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UMI
Synthesis of low-valency Neoglycoconjugates

Using Transition

Metal Catalyzed Reactions

&

Synthesis of Phenylethanoid Glycosides

Joe Nahra

Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
University of Ottawa
in partial fulfillment of the requirements for the
M.Sc. degree in the

Ottawa-Carleton Chemistry Institute
Department of chemistry
University of Ottawa
Ottawa, Ontario CANADA

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0-612-72785-8
To my parents...
Dedications

I would like to dedicate this work to those who had more faith in me than I had in myself

I would like to dedicate this work to my family and my friends

I would like to dedicate this work to the love of my country and especially my wonderful village 'Klayaa'

I would also like to mention on this page the names of dear people to my heart, who never made it to see me graduate, and whom I will never forget as long as I live: my Grand Father Nahra Nahra, my three uncles, Asaad, Ghassan, and Bassam Nahra, and my cousin Carlos Yaacoub
ABSTRACT

In the first part of this thesis, a series of rigid glycodimers were synthesized from sugar alkenes and alkynes, using transition metal catalyzed reactions. The synthesis of these dimers depended on the formation of a new carbon-carbon bond between their monomeric units. Sugars containing terminal alkenes were homodimerized using the olefin metathesis reaction, catalyzed by Grubbs' ruthenium catalyst. Terminal alkene carbohydrate derivatives were also coupled with aryl halide carbohydrates by the Heck coupling reaction, using Pd (0) catalyst, to form homo- and hetero- carbohydrate dimers selectively. Glycodimers were also obtained from sugar alkynes, using the Sonogashira coupling reaction. The dimerization of aryl halide carbohydrate derivatives using Pd (0) catalyst, and the cyclotrimerization of alkyne carbohydrates, using Grubbs' catalyst, were also attempted but were not successful.

In the second part of this thesis, phenylethanoid glycosides were synthesized by glycosidation reactions. This family of compounds was shown to have numerous biological activities. A multi-step synthesis of Echinacoside, a phenylethanoid glycoside, was attempted.
ACKNOWLEDGEMENTS

I would like to thank God for watching over me and for guiding me all the way. I would also like to thank my supervisor Dr. Rene Roy for giving me the opportunity to work with him, for his encouragement, his support, his understanding, and his patience.

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## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetate</td>
</tr>
<tr>
<td>AcCl</td>
<td>Acyl Chloride</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>Cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>CAMD</td>
<td>Computer-aided molecular design</td>
</tr>
<tr>
<td>CM</td>
<td>Cross metathesis</td>
</tr>
<tr>
<td>Con.A</td>
<td>Concanavalin A</td>
</tr>
<tr>
<td>COSY</td>
<td>Shift correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphor sulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublet</td>
</tr>
<tr>
<td>ddd</td>
<td>doublet of doublet of doublet</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>E</td>
<td>entgegen = opposite, stands for trans isomers</td>
</tr>
<tr>
<td>EDC</td>
<td>1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>ELAM</td>
<td>Endothelial leukocyte adhesion molecule</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme linked lectin assays</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast atom bombardment</td>
</tr>
<tr>
<td>Gal</td>
<td>Galactose</td>
</tr>
<tr>
<td>GalNAc</td>
<td>2-amino-2-deoxy-D-Galactose</td>
</tr>
<tr>
<td>GlcNAc</td>
<td>2-amino-2-deoxy-D-Glucose</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
</tbody>
</table>
IR
Infrared

M
Metal

MM
Molecular mechanics

m
Multiplet

Me
Methyl

MeOH
Methanol

MHZ
Megahertz

min
Minutes

mL
Milli Liters

mmol
Milli moles

MO
Molecular orbital

MP
Meting point

MS
Mass spectra

NaOMe
Sodium methoxide

NMR
Nuclear magnetic resonance

ppm
Parts per millions

PTC
Phase transfer catalyzed

r.t.
Room temperature

RCM
Ring-closing metathesis

Rf
Retention factor

ROM
Ring-opening metathesis

ROMP
Ring-opening metathesis polymerization

TBACl
Tetra butyl ammonium chloride

TBAHS
Tetra butyl ammonium hydrogen sulfate

Z
Zusammen = together, stands for cis isomers
CHAPTER I

INTRODUCTION

1.1 Importance of cell surface carbohydrates

Carbohydrates are an essential class of compounds of all living organisms, and are involved in a vast span of activities. They are the main source of energy of living organisms, and they serve as major structural components of cells and tissues. Carbohydrate research has evolved around glycobiology, focusing on cell biology, immunology, bacteriology, virology, and oncology.

The implication of carbohydrates in these areas is not surprising, since cell surface carbohydrates constitute forefront molecules naturally exposed to the surrounding environment. This physiological aspect implicated the cell surface carbohydrates in a wide range of biological processes such as cell-cell recognition, fertilization, embryogenesis, neuronal development, hormonal activities, the proliferation of cells and their organization into specific tissues, viral and bacterial infection, and tumor cell metastasis.

Three major classes of macromolecules, carbohydrates, nucleic acids and proteins are known to carry relevant biological information through their structures. Carbohydrates offer the highest capacity for carrying information because of a distinctive characteristic; the capacity of interconnecting their monomeric units (monosaccharides) at several points, creating linear or highly branched molecules. They can therefore carry much more information per unit weight than either nucleotides or amino acids.

Cell surface carbohydrates, whether they originate from glycoproteins, glycolipids, proteoglycans, glycosaminoglycans, lipopolysaccharides, or capsular polysaccharides (Fig.I.1.1), have been implicated in numerous recognizable interactions. They serve as points of attachment for other cells, toxins, infectious bacteria, and...
mycoplasma, viruses, blood and tumor associated antibodies, as well as a variety of plant and animal lectins (Fig.1.1.2).

Figure 1.1.1: An illustration of a typical cell membrane. The carbohydrate molecules are shown as cyclohexyl polymers attached to lipids and proteins, forming the extra-cellular glycolipids and glycoproteins.
Figure 1.1.2: Illustration of the different extra-cellular interactions occurring through the cell surface carbohydrates.

Adhesion of microbes to host tissues is the key step leading to colonization and subsequent infection. Recognition is mediated by complementary receptor proteins found on pathogen cell membranes. These proteins are called lectins (or hemagglutinins), and they demonstrate exquisite carbohydrate specificity. Some of the cell surface lectin specificities are reported in table 1.1.1.
**Table 1.1.1. Sugar Specificities of Cell Surface Lectins.**

<table>
<thead>
<tr>
<th>Saccharide*</th>
<th>Bacterial/Viral Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Fructose</td>
<td><em>Vibrio cholerae</em></td>
</tr>
<tr>
<td>Lactose</td>
<td><em>Actinomyces spp.</em></td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td>D-Mannose</td>
<td>HIV virus</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td>D-Gal/D-GalNAc</td>
<td>Hepatocytes</td>
</tr>
<tr>
<td></td>
<td>Cholera toxin</td>
</tr>
<tr>
<td>D-GlcNAc</td>
<td>HIV virus</td>
</tr>
<tr>
<td>Sialic Acid (NeuAc)</td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td></td>
<td>Mycoplasma</td>
</tr>
<tr>
<td>Sialyloligosaccharides</td>
<td>Influenza virus (flu)</td>
</tr>
<tr>
<td></td>
<td><em>H. Pylori</em> (gastric ulcer)</td>
</tr>
</tbody>
</table>

* D-Gal = D-galactose; D-GalNAc = N-acetyl-D-galactosamine; D-GlcNAc = N-acetyl-D-glucosamine.

Because of the biological involvement of each cell surface carbohydrate moiety, the design of a suitable glycomimetic inhibitors, having similar or even enhanced binding properties over those of naturally occurring glycoproteins and glycolipids, would have potential applications such as anti-adhesive agents or as cell targeting devices (Fig.1.1.3).
**Figure 1.1.3:** Use of carbohydrates as potential drugs that block bacterial attachment to cell surfaces; (a) Bacterial surface proteins (lectins) attach to carbohydrates on a host's cell surface; (b) A drug formed of similar carbohydrates prevents the attachment of bacteria by binding to the bacterial lectins.

In this thesis, four different monosaccharides with high biological potential constitute the main building blocks of the various synthesized neoglycoconjugates. These carbohydrates are also found in the various glycolipids and glycoproteins of cell surfaces. As listed in figure 1.1.4, those carbohydrates are: \( N \)-acetyl-\( D \) glucosamine (GlcNAc), \( N \)-acetyl-\( D \) galactosamine (GalNAc), \( D \)-galactose (Gal), and lactose.
Figure 1.1.4: Carbohydrates used as building blocks throughout this thesis.
1.2 Multivalency and cluster effect

The recognition of cell-surface carbohydrates by proteins (lectins) represents the basis of many biologically important events. However, intrinsic carbohydrate-protein interactions are usually of low affinity (KD= 0.1-1 mM), unless carbohydrate ligands are organized as multivalent clusters.  

Classical studies by Lee have set the ground for the 'cluster effect', which is defined as an affinity enhancement over and beyond that would be expected from the concentration increase of the determinant sugar in a multivalent ligand. In other words, this effect suggests that both, the number of sugar residues together with its respective propinquity, confer to the glycosylated clusters their important overall binding affinity (avidity).

For that purpose, a large variety of multivalent neoglycoconjugates have been designed (Fig.1.2.1), spanning from low valency clusters to glycopolymers. Low valency neoglycoconjugate ligands (Fig. 1.2.1.c), having enhanced binding properties, are particularly attractive synthetic targets because of their potential biological applications. Their synthetic design consequently requires shape and geometry optimizations through variations of bond length, angles and intra-molecular glycosyl distances to provide improved bindings. This thesis will focus more on the low-valency neoglycoconjugates, especially the homo and hetero glycodimers.
Figure 1.2.1: Structures of some multivalent neoglycoconjugates: a) low-valency glycoconjugate ligands; b) glycopolymers; c) glycodendrimers.
1.3 Glycodendrimers

‘Glycodendrimer’ is a term coined for a carbohydrate dendrimer. The word ‘dendrimer’ itself comes from the Greek words “dendron” which means tree, and “meros” which means part. Therefore these molecules are tree-like and three-dimensional polymers, and they can be prepared by divergent or convergent approaches.

Adopting the strategy of coating carbohydrates on dendritic molecules’ exterior surfaces, the first glycodendrimer based on L-lysine was synthesized by our group in 1993. Afterwards, other glycodendrimers based on L-lysine core bearing N-acetylglucosaminides, α-D mannosides, β-D lactosides, N-acetyllactosaminides, and T-antigens were also prepared in our laboratory. Other types of glycodendrimers based on the different dendritic cores were also synthesized as shown in the following figures (Fig 1.3.1 to Fig 1.3.5).
Figure 1.3.1: Glycodendrimers based on L-lysine dendritic core.
Figure 1.3.2: Glycodendrimers based on gallic acid core and phosphotriester backbone.
Figure 1.3.3: Glycodendrimers based on 3,3’-iminobis(propylamine) core.
Figure 1.3.4: Example of PAMAM glycodendrimers.
Figure 1.3.5: Convergent synthesis of glycosylated dendrimers.
1.4 Glycopolymers

Some of the interesting types of the high-valency neoglycoconjugates are the glycopolymers. They are cheap and easy to prepare in large quantities, and they can be constructed with a wide range of molecular weights, and a variety of desired carbohydrate densities and functionalities. They are also more stable at a wide pH range and microbial degradation. Most importantly, they have been shown to be non-toxic, as well as poorly or non-immunogenic.

Although there are many strategies for the preparation of glycopolymers, most of them are generally prepared in two ways: copolymerization and grafting polymerization.

The early glycopolymers were made from allyl glycosides through copolymerization (Fig 1.4.1) with acrylamide, using persulfate as a radical initiator. However, the ratio of applied and incorporated quantities of the monomers can vary significantly, because the reactivity ratio between carbohydrate-containing monomers and acrylamide is quite different in the polymerization process. An improved strategy was achieved by using carbohydrate derivatives, which contained N-acryloylated groups in the aglycon portions. Both monomers have similar reactivities in the chain reaction process. Consequently, the incorporated monomers’ ratio within the glycomer is almost identical to the ratio of the monomers added to the reaction.

Grafting polymerization (Fig 1.4.1) is the other elegant approach used for the synthesis of glycopolymers with a predictable composition. Thus, the desired carbohydrate haptens can be directly incorporated into pre-formed polymers bearing reactive functionalities. Using this approach, the most common products are obtained by reacting amine-containing carbohydrates with active esters of polyacrylates, such as poly(4-nitrophenyl acrylate) and poly(N-oxysuccinimidyl acrylate). One of the major advantages of this approach is that pre-formed active polymers can be synthesized with the desired molecular weights. Therefore, the grafting polymerization approach can eliminate inconsistencies in molecular weights, which often occurred with the previous approach. Furthermore, the desired carbohydrate content in glycopolymers can be easily achieved by controlling the initial ratio of carbohydrate haptens and pre-formed active polymers.
Figure 1.4.1: Two synthetic strategies to obtain glycopolymers.
1.5 Glycodimers

We have seen so far the effect of multivalency on the increase in the affinity of the carbohydrate-protein interactions. We can also safely say that the high-valency neoglycoconjugates, such as glycodendrimers and glycopolymers, are highly potent inhibitors, and therefore ideally should have a great potential as antiadhesive agents. However in a realistic world, one has to consider all the related factors and limitations that accompany a great strategy. Beside the obvious heterogeneity of their valency and their random distribution, the high-valency neoglycoconjugates can trigger unwanted antibody formation, and in the case of liposomes can be incorporated unspecifically into cell membranes. As a result, their potential therapeutic ability as inhibitors is rather limited. This, along other reasons discussed later in this chapter, has built the driving force that shifted our focus toward the low-valency family, especially the dimers.

1.5.1 Signal transduction

Biological phenomena are based on chemical transformations, and they depend on the structure and interaction of the molecules involved. In principle, most biological processes can be reduced to chemical ones. Many biological phenomena, such as biological signal transduction, have been intensively investigated and analyzed. The increasingly important field of structural biology has become more prominent on the horizon of organic chemistry. Non-covalent interactions between large natural molecules, which are able to determine processes such as protein-protein and protein-DNA interactions, as well as recognition phenomena at cell surfaces, are the focus of “supramolecular chemistry”.

Multicellular organisms maintain functional and survival capacity by ensuring that the growth, differentiation, and metabolism of a large number of cells are coordinated via synthesis, secretion and recognition of signal molecules. Once the signal has been conveyed through the plasma membrane of the target cell, the message is relayed into the cell interior via intracellular signal cascades.
Only recently, however, has it become clear how transmembrane receptors can turn extracellular binding events into an intracellular signal. Results obtained during recent years have given ample evidence that such receptors often are activated by ligand-induced dimerization and oligomerization.  

**Figure 1.5.1:** Models of receptor subclass-specific variations of the mechanism of activation by dimerization; receptor activation may occur by binding of monomeric ligands resulting in a conformational change of the extracellular domain and dimer formation (subclass I), by interaction of the ligand with a disulfide-stabilized receptor dimer and subsequent intracomplex conformational change (subclass II), or by mediation of dimer formation through a dimeric ligand (subclass III).

The use of the proper homo or hetero dimer ligand will help dimerize the target receptor (Fig.1.5.1). This effect could be easily explained by comparing the relatively faster intramolecular reactions versus their corresponding intermolecular ones. Also from
the kinetic point of view, a dimer binding to both active sites of a divalent receptor will conserve more energy and minimize the loss of entropy, than when two monomers bind to the same receptor.

Many examples in the literature have supported this theory. In our group, relative building properties of di-, tri-, and tetra-antennary α-D mannopyranosides clusters were determined by turbidimetric and solid phase enzyme linked lectin assays (ELISA). This was accomplished using two plant lectins (phytohemagglutinins), Concanavalin A (Con A) and pisum salivum (pea lectin), which contain four and two carbohydrate binding sites respectively.21

The results of these assays showed a much higher inhibition in the binding of these bacterial lectins to the yeast mannan, hence explaining the resulting cross linkage of the various lectins in this study. Dimers were shown to be 4 to 8 fold more potent than their respective monomers.

Chi-Huey Wong et al have prepared several sialyl Lewis X dimers anchored onto a galactose template, or attached to 1,4-butanediol or 1,5-pentanediol. They also have proved that the bivalent sialyl Lewis X derivatives acted in about five fold better than their respective monomers, as inhibitors of the glycoprotein E-selection (formerly called endothelial leukocyte adhesion molecule-1 or ELAM-1).22

Jochen Lehman and his coworkers used the haemagglutination assay to study the binding affinity of mono-, di-, and tri-antennary α-D-mannopyranosyl derivatives against Con A. They found that higher affinity and stronger cross-linking were obtained between dimers and trimers of α-D mannopyranosyl derivatives vs their respective monomers.23

As mentioned previously, these carbohydrates are classified as substrates to various extracellular receptors. According to the above studies, their dimers, and especially the ones with the right geometry, should be more efficient in triggering and activating their intracellular receptors. This becomes a potential way of targeting specific receptors on specific cells, therefore activating specific signals. Based on the growing list of these examples, our work in this thesis focused on synthesizing low-valency neoglyconjugates such as dimers, trimers and up to hexamers with different spacer lengths, using carbohydrates with great biological potential as building blocks.
1.5.2 Sugar rods

Taking the binding affinity and the specificity in consideration, the geometry of the synthesized glycoclusters in general, and glycodimers specifically, remains a big concern. Occupying the right place of the active site of the receptor is important. Recently, it has become more critical to find a dimer with the right length and flexibility, that can bind to both sites of the same receptor. This would allow the receptor to dimerize, triggering a signal cascade.

Recently, our group has been constructing semi-rigid sugar dimers, known as a sugar rod. Like many other chemists, we developed a great interest in the rigid-rod molecules. Our interest in this class of molecules was based on two distinct aspects, among many others, that these molecules possess: 1) their physical properties are fascinating. They are formed in a well defined and optimized geometry, and their relative rigidity as spacers in dimer or oligomer molecules conserves the energy of these molecules, and minimizes the loss of entropy once these molecules bind to a receptor or an active site of some kind; 2) they constitute some of the best and most well-defined spacers, and they are considered construction elements in giant molecules and supramolecular assemblies. The rod itself consists of a small number of rigidly connected and axially aligned smaller structural units, called “modules”, at a lower level in the hierarchy of structures.

**Spacers and wires.** Molecular rods offer the opportunity to position two active centers at a known distance apart, and connect them by a medium whose properties can be controlled at least to some degree. The degree of interaction between the centers can be studied by a variety of tools, and provides information about the electronic structure of the rod and about the coupling of the centers to the rod, ultimately contributing to the theory of chemical bonding. It often falls off exponentially with the rod length.

Electronic interaction between the active centers through the molecular rod can be probed by photoelectron spectroscopy and electron transmission spectroscopy, whose simplified interpretation in terms of Koopmans’ theorem provides information about orbital energy splittings that result from the interaction through the rod. Weaker
interactions can be probed by examination of energy or electron transfer between the centers. This transcends the use of the rods as mere spacers and brings us to consider them as photonic, electronic, or ionic wires, which mediate the directional motion of electronic excitation energy, an electron, a proton, or another ion from one active center to the other.

Construction Elements. The construction of complex structures is often easiest with straight beams, hence the need for molecular rods since nature rarely builds with straight beams. The use of molecular rods as construction elements depends critically on our ability to adjust the length of the rod to a desired value, in order to attach the desired terminal or possibly lateral connectors, and to secure sufficient rigidity. In contrast to what would be expected, molecular “rigid” rods are not rigid at all but are highly flexible, even though their equilibrium structure may be linear. At room temperature, even quite short rods bend and flex vigorously, and should be thought of as rubber sticks rather than steel rods. Long rods, many nanometers in length should be thought of as boiled rather than raw spaghetti. To increase the rigidity, it may be possible to bundle the rods, although the rigidity issue is likely to complicate the construction of structures that use rods longer than 2-3 nm. The structures assembled so far have been mostly free-floating in solution. This would be acceptable in some applications, such as rod-based racks used to force a particular conformation on a flexible chain attached to rack ends, or on artificial enzymes in which functional groups have been adjusted into controlled locations by attachment to a scaffold and not in others. By the same means, sugar-rods have been synthesized as potential cell targeting devices or anti-adhesive agents.

Axial rods exist in two types, singly or doubly linked. In the singly linked axial rods, each link connects a pair of atoms on adjacent molecules by a single bond along the rod axis, permitting a more or less free rotation. Synthesizing such sugar rods will be ideal for the biological use in the binding to multivalent receptors in general, and divalent receptors more specifically. These structures will have a well-defined length, and their geometry will be associated with both rigidity and flexibility at the same time.

The preparation of sugar-rods with predetermined lengths represents a considerable synthetic challenge, although as it is shown later in this thesis, the use of
transition metal mediated reactions has made their synthesis a much easier task to handle. As a contribution to this field, the following types of sugar-rods (Fig 1.5.1) were synthesized in order to study their physical and biological properties.

\[ R_1 \equiv \equiv \equiv R_2 \]

\[ R_1 - \text{phenyl} \equiv \equiv R_2 \]

\[ R_1 - \text{phenyl} \equiv \equiv \text{phenyl} - R_2 \]

\[ R_1 - \text{phenyl} - \equiv \equiv - R_2 \]

\[ R_1 - \text{phenyl} - \equiv \equiv - \text{phenyl} - R_2 \]

\[ R_1 - \text{phenyl} - \equiv \equiv - \text{phenyl} - \equiv \equiv - R_2 \]

\[ R_1 - \text{phenyl} - \equiv \equiv - \text{phenyl} - \equiv \equiv - \text{phenyl} - R_2 \]

\[ R_1 - \text{phenyl} - \equiv \equiv - \text{phenyl} - \equiv \equiv - \text{phenyl} - \equiv \equiv - R_2 \]

\[ R_1 - \text{phenyl} - \equiv \equiv - \text{phenyl} - \equiv \equiv - \text{phenyl} - \equiv \equiv - \text{phenyl} - R_2 \]

\[ R_1, R_2 = \text{Sugar moiety} \]

**Figure 1.1.5:** Various sugar-rod neoglyconjugates.
1.6 References

18. This situation is also demonstrated in diverse new journals on subjects such as “Nature – Structural Biology”, “Structure”, etc.
CHAPTER II

SYNTHESIS OF NEOGLYCOCONJUGATES USING TRANSITION METAL CATALYZED REACTIONS.

2.1 Olefin metathesis

INTRODUCTION

Organic synthesis depends tremendously on reactions that can reliably and efficiently form carbon-carbon bonds. One of these reactions is olefin metathesis. It is a transition metal catalyzed reaction in which formally or mutually, exchange of alkylidene groups between two substituted alkenes occurs. The term 'olefin metathesis', which defines the metal catalyzed redistribution of carbon-carbon double bonds, was coined by Calderon and co-workers in 1967. This simple but efficient procedure does not require the use of any additional reagents except for a catalytic amount of metal carbone. The only by-product obtained by this reaction is a volatile ethylene gas.

\[
\begin{align*}
\text{Catalyst} &
\end{align*}
\]

Olefin metathesis can be mainly used in three different applications (Figure 2.1.1): (a) Cross metathesis (CM) in which two different alkenes undergo an intermolecular transformation to form a new olefinic product; (b) Ring-closing (RCM) and ring-opening metathesis (ROM), which are useful for the formation and opening of cyclic compounds; (c) Ring opening metathesis polymerization (ROMP) which form functionalized polymers by the metathetic opening of strained cyclic olefins.¹
Figure 2.1.1: A variety of olefin metathesis reactions.

These metathesis reactions undergo a generally accepted mechanism, the "Chauvin Mechanism" (Figure 2.1.2). It consists of a sequence of formal [2+2] cycloadditions/cycloreversions involving alkenes, metal carbenes, and metallacyclobutane intermediates. In one possible pathway, initial metathesis of metal alkylidene (4) with terminal olefin (1) provides metallacyclobutane (5). Fragmentation of the metallacyclobutane (5) can then provide ethylene gas and a new metal alkylidene (6). Regio- and stereoselective reaction of the metal alkylidene (6) with terminal olefin (2) provides metallacyclobutane (7), which upon cycloreversion, produces the disubstituted product (3) and the initial alkylidene (4).
Chauvin mechanism:

Figure 2.1.2: Chauvin mechanism for cross-metathesis.

The first generation of metathesis catalysts exhibits the characteristics of "mixed" Ziegler catalysts. These systems consist of transition metal salts combined with main group alkylating agents, or deposited on solid supports. Some of the classic combinations include WCl₆·Bu₄Sn, WOCl₆·EtAlCl₂, MoO₃/SiO₂, and Ke₅O₇-Al₂O₃, among many others. These catalysts show high activity at the expense of a poor compatibility with polar functional groups, due to a strong Lewis-acid and alkylating character. The other
established catalyst is dichlorobis(2,6-dibromophenoxy)oxotungsten, \( \text{Cl}_2(\text{ArO})_2\text{W}=0 \). Although this system shows good functional group tolerance, it is considered to be unsuitable for industrial applications due to its complexity and cost.

The discovery of metal alkylidene complexes, and the insight that some species of this type constitute well-behaved single-component catalysts for olefin metathesis, triggered the development of a new generation of high-performance, reasonably stable, and most importantly, exceedingly tolerant catalysts or catalyst precursors.

Olefin metathesis started receiving more attention when Basset and co-workers developed and applied the tungsten catalysts 8 and 9 (Figure 2.1.3) for cross-metathesis reactions. To date, these have been successfully shown to be remarkably tolerant to heteroatoms, including sulfur, silicon, phosphorus, and tin. Unfortunately, the use of these catalysts was limited because of their steric demand toward shorter alkenes, such as allyl groups. This has pushed researchers to maintain their search for alternative catalytic systems for olefin metathesis reactions.

One of the very useful and highly active catalysts for olefin metathesis reactions was the molybdenum catalyst 10 (Figure 2.1.3) developed by Schrock et al. although its high activity is accompanied by a lack of functional group tolerance, and the requirement for rigorously purified and dried substrates and solvents. The high oxophilicity of the metal center renders this catalyst sensitive to oxygen and moisture. Molybdenum catalyst 10 is also difficult to synthesize and its shelf life is limited due to its thermal instability.

![Figure 2.1.3: Tungsten catalysts 8 and 9, developed by Basset and co-workers. Molybdenum catalyst 10, developed by Shrock et al.](image-url)
As the basic research in organometallics continued, Grubbs and co-workers introduced the most popular ruthenium carbene complexes 11, 12, 13, 14 and 15 (Figure 2.1.4). These catalysts showed impressive tolerance to air, moisture, and various functional groups.

![Chemical structures of complexes 11, 12, 13, 14, and 15]

**Figure 2.1.4:** Ruthenium catalysts developed by Grubbs and co-workers.

The advent of single-component catalysts allowed the relationship between structure and reactivity to be more clearly defined. These catalysts were observed to react more selectively with olefins as the metal centers were varied from left to right, and bottom to top on the periodical table. Farthest to the left, titanium and tungsten catalysts are most strongly disposed to olefinate ketones and esters (Table 2.1.1). In comparison, molybdenum catalysts are more reactive toward olefins, although they also react with aldehydes and other polar and protic groups. Farthest to the right, ruthenium reacts preferentially with carbon-carbon double bonds over most other functional groups, which makes these catalysts unusually stable toward alcohols, amides, aldehydes, and carboxylic acids.
Table 2.1.1: Illustration of functional groups tolerance of early and late transition metal olefin metathesis catalysts.  

<table>
<thead>
<tr>
<th>Titanium</th>
<th>Tungsten</th>
<th>Molybdenum</th>
<th>Ruthenium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acids</td>
<td>Acids</td>
<td>Acids</td>
<td>Olefins</td>
</tr>
<tr>
<td>Alcohol, Water</td>
<td>Alcohol, Water</td>
<td>Alcohol, Water</td>
<td>Acids</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>Aldehydes</td>
<td>Aldehydes</td>
<td>Aldehydes</td>
</tr>
<tr>
<td>Ketones</td>
<td>Ketones</td>
<td>Olefins</td>
<td>Ketones</td>
</tr>
<tr>
<td>Esters, Amides</td>
<td>Olefins</td>
<td>Esters, Amides</td>
<td>Esters, Amides</td>
</tr>
</tbody>
</table>

Increasing Reactivity

In this thesis, crossed olefin metathesis reactions were performed on allylic carbohydrate derivatives to obtain the respective homodimers. However, carbohydrates contain a variety of functional groups, such as hydroxy, ethers, esters, and even carboxylic acids and amides. Taking that into consideration, commercially available ruthenium catalyst 12 became the primary choice of catalyst for the olefin metathesis reactions involving our carbohydrate compounds. In the early stage of this thesis, only catalyst 12 was commercially available. Toward the end of this work, the second-generation Grubbs' catalyst 15 became commercially available. This more efficient catalyst, in comparison with ruthenium catalyst 12, was therefore used to increase the yields of the more challenging olefin metathesis reactions.

Development in catalyst design

In retrospect, ruthenium was an excellent metal center, but it was not seriously considered for more than two decades of research. Several reports from the 1960's described the ROMP of norbornene derivatives with RuCl₃(hydrate) in refluxing ethanol and under aqueous emulsion conditions. Unexpectedly, the long initiation periods (20 hrs or more) of ROMP with RuCl₃ (hydrate) in organic solvents were improved to a much faster initiation (30 min) in aqueous solution, which led to the synthesis of Ru(H₂O)₆(tos)₂ [tos = p-toluenesulfonate]. This catalyst was able to ROMP functionalized
norbornene, 7-oxanorbornene, and norbornadiene monomers, including hydroxyl-, carboxyl-, alkoxy-, and carboximide-substituted derivatives. The polymers from these reactions were obtained consistently in greater yields and with higher molecular weights and lower polydispersities, than those prepared by most other catalysts known at that time.

The initiation process remained unclear, but a number of observations suggested that the active species was a ruthenium alkylidene. A breakthrough occurred when the methodology for the synthesis of tungsten alkylidenes, in which 3,3-disubstituted cyclopropenes are used as carbene precursors, was applied to the synthesis of a ruthenium catalyst. The addition of diphenylcyclopropene to RuCl₂(PPh₃) led to the isolation of 16 (Figure 2.1.5).

Although the newly developed catalyst showed exciting initiation behaviour and functional group tolerance, its activity was limited to the ROMP of highly strained monomers. To extend this activity to the ROMP of low-strain monomers and the metathesis of acyclic olefins, the ligand environment was modified in a systematic way. Based on the trend followed by early transition metal catalysts, for which metathesis activity increases with more electron-withdrawing ligands, a variety of cationic complexes and derivatives containing less basic phosphines were prepared and tested by Grubbs and co-workers. Fortuitously, this hard work led to the synthesis of 12, where PCy₃ (Cy = cyclohexyl) was used instead of PPh₃, and to the discovery that the larger and the more basic the phosphine, the higher the metathesis activity.

![Figure 2.1.5: Development of the Grubbs' catalysts.](image-url)
As a result, a newly designed family of $L_2X_2Ru=CHR$ complexes was synthesized based on the improvements in catalytic activity, and was subjected to mechanistic studies. Activity depended highly on the identity of the X- and L-type ligands. Catalyst activity increases with larger and more electron-donating phosphines, whereas it decreases with larger and more electron-donating halides. The overall activity also depends on catalyst initiation and thus on the nature of alkylidene moiety. Among many mechanistic studies, the key insight was that $(Pcy_3)_2Cl_2Ru=CHR$ forms a highly active mono(phosphine) intermediate during the catalytic cycle. As a design motive, this intermediate became a starting point for the development of much improved catalysts.

Taking all these lessons into consideration, Grubbs and co-workers became interested in the potential of $N$-heterocyclic carbene ligands. After exploring a variety of ligand derivatives, they found that a mesityl-substituted $N$-heterocyclic carbene worked the best. This was their initial disclosure of catalyst 14. Soon thereafter, they discovered that catalyst 15, which contains an $N$-heterocyclic carbene with a saturated backbone, is even more active. These new catalysts display performance that was previously possible only with the most early metal systems. The superior activity of catalyst 15 includes high rates of ROMP for low-strain substrates, and even the ROMP of sterically hindered substrates containing trisubstituted olefins. Both catalysts 14 and 15 are able to perform the RCM of sterically demanding dienes to form tri- and tetrasubstituted olefins. In addition, catalyst 15 produced the first example of CM to yield a trisubstituted olefin, as well as CM and RCM reactions where one partner is directly functionalized with a deactivating group, such as acrylate or siloxane.
RESULTS AND DISCUSSION

Grubbs ruthenium catalyst (12) was used in the synthesis of dimers 20, 22, 29, 33, and 40 from their respective terminal olefin monomers 19, 21, 28, 32, and 39.

Compound 20 was obtained in a 66% yield from its O-allyl peracetylated glucosamine monomer (19).

![Chemical structures](image)

**Scheme 2.1.1:** Dimerization reaction of 2-propenyl 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranoside

Compound 19 was poorly soluble in CH₂Cl₂ and its solubility did not increase in either diethyl ether or other aprotic solvents that were tried. The compound was soluble in alcoholic solvents such as methanol or ethanol. This put the Grubbs' catalyst to the test, and it was time to reveal the truth of its tolerance to solvents containing hydroxyl groups, especially when they constitute a much larger quantity than the olefins in solution. Two drops of MeOH were used with 4ml CH₂Cl₂ to fully solubilize the 100 mg starting material and insure the homogeneity of the solution. The result was quite rewarding, and the catalyst stood up to the challenge. This result led us to try the direct dimerization of compound 21, which is the unprotected version of compound 19. Once again, a mixture of CH₂Cl₂:MeOH (4:1) was needed to solubilize the starting material. This reaction was also successful and compound 22 was obtained in 58% yield.
Scheme 2.1.2: Dimerization of 2-propenyl 2-acetamido-2-deoxy-β-D-glucopyranoside.

Furthermore, β-O- Allyl 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-galactopyranoside (28) was treated with the same conditions to obtain the corresponding dimer, compound 29, in 68% yield.

Scheme 2.1.3: Dimerization reaction of 2-propenyl 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-galactopyranoside
Beside the O-allyl carbohydrate derivatives, other terminal olefin sugars, with different spacers, were dimerized using the Grubbs-catalyzed olefin metathesis reaction. Two examples are presented in this chapter. Compound 33 was obtained in 75% yield by the dimerization of its butenamide monomer (32), and a bis galactostilbene (40) was obtained in 82% yield by the dimerization of O-styrene peracetylated galactose (39).

![Reaction Scheme]

scheme 2.1.4: Dimerization reactions of compounds 33 and 40.

All of these dimers were obtained by olefin metathesis in an E:Z ratio that varied between 1.5:1 to 3:1, favoring the formation of the E isomer. These ratios were determined based on the intensity of the $^1$HNMR anomic peaks of both isomers.
Table 2.1.2: Summarized results of the self-metathesis compounds.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Product (E:Z)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>(5:2)</td>
<td>66</td>
</tr>
<tr>
<td>22</td>
<td>(3:1)</td>
<td>58</td>
</tr>
<tr>
<td>29</td>
<td>(3:1)</td>
<td>68</td>
</tr>
<tr>
<td>33</td>
<td>(1.5:1)</td>
<td>75</td>
</tr>
<tr>
<td>40</td>
<td>(1:0)</td>
<td>82, 92*</td>
</tr>
</tbody>
</table>

* Compound 40 was obtained in 92% yield, using catalyst 15.

The stilbene dimer (40) of the 4-ethenylphenyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside was obtained in pure trans. Consequently this compound gained more interest and took priority over the other dimers on the list of potentially biologically active compounds. This compound also has another important property as it belongs to the “rigid rod molecule family”, which will be discussed further in this chapter.

Synthesis of starting materials

The starting materials were synthesized using common and basic methods adopted by our group. The α 2-propanyl 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-galactopyranoside can be easily obtained by Fischer glycolysation (reflux in H+ resin and allylic alcohol). Using these conditions, the α-conformer constituted the major product due to the ‘anomeric effect’. This effect named by Lemieux and described by Edwards explains the tendency of an electronegative substituent to adopt the α axial orientation. However, in peracetylated carbohydrates, a neighboring participation affects the orientation of the nucleophilic attack on the anomeric position. The O-acetate or N-acetate groups on C-2 of the pyranose ring can react with the oxonium intermediate and form a five-member ring. This ring occupies the axial position and therefore forces the nucleophile to attack from the equatorial position, hence leading to the β-conformer. In
general, and in most glycosylation reactions, the resulting anomeric stereochemistry is
derected by the nature of the C2 substituent.

\[ \text{Lewis acid} \]

\[ \text{X = O or NH} \]

\[ \equiv \]

\[ \equiv \]

\[ \equiv \]

**Figure 2.1.6**: Examples of neighboring participation in a glycosylation reaction.

For the preparation of compound 19 (Scheme 2.1.5), commercially available
GlucNAc (17) was treated with acetic anhydride and pyridine, giving the peracetylated
product (18), which was treated with allylic alcohol and a catalytic amount of Borane
triflate in dichloromethane. The glycoside was formed and characterized, although the
yields were not satisfying. This glycosylation reaction under these conditions tends to be
extremely sensitive to moisture. The oxonium intermediate is very reactive and could be
easily hydrolyzed, therefore making this process inconsistent. In order to ameliorate the
yield and be more consistent in the making of this glycoside, another method was
utilized. This method goes through a key intermediate, compound 24, which not only
gives the product in good yields, but also controls the stereochemistry of the anomic position, leading to the formation of only the β conformer. Based on these results, compound 17 was treated with AcCl to give compound 23, which was converted to the fairly stable oxazonyl, compound 24. Refluxing compound 24 in allylic alcohol, in the presence of one equivalent of CSA, gave compound 19 in good yield (80%).

For the preparation of compound 21, compound 19 was treated with sodium methoxide in methanol, deprotecting the sugar from the acetate groups.

Scheme 2.1.5: Synthesis of compounds 19 and 21. a) Pyridine: Ac₂O (1:5), 92%; b) CH₂=CHCH₂OH, BF₃OEt₂, CH₂Cl₂, 40-60%; c) AcCl, 60%; d) TBACl, NaHCO₃, CH₃CN, 55°C, 100%; e) CH₂=CHCH₂OH, CSA, 80%; f) NaOMe, MeOH, 100%.

For the preparation of compound 28, commercially available GalNAc (25), was treated with the same conditions as previously described in the synthesis of compound 19, going through the oxazonyl intermediate (27), which led to the formation of the desired product as described in Scheme 2.1.6.
Scheme 2.1.6: Synthesis of compound 28. a) AcCl, 65% crystals; b) TBACl, NaHCO₃, CH₂CN, 55 °C, 100%; c) CH₂CHCH₂OH, CSA, 78%.

For the synthesis of compound 32, commercially available GlucNAc (17) was also treated with acetyl chloride giving compound 23, which was transformed to the azide derivative by a phase transfer catalyzed (PTC) reaction.

The product of this PTC reaction, compound 30, was then reduced to give the amine derivative (31), which was coupled with commercially available vinylacetic acid, yielding compound 32 as the desired product.
Scheme 2.1.7: Synthesis of compound 32. NaN₃, TBAHS, Na₂CO₃, EtOAc:H₂O (1:1), 100%; b) Pd/C 10%, H₂gas 95%; c) EDC, CH₂Cl₂, 82%.

For the preparation of compound 39, the commercially available galactose (34) was treated with acetic anhydride and pyridine, giving the galactose pentaacetate (35), which was treated with a solution of 33% hydrobromic acid in acetic acid, to give the peracetylated galactopyranosyl bromide (36). Compound 39 can be prepared by PTC reaction of compound 36 with hydroxystyrene 38, which is an unstable compound that tends to polymerize at high concentration. Therefore, the commercially available acetoxyxystyrene 37 was treated with potassium carbonate in methanol, to obtain the hydroxystyrene (38). In order to avoid the polymerization of this compound, a precise amount of water (10 mL) was added to the solution, and the methanol was then evaporated under vacuum, leading to the preparation of the aqueous phase of the PTC reaction, which consisted at that point of hydroxystyrene (38) and potassium carbonate suspended in water. At the same time, compound 36 was dissolved in 10 mL of ethyl acetate, an amount equal to the amount of water in the aqueous phase, leading to the preparation of the organic phase of this particular PTC reaction. Both phases were then
mixed in the presence of tetrabutylammonium hydrogen sulfate, and the reaction succeeded in giving compound 39 in excellent yield (90%).

Scheme 2.1.8: Synthesis of compound 39. a) Pyridine:Ac₂O (5:1), 90%; b) 33% HBr:AcOH, 92%; c) K₂CO₃·MeOH; d) TBAHS·K₂CO₃·EtOAc:H₂O (1:1), 90%.
2.2 Heck coupling

INTRODUCTION

On its long lasting journey, the research in organic chemistry has evolved in a very fashionable and artistic way. A resulting fundamental world was designed by chemists and built by key reactions, reagents and catalysts.

The carbon-carbon bond formation constitutes a main building block in organic synthesis, and the Heck reaction is with no doubt an indispensable unit of this building block. This palladium-catalyzed arylation or alkenylation of alkenes was only discovered in the late sixties by R.F. Heck. Although it received much attention initially as a new method for C-C bond formation, the Heck reaction was not applied and developed extensively.

Since synthetic strategies have become highly directed toward both efficiency and stereoselectivity, concepts in the past decade have been devised to sequentially form several carbon-carbon bonds in a single synthetic step, if possible, even diastereo- and enantioselectively. Convincing initial success was achieved with radical-initiated cascade cyclizations, but soon metal-mediated and metal-catalyzed reactions were specifically employed. During the mid 1980's, many groups recognized that the Heck reaction was underdeveloped and far from being exploited to its full synthetical potential. But this classic reaction experienced a renaissance soon after answers had been found to some important questions regarding the mechanism, the control of substrate selectivity as well as regio- and stereoselectivity, and the increase in efficiency.

Though in specific areas, other palladium-catalyzed transformations such as, e.g., allylic substitution of cross-coupling may seem to be more advanced, none can match Heck chemistry in resourceful versatility, the overwhelming ability to spawn new, and sometimes unexpected applications, and resolving challenges.

The Heck-type reactivity, one of the basic types of reactivity in palladium-driven catalytic cycles, comes from the ability of Pd (0) species to undergo oxidative addition to
various C-X bonds, and the addition of thus formed RPDX intermediates to unsaturated bonds.

The term ‘Heck chemistry’ is associated in the first place with the catalytic arylation and alkenylation of olefins, that is the original Heck or Mizoroki-Heck reaction, discovered independently by Mizoroki \(^{29}\) and Heck \(^{30}\), and developed by Heck in a number of fundamental papers into a general method of organic chemistry.

The reaction can be catalyzed by palladium complexes with or without phosphine ligands (phosphine-assisted vs phosphine-free catalysis). A primary role of phosphine ligands is to support palladium in its zero oxidation state in the form of stable PdL\(_4\) or PdL\(_3\) species.

**Heck catalytic cycle**

Various Palladium catalysts are used, and they all yield a coordinatively unsaturated 14-electron palladium (0) that is usually coordinated with weak donor ligands, such as tertiary phosphanes. Palladium (II) acetate was used to catalyze the Heck reactions accomplished in this thesis. This fairly stable catalyst undergoes a reduction in situ in the presence of triphenylphosphine, before it can participate in the catalytic engine. The Heck catalytic cycle consists of three major steps along with a preactivation step as shown in Figure 2.2.1.

**Preactivation step.** The entry into the catalytic cycle includes the reduction of Pd (II) complexes to Pd (0) and the generation of active species through multiple ligand exchange equilibria. To enter the catalytic cycle through the oxidative addition, palladium (0) species must have a proper coordination shell. No more than two strongly bound ligands are allowed. This requirement places a serious restriction on the choice of ligands and their concentration in the reaction mixture. The primary reduction of Pd (II) to Pd (0) is most likely accomplished by phosphine in the phosphine-assisted catalytic cycles. \(^{31-32}\) In phosphine free systems, the primary reduction of Pd (II) can be effected by amines, if these are used as base, or olefin. It is interesting to note that neither Et\(_3\)N nor olefin have any detectable influence on the reduction rate in the presence of phosphine. \(^{33}\)
Still, it is well known that in the absence of phosphine, olefins are oxidized by Pd (II) via the first turn of a Waker-type catalytic cycle.

**Heck coupling:**

\[
R_1X + \equiv R_2 \xrightarrow{\text{Pd(OAc)\textsubscript{2}, PPh\textsubscript{3}, Et\textsubscript{3}N, Reflux}} R_1\equiv R_2
\]

\(R_1 = \text{alkenyl, aryl}\)

\(R_2 = \text{aryl, alkyl, alkynyl}\)

\(\text{CO}_2\text{R}', \text{etc...}\)

\(X = \text{I, Br, OSO}_2\text{CF}_3\)

**Mechanism:**

\[
Pd(\text{OAc})_2 + n\text{PPh}_3 
\]

\(A\)

\[
\text{HNEt}_2^- \quad \text{Pd(0)L}_2
\]

\(B\)

\(\beta\)-hydride elimination

\(D\)

\(\text{syn addition}\)

\(C\)

\(L = \text{PPh}_3\)

**Figure 2.2.1:** Mechanism of the Heck reaction, using Pd(OAc)\textsubscript{2} as a catalyst.

**Oxidative addition.** In this basic process of organometallic chemistry, the oxidation proceeds as a concerted process in which C-X bond rupture is more or less
perfectly synchronized with the formation of M-C and M-X bonds. Therefore, in this step of the catalytic cycle (Step B), haloalkenes and haloarenes are commonly assumed to oxidatively add to bis(triphenylphosphane)palladium (0), generating a σ-alkenyl or σ-aryl palladium (II) complex. This complex will later lead to the thermodynamically stable trans-σ-alkenyl- or -aryl palladium (II) complex.36-38

**Syn-addition.** (Step C) In this step, an alkene molecule is coordinated after elimination of another phosphane ligand.39 After both ligands have adopted the cis orientation necessary for insertion of the alkene into the σ-alkenyl or σ-aryl C-Pd bond,40 the rotation of the alkene leads to in-plane coordination of the alkene. Afterwards, the alkene inserts into the σ-alkenyl- or -aryl palladium bond to give a σ-alkylpalladium complex via a four-center transition state.

**β-hydride elimination.** After the insertion, comes a step in which palladium (0) is released and launches the next turn of the Heck cycle. There are several possibilities by which this step can occur. The most commonly used one is shown after the cis-addition of the alkene, where the reaction terminates by a β-hydride elimination step (Step D),41 which can generally occur only after internal rotation of the generated alkylpalladium species. This way, the essential syn orientation of a β-hydrogen is provided for elimination. The catalyst is generated after reductive elimination (Step E) of HX in presence of the base.42

Most of the palladium-catalyzed reactions undergo a very similar mechanism. The ability to be inserted in the C-X bond at the oxidative addition step, and the ability to be reduced in a basic environment at the reductive elimination step, highlight the uniqueness of the palladium in this type of reactions, and render the palladium catalysts very interesting catalysts to study, synthesize, and develop.

The homodimerization of terminal alkenes was dominated by the olefin metathesis reactions using Grubbs ruthenium catalysts. Many examples were also done in our group. The slight disadvantage that this method had was the cross coupling of two different olefins or the formation of heterodimers. In most cases, one alkene had the tendency to be more electron-rich than the others, and this caused it to homodimerize faster than cross couple with the other alkene. This effect could be minimized by
changing the stoichiometry, increasing the less electron-rich alkene in the reaction mixture, although the cross metathesis is not as selective as someone would like it to be.

The Heck coupling is a great tool for the synthesis of a carbon-carbon bonded molecule. In some cases, it is a key step in multistep synthesis. A slight disadvantage restricts this reaction as a large number of alkenes could only bond to aryl halide or an alkenyl halide (Fig. 2.2.1). This restriction is compensated by the high selectivity of this reaction, where any aryl or alkenyl halide could be coupled with any terminal alkene, secondary or tertiary alkenes in some cases. In this thesis, the Heck reaction was a very useful tool that helped synthesize various target molecules.
RESULTS AND DISCUSSION:

Stilbene dimers are very interesting molecules to synthesize. They can easily be obtained as pure trans isomers as was shown earlier in section 2.1 via olefin metathesis reaction, or via Heck reaction as we will see in this section. They also belong to the rigid rods family. In this section, Heck reaction was applied to form homo and hetero-carbohydrate dimers.

The first attempted reaction was the coupling of para acetoxy styrene (37) with para acetoxy iodobenzene (41) (Scheme 2.2.1). The acetate group was employed as a substituent for a carbohydrate moiety, in order to test the tolerance of the catalyst, and to have a closer experimental idea of this reaction. This reaction was a success, and compound 42 was obtained in 82% yield. The conditions of the Heck reaction were optimized by utilizing 10% of the catalyst [Pd(OAc)$_2$] and 20% of triphenyl phosphine to a 1:1 mixture of the two starting materials, and refluxing it in triethyl amine.

\[
\text{AcO-} - \text{I-} \xrightarrow{\text{Pd(OAc)$_2$, Ph$_3$P, 10$\%$, } \text{AcONa, Reflux}} \text{AcO-} - \text{AcO-}
\]

Scheme 2.2.1: Synthesis of compound 42 by the optimized Heck reaction conditions using Palladium (0) catalyst.

Following this successful attempt, carbohydrate derivatives containing styrene and para-iodophenyl were prepared as building blocks for the synthesis of glycodimers via Heck reaction.

Using the same conditions, carbohydrate homodimers 40, 52, and 55 were synthesized via Heck coupling of 39 and 45, 49 and 50, and 53 and 54 respectively. The coupling of 39 with 50 led to the formation of heterodimers 43 and 51 respectively, demonstrating the selectivity of this reaction.
Scheme 2.2.2: Synthesis of compounds 40 (60%), 43 (72%), and 51 (62%). Pd(OAc)$_2$ 10%, PPh$_3$ 20%, CH$_2$Cl$_2$, 6-12 hrs.
Scheme 2.2.3: Synthesis of compounds 52 (57%) and 55 (63%): Pd(OAc)$_2$ 10%, PPh$_3$ 20%, CH$_2$Cl$_2$, 6-12 hrs.

Compounds 28 and 37 were commercially available. Compounds 41, 53, and 54 were previously prepared by our group. Compound 45 was obtained by PTC reaction of the bromo-peracetylated galactoside (36) with the commercially available para-iodophenol (44). As for the preparation of compound 49 and 50, the commercially available lactose was treated with acetic anhydride and pyridine leading to the formation of the peracetylated lactoside, which was treated with 33% hydrobromic acid in acetic acid diluted with dichloromethane, to give the desired bromo-peracetylated lactoside (48). From this product, both compounds 49 and 50 were synthesized by PTC reaction. The conditions used for the synthesis of O-styrene peracetylated lactoside (49) were the same as the ones previously used for the preparation of O-styrene peracetylated galactoside (39) described in the previous section.
Scheme 2.2.4: Synthesis of compounds 49 and 50. a) TBAHS, Na$_2$CO$_3$, EtOAc:H$_2$O (1:1), 80%; b) Pyridine:Ac$_2$O (5:1), 84%; c) 33% HBr:AcOH, CH$_2$Cl$_2$, 52%; d) K$_2$CO$_3$, MeOH; e) K$_2$CO$_3$, TBAHS, EtOAc:H$_2$O (1:1), 78%; f) Na$_2$CO$_3$, TBAHS, ETOAc:H$_2$O (1:1), 82%.
2.3 Palladium and Ruthenium catalyzed reactions of alkynes carbohydrates

INTRODUCTION

Symmetric coupling of free acetylenes under mild conditions was discovered over a century ago by Glaser (Scheme 1a), 45,44 and his procedures have been significantly improved since by Eglinton and coworkers 45,46 and Hay (Schemes 2.3.1b and 2.3.1c respectively). 47

Scheme 2.3.1: Symmetric coupling of free acetylenes.

Stannyalted alkynes can also be symmetrically coupled (Scheme 2.3.2). 48

Scheme 2.3.2: Symmetric coupling of Stannyalted alkynes.
Asymmetric coupling of terminal free acetylenes developed by Cadiot and Chodkiewicz (Scheme 2.3.3a) \(^{49}\) can be accomplished under a variety of conditions. \(^{50-56}\) In most of these reactions, copper acetylides seem to be the key intermediates. Coupling of alkynyliodonium salts with copper (I) acetylenides gives diynes in good yields (Scheme 2.3.3b). \(^{57}\) and Stille coupling (Scheme 2.3.3c) of stannylated alkynes provides a copper-free coupling method. \(^{58}\)

\[
\begin{align*}
\text{R} & \equiv \equiv \text{H} & + & \text{X} & \equiv \equiv \text{R'} & \xrightarrow{\text{amine}} (a) \text{Cu}^+ \\
\text{R} & \equiv \equiv \text{I} & \equiv \equiv \text{R''}_2 & - & \text{Cu} & \equiv \equiv \text{R'} & \xrightarrow{\text{amine}} (b) \\
\text{R} & \equiv \equiv \text{SnR''}_3 & - & \text{X} & \equiv \equiv \text{R'} & \xrightarrow{\text{Pd cat.}} (c)
\end{align*}
\]

Scheme 2.3.3: Asymmetric coupling of terminal alkynes.

Other conditions were also established around various palladium catalysts in order to increase the reactivity of these reactions.

In this section, the Sonogashira conditions were used for the dimerization and coupling of the various acetylene glycosides. The Stephens-Castro reaction is the cross-coupling reaction of copper (I) arylacetylenes with iodoalkenes. \(^{59,60}\) Its scope is sometimes limited by the vigorous reaction conditions and by the difficulty in preparing cuprous acetylides. The Sonogashira reaction \(^{61}\) is the palladium-catalyzed version of the Stephen-Castro reaction. By adding catalytic bis(triphenylphosphine)-palladium dichloride and CuI as the co-catalyst. Sonogashira et al. successfully cross-coupled terminal alkynes with aryl- and vinyl halides in the presence of an aliphatic amine under mild conditions (Scheme 2.3.4). The reaction proceeds smoothly in the presence of Palladium-complex catalyst and cuprous iodide co-catalyst.
Scheme 2.3.4: Sonogashira coupling.

As a source of palladium, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> in diethylamine or triethylamine is commonly used. In many cases, Pd(OAc)<sub>2</sub>, or Pd(OAc)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>,<sup>62</sup> or Pd<sub>2</sub>(dba)<sub>3</sub>, or Pd<sub>2</sub>Cl<sub>2</sub>(CH<sub>2</sub>CN)<sub>2</sub> plus two equivalents of a tertiary phosphine, which are reduced in situ to the catalytically active Pd<sup>0</sup>, have been used.<sup>63</sup>

Sonogashira proposed a reaction scheme consisting of a combination of two catalytic cycles A and B (Scheme 2.3.5). This protocol is based on the discovery of CuI-catalyzed transmetallation in amine.<sup>64</sup> When PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> is used, a Pd-acetylide complex is formed, and it undergoes reductive elimination to form the Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>2</sub>. Oxidative addition of the sp<sup>3</sup> halide to Pd (0), which undergoes nucleophilic attack by the acetylide anion and subsequent reductive elimination, affords the disubstituted acetylene and Pd(PPh<sub>3</sub>)<sub>2</sub>.<sup>62</sup>
Scheme 2.3.5: Mechanism of Sonogashira reaction: in a similar manner to the Heck mechanism, the catalyst undergoes an i) oxidative addition, ii) a transmetallation, and iii) reductive elimination.
As a useful tool, the Sonogashira reaction can be used to transform acetylene monomers to homo and hetero dimers, also to trimers, tetramers, and even hexamers as shown in figure 2.3.6.

RXCH₂ → R = sugar
X = C, O, N, or S.

Various methods:
i. Cul, O₂, Pyr. rt
ii. Cul, PdCl₂(PPPh₃)₃, DMF, Et₃N, rt or Reflux
iii. Pd(Ph₃P)₄,Et₃N, DMF
iv. Cu(OAc)₂, Pyr. 60 °C

Scheme 2.3.6: Various methods, including Sonogashira coupling, to dimerize terminal alkyne carbohydrates and to obtain di-, tri-, tetra-, and hexa-mers.

Acetylenes and substituted acetylenes undergo cycloaddition in one step in the presence of a metal catalyst. This carbocyclization is a well-known reaction, and can be achieved with many transition metals including Co⁶⁵, Ni⁶⁶, Pd⁶⁷, Cr⁶⁸, Rh⁶⁹, Fe⁷⁰, Ta⁷¹, and activated Zr-Ti.⁷² Although more recently it was found in our group⁷³ that 2-propanoyl glycosides can undergo a cyclotrimerization reaction in the presence of Grubbs’ catalyst (12) to give a mixture of regioisomeric aryl glycosides (Scheme 2.3.7). This reaction is known as the acetylene metathesis.
Scheme 2.3.7: Acetylene metathesis using Grubbs' catalyst (12).

A common mechanism for this type of reaction is illustrated in scheme 2.3.8. Two alkyne molecules coordinate respectively to a single metal center. Oxidative coupling occurs resulting in the formation of a metallacyclopentadiene and oxidation of the metal, thus opening a coordination site. A third alkyne molecule may insert to give a transient metallacycloheptatriene. Finally, a benzene product is released. Based on this and on the Chauvin mechanism shown in section 2.1, a mechanism of the acetylene metathesis using Grubbs' catalyst (12) was suggested, as it is described in scheme 2.3.9. Interestingly enough, this mechanism explained, based on the regioselectivity and stereoselectivity, the reason why the 1,2,4-trisubstituted benzene is the major product versus the corresponding 1,3,5-trisubstituted derivative.

Scheme 2.3.8: General mechanism for alkyne trimerization.
Scheme 2.3.9: Suggested mechanism of the acetylene metathesis based on the Chauvin mechanism. As it is shown, three cycles will generate the 1,2,4 trisubstituted aryl versus one cycle that generates the 1,3,5 trisubstituted aryl. which explains why the first isomer is the major product of this reaction.
Examples of successful acetylene metathesis were reported by our group. In this thesis, GlcNAc acetylene derivatives were synthesized, but unfortunately their metathesis reactions were not successful. The conditions of this cyclization reaction via acetylene metathesis have not yet been generalized and optimized, as many possible factors such as functional groups, substrate polarity, solvent systems and even reaction temperature could affect the outcome of this reaction. Few acetylene carbohydrate derivatives underwent this reaction successfully under the same conditions, but none of them contained an amide group. GlcNAc on the other hand is a very polar sugar and it also contains an amide group on the C-2 of its pyranose ring. These distinguished characteristics might have affected the outcome of this reaction.
RESULTS AND DISCUSSION

The 4-iodophenyl derivative (56) was synthesized via a PTC reaction from the previously prepared 2-acetamido 2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride (23). The propargyl template was prepared by reacting the oxazoline (24) with propargyl alcohol giving compound 57 in 90% yield. The coupling of the iodophenyl and O-propargyl moieties using the Sonogashira conditions led to the formation of the heterodimer 58 in 58% yield.

Scheme 2.3.10: Synthesis of compound 58. a) TBAHS, Na₂CO₃, EtOAc:H₂O (1:1), 4-iodophenol, 80%; b) CSA, CHCCH₂OH, 90%; c) PdCl₂(PPh₃)₂, DMF, Et₃N, reflux, 58%.
The reaction of commercially available GlcNAc with propargyl amine formed compound 59 in excellent yield (84%). This compound underwent two different reactions under the same Sonogashira conditions, forming two different homodimers. A self-coupling reaction formed compound 60 from 59. Under the same conditions, and in the presence of 1,4-diiodobenzene, compound 61 was obtained, but in low to moderate yield.

![Chemical structures](image)

**Scheme 2.3.11:** Synthesis of compounds 60 (48%) and 61 (40%): a) 1. Propargylamine. 2. Ac₂O:Pyridine (1:5), 84%; b) PdCl₂(PPh)₃, DMF, Et₃N, reflux.

In an attempt to produce a longer and more flexible spacer, compound 62 was synthesized by coupling the previously made amino peracetylated GlcNAc (31) with commercially available pentynoic acid in the presence of EDC. This alkyne was self-coupled under the Sonogashira conditions, giving homodimer 63.
Scheme 2.3.12: Synthesis of compound 63: a) EDC, CH$_2$Cl$_2$, 60% crystals; b) PdCl$_2$(PPh$_3$)$_2$, Et$_3$N, DMF, reflux, 54%.

As previously mentioned, it was recently found in our group that two propynyl glycosides can undergo a glycotrimerization reaction in the presence of Grubbs’ catalyst (12). This reaction was tried with O-propargyl peracetylated α-D-mannoside, β-D-galactoside, and β-D-lactoside, to give the corresponding products in 75%, 72%, and 66% yields respectively.

At this stage, the cyclotrimerization of compounds 57, 59, and 62 was the next step to attempt. Unfortunately, the treatment of each of these compounds with the same reaction conditions (catalyst 12, CH$_2$Cl$_2$, room temperature for 12 hours) did not give any of the expected products. No side reactions were even observed. The starting materials were recovered and identified by NMR.

It was not clear why these reactions failed, but this failure could be related to what was previously noticed in the olefin metathesis reactions (Section 2.1), where β-O-allyl GlcNAc dimers resulted in lower yields (66%) compared to the other O-allyl sugars (75 to 95%). With that in mind, one can say that allylic or propargyl substituted GlcNAc derivatives are not ideal substrates for catalyst 12 under these conditions.
When R and X are:

Scheme 2.3.13: attempts to cyclotrimerize compounds 57, 59, and 62, using catalyst 12.

No additional work was further attempted with these reactions in order to overcome this obstacle, although slight changes in the reaction conditions would have probably affected their success. Heating the reaction mixture or even refluxing it using a higher boiling point solvent might have increased the reactivity of the substrates with the catalyst. The second-generation Grubbs’ catalyst (15) could have also been a more successful catalyst in the trimerization reactions.

Unfortunately, due to time restraints, this project was abandoned at that stage, and no further attempts were made to change any of the reaction conditions.
2.4 Aryl-aryl coupling

INTRODUCTION

Organic chemists usually seek the most efficient way to synthesize their target molecules. In order to achieve their goal, many attempts are usually made, some of which are successful, and some are not. In both cases, the results can be very educational.

In this section of the thesis, attempts to obtain biphenylic glycodimers via aryl-aryl coupling using palladium catalysts are reported. The biphenyl is a very interesting spacer to have between two sugar moieties. It belongs to the rigid-rod molecules' family, and unlike other rod-like molecules, it is strongly anisotropic \(^{74}\), and it has a two-fold symmetry axis along the rod direction.

Earlier methods describing the synthesis of p-oligophenylenes (biphenyl being one of them) (Scheme 2.4.1) \(^{75}\) include reductive coupling of 4-iodophenylarenes with copper \(^{76,\cdots\cdots}\) or silver \(^{8}\) powder, oxidative coupling of unsubstituted arenes with AlCl\(_3\) in nitrobenzene, \(^{79}\) addition of 4-arylphenyllithium to quinone \(^{80}\) or 1,4-cyclohexanedione \(^{81}\) with subsequent dehydration and oxidation, and oxidative coupling of 4-arylphenyllithium reagents with CuCl\(_2\). \(^{82}\)

![Scheme 2.4.1: Early methods of synthesis of p-oligophenylenes.](image-url)
Reductive elimination of biphenyl has also been reported for polyphenyl derivatives of many non-metals as shown in Scheme 2.4.2.\(^8^3\)

\[ R - M \left( \begin{array}{c} \text{Li} \\ \text{Li} \end{array} \right) \xrightarrow{\Delta} R \left( \begin{array}{c} \text{Li} \\ \text{Li} \end{array} \right) - M \left( \begin{array}{c} \text{Li} \\ \text{Li} \end{array} \right) \]

\[ M = \text{Br}, \text{S}, \text{S}_2, \text{SO}_2, \text{Se}, \text{P}, \text{Sb}, \text{As} \]

**Scheme 2.4.2:** Synthesis of biphenyls from nonmetallic precursors or reagents.

All these reactions are potentially applicable, although in most cases, yields or conditions were either low or too harsh to be used with carbohydrate moieties. Besides, trying to introduce a bond between two aromatic rings, either intra- or inter-molecularly, was not so trivial and was a familiar problem to many organic chemists. Needless to say, chemists are known to take on challenges, and try hard to solve synthetic problems. Many approaches were made toward the aryl-aryl coupling reactions, and some of the names, reactions, and conditions are mentioned below.

For more than a decade, the Pschorr reaction\(^8^4\) involved the intramolecular substitution of arenes by aryl radicals\(^8^4\) which are generated by the reduction of arene diazonium salts with copper (I) ion.\(^8^5\)\(^-\)\(^8^8\)

The Comberg, Bachmann, and Hey reaction was another classical route to biaryls.\(^8^0\)\(^-\)\(^8^1\) Formally, this and the Pschorr procedure are related: they both require the decomposition of diazonium salts, one typically in alkaline solution and the other in acid.

The Ullman and Ullman types of biaryl synthesis are reactions by which two molecular equivalents of aryl halide are reacted with one of finely divided copper to form a biaryl and copper halide.\(^9^2\)\(^-\)\(^9^6\) Many developments and changes were made by many chemists to improve this reaction, among them are Koten and Noltes,\(^1^0^0\) and Zeigler et al.\(^1^0^1\)

Classical Ullman reaction procedures are still commonly placed in the literature of organic chemistry, but for symmetrical biaryl synthesis at least, the use of zerovalent Ni appears to be more efficient. The original method was discovered by Semmelhack.\(^1^0^2\)
followed by Kende et al.\textsuperscript{103}, Mori et al.\textsuperscript{104}, Zembyashi et al.,\textsuperscript{105} Takagi et al.\textsuperscript{106} and again by Semmelhack and Rono.\textsuperscript{107}  

Other methods such as photochemical\textsuperscript{108-111} methods of aryl-aryl bond formation, phenolic\textsuperscript{112-116} and anodic\textsuperscript{117-120} oxidations, vanadium, thallium, manganese\textsuperscript{121-123}, selenium and tellurium\textsuperscript{124} oxidations, were also established.

**Coupling of arenes with palladium (II) complexes.**\textsuperscript{125} Biphenyl can be obtained by heating benzene with palladium (II) chloride and sodium acetate at 90\degree C in acetic acid solution.\textsuperscript{126} As the reaction proceeds, Pd metal is deposited, but no coupling occurs unless acetate ion is present. The rate determining step is considered to be the formation of a σ-bonded aryl-Pd (II) complex, followed by a fast breakdown of the complex. The latter is initiated by the attack of acetate anion.

Initially, the use of Palladium chemistry was not very popular, although, after being put on the shelf for quite some time, the palladium chemistry, and as mentioned before in this thesis, was rejuvenated in the last decade or two. So many Palladium catalysts were generated and so many conditions and secondary reagents were associated with every reaction. It became almost impossible to predict which catalyst will give the optimal yield from any particular substrate.

Presently, the most versatile step-by-step approach to biaryls includes a palladium-catalyzed asymmetrical coupling of aryl boronic acids with aryl bromide or aryl halide. This method is known as the Suzuki coupling (Scheme 2.4.3).

\[
R\left(\begin{array}{c}
\text{B(OH)}_2 \\
\end{array}\right)_n + X\left(\begin{array}{c}
\text{R'} \\
\end{array}\right)_m \xrightarrow{\text{Pd cat.}} R\left(\begin{array}{c}
\text{R'} \\
\end{array}\right)_{n-m}
\]

\textbf{Scheme 2.4.3:} Formation of \textit{p}-oligophenylenes by Suzuki coupling.

The use of Suzuki coupling to obtain target biphenyl-glycodimers would have been the ideal situation. Unfortunately, other organic chemistry groups were ahead of us.
in that planning, as they published similar work.\textsuperscript{127, 128} Although, it is important to note that no biphenyl-glycodimers were yet synthesized.

Other conditions were later reported involving the use of Pd (0) as a catalyst in the direct homocoupling of aryl halides.\textsuperscript{129} A paper published by M. Lemaire \textit{et al.} showed very encouraging results in terms of yields and reaction conditions (Scheme 2.4.4).

\begin{equation*}
\begin{array}{c}
\text{Br} \\
\text{R} \\
\text{Pd(OAc)}_2 / n\text{Bu}_4\text{NBr} \\
\text{DMF/H}_2\text{O/(CH}_3)_2\text{CHOH,} \\
\text{Et}_3\text{N or K}_2\text{CO}_3 \\
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{R} \\
\text{R} \\
\end{array}
\end{equation*}

\textbf{Scheme 2.4.4: Cross-coupling of aryl halides as reported by Lemaire \textit{et al.}\textsuperscript{129}}

All coupling reactions in Lemaire's work were carried out at 115 °C with catalytic amount of Pd(OAc)$_2$ in the presence of a mild base such as potassium carbonate or triethylamine. Their yields ranged from 57 to 95%. These conditions were reasonably tolerable for a carbohydrate derivative such as 4-bromo or 4-iodophenyl-\textit{O}-Peracetylated glucosamine. No similar synthesis of a carbohydrate biphenyl dimer had been reported prior to that date. Taking all these factors into consideration, a project targeting the homocoupling of compounds 53 and 61, using a Pd(OAc)$_2$ catalyzed reaction, was set and ready to go. Out of their reported examples, 4-nitro-bromo-1-benzene and 4-methoxy-iodo-1-benzene were dimerized in 85% and 81% yields respectively.

Another method was later reported,\textsuperscript{130} describing the palladium-catalyzed zinc-mediated aryl halide coupling under ambient conditions (Scheme 2.4.5).

\begin{equation*}
\begin{array}{c}
\text{R} \\
\text{X} \\
\text{Pd(0) cat.} \\
\text{Zn, H}_2\text{O/acetone. air} \\
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{R} \\
\text{R} \\
\end{array}
\end{equation*}

\textbf{Scheme 2.4.5: Palladium-catalyzed zinc-mediated aryl halide coupling.\textsuperscript{130}}

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RESULTS AND DISCUSSION

The homocoupling method of an aryl halide carbohydrate was mostly based on Lemaire's work. In their paper, four different conditions were used in the homocoupling reaction, and they are as follows:

"All coupling reactions were carried out at 115 °C with 8.10⁻² mole (1 equiv.) of aryl halide and a Pd(OAc)₂/nBu₄NB₃ (0.05/0.5) mixture. Method A: solvent DMF/H₂O (0.9 mL/0.35mL), isopropanol (1.25 mL) and K₂CO₃ (1 equiv.). Method B: solvent DMF/H₂O (0.9 mL/0.35mL), and K₂CO₃ (1 equiv.). Method C: solvent DMF (0.9 mL), isopropanol (1.25 mL) and NEt₃ (3 equiv.). Method D: solvent DMF (0.9 mL), and NEt₃ (1 equiv.)."

Compound 56 was previously prepared from compound 23 via PTC reaction, and compound 64 was prepared using the exact same conditions, replacing the iodophenol by bromophenol (Scheme 2.4.6).

Each of these two compounds underwent the homocoupling reaction using each of the four conditions listed above. Unfortunately, none of these reactions were successful. Decomposition of the starting materials was observed after two days of reflux in some cases. Traces of the product were probably formed, judging by the mass spectrum and ¹H NMR of the crude reaction mixture. Unfortunately, not enough material was obtained; therefore the products could not be purified and fully characterized.
Scheme 2.4.6: Synthesis of compounds 56 and 64 and attempts to prepare the aryl-aryl dimers.
2.5 Molecular orbital calculations

In the course of this thesis, the geometry of the obtained dimers was determined using the computer-aided molecular design (CAMD) modeling tool for the Microsoft Windows: Quantum CAChe. CAChe for Windows \(^{131}\) enables to draw and model molecules, as well as perform calculations on a molecule to determine its molecular properties and energy values. The calculations experiments, are performed by computational applications, which apply classical mechanics and quantum mechanics equations.

Using classical mechanics, CAChe for Windows can optimize molecular geometry, determine a series of low-energy conformations between high-energy barriers, and simulate the normal motion of atoms according to time, temperature, and the calculated forces of the atoms.

Using quantum mechanics, CAChe for Windows can predict electron density and distribution in a molecule, investigate molecular orbital energies, optimize molecular geometry, determine transition state geometry, and calculate molecular properties such as bond order and atomic partial charge.

Optimization involves finding the most stable geometry, or minimum energy structure, of a chemical sample. The lowest energy, or optimum structure, of a conformation of a molecule displays characteristics and properties that are more likely to reflect the true behavior of a chemical sample. Therefore, using optimization in CAChe, we can achieve more accurate results when analyzing molecular characteristics such as calculating bond lengths and atom distances as we will see throughout this thesis. CAChe usually uses both classical molecular mechanics and semi-empirical quantum mechanics to find minimum energy conformations of our molecules. The program optimizes the molecules using classical mechanics first, and then refines the structure using quantum mechanics. Since the molecules in this thesis are fairly big and due to time constraints, only classical mechanical methods are used since they are much faster than quantum mechanical calculations. As well, experiments tend to yield similar or more accurate optimized geometries when applying classical mechanics to discover a low-energy structure. However, if the sample is in a state where electronic effects have a significant
impact on the structure (e.g., a transition state), its geometry cannot be refined by a classical approach. Similarly, classical mechanical experiments do not yield any molecular orbital information.

Optimizing a molecule involves finding the most stable geometry, or minimum energy structure. Molecular mechanics treat molecules as arrays of hard, impenetrable balls connected by springs. The collection is governed by classical, mechanical principles, so that the energy may be represented as a sum of terms, each representing one possible mode of mechanical deformation of the molecule from an idealized geometry.

\[ E_{total} = E_{stretch} - E_{bend} - E_{torsion} - E_{vdW} - E_{dipole} \]

Where:

\[ E_{stretch} \] = the energy of a pair of atoms as a function of the distance between them (given by a Morse curve).

\[ E_{bend} \] = the bending energy based on a Hooke's Law type of potential.

\[ E_{torsion} \] = the energy arising from bonds not fully staggered. It includes three-fold (like ethane) potentials, as well as two-fold (alkenes, carbonyls) and one-fold (alkynes) potentials.

\[ E_{vdW} \] = the repulsion energies between non-bonded atoms.

\[ E_{dipole} \] = the energy of interaction of bond dipoles and any point charges.

A total steric energy (TSE) is calculated for an input geometry. The molecular geometry then is altered and the TSE is recomputed; the process is repeated until a minimum TSE is found. The method of defining a minimum is crucially important;

CACHe systematically adjusts the atom coordinates in our molecule until the lowest energy conformations are discovered. CACHe examines bond angles and atom distances in the molecule and compares its geometry to the classical mechanical ideal
value. Deviations from the ideal accumulate a relative energy quantity known as steric or potential energy. CAChE calculates these deviations from the ideal, and optimizes a molecule by moving its atoms, in order to lower the sum of the deviations (and thus lower the steric energy) until energy changes are negligible.

For example, the deviation of a dihedral angle from a staggered conformation adds to the steric energy of a certain compound. Other factors, such as hydrogen bonding, are stabilizing, and can therefore reduce the total steric energy for our sample. CAChE performs as many optimization iterations as necessary, and stops when the steric energy change between iterations becomes acceptably small. At the end of an optimization, the chemical sample's geometry corresponds to a steric energy minimum. The following example (Fig 1.6.1) shows how CAChE optimizes p-hydroxystyrene β-D-glucoside with a strained dihedral angle, so that the atoms of the optimized molecule do not deviate from the classical mechanical ideal, and therefore steric energy is minimized. The four atoms implicated in the dihedral angle are H-1, C1, O and C of the Styrene. The orbital overlapping of both the β-glycosidic oxygen atom and the cyclic one is the most crucial factor that will be tested by this program. After running the experiment, the optimized geometry calculated by CaChe showed the most stable conformer (Fig 2.5.1a) of the β-glycoside. In its 3D projection it was clear to see how the molecular orbitals of both oxygens do not overlap. The figure also shows that the least stable conformer is the one where these orbitals overlap (Fig 2.5.1 c). This example is a great indication of the capacity and sophistication of this program. Based on these results CAChE for windows was used to calculate the optimum geometry, spacer lengths, and space distances of two particular atoms of our synthesized dimers. For further clarification, the two oxygens' molecular orbitals do not overlap in both figure 2.5.1.a and figure 2.5.1.b, although in the first one, the styrene and the O-Acetate on C4 of the per acetylated galactose are on opposite sides of the plane. whereas in fig 2.5.1.b, they are on the same side, therefore making the conformer slightly more hindered. This shows further the sensitivity of this program toward the steric hindrance of the molecule. In the energy diagram in graphs 2.5.1 a, b, and c, the potential energy of the molecule is measured at 25 intervals of the 360° rotation of the selected dihedral angle.
Graph 2.5.1 a: Energy diagram showing the most stable conformer of p-hydroxystyrene β-D- galactoside.

Figure 2.5.1 a: The most stable conformer of p-hydroxystyrene β-D- galactoside.
Graph 2.5.1 b: Energy diagram showing a less stable conformer of p-hydroxystyrene β-D- galactoside

Figure 2.5.1 b: A less stable conformer of p-hydroxystyrene β-D- galactoside
Graph 2.5.1 c: Energy diagram showing the least stable conformer of p-hydroxystyrene β-D-galactoside

Figure 2.5.1 c: The least stable conformer of p-hydroxystyrene β-D-galactoside
Based on the previous example CAChe was used to calculate the optimum geometry as well as the distances between X and X', C1 and C1', and C4 and C4' (Fig 2.5.2) of the dimmers that were synthesized in this thesis as shown in table 2.5.1.

![Diagram of carbohydrate dimer](image)

**Figure 2.5.2:** A model of a carbohydrate dimer that illustrate X, X', C1, C1', C4, and C4'.

**Table 2.5.1:** Calculation of the spacer lengths (X to X') and the distances between C1 and C1', C4 and C4' for the synthesized glycodimers.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>X-X' (Å)</th>
<th>C1-C1' (Å)</th>
<th>C4-C4' (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>5.162</td>
<td>7.554</td>
<td>11.794</td>
</tr>
<tr>
<td>22</td>
<td>4.995</td>
<td>7.375</td>
<td>11.895</td>
</tr>
<tr>
<td>29</td>
<td>5.258</td>
<td>7.608</td>
<td>11.725</td>
</tr>
<tr>
<td>33</td>
<td>5.723</td>
<td>6.889</td>
<td>10.247</td>
</tr>
<tr>
<td>40</td>
<td>12.015</td>
<td>13.711</td>
<td>17.501</td>
</tr>
<tr>
<td>42</td>
<td>12.097</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>43</td>
<td>12.029</td>
<td>13.915</td>
<td>**</td>
</tr>
<tr>
<td>58</td>
<td>10.311</td>
<td>11.147</td>
<td>13.734</td>
</tr>
<tr>
<td>60</td>
<td>12.250</td>
<td>14.163</td>
<td>17.890</td>
</tr>
<tr>
<td>61</td>
<td>12.346</td>
<td>15.057</td>
<td>19.754</td>
</tr>
</tbody>
</table>

These results can be an important factor in the biological studies of glycodimer-protein interactions. The length of the spacers can be a determining factor in the selection of the proper glycodimer that fits a given active site of a certain enzyme or protein receptor. CAChe in this case can also be a useful tool to predict and prioritize the selection of the synthesis of one glycodimer over another.
2.6 Conclusion

Terminal alkene carbohydrate derivatives were successfully dimerized by olefin metathesis reactions, using Grubbs' Ruthenium catalyst. This method has proved to be a very useful and efficient tool in the synthesis of homodimers.

Glycodimers were also obtained by the coupling of carbohydrate alkenes with aryl halide carbohydrate derivatives, using the Heck coupling reaction. This reaction enabled the formation of selective heterodimers. This reaction was not as efficient as the olefin metathesis reaction in the formation of homodimers; however, the synthesis of the obtained heterodimers in good yields was only feasible via Heck reaction.

Homo and hetero glycodimers were also successfully synthesized from sugar alkynes using Sonogashira coupling reaction.

The cyclotrimerization reactions of the terminal alkyne GlcNAc derivatives using Grubbs' catalyst (12) did not succeed even that it have previously worked with other terminal alkyne carbohydrates. It was also proven that homodimers of aryl halide carbohydrates can not be obtained using Pd(OAc)$_2$ catalyzed reactions.

The spacer lengths and distances separating two atoms of the obtained dimers were calculated using CAChE for Windows software.
2.7 Experimental Methods

General methods

$^1$H NMR and $^{13}$C NMR spectra were obtained from either a Varian Gemini-200 z or a Bruker AMX500 spectrometer at 500, 300; or 200 MHz for protons and 125.7; 75; or 50.3 MHz for carbons, respectively. Proton chemical shifts are given relative to internal chloroform (7.24 ppm) for CDCl$_3$ solutions. Carbon chemical shifts were performed by the first order approximations and were based on shift correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), and 1- and 2- dimensional distortionless enhancement by polarization transfer (DEPT) experiments. Multiplicities of the NMR signals were reported using the following abbreviations: singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), multiplet (m).

Mass spectra were recorded on a Kratos IIH (FAB-glycerol) instrument. Xenon was used as the neutral carrier atom in FAB-MS experiments.

Infrared spectra were obtained on a Bomem-Michelson MB-100 FT-IR spectrophotometer neat on KBr plates.

Reactions were monitored by thin-layer chromatography using Kieselgel 60 F$_{254}$ precoated 0.25 mm thick aluminum backed plates and the compounds were detected by short wave UV light or by an ammonium molybdate solution (2.5% w/v). TLC plates were heated to 150$^\circ$C when necessary.

Purifications were performed by gravity or flash column chromatography on ing silica gel (230-400 mesh. E. Merck No. 9385).
2-acetamido 1,3,4,6-tetra-O-acetyl-2-deoxy-β-D-glucopyranose (18)

GlcNAc (compound 17, 5.0 g) was dissolved in pyridine (20 mL). This mixture was cooled to -10 °C under N₂ inert atmosphere, at which point acetic anhydride (4 mL) was added. The reaction mixture was allowed to warm up to room temperature, and was left stirring overnight, at which time TLC (EtOAc/MeOH, 9:1) indicated the consumption of all starting materials. The solution was concentrated under reduced pressure, and the crude product was dissolved in CH₂Cl₂, and then washed 3x with NaHCO₃ saturated solution. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure, giving the desired product (4.9 g, 92%). This yellowish white solid was then crystallized in EtOH, giving compound 18 as a white crystal (3.33 g, 61%). \(^1\)H NMR (CDC₃, 500 MHz): δ(ppm) 6.12 (N-H, d, J = 3.7 Hz, 1H), 5.88 (H-1, d, J:2 = 9.1 Hz, 1H), 5.19 (H-3, dd, J₂,3 = 9.4 Hz, J₂,4 = 8.1 Hz, 1H), 5.1 (H-4, dd, 1H), 4.02 (H-6, m, 1H), 3.98 (H-5, m, 1H), 1.86, 1.97, 1.98, 2.01 (OAc, 4 s, 12H), 2.12 (NAc, s, 3H); \(^13\)C NMR (CDCl₃, 75 MHz): δ(ppm) 169 (C=O), 90.2 (C-1), 69.8, 69.5, 68.9, 66.9, 61.5 (C-3, C-5, C-2, C-4, C-6). 20 (Ac).

2-propenyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (19) \(^{132, 133}\)

From compound 18: To an ice-bath cooled solution of compound 18 (1.0 g) and allyl alcohol (250 μL, 1.5 eq.) in CH₂Cl₂ (5 mL), was added BF₃Et₂O (480 μL, 1.5 eq.) via a syringe. The reaction mixture was allowed to warm up to room temperature, and was left stirring for 4 hrs, at which point, TLC (EtOAc/hexane, 3:1) indicated the consumption of all starting materials. The solution was dissolved CH₂Cl₂ (20 mL), transferred to a separatory funnel, and then washed 2x with a saturated solution of Na₂CO₃ and 1x with H₂O. The organic phase was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was passed through column chromatography on silica gel. Two compounds were isolated: the major compound was the hydroxylation product of the anomeric position of compound 18, and the minor product was the desired product, and was obtained in 40% yield.
From compound 24: To a solution of compound 24 (200 mg) in allyl alcohol (5 mL), was added camphorsulfonic acid (10 mg, 1 eq.). The reaction mixture was stirred overnight under reflux, and the TLC (EtOAc/hexane, 4:1) indicated the consumption of all starting materials. The solution was concentrated under reduced pressure, and the crude product was dissolved in CH₂Cl₂, and then washed 3x with a saturated solution of NaHCO₃ and 1x with H₂O. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel, using EtOAc/hexane, 3:1 as eluent. The wanted fractions were combined and concentrated under reduced pressure, giving compound 19 (195 mg, 80%). ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 6.2 (NH, bd, 1H), 5.9 (CH, m, 1H), 5.5 (H-3, bd, J₂,₂ = 9.1 Hz, 1H), 5.2 (H-4, dt, 1H), 5.19 (Ha of CH₂, dd, 1H), 4.8 (H-1, d, J₁,₁ = 8.4 Hz, 1H), 4.3 (Hb of CH₂, dd, 1H), 4.25 (H-2, dd, 1H), 4.15 (H-6, dd, 1H), 3.95 (H-6', dd, 1H), 3.72 (H-5, m, 1H). 2.45 (CH, s, 1H), 2.1, 2.05, 2.0, 1.95 (Ac, 4 s, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 172 (NCO), 170.6-170.3 (C=O), 133.8 (CH), 117.7 (=CH₂), 96.8 (C-1). 72.3. 71.8. 68.6. 62.1. 49.8 (C-3. C-5. C-6. C-4. C-2). 68.2 (CH₂); FAB-MS [M+1]+: 388.3.

1.4-bis(2-acetamido-3.4.6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-2-butene (20)

Two drops of MeOH were added to a partially soluble solution of compound 19 (300 mg) in CH₂Cl₂ (4mL). After dissolution, ruthenium catalyst 12 (33 mg) was added, and the reaction mixture was refluxed for 36 hrs. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc isopropanol. 9:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 20 as a white solid (195 mg, 66%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 6.45 (NH, bp, 2H), 5.68 (CH, bdd, 2H), 5.25 (H-3, m, 2H), 5.05 (H-4, dt, 2H), 4.68 (H-1 \textit{trans}, d, J₁,₁ = 8.23 Hz, 1H), 4.68 (H-1 \textit{cis}, d, J₁,₁ = 8.23 Hz, 1H), 4.15, 4.25 (H-a.b of CH₂, H-6, 24H), 2 m, 8H), 3.65 (H-5, m, 2H), 2.1-1.95 (Ac, 4 s, 24H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 170.7, 170.6, 170.4, 169.4 (C=O), 128.9, 128.8 (CH), 100.0, 99.6 (C-1), 72.3, 71.8. 68.6. 62.1. 49.8 (C-3. C-5. C-6. C-4. C-2). 68.1. 64.4 (CH₂); FAB-MS [M+1]+: 747.4.
Analytical calculation for C_{32}H_{46}N_{2}O_{18}: C, 51.47; H, 6.21; N, 3.75. Found: C, 50.91; H, 6.20; N, 3.89.

**2-propenyl 2-acetamido-2-deoxy-β-D-glucopyranoside (21)**

To a solution of compound 19 (100 mg) in MeOH, was added NaOMe solution until pH reached 9. The reaction mixture was stirred for 2 hrs, at which point TLC (CH_{2}Cl_{2}/MeOH, 9:1) indicated the consumption of all starting materials. H^{+} resin was added to acidify the reaction mixture and the solution was then stirred for 10 minutes, then filtered and concentrated under reduced pressure, giving compound 21 (63mg, 100%). Clean reaction: only mass spectrum was taken; FAB-MS [M+1]^{+}: 246.4.

**1,4-bis(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-butene (22)**

To a solution of compound 21 (100 mg) in MeOH (1 mL) and CH_{2}Cl_{2} (1 mL), was added ruthenium catalyst 12 (33 mg, 10%). The reaction mixture was refluxed overnight. A white solid was formed and floated to the surface upon cooling of the reaction mixture. This solid was filtered, dried, and was identified by NMR and MS as compound 22 (109 mg, 58%). \(^1\)H NMR (D_{2}O, 500 MHz): δ(ppm) spectrum not very clear for interpretation. \(^13\)C NMR (CDCl_{3}, 75 MHz): δ(ppm) 171.93 (C=O), 129.72 (CH), 100.68 (C-1), 76.59, 75.11, 72.1, 61.95, 55.91 (C-5, C-3, C-4, C-6, C-2), 67.01 (CH_{2}), 22.55 (Ac); FAB-MS [M+1]^{+}: 463.4.

**2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl chloride (23)**\(^{134}\)

GlcNAc (compound 17, 7.0 g) was dissolved in acetyl chloride (50 mL). The reaction mixture was stirred overnight in a well-sealed flask. The resulting clear pink solution was concentrated under reduced pressure, and the crude product was dissolved in EtOAc (200 mL). It was then washed 2x with a saturated solution of NaHCO_{3} and 1x with H_{2}O. The organic layer was isolated, dried over Na_{2}SO_{4}, filtered, and concentrated at 40 °C and under reduced pressure to 20 mL. Warm ether was then added, causing the
precipitation of white crystalline solid, which was filtered to give compound 23 (4.3 g, 65%); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) (ppm) 6.12 (N-H, d, J = 3.7 Hz, 1H), 5.9 (H-1, d, J\(_{1,2}\) = 9.1 Hz, 1H), 5.19 (H-3, dd, J\(_{2,3}\) = 9.4 Hz, J\(_{3,4}\) = 8.1 Hz, 1H), 5.1 (H-4, dd, 1H), 4.02 (H-6, m, 1H), 3.98, (H-5, m, 1H), 1.86, 1.97, 1.98, 2.01 (OAc, 3 s, 9H), 2.12 (NaC, s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) (ppm) 170.9, 170.5, 170 (C=O), 168.7 (NCO), 95.1 (C-1), 71.9, 70.9, 67.8, 60.5, 53.9 (C-5, C-3, C-4, C-6, C-2).

2-Methyl-4,5-(3,4,6-tri-O-acetyl-2-deoxy-\(\alpha\)-D-glucopyranosyl)-\(\Delta^2\)-oxazoline (24) \(^{135}\)

To a solution of compound 23 (1.0 g) in CH\(_2\)CN (15 mL), were added tetra-butyl ammonium chloride (3.5 g, 1.1 eq.) and NaHCO\(_3\) (2.11 g, 2.2 eq.), and the reaction mixture was stirred for 20 minutes at 55 °C, at which time TLC (EtOAc/hexane, 4:1) indicated the consumption of all starting materials. The solution was concentrated under reduced pressure, and the crude product was dissolved in CH\(_2\)Cl\(_2\), and then washed 2x with H\(_2\)O. The organic layer was isolated, dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure to give compound 24 as a white solid (870 mg, 100%); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) (ppm) 5.97 (H-1, d, J\(_{1,2}\) = 7.3 Hz, 1H), 5.27 (H-3, dd, J\(_{3,4}\) = 6.2 Hz, 1H), 4.94 (H-4, dq, J\(_{4,5}\) = 9.2 Hz, 1H), 4.18 (H-6.6', d, 2H), 2.09 (CCH\(_3\), s, 3H), 2.10, 2.08 (Ac, 3 s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) (ppm) 172.1, 170.1, 170.6 (C=O), 160 (NCO), 106 (C-1), 71.1, 71.2, 71.1, 62.1, 58.0 (C-5, C-3, C-4, C-6, C-2), 20.7 (Ac), 14.7 (NCCH\(_3\)); FAB-MS [M+1\(^+\)]: 330.2.

2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-\(\beta\)-D-galactopyranosyl chloride (26)

Following the same procedure adopted in the synthesis of compound 23, the commercially available GalNAc (compound 25, 1.0 g) was converted to compound 26 (614 mg, 65%) in crystal form; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) (ppm) 6.12 (N-H, d, J = 3.7 Hz, 1H), 5.88 (H-1, d, J\(_{1,2}\) = 9.1 Hz, 1H), 5.19 (H-3, dd, J\(_{2,3}\) = 2.2 Hz, J\(_{3,4}\) = 8.1 Hz, 1H), 5.1 (H-4, dd, 1H), 4.02 (H-6, m, 1H), 3.98, (H-5, m, 1H), 1.86, 1.97, 1.98, 2.01 (COCH\(_3\), 3 s, 9H), 2.12 (NCCH\(_3\), s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) (ppm) 170.9.
170.5, 170.0 (C=O), 168.7 (NCO), 95.1 (C-1), 71.9, 70.8, 67.8, 60.5, 53.8 (C-5, C-3, C-4, C, C-2), 23.01-20.70 (Ac).

2-Methyl 4.5-(3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyrano)-Δ²-oxazoline (27)

Following the same procedure adopted in the synthesis of compound 24, compound 26 (1.0 g) was reacted under the same conditions to give compound 27 (868 mg, 100%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 5.97 (H-1, d, J₁₂ = 7.3 Hz, 1H), 5.27 (H-3, dd, J₃₄ = 8.1 Hz, 1H), 4.94 (H-4, dq, J₄₅ = 9.2 Hz, 1H), 4.18 (H-6, 6’, d, 2H), 2.09 (CCH₃, s, 3H), 2.12, 2.10, 2.08 (Ac, 3 s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 172.2, 170.1, 170 (C=O), 160.0 (NCO), 106.1 (C-1), 71.7, 71.2, 71.1, 62.1, 58.0 (C-5, C-3, C-4, C-6, C-2), 20.7 (CH₃), 14.7 (NCCH₃); FAB-MS [M+1]⁺: 330.2.

2-propenyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranose (28)

Following the same procedure adopted in the synthesis of compound 19, compound 27 (1.0 g) was reacted under the same conditions to give compound 28 (1.56 g, 78%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 6.2 (NH, bd, 1H), 5.9 (CH, m, 1H), 5.5 (H-3, bd, J₃₄ = 2.3 Hz, 1H), 5.2 (H-4, dt, 1H), 5.19 (Ha of CH₂, dd, 1H), 4.8 (H-1, d, J₁₂ = 8.4 Hz, 1H), 4.3 (Hb of CH₂, dd, 1H), 4.25 (H-2, dd, 1H), 4.15 (H-6, dd, 1H), 3.95 (H-6’, dd, 1H), 3.72 (H-5, m, 1H), 2.45 (CH, s, 1H), 2.1, 2.05, 2.0, 1.95 (Ac, 4 s, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 172 (NCO), 170.6, 170.3, 170.0 (C=O), 133.8 (CH), 117.7 (=CH₂), 96.8 (C-1), 72.3, 71.8, 68.7 (C-3, C-5, C-4), 68.2 (CH₂), 62.2, 49.8 (C-6, C-2), 23.0 (NAc), 20.7 (OAc); FAB-MS [M+1]⁺: 388.3.

1,4-bis(2-acetamido-2-deoxy-β-D-galactopyranosyl)-2-butene (29)

To a solution of compound 28 (100 mg) in MeOH (1 mL) and CH₂Cl₂ (4 mL), was added ruthenium catalyst 12 (33 mg, 10%). The reaction mixture was refluxed overnight. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/isopropanol, 9:1 as
eluent. The wanted fractions were combined and concentrated under reduced pressure, giving compound 29 as a white solid (65.5 mg, 68%); $^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 6.45 (NH, bp, 2H), 5.68 (CH, bdd, 2H), 5.15 H-3, m, 2H), 5.05 (H-4, dt, 2H), 4.68 (H-1 trans, d, J$_{1-2}$ = 8.23 Hz, 1H), 4.68 (H-1 cis, d, J$_{1-2}$ = 8.23 Hz, 1H), 4.15, 4.25 (H-a,b of CH$_2$, H-6, 2 m, 3.65 (H-5, m, 2H), 2.1-1.95 (Ac, 4 s, 24H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 170.7, 170.6, 170.4, 169.4 (C=O), 128.9, 128.8 (CH), 100.0, 99.6 (C-1), 72.3, 71.8, 68.6, 62.1, 49.8 (C-3, C-5, C-6, C-4, C-2), 68.1, 64.4 (CH$_2$); FAB-MS [M+1]$^+$: 748.6.

2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl azide (30) $^{136}$

A solution of compound 23 (500 mg) in EtOAc (10 mL) was added to a solution of NaN$_3$ (192 mg, 1.5 eq.) and TBAHS (725 mg, 1.1 eq.) in H$_2$O (10 mL). The two-phase mixture was stirred rigorously for 4 hrs. at which time a TLC (EtOAc/hexane, 4:1) of the organic layer indicated the consumption of all starting materials. The two phases were separated, and the organic layer was washed 2x with H$_2$O, then isolated again, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give compound 30 as a white solid (517 mg, 100%); $^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 6.2 (NH, bd, 1H), 5.4 (H-5, bd, 1H), 5.7 (H-4, dt, 1H), 4.56 (H-1, d, J$_{1-2}$ = 8.4 Hz, 1H), 4.25 (H-2, dd, 1H), 4.15 (H-6, dd, 1H), 3.95 (H-6, dd, 1H), 3.72 (H-5, m, 1H), 2.1, 2.05, 2.0, 1.95 (Ac, 4 s, 12H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 172-170 (C=O), 89.3 (C-1), 76.2, 71.2, 65.4, 64 0, 66.8 (C-3, C-4, C-5, C-6, C-2). 23-20 (Ac).

2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosylamine (31)

To a solution of compound 30 (500 mg) in MeOH (10 mL), was added Pd/C 10% (20 mg). H$_2$, was bubbled in the solution, and the reaction mixture was stirred for 6 hrs. at which time TLC (EtOAc/hexane, 4:1) indicated the consumption of all starting materials. The solution was filtered on seelite under vacuum, and the filtrate was concentrated under reduced pressure to give compound 31 as white foam (450 mg, 95%); $^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 6.2 (NH, bd, 1H), 5.4 (H-3, bd, 1H), 5.1 (H-4, dt,
1H), 4.6 (H-1, d, J_{1,2} = 8.4 Hz, 1H), 4.25 (H-2, dd, 1H), 4.15 (H-6, dd, 1H), 3.95 (H-6', dd, 1H), 3.72 (H-5, m, 1H), 2.1, 2.05, 2.0, 1.95 (Ac, 4 s, 12H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 172-169 (C=O), 80.3 (C-1), 75.5, 71.3, 64.8, 63.9, 56.7 (C-3, C-4, C-5, C-6, C-2), 23-20 (Ac).

$N$-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-$\beta$-D-glucopyranosyl) butenamide (32)

To a solution of compound 31 (200 mg) in CH$_2$Cl$_2$ (10 mL), were added 4-Pentenoic acid (104 μL, 1.2 eq.) and EDC (196 mg, 1.2 eq.). The reaction mixture was stirred overnight, at which time TLC (EtOAc/hexane, 5:1) indicated the consumption of all starting materials. The solution was concentrated, dissolved in EtOAc, and washed 2x with H$_2$O. The organic layer was isolated again, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give compound 32 as a white solid (220 mg, 82%) $^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 7.02 (NH, d, J$_{NH,\text{H}}$ = 8.55 Hz, 1H), 6.31 (NH, d, J$_{NH,\text{H}}$ = 8.52 Hz, 1H), 5.72 (CH, m, 1H), 5.15 (H-3, dd, 1H), 5.05 (H-4, m, 1H), 4.97 (H-1, dd, J$_{1,2} = 10.2$ Hz, 1H), 4.27 (H-6, dd, J$_{6,5} = 12.45$ Hz, J$_{6,\text{H}}$ = 2.42 Hz, 1H), 4.11 (H-2, dd, 1H), 4.07 (H-6', dd, 1H), 3.2 (H-5, m, 1H), 2.25 (CH$_2$, m, 4H), 2.03, 2.02, 1.99, 1.90 (Ac, 4 s, 12H); $^{13}$C NMR (CDCl$_3$, 75 MHz); δ(ppm) 172-168 (C=O), 136.2 (CH), 118.3 (=CH$_2$), 80.7 (C-1). TMS 73.6, 68.3, 62.0, 67.0 (C-5, C-3, C-4, C-6, C-2), 35.5, 28.8 (CH$_2$), 23-20 (Ac); FAB-MS [M$^-$1]: 415.3.

1,6-bis[$N$-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-$\beta$-D-glucopyranosyl)]-3-hexenamide (33)

To a solution of compound 32 (100 mg) in CH$_2$Cl$_2$/MeOH, 9:1 (5 mL), was added Ruthenium catalyst 12 (33 mg, 10%). The reaction mixture was refluxed overnight. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/isopropanol, 9:1 as eluent. The wanted fractions were combined and concentrated under reduced pressure, giving compound 33 as a white solid (70 mg, 75%). $^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 7.02 (NH, d, J$_{NH,\text{H}}$ = 8.55 Hz, 2H), 6.31 (NH, d, J$_{NH,\text{H}}$ = 8.52 Hz, 2H), 5.68 (CH, bdd, 2H),
5.15 (H-3, dd, 2H), 5.05 (H-4, m, 2H), 4.68 (H-1 trans, d, J_{1,2} = 8.23 Hz, 1H), 4.68 (H-1 cis, d, J_{1,2} = 8.23 Hz, 1H), 4.27 (H-6, dd, J_{6,5'} = 12.45 Hz, J_{6,6'} = 2.42 Hz, 2H), 4.11 (H-2, dd, 2H), 4.07 (H-6', dd, 2H), 3.2 (H-5, m, 2H), 2.28 (CH_{2}, m, 8H), 2.03, 2.02, 1.99, 1.90 (Ac, 4 s, 12H); \^1^C NMR (CDCl\_3, 75 MHz): δ(ppm) 172-168 (C=O), 121.2 (CH), 80.7, 79.9 (C-1, C-1'), 73.8, 73.6, 68.3, 62.0, 67.0 (C-5, C-3, C-4, C-6, C-2), 35.5, 28.8 (CH_{2}), 23-20 (Ac); FAB-MS [M+1]\^+\: 802.7.

1,2,3,4,6-penta-O-acetyl-\(\beta\)-D-galactopyranoside (35)

Following the same procedure adopted in the synthesis of compound 18, the commercially available Galactose (compound 34, 5.0 g) was reacted with pyridine and acetic anhydride to give compound 35 as a white powder (9.6 g, 90%); \(^1\)H NMR (CDCl\_3, 500 MHz): δ(ppm) 6.12 (N-H, d, J = 3.7 Hz, 1H), 5.88 (H-1, d, J_{1,2} = 9.1 Hz, 1H), 5.19 (H-3, dd, J_{2,3} = 3.2 Hz, J_{3,4} = 8.1 Hz, 1H), 5.1 (H-4, dd, 1H), 4.02 (H-6, m, 1H), 3.98, (H-5, m, 1H), 1.86, 1.97, 1.98, 2.01 (COCH_{3}, 3 s, 9H), 2.12 (NCCH_{3}, s, 3H); \(^1^C NMR (CDCl\_3, 75 MHz): δ(ppm) 169 (C=O), 90.2 (C-1), 69.7, 69.5, 68.9, 66.9, 61.5, (C-3, C-5, C-2, C-4, C-6), 19 (Ac).

2,3,4,6-tetra-O-acetyl-\(\alpha\)-D-galactopyranosyl bromide (36)

Compound 35 (1.0 g) was added to a solution of 33% HBr/AcOH (6 mL), and the reaction mixture was stirred for 1 hr. at which time a small TLC aliquot was taken to be diluted in CH\_2Cl\_2 and washed 2x with NaHCO\_3 saturated solution. The TLC of the organic layer indicated the consumption of all starting materials. At this time, the reaction mixture was diluted in CH\_2Cl\_2 and poured into a beaker containing ice, to which was added NaHCO\_3. The mixture was stirred until all the ice melted. The organic layer was washed 3x with NaHCO\_3 saturated solution and 1x with H\_2O. The organic layer was then isolated, dried over Na\_2SO\_4, filtered, and concentrated under reduced pressure to give compound 36 as a white solid (852 mg, 82%); \(^1\)H NMR (CDCl\_3, 500 MHz): δ(ppm) 6.2 (NH, bd, 1H), 5.5 (H-3, bd, J_{3,4} = 2.6 Hz, 1H), 5.2 (H-4, dt, 1H), 5.1 (H-1, d, J_{1,2} = 8.4 Hz, 1H), 4.25 (H-2, dd, 1H), 4.15 (H-6, dd, 1H), 3.95 (H-6', dd, 1H), 3.72 (H-5, m, 1H),
2.45 (CH, s, 1H), 2.1, 2.05, 2.0, 1.95 (Ac, 4 s, 12H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 170-166 (C=O), 86.5 (C-1), 72.1, 67.8, 67, 66.8, 60.8 (C-5, C-2, C-4, C-3, C-6), 20.0 (Ac).

4-ethenylphenyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (39)

Compound 39 was prepared by PTC reaction, in which the organic layer was simply the solution of compound 36 (425 mg) in EtOAc (10 mL). Due to the instability of 4-hydroxyxystyrene, the aqueous phase was prepared as follows:

K$_2$CO$_3$ (550 mg, 2 eq.) was added to a solution of the commercially available 4-acetoxyxystyrene (400 µL, 2 eq.) in methanol (5 mL). The reaction mixture was stirred for 2 hrs, at which time TLC (EtOAc/hexane, 4:1) indicated the consumption of all starting materials. At this point, H$_2$O (10 mL) was added, and the solution was concentrated under reduced pressure to 10 mL, eliminating the 5 mL of MeOH. This 10 mL resulting solution constituted the aqueous layer of the PTC reaction, and was added to the prepared organic layer. To these two layers, TBAHS was added (352 mg, 1 eq.), and the two-phase solution was stirred vigorously for 4 hrs, at which time TLC (hexane/EtOAc, 3:2) indicated the consumption of all starting materials. The mixture was diluted in EtOAc and was washed 2x with H$_2$O. The organic layer was then isolated, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give compound 39 as a white solid (445 mg, 90%); $^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 7.3, 6.91 (Ar, 2d, 4H), 6.62 (CH, dd, J = 10.9 Hz), 5.6 (Ha of CH$_2$, dd, J = 17.6 Hz. J$_{ab}$ = 0.77 Hz, 1H), 5.42 (H-2, dd, 1H), 5.41 (H-4, dd, 1H), 5.14 (Hb of CH$_2$, d, 1H), 5.09 (H-3, dd, J$_{2,3}$ = 10 Hz, J$_{3,4}$ = 3.4 Hz), 5.0 (H-1, d, J$_{1,2}$ = 7.94 Hz, 1H), 4.1 (H-6.6', H-5, m, 3H), 2.02, 2.01, 1.99, 1.96 (Ac, 4 s, 12H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 170 (C=O). Ar: 158.0 (C=O ipso), 133.2 (C-CH ipso), 129.2, 118.6 (o. m), 136.7 (CH), 114.0 (=CH$_2$), 98.0 (C-1), 72.3, 72.2, 71, 67.8, 61.9 (C-5, C-3, C-2, C-4, C-6), 20.0 (Ac); FAB-MS [M-1]$^-$: 451.3.
4,4'-bis(2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside) stilbene (40)

**First lot:** To a solution of compound 39 (100 mg) in CH$_2$Cl$_2$ (4 mL), was added Ruthenium catalyst 12 (33 mg, 10%). The reaction mixture was refluxed overnight. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/isopropanol, 9:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 40 as a white solid (78 mg, 82%).

**Second lot:** To a solution of compound 39 (100 mg) in CH$_2$Cl$_2$ (4 mL), was added Ruthenium catalyst 15 (25 mg, 10%). The reaction mixture was refluxed for 4 hrs. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/isopropanol, 9:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 40 as a white solid (89 mg, 91%).

**Third lot:** To a solution of compound 39 (50 mg, 1 eq.) and compound 45 (90 mg, 1.5 eq.) in Et$_3$N (6 mL), were added Pd(OAc)$_2$ (2.5 mg, 0.1 eq.) and PPh$_3$ (6 mg, 0.2 eq.). The reaction mixture was refluxed overnight. TLC (EtOAc/hexane, 6:5) indicated the consumption of all starting materials. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/hexane, 6:5 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 40 as a white solid (3 mg, 60%).

$^1$H NMR (CDCl$_3$, 300 MHz): δ (ppm) 7.46, 6.98 (Ar, 2d, 4 + 4H), 6.97 (CH, s, 2H), 5.44 (H-2, dd, J=10.5 Hz, J=7.9 Hz, 2H), 5.43 (H-4, dd, J=3.5 Hz, J=1.1 Hz, 2H), 5.08 (H-3, dd, J$_{2,3}$=10.5 Hz, J$_{3,4}$=3.5 Hz, 2H), 4.98 (H-1, d, J=7.9 Hz, 2H), 4.19 (H-6a, dd, J$_{6a,6b}$=11.13 Hz, J$_{5-6a}$=7.2 Hz, 2H), 4.03 (H-6b, dd, J$_{6a,6b}$=11.3 Hz, J$_{5-6b}$=6.0 Hz, 2H), 4.03 (H-5, dd, J$_{5-6a}$=7.2 Hz, J$_{5-6b}$=6.0 Hz, 2H), 2.15, 2.04, 2.04, 1.98 (COCH$_3$, 4 s, 12H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ (ppm) 170.4, 170.3, 170.1, 169.4 (C=O), 156.3, 132.7, 128.5, 127.4 (CH), 99.5 (C-1), 71.2, 70.8, 68.6, 66.8 (C-2, C-3, C-4, C-5), 61.4 (C-6), 20.8, 20.7, 20.6 (Ac); FAB-MS [M+1]$^+$: 874.8.
4,4'-diacetoxy stilbene (42)

To a solution of 4-acetoxy styrene (compound 37, 20 µL, 1 eq.) and 4-acetoxy iodobenzene (compound 41, 50 mg, 1.5 eq.) in Et₃N (4 mL), were added Pd(OAc)₂ (3 mg, 0.1 eq.) and PPh₃ (6 mg, 0.2 eq.). The reaction mixture was refluxed overnight, at which time TLC (EtOAc/hexane, 4:1) indicated the consumption of all starting materials. The solution was diluted with CH₂Cl₂, filtered through silicic, and the filtrate was concentrated under reduced pressure, giving compound 42 as brown oil (32 mg, 82%); ¹H NMR (CDCl₃, 300 MHz): δ(ppm) 7.61, 7.08 (Ar, 2dd, 8H), 6.9 (CH, s, 2H), 2.3 (CH₃, s, 6H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 169.2 (C=O), Ar: 152.4 (C=O ipso), 135.2 (C-CH ipso), 127.6, 122.0 (o. m), 128.1 (CH), 20.9 (Ac); FAB-MS [M–1]⁻: 297.2.

4-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl) 4’-acetoxy-stilbene (43)

To a solution of compound 39 (50 mg, 1 eq.) and 4-acetoxy iodobenzene (compound 41, 22 µL, 1.5 eq.) in Et₃N (4 mL), were added Pd(OAc)₂ (3 mg, 0.1 eq.) and PPh₃ (7 mg, 0.2 eq.). The reaction mixture was refluxed overnight, at which time TLC (EtOAc/hexane, 4:1) indicated the consumption of all starting materials. The solution was diluted with CH₂Cl₂, filtered through silicic, and the filtrate was concentrated under reduced pressure. The crude oil was further purified by silica gel chromatography using hexane/EtOAc, 1:1 as eluent. The filtrate was concentrated under reduced pressure, giving compound 43 (47 mg, 72%); ¹H NMR (CDCl₃, 300 MHz): δ(ppm) 7.13, 7.08 (PhOAc, 2d, 4H), 7.05, 7.18 (Sugar-O-Ph, 2d, 4H), 5.42 (H-2, dd, 1H), 5.41 (H-4, dd, 1H), 5.09 (H-3, dd, J₂,₃ = 10 Hz, J₂,₄ = 3.4 Hz), 5.0 (H-1, d, J₁,₂ = 7.94 Hz, 1H), 4.1 (H-6,6'. H-5, m, 3H), 2.14, 2.02, 2.01, 1.99, 1.96 (Ac, 5 s, 15H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 169.94, 169.23 (C=O), 156.87, 152.38, 135.18, 129.91, 128.4, 127.6, 122.0, 118.56 (Ar), 128.1 (CH), 98.54 (C-1), 72.35, 72.24, 71.09, 67.78, 61.84 (C-5, C-3, C-2, C-4, C-6), 20.9, 20.5 (Ac).
4-Iodophenyl 2,3,4,6-tetra-\textit{O}-acetyl-\textit{\beta}-D-galactopyranoside (45)

To a solution of compound 36 (425 mg, 1 eq.) in EtOAc (10 mg), were added 4-Iodophenol (compound 44. 295 mg, 1.3 eq.), TBAHS (352 mg, 1 eq.), and H$_2$O (10 mL). The two-phase solution mixture was stirred vigorously for 3 hrs, at which time a TLC (hexane/EtOAc, 6:5) of the organic layer indicated the consumption of all starting materials. The mixture was diluted with EtOAc, and the organic layer was washed 2x with H$_2$O, isolated, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using hexane/EtOAc, 6:5 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 45 as a white solid (350 mg, 80%); $^1$H NMR (CDCl$_3$, 300 MHz): δ(ppm) 7.56 (C$_6$H$_5$, 2d. J=8.9 Hz, 2H), 6.75 (C$_6$H$_5$, 2d. J=8.9 Hz, 2H), 5.44 (H-2, dd. J=10.5, J=7.9, 1 H), 5.43 (H-4, dd. J=3.5, J=1.1 Hz, 1H), 5.08 (H-3, dd, J$_{2,3}$=10.5 Hz, J$_{3,4}$=3.5 Hz, 1H), 4.98 (H-1, d. J=7.9 Hz, 1H), 4.19 (H-6a, dd. J$_{6a,6b}$=11.13 Hz, J$_{5,6a}$=7.2 Hz, 1H). 4.03 (H-6b, dd. J$_{6a,6b}$=11.3 Hz, J$_{5,6b}$=6.0 Hz, 1H), 4.03 (H-5, dd, J$_{5,6a}$=7.2 Hz, J$_{5,6b}$=6.0 Hz, 1H). 2.15, 2.04, 2.04, 1.98 (COCH$_3$, 4 s, 12H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 170.4, 170.3, 170.1, 169.4 (C=O), 156.6, 138.2, 121.6, 82.7 (Ar), 99.5 (C-1), 71.2, 70.8, 68.6, 66.8 (C-2, C-3, C-4, C-5), 61.4 (C-6), 20.8, 20.7, 20.6 (Ac).

Lactose octaacetate (47)

Following the same procedure adopted in the synthesis of compound 18, the commercially available lactose (compound 46, 2.0 g) was converted to compound 47 (3.9 g, 75%). $^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 5.64 (H-1, d, J$_{1,2}$ = 8.6 Hz, 1H), 5.33 (H-4', dd, J$_{4',5'}$ = 1 Hz, 1H), 5.22 (H-3, dd. J$_{3,4}$=9.1 Hz, 1H), 5.09 (H-2, dd, J$_{2,3}$ = 9.4 Hz, 1H). 5.09 (H-2', dd, J$_{2',3'}$ = 10.8 Hz, 1H), 4.92 (H-3', dd. J$_{3',4'}$ = 3.4 Hz, 1H), 4.45 (H-1', d, J$_{1',2'}$ = 7.9 Hz, 1H), 4.02-4.13 (H-6 & H-6', m, 4H), 3.85 (H-5', ddd, 1H), 3.82 (H-4, dd. J$_{4,5}$ = 8.7, 1H), 3.68 (H-5, m, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 170.5, 170.2, 170.0, 169.3, 169 (C=O), 99.4 (C-1'), 86.5 (C-1), 79.5-61.26 (10 peaks: C-2 to C-6, C-2' to C-6'). 20 (Ac).
(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1-4)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl bromide (48)

To a solution of peracetylated lactoside (compound 47, 1.0 g) in CH$_2$Cl$_2$ (2 mL), was added a solution of 33% HBr/AcOH (1 mL, 3 eq.), and the reaction mixture was stirred for 1 hr, at which time a small TLC aliquot was taken to be diluted in CH$_2$Cl$_2$ and washed 2x with NaHCO$_3$ saturated solution. The TLC of the organic layer indicated the consumption of all starting materials. At this time, the reaction mixture was diluted in CH$_2$Cl$_2$ and poured into a beaker containing ice, to which was added NaHCO$_3$. The mixture was stirred until all the ice melted. The organic layer was washed 3x with NaHCO$_3$ saturated solution and 1x with H$_2$O. The organic layer was then isolated, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give compound 48 as a white solid (540 mg, 52%). $^1$H NMR (CDCl$_3$, 500 MHz): δ/ppm 5.64 (H-1, d, J$_{1,2}$ = 3.2 Hz, 1H), 5.33 (H-4', dd, J$_{4',5'}$ = 1 Hz, 1H), 5.22 (H-3, dd, J$_{3,4}$ = 9.1 Hz, 1H), 5.09 (H-2', dd, J$_{2',3'}$ = 9.4 Hz, 1H), 5.09 (H-5, dd, J$_{5,6}$ = 10.8 Hz, 1H), 4.92 (H-3', dd, J$_{3',4'}$ = 3.4 Hz, 1H), 4.45 (H-1', d, J$_{1',2'}$ = 7.9 Hz, 1H), 4.02-4.13 (H-6 & H-6', m, 4H), 3.85 (H-5', ddd, 1H), 3.82 (H-4, dd, J$_{4,5}$ = 8.7, 1H), 3.68 (H-5, m, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ/ppm 170.5, 170.2, 170.0, 169.3, 169 (C=O), 99.4 (C-1'), 86.5 (C-1), 79.5-61.26 (10 peaks: C-2 to C-6, C-2' to C-6'). 20 (Ac).

4-ethenylphenyl-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1-4)-2,3,6-tri-O-acetyl-β-D-glucopyranoside (49)

Compound 49 was prepared by PTC reaction, in which the organic layer was simply the solution of compound 48 (1.0 g) in EtOAc (10 mL). Due to the instability of 4-hydroxyxystyrene, the aqueous phase was prepared as follows:

K$_2$CO$_3$ (483 mg, 2.5 eq.) was added to a solution of the commercially available 4-acetoxyxystyrene (400 µL, 2 eq.) in methanol (5 mL). The reaction mixture was stirred for 2 hrs. at which time TLC (EtOAc/hexane, 1:1) indicated the consumption of all starting materials. At this point, H$_2$O (10 mL) was added, and the solution was concentrated under reduced pressure to 10 mL, eliminating the 5 mL of MeOH. This 10 mL resulting
solution constituted the aqueous layer of the PTC reaction, and was added to the prepared organic layer. To these two layers, TBAHS was added (475 mg, 1 eq.), and the two-phase solution was stirred vigorously for 4 hrs, at which time TLC (hexane/EtOAc, 1:1) indicated the consumption of all starting materials. The mixture was diluted in EtOAc and was washed 2x with H₂O. The organic layer was then isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give compound 49 as a white solid (820 mg, 78%). ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.29, 6.9 (Ar, 2d, 2 + 2H), 6.61 (CH, dd, 1H), 5.6 (Ha of CH₂, d, 1H), 5.44 (H-1', d, J₁₂ = 8.4 Hz, 1H), 5.33 (H-4', dd, J₂₋₄' = 1 Hz, 1H), 5.22 (H-3', dd, J₃₋₂' = 9.1 Hz, 1H), 5.15 (Hb of CH₂, d, 1H), 5.09 (H-2', dd, J₂₋₃ = 9.4 Hz, 1H), 5.09 (H-2', dd, J₂₋₃' = 10.8 Hz, 1H), 4.92 (H-3', dd, J₃₋₄' = 3.4 Hz, 1H), 4.45 (H-1', d, J₁₋₂' = 7.9 Hz, 1H), 4.02-4.13 (H-6 & H-6', m, 4H), 3.85 (H-5', ddd, 1H), 3.82 (H-4, dd, J₄₋₅ = 8.7, 1H), 3.68 (H-5, m, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 170.26, 170.2, 170.05, 169.95, 169.65, 169.5, 169 (C=O), 156.4, 132.9, 127.3, 116.9 (Ar), 135.8 (CH), 112.9 (CH₂), 101.1, 98.7 (C-1', C-1'). 77.2-60.79 (10 peaks: C-2 to C-6, C-2' to C-6'). 20 (Ac); FAB-MS [M+1]⁺: 739.6.

4-iodophenyl-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1-4)-2,3,6-tri-O-acetyl-β-D-glucopyranoside (50)

To a solution of compound 48 (500 mg, 1 eq.) in EtOAc (10 mg), were added 4-Iodophenol (compound 44. 195 mg, 1.3 eq.), TBAHS (240 mg, 1 eq.), and H₂O (10 mL). The two-phase solution mixture was stirred vigorously for 3 hrs, at which time TLC (hexane/EtOAc, 1:1) of the organic layer indicated the consumption of all starting materials. The mixture was diluted with EtOAc, and the organic layer was washed 2x with H₂O, isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using hexane/EtOAc, 1:1 as eluent. The wanted fractions were combined and concentrated under reduced pressure, giving compound 50 as a white solid (485 mg, 82%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.29, 6.9 (Ar, 2d, 2 + 2H), 5.54 (H-1', d, J₁₋₂ = 8.4 Hz, 1H), 5.38 (H-4', dd, J₂₋₄' = 1 Hz, 1H), 5.22 (H-3', dd, J₃₋₂' = 9.1 Hz, 1H), 5.09 (H-2', dd, J₂₋₃ = 9.4 Hz, 1H), 5.09 (H-2', dd, J₂₋₃' = 10.8 Hz, 1H), 4.92 (H-3', dd, J₃₋₄' = 3.4 Hz, 1H), 4.45 (H-1', d, J₁₋₂' = 7.9 Hz, 4.45 (H-1', d, J₁₋₂' = 7.9 Hz,
4-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl), 4′[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1-4)-2,3,6-tri-O-acetyl-β-D-glucopyranoside] stilbene (51)

To a solution of compound 39 (50 mg, 1 eq.) and compound 50 (60 mg, 1.5 eq.) in Et$_3$N (6 mL), were added Pd(OAc)$_2$ (2 mg, 0.1 eq.) and PPh$_3$ (4 mg, 0.2 eq.). The reaction mixture was refluxed overnight, at which time TLC (EtOAc/hexane, 6:5) indicated the consumption of all starting materials. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/hexane, 6:5 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 51 as a white solid (43 mg, 62%): H NMR (CDCl$_3$, 500 MHz): δ (ppm) 7.39, 6.92 (Ar, 2 m, 4–4H), 6.96, 6.94 (CH, 2 d, J$_{H-H}$ = 15.3, 2H), 5.5–3.7 (H1-H6 – H’1-H’6 – H”1-H”6, 21H), 2.16–1.94 (Ac, 11 s, 33H); C NMR (CDCl$_3$, 75 MHz): δ (ppm) 170.3–169.0 (C=O) 156.33, 156.22 (Ar-ipso), 127.46, 127.44 (Ar-meta), 117.1 (Ar-para), 126.9 (CH), 101.05, 99.6, 98.7 (C-1′, C-1, C-1″), 76.1–60.8 (C-2 to C-6, C2′ to C-6′, C-2″ to C-6″) 20.7–20.4 (Ac); FAB-MS [M+1]$^+$: 839.5.

4,4′-bis[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1-4)-2,3,6-tri-O-acetyl-β-D-glucopyranoside] stilbene (52)

To a solution of compound 49 (50 mg, 1 eq.) and compound 50 (85 mg, 1.5 eq.) in Et$_3$N (6 mL), were added Pd(OAc)$_2$ (2 mg, 0.1 eq.) and PPh$_3$ (4 mg, 0.2 eq.). The reaction mixture was refluxed overnight. TLC (EtOAc/hexane, 6:5) indicated the consumption of all starting materials. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/hexane, 6:5 as eluent. Fractions containing the product were combined and
concentrated under reduced pressure, giving compound 52 as a white solid (52 mg, 53%); 
$^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 7.29, 6.9 (Ar, 2 d, 4 + 4H), 6.61 (CH, s, 2H), 5.44 (H-1, d, J$_{1,2}$ = 8.4 Hz, 2H), 5.33 (H-4', dd, J$_{4,5,2}$ = 1 Hz, 2H), 5.22 (H-3, dd, J$_{3,4}$ = 9.1 Hz, 2H), 5.09 (H-2', dd, J$_{2,3}$ = 9.4 Hz, 2H), 5.09 (H-2', dd, J$_{2,3}$ = 10.8 Hz, 2H), 4.92 (H-3', dd, J$_{3,4,2}$ = 3.4 Hz, 2H), 4.45 (H-1', d, J$_{1,2}$ = 7.9 Hz, 2H), 4.02-4.13 (H-6 & H-6', m, 8H), 3.85 (H-5', ddd, 2H), 3.82 (H-4, dd, J$_{4,5}$ = 8.7, 2H), 3.68 (H-5, m, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 170.26, 170.2, 170.05, 169.95, 169.65, 169.5, 169 (C=O), 156.4, 132.9, 127.3, 116.9 (Ar), 132.4 (CH), 101.1, 98.7 (C-1, C-1'), 77.24-60.79 (10 peaks: C-2 to C-6, C-2' to C-6'). 20 (Ac); FAB-MS [M+1]$^+$: 1594.0.

1,4-bis(E)-[1-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl) prop-2-ene)-benzene (55)

With the same general procedure of the Heck reaction adopted in the synthesis of compound 51, the already prepared compound 53 (100 mg, 2.2 eq.) and the commercially available 1,4-diodobenzene (54, 40 mg, 1 eq.) were coupled in the presence of Pd(Ac)$_2$ (10%) and PPh$_3$ (20%) in Et$_3$N. to give compound 55 (62 mg, 63%); $^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 6.4 (Ar, d, 4H), 6.1 (CH, m, 2H), 5.4 (H-2, t, J = 1.2 Hz, 2H), 5.2 (H-3, CH, m, 4H), 4.35 (H-4, m, 2H), 4.2, 4.1 (H-6.6', 2 m, 4H), 4.05 (H-5, H-1, m, 4H), 2.6, 2.5 (CH$_2$, 2m, 4H), 2.1, 2.06, 2.04, 1.84 (Ac, 4 s, 24H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 170.77, 170.34, 169.66, 168.31 (C=O), 137.91, 127.79 (Ar), 129.53 (CH), 128.56 (CH'), 75.72 (C-1), 72.17 (C-2), 71.43 (C-4), 71.39 (C-3), 62.24 (C-6), 35.6 (CH$_2$), 20.84, 20.64 (Ac); FAB-MS [M+1]$^+$: 819.7.

4-iodophenyl-2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (56)

To a solution of compound 23 (500 mg, 1 eq.) in EtOAc (10 mg), were added 4-iodophenol (compound 44, 392 mg, 1.3 eq.), TBAHS (465 mg, 1 eq.), and H$_2$O (10 mL). The two-phase solution mixture was stirred vigorously for 3 hrs. at which time a TLC (hexane:EtOAc, 1:5) of the organic layer indicated the consumption of all starting
materials. The mixture was diluted with EtOAc, and the organic layer was washed 2x with H₂O, isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using hexane/EtOAc, 1:5 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 56 as a white solid (600 mg, 80%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.52, 6.73 (Ar, 2d, 4H), 5.95 (NH, d, 1H), 5.4 (H-3, dd, J₂,₄ = 9.1 Hz, 1H), 5.25 (H-1, d, J₁,₂ = 8.4 Hz, 1H), 5.1 (H-4, dd, 1H), 4.25 (H-2, dd, 1H), 4.15 (H-6, dd, 1H), 4.05 (H-6', dd, 1H), 3.85 (H-5, m, 1H), 2.1, 2.05, 2.0, 1.95 (Ac, 4 s, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 170.6 (C=O), 169.8 (NCO), 156.6, 138.2, 121.6, 82.7 (Ar), 96.8 (C-1), 72.3, 71.8, 68.6, 62.1, 49.8 (C-3, C-5, C-6, C-4, C-2), 20.21, 20.12 (Ac); FAB-MS [M+1]⁺: 550.2.

2-propynyl-2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (57)

To a solution of compound 24 (200mg) in propargyl alcohol (5 mL), was added Camphorsulfonic acid (10mg, 1 eq.). The reaction mixture was stirred overnight under reflux, and the TLC (EtOAc/hexane, 4:1) indicated the consumption of all starting materials. The solution was concentrated under reduced pressure, and the crude product was dissolved in CH₂Cl₂, and then washed 3x with a saturated solution of NaHCO₃ and 1x with H₂O. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel, using EtOAc/hexane, 3:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 57 (210 mg, 90%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 6.2 (NH, bd, 1H), 5.5 (H-3, bd, 1H), 5.2 (H-4, dt, 1H), 4.8 (H-1, d, J₁,₂ = 8.4 Hz, 1H), 4.3 (CH₂, s, 2H), 4.25 (H-2, dd, 1H), 4.15 (H-6, dd, 1H), 3.95 (H-6', dd, 1H), 3.72 (H-5, m, 1H), 2.45 (CH, s, 1H), 2.1, 2.05, 2.0, 1.95 (Ac, 4 s, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 172-170 (C=O), 103.7 (C-1), 72.3, 71.8, 68.7, 62.1, 51.0 (C-3, C-5, C-4, C-6, C-2), 79.7 (C), 73.9 (CH), 53.8 (CH₂), 23-20 (Ac); FAB-MS [M+1]⁺: 386.3.
1-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside), 4-(2-propynyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside) benzene (58)

To a solution of compound 57 (80 mg, 1 eq.) and compound 56 (103 mg, 1.1 eq.) in Et$_3$N (6 mL), was added PdCl$_2$(PPh$_3$)$_2$ (10 mg, 0.2 eq.). The reaction mixture was refluxed overnight. TLC (EtOAc/hexane, 5:1) indicated the consumption of most starting materials. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/hexane, 5:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 58 as a white solid (96 mg, 58%). $^1$H NMR (CDCl$_3$, 500 MHz): δ(ppm) 7.3, 6.85 (Ar, 2d, 4H), 5.8 (NH, bd, 2H), 5.4 to 3.7 (H-1 to H-6, H-1’ to H-6’; CH$_2$, 16H), 2.1-1.9 (Ac, 24H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ(ppm) 172.02, 171.43, 170.64, 170.30 (C=O), 157.41, 130.89, 114.09, 112.12 (Ar), 103.69 (C-1), 97.61 (C-1’), 87.86, 87.03 (-C≡C-), 72.30, 71.84, 68.67, 62.16, 53.37 (C-3, C-5, C-4, C-6, C-2), 71.65, 70.19, 68.25, 61.63, 53.82 (C-3’, C-5’, C-4’, C-6’, C-2’). 23.17, 20.69 (Ac); FAB-MS [M-1]$: 807.7.

N-2-propynyl, N-acetyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosylamine (59)

Commercially available GlucNAc (compound 17, 500 mg) was added to propargylamine (2.5 mL), and the reaction mixture was stirred for 3 hrs. at which time a TLC aliquot was taken out, and mixed with acetic anhydride and pyridine for 10 minutes. This aliquot indicated by TLC the consumption of all starting materials. In the same way, the solution was concentrated, diluted with pyridine (5 mL), and cooled to 0 °C. Ac$_2$O was then added, and the mixture was stirred for 30 minutes. The solution was once again concentrated under reduced pressure, diluted in EtOAc and washed 2x with H$_2$O. The organic layer was isolated, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel, using EtOAc/hexane, 3:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 59 (810 mg, 84%); IR (KBr)
1817, 2352, 3267 cm⁻¹, ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 6.05 (NH, d, J = 9.4 Hz, 1H), 5.73 (H-1, d, J₁₂ = 9.9 Hz, 1H), 5.12 (H-3, dd, 1H), 5.07 (H-4, dd, 1H), 4.17 (H-2, H-6, m, 3H), 4.02 (CH₂, d, ¹J = 2.1 Hz, 2H), 3.75 (H-5, m, 1H), 2.22 (CH, s, 1H), 2.2 (NaC, s, 3H), 2.04, 1.99, 1.98 (OAc, 3 s, 9H), 1.81 (NHAc, s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 172.1, 170.1, 169.8, 165.1, 164.9 (C=O), 83.1 (C-1), 73.7, 73.3, 68.3, 60.4, 56.3 (C-3, C-5, C-4, C-6, C-2), 77.6 (C), 72.7 (CH), 38.4 (CH₂), 20.4-20 (Ac); FAB-MS [M+1]⁺: 427.3.

1.6-bis(N-acetyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosylamine)-2,4-hexadiyne (60)

To a solution of compound 59 (100 mg) in DMF-Et₃N (6 mL, 1:1 v:v), was added PdCl₂(PPh₃)₂ (10 mg, 0.2 eq.). The reaction mixture was refluxed for 48 hrs. TLC (EtOAc/hexane, 3:1) indicated the consumption of most starting materials. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/hexane, 3:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 60 as a dirty white solid (47 mg, 48%); IR (KBr) 1817, 2352 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 6.05 (NH, d, 2H), 5.73 (H-1, d, J₁₂ = 9.9 Hz, 2H), 5.12 (H-3, dd, 2H), 5.07 (H-4, dd, 2H), 4.17 (H-2, H-6, m, 6H), 4.02 (CH₂, d, 4H), 3.75 (H-5, m, 2H), 2.2 (NaC, s, 6H), 2.04, 1.99, 1.98 (OAc, 3 s, 18H), 1.81 (NHAc, s, 6H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 172.1, 170.1, 169.8, 165.1, 164.9 (C=O), 83.1 (C-1), 73.7, 73.3, 68.3, 60.4, 56.3 (C-3, C-5, C-4, C-6, C-2), 78.2, 77.6 (C), 38.4 (CH₂), 20.4-20 (Ac); FAB-MS [M+1]⁺: 851.7.

1.4-bis(N-2-propynyl, N-acetyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosylamine) benzene (61)

To a solution of compound 59 (100 mg, 2.2 eq.) and the commercially available 1.4-Diiodobenzene (compound 54, 38 mg, 1 eq.) in Et₃N (6 mL), was added PdCl₂(PPh₃)₂ (10 mg, 0.2 eq.). The reaction mixture was refluxed overnight. TLC (EtOAc/hexane, 3:1)
indicated the consumption of most starting materials. The solution was concentrated under reduced pressure, and the product was purified by column chromatography on silica gel, using EtOAc/hexane, 3:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 61 as a white solid (66 mg, 62%); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) (ppm) 7.1 (Ar, d, 4H), 6.05 (NH, d, 2H), 5.73 (H-1, d, J\(_{1,2}\) = 9.9 Hz, 2H), 5.12 (H-3, dd, 2H), 5.07 (H-4, dd, 2H), 4.17 (H-2, H-6, m, 6H), 4.02 (CH\(_2\), d, 4H), 3.75 (H-5, m, 2H), 2.2 (NAc, s, 6H), 2.04, 1.99, 1.98 (OAc, 3 s, 18H), 1.81 (NHAc, s, 6H); \(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) (ppm) 172.1, 170.1, 169.8, 165.1, 164.9 (C=O), 129.47, 112.63 (Ar), 83.1 (C-1), 73.7, 73.3, 68.3, 60.4, 56.3 (C-3, C-5, C-4, C-6, C-2), 78.2, 77.6 (C), 38.4 (CH\(_2\)), 20.4-20 (Ac); FAB-MS [M-1]\(^+\): 927.7.

\(N\)-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-\(\beta\)-D-glucopyranosyl) 4-pentynamide (62)

To a solution of compound 31 (200 mg) in CH\(_2\)Cl\(_2\), were added 4-pentynoic acid (100 mg, 1.2 eq.) and EDC (196 mg, 1.2 eq.). The reaction mixture was stirred overnight. TLC (EtOAc/hexane, 4:1) indicated the consumption of all starting materials. The solution was diluted with CH\(_2\)Cl\(_2\), and washed 2x with H\(_2\)O. The organic layer was isolated, dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude product was then crystallized in EtOH. The crystals were filtered and dried, giving compound 62 (168 mg, 60%); IR (KBr) 1817, 2352, 3267 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) (ppm) 7.05 (C-1NH, d, 1H), 6.4 (C-2NH, d, 1H), 5.1 (H-4, H-3, H-1, m, 3H), 4.25 (H-6, dd, 1H), 4.15 (H-2, dd, 1H), 4.07 (H-6', dd, 1H), 3.8 (H-5, m, 1H), 2.45 (CH\(_2\), m, 4H), 2.07, 2.05, 2.0, 1.92 (Ac, 4s, 12H), 1.93 (CH, s, 1H); \(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) (ppm) 172.1, 170.1, 169.9, 168.7, 168.3 (C=O), 80.4 (C-1), 73.8, 73.3, 68.3, 62.1, 56.0 (C-5, C-3, C-4, C-6, C-2), 89.9 (C), 70.8 (CH), 35.7 (COCH\(_2\)), 17.2 (CH\(_2\)), 23-20 (Ac); FAB-MS [M-1]\(^+\): 427.3.
1.10-bis[N-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)] 4,6-decadiyne (63)

Under the same conditions adopted in the synthesis of compound 60, compound 62 (60 mg) gave compound 63 (64 mg, 54%); IR (KBr) 1817, 2352 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.05 (C-1NH, d, 2H), 6.4 (C-2NH, d, 2H), 5.1 (H-4, H-3, H-1, m, 6H), 4.25 (H-6, dd, 2H), 4.15 (H-2, dd, 2H), 4.07 (H-6', dd, 2H), 3.8 (H-5, m, 2H), 2.45 (CH₂, m, 8H), 2.09, 2.05, 2.0, 1.92 (Ac, 4 s, 24H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 172.1, 170.1, 169.9, 168.7, 168.3 (C=O), 80.4 (C-1), 73.8, 73.3, 68.3, 62.1, 56.0 (C-5, C-3, C-4, C-6, C-2). 87.3 (C). 35.7 (NCOCH₂), 17.2 (CH₂), 23-20 (Ac); FAB-MS [M-1]⁺: 551.7.
2.8 References


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CHAPTER III

SYNTHESIS OF PHENYLETHANOID GLYCOSIDES.

3.1 Introduction

Phenylethanoloid glycosides (PhGs) are a group of water-soluble natural products widely distributed in the plant kingdom, most of which are isolated from medicinal plants. Structurally, they are characterized by cinnamic acid and hydroxylphenylethyl moieties, attached to a β-glucopyranose through ester and glycosidic linkages respectively. Rhamnose, xylose, apirose, etc. may also be attached to the glucose residue, which in most cases forms the core of the molecule. 

The first literature references to phenylethanoloid glycosides concerned the isolation of echinacose (Figure 3.1.1) from Echinacea angustifolia (Asteraceae) in 1950, and verbacose (Figure 3.1.1) from Verbascum sinuatum (Scrophulariaceae) in 1963, but their structures were not determined at the time. Verbacose was isolated again in 1966 from Syringa vulgaris (Oleacea) and its structure determined to be β-(3,4-dihydroxyphenyl)ethyl-O-α-L-rhamnopyranosyl (1’→3’)-β-D-(4’-O-caffeoyl) glucopyranoside, but it was named as acteoside.

In 1982, Andary et al. found that the structures of verbacose and acteoside were identical. A year later, Kusaginin was isolated from Clerodendron tricholomum (Verbenaceae), and subsequently shown to be identical to verbacose (acteoside). Acteoside is now the accepted name for this natural product. However, the structure of echinacose, isolated for the first time in 1950, was not definitively elucidated until 1983 by Andary and co-workers.

The phenylethanoloid glycosides are classified according to the number and type of sugars they contain. The monosaccharides are glucopyranosides, with caffeic and gallic acids being the most common aromatic groups bonded to the glucose. PhG
monosaccharides with a modified aglycone also occur. The disaccharides are classified according to the sugar attached to the glucose. Some contain a rhamnose attached to C-3 of glucose. The trisaccharides are the most common PhGs. They all contain rhamnose as the second sugar unit. They have been distributed into two subgroups according to the point of attachment of this sugar, those bonded to C-3 and those bonded to C-6. The third sugar unit may be glucose, xylose, arabinose, apiose, galactose, lyxose, or rhamnose. Caffeic, ferulic and cinnamic acids are the most common aromatic acids usually linked to the C-4 of the glucose, although others such as gallic and vanillic acids also occur.

Based on pharmacological testing, some of these phenylethanoids exhibit diverse biological activities, including antibacterial, antitumour, antiinflammatory, analgesic, antiallergic, and immunosuppressant activities. Others had antihypertensive, antistress, cytotoxic, antioxidant, and enzyme inhibition properties. For instance, verbacoside alone, a disaccharide phenylethanoid, was shown to be an inhibitor of Protein Kinase C (PKC), aldose reductase, and 5-HETE formation. It was also found to be an antibacterial, an antioxidant, an antihepatotoxic, an immunosuppressant and a cytotoxic agent, as well as shown to have antitumor, antihypertensive, and analgesic properties. Echinacoside, a trisaccharide phenylethanoid was found to be an antiviral, an antihepatotoxic, an antistress, as well as a protective agent against the decrease of sexual and learning behaviours in mice. Finally, Eutigoside A (Figure 3.1.1), a monosaccharide phenylethanoid, showed biological activity as an antitumour agent.
Figure 3.1.1: Structures of Eutigoside A, a monosaccharide phenylethanoid; Verbascoside, a disaccharide phenylethanoid; and Echinacoside, a trisaccharide phenylethanoid.

In the synthesis of large carbohydrate molecules such as Echinacoside, protection and deprotection of the sugars hydroxy groups, as well as the most often used glycosidation reactions, should be considered.

The selection of protecting groups demands a careful planning of the synthesis, especially in the case of carbohydrate chemistry, since these molecules contain many functional groups. Many protecting groups can be added and/or removed in acidic, basic, or neutral conditions. Therefore, in this particular synthetic scheme, the regioselectivity of protecting groups could critically depend on the reaction conditions.
Many studies have been done in this field. Several of them were beneficial and essential for the planning of this synthesis of Echinacoside, although the size and the level of this thesis do not allow further explanation and emphasis.

Echinacoside contains an alkene group on its caffeolic acid chain. This chain binds by an ester linkage to the rest of the molecule. To avoid the reduction of this alkene and the saponification of this ester, neither an acetate group nor a benzyl could be used to protect the free hydroxy groups of the target molecule. This is an example of the many restrictions that can complicate the synthesis and force the use of alternative and not so popular routes. Chloroacetate is a similar protecting group to acetate, although it can be cleaved with just NaHCO₃ in MeOH/H₂O (5:1), a mildly basic condition that does not destroy the ester group on C-4. The benzyl group could be replaced by para-methoxy benzyl, which is cleaved by DDQ instead of Pd/C, hence avoiding the reduction of the alkene group. Based on these examples, two strategies to synthesize Echinacoside were established as shown in section 3.2.

The glycosidation reaction conditions are an essential tool in obtaining the proper conformer of the product.

The earliest known glycosidation method is that of Koenigs and Knorr (Scheme 3.1.1 a), which was first reported a century ago. This reaction involves the coupling of a glycosyl bromide or chloride with a hydroxy component upon activation of the former with a heavy metal ion, typically silver or mercury.

In most glycosidation reactions, the resulting anomic stereochemistry is controlled by the nature of the C2 substituent. Thus, as previously mentioned, when the C2 oxygen is protected with an alkyl or a benzyl group, the anomic effect dominates and the α-anomer is preferentially formed. The same configuration is obtained with 2-deoxyglycosyl donors. However, when the C2 position is occupied by a participating group such as an ester, a phenylthio, or a phenylseleno group, the stereochemical outcome is opposite of that of the C2 substituent (either α or β), and a 1,2-trans product is formed as shown in figure 2.1.6. Extensions of the Koenigs-Knorr conditions include the use of Lewis acids and phase-transfer catalysis to activate the anomeric halides, as previously shown in chapter 2.
Scheme 3.1.1: a) The Koenigs-Knorr method; b) the trichloroacetimidate method; c) the thioglycoside method; d) the acyl method.

Although many glycosidation methods have been established and applied, three of them remain the most popular and the most often used by carbohydrate chemists.

Of the large list of glycosidation methods, the trichloroacetimidate-mediated glycosidation procedure (Scheme 3.1.1b), reported by Schmidt et al. in 1980, is a very powerful one, and it has been widely used in complex molecular synthesis. The trichloroacetimidate donors are easily prepared from lactols and trichloroacetonitrile in
the presence of a base, such as NaH or DBU. They are activated by acids, usually Lewis acids such as TMSOTf\textsuperscript{14} or BF\textsubscript{3}.Et\textsubscript{2}O.

Thioglycosides, in particular, phenylthio- and ethylthioglycosides (Scheme 3.1.1 c), have been widely applied in glycosidation and related reactions due to their ease of formation, their relative stability to various reactive conditions, and their convenient activation with electrophilic reagents\textsuperscript{15} or oxidizing agents.

Finally, a related method used in this thesis is the direct conversion of $O$-acyl glycosyl donors, particularly the $O$-acetyl glycosyl donor, to the respective glycosides. These donors are easily accessible, and they have been used extensively in glycosidation reactions upon activation with Lewis acids\textsuperscript{16} such as BF\textsubscript{3}.OEt\textsubscript{2}. These reactions work well, although their consistency greatly depends on extremely anhydrous conditions.

The last two techniques were used in this thesis due to their simplicity, affordability, and acceptable efficiency. Of course, had any obstacles been raised, alternative routes of glycosidation would have been employed.

In this thesis, an interesting side reaction that took place in the thioglycosidation method is reported. An investigation indicated that the reaction conditions used in this synthesis catalyzed the formation of a thioether bond on electron-rich aryl group. Formation of thioether under these conditions has not yet been reported. This side reaction will be discussed in more depth in the 'Results and Discussion' section of this chapter.
3.2 Synthetic Strategies

Two synthetic strategies were designed and planned. The PhGs' biological activities were only recently studied; hence, a structure-activity relationship might be easily established by slight modification of their structures. Therefore, synthetic strategies should be quite divergent to permit alternative routes that can accommodate possible modification to the final product. Targeting the largest family of PhGs, Echinacoside, a trisaccharide PhG was made our synthetic target. Slight modification of intermediates leading to Echinacoside can lead to the formation of other PhGs such as verbascoside and eutagoside A. With these factors in mind, two strategies were drafted and they are as follows:

First Strategy

The first strategy consisted of the glycosylation of peracetylated glucose with substituted phenyl ethanols, then creating a benzylidene intermediate, which leaves only OH-2 and OH-3 unprotected. Earlier studies have shown that in similar substrates, OH-3 would be more selective towards a given glycosylation. Therefore the rhamnosylation of the benzylidene glycopyranoside at this stage would have to take place regioselectively on C-3. Afterwards OH-2 would be protected. The benzylidene ring would be regioselectively opened by LiAlH₄-AlCl₃, creating a free hydroxyl on C-6, and an O-benzyl on C-4. It is important to note that this same benzylidene ring could also be regioselectively opened using NaCNBH₃-HCl, which will give a free hydroxyl on C-4 this time, and a benzyl on C-6 (Scheme 3.2.1). This second route will lead to the synthesis of verbascoside. At this point, the glucosylation of OH-6 should be an easy step, leading to the formation of the trisaccharide. The reductive deprotection of OH-4 would set the stage for its coupling with the caffeolic acid.

Perchloroacetylated rhamnothioside and perchloroacetylated glucothioside should be attached at C-3 and C-6 respectively so they can be deprotected without harming the ester bond between the caffeolic acid and the glycopyranoside at C-4.
Scheme 3.2.1: First strategy to synthesize Echinacoside.
Second Strategy

The second strategy utilized the rhamnosylation of the commercially available 1,2:5,6-diisopropylidene-D-glucofuranose on its only unprotected hydroxyl group OH-3. The deacetonation of the newly formed glucofuranose with trifluoroacetic acid at elevated temperature, followed by acid-catalyzed benzylidena
tion using benzaldehyde dimethyl acetal in acetonitrile, would give the benzylidene disaccharide in one pot. The phenylthaneanoid glycoside should be formed by glycosidation. Once again, the regioselective opening of the benzylidene ring will allow the addition of the glucose on C-6, and the caffeolic acid on C-4.
Scheme 3.2.2: Second strategy to synthesize *Echinacoside*. 
The glycosylation step is a critical step in this synthesis. It usually occurs in low yield due to its moister sensitivity and the limited equipment used in our laboratory. Therefore, starting with this step will minimize the loss of a large quantity of the main compound at a later stage of the synthesis. Based on this concept the first strategy was favoured over the second one. At this time, no record of previous or similar synthesis of the Echinacoside was found. While working on this project, few papers were published showing the synthesis of some phenylpropanoid glycosides and the synthesis of Conandroside by Toshinari Kawada et al., as well as the synthesis of Verbascoside (Fig 3.1.1) by Jacques H. van Boom et al.
3.3 Results and Discussion

The work on this project started toward the end of my graduate studies. The research was in part a contribution to the synthesis of PhGs with the hope that other colleagues could carry this work forward in the upcoming years.

Compound 67, which is an unsubstituted phenyl ethanol, was used in the first attempt. The advantage of using this phenethyl alcohol was to take the obtained glycoside forward in the synthesis without being concerned about the two hydroxyl groups on the aryl ring. The use of compound 67 would also lead to the formation of other PhGs. Compound 67 was prepared by the reduction of the commercially available ethyl phenylacetate (Scheme 3.3.1). In our second attempt, Compound 70, which has two methoxy groups at the exact same position of the two hydroxyl groups found on the aryl ring of the target molecule, was used. This substituted phenyl ethanol was also used to test the feasibility of the synthetic route without being very concerned about the stability of protecting groups of the two hydroxyl groups on the phenyl ring. Compound 70 was prepared from the commercially available (3,4-dimethoxyphenyl) acetic acid (68). The direct reduction of the acetic acid (68) gave the alcohol (70) in low yield. The Fisher esterification of the carboxylic acid (68) using H⁺ resin in methanol, gave compound 69 in 100% yield, which was then reduced to the alcohol (70) in high yield (78%).

Since 3,4-dihydroxyphenyl ethanol was not commercially available, 3,4-dihydroxyphenyl acetic acid (71) was used to synthesize compound 73 (Scheme 3.3.1). The treatment of compound 71 with PMB-Cl protected the two hydroxy groups, and transformed the carboxylic acid to the ester (72), which was further reduced to give the desired phenethyl alcohol (73).
Scheme 3.3.1: Synthesis of various phenyl-ethanols: a) LiAlH₄, THF, 76%; b) LiAlH₄, THF, 50%; c) H⁺ resin, MeOH, 95%; d) LiAlH₄, THF, 78%; e) PMB-Cl, n-BuLi, K₂CO₃, acetone, 55 °C, 75%; f) LiAlH₄, THF, 68%.

The commercially available 4-hydroxyphenethyl alcohol (74) was used towards the synthesis of Eutagose A, which, as mentioned in section 3.1, is an antimour agent. The hydroxy group on the aryl ring is more acidic than the one on the alkyl chain, due to its electron withdrawing effect. Based on this theory, a selective protection of the more
acidic hydroxy group was performed. A PTC reaction of the diol (74) in the presence of Ac₂O gave compound 75. A selective protection was also carried by reacting the dialcohol (74) with one equivalent of PMB-Cl, successfully yielding compound 76. ¹H NMR confirmed the regioselectivity of the protecting groups in both compound 75 and 76.

\[
\text{AcO} \quad \text{HO} \\
\text{75}
\]

\[
\text{PMBO} \quad \text{HO} \\
\text{76}
\]

**Scheme 3.3.2:** Synthesis of para-substituted phenyl ethanols: a) AcCl, TBAHS, Na₂CO₃, EtOAc:H₂O (1:1), 75%; b) PMB-Cl, n-BuNi, K₂CO₃, acetone, 55 °C, 93%.

The acetylation of commercially available glucose (77) provided compound 78, which was further glycosilated with thiophenol to give compound 79 (Scheme 3.3.3). Compounds 78 and 79 are the two donors that were used to synthesize phenyl ethanoid glycosides 80, 81, 82, 83, and 84, from the respective phenyl ethanol acceptors, as shown in Scheme 3.3.4.

\[
\text{HO} \quad \text{HO} \quad \text{OH} \\
\text{O} \quad \text{OH} \quad \text{OH} \\
\text{O} \quad \text{OH} \quad \text{OH} \\
\text{77}
\]

\[
\text{AcO} \quad \text{AcO} \quad \text{AcO} \\
\text{OAc} \quad \text{OAc} \quad \text{OAc} \\
\text{SPh} \\
\text{79}
\]

**Scheme 3.3.3:** Preparation of the thioglycoside donor; a) pyridine, Ac₂O, 68%; b) PhSH, BF₃·OEt₂, CH₂Cl₂, 68%.
Scheme 3.3.4: Synthesis of phenylethanoid glycosides.

Due to its similarity with the target structure and to its stability, glycoside 81 was taken forward in the synthesis (Scheme 3.3.5). The Zemplin reaction of compound 81 provided compound 85. This was then treated with benzaldehyde dimethyl acetal to form the benzylidene derivative, compound 86, which constitutes the main intermediate of this synthesis.
Scheme 3.3.5: Synthesis of di- and tri-phenylethanoïd glycosides: a) NaOMe·MeOH, 95%; b) C₆H₅CH(OMe)₂, PTSA, DMF, 64%; c) pyridine, Ac₂O, 68%; d) PhSH, BF₃·OEt₂, CH₂Cl₂, 68%; e) NIS, TfOH, MS (4 Å). CH₂Cl₂, 0 °C, 48%.
At this point, it all came down to the rhamnosylation of OH-3 in compound 86. For that purpose, thiophenyl peracetylated rhamnoside (89) was prepared by the thioglycosidation of the peracetyl donor, compound 88. This donor was previously prepared by the acetylation of the commercially available rhamnose (87).

The reaction of compound 86 with compound 89, under the standard glycosidation conditions (NIS, TfOH, -35 °C), led to the formation of two products, one of them being major. The separation of these two products was done by column chromatography on silica gel. Judging by the \(^1\)HNMR, it was safe to predict that the major compound was a disaccharide, whereas the minor compound was a trisaccharide, which can be explained by a rhamnosylation of OH-3 and OH-2. The common problem was the irregularity of the aromatic peaks of both compounds. Neither the number nor the shift of peaks nor their integrations coincided with the expected structure. The mass spectrum also did not show the proper mass.

This unexpected result was then suddenly related to a similar problem that was encountered in the reaction between compounds 79 and 70. A side product was then formed, but disregarded at the time. However, in trying to find a solution for this problem, this side product was once again closely investigated by \(^1\)HNMR, \(^13\)CNMR, and MS. The peaks in the aromatic area integrated for seven protons with respect to the rest of the molecule. Out of these peaks, two distinct singlets were observed, integrating for two protons. Also the MS and the \(^13\)CNMR interpretations confirmed that this product (compound 92) contained a thioether (Scheme 3.3.6) on its aromatic ring, positioned ortho to the ethanoid, and para and meta to the methoxy groups respectively. This result helped identify the products obtained by the reaction of compounds 86 and 89, as being compounds 90 and 91. The \(^1\)HNMR, \(^13\)CNMR and MS were closely interpreted, and were found to match the structures. A thioether group was obviously added to the aromatic ring of each expected product.

A mechanism was proposed in order to explain this unexpected result. A logical proposition suggested the nucleophilic attack of the electron-rich aromatic ring on the PhSi, which the reaction of NIS and TfOH with the thiophenyl glycoside was suspected to be formed (Scheme 3.3.7).
Scheme 3.3.6: A side product of the thioglycoside method; a) NIS, TfOH, MS (4 Å), CH$_2$Cl$_2$, 0 °C, 68%.

Scheme 3.3.7: Formation of the thioether bond under the thioglycoside glycosidation method.
To further verify and prove this mechanism, compound 70 was reacted with thiophenol in the presence of NIS, and TfOH at -35°C. Compound 93 was obtained in 85% yield. NMR and MS characterized the compound, and proved once again the formation of a thioether bond between the thiophenol and the 3,4-dimethoxyphenyl ethanol following the previously proposed mechanism.

![Chemical reaction diagram]

Scheme 3.3.8: Formation of a thioether bond.

At this point, many questions were raised concerning the generality of this method. Would it work on any aromatic ring, or only on the electron-rich ones? Is it possible to form other thioether bonds on the aromatic or just the aryl-aryl thioether? These two main questions and many others could be answered with more experimental data, which were not obtained due to the end of my graduate studies' period.
3.4 Conclusion

The synthesis of Echinacoside, a phenyl ethanoid glucoside, was attempted. Many PhGs intermediates were successfully synthesized by glycosilation reaction of peracetylated glucopyranoside with substituted phenyl ethanol templates in the presence of BF$_3$OEt$_2$ Lewis acid, and glycosilation reaction of phenyl thioglucopyranoside with substituted phenyl ethanol templates in the presence of NIS and TfOH. The last glycosilation techniques led to the formation of a thioether biproduct.

A phenyl-phenyl thioether bond was established in high yield by reacting thiophenol with 2-(3,4-dimethoxyphenyl) ethanol in the presence of NIS and TfOH. The mechanism of this reaction was proposed and verified. Due to time restriction, this reaction was not further explored and generalized on other thiols and other aromatic systems.
3.5 Experimental methods

General methods

$^1$H NMR and $^{13}$C NMR spectra were obtained from either a Varian Gemini-200 z or a Bruker AMX500 spectrometer at 500, 300; or 200 MHz for protons and 125.7; 75; or 50.3 MHz for carbons, respectively. Proton chemical shifts are given relative to internal chloroform (7.24 ppm) for CDCl$_3$ solutions. Carbon chemical shifts were performed by the first order approximations and were based on shift correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), and 1- and 2- dimensional distortionless enhancement by polarization transfer (DEPT) experiments. Multiplicities of the NMR signals were reported using the following abbreviations: singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), multiplet (m).

Mass spectra were recorded on a Kratos IIH (FAB-glycerol) instrument. Xenon was used as the neutral carrier atom in FAB-MS experiments.

Infrared spectra were obtained on a Bomem-Michelson MB-100 FT/IR spectrophotometer neat on KBr plates.

Reactions were monitored by thin-layer chromatography using Kieselgel 60 F$_{254}$ precoated 0.25 mm thick aluminum backed plates and the compounds were detected by short wave UV light or by an ammonium molybdate solution (2.5% w/v). TLC plates were heated to 150$^\circ$C when necessary.
2-Phenylethanol (67)

To a solution of ethylphenyl acetate (compound 66, 500 mg) in dry THF (10 ml) at 0° C, was slowly added LiAlH₄ (116 mg, 1 eq.). The reaction mixture was stirred for 30 minutes, at which time TLC (hexane/ EtOAc, 7:3) indicated the consumption of all starting materials. A solution of 5% NaOH was added to quench the excess of LiAlH₄. The solution was filtered under vacuum, washed with EtOAc, then extracted and washed 2x with H₂O. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel, using EtOAc/hexane, 1:4 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 67 (250 mg, 76%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.3 (Ph, m, 5H), 3.8 (CH₂OH, t, 2H), 2.85 (PhCH₂, t, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 138.9, 128.6, 128.4, 126.3 (Ar), 63 (CH₂OH), 39 (PhCH₂).

Ethyl (3,4-dimethoxyphenyl) acetate (69)

To a solution of 3,4-dimethoxyphenylethanoic acid (compound 68, 500 mg) in MeOH (10 ml), was added H⁺ resin. The reaction mixture was stirred for 1 hr. at which time TLC (hexane: EtOAc, 1:1) indicated the consumption of all starting materials. The solution was filtered and concentrated under reduced pressure, giving compound 69 (510 mg, 95%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 6.75 (Ph, m, 3H), 4.35 (COOCH₃, s, 3H), 3.83 (OMe, s, 6H), 2.95 (PhCH₂, t, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 171.5 (C=O), 149, 148.6, 129.5, 121.3, 113, 112.5 (Ar), 56 (ArOMe), 52 (COOMe), 40 (CH₂).

2-(3,4-dimethoxyphenyl) ethanol (70)

From compound 68: using the exact same conditions adopted in the synthesis of compound 67, compound 68 (1.0 g) gave compound 70 (450 mg, 50%).

From compound 69: using the exact same conditions adopted in the synthesis of compound 67, compound 69 (500 mg) gave compound 70 (338 mg, 78%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 6.72 (Ar, m, 3H), 3.85 (OMe, 2s, 6H), 3.8 (CH₂OH, t, 2H),
2.75 (PhCH₂, t, 2H), 1.85 (OH, bs, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 149.3, 148, 131.3, 121.3, 112.5, 111.7 (Ar), 64.1 (CH₂OH), 56.3, 56.2 (OMe), 39.1 (PhCH₂).

4-methoxybenzyl [3,4-bis(4-methoxybenzyl) phenyl] acetate (72)

To a solution of 3,4-dihydroxyphenylethanoic acid (compound 71, 100 mg) in acetone (10 ml), were added n-BuNI (800 mg, 3.5 eq.), K₂CO₃ (500 mg, 6 eq.) and PMB-Cl (285μl, 3.5 eq.). The reaction mixture was stirred for 3 hrs at 55 °C, at which time TLC (hexane: EtOAc, 1:1) indicated the consumption of all starting materials. The solution was concentrated under reduced pressure, and the crude product was dissolved in CH₂Cl₂ and washed 3x with H₂O. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel, using EtOAc/hexane, 1:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 72 (228 mg, 75%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.3, 6.9 (Ph, 2m, 6 – 9H), 5.08, 5.06, 5.0 (CH₂O, 3s, 2 – 2 – 2H), 3.78 (OMe, s, 9H), 3.56 (PhCH₂CO, s, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 171 (C=O), 159.6-113.8 (Ar), 71.28, 71.13, 66.35 (CH₂O), 55.2 (OCH₃), 40.8 (PhCH₂CO); FAB-MS [M-1]⁺: 537.6.

2-[3,4-bis(4-methoxybenzyl) phenyl] ethanol (73)

Using the same conditions adopted in the synthesis of compound 67, compound 72 (500 mg) gave compound 73 (251 mg, 68%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.3-6.8 (Ar, m, 11H), 5.1, 5.05 (CH₂O, 2s, 2 – 2H), 3.78, 3.75 (OMe, 2s, 3 + 3H), 3.7 (CH₂OH, t, 2H), 3.49 (OH, bs, 1H), 2.75 (PhCH₂, t, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 158.9, 149.1, 146.6, 133.2, 130.3 129.2, 121.7, 114.6, 114.2, 112.6 (Ar), 70.9, 70.8 (CH₂O), 64.5 (CH₂OH), 55.2, 55 (OMe), 39.1 (PhCH₂); FAB-MS [M+1]⁺: 395.5.
2-(4-acetoxyphenyl) ethanol (75)

A solution of 4-hydroxyphenethyl alcohol (compound 74, 100 mg) in EtOAc (3 ml), were added a solution of Na₂CO₃ (1 M, 3 ml), AcCl (77 μl, 1.5 eq.), and TBAHS (245 mg, 1 eq.). The two-phase solution was stirred vigorously for 3 hrs, at which time TLC (hexane/ EtOAc, 1:1) indicated the consumption of all starting materials. The organic layer was separated, and washed 2x with H₂O. It was then isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel, using EtOAc/hexane, 1:1 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 75 (228 mg, 75%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.2, 7.0 (Ar, 2d, 2 + 2H), 3.8 (CH₂OH, t, 2H), 2.82 (PhCH₂, t, 2H), 2.27 (CH₃, s, 3H), 1.58 (OH, bs, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 168.9 (C=O), 150.2, 136.9, 130.9, 118.5 (Ar), 63.0 (CH₂OH), 39.0 (PhCH₂), 21.0 (CH₃).

2-[4-(4-methoxybenzyl)-phenyl] ethanol (76)

Using the same conditions adopted in the synthesis of compound 72, commercially available 4-hydroxyphenethyl alcohol (compound 74, 300 mg) gave compound 76 (520 mg, 93%); ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.35, 7.15, 6.9 (Ar, 2d, dd, 2 + 2 + 4H), 4.95 (CH₂, s, 2H), 3.8 (CH₂, t, 2H), 3.8 (CH₃, s, 3H), 2.8 (CH₂OH, t, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 158.9, 129.28, 128.16 (Ar-PMB), 157.61, 131.19, 114.18 (Ar), 70.07 (OCH₂), 63.01 (CH₂OH), 55.2 (OMe), 39.0 (CH₂).

Phenyl 2,3,4,6-tetra-O-acetyl-β-D-thioglucopyranoside (79)

To an ice-bath cooled solution of glucose pentaacetate (compound 78, 1.0 g) and thiophenol (315 μl 1.2 eq.), in dry CH₂Cl₂ (10 ml), and under N₂ inert atmosphere, was added BF₃·OEt₂ (300 μl, 1 eq.) via a syringe. The reaction mixture was allowed to warm up to room temperature, and was left to stir for 4 hrs, at which time TLC (hexane/ EtOAc, 3:2) indicated the consumption of most starting materials. The solution was diluted with
CH₂Cl₂, washed 2x with Na₂CO₃, and 1x with H₂O. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel, using EtOAc/hexane, 3:2 as eluent. Fractions containing the product were combined and concentrated under reduced pressure, giving compound 79 (767 mg, 68%): ¹H NMR (CDCl₃, 500 MHz): δ (ppm) 7.45, 7.25 (Ar, 2m, 2 +3H), 5.2 (H-3, t, 1H), 5.01 (H-4, t, 1H), 4.98 (H-2, t, 1H), 4.7 (H-1, d, J₁₋₂=11 Hz, 1H), 4.17 (H-6, 6, m, 2H), 3.7 (H-5, m, 1H), 2.04, 1.98, 1.96 (Ac, 3s, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ (ppm) 170.5, 169.4, 168.03 (C=O), 132.65, 131.67, 128.98, 128.36 (Ar), 85.3 (C-1), 74.7, 71.6, 67.9, 67.0, 61.23 (C-5, C-3, C-2, C-4, C-6), 20.5 (Ac).

Compounds 80-84

Acyl method: general method used for the synthesis of compounds 80, 81, 82, 83, and 84 from glucose pentaacetate (compound 78):

To an ice-bath cooled solution of compound 78 (1 eq.) and phenethyl alcohol (1.5 eq.), in dry CH₂Cl₂, and under N₂ inert atmosphere, was added BF₃·OEt₂ (1.5 eq.) via a syringe. The reaction mixture was stirred, and allowed to warm up to room temperature. It was then monitored by TLC. Upon completion of the reaction, the solution was diluted with CH₂Cl₂, washed 2x with Na₂CO₃, and 1x with H₂O. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel.

Thioglycoside method: general method used for the synthesis of compounds 80, 81, 82, 83, and 84 from 2,3,4,6-tetra-O-acetate phenylthioglucopyranose (79)

A solution of compound 79 (1 eq.), phenethyl alcohol (1.5 eq.), and molecular sieves (4 Å), in dry CH₂Cl₂ and under N₂ inert atmosphere, was cooled to -30 °C using a bath of dry ice in acetonitrile. To this solution, were then added NIS (1.1 eq.) and TfOH (catalytic amount). The reaction time varied from 30 to 50 minutes at -30°C, and was
monitored by TLC. Upon completion of the reaction, the solution was diluted with CH₂Cl₂, washed 2x with Na₂CO₃, and 1x with H₂O. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel.

*In both methods, yields varied between 40% and 70%.*

2-Phenethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (80)

$$^1$$H NMR (CDCl₃, 500 MHz): δ(ppm) 7.2, 7.0 (Ar, 2m, 2 + 2H), 5.14 (H-3, t, 1H), 5.05 (H-4, t, 1H), 4.95 (H-2, t, 1H), 4.45 (H-1, t, J₁₂ = 7.9 Hz, 1H), 4.23 (H-6, dd, 1H), 4.08 (H-6' & Ha, m, 2H), 3.63 (H-5 & Hb, m, 2H); [Ha & Hb of OCH₂], 2.85 (PhCH₂, m, 2H), 2.04, 1.97, 1.95, 1.85 (Ac, 4s, 12H); $$^{13}$$C NMR (CDCl₃, 75 MHz): δ(ppm) 170.5, 170.1, 169.3, 169.2 (C=O), 138.4, 128.9, 128.3, 126.2 (Ar), 100.7 (C-1), 72.7, 71.7, 71.1 (C-3, C-2, C-4), 70.5 (OCH₂), 68.4 (C-5), 61.9 (C-6), 35.8 (PhCH₂), 20.6 (CH₃); FAB-MS [M+1]⁺: 453.2.

2-(3,4-dimethoxyphenyl)ethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (81)

$$^1$$H NMR (CDCl₃, 500 MHz): δ(ppm) 6.75, 6.7 (Ar, 2m, 1 + 2H), 5.14 (H-3, t, 1H), 5.05 (H-4, t, 1H), 4.95 (H-2, t, 1H), 4.45 (H-1, d, J₁₂ = 7.9 Hz, 1H), 4.23 (H-6, dd, 1H), 4.08 (H-6' & Ha, m, 2H), 3.85 (OMe, s, 3H), 3.8 (OMe, s, 3H), 3.63 (H-5 & Hb, m, 2H); [Ha & Hb of OCH₂], 2.79 (PhCH₂, t, 2H), 2.04, 1.97, 1.95, 1.85 (Ac, 4s, 12H); $$^{13}$$C NMR (CDCl₃, 75 MHz): δ(ppm) 170.5, 170.2, 169.3, 169.2 (C=O), 148.7, 147.5, 131.0, 120.7, 112.5, 111.2 (Ar), 100.8 (C-1), 72.7, 71.6 (C-3, C-2), 71.1 (OCH₂), 70.9, 68.4, 61.9 (C-4, C-5, C-6), 55.8, 55.7 (OMe), 35.5 (PhCH₂), 20.5 (CH₃); FAB-MS [M+1]⁺: 513.7.

2-[3,4-bis(4-methoxybenzyl)phenyl]ethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (82)

$$^1$$H NMR (CDCl₃, 500 MHz): δ(ppm) 7.32, 7.1, 6.75, 6.7 (Ar-PMB, 2d, 8H), 5.14 (H-3, t, 1H), 5.09 (CH₂, 2s, 4H), 5.05 (H-4, t, 1H), 4.95 (H-2, t, 1H), 4.45 (H-1, d, J₁₂ = 7.9 Hz, 1H), 4.23 (H-6, dd, 1H), 4.08 (H-6' & Ha, m, 2H), 3.85 (OMe, s, 3H), 3.8 (OMe,
s, 3H), 3.63 (H-5 & Hb, m, 2H); [Ha & Hb of OCH₂], 2.79 (PhCH₂, t, 2H), 2.04, 1.97, 1.95, 1.85 (Ac, 4s, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 171.0, 170.5, 170.1, 169.3, 169.1 (C=O), 149.0, 146.7, 133.2, 130.3, 129.2, 121.4, 114.2, 112.7 (Ar), 101.7 (C-1), 72.0, 71.0 (C-3, C-2), 70.9, 70.87 (PhCH₂O), 69.7 (CH₂O), 68.7, 67.9, 62.0 (C-4, C-5, C-6), 55.2 (OMe), 36.7 (PhCH₂), 20.8 (Ac); FAB-MS [M+1]⁺: 725.7.

2-(4-acetoxyphenyl)ethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (83)

¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.5, 7.1, 6.9, (Ar, 3dd, 2 + 2 + 4H), 5.14 (H-3, t, 1H), 5.05 (H-4, t, 1H), 4.95 (H-2, t, 1H), 4.45 (H-1, d. J₁₂= 7.8 Hz, 1H), 4.23 (H-6, dd, 1H), 4.08 (H-6' & Ha, m, 2H), 3.85 (OMe, s, 3H), 3.63 (H-5 & Hb, m, 2H); [Ha & Hb of OCH₂], 2.75 (PhCH₂, t, 2H), 2.04, 1.97, 1.95, 1.85 (Ac, 4s, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 170.7, 168.7, 167.9, 167.0 (C=O), 159.0, 157.5, 131.8, 130.8, 129.3, 129.2, 114.2 (Ar), 101.7 (C-1), 71.9, 71.0 (C-3, C-2), 70.9 (CH₂O), 70.0 (PhCH₂O), 68.6, 67.9, 62.0 (C-4, C-5, C-6), 55.2 (OMe), 36.0 (PhCH₂), 21.0 (Ac); FAB-MS [M+1]⁺: 589.5.

2-[4-(4-methoxybenzyl)-phenyl]ethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (84)

¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.16, 6.95 (Ar, 2d, 2 + 2H), 5.24 (H-3, t, 1H), 5.05 (H-4, t, 1H), 4.95 (H-2, dd, 1H), 4.45 (H-1, d. J₁₂= 7.9 Hz, 1H), 4.23 (H-6, dd, 1H), 4.08 (H-6' & Ha, m, 2H), 3.63 (H-5 & Hb, m, 2H); [Ha & Hb of OCH₂], 2.83 (PhCH₂, m, 2H), 2.24 (Ac, s, 3H), 2.04, 1.97, 1.95, 1.87 (Ac, 4s, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 170.5, 170.1, 169.4, 169.3, 169.2 (C=O), 149.1, 136.1, 129.9, 121.5 (Ar), 100.7 (C-1), 72.7, 71.7, 71.1, 70.3 (C-2, C-3, C-4, C-5), 68.4 (CH₂O), 61.9 (C-6), 35.2 (PhCH₂), 20.6 (Ac); FAB-MS [M+1]⁺: 511.4.

2-(3,4-dimethoxyphenyl)ethyl-β-D-glucopyranoside (85)

To a solution of compound 81 (200 mg) in MeOH (10 ml), was added MeONa:MeOH solution dropwise, until a pH of 9 was reached. The reaction mixture was stirred for 1 hr. at which time TLC (hexane/ EtOAc, 1:9) indicated the consumption of all
starting materials. H⁺ resin was added until a pH of 5 was reached. The solution was then filtered and concentrated under reduced pressure, giving compound 85 (127 mg, 95%).

2-(3,4-dimethoxyphenyl)ethyl 4,6-benzylidene-β-D-glucopyranoside (86)

To a solution of compound 85 (110 mg, 1 eq.) in DMF (10 ml), were added benzaldehyde dimethyl acetal (145 μl, 3 eq.) and para-toluene sulfonic acid (catalytic amount). The reaction mixture was stirred for 2 hrs, at which time TLC (hexane/ EtOAc, 1:9) indicated the consumption of all starting materials. The solution was diluted with diethyl ether, and was washed 3x with NaCl saturated solution. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was then purified by column chromatography on silica gel, giving compound 86 (88 mg, 64%). ¹H NMR (CDCl₃, 500 MHz): δ (ppm) 7.16, 6.95 (Ar, 2d, 2 × 2H), 5.24 (H-3, t, 1H), 5.05 (H-4, t, 1H), 4.95 (H-2, dd, 1H), 4.45 (H-1, d, J₁₂= 7.9 Hz, 1H), 4.23 (H-6, dd, 1H), 4.08 (H-6‘ & Ha, m, 2H), 3.63 (H-5 & Hb, m, 2H); [Ha & Hb of OCH₂], 2.83 (PhCH₂, m, 2H), 2.24 (Ac, s, 3H), 2.04, 1.97, 1.95, 1.87 (Ac, 4s, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ (ppm) 170.5, 170.1, 169.4, 169.3, 169.2 (C=O), 149.1, 136.1, 129.9, 121.5 (Ar), 100.7 (C-1), 72.7, 71.7, 71.1, 70.3 (C-2, C-3, C-4, C-5), 68.4 (CH₂O), 61.9 (C-6), 35.2 (PhCH₂), 20.6 (Ac); FAB-MS [M+1]⁺: 433.4.

1,2,3,4-tetra-O-acetyl-α-L-rhamnopyranoside (88)

To a solution of the commercially available α-L-rhamnose (compound 87, 1.0 g) in pyridine (20 ml), was added acetic anhydride (6 ml). The reaction was stirred for 3 hrs, at which time TLC (hexane/ EtOAc, 1:1) indicated the consumption of all starting materials. The solution was concentrated under reduced pressure. The crude product was diluted in ethyl acetate, washed 2x with Na₂CO₃, 2x with HCl 1M, and 1x with H₂O. The organic layer was isolated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure, giving compound 88 (2.02 g, 95%); NMR (CDCl₃, 500 MHz): δ (ppm) 5.92 (H-1, d, 1H), 5.21 (H-3, dd, 1H), 5.11 (H-4, m, 1H), 4.97 (H-2, dd, 1H), 4.21 (H-5, m, 1H), 2.06, 1.99, 1.97, 1.96 (Ac, 4s, 12H), 1.24 (CH₃, d, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ (ppm)
169.87, 169.45, 169.64 (C=O), 90.31 (C-1), 70.02, 70.77, 67.65, 66.21 (C-4, C-2, C-3, C-5), 20.70, 19.8 (Ac), 17.3 (CH₃).

**Phenyl 2,3,4-tetra-O-acetyl-α-L-thiorhamnopyranoside (89)**

Using the same conditions of the acyl method described above, compound 89 (652 mg, 67%) was obtained from compound 88 (900 mg) and thiophenol; NMR (CDCl₃, 500 MHz): δ(ppm) 7.3, 7.2 (Ar, 2m, 2 + 3 H), 5.8 (H-1, d, 1H), 5.1 (H-3, dd, 1H), 5.04 (H-4, m, 1H), 4.98 (H-2, dd, 1H), 4.0 (H-5, m, 1H), 2.06, 1.99, 1.96 (Ac. 3 s, 9H), 1.24 (CH₃, d, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 169.43, 168.7 (C=O), 136.2, 132.65, 128.75, 128.36 (Ar), 85.6 (C-1), 71.2, 71.0, 69.3, 67.7 (C-2, C-4, C-3, C-5), 20.67, 20.53, 20.1 (Ac), 17.2 (CH₃).

**3,4-dimethoxy-2-phenylthiophenyl ethanol (93)**

Using the same conditions of the thioglycoside method described above, compound 93 (74 mg, 55%) was obtained from compound 70 (55 mg) and thiophenol: ¹H NMR (CDCl₃, 500 MHz): δ(ppm) 7.2, 7.1, 7.02 (Ar. m. 2 + 1 + 2H), 7.02, 6.88 (Ar. 2 s, 1 - 1H), 3.9, 3.79 (OMe, 2 s, 6H), 3.78 (CH₂OH, dt, 2H), 2.98 (CH₂, t, 2H), 1.65 (OH, bs. 1H); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) 150.23, 148.44, 139.13, 122.55, 119.27, 113.28 (Main Ar), 135.74, 129.35, 127.07, 125.71 (Sph), 63.80 (CH₂OH), 56.44, 56.35 (OMe), 57.78 (CH₂); FAB-MS [M-1]⁺: 291.3.
3.6 References

Claims to original research

1. Sugars containing terminal alkenes were homodimerized using the olefin metathesis reaction, catalyzed by Grubbs' ruthenium catalyst.

2. Homo- and hetero-carbohydrate dimers were synthesized by the coupling of terminal alkene carbohydrate derivatives with aryl halide carbohydrate derivatives using the Heck coupling reaction catalyzed by Pd(OAc)$_2$.

3. Terminal alkyne carbohydrate derivatives were homodimerized using the Sonogashira coupling reaction.

4. Sonogashira reaction conditions were also used to dimerize terminal alkyne carbohydrate derivatives with aryl halide carbohydrate derivatives.

5. Phenylethanoid glycosides were synthesized by glycosidation reactions using the thioglycoside method and the acyl method.

6. A diphenyl thioether compound was obtained by reacting thiophenol with an electron rich aromatic ring in the presence of NIS and TIOH.
Compound 51
**Compound 62**

![Chemical Structure of Compound 62]

- AcO
- NMe
- OAc
- OAc

**References:**

1. Example 1 (Referenced Text)
2. Example 2 (Referenced Text)
Compound 93

\[
\begin{array}{c}
\text{Ph-S-Ph} \\
\text{MeO-OH} \\
\text{MeO} \\
\end{array}
\]