, *J* = 3.0 Hz, 1H), 7.27 – 7.37 (m, 12H), 7.42 (m, 4H), 7.46 – 7.68 (m, 6H), 7.81 – 7.89 (m, 2H), 7.98 – 8.02 (m, 2H), 8.02 – 8.07 (m, 2H), 8.10 – 8.16 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 28.7, 30.3, 62.1, 67.1, 68.2, 69.7, 69.8, 71.6, 71.8, 72.0, 73.4, 80.6, 82.7, 88.4, 101.2, 106.4, 114.9, 127.6 – 128.4 (20C), 128.5 – 130.0 (10C), 133.3, 133.3, 133.4, 133.6, 137.9, 138.1, 138.1, 165.1, 165.5, 165.6, 166.0; HRMS (ESI-MS): m/z calcd for $[C_{58}H_{56}O_{14}Na]^+$: 999.3568; Found: 999.3573.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4-tri-*O*-benzoyl α-L-rhamnopyranosyl) α-D-glucopyranoside (**59**): mp (^{0}C): 61.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +83.4; IR (cm^{-1}, $CHCl_3$): 3020, 2929, 1728, 1600, 1452, 1267, 1102, 1029, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.32 (d, *J* = 6.2 Hz, 3H), 3.62 (s, 3H), 3.88 (dd, *J* = 11.9, 7.1 Hz, 1H), 3.99 (dd, *J* = 11.8, 2.4 Hz, 1H), 4.19 (dt, *J* = 12.5, 6.2 Hz, 1H), 4.35 – 4.49 (m, 1H), 5.19 (s, 1H), 5.27 – 5.39 (m, 2H), 5.57 (t, *J* = 9.9 Hz, 1H), 5.68 (t, *J* = 9.9 Hz, 1H), 5.73 – 5.79 (m, 1H), 5.84 (dd, *J* = 10.1, 3.5 Hz, 1H), 6.25 (t, *J* = 9.4 Hz, 1H), 7.25 – 7.36 (m, 4H), 7.37 – 7.47 (m, 8H), 7.48 – 7.67 (m, 6H), 7.81 – 7.88 (m, 2H), 7.89 – 7.96 (m, 2H), 7.96 – 8.07 (m, 6H), 8.10 – 8.16 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 17.6, 55.9, 66.8, 67.0, 69.6, 69.8, 69.9, 70.4, 70.6, 71.8, 72.1, 96.9, 98.3, 128.2 – 128.6 (12C), 128.9, 129.1, 129.2, 129.3, 129.3, 129.5, 129.7 – 130.0 (12C), 133.0, 133.1, 133.3, 133.4, 133.4, 133.5, 165.4, 165.4, 165.5, 165.8, 165.8, 165.8; HRMS (ESI-MS): m/z calcd for $[C_{55}H_{48}O_{16}Na]^+$: 987.2840; Found: 987.2831.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzoyl α-L-rhamnopyranosyl) α-D-glucopyranoside (**60**): mp (^{0}C): 57.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +41.3; IR (cm^{-1}, $CHCl_3$): 3293, 3021, 2932, 1729, 1604, 1453, 1267, 1103, 910, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.0 Hz, 3H), 3.41 (s, 3H), 3.62 – 3.69 (m, 1H), 3.74 (d, *J* = 11.0 Hz, 1H), 3.87 (dd, *J* = 20.5, 10.1 Hz, 2H), 3.94 – 4.07 (m, 2H), 4.38 (td, *J* = 7.7, 6.9, 3.0 Hz, 1H), 4.57 (q, *J* = 11.9 Hz, 2H), 4.62 – 4.67 (m, 2H), 4.74 – 4.80 (m, 1H), 4.86 (d, *J* = 11.1 Hz, 1H), 5.15 – 5.28 (m, 2H), 5.56 – 5.58 (m, 1H), 5.62 (t, *J* = 10.0, 1.8 Hz, 1H),

5.79 (dt, *J* = 10.2, 2.5 Hz, 1H), 7.09 – 7.22 (m, 6H), 7.24 – 7.35 (m, 9H), 7.36 – 7.50 (m, 7H), 7.50 – 7.63 (m, 2H), 7.79 – 7.96 (m, 4H), 8.02 – 8.14 (m, 2H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 17.3, 55.4, 67.1, 68.4, 70.1, 70.2, 71.4, 71.8, 73.4, 73.5, 74.9, 75.6, 79.8, 80.4, 97.1, 98.1, 127.4 – 128.1 (8C), 128.3 – 128.7 (15C), 129.3 – 130.0 (7C), 133.3, 133.4, 133.6, 137.8, 138.0, 138.8, 165.8, 165.9, 165.9; HRMS (ESI-MS): m/z calcd for $[C_{55}H_{54}O_{13}Na]^+$: 945.3462; Found: 945.3474.

Pent-4-enyl 3,5-di-*O*-benzyl-2-*O*-(2,3,4-tri-*O*-benzoyl α-L-rhamnopyranosyl) α-D-arabinofuranoside (**61**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +82.7; IR (cm^{-1}, $CHCl_3$): 3012, 2974, 1736, 1515, 1453, 1367, 1270, 1217, 1104, 909, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.32 (d, *J* = 6.1 Hz, 3H), 1.70 (p, *J* = 6.9 Hz, 2H), 2.13 (q, *J* = 7.1 Hz, 2H), 3.43 – 3.56 (m, 1H), 3.61 – 3.84 (m, 3H), 4.07 – 4.18 (m, 1H), 4.17 – 4.24 (m, 1H), 4.24 – 4.31 (m, 1H), 4.42 (s, 1H), 4.54 – 4.76 (m, 4H), 4.93 (d, *J* = 10.1 Hz, 1H), 5.01 (d, *J* = 17.1 Hz, 1H), 5.16 (d, *J* = 11.3 Hz, 2H), 5.62 – 5.74 (m, 2H), 5.73 – 5.90 (m, 2H), 7.17 – 7.43 (m, 15H), 7.45 – 7.65 (m, 4H), 7.76 – 7.87 (m, 2H), 7.89 – 7.98 (m, 2H), 8.04 – 8.14 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 17.6, 28.8, 30.3, 67.2, 67.4, 69.7, 69.7, 70.9, 71.8, 72.4, 73.6, 80.8, 83.5, 86.1, 97.0, 105.8, 114.8, 127.7 – 127.9 (6C), 128.3 – 128.6 (10C), 129.2, 129.3, 129.4, 129.7 – 130.0 (6C), 133.2, 133.4, 133.6, 137.8, 138.1, 138.2, 165.5, 165.6, 165.8; HRMS (ESI-MS): m/z calcd for $[C_{51}H_{52}O_{12}Na]^+$: 879.3356; Found: 879.3361.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl α/β D-glucopyranosyl) α-D-glucopyranoside [α:β (3.3:1.0)] (**62**): mp (^{0}C): 50.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +49.5; IR (cm^{-1}, $CHCl_3$): 3030, 2923, 2863, 1729, 1600, 1453, 1269, 1097, 917, 706; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.44 (s, 3H), 3.49 (s, 3H), 3.52 – 3.76 (m, 10H), 3.85 – 4.07 (m, 5H), 4.15 – 4.43 (m, 3H), 4.43 – 4.72 (m, 8H), 4.73 – 4.88 (m, 6H), 4.87 – 5.16 (m, 4H), 5.23 – 5.37 (m, 4H), 5.49 – 5.66 (m, 2H), 6.15 – 6.31 (m, 2H), 7.15 – 7.23 (m, 4H), 7.24 – 7.48 (m, 50H), 7.50 – 7.61 (m, 4H), 7.84 – 8.10 (m, 12H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.6, 55.6, 66.7, 68.4, 68.6, 68.7, 68.9, 69.1, 69.7, 70.0, 70.3, 70.6, 70.7, 72.2, 72.3, 72.3, 73.1, 73.4, 73.4, 73.5, 74.8, 74.8, 75.0, 75.0, 75.6, 75.7, 80.1, 81.8, 82.4, 84.6, 96.8, 96.9, 97.3, 104.0, 127.5 – 127.6 (8), 127.7 – 127.7 (8), 127.8 – 127.8 (8), 127.9 – 128.0 (14), 128.2 – 128.4 (14), 129.0, 129.1, 129.1, 129.1, 129.3, 129.3, 129.7 – 129.7 (6), 129.9 – 130.0 (6), 133.1, 133.1, 133.4, 133.4, 133.4, 133.4, 138.0, 138.1, 138.2, 138.4, 138.5, 138.6, 138.7, 138.9, 165.3, 165.5, 165.8,

165.9, 165.9, 165.9; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{60}O_{14}Na]^+$: 1051.3881; Found: 1051.3875.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl α/β D-glucopyranosyl) α-D-glucopyranoside [α:β (2.2: 1] (**63**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +31.9; IR (cm^{-1}, $CHCl_3$): 3025, 2934, 1740, 1509, 1455, 1367, 1216, 1094, 908, 741, 699 ; ^1H NMR (400.31 MHz, $CDCl_3$): δ 3.27 – 3.41 (m, 8H), 3.43 – 3.76 (m, 13H), 3.80 – 3.94 (m, 5H), 3.94 – 4.32 (m, 5H), 4.35 – 4.64 (m, 16H), 4.65 – 5.75 (m, 15H), 6.90 – 7.58 (m, 70H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 55.3, 55.5, 68.0, 68.3, 69.1, 69.1, 69.7, 70.1, 71.1, 72.3, 73.3, 73.4, 73.5, 73.5, 73.6, 73.8, 74.6, 75.0, 75.1, 75.1, 75.3, 75.6, 75.7, 75.7, 75.8, 76.7, 77.8, 78.2, 78.9, 79.6, 80.3, 80.6, 82.2, 82.2, 83.0, 85.0, 96.8, 97.9, 98.6, 102.6, 126.9 – 127.9 (28) , 127.9 – 128.5 (28), 128.5 – 128.6 (14), 138.0, 138.0, 138.1, 138.1, 138.3, 138.4, 138.5, 138.6, 138.7, 138.7, 138.7, 138.9, 139.1, 139.7; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{66}O_{11}Na]^+$: 1009.4503; Found: 1009.4448.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl α/β D-mannopyranosyl) α-D-glucopyranoside [α:β (2.2:1)] (**64**): mp (^0C): 60.9; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +34.2; IR (cm^{-1}, $CHCl_3$): 3018, 2968, 1736, 1512, 1455, 1367, 1217, 1102, 907, 707; ^1H NMR (400.31 MHz, $CDCl_3$): δ 3.40 (s, 3H), 3.45 (s, 3H), 3.49 – 3.59 (m, 2H), 3.60 – 3.96 (m, 11H), 3.96 – 4.11 (m, 2H), 4.15 – 4.40 (m, 3H), 4.41 – 4.60 (m, 10H), 4.65 – 4.78 (m, 4H), 4.89 – 5.10 (m, 4H), 5.16 – 5.35 (m, 4H), 5.47 – 5.66 (m, 2H), 6.05 – 6.26 (m, 2H), 7.13 – 7.22 (m, 4H), 7.21 – 7.45 (m, 50H), 7.48 – 7.57 (m, 4H), 7.83 – 8.06 (m, 12H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 55.6, 55.7, 66.3, 68.2, 68.7, 69.0, 69.1, 69.5, 69.6, 69.9, 70.7, 70.7, 71.5, 72.1, 72.2, 72.2, 72.3, 72.7, 73.4, 73.5, 74.0, 74.2, 74.8, 74.9, 74.9, 75.2, 75.3, 76.1, 80.0, 82.2, 97.0, 97.1, 98.4, 102.4, 127.5 – 127.7 (8), 127.8 – 127.9 (8), 127.9 – 128.0 (8), 128.1 – 128.2 (14), 128.3 – 128.5 (14), 128.5 – 128.6 (6), 129.0, 129.2, 129.2, 129.2, 129.4, 129.4, 129.8 – 129.8 (6), 133.2, 133.2, 133.4, 133.4, 133.5, 133.5, 133.5, 133.6, 138.3, 138.5, 138.6, 138.7, 138.8, 138.9, 165.2, 165.6, 165.9, 166.0, 166.0, 166.0.; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{60}O_{14}Na]^+$: 1051.3881; Found: 1051.3904.

Methyl 2,3,6-tri-*O*-benzyl-4-O-(2,3,4,6-tetra-*O*-benzyl α-D-mannopyranosyl) α-D-glucopyranoside (**65**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +3.9; IR (cm^{-1}, $CHCl_3$): 3021, 2966, 1740, 1514, 1455, 1367, 1217, 1102, 905, 742, 699; ^1H NMR (400.31 MHz, $CDCl_3$): δ 3.42 (s, 3H), 3.54 – 3.63 (m, 2H), 3.70 (dd, *J* = 10.8, 4.7 Hz, 1H), 3.74 – 3.79

(m, 5H), 3.79 – 3.94 (m, 3H), 4.01 (t, *J* = 9.4 Hz, 1H), 4.25 (d, *J* = 12.1 Hz, 1H), 4.35 (d, *J* = 12.1 Hz, 1H), 4.46 (dd, *J* = 12.0, 3.1 Hz, 2H), 4.50 – 4.59 (m, 3H), 4.62 (m, 3H), 4.64 (t, *J* = 3.8 Hz, 2H), 4.70 (d, *J* = 12.1 Hz, 1H), 4.88 (d, *J* = 10.9 Hz, 1H), 5.13 (d, *J* = 11.7 Hz, 1H), 5.33 (s, 1H), 7.16 – 7.25 (m, 9H), 7.26 – 7.35 (m, 26H).; ^{13}C NMR (100.67MHz, $CDCl_3$): δ 55.4, 69.5, 69.5, 69.9, 72.2, 72.4, 73.1, 73.3, 73.4, 73.5, 74.9, 75.1, 75.1, 76.4, 77.9, 79.9, 80.1, 81.7, 97.8, 100.6, 126.8 – 127.6 (14), 127.7 – 127.9 (14), 128.1, 128.2, 128.3, 128.4, 128.5, 128.5, 128.6, 138.0, 138.5, 138.5, 138.7, 138.7, 138.8, 138.9; HRMS (ESI-MS): m/z calcd for$[C_{62}H_{66}O_{11}Na]^+$: 1009.4503; Found: 1009.4510.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,6-tri-O-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl α-D-glucopyranosyl) β-D-glucopyranosyl) α-D-glucopyranoside (**66**): mp (^{0}C): 88.9; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +50.2; IR (cm^{-1}, $CHCl_3$): 3067, 2957, 1728, 1601, 1509, 1452, 1268, 1099, 1032, 853, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.06 (s, 3H), 3.79 (dd, *J* = 11.5, 7.7 Hz, 1H), 4.03 – 4.17 (m, 2H), 4.17 – 4.32 (m, 2H), 4.31 – 4.59 (m, 3H), 4.75 (dd, *J* = 12.2, 4.1 Hz, 1H), 4.85 – 5.03 (m, 3H), 5.12 (dd, *J* = 10.2, 3.6 Hz, 1H), 5.24 – 5.46 (m, 3H), 5.68 (t, *J* = 9.8 Hz, 1H), 5.76 (d, *J* = 3.9 Hz, 1H), 5.83 (t, *J* = 9.3 Hz, 1H), 6.10 (q, *J* = 10.5 Hz, 2H), 7.19 – 7.62 (m, 32H), 7.67 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.74 – 7.84 (m, 5H), 7.89 (m, 5H), 7.93 – 7.97 (m, 2H), 8.00 – 8.03 (m, 2H), 8.11 (m, 2H).; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.1, 62.6, 63.6, 68.8, 68.9, 69.2, 69.3, 69.7, 70.0, 70.5, 71.0, 72.1, 72.4, 73.1, 73.3, 75.0, , 96.5, 96.5, 101.4, 128.2 –128.5 (20), 128.6, 128.7, 128.8, 128.9, 128.9, 129.1, 129.2, 129.3, 129.4, 129.5, 129.6-130.1 (20), 133.1, 133.1, 133.1, 133.2, 133.3, 133.3, 133.4, 133.5, 133.5, 133.5, 165.1, 165.2, 165.4, 165.5, 165.6, 165.7, 165.8, 165.8, 165.9, 166.2.; HRMS (ESI-MS): m/z calcd for $[C_{89}H_{74}O_{26}Na]^+$: 1581.4366; Found: 1581.4356.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,6-tri-O-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl α-D-glucopyranosyl) β-D-glucopyranosyl) α-D-glucopyranoside (**67**): mp (^{0}C): 86.8; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +42.8; IR (cm^{-1}, $CHCl_3$): 3024, 2938, 1732, 1603, 1509, 1453, 1266, 1097, 1036, 912, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.24 (s, 3H), 3.31 – 3.38 (m, 1H), 3.43 (td, *J* = 8.1, 6.7, 2.9 Hz, 2H), 3.54 – 3.67 (m, 2H), 3.83 (t, *J* = 9.1 Hz, 1H), 3.89 – 3.97 (m, 1H), 4.15 (dd, *J* = 12.3, 3.3 Hz, 1H), 4.22 – 4.36 (m, 3H), 4.41 (t, *J* = 9.2 Hz, 1H), 4.51 – 4.57 (m, 2H), 4.58 – 4.65 (m, 3H), 4.66 – 4.76 (m, 3H), 5.06 (d, *J* = 11.5 Hz, 1H), 5.20 (dd, *J* = 10.5, 3.8 Hz, 1H), 5.28 (dd, *J* = 9.7, 8.1 Hz, 1H), 5.52 (t, *J*

= 9.3 Hz, 1H), 5.62 – 5.70 (m, 2H), 6.12 (t, *J* = 10.0 Hz, 1H), 7.03 – 7.12 (m, 3H), 7.17 – 7.48 (m, 33H), 7.62 – 7.70 (m, 2H), 7.72 – 7.81 (m, 4H), 7.81 – 7.91 (m, 4H), 7.95 – 8.07 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.3, 62.4, 63.6, 67.6, 69.0, 69.1, 69.5, 69.9, 71.2, 72.6, 72.7, 72.7, 73.6, 73.7, 75.3, 75.3, 77.4, 78.8, 80.1, 96.0, 98.5, 100.2, 127.1– 128.4 (25C), 128.5 – 129.4 (10C), 129.6 – 130.0 (15C), 133.1, 133.1, 133.1, 133.2, 133.3, 133.3, 133.4, 137.7, 138.4, 139.3, 164.9, 165.0, 165.1, 165.6, 165.7, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{89}H_{80}O_{23}Na]^+$: 1539.4988; Found: 1539.4966.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl α-D-glucopyranosyl) α-D-glucopyranosyl) β-D-glucopyranosyl) α-D-glucopyranoside (**68**): mp (^{0}C): 119.8; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +57.0; IR (cm^{-1}, $CHCl_3$): 3067, 3025, 2958, 1726, 1601, 1509, 1452, 1265, 1098, 1030, 935, 754, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.09 (s, 3H), 3.80 (dd, *J* = 11.5, 7.6 Hz, 1H), 4.11 (dd, *J* = 8.7, 2.7 Hz, 2H), 4.19 – 4.33 (m, 2H), 4.39 – 4.53 (m, 5H), 4.61 – 4.78 (m, 3H), 4.89 – 5.02 (m, 3H), 5.14 (ddd, *J* = 10.0, 3.7, 1.4 Hz, 2H), 5.27 – 5.41 (m, 3H), 5.63 (d, *J* = 3.9 Hz, 1H), 5.70 – 5.82 (m, 3H), 5.97 (dd, *J* = 9.8, 8.3 Hz, 1H), 6.13 (dt, *J* = 19.7, 9.9 Hz, 2H), 7.11 – 7.32 (m, 15H), 7.32 – 7.47 (m, 17H), 7.47 – 7.58 (m, 9H), 7.59 – 7.67 (m, 5H), 7.75 – 7.84 (m, 6H), 7.87 – 8.03 (m, 9H), 8.06 – 8.11 (m, 2H), 8.19 – 8.26 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.0, 62.3, 63.0, 63.2, 68.7, 68.9, 69.1, 69.1, 69.6, 70.1, 70.4, 70.7, 70.9, 71.7, 72.0, 72.4, 73.0, 73.7, 73.7, 74.9, 77.3, 96.5, 96.5, 96.8, 101.2, 127.9 – 128.4 (26), 128.5, 128.6, 128.6, 128.6, 128.6, 128.8, 128.9, 128.9, 129.1, 129.1, 129.3, 129.3, 129.4, 129.5 – 130.0 (26), 132.9, 133.0, 133.0, 133.0, 133.0, 133.1, 133.2, 133.3, 133.3, 133.3, 133.3, 133.4, 133.4, 164.8, 164.9, 165.1, 165.2, 165.4, 165.4, 165.5, 165.6, 165.7, 165.7, 165.8, 165.9, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{116}H_{96}O_{34}Na]^+$: 2055.5681; Found: 2055.5711.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl α-D-glucopyranosyl) α-D-glucopyranosyl) β-D-glucopyranosyl) α-D-glucopyranoside (**69**): mp (^{0}C):102.1; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +34.4; IR (cm^{-1}, $CHCl_3$): 3021, 2928, 2863, 1730, 1602, 1452, 1264, 1094, 1031, 917, 752, 706; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.24 (s, 3H), 3.33 – 3.54 (m, 4H), 3.63 (dd, *J* = 10.6, 2.4 Hz, 1H), 3.83 (t, *J* = 9.1 Hz, 1H), 3.93 (t, *J* = 9.3 Hz, 1H), 4.18 – 4.44 (m,

7H), 4.46 – 4.63 (m, 6H), 4.64 – 4.79 (m, 4H), 4.96 – 5.13 (m, 2H), 5.23 (dd, *J* = 9.6, 8.1 Hz, 1H), 5.30 (dd, *J* = 10.5, 3.9 Hz, 1H), 5.43 (t, *J* = 9.3 Hz, 1H), 5.52 (d, *J* = 3.8 Hz, 1H), 5.70 (t, *J* = 9.8 Hz, 1H), 5.76 (d, *J* = 3.9 Hz, 1H), 5.96 (dd, *J* = 9.8, 7.9 Hz, 1H), 6.13 (t, *J* = 10.1 Hz, 1H), 7.08 – 7.16 (m, 7H), 7.16 – 7.26 (m, 10H), 7.37 (m, 23H), 7.46 – 7.60 (m, 9H), 7.64 – 7.72 (m, 2H), 7.73 – 7.80 (m, 6H), 7.88 – 7.94 (m, 2H), 7.94 – 8.00 (m, 2H), 8.00 – 8.06 (m, 2H), 8.12 – 8.20 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.3, 62.3, 62.9, 63.3, 67.6, 69.1, 69.1, 69.5, 70.0, 70.2, 70.9, 70.9, 71.7, 72.5, 72.8, 73.4, 73.4, 73.6, 73.7, 75.3, 75.3, 77.3, 78.8, 80.0, 96.3, 96.8, 98.5, 99.9, 127.1, 127.4, 127.4, 127.4, 127.7, 127.7, 128.0 – 128.4 (20C), 128.5, 128.5, 128.6 (6C), 128.7, 128.7, 128.8, 128.9, 128.9, 129.0 (3C), 129.1, 129.2, 129.4, 129.5 – 130.1 (20C), 133.0, 133.0, 133.0, 133.0, 133.1, 133.1, 133.2, 133.2, 133.4, 133.4, 137.7, 138.4, 139.3, 164.8, 164.9, 165.0, 165.1, 165.4, 165.5, 165.6, 165.8, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{116}H_{102}O_{31}Na]^+$: 2013.6303; Found: 2013.6343.

Cholesteryl 2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranoside (**71**): mp (^{0}C): 198.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -18.8; IR (cm^{-1}, $CHCl_3$): 2929, 2858, 2318, 1733, 1602, 1515, 1454, 1368, 1266, 1106, 968, 711; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.67 (s, 3H), 0.87 (m, 3H), 0.89 (m, 3H), 0.90 – 0.95 (m, 7H), 0.97 – 1.20 (m, 9H), 1.29 – 1.47 (m, 6H), 1.54 (m, 5H), 1.68 – 1.77 (m, 1H), 1.84 (ddd, *J* = 12.9, 9.2, 3.5 Hz, 1H), 1.90 – 1.98 (m, 2H), 1.97 – 2.06 (m, 1H), 2.11 – 2.24 (m, 2H), 3.55 (tt, *J* = 10.3, 5.2 Hz, 1H), 4.17 (ddd, *J* = 9.5, 5.8, 3.4 Hz, 1H), 4.54 (dd, *J* = 12.0, 5.9 Hz, 1H), 4.62 (dd, *J* = 12.0, 3.3 Hz, 1H), 4.96 (d, *J* = 7.9 Hz, 1H), 5.24 (d, *J* = 5.1 Hz, 1H), 5.52 (dd, *J* = 9.7, 8.0 Hz, 1H), 5.65 (t, *J* = 9.7 Hz, 1H), 5.92 (t, *J* = 9.6 Hz, 1H), 7.26 – 7.45 (m, 9H), 7.48 – 7.59 (m, 3H), 7.83 – 7.87 (m, 2H), 7.89 – 7.95 (m, 2H), 7.95 – 8.01 (m, 2H), 8.01 – 8.06 (m, 2H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 11.8, 18.7, 19.3, 21.0, 22.6, 22.8, 23.8, 24.3, 28.0, 28.2, 29.6, 31.8, 31.9, 35.8, 36.2, 36.6, 37.1, 38.8, 39.5, 39.8, 42.3, 50.1, 56.2, 56.8, 63.4, 70.1, 72.1 (2C), 73.1, 80.5, 100.2, 122.0, 128.3 – 128.4 (8C), 128.8, 128.9, 129.5, 129.7, 129.7 – 129.8 (8C), 133.1, 133.1, 133.2, 133.4, 140.3, 165.1, 165.3, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{61}H_{72}O_{10}Na]^+$: 987.5023; Found: 987.5019.

Phenyl 2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranoside (**73**): mp (^{0}C): 64.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +21.0; IR (cm^{-1}, $CHCl_3$): 3065, 2925, 1726, 1597, 1493, 1452, 1261, 1095, 978, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 4.38 (dd, *J* = 10.8, 5.3 Hz, 1H), 4.58 (dd, *J* = 11.9, 6.7 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 5.46 (d, *J* = 7.7 Hz, 1H), 5.77 (t, *J*

= 9.6 Hz, 1H), 5.83 – 5.91 (m, 1H), 6.05(t, *J* = 9.5 Hz, 1H), 7.05 (t, 3H), 7.17 – 7.24 (m, 2H), 7.30 – 7.64 (m, 12H), 7.88 – 7.92 (m, 2H), 7.96 – 8.02 (m, 4H), 8.05 – 8.10(m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 63.3, 69.7, 71.8, 72.6, 72.9, 99.7, 117.3, 117.3, 123.4, 128.4 – 128.5 (8C), 128.7, 128.8, 129.1, 129.5, 129.5, 129.6, 129.8 – 129.9 (8C), 133.2, 133.3, 133.3, 133.6, 157.0, 165.1, 165.3, 165.8, 166.1; HRMS (ESI-MS): m/z calcd for$[C_{40}H_{32}O_{10}Na]^+$: 695.1893; Found: 695.1885.

4-*O*-(2′,3′,4′,6′-Tetra-*O*-benzoyl-β-D-glucopyranosyl) *epi*-podophyllotoxin (**75**): mp (^{0}C): 80.7; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -12.4; IR (cm^{-1}, $CHCl_3$): 3030, 2910, 2823, 1720, 1635, 1445, 1340, 1238, 1127, 963, 718; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.75 (dd, J = 14.4, 4.7 Hz, 1H), 2.88 – 3.01 (m, 1H), 3.70 (s, 3H), 3.76 (s, 6H), 4.09 (dd, J = 10.2, 8.8 Hz, 1H), 4.17 – 4.24 (m, 1H), 4.46 – 4.58 (m, 2H), 4.71 (dd, J = 12.3, 2.8 Hz, 1H), 5.01 (dd, J = 8.9, 6.3 Hz, 1H), 5.65 (dd, J = 9.1, 7.1 Hz, 1H), 5.70 (t, J = 8.9 Hz, 1H), 5.93 – 5.98 (m, 2H), 6.36 (s, 1H), 6.36 (s, 1H), 6.50 (s, 1H), 7.16 – 7.21 (m, 2H), 7.27 – 7.33 (m, 4H), 7.34 – 7.42 (m, 6H), 7.42 – 7.48 (m, 1H), 7.50 – 7.57 (m, 3H), 7.81 – 7.85 (m, 2H), 7.87 – 7.91 (m, 2H), 7.93 – 7.97 (m, 4H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 38.5, 44.0, 45.5, 56.4, 60.6, 62.9, 69.6, 71.1, 71.8, 72.7, 72.8, 80.0, 99.0, 101.5, 108.0, 108.6, 109.5, 127.7, 128.1, 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.6, 128.7 (4C), 129.1(2C), 129.2 (2C), 129.6 (2C), 129.7 (4C), 129.8 (2C), 133.4, 133.2, 133.4, 133.6, 135.0, 137.4, 147.7, 148.1, 152.6, 164.9, 165.2, 165.8, 166.0, 173.7; HRMS (ESI-MS): m/z calcd for$[C_{56}H_{48}O_{17}Na]^+$: 1015.2789; Found: 1015.2796.

Benzyl-*N*-(fluorenylmethyloxycarbonyl)-*O*-(2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranosyl) L-serinate (**77**): mp (^{0}C): 58.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +3.9; IR (cm^{-1}, $CHCl_3$): 3012, 2968, 1736, 1594, 1453, 1367, 1217, 1104, 909, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.87-3.98 (dd, *J* = 10.3, 3.0 Hz, 1H), 4.02-4.15 (dd, *J* = 8.8, 5.5 Hz, 2H), 4.22 (dd, *J* = 10.4, 7.3 Hz, 1H), 4.39 – 4.40 (m, 2H), 4.42 – 4.47 (m, 1H), 4.49 – 4.56 (m, 1H), 4.63(dd, *J* = 12.2, 2.9 Hz, 1H), 4.77 (d, *J* = 7.8 Hz, 1H), 5.15 (ABq, *J* = 12.2 Hz, 2H), 5.47-5.53 (m, 1H), 5.66 (dd, *J* = 18.1, 8.8 Hz, 2H), 5.91 (t, *J* = 9.7 Hz, 1H), 7.21 – 7.44(m, 19H), 7.45-7.58 (m, 4H), 7.75 – 7.81 (m, 2H), 8.03 (m, 2H), 7.89 – 7.95 (m, 4H), 8.02 (m, 2H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 47.2, 54.5, 63.1, 67.1, 67.6, 69.6, 69.6, 71.4, 72.9, 72.7, 101.5, 120.1, 120.1, 125.3, 125.3, 127.2, 127.2, 127.9, 127.9, 128.4-128.7 (16C), 128.8, 129.1, 129.6, 129.9-129.9 (6C), 133.3, 133.4, 133.4,

133.6, 135.3, 141.4, 141.4, 143.8, 144.0, 156.0, 165.2, 165.3, 165.9, 166.2, 169.4; HRMS (ESI-MS): m/z calcd for $[C_{59}H_{49}NNaO_{14}]^+$: 1018.3051; Found: 1018.3057.

1-*deoxy*-1-allyl 2,3,4,6-tetra-O-benzyl α-D-glucopyranoside (**79**): mp (^{0}C): 60.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +54.0; IR (cm^{-1}, $CHCl_3$): 3065, 3044, 2910, 1605, 1485, 1337, 1250, 1090, 970, 712; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.44 – 2.55 (m, 2H), 3.60 – 3.68 (m, 3H), 3.71 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.75 – 3.83 (m, 2H), 4.14 (dt, *J* = 10.2, 5.1 Hz, 1H), 4.43 – 4.53 (m, 2H), 4.62 (s, 1H), 4.64 (s, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.81 (dd, *J* = 10.7, 1.6 Hz, 2H), 4.94 (d, *J* = 10.9 Hz, 1H), 5.10 (dt, *J* = 10.2, 5.2 Hz, 2H), 5.82 (ddt, *J* = 17.2, 10.2, 6.8 Hz, 1H), 7.11 – 7.13 (m, 2H), 7.25 – 7.38 (m, 18H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 29.9, 68.9, 71.1, 73.2, 73.6, 73.8, 75.2, 75.6, 78.1, 80.1, 82.5, 117.0, 127.7 (2C), 127.9 (4C), 128.0 (2C), 128.1 (4C), 128.4 (2C), 128.5 (6C), 134.8, 138.1, 138.2, 138.3, 138.8; HRMS (ESI-MS): m/z calcd for$[C_{37}H_{40}O_5Na]^+$: 587.2773; Found: 587.2770.

1-*deoxy*-1-(2-propanone) 2,3,4,6-tetra-O-benzyl α/β-D-glucopyranoside [α:β (5.0:1.0)] (**81**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +69.0; IR (cm^{-1}, $CHCl_3$): 3040, 3020, 2915, 1732, 1633, 1456, 1317, 1250, 1090, 973, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.13 (s, 3H), 2.14 (s, 3H), 2.51 – 2.94 (m, 5H), 3.27 – 3.87 (m, 11H), 4.40 – 4.98 (m, 17H), 7.05 – 7.58 (m, 40H) ; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 30.7, 31.0, 41.1, 46.0, 68.9, 68.9, 71.0, 72.5, 73.5, 73.5, 73.6, 73.6, 75.1, 75.5, 75.6, 75.7, 75.7, 77.8, 78.5, 79.0, 79.5, 81.3, 82.2, 87.3, 127.8 (6C), 127.9 (2C), 128.0 (6C), 128.1 (4C), 128.2 (4C), 128.5 (12C), 128.6 (6C), 138.0 (4C), 138.2, 138.2, 138.6, 138.7, 206.3, 206.8; HRMS (ESI-MS): m/z calcd for$[C_{37}H_{40}O_6Na]^+$: 603.2723; Found: 603.2731.

1-*deoxy*-1-cyclohexanone 2,3,4,6-tetra-O-benzyl α-D-glucopyranoside (**83**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +40.0; IR (cm^{-1}, $CHCl_3$): 3050, 3025, 2923, 1720, 1615, 1470, 1322, 1264, 1105, 989, 725; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.87 – 0.93 (m, 1H), 1.59 – 1.66 (m, 3H), 1.73 – 1.81 (m, 3H), 2.25 – 2.40 (m, 3H), 2.41 – 2.59 (m, 1H), 3.06 (dt, *J* = 10.2, 5.1 Hz, 1H), 3.61 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.64 – 3.80 (m, 2H), 3.87 – 3.92 (m, 2H), 4.45 – 4.51 (m, 2H), 4.54 – 4.62 (m, 2H), 4.73– 4.77 (m, 3H), 7.18 – 7.23 (m, 2H), 7.29 – 7.39 (m, 18H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.1, 28.3, 29.8, 41.1, 50.9, 68.8, 70.0, 73.1, 73.2, 73.4, 73.9, 74.3, 76.3, 78.4, 79.9, 127.5, 127.6, 127.7, 127.8 (4C), 127.9 (3C), 128.1(2C), 128.3 (4C), 128.4 (8C), 137.9, 138.2, 138.3

(2C), 211.8; HRMS (ESI-MS): m/z calcd for$[C_{40}H_{44}O_6Na]^+$: 643.3036; Found: 643.3029.

1-*deoxy*-1-cyano 2,3,4,6-tetra-O-benzyl α-D-glucopyranoside (**85**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +46.8; IR (cm^{-1}, $CHCl_3$): 3025, 2190, 1635, 1472, 1240, 1090, 975, 705; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.66 – 3.73 (m, 3H), 3.78 (dd, *J* = 10.9, 3.2 Hz, 1H), 3.85 – 3.89 (m, 1H), 3.94 (t, *J* = 9.3 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 4.60 (d, *J* = 12.1 Hz, 1H), 4.65 (s, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.85 (t, *J* = 10.9 Hz, 2H), 4.89 (d, *J* = 9.2 Hz, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 7.16 – 7.21 (m, 2H), 7.30 – 7.40 (m, 18H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 67.1, 67.9, 73.7, 74.0, 75.4, 76.1, 76.3, 76.4, 77.2, 83.3, 115.6, 127.9, 127.9, 128.0, 128.0, 128.0, 128.1, 128.1, 128.1, 128.3, 128.3, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.9, 128.9, 137.3, 137.6, 138.0, 138.4; HRMS (ESI-MS): m/z calcd for$[C_{35}H_{35}NO_5Na]^+$: 572.2413; Found: 572.2414.

1-*deoxy*-1-Azido 2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranoside (**87**): mp (^{0}C): 53.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +0.86; IR (cm^{-1}, $CHCl_3$): 3068, 2960, 2119, 1728, 1603, 1452, 1261, 1094, 940, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 4.23-4.30(m, 1H), 4.52 (dd, *J* = 12.3, 5.0 Hz, 1H), 4.68 (d, *J* = 8.2Hz, 1H), 4.98 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.50 (td, *J* = 9.3, 2.2 Hz, 1H), 5.72 (td, *J* = 9.8, 2.1 Hz, 1H), 5.93 (td, *J* = 8.0, 4.0 Hz, 1H), 7.23 – 7.28 (m, 2H), 7.32 – 7.344(m, 7H), 7.46 – 7.57 (m, 3H), 7.79 – 7.84 (m, 2H), 7.86 – 7.92 (m, 2H), 7.94– 7.98 (m, 2H), 8.01 – 8.07 (m, 2H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 62.9, 69.2, 71.3, 72.8, 74.5, 88.4, 128.4 – 128.6 (8C), 128.6, 128.6, 128.8, 129.5, 129.8 – 130.0 (8C), 133.3, 133.5, 133.7, 133.7, 165.1, 165.2, 165.8, 166.2 HRMS (ESI-MS): m/z calcd for$[C_{34}H_{27}N_3O_9Na]^+$: 644.1645; Found: 644.1660.

1-*deoxy*-1-Thymine-2,3,4,6-tetra-*O*-benzoyl β-D-glucopyranoside (**89**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +5.1; IR(cm^{-1}, $CHCl_3$): 3012, 2968, 1727, 1512, 1452, 1267, 1090, 909, 707; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.93 (d, *J* = 1.2 Hz, 3H), 4.34 – 4.44 (m, 1H), 4.48 (dd, *J* = 12.4, 5.1 Hz, 1H), 4.67 (dd, *J* = 12.4, 2.7 Hz, 1H), 5.68 (t, *J* = 9.5 Hz, 1H), 5.78 (t, *J* = 9.8 Hz, 1H), 6.08 (t, *J* = 9.7 Hz, 1H), 6.26 (d, *J* = 9.5 Hz, 1H), 7.23 – 7.46 (m, 10H), 7.47 – 7.62 (m, 3H), 7.76 – 7.84 (m, 2H), 7.84 – 7.89 (m, 2H), 7.90 – 7.96 (m, 2H), 8.01 – 8.07 (m, 2H), 8.51 (s, 1H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 12.7, 62.7, 68.9, 70.2, 73.0, 75.4, 80.6, 112.3, 128.0, 128.0, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 129.4, 129.4, 129.8, 129.8, 129.9, 129.9, 130.0, 130.0, 130.1,

130.1, 133.4, 133.5, 133.8, 133.9, 134.6, 150.3, 163.1, 165.3, 165.3, 165.5, 166.1; HRMS (ESI-MS): m/z $[M + H]^+$calcd for $[C_{39}H_{33}N_2O_{11}]^+$: 705.2084; Found: 705.2089.

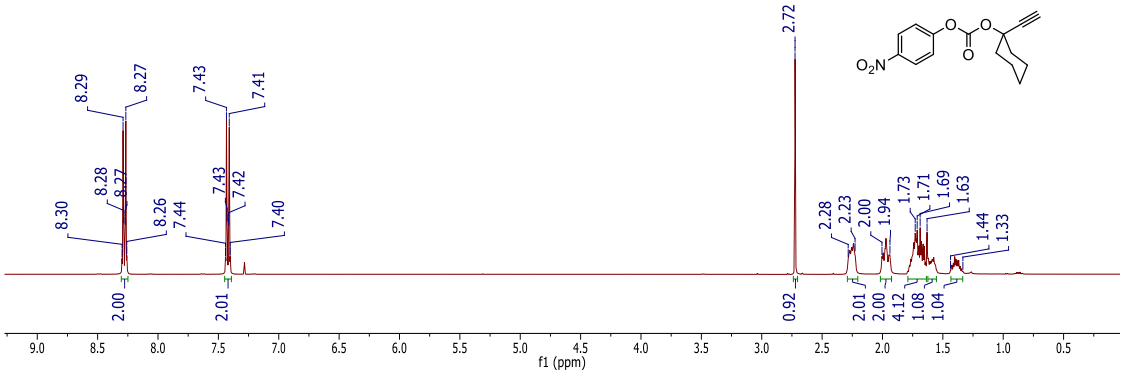
1-*deoxy*-1-(2-oxoquinolin-1-yl) 2-*O*-benzoyl-3,4,6-tri-O-benzyl β-D-glucopyranoside (**91**): mp (^{0}C): 78.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +25.6; IR (cm^{-1}, $CHCl_3$): 3020, 2930, 1720, 1610, 1460, 1330, 1090, 980, 720; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.88 (dd, *J* = 10.8, 1.7 Hz, 1H), 3.98 – 3.93 (m, 1H), 4.03 (dd, *J* = 10.8, 2.8 Hz, 1H), 4.19 (t, *J* = 9.1 Hz, 1H), 4.30 (t, *J* = 9.4 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 5.03 (d, *J* = 10.9 Hz, 1H), 6.25 (t, *J* = 9.4 Hz, 1H), 6.48 (d, *J* = 9.4 Hz, 1H), 7.07 (d, *J* = 9.9 Hz, 1H), 7.29 – 7.14 (m, 6H), 7.57 – 7.32 (m, 16H), 7.97 – 7.81 (m, 2H), 8.26 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 68.2, 70.4, 73.4, 75.4, 75.5, 77.4, 78.2, 80.9, 83.9, 117.5, 120.4, 121.2, 123.0, 127.4 (2C), 127.7, 127.8, 128.0, 128.1 (4C), 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.6 (2C), 129.1, 129.2, 129.8 (2C), 130.3, 133.2, 137.7, 137.9, 138.1, 138.3, 140.8, 162.6, 164.9; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{39}NO_7Na]^+$: 704.2624; Found: 704.2620.

N^2-Benzyloxycarbonyl-N^4-(2-*O*-benzoyl-3,4,6-tri-O-benzyl b-D-glucopyranosyl)-L-asparagine benzyl ester (**93**): mp (^{0}C): 82.8; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +45.2; IR (cm^{-1}, $CHCl_3$): 3068, 2927, 1726, 1603, 1452, 1261, 1099, 1029, 974, 754, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.70 – 2.98 (m, 2H), 3.77 – 4.20 (m, 5H), 4.42 – 4.70 (m, 5H), 4.75 – 4.90 (m, 2H), 4.95 – 5.30 (m, 4H), 5.49 – 5.69 (m, 1H), 5.74 – 5.89 (m, 1H), 6.01 – 6.18 (m, 1H), 7.05 – 7.48 (m, 27H), 7.51 – 7.66 (m, 1H), 8.09 – 8.15 (m, 2H) {anomeric N<u>H</u>CO proton generally not observed in $CDCl_3$}; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 38.2, 50.8, 67.1, 67.6, 68.7, 69.4, 72.2, 73.5, 73.9, 74.4, 75.2, 77.0, 81.1, 127.6 (4C), 127.8, 127.9, 128.0 (3C), 128.1(3C), 128.2 (3C), 128.4 (8C), 128.5 (4C), 128.6 (3C), 133.6, 135.3, 136.1, 137.7, 134.0, 138.4, 156.4, 165.9, 169.9, 170.9; HRMS (ESI-MS): m/z calcd for$[C_{53}H_{52}N_2O_{11}Na]^+$: 915.3469; Found: 915.3468.

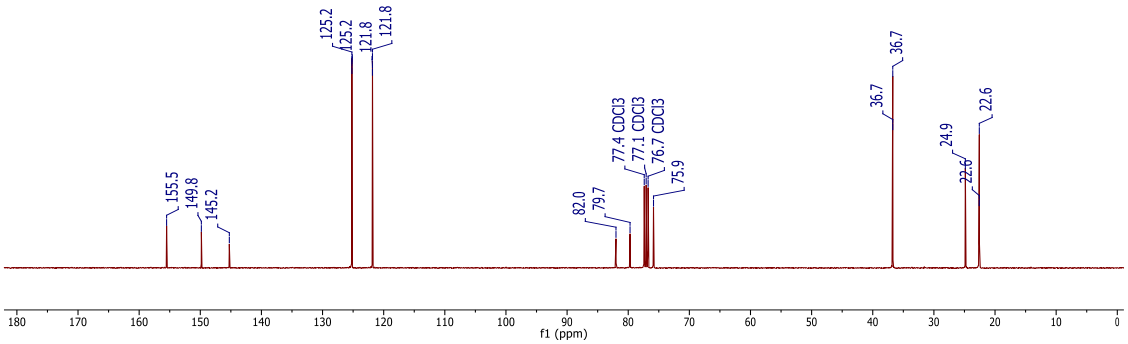
2.8 – Spectral Charts of Representative Compounds

{Kindly see the supporting documents file in *Angew. Chem. Int. Ed.* **2016**, *128*, 7917–7922 for spectral charts of all compounds excluding compound no **44q**, **75**, **79**, **81**, **83**, **85**, **91** and **93}**

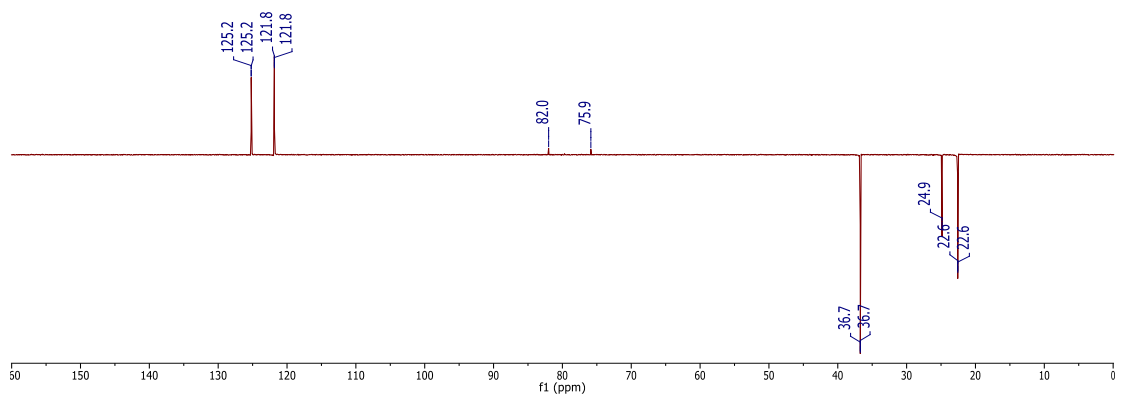
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **42**



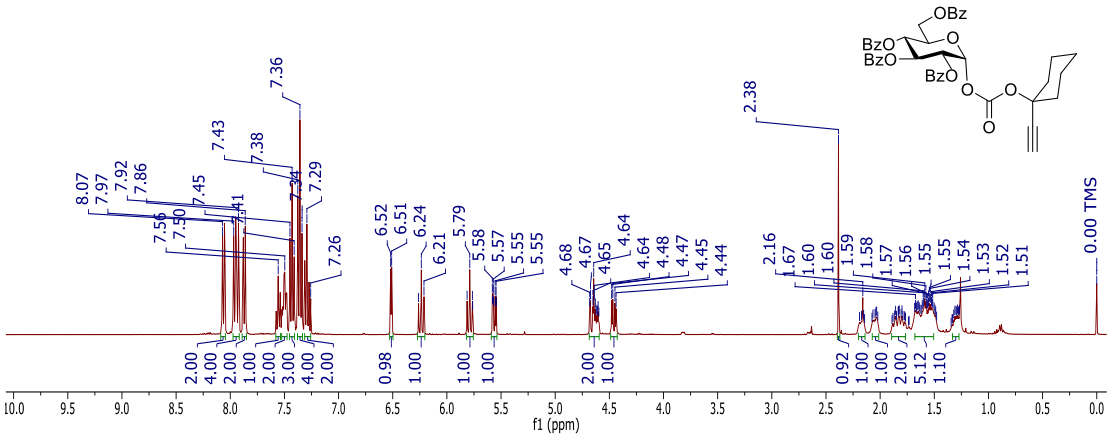
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **42**



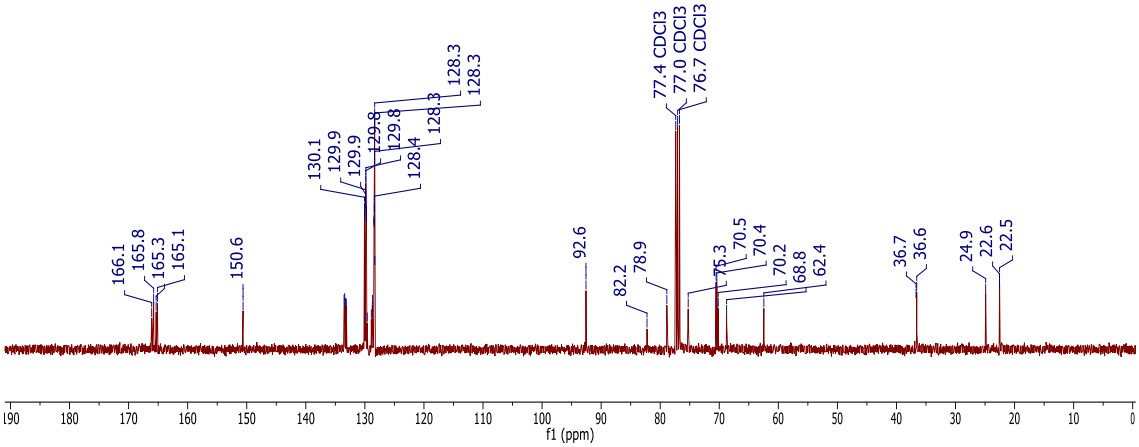
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **42**



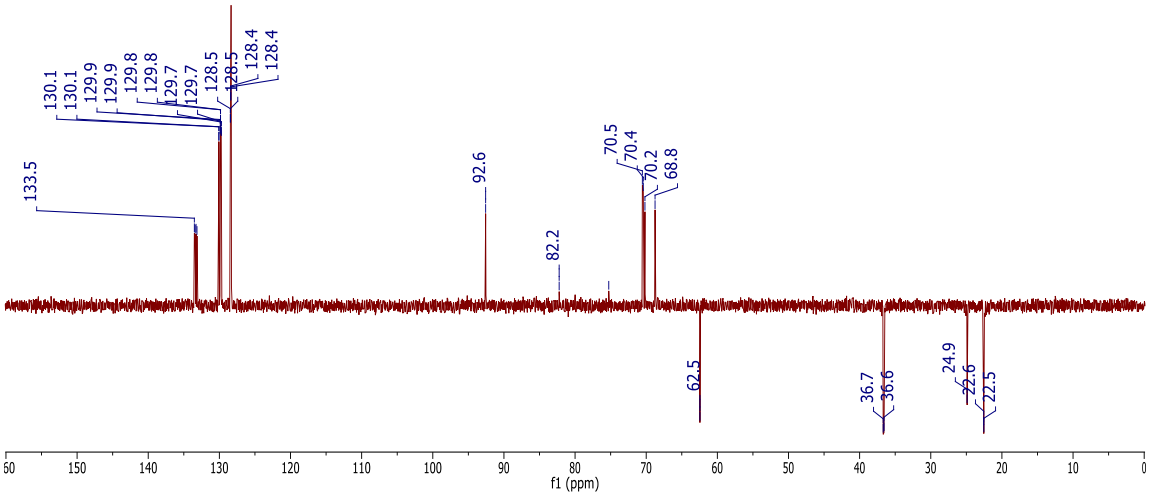
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **44aα**



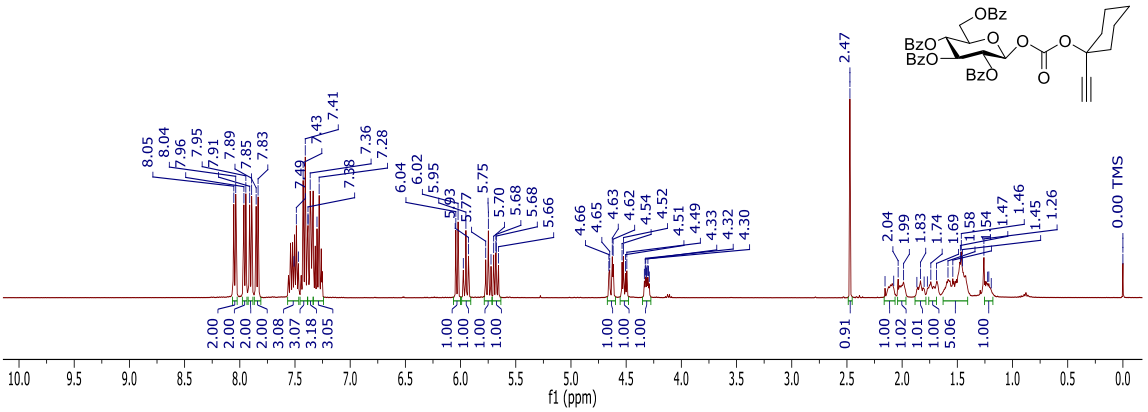
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44aα**



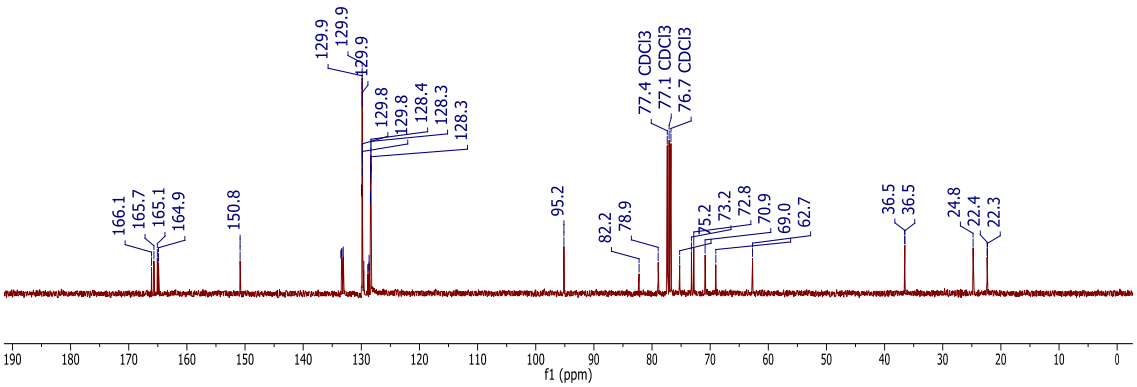
DEPT Spectrum (100.67 MHz, $CDCl_3$) of compound **44aα**



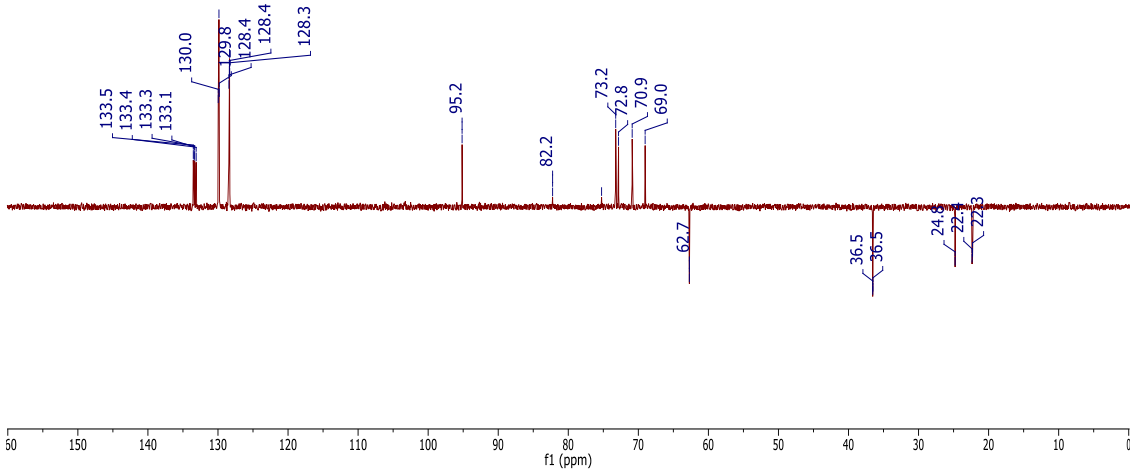
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **44aβ**



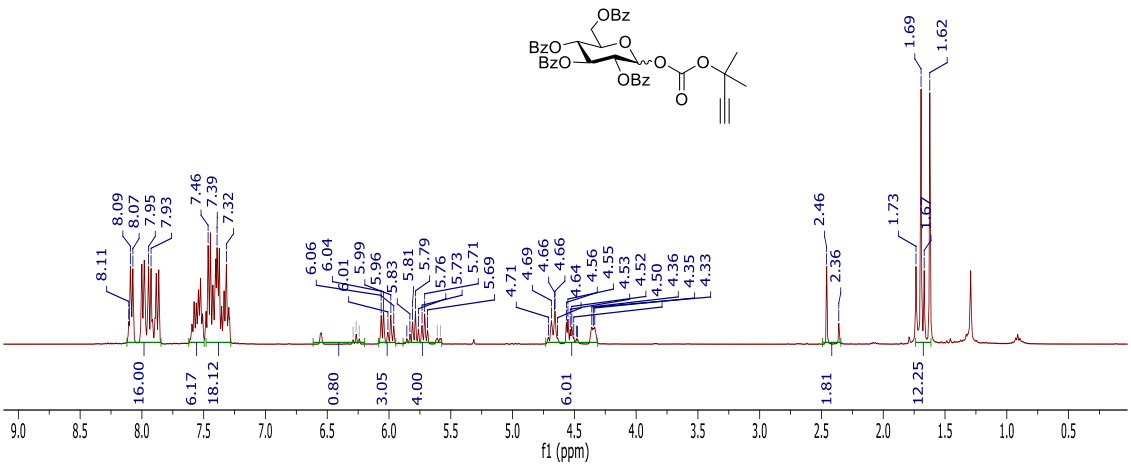
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44aβ**



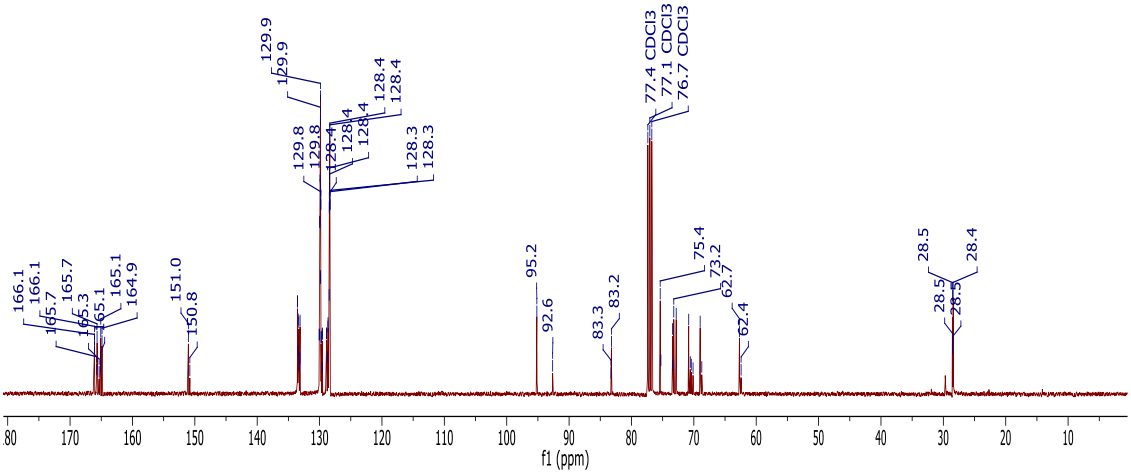
DEPT Spectrum (100.67 MHz, $CDCl_3$) of compound **44aβ**



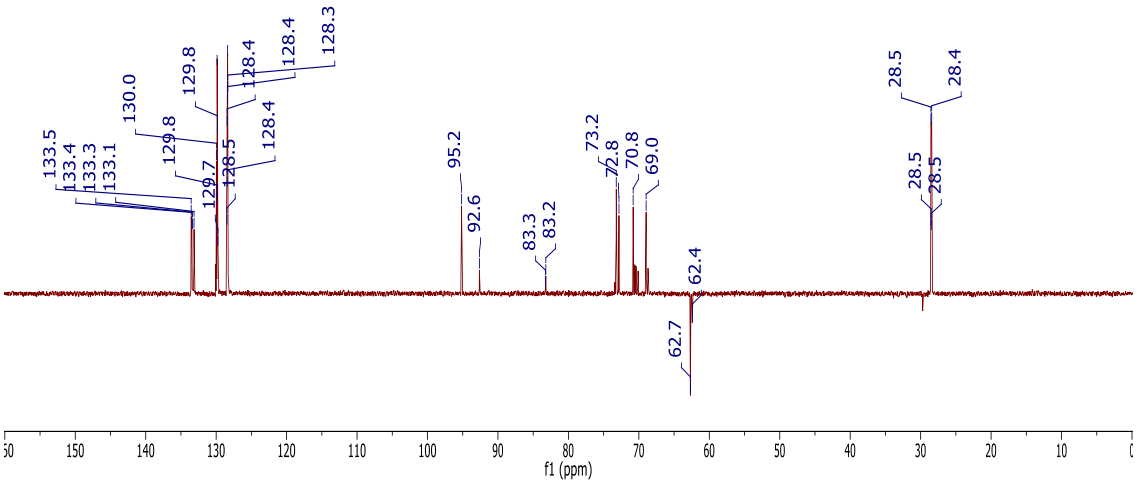
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **44d**



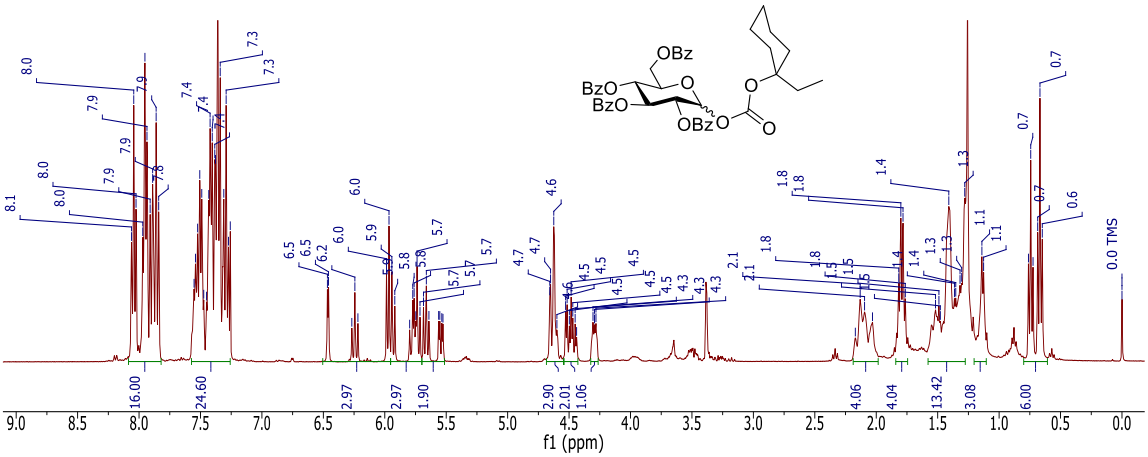
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44d**



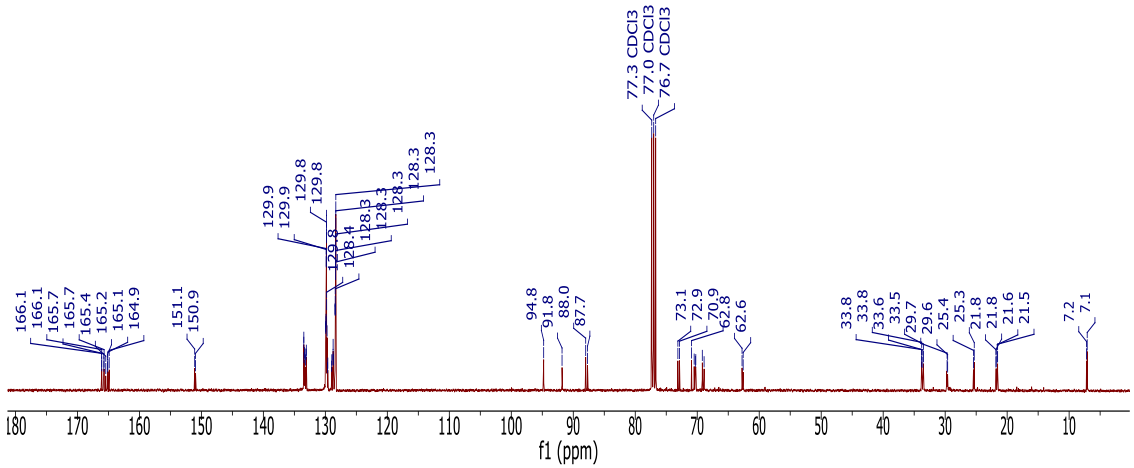
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **44d**



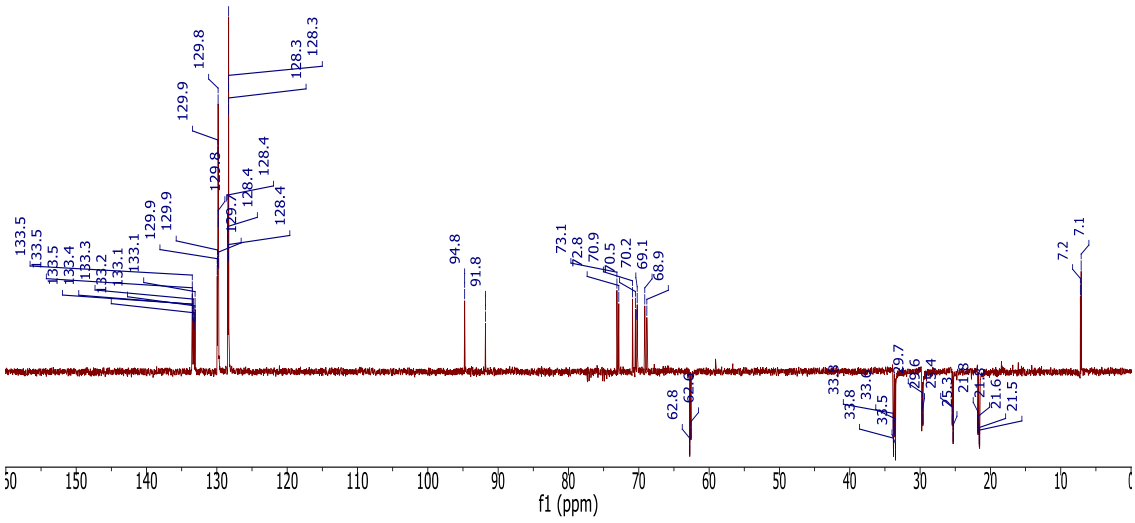
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **44i**



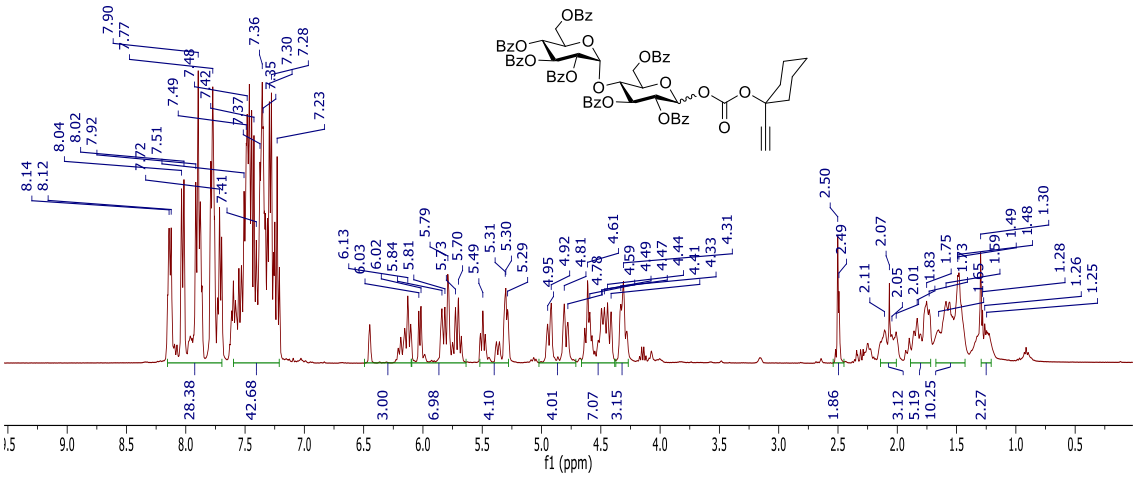
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44i**



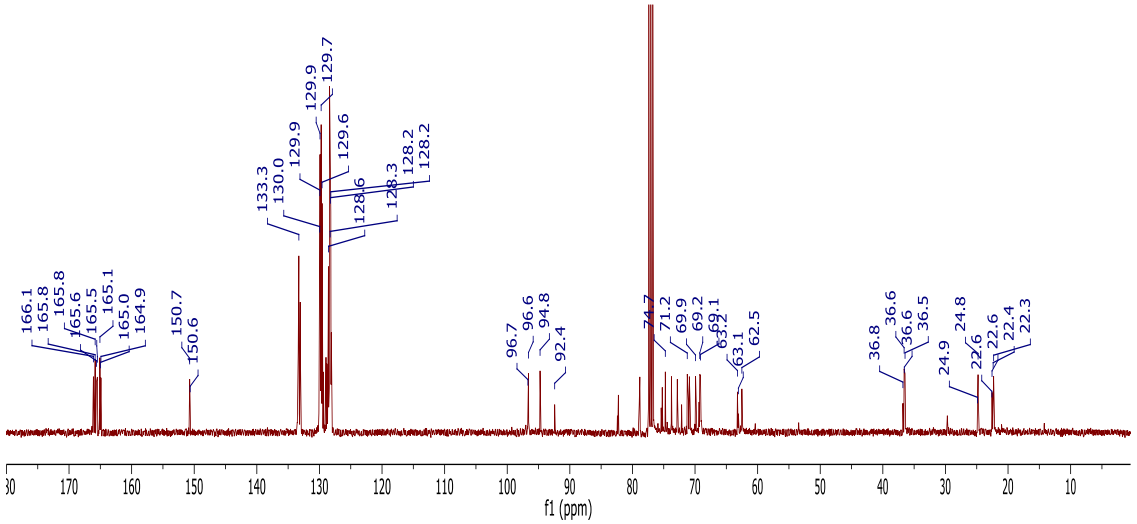
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **44i**



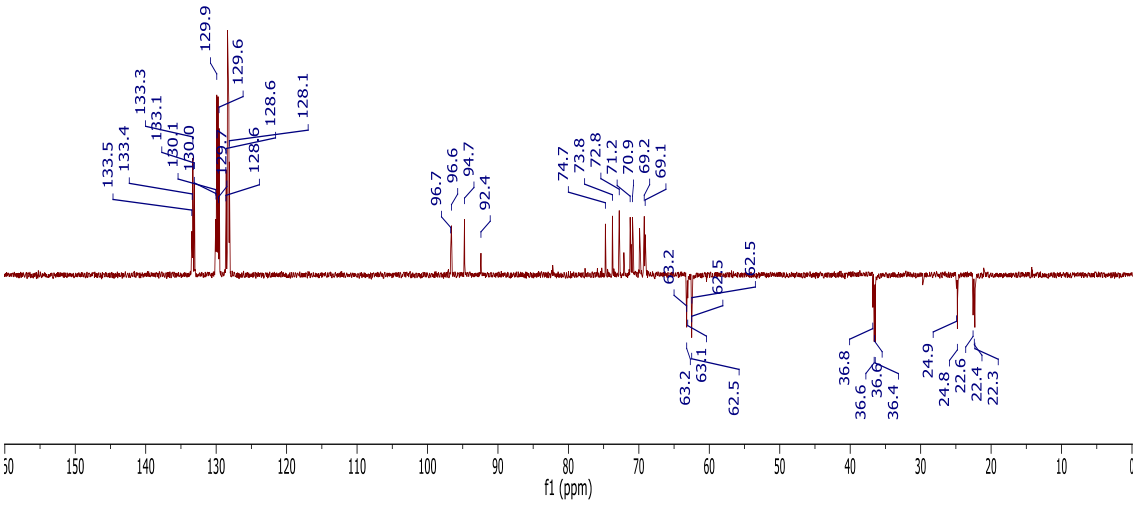
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **44m**



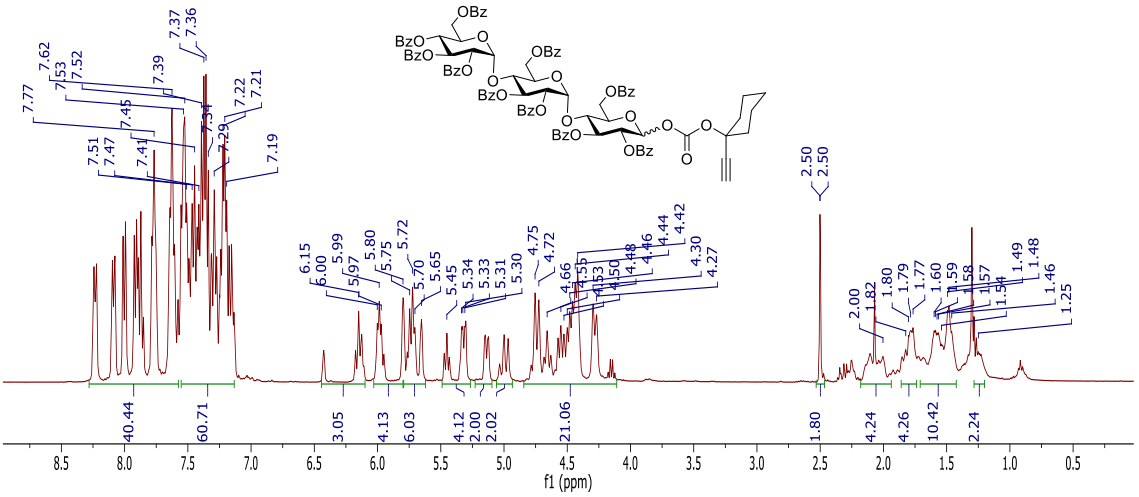
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44m**



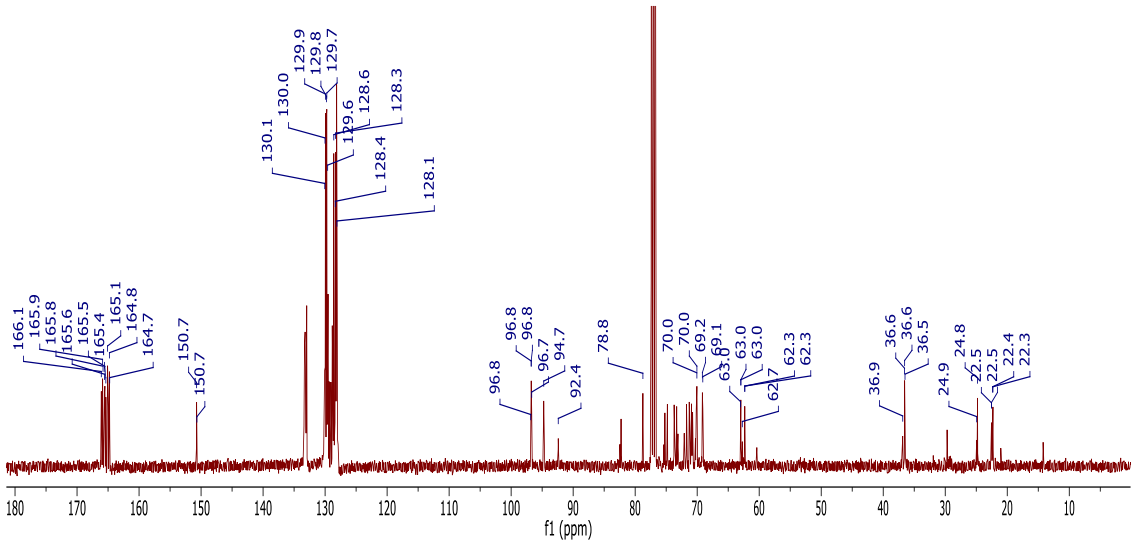
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44m**



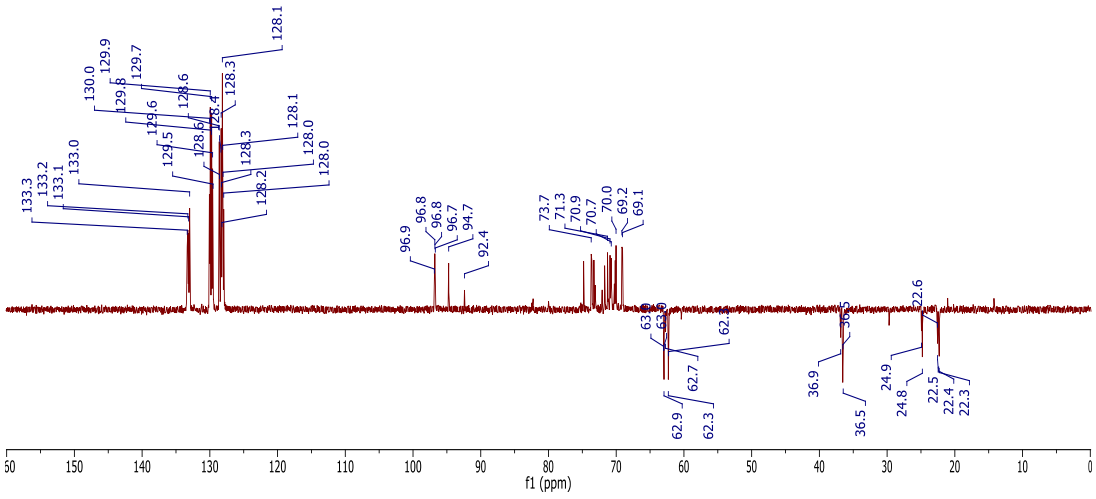
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **44n**



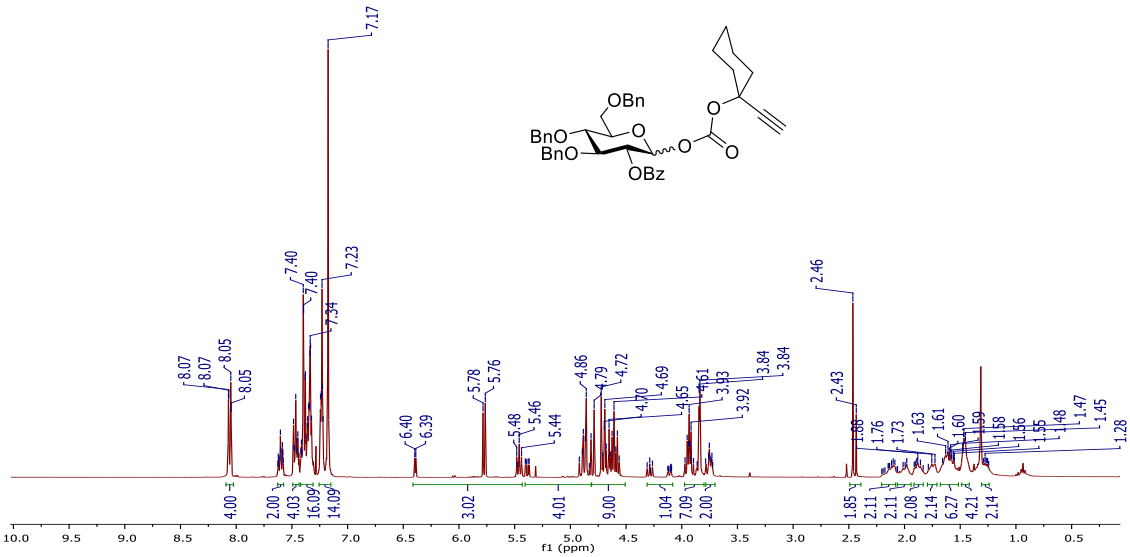
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44n**



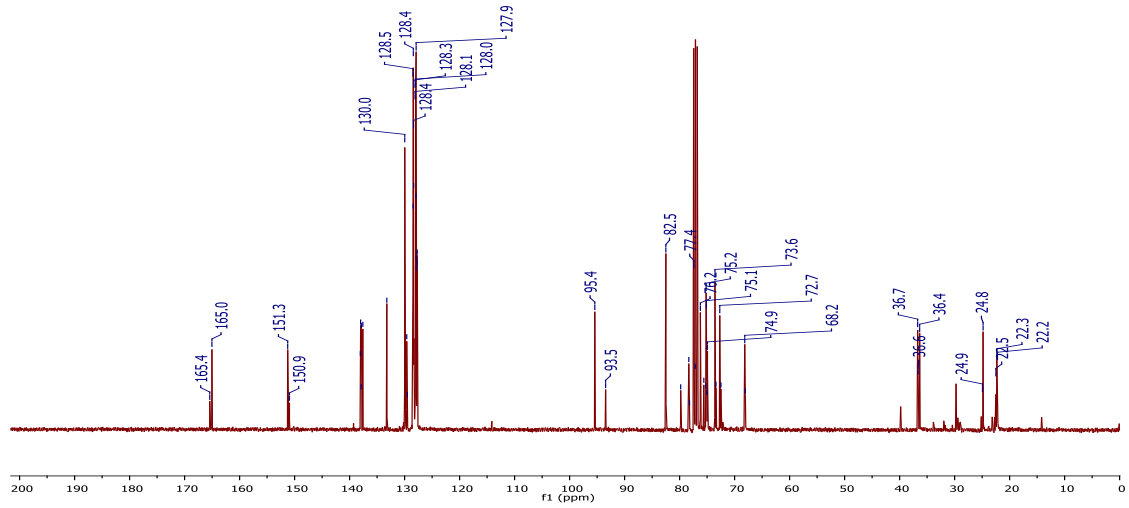
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44n**



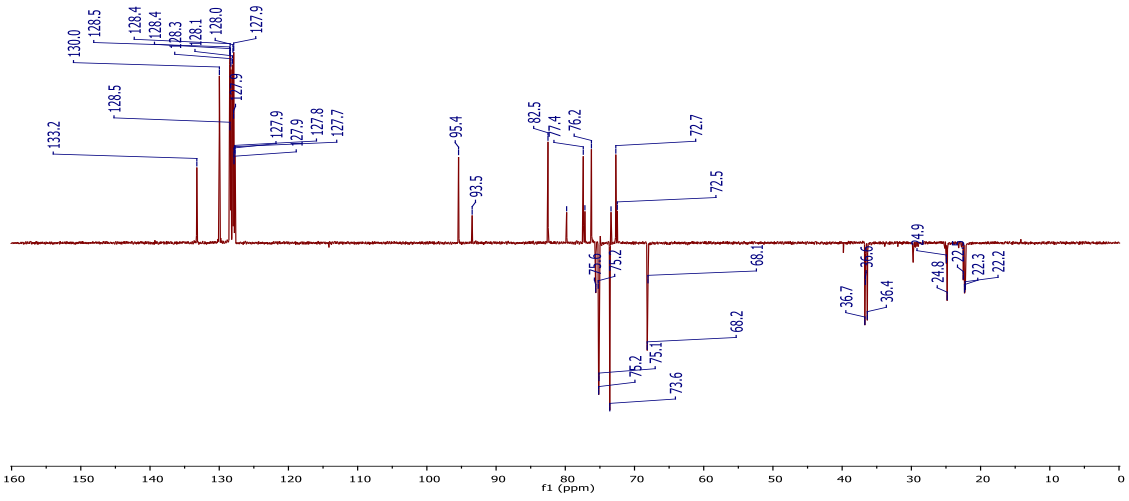
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **44q**



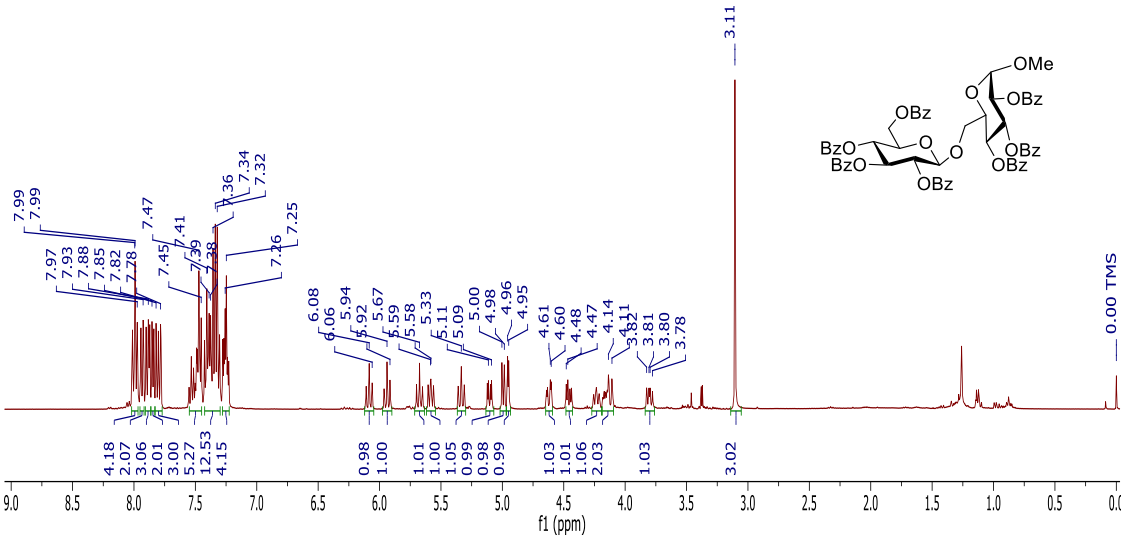
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44q**



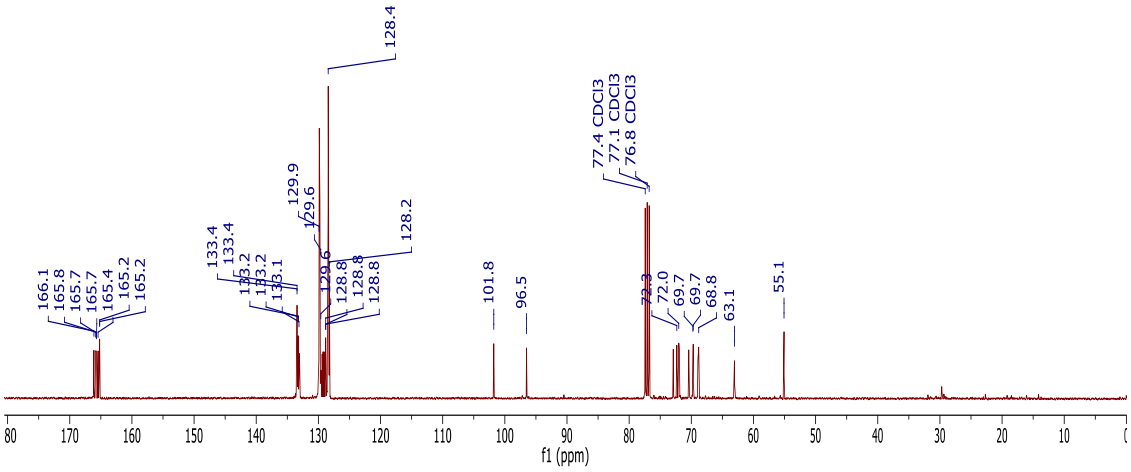
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **44q**



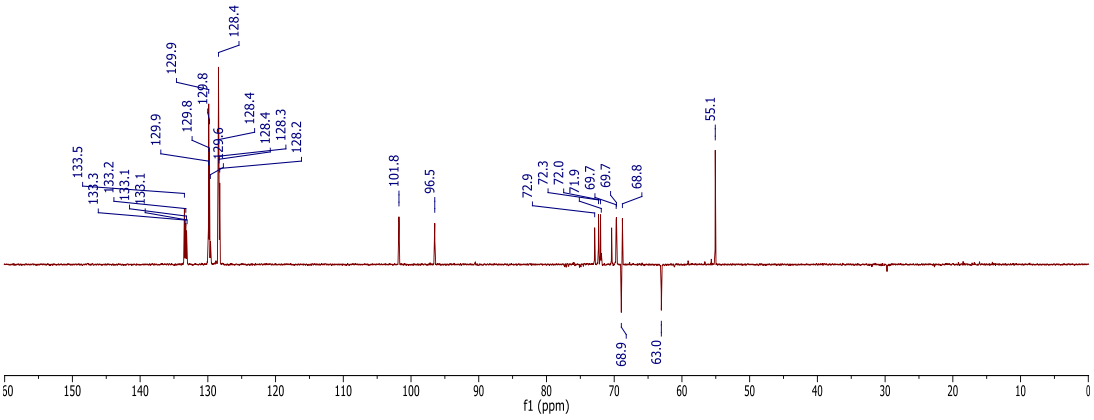
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **46**



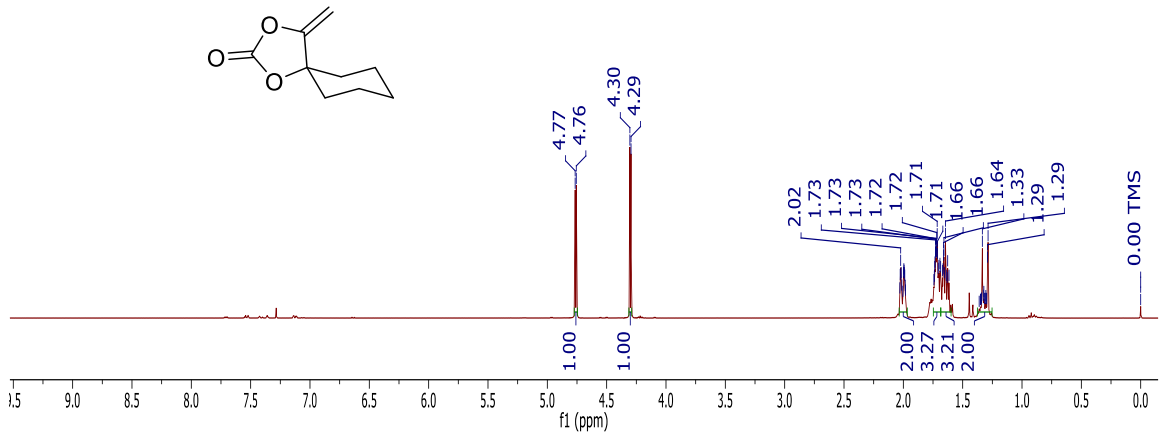
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **46**



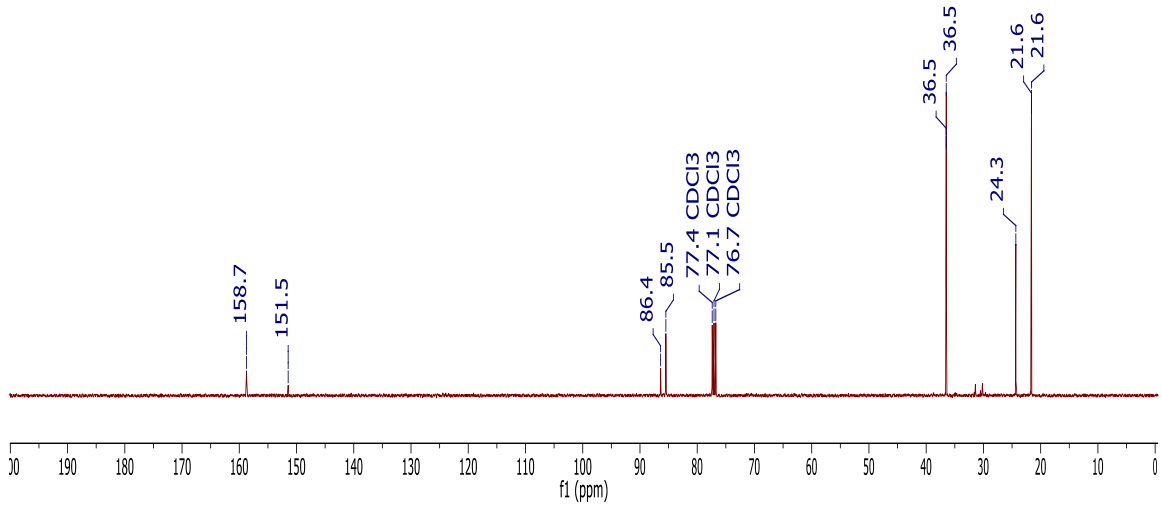
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **46**



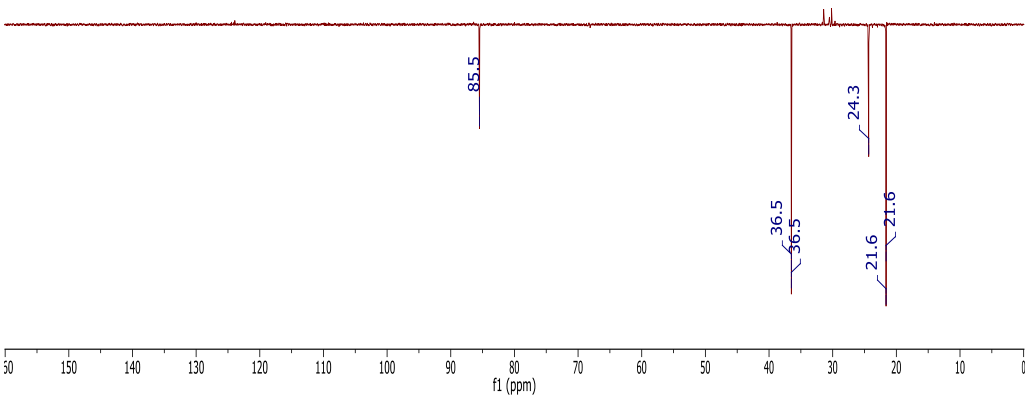
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **22**



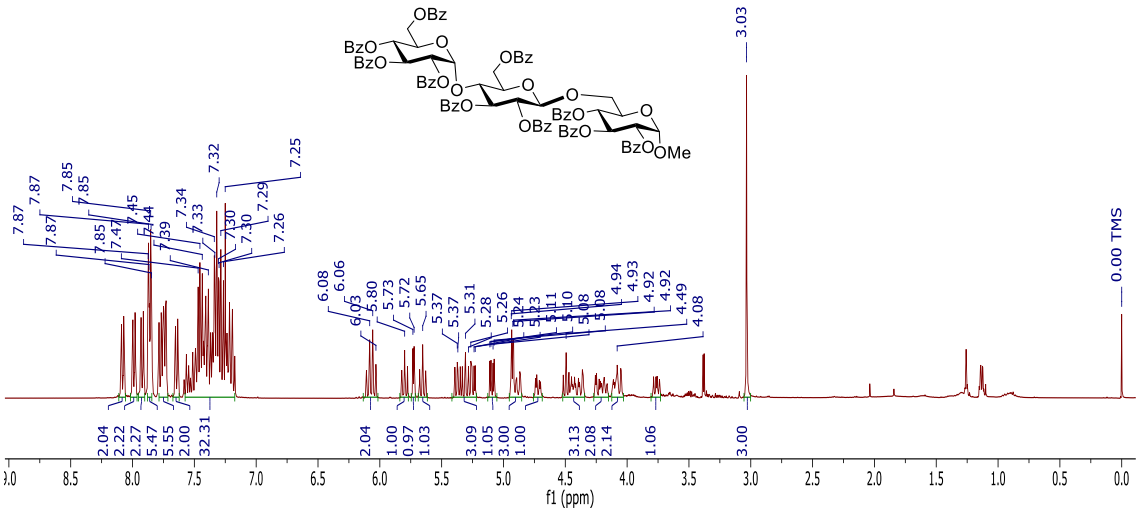
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **22**



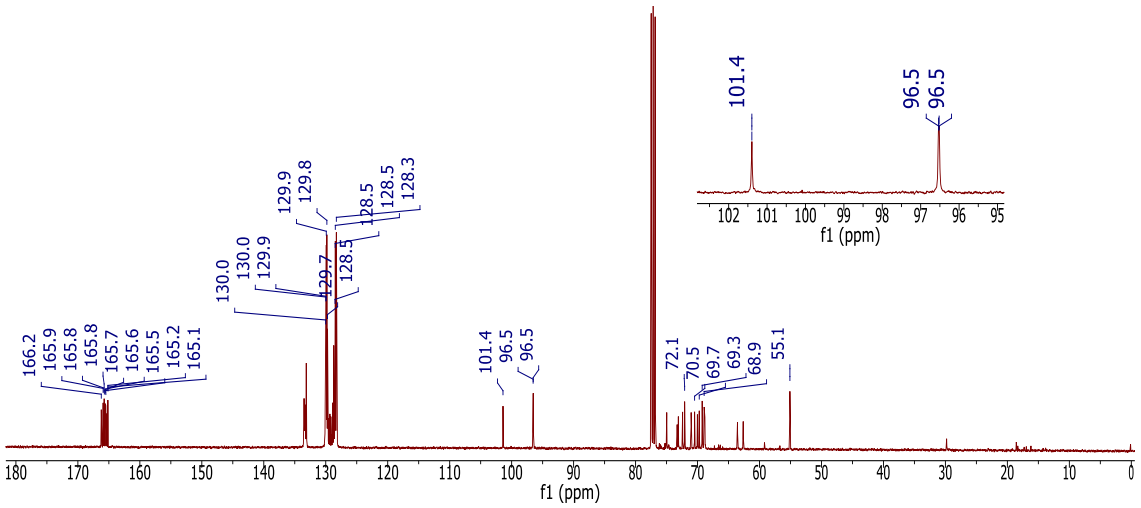
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **22**



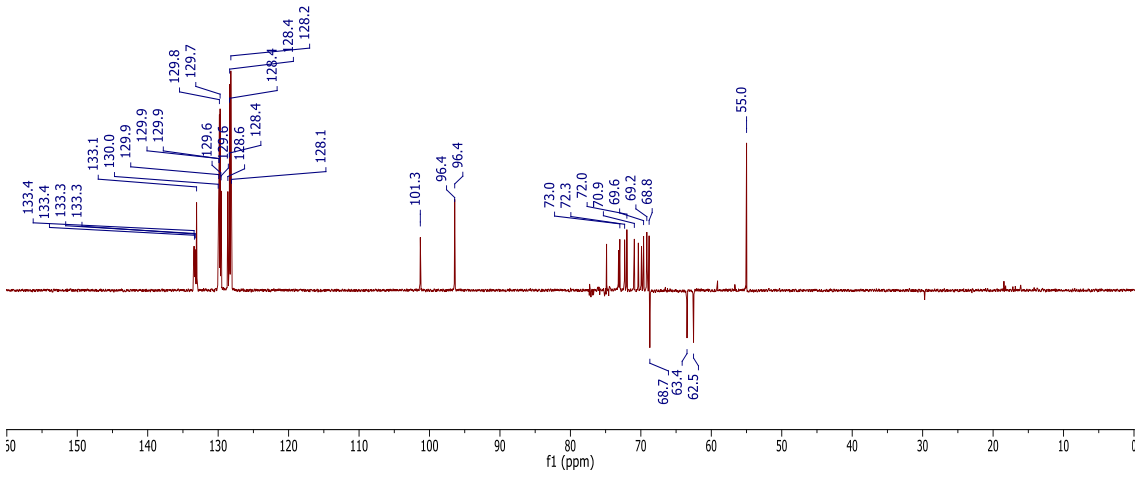
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **66**



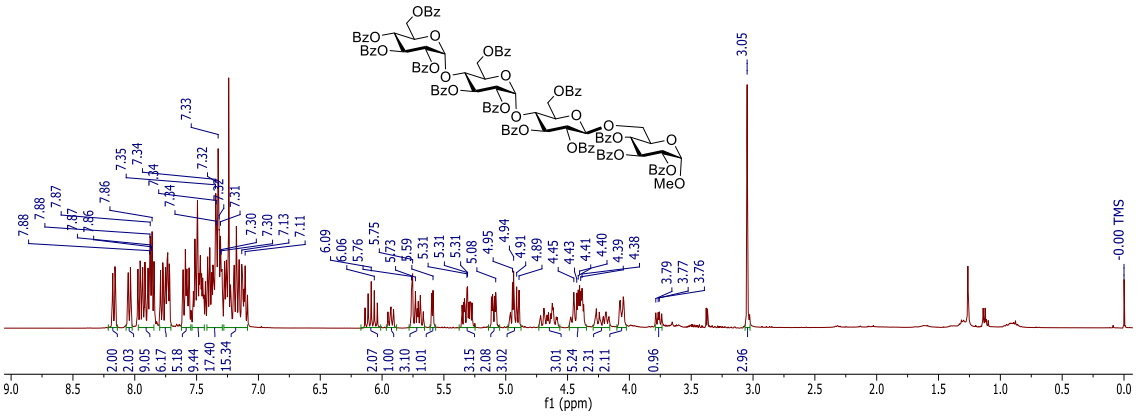
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **66**



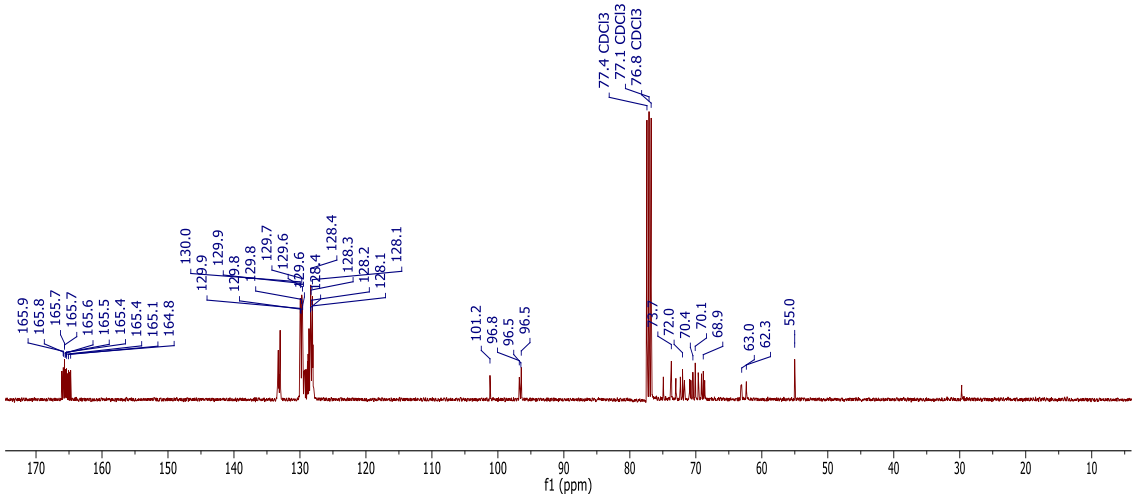
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **66**



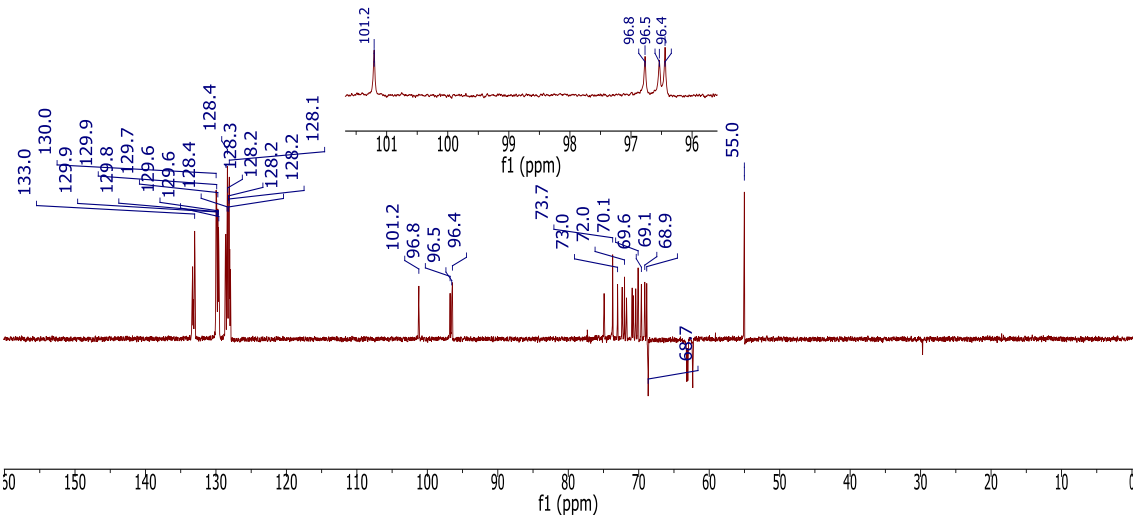
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **68**



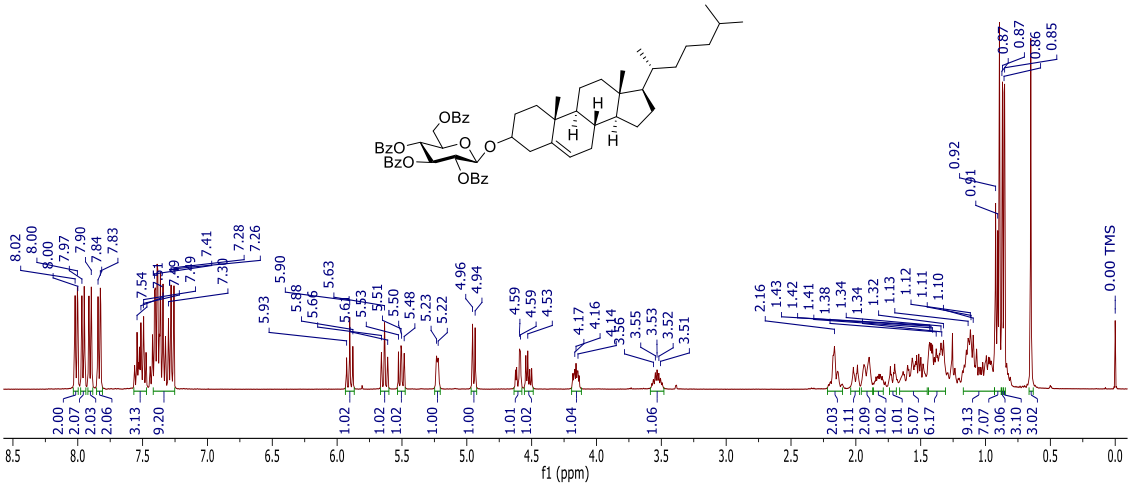
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **68**



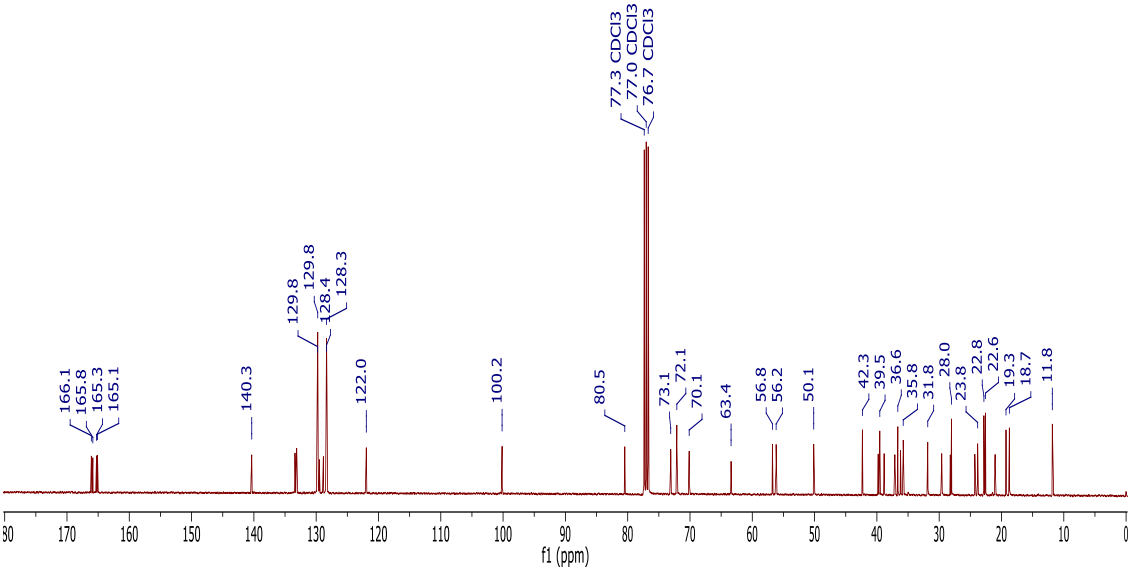
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **68**



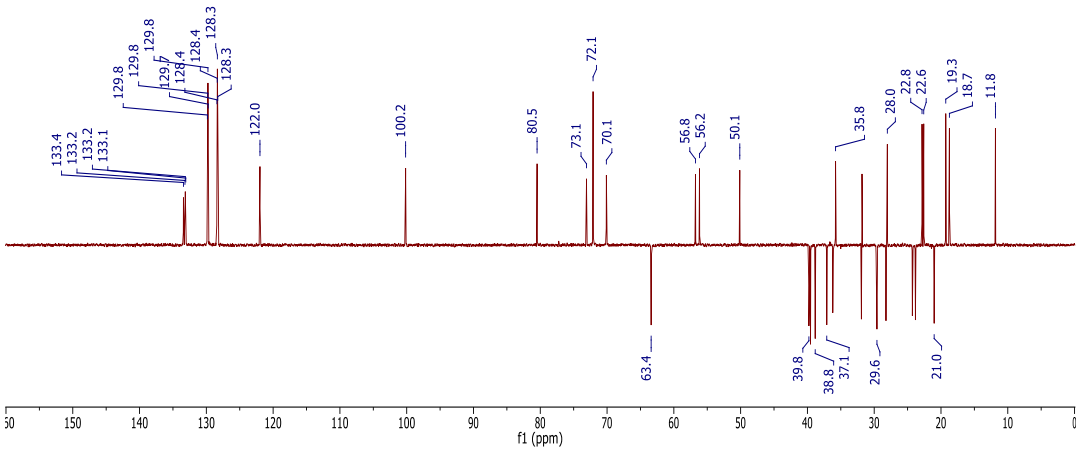
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **71**



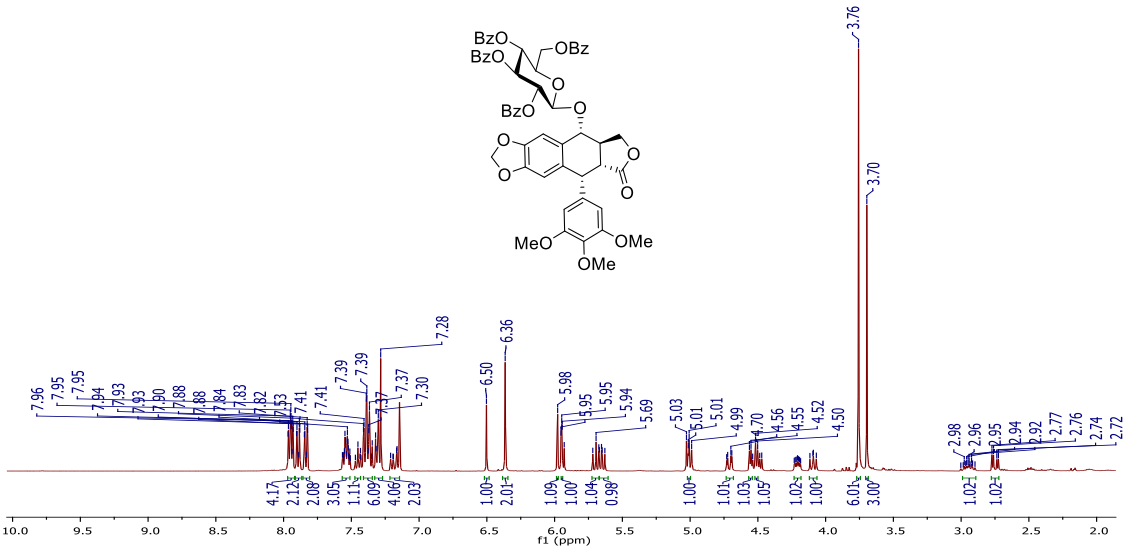
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **71**



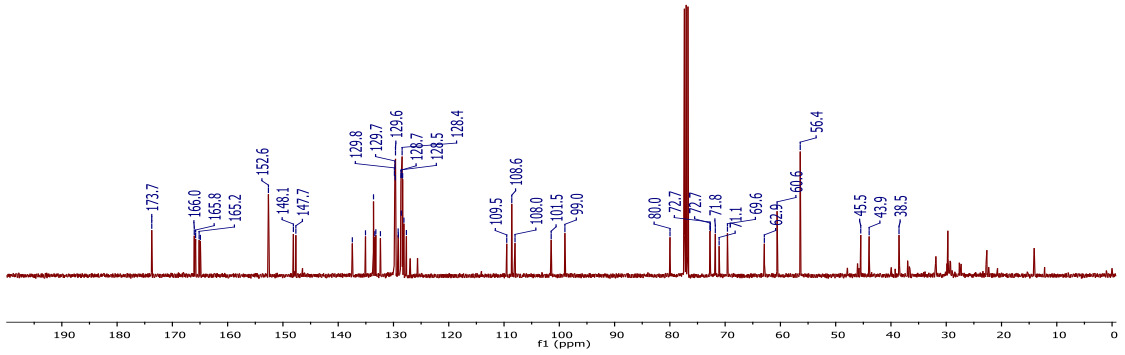
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **71**



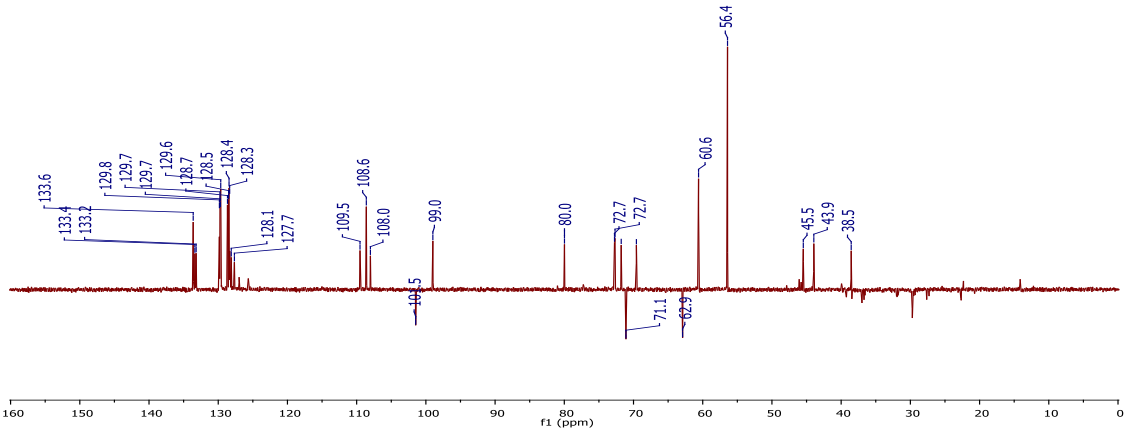
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **75**



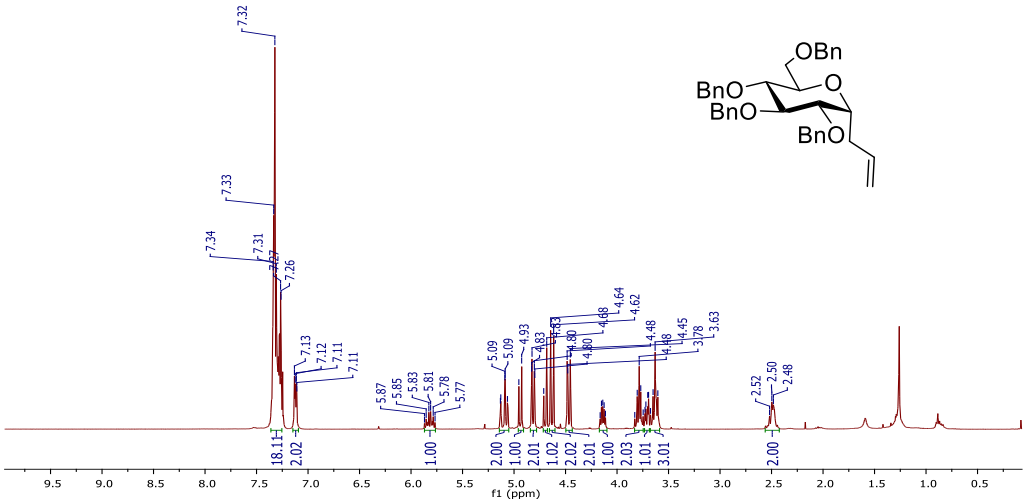
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **79**



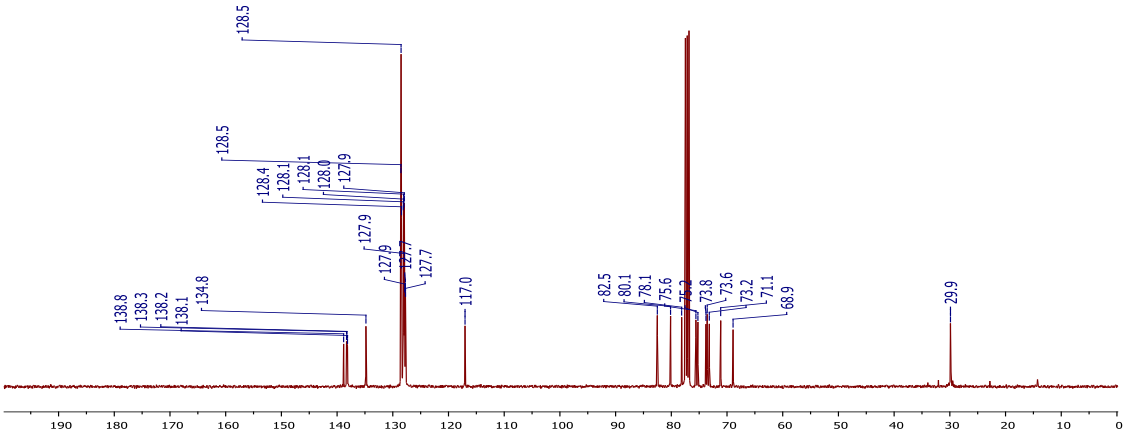
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **79**



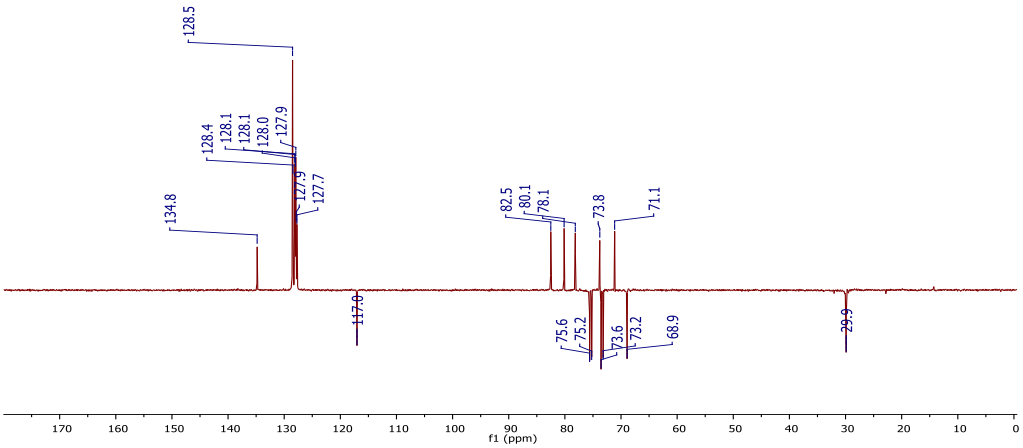
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **79**



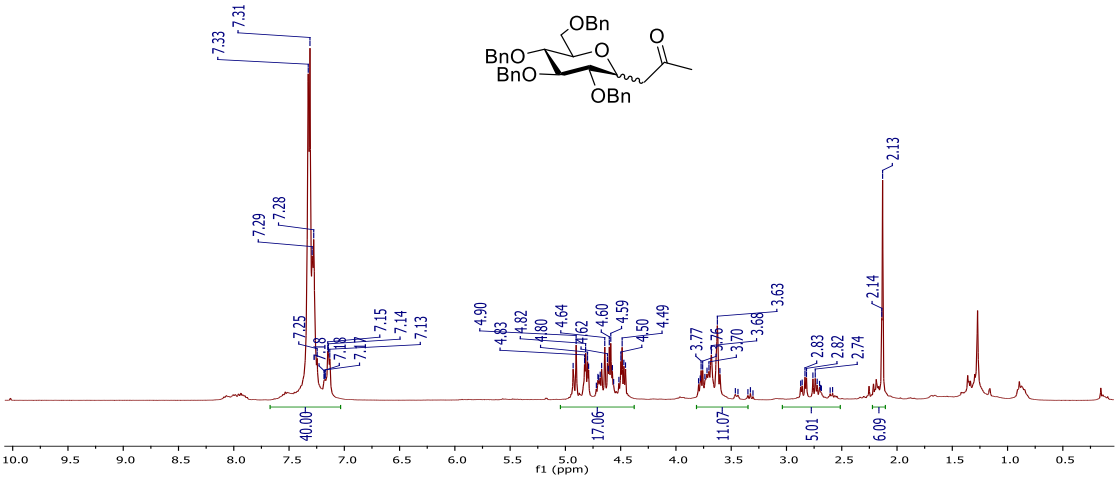
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **79**



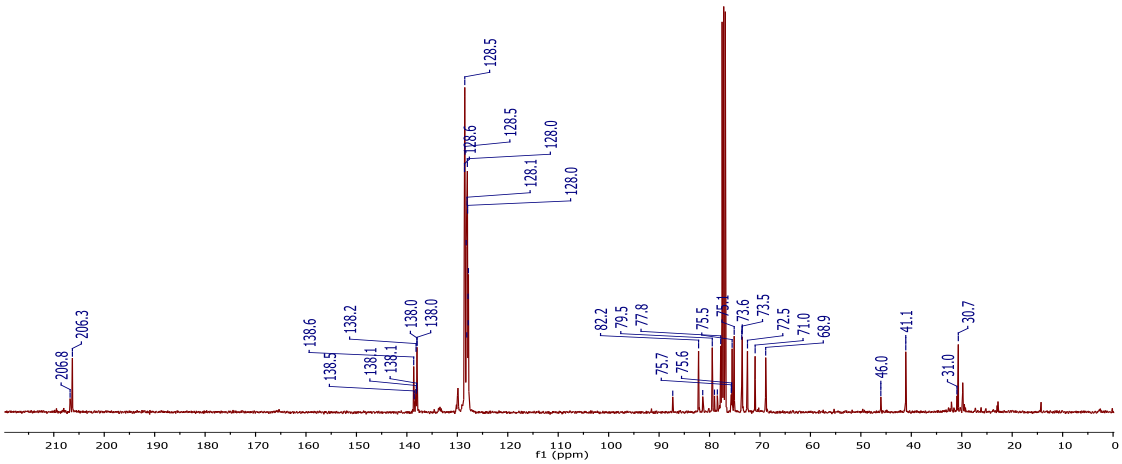
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **79**



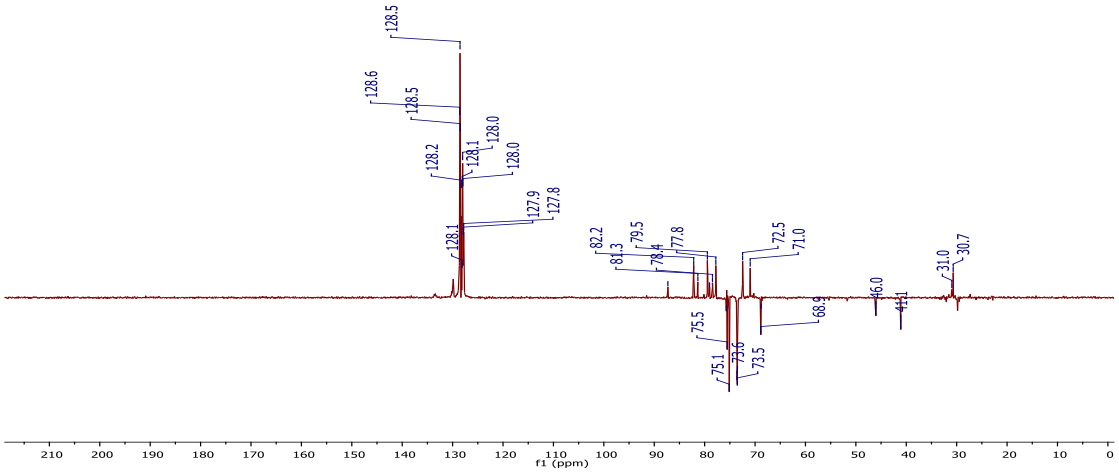
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **81**



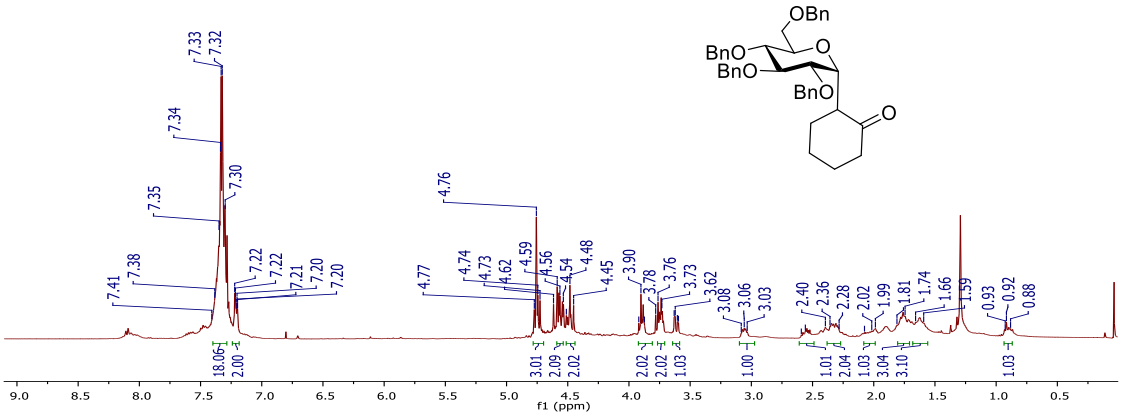
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **81**



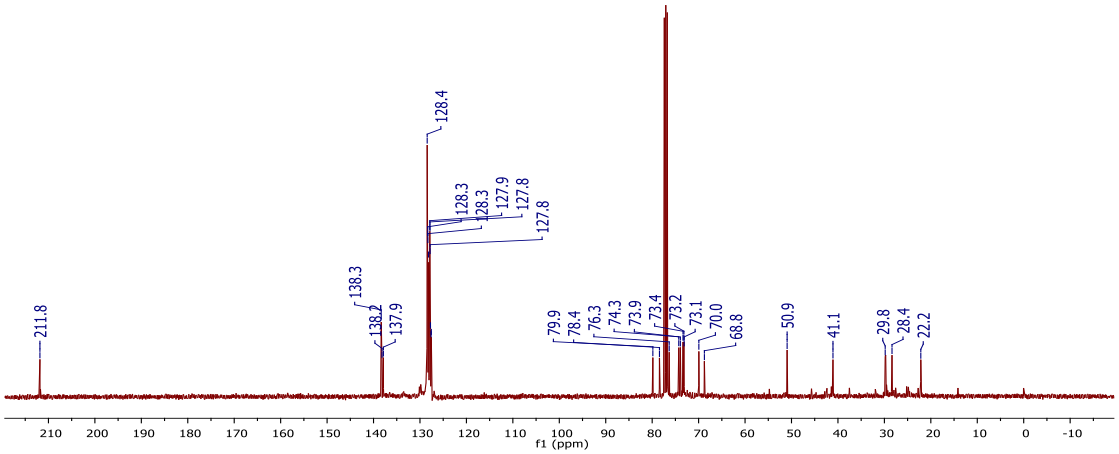
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **81**



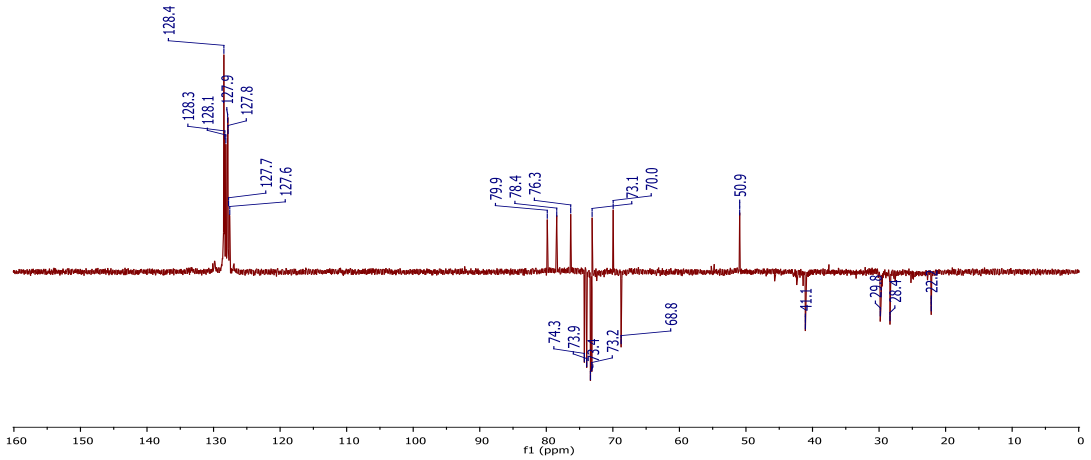
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **83**



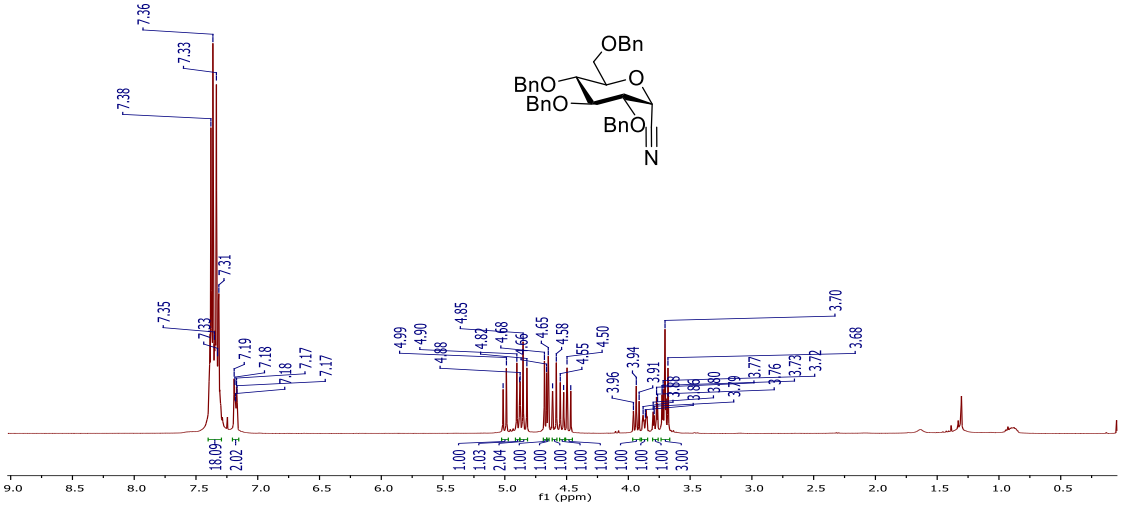
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **83**



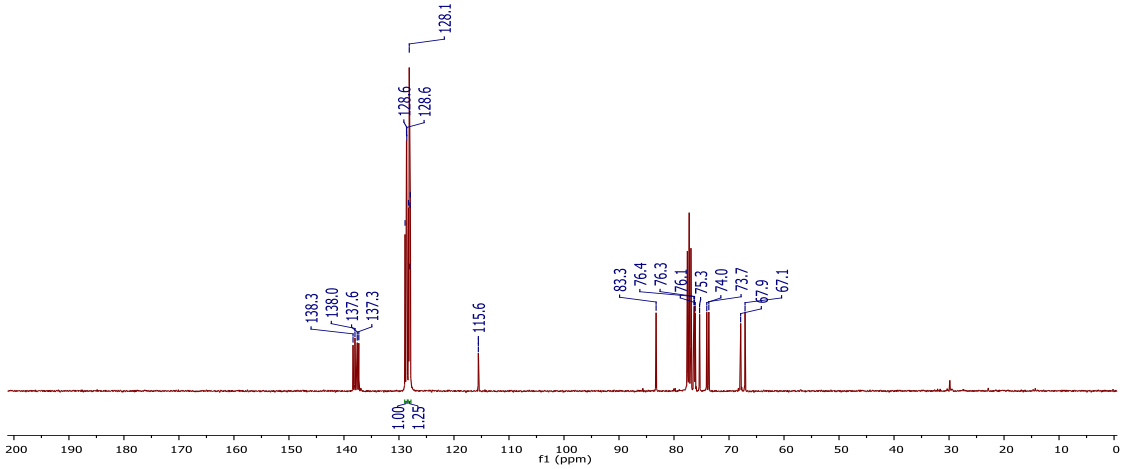
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **83**



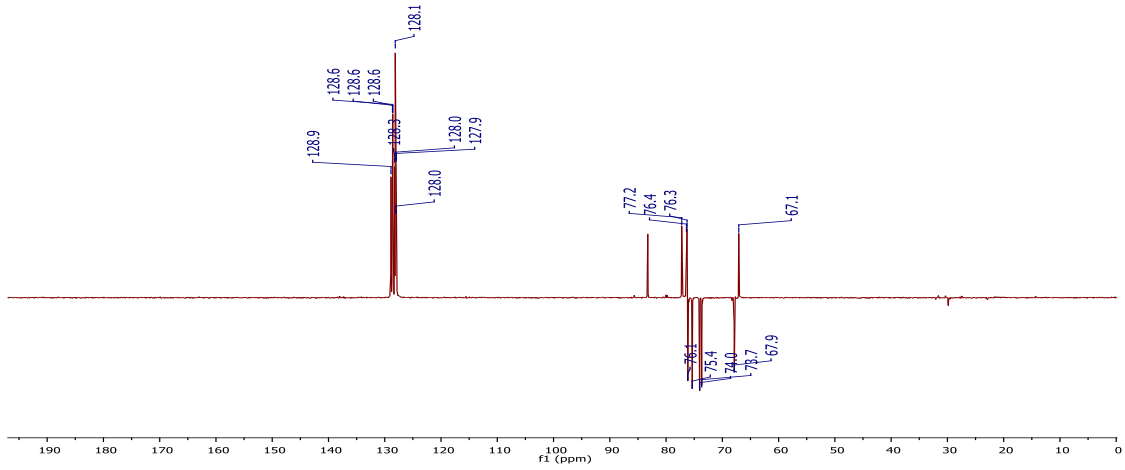
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **85**



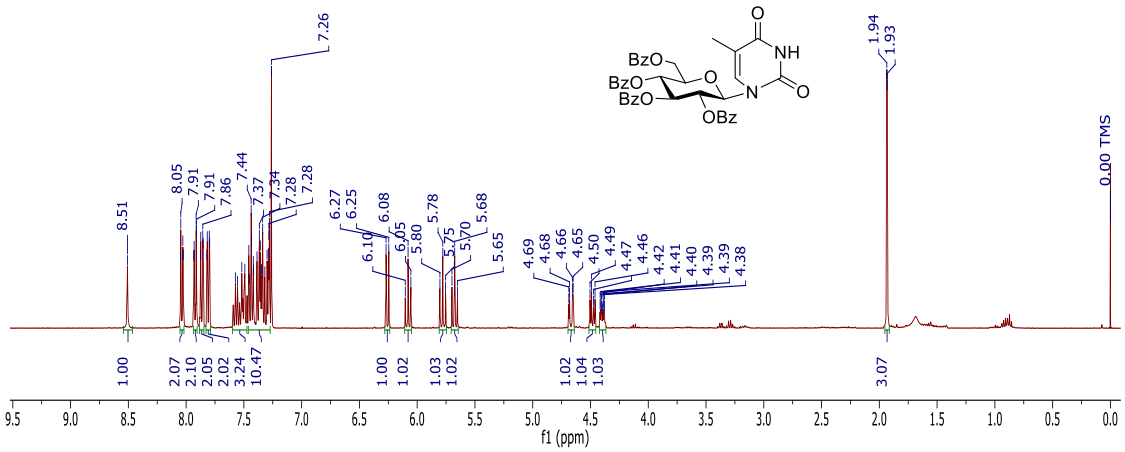
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **85**



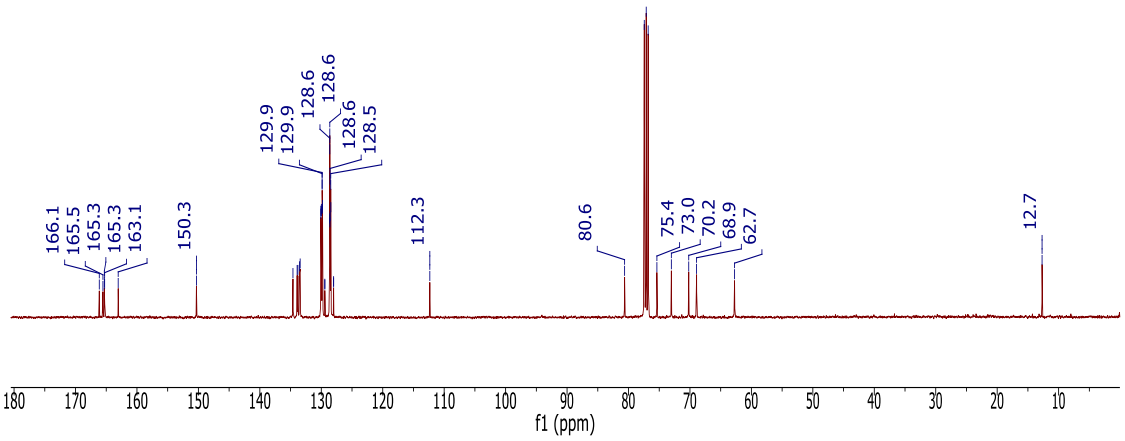
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **85**



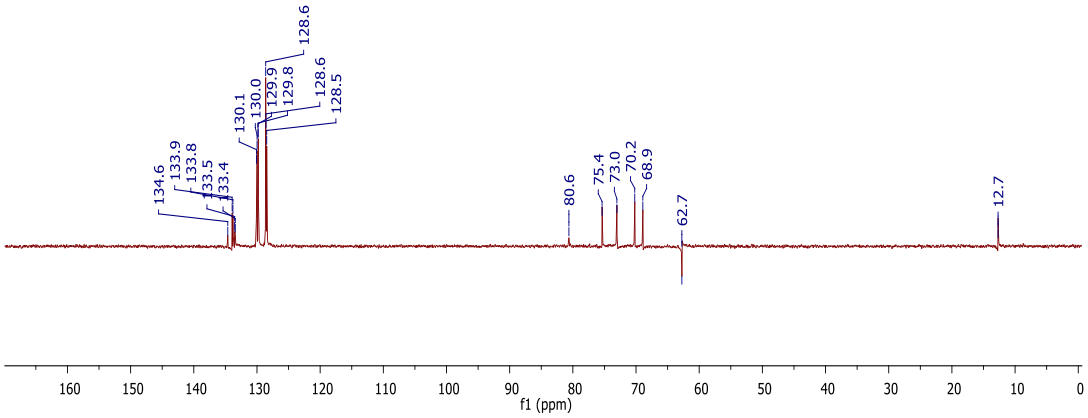
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **89**



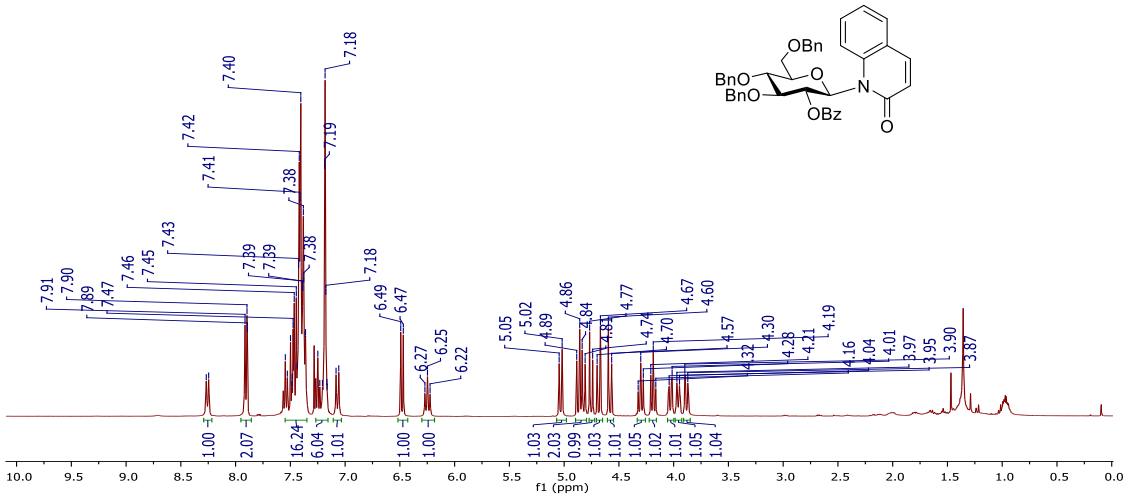
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **89**



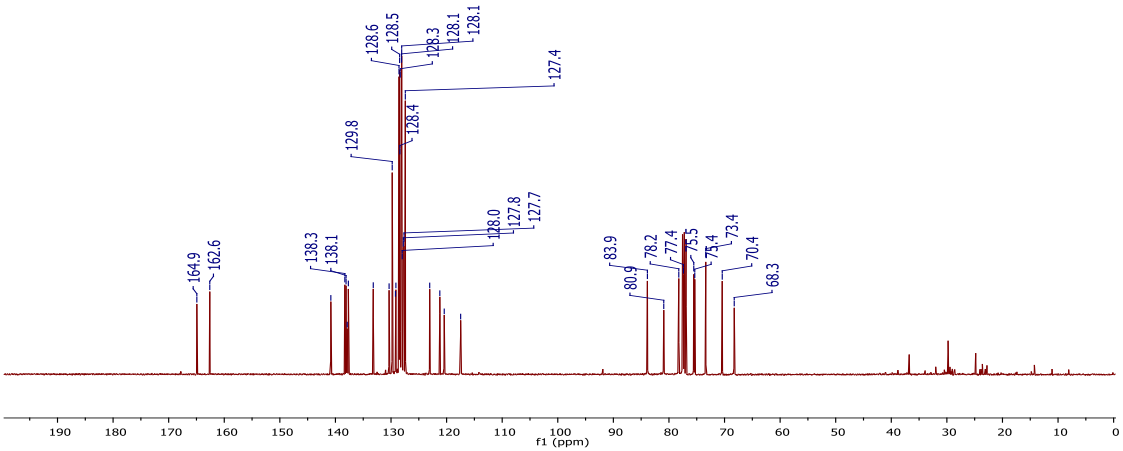
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **89**



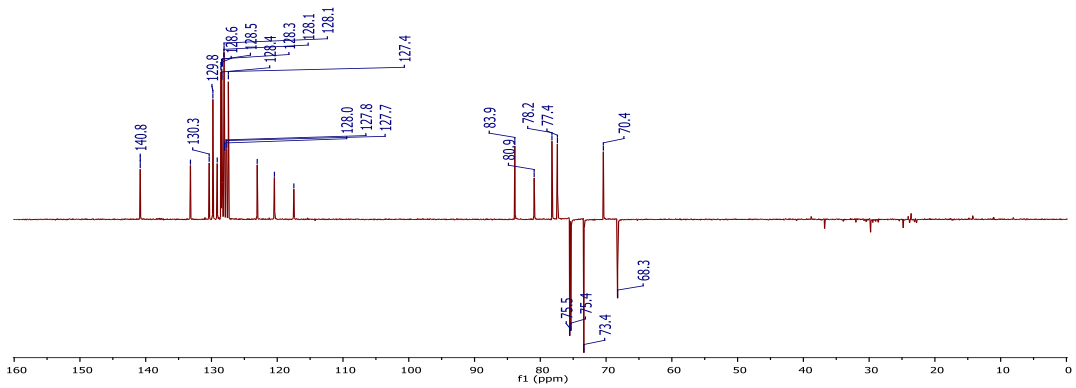
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **91**



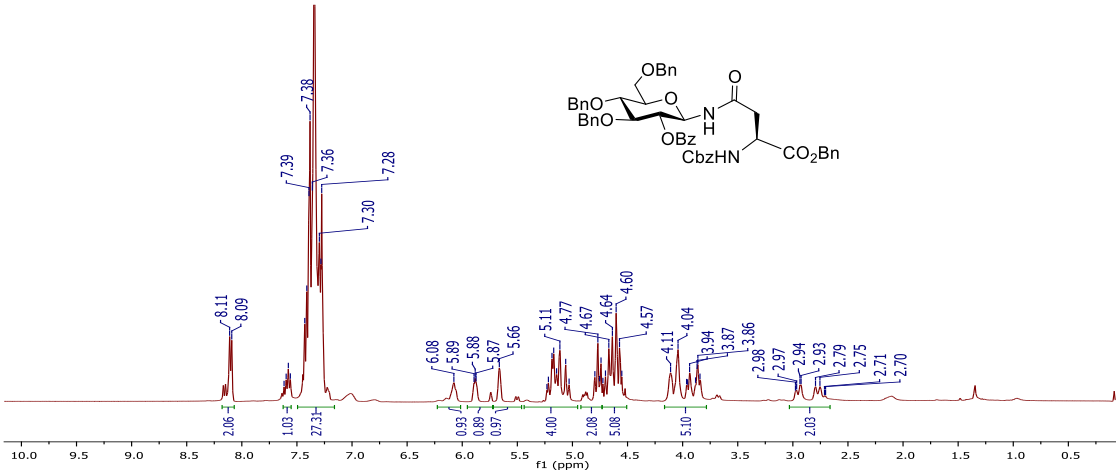
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **91**



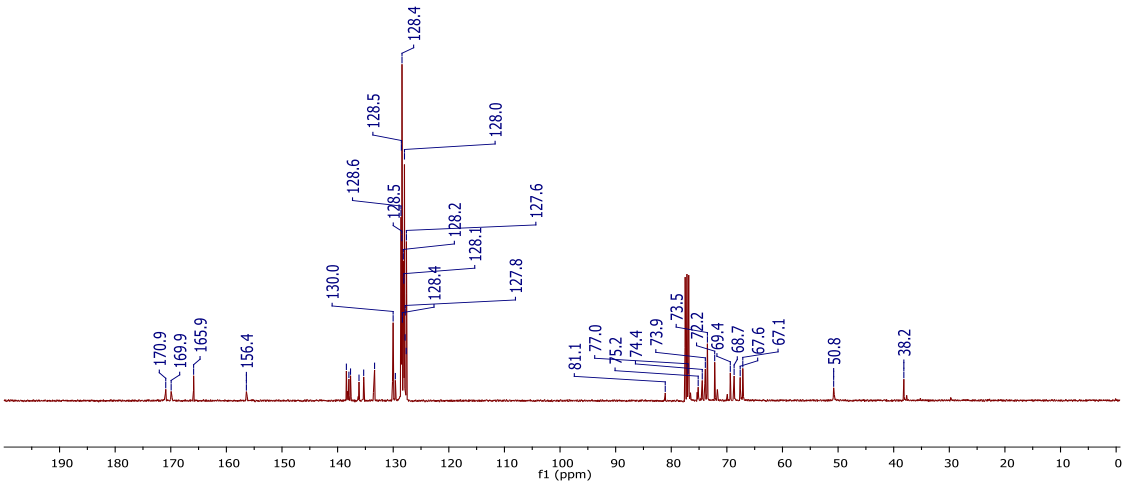
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **91**



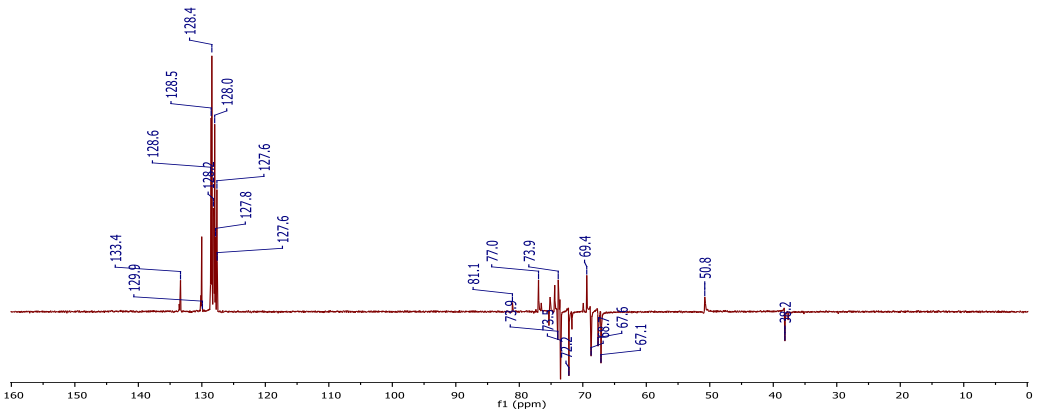
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **93**



^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **93**



DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **93**



2.9 – References

1. (a) Kashyap, S.; Hotha, S. *Tetrahedron Lett*. **2006**, *47*, 2021–2023; (b) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc*. **2006**, *128*, 9620–9621; (c) Kayastha, A. K.; Hotha, S. *Chem. Commun*. **2012**, *48*, 7161–7163; (d) A. K. Kayastha, S. Hotha, *Beilstein J. Org. Chem.* **2013**, *9*, 2147–2155; (e) A. K. Kayastha, S. Hotha, *Tetrahedron Lett.* **2010**, *51*, 5269–5372. (f) Sureshkumar, G.; Hotha, S. *Tetrahedron Lett*. **2007**, *48*, 6564–6568; (g) Thadke, S. A.; Mishra, B.; Hotha, S. *Org. Lett.* **2013**, *15*, 2466–2469.
2. (a) Shaikh, A.Y.; Sureshkumar, G.; Pati D.; Sen Gupta S.; Hotha, S. *Org. Biomol. Chem.* **2011**, *9*, 5951–5959; (b) Rao, B. V.; Manmode, S.; Hotha, S. *J. Org. Chem.* **2015**, *80*, 1499–1505; (c) Rao, B. V.; Manmode, S.; Hotha, S. *Carbohydr. Res.* **2015**, *417*, 103–108; (d) Vidadala, S. R.; Thadke, S. A.; Hotha, S. *J. Org. Chem.* **2009**, *74*, 9233–9236; (e) Sureshkumar, G.; Hotha S. *Chem. Commun*. **2008**, 4282–4284; (f) Thadke, S. A.; Hotha, S. *Org. Biomol. Chem.* **2014**, *12*, 9914–9920.
3. (a) Zhu, Y.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 8329–8332; (b) Adhikari, S.; Li, X.; Zhu, J. *J. Carbohydr. Chem*. **2013**, 32, 336–359; (c) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515–518; (d) Zhang, Y.-X.; Guo, L.; Wang, Y.-H.; Zhu, L.-L.; Chen, Z. *Tetrahedron* **2010**, *66*, 321–328; (e) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J.* **2010**, *16*, 1871–1882.
4. (a) Inaba, S.; Yamada, M.; Yoshino, T.; Ishido, Y. *J. Am. Chem. Soc.* **1973**, *95*, 2062–2063; (b) Marra, A.; Esnault, J.; Veyrieres, A.; Sinay, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354–6360; (c) Iimori, T.; Shibazaki, T.; Ikegami, S. S. *Tetrahedron Lett.* **1996**, *37*, 2267–2270; (d) Mukaiyama, T.; Miyazaki, K.; Uchiro, H. *Chem. Lett.* **1998**, *27*, 635–636; (e) Liu, W.; Chen, Q.; Liang, J.; Du, Z.; Zhang, K.; Zheng, X.; O'Doherty, G. A. *Synlett* **2015**, *26*, 1683–1686.
5. (a) Yu, T.; Li, J.; Zhu, Y.; Li, Y.; Yu, B. *J. Am. Chem. Soc.* **2013**, *135*, 18396–18405; (b) Pahi, A.; Czifrak, K.; Kover, K. E.; Somsak, L. *Carbohydr. Res.* **2015**, *403*, 192–201.
6. (a) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc*. **2012**, *134*, 9012–9019; (b) Song, X.-R.; Xia, X.-F.; Song, Q.- B.; Yang, F.; Li, Y.-X.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2012**, *14*, 3344–3347; (c) Homs, A.; Escofet, I.;

Echavarren, A. M. *Org. Lett*. **2013**, *15*, 5782–5785; d) Su, Y.; Lu, M.; Dong, B.; Chen, H.; Shi, X. *Adv. Synth. Catal*. **2014**, *356*, 692–696; (e) Ranieri, B.; Escofet, I.; Echavarren, A. M. *Org. Biomol. Chem*. **2015**, *13*, 7103–7118.

7. (a) Albrecht, U.; Langer, P. *Tetrahedron* **2007**, *63*, 4648–4654; (b) Jegelka, M.; Plietker, B. *Org. Lett*. **2009**, *11*, 3462–3465.
8. (a) Islam, M.; Gayatri, G.; Hotha, S. *J. Org. Chem.* **2015**, *80*, 7937–7945 (b) Liu, H.; Liao, J.-X.; Hu, Y.; Tu, Y.-H.; Sun, J.-S. *Org. Lett*. **2016**, *18*, 1294–1297.
9. (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742–760; (b) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299–1331. (c) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545–8599; (d) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*, Pergamon, Oxford, **1995**; (e) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959.
10. (a) Nicotra, F. *Top. Curr. Chem*. **1997**, *187*, 55–83; (b) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed*. **1999**, *38*, 2300–2324; (c) Dondoni, A.; Marra, A. *Chem. Rev*. **2000**, *100*, 4395–4421; (d) Compain, P.; MartinO. R. *Bioorg. Med. Chem*. **2001**, *9*, 3077–3092; (e) Stambasky, J.; Hocek, M.; Kocovsky, P. *Chem. Rev*. **2009**, *109*, 6729–6764.
11. (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc*. **1982**, *104*, 4976–4978; (b) Hosomi, A.; Sakata,Y.; Sakurai, H. *Tetrahedron Lett*. **1984**, *25*, 2383–2386; (c) Hoffmann, M. G.; Schmidt, R. R. *Liebigs Ann. Chem*. **1985**, 2403–2419; (d) Araki,Y.; Kobayashi, N.; Ishido, Y.; Nagasawa, J. *Carbohydr. Res*. **1987**, *171*, 125–139; (e) Mukaiyama, T.; Kobayashi, S. *Carbohydr. Res*. **1987**, *171*, 81–87; (f) Hosomi, A.; Sakata,Y.; Sakurai, H. *Carbohydr. Res*. **1987**, *171*, 223–232; (g) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Chem. Soc. Chem. Commun*. **1987**, 1245–1246; (h) Panek, J. S.; Sparks, M. A. *J. Org. Chem*. **1989**, *54*, 2034–2038; (i) McGarvey, G. J.; LeClair, C. A.; Schmidtmann, B. A. *Org. Lett*. **2008**, *10*, 4727–4730.
12. (a) Koppolu, S. R.; Niddana, R.; Balamurugan, R. *Org. Biomol. Chem*. **2015**, *13*, 5094–5097; (b) Chen, X.; Wang, Q.; Yu, B. *Chem. Commun.* **2016**, *52*, 12183–12186.
13. (a) Stagg, J.; Smyth, M. J. *Oncogene* **2010**, *29*, 5346–5358; (b) De Clercq, E. *Med. Res. Rev*. **2010**, *30*, 667–707; (c) Uhlmann, E.; Peyman, A. *Chem. Rev*.

1990, *90*, 543–584; (d) Englisch, U.; Gauss, D. H. *Angew. Chem., Int. Ed*. **1991**, *30*, 613–629; (e) Egli, M. *Angew. Chem. Int. Ed*. **1996**, 35, 1894–1909.

14. (a) Audisio, D.; Messaoudi, S.; Cegielkowski, L.; Peyrat, J. -F.; Brion, J. -D.; Methy-Gonnot, D.; Radanyi, C.; Renoir, J. -M.; Alami, M. *Chem. Med. Chem.* **2011**, *6*, 804–807; (b) Hewawasam, P.; Chen, N.; Ding, M.; Natale, J. T.; Boissard, C. G.; Yeola, S.; Gribkoff, V. K.; Starrett, J.; Dworetzky, S. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1615–1619.
15. (a) Tan, Z.; Wang, Lai-xi *Chemical biology of glycoproteins*, RSC press, Cambridge, UK, **2017**; (b) Roy, R. *Carbohydrate based vaccines*, ACS press, Washington DC, **2008**.
16. (a) Tomabechi, Y.; Squire, M. A.; Fairbanks, A. *J. Org. Biomol. Chem*. **2014**, *12*, 942–955; (b) Bianchi, A.; Bernardi, A. *J. Org. Chem*. **2006**, *71*, 4565–4577; (c) Doores, K. J.; Mimura, Y.; Dwek, R. A.; Rudd, P. M.; Eliott, T.; Davis, B. G. *Chem. Comm*. **2006**, 1401–1403; (d) Dedola, S.; Nepogodiev, S. A.; Field, R. A. Org. Biomol. Chem. 2007, *5*, 1006–1017; (e) Lim, D.; Brimble, M. A.; Kowalczyk, R.; Watson, A. J. A.; Fairbanks, A. J. *Angew. Chem., Int. Ed*. **2014**, *53*, 11907–11911; (f) Meldel, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015.
17. (a) Korytnyk, W.; Mills, J. A. *J. Chem. Soc*. **1959**, 636–649; (b) Martichonok, V.; whitesides, G. M. *J. Org. Chem*. **1996**, *61*, 1702–1706; (c) Baluja, G.; Chase, B. H.; Kenner, G. W.; Todd, A. *J. Chem. Soc*. **1960**, 4678–4681; (d) Lee, D. J.; Mondal, K.; Harris, P. W. R.; Brimble, M. A.; kent, S. B. H. *Org. Lett*. **2009**, *11*, 5270–5273; (e) Tosin, M.; Murphy, P. V. *Org. Lett.* **2002**, *4*, 3675–3678.
18. (a) Niedballa, U.; Vorbruggen *Angew. Chem., Int. Ed*, **1970**, *9*, 461–462; (b) Nishimura, T.; Shimizu, B.; Iwai, I. *Chem. Pharm. Bull.* **1963**, *11*, 1470–1472; (c) Capon, B.; McManus, S. P. *Neighboring Group Participation*, Plenum Press, New York, **1976**; (d) Fraser-Reid, B.; Ganney, P.; Ramamurty, C. V. S.; Gomez, A. M.; Lopez, J. C. *Chem. Comm.* **2013**, *49*, 3251–3253; (e) Wilson, L. J.; Hager, M. W.; El-Kattan, Y. A.; Liotta, D. C. *Synthesis* **1995**, 1465–1479; (f) Sniady, A.; Bedore, M. W.; Jamison T. F. *Angew Chem., Int. Ed.* **2011**, *50*, 2155–2158; (g) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang, F.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 4933–4936; (h) Yang, F.; Zhu, Y.; Yu, B. *Chem. Commun.* **2012**, *48*, 7097–7099.

19. (a) Mustafa, A.; Mansour, A. K. *Arch. Pharm*. **1965**, *298*, 824–827; (b) Niedballa, U.; Vorbrueggen, H. *J. Org. Chem*. **1974**, *39*, 3668–3673; (c)Luong, T. T. H.; Brion, Jean-Daniel; Lescop, E.; Alami, M.; Messaoudi, S. *Org. Lett.* **2016**, *18*, 2126−2129.

20. (a) Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. *J. Am. Chem. Soc*. **1989**, *111*, 6881–6882; (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc*. **2000**, *122*, 4269–4279; (c) Tanaka, H.; Iwata, Y.; Takahashi, D.; Adachi, M.; Takahashi, T. *J. Am. Chem. Soc*. **2005**, *127*, 1630–1631; (d) Tanaka, K.; Miyagawa, T.; Fukase, K. *Synlett* **2009**, 1571–1574; (e) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J.* **2010**, *16*, 1871–1882.

*****

Chapter 3

Expedient Syntheses of Linear as well as Branched Oligosaccharides of M. tuberculosis Cell Wall

3.1 – Introduction

Tuberculosis (TB) is one of the top 10 most deadly diseases that has affected mankind for thousands of years and still continues to impact severely millions of people mostly in developing countries. Currently, about 1.7 billion people or approximately 23% of the global population are assessed with latent TB infection and thus at high risk of developing active TB disease anytime during their lifetime. As per the 2017 World Health Organisation (WHO) report, globally about 10 million people effected by TB disease along with an 1.3 million deaths among HIV-negative people and an additional 300000 deaths from TB among HIV-positive people (**Figure 3.1**).[1a] Apart from the complex situation arising due to the co-infection with HIV, prevalence of multi-drug resistant (MDR) and extensively-drug (XDR) resistant continues as a major public health crisis. Worldwide in 2017, nearly 558000 people have developed tuberculi that are resistant to rifampicin (RR-TB), the most effective first line drug, and of these, 82% had multidrug-resistant TB (MDR-TB) (**Figure 3.2**).[1a] Among cases of MDR-TB, 8.5% were estimated to have extensively drug-resistant TB (XDR- TB). In order to prevent

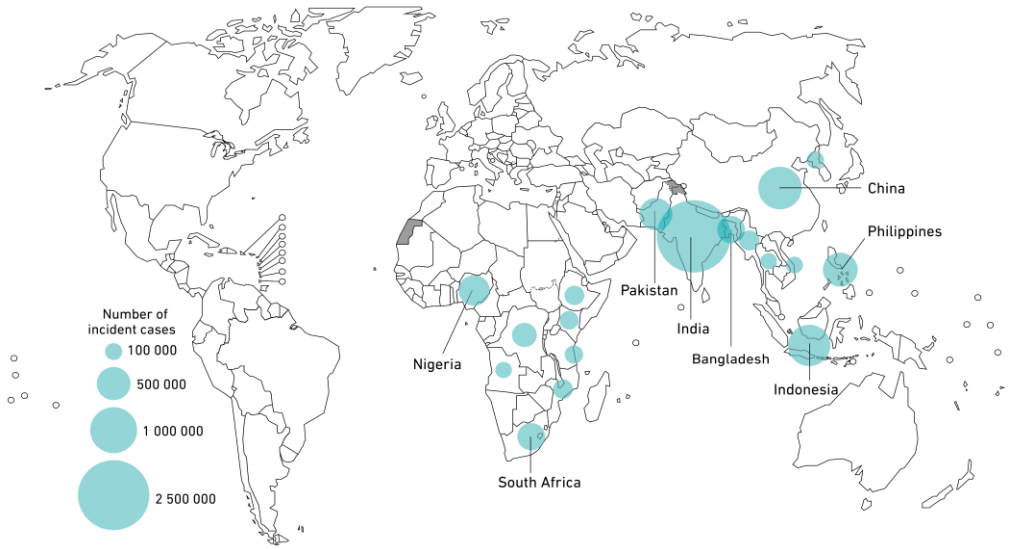


Figure 3.1 Worldwide estimated TB incidence in 2017, for countries with at least 100 000 incident cases *(Source: Global Tuberculosis Report, WHO, 2018)*

deaths among TB infected people and restrict its further transmission to the healthy one, rapid and accurate diagnosis of tuberculosis (TB), HIV-associated TB and drug-resistant TB, followed by appropriate treatment in line with international standards is highly recommended. Out of various diagnostic tests available for TB disease (i.e. X-ray, sputum smear microscopy, skin tuberculin test or acid fast test and culture-based

methods), the only rapid test which is currently recommended by WHO is the Xpert® MTB/RIF assay (Cepheid, USA). The major advantage of this assay is that it allows knowing the result within 2 hours. Inspite of being a deadly disease for centuries, the first effective drug treatments were developed in the 1940s. As per WHO guidelines, currently recommended treatment for new pulmonary TB patients is a 6 -month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide.[1b] There are another 20 new TB drugs in clinical trials, and combination regimens.

Figure 3.2: Estimated incidence of MDR/RR-TB in 2017, for countries with at least 1000 incident cases *(Source: Global Tuberculosis Report, WHO, 2012)*

Relying on the "prevention is better than cure" strategy, the first vaccine against TB, known as Bacilli Calmette- Guérin (BCG) vaccine after the name of Albert Calmette and Camille Guerin was developed almost 100 years ago. The BCG vaccine has been proven to be very effective against severe forms of TB in children and is still widely used.[1c-d]

3.2 – *Mycobacterium tuberculosis* (Mtb)

On 24 March 1882, Dr Robert Koch announced that he had discovered the bacillus *Mycobacterium tuberculosis (*Mtb), the etiological agent of tuberculosis (TB), an event that is now celebrated every year as the World TB Day.[2a] *M. tuberculosis* is a bacterial species from the mycobacteriaceae family and primarily a pathogen of mammalian

respiratory system or the lungs but can also affect the central nervous system, lymphnodes, bones and skin.[2b] M.tb complex consist of at least 9 sub-species, out of which *M. tuberculosis*, *M africanum* and *M. bovis* are the three causative agents for human TB infection. These species are slow-growing with a doubling time of ~20 hours in laboratory media such as Lowenstein-Jensen (L-J) or 7H10/7H11 Middlebrooks agar and generally requires several weeks to appear as visible colonies.[2c-d] *M. tuberculosis* an aerobic, rod like shaped measuring 0.5 μm in width and 3 μm in length are classified as acid fast bacilli by staining features. The presence of rich and flexible metabolic repertoire allow Mtb to survive in variable environments and can persist in humans for decades before reactivating to cause post-primary tuberculosis (TB).[2e-f]

3.2.1 – Pathogenesis of Mtb

The Mtb infection usually spreads *via* coughing, sneezing and talking to a person suffering from pulmonary tuberculosis. Once Mtb enters the alveolar spaces through inhalation route bypassing the mucociliary clearance, the first line of defence in host, is taken up by alveolar macrophages and reaches to lungs. Following ingestion by macrophages, the Mtb continue to multiply slowly in 2–3 days intervals. After Mtb gets engulfed by the macrophages, it starts to produce proteolytic enzymes and cytokines to

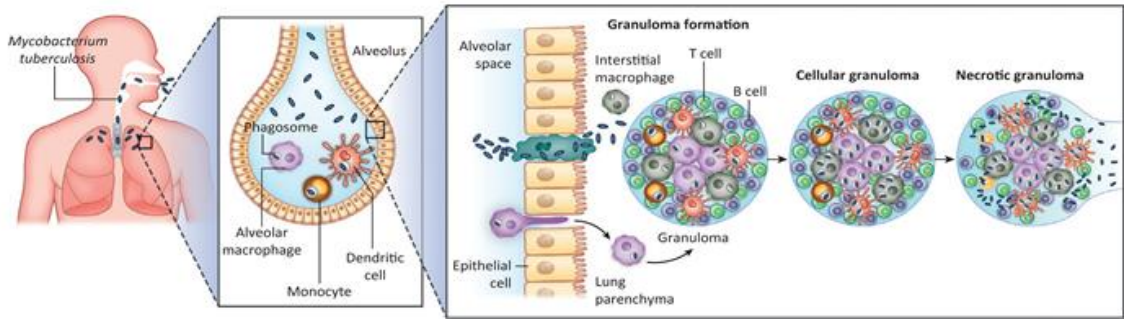


Figure 3.3: Pathogenesis of *Mycobacterium Tuberculosis* (Source: Koch, A.; Mizrahil, V. *Trends in Microbiology*, **2018**)[3b]

destroy the Mtb bacteria. These cytokines recruit T lymphocytes invoking cell mediated immune response. All these early measures continue up to 12 weeks. Thereafter, defensive granuloma around the mycobacteria form due to intact cell mediated immune function which limits replication and spread of Mtb. The low pH and low oxygen environment inside the granuloma destroys macrophages with necrosed centre in the lesion, though the Mtb are able to adapt and survive. By 2–3 weeks, the necrotic soft

debris appears cheese like and called caseation. If immune function is good, the caseous material undergoes fibrosis and calcification with embedded dormant mycobacteria in 'healed' lesions and allows primary progressive tuberculosis. Whereas, the caseous material becomes liquefied and may drain in to nearby bronchus or blood vessel if the immunity is in poor state, leaving behind an airfilled cavity. Mycobacteria carrying droplets may finally be coughed out from the bronchus route. As the immunity power varies from person to person, so as tuberculosis infection e.g. latent infection, primary progressive disease, extrapulmonary disease, in people is understandable.[3a]

3.2.2 – Structure of Mtb Cell wall

There is a continuous increase in the incidence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases every year and the compositional and architectural complexity of the Mtb cell wall is considered to play vital role behind it. The Mtb cell wall is substantially different from both Gram-negative and Gram-positive bacteria. The high content of lipid (40% of the dry mass of the cell) on Mtb cell wall

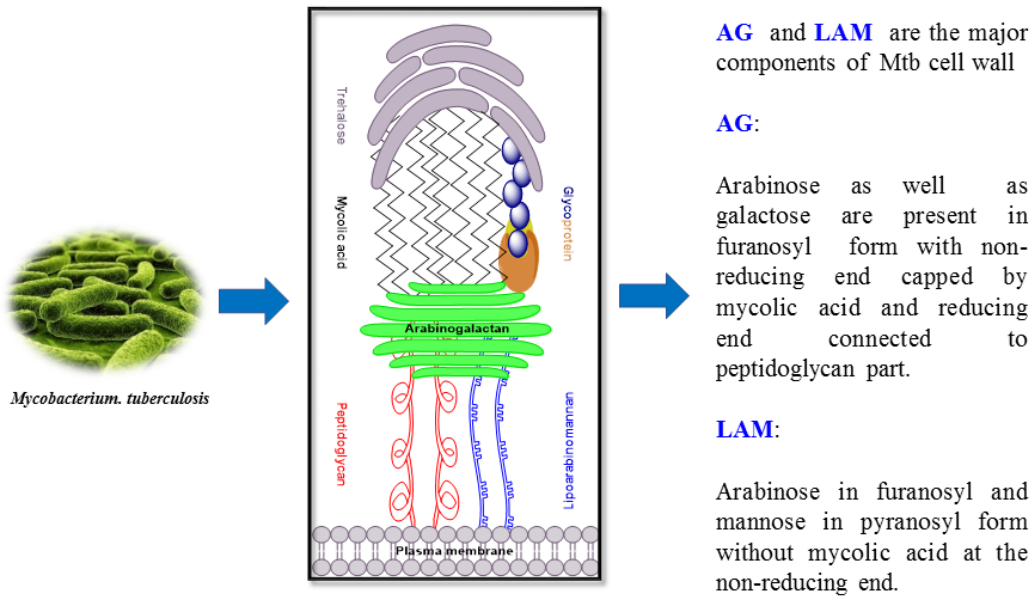


Figure 3.4: Representative structure of Mtb cell wall

make it unusually less permeable to any foreign materials and accounts for strong resistance towards common antibiotics or chemotherapeutic agents.[3b] Considering these facts, intensive efforts have been placed to find out the proper structure of Mtb cell wall and its biosynthetic route to develop new kind of drugs. After enormous investigation and in-depth analysis by mass spectroscopic studies, Brenan *et al* in 1980 postulated the

tentative structure of Mtb cell wall.[4a] The cellular envelope is made up of three major segments: the inner membrane or plasma membrane, the cell wall core and the outer membrane. The inner membrane phospholipid bilayer contains glycolipids that extend into the periplasmic space. The cell wall core consists of two major components: (i) The mycolyl-arabinogalactan-peptidoglycan complex in which heteropolysaccharide arabinogalactan (AG) is covalently attached to the peptidoglycan (PG) via reducing end and to long-chain (C_{70}–C_{90}) mycolic acid (MA) at the non-reducing end and (ii) lipoglycans, composed of lipomannan (LM) and lipoarabinomannan (LAM). The outer membrane of Mtb cellular envelope composed of various solvent extractable lipids, non-covalently connected glycolipids and proteins (Figure 3.4).[4b-c]

3.2.2.1 – Structure of mycolic acid (MA)

In 1938, the first isolation of mycolic acids from an extract of Mtb was reported by Stodola and co-workers.[5a] A decade later, Asselineau and Lederer[5b] identified these mycolic acids as a unique long chain α-alkyl-β-hydroxy fatty acids comprising a meromycolate chain of C_{42}–C_{62} functionalized with double bonds, cyclopropane rings or oxygen bearing functional groups and a long saturated alkyl side chain C_{24}–C_{26} at α-position.[5c] Based on the functional groups present in meromycolate chain, mycolic

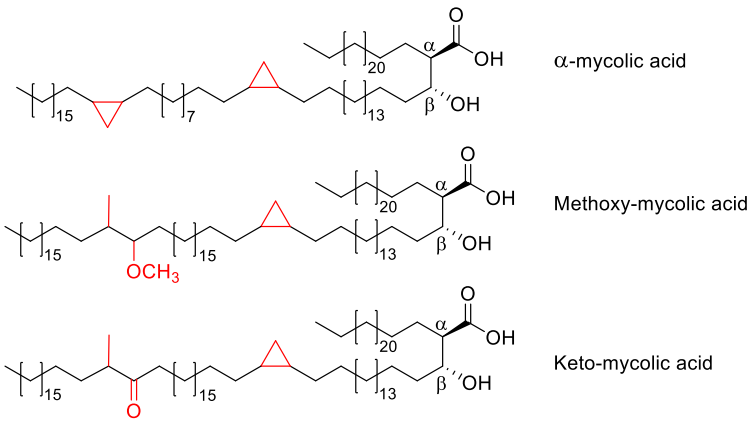


Figure 3.5: Structures of mycolic acids found in Mtb

acids are further categorized into three subclasses: α-mycolic acid, containing cyclopropane rings in the cis-configuration; methoxy-mycolic acid having methoxy functional groups and keto-mycolic acid containing ketone groups along with cis- or trans- configured cyclopropane rings.[5d-e] The natural abundance of α-mycolic acid in various mycobacteria strains is more than 70% of the total lipid content, whereas

methoxy- and keto-mycolic acids together constitutes less than 30%. The exact roles of mycolic acids are still not well understood, but it is well accepted that mycolic acids contributes significantly to the permeability of the cell wall and hence is essential for the cell viability.

3.2.2.2 – Lipoglycans (Lipoarabinomannan (LAM) and Lipomannan (LM))

Phosphatidyl-*myo*-inositol mannosides (PIMs) and the related lipoglycans, lipomannan (LM) and lipoarabinomannan (LAM), are the most abundant non-covalently linked glycophospholipids in the mycobacterial cell wall and closely related Actinomycetes.[6a] LAM has structural resemblance to the LM present in the mycobacterial plasma membrane and is comprised of three different structural units: i) a mannosyl phosphate inositol anchor, ii) a mannan backbone and iii) capping moieties. The mannan backbone of both LAM and LM contains 21–34 Man*p* residues linked via α-Man*p*(1→6)Man*p* linear fashion with a further branch of 5–10 units of single α(1→2)Man*p* side chains.[6b-c] In case of LAM, the mannan backbone also contains an arabinan domain made up of nearly 55–70 Ara*f* residues linearly linked via α-Ara*f*(1→5)Ara*f* linkage with branching via C3-position in some bacterial strains.[6c-d] As similar to AG, two types of arabinan motifs are observed in the arabinan domain (i) branched hexaarabinofuranosyl motif, [β-D-Ara*f*(1→2)-α-D-Ara*f*]$_2$-3,5-α-D-Ara*f*(1→5)-α-D-Ara*f* and (ii) linear tetraarabinofuranoside, β-D-Ara*f*(1→2)-α-D-Ara*f*(1→5)-α-D-Ara*f*(1→5)-α-D-Ara*f*. Hence both the arabinan motifs have a unique disaccharide subunit β-D-Ara*f*(1→2)-α-D-Ara*f*- as common feature.[6e-g] The capping moieties in arabinan vary significantly from one mycobacterial species to others. Three types of capping fragments are commonly observed which include: (i) mannan capped (ManLAM) in slow growing bacterium, such as M. tuberculosis, (ii) phosphoinositol capped (PILAM) in growing bacterium, such as M. smegmatis, and (iii) uncapped LAM known as AraLAM in *Mycobacterium chelonae*.[6f,6h] The number of mannose units in mannan cap also varies from mono-, di- to tri-α(1→2)-D-Man*p* saccharide within the *M. tuberculosis*.[6h]

3.2.2.3 – Arabinogalactan (AG)

Mycolyl–arabinogalactan–peptidoglycan (mAGP) complex is another major constituent (~35%) of the Mtb cell wall and arabinogalactan (AG) is the key structural component of it.[4c] One of the unique features about AG is that none of the sugar residues are in

pyranose form and unlike other bacterial polysaccharides, it lacks simple monosaccharide repeating units.[7a] Detailed analysis of the methylated oligomers, generated through partial depolymerization of per-*O*-alkylated AG residues using advanced spectroscopic techniques such as GC-MS, NMR and FABMS deciphered the

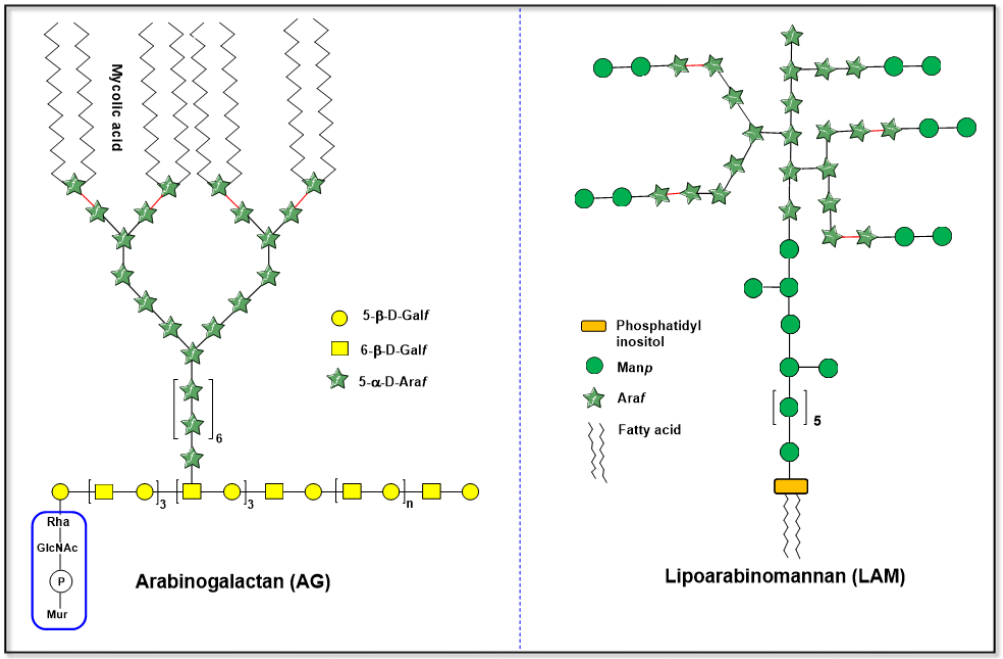


Figure 3.6: Structure of AG and LAM present in Mtb

complete structure of AG.[5] The galactan component of AG is connected to the the C-6 of muramyl residues of peptidoglycan (PG) through a diglycosylphosphoryl bridge, α-L-Rha*p*-(1→3)-α-D-GlcNAc-(1→P).[7b] The linear galactan chain consists of approximately 30 galactofuranose (Galf) residues which are connected *via* alternating β(1→5) and β(1→6) linkage in a linear fashion.[3] Galactan part is further extended by three highly branched arabinan chains attached by the *C*-5 of β(1→6) Gal*f* residues selectively at 8th, 10th and 12th positions of the galactan core in *Corynebacterium glutamicum*.[7c] Each arabinan part contains linearly arranged α(1→5) linked Ara*f* residues with branching at the *C*-3 position forming 3,5-Ara*f*-linked residues. There are altogether twenty-six 1,2-*trans* and four 1,2-*cis* glycosidic bonds that constitute the whole arabinan part. The non-reducing termini of arabinan structure possesses a distinctive 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*], where the terminal β-Ara*f* units serve as the anchoring points for the mycolic acids.[7d]

3.2.2.4 – Biosynthesis of AG and LAM

Biosynthetic pathways involved in AG and LAM synthesis of Mtb cell wall are of great practical importance due to their vulnerability targets for the discovery of new therapeutic agents. Inspite of enormous efforts, the biosynthesis of AG and LAM is still not fully understood. In AG biosynthesis, the first step begins with the GlcNAc transferase WecA (Rv1302) assisted transfer of GlcNAc-1-P from UDP-GlcNAc to the decaprenyl phosphate(C_{50}-P) lipid carrier, followed by attachment of the rhamnosyl residue (Rha-) to the C_{50}-P-PGlcNAc by rhamnosyltransferase WbbL (Rv3265c) yielding C_{50}-P-P-GlcNAc-Rha and thus forming the linker unit of AG.[8a-b] Further, sequential addition of approximately thirty Gal*f* residues on linker unit in a linear fashion results in the formation of oligogalactan part. Till date, two bifunctional galactofuranosyltransferases, Gal*f*T1 (Rv3782) and Gal*f*T2 (Rv3808c) have been identified which are involved in the biosynthesis of linear galactan synthesis and both of these use UDP-Gal*f* as the glycosyl donor.[8c-d] Various *in vitro* studies suggest that the attachment of Ara*f* units to synthesize the full length AG part proceeds by a family of arabinofuranosyltransferases (Ara*f*Ts), EmbA and EmbB, utilizing decaprenylmonophosphoryl-D-arabinose (DPrA).[8e]

As compared to AG part, LAM is more heterogeneous in nature and biosynthesis of LAM from PI follows a sequential order. At first, sequential addition of six mannose residues to the PI (i.e. PI → PIM_2→ PIM_4 → PIM_6) occurs on the cytosolic side, employing GDP-Man as a high energy substrate by glycosyltransferases (GTs) PimA, PimB and PimC/D respectively.[8f-g] Acyltransferase Rv2611c catalyses the acylation of the Man*p* residue of PIM_1 before or after another mannosylation depending upon the species of mycobacteria. Another acyltransferase that converts Ac_1PIM_2 to Ac_2PIM_2 is still not fully characterized.[8f] Once the Ac_1PIM_4/Ac_2PIM_4 forms, it is first flipped across the membrane by an unknown flippase enzyme and then sequentially gets extended by mannosyltransferases Mp*t*A, Mp*t*B and MptC to generate mature LM. Modification of LM to LAM proceeds via the attachment of 50–80 Ara*f* residues with the help of EmbC, Af*t*B, Af*t*D and Af*t*C enzymes.[8h] Finally, LAM gets converted to ManLAM by Ca*p*A in conjunction with Rv2181 to generate ManLAM.[6f,8i]

3.3 – Chemical synthetic approaches towards Mtb major fragments

Accessibility of various AG and LAM fragments is highly demanding for (i) proper understanding of the biosynthetic pathways involved in Mtb cellular envelope

formation; (ii) high-throughput screenings of newly isolated enzymes for ligand binding studies and (iii) the development of a rational enzyme inhibitors. Although enzymatic synthesis of AG and LAM fragments are mostly straight forward and high yielding, but finding out the appropriate enzymes along with their tedious isolation and purification processes makes it a less attractive alternate approach. Hence, much of the efforts have been placed to develop chemical methods for AG and LAM fragments synthesis. In the last 20 years, various groups have involved in the concise synthesis of different oligosaccharide fragments of Arabinogalactan (AG), Lipoarabinomannan (LAM) and Oligoarabinan (OA) residues. Major and selected efforts for the synthesis of oligosaccharides of mycobacterial cell wall are described below.

3.3.1 – Mukund K. Gurjar *et al*.[9a-c]

First total synthesis of branched pentaarabinofuranosyl motif A, Ara_5 from Mtb cell wall was accomplished by Gurjar and co-workers utilising pent-4-enyl arabinofuranoside and thiopyridyl arabinofuranosides as glycosyl donors. Later, motif C which is diarabinofuranoside and motif D which is triarabinofuranoside were synthesized in a stereocontrolled fashion employing glycosyl trichloroacetimidate and pent-4-enyl arabinofuranosyl donors.

3.3.2 – Peter Seeberger *et al*.[10]

The automated solid phase synthesis, solely developed by Seeberger group has been extensively utilized for the synthesis of various AG and AM fragments from Mtb. A dodecasaccharide arabinomannan (AM) fragment consisting of six α-D-Ara*f* and six α-Man*p* residues was prepared *via* a [6+6] coupling strategy in solution phase using glycosyl phosphate donor. Quite recently, the group has further extended the application of automated synthesis for the linear and branched oligoarabinofuranosides with the synthesis of a polymannoside containing 50-mannose residues exploiting thioethyl glycosyl donor chemistry.

3.3.3 – Bert Fraser Reid *et al*.[11]

Synthesis of a 28-mer LAM fragment composed of fifteen α-Man*p*, and twelve α-Ara*f* residues from Mtb has been successfully completed by the Fraser-Reid group using [12+16] coupling between arabinomannan trichloroacetimidate donor and the

mannosylated inositol acceptor as a key glycosylation step. Later, a dodecasaccharide lipomannan (LM) fragment consists of a 1,6-α-linked backbone with α-linked mannosides branching at position *O*-2, not necessarily regularly was further synthesized by the use of *n*-pentenyl orthoester chemistry promoted by $Yb(OTf)_3$/NIS system.

3.3.4 – Todd Lowary *et al*.[12]

First total synthesis of the 22-mer arabinan residue of mycobacterial arabinogalactan part containing synthetically challenging β-Ara*f* unit was successfully completed by Lowary and co-workers. The key feature of the 22-mer synthesis was its highly convergent [(2x5)+7+5] coupling strategy using glycosyl trichloroacetimidate and thiotolyl donors. Further, a number of arabinomannan fragments have been synthesized based on the orthogonal protection strategy developed by them.

3.3.5 – Yukishige Ito *et al*.[13]

Around the same time of Lowary's work, Ito group also synthesized the same 22-mer arabinan residue but using totally different synthetic strategy in [(2x7)+8] manner. Another key feature of the 22-mer synthesis was the installation of β-Ara*f* unit via double intramolecular aglycon delivery using *O*-NAP ethers in a stereoselective fashion.

3.3.6 – Leonid O. Kononov *et al*.[14]

Synthesis of linear α(1→5)-linked oligoarabinofuranosides of various chain length from single arabinofuranose 1,2,5-orthobenzoate precursor activated through $SnCl_4$ has been achieved by Kononov group. The group has also explored the benzyl-free approach for the synthesis of penta- or hexasaccharide fragment of LAM from Mycobacteria.

3.3.7 – Srinivas Hotha *et al*.[15]

The use of Au-catalysed glycosylation for the synthesis of various AG and LAM fragments was pioneered by Hotha *et al*. The robust propargyl 1,2-orthoester strategy developed by Hotha′s group was first employed for the synthesis of branched hexaarbinofuranoside, a common motif in both AG and LAM fragments of Mtb cell wall. The use of single donor chemistry for the stereoselective 1,2-*trans* as well as

highly challenging 1,2-*cis* glycosidic bond formation in arabinofuranosyl system under Au-catalysed glycosylation condition was the key feature of the synthetic strategy. The propargyl 1,2-orthoester donor chemistry was further extended for the synthesis of a linear pentaarabinofuranoside motif using linear approach and a full length 21-mer arabinogalactan motif in highly convergent [(2x4)+7+6] manner. The most important feature in the 21-mer arabinogalactan synthesis was the installation of galatofuran (Gal*f)* disaccharide motif to the 19-mer oligoarabinan part which was previously not accomplished by other groups.

Apart from these, several other groups has also succefully synthesized various oligosaccharide motifs related to AG, LM and LAM fragments from Mtb cell wall and used for biological studies.[16]

3.4 – Present work

The accessibility of various natural and nature mimic fragments of Arabinogalactan (AG) and Lipoarabinomannan (LAM) is highly demanding for their direct implication in new vaccine design and drug development. Furthermore, the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR- TB) stains requires urgent action on finding out new targets for drugs where the use of synthetic AG and LAM fragments are also of great importance for high-throughput screening. As a result, synthesis of different AG and LAM motifs has continuously been a topical subject in efforts to develop new therapeutic agents. Although, tremendous efforts have been placed by several groups for successful synthesis of different AG and LAM motifs, but probably the use of less efficient glycosyl donors or glycosylation methods with very poor overall yields confined their accessibility. Various glycosyl donors and recently propargyl 1,2-orthoester donor employed for these oligosaccharides synthesis. However, some in-built downsides associated with these donors, such as: (i) longer glycosylation reaction; (ii) moderate glycosylation yields; (iii) use of excess activator in some cases and (iv) difficulty of donor preparation at oligosaccharide level somewhat restricted these reported synthetic procedures to synthesize AG and LAM motifs.

In this premise, glycosyl alkynyl carbonate donor chemistry identified (Chapter 2) is quite promising for the synthesis of large oligosaccharide as the glycosylation is fast, high yielding, catalytic and the donor is quite easy to prepare. Towards this objective, synthesis of two large oligosaccharide fragments from AG and LAM present in the Mtb cell wall were investigated.

3.4.1 – Total synthesis of linear nonadecaarabinofuranoside motif from AG part

The first oligosaccharide fragment that we have chosen is a nonadecaarabinofuranoside with 19 α-Ara*f*(1→5)-Ara*f* linkages present in the AG part of *Mycobacterium tuberculosis* cell wall. Although oligoarabinan in AG contains different glycosidic linkages such as α-Ara*f*-(1→5)-α-Ara*f*, α-Ara*f*-(1→3)-α-Ara*f* and β-Ara*f*-(1→2)-α-Ara*f* linkages, α-Ara*f*-(1→5)-α-Ara*f* linkages are predominant and hence form the major constituent of the AG part (**Figure 3.7**).[17] This feature of oligoarabinan is conserved in AG and also found in LAM and hence, developement of a strategy for oligoarabinan synthesis becomes important.

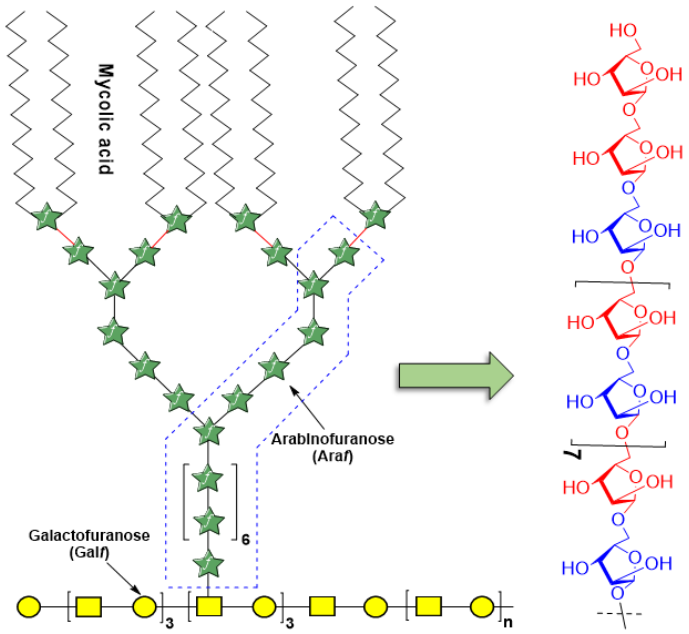


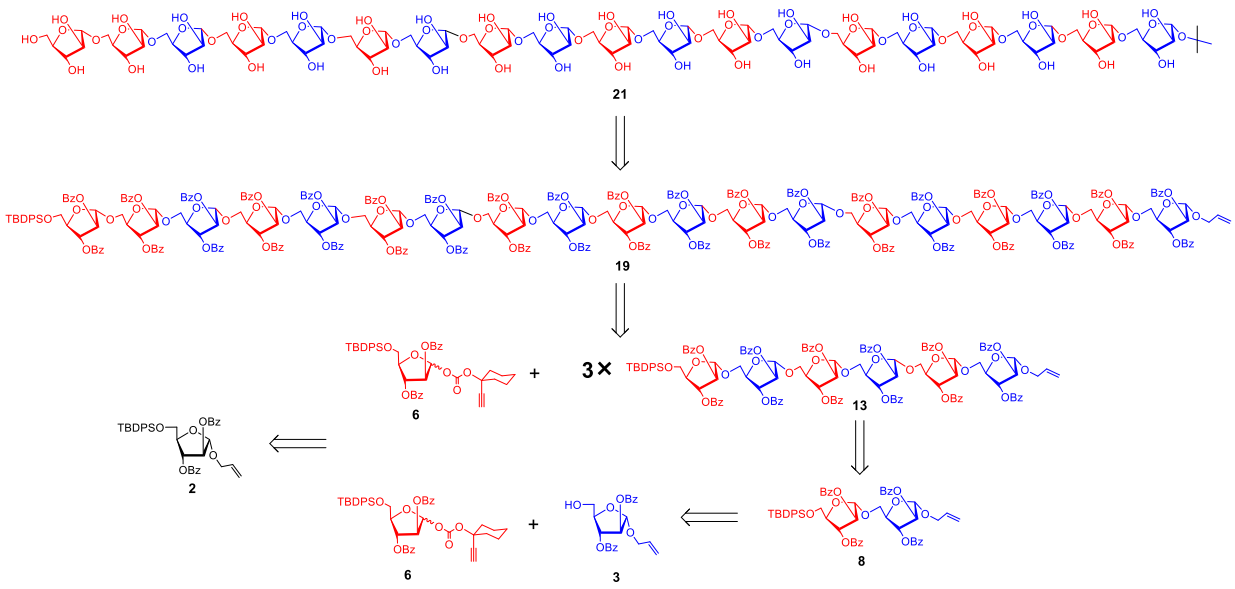
Figure 3.7: Cartoon representation of arabinogalactan (AG) from *M. tb* cell wall and the target nonadecaarabinofuranoside motif

3.4.1.1 – Retrosynthetic disconnection of nonadecaarabinofuranoside

From the perspective of having a single arabinose repeating unit connected through 1,2-*trans* glycosidic linkage in a linear α(1→5)-fashion, a careful retrosynthetic analysis of the target nonadecaarabinofuranoside (**21**) molecule was planned which advocated to use a single arabinose residue (**2**) for the full length synthesis of nonadecaarabinofuranoside (**21**) utilizing our recently developed alkynyl carbonate donor chemistry.

In order to synthesize the nonadecaarabinofuranoside **21**, we have opted a highly convergent Split-React-Coupled strategy wherein the same precursor was used for both the glycosyl donor and glycosyl acceptor preparation. In this strategy, at first the precursor saccharide was *split* into two portions and then allowed to *react* separately with suitable reagents to prepare the respective glycosyl donor and acceptor, which were further *coupled* to get the glycoside. This strategy is going to be a prevailing approach as it not only diminishes the steps substantially required for the donor or acceptor preparation separately but also provides an enhanced convergence to the overall synthetic protocol.

Retrosynthetic disconnection plan for nonadecaarabinofuranoside **21** is depicted



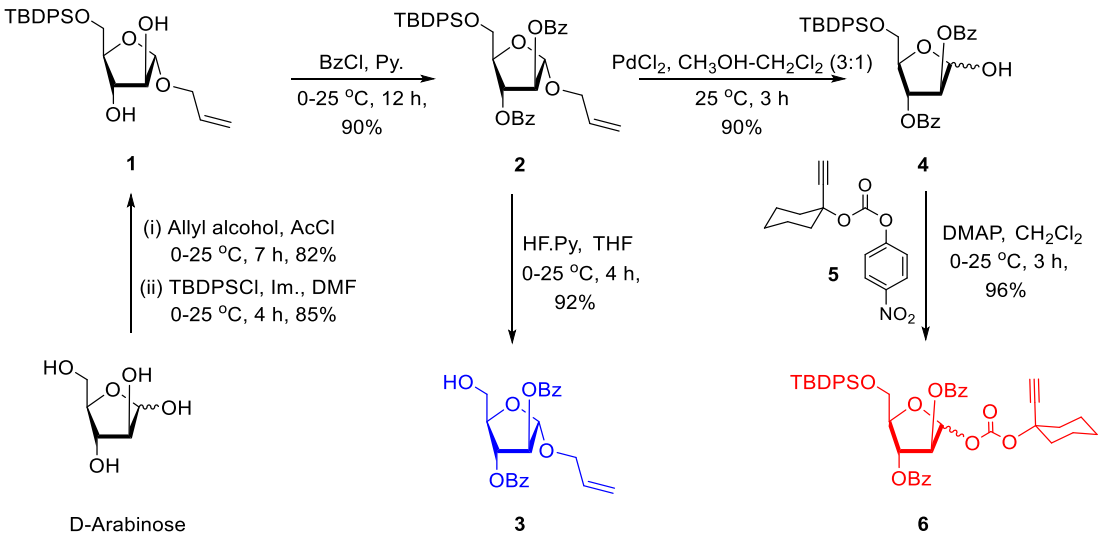
Scheme 3.1: **Retrosynthetic analysis for nonadecaarabinofuranoside**

in **Scheme 3.1**, which illustrates that the oligosaccharide **21** can be synthesized from single arabinofuranosyl monosaccharide unit (**2**). Allyl group at the reducing end of saccharide **21** was kept purposefully to transform it for envisaged bio-physical studies. The synthetic route for nonadecaarabinofuranoside **21** was designed based on the recently identified glycosylation protocol (Chapter 2) in which the glycosyl alkynyl carbonates are activated in the presence of [Au]/[Ag]-catalytic system.[18]

3.4.1.2 – Synthesis of monosaccharide carbonate donor and acceptor

Our synthetic endeavor started with the synthesis of key arabinofuranoside derivative **2**. At first, allylation of D-arabinose was performed under acidic conditions using allyl alcohol and catalytic amount of acetyl chloride to obtain the desired allyl arabinofuranoside **1**. Further protection of the allyl arabinofuranoside at the *C*-5 position using TBDPSCl/Imidazole, followed by benzoylation of the remaining secondary hydroxyl groups using BzCl/Py/DMAP produced the compound **2**. Having the key arabinofuranoside precursor **2** in hand, it was split into two fractions. The first fraction was converted to the corresponding glycosyl acceptor **3** by cleaving the TBDPS-ether bond in presence of HF·Py in THF in 92% yield, while the second fraction was treated with $PdCl_2$ in CH_2Cl_2: MeOH (3:1) to undergo deprotection of allyl ether and generate the hemiacetal **4** in 90% which was further reacted with easily

available ethynylcyclohexyl (4-nitro phenyl) carbonate **5** to afford the glycosyl donor **6** in 96% yield (**Scheme 3.2**).



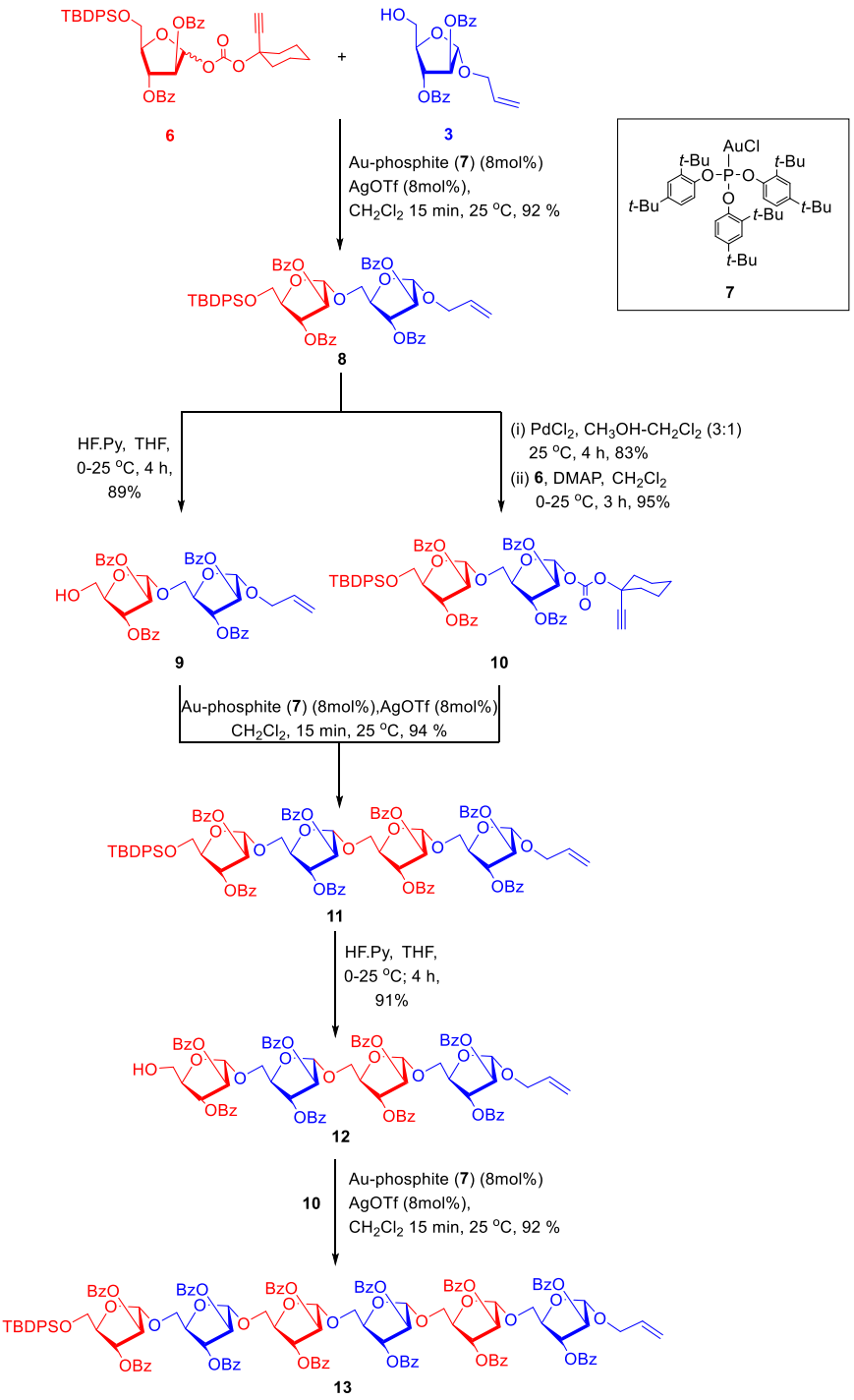
Scheme 3.2: **Synthesis of monosaccharide donor and acceptor**

3.4.1.3 – Synthesis of linear hexaarabinofuranoside

The glycosyl carbonate donor **6** and the glycosyl acceptor **3** were *coupled* utilizing our recently developed glycosylation protocol. The first glycosylation (or couping) was performed by treating the arabinofuranosyl carbonate donor **6** with the arabinofuranosyl acceptor **3** in presence of 8 mol% each of gold-phosphite (**7**) and AgOTf together in CH_2Cl_2 to afford the desired disaccharide **8** in 92% yield (**Scheme 3.2**). Formation of the disaccharide **8** was confirmed by NMR and mass spectral analysis. In the ^{1}H NMR spectrum of compound **8**, two anomeric protons of 1,2-*trans* Ara*f* linkage appeared as singlets at δ 5.35 and 5.50 ppm whilst resonances due to vinylic-C<u>H</u> moiety and the *tert*-butyl group of the TBDPS-group were noticed at δ 5.96 (dddd, *J* = 16.4, 10.6, 5.9, 5.0 Hz, 1H) and at δ 1.04 (s, 9H) ppm respectively. Remaining furanoside ring protons appeared between δ 3.96–5.66 ppm in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, characteristic anomeric carbons were idenfied at δ 105.0 and 106.1 ppm and vinylic carbons were noticed at δ 117.5 (<u>C</u>H_2) and 133.8 (<u>C</u>H) ppm. Further, resonances due to four carbonyl moieties at δ 165.4, 165.5, 165.6, 165.8 ppm revealed the presence of four benzoate groups thereby confirming the overall structural homogeneity.

In continuation, the disaccharide **8** was further split into two fractions. One fraction was transformed into the corresponding disaccharide alkynyl carbonate **10** in

two steps: (i) cleavage of the allyl glycoside under Pd-catalysed conditions; (ii) protection of the hemiacetal with carbonate reagent **5** in the presence of DMAP. The



Scheme 3.3: Synthesis of hexasaccharide

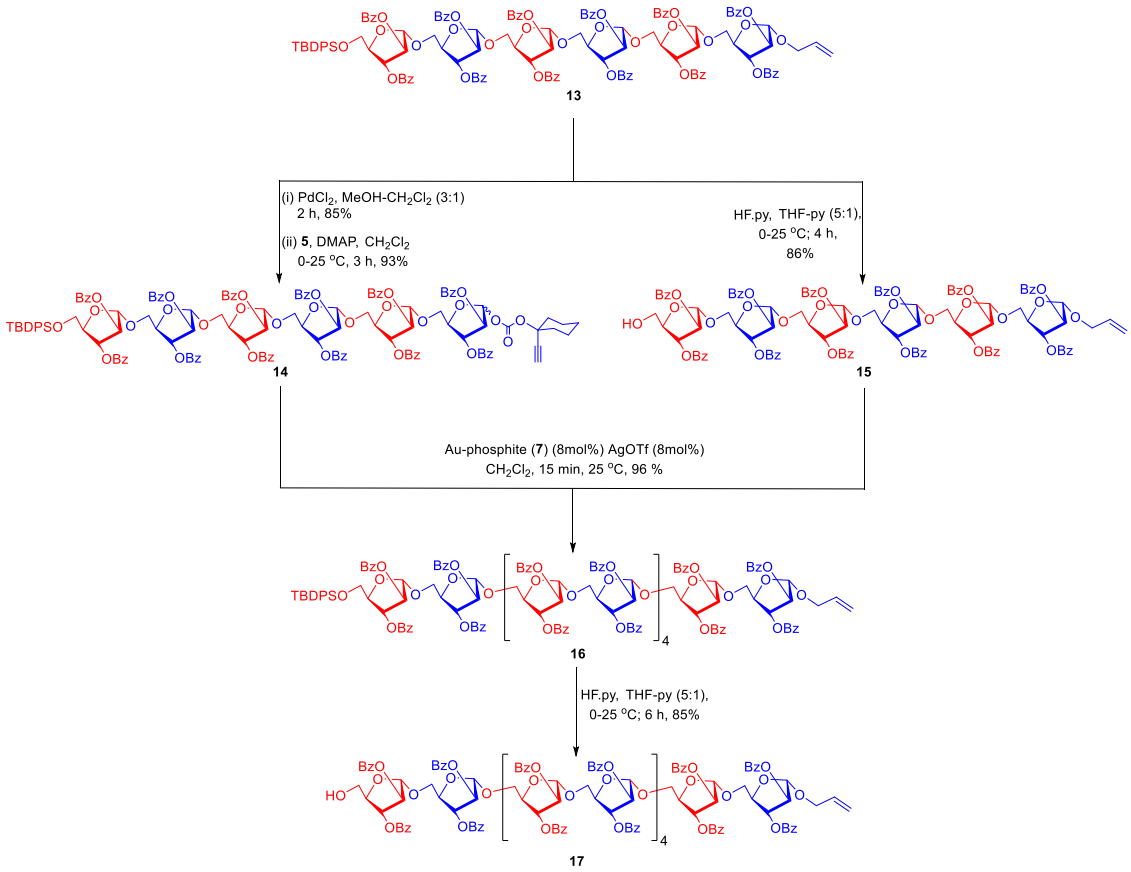
second fraction was converted to the required disaccharide acceptor **9** through cleavage of the TBDPS-ether bond by using HF·Py in THF. Subsequent glycosylation of disaccharide acceptor **9** with disaccharide donor **10** under [Au]/[Ag]-catalysis condition resulted in the linear tetraarabinofuranoside **11** with an excellent yield of 94% (**Scheme**

3.2). Removal of TBDPS protecting group from tetrasaccharide **11** by HF·Py afforded the tetrasaccharide acceptor **12**, which was further promoted to react with disaccharide carbonate donor **10** in the presence of 8mol% each of gold-phosphite complex (**7**) and AgOTf in CH_2Cl_2 to produce the required hexaarabinofuranoside **13** in 92% yield (**Scheme 3.2**).Formation of hexaarabinofuranoside **13** was confirmed by thorough NMR and mass spectral studies.

In the ^{1}H NMR spectrum, appearance of six anomeric protons as singlets at δ 5.27, 5.35, 5.39, 5.39, 5.40 and 5.41 ppm along with the vinylic-C<u>H</u> resonances at δ 5.93 (dddd, *J* = 16.5, 10.6, 5.9, 5.1 Hz, 1H) ppm and nine protons from *tert*-butyl moiety of TBDPS-group at δ 1.01 (s, 9H) ppm. In addition, in the ^{13}C NMR spectrum, presence of anomeric carbon resonances at δ 104.9, 105.8, 105.9, 105.9, 106.0, 106.0 ppm, the vinylic carbons at δ 117.5 (<u>C</u>H_2) and 133.8 (<u>C</u>H) ppm and twelve carbonyl carbons between δ 165.2–165.8 ppm along with all remaining carbons confirmed the assigned structure of the synthesized hexaarabinofuranoside **13**. Furthermore, successful synthesis of hexaarabinofuranoside **13** was further confirmed by HRMS analysis, *m/z* calculated for $C_{133}H_{120}O_{37}SiNa^+$, [M+$Na^+$]: 2360.7209; Found: 2360.7206.

3.4.1.4 – Synthesis of linear dodecaarabinofuranoside and the corresponding alcohol

Split-React-Coupled strategy was continued for the synthesis of linear dodecaarabinofuranoside. Accordingly, the hexasaccharide **13** was split into two fractions and the first fraction was converted to the hexasaccharide carbonate donor **14** in 93% yield following the above delineated sequence of steps; the second fraction was converted into the corresponding hexasaccharide acceptor **15** via removal of TBDPS protecting group in HF·py conditions in 86% yield. The *coupling* between glycosyl donor **14** and glycosyl acceptor **15** under the standard [Au]/[Ag]-catalysed conditions produced the linear dodecaarabinofuranoside **16** in 96% yield. Formation of the dodecaarabinofuranoside **16** was confirmed by thorough NMR and mass spectral analysis. In the ^{1}H NMR spectrum, resonances due to twelve anomeric protons were identified between δ 5.33 and 5.48 ppm. The appearances of signals due to the olefinic C<u>H</u> proton at δ 5.95 (dddd, *J* = 16.5, 10.4, 5.9, 4.9 Hz, 1H) ppm and *tert*-butyl C<u>H</u>$_3$ protons at δ 1.04 (s, 9H) ppm proved the presence of TBDPS and allyl moieties in the dodecasaccharide **16**. In the ^{13}C NMR spectrum of compound **16**, resonances due to



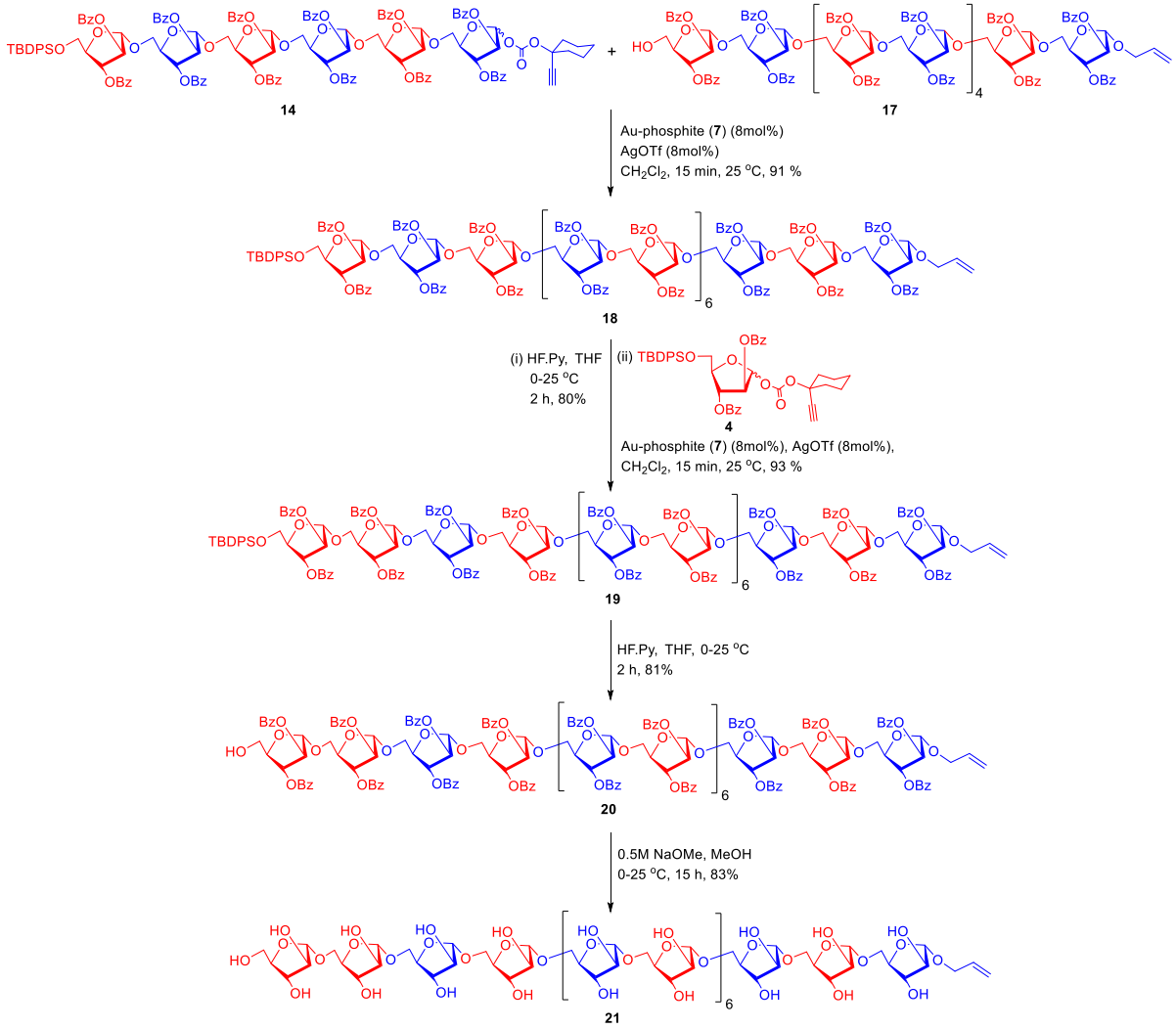
Scheme 3.4: Synthesis of dodecaarabinofuranoside alcohol

twelve anomeric carbons were identified at δ 104.9, 105.9, 106.0 (8C), 106.1 (2C), vinylic carbons at δ 117.5 ($\underline{C}H_2$) and 133.9 ($\underline{C}H$) ppm and 24 carbonyl carbons of 24 benzoates from δ 165.2 to 165.8 ppm confirmed the assigned dodecaarabinofuranoside **16** structure. In addition, dodecasaccharide **16** was further confirmed by MALDI-TOF analysis, *m/z* calculated for $C_{247}H_{216}O_{73}SiNa$, $[M+Na^+]$: 4402.2924; Found: 4402.4847.

Deprotection of the silyl group in compound **16** was performed under HF•Py conditions to afford the dodecaarabinofuranoside alcohol **17** for further elongation. Disappearance of signals from the *tert*-butyl $C\underline{H}_3$ protons at δ 1.04 (s, 9H) ppm in the ^{1}H NMR spectrum and for the carbons at δ 19.4 $[\underline{C}(CH_3)_3]$ and 26.9 $[C(\underline{C}H_3)_3]$ ppm in the ^{13}C NMR spectrum along with MALDI-TOF analysis (*m/z* of $C_{231}H_{198}O_{73}Na^+$: calcd.: 4164.1746; found: 4164.4248) clearly indicated the complete removal of TBDPS group and formation of dodecaarabinofuranoside alcohol **17**.

3.4.1.5 – Synthesis of linear nonadecaarabinofuranoside target motif

The furanosylation between the dodecaarabinofuranoside alcohol **17** and hexasacchari-



Scheme 3.5: Synthesis of nonadecasaccharide motif

-de carbonate donor **14** employing 8 mol% each of Au-phosphite complex **7** and AgOTf in CH_2Cl_2 afforded the linear octadecaarabinofuranoside **18** in 91% yield within 15 minutes (**Scheme 3.5**). In addition to the ^{1}H and ^{13}C NMR spectroscopy (**Table 3.1**), the successful synthesis of this octadecaarabinofuranoside **18** was confirmed by MALDI-TOF analysis, *m/z* calculated for $C_{361}H_{312}O_{109}SiNa$, $[M+Na]^+$: 6444.8672, found 6446.9458.

Finally, attachment of an additional arabinofuranoside residue to the non-reducing end of octadecaarabinofuranoside **18 was** performed by two-step sequence of HF·Py mediated TBDPS ether bond cleavage followed by the glycosylation using monosaccharide carbonate donor **6** under [Au]/[Ag]-catalysed conditions to afford the linear nonadecaarabinofuranoside **19** in excellent yield (**Scheme 3.5**).

It is quite overwhelming to notice that the yield for all glycosylation steps, even

Entry	^{1}H NMR (δ ppm)	^{13}C NMR (δ ppm)
Anomeric	5.37 – 5.47 (m, 18H)	104.9, 105.9 (10 C), 106.0 (7 C)
TBDPS	1.08 (s, 9H), 7.35–7.95 (m, 10H)	19.3, 26.8 (3C), 127.7–135.7 (12C)
Allyl	6.00 (dddd, *J* = 16.5, 10.6, 5.9, 5.1 Hz, 1H), other resonances merged with sugar ring protons	67.8, 117.4, 133.8
Benzoate	7.20–8.06 (m, 180H)	127.7–133.5 (216C), 165.2 (16C), 165.4 (2C), 165.5 (2C), 165.6 (12C), 165.7 (4C)

Table 3.1: Characteristic ^{1}H and ^{13}C NMR signals of octadecasaccharide 18

At nonadecasaccharide level, remained consistently higher than 90%. Attachment of an additional arabinofuranoside in nonadecasaccharide **19** was again confirmed by NMR (**Table 3.2**) along with MALDI-TOF analysis, *m/z* calculated for $C_{380}H_{328}O_{115}SiNa$, $[M+Na]^{+}$: 6784.9619, found 6784.8623.

Thereafter, treatment of nonadecaarabinofuranoside **19** with HF·Py in THF promoted the cleavage of the silyl ether to afford the compound **20** in 81% yield and finally the global deprotection of benzoates under Zemplén saponification condition using 0.5M NaOMe in MeOH solution provided the fully deprotected allyl nonadecaarabinofuranoside **21** in 83% yield which appeared as a fluffy white powder after purification. The final unprotected target oligoarabinan motif nonadecasaccharide **21** was confirmed through NMR and Mass spectral analysis.

Entry	^{1}H NMR (δ ppm)	^{13}C NMR (δ ppm)
Anomeric	5.37 – 5.47 (m, 19H)	104.8, 105.8 (16C), 106.0 (2C)
TBDPS	1.09 (s, 9H), 7.36–7.91(m, 10H)	19.3, 26.8(3C), 127.7–135.7 (12C)
Allyl	6.01 (dddd, *J* = 16.5, 10.7, 5.8, 5.2 Hz, 1H)	67.8, 117.4, 133.8
Benzoates	7.20–8.06 (m, 185H)	127.7–133.5 (222C), 165.1 (16C), 165.2, 165.2, 165.4, 165.5, 165.6 (17C), 165.7

Table 3.2: Characteristic ^{1}H and ^{13}C NMR signals of nonadecasaccharide 19

In the ^{1}H NMR spectrum, resonances due to nineteen anomeric protons were identified between δ 5.35 and 5.48 ppm. Appearance of olefinic C<u>H</u> proton signals at δ 5.97 (dddd, *J* = 16.5, 10.8, 5.7, 5.3 Hz, 1H) ppm confirmed the presence of allyl moiety. In the ^{13}C NMR spectrum, resonances due to the nineteen anomeric carbons were

observed at δ 107.1, 107.9, 108.0 (17C) ppm, the vinylic carbons were found to resonate at δ 119.1 ($\underline{C}H_2$) and 133.9 ($\underline{C}H$) ppm. Besides, complete disappearance of signals in both aliphatic and aromatic regions along with the MALDI-TOF analysis, *m/z* calculated for $C_{98}H_{158}O_{77}Na$, $[M+Na]^+$: 2590.8379, found 2590.1692 confirmed the successful synthesis of the target nonadecasaccharide **21** motif of arabinogalactan part from Mtb cell wall.

3.4.2 – Total synthesis of tridecasaccharide reminiscent from Mtb cell wall

Successful synthesis of linear nonadecaarabinofuranoside motif from AG part of Mtb cell wall with excellent glycosylation yields provoked us to target a more complex and highly

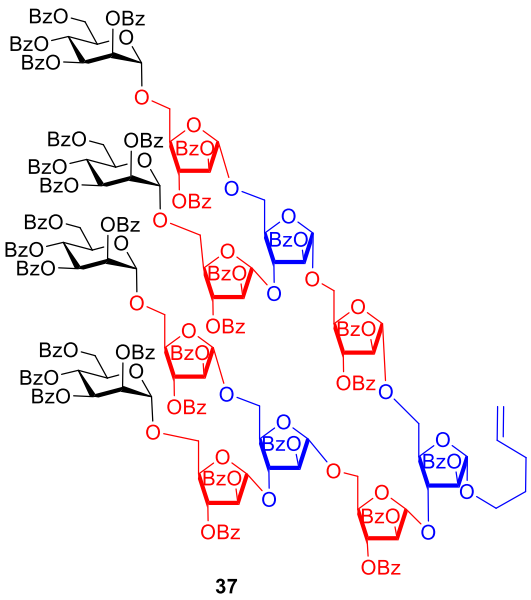


Figure 3.8: Target tridecasaccharide reminiscent of LAM from *M. tb* cell wall

branched mannose capped arabinan reminiscent of the lipoarabinomannan complex from Mtb cell wall. The tridecasaccharide motif **37** of interest consisted of 4 mannopyranose and 9 arabinofuranose residues connected through 1,2-*trans* glycosidic linkages in highly branched manner. The arabinan domain of **37** contained 6 α-Ara*f*-(1→5)-α-Ara*f* as well as 2 α-Ara*f*-(1→2)-α-Ara*f* linkages to form the core part wherein the non-reducing ends of arabinan domain are capped with 4 mannose residues (**Figure 3.8**).[20]

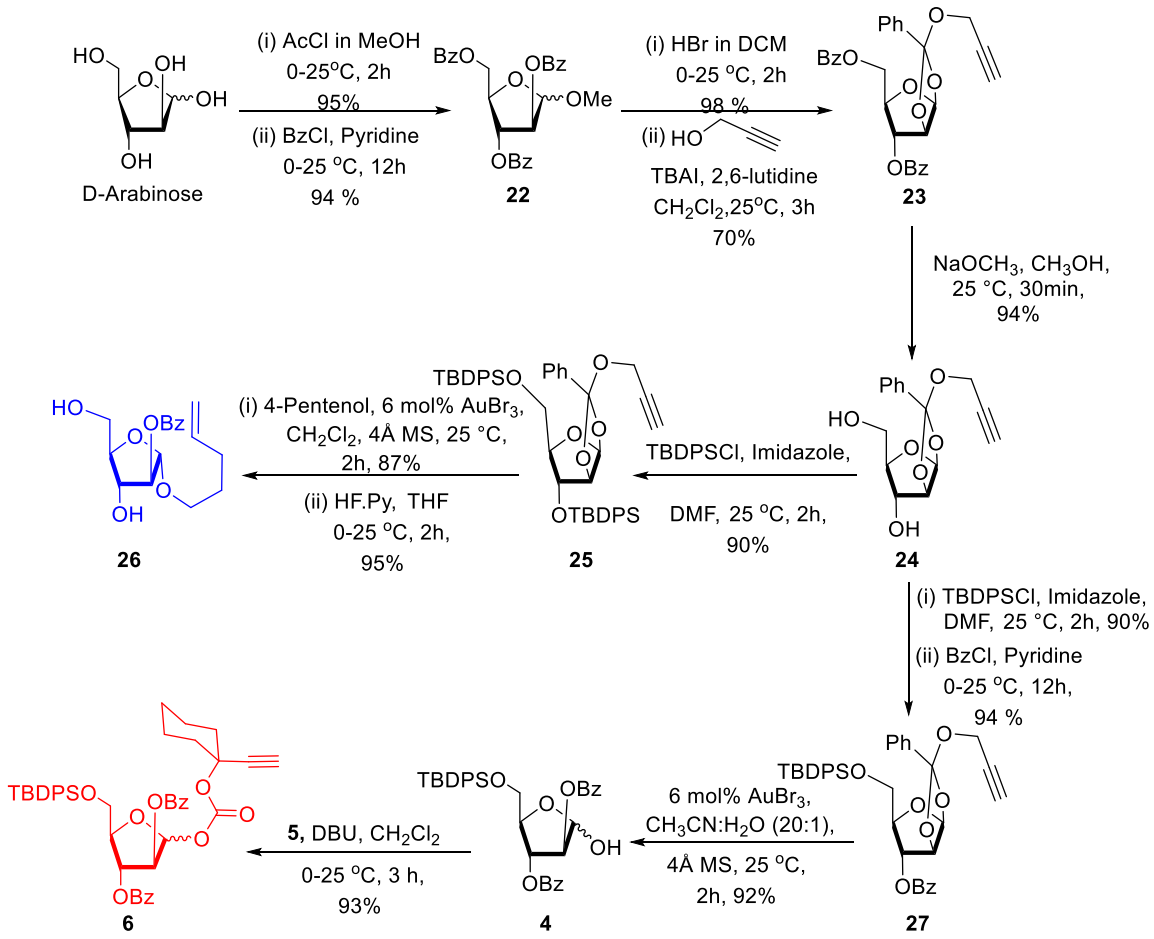
3.4.2.1 – Retrosynthetic analysis of tridecasaccharide arabinomannan

Retrosynthetic analysis of the tridecasaccharyl arabinomannan was carried out considering the salient features of recently developed [Au]/[Ag]-catalysed glycosylation protocol. As the terminal portion in the arabinomannan is capped by mannopyranosyl sugar residues and thus the first disconnection was envisioned to install four terminal mannospyranosyl sugar units onto a branched nonaarabinofuranoside motif **35**. The nonaarabinofuranoside (**35**) fragment can be further disconnected into three identically branched arabinofuranosyl trisaccharide motifs (**31**) which in turn can be obtained from two arabinofuranosyl monosaccharide residues. Thus, the successful synthesis of tridecasaccharyl arabinomannan requires three building blocks viz. two arabinofuranosides **6** and **26** and one mannopyranosyl building block **30**.

3.4.2.2 – Synthesis of various building blocks

Our journey began with the key arabinofuranosyl derivative, propargyl 1,2-*O*-orthoester **23** preparation as reported earlier.[15a] At first, methyl arabinofuranoside was prepared from D-arabinose in presence of MeOH•HCl which was generated *in situ* by acetyl chloride in MeOH and then benzoylation of the remaining secondary hydroxyl groups by BzCl/Py/DMAP afforded the arabinofuranoside **22** in 89% yield over two steps. Further reaction of arabinofuranoside **22** with AcBr/MeOH at 0 °C for 2 h generated the arabinofuranosyl bromoside which on subsequent treatment with propargyl alcohol, 2,6-lutidine and a catalytic amount of TBAI in CH_2Cl_2 provided the desired 3,5-di-*O*-benzoyl-α-D-arabinofuranosyl propargyl 1,2-orthoester **23** in overall 61% yield after 4 steps (**Scheme 3.7**). The ^1H and ^{13}C NMR spectrums of the synthesized 3,5-di-*O*-benzoyl-α-D-arabinofuranosyl propargyl 1,2-orthoester **23** were perfectly matching with the reported one.[15a] The orthoester **23** was further confirmed by HRMS analysis (*m/z* $[M + Na]^+$ calcd for $C_{29}H_{24}O_8Na^+$ 523.1369, Found: 523.1365).

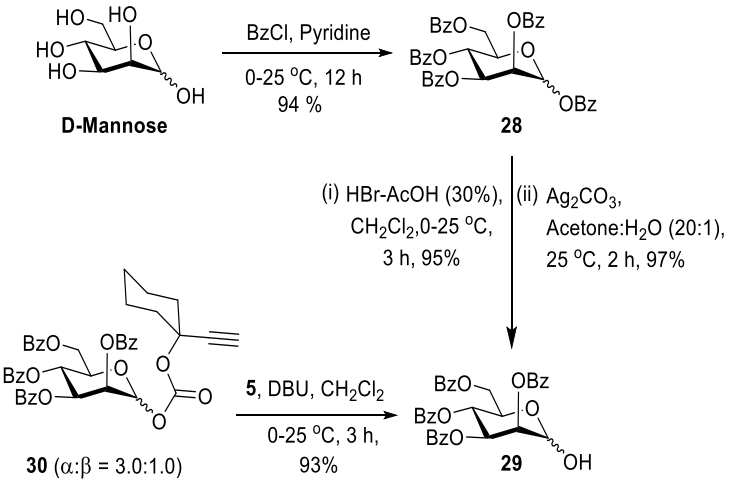
Propargyl 1,2-orthoester **23** was further utilized to access two monosaccharide building blocks **6** and **26** required for assembling the branched trisaccharide. Accordingly, benzoyl groups of orthoester **23** were saponified under Zemplén conditions to afford the propargyl 1,2-*O*-orthoester diol **24**[15a] in 94% yield which without any further purification was treated with excess of TBDPS-Cl and Imidazole in DMF to get the di-silyl protected propargyl 1,2-*O*-orthoester **25** in 90% yield. Furthermore, glycosylation of orthoester **25** with 4-penten-1-ol in the presence of catalytic amount of gold tribromide (6 mol% $AuBr_3$) and 4Å MS powder in CH_2Cl_2



Scheme 3.7: Synthesis of arabinofuranosyl donor and acceptor

followed by the deprotection of silyl group using HF•Py conditions afforded the *n*-pentenyl furanoside **26** in 79% yield over two steps. In the ^{1}H NMR spectrum of **26**, resonances for the anomeric proton were noticed at δ 5.24 ppm as singlet and those for the terminal olefinic -C<u>H</u>=CH$_2$ were displayed at δ 5.82 (ddt, *J* = 16.7, 10.7, 5.4) ppm whilst two vinylic protons [-CH=C<u>H</u>$_2$] were identified as multiplets between δ 4.95 and 5.05 ppm. Characteristic resonances due to the *n*-pentenyl moiety were noticed at δ 3.71 and 3.40. In the ^{13}C NMR spectrum, presence of anomeric carbon resonances at δ 105.4 ppm, the vinylic carbons at δ 115.1 (<u>C</u>H$_2$) and 137.9 (<u>C</u>H) ppm and one carbonyl carbon of the lone benzoate at δ 166.7 ppm along with other residual carbons peaks confirmed the assigned *n*-pentenyl furanoside **26**. In addition, the assigned structure of compound **26** was further confirmed by the satisfactory confirmation of molecular weight in the HRMS spectrum (*m/z* [M + Na]$^{+}$ calcd for $C_{17}H_{22}O_6Na^{+}$ 345.1314, Found: 345.1314).

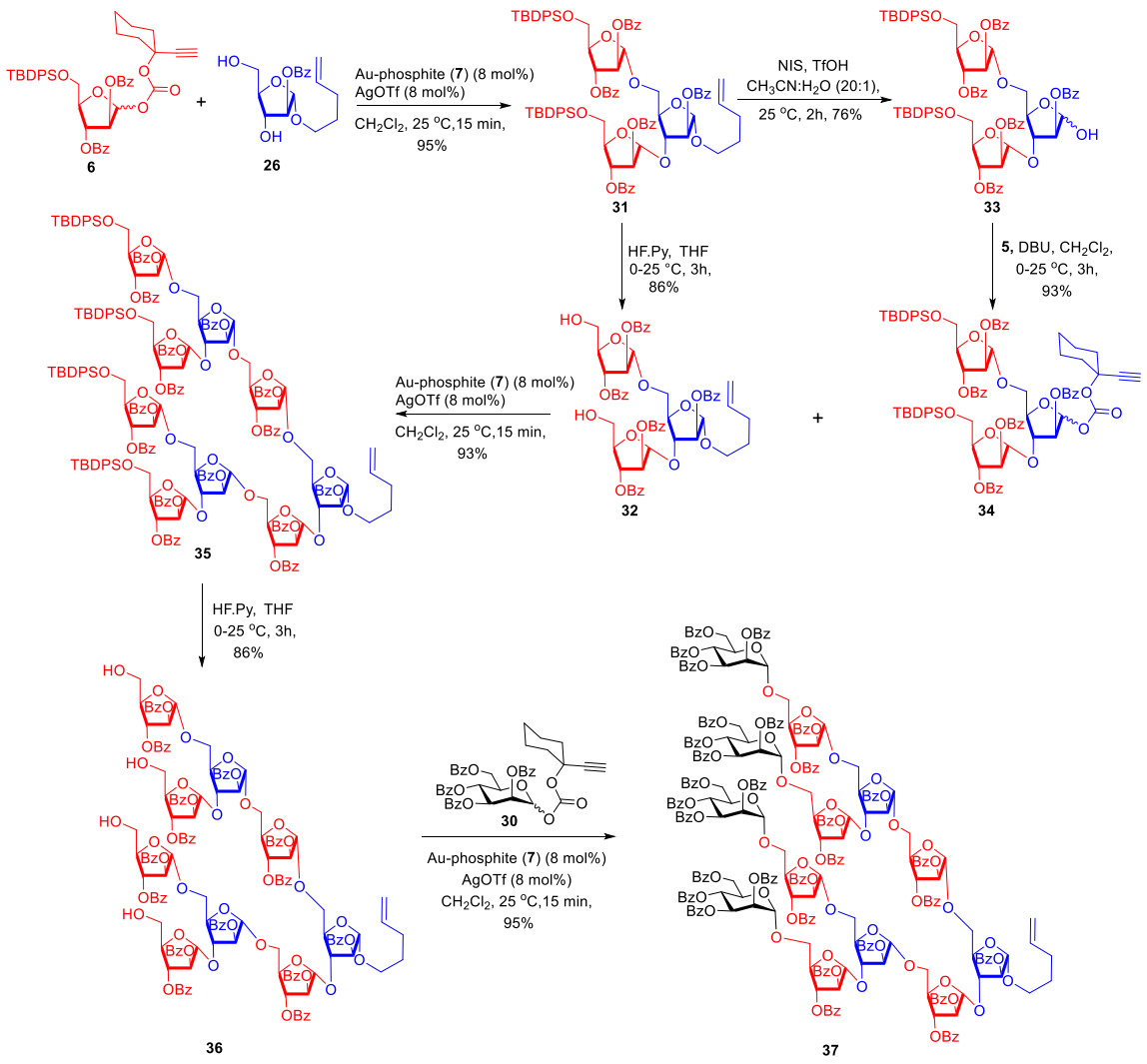
On the other hand, regioselective protection of crude propargyl 1,2-*O*-orthoester diol **24** with one equivalent of TBDPS-Cl/Imidazole in DMF followed by benzoylation using BzCl/Py produced the compound **27** in 91% yield. The orthoester **27** upon treatment with 6 mol% $AuBr_3$ in CH_3CN-H_2O (20:1) solvent system at 25 ^{0}C for 2 h afforded the required hemiacetal **4** which on further reaction with ethynylcyclohexyl (4-nitro phenyl) carbonate **5** and DBU in CH_2Cl_2 afforded the desired furanosyl donor **6** in 93% yield (**Scheme 3.7**). In the ^{13}C NMR spectrum of furanosyl donor **6**, presence of two anomeric carbons at δ 97.0 and 102.5 ppm (for β-and α-anomer) and characteristic signals for carbonate carbons at δ 151.0 (2C) ppm along with those of four carbonyl carbons at δ 165.1, 165.4, 165.4, 165.5 ppm indicated the successful formation of donor **6**. Additional confirmation was obtained by mass spectral studies (*m/z* $[M + Na]^+$ calcd for $C_{44}H_{46}O_9SiNa^+$ 769.2809, Found: 769.2805).



Scheme 3.8: Preparation of mannopyranosyl carbonate donor

The third monosaccharide building block **30** was obtained from D-mannose. per *O*-benzoylation of D-mannose using BzCl/Py provided the penta-*O*-benzoylmannoside **28**[21a] in 94% yield as α/β mixture. Subsequent treatment of **28** with HBr-AcOH (30%) in CH_2Cl_2 at 0 ^{0}C for 3 h followed by hydrolysis of mannose bromoside in presence of Ag_2CO_3 in H_2O-Acetone (1:20) at 25 ^{0}C for 2 h resulted the hemiacetal **29**[21b] in 92% yield over two steps. The hemiacetal **29** was further treated with carbonate reagent **5** and DBU in CH_2Cl_2 to afford the desired mannopyranosyl carbonate donor **30** as α/β (3.0:1.0) mixture with 93% yield (**Scheme 3.8**).

3.4.2.3 – Synthesis of tridecasaccharide



Scheme 3.9: Synthesis of highly branched tridecasaccharide reminiscent motif

Having all the three building blocks in hand, synthesis of tridecasaccharide motif was initiated with the first glycosylation reaction between acceptor **26** and 2.5 equivalents of arabinofuranosyl carbonate donor **6** under [Au]/[Ag]-catalysed glycosidation conditions employing 8 mol% each of Au-phosphite complex (**7**) and AgOTf , which afforded the desired triarabinofuranoside **31** in 95% yield. In the ^{1}H NMR spectrum of trisaccharide **31**, three 1,2-*trans* anomeric protons were noticed as individual singlets at δ 5.29, 5.42 and 5.52 ppm. The resonances at δ 5.01 (dt, J = 10.4, 1.7 Hz), 5.09 (dt, J = 17.1, 1.7 Hz) and 5.86 (ddt, J = 16.9, 10.5, 6.7 Hz) corresponding to the olefinic methylenes and methine protons were also identified. Characteristic resonances of *tert*-butyl moiety at δ 1.06 (s, 9H), 1.10 (s, 9H) ppm from two TBDPS groups were also noted. In the ^{13}C

NMR spectrum, presence of three anomeric carbons at δ 105.4, 106.0 and 106.2 ppm and distinctive methylene carbon at 115.0 ppm along with residual carbons confirmed the successful synthesis of the trisaccharide **31**. Additional confirmation was obtained by HRMS analysis (*m/z* $[M + Na]^+$ calcd for $C_{87}H_{90}O_{18}Si_2Na^+$ 1501.5563, Found: 1501.5562).

Synthesis of highly branched nonaarabinofuranoside from triarabinofuranoside **31** was accomplished using the previously used convergent Split-React-Couple strategy. Consequently, the *n*-pentenyl trisaccharide **31** was split into two portion and the first portion was treated with NIS/TfOH in CH_3CN-H_2O (20:1) at 25 ^{0}C for 2h to generate trisaccharide hemiacetal **33** in 76% yield, followed by reaction with carbonate reagent **5** and DBU afforded the trisaccharide carbonate donor **34** in 92% yield whilst the second portion was transformed into the corresponding trisaccharide-diol (**32**) via silyl ether bond clevage in HF·Py condition in 86% yield. The key glycosylation between one equivalent of trisaccharide-diol **32** and 2.5 molar equivalents of trisaccharide carbonate

Entry	^{1}H NMR (δ ppm)	^{13}C NMR (δ ppm)
Anomeric or C-1	5.14 (s, 1H), 5.28 (s, 1H), 5.30 (s, 1H), 5.33 (s, 1H), 5.39 (s, 1H), 5.41 (s, 1H), 5.43 (s, 1H), 5.45 (s, 1H), 5.46 (s, 1H)	105.9, 106.2, 106.4, 106.5, 106.6, 106.6, 106.6, 106.9, 106.9
TBDPS	0.90 (s, 18H), 0.96 (s, 18H), 7.11–7.67 (m, 40H)	19.9 (2C), 20.0 (2C), 27.4 (6C), 27.5 (6C), 128.3–136.3 (48C)
n-pentenyl	5.87 (ddt, *J* = 16.9, 10.5, 6.7 Hz 1H), 4.91 (m, 1H), 4.98 (m, 1H), 3.43 (dt, *J* = 9.6, 6.5 Hz, 1H), 3.69 (dt, *J* = 9.6, 6.5 Hz, 1H), 2.09 (q, *J* = 7.3 Hz, 2H), 1.64 (p, *J* = 9.2, 8.1 Hz, 2H)	30.5, 30.9, 67.3, 115.6, 138.9
Benzoates	7.11–8.01 (m, 75H)	128.3–134.0 (90C), 165.6, 165.6, 165.8, 165.8, 165.9, 166.0, 166.0, 166.0, 166.1, 166.1, 166.2, 166.2, 166.2, 166.3

Table 3.3: Characteristic ^{1}H and ^{13}C NMR signals of nonaarabinofuranoside 35

donor **34** in presence of 8 mol% each of Au-phosphite complex (**7**) and AgOTf underwent smoothly affording the highly branched nonaarabinofuranoside **35** in 93% yield. In addition to the ^{1}H and ^{13}C NMR spectroscopy (**Table 3.3**), the successful synthesis of this nonaarabinofuranoside **35** was confirmed by HRMS analysis *m/z* calculated for $C_{219}H_{214}O_{52}Si_4Na$, $[M+Na]^+$: 3810.3076, found 3812.2544. Deprotection

of four TBDPS group in compound **35** using HF·py conditions resulted in the formation of the nonaarabinofuranoside tetraol **36** which was directly reacted as an acceptor required for the targeted tridecasaccharide synthesis under Au-Ag catalysed glycosylation conditions. The attachment of four mannose sugar residues on the non-reducing ends of nonasaccharide tetra-ol **36** was performed by treating 5 equivalents of mannose-carbonate donor **30** with one equivalent of tetraol acceptor **36** in presence of 8 mol% each of Au-phosphite complex (**7**) and AgOTf at 25 ^{0}C for 15 minutes which resulted into the targeted tridecasaccharide **37** in 95% yield (**Scheme 3.9**). In addition

Entry	^{1}H NMR (δ ppm)	^{13}C NMR (δ ppm)
Anomeric region	5.21 (s, 1H), 5.21 (s, 1H), 5.36 (s, 1H), 5.38 (s, 1H), 5.39 (s, 1H), 5.44 (s, 1H), 5.46 (s, 1H), 5.46 (s, 1H), 5.54 (s, 1H), 5.85 (d, *J* = 3.1Hz, 1H), 5.87 (d, *J* = 3.0 Hz, 1H), 5.91 (d, *J* = 3.0 Hz, 1H), 5.93 (d, *J* = 3.1 Hz, 1H),	98.8, 98.8, 98.8, 98.8, 105.9, 106.3, 106.4, 106.4, 106.5, 106.6, 106.6, 106.7, 106.8
n-pentenyl	5.75 (ddt, *J* = 16.8, 10.4, 6.8 Hz 1H), 4.91 (m, 1H), 4.98 (m, 1H), 3.43 (dt, *J* = 9.6, 6.5 Hz, 1H), 3.69 (dt, *J* = 9.6, 6.5 Hz, 1H) 1.75 (p, *J* = 9.2, 8.1 Hz, 2H), 2.20 (q, *J* = 7.3 Hz, 2H),	29.4, 30.9, 67.7, 115.7, 138.9
Benzoates	7.26–8.11 (m, 155H)	128.3–134.0 (186C), 165.6 (2C), 165.7 (2C), 165.8 (3C), 165.9 (2C), 166.0, 166.1 (5C), 166.2 (5C), 166.3, 166.4, 166.5 (2C), 166.6 (2C), 166.8 (5C)

Table 3.4: Characteristic ^{1}H and ^{13}C NMR signals of tridecasaccharide 37

to the clean ^{1}H and ^{13}C NMR spectral data (**Table 3.4**), the successful synthesis of the tridecasaccharide **37** was confirmed by HRMS analysis, *m/z* calculated for $C_{291}H_{246}O_{88}K$, $[M+K]^{+}$: 5186.4412, found 5185.4000.

3.5 – Conclusion

In summary, we have demonstrated the excellent features of the recently developed glycosyl alkynyl carbonate donor chemistry through successful total synthesis of the linear nonadecaarabinofuranoside motif as well as the highly branched tridecasaccharide reminiscent of mycobacterial cell surface. The preparation of glycosyl donor and acceptor from the same precursor and their repititive use in a highly

convergent fashion allowed the effortless synthesis of the targeted molecules in minimum number of steps with excellent overall yields, such as ttargeted nonadecasaccharide synthesis was achieved utilizing 23 steps in 6.4% overall yield. Importantly, assembling the highly branched glycan with 13 residues was accomplished in mere 14 synthesis steps starting from the corresponding aldose. Due to its simple operational protocol and excellent glycosylation yields at complex donor or acceptor level, the alkynyl carbonate donor chemistry can be invoked as a good alternative for the synthesis of many other linear and branched oligosaccharides of biological importance in a very facile manner.

Note: Characterization data and full spectral charts for all compounds can also be found in *Eur. J. Org. Chem.* **2017,** 4794−4802 and *Angew. Chem. Int. Ed.* **2016**, *128,* 7917–7922.

3.6 – Experimental section

Synthesis of Allyl 5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranoside (1): Allyl alcohol (100 mL) was taken and acetyl chloride (2.5 mL) was added at 0 ^{0}C and stirred for 1 h. Then D-arabinose (10.0 g, 66.6 mmol) was added to that mixture and was stirred for another 1 h at 25 ^{0}C and kept at 80 ^{0}C for another 5 h. The product was purified by column chromatography using acetone-CH_2Cl_2 (6:4) to obtain compound allyl α-D-arabinofuranoside as off-white solid (10.39 g, 82%). In continuation, allyl α-D-arabinofuranoside (5.00 g, 26.29 mmol) prepared *vide supra* was redissolved in DMF (30 mL), imidazole (5.37 g, 78.87 mmol) was added and stirred at 25 ^{0}C. TBDPSCl (8.20 mL, 8.67 g, 31.55 mmol) was added dropwise at 0 ^{0}C and stirred at 25 ^{0}C. After 4 h, the reaction mixture was diluted with water and extracted with ethyl acetate (3x50 mL) and combined ethyl acetate layers were washed with brine solution. The organic layer was filtered and the filtrate was concentrated *in vacuo* to obtain an oily residue that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford compound **1** (9.58 g, 85%).

Synthesis of Allyl 2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranoside (2): To a solution of compound **1** (8.00 g, 18.67 mmol) in pyridine (50 mL), benzoyl chloride (5.42 mL, 6.56 g, 46.66 mmol) was added dropwise at 0 ^{0}C and the reaction mixture was heated to 25 ^{0}C and stirred for 12 h. Progress of the reaction and formation of compound **2** was checked by TLC. The reaction mixture was diluted with 5*N* HCl (100 mL), CH_2Cl_2 (100 mL) and washed with water, sat. aq. Sodium bicarbonate solution, brine solution. Combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the resulting crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain compound **2** (8.70 g, 90%).

Synthesis of Allyl 2,3-di-O-benzoyl-α-D-arabinofuranoside (3): To a solution of silyl ether **2** (7.0 g, 10.99 mmol) in 50 mL of THF:Py (5:1) was added HF·Py (2.0 mL) at 0 ^{0}C and stirred at 25 ^{0}C. After 4 h, the reaction mixture was cooled to 0 ^{0}C and 15 g of silica gel was added to the reaction mixture and a filter column chromatography was performed. The compound containing fractions were concentrated under diminished pressure and the resulting residue was further redissolved in CH_2Cl_2 (40 mL) and washed with 1*N* HCl (1x20 mL), sat. aq. $NaHCO_3$ (1x20 mL) and brine (20 mL)

solution. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4, decanted and concentrated *in vacuo* to afford compound **3** (4.03 g, 92%) as a thick syrup.
The same procedure was utilized for the synthesis of compounds **9**, **12**, **15**, **17**, **20**, **32**, **36** and while synthesizing **19**.

Synthesis of 2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α/β-D-arabinofuranose (4) via allyl deprotection: To a solution of compound **2** (5.00 g, 7.85 mmol) in 3:1 mixture of CH_3OH-CH_2Cl_2 (30 mL) was added dropwise $PdCl_2$ (278.5 mg, 1.57 mmol) in CH_3OH (5 mL) and stirred at 25 ^{0}C. After 3 h, the reaction mixture was quenched by addition of excess triethylamine and concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain the title compound **4** (4.22 g, 90%) as a pale yellow solid.
The same procedure was repeated while synthesizing compounds **10** and **14** also.

Synthesis of 2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α/β-D-arabinofuranose (4) using Au(III) catalyst: To a CH_3CN solution (10 mL) containing orthoester **27** (2.0 g, 3.16 mmol) and water (568 μL, 31.50 mmol)) was added a catalytic amount of $AuBr_3$ (82 mg, 189 μmol) and stirred at room temperature. After 2 h, the reaction mixture was neutralized by the addition of Et_3N (1 mL) and filtered through celite and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain lactol (1.73 g, 92%) as thick syrup.

Synthesis of 2-*O*-benzoyl-3,5-di-*O*-[2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl α-D-arabinofuranosyl]- α/β -D-arabinofuranose (33) via 4-pentenyl deprotection: To a CH_3CN solution (10 mL) containing n-pentenyl glycoside **32** (500 mg, 0.338 mmol) and water (69 μL, 3.38 mmol)) was added NIS (228 mg, 1.01 mmol) and catalytic amount of TfOH. The reaction mixture was stirred at 25 ^{0}C for 2 h, the reaction mixture was quenched with saturated aq solution of $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (2x15 mL). Combined organic layers were washed with saturated aqueous solution of sodium bicarbonate and brine solution. The solution was decanted and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain compound **33** (363 mg, 76%) as a thick syrup.

Synthesis of 2,3,4,6-tetra-*O*-benzoyl- α/β-D-mannopyranose (29): To an ice cold solution of penta-*O*-benzoylmannoside **28** (3.00 g, 4.28 mmol) in CH_2Cl_2 (20 mL), HBr-AcOH (30%) (2mL) was added drop-wise and allowed to come to 25 ^{0}C. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_3$ solution (2x20 mL), brine solution (20 mL) and finally with water (20 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and dried to an off-white solid overnight. The crude bromoside residue (2.68 g, 4.06 mmol) was further redissolved in 20:1 mixture of Acetone-H_2O (21 mL) and Ag_2CO_3 (1.12 g, 4.06 mmol) was added. The reaction mixture was stirred for another 2 h and filtered over celite and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain the mannose hemiacetal **29** (2.35, 97%) as white solid.

Synthesis of 1-Ethynylcyclohexyl 4-nitrophenyl carbonate (**5**): To an ice cold solution of commercially available 1-ethynylcyclohexanol (5 g, 40.25 mmol) in anhydrous CH_2Cl_2 (40 mL) was added pyridine (20 mL, 0.25 mol) and stirred for 15 min. A solution of *p*-nitrophenyl chloroformate (10.55 g, 52.35 mmol) in anhydrous CH_2Cl_2 (15 mL) was added drop-wise and stirred at 0 ^{0}C for 20 min. Subsequently, the reaction mixture was stirred at 25 ^{0}C for 2.5h. The reaction was stopped by the addition of 2N HCl (100 mL) and extracted into CH_2Cl_2 (2x100mL), the combined CH_2Cl_2 layers was washed with saturated $NaHCO_3$ solution (50mL) followed by brine solution. CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain a pale yellow coloured solid that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford compound **5** (9.90 g, 85%) as a white solid.

Synthesis of ethynylcyclohexylglycosyl carbonate donor using DMAP (6): To a solution of hemiacetal **4** (1mmol) in anhydrous CH_2Cl_2 (40 mL) was added DMAP (1.23 g, 10.05 mmol) and stirred for 20 min. Reagent **5** (2.91 g, 10.05 mmol) was added portion-wise (3x) after every 30 min and stirred at 25 ^{0}C for 1 h. The reaction was concentrated *in vacuo* and the oily residue was partially purified by silica gel column chromatography (*n*-hexane/EtOAc). Eluents containing compound **6** along with trace quantities of 4-nitrophenol were concentrated under diminished pressure. The crude residue was diluted with CH_2Cl_2 (30 mL) and washed with an aqueous saturated

$NaHCO_3$ solution (20 mL) to remove 4-nitrophenol and obtained alkynyl arabinofuranosyl donor **6** (6.00 g, 96%) as a fluffy white solid.

The same procedure was repeated for the synthesis of alkynyl carbonate donors **10** and **14** also.

Synthesis of ethynylcyclohexylglycosyl carbonate donor using DBU (6): To an ice cooled solution of hemiacetal **4** (4 g, 6.70 mmol) in anhydrous CH_2Cl_2 (25 mL) was added DBU (2 mL, 13.41 mmol) and stirred for 20 min. A solution of carbonate reagent **5** (2.33g, 8.04 mmol) in anhydrous CH_2Cl_2 (5mL) was added drop-wise and stirred at 0 ^{o}C for 30 min. Subsequently, the reaction mixture was stirred at 25 ^{0}C. After 2h, the reaction was concentrated *in vacuo* to obtain an oily residue that was partially purified by silica gel column chromatography (*n*-hexane/EtOAc). Fractions containing compound **6** along with trace quantities of *p*-nitrophenol were concentrated *in vacuo*. The crude residue was redissolved in CH_2Cl_2 (30mL) and washed with an aqueous saturated $NaHCO_3$ solution to remove *p*-nitrophenol and obtain pure alkynyl glucosyl donor **6** (4.66 g, 93%) as white solid.

The same procedure was repeated for the synthesis of alkynyl carbonate donors **30** and **34** also.

Synthesis of pent-4-enyl 2-*O*-benzoyl-α-D-arabinofuranoside (26): To a CH_2Cl_2 solution (10 mL) containing propargyl 1,2-*O*-orthoester **25** (1 g, 1.3 mmol) and 4-pentene-1-ol (162 μL, 1.56 mmol)) with 4 Å MS powder (200 mg) was added a catalytic amount of $AuBr_3$ (34 mg, 78 μmol) and stirred at room temperature. After 2 h, the reaction mixture was neutralized by the addition of Et_3N (1 mL) and filtered through celite and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain n-pentenyl furanoside (900 mg, 87%) as a thick syrup. In continuation, n-pentenyl furanoside (800 mg, 1 mmol) prepared *vide supra* was redissolved in 10 mL of THF:Py (5:1) and HF·Py (150 μL) was added at 0 ^{0}C and stirred at 25 ^{0}C. After 2 h, the reaction mixture was cooled to 0 ^{0}C and 5 g of silica gel was added to the reaction mixture and a filter column chromatography was performed. The compound containing fractions were concentrated under diminished pressure and the resulting residue was further redissolved in CH_2Cl_2 (40 mL) and washed with 1*N* HCl (1x20 mL), sat. aq. $NaHCO_3$ (1x20 mL) and brine

(20 mL) solution. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4, decanted and concentrated *in vacuo* to afford compound **26** (297 mg, 92%) as a thick syrup.

Synthesis of 3,5-Di-*O*-tert-Butyldiphenylsilyl β-D-arabinofuranoside propyn-3-yl-1,2-orthobenzoate (25): To a solution of diol **24** (1.00 g, 3.42 mmol), imidazole (0.58 g, 8.55 mmol) in anhydrous DMF (10 mL) at 25 ^{0}C was added TBDPS-Cl (2.22 mL, 8.55 mmol) and stirred for 2 h. At the end of reaction, the reaction mixture was diluted with diethyl ether (50 mL) and washed with water and brine. Combined organic layers were dried over anhydrous sodium sulphate, filtered and the filtrate was concentrated *in vacuo* to obtain a crude residue which was purified on silica gel column chromatography (*n*-hexane/EtOAc) to afford compound **25** (2.37 g, 90%) as pale yellow syrup.

Synthesis of 3-*O*-benzoyl-5-*O*-*tert*-Butyldiphenylsilyl-β-D-arabinofuranoside propyn-3-yl-1,2-orthobenzoate (27): To a solution of diol **24** (1.00 g, 3.42 mmol), imidazole (0.58 g, 8.55 mmol) in DMF (10 mL) at 25 ^{0}C was added TBDPS-Cl (1.06 mL, 4.11 mmol) and stirred for 2 h. After 2 h, the reaction mixture was diluted with water and extracted with ethyl acetate (3x50 mL) and combined ethyl acetate layers were washed with brine solution. The organic layer was filtered and the filtrate was concentrated *in vacuo* to obtain an oily residue that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain mono TBDPS protected propargyl 1,2-*O*-orthoester (1.38 g, 76%) as pale yellow syrup. In continuation, propargyl 1,2-*O*-orthoester (1.3 g, 2.45 mmol) prepared *vide supra* was redissolved in 10 mL of Pyridine and benzoyl chloride (341 μL, 2.94 mmol) was added dropwise at 0 ^{0}C and the reaction mixture was heated to 25 ^{0}C and stirred for 12 h. Progress of the reaction and formation of compound **2** was checked by TLC. The reaction mixture was diluted with 5*N* HCl (50 mL), CH_2Cl_2 (50 mL) and washed with water, sat. aq. Sodium bicarbonate solution, brine solution. Combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the resulting crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain compound **27** (1.46 g, 94%) as a thick syrup.

Glycosylation using ethynylcyclohexylglycosyl carbonate donors (8): AgOTf (138 mg, 0.54 mmol) and Au-phosphite (**7**) (471 mg, 0.54 mmol) were added to a solution of donor **6** (5.00 g, 6.69 mmol) and acceptor **3** (2.67 g, 6.69 mmol) in anhydrous CH_2Cl_2

(40 mL) containing 4Å MS powder (400 mg) and stirred at 25 ^{0}C for 15 min, concentrated *in vacuo*, and resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford disaccharide **8** (6.02 g, 92%) as a thick syrup.

The same procedure was utilized for the synthesis of **11**, **13**, **16**, **18**, **19**, **31**, **35**, **37** also.

Synthesis of compound 21: To a solution of compound **20** (120 mg, 18.4 µmol) in CH_3OH was added 2 mL of 0.5 M solution of NaOMe in CH_3OH and stirred at 25 ^{0}C. At the end of 15 h, the reaction mixture was neutralized with Amberlite IR 120 (H^+) resin, filtered and concentrated under diminished pressure. The residue was washed with ethyl acetate (2x2 mL) and CH_3OH (2x2 mL) to obtain the compound **21** (39 mg, 83%).

Allyl-2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranoside (**2**): Yield: (90%); mp (^{0}C): 62.7; $[\alpha]_D^{25}$ ($CHCl_3$, *c* 1.0): -14.6 ; IR (cm^{-1}, $CHCl_3$): 3068, 2928, 2858, 1727, 1599, 1456, 1268, 1108, 1066, 971, 932, 707; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.05 (s, 9H), 4.02 (d, *J* = 4.6 Hz, 2H), 4.11 (ddt, J = 13.1, 6.0, 1.3 Hz, 1H), 4.29 (ddt, *J* = 13.2, 5.0, 1.5 Hz, 1H), 4.40 (q, *J* = 4.6 Hz, 1H), 5.22 (dq, *J* = 10.5, 1.3 Hz, 1H), 5.27 (s, 1H), 5.37 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.49 (d, *J* = 1.5 Hz, 1H), 5.62 (d, *J* = 1.4 Hz, 1H), 5.96 (dddd, *J* = 16.5, 10.6, 5.9, 5.1 Hz, 1H), 7.31 – 7.41 (m, 8H), 7.43 – 7.47 (m, 2H), 7.54 – 7.60 (m, 2H), 7.70 – 7.73 (m, 4H), 7.98 – 8.00 (m, 2H), 8.05 – 8.07 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.4, 26.8, 26.8, 26.9, 63.7, 67.9, 77.5, 82.6, 83.1, 105.0, 117.4, 127.7, 127.7, 127.7, 127.7, 128.4, 128.4, 128.4, 128.4, 129.3, 129.5, 129.7, 129.7, 130.0, 130.0, 130.0, 130.0, 133.3, 133.4, 133.4, 133.4, 134.0, 135.7, 135.7, 135.7, 135.7, 165.5, 165.7; HRMS (ESI-MS): m/z calcd for $[C_{38}H_{40}O_7SiNa]^+$: 659.2441; Found: 659.2439.

Allyl-2,3-di-*O*-benzoyl-a-D-arabinofuranoside (**3**): Yield: (92%); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -29.5; IR (cm^{-1}, $CHCl_3$): 3489, 3068, 2927, 1723, 1603, 1453, 1268, 1110, 1067, 1033, 982, 712; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.70 (s, 1H), 3.97 – 4.08 (m, 2H), 4.13 (ddt, *J* = 13.1, 5.9, 1.4 Hz, 1H), 4.31 (ddt, *J* = 13.1, 4.9, 1.6 Hz, 1H), 4.38 (q, *J* = 4.0 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.5 Hz, 1H), 5.32 (s, 1H), 5.39 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.49 (dd, *J* = 5.0, 1.4 Hz, 1H), 5.59 (d, *J* = 1.4 Hz, 1H), 5.97 (dddd, *J* = 16.4, 10.5, 5.9, 5.1 Hz, 1H), 7.45 (m, 4H), 7.55 – 7.62 (m, 2H), 8.08 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 62.3, 67.9, 77.8, 82.0, 83.8, 104.8, 117.4, 128.5, 128.5, 128.5,

128.5, 129.1, 129.2, 129.9, 129.9, 129.9, 129.9, 133.5, 133.6, 133.7, 165.4, 166.2; HRMS (ESI-MS): m/z calcd for $[C_{22}H_{22}O_7Na]^+$: 421.1263; Found: 421.1260.

2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α/β-D-arabinofuranose [α:β (1:1.1)] (**4**): Yield: (90%); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -41.1; IR (cm^{-1}, $CHCl_3$): 3012, 2935, 2860, 1728, 1603, 1455, 1366, 1268, 1107, 952, 704; ^1H NMR (399.78 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.10 (s, 9H), 3.42 (d, *J* = 4.1 Hz, 1H), 3.91 (dd, *J* = 11.1, 2.5 Hz, 1H), 3.97 (dd, *J* = 4.6, 1.2 Hz, 2H), 4.06 (dd, *J* = 11.1, 3.0 Hz, 1H), 4.22 – 4.27 (q, *J* = 4.6 Hz, 1H), 4.38 (d, *J* = 10.5 Hz, 1H), 4.56 (q, *J* = 4.6 Hz, 1H), 5.47 (d, *J* = 1.7 Hz, 1H), 5.55 (dd, *J* = 5.6, 4.9 Hz, 1H), 5.60 (d, *J* = 3.7 Hz, 1H), 5.64 (dd, *J* = 4.8, 1.5 Hz, 1H), 5.71 (dd, *J* = 10.5, 4.8 Hz, 1H), 6.02 (dd, *J* = 5.7, 4.1 Hz, 1H), 7.27 – 7.46 (m, 20H), 7.48 – 7.59 (m, 4H), 7.68 – 7.71 (m, 6H), 7.78 – 7.80 (m 2H), 7.94 – 7.97 (m, 2H), 7.99 – 8.10 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.5, 19.5, 26.9, 27.0, 27.0, 27.0, 27.1, 27.1, 63.8, 65.2, 76.6, 77.7, 79.5, 82.8, 83.1, 83.6, 95.6, 101.3, 127.9, 127.9, 127.9, 127.9, 127.9, 127.9, 127.9, 127.9, 128.2, 128.2, 128.6, 128.6, 128.6, 128.6, 128.7, 128.7, 129.3, 129.3, 129.4, 129.5, 129.9, 129.9, 130.0, 130.0, 130.1, 130.1, 130.1, 130.2, 130.3, 130.4, 131.9, 132.2, 133.3, 133.4, 133.6, 133.6, 133.6, 133.6, 133.7, 133.7, 135.7, 135.7, 135.8, 135.8, 135.8, 135.9, 136.1, 136.1, 165.8, 165.8, 166.0, 166.3; HRMS (ESI-MS): m/z calcd for$[C_{35}H_{36}O_7SiNa]^+$: 619.2128; Found: 619.2126.

1-Ethynylcyclohexyl 4-nitrophenyl carbonate (**5**): Yield: (85%); mp (^0C): 82.3; IR (cm^{-1}, $CHCl_3$): 3290, 2940, 2863, 1770, 1593, 1493, 1268, 1206, 1008, 771; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.39 (dtt, *J* = 13.7, 9.3, 4.3 Hz, 1H), 1.54 – 1.63 (m, 1H), 1.64 – 1.80 (m, 4H), 1.91 – 2.04 (m, 2H), 2.17 – 2.34 (m, 2H), 2.72 (s, 1H), 7.44 – 7.40 (m, 2H), 8.30 – 8.26 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.6, 22.6, 24.9, 36.8, 36.8, 75.9, 79.7, 82.0, 121.8, 121.8, 125.2, 125.2, 145.2, 149.8, 155.5; HRMS (ESI-MS): m/z calcd for $[C_{15}H_{15}NO_5Na]^+$: 312.0848; Found: 312.0846.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3-di-*O*-benzoyl-5-*O*-tert-Butyldiphenyl silyl- α/β- D-arabinofuranoside [α:β (2:1)] (**6**): Yield: (96%); mp (^0C): 51.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -21.0; IR (cm^{-1}, $CHCl_3$): 3067, 2929, 2857, 1762, 1729, 1598, 1454, 1240, 1108, 1071, 1018, 945, 910, 849, 707; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.04 (s, 9H), 1.29 – 1.40 (m, 3H), 1.45 – 1.48 (m, 1H), 1.49– 1.60 (m, 3H), 1.61 – 1.73 (m, 6H), 1.89 – 1.97 (m, 3H), 1.98 – 2.24 (m, 4H), 2.37 (s, 1H), 2.65 (s, 1H), 3.93 – 4.02 (m, 4H), 4.34 (q, *J* = 5.6 Hz, 1H), 4.58 (q, *J* = 4.6 Hz, 1H), 5.67 (d, *J* = 1.5 Hz,

1H), 5.73 – 5.76 (m, 2H), 6.11 (dd, *J* = 7.2, 6.1 Hz, 1H), 6.32 (s, 1H), 6.47 (d, *J* = 4.6 Hz, 1H), 7.31 – 7.48 (m, 20H), 7.53 – 7.71 (m, 12H), 7.94 – 8.12 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.3, 19.4, 22.4, 22.4, 22.6, 22.6, 25.0, 25.1, 26.8, 26.8, 26.8, 26.9, 26.9, 26.9, 36.6, 36.8, 36.8, 36.9, 63.2, 64.7, 74.7, 75.4, 76.6, 76.8, 78.0, 78.4, 81.5, 82.2, 82.6, 82.7, 85.5, 85.5, 97.1, 102.6, 127.8, 127.8, 127.8, 127.8, 127.8, 127.8, 127.8, 127.8, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.9, 129.1, 129.3, 129.4, 129.8, 129.8, 129.8, 129.8, 130.0, 130.1, 130.1, 130.1, 130.1, 130.1, 130.1, 130.3, 133.1, 133.1, 133.2, 133.2, 133.4, 133.5, 133.5, 133.6, 135.7, 135.7, 135.7, 135.7, 135.8, 135.8, 135.8, 135.8, 151.1, 151.1, 165.2, 165.5, 165.5, 165.6; HRMS (ESI-MS): m/z calcd for $[C_{44}H_{46}O_9SiNa]^+$: 769.2809; Found: 769.2805.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranosyl) α-D-arabinofuranoside (**8**): Yield: (92%); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -7.23; IR (cm^{-1}, $CHCl_3$): 3068, 2930, 2860, 1724, 1600, 1454, 1356, 1266, 1106, 1065, 1027, 968, 707; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.04 (s, 9H), 3.96 (dd, *J* = 11.2, 2.9 Hz, 2H), 4.01 (dd, *J* = 4.4, 1.3 Hz, 1H), 4.09 (ddt, *J* = 13.2, 4.9, 1.4 Hz, 1H), 4.23 (dd, *J* = 11.2, 4.6 Hz, 1H), 4.31 (ddt, *J* = 13.2, 4.9, 1.4 Hz, 1H), 4.54 (m, 2H), 5.22 (dd, *J* = 10.5, 1.3 Hz, 1H), 5.30 (s, 1H), 5.37 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.41 (s, 1H), 5.58 (d, *J* =1.1 Hz, 1H), 5.60 (d, *J* =1.1 Hz, 1H), 5.66 (t, *J* = 4.9 Hz, 2H), 5.96 (dddd, *J* = 16.4, 10.6, 5.9, 5.0 Hz, 1H), 7.28 – 7.40 (m, 11H), 7.40 – 7.52 (m, 5H), 7.57 (m, 2H), 7.69 – 7.75 (m, 4H), 7.92 – 7.97 (m, 2H), 7.97 – 8.03 (m, 4H), 8.05 – 8.11 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.4, 26.9, 26.9, 26.9, 63.5, 66.2, 67.9, 77.5, 77.5, 82.0, 82.0, 82.3, 83.3, 105.0, 106.1, 117.5, 127.8, 127.8, 127.8, 127.8, 128.3, 128.4, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 129.1, 129.4, 129.4, 129.4, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 130.0, 130.0, 130.1, 130.1, 133.2, 133.3, 133.4, 133.4, 133.5, 133.5, 133.9, 135.8, 135.8, 135.8, 135.8, 165.4, 165.5, 165.6, 165.8; HRMS (ESI-MS): m/z calcd for $[C_{57}H_{56}O_{13}SiNa]^+$: 999.3388; Found: 999.3389.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**9**): Yield: (89%); mp (^{0}C): 120.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -20.4; IR (cm^{-1}, $CHCl_3$): 3524, 3067, 2929, 1718, 1602, 1490, 1453, 1257, 1176, 1106, 1066, 1027, 969, 712; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.37 (s, 1H), 3.91 (dd, *J* = 11.2, 2.9 Hz, 2H,), 3.96 (dd, *J* = 13.1, 5.9 Hz, 1H), 4.02 (dd, *J* = 13.1, 5.9 Hz, 1H), 4.14 (dd, *J* = 11.2, 4.5 Hz, 1H), 4.21 (dd, *J* = 13.1, 4.8 Hz, 1H), 4.38 – 4.47 (m, 2H), 5.13 (d, *J* = 10.4

Hz, 1H), 5.22 (s, 1H), 5.28 (d, *J* =11.2 Hz, 1H), 5.35 (s, 1H), 5.37 (d, *J* = 4.5 Hz, 1H), 5.50 (s, 1H), 5.57 (d, *J* = 5.1 Hz, 1H), 5.59 (s, 1H), 5.86 (dddd, *J* = 16.6, 10.4, 5.8, 5.1 Hz, 1H), 7.21 (m, 2H), 7.37 (m, 8H), 7.50 (m, 2H), 7.87 (m, 2H), 7.97 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 62.2, 66.0, 67.7, 77.3, 77.7, 81.6, 81.8, 81.8, 83.7, 104.7, 105.7, 117.3, 128.2, 128.2, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.9, 129.0, 129.1, 129.1, 129.7, 129.7, 129.7, 129.7, 129.8, 129.8, 129.8, 129.8, 133.2, 133.3, 133.4, 133.4, 133.7, 165.0, 165.3, 165.7, 166.0; HRMS (ESI-MS): m/z calcd for $[C_{41}H_{38}O_{13}Na]^+$: 761.2210; Found: 761.2207.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranosyl)-α/β-D-arabinofuranoside [α:β (6:1)] (**10**): Yield: (79% over two steps); mp (^{0}C): 69.8; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -6.0; IR (cm^{-1}, $CHCl_3$): 3067, 2935, 2860, 1760, 1725, 1599, 1453, 1265, 1175, 1106, 1067, 1022, 965, 824, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.01 (s, 9H), 1.04 (s, 9H), 1.30 – 1.40 (m, 1H), 1.43 – 1.47 (m, 1H), 1.50 – 1.60 (m, 2H), 1.59 – 1.79 (m, 8H), 2.08 (m, 8H), 2.35 (s, 1H), 2.66 (s, 1H), 3.91 – 4.06 (m, 6H), 4.12 – 4.28 (m, 2H), 4.49 – 4.72 (m, 4H), 5.35 – 5.39 (m, 2H), 5.55 (m, 2H), 5.64 – 5.72 (m, 2H), 5.74 – 5.75 (m, 3H), 5.78 – 6.13 (m, 1H), 6.25 – 6.90 (m, 2H), 7.31 – 7.41 (m, 24H), 7.42 – 7.50 (m, 7H), 7.53 – 7.61 (m,5H), 7.69 – 7.65 (m, 8H), 7.94 – 8.04 (m, 12H), 8.09 – 8.19 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.4, 19.4, 22.6, 22.6, 22.7, 22.7, 24.9, 25.1, 26.9, 26.9, 26.9, 26.9, 26.9, 27.0, 36.6, 36.6, 36.8, 36.9, 63.4, 63.5, 65.9, 67.7, 74.9, 75.2, 75.5, 76.3, 76.9, 77.2, 77.3, 77.4, 78.3, 78.5, 80.9, 81.0, 82.2, 82.6, 82.7, 83.4, 83.6, 84.4, 96.9, 102.5, 106.0, 106.3, 127.8, 127.8, 127.8, 127.8, 127.8, 127.8, 127.8, 127.8, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.7, 128.7, 128.7, 128.7, 128.9, 129.0, 129.3, 129.3, 129.3, 129.3, 129.4, 129.6, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 130.0, 130.0, 130.0, 130.0, 130.0, 130.1, 130.1, 130.1, 130.1, 130.1, 130.1, 130.1, 130.3, 130.3, 133.2, 133.3, 133.3, 133.3, 133.4, 133.4, 133.4, 133.4, 133.6, 133.6, 133.7, 133.7, 135.8, 135.8, 135.8, 135.8, 135.8, 135.8, 135.8, 135.8, 135.8, 151.1, 151.1, 165.2, 165.4, 165.4, 165.6, 165.6, 165.7, 165.7, 165.7; HRMS (ESI-MS): m/z calcd for $[C_{63}H_{62}O_{15}SiNa]^+$: 1109.3756; Found: 1109.3752.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-

arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**11**): Yield: (94%); mp (^{0}C): 65.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +6.3; IR (cm^{-1}, $CHCl_3$): 3067, 2927, 2858, 1723, 1601, 1454, 1426, 1265, 1176, 1107, 966, 707; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.09 (s, 9H), 4.03 (m, 5H), 4.12 – 4.19 (m, 1H), 4.22 – 4.39 (m, 4H), 4.57 (m, 2H), 4.71 (m, 2H), 5.26 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.35 (s, 1H), 5.42 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.47 (s, 1H), 5.49 (s, 1H), 5.50 (s, 1H), 5.65 (d, *J* = 1.1 Hz, 1H), 5.66 (d, *J* = 1.1 Hz, 1H), 5.69 – 5.77 (m, 6H), 6.00 (dddd, *J* = 16.5, 10.6, 5.9, 5.1 Hz, 1H), 7.28 – 7.51 (m, 25H), 7.58 (m, 5H), 7.77 (m, 4H), 7.94 – 8.01 (m, 6H), 8.02 – 8.07 (m, 4H), 8.07 – 8.14 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.3, 26.8, 26.8, 26.8, 63.5, 65.9, 66.0, 66.0, 67.8, 77.3, 77.4, 77.4, 77.4, 81.6, 81.6, 82.0, 82.0, 82.2, 82.2, 82.2, 83.3, 104.9, 105.9, 106.0, 106.0, 117.4, 127.7, 127.7, 127.7, 127.7, 127.7, 127.7, 128.3, 128.3, 128.3, 128.3, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 129.1, 129.1, 129.2, 129.2, 129.2, 129.3, 129.3, 129.3, 129.7, 129.7, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 130.0, 130.0, 130.0, 133.1, 133.2, 133.2, 133.2, 133.3, 133.3, 133.4, 133.4, 133.4, 133.5, 133.8, 135.7, 135.7, 135.7, 135.7, 165.2, 165.2, 165.2, 165.4, 165.5, 165.6, 165.7, 165.7; HRMS (ESI-MS): m/z calcd for $[C_{95}H_{88}O_{25}SiNa]^+$: 1680.5315; Found: 1680.5317.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-α-D-arabinofuranosyl)-α-D- arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**12**): Yield: (91%); mp (^{0}C): 85.1; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +2.2; IR (cm^{-1}, $CHCl_3$): 3532, 3067, 2928, 2860, 1722, 1602, 1453, 1266, 1176, 1109, 1068, 1027, 966, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.41 (s, 1H), 3.98 (m, 5H), 4.12 (ddt, *J* = 13.1, 5.9, 1.5 Hz, 1H), 4.17 – 4.27 (m, 3H), 4.31 (ddt, *J* = 13.1, 4.9, 1.6 Hz, 1H), 4.50 (m, 2H), 4.65 (m, 2H), 5.23 (dd, *J* = 10.5, 1.4 Hz, 1H), 5.31 (s, 1H), 5.38 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.42 – 5.48 (m, 4H), 5.59 (d, *J* = 1.4 Hz, 1H), 5.61 – 5.72 (m, 6H), 5.97 (dddd, *J* = 16.4, 10.5, 5.9, 5.1 Hz, 1H), 7.22 – 7.33 (m, 6H), 7.38 – 7.49 (m, 13H), 7.50 – 7.63 (m, 5H), 7.86 – 7.99 (m, 6H), 8.00 – 8.13 (m, 10H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 62.3, 65.9, 65.9, 66.1, 67.8, 77.3, 77.3, 77.3, 77.7, 81.6, 81.6, 81.7, 81.9, 81.9, 82.0, 82.1, 83.7, 104.8, 105.8, 105.9, 105.9, 117.4, 128.3, 128.3, 128.3, 128.3, 128.3, 128.3, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 129.0, 129.0, 129.1, 129.1, 129.1, 129.1, 129.2, 129.3, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9,

129.9, 133.2, 133.2, 133.3, 133.4, 133.4, 133.4, 133.4, 133.5, 133.8, 165.1, 165.2, 165.2, 165.4, 165.7, 165.7, 165.7, 166.1; HRMS (ESI-MS): m/z calcd for $[C_{79}H_{70}O_{25}Na]^+$: 1441.4104; Found: 1441.4098.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**13**): Yield: (92%); mp (^{0}C): 109.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +12.2; IR (cm^{-1}, $CHCl_3$): 3067, 2933, 2859, 1723, 1602, 1453, 1356, 1266, 1176, 1108, 1069, 1027, 966, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.01 (s, 9H), 3.88 – 3.95 (m, 5H), 3.95 – 3.99 (m, 2H), 4.08 (ddt, *J* = 13.3, 6.0, 1.3 Hz, 1H), 4.19 (m, 5H), 4.28 (ddt, *J* = 13.2, 4.9, 1.5 Hz, 1H), 4.48 (m, 2H), 4.61 (m, 4H), 5.20 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.27 (s, 1H), 5.34 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.35 (s, 1H), 5.39 (s, 1H), 5.39 (s, 1H), 5.40 (s, 1H), 5.41 (s, 1H), 5.55 – 5.58 (m, 2H), 5.65 (m, 10H), 5.93 (dddd, *J* = 16.5, 10.6, 5.9, 5.1 Hz, 1H), 7.18 – 7.46 (m, 36H), 7.46 – 7.61 (m, 6H), 7.64 – 7.75 (m, 4H), 7.82 – 7.93 (m, 10H), 7.95 – 7.98 (m, 4H), 8.00 – 8.06 (m, 10H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.4, 26.8, 26.8, 26.8, 63.4, 65.8, 65.9, 65.9, 65.9, 66.0, 67.8, 77.3, 77.3, 77.3, 77.3, 77.4, 77.4, 81.5, 81.6, 81.6, 81.6, 82.0, 82.0, 82.1, 82.2, 82.2, 82.2, 82.2, 83.2, 104.9, 105.8, 105.9, 105.9, 106.0, 106.0, 117.5, 127.7, 127.7, 127.7, 127.8, 127.8, 127.8, 128.3, 128.3, 128.3, 128.3, 128.3, 128.3, 128.3, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 129.1, 129.1, 129.1, 129.1, 129.1, 129.1, 129.2, 129.2, 129.2, 129.3, 129.3, 129.3, 129.7, 129.7, 129.7, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 130.0, 130.0, 130.0, 130.0, 133.1, 133.2, 133.2, 133.2, 133.2, 133.3, 133.3, 133.4, 133.4, 133.4, 133.5, 133.5, 133.5, 133.5, 133.8, 135.7, 135.7, 135.7, 135.7, 165.2, 165.2, 165.2, 165.2, 165.3, 165.5, 165.6, 165.6, 165.7, 165.7, 165.7, 165.8; HRMS (ESI-MS): m/z calcd for $[C_{133}H_{120}O_{37}SiNa]^+$: 2360.7209; Found: 2360.7206.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-

arabinofuranosyl)-α/β-D-arabinofuranoside [α:β (4:1)] (**14**): Yield: (79%); mp (^{0}C): 114.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +10.8; IR (cm^{-1}, $CHCl_3$): 3065, 2936, 2858, 1760, 1725, 1601, 1453, 1269, 1176, 1110, 1069, 1028, 910, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.10 (s, 9H),1.26 – 1.43 (m, 2H), 1.52 – 1.78 (m, 10H), 1.99 (m, 4H), 2.27 (m, 4H), 2.51 (s, 1H), 2.74 (s, 1H), 4.05 (m, 14H), 4.30 (m, 10H), 4.46 – 4.82 (m, 12H), 5.50 (m, 10H), 5.64 – 5.80 (m, 21H), 5.80 – 6.70 (m, 5H), 7.26 – 7.41 (m, 34H), 7.47 (m, 37H), 7.52 – 7.65 (m, 13H), 7.78 (m, 8H), 7.97 (m, 19H), 8.10 (m, 29H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.4, 19.4, 22.6, 22.6, 22.6, 22.6, 24.8, 25.0, 26.8, 26.8, 26.9, 26.9, 26.9, 26.9, 36.6, 36.6, 36.8, 36.9, 63.5, 63.5, 65.8, 65.8, 65.9, 65.9, 65.9, 65.9, 65.9, 65.9, 66.0, 66.0, 74.5, 75.3, 75.6, 76.2, 76.8, 77.2, 77.2, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.4, 77.4, 77.4, 78.3, 78.4, 80.7, 81.0, 81.6, 81.6, 81.6, 81.6, 81.9, 82.2, 82.2, 82.2, 82.2, 82.2, 82.2, 82.3, 82.3, 82.6, 82.6, 83.3, 83.3, 83.3, 83.3, 84.4, 84.4, 96.6, 102.4, 105.7, 106.0, 106.0, 106.0, 106.0, 106.0, 106.0, 106.1, 106.1, 106.1, 127.7 – 127.8 (12C), 128.3 (16C), 128.4 (6C), 128.5 (4C), 128.6 (16C), 128.7 (6C), 129.1 (10C), 129.2 (6C), 129.3 (8C), 129.7 (4C), 129.8 (20C), 129.9 (16C), 130.0 (6C), 130.1, 130.2, 133.1 (2C), 133.2 (8C), 133.3 (3C), 133.4 (7C), 133.5 (3C), 133.6 (2C), 133.7 (3C), 135.7, 135.7, 135.7, 135.7, 135.7, 135.7, 135.7, 135.7, 151.0, 151.1, 165.1 (3C), 165.2 (9C), 165.5 (3C), 165.6 (4C), 165.7 (4C), 165.8; HRMS (ESI-MS): m/z calcd for $[C_{139}H_{126}O_{39}SiNa]^+$: 2470.7577; Found: 2470.7568.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**15**): Yield: (86%); mp (^{0}C): 123.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +13.3; IR (cm^{-1}, $CHCl_3$): 3067, 2931, 2857, 1721, 1602, 1490, 1453, 1259, 1176, 1106, 1069, 1026, 965, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.60 (s, 1H), 3.93 – 4.08 (m, 7H), 4.14 (dd, *J* = 13.2, 5.9 Hz, 1H), 4.18 – 4.40 (m, 6H), 4.52 (q, *J* = 4.5 Hz, 2H), 4.65 – 4.70 (m, 4H), 5.24 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.34 (s, 1H), 5.40 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.46 – 5.48 (m, 6H), 5.63 (d, *J* = 1.1 Hz, 1H), 5.65 – 5.77 (m, 10H), 5.98 (dddd, *J* = 16.6, 10.5, 5.9, 5.1 Hz, 1H), 7.28 (m, 10H), 7.44 (m, 20H), 7.50 – 7.57 (m, 4H), 7.59 (m, 2H), 7.84 – 8.02 (m, 10H), 8.08 (m, 14H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 62.3, 65.9, 65.9, 65.9, 65.9, 66.1, 67.8, 77.2, 77.3, 77.3, 77.3, 77.3, 77.7, 81.6, 81.6, 81.6, 81.6, 81.7, 82.0, 82.0, 82.1, 82.2, 82.2, 82.2, 83.8, 104.8, 105.8, 105.9, 105.9, 105.9, 105.9, 117.4, 128.3, 128.3, 128.3, 128.3, 128.3,

128.3, 128.3, 128.3, 128.3, 128.3, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 129.0, 129.0, 129.1, 129.1, 129.1, 129.1, 129.1, 129.1, 129.1, 129.1, 129.2, 129.3, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 129.9, 133.2, 133.2, 133.2, 133.2, 133.3, 133.4, 133.4, 133.4, 133.5, 133.5, 133.5, 133.5, 133.8, 165.1, 165.1, 165.2, 165.2, 165.2, 165.4, 165.6, 165.7, 165.7, 165.7, 165.7, 166.0; HRMS (ESI-MS): m/z calcd for $[C_{117}H_{102}O_{37}Na]^+$: 2122.6031; Found: 2122.6033.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**16**): Yield: (96%); mp (^{0}C): 125.6; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +15.9; IR (cm^{-1}, $CHCl_3$): 3066, 2926, 2860, 1723, 1602, 1453, 1267, 1176, 1109, 1070, 1027, 966, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.04 (s, 9H), 3.92 – 4.01 (m, 13H), 4.05 – 4.34 (m, 14H), 4.47 – 4.66 (m, 12H), 5.22 (d, *J* = 10.5 Hz, 1H), 5.30 (s, 1H), 5.33 – 5.48 (m, 12H), 5.56 – 5.62 (m, 2H), 5.65 – 5.70 (m, 21H), 5.95 (dddd, *J* = 16.5, 10.4, 5.9, 4.9 Hz, 1H), 7.21 – 7.29 (m, 21H), 7.32 – 7.46 (m, 45H), 7.45 – 7.61 (m, 12H), 7.70 – 7.73 (m, 4H), 7.87 – 7.94 (m, 22H), 7.99 – 8.07 (m, 26H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.4, 26.9, 26.9, 26.9, 63.5, 65.9, 65.9, 65.9, 65.9, 65.9, 65.9, 65.9, 65.9, 66.0, 66.0, 66.0, 67.9, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.4, 77.4, 77.4, 77.5, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.7, 81.7, 81.7, 82.0, 82.1, 82.2, 82.2, 82.2, 82.2, 82.2, 82.2, 82.2, 82.2, 82.2, 82.2, 82.3, 83.3, 104.9, 105.9, 106.0, 106.0, 106.0, 106.0, 106.0, 106.0, 106.0, 106.0, 106.1, 106.1, 117.5, 127.8, 127.8, 127.8, 127.8, 128.4 (20C), 128.5 (4C), 128.6 (24C), 129.1 (10C), 129.2 (12C), 129.4 (2C), 129.8 (2C), 129.9 (32C), 130.0 (14C), 130.1 (2C), 133.2 – 133.3 (12C), 133.4 – 133.5 (14C), 133.9, 135.8, 135.8, 135.8, 135.8, 165.2 (9C), 165.3 (2C), 165.5, 165.6, 165.7(10C), 165.8; MALDI-TOF: m/z calcd for $[C_{247}H_{216}O_{73}SiNa]^+$: 4402.2924; Found: 4402.4847.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**17**): Yield: (85%); mp (^{0}C): 137.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +18.1; IR (cm^{-1}, $CHCl_3$): 3066, 2927, 2856, 1722, 1602, 1453, 1176, 1108, 1070, 1027, 965, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.44 (s, 1H), 3.89 – 4.07 (m, 13H), 4.10 – 4.27 (m, 12H), 4.32 (dd, *J* = 13.2, 4.9 Hz, 1H), 4.51 (m, 2H), 4.56 – 4.70 (m, 10H), 5.24 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.32 (s, 1H), 5.39 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.43 – 5.47 (m, 12H), 5.61 (d, *J* = 1.2 Hz, 1H), 5.66 – 5.73 (m, 22H), 5.97 (dddd, *J* = 16.5, 10.6, 5.8, 5.3 Hz, 1H), 7.24 – 7.31 (m, 22H), 7.40 – 7.48 (m, 37H), 7.49 – 7.63 (m, 13H), 7.89 – 7.96 (m, 22H), 8.02 – 8.11 (m, 26H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 62.3, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.9, 66.1, 67.8, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.3, 77.3, 77.3, 77.7, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.6, 81.6, 81.6, 81.7, 81.9, 82.0, 82.0, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 83.7, 104.8, 105.8, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 117.4, 128.3 (24C), 128.5 (24C), 129.0 (2C), 129.1 (20C), 129.2, 129.3, 129.8 (40C), 129.9 (8C), 133.1 (8C), 133.2 (2C), 133.3, 133.4 (12C), 133.5, 133.8, 165.1 (10C), 165.2, 165.4, 165.6 (10C), 165.7, 166.1; MALDI-TOF: m/z calcd for $[C_{231}H_{198}O_{73}Na]^+$: 4164.1746; Found: 4164.4248.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-

arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (18): Yield: (91%); mp (^{0}C): 130.8; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +23.6; IR (cm^{-1}, $CHCl_3$): 3067, 2932, 2858, 1722, 1602, 1490, 1453, 1176, 1069, 1026, 965, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.08 (s, 9H), 4.00 (m, 19H), 4.11 – 4.42 (m, 20H), 4.49 – 4.78 (m, 18H), 5.26 (d, *J* = 10.5 Hz, 1H), 5.35 (s, 1H), 5.47 (m, 18H), 5.65 (m, 2H), 5.72 (m, 33H), 6.00 (dddd, *J* = 16.5, 10.6, 5.9, 5.1 Hz, 1H), 7.20 – 7.34 (m, 34H), 7.35 – 7.50 (m, 62H), 7.55 (m, 18H), 7.76 (m, 4H), 7.95 (m, 33H), 8.06 (m, 39H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.3, 26.8, 26.8, 26.8, 63.5, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.9, 65.9, 65.9, 65.9, 65.9, 65.9, 66.0, 67.8, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.3, 77.3, 77.4, 77.4, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 82.0, 82.0, 82.1, 83.3, 104.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 106.0, 106.0, 106.0, 106.0, 106.0, 106.0, 106.0, 117.4, 127.7 (6C), 128.3 (30C), 128.4 (6C), 128.5 (36C), 129.1 (14C), 129.2 (18C), 129.3 (4C), 129.7, 129.7, 129.8 (30C), 129.9 (38C), 130.0, 130.0, 133.1 (2C), 133.2 (16C), 133.3 (2C), 133.4 (14C), 133.5 (4C), 133.8, 135.7, 135.7, 135.7, 135.7, 165.2 (16C), 165.4, 165.4, 165.5, 165.5, 165.6 (12C), 165.7, 165.7, 165.7, 165.7; MALDI-TOF: m/z calcd for $[C_{361}H_{312}O_{109}SiNa]^+$: 6444.8672; Found: 6446.9458.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-

arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**19**): Yield: (93%); mp (^{0}C): 155.8; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +25.2; IR (cm^{-1}, $CHCl_3$): 3066, 2926, 1723, 1602, 1453, 1265, 1176, 1108, 1070, 1028, 966, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.09 (s, 9H), 3.96 – 4.01 (m, 18H), 4.02 – 4.06 (m, 2H), 4.16 (dd, *J* = 13.2, 6.0 Hz, 1H), 4.20 – 4.29(m, 18H), 4.35 (dd, *J* = 13.2, 4.7 Hz, 1H), 4.51 – 4.60 (m, 2H), 4.65 – 4.75 (m, 17H), 5.28 (d, *J* = 10.4 Hz, 1H), 5.35 (s, 1H), 5.41 – 5.48 (m, 19H), 5.64 (m, 2H), 5.70 – 5.72 (m, 36H), 6.01 (dddd, *J* = 16.5, 10.7, 5.8, 5.2 Hz, 1H), 7.24 – 7.35 (m, 36H), 7.36 – 7.51 (m, 66H), 7.54 – 7.61 (m, 18H), 7.77 (m, 4H), 7.92 – 7.99 (m, 36H), 8.04 – 8.13 (m, 40H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.3, 26.8, 26.8, 26.8, 63.4, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.9, 65.9, 65.9, 65.9, 65.9, 65.9, 66.0, 67.8, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.3, 77.3, 77.4, 77.4, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.5, 81.6, 81.6, 81.6, 81.6, 81.9, 81.9, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 83.2, 104.8, 105.8, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 106.0, 106.0, 117.4, 127.7 (6C), 128.3 (34C), 128.4 (4C), 128.5 (38C), 129.1 (35C), 129.3 (3C), 129.7 (2C), 129.8 (70C), 129.9 (2C), 130.0 (2C), 133.0, 133.1 (16C), 133.2 (2C), 133.3 (4C), 133.4 (17C), 133.8, 135.7, 135.7, 135.7, 135.7, 165.1 (16C), 165.2, 165.2, 165.4, 165.5, 165.6 (17C), 165.7; MALDI-TOF: m/z calcd for $[C_{380}H_{328}O_{115}SiNa]^+$: 6784.9619; Found: 6784.8623.

Allyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)- α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)- α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**20**): Yield: (81%); mp (^{0}C): 135.3; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +22.4; IR (cm^{-1}, $CHCl_3$): 3065, 2931, 2861, 1722, 1602, 1490, 1453, 1176, 1102, 1069, 1027, 965, 709; ^{1}H NMR (400.31

MHz, $CDCl_3$): δ 2.47 (s, 1H), 3.90 – 4.95 (m, 20H), 4.12 (dd, J = 6.5, 1.7 Hz, 1), 4.15 (dd, J = 6.5, 1.7 Hz, 1H), 4.20 – 4.28 (m, 16H), 4.33 (dd, J = 13.2, 4.9 Hz, 1H), 4.52 (q, J = 4.7 Hz, 2H), 4.61 – 4.69 (m, 16H), 5.25 (dd, J = 10.5, 1.5 Hz, 1H), 5.33 (s, 1H), 5.36 – 5.49 (m, 19H), 5.62 (d, J = 1.2 Hz, 1H), 5.67 – 5.72 (m, 33H), 5.98 (dddd, J = 16.6, 10.5, 5.9, 5.0 Hz, 1H), 7.24 – 7.30 (m, 35H), 7.40 – 7.48 (m, 55H), 7.49 – 7.63 (m, 18H), 7.90 – 7.97 (m, 34H), 8.05 – 8.10 (m, 38H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 62.3, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.8, 65.9, 66.1, 67.8, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.2, 77.3, 77.3, 77.3, 77.7, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.6, 81.7, 82.0, 82.0, 82.0, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 82.1, 83.7, 104.8, 105.8, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 105.9, 117.4, 128.3 (36C), 128.5 (36C), 129.0, 129.0, 129.0, 129.0, 129.1(28C), 129.2, 129.2, 129.3, 129.3, 129.8 (32C), 129.9 (40C), 133.2 (16C), 133.3, 133.4 (12C), 133.5 (6C), 133.6, 133.8, 165.1 (12C), 165.2 (5C), 165.4, 165.6 (12C), 165.7 (5C), 166.1; MALDI-TOF: m/z calcd for $[C_{345}H_{294}O_{109}Na]^+$: 6206.7494; Found: 6206.1763.

Allyl 5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(5-*O*-(α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**21**): Yield: (83%); mp (^0C): 254.3; $[\alpha]^{25}_D$ (H_2O, *c* 1.0): +113.2; IR (cm^{-1}, $CHCl_3$): 3355, 1696, 1642, 1425, 1368, 1237, 1095; ^1H NMR (600.40 MHz, D_2O, Internal standard CH_3COCH_3): δ 2.22 (CH_3COCH_3), 3.71 (dd, *J* = 12.3, 5.8 Hz, 1H), 3.78 – 3.82 (m, 18H), 3.84 – 3.90 (m, 19H), 3.95 (dd, *J* = 6.0, 3.3 Hz, 1H), 4.00 – 4.01 (m, 18H), 4.08 – 4.10 (m, 3H), 4.11 – 4.13 (m, 18H), 4.18 – 4.23 (m, 18H), 4.23 – 4.27 (m, 1H), 5.07 – 5.09 (m, 19H), 5.28 (dt, *J* = 10.5, 1.4 Hz, 1H), 5.36 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.97 (dddd, *J* = 16.5, 10.8, 5.7, 5.3 Hz, 1H); ^{13}C NMR (100.67 MHz, D_2O, Internal standard CH_3COCH_3): δ 30.8 (CH_3), 61.7, 67.3, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4, 67.4,

67.4, 67.4, 69.4, 77.0, 77.0, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 77.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.3, 81.4, 81.4, 82.6, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 82.9, 84.5, 107.1, 107.9, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 108.0, 119.1, 133.9, 215.9 (CO); MALDI-TOF: m/z calcd for $[C_{98}H_{158}O_{77}Na]^+$: 2590.8379; Found: 2590.1692.

3,5-Di-*O*-tert-Butyldiphenylsilyl β-D-arabinofuranoside propyn-3-yl-1,2-orthobenzoate (**25**): Yield: (90%); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +70; IR (cm^{-1}, $CHCl_3$): 3016, 2957, 2860, 1738, 1515, 1367, 1218, 1109, 983, 702; ^1H NMR (400.31 MHz, $CDCl_3$): δ 0.84 (s, 9H), 1.09 (s, 9H), 2.27 (t, *J* = 2.4 Hz, 1H), 3.09 – 3.25 (m, 1H), 3.27 – 3.43 (m, 1H), 3.67 – 3.88 (m, 2H), 4.26 – 4.39 (m, 1H), 4.42(s, 1H), 4.83 (d, *J* = 4.1 Hz, 1H), 6.26 (d, *J* = 3.8 Hz, 1H), 7.05 – 7.14 (m, 2H), 7.18 – 7.26 (m, 4H), 7.28 – 7.45 (m, 15H), 7.59 – 7.67 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.0, 19.2, 26.7, 26.7, 26.7, 26.9, 26.9, 26.9, 51.7, 63.7, 73.5, 77.2, 79.5, 87.1, 90.2, 106.7, 122.1, 126.3, 127.5, 127.5, 127.5, 127.5, 127.7, 127.8, 127.8, 127.9, 127.9, 128.1, 128.1, 128.4, 129.3, 129.4, 129.5, 129.6, 130.0, 130.0, 132.9, 132.9, 133.1, 133.3, 133.4, 134.6, 135.4, 135.5, 135.6, 135.7, 135.7; HRMS (ESI-MS): m/z calcd for $[C_{47}H_{52}O_6Si_2Na]^+$: 791.3200; Found: 791.3198.

Pent-4-enyl 2-*O*-benzoyl-α-D-arabinofuranoside (**26**): Yield: (83% over two steps); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -12.6; IR (cm^{-1}, $CHCl_3$): 3446, 2931, 1723, 1515, 1450, 1368, 1268, 1109, 982, 713; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.73 (p, *J* = 6.8 Hz, 2H), 2.01 – 2.22 (m, 3H), 3.43 (s, 1H), 3.50 (dt, *J* = 9.5, 6.5 Hz, 1H), 3.80 (dt, *J* = 9.6, 6.5 Hz, 2H), 3.93 (d, *J* = 12.0 Hz, 1H), 4.19 (t, *J* = 2.9 Hz, 2H), 4.96 – 5.01 (m, 1H), 5.01 – 5.08 (m, 1H), 5.09 (dd, *J* = 2.4, 0.9 Hz, 1H), 5.24 (s, 1H), 5.82 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 7.39 – 7.49 (m, 2H), 7.53 – 7.64 (m, 1H), 7.94 – 8.10 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 28.6, 30.2, 62.0, 67.3, 76.5, 84.1, 86.1, 105.4, 115.1, 128.5, 128.5, 129.1, 129.8, 129.8, 133.6, 137.9, 166.7; HRMS (ESI-MS): m/z calcd for $[C_{17}H_{22}O_6Na]^+$: 345.1314; Found: 345.1314.

3-*O*-benzoyl-5-*O*-*tert*-Butyldiphenylsilyl-β-D-arabinofuranoside propyn-3-yl-1,2-orthobenzoate (**27**): Yield: (85% over two steps); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -15.9; IR (cm^{-1}, $CHCl_3$): 3011, 2960, 1732, 1515, 1454, 1367, 1266, 1104, 986, 703; ^1H NMR

(400.31 MHz, $CDCl_3$): δ 0.96 (s, 9H), 2.35 (t, *J* = 2.4 Hz, 1H), 3.60 (dd, *J* = 7.5, 4.0 Hz, 2H), 3.92 (dd, *J* = 2.4, 1.2 Hz, 2H), 4.43 (d, *J* = 6.6 Hz, 1H), 5.07 (d, *J* = 4.3 Hz, 1H), 5.64 (s, 1H), 6.31 (d, *J* = 4.3 Hz, 1H), 7.22 – 7.31 (m, 6H), 7.32 – 7.40 (m, 3H), 7.43 – 7.56 (m, 8H), 7.57 – 7.64 (m, 1H), 8.00 – 8.11 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.1, 26.8, 26.8, 26.8, 51.9, 63.5, 73.7, 76.7, 77.6, 79.4, 85.1, 87.3, 106.6, 122.5, 126.4, 127.6, 127.6, 127.7, 127.7, 127.7, 128.3, 128.3, 128.4, 128.5, 128.5, 129.4, 129.6, 129.7, 129.7, 129.9, 130.0, 133.2, 133.3, 133.5, 134.4, 135.4, 135.5, 165.2; HRMS (ESI-MS): m/z calcd for$[C_{38}H_{38}O_7SiNa]^+$: 657.2284; Found: 657.2281.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl α-D-mannopyranoside (α-anomer of **30**): mp (^{0}C): 74.9; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): - 28.9; IR (cm^{-1}, $CHCl_3$): 3291, 2941, 1730, 1516, 1451, 1237, 1161, 1102, 908, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.32 – 1.47 (m, 1H), 1.56 – 1.82 (m, 5H), 1.86 – 2.05 (m, 2H), 2.20 – 2.36 (m, 2H), 2.68 (s, 1H), 4.51 (dd, *J* = 12.3, 4.3 Hz, 1H), 4.62 (ddd, *J* = 10.1, 4.3, 2.4 Hz, 1H), 4.76 (dd, *J* = 12.3, 2.5 Hz, 1H), 5.86 (dd, *J* = 3.4, 2.0 Hz, 1H), 6.00 (dd, *J* = 10.2, 3.3 Hz, 1H), 6.20 (t, *J* = 10.1 Hz, 1H), 6.30 (d, *J* = 2.0 Hz, 1H), 7.25 – 7.34 (m, 2H), 7.36 – 7.48 (m, 7H), 7.50 – 7.68 (m, 3H), 7.84 – 7.90 (m, 2H), 7.96 – 8.02 (m, 2H), 8.07 – 8.11 (m, 2H), 8.11 – 8.17 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.7, 22.7, 24.9, 36.8, 36.8, 62.5, 66.3, 69.2, 69.7, 70.9, 77.4, 79.2, 82.2, 93.7, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 128.7, 128.7, 128.7, 128.8, 128.9, 129.0, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9, 133.1, 133.3, 133.5, 133.7, 150.1, 165.1, 165.3, 165.5, 166.0; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2260.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzoyl β-D-mannopyranoside (β-anomer of **30**): mp (^{0}C): 75.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): - 65.4; IR (cm^{-1}, $CHCl_3$): 3292, 2940, 1730, 1603, 1510, 1452, 1265, 1176, 1099, 912, 712; ^{1}H NMR (400.31 MHz, $CDCl_3$) :δ 1.26 – 1.35 (m, 1H), 1.49 – 1.71 (m, 5H), 1.85 (dq, *J* = 13.2, 4.4 Hz, 2H), 2.12 – 2.22 (m, 2H), 2.65 (s, 1H), 4.27 – 4.43 (m, 1H), 4.60 (dd, *J* = 12.3, 4.5 Hz, 1H), 4.79 (dd, *J* = 12.2, 2.9 Hz, 1H), 5.76 (ddd, *J* = 9.9, 3.8, 2.0 Hz, 1H), 6.07 – 6.18 (m, 3H), 7.27 – 7.34 (m, 2H), 7.35 – 7.56 (m, 8H), 7.57 – 7.67 (m, 2H), 7.82 – 7.92 (m, 2H), 7.94 – 8.00 (m, 2H), 8.09 – 8.13 (m, 2H), 8.13 – 8.19 (m, 2H); ^{13}C NMR (101.67 MHz, $CDCl_3$): δ 22.5, 22.5, 24.9, 36.6, 36.7, 62.7, 66.4, 68.7, 71.4, 73.3, 75.5, 79.1, 82.3, 93.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5,

128.7, 128.8, 129.3, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 130.1, 130.1, 133.1, 133.4, 133.4, 133.6, 150.7, 165.2, 165.4, 165.4, 166.1; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{38}O_{12}Na]^+$: 769.2261; Found: 769.2261.

Pent-4-enyl 2-*O*-benzoyl-3-*O*-[2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl α-D-arabinofuranosyl]-5-*O*-[2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl α-D-arabinofuranosyl] α-D-arabinofuranoside (**31**): Yield: (86%); mp (^{0}C): 60.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): 6.4; IR (cm^{-1}, $CHCl_3$): 3012, 2933, 2860, 1726, 1649, 1516, 1454, 1366, 1262, 1105, 967, 793; ^{1}H NMR (399.78 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.10 (s, 9H), 1.79 (td, *J* = 6.3, 2.1 Hz, 2H), 2.22 (d, *J* = 7.3 Hz, 2H), 3.54 – 3.63 (m, 1H), 3.80 – 3.90 (m, 1H), 3.94 – 4.11 (m, 5H), 4.18 (dd, *J* = 11.4, 5.1 Hz, 1H), 4.45 – 4.61 (m, 4H), 5.01 (dt, *J* = 10.4, 1.7 Hz, 1H), 5.09 (dt, *J* = 17.1, 1.7 Hz, 1H), 5.29 (s, 1H), 5.42 (s, 1H), 5.52 (s, 1H), 5.63 (s, 1H), 5.68 (s, 2H), 5.73 (dd, *J* = 9.7, 4.7 Hz, 2H), 5.86 (ddt, *J* = 16.9, 10.5, 6.7 Hz, 1H), 7.27 – 7.65 (m, 27H), 7.70 – 7.81 (m, 8H), 7.99 – 8.18 (m, 10H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.3, 19.4, 26.8 (3C), 26.9 (3C), 28.7, 30.3, 63.4, 63.6, 66.3, 66.7, 77.3, 77.4, 80.9, 81.7, 82.1, 82.2, 82.7, 83.5, 84.0, 105.4, 106.0, 106.2, 115.0, 127.7-128.5 (20C), 129.3, 129.3, 129.4, 129.4, 129.5, 129.7-130.1 (20C), 133.1, 133.2, 133.2, 133.3, 133.3, 133.4, 135.6, 135.7, 135.7, 138.1, 165.2 (2C), 165.5, 165.5, 165.6; HRMS (ESI-MS): m/z calcd for$[C_{87}H_{90}O_{18}Si_2Na]^+$: 1501.5563; Found: 1501.5562.

Pent-4-enyl 2-*O*-benzoyl-3,5-di-*O*-[2,3-di-*O*-benzoyl α-D-arabinofuranosyl]-α-D-arabinofuranoside (**32**): Yield: (95%); mp (^{0}C): 62.6; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -1.7; IR (cm^{-1}, $CHCl_3$): 3016, 2934, 2860, 1726, 1648, 1516, 1453, 1366, 1265, 1109, 970, 714; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.64 (p, *J* = 7.1 Hz, 2H), 2.06 (p, *J* = 8.7, 7.9 Hz, 2H), 2.63 (s, 1H), 2.63 (s, 1H), 3.43 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.61 – 3.73 (m, 1H), 3.75 – 3.91 (m, 4H), 3.94 (dd, *J* = 11.6, 3.6 Hz, 2H), 4.20 – 4.27 (m, 2H), 4.27 – 4.37 (m, 1H), 4.45 (d, *J* = 6.0 Hz, 1H), 4.87 (d, *J* = 10.2 Hz, 1H), 4.94 (d, *J* = 17.2 Hz, 1H), 5.10 (s, 1H), 5.18 (d, *J* = 4.6 Hz, 1H), 5.19 – 5.26 (m, 3H), 5.31 (s, 1H), 5.49 (s, 1H), 5.54 (s, 1H), 5.72 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 7.05 – 7.20 (m, 2H), 7.34 (dq, *J* = 21.0, 7.1, 6.6 Hz, 9H), 7.40 – 7.48 (m, 2H), 7.48 – 7.55 (m, 2H), 7.80 – 7.88 (m, 2H), 7.88 – 8.02 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 28.7, 30.2, 62.7, 62.7, 65.1, 66.8, 77.8, 78.2, 80.3, 81.0, 81.3, 81.5, 82.7, 84.1, 84.5, 105.2, 105.2, 105.8, 115.0, 128.4-128.5 (10C), 128.9, 129.1, 129.1, 129.1, 129.4, 129.7-129.9 (10C), 133.4, 133.5, 133.5, 133.6,

133.6, 138.1, 165.0, 165.1, 165.6, 166.0, 166.2; HRMS (ESI-MS): m/z calcd for $[C_{55}H_{54}O_{18}Na]^+$: 1025.3208; Found: 1025.3204.

2-*O*-benzoyl-3,5-di-*O*-[2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl α-D-arabinofuranosyl]-α-D-arabinofuranose [α:β (1:1)] (**33**): Yield: (76%); mp (^{0}C): 74.8; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -7.4; IR (cm^{-1}, $CHCl_3$): 3067, 2941, 2862, 1726, 1596, 1440, 1453, 1269, 1109, 970, 708; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.98 (s, 9H), 1.00 (s, 9H), 1.00 (s, 9H), 1.03 (s, 9H), 3.30 (s, 1H), 3.81 (m, 2H), 3.88 – 4.02 (m, 8H), 4.03 – 4.24 (m, 4H), 4.35 – 4.44 (m, 3H), 4.44 – 4.91 (m, 4H), 5.23 – 5.39 (m, 3H), 5.38 – 5.53 (m, 6H), 5.54 – 5.75 (m, 7H), 7.25 – 7.37 (m, 40H), 7.40 – 7.57 (m, 15H), 7.62 – 7.74 (m, 15H), 7.85 – 7.89 (m, 2H), 7.90 – 7.98 (m, 10H), 7.98 – 8.07 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.2, 19.2, 19.3, 19.3, 26.8 (6C), 26.8 (3C), 26.8 (3C), 63.4 (3C), 63.5, 66.7 (2C), 76.9, 77.0, 77.1, 77.2, 78.6, 79.2, 79.6, 80.3, 82.0, 82.2, 82.4, 82.4, 82.5, 82.7, 83.2, 83.4, 83.8, 83.9, 95.0, 101.2, 105.3, 106.1, 106.2, 106.8, 127.6 – 127.7 (16C), 128.3 – 128.4 (20C), 128.5, 128.9, 129.1, 129.1, 129.1, 129.2, 129.3, 129.4, 129.4, 129.4, 129.7 – 130.0 (36C), 133.1 – 133.5 (18C), 135.6 – 135.8 (8C), 165.2(2C), 165.5 (4C), 165.6, 165.6, 165.9, 166.0; HRMS (ESI-MS): m/z calcd for$[C_{82}H_{82}O_{18}Si_2Na]^+$: 1433.4937; Found: 1433.4955.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,5-di-*O*-[2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldi phenylsilyl α-D-arabinofuranosyl]-α-D-arabinofuranose [α:β (4.6:1)] (**34**)**:** Yield: (93%); mp (^{0}C): 68.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +6.6; IR (cm^{-1}, $CHCl_3$): 3055, 2929, 2858, 1725, 1600, 1454, 1262, 1105, 1026, 910, 706; ^{1}H NMR (400.31 MHz, $CDCl_3$) δ 0.96 (s, 9H), 0.99 (s, 9H), 1.00 (s, 9H), 1.00 (s, 9H), 1.29 – 1.69 (m, 14H), 1.81 – 1.92 (m, 3H), 2.16 – 2.27 (m, 3H), 2.62 (s, 1H), 2.63 (s, 1H), 3.85 – 3.97 (m, 10H), 4.04 – 4.40 (m, 6H), 4.42 – 4.83 (m, 4H), 5.27 – 5.48 (m, 5H), 5.53 – 5.71 (m, 9H), 6.34 (s, 1H), 6.47 (d, *J* = 4.4 Hz, 1H), 7.23 – 7.44 (m, 40H), 7.44 – 7.52 (m, 7H), 7.52 – 7.62 (m, 7H), 7.65 – 7.77 (m, 16H), 7.82 – 8.14 (m, 20H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 19.2, 19.2, 19.3, 19.3, 22.5, 22.5, 22.6, 22.6, 24.8, 25.0, 26.8 (6C), 26.8 (6C), 36.5, 36.6, 36.7, 36.9, 63.2, 63.3, 63.3, 63.5, 65.8, 67.4, 74.9, 75.3, 76.9, 77.0, 77.0, 77.2, 77.5, 77.7, 80.3, 80.4, 82.0, 82.0, 82.1, 82.1, 82.2, 82.4, 82.5, 82.7, 83.5, 83.6, 83.9, 83.9, 84.0, 84.1, 96.7, 102.9, 105.5, 105.7, 106.1, 106.3, 127.6 – 127.7 (16C), 128.4 – 128.4 (28C), 128.9, 129.0, 129.1, 129.2, 129.3, 129.3, 129.3, 129.4, 129.5, 129.5, 129.6 – 129.7 (16C), 129.8 – 130.0 (20C), 133.1 – 133.4 (10C),

135.5, – 135.6 (8C), 150.9, 151.2, 165.2, 165.2, 165.2, 165.3, 165.3, 165.3, 165.4, 165.5, 165.5, 165.6; HRMS (ESI-MS): m/z calcd for$[C_{91}H_{92}O_{20}Si_2Na]^+$: 1583.5618; Found: 1583.5627.

Pent-4-enyl 2-*O*-benzoyl-3,5-di-*O*-[2,3-di-*O*-benzoyl-5-*O*-(2-*O*-benzoyl-3,5-di-O-(2,3-di-*O*-benzoyl-5-*O*-tert-butyl diphenylsilyl α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (**35**): Yield: (93%); mp (^{0}C): 84.8; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +23.6; IR (cm^{-1}, $CHCl_3$): 3066, 2930, 2860, 1724, 1600, 1509, 1454, 1262, 1106, 1026, 967, 706; ^{1}H NMR (500.20 MHz, $CDCl_3$) δ 0.90 (s, 18H), 0.96 (s, 18H), 1.58 – 1.67 (m, 2H), 2.08 (d, *J* = 6.6 Hz, 2H), 3.42 (dt, *J* = 9.6, 6.2 Hz, 1H), 3.64 – 3.72 (m, 1H), 3.83 (dd, *J* = 29.7, 16.5 Hz, 13H), 4.03 (d, *J* = 9.1 Hz, 3H), 4.09 – 4.18 (m, 2H), 4.27 – 4.52 (m, 12H), 4.90 (d, *J* = 10.1 Hz, 1H), 4.97 (d, *J* = 17.1 Hz, 1H), 5.13 (s, 1H), 5.30 (d, *J* = 21.6 Hz, 5H), 5.35 – 5.62 (m, 17H), 5.70 (s, 1H), 5.87 (ddt, *J* = 16.9, 10.5, 6.7 Hz 1H), 7.11 – 7.42 (m, 67H), 7.49 (m, 4H), 7.54 – 7.67 (m, 16H), 7.79 – 8.01 (m, 23H), 7.79 –8.01(m, 5H); ^{13}C NMR (125.79 MHz, $CDCl_3$): δ 19.9 (2C), 20.0 (2C), 27.4 (6C), 27.5 (6C), 30.5, 30.9, 63.8, 63.9, 64.0, 64.0, 66.0, 66.1, 66.4, 66.5, 67.2, 67.3, 76.7, 76.8,77.1, 77.1, 77.2, 77.2,77.3, 81.5, 81.6, 81.7, 82.2, 82.4, 82.4, 82.7, 82.7, 82.8, 82.8, 83.0, 83.1, 83.1, 83.3, 83.4, 83.7, 84.2, 84.2, 84.4, 84.5, 105.9, 106.2, 106.4, 106.5, 106.6, 106.6, 106.6, 106.9, 106.9, 115.6, 128.3 – 128.4 (16C), 128.9 – 129.1 (38C), 129.7 – 130.0 (15C), 130.3 – 130.7 (46C), 133.8 – 134.0 (15C), 136.2 – 136.3 (8C), 138.9, 165.6, 165.6, 165.8, 165.8, 165.9, 166.0, 166.0, 166.0, 166.1, 166.1, 166.2, 166.2, 166.2, 166.2, 166.3; HRMS (ESI-MS): m/z calcd for $[C_{219}H_{214}O_{52}Si_4Na]^+$: 3810.3076; Found: 3812.2544.

Pent-4-enyl 2-*O*-benzoyl-3,5-di-*O*-[2,3-di-*O*-benzoyl-5-*O*-(2-*O*-benzoyl-3,5-di-O-(2,3-di-*O*-benzoyl- α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (**36**): Yield: (86%); mp (^{0}C): 98.6; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): 17.8; IR (cm^{-1}, $CHCl_3$): 3068, 2927, 1723, 1600, 1452, 1264, 1108, 1027, 969, 711; ^{1}H NMR (500.20 MHz, $CDCl_3$): δ 1.68 – 1.80 (p, *J* = 9.2, 8.1 Hz, 2H), 2.18 (q, *J* = 7.2 Hz, 2H), 2.85 (s, 4H), 3.54 (ddt, *J* = 15.8, 10.0, 5.3 Hz, 1H), 3.75 – 3.83 (m, 1H), 3.85 – 3.90 (m, 3H), 3.94 (dd, *J* = 11.4, 5.1 Hz, 8H), 4.03 (d, *J* = 7.3 Hz, 4H), 4.11 (dd, *J* = 11.3, 5.0 Hz, 1H), 4.22 (d, *J* = 10.7 Hz, 2H), 4.35 (s, 2H), 4.39 – 4.47 (m, 4H), 4.54 (td, *J* = 16.7, 4.6 Hz, 6H), 5.00 (d, *J* = 10.2 Hz, 1H), 5.06 (d, *J* = 17.1 Hz, 1H), 5.21 – 5.26 (m, 3H), 5.31 (d, *J* = 4.7 Hz, 2H), 5.35 (s, 2H), 5.37 (s, 1H), 5.40 (dd,

J = 9.0, 4.5 Hz, 4H), 5.44 (s, 2H), 5.47 (s, 1H), 5.52 (s, 1H), 5.55 (s, 1H), 5.58 (s, 1H), 5.61 (s, 3H), 5.63 (s, 1H), 5.68 (d, *J* = 4.6 Hz, 1H), 5.76 (d, *J* = 4.5 Hz, 1H), 5.79 – 5.89 (m, 1H), 7.29 (m, 10H), 7.36 – 7.55 (m, 31H), 7.58 – 7.65 (m, 4H), 7.90 – 8.11 (m, 30H); ^{13}C NMR (125.79 MHz, $CDCl_3$): δ 29.4, 30.9, 63.3, 63.3, 63.4, 63.4, 65.5, 65.6, 65.9, 66.1, 66.8, 67.3, 77.5, 77.7, 78.5, 78.6, 78.8, 78.8, 81.3, 81.5, 81.5, 81.9, 81.9, 82.1, 82.2, 82.2, 82.3, 82.4, 82.4, 82.4, 83.2, 83.5, 83.5, 83.5, 83.6, 84.7, 84.7, 84.7, 84.8, 105.9, 105.9, 106.0, 106.0, 106.1, 106.3, 106.4, 106.5, 106.6, 115.7, 129.0 – 129.2 (30), 129.6, 129.6, 129.6, 129.6, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 129.9, 130.0, 130.0, 130.0, 130.4 –130.6 (30), 134.0, 134.0, 134.0, 134.1, 134.1, 134.1, 134.1, 134.1, 134.1, 134.1, 134.1, 134.2, 134.2, 134.3, 134.3, 138.8, 165.4, 165.5, 165.8, 165.8, 165.9, 166.0, 166.1, 166.1, 166.3, 166.3, 166.3, 166.8, 166.8, 166.8, 166.8; HRMS (ESI-MS): m/z calcd for$[C_{155}H_{142}O_{52}Na]^+$: 2857.8365; Found: 2857.9429.

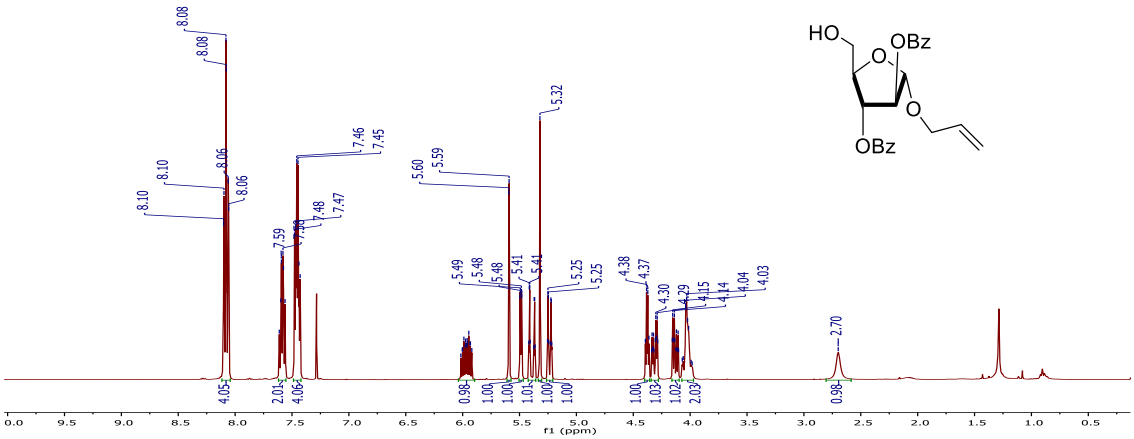
Pent-4-enyl 2-*O*-benzoyl-3,5-di-*O*-[2,3-di-*O*-benzoyl-5-*O*-(2-*O*-benzoyl-3,5-di-O-(2,3-di-*O*-benzoyl-5-*O*-(2,3,4,6-tetra-*O*-benzoyl α-D-mannopyranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (**37**): Yield: (95%); mp (^{0}C): 104.9; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): 3.3; IR (cm^{-1}, $CHCl_3$): 3067, 2926, 1724, 1600, 1488, 1452, 1261, 1103, 970, 756,714; ^{1}H NMR (500.20 MHz, $CDCl_3$): δ 1.75 (p, *J* = 9.2, 8.1 Hz, 2H), 2.20 (q, *J* = 7.3 Hz, 2H), 3.54 (dt, *J* = 9.4, 6.3 Hz, 1H), 3.75 – 3.85 (m, 1H), 3.90 – 3.99 (m, 2H), 4.00 – 4.19 (m, 8H), 4.22 – 4.40 (m, 8H), 4.46 – 4.60 (m, 10H), 4.60 – 4.65 (m, 2H), 4.65 – 4.82 (m, 12H), 5.01 (d, *J* = 10.2 Hz, 1H), 5.09 (d, *J* = 17.1 Hz, 1H), 5.22 – 5.33 (m, 5H), 5.43 – 5.49 (m, 3H), 5.50 – 5.57 (m, 3H), 5.59 – 5.79 (m, 16H), 5.81 – 5.91 (m, 6H), 5.94 (dd, *J* = 10.1, 3.1 Hz, 2H), 6.00 (dd, *J* = 10.1, 3.1 Hz, 2H), 6.13 – 6.26 (m, 4H), 7.26 – 7.52 (m, 85H), 7.55 – 7.67 (m, 8H), 7.77 – 7.86 (m, 8H), 7.91 – 8.03 (m, 20H), 8.03 – 8.11 (m, 14H), 8.11 – 8.19 (m, 20H); ^{13}C NMR (125.79 MHz, $CDCl_3$): δ 29.4, 30.9, 63.4 (4C), 65.9, 66.1, 66.5, 66.6, 67.2(3C), 67.3, 67.5, 67.5, 67.6, 67.6, 67.6, 67.7, 67.7, 69.7, 69.8, 69.8, 69.8, 70.8, 70.8, 70.8, 70.9, 71.0, 71.0, 71.0, 71.0, 76.3, 77.7, 78.0 (4C), 81.6, 81.8, 82.0, 82.3, 82.5, 82.5, 82.5, 82.6, 82.6, 82.6, 82.7, 82.8, 83.1, 83.1, 83.2, 83.2, 83.2, 83.4, 83.4, 83.5, 83.8, 98.8, 98.8, 98.8, 98.8, 105.9, 106.3, 106.4, 106.4, 106.5, 106.6, 106.6, 106.7, 106.8, 115.7, 128.9 – 129.3 (62C), 129.7 – 130.2 (31C), 130.4 – 130.8 (62C), 133.6 – 133.7 (8C), 134.0 – 134.1 (23C), 138.9, 165.6 (2C), 165.7, 165.7, 165.8 (2C), 165.8, 165.9, 165.9, 166.0, 166.1, 166.1, 166.1 (2C),

166.1, 166.2 (2C), 166.2 (2C), 166.2, 166.3, 166.4, 166.5 (2C), 166.6, 166.6, 166.8 (5C); HRMS (ESI-MS): m/z calcd for $[C_{291}H_{246}O_{88}K]^+$: 5186.4412; Found: 5185.4000.

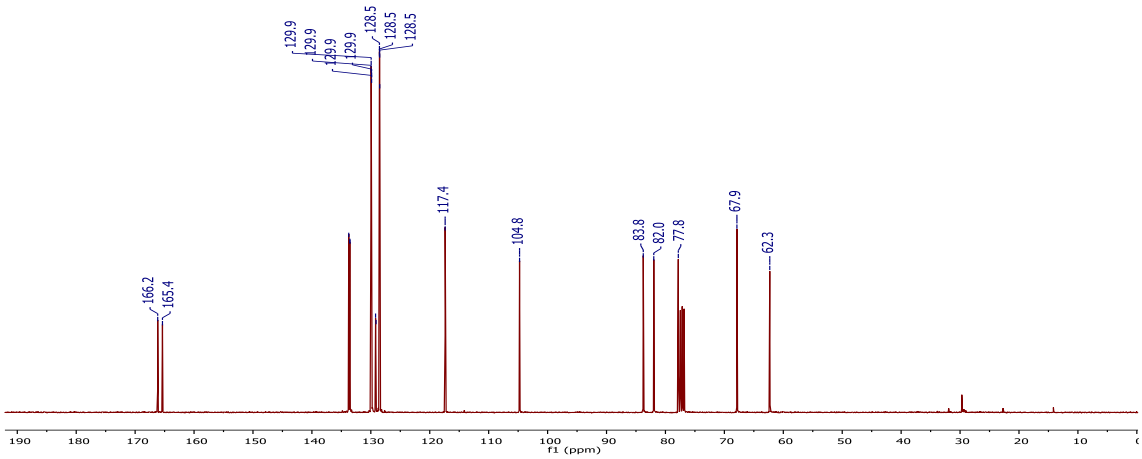
3.7 – Spectral Charts of Representative Compounds

{Kindly see the supporting documents files in *Eur. J. Org. Chem.* **2017,** 4794−4802 and *Angew. Chem. Int. Ed.* **2016**, *128*, 7917–7922 for spectral charts of all compounds**}**

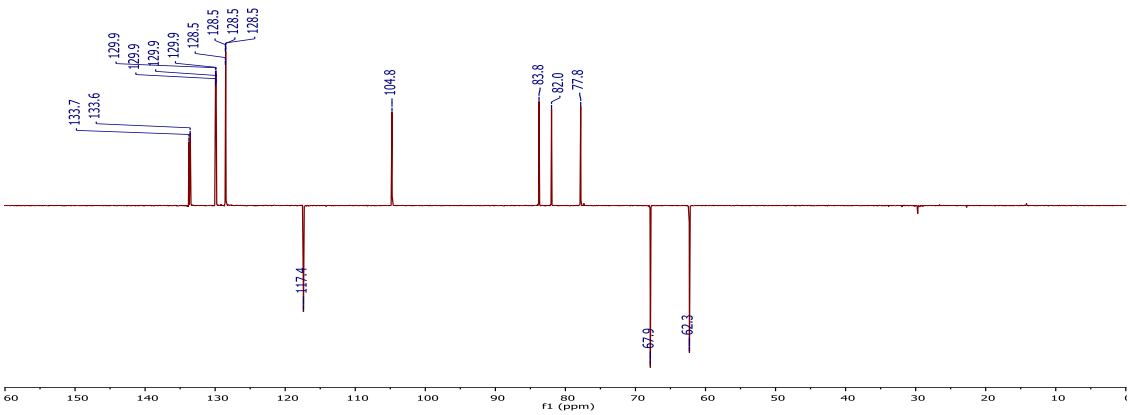
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **3**



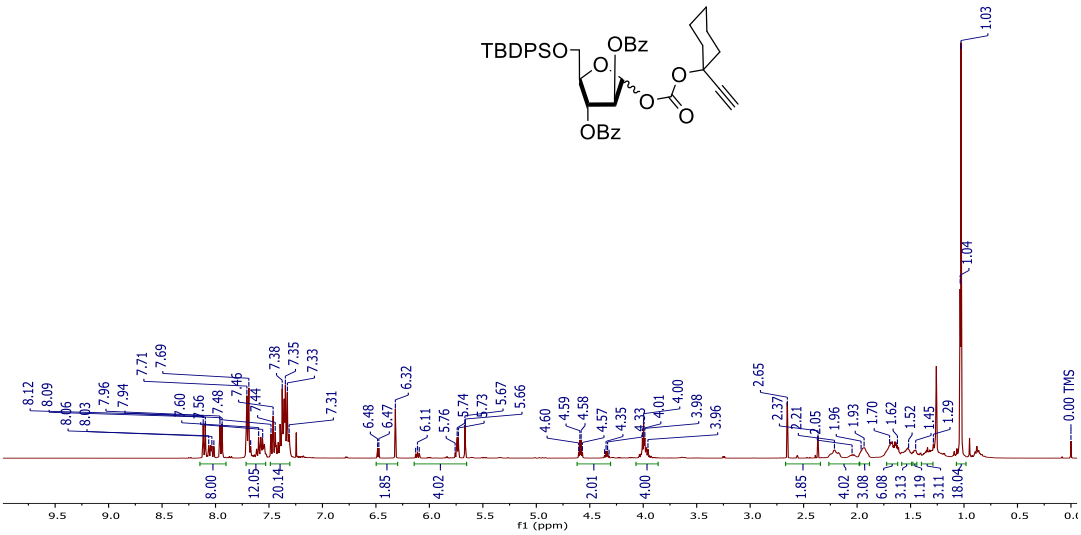
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **3**



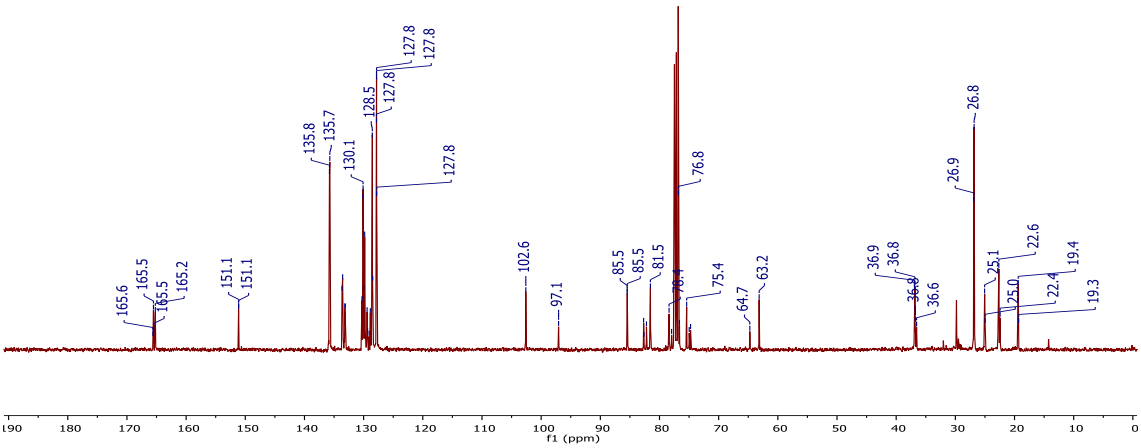
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **3**



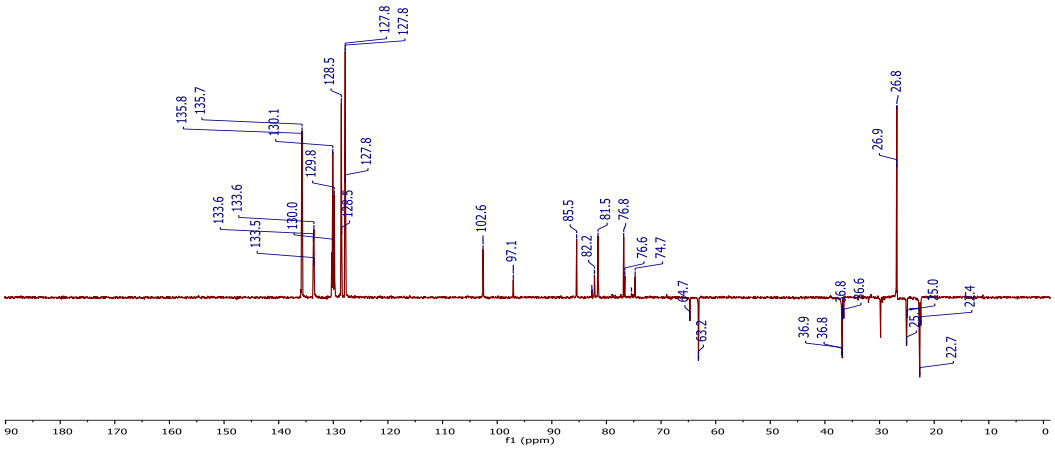
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **6**



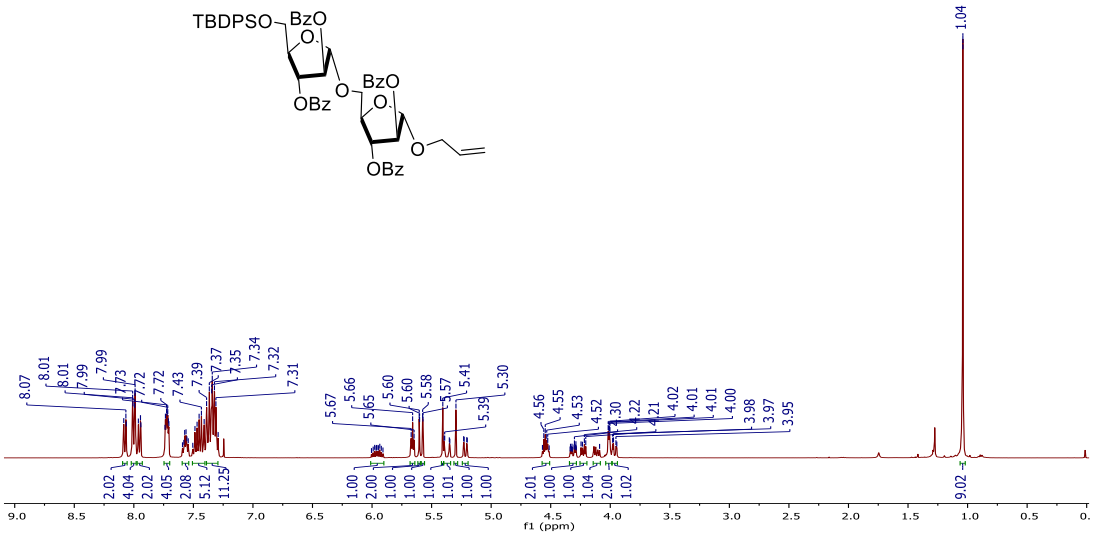
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **4**



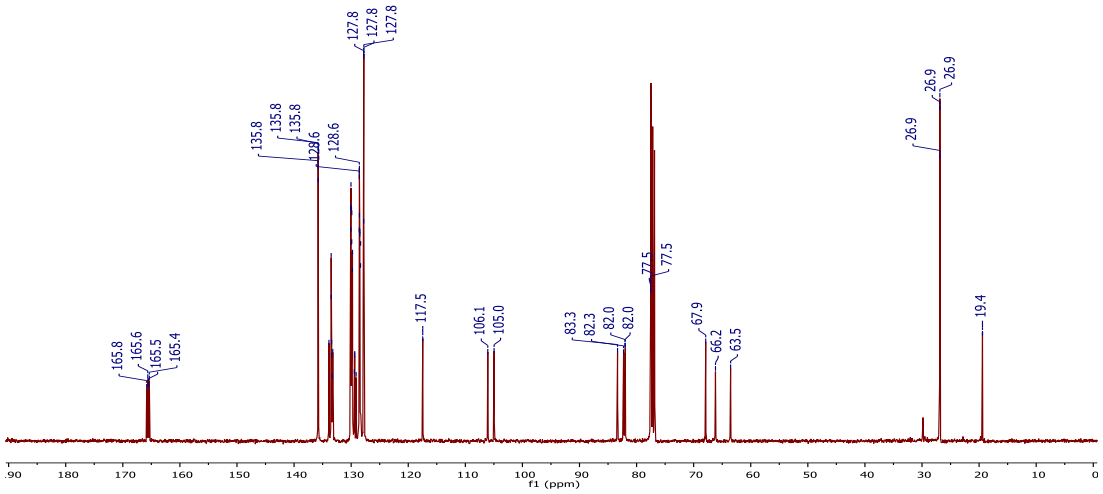
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **4**



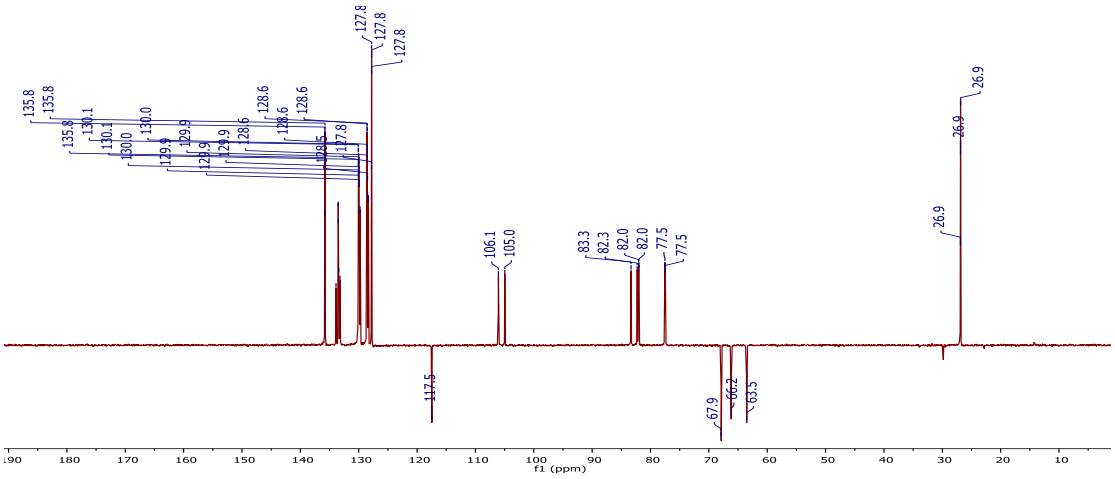
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **8**



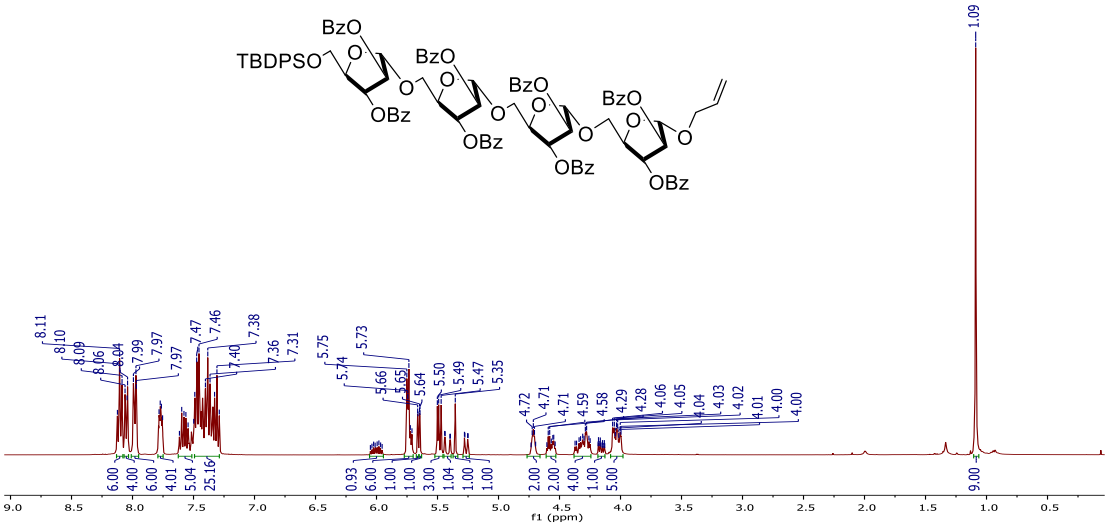
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **8**



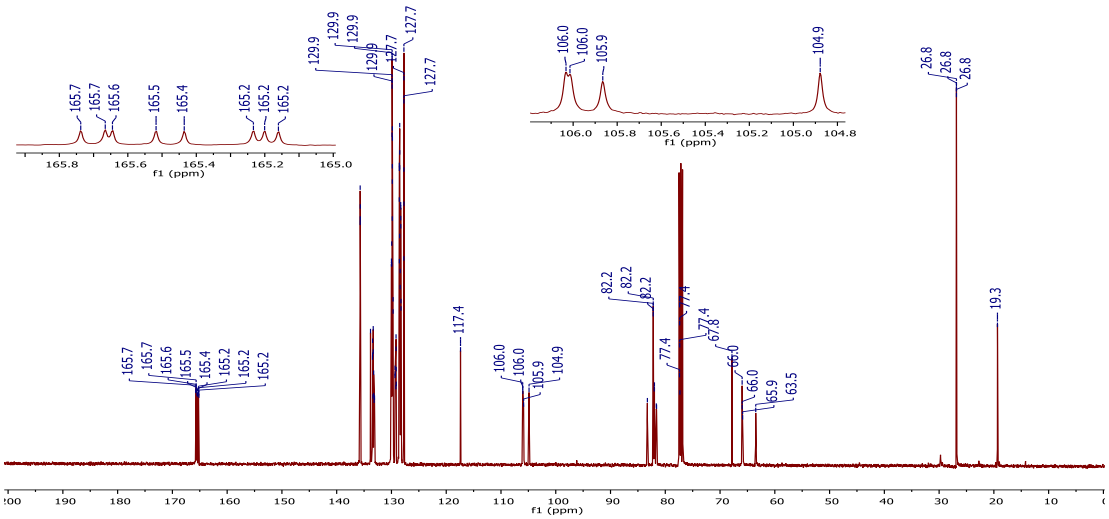
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **8**



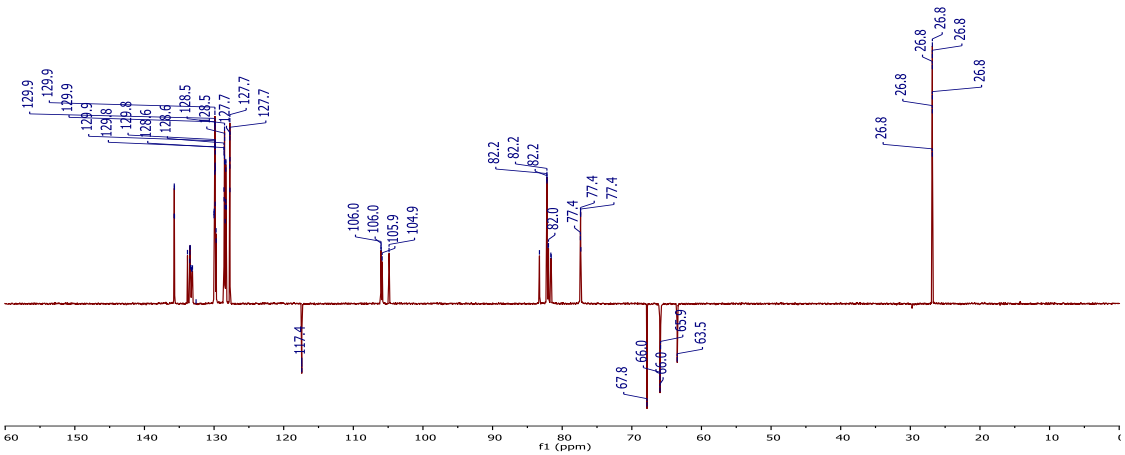
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **11**



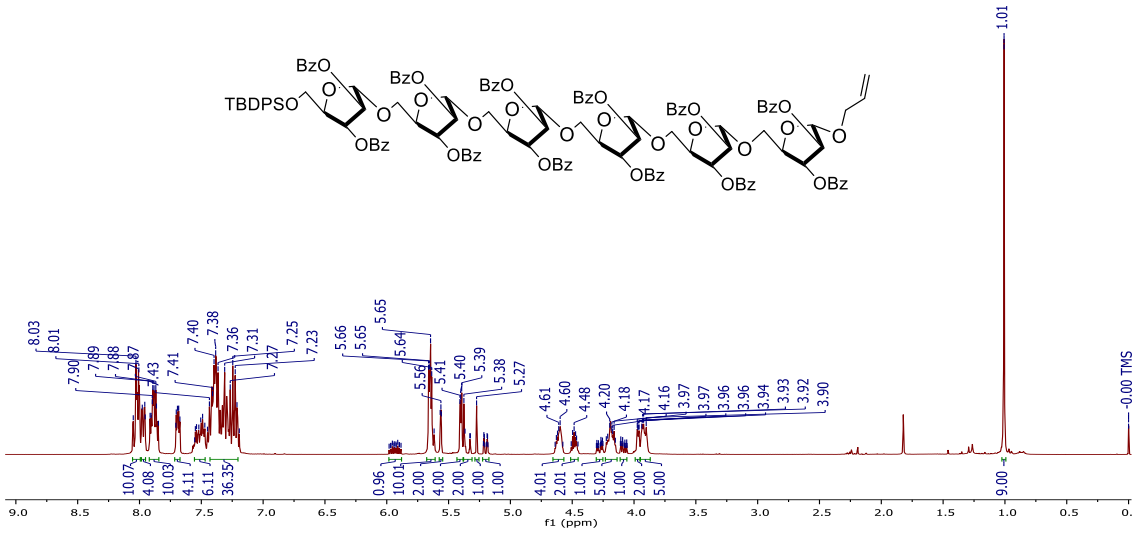
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **11**



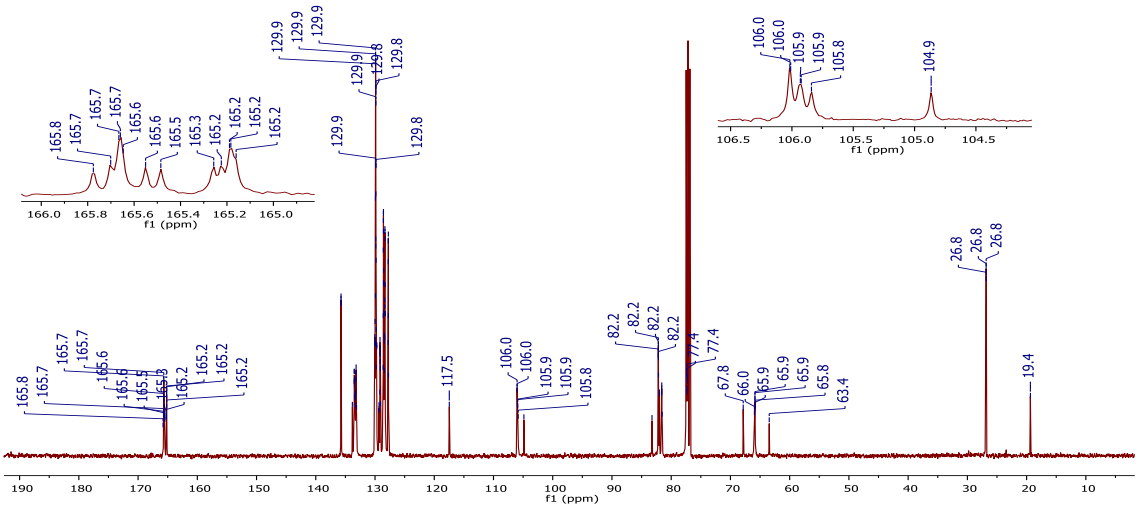
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **11**



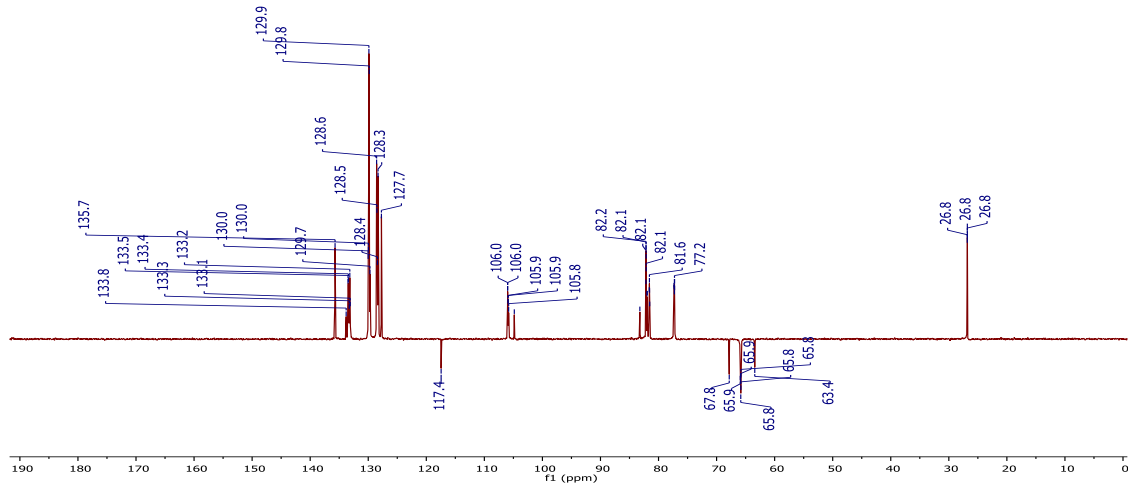
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **13**



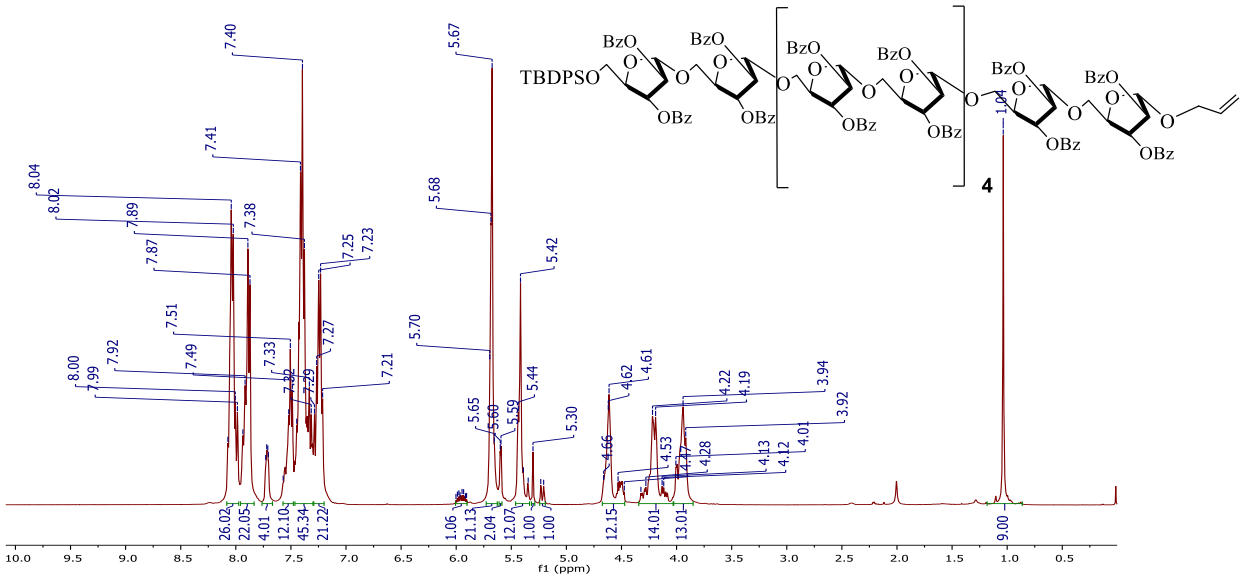
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **13**



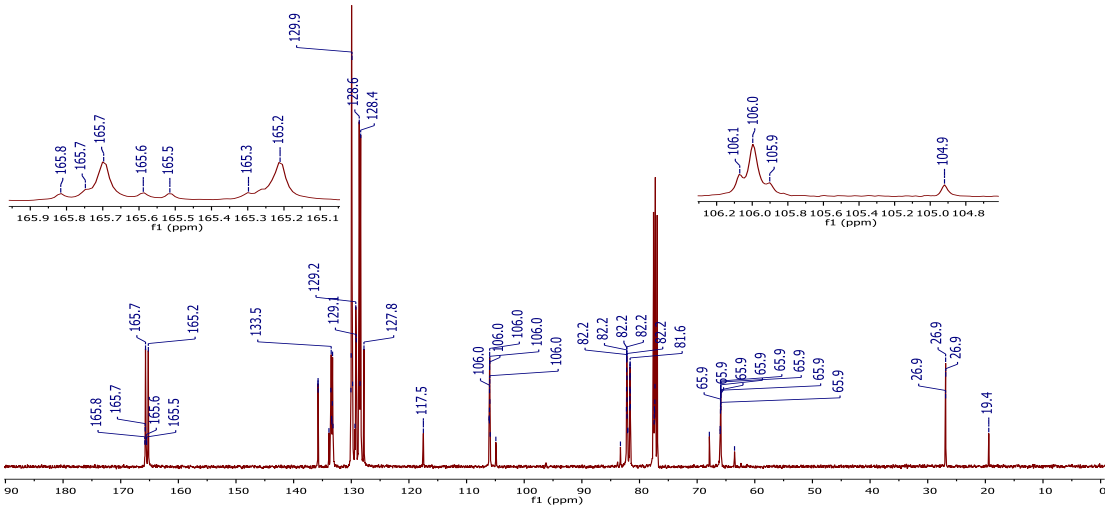
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **13**



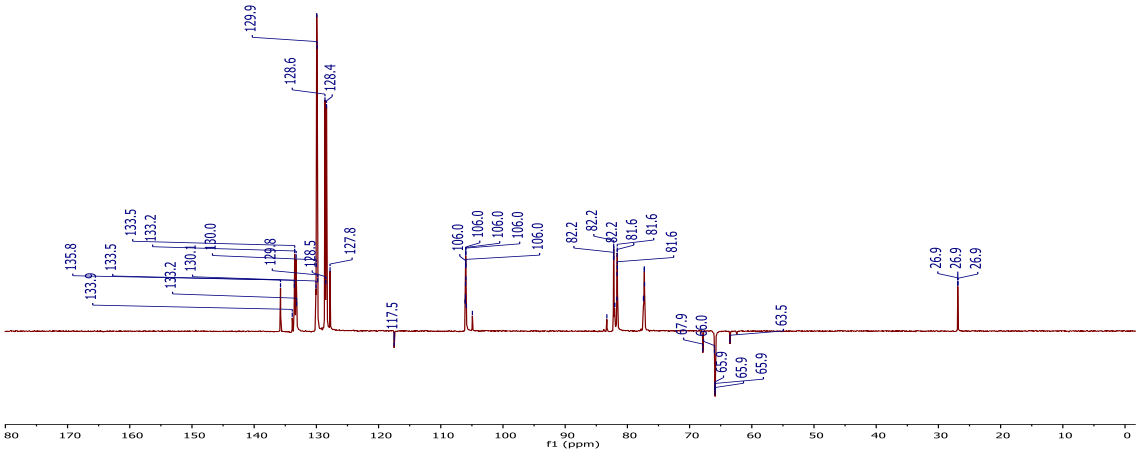
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **16**



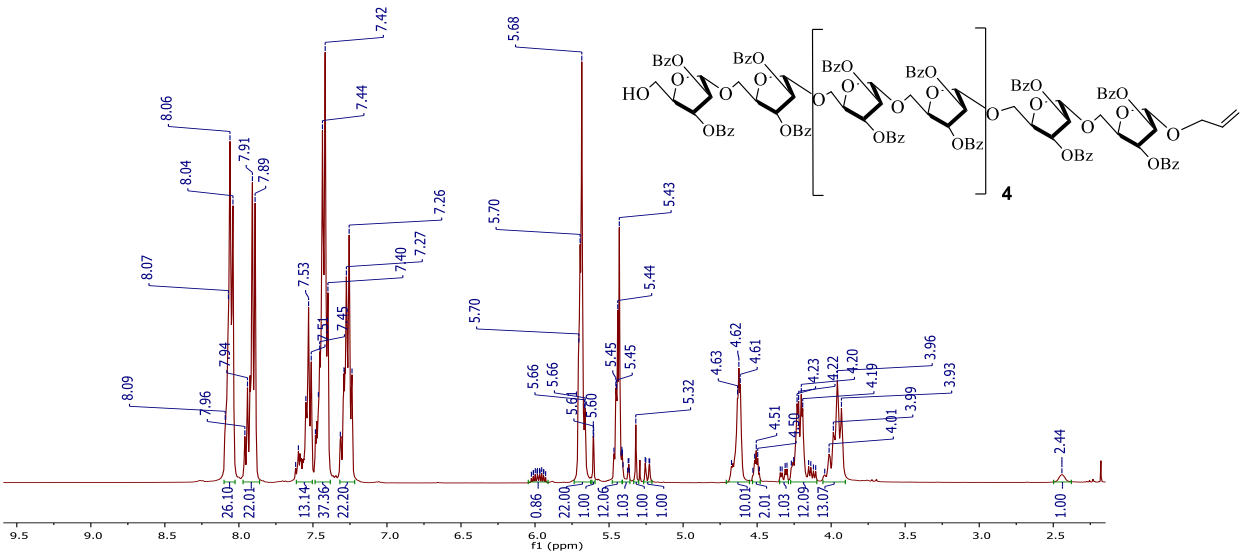
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **16**



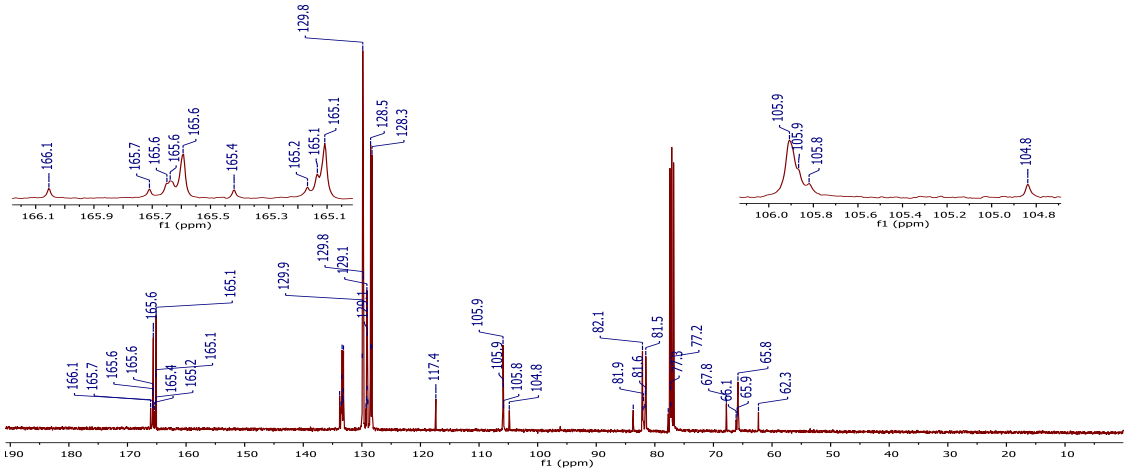
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **16**



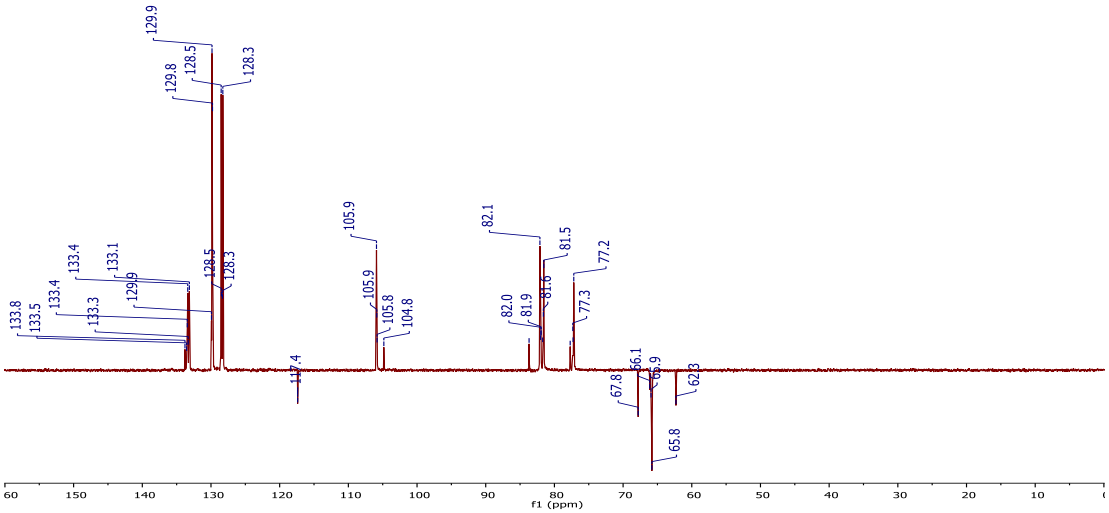
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **17**



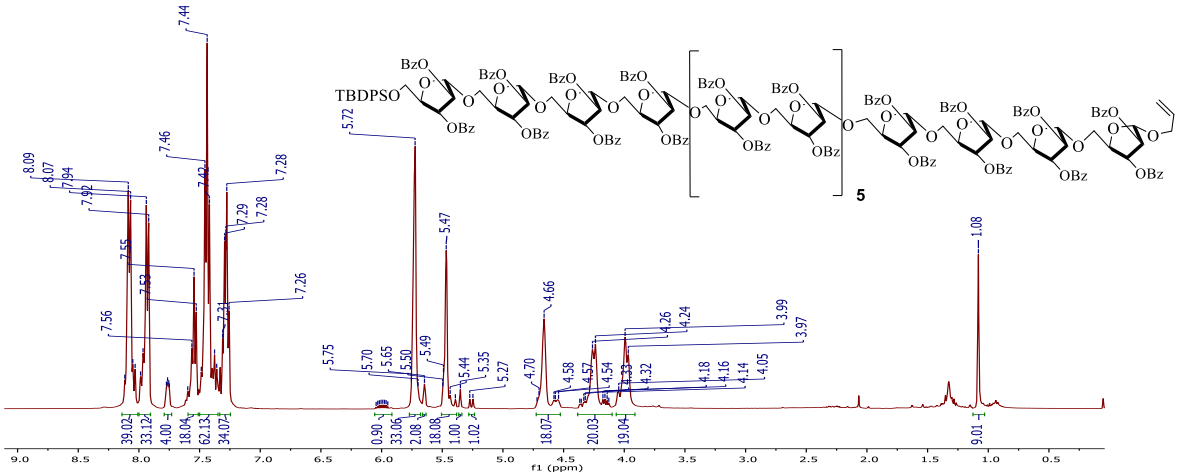
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **17**



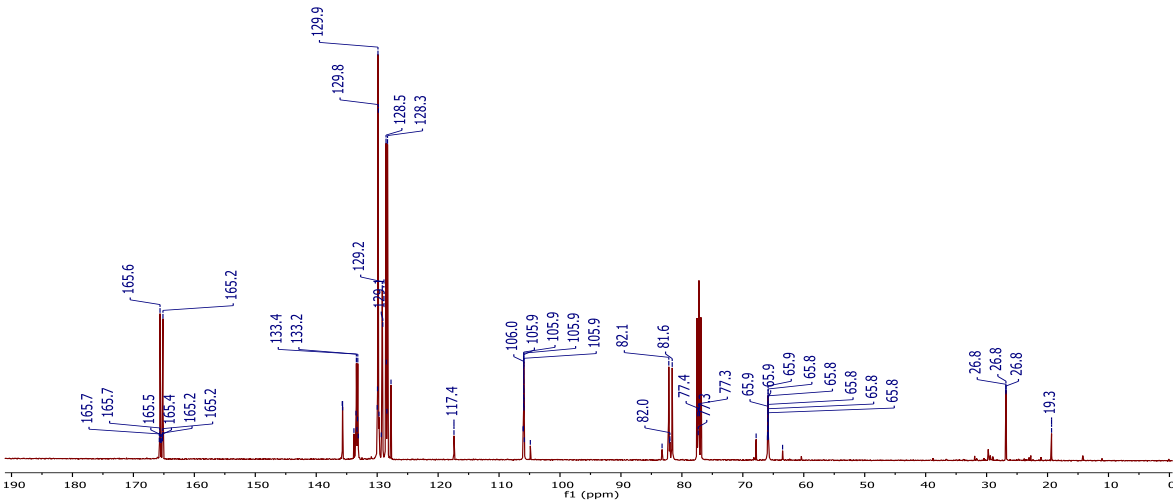
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **17**



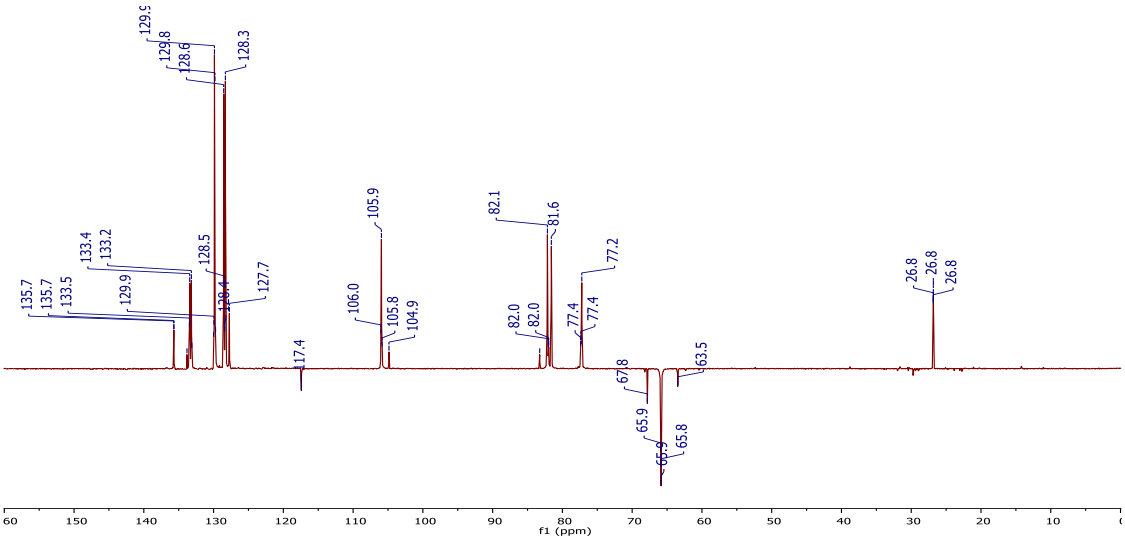
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **18**



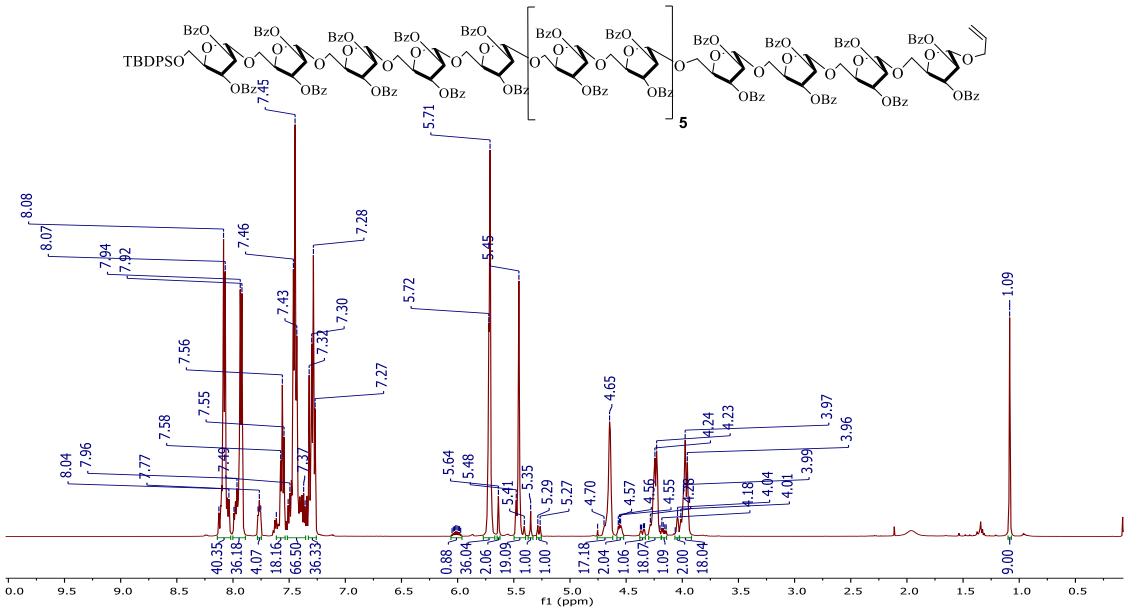
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **18**



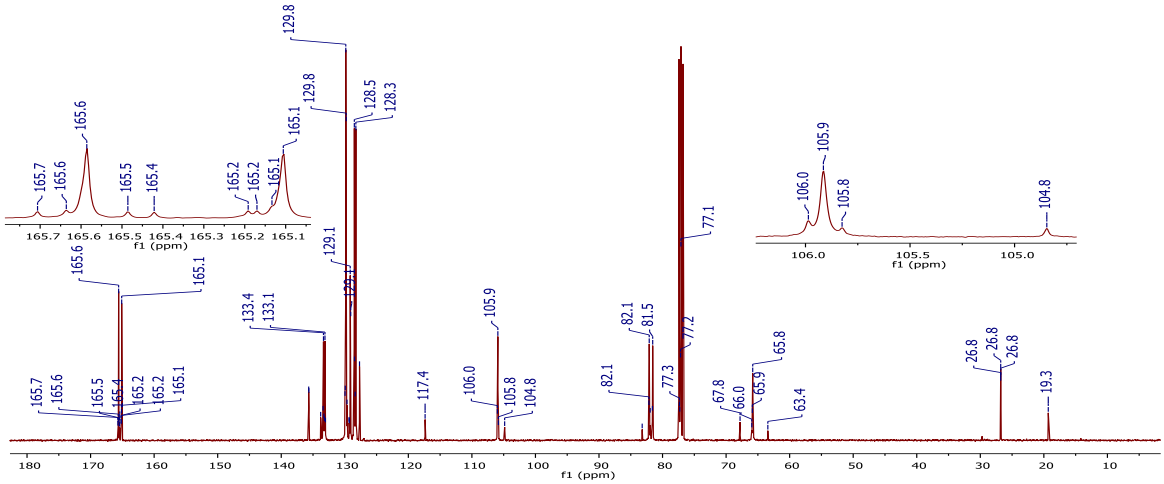
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **18**



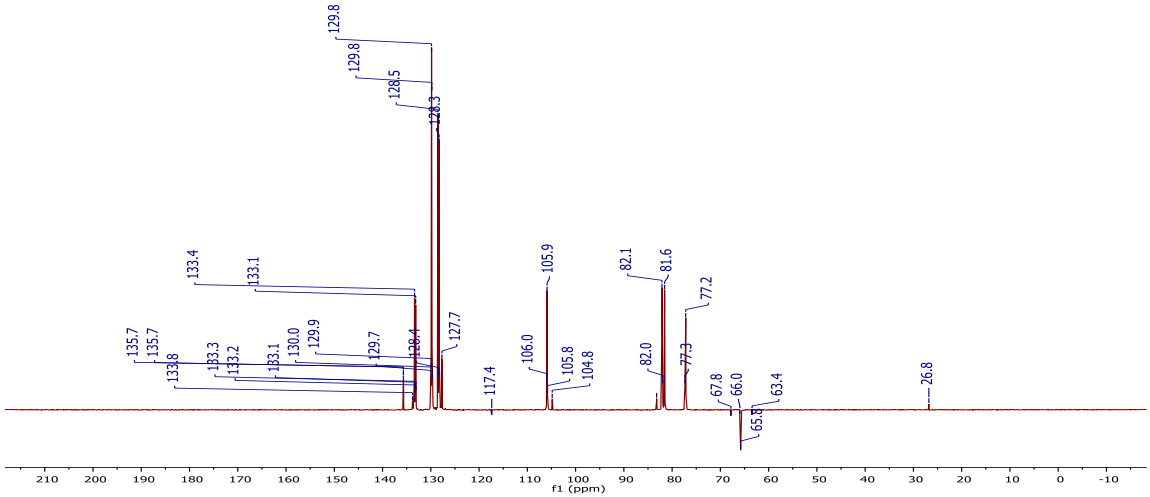
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **19**



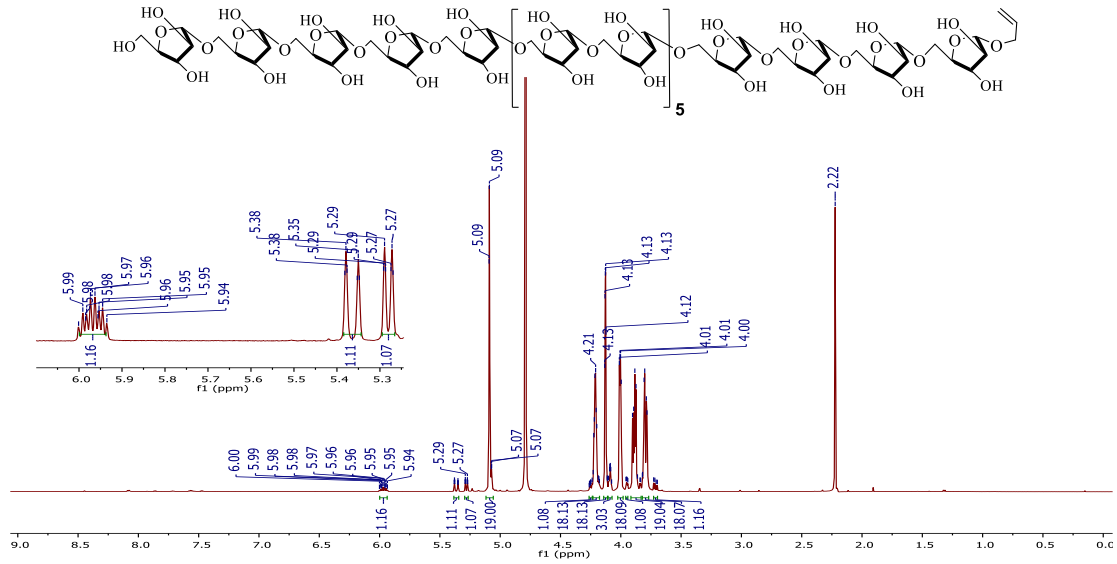
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **19**



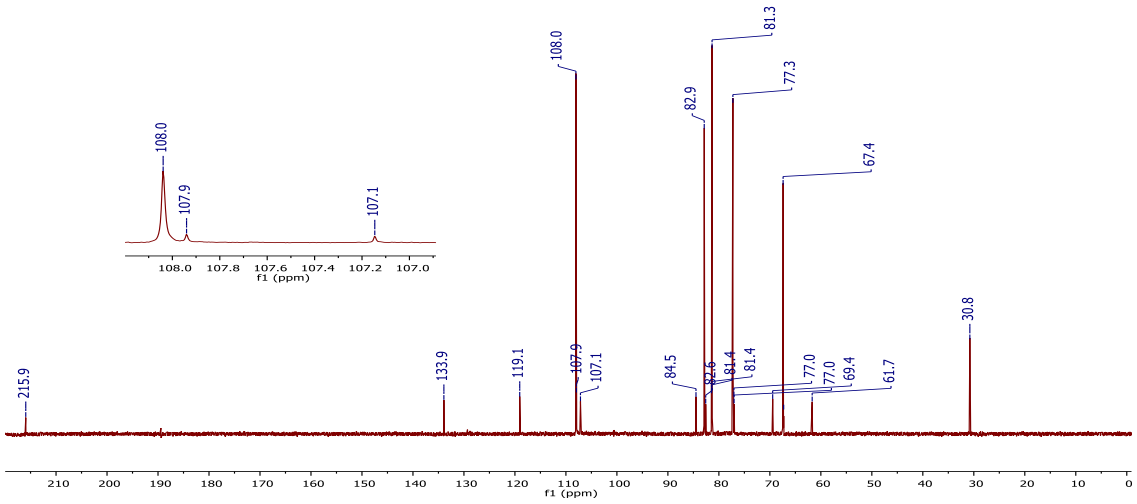
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **19**



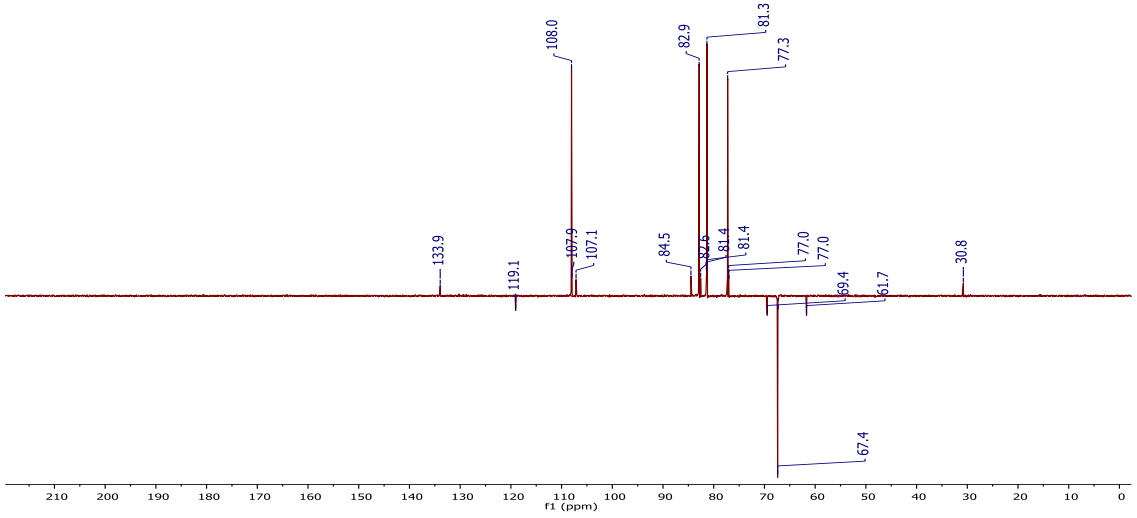
^{1}H NMR Spectrum (600.40 MHz, D_2O) of compound **21**



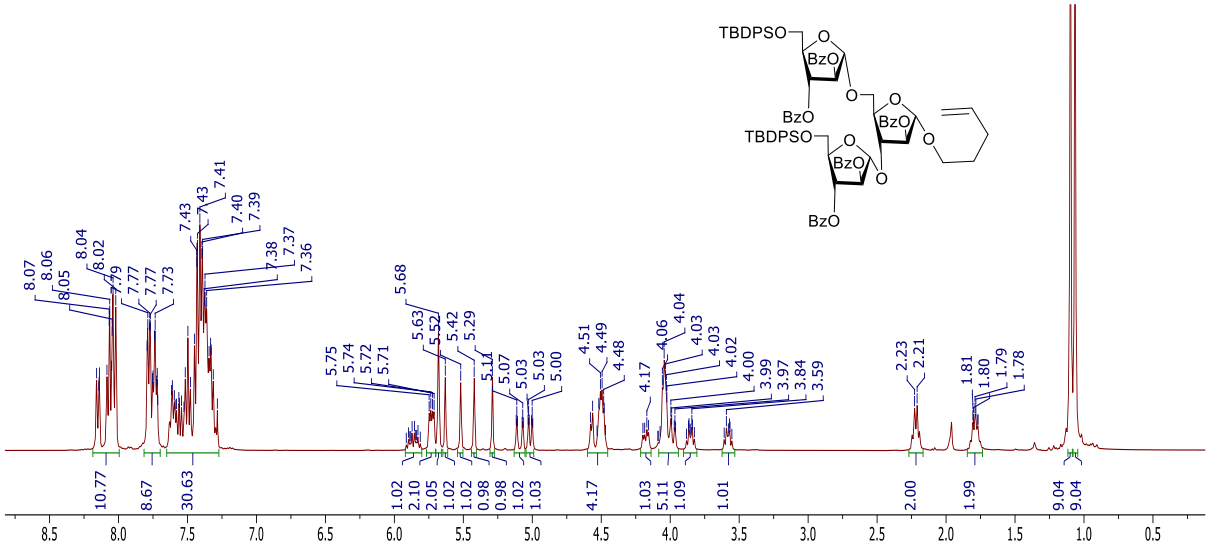
^{13}C NMR Spectrum (150.99 MHz, D_2O) of compound **21**



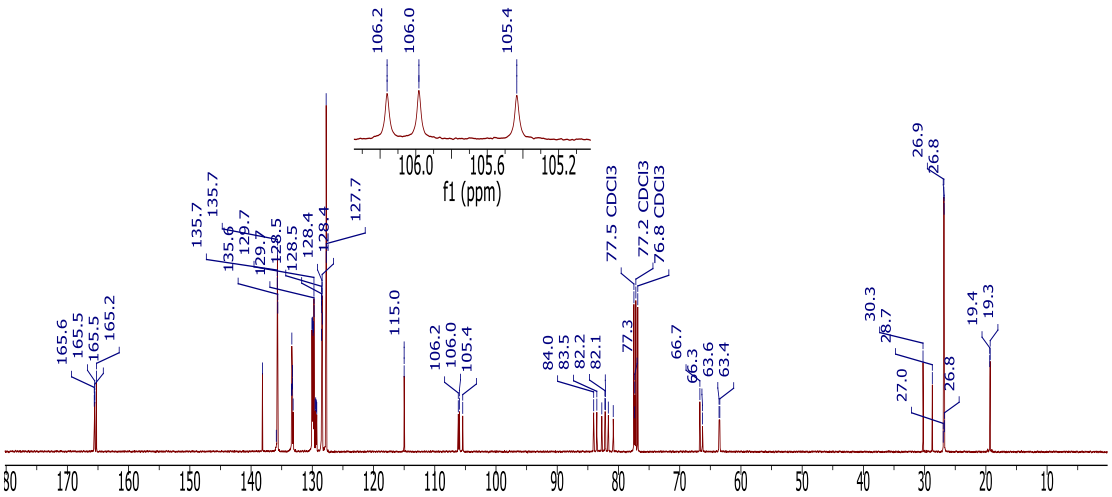
DEPT NMR Spectrum (150.99 MHz, D_2O) of compound **21**



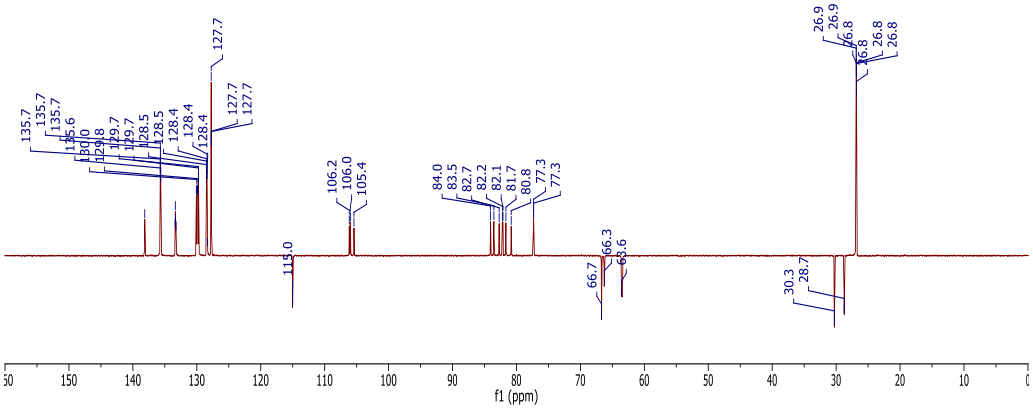
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **31**



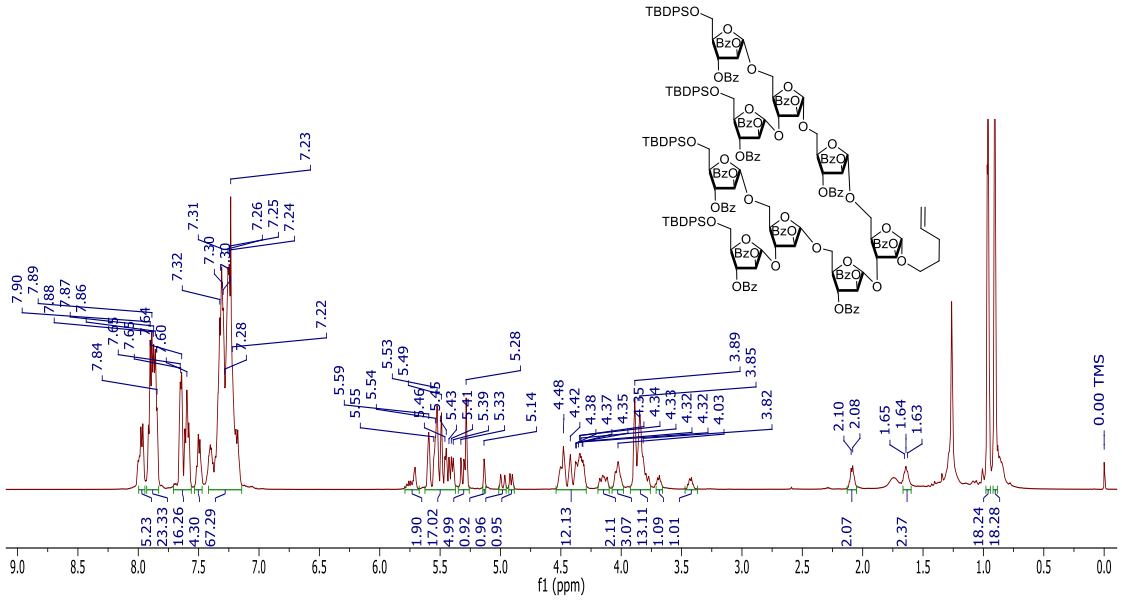
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **31**



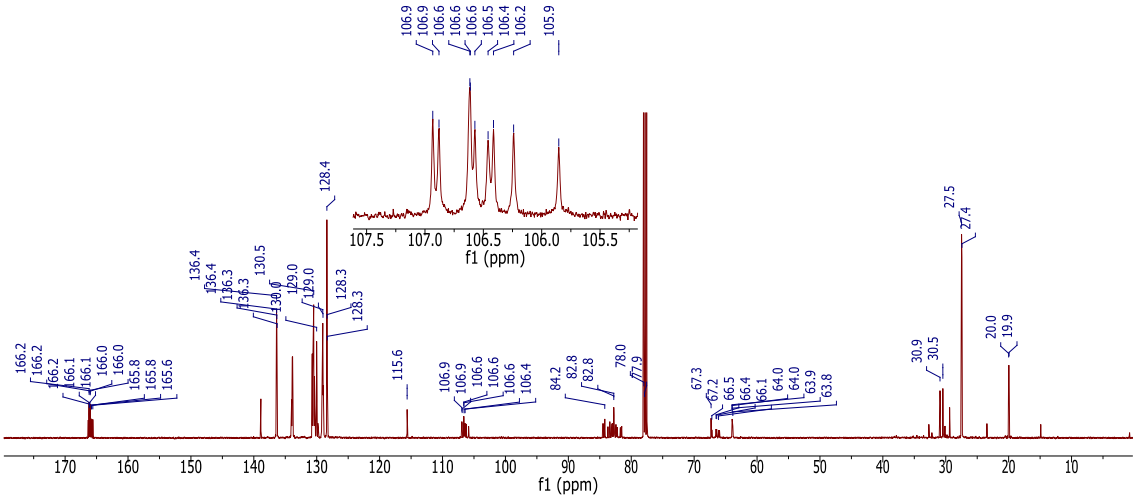
DEPT NMR Spectrum (100.67 MHz, $CDCl_3$) of compound **31**



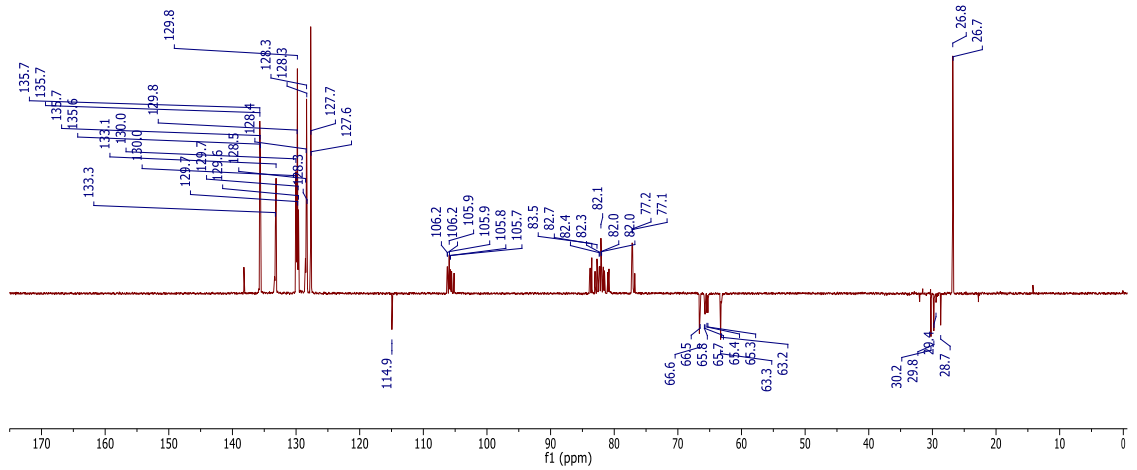
^{1}H NMR Spectrum (500.20 MHz, $CDCl_3$) of compound **35**



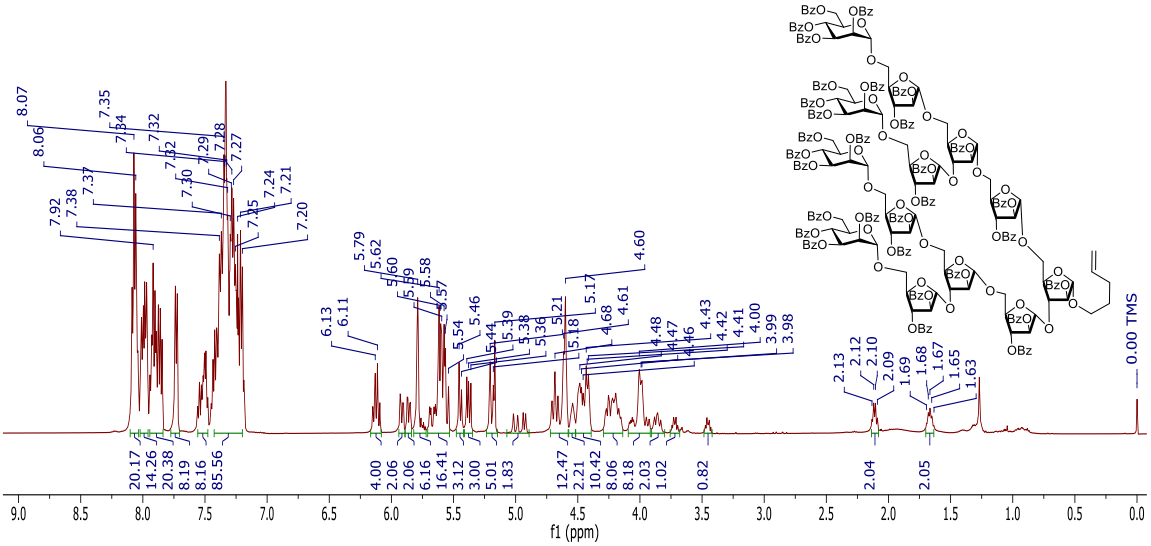
^{13}C NMR Spectrum (125.79 MHz, $CDCl_3$) of compound **35**



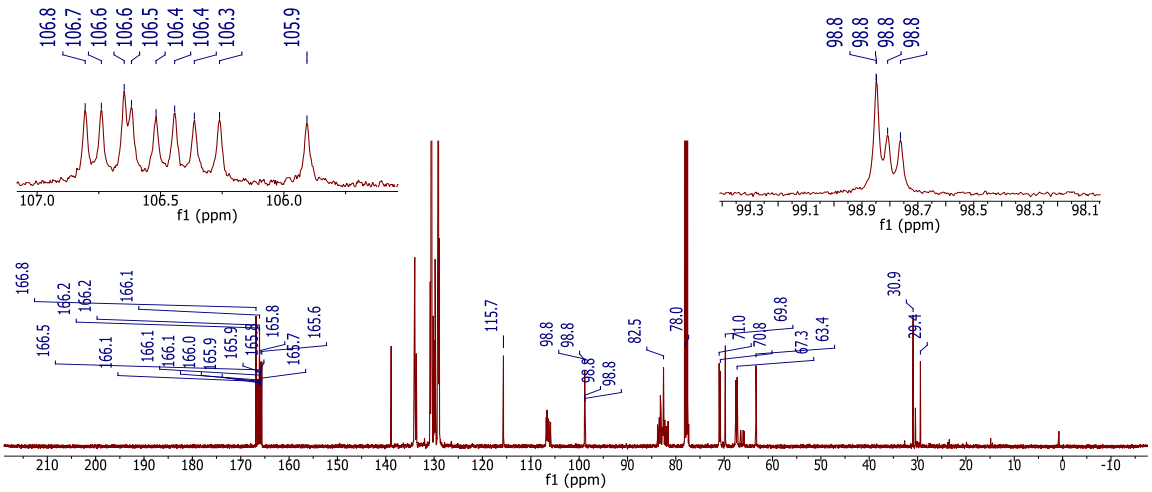
DEPT NMR Spectrum (125.79 MHz, $CDCl_3$) of compound **35**



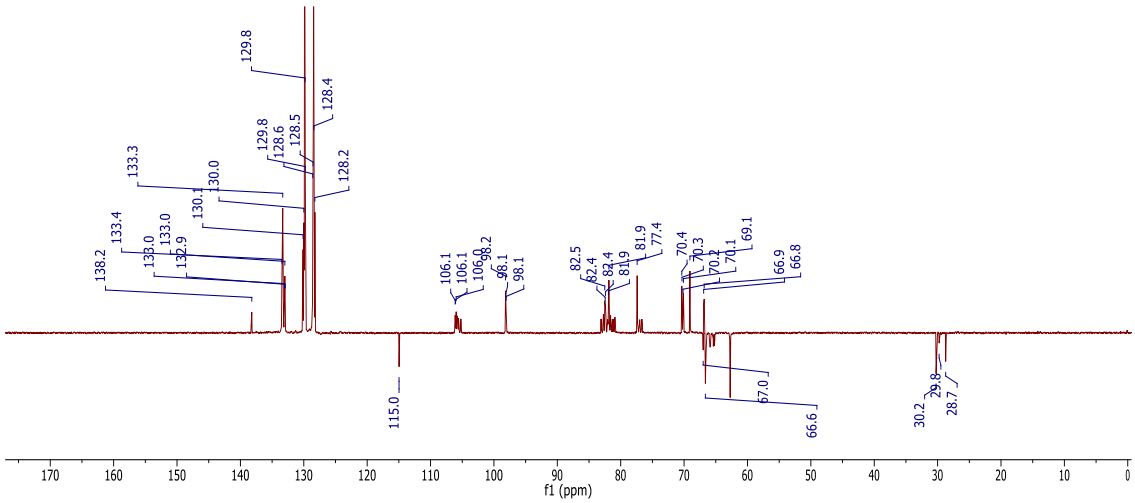
^{1}H NMR Spectrum (500.20 MHz, $CDCl_3$) of compound **37**



^{13}C NMR Spectrum (125.79 MHz, $CDCl_3$) of compound **37**



DEPT NMR Spectrum (125.79 MHz, $CDCl_3$) of compound **37**



3.8 – References

1. (a) World Health Organization. **2018**. "*Global tuberculosis Report* " pages 1–78; (b) WHO. Treatment of Tuberculosis Guidelines. 4th ed. Geneva: WHO; 2009. WHO/HTM/TB/2009 420. (c) BCG vaccine: WHO position paper, *Vaccine* **2018** *36*, 3408-3410. (doi: 10.1016/j.vaccine.2018.03.009); (d) Mathe, G.; Halle-Pannenko, O.; Bourut, C. *Natl. Cancer, Inst. Monogr.* **1973**, *39*, 107–113.
2. (a) Sakula, A. *Robert Koch: centenary of the discovery of the tubercle bacillus, 1882*. *Thorax*, **1982**, 37, 246–251; (b) Lawn, S. D.; Zumla, A. *The Lancet* **2011**, *378*, 57−72; (c) Ducati, R. G.; Ruffino-Netto, A.; Basso, L. A.; Santos, D. S. *Mem Inst Oswaldo Cruz* **2006**, *101*, 697−714; (d) Ghosh, J.; Larsson, P.; Singh, B.; Pettersson, B. M.; Islam, N. M.; Sarkar, S. N.; Dasgupta, S.; Kirsebom, L. A. *Proc. Natl. Acad. Sci.* **2009**, *106*, 10781−10786; (e) Cook, G. M.; Berney, M.; Gebhard, S.; Heinemann, M.; Cox, R. A.; Danilchanka, O.; Niederweis, M. *Adv. Microb. Physiol.* **2009**, *55*, (81−182), 318−319; (f) Middlebrook, G.; Dubos, R. J.; Pierce, C. *Journal of experimental medicine* **1947**, *86*, 175−184.
3. (a) Pandit, A. *Tuberculosis: A basic discourse*, Apollo Medicine (2015), (http://dx.doi.org/10.1016/j.apme.2015.01.001); (b) Koch, A.; Mizrahi1, V. *Trends in Microbiology* **2018**, (https://doi.org/10.1016/j.tim.2018.02.012).
4. (a) Besra, G. S.; Khoo, K. -H.; McNeil, M. R.; Dell, A.; Morris, H. R.; Brennan, P. J. *Biochemistry* **1995**, *34*, 4257–4266; (b) Bhamidi, S.; Scherman, M. S.; Rithner, C. D.; Prenni, J. E.; Chatterjee, D.; Khoo, K. -H.; McNeil, M. R. *J. Biol. Chem*. **2008**, *283*, 12992–13000; (c) Jankute, M.; Grover, S.; Rana, A. K.; Besra, G. S. *Future Microbiol.* **2012**, *7*, 129–147.
5. (a) Stodola, F. H. *ibid*. **1938**, *126*, 505; (1938) (b) Asselineau, J.; Lederer, E. *Nature* **1950**, *166*, 782–783; (c) Takayama, K.; Wang, C.; Besra, G. S. *Clinical Microbiology Reviews* 2005, *18*, 81–101; (d) Brennan, P. J.; Nikaido, H. *Annual Review of Biochemistry* **1995**, *64*, 29–63. (e) Watanabe, M.; Aoyagi, Y.; Ridell, M.; Minnikin, D. E. *Microbiology* **2001**, *147*, 1825–1837.
6. (a) Angala, S. K.; Belardinelli, J. M.; Huc-Claustre, E.; Wheat, W. H.; Jackson, M. *Crit Rev Biochem Mol Biol.* **2014**, 1–39 (DOI: 10.3109/10409238.2014.925420); (b) Chatterjee, D.; Hunter, S. W.; Mcneil, M.; Brennan, P. J. *J. Biol. Chem.* **1992**, *267*, 6228–6233; (c) Dinadayala, P.; Kaur, D.; Berg, S. *et al. J. Biol. Chem.* **2006**, *281*, 20027–20035; (d) Birch, H. L.;

Alderwick, L. J.; Appelmelk, B. J. *et al. Proc. Natl Acad. Sci. USA* **2010**, *107*, 2634–2639; (e) Chatterjee, D.; Bozic, C. M.; McNeil, M.; Brennan, P. J. *J. Biol.Chem.* **1991**, *266*, 9652–9660; (f) Chatterjee, D.; Khoo, K. H.; McNeil, M. R.; Dell, A.; Morris, H. R.; Brennan, P. J. *Glycobiology* **1993**, *3*, 497–506; (g) McNeil, M. R.; Robuck, K. G.; Harter, M.; Brennan, P. J. *Glycobiology* **1994**, *4*, 165–173; (h) Chatterjee, D.; Lowell, K.; Rivoire, B.; McNeil, M. R.; Brennan, P. J. *J. Biol. Chem.* **1992**, *267*, 6234–6239.

7. (a) McNeil, M.; Wallner, S. J.; Hunter, S.W.; Brennan, P. J. *Carbohydr. Res.* **1987**, *166*, 299–308; (b) McNeil, M.; Daffe, M.; Brennan, P. J. *J. Biol. Chem.* **1990**, *265*, 18200–18206; (c) Alderwick, L. J.; Seidel, M.; Sahm, H.; Besra, G. S.; Eggeling, L. *J. Biol. Chem.* **2006**, *281*, 15653–15661; (d) McNeil, M.; Daffe, M.; Brennan, P. J. *J. Biol. Chem.* **1991**, *266*, 13217–13223.

8. (a) Mikusova, K.; Mikus, M.; Besra, G. S.; Hancock, I.; Brennan, P. J. *J. Biol. Chem.* **1996**, *271*, 7820–7828; (b) Jin, Y.; Xin, Y.; Zhang, W.; Ma, Y.; *FEMS Microbiol. Lett.* **2010**, *310*, 54–61; (c) Kremer, L.; Dover, L. G.; Morehouse, C. *et al. J. Biol.Chem.* **2001**, *276*, 26430–26440; (d) Szczepina, M. G.; Zheng, R. B.; Completo, G. C.; Lowary, T. L. Pinto, B. M. *Bioorg. Med. Chem.* **2010**, *18*, 5123–5128; (e) Wolucka, B. A.; McNeil, M. R.; De Hoffmann, E.; Chojnacki, T. Brennan, P. J. *J. Biol. Chem.* **1994**, *269*, 23328–23335; (f) Mishra, A. K.; Driessen, N. N.; Appelmelk, B. J.; Besra, G. S. *FEMS Microbiol. Rev.* **2011**, *35*, 1126–1157; (g) Besra, G. S.; Brennan, P. J. *Biochem. Soc. Trans.* **1997**, *25*, 845–850; (h) Mishra, A. K.; Alderwick, L. J.; Rittmann, D. *et al. Mol. Microbiol.* **2008**, *68*, 1595–1613; (i) Venisse, A.; Berjeaud, J. M.; Chaurand, P.; Gilleron, M.; Puzo, G. *J. Biol.Chem.* **1993**, *268*, 12401–12411.

9. (a) Mereyala, H. B.; Hotha, S.; Gurjar, M. K. *Chem. Commun.* **1998**, 685−686; (b) Gurjar, M. K.; Reddy, L. K.; Hotha, S. *Org. Lett.* **2001**, *3*, 321–323; (c) Gurjar, M. K.; Reddy, L. K.; Hotha, S. *J. Org. Chem.* **2001,** *66*, 4657–4660.

10. (a) Kandasamy, J.; Hurevichza, M.; Seeberger, P. H. C*hem. Commun.* **2013**, *49*, 4453–4455; (b) Naresh, K.; Schumacher, F.; Hahm, H. S.; Seeberger, P. H. *Chem. Commun.* **2017**, *53*, 9085–9088.

11. (a) Bert, F. -R.; Lu, J,; Jayprakash, K. N.; López, J. C. *Tetrahedron*: *Asymmetry* **2006**, *17*, 2449–2463; (b) Fraser-Reid, B.; López, J. C.; Radhakrishnan, K. V.; Nandakumar, M. V.; Gómez, A. M.; Uriel, C. *Chem. Commun.* **2002**, 2104–2105;

(c) Lo´pez, J. C.; Agocs, A.; Uriel, C.; Go´mez, A. M.; Fraser-Reid, B. *Chem. Commun.* **2005**, 5088–5090; (d) Uriel, C.; Agocs, A.; Go´mez, A. M.; Lo´pez, J. C.; Fraser-Reid, B. *Org. Lett.* **2005**, *7*, 4899–4902; (e) Ramamurthy, C. V. S.; Ganney, P.; Rao, C. R.; Fraser-Reid, B. *J. Org. Chem*. **2011**, *76*, 2245-2247.

12. (a) D'Souza, F. W.; Ayers, J. D.; McCarren, P. R.; Lowary, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 1251−1260; (b) D′Souza, F. W.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 1493−1495; (c) Yin, H.; D'Souza, F. W.; Lowary, T. L. *J. Org. Chem.* **2002**, *67*, 892−903; (d) Gadikota, R. R.; Callam, C. S.; Wagner, T.; Del Fraino, B.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 4155−4165. (e) Joe, M.; Bai, Y.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc*. **2007**, *129*, 9885–9901; (f) Sahloul, K.; Lowary, T. L. *J. Org. Chem.* **2015**, *80*, 11417−11434.
13. (a) Ishiwata, A.; Ito, Y. *J. Am. Chem. Soc*. **2011**, *133*, 2275–2291; (b) Ishiwata, A.; Akao, H.; Ito, Y. *Org. Lett.* **2006**, *8*, 5525−5528.
14. (a) Abronina, P. I.; Podvalnyy, N. M.; Kondakov, N. N.; Chizhov, A. O.; Torgov, V. I.; Kononov, L. O. *Carbohydr. Res.* **2012**, *357*, 62–67; (b) Podvalnyy, N. M.; Abronina, P. I.; Fedina, K. G.; Kondakov, N. N.; Zinin, A. I.; Chizhov, A. O.; Torgov,V. I.; Kachala,V. V.; Kononov, L. O. *Russian Chemical Bulletin, International Edition* **2015**, *64*,1149–1162; (c) Podvalnyy, N. M.; Chizhov, A. O.; Zinin, A. I.; Kononov, L. O. *Carbohydr. Res.* **2016**, *431*, 25–32; (d) Panova, M. V.; Podvalnyy, N. M.; Okun, E. L.; Abronina, P. I.; Chizhov, A. O.; Kononov, L. O. *Carbohydr. Res.* **2018**, *456*, 35–44.
15. (a) Thadke, S. A.; Mishra, B.; Hotha, S. *Org. Lett.* **2013**, *15*, 2466−2469; (b) Thadke, S. A.; Hotha, S. *Org. Biomol. Chem.* **2014**, *12*, 9914–9920; (c) 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** (doi:10.1038/ncomms14019)
16. (a) Lee, Y. J.; Lee, K.; Jung, E. H.; Jeon, H. B.; Kim, K. S. *Org. Lett*. **2005**, *7*, 3263–3266; (b) Lee, B. -Y.; Oh, J. W.; Baek, J. Y.; Jeon, H. B.; Kim, K. S. *J. Org. Chem*. **2016**, *81*, 11372−11383; (c) Deng, L. -M.; Liu, X.; Liang, X. -Y.; Yang, J. -S. *J. Org. Chem*. **2012**, *77*, 3025−3037; (d) Wang, H.; Ning, J. *J. Org. Chem.* **2003**, *68*, 2521−2524; (e) Wang, L.; Feng, S.; Wang, S.; Li, H.; Guo, Z.; Gu, G. *J. Org. Chem.* **2017**, *82*, 12085−12096; (f) Wang, L.; Feng, S.; An, L.; Gu,

G.; Guo, Z. *J. Org. Chem*. **2015**, *80*, 10060−10075; (g) Wu, Y.; Xiong, D. -C.; Chen, S. -C.; Wang, Y. -S.; Ye, X. -S. *Nat. Commun.* **2017**, *8*, 14851−14857.

17. (a) Torrelles, J. B.; Sieling, P. A.; Zhang, N.; Keen, M. A.; McNeil, M. R.; Belisle, J. T.; Modlin, R. L.; Brennan, P. J.; Chatterjee, D. *Glycobiology* **2012**, *22*, 1118−1127; (b) Batt, S. M.; Jabeen, T.; Bhowruth, V.; Quill, L.; Lund, P. A.; Eggeling, L.; Alderwick, L. J.; Fötterer, K.; Besra, G. S. *Proc. Nat. Acad. Sci. USA* **2012**, *109*, 11354−11359.
18. Mishra, B.; Neralkar, M.; Hotha, S. *Angew. Chem. Int. Ed.* **2016**, *128*, 7917–7922.
19. Mishra, B.; Manmode, S.; Panda, R. A.; Hotha, S. *Eur. J. Org. Chem.* **2017**, 4794−4802.
20. (a) Fraser-Reid, B.; Lu, J.; Jayaprakash, K. N.; López, J. C. *Tetrahedron: Asymm.* **2006**, *17*, 2449−2463; (b) Borman, S. *Chem. Engg. News* November 8, **2006**; (c) Ginsberg, A. M.; Spigelman, M. *Nature Med.* **2007**, *13*, 290−294; (d) Lowary, T. L. *Curr. Opin. Chem. Biol.* **2003**, *7*, 749−756.
21. (a) Ness, R. K.; Fletcher, Jr., H. G.; Hudson, C. S. *J. Am. Chem. Soc.* **1950**, *72*, 2200–2204; (b) Fiandor, J.; Garcia-Lopez, M. T.; de las Heras, F. G.; Mendez-Castrillon, P. *Synthesis* **1985**, 1121–l 123.

*****

Chapter 4

Synthesis of Hyper-branched N-linked Semi-conserved Core Hexasaccharide Motif of Chloroviruses

4.1 – Introduction

Chlorella viruses, mostly known as chloroviruses (CV) are plaque forming viruses, present in freshwater throughout the world and infect certain unicellular, eukaryotic, chlorella like green algae, also called Zoochlorellae.[1a] Although, the exact role chloroviruses plays in freshwater ecology is mostly unknown, but increasing evidences indicate that they probably play a dynamic role in regulating microbial/algal communities in ecosystem and contributing significantly to the global carbon and sulphur cycles.[1b,c] Chloroviruses are from the Phycodnaviridae family, which probably share a common ancestor with the poxviruses, iridoviruses, African swine fever virus, and Mimivirus[1d] (**Figure 4.1**).[1d] Based on the nature of their hosts, chloroviruses are categorized into four groups, such as (1) NC64A viruses that infect *Chlorella variabilis*, strain NC64A; (2) SAG viruses that infect *Chlorella heliozoae*, strain 3.83; (3) Syn viruses that infect a different strain of *Chlorella variabilis*, strain Syngen, and (4) Pbi viruses specific for *Micractinium conductrix,* stain Pbi.[1e]

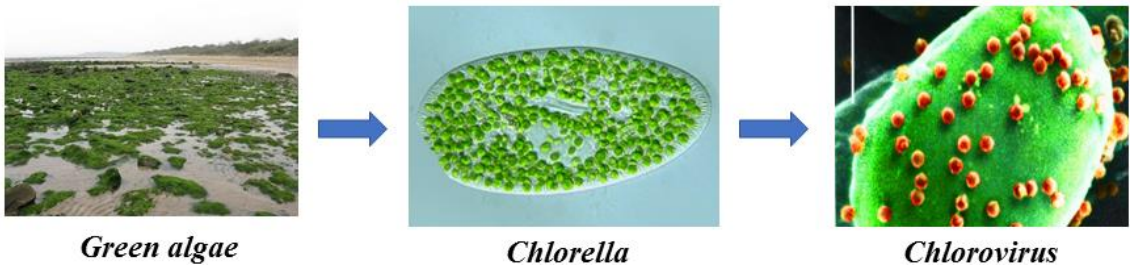


Figure 4.1: Representative images of green algae, chlorella and chlorovirus

Chloroviruses are large, icosahedral (190 nm in diameter), dsDNA-containing viruses with an internal lipid membrane. They have large genomes up to the size of 160 to 560 kb, which contains 330 to 416 protein encoding genes (PEGs). Along with the genetic diversity, these viruses contain various proteins which are quite unexpected for a virus.[1f] Till date, forty three types of chloroviruses from various chlorella hosts have been identified and their genomes were sequenced, assembled and annotated.[1g]

4.2. – Why it is so important?

There are three main reasons for which the in-depth study of chloroviruses are so important. These are as follows:

4.2.1 – The unique glycosylation machinery

One of the most important features these chloroviruses possess is the ability to use their own glycosylation machinery to encode most, if not all, of the components involved in manipulating carbohydrates.[1d] These include enzymes responsible for glycosylation to the major capsid proteins, enzymes that make extracellular polysaccharides, such as hyaluronic, chitin and enzymes involved in nucleotide sugar preparation such as GDP-L-fucose and UDP-L-rhamnose.[1g] It is also quite surprising that all glycosylations are independent of the endoplasmic reticulum (ER) and Golgi apparatus and probably occur in the cytoplasm of the infected cell, which is contrary to the traditional glycosylation process in all known viruses that use host endoplasmic reticulum and Golgi machinery to assemble and transfer the glycans during viral infection.[1g,2a]

The attachment of glycan part to the major capsid protein also does not follow the traditional protein *N*-glycosylation pathway, such as: (i) the asparagine (Asn) moiety of capsid protein connected to the β-D-glucose unit, not to the conventional *N*-acetylglucosamine or *N*-acetylgalactosamine unit; and (ii) none of the Asn- units located in a typical N-X-(T/S) sequence, usually act as a common acceptor site for prokaryotic or eukaryotic enzymes involved in protein *N*-glycosylation.[2b]

4.2.2 – Effect of chlorovirus ATCV-1 infection in cognitive functions in humans and mice

The presence of chlorovirus ATCV-1 in human oropharyngeal virome of 42 samples out of 92 individual (43.5%) and its association with a modest but statistically significant decline in the performance on cognitive assessments of visual processing and visual motor speed in human as well in mouse model as reported by Yolken *et al.*[2c] placed the chlorovirus in news lime light and people started to call it as 'stupid virus'. It was the first report of its kind where algae-infecting viruses are also causing infection in humans or animals, since cross kingdom viral infections are very rare. However in this report, it was not certain that whether the cognitive effects were arising due to virus, algae or both. Later, another report by Petro *et al.*[2d] confirmed the association of ATCV-1 infection with reduced cognitive function by directly injecting purified ATCV-1 intracranially into C57BL/6 mice and observing its results after 8-10 weeks in long-lasting cognitive and behavioral effects. Although, these results were not fully

accepted by whole scientific community due to insufficient statistical data, but one thing is sure that these viruses cross the blood-brain barrier, reach the central nervous system and cause the genetic mutation.[2c] As crossing the blood-brain barrier is highly challenging for any foreign particle, probably the capsid glycoproteins of chlorovirus ATCV-1 play crucial role in doing so.

4.2.3 – Industrial applications of green microalgae or chlorella algae

To date, microalgae are mostly known for their extensive use in the production of food compounds or high-value added compounds like carotenoids, for example, green microalgae *Chlorella vulgaris* from the genus *Chlorella* is a promising source for large-scale production of high value added proteins.[3a-c] Furthermore, due to the presence of photosynthetic machinery, green microalgae are highly efficient in the production of carbohydrates, lipids, and hydrogen by converting sunlight into chemical energy, which make them attractive as a potential new source for biofuels[3d] and biomaterials.[3e]

In addition, there is a growing interest in biopharmaceuticals industry, yielding overall global revenue greater than US$100 billion, to use microalgae as potentially attractive cell factories for biopharmaceutical production. In the last five years, 140 biopharmaceuticals that are produced in various systems ranging from bacteria to mammalian cell cultures, were approved in the European Union (EU) and the United States (US) markets.[3f] However, increasing needs, high production cost and viral contamination problems motivated scientists to explore microalgae as new alternative production system. In comparison of conventional expression systems, microalgae are cheap, easy to grow and like plants and hence, classified in Generally Recognized as Safe (GRAS) organisms. These advantages make them excellent candidates for the large-scale production of recombinant proteins.[3f] Therefore, viral infection of these green microalgae could severely impact the biopharmaceutical and food industry in much way and to eradicate the infection, proper study of these viruses from chlorovirus family is highly important.

4.3 – Structure of the chlorovirus PBCV-1 major capsid glycoprotein

Paramecium bursaria chlorella virus type 1 (PBCV-1) is an NC64A virus which infects *C. variabilis* and was first isolated in 1983.[4a] Cryo-electron microscopy and five fold symmetry averaging three-dimensional reconstruction of PBCV-1 indicated that the

unicellular virus has a multilayer structure consisting of a large (190nm in diameter) outer icosahedral capsid shell, a single lipid bilayered membrane and an inner protein core enclosing the large virus DNA (**Figure 4.2**).[4b] PBCV-1 contains about 64% protein, 21 to 25% dsDNA, and 5 to 10% lipid.[4a] It has been found that presence of the lipid bilayer is crucial for the host infection.[4c] Furthermore, one of the PBCV-1 vertices has a long (560Å) spike structure that projects from the surface and probably help in chlorella algae′s cell wall penetration during infection stage. The projected part of the spike structure is 340Å in length and external diameter varies from 35Å at the tip to 70Å at the base. The spike further widens up inside the capsid and forms a closed cavity between the capsid and inner membrane,

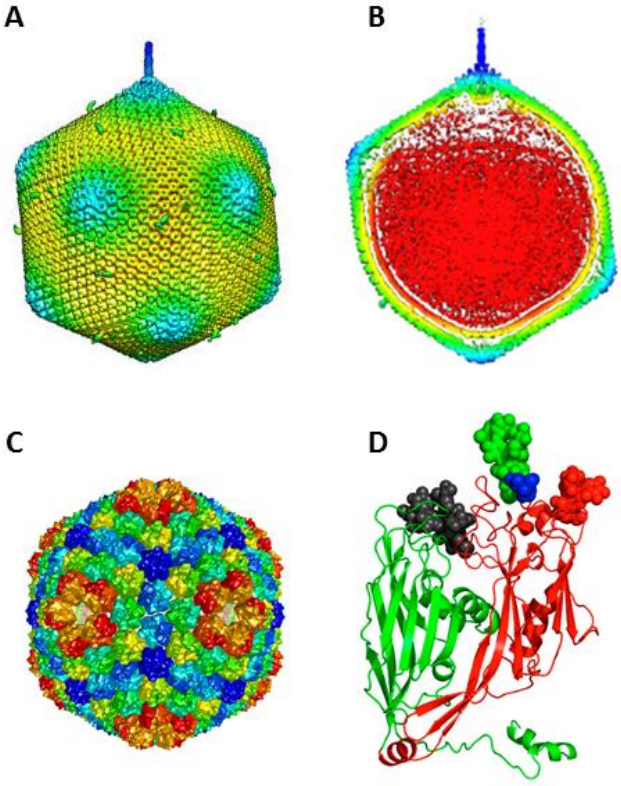


Figure 4.2: (**A**) Fivefold averaged cryo-electron micrograph (cryoEM) of PBCV-1.[4d] (**B**) Central cross-section of the cryoEM density of PBCV-1.[4d] (**C**) The outer icosahedral capsid shell of PBCV-1.[4h] (**D**) Structure of the revised PBCV-1 Vp54 glycoprotein monomer.[1g]

resulting in the icosahedral symmetry loss of viral membrane adjacent to unique vertex (**Figure 4.2**).[4d] The outer icosahedral capsid shell comprises of 20 triangular units (trisymmetrons, each containing 66 trimers) and 12 pentagonal caps (pentasymmetrons, each containing 30 trimers and one pentamer at the icosahedral vertices) at the fivefold

vertices. The outer diameter of the viral capsid measured along the two- and threefold axes is 1,650Å, wherein along the fivefold axes, it is somewhat elongated with a diameter of 1,900Å. The cell capsid also contains some external fibres which probably help in host attachment (**Figure 4.2**).[4e-g]

4.4 – Glycan Structures of Major Capsid Proteins from different Chloroviruses

Early report on the crystal structure of PBCV-1 major capsid protein Vp54 suggested the presence of two *O*-linked and four *N*-linked glycosylation sites.[4b] However, a recent study by DeCastro revealed the absence of any type of *O*-glycosylation sites in the Vp54 glycoprotein.[5a] Combined approach of NMR and MALDI-TOF spectrometry have been used for fully characterizing all *N*-linked glycans associated with the Vp54 major capsid glycoprotein. There are four types of *N*-linked glycoforms present on Vp54 capsid glycoprotein consisting of 8–10 neutral monosaccharide residues.

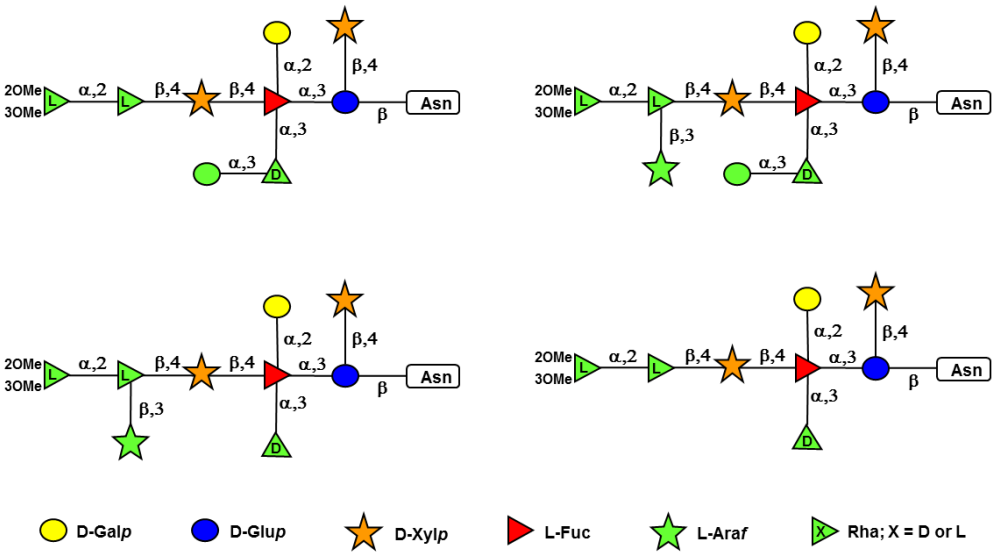


Figure 4.3: Four types of N-linked glycoforms present on Vp54 protein of PBCV-1[2b]

The structures of these glycans are quite unique and do not resemble any glycoform reported earlier in bacteria, archaea and eukarya.[2b] The glycosylation process probably occurs in the cytoplasm rather than the endoplasmic reticulum (ER).[1d,4g] Some of the unusual features that these glycans possesses are: (i) the glycan part attached to the asparagine residue of protein via a β-D-glucose linkage, which is very uncommon and observed only in very few organisms;[5b-d] (ii) The glycoforms share a highly branched

common core structure in which the central fucose residue is substituted at all the available positions along with two rhamnose residues with opposite configurations (L-Rha or D-Rha) and a dimethylated rhamnose as the capping residue; (iii) Two monosaccharides, L-arabinose and D-mannose, present as non-stoichiometric substituents; and (iv) The most abundant glycoform is a nonasaccharide, lacking L-arabinose residue at Asn-302, Asn-399, and Asn-406 of glycoprotein Vp54 (**Figure 4.3**).[5a]

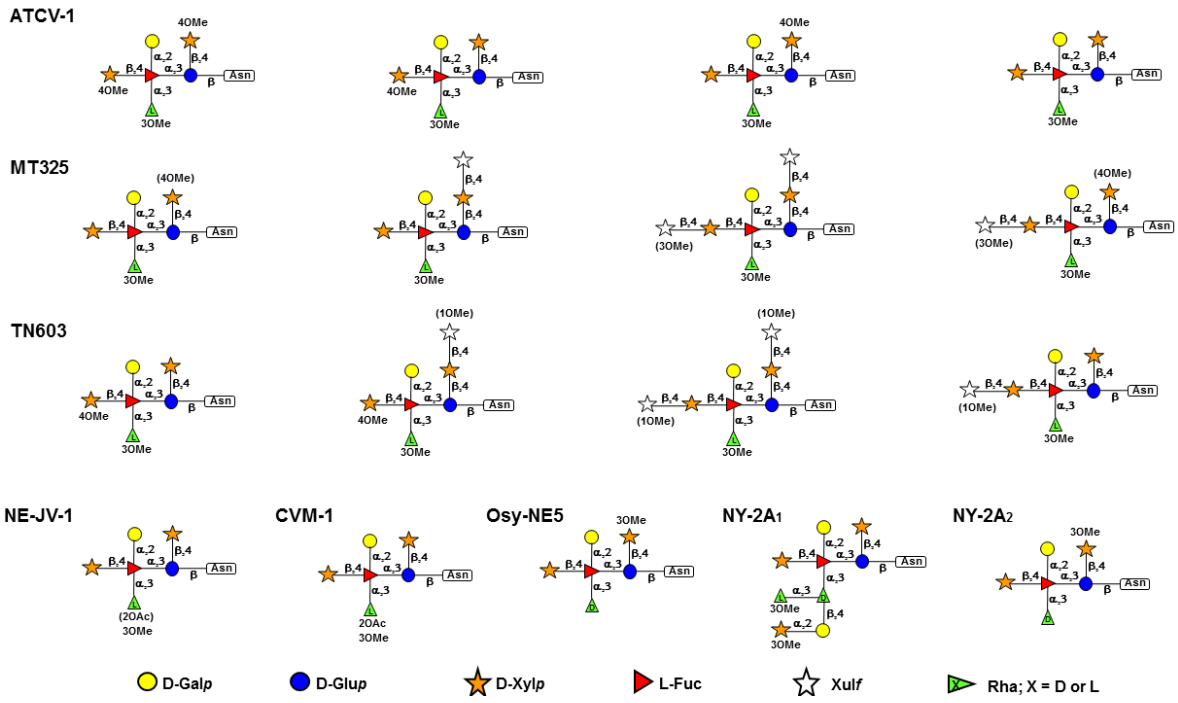


Figure 4.4: Structures of *N*-glycans from seven chloroviruses representing all four chlorovirus types[1g,5f]

Furthermore, analysis of glycan structures of major capsid proteins from seven other chloroviruses that belong to the same PBCV-1 genus {but with different host specificities such as: NY-2A (NC64A virus); OSy-NE5 (OSy viruses); ATCV-1 and TN603 (SAG viruses); and MT325, CMV-1 and NE-JV-1 (Pbi viruses)} has revealed that all these chloroviruses possess *N*-linked glycans with a common core region (**Figure 4.4**).[5e-g] The core motif contains a highly branched hexasaccharide with a hyperbranched fucose unit at the centre, two xylose units (one proximal and one distal xylose), one terminal galactose unit, one glucose unit at the reducing end which is further attached to the asparagine (Asn) moiety of protein in a distinctive X-Asn-(Thr/Ser) sequence and a semi-conserved rhamnose unit, configuration of which is

highly dependent on virus type; for example, NC64A and Syn viruses have the D-isomer of rhamnose and Pbi and SAG viruses contain the L-isomer along with methylation at *O*-3 position (**Figure 4.5**).

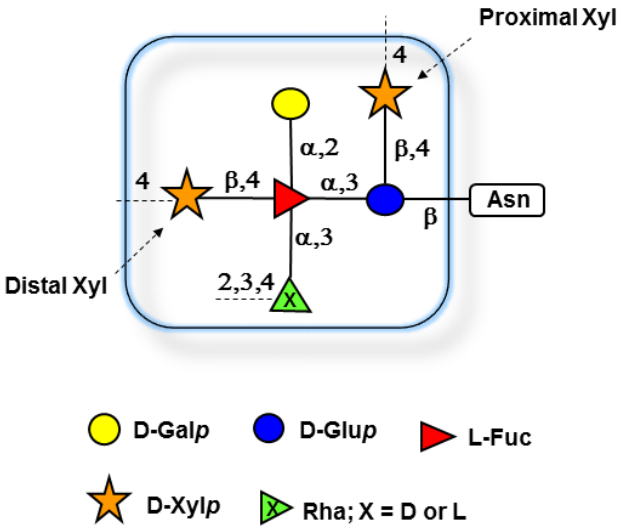


Figure 4.5: Oligosaccharide core structure common to the N-glycans of the MCPs from seven different chloroviruses[1g,5f]

Although, a conserved core structure is present in all chloroviruses, decoration with methyl, acetyl or sugar residue make the *N*-linked glycan a unique signature for each chloroviruses.

4.5 – Present work

Successful syntheses of linear nonadecaarabinofuranoside motif of arabinogalactan (AG) part and highly branched tridecasaccharide reminiscent of lipoarabinomannan (LAM) part from Mtb cell wall exploiting our recently developed [Au]/[Ag] catalysed glycosyl alkynyl carbonate donor chemistry inspired us to apply our glycosylation protocol for the synthesis of a highly branched *N*-linked semi-conserved hexasaccharide core structure present in all seven different types of chloroviruses. In this premise, the *N*-linked hexasaccharide (**1**) from chlorovirus ATCV-1 was chosen as model synthetic target which is reasonably unique in many ways (**Figure 4.6**), such as: (i) the core hexasaccharide contains five different sugar residues in pyranose form; (ii) hyper branched central L-Fucose unit is connected to four different sugar residues; (iii) presence of four 1,2-*trans* glycosidic linkages and two synthetically challenging 1,2-*cis* glycosidic linkages; (iv) existence of glycosidic amide bond [Sugar–NHCOR] at the reducing end of glucose unit instead of commonly observed *N*-acetylglucosamine or *N*-acetylgalactosamine unit; and (v) attachment of sterically crowded asparagine residue [i.e. N-T instead of N-X-T sequence, where N = L-asparagine, T = L-threonine and X = any L-amino acids except L-proline].

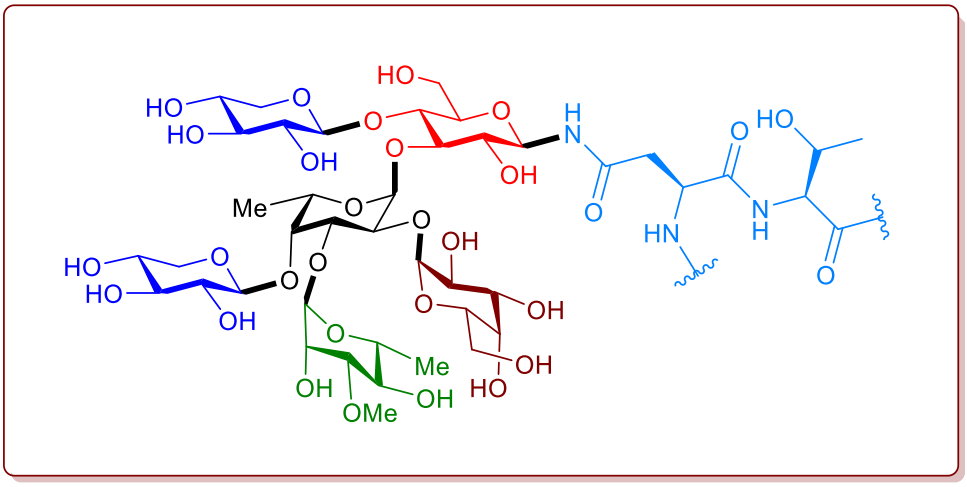
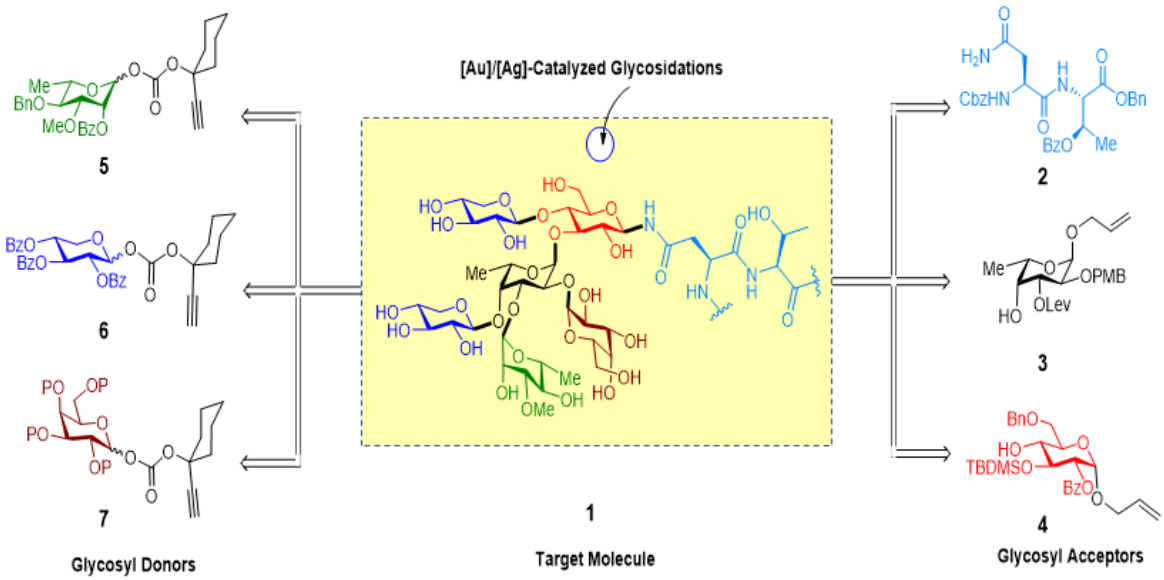


Figure 4.6: N-linked core hexasaccharide from chlorovirus ATCV-1 as synthetic target

4.5.1 – Retrosynthetic analysis of the *N*-linked hexasaccharide

The presence of different types of glycosidic linkages and branching in the *N*-linked hexasaccharide **1** poses adequate challenges for its synthesis. Major challenges for the

hexasaccharide synthesis are: (i) synthesis of hyperbranched central L-fucose unit, (ii) stereoselective installation of α(1→2)-galactose residues at *C*2-position of fucose, (iii) stereoselective installation of α(1→3)-fucose residue at *C*3- position of glucose, (iv) attachment of less nucleophilic N-T dipeptide unit to the reducing end of hexasaccharide unit and (iv) preparation of glycosyl carbonate donor at highly branched tetra-and hexasaccharide level. A careful retrosynthetic analysis of the *N*-linked hexasaccharide **1** was carried out considering all these facts along with the salient features of our newly discovered [Au]/[Ag]-catalysed alkynyl carbonate donor chemistry. The retrosynthetic disconnection of the target *N*-linked hexasaccharide **1** revealed that it can be synthesized from six building blocks, out of which three building blocks (**2**, **3** and **4**) can be used as glycosyl acceptors and three others (**5**, **6** and **7**) as glycosyl donors. Hexasaccharide **1** contains 1,2-*trans* as well as 1,2-*cis* glycosidic linkages. Formation of 1,2-*trans* glycosidic bond using our [Au]/[Ag]-catalysed glycosylation protocol can be easily accomplished by invoking neighboring group participation from the C2-benzoyl protecting group on the glycosyl donor. However, preparation of synthetically more challenging 1,2-*cis* glycoside products using glycosyl carbonate donor chemistry has not been achieved earlier and thus, requires additional optimization studies.

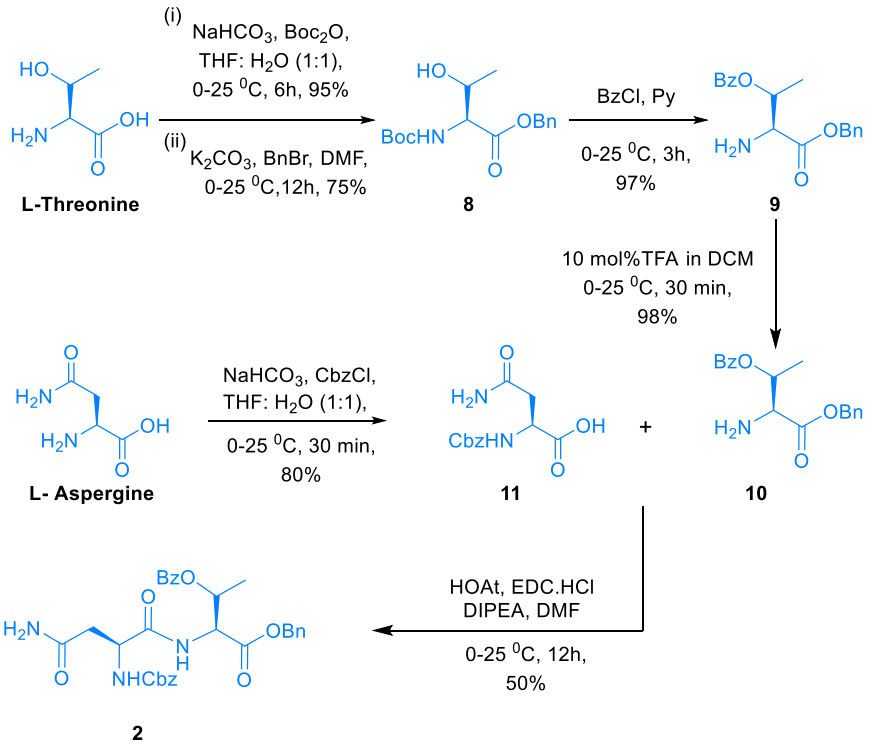


Scheme 4.1: Retrosynthetic analysis of N-linked hexasaccharide target molecule

Our synthetic endeavor started with the synthesis of identified building blocks required for the synthesis of target molecule **1**.

4.5.2 – Preparation of building block 2

Reaction of L-threonine with Boc_2O in presence of $NaHCO_3$ in THF-H_2O (1:1) and subsequent treatment with BnBr using K_2CO_3 base in DMF generated the partially protected L-threonine compound **8** in 71% yield over two steps. Further protection of compound **8** with BzCl/Py generated the fully protected L-threonine derivative **9**, which upon treatment with 10 mol% TFA in DCM resulted in the formation of amine **10** in excellent yield.

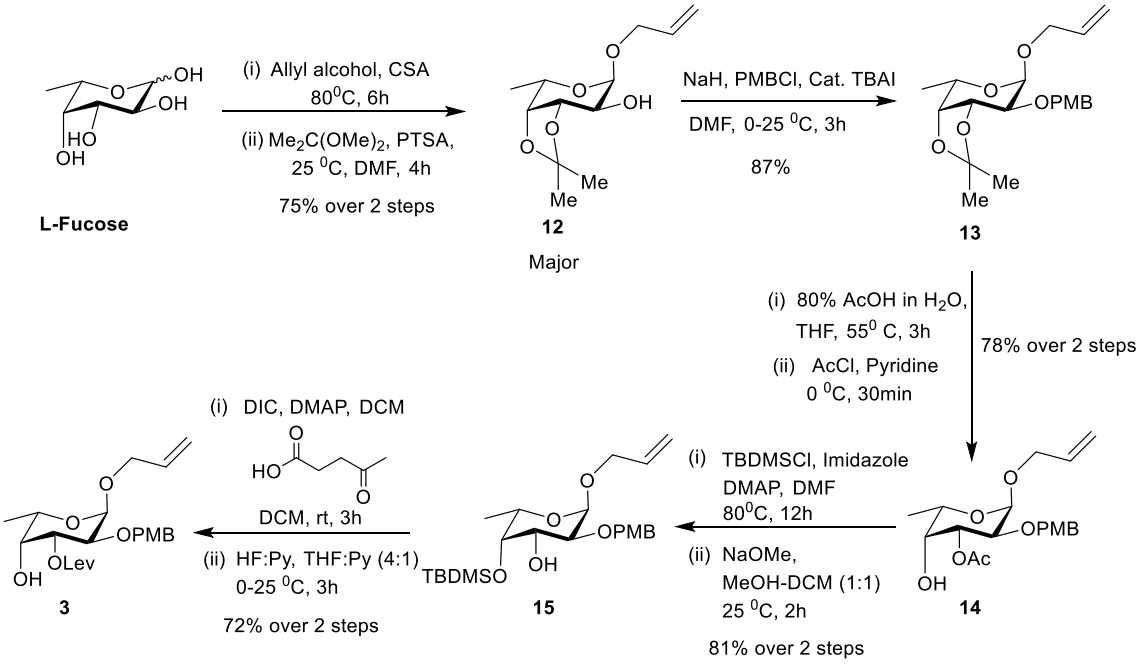


Scheme 4.2: Synthesis of di-peptide building block 2

Similarly, -Cbz protected L-asparagine **11** was prepared from L-asparagine using CbzCl/$NaHCO_3$ in THF-H_2O (1:1) solvent mixture in 80% yield. Amino acid derivatives **10** and **11** were coupled using standard HOAt and EDC.HCl as coupling reagents in the presence of DIPEA base in DMF to afford the desired di-peptide (Asn-Thr) **2** in moderate yield (50%) (**Scheme 4.2**). In the ^{13}C NMR spectrum of compound **2**, appearance of six characteristic carbonyl signals between δ 156.9–172.4 ppm and -$\underline{C}H_3$ signals at δ 16.9 ppm along with other residual resonances as per the assigned structure confirmed the formation of di-peptide **2**. In addition, di-peptide **2** was confirmed by HRMS analysis, *m/z* calculated for $C_{30}H_{31}N_3O_8Na^+$, [M+Na^+]: 584.2009; Found: 584.2017.

4.5.3 – Preparation of building block 3

Reaction of L-fucose with allyl alcohol in the presence of catalytic CSA at 80 °C for 6 h, followed by acetonide protection using 2,2-dimethoxy propane and catalytic amount PTSA in DMF at 25 °C for 4 hours produced the acetonide protected allylfucoside as α/β-mixture from which α-allylfucoside **12** was isolated as a major product (75%). The remaining alcohol of acetonide **12** was protected as a *p*-methoxybenzyl ether using PMBCl/NaH/DMF to form the PMB-ether **13** in 87% yield. Subsequent deprotection



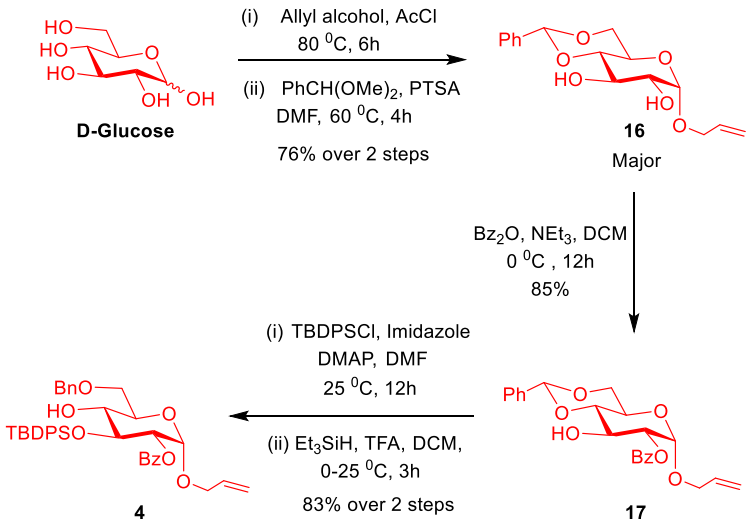
Scheme 4.3: Synthesis of central L-fucose building block 3

of acetonide using 80% AcOH in H_2O-THF at 55 °C for 3 h followed by the regioselective acetylation at *C*3-position using AcCl/Py at 0 °C afforded the required allylfucoside **14** in 87% yield over two steps. Furthermore, silylation of **14** at *C*4-*O* positon with TBDMSCl/Imidazole in DMF and consequent deprotection of the acetyl group using NaOMe in MeOH-DCM (1:1) solvent system advanced the formation of fucoside alcohol **15** in good yield. Finally, coupling of levulinic acid with the alcohol **15** in presence of DIC/DMAP in DCM at room temperature, followed by the cleavage of the silyl ether using HF/Py in THF-Py (5:1) afforded the desired alcohol **3** as an acceptor in good yield (**Scheme 4.3**).

Formation of the central fucose building block **3** was confirmed by the NMR and mass spectral analysis. In the ^{1}H NMR spectrum of compound **3**, anomeric proton appeared as a singlet at δ 5.17 ppm merged with other sugar protons whereas resonances due to vinylic-C<u>H</u> moiety and three -C<u>H</u>$_3$ moieties (from fucose sugar, PMB ether and Lev- ester group) were noticed at δ 5.87 (dddd, *J* = 17.1, 10.4, 6.1, 5.3 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 2.13 (s, 3H) and 3.75 (s, 3H) ppm respectively. Remaining pyranosidic ring protons appeared between δ 3.60–5.28 ppm. In the ^{13}C NMR spectrum, characteristic anomeric carbon was observed at δ 96.0 ppm, vinylic carbons were identified at δ 117.9 (<u>C</u>H$_2$) and 133.9 (<u>C</u>H) ppm. Further, resonances due to two carbonyls at δ 172.9 and 206.9 ppm along with one -<u>C</u>H$_3$ carbon at δ 55.3 ppm revealed the presence of Lev and PMB protecting groups respectively. All other resonances in the ^{13}C NMR spectrum of compound **3** matched perfectly with the assigned structure. In addition, compound **3** was further confirmed by HRMS analysis, *m/z* calculated for $C_{22}H_{30}O_8Na^+$, [M+Na^+]: 445.1838; Found: 445.1831.

4.5.4 – Preparation of building block 4

Conversion of D-glucose under modified Fischer glycosidation conditions with allyl alcohol, catalytic amount of AcCl at 80 ^{o}C for 6 hours afforded the allyl glucopyranoside which was directly taken for the benzylidine protection using benzaldehyde di-methylacetal and catalytic amount of PTSA in DMF at 60 ^{o}C for 4 h to afford the benzylidine protected glucoside **16** as major product in 76% yield.



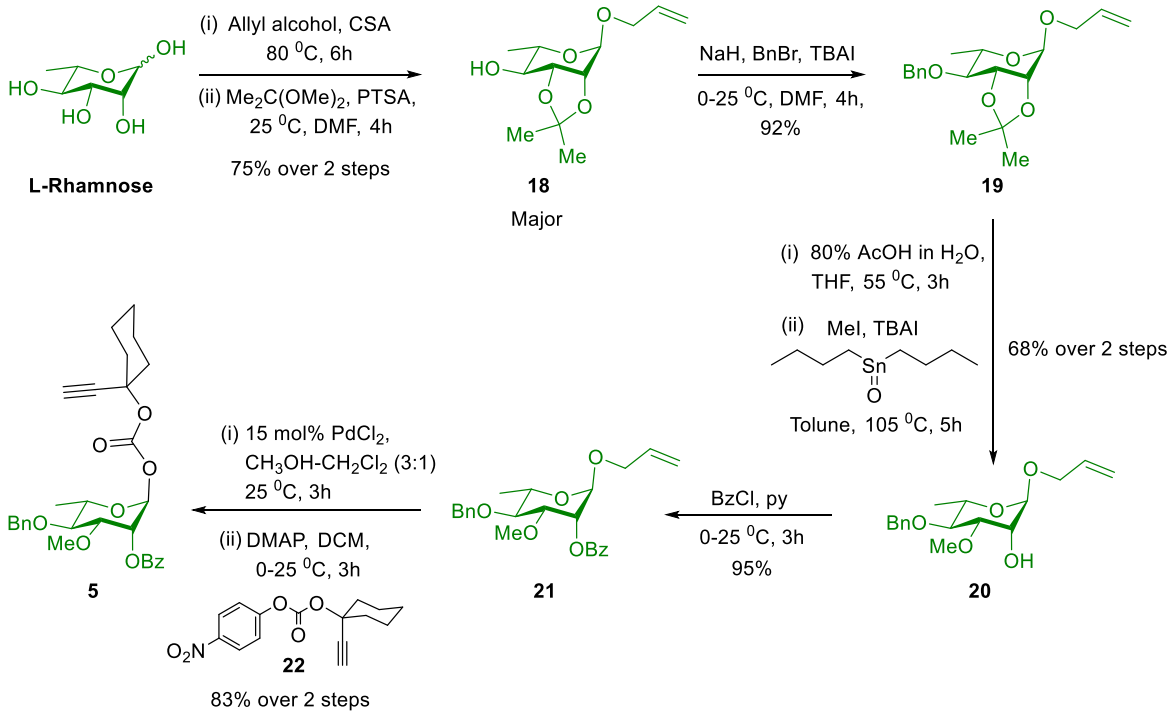
Scheme 4.4: Synthesis of glucose building block 4

Selective protection of benzoyl group at *C*2-*O* positon of compound **16** was carried out using Bz_2O/NEt_3 in DCM at 0 ^oC for 12 hours afforded benzoate **17**. Silylation of compound **17** at *C*3-*O* positon with TBDPSCl /Imidazole /cat. DMAP in DMF at room temperature for 12 hours followed by the reductive cleavage using Et_3SiH and TFA in DCM generated the desired glucoside acceptor **4** in 83% yield over two steps (**Scheme 4.4**). Formation of the glucose building block **4** was confirmed by the thorough NMR and mass spectral analysis. In the ^1H NMR spectrum of compound **4**, resonances due to vinylic-C<u>H</u> moiety and the *tert*-butyl group of the TBDPS-group were noticed at δ 5.86 (dddd, *J* = 16.6, 10.4, 5.8, 5.1 Hz, 1H) and at δ 0.95 (s, 9H) ppm respectively. Remaining pyranosyl ring protons appeared between δ 3.66–5.23 ppm. In the ^{13}C NMR spectrum, characteristic anomeric carbon was observed at δ 95.3ppm whereas vinylic carbons were identified at δ 116.7(<u>C</u>H_2) and 134.3 (<u>C</u>H) ppm. Resonance due to benzoyl carbonyl carbon was noticed at δ 166.2 ppm. All other resonances in the ^{13}C NMR spectrum of compound **4** matched perfectly with the assigned structure. Compound **4** was further confirmed by HRMS analysis, *m/z* calculated for $C_{39}H_{44}O_7Na^+$, [M+Na^+]: 675.2754; Found: 675.2758.

4.5.5 – Preparation of building block 5

Preparation of building block **5** was initiated by reacting L-rhamnose with allyl alcohol in presence of catalytic amount CSA at 80 ^oC for 6 hours followed by acetonide protection using 2,2-dimethoxy propane and catalytic amount PTSA in DMF at 25 ^0C for 4 hours produced the acetonide protected α-allyl rhamnoside **18** as a major product in 75% yield over two steps. Benzylation of the allyl rhamnoside **18** at *C*4-*O* positon was carried out using BnBr/NaH/TBAI in DMF to form the allyl rhamnoside **19** in 92% yield. Further hydrolysis of the acetonide using 80% AcOH in H_2O-THF solvent at 55 ^oC for 3 hours, followed by the stannylene mediated regioselective methylation at *C*3-*O* positon using MeI/TBAI/Bu_2SnO in toluene at 105 ^0C for 5 hours afforded the allyl rhamnoside **20** in 68% yield over two steps. Benzoyl protection at *C*4-*O* position of compound **20** employing BzCl/Py led to the formation of allyl glucoside **21** in 95% yield.

Hydrolysis of the anomeric allyl moiety of allyl rhamnoside **21** employing $PdCl_2$ in MeOH-DCM (3:1) afforded a hemiacetal that was directed taken for the next reaction

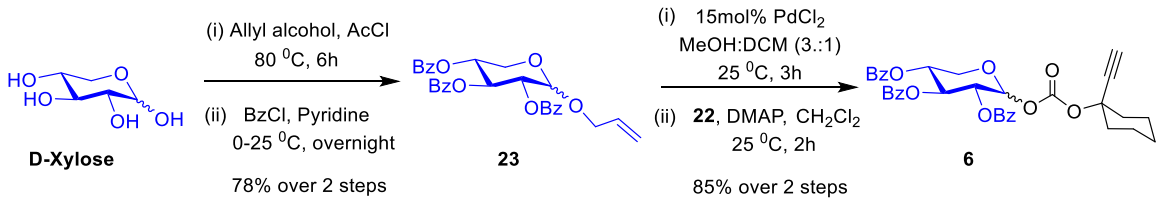


Scheme 4.5: Synthesis of rhamnose building block 5

with easily available ethynylcyclohexyl (4-nitro phenyl) carbonate **22**[6] in the presence of DMAP to afford the desired rhamnosyl alkynyl carbonate donor **5** in 83% yield over two steps (**Scheme 4.5**). Formation of carbonate donor **5** was confirmed by NMR and mass spectral analysis. In the ^{1}H NMR spectrum of compound **5**, resonance due to the anomeric proton was noticed at δ 5.86 (d, *J* = 2.9 Hz) ppm. Resonances due to -C<u>H</u>$_3$ proton was observed at δ 1.44 ppm, whereas -C<u>H</u>$_2$ protons from cyclohexylpropargyl moiety resonated between δ 1.24–2.63 ppm. In the ^{13}C NMR spectrum, anomeric carbon was observed to resonate at δ 94.0 ppm. Characteristic resonance of carbonate carbon appeared at δ 151.1ppm; whilst resonance due to carbonyl carbon from benzoyl moiety was found at δ 165.8 ppm. Furthermore, appearance of -<u>C</u>H$_3$ carbons at δ 57.6 ppm along with other residual carbons as per the assigned structure indicated the successful formation of carbonate donor **5** as α/β mixture. In addition, rhamnose donor **5** was further confirmed by HRMS analysis, *m/z* calculated for $C_{30}H_{34}O_8Na^+$, [M+Na$^+$]: 545.2151; Found: 545.2156.

4.5.6 – Preparation of building block 6

Synthesis of building block commenced with the reaction of D-xylose with allyl alcohol

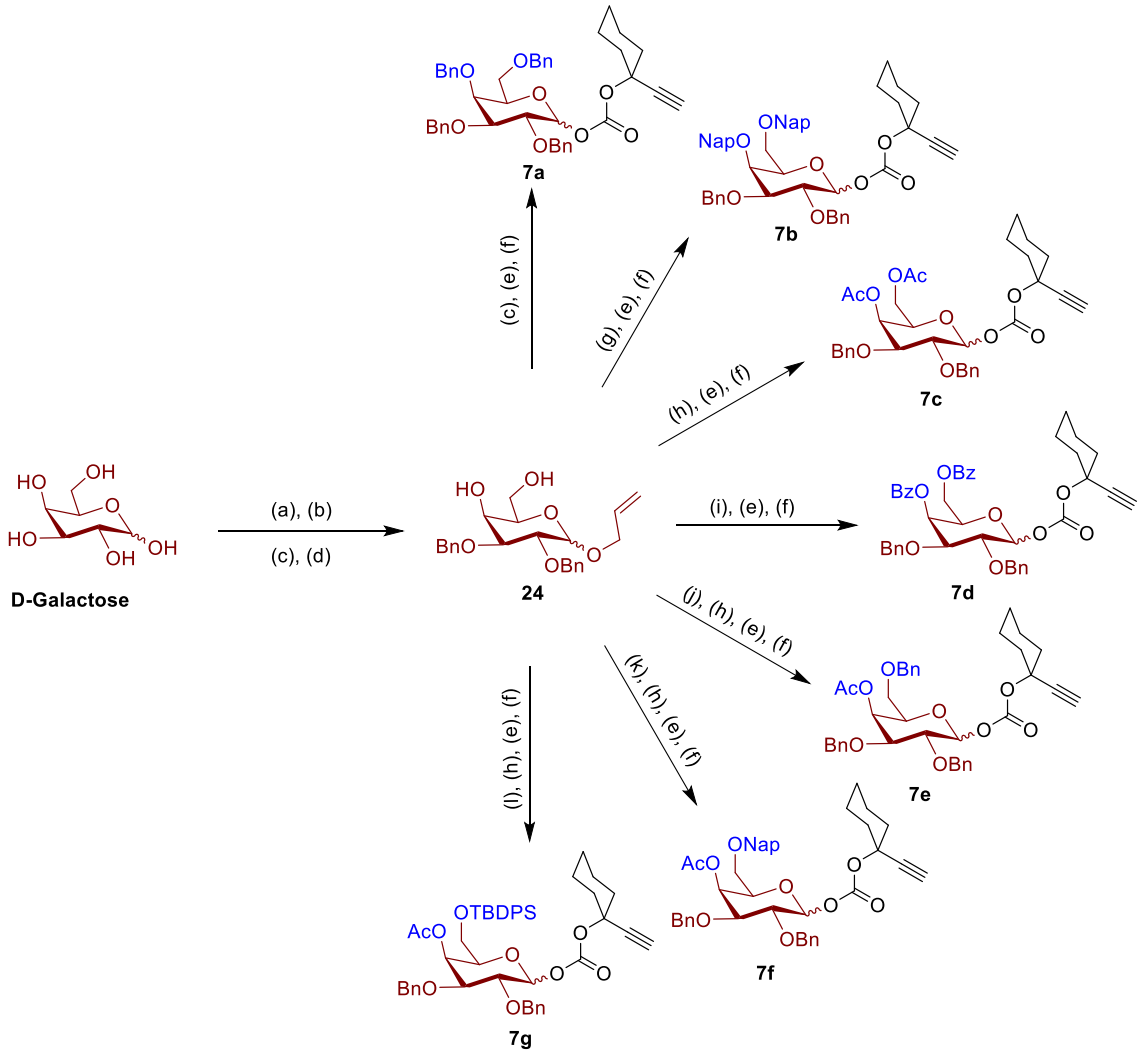


Scheme 4.6: Synthesis of xylose building block 6

in presence of catalytic amount of AcCl at 80 °C for 6 hours, followed by benzoylation using BzCl/Py/DMAP produced the per-*O*-benzoylated allyl xylopyranoside **23** as α/β mixture in 78% yield over two steps. Subsequent hydrolysis of the anomeric allyl moiety of xyloside **23** under aforementioned conditions followed by the reaction with easily available ethynylcyclohexyl (4-nitro phenyl) carbonate **22** in presence of DMAP afforded the xylopyranosyl alkynyl carbonate donor **6** in 85% yield over two steps (**Scheme 4.6**). Formation of carbonate donor **6** was confirmed by the NMR and mass spectral analysis. In the ^{1}H NMR spectrum of compound **6**, two anomeric protons (α/β mixture) appeared to resonate between δ 5.71–6.53 ppm. Resonances due to -C$\underline{H}_2$ protons from xyopyranoside ring were observed between δ 4.27–4.59 ppm, whereas -C$\underline{H}_2$ protons from cyclohexyl propargyl moiety resonated between δ 1.29–2.65 ppm. In the ^{13}C NMR spectrum, two anomeric carbons (α/β mixture) were noticed to resonate at δ 92.8 and 94.8 ppm. Characteristic resonances of carbonate carbons were identified at δ 150.8 and 150.9 ppm, whereas resonances due to carbonyl carbons from benzoyl moiety were found between δ 164.9–165.8 ppm. Furthermore, appearance of other residual carbons as per the assigned structure indicated the successful formation of carbonate donor **6** as α/β mixture. In addition, xylopyranosyl donor **6** was further confirmed by HRMS analysis, *m/z* calculated for $C_{35}H_{32}O_{10}Na^{+}$, [M+Na^{+}]: 635.1893; Found: 635.1891.

4.5.7 – Preparation of various galactose building blocks (7a-g)

One of the most challenging aspects in the synthesis of hexasaccharide **1** is the installation of 1,2-*cis* galactopyranosidic linkage. As delineated above, installation of 1,2-*trans* linkages can be easily achieve by invoking the neighboring group participation. However, the 1,2-*cis* linkages are known to be much tougher to obtain. To study this reaction in detail, several substituted galactoside derivatives **7a-7g** are



Scheme 4.7: Synthesis of various galactosyl carbonate donors. Reagents: (a) Allyl alcohol, AcCl, 80 ^{0}C, 6 h, 85%; (b) $PhCH(OMe)_2$, PTSA, DMF, 60 ^{0}C, 4 h, 90%; (c) 2.5 equiv. BnBr, NaH, TBAI, DMF, 0-25 ^{0}C, 5 h, 94% for **24** and 96% for **7a** ; (d) PTSA, CH_2Cl_2-MeOH (1:1), 25 ^{0}C, 2 h, 96%; (e) $PdCl_2$, CH_2Cl_2-MeOH (1:3), 25 ^{0}C, 3 h, 96% for **7a**, 94% for **7b**, 92% for **7c**, 95% for **7d**, 93% for **7e**, 92% for **7f** and 94% for **7g** respectively; (f) 1-ethynylcyclohexyl (4-nitrophenyl) carbonate (**22**), DMAP, CH_2Cl_2, 25 ^{0}C, 3 h, 95% for **7a**, 93% for **7b**, 94% for **7c**, 92% for **7d**, 95% for **7e**, 96% for **7f** and 93% for **7g** respectively; (g) 3 equiv. NapBr, NaH, TBAI, DMF, 0-25 ^{0}C, 12 h, 86%; (h) AcCl, pyridine, DMAP, 0-25 ^{0}C, 4 h, 94% for **7c**, 96% for **7e**, 95% for **7f**, 92% for **7g**; (i) BzCl, pyridine, DMAP, 0-25 ^{0}C, 6 h, 96%; (j) 1.2 equiv. BnBr, NaH, TBAI, DMF, 0-10 ^{0}C, 5 h, 78%; (k) 1.5 equiv. NapBr, NaH, TBAI, DMF, 0-25 ^{0}C, 12 h, 80%; (l) TBDPS-Cl, Imidazole, DMF, 0-25 ^{0}C, 4 h, 90%.

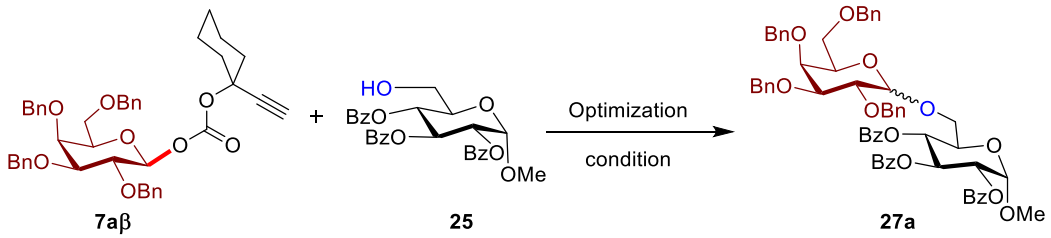
envisaged. Synthesis of them started with the reaction of D-galactose with allyl alcohol in presence of catalytic AcCl at 80 ^{0}C for 6 hours, followed by 4,6-benzylidine protection using benzaldehyde di-methylacetal and catalytic amount PTSA in DMF at 60 ^{0}C for 4 hours produced the benzylidine protected allylgalactoside as α/β-mixture that upon subsequent reaction with BnBr/NaH/TBAI in DMF afforded corresponding benzyl ether. The resulting benzylidene was subjected to ring opening using PTSA in DCM-MeOH (1:1) solvent system to afford the allyl di-*O*-benzyl galactoside **24** in 69% over four steps (**Scheme 4.6**).

Galatosyl carbonate **7a** was obtained from allyl galactoside **24** in 86% over three steps *viz.* benzylation of **24** using BnBr/NaH/TBAI in DMF, hydrolysis of anomeric allyl moiety with $PdCl_2$ in MeOH-DCM (3:1) and finally, reaction with carbonate reagent **22** and DMAP in DCM (**Scheme 4.6**). In a similar fashion, carbonate donor **7b** was achieved from **24** in 74% over three steps; *viz.* di-*O*-napthyl protection of **24** using NapBr/NaH/TBAI in DMF, hydrolysis of anomeric allyl moiety with $PdCl_2$ in MeOH-DCM (3:1) binary solvent and finally, reaction with carbonate reagent **22**/DMAP in DCM (**Scheme 4.6**). Conversion of **24** to carbonate donors **7c** was proceeded via three steps in overall 81% yield; *viz.* acetyl protection of **24** using AcCl/DMAP in pyridine, hydrolysis of the anomeric allyl moiety with $PdCl_2$ in MeOH-DCM (3:1) binary solvent system and treatment with carbonate reagent **22**/DMAP in DCM. Likewise, allyl galactoside **24** was transformed to donor **7d** in 84% over three steps; *viz.* benzoyl protection of **24** using BzCl/DMAP in pyridine as a solvent, hydrolysis of anomeric allyl moiety with $PdCl_2$ in MeOH-DCM (3:1) binary solvent and the final reaction with carbonate reagent **22**/DMAP in DCM (**Scheme 4.6**). Treatment of **24** with 1.2 equiv. of BnBr in presence of NaH and catalytic TBAI in DMF solvent, followed by three subsequent steps; *viz.* acetyl protection using AcCl/DMAP in pyridine, hydrolysis of anomeric allyl moiety with $PdCl_2$ in MeOH-DCM (3:1) and reaction with carbonate reagent **22**/DMAP in DCM afforded the carbonate donor **7e** in overall 75% yield (**Scheme 4.6**). In a similar way, reaction of **24** with 1.5 equiv. of NapBr in presence of NaH and catalytic TBAI in DMF solvent, followed by three subsequent steps; *viz.* acetyl protection using AcCl/DMAP in pyridine, hydrolysis of anomeric allyl moiety with $PdCl_2$ in MeOH-DCM (3:1) and reaction with carbonate reagent **22**/DMAP in DCM resulted in the formation carbonate donor **7f** with 71% yield over four steps (**Scheme 4.6**). The next envisaged carbonate donor **7g** was obtained from **24** in 72%

over four steps; *viz.* silylation of **24** at *C*6-*O* positon with TBDPSCl /Imidazole /cat. DMAP in DMF, acetyl protection at *C*4-*O* positon using AcCl/DMAP in pyridine, hydrolysis of anomeric allyl moiety with $PdCl_2$ in MeOH-DCM (3:1) and finally treatment with carbonate reagent **22**/DMAP in DCM (**Scheme 4.6**). Formation of all the galactosyl carbonate donors **(7a**, **7b**, **7c**, **7d**, **7e**, **7f** and **7g)** were confirmed by NMR and mass spectral analysis.

4.5.8 – Stereoselective *1,2-cis* glycosylation of galactose residue

Our journey on stereoselective 1,2-*cis* glycosylation of galatose residue commenced with the use of our recently developed [Au]/[Ag]- catalysed alkynyl carbonate donor chemistry. Based on the earlier reports of 1,2-*cis* glycosidic bond formation,[7-13] we



Scheme 4.7: Optimization for stereoselective α-galactoside preparation

planned to use the 1,2-*trans* (or β-) isomer of per *O*-benzyl galactosyl alkynyl carbonate (**7aβ**) as glycosyl donor for better α-selectivity and sugar primary alcohol **25**[6c] as a model glycosyl acceptor. Keeping all the factors[7-12] in mind that contribute to the outcome of overall selectivity, a large number of conditions were investigated.

4.5.8.1 – Solvent effect

As explained in the chapter 1, outcome of the glycosylation depend largely on the solvent conditions. In an effort to find the best solvent system for the α-galactosylation, different solvents were screened in presence of 10 mol% each of Au-phosphite **26a** and AgOTf and 4Å molecular sieves powder. The halogenated solvents were found to be superior than other solvents in terms of higher yield and better α-selectivity. The glycosylation reaction did not proceed at all in presence CH_3NO_2 or oxygenated solvents such as DME, THF and 1,4-dioxane. Use of CH_3CN as a solvent was not effective both in terms of selectivity and glycosylation yield. The galactosylation yield decreased significantly without much improvement in α-selectivity when ethereal

solvents are employed. Use of toluene was not encouraging as it increased the β-glycoside product formation. Out of various chlorinated solvents, bromobenzene and

Entry	Solvent	Time	α : β	Yield (%)
1	DCM	15 min	3.5:1.0	98
2	DCE	20 min	3.0:1.0	96
3	$CHCl_3$	15 min	6.0:1.0	97
4	CCl_4	30 min	3.0:1.0	93
5	TCE	15 min	4.0:1.0	95
6	1,2-Dichlorobenzene	30 min	6.0:1.0	95
7	Fluorobenzene	30 min	5.0:1.0	92
8	Chlorobenzene	30 min	8.0:1.0	97
9	Bromobenzene	30 min	10.0:1.0	89
10	Hexafluorobenzene	30 min	6.5:1.0	75
11	1,1,1,-Trichlorotoluene	15 min	4.0:1.0	96
12	Toluene	30 min	2.0:1.0	85
13	1,4-Dioxane	24 h	-	No reaction
14	DME	24 h	-	No reaction
15	THF	24 h	-	No reaction
16	CH_3NO_2	24 h	-	No reaction
17	CH_3CN	24 h	1.0:2.0	20
18	Et_2O	24 h	5.0:1.0	75

Table 4.1: Solvent effect

chlorobenzene afforded better selectivity as compare to the remaining ones. Bromobenzene provided little bit more α-selectivity than chlorobenzene; however, higher boiling nature discouraged us from using bromobenzene and hence, further reactions were carried out in chlorobenzene (**Table 4.1**).

4.5.8.2 – Temperature effect

As variation in temperature also significantly affect the stereochemical outcome of any glycosylation reaction. So, after optimization of solvent system, our next target was to find out the optimum temperature for maximum α-selectivity. It has been noticed the diastereomeric ratio of α-galactopyranoside improved upon decreasing the temperature

of the reaction. At first, variation of reaction temperature was carried out in chlorobenzene solvent and the result was not much encouraging. It was found that with decreasing in temperature, the amount of α-galactoside product also decreased and

Entry	Solvent	Temp. (°C)	Time	α : β	Yield (%)
1	DCM	45	15 min	3.0:1.0	98
2	DCM	25	15 min	3.5:1.0	98
3	DCM	0	30 min	3.0:1.0	96
4	DCM	-20	1 h	3.0:1.0	93
5	DCM	-40	3 h	2.0:1.0	80
6	DCM	-60	12 h	1.5:1.0	65
7	DCM	-78	24 h	1.0:1.0	50
8	DCE	60	15 min	3.0:1.0	95
9	Chlorobenzene	75	30 min	7.5:1.0	98
10	Chlorobenzene	50	30 min	8.0:1.0	96
11	Chlorobenzene	25	30 min	8.0:1.0	97
12	Chlorobenzene	0	30 min	5.0:1.0	96
13	Chlorobenzene	-15	1 h	3.5:1.0	93
14	Chlorobenzene	-30	3 h	2.0:1.0	90
15	Toluene	25	30 min	2.0:1.0	85
16	Toluene	0	1 h	2.0:1.0	85
17	Toluene	-40	24 h	1.0:2.5	75
18	Et_2O	25	24 h	5.0:1.0	75
19	Et_2O	0	12 h	3.0:1.0	65
20	Et_2O	-20	24 h	2.0:1.0	50
21	Et_2O	-40	24 h	1.5:1.0	40
22	Et_2O	-60	24h	1.0:1.0	20

Table 4.2: Temperature effect

attain the minimum at -35 ^{0}C in case of chlorobenzene. Since the melting point of chlorobenzene is -40 ^{0}C, so we could not able to perform the glycosylation reaction below -40 ^{0}C in case of chlorobenzene solvent. In order to understand the common selectivity trend with variation in temperature, others solvents such as DCM, DCE, toluene and Et_2O were also screened at various temperatures. In all the cases, a

decreasing trend in α-selectivity with decrease in temperature has been observed (**Table 4.2**).

4.5.8.3 – Effect of catalyst loading

After solvent and temperature optimization, attention was shifted to identify the role of Au-phosphite complex **26a** or AgOTf mol% required for maximum α-selectivity. In

Entry	Au-phosphite (mol%)	AgOTf (mol%)	Temp. (^{0}C)	α : β	Yield (%)
1	10	10	25	3.5:1.0	98
2	5	10	25	3.5:1.0	80
3	2	10	25	3.5:1.0	30
4	10	40	25	3.5:1.0	93
5	10	100	25	4.0:1.0	95
6	10	10	-20	3.0:1.0	93
7	10	40	-20	3.0:1.0	95
8	10	100	-20	3.0:1.0	98
9	10 (13)	10 (15)	-40	2.0:1.0	75 (97)
10	13	40	-40	2.0:1.0	97
11	13	100	-40	1.5:1.0	96
12	10 (16)	10 (20)	-60	1.5:1.0	65 (96)
13	16	40	-60	1.0:1.0	97
14	16	100	-60	1.0:1.0	96

Table 4.3: Effect of catalyst loading

this regard, we varied the Au-phosphite **26a** loading from 10 mol% to 2 mol% keeping the AgOTf amount fixed at 10mol%. Unfortunately, no change in α-selectivity was observed. Next, loading of AgOTf was varied from 10 mol% to 100 mol% keeping theAu-phosphite **26a** amount fixed as 10 mol% at various temperatures. It was observed that decrease in α-selectivity with increase in AgOTf amount at any temperature (**Table 4.3**) which necessitated us to look at the role of Ag-counter ion.

4.5.8.4 – Effect of counter anions

To get a clear picture about the effect of counter anions on stereochemical outcome of

[Au]/[Ag]-catalysed glycosylation protocol developed by us, a thorough study of Ag catalysts with four different counter anions (i.e. OTf^-, NTf_2^-, SbF_6^- and BF_4^-) has been carried out. A large number of screening conditions with these counter anions at various

Entry	Ag-catalyst	Solvent	Temp. (^{0}C)	α : β	Yield (%)
1	AgOTf	DCM	25	3.5:1.0	98
2	$AgNTf_2$	DCM	25	1.5:1.0	92
3	$AgBF_4$	DCM	25	2.5:1.0	80
4	$AgSbF_6$	DCM	25	2.0:1.0	90
5	AgOTf	DCM	-20	3.0:1.0	93
6	$AgNTf_2$	DCM	-20	1.0:1.0	89
7	$AgBF_4$	DCM	-20	1.5:1.0	70
8	$AgSbF_6$	DCM	-20	2.0:1.0	82
9	AgOTf	DCM	-40	2.0:1.0	97
10	$AgNTf_2$	DCM	-40	1.0:1.5	90
11	$AgBF_4$	DCM	-40	1.0:1.0	40
12	$AgSbF_6$	DCM	-40	1.0:1.5	62
13	AgOTf	DCM	-60	1.5:1.0	96
14	$AgNTf_2$	DCM	-60	1.0:2.0	85
15	$AgBF_4$	DCM	-60	1.0:1.0	20
16	$AgSbF_6$	DCM	-60	1.0:1.5	40
17	AgOTf	Chlorobenzene	25	8.0:1.0	97
18	$AgNTf_2$	Chlorobenzene	25	4.0:1.0	90
19	$AgBF_4$	Chlorobenzene	25	5.0:1.0	72
20	$AgSbF_6$	Chlorobenzene	25	4.5:1.0	87

Table 4.4: Effect of counter anions

temperatures revealed that there is no significant change in the overall stereochemical outcome at higher temperature; but, 1,2-*cis* selectivity decreased significantly with increase in the size of counter anion at low temperatures (**Table 4.4**).

4.5.8.5 – Effect of addition sequence

Based on the literature reports[10] that described the effect of addition sequence of glyco-

syl donor (GA), glycosyl acceptor (GA) and activator on the stereochemical consequences of glycosylation reaction, we also tried to explore the possibilities of getting higher α-selectivity by changing the addition sequence (**Table 4.5**). Four possible addition sequences at various temperature were applied. Unfortunately, in our case no such improvements in α-selectivity has been observed.

Entry	1st Addition	2nd Addition	Temp. (^{0}C)	α : β	Yield (%)
1	GD + GA	Au-phosphite + AgOTf	25	3.5:1.0	98
2	GD + Au-phosphite + AgOTf	GA	25	3.5:1.0	97
3	GA + Au-phosphite + AgOTf	GD	25	4.5:1.0	97
4	GD + GA	Au-phosphite + AgOTf	-40	2.0:1.0	97
5	GD + Au-phosphite + AgOTf	GA	-40	2.0:1.0	95
6	GA + Au-phosphite + AgOTf	GD	-40	3.0:1.0	94
7	GD + GA	Au-phosphite + AgOTf	-60	1.5:1.0	96
8	GD + Au-phosphite + AgOTf	GA	-60	2.0:1.0	94
9	GA + Au-phosphite + AgOTf	GD	-60	2.5:1.0	91
10	GD + GA	Au-phosphite + $AgNTf_2$	25	1.5:1.0	92
11	GD + Au-phosphite + $AgNTf_2$	GA	25	2.0:1.0	91
12	GA + Au-phosphite + $AgNTf_2$	GD	25	2.0:1.0	88
13	GD + GA	Au-phosphite + $AgNTf_2$	-40	1.0:1.0	90
14	GD + Au-phosphite +$AgNTf_2$	GA	-40	1.0:1.0	87
15	GA + Au-phosphite +$AgNTf_2$	GD	-40	1.0:1.0	82
16	GD + GA	Au-phosphite + $AgNTf_2$	-60	1.0:2.0	85
17	GD + Au-phosphite +$AgNTf_2$	GA	-60	1.0:2.0	80
18	GA + Au-phosphite +$AgNTf_2$	GD	-60	1.0:1.5	76

Table 4.5: Effect of addition sequence

4.5.8.6 – Effect of active catalyst addition time

It is known in glycochemistry that slow reactions generally provide better selectivity than the faster ones and hence, we first prepared the active Au-catalyst by mixing Au-phosphite **26a** and AgOTf in DCM and added dropwise to the reaction mixture contain glycosyl donor **7aβ** and glycosyl acceptor **25** over various period of times, starting from

10 minutes to 6 hours to check the stereochemical outcome in our glycosylation reaction. There was an increase in α-selectivity from (8.0:1.0) to (10.0:1.0) in case of chlorobenzene solvent and (3.5:1.0) to (4.5:1.0) in case of DCM solvent as the addition time of active Au-catalyst changed from 5 minutes to 30 minutes. However longer addition time beyond that could not improve the selectivity further (**Table 4.6**).

Entry	Solvent	Temp. (^{0}C)	Addition Time	α : β	Yield (%)
1	DCM	25	5 min	3.5:1.0	98
2	DCM	25	30 min	4.5:1.0	98
3	DCM	25	2 h	4.5 :1.0	96
4	DCM	25	6 h	4.5:1.0	93
5	DCM	-40	3 h	2.5:1.0	80
6	Chlorobenzene	25	5 min	8.0:1.0	97
7	Chlorobenzene	25	30 min	10.0:1.0	96
8	Chlorobenzene	25	3 h	10.0:1.0	97
9	Chlorobenzene	75	30 min	8.0:1.0	96

Table 4.6: Effect of catalyst addition time

4.5.8.7 – Effect of Au-catalyst on stereoselectivity

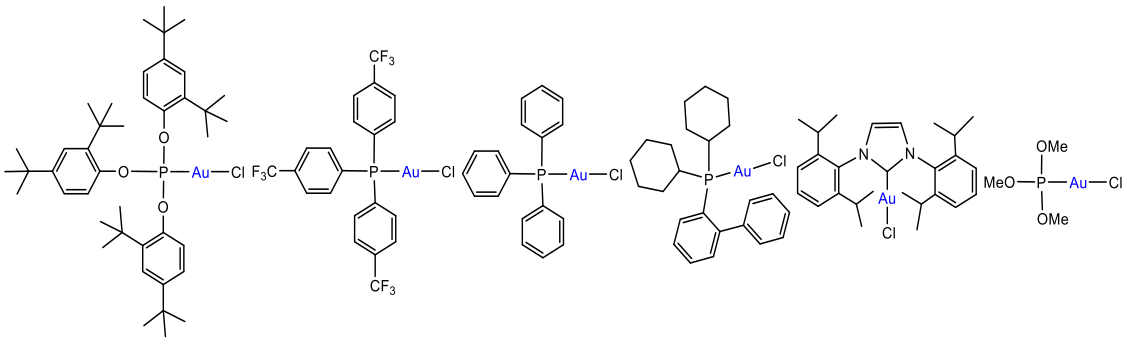


Figure 4.7: List of various Au(I) complexes used for stereoselective α-glycosylation

A number of commercially available Au(I) complexes with different ligands (**Figure 4.7**) have also been subjected to the galactosylation in order to understand the stereo-electronic effect of various Au(I) catalysts on the stereochemical outcome of the

glycosylation reactions. In this regard, a series of glycosylation reactions using 10mol% of various Au(I) precatalysts along with 10mol% of AgOTf in chlorobenzene as well as in DCM at 25 ^{0}C have been conducted. Unfortunately, no significant change in selectivity was noticed (**Table 4.7**). This may be attributed to the S_N1 type nature of the [Au]/[Ag]- catalysed glycosylation reaction.

Entry	Solvent	Catalyst	α : β	Yield (%)
1	DCM	26a	4.5:1.0	98
2	DCM	26b	3.5:1.0	95
3	DCM	26c	3.5 :1.0	90
4	DCM	26d	3.0:1.0	83
5	DCM	26e	3.5:1.0	85
6	DCM	26f	3.0:1.0	98
7	Chlorobenzene	26a	10.0:1.0	97
8	Chlorobenzene	26b	8.5:1.0	93
9	Chlorobenzene	26c	8.5:1.0	87
10	Chlorobenzene	26d	8.0:1.0	75
11	Chlorobenzene	26e	8.0:1.0	84
12	Chlorobenzene	26f	8.0:1.0	98

Table 4.7: Effect of various gold catalyst

4.5.8.8 – Effect of dilution or acceptor concentration

The effect of dilution or acceptor's concentration on α-selectivity was also studied to find out the best optimized condition. For that purpose, we first increased the amount of acceptor **25** from 1 equiv. to 10 equiv. as compared to the glycosyl donor amount and

Entry	Other factors	Solvent	α : β	Yield (%)
1	Acceptor (1 equiv.)	Chlorobenzene	9.0:1.0	96
2	Acceptor (10 equiv.)	Chlorobenzene	5.0:1.0	90
3	0.5M	Chlorobenzene	10.0 :1.0	97
4	0.05M	Chlorobenzene	11.5:1.0	86

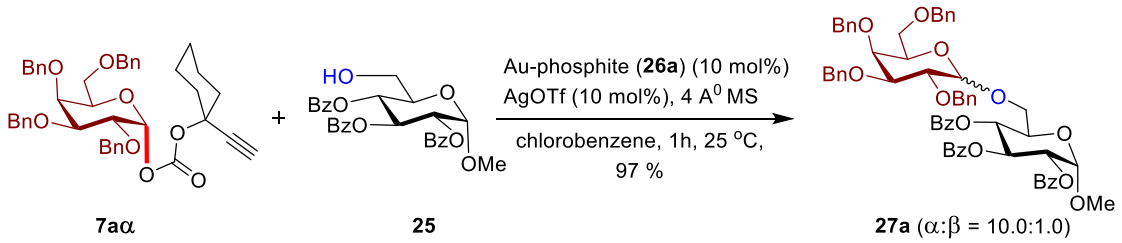
Table 4.8: Effect of dilution and acceptor concentration

performed the glycosylation reaction using 10 mol% each of Au-phosphite **26a** and AgOTf in chlorobenzene solvent at 25 ^{0}C. To our surprise, a significant reduction in α-selectivity [(9.0:1.0) to (5.0:1.0)] was observed. However, a slight increase in the α-selectivity was observed upon addition of ten times chlorobenzene solvent.

So, after optimising various parameters that could potentially affect the stereochemical outcome of [Au]/[Ag]-catalysed glycosylation reaction, the best suitable condition for maximum α-selectivity was obtained as: 10 mol% each of Au-phosphite **26a** and AgOTf as promoter with 30minutes addition time, 4Å molecular sieves powder, chlorobenzene as a solvent, 25 ^{0}C or room temperature as reaction temperature; which provided the disaccharide compound **27** with a α:β ratio of 10:1.

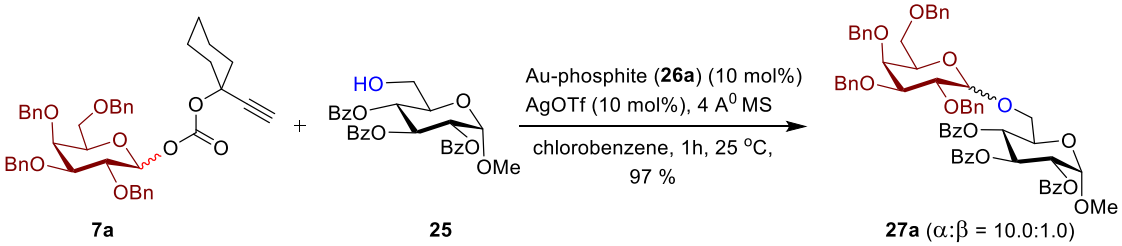
4.5.8.9 – Glycosylation reaction with α/β mixture of galactosyl carbonate donor 7a

Additionally, reaction of 1,2-*cis* (or α-) isomer of per *O*-benzyl galatopyranosyl alkynyl carbonate (**7aα**) with glycosyl acceptor **25** under above optimized glycosylation conditions afforded the disaccharide **27** with the same selectivity (**Scheme 4.8**).



Scheme 4.8: Glycosylation with α-per-*O*-benzyl galactosyl alkynyl carbonate (7aα)

Above reaction clearly showed that both **7aα** and **7aβ** react with glycosyl acceptor **25** under optimized glycosylation conditions provided the disaccharide **27** with similar 1,2-*cis* selectivity; thus, a mixture of **7aα** and **7aβ** as glycosyl donor was subjected to the



Scheme 4.9: Glycosylation with α/β-per-*O*-benzyl galactosyl alkynyl carbonate

same the glycosylation reaction with the same sugar acceptor **25** to notice 10:1 (α:β) ratio of disaccharides (**Scheme 4.9**) signifying strongly that one need not separate individual anomers of the glycosyl donors.

4.5.8.10 – Use of various galactosyl carbonate donors for better α-selectivity

Since the use of per *O*-benzylated galactosyl carbonate **7a** could not improve the selectivity beyond α/β ratio (10:1), so other galactosyl carbonates (**7b-7g**) (**Figure 4.8**) having various types of protecting groups at *C*-4 and *C*-6 positons were utilised as

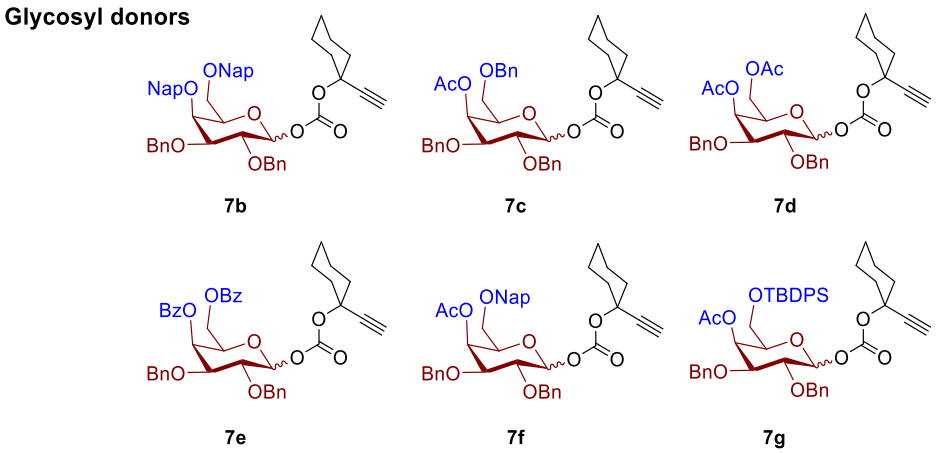


Figure 4.8: List of D-galactosyl donors prepared for stereoselective α-glycosylation

glycosyl donors and treated with various sugar acceptors (**25, 28** and **29**) (**Figure 4.8**) in the presence of 10 mol% each of Au-phosphite **26a** and AgOTf in chlorobenzene at 25 ^{0}C to find out the suitable carbonate donor for maximum α-selectivity. Although,

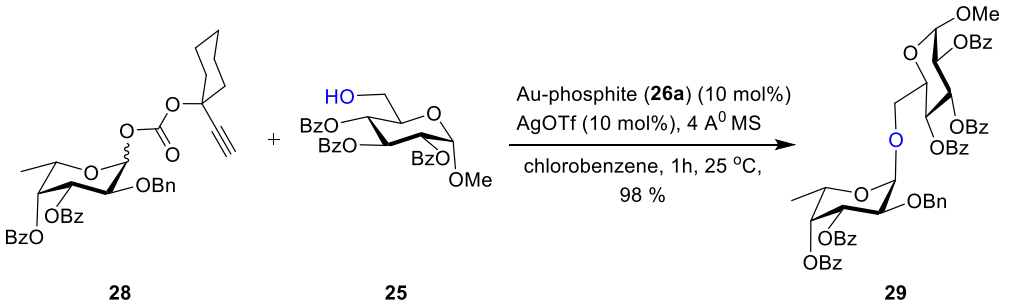
Entry	Glycosyl Donor	Glycosyl Acceptor	α : β	Yield (%)
1	**7b**	25	13.0:1.0	94
2	**7c**	25	16.0:1.0	97
3	**7d**	25	20.0:1.0	96
4	**7e**	25	Pure α	95
5	**7f**	25	20.0:1.0	93
6	**7g**	25	Pure α	97

Table 4.9: Effect of nature of protecting groups in α-galactoside preparation

amount of α-isomers as compared to their β-counterpart increased significantly in all the cases. However, donor **7e** and **7g** afforded superior selectivities as compared to the others donors (**Table 4.9**). So, we planned to use both the galactosyl donors (**7e** and **7g**) for better α-selectivity during our target molecule **1** synthesis.

4.5.9 – Stereoselective *1,2-cis* glycosylation of fucose residue

Along with galactose residue, the target *N*-linked hexasaccharide motif also contains fucose sugar residue in stereoselective 1,2-*cis* fashion. Therefore, finding out the proper



Scheme 4.10: Optimization for stereoselective *1,2-cis* glycosylation of L-fucose residue

glycosylation reaction condition that can afford the maximum 1,2-*cis* selectivity for fucose residue is also very important.[13] In this regard, at first, L-fucose carbonate donor **28** was prepared as per reported procedure[6] and allowed to react with acceptor **25** under recently optimized α-selective glycosylation condition (10 mol% each of Au-phosphite **26a** and AgOTf , chlorobenzene solvent, 4Å MS powder, 25 ^{o}C and reaction time 1 h) (**Scheme 4.10**). By our surprise, the desired disaccharide product **29** was also formed with 100% α-selectivity in 98% yield.

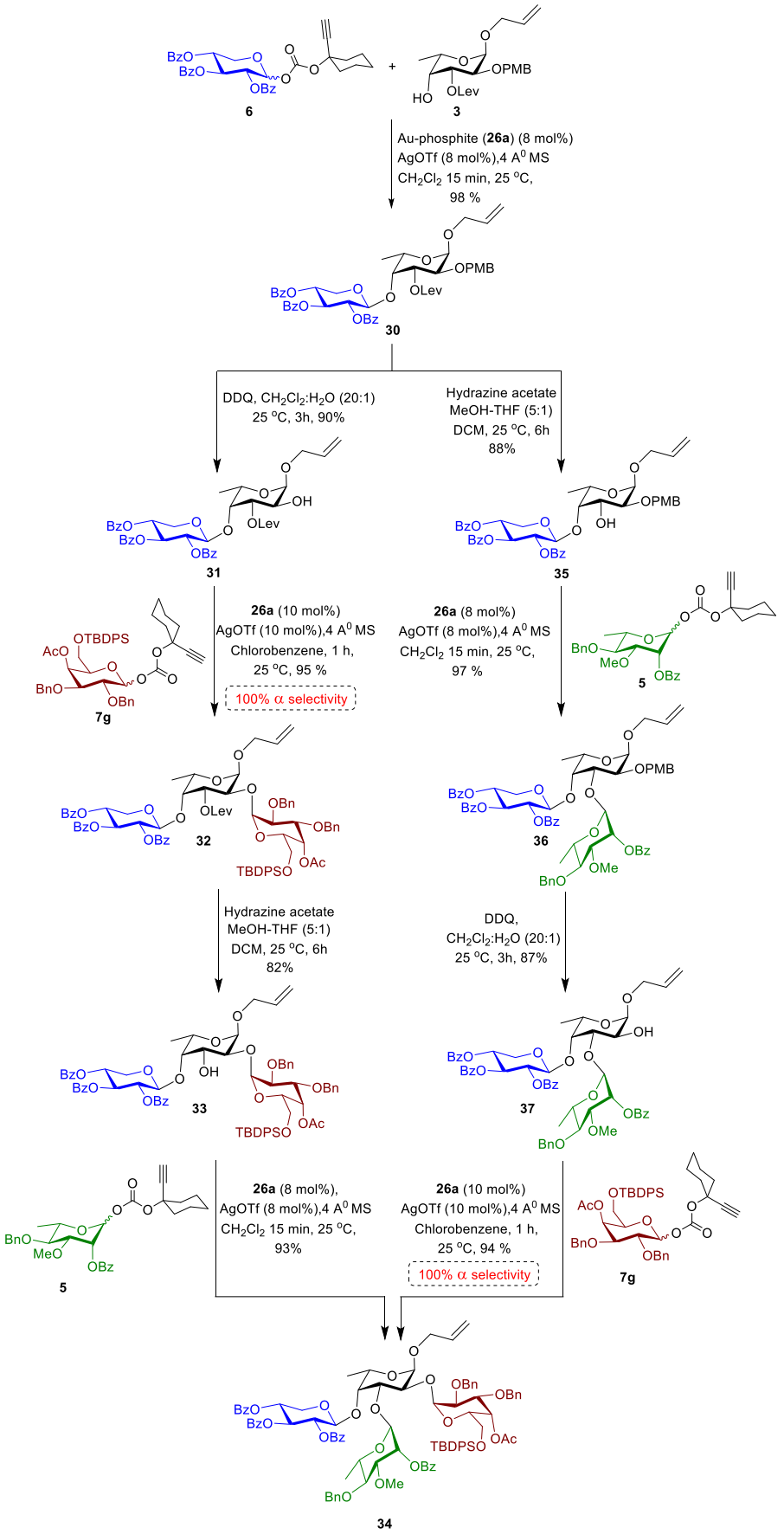
4.5.10 – Synthesis of hyperbranched tetrasaccharide motif

Successful synthesis of all building blocks required and identification of conditions for the stereoselective installation of galactopyranoside and fucopyranoside residues encouraged us to advance the synthesis of hyperbranched tetrasaccharide motif *en route* to the synthesis of hexasaccharide.

The synthesis of hyperbranched tetrasaccharide motif was commenced with the preparation of disaccharide **30** from the above prepared xylose carbonate donor **6** and fucose acceptor **3** in presence of 8mol% each of Au-phosphite **26a** and AgOTf in DCM at 25 ^{0}C with 98% yield. Formation of disaccharide **30** was confirmed through NMR

and mass spectral analysis. In the ^{1}H NMR spectrum of disaccharide **30**, resonances due to vinylic-C<u>H</u> moiety were noticed at δ 5.90 (dddd, *J* = 16.4, 10.6, 5.9, 5.0 Hz, 1H) ppm. In the ^{13}C NMR spectrum of compound **30**, appearance of two anomeric carbons at δ 96.2 and 96.2 ppm respectively revealed the presence of two inter-glycosidic linkages. Characteristic resonances at δ 165.0, 165.3 and 165.6 ppm respectively disclosed the presence of three benzoyl esters from xylopyranose sugar unit. Moreover, resonances due to characteristic acetyl ester and ketone at δ 172.4 and 206.4 ppm confirmed the presence of Lev-group whereas presence of two aromatic carbons at δ 113.9 ppm and one -<u>C</u>H$_3$ carbon at δ 55.3 ppm verified the PMB group. In addition, disaccharide **30** was further confirmed by HRMS analysis, *m/z* calculated for $C_{48}H_{50}O_{15}Na^{+}$, [M+Na^{+}]: 889.3047; Found: 889.3045.

Considering the inherent challenges associated with the stereoselective 1,2-*cis* glycosylation at oligosaccharide levels, two alternative routes were also designed to achieve the desired tetrasaccharide **34** with maximum α-selectivity. For that purpose, disaccharide **30** was splitted into two fractions and the first fraction was converted to the corresponding disaccharide alcohol **31** by cleaving the PMB-ether bond employing DDQ in DCM-H_2O (20:1) binary solvent system in 90% yield (**Scheme 4.11**). The ^{1}H and ^{13}C NMRs of compound **31** were very similar to **30** except the absence of resonances from PMB moiety. Disaccharide alcohol **31** was further treated with galactose carbonate donor **7g** under [Au]/[Ag]- catalysed glycosylation conditions that has been optimized for stereoselective α-galactoside preparation (i.e.10 mol% each of Au-phosphite **26a** and AgOTf in chlorobenzene at 25 ^{0}C for 1 hour) (**Table 4.9**). To our surprise, the desired trisaccharide **32** formed with 100% α-selectivity in 95% yield. Formation of trisaccharide **32** was confirmed through NMR and mass spectral analysis. Although, the anomeric protons of trisaccharide **32** overlapped with the other signals in the ^{1}H NMR spectrum, the ^{13}C NMR spectrum showed the presence of two 1,2-*trans* anomeric carbons at δ 96.5 and 100.5 ppm corresponding to fucopyranose and xylopyranose residues respectively, while the characteristic 1,2-*cis* anomeric carbon for galactose residue was noticed at δ 98.1 ppm. Furthermore, appearance of additional resonances at δ 170.2 ppm corresponding to acetyl ester and at δ 19.2 and 27.5 (3C) corresponding to TBDPS moiety along with all other residual peaks present in disaccharide acceptor **31** confirmed the formation of trisaccharide **32**. In addition,



Scheme 4.11: Synthesis of tetrasaccharide

trisaccharide **32** was further confirmed by HRMS analysis, *m/z* calculated for $C_{78}H_{84}O_{20}SiNa^+$, [M+Na^+]: 1391.5223; Found: 1391.5220. On the other hand, use of galactosyl carbonate donor **7e** for stereoselective synthesis of trisaccharide **32** proven to be less effective with lower α-selectivity (α:β = 15.0:1.0).

Subsequent deprotection of levulinyl ester of trisaccharide **32** using hydrazine hydrate afforded the corresponding trisaccharide alcohol **33** in 82% yield, which was further subjected to [Au]/[Ag]-assisted glycosylation with rhamnose carbonate donor **5** in presence of 8 mol% each of Au-catalyst **26a** and AgOTf in DCM solvent to produce the desired tetrasaccharide **34** in 93% yield (**Scheme 4.11**). Formation of **34** was also confirmed through NMR and mass spectral analysis. In the ^{1}H NMR spectrum of tetrasaccharide **34**, resonances from most of the anomeric protons overlapped with that of sugar ring protons and hence, the structural homogeneity was obtained from the ^{13}C NMR and mass spectral studies. In the ^{13}C NMR spectrum of tetrasaccharide **34**, appearance of an additional anomeric carbon at δ 99.9 ppm along with other three anomeric carbons at δ 98.1, 98.8 and 101.2 ppm showed the presence four inter-glycosidic linkages. Furthermore, presence of characteristic resonances at δ 165.0, 165.5, 165.6 and 166.2 ppm due to four benzoyl esters, at δ 19.2 and 27.0 (3C) ppm due to TBDPS moiety, at δ 170.1 ppm due to acetyl ester and at δ 57.5 ppm due to -O<u>C</u>H_3 group along with other remaining carbons unambiguously confirmed the formation of compound **34**. In addition, tetrasaccharide **34** was confirmed by HRMS analysis, *m/z* calculated for $C_{94}H_{100}O_{23}SiNa^+$, [M+$Na^+$]: 1648.6356; Found: 1648.6360.

In parallel, another fraction of disaccharide **30** was treated with NH_2-NH_2.H_2O and AcOH-Py buffer in DCM to deprotect the Lev group which resulted in the formation of disaccharide alcohol **35** in 88% yield. The ^{1}H and ^{13}C NMRs of compound **35** were very similar to **30** except the absence of resonances from Lev moiety. Subsequent reaction of disaccharide acceptor **35** with rhamnose carbonate donor **5** in presence of 8mol% each of Au-catalyst **26a** and AgOTf in DCM solvent afforded the trisaccharide **36** in 97% yield (**Scheme 4.11**). Formation of trisaccharide **36** was verified by NMR and mass spectral analysis. In the ^{1}H NMR spectrum of **36**, three anomeric protons resonances were overlapped with other protons. Resonances due to vinylic-C<u>H</u> moiety and -OC<u>H</u>$_3$ moieties were noticed at δ 5.92 (dddd, *J* = 17.0, 10.3, 6.6, 5.3 Hz, 1H) ppm, 3.45 (s, 3H) respectively. In the ^{13}C NMR spectrum, three

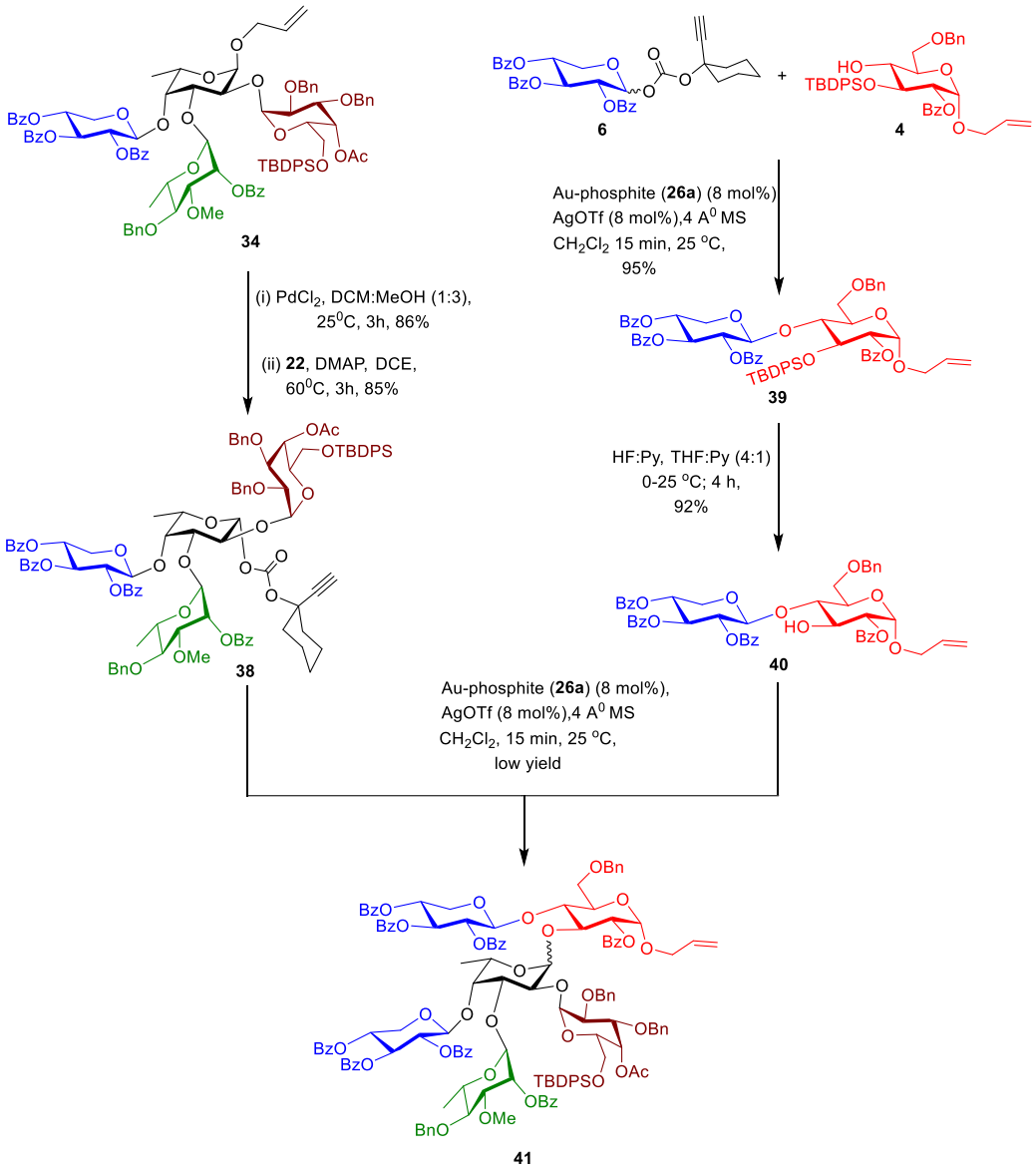
anomeric carbons were observed at δ 96.0, 98.4 and 99.7 ppm and characteristic resonances due to four benzoyl groups appeared at δ 165.0, 165.5, 165.6 and 166.2 ppm. All other resonances in the ^{13}C NMR spectrum matched perfectly with the assigned structure of compound **36**. In addition, trisaccharide **36** was further confirmed by HRMS analysis, *m/z* calculated for $C_{64}H_{66}O_{18}SiNa^+$, [M+Na^+]: 1145.4147; Found: 1145.4144.

In continuation, deprotection of PMB-ether using DDQ in DCM-H_2O (20:1) binary solvent system converted the trisaccharide **36** to the corresponding trisaccharide alcohol **37** in 87% yield, which upon subsequent reaction with rhamnose carbonate donor **5** in presence of 10 mol% each of Au-catalyst **26a** and AgOTf in chlorobenzene at 25 ^{0}C for 1 hour afforded the corresponding tetrasaccharide **34** in 94% yield with 100% α-selectivity too (**Scheme 4.11**). The perfect matching of NMR and mass values of the two tetrasaccharides prepared via two alternative routes strongly confirmed the successful synthesis of tetrasaccharide **34**of interest.

4.5.11 – Synthesis of hexasaccharide motif

As explained in the retrosynthesis section, a [4+2] coupling strategy was envisioned for the synthesis of the hexasaccharide motif. Accordingly, the hyperbranched tetrasaccharide **34** was further treated with $PdCl_2$ in DCM-MeOH (1:3) solvent system at room temperature to generate the hemiacetal, which on subsequent reaction with easily available ethynylcyclohexyl (4-nitro phenyl) carbonate **22** and DMAP afforded the tetrasaccharide alkynyl carbonate donor **38** in 85% yield over two steps (**Scheme 4.12**). Formation of **38** was confirmed through NMR and mass spectral analysis. The ^1H NMR spectrum of **38** showed overall integrity of the envisaged structure; however, most of the resonances overlapped with other sugar ring protons and thus confirmation was obtained solely from the ^{13}C NMR spectroscopy. In the ^{13}C NMR spectrum of carbonate **38**, four anomeric carbons were observed to resonate at δ 95.6, 97.2, 99.1 and 99.6 ppm and characteristic resonances due to the carbonate carbon appeared at δ 151.7 ppm whereas resonances due to four benzoate and one acetate esters were found between δ 165.2 – 170.2 ppm. Moreover, resonances at δ 19.1 and 26.9 (3C) due to the TBDPS moiety along with other residual carbons strictly confirmed the formation of compound **38**. In addition, tetrasaccharide donor **38** was further confirmed by MALDI-

TOF analysis, *m/z* calculated for $C_{100}H_{106}O_{25}SiNa^+$, [M+$Na^+$]: 1758.6724; Found: 1758.6698.

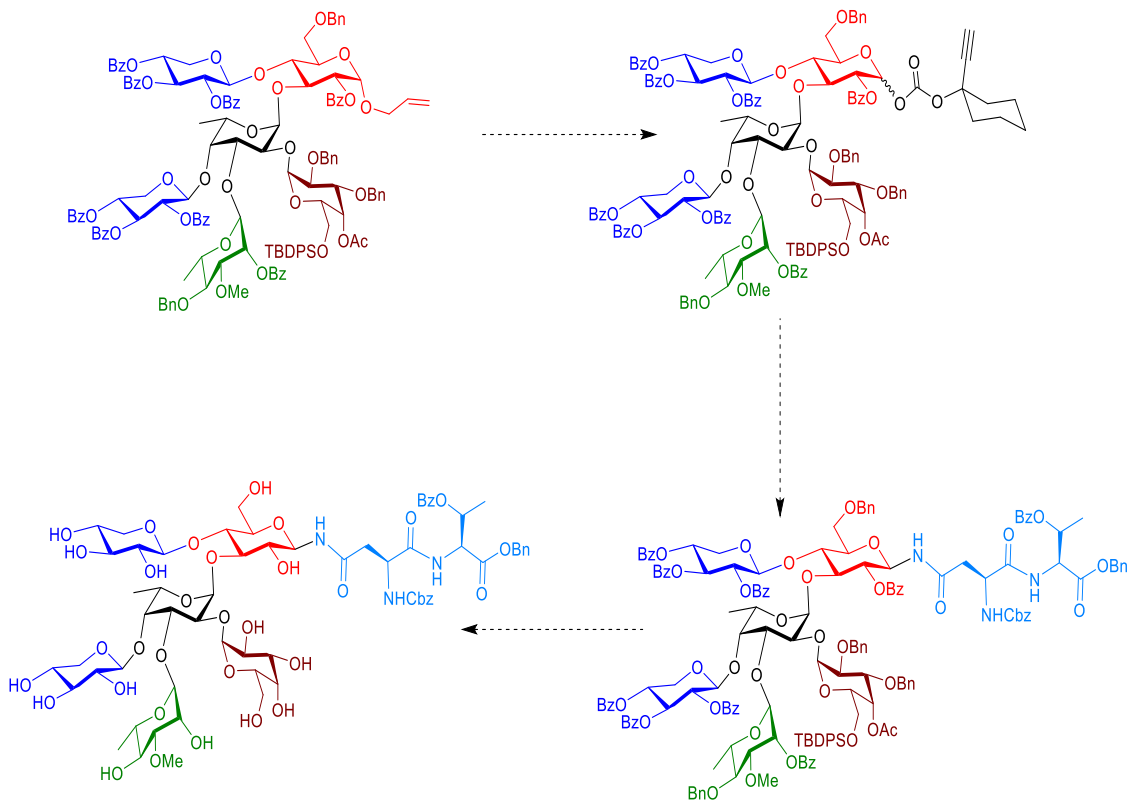


Scheme 4.12: Synthesis of hexasaccharide

In parallel, reaction of xylose carbonate donor **6** with glucose-derived acceptor **3** in the presence of 8 mol% each of Au-phosphite **26a** and AgOTf in DCM at 25 ^oC afforded the disaccharide **39** in 95% yield. Formation of the disaccharide **39** was confirmed through NMR and mass spectral analysis. In the ^{13}C NMR spectrum of **39** spectrum of compound **39** showed two anomeric carbons at δ 97.6 and 100.1 ppm. Furthermore, characteristic resonances due to four benzoyl groups appeared between δ 165.3–165.8 ppm whereas resonances due to the TBDPS moiety were observed at δ 19.1 and 26.7 (3C) ppm. In addition, trisaccharide **39** was further confirmed by HRMS

analysis, *m/z* calculated for $C_{65}H_{64}O_{14}SiNa^+$, [M+Na^+]: 1119.3963; Found: 1119.3967. Further conversion of disaccharide **39** into the corresponding disaccharide alcohol **40** was achieved by the cleavage of TBDPS group using HF·py conditions in 92% yield. The final coupling between tetrasaccharide carbonate **38** and disaccharide alcohol **40** under 10 mol% each of Au-phosphite **26a** and AgOTf in chlorobenzene at 25 ^{0}C for 1 h afforded the hexasaccharide **41** in very low yield (~20-25%) as a complex mixture. Although the formation of hexasaccharide **41** was confirmed through MALDI-TOF mass spectral analysis [m/z calcd for $[C_{140}H_{140}O_{36}SiNa]^+$: 2449.69; Found: 2449.26]. However, due to lack of sufficient quantity, we could not able to get the clear NMR of hexasaccharide **41**. The preparation of hexasaccharide **41** in large scale is currently underway in the laboratory.

4.5.12 – Synthesis of N-linked hexasaccharide



Scheme 4.13: *N*-linked hexasaccharide synthesis

Once we have the hexasaccharide **41** in sufficient amount, few more reactions are needed to be carried out to get the final core hexasaccharide linked with Asn-Thr dipeptide residue at reducing end (**1**) (**Scheme 4.13**).

4.5.13 – Conclusion

To conclude, challenging 1,2-*cis* glycosylation for D-galactose and L-fucose residues have also been achieved using our recently developed [Au]/[Ag]- catalysed alkynyl carbonate donor chemistry. In this endeavour, effects of various factors such as solvent, temperature, catalyst etc. which mostly control the stereochemical outcome of any glycosylation reaction have been thoroughly studied. Synthesis of disaccharide and hyperbranched tetrasaccharide with excellent glycosylation yields has proven that our carbonate donor chemistry can be employed to synthesize any kind of oligosaccharides possessing whatever type of sugars or type of glycosidic linkages within it. Unambiguous characterization of the desired hexasaccharide by NMR spectral studies is still pending for which efforts are currently underway. Overall, we showed that the gold-catalysed glycosidation using alkynyl carbonate glycosyl donors is superior for the installation of both 1,2-*trans* and 1,2-*cis* linkages in a stereoselective fashion. This unique feature of our method is unique and hence, we anticipate that the method is on its path to become a universal glycosyl donor.

4.6 – Experimental section

General procedure for Boc/Cbz protection of amines (8, 11): To a rapidly stirring aqueous solution of amine (1.0 mmol), $NaHCO_3$ (2 mmol) was added at 25 °C and stirred for 10 min. A solution of Boc_2O/CbzCl in THF was the added dropwise into the reaction mixture at 0 °C and gradually warmed up to 25 °C. After complete consumption of the amine, the reaction mixture was neutralised 1*N* HCl and extracted with EtOAc. The organic layer was then concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2/MeOH) to obtain the desired protected amine compound as white solid.

Synthesis of di-peptide (2) To a rapidly stirring solution of (1 mmol) and L-asparagine compound **11** (1 mmol) in anhydrous DMF, DIPEA (5 mmol) (0.3 mmol) EDC.HCl (2 mmol) and HOAT (1.5 mmol) were added sequentially) at 0 ^{0}C under nitrogen atmosphere. After 30 min, L-threonine compound **10** was added dropwise to the rapidly stirring reaxtion mixture at 0 ^{0}C. The reaction mixture was gradually warmed up to 25 °C and stirred for 4 h. After 24 h, the reaction mixture was extracted with ethyl acetate (3x20 mL). The combined organic layer was washed with water (2x20 mL), brine solution (3x20 mL), dried over Na_2SO_4 and evaporated *in vacuo* to obtain a crude residue which was purified on silica gel column chromatography (*n*-hexane/EtOAc) to afford the desired product.

General procedure for synthesis of allyl glycosides (12, 16, 18, 23, 24): AcCl (0.3 mmol) was added dropwise to a rapidly stirring allyl alcohol (as a solvent) at 0 ^{0}C under nitrogen atmosphere. After 30 min, sugar (1.0 mmol) was added and stirred at 25 ^{0}C for 1h. The reaction mixture was further heated to 80 ^{0}C and refluxed for 6 h. After completion of reaction, the reaction mixture was cooled to 0 ^{0}C, quenched with Et_3N and concentrated *in vacuo* to obtain a light brown residue which was purified by column chromatography (CH_2Cl_2/MeOH) to obtain the desired allyl glycoside as white solid.

General procedure for acetonide protection of di-ols (12, 18): To a rapidly stirring solution of di-ol (1.0 mmol) in anhydrous acetone, 2, 2-dimethoxy propane (1.5 mmol) and PTSA (0.2 mmol) were added and the reaction mixture was stirred at 25 °C for overnight (12 h). After complete consumption of the di-ol, the reaction mixture was quenched with Et_3N and concentrated *in vacuo* to obtain a light yellow residue which

was purified by column chromatography (*n*-hexane/EtOAc) to obtain the desired acetonide product as white solid.

General procedure for Bn/PMB/NAP protection of alcohols (13, 19, 24, 7a, 7b, 7e, 7f): To an ice cooled solution of alcohol (1 mmol) in anhydrous DMF (10 mL), NaH (60% oil dispersion, 1.2 mmol per alcohol) was added and stirred for 10 minute at 0 ^{o}C under nitrogen atmosphere. BnBr/PMBCl/NAPBr (1.2 mmol per alcohol) was further added dropwise into the reaction mixture followed by TBAI (0.1 mmol per alcohol) addition at 0 ^{o}C. The reaction mixture was gradually warmed up to 25 °C and stirred for 4 h. After complete consumption of the alcohol as indicated by TLC, the reaction mixture was poured into ice cold water with vigorous shaking, extracted with ethyl acetate (3x20 mL) and combined EtOAc layer was washed with cold water, brine solution, dried over Na_2SO_4. and evaporated *in vacuo*. The crude residue was further purified by column chromatography (*n*-hexane/EtOAc) to obtain the Bn/PMB/NAP ether as pale yellow colored syrup.

General procedure for TBDMS/TBDPS-protection of alcohols (4, 15, 7g): To a rapidly stirring solution of alcohol (1.0 mmol) and imidazole (1.3 mmol) in anhydrous DMF (10 mL) was added TBDMSCl/TBDPSCl (1.2 mmol) dropwise and stirred for 4 h at 25 ^{o}C. At the end of reaction, the reaction mixture was extracted with ethyl acetate (3x20 mL). The combined organic layer was washed with water (2x50 mL), brine solution (1x50 mL), dried over Na_2SO_4 and evaporated *in vacuo* to obtain a crude residue which was purified on silica gel column chromatography (*n*-hexane/EtOAc) to afford the desired product.

General procedure for Levulinoate ester protection of alcohols (3): To a stirring solution of alcohol (1.0 mmol) in anhydrous CH_2Cl_2 (4 mL), DMAP (1.0 mmol), Levulinic acid (1.5 mmol) and *N,N'*-Diisopropylcarbodiimide (1.5 mmol) were added sequentially at 0 °C under nitrogen atmosphere. The reaction mixture was gradually warmed up to 25 °C and stirred for 4 h. After complete consumption of the starting alcohol, the reaction mixture was concentrated *in vacuo* and the purified on silica gel column chromatography (*n*-hexane/EtOAc) to afford corresponding levulinoate ester.

General procedure for benzylidine protection of di-ols (16, 24): To a rapidly stirring solution of di-ol (1.0 mmol) in anhydrous DMF, benzaldehyde 1,1-dimethylacetal (1.5

mmol) and PTSA (0.2 mmol) were added and the reaction mixture was stirred at 25 °C for overnight (12 h). After complete consumption of the di-ol, the reaction mixture was quenched with Et_3N and extracted with ethyl acetate (3x20 mL). The combined organic layer was washed with water (2x50 mL), brine solution (1x50 mL), dried over Na_2SO_4 and evaporated *in vacuo* to obtain a crude residue which was purified on silica gel column chromatography (*n*-hexane/EtOAc) to afford the desired product.

General procedure for benzoate/acetate ester protection of alcohols (9, 14, 21, 23, 7c, 7d, 7e, 7f): To a solution of alcohol (1 mmol) in anhydrous pyridine (10 mL), benzoyl chloride/acetic anhydride (1.2 mmol per alcohol) was added dropwise at 0 ^{0}C under nitrogen atmosphere. The reaction mixture was gradually warmed up to 25 ^{0}C and stirred for 6-12 h. Progress of the reaction and consumption of starting alcohol was checked by TLC. After completion of the reaction, the reaction mixture was quenched by adding ice cooled water and extracted with CH_2Cl_2 (50 mL) and the CH_2Cl_2 layer was washed with 1*N* HCl (2x50 mL), water, sat. aq. $NaHCO_3$ solution and finally with brine solution. Combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the resulting crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain the desired compound.

General procedure for selective benzoate ester protection of alcohol (17): To a solution of alcohol (1 mmol) and anhydrous Et_3N (5 mmol) in anhydrous CH_2Cl_2 (10 mL), Benzoic anhydride (1.2 mmol) was added portion wise over a period of 3 h at 0 ^{0}C under nitrogen atmosphere. The reaction mixture was continued to stir for another 6 h at 0 ^{0}C. Progress of the reaction and consumption of starting alcohol was checked by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1*N* HCl (20 mL), water, sat. aq. $NaHCO_3$ solution and finally with brine solution. Combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the resulting crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain the desired compound.

General procedure for deprotection of Isopropylidene group (14, 20): To a solution of isopropylidene compound (1 mmol) in aqueous THF [THF: H_2O = 7:3] (10 mL), 80% AcOH (2 mL) was added at 25 ^{0}C and the reaction mixture was allowed to stir at 55 ^{0}C for 3 h. Progress of the reaction and complete consumption of the starting material was checked by TLC. At the end of reaction, the reaction mixture was

quenched with sat. aq. $NaHCO_3$ (20 mL) at 0 ^{0}C and extracted with ethyl acetate (50 mL). The organic layer was washed with water (25 mL), brine solution (25 mL), dried over Na2SO4 and evaporated *in vacuo* to obtain a crude residue which was purified on silica gel column chromatography (*n*-hexane/EtOAc) to afford the desired product.

General procedure for deprotection of benzylidine group (24): To a solution of benzylidine compound (1 mmol) in MeOH was added PTSA (0.2 mmol) and the reaction mixture was stirred at 25 °C for 30 minute. After completion of the reaction (as indicated by TLC), the reaction mixture was quenched with Et_3N and concentrated *in vacuo* to obtain a light yellow residue which was purified by column chromatography (*n*-hexane/EtOAc) to afford the desired product.

General procedure for deprotection of the TBDPS-ethers (3, 40): To a solution of silyl ether compound (1 mmol) in 5:1 mixture of THF-Py (10 mL), HF·py (3 mmol) was added dropwise at 0 ^{o}C under nitorgen atmosphere and stirred at 25 ^{o}C. After 4 h, the reaction mixture was quenched with 2N HCl at 0 ^{o}C, diluted with EtOAc (30mL) and washed with ice cold water (2x20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine solution (20 mL) sequentially. The EtOAc layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to furnish corresponding alcohol in very high yield.

General procedure for reductive cleavage of benzylidine ring (4): To a solution of benzylidine compound (1 mmol) in CH_2Cl_2 (10 mL), Et_3SiH (5 mmol) and TFA (5 mmol) were added dropwise at 0 ^{o}C subsequently under nitorgen atmosphere and stirred at 25 ^{o}C. After 3 h, the reaction mixture was quenched with $NaHCO_3$ (20 mL) at 0 ^{o}C, diluted with CH_2Cl_2 (30 mL)and washed with ice cold water (2x20 mL), sat. aq. and brine solution (20 mL) sequentially. The EtOAc layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to furnish corresponding alcohol in very high yield.

General procedure for deprotection of PMB ethers (31, 37): To a solution of PMB ether compound (1 mmol) in 20:1 mixture of CH_2Cl_2-H_2O (10 mL) was added DDQ (2 mmol) at 25 ^{o}C and stirred for 2 h. After completion of the reaction (as indicated by TLC), the reaction mixture was quenched with Et_3N and concentrated *in vacuo* to

obtain a dark yellow residue which was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain the desired alcohol as a colourless syrup.

General procedure for deprotection of Levulinoates (33, 35): To a rapidly stirring solution of levulinoate compound (1.0 mmol) in MeOH (10 mL), Hydrazine acetate (4 mmol) in THF (4 mL) was added at 25 °C. After 4 h, the reaction mixture was quenched with ice cold 1N HCl, extracted with EtOAc and washed with water, sat. aq. $NaHCO_3$ and brine solution sequentially. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to obtain the crude residue which was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford the desired alcohol in good yield.

General procedure for saponification of ester (15): To a solution of benzoate/acetate (1 mmol) in 3:1 mixture of anhydrous CH_2Cl_2-MeOH (20 mL), a freshly prepared 1*M* NaOMe in MeOH (0.3 mmol) was added and the reaction mixture was stirred at 25 °C for 2 h. After complete conversion, the reaction mixture was neutralized with Amberlite resin and concentrated in *vacuo* to obtain a residue that was purified by column chromatography (*n*-hexane/EtOAc) to afford the desired alcohol.

General procedure for deprotection of allyl glycosides (5, 6, 7a-7g, 38): To a solution of allyl glycoside (1 mmol) in 3:1 mixture of CH_3OH-CH_2Cl_2 (10 mL) was added dropwise $PdCl_2$ (0.15 mmol) in CH_3OH (1 mL) and stirred at 25 ^{0}C for 3 h. After completion of the reaction, the reaction mixture was quenched by addition of Et_3N and concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to achieve the desired hemiacetal in 90-95% yield.

General procedure for synthesis of ethynylcyclohexyl glycosyl carbonate donors (5, 6, 7a-7g, 38): DMAP (1 mmol) was added to a stirring solution of hemiacetal (1 mmol) in anhydrous CH_2Cl_2 (10 mL) at 25 ^{0}C. After 20 min, reagent **22** (1.2 mmol) was added portion-wise (3x) after every 30 min and stirred at 25 ^{0}C for 2-3 h. After completion of reaction as indicated by TLC, the reaction mixture was concentrated *in vacuo* and the oily residue was partially purified by silica gel column chromatography (*n*-hexane/EtOAc). Eluents containing alkynyl glycosyl carbonate along with trace quantities of 4-nitrophenol were concentrated under diminished pressure. Further, the crude residue was redissolved in CH_2Cl_2 (30 mL) and washed with sat. aq. $NaHCO_3$

(3x10 mL) and brine solution to remove 4-nitrophenol. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to obtain the alkynyl glycosyl carbonate donor in excellent yield.

In case of tetrasaccharide carbonate donor **38** synthesis, $ClCH_2CH_2Cl$ (DCE) instead of CH_2Cl_2 was used as a solvent and after addition of reagent **22**, the reaction mixture was stirred at 60 ^{0}C for 3 h.

General procedure for selective methyl protection (20): To a solution of alcohol (1 mmol) in toluene (10 mL), Bu_2SnO (1.2 mmol) was added and refluxed at 105 °C. After 2 h, MeI (3 mmol) and TBAI (0.2 mmol) were added and the reaction mixture was stirred at 25 °C for another 3 h. Completion of the reaction was monitored by TLC and upon completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the crude residue which was purified by silica gel column chromatography (CH_2Cl_2/MeOH) to afford the desired methylated as a colourless syrup.

Procedure for Glycosylation:

Procedure A: To a stirred solution of alkynyl carbonate donor (1 mmol) and acceptor (1 mmol) in anhydrous solvent (4 mL) containing 4Å MS powder (100 mg), Au-complex (0.10 mmol) and Ag-salt (0.10 mmol) were added and stirred at 25 ^{0}C. Upon completion of reaction, the reaction mixture was quenched with Et_3N and concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford the desired glycoside.

Procedure B: AgOTf (0.08 mmol) and Au-phosphite (**26a**) (0.08 mmol) were added to a solution of alkynyl carbonate donor (1 mmol) and acceptor (1 mmol) in anhydrous CH_2Cl_2 (4 mL) containing 4Å MS powder (100 mg) and stirred at 25 ^{0}C for 15 min. Upon completion of reaction, the reaction mixture was quenched with Et_3N and concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to achieve the desired glycoside in 90-98% yield.

Procedure C: A solution of premix Au-phosphite (**26a**) (0.10 mmol) and AgOTf (0.10 mmol) in anhydrous CH_2Cl_2 were added dropwise to a solution of alkynyl carbonate donor (1 mmol) and acceptor (1 mmol) in dry chlorobenzene (4 mL) containing 4Å MS

powder (100 mg) over a period of 30 min at 25 ^{0}C and stirred for another 30 min. Upon completion of reaction, the reaction mixture was quenched with Et_3N and concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to achieve the desired glycoside.

(2R,3S)-3-((S)-4-amino-2-(((benzyloxy)carbonyl)amino)-4-oxobutanamido)-4-(benzyloxy)-4-oxobutan-2-yl benzoate (**2**): mp (^{0}C): 170.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -5.7; IR (cm^{-1}, $CHCl_3$): 3200, 3055, 2940, 1730, 1410, 1230, 1017, 933, 712; ^{1}H NMR (400.31 MHz, DMSO-d_6): δ 1.29 (d, *J* = 6.4 Hz, 3H), 2.48 – 2.52 (m, 1H), 2.60 (dd, *J* = 15.8, 5.6 Hz, 1H), 3.68 (d, *J* = 6.1 Hz, 1H), 4.86 (dd, *J* = 9.0, 2.9 Hz, 1H), 4.99 (d, *J* = 5.6 Hz, 1H), 5.09 (dd, *J* = 28.1, 12.6 Hz, 2H), 5.56 (qd, *J* = 6.3, 3.0 Hz, 1H), 7.00 (s, 1H), 7.14 – 7.26 (m, 5H), 7.29 – 7.35 (m, 5H), 7.41 (s, 1H), 7.44 – 7.56 (m, 3H), 7.65 (t, *J* = 7.4 Hz, 1H), 8.00 – 8.07 (m, 2H), 8.26 (d, *J* = 7.6 Hz, 1H), 8.58 (d, *J* = 8.9 Hz, 1H) ; ^{13}C NMR (100.67 MHz, DMSO-d_6): δ 16.9, 37.5, 43.9, 49.8, 55.8, 65.9, 66.9, 71.0, 128.1, 128.1, 128.1, 128.2, 128.4, 128.7, 128.7, 128.8, 128.8, 129.0, 129.8, 130.1, 130.1, 133.9, 136.0, 137.4, 156.9, 165.2, 169.7, 169.7, 172.0, 172.4; HRMS (ESI-MS): m/z calcd for $[C_{30}H_{31}N_3O_8Na]^+$: 584.2009; Found: 584.2017.

Allyl 3,4-*O*-isopropylidene α-L-fucopyranoside (**12**): mp (^{0}C): 123.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -19.5; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.7 Hz, 3H), 1.28 (s, 3H), 1.43 (s, 3H), 2.68 (s, 1H), 3.57 – 3.79 (m, 1H), 3.94 – 4.01 (m, 2H), 4.06 (qd, *J* = 6.6, 2.3 Hz, 1H), 4.12 – 4.19 (m, 1H), 4.78 (d, *J* = 3.9 Hz, 1H), 5.13 (ddd, *J* = 10.4, 2.8, 1.3 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.85 (dddd, *J* = 17.1, 10.4, 6.1, 5.3 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.2, 25.9, 27.8, 63.9, 68.4, 69.4, 75.7, 76.2, 96.8, 109.1, 117.6, 133.8; HRMS (ESI-MS): m/z calcd for $[C_{12}H_{20}O_5Na]^+$: 267.1208; Found: 267.1206.

Allyl 2-*O*-(*p*-methoxybenzyl)-3,4-*O*-isopropylidene α-L-fucopyranoside (**13**): mp (^{0}C): 110.6; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -42.1; IR (cm^{-1}, $CHCl_3$):1605, 1440, 1335, 1245, 1078, 1026, 940, 710; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.7 Hz, 3H), 1.34 (s, 3H), 1.27 (s, 3H), 3.42 (dd, *J* = 7.9, 3.6 Hz, 1H), 3.72 (s, 3H), 3.91 (dd, *J* = 13.0, 6.2 Hz, 1H), 3.96 (dd, *J* = 5.5, 2.5 Hz, 1H), 4.01 – 4.10 (m, 2H), 4.24 (dd, *J* = 7.8, 5.5 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.68 (d, *J* = 3.6 Hz, 1H), 5.13 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.24 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.86 (dddd, *J* = 17.1, 10.4,

6.1, 5.3 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.4, 26.5, 28.3, 55.4, 63.3, 68.4, 72.0, 76.0, 76.0, 76.3, 96.2, 108.8, 113.8, 113.8, 117.8, 129.6, 129.6, 130.6, 134.0, 159.4; HRMS (ESI-MS): m/z calcd for $[C_{19}H_{26}O_7Na]^+$: 387.1784; Found: 387.1784.

Allyl 2-*O*-(*p*-methoxybenzyl)-3-*O*-acetyl α-L-fucopyranoside (**14**): mp (^{0}C): 84.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -6.3; IR (cm^{-1}, $CHCl_3$):1730, 1610, 1430, 1328, 1239, 1063, 1020, 706; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.6 Hz, 3H), 2.02 (s, 3H), 3.72 (s, 3H), 3.78 (dd, *J* = 10.5, 3.7 Hz, 1H), 3.82 (s, 1H), 3.93 (ddd, *J* = 13.0, 7.1, 3.8 Hz, 1H), 3.98 (q, *J* = 6.6 Hz, 1H), 4.07 (ddd, *J* = 7.2, 5.2, 3.3 Hz, 1H), 4.48 (dd, *J* = 29.4, 12.0 Hz, 2H), 4.71 (d, *J* = 3.7 Hz, 1H), 5.07 – 5.20 (m, 2H), 5.24 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.89 (dddd, *J* = 17.1, 10.4, 6.1, 5.3 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.0, 21.2, 55.3, 65.4, 68.5, 70.8, 72.5, 72.8, 72.9, 96.2, 113.8, 113.8, 117.8, 129.5, 129.5, 130.4, 133.9, 1559.4, 170.3; HRMS (ESI-MS): m/z calcd for $[C_{19}H_{26}O_7Na]^+$: 389.1576; Found: 389.1572.

Allyl 2-*O*-(*p*-methoxybenzyl)-3-*O*-(4-oxopentanoyl) α-L-fucopyranoside (**3**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -38.5; IR (cm^{-1}, $CHCl_3$): 1720, 1610, 1453, 1365, 1263, 1090, 1034, 715; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.6 Hz, 3H), 2.13 (s, 3H), 2.55 – 2.80 (m, 5H), 3.60 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.91 (dd, *J* = 12.9, 6.4 Hz, 1H), 3.75 (s, 3H), 4.00 (q, *J* = 6.5 Hz, 1H), 4.05 – 4.13 (m, 1H), 4.53 – 4.62 (m, 2H), 4.79 (d, *J* = 3.5 Hz, 1H), 5.08 – 5.21 (m, 2H), 5.28 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.87 (dddd, *J* = 17.1, 10.4, 6.1, 5.3 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.1, 28.1, 29.9, 38.2, 55.3, 64.9, 68.1, 68.6, 72.4, 73.6, 76.3, 96.0, 113.9, 113.9, 117.9, 129.8 (3C), 130.3, 133.9, 172.9, 206.9; HRMS (ESI-MS): m/z calcd for $[C_{22}H_{30}O_8Na]^+$: 445.1838; Found: 445.1831.

Allyl 4,6-*O*-benzylidene α-D-glucopyranoside (**16**): mp (^{0}C): 130.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +16.5; IR (cm^{-1}, $CHCl_3$): 1438, 1335, 1220, 1045, 965, 718; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 3.44 (t, *J* = 9.4 Hz, 1H), 3.57 (dd, *J* = 9.3, 3.9 Hz, 1H), 3.69 (t, *J* = 10.3 Hz, 1H), 3.82 (td, *J* = 9.9, 4.8 Hz, 1H), 3.93 (t, *J* = 9.3 Hz, 1H), 4.02 (ddt, *J* = 12.9, 6.3, 1.1 Hz, 1H), 4.16 – 4.22 (m, 1H), 4.24 (dd, *J* = 10.1, 4.8 Hz, 1H), 4.86 (d, *J* = 3.7 Hz, 1H), 5.22 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.32 (ddd, *J* = 17.3, 3.0, 1.5 Hz, 1H), 5.50 (s, 1H), 5.92 (dddd, *J* = 15.9, 10.4, 6.2, 5.5 Hz, 1H), 7.34 – 7.39 (m, 3H), 7.47 – 7.53 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 62.6, 68.8, 68.9, 71.2, 72.7, 81.0, 98.1,

101.8, 118.2, 126.4, 126.4, 128.3, 128.3, 129.2, 133.6, 137.1; HRMS (ESI-MS): m/z calcd for $[C_{16}H_{20}O_6Na]^+$: 331.1158; Found: 331.1161.

Allyl 2-*O*-benzoyl-4,6-*O*-benzylidene α-D-glucopyranoside (**17**): mp (^{0}C): 77.3; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +5.1; IR (cm^{-1}, $CHCl_3$): 3045, 2914, 1720, 1625, 1438, 1330, 1225, 1062, 948, 715; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 2.81 (s, 1H), 3.64 (t, *J* = 9.4 Hz, 1H), 3.80 (t, *J* = 10.3 Hz, 1H), 3.98 (dd, *J* = 9.1, 4.0 Hz, 1H), 4.03 (ddt, *J* = 13.2, 5.1, 1.5 Hz, 1H), 4.23 (ddt, *J* = 13.2, 5.1, 1.5 Hz, 1H), 4.34 (dd, *J* = 10.2, 4.9 Hz, 1H), 4.40 (t, *J* = 9.5 Hz, 1H), 5.09 (dd, *J* = 9.7, 3.8 Hz, 1H), 5.17 (ddd, *J* = 10.4, 2.8, 1.3 Hz, 1H), 5.24 (d, *J* = 3.8 Hz, 1H), 5.31 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.59 (s, 1H), 5.85 (dddd, *J* = 17.1, 10.5, 5.9, 5.2 Hz, 1H), 7.38 – 7.44 (m, 3H), 7.45 – 7.51 (m, 2H), 7.52 – 7.57 (m, 2H), 7.58 – 7.63 (m, 1H), 8.10 – 8.15 (m, 2H) ; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 62.4, 68.8, 68.8, 68.9, 74.0, 81.5, 96.0, 102.0, 117.7, 126.4, 126.4, 128.4, 128.4, 128.5, 128.5, 129.3, 129.6, 129.9, 129.9, 133.4, 133.4, 137.1, 166.2; HRMS (ESI-MS): m/z calcd for $[C_{23}H_{24}O_7Na]^+$: 435.1420; Found: 435.1414.

Allyl 2-*O*-benzoyl-3-*O*-*tert*-butyldiphenylsilyl-6-*O*-benzyl α-D-glucopyranoside (**4**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +70.6; IR (cm^{-1}, $CHCl_3$): 3045, 2914, 1715, 1625, 1254, 1163, 1097, 1070, 1025, 968, 710; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 0.95 (s, 9H), 2.2 (s, 1H), 3.66 – 3.79 (m, 3H), 3.85 – 3.90 (m, 2H), 4.10 (ddt, *J* = 13.7, 4.5, 1.6 Hz, 1H), 4.35 (t, *J* = 8.8 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.66 (d, *J* = 12.2 Hz, 1H), 5.01 (dd, *J* = 10.5, 1.4 Hz, 1H), 5.07 – 5.23 (m, 3H), 5.86 (dddd, *J* = 16.6, 10.4, 5.8, 5.1 Hz, 1H), 7.26 – 7.46 (m, 13H), 7.48 – 7.55 (m, 1H), 7.62 – 7.68 (m, 2H), 7.68 – 7.73 (m, 2H), 7.82 – 7.87 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.5, 26.9, 26.9, 26.9, 68.1, 69.3, 70.1, 72.2, 73.6, 74.1, 74.3, 95.3, 116.7, 127.7, 127.7, 127.7, 127.7, 127.8, 127.8, 128.0, 128.0, 128.1, 128.1, 128.5, 128.5, 129.8, 129.9, 129.9, 129.9, 129.9, 130.0, 132.9, 133.0, 133.7, 134.3, 135.7, 136.0, 138.3, 166.2 ; HRMS (ESI-MS): m/z calcd for $[C_{39}H_{44}O_7SiNa]^+$: 675.2754; Found: 675.2758.

Allyl 2,3-*O*-isopropylidene α-L- rhamnopyranoside (**18**): mp (^{0}C): 137.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -25.9; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.3 Hz, 3H), 1.36 (s, 3H), 1.53 (s, 3H), 3.14 (s, 1H), 3.32 – 3.47 (m, 1H), 3.68 (dq, *J* = 9.3, 6.1 Hz, 1H), 4.01 (ddt, *J* = 12.8, 6.2, 1.3 Hz, 1H), 4.07 – 4.12 (m, 1H), 4.14 – 4.22 (m, 2H), 5.02 (s, 1H), 5.22 (ddd, *J* = 10.4, 2.7, 1.2 Hz, 1H), 5.31 (ddd, *J* = 17.2, 3.1, 1.6 Hz, 1H), 5.91 (dddd, *J* = 16.7, 10.4, 6.2, 5.3 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 17.5, 26.2,

28.1, 65.9, 68.0, 74.5, 75.9, 78.6, 96.3, 109.5, 117.9, 133.7; HRMS (ESI-MS): m/z calcd for $[C_{12}H_{20}O_5Na]^+$: 267.1208; Found: 267.1212.

Allyl 2,3-*O*-isopropylidene-4-*O*-benzyl α-L-rhamnopyranoside (**19**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -80.4; IR (cm^{-1}, $CHCl_3$): 1610, 1429, 1320, 1235, 1067, 1045, 718; ^1H NMR (400.31MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.3 Hz, 3H), 1.37 (s, 3H), 1.50 (s, 3H), 3.22 (dd, *J* = 9.8, 7.1 Hz, 1H), 3.71 (dd, *J* = 9.8, 6.2 Hz, 1H), 3.93 – 4.03 (m, 1H), 4.12 – 4.19 (m, 2H), 4.24 – 4.31 (m, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.90 (d, *J* = 11.6 Hz, 1H), 5.00 (s, 1H), 5.20 (ddd, *J* = 10.4, 2.7, 1.2 Hz, 1H), 5.23 – 5.34 (m, 1H), 5.89 (dddd, *J* = 16.7, 10.4, 6.2, 5.3 Hz, 1H), 7.24 – 7.29 (m, 1H), 7.30 – 7.37 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 17.9, 26.5, 28.1, 64.7, 68.0, 73.1, 76.2, 78.8, 81.3, 96.2, 109.3, 117.8, 127.7, 128.1, 128.1, 128.4, 128.4, 133.8, 138.5; HRMS (ESI-MS): m/z calcd for $[C_{19}H_{26}O_5Na]^+$: 357.1678; Found: 357.1673.

Allyl 3-*O*-methyl-4-*O*-benzyl α-L-rhamnopyranoside (**20**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -51.6; IR (cm^{-1}, $CHCl_3$): 1622, 1420, 1320, 1228, 1055, 1036, 720; ^1H NMR (400.31MHz, $CDCl_3$): 1.30 (d, *J* = 6.3 Hz, 3H), 2.81 (s, 1H), 3.39 (t, *J* = 9.3 Hz, 1H), 3.48 (s, 3H), 3.57 (dd, *J* = 9.1, 3.3 Hz, 1H), 3.72 (dq, *J* = 9.7, 6.3 Hz, 1H), 3.96 (ddt, *J* = 12.9, 6.2, 1.3 Hz, 1H), 4.06 (s, 1H), 4.10 – 4.18 (m, 1H), 4.61 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 4.1 Hz, 1H), 4.85 (d, *J* = 5.4 Hz, 1H), 5.17 (ddd, *J* = 10.4, 2.8, 1.2 Hz, 1H), 5.27 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1H), 5.88 (dddd, *J* = 21.9, 10.4, 6.1, 5.2 Hz, 1H), 7.24 – 7.29 (m, 1H), 7.30 – 7.37 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 17.9, 57.4, 67.3, 67.8, 67.9, 75.2, 79.9, 81.8, 98.3, 117.4, 127.6, 127.9, 127.9, 128.3, 128.3, 133.8, 138.5; HRMS (ESI-MS): m/z calcd for $[C_{17}H_{24}O_5Na]^+$: 331.1521; Found: 331.1522.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2- *O*-benzoyl-3- *O*-methyl-4- *O*-benzyl α-L- rhamnopyranoside (**5**): mp (^0C): 66.3; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -40.7; IR (cm^{-1}, $CHCl_3$): 3293, 2940, 1740, 1465, 1372, 1265, 1090, 1032, 708; ^1H NMR (400.31MHz, $CDCl_3$): δ 1.24 – 1.30 (m, 1H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.49 – 1.67 (m, 5H), 1.76 – 1.88 (m, 2H), 2.11 – 2.17 (m, 2H), 2.63 (s, 1H), 3.43 – 3.50 (m, 4H), 3.51 – 3.62 (m, 2H), 4.63 (d, *J* = 10.9 Hz, 1H), 4.89 (d, *J* = 10.9 Hz, 1H), 5.71 (s, 1H), 5.86 (d, *J* = 2.9 Hz, 1H), 7.21 – 7.39 (m, 5H), 7.45 – 7.49 (m, 2H), 7.57 – 7.60 (m, 1H), 8.10 – 8.12 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 18.2, 18.2, 22.5, 25.0, 36.6, 36.8, 57.6, 67.6, 72.7, 75.4, 75.5, 78.7, 79.4, 82.6, 82.8, 94.0, 127.9, 128.2 (2C), 128.5 (4C), 129.9,

130.2 (2C), 133.3, 138.3, 151.1, 165.8; HRMS (ESI-MS): m/z calcd for $[C_{30}H_{34}O_8Na]^+$: 545.2151; Found: 545.2156.

Allyl 2,3,4-tri-*O*-benzoyl α/β-D- xylopyranoside [α:β (2.0:1.0)] (**23**): mp (^{0}C): 74.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +13.5; IR (cm^{-1}, $CHCl_3$): 3277, 2939, 1720, 1634, 1425, 1250, 1095, 910, 717; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 3.75 – 4.18 (m, 6H), 4.29 – 4.38 (m, 2H), 4.45 – 5.24 (m, 4H), 5.32 – 5.37 (m, 5H), 5.42 – 5.97 (m, 4H), 6.24 (t, *J* = 9.4 Hz, 1H), 7.28 – 7.59 (m, 18H), 7.96 – 8.06 (m, 12H),; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 58.8, 61.1, 68.8, 69.1, 69.4, 70.0, 70.2, 70.2, 70.3, 71.9, 95.3, 98.9, 117.7, 117.8, 128.3 – 128.4 (12C), 129.1, 129.1, 129.2, 129.3, 129.4, 129.4, 129.7 – 129.9 (12C), 133.1, 133.3, 133.3, 133.4, 133.4, 133.4, 133.5, 133.5, 165.2, 165.4, 165.6, 165.6, 165.8, 165.8; HRMS (ESI-MS): m/z calcd for $[C_{29}H_{26}O_8Na]^+$: 525.1525; Found: 525.1521.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4-tri-*O*-benzoyl α/β-D-xylopyranoside [α:β (1.0:1.5)] (**6**): mp (^{0}C): 58.7; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +8.4; IR (cm^{-1}, $CHCl_3$): 3277, 2939, 2862, 1727, 1600, 1451, 1263, 1096, 908, 709; ^{1}H NMR (400.31MHz, $CDCl_3$): δ 1.29 – 1.40 (m, 2H), 1.47 – 1.76 (m, 10H), 1.77 – 2.28 (m, 8H), 2.48 (s, 1H), 2.65 (s, 1H), 3.95 – 4.16 (m, 2H), 4.27 – 4.59 (m, 2H), 5.21 – 5.60 (m, 4H), 5.71 – 6.53 (m, 4H), 7.29 – 7.61 (m, 18H), 7.89 – 8.16 (m, 12H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.4, 22.5, 22.5, 22.5, 24.9, 24.9, 36.6, 36.7, 36.7, 36.7, 61.2, 61.4, 67.6, 67.9, 68.0, 69.5, 69.7, 70.3, 75.3, 75.4, 78.5, 78.7, 82.4, 82.4, 92.8, 94.8, 128.4 – 128.5 (12C), 128.8, 128.9 (2C), 129.0, 129.1, 129.2, 129.7 – 130.1 (12C), 133.3, 133.4, 133.5, 133.5, 133.5, 133.5, 150.8, 150.9, 164.9, 164.9, 165.4, 165.5, 165.5, 165.8; HRMS (ESI-MS): m/z calcd for $[C_{35}H_{32}O_{10}Na]^+$: 635.1893; Found: 635.1891.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzyl β-D-galactopyranoside (**7aβ**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +25.7; IR (cm^{-1}, $CHCl_3$): 3280, 3025, 2922, 1760, 1492, 1460, 1255, 1230, 1089, 914, 726; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.33 – 1.41 (m, 1H), 1.52 – 1.58 (m, 1H), 1.62 – 1.72 (m, 4H), 1.90 – 1.97 (m, 2H), 2.15 – 2.22 (m, 2H), 2.62 (s, 1H), 3.59 – 3.76 (m, 4H), 3.95 – 4.06 (m, 2H), 4.47 (q, *J* = 11.7 Hz, 2H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.76 (s, 2H), 4.85 (s, 2H), 5.00 (d, *J* = 11.5 Hz, 1H), 5.53 (d, *J* = 8.0 Hz, 1H), 7.09 – 7.54 (m, 20H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.6 (2C), 25.0, 36.8, 36.9, 68.1, 73.0, 73.3, 73.6, 74.3, 74.8, 75.1, 75.6, 78.2, 78.4, 82.3, 82.8, 97.9, 127.7 (3C), 127.8 (2C), 128.1 (4C), 128.2 (2C),

128.4 (3C), 128.6 (4C), 137.9, 138.4, 138.4, 138.7, 151.5; HRMS (ESI-MS): m/z calcd for $[C_{43}H_{46}O_8Na]^+$: 713.3090; Found: 713.3086.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,4,6-tetra-*O*-benzyl α-D-galactopyranoside (**7aα**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +30.2; IR (cm^{-1}, $CHCl_3$): 3275, 3020, 2935, 1765, 1486, 1468, 1250, 1237, 1076, 910, 715; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.29 – 1.36 (m, 1H), 1.52 – 1.59 (m, 1H), 1.60 – 1.68 (m, 4H), 1.84 – 1.92 (m, 2H), 2.16 – 2.23 (m, 2H), 2.58 (s, 1H), 3.58 (dd, *J* = 6.5, 1.2 Hz, 2H), 3.96 (dd, *J* = 10.1, 2.7 Hz, 1H), 4.05 (d, *J* = 1.8 Hz, 1H), 4.13 (t, *J* = 6.5 Hz, 1H), 4.19 (dd, *J* = 10.0, 3.7 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.72 – 4.80 (m, 3H), 4.86 (d, *J* = 11.8 Hz, 1H), 4.97 (d, *J* = 11.3 Hz, 1H), 6.28 (d, *J* = 3.7 Hz, 1H), 7.26 – 7.42 (m, 20H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.6 (2C), 25.1, 36.7, 37.0, 68.5, 72.1, 73.2, 73.5, 73.6, 74.7, 75.1, 75.6, 78.0, 78.6, 82.3, 82.8, 94.6, 127.5 (2C), 127.7 (2C), 127.8, 127.9, 128.0 (2C), 128.1 (2C), 128.3 (2C), 128.4 (4C), 128.5 (4C), 138.0, 138.2, 138.6, 138.8, 151.7; HRMS (ESI-MS): m/z calcd for $[C_{43}H_{46}O_8Na]^+$: 713.3090; Found: 713.3092.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3-di-*O*-benzyl-4,6-di-*O*-(naphthalen-1-yl methyl) α/β-D- galactopyranoside [α:β (1.0:8.0)] (**7b**): mp (^0C): 78.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +60.5; IR (cm^{-1}, $CHCl_3$): 3245, 2910, 1710, 1628, 1435, 1277, 1102, 924, 718; ^1H NMR (400.31MHz, $CDCl_3$): δ 1.35 – 1.39 (m, 2H), 1.53 – 1.79 (m, 10H), 1.90 – 2.01 (m, 4H), 2.18 – 2.28 (m, 4H), 2.63 – 2.68 (m, 2H), 3.70 – 4.32 (m, 12H), 4.55 – 4.69 (m, 4H), 4.80 – 5.19 (m, 12H), 5.60 – 6.42 (m, 2H), 7.30 – 7.58 (m, 32H), 7.71 – 7.84 (m, 16H);^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.6 (4C), 25.1, (2C), 36.8 (2C), 36.9 (2C), 68.2, 68.6, 72.3, 73.1, 73.3, 73.3, 73.6, 73.8, 74.4, 74.6, 74.8, 75.1, 75.3, 75.3, 75.6, 75.8, 78.1, 78.3, 78.5, 78.8, 82.4, 82.4, 82.9, 83.1, 94.7, 98.0, 126.0 – 126.4 (12C), 126.8 – 127.0 (6C), 127.6 – 127.9 (14C), 128.1 – 128.3 (10C), 128.4 – 128.6 (10C), 133.1, 133.2, 133.3, 133.3, 135.4, 135.4, 136.0, 136.2, 138.3, 138.4, 138.5, 138.9, 151.6, 151.8; HRMS (ESI-MS): m/z calcd for $[C_{51}H_{50}O_8Na]^+$: 813.3403; Found: 813.3400.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3-di- *O*-benzyl-4,6-di-*O*-acetyl α/β-D-galactopyranoside [α:β (1.0:2.5)] (**7c**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +49.3; IR (cm^{-1}, $CHCl_3$): 3271, 2937, 1730, 1453, 1368, 1267, 1090, 1025, 723; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.26 – 1.40 (m, 2H), 1.46 – 1.72 (m, 10H), 1.85 – 1.89 (m, 4H), 2.04 (s, 3H),

2.05 (s, 3H), 2.09 – 2.22 (m, 10H), 2.62 (s, 1H), 2.64 (s, 1H), 3.65 – 3.95 (m, 5H), 4.11 – 4.29 (m, 5H), 4.50 – 4.58 (m, 2H), 4.71 – 4.81 (m, 6H), 5.51 – 6.25 (m, 4H), 7.25 – 7.36 (m, 20H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 20.8 (2C), 20.9 (2C), 22.5 (2C), 22.9, 22.6, 25.0 (2C), 36.6, 36.8, 36.9 (2C), 61.7, 62.1, 66.2, 67.2, 69.3, 71.8, 72.2, 72.3, 73.7, 74.6, 75.2, 75.4, 75.6 (2C), 77.5, 78.2, 78.5, 79.3, 82.6, 82.9, 94.2, 97.3, 127.8 – 128.1 (10C), 128.2 – 128.4 (8C), 128.5 (2C), 137.6, 138.0 (3C), 151.2, 151.4, 170.3 (2C), 170.5 (2C); HRMS (ESI-MS): m/z calcd for $[C_{33}H_{38}O_{10}Na]^+$: 617.2363; Found: 617.2368.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3-di- *O*-benzyl-4,6-di-*O*-benzoyl α/β-D-galactopyranoside [α:β (1.0:2.0)] (**7d**): mp (^{0}C): 62.6; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +64.2; IR (cm^{-1}, $CHCl_3$): 3262, 2930, 1736, 1447, 1362, 1256, 1105, 978, 716; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.28 – 1.38 (m, 2H), 1.52 – 1.70 (m, 10H), 1.83 – 1.96 (m, 4H), 2.16 – 2.27 (m, 4H), 2.59 (s, 1H), 2.65 (s, 1H), 3.78 – 4.42 (m, 7H), 4.43 – 4.65 (m, 5H), 4.67 – 4.77 (m, 4H), 4.77 – 4.90 (m, 2H), 5.67 – 6.36 (m, 4H), 7.25 – 7.36 (m, 20H), 7.41 – 7.50 (m, 8H), 7.52 – 7.64 (m, 4H), 8.00 – 8.18 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.6, 22.7 (3C), 25.1 (2C), 36.8 (2C), 37.0 (2C), 62.5, 62.9, 67.1, 68.2, 69.7, 72.1, 72.2, 72.3, 73.8, 74.3, 75.3, 75.5, 75.7, 75.9, 77.7, 78.3, 78.8, 79.6, 82.6, 82.8, 94.4, 97.5, 127.7 (2C), 127.9 (4C), 127.6, 128.2 (6C), 128.4 (4C), 128.5 (8C), 128.6 (2C), 128.7, 129.6 (2C), 129.7 (2C), 130.0 (4C), 130.1, 130.1, 130.2, 130.2, 133.3, 133.3, 133.5, 133.5, 137.6, 137.9, 138.0, 138.2, 151.2, 151.4, 165.7, 165.8, 166.2, 166.2; HRMS (ESI-MS): m/z calcd for $[C_{43}H_{42}O_{10}Na]^+$: 741.2676; Found: 741.2680.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-4-*O*-acetyl-2,3,6-tri-*O*-benzyl α/β-D-galactopyranoside [α:β (1.0:3.0)] (**7e**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +54.1; IR (cm^{-1}, $CHCl_3$): 3028, 2926, 1740, 1509, 1450, 1362, 1225, 1095, 908, 735, 698 ; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.22 – 1.43 (m, 2H), 1.48 – 1.74 (m, 10H), 1.84 – 2.00 (m, 4H), 2.07 (s, 3H), 2.09 (s, 3H), 2.15 – 2.25 (m, 4H), 2.61 (s, 1H), 2.64 (s, 1H), 3.45 – 3.63 (m, 4H), 3.65 – 3.81 (m, 3H), 3.84 – 4.33 (m, 3H), 4.45 – 4.48 (m, 2H), 4.51 – 4.66 (m, 4H), 4.66 – 4.94 (m, 6H), 5.55 – 6.30 (m, 4H), 6.97 – 7.65 (m, 30H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 21.0 (2C), 22.6 (4C), 25.1 (2C), 36.8 (4C), 66.4 – 68.1 (4C), 70.5, 72.1, 72.2, 73.0, 73.7 (3C), 74.7, 75.3, 75.4, 75.6, 75.9, 77.7, 78.2, 78.4, 79.6, 82.7, 82.9, 94.3, 97.5, 127.8 – 128.1 (10C), 128.2 – 128.4 (11C), 128.5 – 128.6 (9C),

137.7 (2C), 137.8, 138.2, 138.2, 138.3, 151.3, 151.5, 170.3, 170.3; HRMS (ESI-MS): m/z calcd for $[C_{38}H_{42}O_9Na]^+$: 665.2727; Found: 665.2734.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3-di-*O*-benzyl-4-*O*-acetyl-6-*O*-(naphthalen-1-yl methyl) α/β-D- galactopyranoside [α:β (1.0:3.5)] (**7f**): mp (^{0}C): 72.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +82.3; IR (cm^{-1}, $CHCl_3$): 2925, 2858, 2320, 1735, 1604, 1513, 1455, 1360, 1265, 1110, 968, 711; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.25 – 1.41 (m, 2H), 1.47 – 1.77 (m, 10H), 1.91 – 1.93 (m, 4H), 2.03 (s, 3H), 2.04 (s, 3H), 2.14 – 2.18 (m, 4H), 2.50 – 2.66 (m, 2H), 3.48 – 3.73 (m, 6H), 4.76 – 3.42 (m, 4H), 4.47 – 4.66 (m, 4H), 4.70 – 4.92 (m, 8H), 5.49– 6.38 (m, 4H), 7.26 – 7.40 (m, 20H), 7.45 – 7.50 (m, 6H), 7.78 – 7.86 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 21.0 (2C), 22.6 (4C), 25.0 (2C), 36.7, 36.8 (2C), 37.0, 66.5, 67.5, 67.6, 68.1, 70.5, 72.1, 72.2, 73.0, 73.7, 73.8 (2C), 74.7, 75.2, 75.4, 75.6, 75.9, 77.7, 78.2, 78.5, 79.6, 82.6, 82.9, 94.3, 97.5, 126.1 – 126.3 (6C), 126.9, 127.1, 127.8 – 128.1 (13C), 128.3– 128.5 (13C),133.2 (2C), 133.3 (2C), 135.1, 135.2, 137.7, 138.1 (2C), 138.3, 151.3, 151.5, 170.3 (2C); HRMS (ESI-MS): m/z calcd for $[C_{42}H_{44}O_9Na]^+$: 715.2883; Found: 715.2878.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3-di-*O*-benzyl-4-*O*-acetyl-6-*O*-*tert*-butyldiphenyl silyl α/β-D- galactopyranoside [α:β (1.0:2.0)] (**7g**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +10.4; IR (cm^{-1}, $CHCl_3$): 3015, 2935, 2862, 1725, 1615, 1458, 1366, 1260, 1117, 950, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.08 (s, 9H), 1.25 – 1.41 (m, 2H), 1.49 – 1.57 (m, 2H), 1.56 – 1.74 (m, 8H), 1.81 – 1.96 (m, 4H), 2.01 (s, 3H), 2.04 (s, 3H), 2.07 – 2.26 (m, 4H), 2.58 – 2.61 (m, 2H), 3.59 – 3.90 (m, 8H), 3.88 – 4.25 (m, 2H), 4.47 – 4.87 (m, 8H), 5.39 – 6.30 (m, 4H), 7.26 – 7.47 (m, 32H), 7.64 – 7.68 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.2 (2C), 20.9 (2C), 22.5 (2C), 22.6 (2C), 25.0, 25.1, 26.8 (2C), 26.9 (4C), 36.7 – 37.0 (4C), 61.1, 61.5, 65.3, 67.0, 71.7, 72.2, 72.3, 73.7, 74.0, 74.7, 75.2, 75.3,75.7, 76.1, 77.8, 78.2, 78.3, 79.7, 82.6, 82.9, 94.4, 97.4, 127.7 – 128.0 (16C), 128.1 – 128.6 (16C), 129.9 (3C), 130.0, 133.0 (2C), 133.1 (2C), 135.6, 135.7 (2C), 135.8, 137.8, 138.2 (2C), 138.3, 151.3, 151.6, 170.0, 170.1 ; HRMS (ESI-MS): m/z calcd for $[C_{47}H_{54}O_9SiNa]^+$: 813.3435; Found: 813.3427.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl α/β D-galactopyranosyl) α-D-glucopyranoside [α:β (10:1)] (**27a**): mp (^{0}C): 67.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +28.6; IR (cm^{-1}, $CHCl_3$): 3015, 2965, 1730, 1510, 1445, 1365, 1215, 1095, 910, 715; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.38 – 3.39 (m, 6H), 3.43 – 3.57 (m, 5H). 3.61 – 3.65 (m, 2H),

3.84 – 4.13 (m, 10H), 4.28 – 4.53 (m, 6H), 4.53 – 4.65 (m, 2H), 4.67 – 4.74 (m, 2H), 4.74 – 4.80 (m, 2H), 4.82 – 4.99 (m, 7H), 5.17 – 5.32 (m, 4H), 5.53 – 6.24 (m, 4H), 7.12 – 7.31 (m, 26H), 7.33 – 7.56 (m, 32H), 7.83– 8.05 (m, 12H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 55.5, 55.5, 66.7, 66.7, 68.6, 68.6, 68.8, 68.8, 69.4, 69.4, 69.6, 69.6, 70.8, 70.8, 72.3, 72.3, 73.0, 73.0, 73.3, 73.3, 73.3, 73.3, 74.9, 74.9, 75.1, 75.1, 76.5, 76.5, 78.6, 78.6, 96.8, 96.9, 98.0, 104.3, 127.5 – 127.7 (9), 127.8 – 127.9 (8), 127.9 – 128.0 (8), 128.1 – 128.2 (14), 128.3 – 128.5 (14), 128.5 – 128.6 (6), 129.0, 129.2, 129.2, 129.2, 129.4, 129.4, 129.8 – 129.8 (6), 133.2, 133.2, 133.5, 133.5, 133.5, 133.5, 137.9, 138.2, 138.6, 138.7, 138.8, 138.9, 139.1, 165.5, 165.7, 165.9, 165.9, 166.0, 166.3; HRMS (ESI-MS): m/z calcd for $[C_{62}H_{60}O_{14}Na]^+$: 1051.3881; Found: 1051.3885.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzyl-3,4-di-*O*-benzoyl α/β-D-fucopyranoside [α:β (1.0:7.0)] (**28**): mp (^{0}C): 58.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -16.2; IR (cm^{-1}, $CHCl_3$): 3240, 2928, 1735, 1620, 1435, 1250, 1120, 1065, 910, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$) :δ 1.26 (d, *J* = 6.5 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.36 – 1.44 (m, 2H), 1.53 – 1.64 (m, 2H), 1.64 – 1.81 (m, 8H), 1.95 – 2.03 (m, 4H), 2.23 – 2.32 (m, 4H), 2.69 (s, 1H), 2.71 (s, 1H), 4.04 – 4.29 (m, 4H), 4.50 – 5.61 (m, 6H), 5.61 – 6.53 (m, 4H), 7.30 – 7.14 (m, 10H), 7.31 – 7.36 (m, 4H), 7.44 – 7.58 (m, 6H), 7.62 – 7.66 (m, 2H), 7.79 – 7.90 (m, 4H), 7.94 – 8.09 (m, 4H); ^{13}C NMR (101.67 MHz, $CDCl_3$): δ 16.2, 16.2, 22.6, 22.6, 22.6, 22.6, 24.5, 24.5, 36.7, 36.7, 36.9, 36.9, 67.8, 70.3, 70.5, 71.2, 71.8, 72.2, 72.8, 73.4, 75.0, 75.1, 75.4, 75.5, 78.2, 78.7, 82.5, 82.9, 93.9, 97.6, 127.8 – 128.1 (6C), 128.3 – 128.5 (12C), 129.4 – 129.5 (4C), 129.6 – 129.9 (8C), 133.1, 133.2, 133.4, 133.4, 137.3, 137.5, 151.2, 151.5, 165.4, 165.5, 165.8, 165.8; HRMS (ESI-MS): m/z calcd for$[C_{36}H_{36}O_9Na]^+$: 635.2257; Found: 635.2251.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2-*O*-benzyl-3,4-di-benzoyl α-L-fucopyranosyl) α-D-glucopyranoside (**29**): mp (^{0}C): 71.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -29.7; IR (cm^{-1}, $CHCl_3$): 3022, 2950, 1710, 1526, 1440, 1357, 1212, 1086, 912, 720; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.5 Hz, 3H), 3.43 (s, 3H), 3.82 (dd, *J* = 11.8, 6.4 Hz, 1H), 3.92 (dd, *J* = 11.7, 1.8 Hz, 1H), 4.15 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.26 – 4.40 (m, 2H), 4.70 (q, *J* = 12.2 Hz, 2H), 5.18 (d, *J* = 3.5 Hz, 1H), 5.25 (d, *J* = 3.6 Hz, 1H), 5.31 (dd, *J* = 10.2, 3.6 Hz, 1H), 5.59 (t, *J* = 9.9 Hz, 1H), 5.65 (d, *J* = 3.1 Hz, 1H), 5.75 (dd, *J* = 10.5, 3.3 Hz, 1H), 6.20 (t, *J* = 9.8 Hz, 1H), 7.17 – 7.33 (m, 9H), 7.33 – 7.55 (m, 10H), 7.56 –

7.62 (m, 1H), 7.78 – 8.04 (m, 3H); ^{13}C NMR (100.67MHz, $CDCl_3$): δ 16.1, 55.7, 65.1, 67.0, 69.5, 69.8, 70.7, 70.7, 72.3, 72.4, 72.7, 73.4, 96.9, 98.3, 127.8, 128.0, 128.0, 128.3, 128.3, 128.4 (4C), 128.5 (2C), 128.6 (4C), 129.0, 129.2, 129.4, 129.7 (4C), 129.8, 129.8, 129.9, 129.9, 130.0 (4C), 133.0, 133.2, 133.3, 133.5, 133.6, 138.0, 165.5, 165.6, 165.9, 165.9, 166.0; HRMS (ESI-MS): m/z calcd for $[C_{55}H_{50}O_{15}Na]^+$: 973.3047; Found: 973.3039.

Allyl 2-*O*-(*p*-methoxybenzyl)-3-*O*-(4-oxopentanoyl)-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-α-L-fucopyranoside (**30**): mp (^{0}C): 87.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -74.6; IR (cm^{-1}, $CHCl_3$): 3014, 2930, 2849, 1760, 1720, 1628, 1465, 1357, 1265, 1105, 930, 720; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.5 Hz, 3H), 2.01 (s, 3H), 2.13 (ddd, *J* = 14.5, 8.3, 5.5 Hz, 1H), 2.31 (ddd, *J* = 14.5, 8.3, 5.5 Hz, 1H), 2.38 – 2.56 (m, 2H), 3.62 – 3.70 (m, 3H), 3.77(s, 3H), 3.93 – 4.05 (m, 2H), 4.11 (dd, *J* = 12.9, 5.2 Hz, 1H), 4.37 (dd, *J* = 10.2, 3.4 Hz, 1H), 4.50 – 4.81 (m, 4H), 5.05 (d, *J* = 4.1 Hz, 1H), 5.14 – 5.36 (m, 5H), 5.66 (t, *J* = 6.3 Hz, 1H), 5.90 (dddd, *J* = 17.1, 10.4, 6.5, 5.3 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 7.16 – 7.40 (m, 8H), 7.44 – 7.56 (m, 3H), 7.84 – 8.12 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.1, 27.7, 29.7, 37.7, 55.3, 60.9, 64.5, 68.5, 69.0, 69.8, 70.1, 70.1, 72.6, 73.0, 74.0, 96.2, 96.2, 113.9, 113.9, 118.3, 128.4 (4C), 128.5 (2C), 129.4, 129.4, 129.4, 129.8 (2C), 129.9 (2C), 130.0 (2C), 130.1 (2C), 130.4, 133.3, 133.4, 133.5,133.9, 159.4, 165.0, 165.3, 165.6, 172.4, 206.4; HRMS (ESI-MS): m/z calcd for $[C_{48}H_{50}O_{15}Na]^+$: 889.3047; Found: 889.3045.

Allyl 3-*O*-(4-oxopentanoyl)-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-α-L-fucopyranoside (**31**): mp (^{0}C): 97.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -37.4; IR (cm^{-1}, $CHCl_3$): 3025, 2923, 2820, 1735, 1630, 1450, 1365, 1243, 1108, 936, 714; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.12 (d, *J* = 6.6 Hz, 3H), 2.06 (s, 3H), 2.15 – 2.29 (m, 1H), 2.34 – 2.45 (m, 1H), 2.47 – 2.62 (m, 2H), 2.72 (s, 1H), 3.78 (dd, *J* = 12.4, 6.0 Hz, 1H), 3.94 (dd, *J* = 10.0, 3.9 Hz, 1H), 4.00 – 4.15 (m, 3H), 4.22 (ddt, *J* = 12.8, 5.4, 1.3 Hz, 1H), 4.68 (dd, *J* = 12.4, 3.9 Hz, 1H), 5.03 (dd, *J* = 6.3, 4.3 Hz, 2H), 5.22 – 5.28 (m, 2H), 5.29 – 5.37 (m, 3H), 5.73 (t, *J* = 6.6 Hz, 1H), 5.96 (dddd, *J* = 16.9, 10.4, 6.3, 5.5 Hz, 1H), 7.32 – 7.39 (m, 6H), 7.47 – 7.56 (m, 3H), 7.94 – 8.04 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.0, 27.6, 29.7, 37.7, 61.0, 64.9, 67.6, 68.7, 68.9, 69.5, 69.6, 70.1, 75.7, 97.4, 97.6, 118.2, 128.3 (2C), 128.3 (4C), 129.1, 129.2, 129.3, 129.9 (4C), 130.0 (2C), 133.2, 133.4

(2C), 133.6, 164.9, 165.2, 165.5, 172.2, 206.4; HRMS (ESI-MS): m/z calcd for $[C_{40}H_{42}O_{14}Na]^+$: 769.2472; Found: 769.2473.

Allyl 2-*O*-(2,3-di-*O*-benzyl-4-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl α-D-galactopyranosyl)-3-*O*-(4-oxopentanoyl)-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-α-L-fucopyranoside (**32**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -49.7; IR (cm^{-1}, $CHCl_3$): 3280, 3025, 2930, 2855, 1752, 1486, 1450, 1265, 1232, 1105, 1030, 915, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.95 – 1.24 (m, 12H). 1.88 – 2.03 (m, 7H), 2.09 – 2.19 (m, 1H), 2.27 – 2.45 (m, 2H), 3.50 – 3.77 (m, 3H), 3.89 (dd, *J* = 10.2, 3.5 Hz, 1H), 3.93 (dd, *J* = 10.3, 3.5 Hz, 1H), 3.98 – 4.16 (m, 4H), 4.26 (t, *J* = 6.7 Hz, 1H), 4.52 (dd, *J* = 10.3, 3.2 Hz, 1H), 4.62 – 4.77 (m, 3H), 4.85 (d, *J* = 5.8 Hz, 1H), 4.88 (d, *J* = 4.7 Hz, 1H), 4.97 – 5.10 (m, 3H), 5.16 (d, *J* = 10.3 Hz, 1H), 5.27 – 5.36 (m, 4H), 5.75 – 5.79 (m, 2H), 5.93 (dddd, *J* = 16.9, 10.4, 6.3, 5.5 Hz, 1H), 7.22 – 7.56 (m, 25H), 7.57 – 7.72 (m, 4H), 7.81 – 8.07 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.1, 19.2, 21.0, 27.0, 27.5, 27.5, 27.5, 29.7, 37.6, 62.0, 62.9, 64.6, 68.0, 68.7, 69.3, 69.7, 70.8, 71.2, 71.3, 71.4, 72.5, 72.8, 75.5, 75.9, 76.0, 96.5, 98.1, 100.5, 117.6, 127.6 – 127.8 (10C), 128.4 – 128.5 (12C), 129.4, 129.5, 129.6, 129.9 – 130.1 (8C), 132.9, 133.1, 133.3, 133.3, 133.3, 134.3, 135.8, 135.9, 138.5, 138.8, 165.0, 165.5, 165.6, 170.2, 172.3, 206.2; HRMS (ESI-MS): m/z calcd for $[C_{78}H_{84}O_{20}SiNa]^+$: 1391.5223; Found: 1391.5220.

Allyl 2-*O*-(2,3-di-*O*-benzyl-4-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl α-D-galactopyranosyl)-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-α-L-fucopyranoside (**33**): mp (^{0}C): 88.6; ; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -38.3; IR (cm^{-1}, $CHCl_3$): 3020, 2918, 2837, 1730, 1470, 1463, 1255, 1226, 1118, 1026, 917, 715; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.93 (s, 3H), 2.58 (s, 1H), 3.55 (dd, *J* = 12.9, 5.3 Hz, 1H), 3.58 – 3.68 (m, 2H), 3.80 – 3.87 (m, 2H), 3.88 – 3.98 (m, 3H), 4.03 (dd, *J* = 12.9, 5.8 Hz, 1H), 4.09 (dd, *J* = 10.2, 3.3 Hz, 1H), 4.22 – 4.27 (m, 1H), 4.30 (dd, *J* = 10.1, 3.1 Hz, 1H), 4.63 – 4.72 (m, 2H), 4.77 – 4.94 (m, 4H), 4.96 – 5.04 (m, 2H), 5.09 – 5.19 (m, 3H), 5.28 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 5.83 (dd, *J* = 9.5, 7.9 Hz, 1H), 5.91 (dddd, *J* = 17.0, 10.3, 6.6, 5.3 Hz, 1H), 7.22 – 7.28 (m, 1H), 7.30 – 7.44 (m, 17H), 7.45 – 7.58 (m, 7H), 7.57 – 7.65 (m, 4H), 7.86 – 8.02 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.1, 19.1, 20.9, 26.9, 26.9, 26.9, 61.6, 63.0, 65.0, 67.7, 68.2, 68.4, 68.6, 69.4, 70.9, 72.3, 72.8, 73.1, 73.9, 76.0,

76.0, 76.1, 97.1, 98.1, 100.6, 117.2, 127.4 – 127.7 (10C), 128.2 – 128.5 (12C), 128.8, 129.2, 129.4, 129.7 – 129.9 (8C), 132.8, 133.0, 133.3, 133.3, 133.6, 134.2, 135.7, 135.9, 138.5, 139.0, 165.4, 165.6, 165.8, 170.0; HRMS (ESI-MS): m/z calcd for $[C_{73}H_{78}O_{18}SiNa]^+$: 1293.4855; Found: 1293.4862.

Allyl 2-*O*-(2,3-di-*O*-benzyl-4-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl α-D-galactopyranosyl)-3-*O*-(2-O-benzoyl-3-O-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-α-L-fucopyranoside (**34**): mp (^{0}C): 80.6; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -56.3; IR (cm^{-1}, $CHCl_3$): 3023, 2927, 2852, 1720, 1615, 1460, 1345, 1264, 1115, 952, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.01 – 1.15 (m, 12H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.89 (s, 3H), 3.40 (s, 3H), 3.43 – 3.56 (m, 3H), 3.57 – 3.65 (m, 2H), 3.66 – 3.73 (m, 2H), 3.77 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.86 – 3.97 (m, 3H), 4.06 – 4.16 (m, 2H), 4.25 (t, *J* = 6.8 Hz, 1H), 4.31 (dd, *J* = 10.1, 2.5 Hz, 1H), 4.42 (dd, *J* = 12.4, 4.5 Hz, 1H), 4.59 – 4.75 (m, 4H), 4.80 – 4.94 (m, 4H), 4.97 (d, *J* = 3.4 Hz, 1H), 5.01 (d, *J* = 3.4 Hz, 1H), 5.15 – 5.18 (m, 2H), 5.28 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.37 (dd, *J* = 8.2, 5.7 Hz, 1H), 5.50 (d, *J* = 5.7 Hz, 1H), 5.70 (t, *J* = 7.9 Hz, 1H), 5.77 (d, *J* = 5.7 Hz, 1H), 5.89 (dddd, *J* = 17.0, 10.3, 6.6, 5.3 Hz, 1H), 7.05 – 7.17 (m, 3H), 7.20 – 7.48 (m, 28H), 7.49 – 7.66 (m, 6H), 7.81 – 7.83 (m, 2H), 7.86 – 8.13 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.5, 18.3, 19.2, 21.0, 27.0, 27.0, 27.0, 57.5, 61.6, 62.5, 66.0, 67.6, 68.5, 68.5, 69.3, 69.5, 70.2, 71.1, 72.0, 72.6, 73.4, 73.6, 75.1, 75.3, 76.1, 77.7, 79.4, 79.9, 80.3, 98.1, 98.8, 99.9, 101.2, 116.9, 127.6 – 127.8 (8C), 128.1 – 128.5 (22C),129.3, 129.4, 129.5, 129.7 – 130.1 (10C), 132.8, 133.0, 133.2, 133.2, 133.2, 133.3, 134.4, 135.8, 136.0, 138.5, 138.5, 138.8, 165.0, 165.5, 165.6, 166.2, 170.1; HRMS (ESI-MS): m/z calcd for$[C_{94}H_{100}O_{23}SiNa]^+$: 1648.6356; Found: 1648.6360.

Allyl 2-*O*-(*p*-methoxybenzyl)-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-α-L-fucopyranoside (**35**): mp (^{0}C): 93.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -24.9; IR (cm^{-1}, $CHCl_3$): 3015, 2935, 2849, 1715, 1625, 1460, 1355, 1260, 1102, 937, 710; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.16 (d, *J* = 6.6 Hz, 3H), 2.48 (s, 1H), 3.59 (dd, *J* = 12.2, 7.0 Hz, 1H), 3.71 (d, *J* = 4.3 Hz, 1H), 3.76 (s, 3H), 3.77 – 3.89 (m, 2H), 3.96 (dd, *J* = 13.0, 6.6 Hz, 1H), 4.09 (dd, *J* = 13.0, 5.2 Hz, 1H), 4.14 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.47 – 4.60 (m, 2H), 4.67 – 4.77 (m, 2H), 5.02 (d, *J* = 5.1 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 5.28 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.22 – 5.32 (m, 2H), 5.80 (t, *J* = 7.7 Hz, 1H), 5.89 (dddd, *J* =

17.1, 10.4, 6.5, 5.3 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.43 (m, 6H), 7.46 – 7.54 (m, 3H), 7.96 – 8.00 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.1, 55.3, 61.2, 65.2, 68.3, 69.3, 69.6, 70.7, 72.2, 73.0, 74.0, 77.4, 96.1, 98.6, 113.9, 113.9, 118.1, 128.5 (4C), 128.6 (2C), 129.0, 129.2, 129.3, 129.9 (6C), 130.0 (2C), 130.5, 133.5, 133.5, 133.7, 134.0, 159.4, 165.6, 165.6, 165.8; HRMS (ESI-MS): m/z calcd for$[C_{43}H_{44}O_{13}Na]^+$: 791.2680; Found: 791.2682.

Allyl 2-*O*-(*p*-methoxybenzyl)-3-*O*-(2-*O*-benzoyl-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-α-L-fucopyranoside (**36**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -15.5; IR (cm^{-1}, $CHCl_3$): 3068, 2927, 1715, 1610, 1440, 1247, 1108, 1027, 962, 718; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.20 (d, *J* = 6.5 Hz, 3H), 1.38 (d, *J* = 6.1 Hz, 3H), 3.45 (s, 3H), 3.51 (t, *J* = 9.5 Hz, 1H), 3.59 (dd, *J* = 12.3, 6.3 Hz, 1H), 3.71 (s, 3H), 3.72 – 3.74 (m, 1H), 3.76 – 3.83 (m, 2H), 3.90 (dd, *J* = 10.3, 3.7 Hz, 1H), 4.00 (dd, *J* = 12.9, 6.7 Hz, 1H), 4.12 (dd, *J* = 13.0, 5.2 Hz, 1H), 4.17 – 4.27 (m, 2H), 4.55 (d, *J* = 4.3 Hz, 1H), 4.58 (d, *J* = 4.3 Hz, 1H), 4.64 (d, *J* = 13.7Hz, 1H), 4.68 (d, *J* = 13.7Hz, 1H), 4.76 (d, *J* = 13.7Hz, 1H), 4.89 – 4.92 (m, 2H), 5.16 – 5.24 (m, 2H), 5.24 – 5.29 (m, 1H), 5.32 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.38 (dd, *J* = 6.2, 4.7 Hz, 1H), 5.55 (dd, *J* = 2.9, 2.0 Hz, 1H), 5.67 (t, *J* = 6.4 Hz, 1H), 5.92 (dddd, *J* = 17.0, 10.3, 6.6, 5.3 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 7.19 – 7.24 (m, 4H), 7.25 – 7.39 (m, 9H), 7.40 – 7.50 (m, 4H), 7.51 – 7.60 (m, 2H), 7.84 – 7.87 (m, 2H), 7.99 – 8.07(m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.8, 18.5, 55.3, 57.6, 61.0, 66.3, 68.4, 68.5, 68.7, 69.2, 70.2, 71.1, 72.7, 74.6, 75.3, 75.3, 79.2, 79.8, 80.5, 96.0, 98.4, 99.7, 113.8, 113.8, 118.2, 127.7, 128.3 – 128.5 (12C), 129.4, 129.4, 129.5, 129.9 – 130.1 (11C), 130.3, 133.3, 133.3, 133.4, 133.4, 134.1, 138.8, 159.4, 165.0, 165.5, 165.6, 166.2; HRMS (ESI-MS): m/z calcd for$[C_{64}H_{66}O_{18}Na]^+$: 1145.4147; Found: 1145.4144.

Allyl 3-*O*-(2-*O*-benzoyl-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-α-L-fucopyranoside (**37**): Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -8.2; IR (cm^{-1}, $CHCl_3$): 3039, 2935, 1730, 1622, 1430, 1235, 1095, 1014, 970, 709; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.2 Hz, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 2.61 (s, 1H), 3.34 – 3.49 (m, 1H), 3.42 (s, 3H), 3.71 – 3.84 (m, 3H), 3.91 – 3.99 (m, 1H), 3.99 – 4.14 (m, 4H), 4.22 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.56 – 4.70 (m, 2H), 4.80 – 4.85 (m, 2H), 5.00 (s, 1H), 5.16 (d, *J* = 4.7 Hz, 1H), 5.20 – 5.30 (m, 2H), 5.30 – 5.39 (m, 2H), 5.48 – 5.53 (m, 1H), 5.74 (t, *J* = 6.4 Hz, 1H), 5.95 (dddd, *J* = 17.0, 10.3, 6.6,

5.3 Hz, 1H), 7.09 – 7.21 (m, 2H), 7.26 – 7.39 (m, 10H), 7.42 – 7.46 (m, 3H), 7.49 – 7.56 (m, 2H), 7.81 – 7.83 (m, 2H), 7.97 – 8.03 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.9, 18.0, 57.5, 61.1, 66.7, 67.6, 68.4, 68.5, 68.8, 69.2, 69.6, 70.0, 75.3, 77.1, 79.5, 79.7, 80.4, 97.7, 98.2, 99.9, 118.2, 127.7, 128.2 – 128.5 (11C), 129.2, 129.3, 129.8 – 130.1 (11C), 133.2, 133.4, 133.4, 133.4, 133.9, 138.6, 165.2, 165.4, 165.6, 166.1; HRMS (ESI-MS): m/z calcd for$[C_{56}H_{58}O_{17}Na]^+$: 1025.3572; Found: 1025.3570.

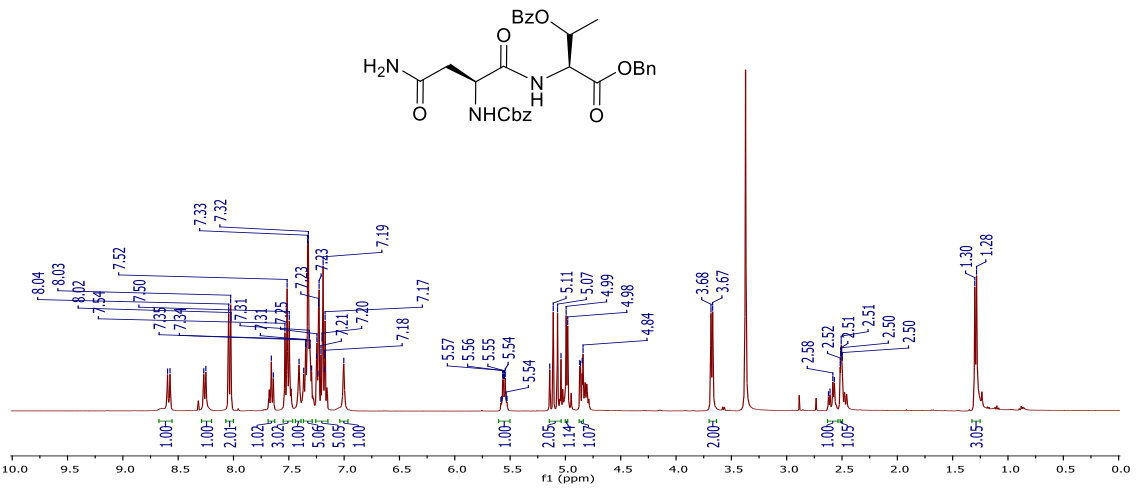
1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-(2,3-di-*O*-benzyl-4-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl α-D- galactopyranosyl)-3-*O*-(2-O-benzoyl-3-O-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-α-L-fucopyranoside (**38**): mp (^{0}C): 74.5; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -27.1; IR (cm^{-1}, $CHCl_3$): 3016, 2942, 2837, 1733, 1628, 1451, 1340, 1245, 1106, 934, 715; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.24 – 1.28 (m, 6H), 1.29 – 1.40 (m, 1H), 1.51 – 1.60 (m, 1H), 1.61 – 1.76 (m, 4H), 1.89 – 1.97 (m, 5H), 2.25 – 2.32 (m, 2H), 2.64 (s, 1H), 3.22 (s, 3H), 3.33 – 3.43 (m, 2H), 3.62 (dd, *J* = 10.1, 6.3 Hz, 1H), 3.68 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.75 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.80 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.82 – 3.95 (m, 2H), 4.02 (dd, *J* = 9.5, 6.2 Hz, 1H), 4.08 (dd, *J* = 10.2, 3.1 Hz, 1H), 4.31 – 4.41 (m, 3H), 4.45 – 4.56 (m, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 8.3 Hz, 1H), 4.83 – 4.97 (m, 5H), 5.20 (d, *J* = 5.9 Hz, 1H), 5.38 (dd, *J* = 8.2, 5.9 Hz, 1H), 5.42 – 5.50 (m, 2H), 5.59 (t, *J* = 8.0 Hz, 1H), 5.72 (d, *J* = 2.5 Hz, 1H), 6.31 (d, *J* = 3.6 Hz, 1H), 7.10 – 7.14 (m, 2H), 7.22 – 7.35 (m, 14H), 7.35 – 7.44 (m, 11H), 7.44 – 7.50 (m, 4H), 7.51 – 7.63 (m, 2H), 7.71 – 7.75 (m, 4H), 7.76 – 7.81 (m, 2H), 7.86 – 7.92 (m, 2H), 7.95 – 7.99 (m, 2H), 8.01 – 8.08 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.9, 18.5, 19.1, 21.0, 22.8, 22.8, 25.1, 26.9, 26.9, 26.9, 36.9, 37.2, 57.4, 62.1, 62.4, 67.8, 68.7, 69.2, 69.7, 69.9, 70.9, 71.4, 72.0, 72.2, 72.8, 74.1, 74.9, 75.1, 75.4, 76.8, 77.2, 78.1, 79.6, 79.8, 83.1, 95.6, 97.2, 99.1, 99.6, 127.4 – 127.9 (8C), 128.1 – 128.5 (22C), 129.2, 129.2, 129.4, 129.8 – 130.1 (11C), 133.1, 133.2, 133.2, 133.2, 133.2, 133.3, 135.8, 135.8, 138.3, 138.8, 139.0, 151.7, 165.2, 165.3, 165.6, 166.3, 170.2; MALDI-TOF: m/z calcd for$[C_{100}H_{106}O_{25}SiNa]^+$: 1758.6724; Found: 1758.6698.

Allyl 2-*O*-benzoyl-3-*O*-*tert*-butyldiphenylsilyl-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-6-*O*-benzyl α-D-glucopyranoside (**39**): mp (^{0}C): 81.7; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +28.2; IR (cm^{-1}, $CHCl_3$): 3025, 2920, 2830, 1725, 1620, 1450, 1347, 1255, 1105, 970, 715; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.95 (s, 9H), 3.26 (dd, *J* = 12.3, 6.4 Hz,

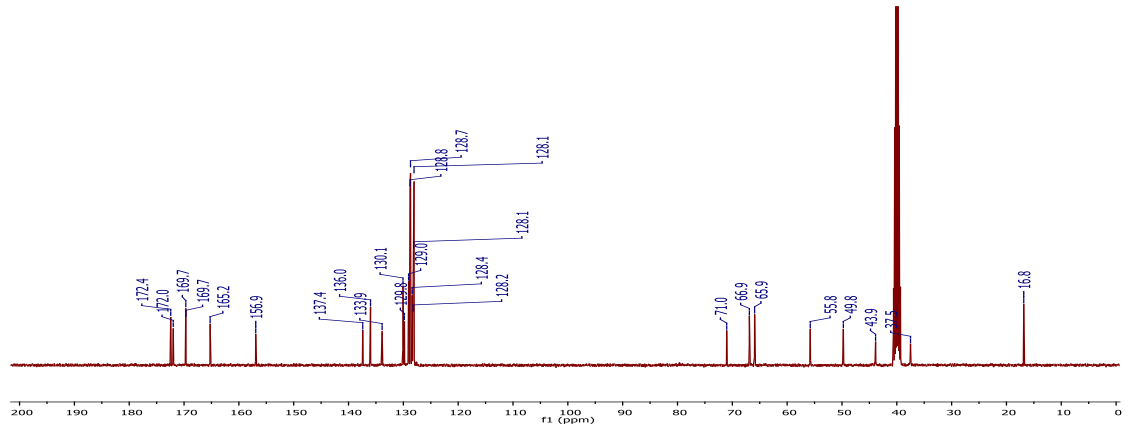
1H), 3.44 – 3.51(m, 1H), 3.59 (ddt, *J* = 12.9, 5.5, 1.4 Hz, 1H), 3.69 – 3.79 (m, 2H), 3.91 – 4.07 (m, 4H), 4.33 (d, *J* = 3.7 Hz, 1H), 4.40 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.83 (d, *J* = 5.2 Hz, 1H), 5.05 (td, *J* = 6.5, 4.2 Hz, 1H), 5.16 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.26 – 5.36 (m, 2H), 5.59 (t, *J* = 7.0 Hz, 1H), 5.86 (dddd, *J* = 15.8, 10.5, 6.1, 5.4 Hz, 1H), 5.95 (t, *J* = 9.3 Hz, 1H), 7.21 – 7.26 (m, 2H), 7.27 – 7.33 (m, 4H), 7.34 – 7.41 (m, 7H), 7.42 – 7.47 (m, 4H), 7.48 – 7.55 (m,4H), 7.56 – 7.62 (m, 4H), 7.72 – 7.74 (m, 2H), 7.87 – 7.90 (m, 2H), 7.96 – 8.04 (m, 4H), 8.10 – 8.20 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.1, 26.7, 26.7, 26.7, 60.9, 67.9, 68.5, 68.9, 69.5, 69.9, 70.0, 72.3,73.4, 73.9, 76.7, 97.6, 100.1, 116.8, 127.5 – 128.0 (8C), 128.1 – 128.5 (12C), 129.1, 129.2, 129.3, 129.7, 129.7 – 130.0 (8C), 131.0, 132.7, 132.7, 133.3,133.3, 133.3, 133.7, 134.2, 135.9, 136.0, 137.9, 164.9, 165.3, 165.4, 165.8; HRMS (ESI-MS): m/z calcd for$[C_{65}H_{64}O_{14}SiNa]^+$: 119.3963; Found: 119.3967.

Allyl 2-*O*-benzoyl-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-6-*O*-benzyl α-D-glucopyranoside (**40**): mp (^{0}C): 77.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +33.0; IR (cm^{-1}, $CHCl_3$): 3029, 2918, 2825, 1730, 1623, 1456, 1340, 1260, 1107, 960, 721; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 2.35 (s, 1H), 3.31 (dd, *J* = 12.3, 6.3 Hz, 1H), 3.55 – 3.65 (m, 1H), 3.75 – 3.85 (m, 3H), 4.00 – 4.12 (m, 2H), 4.13 – 4.26 (m, 2H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.93 (d, *J* = 5.0 Hz, 1H), 5.02 (d, *J* = 3.8 Hz, 1H), 5.07 (td, *J* = 6.4, 4.2 Hz, 1H), 5.22 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.31 (ddt, *J* = 10.0, 3.0, 1.4 Hz, 2H), 5.57 – 5.68 (m, 2H), 5.91 (dddd, *J* = 15.8, 10.5, 6.1, 5.4 Hz, 1H), 7.30 – 7.45 (m, 11H), 7.64 – 7.46 (m, 6H), 7.80 – 7.90 (m, 2H), 7.95 – 8.05 (m, 4H), 8.17 – 8.22 (m, 2H) ; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 60.9, 67.8, 68.8, 68.8, 69.7, 70.0, 70.3, 71.6, 73.4, 74.5, 75.6, 97.6, 99.9, 118.1, 127.9, 127.9, 128.4, 128.4, 128.5 (8C), 129.1 (2C), 129.3 (2C), 129.9 (8C), 130.2, 133.2, 133.4, 133.4, 133.4, 133.4, 137.9, 165.0, 165.3, 165.4, 166.9; HRMS (ESI-MS): m/z calcd for$[C_{49}H_{46}O_{14}Na]^+$: 881.2785; Found: 881.2787.

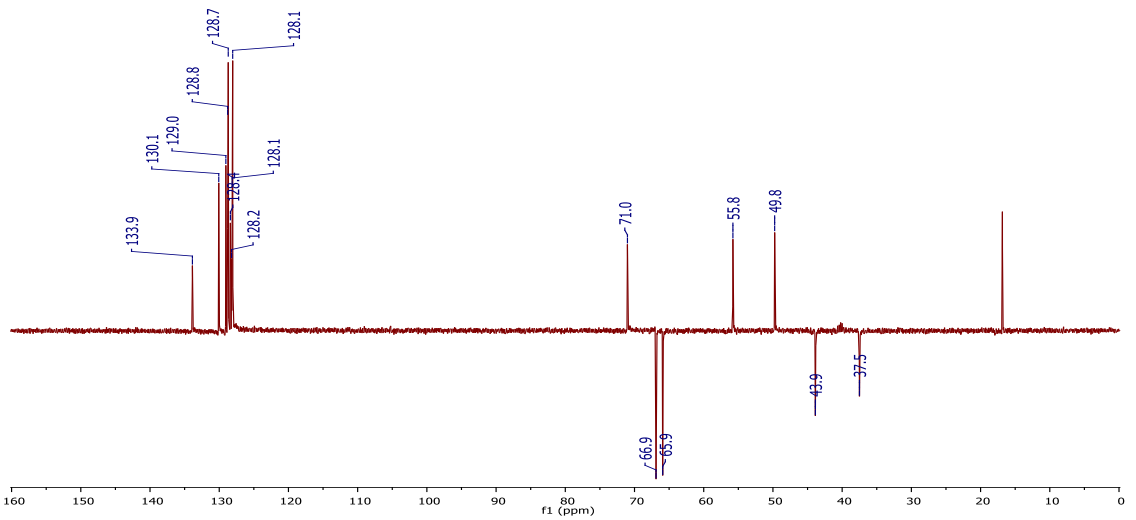
^{1}H NMR Spectrum (400.31 MHz, DMSO-d_6) of compound **2**



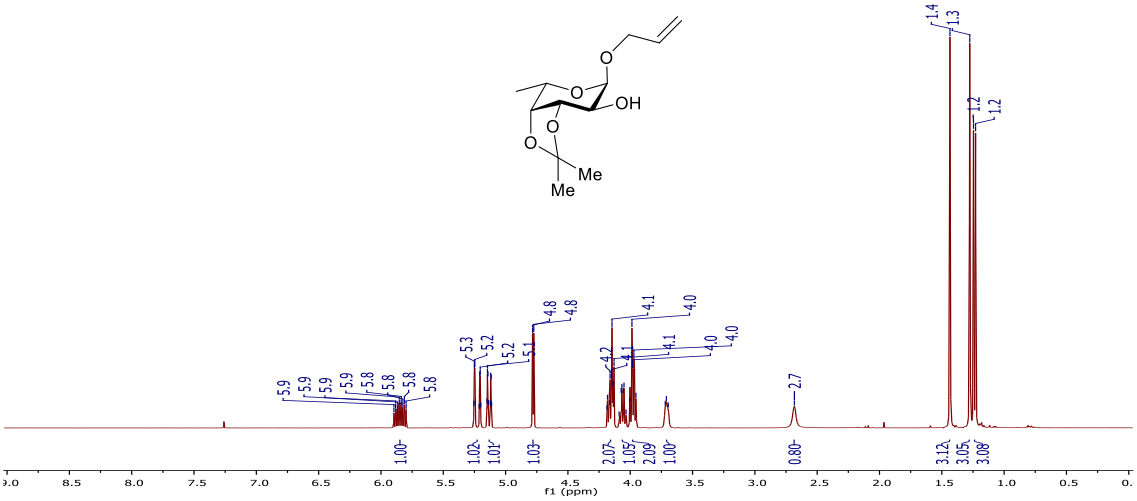
^{13}C NMR Spectrum (100.67MHz, DMSO-d_6) of compound **2**



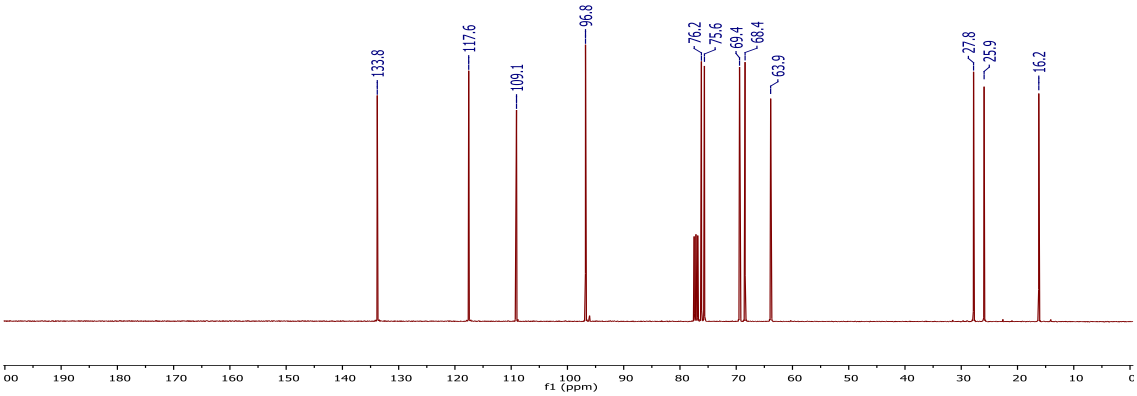
DEPT NMR Spectrum (100.67MHz, DMSO-d_6) of compound **2**



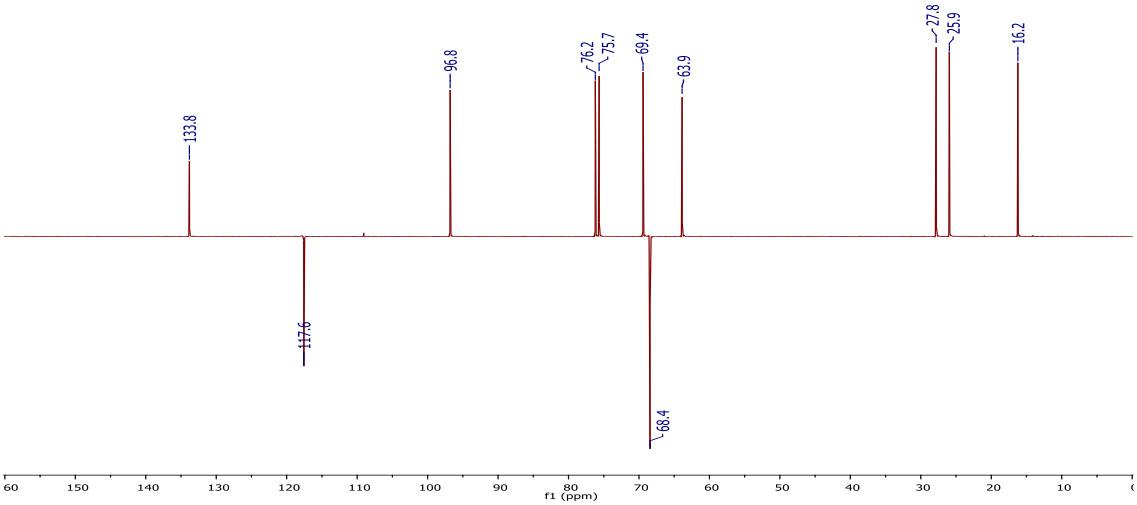
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **12**



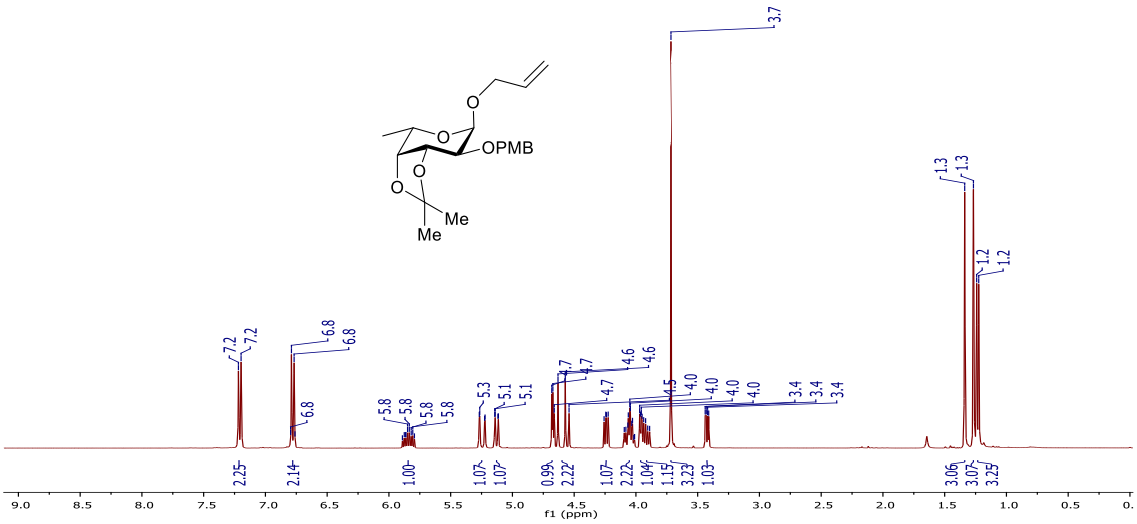
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **12**



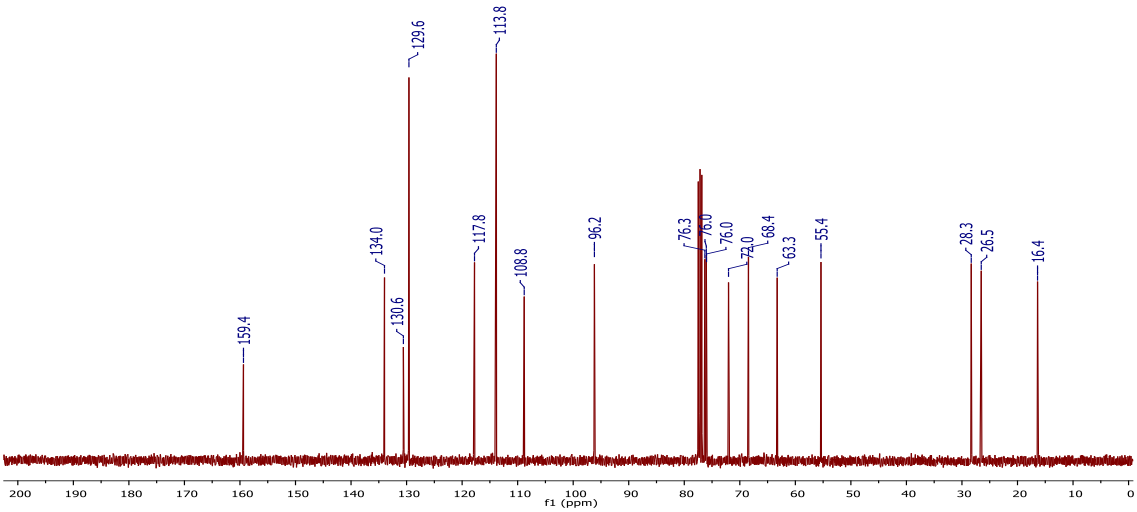
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **12**



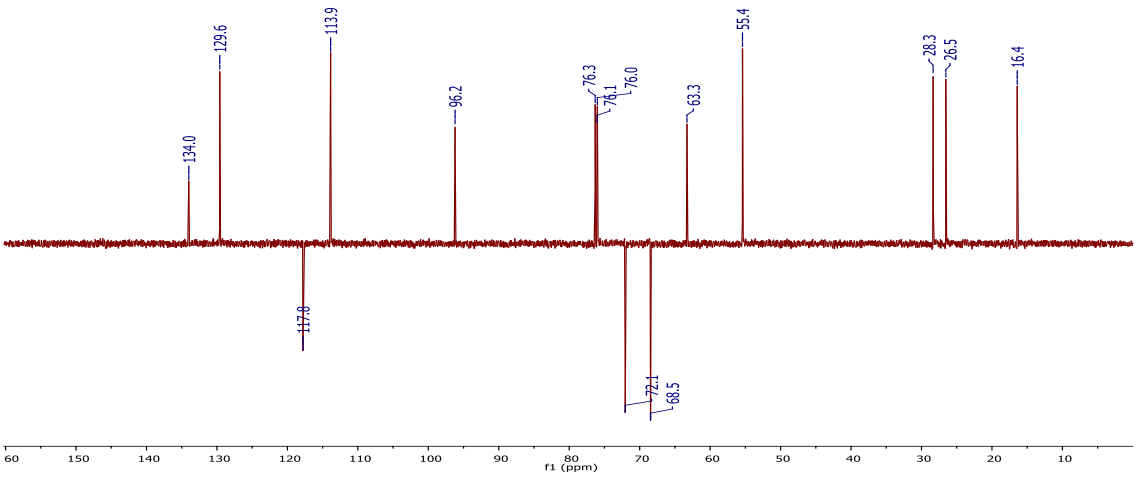
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **13**



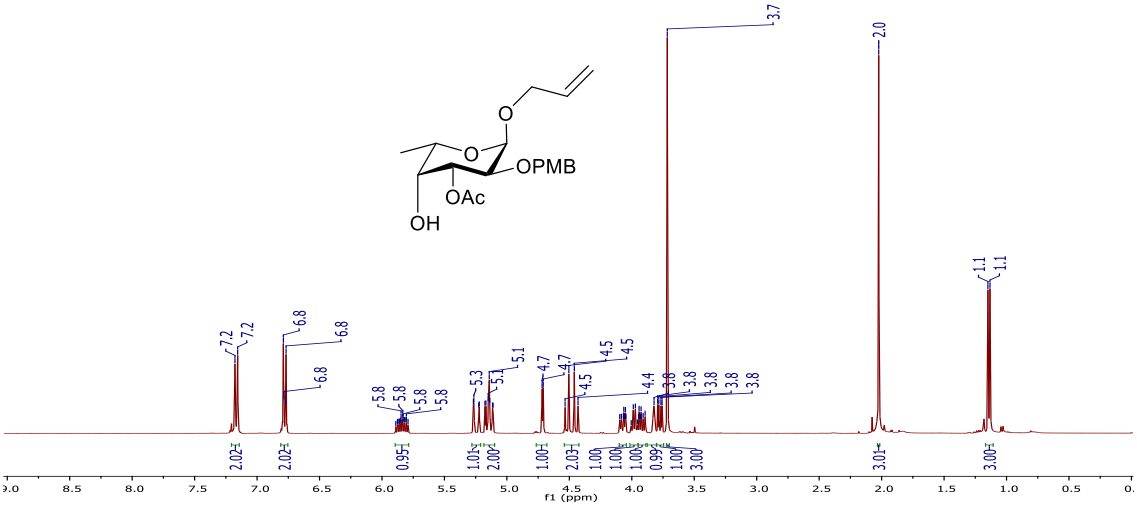
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **13**



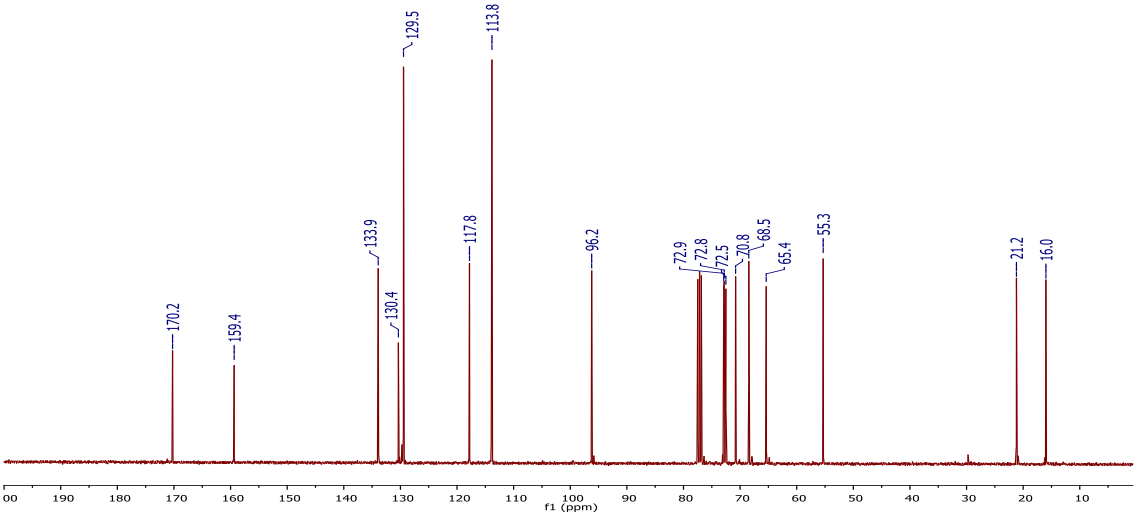
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **13**



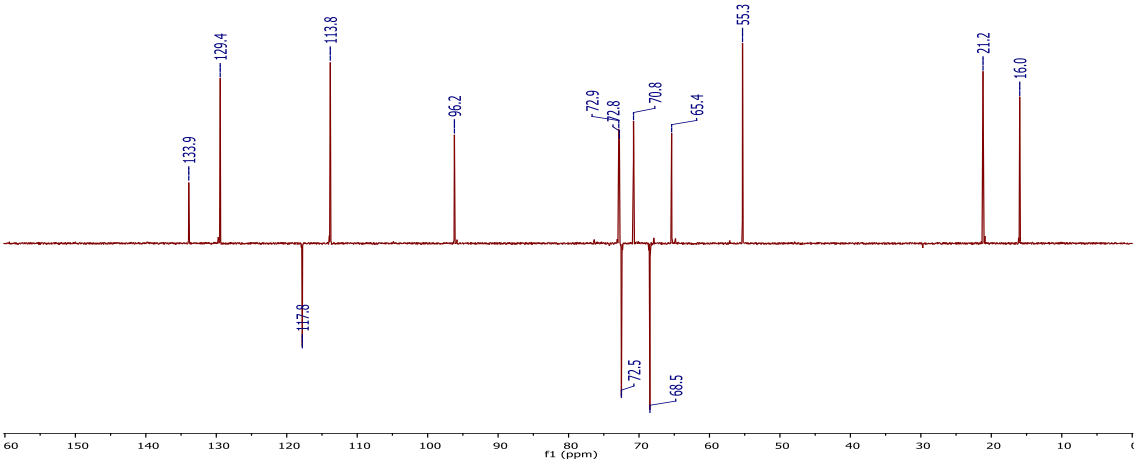
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **14**



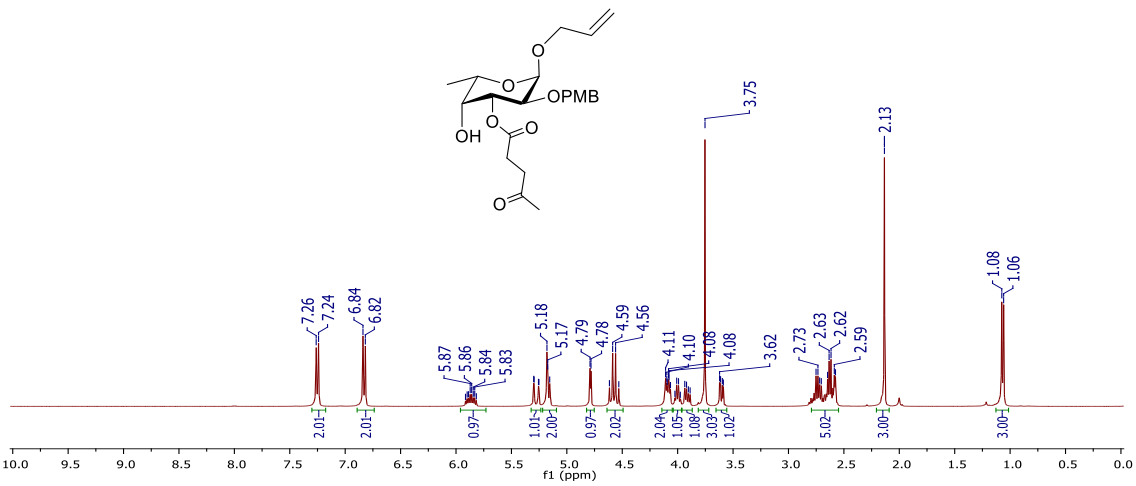
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **14**



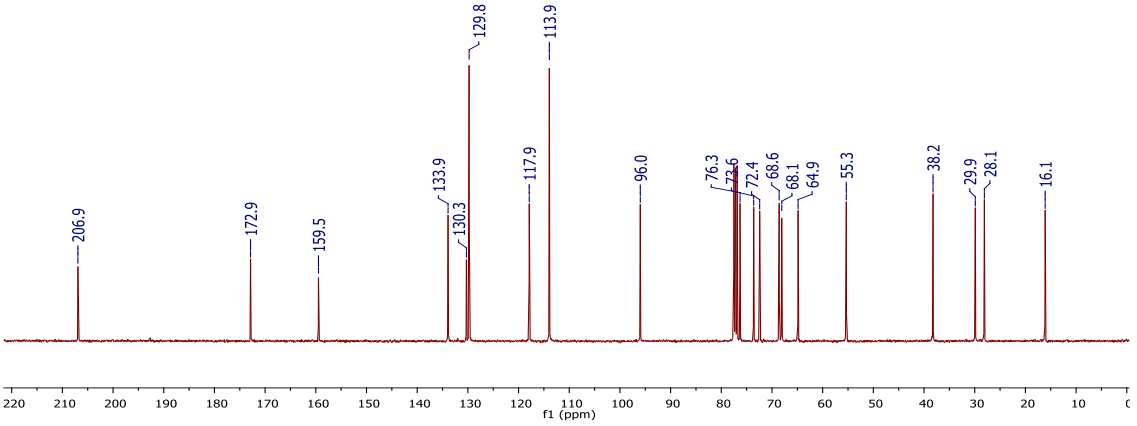
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **14**



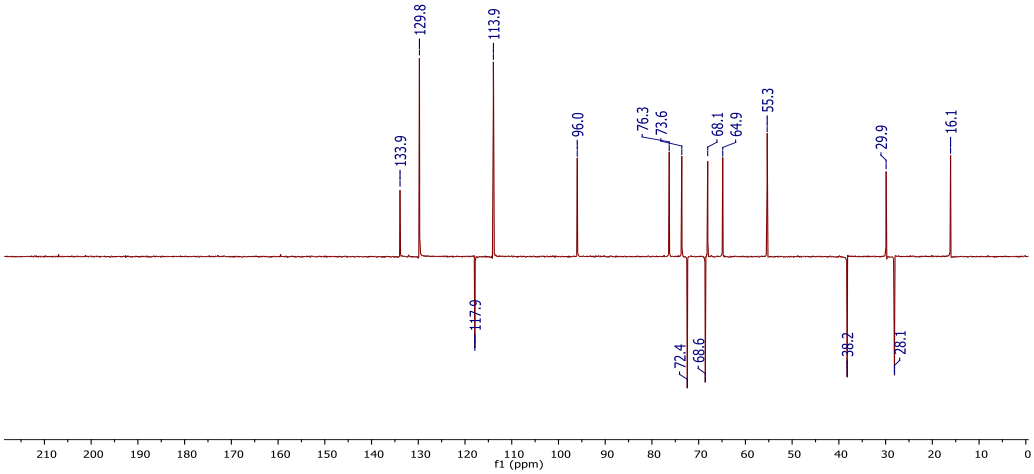
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **3**



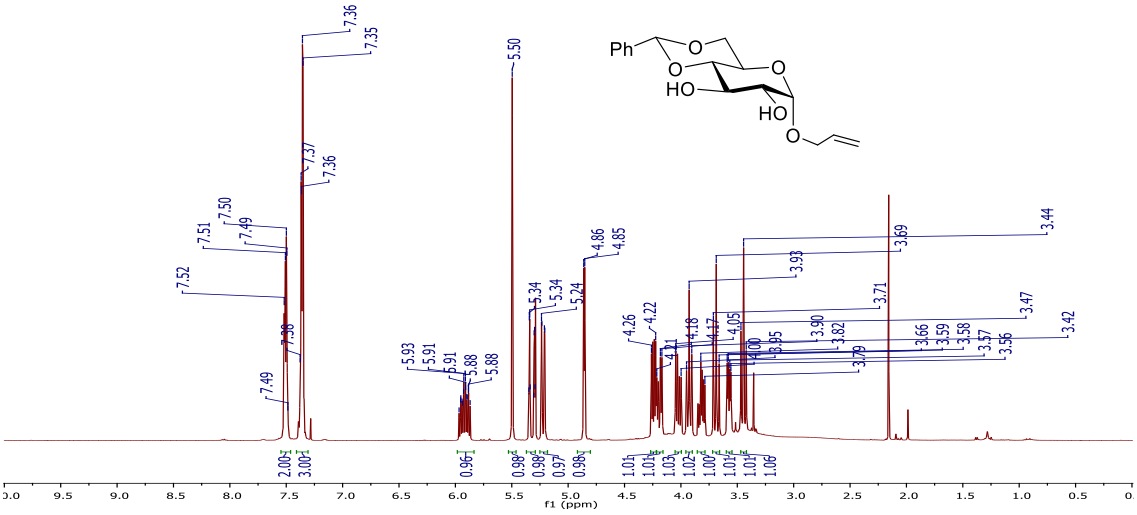
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **3**



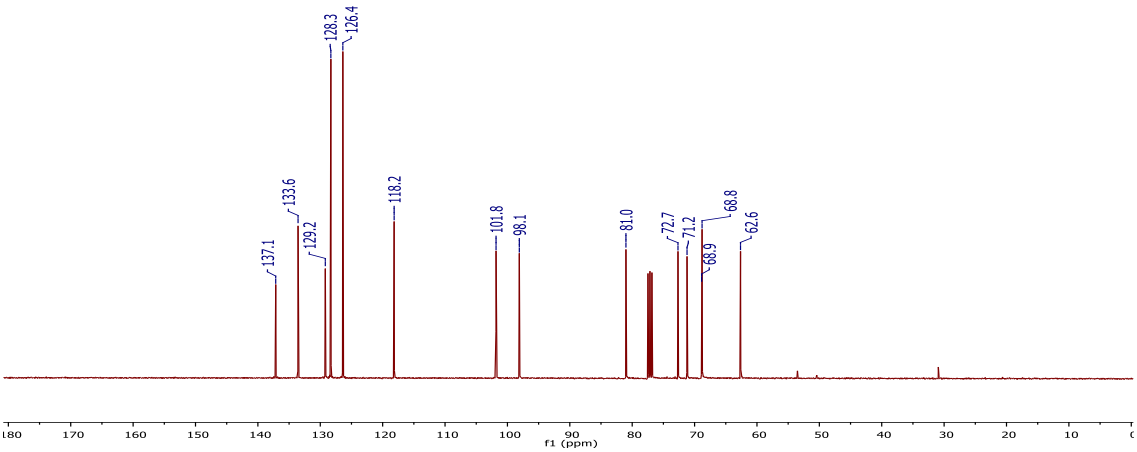
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **3**



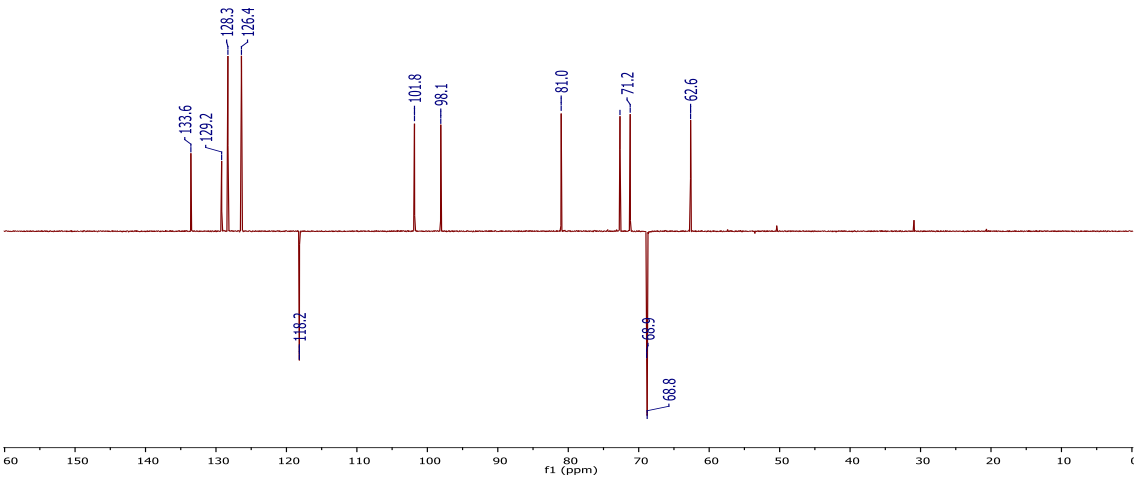
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **16**



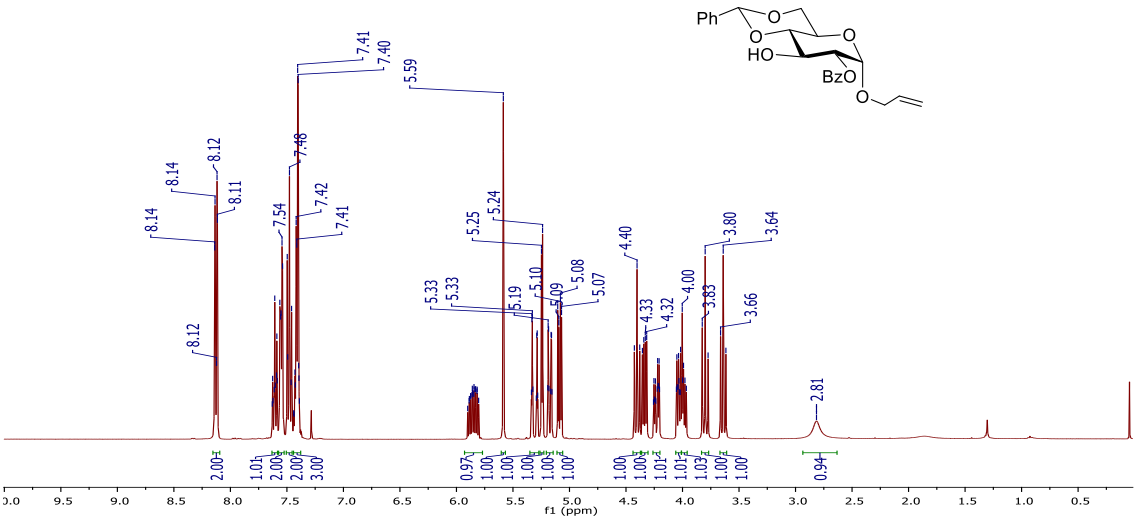
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **16**



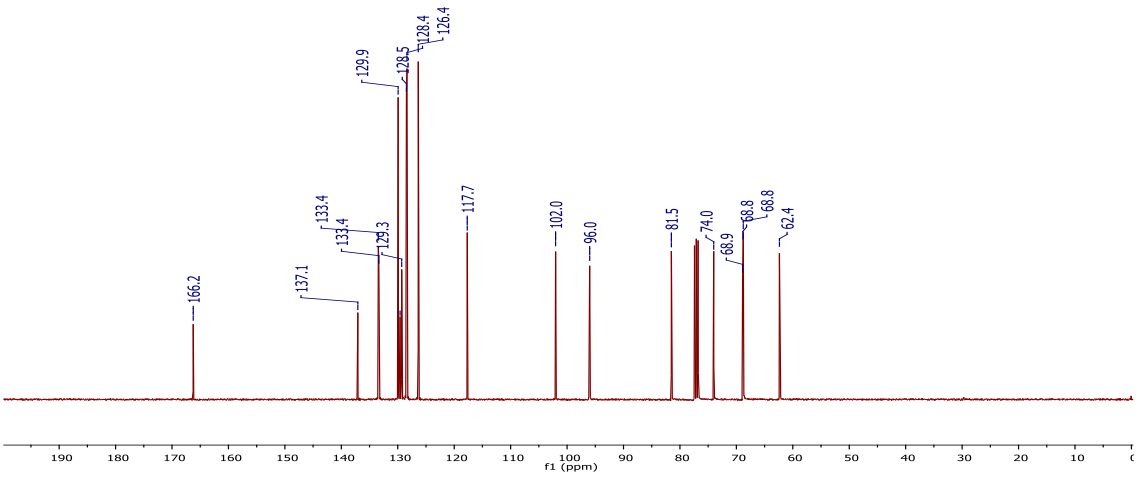
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **16**



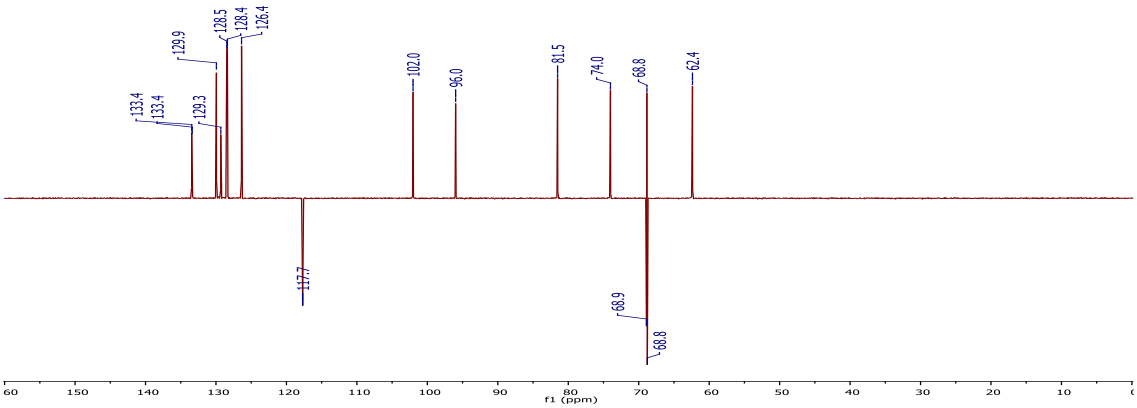
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **17**



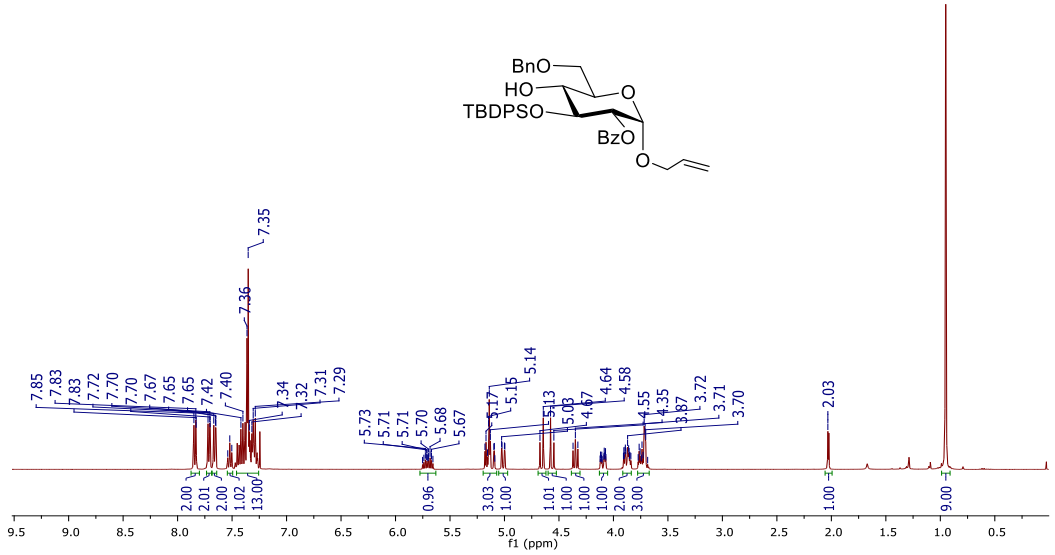
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **17**



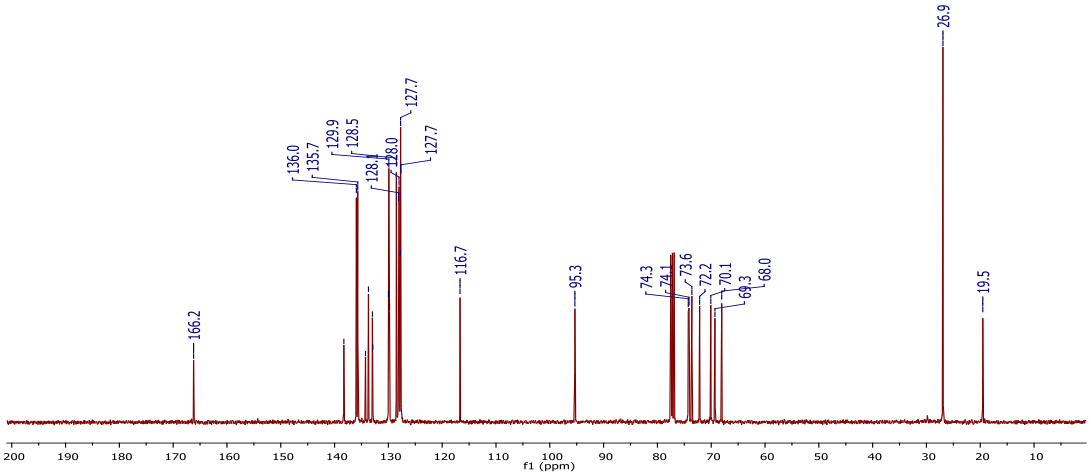
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **17**



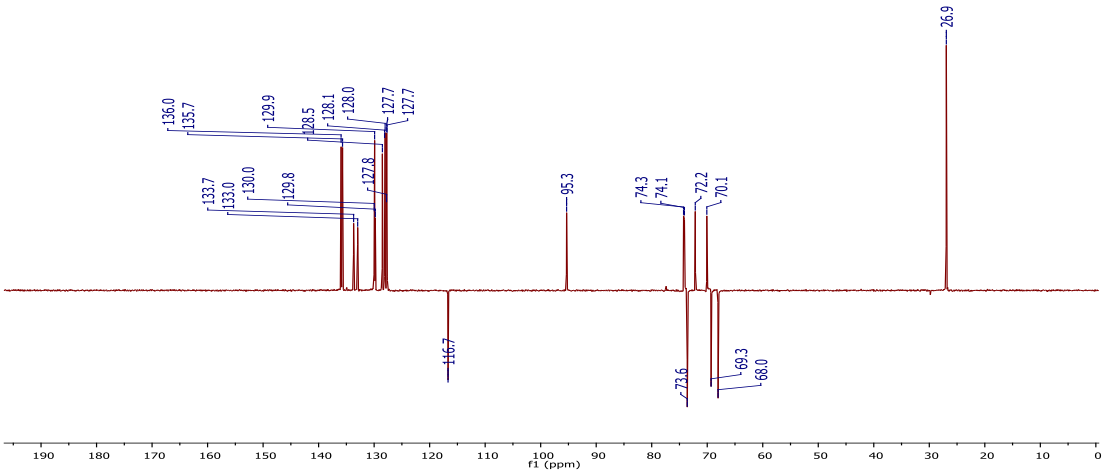
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **4**



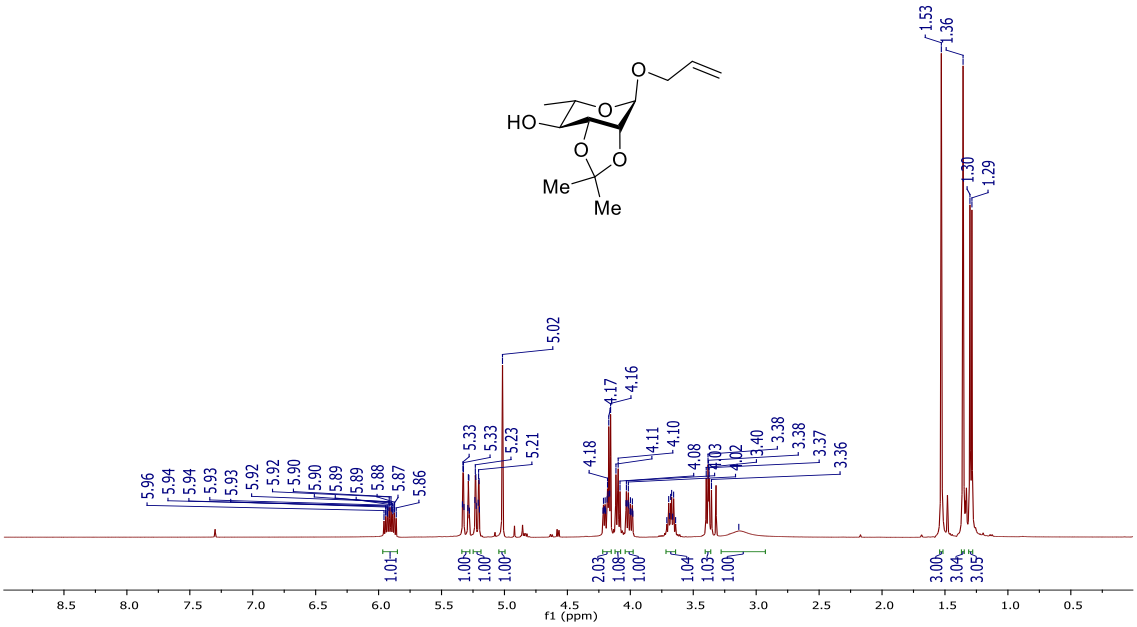
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **4**



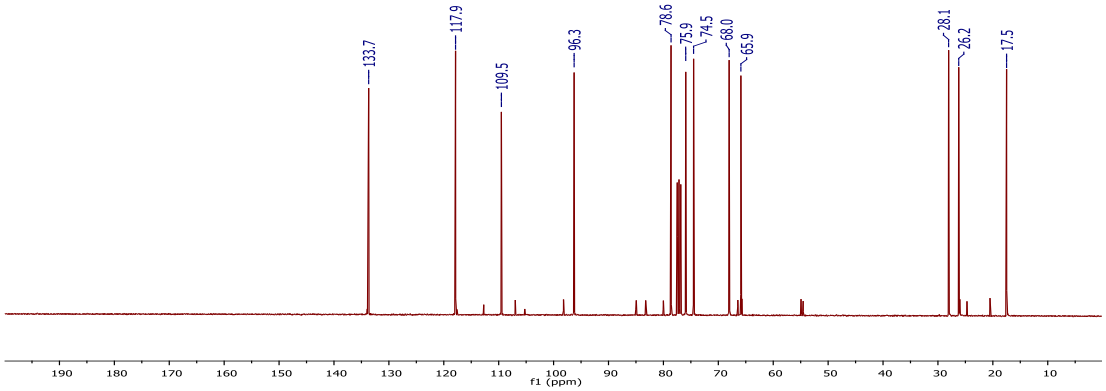
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **4**



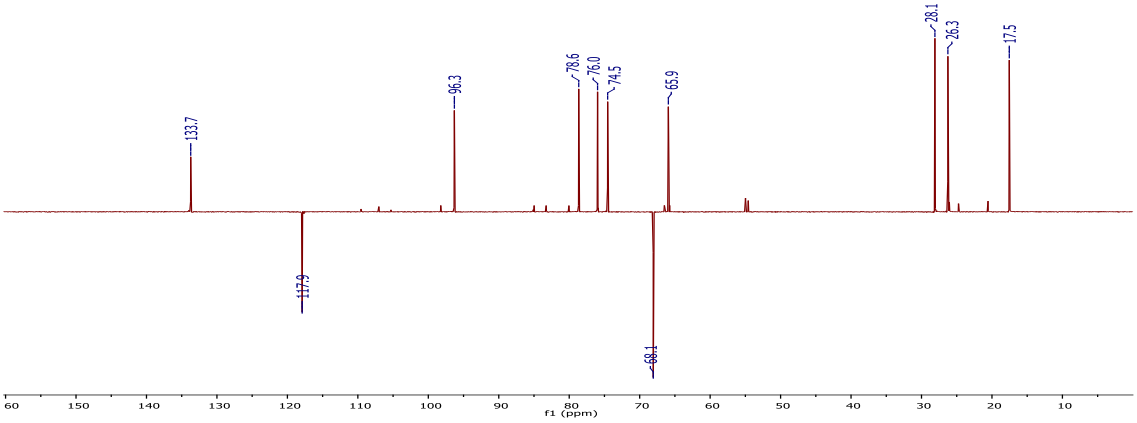
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **18**



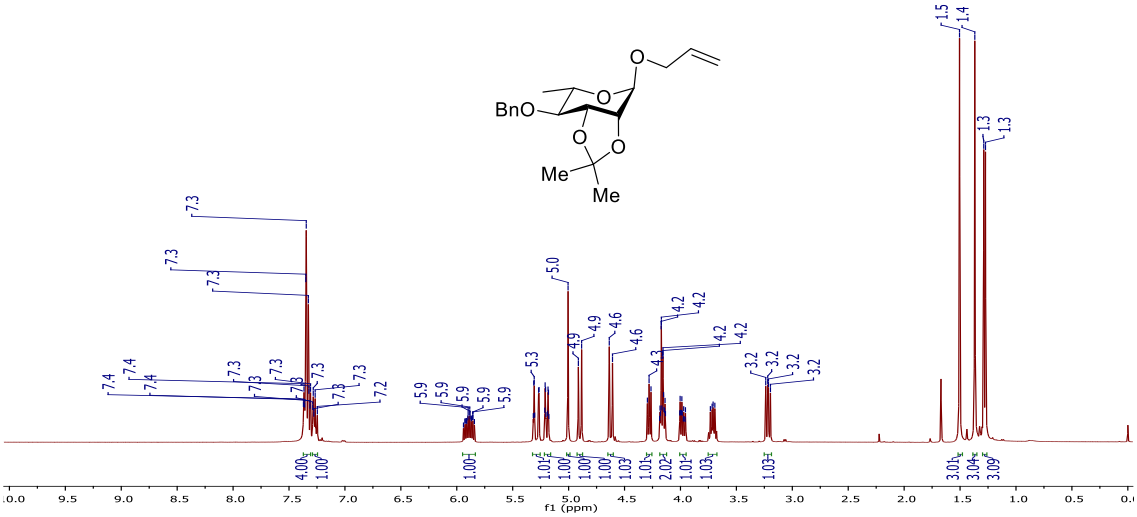
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **18**



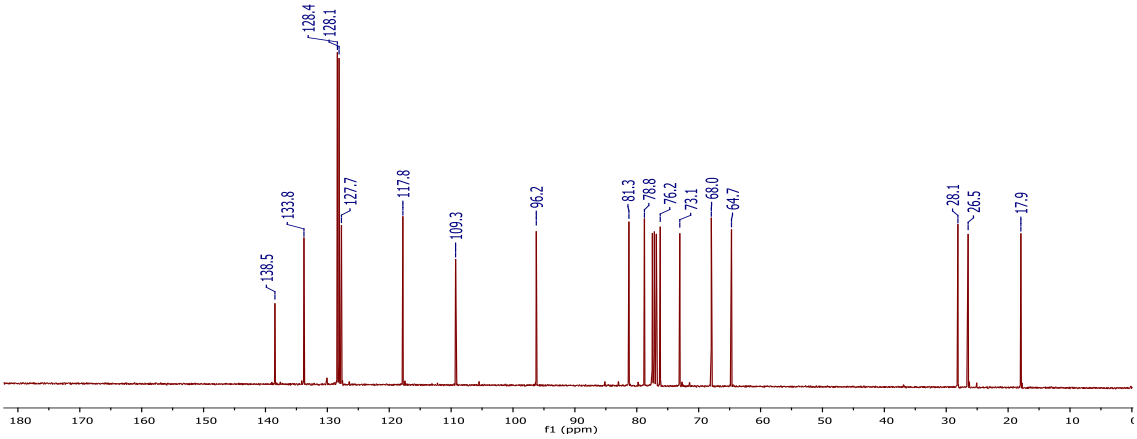
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **18**



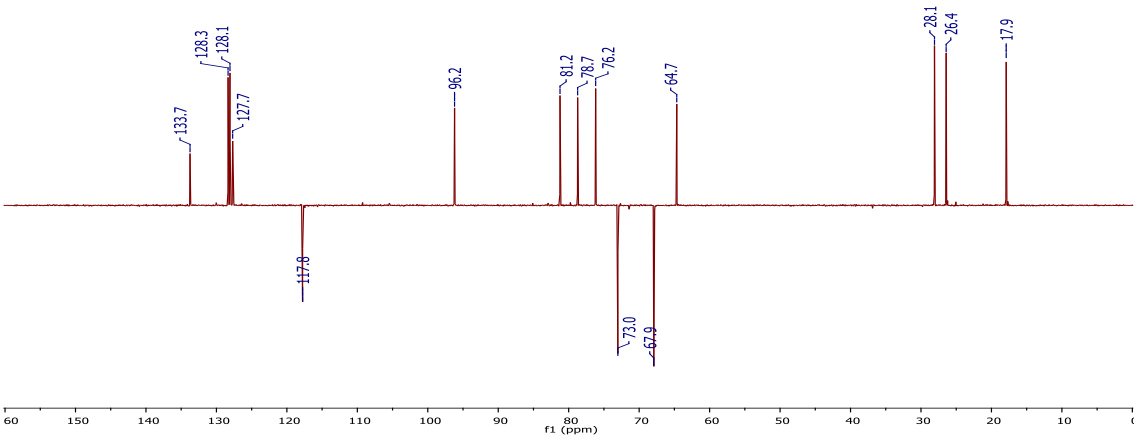
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **19**



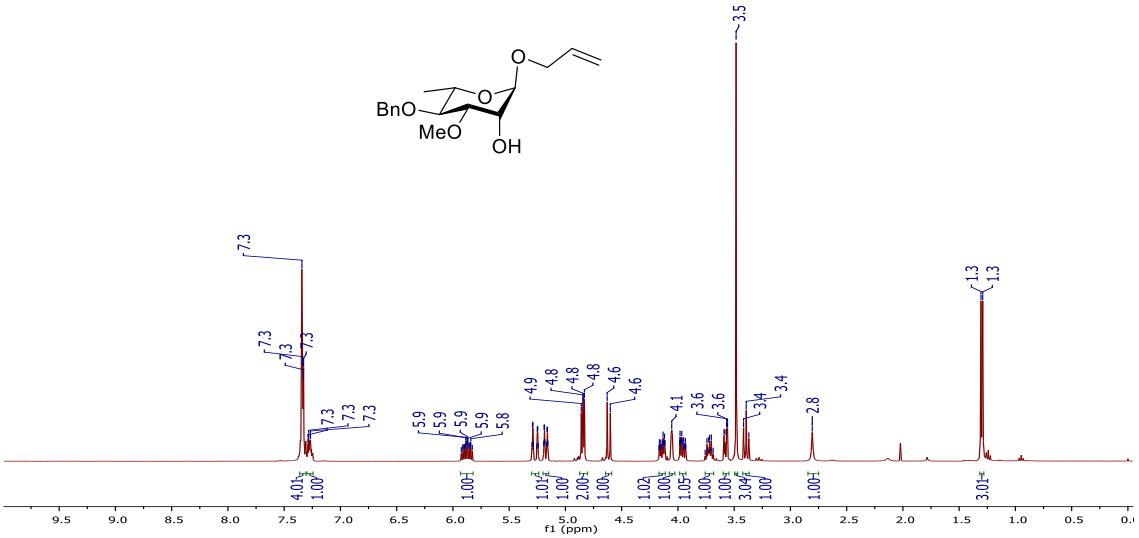
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **19**



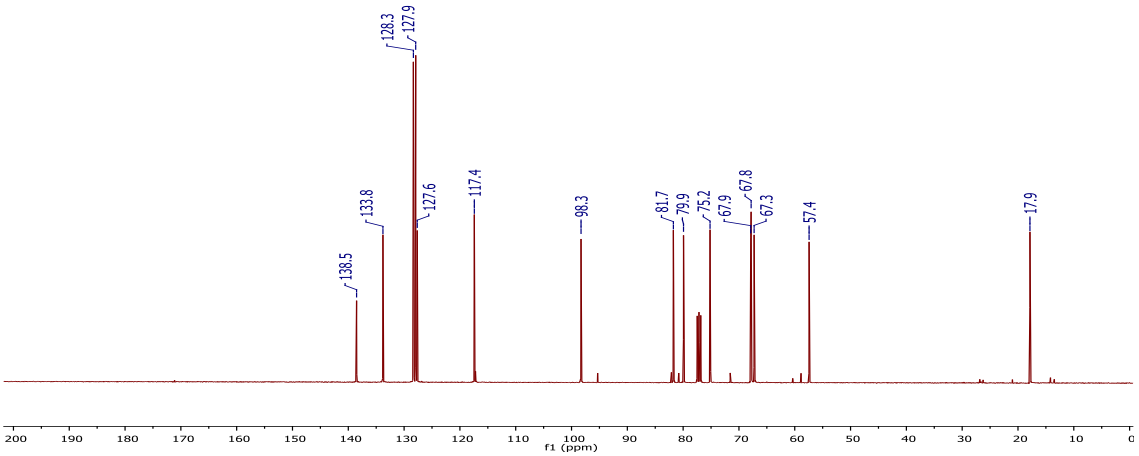
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **19**



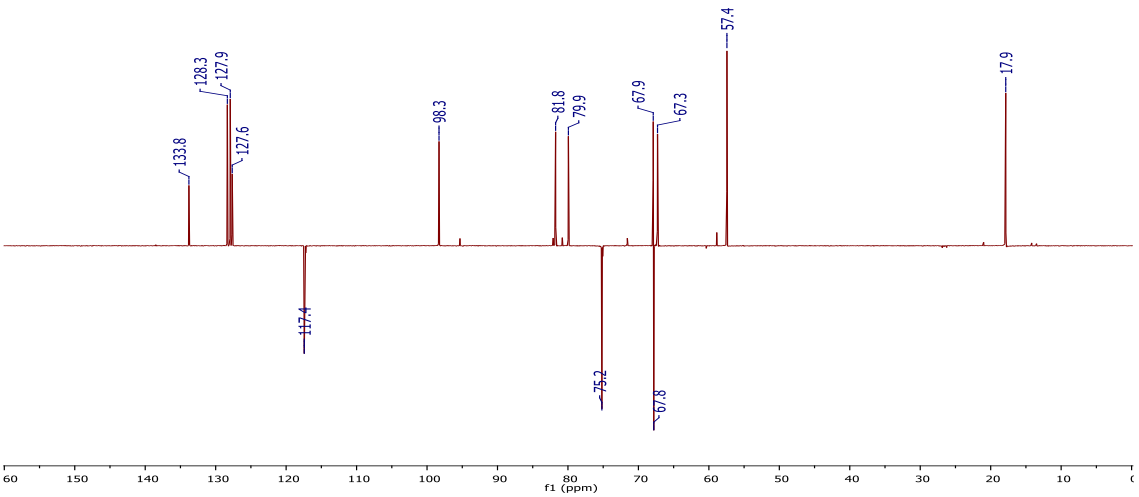
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **20**



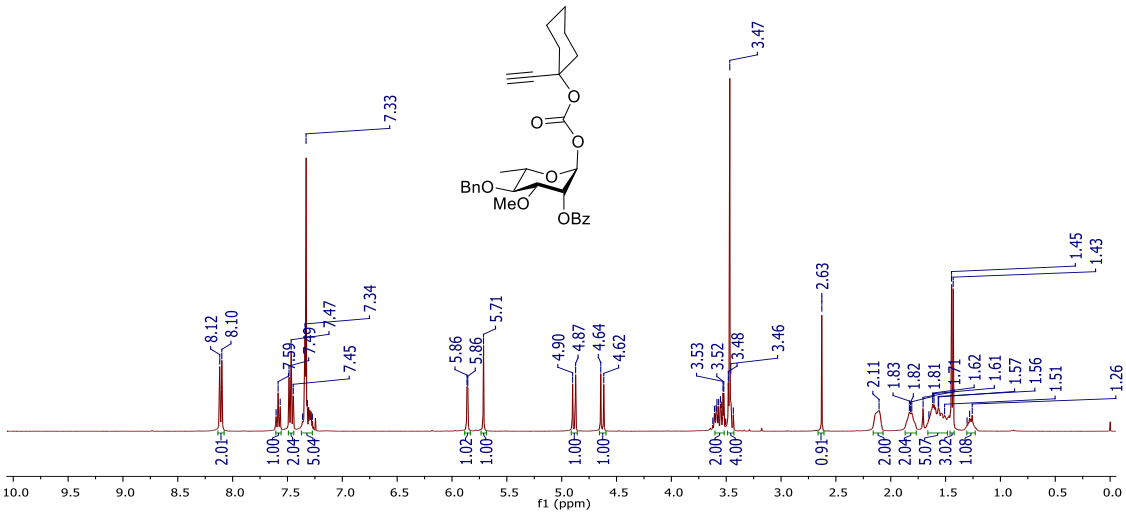
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **20**



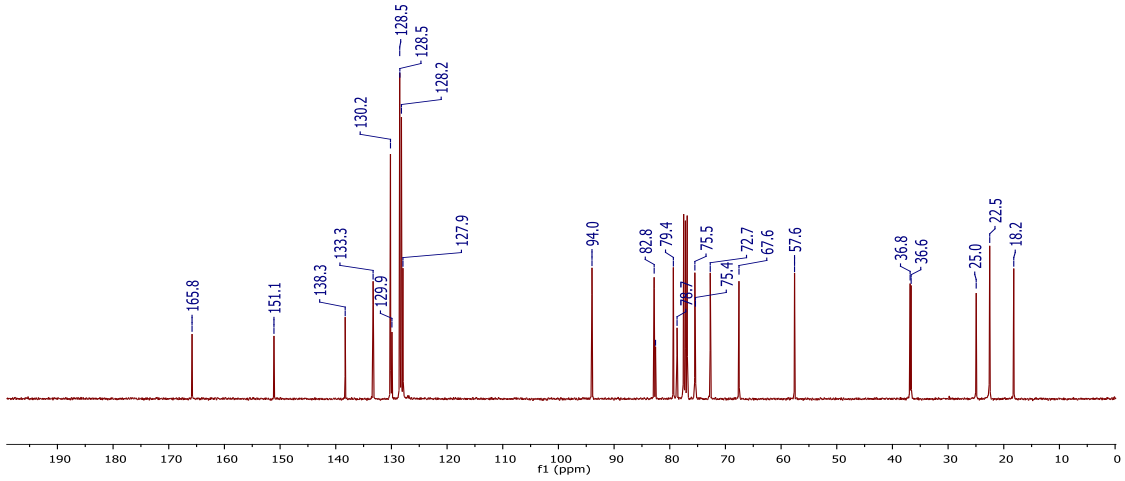
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **20**



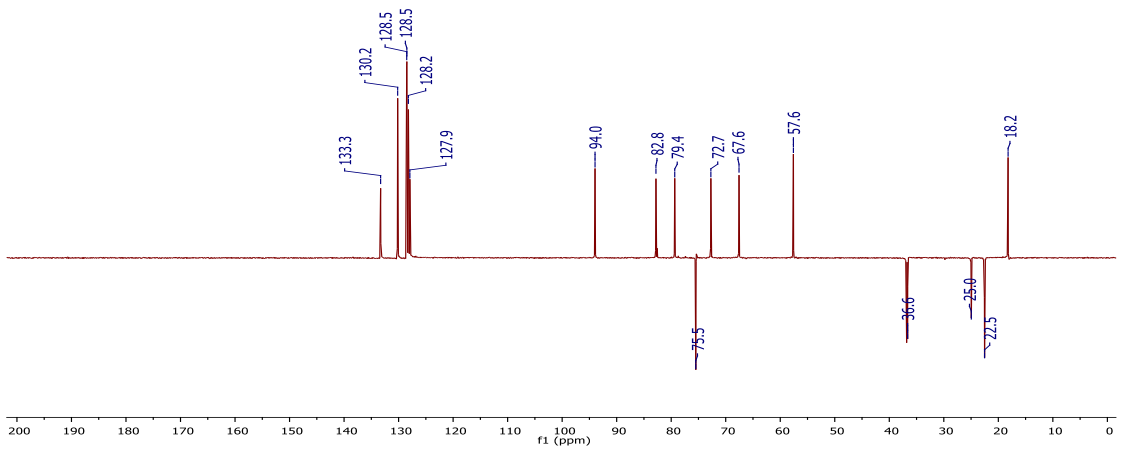
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **5**



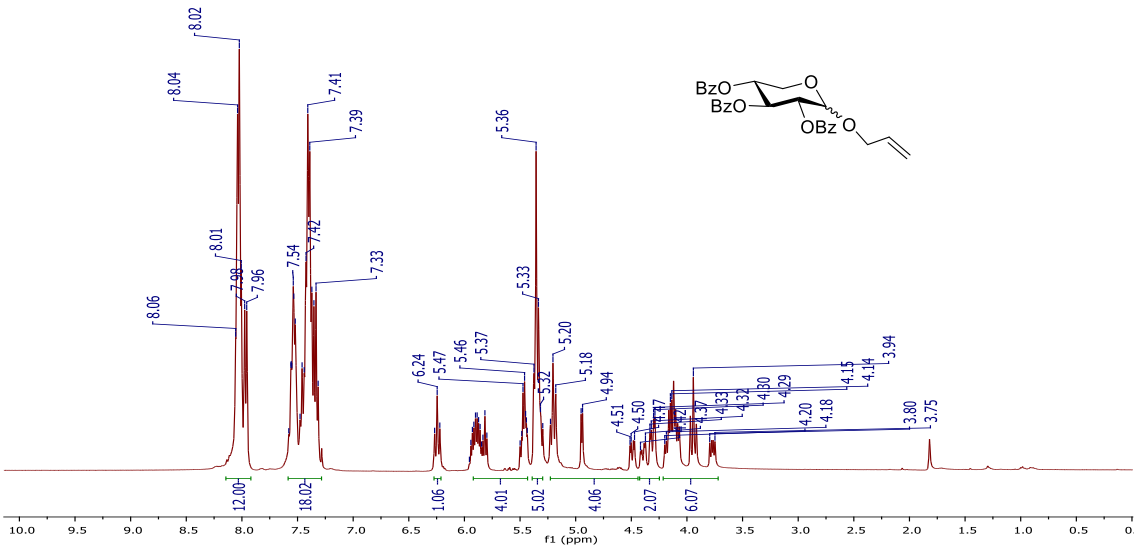
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **5**



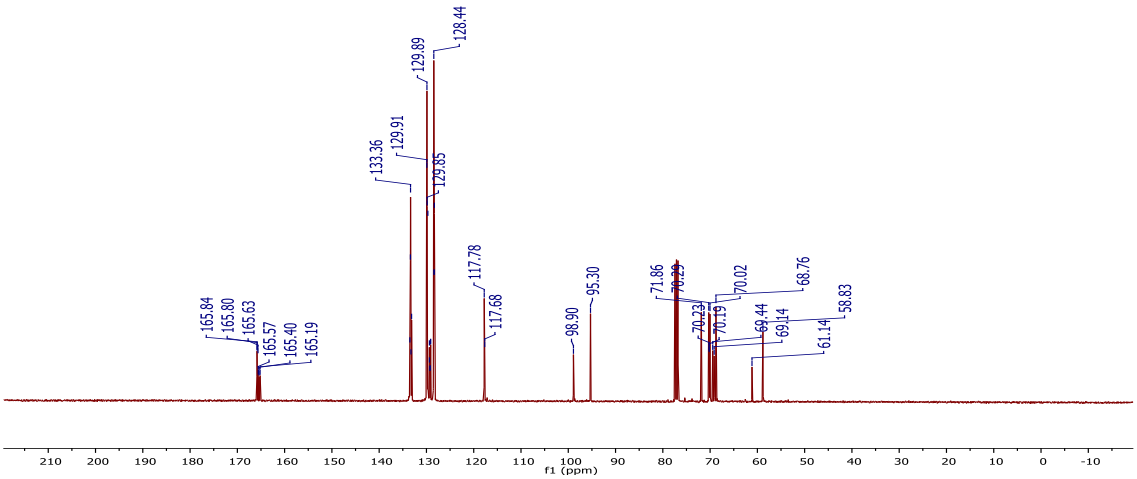
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **5**



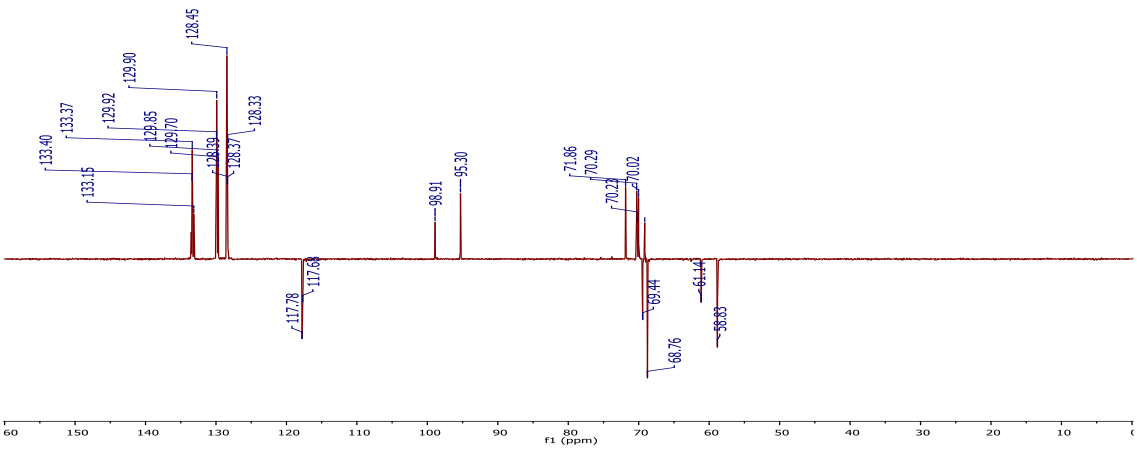
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **20**



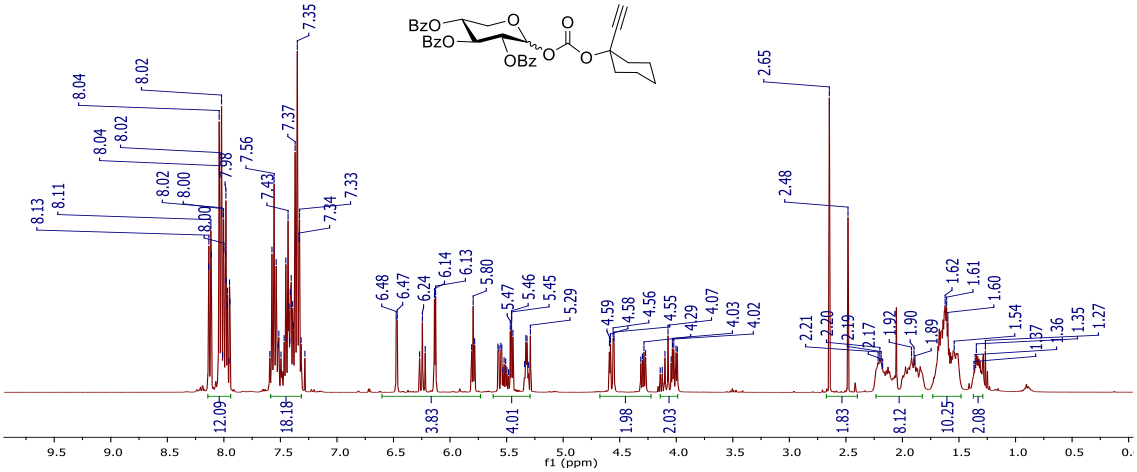
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **20**



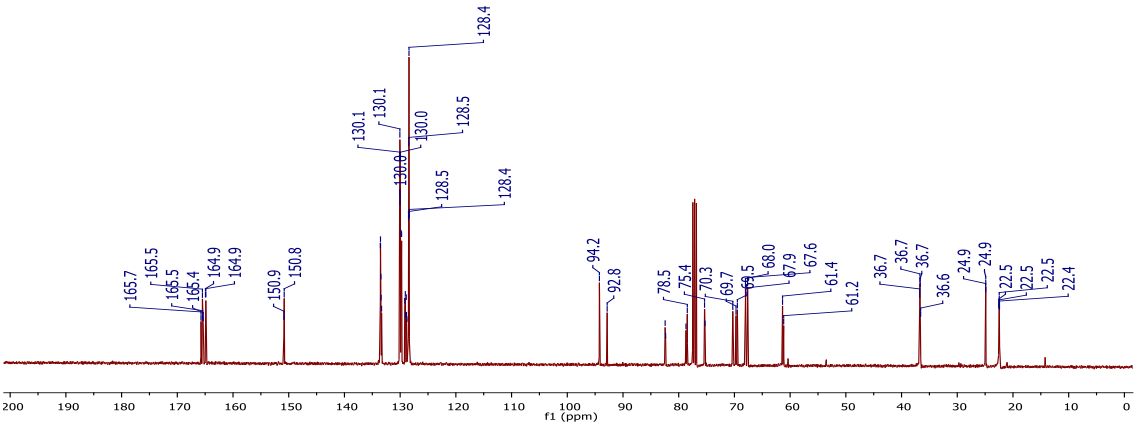
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **20**



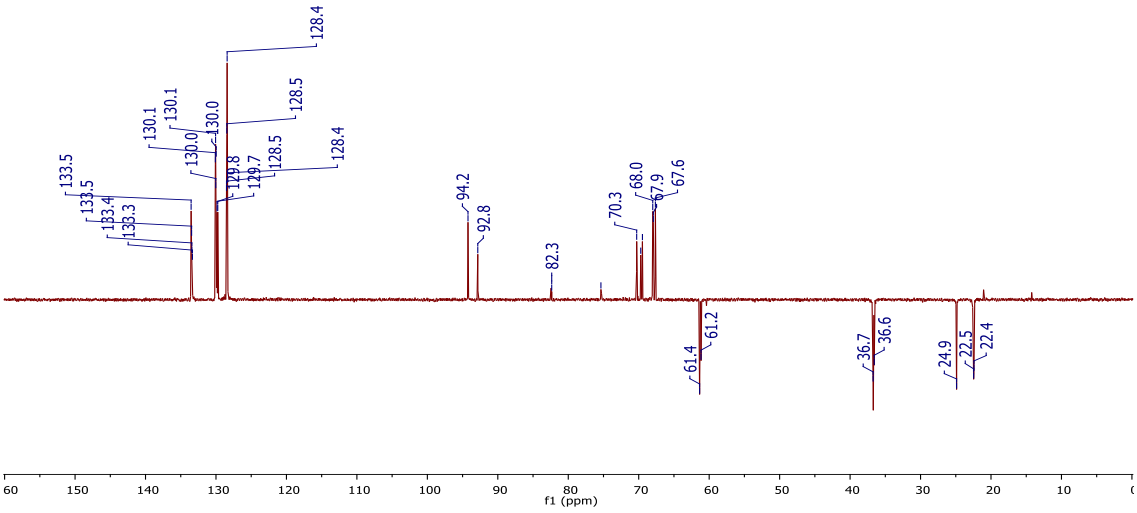
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **6**



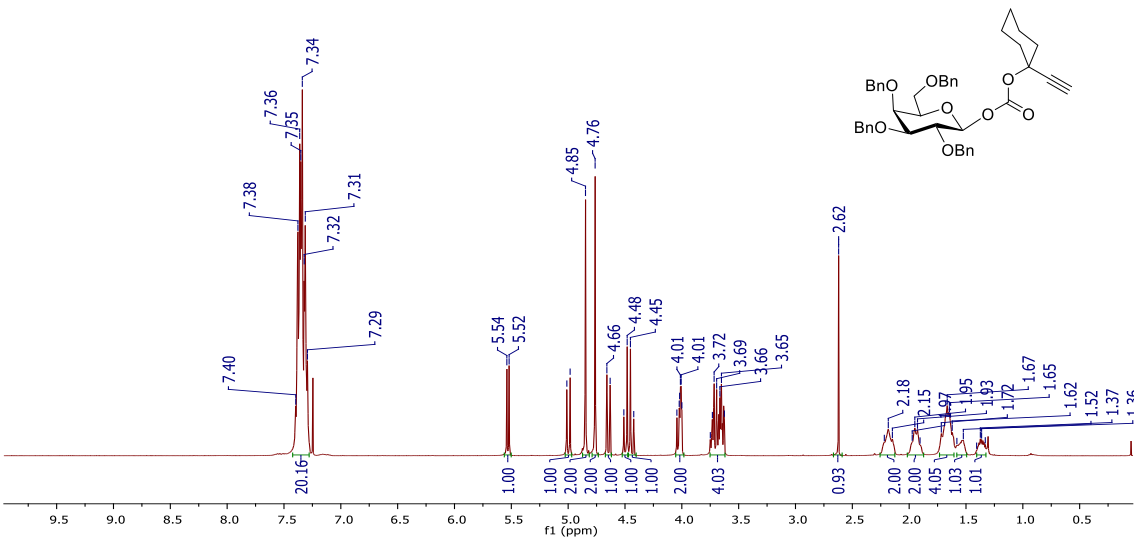
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **6**



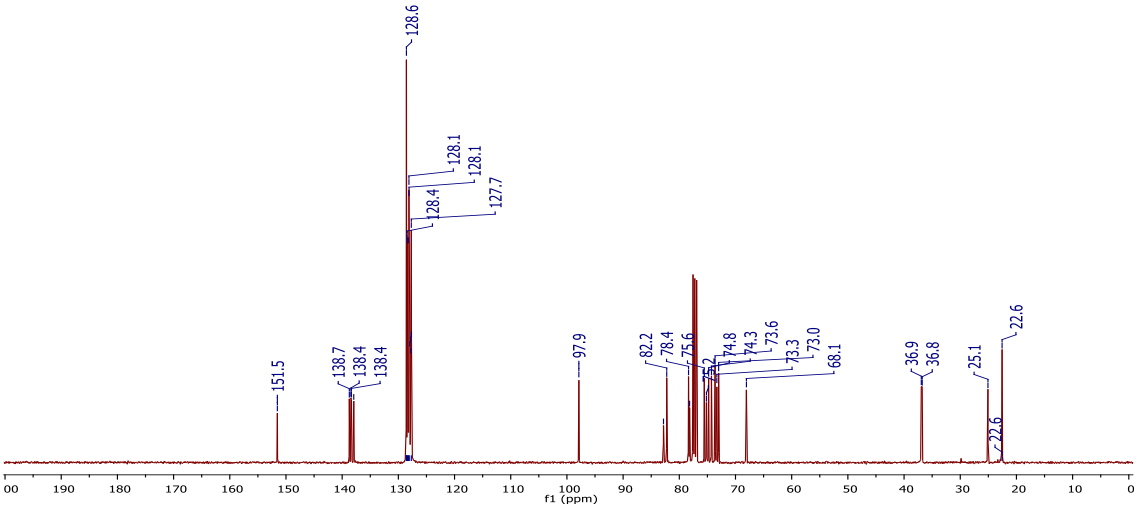
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **6**



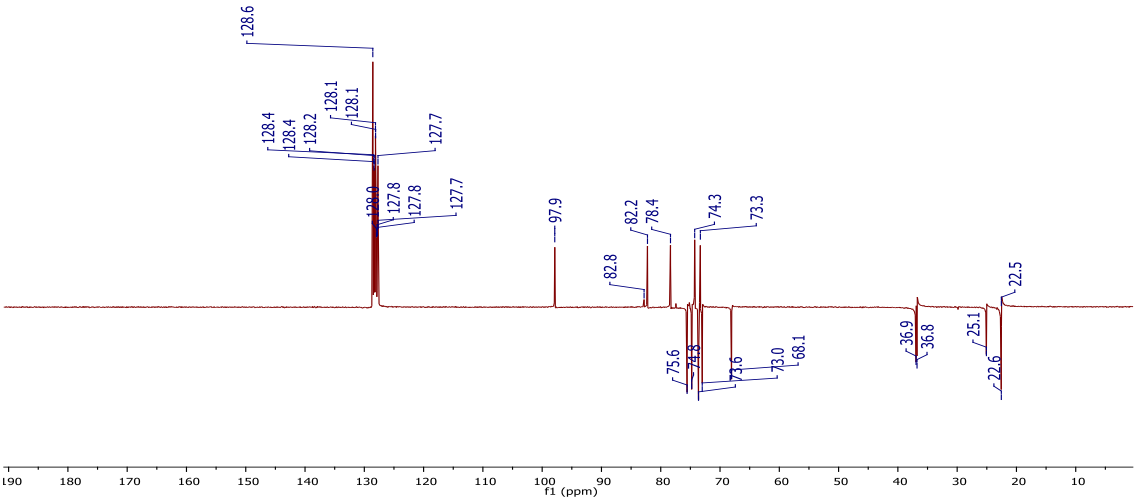
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **7aβ**



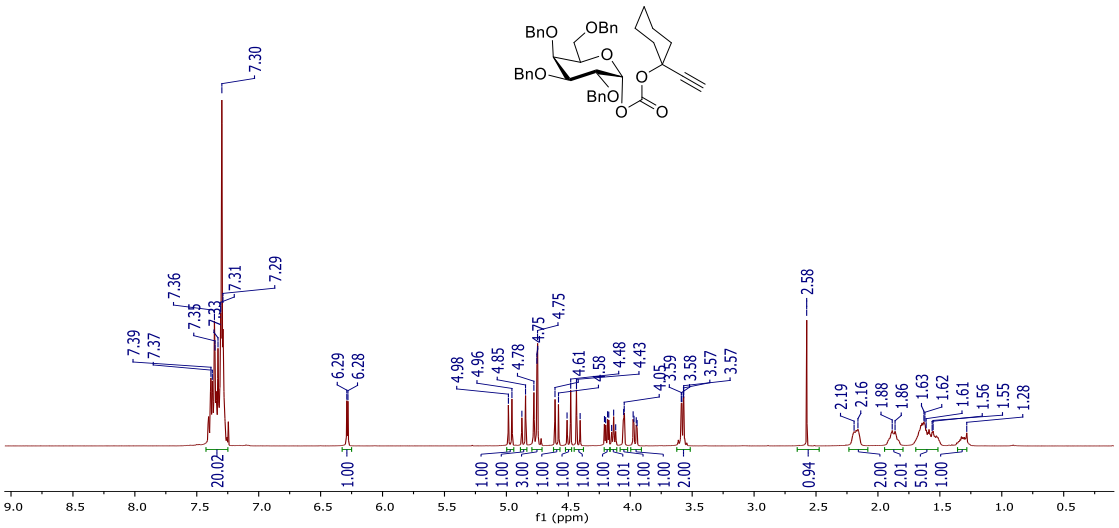
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7aβ**



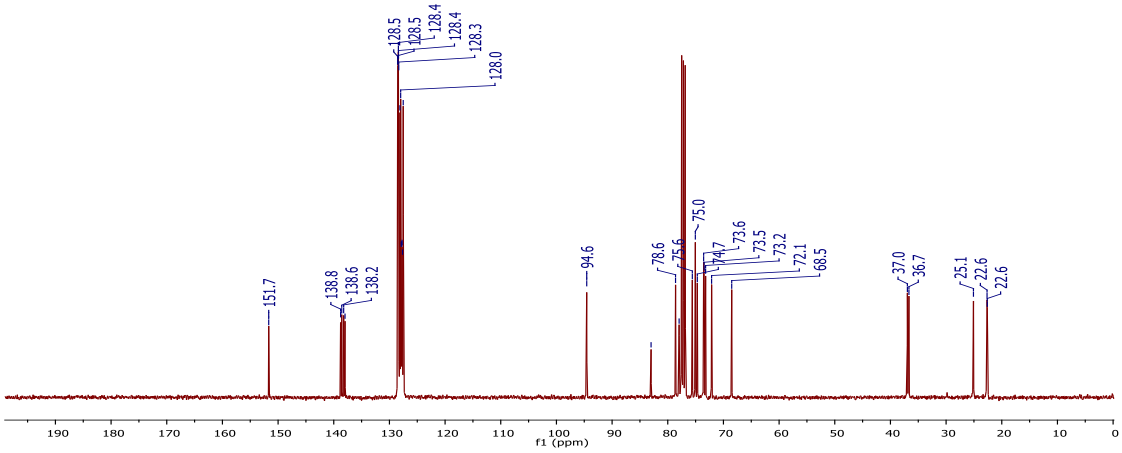
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7aβ**



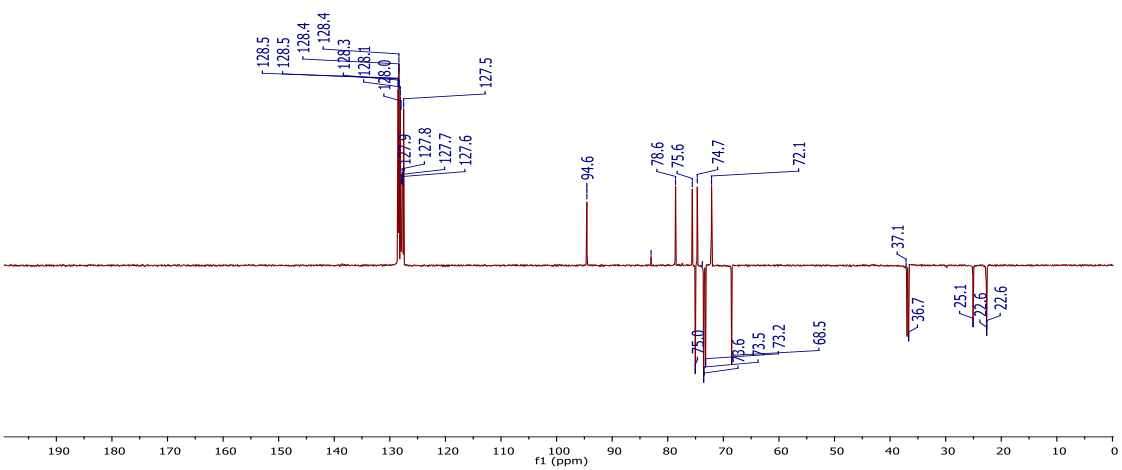
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **7aα**



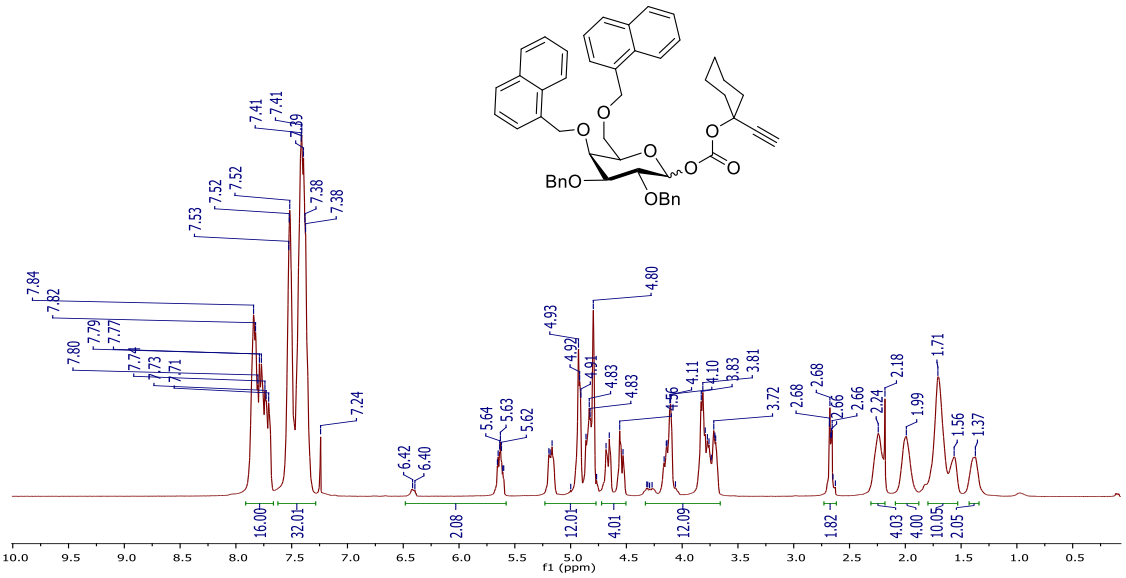
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7aα**



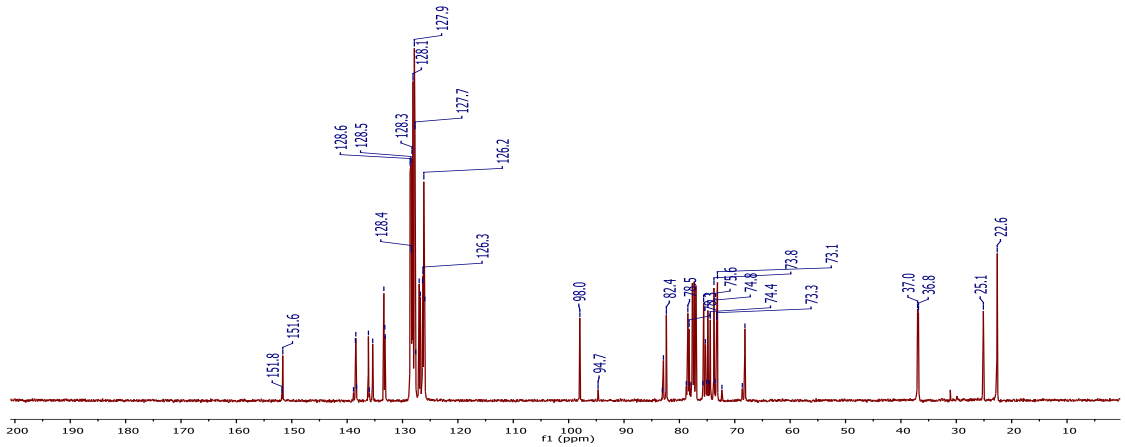
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7aα**



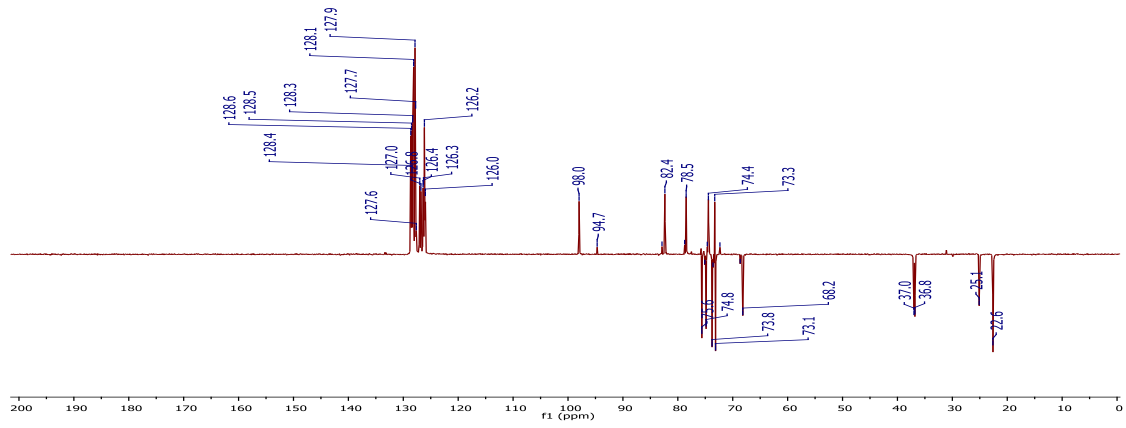
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **7b**



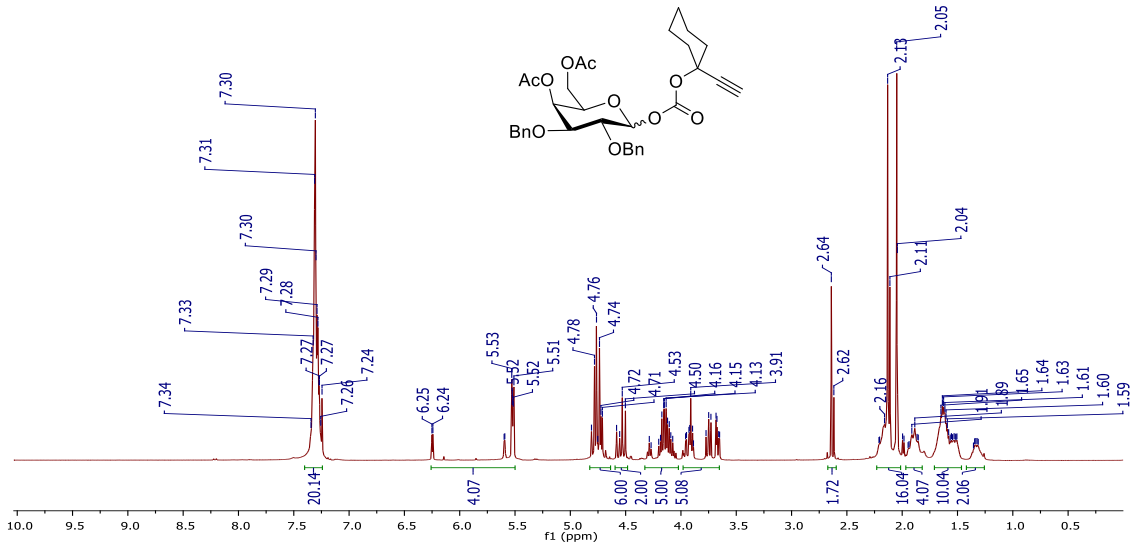
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7b**



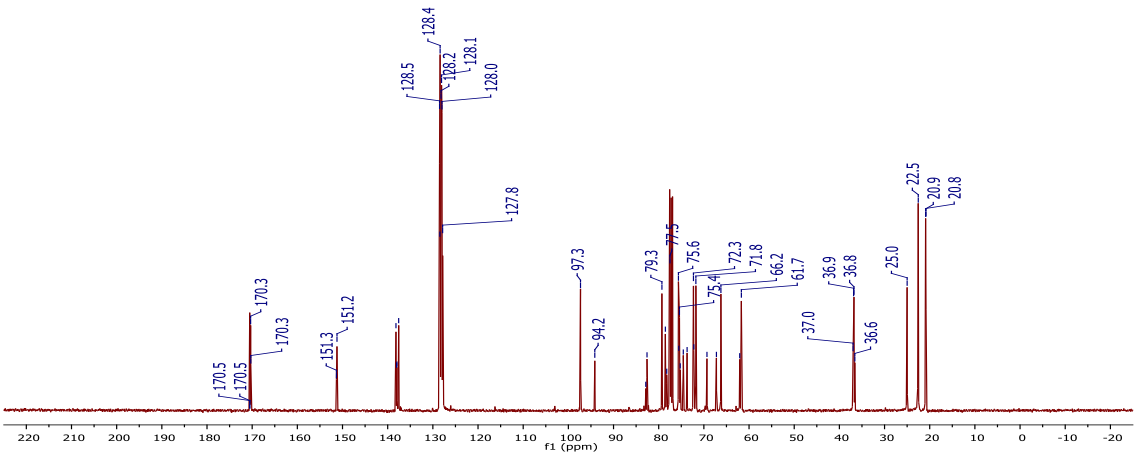
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7b**



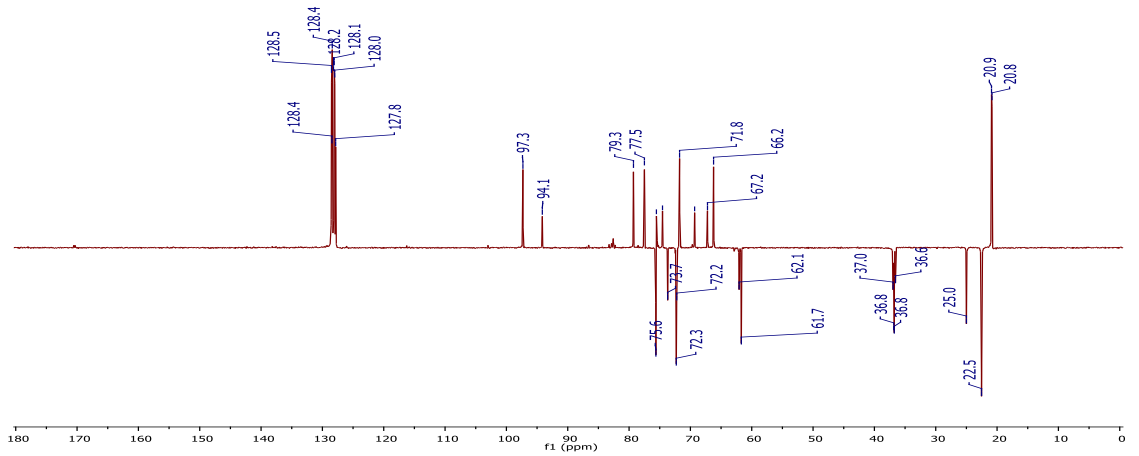
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **7c**



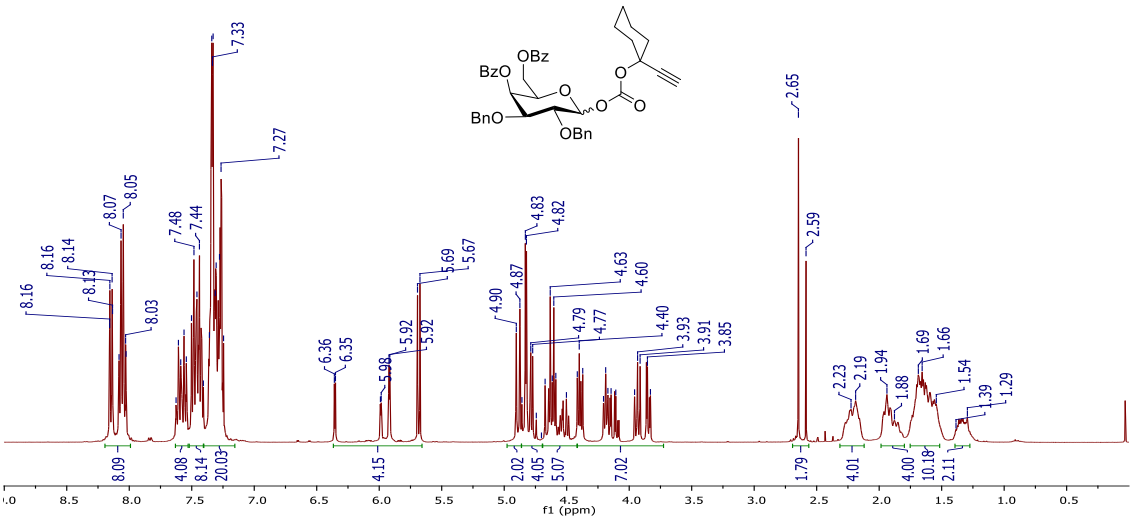
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7c**



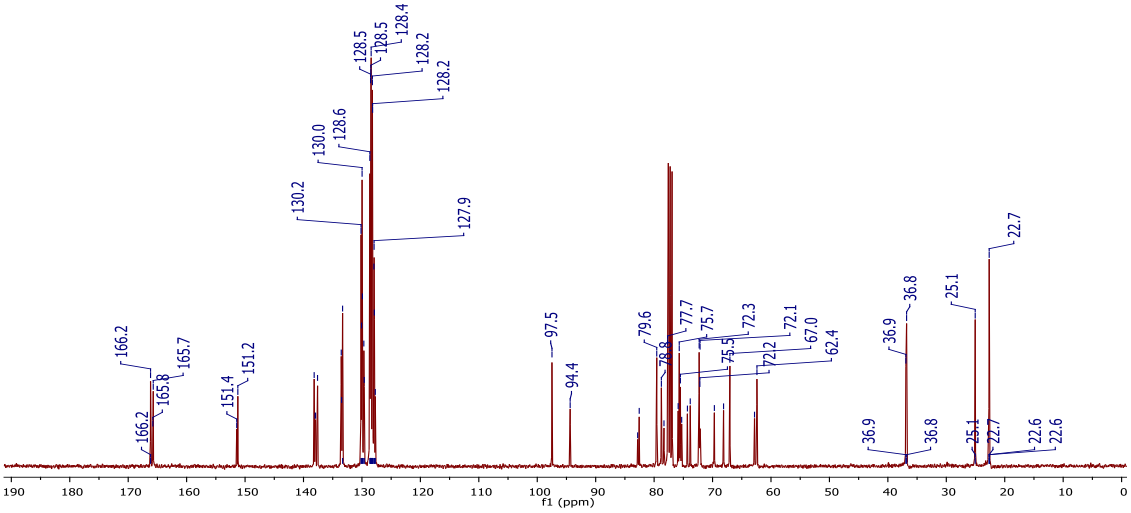
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7c**



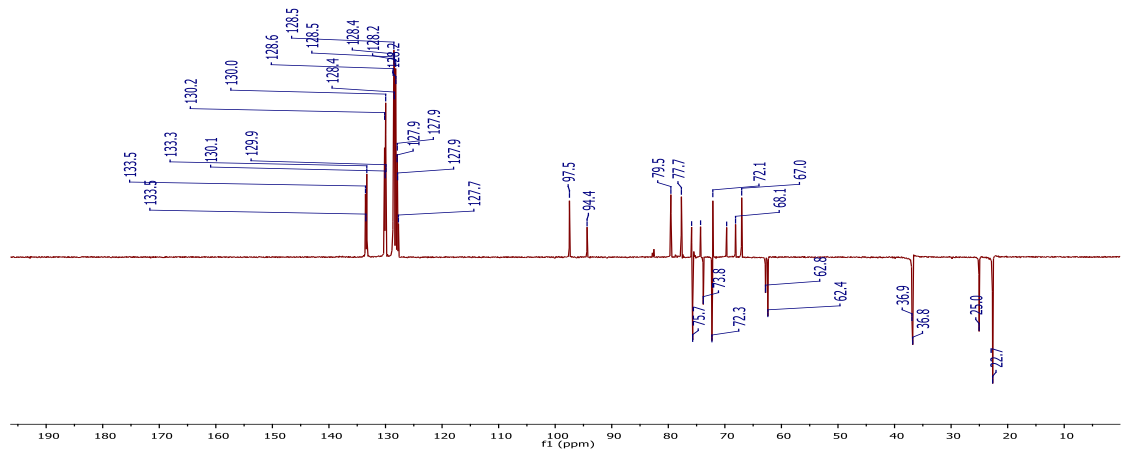
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **7d**



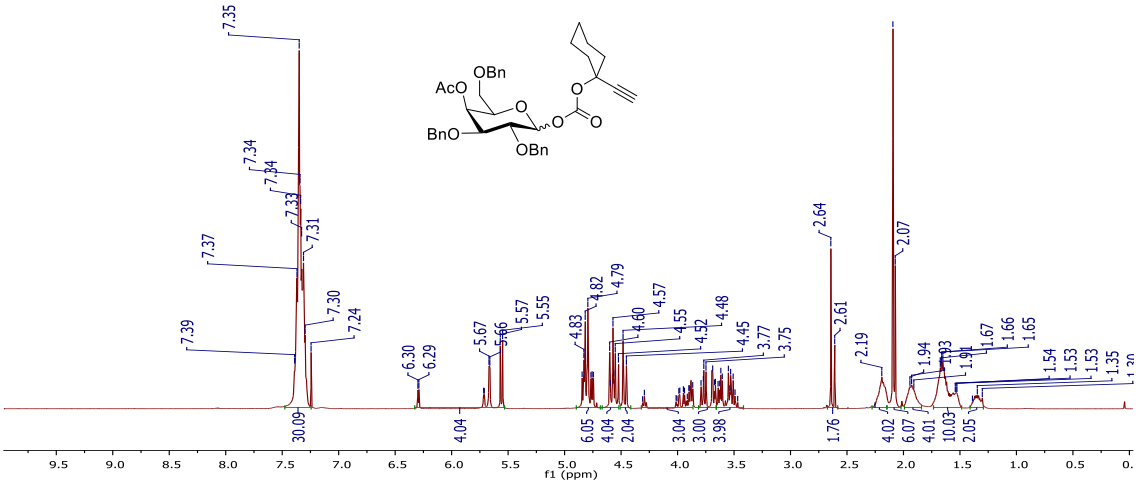
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7d**



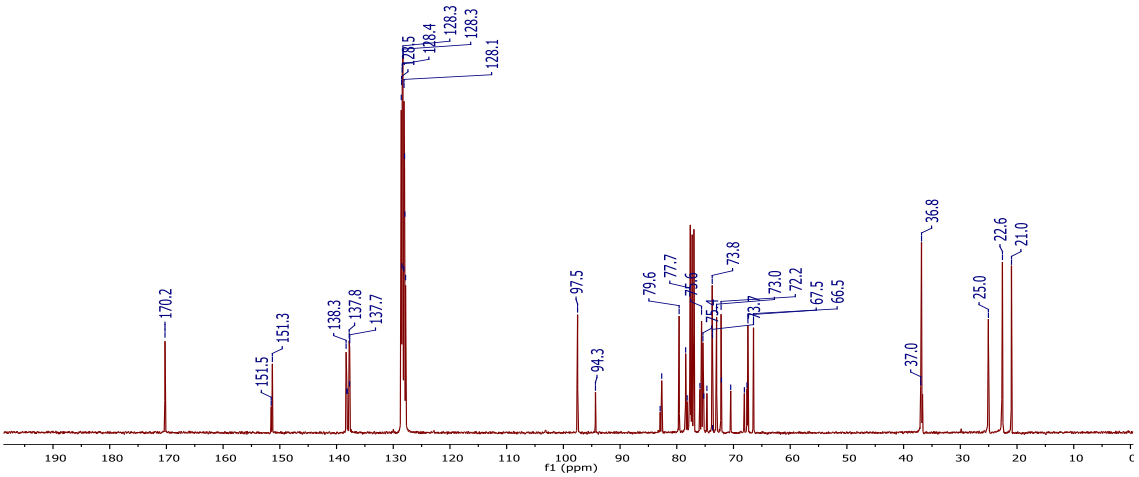
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7d**



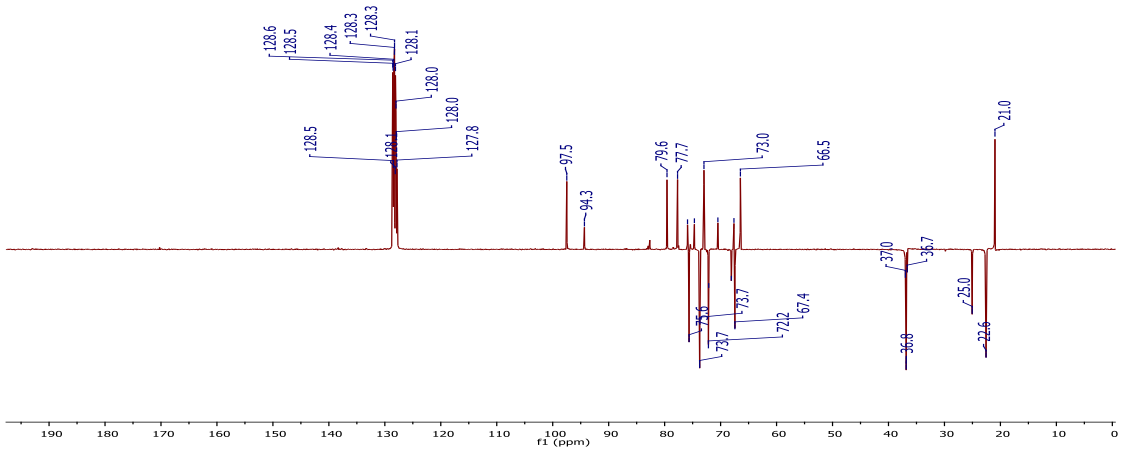
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **7e**



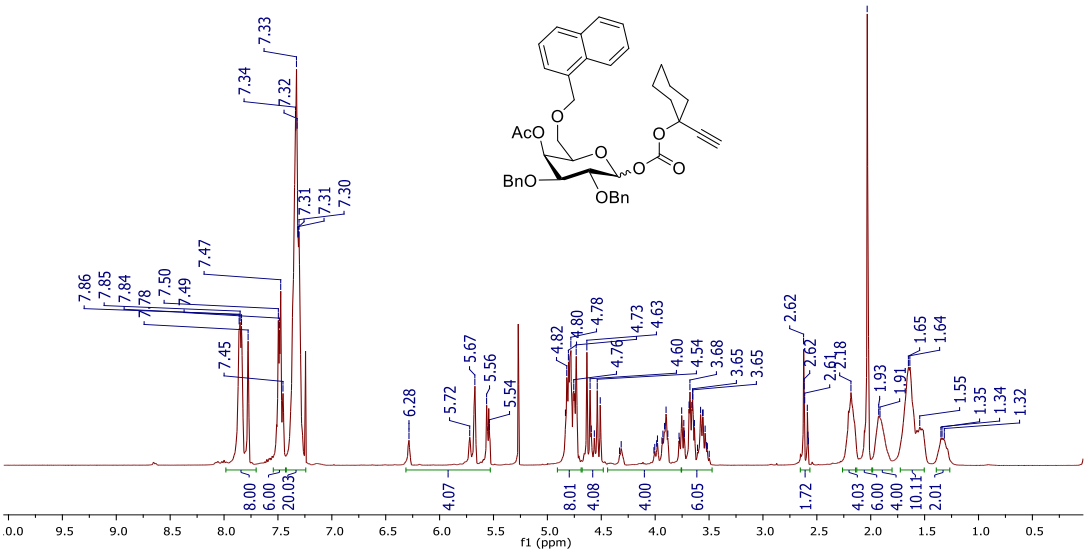
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7e**



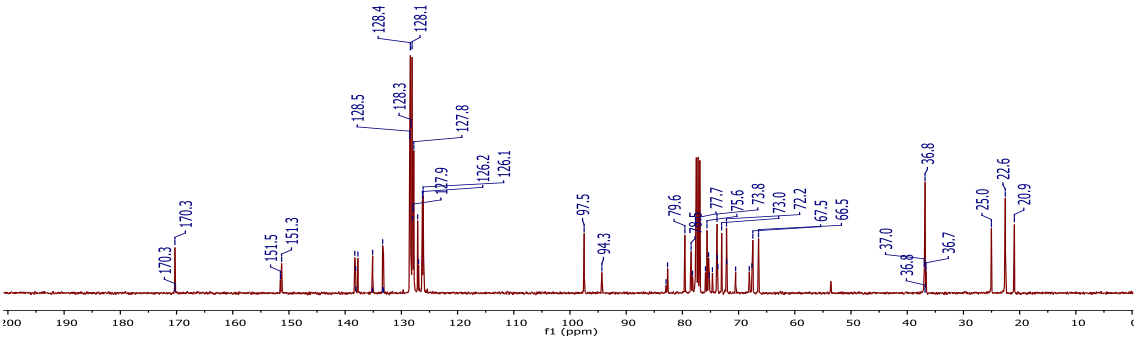
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7e**



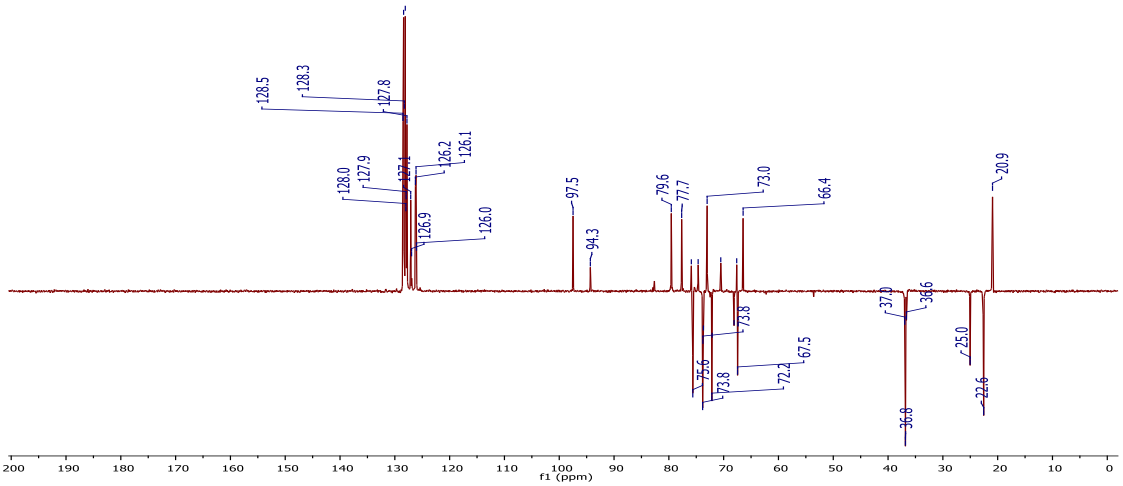
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **7f**



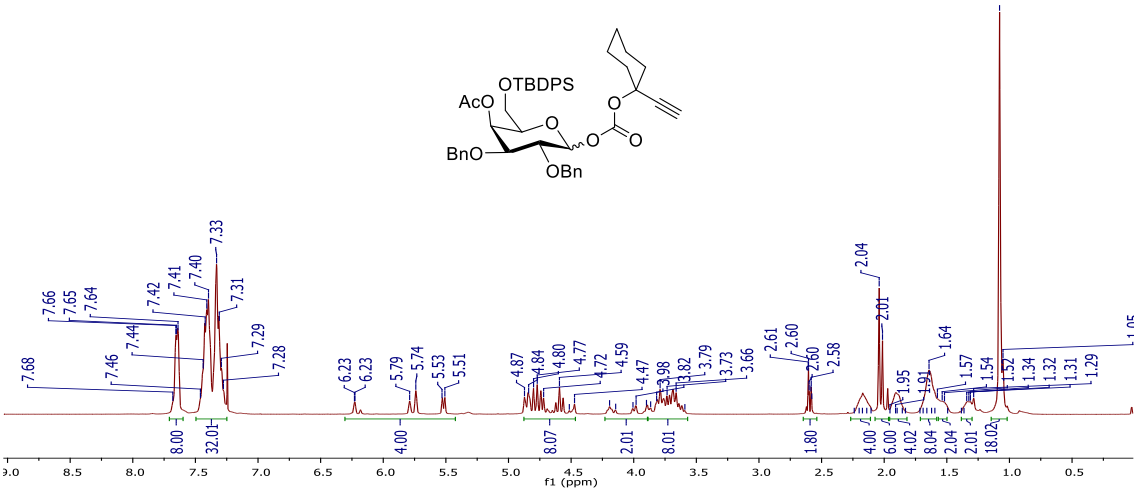
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7f**



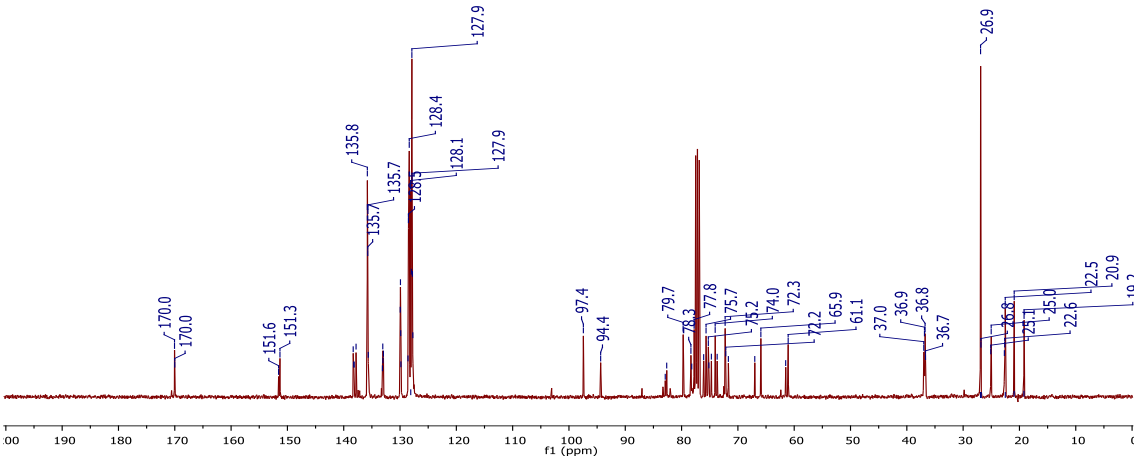
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7f**



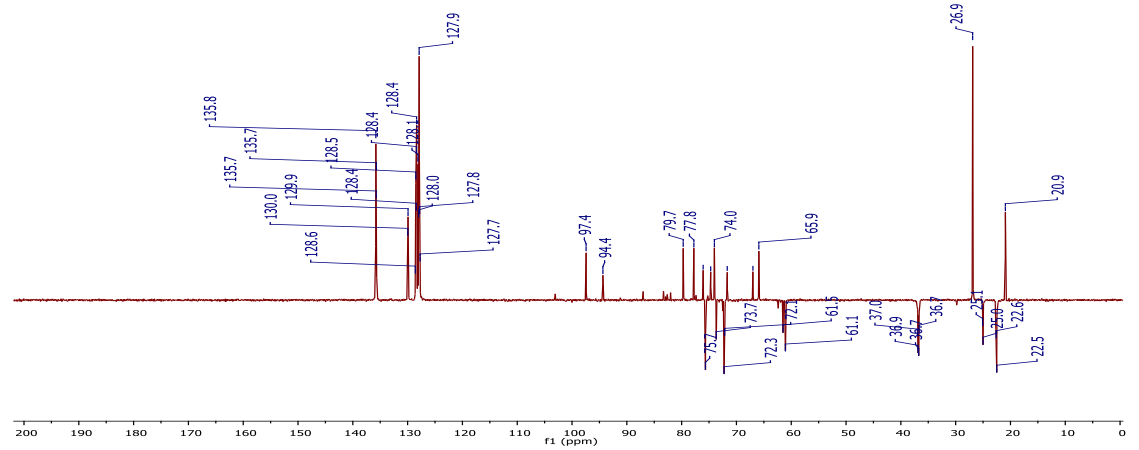
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **7g**



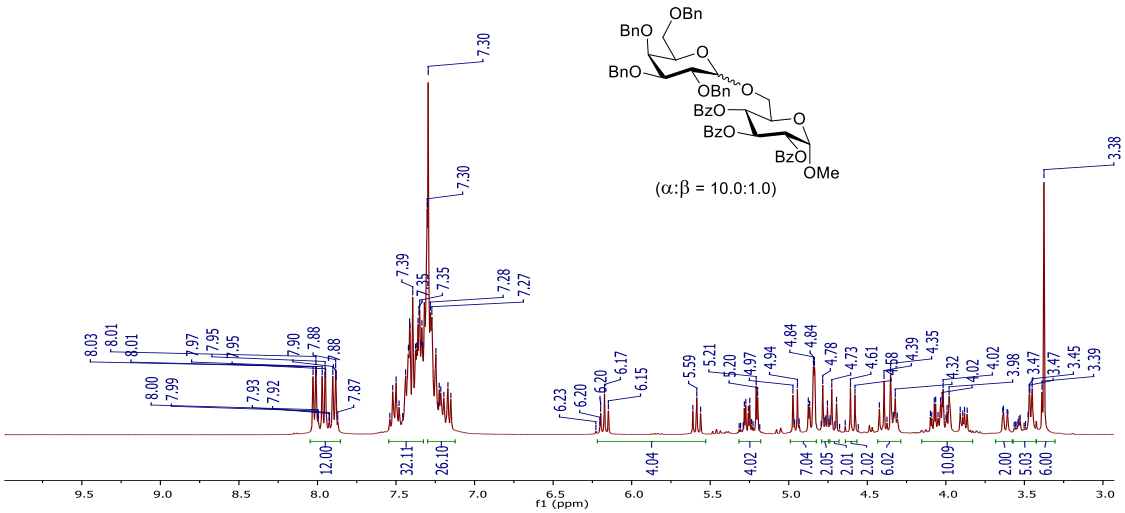
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7g**



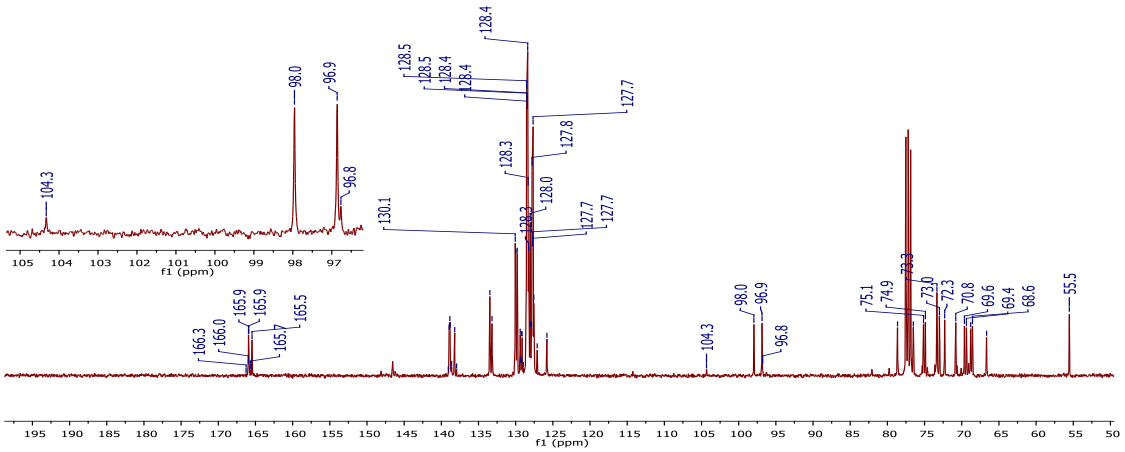
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **7g**



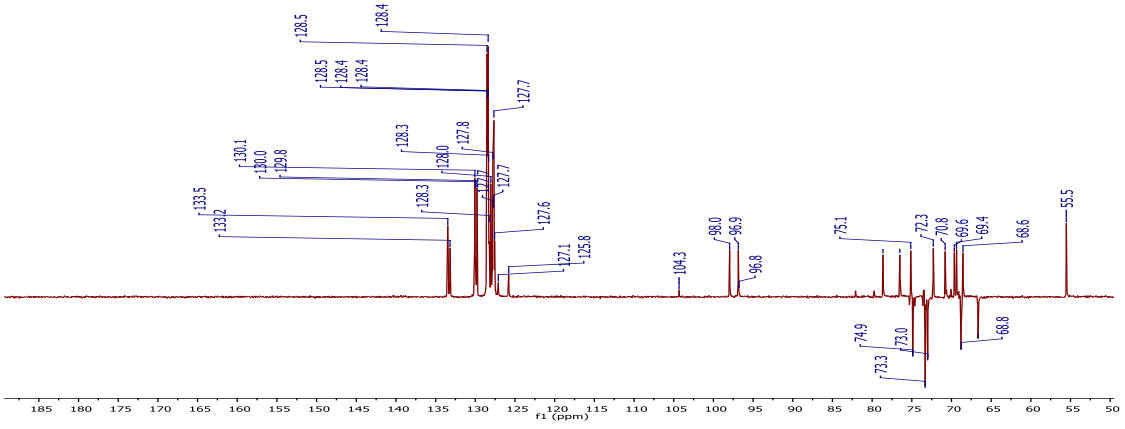
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **27a**



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

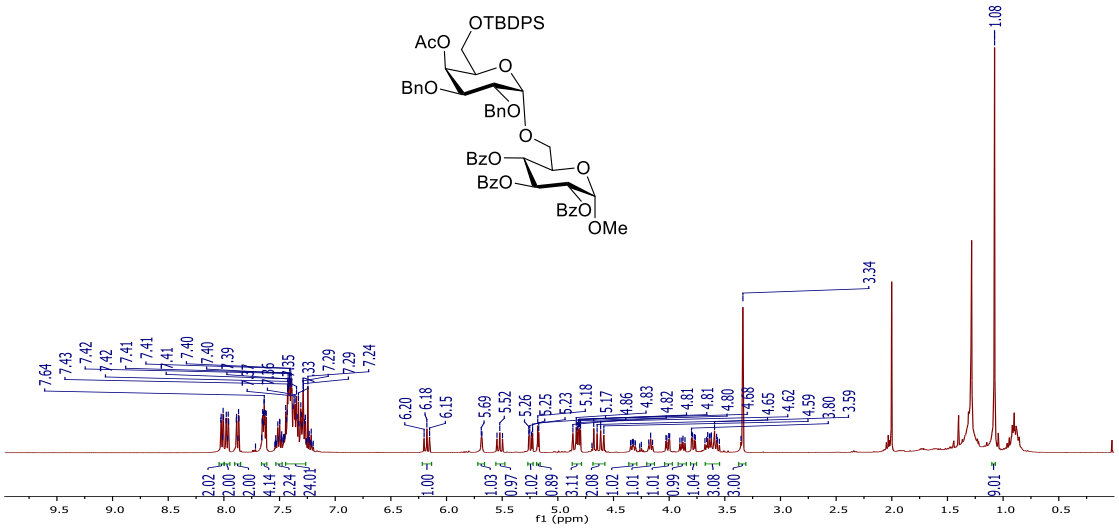


DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **27a**

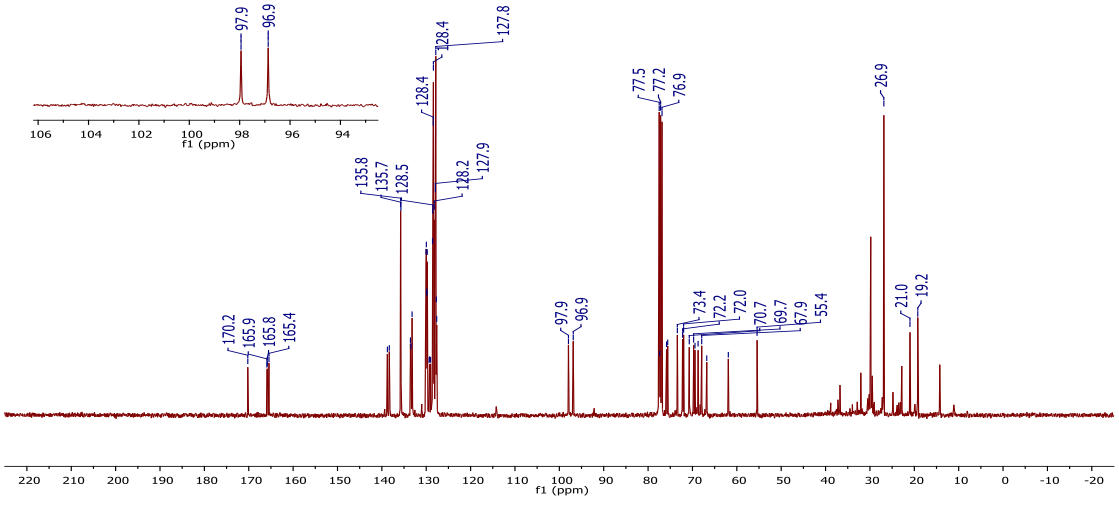


Crude NMR of disaccharide showing exclusive α-galactoside product formation

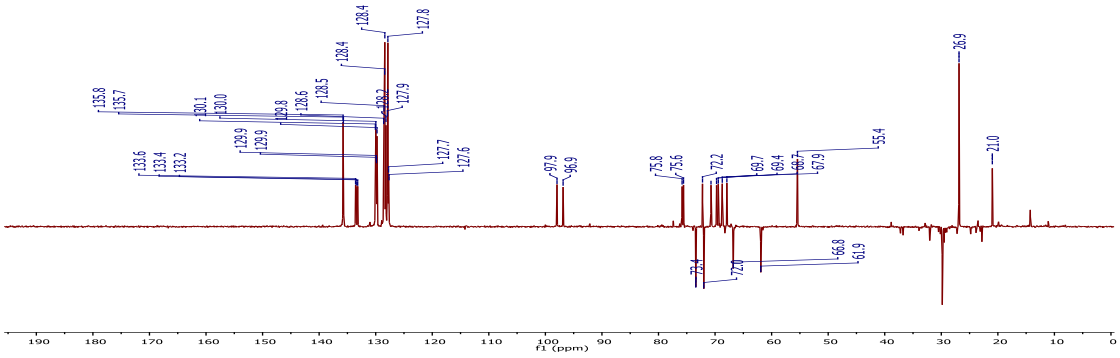
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$)



^{13}C NMR Spectrum (100.67MHz, $CDCl_3$)

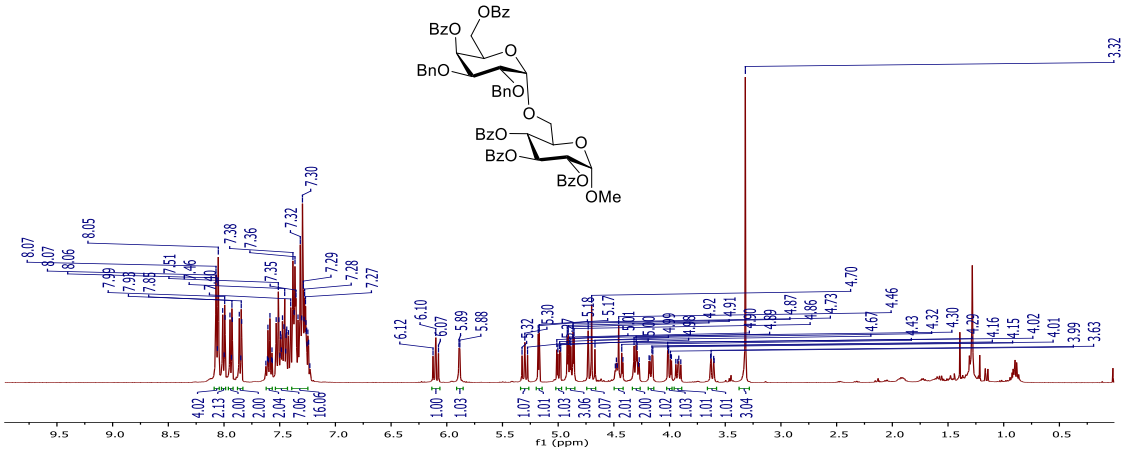


DEPT NMR Spectrum (100.67MHz, $CDCl_3$)

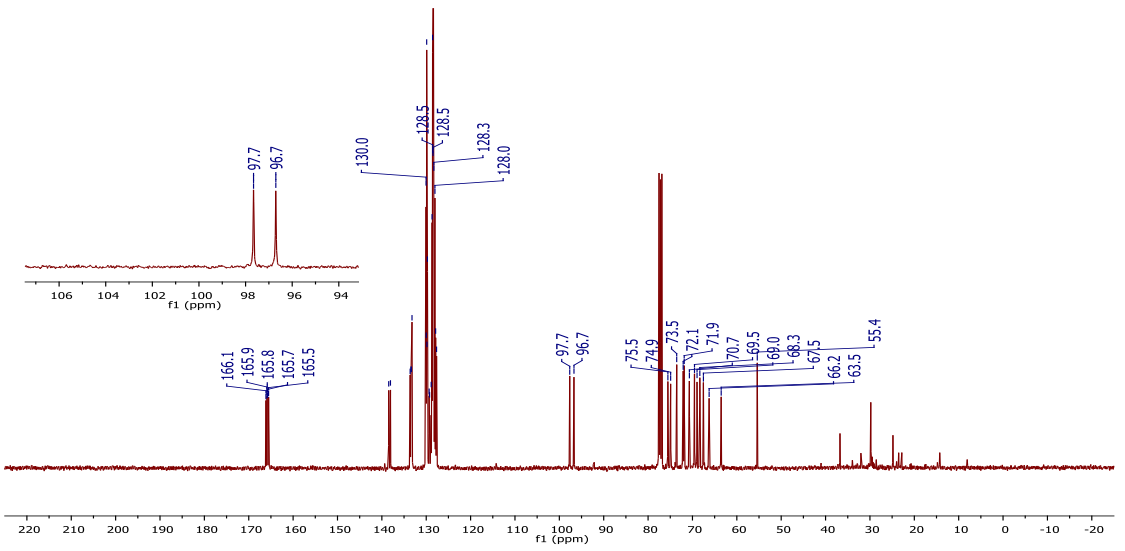


Crude NMR of disaccharide showing exclusive α-galactoside product formation

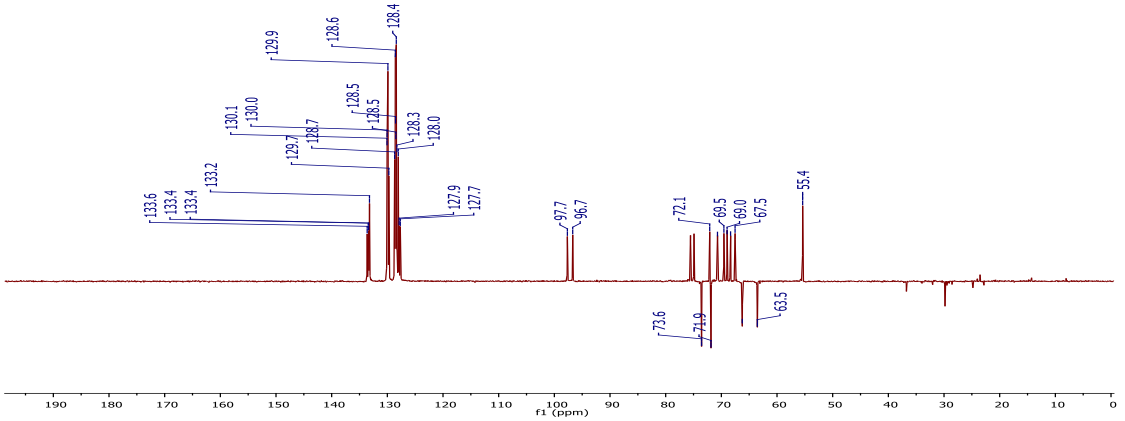
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$)



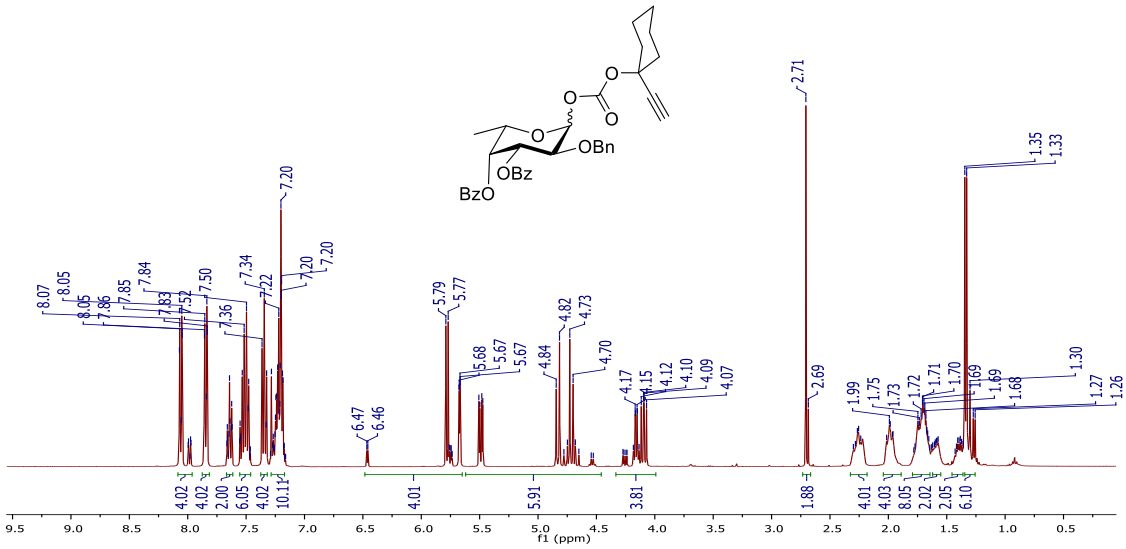
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$)



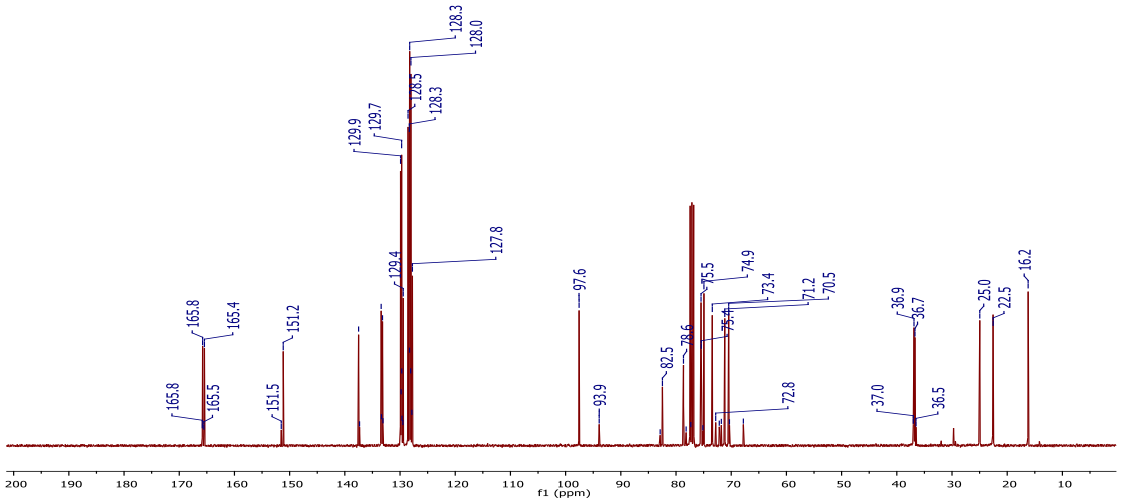
DEPT NMR Spectrum (100.67MHz, $CDCl_3$)



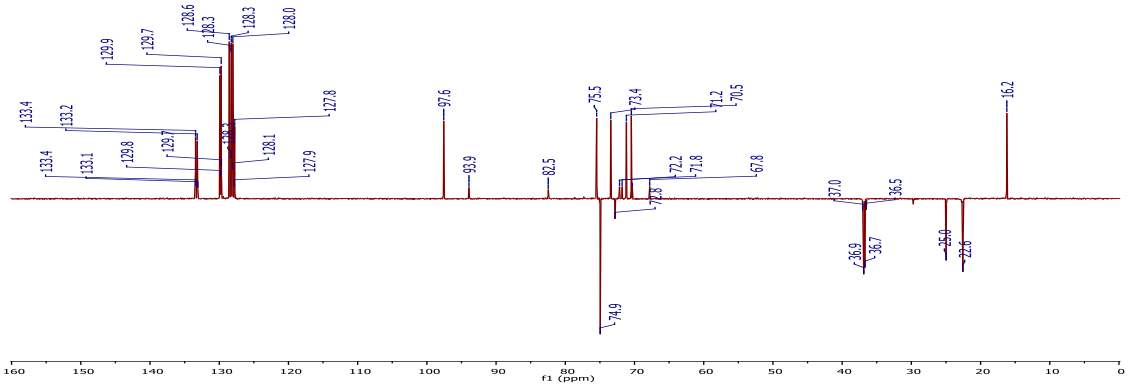
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **28**



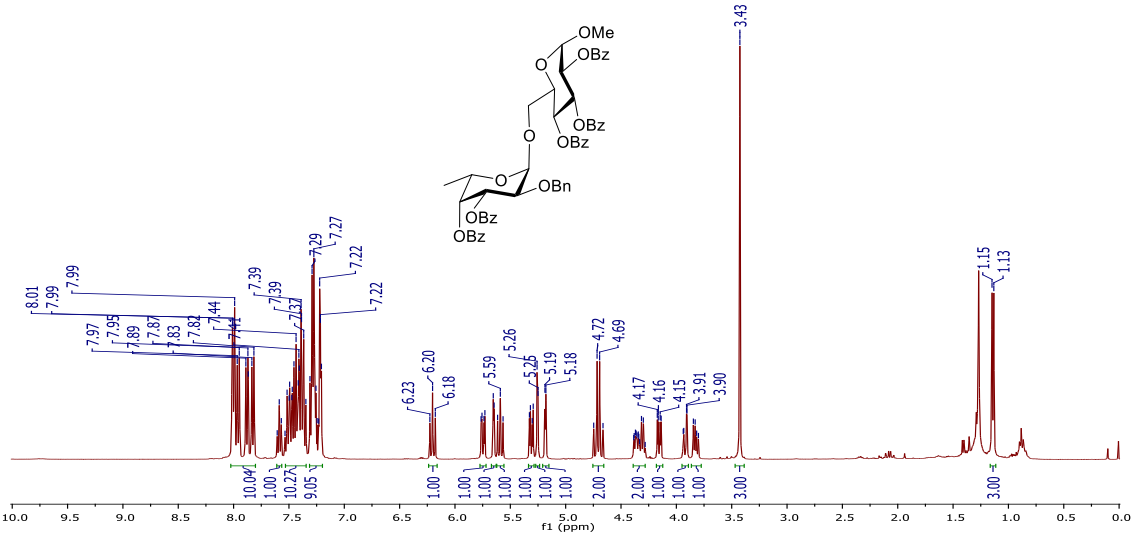
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **28**



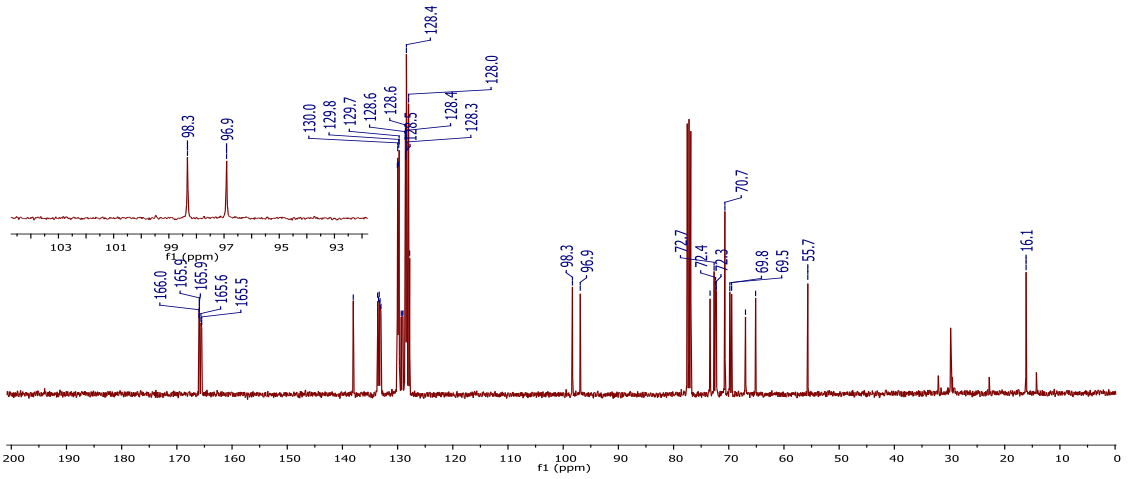
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **28**



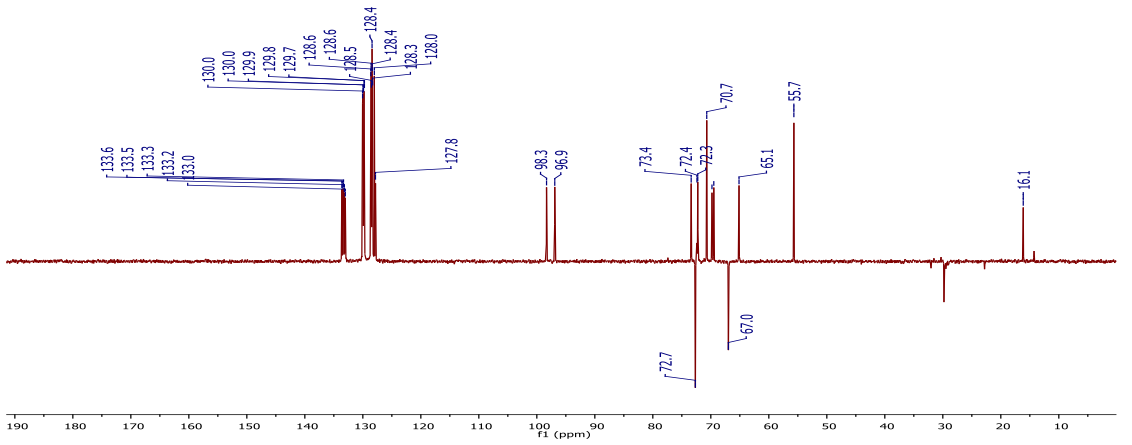
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **29**



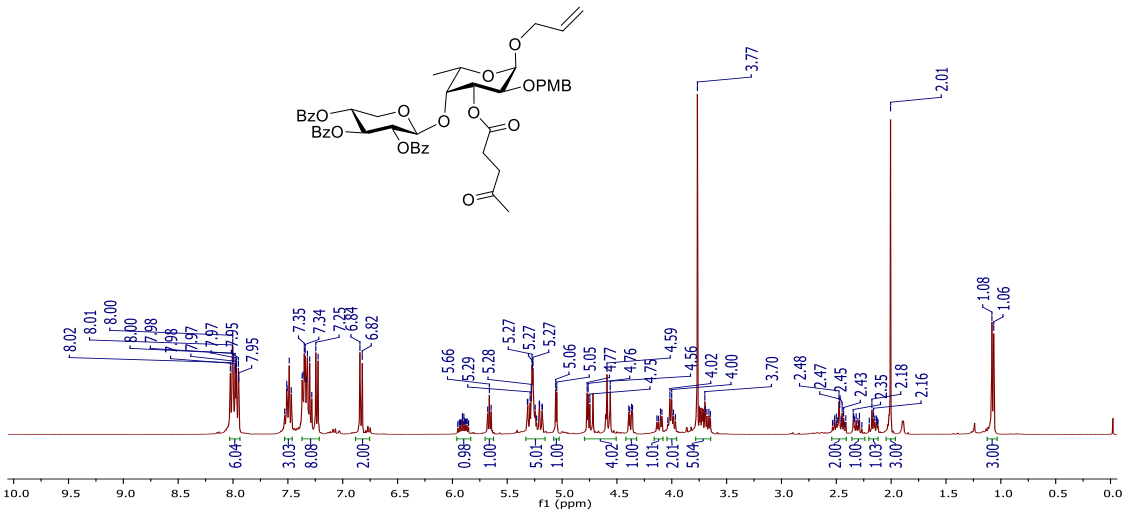
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **29**



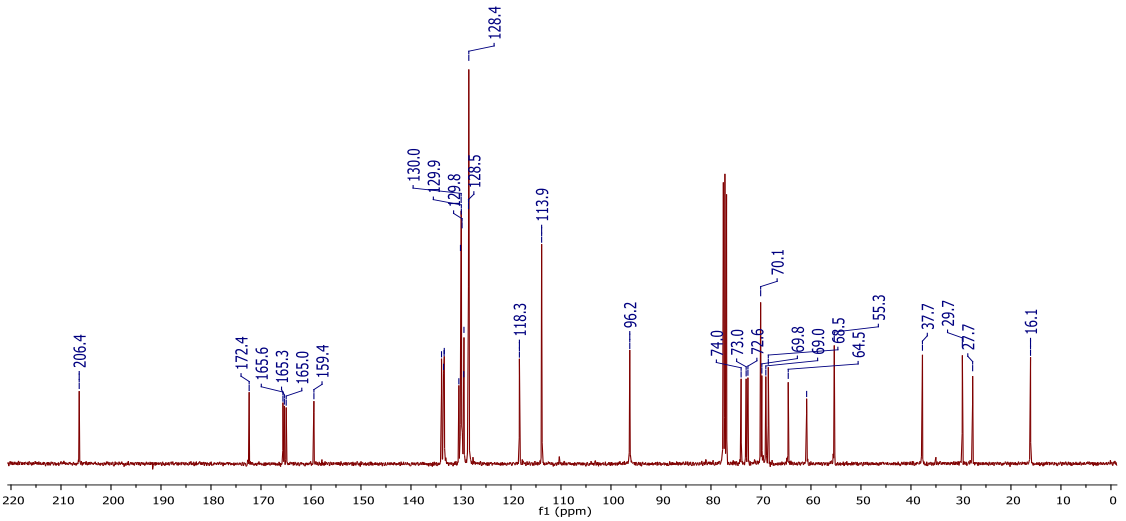
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **29**



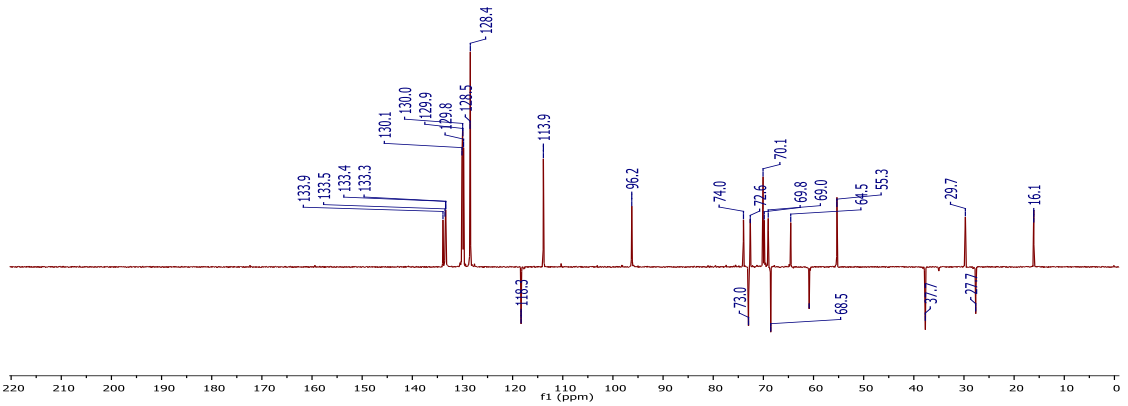
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **30**



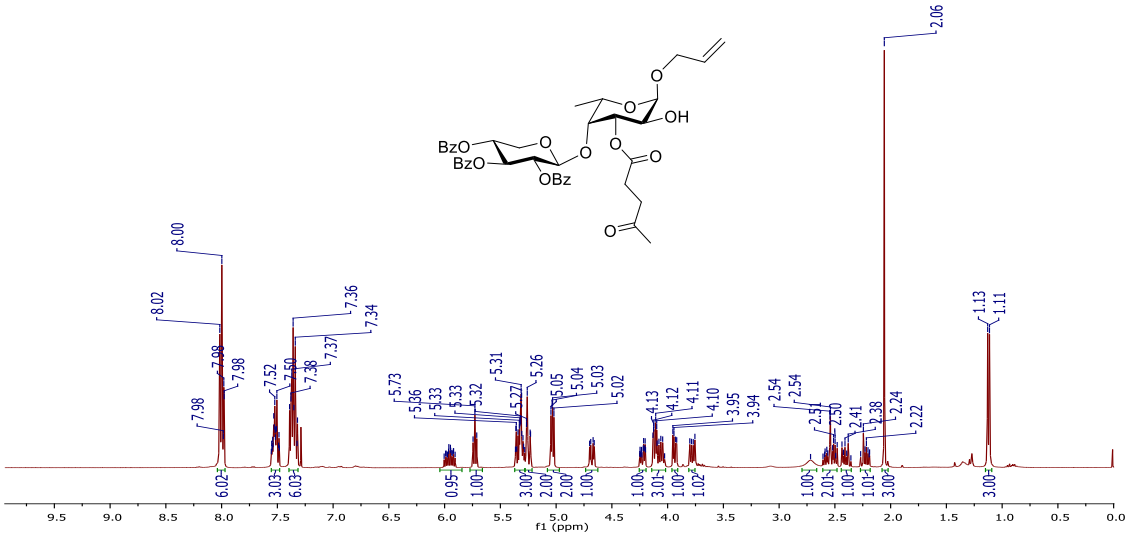
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **30**



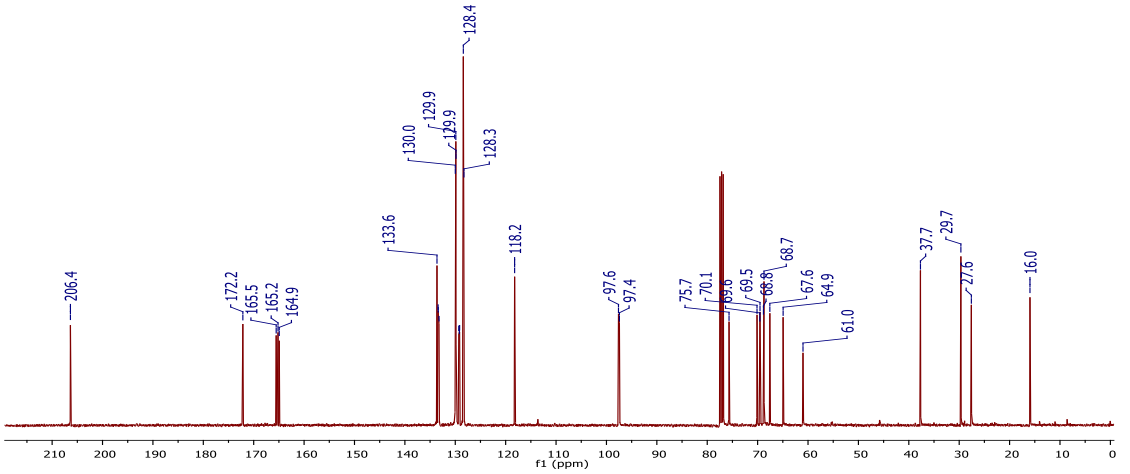
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **30**



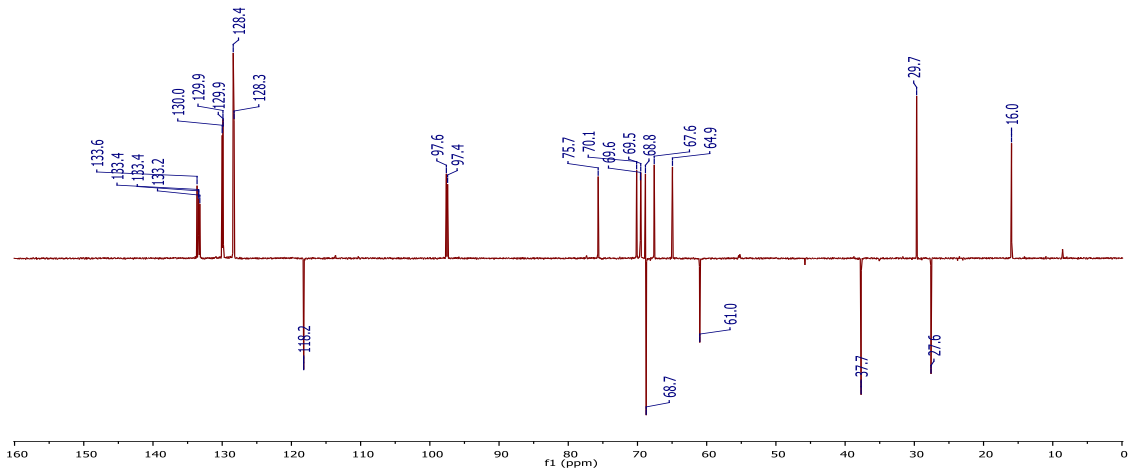
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **31**



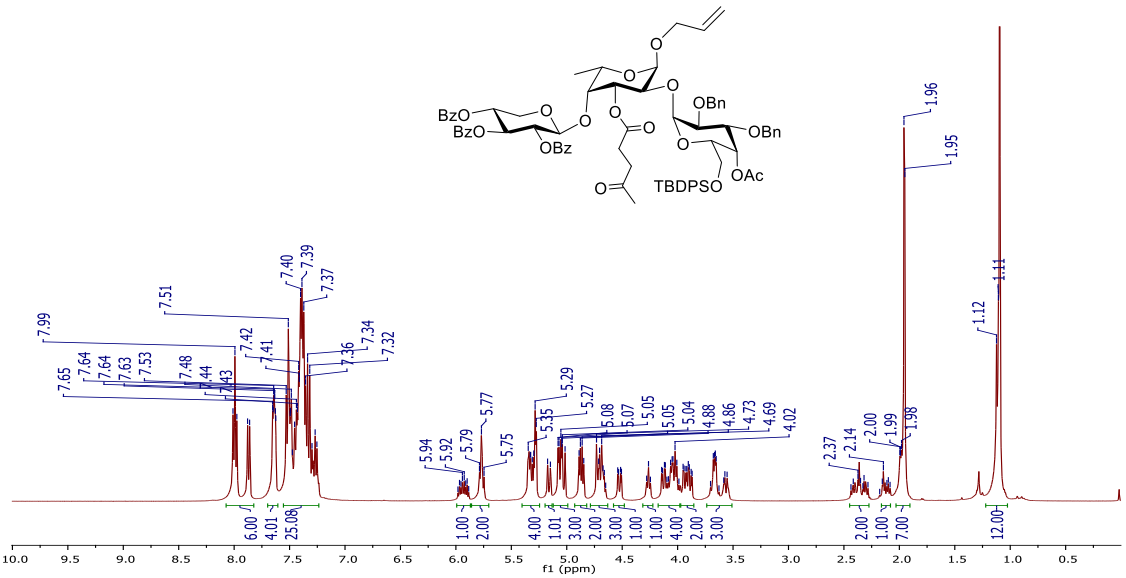
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **31**



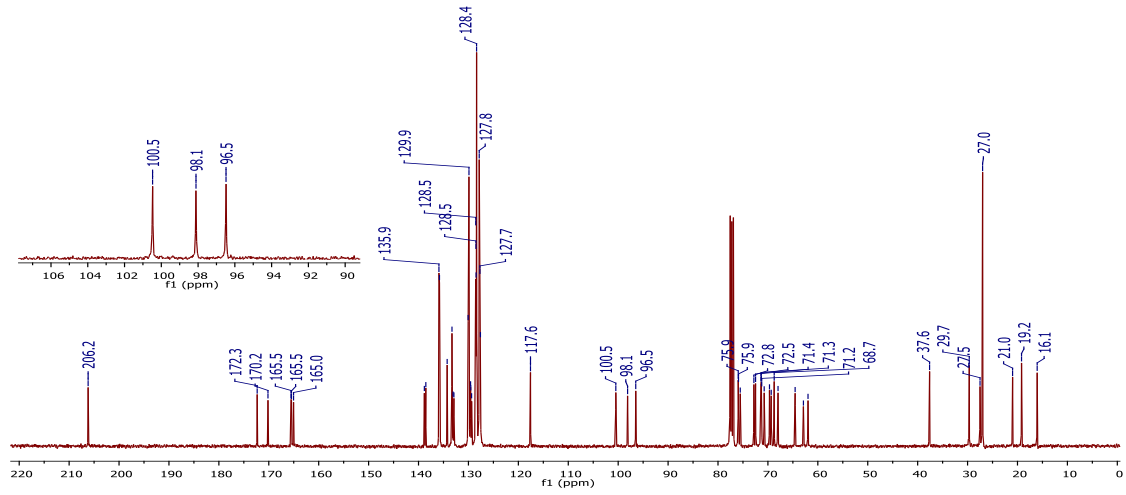
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **31**



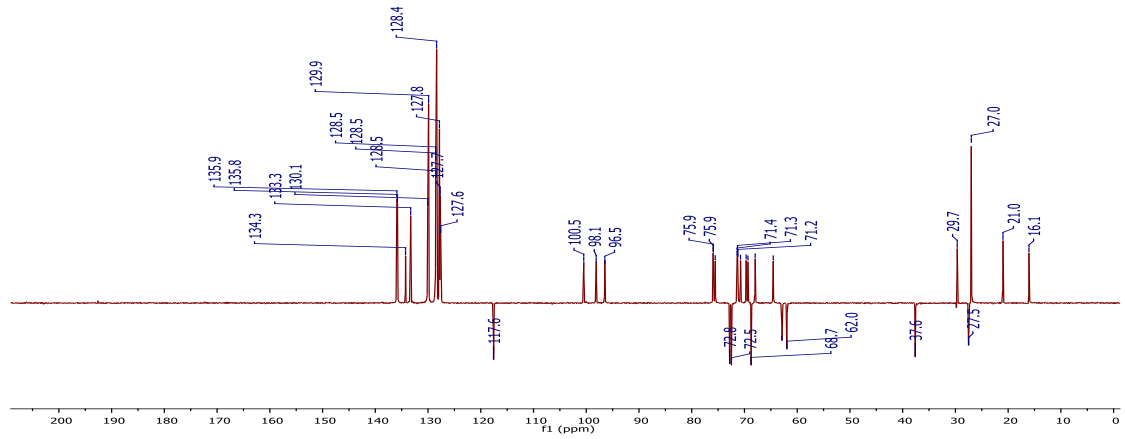
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **32**



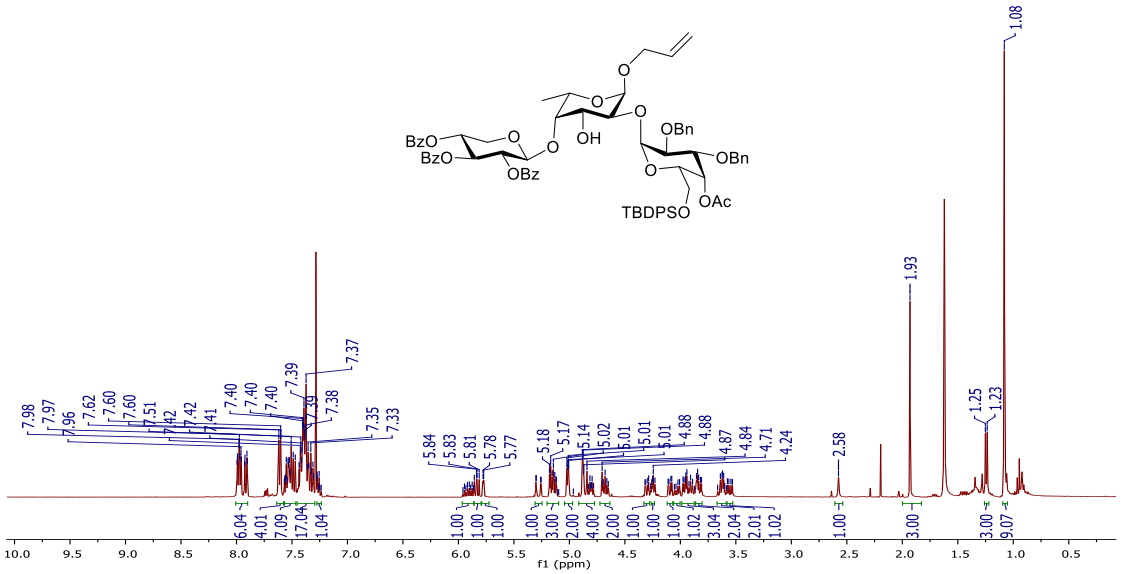
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **32**



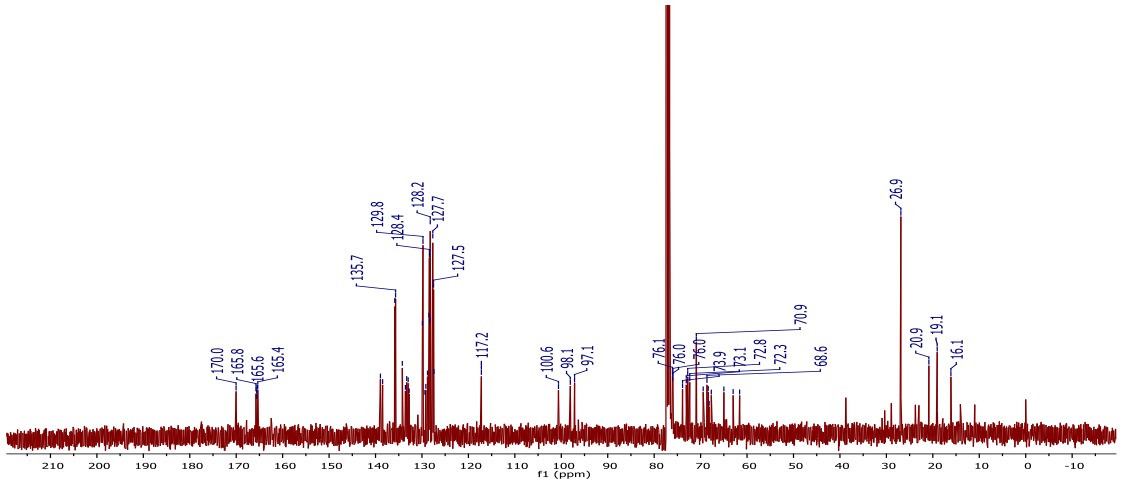
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **32**



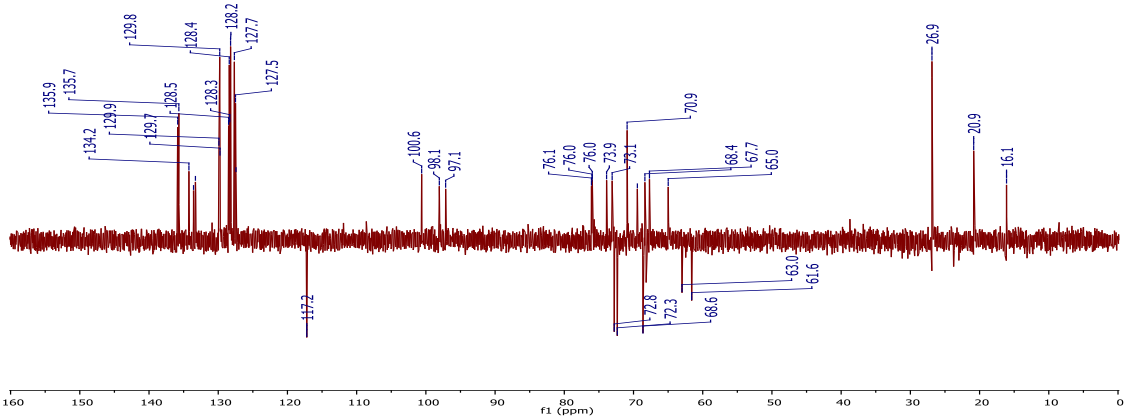
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **33**



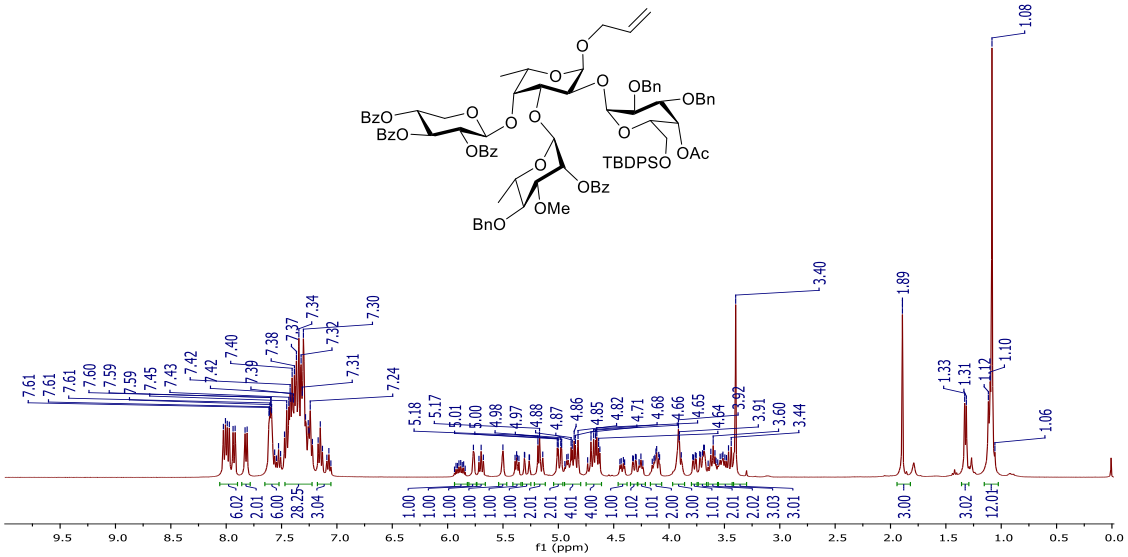
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **33**



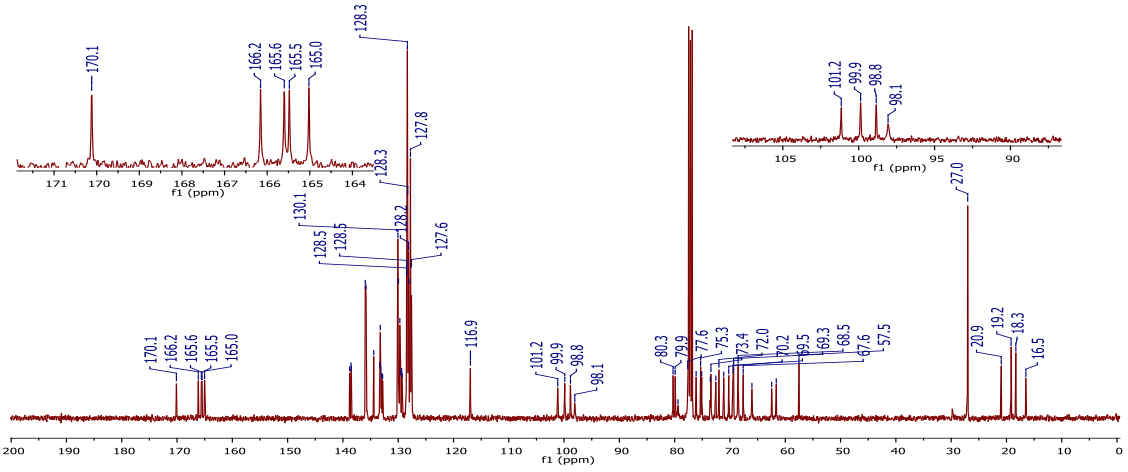
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **33**



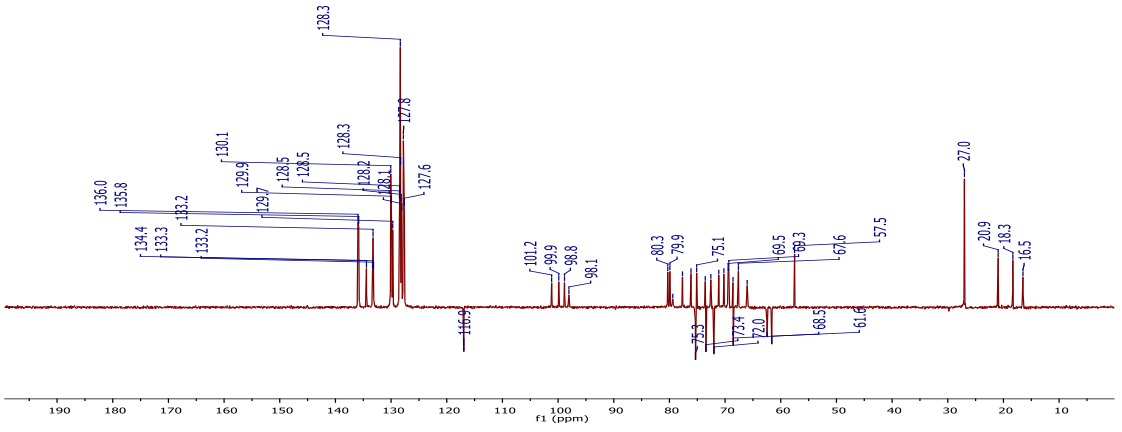
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **34**



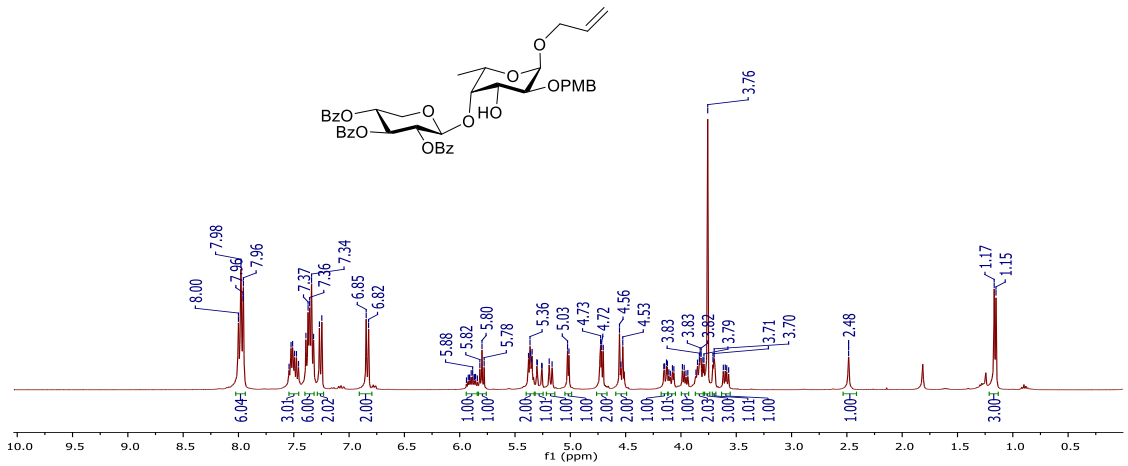
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **34**



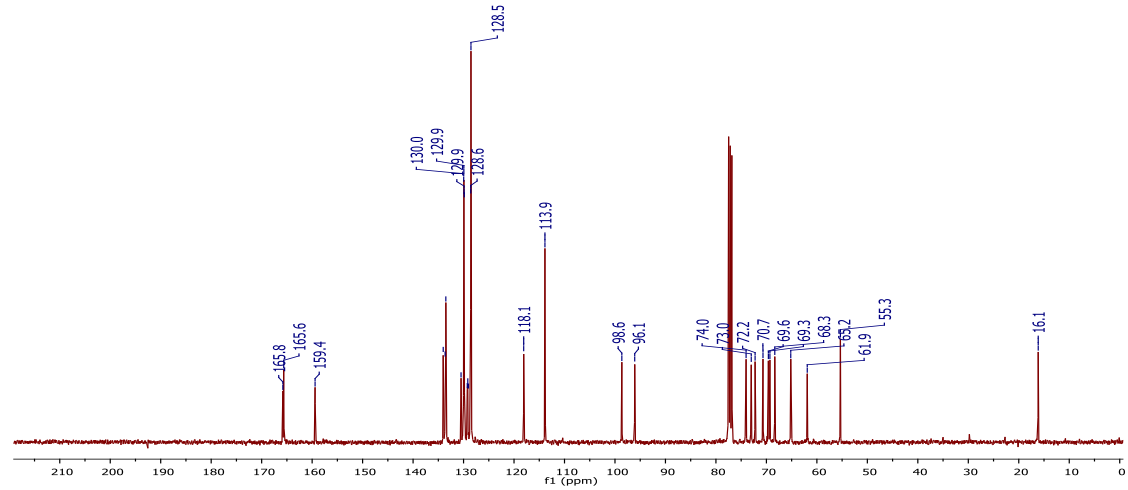
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **34**



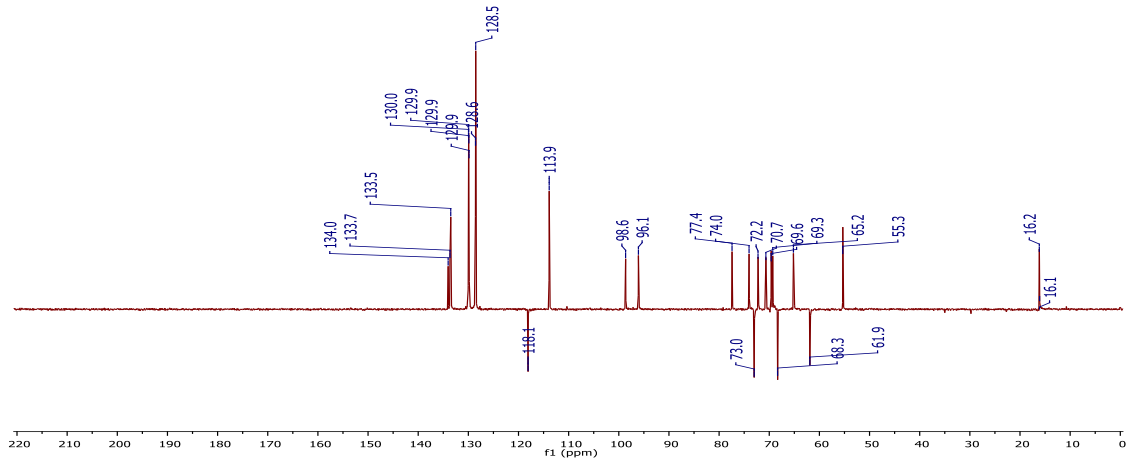
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **35**



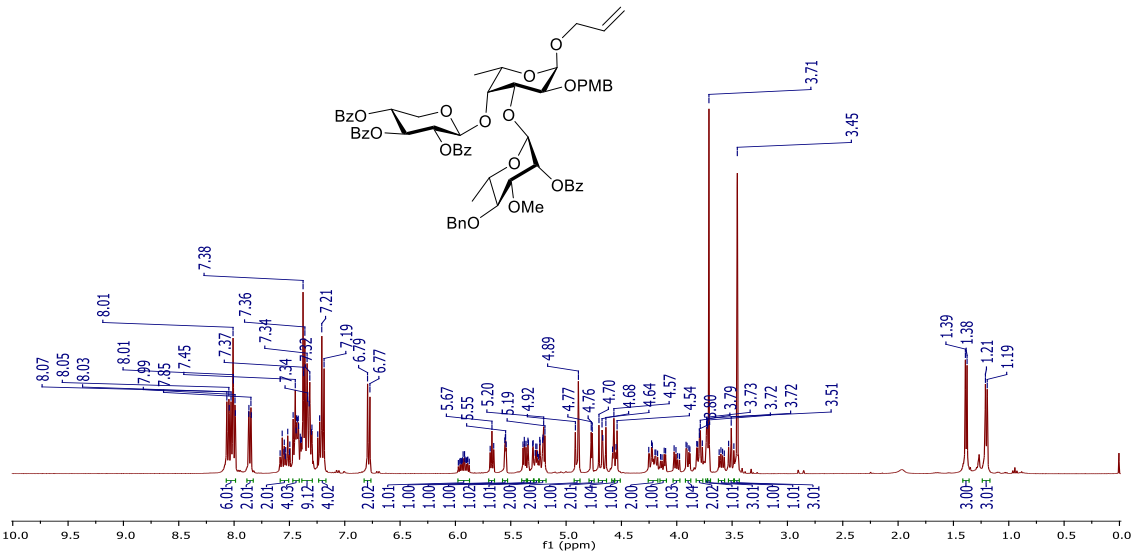
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **35**



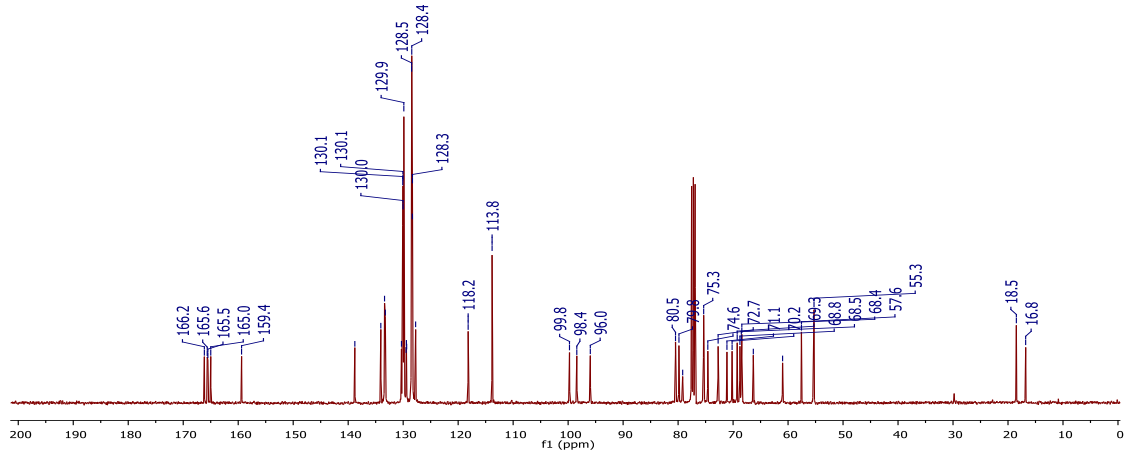
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **35**



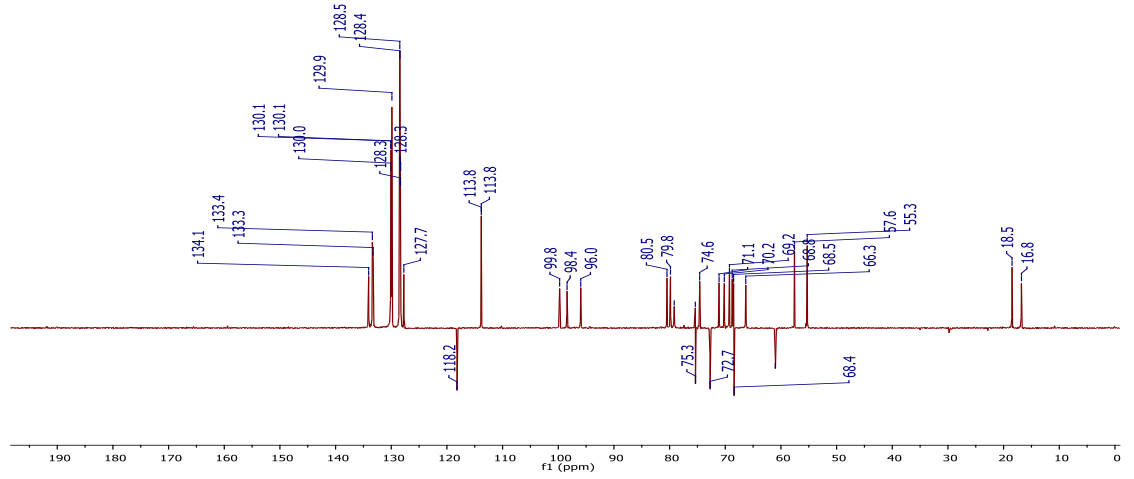
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **36**



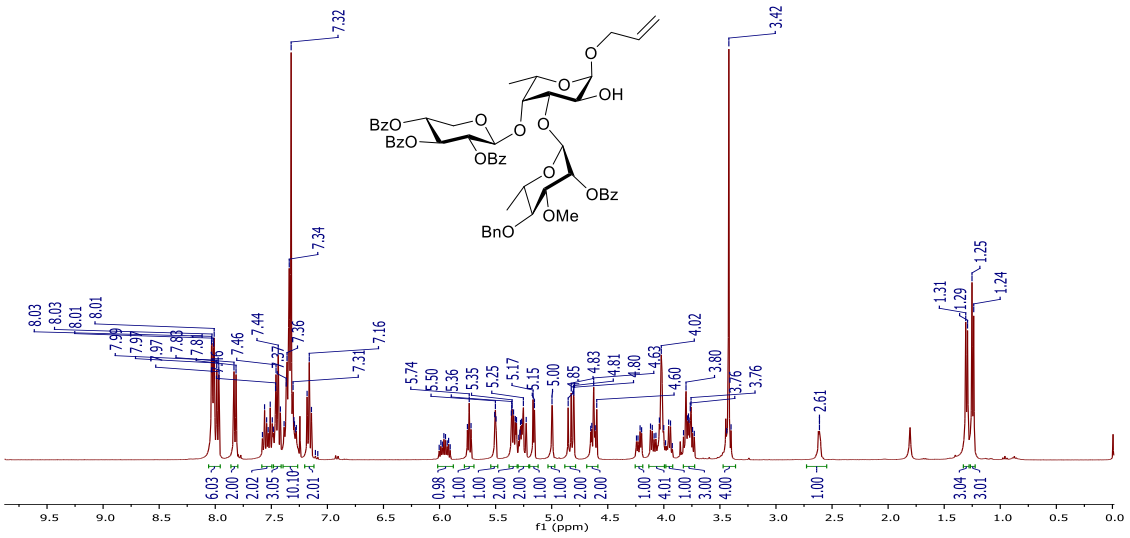
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **36**



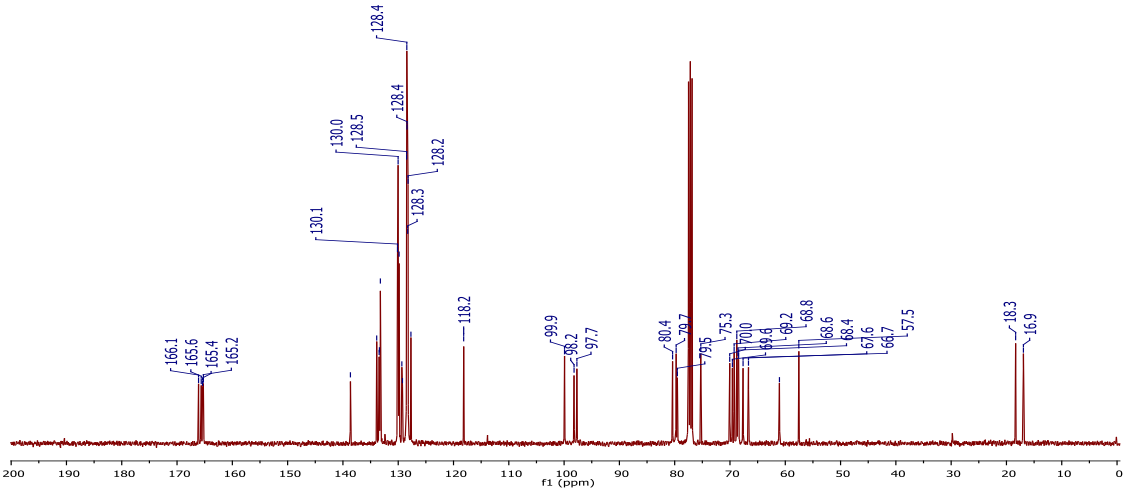
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **36**



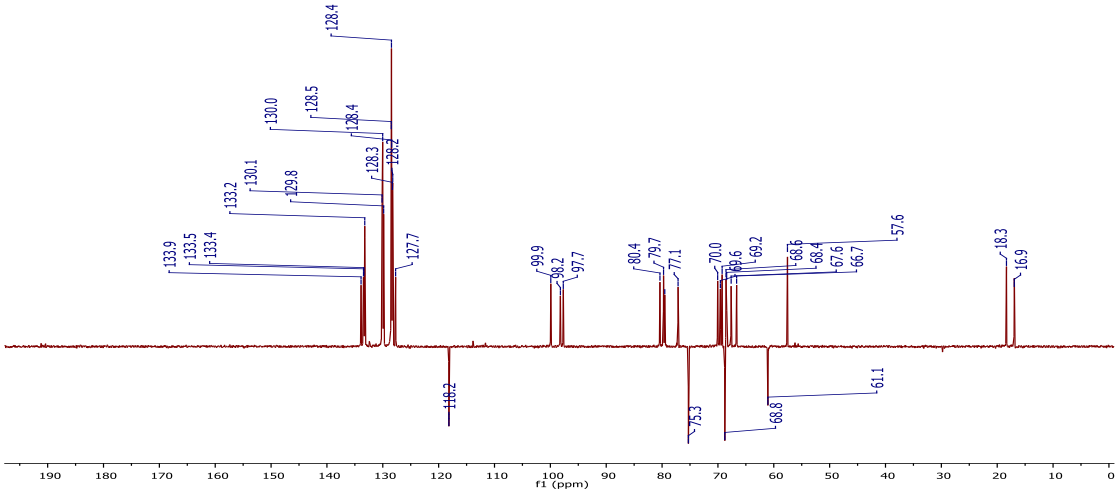
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **37**



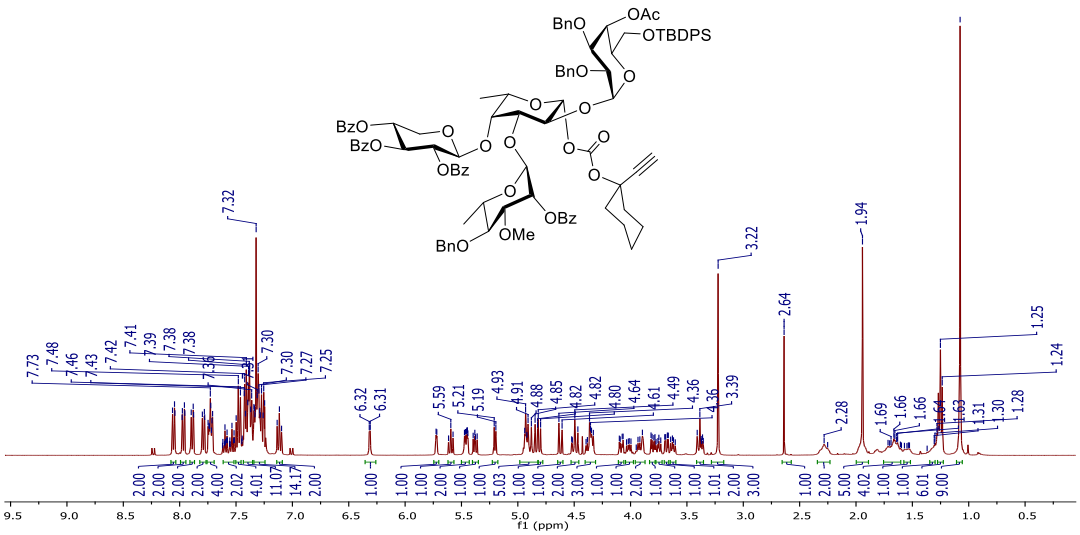
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **37**



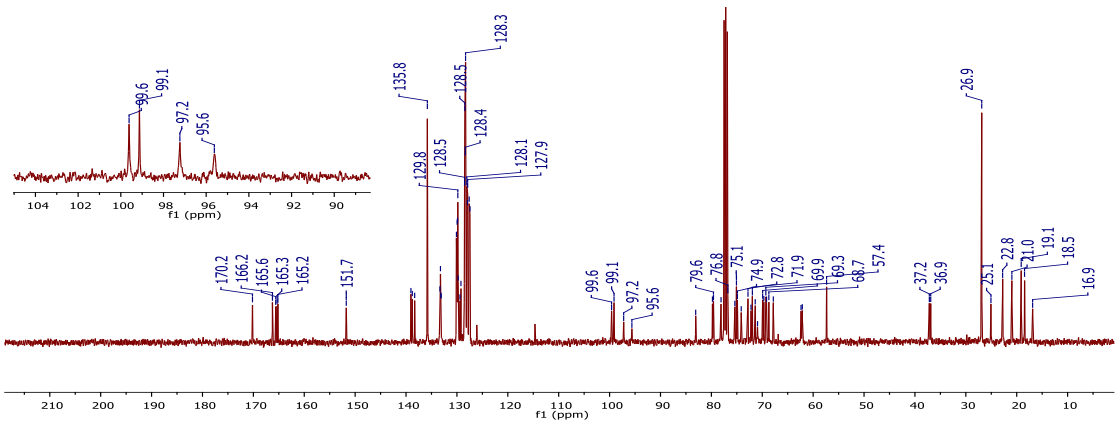
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **37**



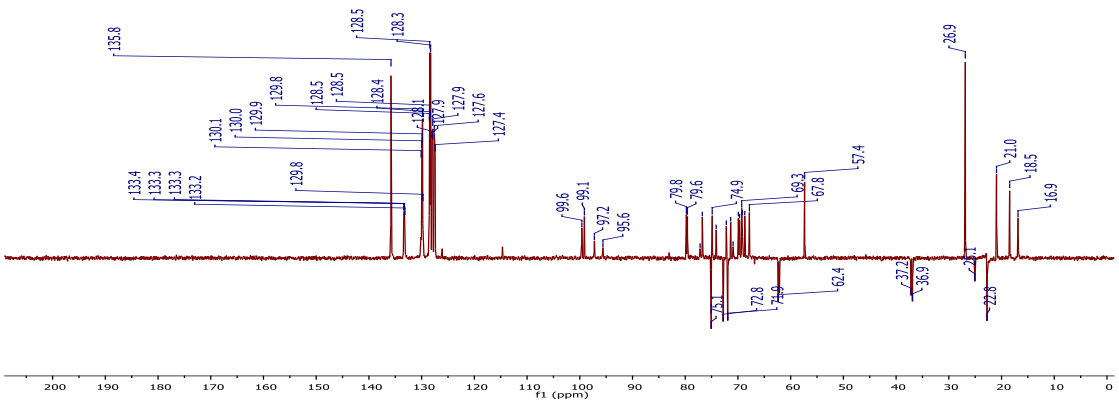
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **38**



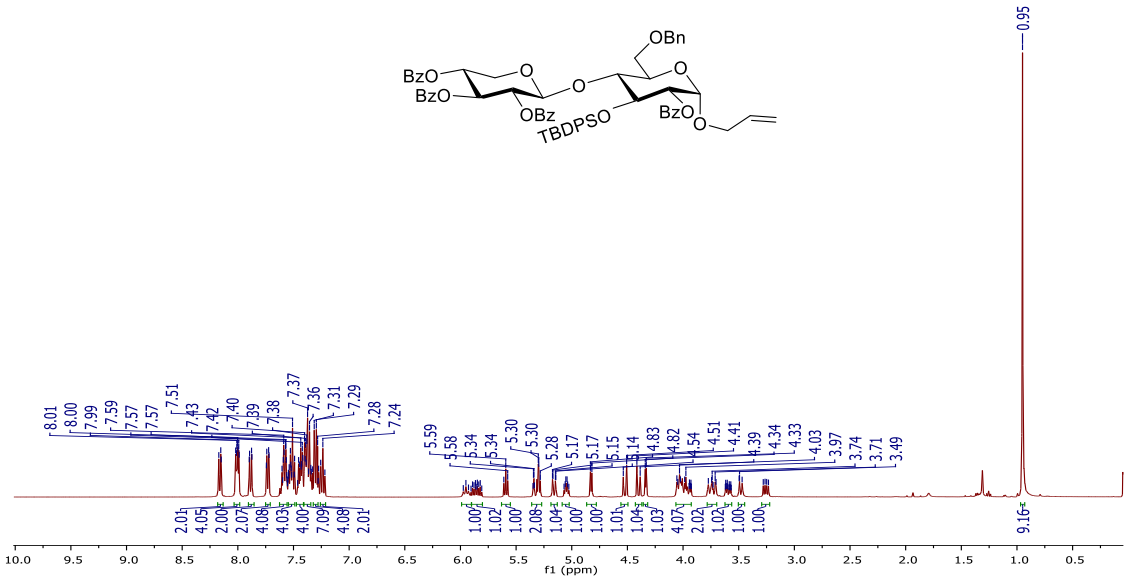
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **38**



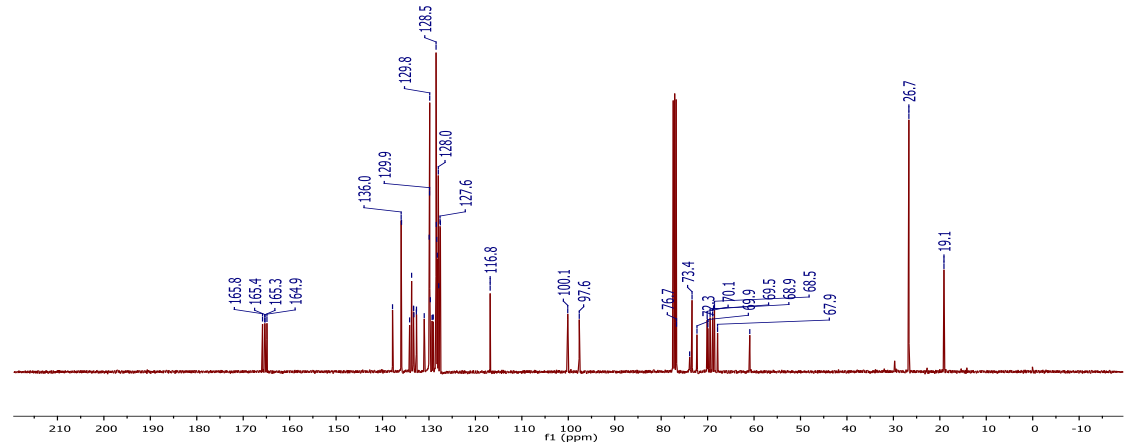
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **38**



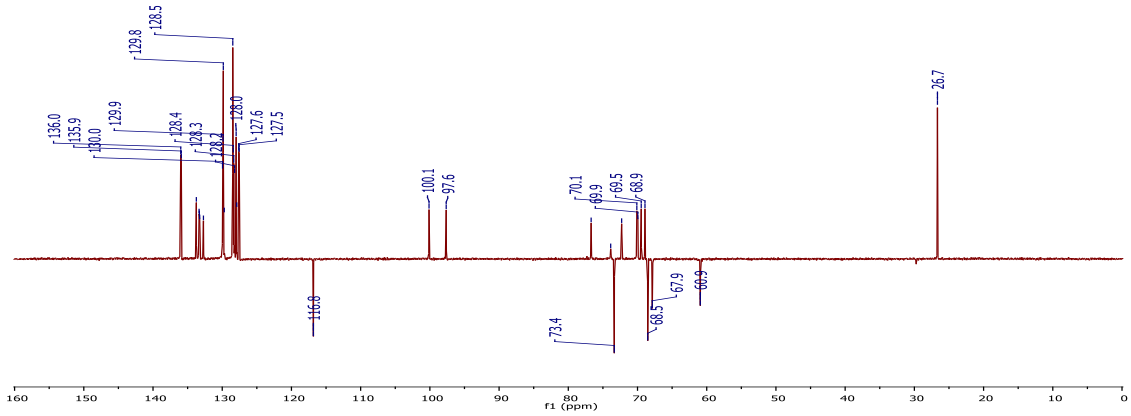
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **39**



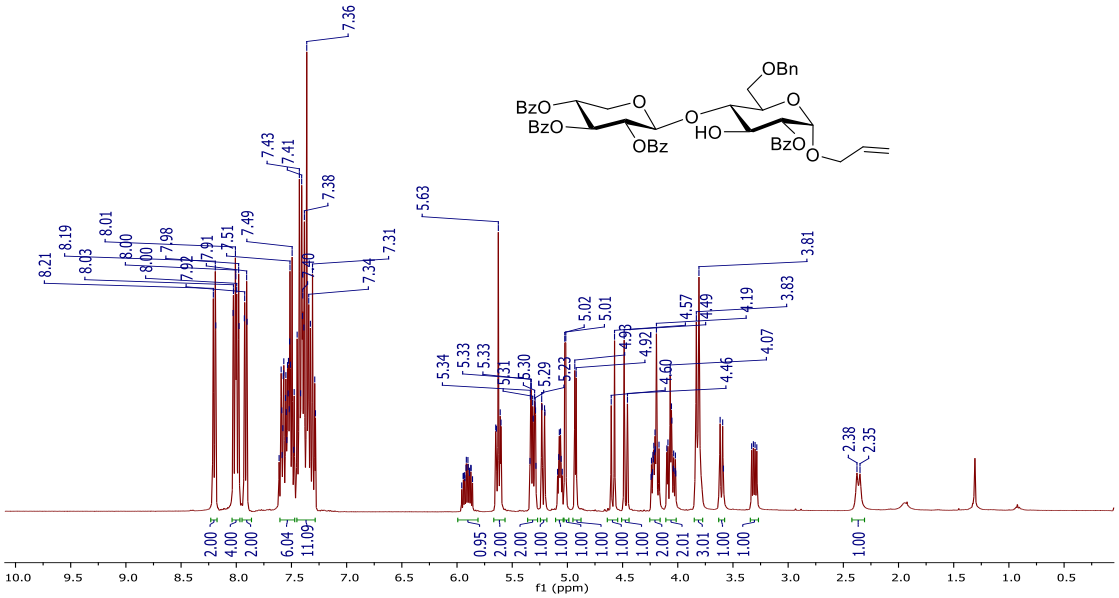
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **39**



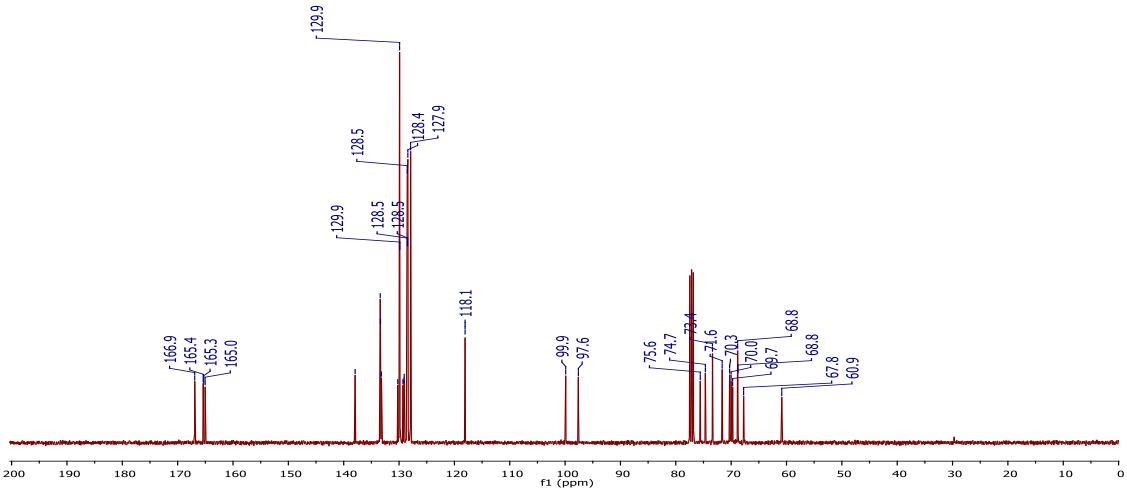
DEPT NMR Spectrum (100.67MHz, $CDCl_3$) of compound **39**



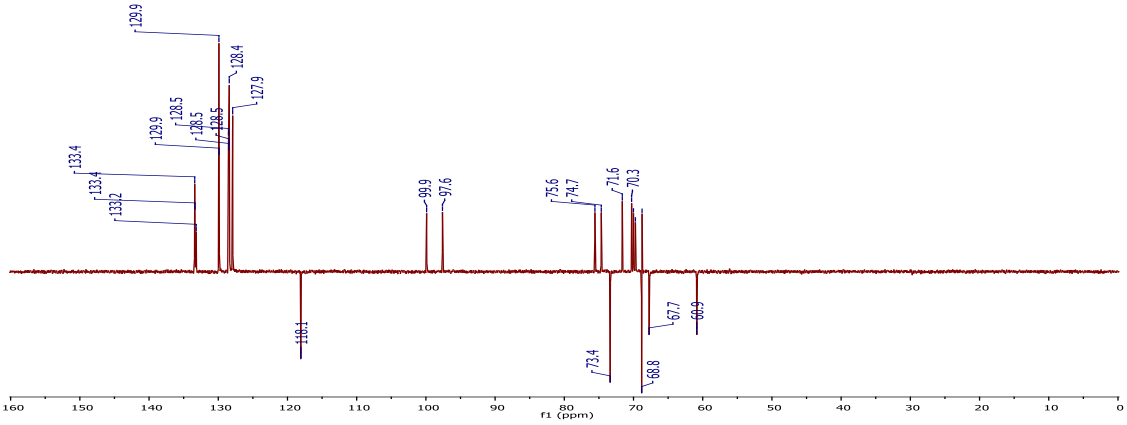
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of compound **40**



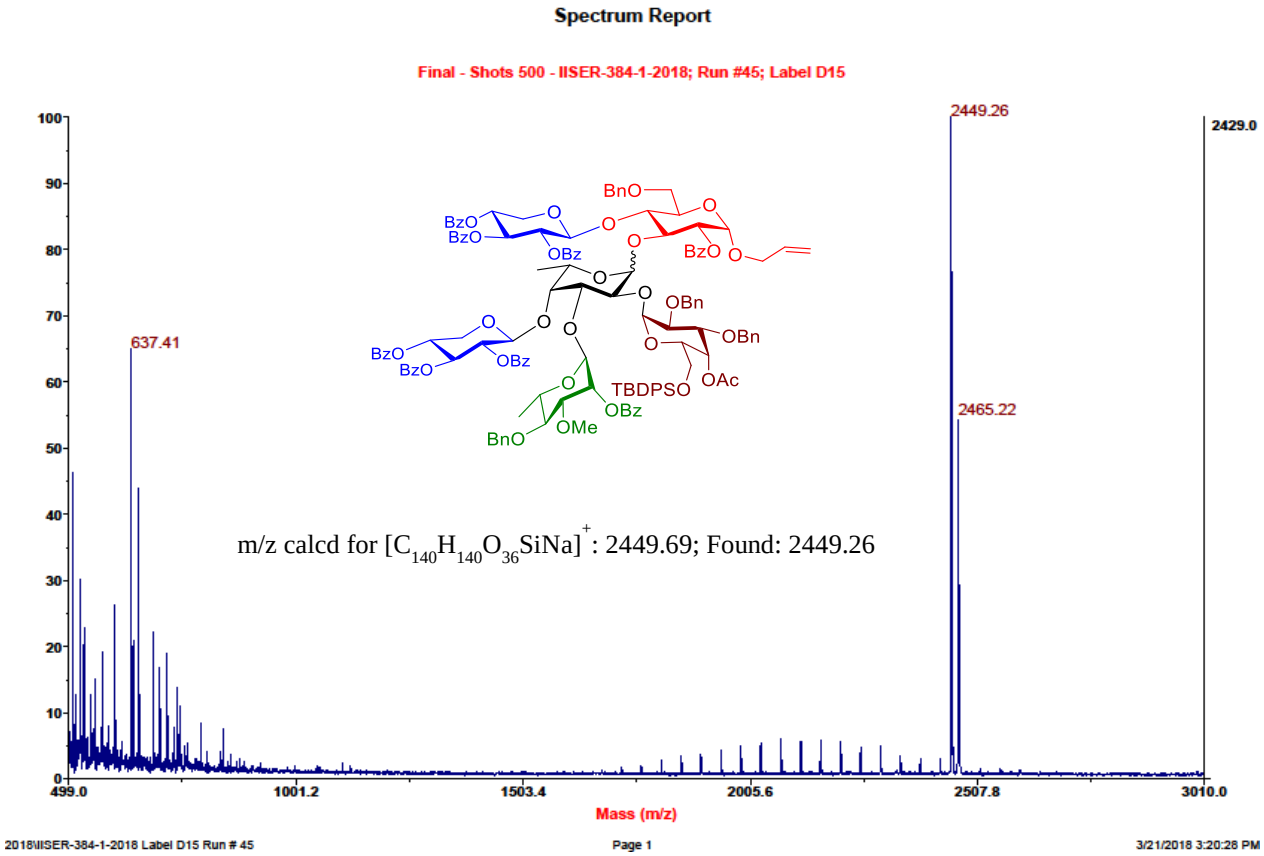
^{13}C NMR Spectrum (100.67MHz, $CDCl_3$) of compound **40**



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



MALDI-TOF of Core Hexasaccharide 41



4.7 – References

1. (a) Piacente, F.; Gaglianone, M.; Laugieri, M. E.; Tonetti, M. G. *Int. J. Mol. Sci*. **2015**, *16*, 29315–29328; (b) Danovaro, R.; Corinaldesi, C.; Dell'Anno, A.; Fuhrman, J. A.; Middelburg, J. J.; Noble, R. T.; Suttle, C. A. *FEMS Microbiol. Rev*. **2011**, *35*, 993–1034; (c) Sharoni, S.; Trainic, M.; Schatz, D.; Lehahn, Y.; Flores, M.J.; Bidle, K. D.; Ben-Dor, S.; Rudich, Y.; Koren, I.; Vardi, A. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 6643–6647; (d) Van Etten, J. L.; Gurnon, J. R.; Yanai-Balser, G. M.; Dunigan, D. D.; Graves, M. V. *Biochimica et Biophysica Acta* **2010**, *1800*, 152–159; (e) Quispe, C.F.; Sonderman, O.; Khasin, M.; Riekhof, W. R.; Van Etten, J. L.; Nickerson, K. W. *Algal Res* **2016**, *18*, 332–340; (f) Dunigan, D. D.; Fitzgerald, L. A.; Van Etten, J. L. *Virus Res* **2006**, *117*, 119–132; (g) Van Etten, J. L.; Agarkova, I.; Dunigan, D. D.; Tonetti, M.; De Castro, C.; Duncan, G. A. *Viruses* **2017**, *9*, 88, 1–23.
2. (a) Schwarz, F.; Aebi, M. *Current Opinion in Structural Biology* **2011**, *21*, 576–582; (b) De Castro, C.; Molinaro, A.; Piacente, F.; Gurnon, J. R.; Sturiale, L.; Palmigiano, A.; Lanzetta, R.; Parrilli, M.; Garozzo, D.; Tonetti, M. G.; Van Etten, J. L. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 13956–13960; (c) Yolkena, R. H.; Jones-Brando, L.; Dunigan, D. D.; Kannan, G.; Dickerson, F.; Severance, E.; Sabunciyan, S.; Talbot Jr., C. C.; Prandovszky, E.; Gurnon, J. R.; Agarkova, I. V.; Leister, F.; Gressitt, K. L; Chen, O.; Deuber, B.; Ma, F.; Pletnikov, M. V.; Van Etten, J. L. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 16106–16111; (d) Petro, M. S.; Agarkova, I. V.; Petro, T. M. *Journal of Neuroimmunology* **2016**, *297*, 46–55.
3. (a) Spolaore, P.; Joannis-Cassan, C.; Duran, E.; Isambert, A. *J. Biosci. Bioeng.* **2006**, *101*, 87–96; (b) Sasso, S.; Pohnert, G.; Lohr, M.; Mittag, M.; Hertweck, C. *FEMS Microbiol. Rev.* **2012**, *36*, 761–785; (c) Blanc, G.; Duncan, G.; Agarkova, I.; Borodovsky, M.; Gurnon, J.; Kuo, A. *Plant Cell Online* **2010**, *22*, 2943–2955; (d) Merchant, S. S.; Kropat, J.; Liu, B.; Shaw, J.; Warakanont, J. *Curr. Opin. Biotechnol.* **2012**, *23*, 352–363; (e) Hempel, F.; Bozarth, A. S.; Lindenkamp, N.; Klingl, A.; Zauner, S.; Linne, U. *Microb. Cell Fact.* **2011**, *10*, 81; (f) Walsh, G. *Nat. Biotechnol.* **2010**, *28*, 917–924; (g) Mathieu-Rivet, E.; Kiefer-Meyer, M. -C.; Vanier, G.; Ovide, C.; Burel, C.; Lerouge, P.; Bardor, M. *Frontiers in Plant Science* **2014**, *5*, 389, 1–39.

4. (a) Van Etten, J. L.; Burbank, D. E.; Xia, Y.; Meints, R. H. *Virology* **1983**, *126*, 117–125; (b) Nandhagopal, N.; Simpson, A. A.; Gurnon, J. R.; Yan, X.; Baker, T. S.; Graves, M. V.; Van Etten, J. L.; Rossmann, M. G. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 14758–14763; (c) Yan, X.; Olson, N. H.; Van Etten, J. L.; Bergoin, M.; Rossmann, M. G.; Baker, T. S. *Nat. Struct. Biol*. **2000**, *7*, 101–103; (d) Cherrier, M. V.; Kostyuchenko, V. A.; Xiao, C.; Bowman, V. D.; Battisti, A. J.; Yan, X.; Chipman, P. R.; Baker, T. S.; Van Etten, J. L.; Rossmann, M. G. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 11085–11089; (e) Zhang, X.; Xiang, Y.; Dunigan, D. D.; Klose, T.; Chipman, P. R.; Van Etten, J. L.; Rossmann, M. G. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14837–14842; (f) Graves, M. V.; Bernadt, C. T.; Cerny, R.; Van Etten, J. L. *Virology* **2001**, *285*, 332–345. (g) Wang, I. N.; Li, Y.; Que, Q.; Bhattacharya, M.; Lane, L. C.; Chaney, W. G.; Van Etten, J. L. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 3840–3844; (h) Sun, S.; La Scola, B.; Bowman, V. D.; Ryan, C. M.; Whitelegge, J. P.; Raoult, D.; Rossmann, M. G. *J. Virol*. **2010**, *84*, 894–897.

5. (a) De Castro, C.; Klose, T.; Speciale, I.; Lanzett, R.; Molinaro, A.; Van Etten, J. L.; Rossmann, M. G. *Proc. Natl. Acad. Sci. USA* **2018**, *118*, E44–E52; (b) Wieland, F.; Heitzer, R.; Schaefer, W. *Proc. Natl. Acad. Sci. USA* **1983**, *80*, 5470–5474; (c) Schreiner, R.; Schnabel, E.;Wieland, F. *J. Cell. Biol*. **1994**, *124*, 1071–1081; (d) Gross, J.; Grass, S.; Davis, A. E.; Gilmore-Erdmann, P.; Townsend, R. R.; St Geme, J. W. *J. Biol. Chem*. **2008**, *283*, 26010–26015; (e) Quispe, C. F.; Esmael, A.; Sonderman, O.; McQuinn, M.; Agarkova, I.; Battah, M.; Duncan, G. A.; Dunigan, D. D.; Smith, T. P.; De Castro, C. *Virology* **2017**, *500*, 103–113; (f) De Castro, C.; Speciale, I.; Duncan, G.; Dunigan, D. D.; Agarkova, I.; Lanzetta, R.; Sturiale, L.; Palmigiano, A.; Garozzo, D.; Molinaro, A.; Tonetti, M.; Van Etten, J. L. *Angew. Chem. Int. Ed*. **2016**, *55*, 654–658; (g) Speciale, I.; Agarkova, I.; Duncan, G. A. Van Etten, J. L.; De Castro, C. **2017**, *Antonie van Leeuwenhoek* doi:10.1007/s 10482-017-0861.

6. (a) Mishra, B.; Neralkar, M.; Hotha, S. *Angew. Chem.* **2016**, *128*, 7917–7922; (b) Mishra, B.; Manmode, S.; Panda, R. A.; Hotha, S. *Eur. J. Org. Chem.* **2017**, 4794−4802; (c) Kayastha, A. K.; Hotha, S. *Chem. Commun*. **2012**, *48*, 7161–7163;

7. (a) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687–2704 and references therein; (b) Demchenko, A. V. *Curr. Org. Chem*. **2003**, *7*, 35–79; (c) Demchenko, A. V. *Synlett* **2003**, 1225–1240; (d) Crich, D. *Acc. Chem. Res*. **2010**, *43*, 1144 – 1153.

8. (a) Ishiwata, A.; Munemura, Y.; Ito, Y. *Tetrahedron* **2008**, *64*, 92–102; (b) Wulff, G.; Rohle, G. *Angew. Chem., Int. Ed.* **1974**, *13*, 157–170; (c) Demchenko, A.; Stauch, T.; Boons, G. J. *Synlett* **1997**, 818–820; (d) Chao, C. S.; Lin, C.; Mulani, Y. S.; Hung, W. C.; Mong, K. K. *Chem. Eur. J.* **2011**, *17*, 12193–12202; (e) Shirahata, T.; Matsuo, J. -I.; Teruya, S.; Hirata, N.; Kurimoto, T.; Akimoto, N.; Sunazuka, T.; Kaji, E.; Omura, S. *Carbohydr. Res.* **2010**, *345*, 740–749; (f) Wasonga, G.; Zeng, Y.; Huang, X. *Sci. China: Chem*. **2011**, *54*, 66–73.

9. (a) Andersson, F.; Fugedi, P.; Garegg, P. J.; Nashed, M. *Tetrahedron Lett.* **1986**, *27*, 3919–3922; (b) Manabe, S.; Ito, Y.; Ogawa, T. *Synlett* **1998**, 628–630; (c) Schmidt, R. R.; Rucker, E. *Tetrahedron Lett*. **1980**, *21*, 1421–1424; (d) Dohi, H.; Nishida, Y.; Tanaka, H.; Kobayashi, K. *Synlett* **2001**, 1446–1448 (e) Frihed, T. G.; Bols, M.; Pedersen, C. M. *Chem. Rev*. **2015**, *115*, 4963−5013.

10. Peng, P.; Schmidt, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 12653-12659.

11. (a) Li, J.; Dai, Y.; Li, W.; Laval, S.; Xu, P.; Yu, B. *Asian J. Org. Chem*. **2015**, *4*, 756 – 762; (b) Xu, P.; Xu, W.; Dai,Y.; Yang,Y.; Yu, B. *Org. Chem. Front*, **2014**, *1*, 405–414; (c) Li, Y.; Yang,.X.; Liu,.Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J*. **2010**, *16*, 1871 – 1882; (d) Ma, Y.; Lian, G.; Li, Y.; Yu, B. *Chem. Commun.* **2011**, *47*, 7515–7517; (e) Zhu, Y.; Shen, Z.; Lia, W.; Yu, B. *Org. Biomol. Chem*. **2016**, *14*, 1536–153.

12. (a) Fraser-Reid, B.; Jayaprakash, K. N.; López, J. C.; Gómez, A. M.; Uriel, C. in *ACS Symp. Ser.* (*Frontiers in Modern Carbohydrate Chemistry*), ed. Demchenko, A. V. *Oxford Univ. Press*, **2007**, *960*, pp. 91–117; (b) Ishikawa, T.; Fletcher, H. G. *J. Org. Chem*. **1969**, *34*, 563–571; (c) Eby, R.; Schuerch, C. *Carbohydr. Res.* **1974**, *34*, 79–90 and references therein; (d) Mukaiyama, T.; Suenaga, M.; Chiba, H.; Jona, H. *Chem. Lett*. **2002**, 56–57; (e) Demchenko, A. V.; Rousson, E.; Boons, G. J. *Tetrahedron Lett*. **1999**, *40*, 6523–6526; (f) Takatani, M.; Matsuo, I.; Ito, Y.; *Carbohydr. Res*. **2003**, *338*, 1073–1081; (g) Ustyuzhanina, N.; Komarova, B.; Zlotina, N.; Krylov, V.; Gerbst, A. G.; Tsvetkov, Y.; Nifantiev, N. E. *Synlett* 2**006**, 921–923; (h) Komarova, B. S.; Orekhova, M. V.; Tsvetkov, Y. E.;

Nifantiev, N. E. *Carbohydr. Res*. **2014**, *384*, 70–86; (i) Crich, D.; Cai, W. *J. Org. Chem*. **1999**, *64*, 4926–4930; (J) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed*. **2004**, *43*, 5386–5389 and references therein; (k) Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. *Org. Lett*. **2005**, *7*, 4415–4418; (l) Imamura, A.; Matsuzawa, N.; Sakai, S.; Udagawa, T.; Nakashima, S.; Ando, H.; Ishida, H.; Kiso, M. *J. Org. Chem*. **2016**, *81*, 9086−9104.

13. (a) Corey, E. J.; Carpino, P. *J. Am. Chem. Soc*. 1989, *111*, 5472–5473; (b) Gerbst, A. G.; Ustuzhanina, N. E.; Grachev, A. A.; Tsvetkov, D. E.; Khatuntseva, E. A.; Nifantiev, N. E. *Mendeleev Commun*. **1999**, 114–116.

*****

List of publications

1. "Stable Alkynyl Glycosyl Carbonates: Catalytic Anomeric Activation and Synthesis of Tridecasaccharide Reminiscent of Mycobacterium tuberculosis Cell Wall Lipoarabinomannan" **Bijoyananda Mishra**, Mahesh Neralkar and Srinivas Hotha; *Angew. Chem. Int. Ed.* **2016**, *55*, 7786-7791.

2. "Expedient Synthesis of a Linear Nonadecaarabinofuranoside of the *Mycobacterium tuberculosis* Cellular Envelope" **Bijoyananda Mishra**, Sujit Manmode, Ravi Raja Adhikari Panda, and Srinivas Hotha; *Eur. J. Org. Chem.* **2017**, 4794–4802.

3. "[Au]/[Ag]-catalyzed expedient synthesis of branched Heneicosafuranosyl arabinogalactan motif of Mycobacterium tuberculosis cell wall" Shivaji A. Thadke,# **Bijoyananda Mishra**,# Maidul Islam, Sandip Pasari, Sujit Manmode, Venkateswara Rao Boddu, Mahesh Neralkar, Ganesh P. Shinde, Gulab Walke and Srinivas Hotha. *Nature Communications* **2017***, 14019 [# equal contribution]*

4. "Nucleofuge Generating Glycosidations by the Remote Activation of Hydroxybenzotriazolyl Glycosides" Mahesh Neralkar, **Bijoyananda Mishra**, and Srinivas Hotha; *J. Org. Chem.* **2017**, *82*, 11494–11504.

5. "Gold(III)-catalysed Glycosidations for 1,2-trans and 1,2-cis Furanosides" Shivaji A. Thadke, **Bijoyananda Mishra**, and Srinivas Hotha; *J. Org. Chem.* **2014**, *79*, 7358–7371.

6. "Facile Synthesis of β- and α-Arabinofuranosides and Application to Cell Wall Motifs of M. Tuberculosis" Shivaji A. Thadke, **Bijoyananda Mishra**, and Srinivas Hotha; *Organic Letters* **2013**, *15*, 3974-3977.

7. "Total Synthesis of Highly Branched N-linked Core Hexasaccharide from Chloroviruses" **Bijoyananda Mishra**, Sujit Manmode, Gulab Walke, Mahesh Neralkar, Saptashwa Chakraborty and Srinivas Hotha [**Manuscript under preparation**].

8. "[Au]/[Ag]-Catalysed Glycosidation of Glycosyl Alkynyl Carbonate Donors for C-glycosides" **Bijoyananda Mishra**, Saptashwa Chakraborty, and Srinivas Hotha [**Manuscript under preparation**].

9. "Glycosyl Alkynyl Carbonate Donors for Catalytic and Stereoselective Synthesis of various *N*-glycosides" **Bijoyananda Mishra**,[#] Saptashwa Chakraborty,[#] Harsha Gouda and Srinivas Hotha *[[#]equal contribution]* [**Manuscript under preparation**].

10. "[Au]/[Ag]-Catalysed Cyclization of 1-Ethynyl Cyclohexyl Carbonate for Etherification" Saptashwa Chakraborty, **Bijoyananda Mishra**, Mahesh Neralkar and Srinivas Hotha [**Manuscript under preparation**].

11. "Silylene Supported Cationic Au(I) η1-Benzene Complex: Structure, Bonding Elucidation and Catalytic Activity for Oligosaccharide Synthesis" Nasrina Parvin,[a] **Bijoyananda Mishra**,[a] Shiv Pal,[a] Susmtia De,[b,c] Pattiyil Parameswaran,*[b] Srinivas Hotha,*[a] and Shabana Khan*[a] [**Manuscript under preparation**].

Glycosidation

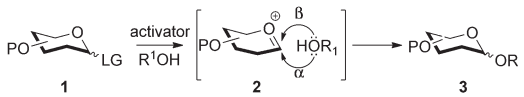
International Edition: DOI: 10.1002/anie.201511695
German Edition: DOI: 10.1002/ange.201511695

Stable Alkynyl Glycosyl Carbonates: Catalytic Anomeric Activation and Synthesis of a Tridecasaccharide Reminiscent of *Mycobacterium tuberculosis* Cell Wall Lipoarabinomannan

*Bijoyananda Mishra, Mahesh Neralkar, and Srinivas Hotha**

Abstract: *Oligosaccharide synthesis is still a challenging task despite the advent of modern glycosidation techniques. Herein, alkynyl glycosyl carbonates are shown to be stable glycosyl donors that can be activated catalytically by gold and silver salts at 25 °C in just 15 min to produce glycosides in excellent yields. Benzoyl glycosyl carbonate donors are solid compounds with a long shelf life. This operationally simple protocol was found to be highly efficient for the synthesis of nucleosides, amino acids, and phenolic and azido glycoconjugates. Repeated use of the carbonate glycosidation method enabled the highly convergent synthesis of tridecaarabinomannan in a rapid manner.*

The chemical synthesis of oligosaccharides has emerged as a viable approach offering advantages including homogeneity, scalability, and the ability to synthesize unnatural glycoconjugates, which can have great ramifications in modern medicine and materials science.[1] Two saccharides are chemically coupled by a glycosidation reaction that involves a glycosyl donor **1**, a fully protected saccharide with a leaving group at the anomeric position, and a glycosyl acceptor (R^1OH), usually containing a single hydroxy group.[2] Promoters activate the leaving group to give a highly reactive oxocarbenium ion intermediate **2** that will be susceptible to the attack of the acceptor, thus resulting in a glycoside **3** (Scheme 1).[2]

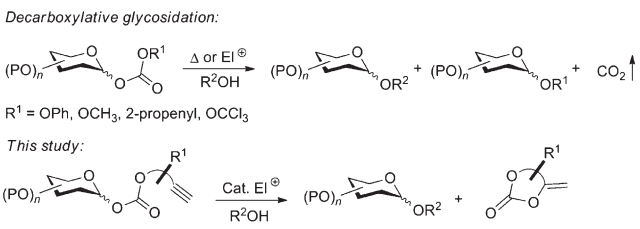


Scheme 1. General glycosidation reaction. LG = leaving group, P = protecting group.

Glycosidation methods that are reliable and scalable and involve stable glycosyl donors are still scarce even after several decades since the first glycoside synthesis. Well-studied glycosyl donors[3] include glycosyl halides,[3a–d] glycosyl esters,[3e] glycosyl trichloroacetamidates,[3f] glycals,[3g] selenoglycosides,[3h] thioglycosides,[3i–k] *n*-pentenyl glycosides,[3l] alkynyl glycosides,[3m] alkyl 1,2-*O*-orthoesters,[3n–p] glycosyl phosphates,[3q] and hemiacetals.[3r] The identification of alkyl glycosyl and thioglycosyl donors has been a transformative advance in the glycosciences, as the alkyl and thio groups serve as stable appendages at the anomeric position, and the compounds can be triggered to become glycosyl donors with an appropriate promoter.

Our own research efforts identified propargyl glycosides as glycosyl donors in the presence of a catalytic amount of $AuCl_3$.[3m] Subsequently, Yu and co-workers reported *o*-alkynyl esters[3s] and Zhu and co-workers reported *S*-but-3-ynyl glycosides[3t] as glycosyl donors with gold catalysts. Gold-catalyzed transglycosidation[3m] has proven to be a robust reaction for the synthesis of glycosides, but has limitations including I) the suitability of only an ether functional group at the C2 position,[3m] II) the lack of stereocontrol through anchimeric assistance,[4a] and III) the hydrolysis of the interglycosidic bond in some instances.[4b,c] Propargyl 1,2-orthoesters were utilized to enable 1,2-*trans* diastereoselectivity.[3p] In the search for a versatile and stable glycosyl donor that can be activated in a catalytic fashion, our attention was drawn to the most popular trichloroacetamidates. However, some glycosyl trichloroacetamidates have a short life time. The hemiacetal precursor to imidates is readily accessible and highly stable; hence, we hypothesized that the conversion of the hemiacetal into a stable, versatile, and reactive glycosyl donor could be highly rewarding.

Methods for the decarboxylative glycosidation of carbonate donors is known; however, they have not been widely utilized owing to forcing reaction conditions and poor yields.[5] Yu and co-workers reported gold-catalysis conditions that can activate *o*-alkynyl esters but not 2-butynyl carbonates even at an elevated temperature (Scheme 2).[6a] The failure to activate 2-butynyl carbonates can be attributed to the possible higher degree of freedom of the leaving group, thereby diminishing the chances of gold–alkyne coordination. In our



Scheme 2. Hypothesis for the use of alkynyl carbonate glycosyl donors.

[*] B. Mishra, M. Neralkar, Prof. S. Hotha
Department of Chemistry
Indian Institute of Science Education and Research
Dr. Homi Bhabha Road, Pune (India)
E-mail: s.hotha@iiserpune.ac.in

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201511695.

ChemPubSoc Europe

DOI: 10.1002/ejoc.201700712

EurJOC European Journal of Organic Chemistry

Full Paper

Oligosaccharide Synthesis

Expedient Synthesis of a Linear Nonadecaarabinofuranoside of the *Mycobacterium tuberculosis* Cellular Envelope

Bijoyananda Mishra,[a] Sujit Manmode,[a] Ravi Raja Adhikari Panda,[a] and Srinivas Hotha*[a]

Abstract: The synthesis of oligosaccharides is demanding as it requires multiple steps and long reaction sequences. The choice of glycosylation method and protecting groups is very important for the successful synthesis of any oligosaccharide. In this paper, we show that ethynylcyclohexyl carbonate glycosyl donors are excellent for the synthesis of a nonadecasaccharide fragment of the *Mycobacterium tuberculosis* glycocalyx using a split/react/couple strategy. The synthesis of the target nonadecasaccharide was accomplished using eight different reactions and 23 steps in 6.4 % overall yield.

Introduction

Infection by multidrug-resistant (MDR) and extremely drug-resistant (XDR) strains of *Mycobacterium tuberculosis* has resulted in an increase in worldwide mortality due to tuberculosis, and this has led to a growing socioeconomic burden.[1–4] Patients suffering from tuberculosis have to undergo chemotherapy for a long period of time; this has been attributed to the diminished passage of chemotherapeutic agents due to a thick and waxy cellular envelope.[5] Lipoarabinomannan (LAM) and arabinogalactan (AG) are the two major structural constituents of the cell wall of *M. tuberculosis*, and arabinan is the common motif in both of these.[6–9] These structural motifs are currently attracting unprecedented attention for the development of drugs, vaccines, and diagnostics owing to the xenobiotic status of the saccharide components: arabinose and galactose are in the furanosyl form.[10] Mycobacterial arabinan biosynthesis is arrested in the presence of ethambutol, and so this is prescribed as a drug in combination with others.[11] Mycobacterial arabinan contains α-Ara*f*-(1→5)-α-Ara*f*, α-Ara*f*-(1→3)-α-Ara*f* and β-Ara*f*-(1→2)-α-Ara*f* linkages; α-Ara*f*-(1→5)-α-Ara*f* linkages are predominant, and terminal α-Ara*f* residues are capped with β-Ara*f*-(1→2) linkages.[12–14] In addition, terminal β-Ara*f*-(1→2) residues are further esterified with mycolic acid. The synthesis of arabinan oligosaccharides has received considerable attention due to their immense significance in disease management. Several groups have attempted the synthesis of arabinan motifs;[15–20] a large oligoarabinan with 22 Ara*f* units,[21,22] a henicosasaccharide[23] fragment of AG, and a much larger fragment with 92 saccharide residues[24] have been reported (Figure 1).

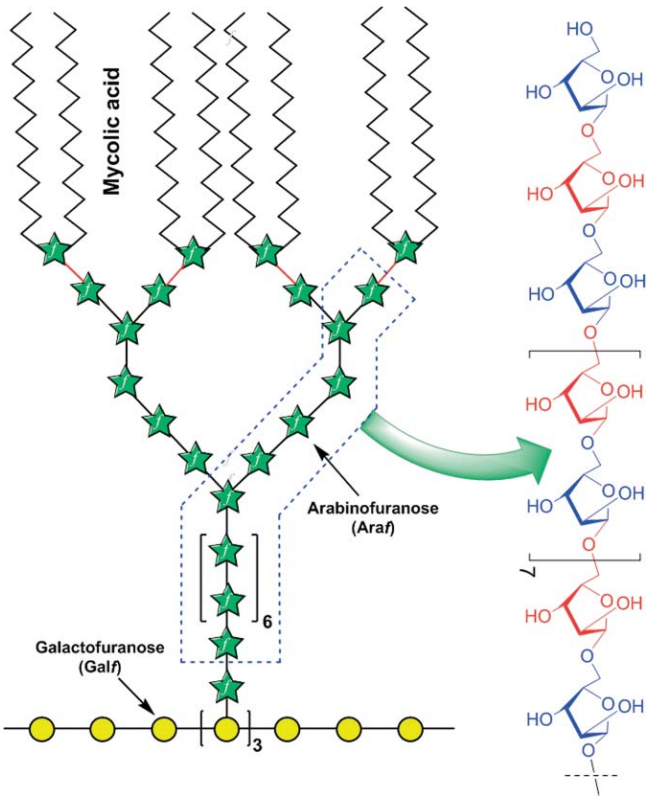


Figure 1. Cartoon representation of arabinogalactan (AG) of the *M. tuberculosis* cell wall, and the target molecule.

Results and Discussion

In this paper, we describe the synthesis of a nonadecaarabinofuranoside with α-Ara*f*(1→5)-Ara*f* linkages, as found in the arabinogalactan of *M. tuberculosis*, using gold-catalysed glycosylations.[25–29] We planned to synthesize the nonadecasaccharide by a split/react/couple strategy in which the glycosyl donor and the acceptor can both be synthesized from the same precursor. The precursor saccharide is *split* into two portions; these then

[a] *Department of Chemistry, Indian Institute of Science Education and Research,*
Dr. Homi Bhabha Road, Pune 411008, India
E-mail: s.hotha@iiserpune.ac.in
www.iiserpune.ac.in/~s.hotha

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.201700712.

nature COMMUNICATIONS

ARTICLE

Received 16 Jun 2016 | Accepted 22 Nov 2016 | Published 25 Jan 2017

DOI: 10.1038/ncomms14019 OPEN

[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.

[1] Department of Chemistry, Indian Institute of Science Education and Research, Dr Homi Bhabha Road, Pune, Maharashtra 411 008, India. * These authors contributed equally to this work. Correspondence and requests for materials should be addressed to S.H. (email: s.hotha@iiserpune.ac.in).

JOC The Journal of Organic Chemistry

Article

Cite This: J. Org. Chem. 2017, 82, 11494-11504

pubs.acs.org/joc

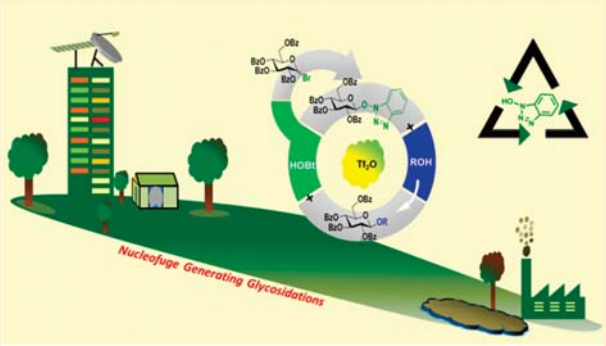
Nucleofuge Generating Glycosidations by the Remote Activation of Hydroxybenzotriazolyl Glycosides

Mahesh Neralkar, Bijoyananda Mishra, and Srinivas Hotha*

Department of Chemistry, Indian Institute of Science Education and Research, Pune, 411 008 MH, India

Supporting Information

ABSTRACT: Hydroxybenzotriazole is routinely used in peptide chemistry for reducing racemization due to the increased reactivity. In this article, very stable hydroxybenzotriazolyl glucosides were identified to undergo glycosidation. The reaction was hypothesized to go through the remote activation by the Tf_2O at the N3-site of HOBt followed by the extrusion of the oxocarbenium ion that was attacked by the glycosyl acceptor. Further, equilibration of the zwitterionic benzotriazolyl species makes the leaving group noncompetitive and generates the nucleofuge that has been reconverted to the glycosyl donor. The reaction is mild, high yielding, fast and suitable for donors containing both C2-ethers and C2-esters as well. The regenerative-donor glycosidation strategy is promising as it enables us to regenerate the glycosyl donor for further utilization. The utility of the methodology for the oligosaccharide synthesis was demonstrated by the successful synthesis of the branched pentamannan core of the HIV1−gp120 complex.



INTRODUCTION

Burgeoning growth in all the allied fields of glycosciences led to the identification of myriad roles played by glycoconjugates and oligosaccharides in many physiological and pathological processes.[1,2] A major impediment holding the exponential growth of the glycosciences is the lack of pure, well characterized and homogeneous oligosaccharides or glycoconjugates.[3] Isolating oligosaccharides from natural sources is a challenging task since they exist in tiny quantities as microheterogeneous forms.[3] Often, totally chemical[4] or chemoenzymatic[5] syntheses are the most popular strategies for obtaining sufficient quantity of oligosaccharides using a bottoms-up approach, wherein saccharide residues are sequentially condensed by a glycosidation reaction.[3] The glycosidation reaction involves two partners termed as glycosyl donor and glycosyl acceptor.[4] The glycosyl donor often contains a nucleofuge at the anomeric carbon which generates an oxocarbenium ion intermediate that will be attacked by the glycosyl acceptor upon the activation by a promoter. Several decades of research culminated into the development of numerous glycosyl donors' viz. glycosyl halides,[6−8] esters,[9] phosphates,[10] imidates,[11] carbonates,[12] thioglycosides,[13] selenyl glycosides,[14] glycals,[15] hemiacetals,[16,17] alkenyl,[18] and alkynyl[19] glycosides.[4]

Propargyl glycosides are observed to undergo glycosidation in the presence of catalytic amount of gold(III) halides in CH_2Cl_2 at 70 °C.[19] They undergo glycosidation when C-2 position is protected as a benzyl ether only.[19] Enhanced reactivity by the addition of hydroxybenzotriazole (HOBt) (**1**) is well documented in the peptide chemistry through the formation of activated ester **2** (Figure 1).[20] In this premise,

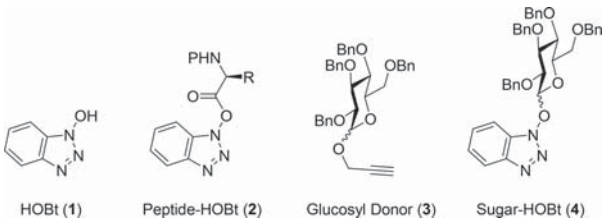


Figure 1. Structures of hydroxybenzotriazole (HOBt) and peptide-HOBt and sugar-HOBt.

addition of HOBt in the gold-catalyzed glycosidation was hypothesized to further increase the overall turnover number (TON) of the gold-catalyzed glycosidation (Scheme 1).

RESULTS AND DISCUSSION

Accordingly, donor **3** was treated with Sug−OH (**5**) and HOBt (**1**, 1.0 equiv) and catalytic amount of $AuCl_3$ in the presence of 4 Å MS powder at 70 °C for 24 h. To our surprise, the required disaccharide **6** was not noticed; instead HOBt glucoside **4** (6%) was observed as the sole product that can be rationalized by the participation of the HOBt as the glycosyl acceptor. HOBt-

Received: August 11, 2017
Published: October 6, 2017

DOI: 10.1021/acs.joc.7b02027
J. Org. Chem. 2017, 82, 11494−11504

JOC The Journal of Organic Chemistry

Article

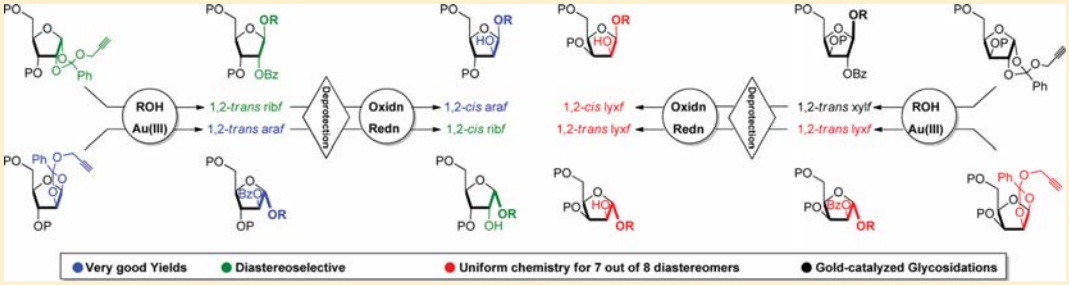
pubs.acs.org/joc

Gold(III)-Catalyzed Glycosidations for 1,2-*trans* and 1,2-*cis* Furanosides

Shivaji A. Thadke, Bijoyananda Mishra, and Srinivas Hotha*

Department of Chemistry, Indian Institute of Science Education and Research, Pune, Maharashtra 411008, India

Supporting Information



ABSTRACT: Stereoselective synthesis of furanosides is still a daunting task, unlike the pyranosides, for which several methods exist. Herein, a unified stereoselective strategy for the synthesis of 1,2-*trans* and 1,2-*cis* furanosides is revealed for seven out of eight possible isomers of pentoses. The identified protocol gives access to diastereoselective synthesis of α- and β-ara*f*, rib*f*, lyx*f*, and α-xyl*f* furanosides. 1,2-*trans* glycosides were synthesized by the use of propargyl 1,2-orthoesters under gold-catalyzed glycosidation conditions, and subsequently, they are converted into 1,2-*cis* glycosides through oxidation−reduction as the key functional group transformation. All the reactions are found to be fully diastereoselective, mild, and high yielding.

INTRODUCTION

Glycoconjugates are known to play pivotal roles in a plethora of intracellular and extracellular biological events.[1] Most often, saccharide constituents are in hexopyranosyl form, but sometimes, hexofuranosyl and pentofuranosyl residues are also noticed.[2] Furanose residues were less prevalent in mammalians and humans, though they are found frequently in many parasitical, fungal, bacterial and plant glycans.[2b] Therefore, biomolecules with furanosyl residues have attracted special attention in order to elucidate their function, metabolism, viability, and virulence.[3] However, glycans are difficult to isolate from nature as they are available in minute quantities as micro and heterogeneous forms.[4] 1,2-*trans* and 1,2-*cis* are the two linkages that are possible in glycosides, and as a result the stereocontrolled synthesis of them is of a great significance. More methods are identified for the stereoselective synthesis of pyranosides than for the furanosides either due to the less frequent occurrence or complexity in their synthesis.[5a] Furthermore, pyranosides can be advantageously synthesized by exploiting the anomeric effect and the neighboring group participation for the 1,2-*cis* and 1,2-*trans* pyranosides, respectively.[5b] The anomeric effect is almost negligible and the steric interactions play a major role in defining the outcome of the stereoselectivity in furanosides. In addition, the furanose form is thermodynamically disfavored, whereas the pyranosyl form is more stable due to lesser steric crowding.[6] As a consequence, locking of aldose as a furanoside is the first challenge, which is often achieved through a kinetically controlled Fischer glycosidation in the presence of acid and alcohol.[7] But Fischer glycosidation for stereoselective synthesis is not really suitable for the synthesis of higher oligosaccharides.

The glycosidation is a reaction wherein a glycosyl donor and hydroxyl-bearing glycosyl acceptor are involved.[8] Glycosyl donors often possess an appendage at the anomeric position that in the presence of an activator departs resulting in an intermediate oxocarbenium ion that will be attacked by a suitable hydroxyl-bearing glycosyl acceptor.[8] Hence, the chemistry of glycosyl donors is of paramount importance in the development of any glycosidation reaction. Many furanosyl donors with a range of appendages at the anomeric position viz. halides,[9a,b] silyl glycosides,[9c] alkyl glycosides,[9d] anomeric esters,[9e] thioglycosides,[9f,g] trichloroacetamidates,[9h] *n*-pentenyl glycosides,[9f] orthoesters,[9i,j] 1,2-anhydro sugars,[9k] and *o*-carboxybenzyl glycosides[9l] are developed over the past few decades for the synthesis of furanosides. Development of these methods greatly benefited the synthetic carbohydrate chemists in synthesizing furanosyl oligosaccharides.[9f,10] Yet, there is no uniform method that enables synthesis of both 1,2-*cis* and 1,2-*trans* isomers of all four pentosyl sugars in a stereoselective manner. In this premise, we hypothesized to utilize gold-catalyzed glycosylation for the synthesis of both the isomers of all the four pentosyl sugars stereoselectively. Our hypothesis stems from a recent observation that *Mycobacterium tuberculosis*, the etiological agent for tuberculosis, synthesizes 1,2-*cis* arabinofuranoside indirectly through an oxidation−reduction

Received: May 14, 2014
Published: July 14, 2014

   dx.doi.org/10.1021/jo501052y | *J. Org. Chem.* 2014, 79, 7358−7371

ORGANIC LETTERS

2013
Vol. 15, No. 10
2466–2469

Facile Synthesis of β- and α-Arabinofuranosides and Application to Cell Wall Motifs of *M. tuberculosis*

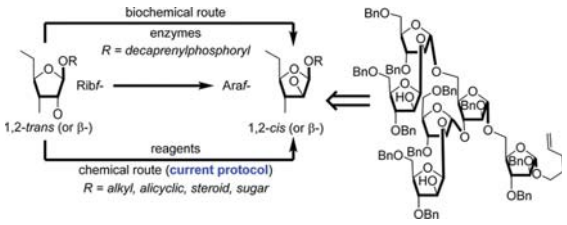
Shivaji A. Thadke, Bijoyananda Mishra, and Srinivas Hotha*

Department of Chemistry, Indian Institute of Science Education and Research, Pune 411 008, India

s.hotha@iiserpune.ac.in

Received April 4, 2013

ABSTRACT



Propargyl 1,2-orthoesters of arabinose are exploited for the synthesis of 1,2-*trans* furanosides; easily accessible 1,2-trans ribofuranosides are converted to challenging 1,2-*cis*-arabinofuranosides by oxidoreduction. Utility of these protocols was demonstrated by the successful synthesis of major structural motifs present in the cell surface of *Mycobacterium tuberculosis*. Key furanosylations were carried out under gold-catalyzed glycosidation conditions.

Tuberculosis (TB) has plagued mankind for centuries and still continues to kill more than two million lives every year globally.[1,2] *Mycobacterium tuberculosis* (Mtb) is the etiological agent, and pioneering efforts from the Brennan group highlighted two major carbohydrate epitopes viz. lipoarabinomannan (LAM) and arabinogalactan (AG) in the cell surface of Mtb.[3] Both LAM and AG have an oligoarabinofuranoside which is highly characteristic to the Mtb cell wall. The xenobiotic nature of arabinofuranose is noteworthy since inhibitors of biosynthetic pathways for oligomerization of arabinofuranoses could offer opportunities for the development of novel therapeutics. Indeed, ethambutol, an antitubercular drug, has been shown to arrest the biosynthesis of arabinan.[4] Specificity and the xenobiotic nature of arabinofuranosides coupled with the challenge in synthesizing 1,2-*trans* (or α-) and 1,2-*cis* (or β-) arabinofuranosides has attracted many to develop strategies.[5,6] Motifs A−C are the structural constituents present in the arabinan part of Mtb (Figure 1); arabinan is ligated to the oligomeric chain of galactofuranoses through a 1→5 *trans* linkage.[3] Among the host of

(1) (a) Ginsberg, A. M.; Spigelman, M. *Nat. Med* **2007**, *13*, 290–294. (b) Zhang, Y. *Annu. Rev. Pharmacol. Toxicol.* **2005**, *45*, 529–564.

(2) (a) Gandhi, N. R.; Moll, A.; Sturm, A. W.; Pawinski, R.; Govender, T.; Lalloo, U.; Zeller, K.; Andrews, J.; Friedland, G. *Lancet* **2006**, *368*, 1575–1580. (b) Samandari, T.; Agizew, T. B.; Nyirenda, S.; Tedla, Z.; Sibanda, T.; Shang, N.; Mosimaneotsile, B.; Motsamai, O. I.; Bozeman, L.; Davis, M. K.; Talbot, E. A.; Moeti, T. L.; Moffat, H. J.; Kilmarx, P. H.; Castro, K. G.; Wells, C. D. *Lancet* **2011**, *377*, 1588–98. (c) WHO Report. *Global tuberculosis control-surveilance, planning, financing*; World Health Organization: Geneva, 2004. (d) Chiang, C.-Y.; Yew, W. W. *Int. J. Tuberc. Lung Dis.* **2009**, *13*, 304–311.

(3) (a) Besra, G. S.; Khoo, K.-H.; McNeil, M. R.; Dell, A.; Morris, H. R.; Brennan, P. J. *Biochem.* **1995**, *34*, 4257–4266. (b) Lee, A.; Wu, S. W.; Scherman, M. S.; Torrelles, J. B.; Chatterjee, D.; McNeil, M. R.; Khoo, K.-H. *Biochem.* **2006**, *45*, 15817–15828.

(4) (a) Lee, R. E.; Mikušová, K.; Brennan, P. J.; Besra, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 11829–11831. (b) Alderwick, L. J.; Birch, H. L.; Mishra, A. K.; Eggeling, L.; Besra, G. S. *Biochem. Soc. Trans.* **2007**, *35*, 1325–1328.

(5) (a) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934. (b) Mereyala, H. B.; Hotha, S.; Gurjar, M. K. *Chem. Commun.* **1998**, 685–686. (c) D'Souza, F. W.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 1493–1495. (d) Yin, H.; D'Souza, F. W.; Lowary, T. L. *J. Org. Chem.* **2002**, *67*, 892–903. (e) Gadikota, R. R.; Callam, C. S.; Wagner, T.; Del Fraino, B.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 4155–4165. (f) Jayaprakash, K. N.; Lu, J.; Fraser-Reid, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5894–5898. (g) Callam, C. S.; Gadikota, R. R.; Krien, D. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 13112–13119. (h) Desire, J.; Prandi, J. *Carbohydr. Res.* **1999**, *317*, 110–118. (i) Lee, Y. J.; Lee, K.; Jung, E. H.; Jeon, H. B.; Kim, K. S. *Org. Lett.* **2005**, *7*, 3263–3266. (j) Ishiwata, A.; Akao, H.; Ito, Y.; Sunagawa, M.; Kusunose, N.; Kashiwazaki, Y. *Bioorg. Med. Chem.* **2006**, *14*, 3049–3061.

(6) (a) Joe, M.; Bai, Y.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc.* **2007**, *129*, 9885–9901. (b) Ishiwata, A.; Ito, Y. *J. Am. Chem. Soc.* **2011**, *133*, 2275–2291. (c) Fraser-Reid, B.; Lu, J.; Jayaprakash, K. N.; Lopez, J. C. *Tetrahedron: Asymm.* **2006**, *17*, 2449–2463. (d) Lu, J.; Fraser-Reid, B. *Chem. Commun.* **2005**, 862–864.

10.1021/ol400931p
Published on Web 05/09/2013