

Synthesis of Anticoagulant Idraparinux and Development of New Glycosylation Methods

A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS OF THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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20173534



**INDIAN INSTITUTE OF SCIENCE EDUCATION AND
RESEARCH PUNE - 411 008**

2022

Dedicated to....

My Family

Srinivas Hotha, Ph.D.

Professor - Chemistry

CERTIFICATE

Certified that, the work incorporated in the thesis entitled, “*Synthesis of Anticoagulant Idraparinux and Development of New Glycosylation Methods*” submitted by Kasdekar Niteshlal Motilal 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: 15th November 2022

Pune (MH), India.



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Acknowledgements

First and foremost, I would like to express my sincere gratitude to my mentor and research supervisor **Prof. Srinivas Hotha** for his excellent guidance, continuous encouragement, and generous support in achieving this entire endeavor. Working with him was really a great pleasure and fetched me a lot of learning experience. His guidance helped me in entire endeavour of my research and I learned how to successfully accomplish a project, how to write and present a research story and to make good presentations. I do sincerely acknowledge the freedom rendered by him in the laboratory for the independent thinking, planning and execution of research projects. Without his encouragement and constant guidance, I could not have completed my doctoral degree.

I am sincerely indebted to my RAC members, Dr. Pinaki Talukdar (IISER-P) and Dr. C. V. Ramana (NCL-Pune) for their insightful comments and valuable suggestions during RAC meetings. I wholeheartedly acknowledge the entire chemistry faculty of IISER-Pune. I also thank technicians (Nitin, Mishra, Suresh Prajapati, Sandip, Ravindar, Abhijit Biswas, Hema mam, Megha mam), IT and administrative staffs Sachin, Mayuresh, Mahesh, Tushar for their valuable support.

I am thankful to University Grant Commission (UGC), for awarding financial support and Prof. J. B. Udgaokar, Director, IISER, Pune for providing world class opportunities in IISER-Pune.

I thank all my teachers, especially, Dr. Pramod Padole, Dr. Wadal, Dr. Mandlik and Dr. Tushar Wankhade for teaching chemistry, and their support and continuous encouragements during initial period of my doctoral studies. I would also like to thank Mrs. Suresh Ingale for enlightening my interest in Science and encouragements during initial studies.

I would like to express my deepest thanks to my fellow lab-mates, Dr. Madhuri mam, Dr. Kapil, Dr. Sujit, Dr. Sandip, Dr. Gulab, Dr. Bijoy, Dr. MaheshDa, Dr. Aparna, Ganesh, Yogesh, Saptashwa, Jayashree, Kamesh, Sumit, Pratim, Pooja, Ankita, Ananay, Kshitij, Daksh, and Dhanashree for the fruitful discussion, kind help and support, negotiation, and all the fun we have had in last five and half years.

I am truly grateful to my batchmates and dear friends, Aman, Manjeet, Vikas, Javedbhai, Surjeet, Nilanjana, Lakshmi, Swati, and Writakshi. My Marathi mandali people Nagesh (NCL), Dhananjay (NCL), Prakash, Iranna, Laxman, Uttareshwar, Bharat, Yogesh More, Bhavin, Debashish and all my cricket teammates (Resonance and Helix). My old but gold heart friends Dharam, Nilkesh, Suraj, Patiram, Pankaj, Rajkumar and Fukrey group Govind, Ganesh, Tushar, Sachin who have been my pillars of mental peace and strength.

Last, but not the least, I dedicate this achievement to my family members who walked along with me, sharing all ups and downs. Finally, it has been a difficult task to capture and express my feelings for my family members. What I am and intend to be in the future is because of the good will and unstinted support of my parents, elder brothers Chironji, Anokhi and Zanak, younger brother Rajesh, sisters Kanta, Mamta, sister-in-law Rajesh Belsare, nephews Naitik, Sachin, Daau, and niece Ranibai who all without knowing much what I am doing exactly, just wishing me all the time with no expectations. No words are enough to acknowledge them for their patience and sacrifice which were always remains a source of inspiration and will remain throughout my life. My success now and always will be dedicated to them.

Words are not enough to express all the feelings.....

Nitesh Kasdekar

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General remarks

- ❖ ^1H NMR spectra were recorded on Bruker AV 400, DRX-500 MHz, JEOL ECX 400 or Bruker Avance 600 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 Bruker 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 and Maldi-TOF.
- ❖ IR spectra were recorded on Perkin-Elmer 1310 and 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 or Rudolph polarimeter and measured in degree.
- ❖ All reactions were monitored by Thin-Layer Chromatography carried out on precoated Merck silica plates (F254, 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 dry freshly prepared solvents under anhydrous conditions and yields refer to chromatographically homogenous materials unless otherwise stated.
- ❖ All evaporators were carried out under reduced pressure on Büchi and Heidolph rotary evaporator 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.

Abbreviation

Ac – Acetate	Manp – mannopyranosyl/mannopyranoside
AcBr – Acetyl bromide	MeOD – Methanol-D4
AcCl – Acetyl chloride	MHz – Megahertz
AcOH – Acetic acid	mmol – millimolar
Ac ₂ O – Acetic anhydride	MS – Molecular sieves
AG – Arabinogalactan	Mtb – <i>Mycobacterium tuberculosis</i>
AIBN – Azobisisobutyronitrile	NAP – <i>N</i> -bromomethyl naphthalene
Araf – arabinofuranosyl/arabinofuranoside	NGP – Neighbouring group participation
Bn – Benzyl	NIS – <i>N</i> -Iodosuccinimide
Bz – Benzoyl	NMR – Nuclear Magnetic Resonance
Calcd – Calculated	NNGP – Non-neighbouring group participation
Cbz – Carbobenzyloxy	NPG – <i>n</i> -Pentenyl glycoside
CAN – Ceric ammonium nitrate	PMBCl – <i>p</i> -Methoxy benzyl chloride
cat. – catalytic	Py – Pyridine
DBU – 1,8-Diazabicycloundec-7-ene	PTSA, TsOH – <i>p</i> -Toluene sulfonic acid
DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	Ribf – ribofuranoside/ribofuranosyl
DEPT – Distortionless Enhancement by Polarization Transfer	rt – room temperature (25 °C)
DIPEA – <i>N,N'</i> -Diisopropylethylamine	sat – saturated
DMAP – <i>N,N'</i> -Dimethylaminopyridine	Tb – tuberculosis
DMF – <i>N,N'</i> -Dimethyl formamide	TBAF – tetra- ^{<i>n</i>} -Butyl ammonium fluoride
δ – chemical shift (in ppm)	TBAI – tetra- ^{<i>n</i>} -Butyl ammonium iodide
eq. – equivalents	TBDMS – ^{<i>t</i>} -Butyldimethylsilyl
Galf – galactofuranosyl/galactofuranoside	TBDMSCl – ^{<i>t</i>} -Butyldimethylchloride
HRMS – High-Resolution Mass Spectrometry	TBDPS – ^{<i>t</i>} -Butyldiphenylsilyl
HSQC – Heteronuclear Single Quantum Coherence	TBDPSCl – ^{<i>t</i>} -Butyldiphenylsilylchloride
Hz – Hertz	TCA – trichloroacetimidate
Im. – Imidazole	TfOH – Trifluoromethanesulfonic acid
IR – Infrared	THF – Tetrahydrofuran
LAM – Lipoarabinomannan	TLC – Thin Layer Chromatography
	TMSOTf – Trimethylsilyltrifluoromethanesulfonate
	µg – microgram
	µmol – micromolar
	µL – microliter

Abstract

The Thesis entitled “***Synthesis of Anticoagulant Idraparinux and Development of New Glycosylation Methods***” is divided into four chapters. Chapter 1 gives the brief introduction about the importance of carbohydrates, carbohydrate-conjugates, and methodologies developed to access the homogeneous, well characterized glycans. Chapter 2 describes the total synthesis of heparin based anticoagulant Idraparinux exploiting the recently developed silver assisted gold-catalyzed glycosidation. In chapter 3A, we investigated the glycosyl esters having alkyne-appended functionality to decipher the role of gold salts in activation of donors for glycosylation. Chapter 3B, describes the investigation of glycosyl vinylogous carbonates as donors using the sub-stoichiometric amount of Brønsted acid TfOH to synthesize glycoconjugates, disaccharides and oligosaccharides.

Chapter 1. Introduction to Carbohydrates

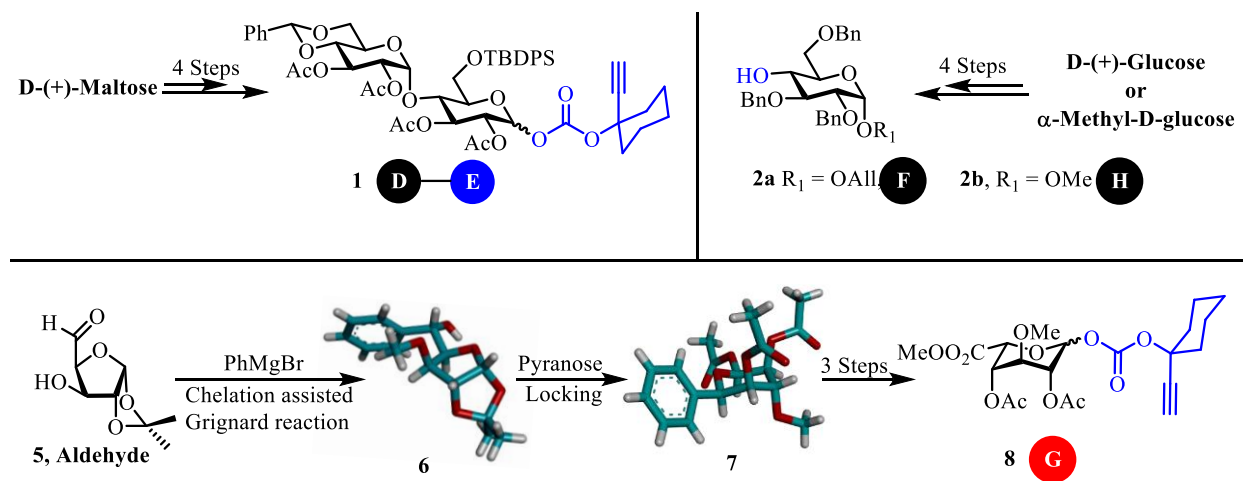
Carbohydrates are the naturally occurring bio-molecules found in the form of oligosaccharides or glycoconjugates. These molecules play pivotal role in many physiologically important processes including the cell-cell communication, signal transduction, fertilization, embryogenesis, immune response and many others. The carbohydrates are also involved in disease progression such as cancer metastasis, neurodegenerative diseases and bacterial or viral infections. Due to the array of biological functions and biocompatible nature, carbohydrates and carbohydrate-conjugates have been investigated as vaccine candidate and for drug development. Many carbohydrate-based drugs and vaccines are approved and many are still under clinical investigation; therefore, carbohydrates emerged as new targets in drug design and vaccine developments. Furthermore, carbohydrates are being used in material chemistry, bio-sensor development, and in drug delivery due to their biocompatibility. Access to homogeneous, well characterized glycans are important to decipher their role in immune modulation or pathogenocyt. Carbohydrates produced by living organisms are highly complex and micro-heterogeneous and hence, accessing these from natural sources is highly cumbersome. Hence the synthesis of glycans by means of enzymatic/chemical reaction has been exploited and many synthetic protocols are developed. In chemical synthesis of carbohydrates, the coupling of monosaccharides is called as glycosylation wherein glycosyl donor (donates sugar unit) and glycosyl acceptor are involved. To date several glycosyl donors have been investigated but only few of them such as glycosyl halides, thioglycosides, imidates, phosphates, *n*-pentenyl glycosides, and *n*-butyl *o*-alkynylbenzoates are

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well explored and proven to be promising donors in oligosaccharide syntheses. One such versatile donor was recently reported from our group wherein glycosyl ethynylcyclohexyl carbonates were activated by the synergetic action of [Au]/[Ag] salts. The mild and selective activation of the donor has been proven to be highly efficient for the syntheses of glycoconjugates and oligosaccharides.

Chapter 2. Synthesis of Anticoagulant Idraparinux Using Silver Assisted Gold-catalysed Glycosidation.

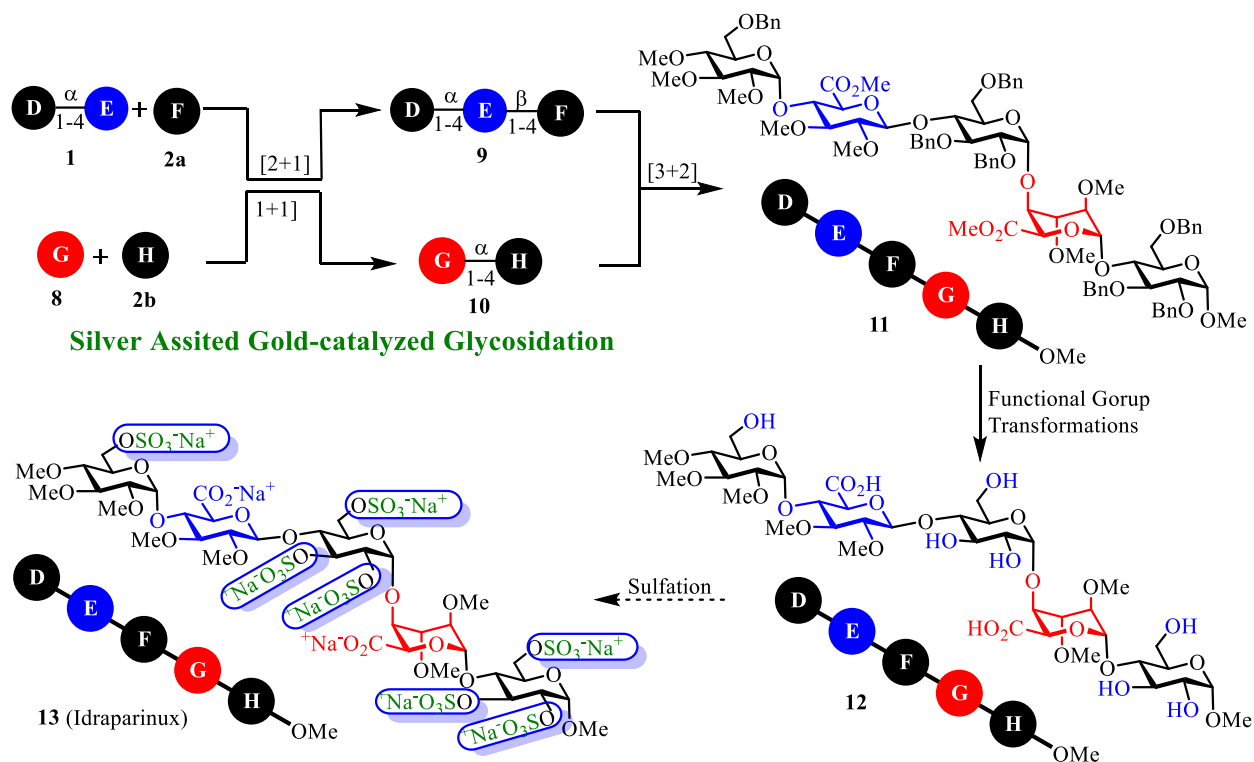
Synthetic heparin-based anticoagulants have emerged as safe alternatives to animal derived heparins which often are associated with plethora of side effects due to the challenges in monitoring the purity. Therefore, the development of efficient synthetic protocols for clinically approved synthetic anticoagulants such as Fondaparinux (Arixtra[®]), Idraparinux and Idrabiotaparinux are at high demand. Recently we have successfully developed a gram scale synthetic protocol for Fondaparinux in 41 steps. In this chapter, a novel synthetic route for second-generation anticoagulant Idraparinux has been developed. The synthetic protocol is built on the solid foundation of silver assisted gold-catalysed glycosidation from novel, commercially available cheap starting materials. The monosaccharide building blocks **2a**, **2b** and **8** are synthesized starting from D-(+)-glucose or α -methyl-D-glucopyranose in good yields. The D-E disaccharide building block **1** was synthesized from maltose to access an in-built 1 $\rightarrow$ 4 α -glycosidic linkage in four steps.



Scheme 1 Synthesis of building blocks

Abstract

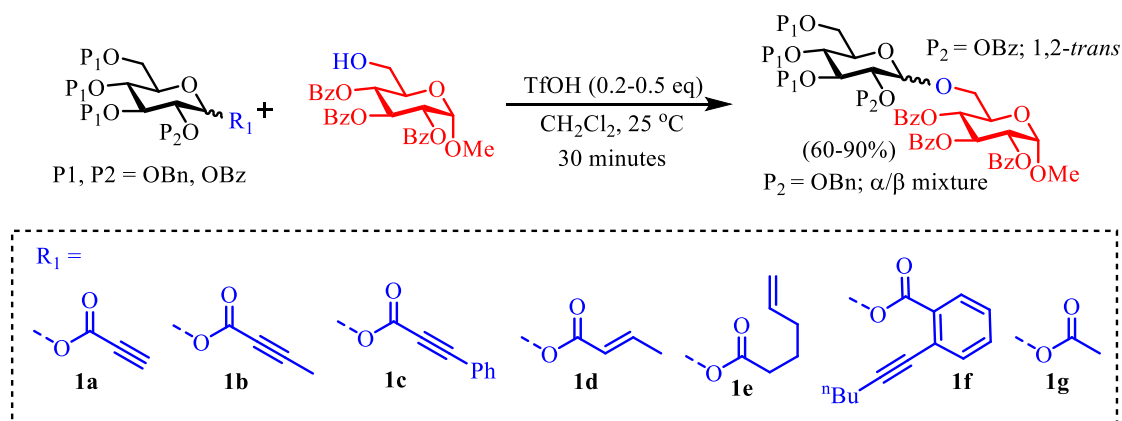
The coupling of building blocks to access pentasaccharide has been achieved in a highly convergent approach. The coupling between D-E disaccharide carbonate **1** and acceptor **2a** (Building block F) smoothly produced the D-E-F trisaccharide **9** with complete β -selectivity during the glycosidation due to the neighbouring group participation through C-2 acetate. The disaccharide **10** was synthesized by coupling the monosaccharide building block G and H in a highly distereoselective fashion. The trisaccharide **9** was converted into anomeric carbonate whereas disaccharide **10** was functionalized as acceptor. Finally, the highly diastereoselective glycosidation between trisaccharide donor **9** and acceptor **10** at $-40\text{ }^{\circ}\text{C}$ produced the pentasaccharide **11** in good yields. The carboxyl functionality of the glucuronic acid was successfully introduced at the pentasaccharide level and removal of protecting groups offered **12** which upon sulfation can be extrapolated to the anticoagulant Idraparinux.



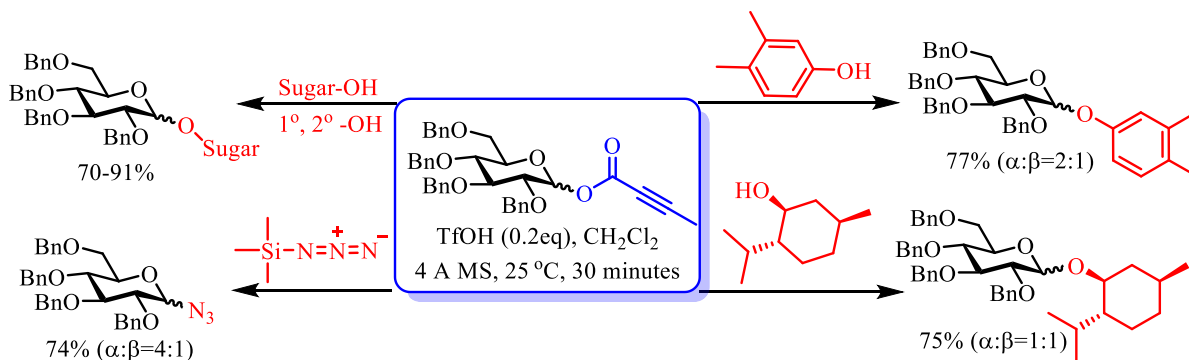
Scheme 2 Building block coupling using silver assisted gold-catalysed glycosidation.

Chapter 3A. Investigation of Alkyne-appendage Glycosyl Ester as Donors under Brønsted acid condition

Glycosyl donors having alkyne-functionality as leaving groups have gained much attention due to their mild and selective activation under gold-catalyzed conditions. In the recent times, the glycosyl ester appendages with alkyne moieties are reported to undergo glycosidation using the Au(I) or Au(III) salts as promoters. However, there are some reports which showed that the alkyne containing glycosyl esters can also be activated without using expensive gold salts. Further very recently, Chai group investigated the role of Lewis acidity in the activation alkyne containing donors and demonstrated that glycosidation can also proceed due to the Lewis acidity of promoters.



Glycosyl Methylpropiolate Donor Substrate Scope



Scheme 3 Investigation of glycosyl ester under Brønsted acid condition

Therefore, in order to understand whether the gold salts are essentially required to activate the alkyne containing glycosyl esters or it can be activated under Lewis/Brønsted acid conditions, different glycosyl esters with leaving groups (1a-1g) were synthesized. The investigation suggested that all the glycosyl esters can be glycosylated using 0.2-0.5 equivalents of Brønsted

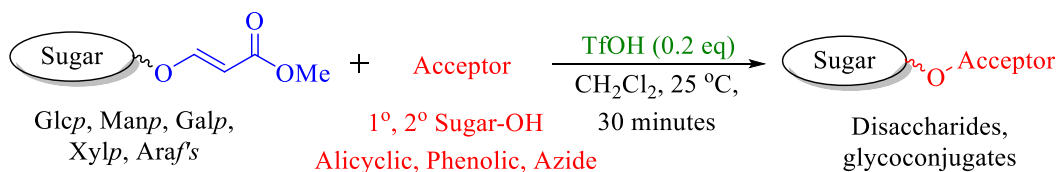
Abstract

acid (TfOH) within 30 minutes. However, the glycosyl ester having alkyne functionality at α -position of the carbonyl was found to be activated using 0.2 equivalents of TfOH to produce disaccharides in excellent yields.

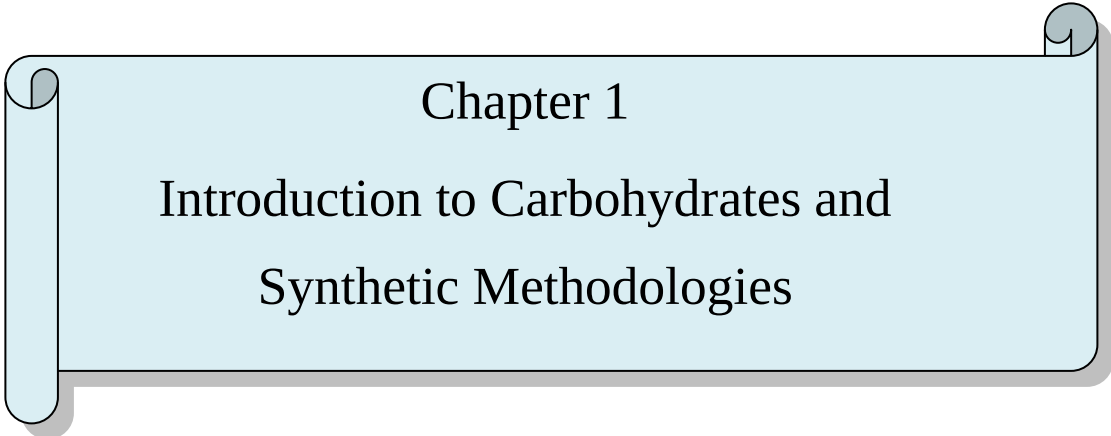
The glycosyl methylpropiolate was further investigated to gauge the substrate scope of this donor. The armed and super-armed donors are activated using 0.2 eq. of TfOH whereas disarmed donor required higher amount of promoter. The donor was found to be suitable to produce the azido glycoside, phenolic glycoside, alicyclic glycosides and disaccharides in good yields. Strongly acidic reaction conditions compromised the application of glycosyl methylpropiolate in oligosaccharides synthesis thereby signifying the importance of gold-salts in the activation of ester glycosyl donors.

Chapter 3B. Glycosyl vinylogous carbonates activation under Metal-free condition.

In this chapter, glycosyl vinylogous carbonates are investigated as donors. The donors could be easily accessed from hemiacetals and commercially available methylpropionate in the presence of catalytic amount of hindered base DABCO to promote 1,4-Michael addition. Thorough screening of donors under a series of Lewis and Brønsted acids showed that the departure of vinylogous carbonate moiety can be effectively promoted using 0.2 eq. of TfOH (Brønsted acid). Both pyranose and furanose sugars such as Glcp, Manp, Galp, Xylp, and Araf are activated under optimized glycosidation conditions. The donor was found to be suitable to produce azido glycosides, alicyclic glycosides, phenolic glycosides, threonine O-glycosides, and many disaccharides in good to excellent yields. Both 1° and 2° sugar and non-sugar acceptors are glycosylated smoothly under identified conditions. The application of the glycosyl vinylogous carbonate donor in the oligosaccharide synthesis has been demonstrated by synthesizing the pentaarabinofuranoside motif present on the cell surface of *Mycobacterium tuberculosis*.



- ✓ Easy access from hemiacetals
- ✓ Shelf-stable
- ✓ Short reaction time
- ✓ More than 25 examples
- ✓ Good to excellent yield (70-91%)
- ✓ Applied for oligosaccharide synthesis



Chapter 1

Introduction to Carbohydrates and Synthetic Methodologies

Chapter 1

1.1 Introduction¹

Nature utilizes the four classes of bio-macromolecules namely proteins, lipids, nucleic acids, and carbohydrates as building blocks of life. Among these, carbohydrates are the most abundant bio-molecules and comprise the major portion of total organic volume present on the earth surface. Naturally, these carbohydrates are synthesized in green plants by a process called photosynthesis. In this process, the atmospheric carbon dioxide (CO_2) combines with water (H_2O) in presence of solar energy and green pigment chlorophyll to produce oxygen (O_2) and glucose ($\text{C}_6\text{H}_{12}\text{O}_6$). Carbohydrates are the major source of energy in all living organisms. The simple carbohydrate glucose is uptaken up by the organisms and converted into other essential and required monosaccharides with the help of enzymes.^{1a}

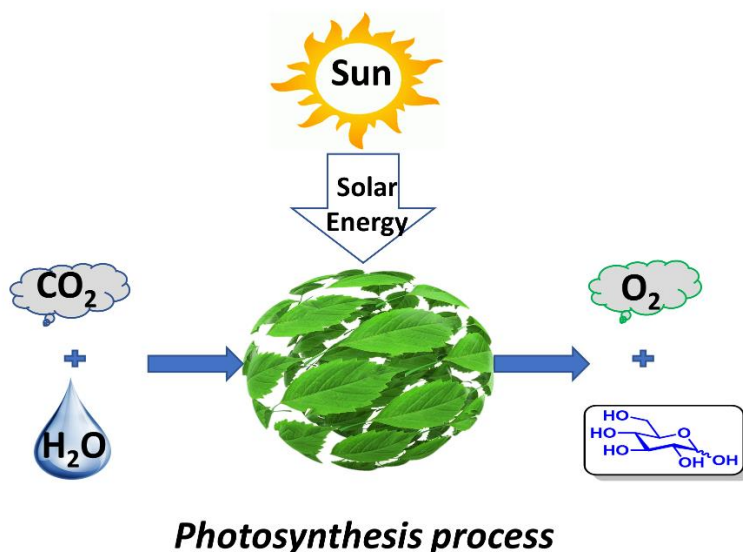


Fig 1.1 Cartoon representation of photosynthesis

Carbohydrates can be found in the form of simple monosaccharides or oligosaccharides, sometimes attached to proteins (glycoproteins) or lipids (glycolipids) at the cell membranes of living organisms.^{1b} Recent studies revealed that glycans could also be found attached to mRNAs and termed them as glycoRNAs.^{1c} It is well-studied that the complex glycan structures found in the living organism are the product of different complex metabolic pathways. The simple monosaccharides taken by living organisms are processed by enzymes and converted into

Chapter 1

complex glycan structures inside the membrane-bound organelles Endoplasmic reticulum and Golgi apparatus, which are then transported to the cell membranes.^{1d}

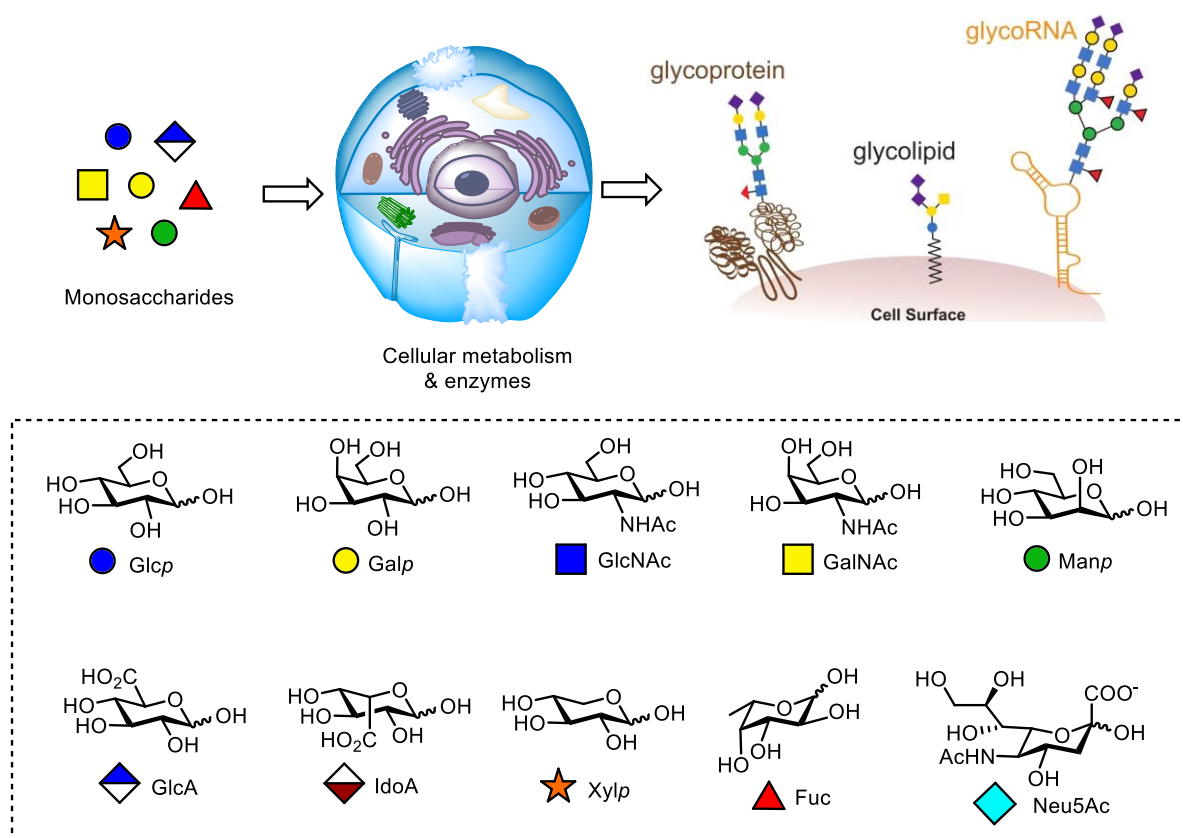


Fig 1.2 Glycans assembly in a eukaryotic cell and common monosaccharide of vertebrates

1.2 Significance of carbohydrates²⁻³

Earlier carbohydrates were majorly known as the primary source of energy and serve as the structural material for plants and anthropods as part of their cellular components. However, carbohydrates are involved in almost every aspect of living organisms and play a key in many physiological functions. Each cell of the living organism is decorated with complex glycans in the form of oligosaccharides or glycoconjugates. These membrane-bound glycans at the cell surface play a pivotal role in cell-cell communication and cell-to-surrounding interactions by hydrogen bonding, metal coordination, van der Waals forces, or hydrophobic interactions.^{2a-b} The carbohydrates are also involved in specific target recognition by acting as receptors at the cell surface via carbohydrate hydroxyl and protein interactions. Furthermore, the carbohydrate-

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protein interaction can lead to many beneficial physiological events, such as fertilization, embryogenesis, signal transduction, hormone balancing, and modulation of the immune response.^{2b-c} These can also be crucial in determining the type of cells due to the coded sequence of glycans at cell surfaces. One such phenomenon is the determination of human blood group types (A, B, AB, and O) which are based on the glycan structures present on the red blood cell surface. Furthermore, carbohydrates also play a role in various detrimental disease processes like inflammation, cancer metastasis, and bacterial or viral infections. For example, the SARS-COV-2 virus, which causes the COVID-19 infection identified utilizes the cell surface glycan heparin sulfates to infect the host cells.^{2d-f}

Furthermore, carbohydrates and carbohydrate-containing molecules are important scaffolds in drug design and vaccine development.^{3a} Several carbohydrate-based antibiotics, including streptomycin, gentamycin, and neomycin, and many anticancer drugs such as adriamycin, azacitidine, and nelarabine have been approved, and many are still under clinical investigation. In fact, in the last two decades, more than 50 carbohydrate-based molecules have been launched as drug candidates worldwide for clinical practices.^{3b} Therefore, carbohydrates have emerged as new targets in drug design and vaccine development. Furthermore, carbohydrates are essential components in many commercial and medicinally important natural products. For example, saponins, which are the class of glycosylated secondary metabolites have been used as natural surfactants in detergents for many years and many natural products such as vancomycin or acarbose are medicinally valued.^{3c} Apart from this, glycoconjugates are also routinely used in other areas such as in diagnostic kits, sensing, chromatography, polymer chemistry, etc.^{3d}

1.3 Glycosylation⁴

The central and most primordial reaction in carbohydrates chemistry is glycosylation. This is a process by which sugar units are covalently attached to an aglycon to form oligosaccharides, glycolipids, or glycoproteins. In general, a glycosylation reaction involves a sugar unit having a leaving group attached at anomeric position termed as glycosyl donor and an aglycon known as glycosyl acceptor. During the glycosylation, the leaving groups are activated with a appropriate promoters or enzymes to depart from anomeric position which allows the nucleophilic attack of an aglycon and forms stable glycosidic linkage. The new covalent bond formed during the glycosylation is termed as the glycosidic bond which usually has -O, -N or -S linkage. In the

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biological system, glycosylation is the post-translation modification of proteins to generate structural diversity. The process of attachment of sugar with specific proteins is governed by various glycosyl transferases. It plays crucial role in its folding via hydrogen bonding between polar sugar and amino acids thereby modulates the structure and function of proteins.

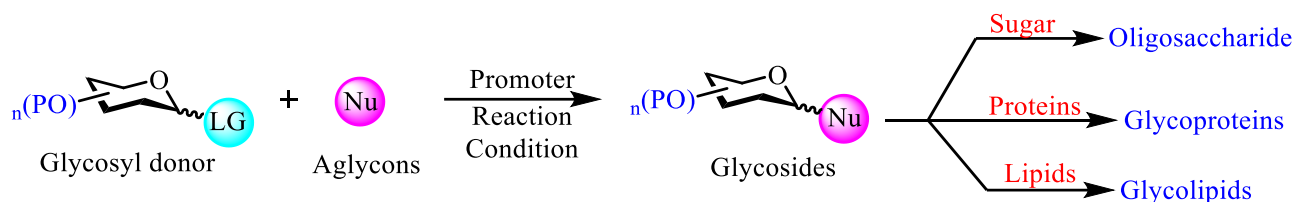
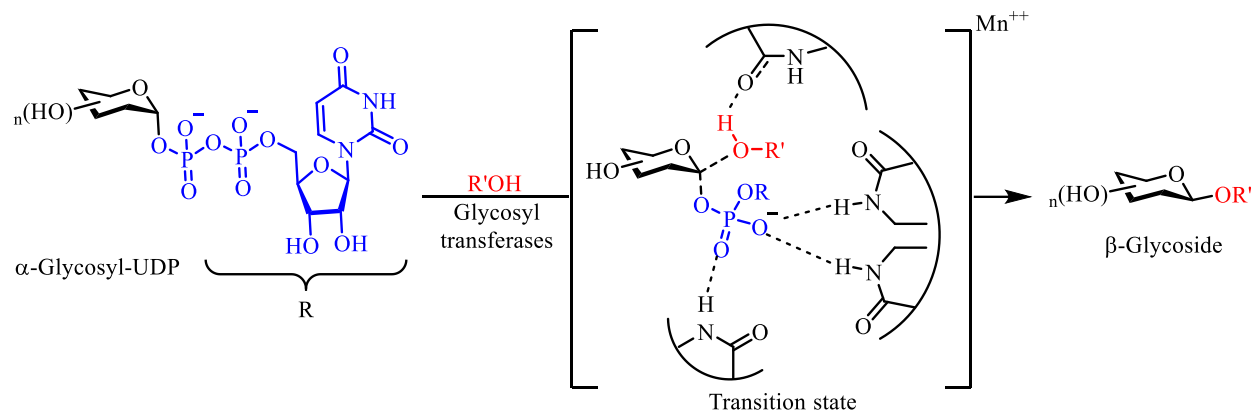


Fig. 1.3 General representation of glycosylation

In the last few decades, the research in carbohydrate synthesis has been highly focused on the development of various glycosylation methodologies. The formation of regio and stereoselective glycosidic linkage is very essential to obtain the specific function or activity of an oligosaccharide and glycoconjugates. However, unlike protein syntheses which are encoded by genes, carbohydrate syntheses is much more complex and have a high level of heterogeneity. In the last 30 years, the development in the field of synthetic carbohydrates chemistry has evolved exponentially and many methods for carbohydrate synthesis have been developed.

1.3.1 Enzymatic synthesis of carbohydrates⁵

In recent times, the enzymatic syntheses of glycoconjugates and oligosaccharides have emerged as the most promising and efficient method. It utilizes the enzymes glycosyl transferases which *in-vivo* bio-synthesize the oligosaccharides by utilizing sugar nucleotides. After the first successful *in-vitro* synthesis of oligosaccharide using the sugar nucleotide donors by Le Levoir, various glycosyl transferases have been identified and many mammalian sugar nucleotides such as UDP-Glc, UDP-GlcA, UDP-Man, UDP-Gal, UDP-Xyl, GDP-Fuc, UDP-GlcNAc, and UDP-GalNAc are now commercially available. The advantage of enzymatic synthesis over others are: (i) protecting group-free transformations (significantly reducing the number of steps), (ii) highly regio- and stereo-specific, (iii) efficient with catalytic amount of enzymes and (iv) the reaction conditions are very mild which facilitates the efficient synthesis of oligosaccharides without forming side products. However, the major limitation for the use of glycosyl transferase enzymes can be attributed to their availability, cost of glycosyl transferases, and sugar nucleotides.^{5a-b}



Scheme 1.1 Representative enzymatic glycosylation reaction

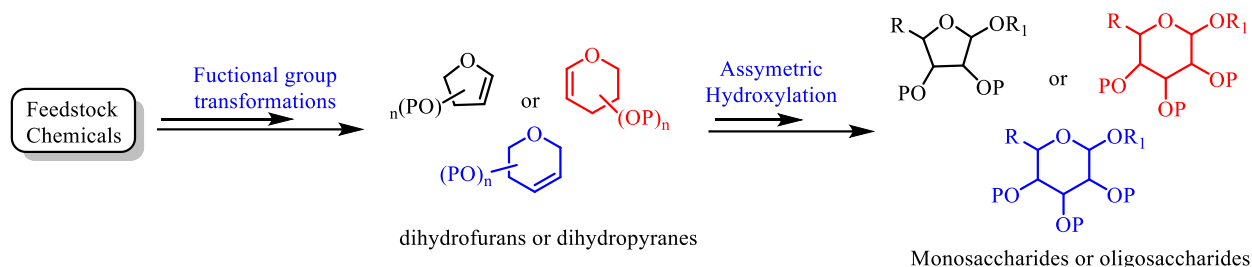
To overcome this limitation another class of enzymes known as glycosidases (in-vivo hydrolyze the oligosaccharides) were introduced by the Whiter group which can synthesize the oligosaccharides by utilizing the reactive donors such as glycosyl halides or *p*-nitrophenol. Glycosidase naturally hydrolyse the glycosidic linkage however it was identified that the activity of glycosidase can be reversed by exposing the enzymes to the large excess of the reaction product to shift the reaction equilibrium in the opposite direction. These enzymes are easily available, very stable, and easy to isolate from the organisms hence they are cheap and can be utilized for the synthesis of oligosaccharides on a preparative scale and can tolerate the variation in substrate scope. However, one of the disadvantages of using these enzymes was found to be the formation of mixtures of anomeric linkage and low yield in some cases.^{5c-d}

1.3.2 De-novo synthesis of oligosaccharides^{6a-b}

Owing to the complexity associated with the stereo-selective synthesis of complex glycans with natural or non-natural sugars in its structure, another approach often opted for producing complex carbohydrate-containing target molecules is de-novo synthesis. The term “de-novo synthesis of carbohydrates” refers to the synthetic methodology which utilizes the non-sugar starting material to obtain sugars/sugar derivatives via series of functional group transformations. The first de-novo synthesis of carbohydrates was demonstrated by Fischer and his coworkers in the synthesis of fructose, sorbose, and other monosaccharide derivatives from formaldehyde in presence of a base and divalent metals. However, the astonishing work in the field was done by O’Doherty and Peter Seeberger’s group using asymmetric catalysis. This methodology utilizes the simple achiral starting materials and majorly relay on stereo-selective glycosidic linkage

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formation, ring expansion or contraction via cyclization reactions, and finally the introduction of hydroxyls using asymmetric catalysis. Some of the advantages are (i) de-novo synthesis enables the diversity-oriented synthesis of both natural and rare carbohydrates analogs (ii) highly regio- and stereo-selective and (iii) protecting group-free transformation as hydroxyls are introduced at later stage.



Scheme 1.2 General scheme of De-nova synthesis of carbohydrates

1.3.3 Chemical synthesis of oligosaccharides⁷

In chemical glycosylation, a protected sugar with leaving group attached to the anomeric position commonly known as glycosyl donor which donates the sugar unit, and a protected sugar with at least one hydroxyl free to accept sugar unit termed as glycosyl acceptor are involved. In the reaction media upon addition of the suitable promoter (usually Lewis/Brønsted acid), the leaving group of glycosyl donor departs from the anomeric position to form a highly electrophilic species termed as “oxocarbenium ion” intermediate. These highly reactive species are generally stabilized by counter ions via close contact ion pair (CCIP) or solvent-separated ion pairs (SSIP) for a short time which then gets attacked by glycosyl acceptor to form glycosidic linkages. Most of the time the new glycosidic bond formed at the anomeric position are the mixture of α and β -configuration. However, the stereo-chemical outcome of the newly forming glycosidic bond depends on various factors such as the nature of the promoter, solvents, temperature, concentration of reaction media, and protecting groups. The most common practice for obtaining the 1,2-*trans* glycosidic linkage is the use of esters (acetate or benzoates) at the C-2 position to obtain the anchimeric assistance hence blocking one phase and preferentially allowing the acceptor attack from another phase to access the exclusive 1,2-*trans* linkage.



In carbohydrate chemistry, all the glycosidic linkages can be classified into two major classes. Based on nomenclature, 1,2-*cis* and 1,2-*trans* or α - and β - linkage at the anomeric position. The presence of specific glycosidic linkage can have a huge influence on its biophysical properties or functions in the biological system. For example, starch and cellulose are the polymers of glucose with $\alpha(1\rightarrow4)$ and $\beta(1\rightarrow4)$ glycosidic linkages respectively, however, only starch can be hydrolyzed to monomer glucose by enzymes and can serve as a source of energy in humans.

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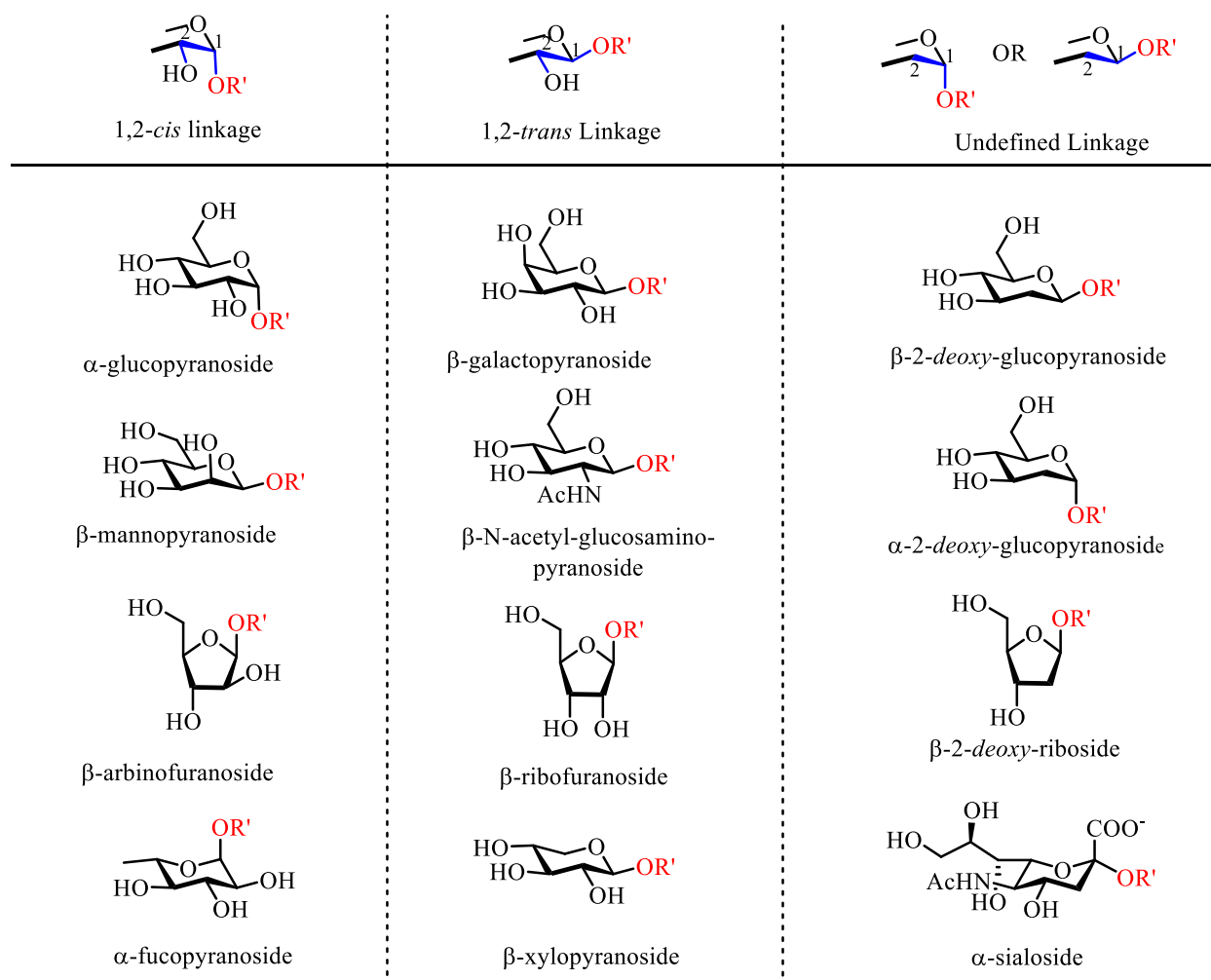


Fig. 1.4 Types of glycosidic linkages and their representative examples

1.5 Factors influence the outcome of glycosylation:

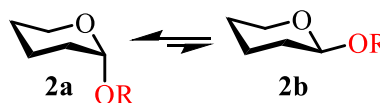
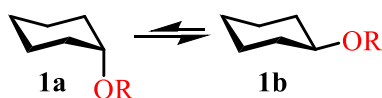
1.5.1 Anomeric Effect^{9a-b}

It is common to experience that during the formation of glycosidic linkage majorly with pyranose sugars in non-polar solvent without neighboring group participation, the α-isomer is always major than β-isomers. This fact was first observed by J T Edward in 1955 and further studied by Lemieux in carbohydrates chemistry and it is known as the anomeric effect or Edward-Lemieux effect. This observation was consistent when the electronegative heteroatoms are attached to anomeric position of sugars in cyclic conformations. Generally, in the chair form of cyclohexane systems, the substituent at the equatorial position (**1b**) is more stable as it

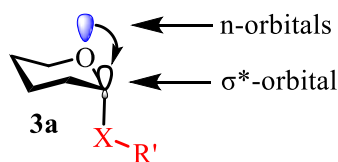
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eliminates the 1,3 diaxial interaction and energetically stabilizes the conformation compared to the axial substituent (**1a**). However, the opposite trend can be seen in sugars having the chair conformation, these observations are supported by the fact that the axially orientated glycosidic linkage (**3a**) is stabilized by hyperconjugation ($n \rightarrow \sigma^*$ orbital) via donation of non-bonding electrons of ring oxygen to the σ^* -anti-bonding orbital of anomeric linkage. This hyperconjugation is more favorable in the case of α -isomer (**3a**) as n and σ^* orbitals are anti-periplanner in orientation which is not possible in the case of β -isomer (**3b**).

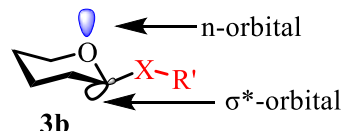
Equilibrium in six membered chair confirmations



Stabilization by hyperconjugation

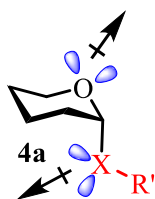


Antiperiplanner orientation
of n - σ^* orbital

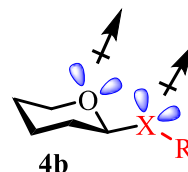


non-antiperiplanner orientation
of n - σ^* orbitals

Stabilization of dipole moment



dipole moment stabilization



dipole moment destabilization
and electrostatic repulsion

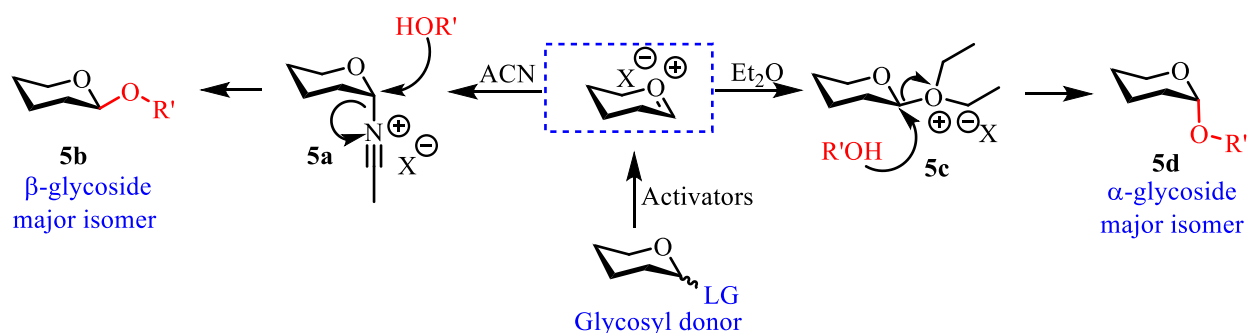
Fig. 1.5 Anomeric effect

Another factor that contributes to the anomeric effect is the dipole moment. In the case of axial orientation (**4a**) the dipole moment of non-bonding electrons of heteroatom attached to the anomeric position and ring oxygen lone pair are opposite to each other hence stabilizing the molecule, on the other hand equatorial orientation (**4b**) will have dipole moment in the same direction which destabilize the molecule due to steric and electronic repulsion.

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1.5.2 Reaction solvents^{10a-c}

The choice of solvent plays a crucial role in the outcome of most glycosylation reactions. In general, the use of polar solvents such as Acetonitrile and *N,N'*-dimethylformamide increases the stereo-selectivity towards β -glycoside (**5b**) formation through charge separation between ring oxygen and equatorial bond. This stereo-selectivity can be explained by the fact that these solvents directly participate in the glycosylation process.^{10a} For example, if the reactions are performed in acetonitrile, the “oxocarbenium ion” intermediate formed during glycosylation is trapped by solvent and preferentially forms the axial nitrilium cation (**5a**) which upon S_N^2 displacement results in the formation of equatorial glycosidic linkage. Contrary to this, ether-type solvents like diethyl ether, THF, and dimethyl ether show participation from the equatorial phase (**5c**) and increase the stereo-selectivity towards α -glycosides (**5d**) formation. However, not all the polar solvents directly participate in glycosylation and therefore this can also result in decreasing the selectivity by separating counter ions and shifting the reaction kinetics towards S_N^1 -type glycosylation. Further, if such kind of selectivity is not desired then non-polar solvents like CH_2Cl_2 , $CHCl_3$, $ClCH_2CH_2Cl$, and toluene can be better choices for the glycosylation. It is observed that the glycosylation in non-polar solvents gives the α -glycoside as major product due to the pronounced anomeric effect in these solvents.^{10b-c}



Scheme 1.4 Solvent participation in glycosylation reactions

1.5.3 Catalyst/Additives^{11a-f}

The nature of the catalyst/promoters and its counter ions generated in the reaction are also crucial for obtaining the stereo-selectivity in glycosylation.^{11a} In general, the use of mild and catalytic activation conditions can increase selectivity in glycosylation. For example, The activation of glycosyl bromide catalyzed by halide ion salt $Et_4N^+Br^-$ was found to undergo the S_N^2 -like

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displacement of leaving group to access α -glucosides and very recently reported Pd(II) Lewis acidity mediated glycosylation of glycosyl chloride donor are the examples.^{11b-c} It is believed that the mild reaction condition and slow activation of glycosyl donors shift the reaction kinetics towards S_N^2 -like glycosylation and hence favor obtaining the stereo-selectivity. In the activation of glycosyl donors which employs triflate salts such as AgOTf, HgOTf, TMSOTf, and Tf₂O, in glycosylation, the formation of axial triflate intermediates is dominant which increases the selectivity for equatorial glycosidic linkage. For example, the stereoselective β -mannosylations are reported at low temperatures using the thioglycoside donors in presence of NIS and triflate source promoters.^{11d} Further, the use of additives is also an important factor in bringing the stereo-selectivity. Most commonly polar solvents such as CH₃CN and Et₂O are used as co-solvents to obtain equatorial and axial glycosidic linkages respectively. Many more additives such as pyridine, *N*-heterocycles, triethylamine, dimethylsulfide, triphenylphosphine, and 1,10-phenanthroline are also been investigated to affect the stereoselectivity in glycosylation.^{11e-f}

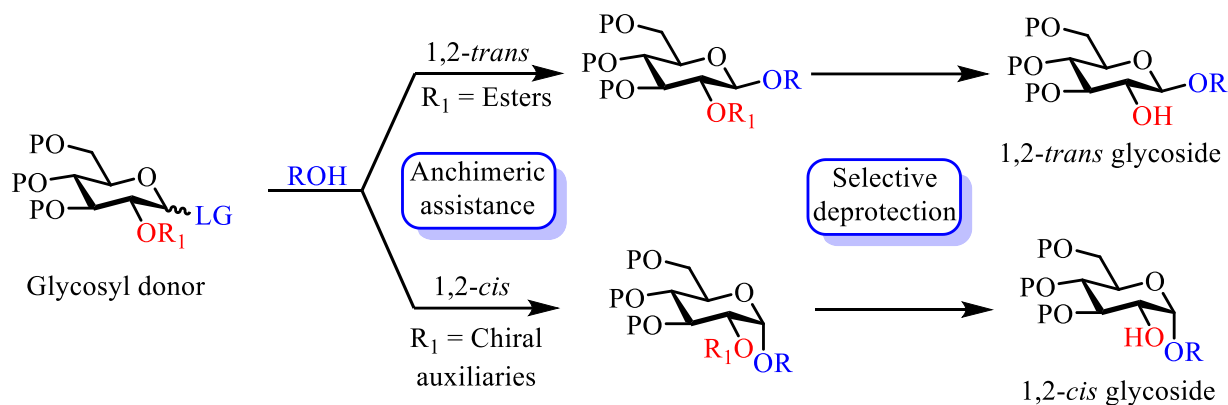
1.5.4 Temperature/Pressure¹²

The ratio of α/β -isomers of glycosylation products also depend on the thermodynamics and kinetics of the reaction. Hence, another factor that can influence the outcome of glycosylation is temperature. The axial glycosidic linkage product which is stabilized by the anomeric effect is the thermodynamic control product whereas equatorial glycosidic linkage is kinetically controlled. Therefore, lowering the reaction temperature can increase the stereo-selectivity toward thermodynamically controlled α -glycosidic linkage formation.^{8a} It is observed that differentially substituted thioglycoside can have different activation energies; hence, temperature can also be used as a control in oligosaccharide syntheses. The impact of pressure on glycosylation has been also investigated and it is found that high pressure can increase the rate of reaction but decrease the selectivity.

1.5.5 Protecting groups¹³

In chemical glycosylation, the protection of free hydroxyls is very essential to eliminate the formation of side products. Most commonly, these hydroxyls are protected, either by ether linkage (O-alkyl, O-silyl) or ester linkage (-OAc, -OBz), and hence can influence the reactivity of both glycosyl donors and acceptors. In the context of obtaining the selectivity in glycosylation

utilizing the protecting groups, the C-2 position of glycosyl donors are protected with esters (-OAc, -OBz) to obtain 1,2-*trans* glycosidic linkage through neighboring group participation.



● LG = Leaving group ● R₁ = Temporary protecting group ● P = Permanent protecting group

Scheme 1.5 Role of protecting groups in stereoselective glycosylation

However, obtaining the 1,2-*cis* linkage is challenging by simply utilizing these protecting groups and hence gained a little more attention. It is identified that bulky protecting groups such as *O*-*tert*-butyldiphenylsilyl, *O*-trityl, and 4,6-*O*-di-*tert*-butylsilylene can be utilized to sterically block one face which allows 1,2-*cis* glycosylation.^{13a-b} Further, the stereoselective glycosylation can be achieved by the use of chiral auxiliary protecting groups (*S*)/(*R*)-ethyl mandelate, (*S*)-(Phenylthio-methyl)benzyl (for α -galactosidation) and 2-pyridylmethyl for obtaining the desired glycosidic linkages.^{13c-d} Apart from helping in stereo-selective glycosylation, the protecting groups can also influence the reactivity of glycosyl donors as well as the acceptors and were noticed by Fraser-Reid and co-workers. According to the armed-disarmed concept, the glycosyl donors protected with ether-protecting groups are armed and can be activated in the presence of disarmed donors carrying ester-protecting groups. This concept has been widely utilized for orthogonal activation in the one-pot oligosaccharide syntheses.^{13e-f}

1.6 Account of glycosyl donors

Knowing the significance of carbohydrates as discussed earlier, synthesizing the glycoconjugates and oligosaccharides with defined regio- and stereochemical glycosidic linkages was of great interest in the synthetic carbohydrates community. In the last hundred years, since the first glycosylation reaction of hemiacetals under acidic conditions with excess of acceptor by Emil

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Fischer in 1893 (awarded Nobel Prize in 1902), several classes of glycosyl donors have been developed. Each donor has its own merits and demerits for glycosylation which are discussed below.

1.6.1 Glycosyl halides¹⁴

In 1902, Wilhelm Koenigs and Edward Knorr introduced glycosyl halides (chloride and bromide) as a relatively stable and useful donors for glycosylation. After its inception, several heavy metal salts such as AgClO_4 , AgOTf , AgNO_3 , Ag_2O , AgCO_3 , Ag-silicate as well as $\text{Hg}(\text{CN})_2$, HgCl_2 , HgBr_2 , and HgI_2 were used for the successful activation glycosyl halides. However, the problem with the use of heavy metal salts was their low solubility in organic solvents and hence required in super-stoichiometric amounts. To overcome this, Lewis acid-based catalysts SnCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, $\text{Sn}(\text{OTf})$ -collidine, $\text{Sn}(\text{OTf})$ -TMU, I_2 -DDQ, LiClO_4 , and very recently $\text{Bi}(\text{OTf})_3$, $[\text{FcB}(\text{OH})_2]\text{SbF}_6$, FcBF_4 are employed for milder reaction conditions and to increase the overall yield.^{14a-c} Because of the high electronegative nature, halides preferentially adopt axial orientation which make them good leaving group, the glycosyl halides are also used in many stereo-selective glycosidations. Lemieux *et al.* introduced the highly stereo-selective glycosylation protocol using glycosyl chloride donors wherein they used $\text{Et}_4\text{N}^+\text{Br}^-$ as a catalyst.^{11b} Further, the use of Et_3N , PPh_3 and Me_2S which forms glycosyl onium species during the reaction to affect the stereo-selective glycosylations was also developed from the same group. Among the glycosyl halides, glycosyl fluoride possesses good thermal and chemical stability and is also a good leaving group when expose to promoters. After the introduction of glycosyl fluoride as donors by Mukayama *et al.* in 1981.^{17e} Many synthetic protocols for glycosyl fluoride and its activation using various Lewis/Brønsted acids for glycosylation are reported.^{14d} Recently in 2017, Jacobsen *et al.* showed the stereo-selective *O*-glycosylation of pyranose derivatives, which again attracted the attention towards glycosyl halides. Many organocatalysts such as chiral ureas, phenanthrolines, and *N*-heterocycles are employed in stereo-selective syntheses of *O*- and *C*-glycosides using the glycosyl halide donors.^{14e-f} The advantage of halide donors over others are their stability and easy access from the corresponding hemiacetals.

1.6.2 Thioglycosides¹⁵

Thioglycosides are the stable and most widely used glycosyl donors in carbohydrate syntheses. In 1973, R J Ferrier introduced phenyl-1-thioglycosides as glycosyl donors wherein they used HgSO_4 or $\text{Hg}(\text{OAc})_2$ for the activation and demonstrated the synthesis of glycosides.^{15a} After this, many metal-based Lewis acids and electrophilic reagents were reported for successful activation of thioglycosides. However, the most practical and highly efficient protocol was developed by Van Boom (NIS/TfOH) and Fraser-Reid (NIS/AgOTf) in 1990 which demonstrated the utility of thioglycoside for oligosaccharide syntheses with improved yield. Many stable thioglycoside donors such as –STol, SEt, SMe, SPh, and SBox and more than 50 different activating reagents are reported.^{15b-c} Some of the notable reasons why thioglycosides are superior to others are: (i) the donor can be easily synthesized from per-*O*-acetylated derivatives of sugars and a mercaptan under Lewis acid such as $\text{BF}_3 \cdot \text{OEt}_2$, TMSOTf, and SnCl_4 or from hemiacetals upon treatment with dithiols in presence of $n\text{Bu}_3\text{P}$ or PPh_3 (ii) the donor is stable and inert to the many functional group transformation reagents employed in carbohydrates syntheses and hence can also be used as temporary anomeric protecting group (iii) reaction condition are very mild and (iv) can be performed under a wide range of temperatures 50 °C to -80 °C.

1.6.3 Glycosyl esters and orthoesters¹⁶

Glycosyl ester as glycosyl donor was first introduced by Helfrich in 1933. The glycosyl esters can be easily obtained from hemiacetals upon treatment with acetic anhydride in presence of catalytic amount of DMAP/ I_2 hence easy access and self-stability are the advantage of this donor. Many Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$, SnCl_4 , FeCl_3 , TMSOTf, and TfOH were employed to activate the glycosyl esters and demonstrated their utility in glycosides and glycoconjugates syntheses.^{16a} However, the high stability and less reactivity of glycosyl esters are the major disadvantages and therefore not suitable for oligosaccharide syntheses. Later on, Kochetkov *et. al.* introduced the glycosyl orthoesters as new class of donors. This donor can be obtained from the treatment of per-*O*-acetylated/per-*O*-benzoylated sugar derivatives with acid halides to generate glycosyl halides which further in presence of a strong base and suitable alcohol form 1,2-*O*-orthoesters.^{16b} Many stable orthoesters such as pentenyl orthoesters, propargyl orthoesters, and methyl orthoesters as glycosyl donors were developed and successfully examined for

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oligosaccharide syntheses.^{16c-e} However, the instability of orthoesters under acidic conditions and direct glycoside formation as side products are the major limitations of these donors.

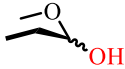
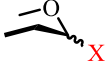
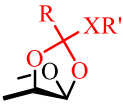
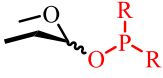
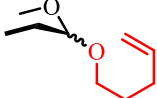
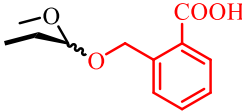
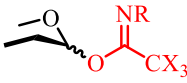
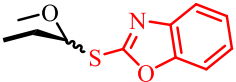
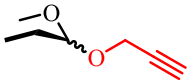
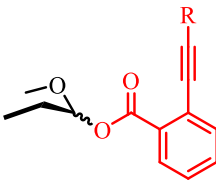
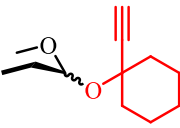
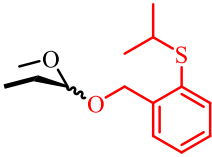
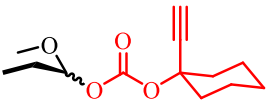
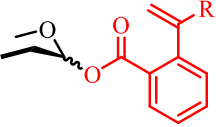
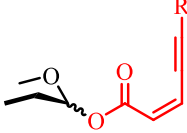
Generations of glycosyl donors & activation	Glycosyl donors possessing anomeric leaving group			
<i>1st generation of glycosyl donors</i>	 Hemiacetals Fischer ^{17a} , Kobayashi ^{17b}	 Glycosyl halides X = Cl, Br, Koenigs Knorr ^{17c} X = I, Garvay ^{17d} ; X = F, Mukayama ^{17e}	 Glycosyl esters Helferich ^{17f}	
<i>Superstoichiometric to Stoichiometric activation</i>	 1,2-Orthoesters X = O,S; Kochetkov ^{16b}	 Glycals Danishefsky ^{17g}	 1,2-Epoxides Danishefsky ^{19h}	 Glycosyl Phosphate Hashimoto & Ikegami ^{20a}
<i>2nd generation of glycosyl donors</i>	 <i>n</i>-Pentenyl Glycosides Fraser-Reid ^{19a}	 Thioglycosides Ferrier ^{15a} , Nicolaou ^{15b} Garegg ^{15b}	 Carboxybenzyl glycosides Kwan Soo Kim ¹⁷ⁱ	
<i>Stoichiometric to catalytic activation</i>	 Glycosyl imidates R = Me, X = H, Sinay ^{18a} R = H, X = Cl, Schmidt ^{18b}	 S-Benzoxazolyl Glycosides Alexi Demchenko ^{17j}	 Propargyl glycosides Srinivas Hotha ^{23a}	
<i>3rd generation of glycosyl donors</i>	 Ortho-alkynylbenzoates R = nBu, Biao Yu ^{21c} ; R = Cyclop ^{21f} , Xiao ^{21g} .	 Ethynylcyclohexyl glycosides Srinivas Hotha ^{23b}	 Ortho-(2-propylthio)benzyl glycoside; Wan^{17k}	
<i>Catalytic activation</i>	 Ethynylcyclohexyl carbonates Srinivas Hotha ^{25a}	 Phenyl-vinyl glycoside R = Ph, Xiao ^{17l} ; R = PhOMe, Kancharla ^{17m}	 Ynenaoates glycoside Liming Zhang ^{21h}	

Fig. 1.6 List of glycosyl donors developed in carbohydrates syntheses

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1.6.4 Glycosyl imidates¹⁸

Glycosyl imidates are one of the most versatile and widely/routinely used donors in carbohydrate syntheses. The donor was first introduced by Sinäy in 1976 and further exploited by Schmidt and co-workers (glycosyl trichloroacetamides (TCA) and trifluoroacetamides (TFA)).^{18a-b} The glycosyl imidates can be easily prepared by reacting hemiacetals with the trichloroacetonitrile in presence of inorganic bases NaH, K₂CO₃, CsF, Cs₂CO₃, or organic base DBU and activated by strong Lewis acids such as BF₃•OEt₂, TMSOTf, Tf₂O, TBDMSOTf, AgOTf and ZnBr₂ for glycosylation.^{18c} However, the low stability of glycosyl TCA and TFA grounded the base for the development of comparatively stable (*N*-phenyl)trifluoroacetamide glycosyl donor. This donor was smoothly activated under very mild conditions using Yb(OTf)₃ or Bi(OTf)₃ for assembling the building blocks for oligosaccharides syntheses.^{18d} Several additional promoters/reagents Sc(OTf)₃, Tb(OTf)₃, Yb(OTf)₃, HClO₄-Silica, acid washed molecular sieves, Amberlyst-15 H⁺ resins, and TMSBr-B(C₆F₅)₄ were employed to activate the glycosyl imidates.^{18c} Recently in 2009, Kunz *et al.* activated trifluoroacetamides using gold (Au) catalysts and later on, Vankar and co-workers also used a combination of AuCl₃ and Au-phenylacetylene as good activating reagents. The scope of gold catalysis in glycosyl imide donors was further demonstrated by Peng and Schmidt by synthesizing various glycosides.^{18e-f} However, the major limitations in using these donors are (i) the low stability of armed or super-armed glycosyl imidates and (ii) the formation of trichloroacetamides as side product.

1.6.5 Alkenyl glycosides¹⁹

Another donor used extensively in glycoconjugates and oligosaccharide syntheses is the *n*-pentenyl glycoside. In 1988, Bert Fraser-Reid group introduced this *n*-pentenyl glycoside as a stable and effective glycosyl donor.^{19a} This donor can be obtained in different ways: (i) Fisher glycosylation of unprotected hemiacetals with *n*-pentenol under acidic conditions, (ii) from the treatment of sugar per-*O*-acetates and glycosyl halides with 4-pent-1-ol under BF₃•OEt₂ and SnCl₄ conditions respectively. The donor was successfully activated using various electrophilic reagents such as IDPC, I₂, Br₂, TMSOTf, and TfOH however the use of combinations of NIS/TMSOTf was found as the best condition for glycosylation.^{14a} The modes of activation of pentenyl moiety rely on the formation of halonium ion at the terminal alkene which facilitates the formation of oxocarbenium ion to get attacked by the aglycon. The requirement of specific

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electrophilic halide-based reagents and the stability under many functional group transformation conditions employed in oligosaccharide synthesis allow this to be used as a temporary anomeric protecting group as well. This donor has been utilized in many latent-active glycosylation strategies as well as in orthogonal activation glycosylations.^{19b}

1.6.6 Glycosyl phosphates²⁰

The sugar derivatives possessing phosphate at the anomeric position as leaving group was first introduced by Hashimoto and Ikegami in 1989. From the same group, glycosyl diphenyl phosphate, glycosyl diphenylphosphineimides and glycosyl phosphoramidites were introduced as effective glycosyl donors, activated by Lewis acid TMSOTf and $\text{BF}_3 \cdot \text{OEt}_2$ to predominantly obtain 1,2-*trans* glycosides.^{20a-b} Later on, glycosyl dimethylphosphinothioates were reported by Inazu as stable glycosyl donors; smoothly activated by $\text{I}_2\text{-TrClO}_4$, AgClO_4 , and TrClO_4 as promoters.^{20c} Further, development in phosphate donor chemistry was extrapolated by Peter Seeberger and coworkers by introducing glycosyl dibutylphosphate as another stable glycosyl donor and demonstrated its applications in glycoconjugates and oligosaccharides syntheses.^{20d} Because of thermal stability and good leaving group ability of donor when exposed to promoters, glycosyl phosphates are also utilized in solid-phase oligosaccharide syntheses and proven as a promising building blocks.^{20e-f} Very recently in 2019, Jacobsen and coworkers utilized glycosyl diphenylphosphates and found them to be activated for stereospecific nucleophilic substitution reactions in presence of chiral catalyst bis-thiourea for *O*- and *S*-glycosylations.^{20g}

1.6.7 Glycals^{8a,14a}

Glycals as glycosyl donors is another interesting component and can be utilized for a diverse range of glycosides synthesis. The most noticeable feature of glycals are their utilization for the synthesis of various 2-*deoxy* and 2,3-unsaturated sugar derivatives. The glycals 3,4,6-tri-*O*-acetyl-D-glucal and 3,4,6-tri-*O*-acetyl-D-galactal are commercially available and can be utilized as or modified with desired protecting groups. Furthermore, the glycals can also be obtained from zinc-promoted elimination of glycosyl halides under acidic conditions or treatment with zinc dust and 1-imidazole in ethylacetate as solvent. Both acidic and basic conditions are suitable for activation of glycals and hence can undergo a diverse range of reactions. The glycals are activated and glycosylated in many ways such as electrophilic addition, cycloaddition,

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nucleophilic addition, and rearrangement reactions to alkene as well as can be converted into other glycosyl donors. The effective utilization of glycols for the syntheses of 2-*deoxy*-glycosides, 2-halo-2-*deoxy*-glycosides, 2-amino-2-*deoxy*-glycosides, and 2,3-*dideoxy*-glycosides via Ferrier rearrangement are well documented in the literature.

1.6.8 Alkynyl glycosides^{21,22}

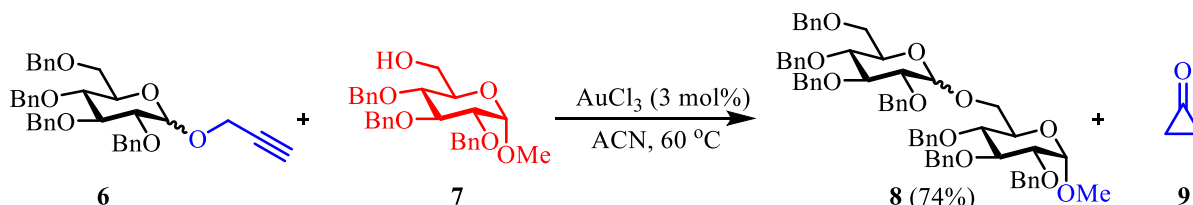
In recent times alkynyl glycosides have emerged as highly potential and promising glycosyl donors for assembling the sugar building blocks towards glycoconjugate and oligosaccharide syntheses.^{21a} At first, the utilization of alkynyl glycoside as glycosyl donor was demonstrated by Nishizawa and coworkers in 2006. The glycosyl alkynoates were activated with a catalytic amount (5 mol %) of Hg(OTf)₂ in acetonitrile to synthesize the glycosides in good yield with sugar and non-sugar acceptors.^{21b} Around the same time, Hotha and Kashyap reported novel Au(III) catalysis for glycosides with propargyl moiety at anomeric position as leaving group. Furthermore, the 1-ethynylcyclohexyl glycoside was also introduced from the same group; activated with 5 mol% of AuCl₃ and AgSbF₆ at room temperature, and demonstrated the application of gold catalysis in glycosylation.^{21c} Several additional alkyne-based donors such as dipropargyl-substituted cyanoacetyl glycosides, *S*-but-3-ynyl and gem-dimethyl *S*-but-3-ynyl thioglycosides are also reported to undergo glycosylation under Au(III) catalyzed conditions.^{21d-e} In the same direction, Yu and coworkers in 2008, introduced glycosyl *n*-butyl-*o*-alkynylbenzoates, as stable and effective donors activated by Au(I) complexes and demonstrated the synthesis of glycosides for both *O*-benzyl (armed) and *O*-benzoyl (dis-armed) protected glycosyl donors. The donor was thoroughly explored for the synthesis of complex and challenging glycoconjugates and oligosaccharides.^{21a} However major limitations in using *n*-butyl-*ortho*-alkynylbenzoates as donors are the requirement of extra efforts for the synthesis of leaving group which includes Sonogashira coupling between arylhalidebenzoates and *n*-butyl alkyne, hydrolysis of benzoate and then coupling with hemiacetals. In 2016, Hotha and coworkers introduced another stable, highly efficient, and versatile donor; glycosylethynylcyclohexyl carbonates were activated by 8 mol% of gold-phosphite and AgOTf at room temperature and demonstrated the robustness of the method by synthesizing tridecasaccharide mannose-capped arabinan in high yield.^{21c} In recent times several alkyne-based glycosides such as *ortho*-cyclopropylethynylbenzoates, directing group substituted cyclopropyl-*ortho*-alkynylbenzoates activated by Au(I) promoters.^{21f-g} Further

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the glycosides cyclopropylideneoates, ⁿbutylideneoates and glycosyl phenyl propiolates activated by Au(III) promoters are well documented for glycosylation.^{21h-i}

Further, the alkyne-based glycosides are also investigated for their activation without using expensive gold salts. In 2015, Biao Yu and his coworkers introduced glycosyl-*ortho*-(methyltosylaminoethynyl)benzyl as donors, activated using Lewis acid TMSOTf (10 mol%) and observed the formation of glycosylated product in good yield. later on, *ortho*-(*p*-methoxyphenylethynyl)phenyl (MPEP) glycoside, and 3,5-dimethyl-4-(2'-phenylethynylphenyl)phenyl glycoside as well as glycosyl hexynyl-*ortho*-benzoates are reported utilizing the NIS/TMSOTf as promoters.^{22a-d}

1.7 Development of gold-catalyzed glycosylation from our group²³



Scheme 1.6 Activation of propargyl glycoside donors

In 2006, Hotha and Kashyap introduced the first practical gold-catalyzed glycosidation protocol for stable propargyl glycoside donors. The per-*O*-benzylated propargyl glucoside (**6**) was activated in presence of acceptor (**7**) using 3 mol% of AuCl₃ at 60 °C in acetonitrile and observed the formation of disaccharide (**8**) in good yield. Based on the proposed mechanism, the key to the successful activation of anomeric leaving group was the utilization of alkynophilic Au(III) salt which preferentially forms π -conjugation with terminal alkyne and facilitates the expulsion stable hypothesized by product cyclopropanone (**9**) and forms an electrophilic intermediate species “oxocarbenium ion” contact ion pair which then be attacked by aglycon. Later on the mechanistic investigations shows that the cyclopropanone did not form but it extrudes only the propargyl alcohol. To demonstrate the utility of gold-catalyzed glycosidation; propargyl glycosides of per-*O*-benzylated glucopyranose, mannopyranose, and galactopyranose were investigated to undergo glycosylation smoothly with both 1° and 2° sugar as well as non-sugar acceptors. However, the low yields were reported in the case of secondary alcohol acceptors and tertiary alcohols were not reported. Furthermore, the low anomeric selectivity was observed with

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C-2 non-participating glycosyl donors and glycosyl propargyl donors with C-2 benzoates were unreactive to undergo the glycosylation.^{23a}

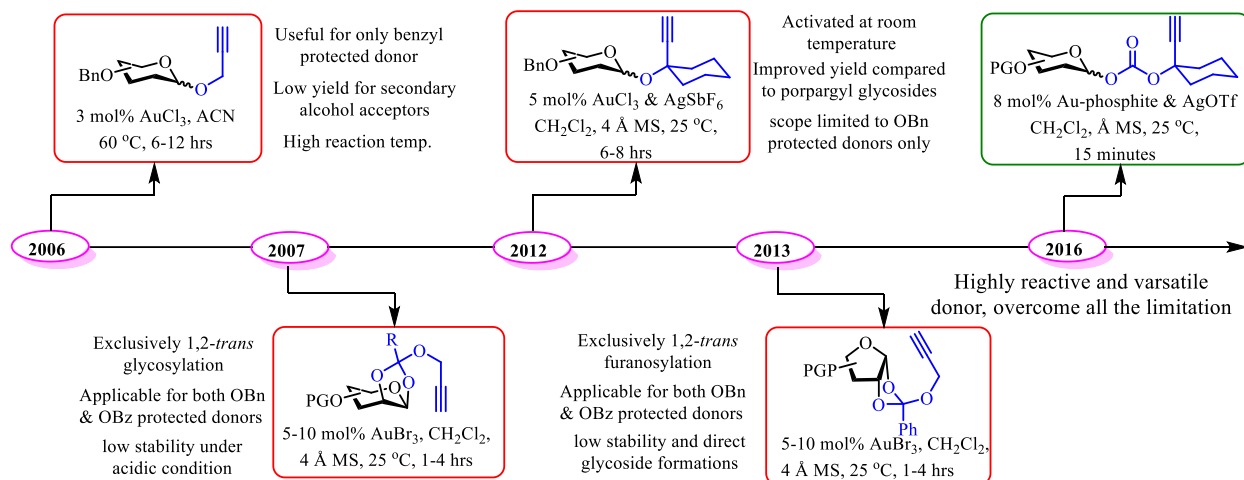


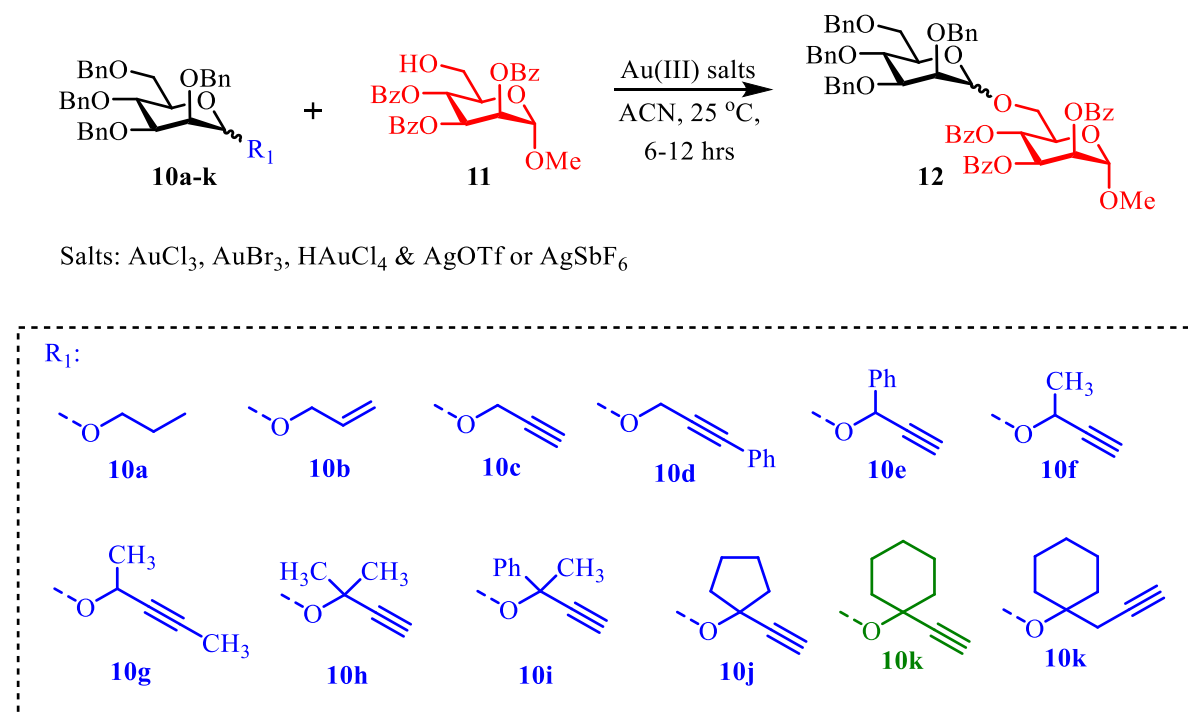
Fig. 1.7 Development of gold-catalyzed glycosidation from Hotha group

The nonreactive nature of C-2 benzoates, poor anomeric selectivity, and the requirement of high reaction temperature for the activation of glycosyl propargyl glycosides prompted Hotha and Kayastha to investigate the other alkyne-appendaged glycosides under gold catalysis. Several differentially substituted alkynyl glycosides were prepared and subjected for its activation in presence of gold salt AuCl₃/AuBr₃ in combination with AgOTf/AgSbF₆ as promoters. In this study, the glycosides having anomeric leaving group (**10a-10g**) either did not react or gave unsatisfactory yields whereas the *gem*-dialkylated alkynyl glycosides (**10h-10k**) were found to be more reactive under gold-catalyzed glycosidation conditions. After the thorough screening, ethynylcyclohexyl glycoside (**10k**) was found to be highly reactive to undergo the glycosidation using 5 mol% each of AuCl₃ and AgSbF₆ at room temperature. The application of this donor was demonstrated by synthesizing several disaccharides and glycosides with improved yield for both 1° and 2° alcohol acceptors and the good leaving group ability of *gem*-dialkylated glycosides was attributed to the well-known Thorpe-Ingold effect.

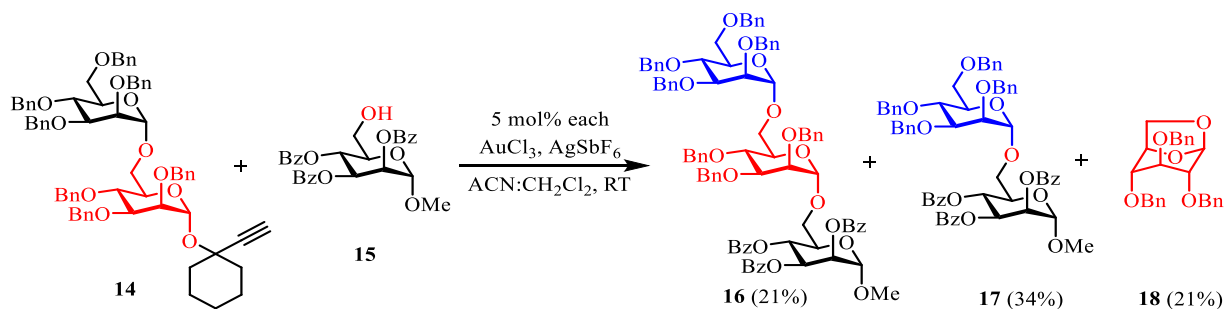
It was also noticed that the per-*O*-benzoyl-protected ethynylcyclohexyl glycosides were still resistant to undergo transglycosidation. This difference in the reactivity of *O*-benzyl and *O*-benzoyl-protected donors were cleverly utilized by the authors and demonstrated the synthesis of trimannoside using armed/disarmed glycosylation strategy. Overall the glycosyl

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ethynylcyclohexyl propargyl donor was successful to overcome some of the drawbacks of propargyl glycosides as it was activated at room temperature and the yield of the glycosidation reaction was improved. However, the C-2 benzoyl-protected donors were still resistant to undergo the glycosidation therefore the utility of donors was limited to the C-2-benzyl donors which usually results in the anomeric mixture of products. Furthermore, the application of donor in oligosaccharide synthesis was not desirable as the synthesis of trisaccharide (**16**) resulted in the interglycosidic bond cleavage and formation of anhydrosugar (**18**) and disaccharide (**17**) most likely due to high oxophilicity of gold salts (Scheme 1.8).^{23b-c}



Scheme 1.7 Investigation of glycosyl alkynes as glycosyl donors^{23b}

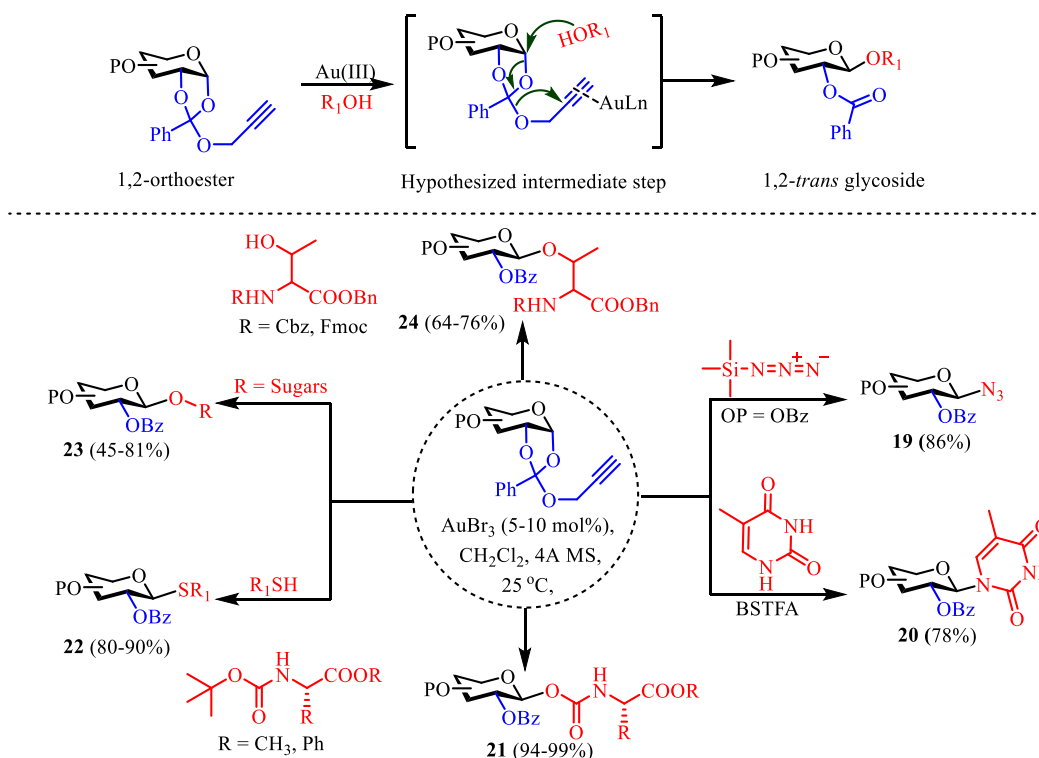


Scheme 1.8 Limitation of propargyl cyclohexyl glycosides under gold catalysis^{23c}

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1.7.1 Activation of propargyl orthoester²⁴

Generally, the 1,2-*trans* selectivity was obtained in the glycoside syntheses by placing benzoates, acetates, or any other esters at the C-2 position. However, the propargyl glycosides protected with C-2 benzoates were still unreactive under gold-catalyzed condition. Therefore, to synthesize the 1,2-*trans* linked glycosides, Sureshkumar and Hotha hypothesized the propargyl 1,2-orthoester as glycosyl donors. This donor was activated using 5-10 mol% of AuCl₃/AuBr₃ in combination with AgOTf/AgSbF₆ to obtain the exclusive 1,2-*trans* glycosidic linkages.^{24a} In the activation of propargyl orthoesters, promoter AuBr₃ was found to be superior due to its balanced Lewis and Brønsted acidities compared to AuCl₃. Both furanose and pyranose 1,2-orthoesters were found to undergo glycosidation smoothly with azide (19), nucleobases (20), acids (21), thiols (22), alicyclic alcohols, sugar (23) and non-sugar (24) acceptors to obtain respective glycoside in good yield. The mild and selective activation of propargyl glycosides was demonstrated by synthesis of highly challenging branched heneicosasaccharide (29) (19 Araf's and 2 Gal's) in 47 steps with 0.09% overall yield. Furthermore, the selective activation of propargyl 1,2-orthoesters in the presence of propargyl ethers was also investigated to synthesize disaccharides with the propargyl group at the reducing end.^{24b-e}

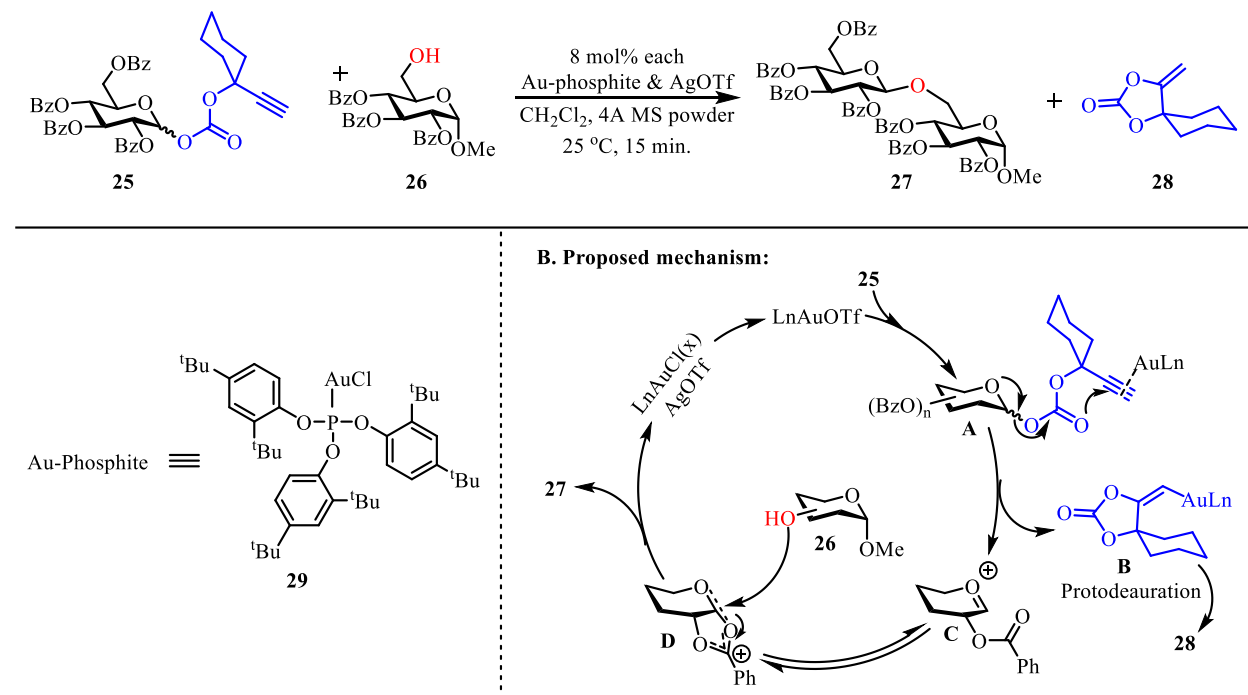


Scheme 1.9 propargyl 1,2-orthoesters as glycosyl donors²⁴

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1.7.2 Glycosyl ethynylcyclohexyl carbonate donor²⁵

Continuous efforts toward improving the overall efficacy of gold-catalyzed glycosidation from the Hotha group disclosed the glycosyl ethynylcyclohexyl carbonates as a shelf-stable, versatile, and highly efficient donors. In 2016 Mishra *et al.* investigated the differentially substituted alkyne-appendaged glycosyl carbonates and identified that the donor **25** could be activated using 8 mol% each of gold-phosphite **29** and AgOTf at room temperature to obtain the disaccharide **27** in the presence of aglycon **26** along with a cyclized yet stable by product **28**. The key behind the efficient activation of donor was the exploitation of strategically positioned alkyne functionality and the highly alkynophilic gold-complex in combination with AgOTf as promoters. Most importantly, both armed and disarmed glycosyl donors were found to undergo glycosidation very efficiently at room temperature thus overcoming many of the limitations of previous donors developed by our group. To probe more into the application of this donor authors synthesized the azide glucoside, serinyl glucoside, nucleosides, phenolic glucoside, alicyclic glycosides, and several disaccharides and oligosaccharides with excellent yield. Overall the donor was found highly efficient for the synthesis of any kind of glycosides that one can wish.



Scheme 1.10 Silver assisted gold-catalyzed glycosidation reaction; **B. Proposed mechanism of the glycosidation reaction.**

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Based on the proposed mechanism, the activation of glycosyl ethynylcyclohexyl carbonate **25** requires both gold-phosHITE & AgOTf which *in-situ* leads to the formation of active catalyst L_nAuOTf . The active catalyst then coordinates with the alkyne group and forms a gold-alkyne complex **A** which further upon electron cascade push from endo-cyclic oxygen collapses into cyclic vinylideneauric carbonate **B** and oxocarbenium intermediate **C**. The cationic charge on **C** can delocalize and form intermediate **D** through neighboring group participation and can get attacked by the aglycon **25** to form the stable disaccharide with release of a proton which causes intermediate **B** to undergo protodeauration to extrude alkene **28** and the catalytic Au-species.^{25a}

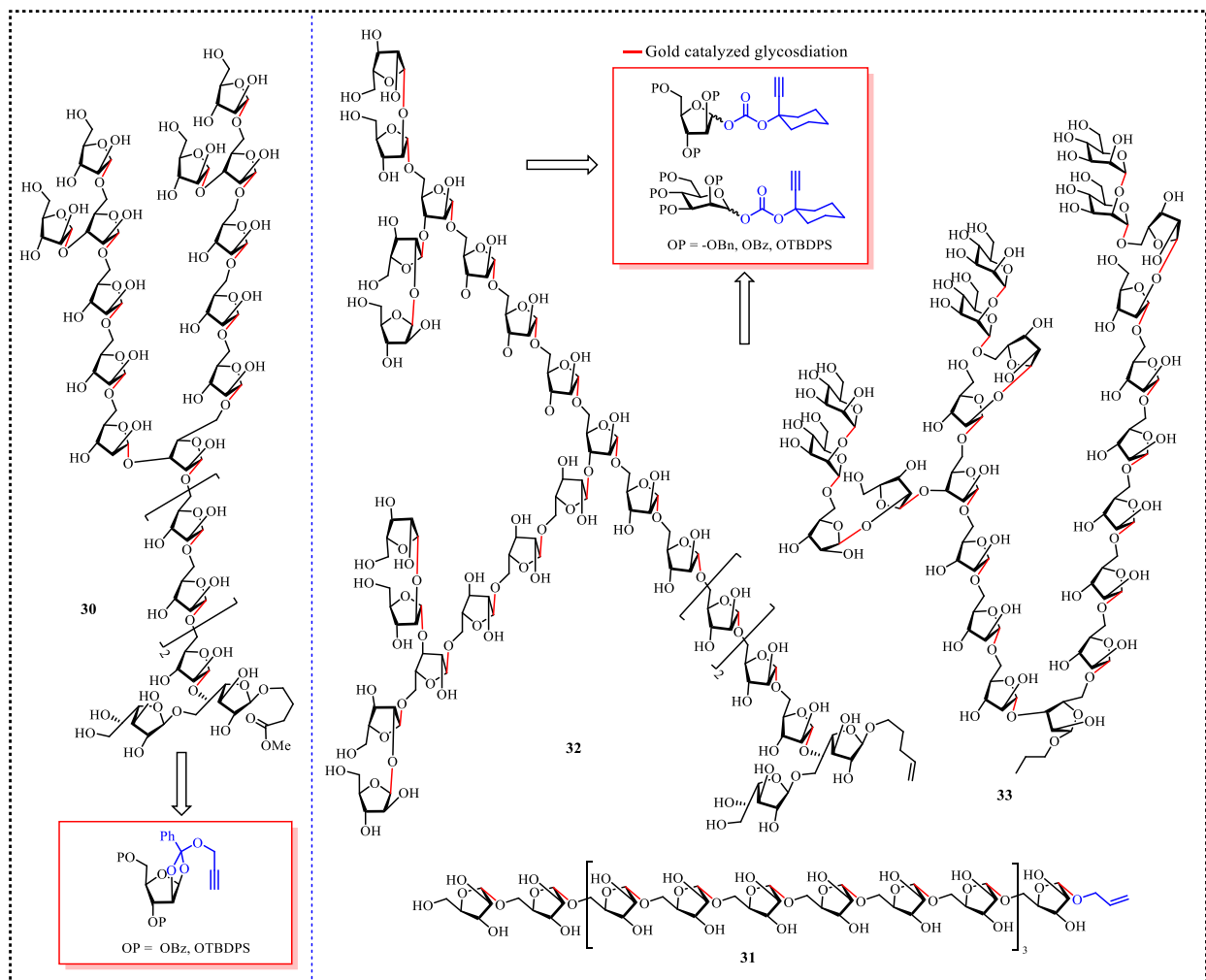


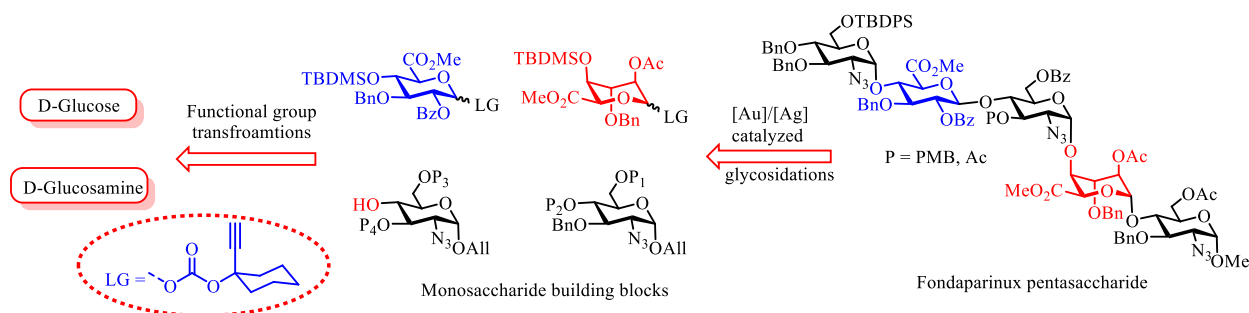
Fig. 1.8 Glycan motifs of *Mycobacterium tuberculosis* cell wall synthesized by Gold catalysis

The donor has been explored for the synthesis of many interesting glycosides and emerged as a highly efficient and promising candidate for the oligosaccharide syntheses. For example,

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syntheses of oligofuranosides from the *Mycobacterium tuberculosis* cell wall have been demonstrated. The synthesis of nonadecaarabinofuranoside (19 Araf_s) of the arabinogalactan, a heneicosaccharide (15 Araf_s and 6 Man_ps) from lipoarabinomannan portion and a pentacosasaccharide (23 Araf_s and 2 Gal_fs) moiety of arabinogalactan were achieved employing the glycosyl carbonate donor chemistry.^{25b-d}

Very recently in 2021, we exploited this donor chemistry for the synthesis of clinically approved anticoagulant Fondaparinux (Arixtra[®]). This synthetically challenging pentasaccharide is based on antithrombin-binding domain heparin sulfates which contains glucosamine, glucuronic acid, and iduronic acid in its sequence. The monosaccharide building block was synthesized from D-glucose and D-glucosamine and assembled under [Au]/[Ag] catalyzed glycosidation condition in complete stereoselective fashion. The pentasaccharide fondaparinux was synthesized by assembling the monosaccharide building blocks in highly convergent [3+2] or [2+1+1] glycosidation strategy to produce the gram scale of pentasaccharide in 41 steps.^{25e}



Scheme 1.11 Fondaparinux pentasaccharide synthesized using gold-catalyzed glycosidation

Encouraged by the phenomenal application of gold-catalyzed glycosidation for higher oligosaccharide syntheses and our continuing interest in heparin-based anticoagulant synthesis using silver-assisted gold catalysis, the second-generation anticoagulant Idraparinux was targeted to develop a novel and highly efficient synthetic protocol which is discussed in Chapter 2.

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Chapter 2

Synthesis of Anticoagulant Idraparinux using Silver Assisted Gold-catalyzed Glycosidation

2.1 Introduction

Glycosaminoglycans (GAGs) are the heterogeneous, polyanionic, polysulfated polymers found abundantly on cell surfaces and extracellular matrix (ECM). These are the highly negatively charged, linear polysaccharides containing hundreds to several thousand of repeating disaccharide units.^{1,2} Each disaccharide repeating unit is made of an amino sugar (*N*-substituted glucosamine or *N*-acetylgalactosamine) and uronic acids (glucuronic or iduronic acids). These disaccharides may display different monosaccharide building blocks with regio- & stereo-defined glycosidic linkages therefore can generate highly diverse and complex structures. The polymers may contain the monosaccharide's ranging from 10-1000 units and each building block can be sulfated at various positions. Furthermore, the presence of specific amino sugar, *N*-acetylation or *N*-sulfation, and possibility of different regio-specific *O*-sulfation patterns bring the high degree of heterogeneity in the GAG's composition.³

The GAGs can be broadly classified into two major classes based on the type of amino sugar present in the disaccharide carbohydrate structure: **(A) Galactosaminoglycans:** This is the family of GAGs having *N*-acetyl galactosamine (GalNAc) and uronic acids disaccharide repeating unit. This class of GAGs are the Chondroitin sulfate (CS) and Dermatan sulfate (DS), composed of basic disaccharide repeating unit $\alpha,\beta(1\rightarrow3)$ -linked uronic acid with GalNAc residue. These disaccharides are then connected through a glycosidic linkage as $\beta(1\rightarrow3)$ in its oligomeric structure. The CS exclusively contains the GlcA epimer in the oligosaccharide chain whereas DS contains >10% IdoA epimer and are sulfated at C-4, C-6 of GalNAc and C-2 of uronic acid derivatives.⁶ **(B) Glucosaminoglycans:** the family of GAGs made of D-glucosamine and uronic acids disaccharide unit, except keratan sulfate which contain neutral galactose sugar. The group can be divided into 3 major class: (i) Hyluronan (HA), which are the only non-sulfated GAGs composed of disaccharide repeating unit $\text{GlcA}\alpha(1\rightarrow3)\text{GlcNAc}$, connected to each other via $\beta(1\rightarrow4)$ glycosidic linkage. (ii) Keratan sulfate (KS), these are structurally small oligosaccharides ranging from 5-30 disaccharide units made of $\text{Gal}\beta(1\rightarrow3)\text{GlcNAc}$ residue. The KS are the least sulfated GAGs with sulfation at C-6 of Gal and GlcNAc and are linked via $\beta(1\rightarrow3)$ -glycosidic linkage. (iii) Heparan (HP)/Heparan sulfate (HS) are made of basic disaccharide uronic acids $(1\rightarrow4)$ glycosidically connected to D-glucosamine. The HP and HS are differentiated based on the percentage of uronic acids in their polymeric structure. In the

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heparans (HP) 90% of uronic acid is present in the form of IdoA with very small portion of up to 10% as GlcA whereas heparin sulphate (HS) contains 10-50% of GlcA.³⁻⁸

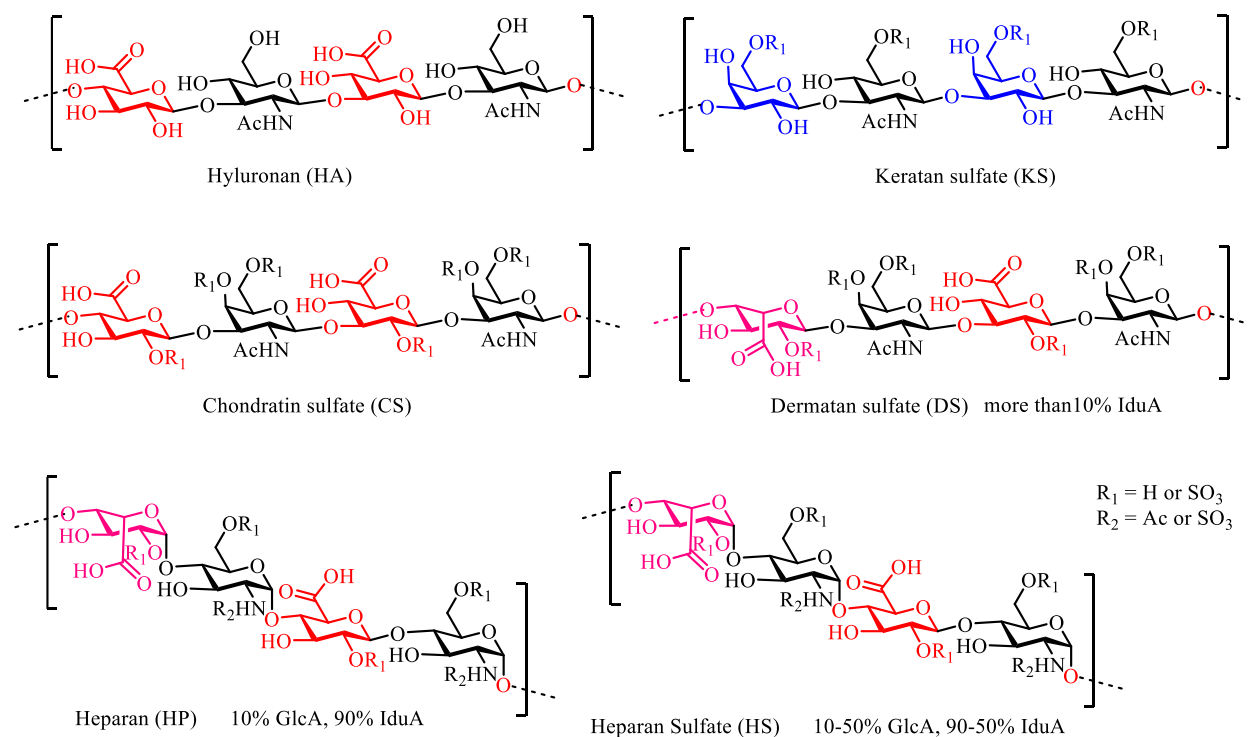


Fig. 1 Composition of disaccharide repeating unit of GAG's

Biologically, GAGs are synthesized in the endoplasmic reticulum and golgi apparatus utilizing the UDP-sugar nucleotides and glycosyl transferases, except hyluronan acid (HA) which exclusively forms at inner plasma membrane.⁹ The basic repeating disaccharide units synthesized are then transported to cell membranes where it gets attached to the membrane bound proteins through a GAGs protein linker tetrasaccharide (GlcA β (1 $\rightarrow$ 3)Gal β (1 $\rightarrow$ 3)Gal β (1 $\rightarrow$ 4)Xyl α (1 $\rightarrow$ O)-Ser) or secreted to the extracellular matrix.¹⁰ The proteoglycans at cell surface undergo the chain elongation with disaccharide units employing the UDP-sugars and enzymes glycosyl transferases or glycosidases and form glycocalyx at the cell surface.^{10,11} These GAGs being ubiquitously expressed at the cell surface, play crucial roles in cell to surrounding interactions, cell-cell recognition, signal transduction, cell division, inflammation, and many others.^{11,12} Furthermore each class of glycosaminoglycan can have different functions in the biological processes. For example, the exclusively non-sulfated HA in high concentration gives the rigidity to the tissues and is essential component of connective tissues such as skin, heart valve, lungs,

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umbilical cord etc. The HA present as synovial fluids of joints act as mechanical shock absorbers because of their high viscosity.^{13,14} The polysulfated GAGs predominantly found in bones, cartilages, and arterial valves give the elasticity to the tissues.^{15,16} Furthermore these negatively charged sulfated polysaccharides can also act as ligands for proteins thus mediating several physiologically important processes.^{16,17} For example, CS/DS interaction with cytokines, chemokines, and growth factors play key roles in cellular events during central nervous system development, tumour progression, inflammation and wound healing.¹⁸⁻²² Furthermore, many viruses such as rabies virus, dengue virus, and human deficiency virus (HIV) utilize the heparan sulphates to infect their host's cells.²³⁻²⁶ For example the coronaviruses, including SARS-CoV-2, bind to heparin sulfates and increase the virus density on the cell's surface, thus facilitating their interaction with ACE2 receptors to enter the host cell.²⁷

2.2 Clinical application of heparin & heparin sulphates

As stated earlier that the heparins are highly expressed at cell surfaces and extracellular matrix (ECM), therefore, become the first site of interaction for proteins or any foreign particles and hence they are involved in the vast array of functions to regulate the interactions between cells and their microenvironments.⁴⁻⁸ Hundreds of heparin-binding proteins have been identified and found to have the profound implications in many physiological processes. One of the most highlighted clinical applications of heparins was discovered in 1916 by McLean is its ability to act as a powerful anticoagulant;²⁸ though, very little was known about the structure of heparins at that time. Later clinical investigations, it was discovered that the thrombin was gradually inhibiting when heparins are added to the defibrinated plasma due to the presence of antithrombin-III.²⁹⁻³¹ Later on this hypothesis was confirmed through isolation of pure AT-III by Abildgaard and coworkers in 1968 and suggested that the activity of AT-III gets accelerated when heparins are added to the blood plasma.^{32,33}

In brief the HP and HS being polysulfated, carboxylate anions possess the high density negative charge which enables to interact with positively charged Antithrombin-III (AT-III), Factor Xa and XIa present in the blood plasma. The formation of heparin-AT-III complex brings the conformational change in AT-III thereby increasing the inhibition of thrombin, factors Xa and XIa which are important for clotting in blood coagulation cascade.^{34,35} These discoveries

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subsequently led to the low molecular weight (LMWH's, avg~6000 Da) heparin based anticoagulants which are being marketed by different trade names such Reviparin, Nadroparin, Enoxaparin, Tinzaparin, and Certoparin based on the type of depolymerisation process.^{36,37} For example, the Nadroparin is isolated by deaminative cleavage employing the nitrous acid whereas Enoxaparin is obtained by β -elimination of unfractionated heparins (UFH) under strong alkaline conditions. The majority of UFHs are isolated from animal sources either from the bovine or porcine intestines which are subjected to depolymerisation under strongly alkaline conditions or treating with strong acids.³⁸ Thus the LMWHs are the heterogeneous mixture of heparin fragments with molecular weight (~1500 - 4500 Da) and hence are associated with the plethora of side effects such as thrombocytopenia, excess bleeding, osteoporosis and allergic reactions.^{39,40} The impending problem associated with monitoring the purity of LMWHs has been the most challenging task in obtaining the safe heparin based anticoagulants. As consequence, many fatalities were witnessed in 2008 because of LWMHs contaminated with oversulfated chondratan sulphate (CS).^{41,42}

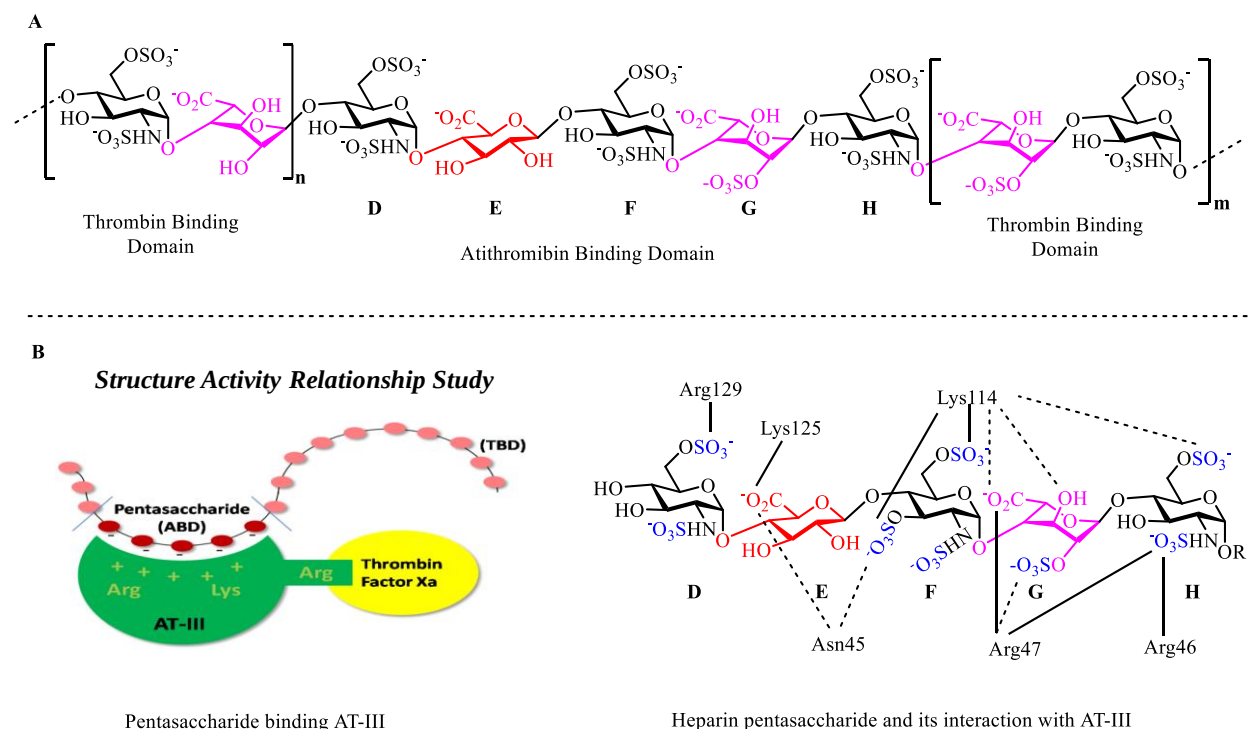


Fig. 2 (A) Heparin chain with thrombin & Antithrombin-III binding domain, (B) Interaction of heparin pentasaccharide with AT-III

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The investigation of enzymatically depolymerised heparins suggested that the heparins with 6 to 10 monosaccharide unit are good enough to produce the required anticoagulant activity.⁴³ thus the identification of precise structural component responsible for its anticoagulant activity begun with finding of antithrombin-III binding domain. The thorough structure activity relationship (SAR) study performed by Petitou and co-workers in early 1990's led to the discovery of a pentasaccharide motif responsible to interact with AT-III.^{44,45} The structural requirement of pentasaccharide binding to the antithrombin-III was elucidated with a series of synthetic heparin fragments which suggested the essential sulphate groups and carboxylates.^{46,47} The presence or the absence of specific sulphate group and its positions was found to have significant impact on binding affinity of the pentasaccharide. For example, the 3-*O*-sulfate of monosaccharide unit F was found to enhance the binding affinity by ~10,000 fold compared to the pentasaccharide derivative without 3-*O*-sulphate group.⁴⁸ The other sulfates and carboxylates were found to interact with the AT-III through coulombic interactions and provided the basis for the development of other LMW heparin based anticoagulants.⁴⁹

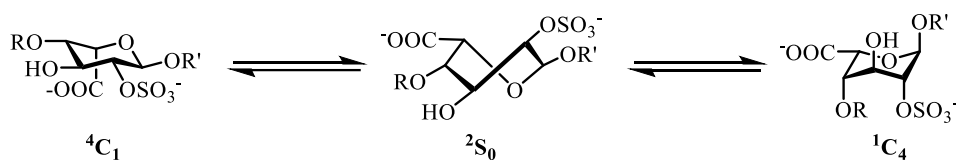


Fig. 3 Three energetically stable conformers of IdoA

Further, adding to the diversity of sulphate group positions, the activity and selectivity are also affected by the conformation and three dimensional structures. In particular the epimerisation of GlcA to IdoA was found to have profound effect on the three dimensional structure as it undergoes the conformational change.⁵⁰ Theoretical studies of iduronic acid unit revealed that the residue can exist in three different conformations (⁴C₁, ²S₀, ¹C₄) and the ratio of these conformers are dependent on the sulfation patterns and the chain length.^{51,52} The effect of these conformations on binding affinity was studied and it was discovered that the heparins containing IdoA bind stronger compared to the heparins without IdoA. For example, the binding capacity of HS was found to be higher compared to that of CS containing only GlcA though both have similar charge density.⁵³

2.3 Heparin based synthetic anticoagulants

The discovery of pentasaccharide motif containing three alternative glucosamine units, one each glucuronic and iduronic acid sequence with various sulfation patterns drastically accelerated the development of synthetic anticoagulants. In 2001, Fondaparinux **1** (trade name - Arixtra[®]), a solely synthetic pentasaccharide anticoagulant was introduced to the market because of its higher half life ($t_{1/2}$ = 24 h) compared to that of LMWHs (1 h). The pentasaccharide fondaparinux specifically binds to the AT-III thereby bringing the conformational change in its structure which significantly increased the thrombin-AT-III binding and inhibited the Factor Xa in blood coagulation cascade.^{47,49} Because of the complete bioavailability after subcutaneous injection, the molecule is highly effective in preventing the thromboembolism thus has been used in major orthopedic procedures such as hip or knee replacement, abdominal surgery, etc. The use of well characterized synthetic heparin based anticoagulants significantly eliminated the risk of contamination and side effects. Thus, in last two decades lot of efforts have been taken for the development of highly efficient, cost effective, synthetic protocols for pentasaccharide fondaparinux.⁵⁴ however; the lengthy and demanding synthetic protocols for fondaparinux insisted the research community to design simplified analogues in terms of its synthetic complexity. Further research on the development of synthetic anticoagulants led to the discovery of highly potent second-generation anticoagulant pentasaccharide Idraparinux **2**.

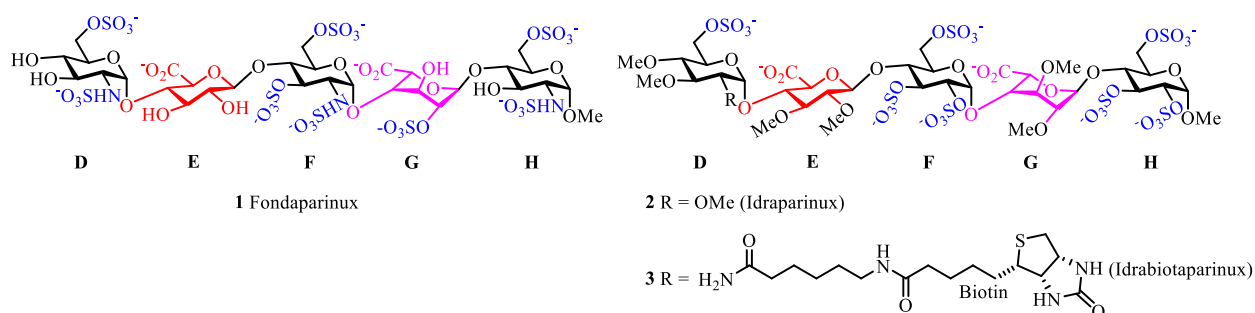


Fig. 4 (A) Synthetic anticoagulant Fondaparinux (Arixtra[®]) (1); pentasaccharide Idraparinux (2) & Idrabioparinux (3)

Idraparinux **2** is a non-glucosaminoglycan analogue pentasaccharide containing O-methylation and O-sulfation functionalities instead of N-sulfations and free hydroxyls of fondaparinux. The pentasaccharide was modified by replacing three alternative D-glucosamine units with neutral D-glucose thus simplifying the molecule in terms of its synthetic complexity. The modified

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structure having -OMe instead of free hydroxyls was shown to have higher anti-Xa activity ($K_d = 1.4 \pm 0.3$ nM) and longer half life (5 days during trial) compared to the pentasaccharide fondaparinux. It is believed that the presence of -OMe increases the binding capacity through hydrophobic interactions with AT-III amino acids. Additionally, the modification at 2-O of Iduronic acid unit from charged O-sulfate group to neutral -OMe allows the IdoA to attain 2S_0 conformation thus increases the anticoagulant activity. The presence of extra 3-O-sulfate of reducing end glucose unit was also a critical functionality to obtain the higher binding capacity via charge interaction. The molecule was developed into phase-III clinical trial for the treatment of patients with arterial fibrillation and venous thromboembolic events (VTE). The increased half-life period made the treatment easier as once a week administration of idraparinix compared to the LMWH's and fondaparinux which required regular doses. However, the longer anticoagulant effect and lack of neutralizing agents was proved as a double-edge sword and resulted in major bleeding complications in elderly patients and those with renal impairment during long time treatment (more than 6 months). Further progress in view of improving the safety of Idraparinix, the pentasaccharide was functionalised with a biotin moiety at the C-2 of non-reducing end glucose unit and termed as Idrabiotaparinix **3**. Initial studies have demonstrated that the anticoagulant activity of Idrabiotaparinix can be neutralised by avidin injection in case of overdose or major bleeding complications. However, the molecule is still under clinical trials and the approval of molecule for clinical practice is subjected to the safety of avidin use which needs to be injected subcutaneously to remove the molecule from patient's body.⁵⁵⁻⁵⁷

New antidotes are emerging in heparin based anticoagulant therapies to make the treatment safe. Recently, in 2018, FDA approved "protamine" a recombinant protein mixture with molecular weight below 5KDa as an anticoagulant-reversal agent in case of severe complications using heparin based anticoagulants in ACV treatment. Furthermore, many antidotes are being investigated including small molecules, cationic polymers, and cationic peptides for clinical uses.⁵⁸⁻⁶¹

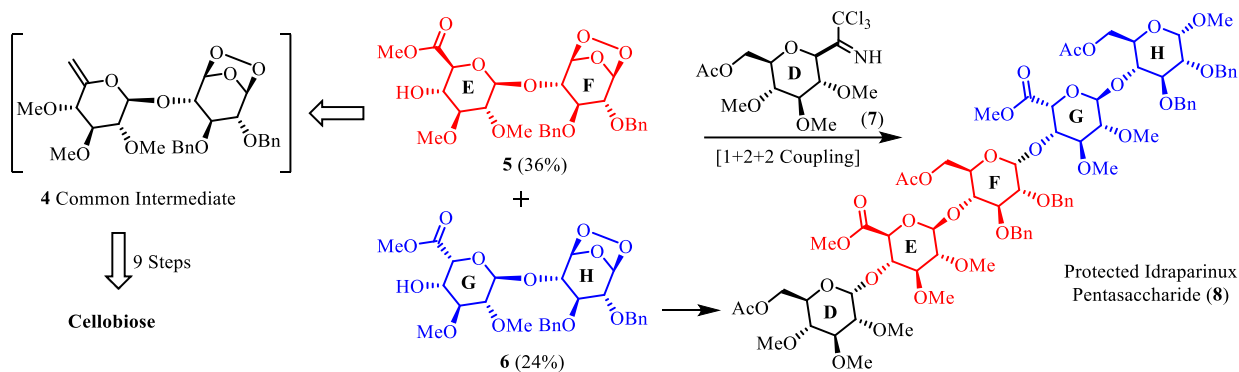
2.4 State of the art in Idraparinux synthesis

Despite simplified structure, the synthesis of Idraparinux is still a challenging task on accounts of stereoselective glycosidic linkages with regio-defined *O*-sulfations and *O*-methylations. The molecule contains the synthetically challenging and rare sugar iduronic acid thus difficulties in obtaining the L-idosyl building block is also the formidable task as it requires extrajudicial work. To date, five synthetic protocols are reported for Idraparinux. The first complete synthesis was reported by Overklist and co-workers in 1994.⁶² Fifteen years later, Yu and co-workers reported the modified synthesis of Idraparinux in total 51 steps from D-glucose using the trichloroacetimidate donor in overall 4% yield.⁶³ Further development of Idraparinux synthesis was focused on decreasing the number of synthetic steps and process development for scalable and cost effective protocols.

2.4.1 Synthesis by Jacek Mlynarski and co-workers⁶⁴

After the long 51 steps synthesis of Idraparinux by Yu group in 2009, a novel, short route for the fully protected pentasaccharide Idraparinux **8** was developed in 2017 by Mlynarsky group. The protocol demonstrates the synthesis of EF-disaccharide fragment **5** and its C-5 epimerised GH-disaccharide **6** from a common intermediate which could be obtained from cellobiose in 9 steps. The key reaction in this protocol is an epimerisation of C-5 hydroxyl through a distereoselective hydroboration/oxidation of disaccharide alkene **4**. In depth, the disaccharide alkene **4** was treated with BH_3 in THF and then cleaved off with $\text{NaOH}/\text{H}_2\text{O}_2$ to obtain both Glcp and Idop derivatives in a ratio of 1.4:1, which were further oxidized to corresponding carboxylic acid derivatives using TEMPO/BAIB and subsequently, esterified as methyl esters to get desired disaccharides **5** (36%) and **6** (24%) respectively. The major highlight of this protocol is the tactical utilization of both these derivatives that allowed them to synthesize the protected pentasaccharide **8** in 32 steps comprising 23 linear steps. The methodology uses the trichloroacetimidate donor chemistry to assemble those building blocks. The pentasaccharide was synthesized using [1+2+2] glycosidation strategy where the DEF trisaccharide was synthesized by coupling building block **7** and EF disaccharide acceptor **5** using TMSOTf at $-20\text{ }^\circ\text{C}$ as 7:1 ($\alpha:\beta$) anomeric mixture. The resulting trisaccharide upon functional group transformations converted into the trisaccharide donor that was coupled with GH-disaccharide acceptor **6** to offer the protected pentasaccharide in overall 1.7% yield.

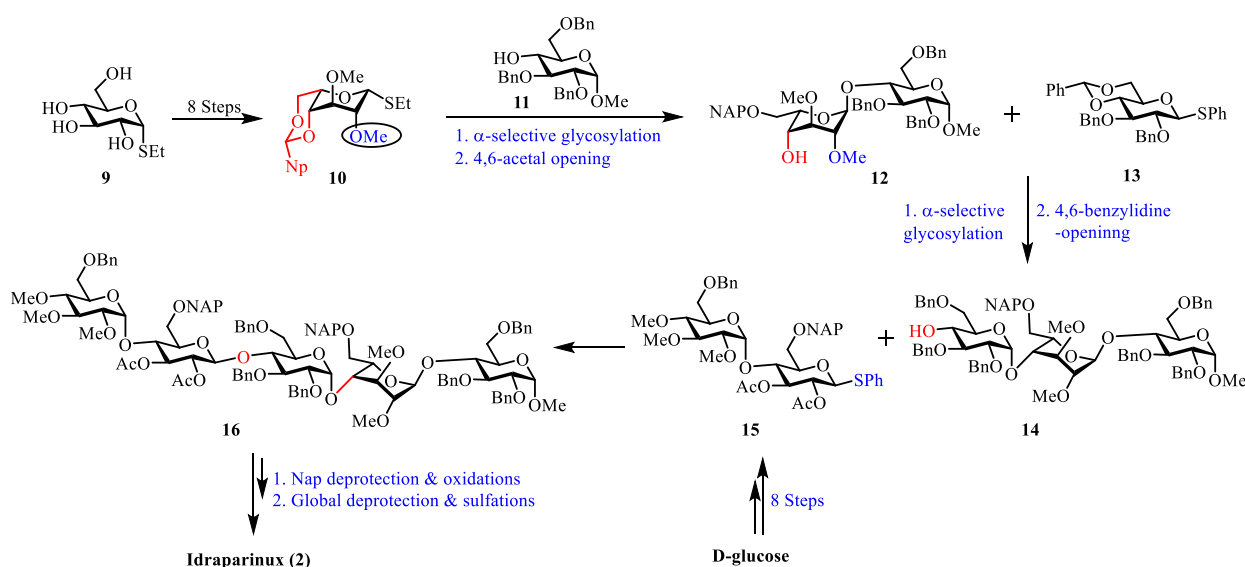
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Scheme 1 Mlynarski group's approach for protected Idraparinux pentasaccharide

The use of cellobiose for both EF and GH disaccharides significantly reduced the number of steps to obtain the pentasaccharide and hence the strategy developed was the shortest synthetic route. However, further development of a process for Idraparinux is still required due to the number of steps involved in spite of the use of cellobiose.

2.4.2 Synthesis by Aniko Borbas and co-workers⁶⁵

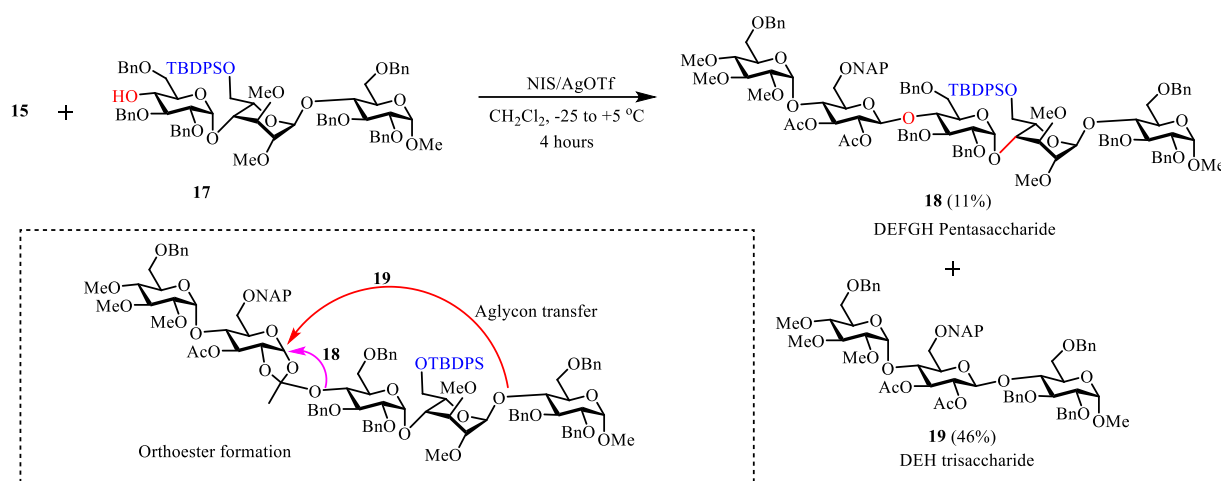


Scheme 2 Synthesis of Idraparinux applying 2-O-Methyl-4,6-O-arylmethylene thioidoside for 1,2-*trans*- α -selective glycosidation

In 2018, another short synthetic route was developed starting from D-glucose and methyl α -D-glucopyranoside. The synthesis highlights the use of 4,6-cyclic-acetal-protected L-idosyl

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thioethyl glycoside **10** as donor to selectively construct 1,2-*trans*- α -glycosidic linkage of GH disaccharide **12** that has a C-2 non-participating group. It is claimed that exclusive α -selectivity was obtained because of the steric hindrance of C-2 protecting group and benzylidene acetal. The pentasaccharide **16** was synthesized in [2+1+2] coupling strategy, activating the thioglycosides using NIS/AgOTf or NIS/TfOH. In the assembly of pentasaccharide, the benzylidene protected thioglycoside **13** was coupled with GH disaccharide acceptor **12** to effectively utilize the 4,6-*O*-benzylidene ring for the construction α -glycosidic linkage and then opened to access FGH trisaccharide acceptor **14**. Finally, coupling of disaccharide thioglycoside **15** with acceptor **14** under NIS/TfOH promoted glycosidation offered pentasaccharide **16** in 70% yield. In the synthesis of Idraparinux one challenge is to deal with the acid functionality of GlcA and IdoA unit which are known to decrease the reactivity of building blocks and are more prone to undergo elimination under basic condition. Hence the authors have strategically incorporated the surrogate of GlcA and IdoA in pentasaccharide and performed the late stage oxidation. However, the developed synthetic route still required 38 steps with compromised yields during glycosidations.



Scheme 3 Effect of remote protecting group on glycosidation

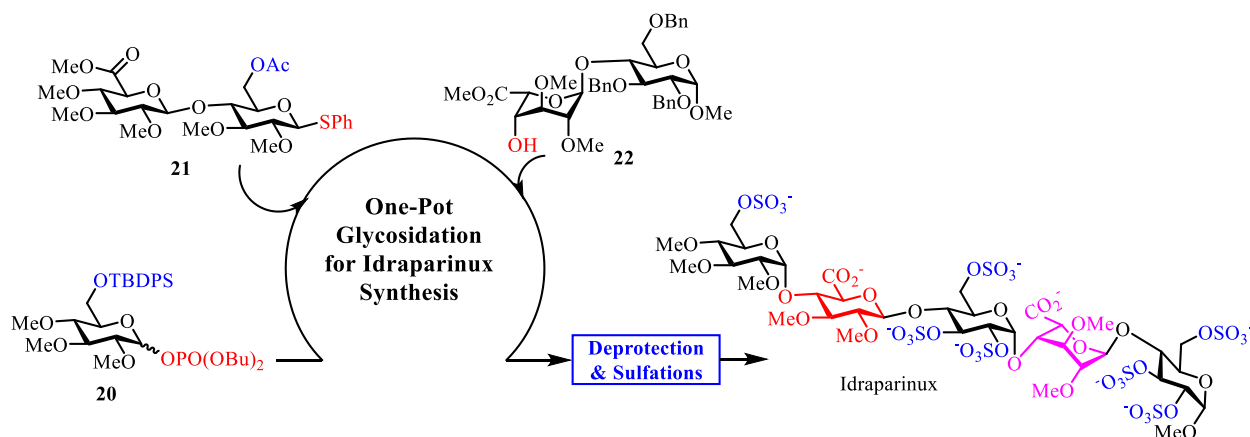
Furthermore, it is interesting to note that during the synthesis, an aglycon transferred DEH trisaccharide **19** (46%) was noticed along with their initially hypothesized orthogonally protected pentasaccharide **18** (11%). The major reason was attributed to steric and electronic properties of remote protecting groups TBDPS-, Nap- and activator NIS/AgOTf which they believed promoted the orthoester formation and then aglycon transfer. Therefore, the nature of protecting

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groups and choice of glycosidation conditions are also very much crucial for the oligosaccharide synthesis.

2.4.3 One-pot synthesis of Idraparinux by Wong group⁶⁶

Recently, a highly efficient, one-pot synthesis of Idraparinux pentasaccharide using orthogonal activation of glycosyl donors is reported; wherein, the modular assembly of building blocks was achieved in [1+2+2] coupling strategy. The glycosyl phosphate donor protected with bulky C-6-*O*-*t*-butyldiphenylsilyl ether **20** was coupled with D-glucuronic acid containing disaccharide thioglycoside **21** to obtain DEF trisaccharide thioglycoside using stoichiometric quantity of TMSOTf as promoter at -45 °C. Further, the addition of iduronic acid containing disaccharide acceptor **22** and NIS/TfOH at the same temperature furnished the required pentasaccharide in overall 70% yield. Later, the pentasaccharide was subjected to the deprotection of silyl ether, esters and then hydrogenolysis under H₂/Pd-C conditions for global deprotection enabled synthesis of the pentasaccharide which under sulfation shall yield the Idraparinux.



Scheme 4 One-pot assembly of building blocks for Idraparinux

Though the synthesis of pentasaccharide was done with the one-pot assembly of building blocks, the synthetic route took 38 steps to complete Idraparinux. Another important aspect to notice is that, authors have used highly expensive cellobiose as one of starting material for EF disaccharide synthesis hence it is not cost effective. Furthermore, the synthetic strategy is based on the utilization of two different glycosidation strategies that requires preparation of glycosyl donors separately. Hence the development of alternative, efficient protocol that is scalable and cost effective is still in demand.

2.5 Present work

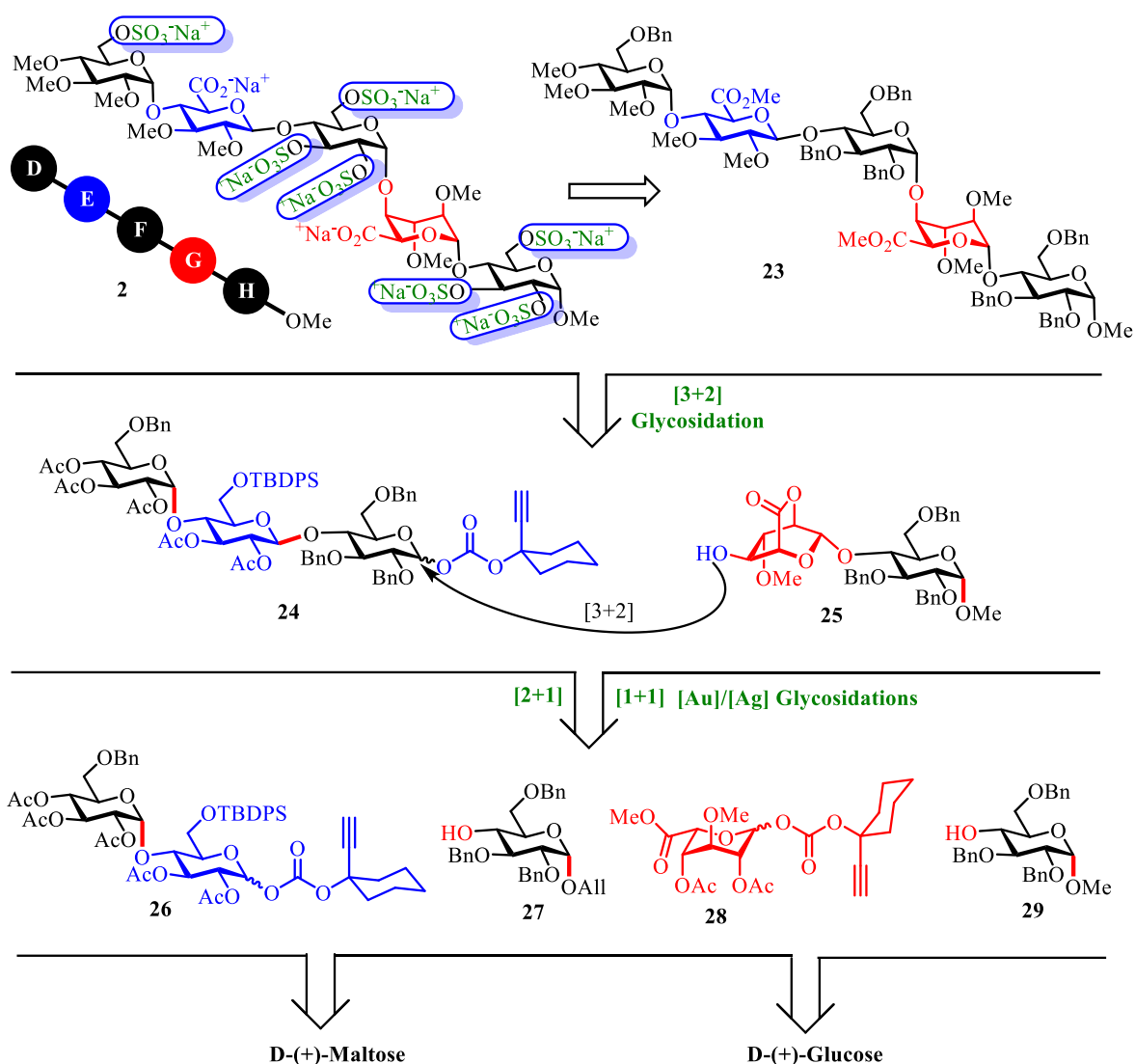
The foregoing discussion clearly shows the increasing importance of LMW heparin-based anticoagulants and the risk of contamination from animal sources. The synthetic heparin based anticoagulants like Fondaparinux (Aritra[®]), Idraparinux and Idrabiotaparinux have emerged as safe alternatives to the LMWH's which are currently utilized in clinics. Thus in the past two decades, the development of novel and efficient synthetic protocol for these molecules was at the top in synthetic carbohydrates community.⁵⁴ For example, the report from Yu group demonstrates the synthetic protocol using modular assembly of thioglycosides in total 51 steps. Another report from Wong and co-workers developed the one pot synthetic protocol based on orthogonal activation of glycosyl donors.⁶⁶ In a similar direction, very recently we have developed a novel, efficient protocol based on modular assembly of building blocks using silver-assisted gold-catalyzed glycosidations. The synthetic protocol allows the access to Fondaparinux in total 41 steps (shortest route reported) from easily available D-glucose and D-glucosamine which is scalable up to a 10 gram scale in a pilot endeavor.⁶⁷ Thus in continuation with our interest towards synthesis of heparin based anticoagulants by exploiting the silver-assisted gold-catalyzed glycosidation, the synthesis of second-generation anticoagulant Idraparinux was targeted.

2.5.1 Retrosynthesis of Idraparinux

Knowing the state of the art applied for the synthesis of anticoagulant Idraparinux, a new retrosynthetic scheme was designed starting from novel building blocks. The major challenges in pentasaccharide Idraparinux synthesis are: (i) the construction of 1,2-*cis* glycosidic linkage as there is no general protocol to exclusively access such type of linkage; (ii) the molecule contains regio-defined *O*-sulfations, and *O*-methylations at various positions hence a careful design of protection and deprotection strategy is required; and (iii) synthesis of IdoA building block which remained as major challenge in anticoagulants GAGs including Fondaparinux and various heparin based clinically important molecules. The thoughtful analysis of pentasaccharide Idraparinux **2** and disconnection between monosaccharide units led to D-glucose and D-maltose as new set of starting materials. Idraparinux **2** was envisioned from orthogonally protected pentasaccharide **23** which can be obtained from [3+2] coupling of building block **24** and **25**. The trisaccharide can be synthesized from [2+1] coupling of **26** and **27** whereas [1+1] coupling

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between monosaccharides **28** and **29** was hypothesized for disaccharide under silver assisted gold-catalyzed glycosidation condition. All these monosaccharide building blocks **26-29** can be synthesized from D-glucose using functional group transformations. However, we thoughtfully choose D-maltose as another starting material as it is easily available and very cheap (100g/2,992.0 INR) when compared to the expensive cellobiose (100g/29,168.0 INR). Additionally, maltose is a disaccharide with an in-built α -glycosidic linkage hence the molecule was envisioned as suitable candidate for DE disaccharide unit having $\alpha(1\rightarrow4)$ linkage.

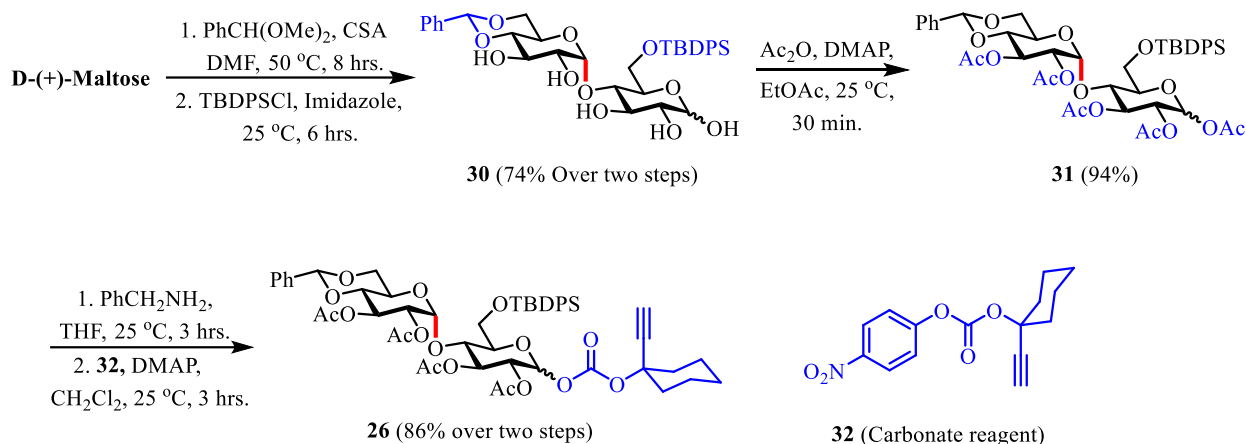


Scheme 5 Retro-synthetic analysis of pentasaccharide **Idraparinux(2)**

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2.5.2 Synthesis of DE disaccharide donor

Our synthetic endeavour started with the treatment of D-(+)-Maltose with benzaldehyde dimethylacetal in presence of catalytic amount of PTSA for regioselective protection of the non-reducing unit's C-4, C-6 hydroxyls as benzylidene acetal which then treated with 1.0 equivalents of TBDPSCl and 1.5 equivalents of imidazole to selectively protect C-6 hydroxyl as silyl ether to obtain compound **30** in 71% yield as anomeric mixture ($\alpha:\beta=1.2:1$). The thorough characterization using NMR spectroscopy was performed. In the ^1H NMR spectrum of compound **30**, the resonances at δ 7.85 – 7.22 (m, 15H) characteristic for three aromatic ring protons and δ 1.2 ppm (s, 9H) for the *tert*-butyl CH_3 's was observed. In the ^{13}C spectrum, the appearance two characteristic resonances at δ 100.1(β) & 96.0(α) ppm corresponds to two anomeric carbons of major isomer was identified along with characteristics δ 101.9 ppm resonance due to the benzylidene -CH.



Scheme 6 Synthesis of DE disaccharide carbonate donor

The compound **30** was then subjected to esterification of remaining free hydroxyls using Ac_2O /DMAP in ethyl acetate that offered compound **31** in 94% yield. Finally, the regioselective deacetylation of anomeric position was performed using benzylamine in THF to access hemiacetals, which upon treatment with carbonate reagent **32** and DMAP converted into DE disaccharide carbonate **26** in 86% yield (over two steps). The formation of desired disaccharide donor was confirmed through NMR analysis. In the ^1H spectrum of **26**, signals at δ 2.65 (s, 1H, -Alkyne CH), along with δ 1.92 – 1.85 (m, 2H), 1.64 – 1.49 (m, 4H), 1.41 – 1.25 (m, 2H) specific

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for cyclohexyl -CH₂'s were noticed. The presence of four acetyl moieties was confirmed by resonances of CH₃'s at δ 2.10 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H) and the resonance for *tert*-butyl CH₃'s was identified at δ 1.08 (s, 9H) ppm. Additionally, the resonances in the ¹³C NMR spectrum at δ 151.0 ppm characteristic for the carbonate carbonyl and two anomeric carbons at δ 96.8 & 92.4 ppm confirmed the desired disaccharide carbonate **26**.

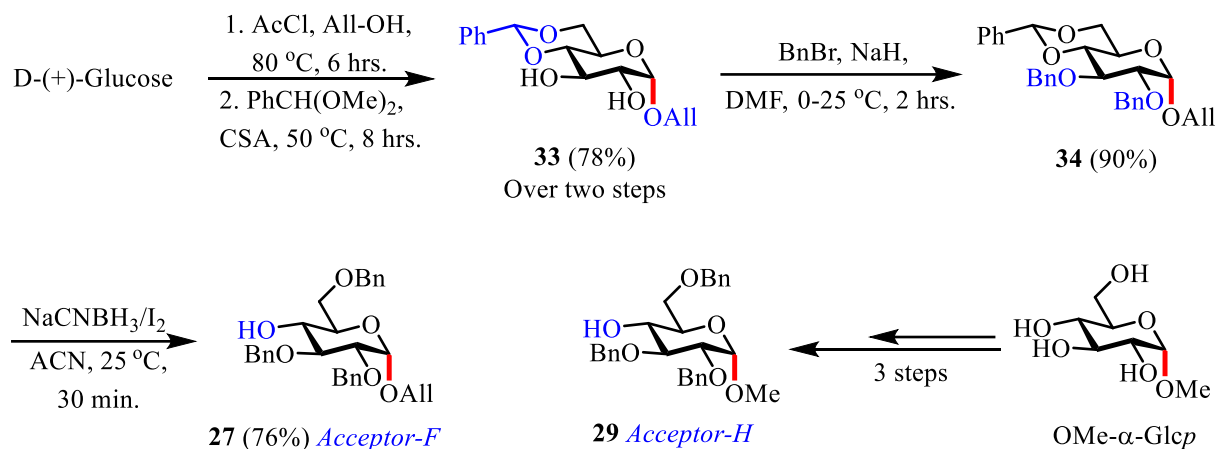
After the successful synthesis of **DE** disaccharide carbonate donor **26**, we turned our attention to the synthesis of monosaccharide building blocks **F** (**27**) and **H** (**29**). According to our retrosynthesis plan, building blocks **F** and **H** were required as acceptors to couple with building blocks **DE** and **G** to obtain **DEF** trisaccharide and **GH** disaccharide respectively. Knowing the similarity in monosaccharide building blocks and required protecting groups as benzyl ether the common synthetic route was developed.

2.5.3 Synthesis of building blocks **F** and **H**

The synthesis of building block **27** commenced with boiling of D-glucose with 1.5 equivalents of acetyl chloride in allyl alcohol at 80 °C to mask the anomeric hydroxyl as *O*-allyl glycoside which upon treatment with benzylidene dimethylacetal in presence of catalytic *p*-toluenesulfonic acid (PTSA) afforded **33** in 78% yield as anomeric mixture (α : β =4:1). The mixture was separated using column chromatography and major isomer was characterized with the help of NMR spectroscopy. In the ¹H NMR spectrum of compound **33**, characteristic peaks at δ 7.52 – 7.31 (m, 5H, -Aromatic), 5.96 – 5.85 (m, 1H, -Allyl -CH), 4.87 (d, *J*= 3.9 Hz, 1H, -anomeric proton) and in the ¹³C NMR spectrum, resonances at δ 118.3 (-Allyl CH₂) and δ 98.0(α) ppm (anomeric carbon) were seen. The other resonances observed in both spectra were in complete accordance with the proposed structure. After the thorough characterization of **33**, the C-2, C-3 hydroxyls were protected as benzyl ethers using benzyl bromide (BnBr) and sodium hydride (NaH) to obtain compound **34** in 90%. Finally, the regioselective opening of benzylidene using NaCNBH₃/I₂ in acetonitrile was performed to get C-6 *O*-benzyl and C-4 hydroxyl compound **27** which is the required building block **F** acceptor. In the ¹H NMR spectrum of **27**, characteristic peaks at δ 7.40 – 7.29 (m, 15H, Aromatics), 6.04 – 5.91 (m, 1H, Allyl -CH), 4.87 (d, *J* = 3.5 Hz, 1H, H-1) were noticed. Further, the resonances in the ¹³C NMR spectrum at δ 138.9, 138.2, 138.1 ppm for quaternary carbons of three aromatic rings, δ 118.3 ppm for allylic -CH₂ and

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δ 95.7(α) ppm for C-1 were identified. Additionally, 2D NMR experiments confirmed carbons and protons as per the assigned structure. In the ^1H - ^1H COSY spectrum, the correlation between C4-OH and C4-H was seen which confirmed the presence of hydroxyl at C-4 position in compound **27** (relation shown in COSY spectrum).



Scheme 7 Synthesis of monosaccharide building block F & H acceptor

Residue	Spectral Analysis	Chemical Shifts(δ in ppm)					
		C1	C2	C3	C4	C5	C6 (CH ₂)
Compound 27	^1H	4.87 (d) $J = 3.5$ Hz	3.57 (dd) $J = 9.6, 3.6$ Hz	3.86 (t) $J = 9.2$ Hz	3.65 (t) $J = 9.3$ Hz	3.83 -3.77 (m)	3.71 (d) $J = 3.9$ Hz
	^{13}C	95.7	81.6	79.7	70.8	70.2	69.5

Table. 1 Assignment of resonance for protons and carbons of compound 27

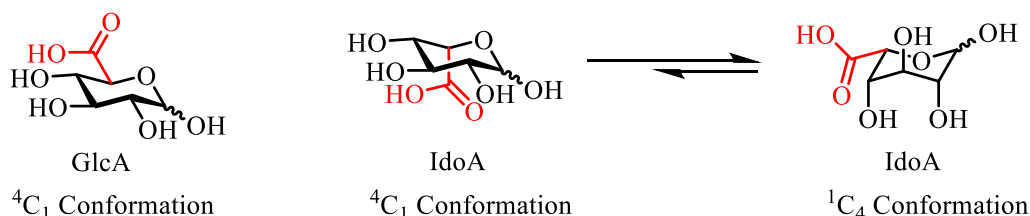
After the successful synthesis of acceptor F, another functionally similar building block H was targeted. Commercially available methyl α -D-glucopyranoside was treated with 1.0 equivalents of benzylidene dimethylacetal in the presence of catalytic amount of PTSA to selectively mask C-4, C-6 hydroxyls as benzylidene acetal. Further, acceptor **29**⁷¹ was synthesized following the similar functional group transformations as used for **27** with 58% yield in four steps.

Successful synthesis of building blocks **26**, **27** and **29** allowed us to look at the more challenging Iduronic acid building block. Structurally the iduronic acid (IdoA) is the C5 epimer of glucuronic acid (GlcA) with axial stereochemistry in $^4\text{C}_1$ conformation. In the $^4\text{C}_1$ conformation, the diaxial interaction of acid group with ring protons increases, thus forces the molecule to adopt more

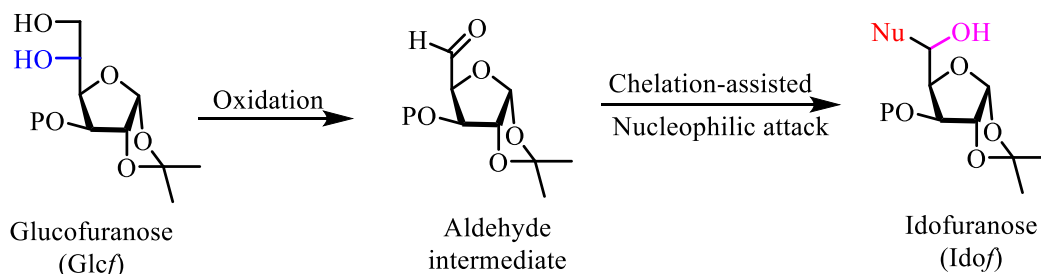
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stable 1C_4 conformation wherein the acid group occupies equatorial stereochemistry. As IdoA is the C-5 epimer of GlcA, the cheap and easily available D-glucose has been effectively utilized by many groups and epimerized at the C-5 positions.⁶⁸⁻⁶⁹

A. Structure of glucuronic and iduronic acid



B. Strategy for C5-OH inversion

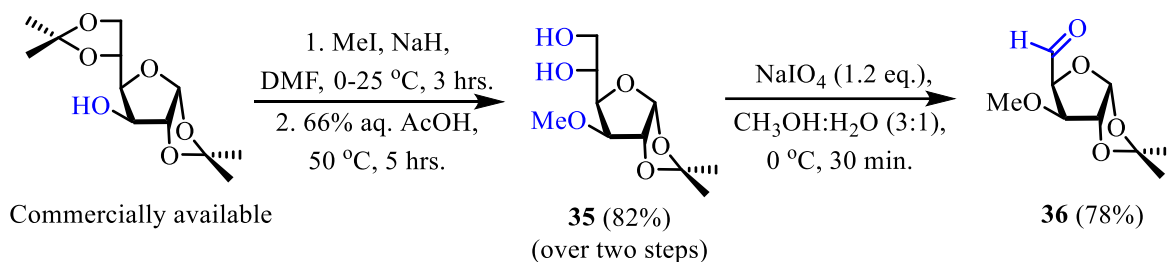


Scheme 8 A. Structure of uronic acids; B. Strategy for conversion of GlcF into Idof

2.5.4 Synthesis of building block G

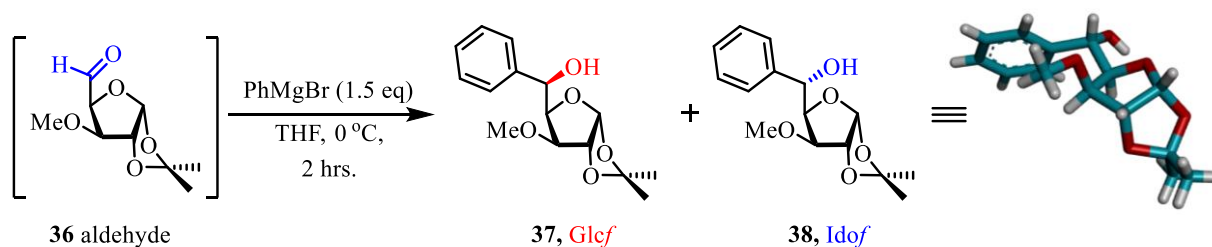
We envisioned that the idose can be synthesized from glucose by employing chelation assisted Grignard addition to the C-5-aldehyde which can be easily accessed from the commercially available diacetonide glucofuranoside. Accordingly, glucose diacetonide was cleanly transferred into its C-3 *O*-methyl ether using MeI/NaH in DMF which further upon treatment with 66% aq. acetic acid gave diol **35** in 82% yield (over two steps). In the 1H NMR spectrum of diol, characteristic resonances at δ 5.84 (d, J = 3.8 Hz, 1H, H-1), 3.41 (s, 3H, -OCH₃), 1.44 (s, 3H, -CH₃), 1.27 (s, 3H, CH₃) were assigned and those peaks in the ${}^{13}C$ spectrum at δ 105.1 (C-1), 57.9 (-OMe), 26.7 (-CH₃), 26.2 (-CH₃) ppm confirmed the structural homogeneity of diol. In continuation, the diol **35** was exposed to the NaIO₄ in 3:1 ratio of CH₃OH:H₂O for the oxidative cleavage to obtain aldehyde **36** in 78%.

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Scheme 9 Synthesis of aldehyde intermediate

The phenyl was identified as a surrogate for the carboxylic acid as phenyl group can be oxidized to carboxylic acid at a later stage. Hence, the aldehyde **36** was subjected to chelation-assisted nucleophilic addition using freshly prepared PhMgBr in THF under cooling conditions. Unfortunately, the transformation has resulted in a mixture of both **37** (Glc f) and **38** (Ido f) in the ratio of 1:12 that could be confirmed by crude NMR analysis with 87% yield. Thus to obtain the isomers in pure form, several attempts were made using different solvent systems however the mixture was chromatographically inseparable. Interestingly, it is found that one of isomers was crystallizing out from the mixture; therefore, the crude product was dissolved in CH₂Cl₂:hexane (2:1) and allowed to slow evaporation for 15 h. After formation of white needle like crystals, the solution was decanted and pure crystal were obtained which upon single crystal X-ray analysis confirmed the desired isomer as **38** (Ido f) (ORTEP diagram attached).

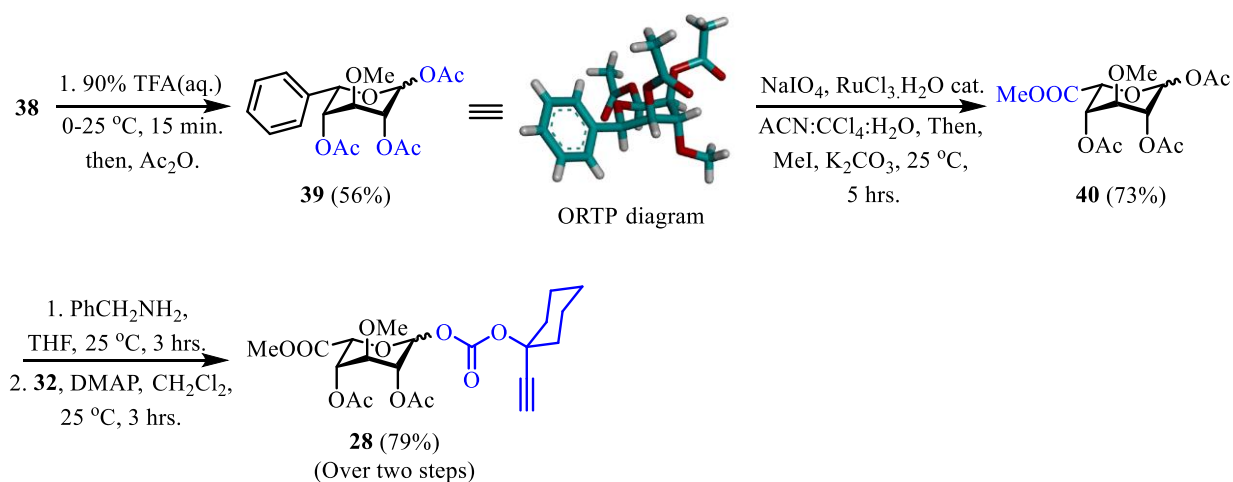


Scheme 10 Chelation-assisted nucleophilic attack of phenyl (Grignard reaction)

Once the idofuranoside **38** was obtained in pure and sufficient quantity, locking of the idofuranose into idopyranose ring was attempted. Idofuranoside **38** was treated with aqueous 90% TFA to deprotect the 1,2-acetonide to form hemiacetals, which was further subjected to esterification using acetic anhydride to obtain the Idose locked pyranose conformation as in **39** as an α/β -anomeric mixture in 56% isolated yield. During the chromatographic purification, β -isomer was obtained in pure form and the identity of compound was confirmed by NMR spectral

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analysis. In the ^1H NMR spectrum, the resonating peaks at δ 7.39 – 7.25 (m, 5H, Aromatic), 6.18 (d, J = 1.8 Hz, H-1), 3.58 (s, 3H, $-\text{OCH}_3$), and three singlets at δ 2.17, 2.13 & 1.87 ppm for acetyl CH_3 's were noticed. Additionally, the up-field shift of anomeric carbon from δ 105.2 ppm (furanose) to 90.7 ppm was noticed in the ^{13}C NMR spectrum that indicate the locking of aldose in pyranose conformation. Additionally, the single crystal X-ray structure analysis showed the energetically stable $^4\text{C}_1$ conformation where phenyl group occupied the equatorial position (see ORTEP diagram in scheme 11). Further the phenyl moiety was oxidized using catalytic $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ and 3.0 equivalents of NaIO_4 in a ternary solvent system $\text{CH}_3\text{CN}:\text{CCl}_4:\text{H}_2\text{O}$ to corresponding carboxylic acid functionality and protected as its methyl ester using $\text{MeI}/\text{K}_2\text{CO}_3$ in DMF to furnish **40** in 73% isolated yield. In the ^1H NMR spectrum of compound **40**, disappearance of aromatic protons and the appearance of a new singlet at δ 3.79 ppm characteristics for $-\text{COOCH}_3$ along with other resonances in complete agreement with proposed structure were noticed. Finally, the compound **40** was subjected for regioselective anomeric deacetylation using benzylamine in THF for hemiacetal formation which was further extrapolated to desired IdoA carbonate **28** using ethynylcyclohexyl(4-nitrophenol) carbonate **32** and DMAP in CH_2Cl_2 at room temperature. The thorough structural analysis was done wherein the resonances in the ^1H NMR spectrum at δ 5.91 (d, J = 1.8 Hz, 1H, H-1), 3.78 (s, 3H, COOCH_3), 2.13 (s, 3H, COCH_3), 1.89 (s, 3H, COCH_3), 1.89 (s, 3H, COCH_3), and δ 1.91 – 1.85 (m, 2H), 1.63 – 1.50 (m, 4H), 1.36 – 1.30 (m, 2H) were identified.



Scheme 11 Synthesis of idopyranose carbonate donor

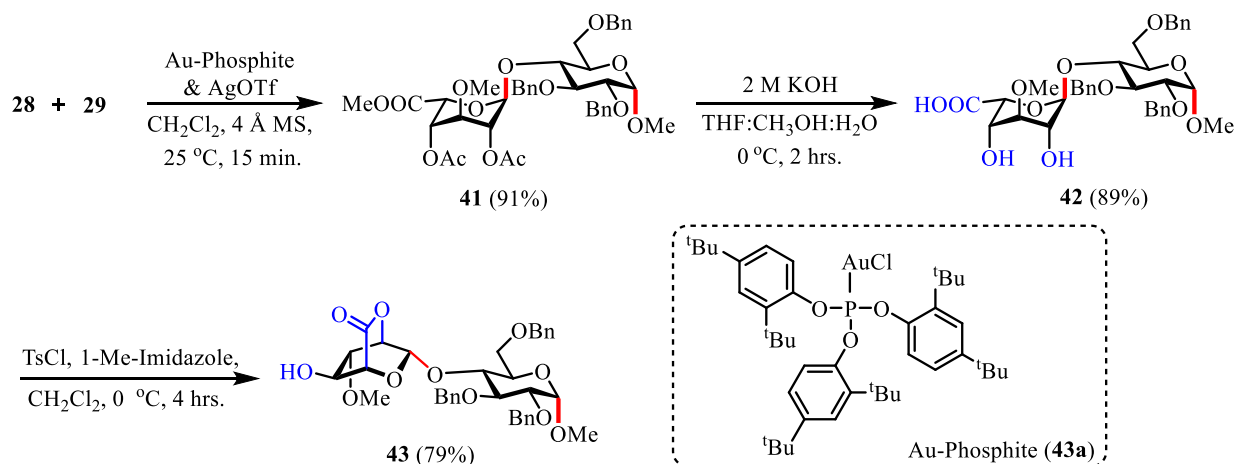
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Additionally, ^{13}C NMR spectrum showed three ester carbonyls for major isomer, seen at δ 170.1, 169.9, 167.5 ppm along with characteristic carbonate carbonyl at δ 150.9 ppm, and anomeric carbon at δ 92.7 ppm confirmed the compound **28**.

The successful synthesis of required building blocks viz. DE disaccharide carbonate **26**, monosaccharide acceptors **27** & **29** (F & H), and iduronate carbonate **28** (G unit) in sufficient amounts. The pentasaccharide DEFGH was envisaged by the modular assembly of these building blocks in [2+1+2] coupling strategy using silver assisted gold-catalyzed glycosidations.

2.5.5 Synthesis of GH disaccharide acceptor

Carbonate donor **28** and acceptor **29** were dissolved in CH_2Cl_2 and stirred in presence of 10 mol% each gold-phosphite (**43a**) and silver triflate for 15 minutes to afford the disaccharide **41** in 91% yield. The presence of C-2 acetate in the glycosyl donor allowed the effective construction of 1,2-*trans* glycosidic linkage. In the ^1H spectrum of disaccharide **41**, characteristic resonances at δ 7.38 – 7.26 (m, 15H, Aromatic), 5.15 (s, 1H, H-1'), 4.59 (s, 1H, H-1), 3.55 (s, 3H, COOCH_3), 3.39 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 2.03 (s, 3H, COCH_3), 2.03 (s, 3H, COCH_3) were noticed. The stereochemistry of the glycosidic linkage was confirmed due to the characteristic resonances for anomeric carbons at δ 98.1(α) & 97.1(α) ppm in the ^{13}C spectrum along with the rest of peaks in complete agreement with proposed structure. Further, the HRMS analysis showed the molecular ion peak $[\text{M}+\text{Na}^+]$ m/z 775.2993 matching with that of calculated m/z of 775.2988 Da.



Scheme 12 Synthesis of GH disaccharide acceptor

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Further glycosidation at the C-4 position is need on this compound **41**. To do so, locking of the conformation between C-2 hydroxyl and C-6 carboxylic acid was envisioned so that additional steps to protect C2-OH will not be necessary. Additionally, the effect of such type of bi-cyclic lactones in sugar acceptors have been investigated earlier and found to decrease the reactivity of systems therefore slows down the rate of reaction and helps in obtaining 1,2-*cis*-glycosidic linkages.⁷⁰ Thus compound **41** was subjected to saponification using 2M KOH in ternary mixture of THF:CH₃OH:H₂O (2:1:1) at 0 °C to offer white solid disaccharide acid **42** in 89% yield. The disappearance of resonances from δ 3.55 (s, 3H, COOCH₃), 2.03 (s, 3H, COCH₃), 2.03 (s, 3H, COCH₃) in the proton NMR spectrum and broad stretching frequency in IR at 3600 – 3250 & 2900-2600 cm⁻¹ characteristic of the presence of free hydroxyls and acid functionalities confirmed the complete saponification. Further, disaccharide acid **42** was treated with tosyl chloride and 1-methyl imidazole in CH₂Cl₂ to access disaccharide lactone **43** in 79% isolated yield. The complete structural analysis was done using 2D NMR experiments and all protons and carbons were assigned (Table 2).

Residue Ring		Spectral Analysis	Chemical Shifts (ppm)						
			C1	C2	C3	C4	C5	C6	C6'
G	Ido-A	¹ H	5.16(s)	4.05(t)	3.36(m)	4.03(t)	3.97(dd)	--	--
		¹³ C	97.6	72.0	83.1	70.9	71.3	68.5	
H	Glc	¹ H	4.61(s)	3.53(t)	3.68(m)	3.80(t)	3.89(t)	3.66(m)	3.56(m)
		¹³ C	98.3	79.8	69.4	77.4	80.1	66.8	

Table. 2 Assignment of proton and carbon resonances of the compound 43

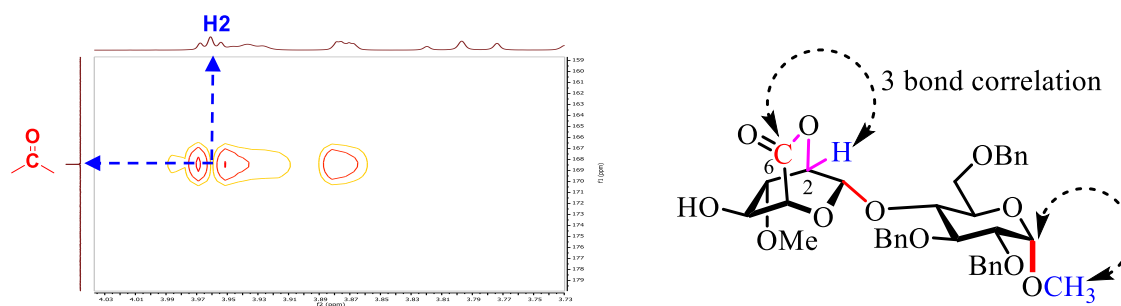


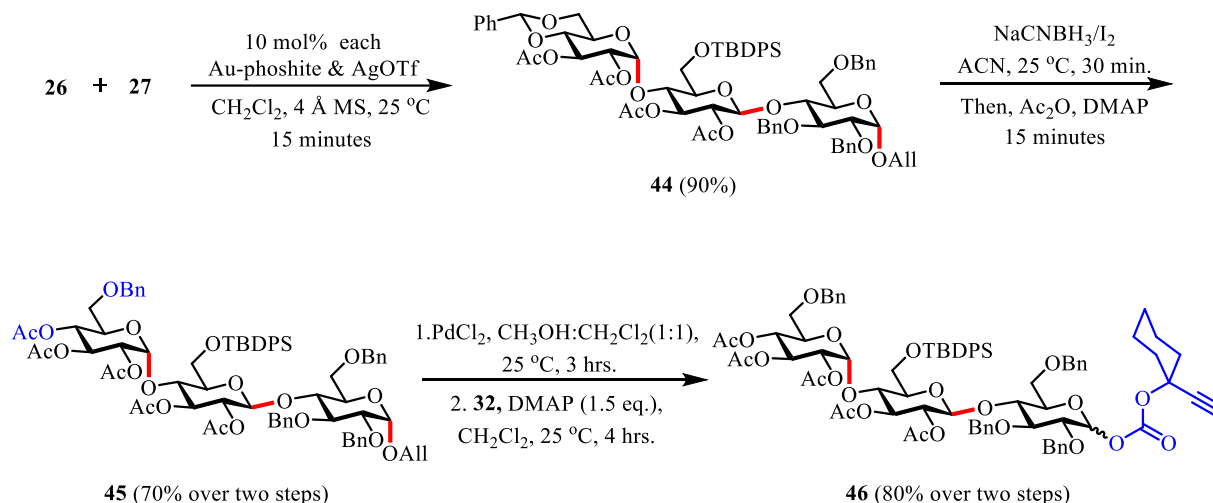
Fig. 5 Showing three bond correlation between H-2 proton and C-6 carbonyl carbon

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The regio-specific lactonization was confirmed by analyzing the HMBC spectrum where three bond correlation between H-2 and C-6 carbonyl carbon was seen which possible only when lactone is formed between C-2 & C-6 positions.

2.5.6 Synthesis of DEF trisaccharide donor

Based on proposed coupling strategy, synthesis of DEF trisaccharide and its conversion into corresponding glycosyl donor *via* functional group transformations was attempted. The coupling reaction between DE disaccharide carbonate donor **26** and acceptor **27** in CH₂Cl₂ and 4 Å molecular sieves under silver assisted gold-catalyzed conditions was performed. The anchimeric assistance from C-2 acetate during the glycosidation allowed the formation of complete β-selective linkage to obtain DEF trisaccharide in 90% isolated yield.



Scheme 13 Synthesis of DEF trisaccharide carbonate donor

In the ¹H NMR spectrum of trisaccharide **44**, the three anomeric protons were identified at δ 5.22 (d, *J* = 7.3 Hz, 1H, 1,2-*trans*), 4.80 (d, *J* = 3.7 Hz, 1H, 1,2-*cis*), and 4.73 (s, 1H, 1,2-*cis*) ppm. Additionally, the presence of resonances characteristic for allylic –CH at δ 5.99 – 5.96 (m, 1H) and four singlets at δ 2.09 (s, 3H), 2.04 (s, 3H), 1.92 (s, 3H), 1.92 (s, 3H) for COCH₃'s & 1.05 (s, 9H) ppm for *tert*-butyl of CH₃'s were observed. Further, the presence of benzylidene and stereochemistry of three glycosidic linkages was also confirmed by ¹³C NMR spectrum wherein peaks at δ 101.6 (benzylidene -CH) and δ 99.3(β), 96.8(α), 96.1(α) ppm were identified along with whole spectrum in complete agreement with the proposed structure **44**. The HMRS

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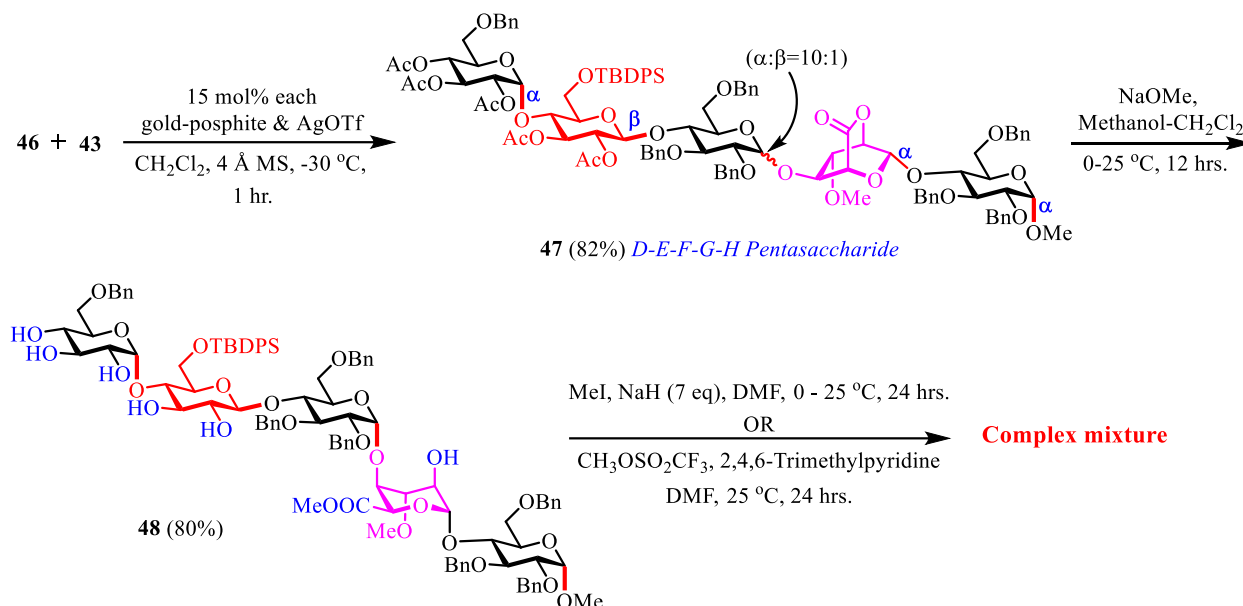
analysis had shown the molecular ion peak of m/z at 1131.5220 Da that exactly matched with that of calculated m/z of 1131.5223 Da. After the confirmation of desired trisaccharide, the trisaccharide **44** was subjected to reductive opening of the benzylidene ring using NaCNBH_3 and molecular iodine (I_2) in anhydrous acetonitrile to obtain C-6-*O*-benzyl and C-4 hydroxyl which upon addition of acetic anhydride, pyridine afforded compound **45** in 70% yield. In the next step, methanolysis of anomeric *O*-allyl using 15mol% PdCl_2 in equimolar mixture of $\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$ was performed to access the hemiacetal which further upon treatment with ethynylcyclohexyl(4-nitrophenol) carbonate **32** and 1.5 equivalents of DMAP in CH_2Cl_2 for 4 hours at 25 °C offered DEF trisaccharide carbonate **46** in 80% yield (over two steps). In the ^1H NMR spectrum, three anomeric proton resonances appeared at δ 5.37 (d, $J = 7.8$ Hz, 1H, H-1), 5.22 (s, 1H, H-1'), and 4.45 (d, $J = 3.1$ Hz, 1H, H-1'') ppm along with peaks at δ 2.53 (s, 1H, alkyne-CH), 1.83 – 1.77 (m, 2H), 1.57 – 1.43 (m, 4H), 1.37 – 1.10 (m, 2H) ppm characteristic for cyclohexyl $-\text{CH}_2$'s were identified. Further the carbonate carbonyl resonances at δ 151.4 ppm and three anomeric carbons at δ 99.0(β), 97.4(α), 95.8(α) ppm were observed in the ^{13}C NMR spectrum. The rest of the resonances were in complete agreement with the proposed structure of compound **46**.

2.5.7 Synthesis of pentasaccharide

Finally, the [3+2] coupling under silver-assisted gold-catalyzed conditions was planned to obtain pentasaccharide. The construction of challenging 1,2-*cis* glycosidic linkage was foreseen by lowering the reaction temperature which was found to increase the α -selectivity evident from our previous optimizations.⁶⁷ Thus, the glycosidation between DEF trisaccharide carbonate **46** and GH disaccharide acceptor **43** was promoted using 15mol% of each gold-phosphite (**43a**) and silver triflate in CH_2Cl_2 and 4 Å molecular sieves. The reaction was carried out at -30 °C to control the reactivity and enhance the α -selectivity during the reaction. It is important to mention that the reaction was found to be slower; however, excellent selectivity ($\alpha:\beta=10:1$) was observed for pentasaccharide **47**. In the ^1H NMR spectrum of chromatographically purified major isomer, five anomeric protons were resonanced at δ 5.32 (d, $J = 4.0$ Hz, 1H, 1,2-*cis*), 5.26 (s, 1H, 1,2-*cis*), 4.67 (s, 1H, 1,2-*cis*), 4.62 (d, $J = 5.8$ Hz, 1,2-*trans*), 4.35 (d, $J = 8.2$ Hz, 1H, 1,2-*trans*) ppm. The ^{13}C NMR spectrum showed five anomeric carbons at δ 100.1 (1,2-*trans*), 98.9 (1,2-*trans*), 98.4 (1,2-*cis*), 98.4 (1,2-*cis*) & 95.9 (1,2-*cis*) ppm along with all other peculiar resonances for the pentasaccharide and thus, confirming compound **47**. Additionally, the stereochemistry of

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the glycosidic linkages was also identified by performing coupled-HSQC experiments to visualize the J_{C-H} coupling of anomeric carbons. In the spectrum, The J_{C-H} coupling >170 Hz characteristics for α -glycosidic linkage were seen for four anomeric carbon resonances along with J_{C-H} 168.0 Hz (<170) because of one β -linkage.



Scheme 14 Synthesis of orthogonally protected pentasaccharide Idraparinux

Having pentasaccharide **47** in hand, the functional group transformations started to reach the target molecule Idraparinux. The unmasking of ester-protected hydroxyls to functionalize it as required *O*-methyl ether was attempted prior to the silyl ether deprotection and its oxidation into acid functionality which may hamper the reactivity. Thus, pentasaccharide **47** was stirred in an equimolar mixture of $CH_3OH:CH_2Cl_2$ and 3.0 equivalents of sodium methoxide to deprotect the acetates as well as the opening of lactone as methyl ester to unmask the C-2 hydroxyl. In the 1H NMR spectrum of compound **48**, the characteristic singlets corresponding to acetate $-COCH_3$ were disappeared along with simultaneous appearance of new resonances at δ 3.32 (s, 3H) because of methyl ester and broad singlets for free hydroxyls. Further, in the next step, the compound **48** was forwarded for *O*-methylation using MeI/NaH in DMF; however, a complex mixture was formed which was persistent even after 24 hours of stirring. The MALDI-TOF analysis revealed the complex mixture as partially *O*-methylated derivatives therefore the excess of NaH and methyl iodide was added to drive the reaction forward. However, the harsh reaction

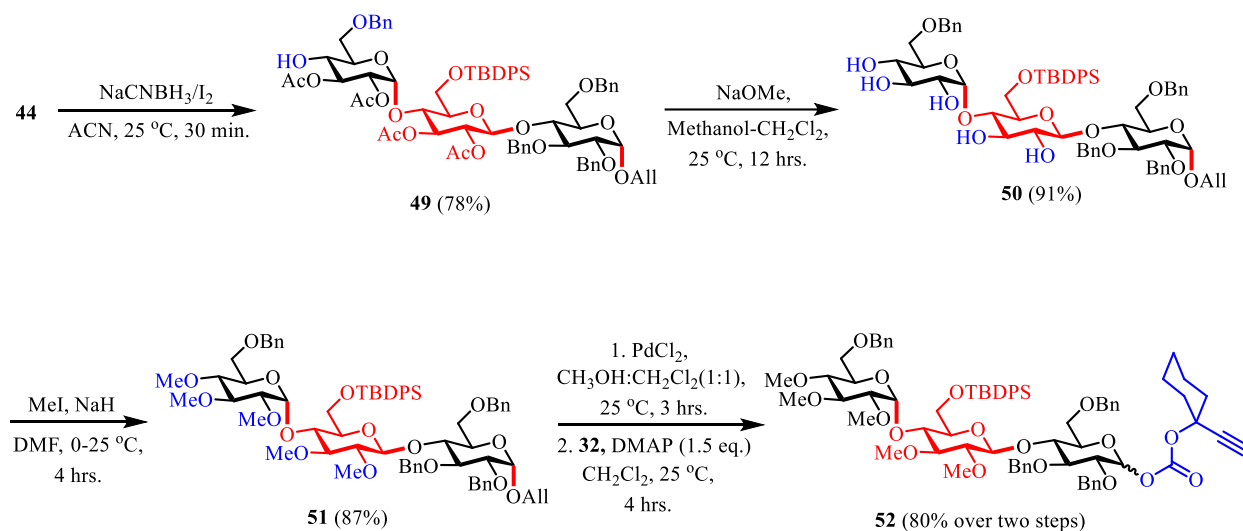
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condition compromised the silyl ether as well as methyl ester functionality and hence we could not get the desired product.

Thus in another set of reaction, the pentasaccharide **48** was treated with highly electrophilic methylating reagent methyl trifluoromethanesulfonate in the presence of hindered base 2,4,6-trimethylpyridine to access its *O*-methyl derivative. However, similar results were obtained with approx. 10% desired product formation. The variation in solvents and temperature could not give a promising increase in yield. Therefore, the formation of required methyl ethers was planned at the trisaccharide level to solve the problem encountered.

2.5.8 Synthesis of revised DEF trisaccharide carbonate

The DEF trisaccharide **44** was treated with NaCNBH₃ and molecular iodine (I₂) in ACN for reductive benzylidene opening to obtain compound **49** which upon treatment with NaOMe in an equimolar mixture of methanol-CH₂Cl₂ offered trisaccharide **50** in 91% isolated yield.



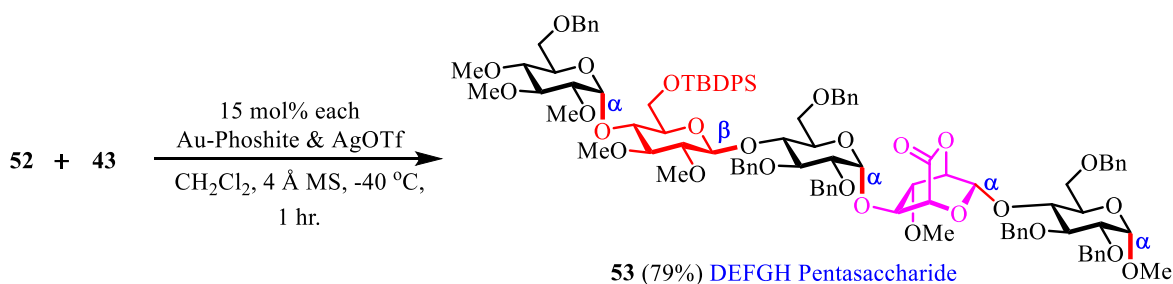
Scheme 15 Synthesis of revised DEF-trisaccharide carbonate donor

The disappearance of peculiar singlets for COCH₃ and the appearance of broad singlets characteristics for free hydroxyls in ¹H NMR with the rest of resonance peaks in complete agreement with compound **50** were seen. The free hydroxyl moiety was then converted into its methyl ether using MeI/NaH in DMF upon vigorous stirring for 4 hours at 25 °C. The ¹H NMR analysis of compound **51** showed five singlets at δ 3.65 (s, 3H), 3.58 (s, 3H), 3.55 (s, 3H), 3.51 (s, 3H) & 3.41 (s, 3H) characteristic for –OCH₃'s confirmed the proposed structure. Finally,

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anomeric *O*-allyl was cleaved off using catalytic amount of PdCl₂ as delineated above to access hemiacetals which were further upon treatment with ethynylcyclohexyl(4-nitrophenol) carbonate **32** and DMAP in CH₂Cl₂ offered the desired trisaccharide carbonate **52** in 80% yield (over two steps). The compound was thoroughly characterized using NMR spectroscopy.

2.5.9 Synthesis of pentasaccharide



Scheme 16 Synthesis of pentasaccharide employing [3+2] coupling

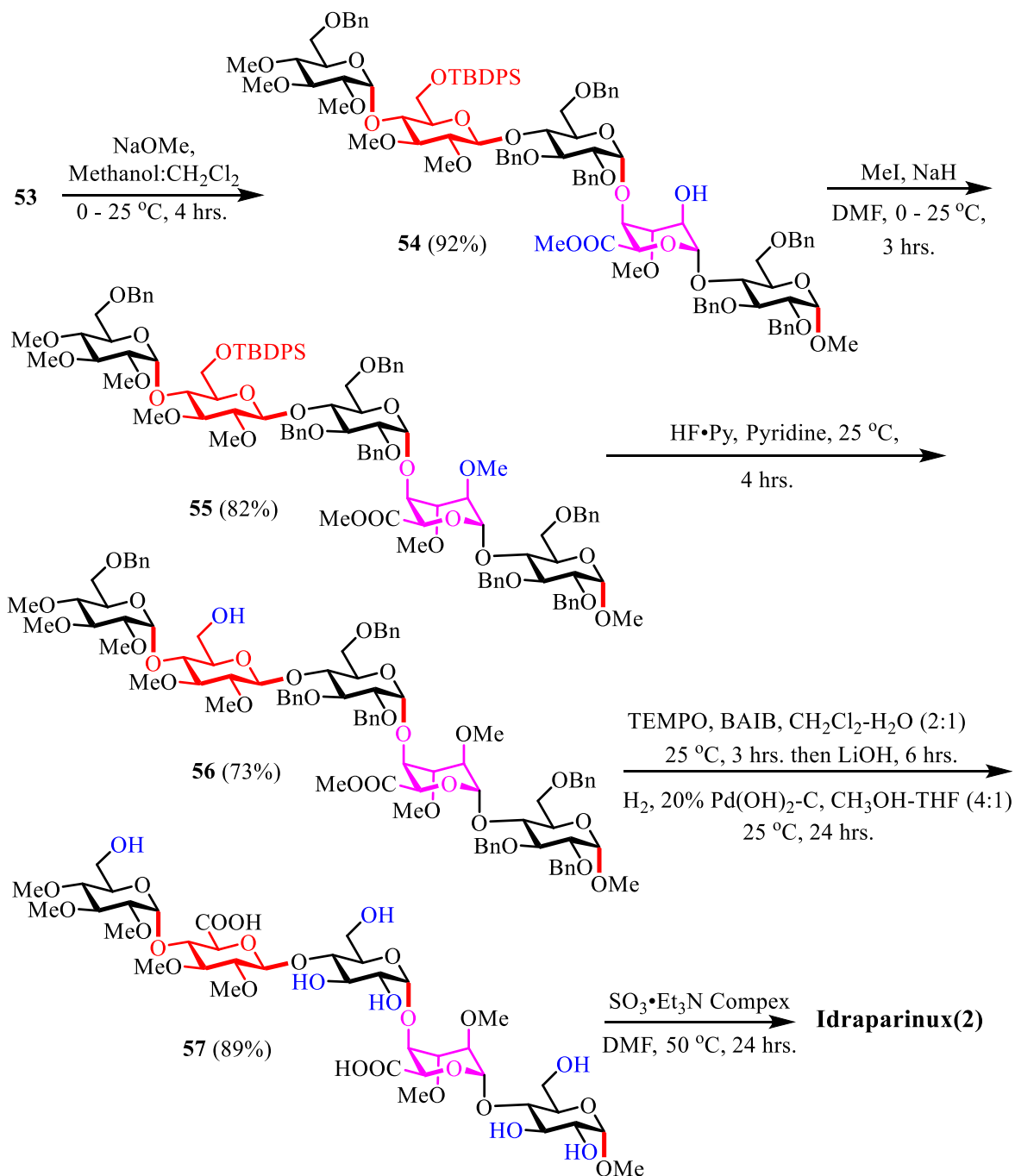
The glycosidation between trisaccharide carbonate donor **52** and disaccharide acceptor **43** at -40 °C under silver assisted gold-catalyzed condition offered pentasaccharide **53** as the sole isomer in the reaction. In the ¹H NMR spectrum of compound **53**, three 1,2-*cis* anomeric resonances were identified at δ 5.23 (s, 1H), 4.66 (s, 1H), 4.61 (s, 1H) while remaining 1,2-*trans* resonances were seen at δ 5.43 (d, *J* = 3.9 Hz, 1H) and 4.34 (d, *J* = 7.9 Hz, 1H) ppm. The carbon resonances at δ 102.1 (1,2-*trans*), 100.2 (1,2-*trans*), 98.4 (1,2-*cis*), 98.2 (1,2-*cis*), 97.1 (1,2-*cis*) ppm confirmed respective five anomeric carbons. Further, the stereochemistry of each glycosidic linkage was assigned by performing the HSQC-coupled experiment wherein *J*_{C-H} coupling for four anomeric centers was found >170.0 Hz (α-linkage) while *J*_{C-H} for β-glycosidic linkage was found to be 164.0 Hz (See 2D spectrum, in experimental section). The HRMS spectrum showed [M+Na⁺] peak at *m/z* 1813.7888 Da while calculated one was *m/z* 1813.7891, thus, confirming the pentasaccharide **53**.

2.5.10 Functional group transformations for Idraparinux

Having sufficient quantity of thoroughly characterized pentasaccharide **53**, the functional group transformation for obtaining Idraparinux was critically planned. The pentasaccharide **53** was first subjected to lactone opening using NaOMe as its methyl ester and unmasking the C-2 hydroxyl

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to access **54** which was further treated with MeI/NaH in DMF to get the required O-methylation at the C-2 position to obtain compound **55** in 82% isolated yield.



Scheme 17 Functional group transformations for Idraparinux synthesis

The emergence of a new singlet at δ 3.60 ppm for 3H required for COOCH_3 and eight singlets between δ 3.55 to 3.33 ppm for $8\times\text{OCH}_3$'s along with other resonances in the complete

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agreement confirmed the compound **55**. In the next step, the silyl ether was cleaved off using HF•Py in pyridine to obtain C-6 hydroxyl which further upon oxidation using TEMPO/BAIB in CH₂Cl₂:H₂O (1:1) and treatment with LiOH offered diacid pentasaccharide **56** in 73% yield. Finally, the global deprotection of benzyl ethers by 20% Pd(OH)₂/C in CH₃OH:THF (4:1) was performed which upon C-18 bond-elute column purification yielded Idraparinux pentasaccharide **57** in 89% as white solid. In the ¹H NMR spectrum of compound **57**, the disappearance of aromatic protons confirmed the complete debenzylation. The five anomeric proton resonances were noticed at δ 5.43 (d, *J* = 3.6 Hz, 1H, α), 5.15 (s, 1H, α), 5.04 (d, *J* = 3.2 Hz, 1H, α), 4.67 (d, *J* = 3.0 Hz, 1H, α), 4.56 (d, *J* = 7.5 Hz, 1H, β) ppm and the corresponding anomeric carbons were identified at δ 98.2(α), 100.1(α), 98.6(α), 101.1(α), 103.1(β) ppm respectively in the ¹³C spectrum. Further, the ¹³C NMR resonances for two acid carbonyls were identified at δ 170.3, 170.1 ppm and presence of resonances due to eight -OCH₃'s at δ 61.0, 61.0, 60.7, 60.6, 59.9, 59.3, 58.6, and 55.6 ppm confirmed the successful synthesis of the Idraparinux pentasaccharide **57**.

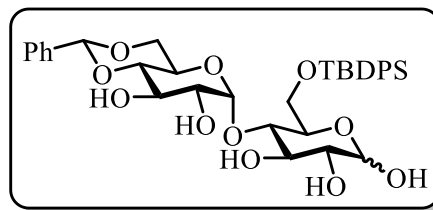
2.6 Conclusions

In conclusion, the total synthesis of anticoagulant Idraparinux pentasaccharide has been accomplished in 31 steps (the shortest literature route was 38 steps). The synthetic strategy was completely built on the solid foundation of silver assisted gold-catalyzed glycosidations. The starting materials were D-glucose and D-maltose which are easily available and cheap starting materials. The highlights of this strategy are (i) the utilization of D-maltose for the DE disaccharide unit to access an in-built α-glycosidic linkage for reducing the number of synthetic steps, (ii) the challenging iduronic acid was obtained by chelation-assisted nucleophilic attack of phenylmagnesium bromide on the C-5 aldehyde of glucofuranose derivative, and (iii) Phenyl group as a surrogate for the carboxylic acid.

2.7 Experimental Section

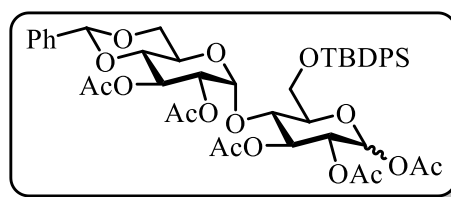
6-O-tert-butyl-diphenylsilyl-4-O-(4,6-O-benzylidene- α -D-glucopyranosyl)- α / β -D-glucopyranoside (30):

To a solution of D-(+)-maltose (20 g, 28.53 mmol) in 200 mL of anhydrous DMF, benzaldehyde dimethylacetal (10.52 mL, 70.11 mmol) and *p*-Toluenesulfonic acid (1.85 g, 11.69 mmol) was added at room temperature and then stirred at 50 °C for overnight. After 12 hours assuming the completion, the reaction was quenched by adding excess of triethylamine (5 mL) and then 100 mL of *n*-hexane was added. The resultant biphasic mixture was stirred vigorously for 10 minutes and then top layer (*n*-hexane fraction) was separated by pipette to remove the excess benzaldehyde dimethylacetal from reaction mixture. The process was repeated for two more times to ensure the removal of maximum amount of benzaldehyde dimethylacetal; **Step 2:** After this, *tert*-butyl(chloro)diphenylsilane (16.26 mL, 63.89 mmol) and imidazole (9.89 gm, 145.29 mmol) were added to the same solution and mixture was stirred for 6 hours at room temperature. The reaction mixture was poured in ice-cold water then filtered through the Buchner funnel to obtain the crude white solid compound which was purified by silica gel column chromatography using 15% methanol in dichloromethane to obtain 21.56 gm of desired compound as thick syrup (54% over two steps); $[\alpha]_D^{25}$ (CHCl₃, *c* 1.0): +02.0°; ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.87 – 7.68 (m, 4H), 7.54 – 7.31 (m, 11H), 5.53 (d, *J* = 5.3 Hz, 1H), 5.23 (d, *J* = 15.3 Hz, 1H), 4.55 (d, *J* = 7.8 Hz, 1H), 4.04 – 3.41 (m, 13H), 3.33 – 3.15 (m, 1H), 2.98 – 2.81 (m, 1H), 1.06 (s, 9H); ¹³C NMR (101 MHz, Methanol-*d*₄) δ 137.8, 135.7(4C), 135.5(3), 135.5(3C), 133.6, 133.4, 133.1, 133.0, 129.5, 129.5(2C), 129.5, 128.6, 127.7(5C), 127.5, 127.4, 127.4(2C), 127.3(2C), 126.2(5C), 102.4, 102.4, 101.5, 101.5, 96.7, 92.5, 81.3, 81.1, 81.1, 81.0, 76.4, 75.2, 74.5, 73.7, 73.5, 73.2, 72.3, 70.7, 70.7, 70.5, 68.4, 68.4, 63.7(2C), 63.0, 62.9, 26.1(6C), 18.8, 18.8; HRMS (ESI-MS): *m/z* calculated for C₃₅H₄₄O₁₁Si [M+Na]⁺: 691.2551, Found: 691.2550.



1,2,3-tri-O-Acetyl-6-O-tert-butyl-diphenylsilyl-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene- α -D-glucopyranosyl)- α / β -D-glucopyranoside (31):

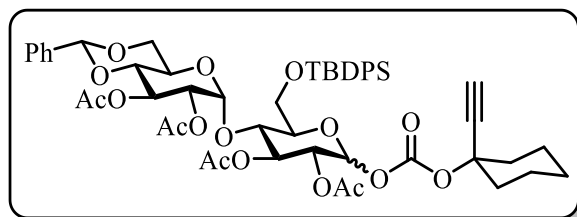
To a solution of compound 30 (21.0 g, 31.40 mmol) in 100 mL anhydrous DMF, Acetic anhydride (15.73 mL, 166.41 mmol) and 4-dimethylaminopyridine (3.84 g, 31.40 mmol) were



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added and the reaction mixture was stirred at room temperature for 30 minutes. After the completion (as adjudged by TLC), the reaction was quenched by adding 50 mL of ice-cold water and extracted with EtOAc (100 mL) for three times. The resultant organic layer was combined, washed by sat. NaHCO₃ solution and then with sat. brine solution, dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using 30% EtOAc in *n*-hexane to obtain 15.60 g of desired compound as white solid (91.30%) ($\alpha:\beta=1:1$); $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +15.0°; IR (cm⁻¹, CHCl₃): 2922, 2857, 1731, 1457, 1376, 1266, 1114, 964, 715; ¹H NMR (400 MHz, CDCl₃) δ 7.68 – 7.60 (m, 4H), 7.43 – 7.26 (m, 11H), 5.71 (d, *J* = 8.1 Hz, 1H), 5.57 – 5.22 (m, 4H), 5.03 – 4.77 (m, 2H), 4.19 (td, *J* = 9.2, 6.1 Hz, 1H), 4.09 – 3.78 (m, 5H), 3.67 – 3.46 (m, 2H), 2.13 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.08 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 170.8, 170.8, 170.3, 170.2, 170.1, 169.9, 169.9, 169.8, 169.2, 168.9, 137.0, 137.0, 136.1, 136.1, 136.0, 136.0, 135.8, 135.7, 135.7, 135.6, 135.6, 133.8, 133.6, 132.9, 129.9, 129.9, 129.8, 129.8, 129.8, 129.1, 128.2, 128.2(2C), 128.2, 128.2, 127.8, 127.8(2C), 127.7, 127.7, 126.3(2C), 126.3, 101.6, 101.5, 96.9, 96.6, 91.4, 89.0, 79.1, 79.1, 75.7, 75.5, 73.2, 72.8, 72.4, 72.1, 71.2, 71.2, 71.0, 70.0, 68.7, 68.6, 68.5, 68.5, 63.8, 63.8, 62.7, 62.6, 27.0(6C), 21.1, 21.1, 21.1, 21.0, 20.9, 20.9, 20.8, 20.7, 20.7, 20.6, 19.6, 19.6; HRMS (ESI-MS): *m/z* calculated for C₄₅H₅₄O₁₆Si [M+Na]⁺: 901.3079, Found: 901.3066.

Methyl-1-O-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3-di-O-Acetyl-6-O-tert-butyldiphenylsilyl-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene- α -D-

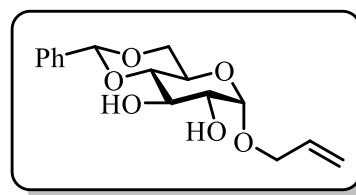


glucopyranosyl)- α/β -D-glucopyranoside (26): **Step 1. Preparation of hemiacetals:** In a solution of compound **31** (10.2 g, 11.22 mmol) in an anhydrous THF (50 mL), N, N'-dimethylpropane-1,3-diamine (2.12 mL, 16.83 mmol) was added in drop wise manner and stirred the mixture for 3 hours at 25 °C. After completion (confirmed by TLC), the reaction was quenched by adding 50 mL sat. brine solution and diluted 50 mL ice-cold water, extracted with EtOAc (100 mL) for three times, organic layers were combined, dried over Na₂SO₄ and concentrated under reduced pressure. Finally the purification by silica gel column chromatography using 30% EtOAc in *n*-hexane offered 8.92 gm of hemiacetals (92%); **Step 2. Preparation of carbonate donor:** To the hemiacetals (8.90 g, 10.27 mmol) dissolved in 40 mL of an anhydrous CH₂Cl₂ were added 1-ethynylcyclohexyl-(4-nitrophenyl) carbonate (3.65 g,

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12.32 mmol) and 4-dimethylaminopyridine (1.88 g, 15.40 mmol) and stirred it for 3 hours at room temperature. After completion, the reaction mixture was diluted with 50 mL of CH_2Cl_2 , washed with sat. NaHCO_3 solution (200 mL each time) till the yellow colour of nitrophenol was coming and then with brine solution, dried over Na_2SO_2 and concentrated under reduced pressure. The crude compound was then purified by silica gel column chromatography using 25% ethylacetate in *n*-hexane as eluent to obtain 9.62 gm thick syrup of desired compound **26** (92%); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +06.0°; IR (cm^{-1} , CHCl_3): 2922, 2857, 2259, 1745, 1400, 1302, 1260, 1089, 921, 815; ^1H NMR (400 MHz, CDCl_3) δ 7.68 – 7.60 (m, 4H), 7.40 – 7.28 (m, 11H), 6.09 (d, J = 3.7 Hz, 1H), 5.72 – 5.54 (m, 1H), 5.47 – 5.34 (m, 3H), 4.92 (td, J = 9.9, 3.8 Hz, 2H), 4.27 – 4.12 (m, 1H), 4.11 – 3.90 (m, 4H), 3.86 (dd, J = 9.6, 4.5 Hz, 1H), 3.63 – 3.55 (m, 2H), 2.65 (s, 1H), 2.29 – 2.12 (m, 2H), 2.10 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.92 – 1.85 (m, 2H), 1.64 – 1.49 (m, 4H), 1.41 – 1.25 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.8, 170.1, 170.1, 169.8, 151.0, 137.0, 136.1, 136.0(2C), 135.7(3C), 135.7(2C), 133.6, 133.0, 129.9, 129.8, 129.1, 128.2(2C), 127.8(3C), 127.7, 126.4(2C), 101.6, 96.8, 92.4, 79.1, 77.4, 75.4, 73.3, 72.7, 72.3, 71.2, 70.0, 68.7, 68.5, 63.8, 62.7, 37.1, 36.6, 27.1, 25.0, 22.6, 21.1, 20.9, 20.8, 20.7, 19.6; HRMS (ESI-MS): m/z calculated for $\text{C}_{52}\text{H}_{62}\text{O}_{17}\text{Si}$ $[\text{M}+\text{Na}]^+$: 986.3756, Found: 986.3350.

Allyl 4,6-O-benzylidene- α -D-glucopyranoside (33): In a solution of compound tetra-ol (20 g, 90.82 mmol) and benzaldehyde dimethylacetal (16.36 mL, 108.98 mmol) in 100 mL anhydrous DMF, *p*-toluenesulfonic acid monohydrate (3.91



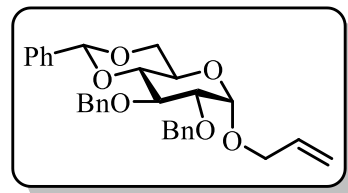
g, 22.70 mmol) was added and stirred at 50 °C for 12 hours. After satisfactory conversion, the reaction was neutralized by adding excess of triethylamine (5 mL) and 100 mL of ice-cold water was added and further stirred for 20 minutes to precipitate out the compound. The mixture was then filtered using Buchner funnel and residue was washed with hexane to remove excess of benzaldehyde dimethylacetal and reprecipitated using *n*-hexane (200 mL) to obtain 22.8 g of product (81%); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +16.0°; IR (cm^{-1} , CHCl_3): 3500-3300 (broad), 2900, 2902, 1352, 1296, 1200, 1113, 820, 702; ^1H NMR (400 MHz, CDCl_3) δ 7.52 – 7.47 (m, 2H), 7.38 – 7.31 (m, 3H), 5.96 – 5.85 (m, 1H), 5.49 (s, 1H), 5.27 (m, 2H), 4.87 (d, J = 3.9 Hz, 1H), 4.28 – 4.17 (m, 2H), 4.02 (dd, J = 12.9, 6.3 Hz, 1H), 3.91 (t, J = 9.3 Hz, 1H), 3.85 – 3.78 (m, 1H), 3.69 (t, J = 10.3 Hz, 1H), 3.58 (dd, J = 9.2, 4.0 Hz, 1H), 3.55 – 3.50 (m, 1H), 3.44 (t, J = 9.2 Hz, 1H),

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2.88 (d, $J = 9.3$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 137.1, 133.5, 129.3, 128.4(2C), 126.4(2C), 118.3, 101.9, 98.0, 81.0, 72.8, 71.5, 68.9, 68.9, 62.6; HRMS (ESI-MS): m/z calculated for $\text{C}_{16}\text{H}_{20}\text{O}_6$ $[\text{M}+\text{K}]^+$: 347.0892, Found: 347.0890.

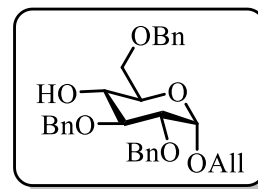
Allyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene- α -D-glucopyranoside

(34): To an ice-cold solution of compound **33** (10.0 g, 33.42 mmol) in 50 mL of anhydrous DMF, Sodium hydride (1.87 g, 77.84 mmol) in portion wise and benzyl bromide (9.25 mL, 77.84 mmol) were



added. The reaction mixture was then allowed reach room temperature gradually and stirred for 3 hours. After completion (as adjudged by TLC), 100 mL of ice-cold water was added, extracted with ethylacetate (3 X 100 mL), all the organic layers was combined, and washed with brine solution (100 ML), dried over Na_2SO_4 , and concentrated under *vacuo*. The crude was subjected for silica gel column chromatography purification using binary mixture of ethylacetate:hexane to obtain 14.68 g of compound (93%); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): $+18.6^\circ$; ^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.29 (m, 15H), 6.01 – 5.91 (m, 1H), 5.57 (s, 1H), 5.36 (dq, $J = 10.4$, 1.7 Hz, 1H), 5.26 (dq, $J = 10.4$, 1.4 Hz, 1H), 4.96 – 4.86 (ABq, $J = 11.2$ Hz, 2H), 4.82 (d, $J = 3.8$ Hz, 1H), 4.79 (ABq, $J = 10.1$ Hz, 2H), 4.28 (dd, $J = 10.2$, 4.9 Hz, 1H), 4.23 – 4.17 (m, 1H), 4.12 – 4.08 (m, 1H), 4.08 – 4.02 (m, 1H), 3.91 (dd, $J = 10.0$, 4.8 Hz, 1H), 3.72 (t, $J = 10.3$ Hz, 1H), 3.66 – 3.57 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 138.9, 138.3, 133.7, 129.0, 128.5(2C), 128.5, 128.4(2C), 128.3(2C), 128.2(2C), 128.1(2C), 128.0, 127.7, 126.1(2C) 118.5, 101.3, 96.8, 82.3, 79.3, 78.7, 75.5, 73.7, 69.1, 68.6, 62.6; HRMS (ESI-MS): m/z calculated for $\text{C}_{30}\text{H}_{32}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 511.2097, Found: 511.2094.

Allyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (27): To a vigorously stirring solution of compound **33** (8.5 g, 17.40 mmol), sodium cyanoborohydride (5.47 g, 86.99 mmol) and 4 Å MS (Appr. 1.0 g) in 50 mL anhydrous THF. Molecular iodine (13.25 g, 52.19 mmol) was



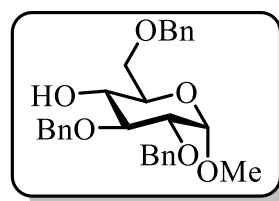
added portion wise over the period of 15 minutes and stirred for another 1 hour at room temperature. After the completion, reaction was quenched by adding excess of triethylamine, diluted with 50 mL CH_2Cl_2 and filtered through celite[®]. The filtrate was then washed with saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (2 X 50 mL) and then saturated brine solution (50 mL), dried over Na_2SO_4 , and concentrated under *vacuo*. The crude compound was subjected for silica gel column chromatography using ethylacetate:hexane as eluent to obtain 5.98 g of desired compound

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(70%); $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): $+86.0^\circ$; IR (cm^{-1} , CHCl_3): 3470, 3054, 2916, 1454, 1361, 1250, 1051, 925; ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.29 (m, 15H), 6.04 – 5.91 (m, 1H), 5.40 – 5.22 (m, 2H), 5.04 (d, J = 11.4 Hz, 1H), 4.87 (d, J = 3.5 Hz, 1H), 4.81 – 4.73 (m, 2H), 4.67 (d, J = 12.0 Hz, 1H), 4.59 (q, J = 12.2 Hz, 2H), 4.20 (dd, J = 13.0, 5.1 Hz, 1H), 4.04 (dd, J = 13.0, 6.6 Hz, 1H), 3.86 (t, J = 9.2 Hz, 1H), 3.83 – 3.77 (m, 1H), 3.71 (d, J = 3.9 Hz, 2H), 3.65 (t, J = 9.3 Hz, 1H), 3.57 (dd, J = 9.6, 3.6 Hz, 1H), 2.49 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 138.9, 138.2, 138.1, 133.8, 128.6(2C), 128.5(2C), 128.4(2C), 128.1(2C), 128.0, 128.0(2C), 127.9, 127.7, 127.7(2C), 118.3, 95.7, 81.6, 79.7, 75.5, 73.6, 73.0, 70.8, 70.2, 69.5, 68.3; HRMS (ESI-MS): m/z calculated for $\text{C}_{30}\text{H}_{34}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 513.2253, Found: 513.2246.

Methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (29): Procedure as used

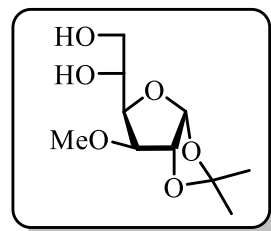
for compound **27**; $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): $+11.0^\circ$; ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.27 (m, 15H), 5.02 (d, J = 11.5 Hz, 1H), 4.80 – 4.73 (m, 2H), 4.69 – 4.64 (m, 2H), 4.62 – 4.53 (m, 2H), 3.84 – 3.78 (m, 1H), 3.75 –



3.70 (m, 1H), 3.69 (m, 2H), 3.65 – 3.58 (m, 1H), 3.55 (dd, J = 9.6, 3.5 Hz, 1H), 3.40 (s, 3H), 2.46 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 138.9, 138.2, 138.1, 128.7, 128.6, 128.5, 128.2, 128.1, 128.1, 127.9, 127.7, 98.3, 81.6, 79.7, 75.5, 73.7, 73.3, 70.8, 70.0, 69.6, 55.4; HRMS (ESI-MS): m/z calculated for $\text{C}_{30}\text{H}_{34}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 487.2097, Found: 487.2096.

1,2-*O*-isopropylidene-3-*O*-methyl- α -D-glucofuranoside (35):

Step 1: In a 1000 mL clean and oven dried round bottom flask, 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose (50 g, 192.10 mmol) was dissolved in 200 mL DMF and cooled to 0°C using ice bath. Then the sodium hydride (5.53 g 230.52 mmol) was added portion wise over the



period of 10 minutes and methyl iodide (17.94 mL, 288.14 mmol) was added drop-wise using dropping funnel. The reaction mixture was then stirred for 30 minutes and the completion of reaction was confirmed by TLC analysis. The reaction was arrested by adding 250 mL ice-cold water, extracted using EtOAc (200 mL X 3), the organic layers was combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was used as it is for next reaction; **Step 2:** To the previous step crude compound (42.5 g, 173.16 mmol), 66.66% glyacial acetic acid in water (250 mL) was added and stirred at 50°C for 2.5 hours. After completion, the reaction solvent was evaporated under reduced pressure to remove acetic acid. The crude was then twice co-evaporated with water (20 mL) and twice with toluene (20 mL).

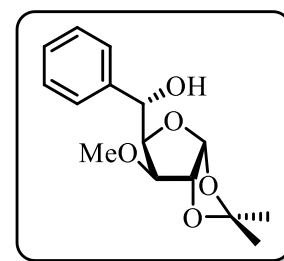
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Finally, the crude was purified by silica gel column chromatography using binary mixture of ethylacetate:hexane to obtain the desired compound (74 g) in 91.24% yield; $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): $+56.0^\circ$; IR (cm^{-1} , CHCl_3): 3330, 2924, 1460, 1276, 1344, 1050, 921, 894; ^1H NMR (400 MHz, CDCl_3) δ 5.84 (d, $J = 3.8$ Hz, 1H), 4.53 (d, $J = 3.8$ Hz, 1H), 4.04 (dd, $J = 8.2, 3.2$ Hz, 1H), 3.94 – 3.89 (m, 1H), 3.83 (d, $J = 3.1$ Hz, 1H), 3.77 (dd, $J = 11.6, 3.2$ Hz, 1H), 3.64 (dd, $J = 11.6, 5.7$ Hz, 1H), 3.47 (s, 1H), 3.41 (s, 3H), 3.29 (s, 1H), 1.44 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 111.7, 105.1, 84.2, 81.4, 79.8, 69.1, 64.4, 57.9, 26.7, 26.2; HRMS (ESI-MS): m/z calculated for $\text{C}_{10}\text{H}_{18}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 257.1001, Found: 257.1013.

5-(S)-1,2-O-(isopropylidene)-3-O-methyl-5-C-phenyl- α -D-

xylofuranose (38): Aldehyde was prepared using the synthetic procedure

as in reference number 67. **Grignard Reaction:** Aldehyde compound **36** (38.84 g, 192.08 mmol) was dissolved in 200 mL of the anhydrous THF and added slowly to the freshly prepared Grignard reagent (1.5

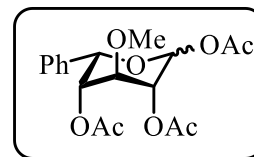


eq) at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to stir at 25 °C for 3 hours. After completion, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution, diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine solution (150 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography using 3-5% Acetone in 1:1 CH_2Cl_2 : hexane as a mobile phase to afford **37:38** as corresponding Ido:Glc (85:15) isomers; **Reagent Preparation:** To a freshly activated Mg-metal (1.5 eq) in 400 mL of the anhydrous THF in two neck round bottom flask equipped with a condenser and cooled to 0 °C. phenyl bromide (1.5 eq) was added slowly under argon atmosphere and the mixture was stirred at 70 °C for 1 hours; Desired compound **38** was isolated in pure form thus characterized as; $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): $+86.0^\circ$; IR (cm^{-1} , CHCl_3): 3470, 3054, 2916, 1454, 1361, 1250, 1051, 925; ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.25 (m, 5H), 5.95 (d, $J = 3.8$ Hz, 1H), 4.98 (d, $J = 7.9$ Hz, 1H), 4.51 (dd, $J = 3.8, 1.2$ Hz, 1H), 4.22 (dd, $J = 7.9, 3.1$ Hz, 1H), 3.25 (d, $J = 3.0$ Hz, 1H), 3.23 (s, 3H), 3.02 (s, 1H), 1.45 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 139.9, 128.3(2C), 128.0, 127.0(2C), 111.8, 105.2, 84.7, 83.9, 81.5, 72.3, 57.3, 26.7, 26.2; HRMS (ESI-MS): m/z calculated for $\text{C}_{15}\text{H}_{20}\text{O}_5$ $[\text{M}+\text{Na}]^+$: 303.1208, Found: 303.1210.

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5-(S)-1,2,4-tri-O-acetyl-3-O-methyl-5-C-Phenyl xylopyranoside (39):

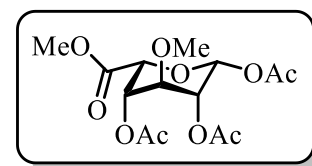
Compound **38** (19.4 g, 69.21 mmol) was dissolved in 90% aqueous trifluoroacetic acid (120 mL) and stirred for 15 min at room temperature.



After completion, the solvent was evaporated and the residue was co-evaporated twice with water and twice with toluene to afford the crude product. The residue was again dissolved in anhydrous pyridine (100 mL), acetic anhydride (15.97 mL, 1.5 eq/-OH) was added drop-wise at 0 °C under an inert atmosphere, and catalytic amount of DMAP was added. The reaction mixture was allowed to reach room temperature gradually and stirred for 12 h. After completion, ice-cooled water (100 mL) was added and extracted with EtOAc (2 x 100 mL). The organic layer was washed with aqueous 1N HCl (2 x 200 mL) and brine solution (1 x 200 mL), dried over anhydrous Na₂SO₄, concentrated in *vacuo* and the crude residue was purified by silica gel column chromatography using 25% ethyl acetate in *n*-hexane as a mobile phase to obtain 8.94 g (54%) **39**; [α]_D²⁵ (CHCl₃, *c* 1.0): +28.0°; IR (cm⁻¹, CHCl₃): 2910, 2800, 1745, 1412, 1325, 1201, 1021, 929; ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.25 (m, 5H), 6.18 (d, *J* = 1.8 Hz, 1H), 5.16–5.14 (m, 1H), 5.09–5.07 (m, 1H), 5.04–5.02 (m, 1H), 3.71 (t, *J* = 2.8 Hz, 1H), 3.58 (s, 3H), 2.17 (s, 3H), 2.13 (s, 3H), 1.87 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 170.2, 169.9, 168.8, 136.2, 128.2(2C), 128.0, 126.5(2C), 90.7, 77.5, 77.1, 76.8, 76.3, 75.7, 68.2, 66.1, 58.8, 21.1, 21.0, 20.6; HRMS (ESI-MS): *m/z* calculated for C₁₈H₂₂O₈ [M+H]⁺: 367.1393, Found: 367.1389.

Methyl 1,2,4-tri-O-acetyl-3-O-methyl-L-idopyranuronate (40):

To a solution of **39** (5.0 g, 13.65 mmol) in CCl₄:CH₃CN (25 mL, 1:1) was added solution of NaIO₄ (23.35 g, 109.18 mmol) in H₂O (12.5 mL) at 25 °C and stirred for 10 minutes, RuCl₃·3H₂O (5 mol%) was added and

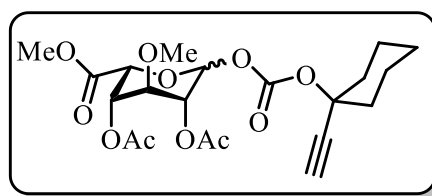


the mixture was stirred vigorously for 24 hours. After completion, reaction mixture was passed through the pad of celite® and filtrate was concentrated in *vacuo*. The crude was then resuspended into ethyl acetate and passed through Na₂SO₄ and concentrated in *vacuo* and co-evaporated twice with toluene. To the solution of crude product in anhydrous DMF (25 mL) was added 1.5 equivalent of K₂CO₃ (2.83 g, 20.46 mmol) and stirred for 15 minutes. After this, iodomethane (2.12 mL, 30.10 mmol) was added under nitrogen atmosphere and the mixture was stirred at 25 °C for 8 hours in a dark place. After complete consumption, the reaction was quenched by the addition of excess amount of saturated solution of Na₂S₂O₃, followed by addition of brine (25 mL), water (25 mL) and extracted with EtOAc (2 x 50 mL). The combined

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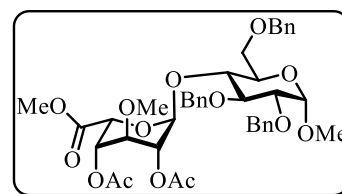
organic phases were washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography using binary mixture of ethylacetate:hexane to obtain 3.8 g, (80%) of compound; In the chromatographic purification β -isomer was isolated in pure form thus characterized as; $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +99.2°; ^1H NMR (400 MHz, CDCl_3) δ 6.03 (d, J = 1.4 Hz, 1H), 5.15 – 5.12 (m, 1H), 5.03 (dd, J = 2.1, 8.2 Hz, 1H), 4.74 (dd, J = 2.1, 8.2 Hz, 1H), 3.79 (s, 3H), 3.75 (t, J = 2.9 Hz, 1H), 3.56 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.0, 169.8, 168.6, 167.4, 89.9, 75.2, 73.3, 66.8, 65.8, 58.9, 52.7, 20.9, 20.9, 20.7; HRMS (ESI-MS): m/z calculated for $\text{C}_{14}\text{H}_{20}\text{O}_{10}$ $[\text{M}+\text{Na}]^+$: 371.0954, Found: 371.0952.

Methyl-1-O-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,4-O-acetyl-3-O-methyl-L-idopyranuronate (28): To a vigorously stirring solution of compound **40** (5.20 g, 14.93 mmol) in 25 mL anhydrous THF, benzylamine (2.12 mL,



19.41 mmol) was added and stirred at 25 °C for 4 hours. After completion (as adjudged by TLC), reaction was quenched by adding 30 mL of brine, diluted with 30 mL water, and extracted with EtOAc (3 X 50 mL), the organic layer was combined, dried over Na_2SO_4 and concentrated under *vacuo*. The crude was then dissolved in 20 mL CH_2Cl_2 , and carbonate reagent (4.68 g, 16.16 mmol) and DMAP (1.97 g, 16.16 mmol) were added and stirred for 3 hours at room temperature. After completion, reaction mixture was diluted with 20 mL CH_2Cl_2 , and washed with NaHCO_3 (3 X 40 mL), followed by brine (40 mL) and organic portion was then dried over Na_2SO_4 , concentrated under *vacuo* and purified by silica gel column chromatography using binary mixture of ethylacetate:hexane to obtain 6.2 g of compound **28** with 92% (α : β =4:1); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +86.0°; IR (cm^{-1} , CHCl_3): 2916, 2256, 1752, 1413, 1246, 1001, 956; ^1H NMR (400 MHz, CDCl_3) δ 5.91 (d, J = 1.8 Hz, 1H), 5.12 (ddd, J = 3.2, 2.3, 0.9 Hz, 1H), 5.04 (ddd, J = 3.5, 1.8, 0.9, 1H), 4.72 (d, J = 2.3 Hz, 1H), 3.79 (d, J = 1.5 Hz, 1H), 3.78 (s, 3H), 3.56 (s, 3H), 2.64 (s, 1H), 2.22 – 2.15 (m, 2H), 2.13 (s, 3H), 2.05 (s, 3H), 1.89 (m, 2H), 1.63-1.50 (m, 4H), 1.34 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.1, 169.9, 167.5, 150.9, 92.7, 82.5, 78.9, 75.4, 75.1, 73.2, 67.1, 66.1, 59.1, 52.7, 36.9, 36.7, 25.0, 22.6(2C), 21.0, 20.8; HRMS (ESI-MS): m/z calculated for $\text{C}_{21}\text{H}_{28}\text{O}_{11}$ $[\text{M}+\text{Na}]^+$: 479.1529, Found: 479.1500.

Methyl 2,3,6-tri-O-benzyl-4-O-(2,3-di-O-acetyl-3-O-methyl-5R-5-methoxycarbonyl- α -D-xylopyranosyl)- α -D-glucopyranoside (41):

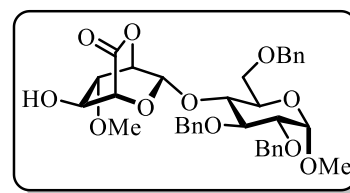


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In a solution of glycosyl donor compound **28** (2.50 g, 5.48 mmol) and glycosyl acceptor **29** (3.05 g, 6.57 mmol) in 12.5 mL of anhydrous CH_2Cl_2 and 4 Å molecular sieves. Gold-phosphite (0.48 g, 0.54 mmol) and silver triflate (0.14 g, 0.54 mmol) was added and stirred for 15 minutes at 25 °C. After completion, reaction was quenched by adding 100 μL of triethylamine, filtered using celite[®] and concentrated under reduced pressure. The crude compound was purified using silica gel column chromatography with binary mixture of ethylacetate:hexane as eluent to obtain 3.81 g of compound **41** (92%); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +12.0°; ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.27 (m, 15H), 5.15 (s, 1H), 5.05 (d, J = 2.3 Hz, 1H), 5.03–4.99 (m, 2H), 4.82 (m, 1H), 4.76 (ABq, J = 12.1 Hz, 1H), 4.59 (s, 1H), 4.57 (d, J = 6.2 Hz, 1H), 4.56 (ABq, J = 12.5, 2H), 3.99 (t, J = 9.5 Hz, 1H), 3.87 (t, J = 9.4 Hz, 1H), 3.81–3.75 (m, 2H), 3.69–3.64 (m, 1H), 3.60 (dd, J = 9.6, 3.7 Hz, 1H), 3.58–3.56 (m, 1H), 3.55 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.2, 169.8, 168.8, 138.9, 138.1, 138.1, 128.5(2C), 128.4(2C), 128.3(2C), 128.2(2C), 128.0, 127.8(2C), 127.6, 127.2(2C), 127.1, 98.1, 97.1, 80.3, 79.8, 75.0, 74.4, 74.2, 73.5, 73.3, 70.2, 68.4, 67.4, 67.0, 66.1, 58.5, 55.3, 52.0, 21.0, 20.9; HRMS (ESI-MS): m/z calculated for $\text{C}_{40}\text{H}_{48}\text{O}_{14}$ $[\text{M}+\text{Na}]^+$: 775.2942, Found: 775.2938.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(3-*O*-methyl-2,6-lactone- α -D-xylopyranosyl)- α -D-glucopyranoside (43**):**

Step 1. Ester hydrolysis: The compound **41** (3.50 g, 4.65 mmol) was dissolved in THF/MeOH (15 mL 10:3 v:v) and the mixture was cooled to 0

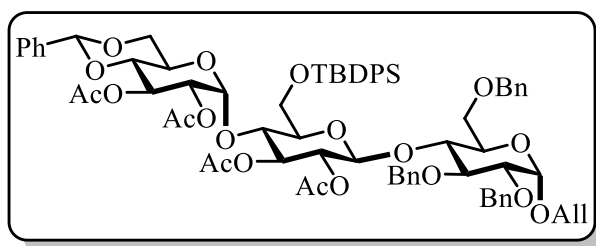


°C, then KOH (0.91 g, 16.27 mmol) dissolved in H_2O (20 mL) was added. After stirring for 2 hours, the reaction mixture was extracted with EtOAc (50 mL)/HCl 0.3 M (50 mL) and the organic phase dried over Na_2SO_4 , filtered, and evaporated. The crude was purified using silica gel flash column chromatography (EtOAc/hexane, 1:1 v:v + 1% HCOOH). This yielded intermediate iduronic acid disaccharide **42** (2.89 g, 95%) as a foam. **Step 2:** The iduronic acid disaccharide **42** (2.89 g, 25.3 mmol) was dissolved in anhydrous DCM (15 mL), the mixture cooled to 0 °C, 1-methylimidazole (0.38 mL, 4.86 mmol) added, and after 5 minutes, tosyl chloride (0.93 g, 4.86 mmol) added in one portion. The reaction mixture was stirred for 1 hours and another portion of 1-methylimidazole (0.38 mL, 4.86 mmol) added over 10 minutes. After stirring for 3 h, the reaction mixture was quenched by adding water (20 mL), extracted with DCM (3 X 30 mL), and the organic phase was dried over Na_2SO_4 , concentrated under reduced pressure. The crude product was purified using silica gel flash column chromatography to obtain

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2.38 g of compound **43** (79%); $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): -15.0°; IR (cm⁻¹, CHCl₃): 3054, 2900, 1496, 1305, 1186, 1002, 956; ¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.19 (m, 15H), 5.07 (dd, *J* = 2.4, 1.2 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.73 (d, *J* = 10.9 Hz, 1H), 4.64 (ABq, *J* = 12.2 Hz, 2H), 4.55 – 4.51 (m, 2H), 4.30 (d, *J* = 12.1 Hz, 1H), 3.97 – 3.92 (m, 2H), 3.87 (d, *J* = 3.3 Hz, 1H), 3.80 (t, *J* = 9.2 Hz, 1H), 3.70 (t, *J* = 9.4 Hz, 1H), 3.62 – 3.56 (m, 2H), 3.47 (d, *J* = 3.3 Hz, 1H), 3.46 – 3.43 (m, 1H), 3.28 (s, 3H), 3.26 (s, 1H), 3.23 (s, 3H), 2.61 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 168.5, 139.1, 138.0, 137.4, 128.6(2C), 128.5(2C), 128.4(2C), 128.3, 128.3(2C), 128.2(2C), 128.0, 127.6(2C), 127.5, 98.3, 97.6, 83.1, 80.1, 79.8, 77.4, 75.2, 73.7, 73.4, 72.0, 71.3, 70.9, 69.4, 67.8, 58.1, 55.4; HRMS (ESI-MS): *m/z* calculated for C₃₅H₄₀O₁₁ [M+Na]⁺: 659.2468, Found: 659.2464.

Allyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-acetyl-6-*O*-tert-butylidiphenylsilyl-4-*O*-(2,3-di-*O*-acetyl-4,6-benzylidene- α -D-glucopyranosyl)- β -D-glucopyranosyl)- α -D-glucopyranoside (44**):** Glycosyl donor **26** (1.52 g, 1.54 mmol)

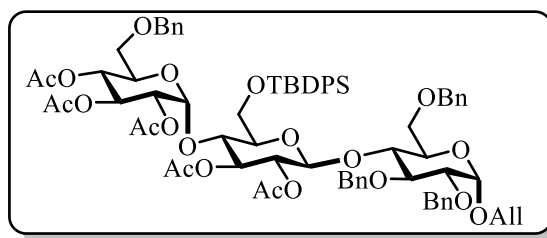


and glycosyl acceptor **27** (0.83 g, 1.69 mmol) was dissolved in 8 mL anhydrous CH₂Cl₂, 4 Å molecular sieves (Appr. 500 mg) was added and stirred for 10 minutes at room temperature. Then Gold-phosphite (0.13 g, 0.15 mmol) and silver (0.039 g, 0.15 mmol) were added and stirred for 30 minutes. After completion, the reaction was quenched by adding 50 μ L triethylamine, filtered through pad of celite®, and concentrated under reduced pressure. The crude was then purified by silica gel column chromatography using ethylacetate:hexane as eluent to obtain 1.86 g of D-E-F trisaccharide **44** (92%); $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +67.0°; ¹H NMR (400 MHz, CDCl₃) δ 7.68 – 7.60 (m, 4H), 7.38 – 7.22 (m, 26H), 5.99 – 5.90 (m, 1H), 5.42 – 5.30 (m, 4H), 5.24 – 5.20 (m, 2H), 4.98 (t, *J* = 9.0 Hz, 1H), 4.86 (dd, *J* = 10.2, 4.1 Hz, 1H), 4.80 (d, *J* = 3.7 Hz, 1H), 4.73 (s, 1H), 4.71 (d, *J* = 1.6 Hz, 2H), 4.67 (t, *J* = 4.0 Hz, 1H), 4.56 (d, *J* = 12.3 Hz, 1H), 4.50 (d, *J* = 8.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.20 – 4.15 (m, 1H), 4.04 – 3.99 (m, 1H), 3.95 – 3.91 (m, 1H), 3.86 – 3.81 (m, 2H), 3.76 – 3.69 (m, 5H), 3.63 – 3.60 (m, 1H), 3.58 – 3.56 (m, 1H), 3.53 (dd, *J* = 9.9, 3.0 Hz, 2H), 3.45 – 3.41 (m, 1H), 3.01 – 2.95 (m, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H), 1.92 (s, 3H), 1.05 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 170.8, 170.5, 170.0, 169.8, 139.8, 138.5, 137.8, 137.0, 135.9, 135.8, 134.0, 133.6, 133.1, 130.1, 129.8, 129.1, 128.8, 128.8, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8,

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127.8, 127.1, 127.1, 126.9, 126.4, 126.4, 118.2, 101.6, 99.3, 96.8, 96.1, 80.4, 80.2, 79.1, 79.0, 77.5, 77.2, 76.8, 76.5, 76.0, 75.3, 74.7, 74.5, 73.9, 73.4, 71.1, 70.2, 68.8, 68.5, 68.4, 68.2, 63.5, 63.4, 27.1, 21.1, 20.9, 20.9, 20.8, 19.4; HRMS (ESI-MS): m/z calculated for $C_{73}H_{84}O_{20}Si$ $[M+Na]^+$: 1331.5223, Found: 1331.5219.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-4-*O*-(2,3,4-tri-*O*-acetyl-4-*O*-benzyl- α -D-glucopyranosyl)- β -D-glucopyranosyl)- α -D-glucopyranoside (45): Step



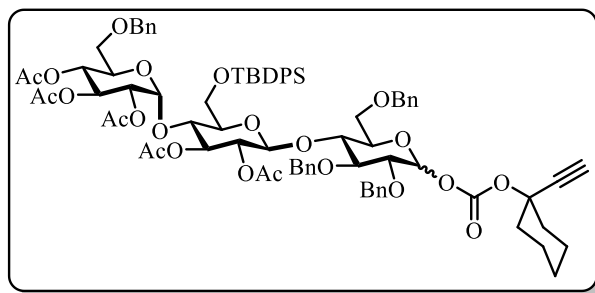
1. Benzylidene opening: To solution of

trisaccharide **44** (1.8 g, 1.37 mmol), sodium cyanoborohydrate (0.43 g, 6.87 mmol) and 4 Å molecular sieves powder (0.5 g) in 10 mL anhydrous acetonitrile. Molecular iodine (1.05 gm, 4.12 mmol) was added portion wise in period of 10 minutes and mixture was stirred at room temperature for 3 hours. After completion, the reaction was diluted with 20 mL of CH_2Cl_2 , filtered through pad of celite®, and concentrated under reduced pressure. The crude was dissolved in 40 mL ethyl acetate and washed with sat. $Na_2S_2O_3$ (40 mL x 2), with brine (40 mL), dried over Na_2SO_4 , and concentrated under *vacuo*; **Step 2. Acetylation:** the crude was dissolved in 10 mL CH_2Cl_2 to which acetic anhydride (0.26 mL) and DMAP (83.0 mg, 0.686 mmol) were added and the mixture was stirred at room temperature for 15 minutes. After completion, the reaction was diluted with 20 mL CH_2Cl_2 and washed with sat. solution $NaHCO_3$ (40 mL X 2), with brine solution (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography using ethyl acetate:hexane as mobile phase to obtain 1.6 g, of trisaccharide **45** (70%); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +60.0°; 1H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 4H), 7.40 – 7.14 (m, 26H), 6.03 – 5.89 (m, 1H), 5.39 – 5.33 (m, 1H), 5.32 (s, 1H), 5.34 – 5.28 (m, 1H), 5.23 (dd, J = 10.4, 1.4 Hz, 1H), 5.14 (d, J = 9.9 Hz, 1H), 4.99 (t, J = 9.0 Hz, 1H), 4.87 (dd, J = 10.5, 3.9 Hz, 1H), 4.81 (d, J = 3.7 Hz, 1H), 4.80 – 4.72 (m, 2H), 4.75 – 4.68 (m, 2H), 4.67 (s, 1H), 4.62 – 4.45 (m, 2H), 4.47 (s, 1H), 4.45 – 4.22 (m, 2H), 4.20 – 3.98 (m, 2H), 3.88 – 3.82 (m, 1H), 3.85 – 3.80 (m, 1H), 3.80 – 3.73 (m, 2H), 3.74 (s, 1H), 3.76 – 3.71 (m, 2H), 3.69 – 3.63 (m, 1H), 3.64 – 3.58 (m, 1H), 3.44 (dd, J = 6.2, 3.4 Hz, 1H), 3.20 – 3.01 (m, 2H), 3.05 – 2.94 (s, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.82 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 170.5, 170.1, 169.8, 169.3, 139.7, 138.5, 137.6, 137.6, 135.8, 135.6, 133.9, 133.7, 133.3, 129.9, 129.7, 128.8, 128.5, 128.4,

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128.4, 128.3, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.8, 127.8, 127.7, 127.4, 126.9, 118.2, 99.1, 96.1, 95.8, 80.1, 78.9, 76.3, 76.2, 75.4, 74.8, 74.3, 73.9, 73.6, 73.4, 73.3, 70.3, 70.2, 70.0, 69.2, 68.5, 68.4, 68.0, 67.1, 64.2, 27.0, 21.1, 20.9, 20.8, 20.8, 20.6, 19.3; HRMS (ESI-MS): m/z calculated for $C_{75}H_{88}O_{21}Si$ $[M+Na]^+$: 1375.5485, Found: 1375.5480.

Methyl-1-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-acetyl-6-*O*-tert-butyldiphenylsilyl-4-*O*-(2,3,4-tri-*O*-acetyl-4-*O*-benzyl- α -D-glucopyranosyl)- β -D-glucopyranosyl)- α -D-glucopyranoside (46):



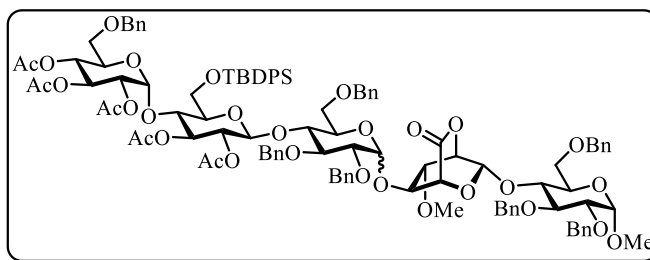
Step 1. Hemiacetal formation: o a solution of

trisaccharide **45** (1.56 g, 1.15 mmol) in 40 mL ternary mixture of solvents $CH_2Cl_2:CH_3OH:DME$ (1:2:1), palladium(II) chloride (0.05 g, 0.28 mmol) was added and stirred for 3 hours at room temperature. After completion (confirmed by TLC), the reaction was arrested by adding excess of triethylamine (200 μ L), filtered through pad of celite®, and concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using binary mixture of ethylacetate:hexane to obtain 1.23 g of hemiacetal (90%); **Step 2. Carbonate preparation:** To the trisaccharide hemiacetal (1.23 g, 0.93 mmol) dissolve in anhydrous CH_2Cl_2 (7.5 mL) was added ethynylcyclohexyl-(4-nitrophenyl) carbonate (0.33 g, 1.2 mmol) and 4-(*N,N*-Dimethylamino)pyridine (0.17 g, 1.40 mmol) and stirred for 3 hours at room temperature. after completion, diluted with 25 mL CH_2Cl_2 , washed with $NaHCO_3$ (5 X 40 mL), saturated brine solution, dried over Na_2SO_4 , and concentrated under *vacuo*. The crude was then purified by silica gel column chromatography using binary mixture of ethylacetate:hexane as eluent to obtain 1.30 g of trisaccharide carbonate 80% ($\alpha:\beta=10:2$) **46**; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +87.0°; IR (cm^{-1} , $CHCl_3$): 3058, 2902, 2281, 1756, 1300, 1125, 1025, 949; 1H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 4H), 7.30 – 6.99 (m, 26H), 5.37 (d, J = 7.8 Hz, 1H), 5.22 (s, 1H) 5.25 – 5.19 (m, 1H), 5.02 (dd, J = 9.8, 4.9 Hz, 1H), 4.94 (t, J = 9.1 Hz, 1H), 4.78 – 4.68 (m, 2H), 4.63 (d, J = 8.9 Hz, 1H), 4.59 (m, 3H), 4.56 – 4.51 (m, 1H), 4.45 (d, J = 8.1 Hz, 1H), 4.38 (d, J = 8.4 Hz, 1H), 4.35 (d, J = 7.9 Hz, 1H), 4.15 (d, J = 12.2 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.75 – 3.68 (m, 1H), 3.65 (m, 3H), 3.61 (d, J = 8.6 Hz, 1H), 3.54 (dd, J = 10.4, 5.4 Hz, 1H), 3.45 (t, J = 8.9 Hz, 1H), 3.41 – 3.23 (m, 2H), 3.06 (dt, J = 11.0, 3.3 Hz, 1H), 2.97 – 2.87 (m, 2H), 2.51 (d, J = 8.9 Hz, 1H), 2.15 – 2.04 (m, 2H), 1.99 (s, 3H), 1.91 (s, 3H), 1.87 (s, 3H), 1.85 (s, 3H), 1.83 – 1.77 (m, 2H), 1.73 (s, 3H), 1.57

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– 1.43 (m, 4H), 1.37 – 1.10 (m, 2H), 0.95 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.5, 170.5, 170.1, 169.8, 169.3, 151.4, 139.1, 138.1, 137.7, 137.6, 135.8, 135.6(2C), 133.6, 133.2, 129.9, 129.8, 128.8(2C), 128.8, 128.5(2C), 128.5, 128.4(2C), 128.3(2C), 128.3, 128.2(2C), 128.0, 128.0, 127.9(2C), 127.8, 127.7, 127.6(2C), 127.3, 127.1, 99.0, 97.4, 95.8, 82.7, 82.2, 80.2, 78.4, 76.1, 75.6, 75.5, 75.3, 75.1, 74.6, 74.3, 73.9, 73.6, 73.1, 70.3, 70.0, 69.2, 68.4, 67.5, 67.1, 64.2, 36.9, 36.8, 27.0, 25.0, 22.6, 21.0, 20.8, 20.8, 20.7, 20.6, 19.3; HRMS (ESI-MS): m/z calculated for $\text{C}_{81}\text{H}_{94}\text{O}_{23}\text{Si}$ $[\text{M}+\text{Na}]^+$: 1485.5853, Found: 1485.5850.

Methyl 2,3,6-tri-O-benzyl-4-O-(3-O-methyl-2,6-lactone-4-O-(2,3,6-tri-O-benzyl-4-O-(2,3-di-O-acetyl-6-O-tert-butylidiphenylsilyl-4-O-(2,3,4-tri-O-acetyl-6-O-benzyl- α -D-glucopyranosyl)- β -D-glucopyranosyl)- α / β -D-glucopyranosyl)- α -L-idopyranosyl)- α -D-glucopyranoside (47):

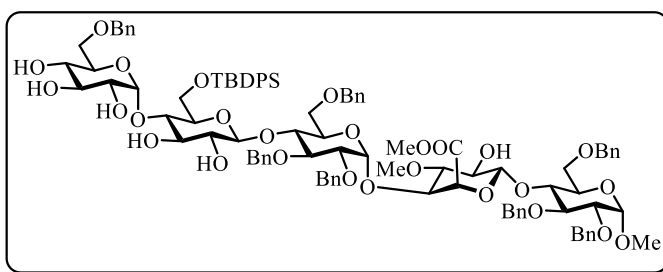


To a solution of D-E-F trisaccharide carbonate **46** (0.50 g, 0.34 mmol) and G-H disaccharide acceptor **43** (0.21 g, 0.30 mmol) in 5 mL anhydrous CH_2Cl_2 was added 4 Å molecular sieves (Appr. 250 mg) and stirred for 15 minutes. After this, gold-phosphite (29.56 mg, 0.034 mmol) and silver triflate (9.0 mg, 0.034 mmol) were added and stirred for 30 minutes at room temperature. After completion (as adjudged by TLC), the reaction was quenched by adding 50 μL triethylamine, passed through pad of celite[®], and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using ethylacetate:hexane to obtain 0.54 g of D-E-F-G-H pentasaccharide (82%) ($\alpha:\beta=10:1$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +38.0°; ^1H NMR (400 MHz, CDCl_3) δ 7.67 – 7.61 (m, 4H), 7.41 – 7.13 (m, 41H), 5.37 (t, J = 10.0 Hz, 1H), 5.32 (d, J = 1.8 Hz, 1H), 5.26 (s, 1H), 5.13 (t, J = 9.8 Hz, 1H), 4.98 (d, J = 8.8 Hz, 1H), 4.95 – 4.92 (m, 2H), 4.90 – 4.82 (m, 3H), 4.77 – 4.71 (m, 2H), 4.70 (s, 1H), 4.67 (s, 1H), 4.65 (m, 2H), 4.63 (s, 1H), 4.62 (s, 1H), 4.52 (s, 1H), 4.48 (s, 1H), 4.45 (s, 1H), 4.41 (m, 2H), 4.35 (d, J = 8.2 Hz, 1H), 4.28 (d, J = 12.2 Hz, 1H), 4.00 (t, J = 2.6 Hz, 1H), 3.96 (d, J = 9.2 Hz, 1H), 3.92 (d, J = 2.5 Hz, 1H), 3.90 (s, 1H), 3.88 – 3.84 (m, 2H), 3.83 – 3.81 (m, 1H), 3.79 (s, 1H), 3.77 – 3.73 (m, 2H), 3.71 (s, 1H), 3.69 (s, 1H), 3.67 (s, 1H), 3.64 (d, J = 4.4 Hz, 1H), 3.61 (s, 1H), 3.59 – 3.54 (m, 2H), 3.53 (d, J = 3.3 Hz, 1H), 3.42 – 3.40 (m, 3H), 3.34 (dd, J = 9.8, 3.7 Hz, 1H), 3.27 (s, 3H), 3.17 (d, J = 11.1 Hz, 1H), 3.02 (d, J = 7.7 Hz, 2H), 2.14 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.85 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.6, 170.5, 170.2, 170.2, 169.4, 168.1,

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139.6, 139.0, 138.4, 138.1, 137.6, 137.6, 137.6, 135.8, 135.8, 135.7, 135.7, 133.7, 133.4, 129.9, 129.7, 129.7, 129.0, 129.0, 128.8, 128.8, 128.7, 128.7, 128.7, 128.7, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4(2C), 128.3, 128.3, 128.1, 128.1, 128.0, 128.0, 127.9(2C), 127.9(2C), 127.9, 127.9, 127.8, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 126.9, 100.0, 98.9, 98.4, 98.4, 95.9, 81.1, 80.9, 80.4, 79.7, 79.4, 78.4, 77.8, 77.4, 76.2, 75.5, 75.5, 75.3, 74.7, 74.6, 74.0, 73.8, 73.7, 73.6, 73.6, 73.1, 72.6, 71.0, 70.3, 70.1, 69.7, 69.4, 69.3, 68.4, 67.8, 67.6, 67.1, 64.5, 58.5, 55.5, 27.0, 21.1, 20.8, 20.8, 20.7, 20.7, 19.3; HRMS (ESI-MS): m/z calculated for $C_{107}H_{122}O_{31}Si$ $[M+Na]^+$: 1953.7637, Found: 1953.7634.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(3-*O*-methyl-5-*O*-methoxycarbonyl)-4-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-(6-*O*-tert-butylidiphenylsilyl-4-*O*-(6-*O*-benzyl- α -D-glucopyranosyl)- β -D-glucopyranosyl)- α / β -D-glucopyranosyl)- α -L-iduronosyl)- α -D-glucopyranoside (48):



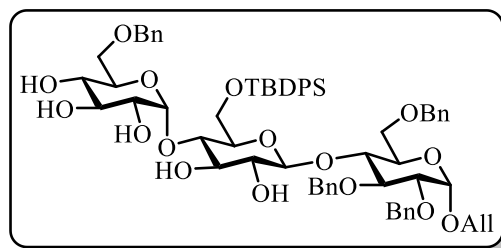
To an ice-cold solution of pentasaccharide **47** (0.30 g, 0.15 mmol) in 2 mL of dichloromethane, 0.5 mL of 1 M sodium methoxide solution in methanol was added and reaction mixture was allowed to reach room temperature gradually and stirred for 4 hours at room temperature. After completion, the reaction was neutralized by IR-120 H^+ resin and filtered through centered funnel, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using MeOH:CH₂Cl₂ as eluent to obtain 0.21 g desired compound (77%) **48**; $[\alpha]^{25}_D$ (CHCl₃, c 1.0): +48.0°; IR (cm⁻¹, CHCl₃): 3400-300 (broad), 2910, 1740, 1400, 1305, 1122, 1052, 899; ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.56 (m, 4H), 7.31 – 7.16 (m, 41H), 5.12 (s, 1H), 4.94 – 4.90 (m, 2H), 4.87 (d, J = 11.5 Hz, 1H), 4.74 (s, 1H), 4.71 – 4.69 (m, 1H), 4.59 – 4.47 (m, 10H), 4.45 – 4.33 (m, 4H), 4.27 (d, J = 11.9 Hz, 1H), 3.98 – 3.92 (m, 2H), 3.89 – 3.79 (m, 4H), 3.78 – 3.66 (m, 4H), 3.65 – 3.56 (m, 6H), 3.52 – 3.35 (m, 15H), 3.32 (s, 3H), 3.27 (s, 3H), 3.19 (s, 3H), 3.14 (t, J = 8.3 Hz, 1H), 0.92 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 170.1, 139.3, 139.2, 138.2, 137.9, 137.9, 137.6, 137.4, 136.1, 136.1, 135.9, 135.9, 133.9, 133.4, 130.0, 129.7, 128.8, 128.8, 128.7, 128.6, 128.6, 128.6, 128.6, 128.5(3C), 128.5(2C), 128.3, 128.3, 128.3(2C), 128.2, 128.2, 128.2, 128.2, 128.1(2C), 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8(2C), 127.8, 127.7, 127.4, 127.3, 127.3, 127.1, 126.9, 126.8, 126.8, 102.7, 101.8, 101.1, 98.1, 95.9, 80.8, 80.6, 80.4, 79.9, 78.1, 77.4, 76.0, 76.0, 75.8, 74.8, 74.7, 74.6, 74.6, 74.3, 74.2, 74.1, 73.9, 73.7, 73.7,

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73.5, 73.0, 71.7, 71.2, 71.0, 70.6, 70.3, 69.7, 68.9, 68.5, 67.2, 66.1, 62.5, 58.0, 55.3, 52.0, 27.0, 19.4; HRMS (ESI-MS): m/z calculated for $C_{98}H_{116}O_{27}Si$ $[M+H]^+$: 1753.7552, Found: 1753.7549.

Allyl 2,3,6-tri-O-benzyl-4-O-(6-O-tert-butyl-diphenylsilyl-4-O-(6-O-benzyl- α -D-glucopyranosyl)- β -D-glucopyranosyl)- α -D-glucopyranoside (50): **Step**

1. Benzylidene opening: To solution of trisaccharide **44** (1.8 g, 1.37 mmol), sodium cyanoborohydrate (0.43

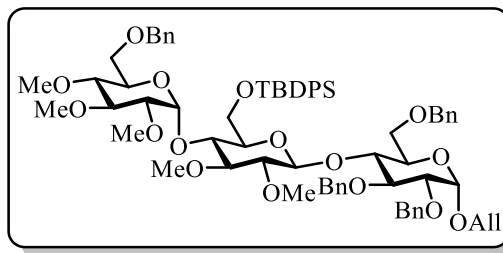


g, 6.87 mmol) and 4 Å molecular sieves powder (0.5 g) in 10 mL anhydrous acetonitrile. Molecular iodine (1.05 gm, 4.12 mmol) was added portion wise in period of 10 minutes and mixture was stirred at room temperature for 3 hours. After completion, the reaction was diluted with 20 mL of CH_2Cl_2 , filtered through pad of celite®, and concentrated under reduced pressure. The crude was dissolved in 40 mL ethyl acetate and washed with sat. $Na_2S_2O_3$ (40 mL x 2), with brine (40 mL), dried over Na_2SO_4 , and concentrated under vacuo; **Step 2. Deacetylation:** The crude trisaccharide **49** (1.12 g, 0.85 mmol) in 6 mL anhydrous CH_2Cl_2 , sodium methoxide (3.59 mL, 3.59 mmol) in methanol solution was added in portion wise and stirred for 10 hours at room temperature. The reaction was quenched with IR-120- H^+ resin to completely neutralized the reaction media, then filtered through centered funnel, and concentrated under reduced pressure. The crude was passed through small bed of silica gel column chromatography using ethylacetate to obtain 0.89 g homogeneous sticky trisaccharide (70% Over two steps); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +61.0°; 1H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4H), 7.37 – 7.24 (m, 22H), 7.13 – 7.08 (m, 4H), 5.99 – 5.90 (m, 1H), 5.33 (d, J = 1.6 Hz, 1H), 5.23 (d, J = 7.6 Hz, 1H), 5.00 (d, J = 3.5 Hz, 1H), 4.83 – 4.78 (m, 2H), 4.78 – 4.67 (m, 2H), 4.67 – 4.60 (m, 2H), 4.59 – 4.52 (m, 2H), 4.52 – 4.44 (m, 2H), 4.42 (s, 1H), 4.34 (d, J = 11.9 Hz, 1H), 4.20 – 4.05 (m, 2H), 4.00 – 3.98 (m, 2H), 3.96 – 3.90 (m, 2H), 3.79 (dd, J = 10.9, 9.4 Hz, 2H), 3.72 – 3.66 (m, 2H), 3.61 (dd, J = 12.5, 2.7 Hz, 2H), 3.58 – 3.55 (m, 2H), 3.55 – 3.51 (m, 2H), 3.49 (dd, J = 8.7, 3.7 Hz, 2H), 3.46 – 3.31 (m, 2H), 3.28 (t, J = 7.5 Hz, 1H), 3.26 – 3.18 (m, 1H), 2.91 – 2.84 (m, 1H), 0.98 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 138.3, 138.0, 137.6, 136.0, 136.0, 135.9, 135.9, 133.9, 133.8, 133.5, 129.8, 129.7, 128.6, 128.6, 128.6(2C), 128.6, 128.5, 128.5, 128.4, 128.2(2C), 128.2(2C), 128.2, 128.2, 128.1, 128.1(2C), 128.0, 127.9, 127.9, 127.8(2C), 127.8(2C), 126.9, 126.9, 118.3, 102.6, 101.8, 95.9, 80.9, 80.6, 79.6, 76.6, 76.0, 75.9, 74.7, 74.7, 74.4, 73.8, 73.8,

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73.4, 73.1, 71.2, 71.0, 69.9, 69.7, 68.9, 68.4, 62.6, 27.0, 19.4; HRMS (ESI-MS): m/z calculated for $C_{65}H_{78}O_{16}Si[M+Na]^+$: 1331.5223, Found: 1331.5220.

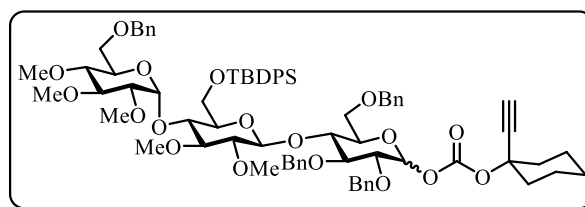
Allyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-methyl-6-*O*-tert-butyl-diphenylsilyl-4-*O*-(2,3,4-tri-*O*-methyl-6-*O*-benzyl- α -D-glucopyranosyl)- β -D-glucopyranosyl)- α -D-glucopyranoside (51):



Compound **50** (1.25 g, 1.09 mmol) in 12.5 mL

anhydrous THF was added 60% NaH in mineral oil (0.24 g, 6.01 mmol) at 0 °C and allowed to warm gradually to room temperature with constant stirring. After this, methyl iodide (1.15 mL, 21.86 mmol) was added drop-wise and stirred in dark place for 4 hours. After completion, reaction was quenched by adding 20 mL ice-cold water and extracted with ethylacetate (3 X 25 mL), organic layer was combined, washed with saturated solution of $Na_2S_2O_3$, saturated brine solution, dried over Na_2SO_4 and concentrated under *vacuo*. The crude compound was purified by silica gel column chromatography using ethyl acetate:hexane as eluent to obtain 1.16 gm of compound trisaccharide (87%); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +61.0°; 1H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 4H), 7.42 – 7.28 (m, 23H), 7.22 – 7.17 (m, 3H), 6.04 – 5.94 (m, 1H), 5.45 (d, J = 3.8 Hz, 1H), 5.30 (dd, J = 10.3, 1.3 Hz, 2H), 5.00 – 4.83 (m, 2H), 4.80 – 4.78 (m, 2H), 4.68 – 4.61 (m, 2H), 4.61 – 4.52 (m, 2H), 4.41 – 4.30 (m, 2H), 4.25 – 4.18 (m, 1H), 4.10 – 4.06 (m, 1H), 4.06 – 4.02 (m, 1H), 3.92 (t, J = 9.3 Hz, 1H), 3.89 – 3.86 (m, 1H), 3.86 – 3.79 (m, 2H), 3.73 (s, 1H), 3.72 – 3.68 (m, 1H), 3.63 (s, 3H), 3.58 (s, 3H), 3.55 (s, 3H), 3.53 (d, J = 6.3 Hz, 1H), 3.51 (s, 3H), 3.50 – 3.48 (m, 1H), 3.41 (s, 3H), 3.39 – 3.35 (m, 1H), 3.35 – 3.32 (m, 1H), 3.30 (d, J = 3.4 Hz, 1H), 3.27 (m, 2H), 3.25 – 3.21 (m, 1H), 3.18 (dd, J = 10.7, 1.9 Hz, 1H), 3.16 – 3.12 (m, 1H), 2.98 (dd, J = 9.0, 7.9 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 138.6, 138.2, 138.0, 135.8, 135.8, 135.8, 135.8, 134.1, 134.1, 133.9, 133.7, 129.7, 129.5, 128.6, 128.4, 128.4, 128.4, 128.4, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 126.9, 118.1, 102.0, 97.1, 96.1, 86.5, 85.0, 83.4, 81.8, 80.3, 79.1, 79.0, 76.0, 75.7, 75.0, 75.0, 73.6, 73.5, 73.5, 71.0, 70.6, 68.4, 68.3, 68.0, 64.3, 60.8, 60.4, 60.1, 59.9, 59.7, 27.0, 19.4; HRMS (ESI-MS): m/z calculated for $C_{70}H_{88}O_{16}Si[M+Na]^+$: 1235.5739, Found: 1235.5736.

Methyl-1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-methyl-6-*O*-tert-



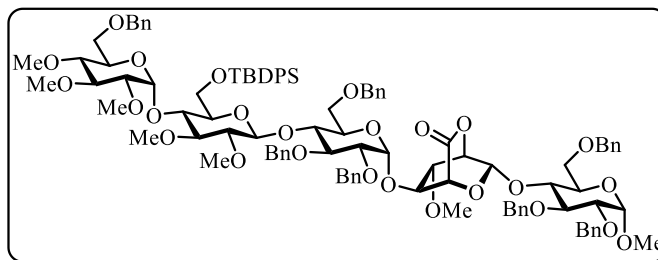
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butyl-diphenylsilyl-4-O-(2,3,4-tri-O-methyl-6-O-benzyl- α -D-glucopyranosyl)- β -D-

glucopyranosyl)- α -D-glucopyranoside (52): **Step 1. Preparation of hemiacetal:** To a solution of trisaccharide **51** (1.1 g, 0.90 mmol) in mixture of 24 mL CH₂Cl₂:CH₃OH:DME (1:2:1), palladium(II) chloride (0.04 g, 0.22 mmol) was added and stirred for 4 hours at room temperature. After completion, reaction was quenched with 50 μ L of triethylamine, filtered through pad of celite®, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using binary mixture of ethylacetate:hexane as eluent to obtain 0.92 g of hemiacetal (86%); **Step 2. Preparation of trisaccharide carbonate:** In a vigorously stirring solution of hemiacetal (0.92 g, 0.78 mmol) in 5 mL CH₂Cl₂, carbonate reagent (0.28 g, 0.94 mmol) and N,N-Dimethylaminopyridine (0.14 g, 1.18 mmol) were added and stirred for 6 hours at room temperature. After completion (as Adjudged by TLC), reaction mixture was diluted with 10 mL CH₂Cl₂ and washed with saturated solution of NaHCO₃ (3 X 20 mL), brine solution (25 mL), and the organic portion was then dried over Na₂SO₄, concentrated under reduced pressure. The crude was purified by silica gel column chromatography using binary mixture of ethyl acetate:hexane to obtain 0.98 gm of D-E-F trisaccharide carbonate **52** (95%); $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +52.0°; IR (cm⁻¹, CHCl₃): 3054, 2900, 2295, 1425, 1300, 1105, 1025, 925; ¹H NMR (400 MHz, CDCl₃) δ 7.65 – 7.61 (m, 4H), 7.35 – 7.13 (m, 26H), 5.51 (d, *J* = 8.0 Hz, 1H), 5.43 (d, *J* = 8.6 Hz, 1H), 4.90 (d, *J* = 12.1 Hz, 1H), 4.76 (d, *J* = 4.6 Hz, 1H), 4.73 – 4.69 (m, 2H), 4.67 – 4.58 (m, 2H), 4.58 – 4.47 (m, 2H), 4.46 – 4.40 (m, 1H), 4.28 (d, *J* = 12.2 Hz, 1H), 4.12 (d, *J* = 3.5 Hz, 1H), 3.87 – 3.77 (m, 3H), 3.72 – 3.66 (m, 1H), 3.66 – 3.62 (m, 1H), 3.60 (s, 3H), 3.56 (s, 3H), 3.52 (s, 3H), 3.51 (t, *J* = 1.1 Hz, 1H), 3.49 (d, *J* = 1.8 Hz, 1H), 3.48 (s, 3H), 3.38 (s, 3H), 3.35 – 3.31 (m, 1H), 3.31 – 3.29 (m, 1H), 3.28 – 3.25 (m, 2H), 3.25 – 3.23 (m, 1H), 3.22 – 3.18 (m, 1H), 3.18 – 3.13 (m, 1H), 3.13 – 3.09 (m, 1H), 2.98 – 2.92 (m, 1H), 2.61 – 2.59 (m, 1H), 2.25 – 2.13 (m, 2H), 1.97 – 1.86 (m, 2H), 1.65 – 1.51 (m, 4H), 1.39 – 1.25 (m, 2H), 1.02 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 151.4, 139.2, 138.2, 138.2, 138.1, 135.8(2C), 135.8(2C), 133.9, 133.6, 129.7, 129.6, 128.6, 128.5, 128.4(2C), 128.3(2C), 128.2, 128.1(2C), 128.0(2C), 128.0, 127.9(3C), 127.9(2C), 127.8(2C), 127.7, 127.7, 127.2, 127.0, 101.9, 97.5, 97.1, 86.5, 85.0, 83.4, 82.7, 82.3, 81.8, 80.4, 79.1, 78.3, 77.4, 76.2, 75.7, 75.3, 75.2, 74.9, 74.7, 73.6, 73.5, 73.4, 70.9, 67.9, 67.8, 64.3, 60.8, 60.4, 60.1, 60.1, 59.7, 37.0, 36.8, 27.0(3C), 25.0, 22.7, 22.6, 19.4; HRMS (ESI-MS): *m/z* calculated for C₇₆H₉₄O₁₈Si [M+Na]⁺: 1345.6107, Found: 1345.6102.

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Methyl 2,3,6-tri-O-benzyl-4-O-(3-O-methyl-2,6-lactone-4-O-(2,3,6-tri-O-benzyl-4-O-(2,3-di-O-methyl-6-O-tert-butyl-diphenylsilyl-4-O-(2,3,4-tri-O-methyl-6-O-benzyl- α -D-glucopyranosyl)-



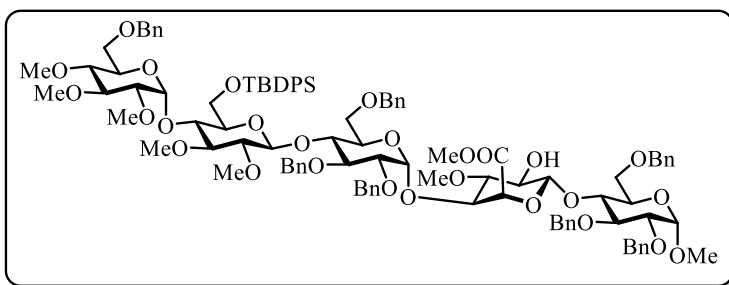
β -D-glucopyranosyl)- α -D-glucopyranosyl)- α -L-idopyranosyl)- α -D-glucopyranoside (53): To

a solution of trisaccharide carbonate **52** (0.61 g, 0.46 mmol), G-H disaccharide acceptor **43** (0.29 g, 0.46 mmol) in 6 mL anhydrous CH_2Cl_2 was added 4 Å molecular sieves (appr. 500 mg) and stirred for 15 minutes at room temperature. After this, reaction mixture was cooled to -40°C , Then gold-phosphite (59.82 mg, 69.13 μmol), and silver triflate (17.76 mg, 69.13 μmol) were added and stirred for 1 hours. After completion (as adjudged by TLC), the reaction was quenched with 100 μL triethylamine, filtered through pad of celite[®], and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethylacetate:hexane as mobile phase to obtain 0.63 g D-E-F-G-H pentasaccharide **53** (76%); $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , c 1.0): $+43.0^\circ$; ^1H NMR (400 MHz, CDCl_3) δ 7.65 – 7.61 (m, 4H), 7.37– 7.14 (m, 41H), 5.43 (d, J = 3.9 Hz, 1H), 5.23 (s, 1H), 4.98 – 4.92 (m, 2H), 4.91 – 4.76 (m, 2H), 4.75 – 4.70 (m, 2H), 4.70 – 4.67 (m, 2H), 4.66 (s, 1H), 4.65 – 4.60 (m, 2H), 4.61 (s, 1H), 4.60 – 4.52 (m, 2H), 4.49 (d, J = 4.6 Hz, 1H), 4.47 (d, J = 4.8 Hz, 1H), 4.39 (d, J = 12.1 Hz, 1H), 4.34 (d, J = 7.9 Hz, 1H), 4.29 (d, J = 12.2 Hz, 1H), 4.06 (t, J = 9.5 Hz, 1H), 4.00 (t, J = 2.7 Hz, 1H), 3.96 – 3.93 (m, 1H), 3.93 – 3.90 (m, 2H), 3.87 – 3.84 (m, 1H), 3.79 (d, J = 8.9 Hz, 1H), 3.77 – 3.75 (m, 1H), 3.73 – 3.69 (m, 2H), 3.70 (d, J = 3.2 Hz, 1H), 3.66 (dd, J = 6.1, 2.4 Hz, 1H), 3.61 (s, 3H), 3.57 – 3.56 (m, 1H), 3.56 (s, 3H), 3.54 (s, 1H), 3.53 (s, 3H), 3.50 (s, 3H), 3.48 – 3.41 (m, 2H), 3.39 (s, 3H), 3.38 (s, 3H), 3.33 (t, J = 3.3 Hz, 1H), 3.31 – 3.28 (m, 2H), 3.28 – 3.25 (m, 2H), 3.25 (s, 3H), 3.23 (s, 1H), 3.21 – 3.18 (m, 1H), 3.16 – 3.10 (m, 2H), 2.94 (dd, J = 8.9, 7.9 Hz, 1H), 1.03 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.1, 139.7, 139.0, 138.5, 138.2, 138.1, 138.0, 137.6, 135.8, 135.8, 135.8, 133.9, 133.7, 129.6, 129.5, 128.7, 128.7, 128.6, 128.6, 128.6, 128.6, 128.5, 128.5, 128.3(2C), 128.3, 128.3(2C), 128.3, 128.0, 128.0, 128.0, 127.9(2C), 127.9(2C), 127.9, 127.8, 127.8(2C), 127.8, 127.8, 127.6(3C), 127.6, 127.6, 127.6, 126.9, 102.1, 100.2, 98.4, 98.2, 97.1, 86.3, 85.1, 83.3, 81.8, 81.2, 80.6, 80.3, 79.6, 79.6, 79.1, 78.6, 77.7, 77.5, 77.4, 77.2, 76.8, 75.7, 75.5, 75.3, 75.0, 74.7, 73.8, 73.7, 73.7, 73.6, 73.5, 73.4, 73.4, 72.5, 71.4,

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70.9, 69.7, 69.3, 67.9, 67.8, 64.4, 60.8, 60.4, 60.1, 60.0, 59.7, 58.4, 55.4, 27.0(3C), 19.4; HRMS (ESI-MS): m/z calculated for $C_{102}H_{122}O_{26}Si$ $[M+Na]^+$: 1813.7891, Found: 1813.7890.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(3-*O*-methyl-5(C)-methoxycarbonyl-4-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-methyl-6-*O*-tert-butyldiphenylsilyl-4-*O*-(2,3,4-tri-*O*-methyl-6-*O*-benzyl- α -D-glucopyranosyl)- β -D-

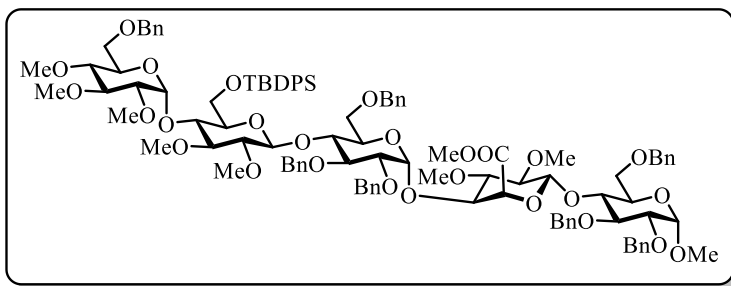


glucopyranosyl)- α -D-glucopyranosyl)- α -L-idopyranosyl)- α -D-glucopyranoside (54): In an ice-cold solution of pentasaccharide lactone **53** (0.36 g, 0.20 mmol) in 3 mL anhydrous CH_2Cl_2 was added 0.61 mL of 1 M NaOMe in methanol solution and stirred for 4 hours at room temperature. After completion, the reaction mixture was neutralized using IR-120- H^+ resin and filtered using centered funnel. The filtrate was concentrated under reduced pressure and crude compound was purified by silica gel column chromatography using binary mixture of ethyl acetate:hexane as mobile phase to obtain 0.31 g of compound **54** (86%); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +33.0°; 1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 4H), 7.40 – 7.13 (m, 41H), 5.41 (d, J = 3.9 Hz, 1H), 5.17 (s, 1H), 5.00 (s, 1H), 4.99 – 4.93 (m, 2H), 4.81 (d, J = 11.4 Hz, 1H), 4.77 (d, J = 4.0 Hz, 1H), 4.71 (d, J = 12.3 Hz, 1H), 4.69 – 4.65 (m, 2H), 4.63 (m, 2H), 4.59 (m, 2H), 4.57 (s, 1H), 4.57 (d, J = 1.9 Hz, 1H), 4.54 (m, 2H), 4.52 – 4.42 (m, 2H), 4.29 (d, J = 9.8 Hz, 1H), 4.27 (d, J = 5.4 Hz, 1H), 4.18 (d, J = 11.3 Hz, 1H), 4.06 – 4.02 (m, 2H), 3.94 (t, J = 9.5 Hz, 1H), 3.86 (m, 2H), 3.80 (m, 2H), 3.77 (d, J = 5.2 Hz, 1H), 3.71 – 3.65 (m, 4H), 3.61 (s, 3H), 3.57 (d, J = 2.4 Hz, 2H), 3.54 (s, 3H), 3.53 (s, 3H), 3.49 – 3.47 (m, 1H), 3.46 (s, 3H), 3.42 (s, 1H), 3.41 (s, 3H), 3.39 (d, J = 2.2 Hz, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 3.31 (d, J = 2.1 Hz, 1H), 3.27 (s, 3H), 3.25 (d, J = 3.5 Hz, 1H), 3.22 – 3.19 (m, 2H), 3.18 (d, J = 8.6 Hz, 1H), 3.15 – 3.11 (m, 2H), 2.93 – 2.88 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 139.6, 139.2, 138.2(2C), 137.9, 137.9, 137.7, 135.7(2C), 135.7(2C), 133.8, 133.7, 129.7, 129.5, 128.8(2C), 128.7(2C), 128.6, 128.5(4C), 128.4(2C), 128.4, 128.3, 128.2(2C), 128.2, 128.1(2C), 128.1(4C), 127.9(4C), 127.9(6C), 127.8(2C), 127.7, 127.7, 127.4, 127.2(2C), 127.0, 127.0, 101.8, 101.1, 98.0, 97.1, 95.9, 86.4, 85.1, 83.4, 81.7, 80.4, 80.3, 79.8, 79.1, 77.4, 75.8, 75.4, 75.1, 75.0, 74.8, 74.6, 74.2, 73.7, 73.6, 73.5, 73.4, 71.2, 71.0, 70.9, 70.3, 68.8, 67.8, 67.6, 67.1, 66.3, 64.4, 60.7, 60.4, 60.1,

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59.9, 59.7, 58.0, 55.3, 51.7, 27.0, 19.3; HRMS (ESI-MS): m/z calculated for $C_{103}H_{126}O_{27}Si$ $[M+H]^+$: 1823.8334, Found: 1823.8331.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-*O*-methyl-5(C)-methoxycarbonyl-4-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-methyl-6-*O*-tert-butylidiphenylsilyl-4-*O*-(2,3,4-tri-*O*-methyl-6-*O*-benzyl- α -D-



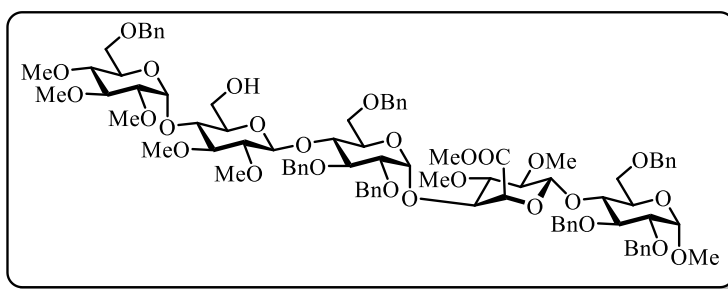
glucopyranosyl)- β -D-glucopyranosyl)- α -D-glucopyranosyl)- α -L-idopyranosyl)- α -D-

glucopyranoside (55): To a solution of compound **54** (0.28 g, 0.15 mmol) in 3 mL binary mixture of solvent DMF:THF (1:1) at 0 °C, Methyl iodide (47.48 μ L, 0.76 mmol) and 60% sodium hydride in mineral oil (7.37 mg, 0.18 mmol) were added. The reaction was allowed to reach room temperature gradually and stirred for 3 hours. After the completion (as adjudged by TLC), reaction was quenched by adding 5 mL of ice-cold water and extracted with EtOAc (3 X 10 mL), the organic portion was combined, washed with saturated $Na_2S_2O_3$ solution, saturated brine solution, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude compound was passed through silica gel column chromatography to obtain 0.24 g of compound **55** (86%); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +29.0°; 1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 4H), 7.39 – 7.12 (m, 41H), 5.42 (d, J = 3.8 Hz, 1H), 5.29 (d, J = 6.8 Hz, 1H), 5.12 (d, J = 3.6 Hz, 1H), 4.94 – 4.69 (m, 8H), 4.66 (d, J = 2.4 Hz, 1H), 4.63 – 4.47 (m, 7H), 4.42 (d, J = 6.2 Hz, 1H), 4.32 – 4.25 (m, 2H), 4.03 (t, J = 9.5 Hz, 1H), 3.90 – 3.79 (m, 8H), 3.75 – 3.63 (m, 7H), 3.60 (s, 3H), 3.55 (s, 3H), 3.53 (s, 3H), 3.50 (s, 3H), 3.47 (s, 3H), 3.44 (s, 3H), 3.43 (d, J = 3.2 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 3.33 (s, 3H), 3.24 – 3.16 (m, 4H), 3.15 – 3.09 (m, 2H), 2.99 – 2.90 (m, 2H), 0.99 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 139.6, 139.2, 138.6, 138.5, 138.3, 138.2, 137.8, 135.8, 135.8, 135.8, 135.8, 133.9, 133.7, 129.6, 129.6, 129.5, 129.5, 128.7, 128.7, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.2, 128.2, 128.2, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 127.4, 127.3, 127.2, 127.1, 127.0, 126.9, 126.9, 102.1, 100.2, 99.2, 98.4, 97.1, 86.4, 85.2, 83.6, 83.4, 81.8, 80.8, 80.3, 79.5, 79.1, 79.0, 78.6, 77.4, 75.7, 75.7, 75.5, 75.0, 74.5, 73.8, 73.6, 73.4, 73.4, 73.1, 72.7, 71.3, 70.9, 70.4, 68.1, 67.9, 67.7, 64.3, 60.9, 60.8, 60.4, 60.1, 60.0, 60.0,

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59.7, 55.4, 51.5, 27.0, 19.3; HRMS (ESI-MS): m/z calculated for $C_{104}H_{128}O_{27}Si$ $[M+Na]^+$: 1859.5739, Found: 1859.5736.

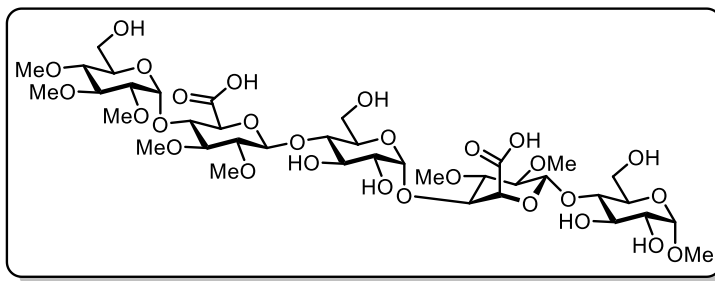
Methyl 2,3,6-tri-O-benzyl-4-O-(2,3-O-methyl-5(C)-methoxycarbonyl-4-O-(2,3,6-tri-O-benzyl-4-O-(2,3-di-O-methyl-4-O-(2,3,4-tri-O-methyl-6-O-benzyl- α -D-glucopyranosyl)- β -D-



glucopyranosyl)- α -D-glucopyranosyl)- α -L-idopyranosyl)- α -D-glucopyranoside (56):

Pentasaccharide **55** (0.20 g, 108.21 μ mol) dissolved in 3 mL anhydrous pyridine was cooled to 0 °C using ice-bath. 70% Hydrogen fluoride in pyridine (56.02 μ L, 435.20 μ mol) was added in drop wise manner and stirred for 4 hours at room temperature. After the complete consumption of starting material, the reaction was arrested with adding 5 mL ice-cold water, diluted with 1 N HCl solution (5 mL), extracted with ethylacetate (3 X 10 mL), and organic layer was combined, washed with brine (10 mL) and concentrated under reduced pressure. The residue was then purified by silica gel flash column chromatography using mixture of ethylacetate:hexane as eluent to obtain 0.15 g of pentasaccharide **56** (87%); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +24.0°; 1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.11 (m, 35H), 5.44 (d, J = 3.9 Hz, 1H), 5.19 (d, J = 6.7 Hz, 1H), 5.05 (d, J = 3.6 Hz, 1H), 4.80 (m, 2H), 4.76 – 4.65 (m, 4H), 4.64 – 4.54 (m, 4H), 4.51 (s, 1H), 4.49 – 4.43 (m, 4H), 4.35 (d, J = 6.1 Hz, 1H), 4.17 (d, J = 7.9 Hz, 1H), 3.81 – 3.71 (m, 8H), 3.64 (m, 2H), 3.61 (s, 1H), 3.58 (d, J = 4.5 Hz, 1H), 3.54 (s, 3H), 3.50 (s, 3H), 3.47 (s, 3H), 3.45 (s, 1H), 3.41 (s, 2X3H), 3.38 (s, 3H), 3.37 (s, 3H), 3.35 (s, 3H), 3.29 (s, 3H), 3.27 – 3.18 (m, 2H), 3.17 (s, 1H), 3.14 – 3.07 (m, 2H), 3.07 – 3.02 (m, 1H), 2.91 – 2.83 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 139.2, 139.1, 138.4, 138.4, 138.3, 138.1, 137.9, 128.7(2C), 128.5, 128.5(2C), 128.5, 128.4, 128.4, 128.3(2C), 128.3(2C), 128.2(2C), 128.2(2C), 128.1, 128.1, 128.0(2C), 128.0(3C), 127.9, 127.8(2C), 127.8, 127.8(3C), 127.8, 127.7, 127.5, 127.4, 127.4, 102.8, 100.1, 99.0, 98.4, 96.8, 86.5, 85.0, 83.5, 83.5, 81.8, 80.6, 80.3, 79.5, 79.5, 79.4, 78.7, 77.4, 76.7, 75.8, 75.7, 75.3, 74.3, 73.7, 73.6, 73.5, 73.4, 73.1, 73.0, 72.6, 71.1, 71.0, 70.3, 68.5, 68.1, 67.4, 62.0, 60.9, 60.8, 60.5, 60.3, 60.3, 60.1, 59.7, 55.4, 51.6; HRMS (ESI-MS): m/z calculated for $C_{88}H_{110}O_{27}$ $[M+Na]^+$: 1621.7132, Found: 1621.7130.

Methyl 4-O-(2,3-di-O-methyl-5C-carboxylate-4-O-(4-O-(2,3-di-O-methyl-5C-carboxylate-4-O-2,3,4-tri-O-methyl- α -D-glucopyranosyl)- β -D-glucoronopyranosyl)- α -D-glucopyranosyl)- α -L-idopyranosyl)- α -D-glucopyranoside (57):



Step 1. C-6 Hydroxyl oxidation: To a biphasic solution of pentasaccharide **56** (100 mg, 62.51 μ mol) in 3 mL $\text{CH}_2\text{Cl}_2\text{:H}_2\text{O}$ (2:1) was added (diacetoxyiodo)benzene (50.33 mg, 156.27 μ mol) and TEMPO (2.95 mg, 18.75 μ mol) simultaneously and stirred vigorously at room temperature. After 4 hours, the reaction was arrested by adding saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (Appr. 5 mL), extracted with CH_2Cl_2 (3 X 10 mL), combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude was washed with n-pentane (2 X 5 mL) to remove excess reagents, redissolved in 1.5 mL THF and cooled to 0 $^\circ\text{C}$. Then an aqueous solution of 30% H_2O_2 (0.5 mL) and 1 M solution of LiOH (0.5 mL) was added in drop wise manner at same temperature. After 10 hours, as the reaction was not completed 1 M KOH solution (0.5 mL) was added and further stirred for 24 hours at room temperature. After good conversion, the reaction mixture was neutralized with AcOH, solvents were evaporated under reduced pressure. The crude was then passed through pad of silica gel using 5% CH_3OH in CH_2Cl_2 to obtain xx mg white powder; **Step 2. Hydrogenolysis procedure:** In a vigorously stirring solution of crude pentasaccharide (40 mg, 25.00 μ mol) dissolved in 1.5 mL methanol, 0.2 mL formic acid and 20% $\text{Pd}(\text{OH})_2/\text{C}$ (20 mg) was added and stirred for 36 hours at room temperature. After completion, reaction was passed through small bed of celite[®] column to remove black particles and concentrated under reduced pressure. The crude was passed through bond-elute column using 25% methanol in water as mobile phase, collected in vials, and lipolysed to obtain 18 mg white solid compound (74%); $[\alpha]_D^{25}$ (MeOH, c 1.0): +15.0 $^\circ$; ^1H NMR (400 MHz, MeOD) δ 5.43 (d, J = 3.6 Hz, 1H), 5.15 (s, 1H), 5.04 (d, J = 3.2 Hz, 1H), 4.98 (s, 1H), 4.67 (d, J = 3.0 Hz, 1H), 4.56 (d, J = 7.5 Hz, 1H), 4.13 (s, 1H), 3.96 (s, 1H), 3.88 (s, 1H), 3.85 (s, 1H), 3.82 (s, 1H), 3.80 – 3.63 (m, 10H), 3.62 (s, 3H), 3.61 – 3.60 (m, 1H), 3.59 (s, 3H), 3.45 – 3.43 ((s, 3H), 3.56 (s, 3H), 3.54 (s, 3H), 3.52 (s, 3H), 3.50 (s, 3H), 3.49 m, 1H), 3.42 – 3.40 (m, 2H), 3.39 (s, 3H), 3.36 – 3.33 (m, 1H), 3.19 (t, J = 6.0 Hz, 1H), 3.15 – 3.10 (m, 1H),

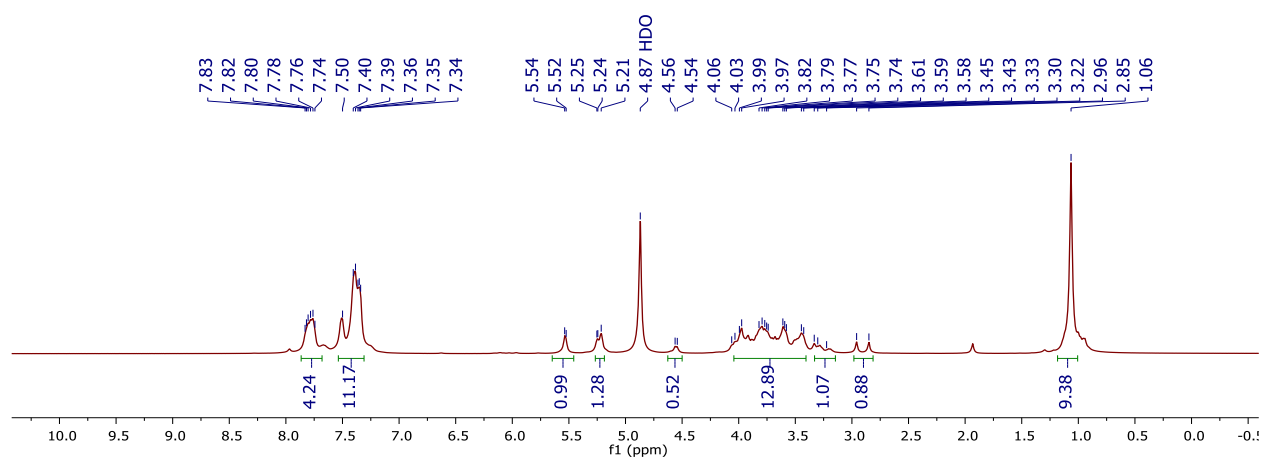
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3.05 (t, $J = 8.1$ Hz, 1H); ^{13}C NMR (151 MHz, MeOD) δ 173.1, 170.7, 103.9, 101.1, 100.1, 98.6, 98.2, 86.9, 85.2, 85.0, 84.4, 84.3, 83.1, 82.9, 79.9, 79.9, 79.4, 78.8, 77.4, 76.2, 73.7, 73.6, 73.5, 73.3, 72.7, 72.6, 72.3, 61.8, 61.1, 61.0, 61.0, 61.0, 60.7, 60.6, 59.9, 59.3, 58.6, 55.6; HRMS (ESI-MS): m/z calculated for $\text{C}_{38}\text{H}_{64}\text{O}_{28} [\text{M}+\text{H}]^+$: 969.3662, Found: 969.3630.

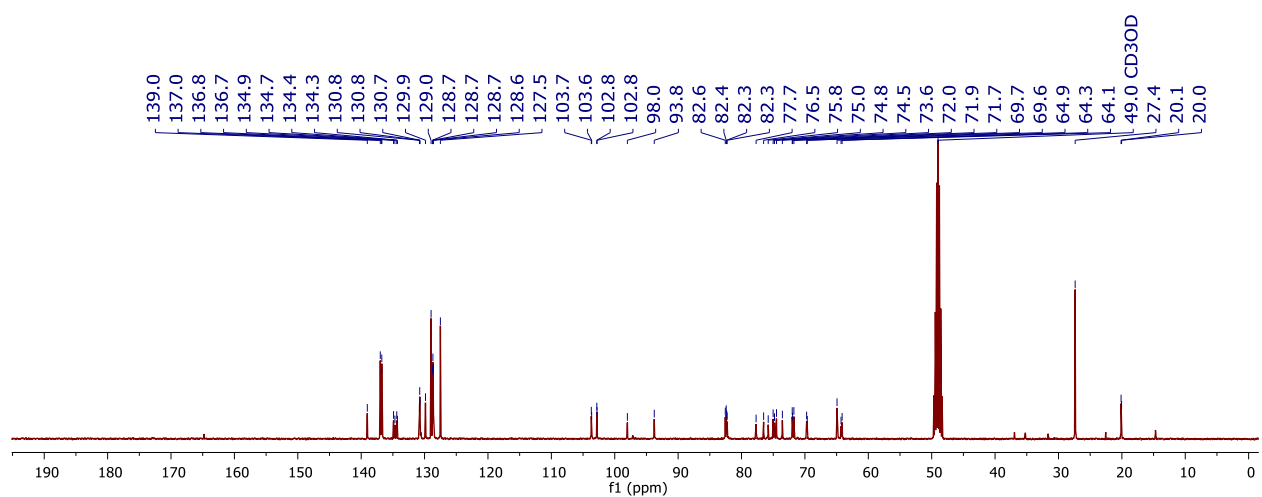
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2.8 Spectral Charts

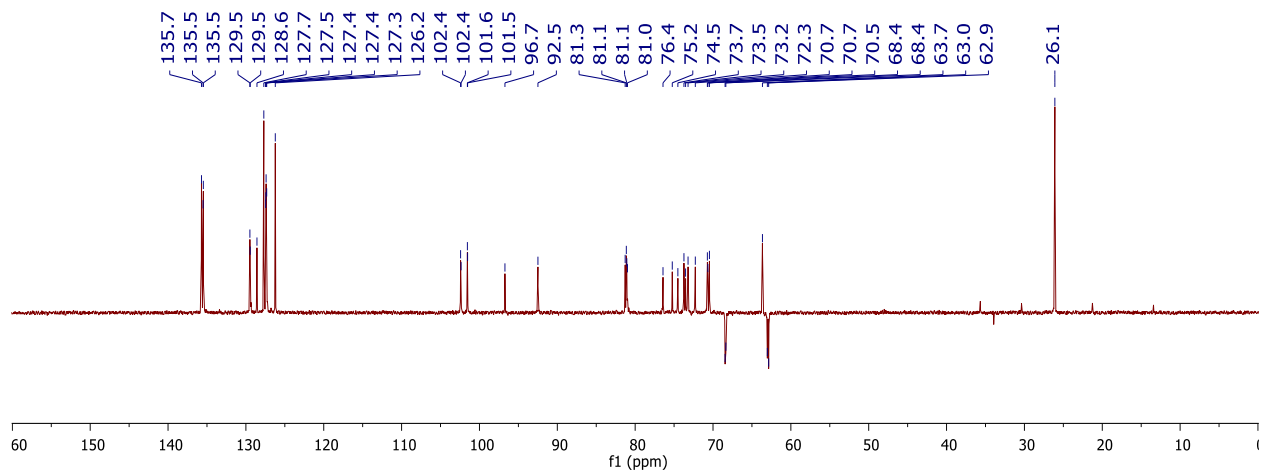
^1H NMR Spectrum (400 MHz, MeOD_4) of compound **30**



^{13}C NMR Spectrum (100 MHz, MeOD_4) of compound **30**

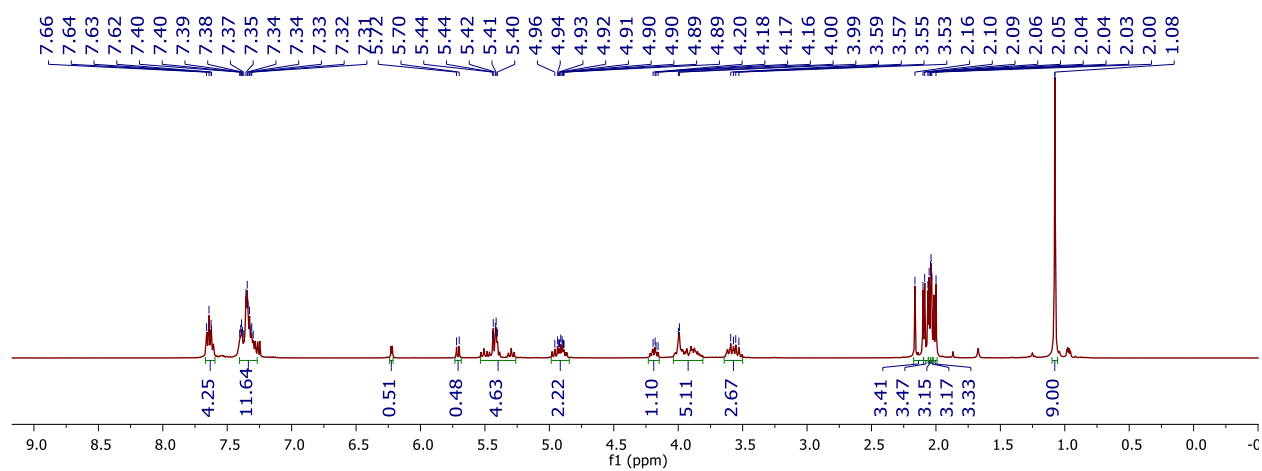


DEPT-135 NMR Spectrum (100 MHz, MeOD_4) of compound **30**

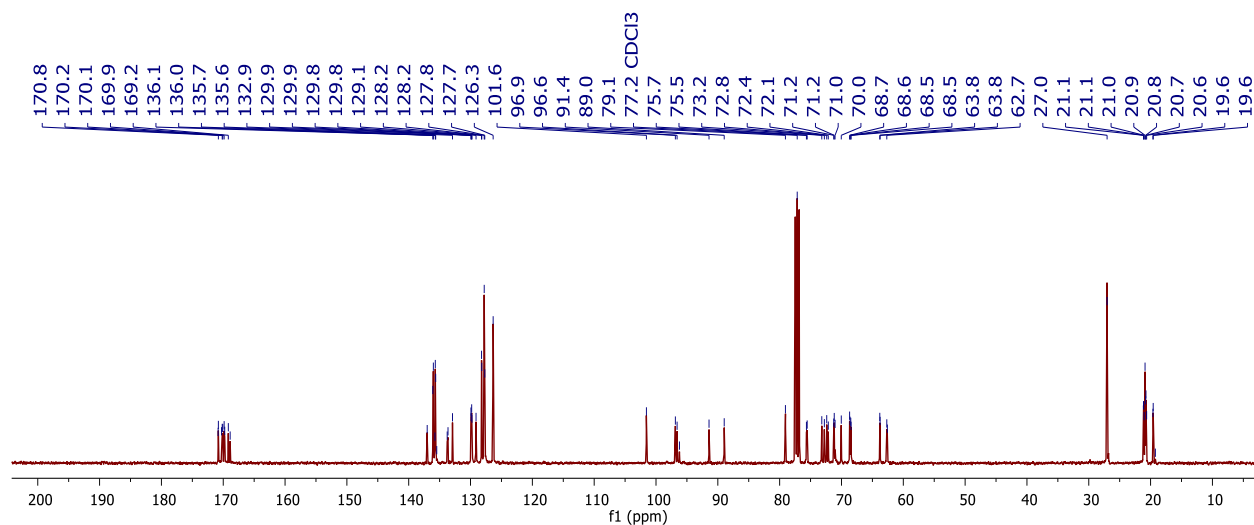


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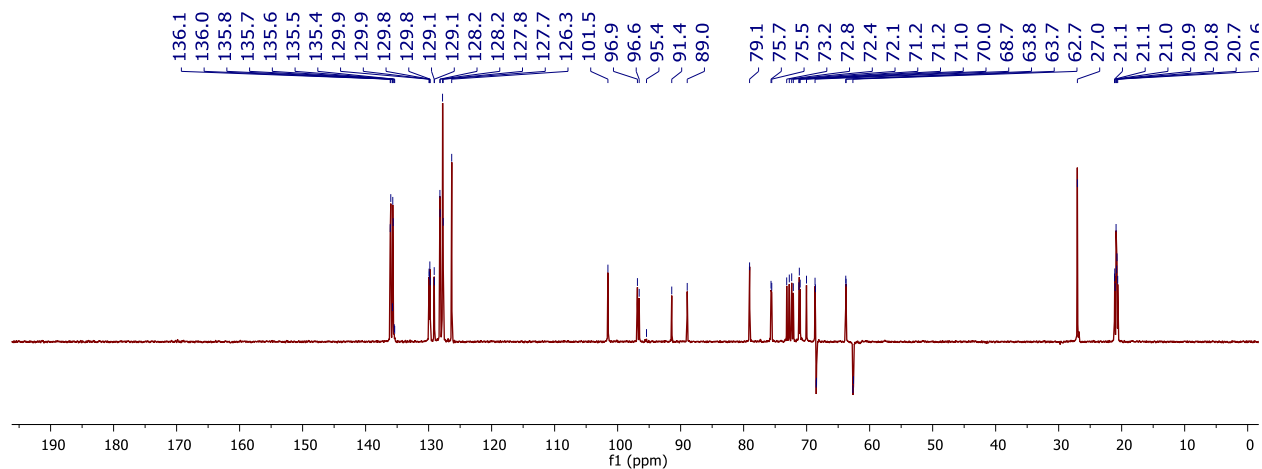
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **31**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **31**

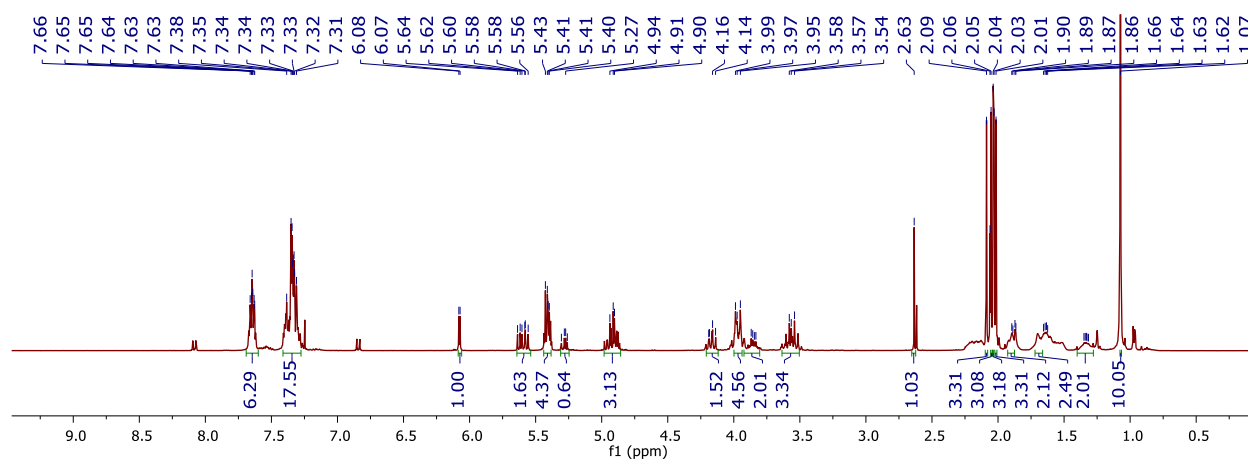


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of compound **31**

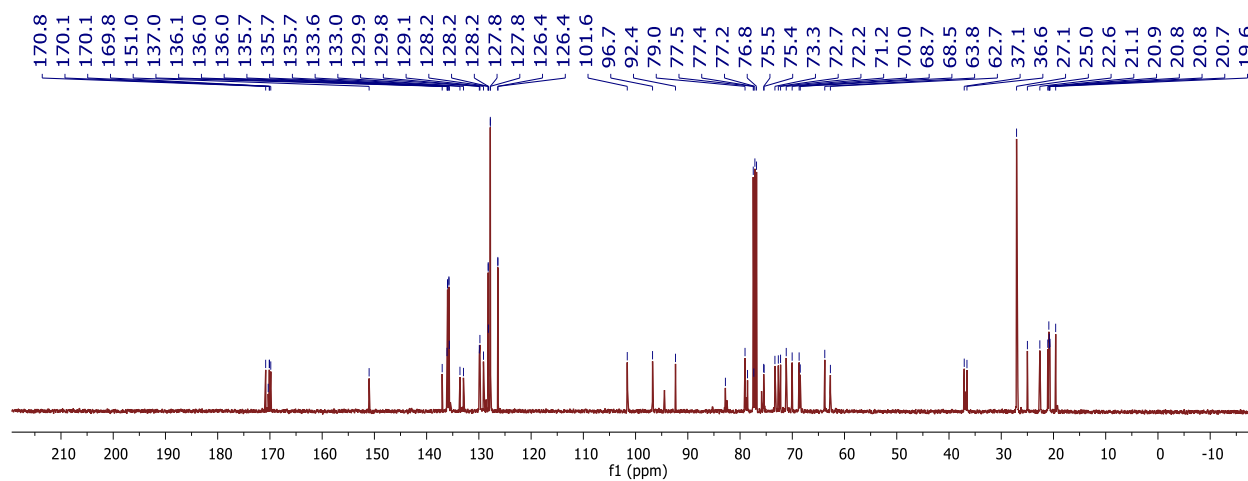


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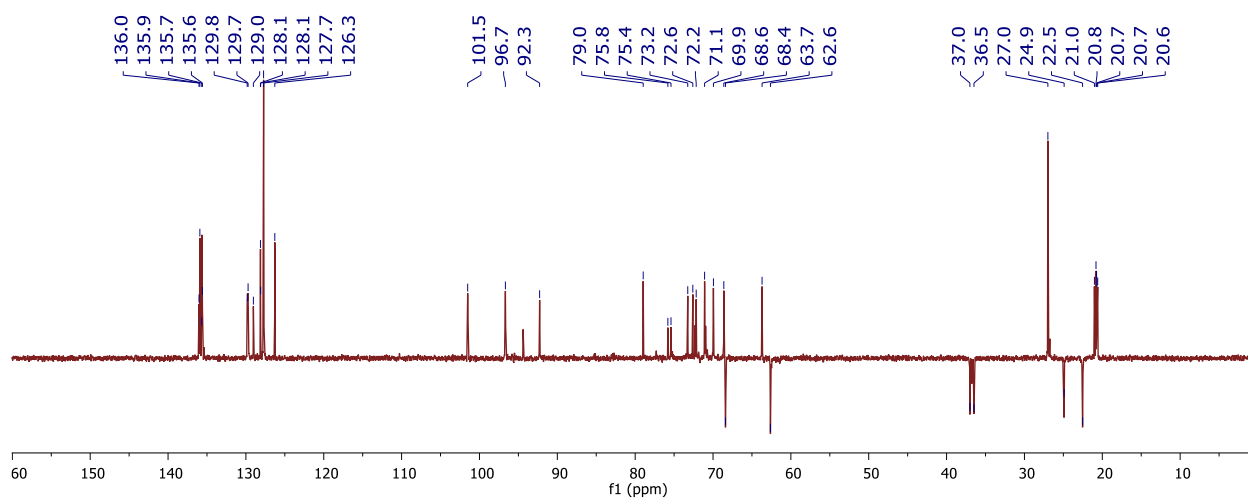
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **26**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **26**

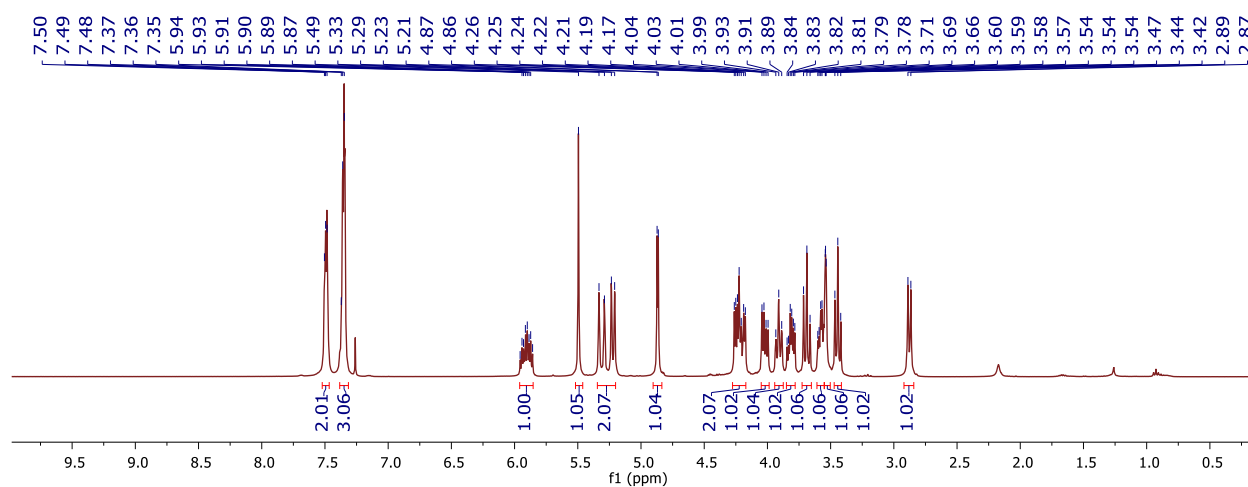


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of compound **26**

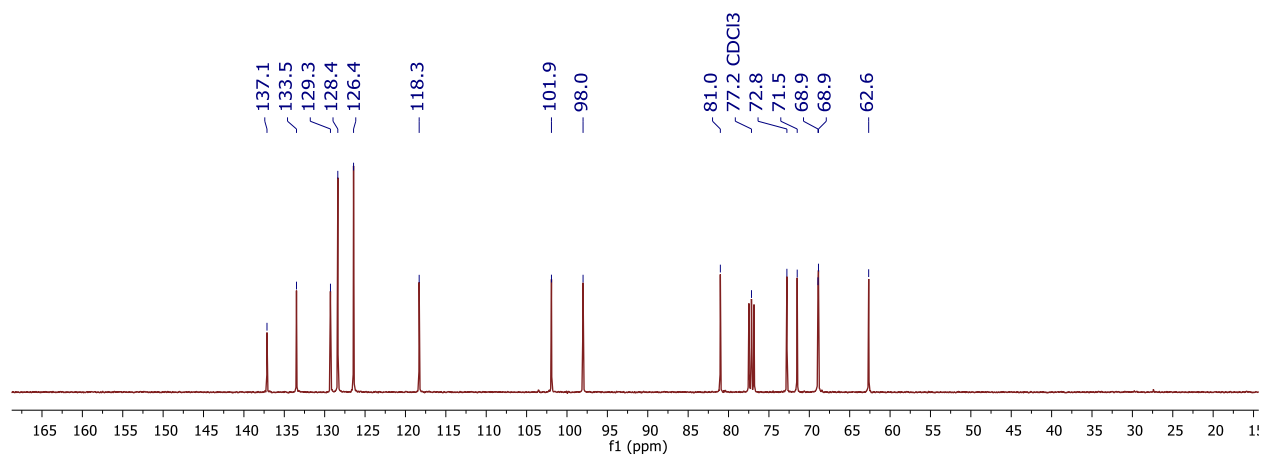


Chapter 2

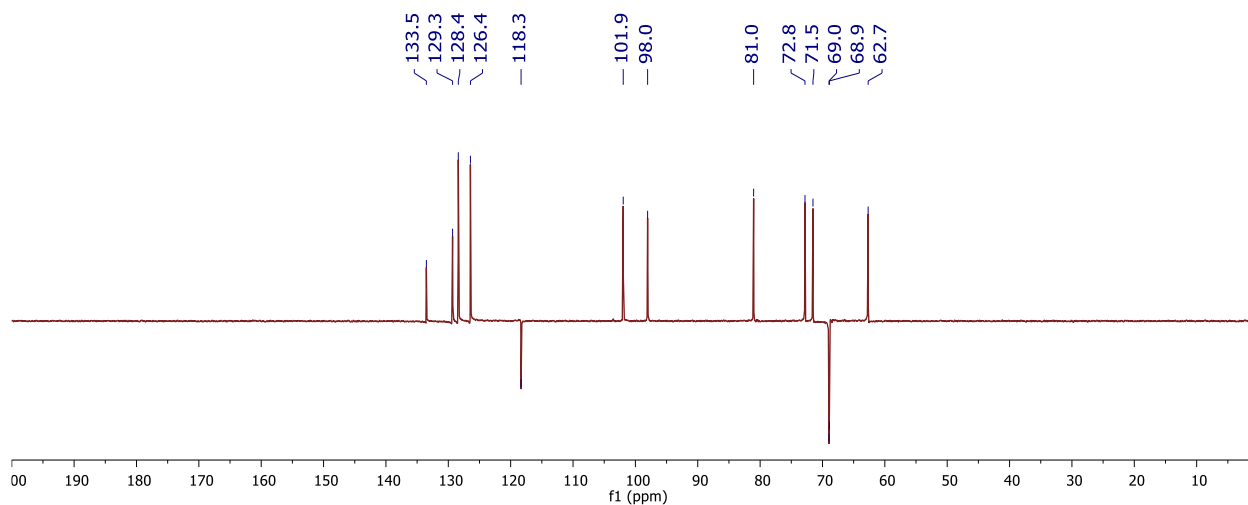
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **33**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **33**

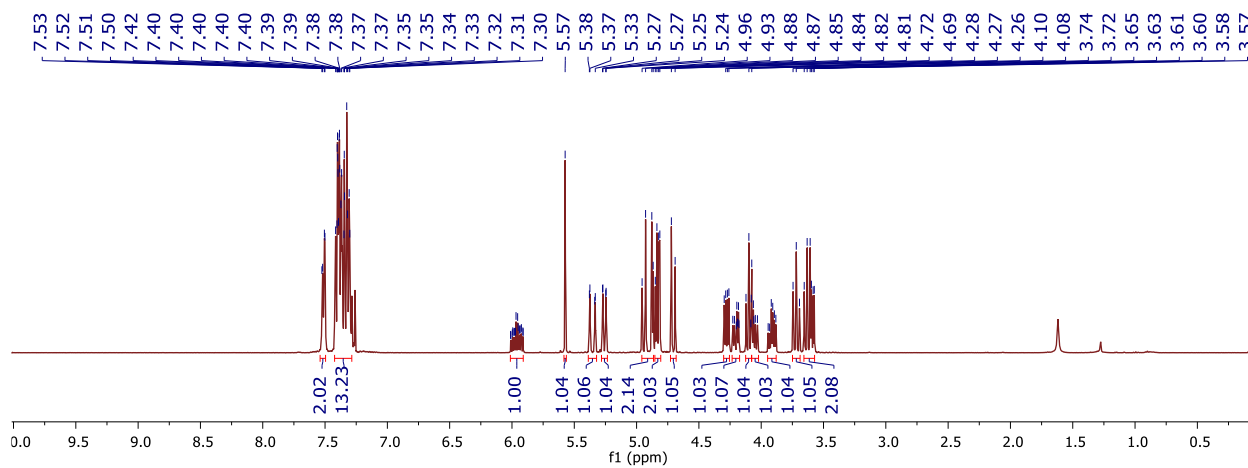


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **33**

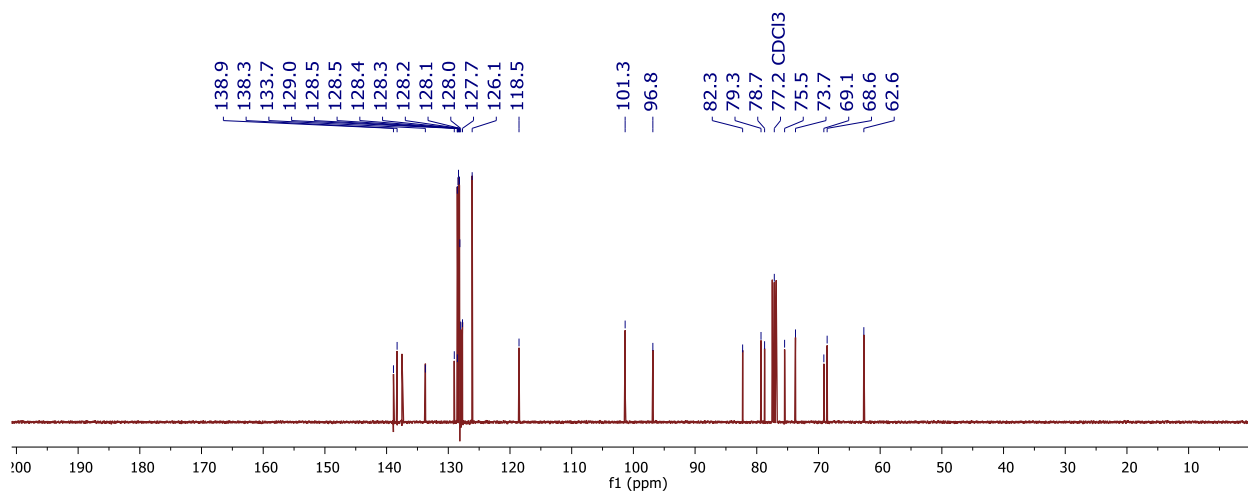


Chapter 2

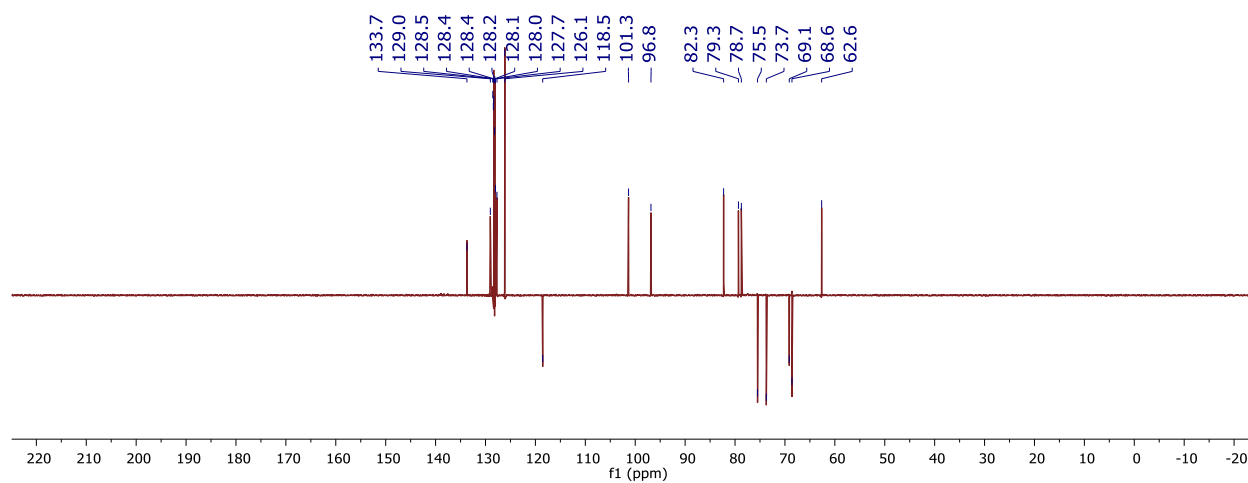
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **34**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **34**

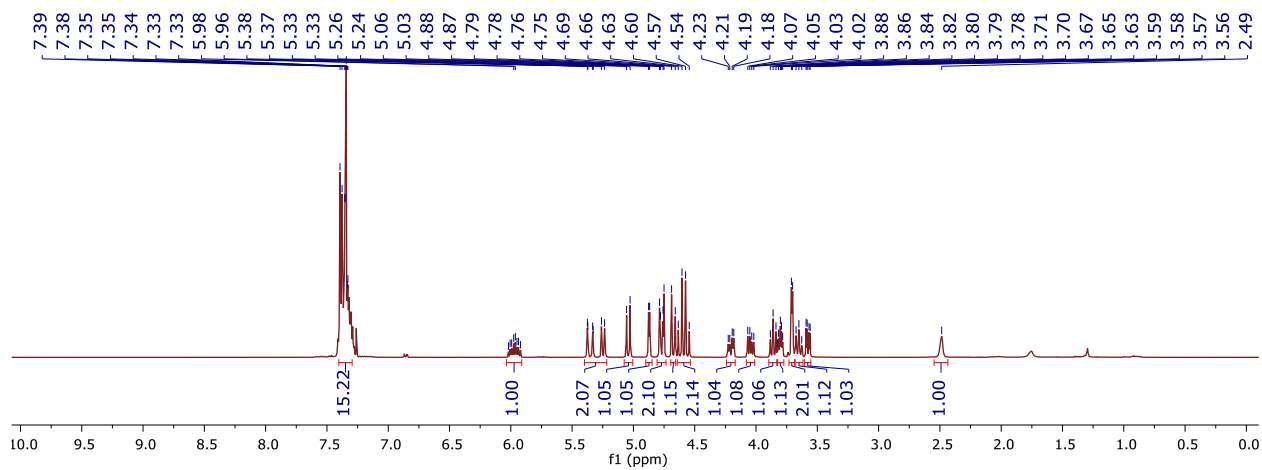


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **34**

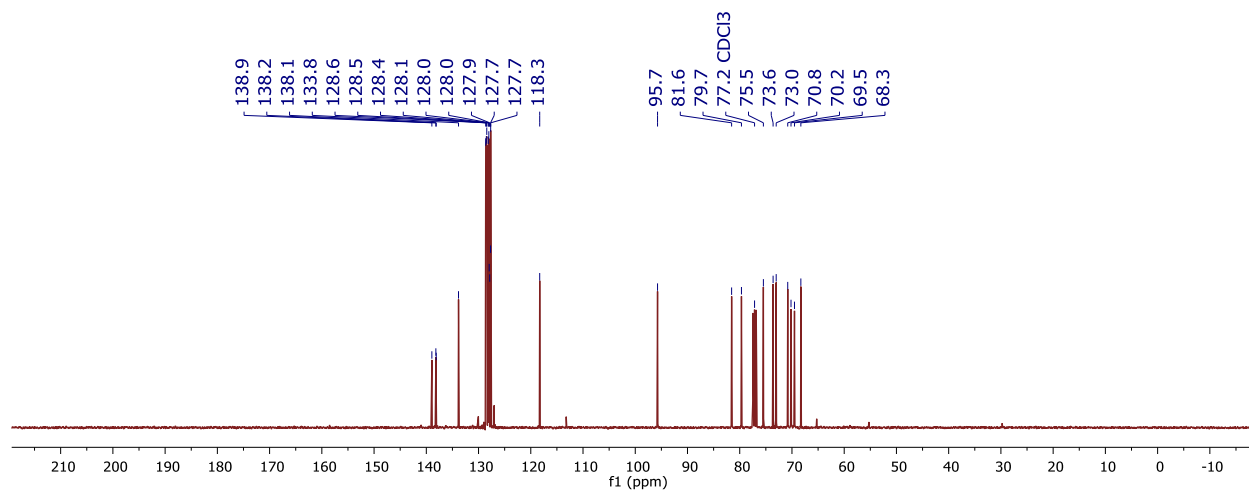


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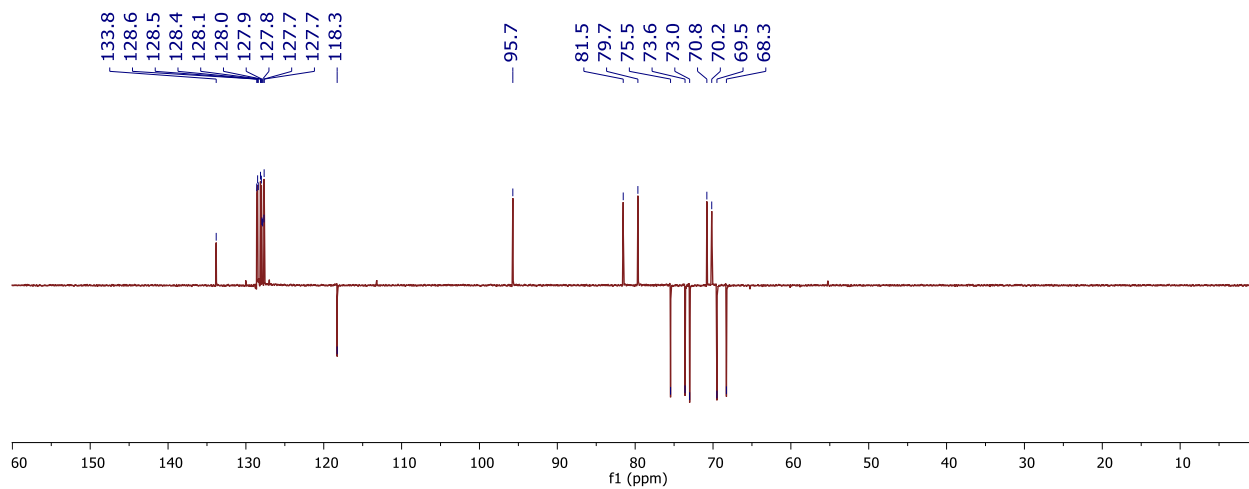
^1H NMR Spectrum (400 MHz, CDCl_3) of compound 27



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound 27

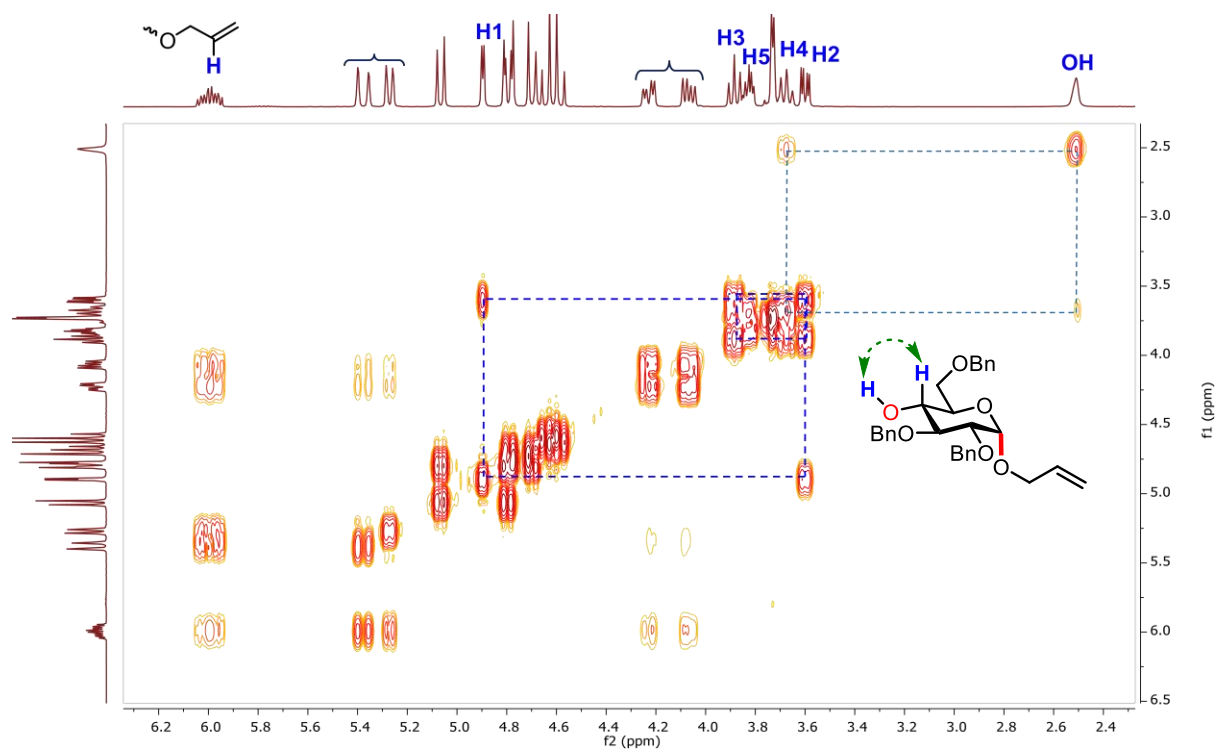


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound 27

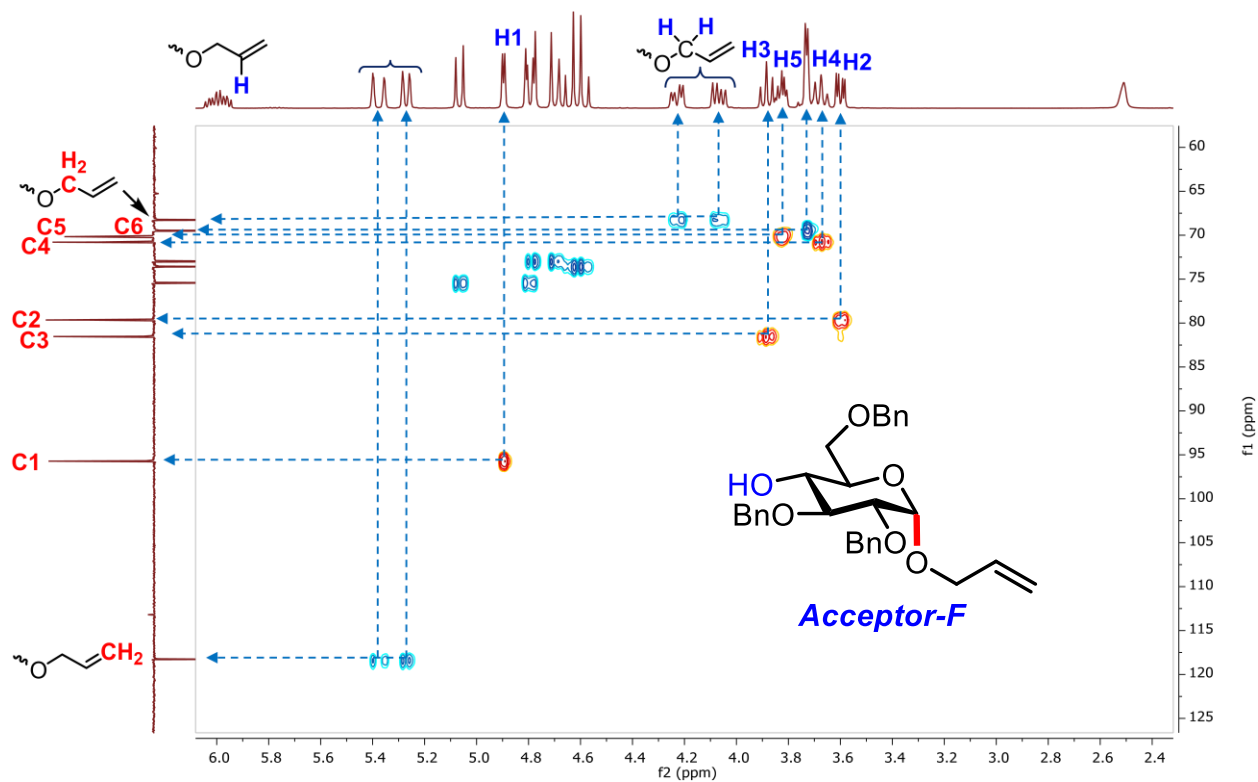


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^1H - ^1H COSY Spectrum (400 MHz, CDCl_3) of compound 27

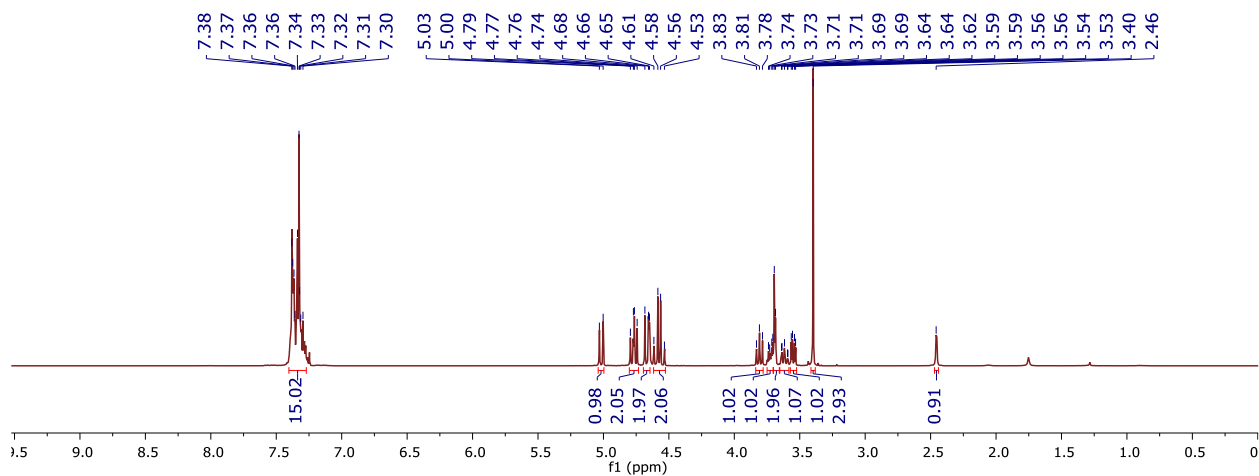


HSQC Spectrum (400 MHz, CDCl_3) of compound 27

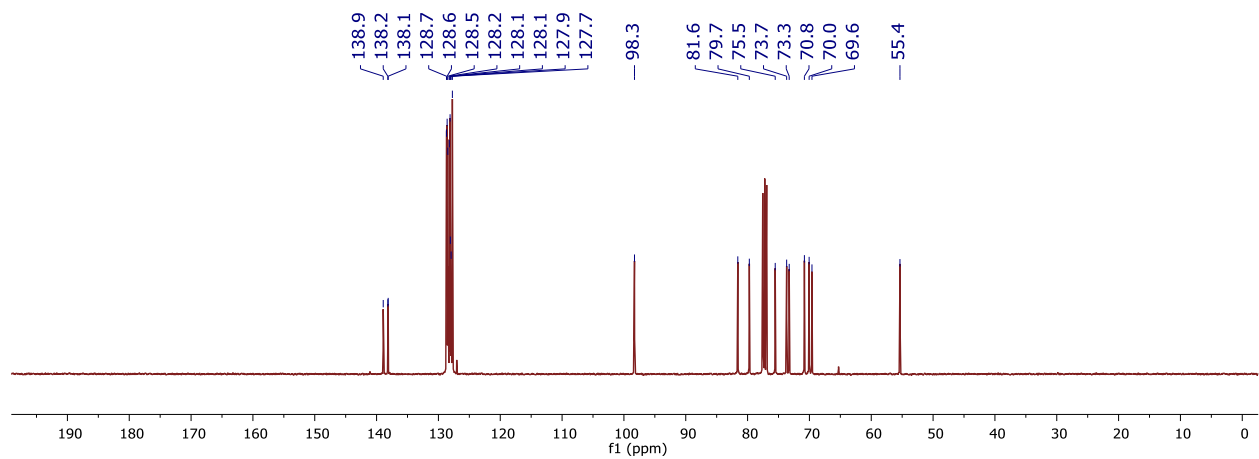


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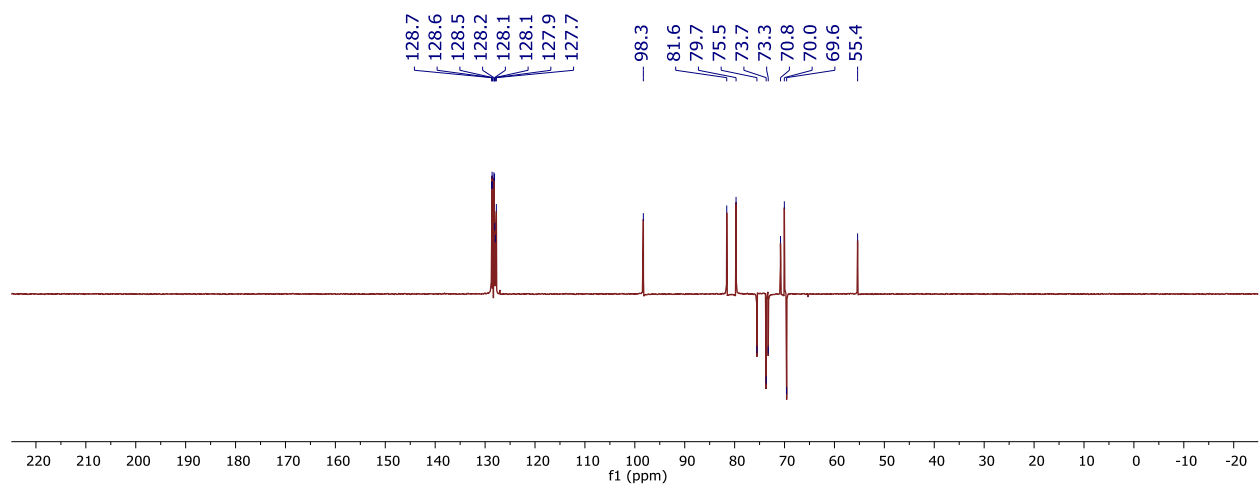
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **29**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **29**

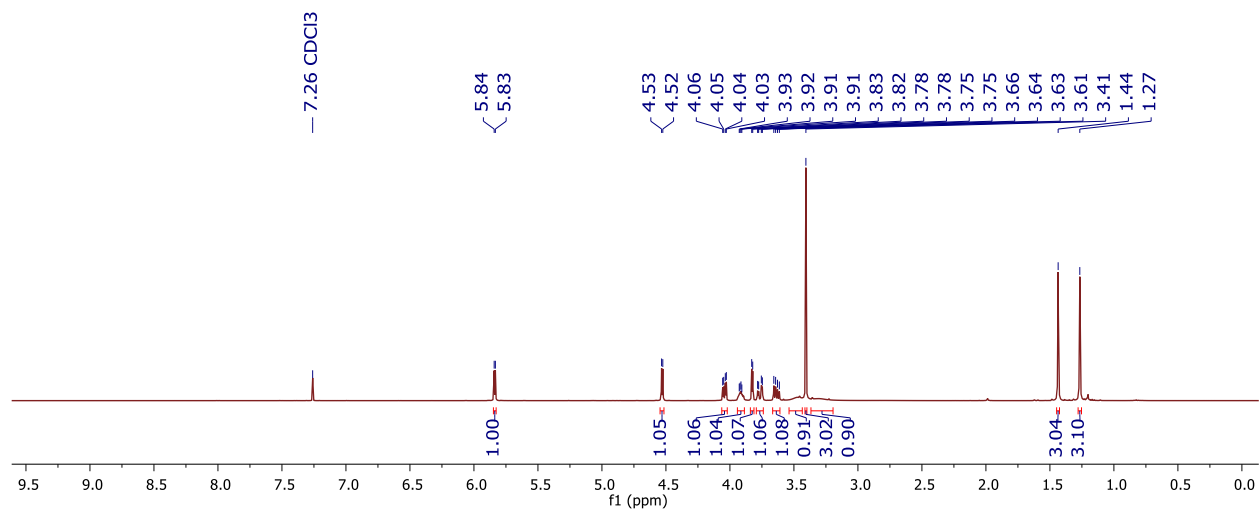


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **29**

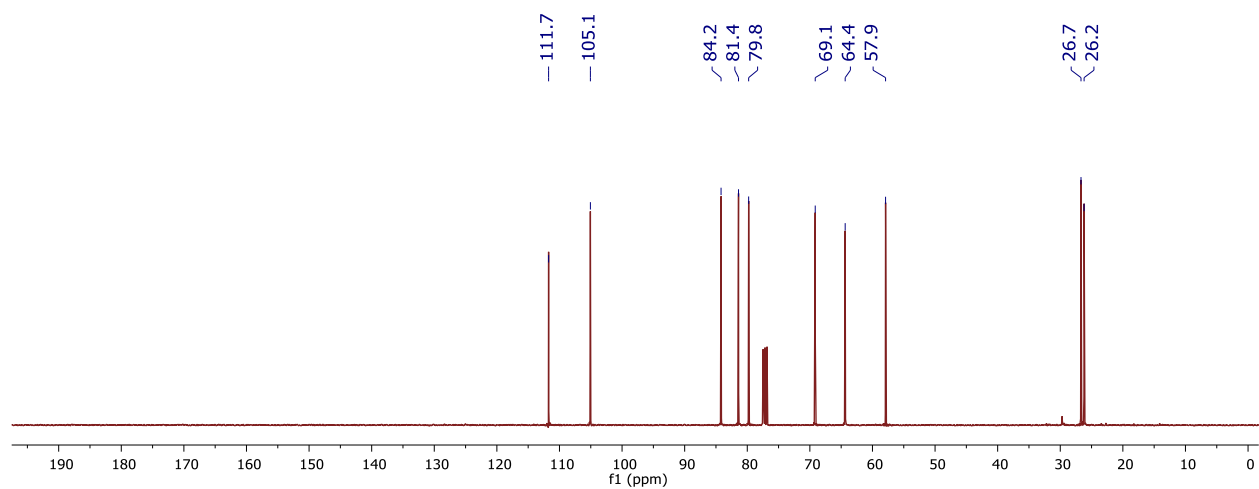


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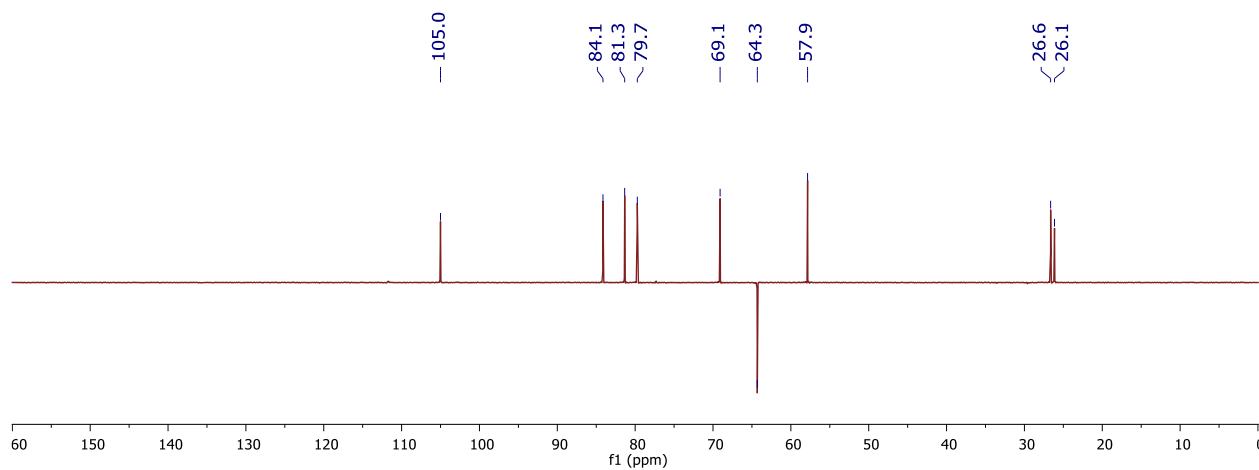
^1H NMR Spectrum (400 MHz, CDCl_3) of compound 35



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound 35

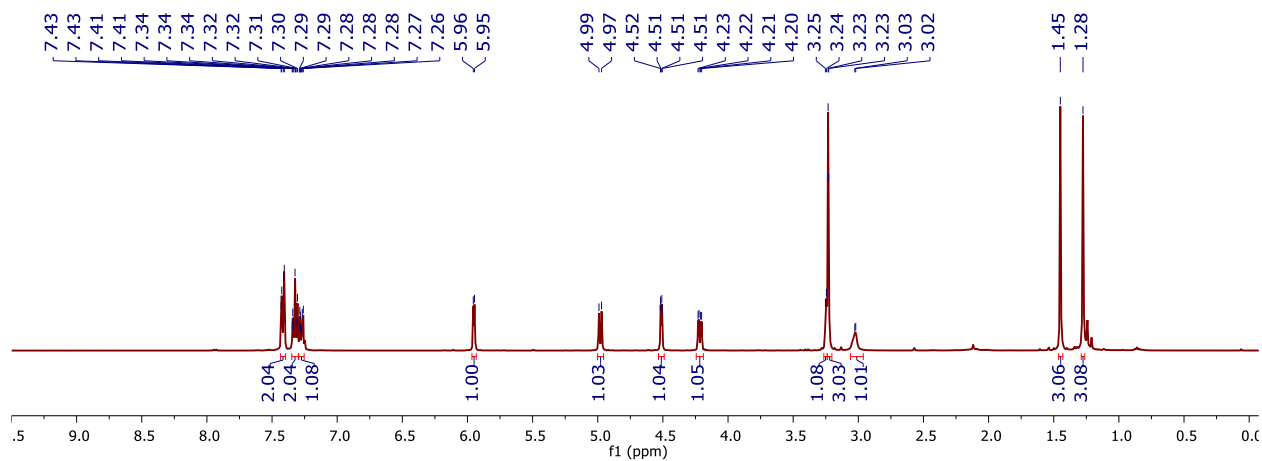


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of compound 35

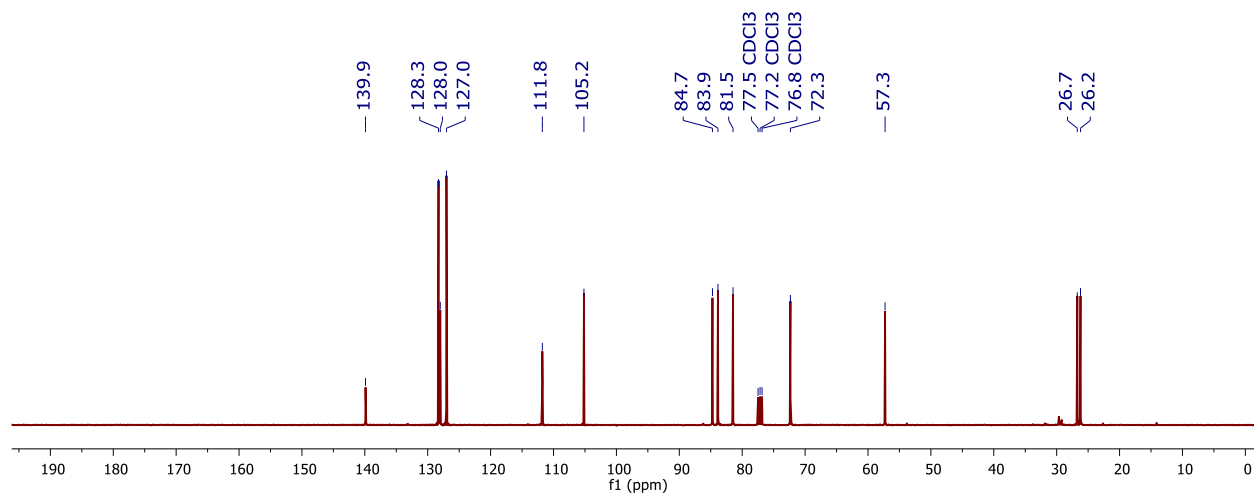


Chapter 2

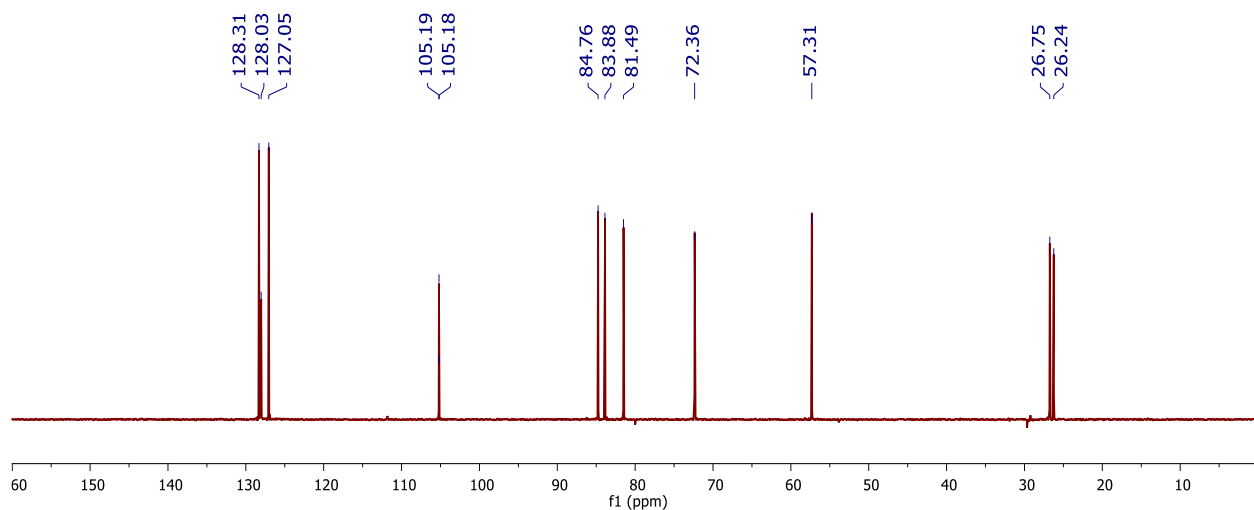
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **38**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **38**

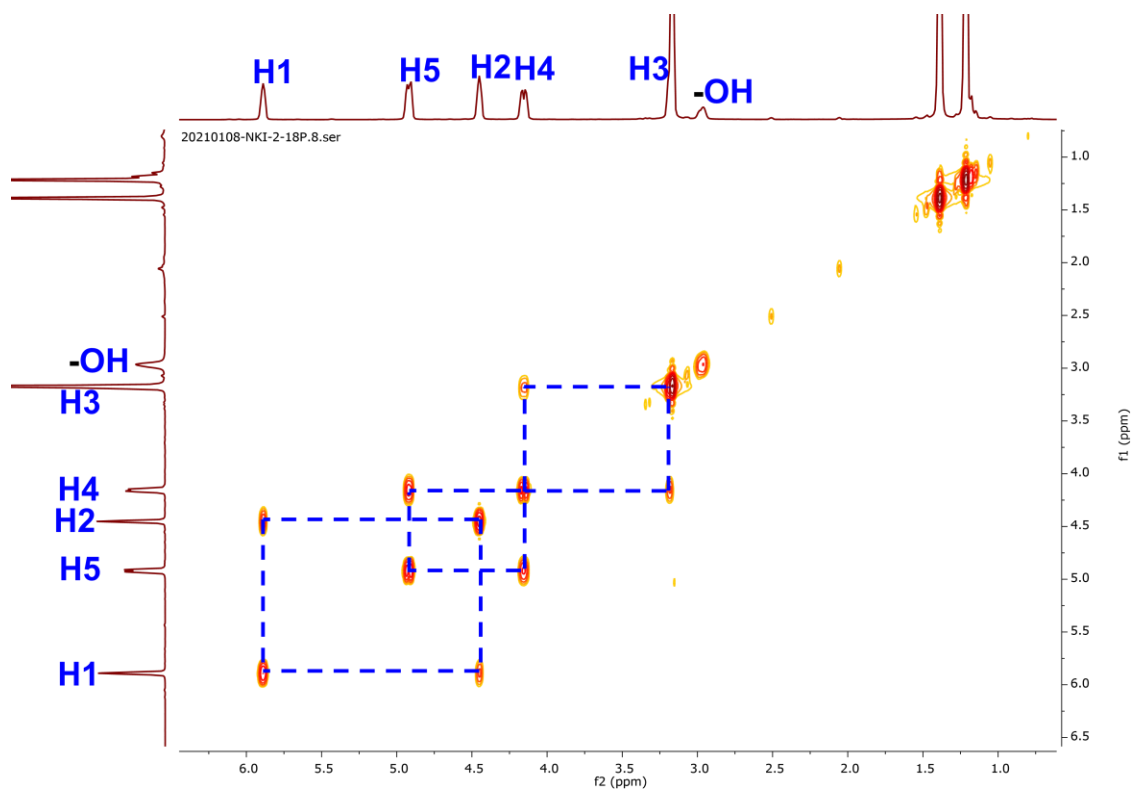


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of compound **38**

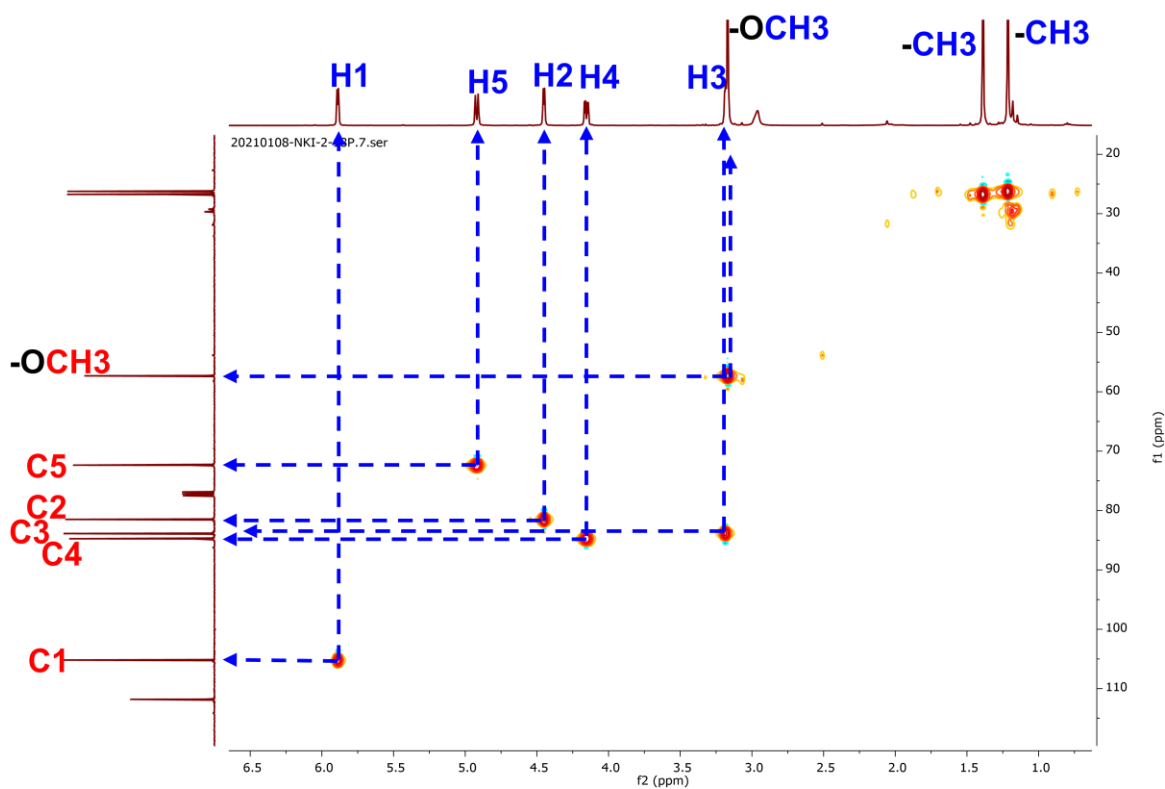


Chapter 2

^1H - ^1H COSY Spectrum (400 MHz, CDCl_3) of compound **38**

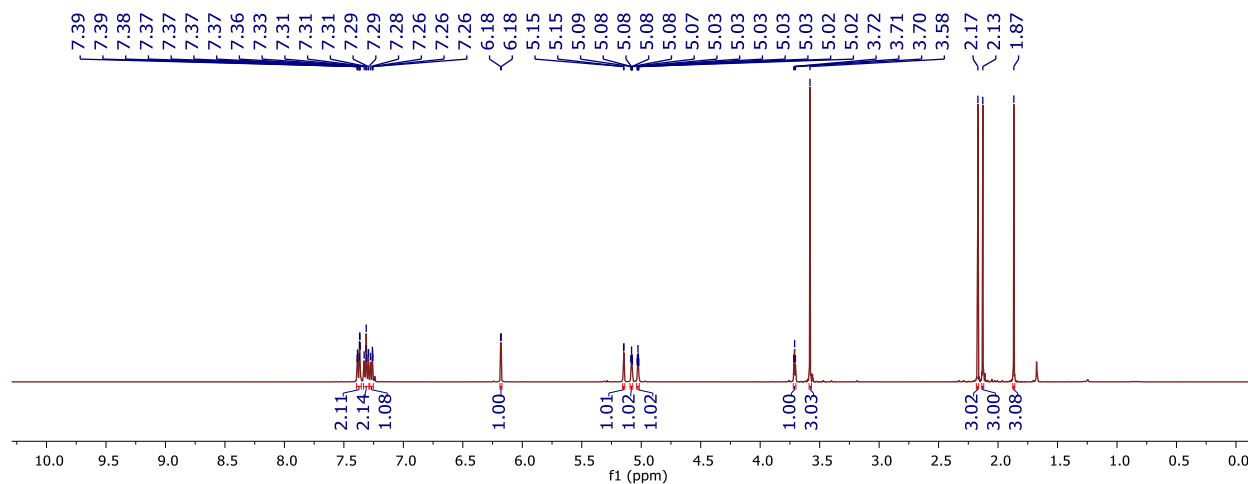


HSQC Spectrum (400 MHz, CDCl_3) of compound **38**

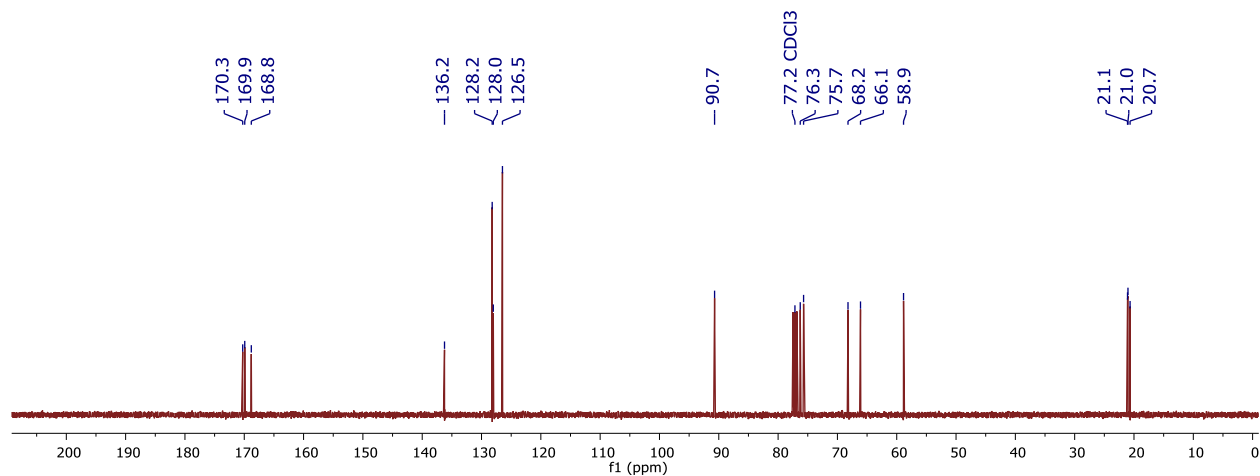


Chapter 2

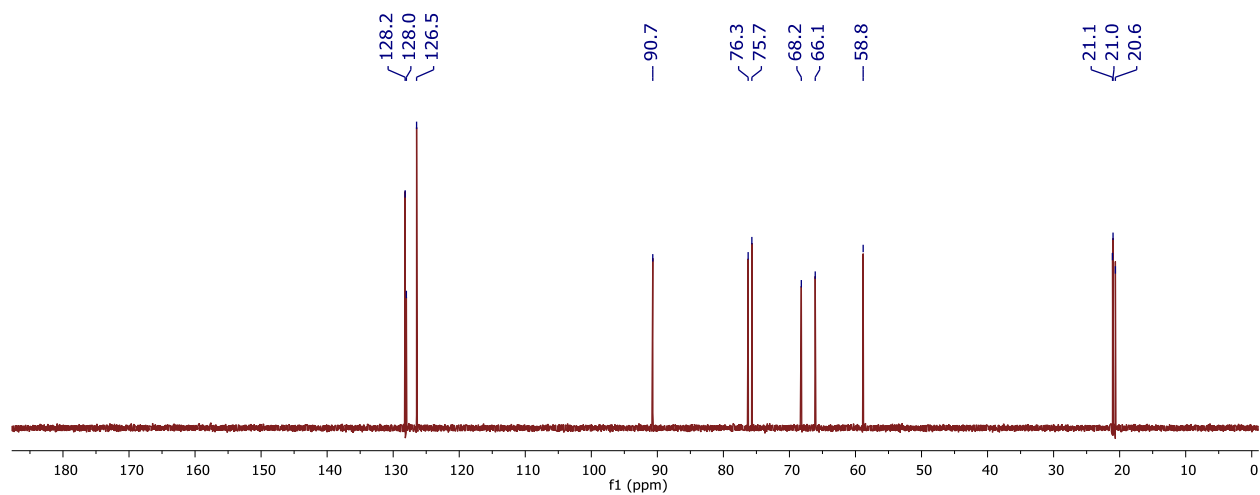
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **39**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **39**

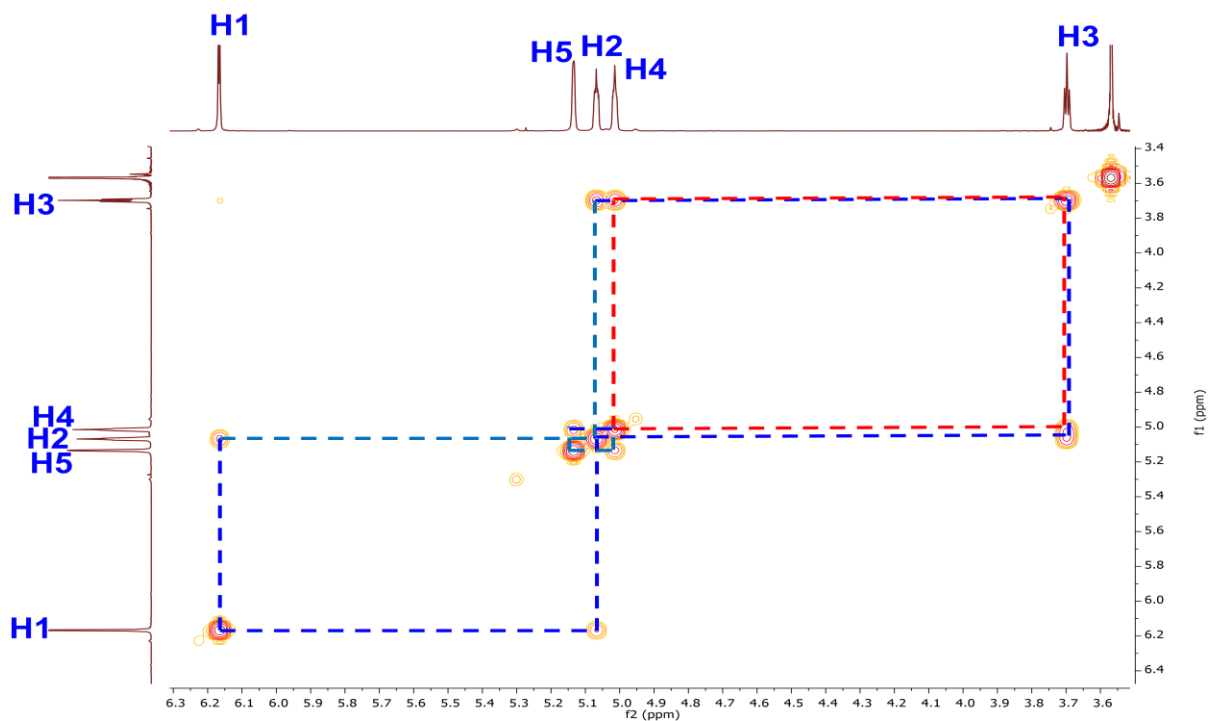


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of compound **39**

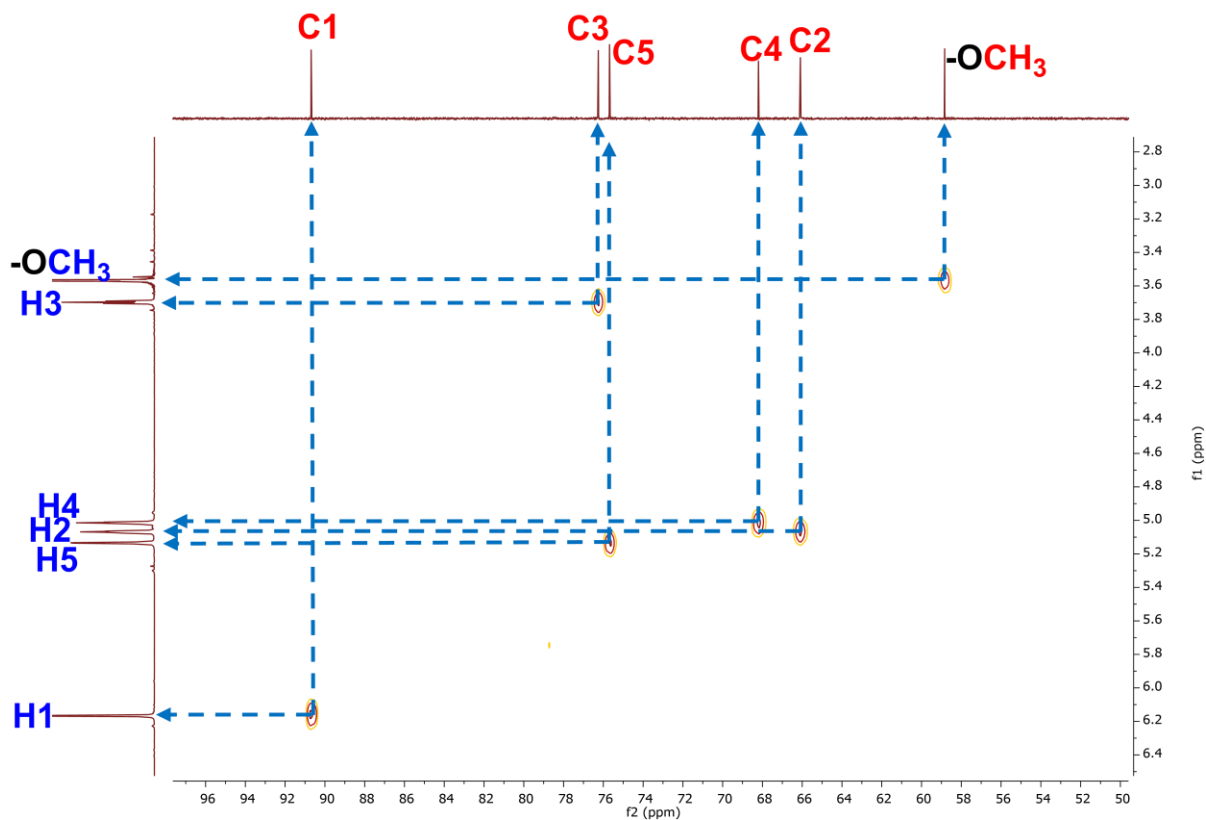


Chapter 2

^1H - ^1H COSY Spectrum (400 MHz, CDCl_3) of compound **39**

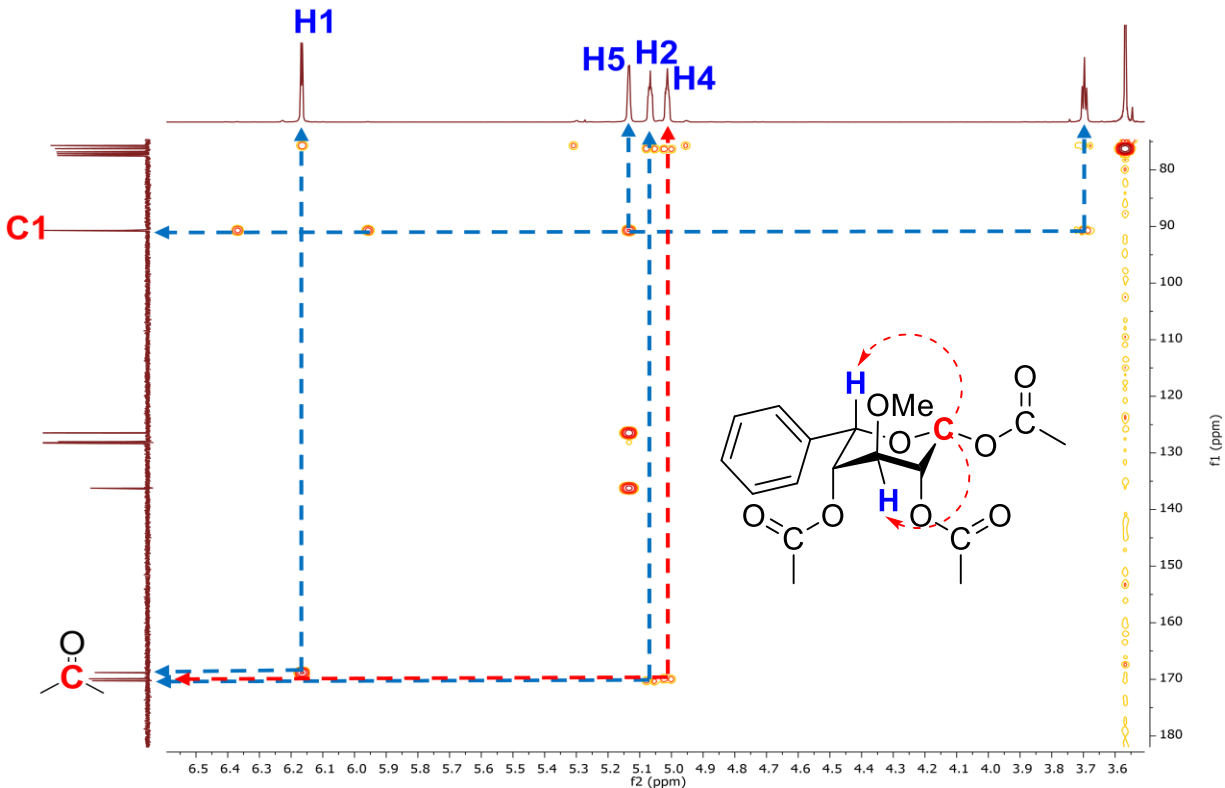


HSQC Spectrum (400 MHz, CDCl_3) of compound **39**

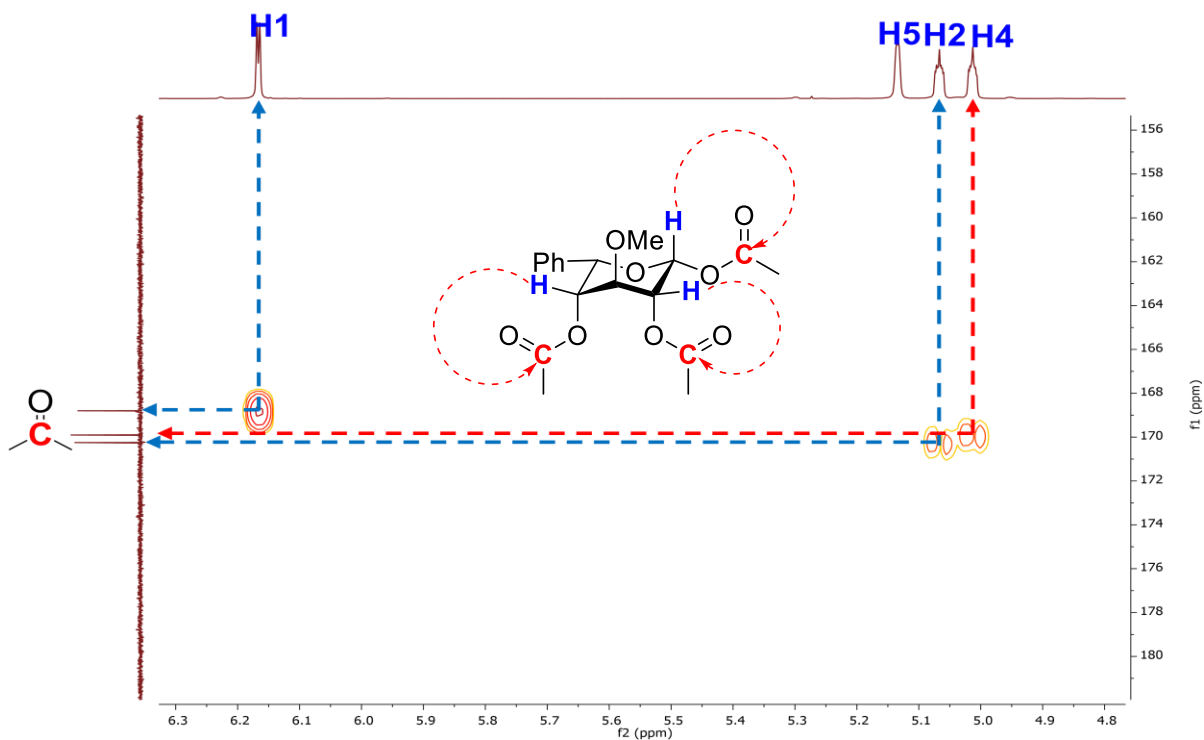


Chapter 2

HMBC Spectrum (400 MHz, CDCl₃) of compound **39**

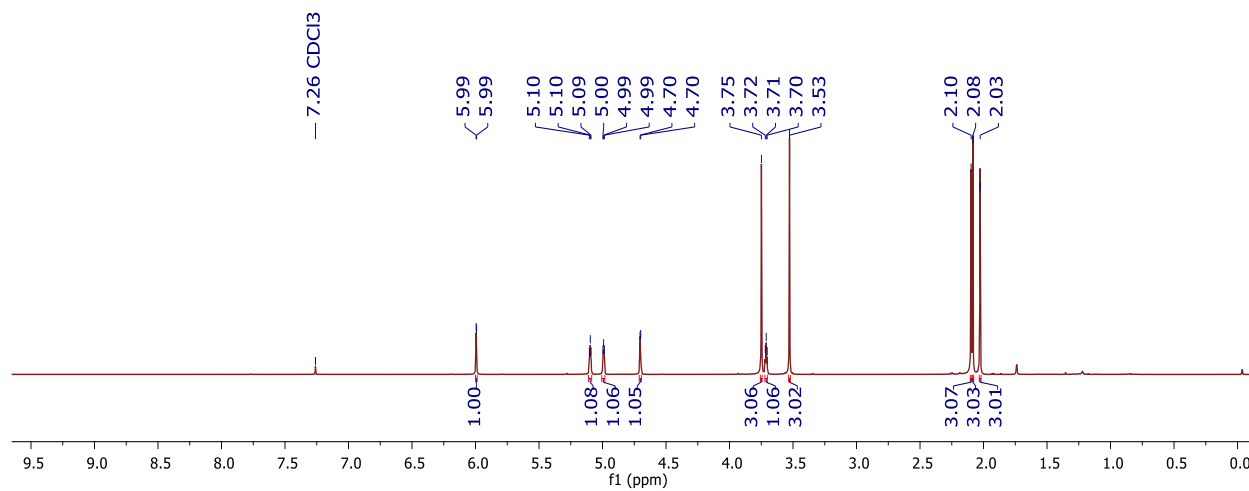


HMBC (Expanded) Spectrum (400 MHz, CDCl₃) of compound **39**

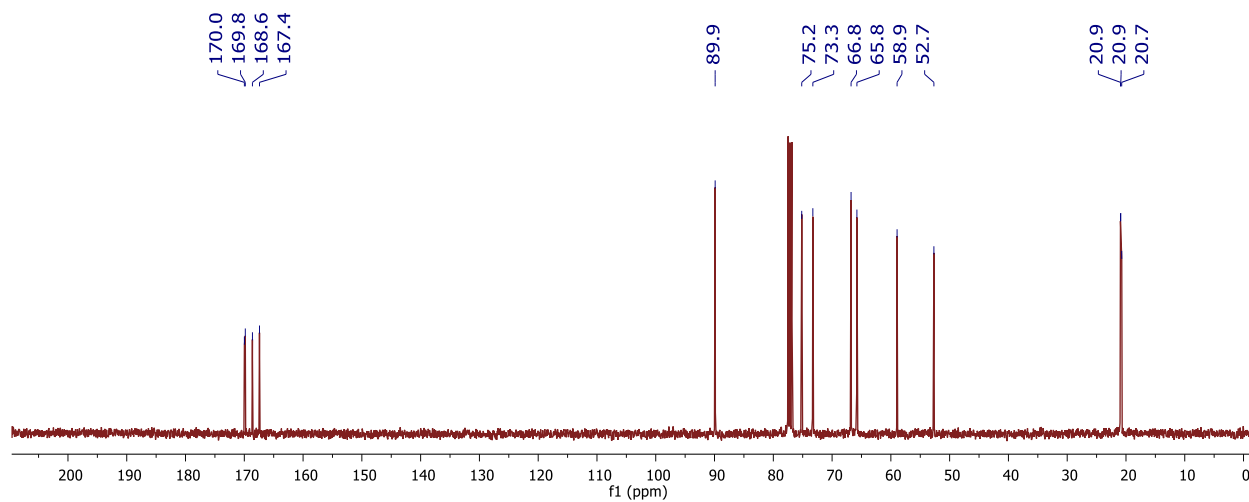


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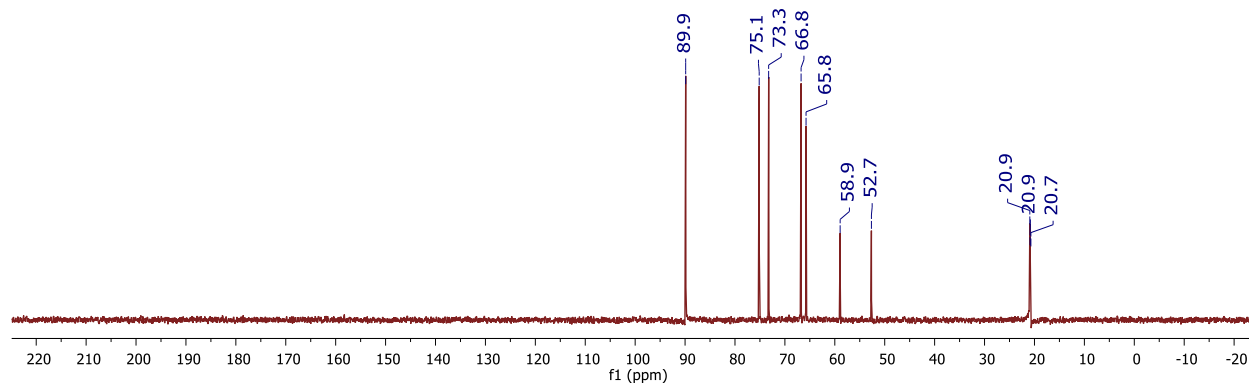
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **40**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **40**

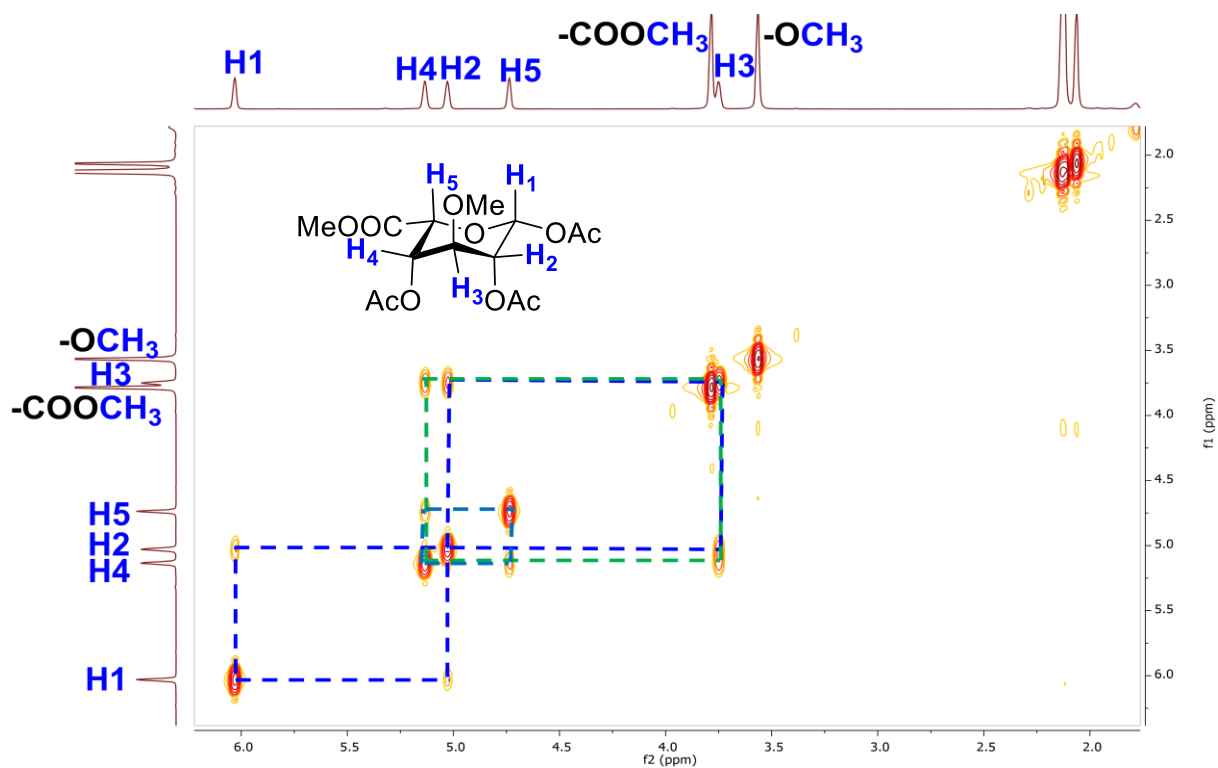


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of compound **40**

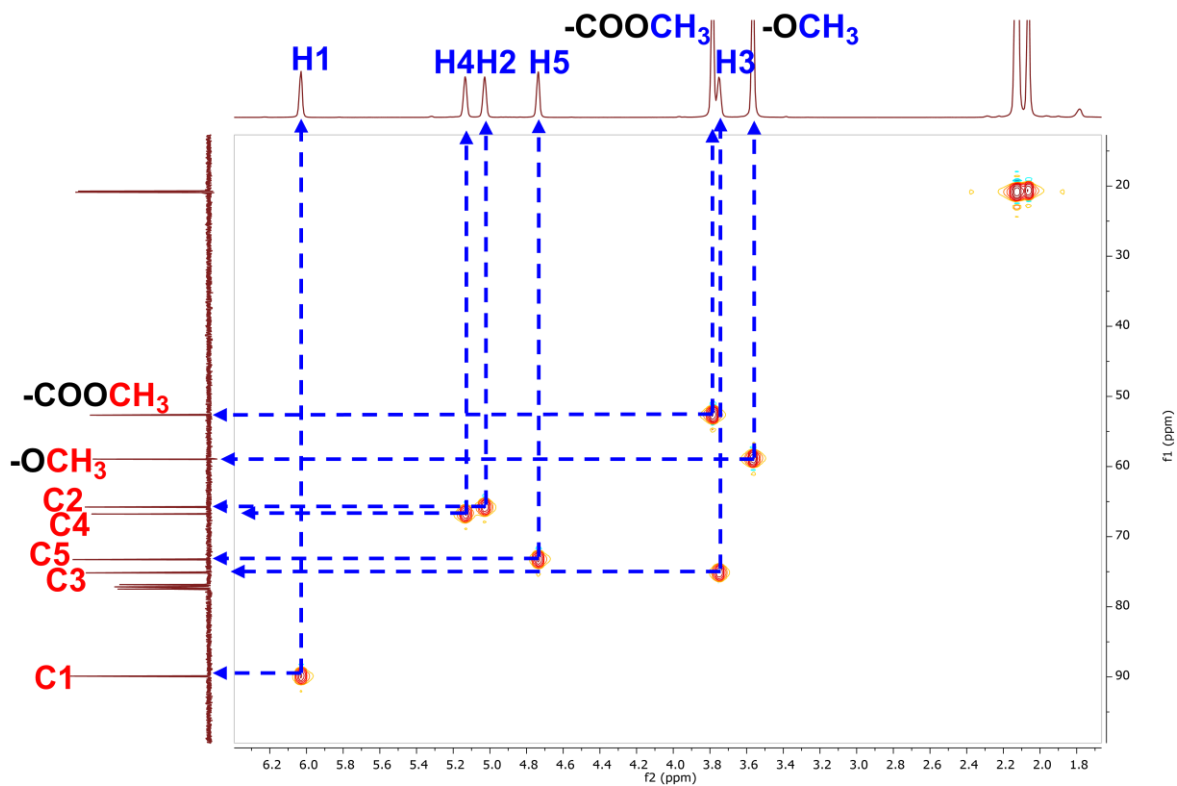


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^1H - ^1H COSY Spectrum (400 MHz, CDCl_3) of compound **40**

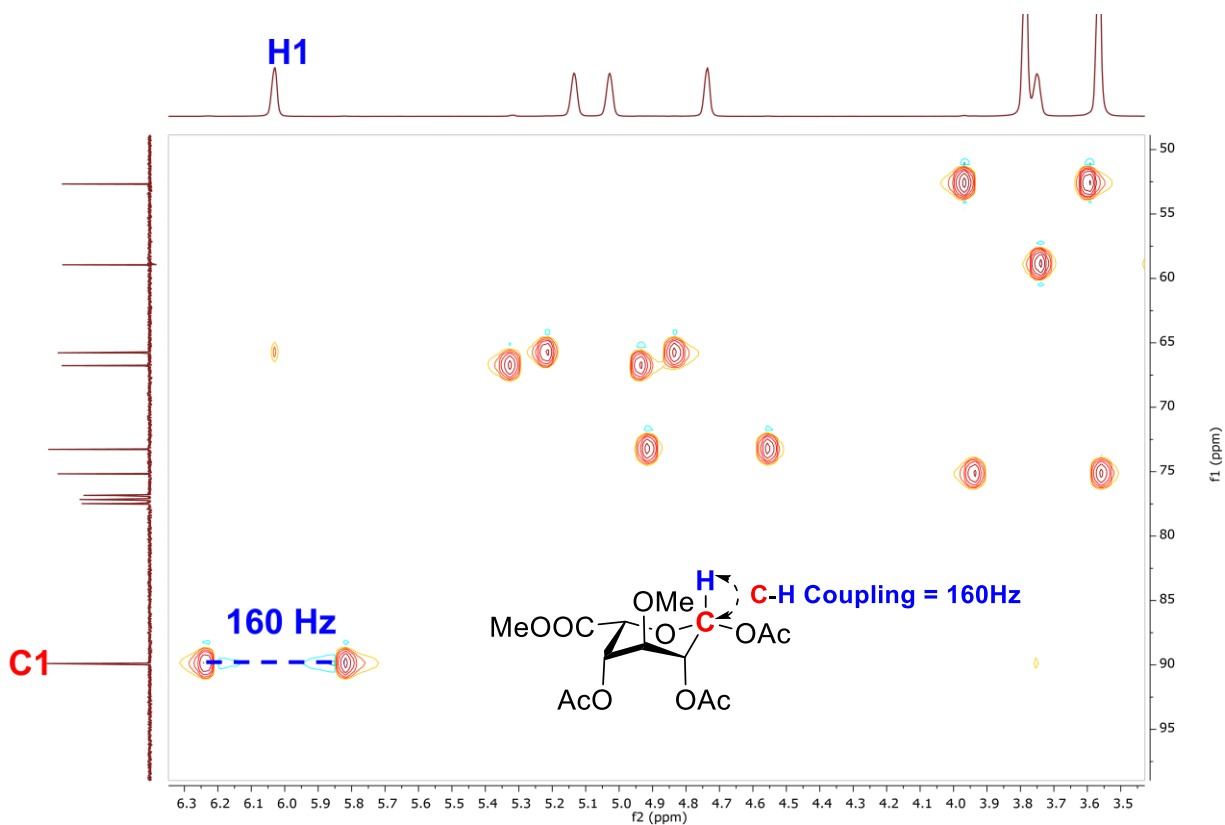


HSQC Spectrum (400 MHz, CDCl_3) of compound **40**

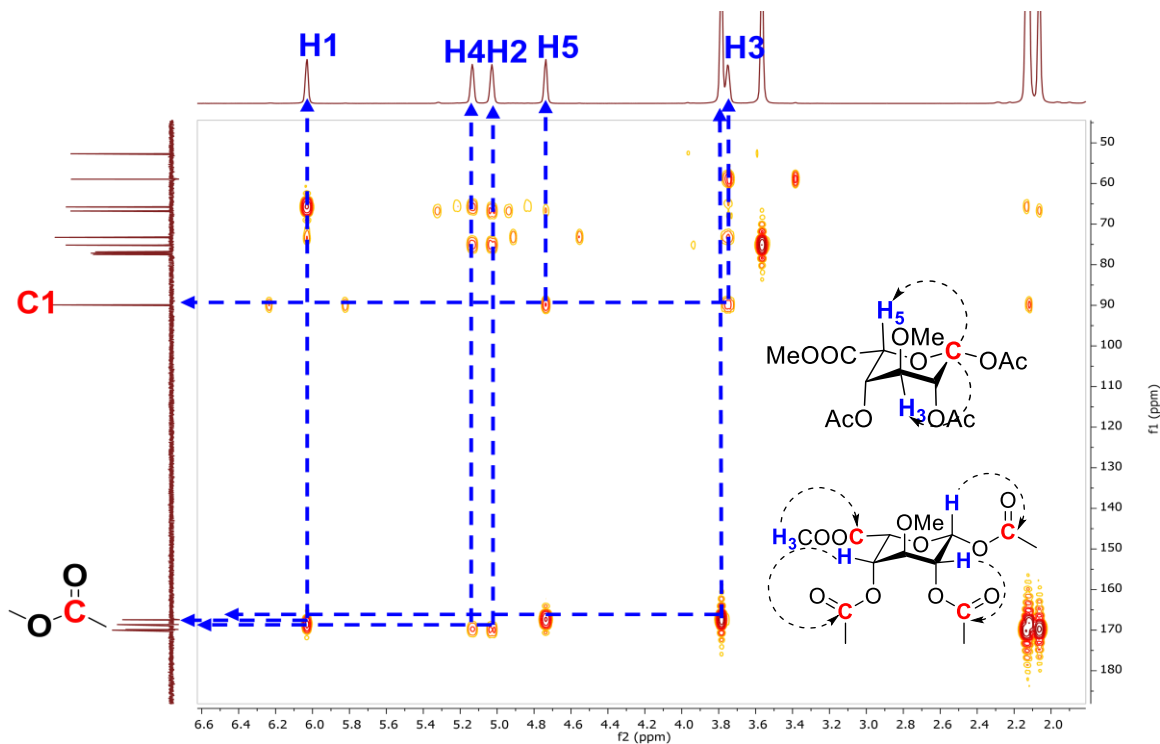


Chapter 2

Coupled-HSQC Spectrum (400 MHz, CDCl_3) of compound **40**

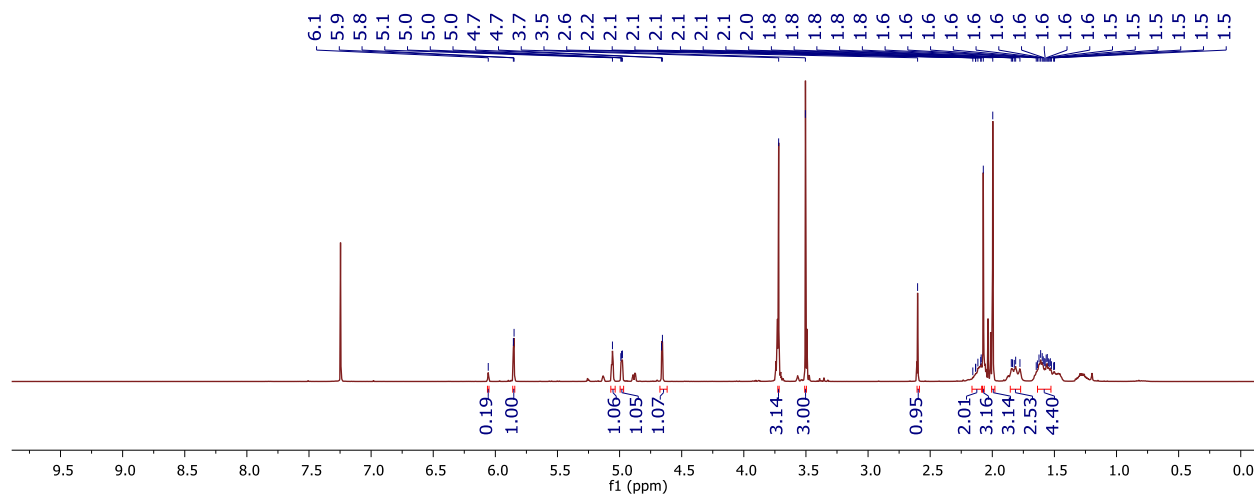


HMBC Spectrum (400 MHz, CDCl_3) of compound **40**

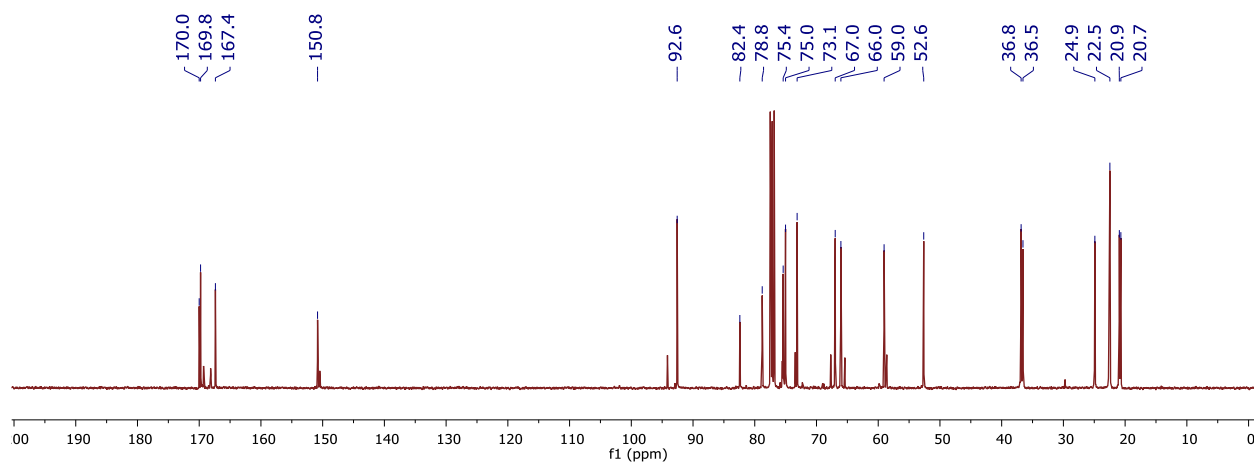


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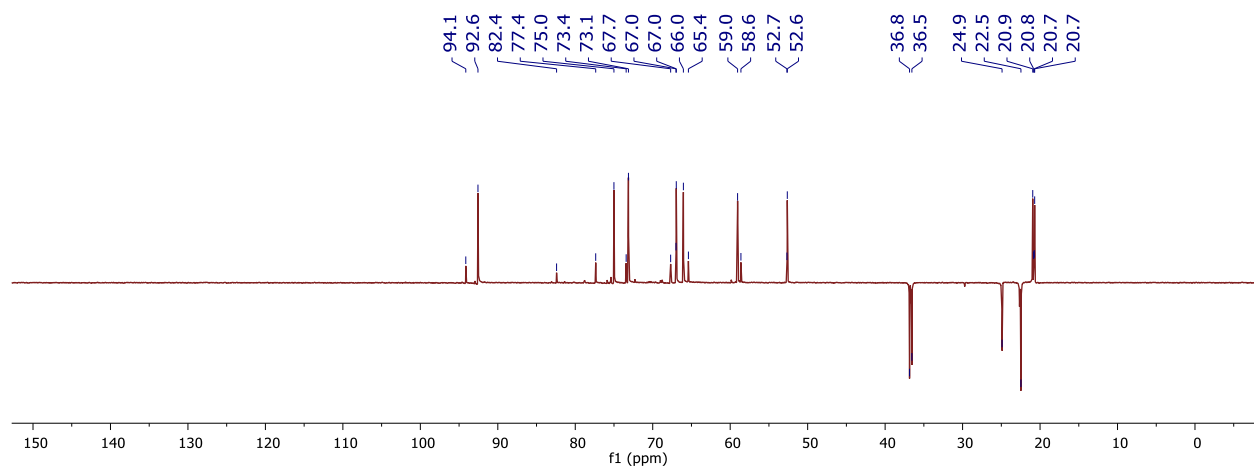
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **28**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **28**

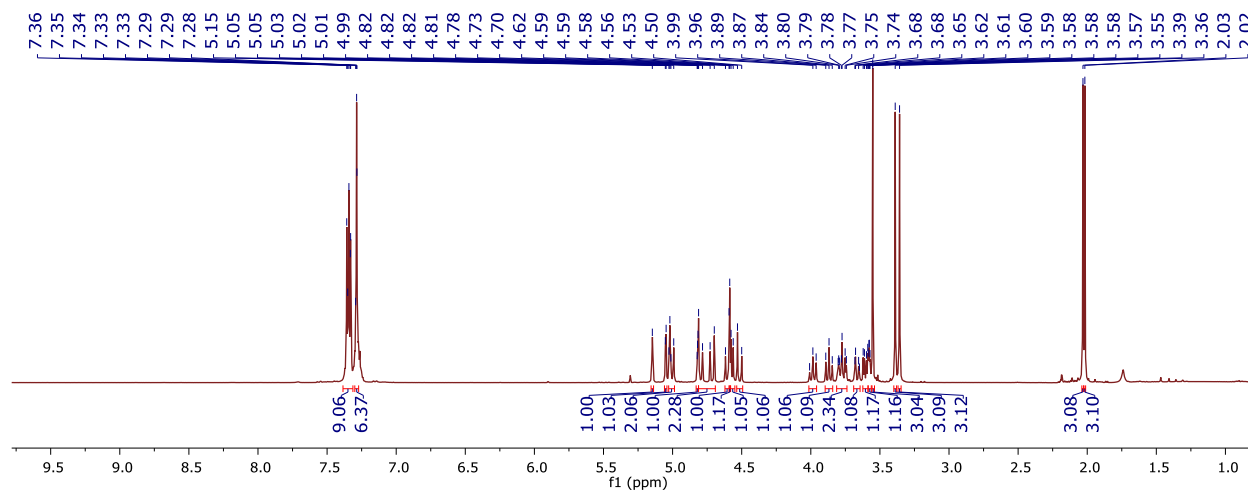


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **28**

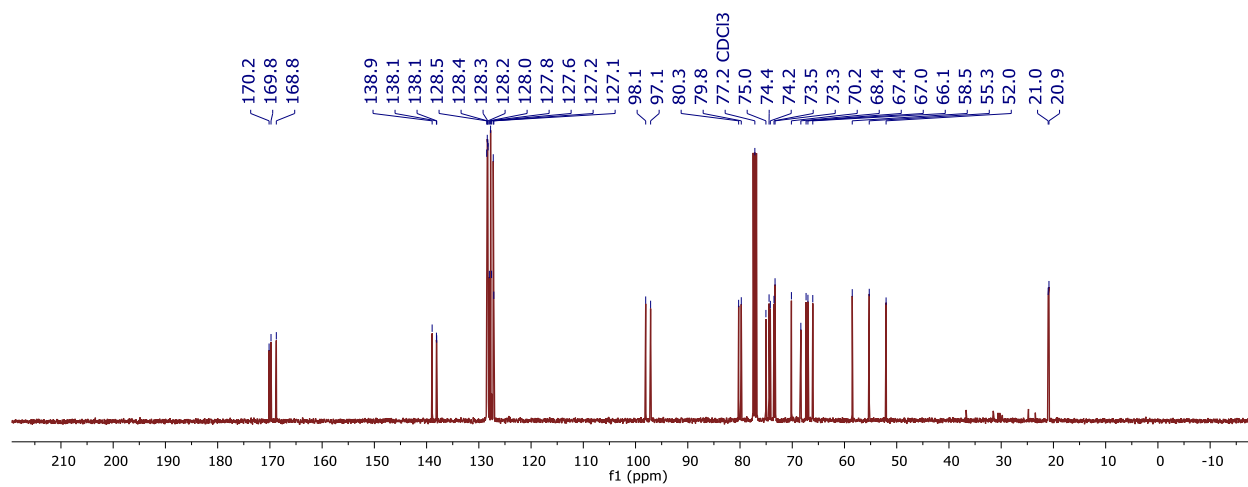


Chapter 2

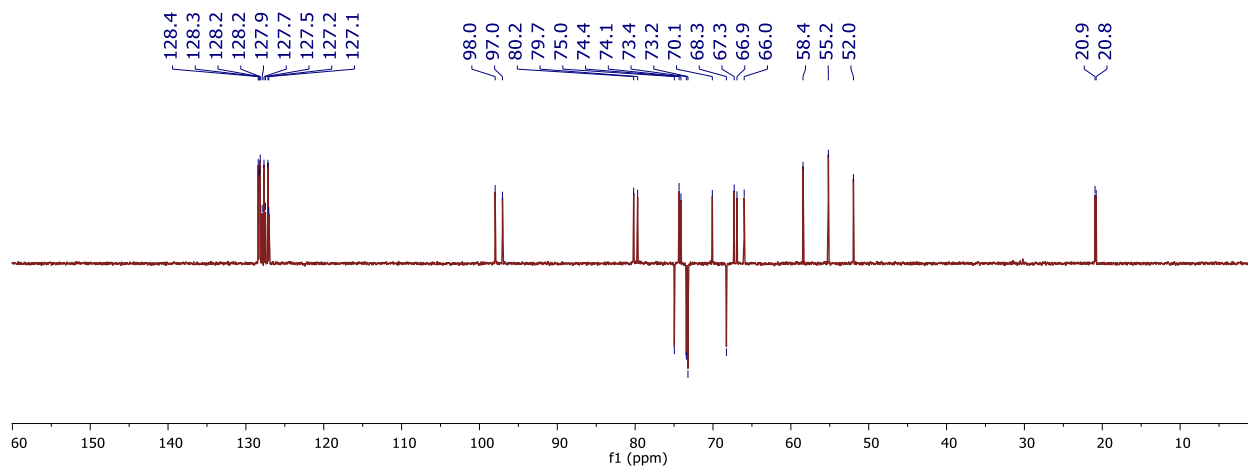
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **41**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **41**

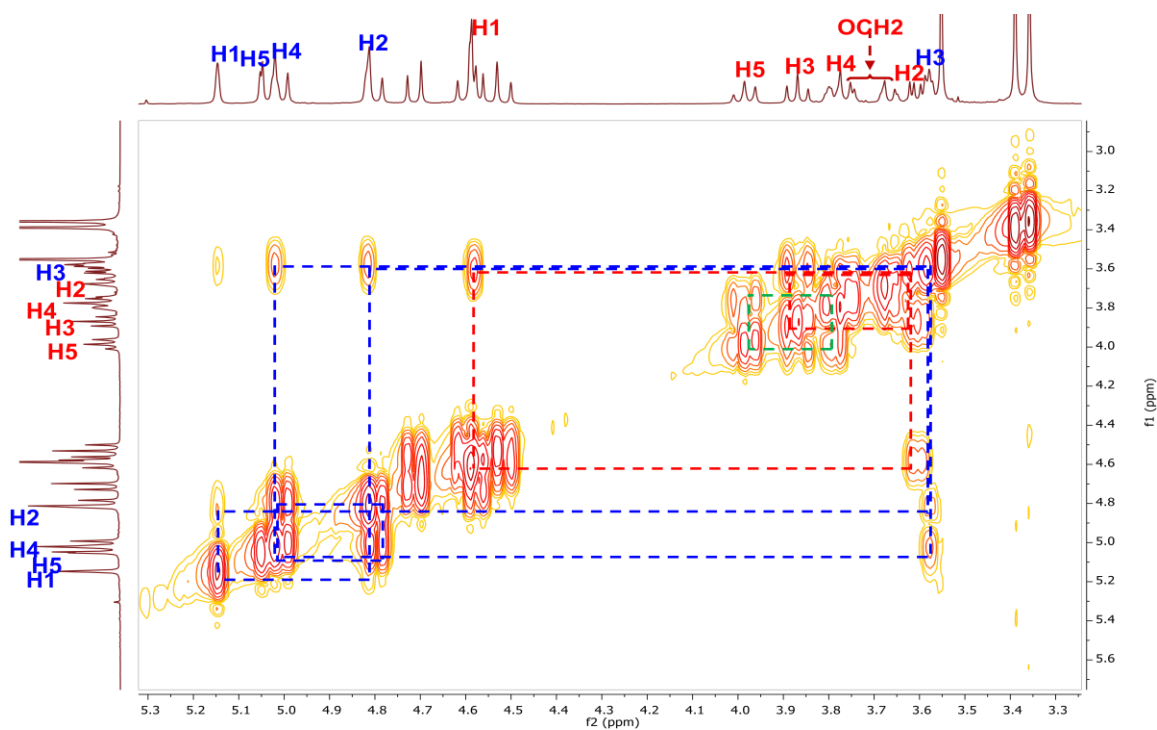


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **41**

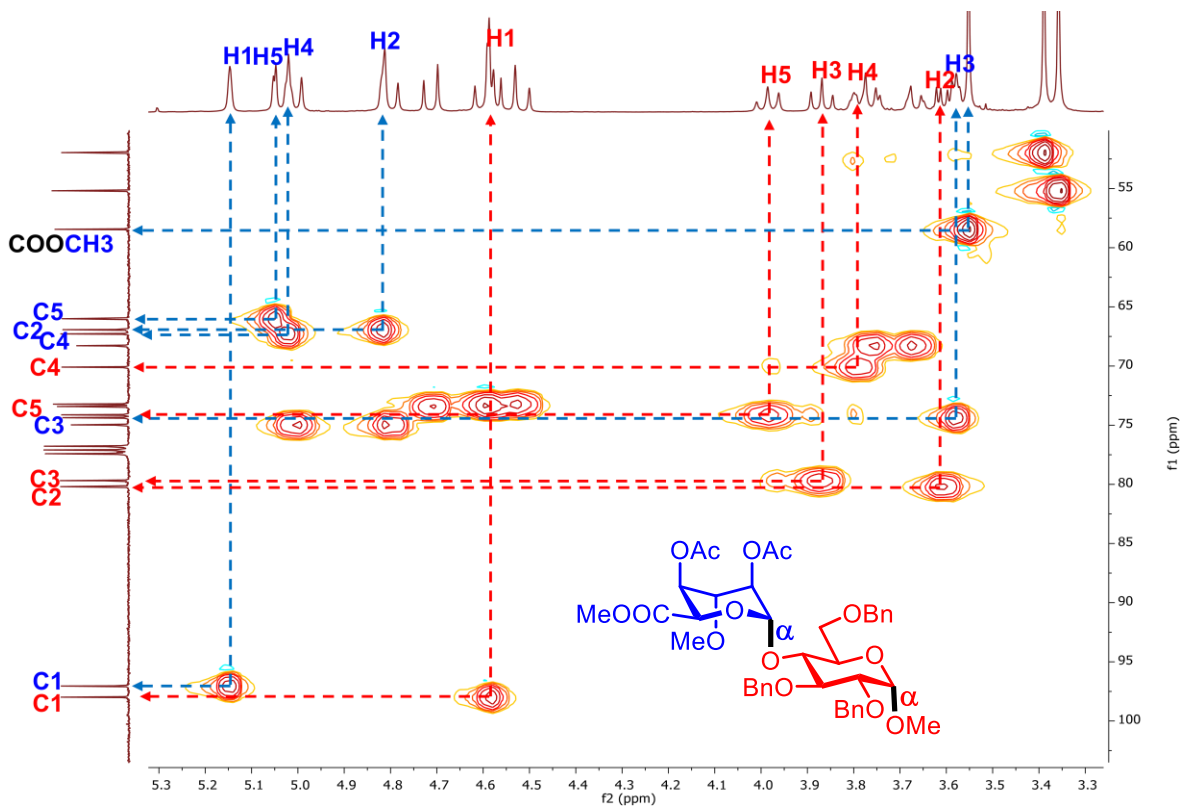


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^1H - ^1H COSY Spectrum (400 MHz, CDCl_3) of compound **41**

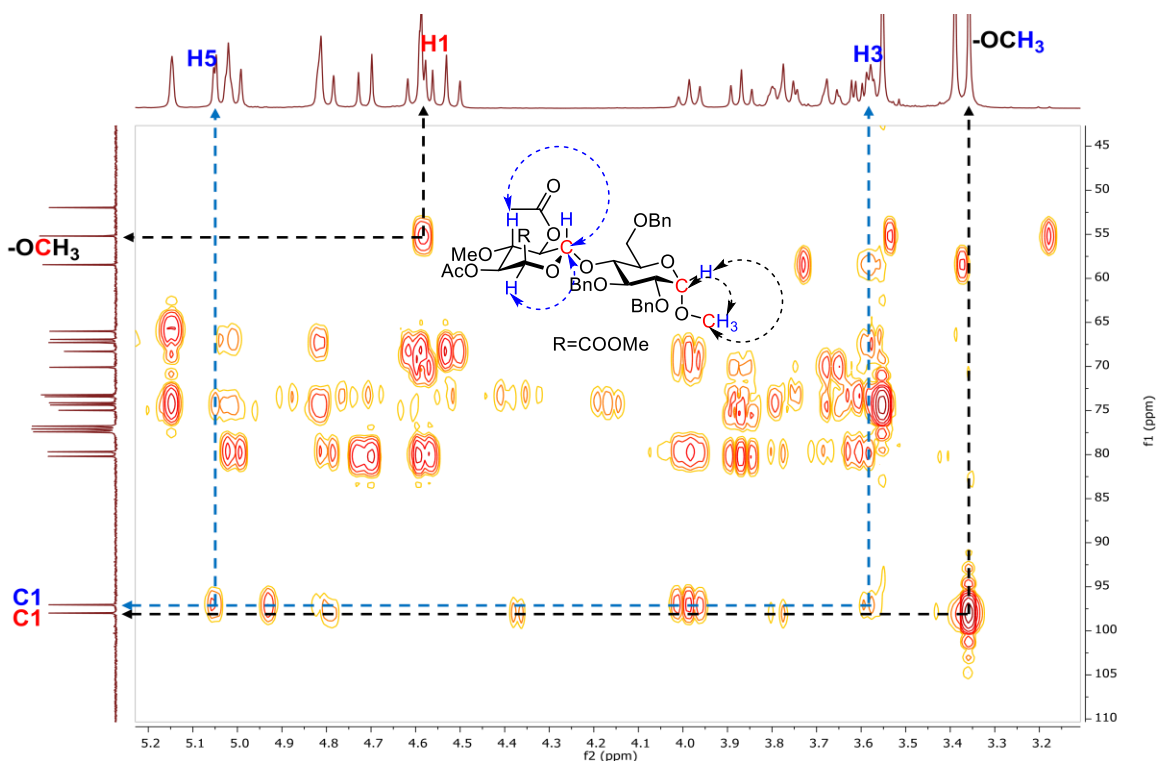


HSQC Spectrum (400 MHz, CDCl_3) of compound **41**

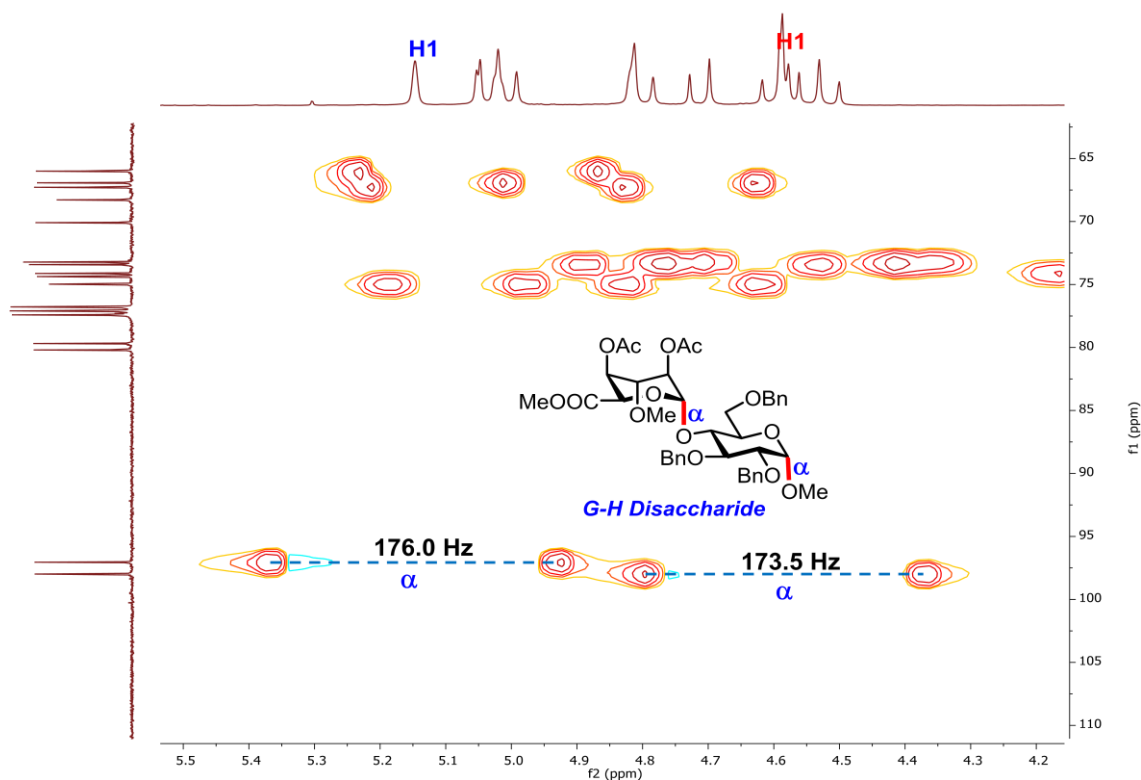


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HMBC Spectrum (400 MHz, CDCl₃) of compound **41**

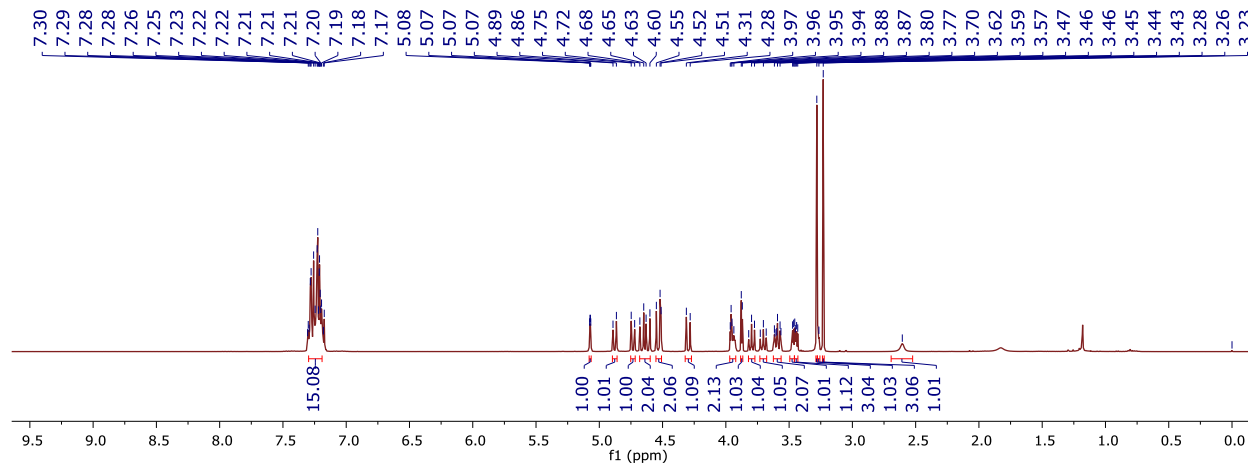


HSQC-Coupled Spectrum (400 MHz, CDCl₃) of compound **41**

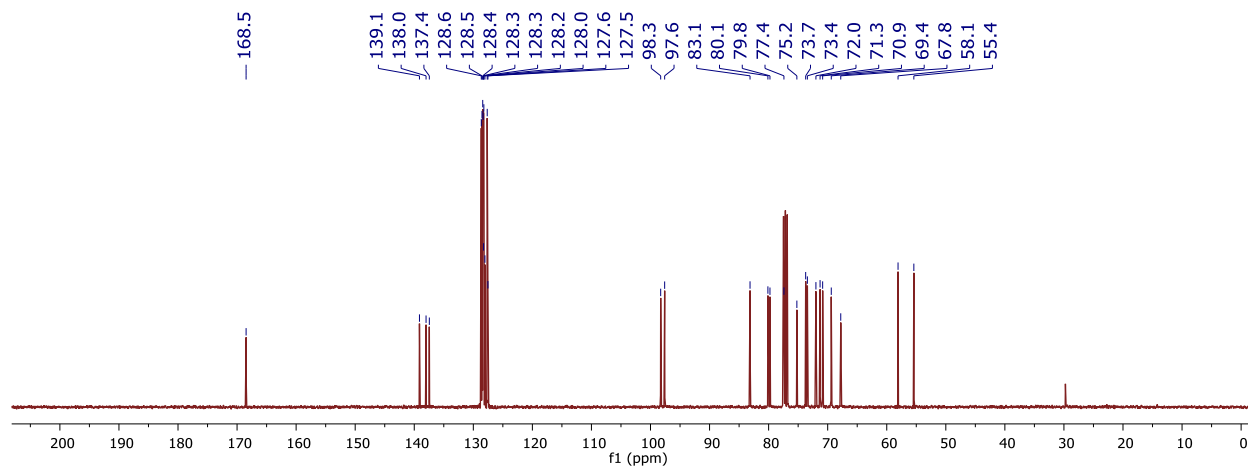


Chapter 2

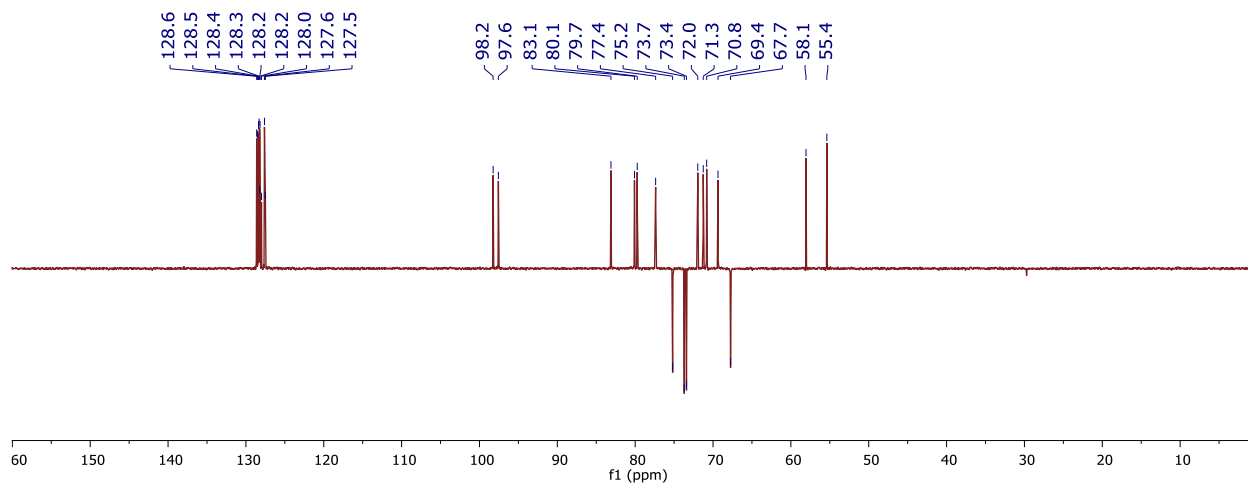
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **43**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **43**

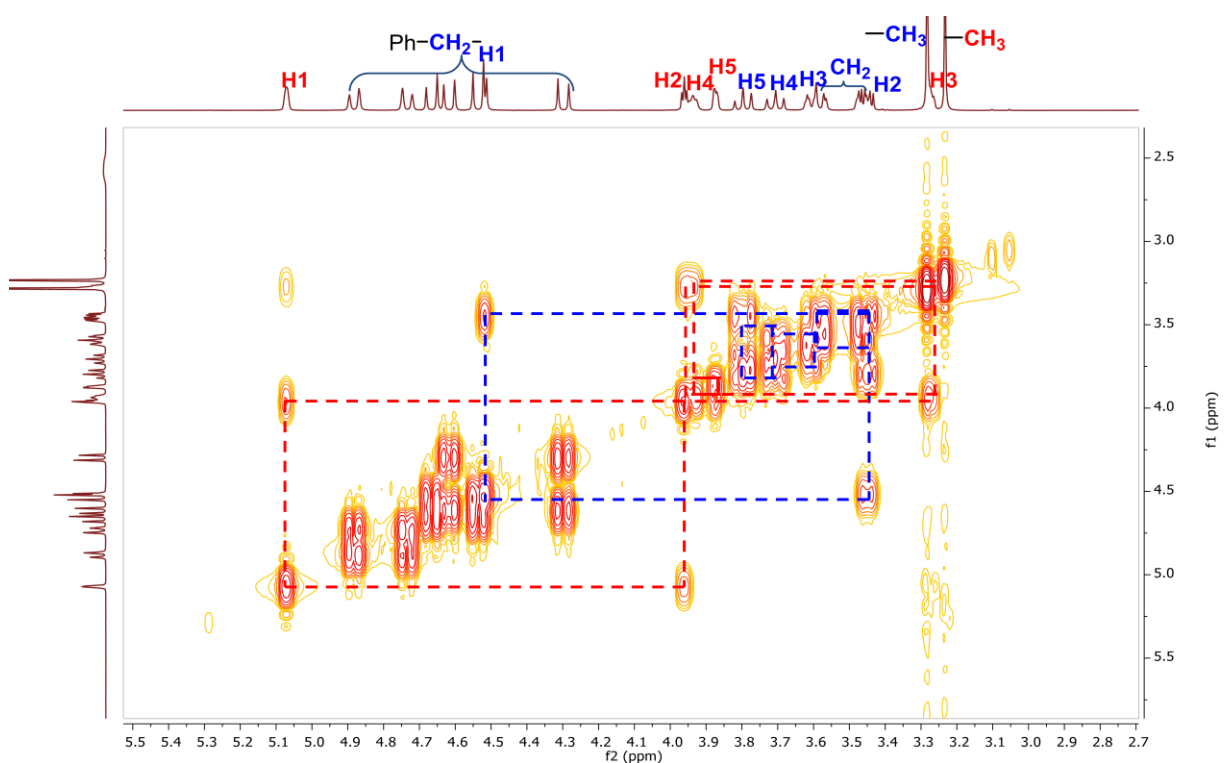


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **43**

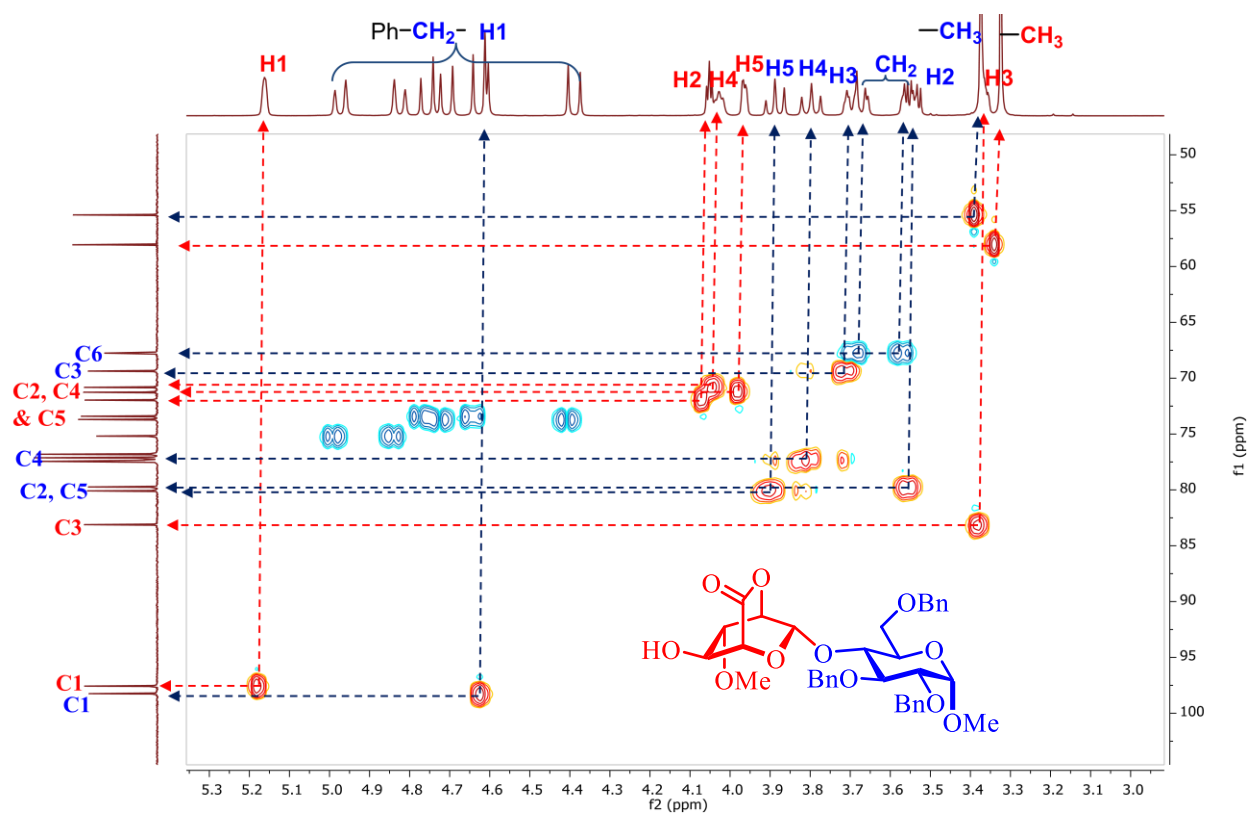


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^1H - ^1H COSY Spectrum (400 MHz, CDCl_3) of compound **43**

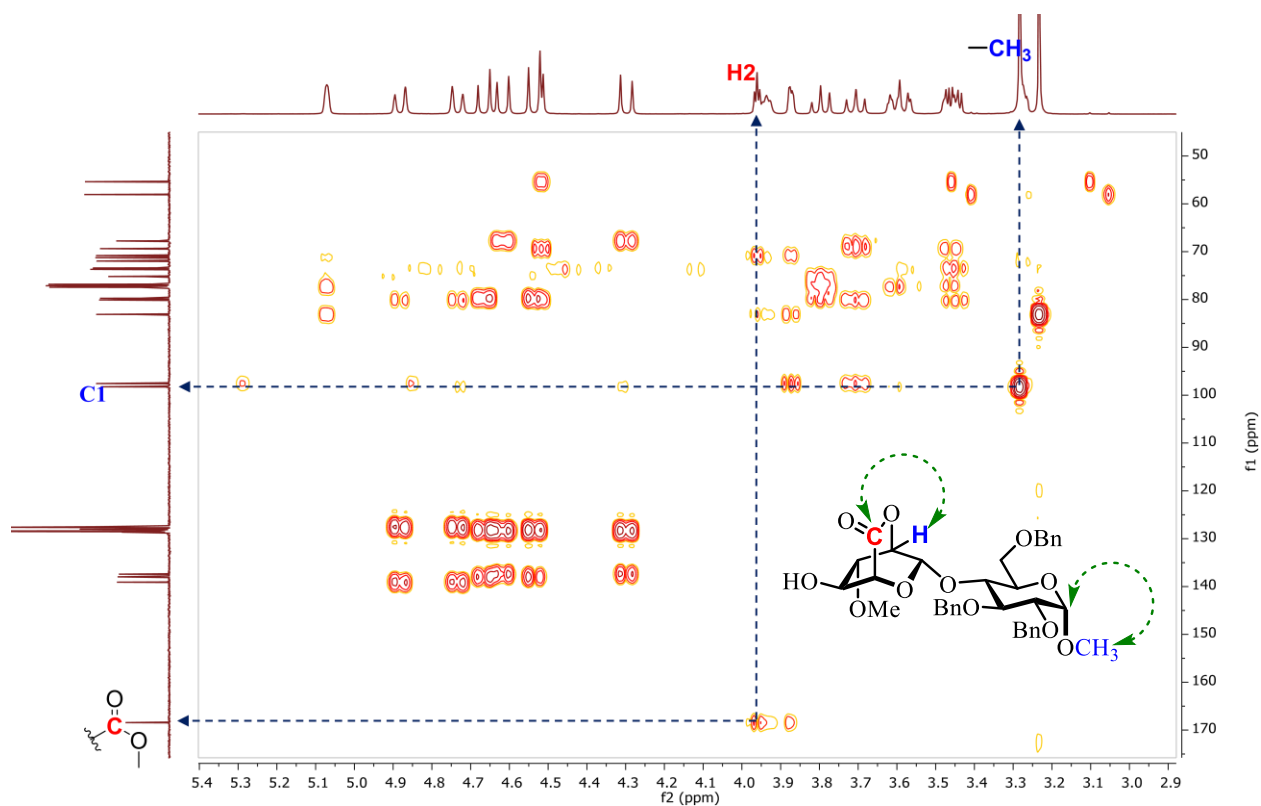


HSQC Spectrum (400 MHz, CDCl_3) of compound **43**

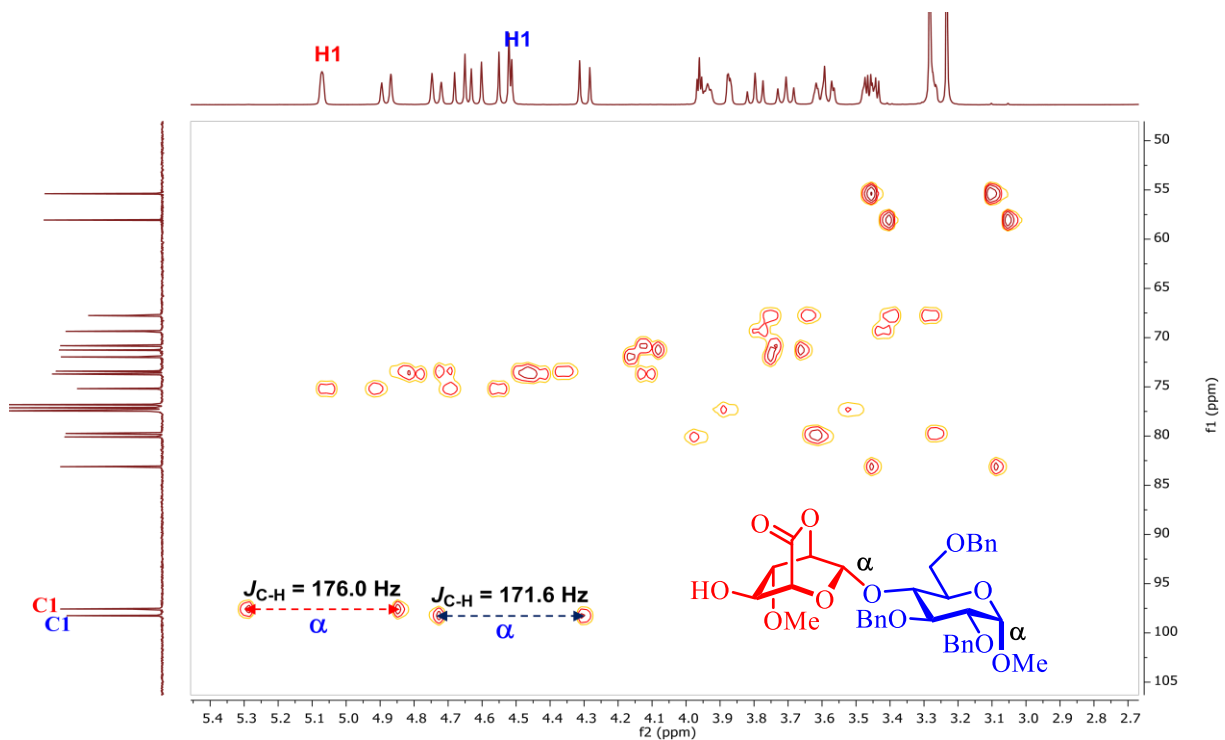


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HMBC Spectrum (400 MHz, CDCl₃) of compound **43**

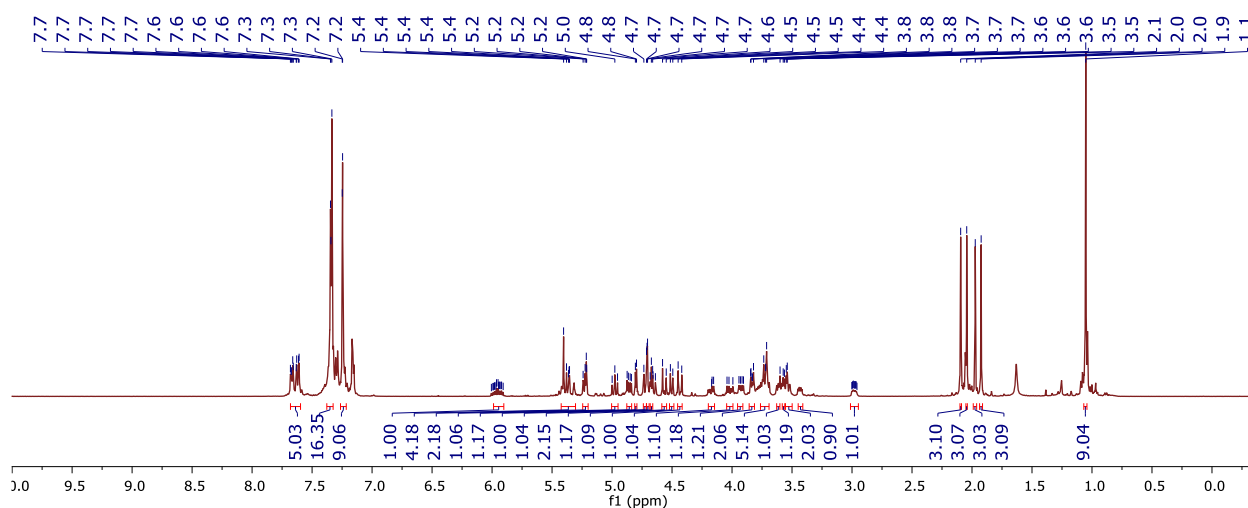


HSQC-Coupled Spectrum (400 MHz, CDCl₃) of compound **43**

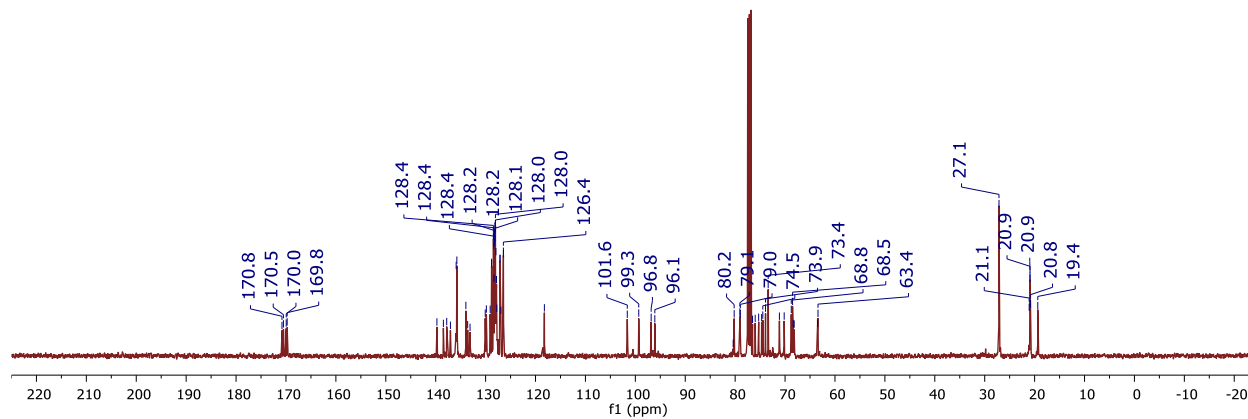


Chapter 2

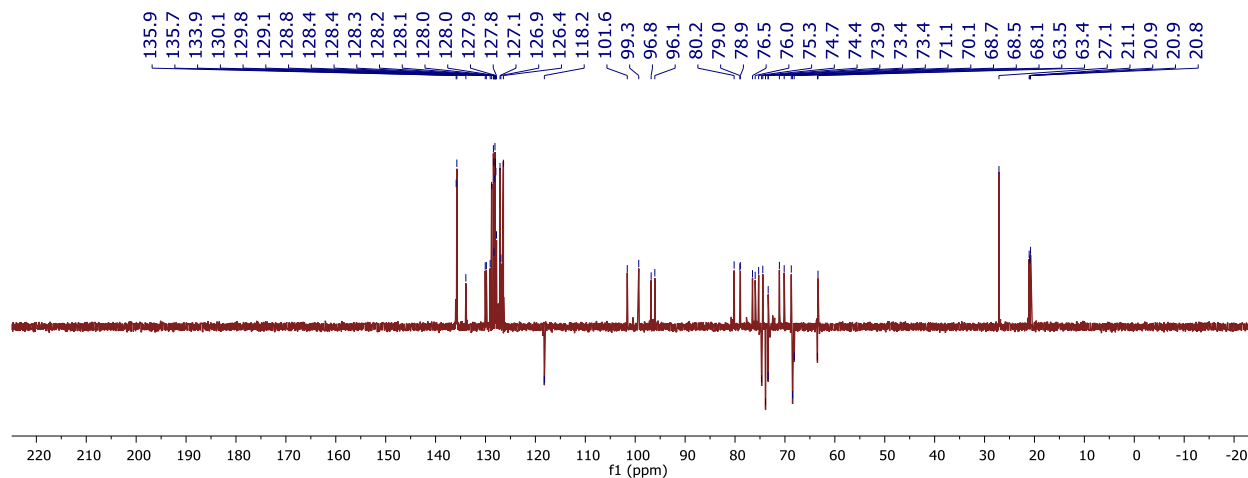
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **44**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **44**

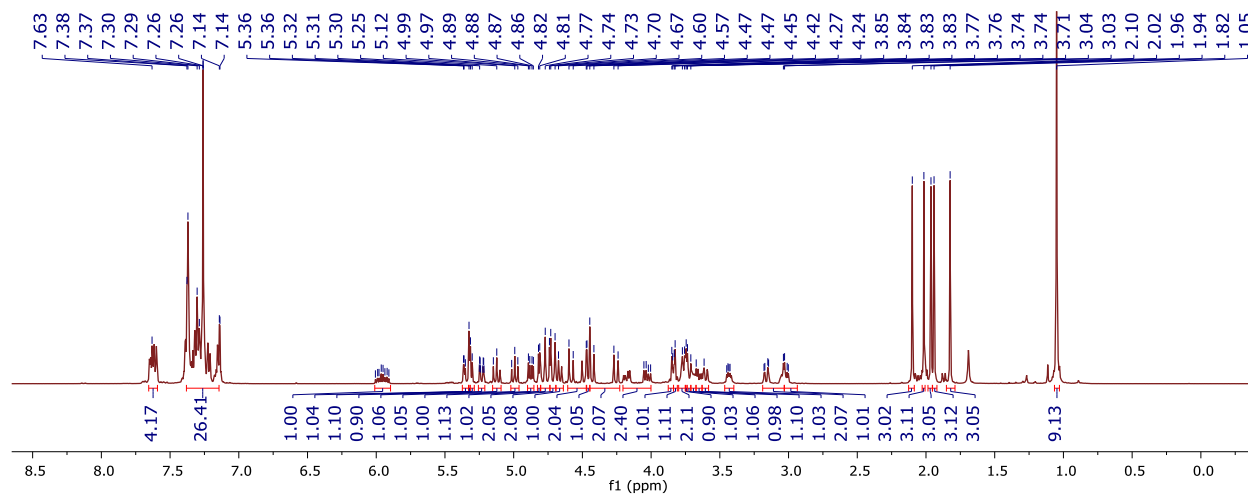


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **44**

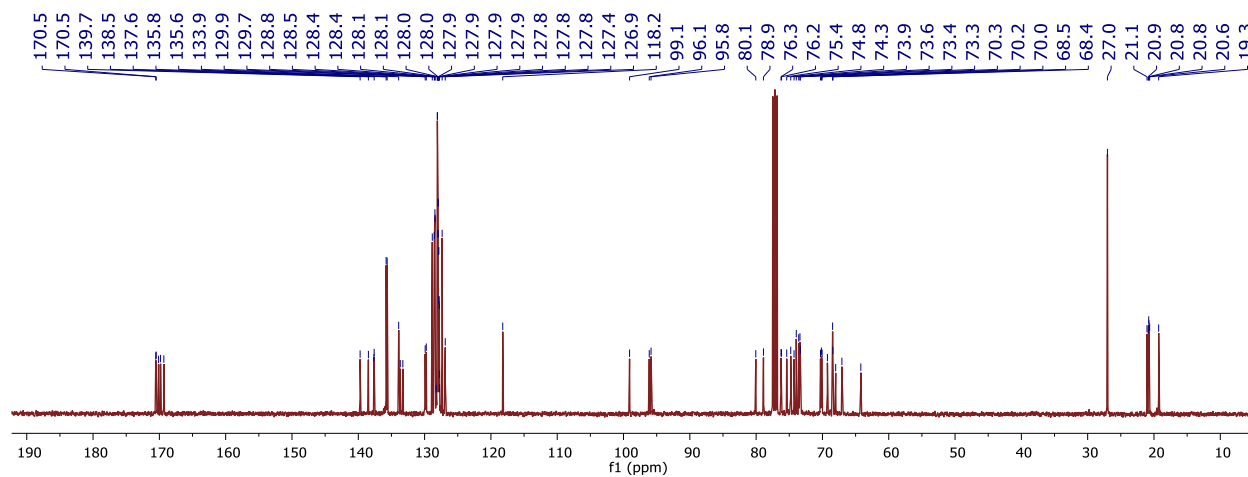


Chapter 2

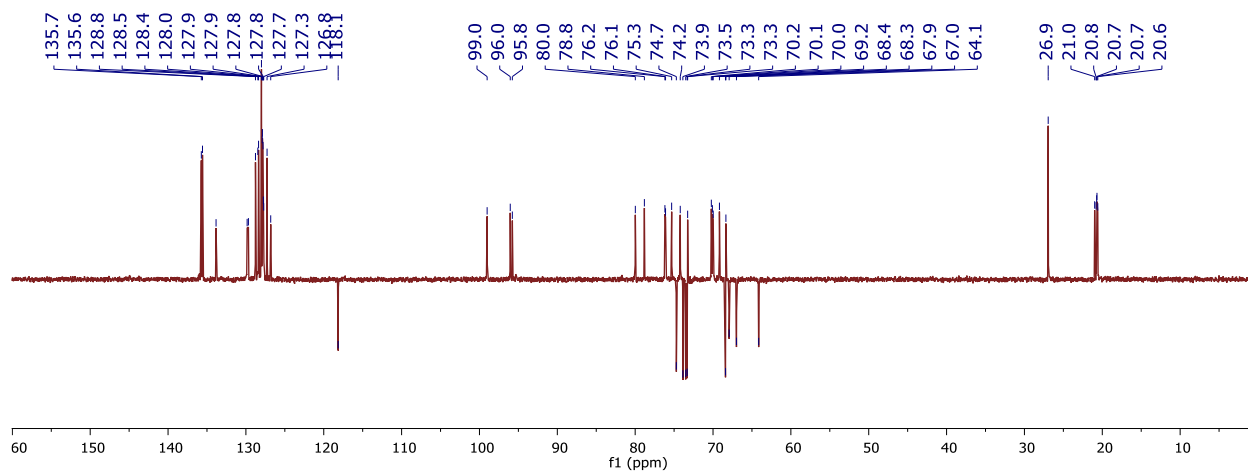
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **45**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **45**

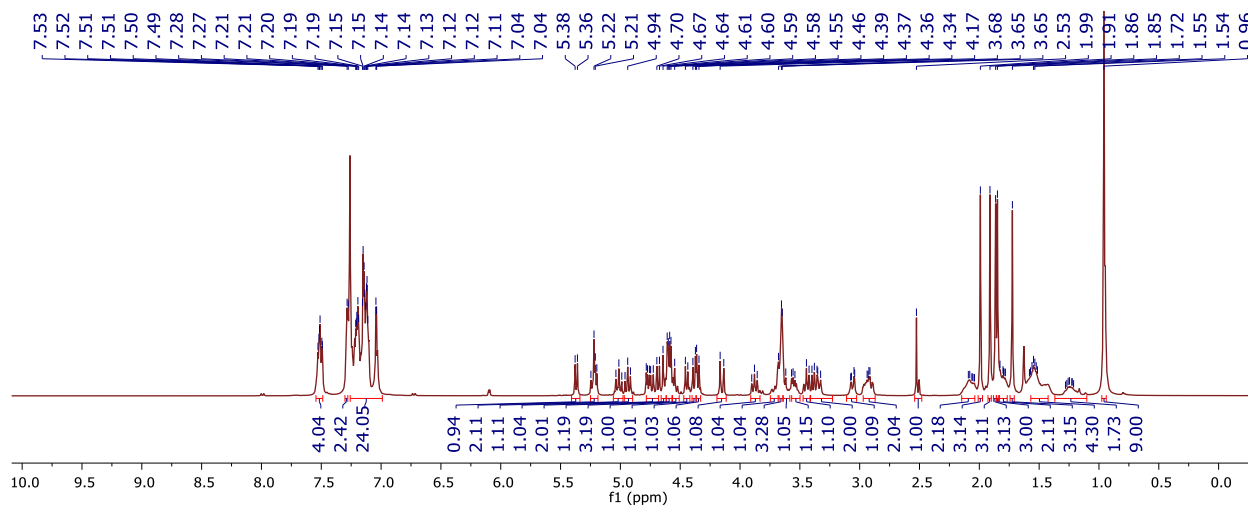


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **45**

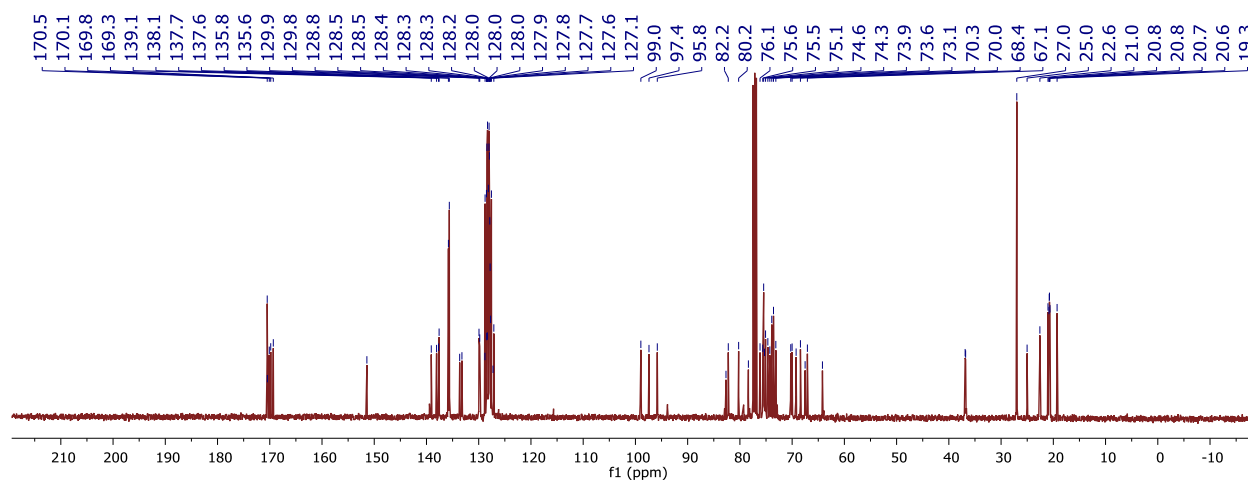


Chapter 2

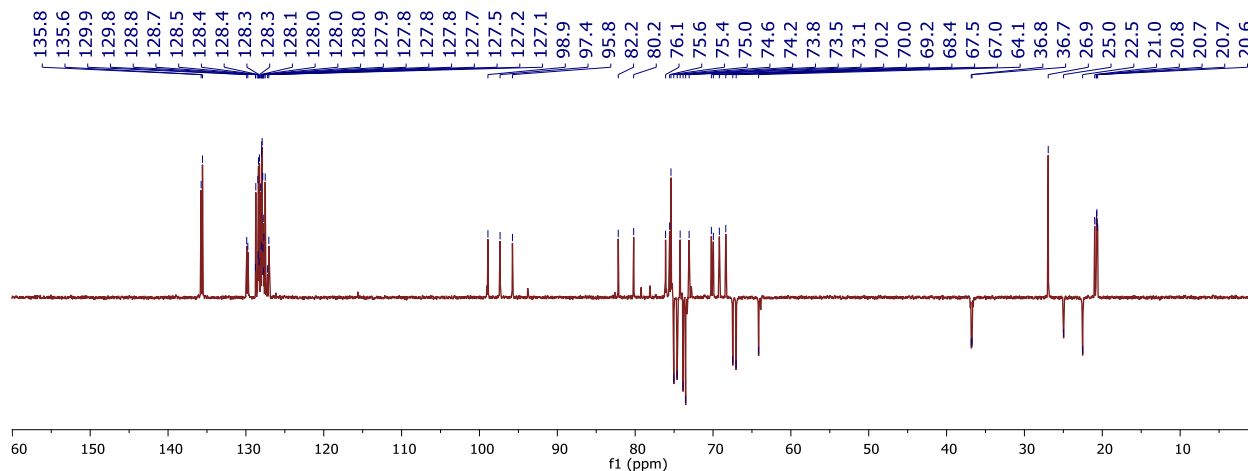
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **46**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **46**

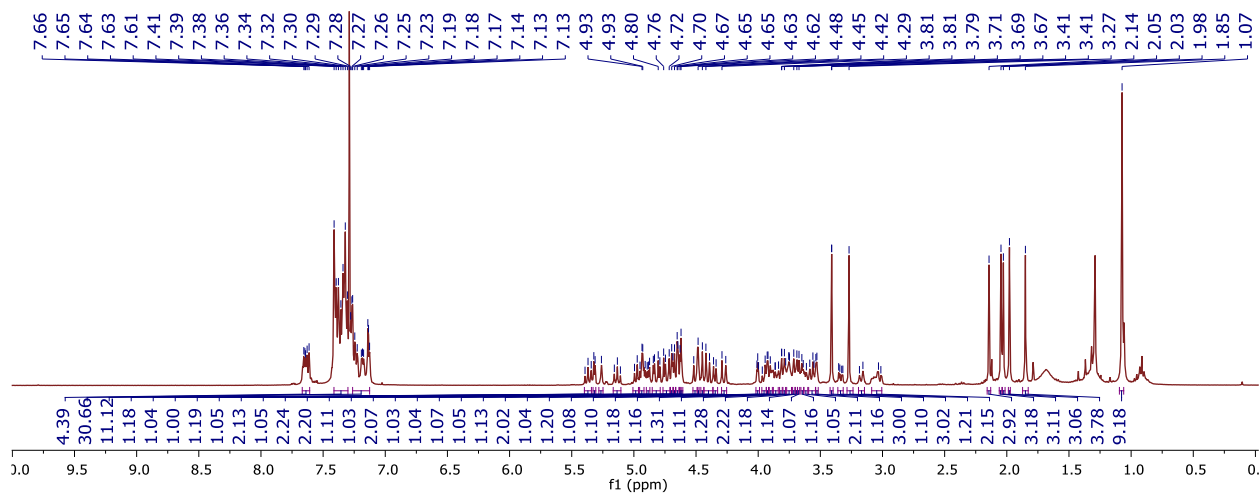


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **46**

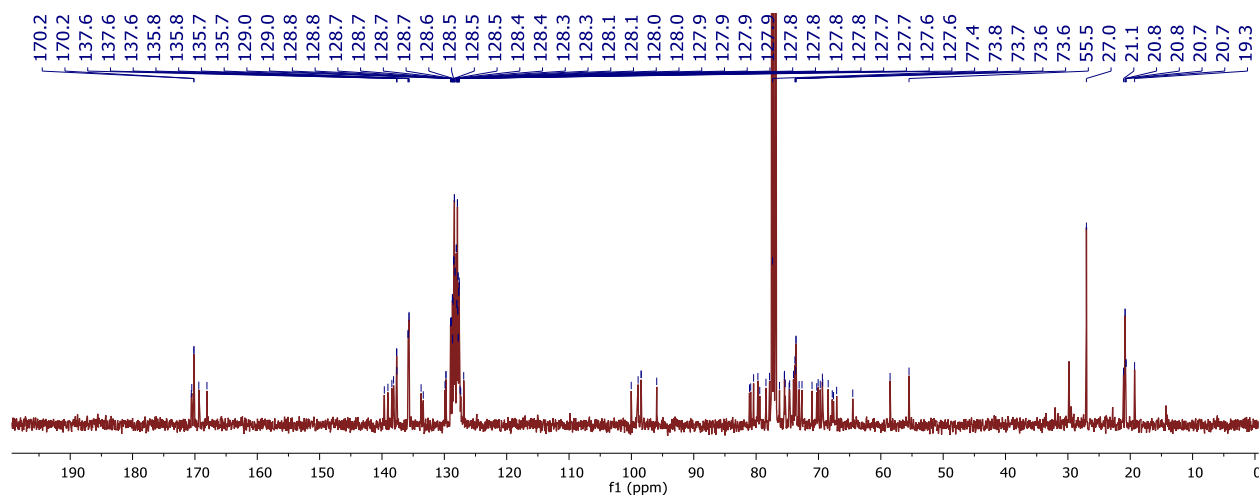


Chapter 2

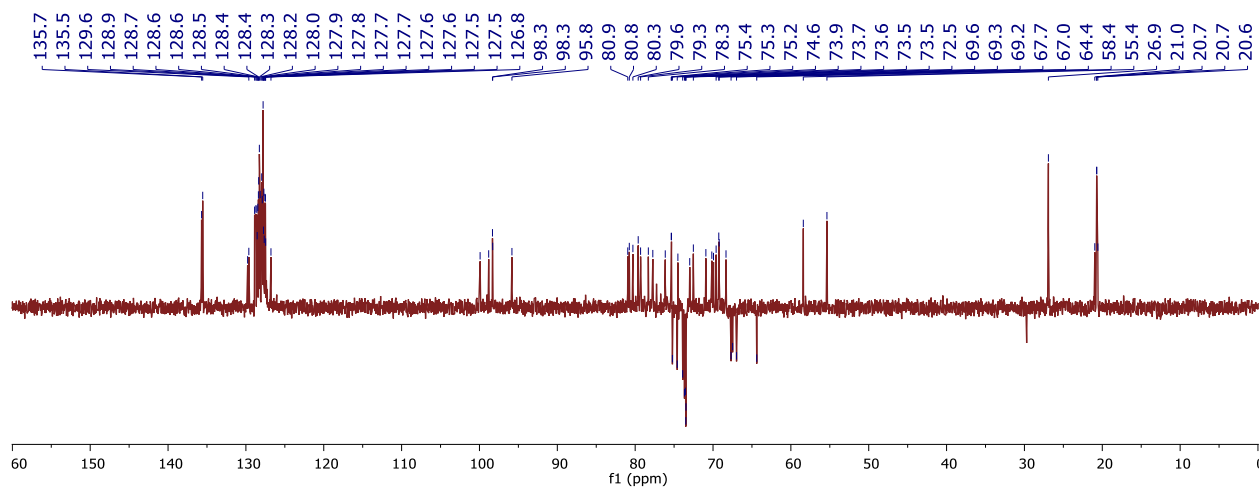
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **47**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **47**

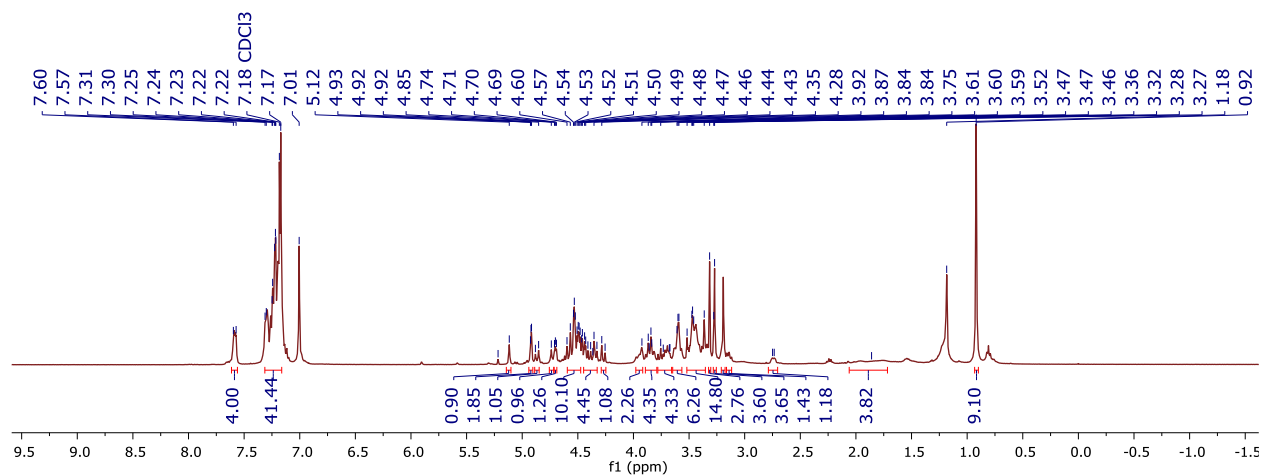


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **47**

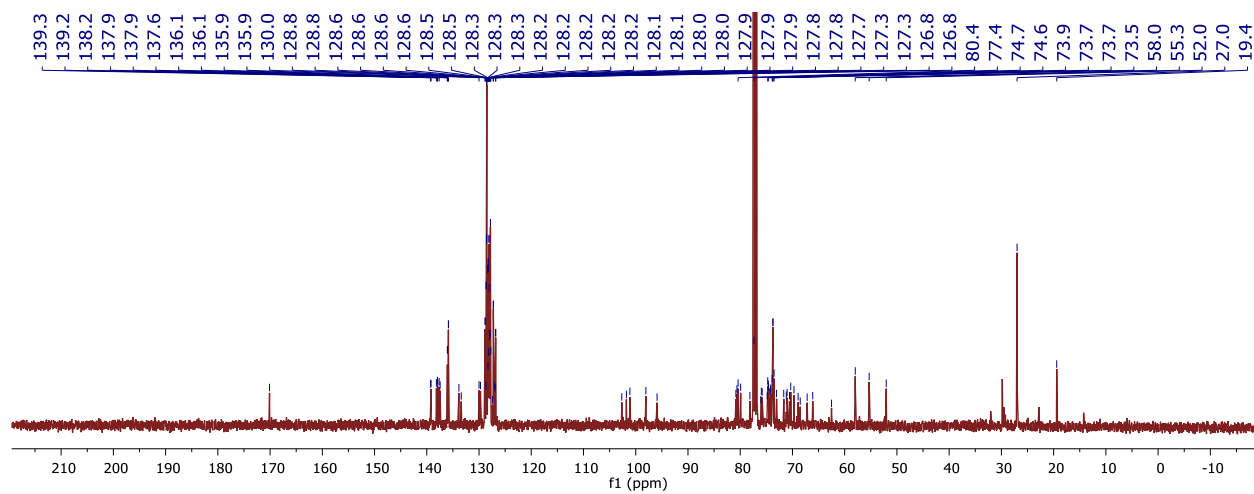


Chapter 2

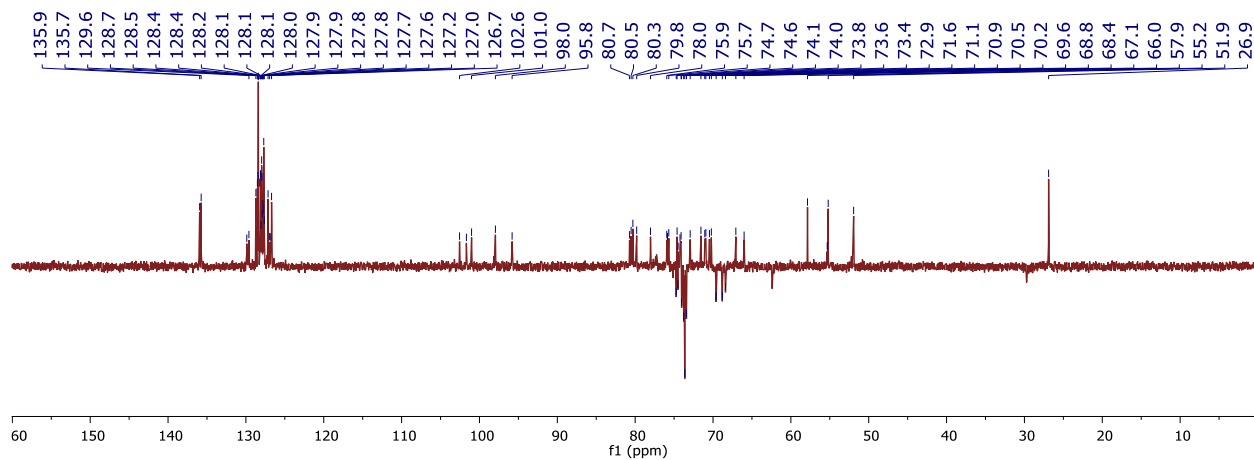
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **48**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **48**

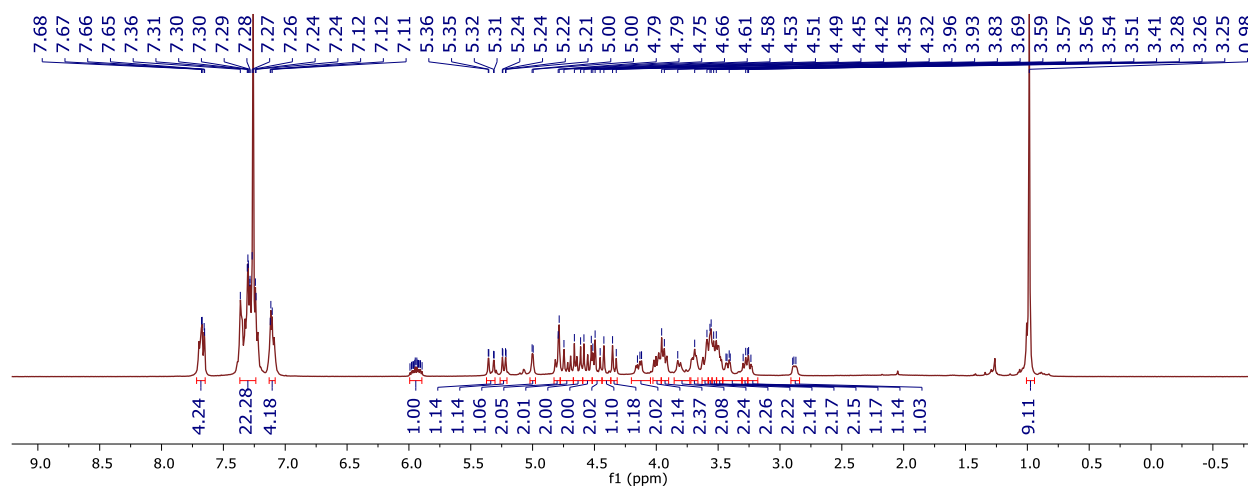


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **48**

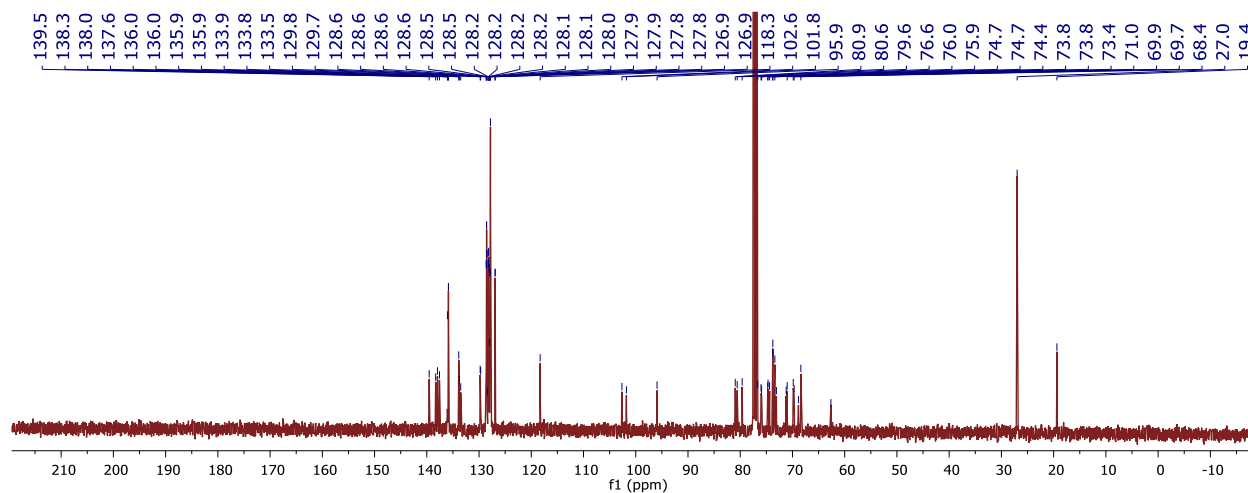


Chapter 2

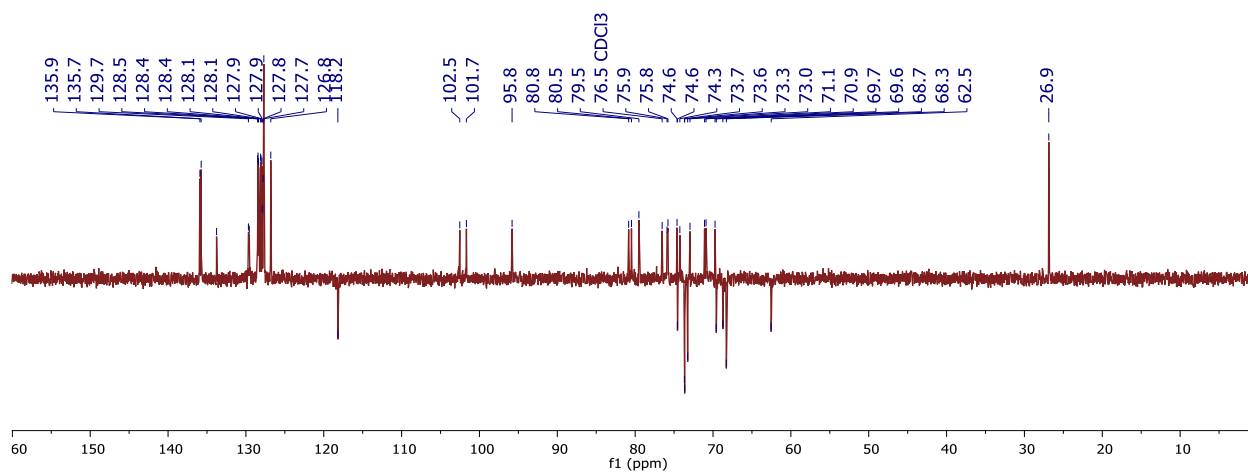
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **50**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **50**

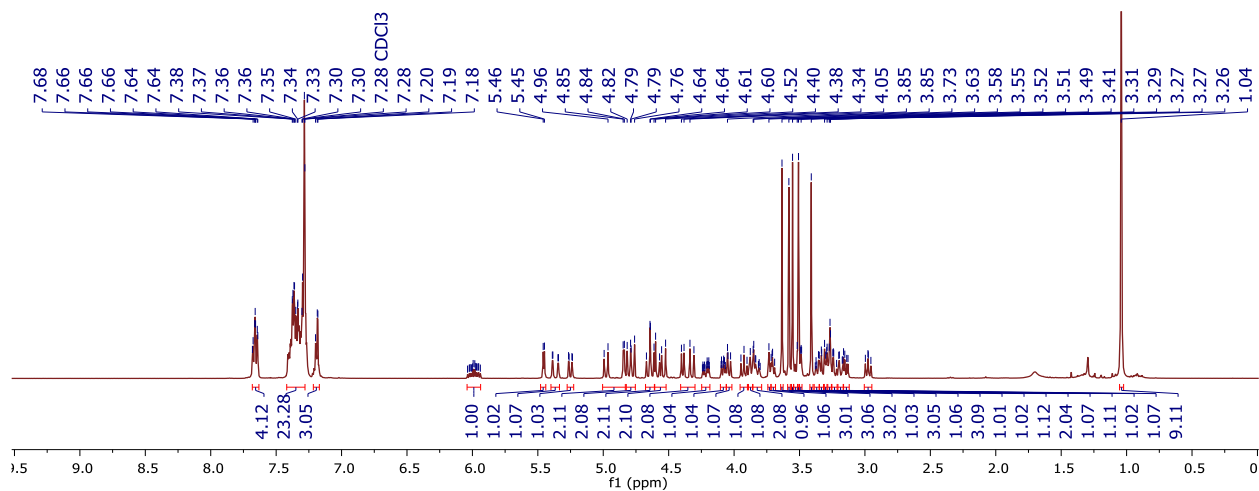


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **50**

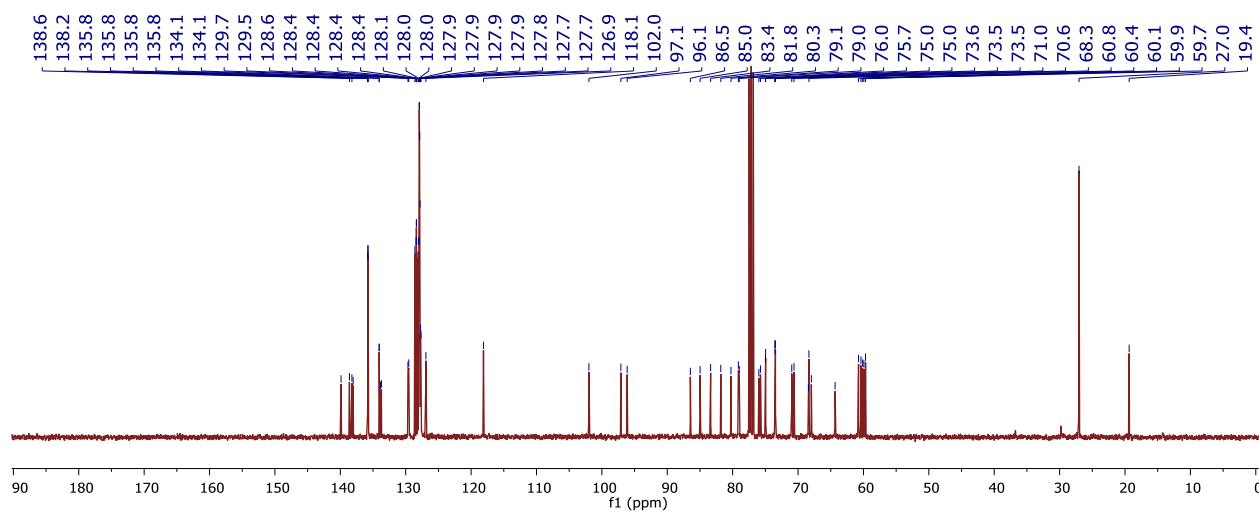


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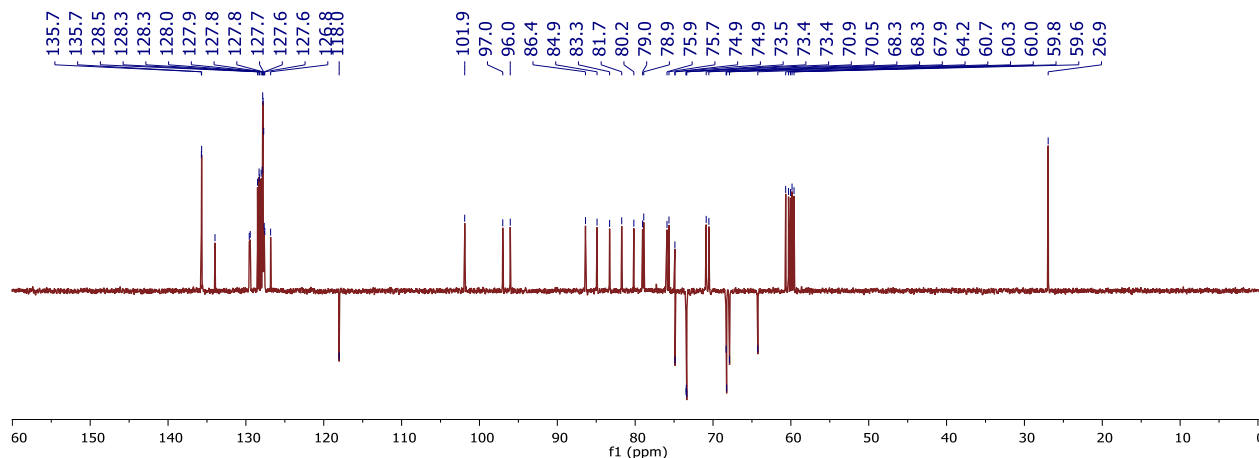
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **51**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **51**

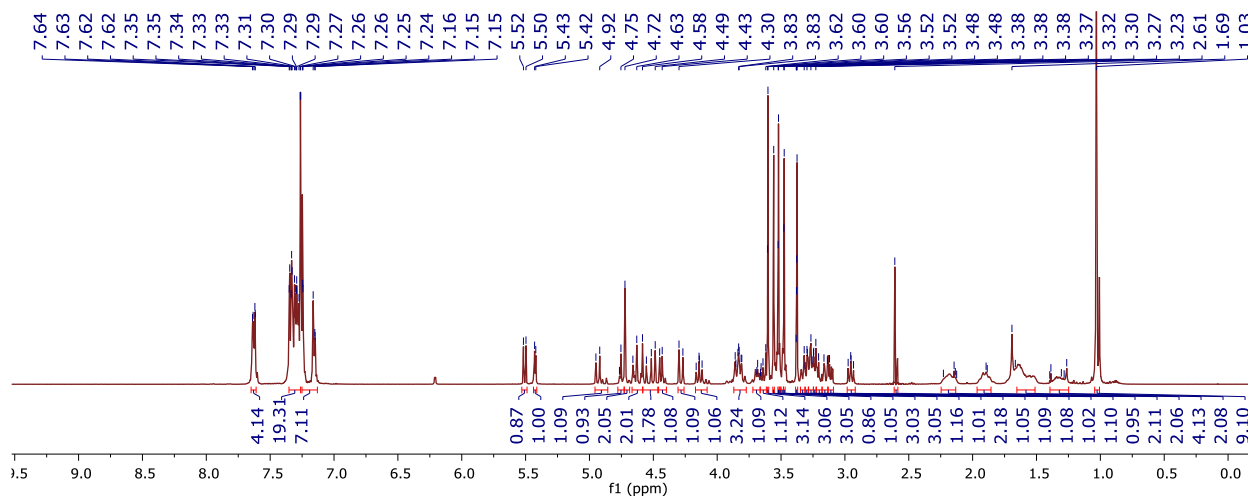


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **51**

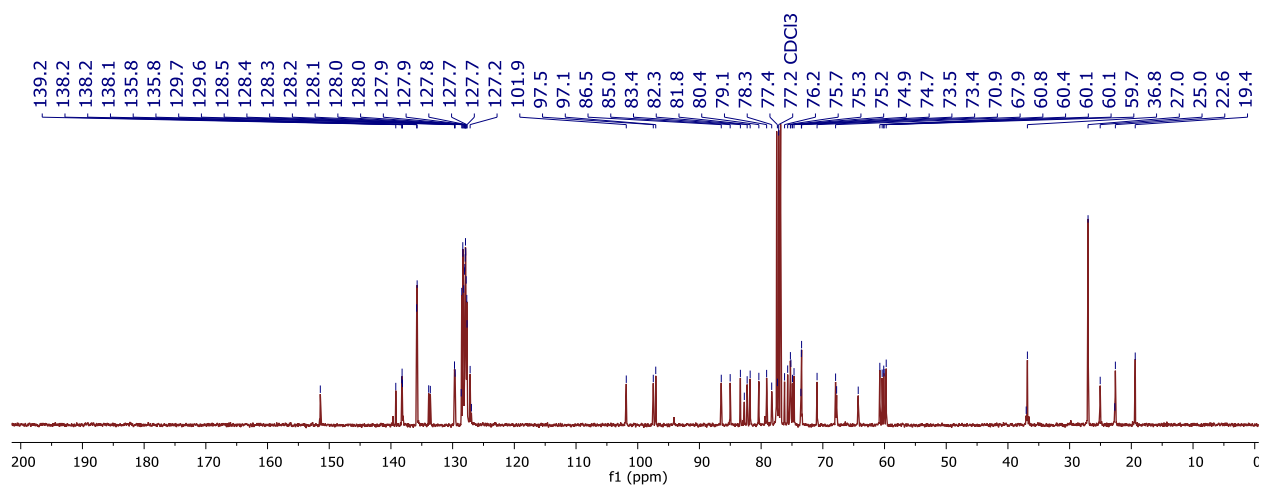


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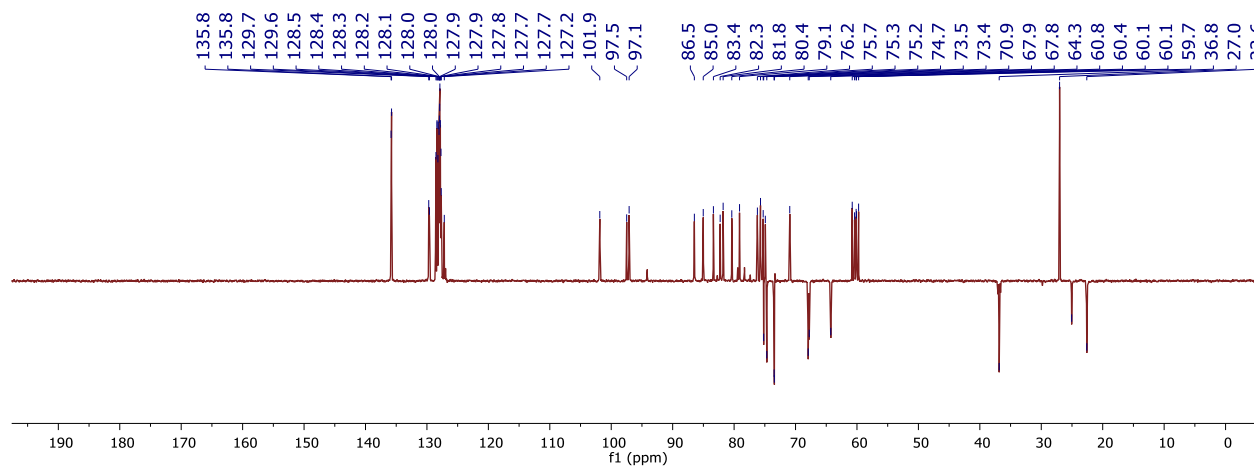
^1H NMR Spectrum (400 MHz, CDCl_3) of compound 52



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound 52

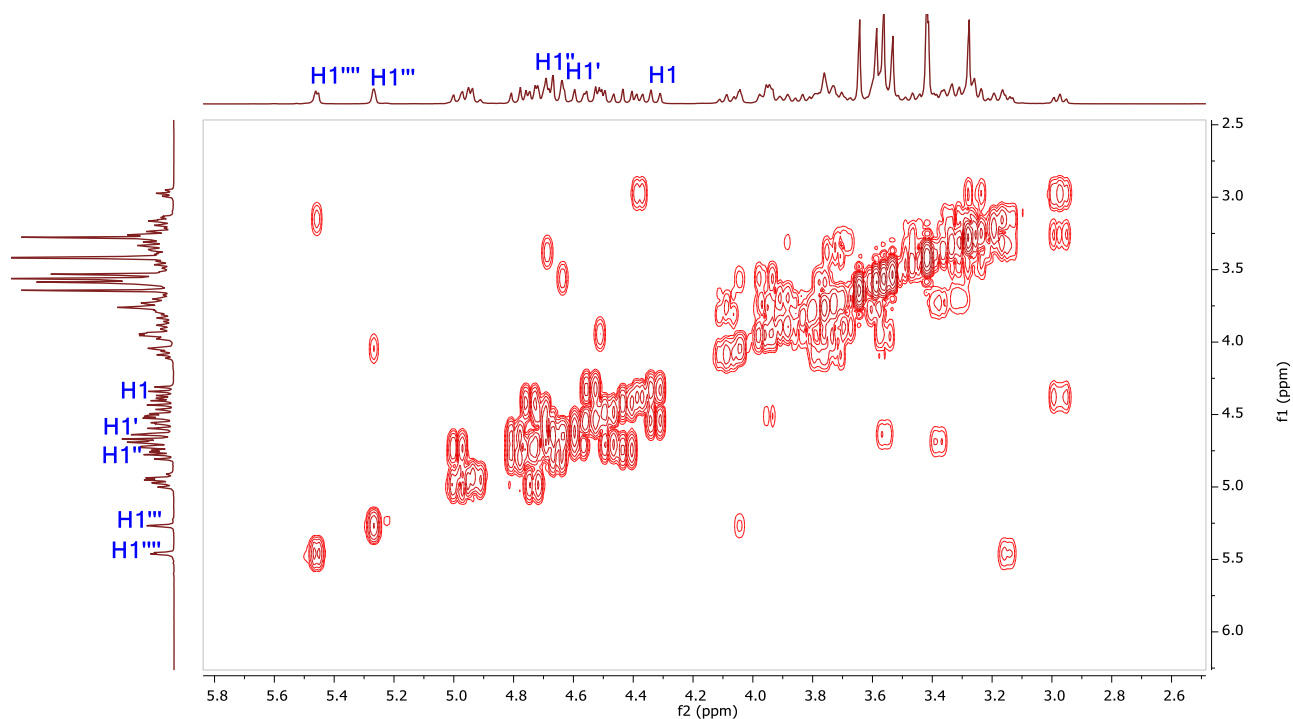


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound 52

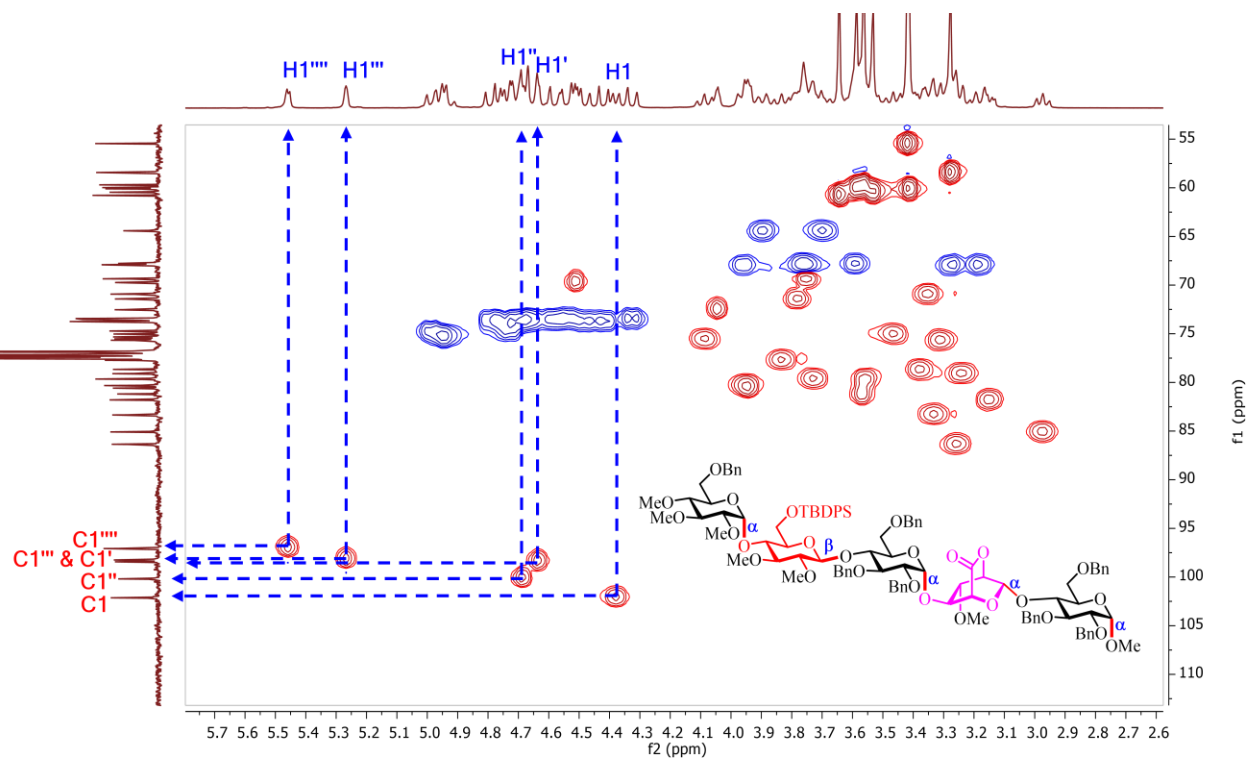


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^1H - ^1H COSY NMR Spectrum (400 MHz, CDCl_3) of compound **53**

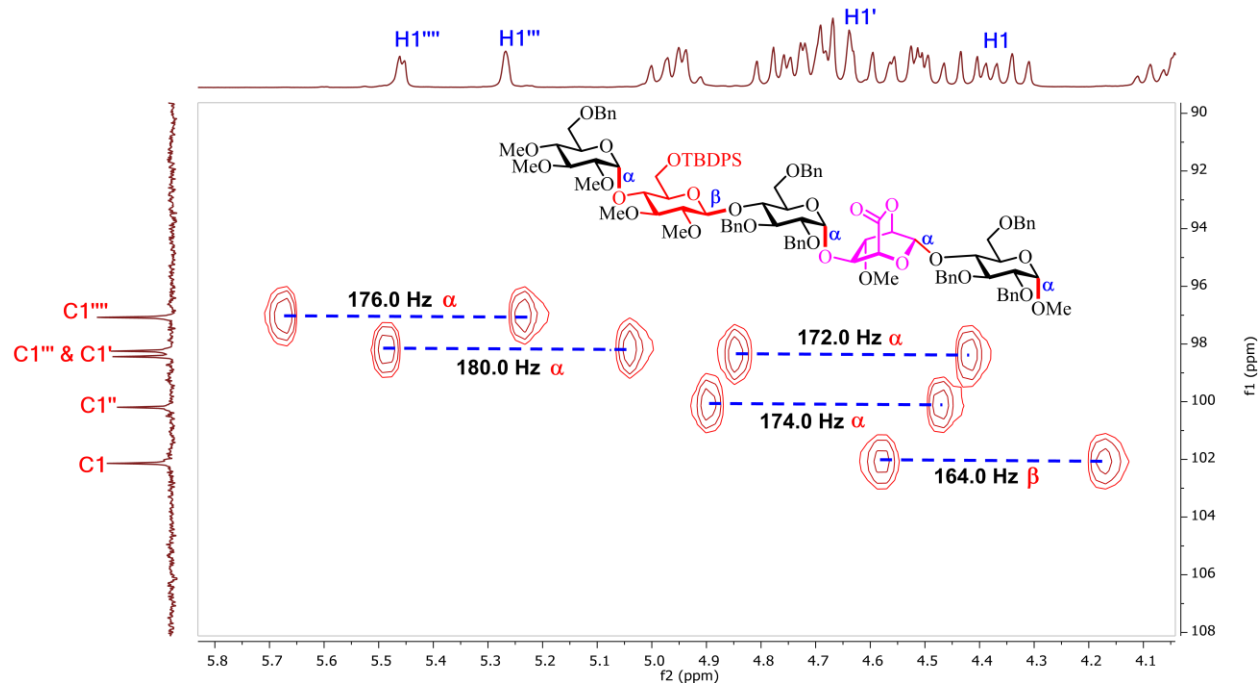


HSQC NMR Spectrum (400 MHz, CDCl_3) of compound **53**

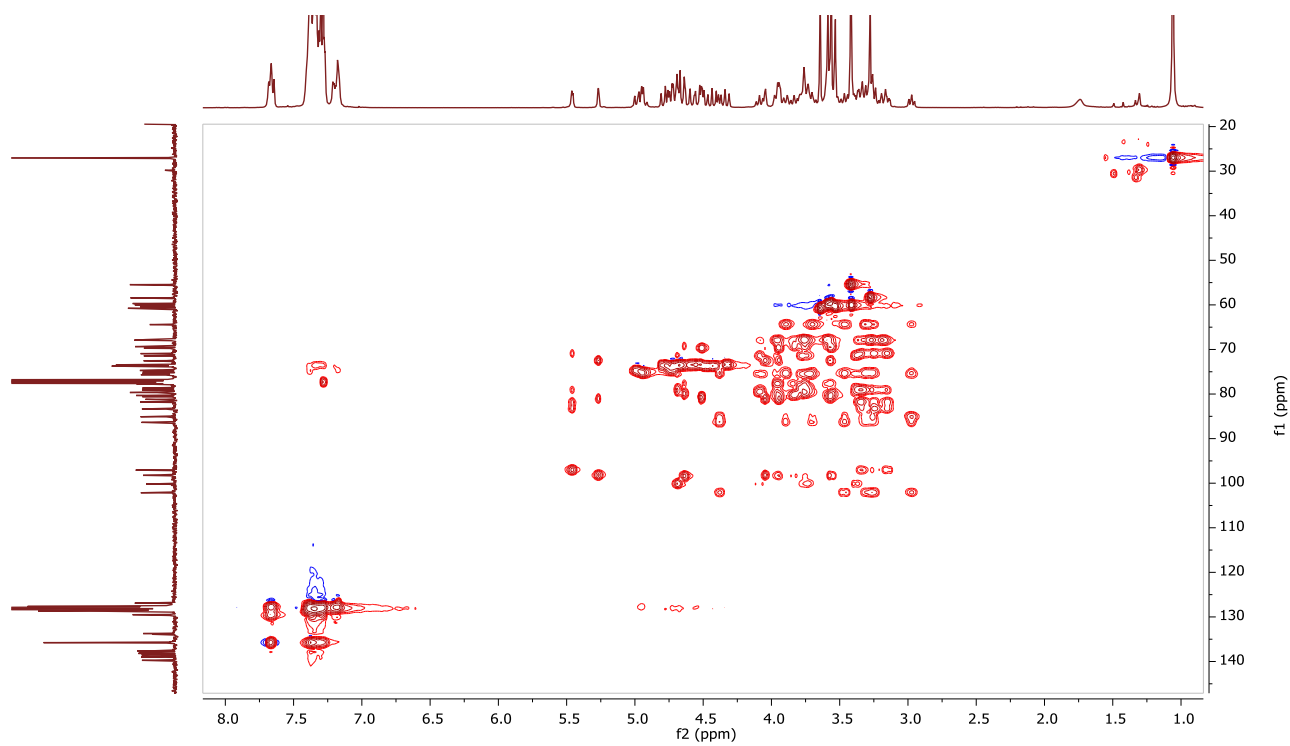


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HSQC NMR Spectrum (400 MHz, CDCl₃) of compound **53**

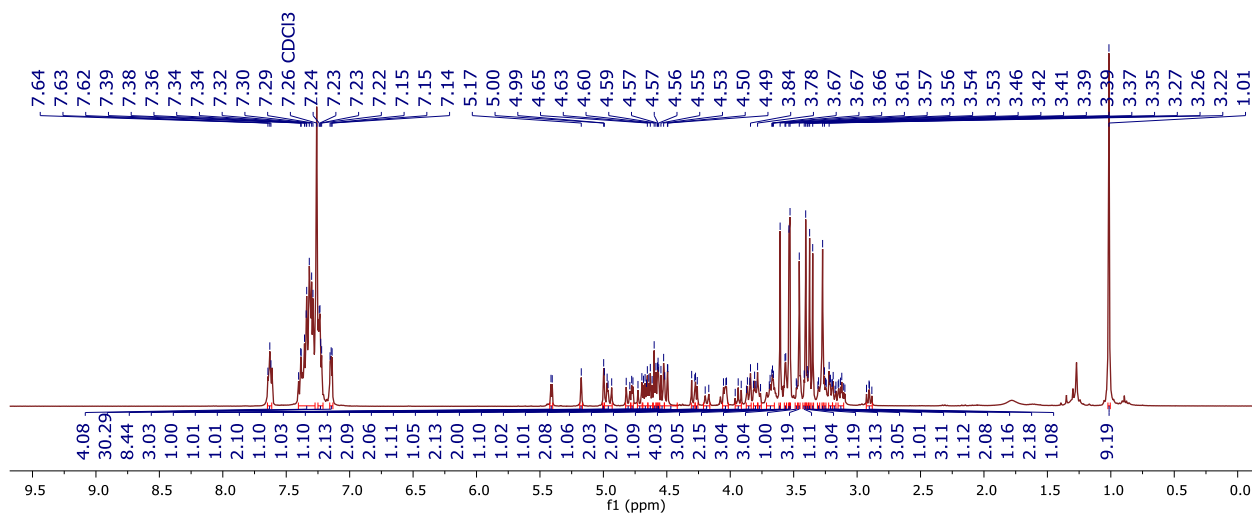


HMBC NMR Spectrum (400 MHz, CDCl₃) of compound **53**

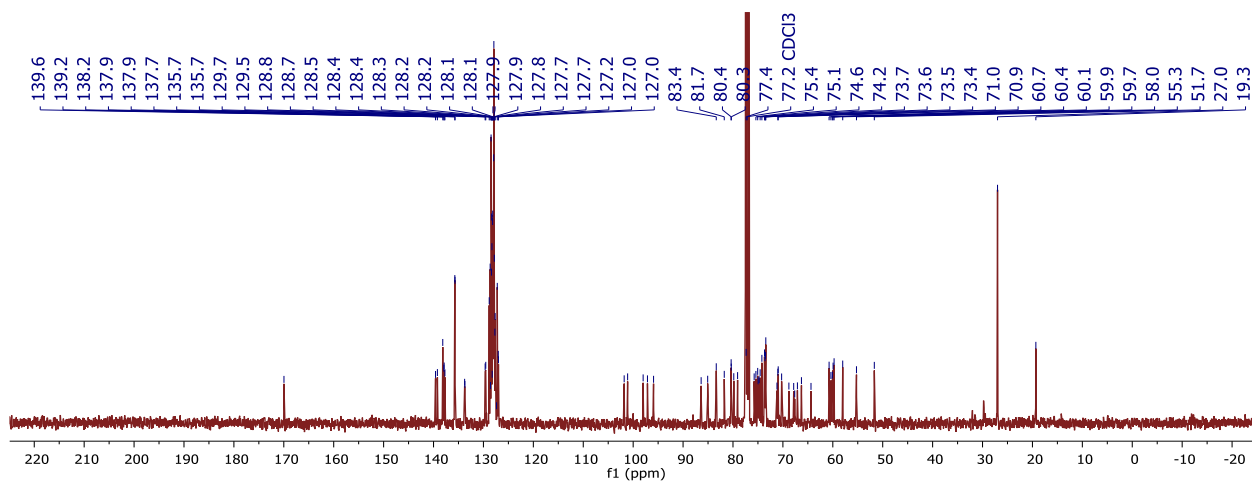


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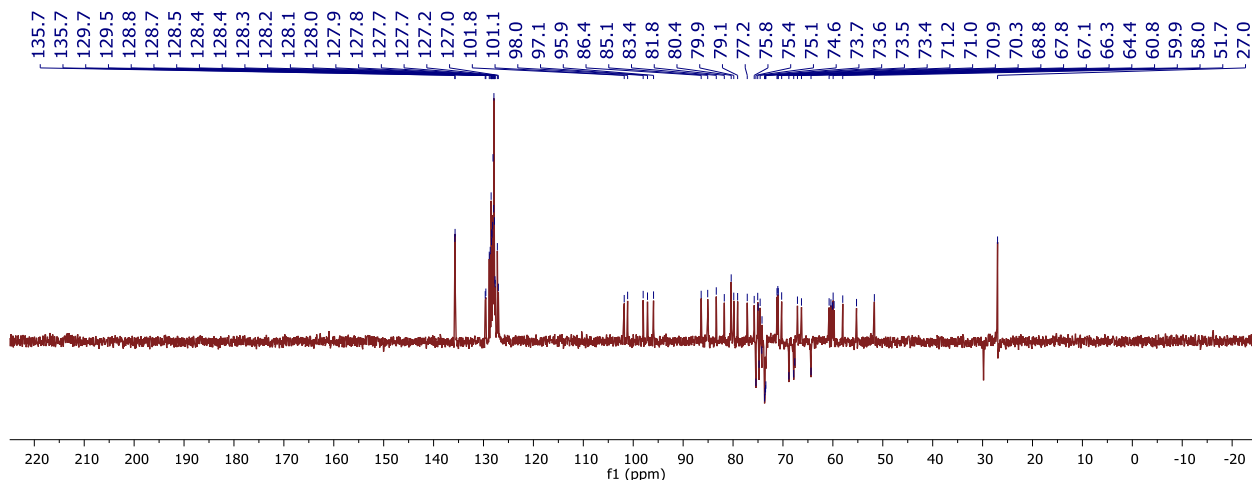
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **54**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **54**

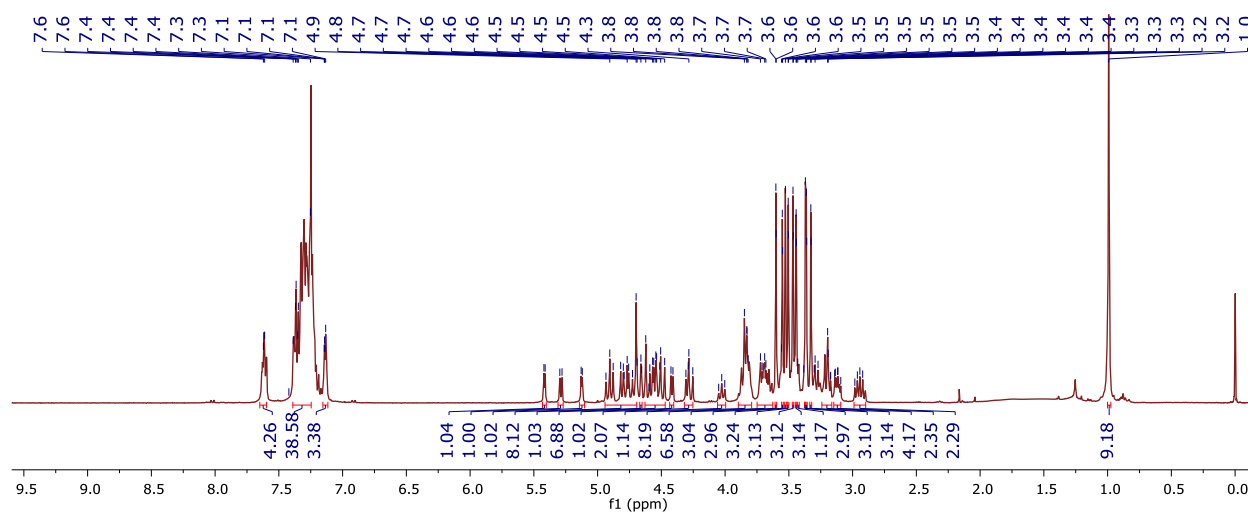


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **54**

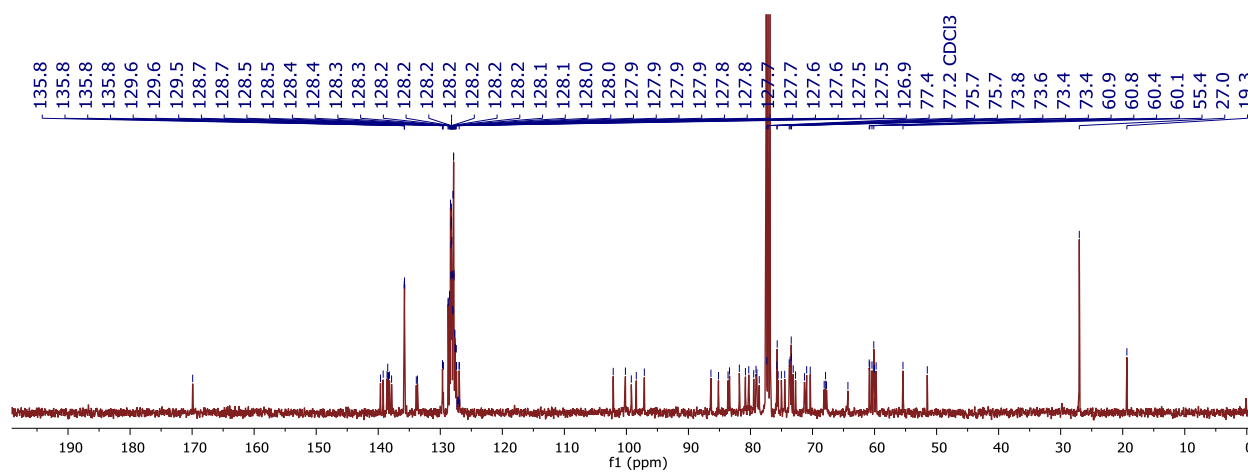


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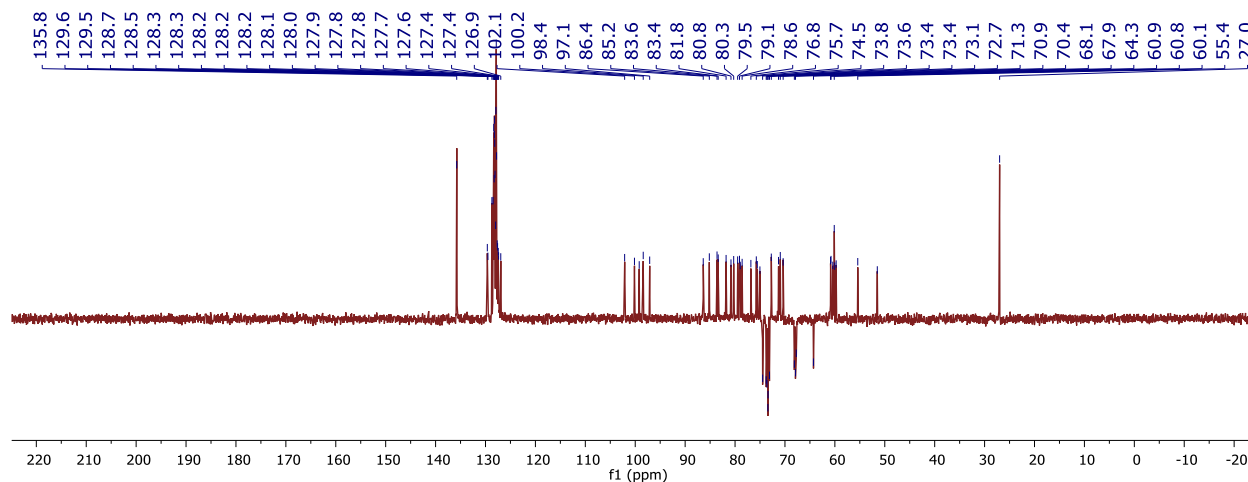
^1H NMR Spectrum (400 MHz, CDCl_3) of compound 55



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound 55

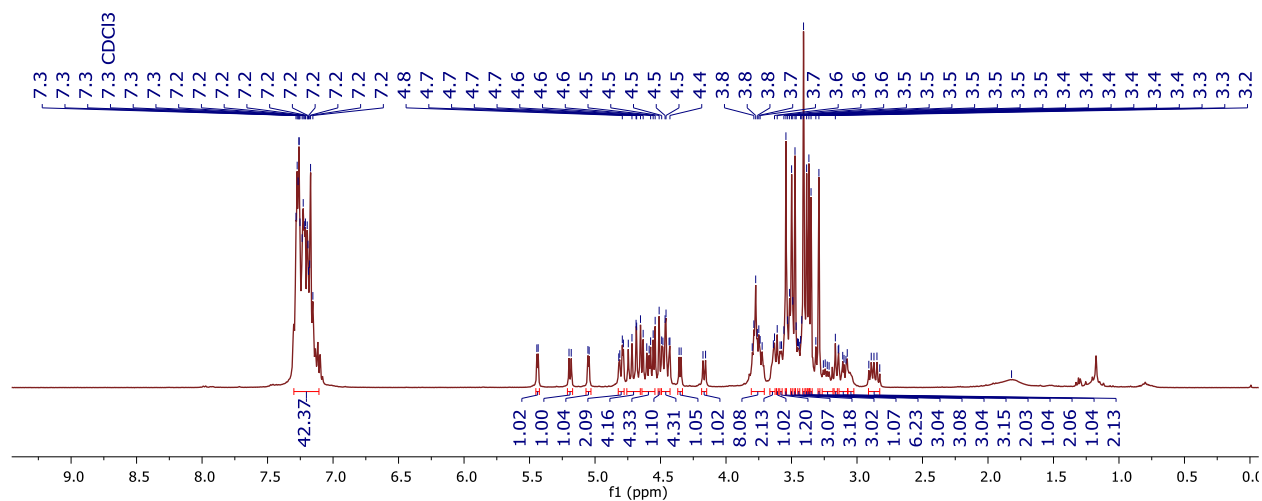


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound 55

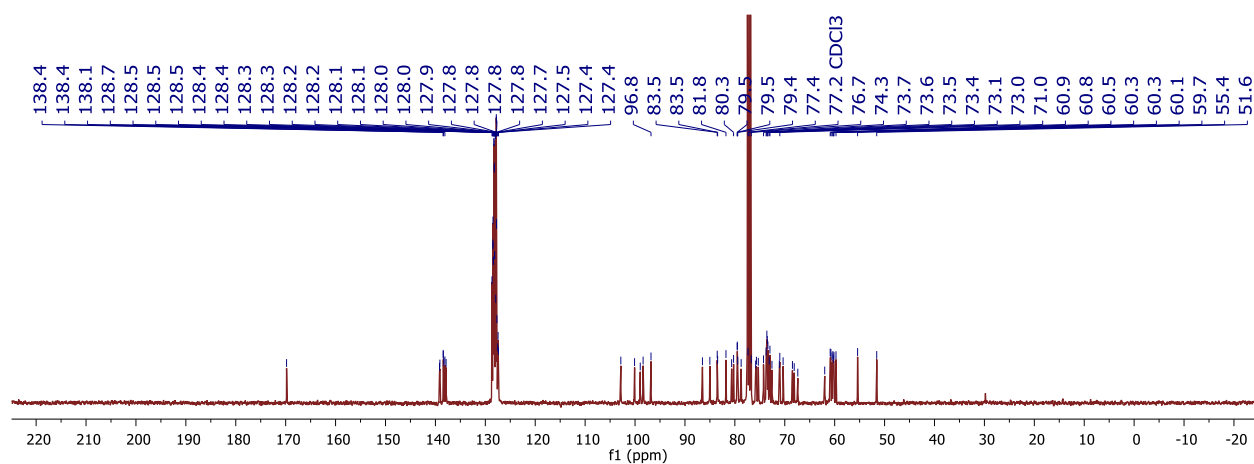


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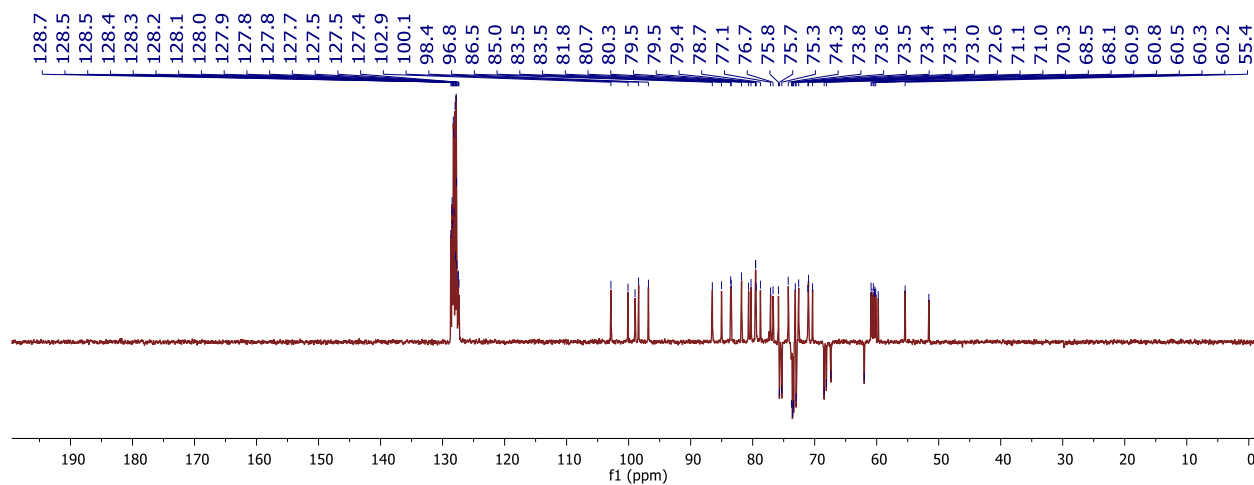
^1H NMR Spectrum (400 MHz, CDCl_3) of compound **56**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of compound **56**

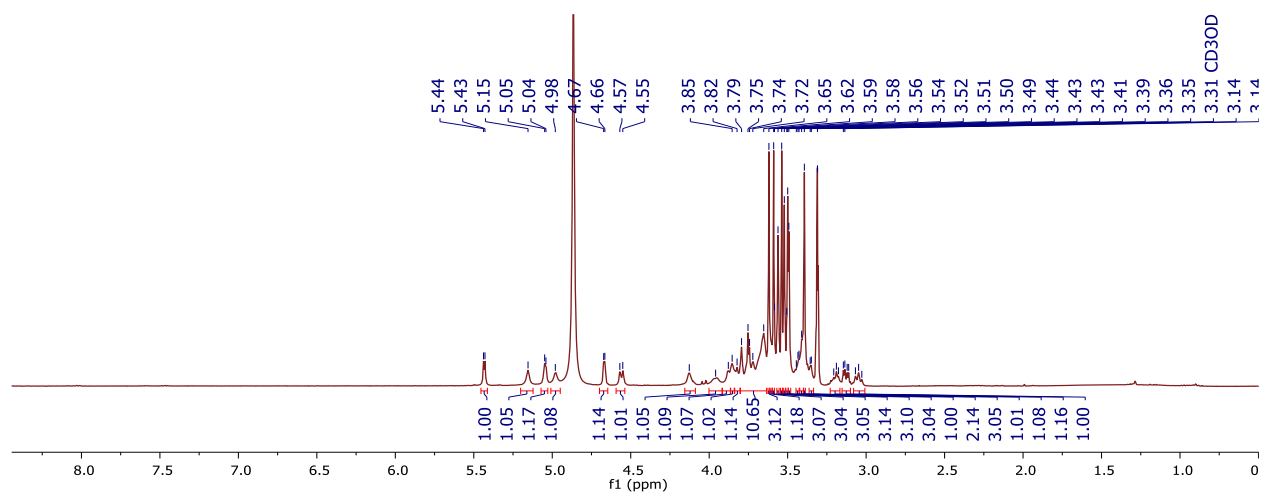


DEPT-135 Spectrum (100 MHz, CDCl_3) of compound **56**

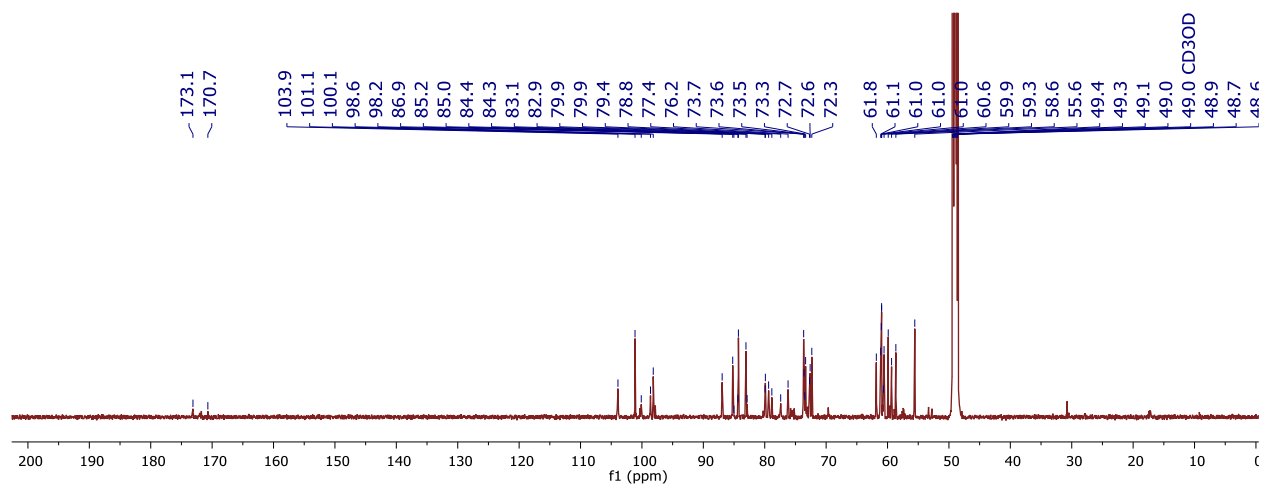


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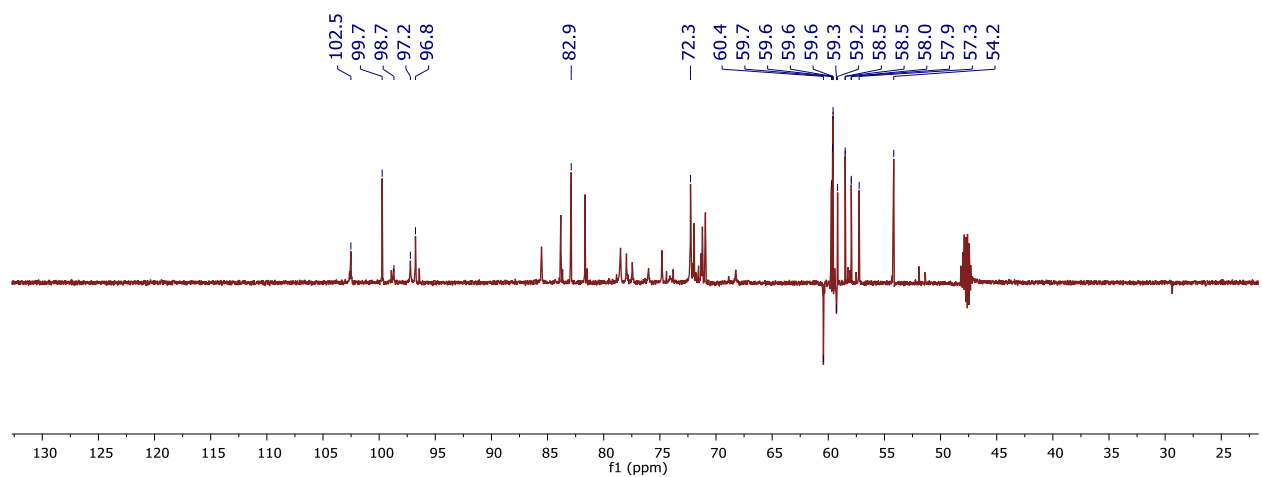
^1H NMR Spectrum (400 MHz, MeOD_4) of compound 57



^{13}C NMR Spectrum (100 MHz, MeOD_4) of compound 57



DEPT-135 Spectrum (100 MHz, MeOD_4) of compound 57



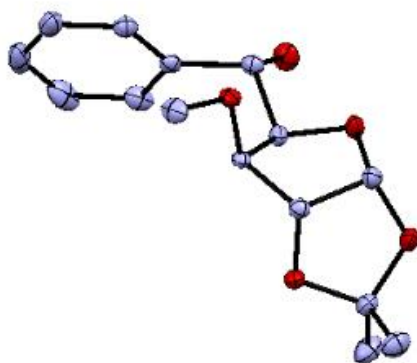


Figure S1 ORTEP diagram of compound **38** (5-(*S*)-1,2-*O*-(isopropylidene)-3-*O*-methyl-5-*C*-phenyl- α -D-xylofuranose, CCDC **2219829**). Ellipsoids are drawn to 50% probability and hydrogen atoms are not shown for clarity.

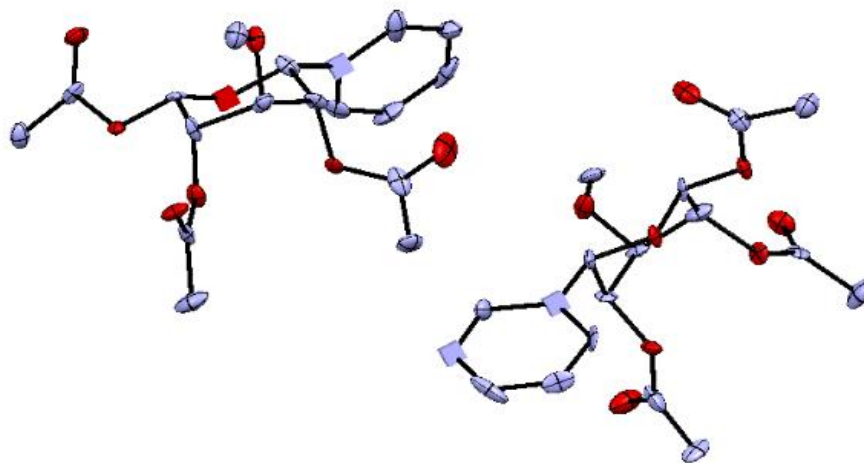


Figure S1 ORTEP diagram of compound **39** (5-(*S*)-1,2,4-tri-*O*-acetyl-3-*O*-methyl-5-*C*-phenyl xylopyranoside, CCDC **2219824**). Ellipsoids are drawn to 50% probability and hydrogen atoms are not shown for clarity.

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Chapter 3A

Investigation of Alkyne-appendage Glycosyl Ester as
Donors under Brønsted acid Condition

3A.1 Introduction¹

Carbohydrates are the ubiquitous bio-molecules present in the form of glycoconjugates that are mostly attached to cell membrane-bound proteins or lipids, or as simple oligosaccharides. These glycoconjugates and oligosaccharides are implicated in myriads of physiologically important processes such as cell-cell communications, fertilization, differentiation, embryogenesis, signal transduction, and many others.^{1a-b} Along with its involvement in beneficial biological processes, these bio-molecules also play crucial roles in viral or bacterial infections, and disease progressions such as neurodegenerative diseases or cancer metastasis thereby can be identified as the biomarkers in different life-threatening diseases.^{1c-d} For example, the changes in sialic acid expressions in malignancy or the increase in the cell surface hyaluronans density in breast cancers allow cancer cells not to be recognized by the host immune system. The recent emergence of new technologies in glycan analysis revealed carbohydrates as new targets for drug design and vaccine development.^{1e} Furthermore, recent studies on carbohydrates revealed the importance of these molecules in material science as a choice for biocompatible materials, therefore, opening a new vista to this burgeoning glycoscience.^{1f} These carbohydrates are abundantly produced by nature; however, due to their high heterogeneity, obtaining these in homogeneous and pure forms from natural sources is highly cumbersome. Access to the sufficient amount of well-defined, homogeneous mixture of glycans is needed to investigate their pathogenicity or the immunological response to facilitate drug design and vaccine development.^{1g-h} The chemical synthesis of glycoconjugates or oligosaccharides is of great interest. To date, many synthetic protocols have been developed invoking the enzymes and chemical reagents. In comparison to the enzymatic synthesis, the chemical synthesis of glycans has emerged as the most promising methodology as it is scalable and applied to the larger pool of glycosides syntheses. In the last 100 years of glycoscience, several chemical methodologies have been developed for the synthesis of structurally defined natural and unnatural glycosides.¹ⁱ In particular, the major focus was on the construction of *O*-glycosidic linkage which connects the two sugar building blocks and the process is called glycosylation.

3A.2 Chemical glycosylation²

A typical chemical glycosylation reaction involves two coupling partners viz. a glycosyl donor and an acceptor. The glycosyl donor is prepared in such a way that all the hydroxyls are masked except the anomeric position which usually bears a leaving group that can be activated using suitable promoters. The departure of the leaving group from the anomeric position leads to the formation of highly electrophilic species known as the “oxocarbenium ion” intermediate which will be attacked by an acceptor to form a stable glycosidic linkage. Identification of a suitable leaving group and a promoter system is of prime importance for any successful glycosylation. Thus, from the inception of the first glycosylation reaction by Emil Fischer using the hemiacetal as a glycosyl donor, lots of efforts have been taken to develop suitable leaving group-promoter combinations to perform glycosylations for the larger pool of glycosides. Several glycosyl donors have been investigated to undergo glycosylation employing the organic reagents or inorganic metal salts. However, very few of them such as glycosyl halides, esters, orthoesters, thio-glycosides, *n*-pentenyl glycosides, imidate donors, ethynylcyclohexyl carbonates are well explored and are proven suitable for higher oligosaccharide synthesis (discussed in chapter 1).

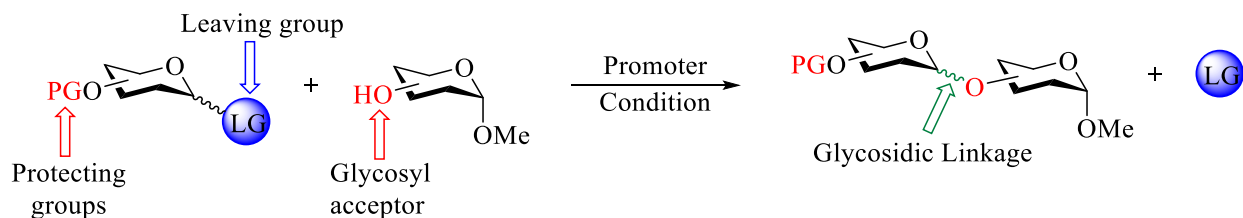


Fig. 1 General scheme of chemical glycosidation reaction

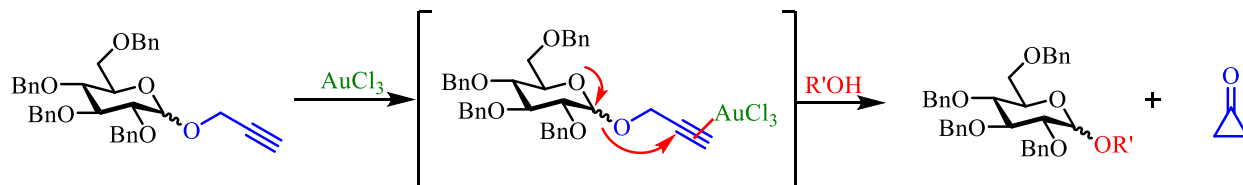
3A.3 Gold-catalysed glycosidations

Among all, the glycosyl donors containing alkyne functionality has gained a lot of attention in recent times because of its mild and selective activation conditions. In 2006, Hotha group reported a novel Au(III)-catalyzed glycosidation protocol for glycosides containing alkyne appendages as a leaving group. In this investigation, the propargyl glycosides were activated exploiting the π -acidity of AuCl_3 to coordinate with alkyne functionality to make the propargyl group as leaving group. The formation of alkyne-Au complex facilitates the departure of leaving group from the anomeric position to generate oxocarbenium ion which then gets attacked by an

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aglycon to form glycosides along with the liberation of hypothesized stable by-product cyclopropanone (Fig. 2).^{3a}

A. Activation of propargyl glycoside



B. Other donors developed by Hotha group based on gold catalysis

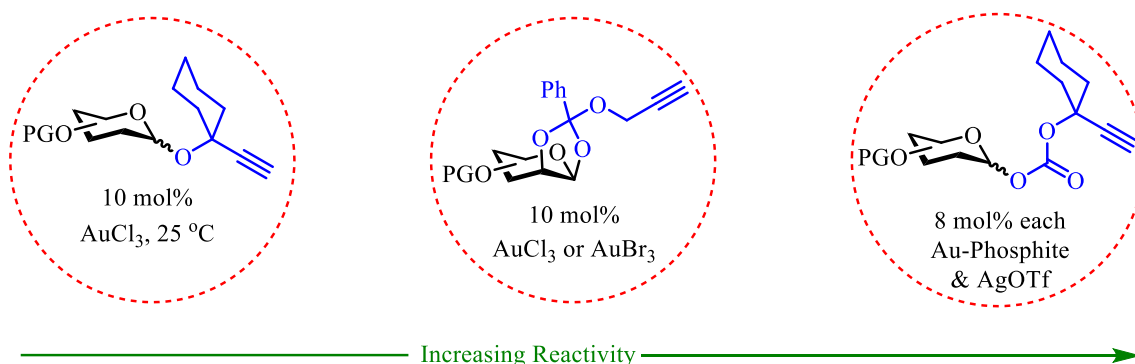


Fig. 2 Development of gold-catalyzed glycosylation by Hotha group

The benzyl-protected propargyl glycosides were activated using the 3mol% of AuCl_3 in acetonitrile at elevated temperature whereas the C-2-benzoyl-protected propargyl glycosides did not undergo glycosidation. Thus to circumvent the low reactivity of propargyl glycosides activation, various derivatives of alkyne-bearing appendages as leaving group were investigated to find that the cyclohexyl propargyl glycosides are yet another shelf-stable glycosyl donor. This donor was smoothly activated at room temperature with 10mol% of AuCl_3 to obtain glycosides with improved yield; however, the benzoyl-protected glycosyl donors were still persistent to undergo transglycosidation. The improved reactivity was attributed to the well-known Thorpe-Ingold effect of *gem*-dialkyl groups due to the cyclohexyl group.^{3b} In yet another facet, Hotha group reported the activation of glycosyl propargyl orthoesters for synthesizing 1,2-*trans* glycosidic linkages. The orthoester activation was accomplished by 10mol% of AuCl_3 or AuBr_3 at room temperature.^{3c} The mild and selective activation of propargyl orthoester was demonstrated by synthesizing the 21-mer arabinogalactan motif present on the cell surface of

Mycobacterium tuberculosis.^{3d} However, the instability of orthoesters under acidic conditions and the formation of direct glycosides during glycosidations are the major concerns while activating propargyl orthoester donors. Further investigation on improving the overall efficacy of gold-catalyzed glycosidation from the same group discovered the glycosyl ethynylcyclohexyl carbonates as highly efficient, shelf-stable, and versatile glycosyl donors. The donor was found to smoothly undergo glycosidations using 8mol% each of Au-phosphite and AgOTf to obtain O-, N-, and C-glycosides in good to excellent yield.^{3e} The versatility of donor chemistry to the synthesis of higher oligosaccharides was demonstrated by synthesizing the highly complex mannose-capped tridecasaccharide arabinofuranoside (13mer), branched heneicosafuranosyl arabinogalactan (21mer), pentacosafuranoside arabinogalactan (25mer).^{3f}

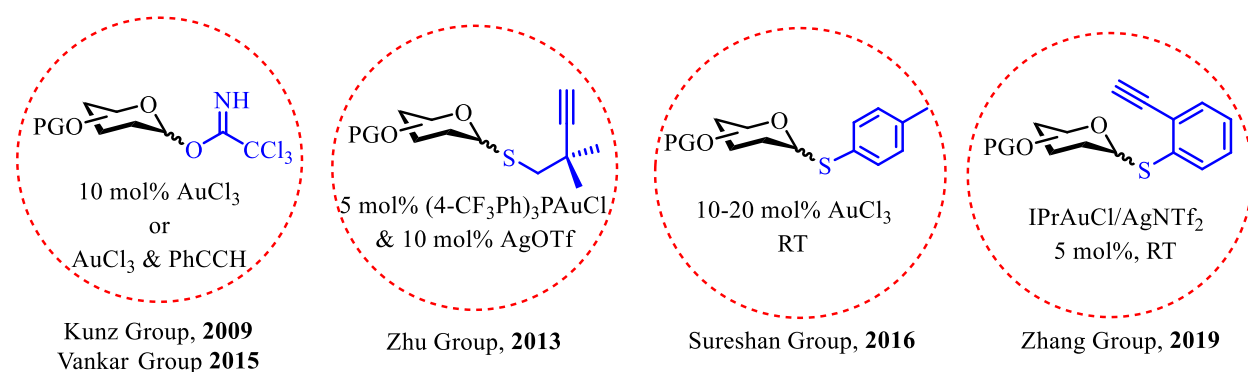
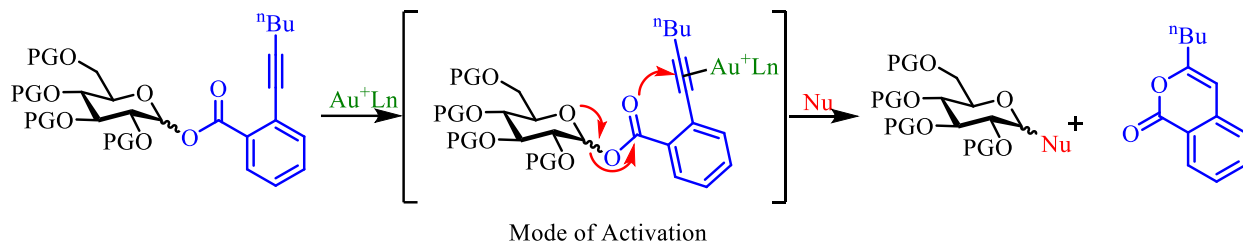


Fig. 3 Other glycosyl donors activated under gold catalysis conditions

The inception of the gold-catalyzed glycosidation protocol by Hotha group spurred great interest in the synthetic carbohydrate chemistry community to investigate the other glycosyl donors under gold catalysis. The Kunz group reported the activation of trichloroacetimidate donors under gold-catalyzed conditions for which the mechanism was recently investigated by Schmidt group through NMR spectroscopic studies.^{4a-b} Furthermore, Roy *et al.* identified the use of AuCl₃ alone or in combination with phenylacetylene as novel catalytic system for the activation of glycosyl imidate donors and demonstrated its applications for the synthesis of glycosides and glycoconjugates.^{4c} The Zhu group investigated the alkyne-containing anomeric 2,2-dimethylbut-3-ynyl thioglycosides and identified its activation using 10mol% of AuCl₃ and 30mol% AgOTf to undergo glycosidation.^{4d} The utility of this donor was demonstrated by the successful synthesis of several disaccharides containing benzoyl or benzyl-protected sugars and small glycoconjugates.^{4e} Zhang group identified the o-ethynylphenyl thioglucosides as effective donor

for α -D-glucosides syntheses.^{4f} Recently, Sureshan and coworkers reported the activation of *p*-tolyl thioglycosides using the sub-stoichiometric amount of AuCl₃ to undergo glycosidation.^{4g} Furthermore, the glycosyl sulfoxides are also investigated under gold catalysis conditions and shown that they can be utilized as glycosyl donors.^{4h}

3A.4 Activation of alkyne containing glycosyl esters



Scheme 1 Activation of ortho-alkynyl benzoates using gold catalysis

Glycosyl esters containing alkyne functionality as the leaving group at the anomeric position have been investigated under gold-catalyzed conditions. In 2008, the Yu group identified the *n*-butyl-*o*-alkynyl benzoates as stable, efficient, and versatile glycosyl donors which can be effectively activated using the catalytic amount of Ph₃PAuOTf or Ph₃PAuNTf₂.^{5a} This donor has been thoroughly explored and found suitable for synthesizing *O*-, *N*- and *C*-glycosides as well as complex glycoconjugates and oligosaccharides.^{5b} Later, Balamurugan group reported another glycosyl donor having dipropargyl-substituted cyanoacetyl glucosides as leaving groups under gold-catalyzed conditions in 2015. The donor was activated using 10mol% of AuCl₃ in combination with 30mol% of AgSbF₆ and found useful for the synthesis of *O*-glycosides.⁶ Glycosyl ynenates are activated with 20mol% each of Ph₃PAuOTf and TfOH and have been effectively utilized for highly convergent synthesis of polymannosides (32 mer).^{7a-b} In 2019, Xiao and coworkers introduced the cyclopropyl *o*-alkynylbenzoates as glycosyl donors and investigated them as an orthogonal glycosyl donor that could be activated in presence of thioglycosides, *n*-pentenyl glycosides, and trichloroacetimidate donors.⁸ Glycosyl phenylpropiolate was reported by Amit Kumar group employing 10mol% of AuCl₃ to undergo glycosylation at elevated temperature.^{9a} Very recently, *o*-alkynylbenzoates having aglycon directing appendage on the leaving group appeared from the Xang group. The donor was

examined for the synthesis of 1,2-*cis* glycosidic linkage and demonstrated its application in oligosaccharide synthesis.^{9b}

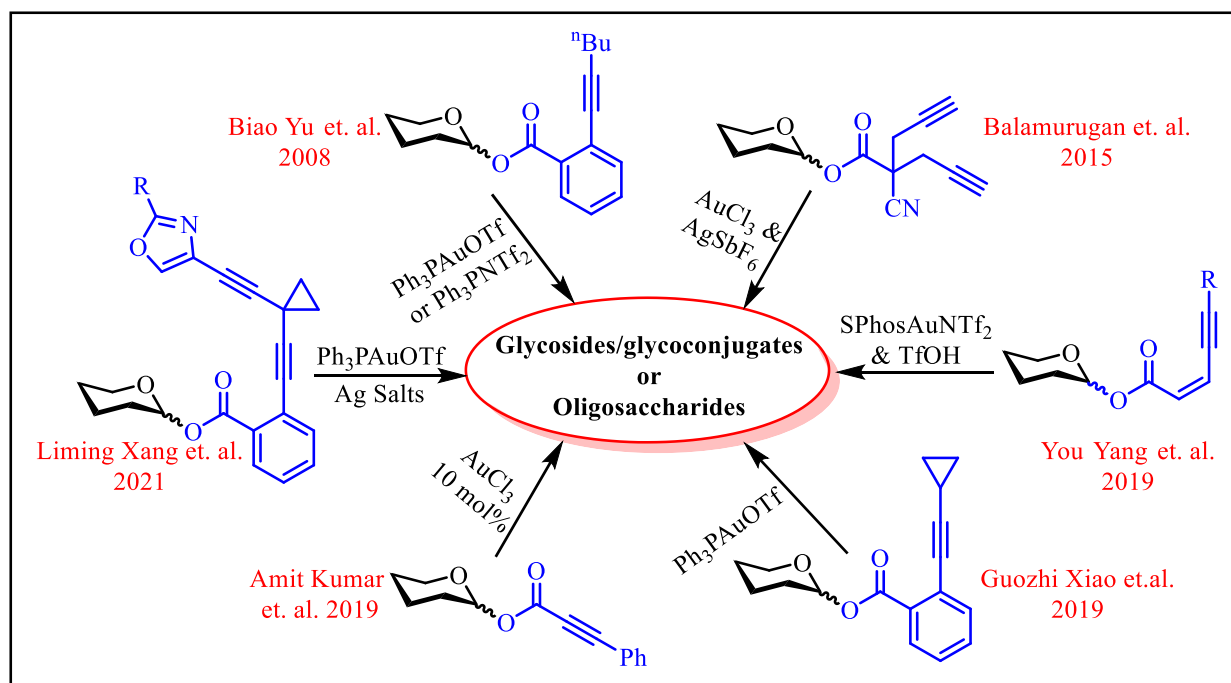
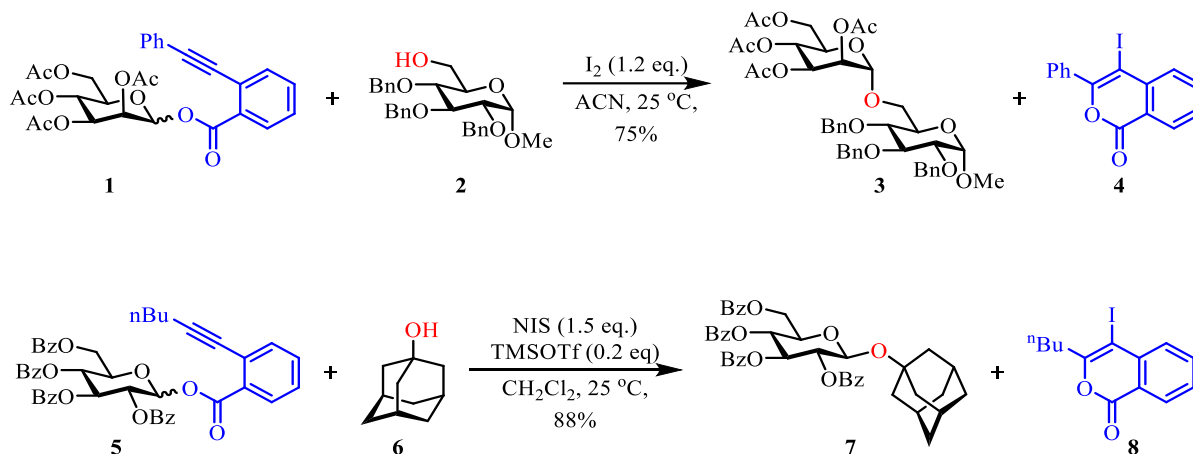


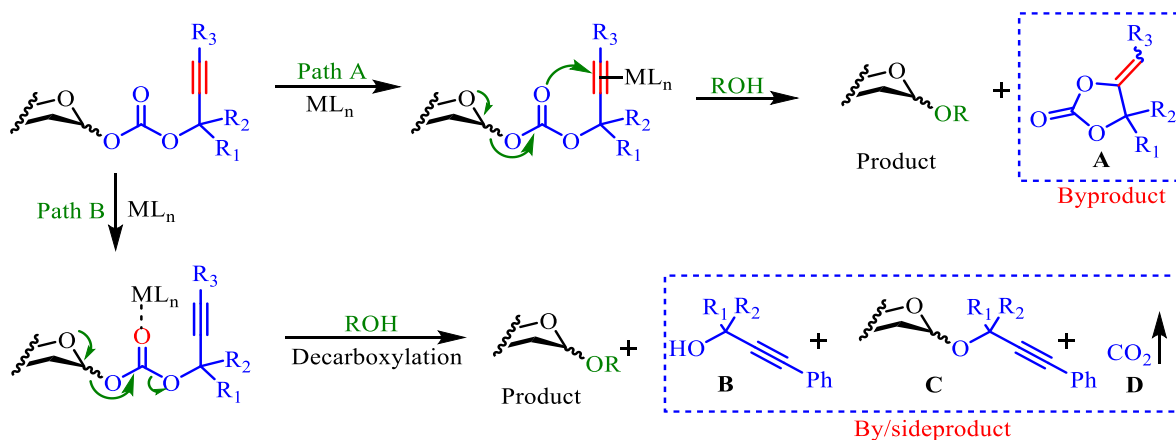
Fig. 4 Selected anomeric esters with alkyne as glycosyl donors under gold catalysis

While the gold-catalyzed glycosidation of glycosyl ester donors containing alkyne functionality was booming rapidly, Dutta *et al.* showed that glycosyl *o*-alkynylbenzoates type donors can also be activated using simple molecular iodine. For example, the phenyl *o*-alkynylbenzoate mannopyranoside **1** was activated in the presence of acceptor **2** using stoichiometric amount of molecular iodine to obtain disaccharide **3** in 75% yield along with non-nucleophilic cyclized by-product **4** at room temperature. Additionally, the authors demonstrated that this donor can be selectively activated in the presence of thioglycosides as well.^{10a} Another report from the Yang group demonstrated the activation of *n*-butyl *o*-alkynylbenzoates under the NIS/TMSOTf conditions. 1.5 Equivalents of NIS and sub-stoichiometric amount of Lewis acid is essential for the effective activation of glycosyl donors. The versatile nature of donor and mild activation condition were demonstrated by the successful synthesis of disaccharides employing both armed/disarmed glycosyl donors, *N*-glycosides such as purine, pyrimidine, and *C*-glycosides in good yields.^{10b}



Scheme 2 Activation of alkyne containing glycosyl ester without gold salts.

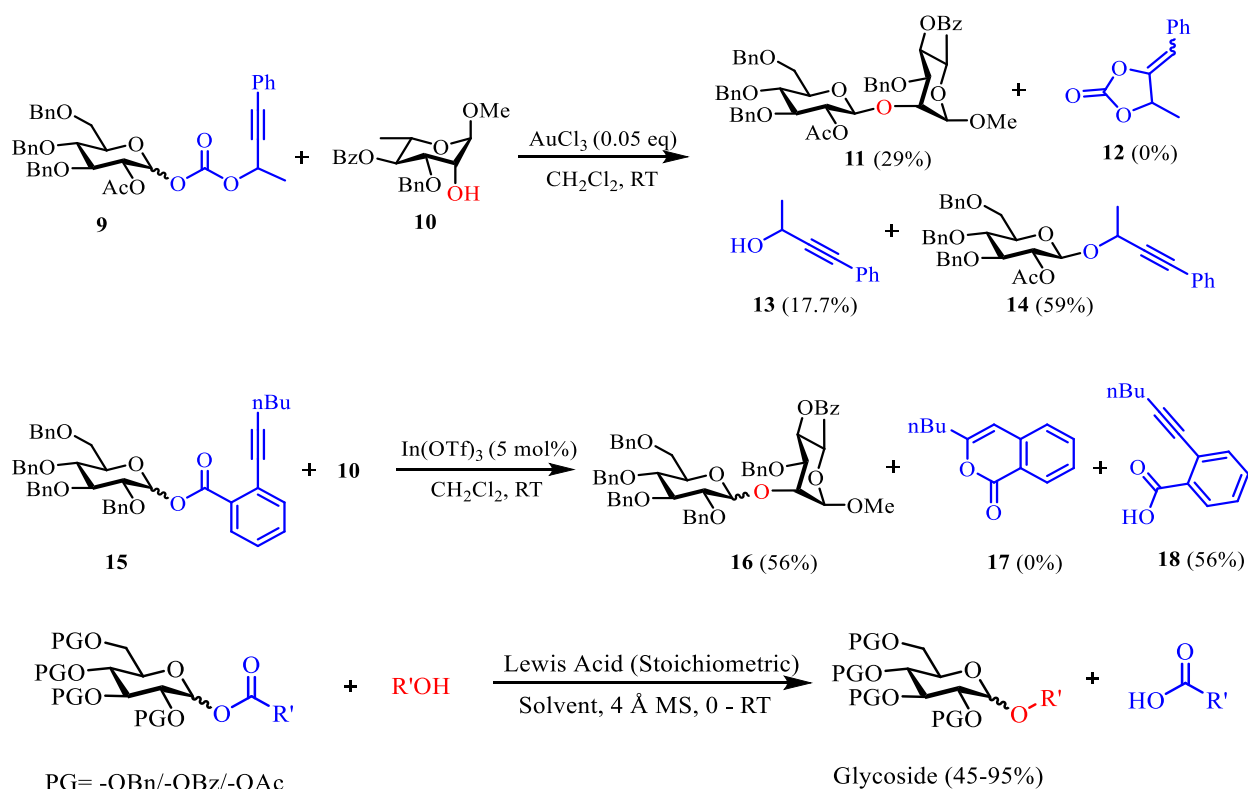
It is known for a long time that Lewis acids activate anomeric esters to afford glycosides. To probe this, very recently, Chai group investigated the activation of alkyne-installed glycosyl donors employing the dual acidic metal catalyst.^{11a} To identify the mode of activation authors evaluated the percentage of by-products formed in the glycosylation reaction (as shown in scheme 3). For example, if the activation of leaving group is promoted due to the π -acidity of catalyst the path A will be followed. The formation of metal-alkyne complex intermediate and its collapse due to cascade of electron push from endo-cyclic oxygen lone pair can lead to the formation of glycoside in the presence of an aglycon and a stable cyclized by-product **A**. Whereas, if the activation happens due to the Lewis acidity of metal salts (path B), the intermediate will collapse *via* decarboxylative glycosidation and produce the side/by-product **B**, **C**, and **D**.



Scheme 3 Possible modes of activation in alkyne containing carbonates as leaving group

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This investigation disclosed that the mode of activation is dependent on different factors such as the structure of aglycon, type of protecting groups on sugar ring, and different π and Lewis acidity nature of catalysts. However, it was evident that the donors containing alkyne can also be activated due to the Lewis acidity of promoter. For example, the activation of super-armed glycoside **9** in presence of acceptor **10** using 5 mol% AuCl_3 at room temperature resulted in the formation of disaccharide **11** (29%) along with side products **13** (17.7%) and **14** (59%) which suggest that the activation is promoted due to the Lewis acidity of the promoter (path B). Furthermore, the activation of *n*-butyl-alkynylbenzoate glycoside **15** in presence of Lewis acid $\text{In}(\text{OTf})_3$ (5mol%) successfully formed the disaccharide **16** (56%) and *n*-butyl benzoic acid **18** (56%) as the sole by-product in the glycosidation. This investigation from Chai group revealed the possibility of activation for alkyne containing glycosyl esters exploiting the Lewis acid characters of metal salts.



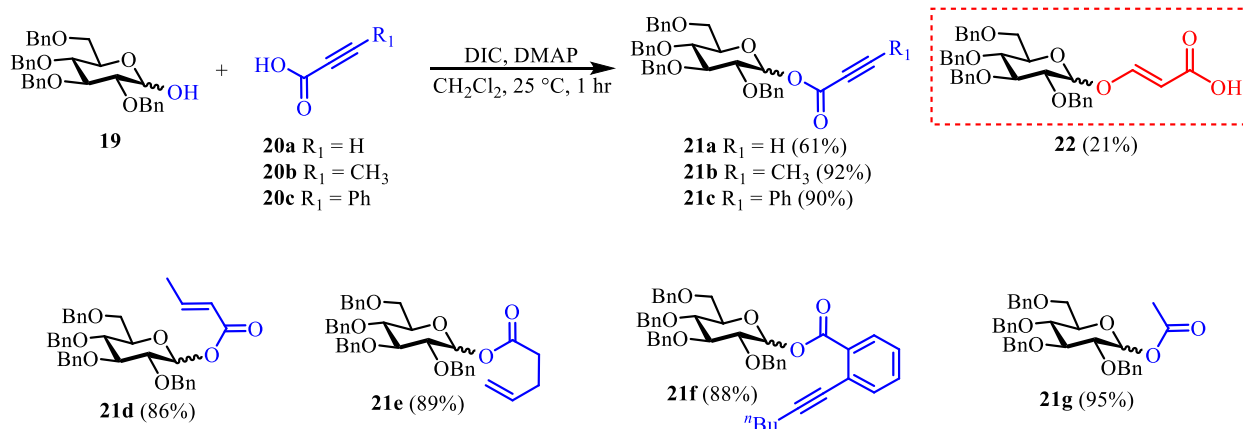
Scheme 4 Activation of alkyne-containing glycosyl donors employing the Lewis acidity of metal salts.

3A.5 Present Work

In order to investigate the Lewis/Brønsted acid activation of alkyne-containing glycosyl esters, the glycosyl propiolates **21a-21c** were hypothesized as suitable candidates as they have both ester functionality and an alkyne as well. The study was aimed to investigate whether the glycosyl esters containing alkyne functionality essentially require the gold salts or it can be activated under simple Lewis/Brønsted acid conditions. Therefore, three different propiolic acid moieties **20a-20c** having alkyne functionality were selected for coupling with 2,3,4,6-tetra-*O*-benzylglucopyranoside **19** employing the Steglich esterification conditions. Accordingly, donors **21a-21c** were prepared invoking the well-reported DIC/DMAP conditions with excellent yields except for donor **21a** that gave the reverse-addition product **22**, most likely due to the 1,4 Michel addition of hemiacetal on the unsubstituted alkyne. The alkyne-containing glycosides were selected as model substrates to optimize the glycosidation condition in the presence of commercially available methyl 2,3,4,6-tetra-*O*-benzoyl- α -D-glucopyranoside **23a** as an acceptor. The experiments started with Lewis acid-mediated catalysis; therefore, the recently reported 10mol% AuCl₃/CH₂Cl₂ condition was employed to activate donors **21a-21c** at room temperature to couple with aglycon **23a**. We noticed the formation of disaccharide **24** in low yields (Scheme 6, Entry 1-4). Therefore, further investigation was continued using the triflate containing Lewis acids which can *in situ* generate the Brønsted acid. The glycosidation between donor **21b** and acceptor **23a** using stoichiometric amount of TMSOTf showed the complete consumption of both reactants which upon silica gel column chromatographic purification gave the disaccharide **24** in 85% yield as α/β (2:1) anomeric mixture. The disaccharide **24** was thoroughly characterized using NMR spectroscopic analysis wherein two anomeric carbons for major isomer (α) were identified at δ 97.6 & 96.9 ppm along with the rest of the resonances in complete agreement with the assigned structure. The HRMS analysis showed the molecular ion peak [M+H]⁺ *m/z* at 1029.4075 which matched with that of the calculated *m/z* of 1029.4061 Da.

However, knowing that the 1 equivalent of TMSOTf could be the harsh condition to perform glycosidation, the investigation was continued to identify milder conditions. Lowering the equivalents of TMSOTf from 1.0 to 0.5 equiv did not show much impact on the reaction yield; further decrease suddenly dropped the reaction yield to 37% and the donor was recovered up to 40% (Scheme 6, Entry 5-7).

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Scheme 5 Synthesis of glycosyl esters

In another set of reactions, donor **21b** was promoted to undergo the glycosidation using stoichiometric amount of Tf_2O which could also generate the TfOH *in-situ*. Donor got activated to give the disaccharide in 52% yield though donor was recovered in 30% yield (entry 8). Therefore, the donor **21b** was directly exposed to the 0.5 equivalents of Brønsted acid TfOH to afford the disaccharide in 88% yield; further decrease of promoter to 0.2 equivalents did not hamper the reaction yield and offered 90% disaccharide. Whereas, further lowering the TfOH to 0.1 equivalents indeed showed the decrease in the yield to 58% (scheme 6, entry 9-11). Therefore 0.2 equivalents of Brønsted acid TfOH was identified as a minimum amount of catalyst that can promote the departure of leaving group at room temperature. On identifying the suitable catalyst, the effect of different solvents was examined to improve the overall efficacy of glycosylation. Solvents have very little role in these reactions; optimized reaction conditions were identified as 0.2 equivalents of TfOH in CH_2Cl_2 at room temperature as best conditions for glycosidation (Scheme 6, entry 12-16).

Next in our investigation, we were interested in understanding the role of α -positioned alkyne functionality in the activation of glycosyl esters using TfOH as it can act as electron withdrawing group and promote the departure of leaving group. To investigate this, glycosyl esters **21d-21g** having alkyne, alkene, and complete saturation at α -position of glycosyl esters carbonyl were synthesized. The glycosidation between unsubstituted propiolate donor **21a** and acceptor **23a** in presence of 20 mol% TfOH produced 88% yield of disaccharide **24** as α/β anomers. Changing the donor to phenylpropiolate **21c** afford 78% yield of disaccharides (Scheme 6, Entry 17,18).

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Interestingly, the glycosyl esters without alkyne at α -position were also found to be effectively activated under aforementioned optimized conditions.

21a - 21g + 23a → 24 Glycosyl Donors + Acceptor Conditions: 25 °C, 30 min, 4Å MS Powder				
Entry	Donor	Conditions	% Yield	$\alpha:\beta$ ratio
1	21a	AuCl ₃ /0.1 eq./CH ₂ Cl ₂ /RT	~20	
2	21b	AuCl ₃ /0.1 eq./CH ₂ Cl ₂ /RT	~30	
3	21c	AuCl ₃ /0.1 eq./CH ₂ Cl ₂ /RT	~20	
4	21b	AuCl ₃ /0.1 eq./CH ₂ Cl ₂ /45 ⁰ C	70	
5	21b	TMSOTf/1.0 eq./CH ₂ Cl ₂	85	1:0.9
6	21b	TMSOTf/0.5 eq./CH ₂ Cl ₂	83	--
7	21b	TMSOTf/0.2 eq./CH ₂ Cl ₂	37 ¹	--
8	21b	Tf ₂ O/1.0 eq./CH ₂ Cl ₂	52 ²	
9	21b	TfOH/0.5 eq./CH ₂ Cl ₂	88	--
10	21b	TfOH/0.2 eq./CH ₂ Cl ₂	91	1:0.9
11	21b	TfOH/0.1 eq./CH ₂ Cl ₂	58 ³	
12	21b	TfOH/0.2 eq./Et ₂ O	52	--
13	21b	TfOH/0.2 eq./CH ₃ CN	43	--
14	21b	TfOH/0.2 eq./THF	38	--
15	21b	TfOH/0.2 eq./CHCl ₃	78	--
16	21b	TfOH/0.2 eq./Toluene	10	--
17	21a	TfOH/0.2 eq./CH ₂ Cl ₂	88	1:1
18	21c	TfOH/0.2 eq./CH ₂ Cl ₂	78	1:0.7
19	21d	TfOH/0.2 eq./CH ₂ Cl ₂	79	1:1
20	21e	TfOH/0.2 eq./CH ₂ Cl ₂	75	1:0.8
21	21f	TfOH/0.2 eq./CH ₂ Cl ₂	62	1:0.9
22	21g	TfOH/0.2 eq./CH ₂ Cl ₂	72	1:0.9

^[1]40% donor recovered; ^[2]30% donor recovered; ^[3]37% donor recovered

Scheme 6 Investigation of glycosyl esters as glycosyl donors

Interestingly, donor **21d** that has 1,2-olefinic system with ester gave 79% of disaccharide whereas donor **21e** having alkene group at 3,4-position of the ester gave 75% of disaccharide **24** (Scheme 6, Entry 19, 20). The Above results encouraged us to investigate the other well-established ester-based donors to see whether that can also be activated using Brønsted acid. Subsequently, *n*-butyl-*o*-alkynylbenzoate **21f** was promoted in presence of acceptor **23a** to

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undergo glycosidation to give 62% of the disaccharide with some amount of recovered donor (which could completely consumed when 0.5 Equiv TfOH was used). Further, the simple anomeric acetate donor **21g** also got activated lucratively with good yields (Scheme 6, Entry 21, 22). Overall, these results indicated that the glycosyl esters can be effectively activated using 20-50 mol% of Brønsted acid TfOH.

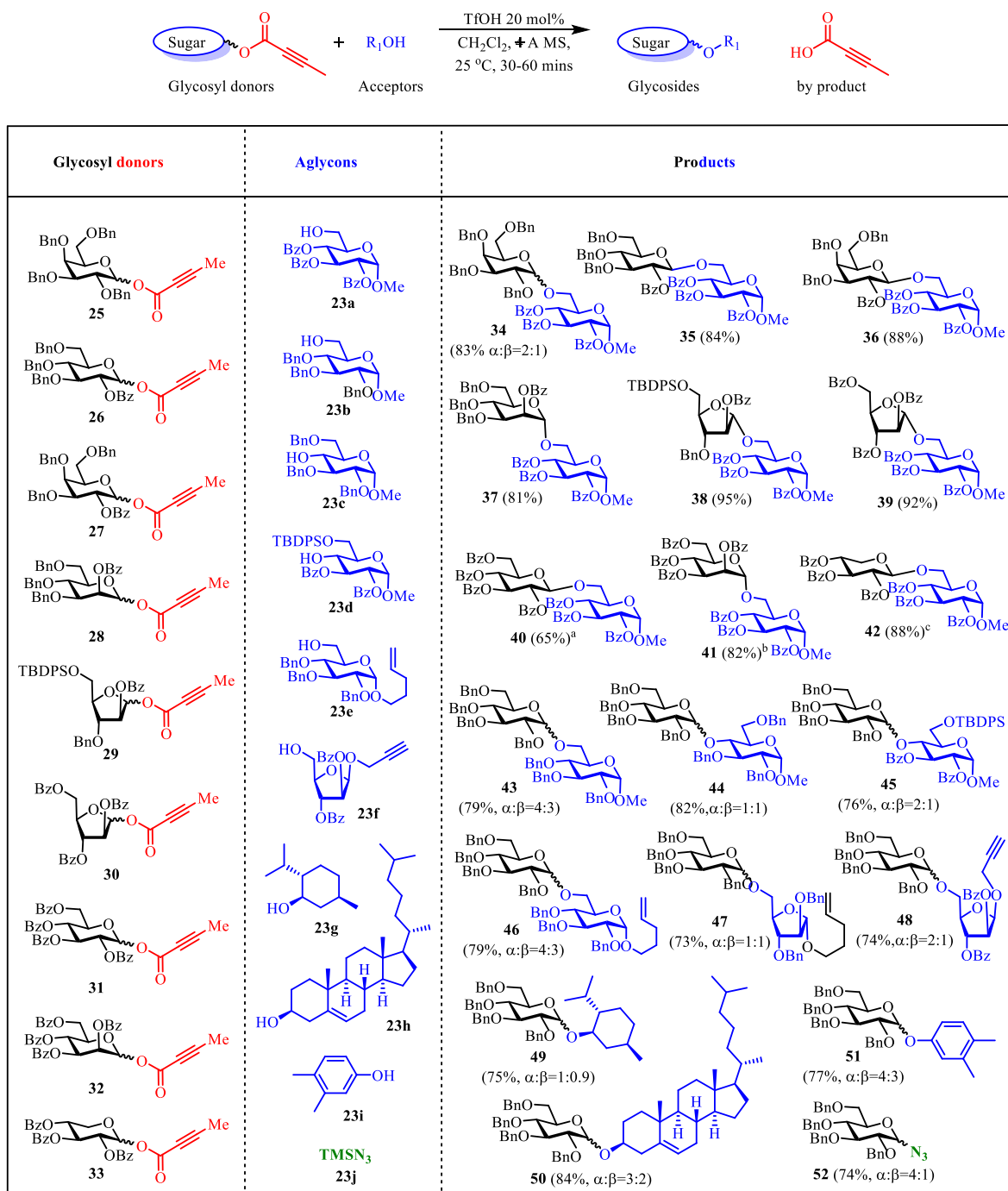
The efficacy of any glycosyl donor can be gauged by its substrate scope to construct different glycosidic linkages. The methylpropiolate glycoside **21b** was selected to continue for the study considering the entry 10 where 20mol% of TfOH at room temperature gave excellent yield. Different glycosyl methylpropiolates including Glcp, Manp, Galp, Xylp, and Araf donors **25-33** were prepared from corresponding hemiacetals by invoking the DIC/DMAP conditions and subjected to glycosylations with the model acceptor **23a**. The per-*O*-benzylated galactopyranosyl methylpropiolate **25** smoothly produced the disaccharide **34** as anomeric mixture in 83% yield. Changing donor from armed to super-armed **26-29** found good to excellent reaction yield as single anomer of the disaccharides **35-38** due to neighboring group participation of C-2-benzoate (Scheme 7).

Next, in our journey, we explored this methodology for disarmed donors as that was failed to be glycosylated in recently reported AuCl₃ catalyzed glycosidation of phenylpropiolate donors.^{9a} Interestingly, glycosylation of per-*O*-benzoylated arabinofuranosyl methylpropiolate **30** with acceptor **23a** afforded disaccharide **39** in 92% yields may be due to the high reactivity of furanosyl sugars. The reaction of disarmed glucopyranosyl methylpropiolate **31** and **23a** produced 15% of disaccharide only under the standard optimized glycosidation condition; however, it was found that yield of reaction can be enhanced by increasing either catalyst loading to 1.0 equivalent of TfOH or keeping the reaction for longer time. Furthermore, similar trends were observed for per-*O*-benzoylated mannoparanosyl donor **32** which was activated using the 60 mol% of TFOH to obtain the disaccharide **41** in 82% yield. The disarmed xylopyranosyl donor **33** was also activated using 0.4 equivalent of TfOH to access the glycosylated product **42** in 88% yield.

Next, we thoughtfully selected acceptors **23a-23j** containing 1° or 2° hydroxyl free for glycosidic bond formation to gauge the methodology for different acceptors during the glycosidation with glycosyl donor **21b**. Accordingly, reactions performed with sugar acceptors

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23b-23e resulted in the isolation of corresponding disaccharides **43-46** as their α/β anomeric mixtures in good yield.



Reaction condition: TfOH (0.2 eq)/CH₂Cl₂/RT/40min, ^a1.0 eq of TfOH used with 1h stirring, ^b0.6 eq of TfOH used with 2h stirring, ^c0.4 eq of TfOH used, 1h stirring

Scheme 7 Substrate scope for methylpropiolate glycosyl donor

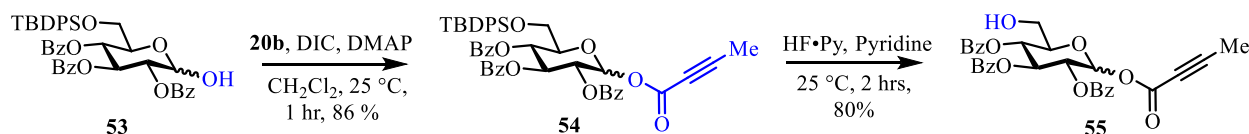
Notably, the glycosidation between donor **21b** and acceptor **23d** proceeded smoothly to give disaccharide **45** as anomeric mixture in 76% yield without affecting the silyl ether protection.

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Furthermore, the acceptors **23e** and **23f** which have aglycon *n*-pentenyl and propargyl moiety at the anomeric position also underwent glycosylation to produce disaccharides **46** and **48** respectively.

Similarly, alicyclic acceptors such as (*S*)-Menthol and Cholesterol were glycosylated with **21b** to produce corresponding glycosides **49** and **50** in 75% and 84% yields respectively. Phenolic glycoside **51** was also produced by coupling 3,4-dimethylphenol with donor **21b** in 77% as anomeric mixture. Interestingly, the *N*-glycosidation was also noticed as the glycosidation between **21b** and TMSN₃ produced the 1-azido-glucoside **52** in 74% as 4:1 α : β anomeric mixture. The formation of azido glycoside was successfully confirmed by analyzing ¹³C NMR where the up-field shift in anomeric carbon resonances was noticed at δ 90.0 ppm along with all other resonances in complete agreement with that of the compound **52**. The presence of azido group was further confirmed by the IR analysis which showed the stretching frequency characteristic for azide at 2210 cm⁻¹.

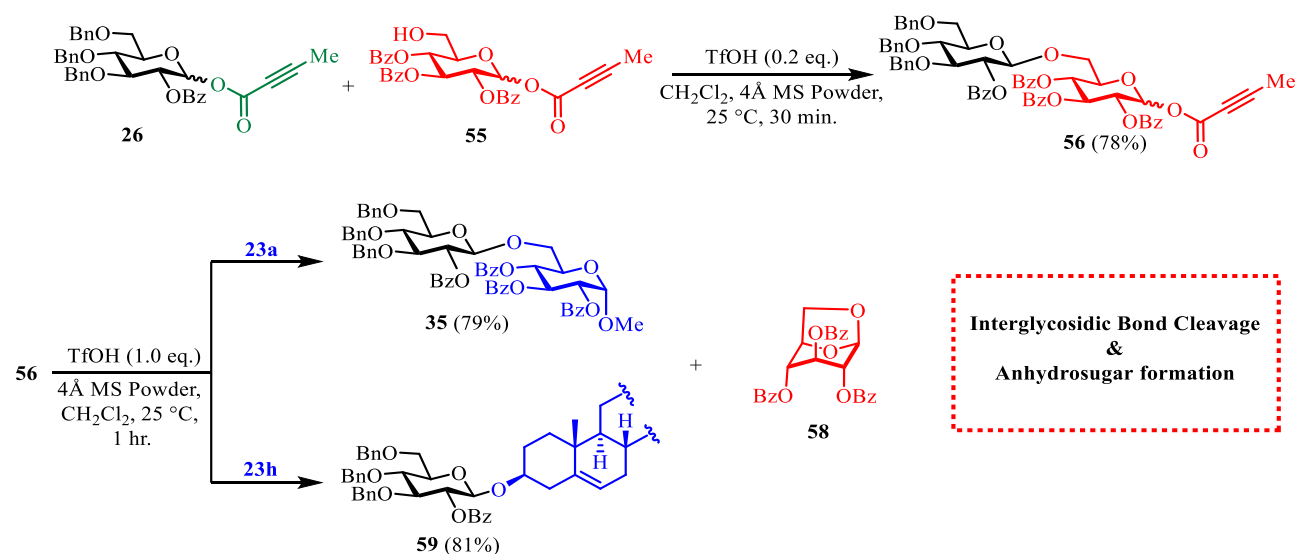
The investigation of differentially protected glycosyl donors revealed that the per-*O*-benzyl-protected sugar derivatives could be activated with 0.2 eq. of TfOH whereas the per-*O*-benzoyl-protected donors require higher amount of TfOH. Therefore, we considered the reactivity-based glycosidation exploiting the reactivity differences between armed/disarmed glycosyl donors. Consequently, compound **55** having benzoyl protection with unmasked C6-OH and leaving group methylpropiolate at the anomeric position was synthesized. The hemiacetal **53** was coupled with propiolic acid **20b** under DIC/DMAP condition to obtain donor **54** in 86% yields as an anomeric mixture. Further, the silyl ether was cleaved off using HF•py which gave desired compound **55** in 80% yields. In the ¹H NMR spectrum of compound **55** (α -isomer), the anomeric proton was noticed at δ 6.66 ppm as a doublet (J = 3.7 Hz) and singlets characteristics for C-6 free hydroxyl and terminal methyl at δ 2.69 (broad) and 2.37 ppm respectively. The presence of three benzoate carbonyls was noticed at δ 166.3, 165.9, and 165.5 ppm along with the resonances at δ 151.5 ppm for ester carbonyl of the methyl propionate in ¹³C NMR spectrum.



Scheme 8 Synthesis of disarmed glycosyl donor **55**

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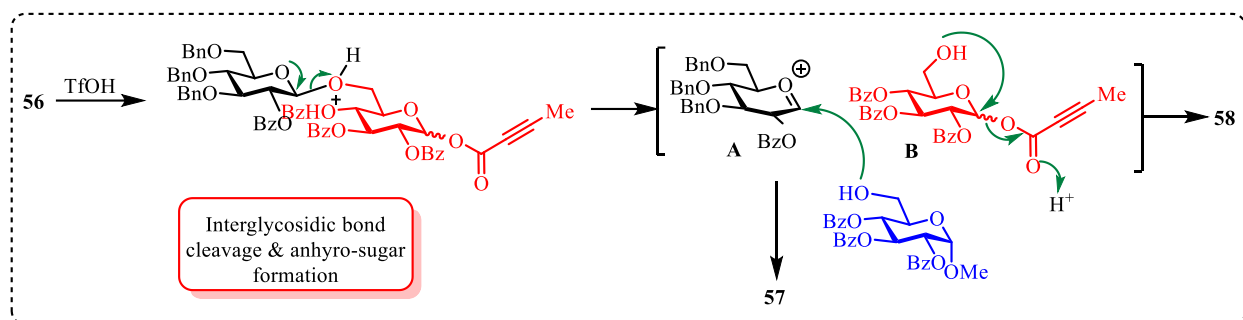
Next, in a competitive experiment, the glycosyl donor **26** and acceptor **55** were treated with 20mol% of TfOH to afford the disaccharide **56** in 78% yield without affecting the leaving group on the disarmed sugar. The disaccharide **56** was thoroughly characterized by NMR spectral analysis. In the ^{13}C NMR spectrum, the two anomeric carbons were noticed at δ 101.3 and 90.2 ppm respectively for β and α -linkages of the major isomer. The four benzoate ester carbonyls were identified at δ 165.8, 165.8, 165.3, and 165.1 ppm, and the anomeric leaving group ester carbonyl at δ 151.2 ppm along with terminal methyl at δ 4.1 ppm. The disaccharide donor **56** was subjected to the glycosylation with the acceptor **23a** using the 1.0 eq. TfOH. To our dismay, we could not obtain the trisaccharide. Only compounds that formed were characterized to be 1,6-anhydrosugar **58** and disaccharide **57**. The formation of these can be attributed to the strongly acidic reaction conditions. In another reaction, donor **56** was promoted in the presence of acceptor **23h** anticipating that the higher nucleophilicity of non-sugar alcohols might facilitate the glycosidation. However, similar results were observed producing the anhydrosugar **58** and glycoside **59**.



Scheme 9 Exploration of armed/disarmed glycosylation strategy

Mechanistically, strongly acidic conditions led to the formation of super-armed oxocarbenium intermediate **A** which is more favorable than the departure of leaving group from the disarmed sugar to form intermediate **B**. The oxocarbenium intermediate **A** further gets attacked by the

acceptor **23a** to produce disaccharide **57** whereas the intramolecular reaction of intermediate **B** leads to the formation of 1,6-anhydrosugar **58**.



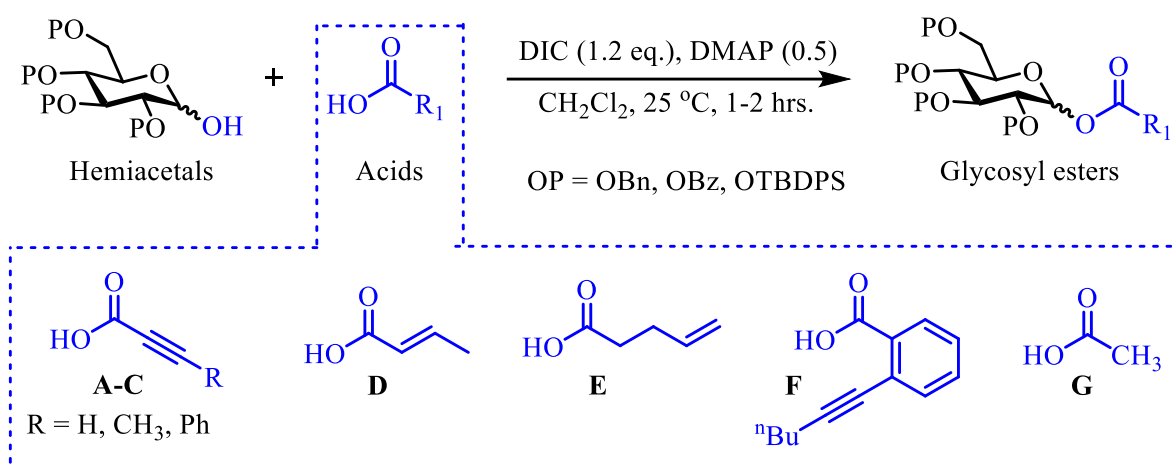
Scheme 10 Plausible mechanism of interglycosidic bond cleavage and anhydrosugar formation under acidic condition

3A.6 Conclusions

In summary, esters can be activated using simple Brønsted acids such as TfOH ; however, the strongly acidic conditions might cause hydrolysis of the interglycosidic bonds. Different armed/super-armed methylpropiolate glycosides including *Glcp*, *Manp*, *Galp*, *Xylp*, and *Araf* were successfully activated using 20mol% TfOH , whereas disarmed donors required up to 0.5 equivalent of TfOH . Several 1° and 2° sugar acceptors as well as non-sugar acceptors smoothly underwent the glycosidation to produce disaccharides and glycosides in good yields. The major protecting groups which are commonly employed in carbohydrates syntheses such as benzyl ethers, benzoyl esters, *n*-pentenyl, propargyl, and silyl ethers were tolerated under identified glycosidation condition. The armed/disarmed nature of glycosyl donors was exploited to produce the disaccharide in one-pot which on further glycosidation uneventfully resulted in the cleavage of inter-glycosidic bond and led to the formation of 1,6-anhydrosugar.

3A.7 Experimental Section

General procedure for glycosyl esters synthesis: To a solution of hemiacetals (1.0 eq) and acid **A-G** (1.1 eq) in anhydrous CH_2Cl_2 (2 mL/100 mg) was added *N, N'*-diisopropylcarbodiimide (1.2 eq), 4-dimethylaminopyridine (0.5 eq) at room temperature and stirred for 1-2 hours. After completion, the reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of celite®, the filtrate was then washed with ice-cold water, saturated brine solution, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using ethylacetate:hexane as eluent to obtain desired glycosyl esters.

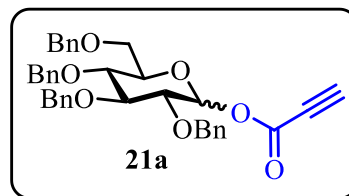


Scheme S1 Synthesis of glycosyl esters

General procedure for glycosylation: Glycosyl methylpropiolates (1.0 eq) and glycosyl acceptor (1.1 eq) were taken in 5 mL round bottom flask and kept under high vacuum for 5 minutes, then provided inert atmosphere with Nitrogen balloon. CH_2Cl_2 (2 mL/100 mg of glycosyl donor), 4 Å molecular sieves (appr. 100 mg), and then after 5 minutes, trifluoromethanesulfonic acid (0.2 eq) (note- appr. 1.0 eq. for disarmed donors) was added and stirred for 30-40 minutes. After completion (as adjudged by TLC), the reaction was quenched with excess of triethylamine, filtered through celite®, and concentrated under reduced pressure. The crude compound was then purified by silica gel column chromatography using ethylacetate:hexane as eluent to obtain desired compounds.

Propyno-yl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside

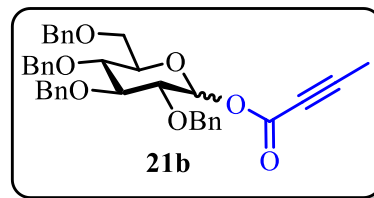
(21a): Yield 61%; ($\alpha:\beta = 1:1$); $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +42.2°; IR (cm⁻¹, CHCl₃): 2920, 2865, 2119, 1727, 1455, 1215, 1078, 742; ¹H NMR (400.31 MHz, CDCl₃) δ 7.36 – 7.28 (m, 36H), 7.18 –



7.13 (m, 4H), 6.39 (d, *J* = 3.5 Hz, 1H), 5.67 (d, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 10.9 Hz, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.87 – 4.75 (m, 6H), 4.74 – 4.68 (m, 2H), 4.66 – 4.60 (m, 2H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.53 (d, *J* = 3.7 Hz, 1H), 4.51 (s, 1H), 4.48 (d, *J* = 7.3 Hz, 1H), 3.99 (t, *J* = 9.4 Hz, 1H), 3.93 (dt, *J* = 10.3, 2.3 Hz, 1H), 3.80 – 3.72 (m, 6H), 3.72 – 3.66 (m, 2H), 3.66 – 3.62 (m, 1H), 3.60 (dt, *J* = 9.4, 2.7 Hz, 1H), 3.00 (s, 1H), 2.97 (s, 1H); ¹³C NMR (100.67 MHz, CDCl₃) δ 151.2, 151.1, 138.7, 138.4, 138.1, 138.0, 137.8, 137.6, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 95.4, 92.1, 84.7, 81.6, 80.7, 78.7, 77.2, 76.8, 76.7, 76.3, 75.9, 75.8, 75.4, 75.3, 75.2, 74.4, 74.3, 73.7, 73.6, 73.4, 68.1, 68.0; HRMS (ESI-MS): *m/z* calcd for C₃₇H₃₆O₇ [M+Na]⁺: 615.2359, Found: 615.2379.

But-2-yno-yl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside

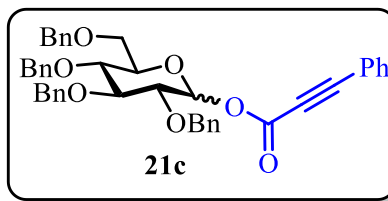
(21b): Yield 92%; ($\alpha:\beta = 2:1$); $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +55.6°; IR (cm⁻¹, CHCl₃): 2916, 2868, 2240, 1721, 1362, 1248, 1062, 742; ¹H NMR (400.31 MHz, CDCl₃) δ 7.41 – 7.33 (m, 36H), 7.24 –



7.19 (m, 4H), 6.43 (d, *J* = 3.5 Hz, 1H), 5.73 (d, *J* = 7.9 Hz, 1H), 5.04 (d, *J* = 10.9 Hz, 1H), 4.95 – 4.87 (m, 5H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.79 – 4.70 (m, 3H), 4.68 (d, *J* = 3.4 Hz, 1H), 4.64 (d, *J* = 9.6 Hz, 1H), 4.60 (d, *J* = 5.2 Hz, 1H), 4.58 – 4.55 (m, 2H), 4.53 (d, *J* = 8.7 Hz, 1H), 4.07 (t, *J* = 9.3 Hz, 1H), 4.00 (dt, *J* = 10.2, 2.6 Hz, 1H), 3.86 – 3.70 (m, 9H), 3.65 (d, *J* = 9.2 Hz, 1H), 2.04 (d, *J* = 5.9 Hz, 6H); ¹³C NMR (100.67 MHz, CDCl₃) δ 152.1, 151.9, 138.7, 138.4, 138.1, 138.0, 137.9, 137.8, 137.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 95.0, 91.3, 87.9, 87.4, 84.6, 81.7, 80.8, 78.7, 77.2, 76.8, 75.8, 75.7, 75.3, 75.1, 73.6, 73.5, 73.4, 73.1, 72.2, 72.1, 68.2, 68.0, 3.9, 3.9; HRMS (ESI-MS): *m/z* calcd for C₁₆H₂₂O₆ [M+Na]⁺: 629.2515, Found: 629.2517.

Phenylpropyno-yl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside (21c):

Yield 90%; ($\alpha:\beta = 2:1$); $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +49.2°; IR (cm⁻¹, CHCl₃): 3031, 2867, 2222, 1720, 1285, 1086, 752, 689; ¹H NMR (400.31 MHz, CDCl₃) δ

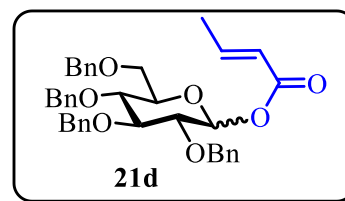


7.65 (m, 4H), 7.50 (m, 2H), 7.45 – 7.32 (m, 40H), 7.24 – 7.16 (m, 4H), 6.50 (d, *J* = 3.4 Hz, 1H), 5.80 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 10.9 Hz, 1H), 4.97 (d, *J* = 10.9 Hz, 1H), 4.93 – 4.88 (m,

4H), 4.87 – 4.83 (m, 1H), 4.77 (m, 3H), 4.70 (d, $J = 8.3$ Hz, 1H), 4.67 (d, $J = 8.4$ Hz, 1H), 4.63 – 4.55 (m, 3H), 4.53 (d, $J = 6.6$ Hz, 1H), 4.11 (t, $J = 9.3$ Hz, 1H), 4.05 (dt, $J = 10.0, 2.6$ Hz, 1H), 3.88 – 3.77 (m, 7H), 3.76 – 3.70 (m, 2H), 3.67 (d, $J = 9.3$ Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 152.5, 152.4, 138.7, 138.4, 138.0, 137.9, 137.8, 137.6, 133.2, 131.1, 130.9, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 119.5, 119.4, 95.2, 91.7, 88.5, 87.9, 84.7, 81.7, 80.8, 80.4, 80.3, 78.8, 77.2, 76.9, 75.9, 75.8, 75.4, 75.2, 75.1, 73.6, 73.5, 73.2, 68.2, 68.1; HRMS (ESI-MS): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 691.2672, Found: 691.2667.

But-2-eno-yl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside

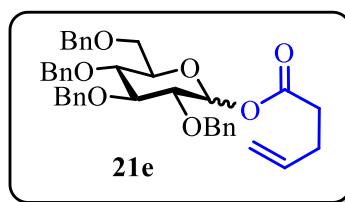
(21d): Yield 86%; ($\alpha:\beta = 1:3$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +30.4°; IR (cm^{-1} , CHCl_3): 2917, 2867, 1735, 1656, 1452, 1363, 1075, 833, 741; ^1H NMR (400.31 MHz, CDCl_3) δ 7.39 – 7.30 (m, 36H), 7.21



– 7.17 (m, 4H), 7.11 (m, 2H), 6.47 (d, $J = 3.5$ Hz, 1H), 5.91 (tq, $J = 15.5, 1.7$ Hz, 2H), 5.75 (d, $J = 8.0$ Hz, 1H), 5.02 (d, $J = 10.9$ Hz, 1H), 4.95 (d, $J = 11.0$ Hz, 1H), 4.92 – 4.85 (m, 4H), 4.84 – 4.78 (m, 3H), 4.76 (d, $J = 8.2$ Hz, 1H), 4.68 (t, $J = 5.8$ Hz, 1H), 4.64 (d, $J = 6.2$ Hz, 1H), 4.60 – 4.50 (m, 4H), 4.03 (t, $J = 9.3$ Hz, 1H), 3.93 (m, 1H), 3.83 (d, $J = 8.9$ Hz, 1H), 3.80 – 3.77 (m, 5H), 3.76 (q, $J = 1.7$ Hz, 1H), 3.71 – 3.67 (m, 2H), 3.66 – 3.62 (m, 1H), 1.94 (m, 6H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 164.7, 164.6, 146.9, 146.5, 138.8, 138.5, 138.1, 138.0, 137.9, 137.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 122.3, 122.1, 94.1, 89.9, 84.9, 81.9, 81.1, 79.0, 77.4, 77.1, 75.8, 75.6, 75.4, 75.1, 73.6, 73.1, 72.9, 68.2, 18.3, 18.2; HRMS (ESI-MS): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 631.2672, Found: 631.2667.

Pent-4-eno-yl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside

(21e): Yield 89%; ($\alpha:\beta = 1:1$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +18.4°; IR (cm^{-1} , CHCl_3): 2922, 2864, 1738, 1453, 1262, 1086, 914, 708; ^1H NMR (400.31 MHz, CDCl_3) δ 7.37 – 7.26 (m, 36H), 7.18 – 7.12



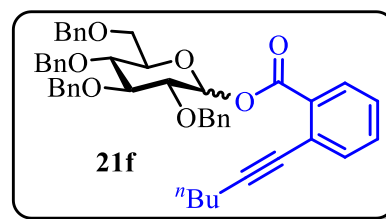
(m, 4H), 6.40 (d, $J = 3.5$ Hz, 1H), 5.82 – 5.70 (m, 2H), 5.63 (d, $J = 8.1$ Hz, 1H), 5.03 (d, $J = 1.8$ Hz, 1H), 5.01 – 4.96 (m, 3H), 4.93 (d, $J = 10.2$, 1H), 4.87 (d, $J = 8.2$ Hz, 1H), 4.82 (m, 3H), 4.77 (d, $J = 2.8$ Hz, 1H), 4.71 (d, $J = 11.4$ Hz, 1H), 4.65 (s, 1H), 4.63 – 4.59 (m, 2H), 4.56 – 4.47 (m, 4H), 3.93 (t, $J = 9.3$ Hz, 1H), 3.87 (ddd, $J = 10.1, 3.4, 2.0$ Hz, 1H), 3.79 – 3.68 (m, 7H), 3.65 (dd, $J = 10.8, 2.0$ Hz, 1H), 3.62 – 3.55 (m, 2H), 2.43 – 2.24 (m, 4H), 2.10 (m, 4H), 1.74 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.1, 138.8, 138.5, 138.2, 138.1, 138.0, 137.8, 137.7, 137.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 115.6, 94.1, 90.0, 85.0, 81.8, 81.2, 79.1, 77.4, 77.1,

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75.8, 75.6, 75.4, 75.1, 73.7, 73.6, 73.3, 73.0, 68.2, 33.7, 33.6, 33.0, 24.1, 23.7; HRMS (ESI-MS): m/z calcd for $C_{40}H_{44}O_7$ $[M+Na]^+$: 659.2985, Found: 659.2984.

2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl ortho-hexynylbenzoate (**21f**):

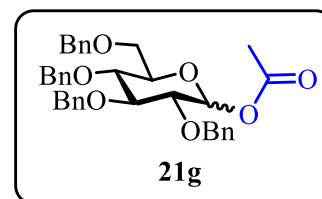
Yield 88%; ($\alpha:\beta = 1:1$); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +23.8°; IR (cm^{-1} , $CHCl_3$): 2932, 2860, 1733, 1459, 1246, 1071, 743; 1H NMR (400.31 MHz, $CDCl_3$) δ 8.04 (dd, $J = 7.9, 1.4$ Hz, 1H), 8.00 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.61 (d, $J = 1.3$ Hz,



1H), 7.59 (d, $J = 1.3$ Hz, 1H), 7.48 (tdd, $J = 7.7, 2.6, 1.4$ Hz, 2H), 7.42 – 7.28 (m, 36H), 7.27 – 7.26 (m, 1H), 7.25 – 7.19 (m, 5H), 6.76 (d, $J = 3.5$ Hz, 1H), 5.98 (d, $J = 7.5$ Hz, 1H), 5.04 (d, $J = 10.9$ Hz, 1H), 4.99 (d, $J = 11.0$ Hz, 1H), 4.94 (d, $J = 8.2$ Hz, 1H), 4.93 – 4.87 (m, 4H), 4.86 – 4.81 (m, 2H), 4.74 – 4.63 (m, 4H), 4.61 (d, $J = 10.6$ Hz, 1H), 4.58 – 4.50 (m, 2H), 4.18 – 4.12 (m, 2H), 3.93 – 3.79 (m, 8H), 3.76 – 3.71 (m, 2H), 2.53 (m, 4H), 1.70 – 1.53 (m, 5H), 1.52 – 1.43 (m, 3H), 1.00 (t, $J = 7.3$ Hz, 3H), 0.95 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 164.7, 164.6, 146.9, 146.5, 138.8, 138.5, 138.1, 138.0, 137.9, 137.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 122.3, 122.1, 94.1, 89.9, 84.9, 81.9, 81.1, 79.0, 77.4, 77.1, 75.8, 75.6, 75.4, 75.1, 73.6, 73.1, 72.9, 68.2, 18.3, 18.2; HRMS: m/z calcd for $C_{16}H_{22}O_6$ $[M+K]^+$: 763.3611, Found: 763.5602.

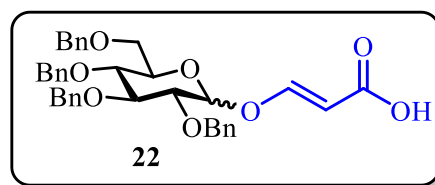
Acetyl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside (**21g**):

Yield 95%; ($\alpha:\beta = 1:1$); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +38.2°; IR (cm^{-1} , $CHCl_3$): 2919, 2872, 1753, 1367, 1225, 1079, 742; 1H NMR (399.78 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 36H), 7.18 – 7.13 (m, 4H), 6.38 (d, $J = 3.5$



Hz, 1H), 5.63 (d, $J = 8.2$ Hz, 1H), 4.98 (d, $J = 10.9$ Hz, 1H), 4.92 (d, $J = 10.9$ Hz, 1H), 4.88 – 4.82 (m, 4H), 4.82 – 4.75 (m, 2H), 4.72 (d, $J = 11.5$ Hz, 1H), 4.67 – 4.61 (m, 3H), 4.56 – 4.48 (m, 4H), 3.97 (t, $J = 9.3$ Hz, 1H), 3.89 (dt, $J = 9.9, 2.5$ Hz, 1H), 3.80 – 3.69 (m, 7H), 3.66 (dd, $J = 10.8, 1.9$ Hz, 1H), 3.64 – 3.57 (m, 2H), 2.15 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.6, 169.4, 138.7, 138.5, 138.2, 138.1, 138.0, 137.9, 137.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 94.2, 90.1, 84.9, 81.8, 81.2, 79.0, 77.3, 77.1, 75.8, 75.6, 75.4, 75.2, 75.1, 73.7, 73.6, 73.3, 72.9, 68.2, 21.2; HRMS (ESI-MS): m/z calcd for $C_{16}H_{22}O_6$ $[M+Na]^+$: 605.2515, Found: 605.2255.

Compound 22: Yield 21%; ($\alpha:\beta = 3:1$); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +42.2°; IR (cm^{-1} , $CHCl_3$): 2919-2600(broad), 2550,

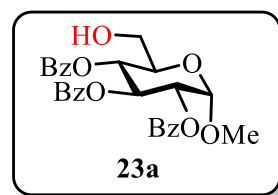


Chapter 3A

1753, 1367, 1225, 1079, 742; ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, $J = 12.5$ Hz, 1H), 7.36 – 7.10 (m, 18H), 7.16 – 7.10 (m, 2H), 5.50 (d, $J = 12.4$ Hz, 1H), 5.10 (d, $J = 3.5$ Hz, 1H), 4.97 (d, $J = 10.9$ Hz, 1H), 4.90 – 4.75 (m, 4H), 4.65 – 4.55 (m, 2H), 4.51 – 4.41 (m, 2H), 4.00 (t, $J = 9.1$ Hz, 1H), 3.76 – 3.58 (m, 5H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.6, 161.2, 138.6, 138.1, 137.8, 137.7, 128.8, 128.6, 128.6, 128.4, 128.3, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.7, 127.7, 127.7, 100.4, 98.9, 81.7, 79.1, 76.0, 75.3, 74.0, 73.7, 71.9, 67.8; HRMS (ESI-MS): m/z calcd for $\text{C}_{37}\text{H}_{38}\text{O}_8$ $[\text{M}+\text{H}]^+$: 610.2567, Found: 610.2250.

Methyl 2,3,4-tri-*O*-benzoyl- α -D-glucopyranoside (23a): $[\alpha]^{25}_{\text{D}}$

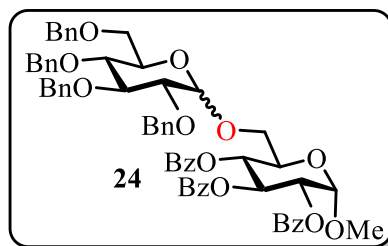
(CHCl_3 , c 1.0): -55.8° ; IR (cm^{-1} , CHCl_3): 3068, 2940, 1723, 1598, 1451, 1259, 1099, 1033; ^1H NMR (399.78 MHz, CDCl_3) δ 8.03 – 7.93 (m, 4H), 7.89 – 7.81 (m, 2H), 7.57 – 7.45 (m, 3H), 7.41 – 7.35 (m,



4H), 7.26 (m, 2H), 6.23 (t, $J = 9.4$ Hz, 1H), 5.51 (t, $J = 9.7$ Hz, 1H), 5.32 – 5.20 (m, 2H), 4.13 – 3.89 (m, 1H), 3.88 – 3.63 (m, 2H), 3.54 – 3.31 (m, 4H), 2.77 (s, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 166.5, 165.9, 133.8, 133.5, 133.2, 130.1, 130.0, 129.7, 129.3, 129.1, 128.7, 128.6, 128.5, 128.4, 97.2, 72.2, 70.2, 69.9, 69.6, 61.2, 55.7; HRMS (ESI-MS): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{O}_6$ $[\text{M}+\text{K}]^+$: 545.1214, Found: 545.1202.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl)- α -D-glucopyranoside (24): Yield

89%; ($\alpha:\beta = 2:1$); mp 52-54°C; $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): $+93.8^\circ$; IR (cm^{-1} , CHCl_3): 2924, 2866, 1729, 1453, 1267, 1093, 705; ^1H NMR (400.31 MHz, CDCl_3) δ 8.05 – 7.95 (m, 4H), 7.93 –



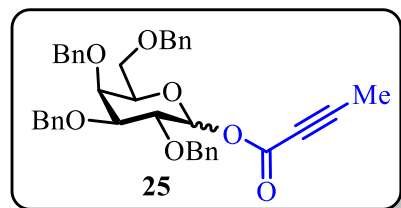
7.87 (m, 2H), 7.57 – 7.50 (m, 2H), 7.48 – 7.29 (m, 24H), 7.27 – 7.23 (m, 1H), 7.20 – 7.15 (m, 2H), 6.20 (dt, $J = 13.4, 9.6$ Hz, 1H), 5.55 (dt, $J = 10.2, 6.5$ Hz, 1H), 5.35 – 5.23 (m, 2H), 4.96 (d, $J = 10.9$ Hz, 1H), 4.89 – 4.77 (m, 4H), 4.70 (dd, $J = 11.5, 7.3$ Hz, 1H), 4.62 – 4.46 (m, 3H), 4.42 (d, $J = 12.1$ Hz, 1H), 4.36 (m, 1H), 4.01 (t, $J = 9.3$ Hz, 1H), 3.94 – 3.83 (m, 2H), 3.72 – 3.63 (m, 3H), 3.62 – 3.50 (m, 2H), 3.45 (m, 3H); ^{13}C NMR (100.66 MHz, CDCl_3) δ 166.0, 165.9, 165.6, 165.4, 139.0, 138.7, 138.6, 138.5, 138.2, 138.0, 133.5, 133.2, 130.0, 129.8, 129.4, 129.2, 129.1, 129.0, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 104.1, 97.4, 96.9, 96.9, 84.7, 82.5, 81.9, 80.1, 77.8, 77.7, 75.8, 75.6, 75.1, 75.0, 74.9, 74.9, 73.6, 73.5, 73.2, 72.4, 72.3, 70.7, 70.6, 70.4, 70.0, 69.8, 69.1, 69.0, 68.8, 68.7, 68.4, 66.8, 55.7, 55.6; HRMS (ESI-MS): m/z calcd for $\text{C}_{62}\text{H}_{60}\text{O}_{14}$ $[\text{M}+\text{H}]^+$: 1029.4061, Found: 1029.4075.

But-2-yno-yl

2,3,4,6-tetra-*O*-benzyl- α/β -D-

galactopyranoside (25):

Yield 86%; ($\alpha:\beta = 1:1.5$) ; $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +138.0°; IR (cm⁻¹, CHCl₃): 2924, 2868, 2240, 1727, 1453, 1254, 1100, 708; ¹H NMR (400.31 MHz, CDCl₃) δ



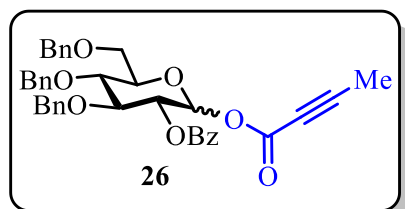
7.41 – 7.27 (m, 34H), 6.40 (d, *J* = 3.6 Hz, 1H), 5.63 (d, *J* = 8.0 Hz, 1H), 4.99 – 4.89 (m, 2H), 4.88 – 4.81 (m, 3H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.73 (s, 2H), 4.75 – 4.73 (m, 2H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.48 (dd, *J* = 11.7, 6.7 Hz, 2H), 4.41 (d, *J* = 11.7 Hz, 2H), 4.19 (dd, *J* = 10.1, 3.7 Hz, 1H), 4.11 (m, 1H), 4.07 (dd, *J* = 2.9, 1.3 Hz, 1H), 4.04 – 3.93 (m, 3H), 3.75 – 3.70 (m, 1H), 3.67 – 3.51 (m, 5H), 2.00 (m, 5H); ¹³C NMR (100.67 MHz, CDCl₃) δ 152.42, 152.15, 138.75, 138.62, 138.56, 138.30, 138.27, 138.05, 137.90, 137.85, 128.55, 128.50, 128.45, 128.39, 128.35, 128.27, 128.20, 128.18, 128.09, 128.03, 127.95, 127.93, 127.88, 127.82, 127.80, 127.77, 127.70, 127.68, 127.65, 127.48, 95.33, 92.29, 87.77, 87.19, 82.29, 78.82, 78.05, 75.52, 75.33, 75.07, 74.80, 74.65, 74.40, 73.65, 73.63, 73.29, 73.26, 73.03, 72.42, 72.19, 72.14, 68.39, 68.08, 4.08, 4.02; HRMS (ESI-MS): *m/z* calcd for C₃₈H₃₈O₇ [M+Na]⁺: 629.2515, Found: 629.2511.

But-2-yno-yl

2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- α/β -D-

glucopyranoside (26):

Yield 89%; ($\alpha:\beta = 3:1$); $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +138.0°; IR (cm⁻¹, CHCl₃): 2924, 2868, 2240, 1727, 1453, 1254, 1100, 708; ¹H NMR (400.31 MHz, CDCl₃) δ 8.05



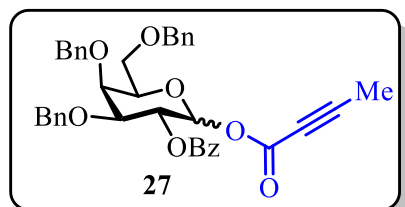
– 7.99 (m, 4H), 7.65 – 7.58 (m, 2H), 7.49 – 7.41 (m, 4H), 7.39 – 7.29 (m, 16H), 7.23 – 7.13 (m, 14H), 6.32 – 6.26 (m, 2H), 5.42 – 5.36 (m, 2H), 4.92 – 4.74 (m, 6H), 4.67 (d, *J* = 12.3 Hz, 2H), 4.62 – 4.52 (m, 4H), 4.24 (t, *J* = 9.5 Hz, 2H), 4.07 – 3.87 (m, 4H), 3.88 – 3.80 (m, 2H), 3.76 – 3.68 (m, 2H), 1.99 – 1.89 (m, 6H); ¹³C NMR (100.67 MHz, CDCl₃) δ 165.5, 165.1, 152.0, 151.7, 138.1, 138.0, 137.9, 137.6, 133.5, 133.4, 130.0, 129.9, 129.5, 129.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 92.9, 91.4, 88.5, 87.8, 82.6, 80.0, 77.4, 77.1, 76.2, 75.7, 75.4, 75.3, 75.2, 73.7, 73.5, 72.4, 72.3, 71.9, 71.8, 68.2, 68.0, 4.0; HRMS (ESI-MS): *m/z* calcd for C₃₈H₃₆O₈ [M+Na]⁺: 643.2308, Found: 643.2307.

But-2-yno-yl

2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- α/β -D-

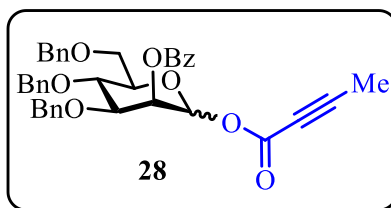
galactopyranoside (27):

Yield 90%; ($\alpha:\beta = 1:1$); mp 110–110.8 °C; $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +135.8°; IR (cm⁻¹, CHCl₃): 2925, 2241, 1720, 1454, 1249, 1079, 704; ¹H NMR (400.31



MHz, CDCl₃) δ 8.02 (d, J = 7.7 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.45 – 7.24 (m, 15H), 6.61 (d, J = 3.7 Hz, 1H), 5.71 (dd, J = 10.3, 3.7 Hz, 1H), 5.00 (d, J = 11.3 Hz, 1H), 4.82 – 4.78 (m, 2H), 4.63 (d, J = 11.4 Hz, 1H), 4.51 – 4.38 (m, 2H), 4.22 – 4.09 (m, 3H), 3.69 (t, J = 8.5 Hz, 1H), 3.57 (dd, J = 9.1, 5.2 Hz, 1H), 1.95 (s, 3H); ¹³C NMR (100.67 MHz, CDCl₃) δ 164.7, 152.9, 138.3, 137.9, 137.7, 133.6, 130.0, 129.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 90.8, 87.0, 76.2, 75.0, 74.0, 73.7, 72.7, 72.2, 72.1, 70.9, 68.1, 4.0; HRMS (ESI-MS): m/z calcd for C₃₈H₃₆O₈ [M+Na]⁺: 643.2308, Found: 643.2300.

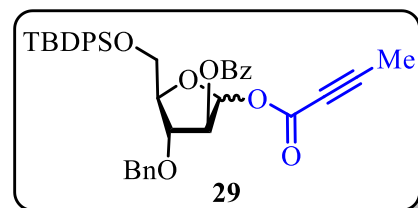
But-2-yno-yl 2-O-benzoyl-3,4,6-tri-O-benzyl- α/β -D-mannopyranoside (28): Yield 79%; ($\alpha:\beta$ = 1:1); [α]_D²⁵ (CHCl₃, c 1.0): +133.5°; IR (cm⁻¹, CHCl₃): 2925, 2241, 1720,



1454, 1249, 1079, 704; ¹H NMR (400.31 MHz, CDCl₃) δ 8.12 – 8.07 (m, 2H), 7.61 – 7.55 (m, 1H), 7.43 – 7.27 (m, 15H), 7.24 (dd, J = 7.5, 2.1 Hz, 2H), 6.33 (d, J = 2.1 Hz, 1H), 5.69 (t, J = 2.5 Hz, 1H), 4.91 (d, J = 10.5 Hz, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.77 (d, J = 11.9 Hz, 1H), 4.62 (t, J = 10.5 Hz, 2H), 4.57 (d, J = 11.9 Hz, 1H), 4.27 – 4.16 (m, 2H), 4.01 (ddd, J = 9.3, 3.5, 1.5 Hz, 1H), 3.96 (dd, J = 11.1, 3.5 Hz, 1H), 3.80 (dd, J = 11.1, 1.8 Hz, 1H), 2.03 (s, 3H); ¹³C NMR (100.67 MHz, CDCl₃) δ 165.43, 151.13, 138.44, 138.23, 137.83, 133.43, 130.11, 129.53, 128.55, 128.46, 128.45, 128.14, 128.12, 127.86, 127.82, 127.62, 92.41, 88.05, 77.92, 75.56, 74.24, 73.67, 73.61, 71.93, 71.86, 68.64, 67.66, 3.96; HRMS (ESI-MS): m/z calcd for C₃₈H₃₆O₈ [M+Na]⁺: 643.2308, Found: 643.2300.

But-2-yno-yl 2-O-benzoyl-3-O-benzyl-5-O-

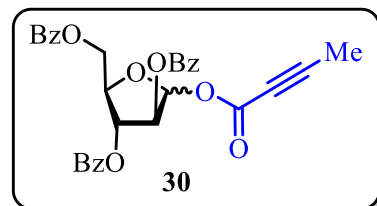
^tbutyldiphenylsilyl- α/β -D-arabinofuranoside (29): Yield 76%; ($\alpha:\beta$ = 3:1); [α]_D²⁵ (CHCl₃, c 1.0): +35.0°; IR (cm⁻¹, CHCl₃): 2936, 2866, 2240, 1721, 1456, 1245, 1104, 940,



700; ¹H NMR (400.31 MHz, CDCl₃) δ 8.08 – 7.96 (m, 2H), 7.75 – 7.70 (m, 1H), 7.66 – 7.58 (m, 4H), 7.51 – 7.27 (m, 13H), 6.41 (s, 1H), 5.57 (d, J = 1.6 Hz, 1H), 4.85 (d, J = 12.0 Hz, 1H), 4.67 (d, J = 12.1 Hz, 1H), 4.45 (q, J = 4.5 Hz, 1H), 4.32 (dt, J = 5.1, 1.2 Hz, 1H), 3.85 (d, J = 4.5 Hz, 2H), 1.93 (s, 3H), 1.06 (s, 9H); ¹³C NMR (100.67 MHz, CDCl₃) δ 165.5, 165.3, 152.3, 152.2, 137.6, 135.8, 135.7, 133.7, 133.6, 133.2, 133.1, 130.0, 129.9, 129.8, 129.2, 129.1, 128.6, 128.5, 128.0, 127.9, 127.8, 127.7, 101.1, 95.1, 87.4, 87.1, 85.9, 82.9, 82.5, 81.6, 79.7, 77.9, 72.6, 72.5, 72.3, 72.2, 64.3, 62.7, 27.0, 26.9, 19.4, 19.4, 4.1, 3.9; HRMS (ESI-MS): m/z calcd for C₃₉H₄₀O₇Si [M+Na]⁺: 671.2441, Found: 671.2440.

But-2-yno-yl 2,3,5-tri-O-benzoyl- α/β -D-arabinofuranoside

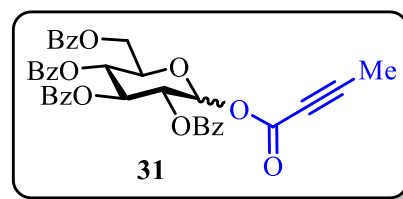
(30): Yield 86%; ($\alpha:\beta = 4:1$); $[\alpha]^{25}_D$ (CHCl₃, c 1.0): -8.2°; IR (cm⁻¹, CHCl₃): 2240, 1722, 1451, 1254, 1105, 937, 708; ¹H NMR (400.31 MHz, CDCl₃) δ 8.20 – 8.11 (m, 2H), 8.10 – 8.02 (m,



4H), 7.67 – 7.58 (m, 2H), 7.53 – 7.42 (m, 5H), 7.34 – 7.29 (m, 2H), 6.54 (s, 1H), 5.71 (d, $J = 1.4$ Hz, 1H), 5.69 – 5.62 (m, 1H), 4.85 – 4.76 (m, 2H), 4.76 – 4.68 (m, 1H), 1.97 (s, 3H); ¹³C NMR (100.67 MHz, CDCl₃) δ 166.2, 165.9, 165.7, 165.5, 165.2, 151.9, 151.8, 133.9, 133.8, 133.3, 133.1, 130.2, 130.1, 130.0, 129.9, 129.8, 129.6, 129.0, 128.8, 128.7, 128.6, 128.4, 128.0, 127.3, 100.4, 94.8, 87.9, 83.6, 81.2, 80.3, 77.3, 76.1, 75.2, 72.0, 71.9, 65.0, 63.6, 4.0, 4.0; HRMS (ESI-MS): m/z calcd for C₃₀H₂₄O₉ [M+Na]⁺: 551.1318, Found: 551.1317.

But-2-yno-yl 2,3,4,6-tetra-O-benzoyl- α/β -D-glucopyranoside (31):

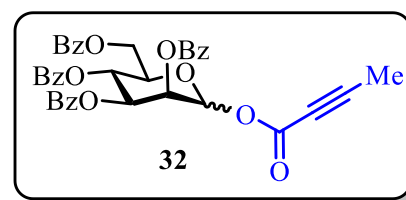
Yield 83%; ($\alpha:\beta = 6:1$); mp 79.3 – 81.6°C; $[\alpha]^{25}_D$ (CHCl₃, c 1.0): +142.2°; IR (cm⁻¹, CHCl₃): 2943, 2240, 1730, 1259, 1164, 1101, 710; ¹H NMR (400.31



MHz, CDCl₃) δ 8.10 – 8.03 (m, 2H), 7.98 – 7.92 (m, 4H), 7.91 – 7.86 (m, 2H), 7.56 – 7.52 (m, 1H), 7.53 – 7.48 (m, 2H), 7.46 – 7.34 (m, 7H), 7.29 (t, $J = 7.7$ Hz, 2H), 6.69 (d, $J = 3.7$ Hz, 1H), 6.25 (t, $J = 10.0$ Hz, 1H), 5.82 (t, $J = 9.9$ Hz, 1H), 5.59 (dd, $J = 10.3, 3.7$ Hz, 1H), 4.65 (dd, $J = 12.1, 2.8$ Hz, 1H), 4.60 (dt, $J = 10.2, 3.4$ Hz, 1H), 4.49 (dd, $J = 12.1, 4.2$ Hz, 1H), 1.99 (s, 3H); ¹³C NMR (100.67 MHz, CDCl₃) δ 166.2, 165.9, 165.7, 165.5, 165.1, 165.0, 151.5, 151.3, 133.7, 133.6, 133.4, 133.3, 133.2, 130.0, 129.9, 129.8, 129.6, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 92.7, 90.4, 89.3, 88.9, 77.4, 73.4, 72.9, 71.7, 71.5, 70.6, 70.2, 68.9, 68.8, 62.7, 62.4, 4.1, 4.0; HRMS (ESI-MS): m/z calcd for C₃₈H₃₀O₁₁ [M+Na]⁺: 685.1686, Found: 685.1688.

But-2-yno-yl 2,3,4,6-tetra-O-benzoyl- α/β -D-mannopyranoside (32):

Yield 88%; ($\alpha:\beta = 6:1$); mp 83–85.5°C; $[\alpha]^{25}_D$ (CHCl₃, c 1.0): -29.4°; IR (cm⁻¹, CHCl₃): 2941, 2240, 1728, 1252, 1102, 958, 708; ¹H NMR (400.31 MHz,



CDCl₃) δ 8.01 (d, $J = 7.7$ Hz, 2H), 7.97 (d, $J = 7.7$ Hz, 2H), 7.87 (d, $J = 7.7$ Hz, 2H), 7.76 (d, $J = 7.7$ Hz, 2H), 7.51 (dt, $J = 13.1, 7.4$ Hz, 2H), 7.43 (t, $J = 7.4$ Hz, 1H), 7.39 – 7.26 (m, 7H), 7.19 (t, $J = 7.6$ Hz, 2H), 6.34 (s, 1H), 6.13 (t, $J = 10.1$ Hz, 1H), 5.89 (dd, $J = 10.3, 3.4$ Hz, 1H), 5.69 (s, 1H), 4.62 (d, $J = 11.5$ Hz, 1H), 4.46 – 4.41 (m, 2H), 2.01 (s, 3H); ¹³C NMR (100.67 MHz, CDCl₃) δ 166.1, 165.6, 165.4, 165.2, 150.8, 133.8, 133.7, 133.5, 133.2, 130.0, 129.9, 129.0,

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128.9, 128.8, 128.6, 128.5, 91.7, 89.1, 71.7, 71.3, 69.7, 69.2, 66.2, 62.4, 4.2; HRMS (ESI-MS): m/z calcd for $C_{38}H_{30}O_{11}$ $[M+Na]^+$: 685.1686, Found: 685.1675.

But-2-yno-yl 2,3,4-tri-*O*-benzoyl- α/β -D-xylopyranoside

(33): Yield 81%; ($\alpha:\beta = 4:1$); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +125.6°;

IR (cm^{-1} , $CHCl_3$): 2920, 2858, 2141, 1727, 1251, 1100, 1022,

709; 1H NMR (400.31 MHz, $CDCl_3$) δ 8.04 – 7.92 (m, 6H),

7.57 – 7.49 (m, 2H), 7.46 – 7.30 (m, 7H), 6.60 (d, $J = 3.6$ Hz, 1H), 6.21 (t, $J = 9.9$ Hz, 1H), 5.57

– 5.46 (m, 2H), 4.27 (dd, $J = 11.2$, 5.8 Hz, 1H), 4.01 (t, $J = 10.9$ Hz, 1H), 2.02 (s, 3H); ^{13}C NMR

(100.66MHz, $CDCl_3$) δ 165.8, 165.6, 165.5, 165.0, 164.8, 151.5, 151.4, 133.6, 133.5, 133.4,

130.2, 130.1, 130.0, 129.9, 129.8, 129.2, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 92.0, 90.6,

88.6, 88.1, 77.4, 71.8, 71.7, 70.1, 69.8, 69.5, 67.8, 67.8, 67.5, 61.4, 61.2, 4.1, 4.0; HRMS (ESI-

MS): m/z calcd for $C_{30}H_{24}O_9$ $[M+K]^+$: 567.1057, Found: 567.1049.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-galactopyranosyl)- α -D-glucopyranoside (34):

Yield 83%; ($\alpha:\beta = 2:1$); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +125.6°; IR (cm^{-1} , $CHCl_3$):

2920, 2858, 2141, 1727, 1251, 1100, 1022, 709; 1H NMR (400

MHz, $CDCl_3$) δ 8.04 – 7.86 (m, 6H), 7.55 – 7.26 (m, 29H), 6.18

(dt, $J = 11.6$, 9.8 Hz, 1H), 5.58 (t, $J = 9.9$ Hz, 1H), 5.32 – 5.18

(m, 2H), 5.07 – 4.93 (m, 1H), 4.88 – 4.82 (m, 2H), 4.80 – 4.69 (m, 2H), 4.61 (dd, $J = 13.1$, 11.5

Hz, 1H), 4.50 – 4.29 (m, 3H), 4.15 – 4.06 (m, 1H), 4.05 – 3.96 (m, 2H), 3.92 – 3.75 (m, 2H),

3.62 (dd, $J = 11.2$, 2.1 Hz, 1H), 3.57 – 3.44 (m, 3H), 3.38 (s, 3H); ^{13}C NMR (100.67 MHz,

$CDCl_3$) δ 165.95, 165.91, 165.88, 165.85, 165.63, 165.43, 138.96, 138.85, 138.81, 138.69,

138.62, 138.21, 137.95, 133.47, 133.44, 133.42, 133.14, 130.03, 129.97, 129.94, 129.77, 129.75,

129.40, 129.36, 129.25, 129.19, 129.14, 128.97, 128.50, 128.45, 128.42, 128.40, 128.36, 128.33,

128.29, 128.25, 128.00, 127.96, 127.85, 127.77, 127.70, 127.66, 127.63, 127.53, 104.33, 97.95,

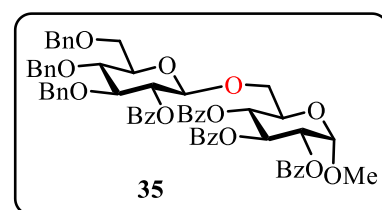
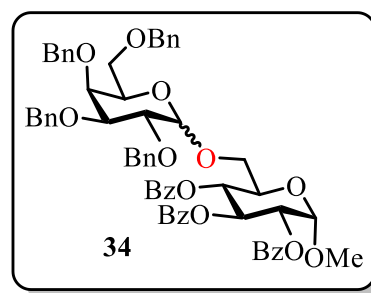
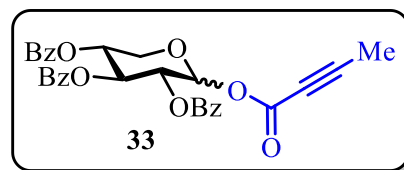
96.86, 96.76, 82.10, 79.74, 78.63, 77.36, 76.52, 75.26, 75.17, 74.86, 74.61, 73.60, 73.52, 73.48,

73.33, 73.27, 73.19, 73.00, 72.28, 70.80, 70.64, 70.08, 69.66, 69.37, 69.08, 69.04, 68.80, 68.73,

68.56, 66.68, 55.53, 55.51; HRMS (ESI-MS): m/z calcd for $C_{62}H_{60}O_{14}$ $[M+Na]^+$: 1051.3881,

Found: 1051.3879.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-glucopyranosyl)- α -D-glucopyranoside (35):

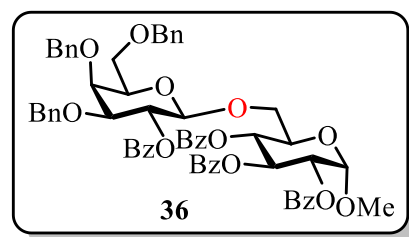


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Yield 83%; mp 82-83 °C; $[\alpha]^{25}_D$ (CHCl₃, c 1.0): +74.2°; IR (cm⁻¹, CHCl₃): 3387, 2910, 2840, 1728, 1453, 1267, 1093, 709; ¹H NMR (400.31 MHz, CDCl₃) δ 8.23 – 8.13 (m, 2H), 8.10 – 8.01 (m, 4H), 7.98 – 7.91 (m, 2H), 7.71 – 7.65 (m, 1H), 7.64 – 7.34 (m, 23H), 7.33 – 7.28 (m, 3H), 6.19 (t, *J* = 9.8 Hz, 1H), 5.48 – 5.35 (m, 2H), 5.20 (dd, *J* = 10.3, 3.5 Hz, 1H), 4.99 – 4.91 (m, 2H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.81 (d, *J* = 11.1 Hz, 1H), 4.75 (d, *J* = 7.9 Hz, 1H), 4.72 – 4.66 (m, 2H), 4.61 (d, *J* = 12.3 Hz, 1H), 4.32 (ddd, *J* = 10.0, 8.0, 1.8 Hz, 1H), 4.21 (dd, *J* = 11.2, 1.9 Hz, 1H), 3.98 (t, *J* = 9.0 Hz, 1H), 3.91 (t, *J* = 9.2 Hz, 1H), 3.86 – 3.76 (m, 3H), 3.67 (dt, *J* = 9.4, 3.0 Hz, 1H), 3.17 (s, 3H); ¹³C NMR (100.67 MHz, CDCl₃) δ 165.8, 165.6, 165.3, 138.1, 137.9, 133.5, 133.4, 133.2, 133.1, 130.2, 130.0, 129.9, 129.7, 129.3, 129.2, 128.9, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 101.9, 96.4, 82.8, 78.0, 75.4, 75.2, 75.1, 73.9, 73.6, 72.1, 70.6, 69.8, 69.0, 68.8, 68.5, 55.0; HRMS (ESI-MS): *m/z* calcd for C₁₆H₂₂O₆ [M+H]⁺: 1043.3854, Found: 1043.3854.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl)-α-*D*-glucopyranoside (36):

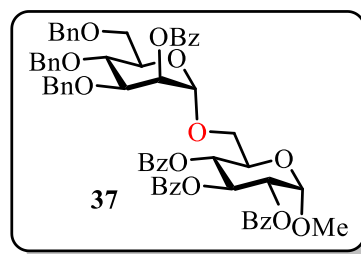
Yield 88%; $[\alpha]^{25}_D$ (CHCl₃, c 1.0): +48.5; IR (cm⁻¹, CHCl₃) 2923, 2865, 1728, 1598, 1452, 1335, 1266, 1157, 1090, 917, 706; ¹H NMR (400 MHz, CDCl₃) δ 8.09 – 7.82 (m, 8H), 7.62 –



7.20 (m, 27H), 6.08 (t, *J* = 9.7 Hz, 1H), 5.34 (t, *J* = 9.5 Hz, 2H), 5.10 (d, *J* = 10.0 Hz, 1H), 4.88 (s, 1H), 4.84 (d, *J* = 11.5 Hz, 1H), 4.80 – 4.48 (m, 6H), 4.22 (t, *J* = 9.3 Hz, 1H), 4.10 (d, *J* = 11.3 Hz, 1H), 3.94 – 3.81 (m, 2H), 3.79 – 3.72 (m, 2H), 3.71 – 3.63 (m, 1H), 3.56 (d, *J* = 9.4 Hz, 1H), 3.07 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 165.8, 165.8, 165.6, 165.4, 138.1, 138.1, 137.9, 133.5, 133.4, 133.2, 133.1, 130.2, 130.0 (2C), 130.0, 129.9, 129.9, 129.8, 129.7, 129.3, 129.2, 128.9, 128.7 (2C), 128.5, 128.5 (2C), 128.5, 128.5, 128.4 (2C), 128.4, 128.3, 128.3, 128.1 (2C), 128.1 (2C), 127.9, 127.9, 127.9 (2C), 127.8, 127.8, 127.7, 127.7, 101.9, 96.4, 82.8, 78.0, 75.4, 75.2, 75.2, 73.9, 73.6, 72.1, 70.6, 69.8, 69.0, 68.8, 68.5, 55.0; HRMS (ESI-MS) *m/z* calcd for C₆₂H₅₈O₁₅ [M + Na]⁺: 1065.3673, Found: 1065.3662.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-α-*D*-glucopyranoside (37):

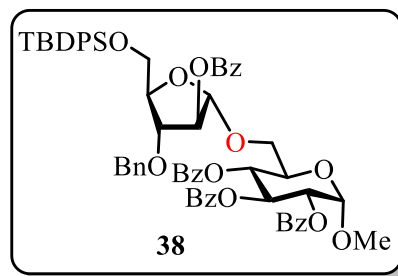
Yield 81%; mp 82-83 °C; $[\alpha]^{25}_D$ (CHCl₃, c 1.0): +74.1°; IR (cm⁻¹, CHCl₃): 3387, 2910, 2840, 1728, 1453, 1267, 1093, 709; ¹H NMR (400.31 MHz, CDCl₃) δ 8.12 – 8.07 (m, 2H), 8.11 – 8.06



(m, 4H), 7.95 – 7.90 (m, 2H), 7.59 – 7.43 (m, 4H), 7.43 – 7.37 (m, 4H), 7.37 – 7.27 (m, 17H), 7.24 (dd, $J = 7.6, 1.9$ Hz, 2H), 6.20 (t, $J = 9.9$ Hz, 1H), 5.68 – 5.60 (m, 2H), 5.34 (dd, $J = 10.2, 3.6$ Hz, 1H), 5.26 (d, $J = 3.7$ Hz, 1H), 5.04 (d, $J = 1.9$ Hz, 1H), 4.92 (d, $J = 10.9$ Hz, 1H), 4.72 (d, $J = 11.4$ Hz, 1H), 4.68 (d, $J = 11.9$ Hz, 1H), 4.56 (d, $J = 10.9$ Hz, 1H), 4.52 (d, $J = 11.4$ Hz, 1H), 4.47 (d, $J = 12.0$ Hz, 1H), 4.28 (ddd, $J = 10.2, 5.3, 3.0$ Hz, 1H), 4.15 – 4.07 (m, 2H), 3.98 (dd, $J = 11.0, 5.4$ Hz, 1H), 3.88 – 3.78 (m, 2H), 3.72 (dd, $J = 11.0, 3.0$ Hz, 1H), 3.65 (dd, $J = 10.7, 1.8$ Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 165.93, 165.91, 165.66, 165.29, 138.67, 138.52, 138.14, 133.44, 133.17, 130.05, 130.03, 129.98, 129.77, 129.33, 129.17, 129.05, 128.53, 128.50, 128.45, 128.39, 128.37, 128.34, 128.18, 128.02, 127.65, 127.62, 127.54, 127.52, 98.06, 96.99, 77.98, 75.22, 74.28, 73.40, 72.20, 71.80, 71.58, 70.62, 69.75, 69.03, 68.92, 68.21, 66.47, 55.61; HRMS (ESI-MS): m/z calcd for $\text{C}_{62}\text{H}_{58}\text{O}_{15} [\text{M}+\text{Na}]^+$: 1065.3673, Found: 1065.3671.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2-*O*-benzoyl-3-*O*-benzyl-5-*O*-*t*-butyldiphenylsilyl)- α -D-arabinofuranosyl)- α -D-

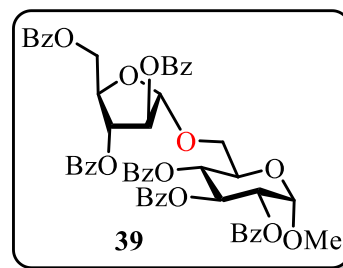
glucopyranoside (38): Yield 95%; $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , c 1.0): +82.6°; IR (cm^{-1} , CHCl_3): 2927, 2849, 1728, 1486, 1267, 1103, 1028; ^1H NMR (399.78 MHz, CDCl_3) δ 8.00 – 7.85 (m, 8H), 7.68 – 7.61 (m, 4H), 7.58 – 7.53 (m, 1H), 7.52 – 7.42 (m, 2H),



7.41 – 7.33 (m, 7H), 7.32 – 7.25 (m, 11H), 7.25 – 7.20 (m, 2H), 6.14 (t, $J = 9.9$ Hz, 1H), 5.58 (t, $J = 9.9$ Hz, 1H), 5.32 (d, $J = 1.6$ Hz, 1H), 5.27 (dd, $J = 10.2, 3.6$ Hz, 1H), 5.22 – 5.16 (m, 2H), 4.73 (d, $J = 11.8$ Hz, 1H), 4.53 (d, $J = 11.8$ Hz, 1H), 4.31 – 4.24 (m, 2H), 4.17 (dd, $J = 5.6, 1.5$ Hz, 1H), 3.97 (dd, $J = 11.1, 5.8$ Hz, 1H), 3.82 – 3.71 (m, 3H), 3.39 (s, 3H), 0.98 (s, 9H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 166.0, 165.9, 165.5, 165.4, 138.0, 135.7, 133.5, 133.4, 133.1, 130.1, 129.9, 129.8, 129.7, 129.6, 129.5, 129.3, 129.2, 128.5, 128.4, 128.0, 127.8, 127.7, 106.0, 96.9, 83.5, 83.0, 82.3, 72.3, 70.8, 70.0, 68.6, 65.7, 63.0, 55.6, 29.8, 26.9, 19.4; HRMS (ESI-MS): m/z calcd for $\text{C}_{63}\text{H}_{62}\text{O}_{14}\text{Si} [\text{M}+\text{K}]^+$: 1109.3546, Found: 1109.3885.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,5-tri-*O*-benzoyl)- α -D-arabinofuranosyl)- α -D-glucopyranoside (39): Yield 92%; $[\alpha]_{\text{D}}^{25}$

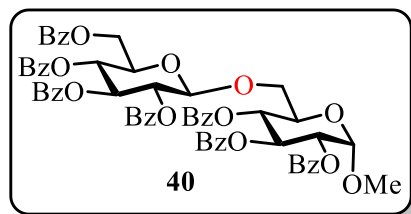
(CHCl_3 , c 1.0): +45.2°; IR (cm^{-1} , CHCl_3): 3032, 2939, 1726, 1601, 1450, 1270, 1105, 1029, 971; ^1H NMR (400.31 MHz, CDCl_3) δ 8.22 – 8.15 (m, 2H), 7.98 – 7.93 (m, 4H), 7.92 (dd, $J = 8.4, 1.4$ Hz, 2H), 7.87 (dd, $J = 8.4, 1.4$ Hz, 2H), 7.70 (dd, $J = 8.3, 1.4$ Hz, 2H), 7.54 – 7.49 (m, 2H), 7.48 –



7.39 (m, 5H), 7.37 – 7.30 (m, 5H), 7.26 (t, $J = 7.8$ Hz, 2H), 7.22 – 7.16 (m, 4H), 6.11 (t, $J = 9.8$ Hz, 1H), 5.71 (t, $J = 9.9$ Hz, 1H), 5.58 (d, $J = 1.1$ Hz, 1H), 5.51 (d, $J = 4.5$ Hz, 1H), 5.32 (s, 1H), 5.28 (dd, $J = 10.2, 3.6$ Hz, 1H), 5.22 (d, $J = 3.6$ Hz, 1H), 4.71 (dd, $J = 11.5, 3.1$ Hz, 1H), 4.65 (td, $J = 4.7, 3.0$ Hz, 1H), 4.58 (dd, $J = 11.5, 4.9$ Hz, 1H), 4.28 – 4.26 (m, 1H), 4.02 (dd, $J = 11.0, 4.2$ Hz, 1H), 3.75 (dd, $J = 11.0, 2.4$ Hz, 1H), 3.39 (s, 3H); ^{13}C NMR (100.66 MHz, CDCl_3) δ 166.3, 166.0, 165.9, 165.4, 165.1, 133.6, 133.4, 133.1, 133.0, 130.1, 130.0, 129.8, 129.5, 129.3, 129.2, 129.1, 128.6, 128.5, 128.3, 105.6, 97.1, 82.0, 81.5, 77.9, 72.2, 70.8, 69.1, 68.5, 65.2, 63.8, 55.7; HRMS (ESI-MS): m/z calcd for $\text{C}_{54}\text{H}_{46}\text{O}_{16} [\text{M}+\text{Na}]^+$: 973.2684, Found: 973.2645.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl- β -glucopyranosyl)- α -D-glucopyranoside (40):

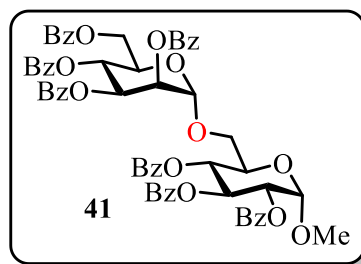
Yield 65%; mp 112–113 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , c 1.0): +48.8 $^{\circ}$; IR (cm^{-1} , CHCl_3): 3387, 2915, 1726, 1597, 1452, 1260, 1100, 759, 707; ^1H NMR



(399.78 MHz, CDCl_3) δ 8.02 – 7.97 (m, 4H), 7.94 (d, $J = 7.3$ Hz, 2H), 7.91 – 7.85 (m, 4H), 7.83 (d, $J = 7.3$ Hz, 2H), 7.79 (d, $J = 7.3$ Hz, 2H), 7.57 – 7.47 (m, 5H), 7.44 – 7.39 (m, 5H), 7.37 – 7.31 (m, 7H), 7.32 – 7.26 (m, 3H), 7.25 (d, 1H), 6.08 (t, $J = 9.8$ Hz, 1H), 5.93 (t, $J = 9.7$ Hz, 1H), 5.67 (t, $J = 9.7$ Hz, 1H), 5.57 (dd, $J = 9.9, 7.9$ Hz, 1H), 5.32 (t, $J = 9.9$ Hz, 1H), 5.09 (dd, $J = 10.3, 3.5$ Hz, 1H), 4.98 (d, $J = 7.9$ Hz, 1H), 4.94 (d, $J = 3.6$ Hz, 1H), 4.62 (dd, $J = 12.2, 3.1$ Hz, 1H), 4.45 (dd, $J = 12.3, 5.1$ Hz, 1H), 4.29 – 4.26 (m, 1H), 4.19 – 4.13 (m, 1H), 4.11 (dd, $J = 11.8, 1.8$ Hz, 1H), 3.79 (dd, $J = 11.4, 7.7$ Hz, 1H), 3.10 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 166.2, 165.9, 165.8, 165.5, 165.3, 133.6, 133.4, 133.3, 133.2, 130.0, 129.9, 129.7, 129.5, 129.3, 129.2, 128.9, 128.5, 128.4, 128.3, 101.9, 96.6, 72.9, 72.4, 72.1, 72.0, 70.4, 69.8, 69.8, 69.1, 68.9, 63.1, 55.2; HRMS (ESI-MS): m/z calcd for $\text{C}_{62}\text{H}_{53}\text{O}_{18} [\text{M}+\text{H}]^+$: 1085.3232, Found: 1085.3247.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl- α -D-mannopyranosyl)- α -D-glucopyranoside (41):

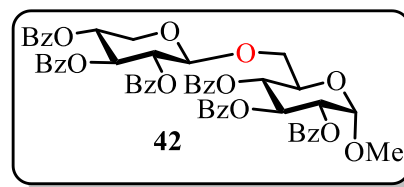
Yield 82%; $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , c 1.0): +11.8 $^{\circ}$; IR (cm^{-1} , CHCl_3): 2931, 1728, 1252, 1102, 958, 708; ^1H NMR (399.78 MHz, CDCl_3) δ 8.12 – 8.08 (m, 2H), 8.07 – 8.04 (m, 2H), 8.02 – 7.95 (m, 6H), 7.93 –



7.90 (m, 2H), 7.87 – 7.83 (m, 2H), 7.61 – 7.56 (m, 2H), 7.51 (t, $J = 7.5$ Hz, 2H), 7.47 – 7.36 (m, 11H), 7.36 – 7.30 (m, 5H), 7.26 – 7.23 (m, 1H), 6.20 (t, $J = 9.9$ Hz, 1H), 6.08 (t, $J = 10.0$ Hz, 1H), 5.98 (dd, $J = 10.1, 3.3$ Hz, 1H), 5.76 (dd, $J = 3.2, 1.8$ Hz, 1H), 5.58 (t, $J = 9.9$ Hz, 1H), 5.32

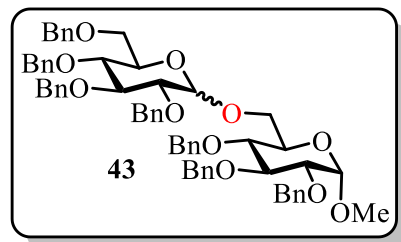
(d, $J = 3.7$ Hz, 1H), 5.25 (dd, $J = 10.1, 3.7$ Hz, 1H), 5.14 (d, $J = 1.7$ Hz, 1H), 4.61 (dd, $J = 12.2, 2.3$ Hz, 1H), 4.52 (ddd, $J = 10.0, 5.0, 2.4$ Hz, 1H), 4.39 – 4.36 (m, 2H), 4.08 (dd, $J = 10.8, 6.1$ Hz, 1H), 3.77 (dd, $J = 10.9, 2.2$ Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 166.2, 165.9, 165.8, 165.6, 165.5, 165.4, 133.6, 133.4, 133.3, 133.2, 133.1, 130.1, 130.0, 129.9, 129.4, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5, 128.4, 97.5, 97.0, 72.2, 70.6, 70.4, 70.1, 69.4, 69.1, 68.4, 66.9, 66.5, 62.8, 55.8; HRMS (ESI-MS): m/z calcd for $\text{C}_{62}\text{H}_{52}\text{O}_{18}$ $[\text{M}+\text{Na}]^+$: 1107.3051, Found: 1107.2175.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4-tri-*O*-benzoyl- β -D-xylopyranosyl)- α -D-glucopyranoside (42): Yield 82%; mp 204–205 °C; $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +23.4°; IR (cm^{-1} , CHCl_3): 3387, 2932, 1639, 1457, 1253, 1216, 1077, 1019, 894, 858,



742, 700; ^1H NMR (400.31 MHz, CDCl_3) δ 8.08 – 7.84 (m, 10H), 7.79 (d, $J = 7.7$ Hz, 2H), 7.56 – 7.42 (m, 6H), 7.41 – 7.28 (m, 10H), 7.25 – 7.19 (m, 2H), 6.08 (t, $J = 9.8$ Hz, 1H), 5.77 (t, $J = 7.6$ Hz, 1H), 5.50 – 5.37 (m, 2H), 5.28 (td, $J = 7.5, 4.4$ Hz, 1H), 5.11 (dd, $J = 10.2, 3.7$ Hz, 1H), 5.02 (d, $J = 3.7$ Hz, 1H), 4.88 (d, $J = 6.0$ Hz, 1H), 4.39 (dd, $J = 12.1, 4.7$ Hz, 1H), 4.22 (dd, $J = 10.3, 6.5$ Hz, 1H), 4.05 (d, $J = 11.2$ Hz, 1H), 3.74 (dd, $J = 11.4, 6.9$ Hz, 1H), 3.65 (dd, $J = 12.1, 7.5$ Hz, 1H), 3.17 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 165.9, 165.6, 165.5, 165.2, 133.5, 133.4, 133.3, 133.2, 130.0, 129.8, 129.5, 129.3, 129.2, 129.0, 128.5, 128.4, 128.3, 101.1, 96.7, 72.2, 70.7, 70.6, 70.5, 69.6, 69.5, 68.9, 68.3, 61.7, 55.3; HRMS (ESI-MS): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 973.2684, Found: 973.2665.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl)- α -D-glucopyranoside (43): Yield 79%; ($\alpha:\beta = 1:0.75$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +78.0°; IR (cm^{-1} , CHCl_3): 3387, 2932, 1639, 1457, 1253, 1216, 1077, 1019, 894, 858,

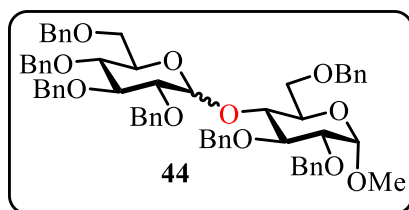


742, 700; ^1H NMR (400.31 MHz, CDCl_3) δ 7.39 – 7.27 (m, 57H), 7.26 – 7.24 (m, 3H), 7.24 – 7.21 (m, 6H), 7.19 (dd, $J = 7.3, 2.2$ Hz, 2H), 7.14 (dd, $J = 7.3, 2.3$ Hz, 2H), 5.12 (d, $J = 3.4$ Hz, 1H), 5.07 (d, $J = 10.9$ Hz, 1H), 4.98 – 4.91 (m, 3H), 4.86 (d, $J = 4.6$ Hz, 1H), 4.85 – 4.81 (m, 2H), 4.80 – 4.75 (m, 3H), 4.73 – 4.71 (m, 3H), 4.70 – 4.67 (m, 4H), 4.65 – 4.60 (m, 8H), 4.58 – 4.54 (m, 2H), 4.51 (d, $J = 8.5$ Hz, 1H), 4.47 (d, $J = 3.7$ Hz, 1H), 4.44 (d, $J = 8.1$ Hz, 1H), 4.28 (dd, $J = 10.7, 1.8$ Hz, 1H), 4.02 (dt, $J = 9.7, 8.4$ Hz, 2H), 3.96 (d, $J = 9.3$ Hz, 1H), 3.93 (t, $J = 3.4$ Hz, 1H), 3.91 – 3.88 (m, 2H), 3.88 – 3.84 (m, 2H), 3.84 – 3.79 (m, 4H), 3.79 – 3.77 (m, 1H),

3.76 – 3.71 (m, 2H), 3.70 – 3.67 (m, 2H), 3.65 (dd, $J = 5.5, 3.3$ Hz, 2H), 3.62 – 3.61 (m, 1H), 3.59 (d, $J = 3.4$ Hz, 1H), 3.56 (d, $J = 3.4$ Hz, 1H), 3.52 (t, $J = 8.1$ Hz, 1H), 3.49 – 3.44 (m, 1H), 3.30 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 139.0, 138.9, 138.8, 138.7, 138.6, 138.4, 138.3, 138.2, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 104.3, 99.1, 99.0, 96.7, 84.8, 82.3, 81.8, 80.4, 80.4, 80.2, 78.0, 77.8, 75.8, 75.6, 75.2, 75.1, 75.1, 75.0, 74.9, 74.7, 73.6, 73.5, 72.9, 72.9, 72.7, 72.3, 72.1, 71.8, 71.5, 70.2, 69.2, 68.6, 66.1, 54.9, 54.9; HRMS (ESI-MS): m/z calcd for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{K}]^+$: 1025.4242, Found: 1025.4285.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl)- α -D-glucopyranoside (44): Yield 82%;

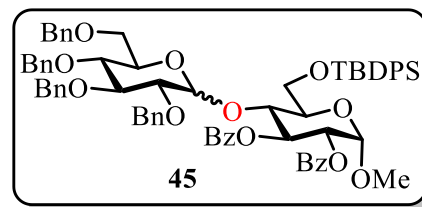
($\alpha:\beta = 1:1$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): $+1.8^\circ$; IR (cm^{-1} , CHCl_3): 2932, 1639, 1457, 1253, 1216, 1077, 1019, 894, 858, 742, 700;



^1H NMR (400.31 MHz, CDCl_3) δ 7.51 – 7.46 (m, 2H), 7.41 – 7.27 (m, 65H), 7.24 (d, $J = 1.8$ Hz, 1H), 7.17 (dd, $J = 6.7, 2.9$ Hz, 2H), 5.76 (d, $J = 3.6$ Hz, 1H), 5.16 (d, $J = 11.3$ Hz, 1H), 5.10 (d, $J = 11.6$ Hz, 1H), 4.94 (dd, $J = 10.9, 5.1$ Hz, 2H), 4.89 (d, $J = 2.5$ Hz, 1H), 4.87 – 4.85 (m, 3H), 4.84 – 4.81 (m, 3H), 4.79 (d, $J = 5.4$ Hz, 1H), 4.76 – 4.73 (m, 1H), 4.68 (d, $J = 2.2$ Hz, 1H), 4.67 – 4.58 (m, 8H), 4.56 (d, $J = 3.4$ Hz, 2H), 4.55 – 4.42 (m, 6H), 4.35 (d, $J = 12.2$ Hz, 1H), 4.18 – 4.08 (m, 2H), 4.07 – 3.96 (m, 2H), 3.96 – 3.87 (m, 4H), 3.81 – 3.76 (m, 2H), 3.74 – 3.70 (m, 2H), 3.69 – 3.62 (m, 4H), 3.60 – 3.51 (m, 5H), 3.48 – 3.40 (m, 8H), 3.36 (dd, $J = 4.8, 2.0$ Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 139.7, 139.1, 138.9, 138.7, 138.6, 138.5, 138.4, 138.3, 138.1, 138.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 126.9, 102.6, 98.6, 97.9, 96.8, 85.0, 83.0, 82.2, 82.2, 80.6, 80.4, 79.6, 79.0, 78.2, 77.8, 76.7, 75.7, 75.7, 75.5, 75.3, 75.1, 75.1, 74.9, 74.6, 73.8, 73.6, 73.5, 73.5, 73.4, 73.3, 72.5, 71.1, 70.1, 69.7, 69.2, 69.1, 68.3, 68.0, 55.4, 55.3; HRMS (ESI-MS): m/z calcd for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{Na}]^+$: 1009.4503, Found: 1009.4515.

Methyl 2,3-di-*O*-benzoyl-6-*O*-*t*-butyldiphenylsilyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl)- α -D-glucopyranoside (45): Yield 76%;

($\alpha:\beta = 1:0.4$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): $+69.6^\circ$; IR (cm^{-1} , CHCl_3): 2932, 1639, 1457,

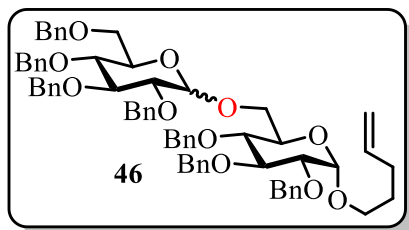


1253, 1216, 1077, 1019, 894, 858, 742, 700; ^1H NMR (400 MHz, CDCl_3) δ 8.16 – 8.02 (m, 4H), 7.89 – 7.77 (m, 4H), 7.60 – 7.18 (m, 32H), 6.29 – 5.99 (m, 1H), 5.29 – 5.21 (m, 3H), 4.97 – 4.76 (m, 4H), 4.60 – 4.28 (m, 5H), 4.24 (dq, $J = 8.3, 4.2$ Hz, 1H), 4.12 – 3.79 (m, 4H), 3.64 (t, $J = 9.5$

Hz, 1H), 3.55 (dd, $J = 11.5, 8.3$ Hz, 1H), 3.43 (s, 3H), 3.42 – 3.31 (m, 2H), 1.17 (s, 9H). ^{13}C NMR (100.53 MHz, CDCl_3) δ 166.3, 165.7, 138.9, 138.6, 138.2, 138.0, 136.1, 135.8, 135.7, 134.0, 133.4, 133.0, 130.2, 130.1, 130.0, 129.9, 129.8, 129.7, 129.4, 129.3, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 98.3, 96.5, 81.6, 79.3, 77.4, 75.6, 75.0, 74.9, 73.5, 72.7, 72.3, 71.6, 71.2, 68.4, 63.0, 55.1, 27.1, 19.6; HRMS (ESI-MS): m/z calcd for $\text{C}_{71}\text{H}_{74}\text{O}_{13}\text{Si}$ $[\text{M}+\text{Na}]^+$: 1185.4796, Found: 1185.4795.

Pent-4-enyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl)- α -D-glucopyranoside (46):

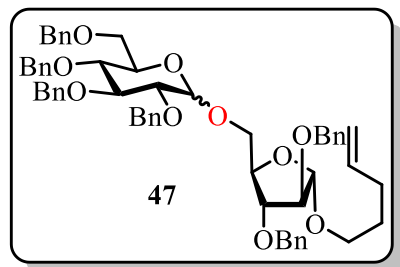
Yield 79%; ($\alpha:\beta = 1:0.7$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +38.0°; IR (cm^{-1} , CHCl_3): 2880, 1454, 1361, 1152, 1082, 917, 739; ^1H NMR (400.31 MHz, CDCl_3) δ 7.42 – 7.35 (m, 5H), 7.35 – 7.26 (m,



28H), 7.18 – 7.13 (m, 2H), 5.84– 5.80 (m, 1H), 5.07 – 4.95 (m, 6H), 4.86 (dd, $J = 10.9, 5.5$ Hz, 2H), 4.81 (d, $J = 10.9$ Hz, 1H), 4.75 – 4.66 (m, 5H), 4.64 – 4.57 (m, 2H), 4.52 – 4.43 (m, 2H), 4.08 – 4.01 (m, 2H), 3.90 – 3.80 (m, 3H), 3.76 – 3.65 (m, 5H), 3.64 – 3.56 (m, 2H), 3.52 – 3.39 (m, 2H), 2.21 – 2.12 (m, 2H), 1.78 – 1.75 (m, 2H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 139.1, 139.0, 138.6, 138.5, 138.2, 138.1, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 115.0, 97.4, 96.8, 82.2, 81.9, 80.5, 80.1, 78.0, 77.7, 75.8, 75.7, 75.2, 75.0, 73.5, 73.3, 72.4, 70.6, 70.4, 68.6, 67.6, 66.2, 30.4, 28.7; HRMS (ESI-MS): m/z calcd for $\text{C}_{66}\text{H}_{72}\text{O}_{11}$ $[\text{M}+\text{K}]^+$: 1079.4712, Found: 1079.4700.

Pent-4-enyl 2,3-di-*O*-benzyl-5-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl)- α -D-arabinofuranoside (47):

Yield 73%; ($\alpha:\beta = 1:1$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +24.2°; IR (cm^{-1} , CHCl_3): 2919, 2864, 1454, 1077, 912, 746, 699; ^1H NMR (400.31 MHz, CDCl_3) δ 7.38 – 7.26 (m, 52H), 7.26 – 7.25 (m,

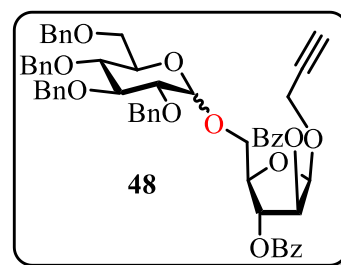


4H), 7.18 – 7.12 (m, 4H), 5.80– 5.76 (m, 2H), 5.06 – 5.00 (m, 4H), 4.98 (q, $J = 1.7$ Hz, 1H), 4.96 – 4.92 (m, 3H), 4.88 (d, $J = 3.7$ Hz, 1H), 4.84 (d, $J = 3.9$ Hz, 1H), 4.82 (d, $J = 3.8$ Hz, 1H), 4.79 (d, $J = 3.3$ Hz, 1H), 4.77 – 4.74 (m, 1H), 4.73 – 4.67 (m, 3H), 4.66 – 4.63 (m, 1H), 4.62 (d, $J = 3.0$ Hz, 1H), 4.59– 4.56 (m, 2H), 4.57 – 4.55 (m, 4H), 4.54 – 4.52 (m, 2H), 4.51 – 4.47 (m, 3H), 4.47 – 4.44 (m, 2H), 4.44 – 4.41 (m, 1H), 4.32 – 4.21 (m, 2H), 4.18 (dd, $J = 10.7, 3.3$ Hz, 1H), 4.05 – 4.03 (m, 2H), 3.99 (d, $J = 9.3$ Hz, 1H), 3.95 (dd, $J = 6.7, 3.4$ Hz, 1H), 3.91 (dd, $J = 7.1, 3.3$ Hz, 1H), 3.85 – 3.76 (m, 2H), 3.73 – 3.63 (m, 8H), 3.62 (t, $J = 2.5$ Hz, 2H), 3.60 – 3.56 (m,

2H), 3.51 – 3.43 (m, 2H), 3.38 (dq, $J = 9.9, 6.4$ Hz, 2H), 2.15 – 2.05 (m, 4H), 1.70 – 1.65 (m, 4H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 139.0, 138.8, 138.7, 138.6, 138.5, 138.4, 138.3, 138.2, 138.1, 138.0, 137.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 114.9, 106.2, 104.1, 97.4, 88.6, 88.6, 84.7, 84.2, 84.1, 82.1, 82.0, 80.2, 80.1, 80.1, 77.9, 77.7, 75.8, 75.7, 75.1, 75.1, 75.0, 74.8, 73.6, 73.6, 72.9, 72.3, 72.3, 72.2, 72.1, 70.3, 70.0, 69.1, 68.5, 67.8, 67.1, 67.0, 30.5, 30.4, 28.9, 28.8; HRMS (ESI-MS): m/z calcd for $\text{C}_{58}\text{H}_{64}\text{O}_{10}$ $[\text{M}+\text{Na}]^+$: 943.4397, Found: 943.4388.

Propargyl 2,3-di-O-benzoyl-5-O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)- β -D-arabinofuranoside (48):

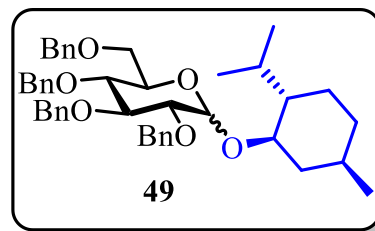
Yield 74%; ($\alpha:\beta = 1:0.65$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): $+25.0^\circ$; IR (cm^{-1} , CHCl_3) : 2923, 2843, 1722, 1585, 1448, 1160, 1007; ^1H NMR (400 MHz, CDCl_3) δ 8.10 – 8.02 (m, 2H), 7.96 – 7.85 (m, 2H), 7.62 – 7.27 (m, 26H),



5.89 – 5.65 (m, 2H), 5.49 (s, 1H), 5.10 – 4.47 (m, 11H), 4.39 – 4.32 (m, 2H), 4.06 – 3.89 (m, 2H), 3.84 – 3.48 (m, 7H), 2.47 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.4, 165.3, 139.0, 138.5, 138.4, 138.0, 133.6, 133.4, 133.4, 130.0, 129.8, 129.4, 129.4, 129.2, 129.1, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 103.2, 97.7, 84.7, 82.0, 80.2, 80.1, 78.8, 77.7, 75.8, 75.5, 75.3, 75.1, 75.0, 73.6, 73.4, 72.5, 70.7, 69.9, 68.5, 54.4; HRMS (ESI-MS): m/z calcd for $\text{C}_{54}\text{H}_{54}\text{O}_{12}$ $[\text{M}+\text{Na}]^+$: 941.0258, Found: 941.0211.

Menthyl 2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranoside (49):

Yield 75%; ($\alpha:\beta = 1:0.9$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): $+18.6^\circ$; IR (cm^{-1} , CHCl_3): 2923, 2881, 1454, 1380, 1070, 739, 698; ^1H NMR (400.31 MHz, CDCl_3) δ 7.41 – 7.26 (m, 36H), 7.26 – 7.23 (m, 2H), 7.16 – 7.12 (m, 2H), 5.06 (d, $J = 3.6$ Hz, 1H), 5.02 – 4.99 (m,

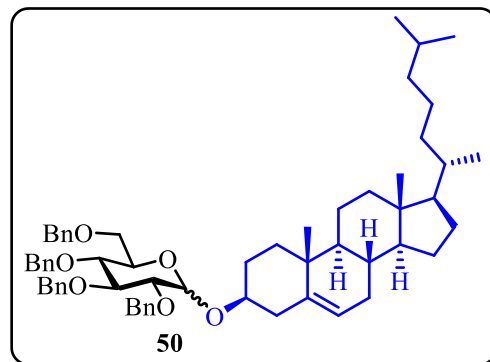


1H), 4.96 (d, $J = 10.9$ Hz, 1H), 4.89 – 4.76 (m, 4H), 4.74 – 4.68 (m, 3H), 4.66 – 4.62 (m, 2H), 4.59 (d, $J = 6.8$ Hz, 1H), 4.56 – 4.48 (m, 3H), 4.08 – 3.98 (m, 2H), 3.78 (dd, $J = 10.5, 3.8$ Hz, 1H), 3.73 (d, $J = 3.3$ Hz, 2H), 3.70 – 3.60 (m, 4H), 3.55 (m, 2H), 3.48 – 3.42 (m, 2H), 3.38 (td, $J = 10.6, 4.3$ Hz, 1H), 2.42 (m, 2H), 2.20 – 2.16 (m, 2H), 1.74 – 1.63 (m, 4H), 1.45 – 1.31 (m, 4H), 1.13 – 0.97 (m, 4H), 1.01 – 0.93 (m, 6H), 0.89 – 0.85 (m, 9H), 0.74 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100.66 MHz, CDCl_3) δ 139.0, 138.7, 138.5, 138.4, 138.2, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 100.9, 98.8, 85.1, 82.3, 82.1, 81.1, 80.7, 78.2, 78.1, 77.9, 75.7, 75.6,

75.2, 75.1, 75.0, 74.9, 73.8, 73.6, 73.3, 70.4, 69.4, 68.8, 48.9, 48.2, 43.2, 41.1, 34.6, 34.4, 31.9, 31.6, 25.4, 24.7, 23.3, 23.1, 22.4, 22.4, 21.2, 21.2, 16.2, 16.1; HRMS (ESI-MS): m/z calcd for $C_{44}H_{54}O_6$ $[M+K]^+$: 718.3636, Found: 718.3634.

Cholesteryl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside (50): Yield 84%; ($\alpha:\beta = 1:0.65$); mp

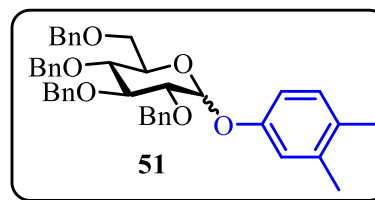
125-126 °C; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +25.8°; IR (cm^{-1} , $CHCl_3$): 2938, 2860, 1456, 1376, 1074, 737; 1H NMR (400.31 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 36H), 7.17–7.12 (m, 4H), 5.36 (d, $J = 4.8$ Hz, 1H), 5.31 (d, $J = 4.7$ Hz, 1H), 5.01 (t, $J = 11.6$ Hz, 2H), 4.97 – 4.92 (m,



2H), 4.89 – 4.81 (m, 4H), 4.82 – 4.78 (m, 2H), 4.71 (d, $J = 11.5$ Hz, 1H), 4.67 – 4.63 (m, 1H), 4.61 (d, $J = 3.4$ Hz, 1H), 4.57 (d, $J = 3.9$ Hz, 1H), 4.56 – 4.45 (m, 4H), 4.03 (t, $J = 9.2$ Hz, 1H), 3.90 (ddd, $J = 10.1, 3.6, 2.0$ Hz, 1H), 3.79 – 3.76 (m, 2H), 3.69 – 3.63 (m, 4H), 3.63 – 3.53 (m, 3H), 3.53 – 3.42 (m, 3H), 2.49 – 2.27 (m, 4H), 2.08 – 1.94 (m, 5H), 1.91 – 1.80 (m, 5H), 1.60 – 1.30 (m, 22H), 1.23 – 1.07 (m, 14H), 1.07 – 0.99 (m, 12H), 0.94 (d, $J = 6.4$ Hz, 2x3H), 0.90 (d, $J = 1.8$ Hz, 2x3H), 0.88 (d, $J = 1.8$ Hz, 2x3H), 0.70 (d, $J = 2.2$ Hz, 2x3H); ^{13}C NMR (100.66 MHz, $CDCl_3$) δ 141.0, 140.7, 139.1, 138.8, 138.6, 138.4, 138.3, 138.1, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 122.1, 121.8, 102.4, 94.7, 85.0, 82.5, 82.2, 80.0, 79.8, 78.1, 78.0, 76.7, 75.8, 75.3, 75.1, 75.1, 74.9, 73.6, 73.5, 73.2, 70.2, 69.3, 68.7, 56.9, 56.9, 56.3, 50.3, 50.2, 42.5, 40.0, 39.9, 39.6, 39.2, 37.4, 37.2, 36.9, 36.9, 36.3, 35.9, 32.1, 32.1, 32.0, 30.1, 28.4, 28.1, 27.6, 24.4, 23.9, 23.0, 22.7, 21.2, 19.5, 19.5, 18.9, 12.0; HRMS (ESI-MS): m/z calcd for $C_{61}H_{80}O_6$ $[M+Na]^+$: 931.5853, Found: 931.5862.

3,4-dimethylphenyl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside (51): Yield 77%; ($\alpha:\beta = 3:1$); $[\alpha]^{25}_D$ ($CHCl_3$,

c 1.0): +54.5°; IR (cm^{-1} , $CHCl_3$): 2922, 2885, 1499, 1453, 1366, 1252, 1144, 1047, 740 ; 1H NMR (400.31 MHz, $CDCl_3$) δ 7.46

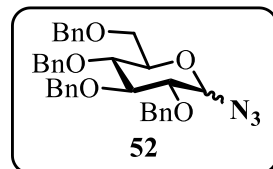


– 7.40 (m, 4H), 7.38 – 7.29 (m, 31H), 7.28 – 7.26 (m, 1H), 7.23 (dd, $J = 7.5, 2.1$ Hz, 1H), 7.19 – 7.16 (m, 3H), 7.10 – 7.06 (m, 2H), 6.96 – 6.93 (m, 2H), 6.90 – 6.85 (m, 2H), 5.50 (d, $J = 3.5$ Hz, 1H), 5.09 (d, $J = 10.8$ Hz, 2H), 5.01 – 4.96 (m, 1H), 4.94 – 4.86 (m, 4H), 4.84 – 4.78 (m, 2H), 4.72 (d, $J = 12.0$ Hz, 2H), 4.65 – 4.60 (m, 2H), 4.55 (dd, $J = 15.0, 11.4$ Hz, 2H), 4.44 (d, $J = 12.0$ Hz, 2H), 4.24 (t, $J = 9.2$ Hz, 2H), 3.94 (ddd, $J = 10.1, 3.4, 2.1$ Hz, 2H), 3.81 (dd, $J = 10.1, 8.9$

Hz, 2H), 3.76 (m, 4H), 3.62 (dd, $J = 10.8, 2.1$ Hz, 2H), 2.24 (m, 4x3H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 155.7, 154.9, 139.0, 138.7, 138.5, 138.4, 138.3, 138.2, 138.0, 137.9, 137.8, 130.9, 130.5, 130.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 118.7, 118.4, 114.3, 114.0, 102.3, 95.6, 84.8, 82.2, 82.2, 79.8, 77.9, 77.6, 75.9, 75.9, 75.2, 75.2, 75.1, 73.6, 73.5, 73.3, 70.8, 69.0, 68.4, 20.1, 20.1, 19.1, 19.0; HRMS (ESI-MS): m/z calcd for $\text{C}_{42}\text{H}_{44}\text{O}_6$ $[\text{M}+\text{H}]^+$: 645.3216, Found: 645.3210.

1-deoxy-1-azido 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside (52):

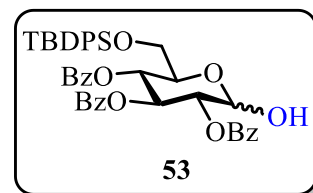
Yield 74%; ($\alpha:\beta = 4:1$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): $+78.2^\circ$; IR (cm^{-1} , CHCl_3): 2916, 2881, 2114, 1460, 1385, 1085, 734; ^1H NMR (400.31 MHz, CDCl_3) δ 7.38 – 7.32 (m, 14H), 7.31 – 7.28 (m, 4H), 7.18 – 7.14 (m,



2H), 5.25 (d, $J = 4.1$ Hz, 1H), 4.95 (d, $J = 10.9$ Hz, 1H), 4.86 – 4.80 (m, 3H), 4.68 (d, $J = 11.9$ Hz, 1H), 4.61 (d, $J = 12.1$ Hz, 1H), 4.51 (d, $J = 5.2$ Hz, 1H), 4.48 (d, $J = 6.4$ Hz, 1H), 3.93 – 3.85 (m, 2H), 3.75 (dd, $J = 10.9, 3.3$ Hz, 1H), 3.69 – 3.63 (m, 3H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 138.6, 138.4, 138.2, 138.0, 137.9, 137.8, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 90.3, 88.2, 85.0, 81.9, 81.8, 79.6, 77.2, 77.2, 76.0, 75.9, 75.3, 75.2, 73.9, 73.7, 73.6, 72.6, 68.5, 68.2; HRMS (ESI-MS): m/z calcd for $\text{C}_{34}\text{H}_{35}\text{N}_3\text{O}_5$ $[\text{M}+\text{Na}]^+$: 588.2474, Found: 588.2470.

2,3,4-tri-*O*-benzoyl-6-*O*-*t*-butyldiphenylsilyl- α/β -D-glucopyranoside (53):

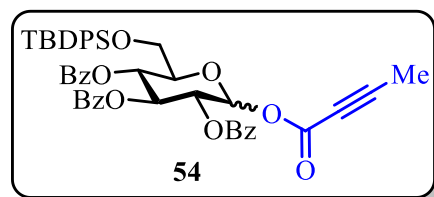
($\alpha:\beta = 3:1$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): $+0.9^\circ$; IR (cm^{-1} , CHCl_3): 3454, 2935, 2857, 1728, 1597, 1453, 1267, 1103; ^1H NMR (400.31 MHz, CDCl_3) δ 8.03 – 7.97 (m, 4H), 7.93 – 7.86 (m, 8H), 7.74 – 7.70 (m,



4H), 7.62 – 7.57 (m, 4H), 7.56 – 7.51 (m, 5H), 7.41 – 7.34 (m, 15H), 7.33 – 7.28 (m, 6H), 7.23 – 7.20 (m, 4H), 6.21 (d, $J = 9.9$ Hz, 1H), 5.89 (t, $J = 9.7$ Hz, 1H), 5.79 – 5.60 (m, 4H), 5.35 – 5.28 (m, 2H), 4.94 (d, $J = 7.9$ Hz, 1H), 4.40 (ddd, $J = 10.3, 4.3, 2.4$ Hz, 1H), 3.91 – 3.80 (m, 5H), 3.25 (s, 1H), 1.06 (s, 2x9H); ^{13}C NMR (100.66 MHz, CDCl_3) δ 166.8, 166.1, 166.0, 165.2, 165.1, 135.9, 135.8, 135.7, 133.6, 133.5, 133.4, 133.3, 133.2, 133.1, 133.0, 130.1, 130.0, 129.9, 129.8, 129.7, 129.4, 129.2, 129.0, 128.6, 128.5, 128.4, 127.8, 127.7, 96.0, 90.5, 75.4, 74.5, 72.9, 72.6, 70.7, 70.5, 69.2, 69.1, 63.0, 62.9, 26.9, 26.9, 19.3, 19.3; HRMS (ESI-MS): m/z calcd for $\text{C}_{43}\text{H}_{42}\text{O}_9\text{Si}$ $[\text{M}+\text{Na}]^+$: 753.2496, Found: 753.2485.

But-2-yno-yl 2,3,4-tri-*O*-benzoyl-6-*O*-*t*-butyldiphenylsilyl- α/β -D-glucopyranoside (54):

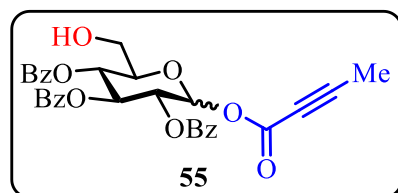
Yield 86%; ($\alpha:\beta = 5:1$); $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): $+8.7^\circ$; IR (cm^{-1} , CHCl_3): 2933, 2860, 1730,



1597, 1453, 1247, 1101, 1020; ^1H NMR (400.31 MHz, CDCl_3) δ 7.99 – 7.86 (m, 6H), 7.70 – 7.67 (m, 2H), 7.60 – 7.50 (m, 4H), 7.47 – 7.42 (m, 1H), 7.39 – 7.34 (m, 7H), 7.34 – 7.28 (m, 3H), 7.17 (t, J = 7.5 Hz, 2H), 6.70 (d, J = 3.7 Hz, 1H), 6.16 (t, J = 9.9 Hz, 1H), 5.85 (t, J = 10.0 Hz, 1H), 5.54 (dd, J = 10.2, 3.7 Hz, 1H), 4.30 (dt, J = 10.2, 2.8 Hz, 1H), 3.88 – 3.80 (m, 2H), 2.06 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100.66 MHz, CDCl_3) δ 166.1, 165.6, 165.0, 151.6, 135.8, 135.7, 133.6, 133.4, 133.3, 133.0, 132.9, 130.1, 130.0, 129.9, 129.8, 129.7, 129.3, 129.2, 128.8, 128.6, 128.5, 128.4, 127.8, 127.7, 90.7, 88.4, 73.3, 71.9, 70.8, 70.6, 68.3, 62.1, 26.8, 19.3, 4.1; HRMS (ESI-MS): m/z calcd for $\text{C}_{47}\text{H}_{44}\text{O}_{10}\text{Si}$ $[\text{M}+\text{K}]^+$: 835.2341, Found: 835.6892.

But-2-yno-yl 2,3,4-tri-*O*-benzoyl- α/β -D-glucopyranoside

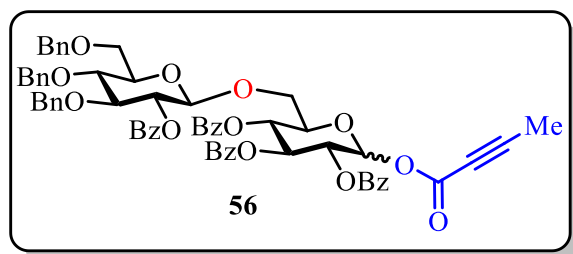
(55): Yield 80%; (α -isomer characterized); mp 71.8–73.8 $^\circ\text{C}$; $[\alpha]_D^{25}$ (CHCl_3 , c 1.0): +69.8 $^\circ$; IR (cm^{-1} , CHCl_3): 2900, 2871, 2165, 1726, 1458, 1252, 1158, 1099, 1016, 707; ^1H NMR



(400.31 MHz, CDCl_3) δ 7.98 (d, J = 7.4 Hz, 2H), 7.93 (d, J = 7.2 Hz, 2H), 7.87 (d, J = 7.4 Hz, 2H), 7.57 – 7.49 (m, 2H), 7.46 – 7.35 (m, 5H), 7.32 – 7.30 (m, 2H), 6.66 (d, J = 3.7 Hz, 1H), 6.26 (t, J = 10.0 Hz, 1H), 5.60 (t, J = 10.0 Hz, 1H), 5.54 (dd, J = 10.3, 3.7 Hz, 1H), 4.21 (ddd, J = 10.4, 3.6, 2.1 Hz, 1H), 3.85 (d, J = 13.4 Hz, 1H), 3.72 (dd, J = 13.1, 3.6 Hz, 1H), 2.69 (s, 1H), 2.07 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl_3) δ 166.3, 165.9, 165.5, 151.5, 134.0, 133.7, 133.5, 130.1, 130.0, 129.8, 129.0, 128.7, 128.6, 128.6, 128.5, 128.5, 90.6, 88.9, 72.9, 71.7, 70.2, 70.0, 68.9, 60.9, 4.2; HRMS (ESI-MS): m/z calcd for $\text{C}_{31}\text{H}_{26}\text{O}_{10}$ $[\text{M}+\text{Na}]^+$: 581.1424, Found: 581.1400.

But-2-yno-yl 2,3,4-tri-*O*-benzoyl-6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-glucopyranosyl)- α/β -D-glucopyranoside

(56): Yield 78%; $[\alpha]_D^{25}$ (CHCl_3 , c 1.0): +118.0 $^\circ$; IR (cm^{-1} , CHCl_3): 2928, 2240, 1731, 1598, 1451,

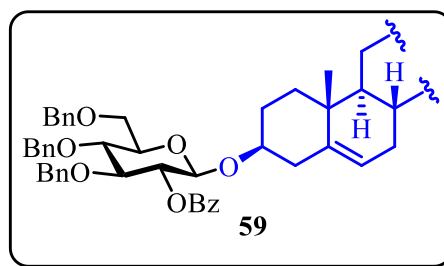


1257, 1095, 1024; ^1H NMR (399.78 MHz, CDCl_3) δ 8.13 – 8.04 (m, 2H), 7.92 – 7.77 (m, 6H), 7.49 – 7.18 (m, 27H), 6.51 (s, 1H), 6.09 (t, J = 9.6 Hz, 1H), 5.56 – 5.46 (m, 1H), 5.39 – 5.26 (m, 2H), 4.82 – 4.52 (m, 7H), 4.44 – 4.34 (m, 1H), 4.07 (d, J = 11.1 Hz, 1H), 3.88 – 3.82 (m, 1H), 3.80 – 3.69 (m, 4H), 3.58 – 3.51 (m, 1H), 1.96 (s, 3H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 165.8, 165.4, 165.3, 165.1, 151.2, 138.2, 138.0, 137.9, 133.5, 133.3, 132.9, 130.1, 129.9, 129.8, 129.0, 128.8, 128.7, 128.5, 128.3, 128.1, 127.9, 127.7, 101.3, 90.2, 88.4, 82.9, 77.9, 75.4, 75.2, 75.1,

73.7, 73.5, 72.2, 71.6, 70.3, 70.2, 68.7, 68.6, 67.2, 4.1; HRMS (ESI-MS): m/z calcd for $C_{65}H_{58}O_{16} [M+Na]^+$: 1117.3623, Found: 1117.3612.

Cholesteryl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-glucopyranoside (59): Yield 81%; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0):

+20.0°; IR (cm^{-1} , $CHCl_3$): 2920, 2853, 1729, 1596, 1449, 1270, 1097; 1H NMR (399.78 MHz, $CDCl_3$) δ 8.02 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.7 Hz,

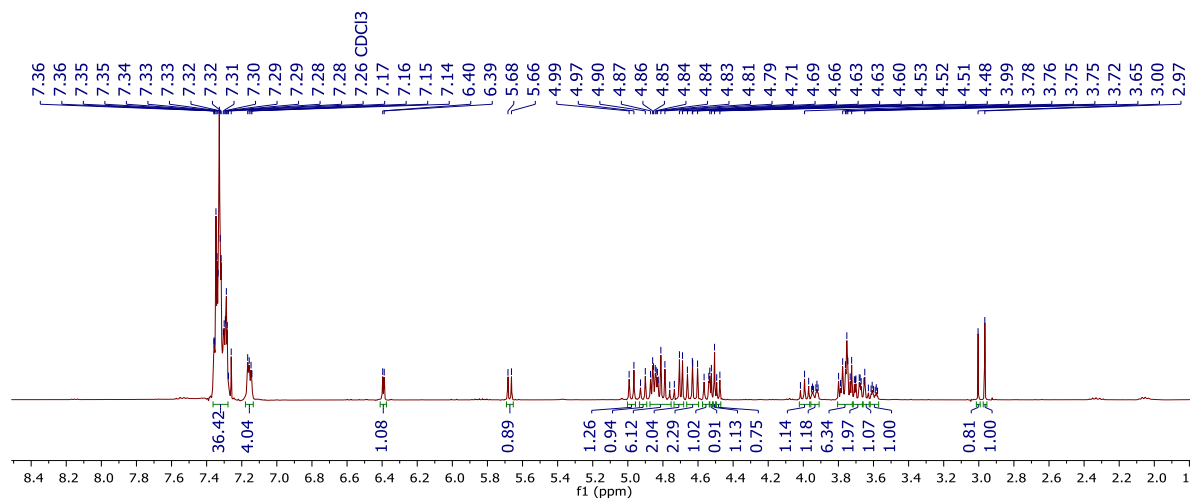


2H), 7.37 – 7.27 (m, 8H), 7.26 (m, 1H), 7.22 – 7.18 (m, 2H), 7.13 – 7.11 (m, 4H), 5.27 – 5.19 (m, 2H), 4.82 (d, J = 11.1 Hz, 1H), 4.73 (d, J = 11.1 Hz, 1H), 4.67 – 4.62 (m, 2H), 4.62 – 4.55 (m, 3H), 3.83 – 3.67 (m, 4H), 3.57 – 3.52 (m, 1H), 3.48 (dt, J = 11.4, 6.2 Hz, 1H), 2.16 – 2.04 (m, 2H), 2.04 – 1.96 (m, 1H), 1.95 – 1.87 (m, 2H), 1.84 – 1.75 (m, 2H), 1.55 – 1.30 (m, 11H), 1.17 – 0.96 (m, 10H), 0.90 (d, J = 7.8 Hz, 6H), 0.87 (d, J = 1.9 Hz, 3H), 0.85 (d, J = 1.9 Hz, 3H), 0.64 (s, 3H); ^{13}C NMR (100.66 MHz, $CDCl_3$) δ 165.4, 140.8, 138.4, 138.1, 138.0, 133.1, 130.3, 129.8, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.7, 121.9, 100.1, 83.0, 79.8, 78.3, 75.4, 75.2, 75.1, 74.2, 73.6, 69.1, 56.9, 56.3, 50.3, 42.5, 39.9, 39.7, 39.0, 37.4, 36.8, 36.3, 35.9, 32.1, 32.0, 29.7, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0; HRMS (ESI-MS): m/z calcd for $C_{61}H_{78}O_7 [M+Na]^+$: 961.5385, Found: 961.5381.

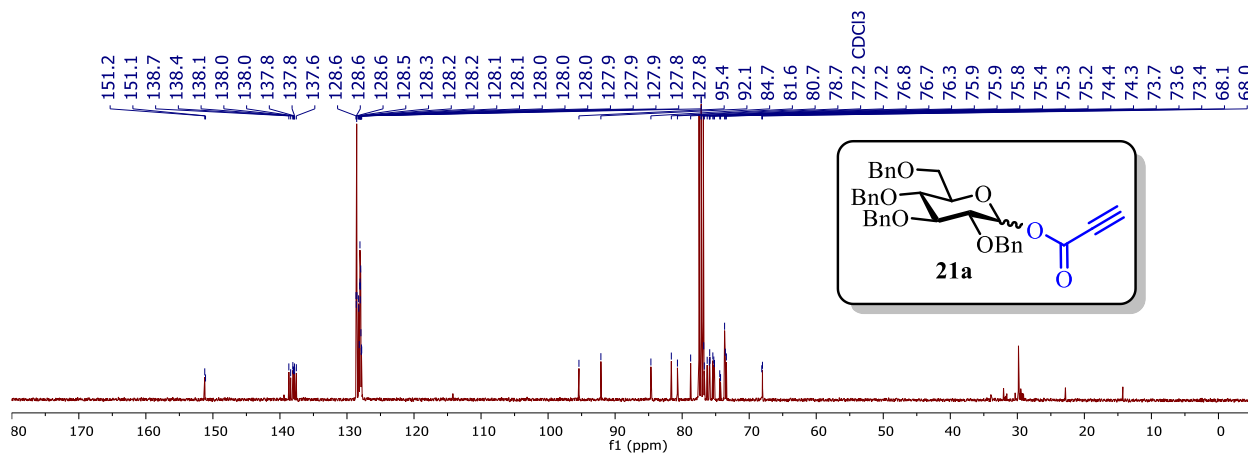
Chapter 3A

3A.8 Spectral charts of compounds

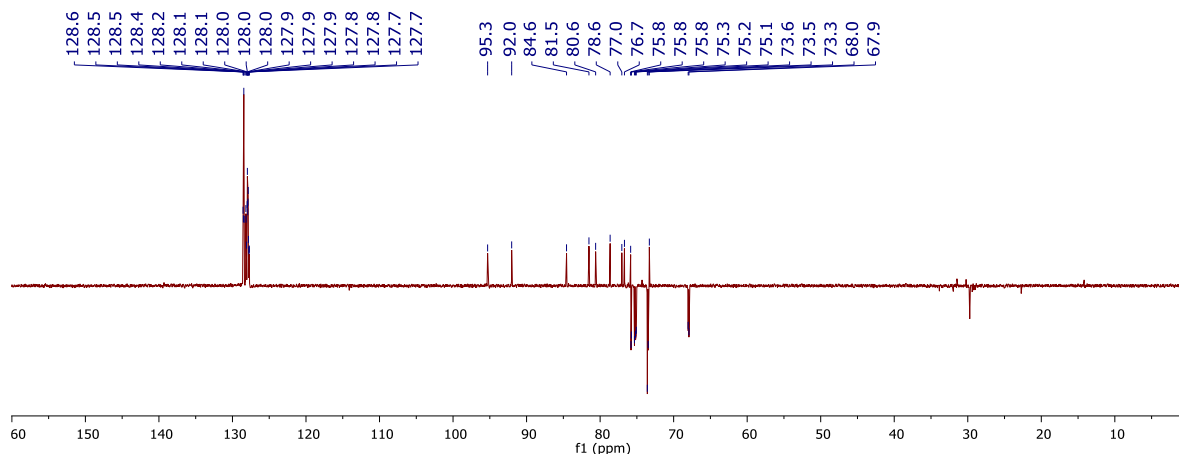
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **21a**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21a**

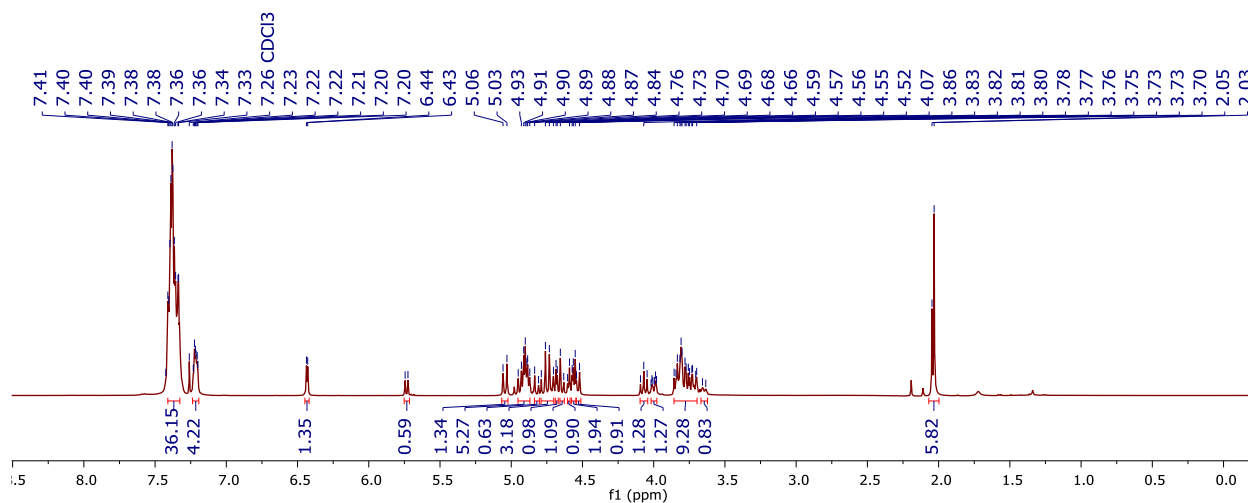


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21a**

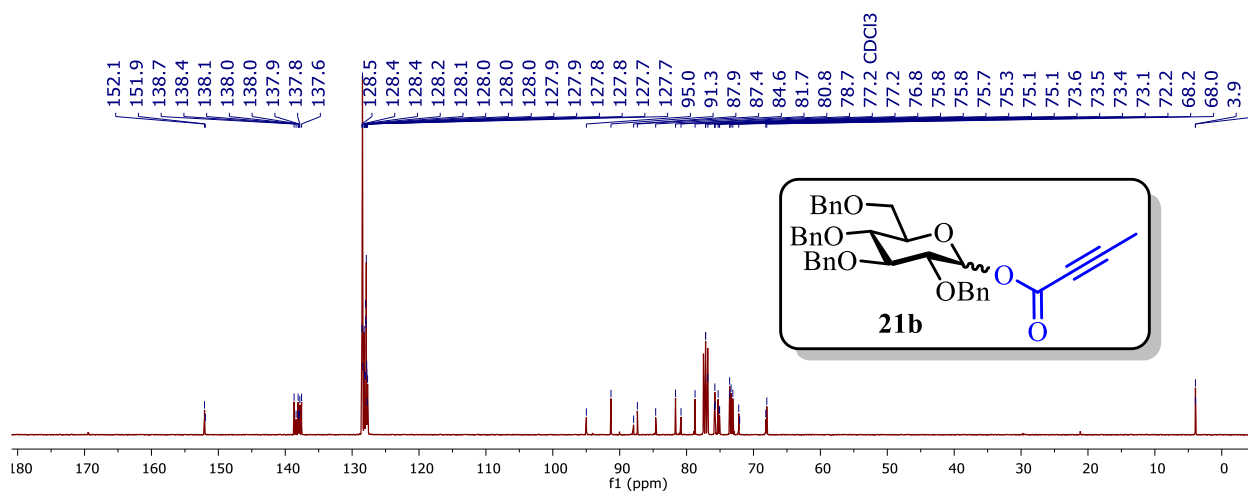


Chapter 3A

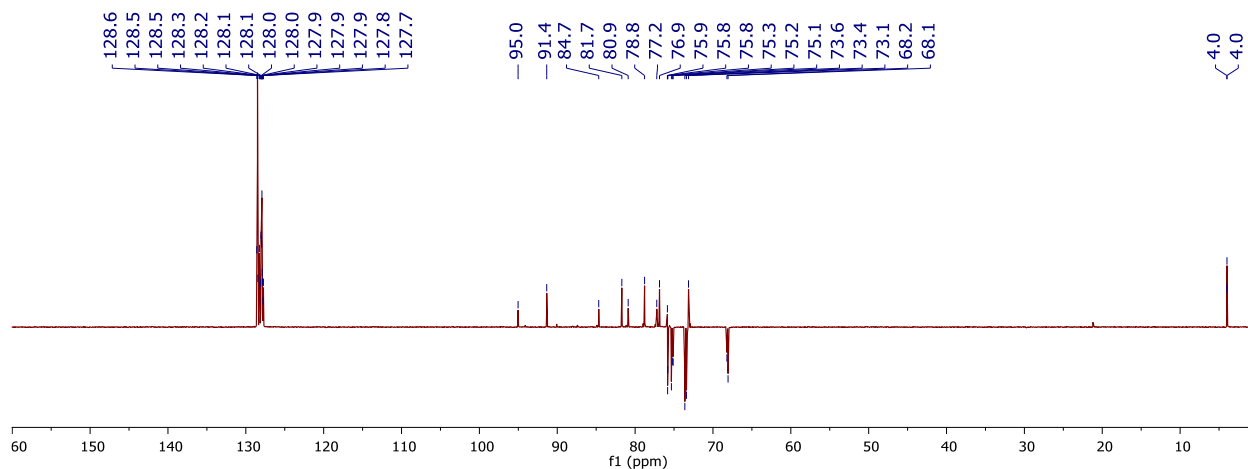
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **21b**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21b**

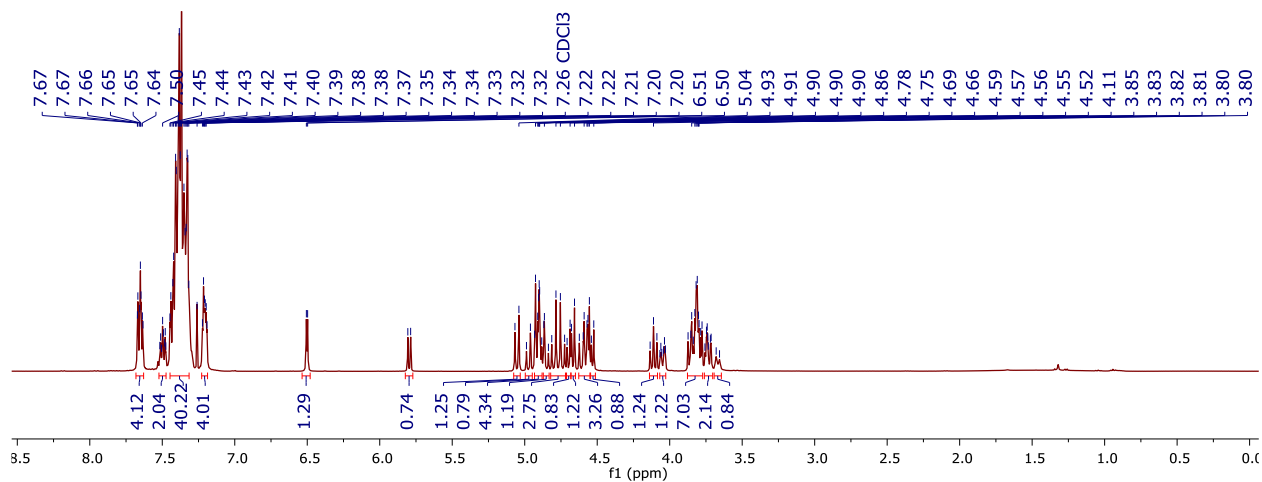


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21b**

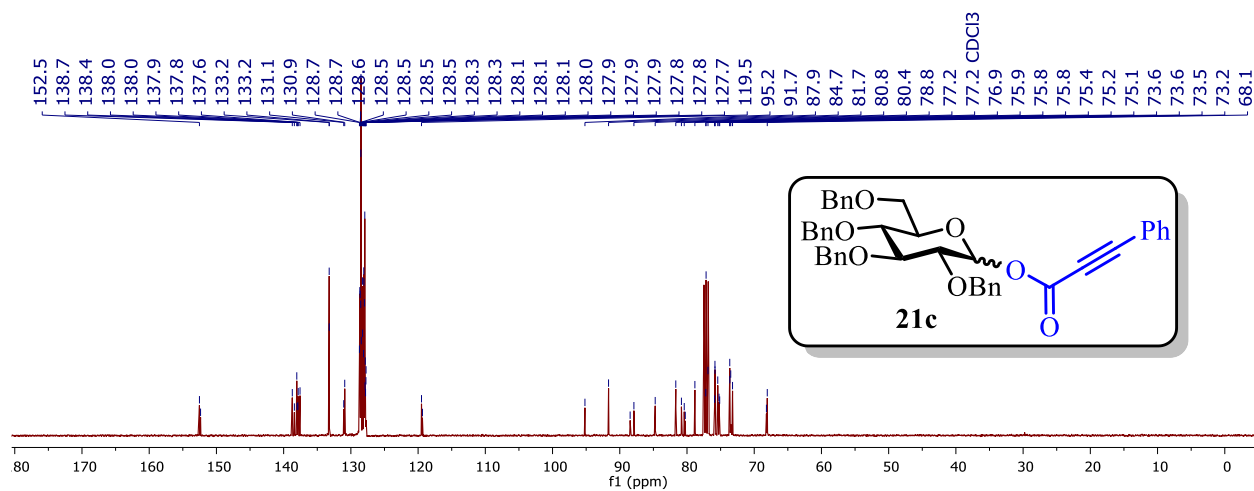


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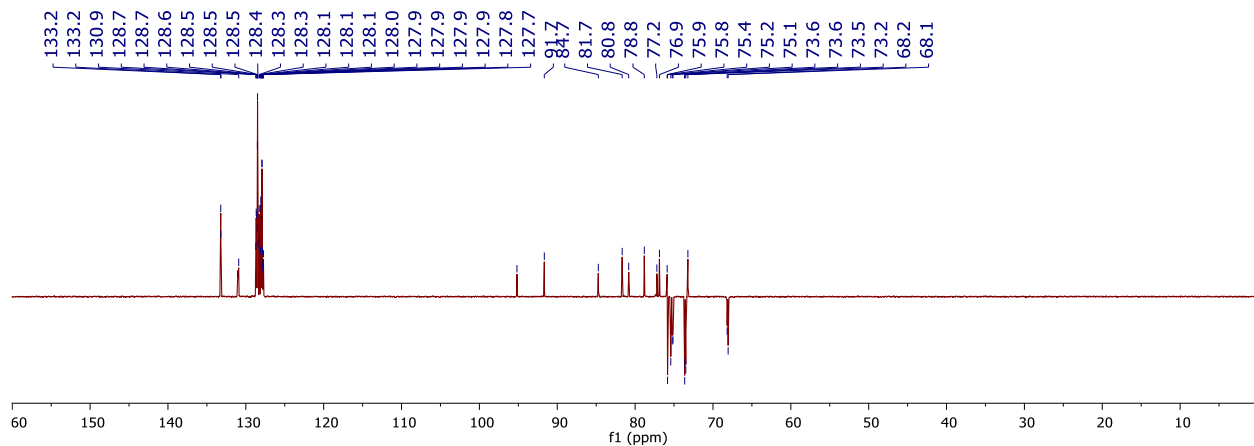
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **21c**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21c**

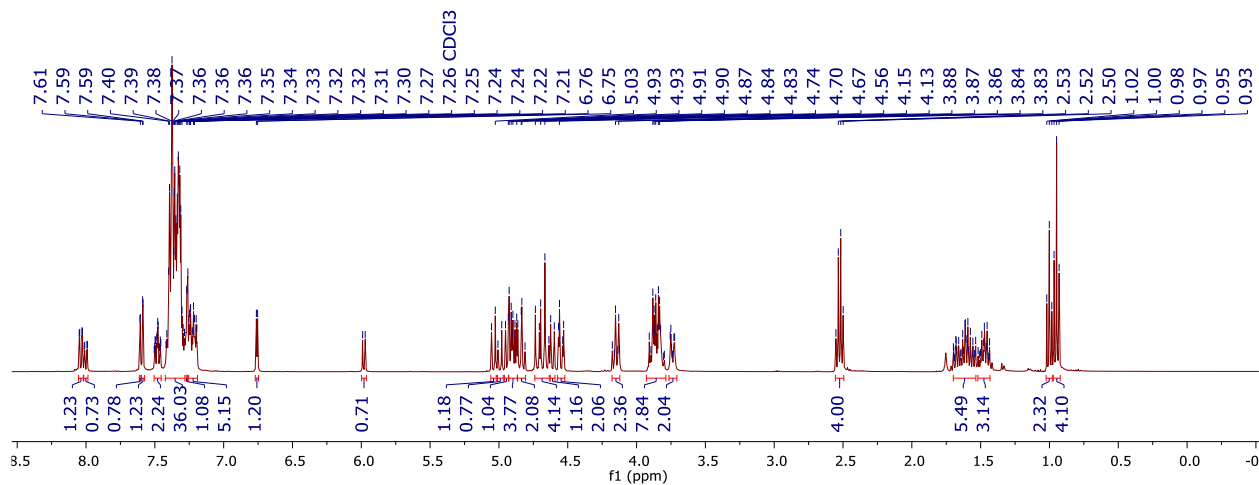


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21c**

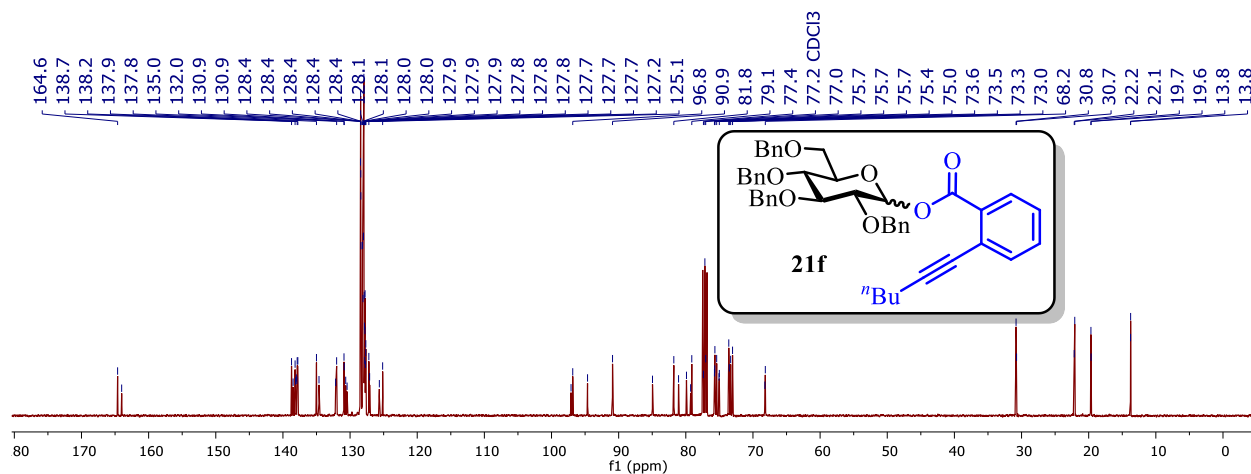


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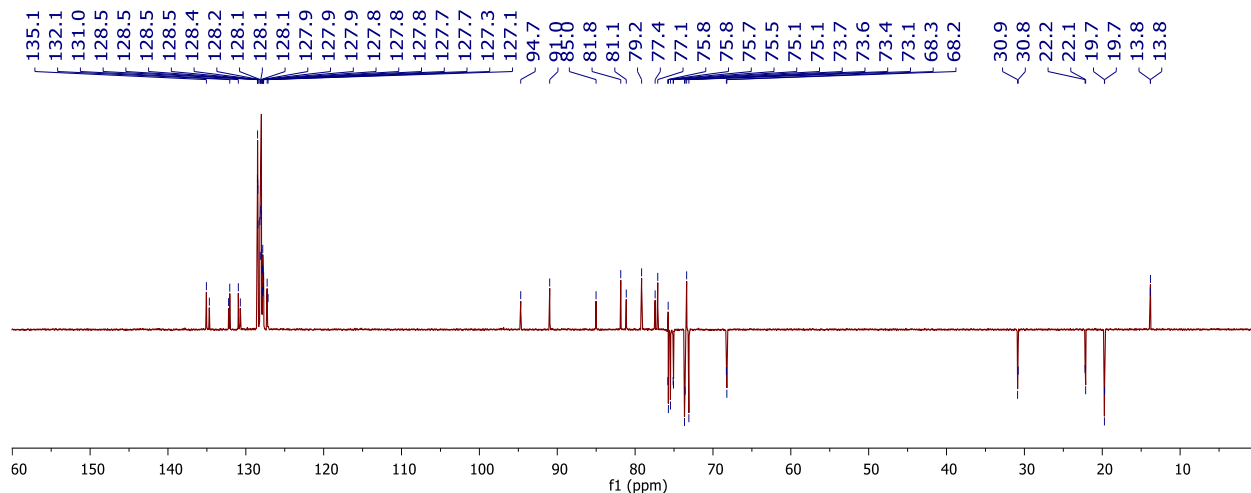
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **21f**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21f**

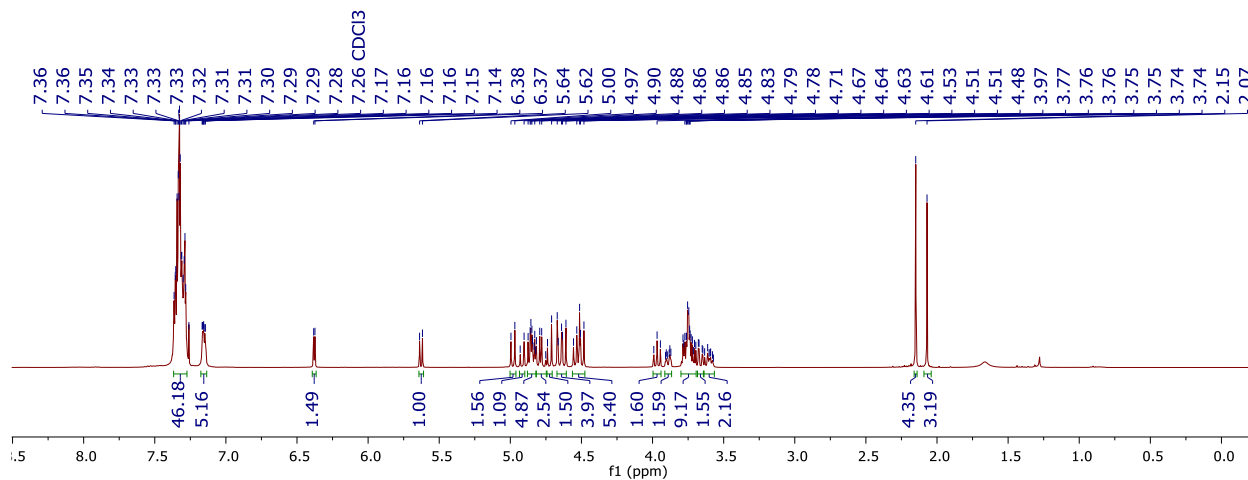


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21f**

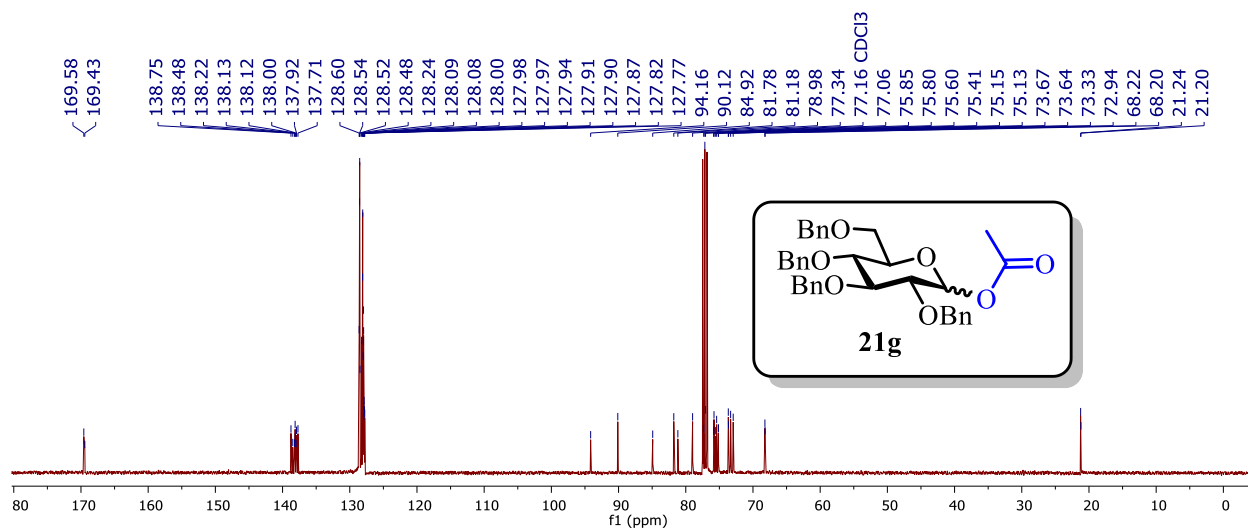


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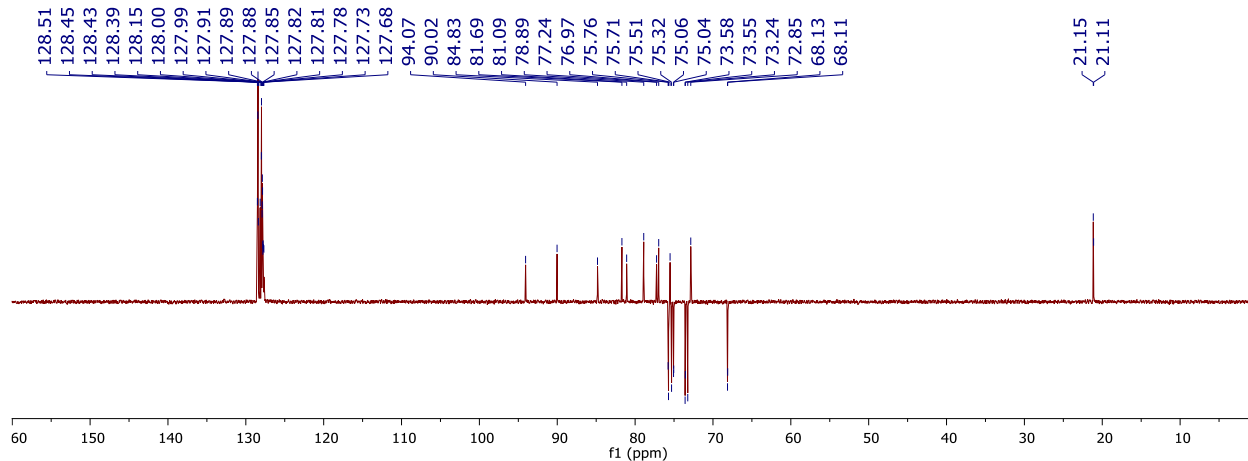
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **21g**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21g**

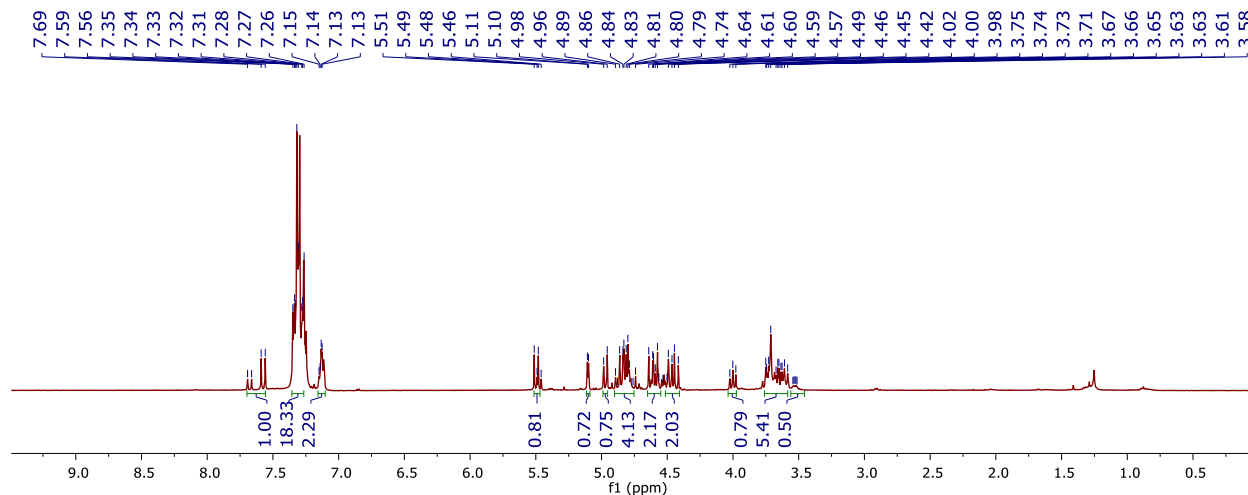


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **21g**

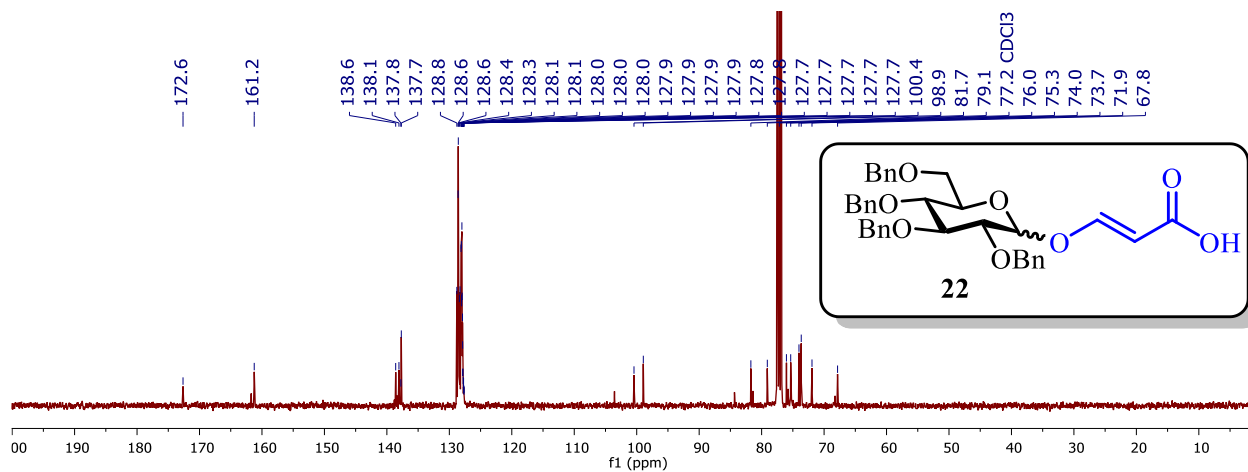


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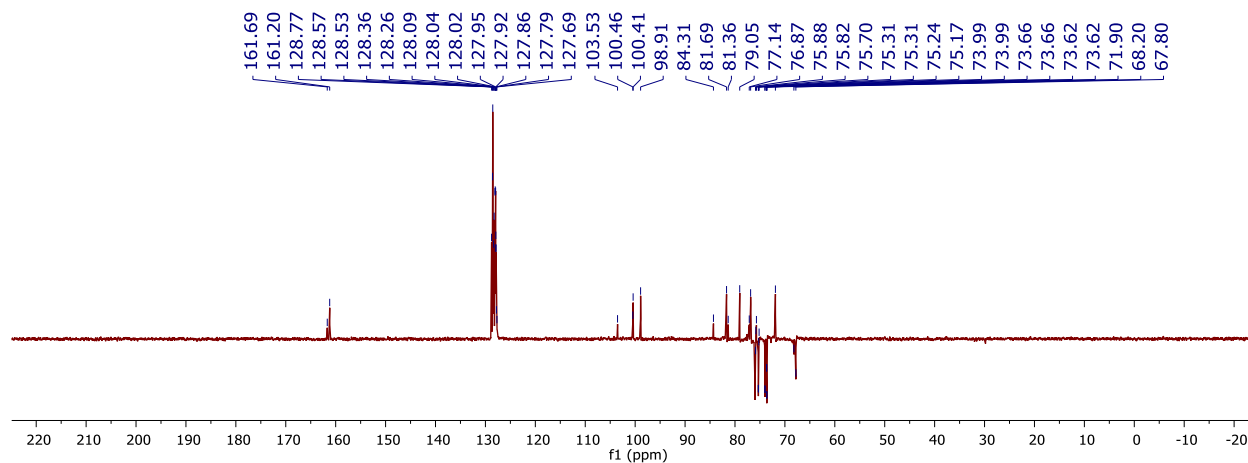
^1H NMR Spectrum (400.0 MHz, CDCl_3) of compound 22



^{13}C NMR Spectrum (100.0 MHz, CDCl_3) of compound 22

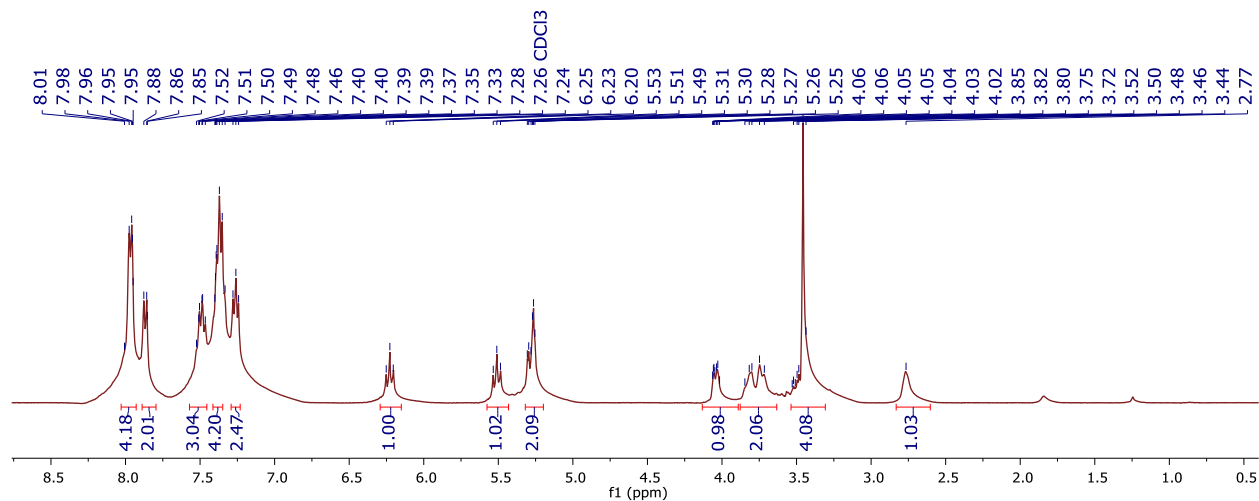


DEPT NMR Spectrum (100.0 MHz, CDCl_3) of compound 22

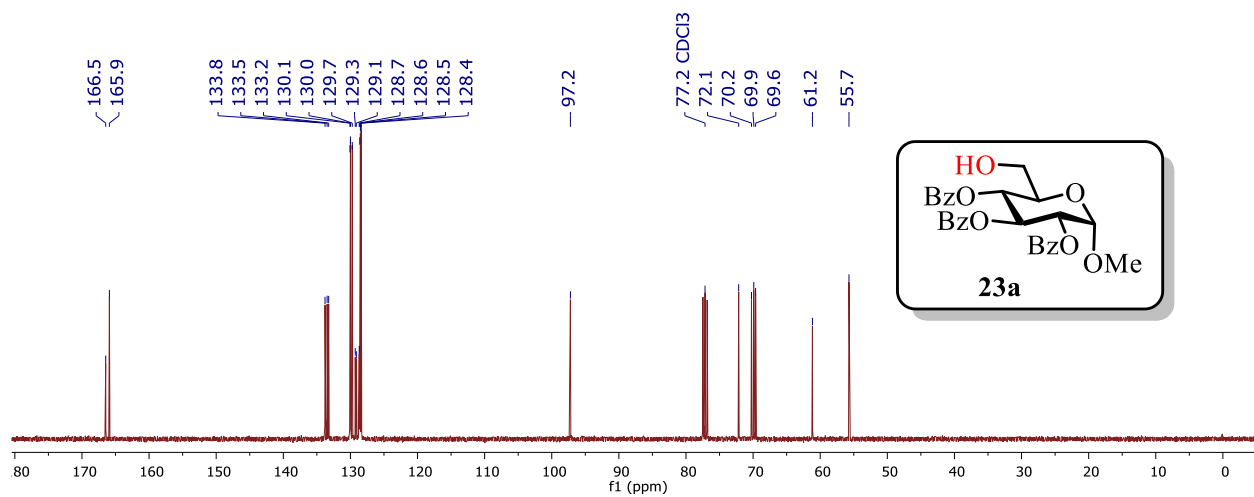


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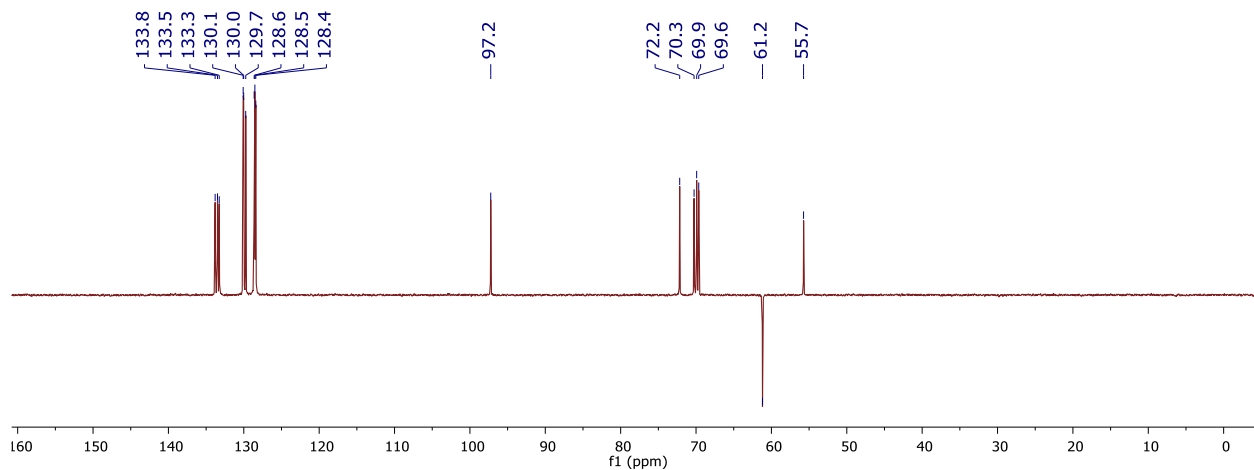
^1H NMR Spectrum (399.78 MHz, CDCl_3) of Compound **23a**



^{13}C NMR Spectrum (100.53 MHz, CDCl_3) of Compound **23a**

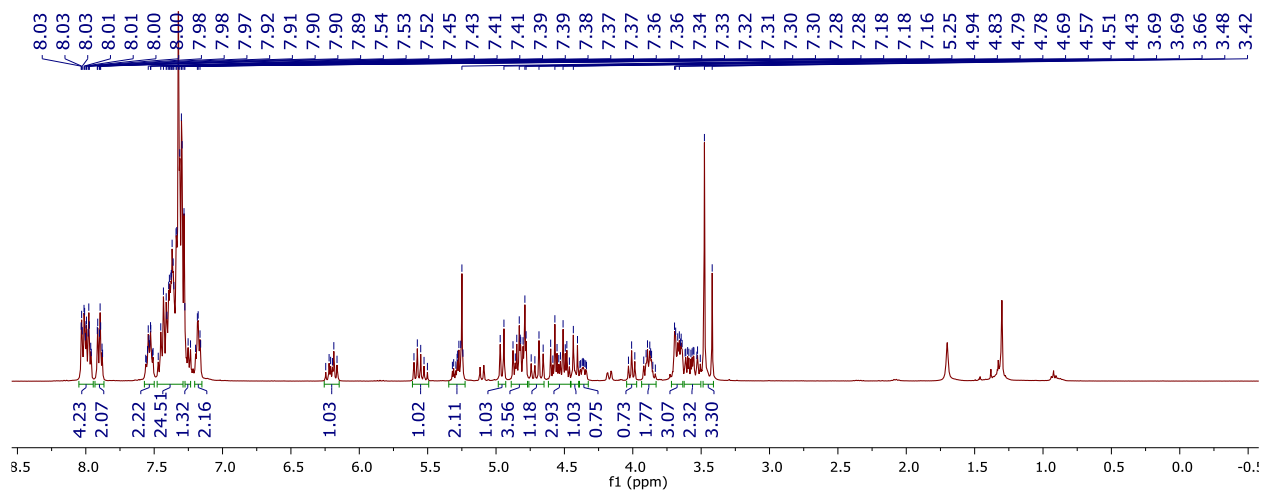


DEPT NMR Spectrum (100.53 MHz, CDCl_3) of Compound **23a**

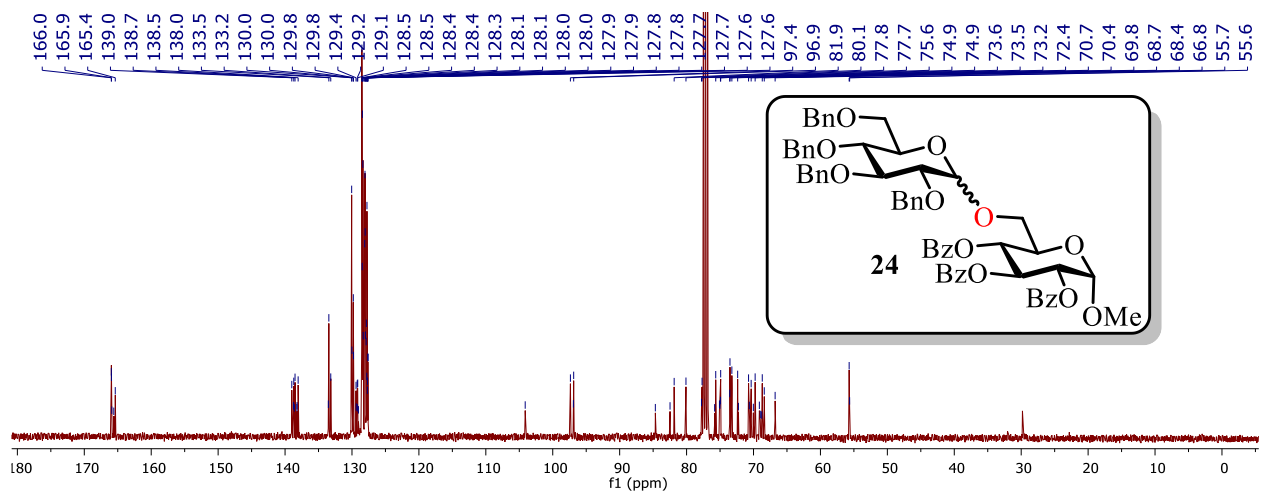


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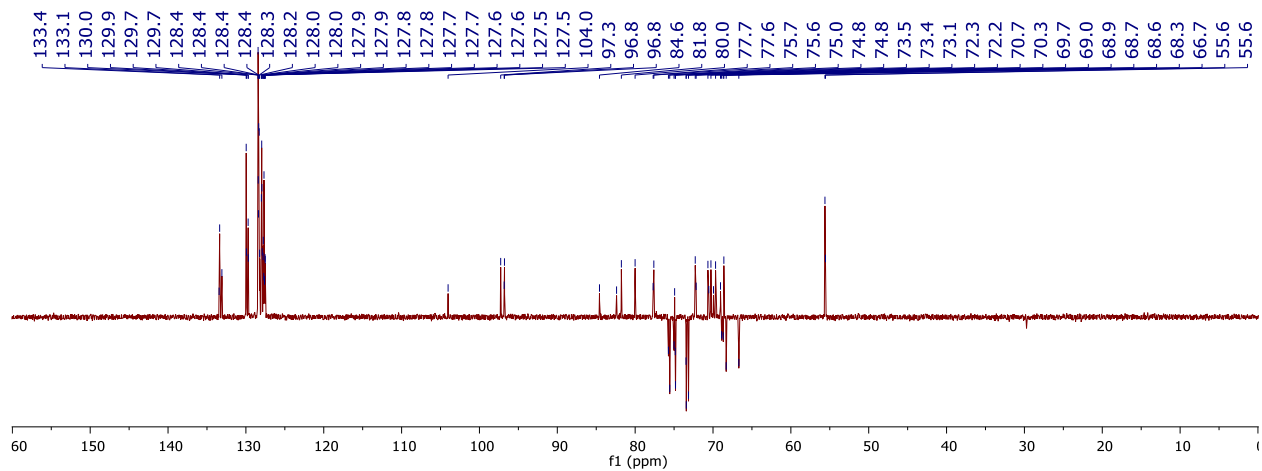
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **24**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **24**

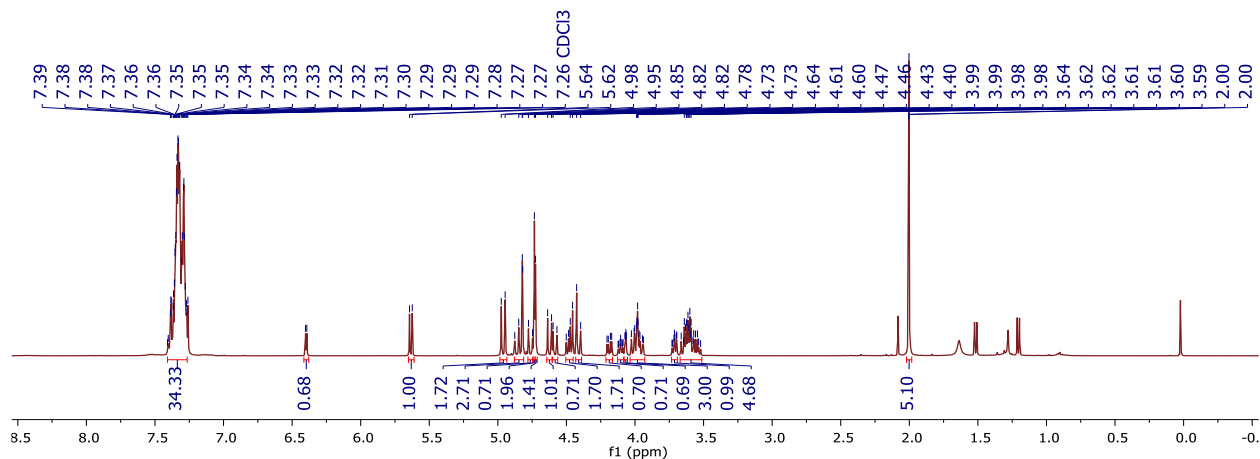


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **24**



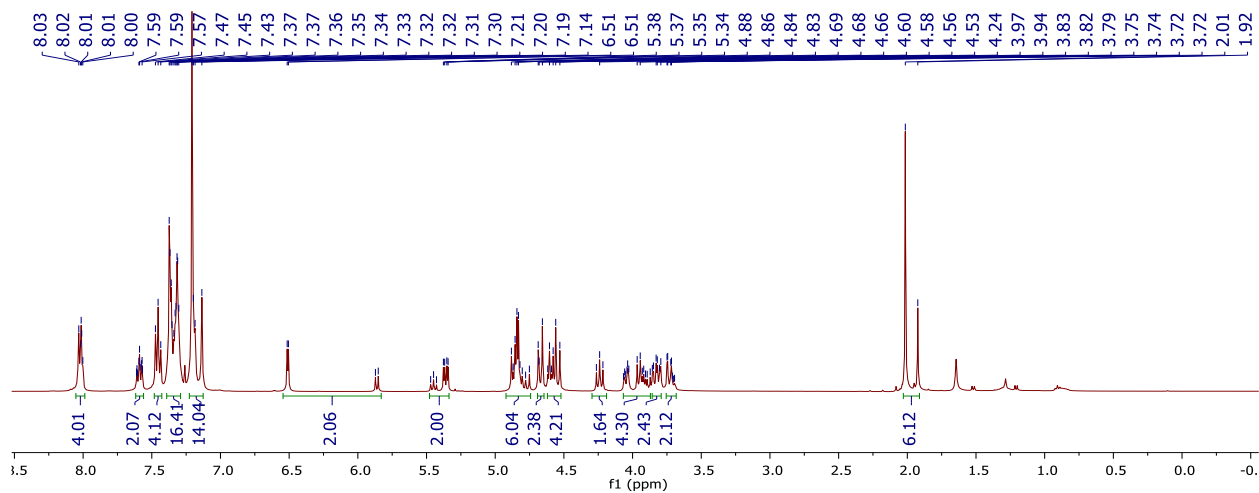
Chapter 3A

^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound 25

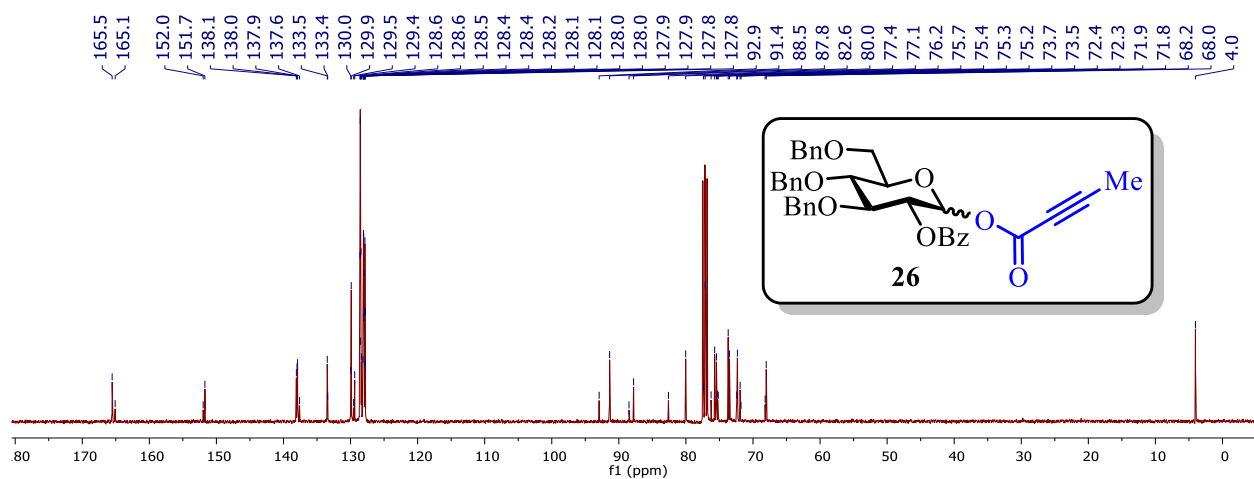


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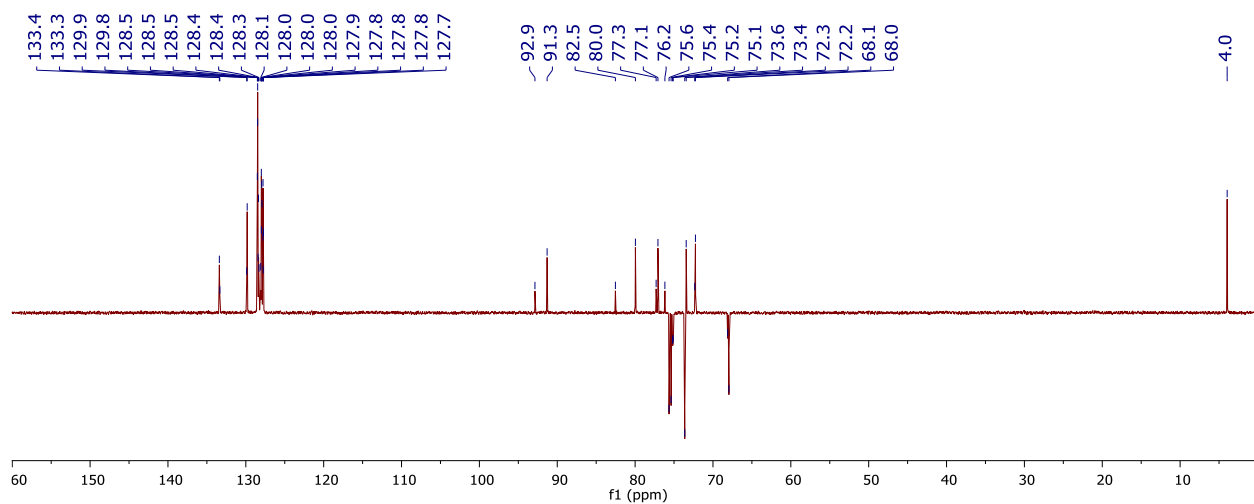
¹H NMR Spectrum (400.31 MHz, CDCl₃) of Compound **26**



¹³C NMR Spectrum (100.67 MHz, CDCl₃) of Compound **26**

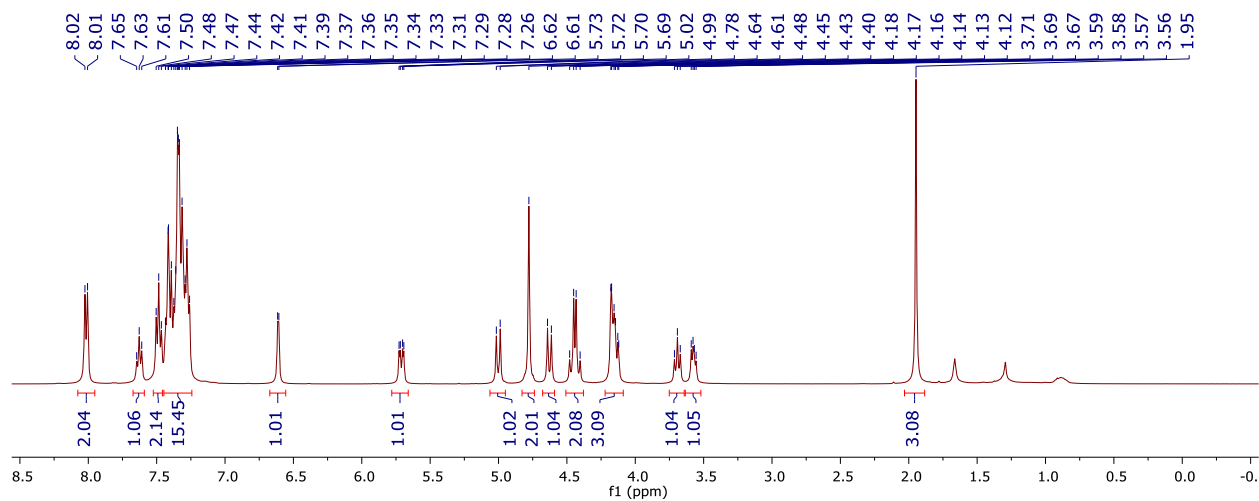


DEPT NMR Spectrum (100.67 MHz, CDCl₃) of Compound **26**

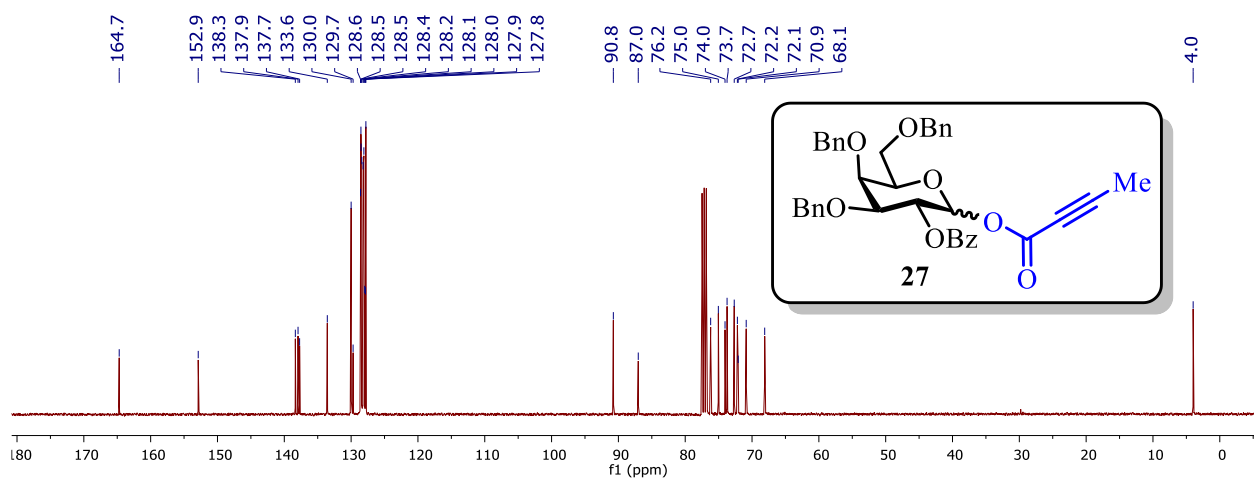


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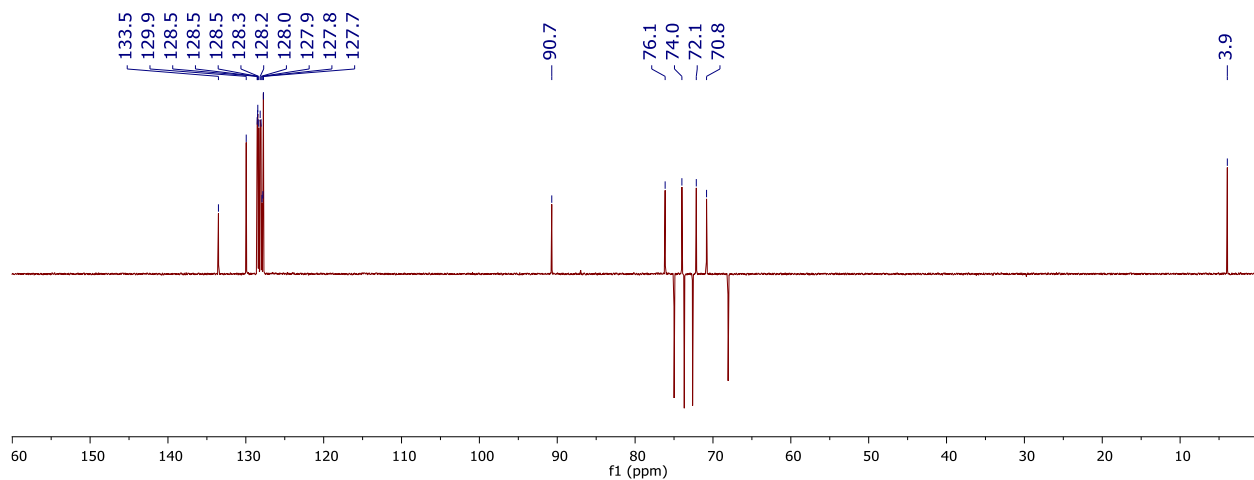
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound 27



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound 27

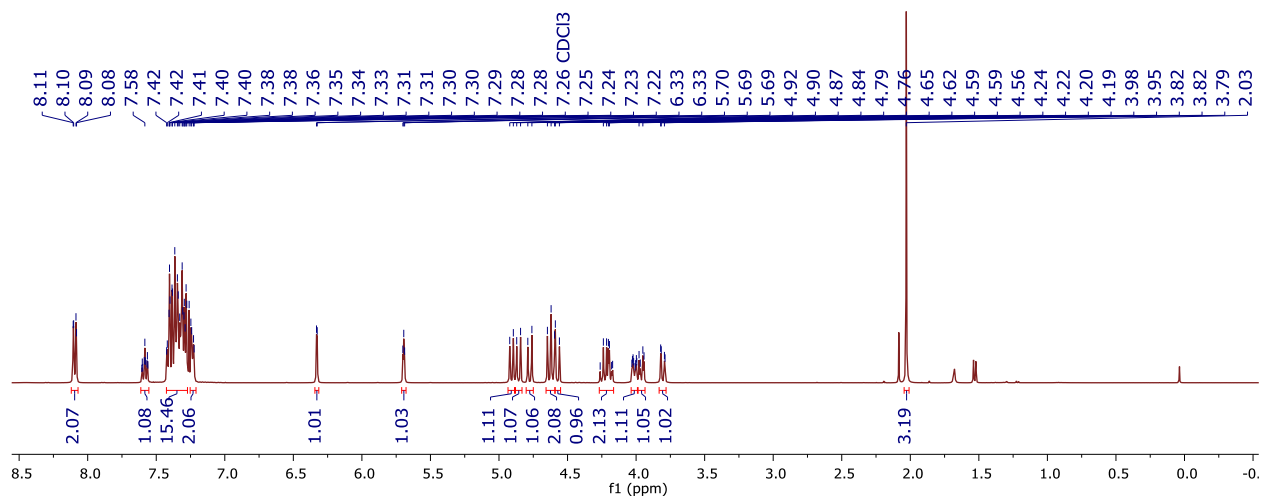


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound 27

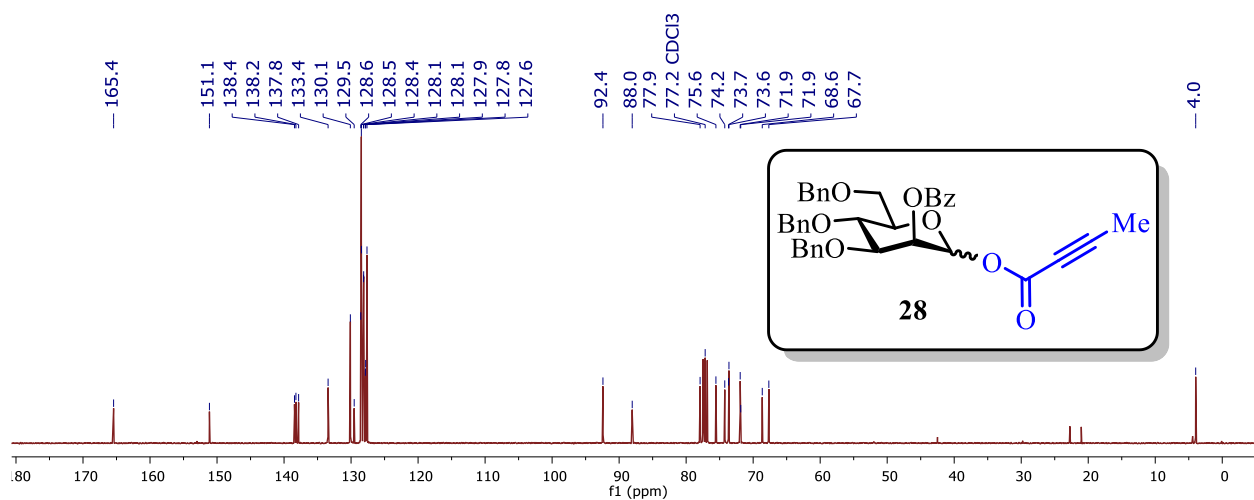


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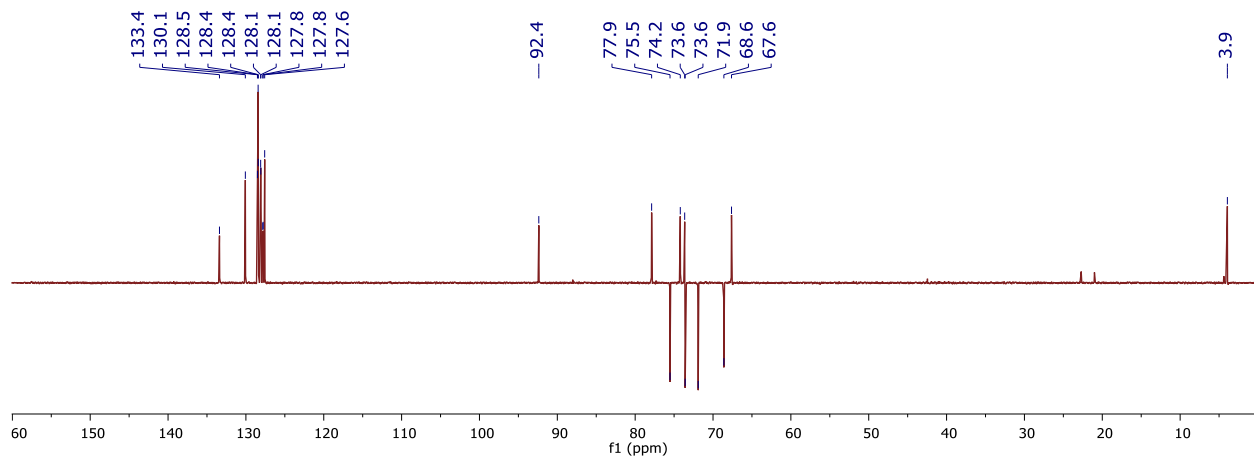
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **28**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **28**

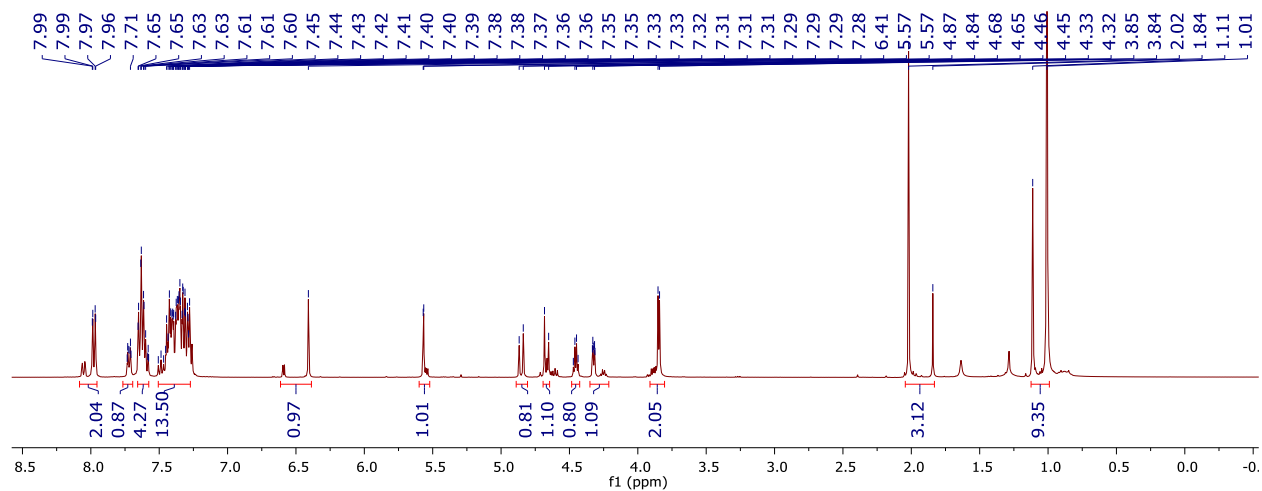


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **28**

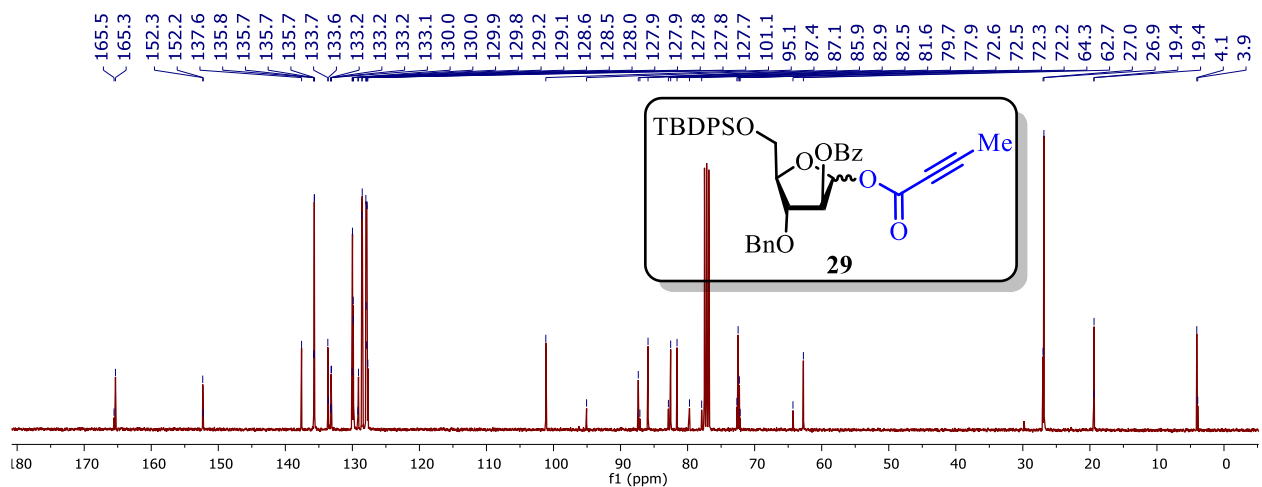


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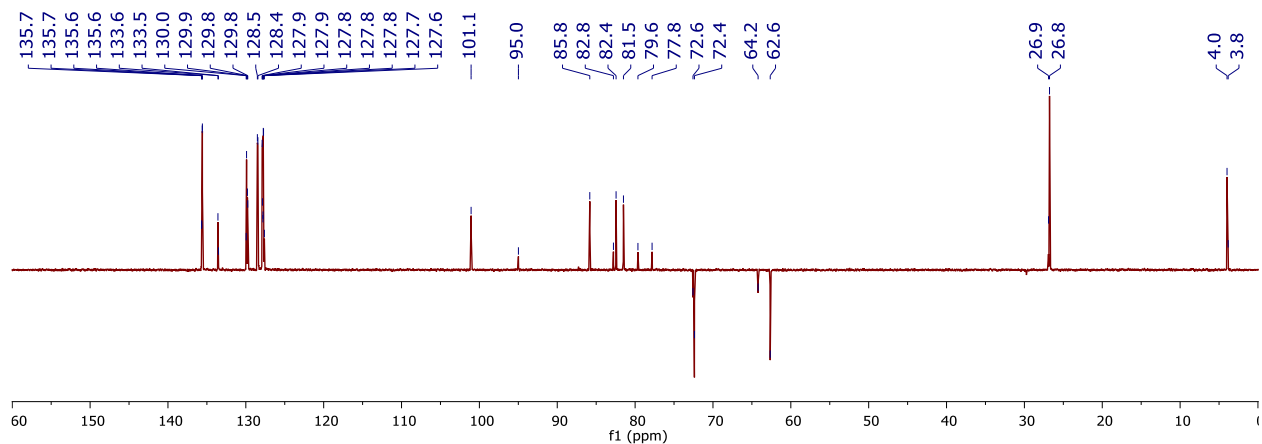
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **29**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **29**

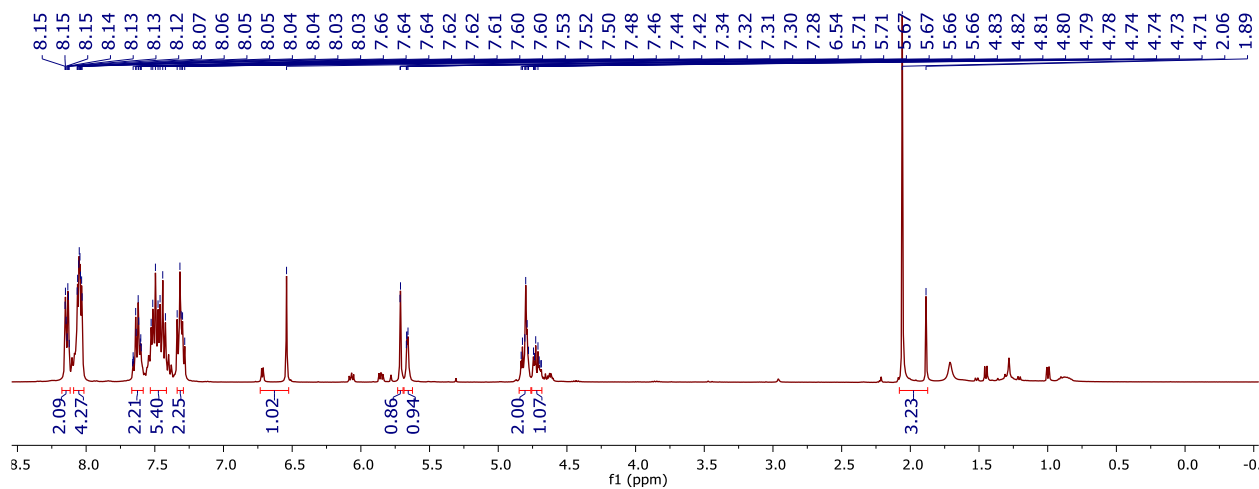


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **29**

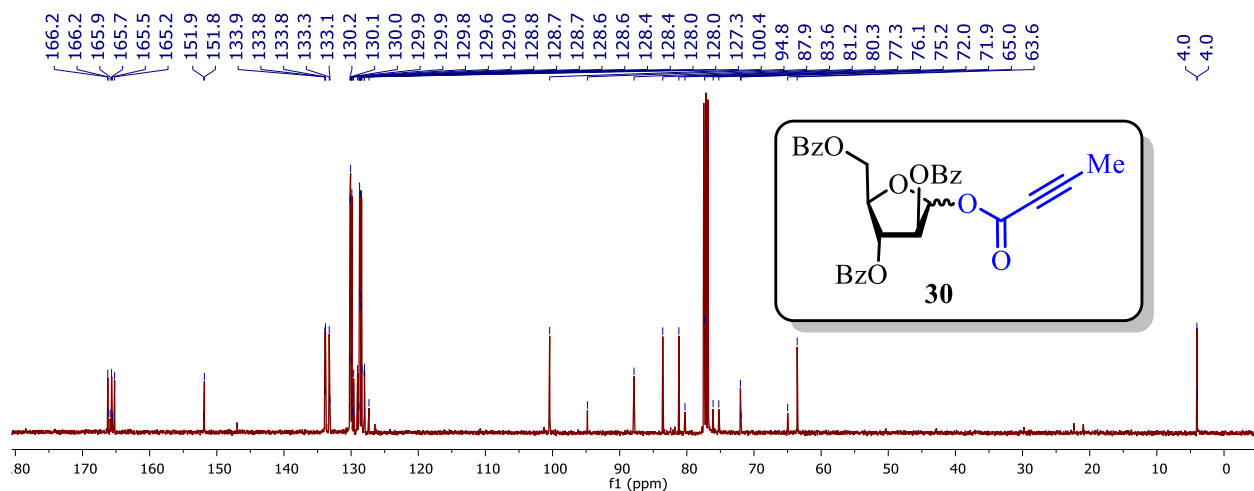


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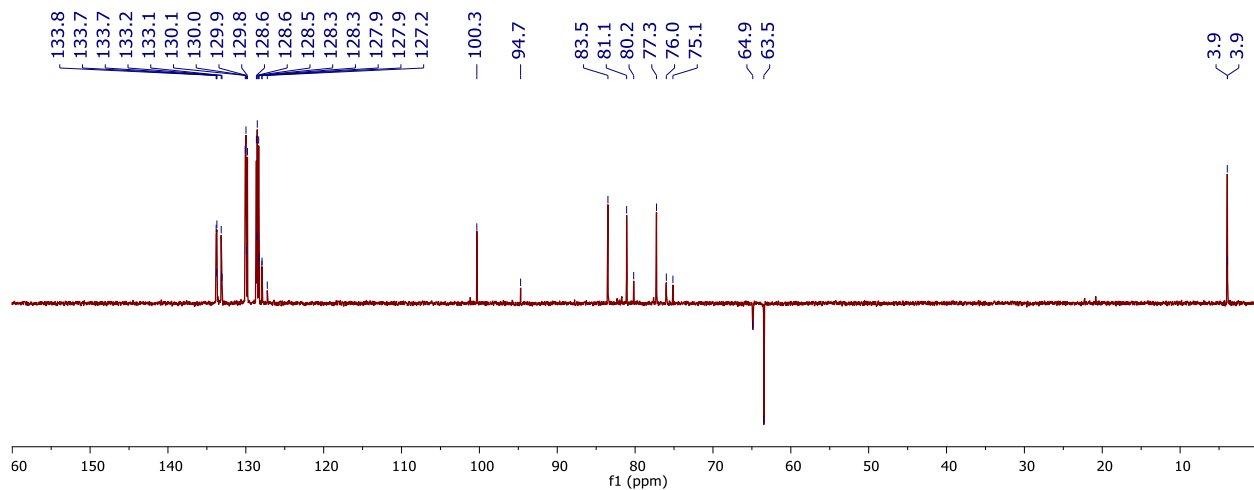
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **30**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **30**

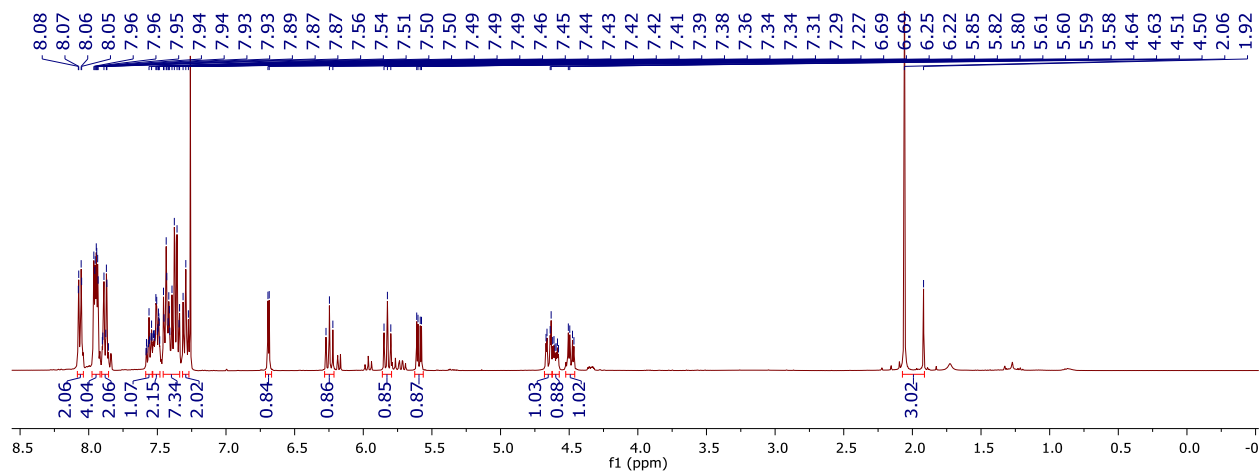


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **30**

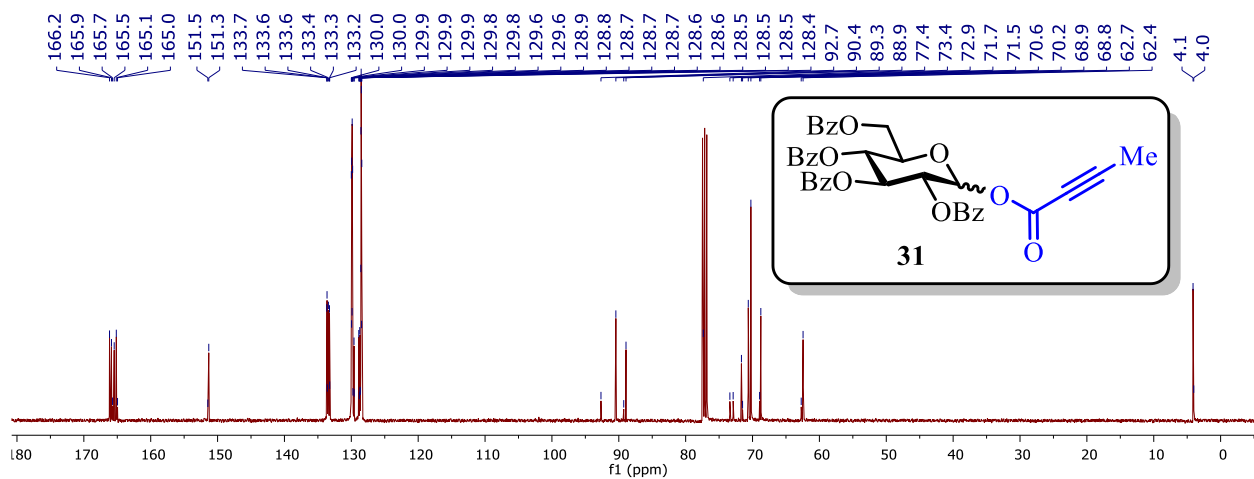


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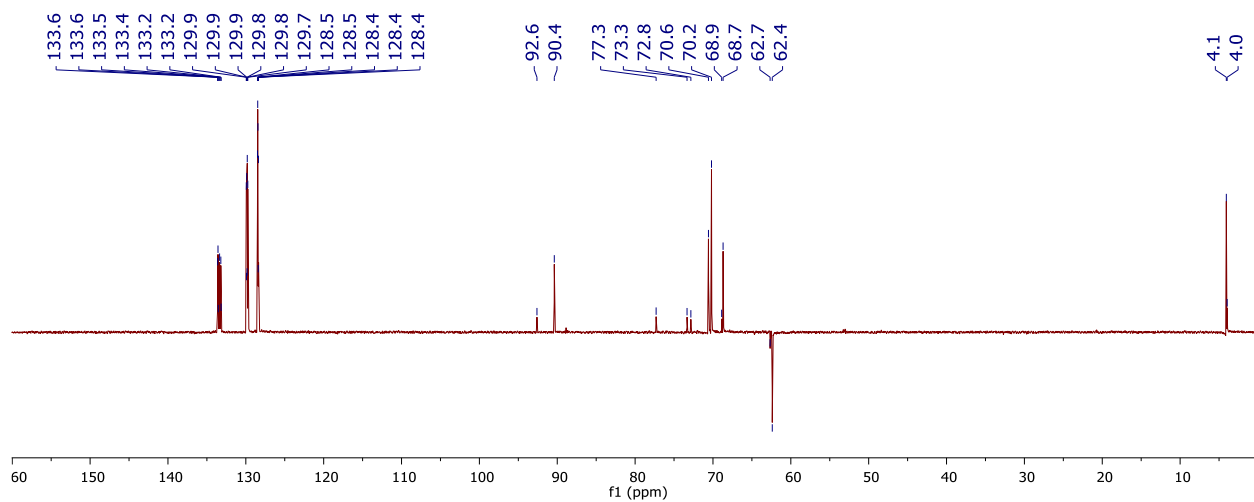
¹H NMR Spectrum (400.31 MHz, CDCl₃) of Compound **31**



¹³C NMR Spectrum (100.67 MHz, CDCl₃) of Compound **31**

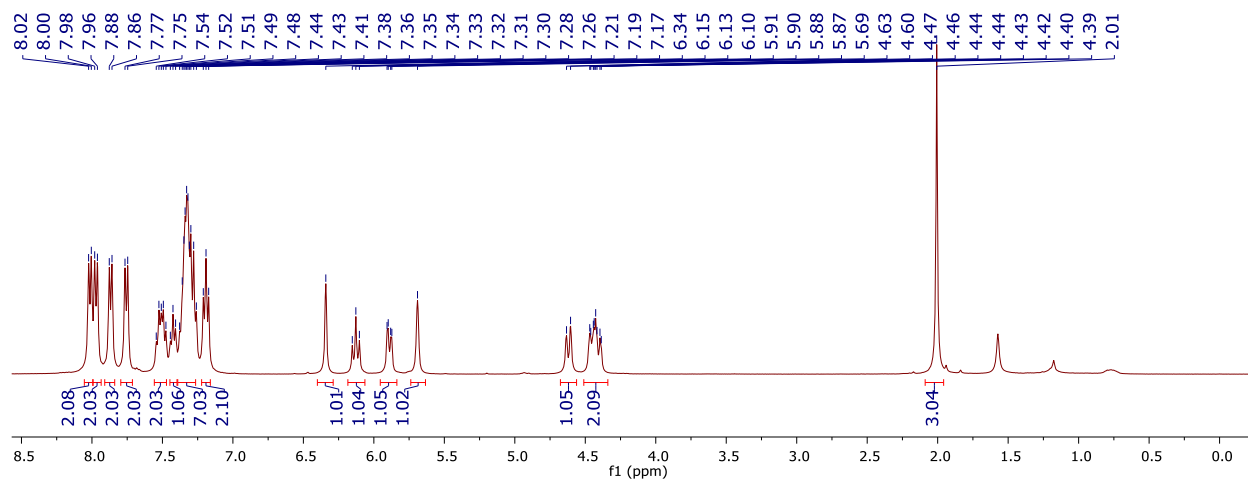


DEPT NMR Spectrum (100.67 MHz, CDCl₃) of Compound **31**

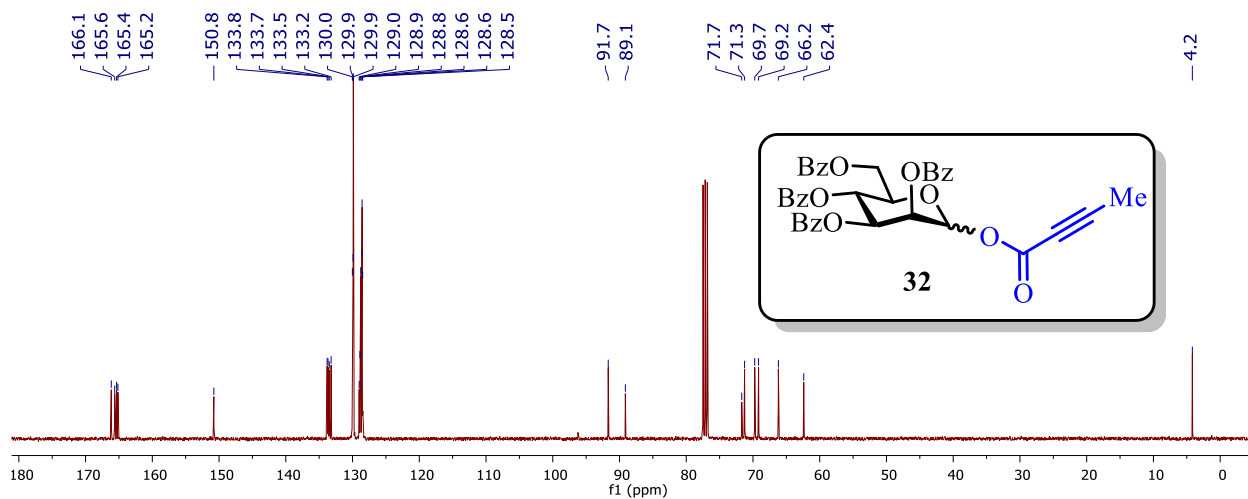


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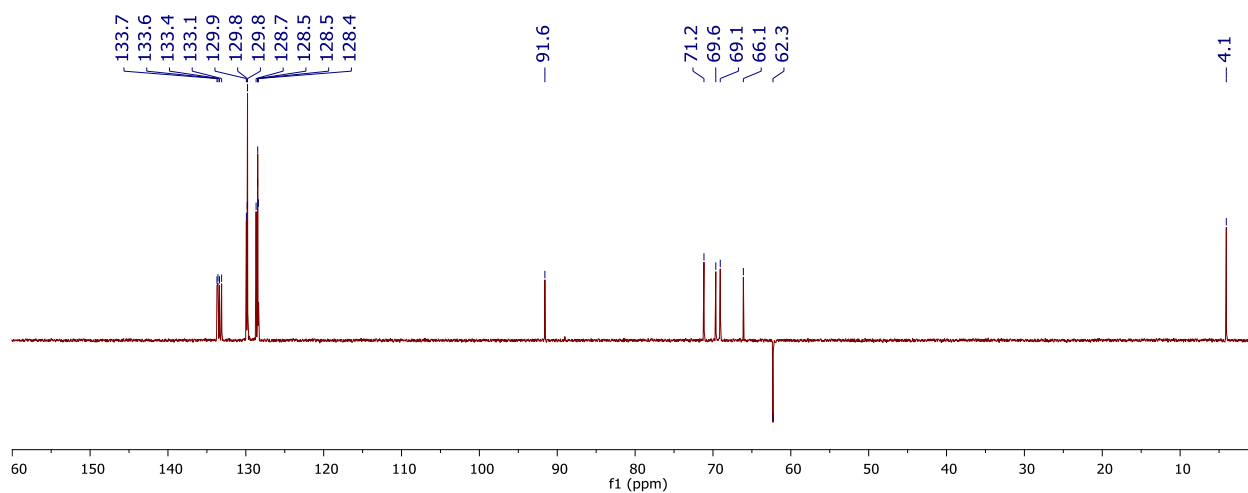
¹H NMR Spectrum (400.31 MHz, CDCl₃) of Compound **32**



¹³C NMR Spectrum (100.67 MHz, CDCl₃) of Compound **32**

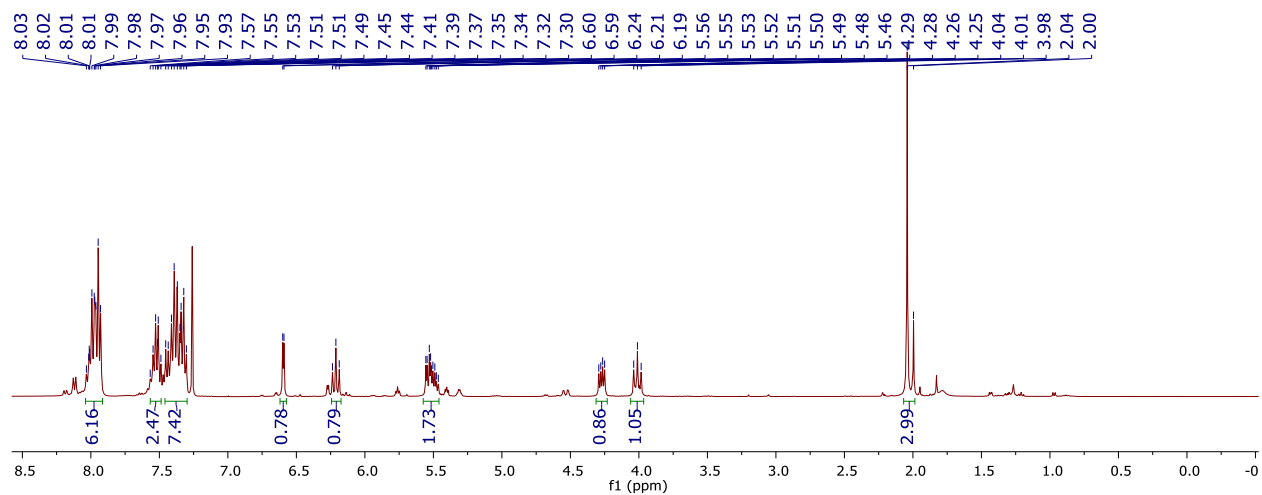


DEPT NMR Spectrum (100.67 MHz, CDCl₃) of Compound **32**

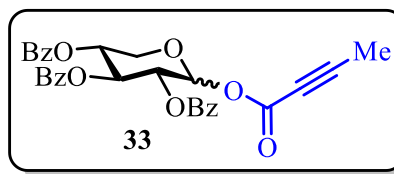
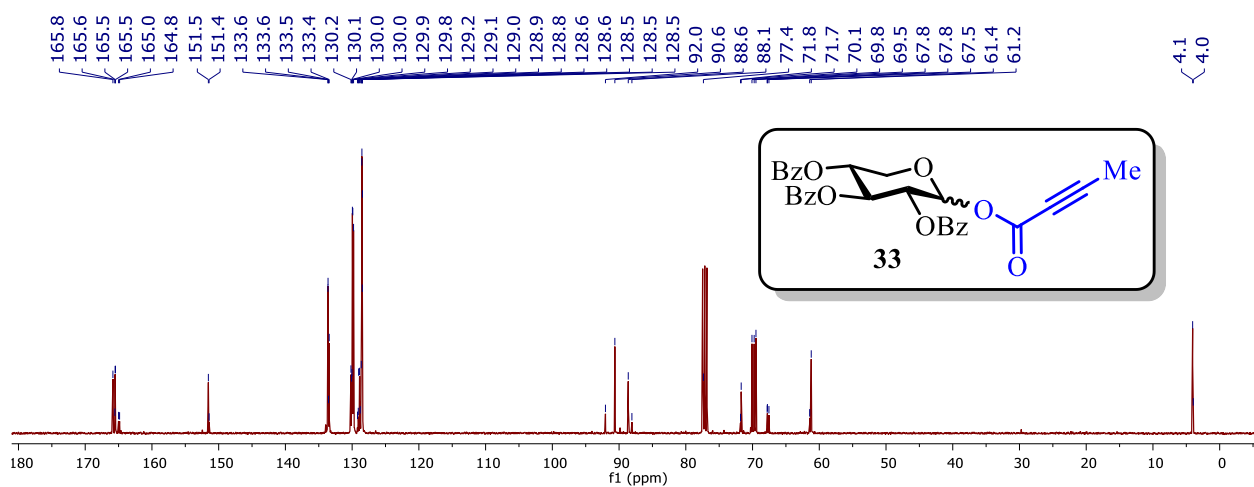


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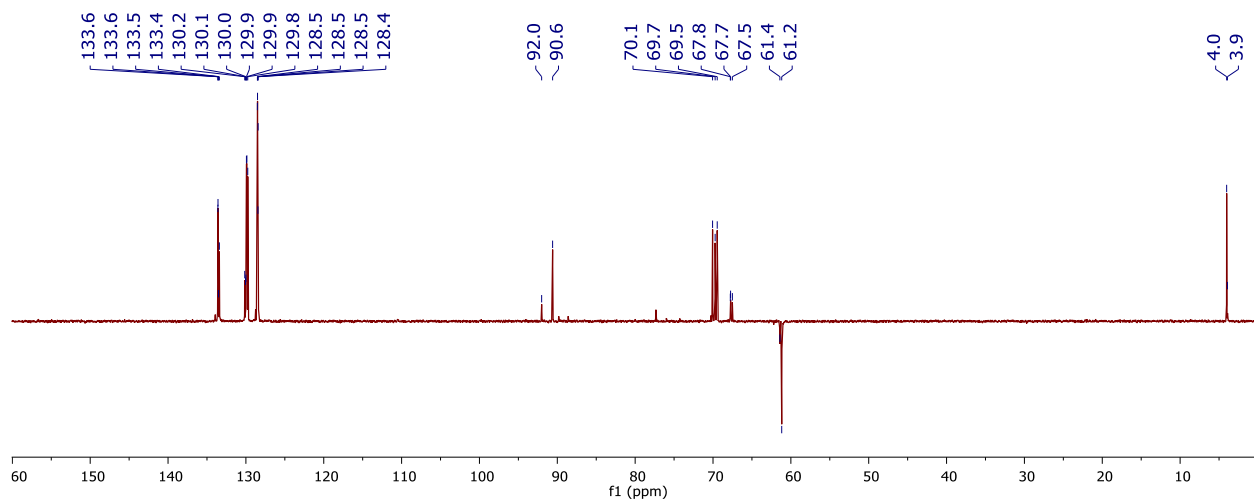
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **33**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **33**

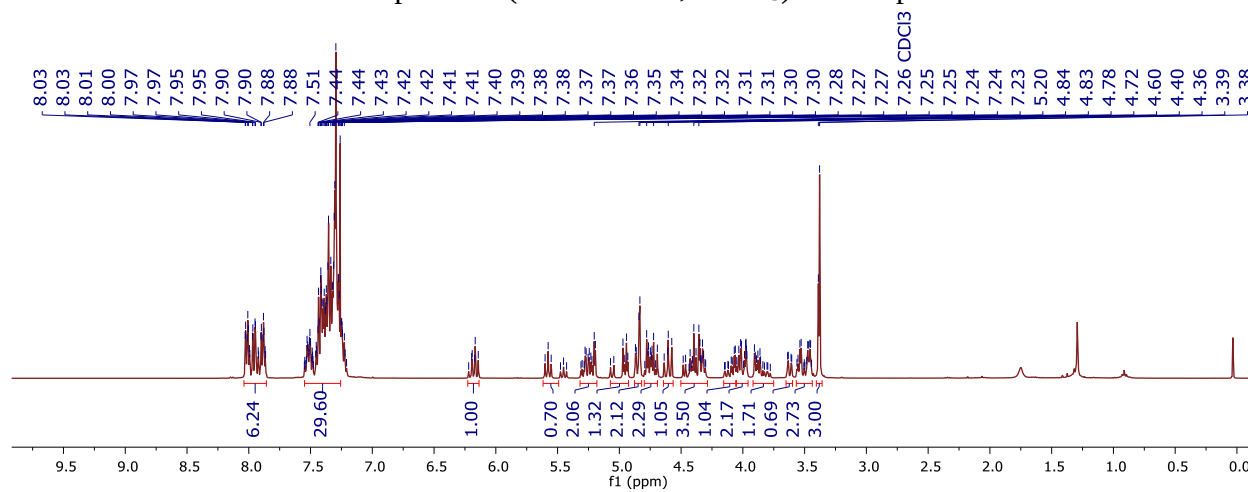


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **33**

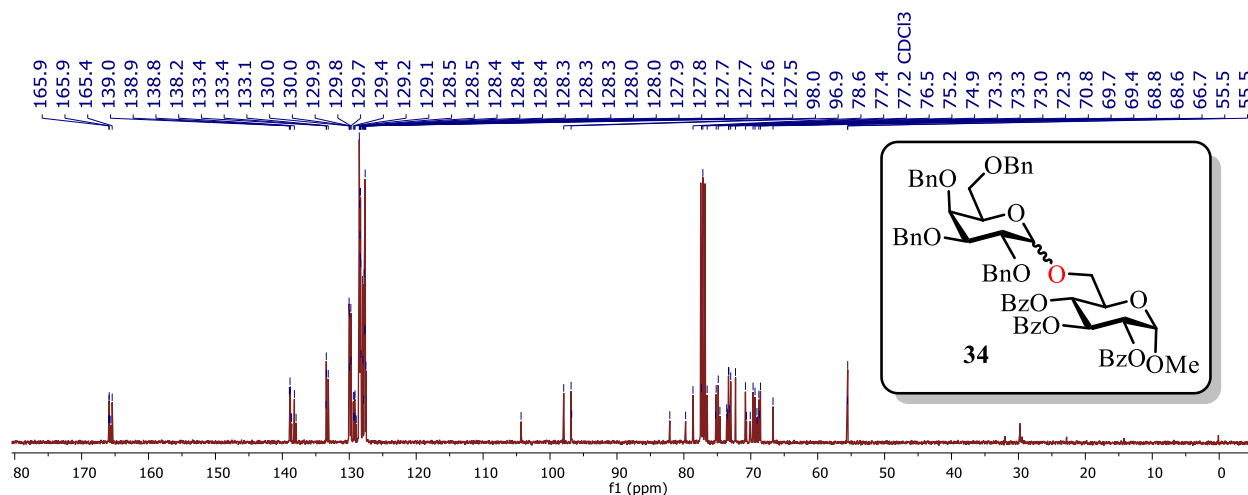


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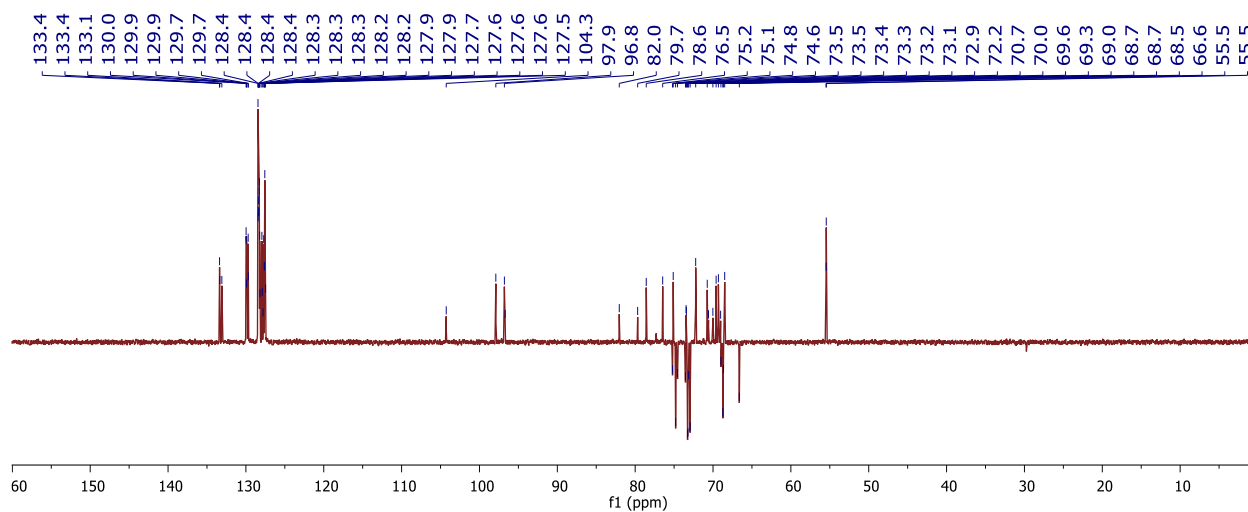
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **34**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **34**

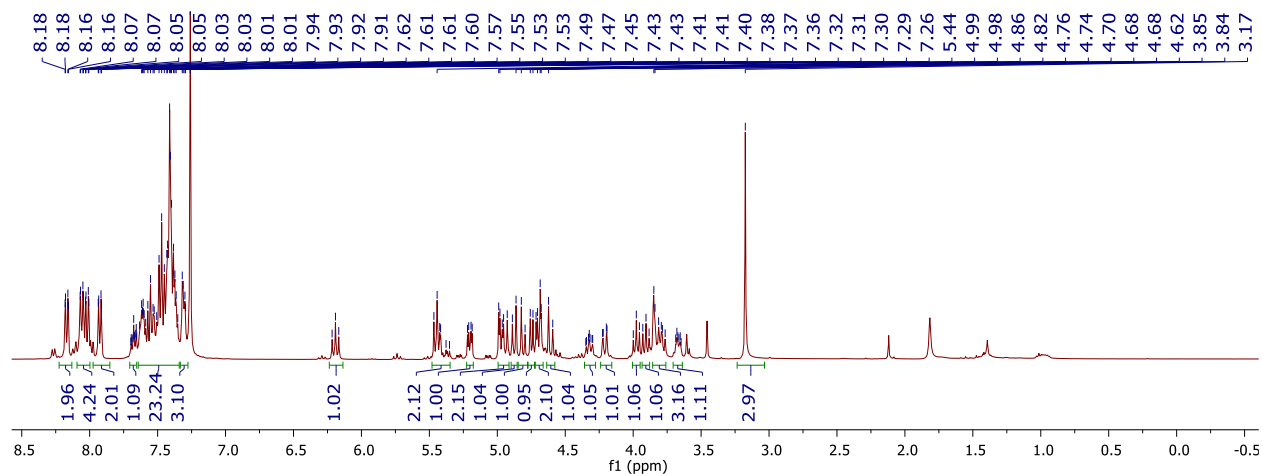


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **34**

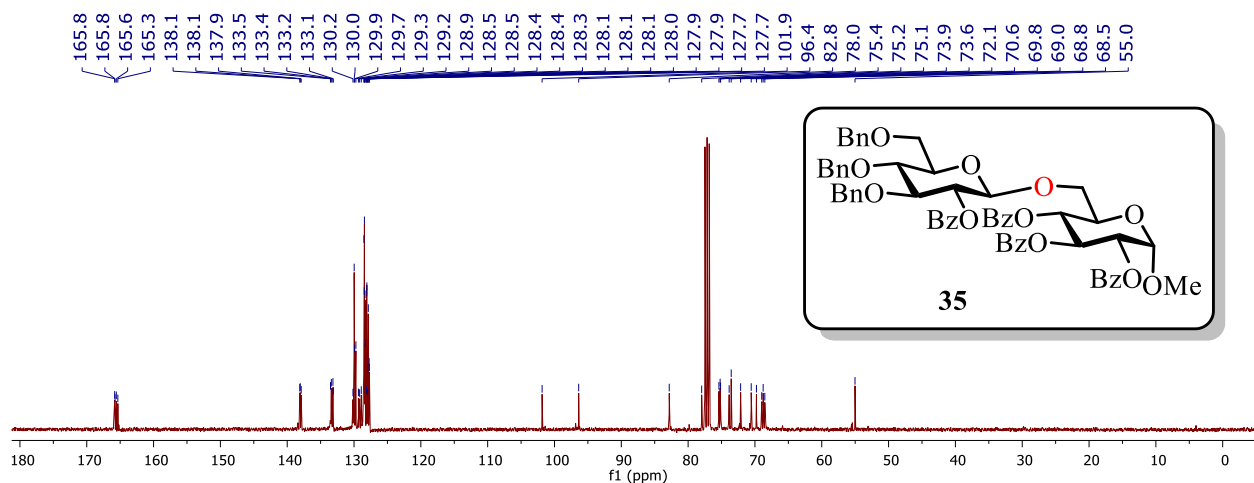


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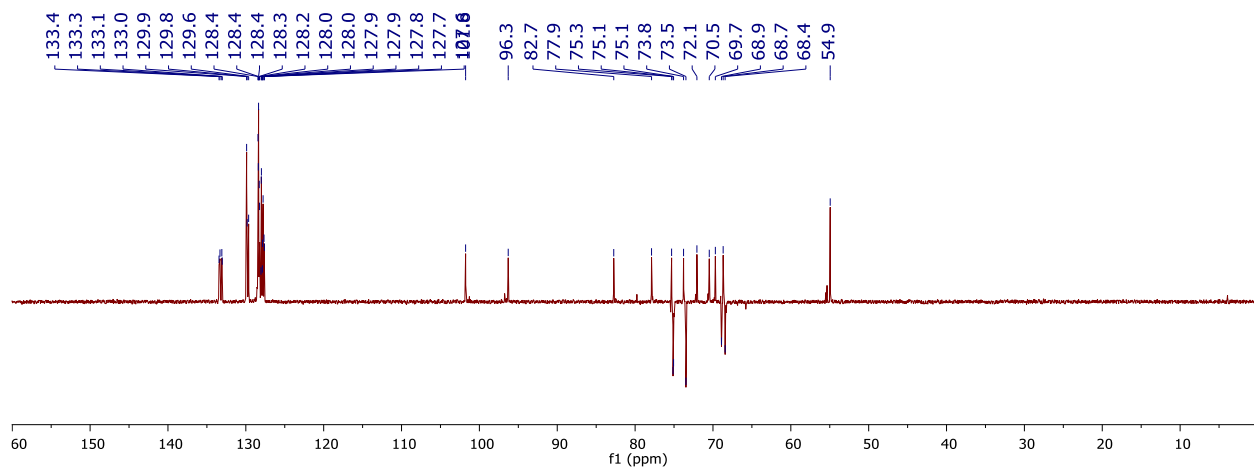
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **35**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **35**

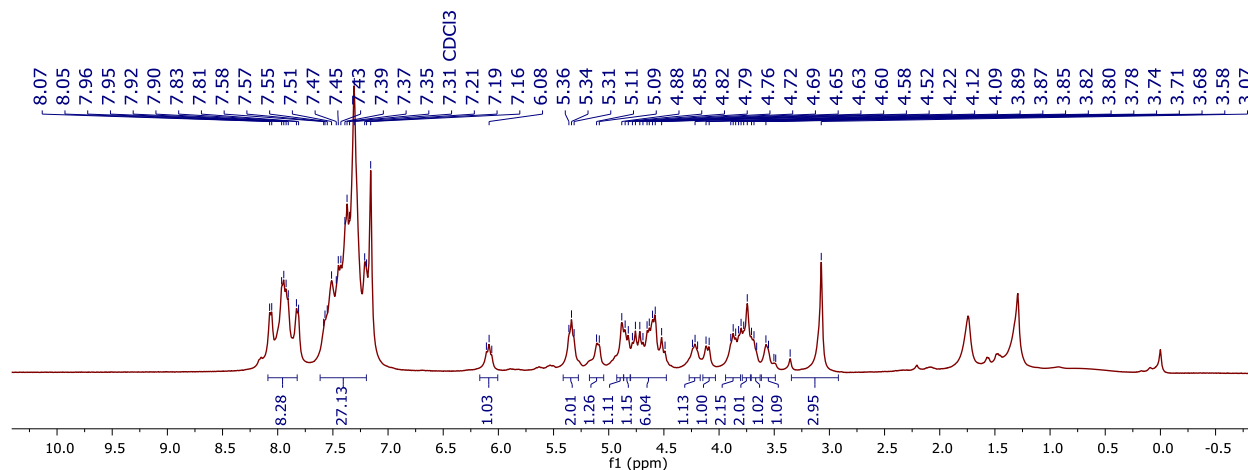


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **35**

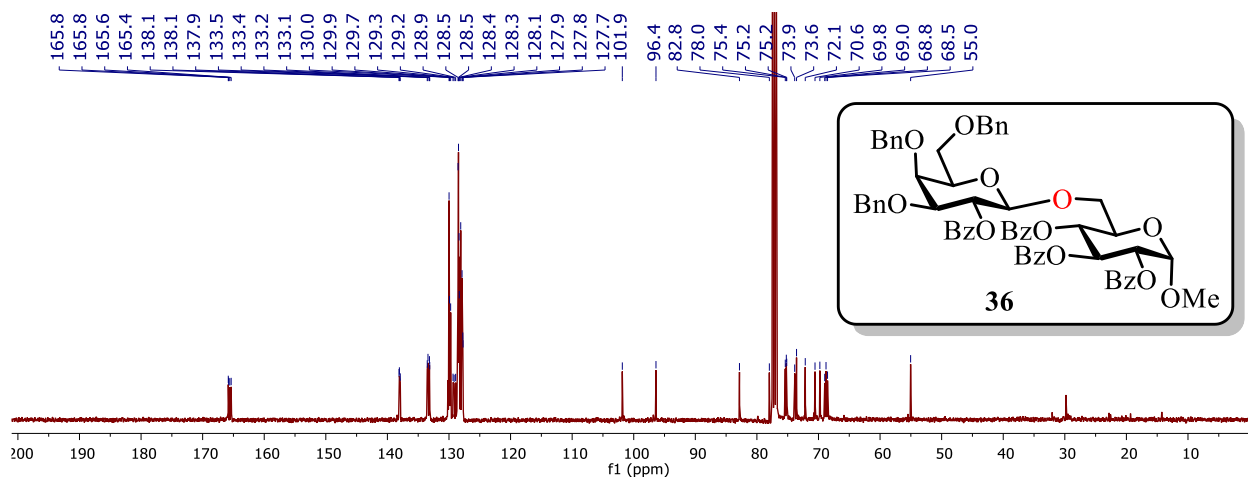


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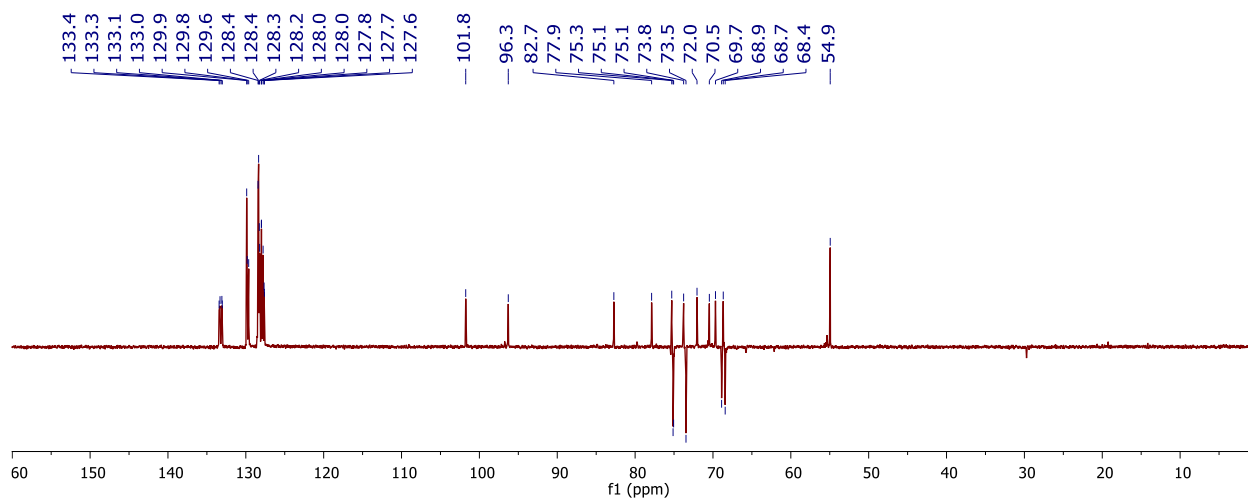
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **36**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **36**

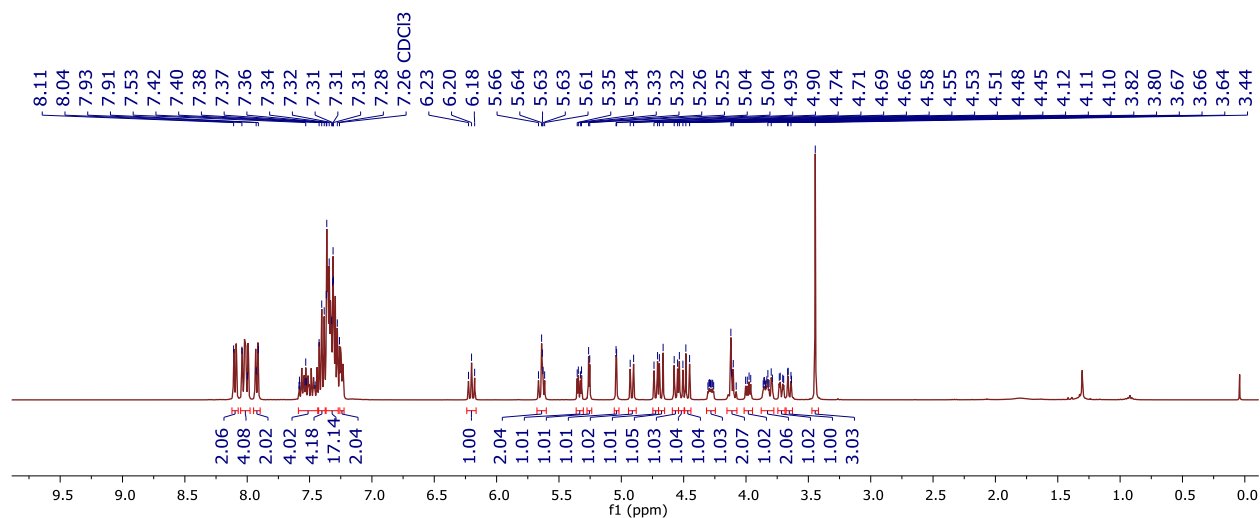


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **36**

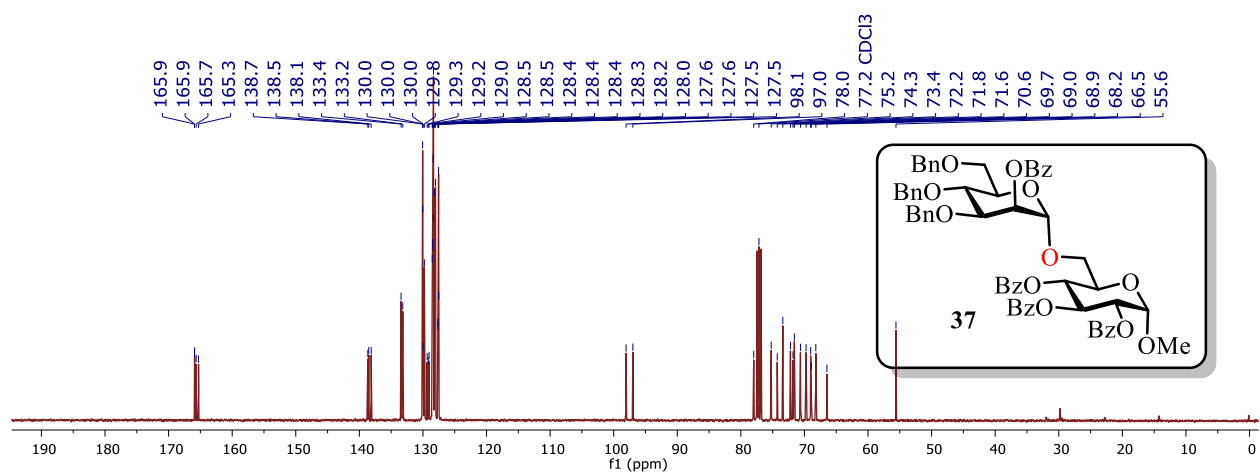


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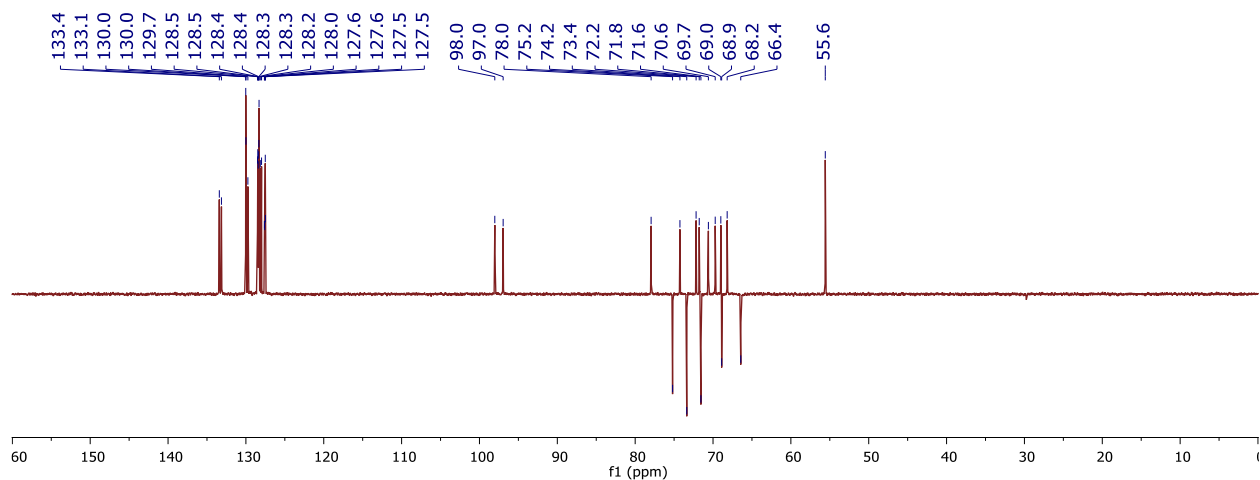
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **37**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **37**

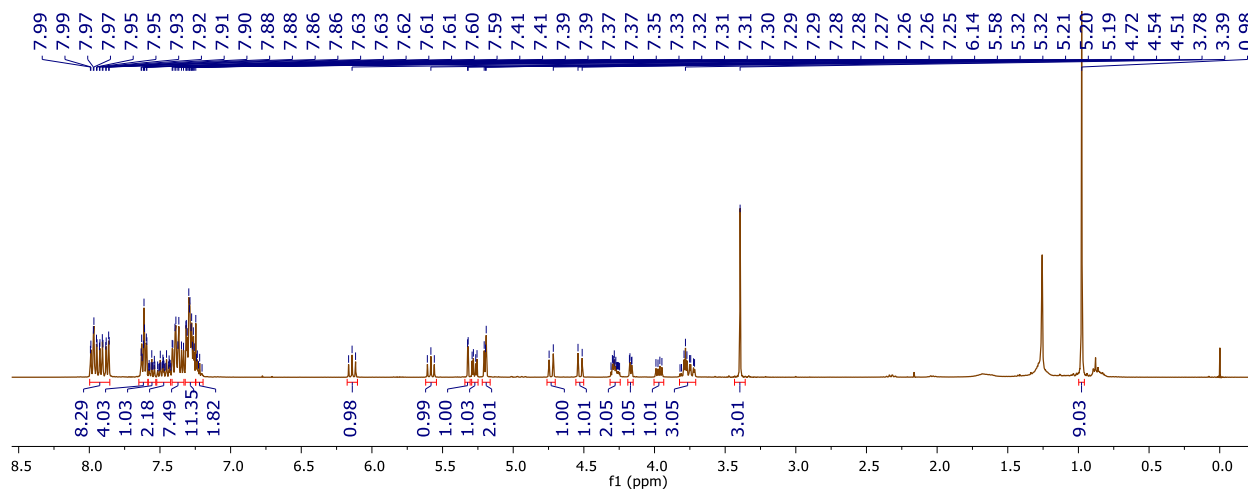


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **37**

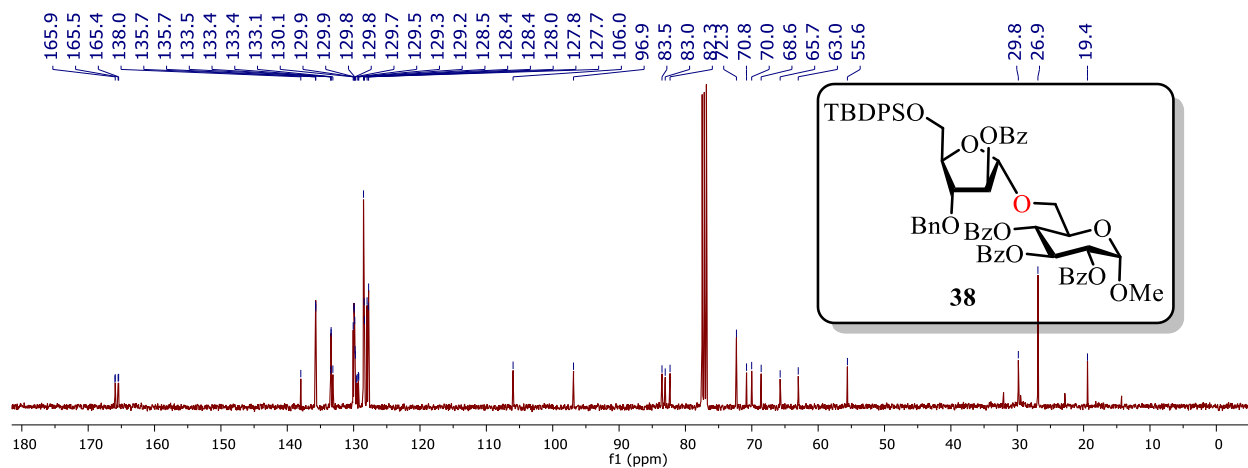


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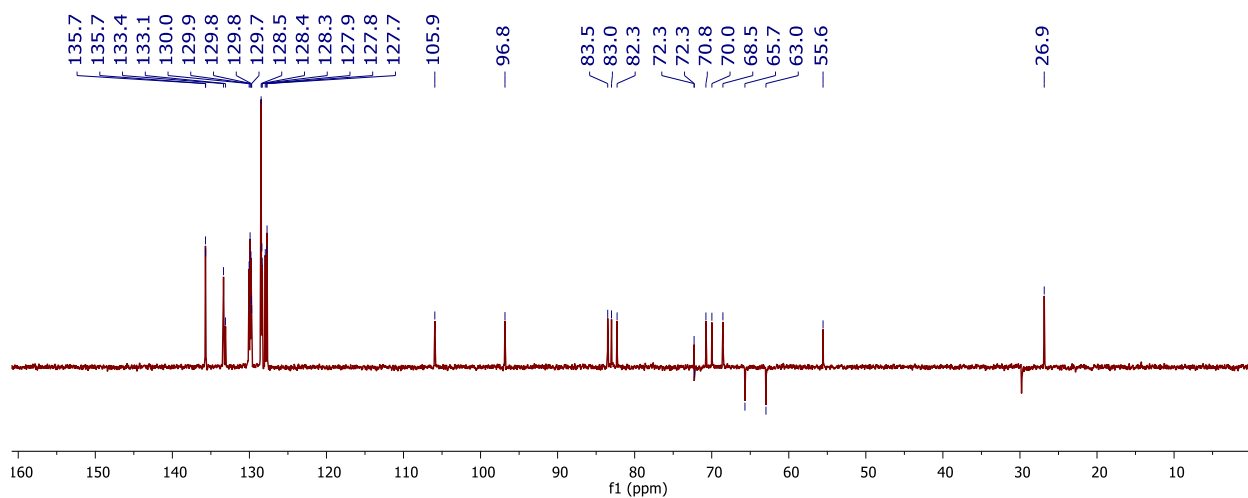
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **38**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **38**

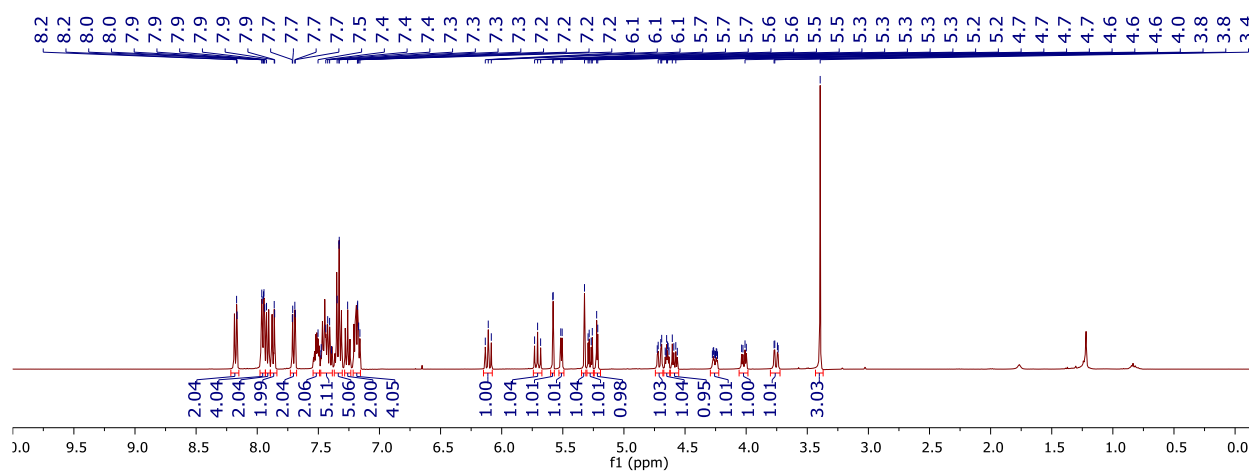


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **38**

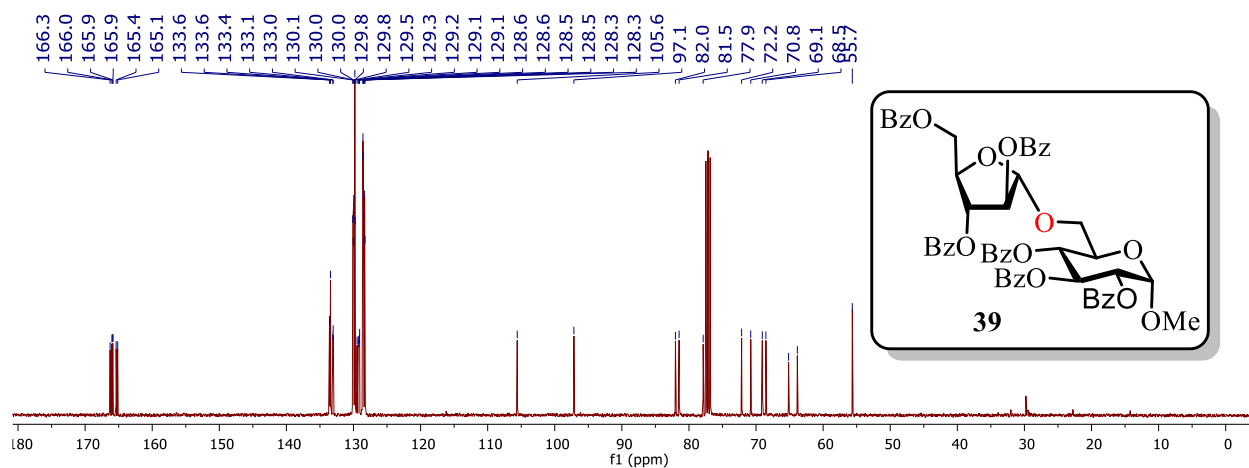


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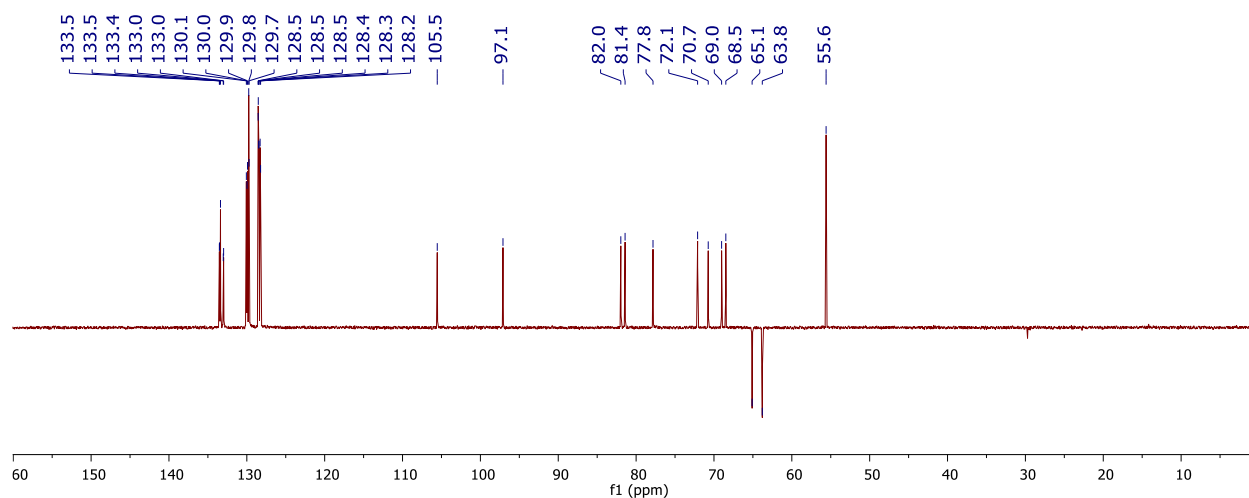
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **39**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **39**

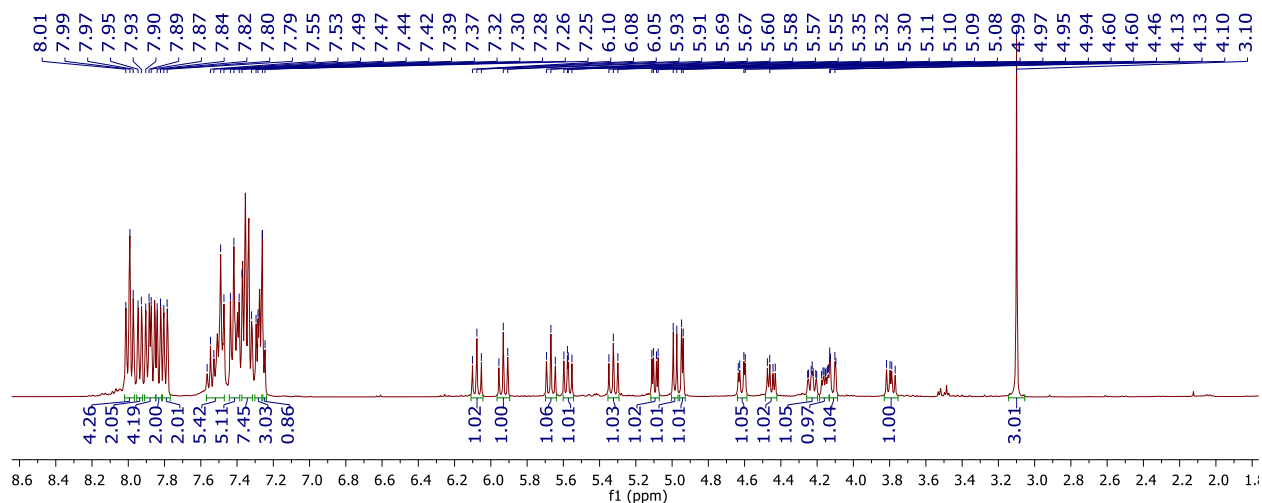


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **39**

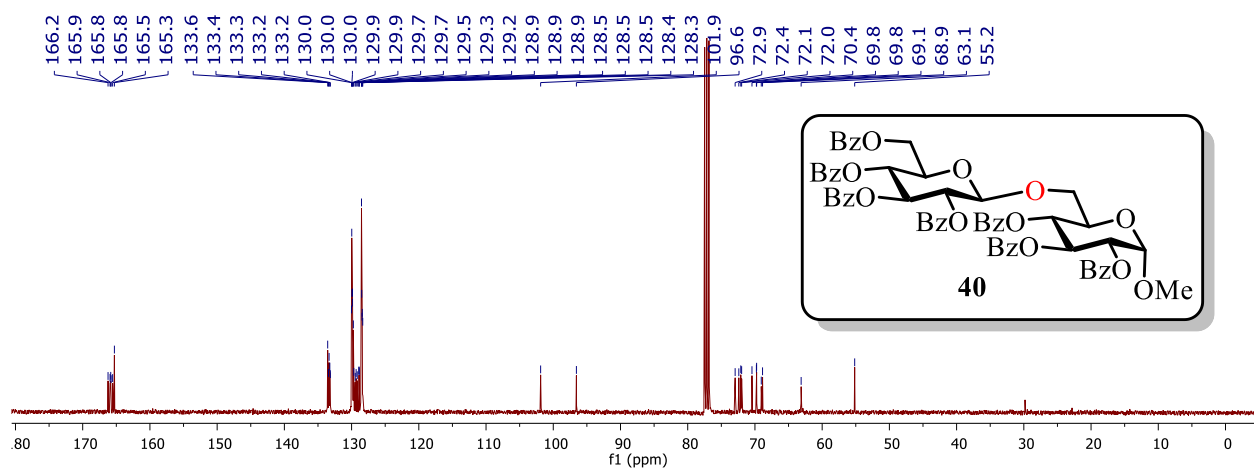


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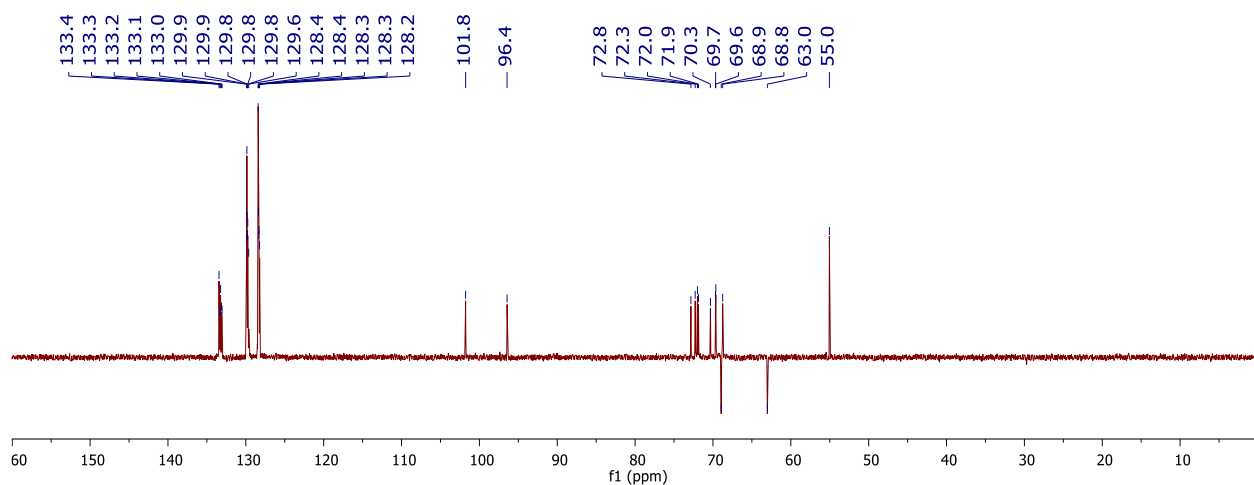
^1H NMR Spectrum (399.78 MHz, CDCl_3) of Compound **40**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **40**

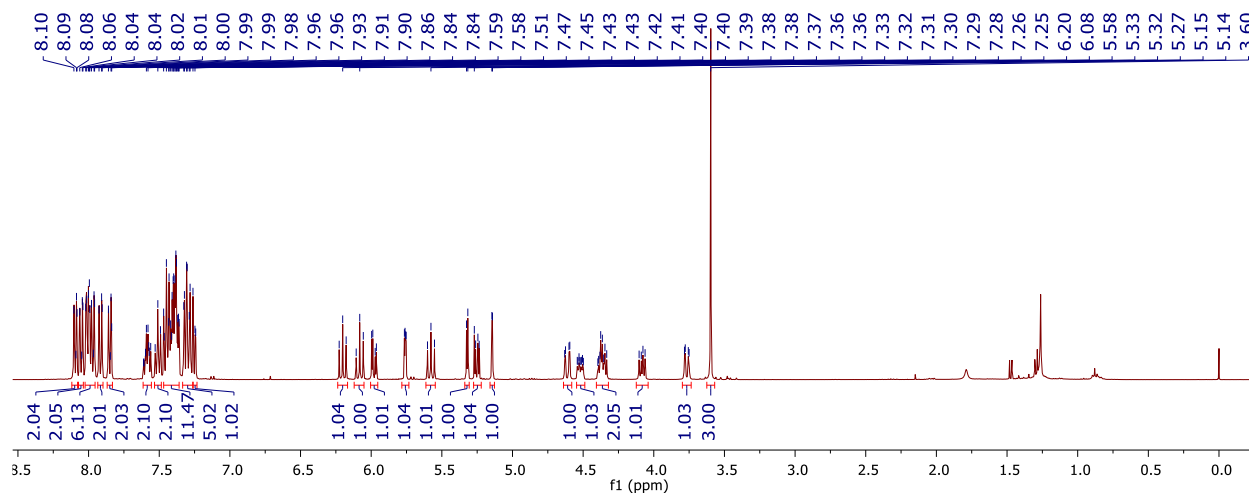


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **40**

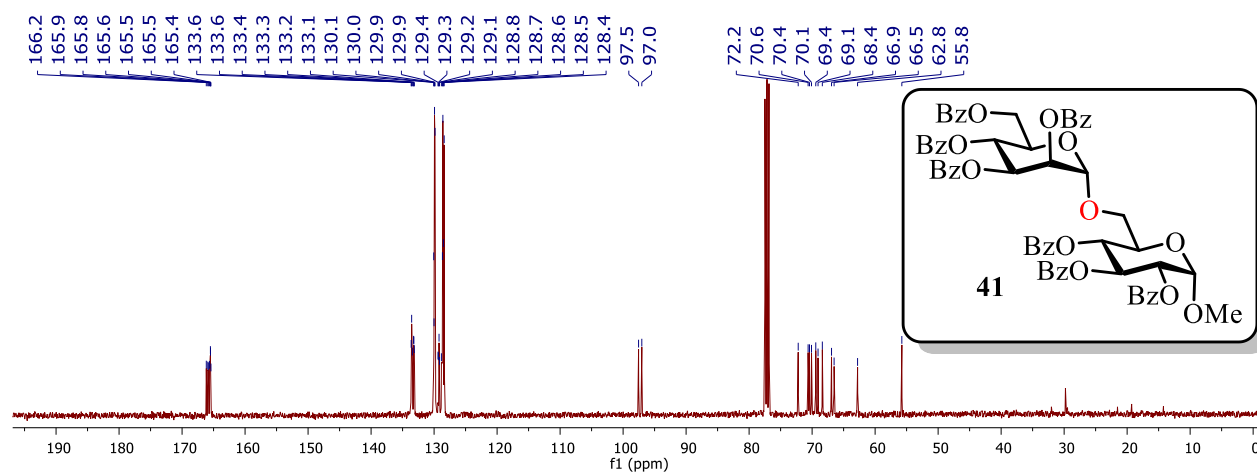


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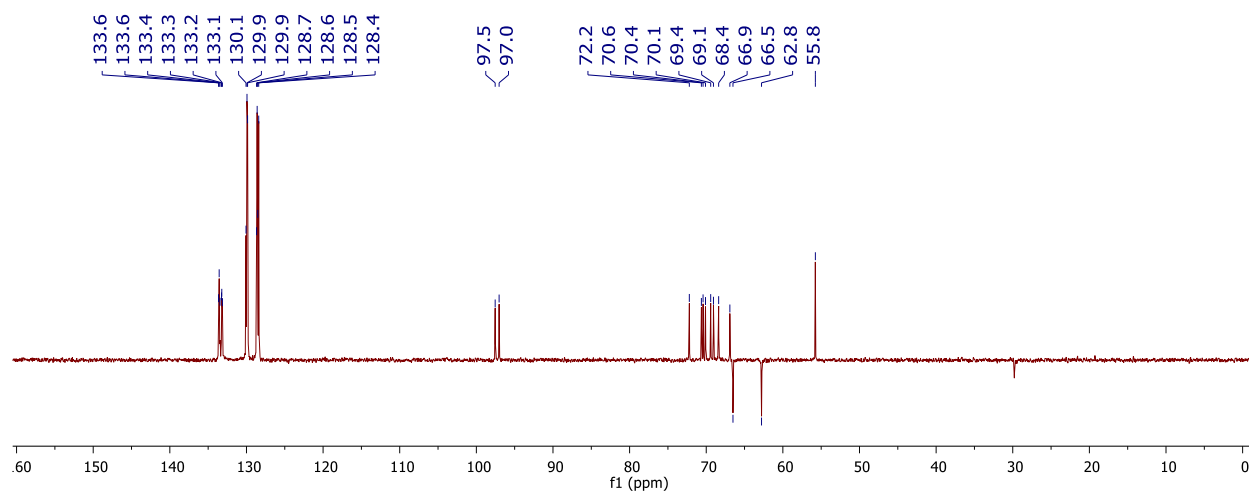
^1H NMR Spectrum (399.78 MHz, CDCl_3) of Compound **41**



^{13}C NMR Spectrum (100.53 MHz, CDCl_3) of Compound **41**

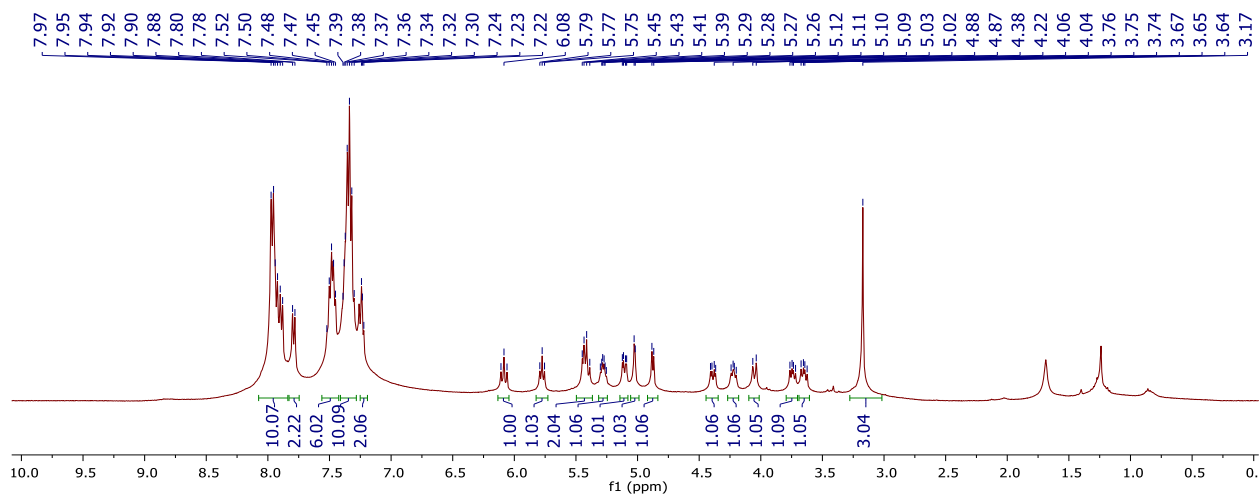


DEPT NMR Spectrum (100.53 MHz, CDCl_3) of Compound **41**

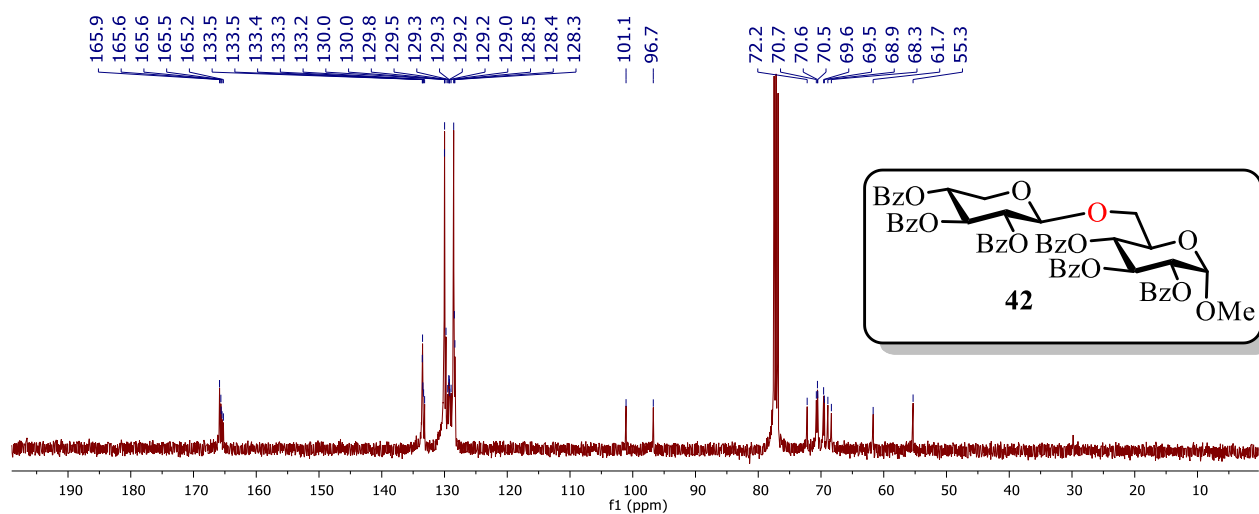


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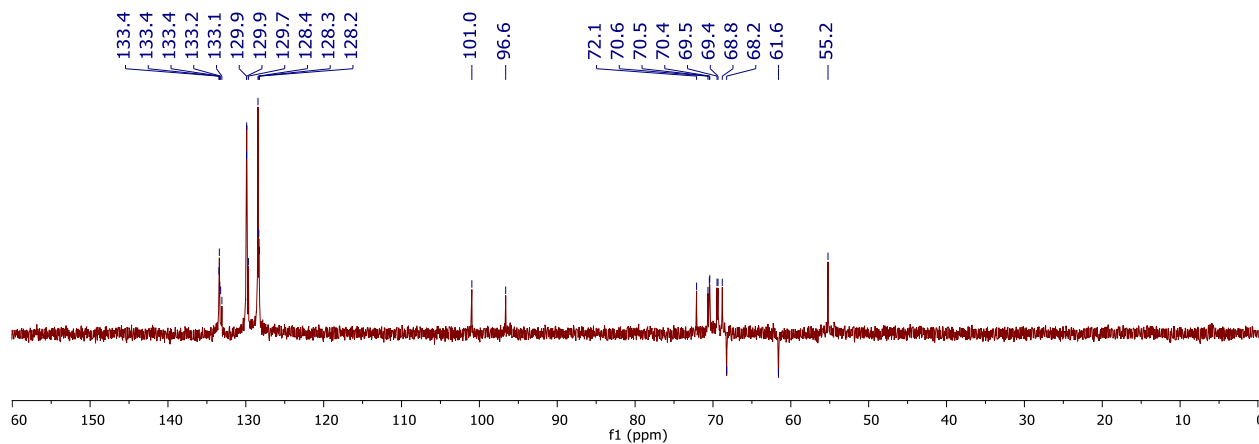
¹H NMR Spectrum (400.31 MHz, CDCl₃) of Compound **42**



¹³C NMR Spectrum (100.67 MHz, CDCl₃) of Compound **42**

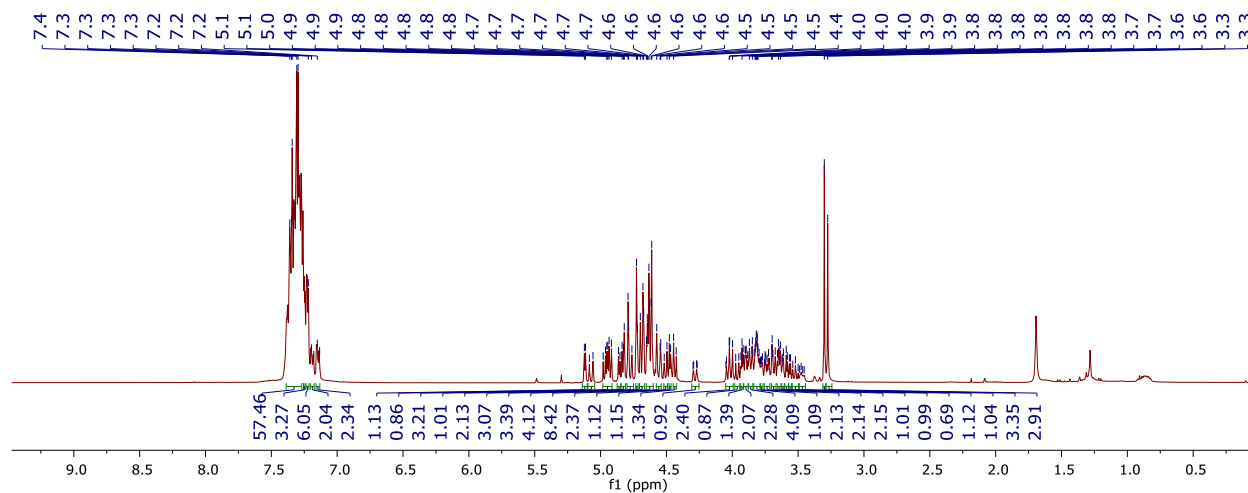


DEPT NMR Spectrum (100.67 MHz, CDCl₃) of Compound **42**

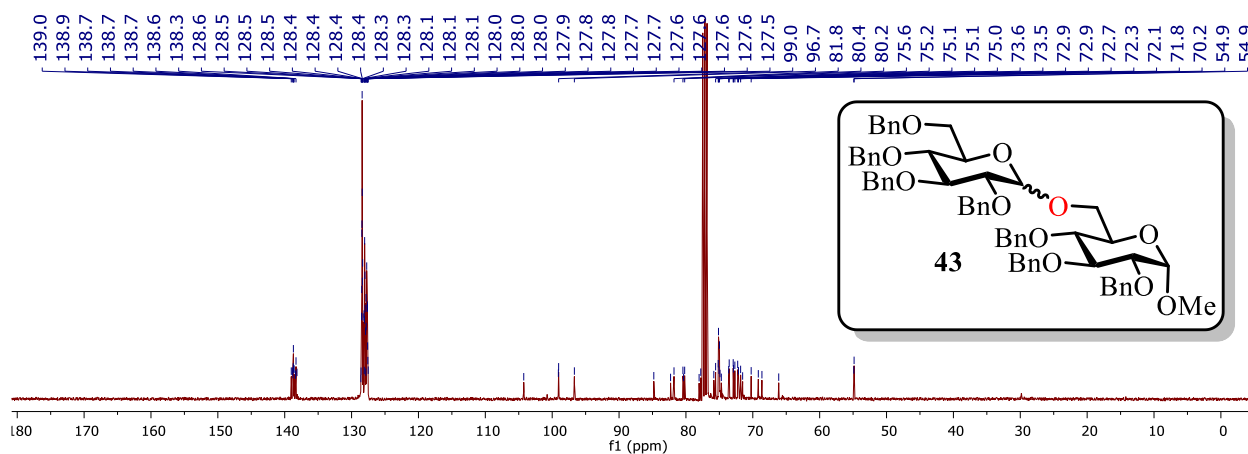


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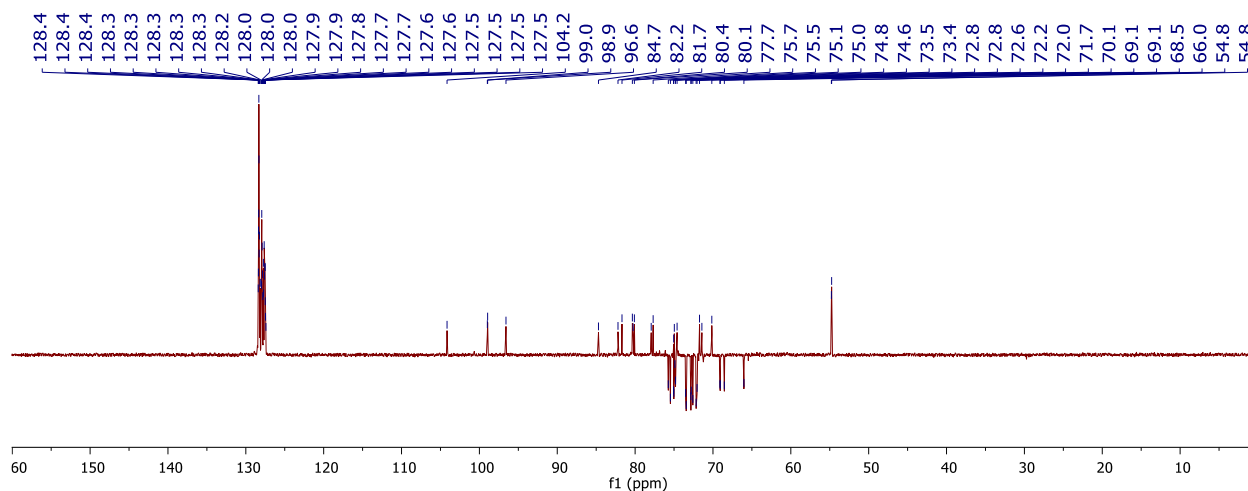
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **43**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **43**

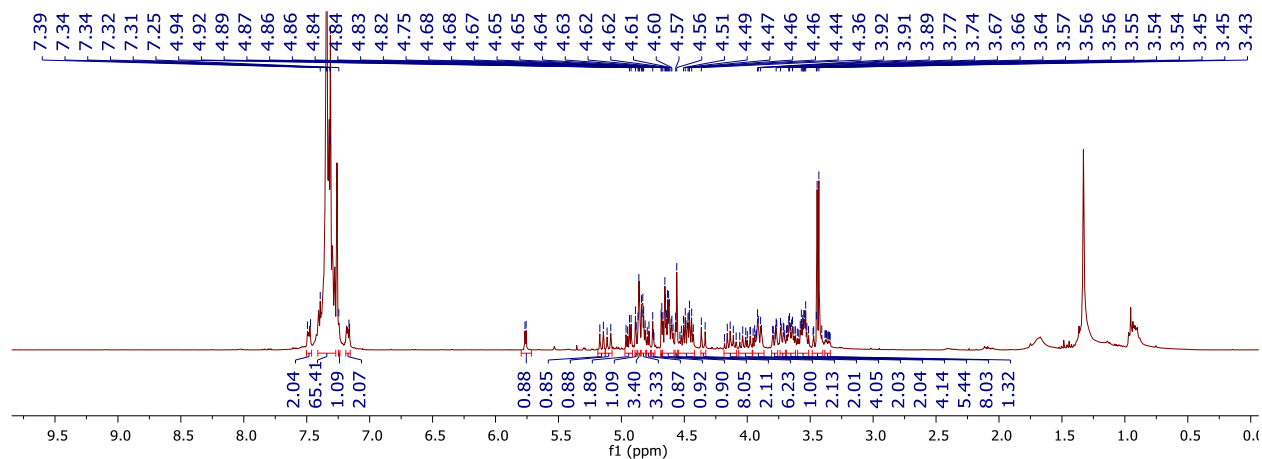


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **43**

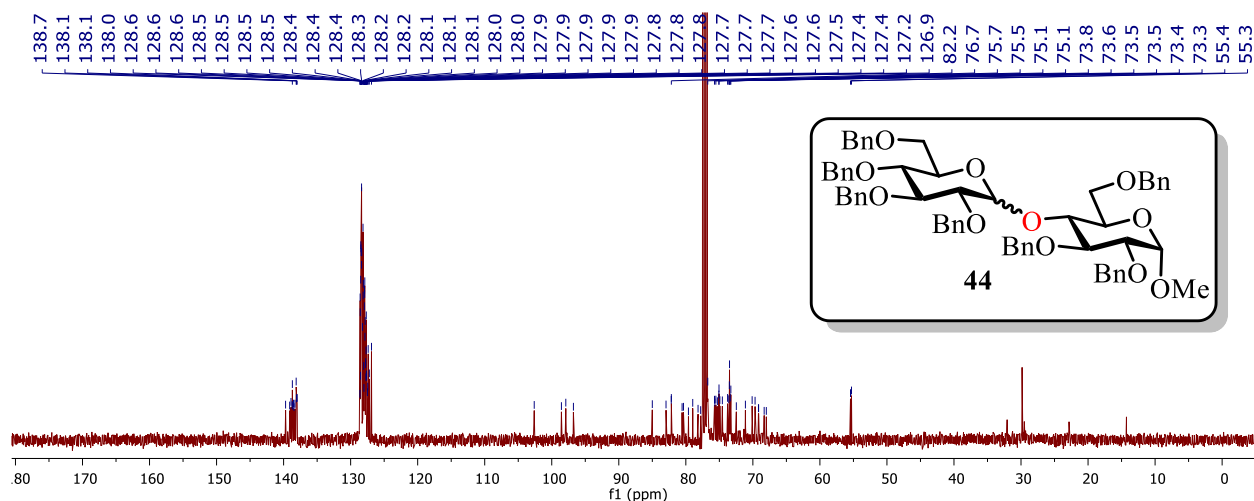


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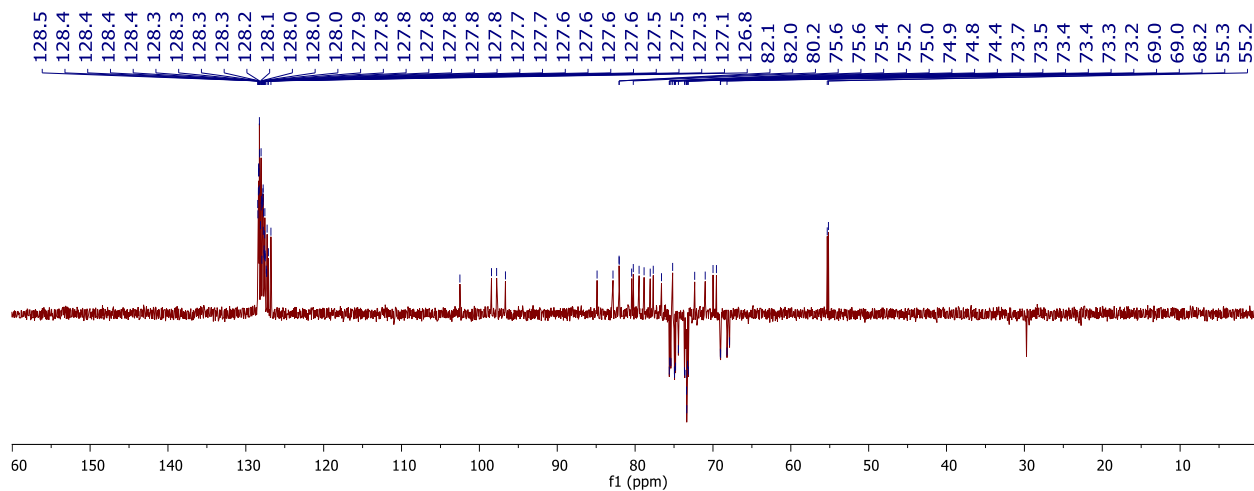
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **44**



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

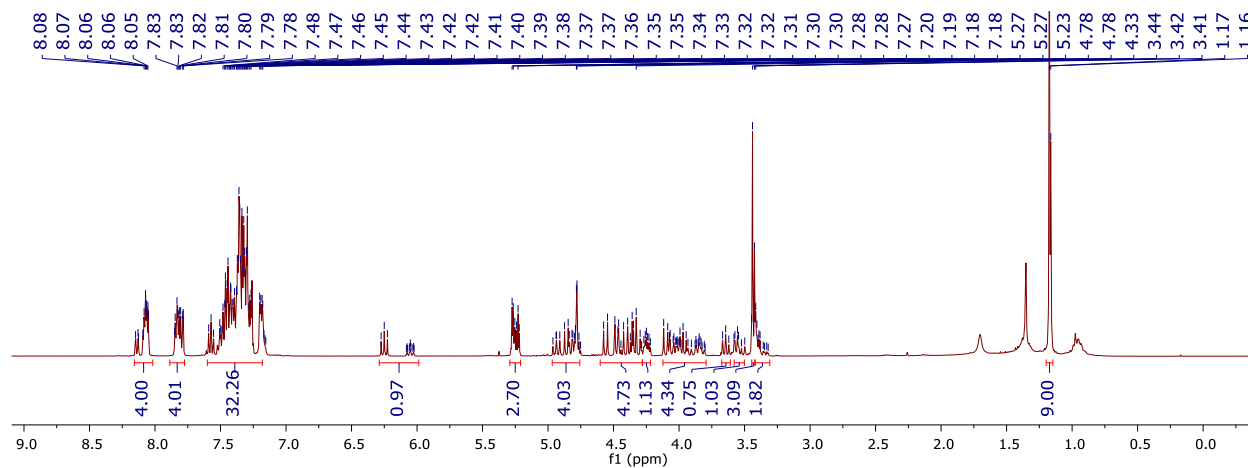


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **44**

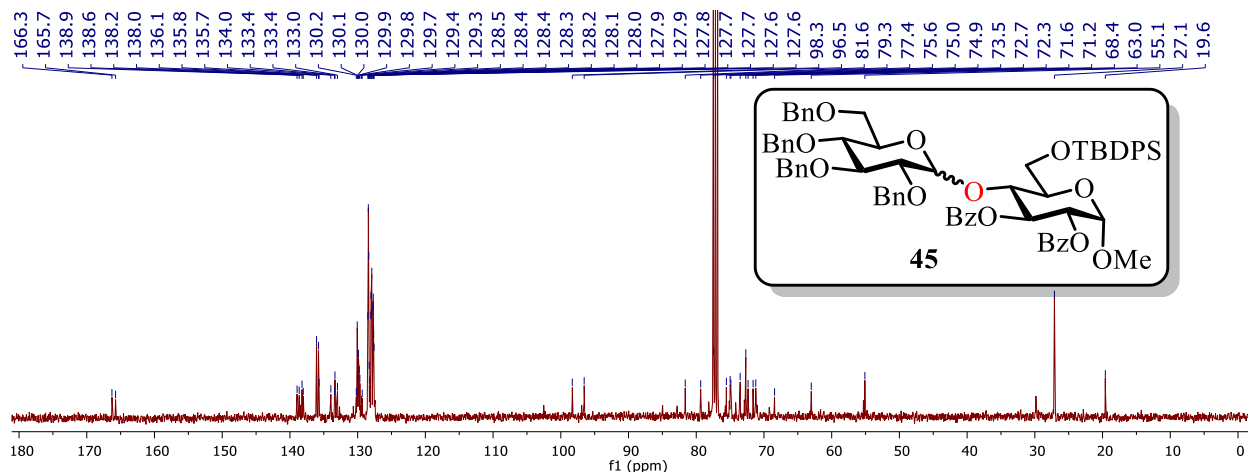


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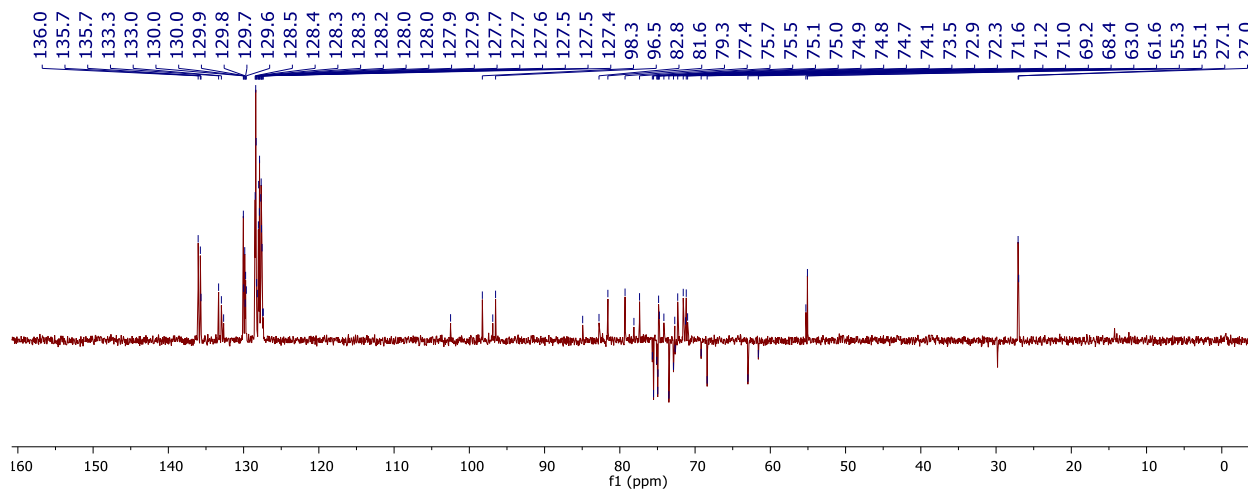
^1H NMR Spectrum (399.78 MHz, CDCl_3) of Compound **45**



^{13}C NMR Spectrum (100.53 MHz, CDCl_3) of Compound **45**



DEPT NMR Spectrum (100.53 MHz, CDCl_3) of Compound **45**



139.1
139.0
138.6
138.6
138.5
138.2
138.1
128.5
128.5
128.5
128.5
128.4
128.1
128.1
128.0
127.9
127.9
127.8
127.7
127.7
127.6
127.6
115.0
97.4
96.8
82.2
81.9
80.5
80.1
78.0
77.7
75.8
75.7
75.2
75.0
73.5
73.3
72.4
70.6
70.4
68.6
67.6
66.2
30.4
28.7

Chemical structure of compound 46 is shown in the inset box.

1H NMR spectrum of compound 10 in CDCl₃. The x-axis represents the chemical shift in ppm, ranging from 0.0 to 9.5. The spectrum shows several peaks: a multiplet between 7.0 and 7.4 ppm, a multiplet between 4.0 and 5.0 ppm, a multiplet between 3.0 and 4.0 ppm, a multiplet between 1.5 and 2.5 ppm, and a multiplet between 0.5 and 1.5 ppm. Integration values are provided below the peaks.

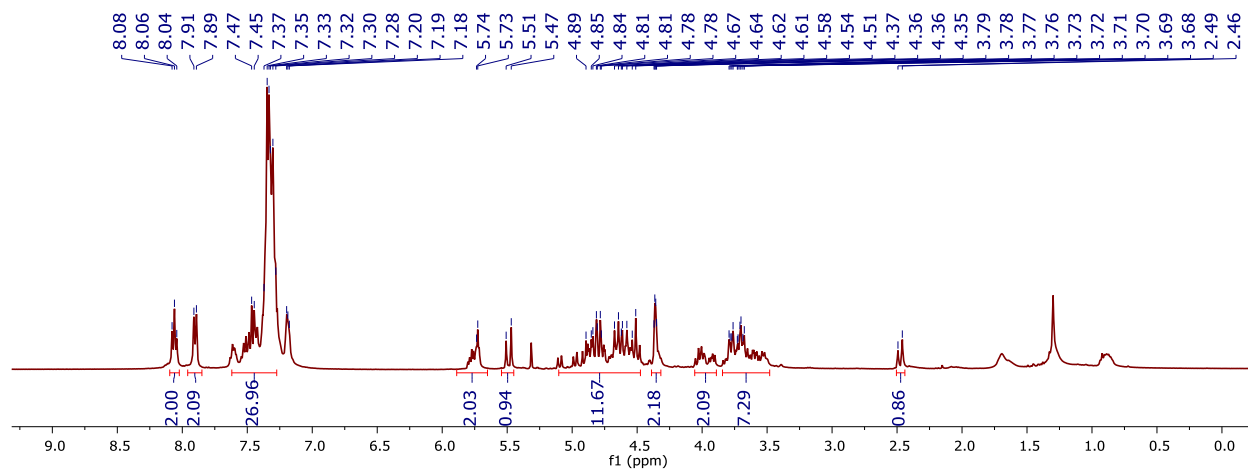
Chemical structure of compound **47** is shown in the inset. The structure is a complex bicyclic ether with multiple benzyl (Bn) protecting groups.

The figure displays a ^{13}C NMR spectrum of compound 10. The x-axis represents the chemical shift in ppm, ranging from 0 to 160. Two traces are shown: a blue trace and a red trace. The blue trace shows a series of sharp peaks, while the red trace shows a similar pattern with some additional features. The peaks are labeled with their corresponding chemical shift values in ppm.

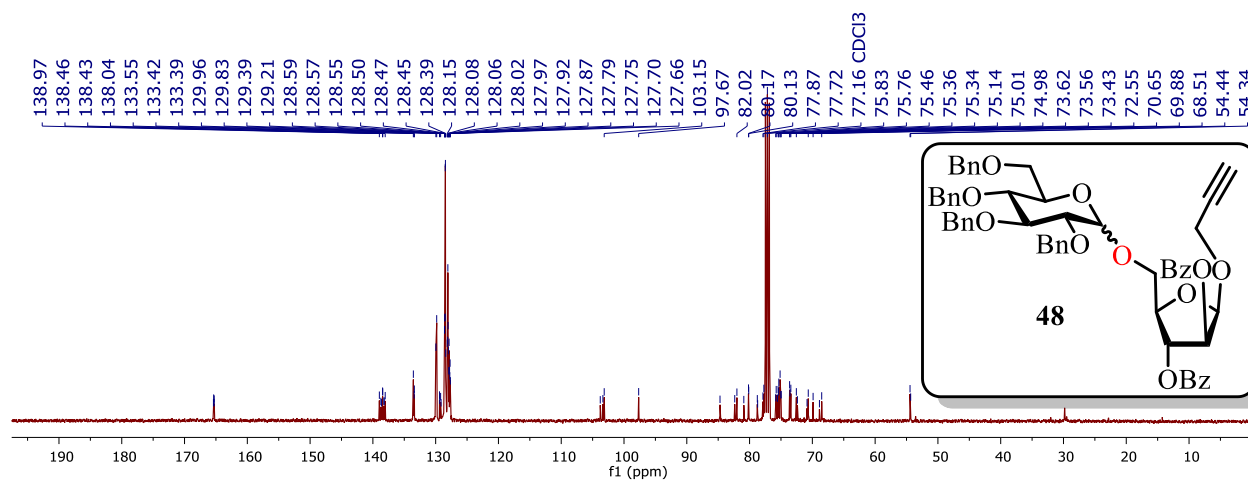
Chemical Shift (ppm)
128.4
128.4
128.4
128.3
128.3
128.3
128.0
127.9
127.9
127.9
127.8
127.7
127.7
127.6
127.6
127.5
127.5
114.8
114.8
106.1
106.0
88.5
84.0
84.0
82.0
80.1
80.0
80.0
75.7
75.6
75.0
75.0
74.6
73.5
73.5
72.8
72.2
72.2
72.1
72.0
72.0
68.9
68.4
67.7
67.0
66.8
30.3
30.3
28.8
28.7

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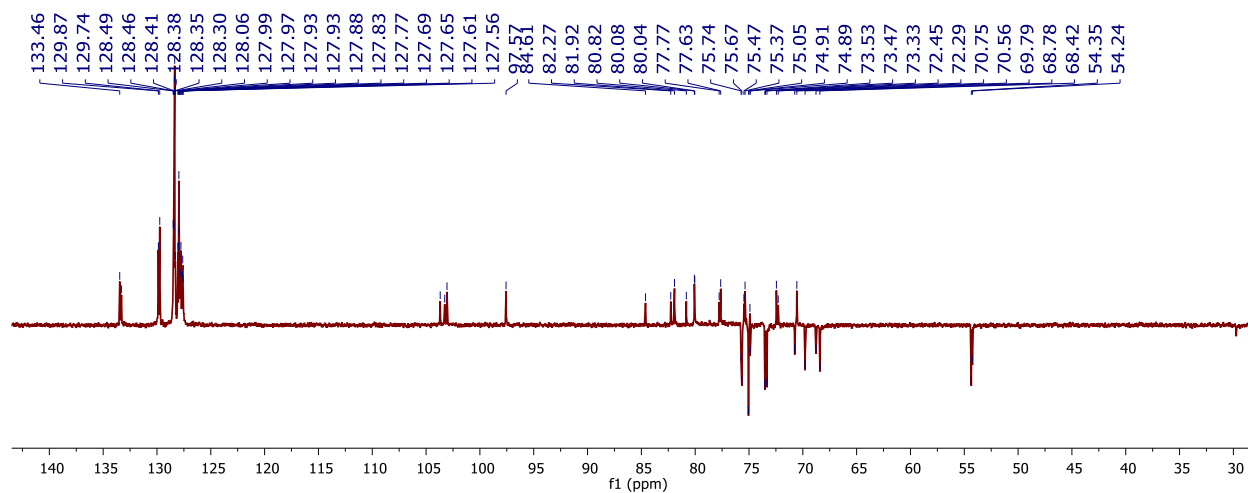
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **48**



^{13}C NMR Spectrum (100.66 MHz, CDCl_3) of Compound **48**



DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **48**



13C NMR spectrum of compound 49 in CDCl₃.

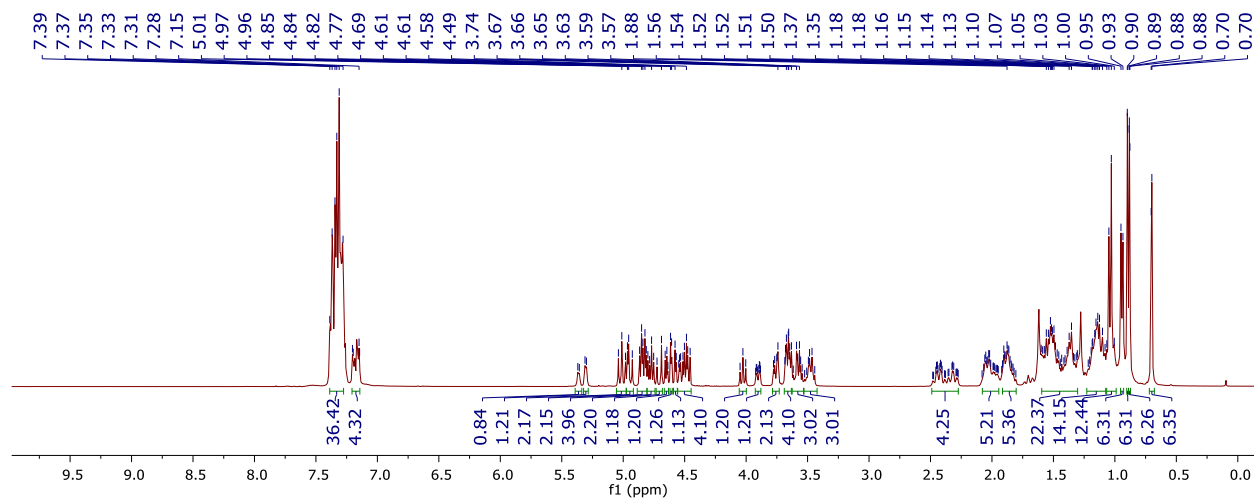
Chemical structure of 49: COCC1(C)CCCC1OC2OCC(OC3CCCCC3)C(OC4CCCCC4)C(OC5CCCCC5)C(OC6CCCCC6)O2

13C NMR peaks (ppm):

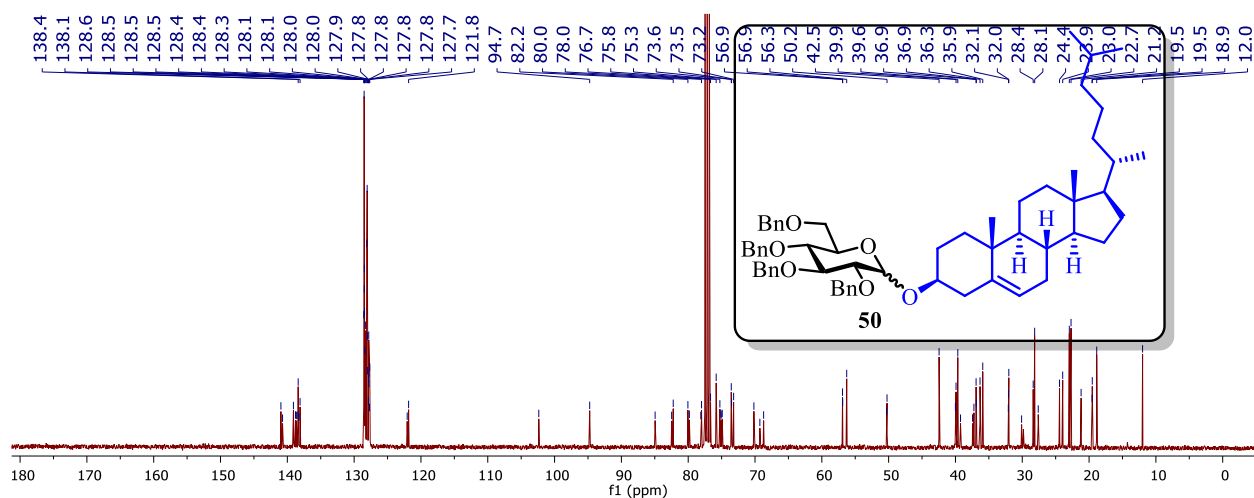
- 138.5, 138.4, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 100.9, 98.8, 85.1, 82.3, 82.1, 81.1, 80.7, 78.2, 78.1, 77.9, 75.7, 75.6, 75.2, 75.1, 75.0, 74.9, 73.8, 73.6, 73.3, 70.4, 68.8, 48.9, 48.2, 43.2, 34.6, 34.4, 31.9, 31.6, 25.4, 24.7, 23.3, 23.1, 22.4, 21.2, 21.2, 16.2, 16.1

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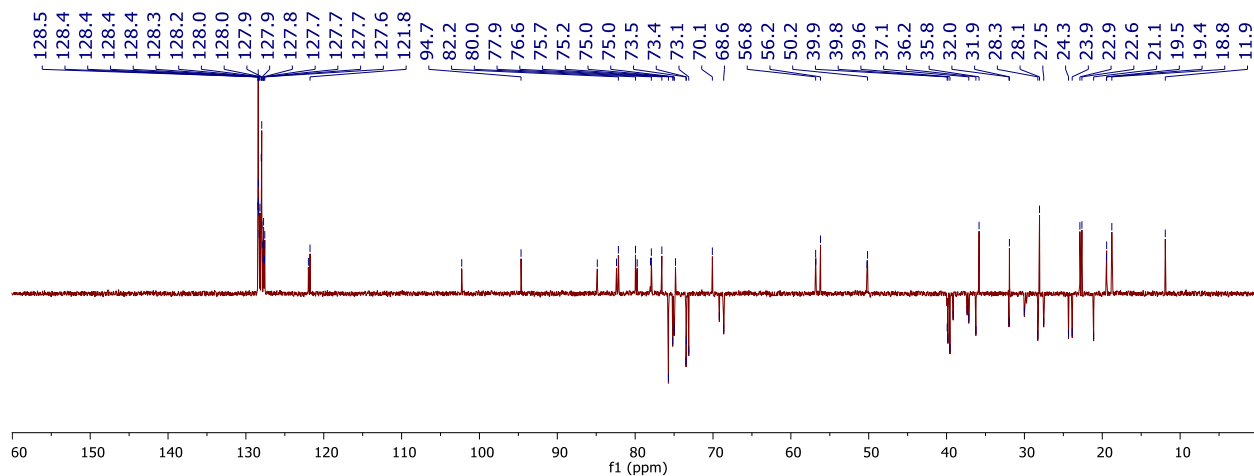
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **50**



^{13}C NMR Spectrum (100.66 MHz, CDCl_3) of Compound **50**

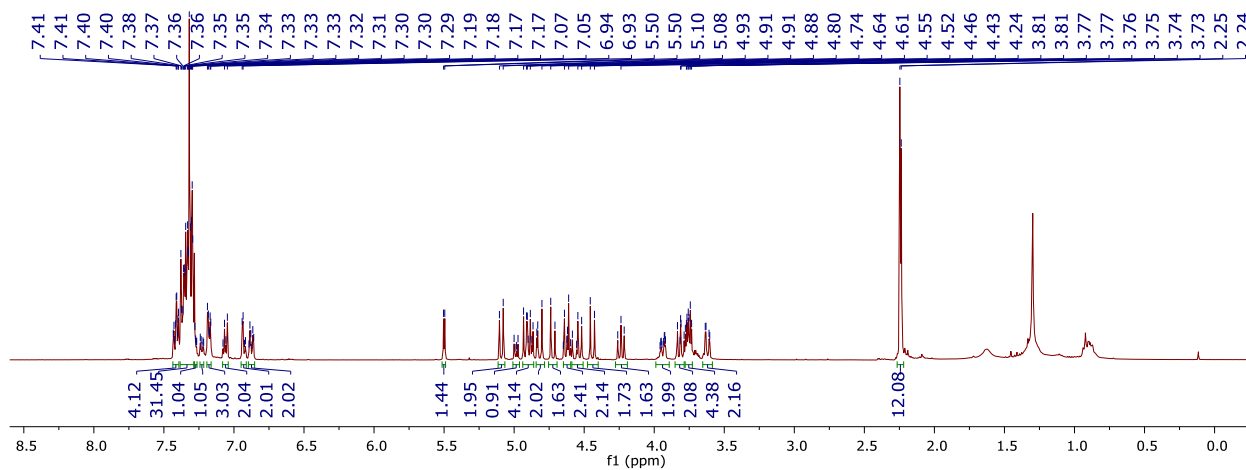


DEPT NMR Spectrum (100.66 MHz, CDCl_3) of Compound **50**

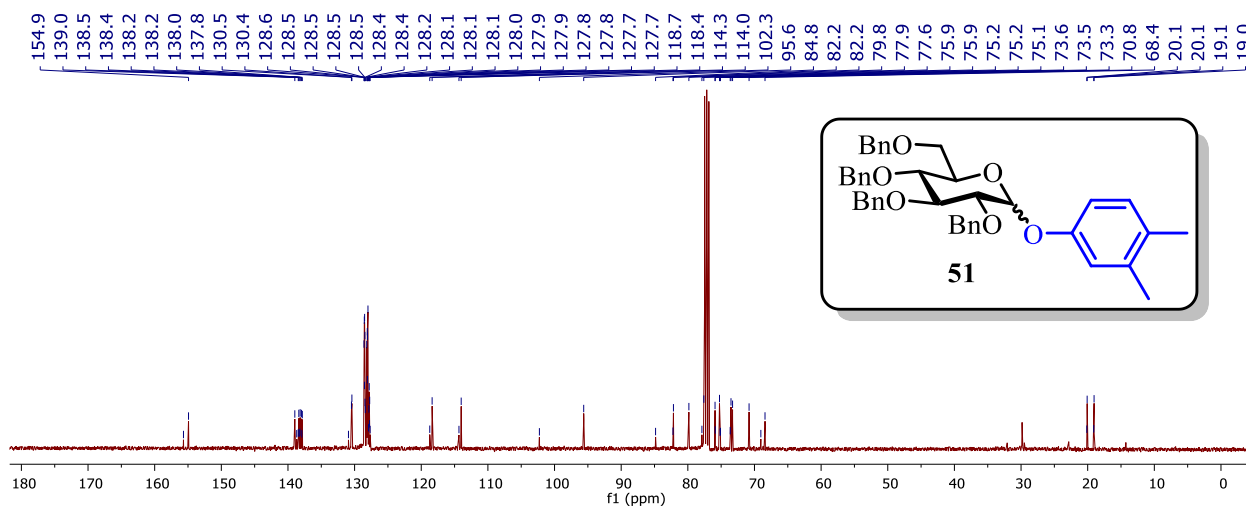


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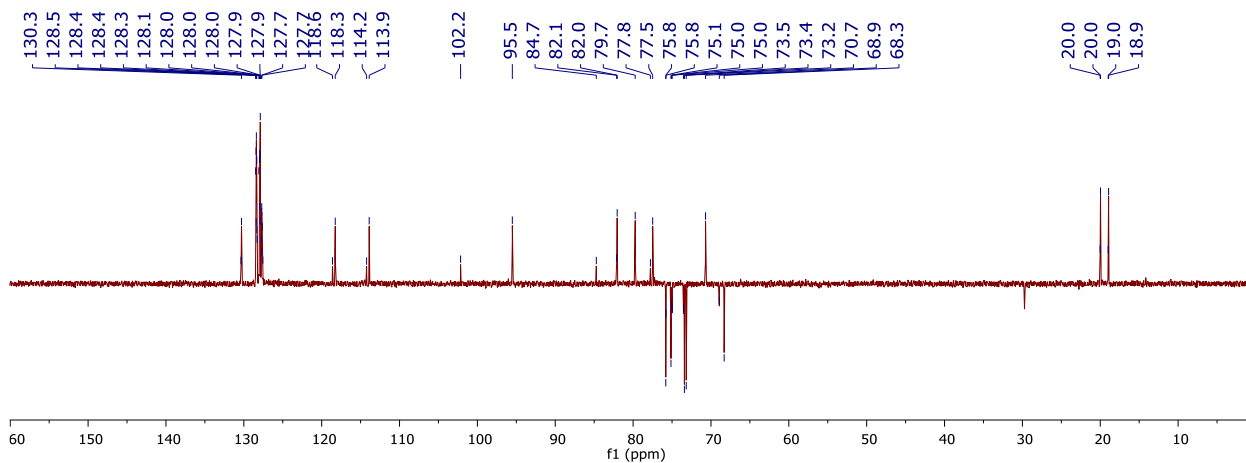
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **51**



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound **51**

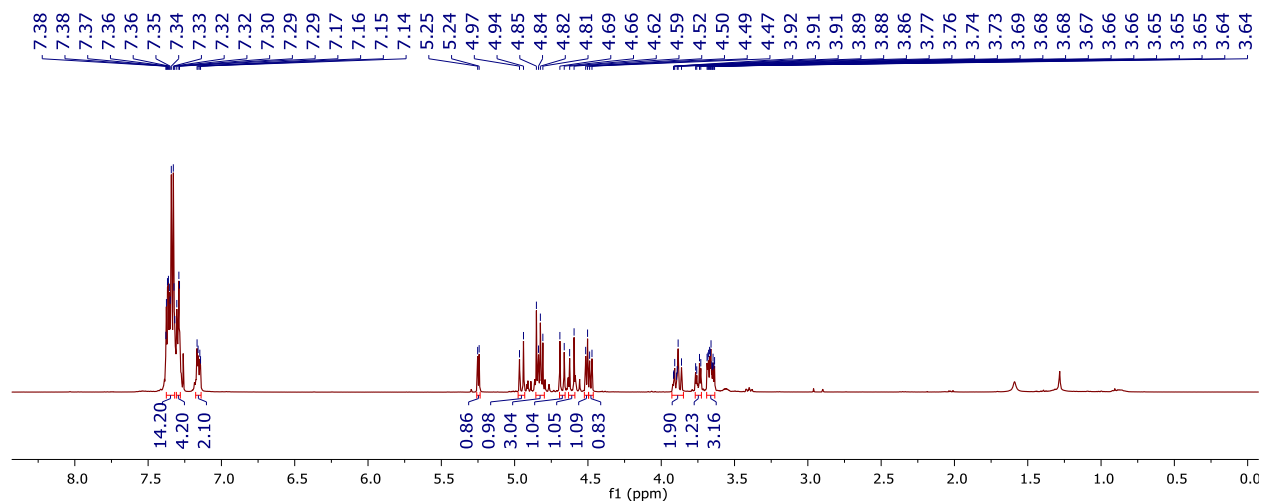


DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound **51**

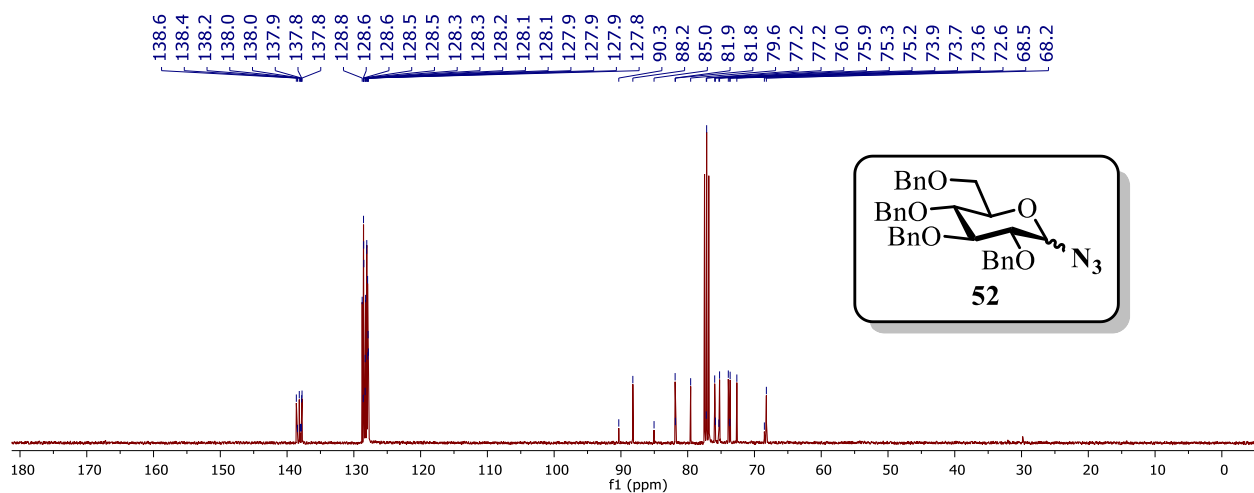


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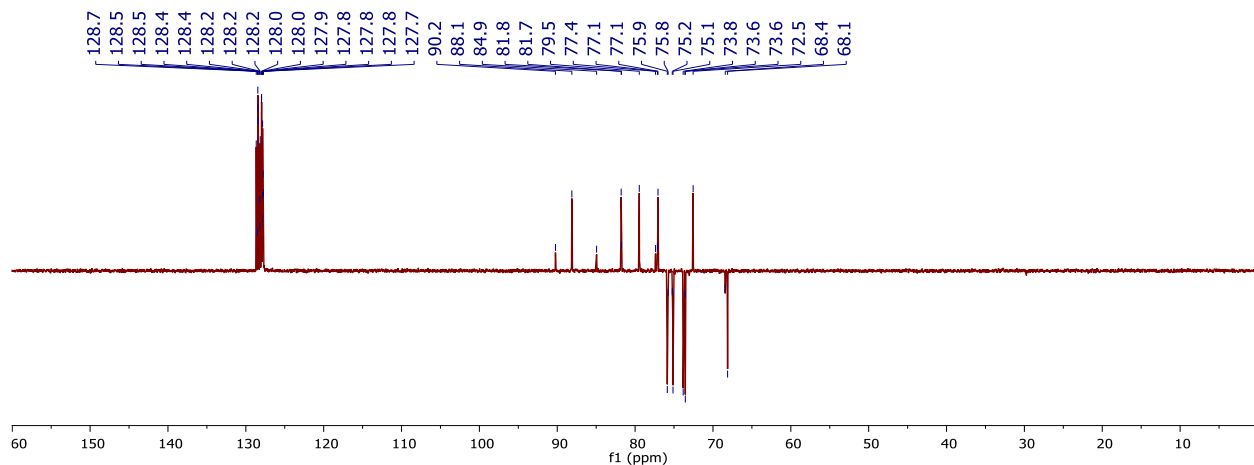
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound 52



^{13}C NMR Spectrum (100.67 MHz, CDCl_3) of Compound 52



DEPT NMR Spectrum (100.67 MHz, CDCl_3) of Compound 52



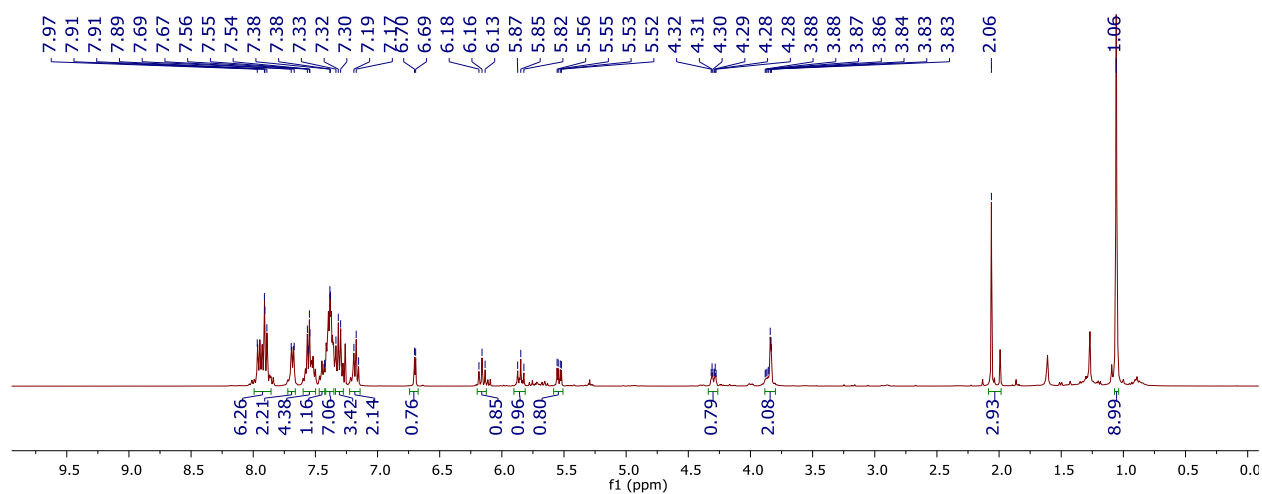
¹H NMR spectrum (CDCl₃) of compound 10a. The x-axis represents chemical shift (ppm) from 10.0 to 0.0. The spectrum shows a complex aromatic region (6.2-8.0 ppm), a methine region (3.8-5.8 ppm), and a methyl region (1.0-1.9 ppm). Integration values are shown below the peaks.

Chemical Shift (ppm)	Integration
8.02	4.38
8.00	8.27
7.92	4.30
7.86	4.33
7.73	5.05
7.71	15.44
7.58	6.42
7.50	4.21
7.48	
7.43	
7.31	
7.19	
6.22	
6.17	
5.91	
5.89	
5.86	
5.76	
5.74	
5.73	
5.71	
5.70	
5.68	
5.35	
5.33	
5.32	
5.31	
5.30	
5.29	
5.29	
4.95	
4.93	
4.42	
4.41	
4.41	
4.40	
4.39	
4.39	
4.38	
3.90	
3.89	
3.87	
3.86	
3.85	
3.85	
3.82	
3.81	
3.25	
1.06	

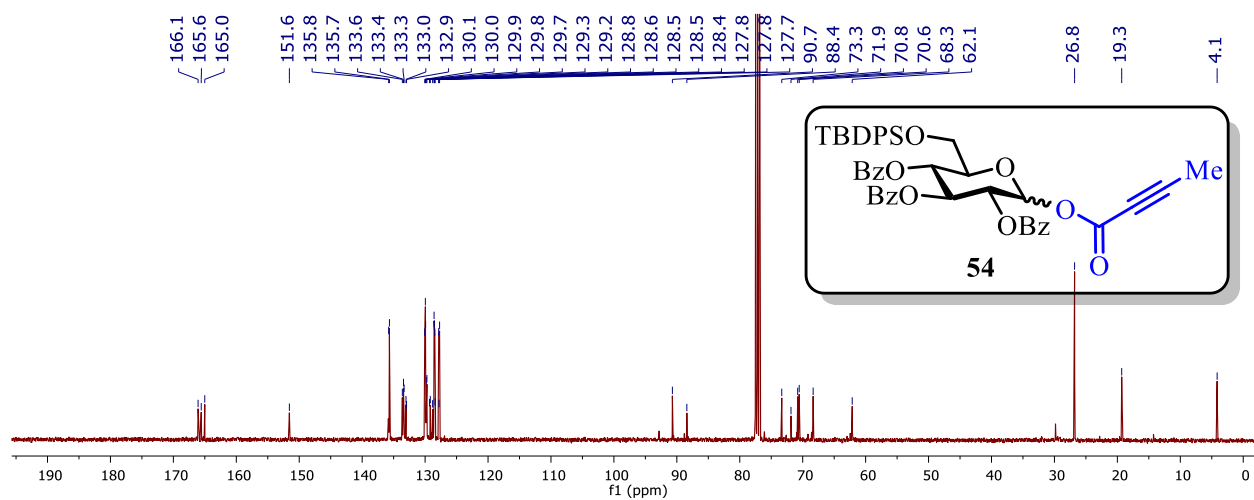
Chemical structure of compound **53** is shown in the inset. The structure is a bicyclic molecule with a TBDPSO group, two BzO groups, and a free OH group.

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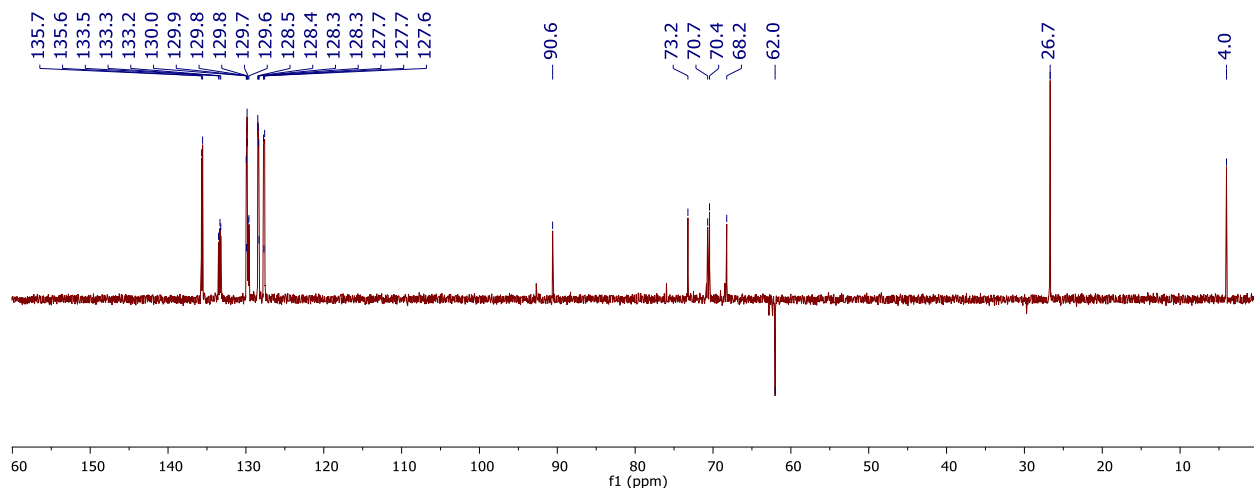
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **54**



^{13}C NMR Spectrum (100.66 MHz, CDCl_3) of Compound **54**

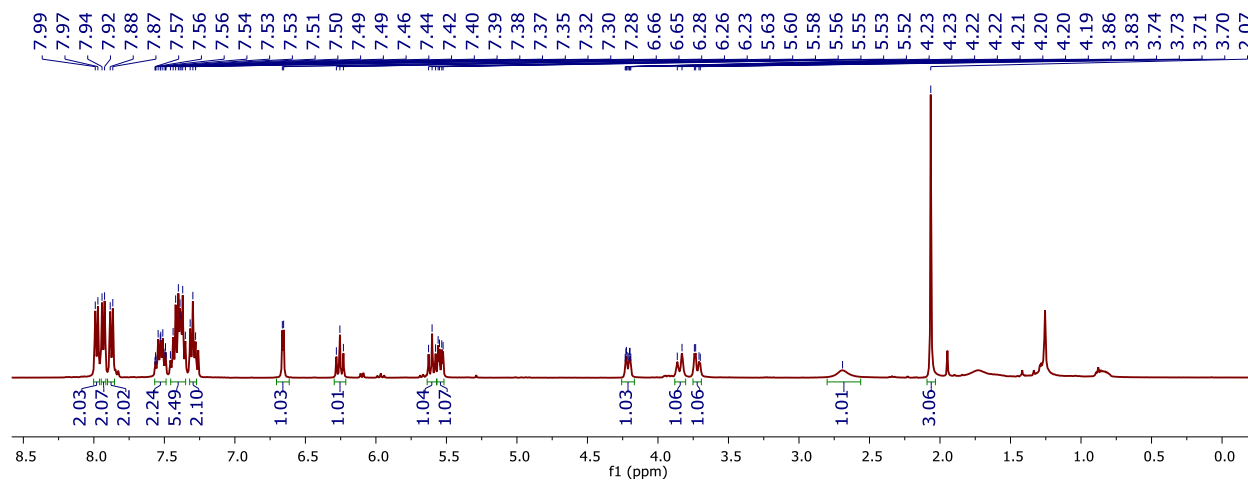


DEPT NMR Spectrum (100.66 MHz, CDCl_3) of Compound **54**

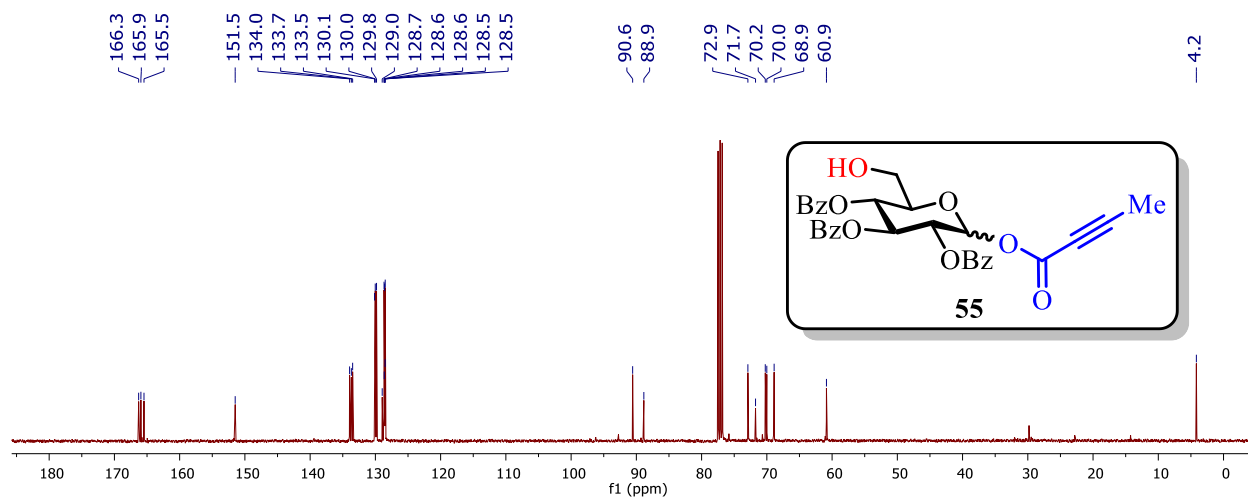


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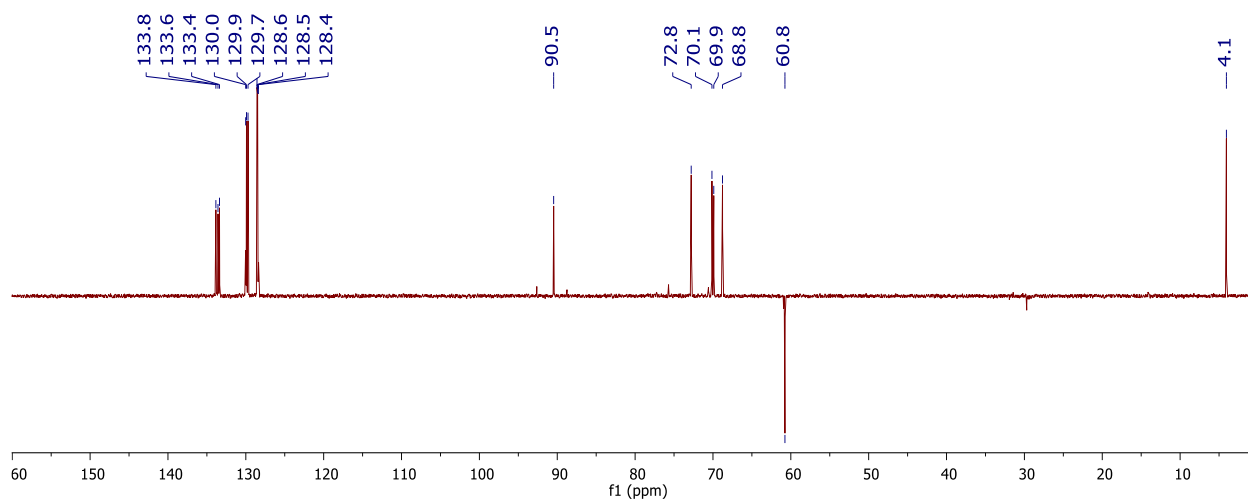
¹H NMR Spectrum (400.31 MHz, CDCl₃) of Compound 55



¹³C NMR Spectrum (100.67 MHz, CDCl₃) of Compound 55

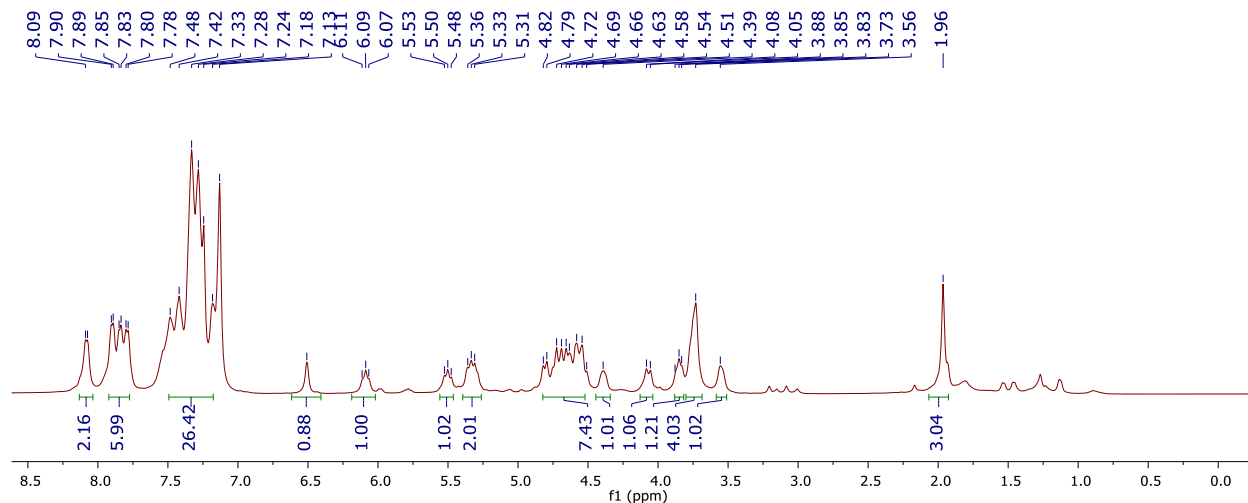


DEPT NMR Spectrum (100.67 MHz, CDCl₃) of Compound 55

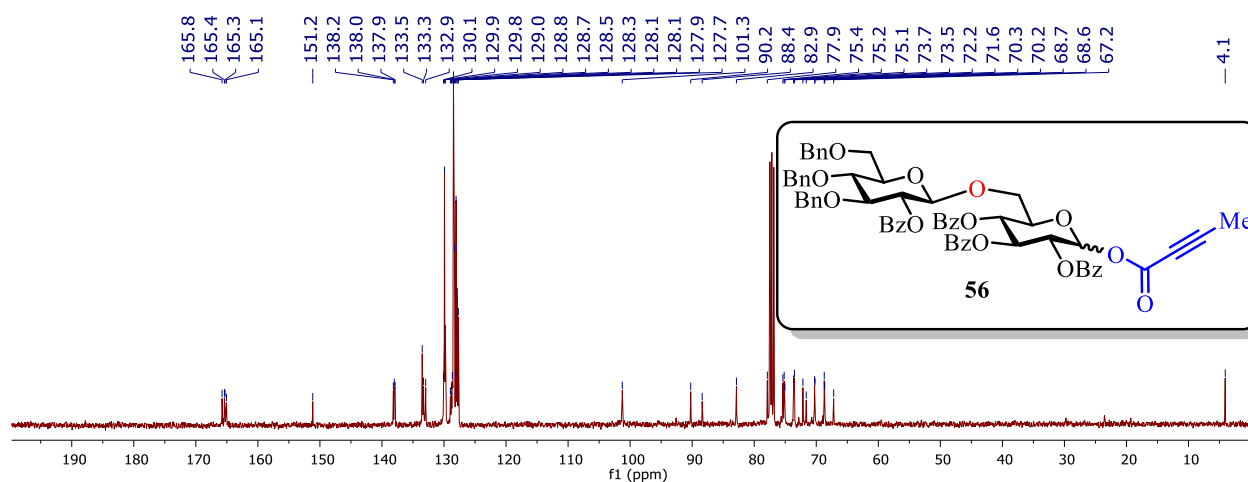


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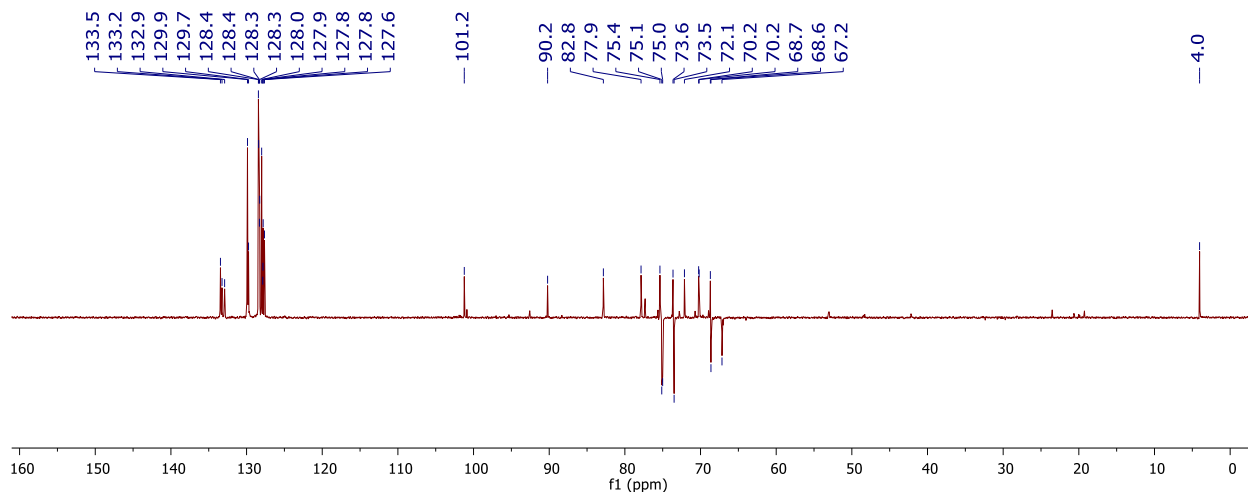
^1H NMR Spectrum (400.31 MHz, CDCl_3) of Compound **56**



^{13}C NMR Spectrum (100.53 MHz, CDCl_3) of Compound **56**

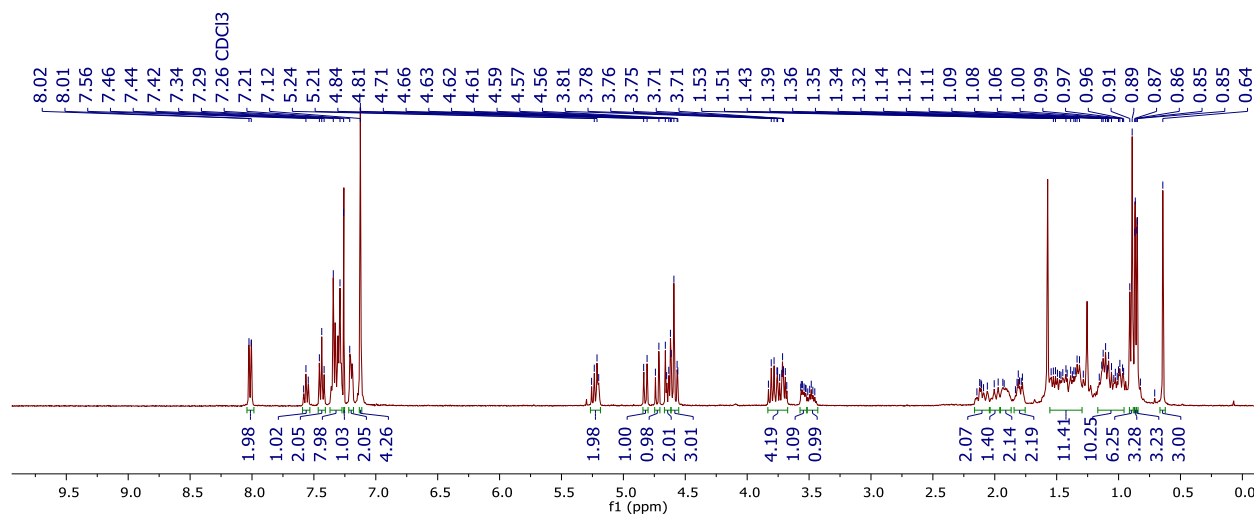


DEPT NMR Spectrum (100.53 MHz, CDCl_3) of Compound **56**

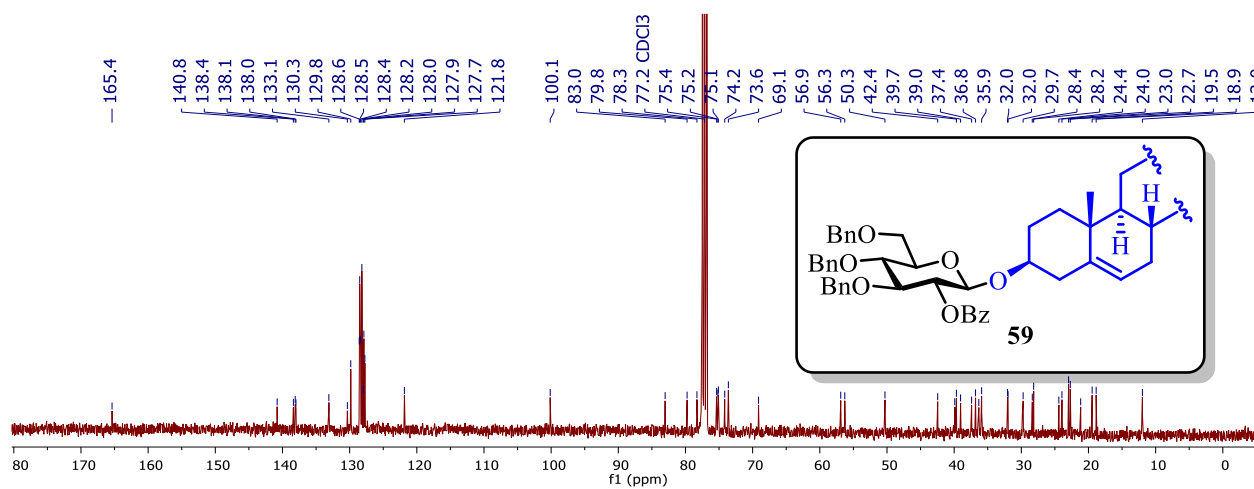


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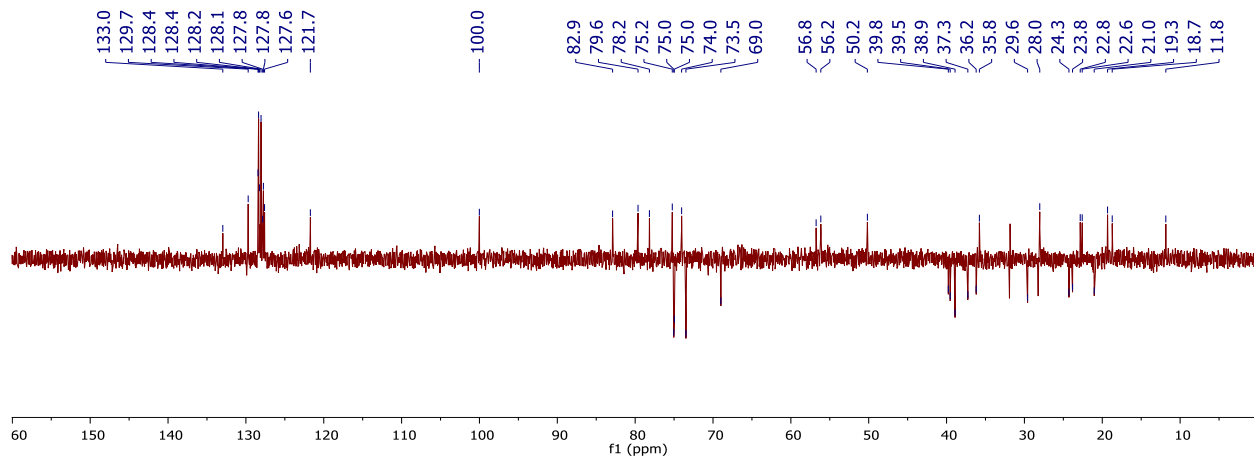
^1H NMR Spectrum (399.78 MHz, CDCl_3) of Compound **59**



^{13}C NMR Spectrum (100.66 MHz, CDCl_3) of Compound **59**



DEPT NMR Spectrum (100.66 MHz, CDCl_3) of Compound **59**



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Chapter 3B

Glycosyl Vinylogous Carbonates as Glycosyl Donors
Using Metal-free Activation

3B.1 Introduction

Glycosyl carbonates are the class of O-carbonyl donors that have been investigated to undergo glycosidation.¹ The expulsion of CO₂ from the carbonate-leaving group make such type of donors highly reactive and found to show distinct reactivity in glycosylation events. For example, the pyrolysis of glycosyl carbonates results in the release of CO₂ and the formation of “oxocarbenium ion” intermediate along with the by-product alkoxide which can serve as the glycosyl acceptor in the glycosylation. Contrarily, the activation using electrophilic reagents in presence of an aglycon can produce the trans-glycosylated product (Fig 1).²

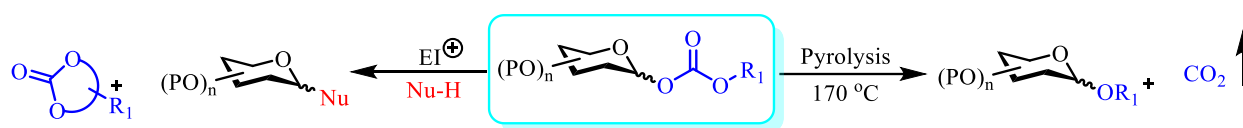
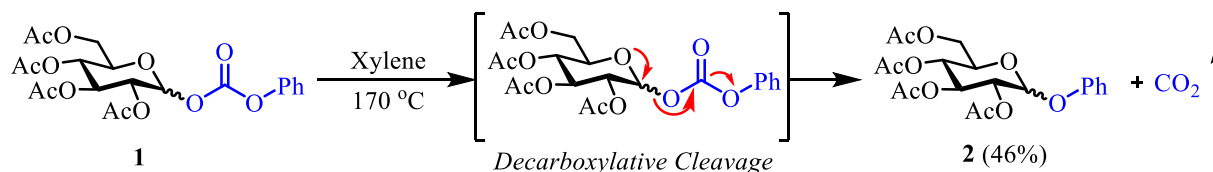


Fig. 1 Modes of activation in glycosyl carbonate donors

The glycosyl carbonates as glycosyl donors were first introduced by Ishido and coworkers in 1973.³ The pyrolysis of glycosyl phenyl carbonate **1** was found to undergo the glycosidation via decarboxylative cleavage of anomeric carbonate to give phenyl glycoside **2** (46%) along with the liberation of CO₂ and other mixed carbonate by-products. This methodology was extended for the synthesis of novel *N*-glycosides under pyrolytic conditions. The pyrolysis of glycosyl phenyl carbonate **1** in the presence of aglycons such as 6-chloropurine, 2,6-dichloropurine, theophylline, 4-methoxy-2(1H)-pyrimidone and 2(1H)-pyridone offered them corresponding glycosides in low to moderate yields. However, harsh condition due to high reaction temperature (140-160 °C) under reduced pressure, formation of side products, and low yield in glycosylation are the major drawbacks of this methodology.

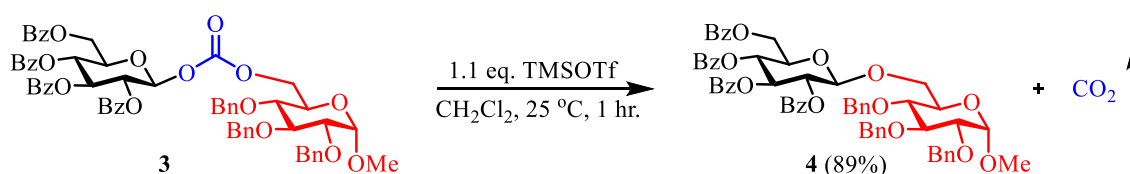


Scheme 1 Pyrolytic decarboxylative glycosidation developed by Ishido *et al.*

Later on, Ikegami and coworkers demonstrated the activation of mixed glycosyl carbonates under Lewis acid conditions.⁴ The bis(glucopyranosyl) carbonate **3** was effectively activated at

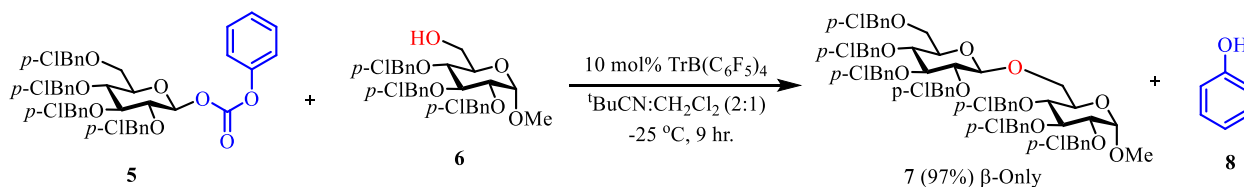
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room temperature using the stoichiometric amount of TMSOTf as promoter to access disaccharide **4** in 89% yield. Furthermore, these types of carbonate donors are investigated for 1,2-*cis* glycosidic linkage formation. The use of sub-stoichiometric amounts of metal salts such as SnCl₄ or AgClO₄ was found to give excellent α -selectivity ($>10:1 = \alpha:\beta$) in diethyl ether.⁵ The application of this methodology was demonstrated by synthesizing several disaccharides containing benzyl and benzoyl-protected sugar derivatives in moderate to good yields. The mechanistic investigation of TMSOTf-promoted decarboxylation by Schmidt revealed that glycosylation is an intermolecular process.⁶



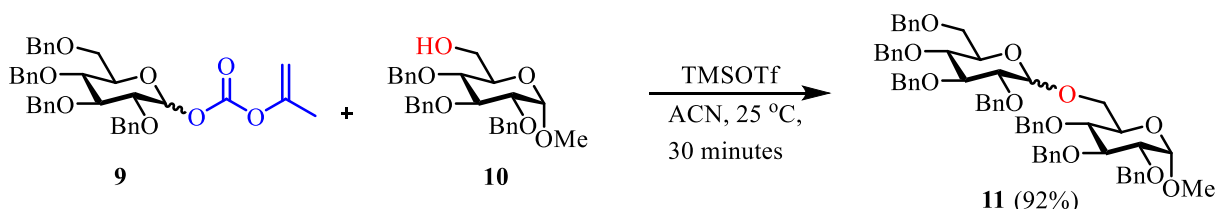
Scheme 2 Activation of carbonates under Lewis acid condition

Another novel, catalytic, and highly stereoselective 1,2-*trans* glycosidation method was developed by Uchiro and coworkers using glycosyl phenyl carbonates as donors.⁷ The *p*-chlorobenzyl-protected glucosyl carbonate was investigated to decipher the effect of protecting groups on stereoselectivity. Accordingly, phenyl carbonate donor **5** was activated in presence of acceptor **6** using 10 mol% trityl tetrakis(pentafluorophenyl)borate at -25 °C to access the disaccharide **7** with complete 1,2-*trans* selectivity. The established protocol was investigated with different sugar and non-sugar acceptors to synthesize the glycosides with high diastereoselectivity.⁸ The origin of excellent selectivity in glycosidation was believed to be due to the *p*-chlorobenzyl ether protection which could reduce the rate of isomerization as evidenced by a comparative study with benzyl-protected donors. The methodology was also successfully employed for the one-pot synthesis of trisaccharides related to mucin-type oligosaccharides.⁹



Scheme 3 Catalytic activation of glycosyl phenyl carbonate donor

The simple alkyl carbonates have been also investigated as glycosyl donors to undergo glycosidation with the addition of external acceptors. Sinäy *et al.* demonstrated the activation of glycosyl isoprenyl carbonates using sub-stoichiometric amounts of TMSOTf in acetonitrile as promoter to afford the disaccharides in good yields.¹⁰ The glycosyl carbonate donor **9** was activated using the TMSOTf in presence of aglycon **10** to afford the disaccharide **11** in 92% as anomeric mixtures. However, it was noticed that the donor was inefficient to produce the glycosides with secondary –OH or hindered acceptors thus limiting the application of this donor in oligosaccharides synthesis.

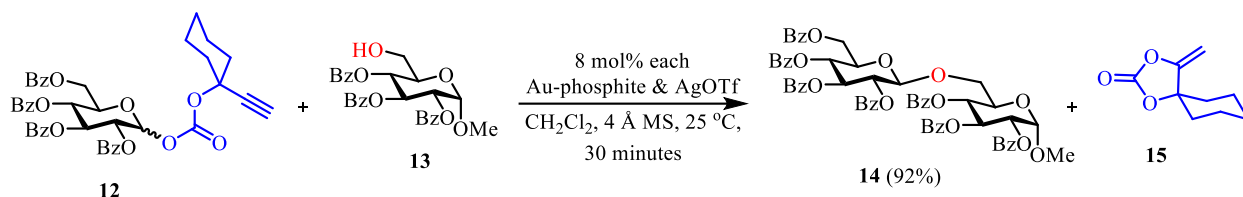


Scheme 4 Glycosyl isoprenyl carbonates as glycosyl donor

Similarly, Mukayama used the glycosyl phenyl (-OPh) and methyl (-OMe) carbonates as glycosyl donors using the sub-stoichiometric amount of trityl tetrakis(pentafluorophenyl)borate as promoter.¹¹ The *O*-benzyl-protected alkyl carbonates were activated to produce the disaccharides in good yield. The stability of thioglycoside under activation conditions was successfully employed in the one-pot-three-component procedure to affect the trisaccharide synthesis.¹² Furthermore, the other modes of electrophilic activation have also been developed by employing the reagents such as SnCl₂, SbI₃, and TeI₄ to produce the glycosides.^{13,14} For example, the methyl carbonate donor was activated using electrophilic reagents such as Lawesson's reagent in combination with AgOTf to produce the 1,2-*trans*-linked ribonucleoside with high efficacy.¹⁵ Additionally, the glycosyl trichloromethyl carbonates have also been investigated to undergo the glycosidation in presence of promoters TMSOTf or BF₃•OEt₂ to produce the glycosides in good yields.¹⁶

Very recently from our group, the glycosyl carbonates containing alkyne functionality was identified as a shelf-stable, highly efficient, and versatile donor.¹⁷ Hotha and coworkers investigated the glycosyl carbonates having the differentially substituted alkyne-appendages as leaving group and identified that the glycosyl ethynylcyclohexyl carbonates undergo

glycosidation very efficiently. The glycosyl carbonate **12** was smoothly activated using the 8 mol% each of gold-phosphite and AgOTf in presence of acceptor **13** to access the disaccharide **14** in 92% yield. The versatile nature of the donor was demonstrated by synthesizing the *O*-, *N*-, and *C*- glycosides with very good yields. Furthermore, the efficacy of the donor towards higher oligosaccharides syntheses has been proved by the successful synthesis of highly challenging branched mannose capped heneicosasaccharide (21mer),¹⁸ a pentacosasaccharide (25mer)¹⁹ moiety of arabinogalactan portion and a linear nonadecaarabinofuranoside (19mer) present on the cell surface of *Mycobacterium tuberculosis*.²⁰

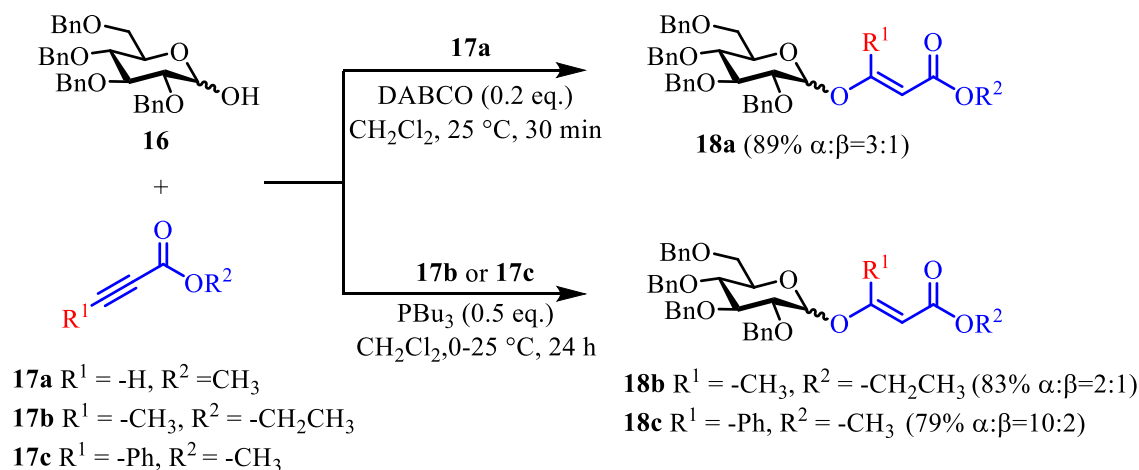


Scheme 5 Glycosyl ethynylcyclohexyl carbonates activation under gold catalysis

3B.2 Present work

In this study glycosyl vinylogous carbonates were considered as glycosyl donors to be activated under mild reaction conditions. It was hypothesized that the vinylene moiety shall facilitate the extrusion of the leaving group in presence of a suitable promoter to generate the intermediate “oxocarbenium ion” which will then be attacked by an aglycon to produce glycosides. The departed leaving group will be the methyl 3-oxopropanoate which shall not be competing with aglycon during the glycosylation. Thus, the vinylogous carbonates **18a-18c** were hypothesized for the investigation of these glycosides as glycosyl donors. Therefore, the solid tetra-*O*-benzyl D-glucopyranose **16** and methyl propiolates **17a-17c** were selected to synthesize the above hypothesized vinylogous carbonates. Accordingly, the hemiacetal **16** was treated with methyl propiolate **17a** in presence of 0.2 equivalents of DABCO at room temperature to obtain desired candidate **18a** in 89% as anomeric mixture ($\alpha:\beta = 3:1$). The compound was thoroughly characterized using the NMR analysis, in the ¹H spectrum of **18a** (α -isomer), the anomeric proton was identified at δ 5.14 ppm as a doublet with a coupling constant of $J = 3.5$ Hz. The *Z*-configuration of alkene at the anomeric position was assigned based on the ¹H coupling $J = 15.4$

Hz for vinylic protons. Additionally, the identity of the molecule was further confirmed by the ^{13}C NMR spectral analysis wherein anomeric carbon was identified at δ 98.6 ppm along with characteristic ester carbonyl at δ 167.8 ppm. The two vinylic-CH resonances were identified at δ 159.3 and 100.9 ppm and all other resonances were found in accordance with the proposed structure **18a**.



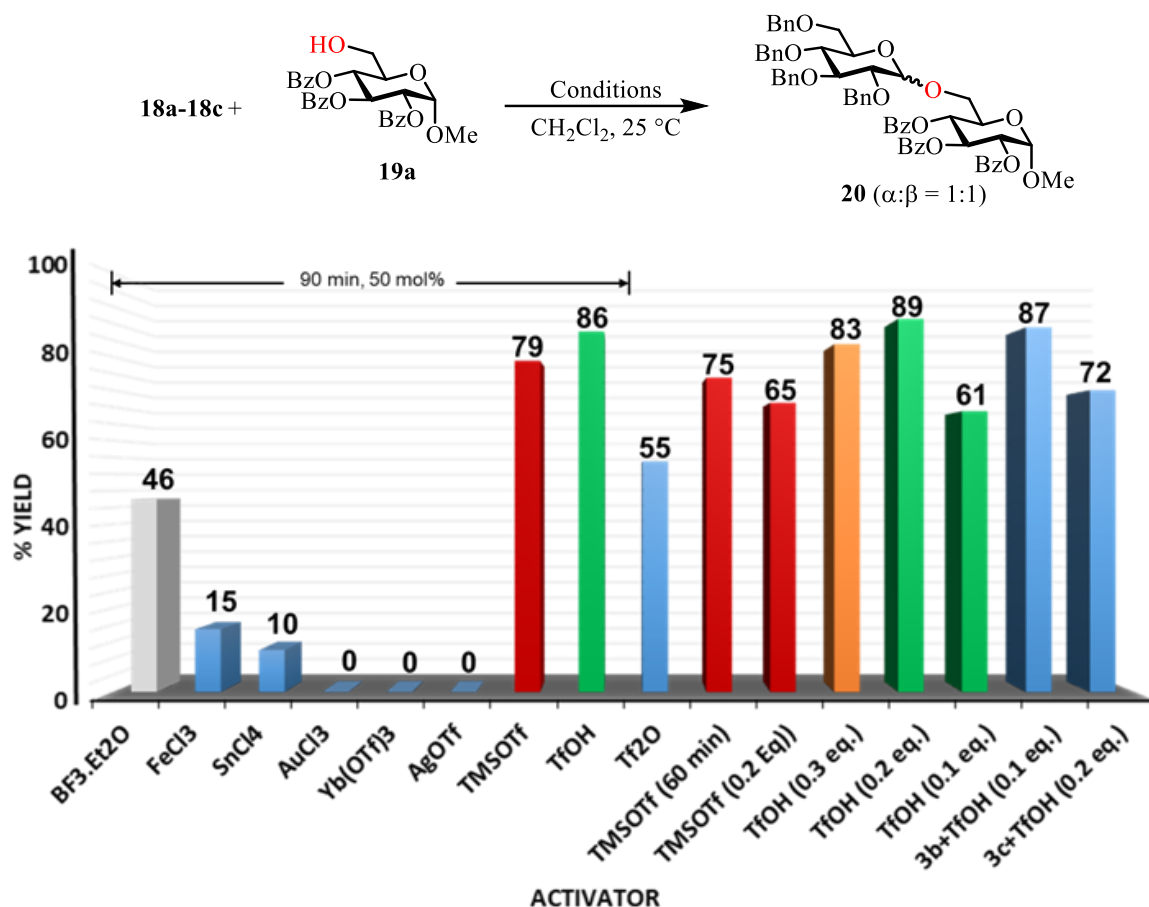
Scheme 6 Synthesis of glycosyl vinylogous carbonate donors

Similar reactions with propiolate **17b** and **17c** did not proceed as envisioned. Therefore, a more convenient procedure for the preparation of glucosyl donors **18b** and **18c** was identified to be the use of sub-stoichiometric amount of $^n\text{Bu}_3\text{P}$ in CH_2Cl_2 at room temperature for 24 hours as per the reported procedure (Scheme 6).²¹ Thus, hemiacetal **16** was treated with propiolates **17b** and **17c** in presence of 0.5 equivalents $^n\text{Bu}_3\text{P}$ to produce the corresponding vinylogous carbonates **18b** (83%) and **18c** (79%) as anomeric mixtures respectively. The successful synthesis of sufficient quantities of the glycosyl vinylogous carbonates **18a-18c** encouraged us to investigate their activation under the selected panel of Lewis/Brønsted acids with the commercially available methyl 2,3,4-tri-*O*-benzyl D-glucopyranoside **19a** as the aglycon (Scheme 7).

The investigation of glycosyl vinylogous carbonates as glycosyl donors was started with Lewis acid catalysts as promoters. The vinylogous carbonate glycoside **18a** was not activated even with 50 mol% of Lewis acids AuCl_3 , $\text{Yb}(\text{OTf})_3$, and AgOTf ; however, small amount of disaccharide **20** was observed with 50 mol% of SnCl_4 (10%) and FeCl_3 (15%). The satisfying amount of disaccharide **20** was noticed with 50 mol% of $\text{BF}_3 \cdot \text{OEt}_2$ (46%) in CH_2Cl_2 at room temperature.

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However, another powerful Lewis acid TMSOTf (50 mol%) showed 79% of the disaccharide **20** as anomeric mixture.



Scheme 7 Investigation of glycosyl vinylogous carbonates as glycosyl donors

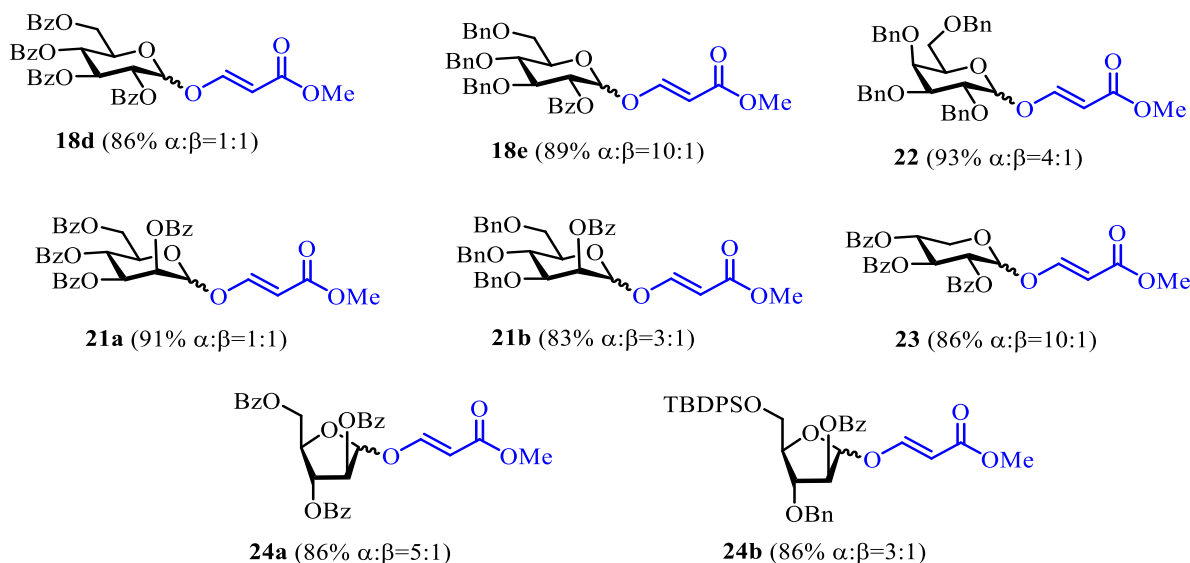
Gratifyingly, the Brønsted acid TfOH gave the disaccharide **20** in 86% yield. The Tf₂O which can also generate the Brønsted acid TfOH *in-situ* gave the disaccharide **20** albeit in diminished yield (56%). Therefore, from this screening, it has become evident that TMSOTf or TfOH are the good conditions to continue. However, reducing the amount of TMSOTf from 50 mol% to 20 mol% led to the decreased yield of disaccharide whereas TfOH did not show such kind of the trend. The disaccharide yield did not drop so much with even 20 mol% TfOH; though, further decrease indeed showed the overall efficacy of glycosylation to 61%. Encouraged by these results, we have performed the glycosylation with the donors **18b** and **18c** under the just identified glycosidation conditions which afforded the disaccharide **20** in 87% and 72% yields respectively. These facts nicely corroborate that the glycans appended with the vinylogous

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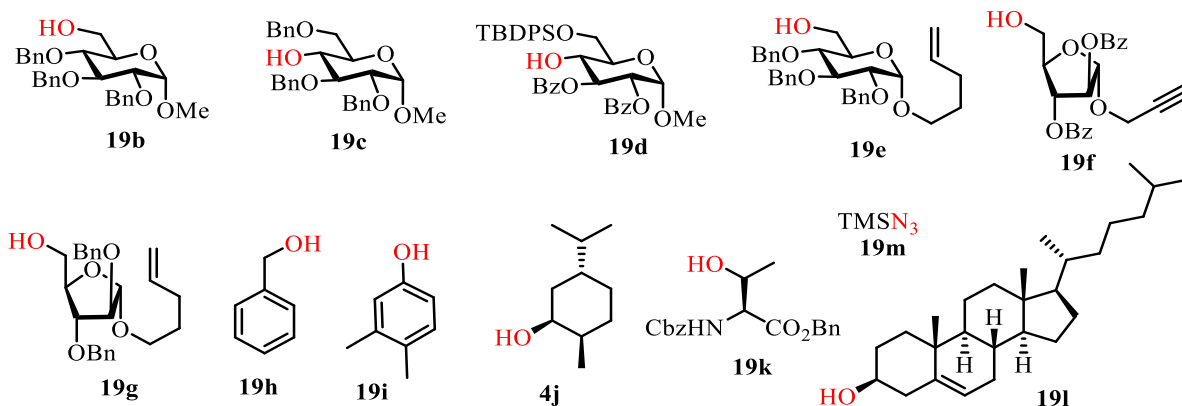
carbonate as a leaving group can be activated by Brønsted acids such as TfOH to give the same oxocarbenium ion pair intermediate as hypothesized earlier.

Encouraged by the activation protocol, we thought of exploring the scope of this glycosylation methodology with a selected panel of aglycons (**19a–19m**) and glycosyl vinylogous carbonates (**18d**, **18e**, **21a**, **21b**, **22**, **23**, **24a**, **24b**) from glucose, galactose, mannose, xylose, and arabinose (Scheme 8). Therefore the glycosyl donors have been prepared by treatment of corresponding hemiacetals with methylpropiolate **17a** invoking the aforementioned conditions in good to excellent yields.

Glycosyl Donors

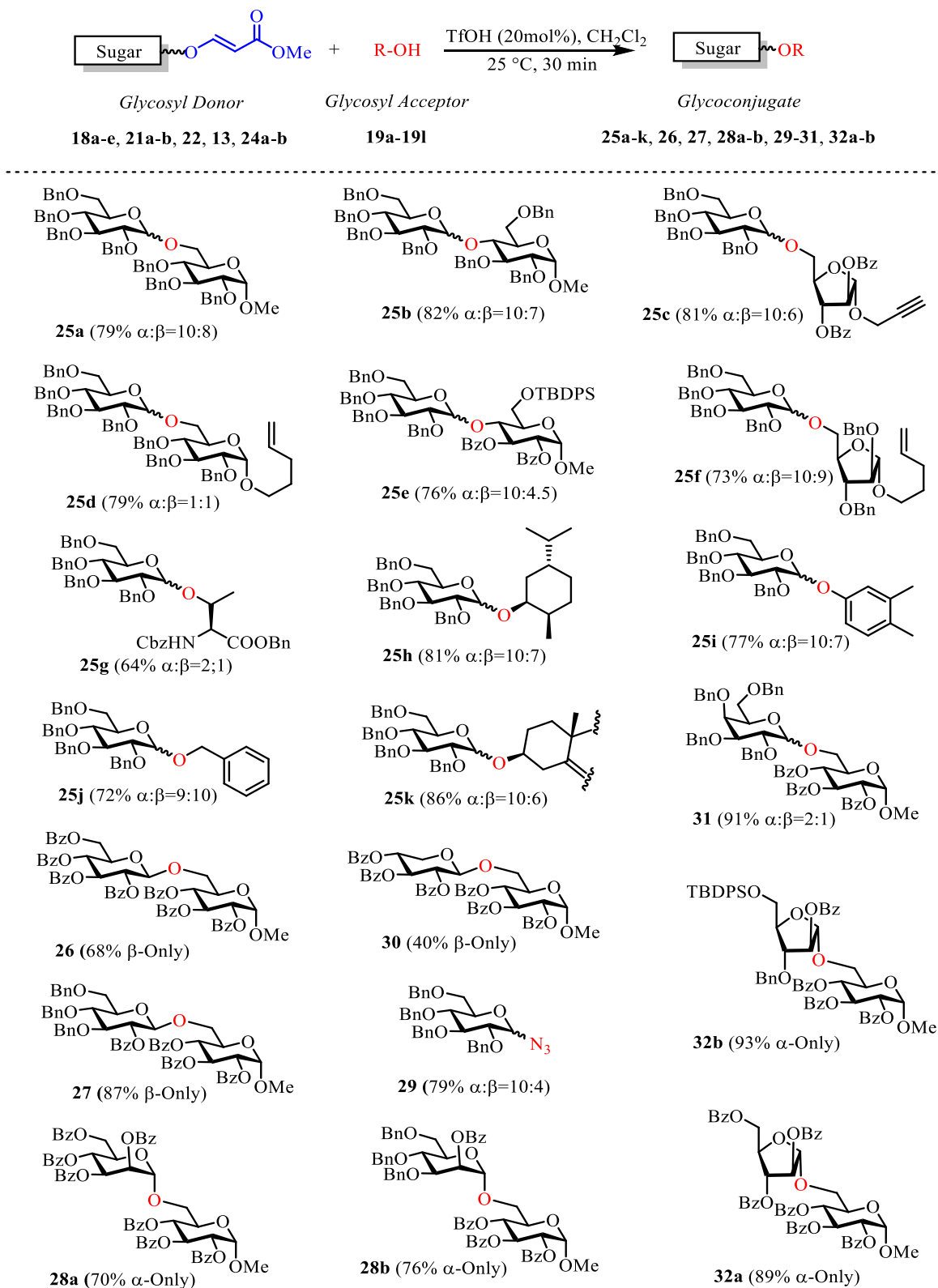


Glycosyl Acceptors



Scheme 8 List of glycosyl vinylogous carbonates and aglycons

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Scheme 9 Substrate scope of glycosyl vinylogous carbonate donors

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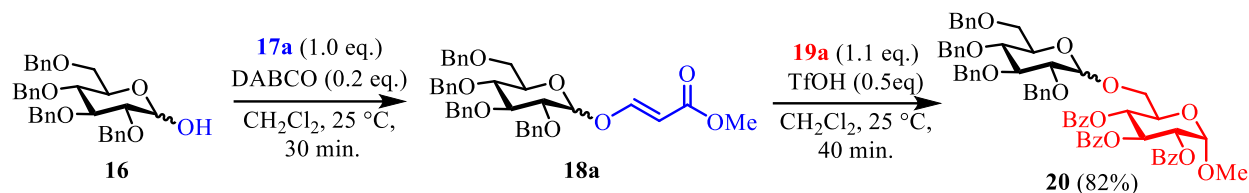
Eight disaccharides (**25a–25f**, **26**, **27**), serine glucoside (**25g**), menthyl glucoside (**25h**), phenolic glucoside (**25i**), benzylic glucoside (**25j**), and steroidal glucoside (**25k**) were synthesized by employing the aforementioned glycosylation conditions. Interestingly, there was no difference in the performance of the glycosylation with 1°-OH, 2°-OH saccharide acceptors, or non-sugar acceptors. In almost all cases, the α -anomer was found to be higher compared to the β -anomer which may be due to the predominant anomeric effect under acidic reaction conditions. Likewise, armed and super-armed glycosyl vinylogous carbonate donors were activated with 20 mol% of TfOH to produce excellent quantities of the corresponding glycoconjugates, whereas disarmed donors **18d**, **21**, and **23** required a higher amount of TfOH to produce the desired yields. It is important to note that the glycosylation between glycosyl donor **18a** and trimethylsilylazide (**25m**) as the aglycon proceeded smoothly to afford azido glucopyranoside **29** in 79% yield as an anomeric mixture (Scheme 9).

In continuation, the glucosyl vinylogous carbonates as glycosyl donors protocol has been tested on other saccharide donors (**21a**, **21b**, **22**, **23**, **24a**, **24b**). The super-armed mannopyranosyl donor **21b** underwent the glycosylation smoothly with aglycon **19a** to afford the disaccharide **28b** in 76% yield, whereas disarmed mannosparonosyl donor **21a** was activated with 50 mol% of promoter TfOH to produce the disaccharide **28a** in 70% yield with complete 1,2-*trans* diastereoselectivity. Similarly, galactopyranosyl donor **22** reacted with aglycon **19a** to produce disaccharide **31** in good yield. The glycosylation chemistry was gauged with pentose-derived donors as well. For example, xylopyranosyl vinylogous carbonate donor **23** produced the disaccharide **30** with complete β -anomeric selectivity. Contrary to this, arabinofuranosyl donors **24a** and **24b** produced disaccharides **32a** and **32b** in excellent yield with full 1,2-*trans* or α -selectivity using the 20 mol% of TfOH. These results clearly establish that this donor chemistry tolerates alkynes, alkenes, benzyl ethers, benzoates, and silyl protecting groups.

Understanding that the glycosyl vinylogous carbonate synthesis requires only 10 mol% of base (DABCO) and the activation of leaving group under acidic conditions, the one-pot synthesis of glycosyl vinylogous carbonate and its activation using the excess of promoter TfOH to undergo glycosidation was hypothesized. Therefore, in another set of experiments, hemiacetal **16** was treated with methyl propiolate **17a** and 0.1 equivalents of DABCO to notice the formation of vinylogous carbonate donor **18a**. Subsequently, aglycon **19a** was introduced, and 0.4 equivalents

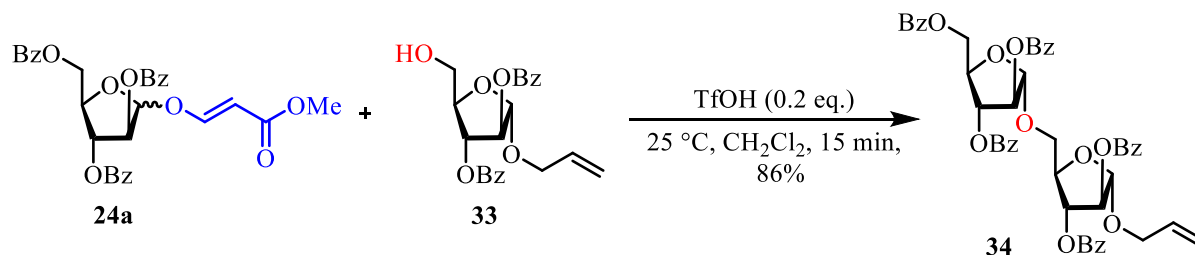
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of activator TfOH were added to obtain the disaccharide **5** in 82% yield. This proves that one can carry out donor preparation and glycosylation in a single pot (Scheme 10).



Scheme 10 One-pot synthesis of glycosyl vinylogous carbonate donor and glycosidation

Another alluring opportunity for studying the nuances of vinylogous glycosyl carbonate donor chemistry was the synthesis of a branched pentaarabinofuranoside motif of the *Mycobacterium tuberculosis* cell wall. Assembly of pentaarabinofuranoside **38** was envisioned from two easily accessible building blocks (**24a** and **33**) in five steps employing the aforementioned glycosidation condition (Scheme 12).

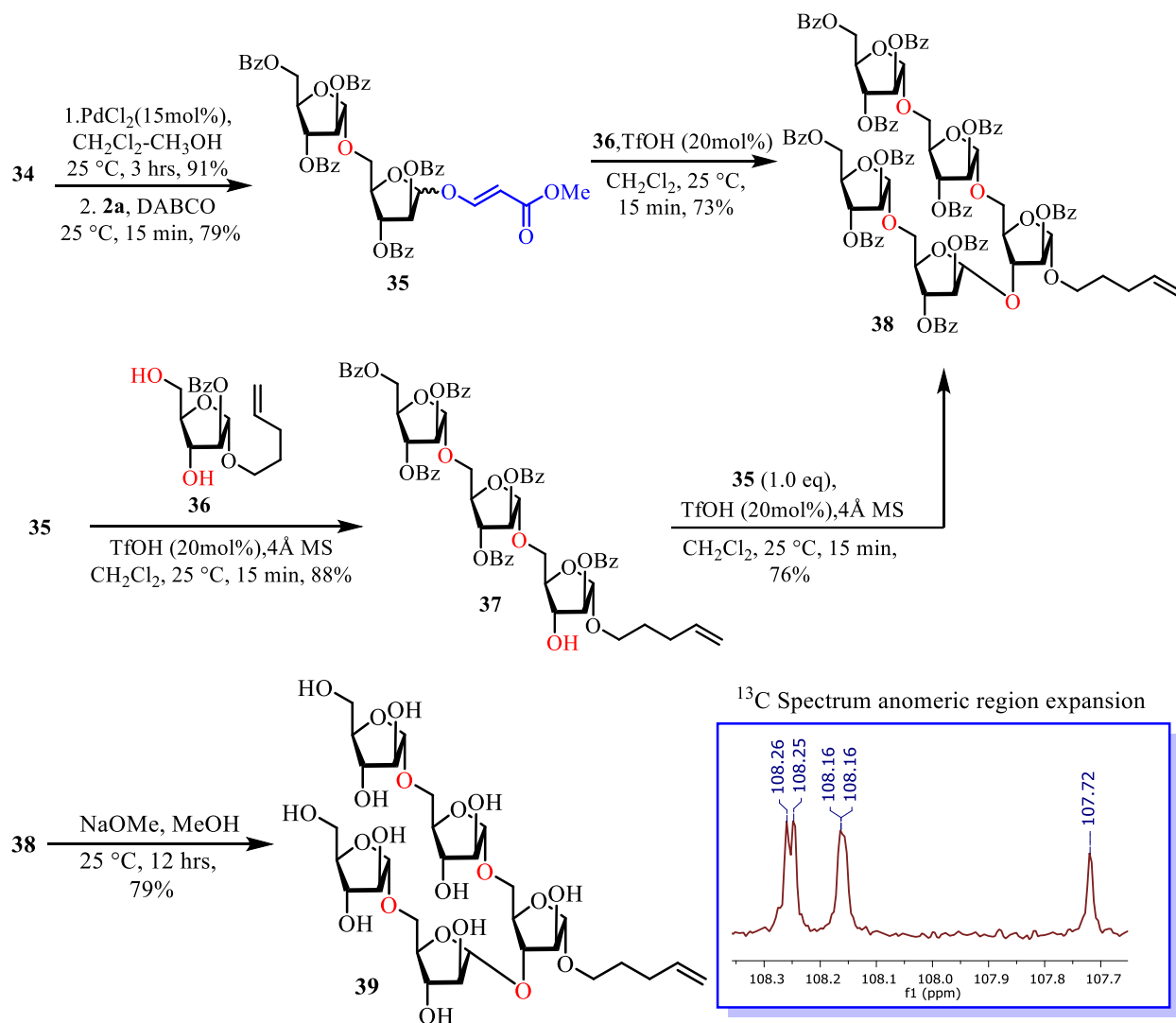


Scheme 11 Synthesis of disaccharide

Synthesis of the pentaarabinofuranoside **38** began with the TfOH-mediated furanosylation between the donor **24a** and the aglycon **33** to afford the disaccharide **34** in 86% yield with the desired 1,2-*trans* selectivity due to the strategically positioned C-2 benzoate. The ^1H NMR spectral analysis of compound **33** showed two anomeric resonances at δ 5.51 and 5.33 ppm as singlets along with a characteristic multiplet for allyl-CH at δ 5.97 ppm. The presence of five benzoates was confirmed due to the ester carbonyl resonances at δ_{C} 166.3, 165.8, 165.7, 165.4, 165.3 ppm, and two anomeric carbons were identified at δ 105.9 and 104.8 ppm. The allyl moiety of the disaccharide **33** was efficiently cleaved under palladium-catalyzed conditions to

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afford hemiacetals that were further extrapolated to the vinylogous carbonates **35**, invoking the above delineated procedure.



Scheme 12 Synthesis of branched pentaarabinofuranoside present on MTb cell surface

Subsequently, the two equivalents of donor **35** were treated with aglycon **36** to afford the pentasaccharide **38** in a 73% yield. The pentasaccharide **38** was thoroughly characterized by the NMR spectroscopic analysis. In the ¹H NMR spectrum, the five anomeric proton resonances were noticed at δ 5.53, 5.37, 5.34, 5.32, 5.18 ppm as singlets, whereas those carbons were identified at δ 106.1 (2C), 106.0 (2C), and 105.3 ppm in the ¹³C NMR spectrum. The characteristic terminal vinylic-CH₂ was observed at δ 115.1 ppm and the presence of benzoyl

esters was confirmed by eleven carbonyl carbon resonances in the spectrum. The rest of the peaks were in complete agreement with the proposed structure thereby confirming the successful synthesis of pentasaccharide **38**. While the reaction is in progress, we observed that the reaction followed a two-step process. Initially, the first glycosylation occurred with the primary alcohol, and then, slowly, the second glycosylation happened with C3-OH. Therefore, in parallel, we also explored a two-step method; initially, aglycon **36** was treated with 1 equivalent of the donor **35** to afford linear trisaccharide **37** in 88% with complete 1,2-*trans* or α -selectivity. The ^1H NMR analysis of trisaccharide **37** showed the three anomeric protons at δ 5.43 (s, 1H), 5.34 (s, 1H), 5.21 (s, 1H), ppm, and those carbons were identified at δ 106.0, 106.0, 105.3 ppm in the ^{13}C NMR spectrum. The characteristic resonances of C-2 free hydroxyl was identified at δ 3.36 ppm as broad singlet with all other resonances in agreement with the proposed structure. The fully characterized trisaccharide **37** was further extrapolated to the pentasaccharide **38** (76% yield) by the treatment of another molar equivalent of glycosyl donor **35**. All of the benzoates were saponified under modified Zemplén conditions using NaOMe and MeOH to afford the fully deprotected pentasaccharide **39** in 79% yield. In the pentasaccharide **39**, characteristic anomeric proton resonances were noticed at δ 5.07, 4.98, 4.98, 4.88, 4.88 as singlets, whereas those resonances were identified at δ 108.3, 108.2, 108.2, 108.2, 107.7 ppm in the ^{13}C NMR spectrum along with very good matching of the molecular ion in the mass spectrum (m/z calcd. for $\text{C}_{30}\text{H}_{50}\text{NaO}_{21}$: 769.2742; found: 769.2747).

3B.3 Conclusions

In summary, we have identified glycosyl vinylogous carbonates as glycosyl donors which can be activated under metal-free conditions using 20 mol % of TfOH. The glycosylation is fast, high yielding, and gauged to be suitable for the synthesis of serine glycosides, alicyclic glycosides, phenolic glycosides, benzylic glycosides, steroidal glycosides, disaccharides, trisaccharides, and pentasaccharides. The newly identified conditions were found to be suitable for Glcp-, Manp-, Galp-, Xylp-, and Araf- as glycosyl donors. Glycosyl vinylogous carbonates armed with C-2 ethers resulted in anomeric mixture of glycosides with greater α -selectivity, whereas those donors possessed with C-2 esters afforded 1,2-*trans* glycosides. Furthermore, the utility of the protocol was demonstrated by synthesizing the branched pentaarabinofuranoside moiety of the *Mycobacterium tuberculosis* cell wall.

3B.4 Experimental section

General experimental procedure for the synthesis of glycosyl vinylogous carbonates: In an oven dried round bottom flask charged with hemiacetals (1.0 eq.) and methylpropiolate (1.1 eq.) and CH₂Cl₂ (2mL/100 mg of hemiacetals) 1,4-diazabicyclo[2.2.2]octane (0.2 eq.) was added and stirred for 30-40 minutes at room temperature. After the complete consumption of hemiacetals, the reaction mixture was diluted with CH₂Cl₂ (2 mL) and purified by silica gel column chromatography using ethylacetate:hexane as mobile phase to obtain desired compounds.

This procedure has been utilized for the synthesis of glycosyl vinylogous carbonate donors: **18a**, **18d**, **18e**, **21a**, **21b**, **23**, **24**, **25a**, **25b**, **35**.

Experimental procedure for the synthesis of glycosyl vinylogous carbonates 18b and 18c:

To a solution of hemiacetals **16** (1.0eq.) in dichloromethane (2 mL/100 mg) at 0 °C was added **17b** or **17c** (1.2 eq.) and *n*-Bu₃P (0.5 eq.) and stirred at 25 °C. After 24 hrs, the reaction mixture was reduced to half the quantity and subjected to silica gel column chromatography using a binary mixture of ethylacetate:hexane as mobile phase.

General experimental procedure for the glycosylation:

To a CH₂Cl₂ (2 mL/100 mg) solution of the glycosyl donor (1.0 eq.) and an acceptor (1.1 eq.), freshly dried 4 Å molecular sieves were added, stirred for 5 minutes and 0.2 eq. of trifluoromethanesulfonic acid (note: 0.5-1.0 eq. for **18d** and **21a**) was added dropwise. The reaction mixture was stirred for 30 minutes at 25 °C, the reaction was arrested by adding excess triethylamine and then passed through the pad of Celite® to remove the molecular sieves. The organic layer was then concentrated under reduced pressure, and the crude compound was purified by silica gel flash column chromatography using ethyl acetate:hexane as mobile phase.

This procedure has been utilized for the synthesis of compounds: **20**, **25a-25k**, **26**, **27**, **28a**, **28b**, **29**, **30**, **31**, **32a**, **32b**, **34**, **37**, **38**.

Procedure for one-pot synthesis of vinylogous carbonate donor and glycosylation:

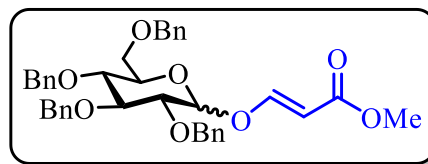
To a solution of 150 mg (0.27 mmol) of hemiacetals (**16**) in dichloromethane (2 mL), 4 Å MS powder (50 mg), 27.5 µL (0.3 mmol) methyl propiolate **17a** and 6.22 mg (0.03 mmol) of DABCO were added and the reaction mixture was then stirred at 25 °C for 30 min. After the complete conversion of hemiacetal into glycosyl vinylogous carbonate **18a** (as adjudged by TLC), 155 mg (0.28 mmol) glycosyl acceptor **19a** and 10µL (0.11 mmol) of trifluoromethanesulfonic acid were added. After 40 min, the reaction mixture was neutralized by

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the addition of excess triethylamine, filtered through a pad of Celite® and filtrate was concentrated under reduced pressure. The desired compound was then purified from the residue by silica gel column chromatography using ethyl acetate:hexane as mobile phase to obtain 235 mg of disaccharide **20** (82%).

(E)-3-methoxy-3-oxoprop-1-en-1-yl 2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranoside (18a) { $\alpha:\beta$ = 3:1}: Eluent

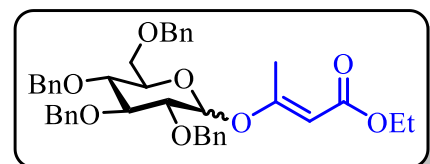
for purification: 15% ethyl acetate in *n*-hexane; yield, 4.1 g from 4.0 g of compound **16** (89%); Thick syrup; $[\alpha]^{25}_D$



(CHCl₃, *c* 1.0): +23.4°; IR (cm⁻¹, CHCl₃): 3587, 1715, 1647, 1450, 1082, 700; ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, *J* = 12.4 Hz, 1H), 7.36 – 7.15 (m, 20H), 5.57 (d, *J* = 12.4 Hz, 1H), 5.14 (d, *J* = 3.5 Hz, 1H), 4.81 (ABq, *J* = 12.8 Hz, 2H), 4.90 – 4.85 (m, 2H), 4.82 (m, 2H), 4.64 (ABq, *J* = 12.0 Hz, 2H), 4.49 (ABq, *J* = 11.4 Hz, 2H), 4.04 (t, *J* = 9.1 Hz, 1H), 3.74 (s, 3H), 3.67 (m, 3H); ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 167.8, 159.3, 138.6, 138.0, 137.9, 137.7, 128.7, 128.5(4C), 128.3, 128.3, 128.2(2C), 128.1(2C), 128.1(2C), 128.0(2C), 128.0, 127.9(2C), 127.9, 127.8, 100.9, 98.6 (C-1), 81.7, 79.0, 76.9, 75.0, 75.3, 73.9, 73.6, 71.7, 67.8, 51.3; HRMS (ESI-MS): *m/z* calculated for C₃₈H₄₀O₈ [M+Na]⁺: 647.2620, Found: 647.2615.

(E)-4-methoxy-4-oxobut-2-en-2-yl 2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranoside (18b) { $\alpha:\beta$ = 2:1}: Eluent for

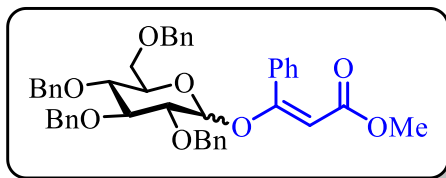
purification: 10-15% ethyl acetate in *n*-hexane; yield, 151 mg from 150 mg of hemiacetals **16** (83%); Thick syrup; $[\alpha]^{25}_D$



(CHCl₃, *c* 1.0): +81.2°; IR (cm⁻¹, CHCl₃): 2909, 2870, 1710, 1632, 1453, 1367, 1258, 1075, 835, 740; ¹H NMR (400 MHz, CDCl₃): δ 7.39 – 7.13 (m, 20H), 5.40 (s, 1H), 5.35 (m, 1H), 5.04– 4.42 (m, 8H), 4.20 – 4.09 (m, 2H), 4.06 (t, *J* = 9.20 Hz, 1H), 3.80 – 3.62 (m, 5H), 2.36 (s, 3H), 1.27 (t, *J* = 6.6 Hz, 3H); ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 169.8, 169.4, 167.9, 167.7, 138.8, 138.5, 138.1, 138.1, 137.9, 137.8(2C), 128.7, 128.5(10C), 128.5(4C), 128.5, 128.4, 128.2, 128.1, 128.0(10C), 127.0(4C), 127.9(3C), 127.9, 127.9, 127.8, 127.8, 127.7, 99.2, 95.9, 95.8, 94.2, 84.6, 81.9, 81.6, 79.4, 77.4, 77.1, 75.9, 75.8, 75.4, 75.3, 75.2, 75.1, 73.6, 73.6, 73.4, 71.5, 68.6, 68.1, 59.7, 59.6, 18.6, 18.4, 14.5, 14.5; HRMS (ESI-MS): *m/z* calculated for C₄₀H₄₄O₈ [M+Na]⁺: 675.2934, Found: 675.2936.

(E)-3-methoxy-3-oxo-1-phenylprop-1-en-1-yl 2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranoside (18c) { $\alpha:\beta$ =

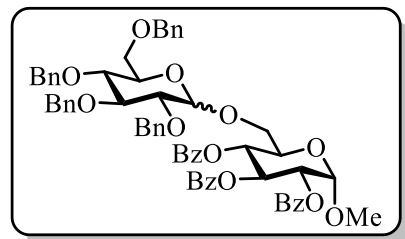
10:1}: Eluent for purification: 10% ethyl acetate in *n*-Hexane; yield, 157 mg from 150 mg of hemiacetals **16**



(79%); Thick syrup; $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +21.8°; IR (cm⁻¹, CHCl₃): 2864, 1714, 1635, 1449, 1364, 1326, 1271, 1157, 1083, 741; ¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.14 (m, 25H), 5.40 (s, 1H), 5.37 (d, *J* = 3.4 Hz, 1H, H-1), 4.98 (ABq, *J* = 10.8 Hz, 2H), 4.76 (ABq, *J* = 11.34 Hz, 2H), 4.67 (ABq, *J* = 12.0 Hz, 2H), 4.48 (m, 1H), 4.38 (ABq, *J* = 11.4 Hz, 2H), 4.29 (dt, *J* = 9.9, 2.7 Hz, 1H), 3.72 (s, 3H), 3.70 – 3.66 (m, 2H), 3.58 (d, *J* = 9.8 Hz, 1H), 3.57 (dd, *J* = 9.9, 2.8 Hz, 1H); ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 165.3, 165.2, 138.8, 138.7, 138.0(2C), 133.8, 130.2, 128.6, 128.6(2C), 128.5(2C), 128.4, 128.4(2C), 128.3(2C), 128.2(2C), 128.2(2C), 128.1, 128.0, 127.9(2C), 127.8, 127.7(2C), 127.6(2C), 127.6, 104.2, 96.0 (C-1), 81.8, 79.5, 77.7, 75.9, 74.8, 74.1, 73.3, 72.3, 68.4, 51.3; HRMS (ESI-MS): *m/z* calculated for C₄₄H₄₄O₈ [M+Na]⁺: 723.2934, Found: 723.2937.

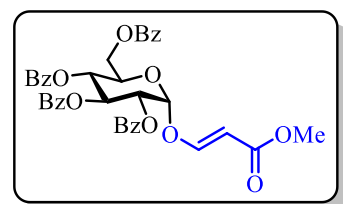
Methyl 2,3,4-tri-O-benzoyl-6-O-[2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl]- α -D-glucopyranoside (20): Eluent for the

purification: 15% ethyl acetate in *n*-hexane; yield, 2.18 g of compound **20** (83%) as a light yellow solid was obtained from 1.60 g (2.56 mmol) of donor **18a** and 1.43 g (2.82 mmol) of



aglycon **19a**; mp 52-54 °C; $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +93.8°; IR (cm⁻¹, CHCl₃): 2923, 2865, 1728, 1598, 1452, 1361, 1266, 1092, 705; ¹H NMR (400 MHz, CDCl₃): δ 8.03 – 7.82 (m, 6H), 7.56 – 7.12 (m, 29H), 6.17 (m, 1H), 5.55 (t, *J* = 9.8 Hz, 1H), 5.30 – 5.21 (m, 2H), 5.12-4.29 (m, 9H), 3.99 (t, *J* = 9.3 Hz, 1H), 3.91-3.81(m, 2H), 3.64 (m, 6H), 3.45 (s, 3H); ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 165.9, 165.9, 165.4, 138.9, 138.7, 138.5, 138.0, 133.5, 133.2, 130.0(3C), 130.0, 129.8, 129.8, 129.4, 129.2, 129.1, 128.5(4C), 128.5, 128.4(2C), 128.4(2C), 128.3, 128.1, 128.0(2C), 128.0(2C), 128.0, 127.9, 127.8(2C), 127.8, 127.7, 127.6, 127.6, 97.4 (C-1), 96.9 (C-1'), 81.9, 80.1, 77.7, 75.6, 74.9, 73.5, 73.2, 72.4, 70.7, 70.3, 69.8, 68.7, 68.4, 66.8, 55.7; HRMS (ESI-MS): *m/z* calculated for C₆₂H₆₀O₁₄ [M+Na]⁺: 1051.3881, Found: 1051.3879.

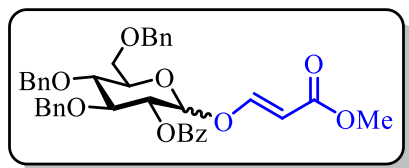
(E)-3-methoxy-3-oxoprop-1-en-1-yl 2,3,4,6-tetra-O-benzoyl- α -D-glucopyranoside (18d- α): Eluent for purification: 20% ethyl



acetate in *n*-hexane; yield, 148 mg from 150 mg of hemiacetals (86%); white solid; While purifying, the α -isomer was isolated in pure form and hence, characterized. mp 152-154 °C; $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +26.6°; IR (cm⁻¹, CHCl₃): 2986, 2968, 1723, 1648, 1448, 1262, 1089; ¹H NMR (400 MHz, CDCl₃): δ 8.07 –(m, 8H), 7.60 (d, *J* = 12.5 Hz, 1H), 7.58 – 7.25 (m, 12H), 6.24 (t, *J* = 10.0 Hz, 1H), 5.80 (d, *J* = 3.6 Hz, 1H, H-1), 5.75 (t, *J* = 9.7 Hz, 1H), 5.70 (d, *J* = 12.7 Hz, 1H), 5.43 (dd, *J* = 10.3, 3.6 Hz, 1H), 4.60 (dd, *J* = 12.0, 2.3 Hz, 1H), 4.45 (m, 2H), 3.65 (s, 3H); ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 167.2, 166.2, 165.8, 165.8, 165.8, 158.1, 133.8, 133.7, 133.4, 133.3, 130.1(2C), 130.0(2C), 129.9(3C), 129.9(3C), 129.6, 128.9, 128.7(2C), 128.6(3C), 128.6(2C), 128.5, 102.3, 96.5 (C-1), 71.1, 70.0, 69.5, 68.8, 62.6, 51.5; HRMS (ESI-MS): *m/z* calculated for C₃₈H₃₂O₁₂ [M+Na]⁺: 703.1791, Found: 703.1794.

(E)-3-methoxy-3-oxoprop-1-en-1-yl 2-O-benzoyl-3,4,6-tri-O-benzyl- α/β -D-glucopyranoside (18e) { $\alpha:\beta$ = 10:1}: Eluent

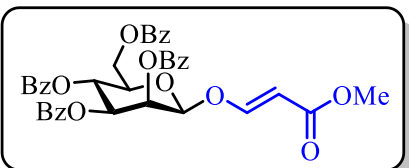
for purification: 15% ethyl acetate in *n*-Hexane; yield 154 mg from 150 mg of hemiacetals (89%); Light yellow thick syrup;



$[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): +116.4°; IR (cm⁻¹, CHCl₃): 3001, 2886, 1721, 1646, 1452, 1268, 1111, 1043, 711; ¹H NMR (400 MHz, CDCl₃): δ 8.02 (m, 2H), 7.52 (d, *J* = 12.5 Hz, 1H), 7.51-7.15 (m, 18H), 5.59 (d, *J* = 3.6 Hz, 1H, H-1), 5.54 (d, *J* = 12.5 Hz, 1H), 5.23 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.83 (s, 2H), 4.71 (ABq, *J* = 10.8 Hz, 2H), 4.57 (ABq, *J* = 12.0 Hz, 2H), 4.22 (t, *J* = 9.2 Hz, 1H), 3.91 (t, *J* = 9.3 Hz, 1H), 3.81 (m, 2H), 3.70-3.63 (m, 1H), 3.65 (s, 3H); ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 167.5, 165.8, 158.8, 138.0, 137.9, 137.8, 133.5, 129.9(2C), 129.3, 128.6(2C), 128.5(4C), 128.4(2C), 128.0(5C), 127.9(3C), 127.9, 127.8, 101.2, 97.5 (H-1), 79.7, 75.7, 75.3, 73.6, 73.0, 72.1, 67.9, 51.3; HRMS (ESI-MS): *m/z* calculated for C₃₈H₃₈O₉ [M+Na]⁺: 661.2413, Found: 661.2408.

(E)-3-methoxy-3-oxoprop-1-en-1-yl 2,3,4,6-tetra-O-benzoyl- β -D-mannopyranoside (21a- β): Eluent for

purification: 20% ethyl acetate in *n*-Hexane; yield, 207 mg from 200 mg of hemiacetals (91%); Thick syrup; While

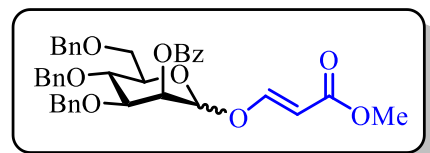


purifying, the β -isomer was isolated in pure form and hence, characterized. $[\alpha]^{25}_D$ (CHCl₃, *c* 1.0): -0.60°; IR (cm⁻¹, CHCl₃): 2985, 2864 1723, 1647, 1448, 1259, 1169, 1100, 974, 703; ¹H NMR (400 MHz, CDCl₃): δ 8.12– 7.82 (m, 8H), 7.67 (d, *J* = 12.5 Hz, 1H), 7.65 – 7.24 (m, 12H), 6.18 (t, *J* = 10.1 Hz, 1H), 5.96 (dd, *J* = 10.2, 3.3 Hz, 1H), 5.84 (dd, *J* = 3.8, 1.0 Hz, 1H), 5.74 (d,

$J = 12.5$ Hz, 1H), 5.58 (d, $J = 1.0$ Hz, 1H, H-1), 4.71 (dd, $J = 12.2, 2.0$ Hz, 1H), 4.49 (dd, $J = 12.3, 4.6$ Hz, 1H), 4.42 (ddd, $J = 10.0, 4.2, 2.0$ Hz, 1H), 3.71 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 167.1, 166.1, 165.5, 165.4, 165.3, 157.4, 133.9, 133.7, 133.5, 133.2, 130.0(2C), 129.9(2C), 129.9(2C), 129.8(2C), 129.7, 128.9, 128.8(2C), 128.8, 128.6(2C), 128.6(3C), 128.5(2C), 102.4, 97.6, 70.3, 69.5, 69.3, 66.2, 62.4, 51.5; HRMS (ESI-MS): m/z calculated for $\text{C}_{38}\text{H}_{32}\text{O}_{12} [\text{M}+\text{Na}]^+$: 703.1791, Found: 703.1784.

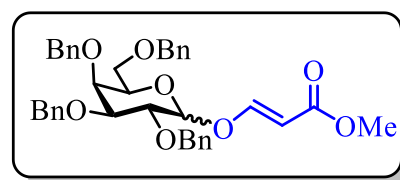
(E)-3-methoxy-3-oxoprop-1-en-1-yl 2-O-benzoyl-3,4,6-tri-O-benzyl- α/β -D-mannopyranoside (21b) $\{\alpha:\beta = 3:1\}$:

Eluent of the purification: 15% ethyl acetate in *n*-Hexane; yield 143 mg from 150 mg of hemiacetals (83%); Light yellow syrup; $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , c 1.0): $+26.0^\circ$; IR (cm^{-1} , CHCl_3): 2986, 2859, 1720, 1647, 1450, 1269, 1109, 1038, 974, 707; ^1H NMR (400 MHz, CDCl_3): δ 8.08 – 8.04 (m, 2H), 7.57 (d, $J = 12.5$ Hz, 1H), 7.63 – 7.20 (m, 18H), 5.72 (dd, $J = 2.1, 2.9$ Hz, 1H), 5.56 (d, $J = 12.5$ Hz, 1H), 5.41 (d, $J = 1.7$ Hz, 1H, H-1), 4.96 – 4.49 (m, 7H), 4.18 (dd, $J = 9.3, 3.3$ Hz, 1H), 4.10 (t, $J = 9.5$ Hz, 1H), 3.98 (dt, $J = 9.8, 2.9$ Hz, 1H), 3.81 (ddd, $J = 9.5, 3.2, 1.6$ Hz, 1H), 3.69 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 167.5, 165.6, 158.0, 138.3, 138.2, 137.7, 133.5, 130.1(3C), 129.5, 128.6(2C), 128.5(4C), 128.4(2C), 128.1, 128.1, 127.9(2C), 127.8, 127.7, 127.6(2C), 101.5, 98.4 (C-1), 77.6, 75.5, 73.6, 73.5, 73.1, 71.9, 68.5, 67.8, 51.4; HRMS (ESI-MS): m/z calculated for $\text{C}_{38}\text{H}_{38}\text{O}_9 [\text{M}+\text{Na}]^+$: 661.2413, Found: 661.2411.



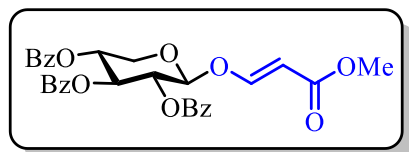
(E)-3-methoxy-3-oxoprop-1-en-1-yl 2,3,4,6-tetra-O-benzyl- α/β -D-galactopyranoside (22) $\{\alpha:\beta = 4:1\}$:

Eluent for purification: 15% ethyl acetate in *n*-hexane; yield, 136 mg from 127 mg of hemiacetals (93%); Pale yellow syrup; $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , c 1.0): $+59.6^\circ$; IR (cm^{-1} , CHCl_3): 3587, 2900, 1715, 1647, 1450, 1082, 700; ^1H NMR (400 MHz, CDCl_3): δ 7.52 (d, $J = 12.5$ Hz, 1H), 7.31–7.13 (m, 20H), 5.53 (d, $J = 12.5$ Hz, 1H), 5.11 (d, $J = 3.4$ Hz, 1H, H-1), 5.09 – 4.39 (m, 9H), 4.02 (dd, $J = 8.9, 9.2$ Hz, 1H), 3.69 (s, 3H), 3.64 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 167.8, 159.3, 138.6, 138.1, 137.7, 137.7, 128.7, 128.5(2C), 128.5(3C), 128.5(3C), 128.3, 128.3, 128.2, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 100.9, 98.5 (C-1), 81.7, 79.1, 76.9, 75.9, 75.3, 73.8, 73.6, 71.7, 67.9, 51.3; HRMS (ESI-MS): m/z calculated for $\text{C}_{38}\text{H}_{40}\text{O}_8 [\text{M}+\text{Na}]^+$: 647.2621, Found: 647.2620.



(E)-3-methoxy-3-oxoprop-1-en-1-yl 2,3,4-tri-O-benzoyl-β-D-xylopyranoside (23β):

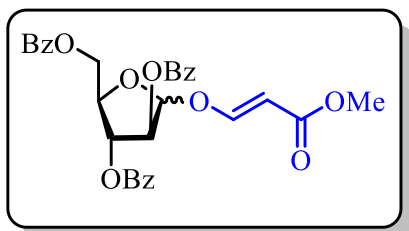
Eluent for purification: 20% ethyl acetate in *n*-hexane; yield, 122 mg from 120 mg of hemiacetals (86%); Thick syrup; While purifying, the β-



isomer was isolated in pure form and hence, characterized. $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): +128.6°; IR (cm^{-1} , CHCl_3): 2903, 2864, 1723, 1647, 1263, 1173, 1104, 1036, 707; ^1H NMR (400 MHz, CDCl_3): δ 7.95 (m, 6H), 7.56 (d, J = 12.5 Hz, 1H), 7.55-7.25 (m, 9H), 6.21 (t, J = 9.9 Hz, 1H), 5.72 (d, J = 3.3 Hz, 1H, H-1), 5.66 (d, J = 12.5 Hz, 1H), 5.49 (td, J = 10.2, 5.9 Hz, 1H), 5.40 (dd, J = 10.1, 3.3 Hz, 1H), 4.20 (dd, J = 11.1, 5.8 Hz, 1H), 3.83 (t, J = 10.9 Hz, 1H), 3.69 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 167.3, 165.8, 165.7, 165.5, 158.4, 133.7, 133.6, 133.4, 130.0(2C), 129.9(2C), 129.8(2C), 129.1, 128.8, 128.6(3C), 128.6(2C), 128.5(2C), 101.9, 97.0 (C-1), 70.9, 69.5(2C), 60.0, 51.4; HRMS (ESI-MS): m/z calculated for $\text{C}_{30}\text{H}_{26}\text{O}_{10}$ $[\text{M}+\text{Na}]^+$: 569.1424, Found: 569.1426.

(E)-3-methoxy-3-oxoprop-1-en-1-yl 2,3,5-tri-O-benzoyl-α/β-D-arabinofuranoside (24a) { $\alpha:\beta$ = 5:1}:

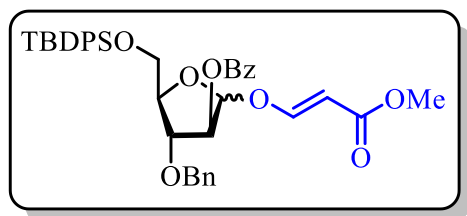
Eluent for the purification: 20% ethyl acetate in *n*-hexane; yield, 161 mg from 150 mg of hemiacetals (91%); Thick syrup; $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): -17.0°; IR (cm^{-1} , CHCl_3): 2900, 2878,



1723, 1267, 1109, 1037, 712; ^1H NMR (400 MHz, CDCl_3): δ 8.09 – 7.96 (m, 6H), 7.64 (d, J = 12.5 Hz, 1H), 7.52 – 7.38 (m, 9H), 5.72 (s, 1H), 5.67 (d, J = 0.9 Hz, 1H), 5.65 (d, J = 3.7 Hz, 1H), 5.58 (d, J = 12.5 Hz, 1H), 4.87 – 4.79 (m, 1H), 4.72 – 4.66 (m, 1H), 4.68 (d, J = 2.0 Hz, 1H), 3.72 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 167.6, 166.2, 165.8, 165.4, 158.1, 134.0, 133.9, 133.3, 130.1(3C), 129.9(2C), 129.6, 128.9, 128.8(3C), 128.7(2C), 128.6, 128.5(2C), 105.8 (C-1), 101.4, 83.2, 81.4, 77.3, 63.4, 51.4; HRMS (ESI-MS): m/z calculated for $\text{C}_{30}\text{H}_{26}\text{O}_{10}$ $[\text{M}+\text{Na}]^+$: 569.1423, Found: 569.1424.

(E)-3-methoxy-3-oxoprop-1-en-1-yl 2-O-benzoyl-3-O-benzyl-5-O-^tbutyldiphenylsilyl-α/β-D-arabinofuranoside (24b) { $\alpha:\beta$ = 3:1}:

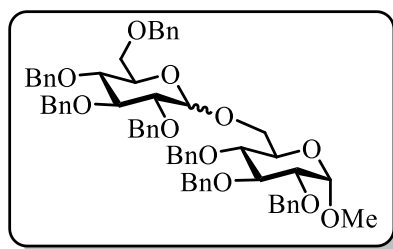
Eluent for purification: 15% ethyl acetate in *n*-hexane; yield, 132 mg from 150 mg of hemiacetals (77%); Light yellow thick



syrup; $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): $+40.4^\circ$; IR (cm^{-1} , CHCl_3): 2926, 2859, 1719, 1644, 1451, 1267, 1099, 961, 827, 798, 702; ^1H NMR (400 MHz, CDCl_3): δ 7.96 (m, 2H), 7.66 – 7.58 (m, 7H), 7.40 – 7.29 (m, 12H), 5.55 (d, J = 7.7 Hz, 1H), 5.53 (d, J = 11.8 Hz, 1H), 4.79 (ABq, J = 12.0 Hz, 2H), 4.61 (d, J = 12.0 Hz, 1H), 4.30 (m, 2H), 3.86 – 3.79 (m, 2H), 3.69 (s, 3H), 1.00 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 167.8, 165.4, 158.5, 137.4, 135.7(2C), 135.7, 135.6(2C), 133.7, 133.2, 133.1, 129.9, 129.9(2C), 129.9, 129.0, 128.6(2C), 128.5(3C), 128.0(2C), 127.9(2C), 127.8, 127.8, 127.7, 106.4 (C-1), 100.6, 85.1, 82.3, 81.8, 72.5, 62.6, 51.3, 26.8, 19.4; HRMS (ESI-MS): m/z calculated for $\text{C}_{39}\text{H}_{42}\text{O}_8\text{Si}$ $[\text{M}+\text{Na}]^+$: 689.2547, Found: 689.2536.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-[2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl]- α -D-glucopyranoside (25a) $\{\alpha:\beta = 10:8\}$:

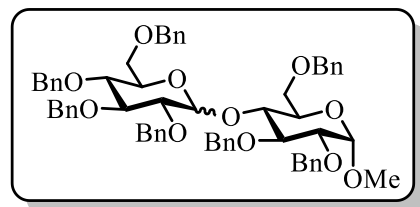
Eluent for purification: 10% ethyl acetate in *n*-hexane; yield, 100 mg from 80 mg of compound **18a** (79%); Thick syrup; $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): $+84.2^\circ$; IR (cm^{-1} , CHCl_3): 2902, 2888,



1645, 1454, 1085, 739; ^1H NMR (400 MHz, CDCl_3): δ 7.40 – 7.28 (m, 35H), 5.15 (d, J = 3.4 Hz, 1H), 4.99 – 4.25 (m, 15H), 4.10–4.38 (m, 12H), 3.32 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 139.0, 138.9(3C), 138.8, 138.7, 138.7, 138.6, 138.4, 138.4, 138.3, 138.2, 128.5, 128.4, 128.4(9C), 128.4(20), 128.3(3C), 128.3, 128.1(5C), 128.1, 128.0(4C), 128.0, 128.0, 127.9, 127.8(3C), 127.8, 127.7(7C), 127.7, 127.6(3C), 127.6(3C), 127.6, 127.5, 104.2, 99.1, 99.0, 96.7, 84.8, 82.3, 81.8, 80.4, 80.3, 80.2, 78.0, 77.8, 77.4, 75.8, 75.6, 75.2, 75.1(3C), 75.1, 75.0(2C), 74.9, 74.7, 73.6, 73.5, 72.9, 72.9, 72.7, 72.3, 72.1, 71.8, 71.5, 70.2, 69.2, 68.6, 66.1, 54.9, 54.8; HRMS (ESI-MS): m/z calculated for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{Na}]^+$: 1009.4503, Found: 1009.4507.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-[2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl]- α -D-glucopyranoside (25b) $\{\alpha:\beta = 10:7\}$:

Eluent for purification: 10% ethyl acetate in *n*-hexane; yield, 108 mg from 83 mg of compound **18a** (82%); Light yellow thick syrup; $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): $+24.6^\circ$; IR (cm^{-1} ,

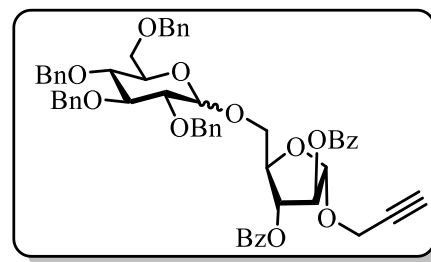


CHCl_3): 2916, 1217, 750, 670; ^1H NMR (400 MHz, CDCl_3): δ 7.48–7.28 (m, 35H), 5.18 – 4.19 (m, 16H), 4.20–3.87 (m, 4H), 3.81–3.49 (m, 7H), 3.43 (s, 3H), 3.48–3.32 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 139.7, 139.1, 138.9, 138.7, 138.7, 138.7, 138.6, 138.5, 138.4, 138.3, 138.1(2C), 138.1, 138.0, 128.6(4C), 128.6, 128.5(4C), 128.5(10C), 128.5, 128.4(6C), 128.4(12C), 128.4(6C), 128.2, 128.2, 128.1, 128.1, 128.1, 128.1, 128.0, 127.9(3C), 127.9(2C),

127.9(2C), 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.5, 127.5, 127.4, 127.2, 126.9, 102.6, 98.6, 97.9, 96.8, 85.0, 82.9, 82.2, 80.5, 80.3, 79.6, 79.0, 78.2, 77.8, 76.7, 75.7, 75.7, 75.5, 75.3, 75.1, 75.0, 74.9, 74.5, 73.8, 73.6, 73.5(3C), 73.5, 73.8, 73.3, 72.4, 71.1, 70.1, 69.7, 69.2, 69.1, 68.3, 68.0, 55.4, 55.3; HRMS (ESI-MS): m/z calculated for $C_{62}H_{66}O_{11}$ $[M+Na]^+$: 1009.4503, Found: 1009.4507.

Propargyl 2,3-di-O-benzoyl-5-O-[2,3,4,6-tetra-O-benzyl-
 α/β -D-glucopyranosyl]- α -D-arabinofuranoside (25c) { $\alpha:\beta$

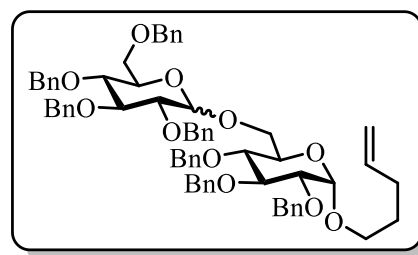
= 10:6}: Eluent for purification: 15% ethyl acetate in *n*-hexane; yield, 119 mg from 100 mg of compound **18a** (81%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +14.6°; IR (cm^{-1} , $CHCl_3$): 2922, 2881, 1730, 1454, 1268, 1070, 705; 1H NMR



(400 MHz, $CDCl_3$): δ 8.12 (m, 2H), 7.96 (m, 2H), 7.63 – 7.36 (m, 26H), 5.85 – 5.76 (m, 2H), 5.61 – 4.43 (m, 12H), 4.13–3.44 (m, 9H), 2.52 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 165.3, 165.2, 165.2, 138.9, 138.6, 138.5, 138.4, 138.3, 138.1, 138.1, 137.9, 133.5(2C), 133.3, 133.3, 129.9(3C), 129.7(3C), 129.3, 129.3, 129.1, 129.0, 128.5(2C), 128.5, 128.4(11C), 128.4(11C), 128.4, 128.3, 128.3, 128.1(2C), 128.0(5C), 128.0, 127.9(3C), 127.9, 127.8(3C), 127.8, 127.7, 127.6(3C), 127.6, 127.6, 103.7, 103.3, 103.1, 97.6, 84.6, 82.3, 81.9, 80.8, 80.1, 80.0, 78.7, 78.6, 77.8, 77.6, 77.3, 75.7, 75.7, 75.5, 75.4, 75.3, 75.2, 75.0, 74.9, 74.9, 73.5, 73.5, 73.3, 72.4, 72.3, 70.7, 70.6, 69.8, 68.8, 68.4, 54.3, 54.2; HRMS (ESI-MS): m/z calculated for $C_{56}H_{54}O_{12}$ $[M+Na]^+$: 941.3513, Found: 941.3516.

Pent-4-enyl 2,3,4-tri-O-benzyl-6-O-[2,3,4,6-tetra-O-
benzyl- α/β -D-glucopyranosyl]- α -D-glucopyranoside (25d)

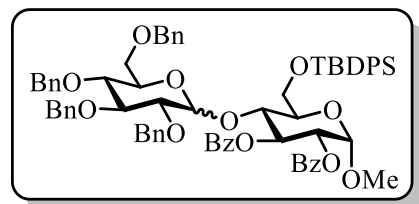
{ $\alpha:\beta$ = 1:1}: Eluent for purification: 10% ethyl acetate in *n*-hexane; yield, 132 mg from 100 mg of compound **18a** (79%); One isomer was isolated and characterized; Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +57.0°; IR (cm^{-1} , $CHCl_3$): 2880,



1454, 1361, 1152, 1082, 917, 739; 1H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.14 (m, 35H), 5.82 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.06 – 4.64 (m, 14H), 4.58 (dd, J = 12.1, 6.7 Hz, 2H), 4.48 (t, J = 12.1 Hz, 2H), 3.99 (m, 2H), 3.89– 3.37 (m, 12H), 2.18 – 2.09 (m, 2H), 1.75 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.1, 139.0, 138.6, 138.6, 138.5, 138.2, 138.1, 128.5(5C),

128.5(2C), 128.5(2C), 128.5(3C), 128.4, 128.1(2C), 128.1(2C), 128.0(4C), 127.9(3C), 127.9(3C), 127.9(2C), 127.8, 127.7(3C), 127.7, 127.7, 127.6, 115.0, 97.4, 96.8, 82.2, 81.9, 80.5, 80.1, 78.0, 77.7, 75.8, 75.7, 75.2, 75.0, 73.5, 73.3, 72.4, 70.6, 70.4, 68.6, 67.6, 66.2, 30.4, 28.7; HRMS (ESI-MS): m/z calculated for $C_{66}H_{72}O_{11}[M+Na]^+$: 1063.4972, Found: 1063.4955.

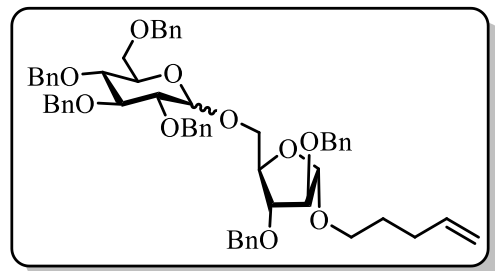
Methyl 2,3-di-O-benzoyl-6-O-^tbutyldiphenylsilyl-4-O-[2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl]- α -D-glucopyranoside (25e) { $\alpha:\beta$ = 10:4.5}: Eluent for



purification: 10% ethyl acetate in *n*-hexane; yield, 138 mg from 100 mg of compound **18a** (76%); Light yellow thick

syrup; Yield (76%); $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +6.0°; IR (cm^{-1} , $CHCl_3$): 3430, 3360, 3285, 2900, 1467, 1267, 1089, 871, 705; 1H NMR (400 MHz, $CDCl_3$): δ 7.91 – 7.88 (m, 4H), 7.65 (m, 6H), 7.24 – 7.11 (m, 30H), 6.07 (t, J = 9.5 Hz, 1H), 5.11 – 5.08 (m, 4H), 4.82–4.03 (m, 12H), 3.98–3.58 (m, 5H), 3.47 (t, J = 9.5 Hz, 1H), 3.40 (dd, J = 10.4, 2.9 Hz, 1H), 3.27 (s, 3H), 3.30–3.13 (m, 2H), 1.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.2, 165.7, 138.9, 138.5, 138.1, 137.9, 136.0(2C), 135.9, 135.7(2C), 135.6, 133.9, 133.3, 133.2, 132.9, 130.1, 130.0(3C), 129.9, 129.8, 129.7, 129.6, 129.2, 128.4, 128.3(9C), 128.3(3C), 128.2(2C), 128.2, 127.9, 127.8, 127.8, 127.6, 127.6, 127.6, 127.6, 127.5, 127.5, 98.2, 96.5, 81.5, 79.3, 77.2, 75.4, 74.9, 74.8, 73.4, 72.6, 72.2, 71.5, 71.1, 68.4, 62.9, 55.0, 27.0(3C), 19.5; HRMS (ESI-MS): m/z calculated for $C_{71}H_{78}O_{11}Si [M+Na]^+$: 1157.5211, Found: 1157.5218.

Pent-4-enyl 2,3-di-O-benzyl-5-O-[2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl]- α -D-arabinofuranoside (25f) { $\alpha:\beta$ = 10:9}: Eluent for



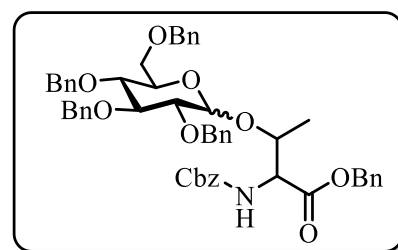
purification: 10% ethyl acetate in *n*-hexane; yield, 108 mg from 100 mg of compound **18a** (73%); Yellowish thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +24.4°; IR (cm^{-1} ,

$CHCl_3$): 2919, 2864, 1454, 1366, 1077, 912, 740, 699; 1H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.14 (m, 30H), 5.83 (ddt, J = 13.2, 10.1, 6.6 Hz, 1H), 5.10 – 4.44 (m, 16H), 4.34 – 3.35 (m, 13H), 2.13 (m, 2H), 1.69 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 138.9, 138.6, 138.6, 138.4, 138.4, 138.2(2C), 138.2(2C), 138.1, 138.0, 138.0, 137.9, 137.6, 137.6, 128.4(4C), 128.4(4C), 128.4(12C), 128.3, 128.3(4C), 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9(9C), 127.9, 127.9, 127.9, 127.8(3C), 127.8(4C), 127.8, 127.7, 127.7, 127.7, 127.6, 127.6,

127.6, 127.5, 127.5, 127.5, 114.8, 114.8, 106.1, 106.0, 103.9, 97.3, 88.5, 88.4, 84.6, 84.0, 84.0, 82.0, 81.9, 80.1, 80.0, 80.0, 75.7, 75.6, 75.0, 75.0, 74.9, 74.6, 73.5, 73.4, 72.8, 72.2, 72.2, 72.1, 72.0, 70.2, 69.8, 68.9, 68.4, 67.7, 67.0, 66.8, 30.3, 30.3, 28.8, 28.7; HRMS (ESI-MS): m/z calculated for $C_{58}H_{64}O_{10}$ $[M+Na]^+$: 943.4397, Found: 943.4390.

Benzyl N-((benzyloxy)carbonyl)-L-allothreoninate 2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranoside (25g) $\{\alpha:\beta = 2:1\}$:

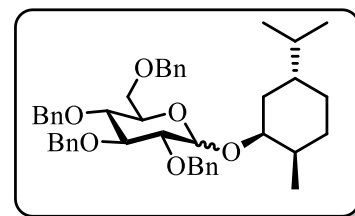
Eluent for purification: 25% ethyl acetate in *n*-hexane; yield, 71 mg from 80 mg of compound **18a** (64%); Light orange thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +38.2°; IR (cm^{-1} , $CHCl_3$): 3753, 2916, 2865, 1728, 1505, 1454, 1210, 1071, 742; 1H



NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.13 (m, 30H), 5.95 (d, $J = 8.5$ Hz, 1H), 5.34-4.31 (m, 13H), 3.94 (t, $J = 9.3$ Hz, 1H), 3.86 (dd, $J = 12.5, 3.3$ Hz, 1H), 3.77 (dd, $J = 10.6, 3.7$ Hz, 1H), 3.74-3.53 (m, 3H), 3.50 (dd, $J = 9.7, 3.7$ Hz, 1H), 3.45 – 3.26 (m, 1H), 1.31 (d, $J = 6.4$ Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.7, 170.4, 156.9, 156.9, 138.8, 138.7, 138.3, 138.2, 138.0, 138.0, 136.4, 136.4, 135.6, 135.4, 128.7(5C), 128.6(5C), 128.5(22C), 128.5, 128.4, 128.3, 128.2(4C), 128.2(5C), 128.1, 128.0(3C), 128.0(4C), 128.0(3C), 127.9(4C), 127.9, 127.8, 127.8, 127.7, 127.7, 101.5, 98.1, 84.6, 82.0, 81.8, 79.7, 77.7, 75.7, 75.7(2C), 75.3, 75.1, 75.1, 74.8, 73.6, 73.5, 73.2, 71.1, 68.7, 68.4, 67.4, 67.3, 67.2, 67.2, 59.2, 59.1, 19.2, 17.8; HRMS (ESI-MS): m/z calculated for $C_{53}H_{55}O_{10}$ $[M+Na]^+$: 888.3724, Found: 888.3727.

Menthyl 2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranoside (25h) $\{\alpha:\beta = 10:7\}$:

Eluent for purification: 10% ethyl acetate in *n*-hexane; yield, 70 mg from 100 mg of compound **18a** (81%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +10.2°; IR (cm^{-1} , $CHCl_3$): 2923, 2852, 1454, 1070, 739; 1H NMR (400 MHz, $CDCl_3$): δ 7.34

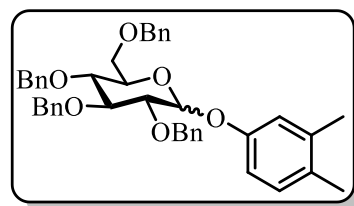


– 7.12 (m, 20H), 5.10 – 4.47 (m, 9H), 4.06 (dd, 12.1, $J = 10.7$ Hz, 1H) 3.85 – 3.36 (m, 7H), 2.44 (m, 2H), 2.19 (dd, $J = 11.2, 3.8$ Hz, 1H), 1.77-1.60 (m, 2H), 1.39 (m, 2H), 0.98-0.73 (m, 10H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.0, 138.9, 138.7, 138.5(2C), 138.4, 138.4, 138.2, 128.5(4C), 128.5(10), 128.4, 128.4, 128.4, 128.2, 128.0(6C), 128.0(2C), 127.9, 127.8(8C), 127.8, 127.7, 127.6(2C), 127.6, 100.9, 98.8, 85.1, 82.3, 82.1, 81.1, 80.7, 78.2, 78.1, 77.9, 75.7, 75.6, 75.2, 75.1, 74.9, 74.9, 73.8, 73.6, 73.3, 70.4, 69.4, 68.8, 48.9, 48.2, 43.2, 41.1, 34.6, 34.4, 31.9,

31.6, 25.4, 24.7, 23.3, 23.1, 22.4, 22.4, 21.2, 21.2, 16.2, 16.1; HRMS (ESI-MS): m/z calculated for $C_{44}H_{54}O_6 [M+Na]^+$: 701.3818, Found: 701.3809.

3,4-dimethylphenyl 2,3,4,6-tetra-*O*-benzyl- α/β -D-

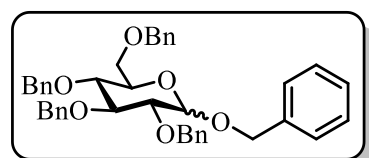
glucopyranoside (25i) $\{\alpha:\beta = 10:7\}$: Eluent for purification: 15% ethyl acetate in *n*-hexane; yield, 67 mg from 100 mg of compound **18a** (77%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +67.6°; IR (cm^{-1} , $CHCl_3$): 2922, 2865, 1499, 1453, 1366, 1253, 1149, 1074, 740; 1H



NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.14 (m, 20H), 7.03 (d, $J = 8.3$ Hz, 1H), 6.85 (dd, $J = 8.2$, 2.5 Hz, 1H), 6.86 (d, $J = 2.5$ Hz, 1H), 5.48 (d, $J = 3.5$ Hz, 1H), 5.10–4.38 (m, 8H), 4.21 (t, $J = 9.3$ Hz, 1H), 3.92 (dt, $J = 10.1$, 2.8 Hz, 1H), 3.80 – 3.72 (m, 3H), 3.60 (dd, $J = 10.7$, 2.0 Hz, 1H), 2.22 (s, 3H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.9, 139.0, 138.4, 138.2, 138.0, 137.8, 130.5, 130.4, 128.6, 128.5, 128.5, 128.5(2C), 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0(2C), 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 118.4, 114.0, 95.6 (C-1), 82.2, 79.8, 77.6, 75.9, 75.2, 73.5, 73.3, 70.8, 68.4, 20.1, 19.0; ; HRMS (ESI-MS): m/z calculated for $C_{42}H_{44}O_6 [M+Na]^+$: 667.3036, Found: 667.3032.

Benzyl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside (25j)

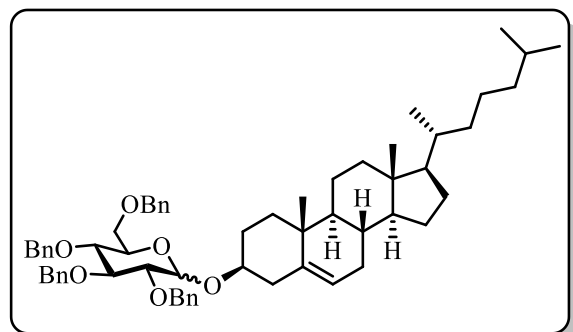
$\{\alpha:\beta = 9:10\}$: Eluent for purification: 5% ethyl acetate in *n*-hexane; yield, 62 mg from 100 mg of compound **18a** (72%)



White solid; mp 64–66 °C; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +31.0°; IR (cm^{-1} , $CHCl_3$): 2923, 2866, 1729, 1598, 1452, 1362, 1266, 1093, 705; 1H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.12 (m, 25H), 5.03– 4.44 (m, 11H), 4.08 – 3.45 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.0, 138.7, 138.5, 138.4, 138.3(2C), 138.2, 138.1, 137.6, 137.3, 128.6, 128.5(18C), 128.5(3C), 128.3, 128.1(11C), 128.0(3C), 128.0, 128.0(3C), 127.9(3C), 127.9, 127.8, 127.8, 127.7, 127.7, 127.7, 102.7, 95.7, 84.9, 82.4, 82.3, 80.0, 78.0, 77.8, 75.8, 75.8, 75.2, 75.1, 75.0, 75.0, 73.6, 73.6, 73.1, 71.3, 70.5, 69.3, 69.1, 68.5; HRMS (ESI-MS): m/z calculated for $C_{41}H_{42}O_6 [M+Na]^+$: 653.2879, Found: 653.2881.

Cholesteryl 2,3,4,6-tetra-*O*-benzyl- α/β -D-

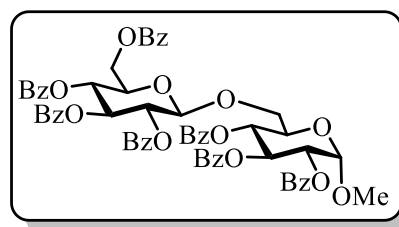
glucopyranoside (25k) $\{\alpha:\beta = 10:6\}$: Eluent for purification: 5% ethyl acetate in *n*-hexane; yield, 150 mg from 120 mg from compound **18a** (86%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +29.4°; IR



(cm^{-1} , CHCl_3): 2923, 2869, 1500, 1453, 1366, 1256, 1149, 1073, 745;); ^1H NMR (400 MHz, CDCl_3): δ 7.37 – 7.31 (m, 20H), 5.30 (d, J = 4.8 Hz, 1H), 5.01 (t, J = 11.6 Hz, 1H), 4.92– 4.45 (m, 8H), 4.03 (t, J = 9.3 Hz, 2H), 3.74 (dd, J = 10.6, 3.6 Hz, 1H), 3.71 – 3.43 (m, 4H), 2.43 – 0.68 (m, 43H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 150.0, 140.7, 139.1, 138.8, 138.6, 138.4(2C), 138.4, 138.3, 138.1, 128.5, 128.5(20C), 128.5(4C), 128.5, 128.4, 128.3, 128.1(6C), 128.0(7C), 128.0, 128.0, 127.9, 127.8(6C), 127.8, 127.8, 127.7, 127.7, 122.1, 121.8, 102.4, 94.7, 84.9, 82.5, 82.2, 80.0, 79.8, 78.1, 78.0, 76.7, 75.8(2C), 75.3, 75.1, 75.1, 74.9, 73.6, 73.5, 73.2, 70.2, 69.3, 68.7, 56.9, 56.9, 56.3, 50.3, 50.2, 42.4(2C), 40.0, 39.9, 39.6(2C), 39.2, 37.4, 37.2, 36.9, 36.9, 36.3, 35.9, 32.1, 32.0, 30.1, 28.4, 28.1, 27.6, 24.4, 23.9, 23.0, 22.7, 21.2, 19.5, 19.5, 18.9, 12.0; HRMS (ESI-MS): m/z calculated for $\text{C}_{61}\text{H}_{80}\text{O}_6[\text{M}+\text{Na}]^+$: 931.5853, Found: 931.5858.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-[2,3,4,6-tetra-*O*-benzoyl- β -D-glucopyranosyl]- α -D-glucopyranoside (26):

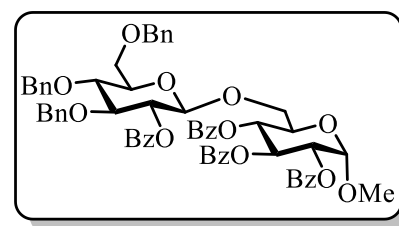
Eluent for purification: 25% ethyl acetate in *n*-hexane; yield, 39 mg from 160 mg of compound **18d** (15%); White solid; mp 112-114 $^{\circ}\text{C}$; $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +52.6 $^{\circ}$; IR (cm^{-1} , CHCl_3): 2923,



2869, 1726, 1597, 1451, 1260, 1099, 853, 758, 706; ^1H NMR (400 MHz, CDCl_3): δ 8.00 – 7.78 (m, 14H), 7.51 – 7.25 (m, 21H), 6.26 (t, J = 9.8 Hz, 1H), 6.11 (t, J = 10.1 Hz, 1H), 6.01 (dd, J = 10.1, 3.2 Hz, 1H), 5.79 (dd, J = 3.2, 1.7 Hz, 1H), 5.61 (t, J = 9.9 Hz, 1H), 5.35 (d, J = 3.7 Hz, 1H), 5.29 (dd, J = 10.1, 3.7 Hz, 1H), 5.18 (d, J = 1.7 Hz, 1H), 4.64 (dd, J = 12.2, 2.3 Hz, 1H), 4.55 (ddd, J = 10.1, 5.0, 2.3 Hz, 1H), 4.40 (m, 2H), 4.10 (dd, J = 10.7, 6.0 Hz, 1H), 3.80 (dd, J = 10.8, 2.3 Hz, 1H), 3.62 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 166.2, 165.9, 165.8, 165.8, 165.5, 165.3(2C), 133.5(2C), 133.4(2C), 133.3, 133.2, 133.2, 130.0(6C), 130.0, 129.9(2C), 129.9(2C), 129.9, 129.7, 129.7, 129.5, 129.3, 129.2, 128.9, 128.9, 128.9, 128.5(10C), 128.5(2C), 128.4, 128.4, 128.3, 101.9, 96.6, 72.9, 72.4, 72.1, 72.0, 70.4, 69.8, 69.7, 69.1, 68.9, 63.1, 55.2; HRMS (ESI-MS): m/z calculated for $\text{C}_{62}\text{H}_{52}\text{O}_{18}[\text{M}+\text{H}]^+$: 1085.3232, Found: 1085.3279.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-[2-*O*-benzoyl-3,4,6-*O*-benzyl- α -D-glucopyranosyl]- α -D-glucopyranoside (27):

Eluent for purification: 20% ethyl acetate in *n*-hexane; yield, 142 mg from 100 mg of compound **18e** (87%); Thick syrup; $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +74.8 $^{\circ}$; IR (cm^{-1} , CHCl_3): 2956, 2856,

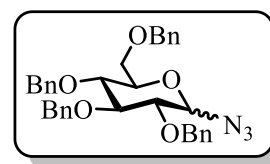


1728, 1451, 1267, 1163, 1098, 709; ^1H NMR (400 MHz, CDCl_3): δ 8.09 – 7.82 (m, 8H), 7.62 –

7.20 (m, 27H), 6.08 (t, $J = 9.5$ Hz, 1H), 5.34 (t, $J = 8.4$ Hz, 1H), 5.10 (d, $J = 6.2$ Hz, 1H), 4.96 – 3.32 (m, 17H), 3.07 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 165.8, 165.8, 165.6, 165.4, 138.1, 138.0, 137.9, 133.5, 133.4, 133.2, 133.1, 130.2, 130.0(5C), 129.9, 129.7, 129.3, 129.2, 128.9, 128.5(5C), 128.5(3C), 128.4(6C), 128.4, 128.3, 128.1(2C), 128.1(2C), 127.9, 127.9, 127.7, 127.7, 101.8, 96.4, 82.8, 78.0, 75.4, 75.2, 75.1, 73.9, 73.6, 72.1, 70.6, 69.8, 69.0, 68.8, 68.5, 55.0; HRMS (ESI-MS): m/z calculated for $\text{C}_{62}\text{H}_{58}\text{O}_{15}$ $[\text{M}+\text{Na}]^+$: 1065.3673, Found: 1065.3678.

1-deoxy-1-azido 2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranoside (29)

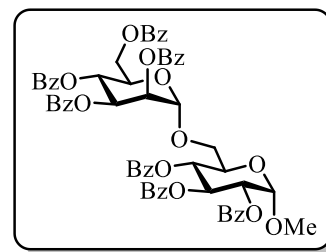
{ α : β = 10:4}: Eluent for purification: 15% ethyl acetate in *n*-hexane; yield, 72 mg from 100 mg of compound **18a** (79%); Thick syrup; $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +111.8°; IR (cm^{-1} , CHCl_3): 2916, 2114, 1460, 1085 734;



^1H NMR (400 MHz, CDCl_3): δ 7.36 – 7.13 (m, 20H), 5.21 (d, $J = 4.1$ Hz, 1H), 4.93 – 4.81 (m, 2H), 4.80 – 4.43 (m, 6H), 3.86 (t, $J = 9.3$ Hz, 1H), 3.72 (dd, $J = 6.3, 3.6$ Hz, 1H), 3.71 – 3.61 (m, 2H), 3.45 (ddd, $J = 6.7, 4.5, 2.4$ Hz, 1H), 3.37 (ddd, $J = 8.9, 6.5, 2.4$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 138.6, 138.4, 138.2, 138.0, 138.0, 137.8, 137.8, 137.7, 128.7(2C), 128.6, 128.5(9C), 128.5(7C), 128.5(3C), 128.3, 128.3, 128.2(2C), 128.1(6C), 128.1(5C), 128.0, 127.9, 127.9, 127.9, 127.8, 90.3, 88.2, 85.0, 81.9, 81.8, 79.5, 77.2, 75.9, 75.8, 75.3, 75.2, 73.9, 73.7, 73.6, 72.6, 68.5, 68.2; HRMS (ESI-MS): m/z calculated for $\text{C}_{34}\text{H}_{35}\text{O}_4\text{N}_3$ $[\text{M}+\text{K}]^+$: 604.2214, Found: 604.2219.

Methyl 2,3,4-tri-O-benzoyl-6-O-[2,3,4,6-tetra-O-benzoyl- α -D-mannopyranosyl]- α -D-glucopyranoside (28a):

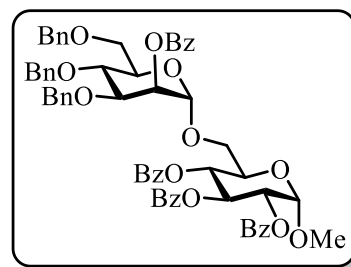
Eluent for purification: 25% ethyl acetate in *n*-hexane; yield, 36 mg from 150 mg of compound **21a** (15%); White solid; mp 98-100 °C; $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +14.2°; IR (cm^{-1} , CHCl_3): 2901, 2856, 1726, 1451,



1262, 1166, 1098, 1036, 757, 705; ^1H NMR (400 MHz, CDCl_3): δ 8.13 – 7.87 (m, 14H), 7.60 – 7.31 (m, 21H), 6.23 (t, $J = 9.8$ Hz, 1H), 6.11 (t, $J = 10.0$ Hz, 1H), 6.01 (dd, $J = 10.1, 3.2$ Hz, 1H), 5.80 (dd, $J = 3.2, 1.7$ Hz, 1H), 5.61 (t, $J = 9.9$ Hz, 1H), 5.35(d, $J = 3.7$ Hz, 1H), 5.29 (d, $J = 10.1, 3.7$ Hz, 1H), 5.18 (d, $J = 1.8$ Hz, 1H), 4.64 (dd, $J = 12.1, 1.8$ Hz, 1H), 4.55 (ddd, $J = 10.1, 5.0, 2.3$ Hz, 1H), 4.44 – 4.33 (m, 2H), 4.11 (dd, $J = 10.7, 6.0$ Hz, 1H), 3.85 – 3.75 (dd, $J = 10.1, 2.3$ Hz, 1H), 3.62 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 166.1, 165.9, 165.8, 165.6, 165.5, 165.5, 165.4, 133.6, 133.5, 133.5, 133.4, 133.2, 133.2, 133.1, 130.0, 130.0(2C), 129.9(2C), 129.9(5C),

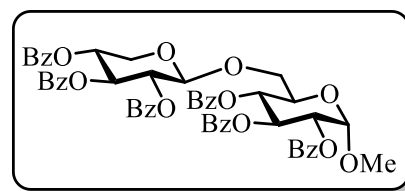
129.8(2C), 129.8(2C), 129.8, 129.3, 129.3, 129.2, 129.2, 129.1, 128.8, 128.6(4C), 128.6, 128.5(2C), 128.5(2C), 128.4(4C), 97.5, 97.0, 77.4, 72.2, 70.6, 70.4, 70.1, 69.4, 69.0, 68.4, 66.9, 66.5, 62.8, 55.7; HRMS (ESI-MS): m/z calculated for $C_{62}H_{52}O_{18}$ $[M+Na]^+$: 1084.3154, Found: 1084.3148.

Methyl 2,3,4-tri-O-benzoyl-6-O-[2-O-benzoyl-3,4,6-tri-O-benzyl- α -D-mannopyranosyl]- α -D-glucopyranoside (28b):



Eluent for purification: 15% ethyl acetate in *n*-hexane; yield, 150 mg from 120 mg of compound **21b** (76%); White solid; mp. 128–130°C; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +03.8°; IR (cm^{-1} , $CHCl_3$): 2959, 2846, 1735, 1451, 1263, 1169, 1098, 705); 1H NMR (400 MHz, $CDCl_3$): δ 8.09 (m, 8H), 7.56 – 7.27 (m, 27H), 6.24 – 6.13 (t, J = 9.7 Hz, 1H), 5.68 – 5.54 (m, 2H), 5.10 (d, J = 7.8 Hz, 1H), 5.00–4.45 (m, 8H), 4.22 (t, J = 9.3 Hz, 1H), 4.10 (d, J = 11.3 Hz, 1H), 3.97–3.46 (m, 6H), 3.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.9, 165.7, 165.3, 138.7, 138.5, 138.1, 133.4, 133.2, 130.0, 130.0, 130.0, 129.8, 129.7, 129.3, 129.2, 129.0, 128.5, 128.5, 128.4, 128.4, 128.4, 128.4, 128.3, 128.2, 128.0, 127.6, 127.6, 127.6, 127.5, 127.5, 98.1 (C-1), 97.0 (C-1'), 78.0, 77.4, 75.2, 74.3, 73.4, 72.2, 71.8, 71.6, 70.6, 69.8, 69.0, 68.9, 68.2, 66.5, 55.6; HRMS (ESI-MS): m/z calculated for $C_{62}H_{58}O_{15}$ $[M+Na]^+$: 1042.3776, Found: 1042.3755.

Methyl 2,3,4-tri-O-benzoyl-6-O-[2,3,4-tri-O-benzoyl- β -D-xyloparanosyl]- α -D-glucopyranoside (30):



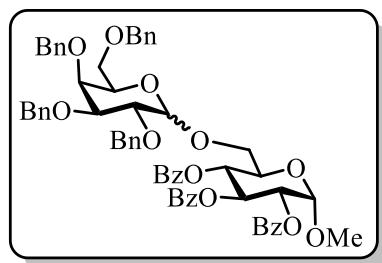
Eluent for purification: 25% ethyl acetate in *n*-hexane; yield, 76 mg from 100 mg of compound **23** (40%); Light yellow thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +03.8°; IR (cm^{-1} , $CHCl_3$): 2928, 2887, 1727, 1454, 1264, 1168, 1094, 972, 707; 1H NMR (400 MHz, $CDCl_3$): δ 8.12 – 7.73 (m, 12H), 7.56 – 7.18 (m, 18H), 6.08 (t, J = 9.8 Hz, 1H), 5.77 (t, J = 7.6 Hz, 1H), 5.42 (d, J = 8.8 Hz, 1H), 5.41 (dd, J = 16.9, 10.3 Hz, 1H), 5.27 (td, J = 7.5, 4.4 Hz, 1H), 5.10 (dd, J = 10.2, 3.7 Hz, 1H), 5.02 (d, J = 3.7 Hz, 1H), 4.87 (d, J = 5.8 Hz, 1H), 4.39 (dd, J = 12.1, 4.5 Hz, 1H), 4.26–4.17 (m, 1H), 4.04 (d, J = 11.3 Hz, 1H), 3.73 (dd, J = 11.4, 7.0 Hz, 1H), 3.64 (dd, J = 12.1, 7.5 Hz, 1H), 3.17 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.9, 165.7, 165.6, 165.5, 165.2, 133.6, 133.5(2C), 133.4, 133.3, 133.2, 130.0(4C), 130.0(6C), 129.8(2C), 129.5, 129.3, 129.3, 129.2, 129.2, 129.0, 128.5(6C), 128.5(3C), 128.4(2C), 128.3(2C), 101.1 (C-1'), 96.7 (C-1), 72.2, 70.7, 70.6, 70.5, 69.6, 69.5,

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68.9, 68.3, 61.7, 55.3; HRMS (ESI-MS): m/z calculated for $C_{54}H_{46}O_{16}$ $[M+Na]^+$: 973.2683, Found: 973.2679.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-[2,3,4,6-tetra-*O*-benzyl α/β -D-galactopyranosyl]- α -D-glucopyranoside (31) $\{\alpha:\beta = 2:1\}$:

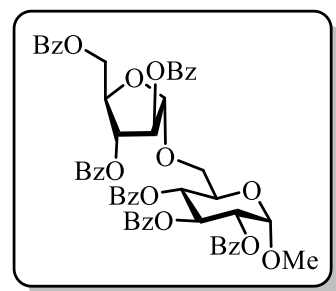
Eluent for purification: 15% ethyl acetate in *n*-hexane; yield, 150 mg from 100 mg of compound **22** (91%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +48.5°; IR (cm^{-1} , $CHCl_3$): 2923, 2865, 1728, 1598, 1452, 1335, 1266, 1157, 1090, 917, 706; 1H NMR (400



MHz, $CDCl_3$): δ 8.03 – 7.85 (m, 6H), 7.46 – 7.27 (m, 29H), 6.23 – 6.14 (m, 1H), 5.54 (dd, $J = 9.6, 9.1$ Hz, 1H), 5.28 (m, 2H), 5.18 – 4.32 (m, 10H), 4.03 (t, $J = 9.3$ Hz, 1H), 3.91 – 3.75 (m, 2H), 3.71 – 3.48 (m, 5H), 3.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.8(2C), 165.8, 165.8, 165.5, 165.3, 138.9, 138.6, 138.6, 138.5, 138.4, 138.1, 138.1, 137.9, 133.4, 133.3, 133.0, 129.9, 129.9(12C), 129.7(6C), 129.7, 129.3, 129.3, 129.1, 129.1, 129.0, 128.9, 128.4(12C), 128.4, 128.4, 128.3(8C), 128.3, 128.3, 128.3, 128.2, 128.0, 127.9(8C), 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 127.5, 104.0, 97.2, 96.8, 96.8, 84.6, 82.4, 81.7, 80.0, 77.7, 77.6, 77.4, 77.2, 77.0, 76.7, 75.7, 75.5, 75.0, 74.9, 74.8, 73.4, 73.1, 72.3, 72.1, 70.6, 70.5, 70.2, 69.9, 69.6, 69.0, 68.9, 68.7, 68.6, 68.3, 66.7, 55.6, 55.5; HRMS (ESI-MS): m/z calculated for $C_{62}H_{60}O_{14}$ $[M+Na]^+$: 1051.3881, Found: 1051.3885.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-[2,3,5-tri-*O*-benzoyl- α -D-arabinofuranosyl]- α -D-glucopyranoside (32a): Eluent for

purification: 20% ethyl acetate in *n*-hexane; yield, 155 mg from 100 mg of compound **24a** (89%); White solid; mp 84-86 °C; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +45.6°; IR (cm^{-1} , $CHCl_3$): 2865, 2855, 1722, 1260, 1099, 1038, 707; 1H NMR (400 MHz, $CDCl_3$): δ 8.34 – 7.77 (m,



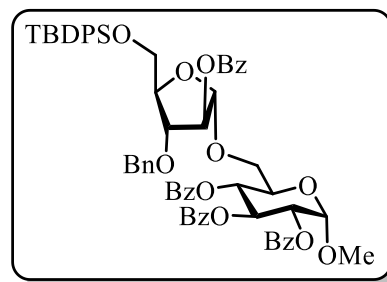
12H), 7.65 – 7.23 (m, 18H), 6.21 (t, $J = 9.9$ Hz, 1H), 5.80 (t, $J = 9.9$ Hz, 1H), 5.68 (s, 1H, H-1'), 5.61 (d, $J = 4.4$ Hz, 1H), 5.42 (s, 1H, H-1), 5.37 (dd, $J = 10.2, 3.6$ Hz, 1H), 5.32 (d, $J = 3.6$ Hz, 1H), 4.81 (dd, $J = 11.5, 2.9$ Hz, 1H), 4.77-4.65 (m, 2H), 4.35 (ddd, $J = 10.2, 4.1, 2.3$ Hz, 1H), 4.12 (dd, $J = 11.0, 4.1$ Hz, 1H), 3.85 (dd, $J = 11.0, 2.3$ Hz, 1H), 3.49 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.3, 166.0, 165.9, 165.9, 165.4, 165.1, 133.6, 133.6, 133.4(2C), 133.1, 133.0, 130.1(2C), 130.0(2C), 130.0(2C), 129.8(5C), 129.8(2C), 129.5, 129.3, 129.2, 129.1, 129.1, 128.6(4C), 128.5(2C), 128.5(2C), 128.3(2C), 128.3(2C), 105.6 (C-1'), 97.1 (C-1), 82.0, 81.5,

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77.9, 72.1, 70.8, 69.1, 68.5, 65.1, 63.8, 55.6; HRMS (ESI-MS): m/z calculated for $C_{54}H_{46}O_{16}$ $[M+Na]^+$: 973.2682, Found: 973.2686.

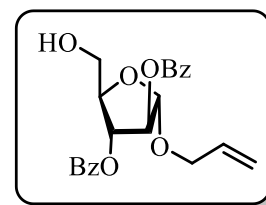
Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-[2-*O*-benzoyl-3-*O*-benzyl-5-*O*-*t*-butyldiphenylsilyl- α -D-arabinofuranosyl]- α -D-

glucopyranoside (32b): Eluent for purification: 15% ethyl acetate in *n*-hexane; yield, 150 mg from 100 mg of compound **24b** (93%); Light yellow thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): +97.6°; IR (cm^{-1} , $CHCl_3$): 2900, 2865, 1727, 1267, 1217, 1103,



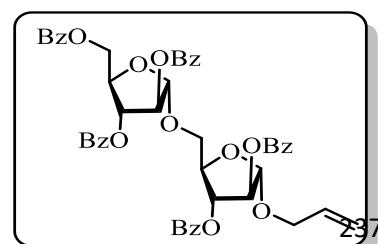
1035, 740; 1H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.87 (m, 8H), 7.68 – 7.25 (m, 27H), 6.17 (t, J = 9.8 Hz, 1H), 5.61 (t, J = 9.8 Hz, 1H), 5.35 (d, J = 1.0 Hz, 1H, H-1'), 5.30 (dd, J = 10.2, 3.6 Hz, 1H), 5.23 (m, 3H), 4.66 (ABq, J = 11.9 Hz, 2H), 4.32 (ddd, J = 8.0, 5.6, 3.4 Hz, 1H), 4.32 (t, J = 4.7 Hz, 1H), 4.20 (d, J = 5.6 Hz, 1H), 4.00 (dd, J = 11.1, 5.7 Hz, 1H), 3.82 (t, J = 4.1 Hz, 1H), 3.76 (dd, J = 11.1, 2.9 Hz, 1H), 3.42 (s, 3H), 1.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.9, 165.9, 165.5, 165.4, 138.0, 135.7(2C), 135.7(2C), 133.5, 133.4, 133.4, 133.4, 133.4, 133.1, 130.0(2C), 129.9(2C), 129.9(2C), 129.8(2C), 129.8, 129.7, 129.6, 129.5, 129.3, 129.2, 128.5(9C), 128.4(2C), 128.3(2C), 128.0(2C), 127.8(2C), 127.7(2C), 106.0 (C-1'), 96.9 (C-1), 83.5, 83.1, 82.3, 72.3, 70.8, 70.0, 68.6, 65.7, 63.0, 55.6, 26.9, 19.4; HRMS (ESI-MS): m/z calculated for $C_{63}H_{62}O_{14}Si$ $[M+Na]^+$: 1093.3807, Found: 1093.3800.

Allyl 2,3-di-*O*-benzoyl- α -D-arabinofuranoside (33): Eluent for purification: 20% ethyl acetate in *n*-hexane; yield, (86%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, c 1.0): -128.2°; IR (cm^{-1} , $CHCl_3$): 1719, 1267, 1099, 1026, 708; 1H NMR (400 MHz, $CDCl_3$): δ 8.09 – 8.03 (m, 4H), 7.61– 7.28 (m, 6H), 5.83 (ddd, J = 10.8, 6.0, 5.0 Hz, 1H), 5.67 (dd, J = 8.1, 5.7 Hz, 1H),



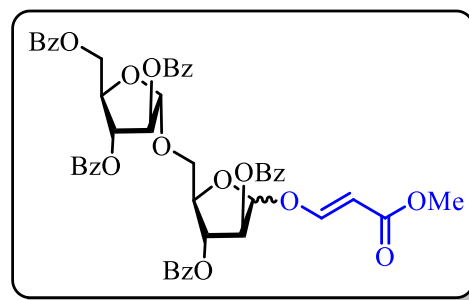
5.41 (dd, J = 8.0, 3.3 Hz, 1H), 5.25 (dq, J = 17.3, 1.7 Hz, 1H), 5.12 (dq, J = 10.4, 1.5 Hz, 1H), 4.75 (d, J = 5.7 Hz, 1H), 4.35 (m, 1H), 4.31 (dt, 5.1, 1.6 Hz, 1H), 4.10 (m, 2H), 3.74 (dd, J = 12.2, 2.5 Hz, 1H), 2.42 (bs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.3, 165.5, 133.8, 133.7, 130.1, 130.0(2C), 129.3, 129.2, 128.7(2C), 128.6(2C), 117.5, 104.8 (C-1), 83.8, 82.1, 77.9, 68.0, 62.4; HRMS (ESI-MS): m/z calculated for $C_{22}H_{22}O_7$ $[M+H]^+$: 399.1444, Found: 399.1440.

Allyl 2,3-di-*O*-benzoyl-5-*O*-[2,3,5-tri-*O*-benzoyl- α -D-arabinofuranosyl]- α -D-arabinofuranoside (34): Eluent for purification: 20% ethyl acetate in *n*-hexane; yield, 470 mg from



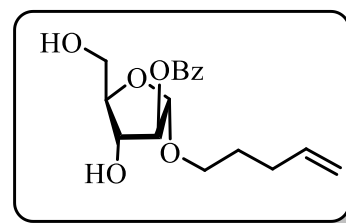
350 mg of compound **24a** (87%); Thick syrup; $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): $+00.2^\circ$; IR (cm^{-1} , CHCl_3): 2923, 1722, 1597, 1453, 1262, 1102, 709; ^1H NMR (400 MHz, CDCl_3): δ 8.10 – 7.98 (m, 10H), 7.61 – 7.27 (m, 15H), 5.97 (ddd, $J = 16.5, 10.6, 5.4$ Hz, 1H), 5.71 (m, 2H), 5.63 (m, 2H), 5.51 (s, 1H, H-1'), 5.39 (dq, $J = 17.2, 1.8$ Hz, 1H), 5.33 (s, 1H, H-1), 5.24 (dq, $J = 10.4, 1.3$ Hz, 1H), 4.89 (dd, $J = 11.8, 3.2$ Hz, 1H), 4.81 (dd, $J = 7.9, 4.4$ Hz, 1H), 4.72 (dd, $J = 11.8, 4.6$ Hz, 1H), 4.54 (dd, $J = 4.7, 2.7$ Hz, 1H), 4.37 – 4.25 (m, 2H), 4.13 (ddd, $J = 13.1, 6.0, 1.6$ Hz, 1H), 4.03 (dd, $J = 11.2, 2.6$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 166.3, 165.8, 165.8, 165.4, 165.3, 133.8, 133.5(2C), 133.5, 133.4, 133.1, 129.9(2C), 129.9(3C), 129.9(2C), 129.8(2C), 129.8(2C), 129.8, 129.3, 129.1, 129.1, 129.0, 128.6(4C), 128.5(2C), 128.4(2C), 128.3(2C), 117.4, 105.9, 104.8, 82.0, 82.0, 81.3, 77.9, 77.4, 67.8, 66.2, 63.7; HRMS (ESI-MS): m/z calculated for $\text{C}_{48}\text{H}_{42}\text{O}_{14}$ $[\text{M}+\text{Na}]^+$: 865.2472, Found: 865.2474.

(E)-3-methoxy-3-oxoprop-1-en-1-yl 2,3-di-O-benzoyl-5-O-[2,3,5-tri-O-benzoyl- α -D-arabinofuranosyl]- α/β -D-arabinofuranoside (35) $\{\alpha:\beta = 5:3\}$: Eluent for purification: 25% ethyl acetate in *n*-hexane; yield, 333 mg from 401 mg of compound **34** (79%) Thick syrup;



$[\alpha]^{25}_D$ (CHCl_3 , c 1.0): -15.0° ; IR (cm^{-1} , CHCl_3): 1721, 1264, 1106, 709; ^1H NMR (400 MHz, CDCl_3): δ 8.12 – 7.92 (m, 10H), 7.65 (d, $J = 12.5$ Hz, 1H), 7.61 – 7.24 (m, 15H), 6.04 (dd, $J = 7.0, 6.5$ Hz, 1H), 5.86-5.24 (m, 6H), 4.89-4.42 (m, 4H), 4.26 (dd, $J = 11.4, 4.3$ Hz, 1H), 3.96 (ddd, $J = 14.5, 11.1, 3.4$ Hz, 1H), 3.70 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 167.6, 167.4, 166.3, 166.0, 165.9, 165.8, 165.7, 165.7, 165.4, 165.4, 158.6, 158.1, 133.9, 133.8, 133.8, 133.6, 133.5, 133.5, 133.5, 133.2, 133.1, 130.1, 130.1, 130.0(10C), 130.0, 129.9(3C), 129.9(2C), 129.9(6C), 129.8, 129.3, 129.1, 129.1, 129.0, 128.9, 128.7(2C), 128.7(2C), 128.6(3C), 128.6(6C), 128.6, 128.5(2C), 128.5, 128.4(2C), 128.4, 106.2(2C), 105.8(2C), 105.8(2C), 101.1, 100.4, 84.0, 82.1, 82.0, 81.6, 81.4, 81.3, 80.7, 77.8, 77.7, 77.4, 77.0, 76.8, 74.6, 67.7, 65.9, 63.7, 63.7, 51.4, 51.3; HRMS (ESI-MS): m/z calculated for $\text{C}_{49}\text{H}_{42}\text{O}_{16}$ $[\text{M}+\text{Na}]^+$: 909.2371, Found: 909.2374.

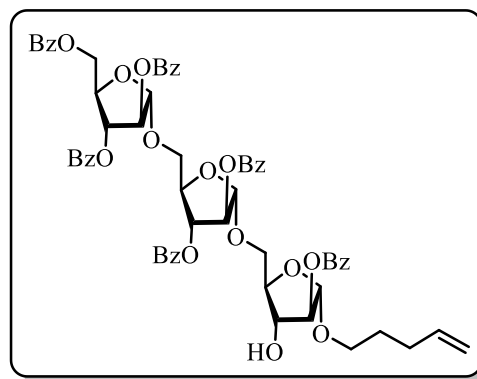
Pent-4-enyl 2-O-benzoyl- α -D-arabinofuranoside (36): Nature of compound: Colorless thick syrup; Yield (78%); $[\alpha]^{25}_D$ (CHCl_3 , c 1.0): $+125.2^\circ$; IR (cm^{-1} , CHCl_3): 1720, 1267, 1099, 1026, 711; ^1H NMR (400 MHz, CDCl_3): δ 8.01 – 7.93 (m, 2H), 7.58 – 7.39



(m, 3H), 5.84 – 5.72 (ddd, $J = 17.0, 10.2, 6.6$ Hz, 1H), 5.22 (s, 1H), 5.11 (d, $J = 1.9$ Hz, 1H, H-1), 5.03 (dq, $J = 17.1, 1.8$ Hz, 1H), 4.97 (dq, $J = 10.2, 1.8$ Hz, 1H), 4.16 (bs, 2H), 3.91 (dd, $J = 12.2, 2.7$ Hz, 1H), 3.83 – 3.71 (m, 3H), 3.47 (dt, $J = 9.6, 6.5$ Hz, 1H), 2.66 (bs, 1H), 2.11 (q, $J = 6.9$ Hz, 2H), 1.72 (q, $J = 6.9$ Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 166.7, 138.0, 133.6, 129.8(2C), 129.1, 128.6(2C), 115.1, 105.4 (C-1), 86.0, 84.1, 76.4, 67.2, 61.9, 30.2, 28.6; ; HRMS (ESI-MS): m/z calculated for $\text{C}_{17}\text{H}_{22}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 345.1313, Found: 345.1310.

Pent-4-enyl 2-O-benzoyl-5-O-[2,3-di-O-benzoyl-5-O-[2,3,5-tri-O-benzoyl- α -D-arabinofuranosyl]- α -D-arabinofuranyl]- α -D-arabinofuranoside (37): Eluent for purification: 30% ethyl acetate in *n*-hexane; yield,

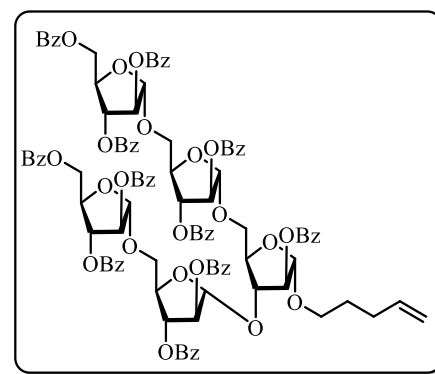
109 mg from 100 mg of compound 35 (88%); Thick syrup; $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +07.2°; IR (cm^{-1} , CHCl_3): 2932, 1719, 1596, 1451, 1259, 1100, 970, 861, 702; ^1H NMR (400 MHz, CDCl_3): δ 8.11 – 7.91 (m, 12H), 7.63



– 7.19 (m, 18H), 5.85 – 5.75 (ddd, $J = 16.7, 11.6, 6.6$ Hz, 1H), 5.63 (s, 2H), 5.59 (s, 2H), 5.43 (s, 1H), 5.34 (s, 1H), 5.21 (s, 1H), 5.09 (s, 1H), 5.00 (d, $J = 17.3$ Hz, 1H), 4.94 (d, $J = 9.9$ Hz, 1H), 4.84 (m, 1H), 4.76 – 4.61 (m, 2H), 4.56 (m, 1H), 4.29 (m, 1H), 4.21 (m, 2H), 3.97 (dt, $J = 16.9, 8.4$ Hz, 2H), 3.78 (m, 2H), 3.44 (m, 1H), 3.36 (bs, 1H), 2.12 (q, $J = 6.9$ Hz, 2H), 1.73 (q, $J = 6.9$ Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 166.9, 166.3, 165.8, 165.8, 165.4(2C), 138.1, 133.7, 133.6(2C), 133.5, 133.4, 133.1, 130.0(2C), 129.9(5C), 129.9(4C), 129.2, 129.2, 129.1, 129.0, 128.6(4C), 128.6(5C), 128.5(2C), 128.4(2C), 128.4(2C), 115.1, 106.0 (C-1''), 106.0 (C-1'), 105.3 (C-1), 85.9, 82.6, 82.1(2C), 81.8, 81.3, 77.9, 77.4, 77.3, 67.3, 66.4, 66.2, 63.8, 30.3, 28.7; HRMS (ESI-MS): m/z calculated for $\text{C}_{62}\text{H}_{58}\text{O}_{19}$ $[\text{M}+\text{Na}]^+$: 1129.3470, Found: 1129.3471.

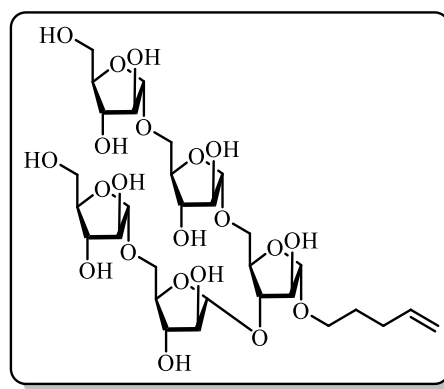
Pent-4-enyl-2-O-benzoyl-3-O-[2,3-di-O-benzoyl-5-O-[2,3,5-tri-O-benzoyl- α -D-arabinofuranosyl]- α -D-arabinofuranosyl]-5-O-[2,3-di-O-benzoyl-5-O-[2,3,5-tri-O-benzoyl- α -D-arabinofuranosyl]- α -D-

arabinofuranosyl]- α -D-arabinofuranoside (38): Eluent for purification: 30% ethyl acetate in *n*-hexane; yield, 74 mg from 60 mg of compound 35 (76%); Light yellow thick syrup; $[\alpha]^{25}_{\text{D}}$ (CHCl_3 , c 1.0): +02.0°; IR (cm^{-1} , CHCl_3):



2922, 2857, 1731, 1457, 1376, 1266, 1114, 964, 715; ^1H NMR (400 MHz, CDCl_3): δ 8.07 – 7.89 (m, 22H), 7.64 – 7.19 (m, 33H), 5.85 – 5.75 (ddd, $J = 17.0, 10.2, 6.7$ Hz, 1H), 5.68–5.54 (m, 5H), 5.53 (s, 1H), 5.42 (d, $J = 2.6$ Hz, 1H), 5.37 (s, 1H), 5.34 (s, 1H), 5.32 (s, 1H), 5.18 (s, 1H), (d, $J = 4.3$ Hz, 1H), 5.64 (d, $J = 5.0$ Hz, 2H), 5.61 (s, 2H), 5.03 (dq, $J = 17.1, 1.8$ Hz, 1H), 4.96 (dq, $J = 10.2, 1.8$ Hz, 1H), 4.80 (td, $J = 12.1, 3.3$ Hz, 2H), 4.80 (q, $J = 4.9$ Hz, 2H), 4.64 (ddd, $J = 12.6, 8.6, 4.6$ Hz, 2H), 4.51 (m, 1H), 4.46 (q, $J = 3.7$ Hz, 1H), 4.38 (td, $J = 5.4, 2.5$ Hz, 1H), 4.23 (dt, $J = 11.2, 3.6$ Hz, 2H), 4.05 (dd, $J = 11.3, 4.9$ Hz, 1H), 3.94 (dd, $J = 11.2, 2.7$ Hz, 1H), 3.91–3.84 (m, 1H), 3.75 (dt, $J = 9.7, 6.7$ Hz, 1H), 3.49 (dt, $J = 9.7, 6.7$ Hz, 1H), 2.14 (q, $J = 7.2$ Hz, 2H), 1.76 – 1.68 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 166.3, 166.3, 165.8(2C), 165.7, 165.7, 165.7, 165.3, 165.3, 165.3, 165.2, 138.2, 133.5, 133.5, 133.4, 133.4, 133.1, 133.1, 130.0(6C), 130.0(3C), 130.0(3C), 129.9(15C), 129.9, 129.8, 129.4, 129.3, 129.2(2C), 129.1, 129.1, 129.0, 129.0, 128.6(8C), 128.6(8C), 128.5, 128.5, 128.4(4C), 128.4(2C), 128.4, 128.4, 115.1, 106.0 (2C, C-1, 1'), 106.0 (2C, C-1'', C-1'''), 105.3 (C-1'''), 82.8, 82.8, 82.5, 82.0, 82.0, 81.6, 81.6, 81.4, 81.3, 81.3, 80.6, 77.9, 77.9, 77.4, 77.3, 66.8, 66.0, 65.9, 65.9, 63.7, 30.3, 28.8; HRMS (ESI-MS): m/z calculated for $\text{C}_{107}\text{H}_{94}\text{O}_{32} [\text{M}+\text{Na}]^+$: 1913.5626, Found: 1913.5635.

Pent-4-enyl3-O-[5-O-[- α -D-arabinofuranosyl]- α -D-arabinofuranosyl]-5-O-[5-O-[- α -D-arabinofuranosyl]- α -D-arabinofuranoside (39): Eluent for the purification 40% methanol in water; yield, 10 mg from 30 mg of compound **38** (79%); white solid: mp 113–115 °C; $[\alpha]^{25}_{\text{D}}$ (MeOD₄, c 1.0): +07.2°; IR (cm^{-1} , MeOD): 3500–3226(broad), 2935, 2800, 1645, 1315, 1250, 1123, 920, 831; ^1H NMR (600 MHz, MeOD): δ 5.84 (ddd, $J =$

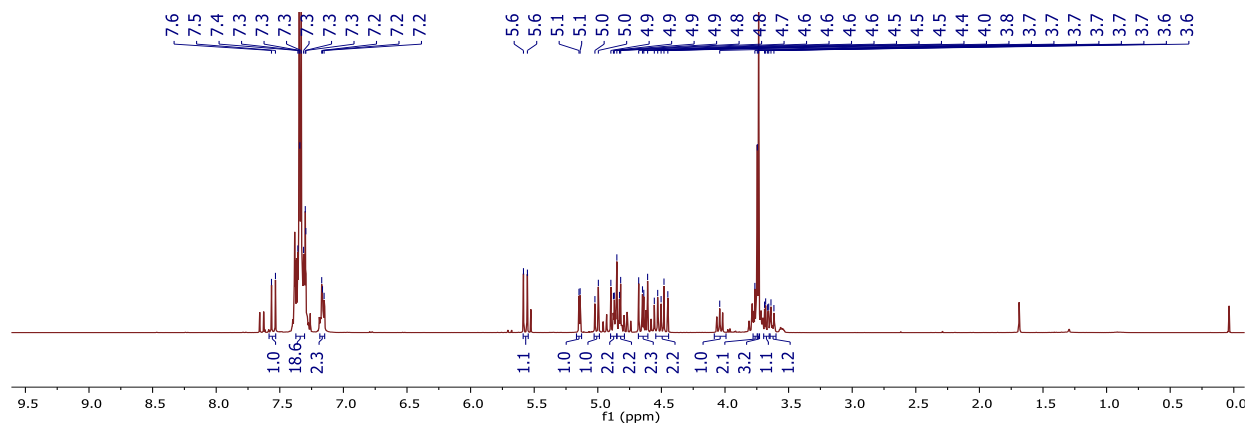


16.9, 10.2, 6.7 Hz, 1H), 5.05 (d, $J = 1.8$ Hz, 1H), 4.98 (s, 1H), 4.97 (s, 1H), 4.89 (s, 1H), 4.88 (s, 1H), 4.20–3.98 (m, 11H), 3.97 – 3.83 (m, 7H), 3.89 – 3.60 (m, 10H), 3.45 (m, 1H), 2.15 (m, 2H), 1.69 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, MeOD): δ 138.0, 113.9, 108.3 (C-1), 108.3 (C-1'), 108.2 (C-1''), 108.2 (C-1'''), 107.7 (C-1'''), 84.5, 84.4, 82.9, 82.7, 82.4, 82.3, 81.8, 81.7, 81.7, 81.2, 80.8, 77.8, 77.7, 77.3, 77.3, 66.7, 66.6, 66.5, 66.4, 61.7, 61.7, 30.0, 28.6. HRMS (ESI-MS): m/z calculated for $\text{C}_{30}\text{H}_{50}\text{O}_{21} [\text{M}+\text{Na}]^+$: 769.2742, Found: 769.2747.

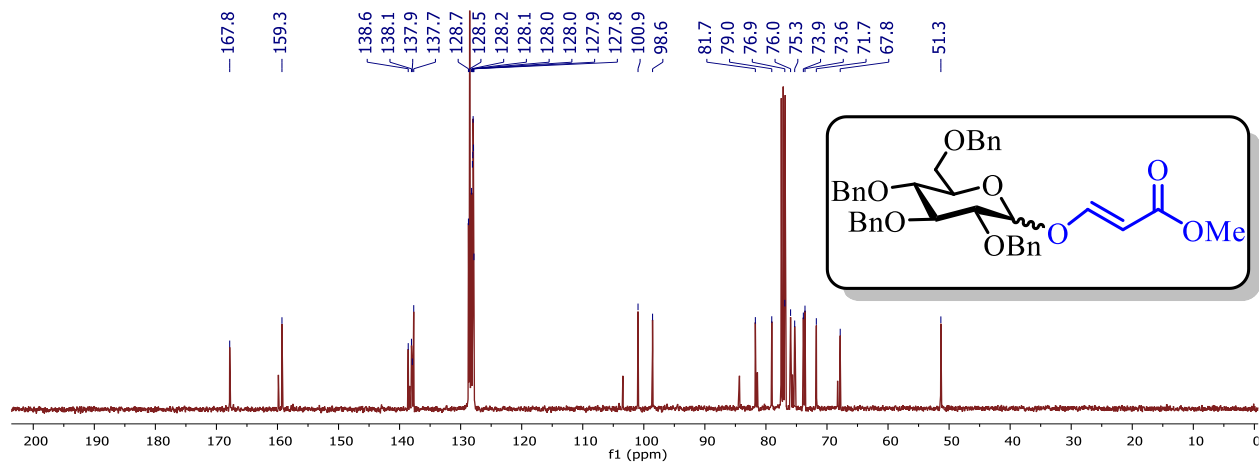
Chapter 3B

3B.5 Spectral Charts

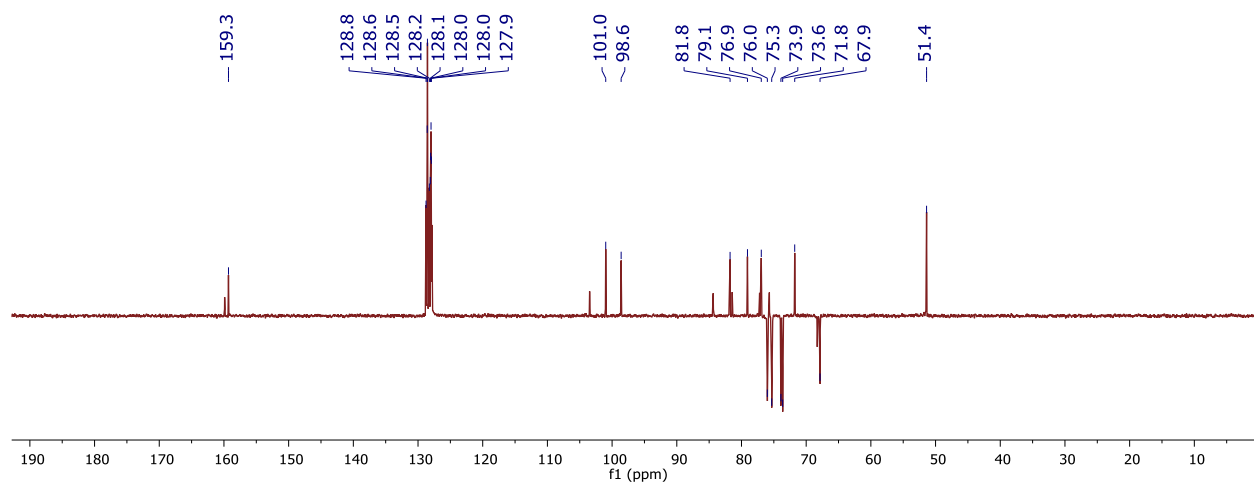
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **18a**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **18a**

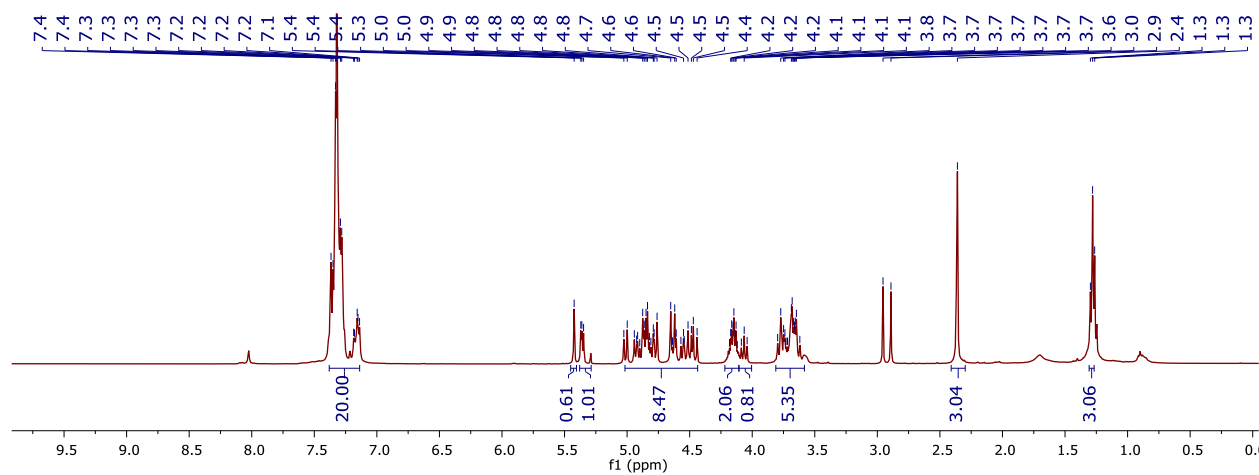


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **18a**

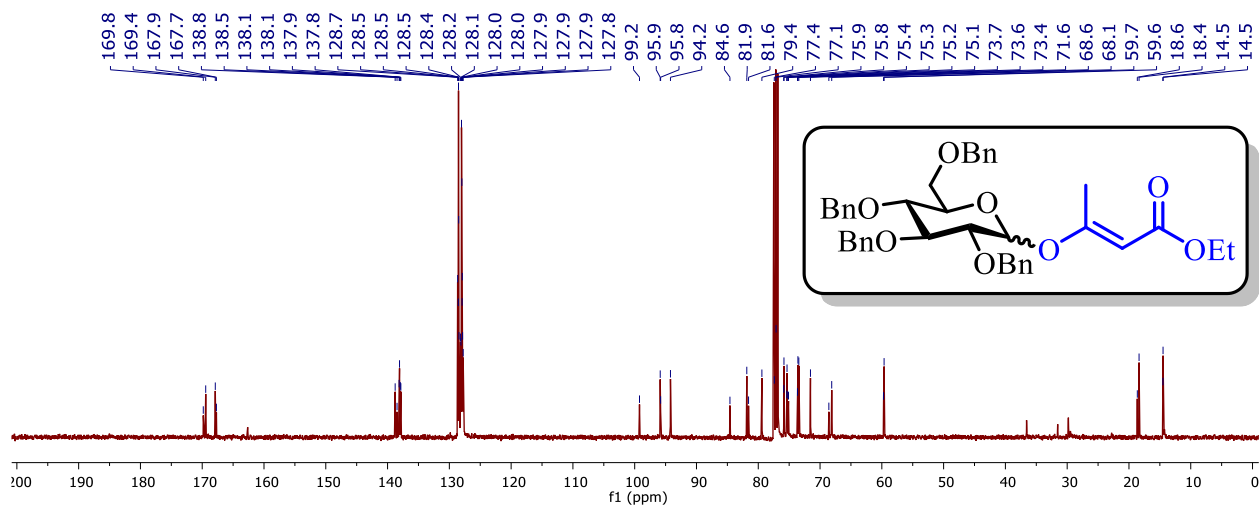


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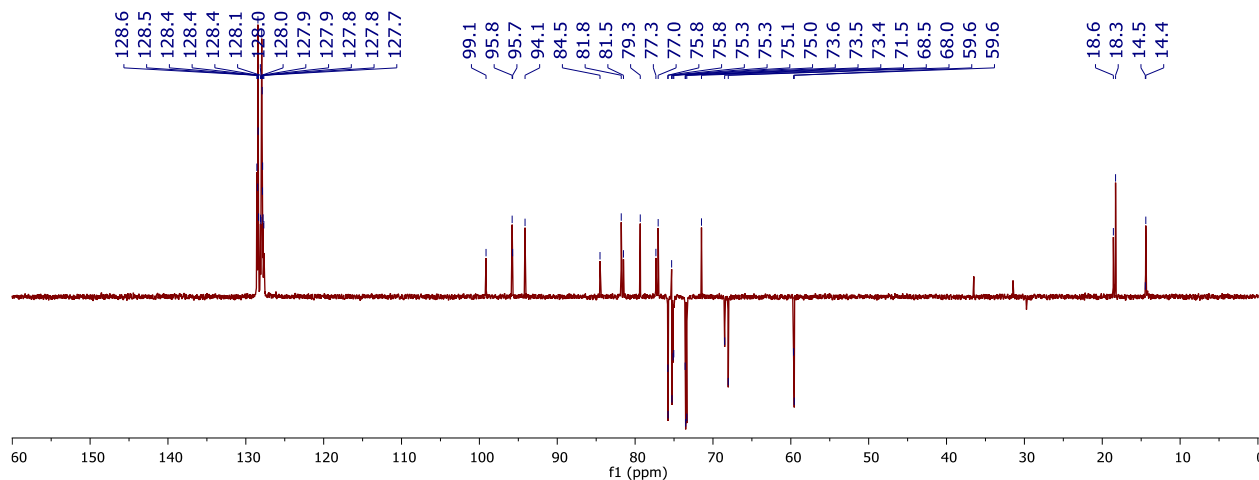
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **18b**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **18b**

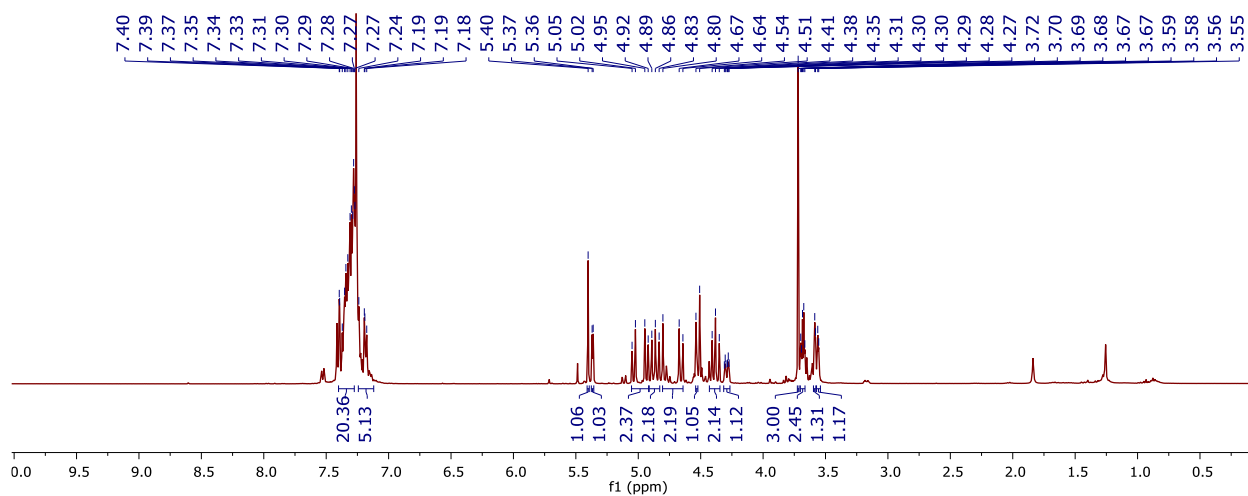


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **18b**

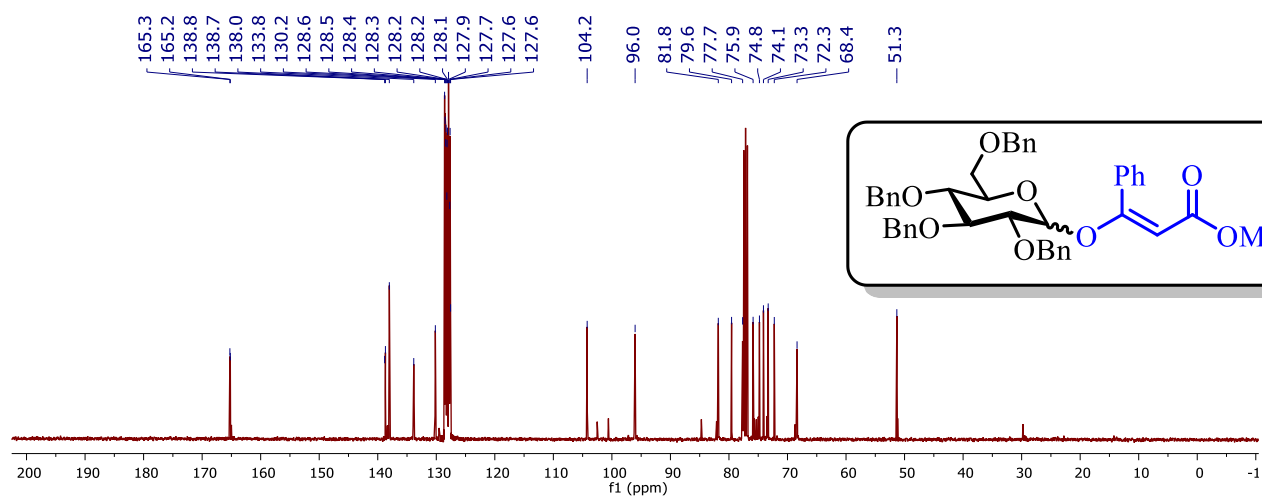


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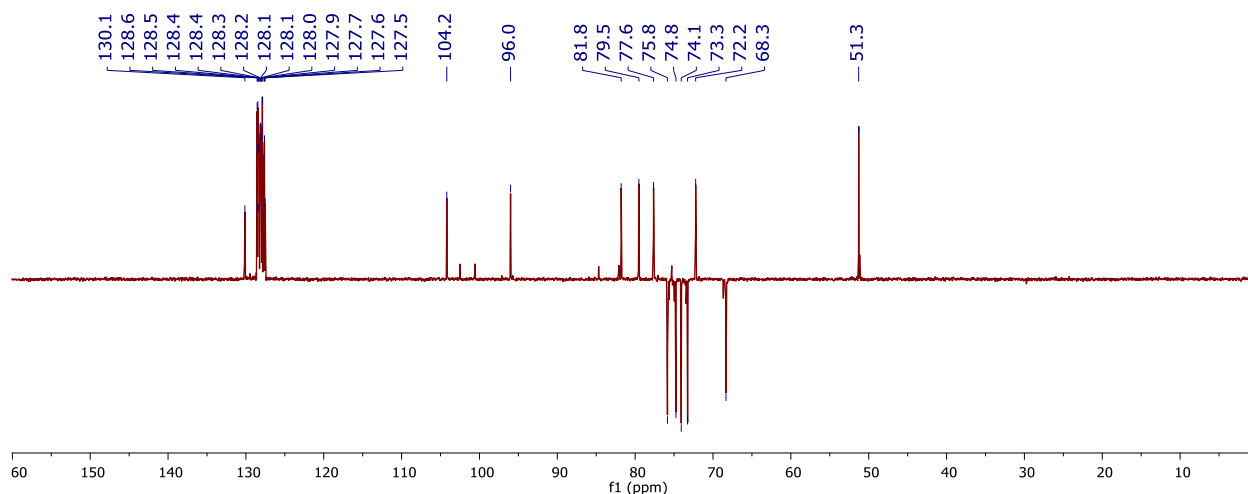
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **18c**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **18c**

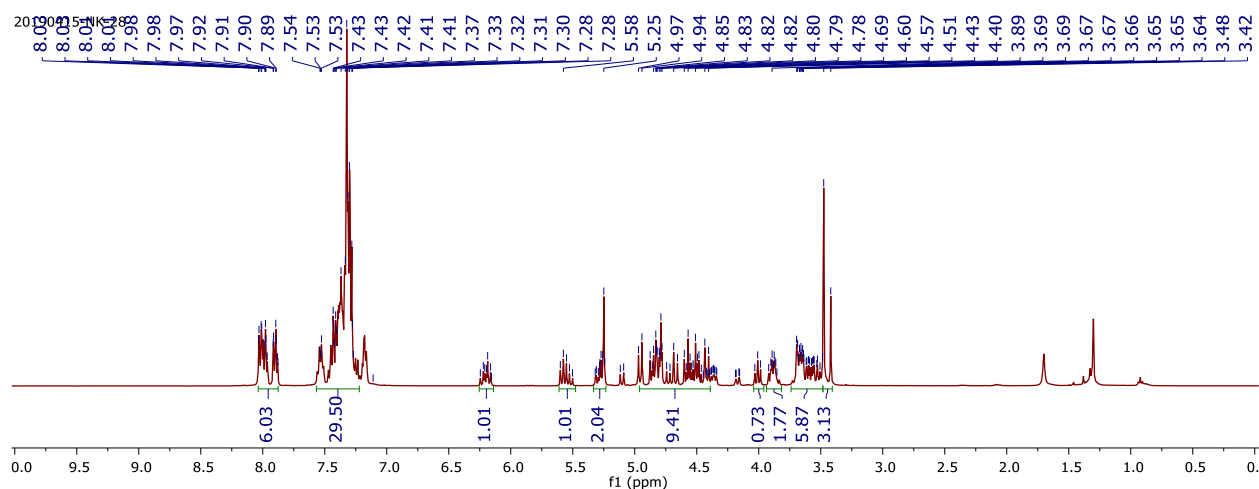


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **18c**

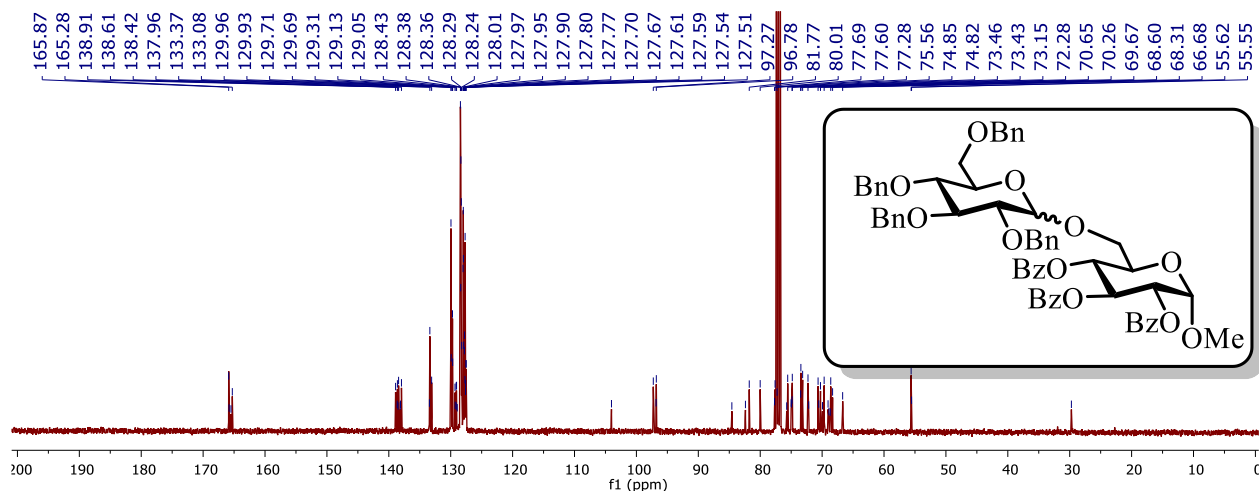


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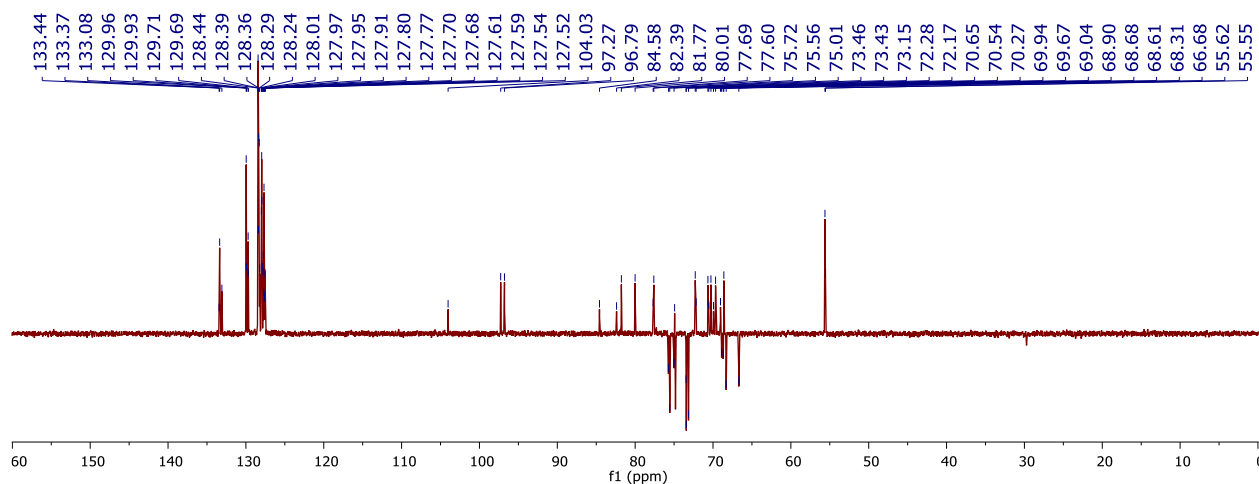
¹H NMR Spectrum (400 MHz, CDCl₃) of Compound 20



¹³C NMR Spectrum (100 MHz, CDCl₃) of Compound 20

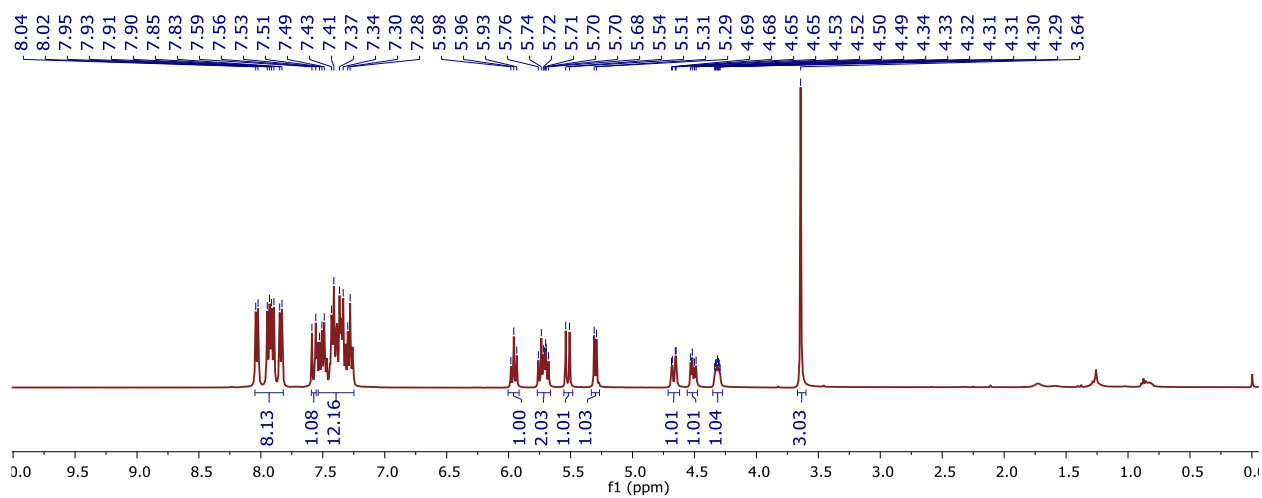


DEPT-135 NMR Spectrum (100 MHz, CDCl₃) of Compound 20

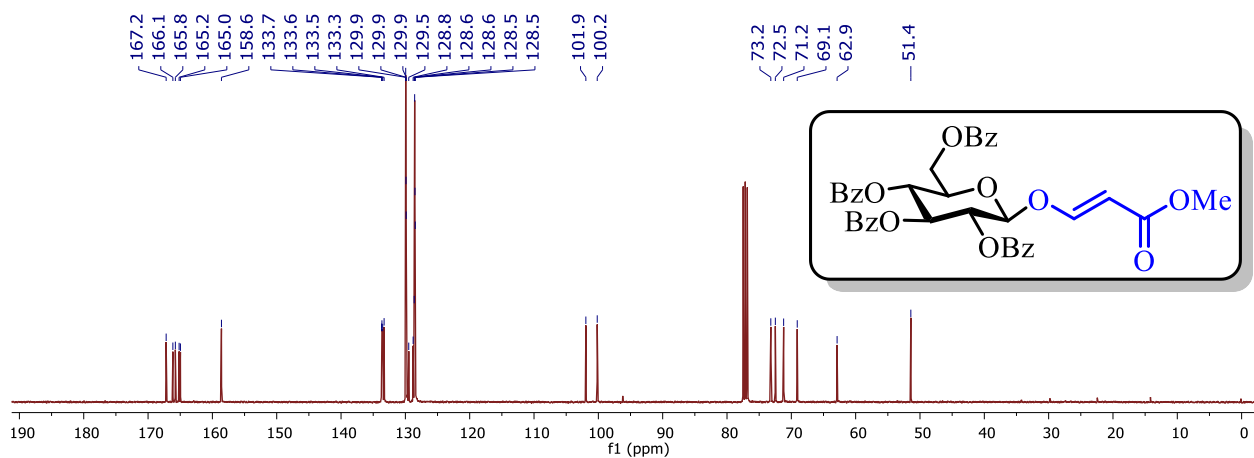


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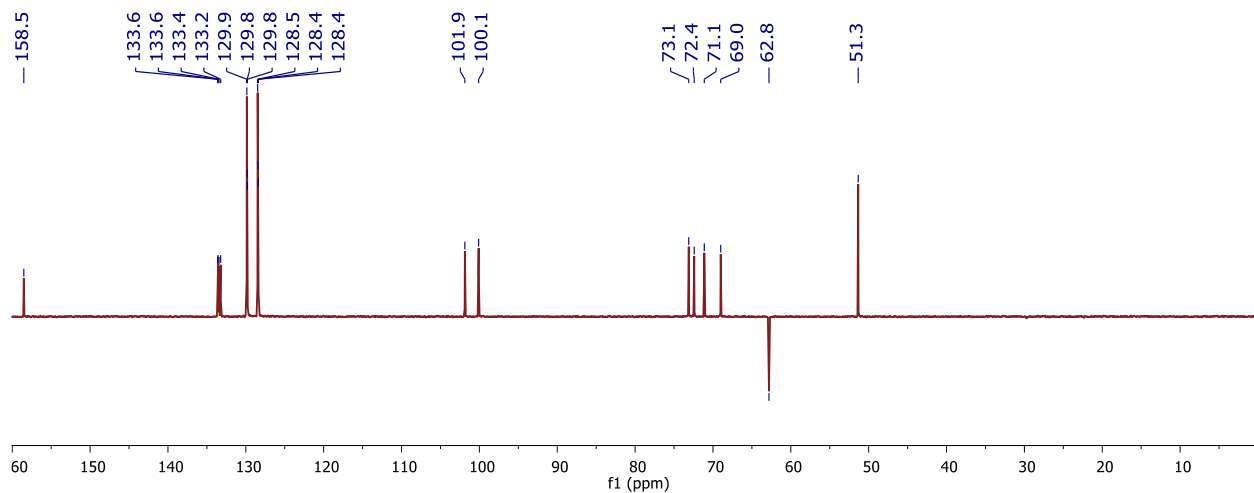
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **18d** (β -isomer)



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **18d** (β -isomer)

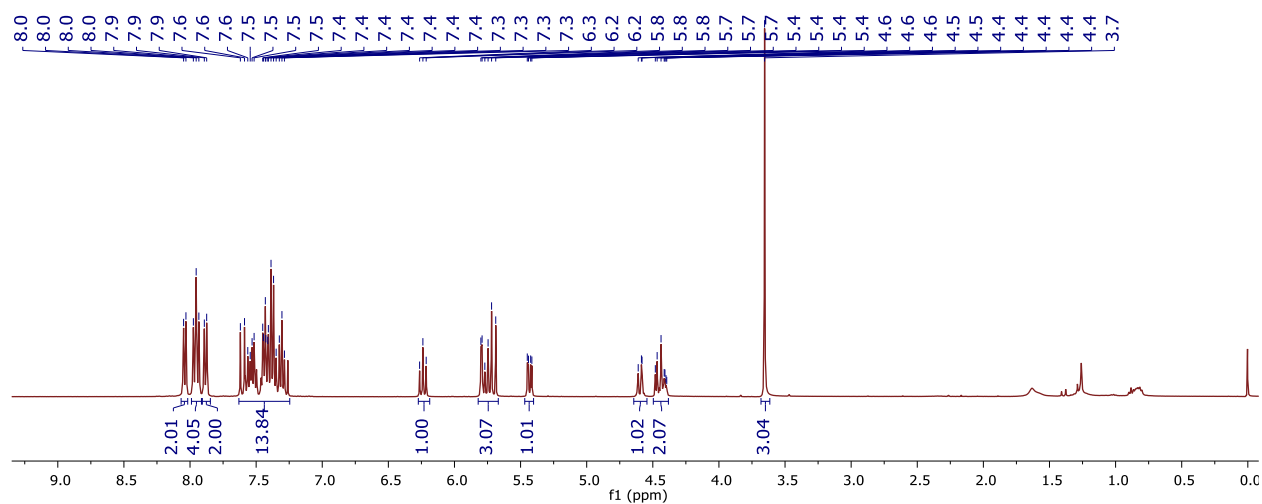


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **18d** (β -isomer)

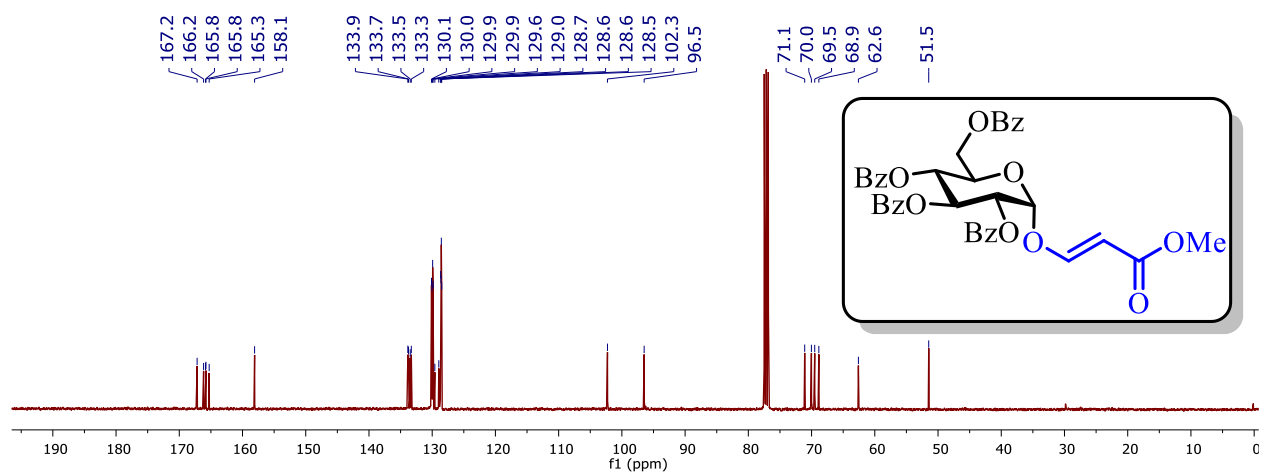


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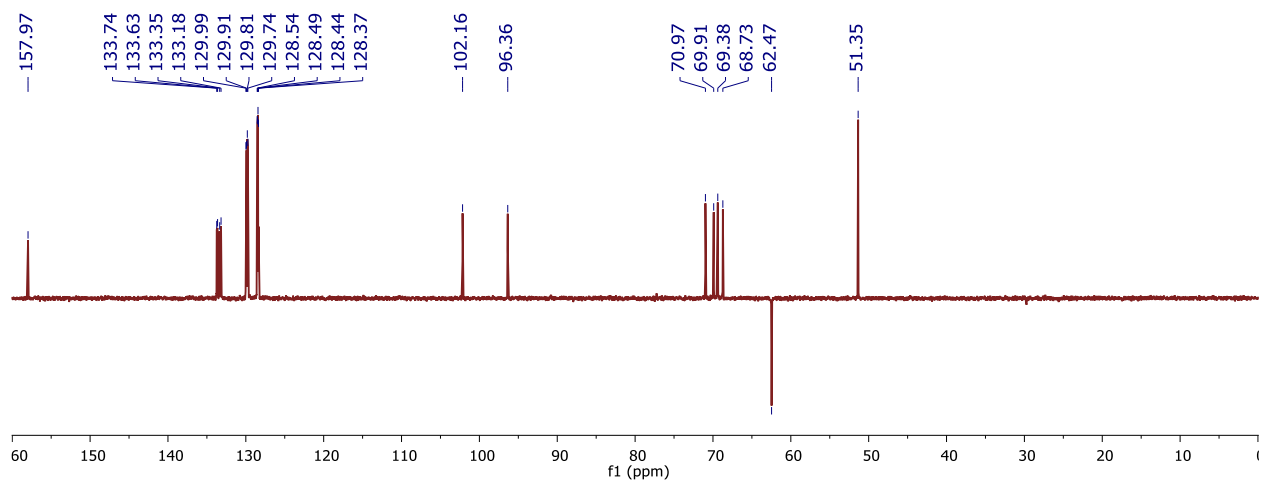
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **18d** (α -isomer)



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **18d** (α -isomer)

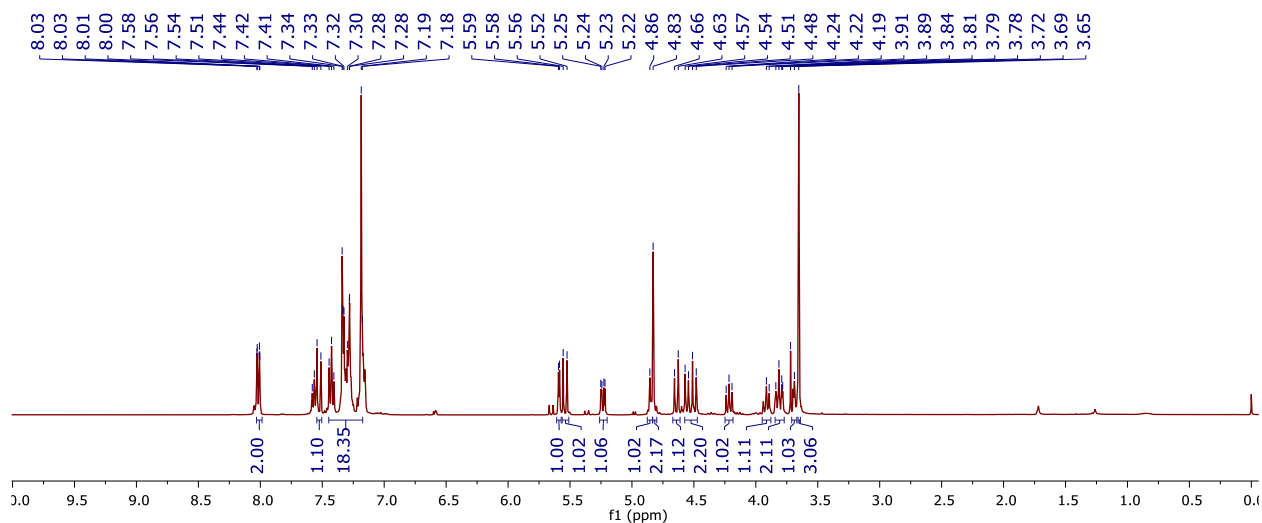


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **18d** (α -isomer)

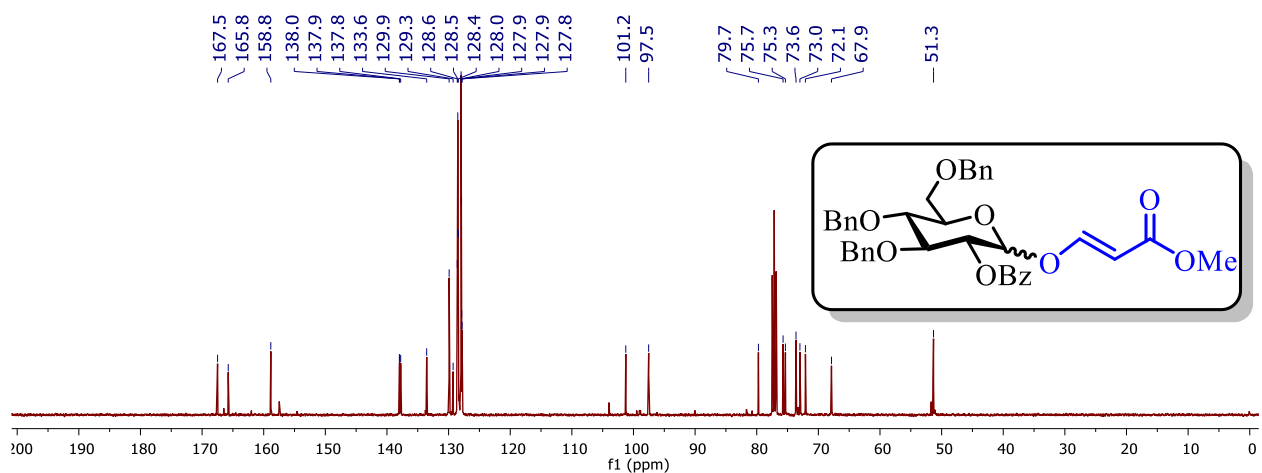


Chapter 3B

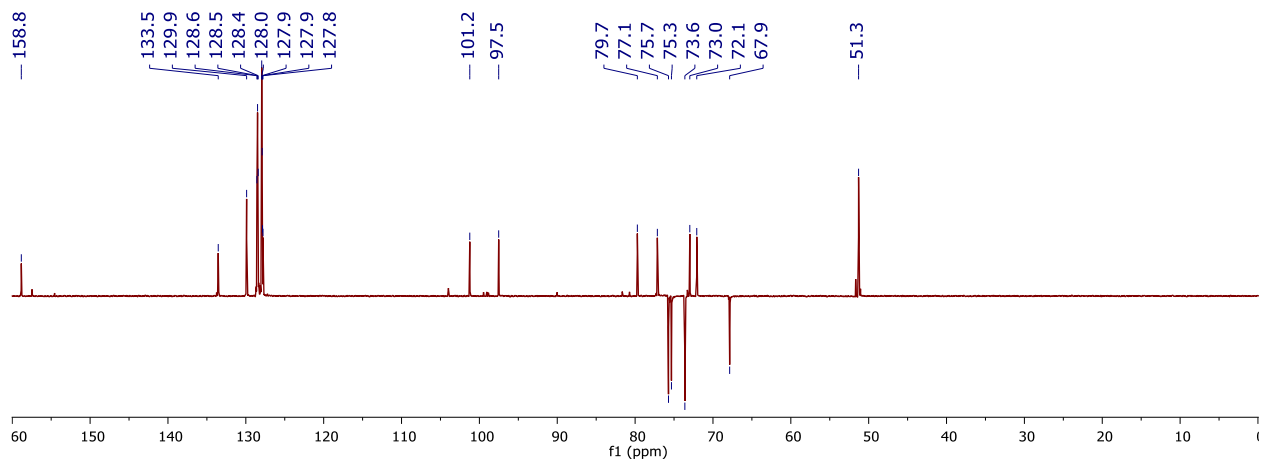
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **18e**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **18e**

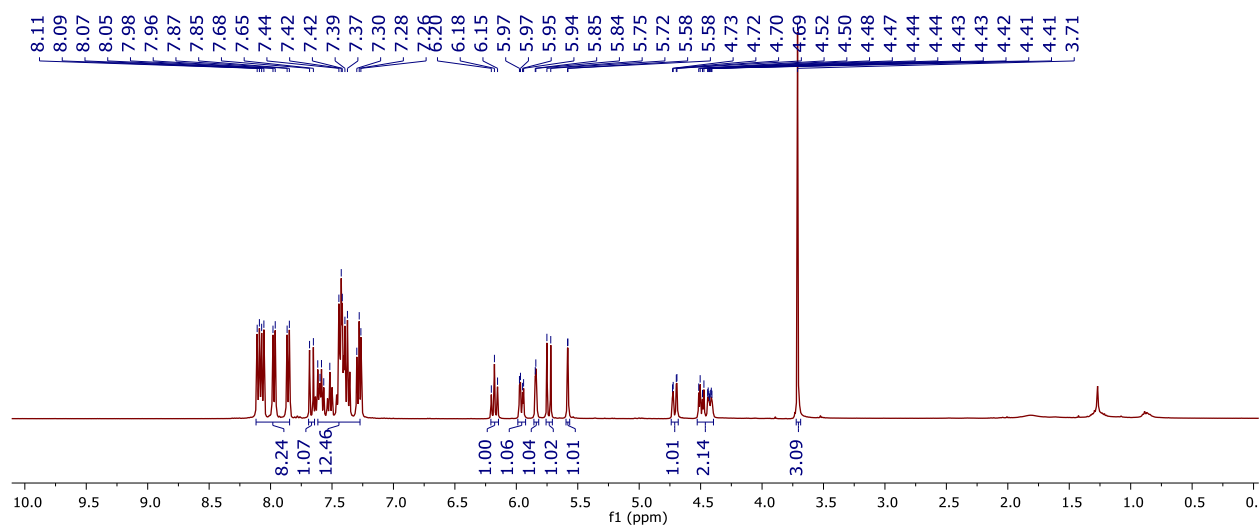


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **18e**

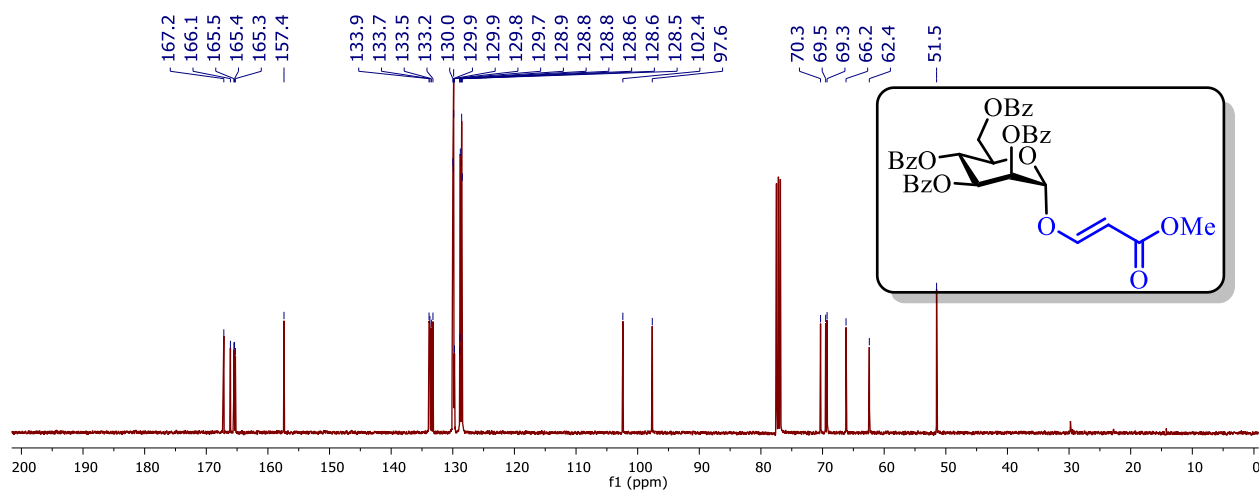


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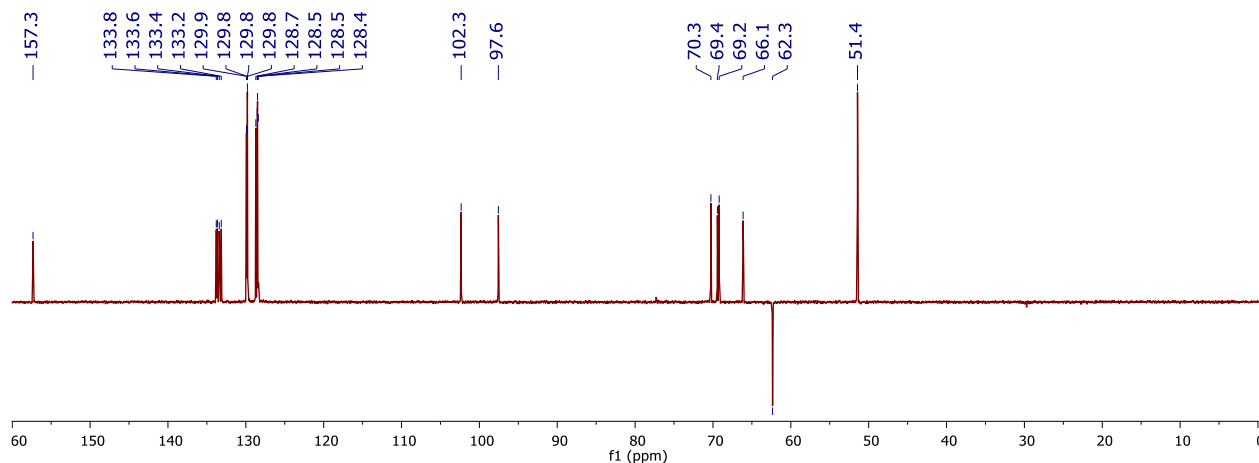
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **21a** (α -Isomer)



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **21a** (α -Isomer)

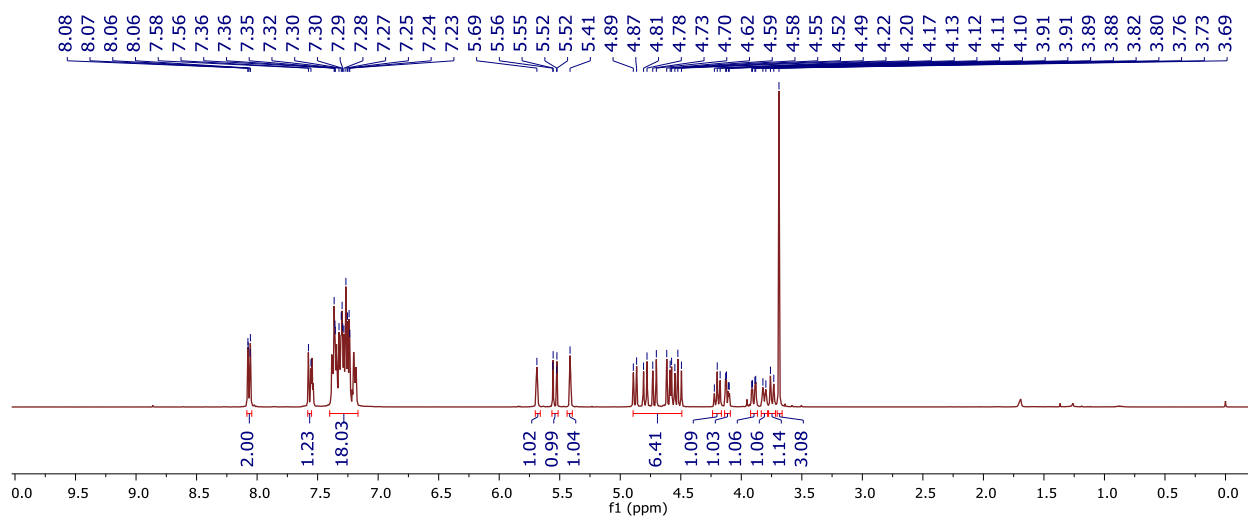


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **21a** (α -Isomer)

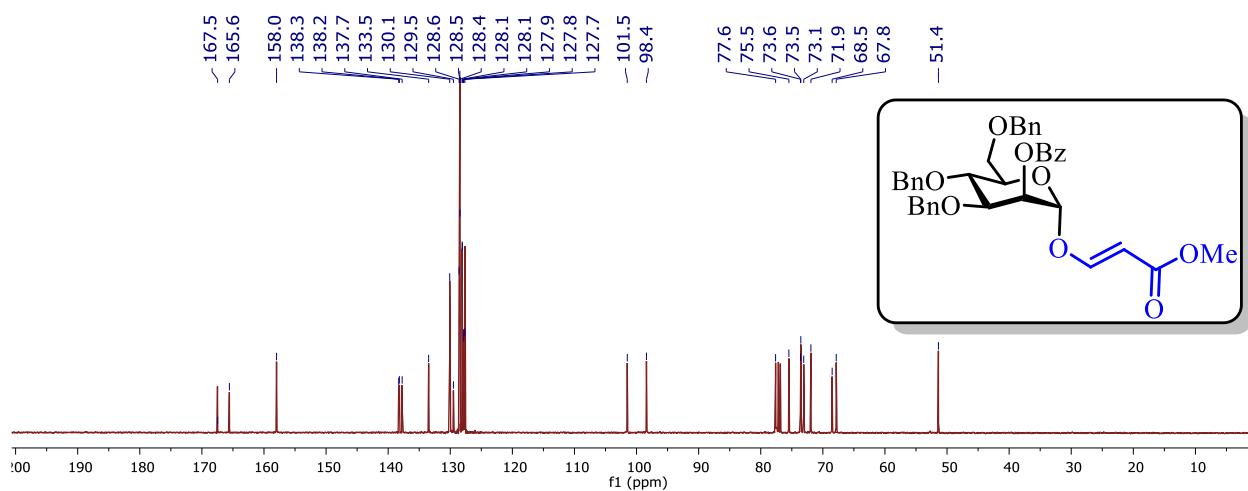


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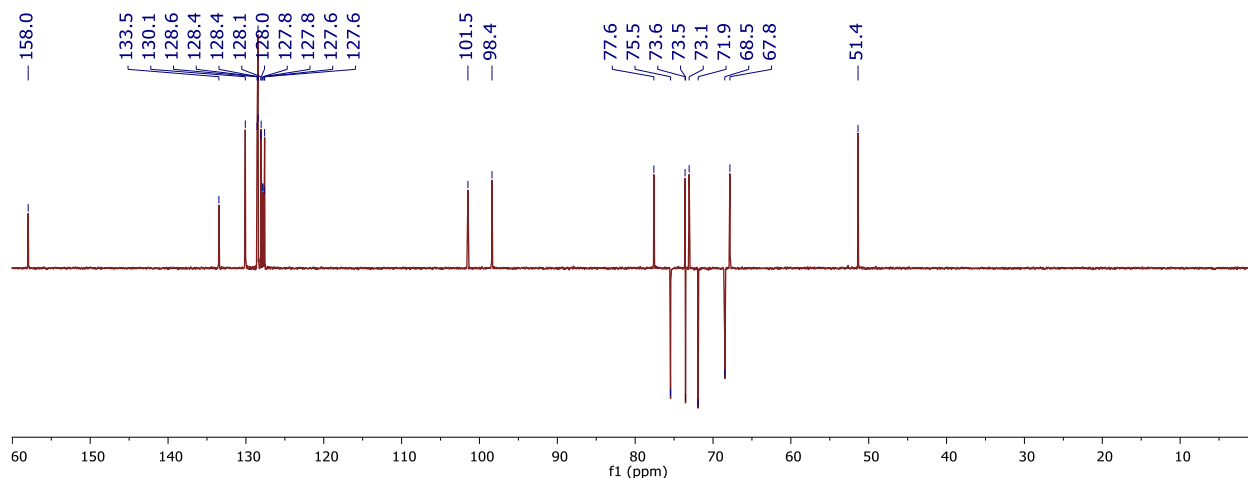
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **21b**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **21b**

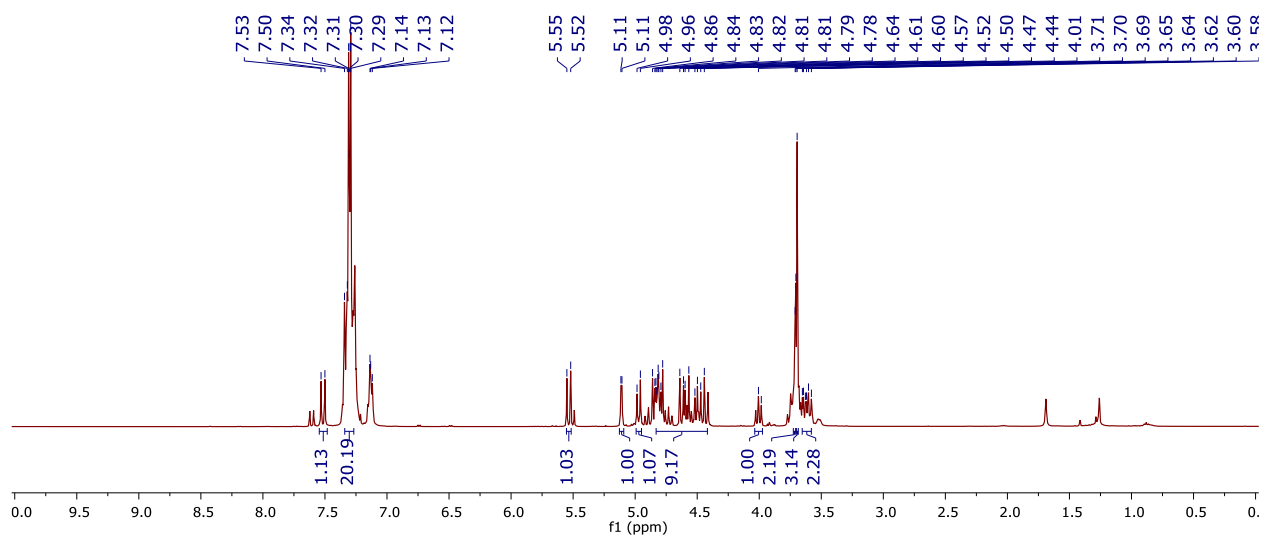


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **21b**

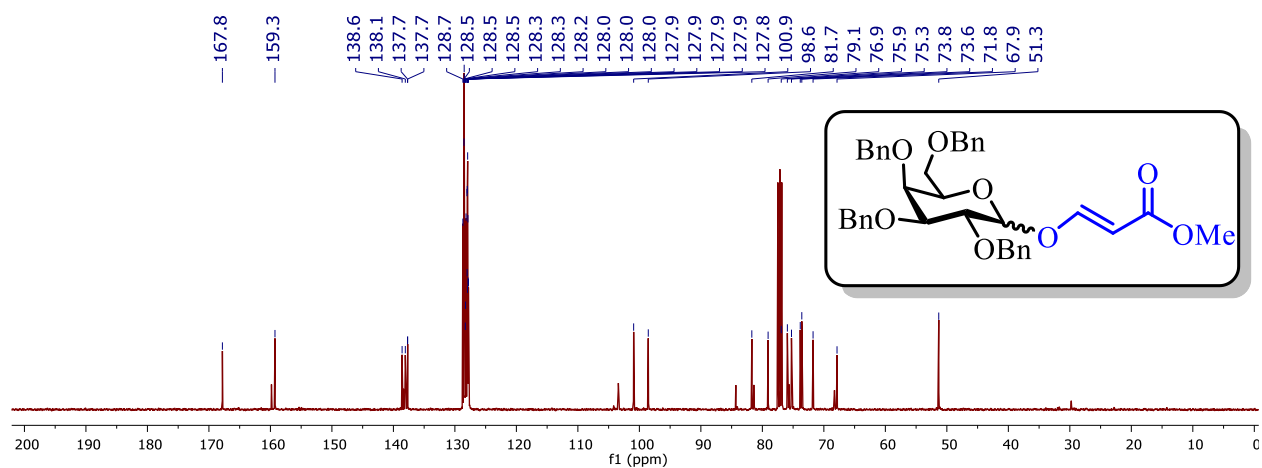


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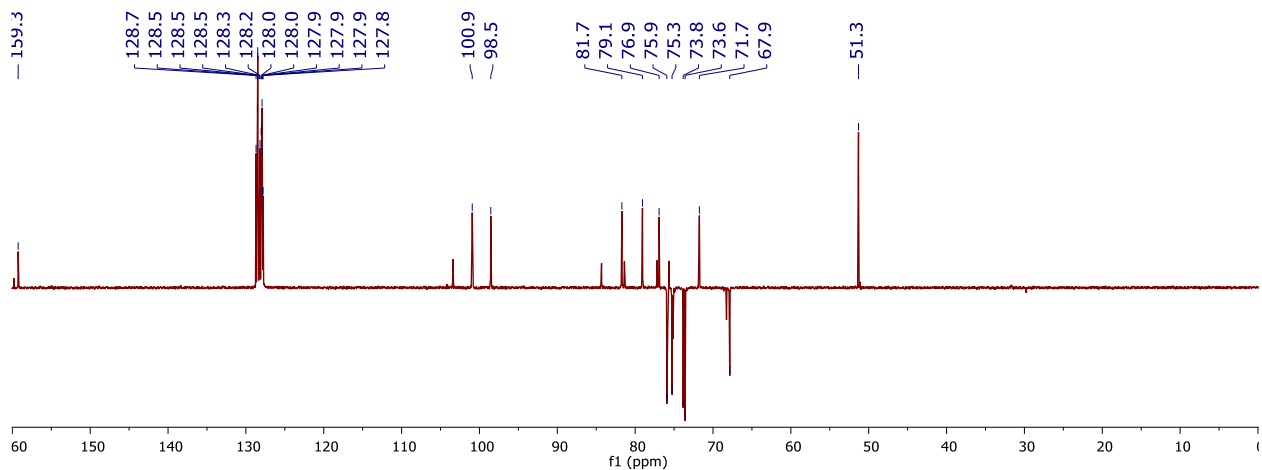
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound 22



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound 22

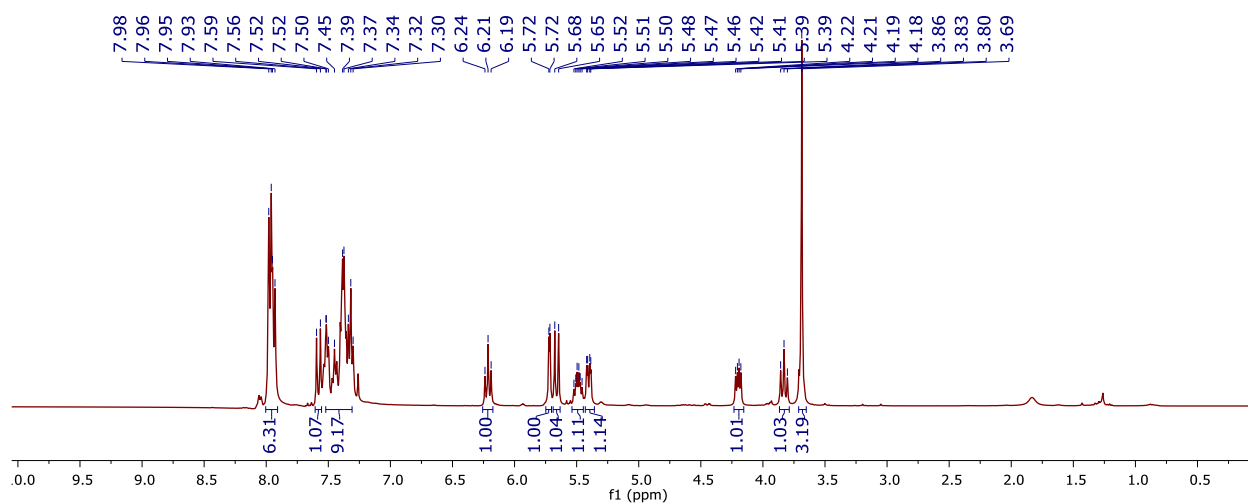


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound 22

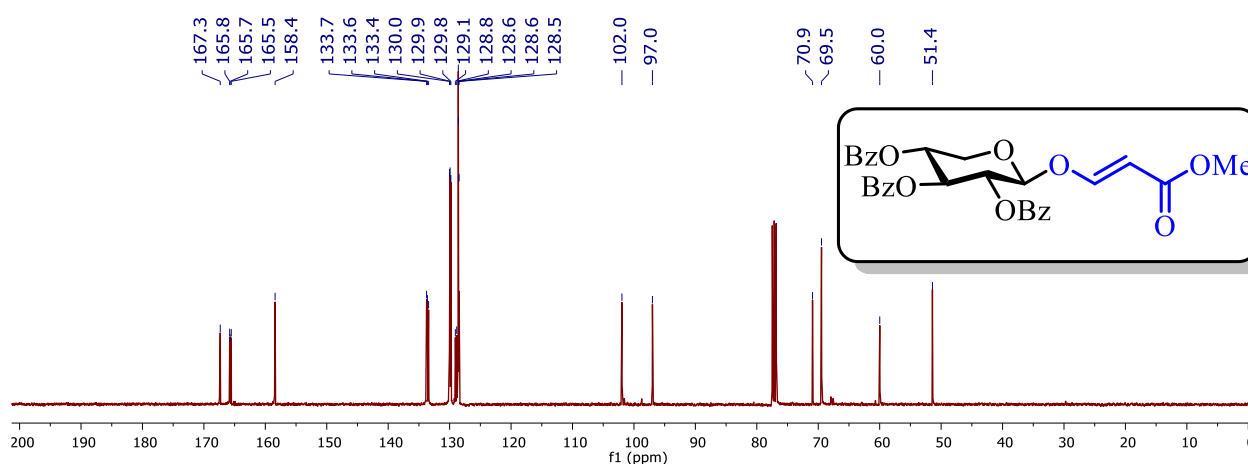


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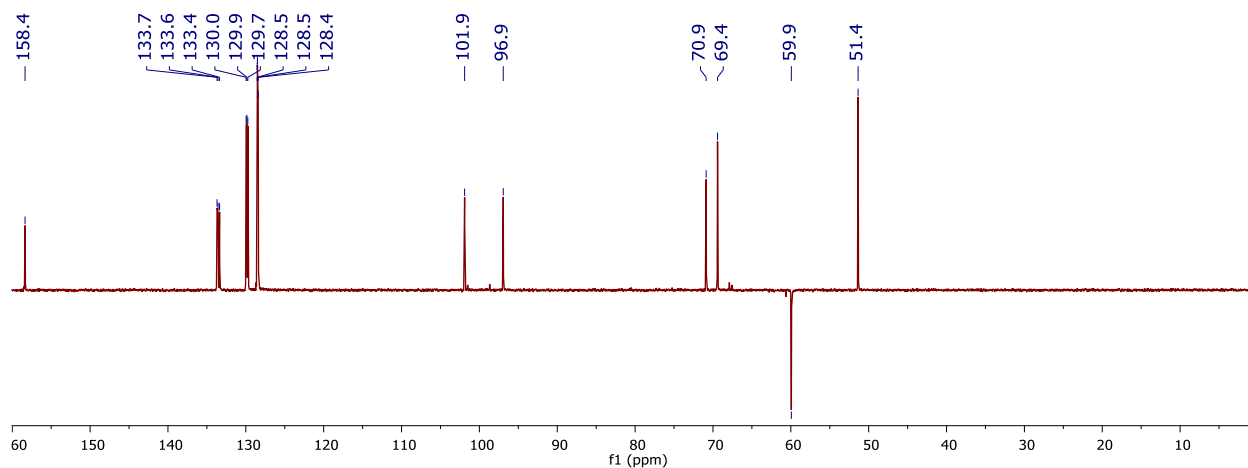
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound 23



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound 23

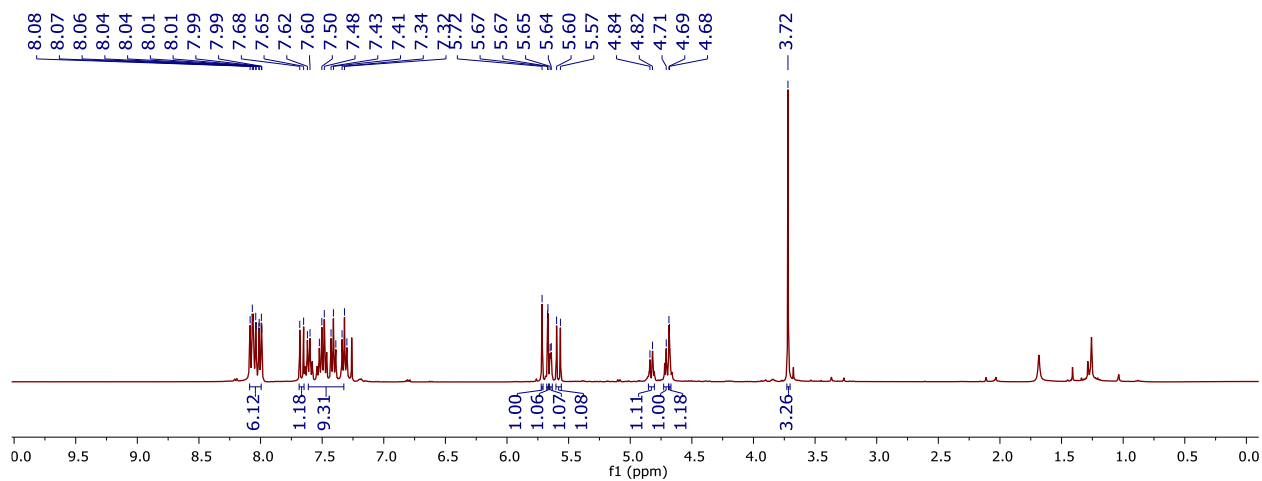


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound 23

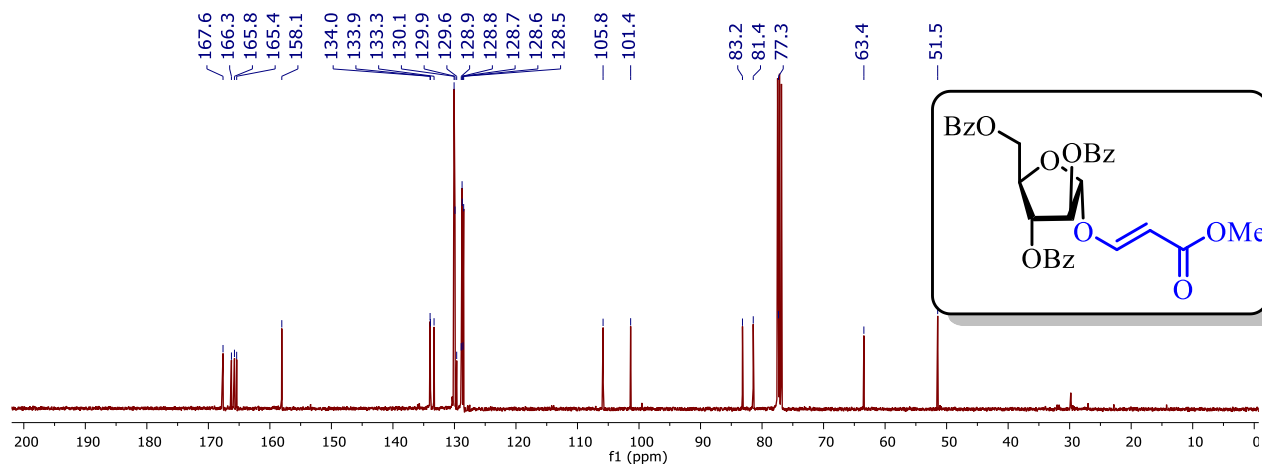


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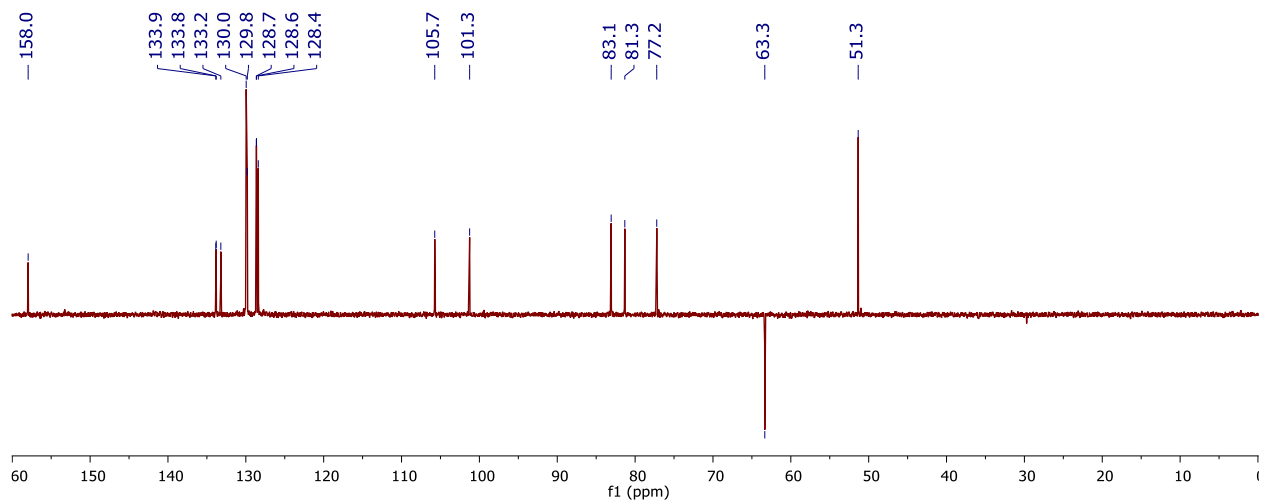
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **24a**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **24a**

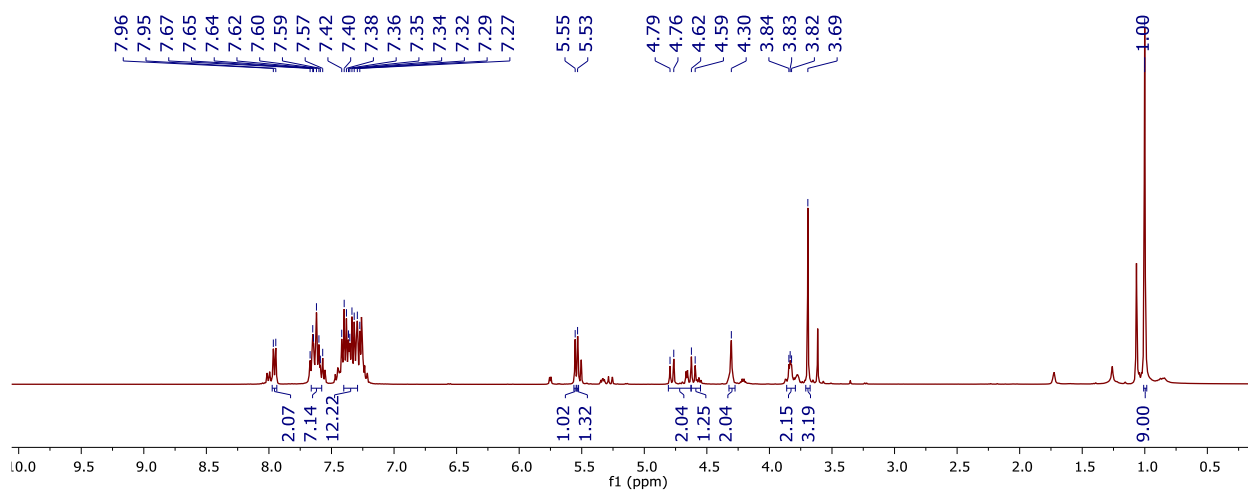


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **24a**

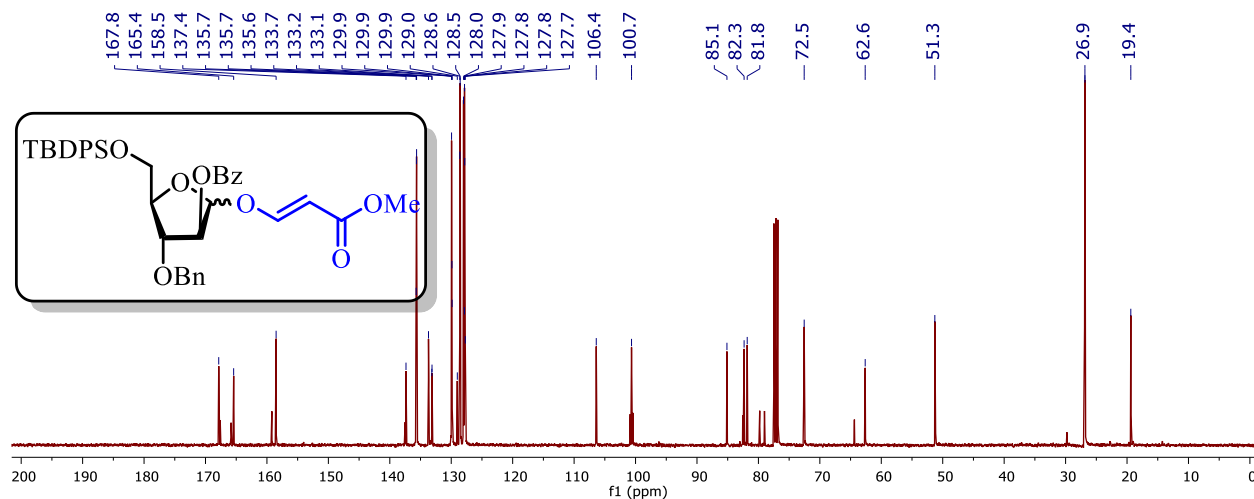


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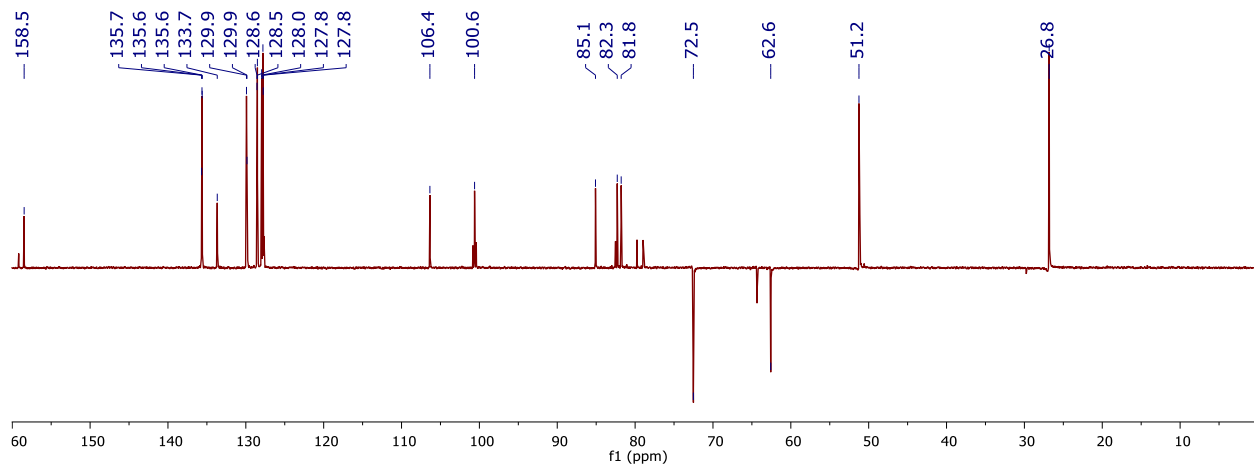
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **24b**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **24b**

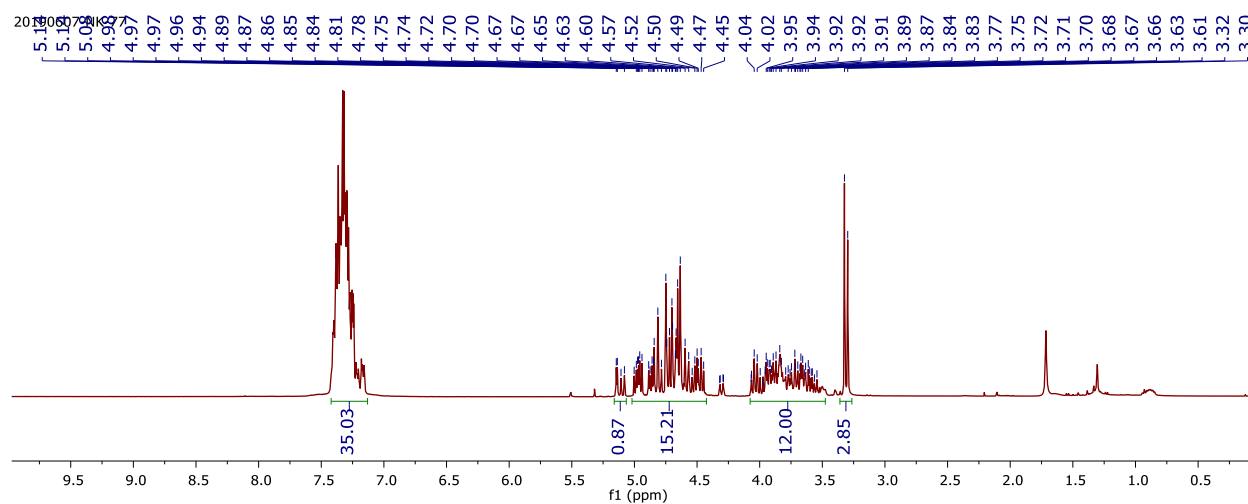


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **24b**

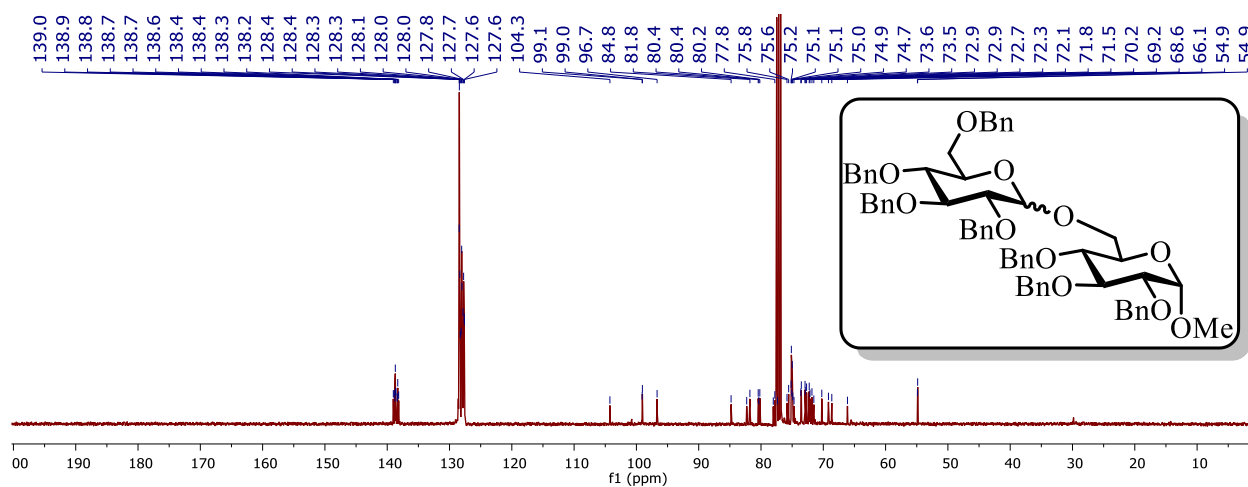


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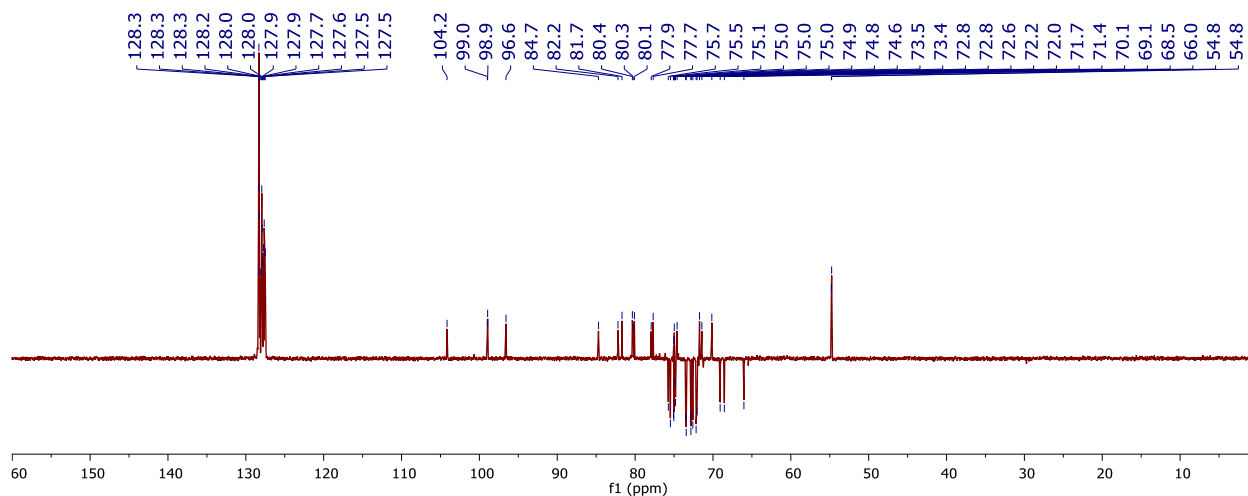
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound 25a



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound 25a

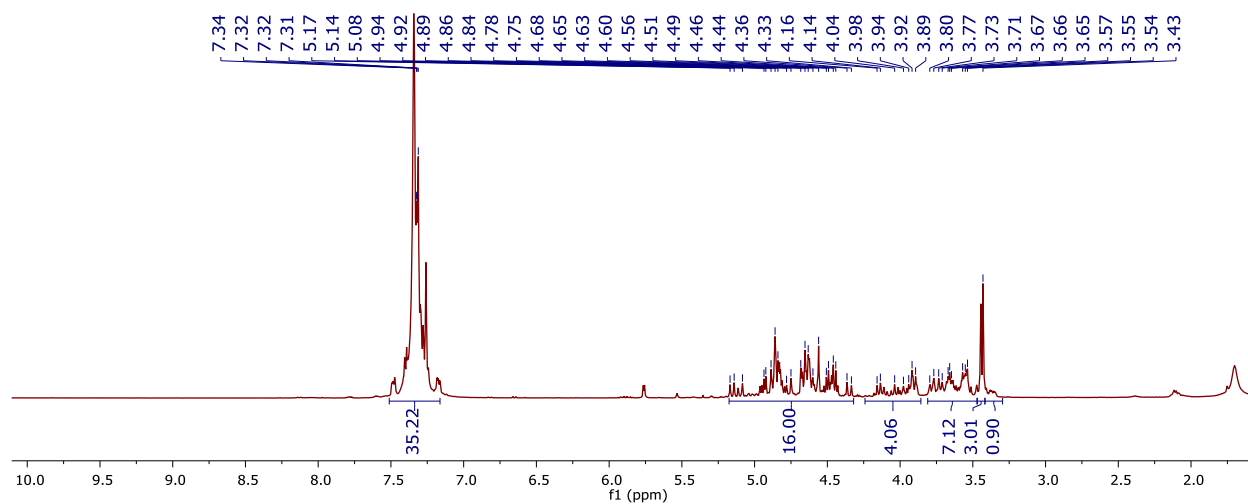


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound 25a

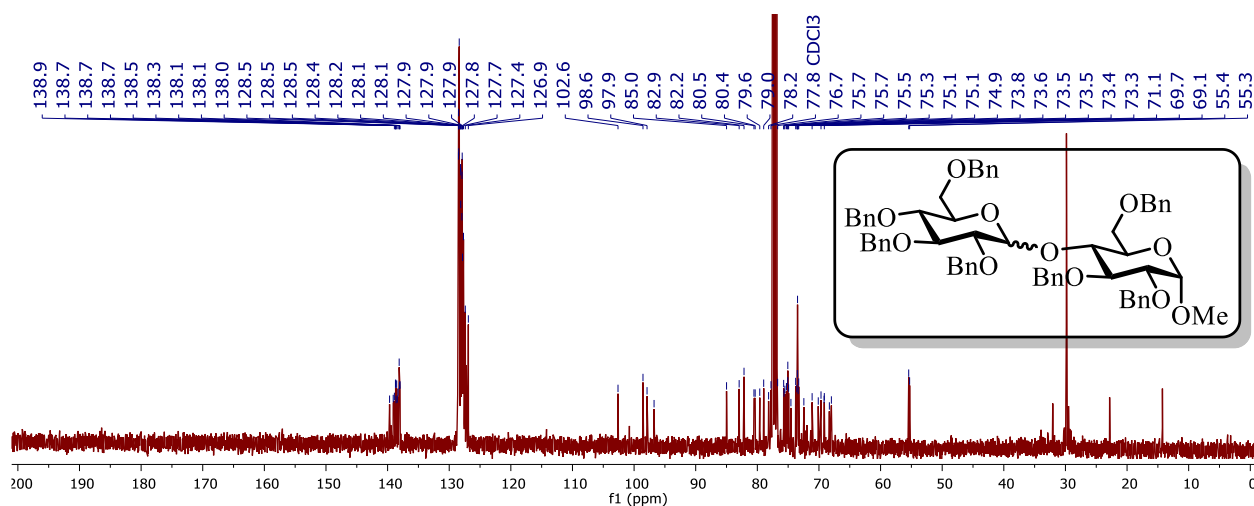


Chapter 3B

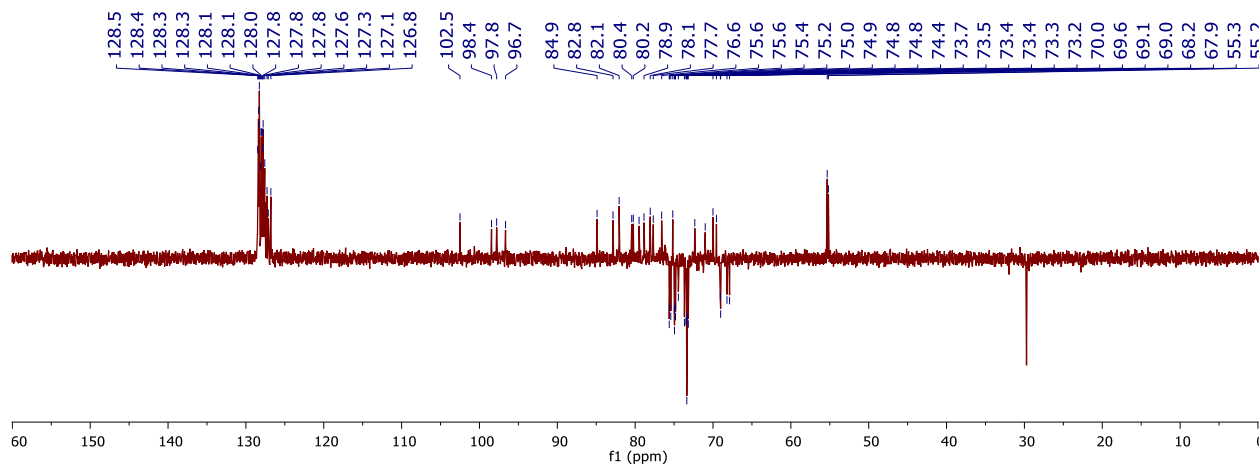
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **25b**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **25b**

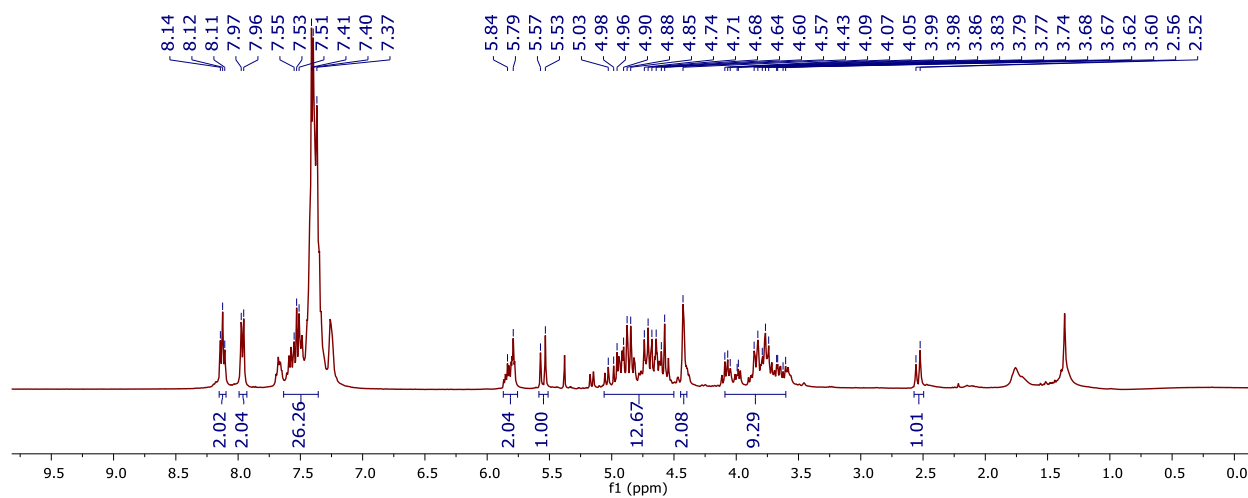


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **25b**

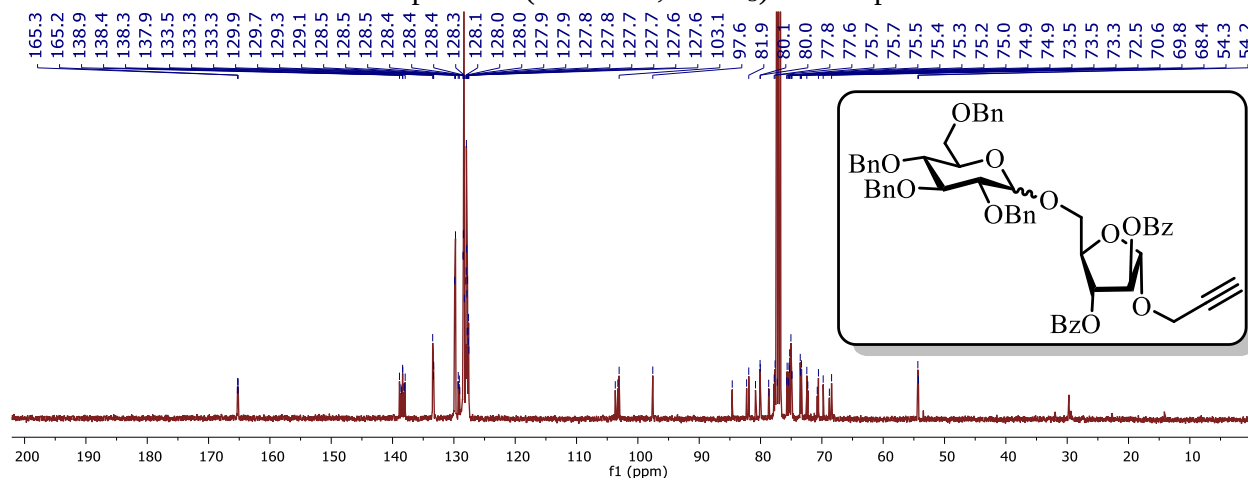


Chapter 3B

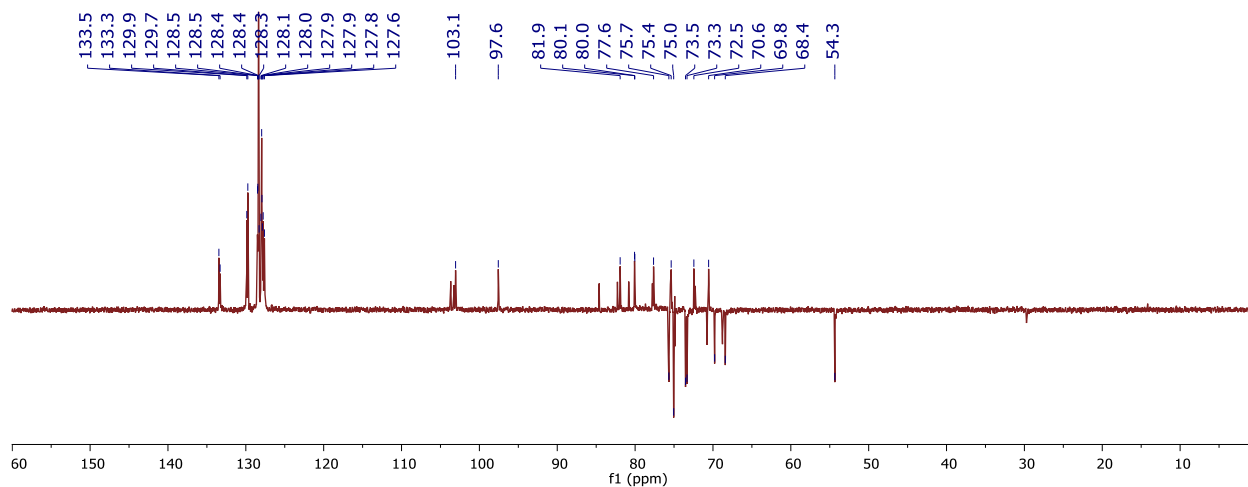
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **25c**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **25c**

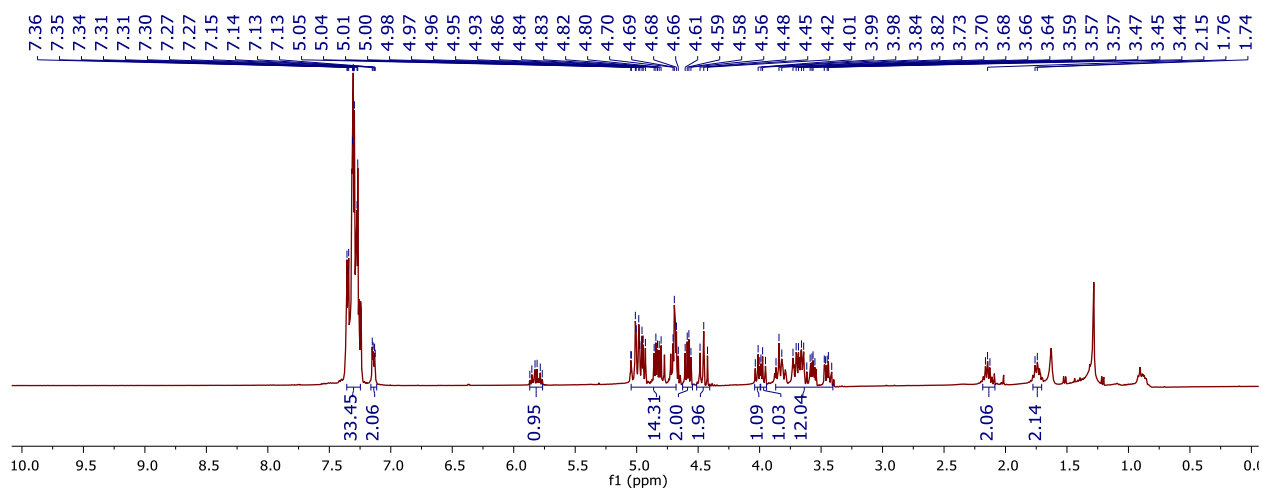


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **25c**

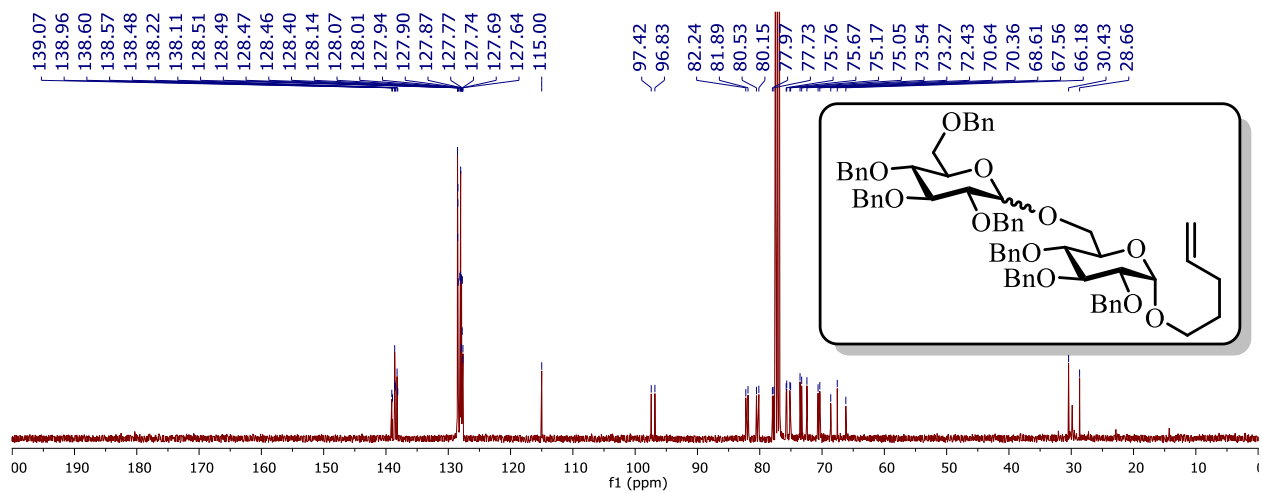


Chapter 3B

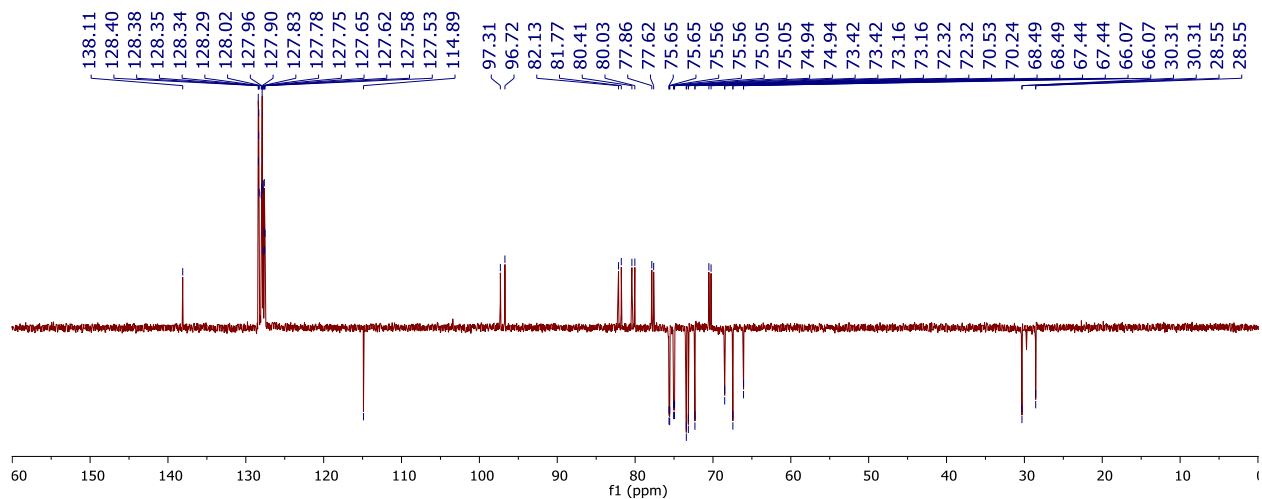
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **25d**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **25d**



DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **25d**



166.2
165.7
138.9
138.5
138.1
138.0
136.0
135.9
135.7
135.6
133.9
133.3
133.2
132.9
130.1
130.0
129.9
129.8
129.7
129.6
129.2
128.4
128.3
128.2
128.2
127.9
127.8
127.8
127.7
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127.6
127.5
127.5
98.2
96.5
91.5
81.5
79.3
77.2
75.4
74.9
74.8
73.4
72.6
72.2
71.5
71.1
68.4
62.9
55.0
27.0
19.5

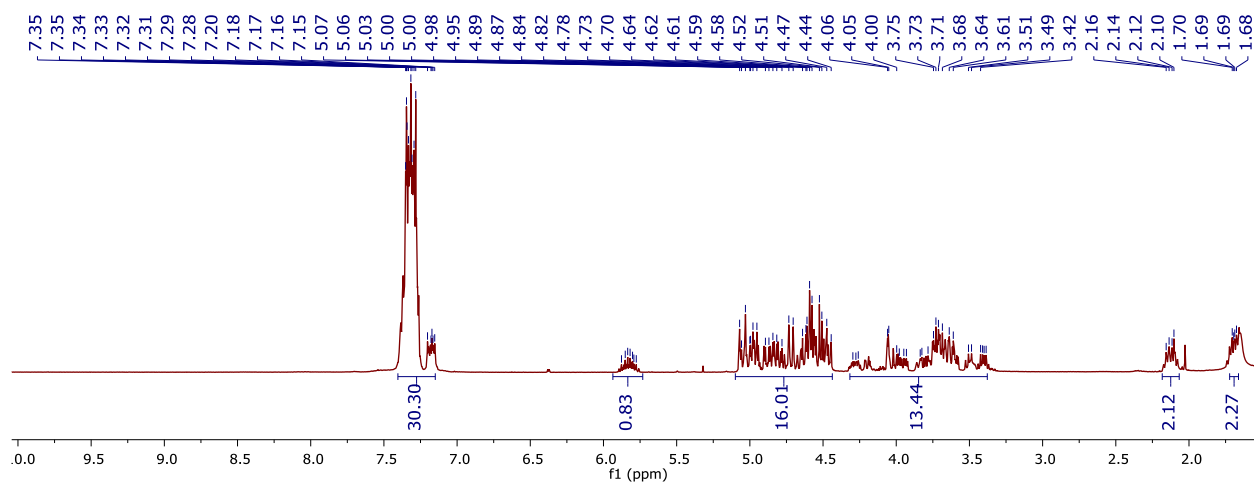
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f1 (ppm)

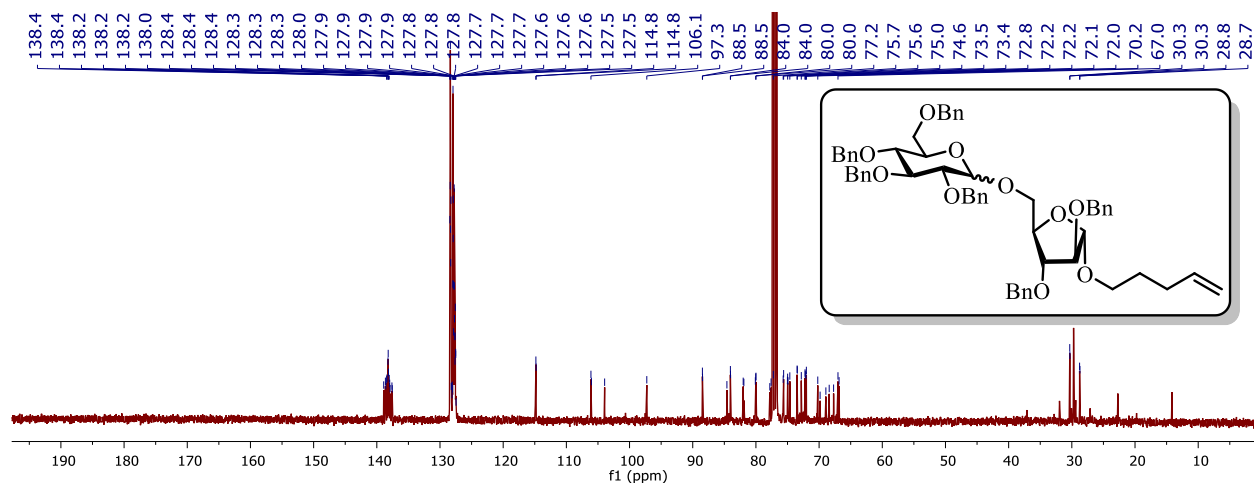
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BnO
BnO
BnO
OTBDPS
BzO
BzO
OMe

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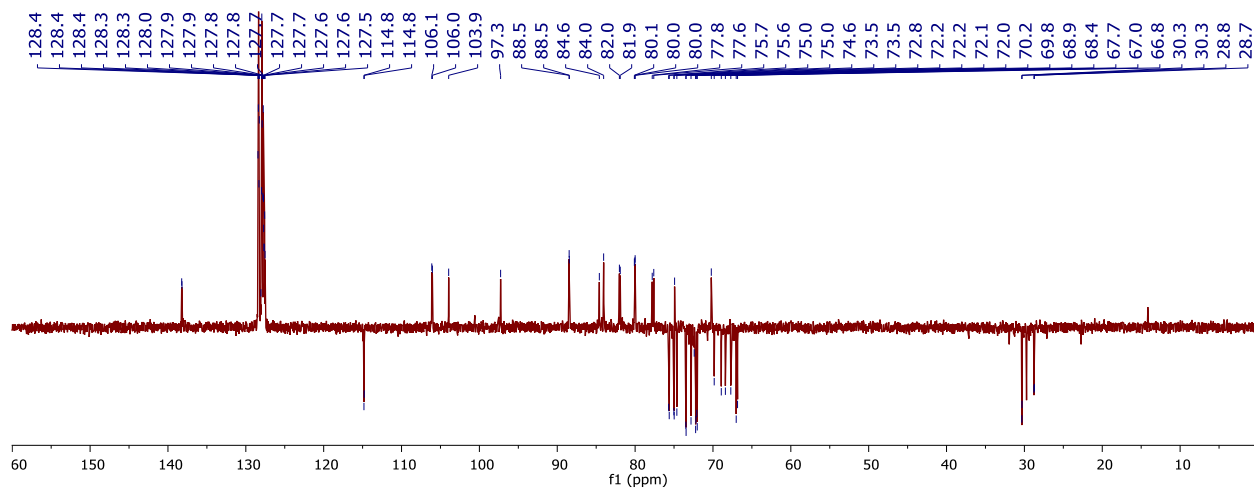
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **25f**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **25f**

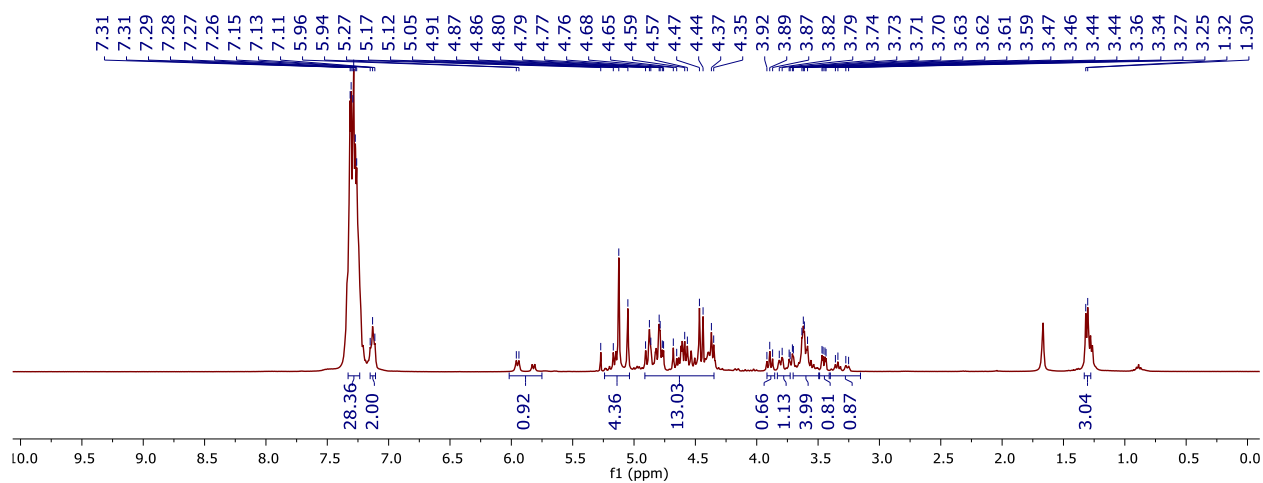


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **25f**

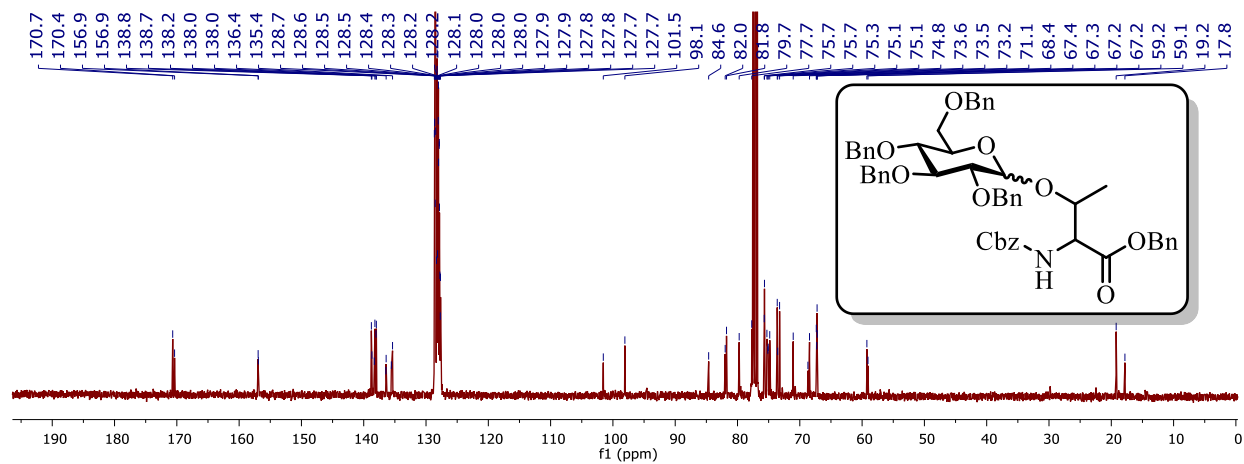


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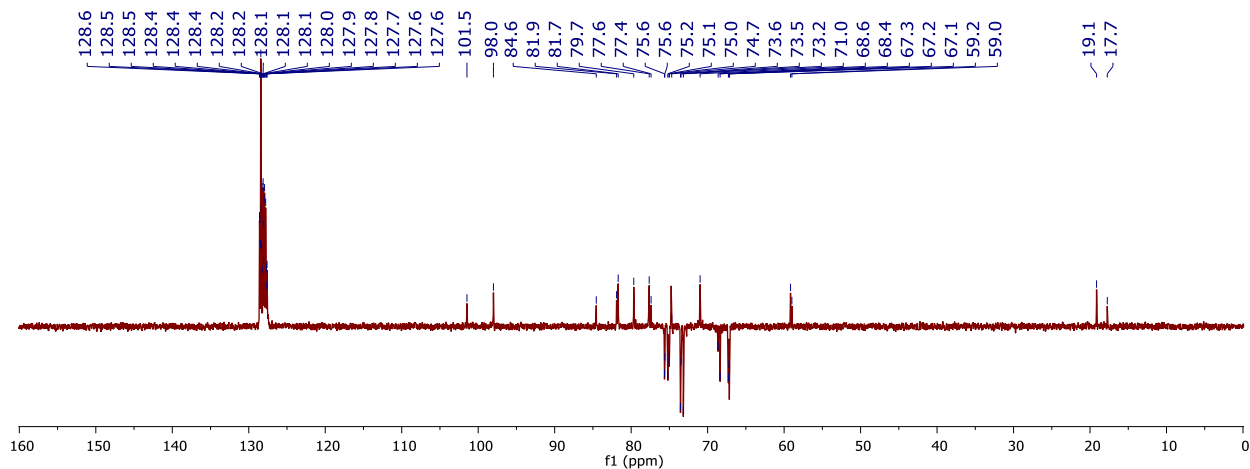
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^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **25g**

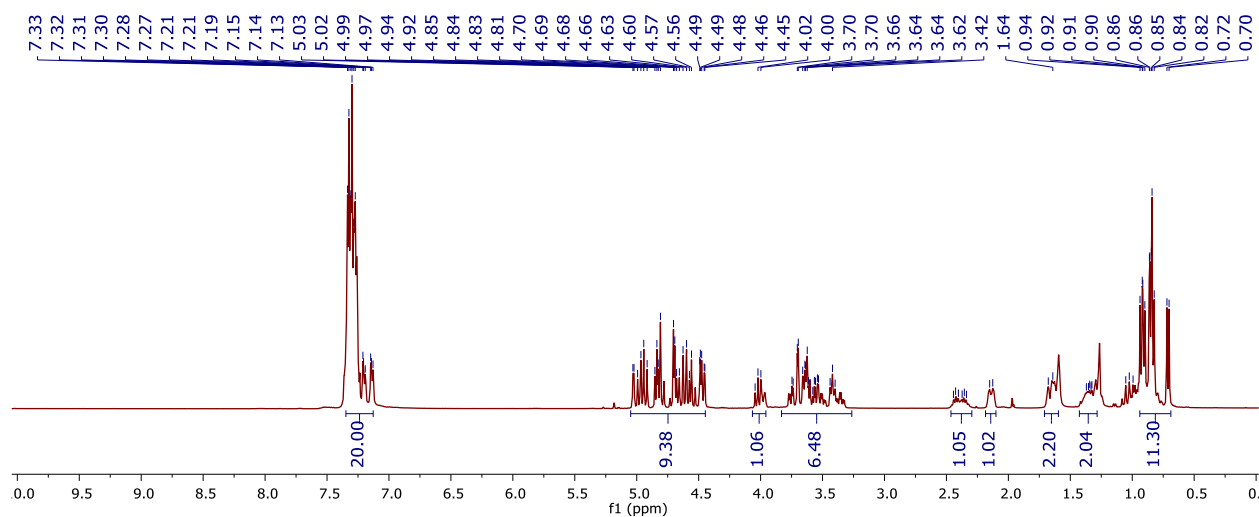


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **25g**

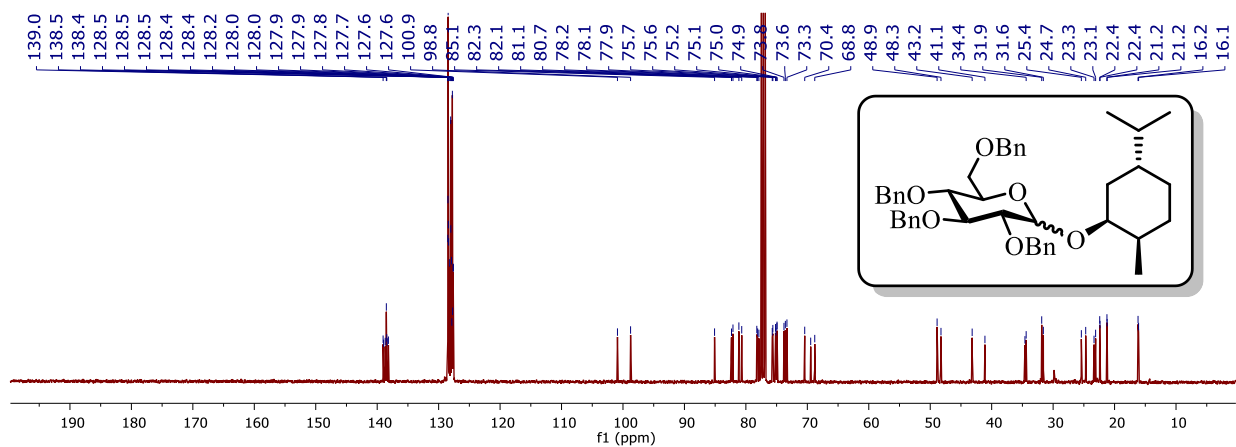


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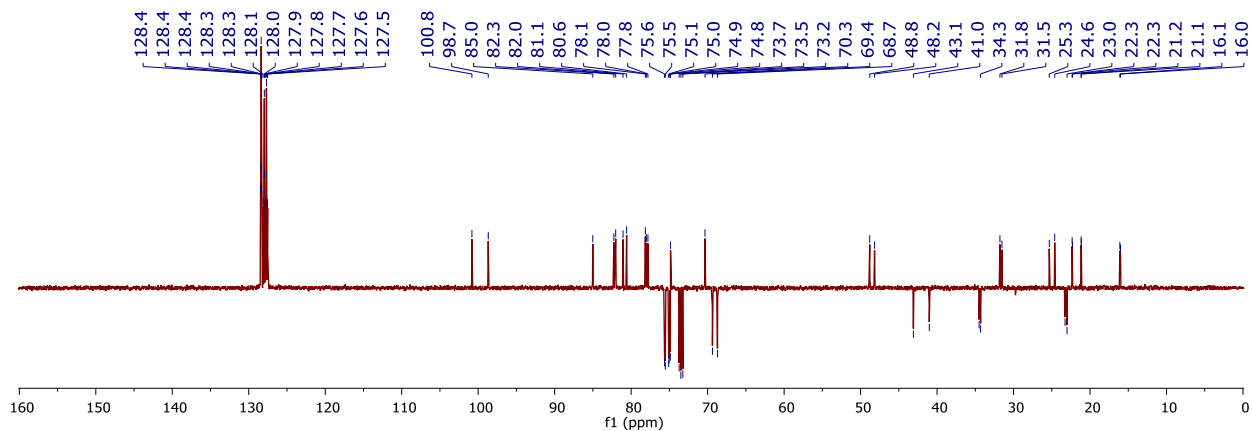
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **25h**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **25h**

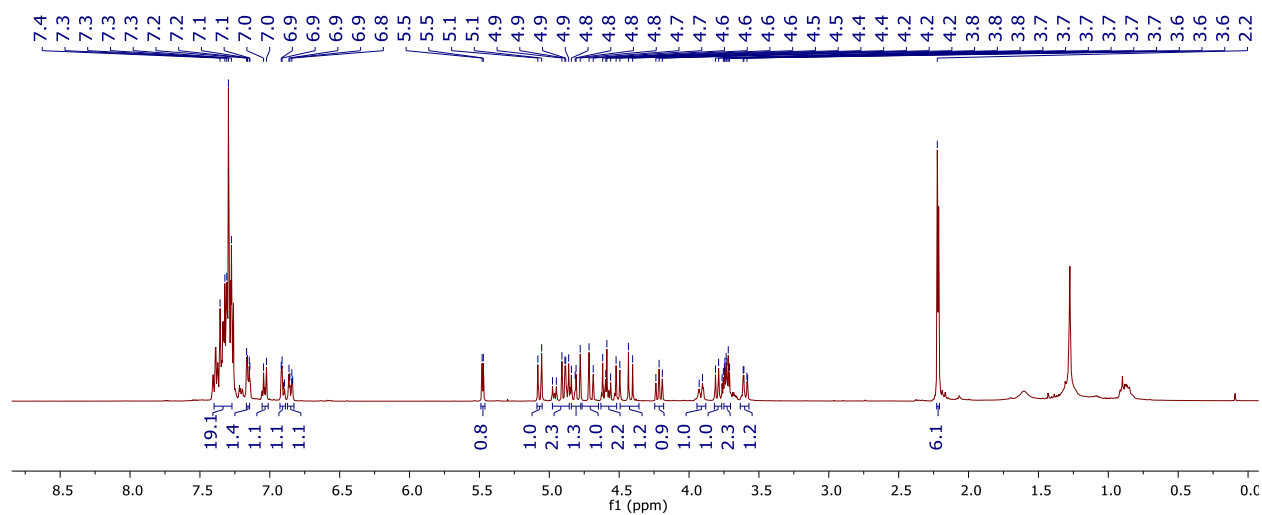


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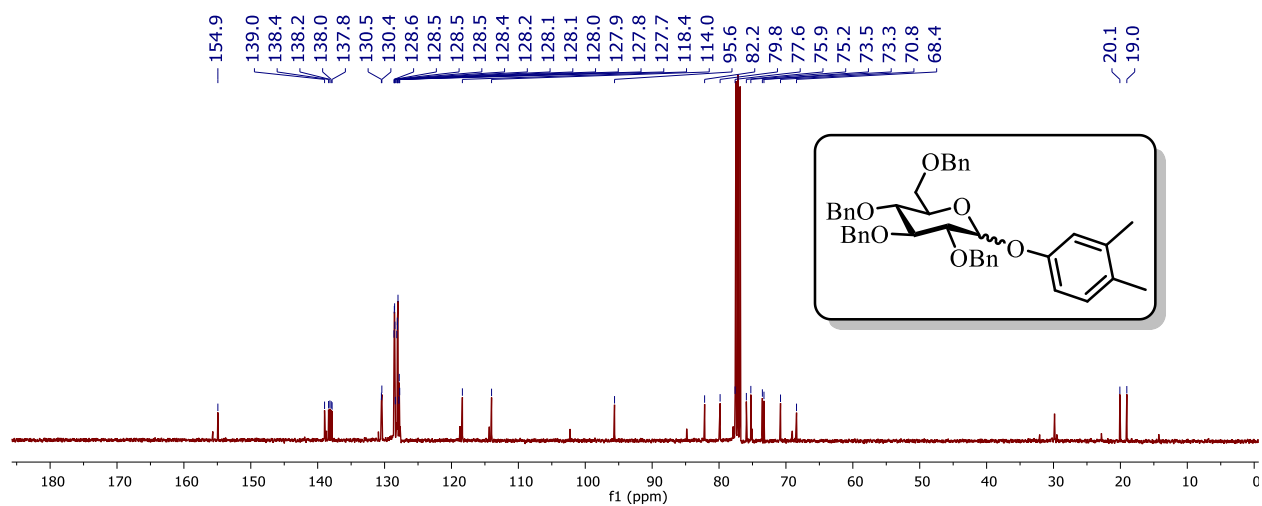


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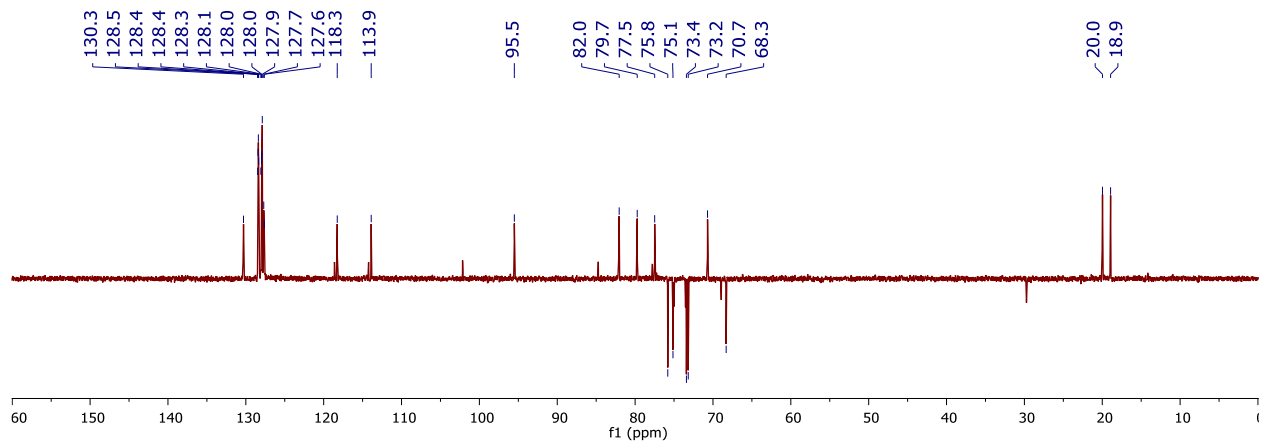
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **25i**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **25i**

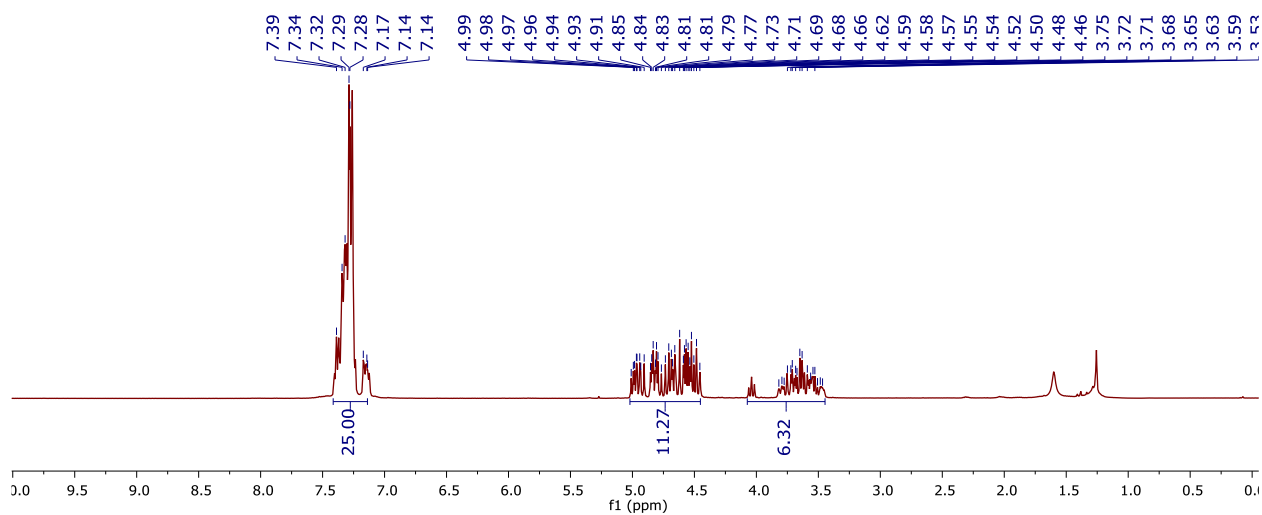


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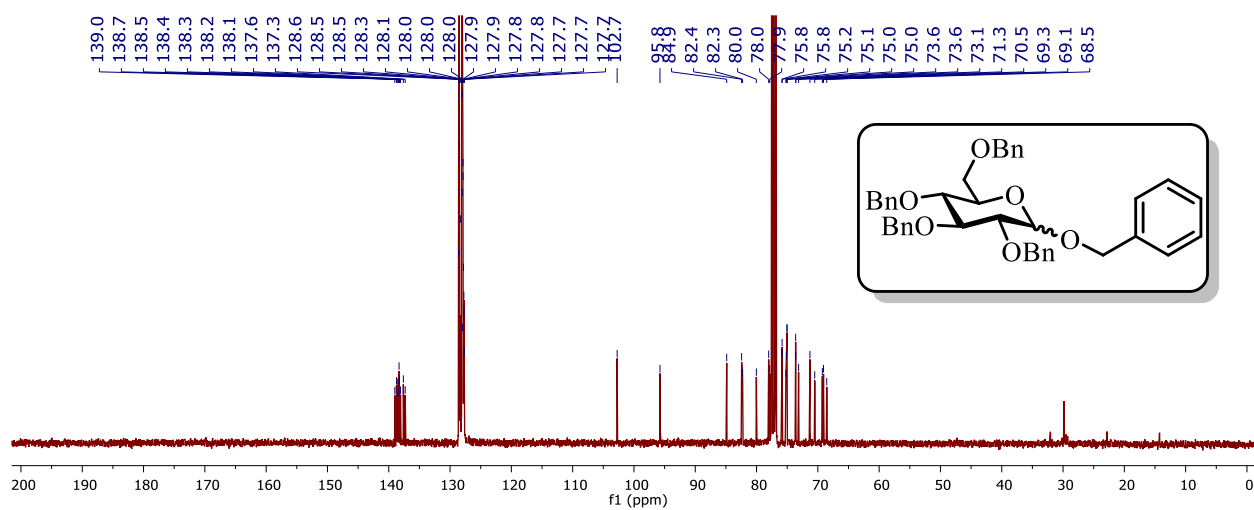


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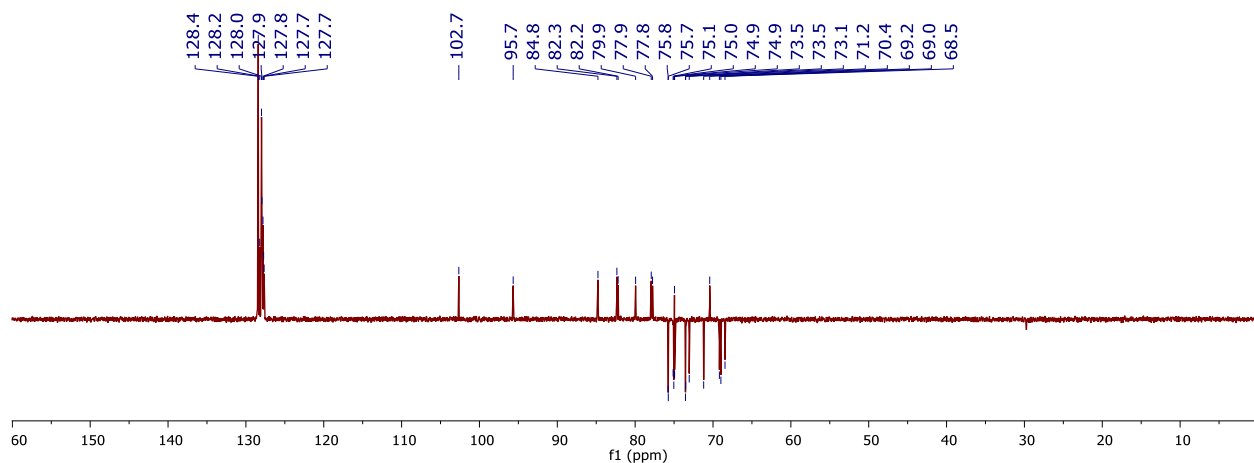
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **25j**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **25j**

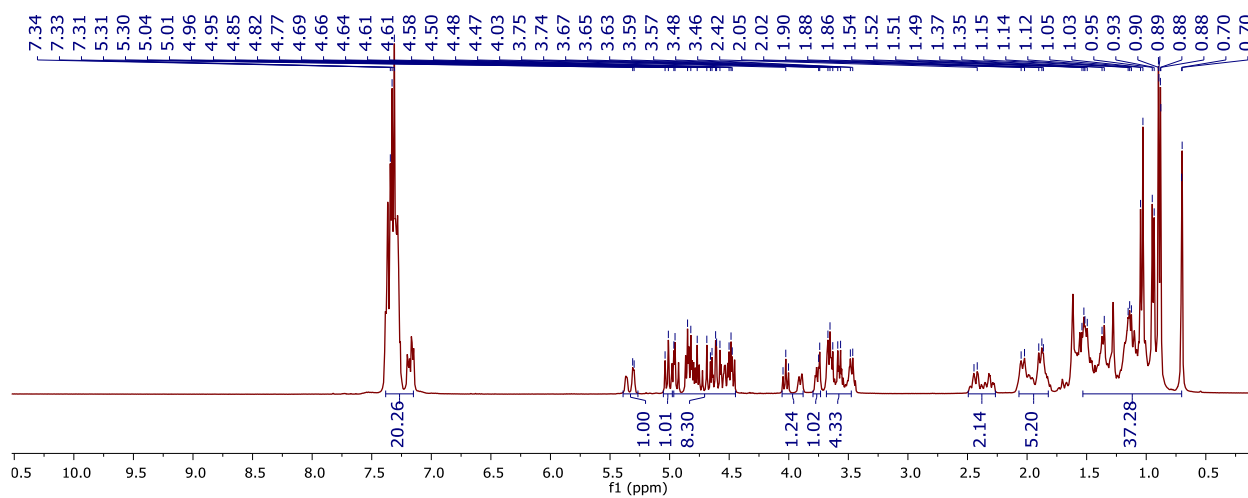


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **25j**

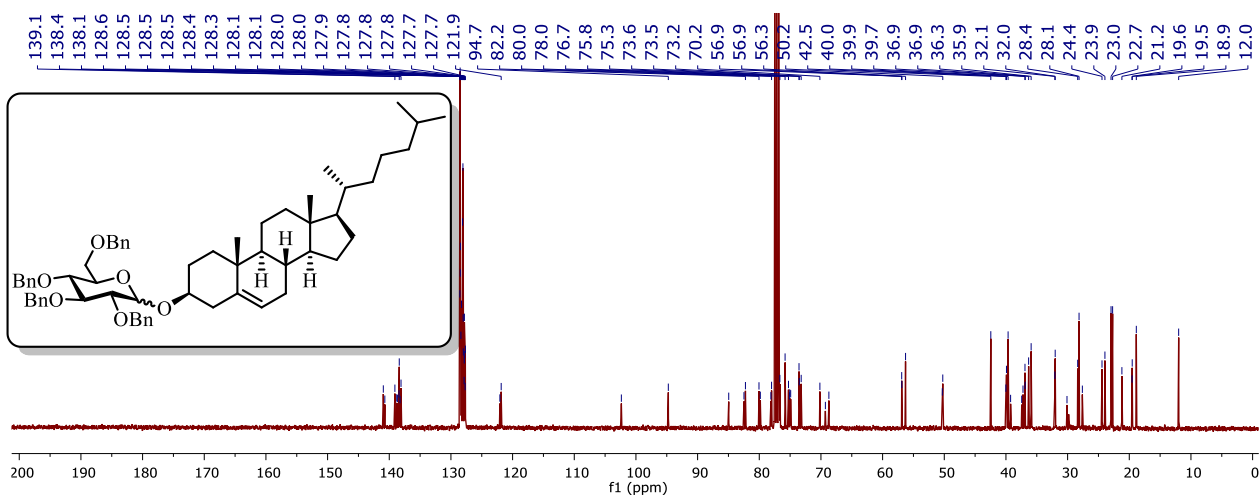


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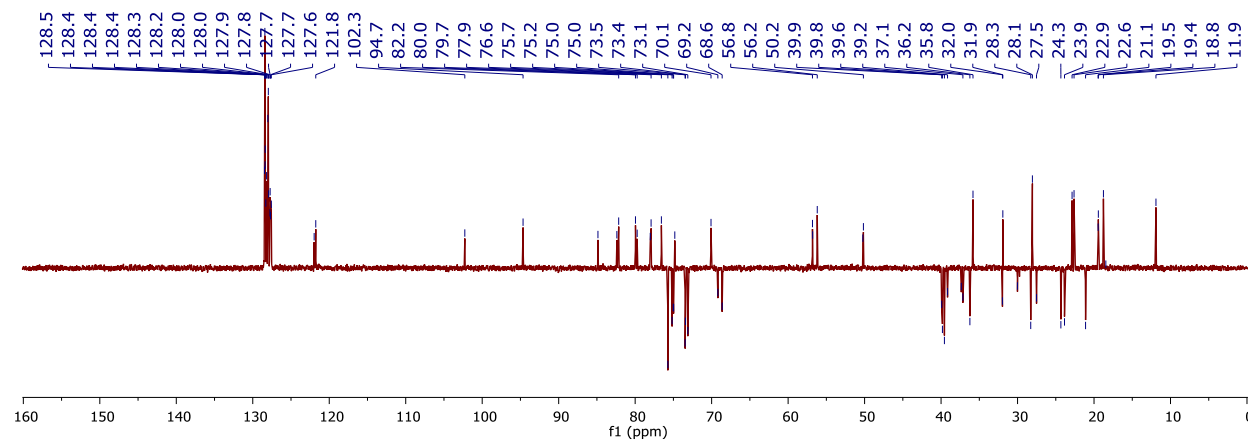
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **25k**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **25k**

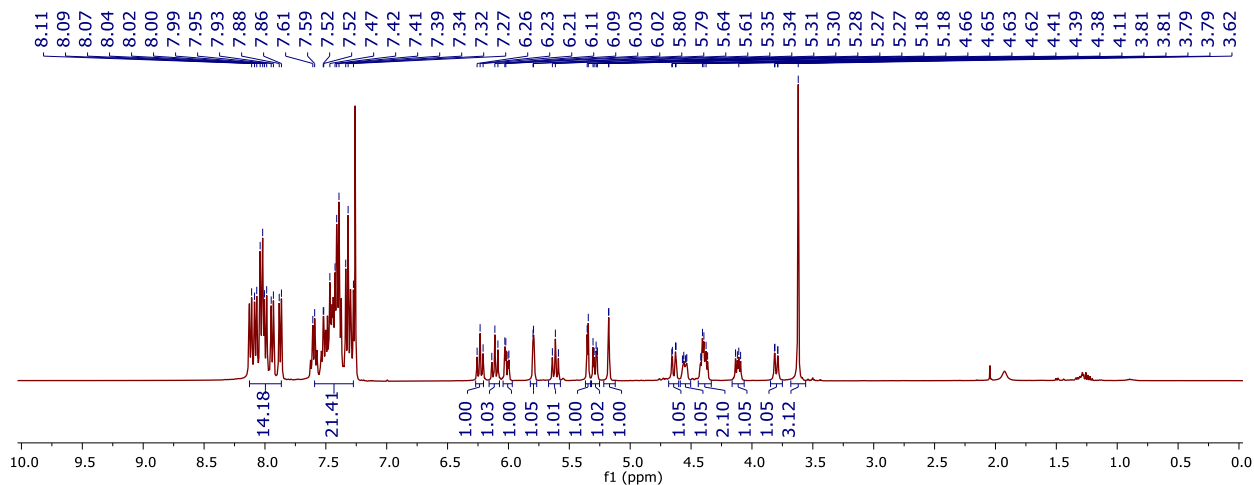


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **25k**

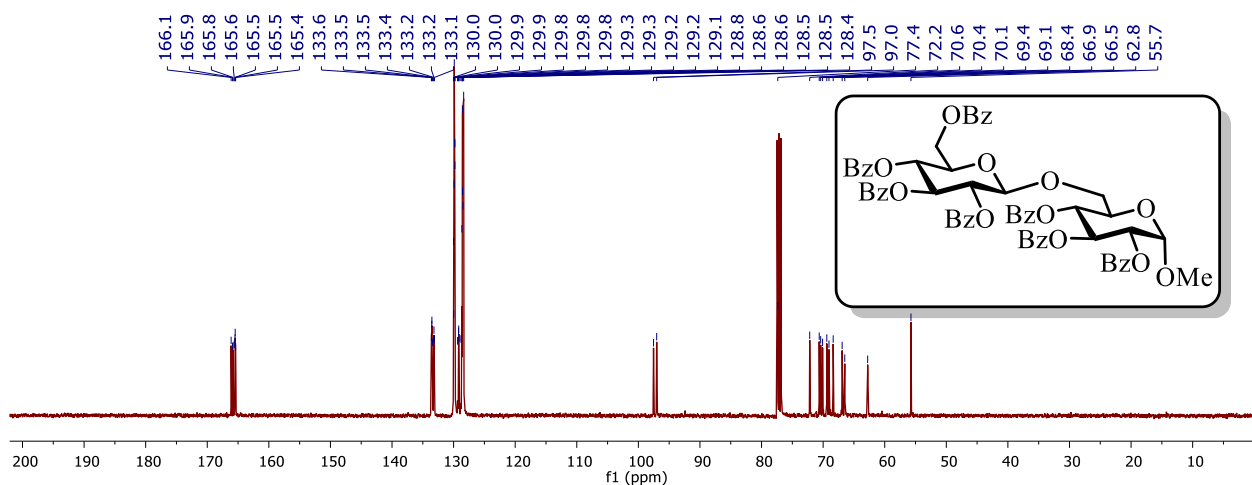


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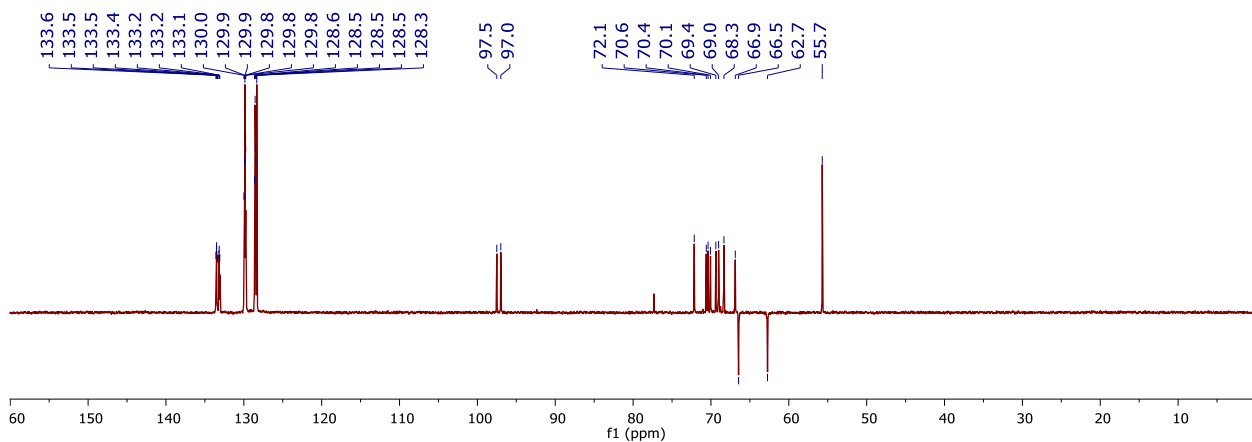
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound 26



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound 26

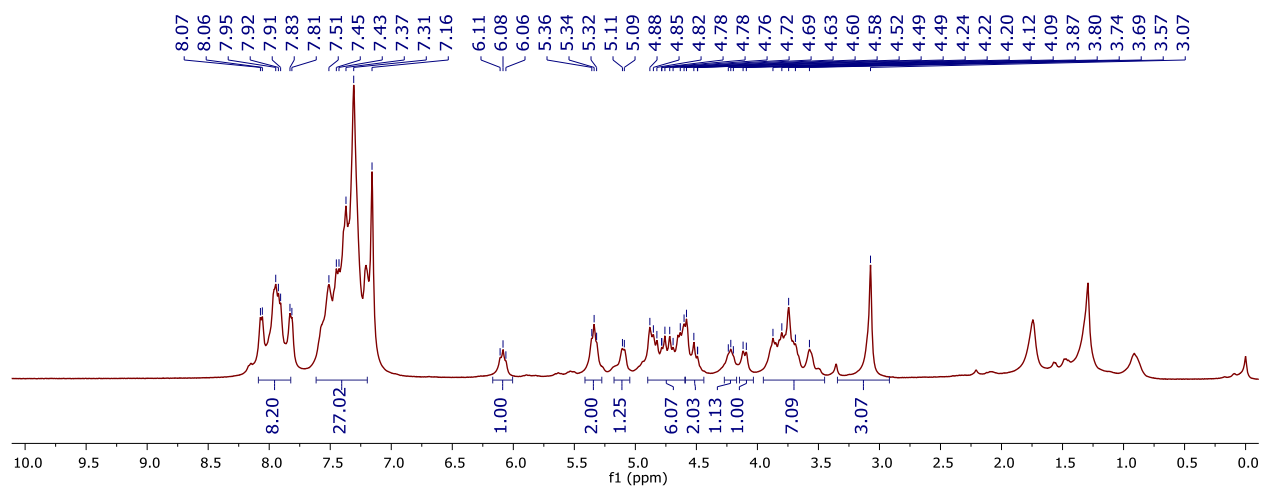


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound 26

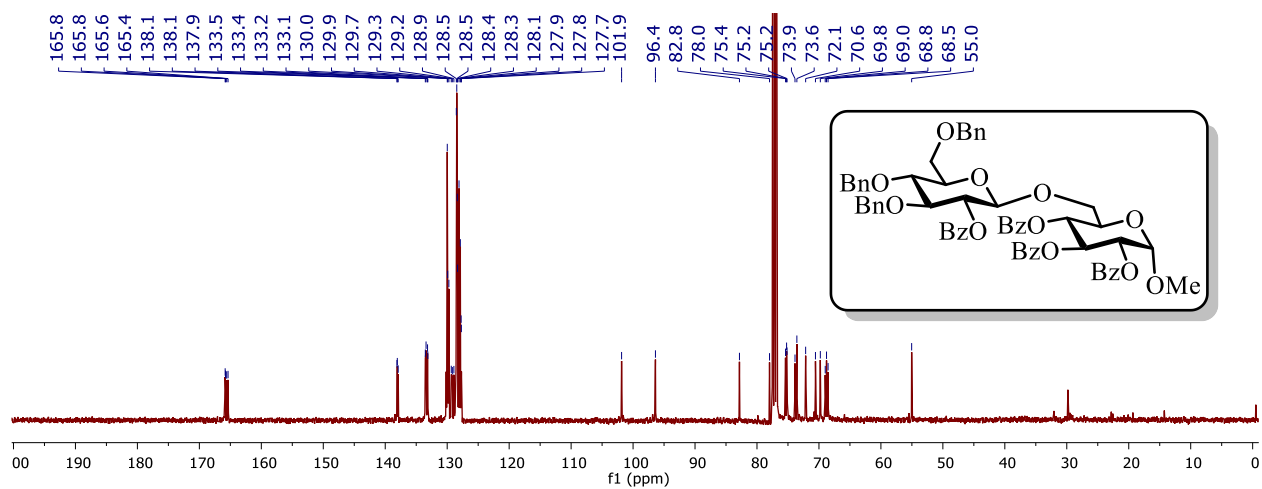


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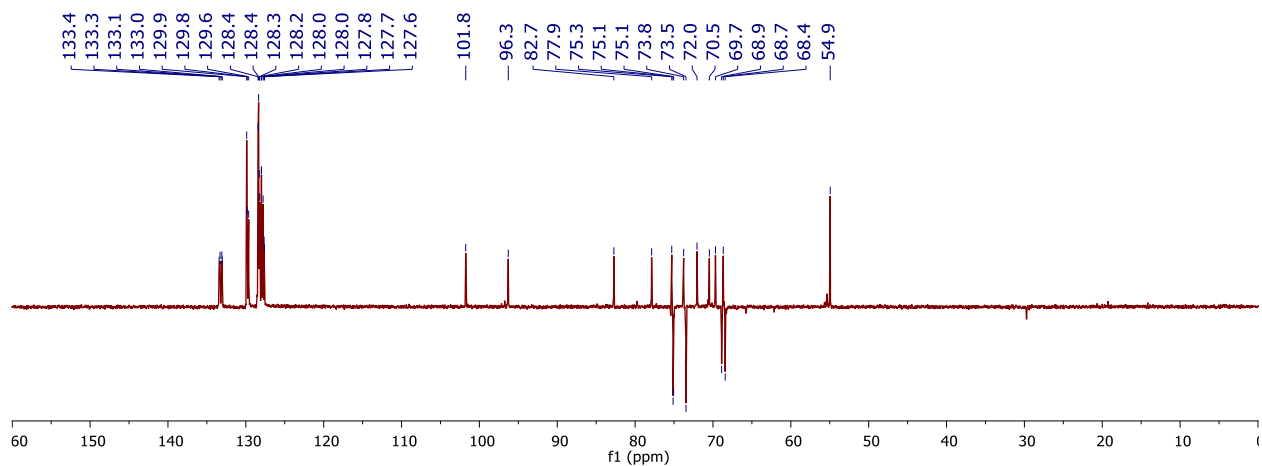
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound 27



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound 27

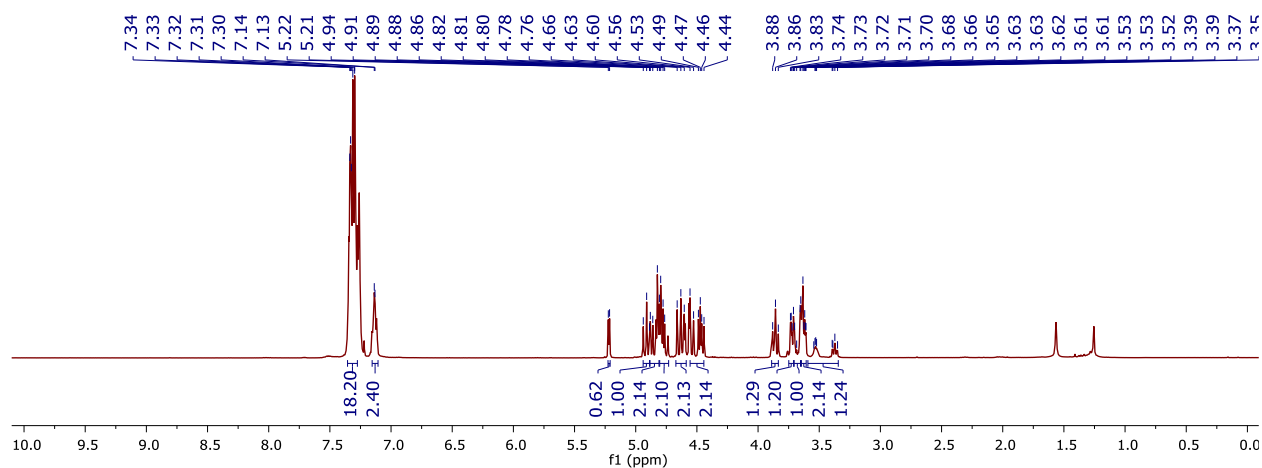


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound 27

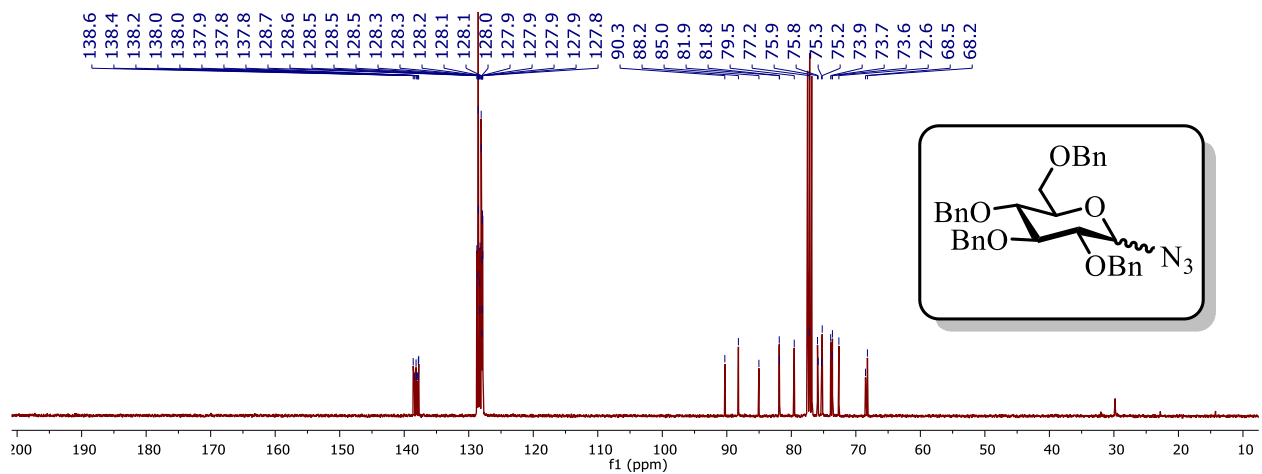


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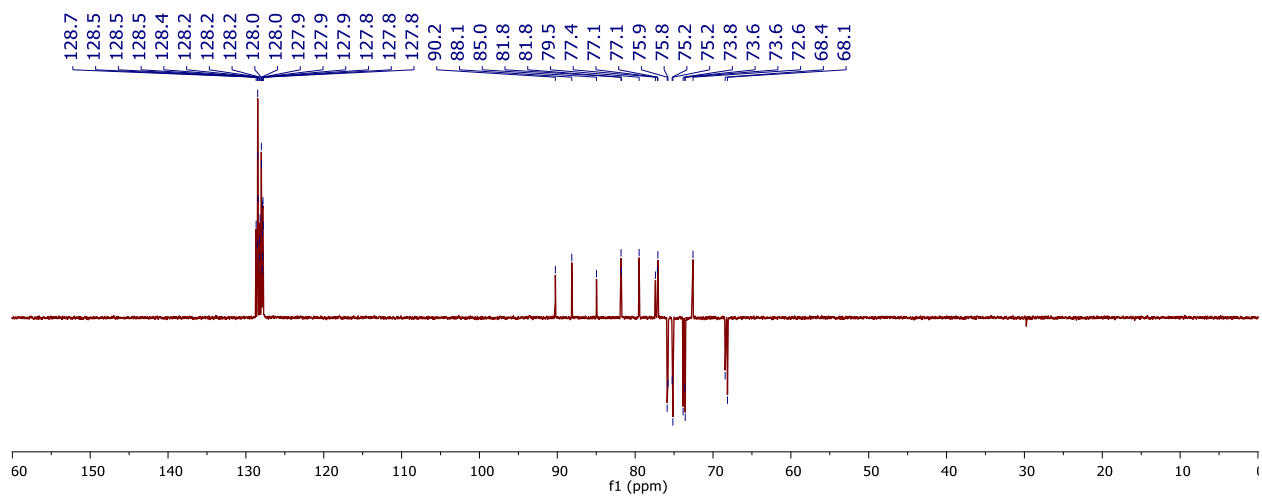
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound 29



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound 29

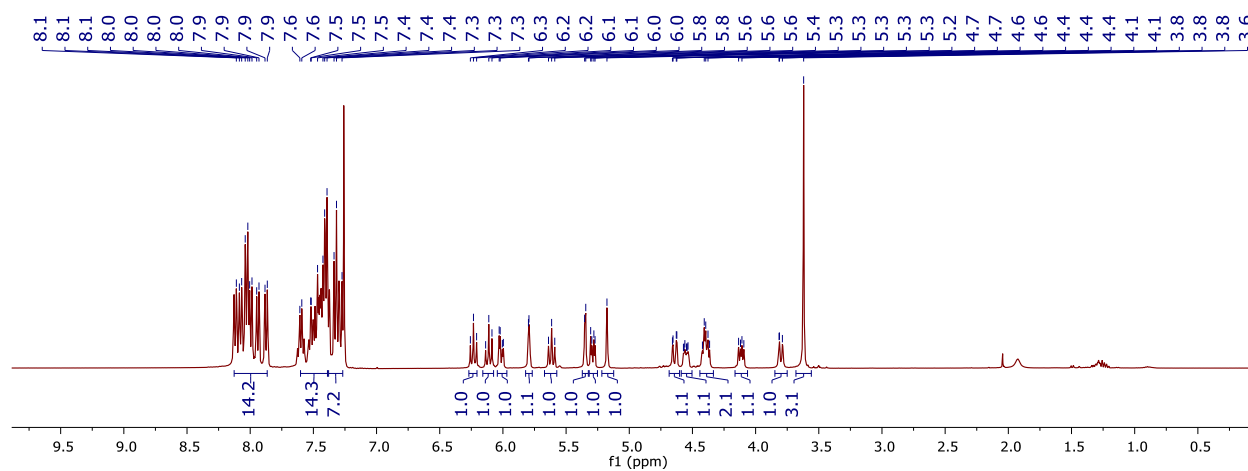


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound 29

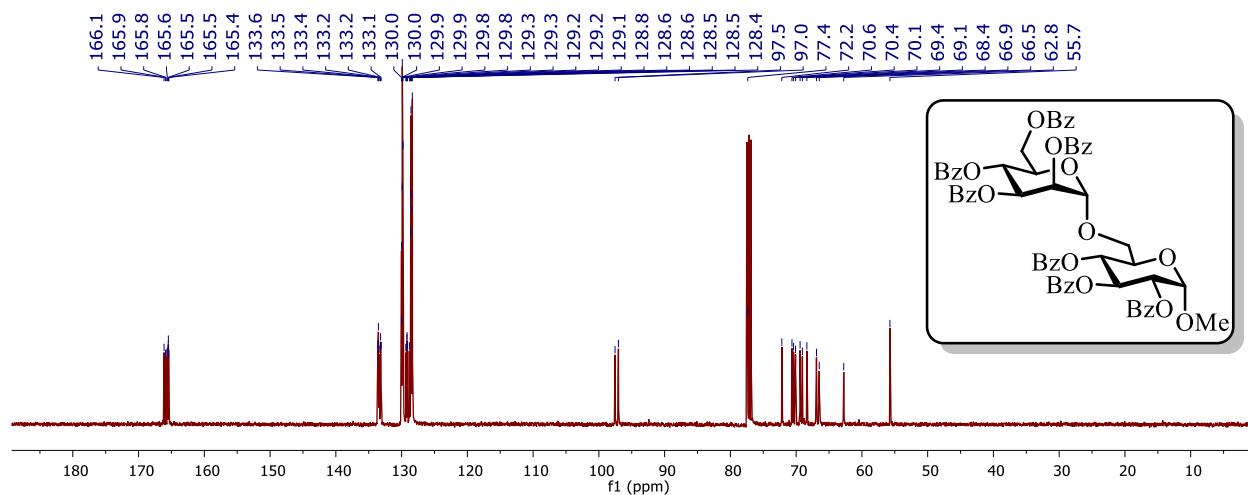


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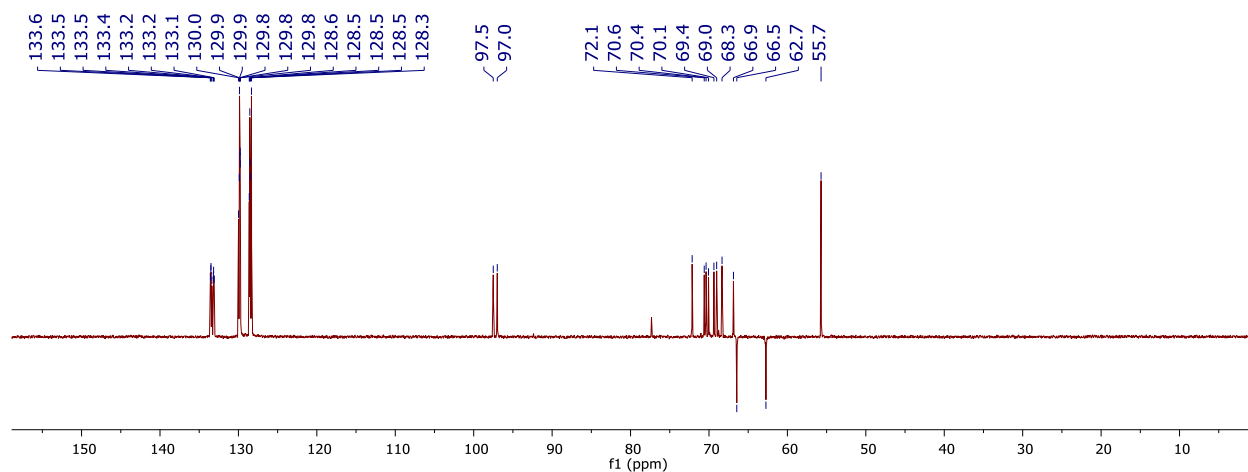
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **28a**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **28a**

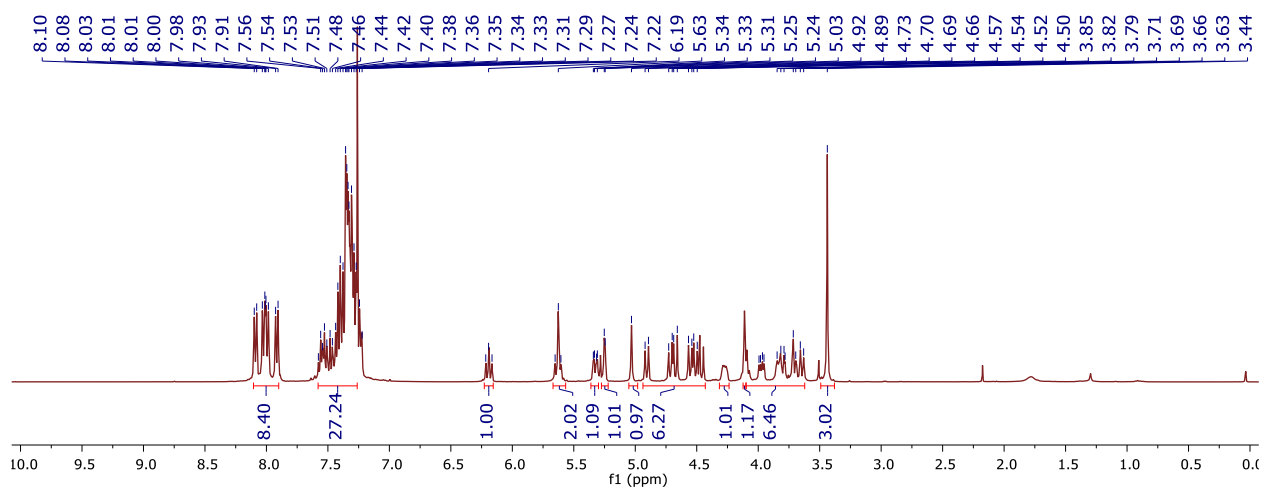


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **28a**

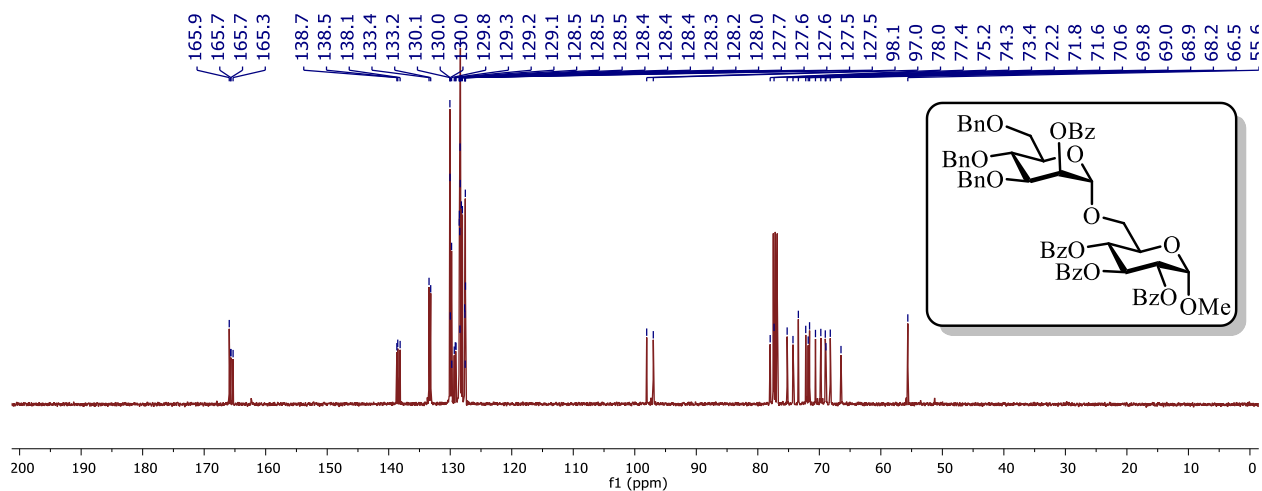


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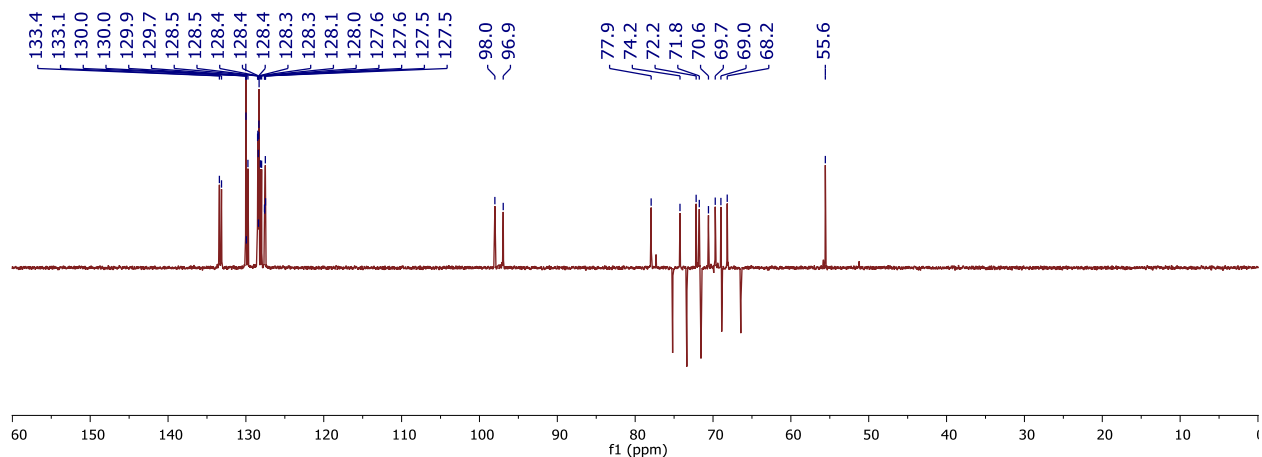
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **28b**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **28b**

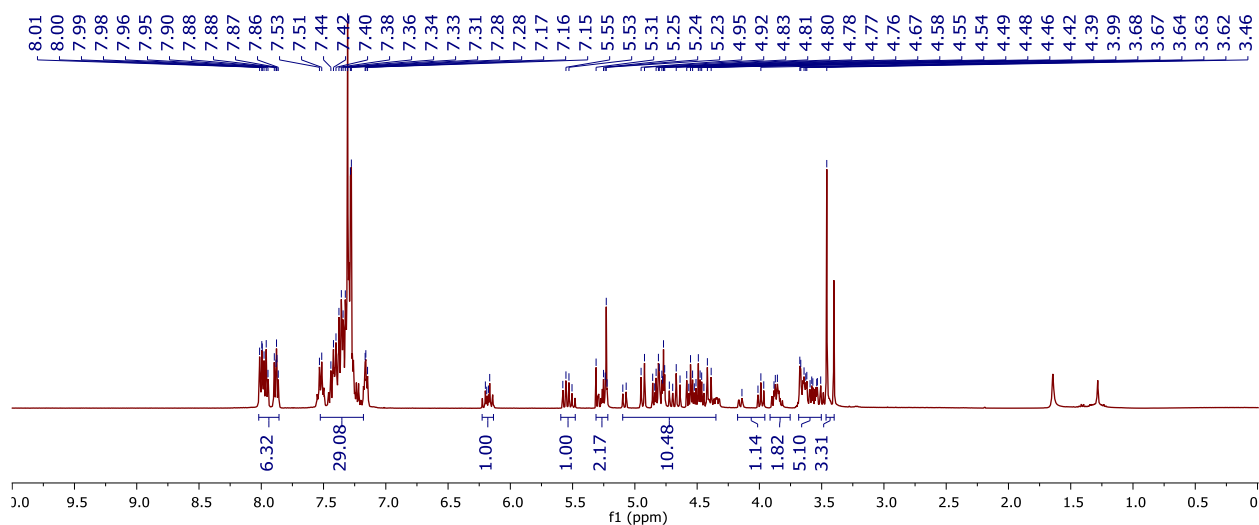


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **28b**

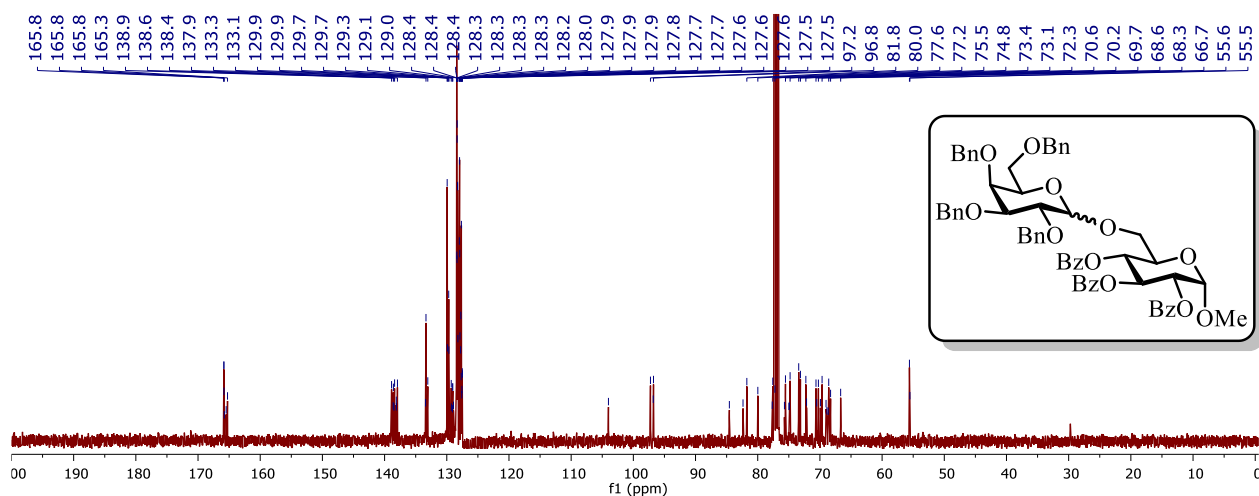


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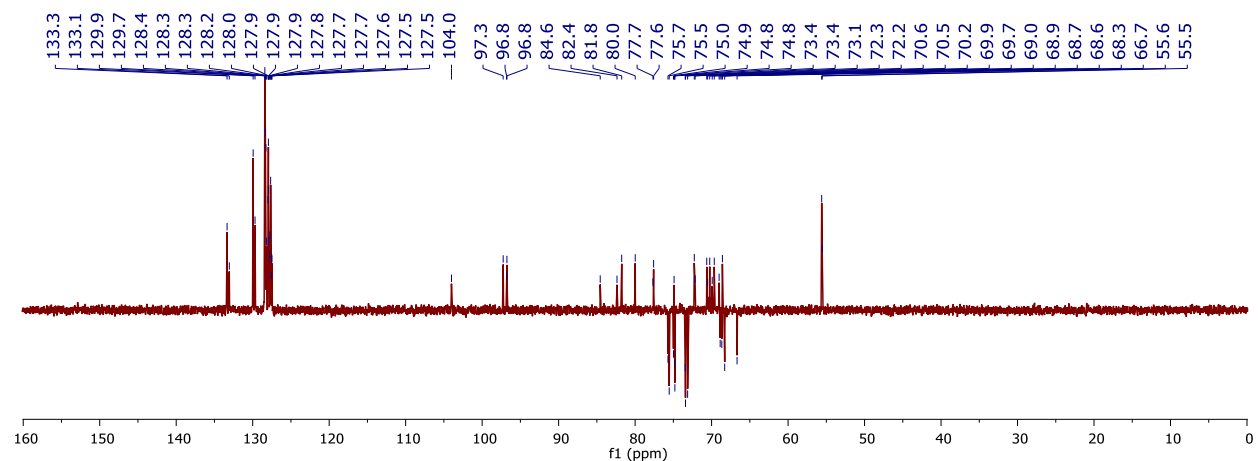
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **31**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **31**

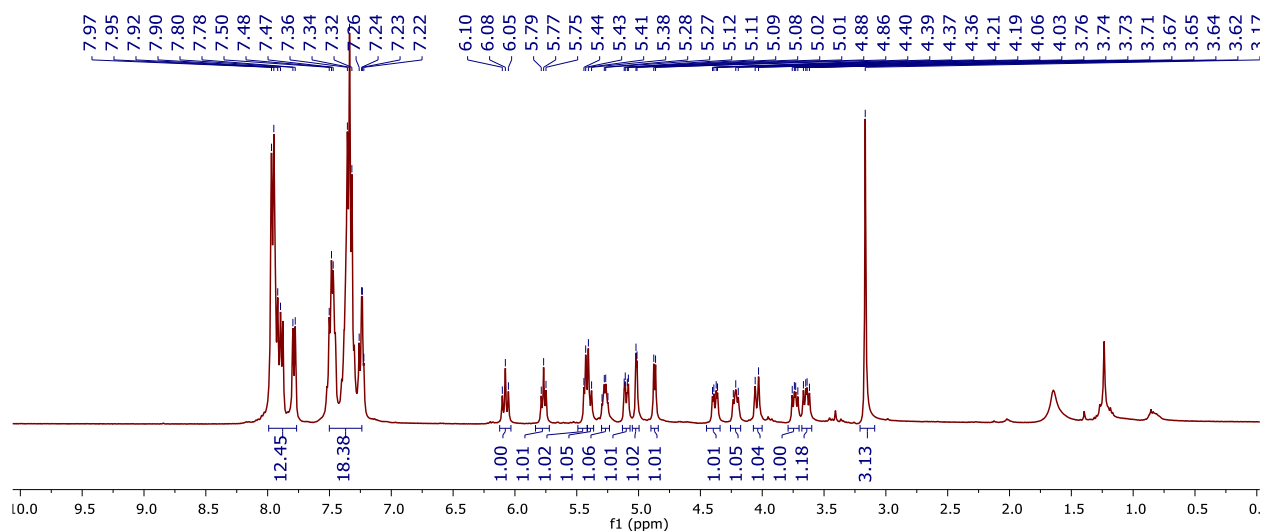


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **31**

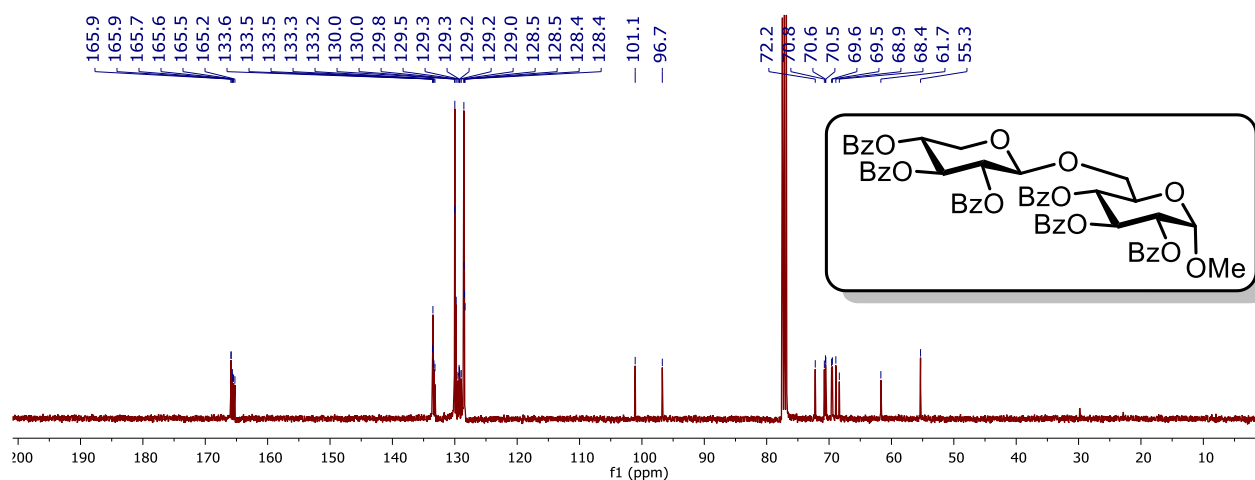


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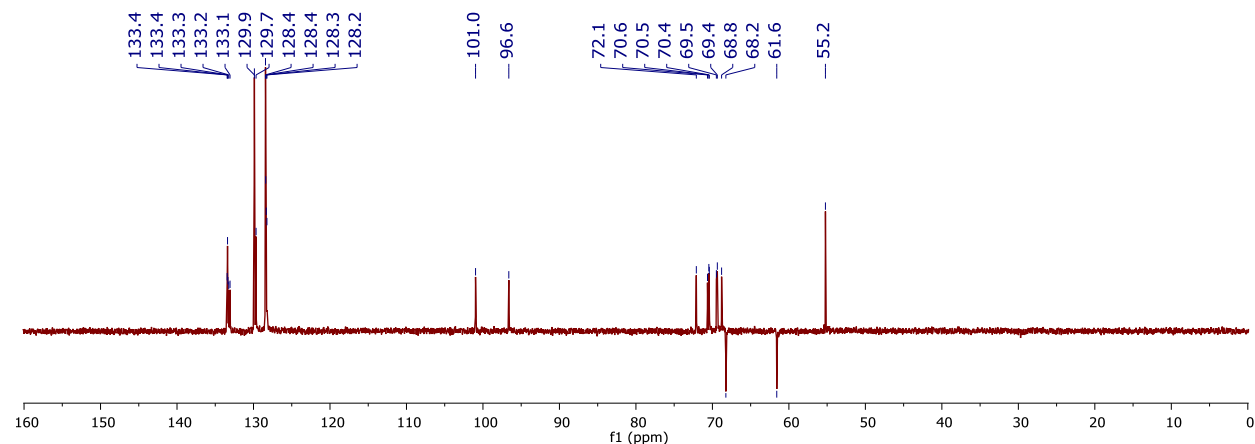
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **30**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **30**

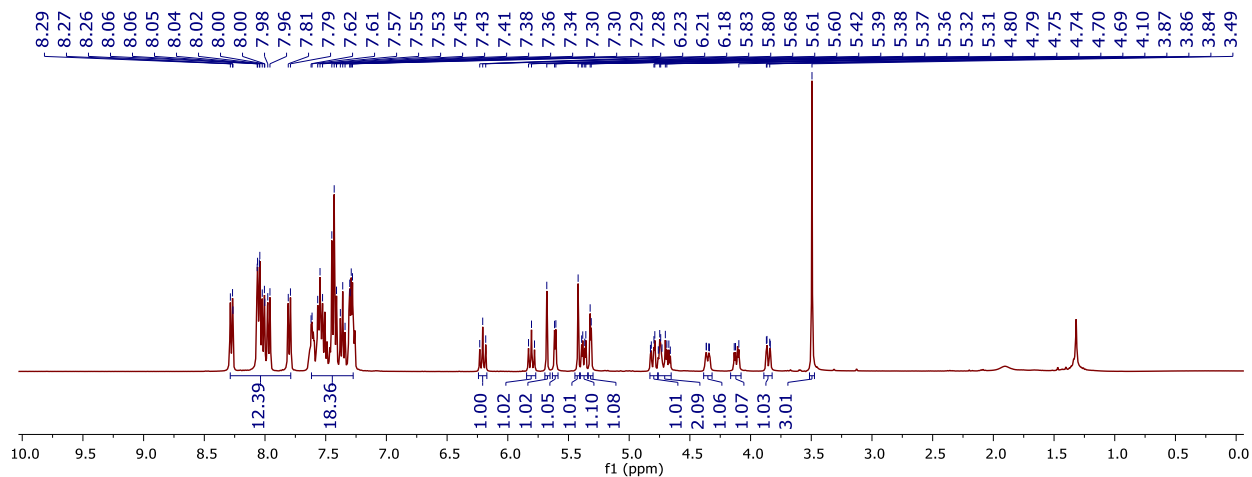


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **30**

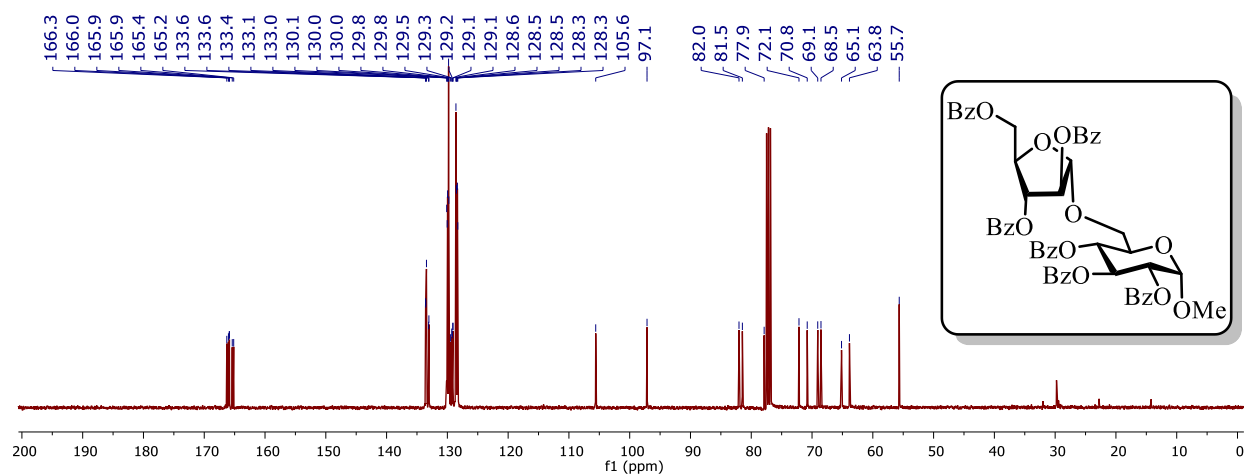


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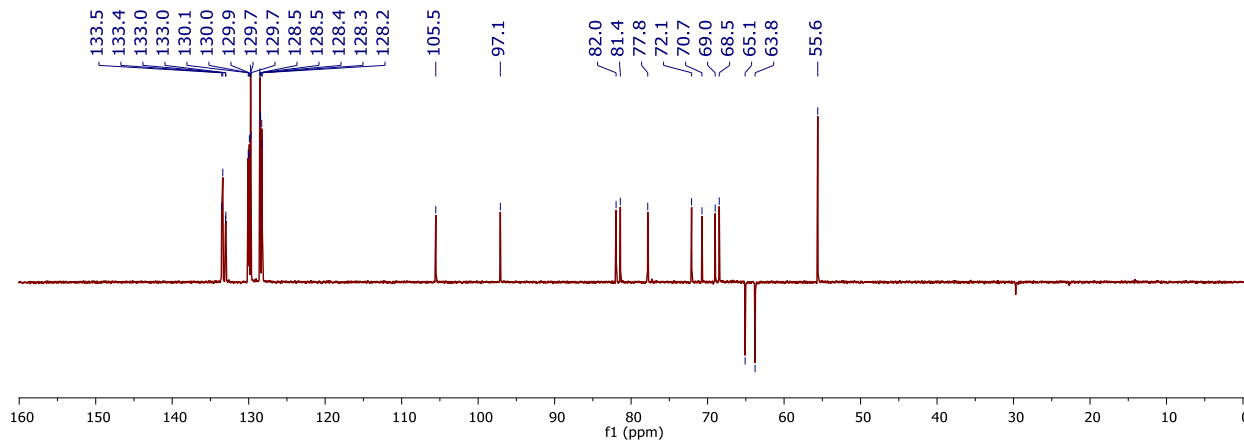
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **32a**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **32a**

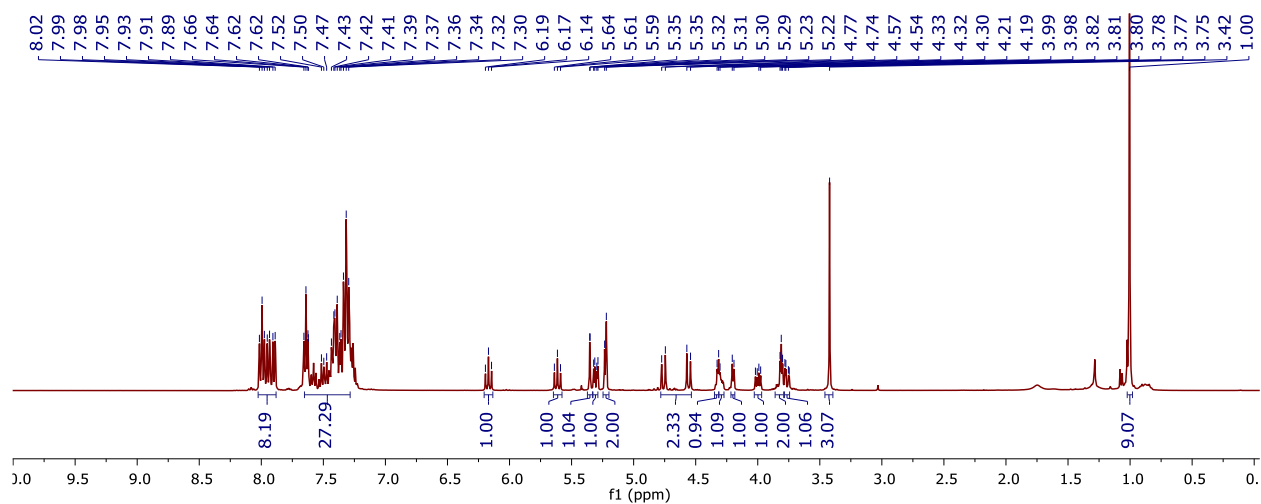


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **32a**

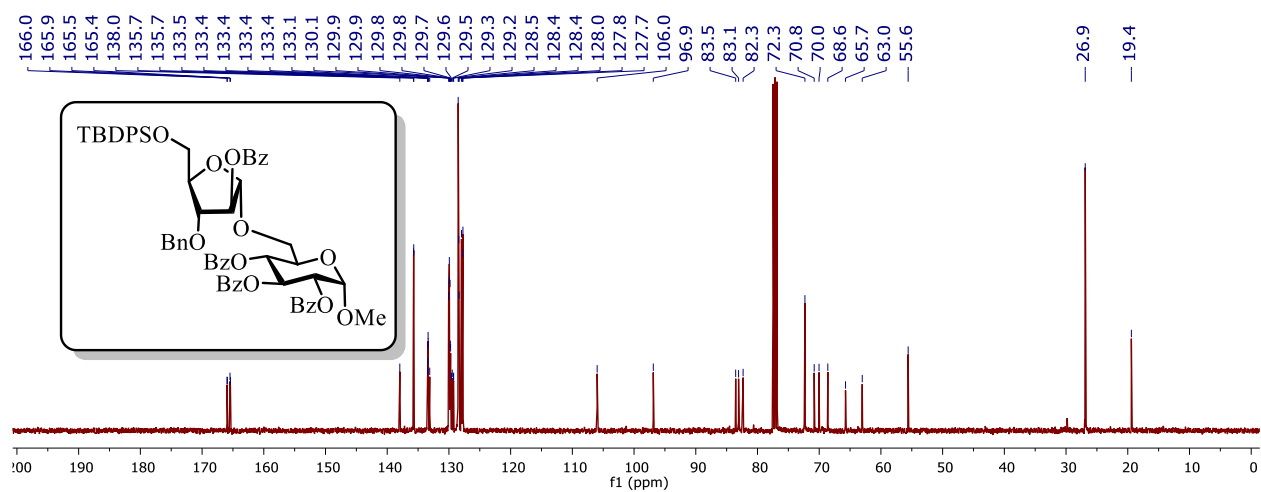


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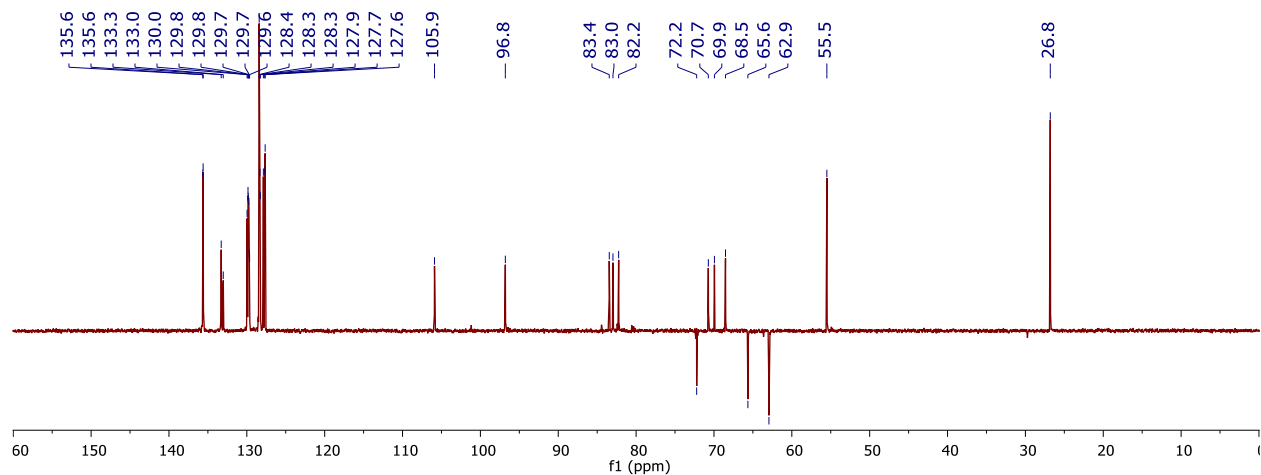
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **32b**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **32b**

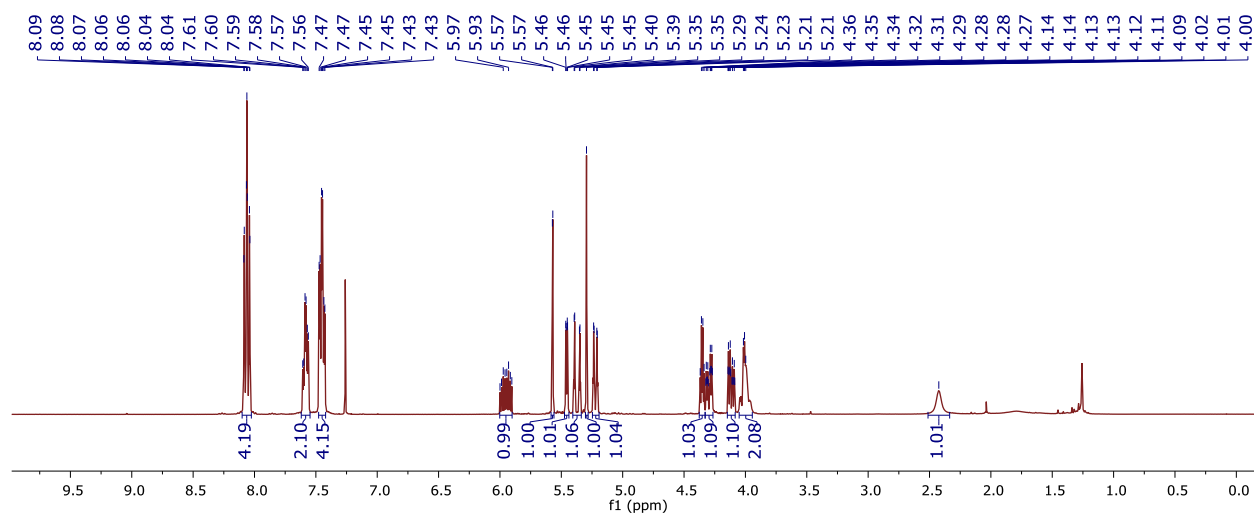


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **32b**

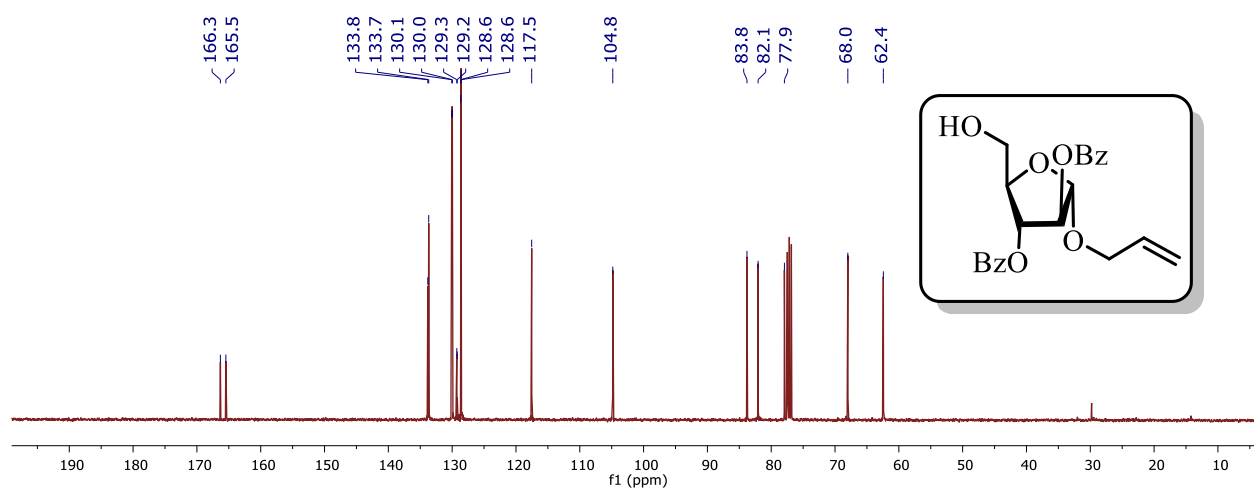


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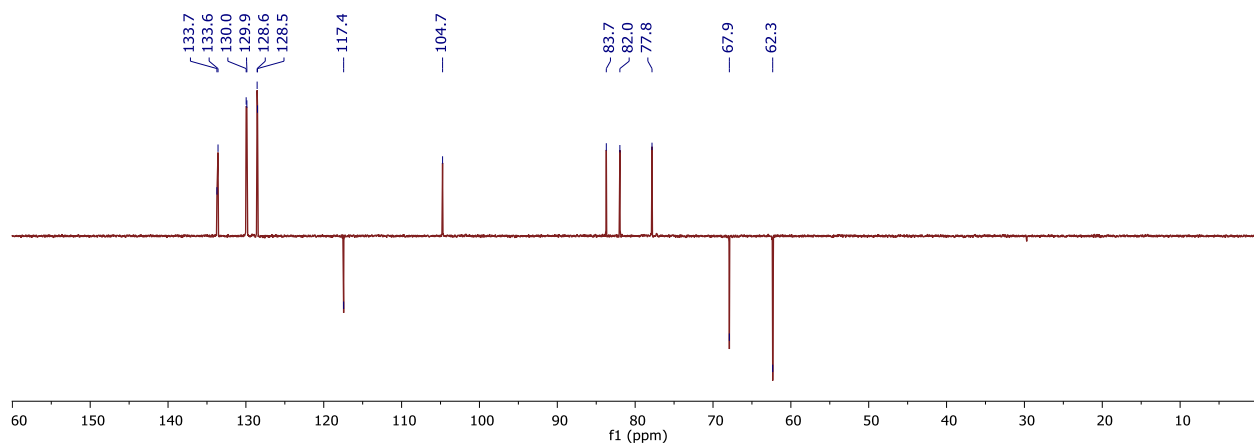
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **33**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **33**

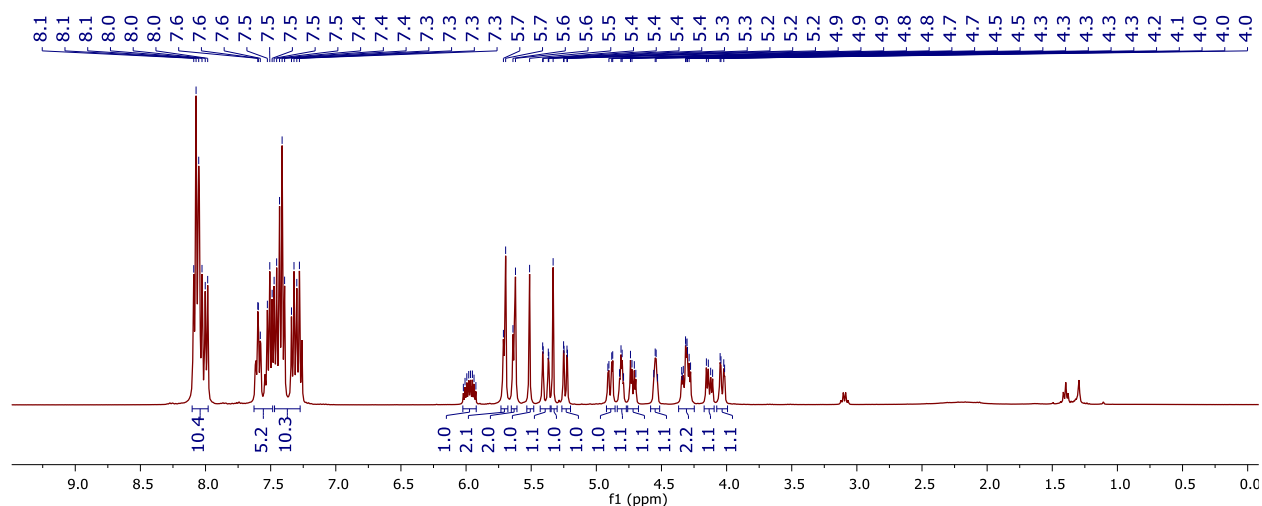


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **33**

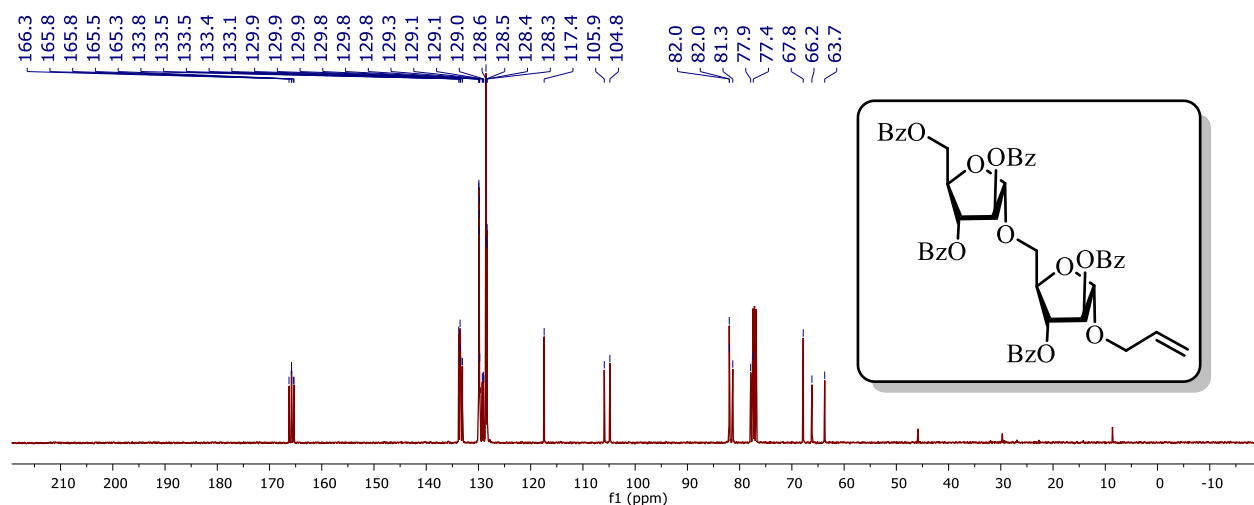


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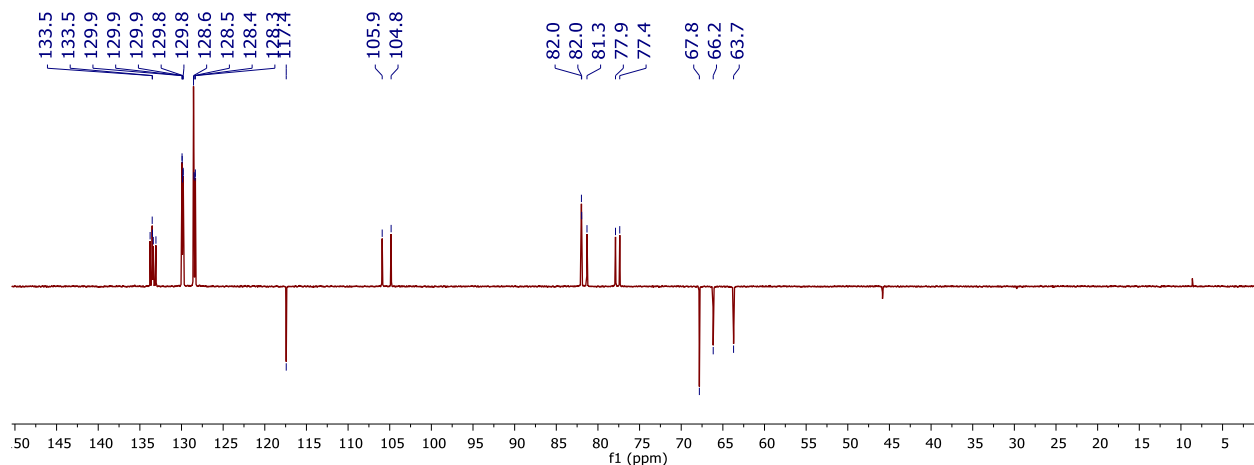
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **34**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **34**

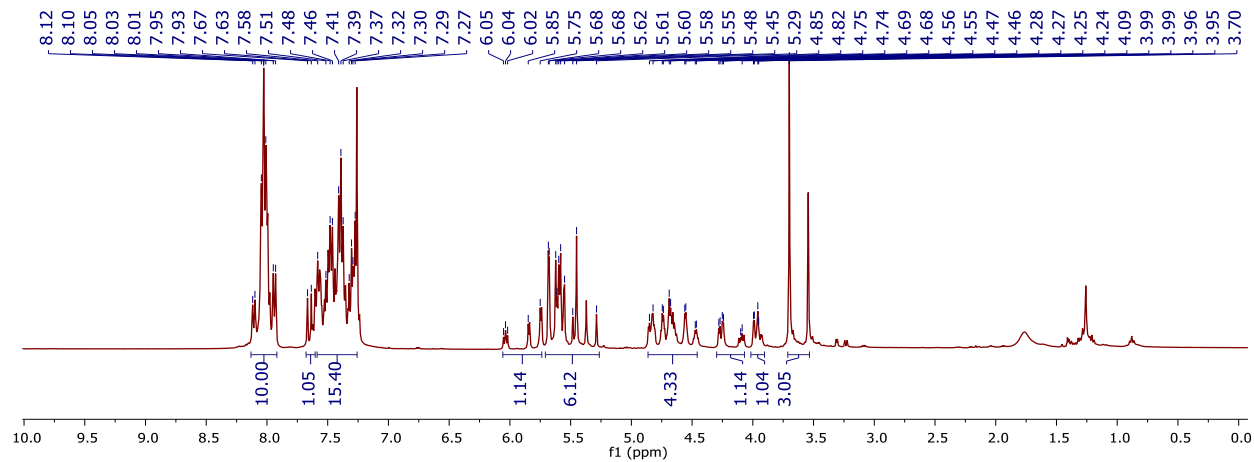


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **34**

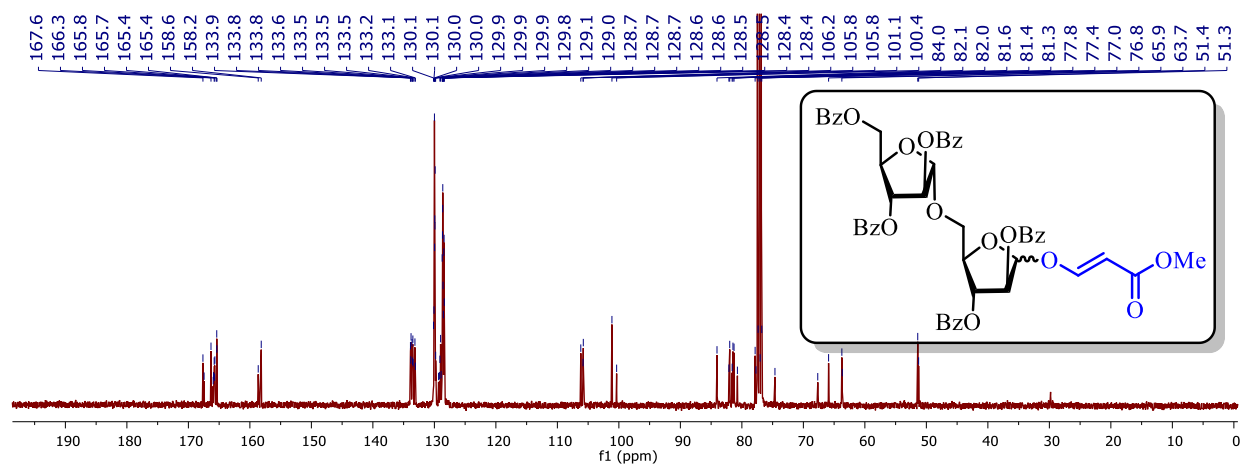


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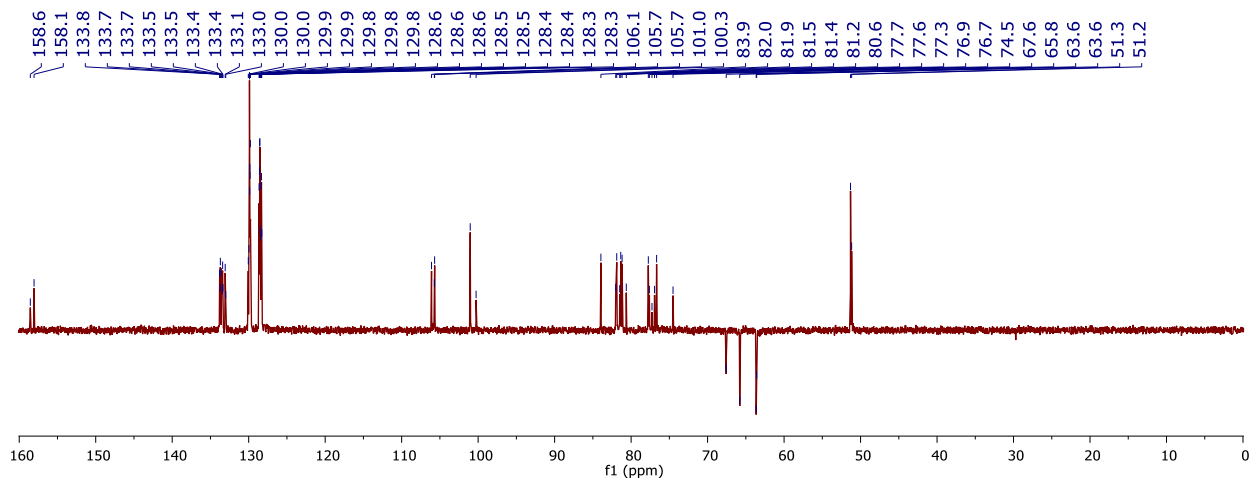
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **35**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **35**

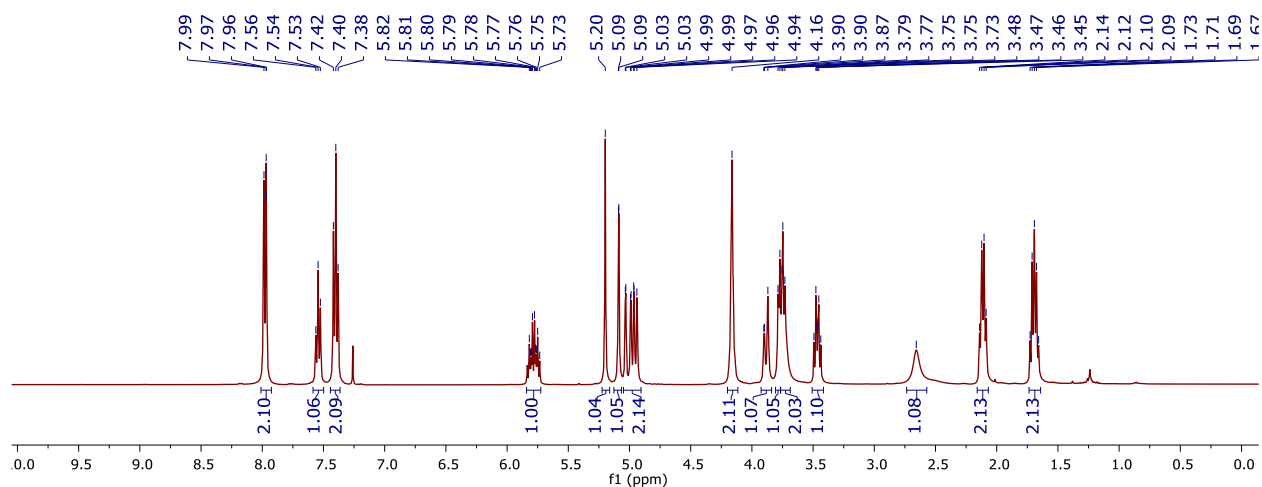


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **35**

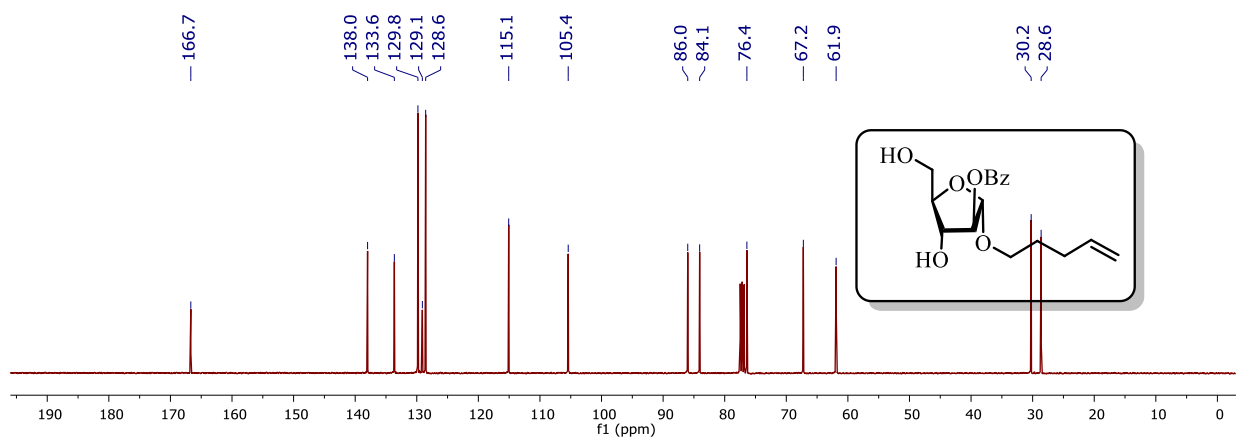


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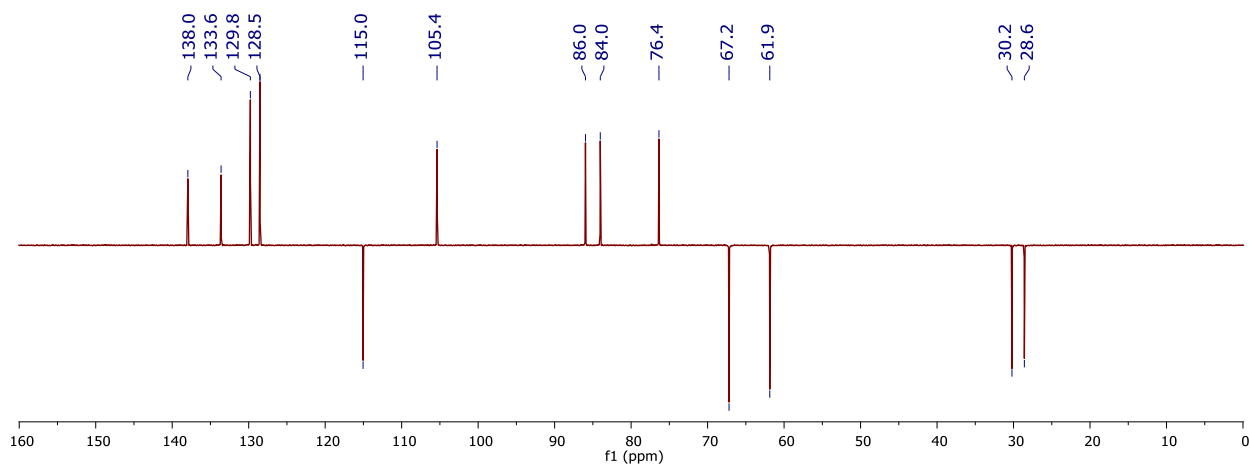
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound **36**



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound **36**

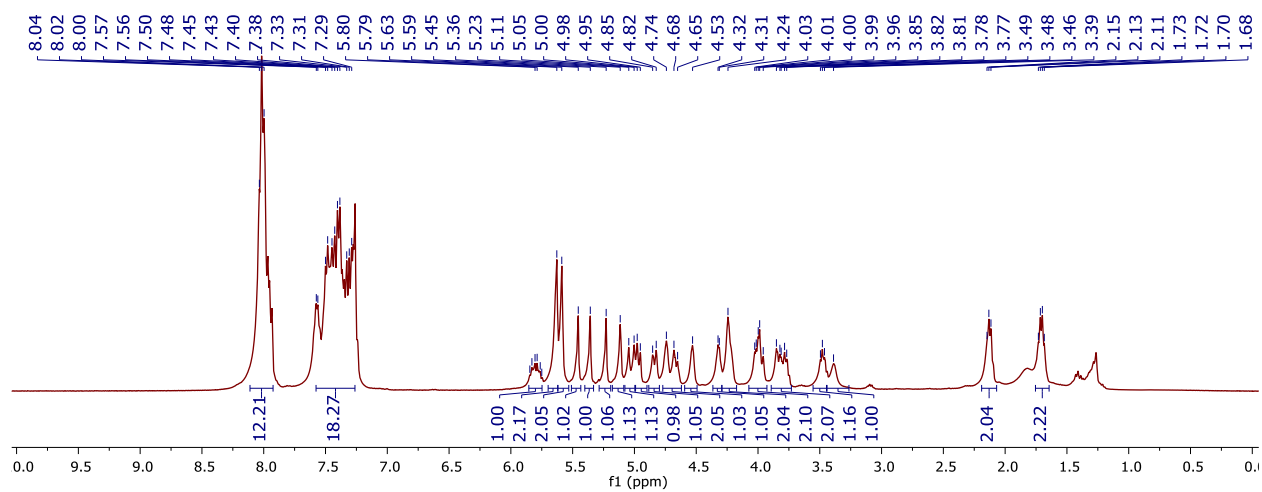


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound **36**

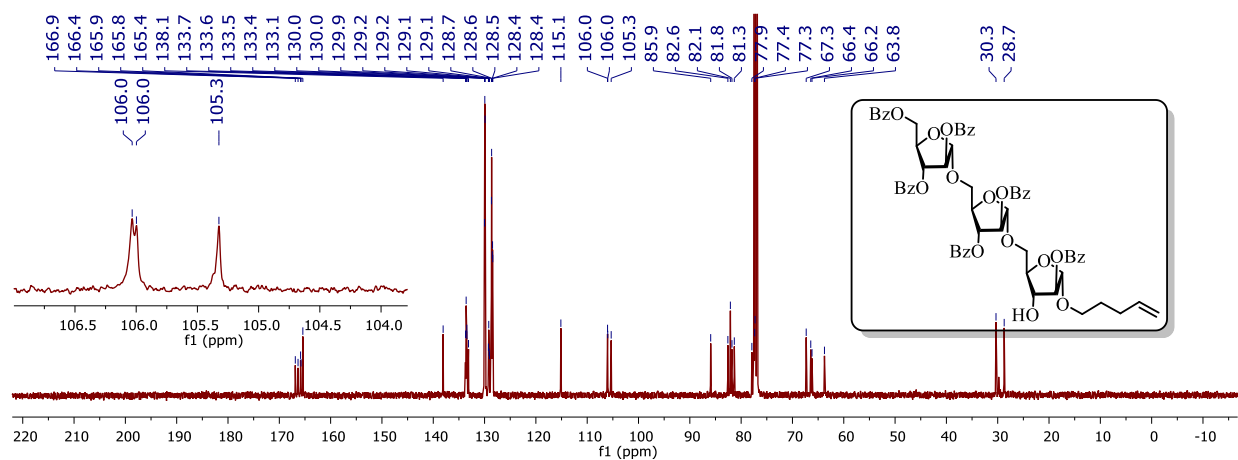


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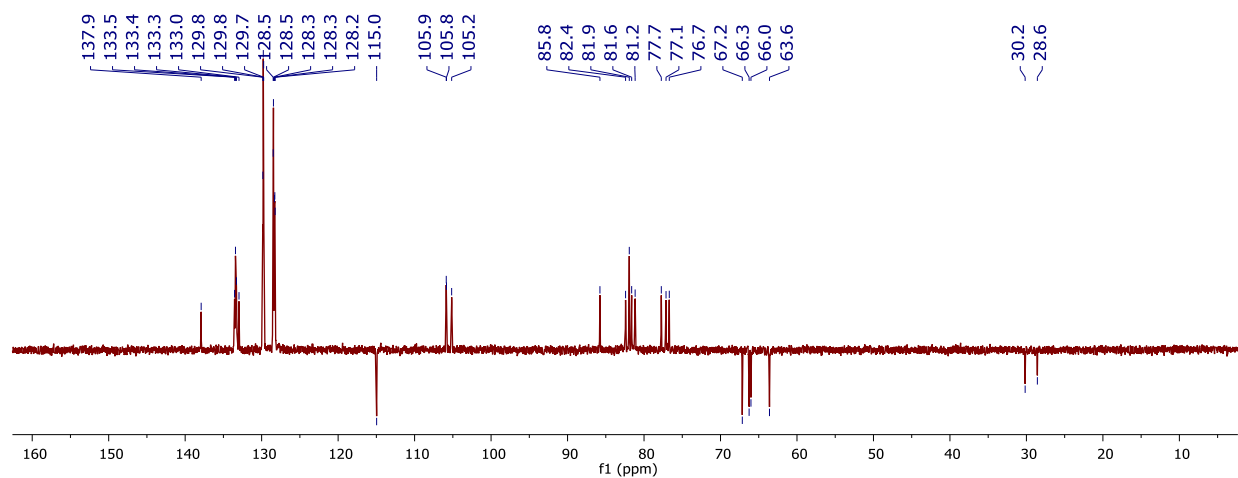
^1H NMR Spectrum (400 MHz, CDCl_3) of Compound 37



^{13}C NMR Spectrum (100 MHz, CDCl_3) of Compound 37

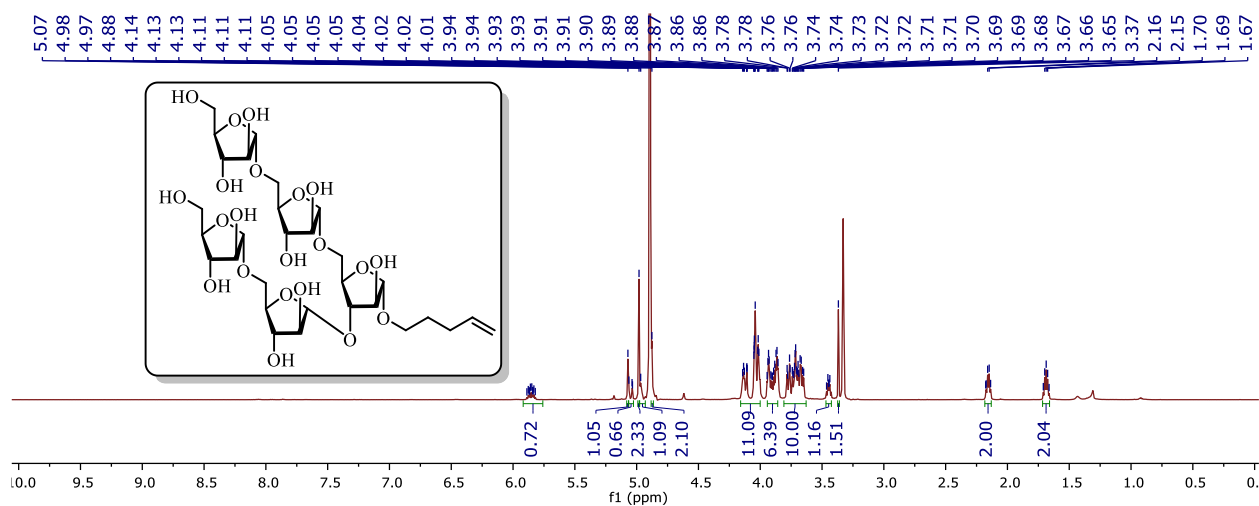


DEPT-135 NMR Spectrum (100 MHz, CDCl_3) of Compound 37

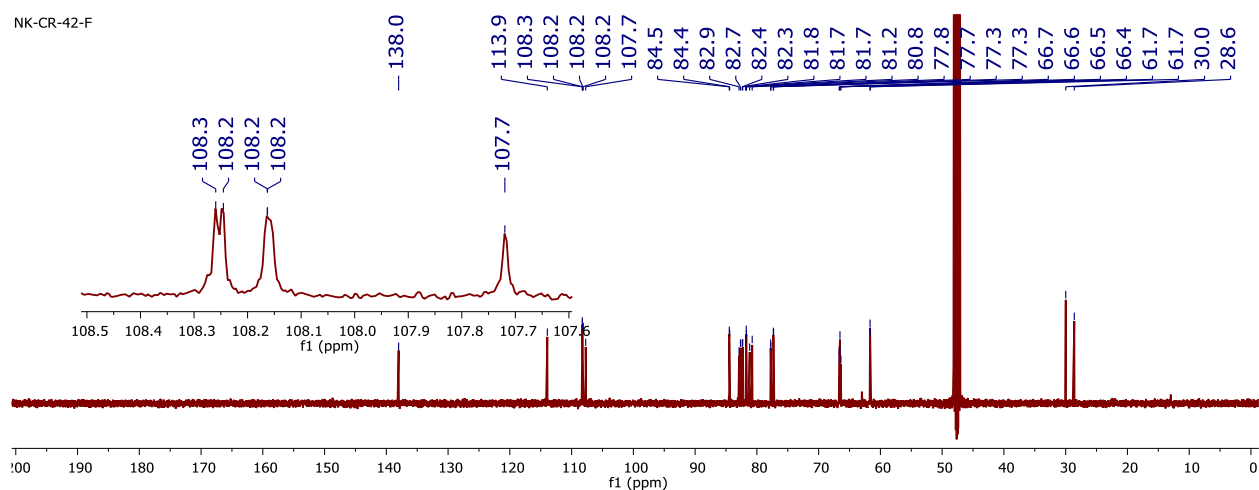


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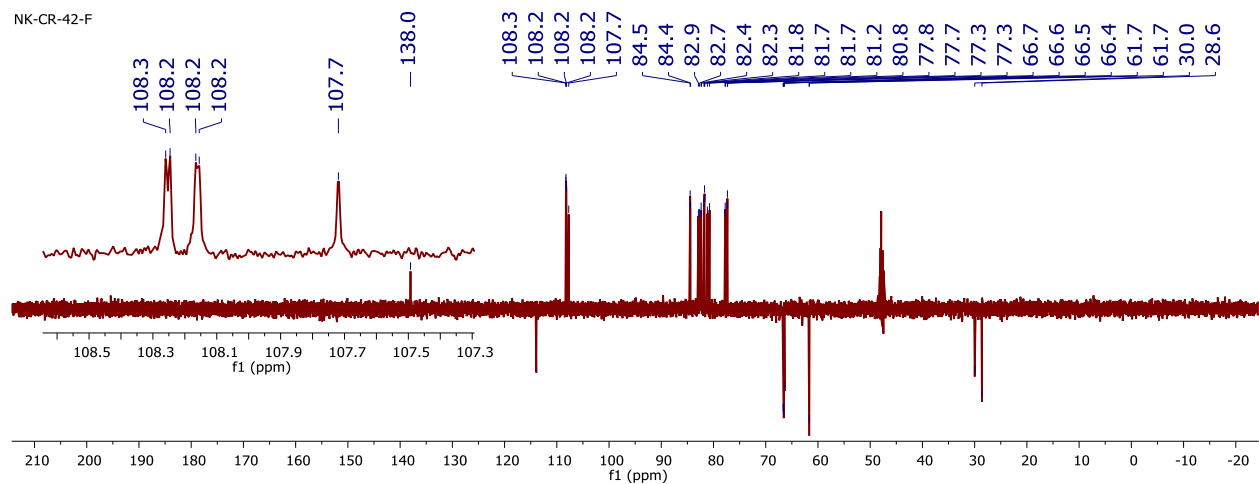
^1H NMR Spectrum (600 MHz, MeOD_4) of Compound **39**



^{13}C NMR Spectrum (150 MHz, MeOD_4) of Compound **39**

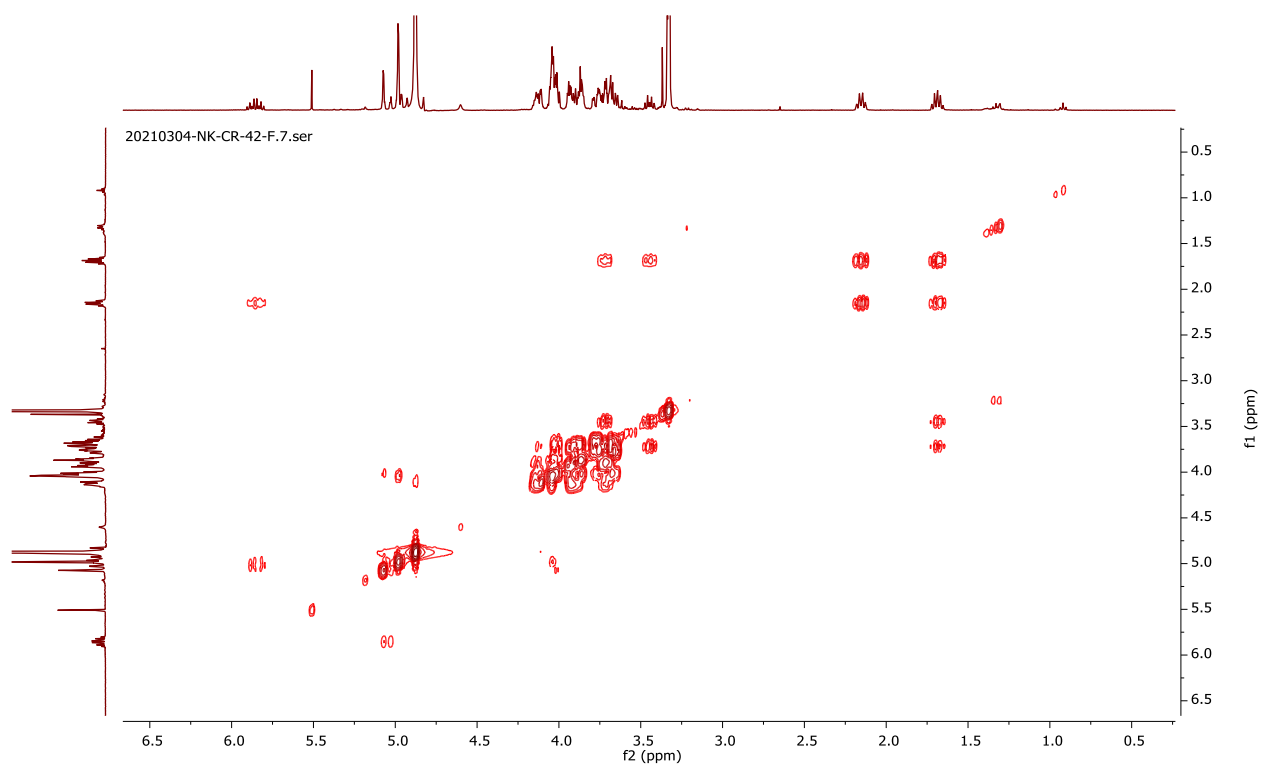


DEPT-135 NMR Spectrum (150 MHz, MeOD_4) of Compound **39**

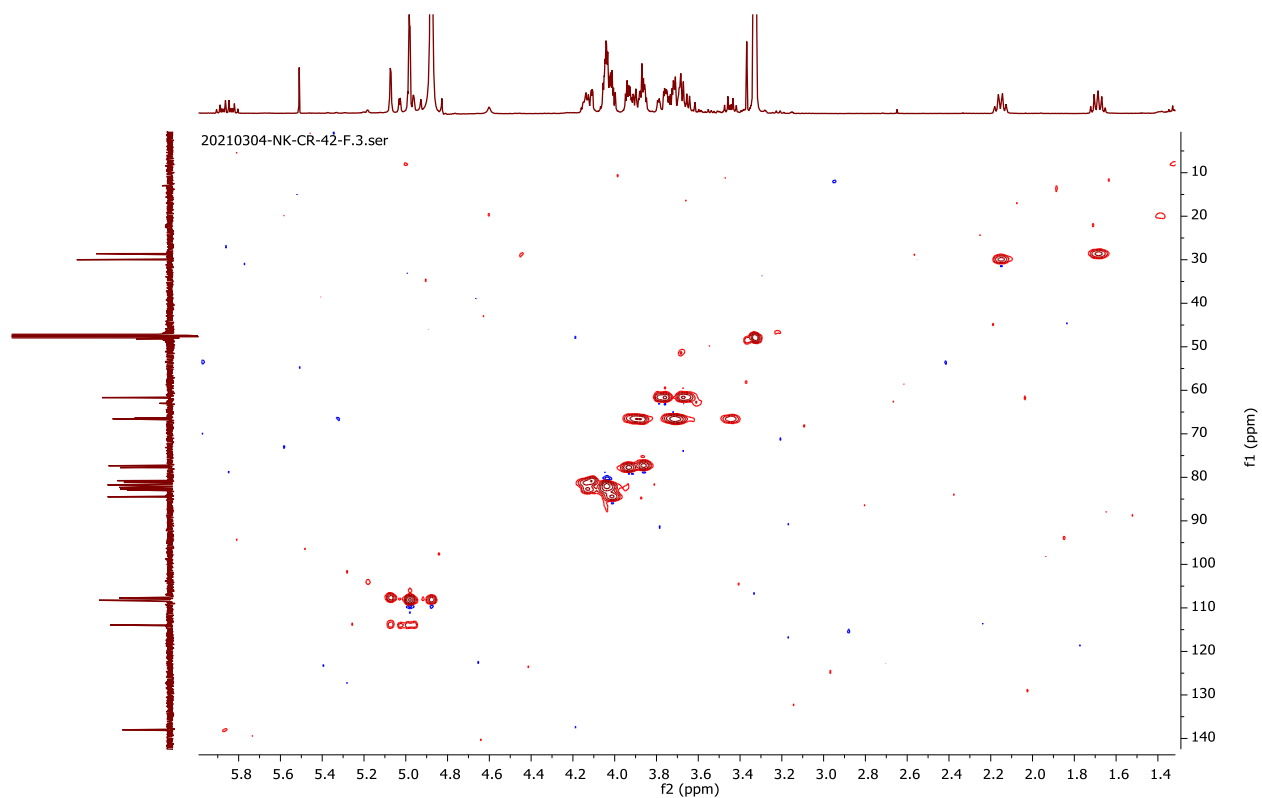


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^1H COSY NMR Spectrum (600 MHz, MeOD_4) of Compound **39**

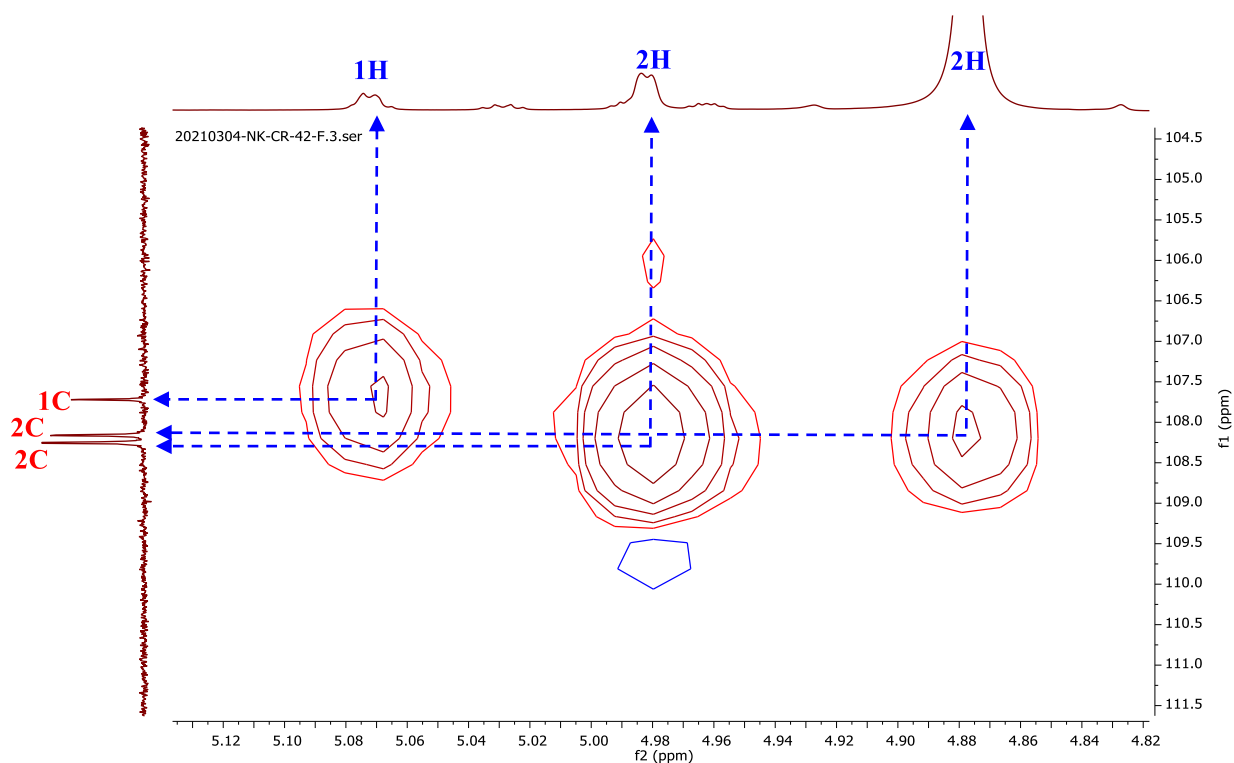


^1H - ^{13}C HSQC NMR Spectrum (600 MHz, MeOD_4) of Compound **39**

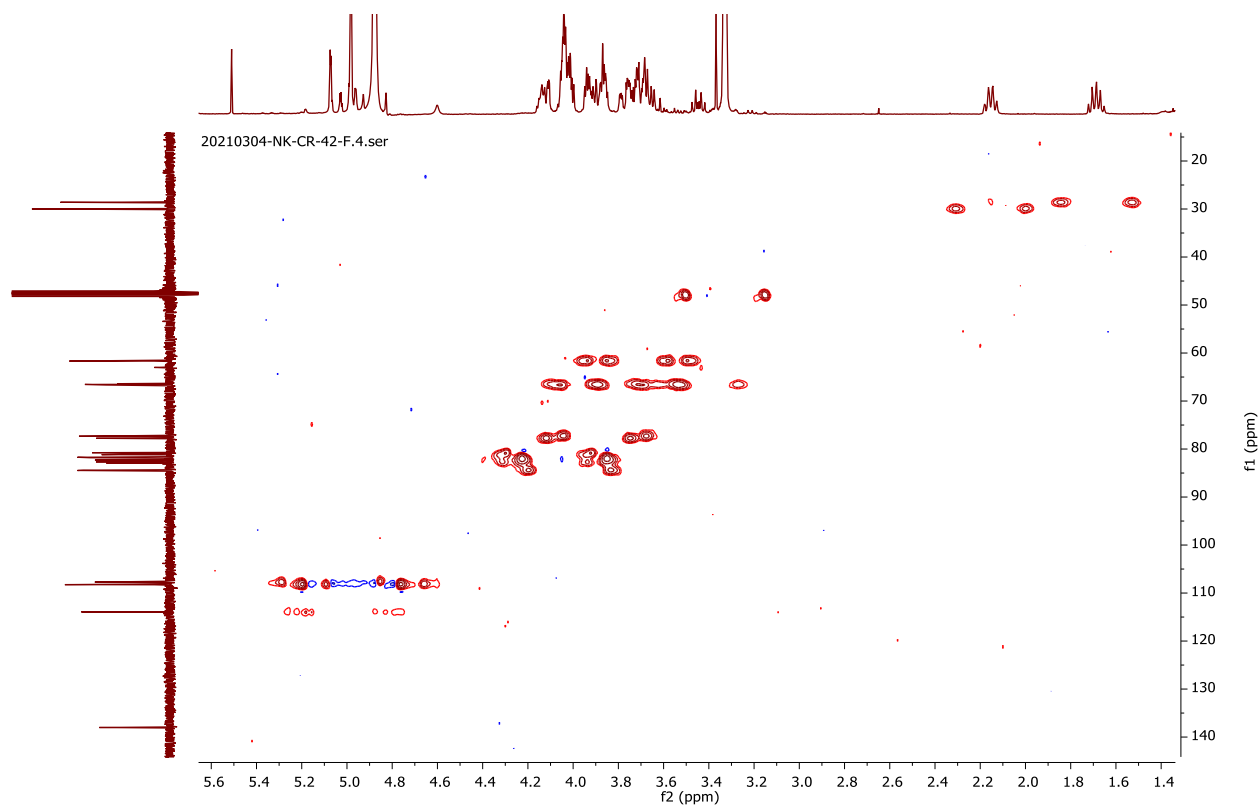


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^1H - ^{13}C HSQC NMR Spectrum (600 MHz, MeOD_4) of Compound **39**(Anomeric Expansion)

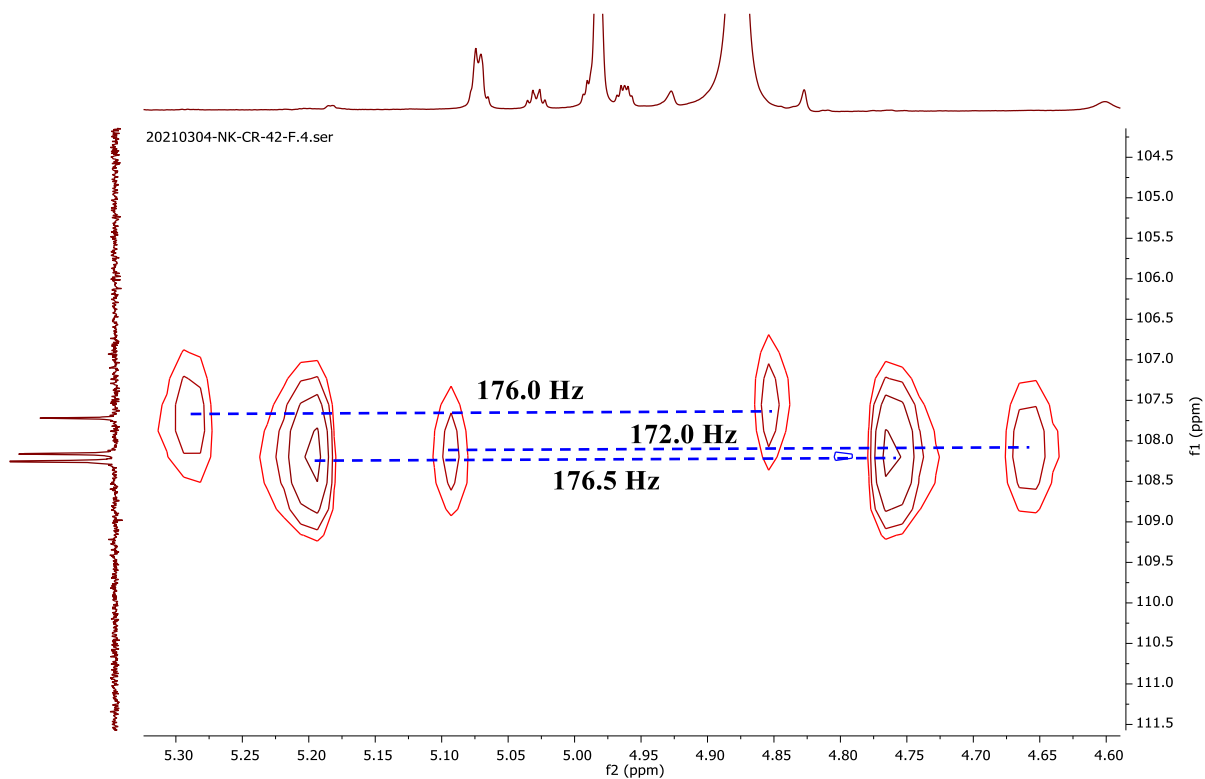


^1H - ^{13}C HSQC-Coupled NMR Spectrum (600 MHz, MeOD_4) of Compound **39**

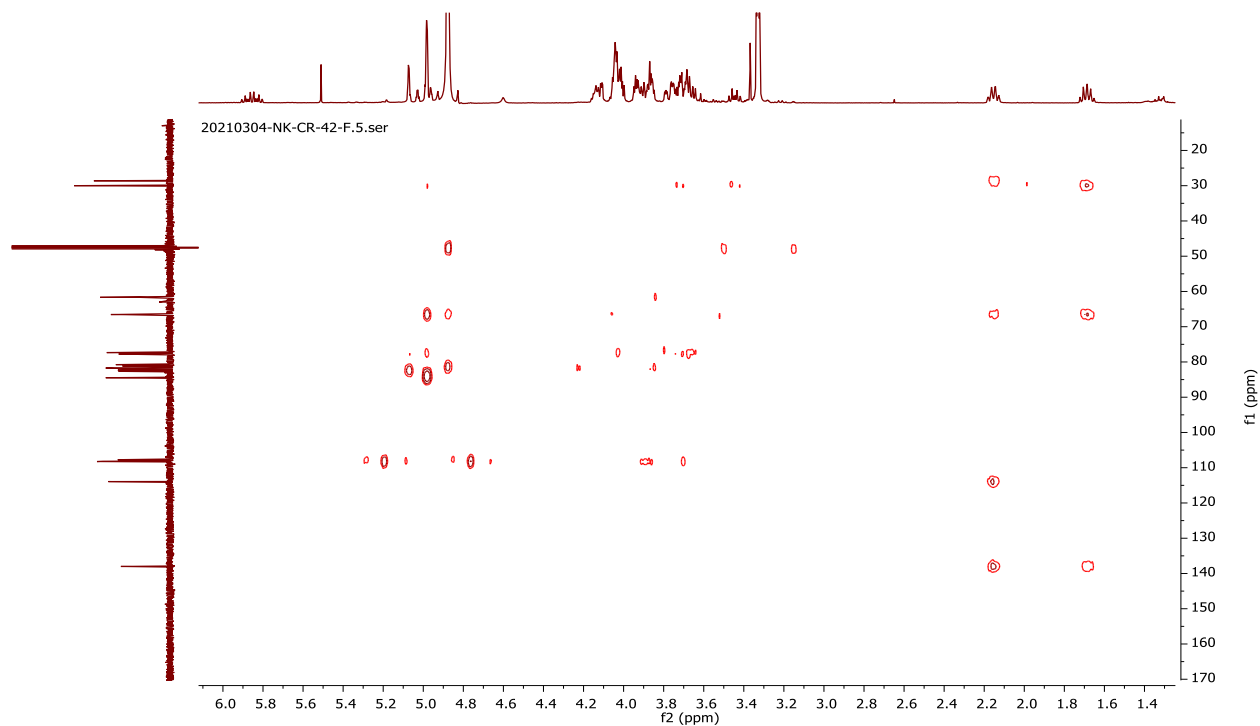


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^1H - ^{13}C HSQC-Coupled NMR Spectrum (600 MHz, MeOD_4) of Compound **39** (Anomeric Expansion)



^1H - ^{13}C HMBC NMR Spectrum (600 MHz, MeOD_4) of Compound **39**



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List of Publications

- 1) Glycosyl vinylogous carbonates as donors using metal-free Activation. Niteshlal Kasdekar, Gulab Walke, Kshitij Deshpande and Srinivas Hotha. *J. Org. Chem.* **2022**, 87, 5472-5484.
- 2) Silver assisted gold-catalyzed formal synthesis of the anticoagulant Fondaparinux pentasaccharide. Gulab Walke, Niteshlal Kasdekar, Yogesh Sutar and Srinivas Hotha. *Commun. Chem.* **2021**, 4, 8-15.
- 3) Silver Assisted Gold Catalysis for the Preparation of Fondaparinux Pentasaccharide and Intermediates. Srinivas Hotha, Gulab Walke, Niteshlal Kasdekar, Yogesh Sutar. PCT/IB2021/060650.
- 4) Synthesis of anticoagulant Idraparinux using silver assisted gold-catalyzed glycosidation. Niteshlal Kasdekar and Srinivas Hotha (manuscript under preparation)
- 5) An efficient glycosylation protocol by benchtop stable propiolate glycosyl donors. Gulab Walke, Niteshlal Kasdekar and Srinivas Hotha. (manuscript under preparation)

Glycosyl Vinylogous Carbonates as Glycosyl Donors by Metal-Free Activation

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Cite This: *J. Org. Chem.* 2022, 87, 5472–5484

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ABSTRACT: Synthesis of glycoconjugates employs a glycosylation reaction wherein an electrophile and a nucleophile known as a glycosyl donor and an aglycon, respectively, are involved. Glycosyl donors often contain a leaving group at the anomeric carbon that upon reaction with activator(s) results in a highly reactive electrophilic species reported as an oxycarbenium ion contact pair that will then be attacked by the aglycon. Therefore, identification of the correct glycosyl donor and activation protocol is essential for the synthesis of all glycoconjugates. Recently identified [Au]/[Ag]-catalyzed activation of ethynylcyclohexyl glycosyl carbonates is one such versatile method for the synthesis of glycosides, oligosaccharides, and glycoconjugates. In this work, stable glycosyl vinylogous carbonates were identified to undergo glycosidation in the presence of a sub-stoichiometric quantity of TfOH. The reaction is fast and suitable for donors containing both C2-ethers and C2-esters. Donors positioned with C2-ethers resulted in anomeric mixtures with greater selectivity toward 1,2-*as* glycosides, whereas those with C2-esters gave 1,2-*trans* selective glycosides. The versatility of the method is demonstrated by conducting the glycosylation with more than 25 substrates. Furthermore, the utility of the glycosyl vinylogous carbonate donors is demonstrated with the successful synthesis of the branched pentaarabinofuranoside moiety of the *Mycobacterium tuberculosis* cell wall.



INTRODUCTION

Glycoconjugates and oligosaccharides are implicated in myriad of biological pathways including embryogenesis, cell–cell communication, fertilization, signal transduction.^{1–4} Recently emerging studies have proved the importance of glycoconjugates in material science, thereby opening a new vista to this burgeoning glycoscience.^{5,6} Furthermore, some glycosides and glycoconjugates are used in clinics as life-saving therapeutics and many are currently explored as preclinical candidates.^{7–9} Synthesis of glycosides, glycoconjugates, or oligosaccharides involves a fundamental reaction known as glycosylation that can be defined as a condensation reaction between a glycosyl donor and an aglycon.¹⁰ Glycosylations are performed by employing enzymes or chemical reagents.^{11–13} In a chemical glycosylation, the glycosyl donor is prepared in such a way that all alcohols are masked except the anomeric carbon that usually bears a leaving group that can be activated by metal or organic catalysts or chemoselective reagents.^{13,14} Several decades of research culminated in the development of many leaving groups and activators that enabled synthesis of complex oligosaccharides and glycoconjugates by stereoselective, regioselective, orthogonal, one-pot, as well as multistep glycosylation strategies.¹⁵ Glycosyl halides, esters, phosphates, imidates, thioglycosides, selenyl glycosides, glycals, hemiacetals, alkenyl and alkynyl glycosides, vinyl glycosides, and 1,2-orthoesters are well established as glycosyl donors.^{16,17} In parallel, we have identified stable ethynylcyclohexyl glycosyl carbonates as glycosyl donors

in the presence of a catalytic amount of a gold phosphite and silver triflate at room temperature.¹⁷ Subsequent investigations demonstrated their versatility by synthesizing many glycosides, oligosaccharides, and glycoconjugates.^{18–23} Glycosyl vinylogous carbonates were considered in this study as the vinylene moiety was hypothesized to facilitate the extrusion of the leaving group under mild reaction conditions. The departed leaving group will be the methyl 3-oxopropanoate that will not be competing with the aglycon during the glycosylation. Importantly, glycosyl vinylogous carbonates can be synthesized from the corresponding hemiacetals and commercially available propiolates in the presence of DABCO or ^tBu₃P at room temperature.²⁴

RESULTS AND DISCUSSION

Solid tetra-*O*-benzyl α -glucopyranose (**1a**) and propiolates (**2a–2c**) were selected to prepare the above hypothesized glycosyl vinylogous carbonates (**3a–3c**). Accordingly, methyl propiolate **2a** was treated with hemiacetal **1a** in the presence of 0.2 equiv of DABCO in dichloromethane at 25 °C to afford the

Received: October 4, 2021

Published: April 13, 2022



Silver-assisted gold-catalyzed formal synthesis of the anticoagulant Fondaparinux pentasaccharide

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Clinically approved anti-coagulant Fondaparinux is safe since it has zero contamination problems often associated with animal based heparins. Fondaparinux is a synthetic pentasaccharide based on the antithrombin-binding domain of Heparin sulfate and contains glucosamine, glucuronic acid and iduronic acid in its sequence. Here, we show the formal synthesis of Fondaparinux pentasaccharide by performing all glycosidations in a catalytic fashion for the first time to the best of our knowledge. Designer monosaccharides were synthesized avoiding harsh reaction conditions or reagents. Further, those were subjected to reciprocal donor-acceptor selectivity studies to guide [Au]/[Ag]-catalytic glycosidations for assembling the pentasaccharide in a highly convergent [3 + 2] or [3 + 1 + 1] manner. Catalytic and mild activation during glycosidations that produce desired glycosides exclusively, scalable route to the synthesis of unnatural and expensive iduronic acid, minimal number of steps and facile purifications, shared use of functionalized building blocks and excellent process efficiency are the salient features.

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