Toward a User-Friendly Stereoselective Glycosylation Strategy

A dissertation submitted by

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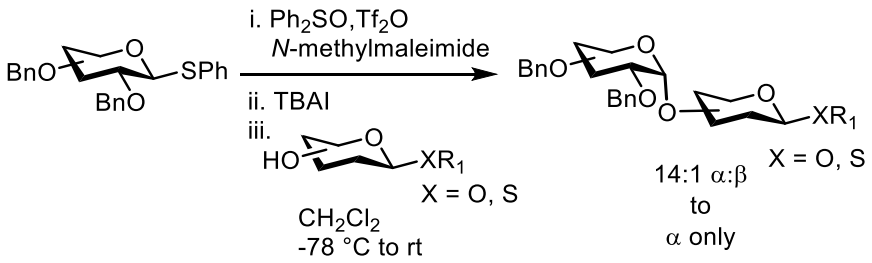
Abstract

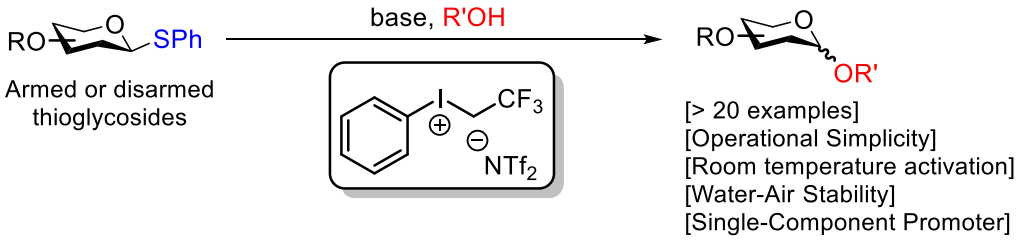
All oligosaccharides are assembled from their corresponding monosaccharide residues via glycosidic bonds. In chemical synthesis, these linkages are formed by chemical glycosylation reactions. This dissertation studies the two fundamental aspects of chemical glycosylations: 1): Stereocontrolled formation of glycosidic linkages and 2): Design of chemical promoters to achieve user-friendly glycosyl donor activations.

Chapter 1 first covers an overview of the biological relevance of carbohydrate molecules as well as the important applications of synthetic chemistry in advancing glycobiology. Following these background introduction, the second part of Chapter 1 reviews general mechanisms of chemical glycosylations, and further discusses the respective advantages/disadvantages of currently employed glycosyl donor activation approaches.



Chapter 2 discusses our contributions in tackling 1,2-*cis*-α glycosides. The synthetic preparation of these linkages has long been considered a daunting task in glycochemistry. The work in this dissertation resulted in the development of a new directing group-free stereoselective glycosylation strategy. As these glycosidic linkages also commonly serve as pathogenic

determinants, we believe that this methodology will find broad applications in synthetic vaccine projects.



Chapter 3 and 4 are focused on the development of user-friendly glycosylations with a new class of thiophilic promoter. Unlike most contemporary approaches, the procedures developed here are characterized by their particular operational simplicity. Later elaboration of these methods further accomplished 1,2-*trans*-β selectivity without invoking the traditional neighboring acyl group participations. We anticipate that these user-friendly glycosylation methodologies will ultimately lead to the development of "glycosylation kits" that can be adopted by the wide chemical biology community, thereby permitting the routine construction of carbohydrate samples.

Acknowledgement

As the final revision for this dissertation marks the official conclusion of my Ph.D. career, I cannot help but appreciate how truly fortunate I am to have the opportunity to mature tremendously in this scientific journey over the past 5 years. I still remember vividly how genuinely excited and yet clueless I was in the summer of 2011 when I decided to move from immunology into the unknown realm of synthetic carbohydrate chemistry under the guidance of my later Ph.D. advisor, Professor Clay Bennett, who also showed me how to run my first reaction in the laboratory: a Zemplén deacetylation on a 20 gram scale. Other than constantly feeling proud to have been trained by my research advisor himself, I have the utmost gratitude in Dr. Bennett for taking me in despite knowing my lack of former experience in synthetic organic chemistry. Absolutely nothing in this dissertation would have been possible without his trust in me, and for that I am forever grateful. To Dr. Bennett: My research career in your group has by all means been a roller coaster ride, a ride during which you have significantly surpassed my expectation as a scientist, a mentor, and most importantly, a source of inspiration. The countless individual discussions between us, whether in your office or outside of the lab, such as during the ACS meeting in Dallas, are going to be the memories that I will always remember. Thank you once again for the patience and guidance along the way of my Ph.D. career.

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I would also like to mention the senior researchers in the Tufts Chemistry department whose help was really appreciated in my thesis work: Dr. Krishna Kumar and Dr. Vittorio Montanari for their contributions in the iodonium salt promoter project; Dr. David Wilbur for the help in NMR experiments and Dr. Charles Mace for assisting with the measurements of solvent refractive indices. In addition, being able to work closely with such a diverse lineup in the department is definitely one of the most joyful aspects over the course of my Ph.D. career. In particular I would like thank Son, Jason, John Paul, Andrei, Jordan, Emily, Dina, Marissa, Danielle, Matt, Cristy, Melissa and Sophia for their encouragement. Interaction with all these interesting personalities always provided motivation that helped me profoundly.

Lastly but most importantly, as I ready myself for the next chapter of my career, I know that I will have the courage to explore the unknown frontiers in whichever path that comes before me, because of the love and support from my family back in motherland Taiwan and my girlfriend Jenn. Life is about making decisions and connecting dots, and family is the origin of all the dots that defines my past, present and future.

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Chapter 1:

Glycobiology and Carbohydrate Chemistry.

1.1. Chemical Glycobiology

1.1.1. Carbohydrates as Critical Mediators in Biology

The central relevance of carbohydrates in the biological system is conceptually straightforward. Glycan moieties are ubiquitous, found both extra- and intracellularly in all living cells and organisms, and have historically been recognized for providing the mechanical framework that supports the structural integrity of cell wall/cytoskeletons as well as serving as the main metabolic source of energy for life.[1] Despite the fact that their existence as co- and post-translational modifications has long been documented,[2] the biological effects of carbohydrate molecules were initially considered to be limited to the prevention of protein degradation.[3] In more recent years, however, there has been increased realization of the wide array of biological events mediated by carbohydrates (Figure 1.1), significantly challenging the long-standing central dogma which limited biological information "codes" to nucleic acids and amino acids.[4-7] It is estimated that up to 90% of human proteins are glycosylated.[8] Glycan-mediated intracellular functions[9] predominantly involve gene regulation (such as STAT and NF-κB transcription factors),[10] protein folding, quality control[11,12], and vesicle trafficking at the endoplasmic reticulum (ER) – Golgi network. On the other hand, glycoconjugates, such as glycoproteins, glycosaminoglycans and glycolipids, have also been found to be densely packed on the cell surface, mediating various cell-cell[13,14] and cell-pathogen[15-18] interactions that are required for their downstream signaling cascades (Figure 1.2).

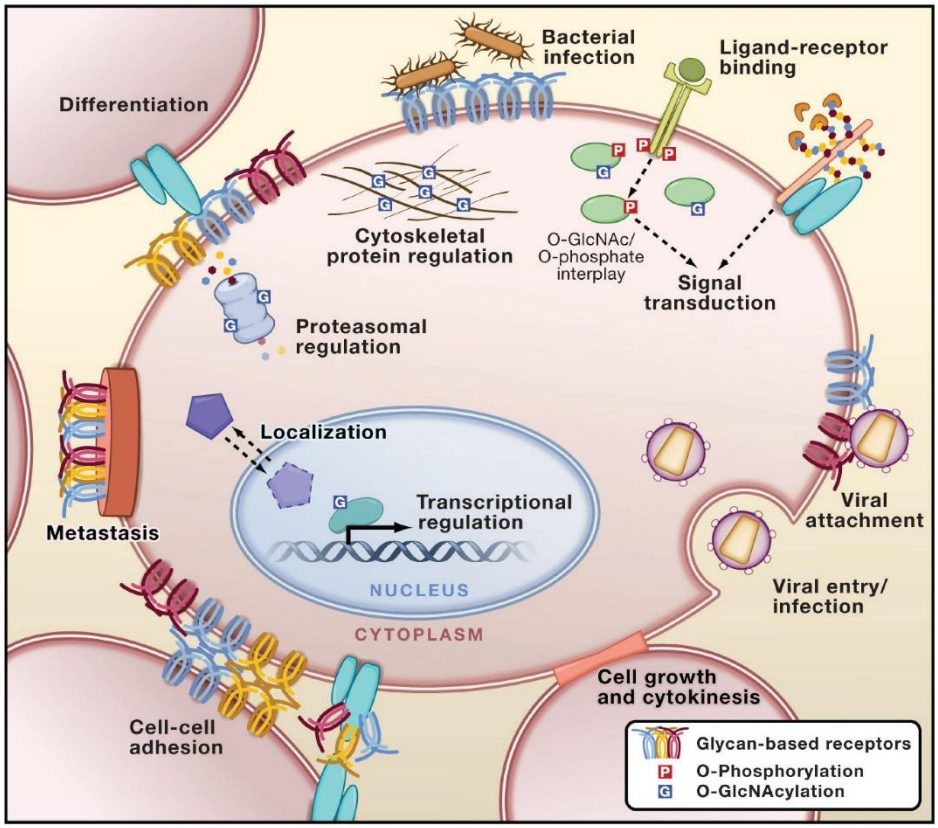


Figure 1.1: Important cellular events mediated by carbohydrates. Adapted from Hart *et al.*, 2010.[4] Used with permission from Elsevier.

The untapped research potential enabled by tackling these important pathways has inspired the pursuit of carbohydrate-based therapeutics in the past several decades.[19-21] To date, a vast variety of glycan-based agents in the forms of small molecule therapeutics (Figure 1.3) have been discovered and produced in the pipeline. These examples further highlight the versatility of carbohydrates in modern medicine.[22-26]

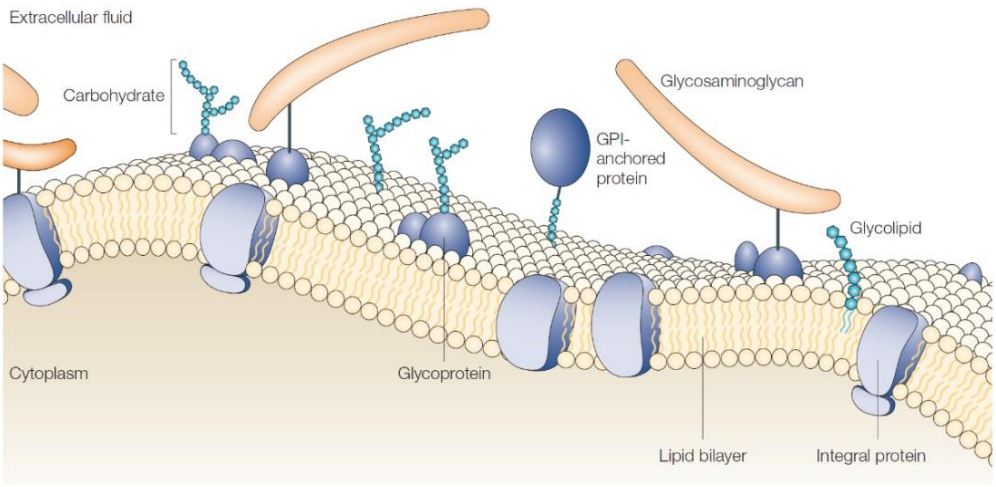


Figure 1.2: Cell-surface distribution of carbohydrate-containing "glycocalyx". Adapted from Seeberger *et al.*, 2005,[27] used with permission from Nature publishing group .

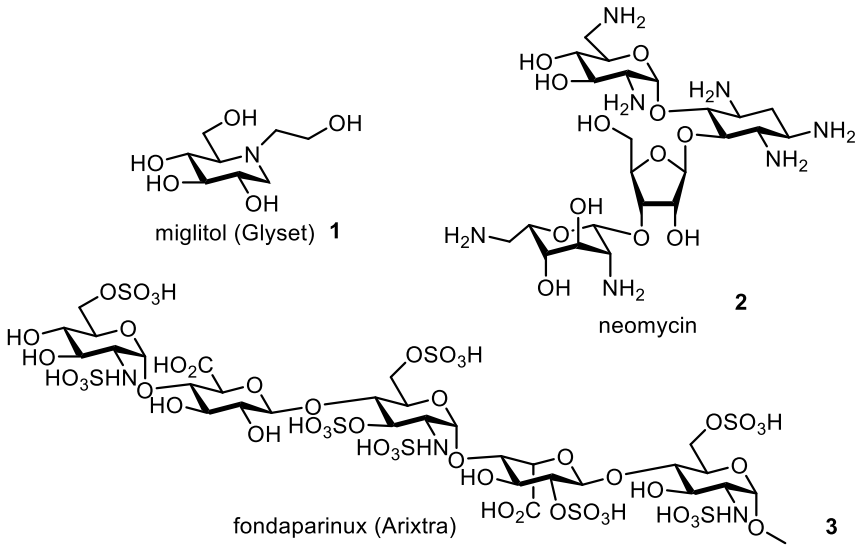


Figure 1.3: Examples of glycan-based small molecule therapeutics currently in the pipeline.

1.1.2. Importance of Carbohydrate Chemistry in Tackling Glycobiology

Since its initial concise definition, the field of glycoscience has seen a boom with regards to the global appreciation of its pivotal presence in virtually all aspects of human health and disease manifestations. Despite clear motivation, glycan therapeutics are often times overshadowed by the more accessible protein-based approaches. One key reason for the lagging advancement of glycobiology lies in the unparalleled structural complexity of the human glycome.[28] Unlike nucleic acids and peptides, which are assembled through linear, achiral chemical linkages, glycans are branched structures that incorporate regiodiversity. In addition, new stereocenters are generated upon glycosidic linkage formation, thereby adding stereodiversity (Figure 1.4). Furthermore, the biosynthesis of complex glycans is not template-driven, but instead is processed by a series of editing and trimming enzymes whose expression levels are highly regulated by multiple cellular factors. As a result, naturally-occurring glycans cannot be routinely manipulated through simple genetic engineering, and are often intractable heterogeneous mixtures.

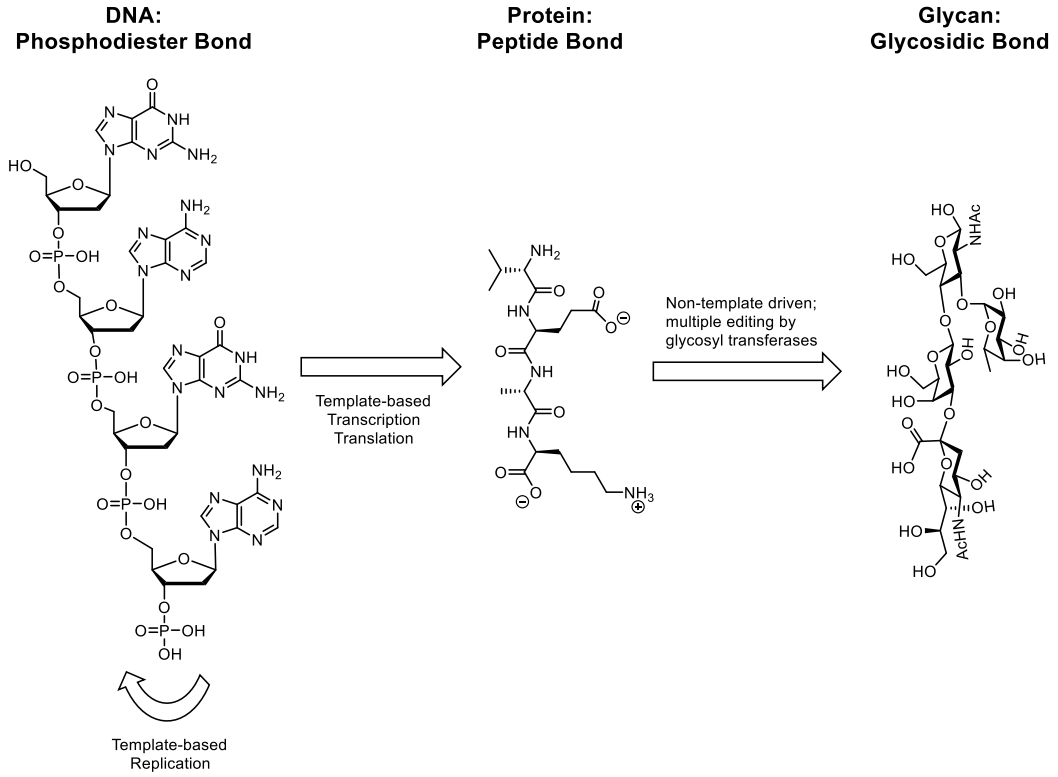


Figure 1.4: Structural comparison between nucleic acid, peptides and carbohydrates-based macromolecules.

The therapeutic impact of carbohydrate microheterogeneity can be largely seen in the recent development of glycosylated monoclonal antibodies (mAb). Notably, distinct glycoforms have been shown to possess different bioactivity and immunogenicity (Table 1.1). For example, it's been shown that monoclonal antibodies lacking core *O*-fucosylation possessed significantly higher binding affinity for FcγRIIIa, and consequently elicited greatly enhanced ADCC (antibody-dependent cell-mediated cytotoxicity).[29] These glycoforms can often vary from batch to batch in cell-based productions, further exemplifying the need for methods to produce homogenous glycoforms.[30-33]

Glycan species	Safety/ immunogenicity	Biologic activity/ efficacy	Clearance (PK/PD)
Galactose	Unknown	+	Unknown
α1,3-galactose	−−	Unknown	Unknown
Fucose	(−)	++	Unknown
Bisecting GlcNac	(−)	+	Unknown
High mannose	Unknown	+	−−
NANA	Unknown	(−)	+
NGNA	−−	(−)	+
β1,2-Xylose/ α1,3-Fucose	−−	Unknown	Unknown
NGHC	Unknown	−	(−)

Table 1.1: Impact of Fc glycans on numerous activities of biologics.[33]

+ Positive impact; - negative impact; ++ high positive impact; -- high negative impact; (+/-) potential impact. NANA: CMP-N-acetylneuraminic acid. NGNA: N-glycolylneuraminic acid. NGHC: non-glycosylated heavy chain. Adapted and used with permission from Oxford Journals.

It has been hypothesized that the ability of carbohydrates to mediate the myriad of downstream biological events is due to their inherent structural diversity. Hence, rapid access to structurally well-defined samples is an essential prerequisite to unambiguously decipher these glycan-encoded information. However, the isolation of pure glycans from natural sources is typically cumbersome due to their microheterogeneity. Therefore, chemical synthesis is often regarded as the only avenue for the production of pure material. Recent advancements in oligosaccharide synthesis, as well as the development of chemical tools to aid in the elucidation of their subcellular localization and functional, have resulted in the emergence of a unique and

powerful sub-discipline of chemical biology, termed "chemical glycobiology".[6,34-41] Some classic examples of chemical glycobiology include surface glycan labeling,[42] metabolic engineering,[43,44] rapid screening of glycan-lectin interactions through carbohydrate arrays,[36,45] and the construction of synthetic glycoprotein therapeutics (Figure 1.5).[46] This research not only significantly broadened our limited understanding of carbohydrates in mediating cellular biology, but also provided the critical information for the rational design of modern glycomedicine. While the field continues to expand, a fundamental bottleneck is the need for general methods for producing homogenous carbohydrates.[28,47-49]

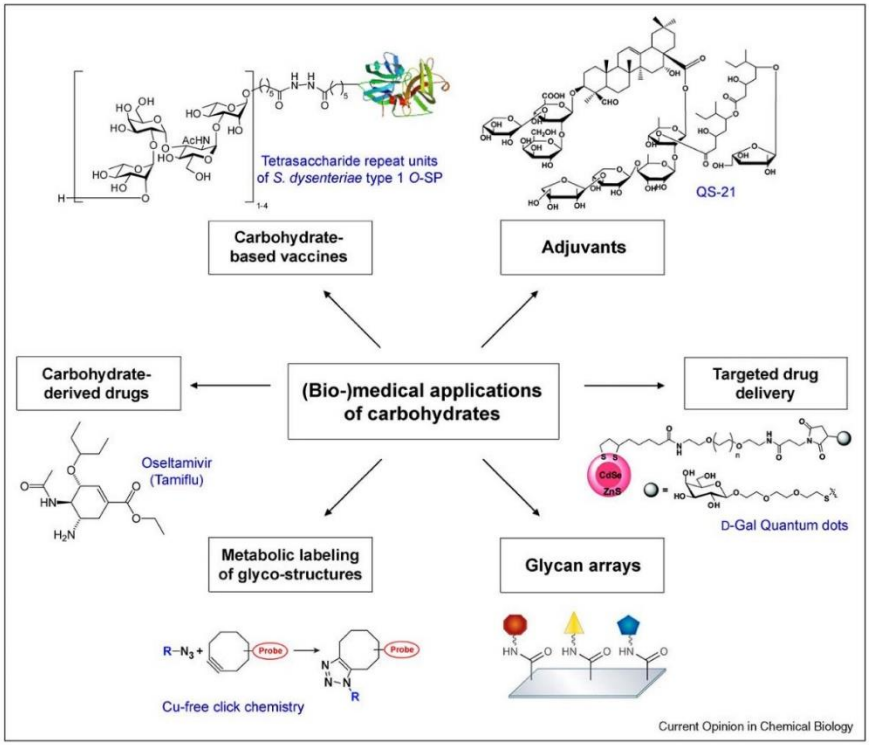


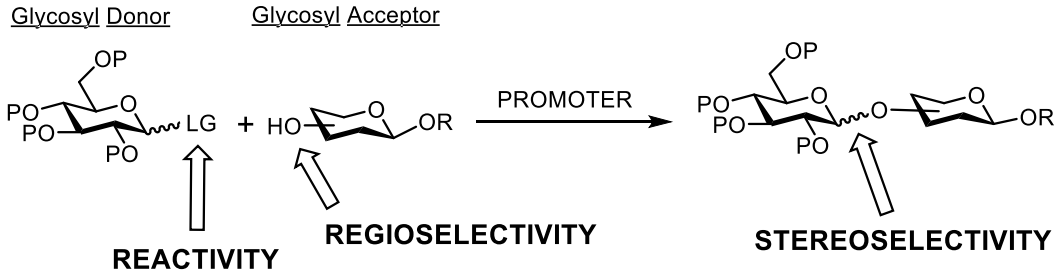
Figure 1.5: Biomedical applications of carbohydrates. Adapted and used with permission from Elsevier.[35]

In light of this, my dissertation is dedicated to the development of general and user-friendly chemical synthetic methods to enable routine construction of carbohydrate molecules. Background introduction and a general review of the field of carbohydrate synthesis will first be discussed in the remainder of this chapter. The rationale for method improvements will then be further connected to my own dissertation work starting in Chapter 2.

1.2. Chemical Glycosylations

The chemical synthesis of complex oligosaccharides is far from a trivial process (Scheme 1.1). Regioselective functionalization of the multiple reactive hydroxyl groups on the pyranose or furanose rings presents a daunting task that inevitably requires tedious protection/deprotection schemes. This largely contributes to the fundamental lack of atom economy in carbohydrate synthesis. However, the key transformation in the field of glycochemistry arguably lies in the chemical glycosylation stage where numerous glycosidic linkages are constructed.[50] Firstly, the design of corresponding promoters to match leaving group reactivity on the glycosyl donor needs to be accomplished. Secondly, the formation of new stereocenters after glycosylations necessarily introduces difficulties associated with controlling stereoselectivity. Finally, various competing side reactions, such as elimination, anomeric hydrolysis and protecting group migration, often complicate the outcomes of the reaction. Despite intensive research and manpower devoted to the field of chemical glycosylation over the past decades, it is pertinent to say that to date no

general synthetic methods are available to cover the entire spectrum of complex glycosidic linkages. As a result, developing universal chemical glycosylation strategies that afford precise stereocontrol still stands out as one of the most difficult synthetic challenges in modern organic chemistry.



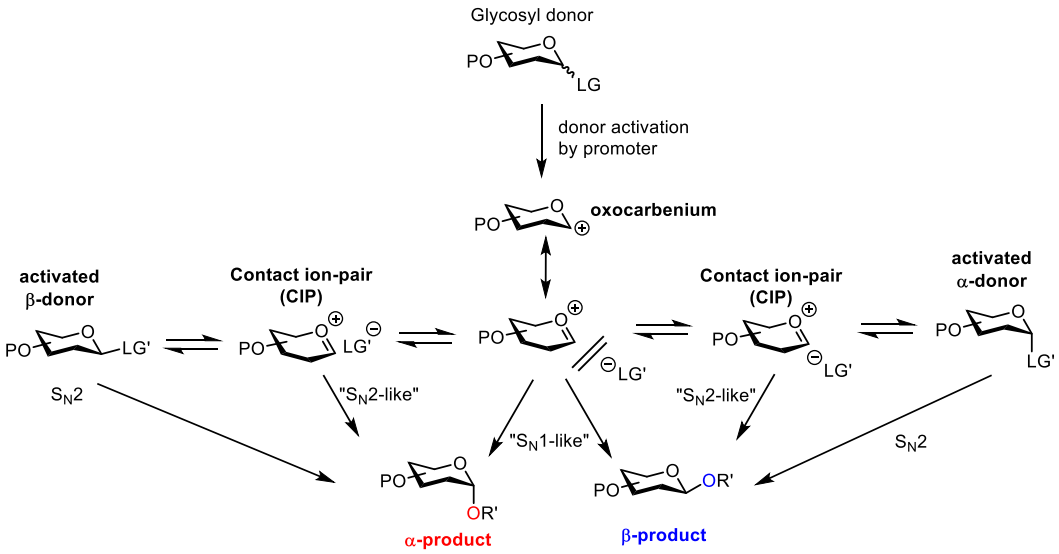
Scheme 1.1: Generic depiction of chemical glycosylation reactions.

Two critical issues in the development of chemical glycosylations will be addressed in this dissertation. The first issue will involve the stereocontrolled formation of difficult glycosidic linkages. This will be followed by the second aim which is to develop alternative chemical promoters for a "user-friendly" donor activation. Lastly, efforts to combine the principles derived from these two parts will be further attempted. In the next section of this chapter, general aspects of chemical glycosylations will first be discussed.

1.2.1. General Mechanistic Considerations

As depicted in Scheme 1.2, chemical glycosylation reactions are typically initiated by donor activation with a promoter. In the absence of additional stereochemical bias, the resulting glycosyl cation reacts through an

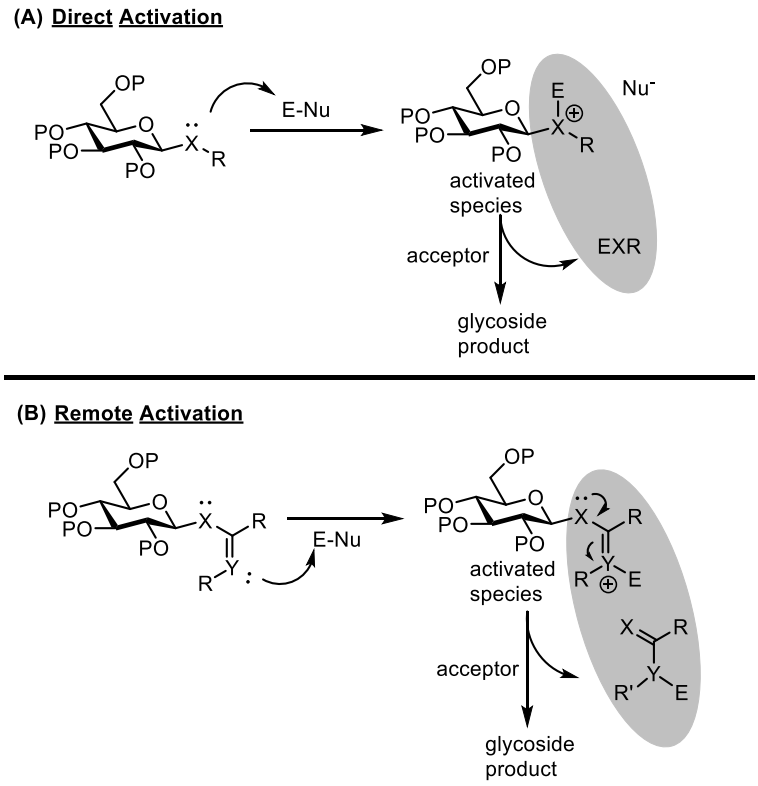
S_N1-manifold. However, contemporary studies have also suggested that there is an equilibrium between the oxocarbenium ions and the corresponding contact ion-pair (CIP) intermediates. If this latter species is sufficiently stabilized it can react through a more S_N2-like pathway. Factors such as solvent polarity, temperature and protecting group patterns have all been shown to impact the equilibrium between these species, thereby affecting the stereochemical outcomes of glycosylation reactions.[51]



Scheme 1.2: Overall depiction of chemical glycosylation mechanisms.

To date, various leaving group activation strategies have been reported. The advantages and limitations of each method will be discussed in the next section. Generally, their modes of action can be classified as follows:

- Direct activation, where the initial activation of the leaving group occurs directly at the atom connected to the anomeric center.
- Remote activation, where the initial activation of anomeric leaving group takes place at a functional group not directly attached to the anomeric center (Scheme 1.3).

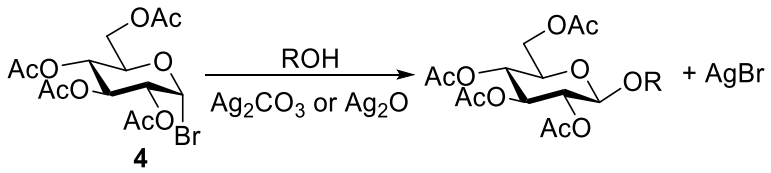


Scheme 1.3: Generic classification of chemical glycosylation reactions into direct (A) or remote (B) donor activation strategies.

1.2.2. Common Classes of Glycosyl Donors

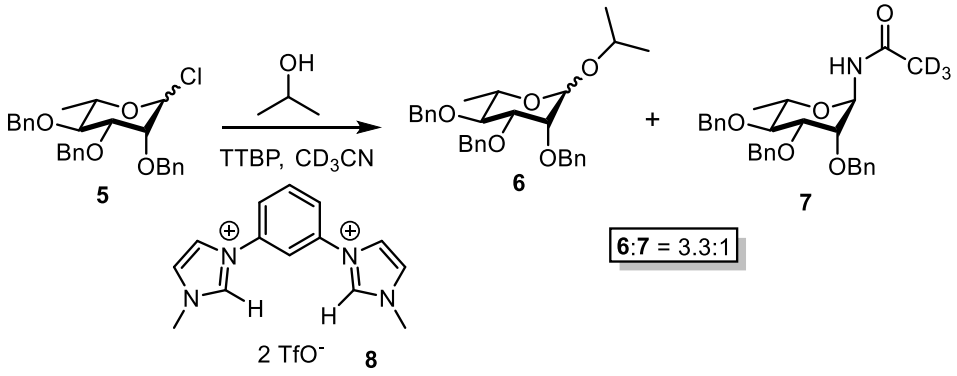
Direct Activation:

Glycosyl Halides



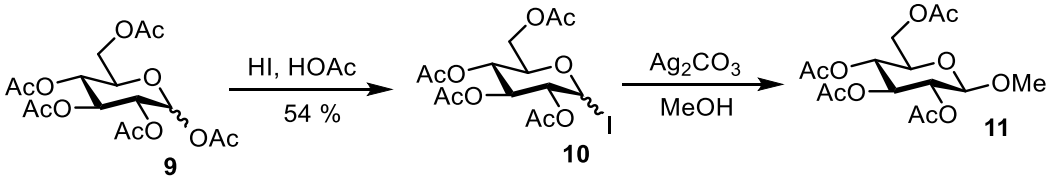
Scheme 1.4: Koenigs/Knorr glycosylation approach with glycosyl halides.[52]

First described by Arthur Michael in 1879,[53] glycosyl halides are one of the earliest-studied glycosyl donors. Several decades afterwards, Koenigs and Knorr reported the synthesis of glycosides through the use of fully acetylated glycosyl halides (either bromide or chloride) with an alcohol in the presence of Ag_2CO_3 or Ag_2O. Since then, glycosyl bromides and chlorides found use through wide variations of what is now known as the Koenigs-Knorr glycosylation. Most of the reagents utilized to activate anomeric chlorides and bromides discovered to date involved using silver (I) and mercury (II)-containing metal salts such as $AgClO_4$, AgOTf, $AgNO_3$, Ag_2O, $Hg(CN)_2$ and combinations thereof.[54,55] In addition to the traditional methods above, a different strategy was presented in the recent work by Codées' research group where they attempted to use halogen bonding catalysis to activate glycosyl chlorides (Scheme 1.5).[56] However, this approach exhibited significantly limited substrate scope and could only efficiently activate deoxy glycosyl donors with simple nucleophilic acceptors.

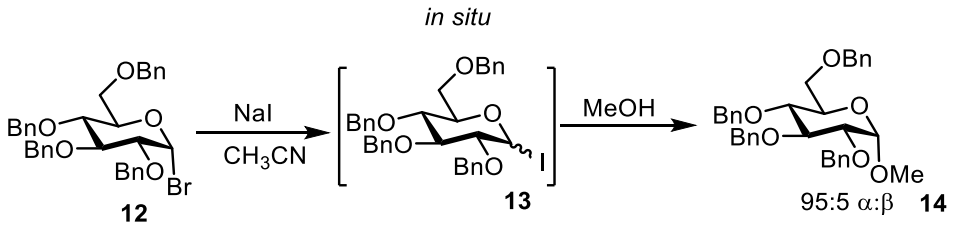


Scheme 1.5: Halogen bonding-promoted activations of glycosyl halides.[56]

On the other hand, glycosyl iodides were long regarded to be too unstable to be synthetically useful.[57] In 1910, Fischer and Fischer isolated glycosyl iodide **10** as an unstable crystalline solid by reacting per-acetylated glucose **9** with HI/acetic acid (Scheme 1.6).[58] They further reacted **10** with silver carbonate in methanol to afford methyl glycoside **11**, representing the first example of using glycosyl iodides as glycosyl donors.[58] Since this seminal report, several Lewis acidic/metal-based activations of glycosyl iodides, such as $LiClO_4$, $FeCl_3$-I_2, CuCl-I_2, have been reported.[59]



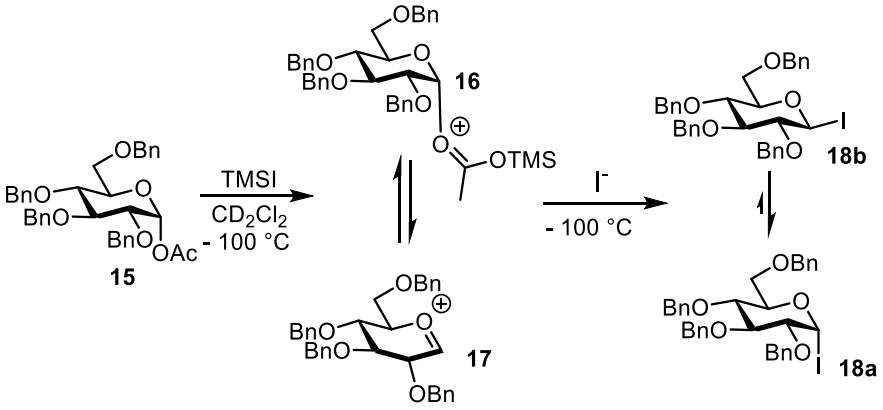
Scheme 1.6: First glycosylation reaction with glycosyl iodide donors.[58]



Scheme 1.7: Early example of *in situ* generation of glycosyl iodides demonstrated by Kozner and Schuerch.[60]

However, the difficulty associated with glycosyl iodide preparation largely prevented a wider use of these donors. In 1974, Kronzer and Schuerch showed an alternative approach in their synthesis of α-glycosides that involved the *in situ* generation of glycosyl iodide **13** (Scheme 1.7), demonstrating a new pathway to take advantage of these reactive donors in carbohydrate synthesis.[60] Shortly after, Thiem and Meyer reported a reliable method to generate glycosyl iodides from a host of precursors, including anhydrosugars, methyl glycosides and pentaacetylated hexoses, with the use of TMSI (trimethylsilyl iodide).[61] These advancements therefore significantly expanded the synthetic utility of glycosyl iodides. In 1997, Gervay-Hague and coworkers adapted this procedure and further characterized the formation of armed glycosyl iodide species by NMR (Scheme 1.8).[62] They found that unlike the substrates previously studied by Thiem and Meyer, these per-*O*-benzylated glycosyl iodide species are highly unstable, and that extremely low temperature (-100 °C) are required in order to detect the β-iodide **18b**. Furthermore, rapid anomerization from the β-glycosyl iodide **18b** to the thermodynamically more stable α-iodide **18a** was also observed in these

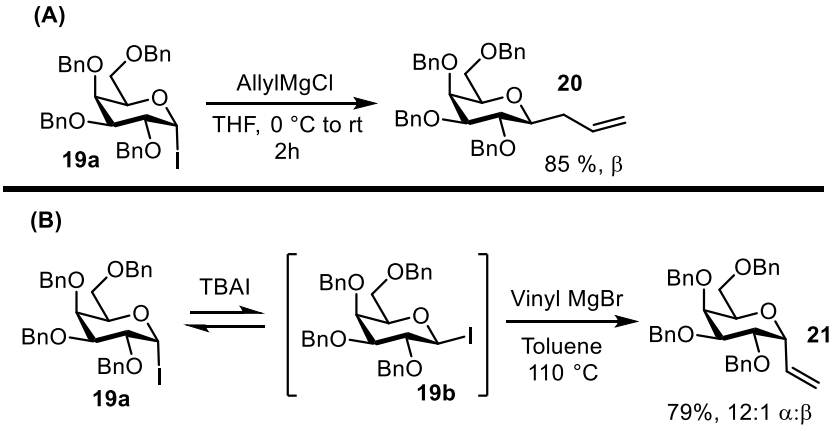
studies, and as a result only the α-anomer was detected at temperatures of -40°C and above.



Scheme 1.8: Synthesis and characterization of armed glycosyl iodides by Gervay-Hague and coworkers.[62]

Importantly, Gervay-Hague and coworkers later showed that under basic conditions, these armed α-glycosyl iodides could undergo direct kinetic S_N2 displacements without the presence of additional promoters. Under these procedures, highly β-selective glycosylation could be achieved.[63] For example, Grignard reagents were shown to be compatible with this method and led to the formation of β-C-glycosides upon reaction with **19a** (Scheme 1.9A). On the other hand, perhaps the most commonly used synthetic approach utilizing glycosyl iodide donors involves the *in situ* anomerization of α/β-glycosyl iodides under Lemieux-type halide-ion exchange conditions,[64] which can further lead to the selective synthesis of α-glycosides. Taking advantage of this principle, Kulkarni and Gervay-Hague also demonstrated a tetrabutylammonium iodide (TBAI)-promoted α-glycosylation scheme with

Grignard reagents, starting from identical glycosyl iodide donor **19a** (Scheme 1.9B).[65] The detailed mechanistic rationale, synthetic deficiencies of this strategy and further improvements attempted in this dissertation will be discussed in Chapter 2.



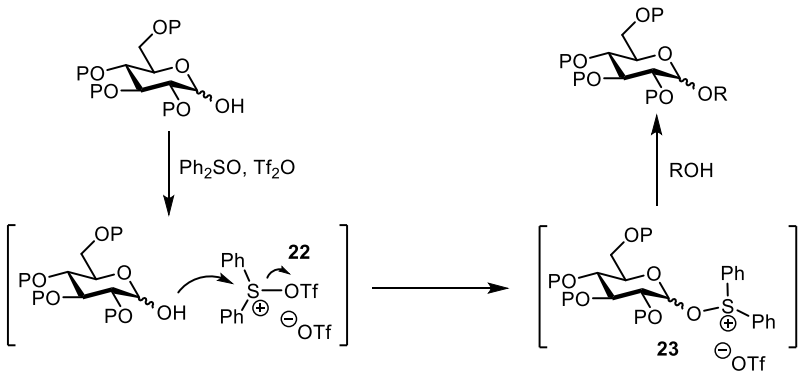
Scheme 1.9: Stereoselective glycosylations with glycosyl iodides.[66]

Glycosyl Hydroxyls (Hemiacetals)

Glycosylation reactions with C-1 unprotected hemiacetal donors present a notable variation to most other procedures. In so-called dehydrative glycosylations, anomeric derivatization and the following activation/nucleophilic displacement are typically combined in a one-pot fashion. Notably, this approach offers the advantage over glycosyl halides in that it eliminates the need to isolate water-sensitive activated donors.

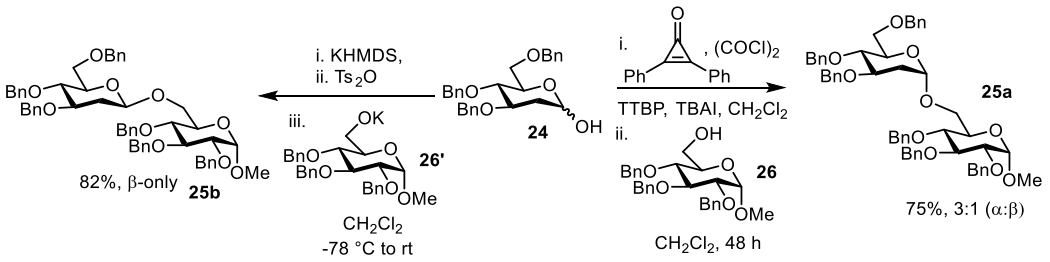
Hemiacetals as glycosyl donors were initially discovered and investigated by Emil Fischer in his pioneering work on Bronsted-acid catalyzed glycosylations. This approach possesses significant drawbacks due

to its harsh reaction conditions. Furthermore, since hemiacetals themselves can behave as nucleophilic glycosyl acceptors, inefficient activation invariably leads to self-condensation and trehalose formation. In the past century, an appreciable amount of work has been devoted to the development of improved activation protocols under milder reaction conditions. Most examples involve Lewis acid-mediated activations such as $Sn(OTf)_2$, $Cu(OTf)_2$, and $BF_3{\cdot}(OEt)_2$.[67,68] Alternative approaches involve using reagents designed to convert the hemiacetal alcohol into reactive leaving groups *in situ*. For example, Mitsunobu activation of hemiacetals can be achieved with phosphorus betaines,[69] whereas sulfonium-based electrophile **22** was demonstrated by Gin and colleagues (Scheme 1.10).[70] Recent modifications of this procedure have further allowed the use of sub-stoichiometric amount of sulfoxide reagent, where 0.2 equiv. of di-(n-butyl)sulfoxide could be employed with benzenesulfonic anhydride as the active promoter system.[71,72]



Scheme 1.10: Sulfonium-based electrophilic activation of hemiacetals.[70]

In line with these efforts, the research program in our laboratory has focused on developing "reagent-controlled stereoselective glycosylations". With these approaches, diastereoselective synthesis of both anomeric glycosides can be achieved from identical coupling partners, with the stereochemical outcomes dictated by the employed glycosylation promoters. We have recently disclosed two distinct strategies that efficiently activate 2-deoxy hemiacetal donors for subsequent α- and β-selective glycosylations, respectively (Scheme 1.11).[73-76] Briefly, hemiacetal donor **24** was first activated by the diphenylcyclopropenium cation, which was generated *in situ* by the combination of oxalyl chloride and diphenylcyclopropenone. This was followed by the sequential addition of TBAI and nucleophile **26**, leading to the α-selective formation of glycoside **25**. Shortly after, an improved modification of this procedure was developed with the use of dibromocyclopropene promoter.[75] This in turn allowed for more robust reactions (12 hours as opposed to 48 hours) and greatly enhanced stereoselectivity (up to α-only). On the other hand, electrophilic activation of **24** by *p*-toluenesulfonic anhydride quantitatively generated α-glycosyl tosylate intermediate. The subsequent stereoinversion by glycosyl acceptor **26'** then afforded glycoside **25** β-specifically.



Scheme 1.11: Reagent-controlled stereoselective glycosylation of 2-deoxy hemiacetal donors reported by the Bennett research group.[73-76]

Remote Activation:

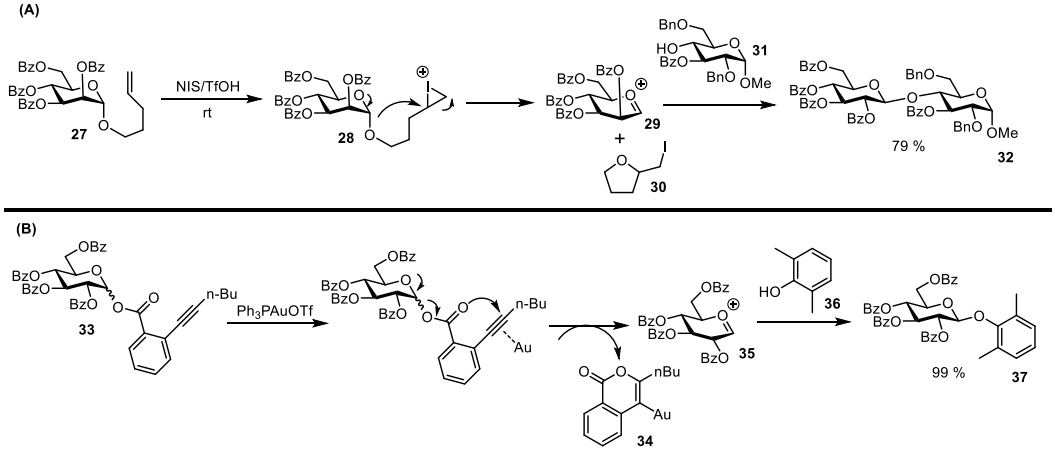
Glycosyl Imidates

Of the various chemical glycosylation strategies developed to date, the use of O-glycosyl imidates as donors is one of the most common. Initially introduced by Schmidt and coworkers,[77] *O*-glycosyl trichloroacetimidates exhibited excellent glycosyl donor properties in terms of their ease of formation and general applicability. Importantly, only a catalytic amount of the promoter is required to achieve rapid and quantitative activation of the donor. This is in contrast to most other glycosyl donors where stoichiometric amounts of promoter are typically needed. Glycosylation reactions with glycosyl trichloroacetimidates typically involve activation with Lewis acids such as TMSOTf and $BF_3{\cdot}OEt_2$, which coordinate to the Lewis basic nitrogen atom on the leaving group. The imidate is expelled as a trichloroacetamide, releasing the Lewis acid for further rounds of donor activation.

Despite its wide popularity, Schmidt glycosylations are not without significant drawbacks. Notably, the highly unstable nature of trichloroacetimidates makes donor purification difficult, and usually requires

the donor to be immediately used in subsequent glycosylations before hydrolysis can occur. Furthermore, premature rearrangement of the trichloroacetimidate often generates glycosyl amide as the major reaction byproduct. Efforts to address this problem led to the discovery of N-phenyl trifluoroacetimidates.[78] However, this latter class of donors has also been shown to possess lower reactivity compared to their glycosyl trichloroacetimidates counterpart, presumably due to the lower nitrogen Lewis basicity.

Glycosyl alkenes and alkynes



Scheme 1.12: Examples of remote activation strategies with glycosyl alkene (A) and alkynes (B).[79,80]

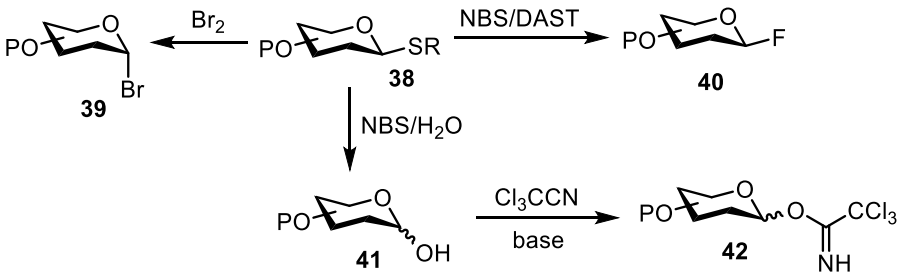
Alkenyl and alkynyl glycosides represent another unique class of glycosyl donors which undergo remote activations. These involve the introduction of leaving groups possessing either terminal or internal olefin/alkyne functionalities onto the anomeric oxygen atoms. Fraser-Reid

first demonstrated the utility of *n*-pentenyl donor **27** in 1988 (Scheme 1.12A).[80] Typical activations of pentenyl glycosides involve the use of soft halonium-based electrophiles, such as N-bromosuccinimide (NBS) and/or N-iodosuccinimide (NIS)/TfOH. These promoters react with the alkene to initially afford a cyclic halonium ion intermediate **28**. This latter species then further reacts to generate the oxocarbenium intermediate **29** ready to couple with the incoming glycosyl acceptors. Later elaboration of this activation concept by Fortin *et al*.[81] resulted in the development of *gem*-Dimethyl 4-pentenyl glycosyl donors that possessed improved reactivity. In these cases, the cyclization of intermediate **28** was likely facilitated by the "*gem*-Dialkyl" or Thorpe-Ingold effect,[82] thereby leading to enhanced donor activation. In addition, analogous approaches incorporating terminal alkynes in glycosyl donors have been reported by Hotha (propargyl) and Yu (alkynyl benzoates, Scheme 1.12B).[79,83,84] One major difference to the respective alkenyl glycoside activations lies in the fact that gold catalysts Au(I) or (III) are employed, with the former being particularly mild and water/air-stable due to its low oxophilicity.[79]

1.3. Thioglycosides as Versatile Building Blocks

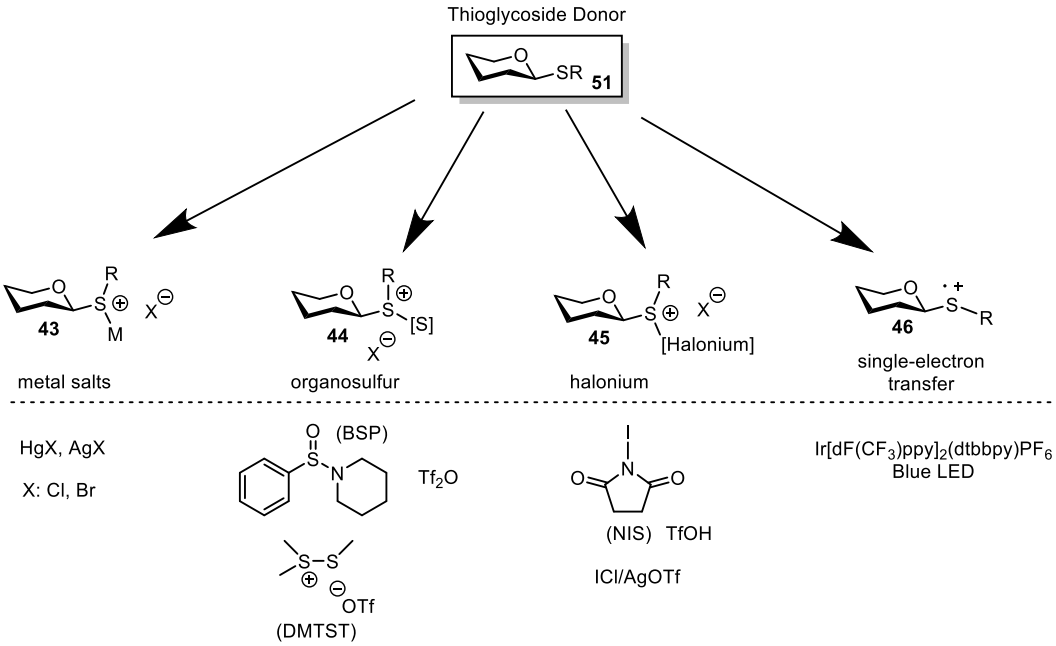
Since their first introduction as glycosyl donors by Ferrier *et al*. in 1973,[85] alkyl and aryl thioglycosides have emerged as one of the most versatile building blocks in oligosaccharide assembly. The advantages offered by thioglycosides stem from their unique combination of stability and tunable

reactivity. Due to their excellent stability, large scale building block production and storage can be reasonably achieved. In addition, anomeric thiol protecting groups can be conveniently functionalized to further afford a wide range of common glycosyl donors (Scheme 1.13), such as hemiacetals, glycosyl halides and glycosyl imidates,[86-88] making them particularly attractive in orthogonal and chemoselective glycosylation assembly strategies. Unlike hemiacetals, thioglycosides possess locked anomeric configurations. This permits the separation of anomeric mixtures of thioglycosides, which can be critical for interpreting spectra during complex molecule synthesis. As the demand for more robust and milder glycosylation chemistries continues, comprehensive studies toward improving thioglycoside activation have become a central focus in modern glycochemistry. Some classic examples and advances will be reviewed below.



Scheme 1.13: Leaving group conversions of thioglycosides.

1.3.1: Review of Thioglycoside Activation Methods



Scheme 1.14: Commonly employed classes of thiophilic promoters.

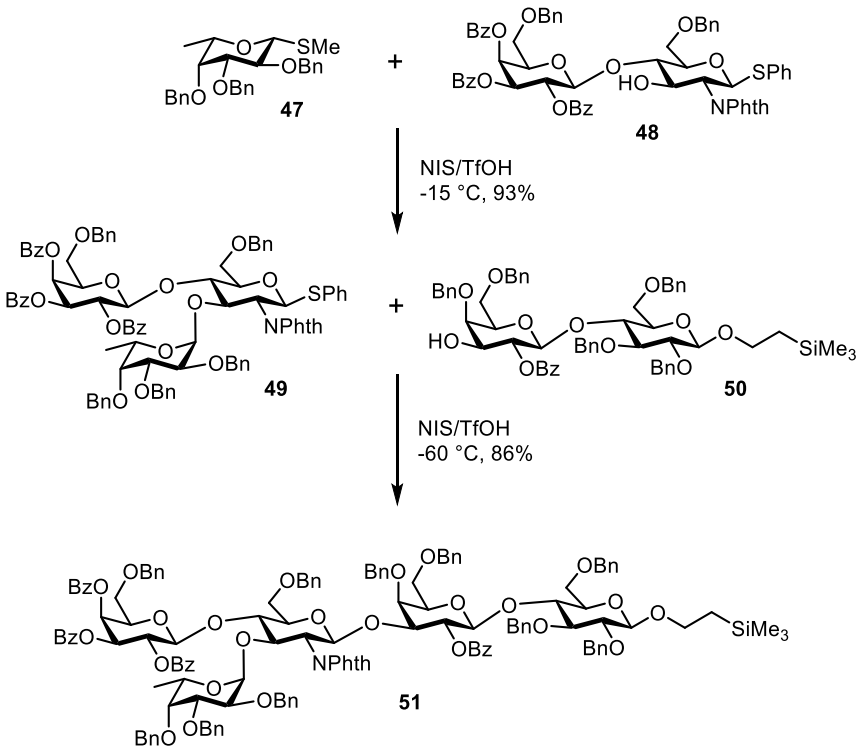
Most thioglycoside activation methodologies developed to date involve the use of thiophilic promoters that can be categorized into the following four major types (Scheme 1.14): (1) metal salts (2) halonium reagents (3) organosulfur reagents (4) single electron transfer approaches. Metal salts were the first class of thiophilic promoters to be described. Common examples in this class include $HgSO_4$, $Hg(OAc)_2$, $HgCl_2$, $Pd(ClO_4)_2$, $Cu(OTf)_2$, AgOTf.[85,89,90] However, heavy metal salts can be hazardous, hygroscopic and/or expensive. This has led to efforts to discover metal-free thioglycoside activators, such as methyl triflate (MeOTf)[91] and phenylselenyl triflate (PhSeOTf)[92] as

alternatives. Nonetheless, these promoters are not without their own faults. For example, methyl triflate has the disadvantage of being highly toxic. In addition, methyl ether formation on the acceptor is a common side reaction. Therefore, there is a continuous search for more potent thiophiles.

Organosulfur reagents have been one the most widely studied class of thiophilic promoters developed to date, as they possess high levels of chemoselectivity toward anomeric thiol groups. Among these, dimethyl(methylthio)sulfonium triflate (DMTST)[93] and benzenesulfinyl piperidine(BSP)-triflic anhydride (Tf_2O) combinations[94] have been regarded as powerful thiophiles that cleanly activate thioglycosides at low temperatures (-78 °C). More recently, minor variations of these approaches have also been devised, such as Ph_2SO/Tf_2O and N-(phenylthio)carpolactam/Tf_2O promoter combinations.[95,96]

Lastly, halonium-based electrophiles have also been shown to exhibit excellent thiophilicity. Pioneering work by Nicolaou[97] demonstrated that NBS is a potent promoter for armed thioglycoside donors. However, this promoter is less effective with disarmed donors. The scope of halonium-based promoter was later significantly expanded through the discovery of NIS/TfOH and iodonium (di-ϒ-collidine) perchlorate (IDCP) by van Boom and coworkers as extremely powerful thiophilic promoters.[98,99]

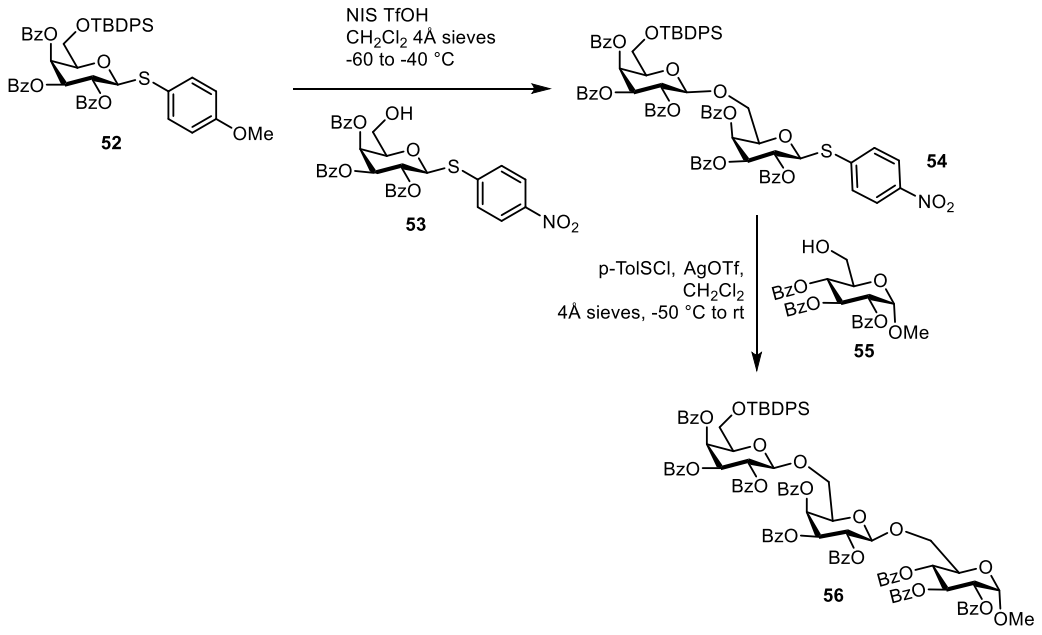
1.3.2: Synthetic applications and Advantages/Disadvantages of Thioglycoside Donors



Scheme 1.15: Iterative chemoselective glycosylation strategies using thioglycosides.[100]

Importantly, the use of thioglycoside coupling partners with distinct reactivities in glycosylations enables chemoselective activation of one desired thioglycoside over the other. This concept was first studied by Ley and coworkers, who quantified the influence of protecting groups and monosaccharide types on the relative reactivities of various ethyl thioglycosides.[101] In 1999, Wong's research group established a comprehensive database of the relative reactivity value (RRV) for commonly used mono- and disaccharide thiocresol analogs.[102] For example, the RRV of

perbenzylated glucose thiocresol was determined to be 2656 (relative to peracetylated mannose thiocresol, RRV = 1.0), and can be activated in the presence of its peracetylated counterpart (RRV = 2.7). This concept later permits the applications of thioglycoside building blocks in iterative, chemoselective oligosaccharide synthesis.[103-106] An example demonstrating these approaches can be illustrated with Scheme 1.15,[100] where the chemoselective coupling between disarmed thioglycoside acceptor **48** and armed thioglycoside donor **47** could be achieved to afford trisaccharide **49**. This product, which contained an unreacted anomeric thiol protecting group, could be directly used as the glycosyl donor in subsequent glycosylations, ultimately leading to the assembly of pentasaccharide **51**.

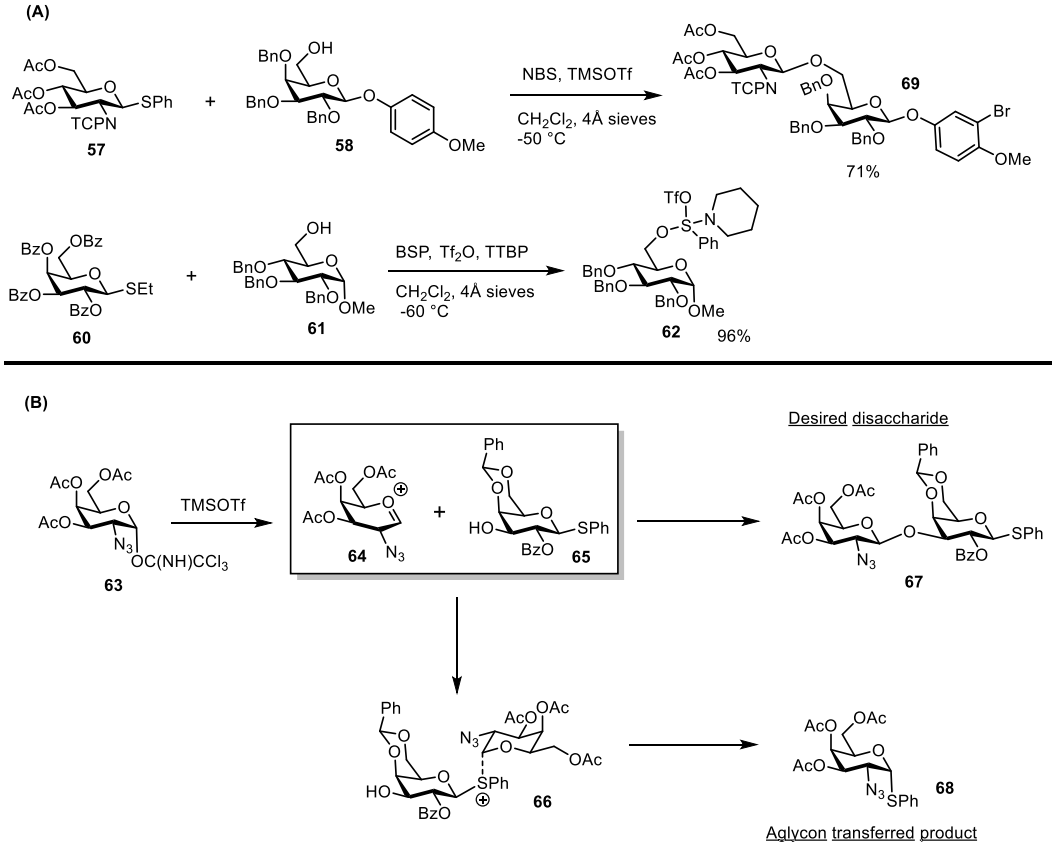


Scheme 1.16: "Active-Latent" oligosaccharide assembly strategy.[107,108]

Another useful aspect of thioglycosides is that the anomeric thiol aglycon provides an additional handle to fine-tune reactivity. An elegant example of this can be seen in the work by Roy *et al*., where they demonstrated the "active-latent" thioglycoside methodology (Scheme 1.16).[109] Here, the inherent differences in thioglycoside reactivity were achieved through manipulating the electronics of the aglycon. Specifically, electron-rich *p*-methoxyphenylthio donor **52** and the electron-deficient p-nitrophenylthio acceptor **53** were chemoselectively coupled with standard NIS/TfOH activations, affording disaccharide **54**. This disarmed disaccharide donor **54**, while unreactive toward mild thiophilic reagents such as NIS/TfOH, could be effectively activated by p-tolenesulfenyl triflate (p-TolSOTf) to afford trisaccharide **56** upon glycosylation with **55**. Furthermore, postglycosylation modifications have also been described by Huang and coworkers, significantly expanding the synthetic utility of this strategy. [107,108] In these cases, $SnCl_2$-mediated reduction of the nitroarene was first conducted, which was followed by approaches such as diazotization and reductive amination to further convert the latent *p*-nitrophenylthio aglycon into more reactive counterparts.

Despite being synthetically versatile, thioglycoside donors still come with notable disadvantages. The first major type of which is associated with the need for stoichiometric amounts of thiophilic promoters in most activation procedures. The highly electrophilic nature of these thiophilic promoters has been demonstrated to be detrimental to the glycosylations by introducing unwanted side-reactions on the coupling partners (Scheme 1.17A).[110,111] In

addition, due to the inherent nucleophilicity of the thiol groups, intermolecular aglycon exchange is also commonly observed (Scheme 1.17B).[112,113] Due to the attractive properties exhibited by thioglycosides as glycosyl donors, we were particularly interested in designing improved thioglycoside glycosylation procedures. Specifically, we approached this with the aim to tackle common deficiencies in current methods mentioned above. Accordingly, the collective studies toward the pursuit of mild, chemo- and stereoselective glycosylations using thioglycoside donors will be the focus of this thesis work in the following chapters.



Scheme 1.17: Common drawbacks of thioglycoside building blocks.

Chapter 2:

Directing-Group Free Stereoselective Synthesis of 1,2-*cis*-α Glycosidic Linkages.

2.1: Background introduction on 1,2-*cis*-α glycosides: Biological Relevance and Synthetic Challenges

The majority of naturally occurring glycoconjugates contain monosaccharide residues linked together by a variety of *O*-glycosidic linkages, which can be broadly defined as either 1,2-*cis* or 1,2-*trans* type *O*-glycosides (Figure 2.1). While both of these linkage types are medicinally important motifs, inherent challenges in accessing 1,2-*cis*-containing glycosides make them particularly appealing synthetic targets. Unlike 1,2-*trans*-β-glycosides, where the selectivity can be reliably achieved by neighboring acyl group participations (Scheme 2.1A), 1,2-*cis*-a glycoside synthesis typically involves the use of non-participating groups (Scheme 2.1B). Consequently, anomeric mixtures are generally afforded as most glycosylation reactions proceed through S_N1 manifolds. As a result, efforts toward 1,2-*cis* glycosylations have been a research area of intense focus in the past two decades.[114-116] Furthermore, as 1,2-*cis*-α linkages are prevalent motifs in bacteria (Fig 2.2),[117] facile synthetic routes toward these structural features are particularly critical for applications in vaccine development (**76-77**)[23,117,118] and adjuvant (**75**)[119] design.

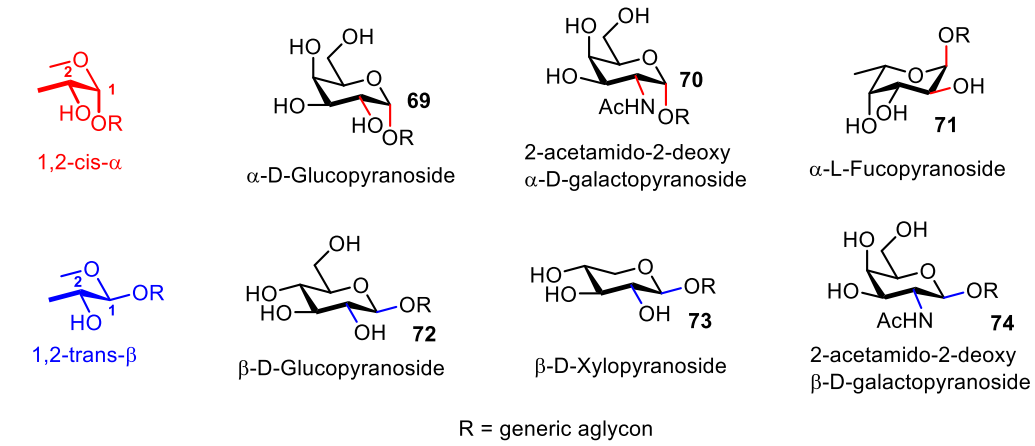
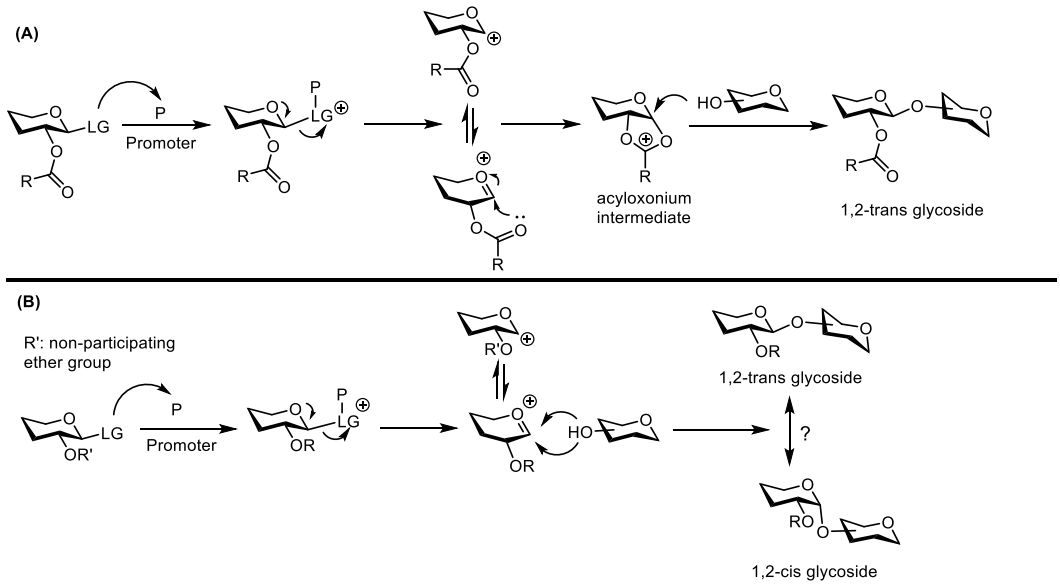


Figure 2.1: Classification of common naturally occurring *O*-glycosides.



Scheme 2.1: Activation pathways leading to glycosidic bond formations with or without the presence of neighboring acyl participating groups.

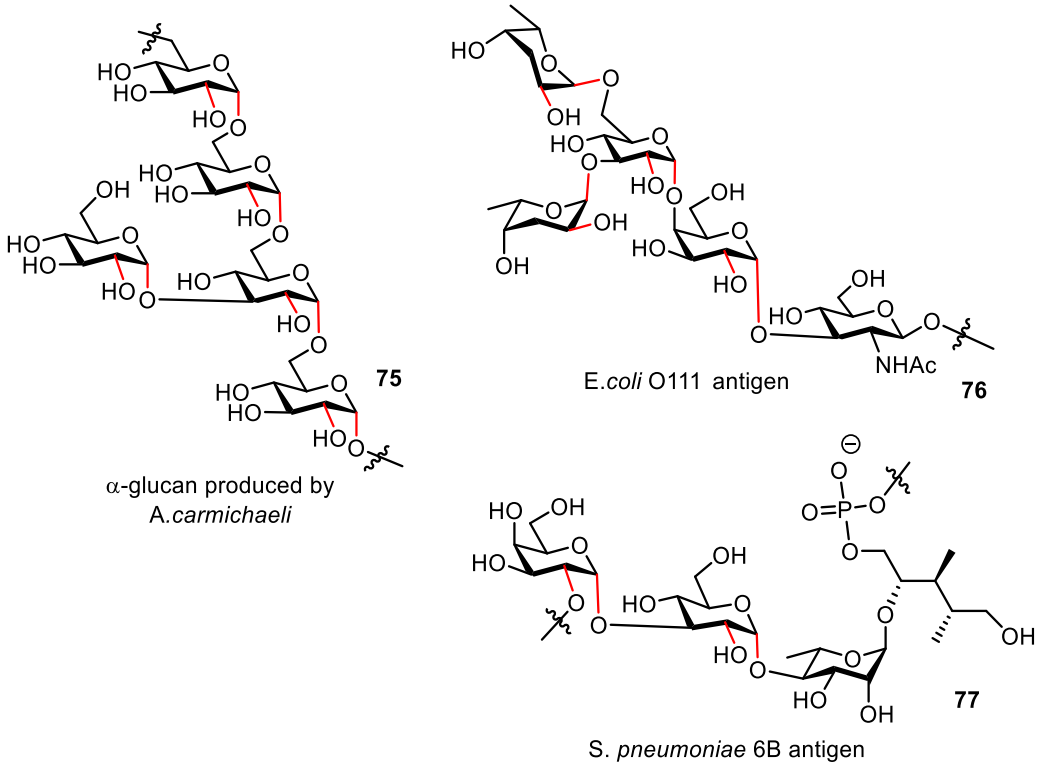


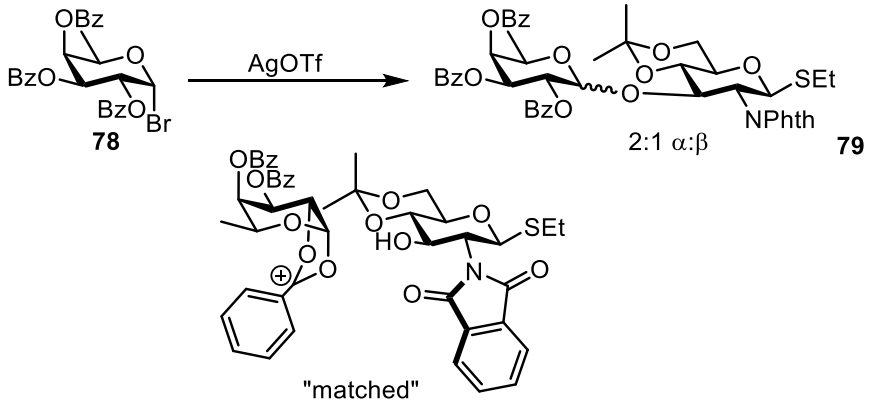
Figure 2.2: Examples of 1,2-*cis*-α glycosidic linkages found in pathogens.

While carbohydrates are historically considered to be T-cell dependent antigens with poor immunogenicity,[120] advances in the accompanying conjugation technologies have re-highlighted the potential of carbohydrate-based vaccines.[23,121-127] Since the 1980s, numerous polysaccharide conjugate vaccines have been successfully developed. This includes, but is not limited to, *Haemophilus influenza* type b (Hib),[128] *Neisseria meningitides* and *Streptococcus pneumoniae*.[129] However, since these carbohydrate antigens typically contain complex structures that exist in heterogeneous forms, concerns with batch-to-batch variability highlighted the need for synthetic homogenous vaccine alternatives. While rapid advancements have been made

toward improved conjugation strategies, carriers[130] and adjuvant formulations,[131] synthetic preparation of the actual glycan remains the bottleneck in the construction of homogeneous vaccines. In this regard, poor stereoselectivity in the construction of glycosides necessarily requires tedious purification of anomeric mixtures. This severely limits the overall synthetic efficiency, and the application in multistep one-pot procedures toward complex carbohydrate synthesis. This chapter will begin with a short review of the various contemporary synthetic approaches toward 1,2-*cis* α-selective chemical glycosylations, followed by my own contributions from this dissertation.

2.2: Current approaches toward stereoselective construction of 1,2-*cis*-α glycosides

2.2.1: Use of stereodirecting groups and conformationally strained glycosyl donors.

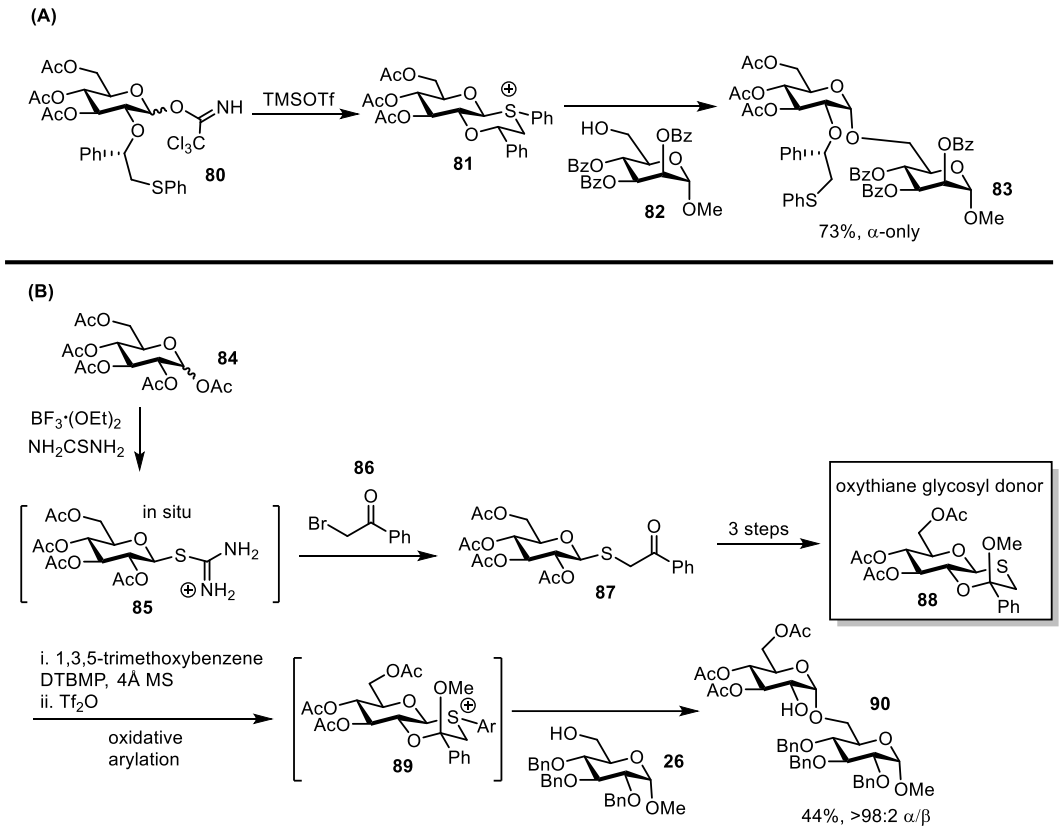


Scheme 2.2: Matching the protecting group patterns on the donor and acceptor pairs can lead to stereoselective glycosylations.[132]

Early synthetic efforts toward *O*-1,2-*cis*-α gluco- and galactopyranosides synthesis mostly relied on extensive protecting group manipulations in order to match the donor and acceptor's intrinsic reactivity and stereochemical preference (Scheme 2.2).[132] However, recent years have seen the development of rational approaches to stereoselective 1,2-*cis*-α glycosylation strategies. One approach involves using "stereodirecting" groups that are pre-installed on the glycosyl donor to control selectivity. An example of this approach is the work by Boons and coworkers who demonstrated that installing a chiral auxiliary at the C-2 position can provide selective access to 1,2-*cis*-*a* glycosides (Scheme 2.3A).[133-135] The key to obtaining α-stereoselectivity here lies in the transient formation of the anomeric trans-decalin β-sulfonium intermediate **81** upon activation of donor **80**. Stereoinversion of **81** with nucleophile **82** then leads to the formation of α-glycoside **83**. Further application of this strategy in solid-supported synthesis of 1,2-*cis*-α-linked glucans was also later demonstrated by this group.[133] This approach, however, requires first the synthetic preparation of the enantiomeric pure thiophenylbenzyl ether auxiliaries. In addition, these sulfanyl ether groups are acid-labile, which can often be problematic during further protecting group manipulations.[136]

Inspired by the Boons approach, a modified method was later proposed by Turnbull and coworkers. Specifically, stable oxathiane **88,** which was synthesized in 3 steps from thioglycoside precursor **87,** was examined as a novel class of glycosyl donor (Scheme 2.3B).[137,138] Subsequent oxidative

arylation then generated the bicyclic sulfonium ion **89** *in situ*, which directly reacted with acceptor **26** to afford high α-selectivity (>98:2 α:β).



Scheme 2.3: Directing group-assisted 1,2-*cis*-α-selective glycosylation strategies demonstrated by Boons and Turnbull.[135,137]

Aside from these investigations on C-2 directing groups, stereodirecting groups located at remote positions[139,140] have also been invoked to promote α-selectivity (Figure 2.3A). Notably, Demchenko and coworkers have demonstrated a hydrogen-bond-mediated aglycon delivery approach to achieve 1,2-*cis*-α-glycosylations with high stereocontrol (Figure

2.3B).[140] Not being able to directly participate at the anomeric center, the remote picoloyl nitrogen atom on **93** instead formed a hydrogen bond with the incoming nucleophile. As a result, high facial selectivity, typically *syn* with respect to the picoloyl groups, was observed. This approach was particularly effective with *S*-ethyl glycosyl donors in high-dilution and low temperature conditions. However, the use of other leaving groups, such as *S*-phenyl or trichloroacetimidates, led to much lower stereoselectivity.[141]

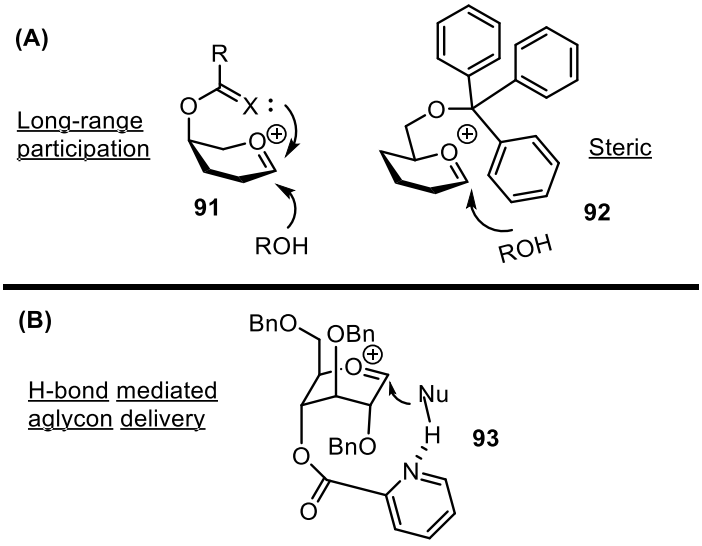
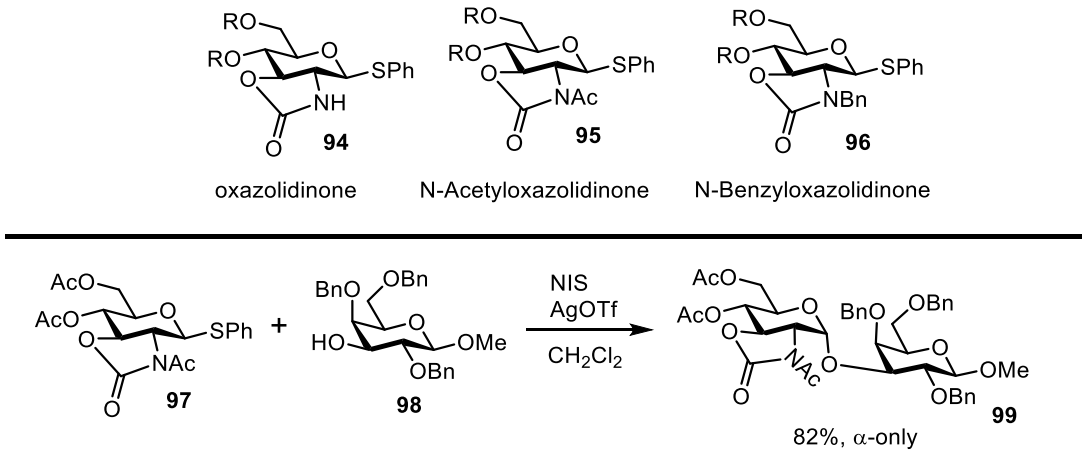


Figure 2.3: Remote directing groups to promote 1,2-*cis*-α-selectivity.

Another method for the stereoselective synthesis of 1,2-*cis*-α-glycosides involves the use of cyclic protecting groups and/or conformationally strained glycosyl donors (Scheme 2.4). Pioneering work by Kerns[142] showed that the non-participating 2,3-trans-oxazolidinone can favor high levels of 1,2-*cis* selectivities when installed on 2-deoxy-2-amino

glucopyranosides. However, glycosyl donors such as **94** often exhibited unwanted side reactions such as N-glycosylations, leading to the later development of N-acyl (**95**) and N-benzyl (**96**) derivatives by Oscarson[143] and Ito,[144,145] respectively. In these approaches, the stereoselectivity is thought to arise through an *in situ* anomerization of the initial products to afford the thermodynamic α-glycosides.



Scheme 2.4: Examples of conformationally-strained α-directing groups.

Also another example of constrained glycosyl donors can be seen with the use of 4-6-*O*-benzylidene acetal protecting groups (Figure 2.4). Fraser-Reid first demonstrated the disarming effects of these strained protecting groups.[146,147] Crich and coworkers further showed that 4-6-*O*-benzylidene protected manno- and glucopyranose derivatives undergo glycosylations with BSP/Tf_2O activations to afford 1,2-*cis*-lined products.[148,149] The roles of the benzylidene acetal in establishing stereoselectivity were later explained by Bols and coworkers.[150] In essence these groups lock the *C*-6-*O*-6 bond

antiperiplanar to the *C*-5-*O*-5 bond, which in turn maximizes the electron-withdrawing effects of the *O*-6 atom on the oxocarbenium ion (Figure 2.4). In the mannose series, this phenomenon effectively shifts the equilibrium toward the covalent or tight ion-pair anomeric triflate species (see Scheme 1.2), thereby establishing 1,2-*cis*-β stereoselectivity. On the other hand, using 4,6-*O*-benzylidene-protected glucose donors in glycosylation proceeds to give modest 1,2-*cis*-α-selectivity. Crich *et al*. later proposed that in the glucose series, the torsional angle around the *O*-2-*C*-2 and *O*-3-*C*-2 bonds opens up during the transition from covalent triflate to oxocarbenium ion species. Therefore, unlike in the mannose series, a small shift in the equilibrium away from glycosyl triflate is expected in benzylidene-protected glucose donors. This in turn results in the accumulation of sufficiently concentrated free solvent-separated oxocarbenium ion pair species (SSIP) for it to dominate in the following α-selective glycosylation.[151]

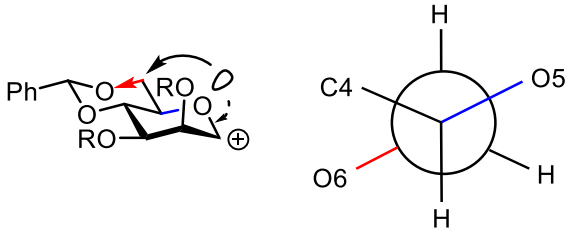
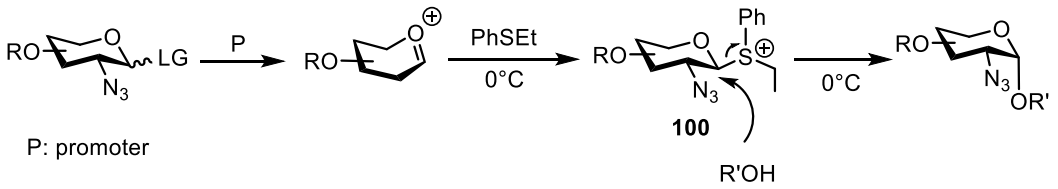


Figure 2.4: Benzylidene acetals and their proposed effects in stereoselectivity.

2.2.2: Additive participation and leaving group strategies

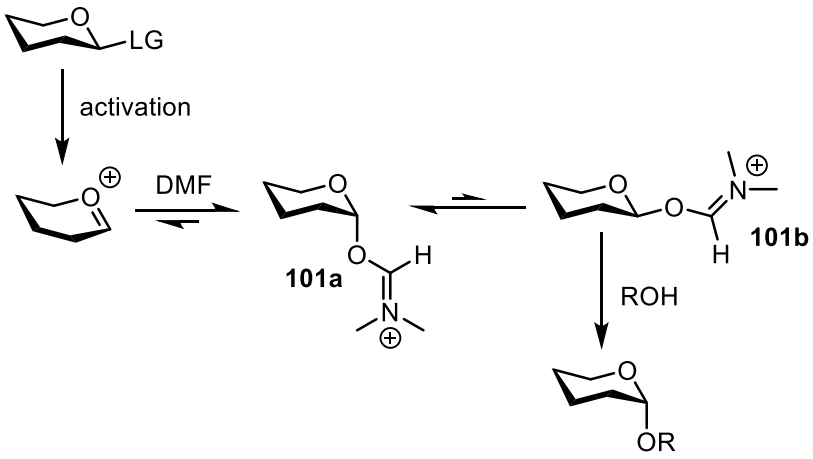
The 1,2-*cis*-α-selective approaches mentioned above, although effective, inevitably require special protecting group manipulations for both

the monosaccharide coupling partners. This in turn significantly increases the time-burden associated with their synthesis. Furthermore, additional protecting group manipulations, such as reductive openings of the pre-installed acetals, are often not compatible with technologies for automated synthetic platforms.[152] In this regard, additive and leaving group strategies serve as appealing alternatives, as in principle they do not rely on the presence of specific directing groups. An example of this approach can be seen in the thiophene/thioether-controlled α-selective glycosylation demonstrated by Boons and coworkers (Scheme 2.5).[153] Mechanistically analogous to their previous strategy (Scheme 2.3),[134,135] β-anomeric sulfonium intermediate **100** was invoked as the reactive glycosylating agent. In these examples, steric effects were invoked to account for the favored formation of β-sulfonium species prior to the nucleophilic attack. Although in theory the α-directing effects here are derived from the participation of thioether additives, the stereochemical outcome is nonetheless still largely dependent on the protecting group patterns. For example, arming donors with benzyl ether-type protecting groups are not compatible with this methodology, and only resulted in non-selective glycosylation reactions.[153]



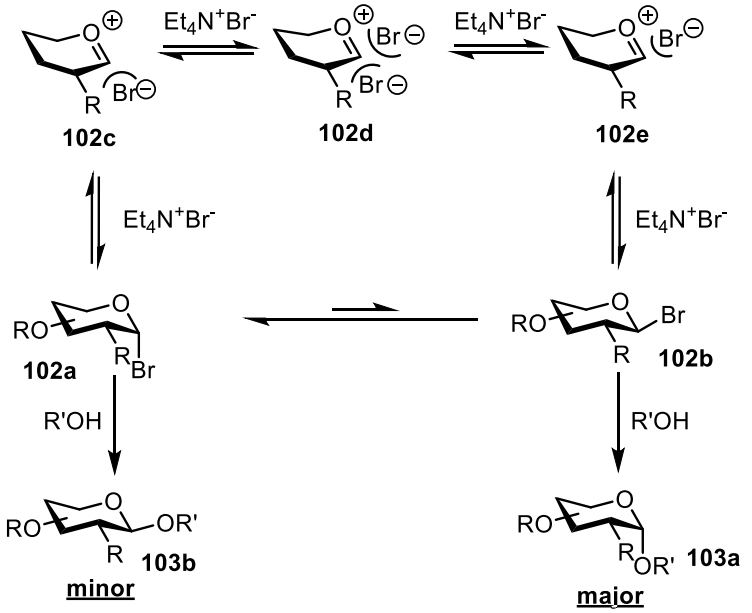
Scheme 2.5: Thioether additive-promoted α-selective glycosylation.[153]

In addition, N,N-dimethylformamide (DMF) has also been shown to possess α-directing effects as a participating co-solvent. DMF has previously been utilized in numerous literature precedent as reaction solvents for chemical glycosylations.[154,155] Importantly, in 1984 Koto *et al*. reported the α-directing effects of DMF and N,N-dimethylacetamide as additives in glycosylations,[156] and further applied these approaches in the synthesis of various α-linked oligosaccharides.[157-161] The origin for stereoselectivity was not discussed in detail, although they hypothesized the transient formation of β-glycosyl imidates as reactive intermediates in these reactions based on the earlier work by Dourtoglou et al.[162] Recently, Mong and coworkers used NMR to further validate this mechanistic role of DMF (Scheme 2.6).[163] Using a pre-activation procedure of thioglycoside donors by NIS/TMSOTf in the presence of DMF at -15 °C, they were able to first observe the formation of glycosyl imidate **101a** after 90 mins. However, the assumed reactive intermediate **101b** was not detectable within these experiments. They accordingly proposed a model which suggests that the nucleophilic trapping of oxocarbenium ions by DMF first leads to the formation of glycosyl imidate **101a**, which is followed by a rapid equilibrium between **101a/b** under reaction conditions. Although **101a** presumably exists as the major anomer, the higher reactivity of **101b** dictates the final α-selectivity.

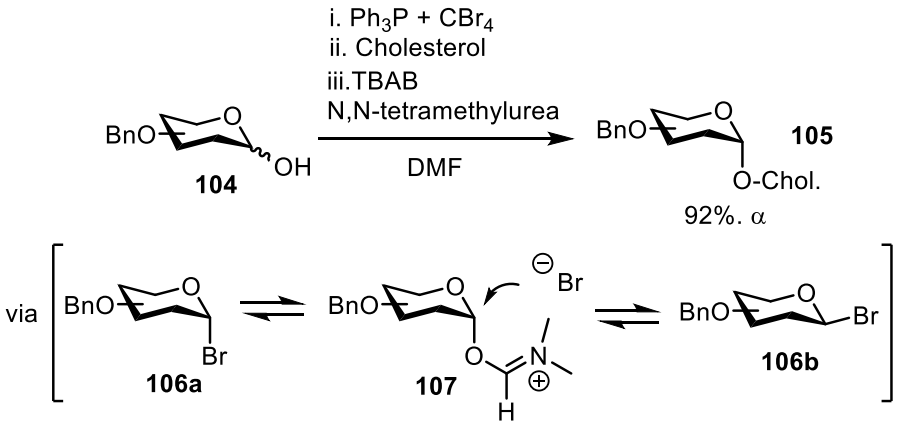


Scheme 2.6: α-directing effects of DMF proposed by Mong and colleagues.[163]

Unlike the examples above, glycosylations with glycosyl halides offer a unique opportunity where the desired 1,2-*cis*-α-selectivity can be obtained by subjecting the anomeric halide to *in situ* anomerization. Since the pioneering series of investigations by Lemieux in 1975,[64] it is now well recognized that a rapid equilibrium between the α- and β-glycosyl bromides can be achieved in the presence of exogenous halide ions (Scheme 2.7). Due to the inherent differences in receiving anomeric stabilization, the β-glycosyl halides **102b** are expected to possess far superior reactivity than their α-counterpart **102a**. As a result**,** pathways leading to **103a** are dominant, whereas there is a higher energy barrier for the transformation from **102a** to **103b**.



Scheme 2.7: General mechanistic pathway of halide ion-promoted *in situ* anomerization and the following α-selective glycosylations.



Scheme 2.8: Dehydrative α-glycosylation approach using Appel agents and tetrabutylammonium bromide (TBAB) by Nishida *et al.*[154]

As a result, halide ion-promoted glycosylations represent an intriguing type of directing group-free stereoselective glycosylation strategy. The

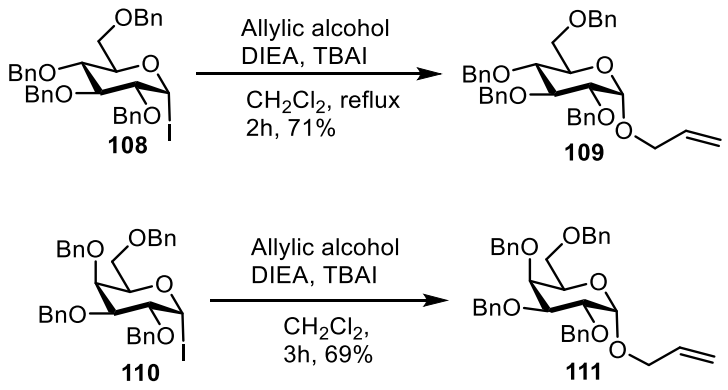
principles derived from which continue to be further elaborated, one example includes the recent work by Demchenko and colleagues.[164] Here they demonstrated that the activation of superdisarmed thioglycoside donors with molecular bromine generated β-glycosyl bromides, which subsequently reacted with nucleophiles to afford exclusive formation of α-glycosides. However, competing *in situ* anomerization from the β-bromide to the unreactive *a*-bromide was also observed, which resulted in reduced yields. Another approach taking advantage of this concept can be seen in the works by Nishida *et al.*, in which they demonstrated α-selective dehydrative glycosylation reactions using Appel agents (Scheme 2.8).[154,165] Similarly, the initial formation of α-glycosyl bromide **106a** upon donor activation was invoked. The following *in situ* anomerization between glycosyl bromides **106a/b** in DMF, presumably via nucleophilic displacement of the glycosyl imidate intermediate **107** by TBAB (tetrabutylammonium bromide), lastly led to the selective formation of α-glycosidic linkages.

2.3: Ph_2SO/Tf_2O/TBAI-promoted glycosylations: Toward the Design of Directing group-Free Stereoselective Synthesis of 1,2-*cis* α glycosides

2.3.1: Background Rationale of Methodology Development

In line with the discussions from above, we were very interested in pursuing efficient glycosylation approaches that afford high levels of 1,2-*cis*-α stereoselectivity in the absence of stereodirecting groups. In this regard, the Lemieux-type glycosylation strategies serve as an appealing platform.

However, the original approach is not without synthetic deficiencies. Halide-ion promoted glycosylations of glycosyl bromides and chlorides are typically sluggish, often taking days to complete.[164] Recently, comprehensive efforts by Gervay-Hague and colleagues in glycosyl iodide studies greatly improved this issue. They first demonstrated an extension of the Thiem-Meyer approach toward the synthesis of armed glycosyl iodides (see Scheme 1.8), thereby allowing the subsequent synthesis of 1,2-*cis*-α glycosides that was not previously applicable to their peracetylated counterparts. They next showed that the use of these reactive donors in combination with tetrabutylammonium iodide (TBAI) effectively reduced the overall reaction time to several hours, while still affording highly α-selective glycosylations (Scheme 2.9).[65,166-168]



Scheme 2.9: TBAI-promoted α-glycosylations using glycosyl iodide donors.[168]

However, glycosyl iodides are often regarded as undesirable building blocks owing to their aforementioned instability and limited shelf-life. While

peracetylated glycosyl iodides have previously been isolated by numerous procedures, such as HI/acetic acid or a Finkelstein-type exchange between glycosyl bromide and sodium iodide in acetone,[58,169] armed glycosyl iodides typically need to be generated and used immediately in subsequent glycosylation reactions.[57,170,171] In addition, these procedures often require the use of harsh Lewis acidic conditions and highly labile reagents, such as anhydrous hydrogen iodide,[172] trimethylsilyl iodide (TMSI)[61] and 2,6-di-tert-butylpyridinium iodide (DTBPI),[171] severely limiting their synthetic utility with acid-sensitive substrates.

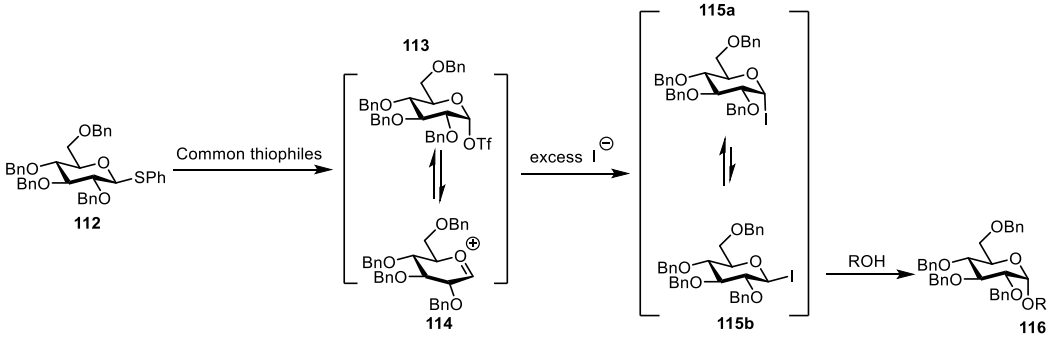
Consequently, in our pursuit of an improved directing group-free stereoselective glycosylation methodology, we decided to first address the important possibility of achieving a new pathway to generate glycosyl iodide species *in situ* from stable glycosyl donors under mild reaction conditions. The successful execution of which can then be followed by subsequent Lemieux-type α-selective glycosylation schemes. As thioglycosides possess the ideal balance between shelf stability and tunable reactivity as glycosylation building blocks, we sought to first examine this potential pathway, using thioglycosides as model glycosyl donors.

2.3.2: Preliminary reaction investigation and optimization

In our previously reported work with cyclopropenium cation-promoted glycosylations,[75,76] we investigated the *in situ* generation of glycosyl iodides from 2-deoxy hemiacetals. These studies demonstrated that it was

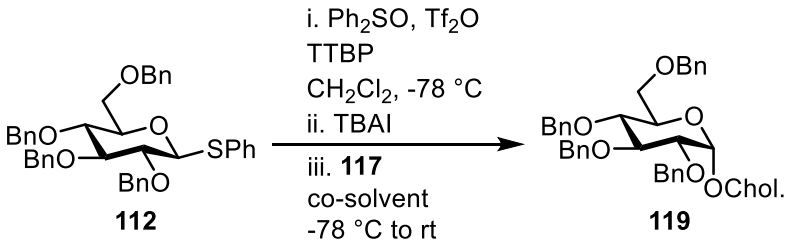
possible to convert a shelf-stable glycosyl donor into a glycosyl halide for subsequent glycosylations. Attempts to extend this methodology to fully-substituted donors revealed that this promoter system is incapable of activating hemiacetals or thioglycosides with oxygenation at C-2.

As illustrated below in Scheme 2.10, many of the commonly employed thioglycoside promoters convert the donor into glycosyl triflate **113**, which are proposed to exist in rapid equilibrium with the oxocarbenium ion species **114**. Based on this, we hypothesized an alternative role of the exogenous nucleophilic iodides. Although traditionally used to promote the *in situ* anomerization of the *pre-generated* glycosyl iodides, we envisioned that they can instead be utilized to trap the electrophilic species **113/114** immediately after formed, thereby converting them into the corresponding glycosyl iodides **115a/b** *in situ*. The presence of excess iodides can also further promote the *in situ* anomerization between **115a/b**, leading to the following α-selective glycosylations.



Scheme 2.10: Mechanistic rationale for the *in situ* generation of glycosyl iodides from stable thioglycoside donors.

To investigate this idea, a preliminary screen was conducted to assess the compatibility of the exogenous iodide source TBAI with a series of thiophilic promoter system. After observing no reaction progression in several initial promoters examined, including Ph_2SO and/or BSP in combinations with mesic anhydride (Me_2O), tosic anhydride (Ts_2O) and tosyl nitroimidizaole, we arrived at a preliminary success using a combination of Ph_2SO, Tf_2O and TBAI. Under these conditions the stable thioglycoside donor **112** was first activated with the Ph_2SO/Tf_2O promoter system[96] at -78 °C. After stirring for 5 mins, the reaction was treated with 3 equiv. of TBAI as the excess iodide source. Upon addition of a slight excess of the model acceptor cholesterol (**117**), we were pleased to see that this activation sequence led to a significant reversal in stereoselectivity, compared to when the activation was performed with Ph_2SO/Tf_2O alone (Table 2.1, entry 1 vs 2). Importantly, 3 equiv. of the non-nucleophilic base 2,4,6-Tri-*tert*-butyl pyrimidine (TTBP, **118**) was added in these reactions as an acid scavenger,[94] eliminating the possibility that the observed α-selectivity was instead a result of the triflic acid-promoted *in situ* anomerization of the glycoside products.



Entry	TBAI (eq)	co-solvent	Sieves	Yield (%)	α : β
1	0	none	none	85	1 : 3
2	3	none	none	68	2.5 : 1
3	3	Et_2O	none	62	3.3 : 1
4	3	1,4-dioxane	none	58	5.2 : 1
5	3	1,4-dioxane	4Å	83	7.7 : 1
6	3	THF	4Å	62	7.1 : 1
7	3	1,4-dioxane	5Å	75	6.6 : 1
8	0	1,4-dioxane	4Å	56	1 : 1.2
9[a]	3	1,4-dioxane	4Å	70	1.3 : 1

a. 1-benzene sulfinylpiperidine (BSP) used in place of Ph_2SO

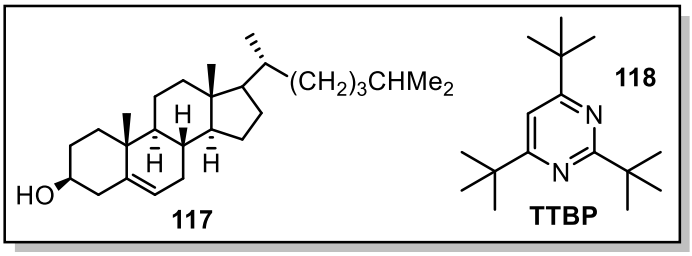


Table 2.1: Preliminary optimizations of the Ph_2SO/Tf_2O/TBAI methodology.

The preferred formation of α-glycosides here indicated that we were indeed generating the active glycosyl iodide intermediates *in situ* which, under iodide-ion conditions, then underwent Lemieux-type α-glycosylations. In light of this, we sought to further optimize this reaction methodology, in terms of both yield and selectivity. The first issue we addressed was the low α-selectivity, as only a modest ratio favoring α-anomer (2.5:1) was observed in

our preliminary success. We speculated that the low stereoselectivity here may be explained by the background glycosylation pathways involving oxocarbenium species, which is expected to lead to scrambling of the pre-set α-selectivity. In light of this, we decided to further explore the "ether effects". In brief, ethereal solvents, such as diethyl ether, dioxane and tetrahydrofuran have been documented with their ability to promote 1,2-*cis*-α selective glycosylations.[173,174] The effects exhibited by these ether solvents presumably act through their preferred coordination with oxocarbenium ions to form equatorial oxonium intermediates (Figure 2.5), which have been proposed to be a result of the reverse anomeric effect.[175] We therefore reasoned that these ether participation effects could effectively improve the modest α-selectivity previously obtained in our reaction methodology.

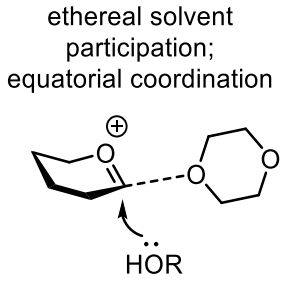


Figure 2.5: Schematic representation of ether-promoted α-stereoselectivity.

As shown in Table 2.1, both the use of diethyl ether and dioxane as co-solvent additives indeed led to improved α-selectivities, with the effect exerted by dioxane being more significant (entry 3 vs 4). Further effort to

optimize the reaction yield was attempted with activated molecular sieves, as they are commonly employed drying agents in chemical glycosylation reactions to prevent competing hydrolysis. Furthermore, the presence of molecular sieves with varying zeolite composition and hydration levels has been documented by Posner and Bull in 1996 to impact the stereochemical outcome of chemical glycosylations.[176] This phenomenon was also further supported in the later report by Demchenko and Boons.[174]

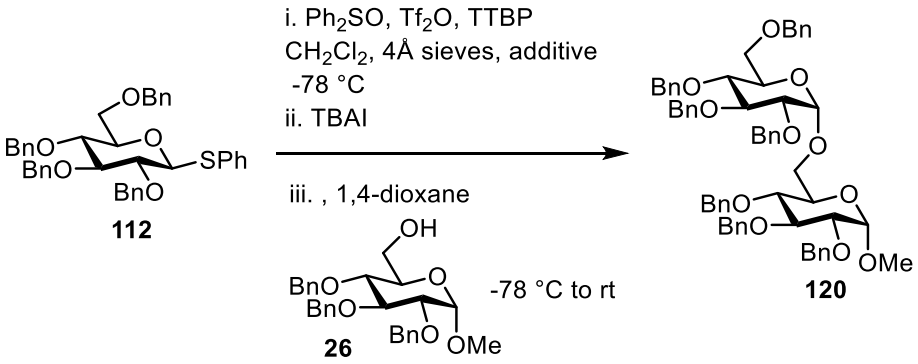
After further condition optimizations, we were able to arrive at the additive combination of 1,4-dioxane and 4Å molecular sieves to promote optimal levels of α-selectivity and reaction yield (Table 2.1, entry 5). Lastly, to rule out the possibility that the stereoselectivity was due chiefly to the additive effects, we performed a control reaction without TBAI under otherwise optimized reaction condition. This reaction was nonselective (1:1.2 α:β, Table, entry 8), clearly demonstrating the critical importance of the iodide source in dictating α-selectivity.

Interestingly, the nature of the promoter system also seemed to be critical for stereoselectivity. For example, a significant loss of α-selectivity was observed when the BSP/Tf_2O activation system was used under otherwise identical reaction sequence (Table 2.1, entry 9). While the exact reason behind this is yet unclear, we hypothesized that in this case incomplete donor activation at low temperature potentially resulted in significant amounts of remaining glycosyl triflate at the time of acceptor **117** addition. As shown above in Scheme 1.2, these armed glycosyl triflate species were expected to

exist in equilibrium with the oxocarbenium ions, thereby resulting in the erosion of stereoselectivity.

2.3.3: Further Reaction Optimizations with Thioscavengers Inspired by the Discovery of Thioglycoside Donor Regeneration

After the preliminary success summarized above, we next turned our attention to investigate the reaction scope with other glycosyl acceptors. An initial experiment with unhindered primary alcohol **26** resulted in highly α-selective glycosylation, albeit in modest yield (Table 2.2, entry 2, 72 %, 11:1 α:β). However, we found that at the end of the reaction in addition to disaccharide **120** there were significant amounts of remaining thioglycoside donor **112**. This is rather surprising, since in our hands complete donor consumption was typically observed within 3 minutes upon Tf_2O treatment. More interestingly, while the use of a large excess of TBAI led to higher α-selectivity, it also correlated with higher amounts of donor remaining at the conclusion of the reaction (Table 2.2, entry 1-3). Intrigued by this observation, we hypothesized that the excess iodide ions in fact promoted a yet unclear competing pathway that effectively led to regeneration of the thioglycoside donor throughout the course of the reaction.

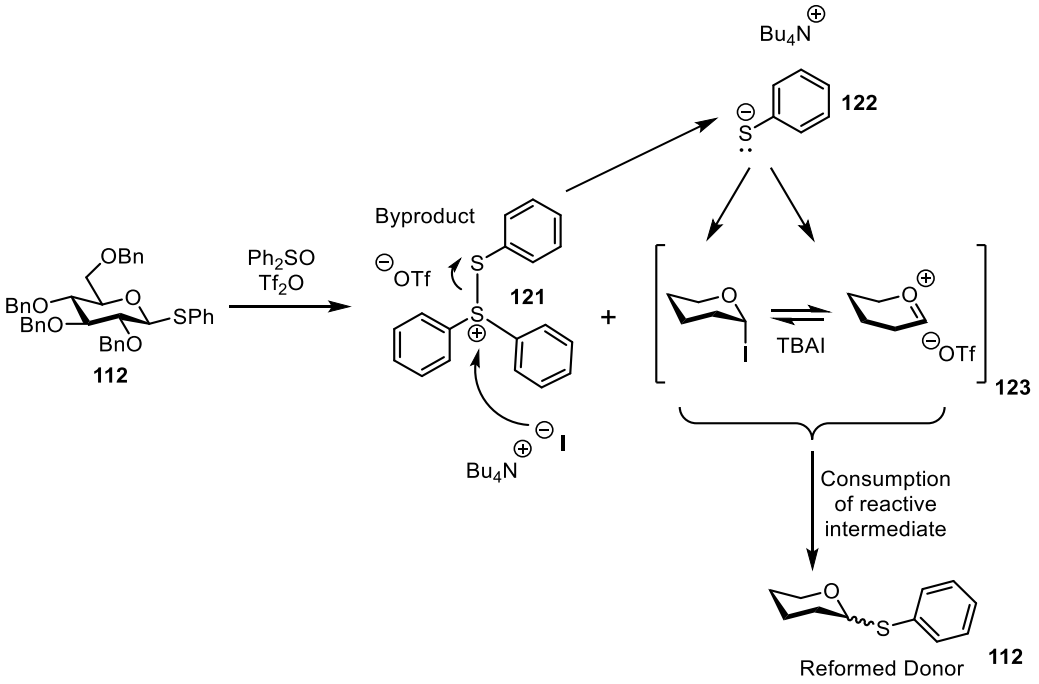


Entry	TBAI (equiv.)	Additive	Yield (%)	α : β
1	2	-	89	4 : 1
2	3	-	72	11 : 1
3	5	-	62	α only
4	5	*N*-methyl maleimide (1.5 equiv.)	87	18 : 1

Table 2.2: Effects of TBAI equivalences and *N*-methyl maleimide.

In order to further validate this hypothesis, we performed a test experiment where the thioglycoside donor was pre-activated with the Ph_2O/Tf_2O/TBAI promoter sequence (5 equiv. of TBAI) in the absence of nucleophilic acceptors, and later followed the reaction course by TLC. With this approach, we were able to observe that while donor consumption at -78 °C was indeed rapid and complete, it was nonetheless slowly regenerated 15 minutes after the addition of TBAI. To account for this unexpected discovery, we hypothesized a competing pathway as illustrated below in Scheme 2.11. In brief, we posited that the excess iodide, instead of trapping the glycosyl triflate/oxocarbenium species, prematurely reacted with the electrophilic byproduct **121** and generated phenyl thiolate **122**. Subsequent nucleophilic

reactions between **122** and **123** therefore regenerated thioglycoside donor **112**, which after consumption of the Tf_2O was essentially inert.

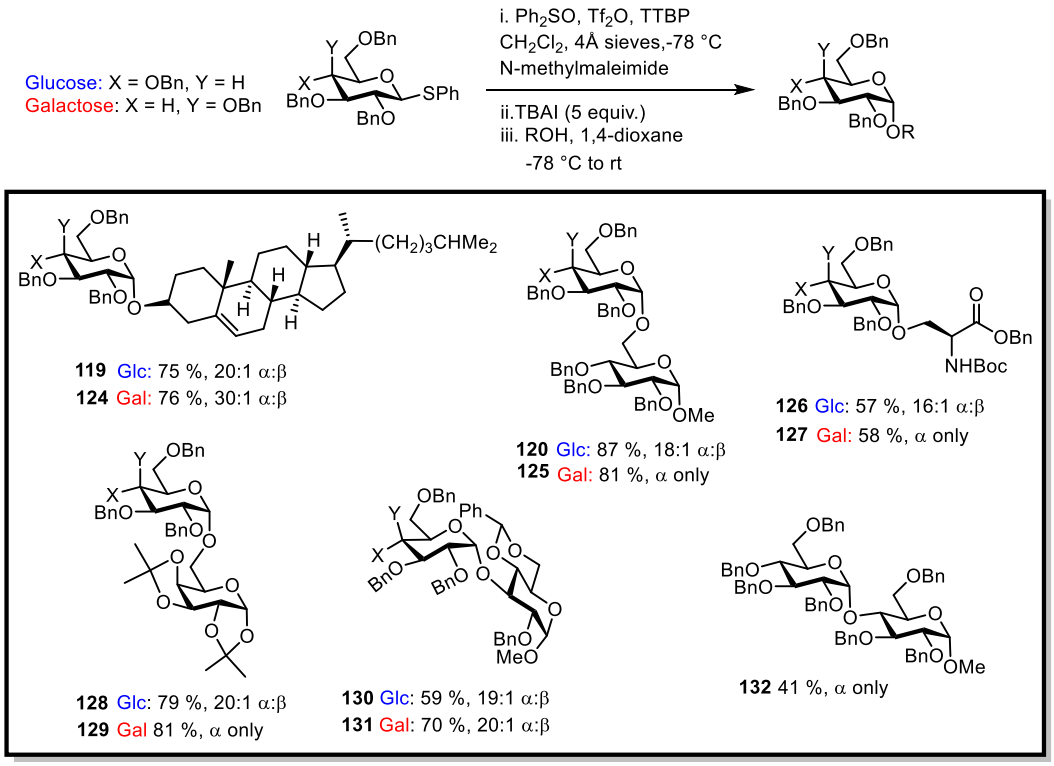


Scheme 2.11: Proposed mechanistic pathways leading to donor reformation.

Realizing this, we reasoned that the presence of a thiol scavenger in the reaction should reduce this undesired competing pathway. This would then allow us to use a large excess of TBAI (5 equiv.) to promote α-selectivity without compromising the reaction yield. To this end, we were delighted to see that the addition of 1.5 equiv. of *N*-methylmaleimide, a Michael acceptor-type thiol scavenger,[177] rescued the overall yield while maintaining excellent stereoselectivity (87%, 18:1 α:β, Table 2.2, entry 4). In summary, we have

developed here an improved modification of our earlier reaction conditions with the implementation of *N*-methylmaleimide thioscavenger.

2.3.4: Substrate Scope Investigation



Scheme 2.12: Substrate scope of 1,2-*cis*-α glycosides examined in this study.

With the modified optimal procedure now in hand, we aimed to further expand the synthetic scope to various 1,2-*cis*-α linked glycosides. As shown in Scheme 2.12, both galactose and glucose thioglycoside donors reacted with a wide range of alcohol acceptors to consistently afford excellent α-stereoselectivity, again suggesting a S_N2-based stereoinversion model of this α-selective glycosylation. This scope first included a re-examination of

cholesterol as a model small molecule acceptor, which under the optimal conditions (5 equiv. of TBAI, *N*-methyl maleimide) reacted with the donor to afford the product with dramatically improved α-selectivity (Scheme 2.12, **119, 124**). It has been observed in multiple reports that using less reactive and/or sterically hindered nucleophilic acceptors in glycosylations can lead to enhanced 1,2-*cis* stereoselectivity.[171,178] This phenomenon is also observed in our hands, where the use of hindered C-4 hydroxyl acceptor **148** led to exclusive formation of α-glycoside **132**. However, the reaction progression was sluggish and significant amount of donor regeneration was observed after 2 days. Pleasingly, another hindered C-3 hydroxyl acceptor **147** reacted smoothly to afford highly α-selective glycosylations in modest yield (Scheme 2.12, **130-131**). In reactions with these less reactive hindered glycosyl acceptors, increased amounts of *N*-methylmaleimide (3 equiv.) had to be introduced to suppress the otherwise dominant donor regeneration pathway. Finally, reactions with primary glycosyl acceptors all proceeded uneventfully and provided excellent yield and α-selectivity (Scheme 2.12, **120, 125, 128-129**).

We were also interested in applying our 1,2-*cis*-α glycosylation methodology toward the construction of important glycoconjugate targets. Notable examples include TN (**133**) and Tf (**134**) family of carbohydrate antigens (Figure 2.6), which contain α-GalNAc or LacNAc linked to serine/threonine residues on mucin-like core peptides.[179] As the overproduction of these structural motifs is often a hallmark of metastasized

tumor cells, they represent important diagnostic markers for tumor development that can be further applied in cancer vaccine designs.[180] To this end, preliminary experiments showed that glycosylations with Boc-protected serine acceptors afforded modest yield and excellent α-selectivity (Scheme 2.12, **126-127**). Unfortunately, later examinations with the use of 2-deoxy-2-azido thioglucoside donors did not result in productive couplings, possibly due to the highly disarming nature of the neighboring azides.[102]

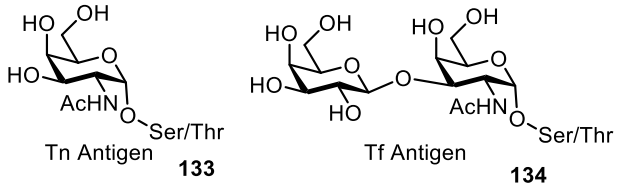
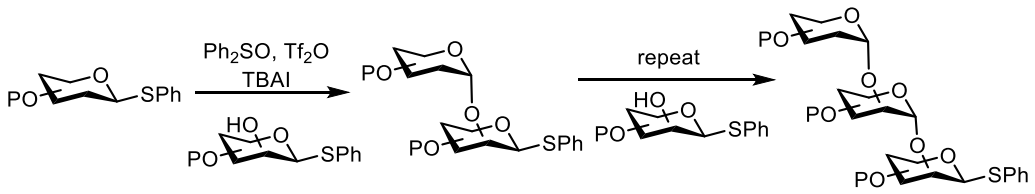


Figure 2.6: Important 1,2-*cis*-α-linked glycopeptide structural motifs**.**

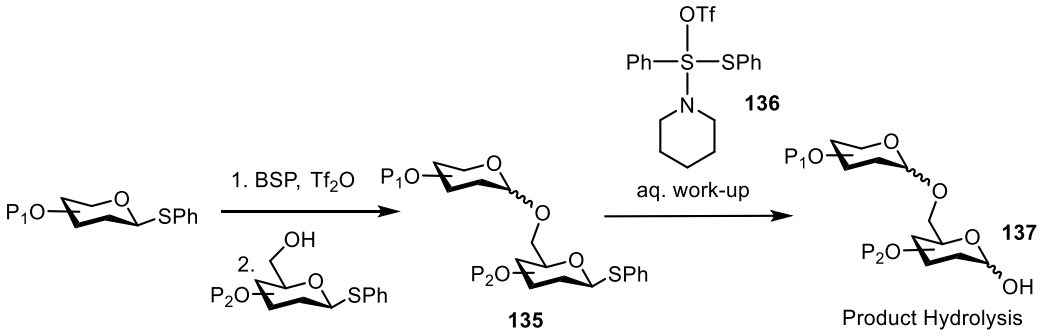
2.3.5: Application toward Iterative 1,2-*cis* Glycosylation Strategies

In our reaction conditions, pre-activation of the donor was performed prior to the addition of alcohol acceptors. The fact that the regenerated thioglycoside donors were not further converted into competent electrophiles prompted us to examine the use of thioglycoside acceptors for this reaction methodology. If thioglycoside acceptors could be used successfully, it would expand the reaction's utility by permitting stereoselective, iterative oligosaccharide synthesis (Scheme 2.13).



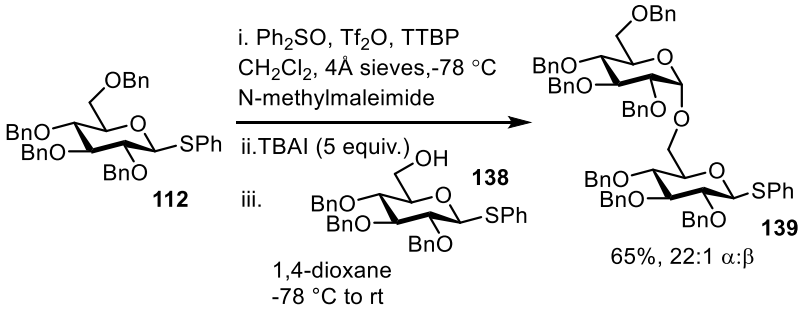
Scheme 2.13: Stereoselective iterative glycosylation scheme.

While iterative glycosylation approaches offer great advantages by eliminating additional anomeric group manipulations between glycosylation steps, their successful execution requires both coupling partners to be stable. In addition, activation chemistry has to be rapid and not generate reactive byproducts that can prematurely activate the acceptor *in situ*. For example, van Boom and coworkers reported that this approach was largely inhibited due to the side-reaction between anomeric thiol **135** and electrophilic intermediate **136** (Scheme 2.14).[96,111] This undesired activation further led to product hydrolysis upon aqueous workup, likely owing to the formation of anomeric sulfonium leaving groups on **135**.



Scheme 2.14: A problem encountered during iterative glycosylations with BSP/Tf_2O promoter system reported by van Boom.[96,111]

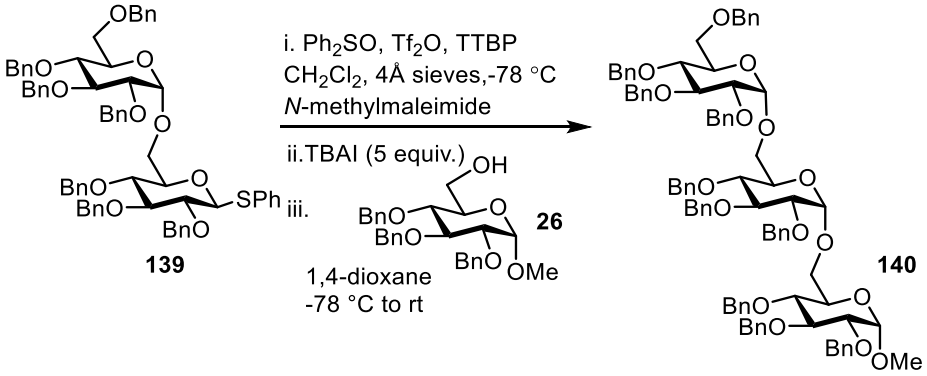
In order to assess the utility of our chemistry in iterative glycosylations, we first demonstrated that the coupling between **112** and **138** proceeded uneventfully to afford disaccharide **139** in good yield and α-selectivity (Scheme 2.15). In addition, the anomeric sulfides on both acceptor **138** and product **139** remained unreacted throughout the course of the reaction. Based on these results, we next examined the use of disaccharide **139** directly as glycosyl donor in a subsequent glycosylation with acceptor **26**. However, this reaction proved to be extremely sluggish, and even though the 1,2-*cis*-α-linked trisaccharide **140** was indeed afforded in excellent stereoselectivity (>20:1 α:β), the yield of the reaction was low (Table 2.3, entry 1).



Scheme 2.15: Ph_2SO/Tf_2O/TBAI-promoted α-glycosylation with thioglycoside acceptor **138**.

We realized that the low yield can again be explained by the competing donor generation, which was often encountered in sluggish entries earlier. Therefore, we attempted a preliminary optimization effort by reversing the donor acceptor stoichiometry, expecting to force reaction to completion with

the use of excess glycosyl donors. Interestingly, the change in donor acceptor stoichiometry did not appear to positively affect the reaction (Table 2.3, entry 2). On the other hand, allowing the reaction to proceed at an 80 °C oil-bath after pre-activation sequences did result in slightly improved reaction yield accompanied by little loss in stereoselectivity (Table 2.3, entry 3). This phenomenon can presumably be attributed to the differential reactivity of glycosyl iodides under halide ion conditions. Specifically, at elevated temperatures a portion of the fully armed α-glycosyl iodides can be expected to overcome the reaction barrier, effectively leading to the erosion of stereoselectivity. Despite the significant room for improvement in reaction yield, we have nonetheless demonstrated the potential application of our established methodology for future iterative synthetic schemes of 1,2-*cis*-a-linked oligosaccharides.



entry	donor : acceptor	t (°C)	Yield	α : β
1	1 : 2	25	30	22 : 1
2	2 : 1	25	35	20 : 1
3	1 : 2	80	42	14 : 1

Table 2.3: Iterative 1,2-*cis*-α glucan synthesis and preliminary optimization.

2.4: Conclusions

In summary, we have shown that activating thioglycosides with Ph_2SO/Tf_2O followed by the addition of TBAI leads to the *in situ* formation of a species that undergoes glycosylation to afford 1,2-cis-α-glycosides in good yield and excellent selectivity without the need for directing groups. The dependence of selectivity on the quantity of TBAI in the reaction indicates that the reaction may be proceeding through a glycosyl iodide intermediate. Excess TBAI can lead to regeneration of the starting donor; however, this can be suppressed with the addition of *N*-methylmaleimide as a thiol scavenger. The fact that the regenerated donor is unreactive prompted us to examine thioglycoside acceptors in the reaction. These latter acceptors can be used without detrimental effects, permitting iterative oligosaccharide synthesis. We envisioned that this approach will largely facilitate oligosaccharide synthesis by eliminating the need to use highly specialized protecting group patterns and/or very unstable glycosyl donors in the construction of 1,2-*cis*-α glycosides.

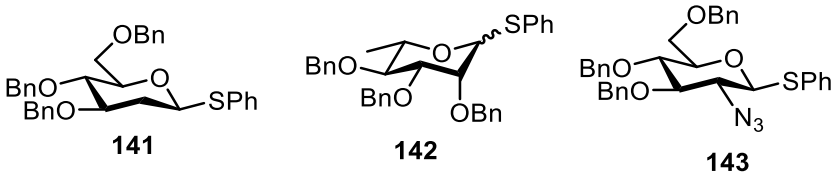


Figure 2.7: Further classes of glycosyl donors to be examined.

Studies to expand the substrate scope into deoxy sugar donors are critically important for this project in the future. Specifically, this will focus on the classes of 2-deoxy **141**, 6-deoxy **142** and 2-deoxy-2-amino **143**

thioglycoside donor derivatives (Figure 2.7). As mentioned above, the use of donor **143** did not afford productive couplings with Boc-protected serine, even when the reaction was heated at 80 °C. On the other hand, while donor **141** did afford efficient couplings with alcohol acceptor **26**, the glycosylation was however non-selective (76%, 1:1 α:β). We reasoned that the highly armed nature of 2-deoxy donor species again led to the loss of differential reactivity of the respective glycosyl iodides, and hence the desired α-stereoselectivity.

These results indicated that further entry-specific optimizations are necessary to further improve the synthetic utility of this methodology, which will be accompanied by the design of improved methods to suppress unwanted donor regeneration. In order to achieve this, more efficient thiol scavengers will have to be introduced. Furthermore, the addition of which cannot interfere with product purification. Preliminary investigations toward this objective will be discussed later in Chapter 3. Ultimately, we envisioned the concepts derived from our methodology to enable target-oriented synthesis of diverse 1,2-*cis*-α-glycoside-containing pathogenic determinants (Figure 2.8) that are critical for polysaccharide vaccine developments.

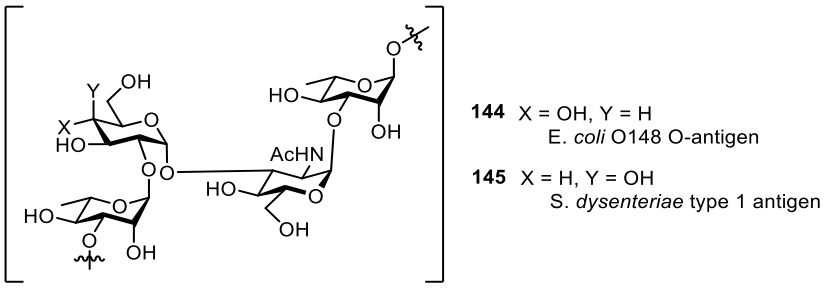


Figure 2.8: Potential 1,2-*cis*-α glycoside-containing synthetic targets.

2.5: Material and Experimental Methods

2.5.1: General Details

Prior to running the glycosylation reactions, all solid reagents were dried by azeotropic removal of water using toluene and a rotary evaporator < 40 °C. All reactions were carried out under an argon atmosphere unless otherwise specified. Solvents were dried using an Innovative Technologies PureSolv 400 solvent purifier. Nitrile co-solvents, other than acetonitrile, were purchased from Sigma Aldrich, and further dried over activated 4 Å molecular sieves before use. Glycosyl donors **112,146** and glycosyl acceptors **26**, **138**, **147**, **148** were synthesized following literature procedures or variations thereof.[181-185] Glycosyl acceptors **149**, **150** were purchased from Acros Chemicals. All other chemicals were purchased at the highest possible purity from commercial sources and used as received. Flash column chromatography was performed on Silicycle silica gel, 230-400 Mesh. Analytical and preparative thin layer chromatography were carried out on EMD silica gel 60 F254 plates. Products were visualized using UV, or by staining with 5% aqueous sulfuric acid, iodine, or ceric ammonium molybdate stains. NMR solvents were purchased from Cambridge Isotope Labs. NMR spectra were recorded on a Bruker Avance III NMR spectrometer at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. Chemical shifts are reported in ppm relative to TMS (for ^{1}H NMR in $CDCl_3$), and $CDCl_3$ (δC = 77.23 for ^{13}C NMR in $CDCl_3$). For ^{1}H NMR spectra, data are reported as follows: chemical shift δ in ppm, multiplicity (s = singlet, m = multiplet, t = triplet, d = doublet, dd = doublet of doublets, q = quartet and combinations

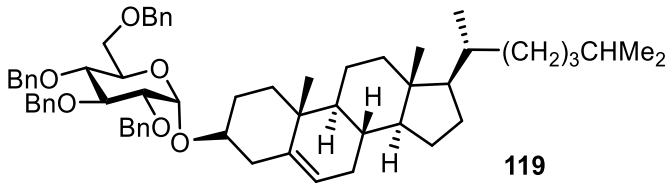
thereof), coupling constants reported in Hertz (Hz), and integration. Low resolution mass spectra (LRMS) were recorded using a Finnigan LTQ ESI-MS with an additional APCI source. High resolution mass spectra (HRMS) were obtained at Massachusetts Institute of Technology Department of Chemistry instrumentation facility using a peak-matching protocol to determine the mass and error range of the molecular ion. Optical rotations were measured on a Rudolph Research Analysis AUTOPUL IV polarimeter @ 589 nm in a 5 cm cell at 24°C.

2.5.2: General Glycosylation Procedure

A solution of donor (1.0 equiv., 0.075 mmol), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl). After stirring for 5 min, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor in 1:1 dichloromethane/dioxane (0.5ml/0.5ml). The reaction mixture was then allowed to slowly warm up to room temperature and was stirred until consumption of the starting donor and formation of the glycosides were

observed by TLC (18 – 64 h). The reaction was then filtered with celite and washed twice with saturated aqueous $NaHCO_3$. The pooled organic layer was dried (Na_2SO_4), filtered and concentrated. The glycosides were isolated by flash column chromatography (silica gel, ethyl acetate/hexanes). Anomeric ratios of the afforded glycosides (α:β) were determined by ^1H NMR (500 MHz).

2.5.3: Experimental Data



119

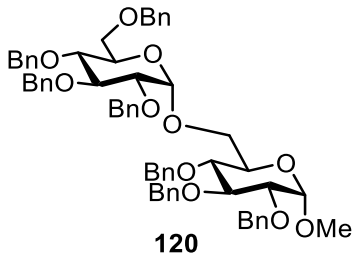
Cholesteryl-O-*2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (119)*:

Following the general procedure for glycosylation, a solution of donor **112** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated

with a solution of acceptor **117** (2.0 equiv., 0.15 mmol, 58.1 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 18 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (5% → 10% ethyl acetate in hexanes) to afford product **119** (0.056 mmol, 51.1 mg, 75% yield, 20:1 α:β), the NMR spectroscopic data of which is in good agreement with those reported previously.[186]

^{1}H NMR (500MHz, $CDCl_3$): δ 7.37 – 7.12 (m, 20H), 5.29 (s, 1H), 5.01 (d, J = 10.9 Hz, 1H), 4.93 (d, J = 4.0 Hz, 1H), 4.83 (d, J = 10.9 Hz, 1H), 4.82 (d, J = 10.9 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 10.9 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.00 (t, J = 9.2 Hz, 1H), 3.89 – 3.86 (m, 1H), 3.74 (dd, J = 10.9, 3.4 Hz, 1H), 3.66 – 3.62 (m, 2H), 3.55 (dd, J = 9.2, 4.0 Hz, 1H), 3.48 (m, 1H), 2.43 (m, 1H), 2.27 (m, 1H), 2.02 (m,1H), 1.95 (m, 1H), 1.88 -1.79 (m, 3H), 1.60 – 0.86 (m, 33H), 0.68 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$) δ 140.9, 139.1, 138.3, 138.1, 128.4, 128.3, 128.1, 127.9, 128.9, 127.8, 127.6, 127.5, 121.7, 94.7, 82.1, 80.0, 78.0, 76.7, 75.6, 75.1, 73.4, 73.0, 70.1, 68.8, 56.8, 56.2, 50.2, 42.3, 39.8, 39.5, 37.1, 36.8, 36.2, 35.7, 31.9, 29.6, 28.2, 27.9, 27.6, 24.3, 23.8, 22.8, 22.5, 21.1, 19.3, 18.7, 11.8.



120

Methyl *O-(2,3,4,6,-tetra-O-benzyl-α-D-glucopyranosyl)-(1->6)-2,3,4-tri-O-benzyl- α-D*-glucopyranoside (*120*):

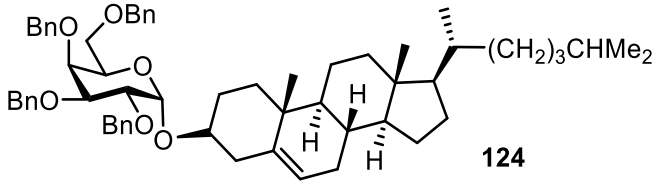
Following the general procedure for glycosylation, a solution of donor **112** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **26** (2.0 equiv., 0.15 mmol, 69.6 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 18 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (20% -> 30% ethyl acetate in hexanes) to afford product **120**

(0.065 mmol, 64.3 mg, 87% yield, 18:1 α:β), the NMR spectroscopic data of which is in good agreement with those reported previously.[186]

^{1}H NMR (500MHz, $CDCl_3$): δ 7.32 – 7.12 (m, 35H), 4.98 – 4.92 (m, 4H), 4.83 – 4.76 (m, 3H), 4.71 – 4.63 (m, 4H), 4.58 – 4.55 (m, 3H), 4.47 – 4.40 (m, 2H), 3.99 – 3.94 (m, 2H), 3.82 – 3.77 (m, 3H), 3.72 – 3.70 (m, 1H), 3.65 – 3.60 (m, 3H), 3.56 – 3.54 (m, 2H), 3.44 (d, J = 8.7Hz, 1H), 3.35 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$) δ 139.0, 138.9, 138.6, 138.3, 138.1, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 98.1, 97.4, 82.3, 81.8, 80.3, 80.1, 77.9, 77.7, 77.4, 75.8, 75.6, 75.1, 75.0, 73.5, 72.5, 70.5, 70.4, 68.6, 66.2, 55.3.

LRMS (ESI, pos. ion) *m/z*: calcd. for $C_{62}H_{66}O_{11}Na$ (M+Na) 1009.46, found 1009.32 .



124

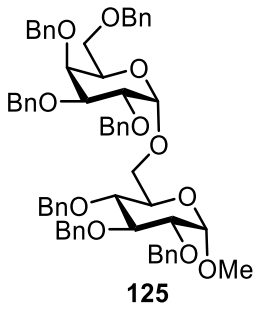
Cholesteryl-O-*2,3,4,6-tetra-O-benzyl-α-D-galactopyranose (124)*:

Following the general procedure for glycosylation, a solution of donor **146** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of

tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **117** (2.0 equiv., 0.15 mmol, 43.5 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 18 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (5% → 10% ethyl acetate in hexanes) to afford product **124** (0.57 mmol, 51.8 mg, 76% yield, 30:1 α:β), the NMR spectroscopic data of which is in good agreement with those reported previously.[187]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.25 (m, 20H), 5.25 (s, 1H), 4.99 (s, 1H), 4.97 (d, J = 11.4 Hz, 1H), 4.85 (d, J = 11.5 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 4.08-4.00 (m, 2H), 3.98-3.94 (m, 2H), 3.53 (d, J = 6.0 Hz, 2H), 3.51-3.43 (m, 1H), 2.44-2.39 (m, 1H), 2.28 (d, J = 13.4 Hz, 1H), 2.00 (d, J = 12.5 Hz, 1H), 1.94 (d, J = 16.2 Hz, 1H), 1.90-1.79 (m, 3H), 1.61-0.87 (m, 33H), 0.68 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$) δ 140.9, 139.0, 138.8, 138.7, 138.1, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 121.6, 95.6, 79.2, 75.3, 74.7, 73.4, 73.2, 69.3, 69.2, 56.8, 56.2, 50.2, 42.4, 40.0, 39.8, 39.6, 37.2, 36.8, 36.2, 35.8, 32.0, 31.9, 28.2, 28.0, 27.7, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.7, 11.9.



125

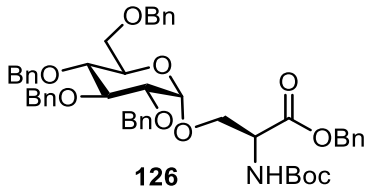
Methyl *O-(2,3,4,6,-tetra-O-benzyl-α-D-galactopyranosyl)-(1->6)-2,3,4-tri-O-benzyl- α-D-glucopyranoside (125):*

Following the general procedure for glycosylation, a solution of donor **146** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **26** (2.0 equiv., 0.15 mmol, 69.6 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 18 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column

chromatography (20% → 30% ethyl acetate in hexanes) to afford product **125** (0.06 mmol, 59.9 mg, 81% yield, α-only), the NMR spectroscopic data of which is in good agreement with those reported previously.[71]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.18 (m, 35H), 4.99 (d, J = 3.5 Hz, 1H), 4.96-4.92 (m, 2H), 4.84 (d, J = 11.0, 1H), 4.80-4.78 (m, 2H), 4.74-4.68 (m, 4H), 4.59-4.65 (m, 2H), 4.54 (d, J = 5.2 Hz, 1H), 4.52 (d, J = 3.51 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.37 (d, J = 11.8 Hz, 1H), 4.02 (dd, J = 5.9, 3.4 Hz, 1H), 3.98-3.88 (m, 4H), 3.80-371 (m, 3H), 3.58 (t, J = 9.2 Hz, 1H), 3.53-3.47 (m, 2H), 3.40 (dd, J = 6.1, 3.5 Hz, 1H), 3.29 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$) δ 138.9, 138.8, 138.5, 138.3, 138.1, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 98.0, 97.9, 82.1, 80.2, 78.3, 78.0, 75.7, 75.2, 75.0, 74.8, 73.4, 73.3, 72.8, 72.5, 70.3, 69.4, 69.0, 66.4, 55.0.



126

_O_-(3,4,6-tri-_O_-benzyl-α-D-glucopyranosyl)-_N_-(_tert_-butoxycarbonyl)-L-serine benzyl ester (_126_):

Following the general procedure for glycosylation, a solution of donor **112** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in

dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **149** (2.0 equiv., 0.15 mmol, 44.3 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 18 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (20% ethyl acetate in hexanes) to afford product **126** (0.043 mmol, 34.9 mg, 57% yield, 16:1 α:β).

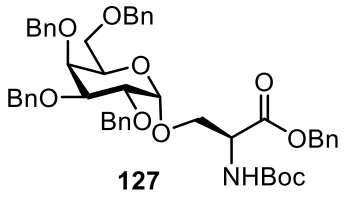
$[\alpha]_D$ = + 0.166 (*c* = 0.016, CH_2Cl_2).

^{1}H NMR (500MHz, $CDCl_3$): δ 7.37 – 7.12 (m, 25H), 5.65 (d, J = 8.5 Hz, 1H), 5.13 – 5.07 (m, 2H), 4.92 (d, J = 10.8 Hz, 1H), 4.79 (dd, J = 13.8, 11Hz, 2H), 4.74 (d, J = 2.7 Hz, 1H), 4.67 – 5.55 (m, 3H), 4.51 – 4.43 (m, 3H), 4.10 (d, J = 10.5 Hz, 1H), 3.87 (t, J =9.3 Hz, 1H), 3.83 (dd, J = 10.7, 2.6 Hz, 1H), 3.73 – 3.71 (m, 2H), 3.66 - 3.62 (m, 2H), 3.52 (dd, J = 9.6, 3.3 Hz, 1H), 1.43 (s, 9H)**.**

^{13}C NMR (125MHz, $CDCl_3$) δ 170.3, 155.5, 138.8, 138.2, 138.2, 137.9, 135.3, 98.5, 81.7, 80.0, 79.9, 77.7, 77.4, 77.3, 77.0, 76.7, 75.6, 75.1, 74.9, 73.6, 73.5, 72.9, 70.8, 69.9, 68.3, 67.3, 54.4, 28.3**.**

LRMS (ESI, pos. ion) *m/z*: calcd. for $C_{49}H_{55}NO_{10}Na$ (M+Na) 840.38, found 840.23.

HRMS (ESI, pos. ion) *m/z*: calcd. for $C_{49}H_{55}NO_{10}Na$ (M+Na) 840.3826, found 840.3718.



127

***O*-(3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-*N*-(*tert*-butoxycarbonyl)-L-serine benzyl ester (*127*):**

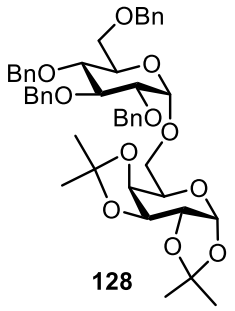
Following the general procedure for glycosylation, a solution of donor **146** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **149** (2.0 equiv., 0.15 mmol, 44.3 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 18 hrs. The

reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (20% ethyl acetate in hexanes) to afford product **127** (0.0435 mmol, 35.5 mg, 58% yield, α-only).

^{1}H NMR (500MHz, C_6D_6): δ 7.34-7.31 (m, 7H), 7.27-7.25 (m, 2H), 7.21-6.97 (m, 16H), 6.09 (d, *J* = 8.65 Hz, 1H), 5.02 (d, *J* = 9.2 Hz, 1H), 5.00 (d, *J* = 7.9 Hz, 1H), 9.90 (d, *J* = 12.5 Hz, 1H), 4.75 (d, *J* = 3.6 Hz, 1H), 4.68-4.64 (m, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.50-4.46 (m, 2H), 4.41 (d, *J* = 11.8 Hz, 1H), 4.36-4.33 (m, 2H), 4.14 (dd, *J* = 9.7, 3.5 Hz, 1H), 4.10 (t, *J* = 6.5 Hz, 1H), 3.99 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.85-3.83 (m, 2H), 3.76-3.75 (m, 2H), 3.72 (dd, *J* = 8.3, 2.8 Hz, 1H), 1.43 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$) δ 170.4, 155.6, 138.8, 138.6, 138.0, 135.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 99.36, 79.9, 78.7, 76.4, 74.5, 73.5, 73.2, 73.1, 70.4, 69.8, 68.7, 67.1, 54.5, 28.3.

HRMS (ESI, pos. ion) *m/z*: calcd. for $C_{49}H_{55}NO_{10}Na$ (M+Na) 840.3899, found 840.3882.



128

O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-(1→6)-1,2;3,4-di-O-isopropylidene-α-D-galactopyranoside (128):

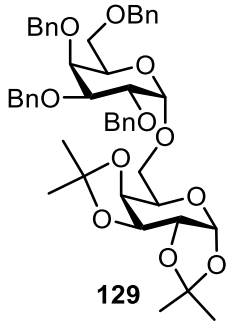
Following the general procedure for glycosylation, a solution of donor **112** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **150** (2.0 equiv., 0.15 mmol, 39 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 18 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (20% → 30% ethyl acetate in hexanes) to afford product **128**

(0.059 mmol, 46.2 mg, 79% yield, 20:1 α:β), the NMR spectroscopic data of which is in good agreement with those reported previously.[186]

^{1}H NMR (500MHz, $CDCl_3$): δ 7.38 – 7.13 (m, 20H), 5.52 (d, J = 5.2Hz, 1H), 5.00 (d, J = 4.0 Hz, 1H), 4.98 (d, J = 10.9 Hz, 1H), 4.83 (d, J = 10.9 Hz, 1H), 4.80 (d, J = 10.9 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.60 (dd, J = 8.0, 2.3 Hz, 1H), 4.48 (d, J = 10.9 Hz, 1H), 4.47(d, J = 12.0Hz), 4.36 (dd, J = 2.3, 8.0 Hz, 1H), 4.32 (dd, J = 5.2, 2.3 Hz, 1H), 4.05 (m, 1H), 3.99 (t, J = 9.7 Hz, 1H), 3.83 (m, 1H), 3.73 – 3.80 (m, 3H), 3.69 (t, J = 9.7 Hz, 1H), 3.65 (dd, J = 1.7, 10.3 Hz, 1H), 3.59 (dd, J = 4.0, 9.7 Hz, 1H), 1.54 (s, 3H), 1.46 (s, 3H), 1.32 (s, 6H).

^{13}C NMR (125MHz, $CDCl_3$) δ 138.9, 138.4, 138.0, 128.6 – 126.6, 109.2, 108.6, 97.0, 96.9, 96.3, 81.8, 79.8, 77.6, 75.6, 74.9, 73.5, 72.3, 70.8, 70.7, 70.5, 68.4, 66.2, 65.7, 26.2, 26.1, 24.9, 24.7.

LRMS (ESI, pos. ion) *m/z*: calcd. for $C_{46}H_{54}O_{11}$ (M+Na) 805.37, found 805.36.



129

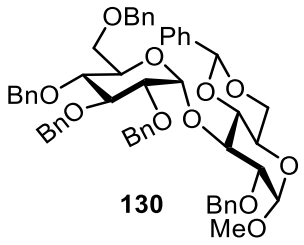
***O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→6)-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside (129):**

Following the general procedure for glycosylation, a solution of donor **146** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg),

TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **150** (2.0 equiv., 0.15 mmol, 39 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 18 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (20% → 30% ethyl acetate in hexanes) to afford product **129** (0.06 mmol, 46.8 mg, 80% yield, α-only), the NMR spectroscopic data of which is in good agreement with those reported previously.[186]

^{1}H NMR (500MHz, $CDCl_3$): δ 7.36 – 7.23 (m, 20H), 5.50 (d, J = 4.9Hz, 1H), 5.00 (d, J = 3.0 Hz, 1H), 4.93 (d, J = 11.4 Hz, 1H), 4.83 (d, J = 11.6 Hz, 1H), 4.75 – 4.71 (m, 3H), 4.59 – 4.55 (m, 2H), 4.47 (d, J = 11.8 Hz, 1H), 4.41 (d, J = 11.8 Hz, 1H), 4.32 – 4.29 (m, 2H), 4.06 – 3.99 (m, 4H), 3.96 – 3.94 (m, 1H), 3.80 – 3.71 (m, 2H), 3.57 (t, J = 8.3 Hz, 1H), 3.53 – 3.49 (m, 1H), 1.51 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$) δ 139.0, 138.8, 138.1, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 109.2, 108.5, 97.6, 96.3, 79.0, 76.5, 75.0, 74.8, 73.4, 73.1, 72.7, 70.9, 70.7, 69.2, 68.7, 66.4, 65.9, 26.2, 26.1, 25.0, 24.6.



130

Methyl-*O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (130)*:

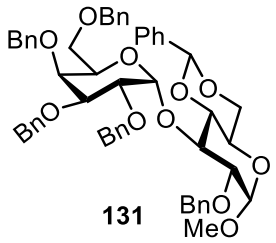
Following a modified general procedure for glycosylation, a solution of donor **112** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (3.0 equiv., 0.225 mmol, 25 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **147** (2.0 equiv., 0.15 mmol, 55.8 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 40 hrs. The reaction was then first filtered with celite and washed twice with saturated

aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (25% ethyl acetate in hexanes) to afford product **130** (0.044 mmol, 39.3 mg, 59% yield, 19:1 α:β), the NMR spectroscopic data of which is in good agreement with those reported previously.[188]

^{1}H NMR (500MHz, $CDCl_3$): δ 7.69 – 6.92 (m, 30H), 5.59 (d, J = 4.0Hz, 1H), 5.47 (s, 1H), 4.99 (d, J = 10.5 Hz, 1H), 4.80 (dd, J = 11.0,1H), 4.79 (d, J = 11.0 Hz, 1H), 4.71 (d, J = 3.5 Hz, 1H), 4.65 (d, J = 11.4Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 11.0 Hz, 1H), 4.38 (t, J = 9.5 Hz, 1H), 4.32 (d, J = 12.5 Hz, 1H), 4.29 (d, J = 12.0 Hz, 1H), 4.24 (dd, J = 10.0, 4.5 Hz, 1H), 4.21 – 4.18 (m, 1H), 3.95 (t, J = 9.6Hz, 1H), 3.89 – 3.63 (m, 5H), 3.52 - 3.45 (m, 3H), 3.41 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$) δ 134.0, 138.9, 138.1, 137.8, 137.4, 137.1, 129.4, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 127.4, 127.3, 126.4, 102.1, 98.5, 96.1, 82.8, 81.6, 78.7, 78.0, 77.5, 74.7, 73.4, 73.3, 72.7, 71.1, 69.8, 69.2, 68.1, 61.7, 55.3.

LRMS (ESI, pos. ion) *m/z*: calcd. for $C_{55}H_{58}O_{11}Na$ (M+Na) 917.39, found 917.27.



131

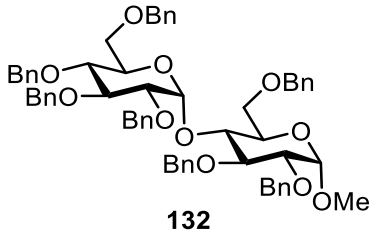
Methyl-*O*-(*2,3,4,6-tetra-O*-benzyl-α-D-*galactopyranosyl*)-(1→3)-2-*O*-benzyl-*4,6-O*-benzylidine-α-D-*glucopyranoside (131)*:

Following a modified general procedure for glycosylation, a solution of donor **146** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (3.0 equiv., 0.225 mmol, 25 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **147** (2.0 equiv., 0.15 mmol, 55.8 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 40 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (25% ethyl acetate in hexanes) to afford product **131** (0.052

mmol, 46.6 mg, 70% yield, 20:1 α:β), the NMR spectroscopic data of which is in good agreement with those reported previously.[188]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.25 (m, 25 H), 7.21-7.17 (m, 1H), 7.14-7.11 (m, 2H), 7.05 (d, J = 7.0 Hz, 2H), 5.65 (d, J = 3.6 Hz, 1H), 5.47 (s, 1H), 4.92 (d, J = 11.3 Hz, 1H), 4.88 (d, J = 11.8 Hz, 1H), 4.78-4.74 (m, 2H), 4.62 (d, J = 12.4, 1H), 4.58-4.55 (m, 3H), 4.47 (d, J = 12.3 Hz, 1H), 4.42-4.37 (m, 3H), 4.36 (d, J = 11.7 Hz, 1H), 4.24 (dd, J = 5.5, 4.8 Hz, 1H), 4.02 (dd, J = 6.4, 3.5 Hz, 1H), 3.99-3.94 (m, 2H), 3.86 (td, J = 10.0, 4.7 Hz, 1H), 3.77 (t, J = 9.3 Hz, 1H), 3.71 (t, J = 10.3 Hz, 1H), 3.66-3.62 (m, 2H), 3.59-3.55 (m, 1H), 3.37 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$) δ 139.0, 138.9, 138.5, 138.4, 138.0, 137.1, 129.2, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.4, 127.3, 127.2, 126.3, 101.8, 98.8, 96.8, 83.0, 78.4, 78.3, 75.8, 75.3, 74.9, 73.5, 73.0, 72.4, 71.7, 69.2, 68.8, 68.5, 61.8, 55.3.



132

Methyl-*O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-O-benzyl-α-D glucopyranoside (132)*:

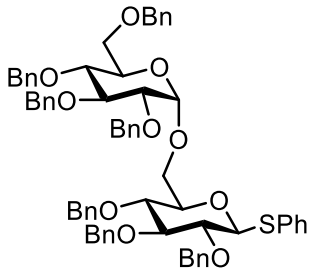
Following a modified general procedure for glycosylation, a solution of donor **112** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (3.0 equiv., 0.225 mmol, 25 mg) and freshly activated 4Å molecular sieves (100 mg) in dry

dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **148** (2.0 equiv., 0.15 mmol, 69.6 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 64 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (30% ethyl acetate in hexanes) to afford product **132** (0.031 mmol, 30.1 mg, 41% yield, α-only), the NMR spectroscopic data of which is in good agreement with those reported previously.[70]

^{1}H NMR (500MHz, $CDCl_3$): δ 7.32 – 7.06 (m, 35H), 5.70 (d, J = 3.6Hz, 1H), 5.04 (d, J = 11.5 Hz, 1H), 4.88 (d, J = 10.8 Hz, 1H), 4.80 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 10.6 Hz, 1H), 4.77 (d, J = 10.9 Hz, 1H), 4.70 (d, J = 12.1 Hz, 1H), 4.60 (d, J = 3.6 Hz, 1H), 4.59 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 12.2 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 4.49 (s, 2H), 4.41 (d, J = 10.8 Hz, 1H), 4.27 (d, J = 12.1 Hz, 1H), 4.09 (t, J = 8.8 Hz, 1H), 4.07 (t, J = 9.0 Hz, 1H), 3.90 (dd, J = 9.8, 8.6 Hz, 1H), 3.84 – 3.67 (m, 5H), 3.59 (dd, J = 9.2, 3.7 Hz, 1H), 3.49 (dd, J = 9.7, 3.6 Hz, 1H), 3.48 (dd, J = 10.7, 2.9 Hz, 1H), 3.38 (J = 10.7, 1.6 Hz, 1H), 3.37 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$) δ 138.9, 138.8, 138.5, 138.2, 138.0, 137.9, 128.5 – 126.8, 97.8, 96.7, 82.0, 79.4, 77.8, 76.8, 75.5, 74.9, 74.4, 73.5, 73.3, 73.2, 73.2, 72.6, 70.9, 69.6, 69.1, 68.3, 55.2.

LRMS (ESI, pos. ion) *m/z*: calcd. for $C_{62}H_{66}O_{11}$ (M+Na) 1009.46, found 1009.28.



139

Phenylthio-(*2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-β-D-glucopyranoside (139)*:

Following a modified general procedure for glycosylation, a solution of donor **112** (1.0 equiv., 0.075 mmol, 47.5 mg), Ph_2SO (2.8 equiv., 0.21 mmol, 42.5 mg), TTBP (3.0 equiv., 0.225 mmol, 55.9 mg), *N*-methylmaleimide (1.5 equiv., 0.1125 mmol, 12.5 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (1 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.105 mmol, 17.6 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.375 mmol, 138 mg) in dichloromethane (0.75 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **138** (2.0 equiv., 0.15 mmol, 81.33 mg) in 1:1

dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 40 hrs. The reaction was then first filtered with celite and washed twice with saturated aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (20% ethyl acetate in hexanes) to afford product **139** (0.049 mmol, 51.9 mg, 65% yield, 23:1 α:β).

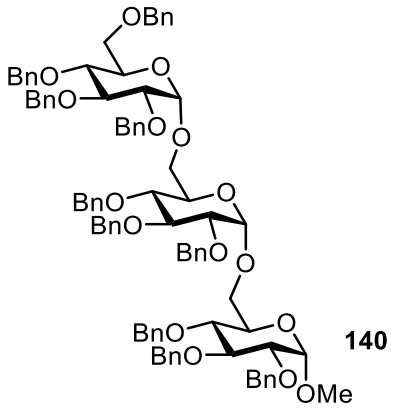
$[\alpha]_D$ = + 0.150 (*c* = 0.019, CH_2Cl_2).

^{1}H NMR (500MHz, $CDCl_3$): δ 7.55 – 7.10 (m, 40H), 5.03 (d, J = 3.4 Hz, 1H), 4.98 (d, J = 10.8 Hz, 1H), 4.89 (m, 1H), 4.86 – 4.85 (m, 2H), 4.83 – 4.79 (m, 3H), 4.77 – 4.72 (m, 2H), 4.68 – 4.64 (m, 1H), 4.62 (d, J = 6.6 Hz, 1H), 4.59 (d, J = 3.3 Hz, 1H), 4.47(d, J = 11Hz, 1H), 4.43 (d, J = 12.2Hz, 1H), 3.98 (t, J = 9.3 Hz, 1 H), 3.87 – 3.83 (m, 2H), 3.79 -3.77 (m, 1H), 3.72 – 3.65 (m, 4H), 3.64 – 3.57 (m, 3H), 3.49 (dd, J = 9.2, 3.5 Hz, 1H), 3.26 (t, J = 9.2 Hz, 1H)**.**

^{13}C NMR (125MHz, $CDCl_3$) δ 138.9, 138.6, 138.5, 138.2, 138.0, 132.0, 129.0, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 97.4, 88.1, 86.7, 81.7, 81.1, 80.1, 78.8, 77.7, 77.6, 77.3, 75.6, 75.5, 74.9, 73.4, 72.4, 70.2, 68.6, 66.3, 53.4.

LRMS (ESI, pos. ion) *m/z*: calcd. for $C_{67}H_{68}O_{10}S$ (M+Na) 1087.45, found 1087.45.

HRMS (ESI, pos. ion) *m/z*: calcd. for $C_{67}H_{68}O_{10}S$ (M+Na) 1087.4533, found 1087.4425.



Methyl-*O-[(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-(1→6)-2,3,6-tri-O-benzyl-α-D-glucopyranosyl]-(1→6)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (140)*:

Following a modified general procedure for glycosylation, a solution of donor **139** (1.0 equiv., 0.065 mmol, 70 mg), Ph_2SO (2.8 equiv., 0.182 mmol, 36.8 mg), TTBP (3.0 equiv., 0.195 mmol, 48.4 mg), *N*-methylmaleimide (3.0 equiv., 0.195 mmol, 21.7 mg) and freshly activated 4Å molecular sieves (100 mg) in dry dichloromethane (0.85 ml) was cooled to -78°C and then treated drop-wise with trifluoromethanesulfonic anhydride (Tf_2O, 1.4 equiv., 0.091 mmol, 15.3 µl) After stirring at low temperature for 5 mins, a solution of tetrabutylammonium iodide (TBAI, 5 equiv., 0.325 mmol, 120 mg) in dichloromethane (0.65 ml) was added to the reaction. Stirring was continued for an additional 10 min at -78°C, after which the reaction mixture was treated with a solution of acceptor **26** (2.0 equiv., 0.13 mmol, 60.3 mg) in 1:1 dichloromethane/dioxane (0.5 ml/0.5 ml). The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 64 hrs. The reaction was then first filtered with celite and washed twice with saturated

aqueous $NaHCO_3$. Pooled organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified by silica gel flash column chromatography (25% → 30% ethyl acetate in hexanes) to afford product **140** (0.0195 mmol, 27.3 mg, 30% yield, 22:1 α:β); alternatively, following the addition of acceptor **26** (2.0 equiv., 0.13 mmol, 60.3 mg) at -78 °C , the reaction mixture was allowed to slowly warm up to room temperature and then heated to 80 °C under reflux for additional 18 hrs, the crude product was then purified by silica gel flash column chromatography (25% → 30% ethyl acetate in hexanes) to afford product **140** (0.027 mmol, 38.2 mg, 42% yield, 14:1 α:β) the NMR spectroscopic data of which is in good agreement with those reported previously.[189]

^{1}H NMR (500MHz, $CDCl_3$): δ 7.32 – 7.10 (m, 50H), 5.01 (d, J = 3.3 Hz, 1H), 4.96 – 4. 88 (m, 6H), 4.80 (dd, J = 10.7, 2.5 Hz, 2H), 4.75 (d, J = 10.9 Hz, 2H), 4.69 – 4.61 (m, 5H), 4.56 – 4.52 (m, 5H), 4.44 (d, J = 10.9 Hz, 1H), 4.42 – 4.39 (m, 1H), 3.98 – 3.92 (m, 3H), 3.81 – 3.77 (m, 3H), 3.73 – 3.69 (m, 3H), 3.67 – 3.59 (m, 5H), 3.53 – 3.50 (m, 2H), 3.42 – 3.38 (m,2H), 3.32 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$) 138.8, 138.7, 138.5, 138.5, 138.2, 138.0, 128.4 – 127.4, 98.0, 97.2, 97.0, 82.1, 81.7, 81.6, 80.3, 80.2, 80.1, 77.8, 77.6, 75.7, 75.5, 75.4, 75.0, 74.9, 74.8, 73.4, 72.3, 72.1, 70.7, 70.5, 70.3, 68.5, 65.8, 55.1.

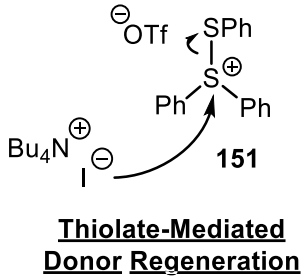
LRMS (ESI, pos. ion) *m/z*: calcd. for $C_{89}H_{94}O_{16}$ (M+Na) 1442.66, found 1442.28.

Chapter 3:

Development of a Water-Air Stable Thioglycoside Activation Strategy

3.1: Rationale and Motivation for Method Development

Despite preliminary success in our development of directing group-free stereoselective 1,2-*cis*-α glycosylation described above, it was not without its limitations. One major drawback of the Ph_2SO/Tf_2O promoter system originated from the generation of electrophilic sulfonium byproduct **151** in the reaction mixture, the detrimental effects of which have been described in multiple reports (Scheme 3.1).[96,111,190] Notably, in our hands the competing thioglycoside regeneration pathway under Ph_2SO/Tf_2O/TBAI activation sequence proved to be problematic, even in the presence of thiol scavengers. Since the thiol-maleimide ligation is known to be reversible, the phenyl thiolate could be regenerated to promote the background donor regeneration. This phenomena was particularly dominant in sluggish reaction entries (Figure 3.1), and higher amounts of N-methyl maleimide (3 equiv.) had to be introduced in these cases. However, this also complicated the purification process as N-methyl maleimide tended to coelute with the glycosylated products.



Scheme 3.1: Drawback with the Ph_2SO/Tf_2O activation system.

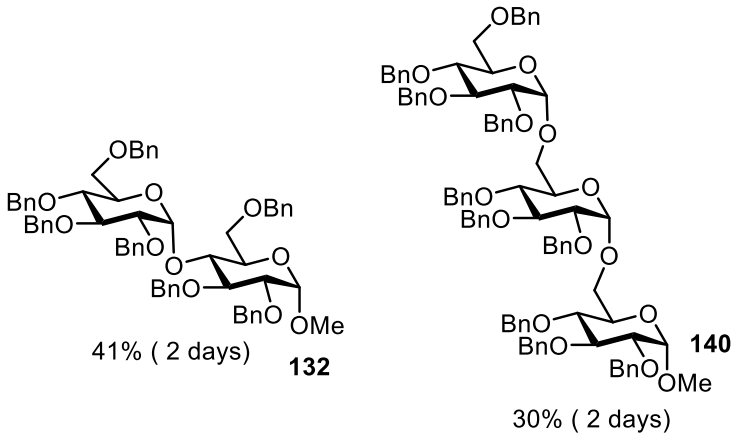
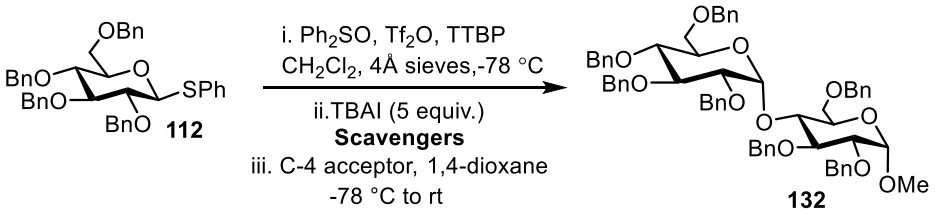


Figure 3.1: Sluggish reaction entries under previous Ph_2SO/Tf_2O/TBAI activation conditions.

In light of this, additional screening of known thiol scavengers, such as 2-iodoacetamide[191] and methyl propiolate[192] (Table 3.1), was conducted. Although the introduction of 2-iodoacetamide in the pre-activation mixture resulted in a slight improvement of reaction yield (47%, α-only, Table 3.1, entry 3) compared the use of *N*-methylmaleimide (41%, Table 3.1, entry 1), a noticeable amount of donor regeneration was nonetheless still observed. On the other hand, adding methyl propiolate in the reaction only led to erosion of stereoselectivity (91%, 2:1 α:β, Table 3.1, entry 2). This was presumably due to the premature trapping of TBAI by methyl propiolate, thus resulting in the inefficient generation of glycosyl iodides *in situ*. Furthermore, in an attempt to circumvent the purification difficulty previously introduced by N-methyl maleimide, the use of solid-phase silica-bound maleimide was also examined in the reaction. These conditions, however, did not result in productive couplings. This was presumably due to either the acidic nature or the residual

moisture associated with the silica (Table 3.1, entry 4). Based on these results, we sought to abandon the Ph_2SO/Tf_2O promoter, and began a search for new thiophilic promoters that did not give reactive byproducts upon glycoside activation.



Entry	Scavenger	Yield (%)	α : β
1	A	41	α-only
2	B	91	2.5 : 1
3	C (5 equiv.)	47	α-only
4	D (5 equiv.)	NR	NR

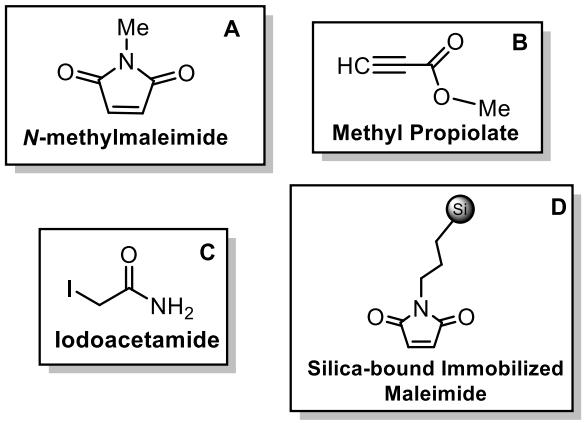


Table 3.1: Additional thiol scavengers screened in this study.

Another major point of method reinvention came from the stringent operational requirements that are typically associated with the use of triflic

anhydride in chemical glycosylations. Due to the hygroscopic nature of this reagent, it is necessary to purify it by distillation immediately prior to use in glycosylations. In addition, activated molecular sieves need to be introduced as desiccants for optimal results. Lastly, low reaction temperatures (as low as -78 °C) are typically required for Ph_2SO/Tf_2O-promoted glycosylations due to the generation of reactive intermediates, potentially creating issues with solubility.[193]

These issues have also been commonly seen in traditional chemical glycosylation approaches, which utilize toxic, unstable, corrosive, and moisture-sensitive reagents to generate reactive intermediates at extreme temperatures.[50] All of these factors contribute to the significant technical barrier that limits routine carbohydrate synthesis to highly specialized laboratories. This situation has recently prompted the National Research Council to put forth a call for more general carbohydrate synthetic procedures that do not require a high level of specialization to execute.[194] Indeed, a number of labs have responded to this call with a variety of user-friendly glycosylation procedures. Some recent examples include the use of Bismuth-based promoters[193] as well as photochemical[195,196] or electrochemical activations.[197] Motivated by these approaches and the potential for improving the methodology described in Chapter 2, we decided to tackle the development of next-generation user-friendly chemical glycosylation approaches. The collective results of this effort, which resulted in the

development of a new hypervalent iodine-promoted glycosylation procedure, will be discussed in this chapter.

3.2: Hypervalent Iodonium Species in Organic Synthesis

In order to achieve this goal, we envisioned that it would be necessary to design a protocol that utilizes shelf-stable donors, such as thioglycosides, with simple-to-use conditions. In other words, we wanted a glycosylation that can be run at ambient temperatures and is not overly sensitive to moisture or air. Furthermore, we decided that the use of scalable, non-toxic and single-component promoter species would be highly desirable from an operational standpoint. Based on a preliminary literature search, we concluded that hypervalent iodine species could serve as intriguing candidates for further investigations.

Since the early 1970s, hypervalent iodine species have emerged as a popular class of reagents in organic synthesis, largely due to their inexpensive synthetic precursors as well as excellent chemoselectivity in numerous transformations.[198-201] Both major classes of hypervalent iodines, iodine(V) and iodine(III) reagents, are now routinely used as alternatives to toxic heavy-metal based reagents in oxidative transformations (Figure 3.2).[202-205] In addition, hypervalent iodine(III) reagents have also been employed in various transformations that are mechanistically analogous to transition metal-catalyzed reactions. This can often be seen in reactions involving iodine(III) iodonium salts, which are characterized by the presence of an iodine center

connected to two separate carbon ligands as well as a closely associated counterion (Scheme 3.2A).

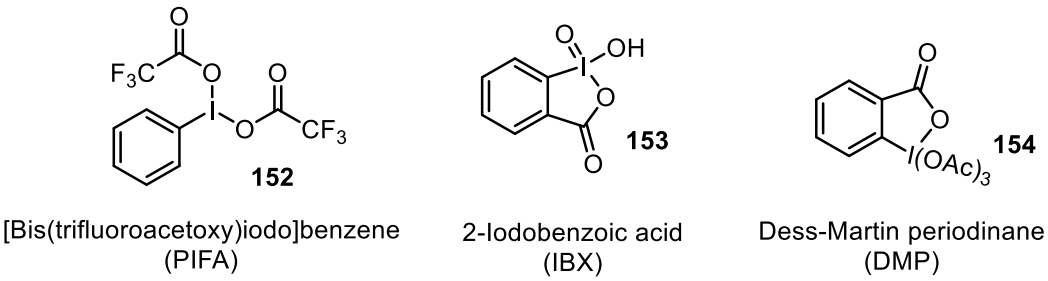
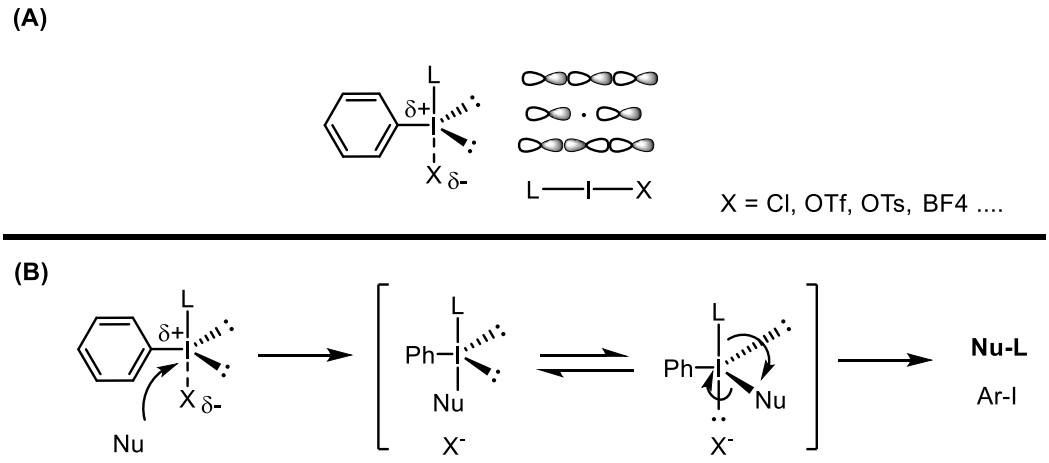


Figure 3.2: Examples of commonly employed hypervalent iodine reagents.

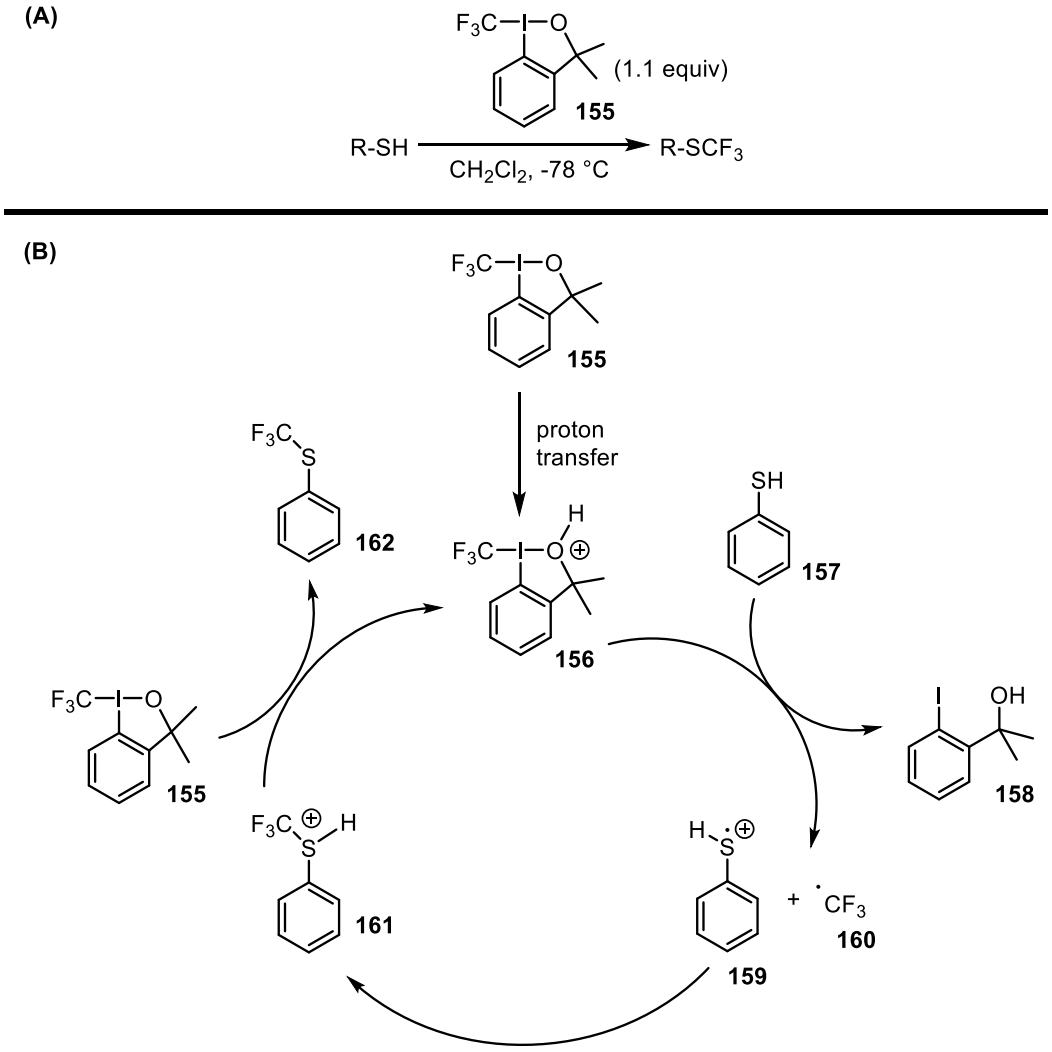


Scheme 3.2: A: Generic structures of hypervalent iodonium(III) salts. **B:** Proposed reaction mechanisms.

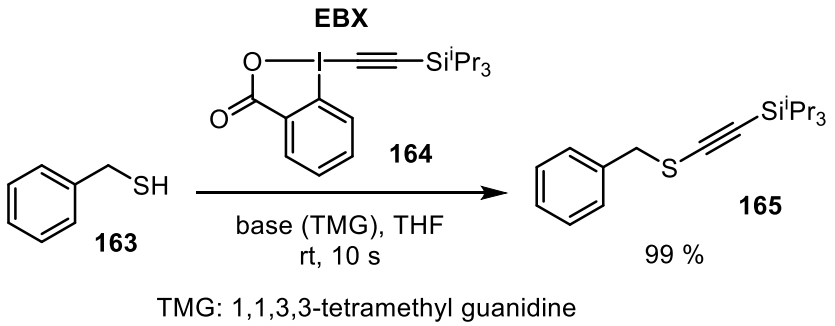
Importantly, in these iodine(III) species, the iodine atom is highly electrophilic. It has been proposed that many of these reactions are initiated by a nucleophilic attack on this atom to form a transient Nu-I bond. The subsequent reductive elimination then afford the coupled product "Nu-L" with the concomitant release of aryl iodide (Scheme 3.2B).[206] This facile reaction pathway makes these hypervalent iodonium salts particularly useful in a wide array of electrophilic ligand-exchange transformations, with arylation and heteroarylation by carbon nucleophiles being the most common.[207-212]

In addition, the direct electrophilic trifluoromethylation of sulfur-centered nucleophiles by hypervalent iodine(III) reagent has also been demonstrated (Scheme 3.3). Initially reported by Togni and coworkers in 2006,[213] trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (**155**) was shown to react with thiols in good yield and chemoselectivity. The substrate scope ranged from simple thiophenol to cysteine side chains in peptides, and a wide array of functional groups including amines, carboxylic acids, thioacetal, alcohols and alkynes could be tolerated.[214] A proposed mechanism for this reaction is illustrated below in Scheme 3.3B.[215] The initial protonation of **155** by thiol **157** upon its coordination to the iodine(III) center leads to the simultaneous formation of thiyl and CF_3 radicals **159** and **160**. This radical-based mechanism is also supported by the generation of disulfide and CF_3H byproducts in the reaction. The following radical coupling then generates acidic sulfonium intermediate **161**, which closes the cycle by protonating another molecule of **155** and simultaneously forming the

trifluoromethylated product **162**. This approach was also later modified and applied to the alkynylation of thiols by Waser's research group (Scheme 3.4).[216]

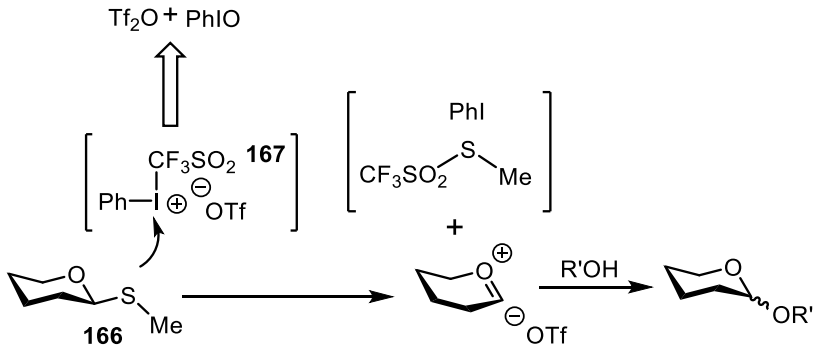


Scheme 3.3: Direct electrophilic trifluoromethylation of sulfur nucleophiles promoted by hypervalent iodine **155**.[216]



Scheme 3.4: Alkynylation of thiols by hypervalent iodine EBX.[216]

Due to the mild and non-toxic nature of hypervalent iodine species, we were particularly interested in examining the utility of these compounds as glycosylation promoters. This rationale was further supported by the literature precedence of Fukase *et al*., who demonstrated that *in situ* mixing of iodosobenzene/triflic anhydride combination generated potent iodine(III) electrophile **167**, which could efficiently promote activation of thioglycoside donor **166** for subsequent glycosylations (Scheme 3.5).[217] This work demonstrated for the first time the potential application of iodine(III) electrophiles in chemical glycosylations. However, the reaction also required the use of relatively unstable triflating reagents. This resulted in the need for activated molecular sieves as well as low reaction temperatures (< -20 °C). Since this did not fit our desired parameters of developing a mild, easy to execute, room temperature glycosylation procedure, we decided to turn our attention to other analogous iodine(III) species.



Scheme 3.5: Iodosobenzene/triflic anhydride-promoted glycosylation.

In this respect, thiophile **167** is structurally and functionally similar to the class of (perfluoroalkyl)phenyliodonium triflates **168** (FITS) reagents, which were first reported by Umemoto and coworkers in 1979 (Figure 3.3).[218,219] These compounds also reacted through mechanisms analogous to those demonstrated in Scheme 3.2. The triflate counterion appeared to be critical for reactivity, as the chloride analog demonstrated low reactivity against non-activated nucleophiles. Several additional FITS analogs were also introduced by Umemoto, such as *p*-fluorophenyl as well sulfonate counterion analogs[220] (Figure 3.3).

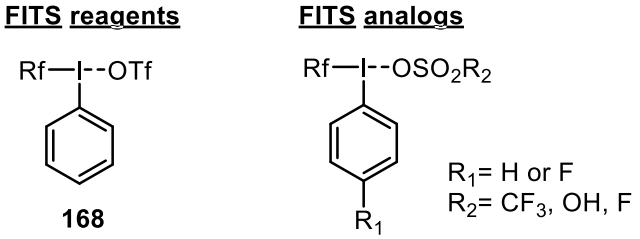


Figure 3.3: (Perfluoroalkyl)phenyliodonium triflates (FITS) and their structural analogs.

Since their initial discovery, FITS reagents have been widely adapted in electrophilic perfluoroalkylations. This is largely because direct perfluoroalkylation of nucleophiles, even with reactive substrates such as Rf-OTf moieties, typically failed, resulting instead in the nucleophilic attack on the sulfur center.[221] However, one drawback of FITS reagents with shorter fluoroalkyl chains lies in their relative instability, which therefore requires special care during storage.[219] To address this issue, Montanari and DesMarteau studied the effects of different counterions on the stability of these species. In 1998, they found that triflimide counterion containing derivatives of such species (**169**) also displayed similar reactivity.[222] Surprisingly, even though **169** was slightly soluble in water, it only hydrolyzed slowly, and could even promote the perfluoroalkylation of protected lysine residue in aqueous media (Figure 3.4).[222-224] This further prompted Montanari and Kumar to employ **169** as capping reagents during solid-phase peptide synthesis.[225,226] Importantly, during these studies methionine was found to be incompatible with **169**, owing to degradation initiated by alkylation of the thioether. Realizing the potential chemoselectivity between the soft-soft sulfur nucleophile-iodine electrophile pairs, we reasoned that **169** could serve as a unique type of thiophilic promoter. Furthermore, due to its extraordinary water-stability, the use of **169** was expected to offer significant advantages in its operational simplicity. The series of investigations of phenyl(trifluoroethyl)iodonium triflimide **169** as a novel thiophilic promoter in chemical glycosylations will be described below.

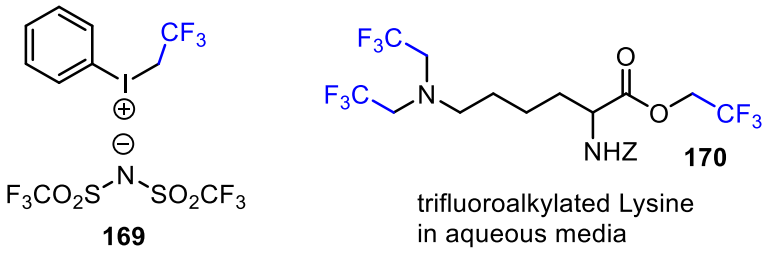
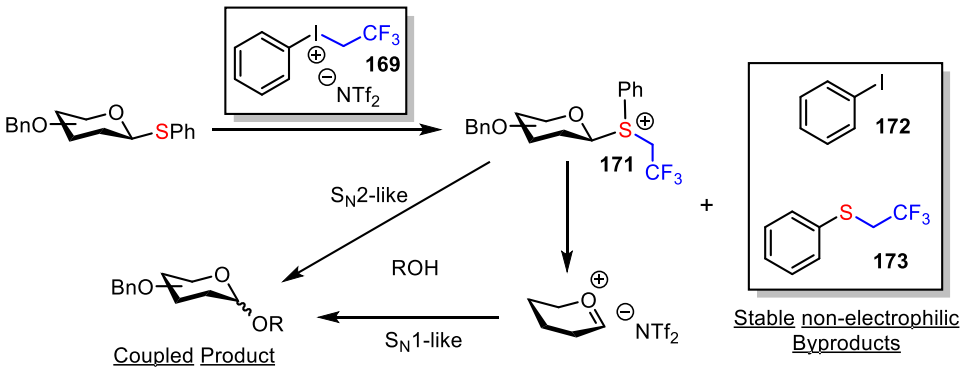


Figure 3.4: (Perfluoroalkyl)phenyl iodonium triflimide and the promoted fluoroalkylations of amino acids in aqueous media.

3.3: Phenyl(trifluoroethyl)iodonium Triflimide as a Single Component Thiophilic Promoter

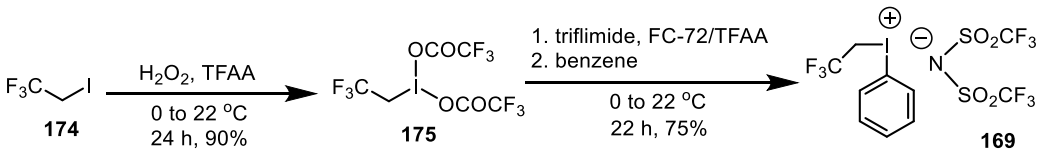
3.3.1: Preliminary Methodology Investigations

Mechanistically, we envisioned that glycosylations with reagent **169** would be initiated by an analogous transfer of trifluoroethyl group onto the nucleophilic sulfide (Scheme 3.6), thus generating the glycosyl sulfonium intermediate **171**. The highly electron-withdrawing trifluoroalkyl group would then promote anomeric leaving group ionization and the following glycosylation with nucleophilic alcohol (ROH). Importantly, since the reaction byproducts would be stable phenyl iodide **172** and thioether **173**, we anticipated that this approach would eliminate the problems with electrophilic byproducts in our previous approach. Encouraged by the potential to circumvent problematic donor regeneration pathways, we sought to investigate the applicability of **169**-promoted thioglycoside activation with our established TBAI-directed 1,2-*cis*-α glycosylation methodology.[190] To this end, we first examined the possibility of room temperature thioglycoside activation in an attempt to simplify this procedure.



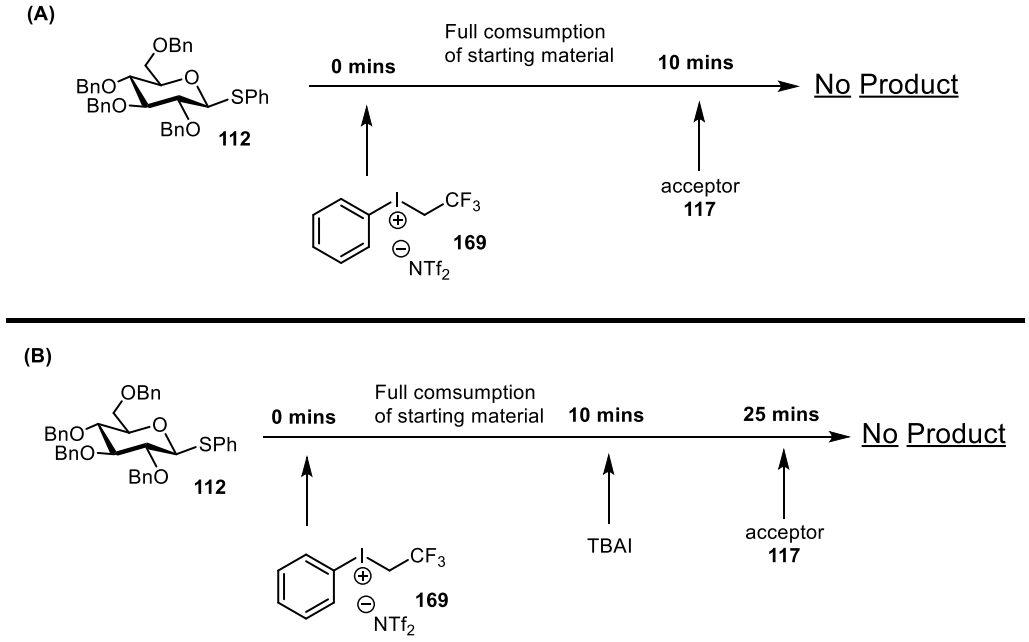
Scheme 3.6: Proposed glycosylation pathways promoted by **169**.

The synthetic preparation of **169** was performed in a two-step sequence, as reported by DesMarteau *et al.* in 1998,[222] starting from commercially available trifluoroethyl iodide **174** (Scheme 3.7). Oxidation of **174** by H_2O_2 in trifluoroacetic anhydride was carried out at 0 °C, due to the exothermic nature of the reaction, and allowed to proceed overnight to generate the shelf-stable intermediate trifluoroethyliodo bis(trifluoroacetate) **175** in 90% yield. **175** could subsequently be subjected to a Friedel-Crafts type reaction with benzene promoted by stoichiometric amounts (1.1 equiv.) of bistriflimide acid. Of particular note is the fact that the iodonium triflimide product **169** was purified by a final crystallization from water to remove residual trifluoroacetic acid, further highlighting its water-stability.



Scheme 3.7: Synthetic preparation of iodonium salt promoter **169**.

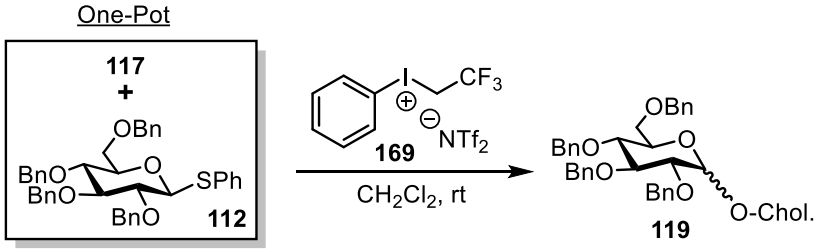
In our preliminary trials, although the pre-activation of thioglycoside **112** with reagent **169** indeed led to donor consumption, treating this mixture with a nucleophile did not provide productive glycosylations (Scheme 3.8A). Furthermore, attempts to use halide ion-promoted glycosylations with promoter **169** by introducing TBAI in the reaction also failed to afford glycosylated products (Scheme 3.8B). To address this, we examined an alternative procedure employing the activation of thioglycoside donor **112** in the presence of nucleophilic acceptor **117** by a slight excess of **169** (1.2 equiv.). This approach instead led to a rapid formation (less than 20 mins) of the glycosylated product **119** at room temperature in 63% yield as a 1.9:1 mixture of anomers (Table 3.2, entry1). Attempts to improve the yield by allowing the reaction to further proceed overnight only resulted in product decomposition (Table 3.2, entry 2). Reasoning that the decomposition could be caused by the generation of acidic bistriflimide, we next examined the use of acid-scavenger in the reaction. Indeed, an improved reaction outcome was observed with the introduction of 3 equiv. of non-nucleophilic base TTBP in the reaction mixture (71%, 1:1 α:β, Table 3.1, entry 3). Under these conditions, the reaction could instead proceed cleanly without noticeable product composition after 1 hour.



Scheme 3.8: Early examinations of donor pre-activation using promoter **169**.

A: Alcohol acceptor was treated after 10 minutes of donor pre-activation.

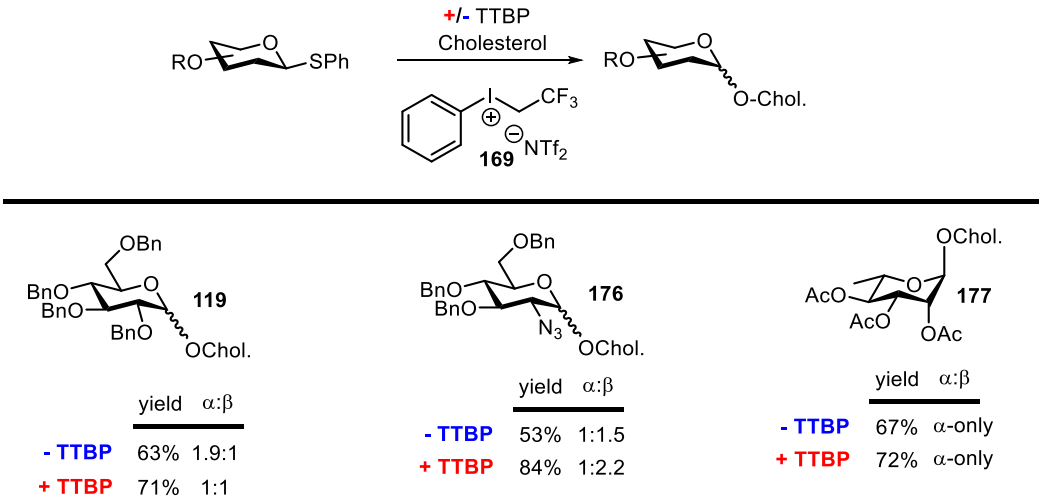
B: Sequential addition of TBAI and alcohol acceptor after donor pre-activation.



entry	time (h)	additive	yield (%)	α:β
1	0.2	——	63	1.9:1
2	24	——	0	N/A
3	**1**	**TTBP**	**71**	**1:1**

Table 3.2: Co-activation optimizations of **169**-promoted glycosylation

To further validate this observation, a quick survey was performed, as illustrated below in Scheme 3.9. To this end, the effects of acid scavenger TTBP in promoting optimal reaction outcomes and suppressing product decomposition were consistently achieved among separate entries. This demonstrated that the phenomenon observed in Table 3.1 was not substrate-specific. With these optimized conditions in hand, we next sought to examine the scope of the reaction.



Scheme 3.9: Further examinations of the effect of acid scavenger TTBP.

3.3.2: Substrate Scope Investigation

Our initial investigations into the scope of the reaction focused on the use of fully-substituted thioglycoside donors. As shown below in Figure 3.5, we examined several glycosyl donor species including benzylated glucose,

galactose and 2-deoxy-2-azido thioglycoside derivatives. All of these donor classes cleanly underwent room temperature glycosylations in good to excellent yields. In most of these cases, the reactions were typically completed within 1 hour. An exception to this was seen with the use of disarming azide[102,227] protected glycosyl donors, where the synthesis of **176, 178-179** generally took more than 3.5 hours to undergo complete reactions. In addition, acid-sensitive substrates, such as benzylidene protected donors, also underwent clean reactions (Figure 3.7, **182**). The glycosylation was also insensitive to the steric environment around the nucleophilic alcohol as glycosides **130-131** were obtained smoothly under the reaction conditions (up to 90% yield), supporting a S_N1-type reaction manifold.

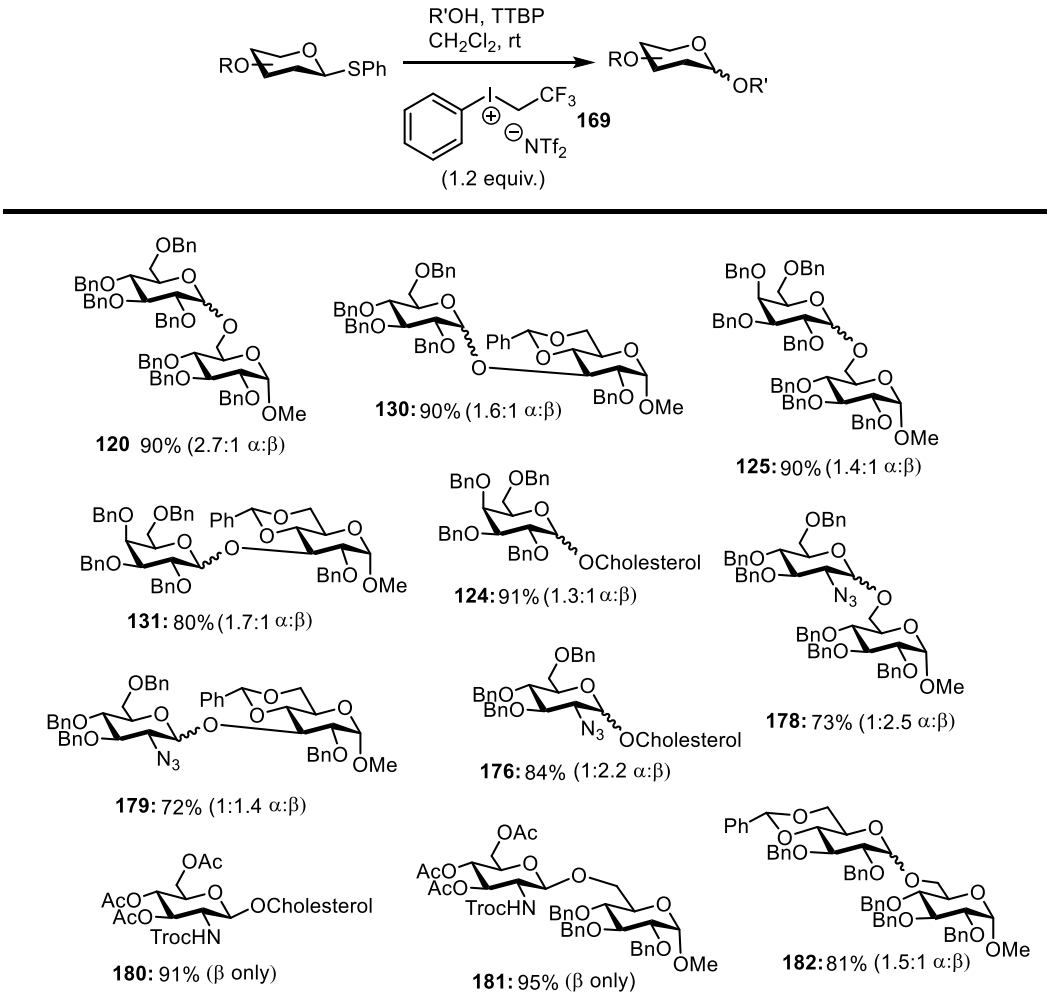
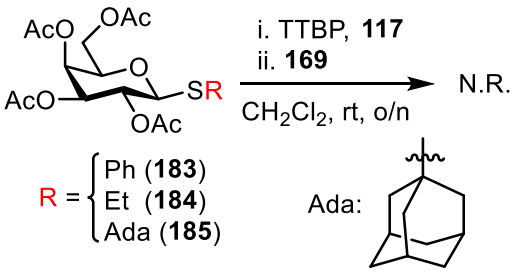


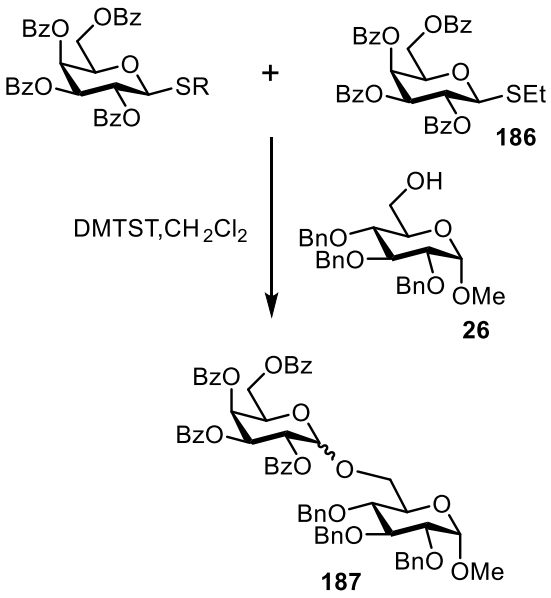
Figure 3.5: Reaction scope with fully-substituted donors.

Having established that our method could rapidly activate armed glycosyl donors, we turned our attention to the less reactive acetylated donors. Pleasingly, we found that fully disarming N-troc protected thioglucoside was also a competent glycosyl donor for this reaction, and the glycosylated products were afforded in excellent yields (Figure 3.5, 91-95 % yield, **180-181**). Notably, in these entries neighboring group participation by the Troc carbamate led to β-specific glycosylations.

Finally, moving onto fully acetylated phenylthioglycoside donor **183** proved to be problematic as donor activation could not be achieved (Scheme 3.10). In an attempt to address this, we decided to enhance the reactivity of these disarmed donor species by modulating the anomeric thiol aglycon. This was based on the comprehensive work by Lahmann and Oscarson in 2002.[228] In this study, a series of competition assays were performed (Scheme 3.11), in an analogous fashion to those seen in the previous work by Wong and coworkers,[102] to determine the relative reactivity between thioglycoside donors equipped with various aglycon moieties.[228] By this approach, the corresponding reactivity of ethylthioglycoside donors were determined to be superior to that of their phenylthio counterparts by 10-fold. In addition, cyclohexyl groups were the most arming aglycon examined in this report. In 2007, Crich and coworkers further introduced 1-adamantane thiol as a desirable aglycon alternative to cyclohexylthio group due to its greater electron donating properties, as well as its nonvolatile nature.[229] However, increasing the donor reactivity through the use of ethyl and 1-adamantyl aglycon derivatives (**184-185**) was not sufficient to promote donor activations with iodonium promoter **169** (Scheme 3.10). These results nonetheless highlighted the critical importance of inherent donor-promoter reactivity matching, and further excluded the compatibility of fully-disarmed glycosyl donors with this reaction methodology.



Scheme 3.10: Fully-disarmed thioglycoside donors examined in this study.



R: Aglycon derivatives that are used to compete with donor **186**.

Scheme 3.11: Competition assay performed by Lahmann and Oscarson to quantify the relative reactivities of aglycon-substituted thioglycosides as determined by the rate of donor disappearance on HPLC.[228]

The second part of the reaction scope involved the use of deoxy-sugar donors. These sugars are important components of many biological systems,

including human glycoproteins,[230] bacterial polysaccharides[231] and natural products.[232] The lack of oxygenation in these molecules, either at C2 or C6, destabilizes these glycosidic linkages relative to other sugars. As a result, product decomposition during the course of reaction can be problematic particularly under acidic reaction conditions.[117,233] We were therefore pleased to see that all of the deoxy sugar donors examined, including L-fucocse, L-rhamnose, and 2-deoxy D-glucose derivatives, reacted smoothly with the promoter **169** to afford the glycosylated products in modest to excellent yields (68% to 97 %, Figure 3.6) In all cases examined, armed donors underwent rapid glycosylations within 0.5 hours (Figure 3.6, **191-196**). In line with our previous results, the disarmed thiorhamnoside donor **197** underwent less efficient activation, and reacted to provide products in reduced yield (72%, Scheme 3.12, entry 1). Since in this case the acceptor **117** was added in excess (2 equiv.) relative to donor **197**, we reasoned that reversing the donor-acceptor stoichiometric ratio could salvage the low reaction yield caused by inefficient donor activation. Indeed, with a modified procedure utilizing glycosyl acceptors as the limiting reagents, we were able to obtain the glycosylated product in a much improved reaction yield (90%, Scheme 3.12, entry 2). Following this, we were able to apply these modified conditions to synthesize other disarmed substrates in good to excellent yields (Figure 3.6, **188-190**). Importantly, under the optimal conditions product decomposition or donor elimination were not observed, even with highly reactive 2-deoxy sugar donors (**194-196**).[74,234] The fact that we were able to make relatively

unstable deoxy glycosides without incident or dramatic modification to the reaction conditions further demonstrates the synthetic utility and mild nature of this new thiophilic promoter.

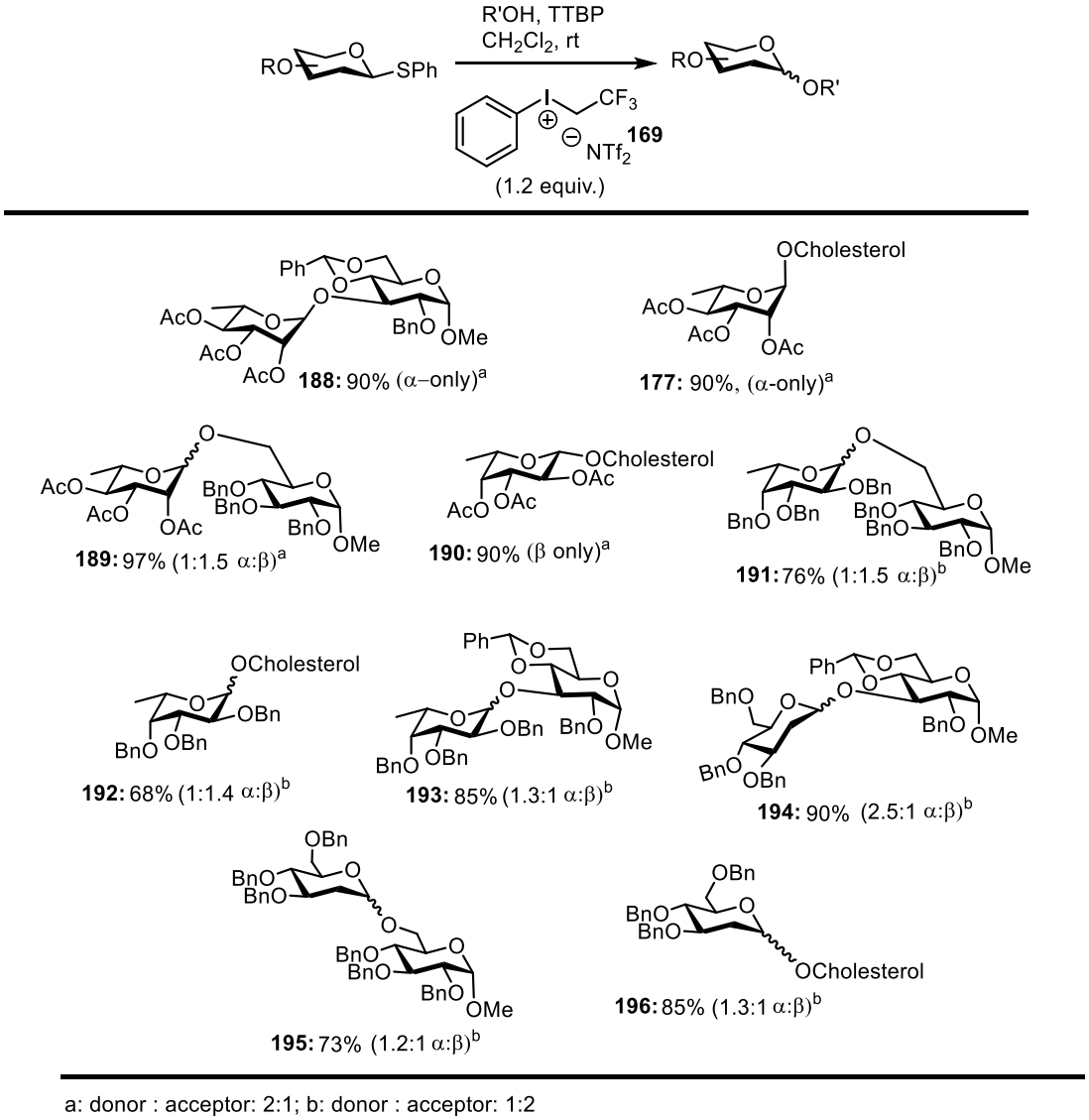
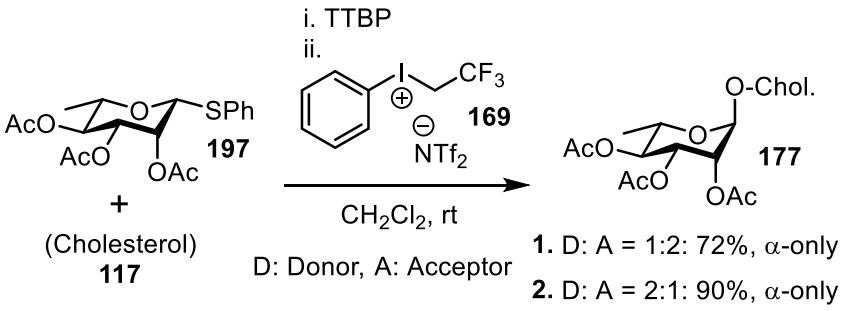
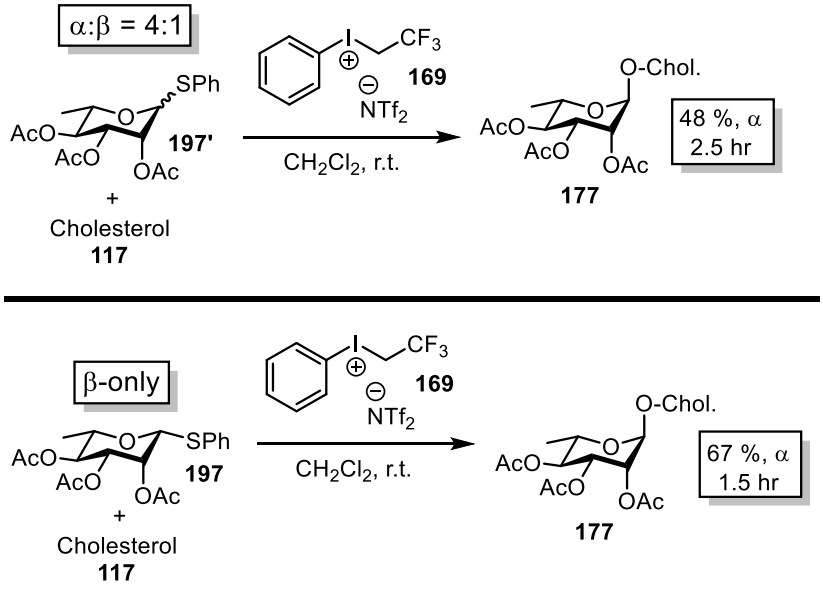


Figure 3.6: Reaction scope with 2-deoxy and 6-deoxy-sugar donors.



Scheme 3.12: Effects of donor-acceptor stoichiometric ratio in the reaction yields obtained with disarmed glycosyl donor **197**.



Scheme 3.13: Effects of the anomeric configurations of donor **197** on **169**-promoted glycosylations.

Lastly, we chose to examine the effect of the aglycon configuration on the outcome of this reaction. In the trial experiment shown in Scheme 3.13, the β-phenyl thioglycoside donor **197** was shown to provide a significantly more

robust reaction compared to the α-linked donor **197'**. We reasoned that this phenomenon was likely due to an enhanced stabilization of axial sulfonium group on **198** through anomeric effects (Figure 3.7).[197] Consequently, leaving group ionization on the α-thioglycoside donor was less favorable, therefore leading to slower reactions.

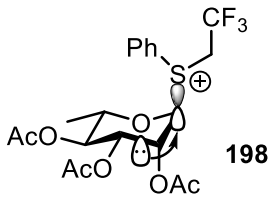
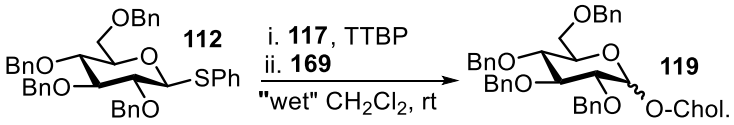


Figure 3.7: Hypothesized leaving group stabilization via anomeric effects.

3.3.3: Applicability of Iodonium Salt Promoter in "Wet Glycosylations"



Entry	Donor : Acceptor	t (hr)	Yield (%)	α : β
1	1 : 2	1	45	1 : 1
2	2 : 1	1	55	1 : 1.2

Table 3.3: Preliminary attempts at "wet" glycosylation using promoter **169**.

As described above, one of the ultimate goals of this study was to design a chemical glycosylation approach that could be routinely executed by non-specialists. A major advantage of this operationally simple procedure lies in

the water stability inherent in the thiophilic promoter **169**. We therefore envisioned this activation protocol to enable a "wet" glycosylation procedure where typical stringent drying protocols could be avoided. To quickly examine this possibility, a trial glycosylation experiment using promoter **169** was carried out without prior azeotropic drying of the reagents or the addition of activated molecular sieves. Furthermore, the reaction solvents were directly obtained from pre-opened reagent-grade dichloromethane bottles, and the entire setup was open to air throughout the course of the reaction. Under these conditions, a modest reaction yield was still achieved (Table 3.3, entry 1, 45 %) without any noticeable product decomposition. The lower yields can be largely attributed to the competing hemiacetal formation resulting from the introduced moisture. Reversing donor-acceptor stoichiometric ratio again slightly improved the reaction outcome (Table 3.3, entry 2, 55%). While the yields were significantly lower under these conditions, they were nonetheless synthetically useful and further provided a unique example of "wet" glycosylations. This is important, since many glycosylation reactions require the use of Lewis Acidic promoters that would be destroyed before they had a chance to react under these conditions.

3.4: Conclusion

In conclusion, we have disclosed here a novel chemical glycosylation strategy using a hypervalent iodide thiophile, the phenyl(trifluoroethyl)iodonium triflimide **169**. Unlike other recently

proposed water/air-tolerant thioglycoside activation procedures which feature thioperoxide/TMSOTf and hypervalent PIFA/TFOH promoter combinations (Figure 3.9),[235,236] the approach described here is distinctly advantageous in the use of a single-component thiophile **169**. This eliminated the need for hydrolytically unstable co-promoters, such as Tf_2O, TfOH or TMSOTf, to generate reactive intermediates *in situ*. While other single component, stable thiophilic promoters, such as N-bromosuccinimide (NBS)[97] or methyl triflate (MeOTf), have been reported in the past, they only efficiently activate highly reactive deoxy sugar donors and are sensitive to water (MeOTf). Hence, iodonium salt promoter **169** possesses notable advantages in terms of both its shelf-stability (> 1 year) and scalability (> 20g can be made in one synthetic round). Together with the mild glycosylation conditions, we envision that this work will lead to technologies that permit investigators with limited synthetic background to construct their own oligosaccharides. Further investigations toward achieving anomeric stereocontrol in this methodology will be discussed below in Chapter 4.

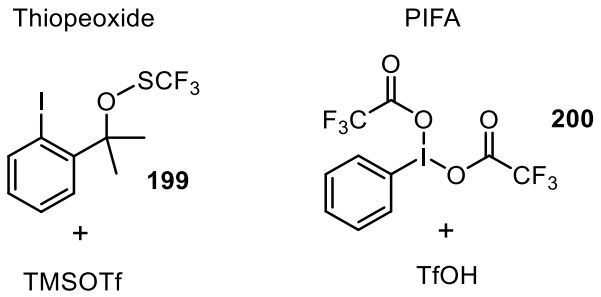


Figure 3.8: Recently reported air/waiter-tolerant thiophilic promoters.

3.5: Material and Experimental Methods

3.5.1: General Details

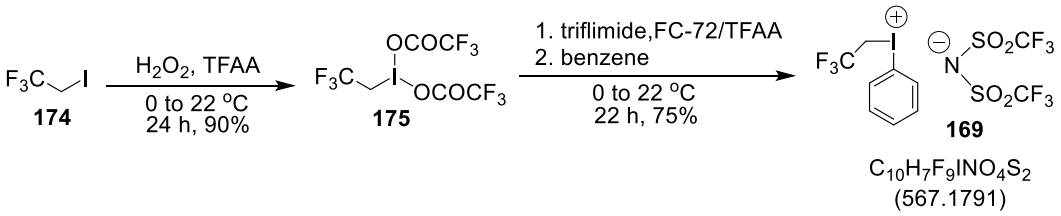
Prior to running the glycosylation reactions, all solid reagents were dried by azeotropic removal of water using toluene and a rotary evaporator < 40 °C. All reactions were carried out under an argon atmosphere unless otherwise specified. Solvents were dried using an Innovative Technologies PureSolv 400 solvent purifier. Nitrile co-solvents, other than acetonitrile, were purchased from Sigma Aldrich, and further dried over activated 4 Å molecular sieves before use. Glycosyl donors **112**, **141-143**, **146, 197, 201-204** and glycosyl acceptors **26**, **147** were synthesized following literature procedures or variations thereof.[181-185,237-241] Aryl(trifluoroethyl)iodonium triflimide **191** were prepared and characterized according to literature.[222,224] FC-72 (perfluorohexanes), N,N-(bis-trifluoromethanesulfonyl) imide (triflimide), trifluoroacetic anhydride and 2,2,2-trifluoroethyl iodide were purchased from Synquest Laboratories. All other chemicals were purchased at the highest possible purity from commercial sources and used as received. Flash column chromatography was performed on Silicycle silica gel, 230-400 Mesh. Analytical and preparative thin layer chromatography were carried out on EMD silica gel 60 F254 plates. Products were visualized using UV, or by staining with 5% aqueous sulfuric acid, iodine, or ceric ammonium molybdate stains. NMR solvents were purchased from Cambridge Isotope Labs. NMR spectra were recorded on a Bruker Avance III NMR spectrometer at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. Chemical shifts are reported in ppm

relative to TMS (for ^{1}H NMR in $CDCl_3$), and $CDCl_3$ (δC = 77.23 for ^{13}C NMR in $CDCl_3$). For ^{1}H NMR spectra, data are reported as follows: chemical shift δ in ppm, multiplicity (s = singlet, m = multiplet, t = triplet, d = doublet, dd = doublet of doublets, q = quartet and combinations thereof), coupling constants reported in Hertz (Hz), and integration. Low resolution mass spectra (LRMS) were recorded using a Finnigan LTQ ESI-MS with an additional APCI source. High resolution mass spectra (HRMS) were obtained at Massachusetts Institute of Technology Department of Chemistry instrumentation facility using a peak-matching protocol to determine the mass and error range of the molecular ion. Optical rotations were measured on a Rudolph Research Analysis AUTOPUL IV polarimeter @ 589 nm in a 5 cm cell at 24°C.

3.5.2: General Glycosylation Procedure

The reaction flask contained glycosyl donor (0.079 mmol), acceptor (0.158 mmol), and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol) dissolved in 2 ml dichloromethane. Meanwhile, Phenyl(trifluoroethyl)Iodonium triflimide **(169)** (0.095 mmol) was separately dissolved in 2 ml dichloromethane with slight warming in a 35°C water bath. After cooling down to room temperature, the solution of **169** was then added drop-wise to the reaction flask. Once the reaction was complete as indicated by TLC (typically 10 min to 3.5 h), it was quenched with triethylamine (Et_3N, 0.1ml) and concentrated in *vacuo*. Flash column chromatography on silica gel afforded the desired product as determined by ^{1}H and ^{13}C NMR.

3.5.3: Synthesis of Phenyl(trifluoroethyl)iodonium Triflimide (169).



1-[Bis(trifluoroacetoxy)iodo]-2,2,2-trifluoroethane **(175)**

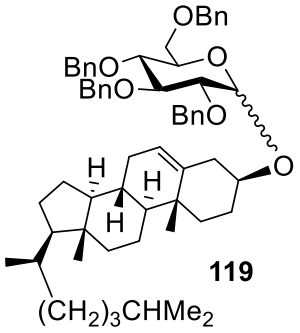
Trifluoroacetic anhydride (57 mL, 270 mmol) was loaded into a 250 mL round-bottom flask, blanketed with argon, and cooled in an ice/NaCl bath. Hydrogen peroxide (30% w/w, 5.50 mL, 44 mmol) was added slowly dropwise with magnetic stirring. After 10 minutes 2,2,2-trifluoroethyl iodide (**174**) (9.26 g, 44 mmol) was added rapidly, the cooling bath was removed, and the reaction was allowed to proceed under argon for 24 hrs. It is best to protect from light with Aluminum foil. The volatiles were removed in a rotary evaporator at ambient temperature, and the resulting oil was held in oil-pump vacuum for 3 hours. Crystallization was induced by cooling. After another hour in vacuum 1-[Bis(trifluoroacetoxy)iodo]-2,2,2-trifluoroethane was obtained as white crystals: 17.41 g (40 mmol, 90%). This intermediate material can be stored long-term in a refrigerator or freezer.

Phenyl(trifluoroethyl)iodonium Triflimide **(169)**

In a typical preparation, 1-(bis-Trifluoroacetoxy)iodo-2,2,2-trifluoroethane (9.97 g, 23 mmol) was added in one portion into a 250 mL, argon-flushed round bottom flask containing $(CF_3SO_2)_2NH$ (7.07 g, 25 mmol). The two solids were stirred in FC-72 (perfluorohexanes, 30 mL) and trifluoroacetic

anhydride (3 mL) was added in one portion. The flask was protected from light with Aluminum foil. A clear solution formed within 15 minutes, at which point benzene (2.5 mL, 27 mmol) was added rapidly while cooling in a tap water bath. The reaction mixture, which gradually separated into two phases, was stirred under static argon atmosphere for 22 hours at RT. After removing the volatile with rotary evaporator, the resin was stirred with ice/H_2O for 30 minutes to produce a white precipitate. This was collected on a glass frit, air-dried, and further dried under 0.1 torr to constant weight (11.36 g) as a white powder. Crystallization was performed by dissolving the solid product in 30 mL dichloromethane while swirling in a warm water bath, then cooling at -20˚C for 12 hours. After crystal formation was complete, the solvent was decanted and the flask washed with 5 mL of cold dichloromethane. **169** was then obtained as colorless crystals: 9.84 g (17.3 mmol, 75%). The ^{1}H and ^{19}F NMR spectroscopic data matched those previously reported.[222,224]

3.5.4: Experimental Data

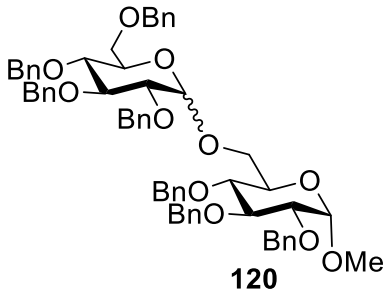


Cholesteryl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (119):

Following the general glycosylation procedure, glycosyl donor **112** (0.079 mmol, 50 mg, 1.0 equiv.), acceptor **119** (0.158 mmol, 61 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 1 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (5% ethyl acetate in hexanes) afforded the desired glycosylated product **119** (50.6 mg, 0.056 mmol, 71%, α:β = 1:1) as determined by ^1H and ^{13}C NMR.

Data for β anomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.16 (m, 20H), 5.35 (m, 1H), 4.97 (d, J = 10.8 Hz, 1H), 4.92 (d, J = 10.9 Hz, 1H), 4.81 (d, J = 10.9 Hz, 1H), 4.78 (d, J = 10.9 Hz, 1H), 4.72 (d, J = 10.8 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 10.9 Hz, 1H), 4.50 (d, J = 8.1 Hz, 1H), 3.73 (dd, J = 10.9, 1.7 Hz, 1H), 3.66-3.57 (m, 3H), 3.54 (t, J = 9.2 Hz, 1H), 3.47-3.43 (m, 2H), 2.41 (m, 1H), 2.34 (m, 1H), 2.03-1.96 (m, 3H), 1.87-1.79 (m, 2H), 1.71-0.86 (m, 33H), 0.68 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 138.9, 138.8, 138.6, 138.4, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8, 127.7, 122.1, 102.5, 85.1, 82.6, 79.9, 78.3, 77.5, 75.2, 75.1, 73.6, 69.4, 57.0, 56.4, 50.4, 42.6, 40.3, 40.0, 39.8, 39.4, 37.6, 37.0, 36.4, 36.0, 32.2, 29.9, 28.5, 28.2, 24.5, 24.1, 23.0, 22.8, 21.3, 19.6, 19.0, 12.1.



120

Methyl O-(2,3,4,6,-tetra-O-benzyl-D-glucopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (120):

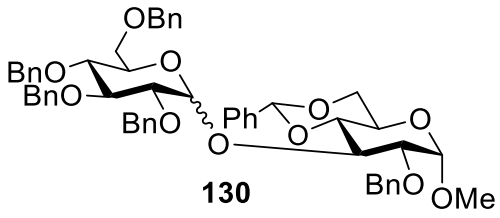
Following the general glycosylation procedure, glycosyl donor **112** (0.079 mmol, 50 mg, 1.0 equiv.), acceptor **26** (0.158 mmol, 73.3 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 0.2 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the desired glycosylated product **120** (70.1 mg, 0.071 mmol, 90%, α:β = 2.7:1) as determined by ^1H and ^{13}C NMR. Pure α compound was isolated using preparative thin layer chromatography (25% diethyl ether in toluene). The NMR spectroscopic data matched those reported previously.[71]

Data for β anomer:

^1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.10 (m, 35 H), 4.96 (d, J =11.0 Hz, 1H), 4.95 (d, J = 10.7 Hz, 1H), 4.89 (d, J = 10.8 Hz, 1H), 4.78 (m, 4 H), 4.73 (d, J = 11.2 Hz, 1H), 4.70 (d, J = 11.1 Hz, 1H), 4.64 (d, J = 12.1 Hz, 1H), 4.59 (d, J = 3.4 Hz, 1H),

4.57 (d, J =10.9 Hz, 1H), 4.51 (m, 3 H), 4.33 (d, J = 7.8 Hz, 1H), 4.17 (dd, J =10.6, 2.0 Hz, 1H), 3.97 (t, J = 9.3 Hz, 1H), 3.81 (m, 1 H), 3.71 (dd, J = 11.1, 1.7 Hz, 1H), 3.66 (dd, J = 10.8, 4.9 Hz, 1H), 3.61 (t, J = 9.0 Hz, 1H), 3.55 (t, J = 9.4 Hz, 1H), 3.50 (m, 3 H), 3.41 (m, 1 H), 3.31 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.7, 138.6, 138.5, 138.4, 138.3, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 104.0, 98.3, 85.0, 82.3, 82.2, 80.0, 78.2, 78.1, 75.2, 75.1, 73.6, 70.1, 69.2, 68.8, 55.4.



130

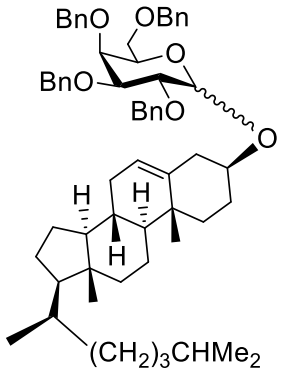
Methyl-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (130):

Following the general glycosylation procedure, glycosyl donor **112** (0.079 mmol, 50 mg, 1.0 equiv.), acceptor **147** (0.158 mmol, 59 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 1.5 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (15%→20% ethyl acetate in hexanes) afforded the desired glycosylated product **130** (58.6 mg, 0.065 mmol, 83%, α:β = 1.6:1) as determined by ^{1}H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[188]

Data for β anomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.14 (m, 30H), 5.47 (s, 1H), 5.06 (d, J = 11.5 Hz, 1H),4.91 (d, J = 11.0 Hz, 1H), 4.89 (d, J = 7.5 Hz, 1H), 4.79-4.71 (m, 4H), 4.53 (d, J = 11.0 Hz, 1H), 4.48-4.46 (m, 4H), 4.36 (t, J = 9.0 Hz, 1H), 4.21 (dd, J = 10.0, 5.0 Hz, 1H), 3.84-3.79 (m, 1H), 3.70-3.56 (m, 7H), 3.49(t, J = 8.5 Hz, 1H), 3.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 139.0, 138.7, 138.5, 138.3, 137.6, 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 126.4, 102.7, 101.7, 98.9, 85.2, 83.2, 80.7, 80.6, 78.3, 76.0, 75.8, 75.1, 75.0, 74.0, 73.8, 69.3, 68.9, 62.4, 55.5.

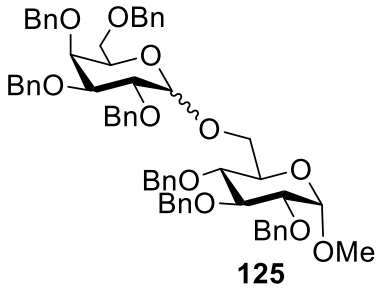


124

Cholesteryl-2,3,4,6-tetra-O-benzyl-D-galactopyranoside (124):

Following the general glycosylation procedure, glycosyl donor **146** (0.079 mmol, 50 mg, 1.0 equiv.), acceptor **117** (0.158 mmol, 61 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54

mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 1 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (5% ethyl acetate in hexanes) afforded the desired glycosylated product **124** (65.4 mg, 0.072 mmol, 91%, α:β = 1.3:1) as determined by ^1H and ^{13}C NMR. Pure α compound was isolated using preparative thin layer chromatography (5% ethyl acetate in hexanes). The NMR spectroscopic data matched those reported previously.[187]



125

Methyl-(2,3,4,6,-tetra-O-benzyl-D-galactopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (125):

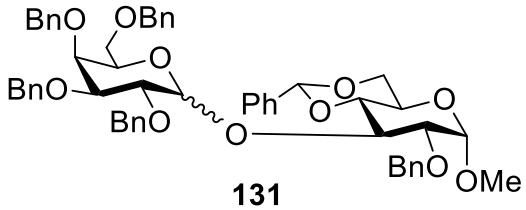
Following the general glycosylation procedure, glycosyl donor **112** (0.079 mmol, 50 mg, 1.0 equiv.), acceptor **26** (0.158 mmol, 73.3 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 0.2 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the desired glycosylated product **125** (70.4 mg,

0.071 mmol, 90%, α:β = 1.4:1) as determined by ^{1}H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[71]

Data for β anomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.15 ppm (m, 35H), 4.97-4.91 (m, 3H), 4.76-4.79 (m, 3H), 4.72-4.69 (m, 3H), 4.64 (d, J = 12.2 Hz, 1H), 4.57 (d, J = 3.2 Hz, 1H), 4.56 (d, J = 11.8 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.30 (d, J = 7.7 Hz, 1H), 4.14 (dd, J = 10.4, 1.8 Hz, 1H), 3.97 (t, J = 9.5 Hz, 1H), 3.84 (t, J = 7.7 Hz, 1H), 3.81 (m, 1H), 3.62-3.47 (m, 6H), 3.46 (t, J= 9.5 Hz, 1H), 3.29 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.7, 138.4, 138.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 104.5, 98.2, 82.6, 82.3, 80.2, 79.5, 78.4, 75.9, 75.4, 75.0, 74.8, 73.8, 73.7, 73.6, 73.5, 73.1, 70.2, 68.9, 68.8, 55.4.

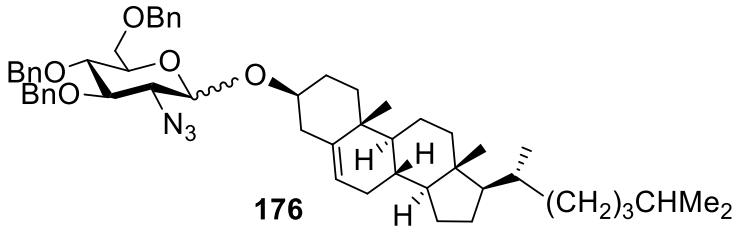


131

Methyl-(2,3,4,6-tetra-O-benzyl-D-galactopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (131):

Following the general glycosylation procedure, glycosyl donor **146** (0.079 mmol, 50 mg, 1.0 equiv.), acceptor **147** (0.158 mmol, 59 mg, 2.0 equiv.) and

2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 0.7 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (15→20% ethyl acetate in hexanes) afforded the desired glycosylated product **131** (56.4 mg, 0.063 mmol, 80%, α:β = 1.7:1) as determined by ^1H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[188]



176

Cholesteryl-3,4,6-tri-O-benzyl-2-azido-2-deoxy-D-glucopyranoside (176):
Following the general glycosylation procedure, glycosyl donor **143** (0.079 mmol, 41.5 mg, 1.0 equiv.), acceptor **117** (0.158 mmol, 61 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 2.5 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (7% ethyl

acetate in hexanes) afforded the desired glycosylated product **176** (56 mg, 0.066 mmol, 84%, α:β = 1:2.2) as determined by ^{1}H and ^{13}C NMR.

Data for α anomer:

[α]$_D$ = +30.1 (c = 0.85, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.14 (m, 15H), 5.31 (d, J = 5.0 Hz, 1H), 5.09 (d, J = 3.5 Hz, 1H), 4.90 (d, J = 10.5 Hz, 1H), 4.86 (d, J = 10.5 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.52-4.46 (m, 2H), 4.02 (dd, J = 10.0, 9.0 Hz, 1H), 3.97-3.91 (m, 1H), 3.81-3.76 (m, 1H), 3.75-3.69 (m, 1H), 3.69-3.64 (m, 1H), 3.55-3.46 (m, 1H), 3.34-3.28 (m, 1H), 2.43-2.32 (m, 2H), 2.04-1.92 (m, 3H), 1.89-1.79 (m, 2H), 1.60-0.85 (m, 33H), 0.67 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 138.3, 138.2, 138.1, 128.7, 128.6, 128.2, 128.1, 128.0, 127.9, 122.2, 96.6, 80.4, 78.7, 78.5, 75.5, 75.3, 73.7, 71.0, 68.6, 63.5, 57.0, 56.4, 50.4, 42.6, 40.3, 40.0, 39.8, 37.3, 37.0, 36.4, 36.0, 32.2, 28.5, 28.2, 28.0, 24.5, 24.1, 23.0, 22.8, 21.3, 19.6, 19.0, 12.1.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{54}H_{73}N_3O_5Na$ (M+Na) 866.5550, found 866.5444.

Data for β anomer:

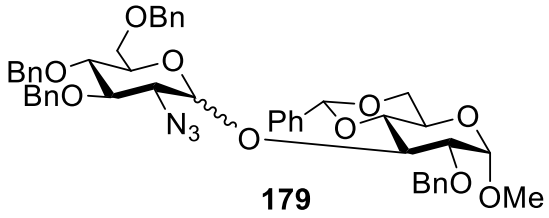
[α]$_D$ = -12.7 (c = 2.16, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.16 (m, 15H), 5.37 (d, J = 5.0 Hz, 1H), 4.88 (d, J = 11.0 Hz, 1H), 4.83-4.76 (m, 2H), 4.59 (d, J = 12.5 Hz, 1H), 4.58-4.51 (m, 2H), 4.38 (d, J = 7.5 Hz, 1H), 3.71 (dd, J = 10.5, 2.0 Hz, 1H), 3.69-3.63 (m, 1H),

3.63-3.54 (m, 2H), 3.44-3.38 (m, 3H), 2.43-2.33 (m, 2H), 2.03-1.97 (m, 3H), 1.87-1.79 (m, 2H), 1.70-0.85 (m, 33H), 0.68 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 140.0, 138.3, 138.2, 128.6, 128.2, 128.1, 128.0, 127.9, 127.8, 122.2, 101.0, 83.4, 80.1, 78.1, 75.7, 75.2, 73.6, 69.1, 66.6, 57.0, 56.4, 50.5, 42.6, 40.0, 39.7, 39.0, 37.5, 37.0, 36.4, 36.0, 32.2, 32.1, 28.4, 28.2, 24.5, 24.0, 23.0, 22.8, 21.3, 19.6, 18.9, 12.1.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{54}H_{73}N_3O_5Na$ (M+Na) 866.5550, found 866.5432.



179

Methyl-(3,4,6-tri-O-benzyl-2-azido-2-deoxy-D-glucopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (179):

Following the general glycosylation procedure, glycosyl donor **143** (0.079 mmol, 41.5 mg, 1.0 equiv.), acceptor **147** (0.158 mmol, 59 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 3.5 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (15% ethyl

acetate in hexanes) afforded the desired glycosylated product **179** (47.5 mg, 0.057 mmol, 72%, α:β = 1:1.4) as determined by ^{1}H and ^{13}C NMR.

Data for α anomer:

[α]$_D$ = +43.2 (c = 1.25, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.12 (m, 25H), 5.58 (s, 1H), 5.52 (d, J = 3.5 Hz), 4.89–4.85 (m, 2H), 4.78 (d, J = 11 Hz, 1H), 4.69 (d, J = 3.6 Hz, 1H), 4.64 (d, J = 11.3 Hz, 1H), 4.58 (d, J = 3.2 Hz, 1H), 4.57-4.55 (m, 1H), 4.47 (d, J = 11.0 Hz, 1H), 4.32 (d, J = 12.0 Hz, 1H), 4.29-4.24 (m, 2H), 4.16-4.13 (m, 1H), 3.99-3.95 (m, 1H), 3.84-3.71 (m, 4H), 3.57 (dd, J = 9.4, 3.6 Hz, 1H), 3.52-3.44 (m, 2H), 3.39 (s, 3H), 3.27 (dd, J = 10.3, 3.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 138.4, 138.2, 137.6, 137.4, 129.2, 128.9, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 127.7, 126.2, 101.6, 98.6, 98.2, 82.9, 80.0, 78.3, 75.5, 75.0, 73.9, 73.6, 70.7, 69.2, 68.1, 63.3, 62.1, 55.5.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{48}H_{51}N_3O_{10}Na$ (M+Na) 852.3574, found 852.3474.

Data for β anomer:

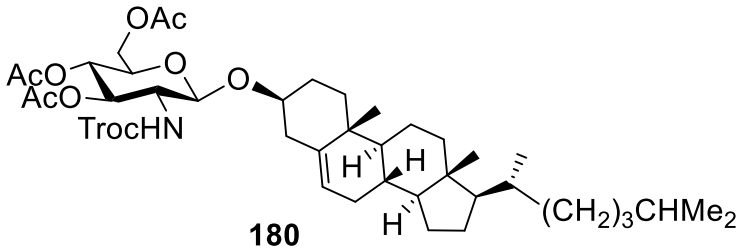
[α]$_D$ = +3.1 (c = 1.13, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.15 (m, 25H), 5.49 (s, 1H), 4.92-4.85 (m, 2H), 4.79 (d, J = 10.5 Hz, 1H), 4.76-4.71 (m, 2H), 4.62 (d, 12.0 Hz, 1H), 4.54 (d, J = 10.5 Hz, 1H), 4.51 (d, J = 3.5 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.39 (d, J =

12.0 Hz, 1H), 4.30 (t, J = 9.5, 1H), 4.22 (dd, J = 10.5, 4.5 Hz, 1H), 3.81 (td, J = 10.0, 4.5 Hz, 1H), 3.72-3.64 (m, 3H), 3.63-3.58 (m, 2H), 3.57-3.53 (m, 1H), 3.52-3.45 (m, 1H), 3.38 (d, J = 9.5 Hz, 1H), 3.34 (s, 3H), 3.27-3.22 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.3, 138.2, 137.6, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.6, 126.4, 101.9, 101.7, 98.8, 83.5, 80.6, 80.1, 78.0, 76.6, 75.7, 75.3, 75.2, 74.0, 73.8, 69.2, 68.6, 66.9, 62.5, 55.5.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{48}H_{51}N_3O_{10}Na$ (M+Na) 852.3574, found 852.3466.



180

Cholesteryl-*3,4,6-tri-O-acetyl-2-deoxy-2-trichloroethoxycarbamoyl-β-D-glucopyranoside (180)*:

Following a modified glycosylation procedure, glycosyl donor **201** (0.105 mmol, 59.4 mg, 2.0 equiv.), acceptor **117** (0.052 mmol, 20.1 mg, 1.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.208 mmol, 51.7 mg, 4.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.125 mmol, 70.8 mg, 2.4 equiv.) in 2 ml anhydrous dichloromethane at room temperature for 2.5 h. The reaction was then quenched with 0.2 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (15%

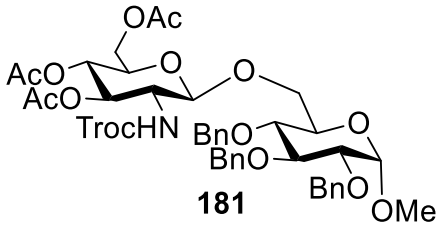
ethyl acetate in hexanes) afforded the desired glycosylated product **180** (40 mg, 0.048 mmol, 91%, β-only) as determined by ^{1}H and ^{13}C NMR.

$[\alpha]_D$ = -10.7 (c = 2.05, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.38 (t, J = 9.9 Hz, 1H), 5.32 (d, J = 4.5 Hz, 1H), 5.17 (d, J = 8.2 Hz, 1H), 5.05 (t, J = 9.6 Hz, 1H), 4.83-4.75 (m, 2H), 4.68 (d, J = 11.9 Hz, 1H), 4.28 (dd, J = 12.2, 4.8 Hz, 1H), 4.1 (d, J = 11.9 Hz, 1H), 3.73-3.67 (m, 2H), 2.25-2.16 (m, 2H), 2.08 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.99-0.86 (m, 38H), 0.67 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.8, 169.7, 154.1, 140.4, 122.4, 99.4, 95.7, 80.1, 74.6, 71.8, 69.1, 62.4, 56.9, 56.4, 50.3, 42.5, 40.0, 39.7, 39.0, 37.4, 36.9, 36.4, 36.0, 32.1, 32.0, 29.7, 28.4, 28.2, 24.5, 24.0, 23.0, 22.8, 21.2, 21.0, 20.9, 20.8, 19.5, 18.9, 12.0.

HRMS (ESI, pos. ion) *m/z*: calcd. for $C_{47}H_{68}Cl_3N_2O_{10}$ (M+NH_4) 865.3596, found 865.3941.

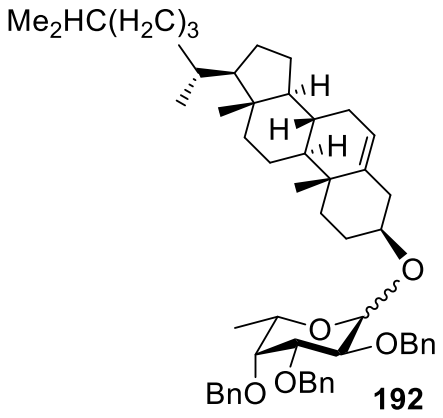


181

Methyl-(3,4,6-tri-O-acetyl-2-deoxy-2-trichloroethoxycarbamoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (181):

Following a modified glycosylation procedure, glycosyl donor **201** (0.105 mmol, 59.4 mg, 2.0 equiv.), acceptor **26** (0.052 mmol, 24.1 mg, 1.0 equiv.) and

2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.208 mmol, 51.7 mg, 4.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.125 mmol, 70.8 mg, 2.4 equiv.) in 2 ml anhydrous dichloromethane at room temperature for 2.5 h. The reaction was then quenched with 0.2 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (15% ethyl acetate in hexanes) afforded the desired glycosylated product **181** (45.6 mg, 0.049 mmol, 95%, β-only) as determined by ^1H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[242]



192

Cholesteryl-2,3,4-tri-O-benzyl-L-fucopyranoside (192):

Following the general glycosylation procedure, glycosyl donor **204** (0.079 mmol, 41.6 mg, 1.0 equiv.), acceptor **117** (0.158 mmol, 61 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 0.5 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and

concentrated in *vacuo*. Flash column chromatography on silica gel (4% ethyl acetate in hexanes) afforded the desired glycosylated product **192** (43 mg, 0.054 mmol, 68%, α:β = 1:1.4) as determined by ^{1}H and ^{13}C NMR. 1% diethyl ether/toluene preparative thin layer chromatography was then employed for the separation of α and β anomeric products. The NMR spectroscopic data of the α anomer matched those reported previously.[154]

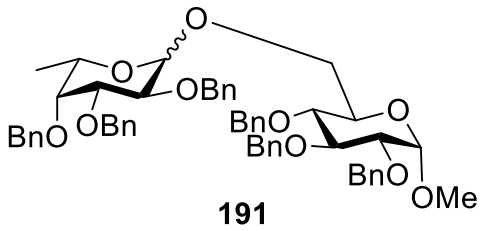
Data for β anomer:

[α]$_D$ = -220 (c = 0.32, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.26 (m, 15H), 5.34-5.33 (m, 1H), 4.97 (d, J = 4.0 Hz, 1H), 4.95 (d, J = 3.5 Hz, 1H), 4.78 (d, J = 11.5 Hz, 1H), 4.75 (d, J = 11.0 Hz, 1H), 4.73-4.67 (m, 2H), 4.42 (d, J = 7.5 Hz, 1H), 3.78 (dd, J = 9.5, 7.5 Hz, 1H), 3.58-3.52 (m, 2H), 3.48 (dd, J = 9.5, 3.0 Hz, 1H), 3.45-3.39 (m, 1H), 2.49-2.43 (m, 1H), 2.41-2.32 (m, 1H), 2.1-0.84 (m, 41H), 0.68 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 139.3, 139.0, 138.9, 132.1, 131.5, 128.8, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 127.7, 121.8, 102.6, 83.0, 79.8, 79.5, 76.6, 75.3, 74.7, 73.4, 70.4, 57.0, 56.4, 50.4, 42.6, 40.6, 40.0, 39.8, 37.4, 37.0, 36.4, 36.0, 32.2, 32.1, 28.6, 28.4, 28.2, 24.5, 24.0, 23.0, 22.8, 21.3, 19.6, 18.9, 17.2, 12.1.

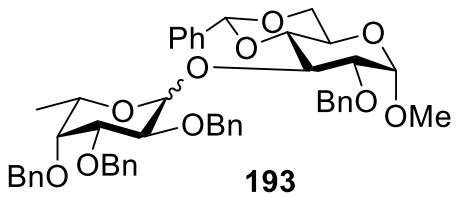
HRMS (ESI, pos. ion) m/z: calcd. for $C_{54}H_{74}O_5Na$ (M+Na) 825.5536, found 825.5418.



191

Methyl-(2,3,4-tri-O-benzyl-L-fucopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (191):

Following the general glycosylation procedure, glycosyl donor **204** (0.079 mmol, 41.6 mg, 1.0 equiv.), acceptor **26** (0.158 mmol, 73.3 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 0.1 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the desired glycosylated product **191** (53.1 mg, 0.059 mmol, 76%, α:β = 1:1.5) as determined by ^1H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[193]



193

Methyl-(2,3,4-tri-O-benzyl-D-fucopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (193):

Following the general glycosylation procedure, glycosyl donor **204** (0.079 mmol, 41.6 mg, 1.0 equiv.), acceptor **147** (0.158 mmol, 59 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 0.1 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the desired glycosylated product **193** (53.2 mg, 0.067 mmol, 85%, α:β = 1.8:1) as determined by ^1H and ^{13}C NMR.

Data for α anomer:

$[\alpha]_D$ = -37.7 (c = 1.95, CH_2Cl_2).

^1H NMR (500 MHz, $CDCl_3$): δ 7.42-7.19 (m, 25H), 5.51 (d, J = 3.5 Hz, 1H), 5.46 (s, 1H), 4.87 (d, J = 11.5 Hz, 1H), 4.82 (d, J = 11.5 Hz, 1H), 4.73-4.63 (m, 4H), 4.60-4.54 (m, 2H), 4.49 (d, J = 3.5 Hz, 1H), 4.30 (t, J = 9.0 Hz, 1H), 4.25-4.18 (m, 2H), 4.03 (dd, J = 10.0, 3.5 Hz, 1H), 3.96 (dd, J = 10.0, 2.0 Hz, 1H), 3.86-3.80 (m, 1H), 3.70-3.64 (m, 2H), 3.60 (t, J = 9.5 Hz, 1H), 3.51 (s, 1H), 3.32 (s, 3H), 0.80 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 139.0, 138.7, 138.5, 137.7, 129.3, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 126.4, 102.0, 98.9, 97.7, 81.3, 80.2, 80.0, 78.1, 76.1, 75.0, 73.4, 73.0, 72.6, 69.4, 66.2, 62.6, 55.5, 16.5.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{48}H_{52}O_{10}Na$ (M+Na) 811.3560, found 811.3441.

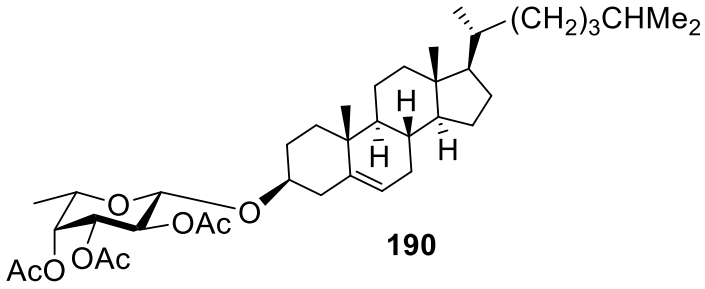
Data for β anomer:

$[\alpha]_D$ = -2.7 (c = 1.41, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.18 (m, 25H), 5.28 (s, 1H), 5.01 (d, J = 11.5 Hz, 1H), 4.93 (d, J = 12.0 Hz, 1H), 4.90 (d, J = 11.5 Hz, 1H), 4.84 (d, J = 8.0 Hz, 1H), 4.78 (d, J = 11.5 Hz, 3H), 4.72 (d, J = 12.0 Hz, 1H), 4.67-4.62 (m, 2H), 4.39 (t, J = 9.5 Hz, 1H), 4.24 (dd, J = 10.0, 5.0 Hz, 1H), 3.82-3.75 (m, 2H), 3.61 (t, J = 10.0 Hz, 1H), 3.56-3.45 (m, 4H), 3.41-3.36 (m, 4H), 1.18 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 139.2, 139.0, 138.8, 137.6, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.3, 126.3, 103.5, 101.3, 99.7, 82.7, 82.5, 80.5, 78.3, 77.5, 76.2, 75.0, 74.8, 73.9, 73.2, 70.5, 69.3, 62.0, 55.5, 17.2.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{48}H_{52}O_{10}Na$ (M+Na) 811.3560, found 811.3441.



190

Cholesteryl-2,3,4-tri-O-acetyl-β-L-fucopyranoside (190):

Following a modified glycosylation procedure, glycosyl donor **203** (0.158 mmol, 60.4 mg, 2.0 equiv.), acceptor **117** (0.079 mmol, 30.5 mg, 1.0 equiv.) and

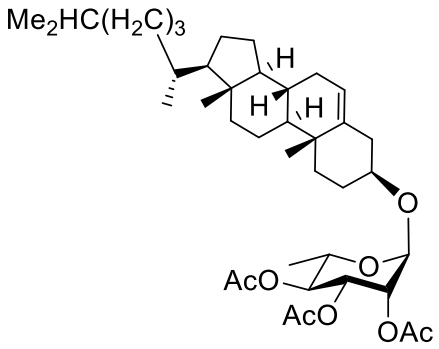
2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.316 mmol, 78.5 mg, 4.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.19 mmol, 107.5 mg, 2.4 equiv.) in 6 ml anhydrous dichloromethane at room temperature for 2.5 h. The reaction was then quenched with 0.7 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (15% ethyl acetate in hexanes) afforded the desired glycosylated product **190** (45.3 mg, 0.068 mmol, 87%, β-only) as determined by ^1H and ^{13}C NMR.

$[\alpha]_D$ = -14.6 (c = 2.16, CH_2Cl_2);

^1H NMR (500 MHz, $CDCl_3$): δ 5.36 (s, 1H), 5.22 (s, 1H), 5.18-5.12 (m, 1H), 5.03-4.97, (m, 1H), 4.52 (d, J = 7.5 Hz, 1H), 3.81-3.74 (m, 1H), 3.53-3.43 (m, 1H), 2.46-2.27 (m, 2H), 2.16 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.90-0.8 (m, 41H), 0.68 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 170.5, 169.7, 140.8, 122.2, 100.2, 80.3, 71.7, 70.6, 69.5, 69.3, 57.0, 56.4, 50.4, 42.5, 40.3, 40.0, 39.7, 37.3, 36.9, 36.4, 36.0, 32.1, 28.6, 24.0, 23.0, 22.8, 21.3, 21.0, 20.9, 20.8, 19.5, 18.9, 16.4, 12.1.

HRMS (ESI, pos. ion) *m/z*: calcd. for $C_{39}H_{62}O_8Na$ (M+Na) 681.4445, found 681.4324.



177

Methyl-(2,3,4-tri-O-acetyl-α-D-rhamnopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (177):

Following a modified glycosylation procedure, glycosyl donor **198** (0.104 mmol, 40 mg, 2.0 equiv.), acceptor **117** (0.052 mmol, 19.4 mg, 1.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.208 mmol, 52 mg, 4.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.125 mmol, 71 mg, 2.4 equiv.) in 3 ml anhydrous dichloromethane at room temperature for 3.5 h. The reaction was then quenched with 0.5 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (15% ethyl acetate in hexanes) afforded the desired glycosylated product **177** (30 mg, 0.046 mmol, 90%, α-only) as determined by ^1H and ^{13}C NMR.

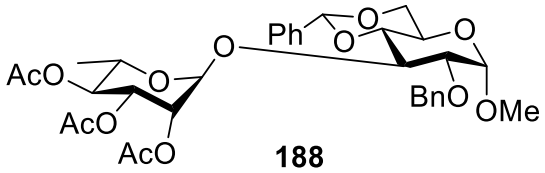
$[\alpha]_D$ = -19.6 (c = 2.13, CH_2Cl_2).

^1H NMR (500 MHz, $CDCl_3$): δ 7.48-7.31 (m, 10H), 5.52 (s, 1H), 5.35 (dd, J = 3.5, 1.5 Hz, 1H), 5.29 (dd, J = 10.0, 3.5 Hz, 1H), 5.12 (s, 1H), 4.96 (t, J = 10.0 Hz, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 3.5 Hz, 1H), 4.29-4.23 (m, 1H), 4.21-4.12 (m, 2H), 3.82 (td, J = 10.0, 4.5 Hz, 1H), 3.70 (t, J = 10.0

Hz, 1H), 3.56-3.50 (m, 2H), 3.37 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 0.76 (d, J = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.2, 137.8, 137.5, 129.2, 128.7, 128.5, 128.3, 128.2, 126.5, 102.0, 98.9, 98.2, 80.6, 79.9, 74.4, 73.6, 71.4, 70.0, 69.6, 69.2, 66.2, 55.6, 21.1, 21.0, 20.9, 16.9.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{33}H_{40}O_{13}Na$ (M+Na) 667.2469, found 667.2362.



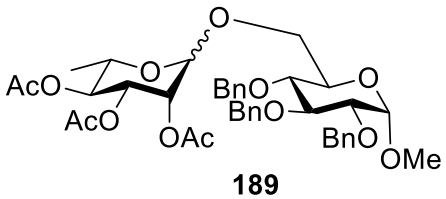
188

Methyl-(2,3,4-tri-O-acetyl-α-D-rhamnopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (188):

Following a modified glycosylation procedure, glycosyl donor **197** (0.104 mmol, 40 mg, 2.0 equiv.), acceptor **147** (0.052 mmol, 19.4 mg, 1.0 equiv.) and 2,4,6-Tri-tert-butylpyrimidine (TTBP, 0.208 mmol, 52 mg, 4.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.125 mmol, 71 mg, 2.4 equiv.) in 3 ml anhydrous dichloromethane at room temperature for 3.5 h. The reaction was then quenched with 0.5 ml of triethylamine (Et_3N) and concentrated in vacuo. Flash column chromatography on silica gel (15% ethyl acetate in hexanes) afforded the desired glycosylated product **188** (30 mg, 0.046 mmol, 90%, α-only) as determined by ^{1}H and ^{13}C NMR.

[α]D = -19.6 (c = 2.13, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.31 (m, 10H), 5.52 (s, 1H), 5.35 (dd, J = 3.5, 1.5 Hz, 1H), 5.29 (dd, J = 10.0, 3.5 Hz, 1H), 5.12 (s, 1H), 4.96 (t, J = 10.0 Hz, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 3.5 Hz, 1H), 4.29-4.23 (m, 1H), 4.21-4.12 (m, 2H), 3.82 (td, J = 10.0, 4.5 Hz, 1H), 3.70 (t, J = 10.0 Hz, 1H), 3.56-3.50 (m, 2H), 3.37 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 0.76 (d, J = 6.0 Hz, 3H).



189

Methyl-*(2,3,4-tri-O-acetyl-L-rhamnopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-α-D*-glucopyranoside *(189)*:

Following a modified glycosylation procedure, glycosyl donor **198** (0.104 mmol, 40 mg, 2.0 equiv.), acceptor **26** (0.052 mmol, 24 mg, 1.0 equiv.) and 2,4,6-Tri-tert-butylpyrimidine (TTBP, 0.208 mmol, 52 mg, 4.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.125 mmol, 71 mg, 2.4 equiv.) in 3 ml anhydrous dichloromethane at room temperature for 3.5 h. The reaction was then quenched with 0.5 ml of triethylamine (Et_3N) and concentrated in vacuo. Flash column chromatography on silica gel (15% ethyl acetate in hexanes) afforded the desired glycosylated product **189** (37 mg, 0.050 mmol, 97%, α:β = 1:1.5) as determined by ^{1}H and ^{13}C NMR.

Data for α anomer:

[α]D = +4.29 (c = 1.63, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.26 (m, 15H), 5.28 (d, J = 2.5 Hz, 1H), 5.03-5.0 (m, 2H), 4.97 (d, J = 10.5 Hz, 1H), 4.85 (d, J = 10.5, 1H), 4.84-4.77 (m, 2H), 4.68-4.60 (m, 3H), 4.55-4.52 (m, 1H), 3.96 (t, J = 9.0 Hz, 1H), 3.77 (dd, J = 10.0, 4.0 Hz, 1H), 3.74-3.69 (m, 1H), 3.67-3.62 (m, 1H), 3.56-3.50 (m, 2H), 3.49-3.43 (m, 1H), 3.36 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.75 (s, 3H), 1.21 (d, J = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.0, 139.0, 138.8, 138.4, 128.7, 128.6, 128.3, 128.02, 128.1, 127.9, 127.8, 124.7, 98.4, 97.4, 82.3, 80.0, 77.7, 76.0, 75.1, 73.6, 71.0, 70.5, 69.6, 69.3, 61.0, 55.4, 25.8, 21.0, 20.9, 17.7.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{40}H_{48}O_{13}Na$ (M+Na) 759.3095, found 759.2998.

Data for β anomer:

[α]D = +10.8 (c = 1.18, CH_2Cl_2).

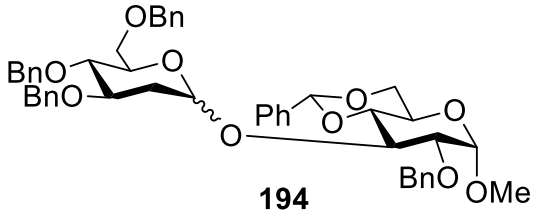
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.26 (m, 15H), 5.27 (dd, J = 10.0, 3.5 Hz, 1H), 5.23-5.20 (m, 1H), 5.07-4.98 (m, 2H), 4.91 (d, J = 11.0 Hz, 1H), 4.84-4.78 (m, 2H), 4.67 (d, J = 12.0 Hz, 2H), 4.59 (d, J = 3.5 Hz, 1H), 4.55 (d, J = 11.5 Hz, 1H), 4.00 (t, J = 9.0 Hz, 1H), 3.89-3.81 (m, 2H), 3.80-3.75 (m, 1H), 3.56-3.48 (m, 2H), 3.44-3.37 (m, 4H), 2.13 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.17 (d, J = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.1, 138.9, 138.4, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 98.1, 98.0, 82.4, 80.3, 78.1, 76.0, 75.3, 73.6, 71.3, 70.2, 70.0, 69.3, 67.0, 66.6, 55.4, 21.1, 21.0, 20.9, 17.5.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{40}H_{48}O_{13}Na$ (M+Na) 759.3095, found 759.2998.

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.2, 137.8, 137.5, 129.2, 128.7, 128.5, 128.3, 128.2, 126.5, 102.0, 98.9, 98.2, 80.6, 79.9, 74.4, 73.6, 71.4, 70.0, 69.6, 69.2, 66.2, 55.6, 21.1, 21.0, 20.9, 16.9.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{33}H_{40}O_{13}Na$ (M+Na) 667.2469, found 667.2362.



194

Methyl-(3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (194):

Following the general glycosylation procedure, glycosyl donor **141** (0.079 mmol, 41.5 mg, 1.0 equiv.), acceptor **147** (0.158 mmol, 59 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54

mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 2.5 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (15% ethyl acetate in hexanes) afforded the desired glycosylated product **194** (56 mg, 0.071 mmol, 90%, α:β = 2.5:1) as determined by ^1H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[76]

Data for α anomer:

^1H NMR (500 MHz, $CDCl_3$): δ 7.42-7.41 (m, 2H), 7.34-7.24 (m, 18H), 7.21-7.19 (m, 3H), 7.16-7.14 (m, 2H), 5.49 (bs, 2H), 4.88 (d, J = 11.1 Hz, 1H), 4.68-4.59 (m, 5H), 4.54.4.49 (m, 2H), 4.37 (d, J = 11.1 Hz, 1H), 4.28-4.23 (m, 2H), 4.10 (d, J = 9.9 Hz, 1H), 3.99 (ddd, J = 11.4, 9.0, 5.0 Hz, 1H), 3.81-3.76 (m, 1H), 3.71-3.62 (m, 3H), 3.57-3.53 (m, 2H), 3.44 (dd, J = 9.2, 3.7 Hz, 1H), 3.37 (s, 3H), 2.30 (dd, J = 12.9, 4.9 Hz, 1H), 1.70-1.66 (m, 1H).

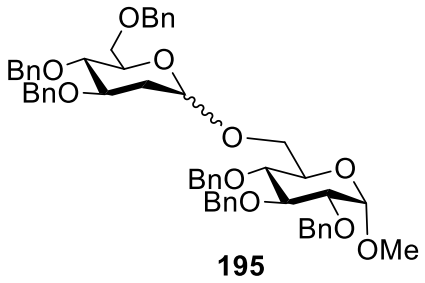
^{13}C NMR (125 MHz, $CDCl_3$): 138.3, 137.6, 137.2, 129.0, 128.5, 128.1, 127.9, 127.5, 127.4, 127.2, 126.0, 114.7, 103.3, 98.7, 97.6, 82.9, 78.2, 78.1, 74.6, 73.3, 72.7, 69.1, 68.6, 61.9, 55.2, 35.3.

Data for β anomer:

^1H NMR (500 MHz, $CDCl_3$): δ 7.49 - 7.44 (m, 2H), 7.38 - 7.20 (m, 21H), 7.20 - 7.16 (m, 2H), 5.50 (s, 1H), 4.84 (d, J = 10.5 Hz, 1H), 4.76 (dd, J = 10.0, 2.0 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.61 - 4.56 (m, 2H), 4.55 - 4.49 (m, 3H), 4.40 (d, J = 12.0 Hz, 1H), 4.23 (dd, J = 10.0, 5.0 Hz, 1H), 4.20 -

4.14 (m, 1H), 3.83 - 3.76 (m, 1H), 3.72 - 3.66 (m, 2H), 3.64 - 3.53 (m, 5H), 3.39 (s, 3H), 3.33 - 3.28 (m, 1H), 2.37 - 2.31 (m, 1H), 1.70 - 1.62 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 138.6, 138.0, 137.5, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 127.8, 127.7, 127.5, 126.3, 101.5, 101.2, 98.9, 80.3, 79.8, 79.7, 78.1, 77.6, 75.5, 75.1, 73.9, 73.6, 71.6, 69.3, 69.1, 62.7, 55.5, 37.0.



195

Methyl-(3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D glucopyranoside (195):

Following the general glycosylation procedure, glycosyl donor **141** (0.079 mmol, 41.5 mg, 1.0 equiv.), acceptor **26** (0.158 mmol, 73.3 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 1.5 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (17→20% ethyl acetate in hexanes) afforded the desired glycosylated product **195** (50

mg, 0.057 mmol, 73%, α:β = 1.2:1) as determined by ^{1}H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[76]

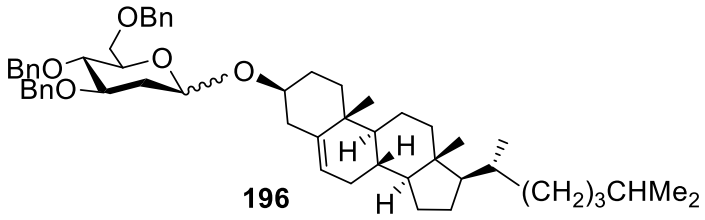
Data for α anomer:

^{1}H NMR (500 MHz, CDCl3): δ 7.37-7.23 (m, 28H), 7.14-7.12 (m, 2H), 4.98-4.95 (m, 2H), 4.91 (d, J = 12.1 Hz, 1H), 4.89-4.88 (m, 1H); 4.81-4.77 (m, 2H); 4.66 (d, J = 13.9, 12.1 Hz, 1H); 4.81-4.77 (m, 2H), 4.55 (t, J = 12.0 Hz, 1H), 3.98-3/95 (m, 1H); 3.92 (m, 1H); 3.81 (dd, J = 11.5, 4.4 Hz, 1H); 3.74-3.71 (m, 1H), 3.66 (d, J = 9.8 Hz, 1H), 3.61-3.55 (m, 3H); 3.53-3.47 (m, 3H); 3.34 (s, 3H), 2.29 (dd, J = 12.5, 5.0 Hz, 1H), 1.70-1.65 (m, 1H).

Data for β anomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.26 (m, 28H), 7.20-7.19 (m, 2H), 4.99 (d, J = 10.8 Hz 1H), 4.88 (d, J = 1.5 Hz, 1H), 4.86 (d, J = 2.3 Hz, 1H), 4.87-4.77 (m, 2H), 4.65 (d, J = 11.8 Hz, 1H), 4.60-4.51 (m, 6H), 4.16 (dd, J = 9.6, 1.5 Hz, 1H), 4.07 (dd, J = 10.6, 1.7 Hz, 1H), 3.99 (t, J = 9.2 Hz, 1H), 3.75-3.71 (m, 2H), 3.44-3.41 (m, 1H), 3.35 (m, 4H), 2.17-2.14 (m, 1H), 1.42 (dd, J = 12.1, 9.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.4, 138.3, 138.1, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6, 127.4, 100.0, 98.0, 82.2, 79.8, 79.3, 78.2, 77.4, 75.7, 74.7, 73.4, 73.3, 71.4, 69.6, 69.5, 67.6, 55.1, 36.5.



196

Cholesteryl-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranoside (196):

Following the general glycosylation procedure, glycosyl donor **141** (0.079 mmol, 41.5 mg, 1.0 equiv.), acceptor **117** (0.158 mmol, 61 mg, 2.0 equiv.) and 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol, 39 mg, 2.0 equiv.) were reacted with phenyl(trifluoroethyl)iodonium triflimide **169** (0.095 mmol, 54 mg, 1.2 equiv.) in 4 ml anhydrous dichloromethane at room temperature for 3 h. The reaction was then quenched with 0.1 ml of triethylamine (Et_3N) and concentrated in *vacuo*. Flash column chromatography on silica gel (5% ethyl acetate in hexanes) afforded the desired glycosylated product **196** (54 mg, 0.067 mmol, 85%, α:β = 1.3:1) as determined by ^1H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[76]

Data for α anomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.25 (m, 13H), 7.18-7.17 (m, 2H), 5.27 (d, J = 3.9 Hz, 1H), 5.1 (d, J = 2.6 Hz, 1H), 4.89 (d, J = 10.8 Hz, 1H), 4.69-4.63 (m, 3H), 4.51 (d, J = 6.3 Hz, 1H), 4.49 (d, J = 8.7 Hz, 1H), 4.05-3.99 (m, 1H), 3.85 (d, J = 9.8 Hz, 1H), 3.80 (dd, J = 10.5, 3.8 Hz, 1H), 3.68 (d, J = 10.3 Hz, 1H), 3.62 (t, J = 9.4 Hz, 1H), 3.49-3.43 (m, 1H), 2.29-2.26 (m, 2H), 2.03-1.93 (m, 2H), 1.89-1.81 (m, 4H), 1.76-1.70 (m, 1H), 1.57-1.20 (m, 12H), 1.16-1.00 (m, 9 H), 0.99 (s, 3H), 0.91 (m, 3H), 0.87 (m, 6H), 0.67 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 138.9, 138.6, 138.3, 128.4, 128.3, 127.6, 127.5, 121.6, 95.1, 78.5, 77.9, 75.9, 75.0, 73.4, 71.8, 70.8, 69.1, 56.8, 56.2, 50.2, 42.4, 40.0, 39.8, 39.5, 37.1, 36.8, 36.2, 35.9, 35.8, 31.9, 28.2, 28.0, 27.7, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.7, 11.9.

Data for β anomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.25 (m, 13 H), 7.23-7.21 (m, 2H), 5.33 (d, J = 5.0 Hz, 1H), 4.89 (d, J = 5.5 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.61-4.52 (m, 5H), 3.76 (dd, J = 10.5, 1.5 Hz, 1H), 3.69-3.64 (m, 2H), 3.58 (m, 1H), 3.49-3.45 (m, 1H), 3.43-3.37 (m, 1H), 2.33-2.22 (m, 2H), 2.03-1.95 (m, 2H), 1.86-1.81 (m, 2H), 1.70-1.62 (m, 1H), 1.59-1.43 (m, 9H), 1.38-1.13 (m, 6H), 1.19-0.98 (m, 8H), 1.00 (s, 3H), 0.92 (m, 3H), 0.86 (m, 6H), 0.67 (s, 3H).

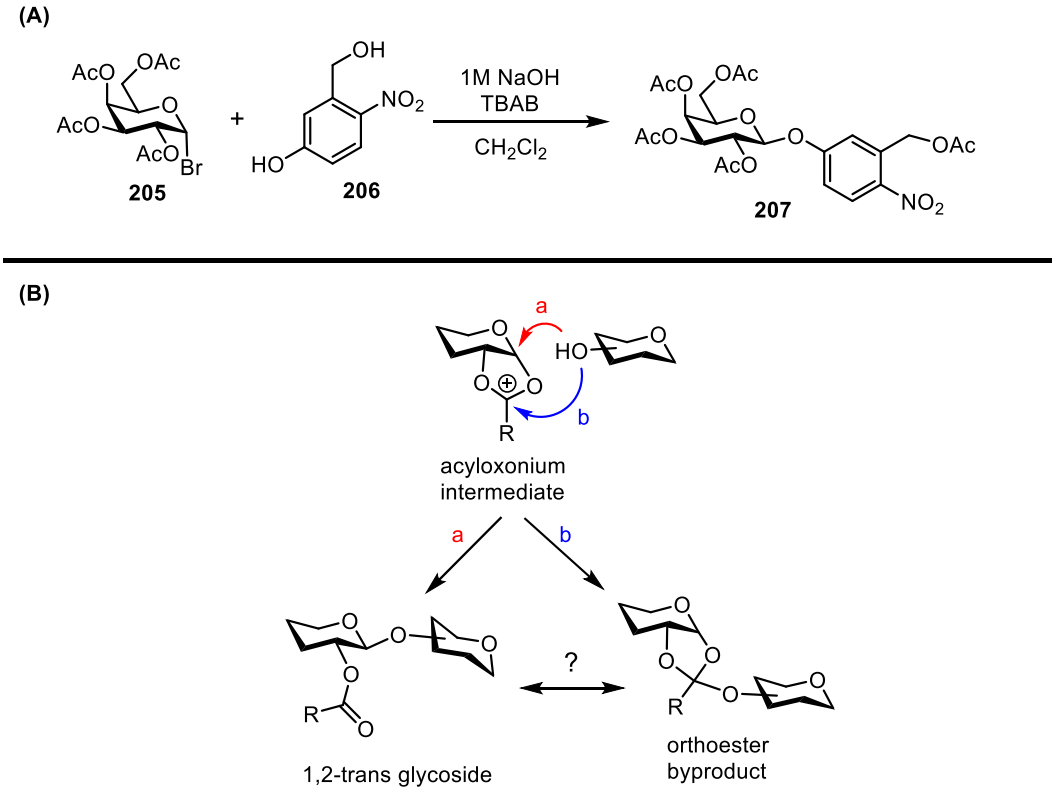
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 138.5, 138.4, 129.4, 128.0, 127.7, 127.6, 127.5, 121.8, 97.9, 79.6, 78.3, 78.2, 75.2, 74.9, 73.4, 71.3, 69.6, 56.8, 56.2, 50.2, 42.4, 39.8, 39.5, 38.9, 37.4, 37.3, 36.8, 36.2, 35.8, 32.0, 31.9, 29.7, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.7, 11.9.

Chapter 4:

Toward User-Friendly Stereoselective Glycosylations using Water/Air-Stable Iodonium Salt Promoter.

4.1: Rationale and Motivation for Method Development

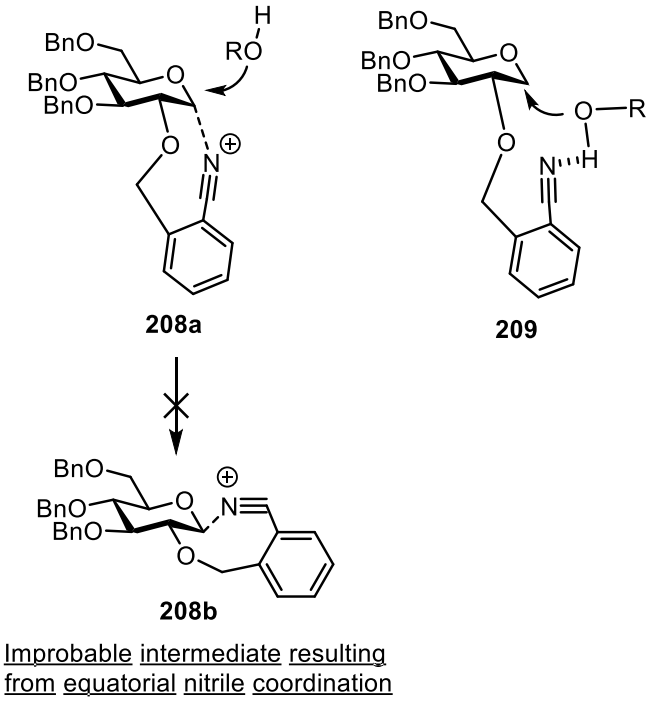
Over the course of our earlier investigations, it became apparent that the iodonium triflimide-promoted glycosylations were unselective in the absence of neighboring group participations (Figure 3.6). Although our preliminary results indicated that iodonium salt promoter **169** is compatible with C-2 acetate functional groups, we also showed that **169** failed to activate fully acetylated thioglycoside donors for subsequent glycosylations (Scheme 3.10). In addition, while neighboring acyl group participation did provide excellent β-selectivity in our hands, the use of these protecting groups has also been shown in numerous reports to be problematic under certain reaction conditions. For example, migration of acyl groups, such as acetyl and benzoyl groups, has been well-documented.[243,244] In these cases, both inter- (Scheme 4.1A)[244] and intramolecular[245] acyl transfer among free hydroxyl positions have been reported under basic conditions, thus limiting their synthetic utility. In addition, undesired orthoester formation can also be a common problem (Scheme 4.1B).[246,247] For example, Nukada and coworkers observed both acyl group migration and orthoester formation in their polymer-supported synthesis of *Streptococcus* capsular polysaccharides,[248] further highlighting the problematic issues inherent in the use of acyl protecting groups. Lastly, this strategy is limited to disarmed sugars, severally limiting its applications.



Scheme 4.1: Problems with the use of ester groups in chemical glycosylations. **A:** Intermolecular acetyl transfer observed by Thiem and coworkers.[244] **B:** Orthoester formations from acyloxonium intermediates.

This issue has recently prompted a number of labs to introduce non-ester directing groups.[249-253] One example illustrated in scheme 4.2 by Hoang and Liu involve the use of arming 2-cyanobenzyl ether moieties as directing groups on the C-2 equatorial positions. Due to the significant bond-angle strain possessed by **208b**, axial coordination of oxocarbenium ions by the linear nitrile was therefore strongly favored, which subsequently directed β-glycoside formation. This model is similar to the earlier report by Demchenko and coworkers, who demonstrated the use of arming, participating picoloyl

groups on the neighboring C-2 position to direct 1,2-*trans*-β stereoselectivity.[253] On the other hand, the presence of neighboring 2-cyanobenzyl ether groups could also lead to 1,2-*cis*-α-selective glycosylations (Scheme 4.2, **209**), which was thought to be a result of hydrogen bond-mediated nucleophilic attacks. Since cyano groups are considered to be weak hydrogen-bond acceptors, this mechanism was dominant only with the use of electron-deficient alcohols, such as 2,2,2,-trifluoroethanol.[251]



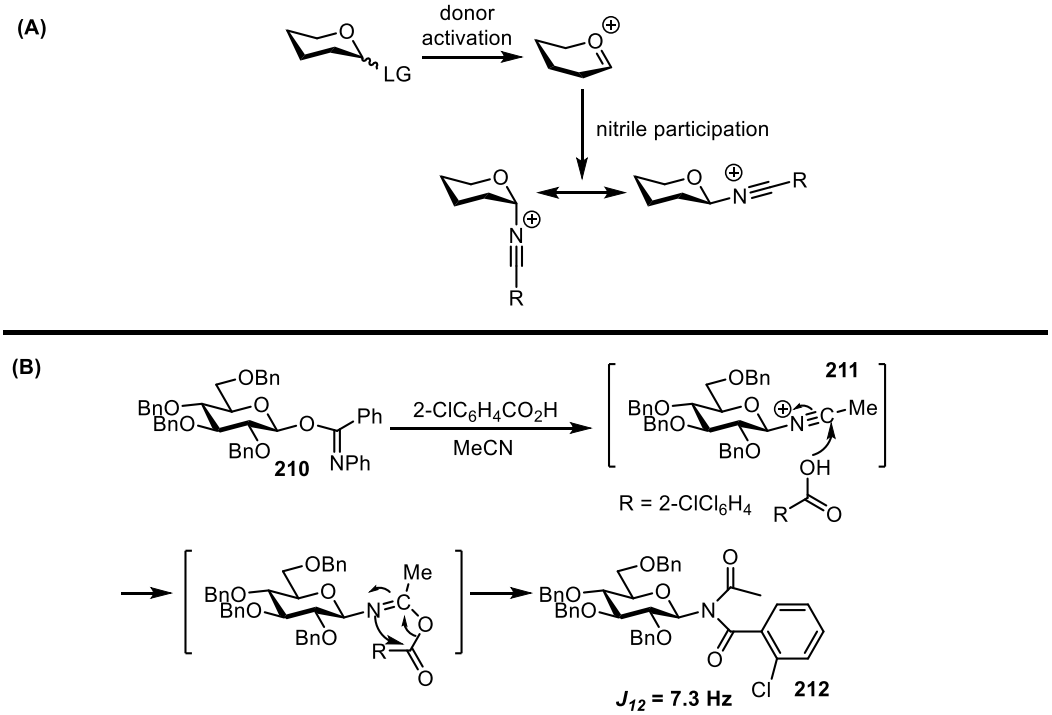
Scheme 4.2: Recent examples of arming directing groups.[251]

In accordance with these efforts, we were interested in developing alternative iodonium salt **169**-promoted glycosylation reactions that achieve

stereoselectivity without relying on acyl group participations. Moreover, the accomplishment of this goal using unmodified benzyl ether groups would be particularly advantageous, as further directing group manipulations could again be avoided. We envisioned that this strategy would lead to user-friendly stereoselective glycosylation platforms, where rapid access to both types of glycosidic linkages can be achieved from standard coupling partners in the absence of directing groups.

4.2: Progress toward achieving 1,2-*trans*-β stereoselectivity

4.2.1: Rationale for examining the compatibility of nitrile-assisted stereoselectivity with iodonium salt promoter

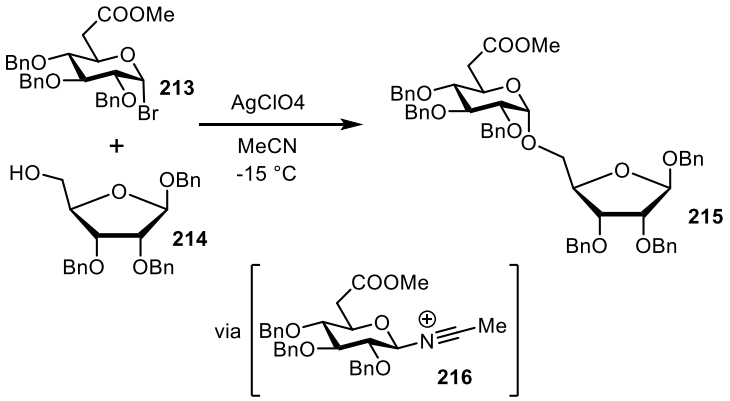


Scheme 4.3: Early assumption of β-glycosyl nitrilium intermediate invoked by Sinaÿ and Pougny.[254]

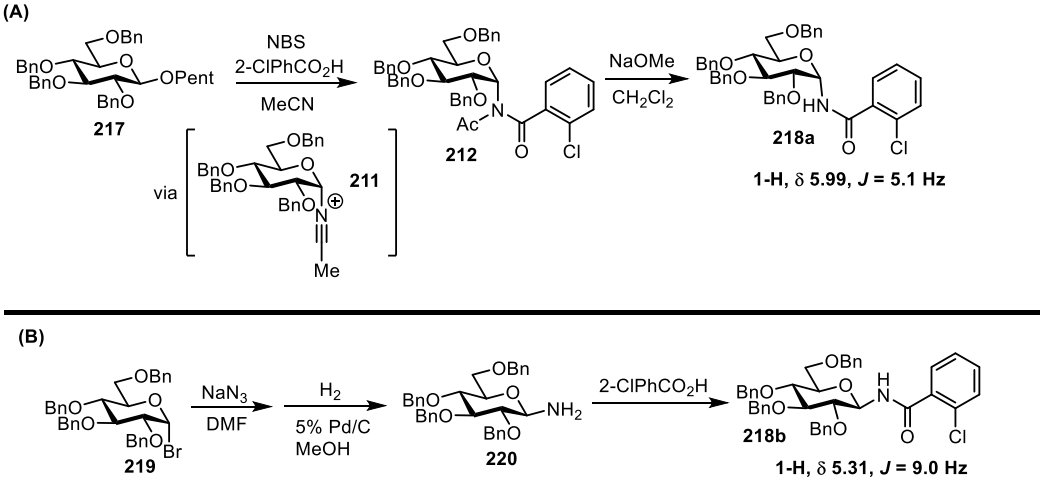
As we aimed to first achieve 1,2-*trans*-β stereoselectivity in **169**-promoted glycosylations, we decided to investigate the well-documented "nitrile-effects". The idea of nitrile solvents interacting with oxocarbenium ions (Scheme 4.3a) was first invoked by Pougny and Sinay in 1976. They proposed that initial activation of glycosyl imidate **210** led to a transient formation of glycosyl nitrilium ion **211**, which then underwent ritter-like trapping by 2-chlorobenzoic acid to afford stable glycosyl amide **212** (Scheme 4.3b).[254] The anomeric configuration of **212** was also assigned in this work to be the β-anomer (J_{12} = 7.3 Hz), which suggested the initial formation of β-glycosyl nitrilium **211** as the reaction intermediate. However, the exact anomeric configuration of these nitrilium intermediates has since been a subject of debate. For example, both Sinay and Schmidt have separately supported the existence of β-nitrilium ions, and attributed this stereochemical preference to be a result of the reverse anomeric effect.[175,254,255] Schmidt and coworkers further invoked this model to explain for their α-selective glycosylations of uronic acid **213** (Scheme 4.4).[255]

On the other hand, Lemiux and Ratcliffe[256,257] have instead argued for the existence of α-nitrilium ions. In 1990, Fraser-Reid and Ratcliffe reassigned the glycosyl amide **212** to be the α-anomer.[257] Specifically, they first synthesized **212** through a similar route as seen in Scheme 4.3, starting from the activation of pentenyl glycoside **217** by NBS (Scheme 4.5A). Base-promoted hydrolysis of **212** then afforded **218a**. Next, they separately synthesized **218b** through a key step involving the direct displacement of α-

glycosyl bromide **219** by sodium azide (Scheme 4.5B). NMR characterization of **218a/b** revealed distinct J_{12} coupling constants (5.1 Hz vs 9.0 Hz), thus confirming the α-anomeric configuration of glycosyl amide **218a** as well as its precursors **212** and **211**.[257]



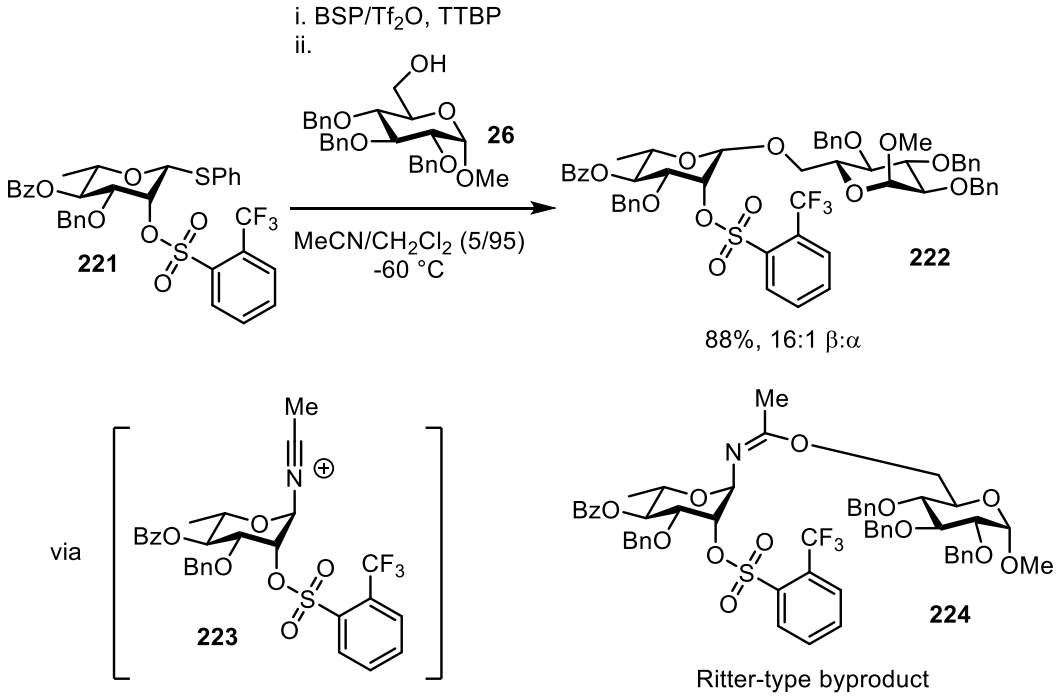
Scheme 4.4: Invoked β-glycosyl nitrilium intermediate in the α-selective glycosylation of uronic acids by Schmidt and colleagues.[255]



Scheme 4.5: Reassigned glycosyl nitrilium **211** by Ratcliff and Fraser-Reid.[257]

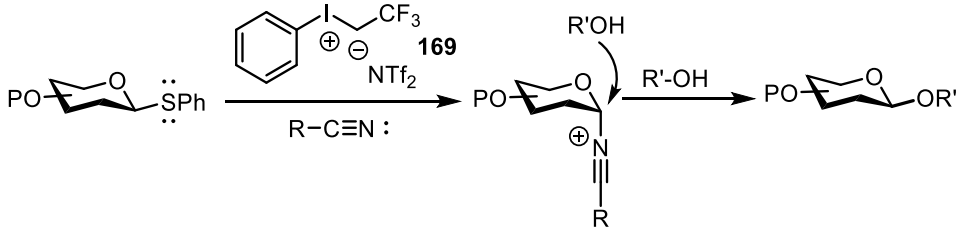
Since then, the kinetic formation of α-glycosyl nitrilium ions as reaction intermediates has been widely accepted to explain for the observed β-selectivity of glycosylations run in the presence of nitrile solvents. Recently, Crich *et al.* further expanded upon the use of nitrile effects to tackle difficult β-rhamnoside linkages (Scheme 4.6).[258] In their previous series of investigations of 1,2-*cis*-β-linked manno- and rhamnosylations, they reasoned that it is imperative to shift the equilibrium from oxocarbenium ions to the α-linked covalent donor intermediates in order to favor S_N2-type stereoinversions by the incoming nucleophiles. They further hypothesized that this shift in equilibrium could be accomplished by destabilizing the developing oxocarbenium ions. After achieving this by the installation of torsionally-strained 4,6-*O*-benzylidene acetal protecting groups,[259,260] they further demonstrated the use of non-participating, disarming protecting groups for the stereoselective synthesis of these linkages.[261,262] These approaches were inspired from the pioneering works by Schuerch and coworkers, who in 1981 demonstrated the use of 2-*O*-sulfonyl groups to stabilize α-mannosyl and rhamnosyl sulfonates.[263] In addition to destabilizing oxocarbenium ions, the effects of these neighboring electron-withdrawing groups were also thought to arise from decreasing the dipolar repulsion in the α-sulfonates. Further extending these principles, Crich applied the use of 2-*O*-trifluoromethylbenzenesulfonyl protecting groups in nitrile assisted β-rhamnosylation reactions.[258] In these examples, BSP/Tf_2O promoted highly β-selective glycosylations (up to 16:1 β:α) in dichloromethane/nitrile solvent

mixtures, presumably through a stabilized α-glycosyl nitrilium intermediate **223**. This assumption was also further supported by the observation of Ritter-type byproduct **224** in the reaction.



Scheme 4.6: β-rhamnosylation with α-glycosyl nitrilium.[258]

4.2.2: Preliminary investigations into the nitrile effects

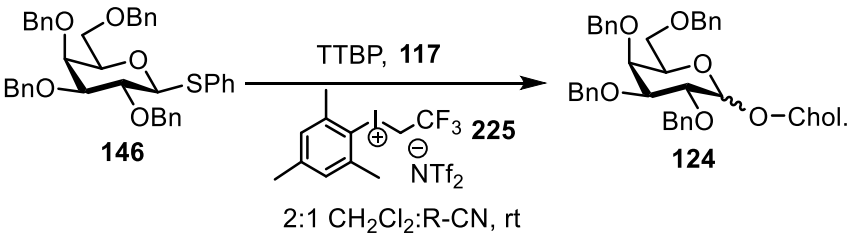


Scheme 4.7: "Nitrile effects" in **169**-promoted glycosylations.

Importantly, we reasoned that the documented nitrile participating effects would be compatible with phenyl(trifluoroethyl)iodonium salt-promoted glycosylations. Specifically, we envisioned that the salt **169** would coordinate to the more nucleophilic thiol aglycon even in the presence of coordinating nitrile solvents. This would in turn lead to the formation of oxocarbenium ions, which upon nitrile participation would generate the α-glycosyl nitrilium to direct subsequent β-selective glycosylations (Scheme 4.7). While most literature precedence invoking nitrile effects required reaction temperatures below -30 °C, we decided to perform our preliminary investigations at room temperature to match with our previously established reaction conditions. Attempts to carry out the glycosylations solely in acetonitrile failed due to the low solubility of the coupling partners and reagents. After additional trials, we settled on the use of dichloromethane/nitrile (2/1, v/v) co-solvent system. To this end, the introduction of acetonitrile co-solvent resulted in the preferred formation of β-glycoside **124** (5.2:1 β:α) compared to when dichloromethane was used alone (Table 4.1, entry 1 vs 2). Unlike typical iodonium salt-promoted glycosylation reactions demonstrated in Chapter 3, the presence of nitrile co-solvent led to slower reactions, and in these cases the reactions were allowed to stir overnight for optimal results. This indicated that, unlike previous entries where rapid oxocarbenium ion formation presumably led to robust glycosylations, the reactions here indeed proceeded through different reactive intermediates.

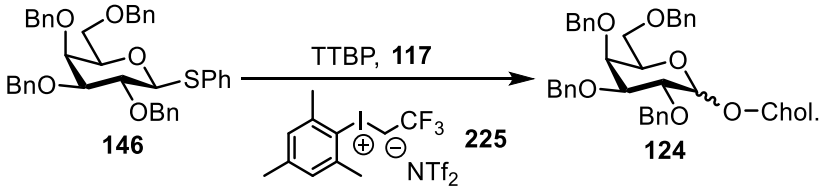
The β-selectivity that was observed in this preliminary experiment led us to believe that α-glycosyl nitrilium intermediate was indeed formed under these modified reaction conditions. In order to further optimize β-selectivity, we hypothesized that stabilizing the developing positive charge on the glycosyl nitrilium intermediate should result in a tighter coordination, and hence, a greater S_N2 character. This hypothesis was based in part on studies by Schmidt and Toepfer, who demonstrated the superior β-directing effects of propionitrile compared to that of benzonitrile and acrylonitrile.[264] We therefore decided to screen various nitrile solvents possessing different σ-bond donating groups on the α-carbon.

As shown in Table 4.1 (entry 2-6), the use of more potent σ-donating nitriles resulted in a slight increase in the afforded β-stereoselectivity, however we did not deem this to be significant. Although the observed β-directing effects were most dominant with trimethylsilyl acetonitrile (Table 4.1, entry 6), the use of this solvent introduced difficulty in the purification of reaction mixture. Finally, introducing trichloroacetonitrile as a co-solvent led to complete erosion of selectivity, suggesting the importance of stabilized nitrilium intermediates in promoting β-selectivity (Table 4.1, entry 7).



Entry	R	Yield (%)	α:β
1	no nitrile	91	1.3:1
2	Me	75	1:5.2
3	Et	81	1:5.6
4	^{i}Pr	91	1:5.1
5	^{t}Bu	78	1:6.4
6	TMS-H_2C——	56	1:7
7	Cl_3C—	81	1:1.1

Table 4.1: Preliminary nitrile solvent screen at room temperature.

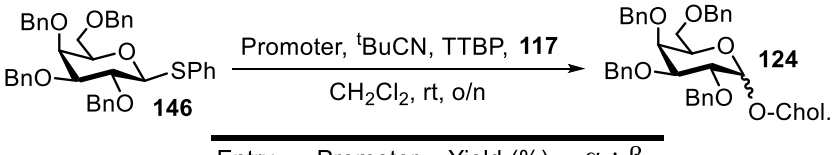


Entry	R	Yield (%)	α:β
1	Me	86	1:4.9
2	Et	81	1:5.6
3	^{i}Pr	87	1:7.5
4	^{t}Bu	78	1:9
5	TMS-H_2C——	48	1:9.6

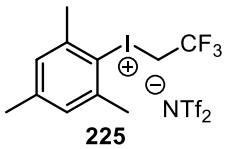
Table 4.2: Preliminary nitrile solvent screen at low temperature.

To further improve the β-selectivity of this reaction, we decided to examine the use of lower reaction temperatures.[265-267] Although NMR analysis

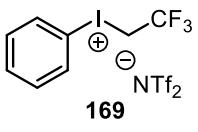
of nitrilium species have been attempted at -30 °C by Sinay and coworkers,[268] we decided to perform our initial experiments at 0 °C (ice bath) for the purpose of operational simplicity. As shown in Table 4.2, these results clearly showed that lower reaction temperatures led to increased β-selectivity. We attributed this to the enhanced stabilization of glycosyl nitrilium ions. Further cooling from 0 °C to -10 °C, however, failed to produce a noticeable improvement in selectivity (70%, 1:8.2 α:β). This suggested that either the plateau for optimal nitrilium stabilization was reached at 0 °C, or that even further cooling (such as -40 °C) was required. However, this was not pursued due to the low solubility of iodonium salt reagent **225** at temperatures below -40 °C. Lastly, in these preliminary nitrile screens, iodonium salt promoter **225** was chosen for its superior solubility in acetonitrile. Both **169** and **225** produced similar results under nitrile-assisted reaction conditions, however, and can be used interchangeably (Table 4.3, entry 1 vs entry 2).



Entry	Promoter	Yield (%)	α : β
1	**225**	78	1 : 6.4
2	**169**	76	1 : 5.6



225

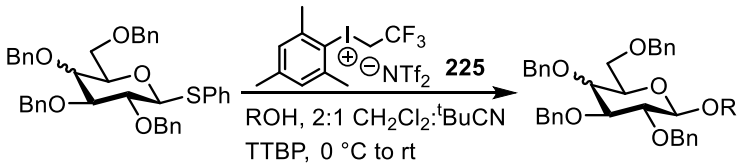


169

Table 4.3: Comparison of nitrile-assisted stereoselective glycosylations promoted by iodonium salt **169** and **225**.

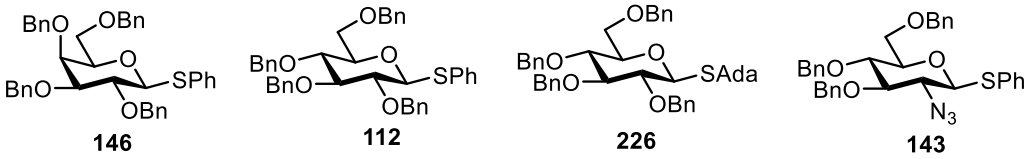
4.2.3: Preliminary substrate scope investigations

Based on these screens we decided to examine the scope for the reaction in the solvent combination of 2:1 CH_2Cl_2:pivalonitrile at 0 °C. To this end, donor **146** reacted with primary alcohol **26** in good yield and selectivity (Table 4.4, entry 1). In addition, sterically hindered acceptor **147** also provided the product in good yield, albeit with lower β-selectivity (Table 4.4, entry 2). Parallel reactions with the less reactive thioglucoside donor **112** and cholesterol again provided the glycosylated product **119** uneventfully (Table 4.4, entry 3). Much to our surprise and disappointment, however, carbohydrate acceptors **26** and **147** both reacted with **112** in much lower yields (Table 4.4, entry 4-5). This phenomenon was also observed when the disarmed 2-deoxy-2-azido thioglucoside donor **143** was used in the reaction. In this latter case, the desired glycosides were obtained in further decreased yields, but with enhanced β-selectivity (Table 4.4, entry 9-11).



Entry	Donor	Acceptor	Product	Yield (%)	α:β
1	**146**	**26**	**125**	82	1:8.5
2	**146**	**147**	**131**	71	1:5.5
3	**112**	**117**	**119**	70	1:12.6
4	**112**	**26**	**120**	46	1:10.2
5	**112**	**147**	**130**	65	1:5.9
6	**226**	**117**	**119**	92	1:14
7	**226**	**26**	**120**	65	1:10.7
8	**226**	**147**	**130**	85	1:6.5
9	**143**	**117**	**176**	49	1:23
10	**143**	**26**	**178**	46	1:10.6
11	**143**	**147**	**179**	45	1:6.6

Donors:



Acceptors:

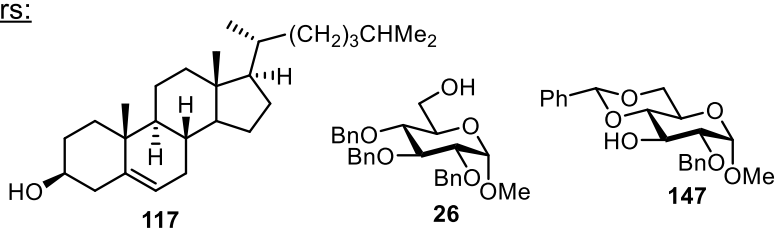
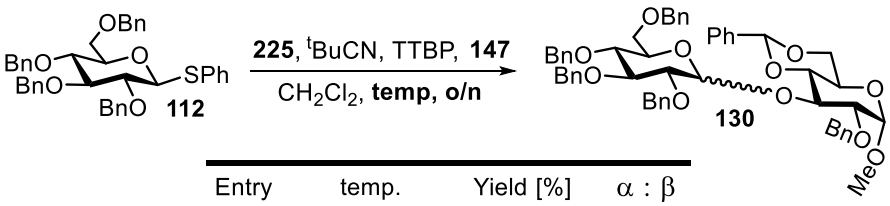


Table 4.4: Scope of reaction in pivalonitrile/CH_2Cl_2.

We reasoned that the high stereoselectivity as well as low reaction yields obtained with glycosyl donors **112** (Relative reactivity value (RRV) = 2656) and **143** (RRV = 200) could both be attributed to their lower reactivity compared to donor **146** (RRV = 1.7x 10^4).[102,234] In essence, free oxocarbenium ions were less stabilized on donors **112** and **143**, and reaction pathways

involving glycosyl nitrilium intermediates were therefore more significant. However, inefficient donor activation likely also contributed to the lower reaction yields. In an attempt to salvage the reaction yields, we turned to examining the use of arming adamantyl thioglycosides in the reactions.[229] Pleasingly, **226** reacted with all nucleophilic acceptors in improved yields (Table 4.4, entry 6-8), confirming our hypothesis. However, the use of donor **226** did not result in further improvements in selectivity. Furthermore, while this donor was particularly effective with secondary acceptors, the lower yield obtained with primary acceptor **26** indicated the need for further reaction optimizations (Table 4.4, entry 7).

Throughout our preliminary investigations the use of sterically hindered alcohol **147** in glycosylations consistently afforded the lowest levels of β-selectivity. We reasoned that this may be due to the fact that **147** was not able to efficiently react with the pre-established α-glycosyl nitrilium intermediate. As a result, the reaction was instead going through a competing background oxocarbenium ion pathway, which led to the attenuated stereoselectivity. In an attempt to suppress this background pathway, a trial experiment was performed whereby the entire reaction set up was kept in the cold room (4 °C) overnight. Although a slight improvement in β-selectivity was observed with this modified procedure (Table 4.5, entry 1 vs 2), we were not able to obtain the same levels of selectivity that were observed with other acceptors. Therefore, we decided to move forward with the established standard procedures (0 °C to room temperature overnight).



Entry	temp.	Yield [%]	α : β
1	0 °C to rt	65	1 : 5.9
2	4°C	57	1 : 7.2

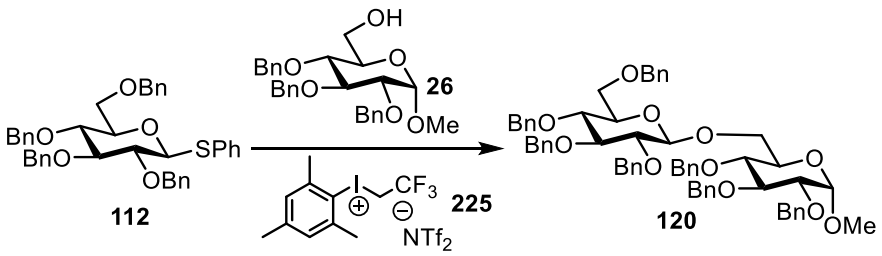
Table 4.5: Further attempt to optimize stereoselectivity with running the reaction at low temperature overnight.

4.2.4: Examinations with mixed nitrile solvent system

We noted that in our hands the use of less hindered nitriles provided slightly higher yields, while more hindered nitriles provided optimal β-selectivity (see Table 4.1 and 4.2). Therefore, we decided to examine the use of mixed nitrile solvent system in the hope of taking advantage of a synergistic effect to provide synthetically useful reaction yields and selectivity. In fact, the use of mixed nitrile solvents in chemical glycosylations is not unheard of. For example, Mong and coworkers have shown that with the nitrile combination of 2:1 (v/v) CH_3CN:EtCN, improved reaction outcomes, both in yield and selectivity, could be achieved as compared to when the respective nitrile component was used alone.[265,266]

We initially settled on using acetonitrile and/or isobutyronitrile as the additional nitrile component, as our preliminary studies indicated that reactions run in these solvents resulted in superior yields (Table 4.6). In all of our investigations with mixed nitrile solvents, we decided to maintain an

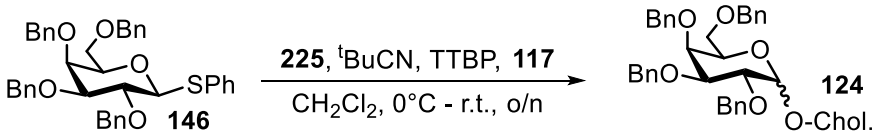
overall 2:1 dichloromethane/nitrile volume ratio since it was shown to be the optimal condition in our earlier screens (Table 4.7). To this end, running the reaction between **112** and **26** in a mixture of 4:1:1 CH_2Cl_2:isobutyronitrile:pivalonitrile improved the yield to 68% accompanied by a slight increase in selectivity to 12.5:1 β:α (Table 4.6, entry 1). A further increase in yield to 77% with little loss in selectivity was achieved with the combination of 4:1:1 CH_2Cl_2:acetonitrile:pivalonitrile (Table 4.6, entry 2). Much to our surprise, the use of quaternary solvent mixture composed of 6:1:1:1 CH_2Cl_2:acetonitrile:isobutyronitrile:pivalonitrile resulted in a dramatic improvement in both yield and selectivity (72%, 17-25:1 β:α, two separate runs, Table 4.6, entry 3).



Entry	Nitrile mix	Yield (%)	α:β
1	^{i}PrCN:^{t}BuCN (1:1)	68	1:12.5
2	MeCN:^{t}BuCN (1:1)	77	1:10
3	MeCN:^{i}PrCN: ^{t}BuCN (1:1:1)	72	1:17-25[a]

a: Results from two separate runs.

Table 4.6: Effects of mixed nitrile solvents on stereoselectivity.



Entry	nitrile/CH_2Cl_2[a]	Yield (%)	α : β
1	1/3	73	1 : 8
2	1/2	78	1 : 9
3	1/1	50	1 : 7

a: v/v ratio

Table 4.7: Optimization of nitrile co-solvent volume ratio.

The fact that predominant formation of 1,2-*trans*-β-glycosides was obtained with all of the examined mixed nitrile combinations suggested that glycosyl nitrilium ions could be invoked as a common intermediate in these cases. However, a rational explanation for the dramatically enhanced β-selectivity achieved by the use of quaternary mixed nitrile co-solvents in Table 4.6 is yet unclear. In this respect, the correlation between solvent polarities and the stereoselectivity obtained in glycosylation reactions is well recognized. Traditionally, it has been viewed that polar solvents preferentially stabilize highly charged solvent-separated oxocarbenium ion species, thereby favoring the following S_N1-like reaction manifolds.[269-272] We were therefore intrigued to see if the phenomenon observed in Table 4.6 could in fact be a result of differential solvent polarities possessed by the various mixed nitrile solvent systems. In order to assess this possibility, we sought to measure the refractive indices (nD) of the utilized mixed nitrile solvents, as the correlation between

solvent refractive indices and the relative dielectric constants (ε) has been documented.[273] As shown in Table 4.8, we did not observe a significant difference of the refractive indices measured between each mixed nitrile combination. These results therefore excluded a definitive role of solvent polarities in dictating the β-selectivity obtained in our reaction settings.

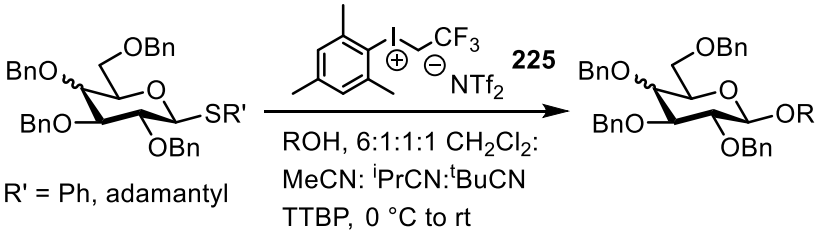
DCM + A	DCM + I	DCM + P	DCM + I + A	DCM + I + P	DCM + I + P + A
1.391	1.399	1.410	1.396	1.405	1.399

Table 4.8: Refractive indices (n_D) measurements of the mixed nitrile solvents. A: Acetonitrile; I: Isobutyronitrile; P: Pivalonitrile. CH_2Cl_2/nitrile = 2:1 (v/v).

4.2.5: Further reaction scopes with quaternary solvent system

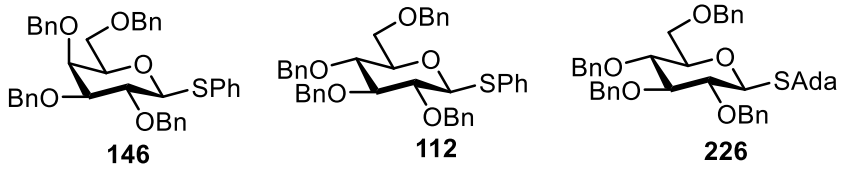
Re-examination of the reaction scope using quaternary mixed nitrile solvent combinations showed a significant increase in yields between **112** and all acceptors examined (Table 4.9). These conditions also led to improved β-selectivity when cholesterol was used as an acceptor, whereas when acceptor **147** was used in the reaction we observed little change in selectivity compared to when the reaction was run in pivalonitrile alone (Table 4.9, entry 2). The impact of this quaternary solvent system on yield and selectivity in reactions with donors **146** and **226**, on the other hand, was trivial (Table 4.9, entry 3 to 8). This further indicated that substrate-specific optimizations with mixed nitrile solvent conditions were not required for reactive donor species. Finally,

an attempt to further improve the β-selectivity with acceptor **147** by employing high-dilution conditions[265] only resulted in a decrease in reaction yield and selectivity (17%, 1:5 α:β).



Entry	Donor	Acceptor	Product	Yield (%)	α:β
1	**112**	**117**	**119**	91	1:18
2	**112**	**147**	**130**	82	1:6.2
3	**146**	**117**	**124**	91	1:9.2
4	**146**	**26**	**125**	80	1:9.5
5	**146**	**147**	**131**	85	1:5.1
6	**226**	**117**	**119**	92	1:15.2
7	**226**	**26**	**120**	84	1:11
8	**226**	**147**	**130**	85	6.3

Donors:



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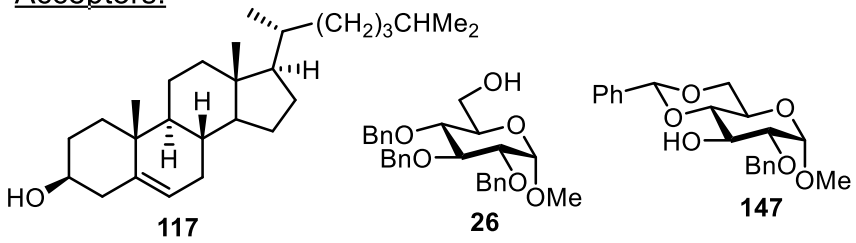
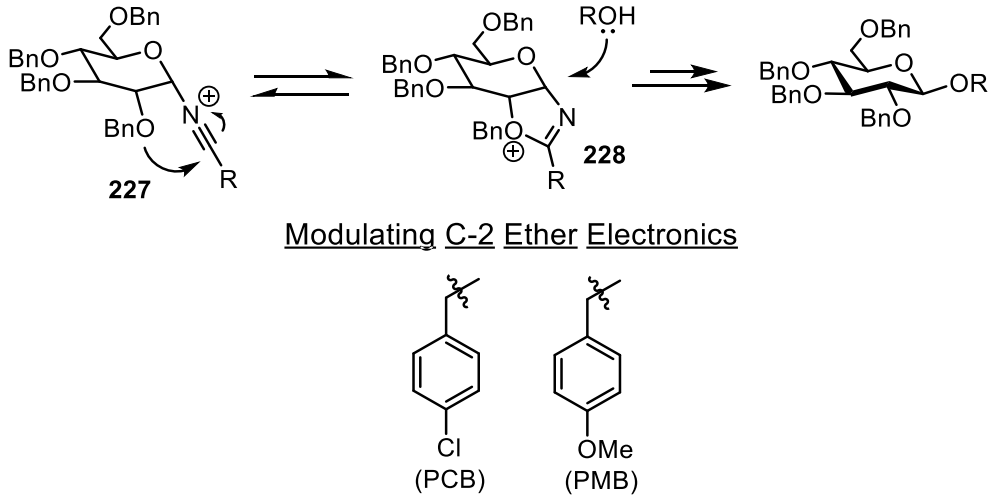


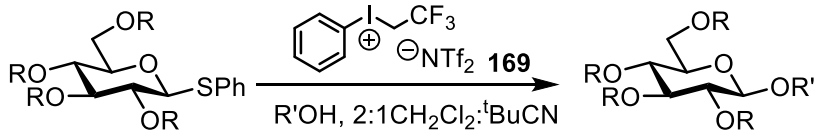
Table 4.9: Scope of reaction with quaternary solvent system.

4.2.6: Mechanistic insights and comparison with known thiophiles

In all entries examined so far, we consistently observed low levels of selectivity with the use of hindered acceptor **147**. In an effort to tackle this problem, we turned our attention to modulating the electronics of the C-2 ether protecting groups. Our motivation for this study arose from Mong's previous report[265,266] that the β-selectivity of glycosylations run in nitrile solvents may be reinforced through the participation of C-2 oxygen into the α-nitrilium ion intermediate **227**, thus leading to the transient formation of oxazolinium ion **228** which blocks the α-face (Scheme 4.8). We reasoned that if this pathway was indeed occurring in our reactions, then the presence of C-2 electron-donating benzyl ether groups could stabilize the developing positive charge on a species such as **228**, thereby further enhancing its β-directing effects.

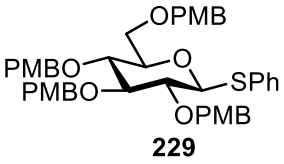


Scheme 4.8: Rationale of investigating differential C-2 ether participations in promoting nitrile-assisted β-selectivity.

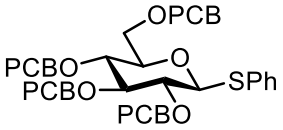


Entry	Donor	Acceptor	Product	Yield (%)	α:β
1	**229**	**26**	**233**	29	β only
2	**229**	**147**	**234**	28	β only
3	**230**	**26**	**235**	67	1:7.8
4	**230**	**171**	**236**	55	1:3.5
5	**232**	**147**	**237**	68	1:4
6	**231**	**26**	**238**	70	1:7.3
7	**231**	**147**	**239**	55	1:3.5

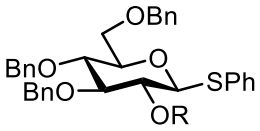
Donors:



229

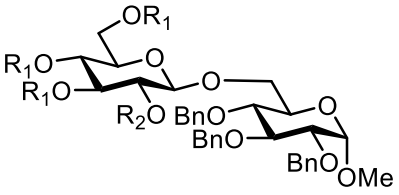


230

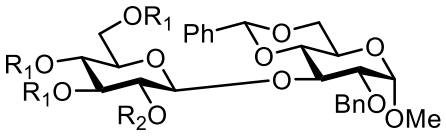


231 R = PMB
232 R = PCB

Products:



233 $R_1 = R_2$ = PMB
235 $R_1 = R_2$ = PCB
238 R_1= Bn, R_2 = PMB



234 $R_1 = R_2$ = PMB
236 $R_1 = R_2$ = PCB
237 R_1 = Bn, R_2 = PCB
239 R_1 = Bn, R_2 = PMB

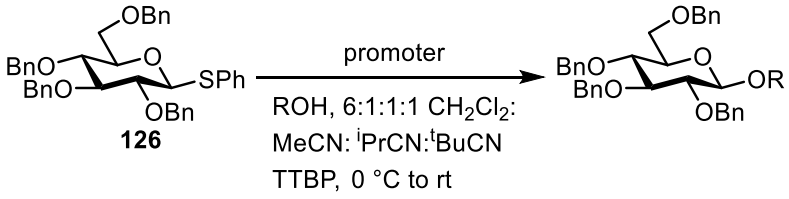
Table 4.10: Effects of C-2 ether group electronics on stereoselectivity.

To this end, we synthesized and examined various thioglycoside donors possessing PMB (p-methoxybenzyl) or PCB[274] (p-chlorobenzyl) protecting groups (Table 4.10). Among these, globally PMB protected donor **229** afforded products with higher levels of β-selectivity (Table 4.10, entry 1-2). These reactions, however, proceeded slowly and were accompanied by significant decomposition of the starting material. The decomposition

appeared to be the result of the loss of 6-*O* PMB group with concomitant 1,6-anhydro sugar formation. As expected, this problem was avoided with the use of donor **231** possessing a single PMB group at the *O*-2 position. However, glycosylation reactions with donor **231** only resulted in decreased β-selectivity compared to when standard perbenzylated donor was used (Table 4.10, entry 6-7). Similarly, the use of PCB-protected donors **230** and **232** also resulted in glycosylations with slightly reduced β-selectivity (Table 4.10, entry 3-5).

Based on these results, we concluded that C-2 ether participation was not a significant factor in the selectivity of this reaction. This led us to consider if the β-selectivity observed could be the result of a mechanism that did not proceed through the classical oxocarbenium/nitrilium pathway, but rather also involved the promoter playing a more direct role. To test this idea, we chose to examine the effects of different promoters on the stereochemical outcomes of the reaction. To this end, three commonly employed thiophilic promoters were used to glycosylate **112** with either **26** or **147**, in the optimal quaternary solvent mixture (Table 4.11). All reactions were conducted at 0 °C and allowed to warm up to room temperature throughout the course of the reactions. Among the entries examined, NIS/TfOH[98] consistently provided glycosylated products in excellent yields, albeit with poor selectivities (Table 4.11, entry 3-4). By comparison, both 1-benzenesulfinyl piperidine (BSP)/Tf_2O[94] and N-bromosuccinimide (NBS)[97] gave diminished yields, again with very low stereoselectivity (Table 4.11, entry 5-8). In the case of BSP/Tf_2O,

this low yield was due to decomposition of the substrates at room temperature, while NBS was not able to completely activate the donor for glycosylation.



Entry	Promoter	Acceptor	Product	Yield (%)	α:β
1	**225**	**26**	**120**	72	1:17-25
2	**225**	**147**	**130**	82	1:6.2
3	NIS/TfOH	**26**	**120**	95	1:1.4
4	NIS/TfOH	**147**	**130**	93	2:1
5	BSP/Tf_2O	**26**	**120**	45	1:1.3
6	BSP/Tf_2O	**147**	**130**	48	1.7:1
7	NBS	**26**	**120**	44	1.3:1
8	NBS	**147**	**130**	45	1.5:1

Promoter

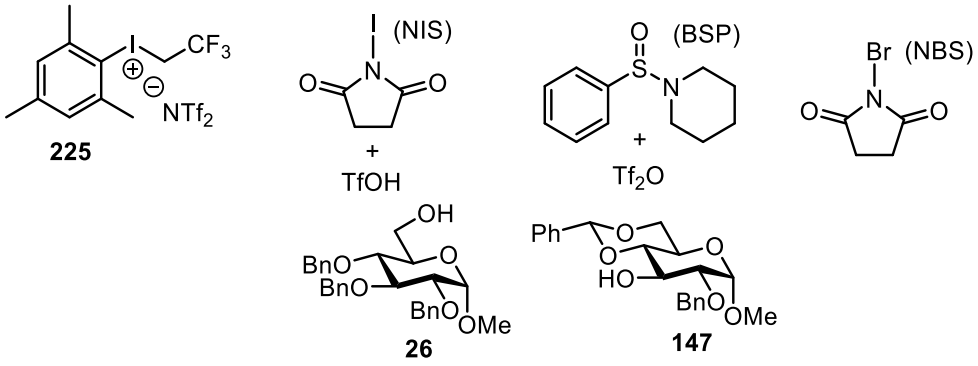
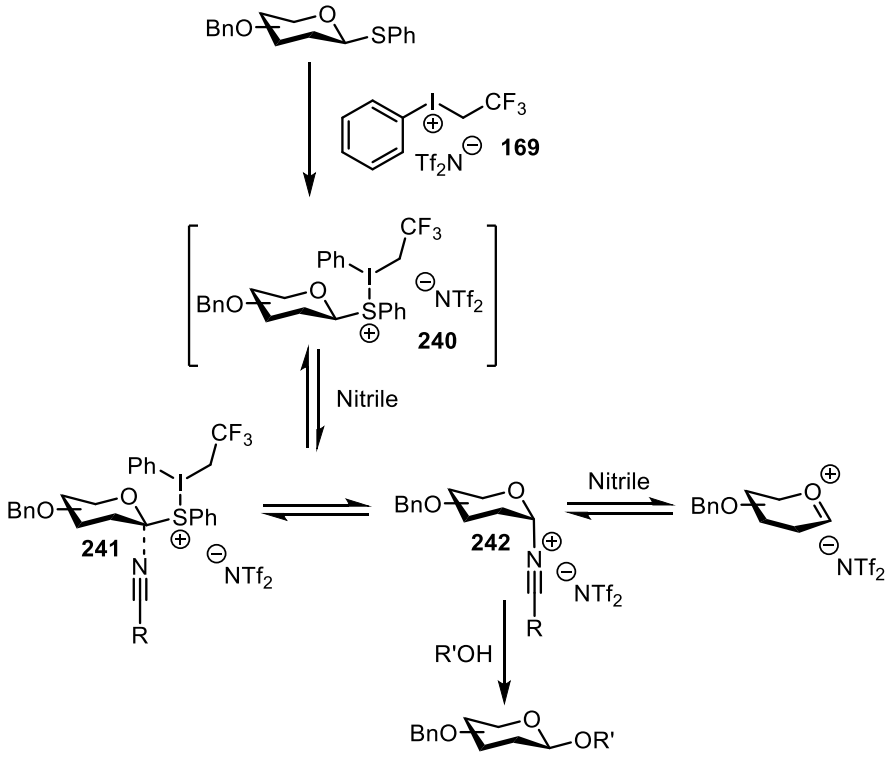


Table 4.11: Comparison of iodonium promoter **225** and common thiophiles in promoting β-selective reactions under quaternary solvent system.

These results suggested that aryl(trifluoroethyl)iodonium triflimide-promoted glycosylations in nitrile solvent were indeed going through a

different manifold. One plausible explanation is that the major reaction pathway does not proceed through the direct formation of α-glycosyl nitrilium intermediate. Instead, **169** activates the donor as a glycosyl sulfonium ion **240** where the activated leaving group is tightly associated with the sugar backbone (Scheme 4.9). This therefore allows the nitrile solvent to pre-organize on the α-face of **241**. Finally, solvent-assisted leaving group departure follows, thereby generating the α-nitrilium intermediate **242** for subsequent β-selective glycosylations.



Scheme 4.9: Proposed origin of nitrile-assisted selectivity with promoter **169**.

Such a model would again be consistent with our earlier results where reactive donors, for example phenylthio galactose (**146**) or 1-adamantanethiol

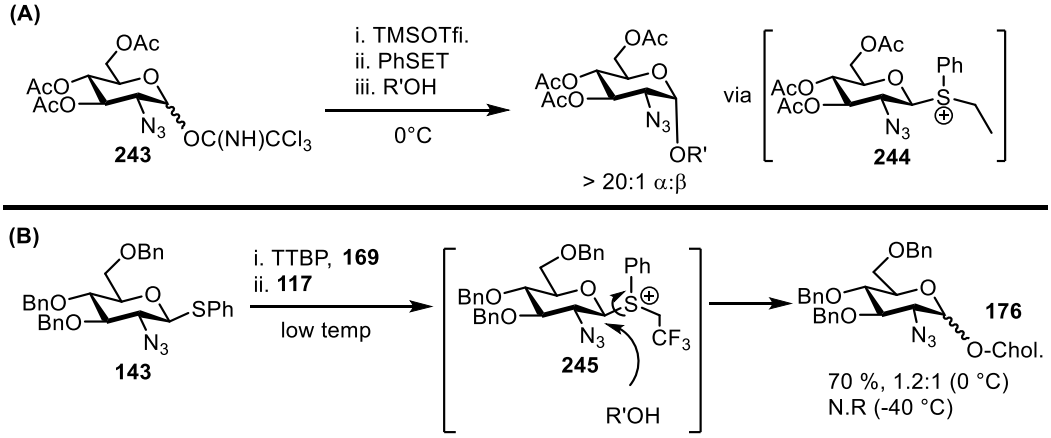
glucose (**226**), provided products with lower levels of selectivity, possibly due to more rapid oxocarbenium cation formation. On the other hand, in the reactions where hindered C-3 alcohol **147** was used as the glycosyl acceptor, the lower β-selectivity may be attributed to the slower rates of nucleophilic attack on the activated donor **242**, and background reactions involving oxocarbenium cations thus became competitive. However, preliminary attempts to acquire glycosyl nitrilium or sulfonium by NMR, either at room temperature or 0 ℃, were unsuccessful. This is also in part similar to multiple previous reports which failed to detect stabilized glycosyl nitrilium ion species with NMR above -30 ℃.[197,258,265,268]

4.3: Ongoing efforts toward user-friendly 1,2-*cis*-α stereoselectivity

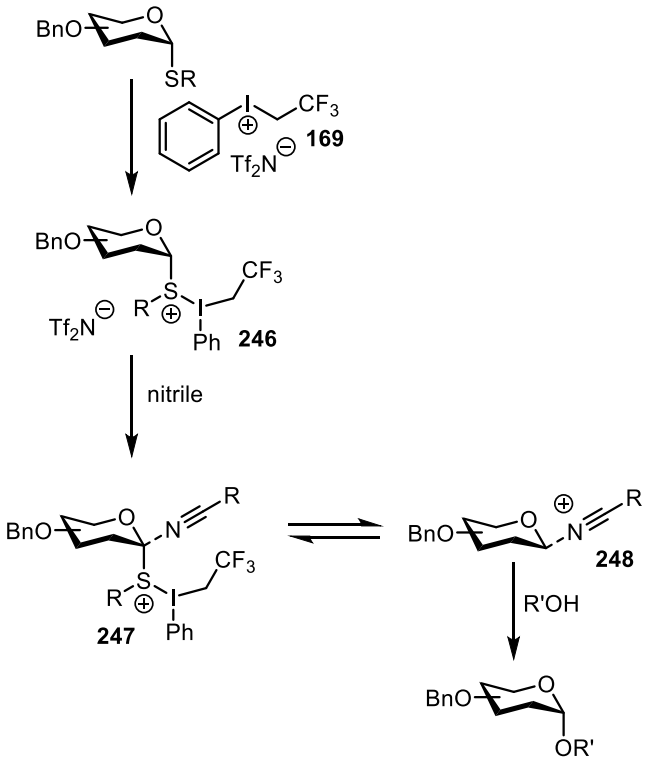
The collective results shown above in section **4.2** demonstrated a promising glycosylation prototype which utilized user-friendly activation procedure to afford highly β-selective reactions in the absence of directing groups. In order to further complement this reaction methodology, exploratory investigations to achieve 1,2-*cis*-α stereoselectivity using iodonium salt promoters were also examined. Our first line of investigation involved looking into the compatibility of exogenous α-directing modulators, such as ethereal solvents and DMF, with **169**-promoted glycosylations. However, in our hands the use of THF, Et_2O and DMF as co-solvents failed to provide productive glycosylations promoted by iodonium salt **169**. We

speculated that in these cases the coordinating solvents potentially reacted with the iodonium center, thereby inhibiting subsequent donor activations.

Another approach examined was inspired by Boon's work which utilized thioethers as α-directing additives (Scheme 4.10A).[153] Since we employed β-thioglycoside donors in our typical glycosylation procedures, we reasoned that the sulfonium leaving group upon activation should in theory exist initially at the equatorial position (Scheme 4.10B). Therefore, the ability to achieve transient stabilization of the β-sulfonium species **245** is critically important, as it allows for the following S_N2-type stereoinversion to afford α-selective glycosides. Unfortunately, attempts to achieve such stabilizations through low temperature[197] conditions were not successful. In brief, reactions carried out at 0 ℃ did not result in a noticeable difference in stereoselectivity compared to standard procedures, while further cooling to -40 ℃ only led to a halted reaction. This was again largely due to the low solubility of the iodonium salt **169** at low temperature. These results indicated that, even at low reaction temperatures, the sulfonium leaving groups on **245** still ionized rapidly after their initial formation. In this regard, aglycon modifications to introduce electron-donating substituents, such as *p*-methoxythiophenol, can be expected in the future to help achieve further stabilization of the glycosyl sulfonium intermediates.



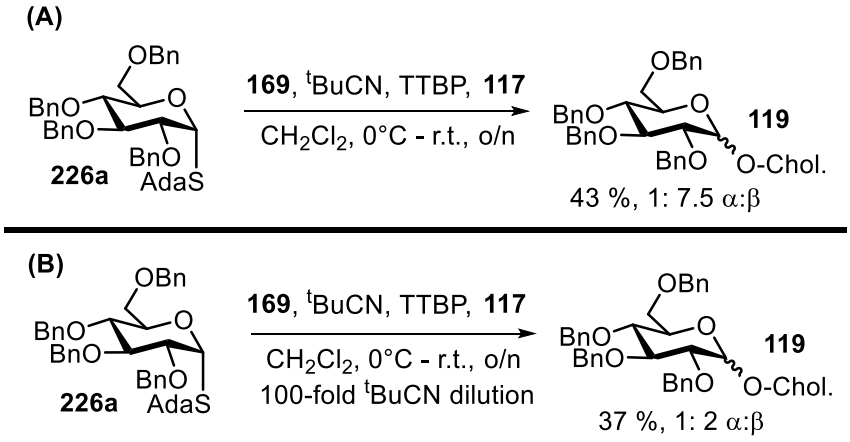
Scheme 4.10: A: Thioether-directed α-glycosylations by Boons *et al*.[153] **B**: Our rationale to achieve analogous reaction pathways using iodonium salt **169**.



Scheme 4.11: Proposed α-glycosylation pathway with iodonium salt **169**.

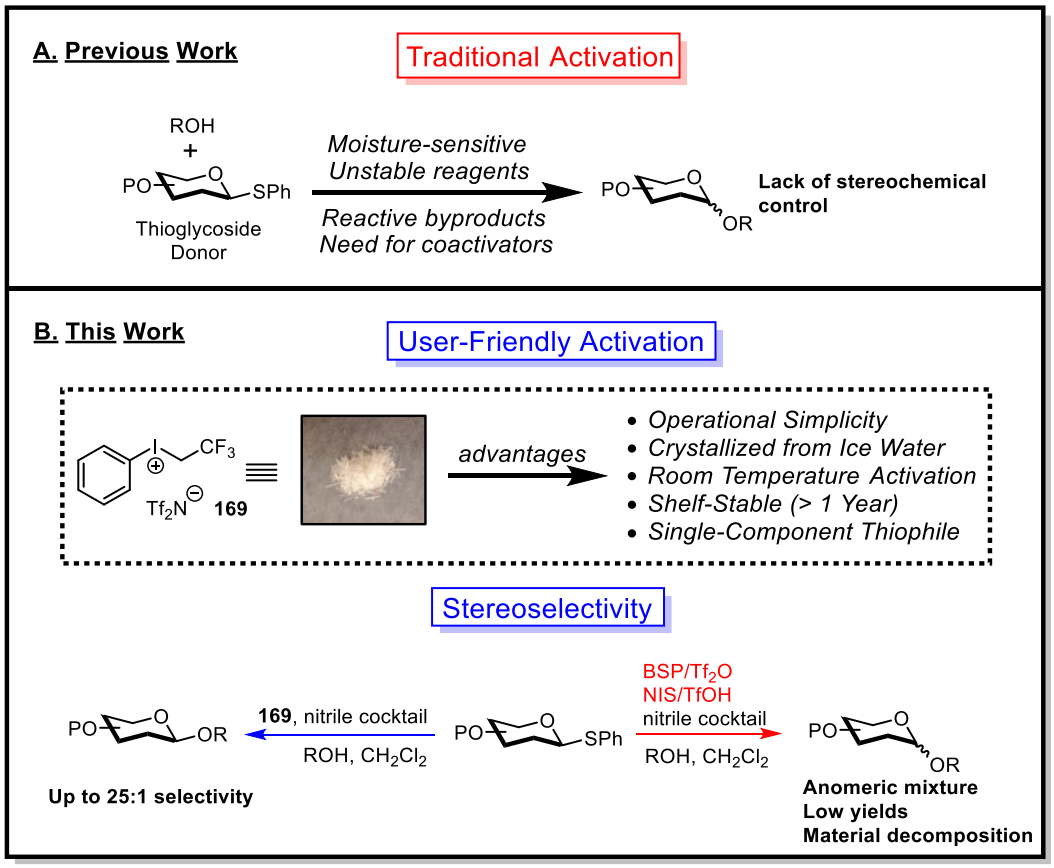
Lastly, we also considered the possibility of a "nitrile-assisted α-glycosylation pathway". In our hypothesized mechanism earlier (Scheme 4.9), the assumption that nitrile-assisted leaving group departure occurred in a stereodefined manner prompted us to explore the alternative pathway as illustrated below in Scheme 4.11. Within this pathway, α-linked thioglycoside donors would instead be employed, and the stereoinversion mediated by nitrile solvent participation could be expected to lead to subsequent α-selective glycosylations.

To examine this hypothesis, α-adamantyl thioglucoside donor **226a** was synthesized and examined under standard pivalonitrile-assisted glycosylation conditions. Unfortunately, these conditions still resulted in the formation of β-selective glycosides (43%, 7.5:1 β-selectivity, Scheme 4.12A). This suggested a possibility that although initial nitrile participation may occur at the β-side of the molecule, further scrambling of anomeric configuration by the excess of nitrile solvent followed and therefore restored the inherent β-selectivity. This hypothesis may be further supported by the observation that under dilute nitrile conditions (100-fold dilution of nitrile concentration), the inherent β-promoting nitrile effect was lost entirely (Scheme 4.12B).



Scheme 4.12: Preliminary trials with α-thioglucoside donor **226a**.

4.4: Conclusion and final remarks

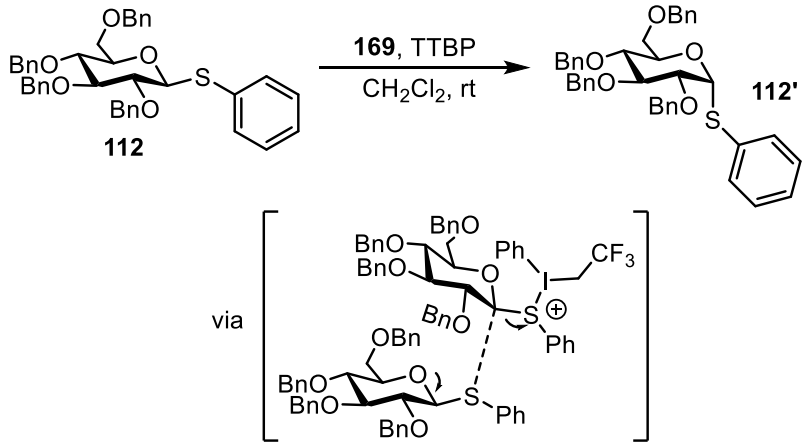


Scheme 4.13: Summary of accomplishments in this work.

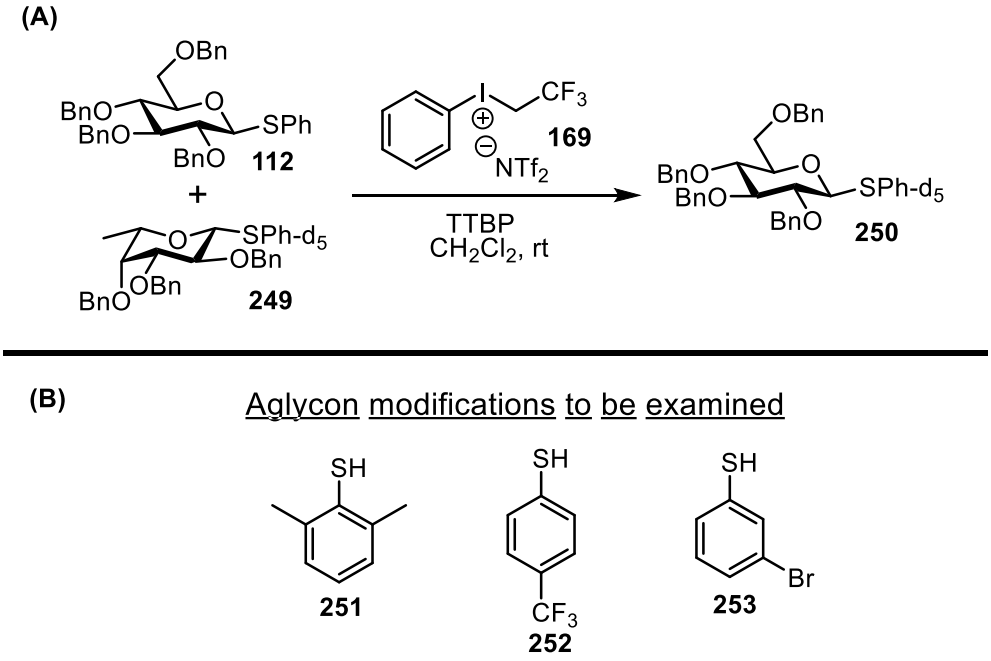
In conclusion, we showed that the use of a combination of aryl(trifluoroethyl)iodonium triflimides and either 2:1 CH_2Cl_2: pivalonitrile or a ternary mixture of CH_2Cl_2 and nitrile solvents (6:1:1:1 CH_2Cl_2:MeCN:^{i}PrCN:^{t}BuCN) permits glycosylations with moderate to excellent selectivity (up to 25:1 α:β). In all entries examined, optimal results could be achieved using armed thioglycoside donors with benzyl ether protecting groups. The reaction was conducted at 0 °C to room temperature, which is a much higher temperature than normally required to take advantage of the nitrile effect. Furthermore, the use of other commonly employed thiophilic promoters under similar reaction conditions failed to provide stereoselective reactions and further led to significant product decomposition. This again highlighted the mild nature as well as extraordinary synthetic utility of aryl iodonium triflimide promoter in chemical glycosylations. Given the operational simplicity of the process, coupled with the stability of all the reagents involved, we believe that this process will help lay the groundwork for technologies that will permit experimentalists with minimal synthetic training to produce their own oligosaccharide standards.

Future goals from this thesis work will continue to combine the core concepts delivered from Chapter 2 to 4. One key unresolved issue in the use of aryl(trifluoroethyl)iodonium triflimide promoters lies in the fact that pre-activation procedures were not compatible with this chemistry. This has largely prevented us from applying our previously established stereoselective glycosylation conditions to these approaches. Upon closer investigation, it was

observed that α-thioglycoside **112'** was formed as a major byproduct during the pre-activation of donor **112** by **169**, which in turn shut down the subsequent glycosylation. Since the acid-scavenger TTBP was present in these reactions, we ruled out the possibility of this phenomenon to be a simple acid-promoted anomerization. Instead, we envisioned that this could be a result of an aglycon transfer pathway (Scheme 4.14).[112] In order to validate this hypothesis, a trial glycosylation experiment between **112** and **249** can be performed (Scheme 4.15A). If we do indeed observe the aglycon-transferred product in the form of deuterated starting material **250**, we will further address this problem by examining aglycon candidates **251-253** that were previously shown to prevent such undesired transfer mechanisms (Scheme 4.15B).[112] To conclude, the development of alternative pre-activation pathways with iodonium salt promoter **169** is particularly important in that it will enable further investigations toward other difficult linkages, such as 1,2-*cis*-α glycosides.



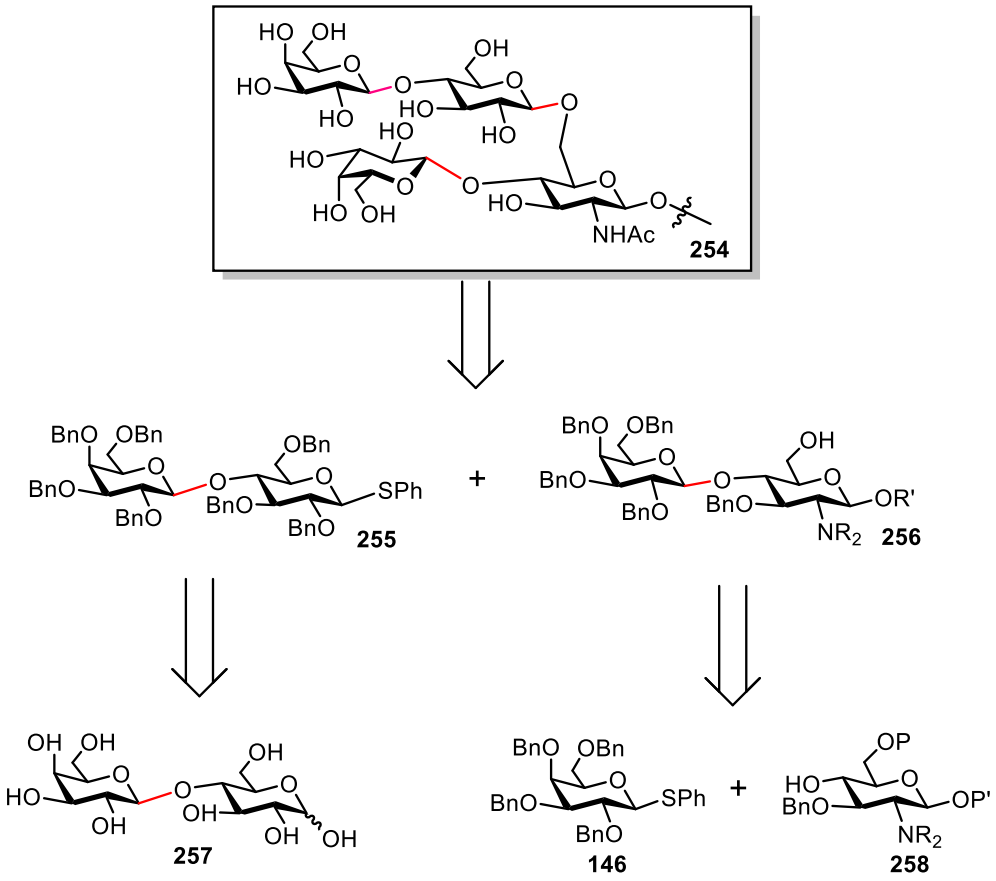
Scheme 4.14: Proposed aglycon transfer in pre-activation attempts.



Scheme 4.15: (A) Trial experiment to determine if aglycon transfer is occurring during pre-activation with **169**. (B) Aglycon modifications to be examined in future studies.

Finally, target-oriented synthesis will further showcase the utility of our methodology. For example, new synthetic routes toward *S. pneumoniae* serotype 14 polysaccharide antigen **254,** can now be designed (Scheme 4.16). Unlike earlier reports,[118] the approach here will only require building blocks equipped with arming benzyl ether groups, thus avoiding the potential problems associated with the use of acyl directing groups (Scheme 4.1). Furthermore, stable thioglycoside donors will be employed, thereby permitting the large-scale synthesis and long-term storage of intermediates that were not previously possible using trichloroacetimidate donors.[118] The successful execution of which is expected to find broad utility in the synthetic

preparation of analogous synthetic capsular polysaccharide vaccine constructs.



Scheme 4.16: Model synthetic target with our β-selective glycosylation method using armed coupling partners and user-friendly thiophilic promoters.

With further development of this project, wide array of both α- and β-linked glycosides can be reasonably accessed with operationally simple procedures. Furthermore, universal thioglycoside building blocks without particular directing group manipulations will be applicable to various linkage

constructions to maximize their synthetic utilities. We believe that these user-friendly approaches will ultimately pave the way toward a set of stereoselective "glycosylation kits" that can be regularly adopted by the wider chemical biology community. This will in turn provide reasonable access to the comprehensive glycan libraries necessary to help decode the roles which complex carbohydrates play in both eukaryotic and prokaryotic systems, opening the doors to new and exciting areas of therapeutic development.

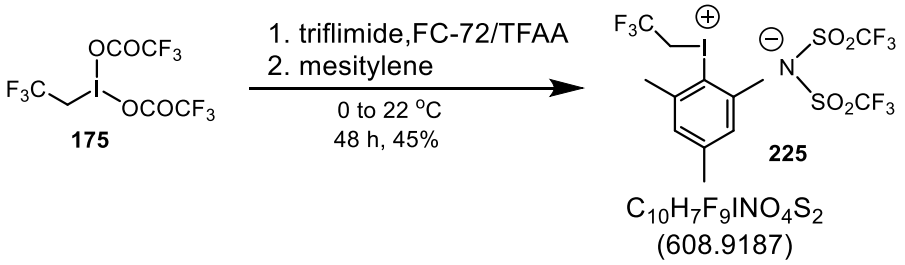
4.5: Material and Experimental Methods

4.5.1: General Details

Prior to running the glycosylation reactions, all solid reagents were dried by azeotropic removal of water using toluene and a rotary evaporator < 40 °C. All reactions were carried out under an argon atmosphere unless otherwise specified. Solvents were dried using an Innovative Technologies PureSolv 400 solvent purifier. Nitrile co-solvents, other than acetonitrile, were purchased from Sigma Aldrich, and further dried over activated 4 Å molecular sieves before use. Glycosyl donors **112**, **143**, **147** and glycosyl acceptor **26**, **147** were synthesized following literature procedures or variations thereof.[181-185,237-241] Aryl(trifluoroethyl)iodonium triflimide **169 and 225** were synthesized and characterized according to literature.[224] FC-72 (perfluorohexanes), N,N-(bis-trifluoromethanesulfonyl) imide (triflimide), trifluoroacetic anhydride and 2,2,2-trifluoroethyl iodide were purchased from Synquest Laboratories. All other chemicals were purchased at the highest possible purity from

commercial sources and used as received. Flash column chromatography was performed on Silicycle silica gel, 230-400 Mesh. Analytical and preparative thin layer chromatography were carried out on EMD silica gel 60 F254 plates. Products were visualized using UV, or by staining with 5% aqueous sulfuric acid, iodine, or ceric ammonium molybdate stains. NMR solvents were purchased from Cambridge Isotope Labs. NMR spectra were recorded on a Bruker Avance III NMR spectrometer at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. Chemical shifts are reported in ppm relative to TMS (for ^{1}H NMR in $CDCl_3$), and $CDCl_3$ ($\delta C = 77.23$ for ^{13}C NMR in $CDCl_3$). For ^{1}H NMR spectra, data are reported as follows: chemical shift δ in ppm, multiplicity (s = singlet, m = multiplet, t = triplet, d = doublet, dd = doublet of doublets, q = quartet and combinations thereof), coupling constants reported in Hertz (Hz), and integration. Low resolution mass spectra (LRMS) were recorded using a Finnigan LTQ ESI-MS with an additional APCI source. High resolution mass spectra (HRMS) were obtained at Massachusetts Institute of Technology Department of Chemistry instrumentation facility using a peak-matching protocol to determine the mass and error range of the molecular ion. Optical rotations were measured on a Rudolph Research Analysis AUTOPUL IV polarimeter @ 589 nm in a 5 cm cell at 24°C.

4.5.2: Synthesis of Mesityl(trifluoroethyl)iodonium Triflimide (225).



Mesityl(trifluoroethyl)iodonium Triflimide **(225)**

In a typical preparation, 1-(bis-Trifluoroacetoxy)iodo-2,2,2-trifluoroethane **(196)** (4.06 g, 10.3 mmol) was added in one portion into a 250 mL, argon-flushed round bottom flask containing $(CF_3SO_2)_2NH$ (2.9 g, 10.3 mmol). The two solids were stirred in FC-72 (perfluorohexanes, 20 mL) and trifluoroacetic anhydride (2 mL) was added in one portion. The flask was protected from light with Aluminum foil. A clear solution formed within 15 minutes, at which point mesitylene (1.6 mL, 11.2 mmol) was added rapidly while cooling in a tap water bath. The reaction mixture, which gradually separated into two phases, was stirred under static argon atmosphere for 24 hours at RT. After removing the volatile with rotary evaporator, the resin was stirred with ice/H_2O for 30 minutes to produce a white precipitate. This was collected on a glass frit, air-dried, and further dried to afford a slight purple/brown powder. Crystallization was performed by dissolving the solid product in 8 mL dichloromethane while swirling in a warm water bath, then cooling at -20˚C for 24 hours. After crystal formation was complete, the solvent was decanted and the flask washed with 5 mL of cold dichloromethane. **225** was then

obtained as slight brown crystals: 2.8 g (4.64 mmol, 45%). The NMR spectroscopic data matched those previously reported.[224]

4.5.3: General Glycosylation Procedure

Typical aryl(trifluoroethyl)iodonium triflimide-promoted glycosylation:

The glycosyl donor (0.079 mmol), acceptor (0.158 mmol), and 2,4,6-Tri-tert-butylpyrimidine (TTBP, 0.158 mmol, 39.2 mg) were dissolved in 3 ml CH2Cl2 and 1 ml mixed nitrile cosolvent, and cooled down to 0 °C. Meanwhile, Aryl(trifluoroethyl)iodonium triflimide (0.095 mmol) was separately dissolved in 1 ml CH_2Cl_2 and 1 ml nitrile co-solvent, the solution of which was then added drop-wise to the cooled reaction mixture and allowed to stir under ambient atmosphere overnight while slowly warming up to room temperature. The total volume (2ml) of the added nitrile solvent was maintained consistent in the entries where mixtures of multiple nitrile co-solvents were utilized. For example, 1:1:1 MeCN:^{i}PrCN:^{t}BuCN stock solution was freshly prepared to both the reaction flask as well as the promoter flask. Upon completion of glycosylation as indicated by TLC the reaction was quenched with Et_3N (0.1ml) and concentrated in *vacuo*. Flash column chromatography on silica gel lastly afforded the desired product as determined by ^{1}H and ^{13}C NMR.

Typical N-bromosuccinimide (NBS)-promoted glycosylation:

A solution cooled of glycosyl donor (0.079 mmol), acceptor (0.158 mmol) and 4 Å molecular sieves (100 mg) in 3 ml CH_2Cl_2 and 1 ml nitrile co-solvent was cooled to 0 °C and allowed to stir for 3 mins before the addition of NBS (0.095 mmol). The reaction was allowed to stir overnight, then diluted with CH_2Cl_2 and washed with 10% $NaHSO_3$, H_2O, and brine. The pooled organics were dried over Na_2SO_4, filtered and concentrated to afford the resulting crude which was subsequently purified by silica gel column chromatography.

Typical N-iodosuccinimide (NIS)-promoted glycosylation:

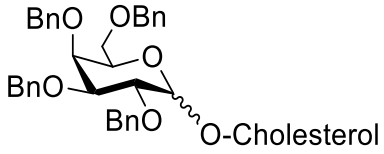
A solution of glycosyl donor (0.079 mmol), acceptor (0.095 mmol) and 4 Å molecular sieves (100 mg) was dissolved in 3 ml CH_2Cl_2 and 1 ml nitrile co-solvent was cooled to 0 ^oC. After stirring for 3 min, the solution was treated with NIS (0.079 mmol) and TfOH (0.008 mmol). The reaction was stirred for 20 min, then allowed to warm up to room temperature and quenched with Et_3N, diluted with CH_2Cl_2 and washed with $Na_2S_2O_3$, H_2O, and brine. The pooled organics were dried over Na_2SO_4, filtered, and concentrated to afford the resulting crude which was subsequently purified by silica gel column chromatography.

Typical 1-benzenesulfinyl piperidine (BSP)/trifluoromethanesulfonic anhydride (Tf_2O)-promoted glycosylation:

A solution of glycosyl donor (0.079 mmol), acceptor (0.158 mmol), 2,4,6-Tri-*tert*-butylpyrimidine (TTBP, 0.158 mmol), BSP(0.221 mmol) and 4 Å molecular sieves (100 mg) in 3 ml CH_2Cl_2 and 1 ml nitrile cosolvent was cooled

to 0 ^{o}C. The reactions was allowed to stir for 3 mins before the drop-wise addition of Tf_2O (0.11 mmol). The reaction was allowed to stir overnight, then quenched with Et_3N and concentrated to afford the resulting crude which was subsequently purified by silica gel column chromatography.

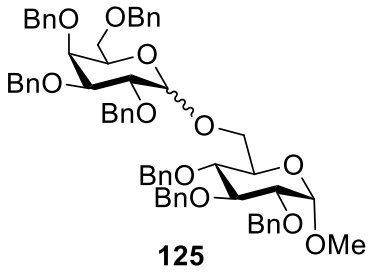
4.5.4: Experimental Data



124

Cholesteryl-2,3,4,6-tetra-O-benzyl-D-galactopyranoside (124):

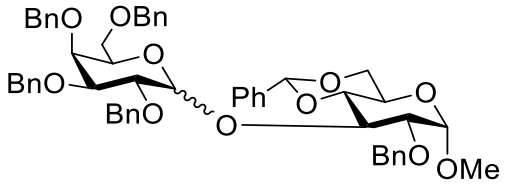
Following the general glycosylation procedure, glycosyl donor **146** (0.079 mmol, 50mg) and acceptor **117** (0.158 mmol, 61.1 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **124** after purification by silica gel flash column chromatography (5% ethyl acetate in hexanes) as determined by ^{1}H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[187]



125

Methyl-(2,3,4,6,-tetra-O-benzyl-D-galactopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (125):

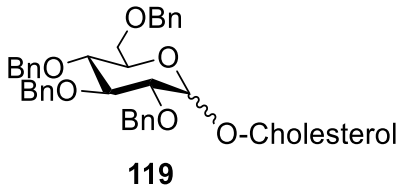
Following the general glycosylation procedure, glycosyl donor **146** (0.079 mmol, 50mg) and acceptor **26** (0.158 mmol, 73.3 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **125** after purification by silica gel flash column chromatography (20% ethyl acetate in hexanes) as determined by ^{1}H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[187]



Methyl-(2,3,4,6-tetra-O-benzyl-D-galactopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (131):

Following the general glycosylation procedure, glycosyl donor **146** (0.079 mmol, 50mg) and acceptor **147** (0.158 mmol, 59 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **131** after purification by silica gel flash column chromatography (15→20% ethyl acetate in hexanes) as

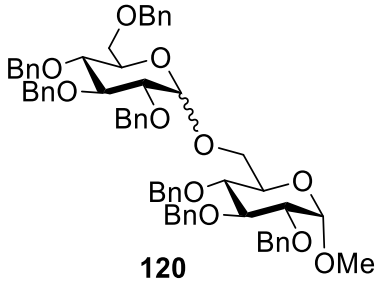
determined by ^{1}H and ^{13}C NMR. The spectroscopic data matched those reported previously.[188]



119

Cholesteryl-*2,3,4,6-tetra-O-benzyl-D-glucopyranoside (119)*:

Following the general glycosylation procedure, glycosyl donor **112** (0.079 mmol, 50mg) and acceptor **117** (0.158 mmol, 61.1 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **119** after purification by silica gel flash column chromatography (5% ethyl acetate in hexanes) as determined by ^{1}H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[186]

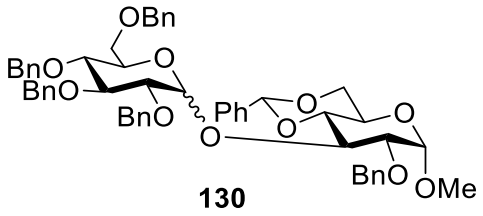


120

Methyl-(2,3,4,6,-tetra-O-benzyl-D-glucopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (120):

Following the general glycosylation procedure, glycosyl donor **112** (0.079 mmol, 50mg) and acceptor **26** (0.158 mmol, 73.3 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of

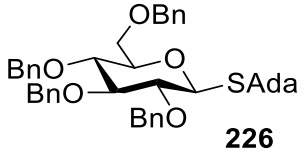
169 or 57.8 mg of **225**) to afford the desired product **120** after purification by silica gel flash column chromatography (20% ethyl acetate in hexanes) as determined by ^{1}H and ^{13}C NMR. Further separation of anomers were carried out using preparative thin layer chromatography (25% diethyl ether in toluene). The NMR spectroscopic data matched those reported previously.[71]



130

Methyl-(2,3,4,6-tetra-O-benzyl-D-galactopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (130):

Following the general glycosylation procedure, glycosyl donor **112** (0.079 mmol, 50mg) and acceptor **147** (0.158 mmol, 59 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **130** after purification by silica gel flash column chromatography (15→20% ethyl acetate in hexanes) as determined by ^{1}H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[188]



226

(1-Adamantyl)-2,3,4,6-tetra-O-benzyl-1-thio-β-D-Glucopyranoside (226):

A cooled (0 °C) solution of peracetylated glucose[275] (5g, 13.3 mmol) and 1-adamantanethiol (2.7g, 16 mmol) in 25 ml CH_2Cl_2 was drop-wise added boron trifluoride diethyl etherate (2.3 g, 16 mmol, 4.3 ml). The cooled reaction was allowed to stir overnight while slowly warming up to room temperature. After which content was taken up in satd. $NaHCO_3$ and extracted twice with CH_2Cl_2. Pooled organics were subsequently washed with $NaHCO_3$ and H_2O, dried over Na_2SO_4, filtered and concentrated. The resulting crude was purified by silica gel column chromatography (17% ethyl acetate in hexanes) to afford the intermediate (1-adamantyl)-2,3,4,6-*tetra*-*O*-acetyl-1-thio-D-glucopyranoside. Only the isolated β-product was progressed further in the following step.

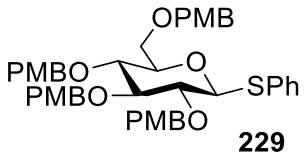
To a cooled (0 °C) suspension of tetrabutylammonium iodide (72 mg, 0.195 mmol) and freshly ground NaOH (1.87 g, 47 mmol) in 10 ml DMF was drop-wise added the solution of (1-adamantyl)-2,3,4,6-*tetra*-*O*-acetyl-1-thio-D-glucopyranoside (0.97 g, 1.95 mmol) in 10 ml DMF. After 15 mins of rigorous stirring on ice, benzyl bromide (2 g, 11.7 mmol, 1.4 ml) was then drop-wise added to the stirring mixture and allowed to react at room temperature overnight. Content was then taken up in H_2O and extracted twice with Et_2O. Pooled organics were subsequently washed with satd. NH_4Cl and H_2O, dried over Na_2SO_4, filtered and concentrated. The resulting crude was purified by silica gel column chromatography (5% ethyl acetate in hexanes) to afford the title compound as a white solid. (1 g, 75%).

$[\alpha]_D$ = +13.7 (c = 0.99, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.18 (m, 20H), 4.97 (d, *J* = 10.1 Hz, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.82 (d, J = 11.0 Hz, 2H), 4.68 (d, J = 10.0 Hz, 1H), 4.65 (d, *J* = 10.0 Hz, 1H), 4.58-4.52 (m, 3H), 3.74-3.73 (m, 1H), 3.69 (t, *J* = 8.5 Hz, 1H), 3.61 (dd, *J* = 10.6, 5.5 Hz, 1H), 3.54-3.49 (m, 2H), 3.39 (t, J = 9.1 Hz, 1H), 2.02-1.97 (m, 9H), 1.68 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.6, 138.5, 138.4, 128.6, 128.5, 128.1, 128.0, 127.8, 127.7, 87.2, 81.9, 81.8, 78.9, 78.4, 76.0, 75.7, 75.2, 73.6, 69.8, 46.7, 44.5, 36.5, 30.1.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{44}H_{50}O_5SNa$ $(M+Na)^+$ 713.3271, found 713.3276.



229

Phenyl-2,3,4,6-tetra-O-(4-methoxybenzyl)-β-D-Glucopyranoside (229):

To a cooled (0 °C) suspension of tetrabutylammonium iodide (42 mg, 0.113 mmol) and freshly ground NaOH (0.6 g, 15 mmol) in 5 ml DMF was drop-wise added the solution of 2,3,4,6-*tetra*-*O*-acetyl-1-thio-β-D-glucopyranoside[276] (0.5 g, 1.13 mmol) in 5 ml DMF. After 15 mins of rigorous stirring on ice, 4-methoxybenzyl chloride (1.06 g, 6.78 mmol, 0.92 ml) was then drop-wise added to the stirring mixture and allowed to react at 90 °C for three hours. Content was then taken up in H_2O and extracted twice with Et_2O. Pooled organics were subsequently washed with satd. NH_4Cl and H_2O, dried over Na_2SO_4, filtered and concentrated. The resulting crude was purified by silica

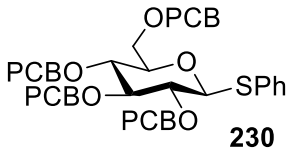
gel column chromatography (5% ethyl acetate in hexanes) to afford the title compound as a white solid (187 mg, 22%).

[α]$_D$ = +9.1 (c = 0.44, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.56 (m, 2H), 7.33-7.31 (m, 2H), 7.27-7.22 (m, 7H), 7.10-7.08 (m, 2H), 6.87-6.81 (m, 8H), 4.84-4.77 (m, 3H), 4.73 (d, *J* = 10.4 Hz, 1H), 4.66 (d, *J* = 9.9 Hz, 1H), 4.63 (d, *J* = 9.8 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.49-4.45 (m, 2H), 3.80-3.79 (m, 12H), 3.73 (dd, *J* = 10.9, 1.7 Hz, 1H), 3.67-3.63 (m, 2H), 3.57 (t, *J* = 9.4 Hz, 1H), 3.48-3.43 (m, 2H),

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 159.5, 159.4, 134.2, 132.0, 131.0, 130.6, 130.5, 130.1, 129.8, 129.6, 129.5, 129.1, 127.5, 114.1, 114.0, 87.7, 86.7, 80.8, 79.4, 77.8, 75.7, 75.2, 74.9, 73.3, 68.9, 55.5.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{44}H_{48}O_9SNa$ $(M+Na)^+$ 775.2911, found 775.2901.



230

Phenyl-2,3,4,6-tetra-O-(4-chlorobenzyl)-1-thio-β-D-Glucopyranoside (230):

To a cooled (0 °C) suspension of tetrabutylammonium iodide (83.8 mg, 0.227 mmol) and freshly ground NaOH (2.18 g, 54.5 mmol) in 10 ml DMF was drop-wise added the solution of 2,3,4,6-*tetra*-*O*-acetyl-1-thio-β-D-glucopyranoside[276] (1 g, 2.27 mmol) in 10 ml DMF. After 15 mins of rigorous stirring on ice, 4-chlorobenzyl bromide (2.8 g, 13.62 mmol) in 5 ml DMF was

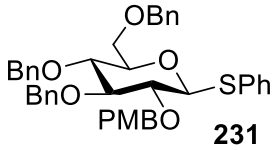
then drop-wise added to the stirring mixture and allowed to react at room temperature for two hours. Content was then taken up in H_2O and extracted twice with Et_2O. Pooled organics were subsequently washed with satd. NH_4Cl and H_2O, dried over Na_2SO_4, filtered and concentrated. The resulting crude was purified by silica gel column chromatography (10% ethyl acetate in hexanes) to afford the title compound as a white solid. (930 mg, 53%).

$[\alpha]_D$ = +13.4 (c = 1.87, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.53 (m, 2H), 7.30-7.24 (m, 15H), 7.14-7.12 (m, 2H), 7.07-7.05 (m, 2H), 4.85 (d, *J* = 10.6 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.3 Hz, 1H), 4.65-4.60 (m, 2H), 4.56 (d, *J* = 12.1 Hz, 1H), 4,52 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 12.1 Hz, 1H), 3.74-3.66 (m, 2H), 3.64-3.57 (m, 2H), 3.47-3.44 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 136.8, 136.6, 133.9, 133.8, 133.7, 133.6, 132.0, 129.6, 129.2, 129.1, 129.0, 128.8, 128.4, 127.8, 87.6, 86.7, 81.0, 79.2, 77.9, 75.0, 74.7, 74.3, 72.8, 69.0.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{40}H_{36}Cl_4O_5SNa$ $(M+Na)^+$ 793.0919, found 793.0906.



231

Phenyl-2-O-(4-chlorobenzyl)-3,4,6-tri-O-benzyl-β-D-Glucopyranoside (231):

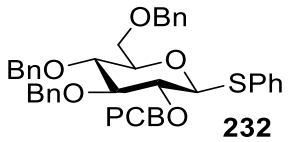
To a cooled (0 °C) suspension of tetrabutylammonium iodide (33 mg, 0.089 mmol) and NaH (45.1 mg, 1.9 mmol, 95% dispersion in mineral oil) in 8 ml DMF was drop-wise added the solution of 3,4,6-*tri*-*O*-benzyl-1-thio-β-D-glucopyranoside[277] (0.5 g, 0.92 mmol) in 5 ml DMF and 1 ml CH_2Cl_2. After 15 mins of rigorous stirring on ice, 4-methoxybenzyl chloride (391 mg, 2.5 mmol, 0.34 ml) was then drop-wise added to the stirring mixture and allowed to react at room temperature for three hours. Content was then taken up in H_2O and extracted twice with Et_2O. Pooled organics were subsequently washed with satd. NH_4Cl and H_2O, dried over Na_2SO_4, filtered and concentrated. The resulting crude was purified by silica gel column chromatography (7% ethyl acetate in hexanes) to afford the title compound as a white solid. (287 mg, 48%).

$[\alpha]_D$ = +6.3 (c = 1.15, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59-7.58 (m, 2H), 7.34-7.18 (m, 20H), 6.86-6.84 (m, 2H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.86-4.80 (m, 3H), 4.66 (d, *J* = 4.8 Hz, 1H), 4.64 (d, *J* = 4.8 Hz, 1H), 4.61-4.57 (m, 2H), 4.54 (d, *J* = 12.0 Hz, 1H), 3.79-3.77 (m, 4H), 3.73-3.70 (m, 1H), 3.68 (d, *J* = 8.6 Hz, 1H), 3.64 (t, *J* = 9.2 Hz, 1H), 3.52-3.48 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 138.7, 138.5, 138.3, 134.1, 132.1, 131.8, 130.5, 130.1, 129.1, 128.7, 128.6, 128.2, 128.0, 127.9, 127.8, 127.6, 114.1, 87.7, 87.0, 80.8, 79.3, 78.0, 76.0, 75.3, 73.6, 69.3, 55.5.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{41}H_{42}O_6SNa$ $(M+Na)^+$ 685.2594, found 685.2587.



232

Phenyl-2-O-(4-methoxybenzyl)-3,4,6-tri-O-benzyl-β-D-Glucopyranoside (232):

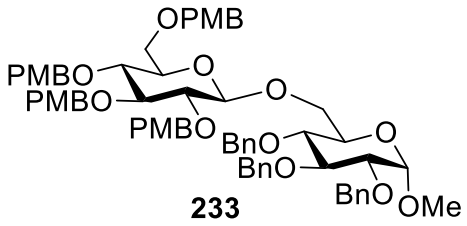
To a cooled (0 °C) suspension of tetrabutylammonium iodide (32 mg, 0.086 mmol) and freshly ground NaOH (0.25 g, 6.25 mmol) in 8 ml DMF was drop-wise added the solution of 3,4,6-*tri-O*-benzyl-2-*O*-acetyl-1-thio-β-D-glucopyranoside[277] (0.5 g, 0.85 mmol) in 6 ml DMF. After 15 mins of rigorous stirring on ice, 4-chlorobenzyl bromide (350 mg, 1.7 mmol) in 2 ml DMF was then drop-wise added to the stirring mixture and allowed to react at room temperature for four hours. Content was then taken up in H_2O and extracted twice with Et_2O. Pooled organics were subsequently washed with satd. NH_4Cl and H_2O, dried over Na_2SO_4, filtered and concentrated. The resulting crude was purified by silica gel column chromatography (7.5-10% ethyl acetate in hexanes) to afford title compound as a white solid. (373 mg, 66%).

$[\alpha]_D$ = +10.9 (c = 1.25, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H), 7.34-7.18 (m, 22H), 4.87-4.81 (m, 4H), 4.67 (d, *J* = 10.6 Hz, 1H), 4.65 (d, *J* = 9.7 Hz, 1H), 4.61 (d, *J* = 9.3 Hz, 1H), 4.59 (d, *J* = 8.2 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 3.79 (dd, *J* = 10.8, 1.8 Hz, 1H), 3.74-3.70 (m, 1H), 3.68-3.63 (m, 2H), 3.52-3.46 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.2, 136.8, 133.9, 133.8, 132.1, 129.7, 129.1, 128.7, 128.6, 128.1, 128.0, 127.9, 127.8, 127.7, 87.6, 86.9, 81.0, 79.3, 78.0, 76.0, 75.3, 74.7, 73.6, 69.2.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{40}H_{39}ClO_5SNa$ $(M+Na)^+$ 689.2099, found 689.2114.



233

Methyl-(2,3,4,6,-tetra-O-(4-methoxybenzyl)-β-D-glucopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (233):

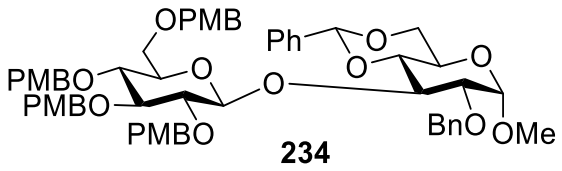
Following the general glycosylation procedure, glycosyl donor **229** (0.079 mmol, 59.4 mg) and acceptor 2**6** (0.158 mmol, 73.3 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **233** after purification by silica gel flash column chromatography (15→20% ethyl acetate in toluene) as determined by ^1H and ^{13}C NMR.

$[\alpha]_D$ = +16.6 (c = 1.01, CH_2Cl_2).

^1H NMR (500 MHz, $CDCl_3$): δ 7.35-7.18 (m, 20H), 7.06-7.05 (m, 2H), 6.84-6.73 (m, 9H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.89 (d, *J* = 10.6 Hz, 1H), 4.83-4.76 (m, 4H), 4.72-4.64 (m, 4H), 4.61 (d, *J* = 3.2 Hz, 1H), 4.53 (t, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 10.3 Hz, 1H), 4.32 (d, *J* = 7.8 Hz, 1H), 4.18 (d, *J* = 10.1 Hz, 1H), 4.00 (t, *J* = 9.0 Hz, 1H), 3.85-3.76 (m, 10H), 3.72 (s, 3H), 3.68-3.65 (m, 2H), 3.62-3.50 (m, 4H), 3.47 (d, *J* = 9.0 Hz, 1H), 3.43 (t, *J* = 7.9 Hz, 1H), 3.33 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 159.4, 139.1, 138.6, 138.4, 131.1, 130.9, 130.6, 129.8, 129.7, 129.6, 129.4, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 127.7, 114.0, 104.1, 98.2, 84.7, 82.2, 82.1, 80.1, 78.3, 77.9, 75.9, 75.5, 75.3, 75.1, 74.8, 74.7, 73.6, 73.3, 70.1, 68.9, 68.8, 54.5, 54.4.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{66}H_{74}O_{15}Na$ $(M+Na)^+$ 1129.4920, found 1129.4912.



234

Methyl-(2,3,4,6-tetra-O-(4-methoxybenzyl)-β-D-glucopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (234):

Following the general glycosylation procedure, glycosyl donor **229** (0.079 mmol, 59.4 mg) and acceptor **147** (0.158 mmol, 59 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **234** after purification by silica gel flash column chromatography (15% ethyl acetate in toluene) as determined by ^{1}H and ^{13}C NMR.

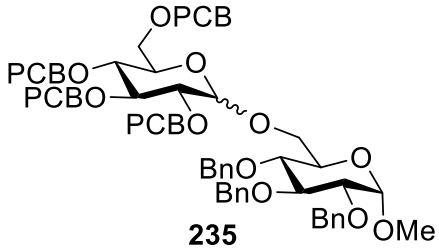
$[\alpha]_D$ = +2.1 (c = 0.75, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.40 (m, 2H), 7.29-7.16 (m, 14H), 7.05-7.04 (m, 2H), 6.84-6.78 (m, 8H), 5.46 (s, 1H), 4.97 (d, *J* = 10.7 Hz, 1H), 4.85-4.81 (m, 2H), 4.74-4.65 (m, 4H), 4.50-4.48 (m, 2H), 4.44-4.32 (m, 4H), 4.22-4.19 (m, 1H),

3.82-3.77 (m, 13H), 3,68-3.63 (m, 2H), 3.60 (dd, *J* = 9.1, 3.8 Hz, 1H), 3.56-3.49 (m, 4H), 3.44(t, *J* = 8.2 Hz, 1H), 3.35 (s, 3H), 3.19-3.17 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 159.3, 138.4, 137.6, 131.4, 131.3, 130.8, 130.7, 129.9, 129.8, 129.6, 129.1, 128.6, 128.5, 128.3, 128.1, 126.4, 114.0, 113.9, 102.7, 101.7, 99.0, 84.9, 83.0, 80.6, 78.0, 76.1, 75.4, 75.0, 74.8, 74.7, 74.0, 73.3, 69.3, 68.6, 62.3, 55.5.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{54}H_{73}N_3O_5Na$ $(M+Na)^+$ 1037.4294, found 1037.4314.



235

Methyl-(2,3,4,6,-tetra-O-(4-chlorobenzyl)-D-glucopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (235):

Following the general glycosylation procedure, glycosyl donor **230** (0.079 mmol, 60.7 mg) and acceptor **26** (0.158 mmol, 73.3 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **235** after purification by silica gel flash column chromatography (20→25% ethyl acetate in hexanes) as determined by ^{1}H and ^{13}C NMR.

Data for α anomer:

$[\alpha]_D$ = +35.6 (c = 1.41, CH_2Cl_2);.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-6.97 (m, 31H), 4.99 (d, *J* = 3.4 Hz, 1H), 4.96 (d, *J* = 10.6 Hz, 1H), 4.93 (d, *J* = 11.1 Hz, 1H), 4.82 (d, *J* = 8.3 Hz, 1H), 4.80 (d, *J* = 7.6 Hz, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.66 (d, *J* = 9.2 Hz, 1H), 4.64 (d, *J* = 9.0 Hz, 1H), 4.59 (d, *J* = 6.1 Hz, 1H), 4.57 (d, *J* = 6.2 Hz, 1H), 4.53-4.51 (m, 3H), 4.37-4.33 (m, 2H), 3.98 (t, J = 9.2 Hz, 1H), 3.89-3.82 (m, 2H), 3.77-3.64 (m, 4H), 3.59-3.45 (m, 4H), 3.39 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 138.6, 138.3, 137.3, 137.0, 136.5, 133.8, 133.6, 133.5, 129.4, 129.3, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 128.1, 127.9, 98.3, 97.2, 82.3, 81.7, 80.3, 80.2, 77.9, 77.7, 76.0, 75.1, 74.7, 74.1, 73.6, 72.8, 71.6, 70.6, 70.3, 68.6, 66.2, 55.4.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{66}H_{62}Cl_4O_{11}Na$ $(M+Na)^+$ 1147.2937, found 1147.2940.

Data for β anomer:

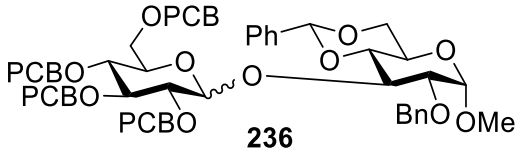
$[\alpha]_D$ = +23.6 (c = 1.79, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.02 (m, 31H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.91 (d, *J* = 11.3 Hz, 1H), 4.80-4.73 (m, 4H), 4.68-4.61 (m, 4H), 4.58 (d, *J* = 3.5 Hz, 1H), 4.55-4.44 (m, 4H), 4.30 (d, *J* = 7.8 Hz, 1H), 4.14-4.13 (m, 1H), 3.99 (t, *J* = 8.7 Hz, 1H), 3.84-3.80 (m, 1H), 3.68-3.63 (m, 3H), 3.53-3.47 (m, 4H), 3.43-3.34 (m, 2H), 3.32 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 138.5, 138.3, 137.1, 136.9, 136.8, 136.7, 133.8, 133.6, 129.3, 129.1, 129.0, 128.8, 128.7, 128.6, 128.3, 128.2, 127.9,

127.8, 104.0, 98.3, 84.7, 82.1, 82.0, 80.0, 78.2, 78.0, 76.0, 75.1, 74.9, 74.2, 74.1, 73.6, 72.8, 70.0, 69.0, 68.9, 55.5.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{66}H_{62}Cl_4O_{11}Na$ $(M+Na)^+$ 1147.2937, found 1147.2938.



236

Methyl-(2,3,4,6-tetra-O-(4-chlorobenzyl)-D-glucopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (236):

Following the general glycosylation procedure, glycosyl donor **230** (0.079 mmol, 60.7 mg) and acceptor **147** (0.158 mmol, 59 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **236** after purification by silica gel flash column chromatography (17→20% ethyl acetate in hexanes) as determined by ^1H and ^{13}C NMR.

Data for α anomer:

$[\alpha]_D$ = +44.5 (c = 1.20, CH_2Cl_2).

^1H NMR (500 MHz, $CDCl_3$): δ 7.38-7.31 (m, 9H), 7.26-7.15 (m, 11H), 7.04-7.02 (m, 2H), 6.94-6.93 (m, 2H), 6.75-6.73 (m, 2H), 5.51 (d, *J* = 3.5 Hz, 1H), 5.43 (s, 1H), 4.89 (d, *J* = 11.3 Hz, 1H), 4.74 (d, *J* = 3.6 Hz, 1H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.65-4.57 (m, 3H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.47 (d, *J* = 12.6 Hz, 1H), 4.34 (t, *J* = 9.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.26-4.15 (m, 4H), 3.90-3.85 (m, 2H), 3.77-

3.69 (m, 2H), 3.64 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.54 (t, *J* = 9.5 Hz, 1H), 3.45-3.34 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 137.5, 137.3, 137.2, 135.6, 136.3, 133.7, 133.5, 133.4, 129.8, 129.6, 129.1, 128.8, 128.7, 128.6, 128.5, 128.3, 126.6, 102.4, 98.6, 96.2, 83.1, 81.7, 78.7, 78.2, 77.7, 74.7, 74.0, 73.4, 73.2, 72.7, 70.3, 69.8, 69.4, 68.3, 62.0, 55.6.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{55}H_{54}ClO_{11}Na$ $(M+Na)^+$ 1055.2309, found 1055.2297.

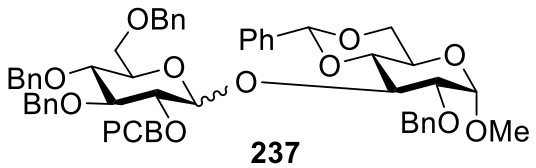
Data for β anomer:

$[\alpha]_D$ = +24.6 (c = 1.70, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.41 (m, 2H), 7.27-7.18 (m, 18H), 7.11-7.09 (m, 4H), 7.03-7.01 (m, 2H), 5.47 (s, 1H), 4.99 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 8.0 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.70-4.61 (m, 4H), 4.53 (d, *J* = 4.0 Hz, 1H), 4.48-4.44 (m, 2H), 4.42-4.31 (m, 3H), 4.23 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.81 (ddd, *J* = 10.0, 9.9, 4.5 Hz, 1H), 3.69 (t, *J* = 10.5 Hz, 1H), 3.63-3.49 (m, 6H), 3.41 (t, *J* = 8.2 Hz, 1H), 3.36 (s, 3H), 3.22-3.20 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.6, 137.4, 137.2, 137.1, 136.8, 133.7, 133.5, 133.4, 129.4, 129.3, 129.2, 129.0, 128.7, 128.6, 128.3, 128.2, 126.4, 102.7, 101.8, 98.7, 84.9, 82.9, 80.7, 80.5, 78.1, 75.9, 74.9, 74.8, 74.1, 73.8, 72.9, 69.3, 68.7, 62.4, 55.6.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{55}H_{54}ClO_{11}Na$ $(M+Na)^+$ 1055.2309, found 1055.2323.



237

Methyl-(2-O-(4-chlorobenzyl)-3,4,6-tri-O-benzyl-D-glucopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (237):

Following the general glycosylation procedure, glycosyl donor **232** (0.079 mmol, 52.6 mg) and acceptor **147** (0.158 mmol, 59 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **237** after purification by silica gel flash column chromatography (17% ethyl acetate in hexanes) as determined by ^{1}H and ^{13}C NMR. The NMR spectroscopic data matched those reported previously.[40]

Data for α anomer:

$[\alpha]_D$ = +65.2 (c = 1.69, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-6.75 (m, 29H), 5.53 (d, *J* = 3.5 Hz, 1H), 5.45 (s, 1H), 4.94 (d, *J* = 10.5 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 3.5 Hz, 1H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 4.56 (d, *J* = 5.0 Hz, 1H), 4.49 (d, *J* = 12.5 Hz, 1H), 4.41-4.34 (m, 2H), 4.30-4.17 (m, 4H), 3.94 (t, *J* = 9.5 Hz, 1H), 3.87 (ddd, *J* = 9.8, 9.8, 4.8 Hz, 1H), 3.77 (d, *J* = 9.0 Hz, 1H), 3.74-3.62 (m, 4H), 3.50-3.40 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 139.0, 138.3, 137.6, 137.3, 136.5, 133.2, 129.7, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2,

128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 126.6, 102.4, 98.7, 96.4, 83.1, 81.8, 78.8, 78.2, 77.8, 75.7, 75.0, 73.6, 73.5, 73.1, 70.4, 70.1, 69.4, 68.3, 62.0, 55.6.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{55}H_{57}ClO_{11}Na$ $(M+Na)^+$ 951.3482, found 951.3466.

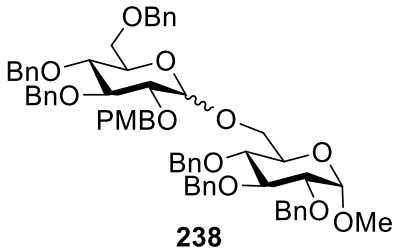
Data for β anomer:

$[\alpha]_D$ = +9.9 (c = 1.01, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.13 (m, 29 H), 5.45 (s, 1H), 4.99 (d, *J* = 11.5 Hz, 1H), 4.86-4.83 (m, 2H), 4.80-4.67 (m, 4H), 4.53-4.47 (m, 5H), 4.34 (t, *J* = 9.5 Hz, 1H), 4.21 (dd, *J* = 10.0, 4.7 Hz, 1H), 3.81 (ddd, *J* = 10.0, 9.8, 4.7 Hz, 1H), 3.69-3.53 (m, 7H), 3.44 (t, *J* = 8.5 Hz, 1H), 3.36 (s, 3H), 3.22-3.19 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 138.6, 138.4, 138.2, 137.6, 133.3, 129.5, 129.1, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 126.4, 102.7, 101.7, 98.8, 85.0, 83.0, 80.7, 80.5, 78.2, 76.3, 75.8, 75.1, 74.9, 74.1, 73.9, 73.7, 69.3, 68.8, 62.3, 55.6;

HRMS (ESI, pos. ion) m/z: calcd. for $C_{55}H_{57}ClO_{11}Na$ $(M+Na)^+$ 951.3482, found 951.3469.



238

***Methyl-(2-O-(4-methoxybenzyl)-3,4,6-tri-O-benzyl-D-glucopyranosyl)-(1->6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (238)**:*

Following the general glycosylation procedure, glycosyl donor **231** (0.079 mmol, 52.3 mg) and acceptor **26** (0.158 mmol, 73.3 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **238** after purification by silica gel flash column chromatography (20% ethyl acetate in hexanes) as determined by ^{1}H and ^{13}C NMR.

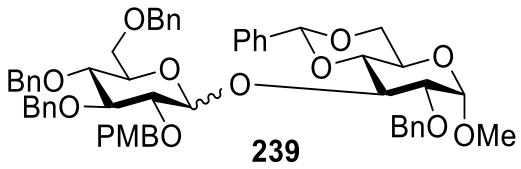
Data for β anomer:

$[\alpha]_D$ = +20.5 (c = 2.65, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.15 (m, 32H), 6.73-6.71 (m, 2H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.90 (d, *J* = 10.7 Hz, 2H), 4.81-4.76 (m, 5H), 4.68-4.51 (m, 7H), 4.34 (d, *J* = 7.7 Hz, 1H), 4.19 (d, *J* = 10.2 Hz, 1H), 4.01 (t, *J* = 9.5 Hz, 1H), 3.85-3.83 (m, 1H), 3.72-3.65 (m, 6H), 3.62-3.53 (m, 4H), 3.47 (t, *J* = 8.5 Hz, 1H), 3.43-3.41 (m, 1H), 3.34 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 138.8, 138.5, 138.3, 130.8, 129.8, 129.4, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 113.9, 104.1, 98.2, 85.0, 82.2, 82.0, 80.1, 78.3, 78.1, 77.5, 77.2, 77.0, 75.9, 75.8, 75.3, 75.2, 75.1, 74.7, 73.6, 70.1, 69.3, 68.8, 55.4.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{63}H_{68}O_{12}Na$ (M+Na) 1039.4603, found 1039.4604.



239

Methyl-(2-O-(4-methoxybenzyl)-3,4,6-tri-O-benzyl-D-glucopyranosyl)-(1→3)-2-O-benzyl-4,6-O-benzylidine-α-D-glucopyranoside (239):

Following the general glycosylation procedure, glycosyl donor **231** (0.079 mmol, 52.3 mg) and acceptor **147** (0.158 mmol, 59 mg) were coupled in the presence of aryl(trifluoroethyl)iodonium triflimide (0.095 mmol, 53.8 mg of **169** or 57.8 mg of **225**) to afford the desired product **239** after purification by silica gel flash column chromatography (8→10% ethyl acetate in toluene) as determined by ^{1}H and ^{13}C NMR.

Data for α anomer:

$[\alpha]_D$ = +30.6 (c = 0.45, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.07 (m, 25H), 6.83-6.82 (m, 2H), 6.61-6.59 (m, 2H), 5.56 (d, *J* = 3.6 Hz, 1H), 5.50 (s, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.79-4.77 (m, 2H), 4.70 (d, *J* = 3.6 Hz, 1H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.59-4.55 (m, 2H), 4.51 (d, *J* = 10.0 Hz, 1H), 4.40-4.36 (m, 2H), 4.30-4.24 (m, 3H), 4.20-4.18 (m, 1H), 3.94 (t, *J* = 9.5 Hz, 1H), 3.87 (ddd, *J* = 9.9, 9.9, 4.6 Hz, 1H), 3.79 (t, *J* = 11 Hz, 1H), 3.74-3.69 (m, 4H), 3.67-3.63 (m, 2H), 3.50-3.41 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 139.3, 139.1, 137.7, 137.3, 129.6, 129.3, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 126.6, 113.8, 102.3, 98.8, 96.4, 83.2, 81.9, 78.5, 78.3, 77.7, 75.7, 75.0, 73.6, 73.5, 72.9, 71.0, 70.0, 69.4, 68.4, 62.0, 55.6, 55.5.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{56}H_{60}O_{12}Na$ $(M+Na)^+$ 947.3977, found 947.3952.

Data for β anomer:

$[\alpha]_D$ = +20.4 (c = 2.65, CH_2Cl_2).

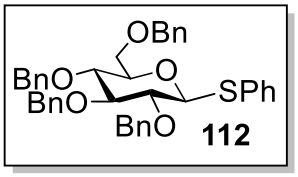
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.13 (m, 27H), 6.80-6.79 (m, 2H), 5.46 (s, 1H), 4.98 (d, *J* = 10.7 Hz, 1H), 4.91 (d, *J* = 11 Hz, 1H), 4.87 (d, *J* = 7.8 Hz, 1H), 4.79-4.70 (m, 4H), 4.53-4.48 (m, 5H), 4.36 (t, *J* = 9 Hz, 1H), 4.22-4.19 (m, 1H), 3.82 (ddd, *J* = 9.9, 9.9, 4.7 Hz, 1H), 3.77 (s, 3H), 3.69-3.55 (m, 7H), 3.48 (t, *J* = 8 Hz, 1H), 3.35 (s, 3H), 3.22 (dt, *J* = 9.5, 3.2 Hz, 1H).

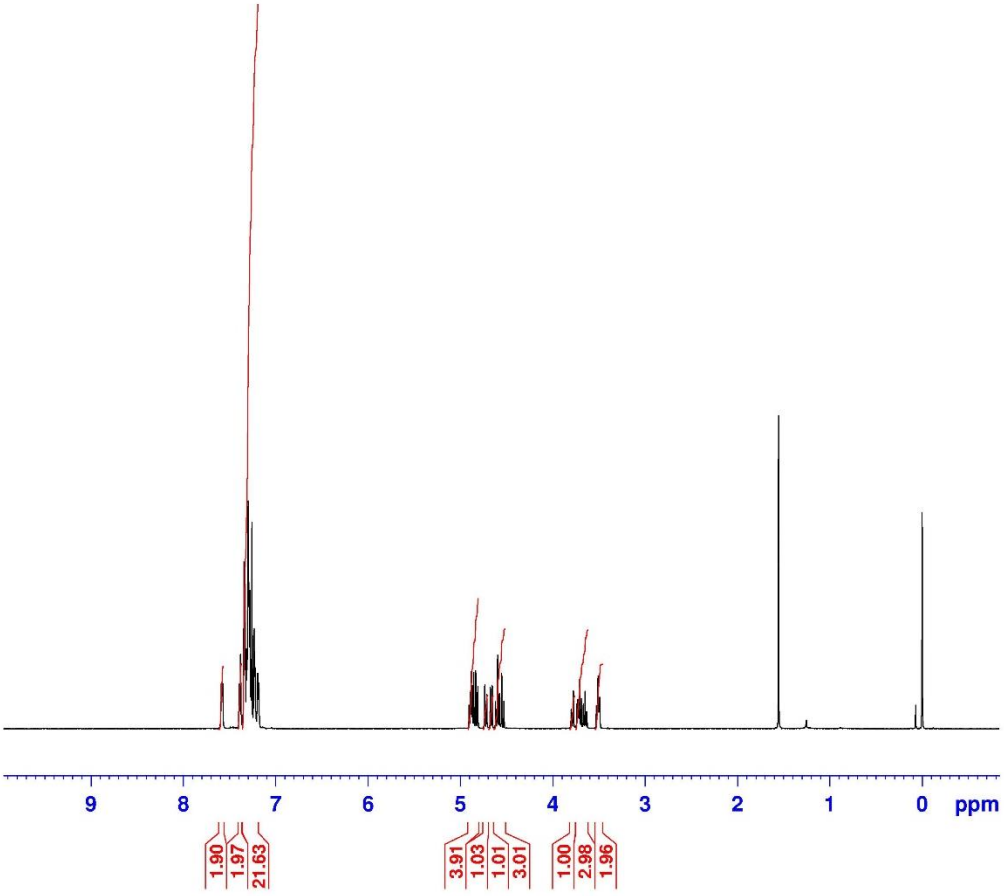
^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 139.0, 138.7, 138.4, 138.3, 137.6, 131.3, 129.9, 129.1, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 126.4, 113.9, 102.7, 101.7, 98.9, 85.1, 82.9, 80.6, 78.2, 77.5, 77.2, 77.0, 76.1, 75.7, 75.1, 74.9, 74.7, 74.0, 73.7, 69.3, 68.9, 62.3, 55.5, 55.4.

HRMS (ESI, pos. ion) m/z: calcd. for $C_{56}H_{60}O_{12}Na$ $(M+Na)^+$ 947.3977, found 947.3977.

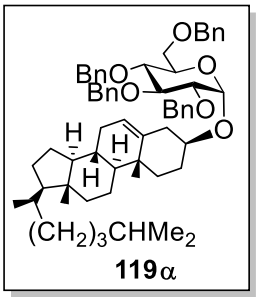
Compound Spectrum

^{1}H NMR (500MHz, $CDCl_3$)

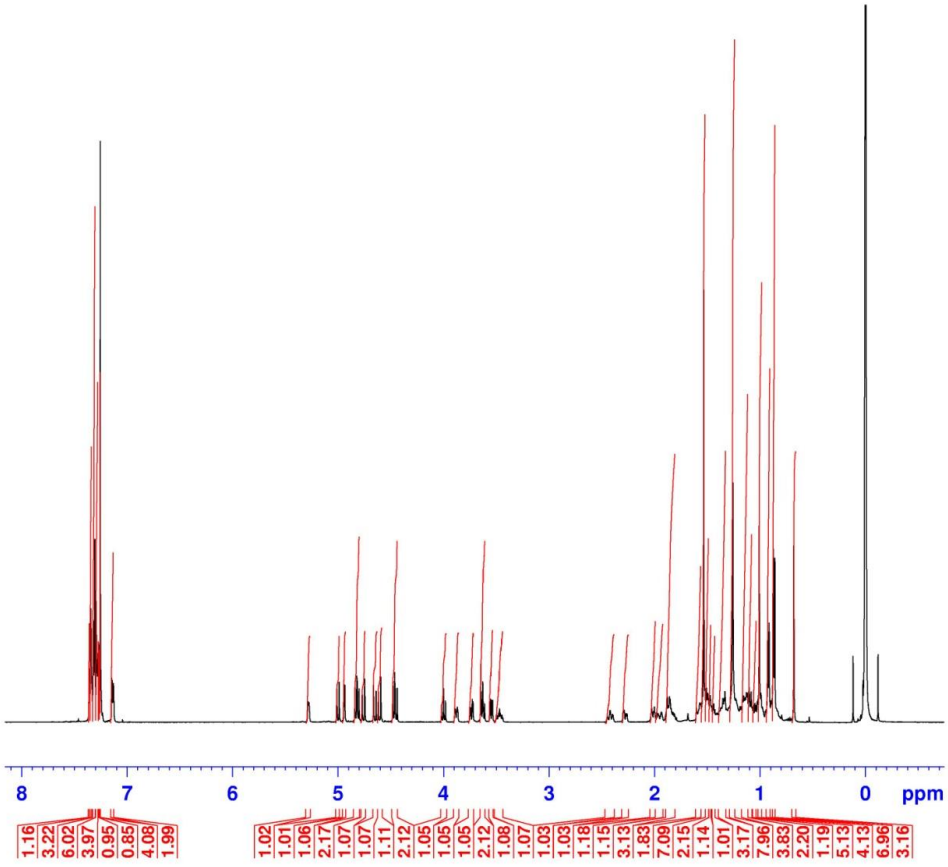




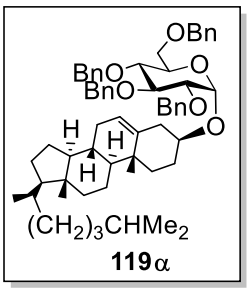
^{1}H NMR (500MHz, $CDCl_3$)



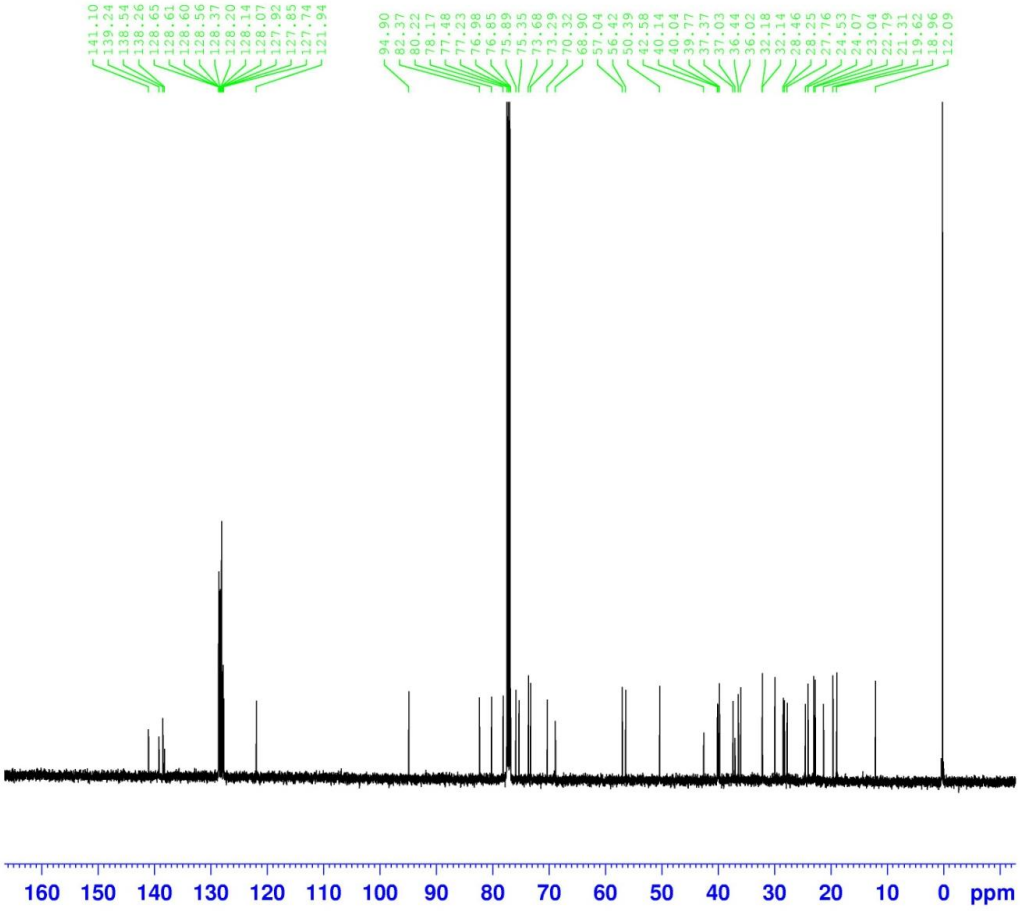
119α



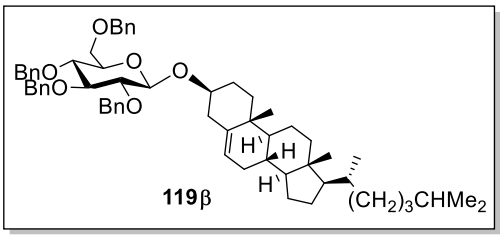
^{13}C NMR (125MHz, $CDCl_3$)

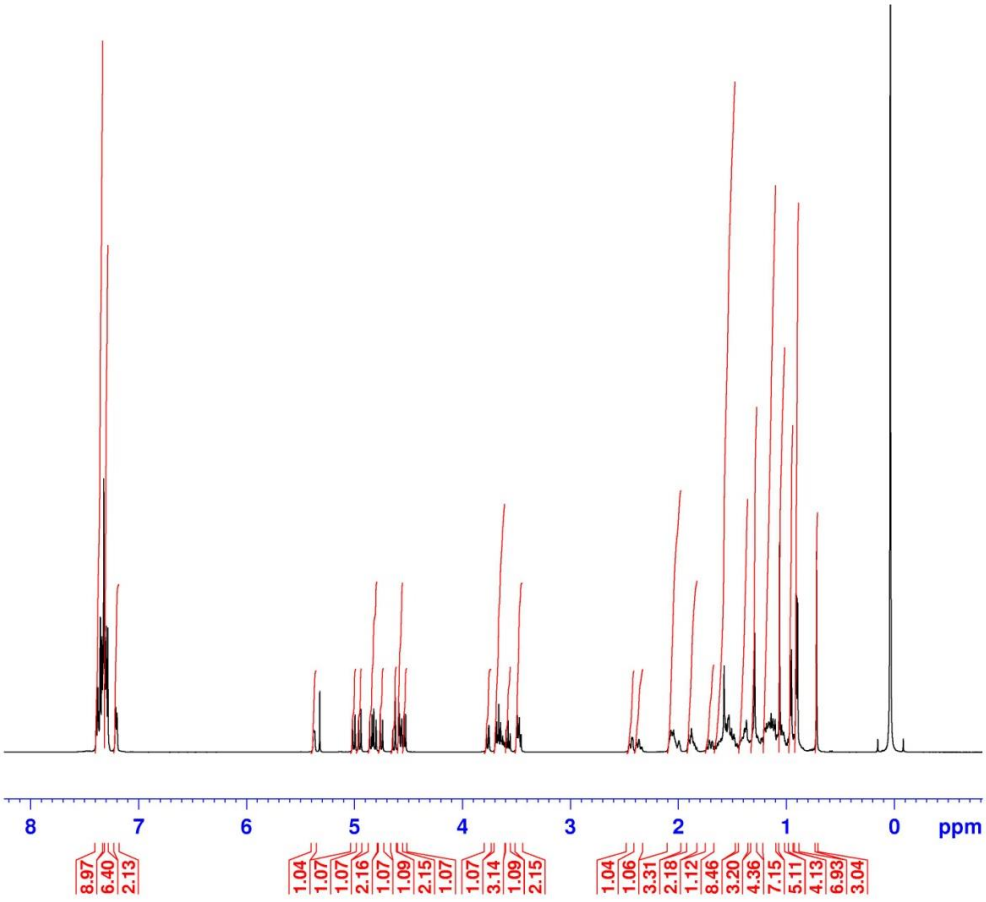


119α

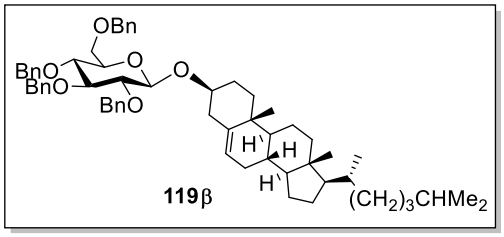


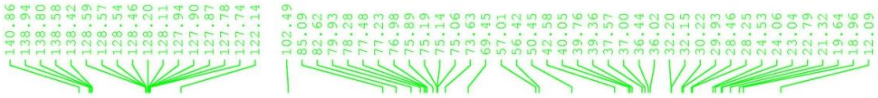
^{1}H NMR (500MHz, $CDCl_3$)

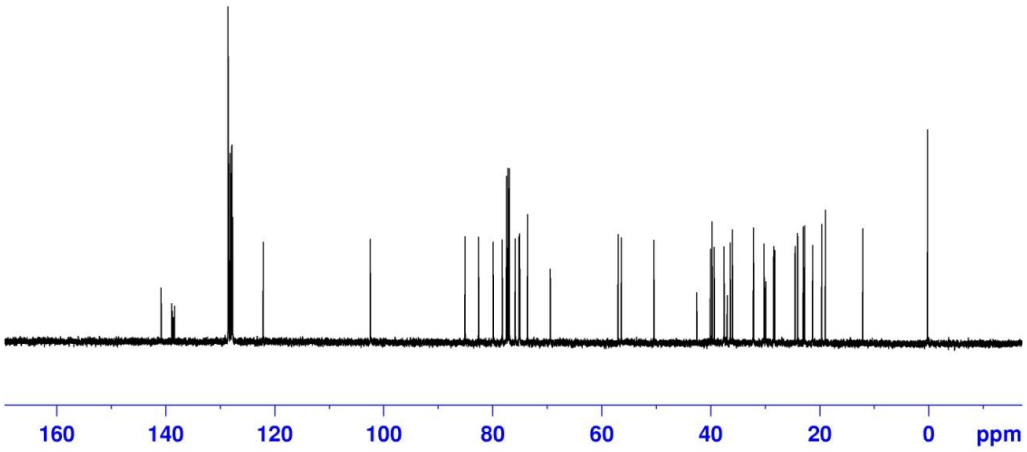




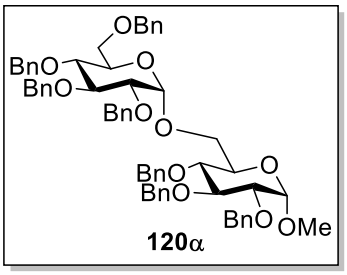
^{13}C NMR (125MHz, $CDCl_3$)



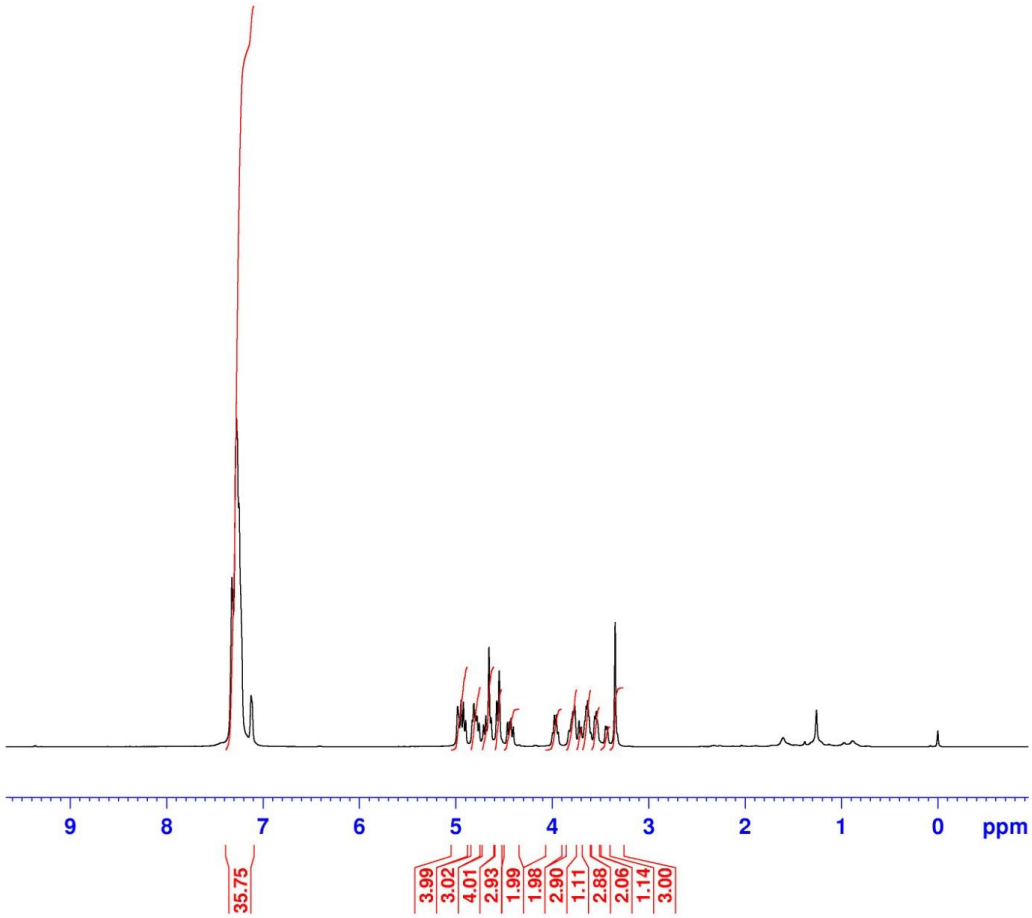




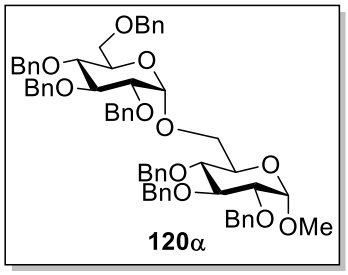
^{1}H NMR (500MHz, $CDCl_3$)

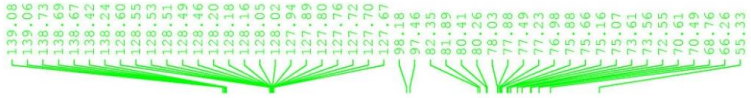


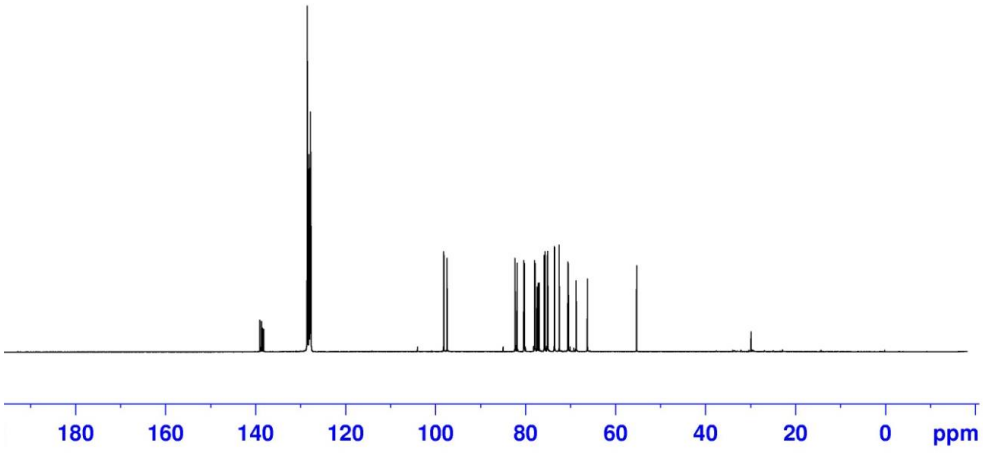
120α



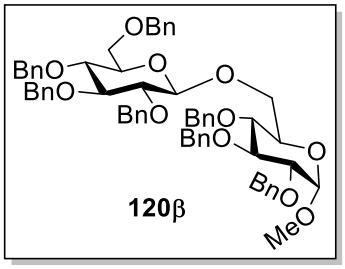
^{13}C NMR (125MHz, $CDCl_3$)

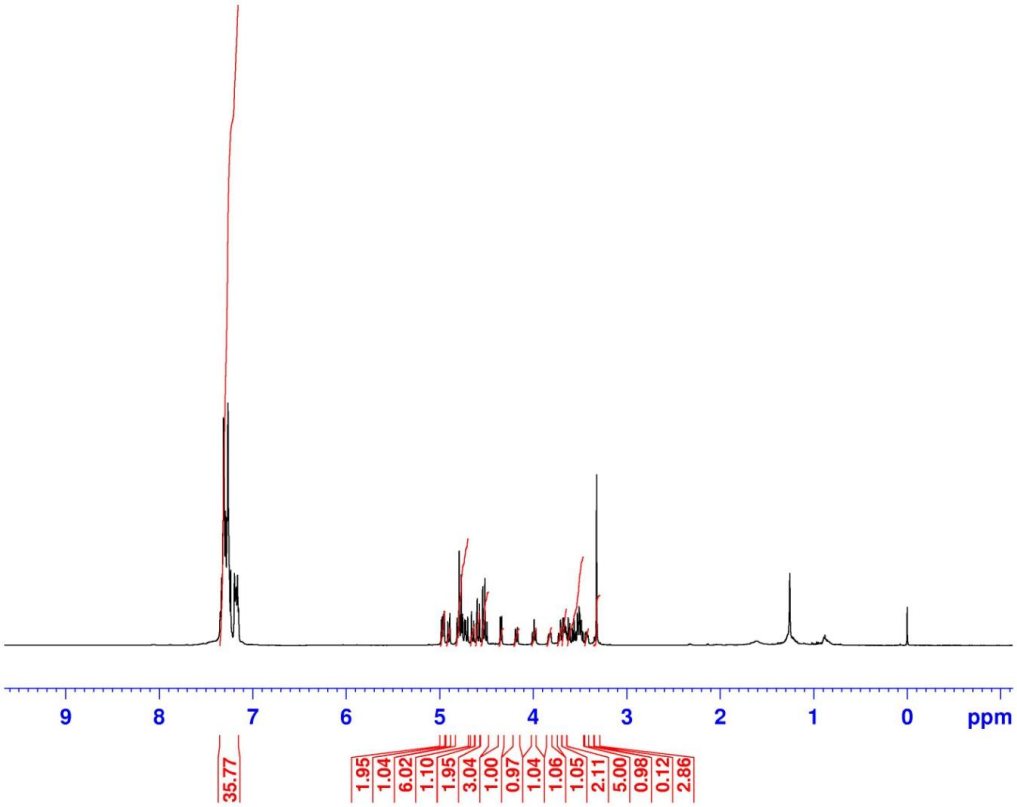




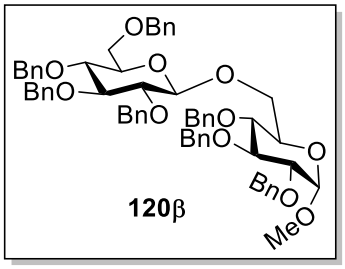


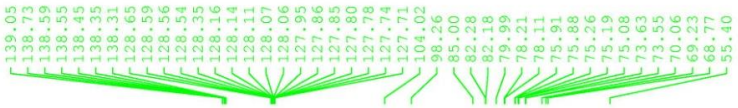
^{1}H NMR (500MHz, $CDCl_3$)

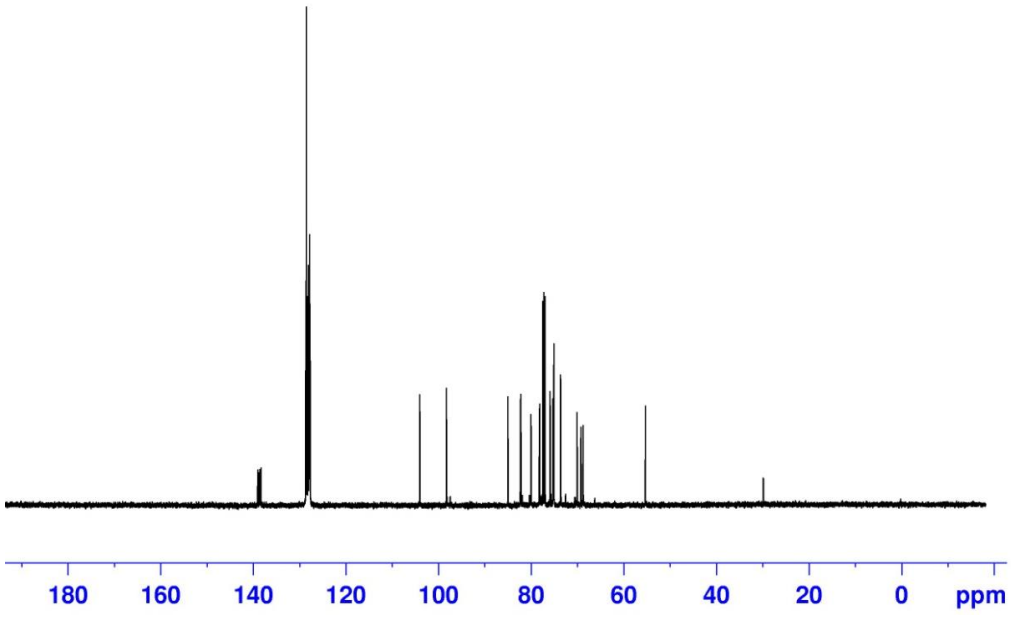




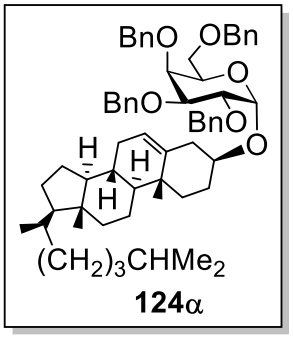
^{13}C NMR (125MHz, $CDCl_3$)

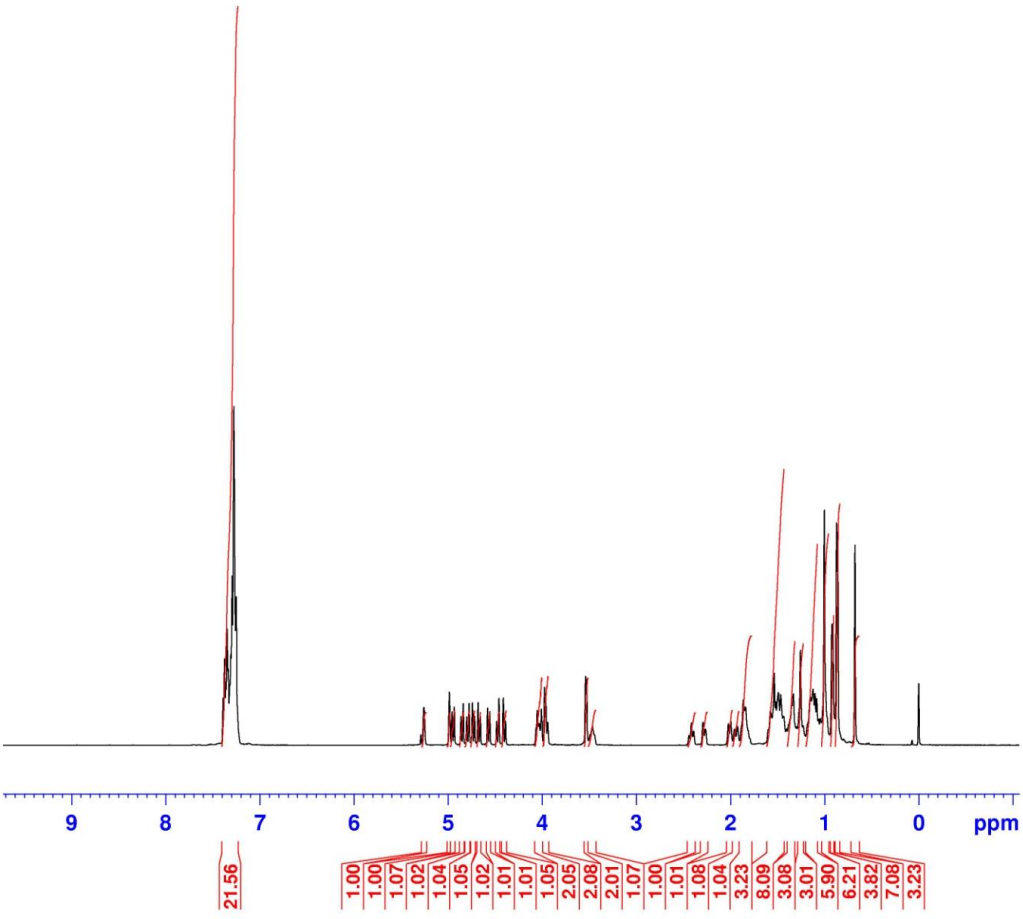




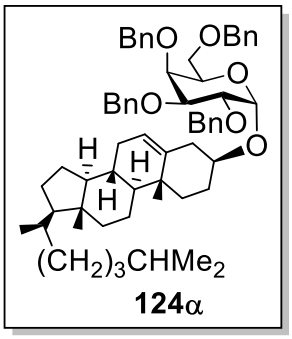


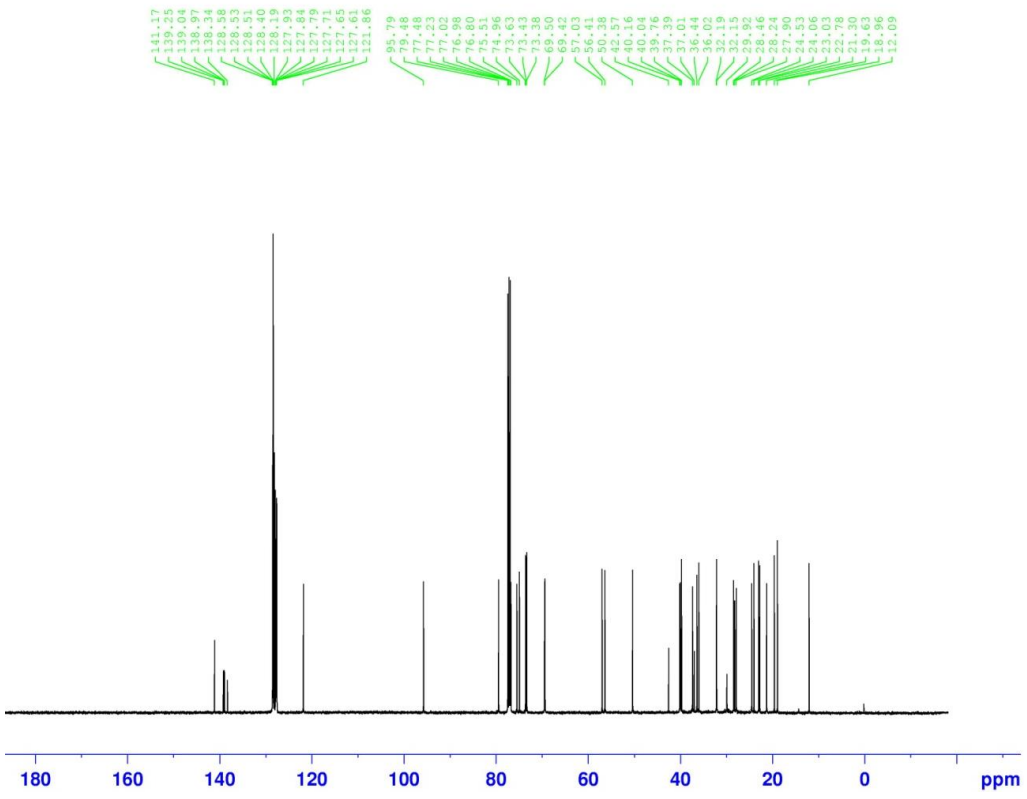
^{1}H NMR (500MHz, $CDCl_3$)



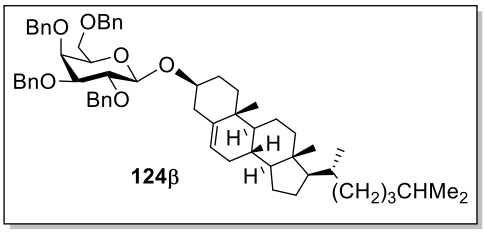


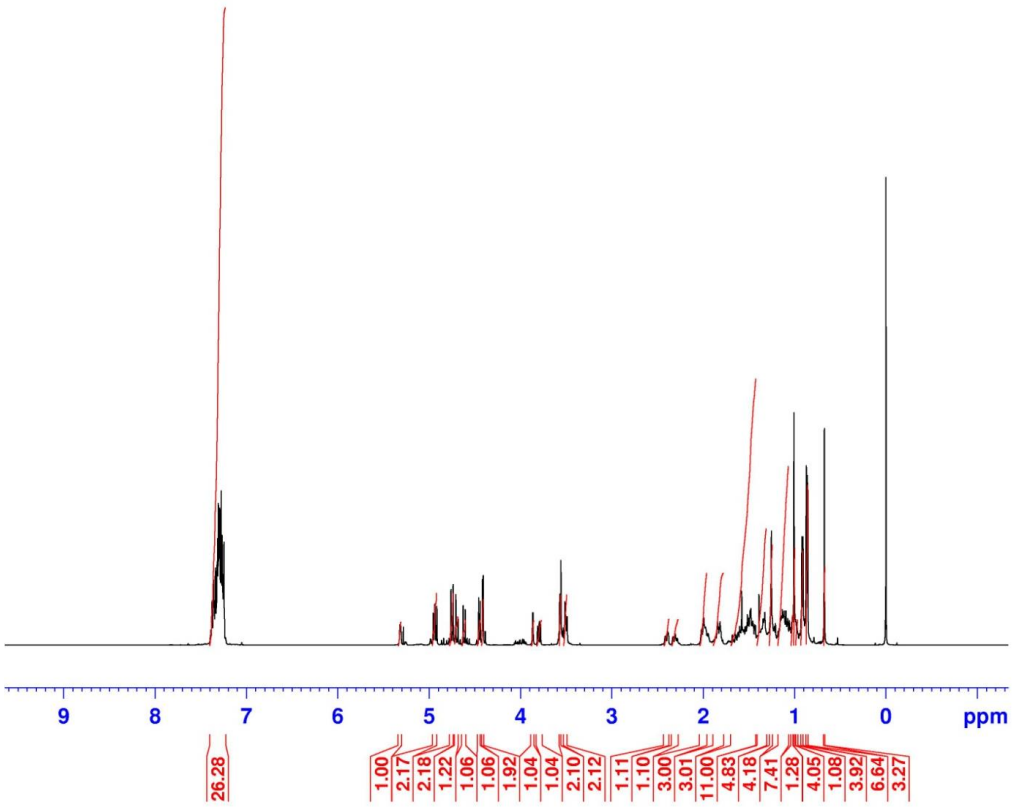
^{13}C NMR (125MHz, $CDCl_3$)



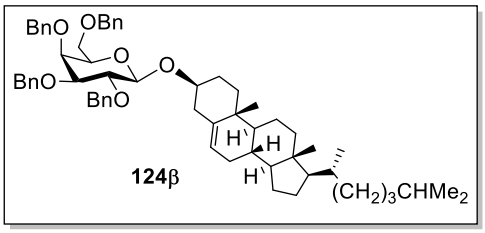


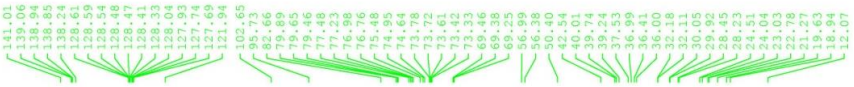
^{1}H NMR (500MHz, $CDCl_3$)

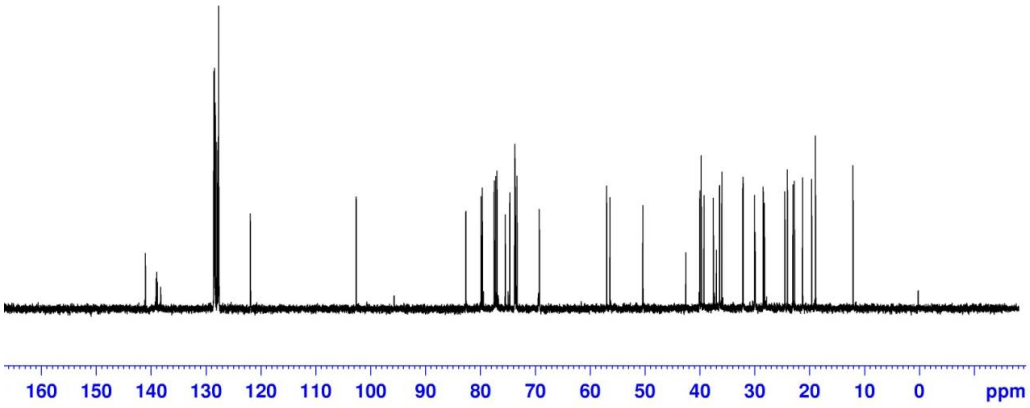




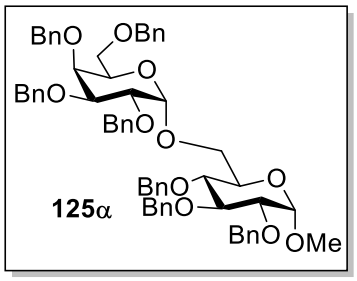
^{13}C NMR (125MHz, $CDCl_3$)



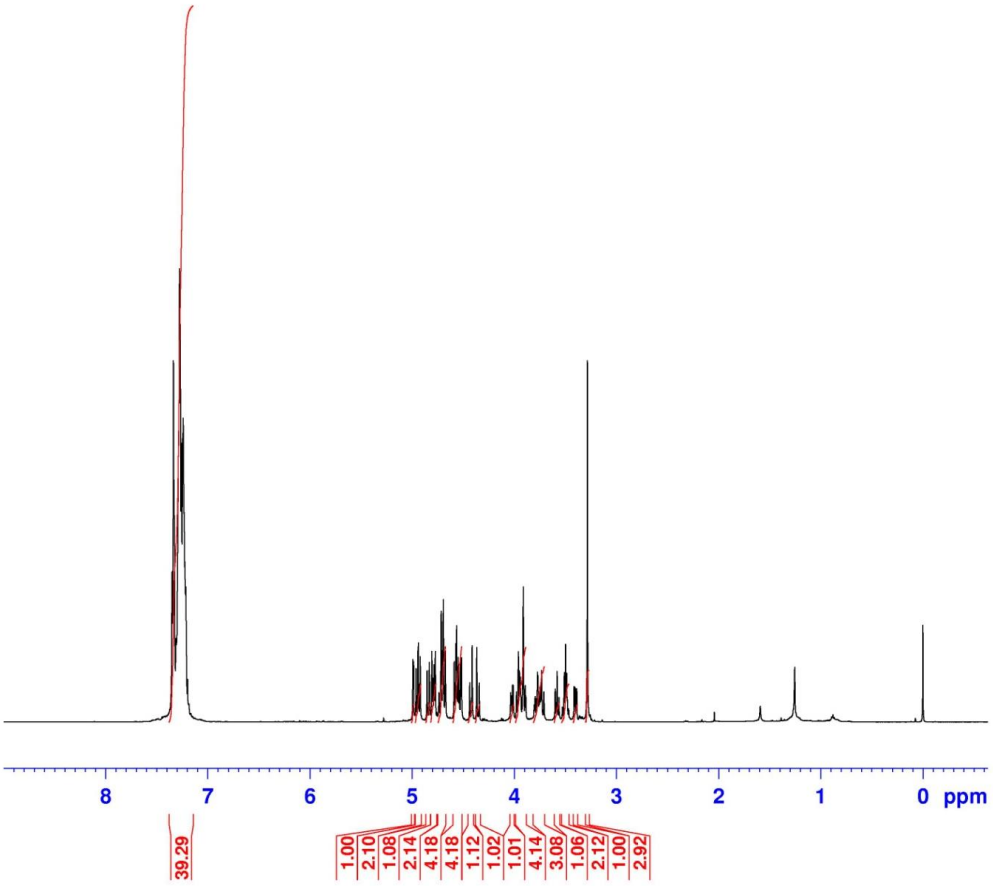




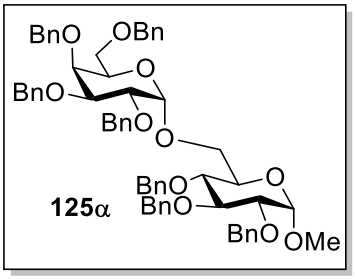
^{1}H NMR (500MHz, $CDCl_3$)



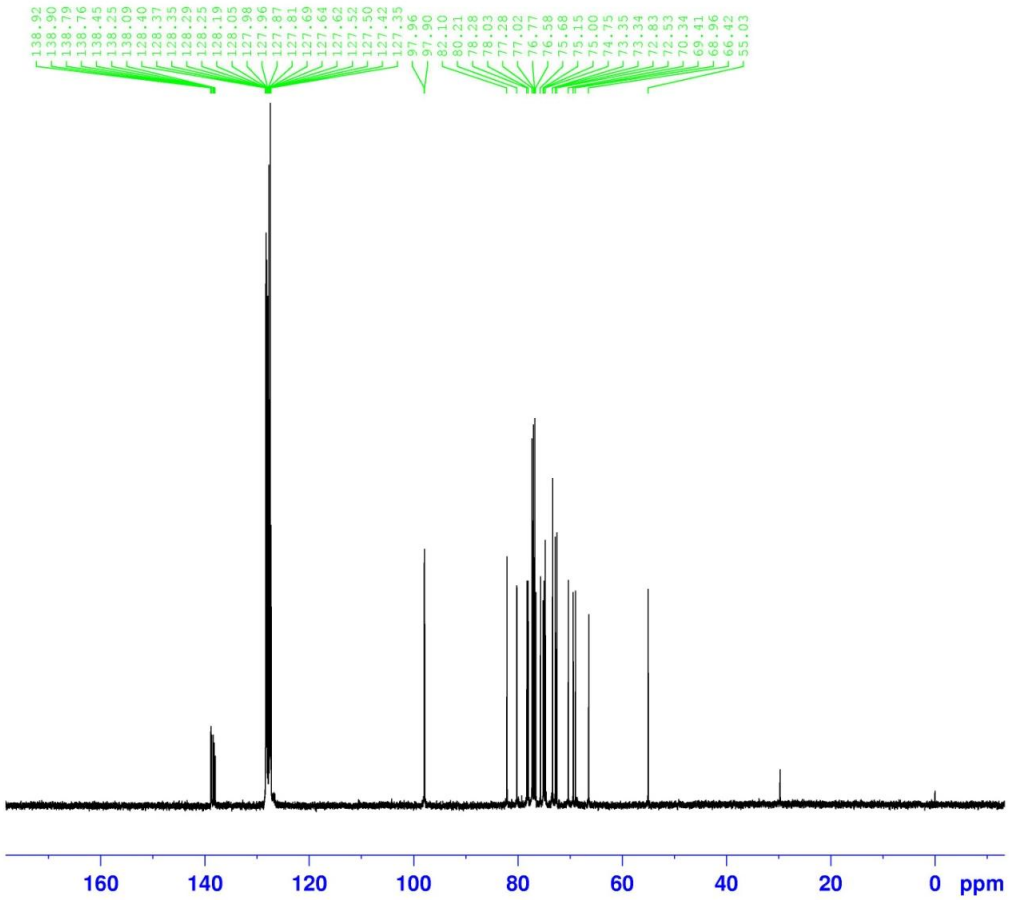
125α



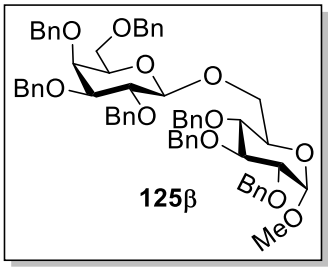
^{13}C NMR (125MHz, $CDCl_3$)

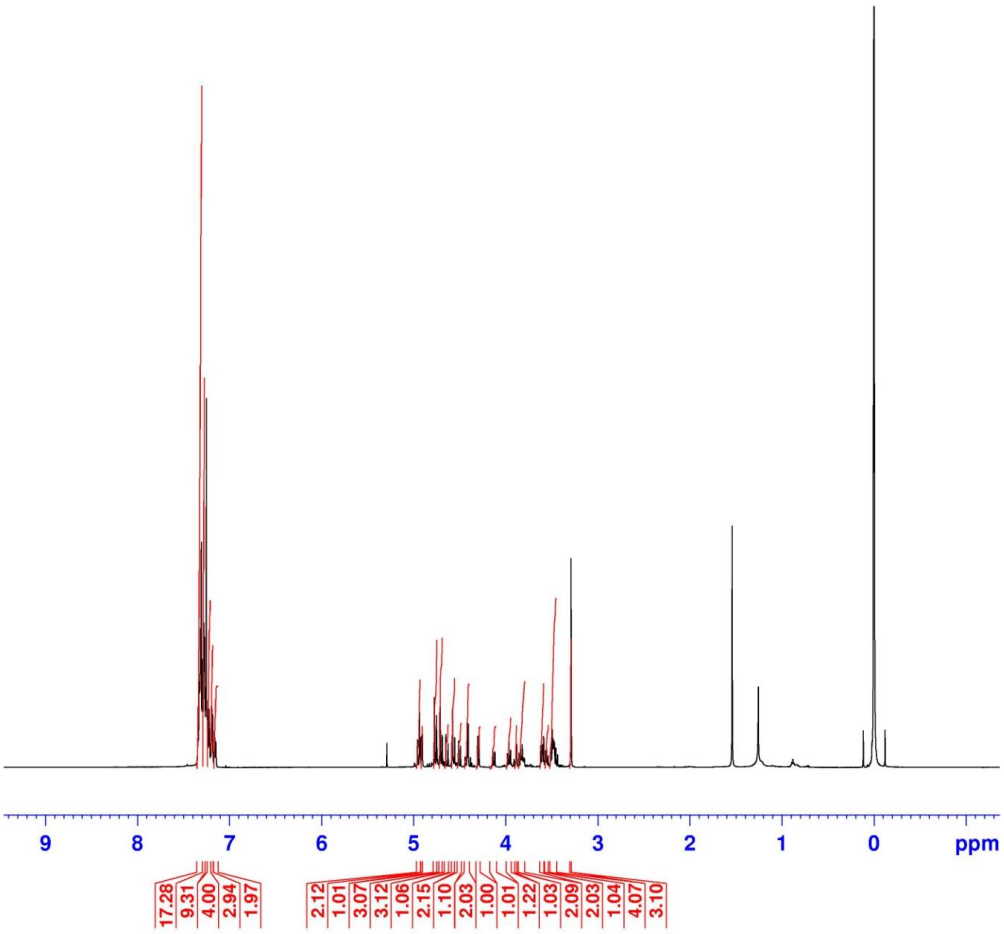


125α

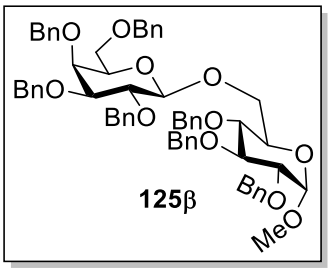


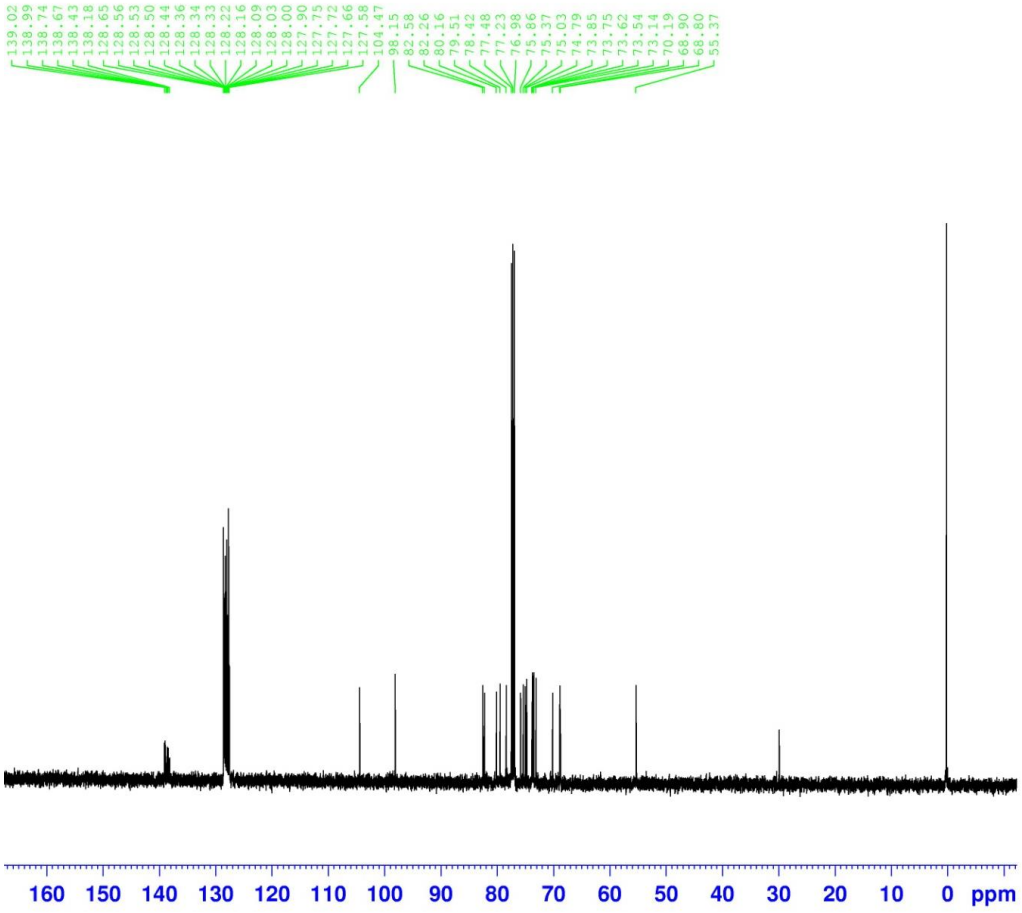
^{1}H NMR (500MHz, $CDCl_3$)



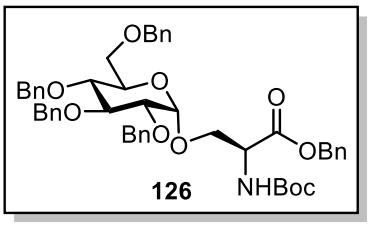


^{13}C NMR (125MHz, $CDCl_3$)

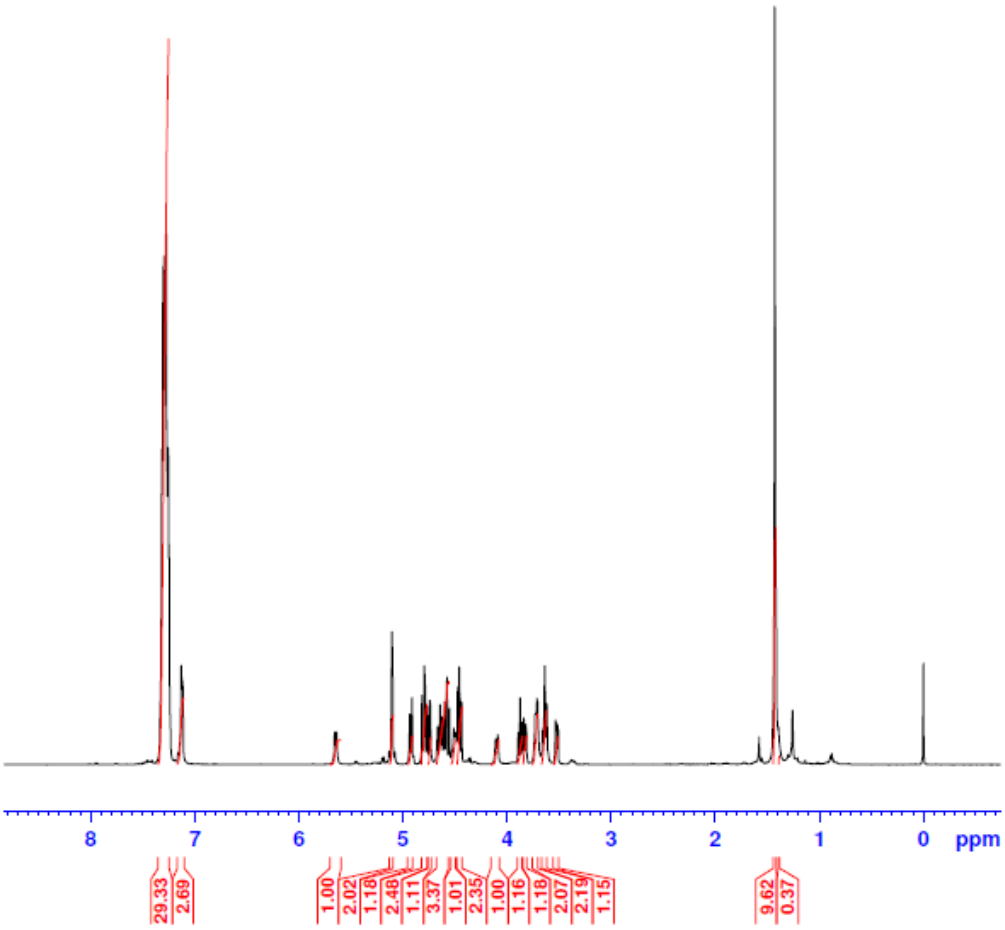




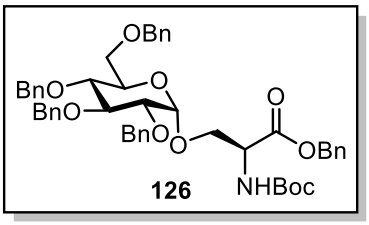
^{1}H NMR (500MHz, $CDCl_3$)

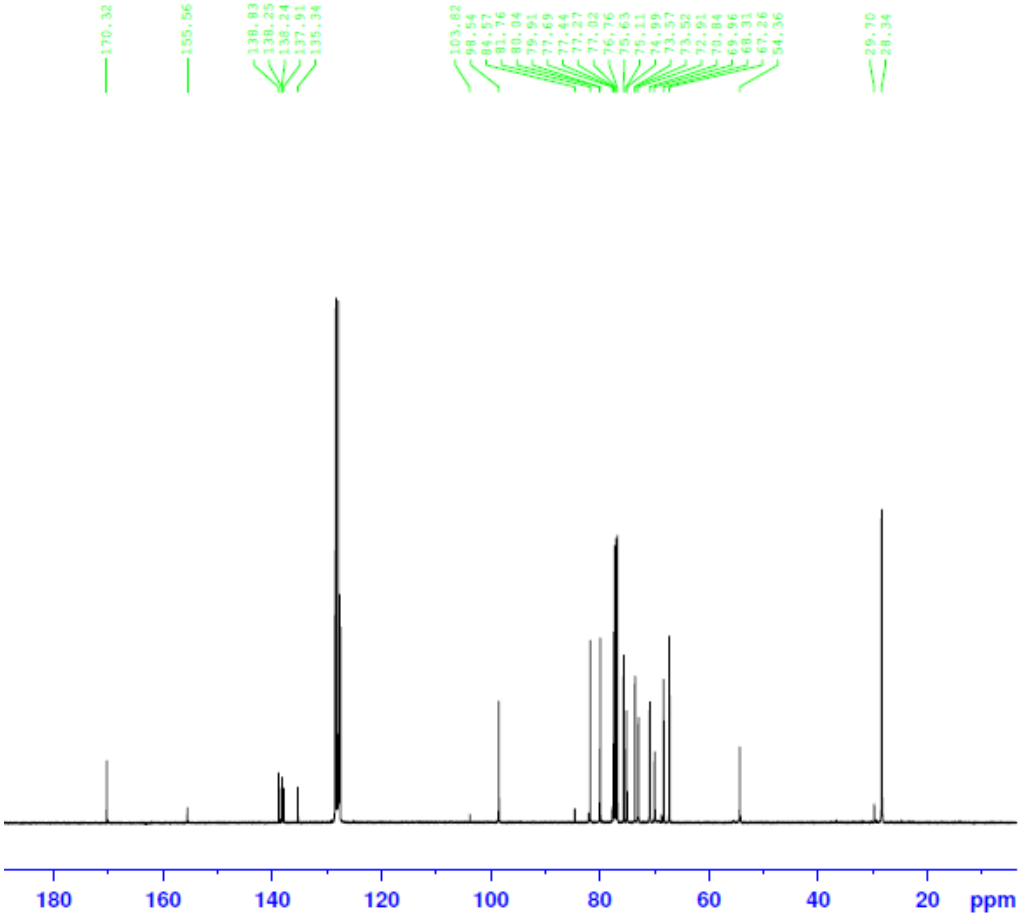


126



^{13}C NMR (125MHz, $CDCl_3$)





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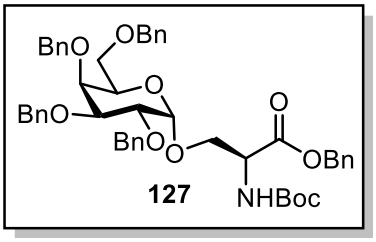

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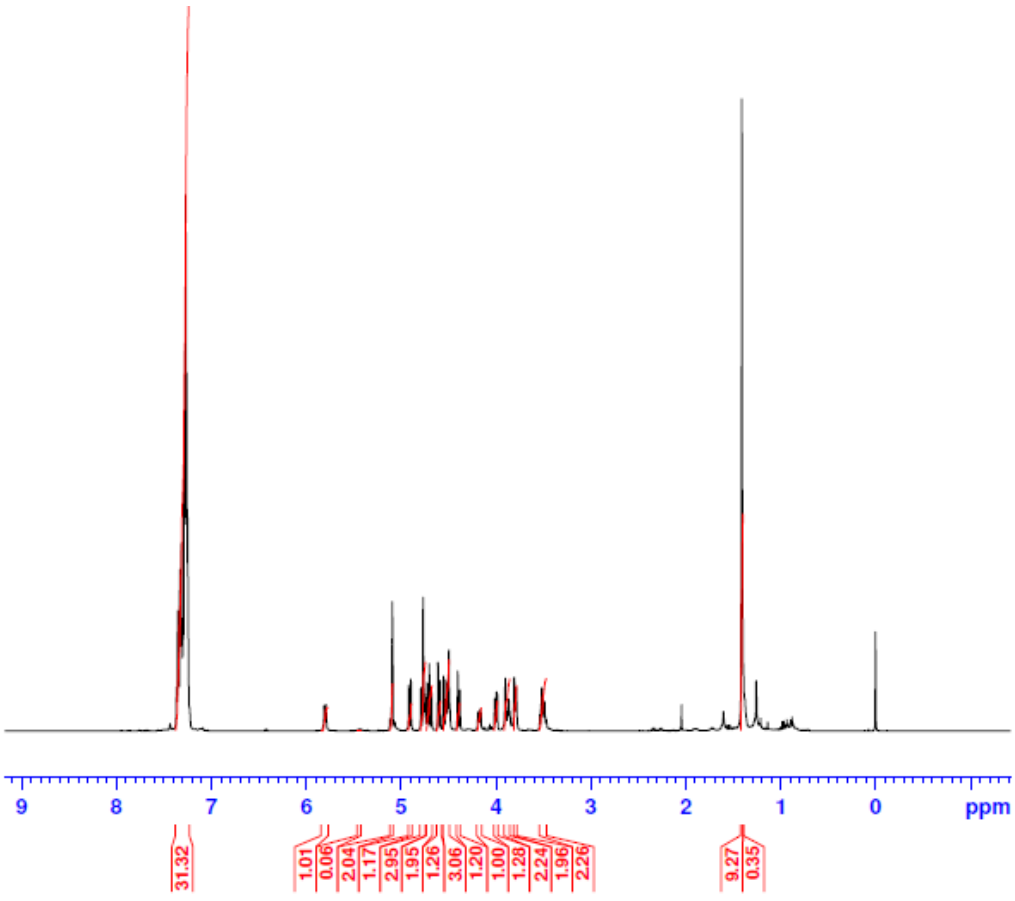
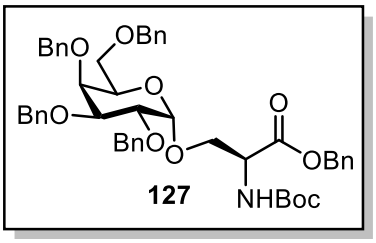
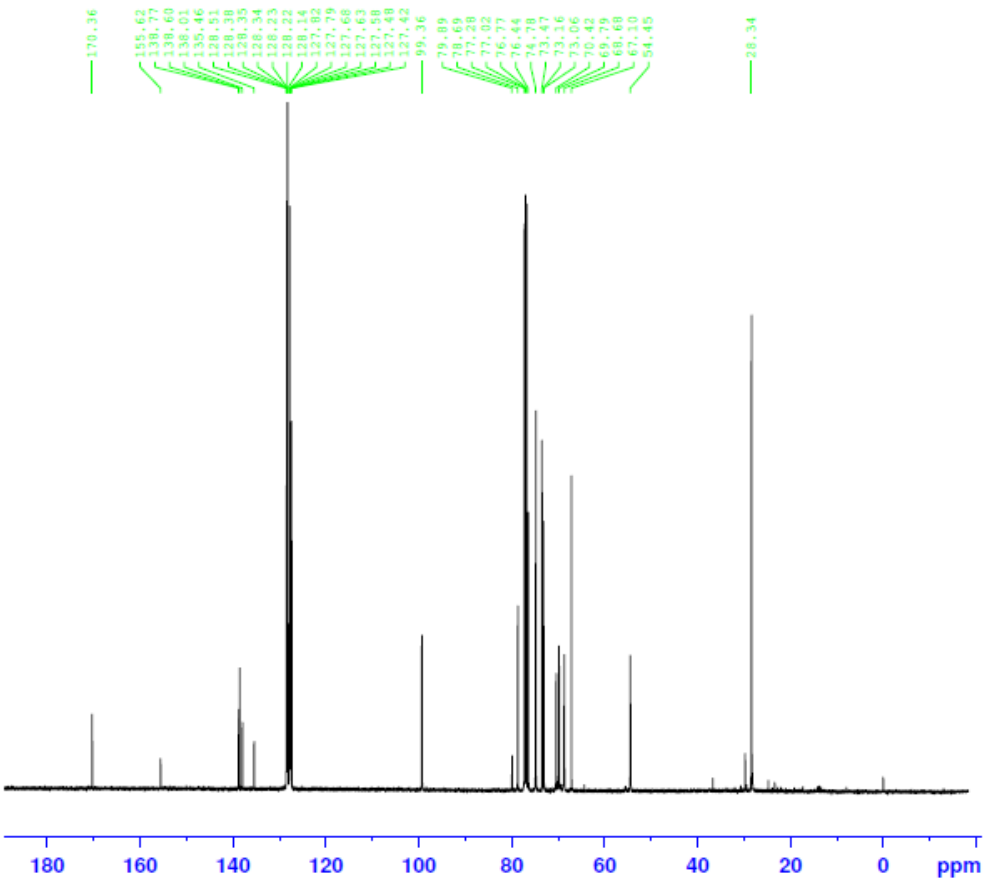
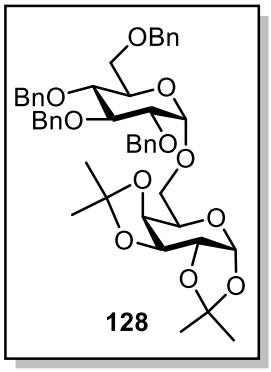


^{13}C NMR (125MHz, $CDCl_3$)





^{1}H NMR (500MHz, $CDCl_3$)



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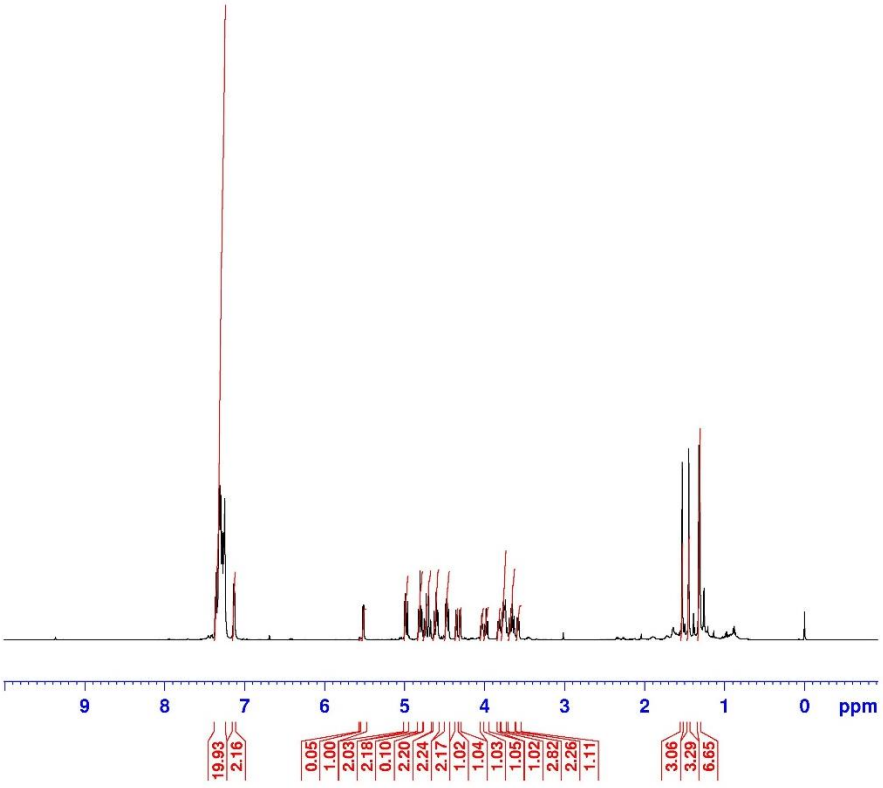
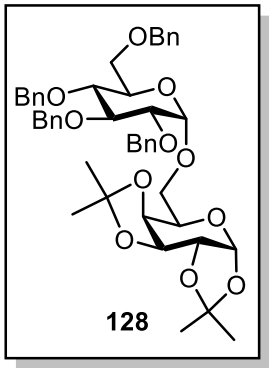
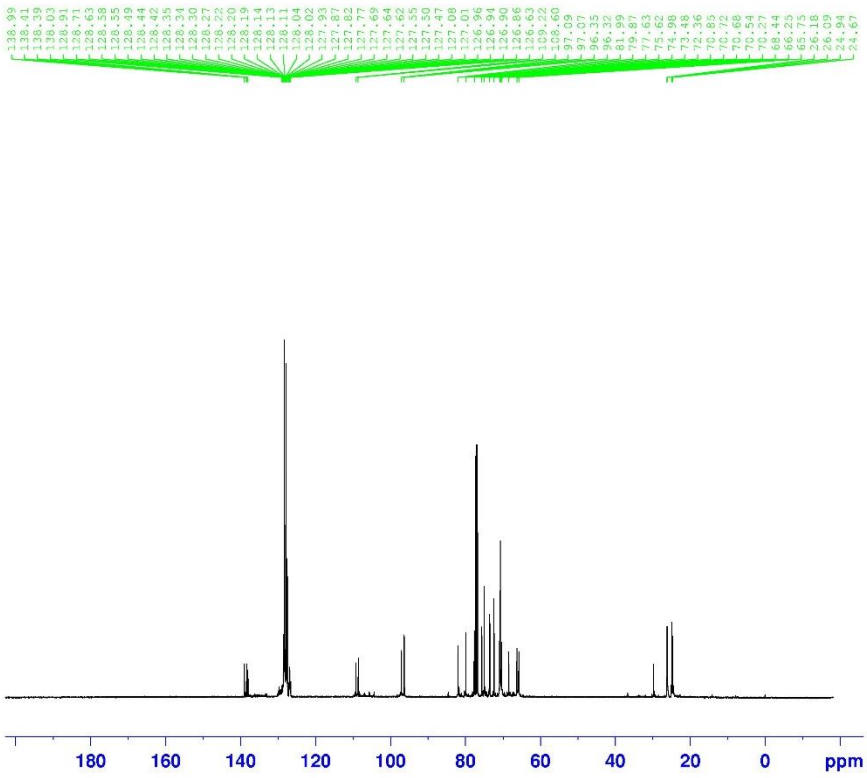


^{13}C NMR (125MHz, $CDCl_3$)





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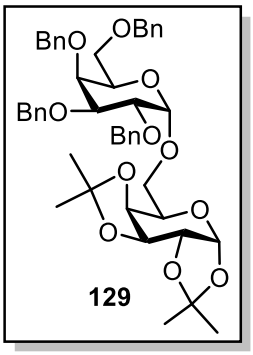

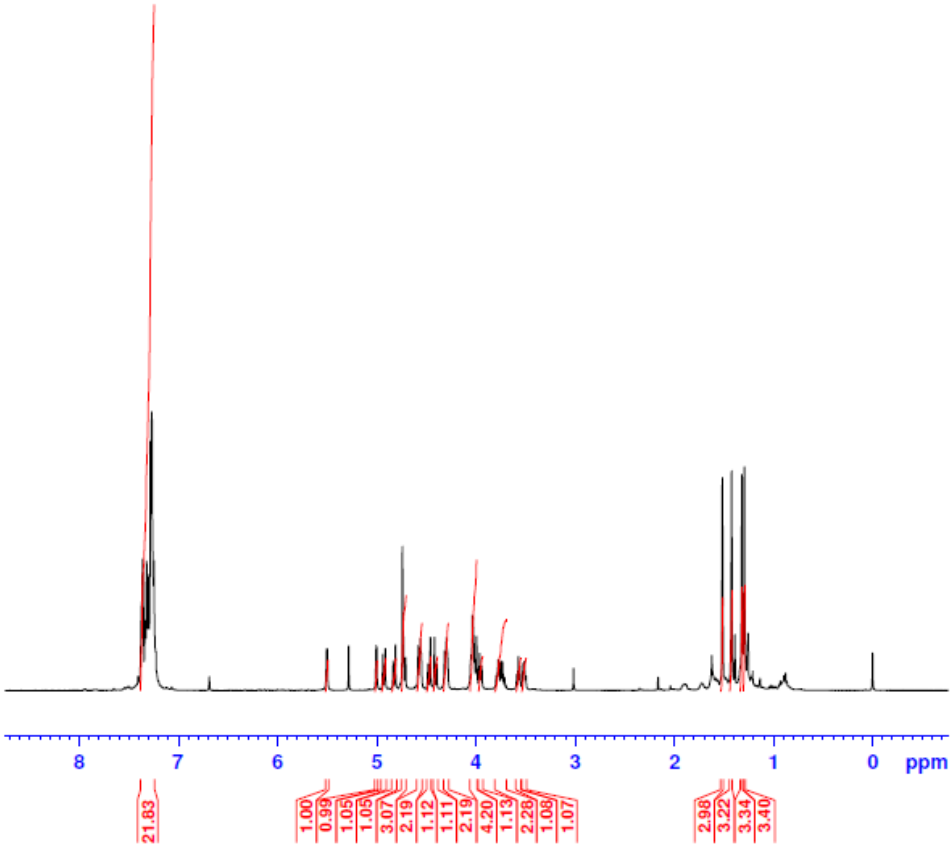

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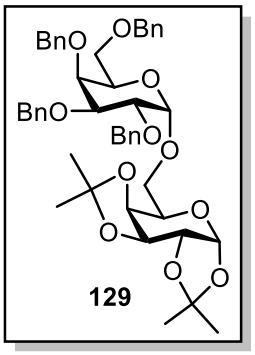
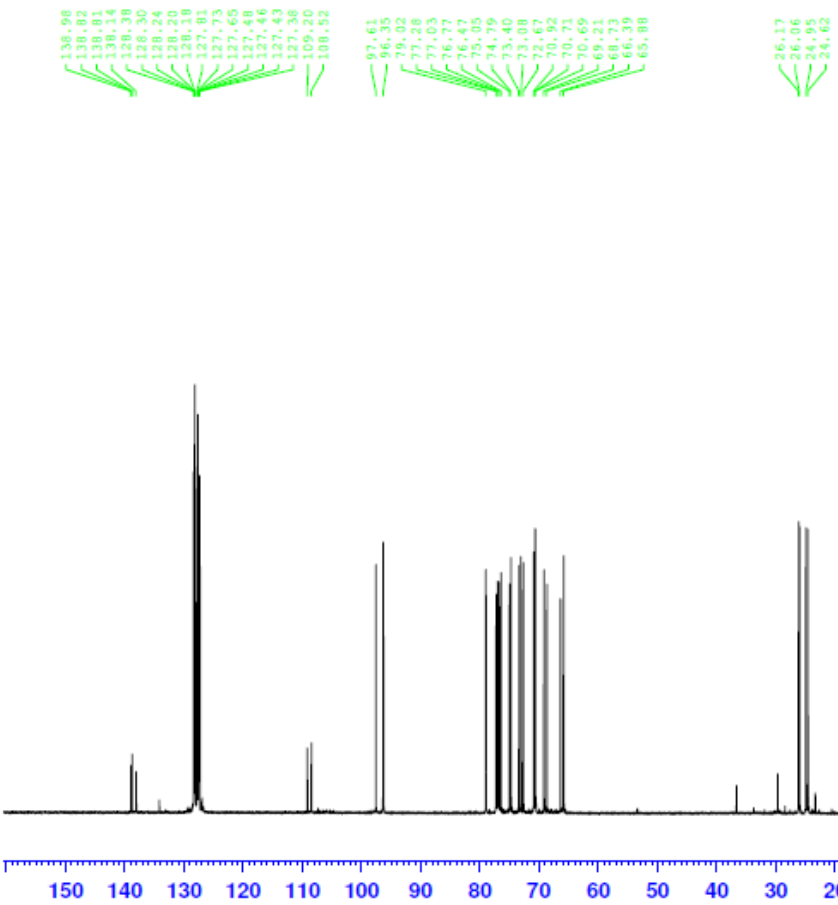
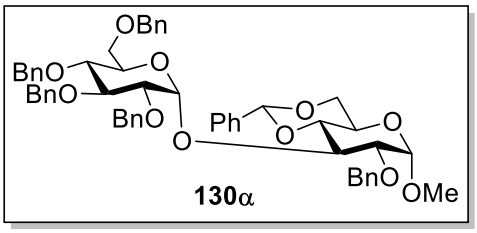
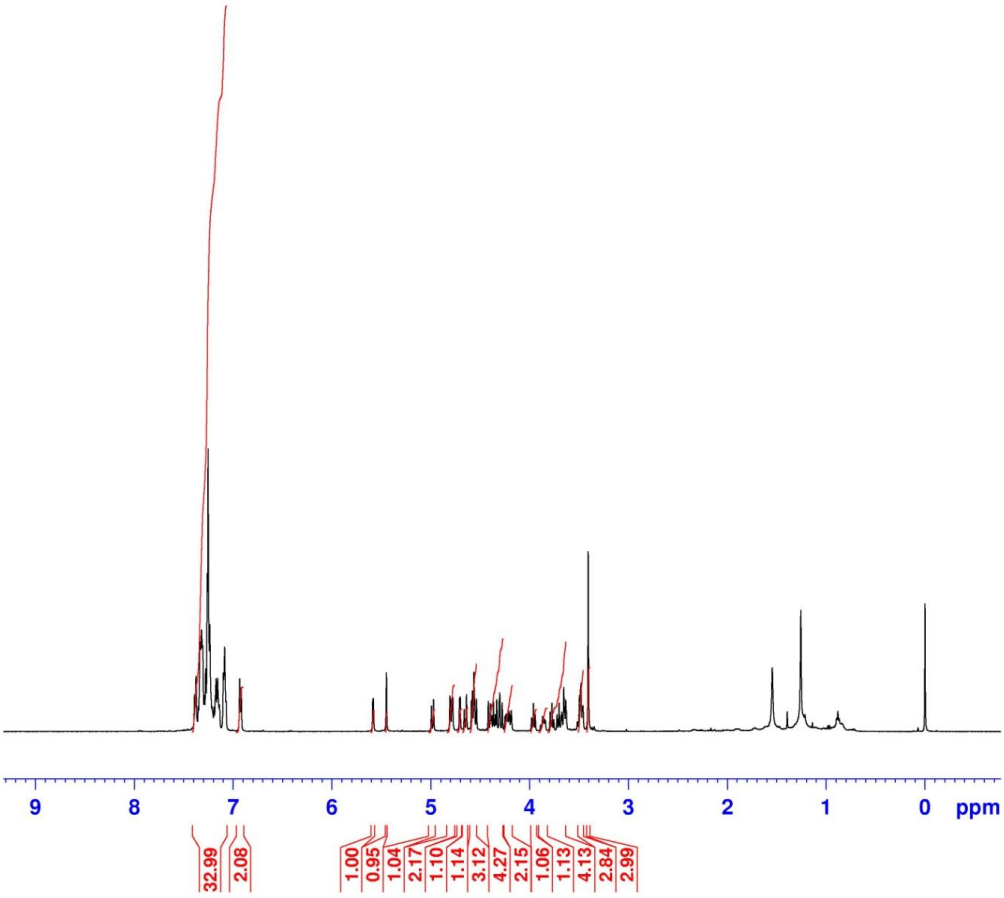




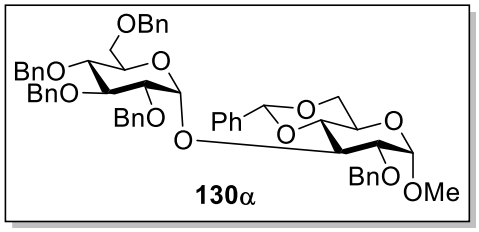
^{1}H NMR (500MHz, $CDCl_3$)



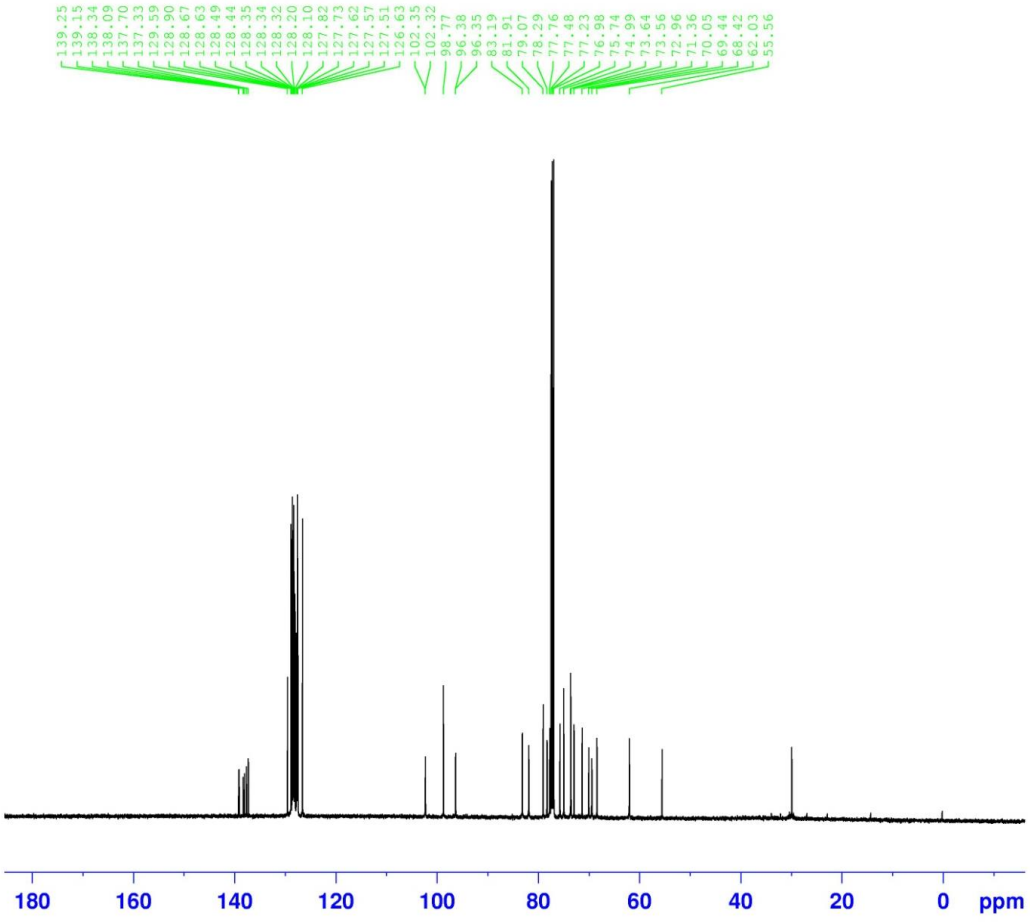
130α



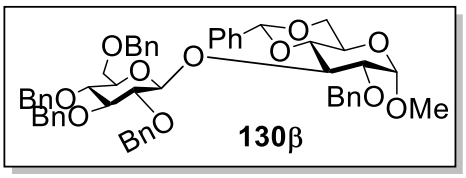
^{13}C NMR (125MHz, $CDCl_3$)



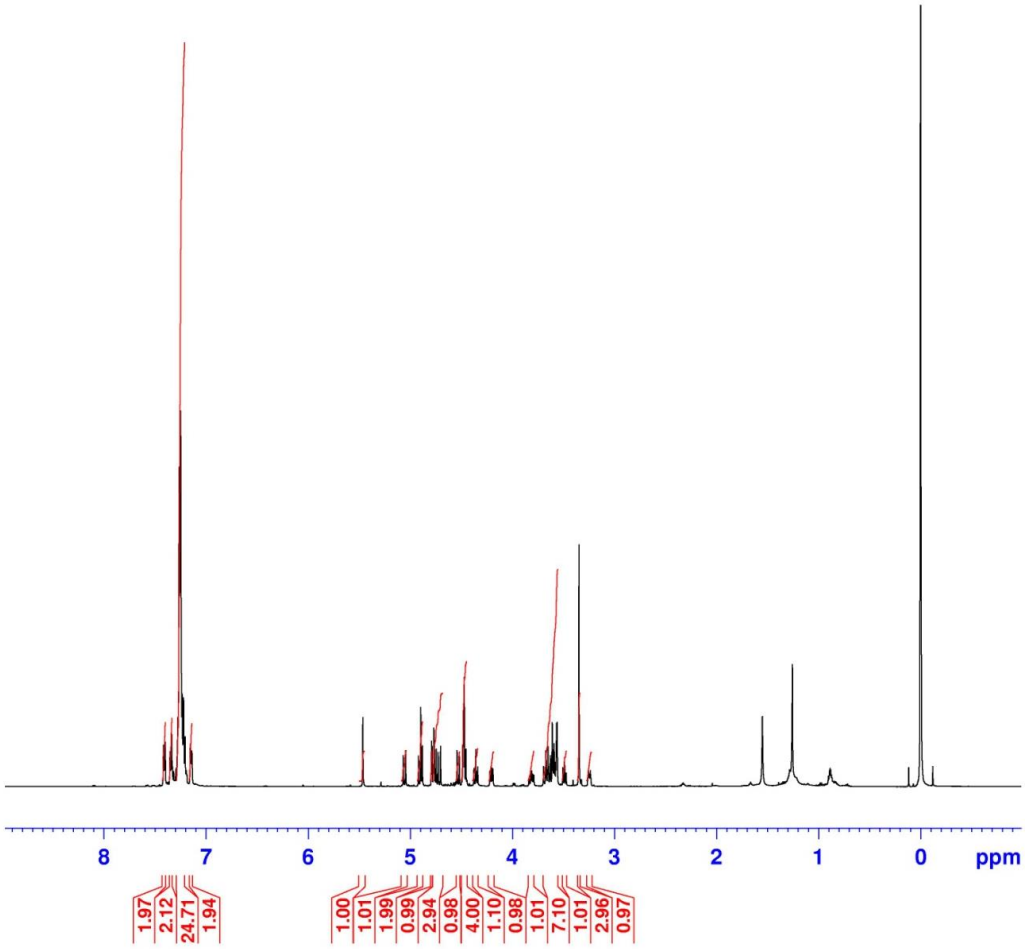
130α



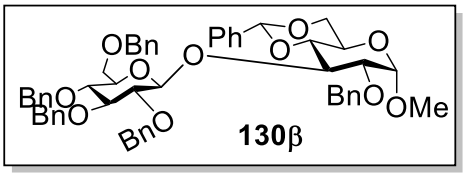
^{1}H NMR (500MHz, $CDCl_3$)

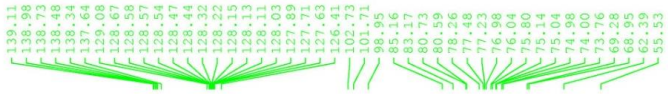


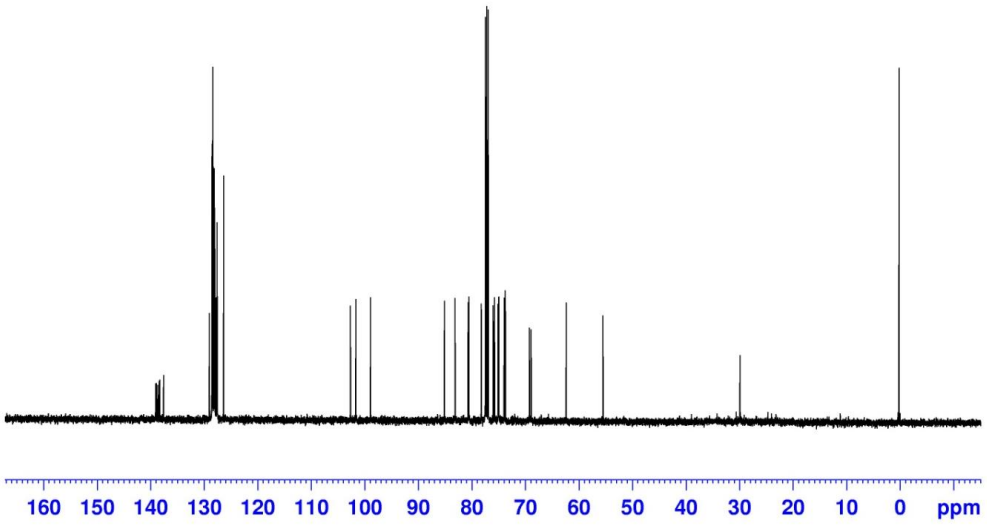
130β



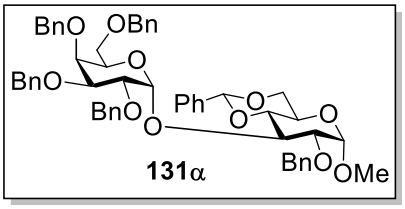
^{13}C NMR (125MHz, $CDCl_3$)



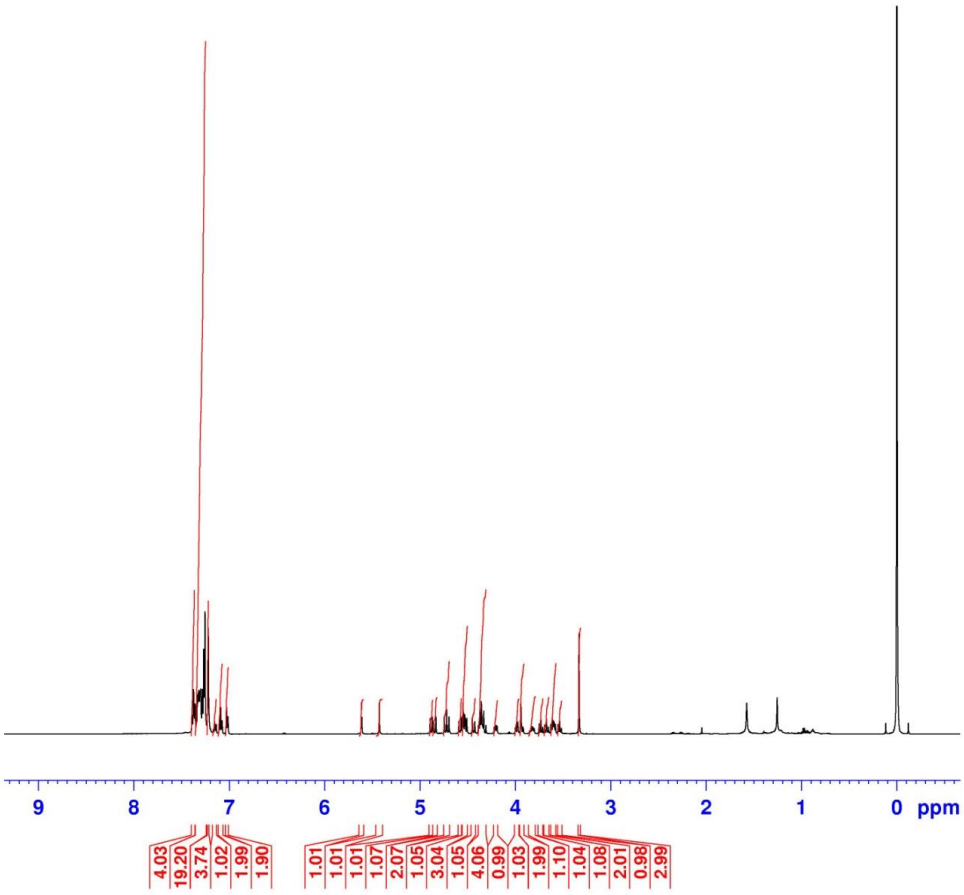




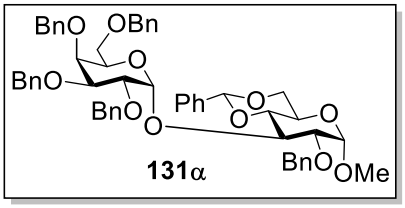
^{1}H NMR (500MHz, $CDCl_3$)

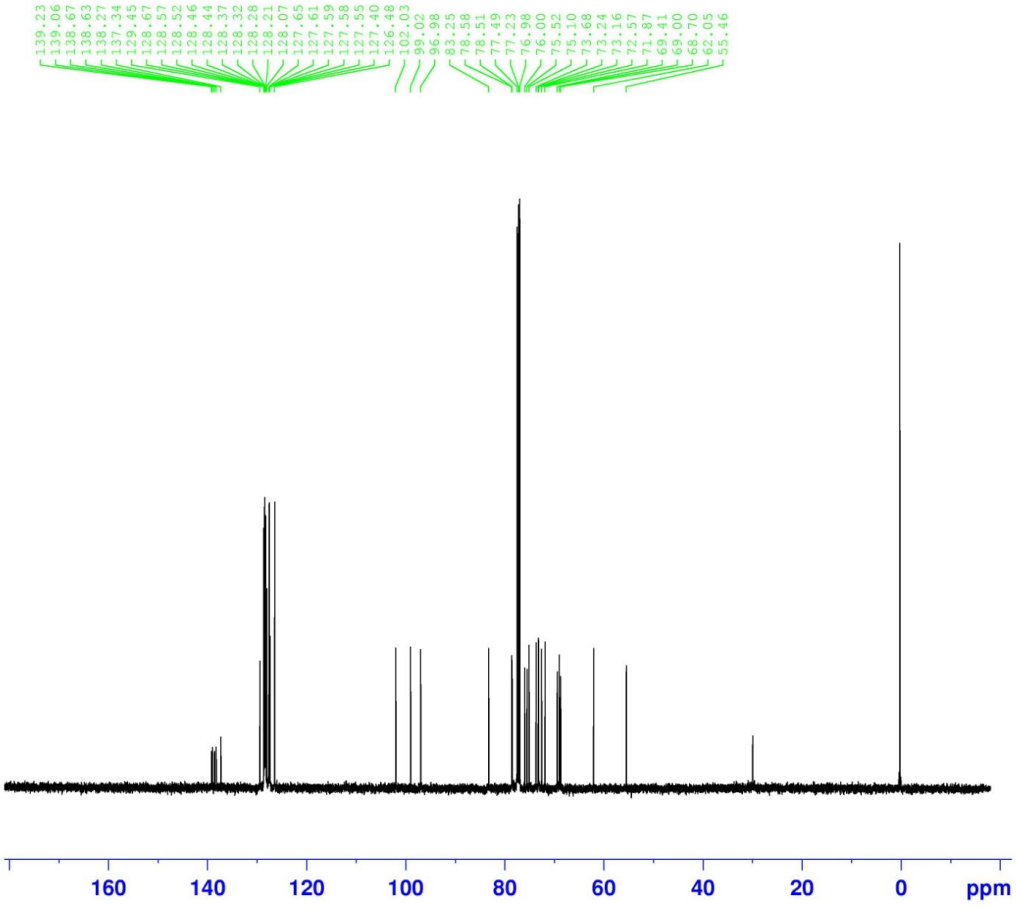


131α

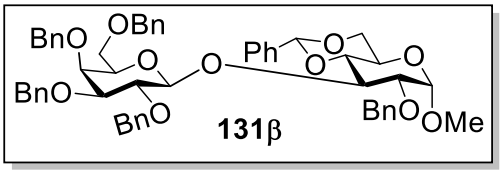


^{13}C NMR (125MHz, $CDCl_3$)

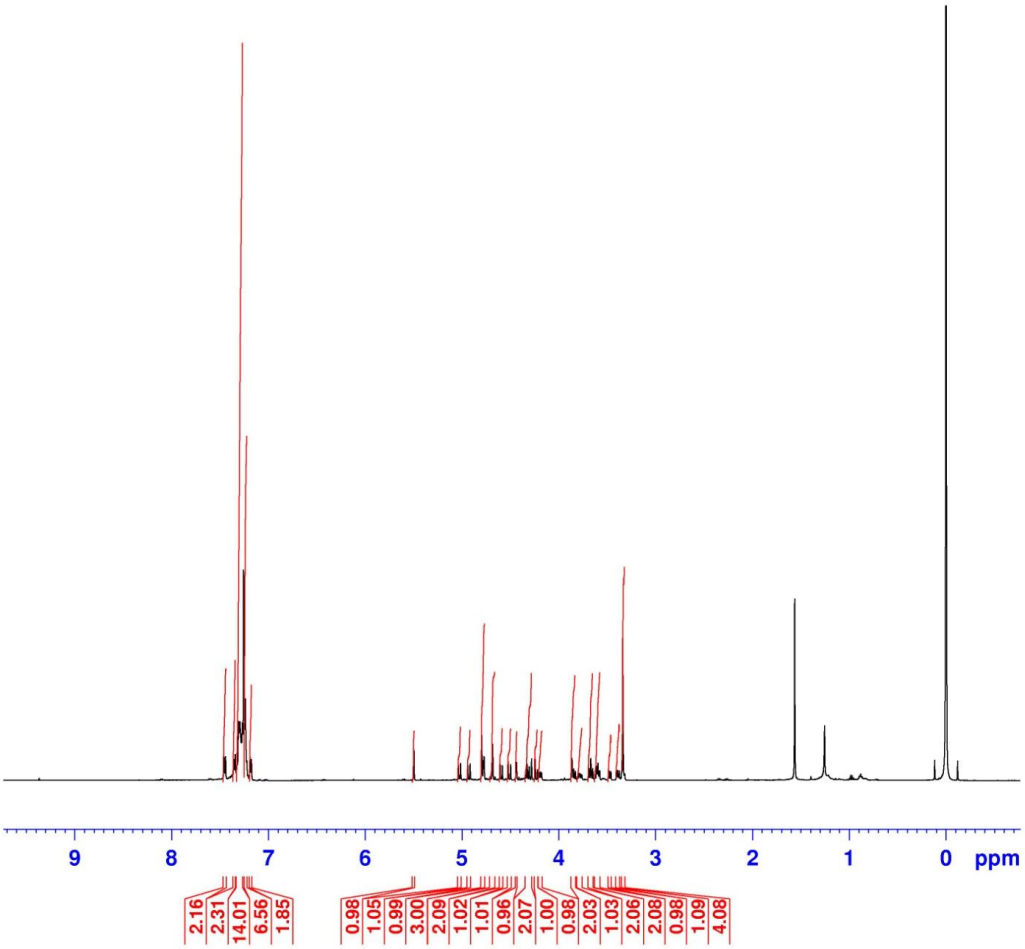




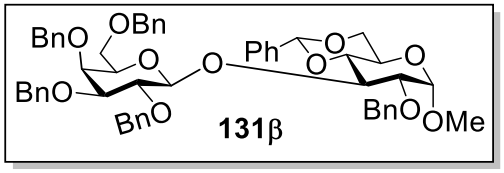
^{1}H NMR (500MHz, $CDCl_3$)

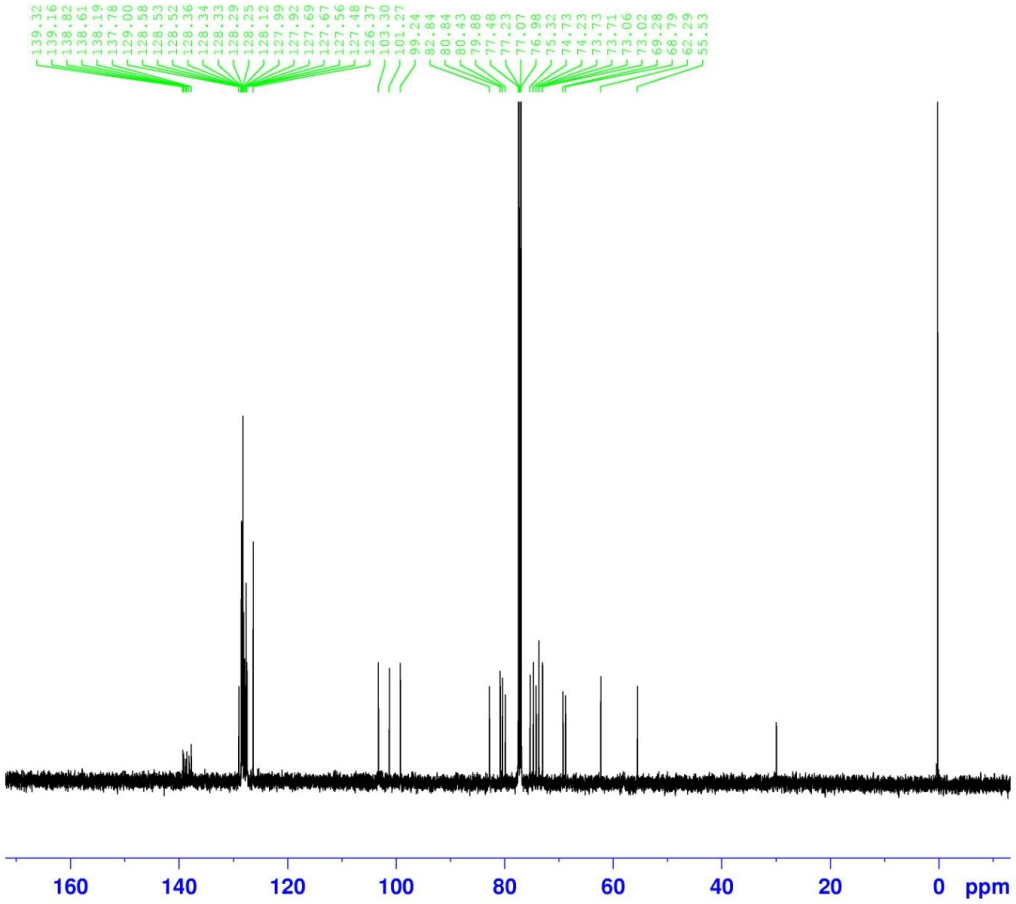


131β

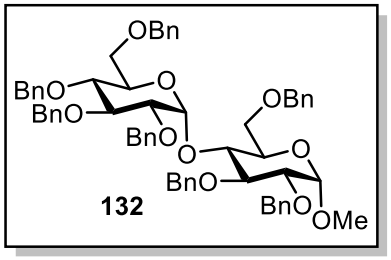


^{13}C NMR (125MHz, $CDCl_3$)





^{1}H NMR (500MHz, $CDCl_3$)



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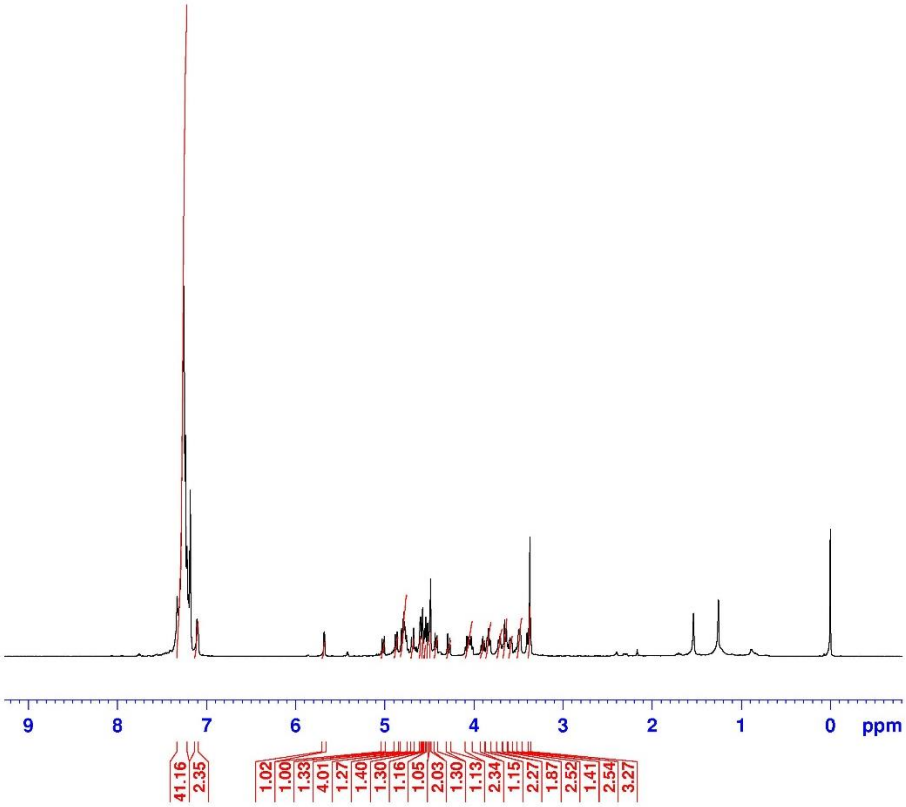
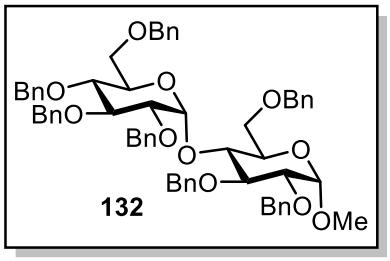


^{13}C NMR (125MHz, $CDCl_3$)



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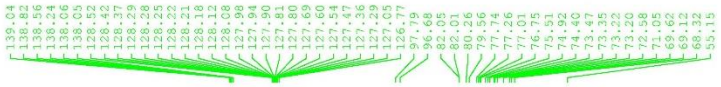
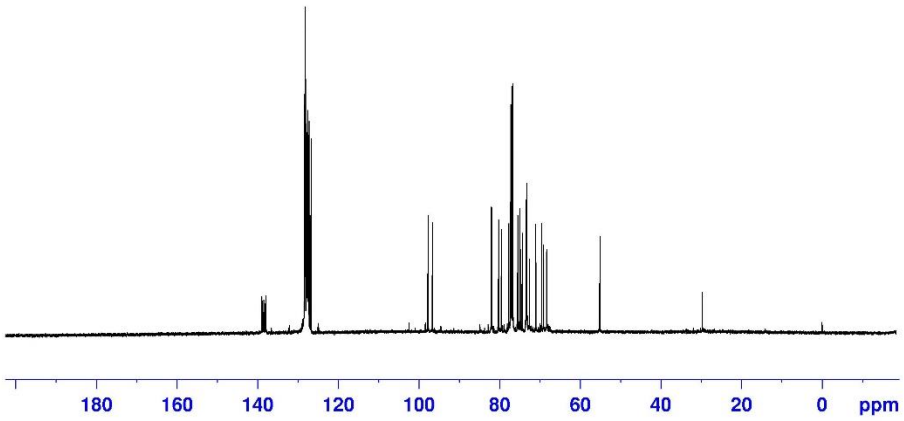
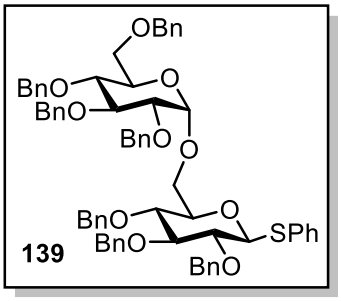
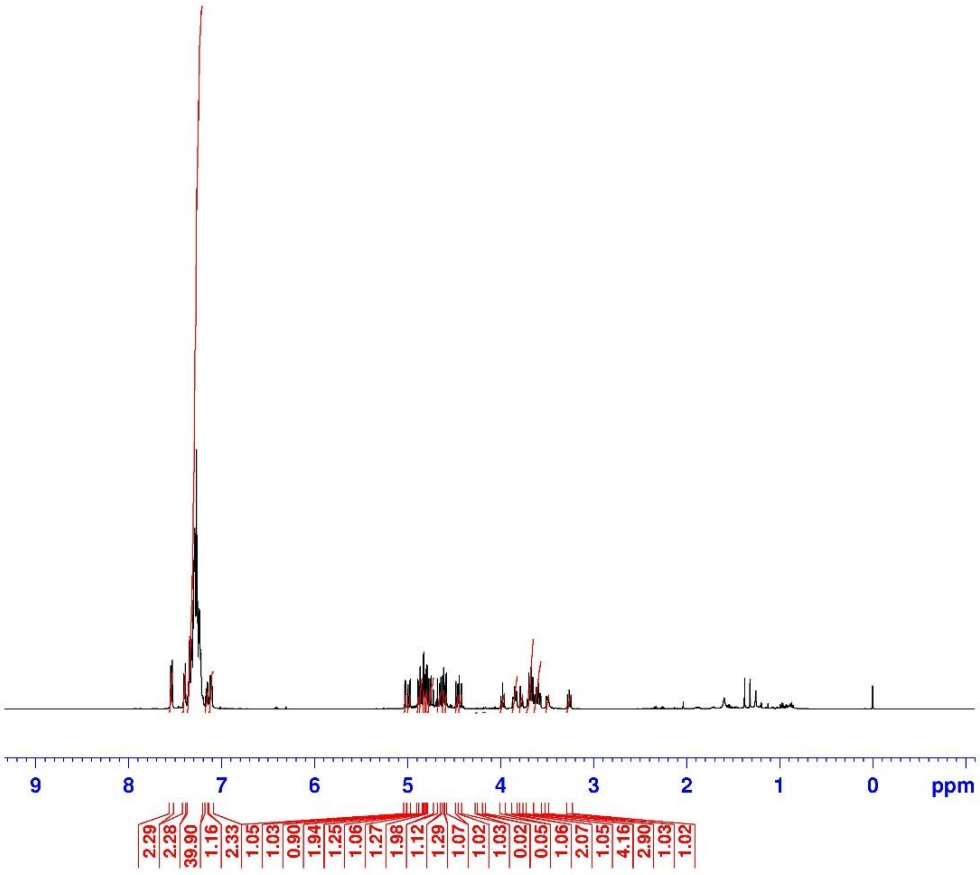


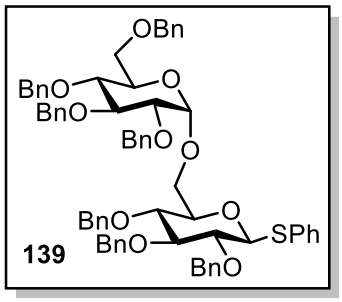


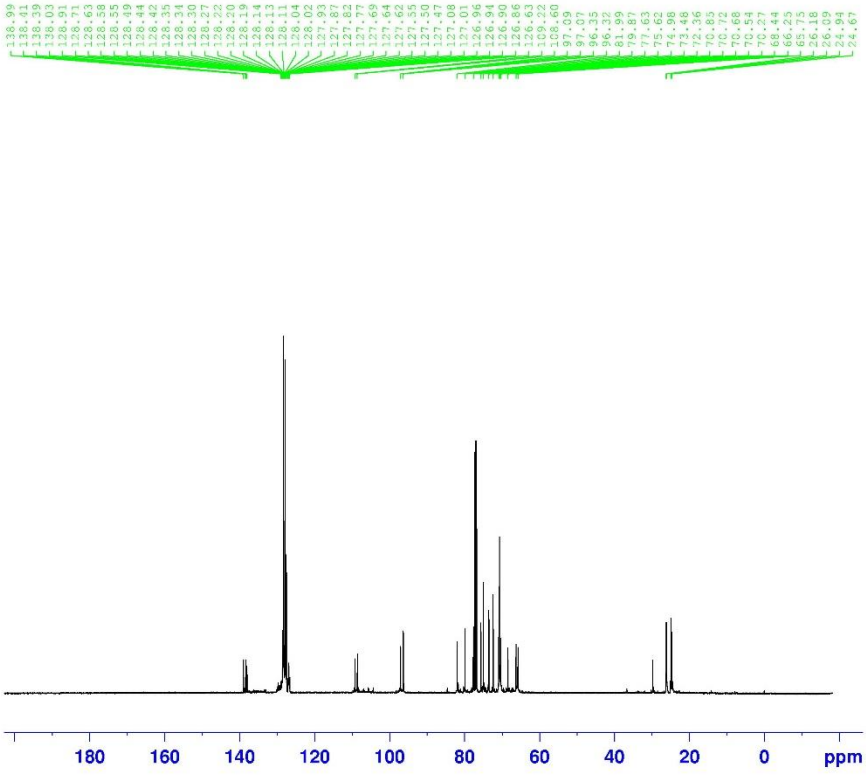
^{1}H NMR (500MHz, $CDCl_3$)



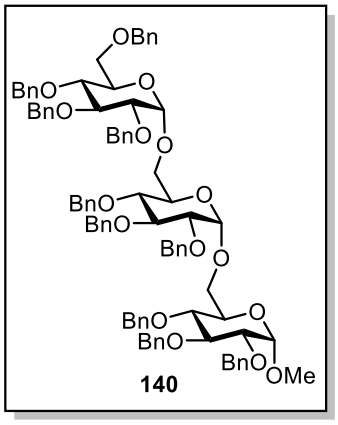


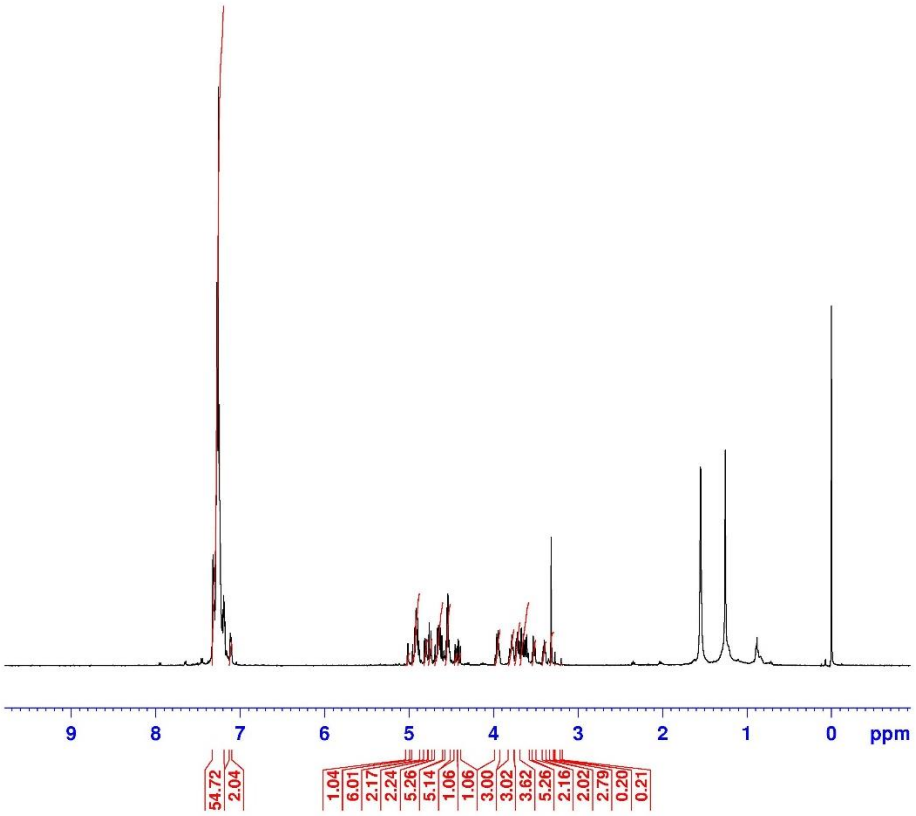
^{13}C NMR (125MHz, $CDCl_3$)



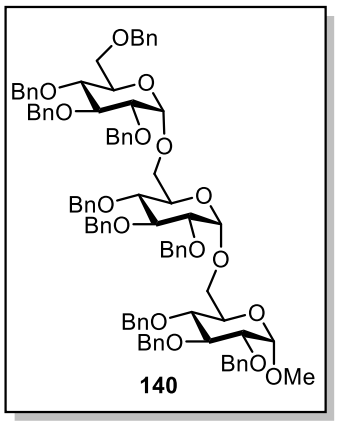


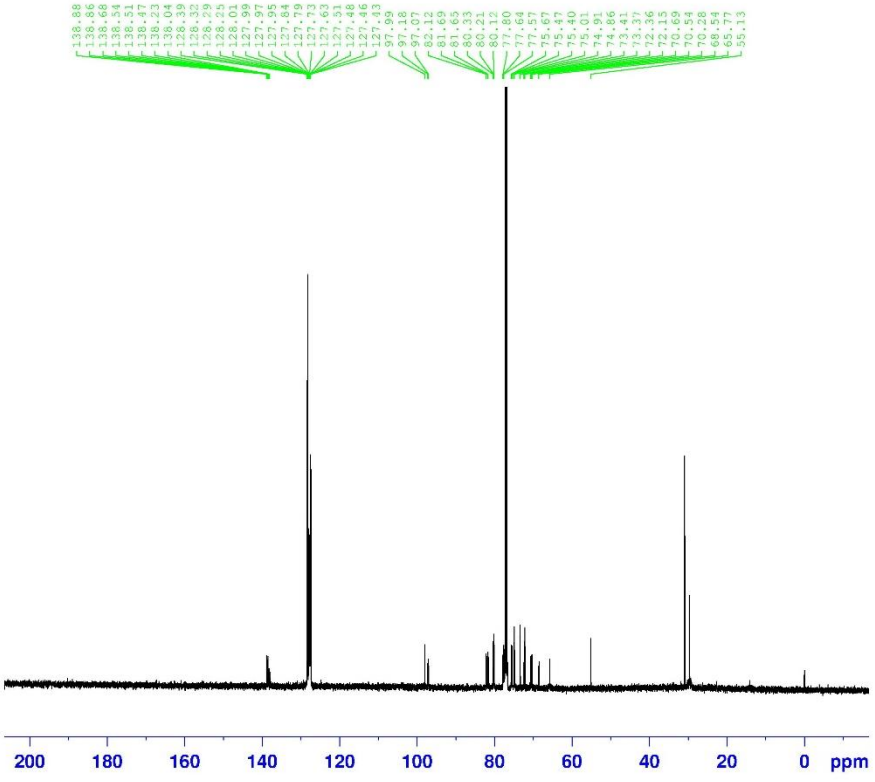
^{1}H NMR (500MHz, $CDCl_3$)



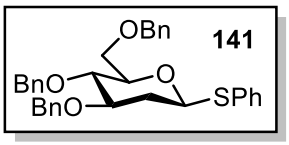


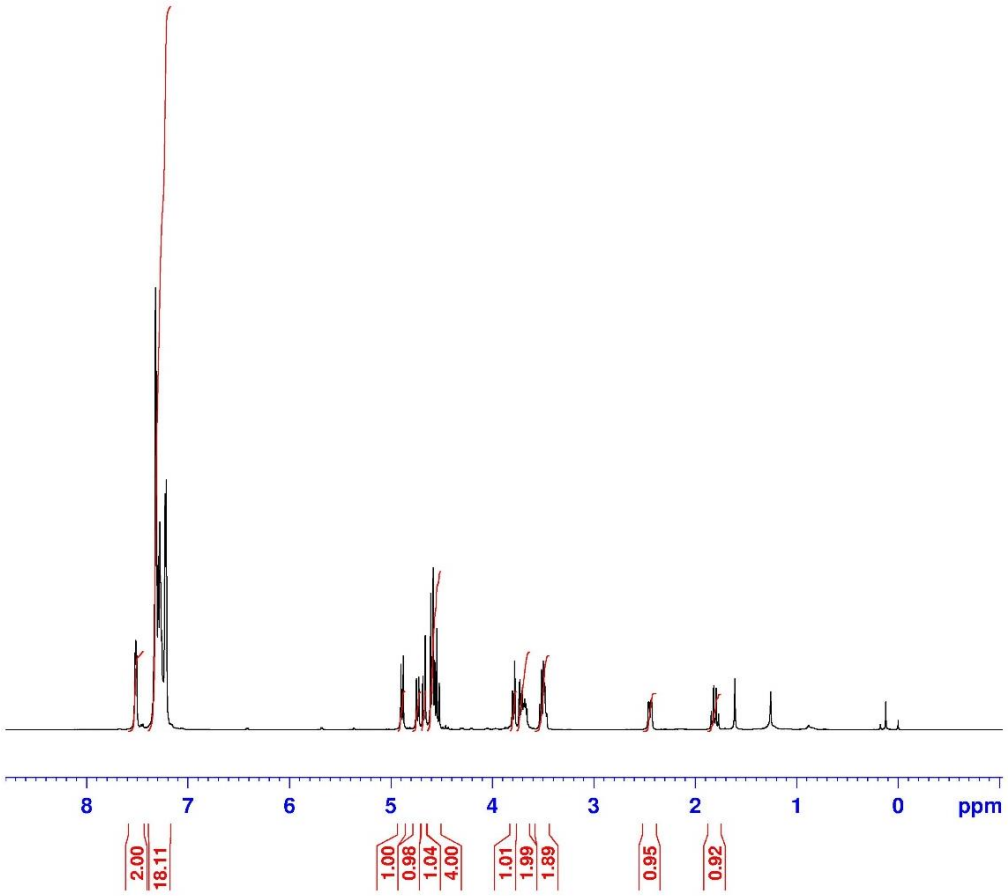
^{13}C NMR (125MHz, $CDCl_3$)



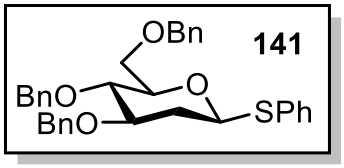


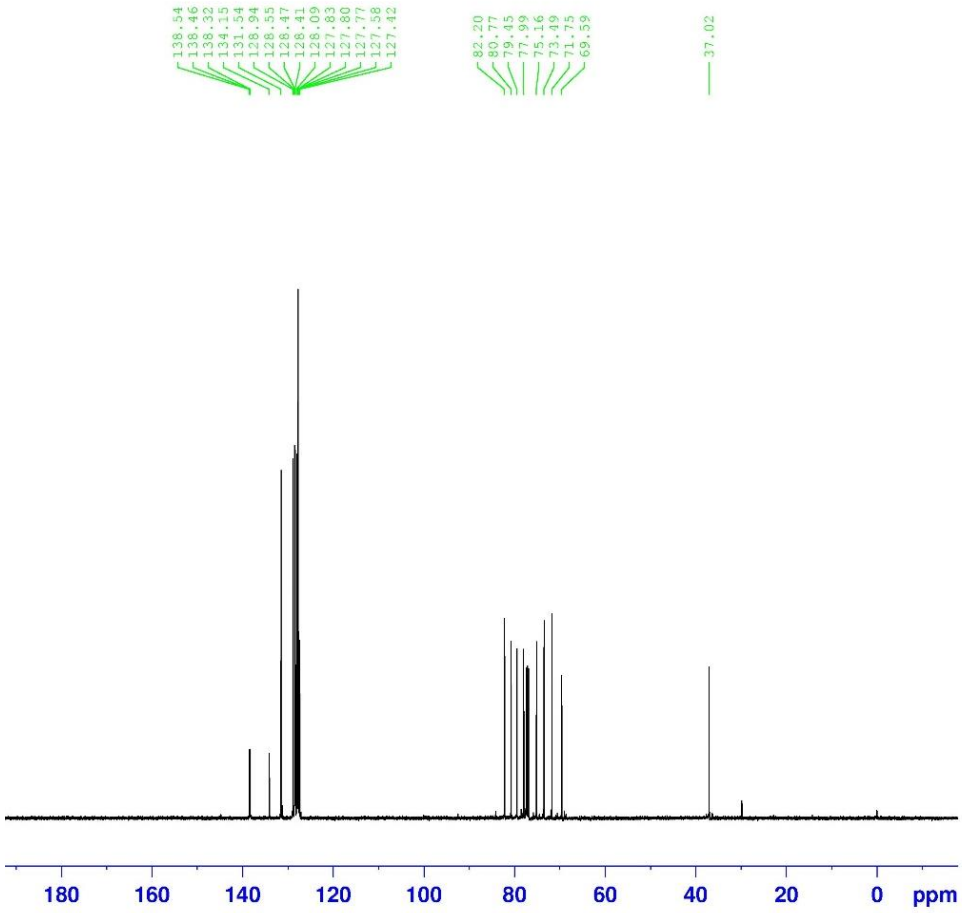
^{1}H NMR (500MHz, $CDCl_3$)



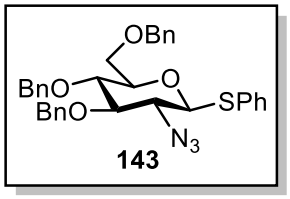


^{13}C NMR (125MHz, $CDCl_3$)

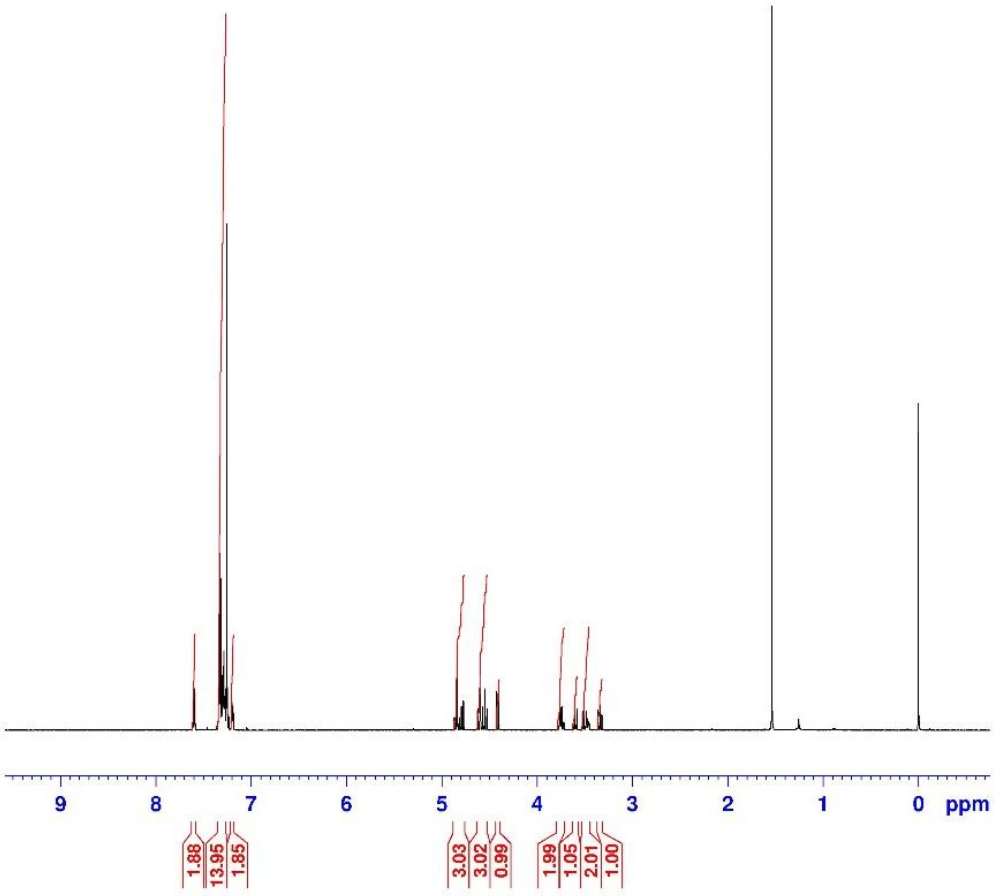




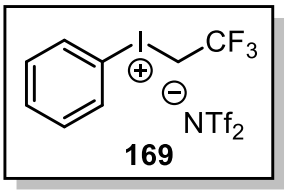
^{1}H NMR (500MHz, $CDCl_3$)



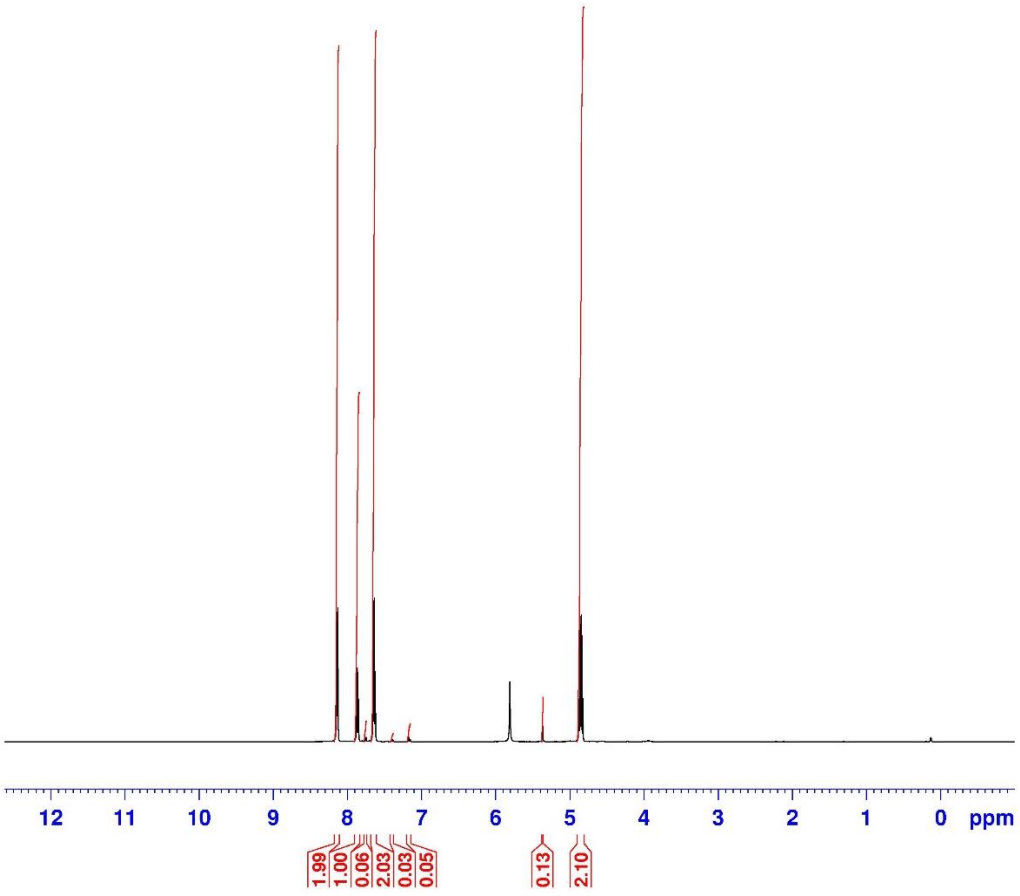
143



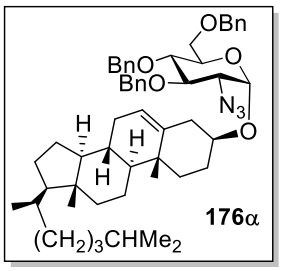
^{1}H NMR (500MHz, CD_2Cl_2)

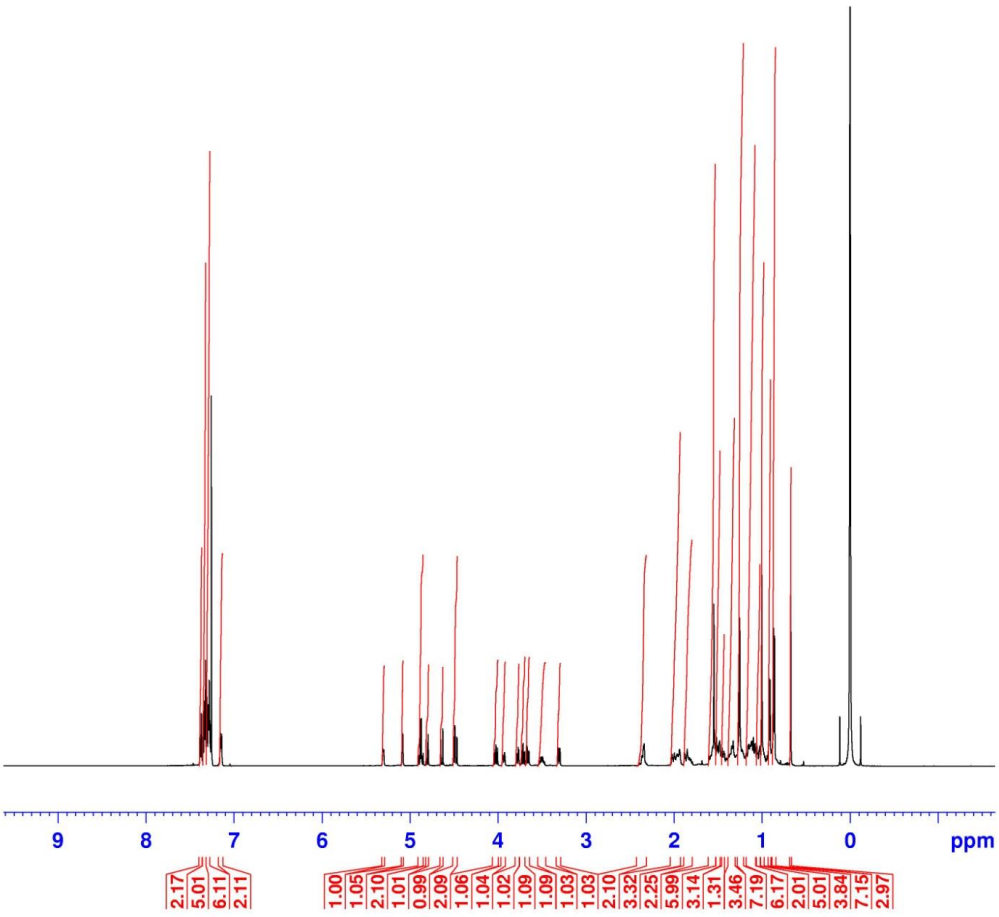


169

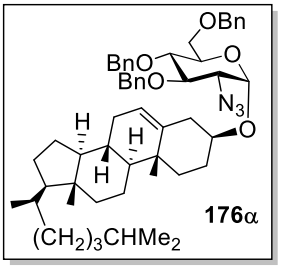


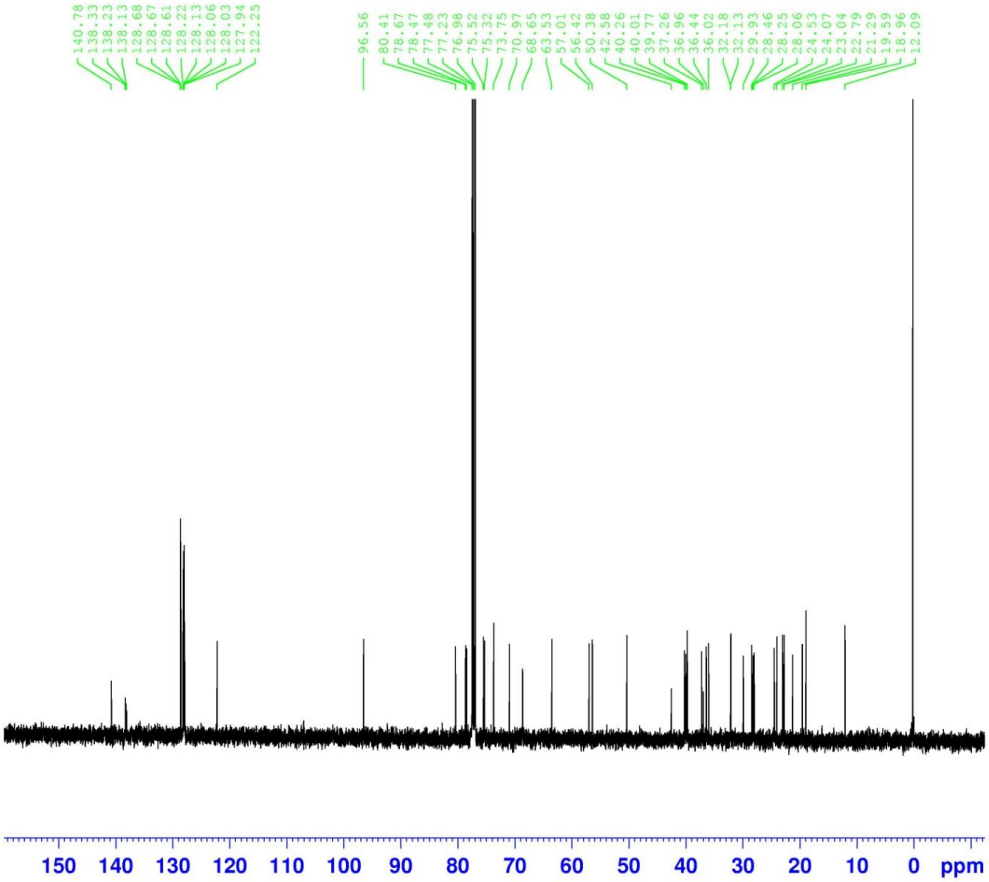
^{1}H NMR (500MHz, $CDCl_3$)



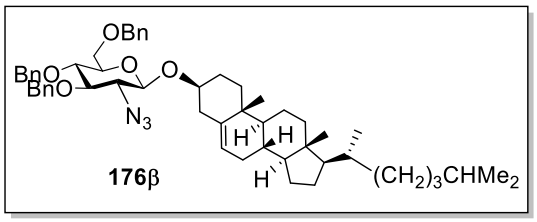


^{13}C NMR (125MHz, $CDCl_3$)

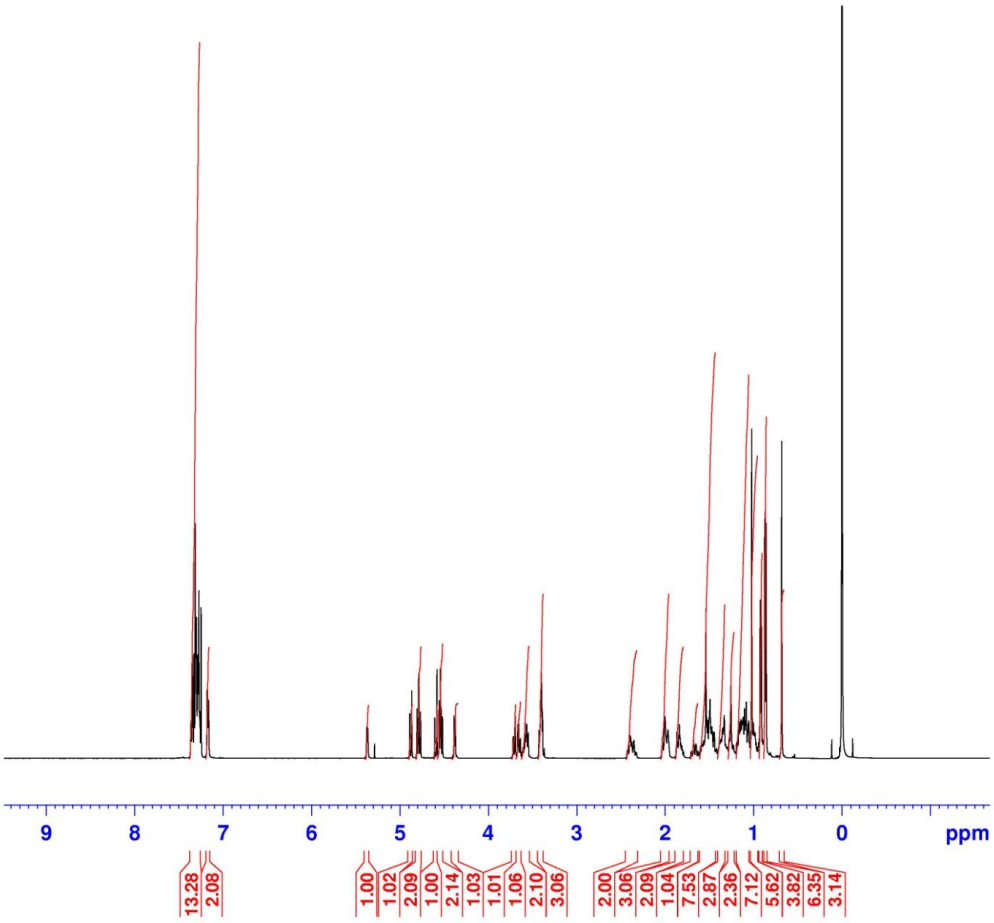




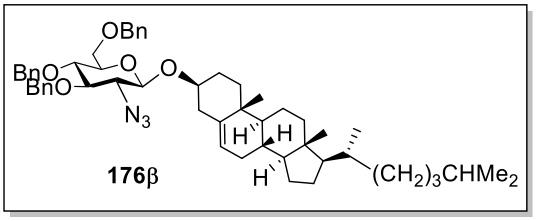
^{1}H NMR (500MHz, $CDCl_3$)

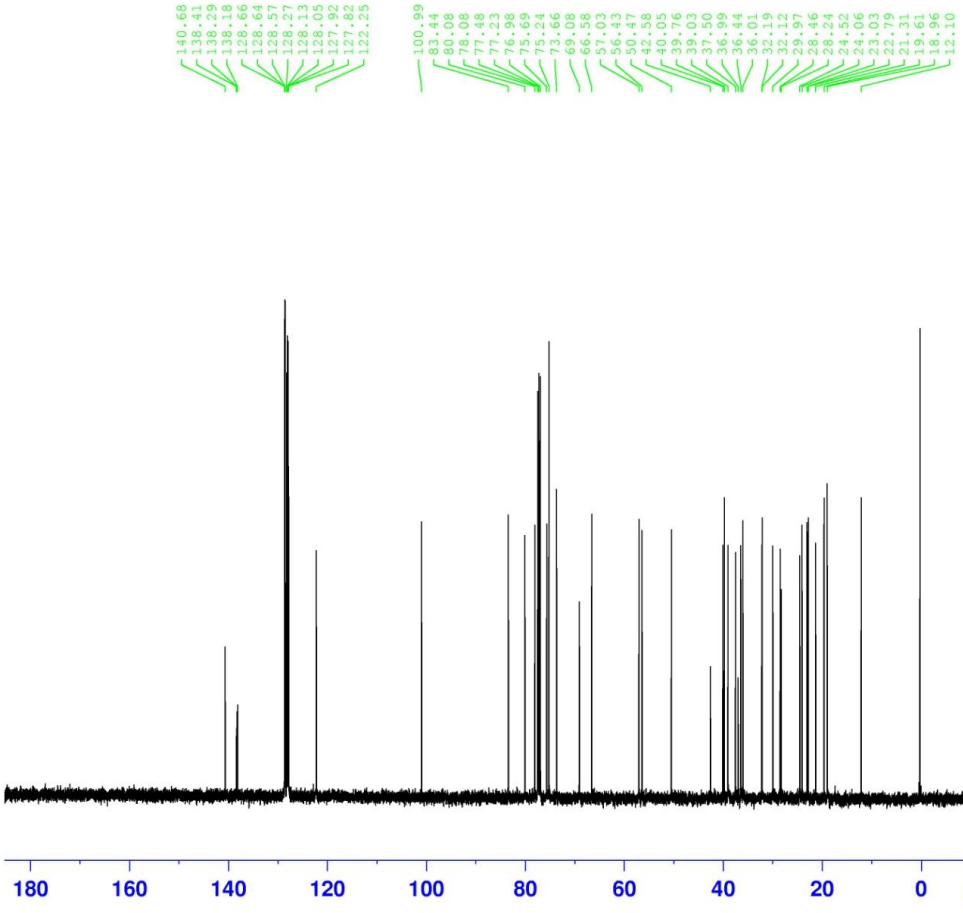


176β

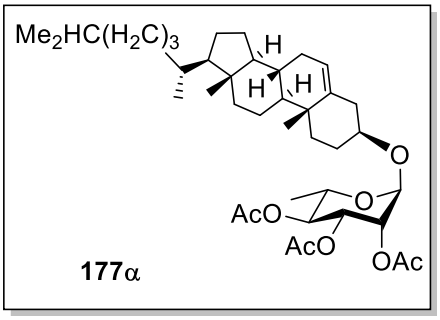


^{13}C NMR (125MHz, $CDCl_3$)

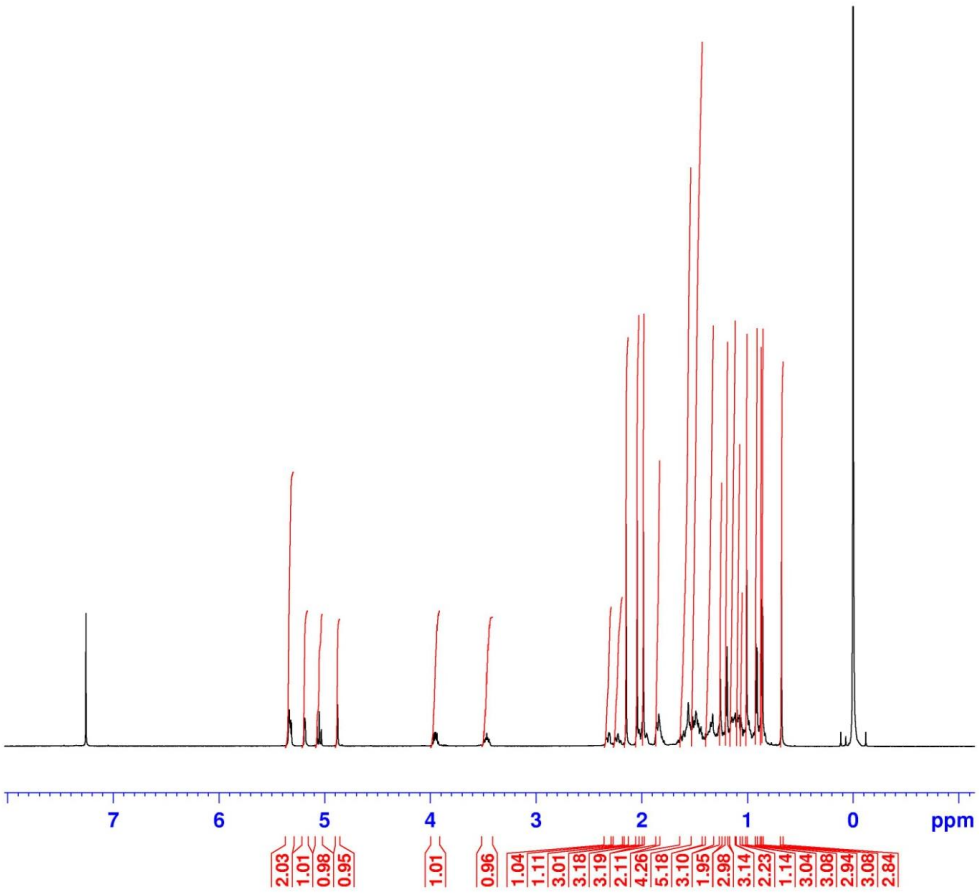




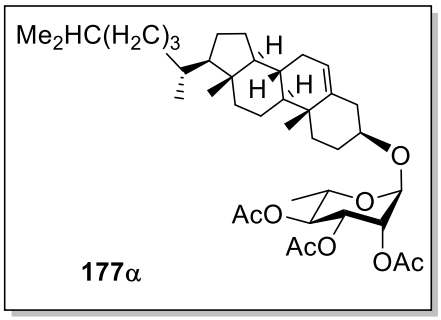
^{1}H NMR (500MHz, $CDCl_3$)

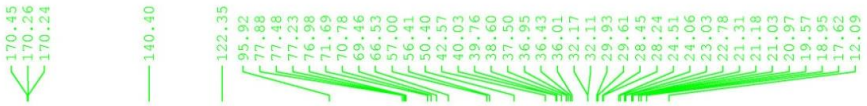


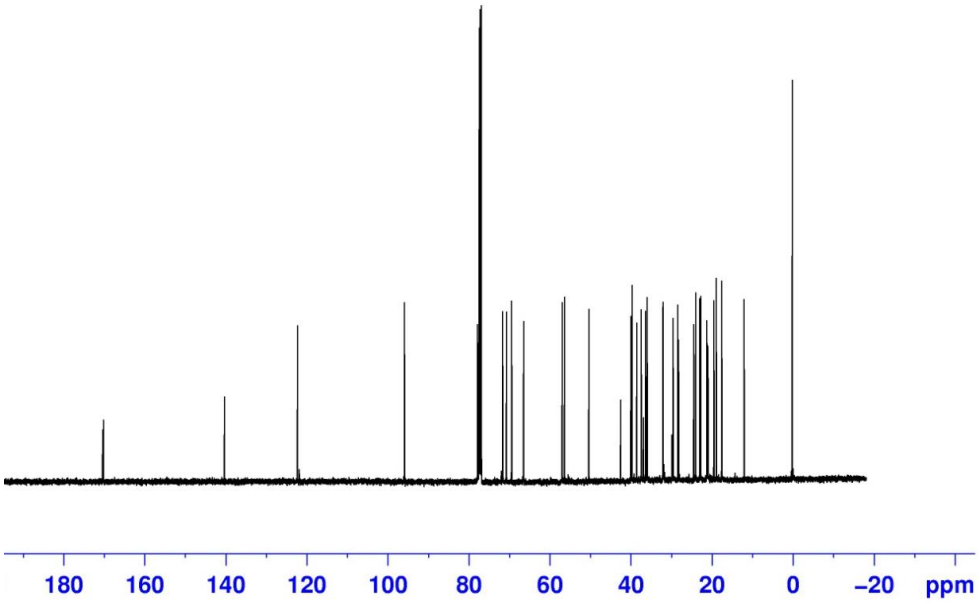
177α



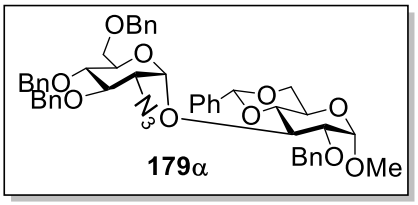
^{13}C NMR (125MHz, $CDCl_3$)



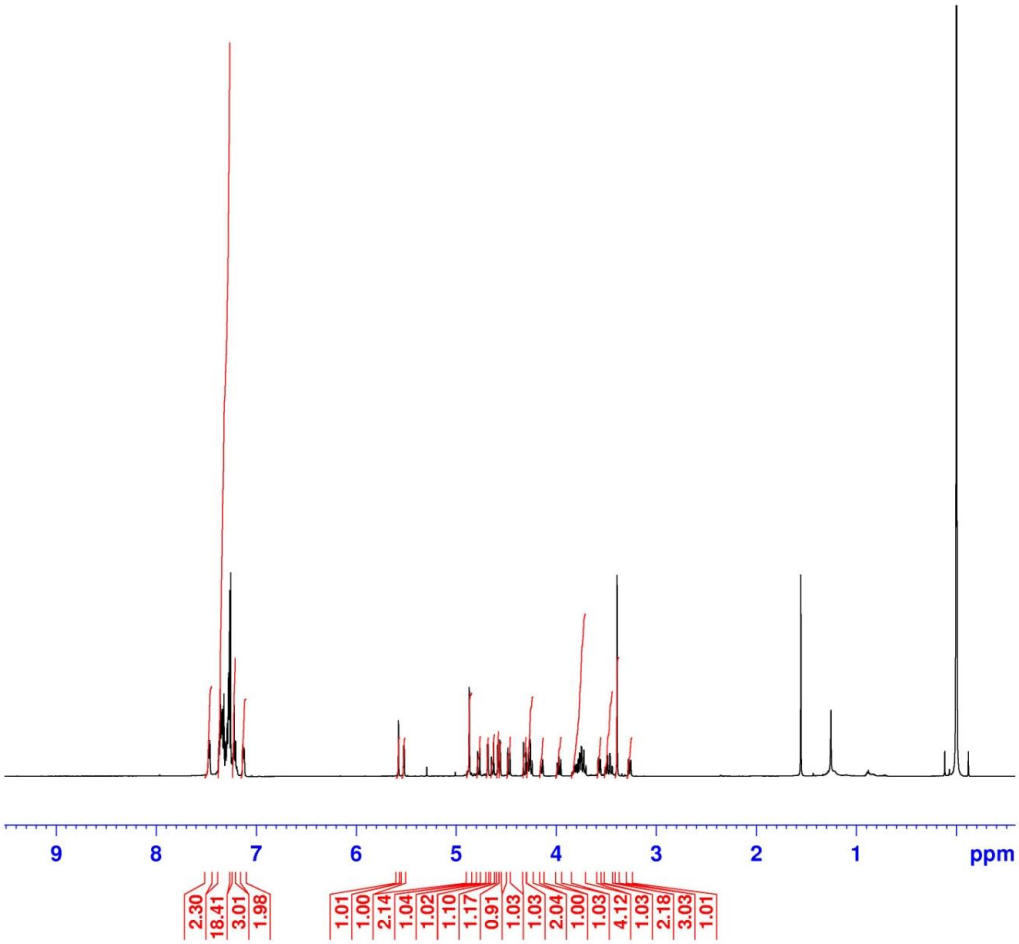




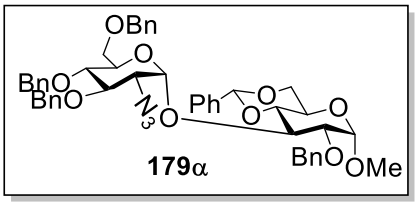
^{1}H NMR (500MHz, $CDCl_3$)



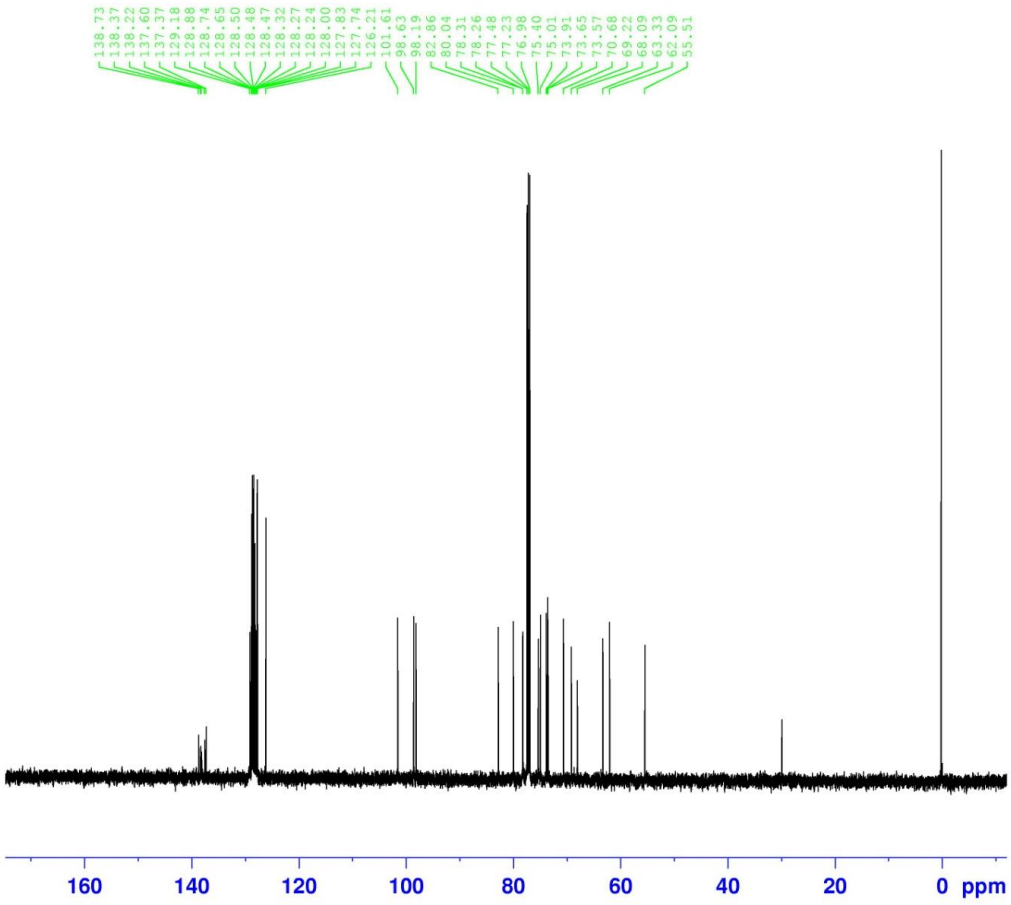
179α



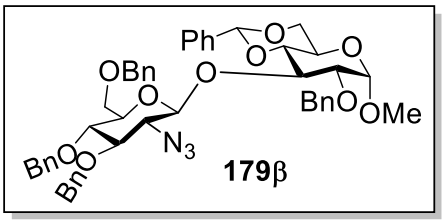
^{13}C NMR (125MHz, $CDCl_3$)



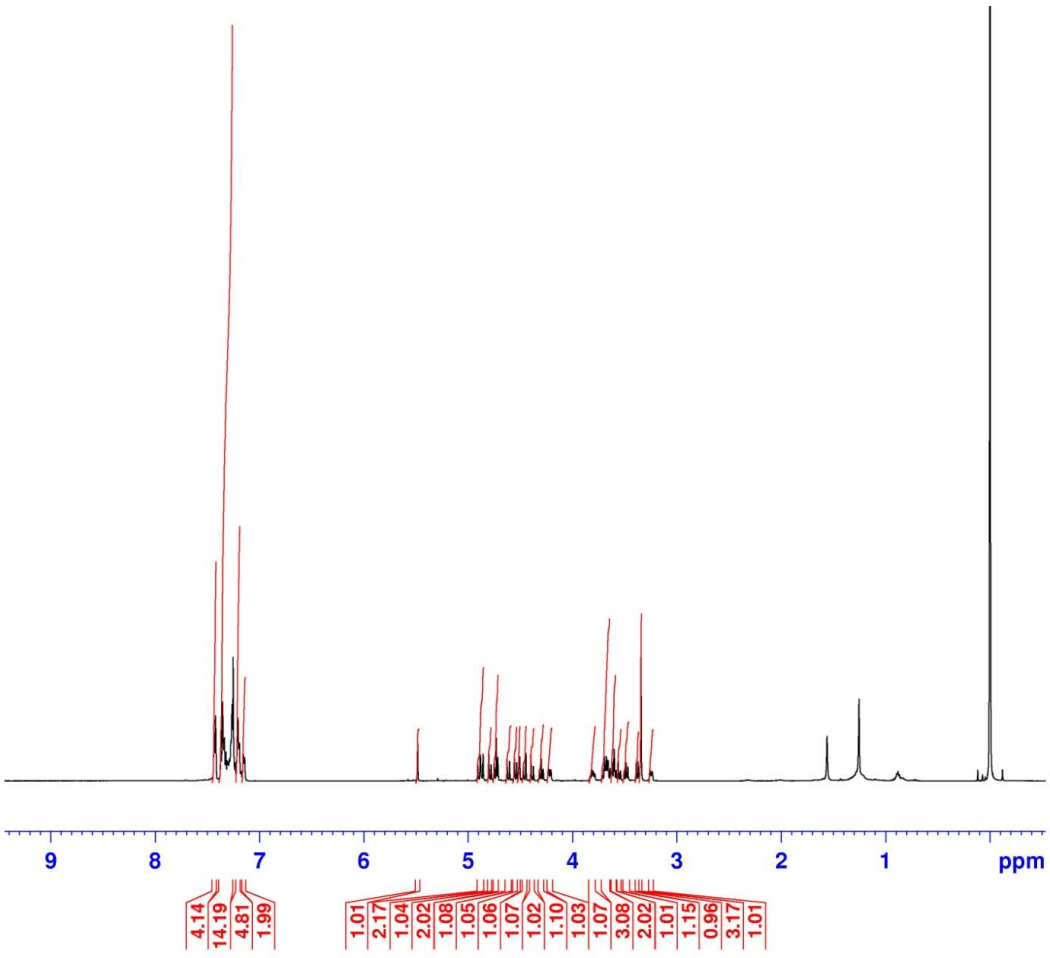
179α



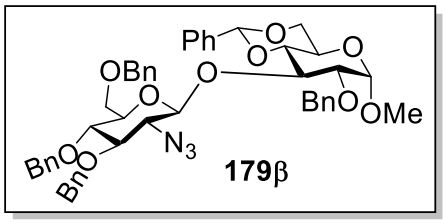
^{1}H NMR (500MHz, $CDCl_3$)

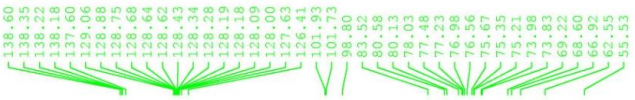


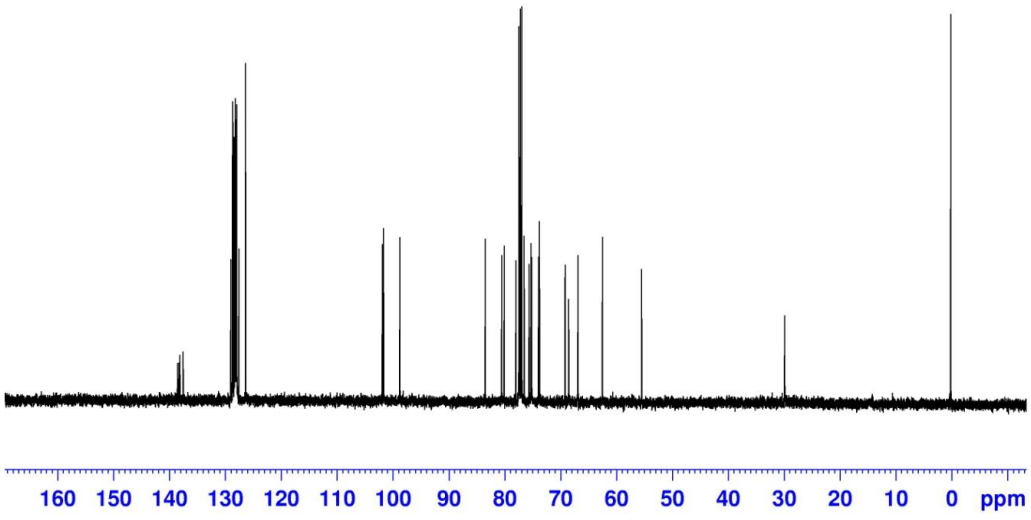
179β



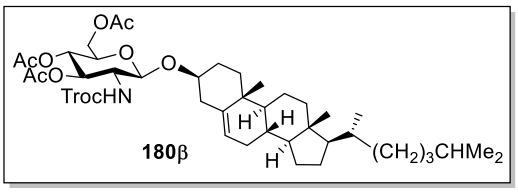
^{13}C NMR (125MHz, $CDCl_3$)

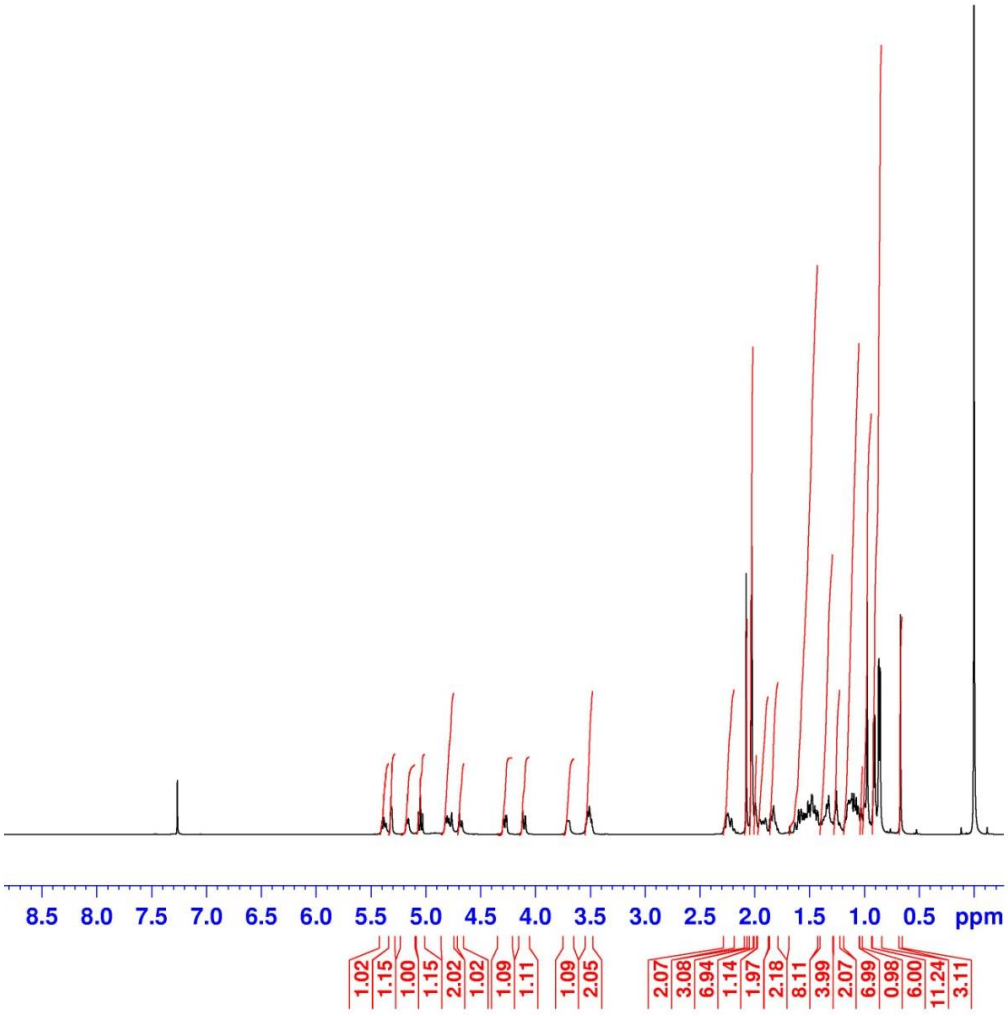




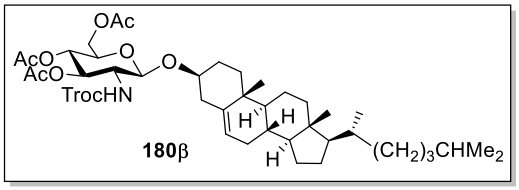


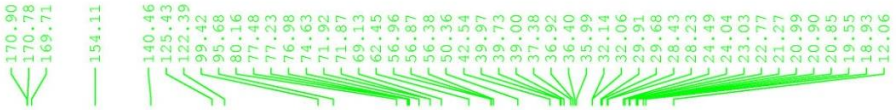
^{1}H NMR (500MHz, $CDCl_3$)

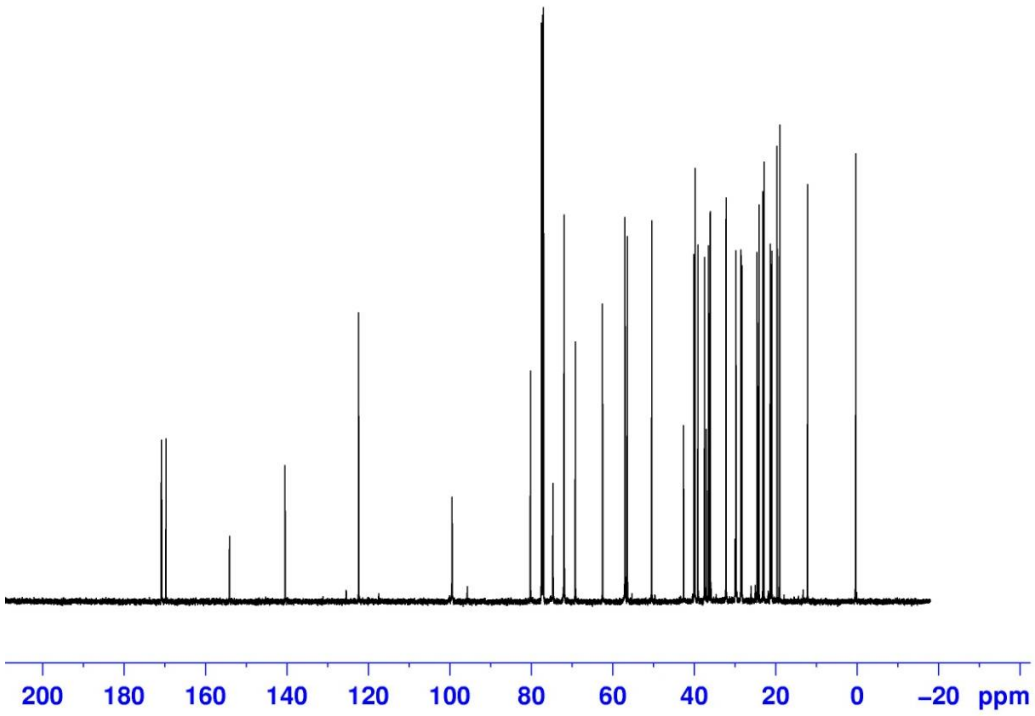




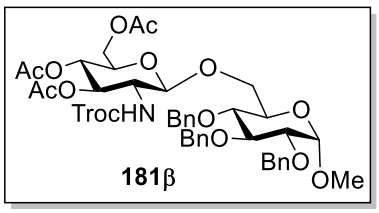
^{13}C NMR (125MHz, $CDCl_3$)

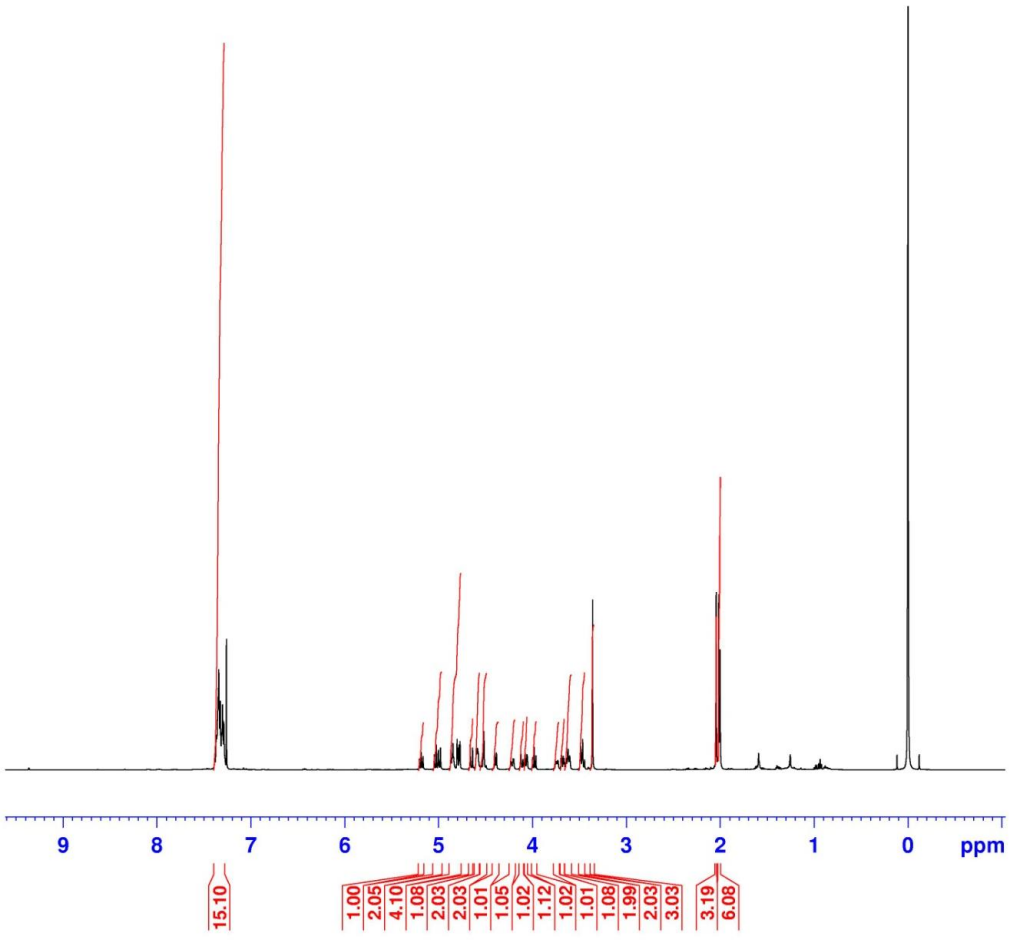




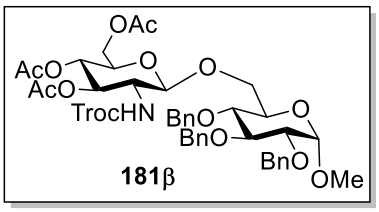


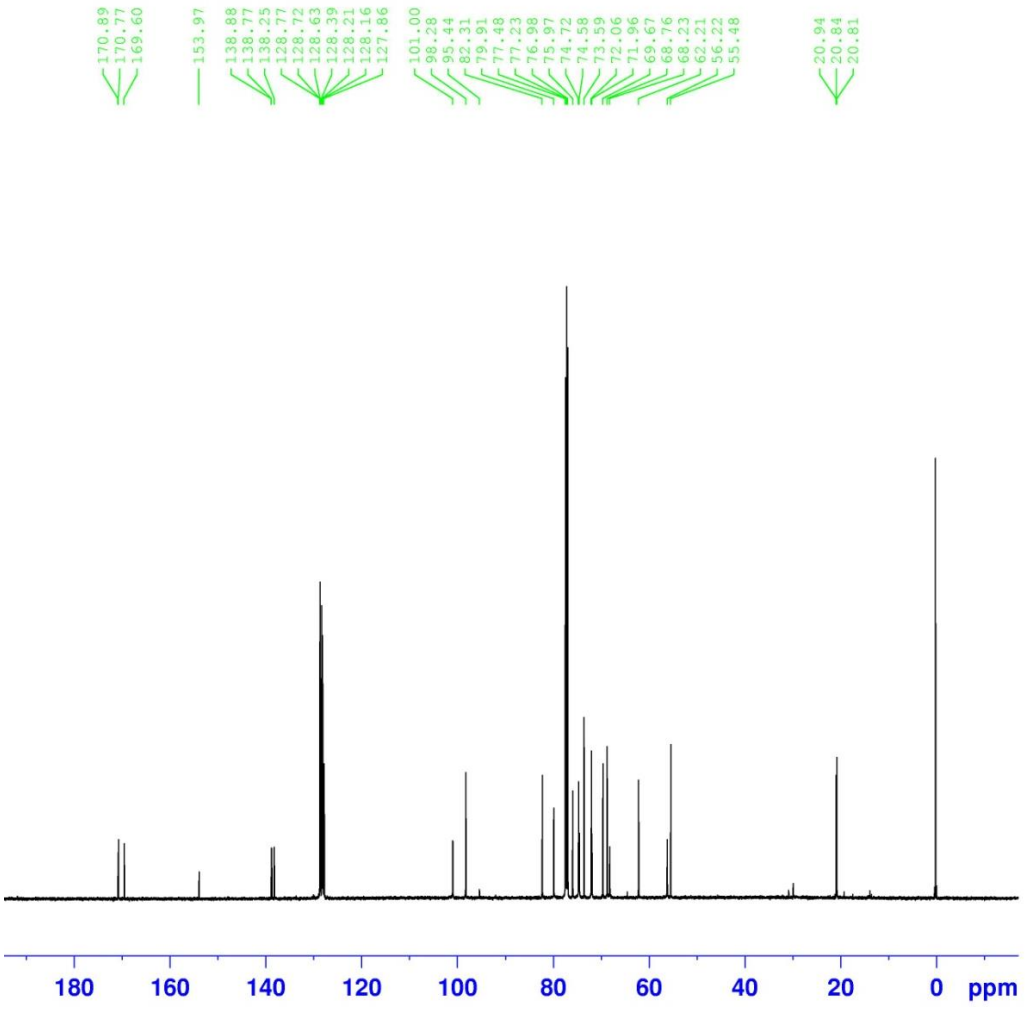
^{1}H NMR (500MHz, $CDCl_3$)



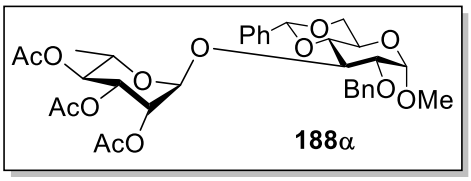


^{13}C NMR (125MHz, $CDCl_3$)

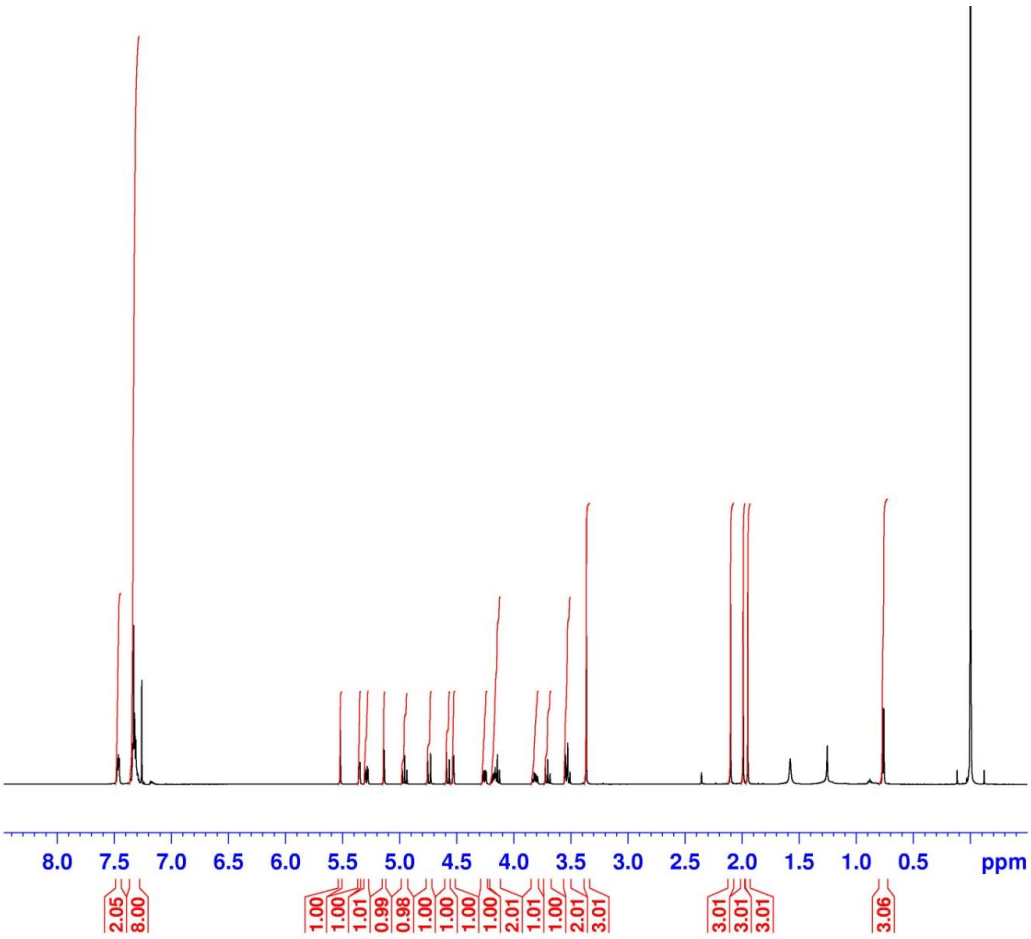




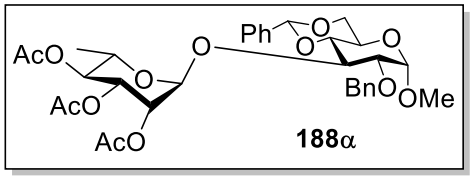
^{1}H NMR (500MHz, $CDCl_3$)



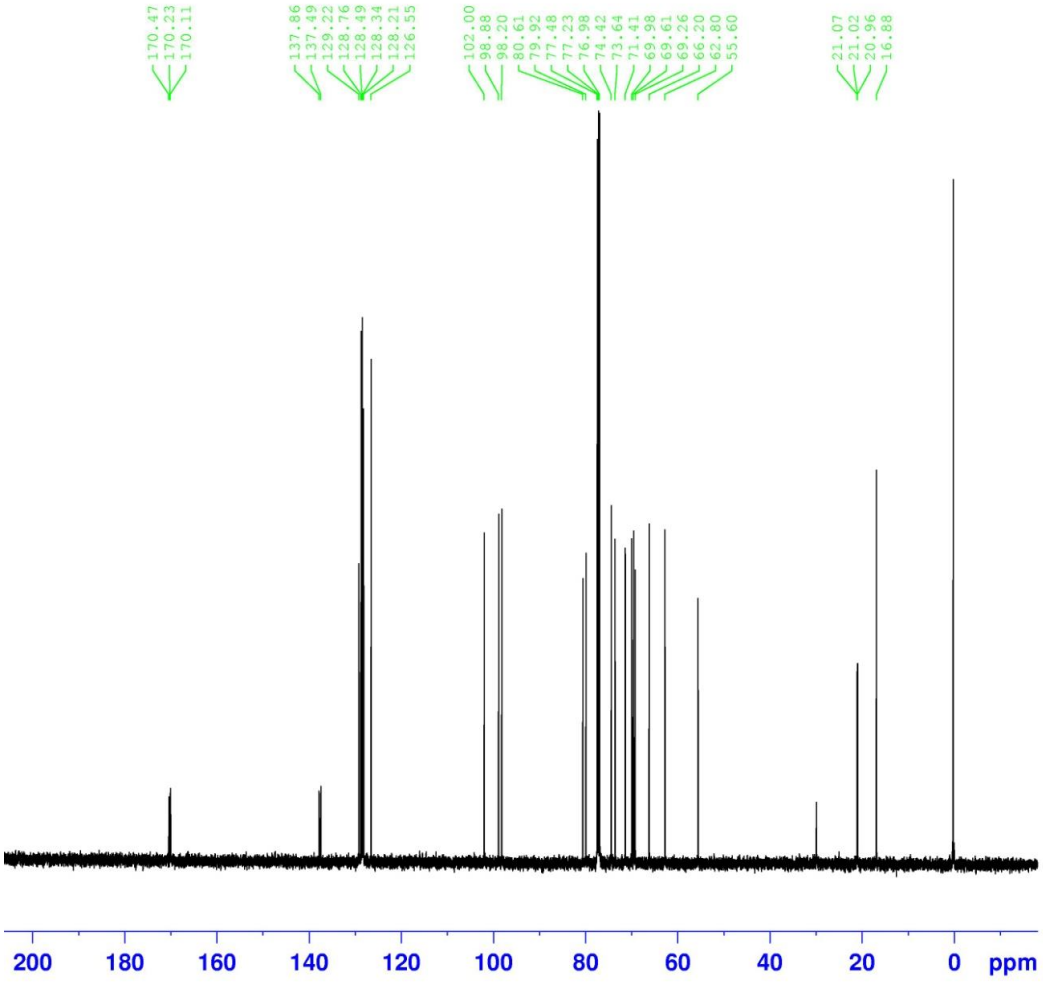
188α



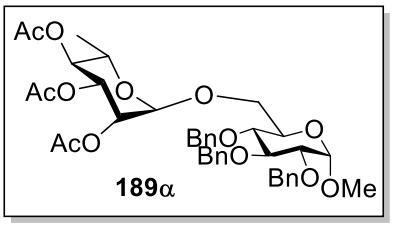
^{13}C NMR (125MHz, $CDCl_3$)



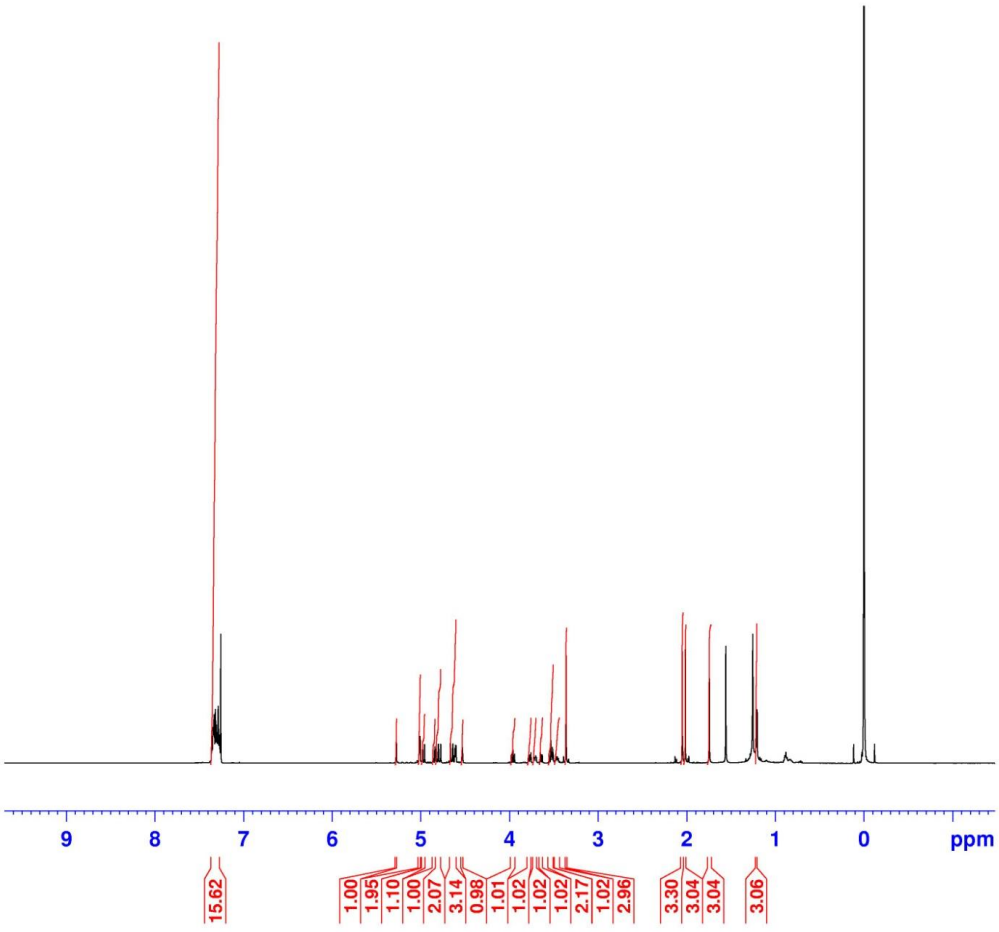
188α



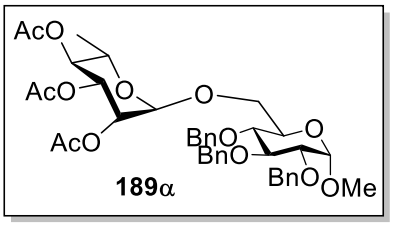
^{1}H NMR (500MHz, $CDCl_3$)



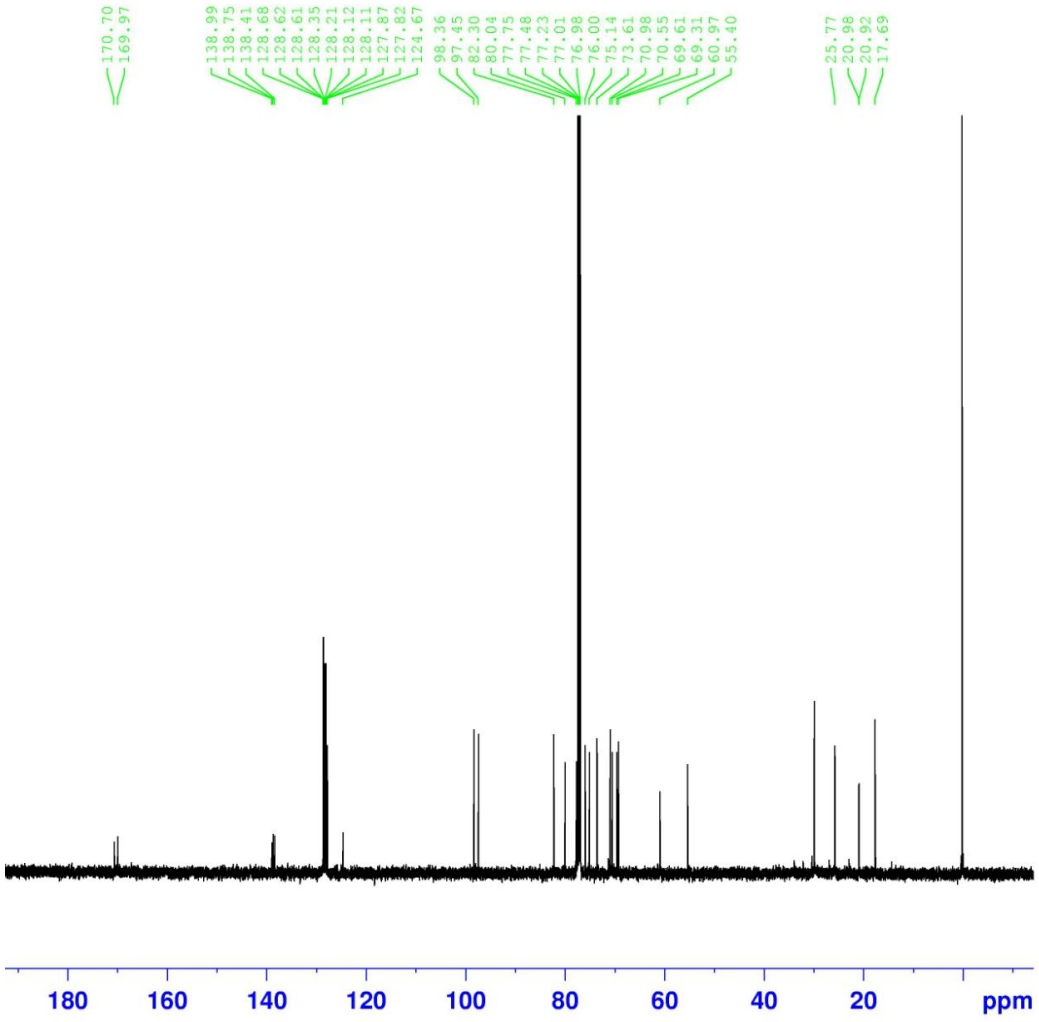
189α



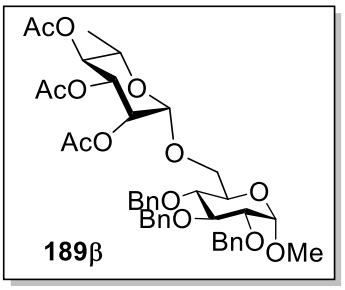
^{13}C NMR (125MHz, $CDCl_3$)

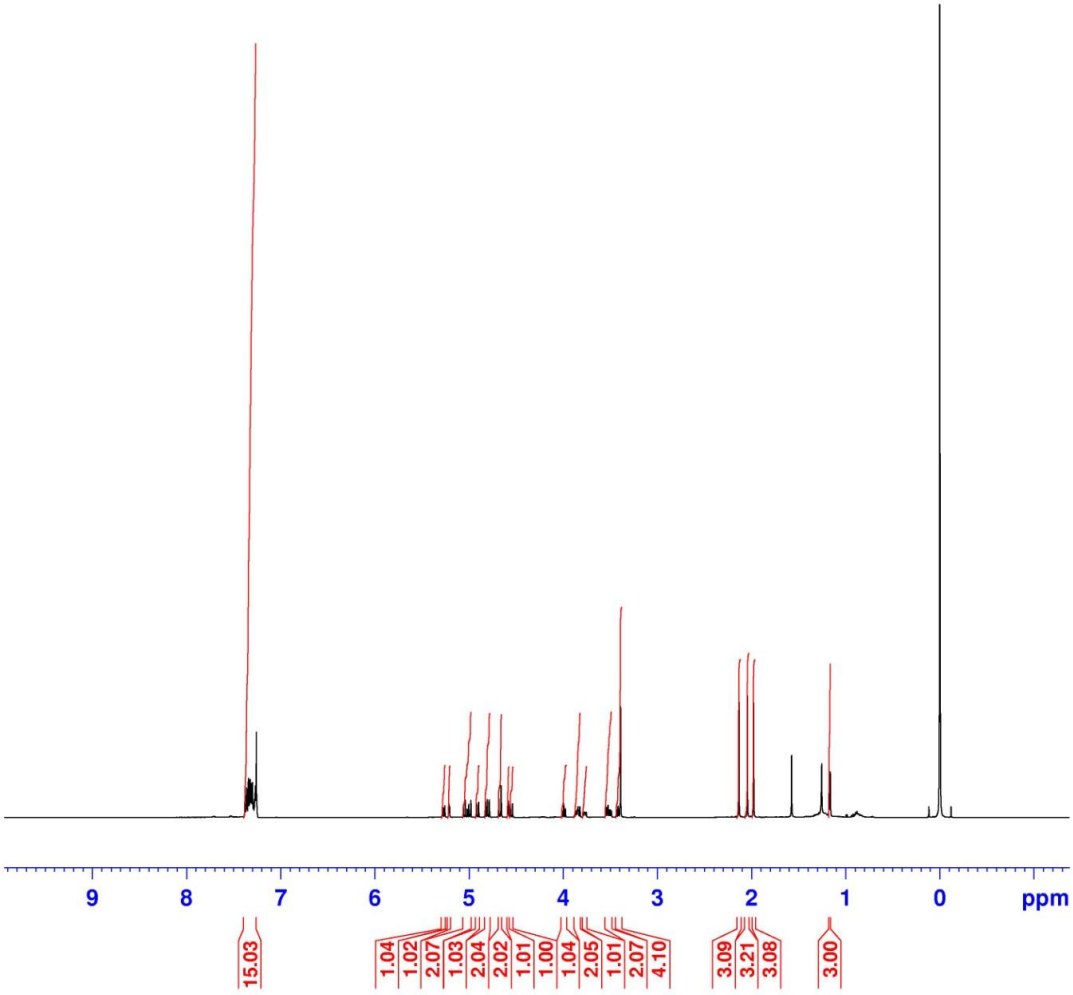


189α

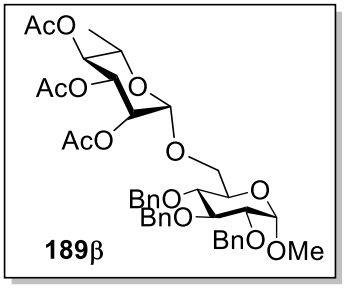


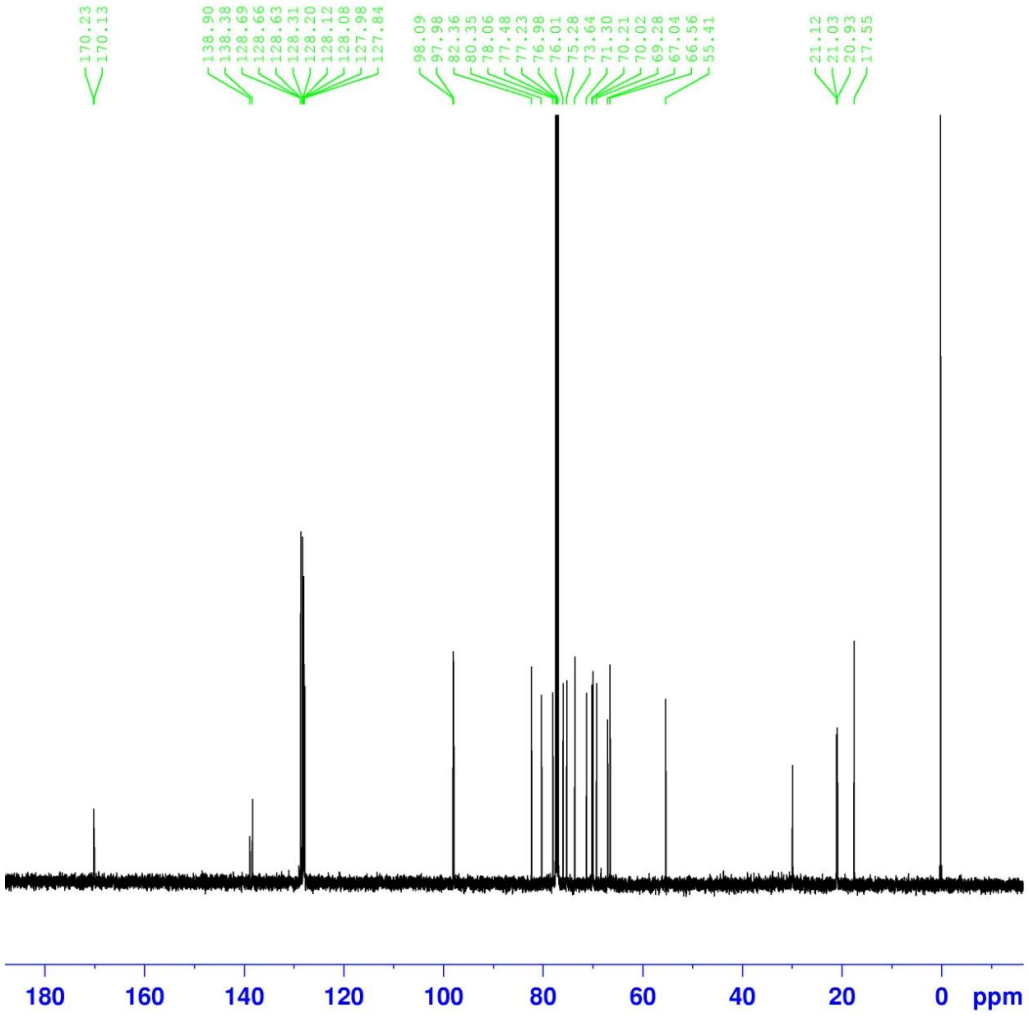
^{1}H NMR (500MHz, $CDCl_3$)



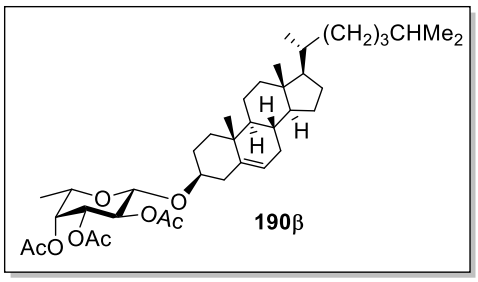


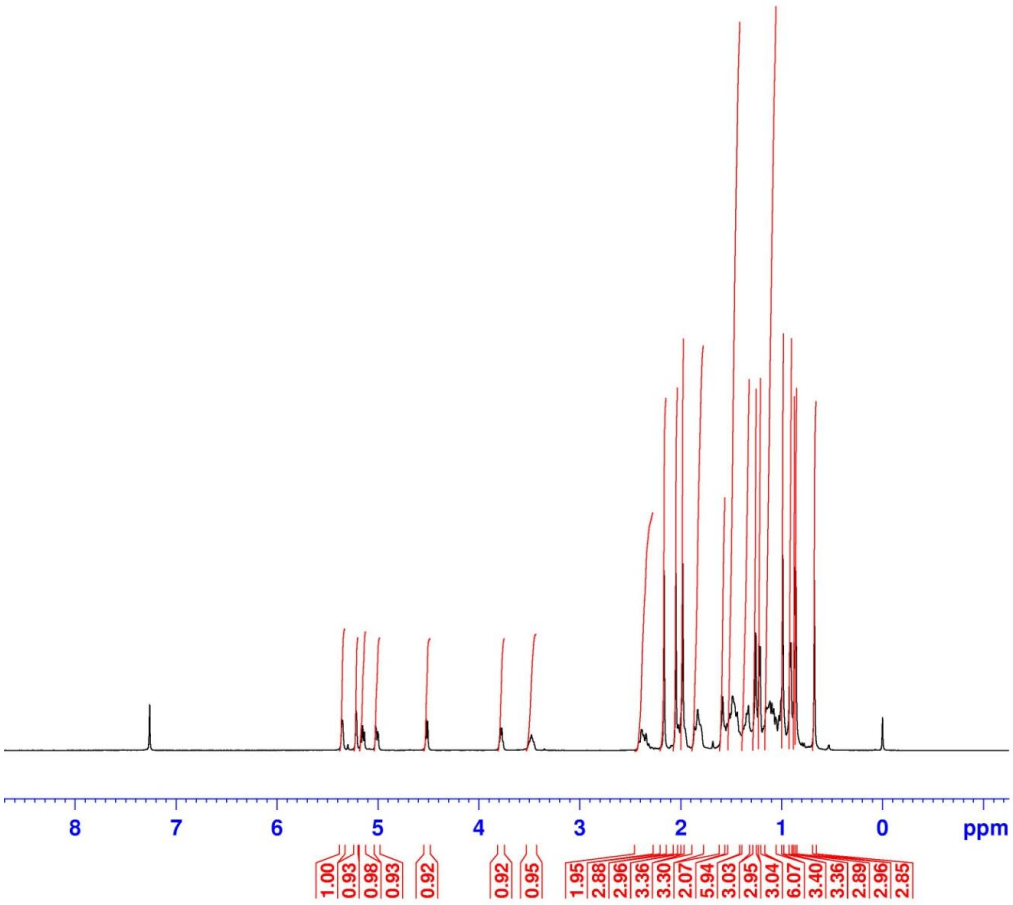
^{13}C NMR (125MHz, $CDCl_3$)



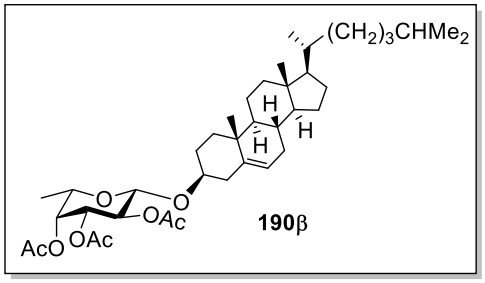


^{1}H NMR (500MHz, $CDCl_3$)

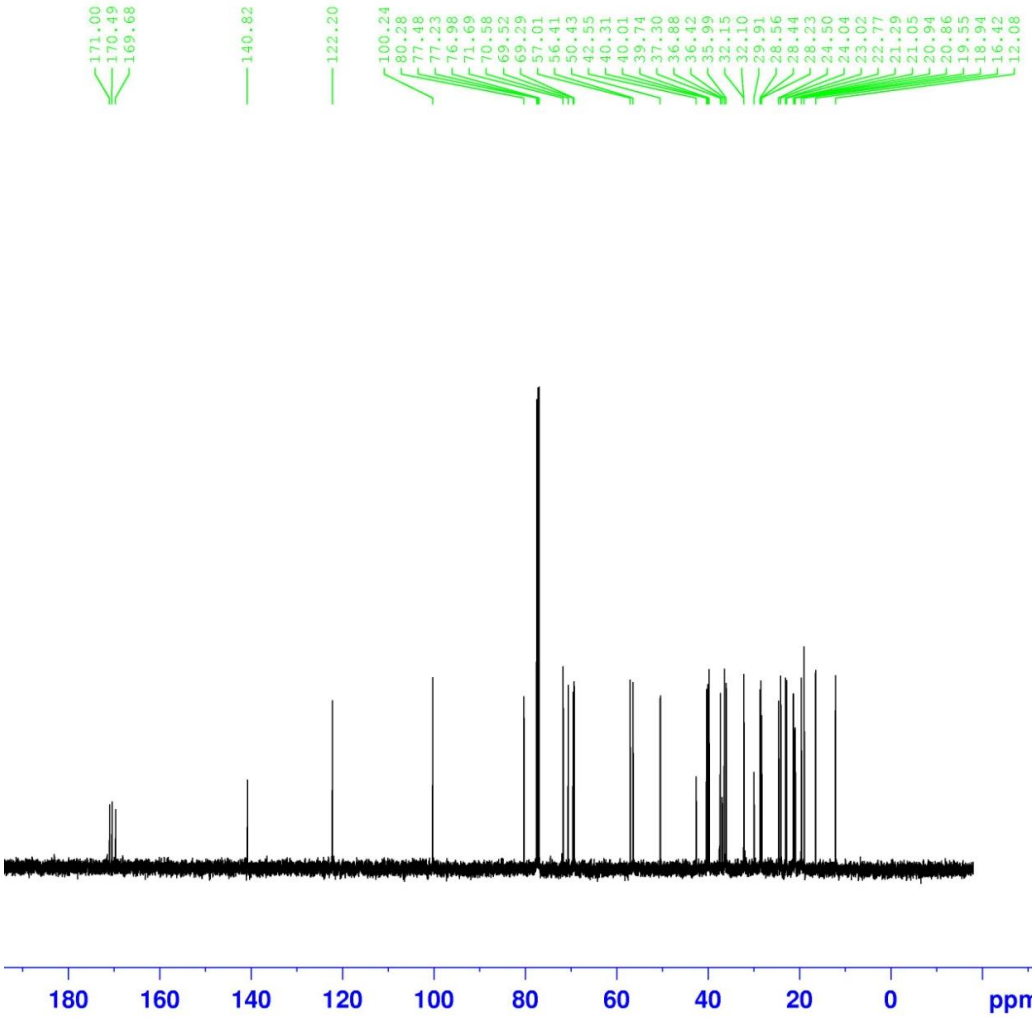




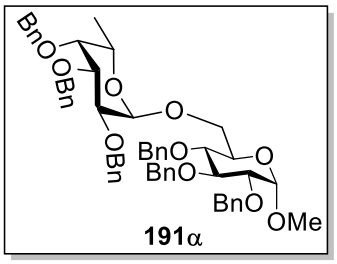
^{13}C NMR (125MHz, $CDCl_3$)



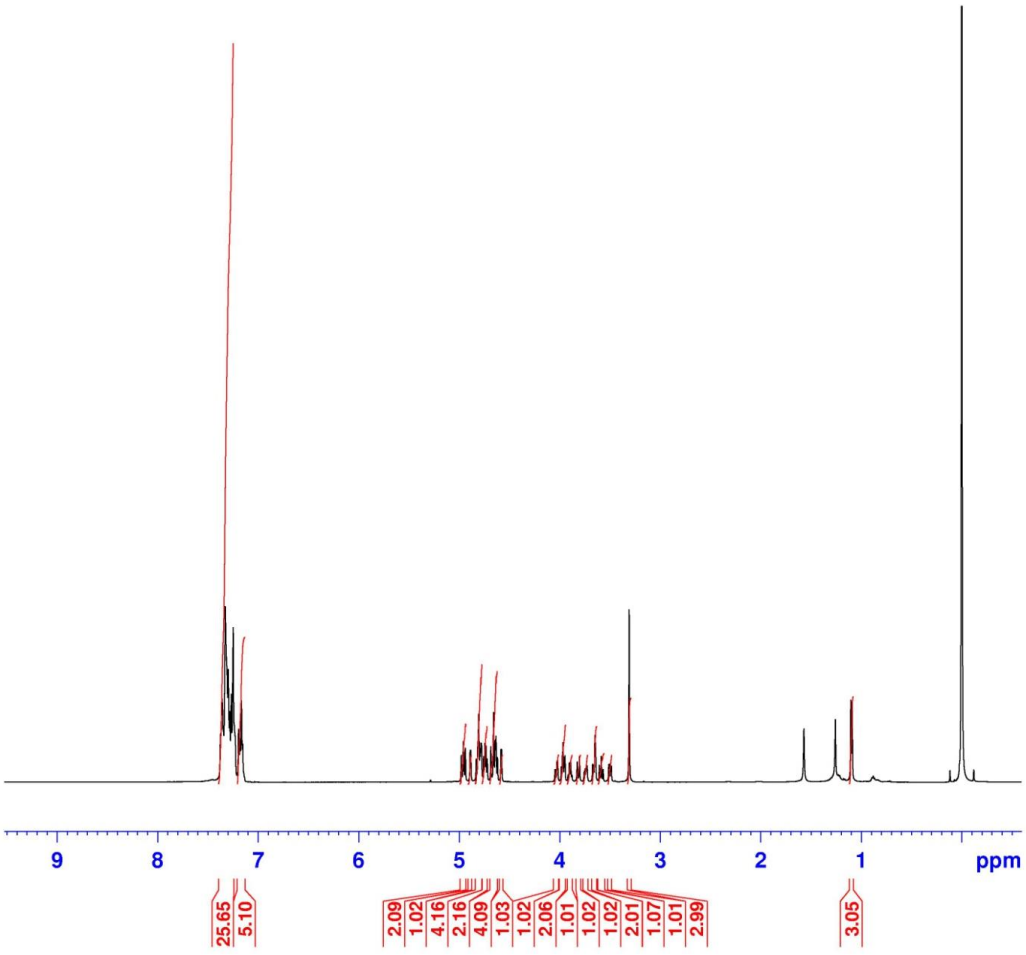
190β



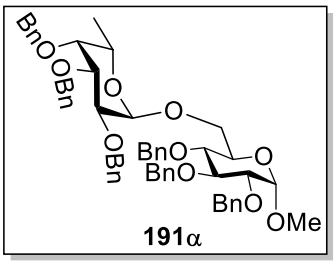
^{1}H NMR (500MHz, $CDCl_3$)



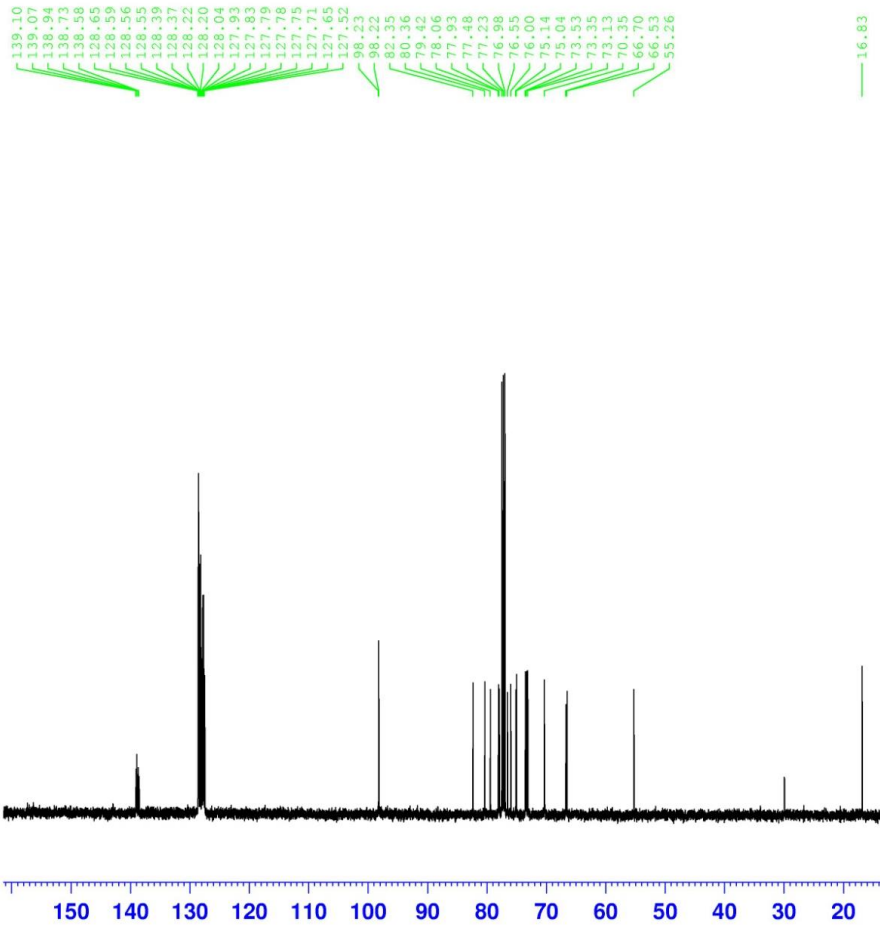
191α



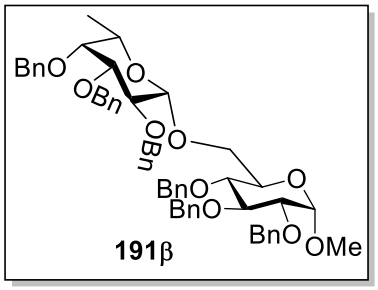
^{13}C NMR (125MHz, $CDCl_3$)



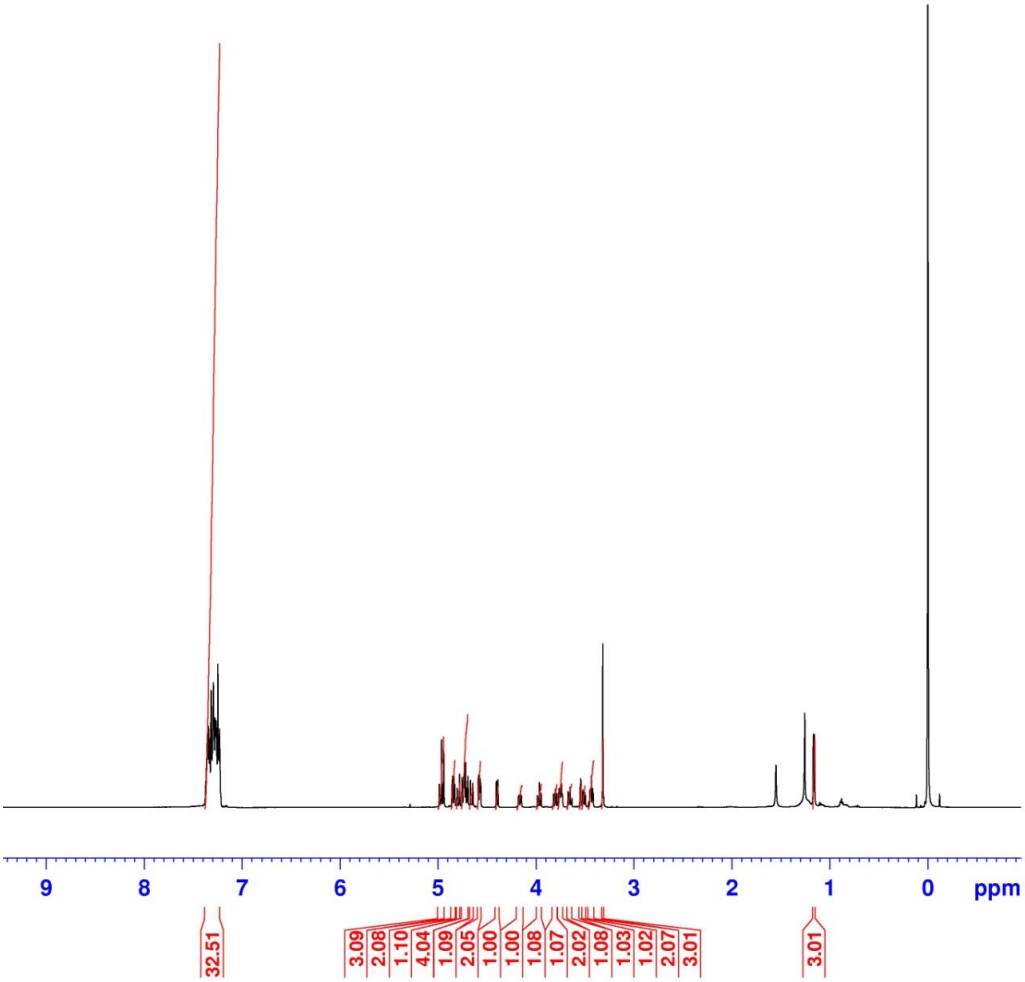
191α



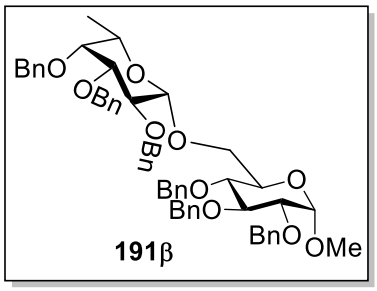
^{1}H NMR (500MHz, $CDCl_3$)

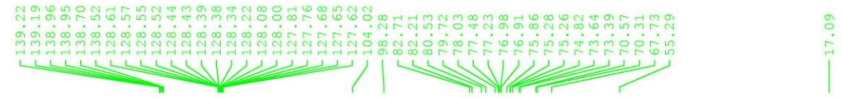


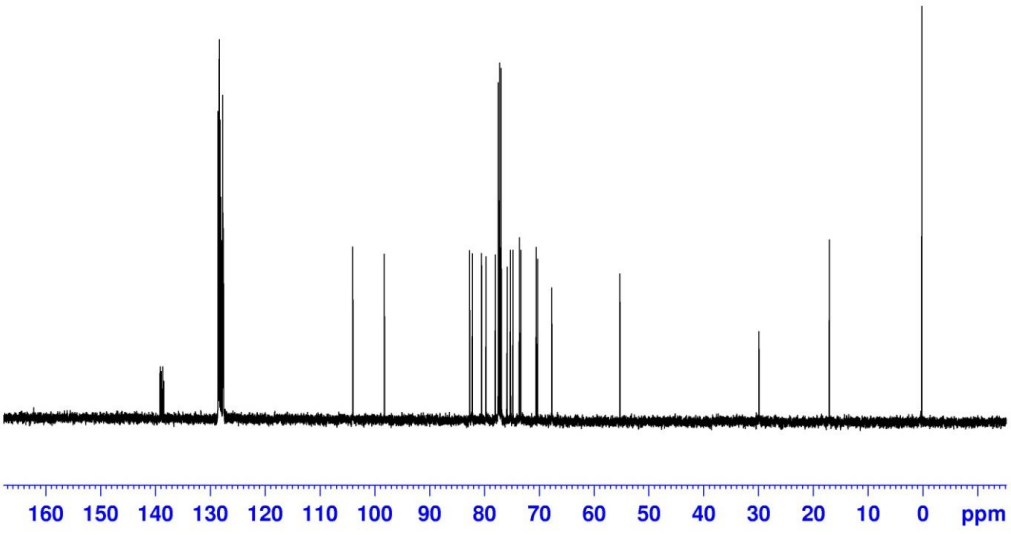
191β



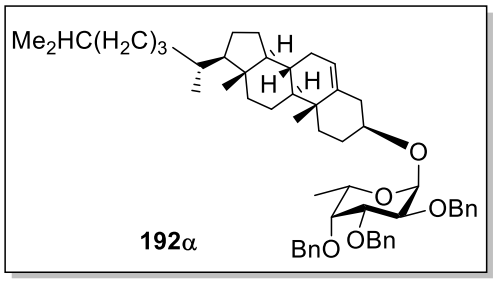
^{13}C NMR (125MHz, $CDCl_3$)



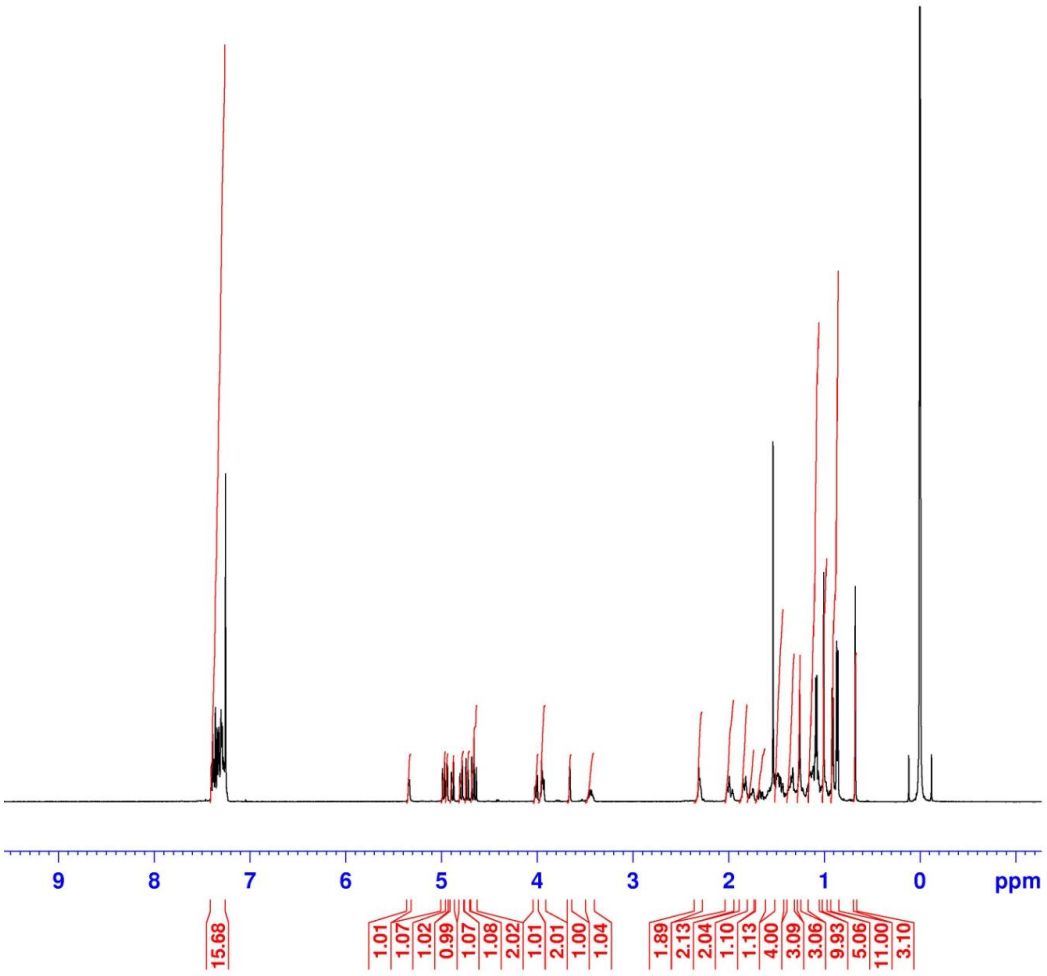




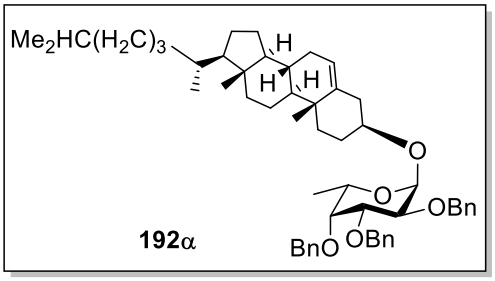
^{1}H NMR (500MHz, $CDCl_3$)



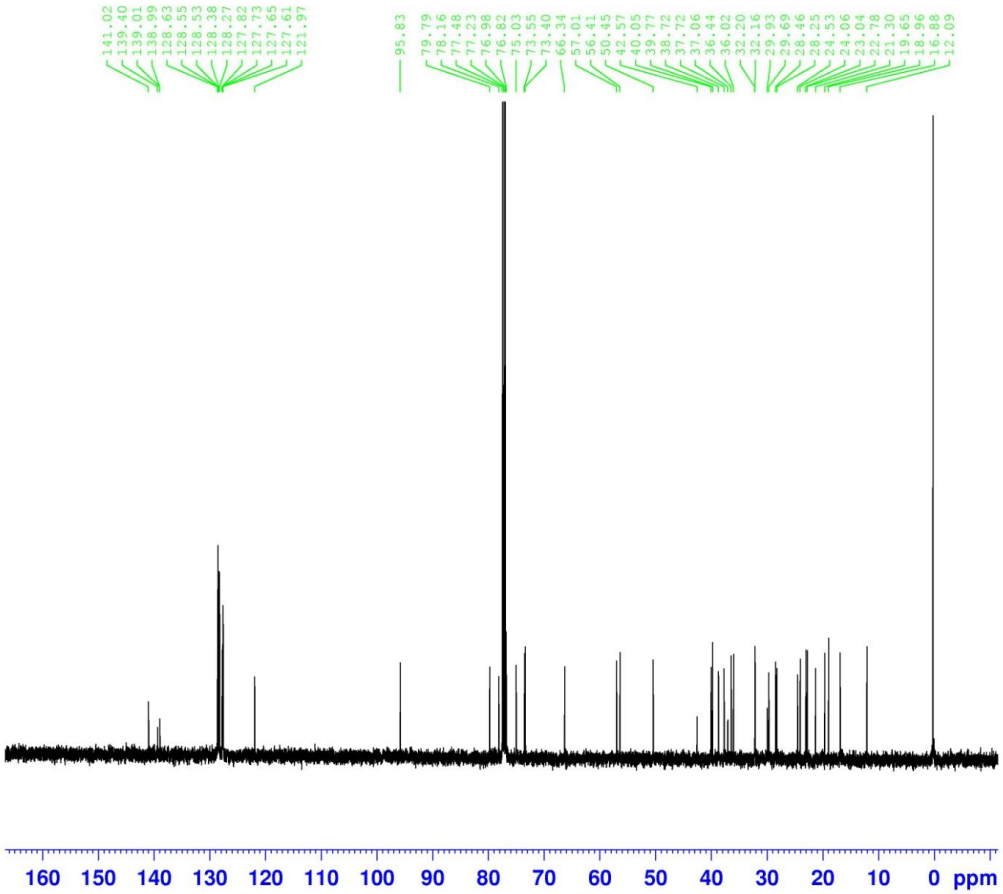
192α



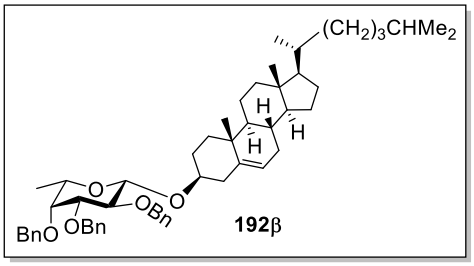
^{13}C NMR (125MHz, $CDCl_3$)



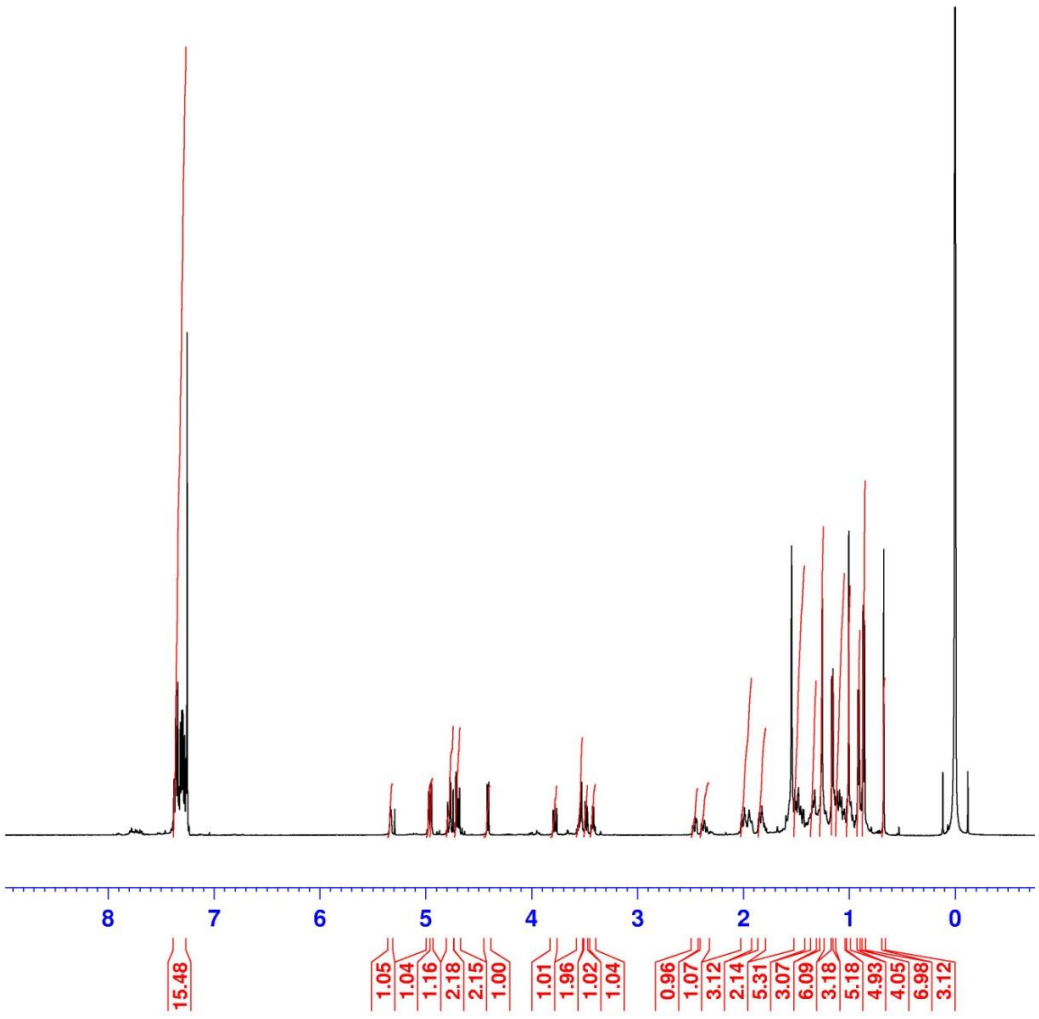
192α



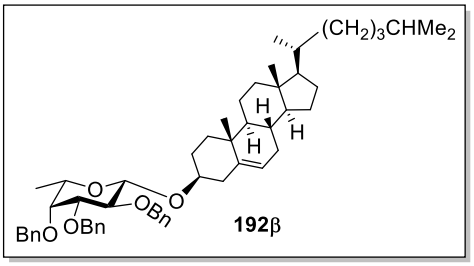
^{1}H NMR (500MHz, $CDCl_3$)

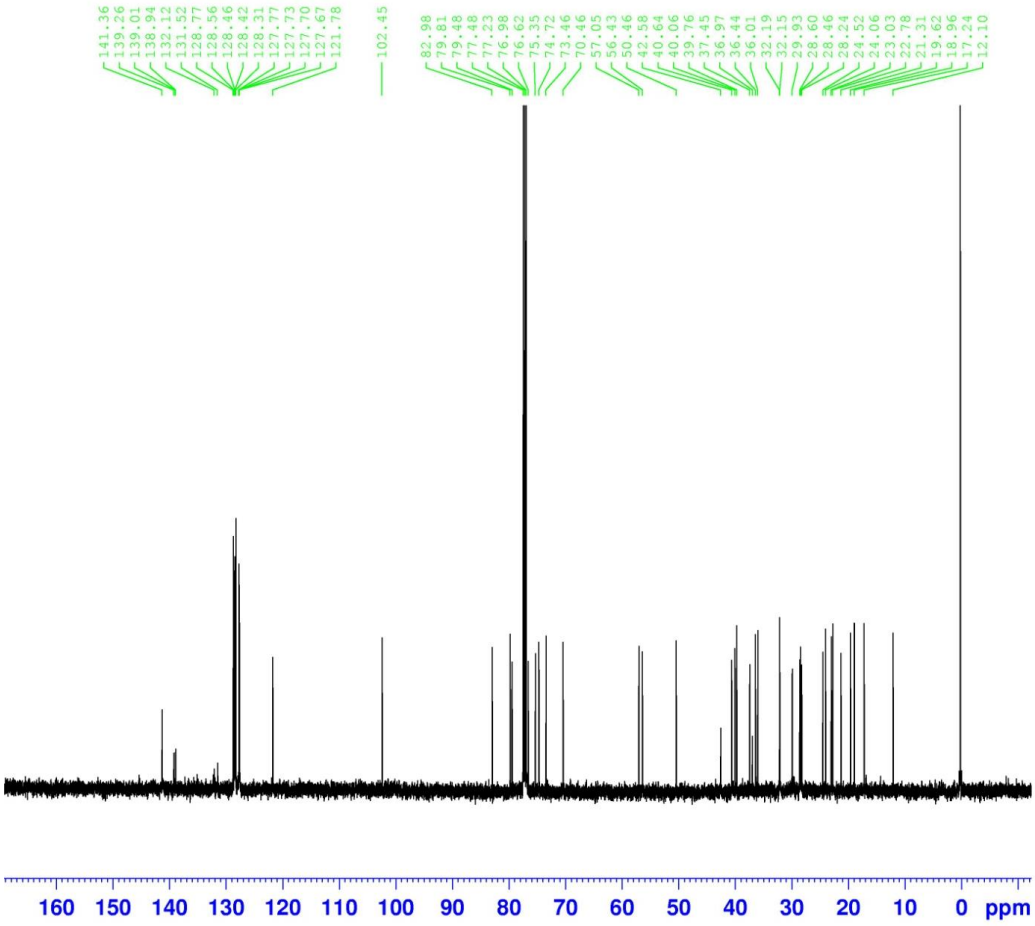


192β

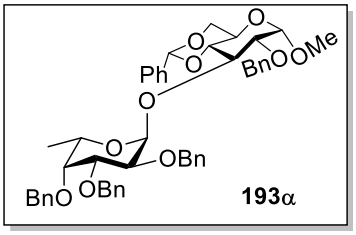


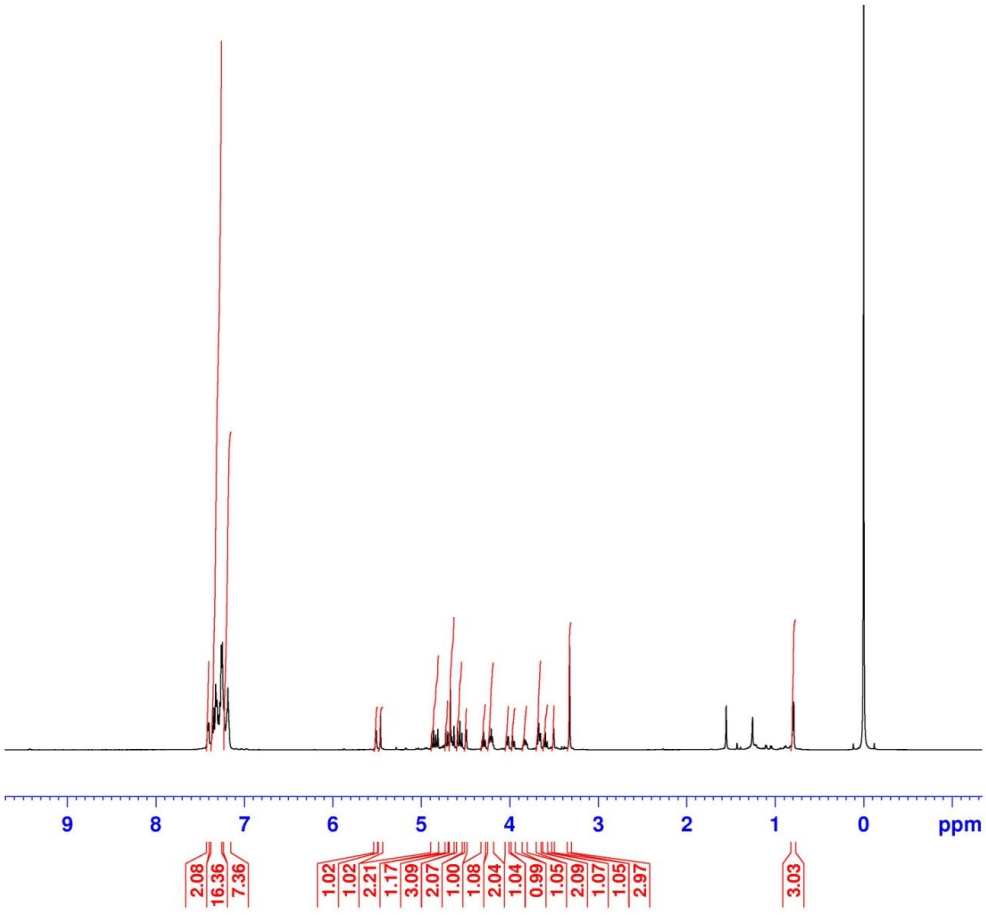
^{13}C NMR (125MHz, $CDCl_3$)



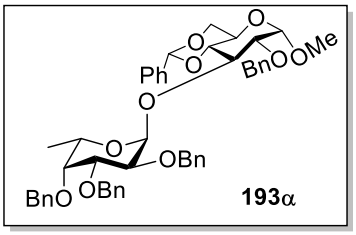


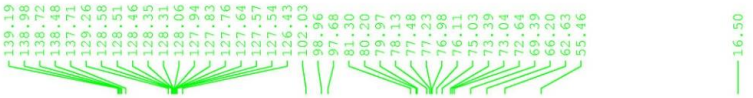
^{1}H NMR (500MHz, $CDCl_3$)

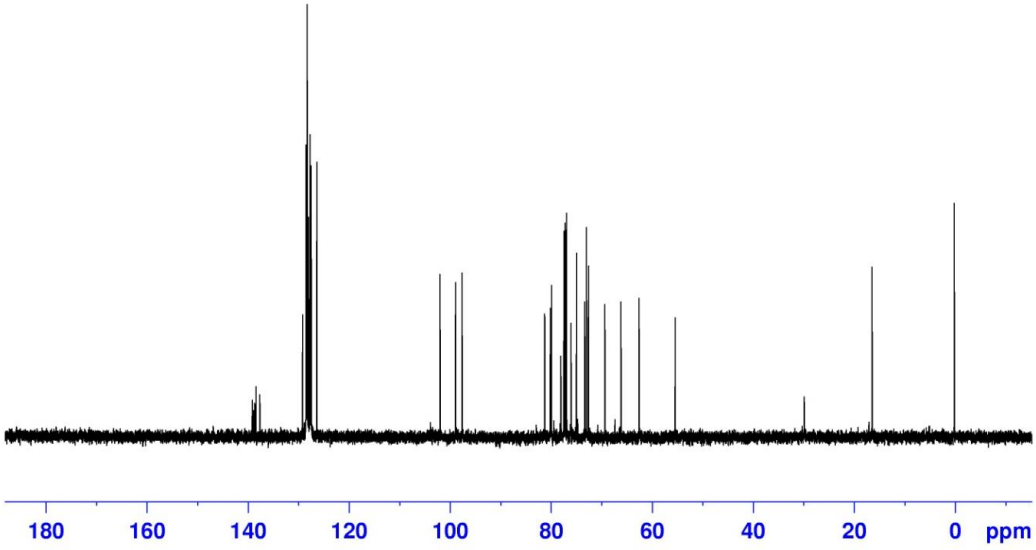




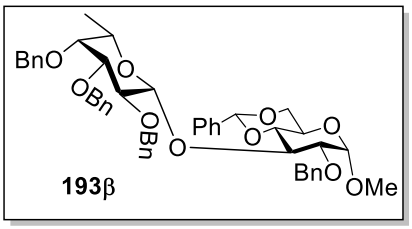
^{13}C NMR (125MHz, $CDCl_3$)



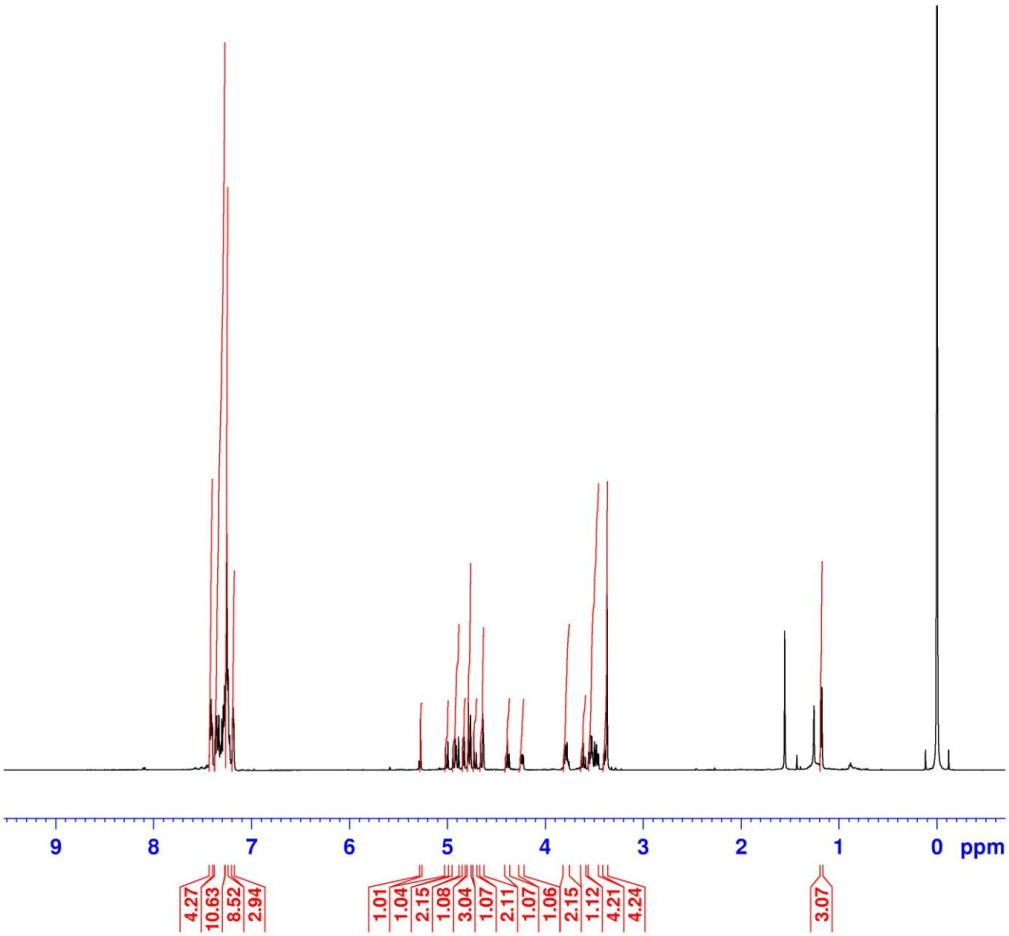




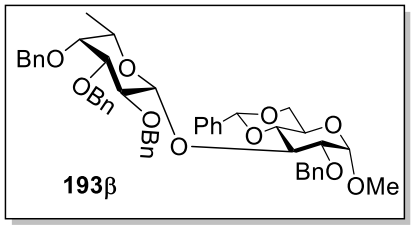
^{1}H NMR (500MHz, $CDCl_3$)

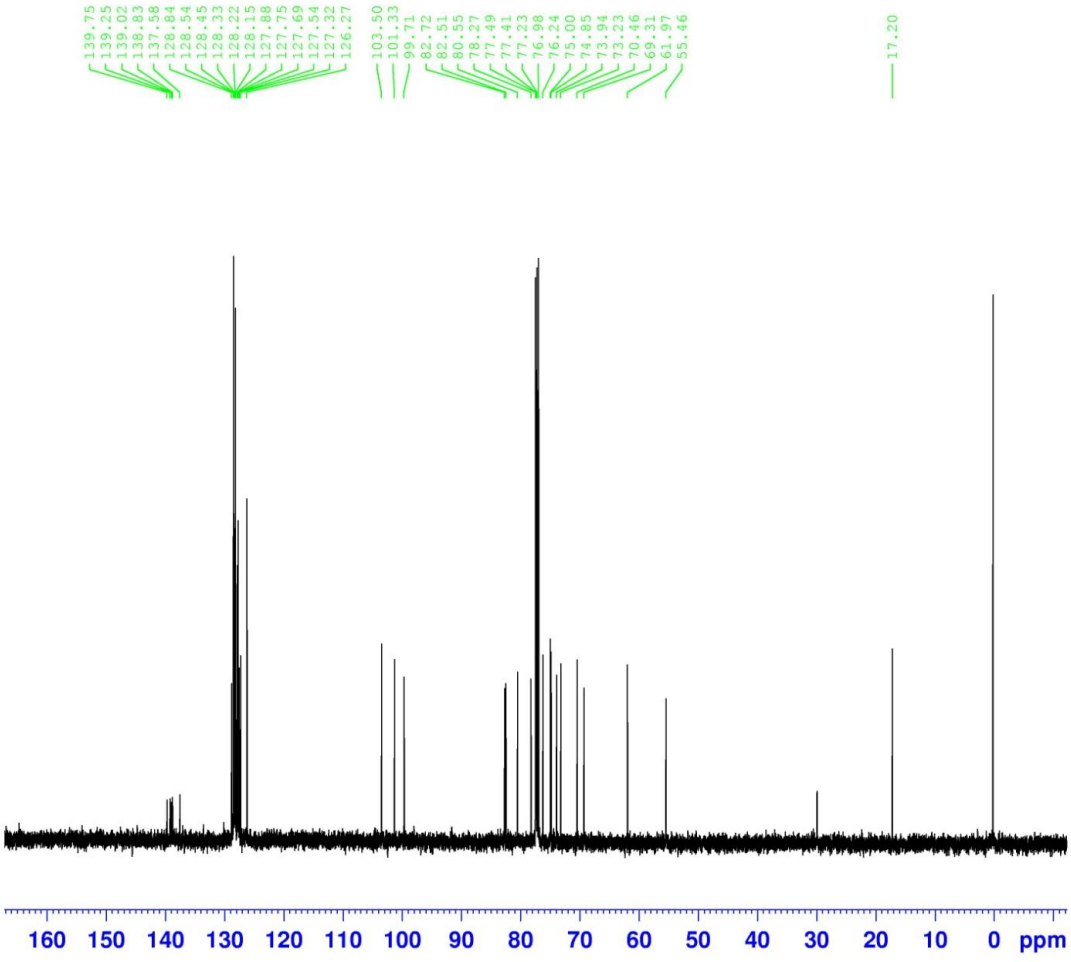


193β

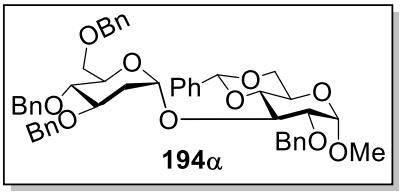


^{13}C NMR (125MHz, $CDCl_3$)

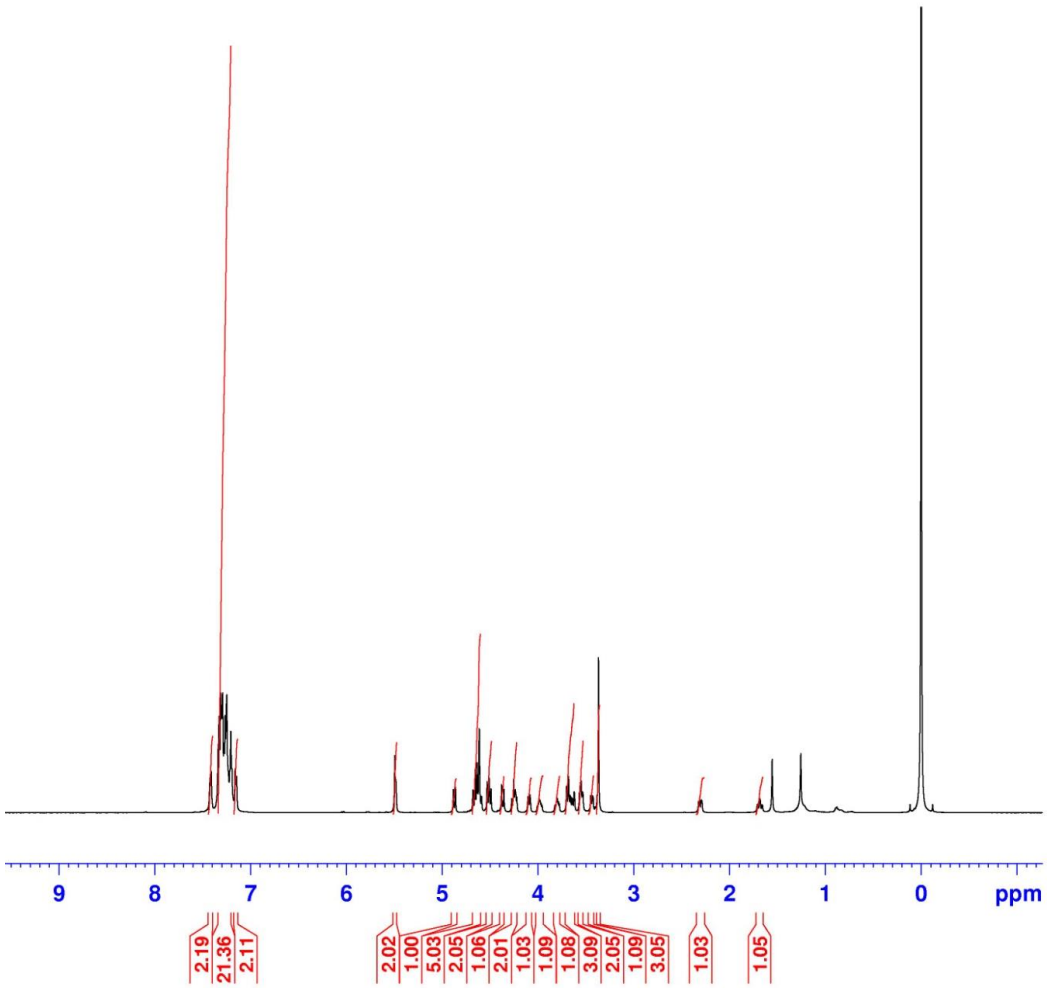




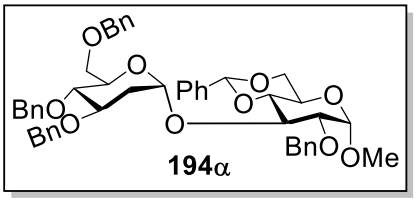
^{1}H NMR (500MHz, $CDCl_3$)



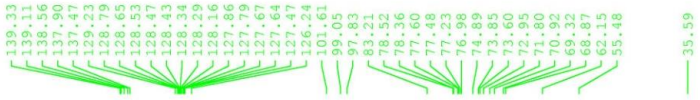
194α

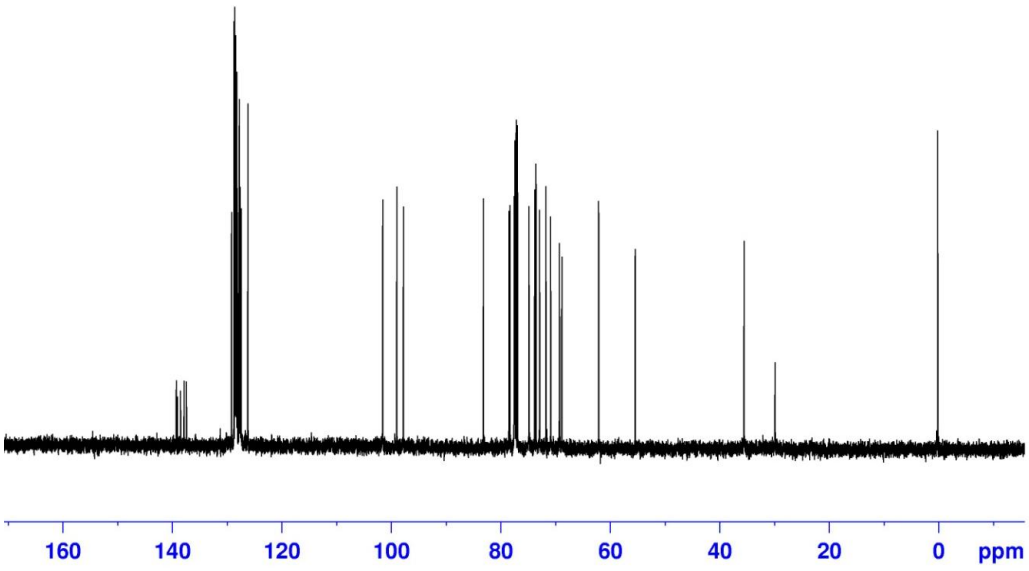


^{13}C NMR (125MHz, $CDCl_3$)

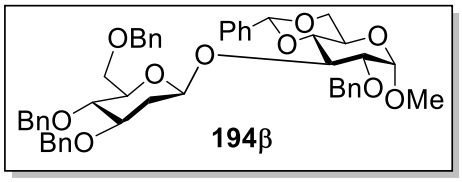


194α

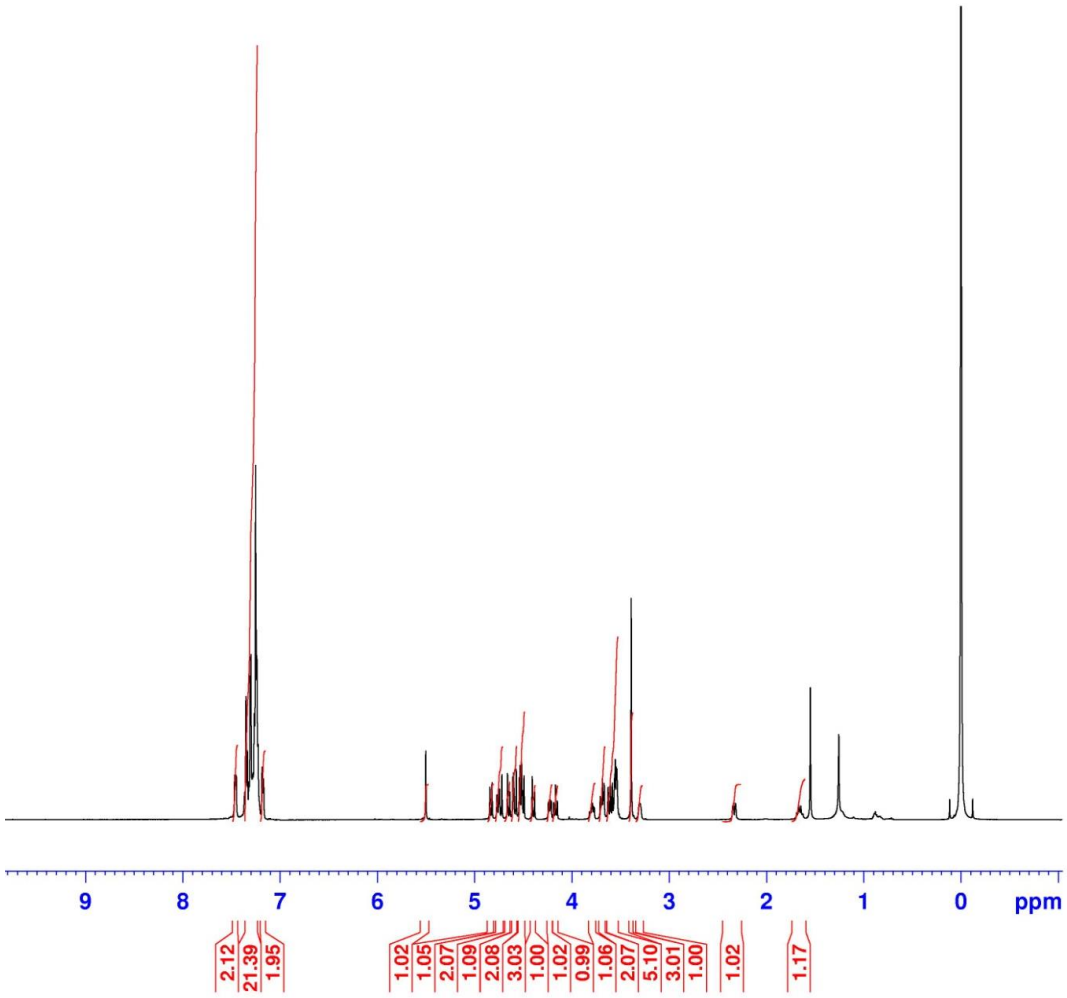




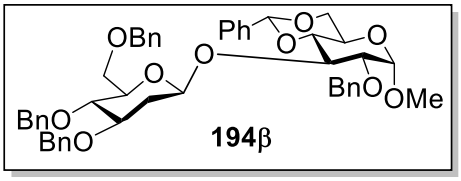
^{1}H NMR (500MHz, $CDCl_3$)

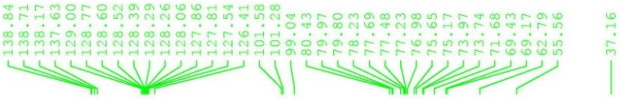


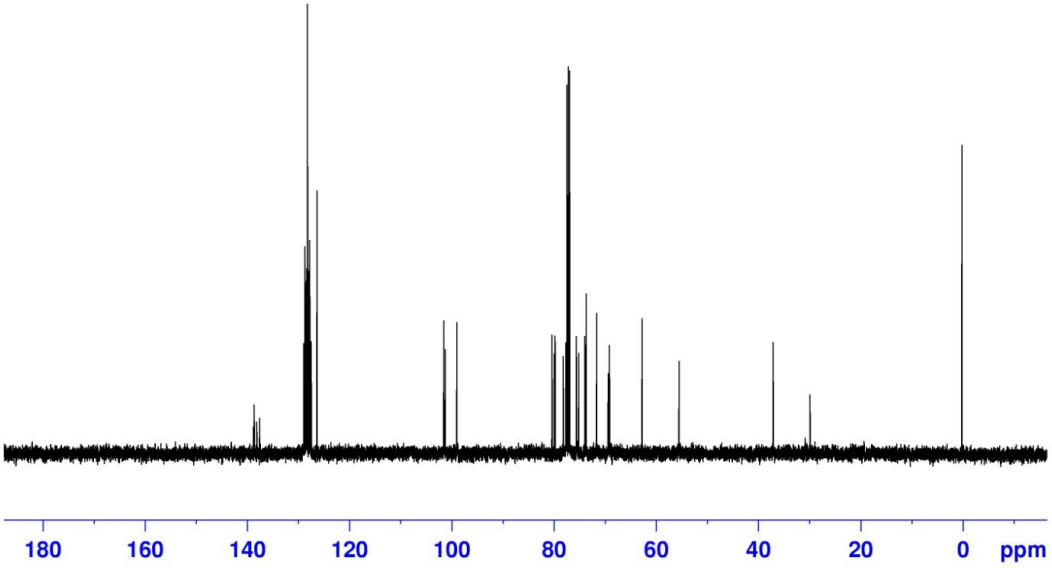
194β



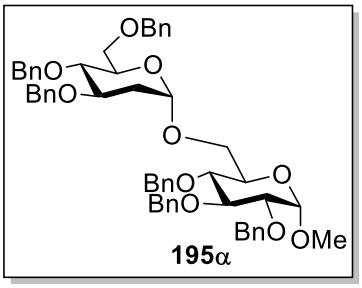
^{13}C NMR (125MHz, $CDCl_3$)



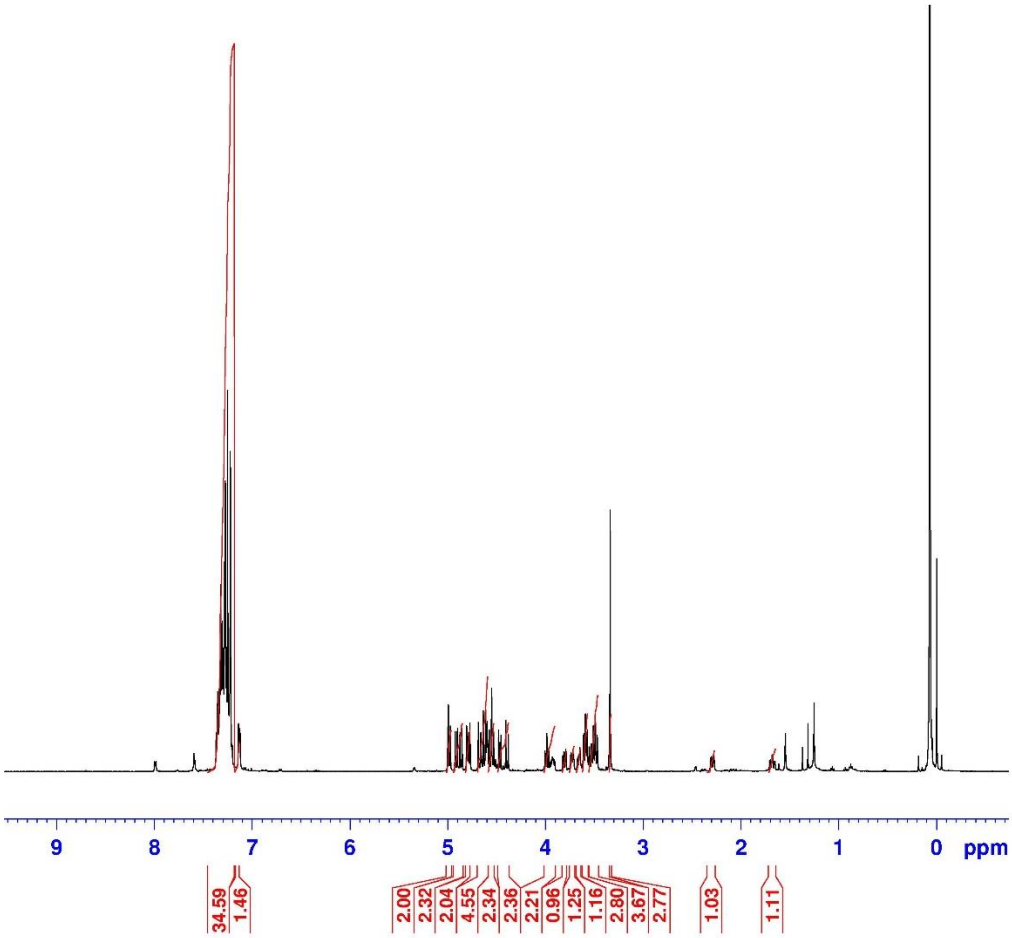




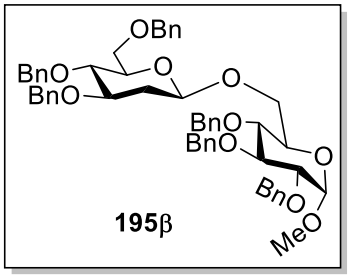
^{1}H NMR (500MHz, $CDCl_3$)

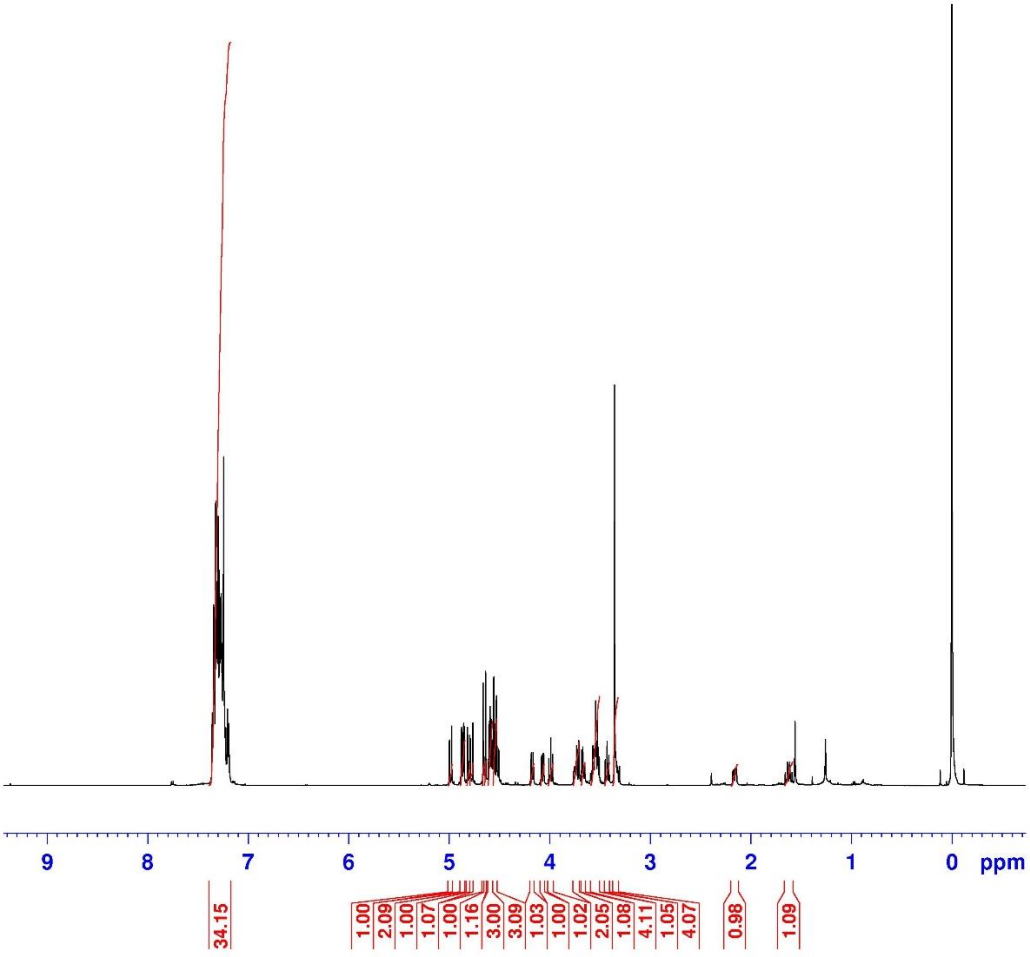


195α

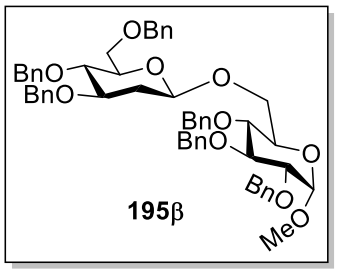


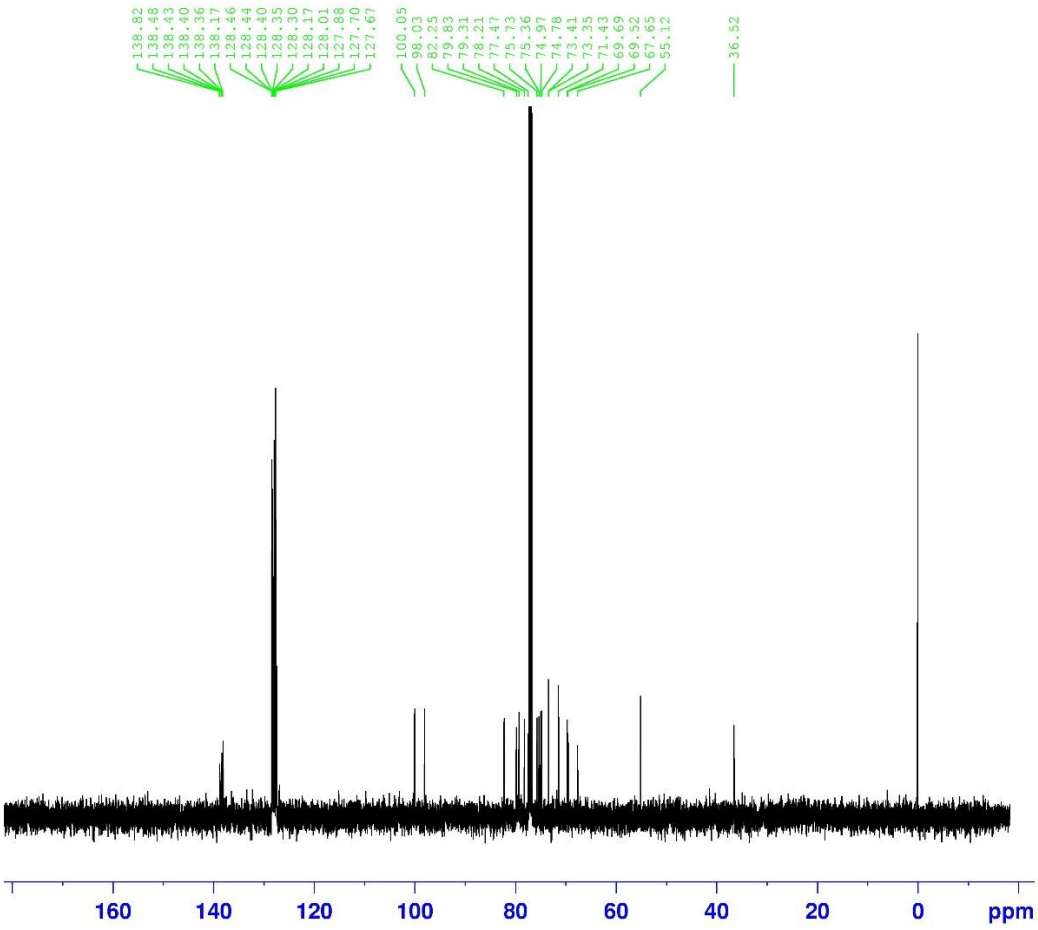
^{1}H NMR (500MHz, $CDCl_3$)



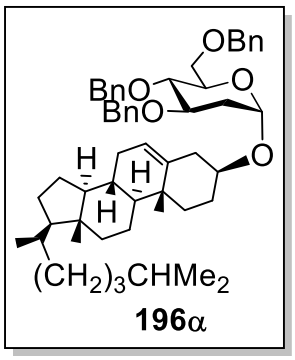


^{13}C NMR (125MHz, $CDCl_3$)

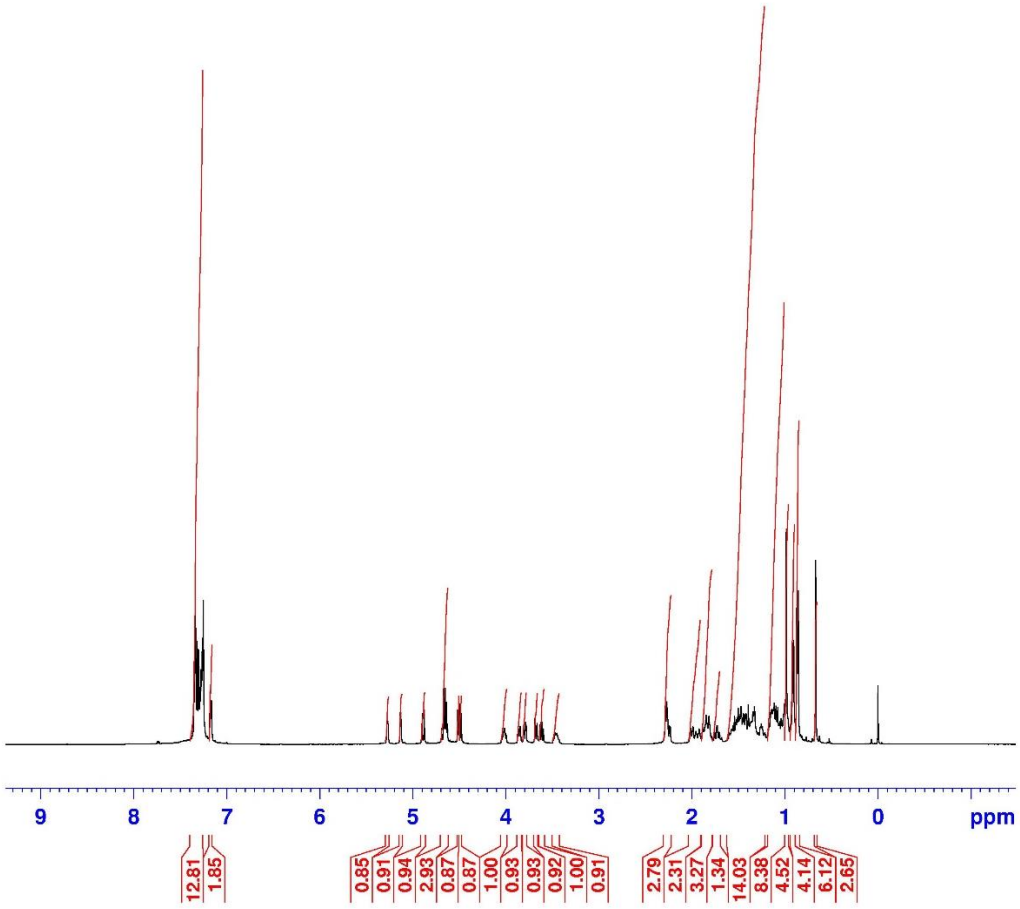




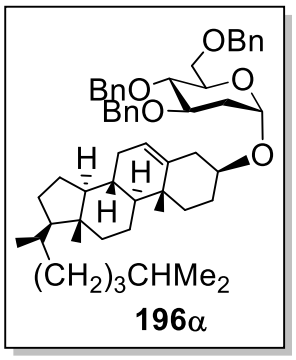
^{1}H NMR (500MHz, $CDCl_3$)

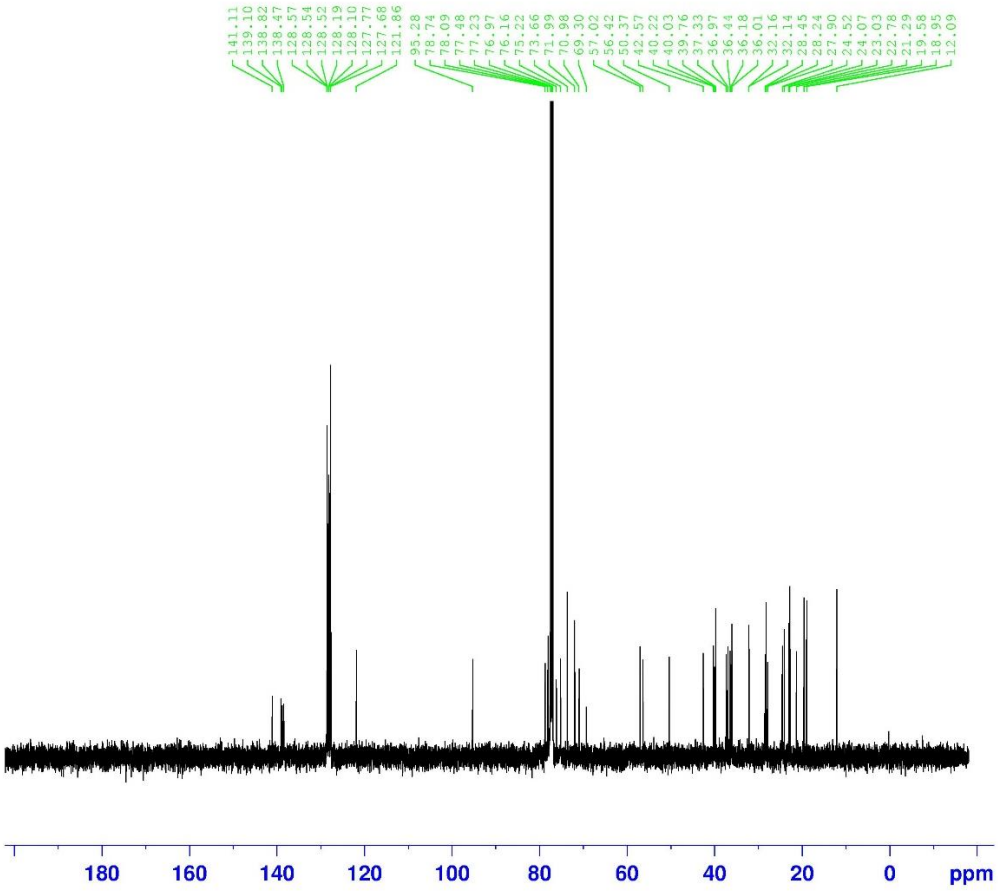


196α

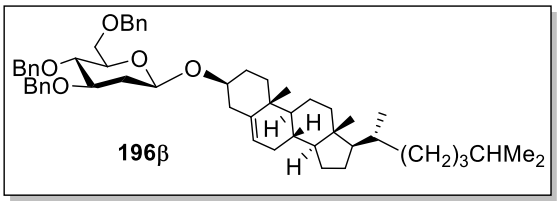


^{13}C NMR (125MHz, $CDCl_3$)

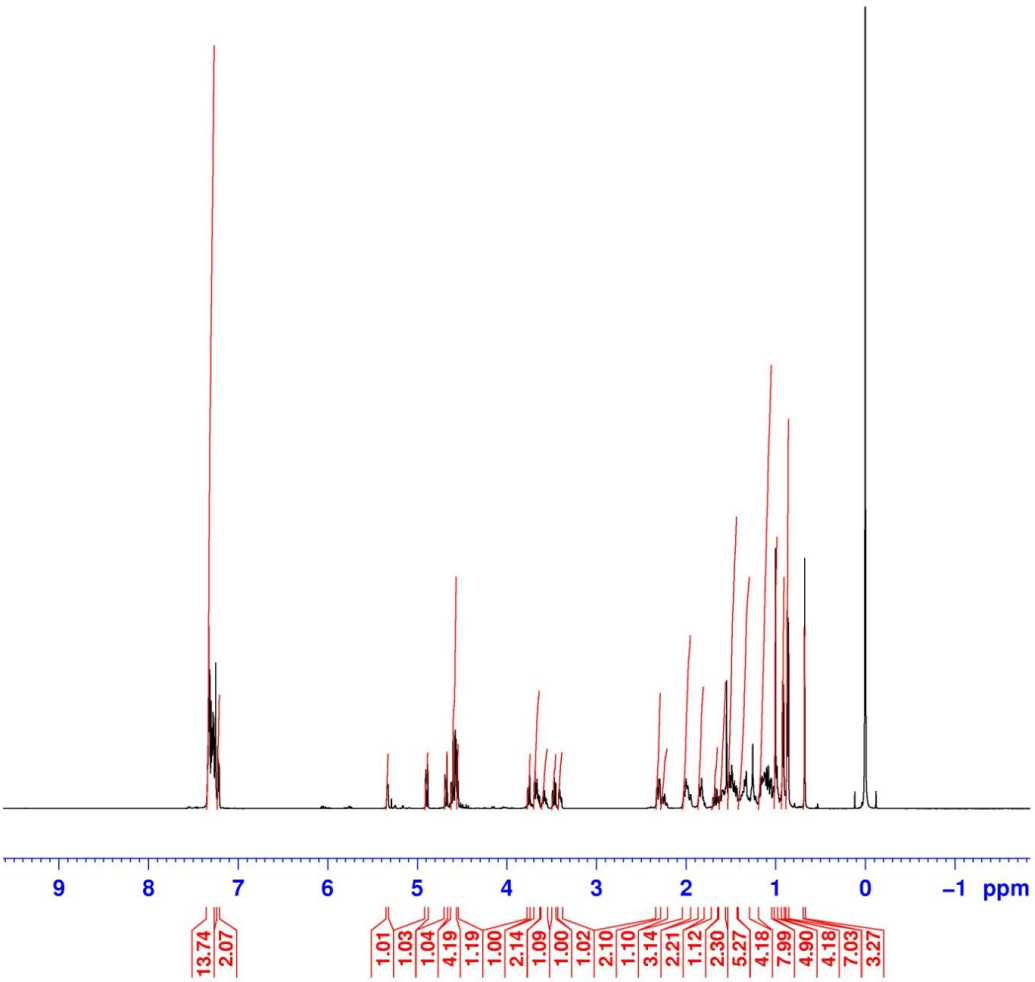




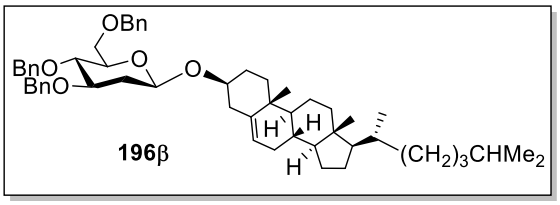
^{1}H NMR (500MHz, $CDCl_3$)



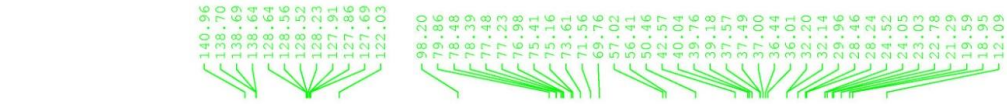
196β

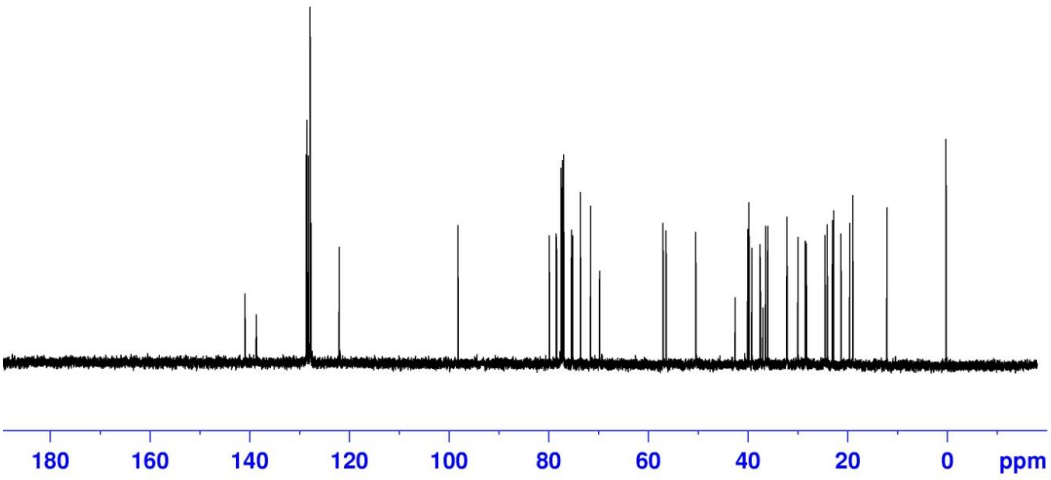


^{13}C NMR (125MHz, $CDCl_3$)

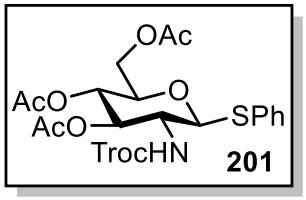


196β





^{1}H NMR (500MHz, CD_2Cl_2)



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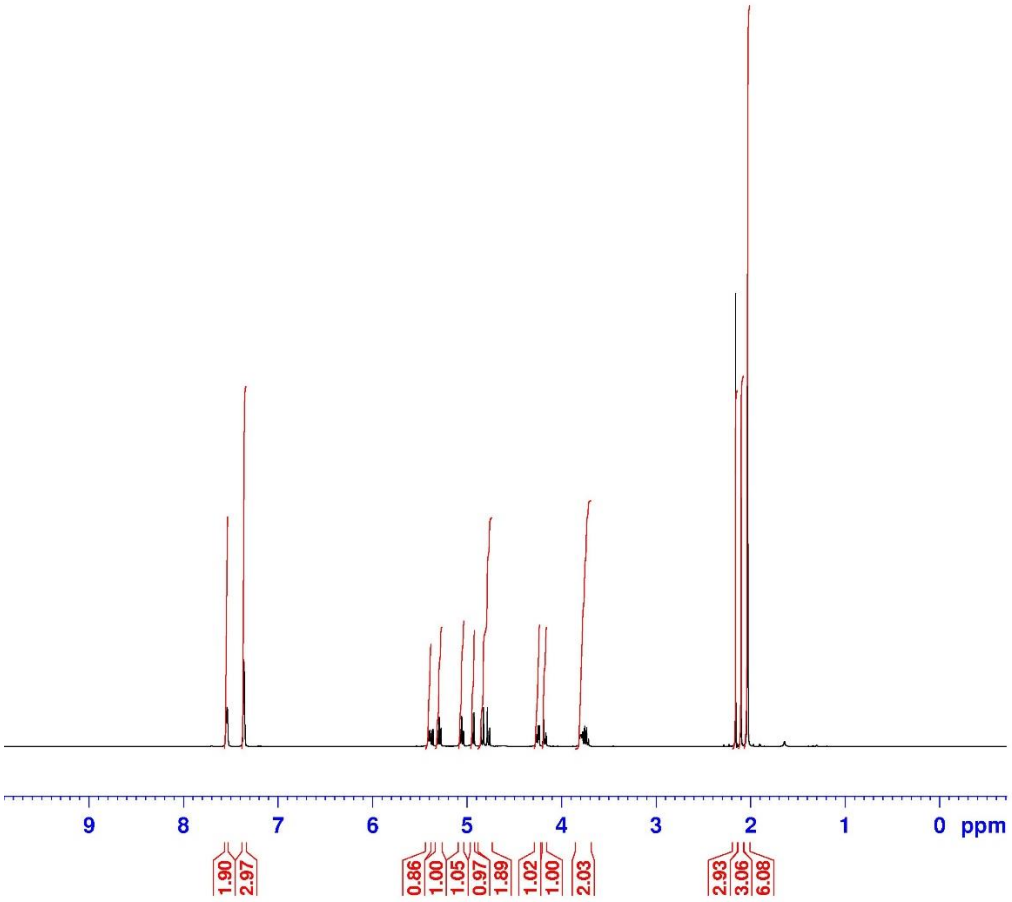
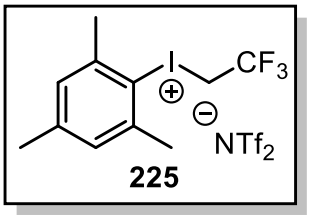


^{1}H NMR (500MHz, CD_2Cl_2)



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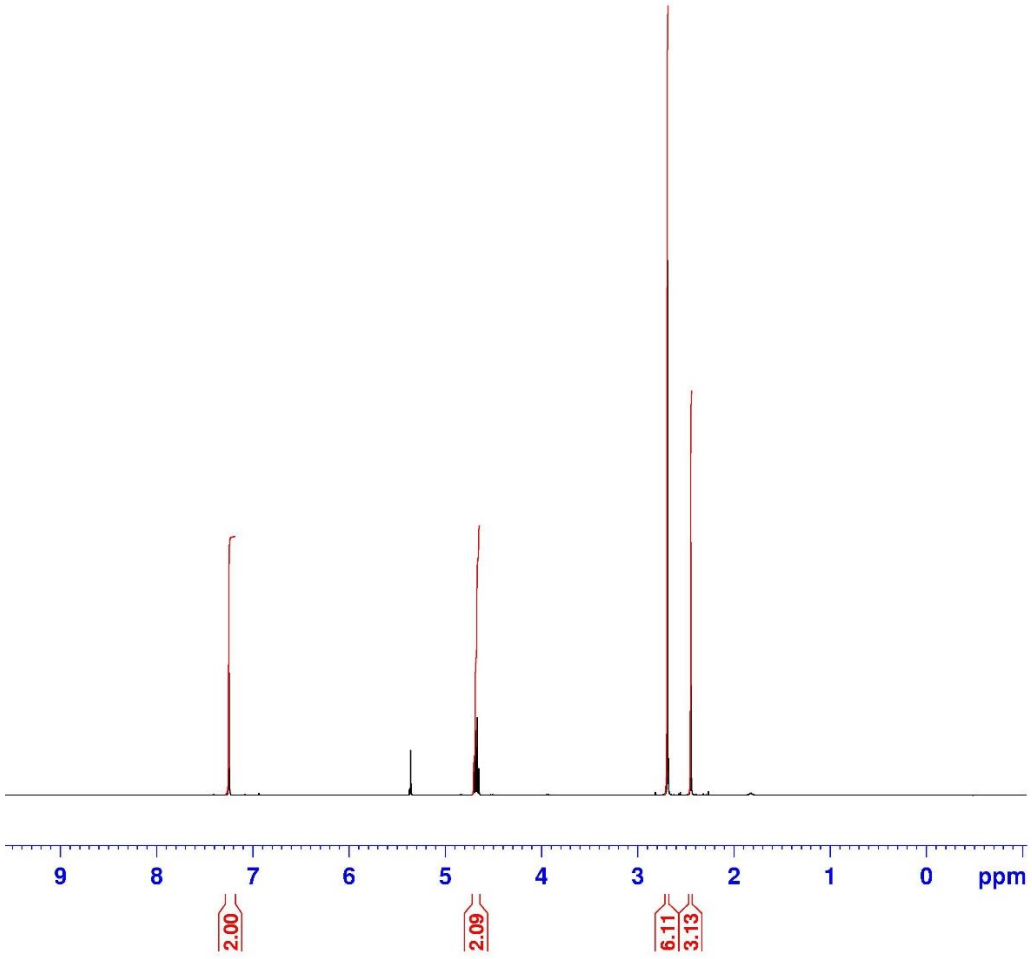
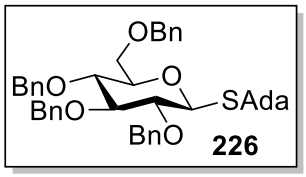


^{1}H NMR (500MHz, $CDCl_3$)



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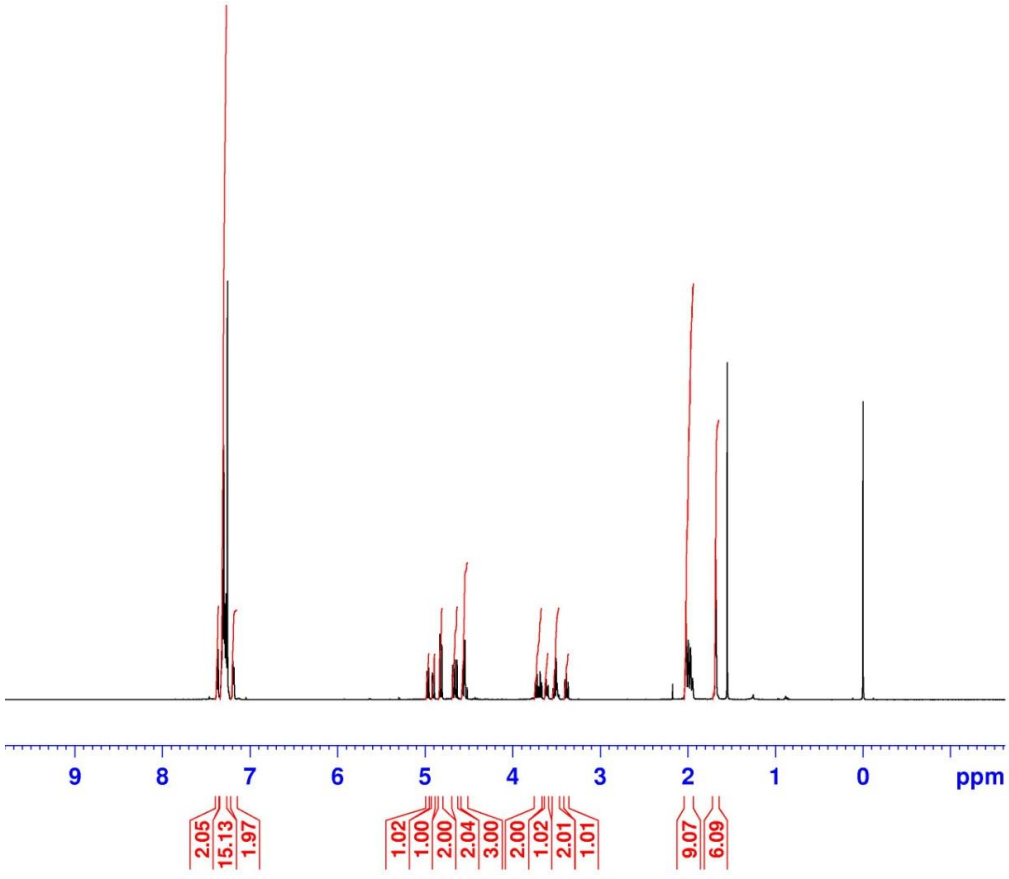
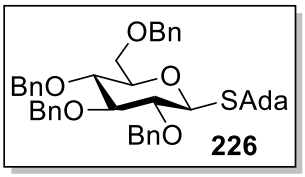


^{13}C NMR (125MHz, $CDCl_3$)



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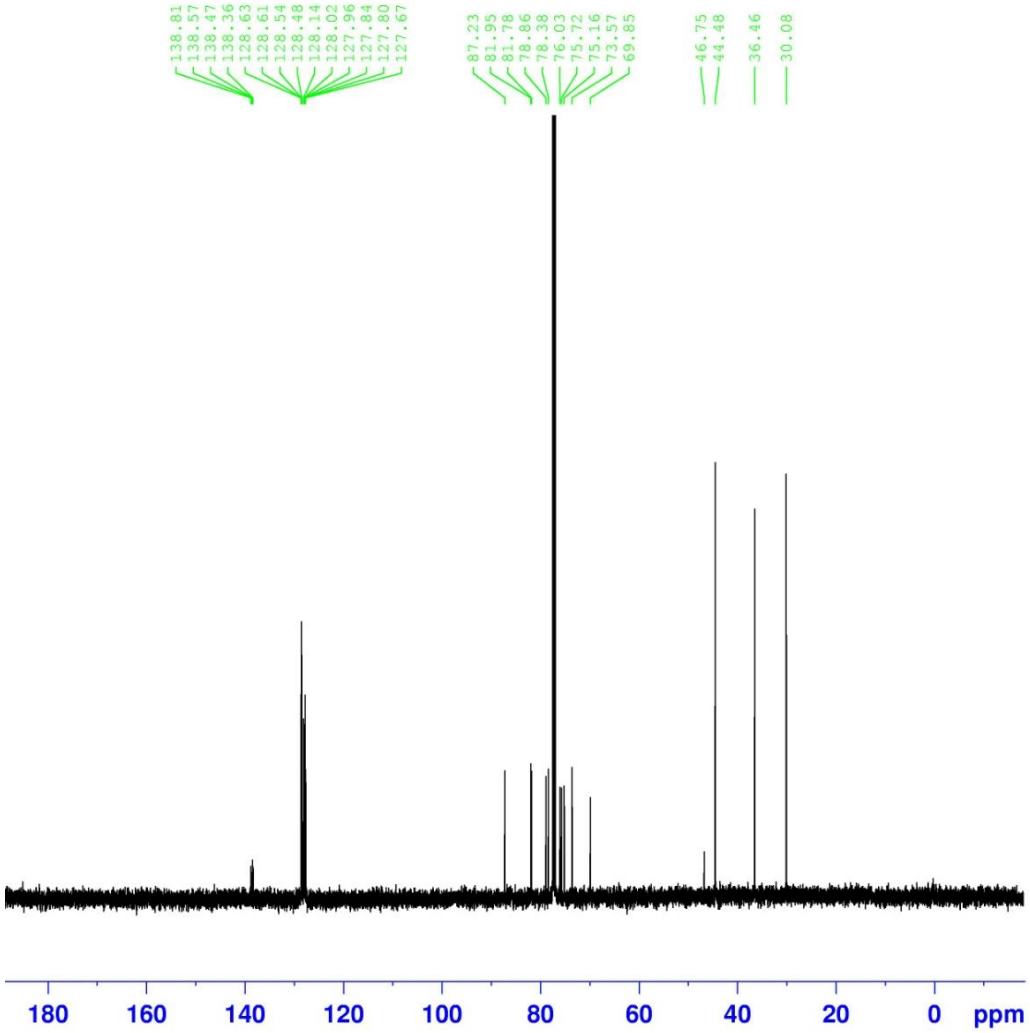
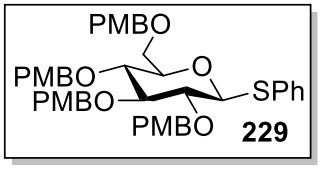


^{1}H NMR (500MHz, $CDCl_3$)



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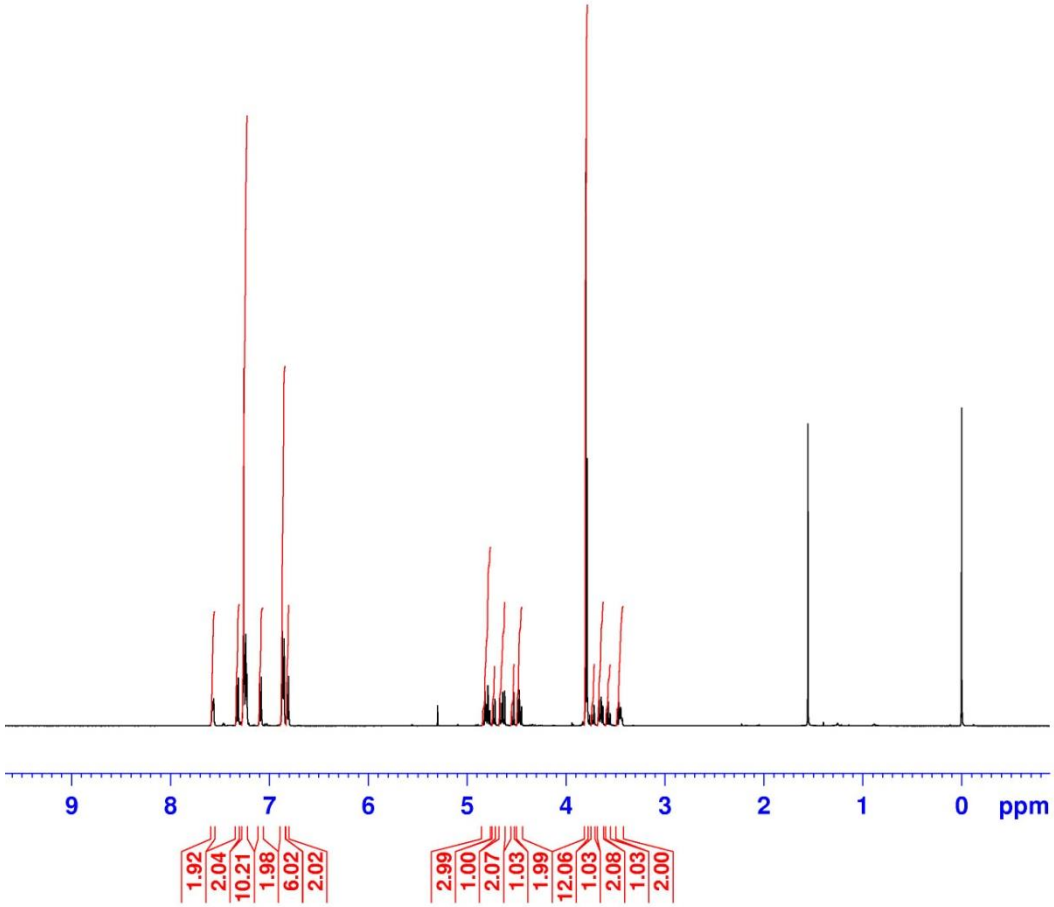
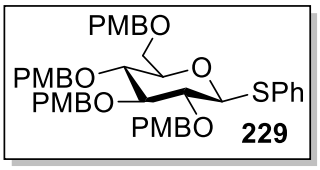
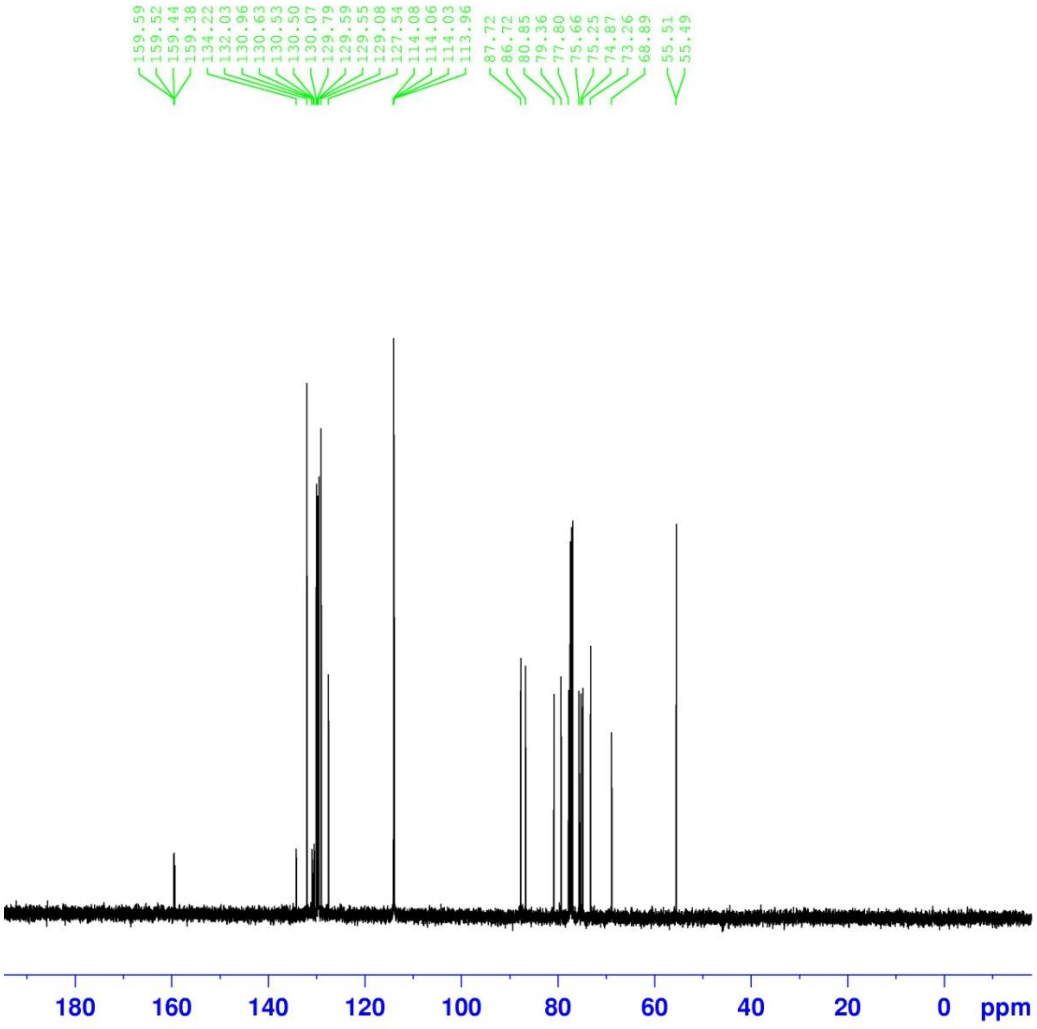
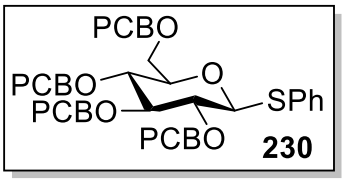


^{13}C NMR (125MHz, $CDCl_3$)





^{1}H NMR (500MHz, $CDCl_3$)



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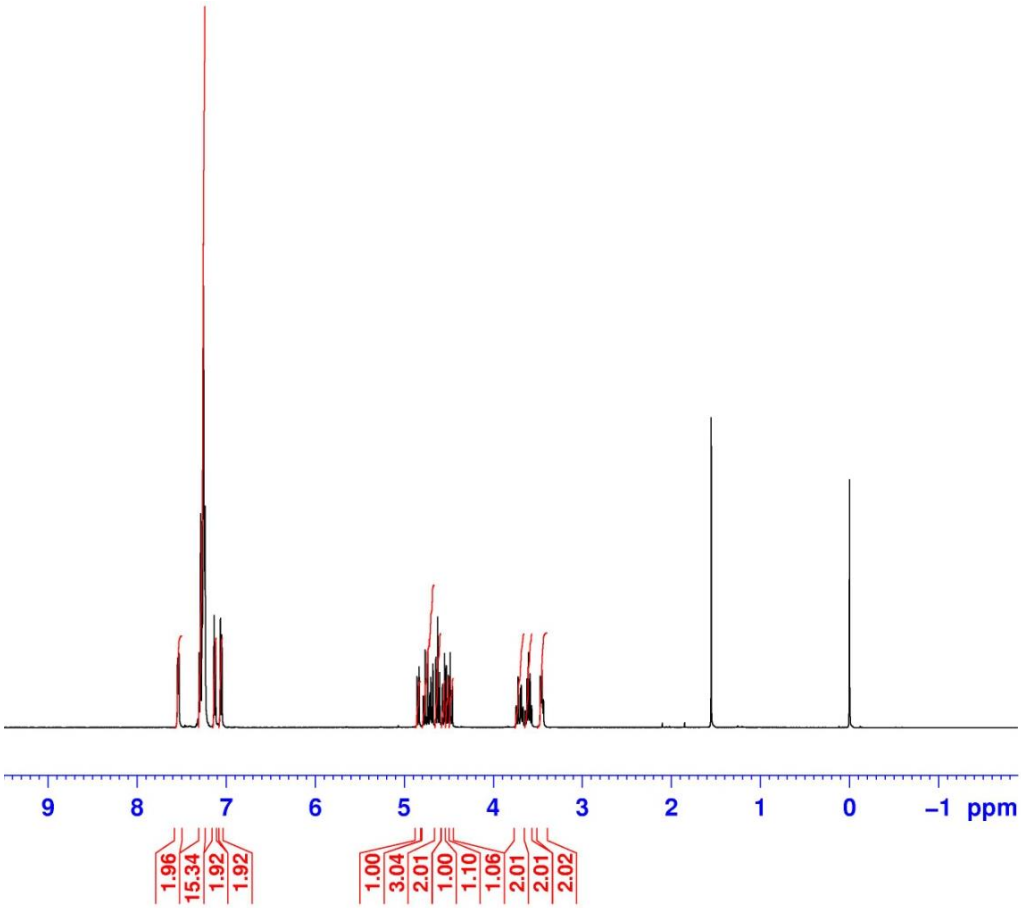
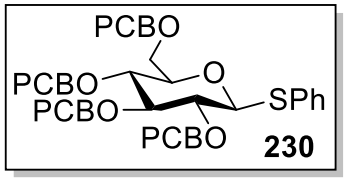
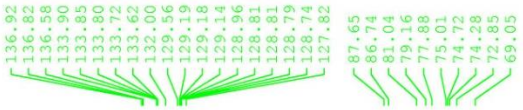
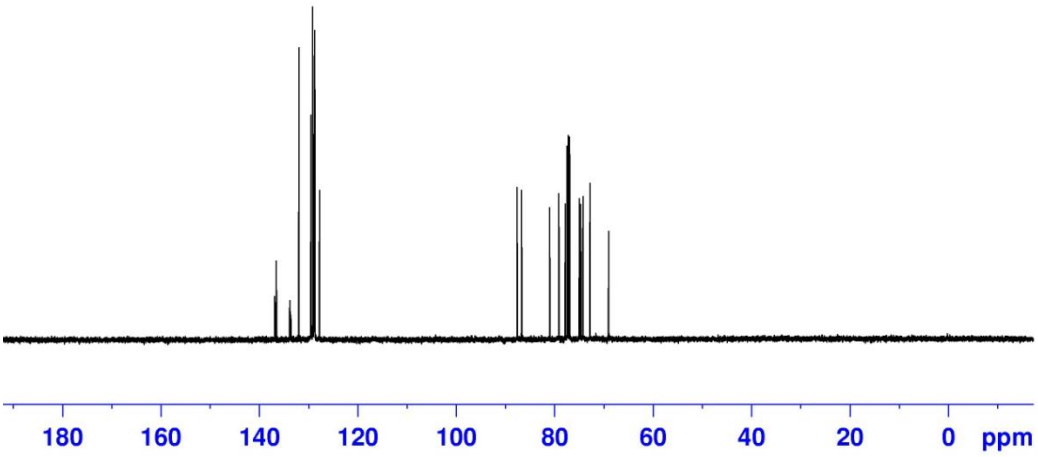


^{13}C NMR (125MHz, $CDCl_3$)







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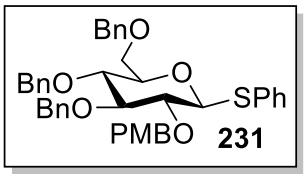

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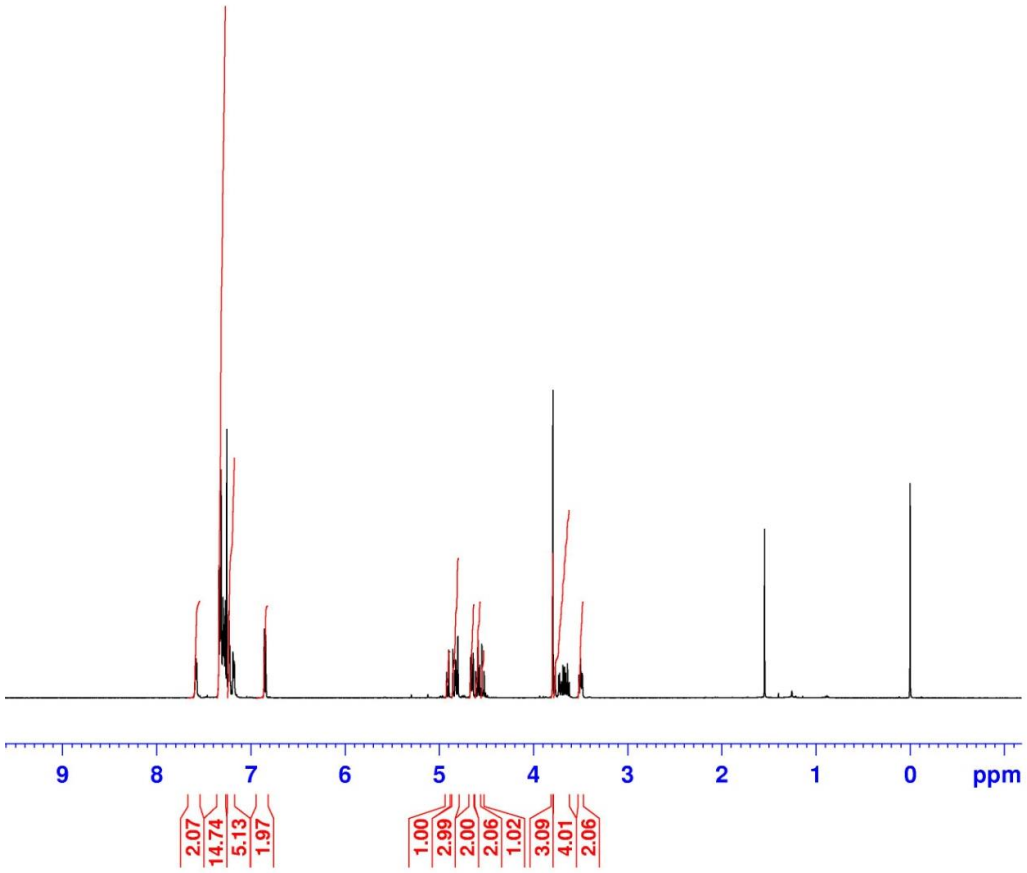
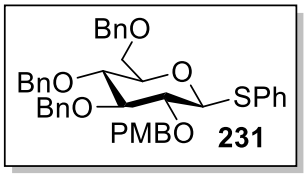
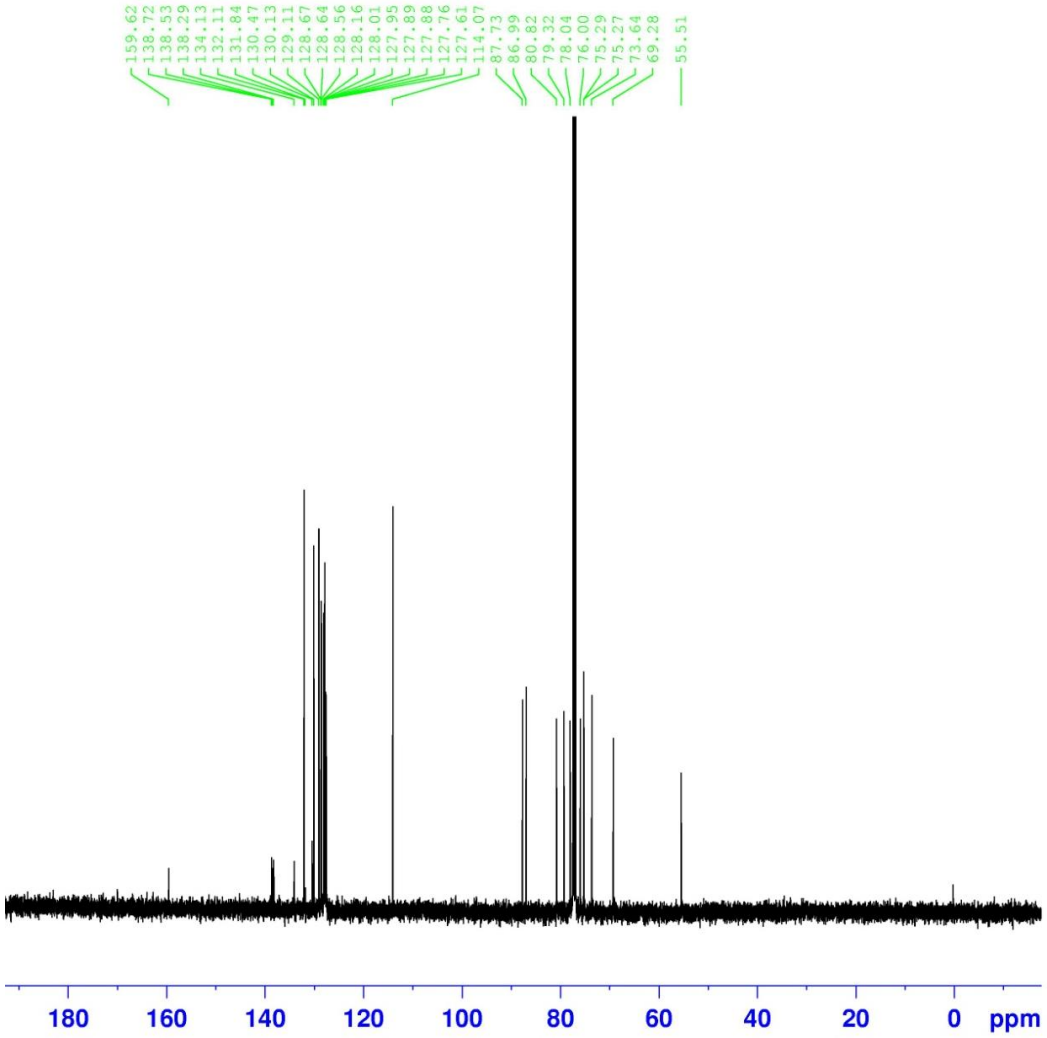
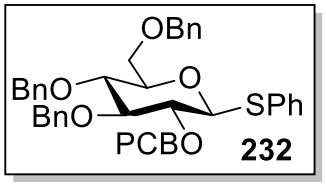


^{13}C NMR (125MHz, $CDCl_3$)





^{1}H NMR (500MHz, $CDCl_3$)



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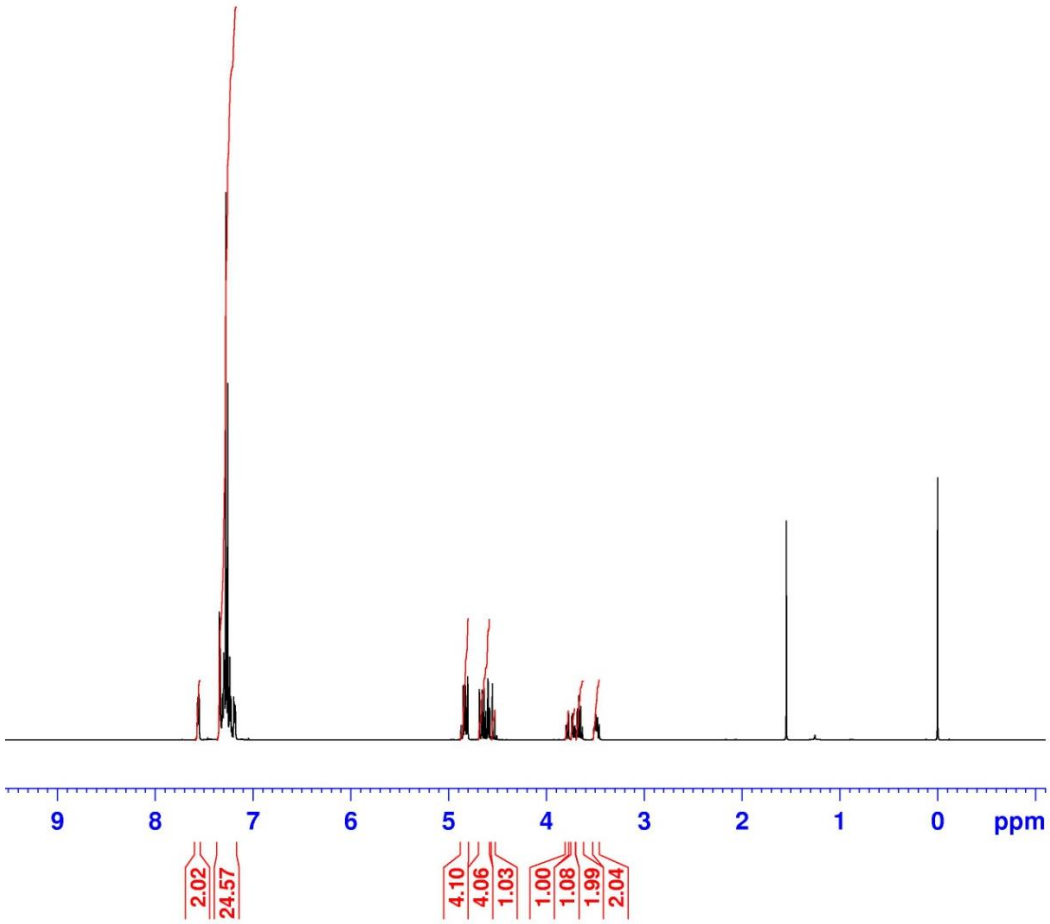

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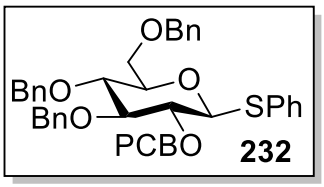

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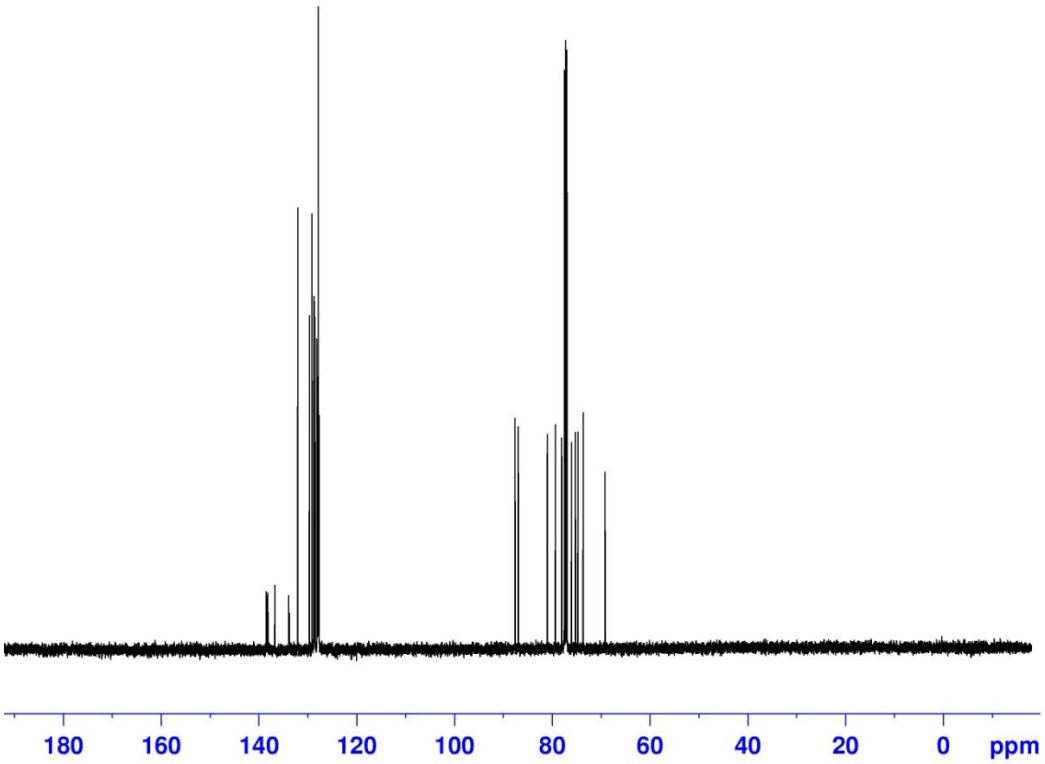

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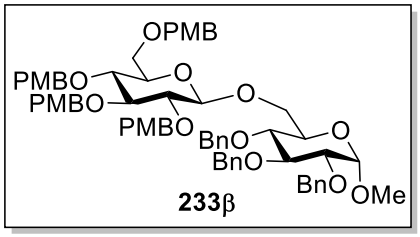
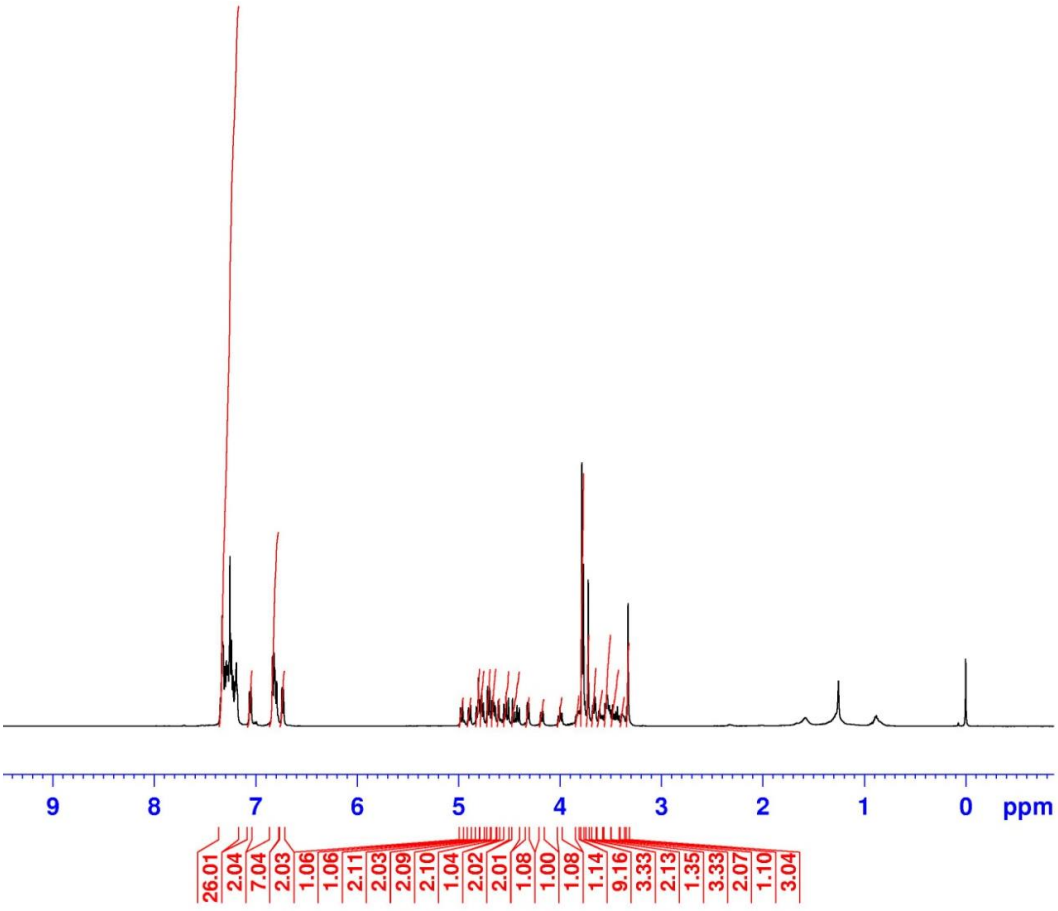


233β



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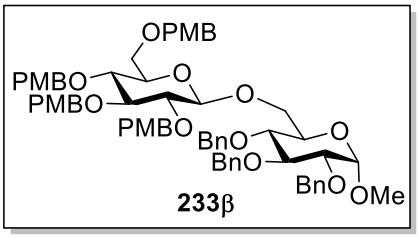

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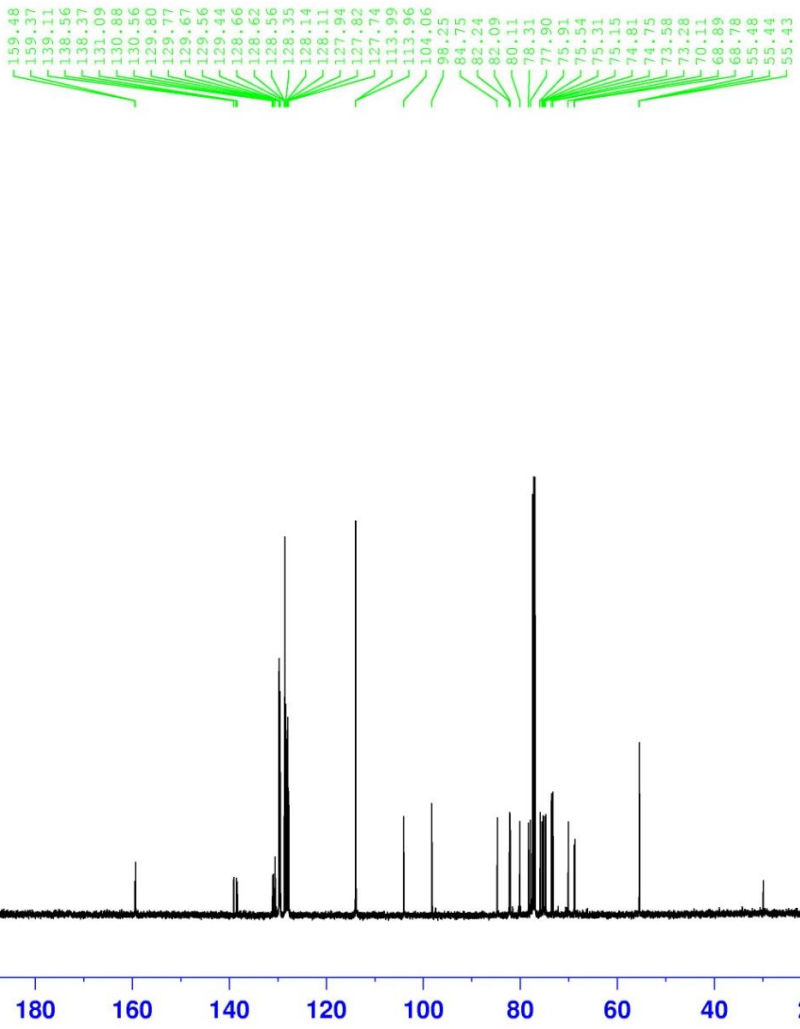

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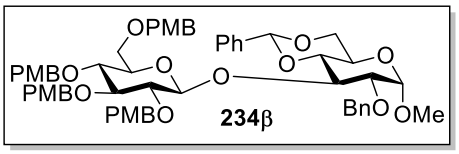

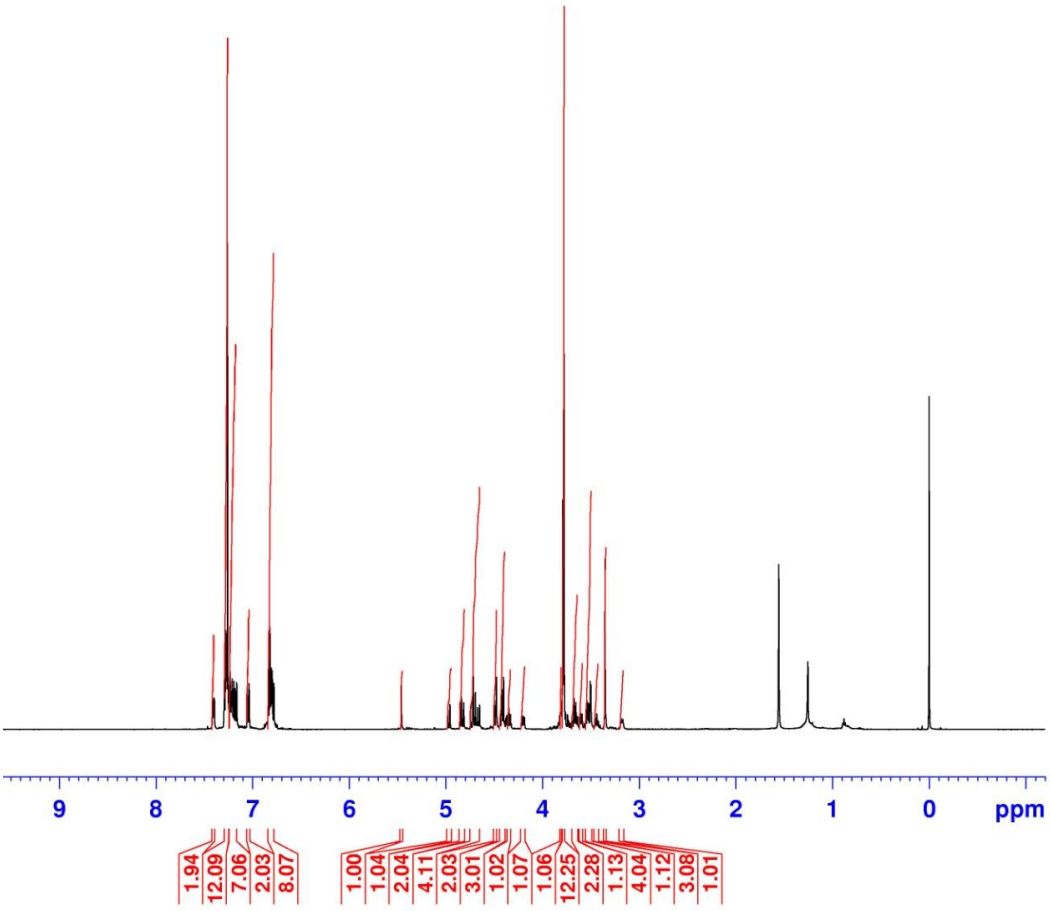

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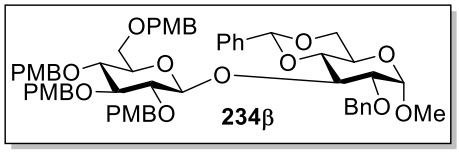

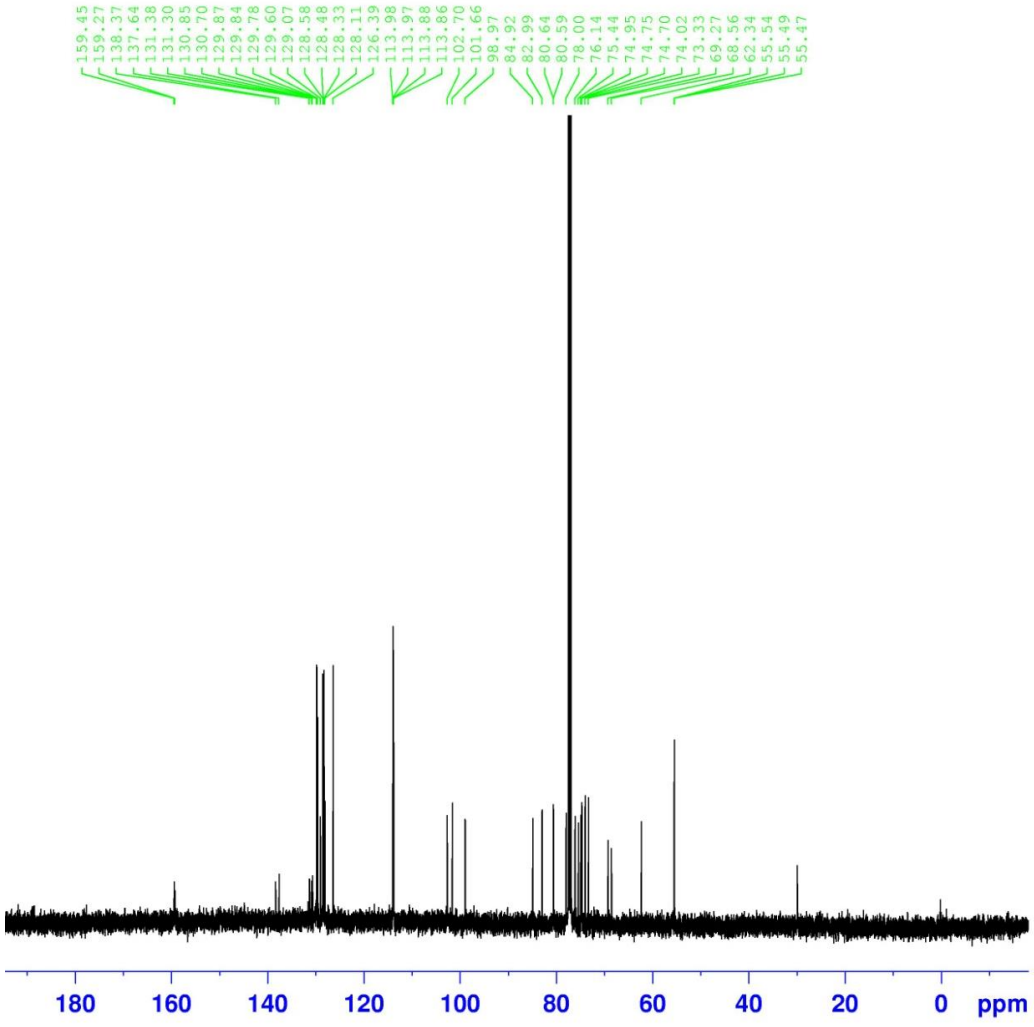

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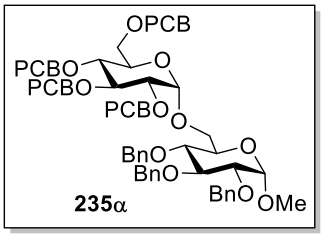
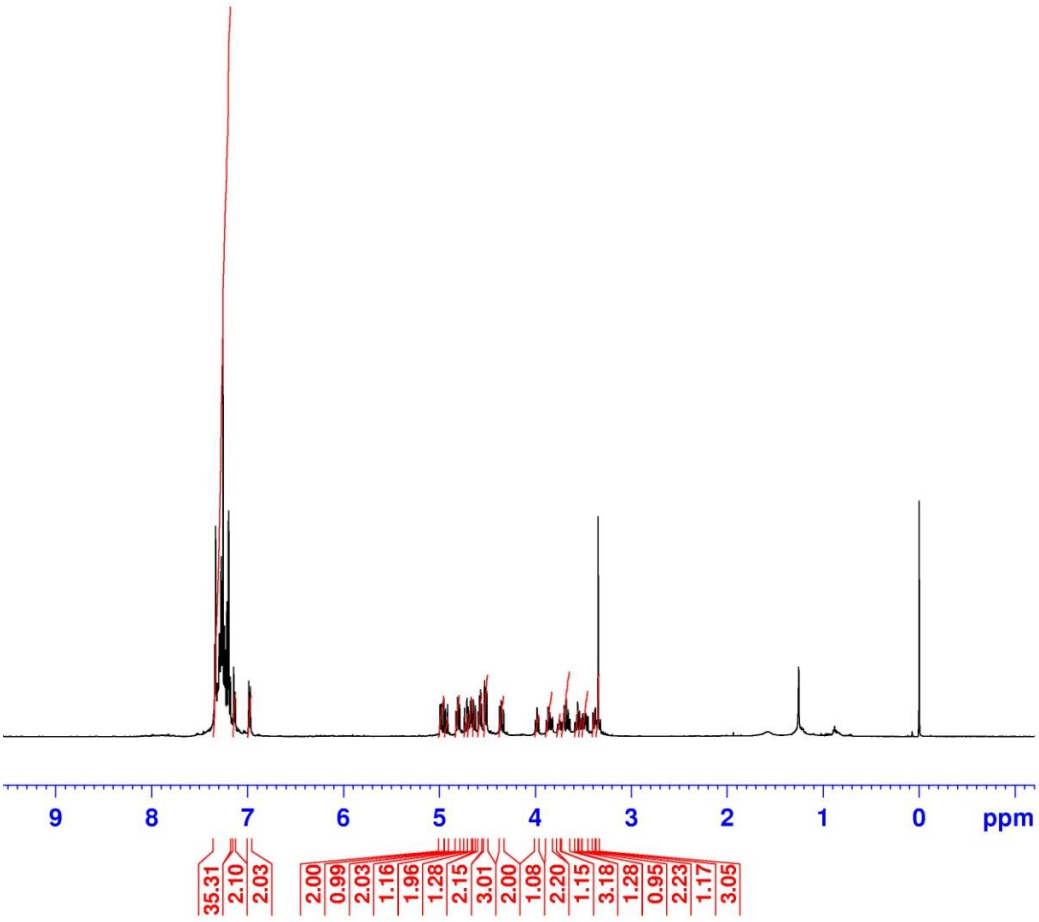
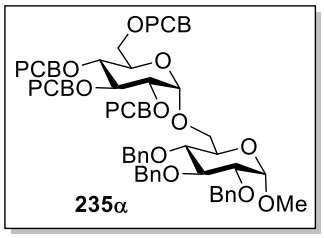
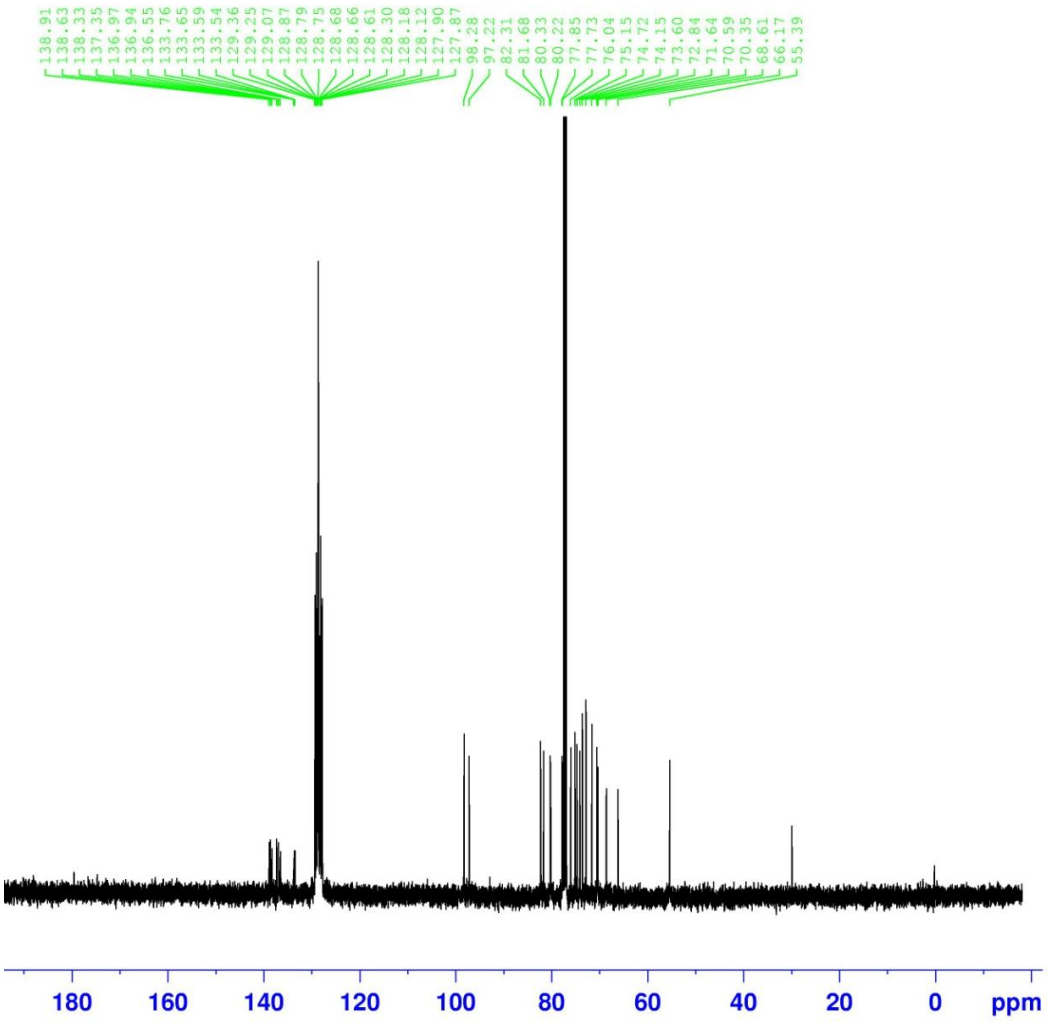




^{13}C NMR (125MHz, $CDCl_3$)





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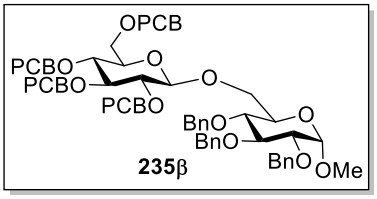
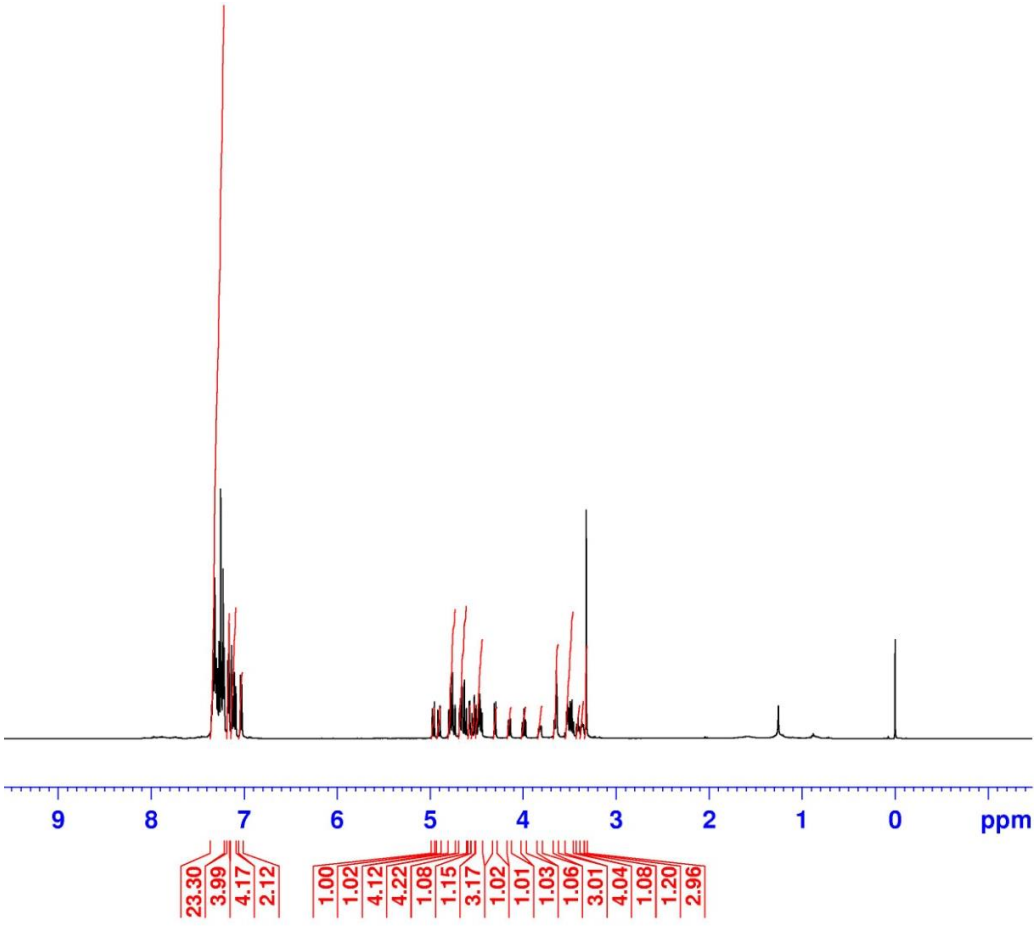
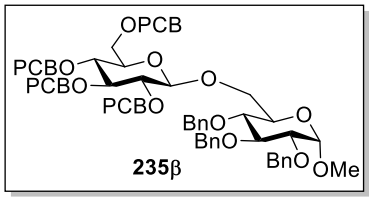
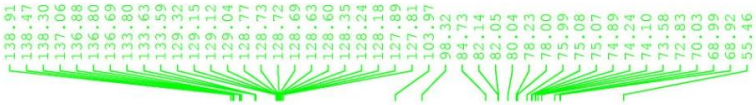
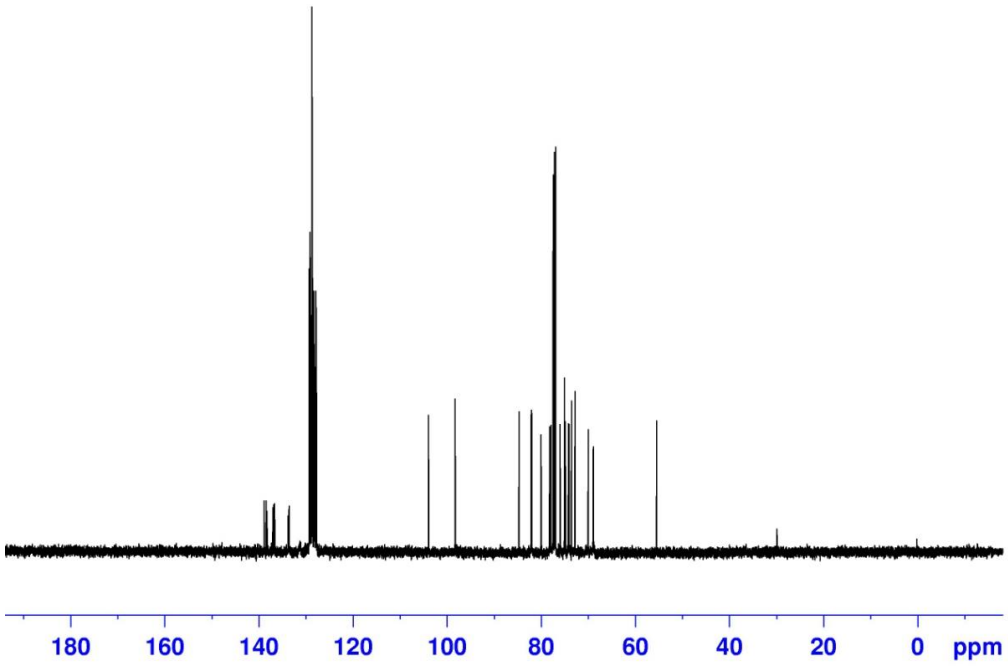




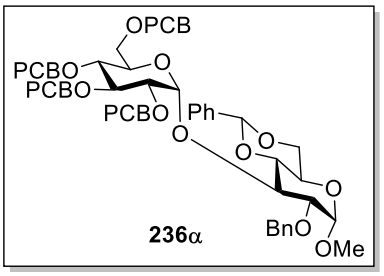
^{13}C NMR (125MHz, $CDCl_3$)



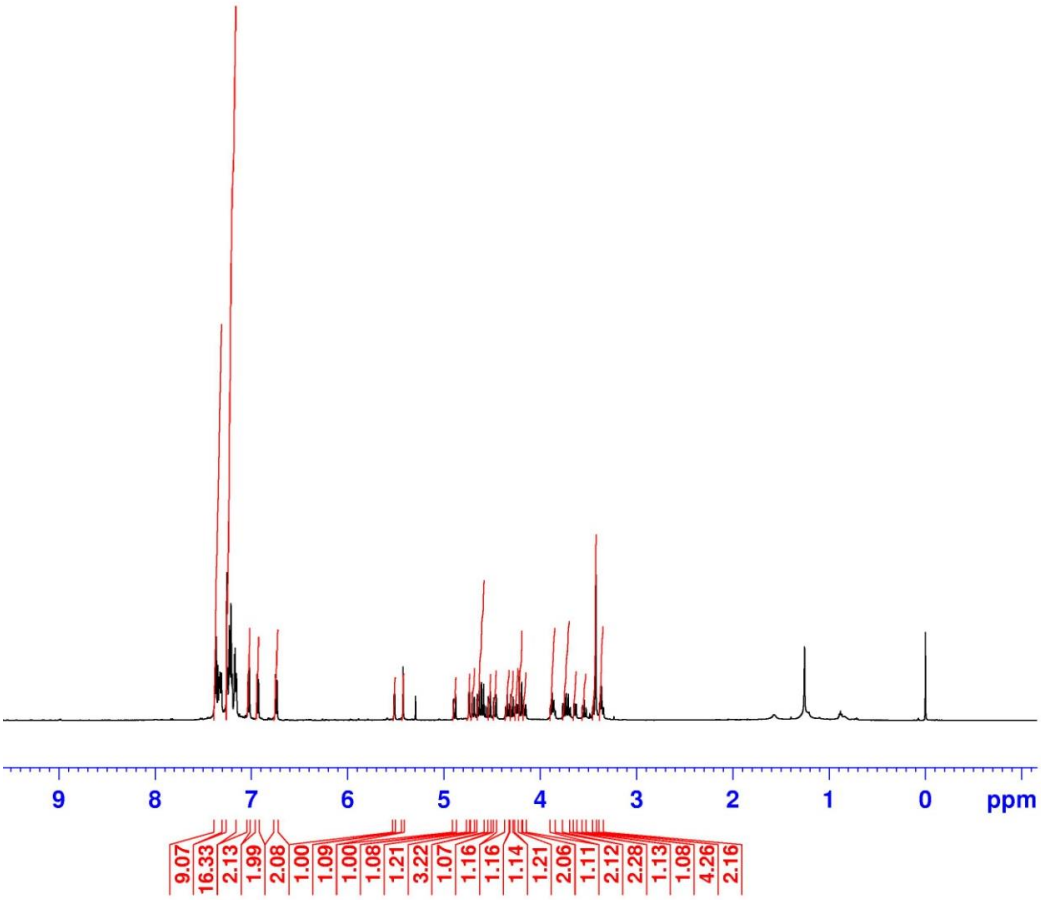




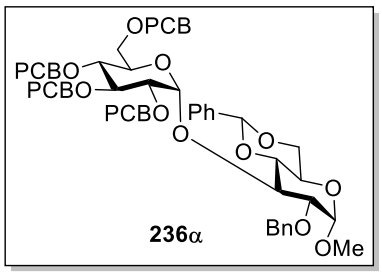
^{1}H NMR (500MHz, $CDCl_3$)

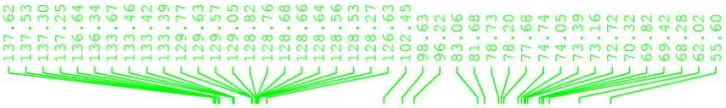


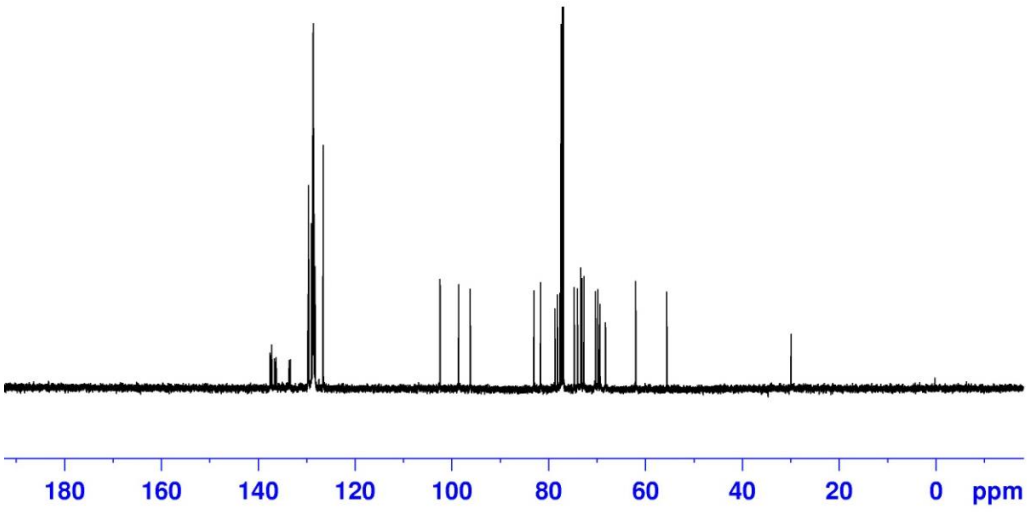
236α



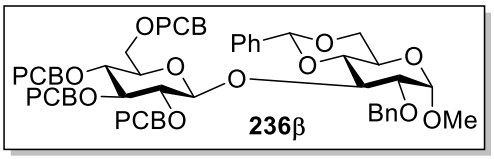
^{13}C NMR (125MHz, $CDCl_3$)



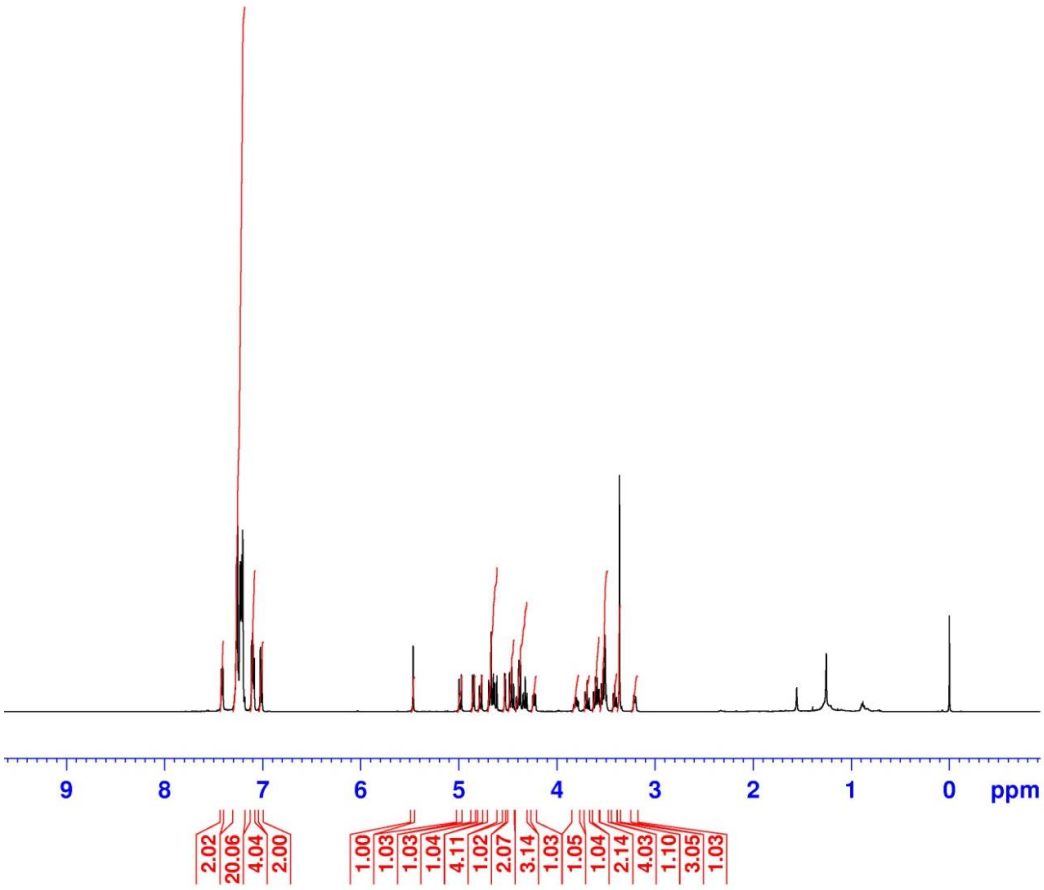




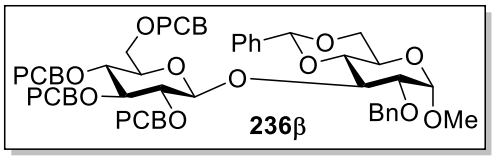
^{1}H NMR (500MHz, $CDCl_3$)

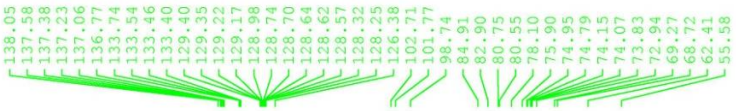


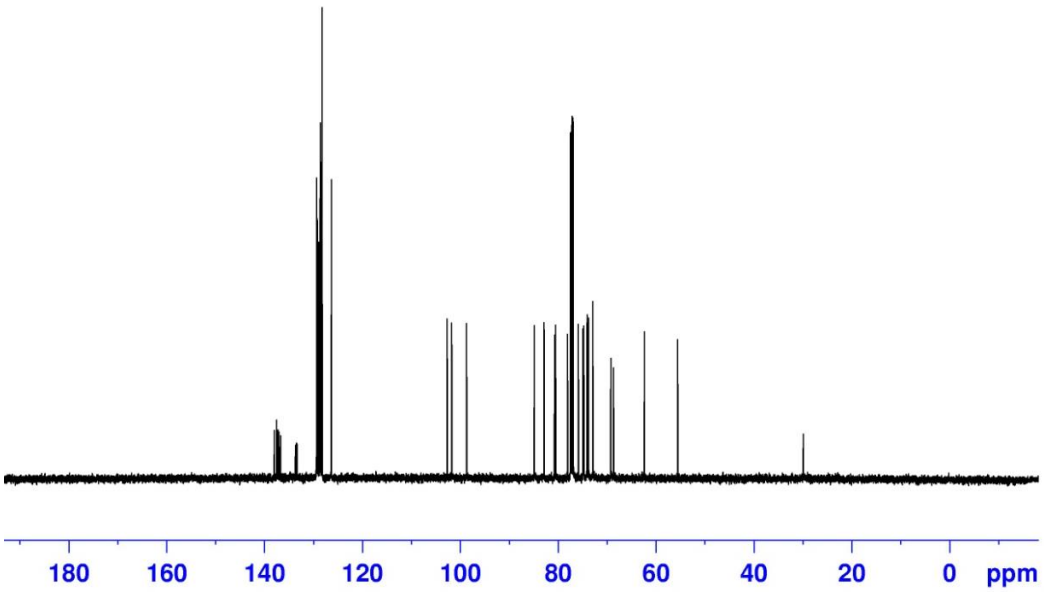
236β



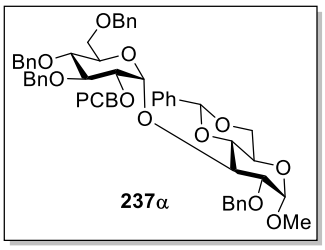
^{13}C NMR (125MHz, $CDCl_3$)

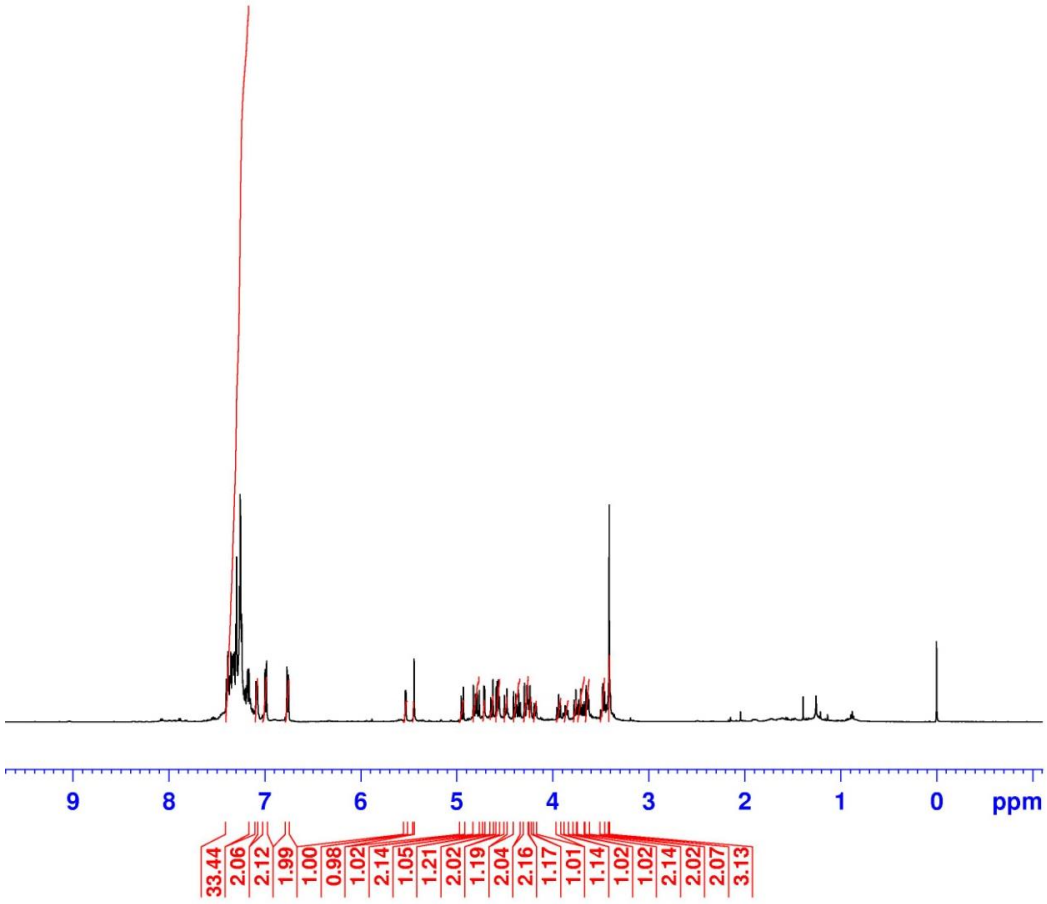




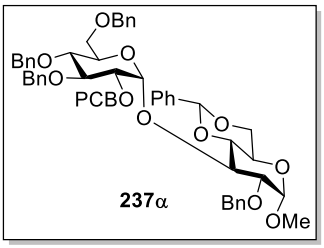


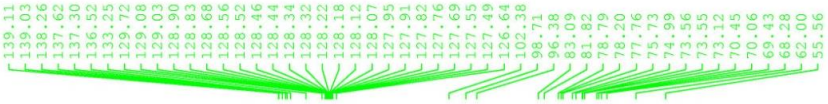
^{1}H NMR (500MHz, $CDCl_3$)

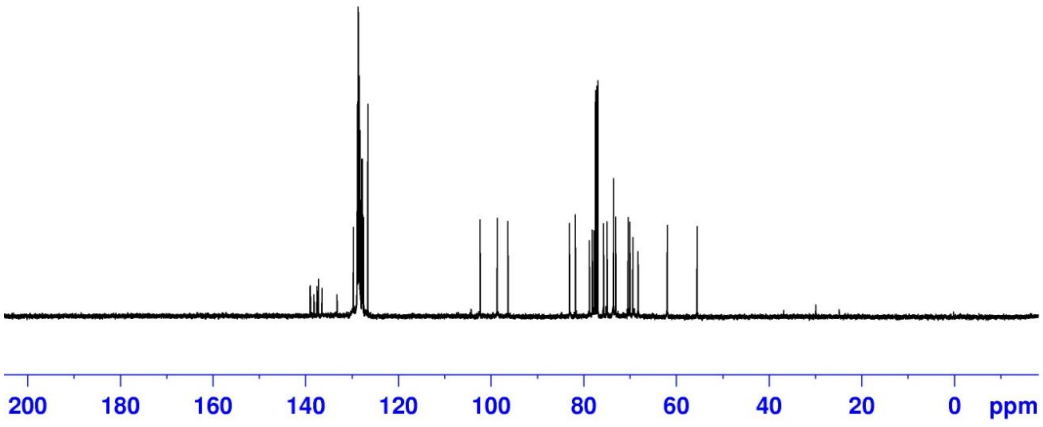




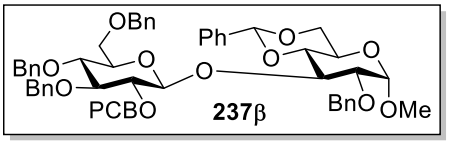
^{13}C NMR (125MHz, $CDCl_3$)

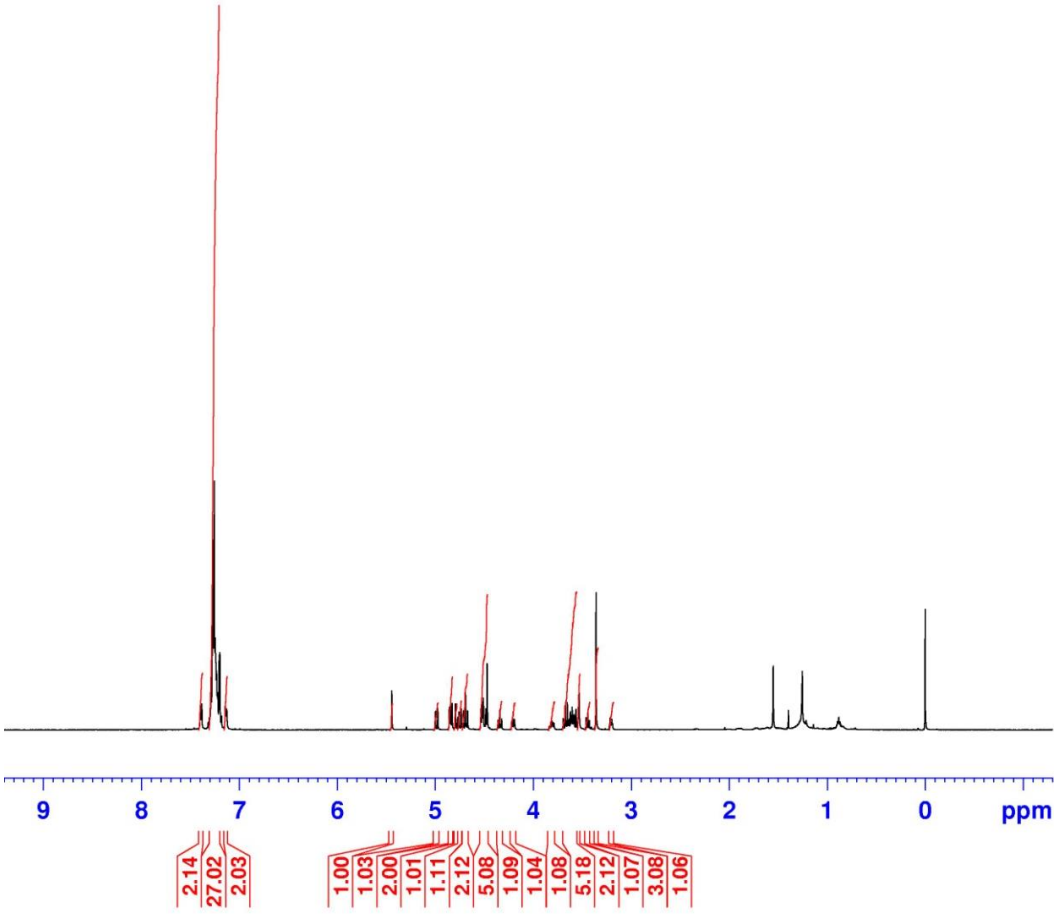




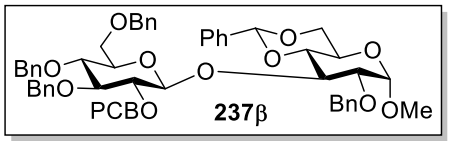


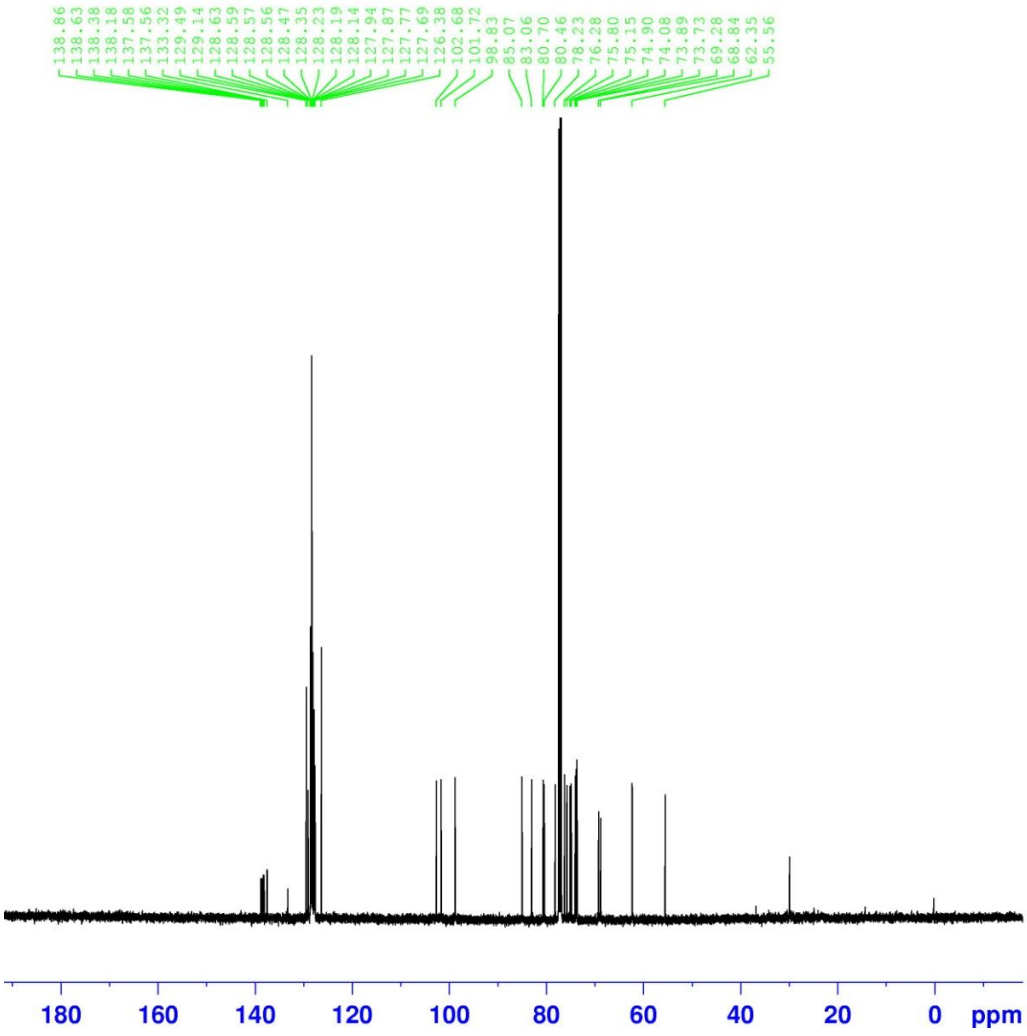
^{1}H NMR (500MHz, $CDCl_3$)



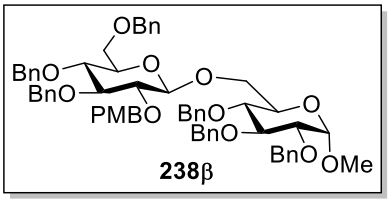


^{13}C NMR (125MHz, $CDCl_3$)

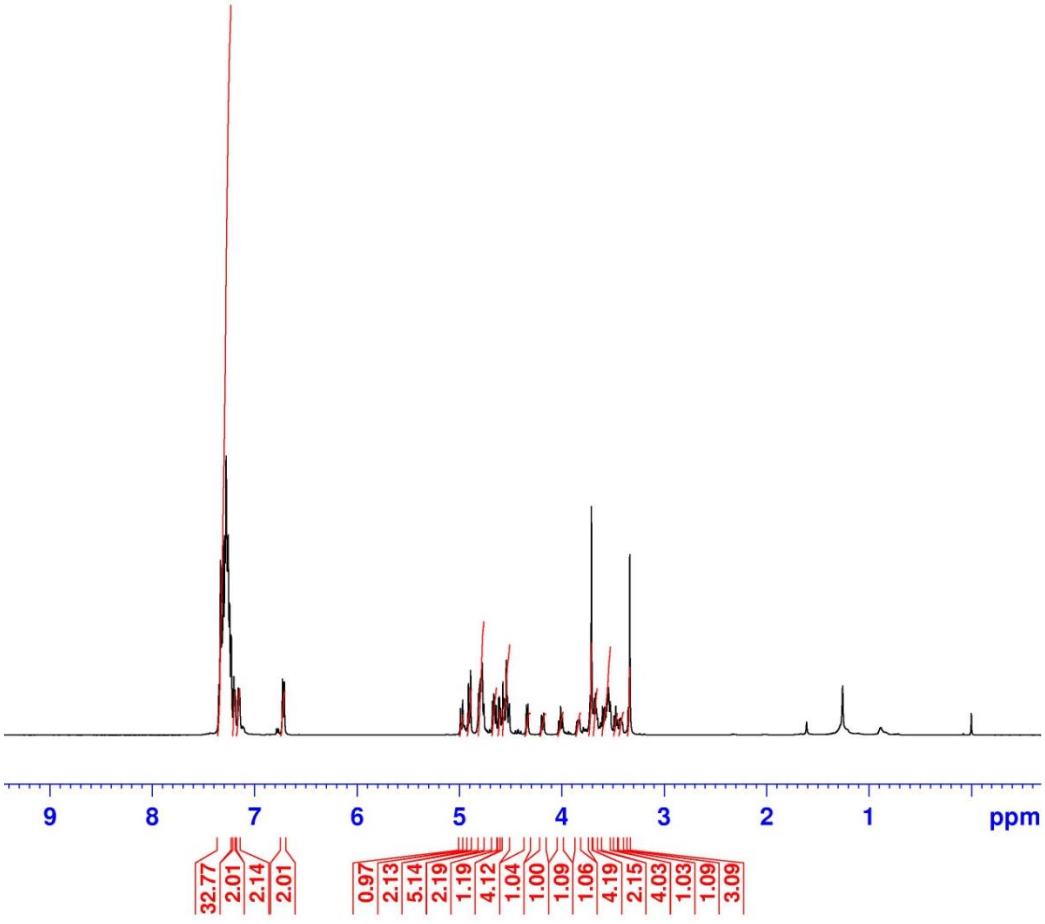




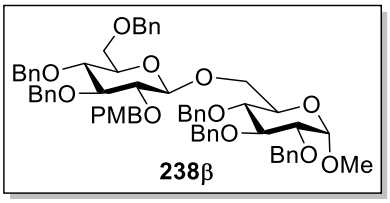
^{1}H NMR (500MHz, $CDCl_3$)



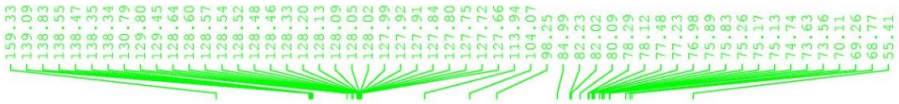
238β

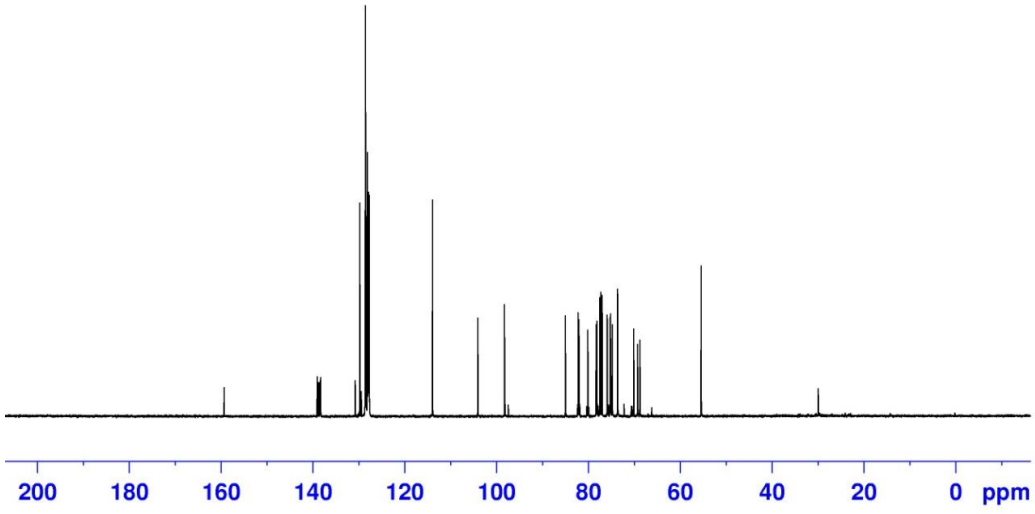


^{13}C NMR (125MHz, $CDCl_3$)

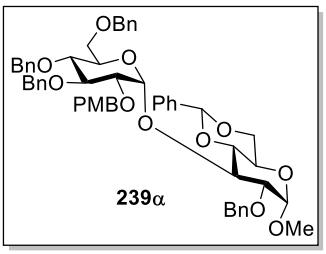


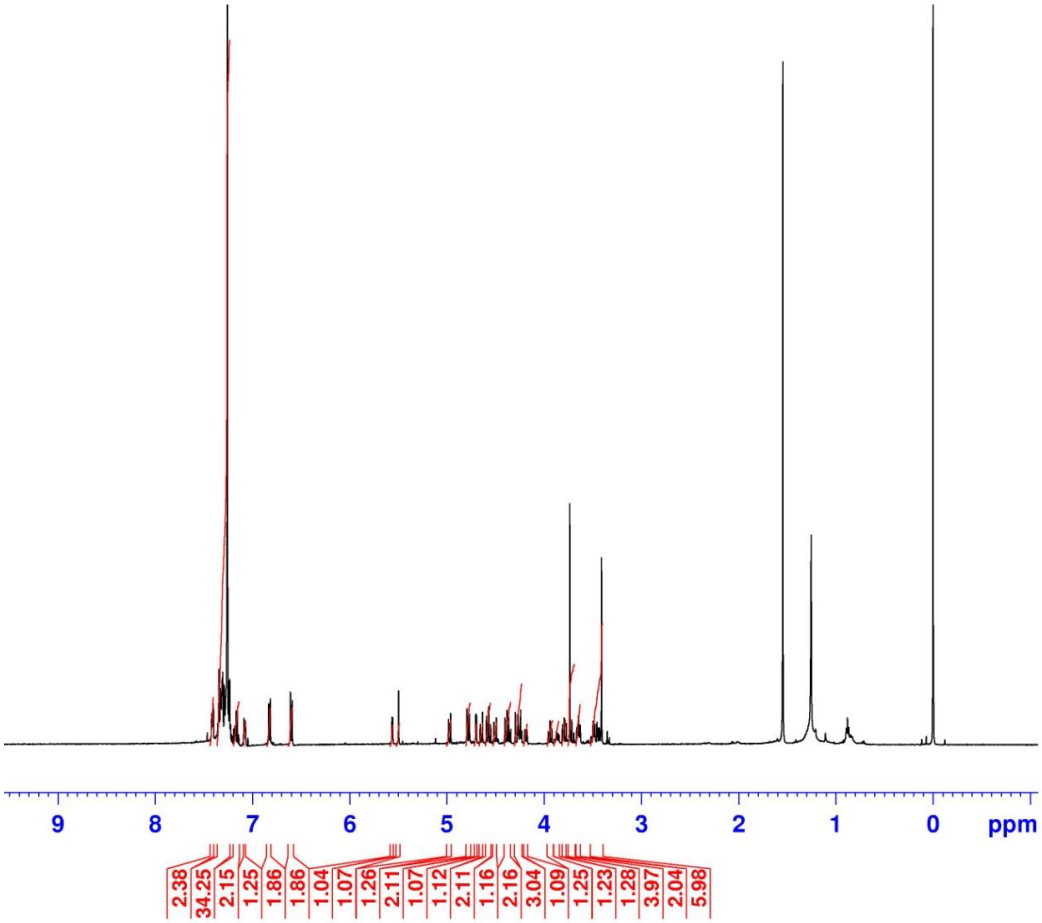
238β



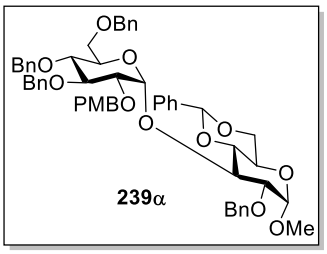


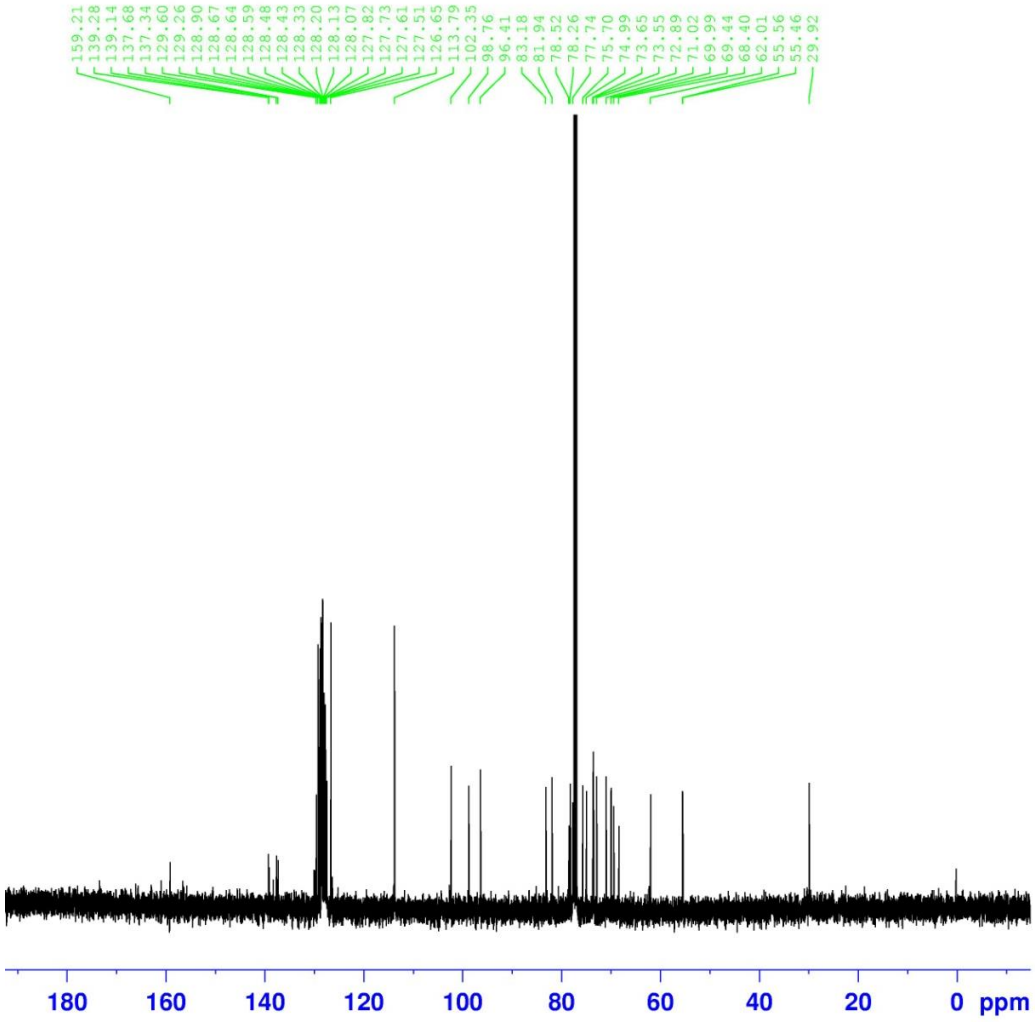
^{1}H NMR (500MHz, $CDCl_3$)



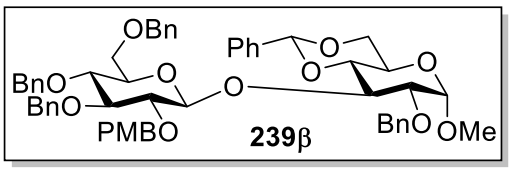


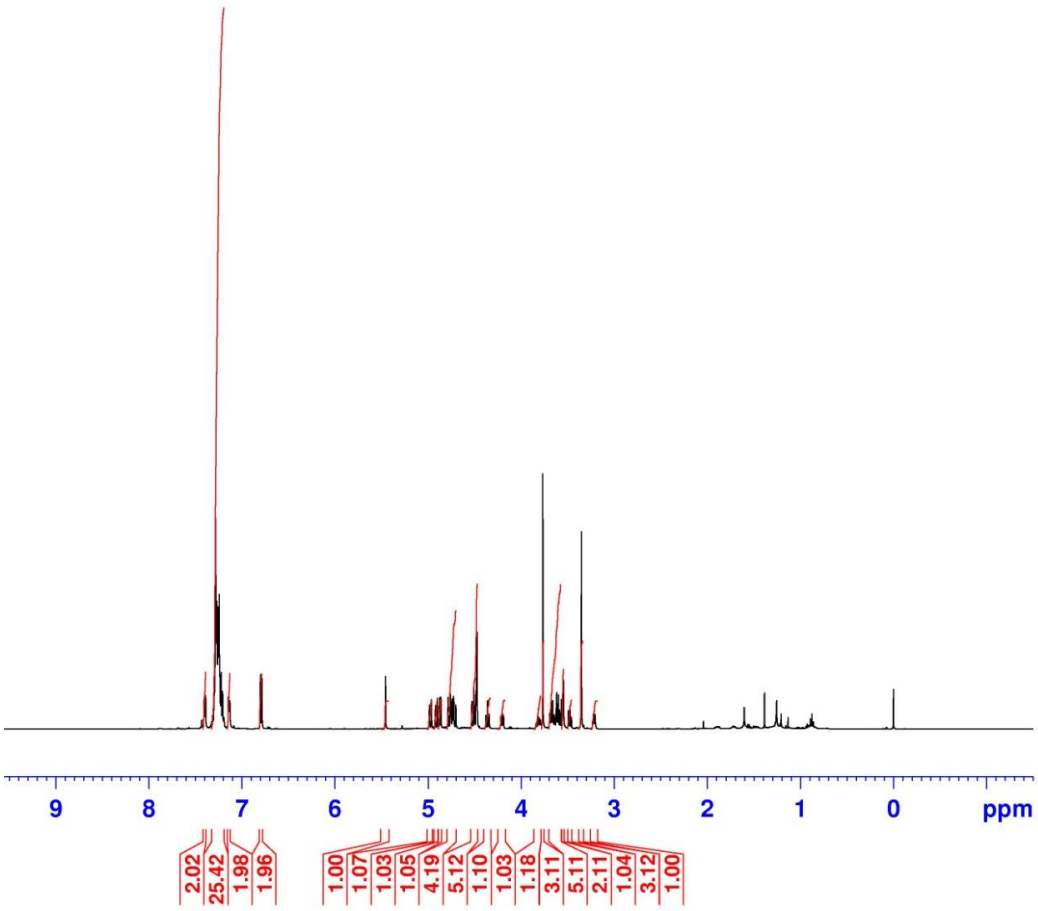
^{13}C NMR (125MHz, $CDCl_3$)



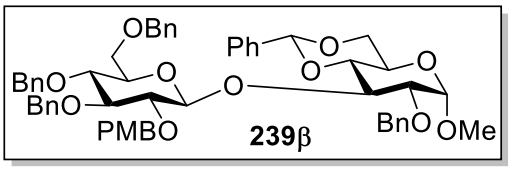


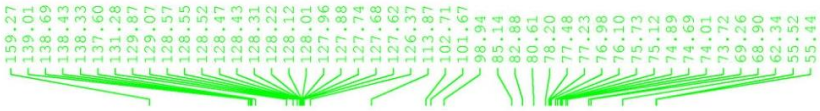
^{1}H NMR (500MHz, $CDCl_3$)

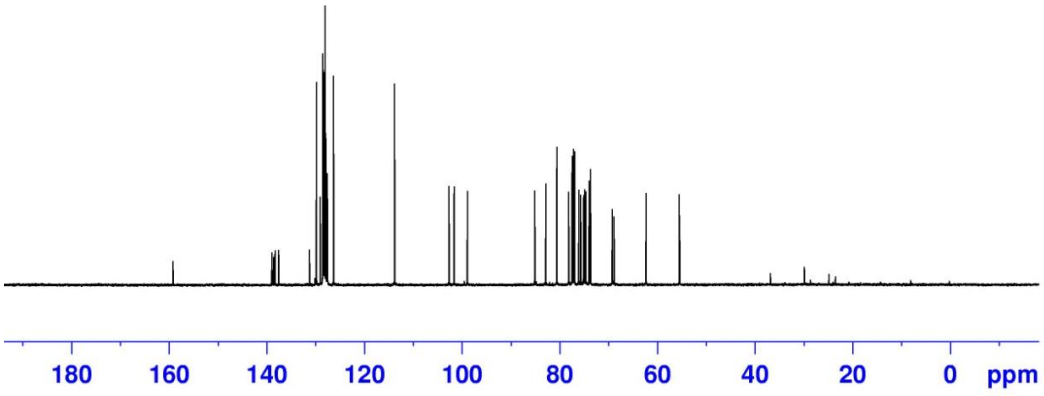




^{13}C NMR (125MHz, $CDCl_3$)







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