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Synthesis Of Oligosaccharide Mimetics By The Desulfurative Rearrangement Of Allylic Disulfides And Stereoelectronic Influence Of C-O Bonds On C- And O-Glycosylation

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SYNTHESIS OF OLIGOSACCHARIDE MIMETICS BY THE DESULFURATIVE REARRANGEMENT OF ALLYLIC DISULFIDES AND STEREOELECTRONIC INFLUENCE OF C-O BONDS ON *C*- AND *O*- GLYCOSYLATION

by

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DEDICATION

A mes très chers parents Marie-Thérèse et Nicolas Moumé-Pymbock.

“La vie c’est comme un vélo;

si tu arrêtes de pédaler tu tombes.” – Mon père –

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A	Pre-exponential factor
Ac	Acetyl
AcCl	Acetyl chloride
AIBN	2,2'-Azobis(isobutyronitrile)
Ala	Alanine
Asp	Aspartic Acid
Asn	Asparagine
Ar	Aryl
BDA	Butane-2,3-diacetal
Bn	Benzyl
BOPCl	Bis(2-oxo-3-oxazolidinyl) phosphonic chloride
Bu	Butyl
BSM	Benzenesulfinyl morpholine
BSP	1-Benzenesulfinyl piperidine
Bz	Benzoyl
C	Concentration
ºC	Celcius
cADP	*cyclic*-Adenosine diphosphate
Cat.	Catalytic
Calcd	Calculated
CDA	Cyclohexane-1,2-diacetal
CIP	Contact ion pair

m-CPBA	*meta*-Chloroperbenzoic acid
CSA	Camphor-10-sulfonic acid
CuAAC	Cu-catalyzed azide-alkyne 1,3-dipolar cycloaddition
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	Dichloromethane
$\Delta S^{\ddagger}$	Entropy of activation
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*'-Diisopropylethylamine
DMAP	4-(Dimethylamino)-pyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethysulfoxide
DNA	Deoxyribonucleic acid
DNP	Dinitrophenyl
DPAP	2,2-Dimethoxy-2-phenyl-acetophenone
DPSO	Diphenyl sulfoxide
DTBS	Di-*tert*-butylsilyl
DTMBP	2,6-Di-tert-butyl-4-methylpyridine
E*a*	Energy of activation
ESI-HRMS	Electrospray ionization high resolution mass spectroscopy
Et	Ethyl
exp	Exponential

gg	*gauche-gauche*
GlcNAc	*N*-Acetyl glucosamine
gt	*gauche-trans*
Hz	Hertz
IDCOTf	Iodonium dicollidine triflate
IDCP	Iodonium dicollidine perchlorate
inf	Infini
k	Rate constant
K	Kelvin
KIE	Kinetic isotopic effect
λ	Wavelength
Leu	Leucine
Lev	Levulinyl (4-oxopentanoyl)
LP	Lone pair
m	meta
Me	Methyl
mmol	Milimole
mp	Melting point
MP	*p*-Methoxyphenyl
MS	Molecular sieves
MW	Microwave irradiation
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance

NOE	Nuclear overhauser enhancement
NPG	Neighboring participating group
NT	3-Nitro-1,2,4-triazole
p	para
PE	Phytoalexin elicitor
PG	Protecting group
Ph	Phenyl
Phth	Phthaloyl
PIA	Polysaccharide intercellular adhesin
Piv	Pivaloyl
pKa	Acid dissociation constant
PMB	*p*-Methoxybenzyl
PNAG	poly *N*-Acetyl β-(1→6)-glucosamine
PNSG	poly *N*-Succinyl β-(1→6)-glucosamine
ppm	Parts per million
PTM	Post-translational modifications
Py	Pyridine
quant.	Quantitatif
RDS	Rate determining step
RNA	Ribonucleic acid
rt	Room temperature
SE	(2-Trimethylsilyl)ethyl
Ser	Serine

SPS	Solid phase synthesis
SSIP	Solvent separation ion pair
T	Temperature
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl triflate
TEC	Thiol-ene coupling
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
*t*g	*trans-gauche*
THF	Tetrahydrofuran
Thr	Threonine
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSBr	Trimethylsilyl bromide
TMSOTf	Trimethylsilyl triflate
Tol	Tolyl
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	p-Toluenesulfonyl
p-TsOH	*p*-toluenesulfonic acid
TTBP	2,4,6-Tri-*tert*-butylpyrimidine
TYC	Thiol-yne coupling

UV	Ultraviolet

PART I: SYNTHESIS OF OLIGOSACCHARIDE MIMETICS BY THE DESULFURATIVE REARRANGEMENT OF ALLYLIC DISULFIDES

CHAPTER 1

INTRODUCTION

1.1 Carbohydrates, an Ubiquitous Component of Nature

Living matter is organized into complex structures made of inorganic (water, mineral salts, trace elements, etc.) and organic molecules. The organic matter comprises four main classes of natural compounds: carbohydrates together with nucleic acids, proteins and lipids. Carbohydrates are by far the most abundant components on Earth[1]; they are synthesized directly from carbon dioxide using the planet's primary source of energy, the sun, with more than 4×10^{11} tons of carbohydrates produced each year by the process of photosynthesis[1]. This ancient, yet fundamental, chemical transformation, preponderantly undertaken by plants and algae, uses water and carbon dioxide to convert sunlight into glucose, a form of energy utilizable by all types of living organisms, and releases oxygen. Thereafter, this energy is stored by animals and plants as glycogen and starch.

Carbohydrates are mostly found in Nature in their polymeric forms as oligo- and polysaccharides, which are composed of repeated units of monosaccharides linked together through *O*-glycosidic bonds. Naturally occurring monosaccharides are also widely distributed, but are of a lesser importance than their corresponding condensed forms from a biological point of view. In contrast to the other classes of bioconjugates (e.g. lipids, proteins or oligonucleotides), which

are only displayed in a linear form, carbohydrates also occur in Nature as highly branched polymers.

Another feature of these molecules is their versatility: carbohydrates are very often used as scaffolds for the biosynthesis of other classes of natural compounds. Covalently bound carbohydrates are found in Nature attached through their reducing end to either lipids, peptides or proteins to form respectively glycolipids, glycopeptides and glycoproteins, all of which are classified as glycoconjugates[2]. They are also a key element of the nucleic acids whose biopolymers in the form of deoxy-ribonucleic acid, DNA or ribonucleic acid, RNA, are the essential carriers of the prokaryotic and eukaryotic genomes. In glycobiology, the reaction that covalently binds a glycan to a biochemical functional group is called glycosylation and is performed by enzymes. Glycan synthesis takes place in cells in the form of post-translational modifications (PTMs) of proteins to which the glycan moiety is attached through a *O*-, *N*-, *C*- or *S*- glycosidic linkage, with the *O*- and *N*- linkages being the most commonly displayed in naturally occurring glycoconjugates, *C*- and *S*- are rarely expressed in Nature. The glycosylation reaction is fundamental for the regulation and modulation of cellular function in higher organisms and different chemical aspects of it will be discussed in this manuscript at the appropriate stages.

1.2 Role and Importance of Carbohydrates in Living Organisms

Until the 1970's, carbohydrates were mostly perceived as the principal source of energy and as structural templates for living organisms. The lack of efficient

analytical/physical tools, as well as limited synthetic methodologies, hindered development of the field. As a result, determining the structure-relationship activity (SAR) of carbohydrate molecules was very difficult, which resulted in a relatively poor understanding of the roles that these molecules played in living organisms. However, many years have passed since the time carbohydrates were only viewed as the fuel of cells and today, it is well established that these macromolecules are essential to life processes.

Nearly all cell surfaces including microbial surfaces comprise carbohydrates in the form of glycoconjugates or polysaccharides, which are involved in most or part of the cell's function. Thus, in the past three decades, a large panel of important biological processes involving carbohydrate molecules has been established[3-8], ranging from cell-cell interaction to immune response, intracellular signaling or receptors for proteins and viruses. The involvement of carbohydrates in the development of autoimmune and proliferative diseases such as cancer has also been supported by copious data[9-12]. The critical roles associated with these molecules in numerous life-dependent processes[3] have aroused the attention of biologists and medicinal chemists who have begun to dismantle the machinery behind their functions since they pose as excellent candidates for drug discovery.

Nonetheless, an important limitation that is most often associated with the studies of these molecules is their low availability and purity from natural sources[13], which makes it hard to isolate them in substantial amounts and characterize them[14]. In contrast with the other classes of macromolecules whose biosynthesis is mostly genetically encoded, glycoconjugates and poly- or

oligosaccharides are assembled through multi-enzymatic step processes, which gives rise to structurally heterogeneous mixture of compounds[15]. To address this problem, chemists have focused their attention on the chemical synthesis of structurally homogenous oligosaccharides and glycoconjugates[16] to use as biological and pharmaceutical probes to elucidate their roles in the cells, with the ultimate goal of opening up new pathways to carbohydrate-based vaccines[17-20].

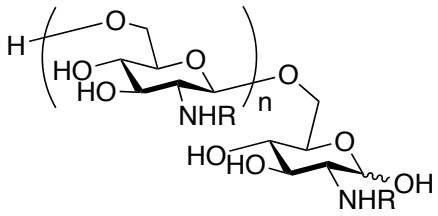
1.3 *Staphyloccocus aureus* and *S. epidermidis*

Colonization of solid surfaces by bacteria - frequently medical devices - through the formation of biofilms accounts for more than 65% of human infections[21]. Many microorganisms, including bacteria, produce biofilms to mediate the parasitic infections through cell-cell adhesion. Once produced by the bacteria, this biofilm acts as a shield, keeping the bacteria away from any type of antimicrobial agents, which confers them a high resistance against antibiotics as well as better resistance to the host's immune system response[22,23].

Gram-positive *Staphylococci* especially *S. epidermidis* and *S. aureus* are some of the most virulent bacteria[24]. Together, they are responsible for the majority of nocosomial infections reported each year[25-27]. Usually located on the skin or in the nose of healthy patients, they coexist in most cases harmlessly in the human body, but can lead to diseases when the host's immune system is weakened[28]. The pathologies associated to their infections vary from mild to very severe such as endocarditis or pneumonia, which can potentially lead to death. The high resistance developed by these classes of bacteria to various antibiotics

has urged the scientific community to develop new potential carbohydrate based-therapeutics miming the structure of their exopolysaccharide matrices so as to prevent their adhesion to host biosurfaces.

In 1996, Mack[29,30] and co-workers isolated and characterized the biofilm produced by *S. epidermidis* and concluded that it mainly consisted of an amorphous linear homopolymer of β-(1→6)-*N*-acetyl-D-glucosamine (PNAG), also referred as to the polysaccharide intercellular adhesin, PIA (Figure 2). PIA is produced during the active growth phase of the bacteria and mediates the adhesion to biosurfaces[29]. Immunological studies have depicted PIA as a potential immunogen for the development of glycoconjugate vaccines[31]. A similar structure to this glycan backbone was also found in *S. aureus*[32] and other biofilm-forming bacteria strains for instance, *Escherichia coli*[33]. In the case of *S*. aureus, the polysaccharide antigen expressed in human infections contains *N*-succinyl residues instead of *N*-acetyl residues and is named poly *N*-succinyl β-(1→6)-glucosamine (PNSG)[34].



R = Ac or H, PIA, R = succinyl, PNSG

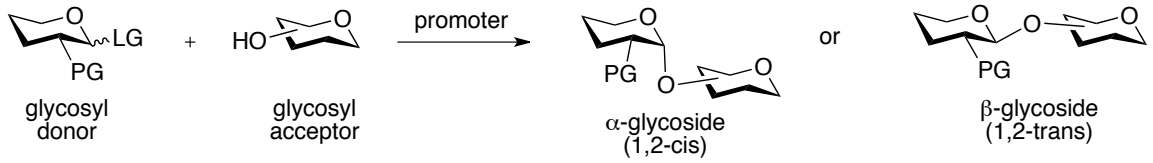
Figure 1: **Structure of the polysaccharide intercellular adhesin**

However, both structures, PNSA and PNSG come as mixtures of poly- and oligosaccharides when extracted directly from their bacterial sources, with

each component of these mixtures generating different immunological responses[35]. Clearly, the chemical synthesis of structurally consistent homogeneous forms of these exopolysaccharide matrices would be a crucial asset for the development of efficient therapeutic means.

1.4 The Glycosylation Reaction, a Central Reaction in Glycochemistry

Glycosidic bond formation, most commonly known as the glycosylation reaction, is the most fundamental reaction in glycochemistry. In a general way, it typically involves three components, a glycosyl donor bearing a leaving group at the anomeric carbon, a glycosyl acceptor, which displays only one free hydroxyl group, and a catalyst or a promoter, until very recently a heterogeneous one, to initiate the departure of the leaving group at the anomeric center with, ultimately, C-O bond formation. The newly formed glycosidic linkage can have either the α or β configuration and be referred to as a 1,2-cis or 1,2-trans glycoside (Scheme 1).

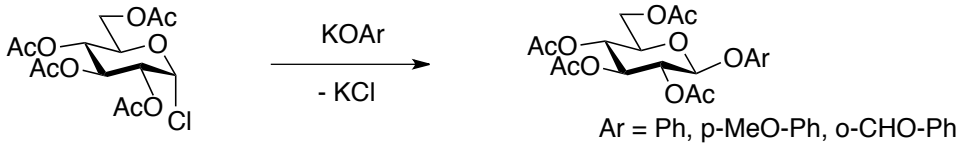


Scheme 1: The glycosylation reaction

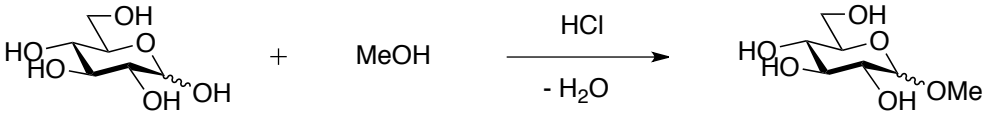
It was in 1879 that A. Michael[36] introduced the first chemical glycosylation reaction; the nucleophilic displacement of an anomeric chlorine with potassium aryloxides. Not long after his discovery, in 1893, E. Fischer[37] proposed a quite different methodology by synthesizing a methyl acetal of D-glucose directly from

an acid-catalyzed condensation of methanol on D-glucose. Then in 1901, Koenigs and Knorr[38] brought an important contribution to the glycosylation reaction by coupling a peracetylated glucosyl bromide with methanol in the presence of a heavy metal ion, silver (I) or mercury (I), initially used as an acid scavenger (Scheme 2).

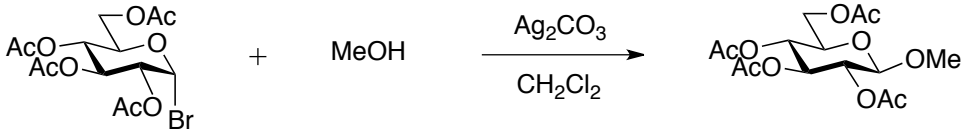
a. Michael glycosylation



b. Fischer glycosylation



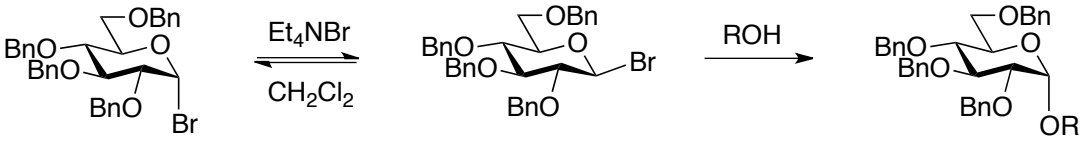
c. Koenigs-Knorr glycosylation



Scheme 2: Glycosylation reactions, the debut

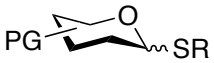
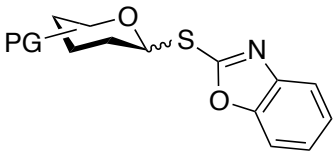
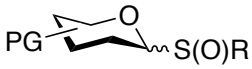
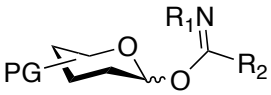
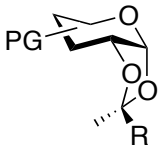
Over the decades, the glycosylation reaction has been refined and has experienced great advances since the inception of these pioneering works. The seminal contribution of Lemieux[39] *et al.*, on the subtle understanding of the reactivity of halogeno-donors, has led to the introduction of the halide-catalyzed glycosylation reaction, providing access to 1,2-cis glycosides. In 1975, Lemieux observed that 2-*O*-benzyl protected α-D-glycosyl bromides anomerized rapidly to their highly reactive β-D-anomer, resulting in the formation of the α-D-glycosides,

in the presence of a catalytic amount of Et_4NBr (Scheme 3)[39]. This anomerization phenomenon was interpreted by Lemieux in terms of a series of ion-pair equilibriating through formation of an oxocarbenium ion, cast light on the fundamental picture of the glycosylation reaction mechanism[39,40]. This general mechanistic scheme will be presented in Part II of this dissertation.



Scheme 3: Halide ion catalyzed glycosylation reaction

Over the years, diverse glycosyl donors were developed as alternatives to the glycosyl halide chemistry, including the versatile thioglycoside donors, or their more reactive forms, the thiosulfoxide donors, or the glycosyl imidates, first used by Sinaÿ[41] then extended by Schmidt[42] in the form of the trichloroacetimidates. These donors have led to the emergence of various glycosylation protocols, and have been, arguably, the most used glycoside donors for the synthesis of 1,2-cis or 1,2-trans glycosides. Synthetic carbohydrate chemists have strived to reproduce chemically and stereoselectively the wide diversity of glycosidic linkages that Nature creates so easily through the help of enzymes[43] and as of today numerous glycosylation methods have been developed[44,45]. An adequate illustration of this community wide effort is found in Hindsgaul's[46] 1995 review, which listed over 700 different chemically synthesized glycosidic linkages for the year of 1994. A selection of the most commonly used glycosylation reactions is listed in Table 1[45].

Entry	Glycosyl Donors	Promoters	Linkages
1	Thioglycosides  R = Tol, Ph, Et	NIS/TfOH, NIS/AgOTf, NIS/$Sn(OTf)_2$ or $Cu(OTf)_2$, $IDCClO_4$ or IDCOTf NBS/$Bi(OTf)_3$, BSP/Tf_2O, Ph_2SO/Tf_2O, BSM/Tf_2O	1,2-cis and 1,2-trans
2	Thioimidates 	NIS/TMSOTf, AgOTf, $Cu(OTf)_2$ MeOTf	1,2-cis and 1,2-trans
3	Thiosulfoxides  R = Tol, Ph, Et	Tf_2O/TTBP or Tf_2O/DTBMP	1,2-cis and 1,2-trans
4	Glycosyl imidates  R_1 = H, R_2 = CCl_3 R_1 = Ph, R_2 = CF_3	TMSOTf, $BF_3.OEt_2$, $Sm(OTf)_3$, $Yb(OTf)_3$, TBSOTf	1,2-cis and 1,2-trans
5	Orthoesters  R = OMe, CN	$TrClO_4$, TMSOTf	1,2-trans
6	Glycosyl phosphates	TMSOTf	1,2-trans

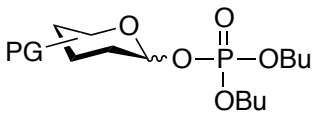
			

Table 1: Common glycosylation methods

Various other important aspects of the glycosylation reaction are not discussed here but are addressed as appropriate throughout the thesis. Such aspects include the nature of the protecting group pattern on both the glycosyl donor and acceptor, the type of activating group at C1, along with its promoter and additives such as solvents, all of which play role in the control of the stereoselectivity of the glycosylation reaction, hence its efficiency.

1.5 Problems in Oligosaccharide Synthesis

The development of simple, efficient and selective synthetic methods to achieve the preparation of complex oligo- and polysaccharides structures has been under the spotlight for quite some time in the carbohydrate chemistry field and enormous efforts have been devoted towards that end[47]. Structurally, carbohydrates are polyhydroxyl-aldehydes or ketones; they therefore possess a high density of functional groups, each of them having different reactivity. Hence, it can be fairly said that the chemical synthesis of oligosaccharides is not an easy task but actually, rather frequently, a difficult and labor-intensive one. A major drawback that has curtailed the endeavors made in this field comes from the lack of general and selective methods, unlike the case of peptides and

oligonucleotides synthesis, and as of today, glycosylation chemistry is still not routine[46]. Consequently, the chemical synthesis of individual oligosaccharides needs, in the vast majority of cases, to be investigated independently. Yet, important improvements have been made in recent years to enable the rapid synthesis of long chains of sugars in the form of convergent syntheses, one-pot synthesis[48,49] methods and automated oligosaccharide synthesis[50,51], to just name a few.

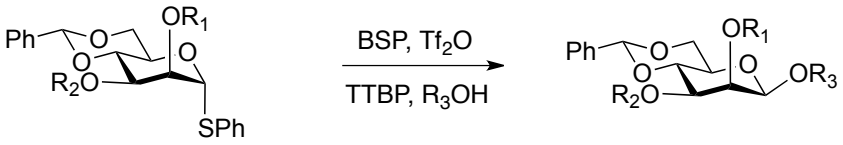
A few years ago, the synthesis of long oligosaccharide chains was perceived as a very daunting prospect. Today, with the emergence of new methodologies, the preparation of oligosaccharides of complex structures can be conducted in a fairly reasonable amount of time. The development of automated tools such as the automated synthesis on solid support introduced by Seeberger[52] in 2001 holds promising potential, as illustrated by the synthesis of a branched dodesaccharide of the PE β-glucan in 17 h and in a 50% overall yield. However, these methods are still highly substrate specific and necessitate special cocktail recipes (protecting group pattern, choice of the anomeric substituent…) limiting the applicability of this methodology to the synthesis of quasi-homogenous oligosaccharides. Oligosaccharides containing diverse or challenging linkages such as 1,2-cis glycosides (α-galactosides, β-mannosides) are not yet amenable to solid phase synthesis protocols. Other important drawbacks to a routine utilization of automated synthesizers arise from first, the coupling efficiency of these reactions, which are not high-yielding, and, second from the difficulty to link the sugars together in a completely stereoselective fashion. Similarly, in solution-

phase protocols, such as the one-pot synthesis methods, based on multiple sequential glycosylations and developed by different groups such as those of Ley and Wong[50,51] have also shown to be beneficial, using simplified protocols with only a single isolation/purification step at the end of the synthesis. However, critical aspects of this methodology include the need for complete consumption of all the reactants to prevent any side reactions leading to undesirable truncated and/or deletion sequences, and low overall yields.

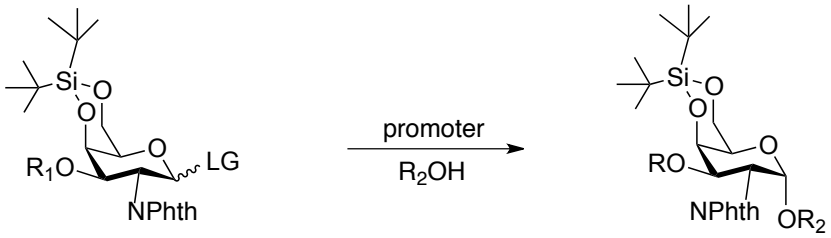
Central to the synthesis of complex oligosaccharides is the control of the stereoselectivity of the glycosidic bond formation. The regioselective construction of glycosidic linkages is relatively promptly achieved, albeit time-consuming, because it mostly relies on a series of selective protection/deprotection manipulation steps. More problematic though, is the stereoselective formation of the glycosidic bond at the anomeric carbon C1 for which complete stereocontrol is necessary. If 1,2-trans glycosides (e.g., β-D-glucosides or α-D-mannosides) can generally be properly prepared via neighboring group participation, accessing stereoselectively 1,2-cis glycosides (e.g., α-D-glucosides or α-D-galactosides) is more complex since the presence of a neighboring participating group at C2 is excluded and as the glycosylation reaction can occur either through S_N1 or a S_N2-like mechanism. Alternative strategies have been investigated and led to the development of novel types of protecting groups to dictate the stereochemistry at the anomeric center. These methods have been based on various effects, for example, the stereoelectronic demand imposed by the 4,6-*O*-benzylidene[53] group or the steric constraints introduced by using silyl

protecting groups such as the 4,6-di-*O*-tert-butylsilylene[54,55] protecting group. Yet a further development is the use of chiral auxiliaries[56] in semi-classic NPG scheme (Scheme 4). Because of these recent advances, it is now as easy to synthesize either 1,2-trans or 1,2-cis glycosides in many sugar series.

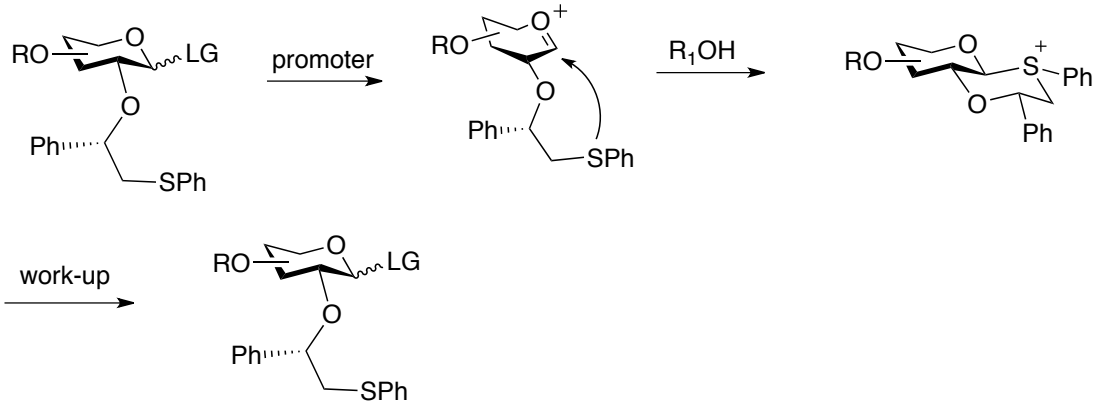
a. 4,6-*O*-benzylidene directed β-mannopyranosylation reaction



b. 4,6-di-*O*-tert-butylsilyl directed α-galactopyranosylation reaction



c. Chiral auxiliary directed 1,2-cis glycosylation



Scheme 4: Methods for controlling 1,2-cis glycoside formation

Nevertheless, despite the advances made to facilitate the elaboration of complex oligosaccharides, most of these methods remain poorly selective in solution and especially on solid support, which reduces their applicability (eg.

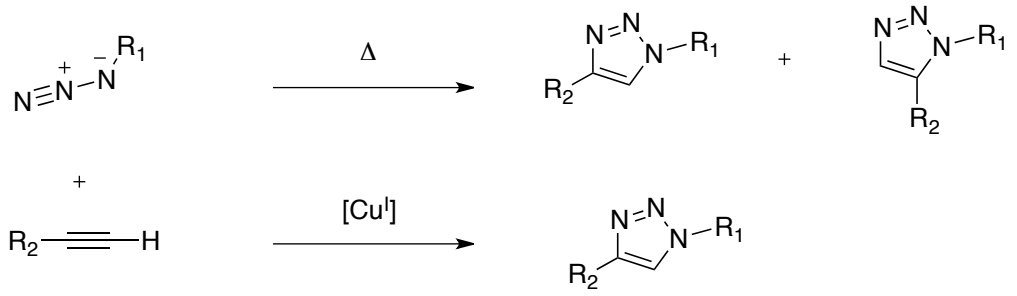
SPS is only suitable for 1,2-trans glycosides). The development of further improved methodologies has been hampered by the poor understanding that lies behind the mechanism of the glycosylation reaction[45], such that even today it is hard, in many cases, to predict and control the outcome of a glycosylation reaction[57]. The synthesis of oligosaccharide mimetics[58] can therefore be considered as an alternative avenue to this problem.

1.6 Click and Thiol-Ene Click

1.6.1 "Click" Chemistry

The term "click chemistry" was first introduced by Sharpless[59] a decade ago to describe the rapid synthesis of new compounds through heteroatom bond formation (C-X-C). This new concept of organic synthesis was developed in parallel with the increasing interest of pharmaceutical companies to access rapidly large combinatorial libraries. According to Sharpless' definition, a click reaction is a reaction that is i) wide in scope, ii) very high yielding, iii) generates only inoffensive byproducts that can be removed by non-chromatographic methods, iv) requires mild aqueous or solventless conditions, v) is stable towards water and oxygen, vi) is atom economical, vii) is stereospecific and viii) draws on a large variety of readily available starting materials. This archetypal concept found its first example with the development of the copper(I)-catalyzed azide-alkyne cylcoaddition (CuAAC), commonly known as "click chemistry". This catalyzed variant of the Huisgen 1,3-dipolar cycloaddition of terminal alkynes and

azides was discovered by Sharpless[59] and Meldal[60] in 2002 and provides access to 1,4-disubstituted 1,2,3-triazole derivatives (Scheme 5).



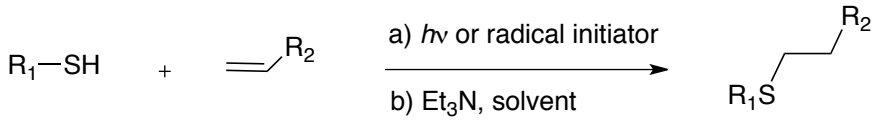
Scheme 5: The Huisgen 1,3-dipolar cycloaddition and the copper(I) variant

Because of its simplicity, mild conditions, high regio- and chemoselectivity, and compatibility with a broad range of functional groups, the CuACC chemistry has been extensively used as a premier conjugation method in numerous fields such as organic synthesis, molecular biology, medicinal chemistry, polymer and material science or biotechnology. Over a thousand papers have been published on the subject[61,62]. Many other well-known chemical transformations, which are capable of generating a broad range of organic compounds, subsequently have been listed as click reactions such as the hetero-Diels-Alder reaction, the addition to carbon-carbon multiple bonds for instance, epoxidation, dihydroxylation, aziridination or the radical addition of thiols to alkenes, which is also known as the thiol-ene coupling reaction (TEC)[63-65].

1.6.2 Thiol-Ene Reaction

Thiols have proven popular targets for chemoselective ligations. The relatively weak sulfur-hydrogen bond of thiols (S-H bond dissociation energy =

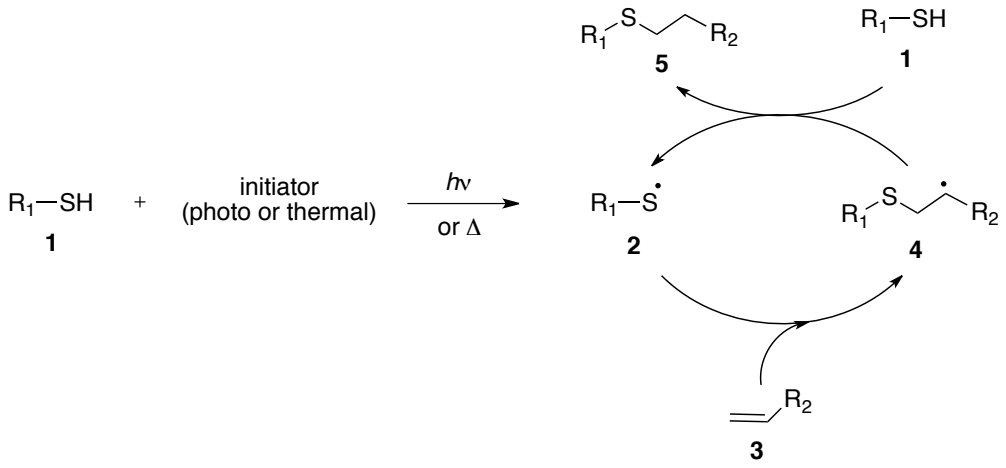
340 – 375 kJ.mol^{-1} *vs.* 390 to 440 kJ.mol^{-1} for analogous O-H bonds in alcohols)[66] has been exploited in a large panel of chemical reactions, because of its ease of reactivity under mild activation conditions,[67] which enables the facile formation of different reactive intermediate species such as thiyl radicals, thiolate anions or sulfenyl cations. The hydrothiolation of terminal alkenes, which corresponds to the addition of thiols across a carbon-carbon double bond or simply “enes”, was discover by Posner[68] more than a century ago. A vast variety of unsaturated functional groups, for instance maleimides, acrylates, and norbornenes or unactivated unsaturated substrates, can be reacted with common thiol reagents – alkyl thiols, thiophenols, thiol propionates and thiol glycolates – under either a photochemically/thermally-induced or base-catalyzed process, to give the sulfide adduct, by respectively, a free-radical chain reaction (the TEC reaction) or a Michael-type nucleophilic addition (termed the thiol Michael addition), the latter being essentially employed on electron poor alkenes (Scheme 6)[63].



Scheme 6: Thiol click reactions by a) thiol Michael addition and b) free-radical addition

The free-radical chain reaction mechanism of the thiol-ene reaction is well established and was proposed by Kharasch[69] and co-workers in 1938. The reaction goes through the formation of a thiyl radical **2** – generated from the thiol precursor **1** upon irradiation or in the presence of a radical initiator – which adds

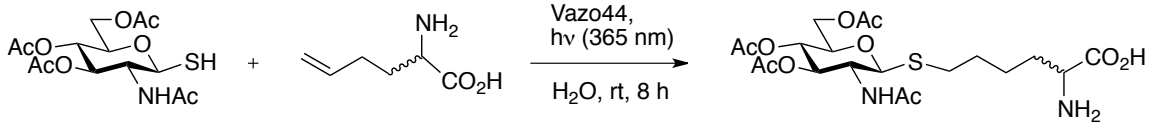
to the alkene **3** in an anti-Markovnikov fashion to give a carbon centered thioalkyl radical **4**. Hydrogen radical abstraction of **4** from another molecule of thiol **1** leads to the thioether adduct **5** and a new thiyl radical ensuring the propagation of the chain (Scheme 7)[64].



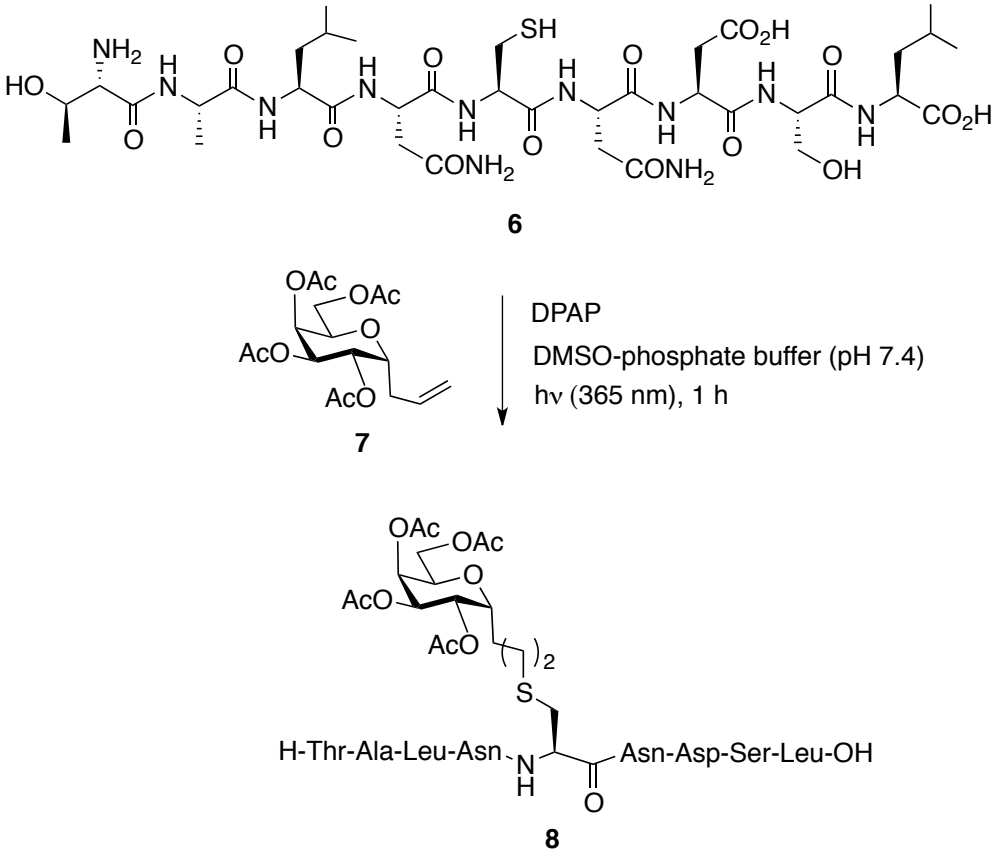
Scheme 7: Mechanism of free-radical thio-ene coupling reaction

Because of its many attributes as a click chemistry, the robustness of the thioether linkage that it generates and the advantages of a photoinitiated process, which allows activation at specific times, thiol-ene chemistry has found many applications in recent years predominantly in network formation[64], polymer functionalization and dendrimer synthesis[70]. Several examples have been reported in the glycochemistry arena for instance the synthesis of glycoconjugates reported by Davis[71] or Dondoni[72,73] as displayed in Scheme 8.

a) *S*-glycosyl amino-acid synthesis[71]



b) *C*-glycosylation of nanopeptide **6** with allyl *C*-galactoside **7**[73]



Scheme 8: Examples of the TEC reactions

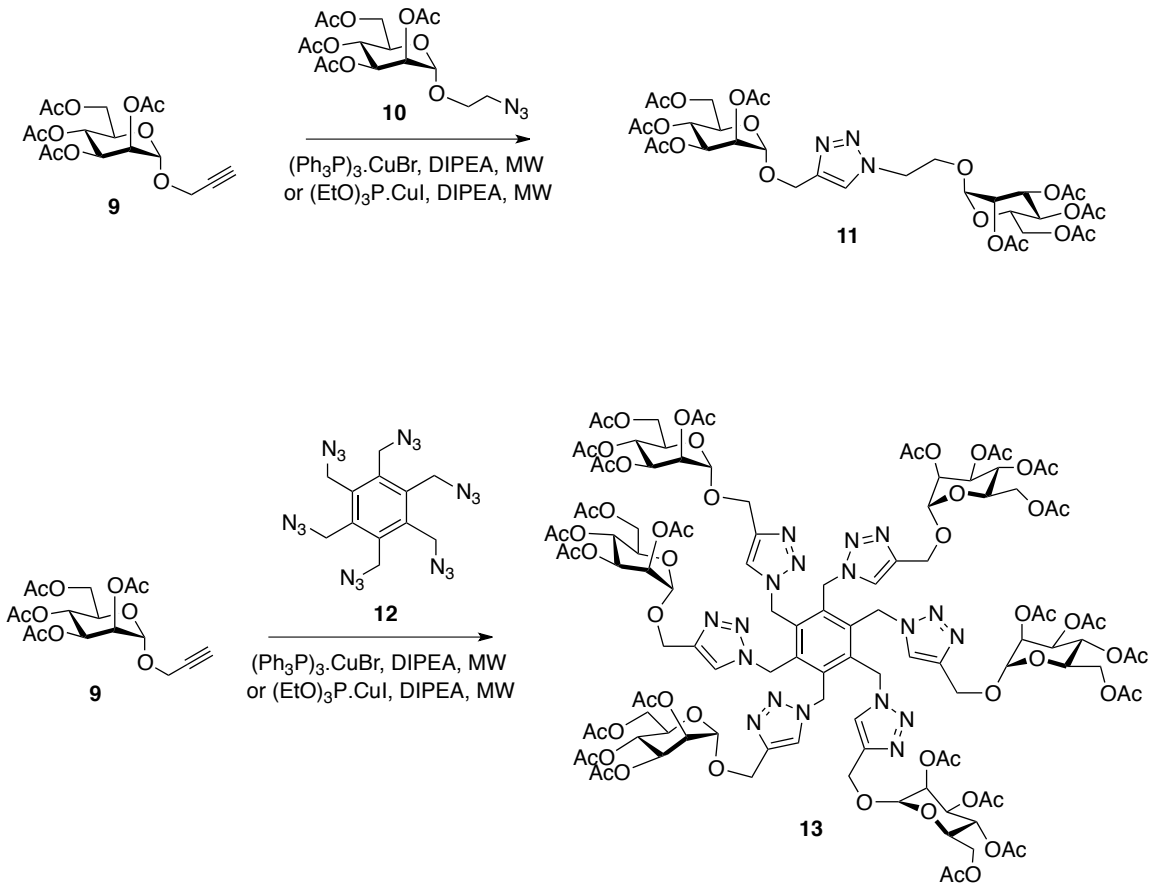
The alkyne equivalent, the thiol-yne coupling reaction (TYC)[65], which consists of the addition of two thiol molecules across a carbon-carbon triple bond, displays the same characteristics as the TEC reaction and has started to emerge in polymer and material science, but has not found yet many applications in glycobiology.

1.7 Synthesis of Oligosaccharide Mimetics

Because of their facile ability to under chemical and enzymatic hydrolysis, poor pharmacokinetics, and low metabolic stability, glycoconjugates or oligosaccharides are not directly used as drugs. The chemical synthesis of structurally improved oligosaccharide mimics is beginning to emerge as an alternative to the preparation of complex oligosaccharides for the production of metabolically stable and potentially pharmacologically active molecules[74-76].

1.7.1 Triazole-Based Oligosaccharide Mimetics

In the quest of synthesizing a panel of various functionalized carbohydrate-based mimetics, different ligation methods have been developed among which the CuAAC chemistry[77] has been the most widely used in chemical biology[61,62,78-81]. The stability of the triazole ring towards enzymatic degradation[82] along with its potential biological and pharmaceutical activities[83,84] supports the synthetic utility of the CuAAC reaction in glycochemistry. Soon after its discovery in 2002, Wong[81] and Santoyo-Gonzáles[80] and co-workers were the first to validate the applicability of this methodology by linking carbohydrates with non-carbohydrate molecules for the synthesis of multivalent glycoclusters anchored to various scaffolds. Below, is represented the synthesis of a triazole-based disaccharide[85] **11** and a triazole-bazed glycocluster[85] **13**, the latter was obtained by reaction of propargyl mannoside **9** with hexakis (azidomethylbenzene) **12** (Scheme 9).



Scheme 9: Synthesis of a triazole-based disaccharide and a glycocluster

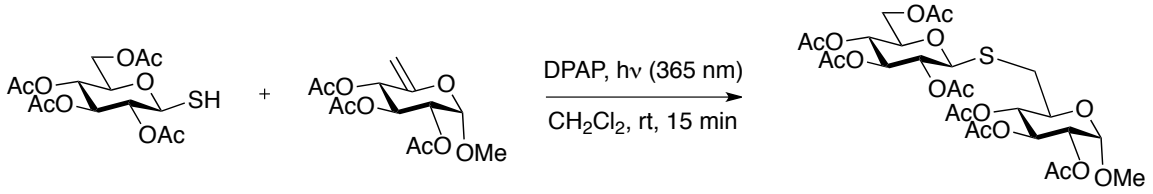
Various applications of "click" chemistry are described in the literature for the synthesis of multivalent saccharide mimetics – in particular, oligomeric structures such as glycodendrimers[86], glycopolymers[87] or glycocusters[85] – since it has been shown that the affinity between protein receptors and their ligands is higher for oligomeric structures owing to the phenomenon known as the "glycoside cluster effect"[88,89].

1.7.2 Sulfur-Based Oligosaccharide Mimetics

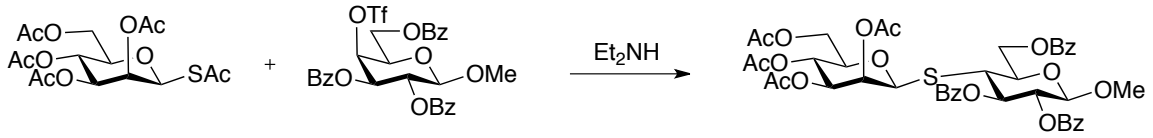
Another approach to the synthesis of glycomimetics involves the preparation of non-natural glycosidic bonds, such as *C*-[90,91] or *S*-glycosides[67], which are of much interest because of their better stability towards enzymatic degradation than their natural analogs *O*- or *N*-glycosides[91] as well as their compatibility with many biological systems.

Various synthetic routes have been employed for the synthesis of thio-linked oligosaccharides mimetics including the thiol-ene reaction[72], Michael-type additions or by *S*-alkylation reactions[92]. Some of these examples are highlighted in the scheme below.

a) β-(1→6) Thiodisaccharide synthesis by thiol-ene reaction[72]



b) *S*-Alkylation and base-promoted *S*-glycosylation[92]

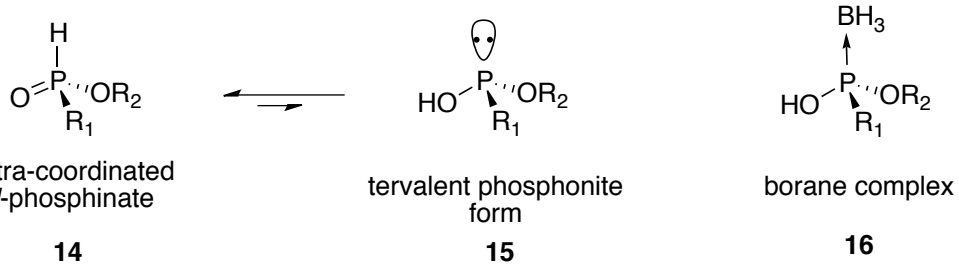


Scheme 10: Examples of sulfur-based disaccharide mimetics

1.7.3 Phosphonate-Based Oligosaccharide Mimetics

Phosphonosugars or phostones[93-98] – sugars in which the anomeric carbon has been substituted by a phosphonate group – have shown promising biological results as potential glycosidase inhibitors and as mimetics of the glycosidic bond[95,97,99]. Very recently, Crich[100] described a novel approach to

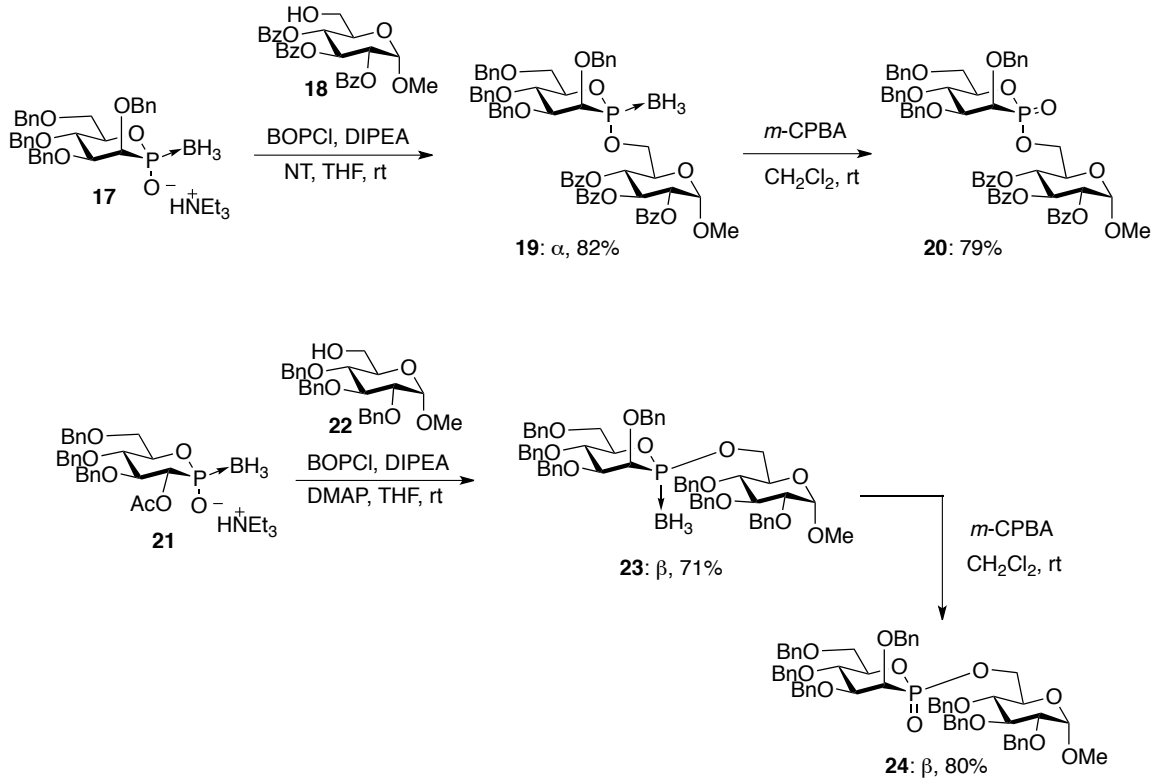
synthesizing phostone-based glycomimetics by coupling P-chiral ammonium phosphonite-borane analogs of glucose or mannose with various carbohydrate- or non-carbohydrate-derived primary alcohols. The coupling reactions proceeded with high diastereoselectivity and, in the case of the mannose series, the α- or β-coupling products can be selectively induced depending on the reaction conditions used. Tervalent P(III) phosphonite compounds **15** are masked in the form of their borane adducts **16** to prevent oxidation at the phosphorus center[101] and to block the *H*-phosphinate in its more reactive tervalent configuration rather than in its tetra-coordinated P(IV) form[102] **14** (Scheme 11).



tetra-coordinated *H*-phosphinate **14** ⇌ tervalent phosphonite form **15** → borane complex **16**

Scheme 11: Tautomeric forms of *H*-phosphinates and their borane complexes

The borane complex is reacted with the primary alcohol in the presence of a nucleophilic catalyst, either 3-nitro-1,2,4-triazole (NT) or DMAP to give the corresponding phophonite-borane adduct, which is subsequently oxidized to its more stable phosphonate form to give the actual glycomimetic. Examples of such disaccharide glycomimetics are outlined in the Scheme below, in the mannose **20** and in the glucose **24** series[100].



Scheme 12: Synthesis of (1→6)-disaccharide phosphonate mimetics

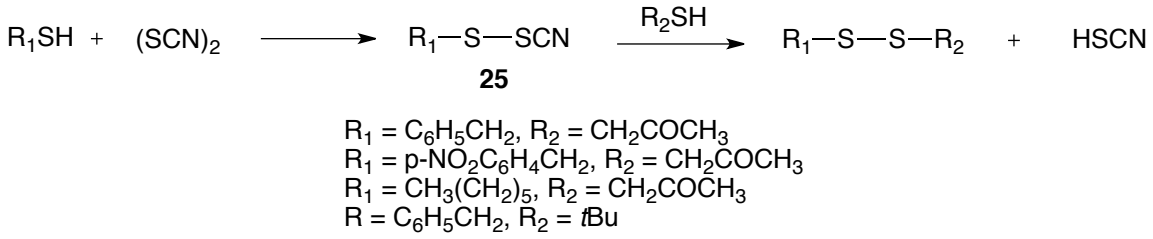
Ultimately, the synthesis of oligosaccharide mimetics is an attractive alternative to circumvent the high level of stereocontrol needed at the anomeric carbon during standard *O*-glycosylation reactions and therefore facilitates the elaboration of complex mimetics of otherwise inaccessible oligosaccharides and/or glycoconjugates.

1.8 Disulfide Ligation, Principles and Problems

Thiol-based ligation reactions have primarily been used in the functionalization of biopolymers, especially peptides and proteins, when they rely on the exploitation of the high nucleophilicity of the sulfhydryl group in cysteine

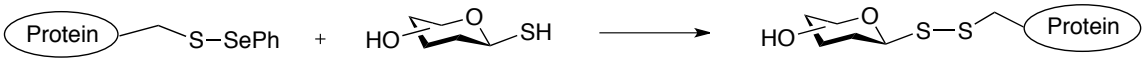
residues for the formation of either stable thioether or amide linkages or for the installation of more labile disulfide bridges. Examples of thiol-based ligations, such as the disulfide ligation or the native chemical ligation (NCL)[103], which enables the formation of native cysteine-containing peptide bonds in aqueous media, demonstrate the use of the sulfhydryl group as a powerful chemoselective ligation device.

The disulfide ligation, one of the oldest ligation methods, allows the formation of mixed disulfides under mild conditions. Indeed, the method is encountered in Nature, when enzymes join together two cysteine-containing peptide chains under oxidative conditions with the formation of a cystine bridge. Several chemical methods have been reported for the synthesis of mixed alkyl or aryl disulfides that rely on, for instance, alkylsulfenyl thiocyanates **25**[104] or aryl disulfides **26** as disulfide precursors when exposed to a thiol molecule (Scheme 13).



Scheme 13: The disulfide ligation reaction

A different variant of the disulfide ligation, introduced by the Davis group, uses selenosulfide derivatives as the disulfide for the attachment of proteins to sugar units (Scheme 14)[105].



Scheme 14: Selenosulfide-mediated glycoprotein ligation

Besides the modifications of peptides and proteins, the practicality of the disulfide ligation has made it a valuable tool for the generation of dynamic combinatorial libraries (DCLs), which take advantage of the reversible nature of the disulfide bond. However, the advantages of the disulfide ligation are offset by the impermanence of S-S bonds, which are labile to reducing agents and which undergo facile thiol-disulfide exchange processes.

1.8.1 Thiol and Disulfide Exchange

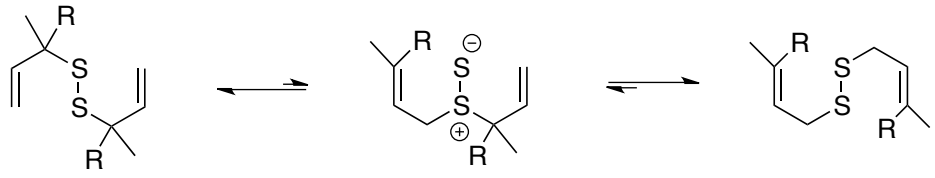
Mixed alkyl or aryl disulfides can undergo disulfide exchange in the presence of a free thiol to give rise to new mixed disulfide derivatives. This phenomenon, the thiol-disulfide exchange, is encountered in biological systems and is believed to take place during the denaturation of proteins by urea. The reaction occurs reversibly under mild basic conditions (pH 7-9) and requires only a catalytic amount of the thiolate to proceed[106]. In 1920, Lecher observed that the reaction between a thiol and a disulfide proceeded via an ionic exchange. However in some cases, a free-radical mechanism with homolytic scission of the sulfur-sulfur bond, giving rise to a short-lived sulfenyl radical may also be

involved. Under acidic conditions or in media free of thiols, the thiol-disulfide exchange does not occur.

The thiol-disulfide exchange reaction is the main limitation of the disulfide ligation and has prompted the development of alternatives, more permanent sulfur-based ligation methods in the Crich group.

1.9 Allylic Disulfide Rearrangement

Early studies carried out by Moore[107-109] and Greenwood[110] showed that symmetrical dialkenyl disulfides reacted with triphenylphosphine upon heating in dry benzene to give dialkenyl monosulfides and triphenylphosphine sulfide almost quantitatively. Similarly, mixed disulfides for instance alkenyl-alkyl disulfides undergo the same transformation and yield alkenyl-alkyl monosulfides along with triphenylphosphine sulfide. Interestingly, dialkyl-, diaryl, and diaralkyl disulfides remained unreactive under similar conditions. Following up on these observations, Baldwin rationalized these results by demonstrating that α-substituted allylic disulfides **27** and **28** rearrange at room temperature in benzene to their thermodynamically more stable isomers **31** and **32** through an intramolecular double [2,3]-sigmatropic rearrangement[111]. This equilibrium proceeds via the formation of a thiosulfoxide intermediate **29** and **30** (Scheme 15).



27: R = H
28: R = Me

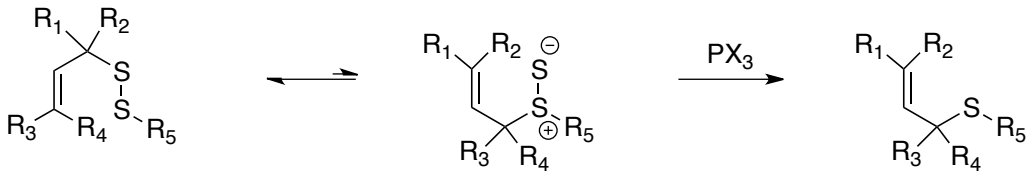
29: R = H
30: R = Me

31: R = H
32: R = Me

R = H, k_{24} = 1.45 x 10^{-4} s^{-1} ($t_{1/2}$ = 79 mins)
R = Me, k_{24} = 8.0 x 10^{-4} s^{-1} ($t_{1/2}$ = 14 mins)

Scheme 15: Double [2,3]-sigmatropic rearrangement of diallyl disulfides

Conversely, mixed alkyl-allyl disulfides were found to be thermally stable upon the same treatment and isolation by distillation was even possible[111]. However, in the presence of a phosphine reagent and upon heating, the equilibrium is driven forward to desulfurization and formation of the corresponding thioether product (Scheme 16).



33 a-f

34 a-f

35 a-f

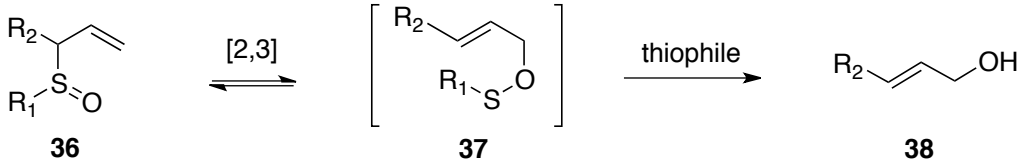
a. R_1 = H, R_2 =Me, R_3 = R_4 = H, R_5 = CH_3; k_{60} = 140 x 10^{-4} s^{-1}
b. R_1 = R_2 = Me, R_3 = R_4 = H, R_5 = Me; k_{60} = 190 x 10^{-4} s^{-1}
c. R_1 = R_2 =H, R_3 = R_4 = Me, R_5 = Me; k_{60} = 0.7 x 10^{-4} s^{-1}
d. R_1 = R_2 =H, R_3 = R_4 = H, R_5 = $CH_2CH{=}CH_2$; k_{60} = 8.9 x 10^{-4} s^{-1}
e. R_1 = R_2 =H, R_3 = R_4 = H, R_5 = Me; k_{60} = 8.6 x 10^{-4} s^{-1}
f. R_1 = H, R_2 = C_6H_5, R_3 = R_4 = H, R_5 = Me, spontaneous loss of S

k: pseudo first order rate constant of the reduction of disulfides in benzene

Scheme 16: Desulfurative rearrangement of mixed allylic disulfides

Kinetics studies revealed that this transformation followed a pseudo-first-order reaction profile with rate constant values indicating that the 2,3-sigmatropic rearrangement is dependent on the substitution pattern[111] as previously observed by Moore and Trego[108]. In the case of mixed alkyl-allyl disulfides, increasing the steric hindrance of R_3, R_4 and R_5 substituents significantly decreases the rate of formation of **35-c** by disfavoring the formation of the thiosulfoxide intermediate **34-c**. On the other hand, the trend goes the opposite way for substitution at the α carbon. Thus, the rate of thioether formation is enhanced as the size of R_1 and R_2 substituents increases and spontaneous desulfurization was observed for compounds **33e** and **33f**. Further, in line with previous results, Baldwin also noted that increasing the solvent polarity had an effect on the rate of the allylic rearrangement as the formation of the thiosulfoxide intermediate was favored.

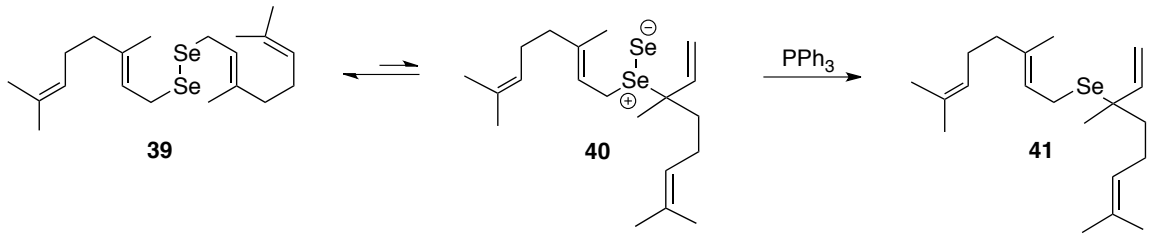
Mechanistically, a close analogy with the well-known Mislow-Evans rearrangement[112] of allylic sulfoxides can be made. In 1968, Mislow and coworkers reported that enantiomerically pure allylic sulfoxides **36** racemized in either benzene or *p*-xylene upon heating through the formation of a sulfenate ester **37** via a [2,3]-sigmatropic rearrangement. Evans then broadened this transformation to the formation of allylic alcohols by trapping the allylic sulfenate ester intermediate using a thiophilic reagent enabling the reversible 1,3-transposition of allylic sulfoxides and allylic alcohol functionalities (Scheme 17).



36 **37** **38**

Scheme 17: Mislow-Evans rearrangement of allylic sulfoxides

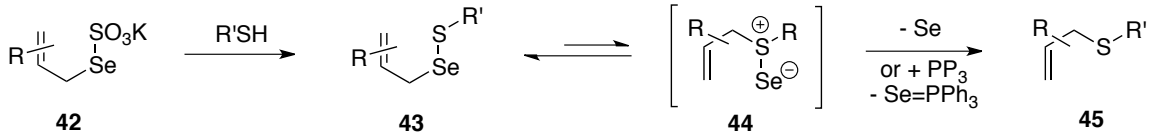
In a similar manner, Sharpless[113] reported in 1972 the first example of the analogous [2,3]-sigmatropic rearrangement of diallylic diselenides and noticed that the selenoallylic rearrangement proceeded faster than its thioallylic counterpart. This was characterized by the difficulty to prepare and isolate diallylic diselenide compounds of which the digeranyl diselenide **39** represented the only example of this type reported in the literature. Treatment of **39** with an excess of triphenyl phosphine at 25 °C in chloroform afforded the corresponding rearranged product with loss of selenium and gave the geranyl linalyl selenide product **41** in a matter of hours (Scheme 18). The half-life reported for this transformation was of 2.5 h at 25 °C.



Scheme 18: Deselenylative rearrangement of digeranyl diselenide

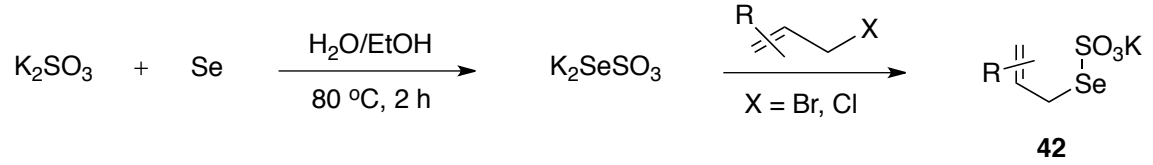
A few years ago, the Crich group[114-117] investigated the scope and limitation of the disulfide rearrangement with the objective of rendering the ligation of thiols permanent, by developing a new method that could proceed at room temperature and in protic media and more importantly, that could benefit biological system studies. For this, the amount of triphenyl phosphine used was cut down to a minimum excess instead of the large excess used in the previous work of Höfle and Baldwin[111]. Screening studies showed that mixed disulfides more specifically allylic Bunte salts **42**[114] (*S*-allyl thiosulfonates) were the most suitable substrates

to meet all of these criteria. The weakness of the Se-S bond was exploited to drive the reaction in the forward direction and facile loss of selenium was observed at room temperature with or without a phosphine reagent, enabling the development of a new, permanent chemical ligation method from the deselenative rearrangement of Se-allylic selenosulfides[114] (Scheme 19).



Scheme 19: Formation and rearrangement of Se-allylic selenosulfides

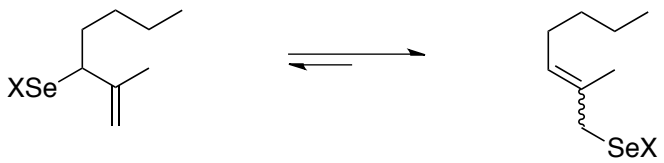
Primary Se-allylic selenosulfates like compound **42**, were obtained according to known protocols[118-120] starting with formation of potassium selenosulfate by reaction of potassium sulfite with selenium powder. Then, potassium selenosulfate was heated in the presence of either allylic bromide or allylic chloride gave the expected product compound **42** (Scheme 20).



Scheme 20: Synthesis of primary Se-allylic selenosulfates

However, it turned out that this synthesis was only suited for the introduction of tertiary allylic sulfides from primary selenosulfides. The preparation of secondary and tertiary Se-allylic selenosulfates did not proceed as required as the standard methodology used to prepare primary Se-allylic selenosufates failed to give the

desired compounds. These results were in accordance with Sharpless'[113] earlier observations when attempting the synthesis of secondary allylic diselenides, which he described as undergoing a fast 1,3 shift to their isomeric primary selenides (Scheme 21).



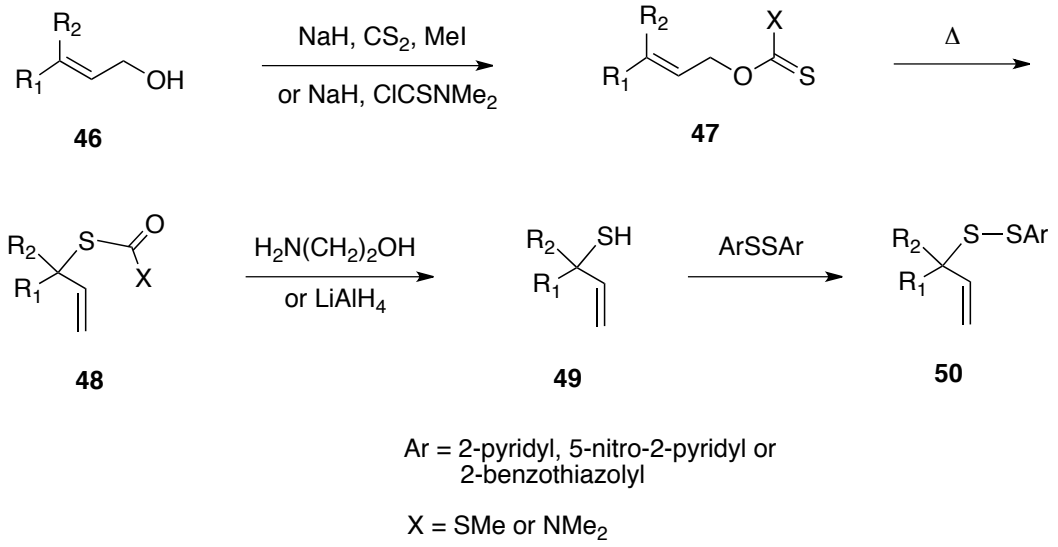
X = CN or SeC_7H_{15}

Scheme 21: [1,3] shift of secondary allylic selenides

Faced with the instability of secondary allylic selenides, the Crich group redirected their investigation towards the allylic disulfide rearrangement using Baldwin's early conclusions on the great influence of the substituents at the α carbon R_1 and R_2 on the rate of this transformation, noticing that secondary and tertiary allylic disulfides conversion proceeded more than 200-fold faster in benzene at 60 °C than that of their primary conterparts (Scheme 9)[111]. The Crich group therefore postulated that the desulfurative rearrangement of allylic disulfides could then take place at room temperature and in protic solvents as was demonstrated to stabilize the dipolar thiosulfoxide intermediate[121], provided that the proper substituent pattern was employed[115,116].

Secondary and tertiary allylic thiols were synthesized from primary allylic thiocarbonyl derivatives via a thermal [3,3]-sigmatropic rearrangement then the allylic thiol **49** were reacted with either 2,2'-dipyridyl disulfide, 2,2'-di(5-nitropyridyl) disulfide or 2,2'-di(1,3-benzothiazolyl) disulfide to give the

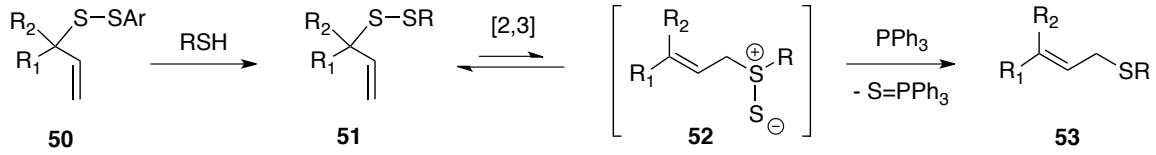
corresponding S-allyl S'-heteroallyl disulfides **50**[116] as presented in the scheme below.



46 **47** **48** **49** **50**

Scheme 22: Preparation of secondary and tertiary allylic disulfides

Subsequent to this point, sulfenyl transfer of **50** to the target thiol was followed with [2,3]-sigmatropic rearrangement and desulfurization occurred upon addition of a thiophilic reagent at room temperature in either methanol or acetonitrile, as anticipated (Scheme 23).



50 **51** **52** **53**

Scheme 23: Desulfurative rearrangement of secondary and tertiary allylic disulfides

To conclude, this novel chemoselective ligation is a mild, electrophile-free transformation that enables the permanent modification of thiols and cysteine

residues. Similarly to “click” reactions, the reaction takes place at room temperature, in polar media and proceeds with high stereoselectivity. The chemoselectivity of this ligation allows the coupling of protecting-group free substrates.

1.10 Goals of Part I

The work presented in this part of the thesis aims to demonstrate the applicability of the 2,3-sigmatropic rearrangement of allylic disulfides as a new ligation method for the synthesis of thioether-linked carbohydrate derivatives, and provides thereby entry to a novel type of oligosaccharide mimetics. Ultimately, the goal is to carry out the ligation step with unprotected sugar building blocks in polar media. The further goal is to apply this method to the synthesis of β-(1→6)-oligo-glucosamine mimetics taking advantage of a building block assembly strategy to ensure maximum convergency.

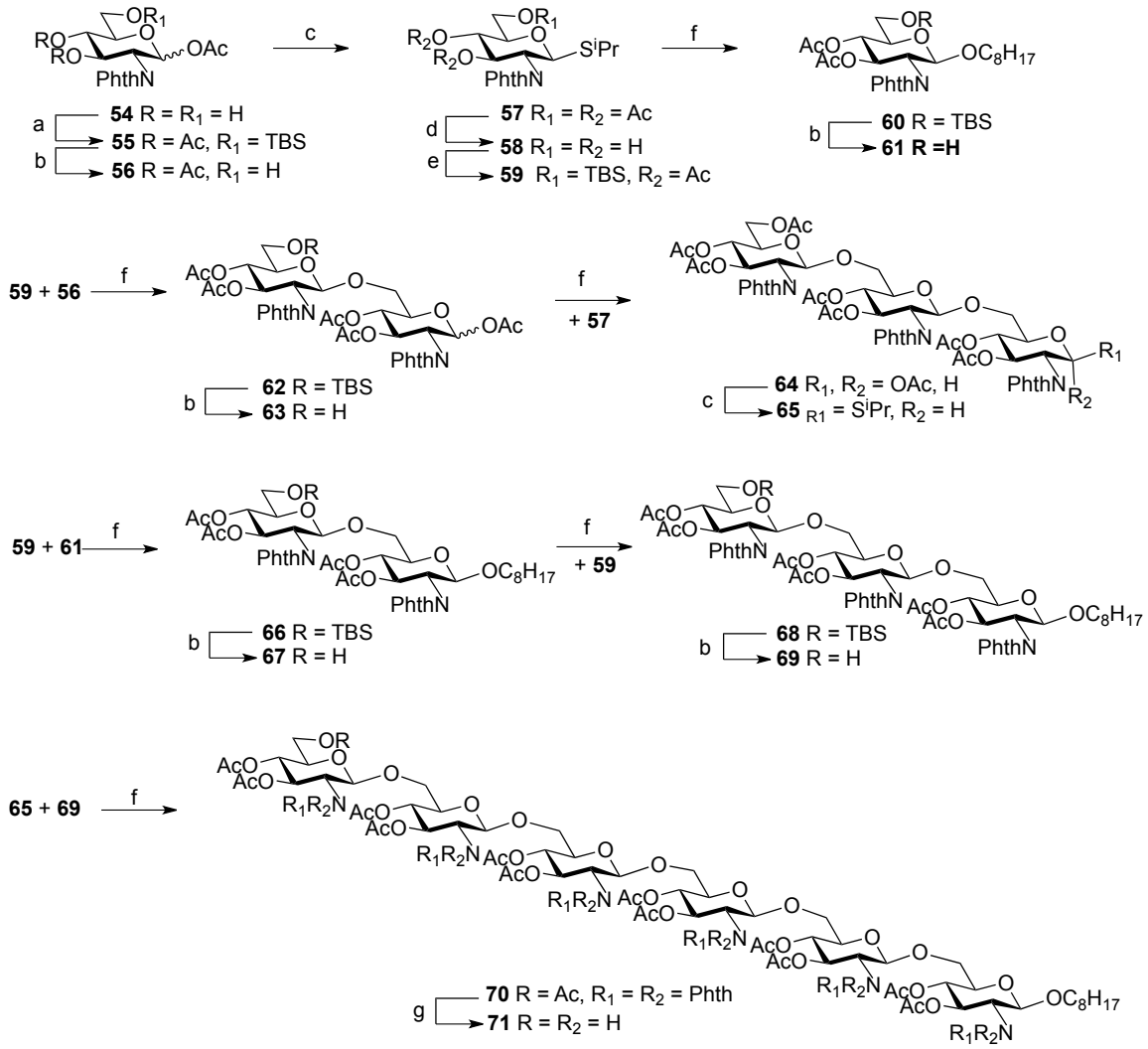
CHAPTER 2

SYNTHESIS OF β-(1→6) GLUCOSAMINE MIMETICS OF *STAPHYLOCOCCUS EPIDERMIDIS* BY DESULFURATIVE REARRANGEMENT OF ALLYLIC DISULFIDES

2.1 Introduction

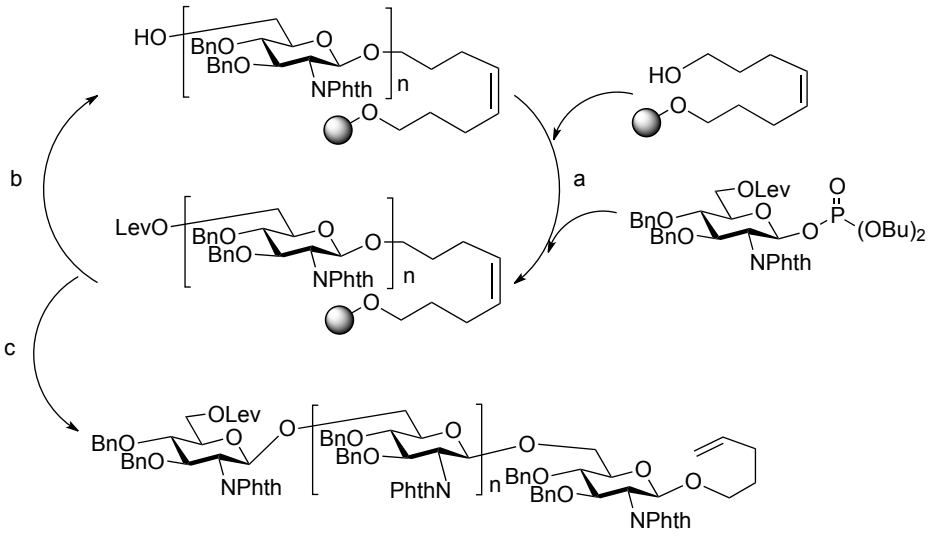
β-D-(1→6) Oligo-glucosamines are important motifs of bacterial surface polysaccharides[29,30,34]. Surprisingly, the linear synthesis of these compounds has not drawn much attention and to date, only a few related papers are found in the literature[122-129]. The first chemical synthesis of a β-(1→6) hexa- and a nonasaccharide of *N*-acetyl-glucosamine was reported by Yang[122,123] and coworkers in 2002, following a convergent blockwise approach. Different strategies have been used for the elaboration of β-(1→6) oligo-glucosamine derivatives, such as the solid phase synthesis developed by the Seeberger group[125], or the one-pot synthesis adopted by the Baasov group[124] (Scheme 1). In this context, herein will be described the synthesis of β-D-(1→6) oligo-glucosamine mimetics based on the desulfurative rearrangement of allylic disulfides, in a blockwise assembly fashion[130].

A. Convergent blockwise synthesis of a hexasaccharide[123]



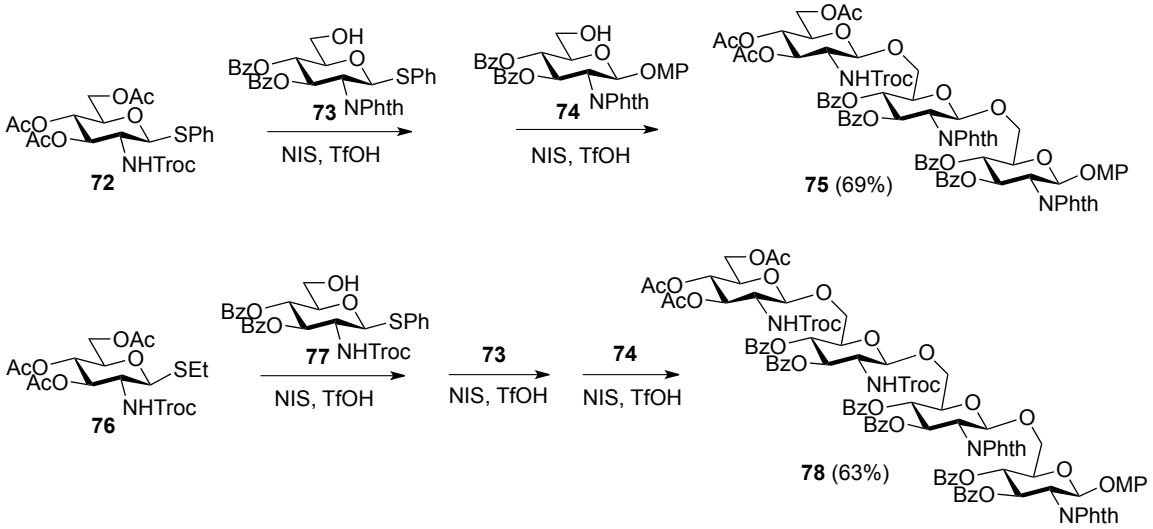
a. NaOMe, MeOH, TBSCl, Py, Ac_2O, 70%; b. $BF_3.Et_2O$, CH_2Cl_2, 95% (**56**); 89% (**61**); 84% (**63**); 88% (**67**) 85% (**69**), c. from 1: Ac_2O, Py, 2-propanethiol, $BF_3.Et_2O$, CH_2Cl_2, 86%; d. NaOMe, MeOH, e. TBSCl, Py, Ac_2O, 78%; f. NIS/TMSOTf, CH_2Cl_2, -20 °C, 95%, (**60**), 94% (**62**), 86% (**64**), 80% (**66**), 92% (**68**), 90% (**70**) g. NH_3, MeOH, 91%

B. Automated synthesis of a trisaccharide[125]



a. TMSOTf, CH_2Cl_2; b. NH_2NH_2, AcOH, Pyr; c. Grubb's catalyst, ethylene, CH_2Cl_2; n = 1, 17%

C. One-pot synthesis of a tri- and a tetrasaccharide[124]

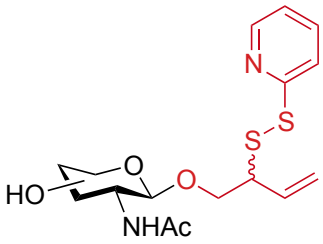


Scheme 24: Examples of oligo β-(1→6) glucosamine syntheses

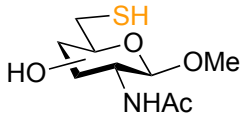
2.2 Results and Discussion

2.2.1 Strategies for the Synthesis of Oligo β-(1→6) Glucosamine Mimetics

The application of the desulfurative rearrangement of allylic disulfides to the synthesis of glycomimetics involves the coupling of a saccharide building block bearing a thiol functionality, in this case at the C6 position of the sugar, with another saccharide building block functionalized with an allylic sulfenyl moiety at the anomeric carbon (Figure 2).



Cabohydrate based allylic sulfenyl



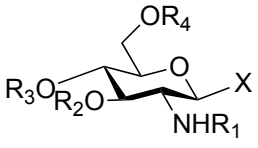
Carbohydrate based thiol

Figure 2: Building blocks for the construction of the glycomimetics

The linear chemical synthesis of the β-D-(1→6) glucosamine di- and tetra-saccharide mimetics was designed using a building block assembly approach; the glycoligation reaction would be performed at room temperature and in protic polar medium according to the protocol developed in the Crich laboratory[114-117]. In order to enable this key transformation to proceed smoothly in protic solvent, the saccharide building blocks were fully deprotected prior to the ligation step. Several factors had to be taken into consideration in designing the synthetic routes for the preparation of the building block moieties such as the choice of the anomeric substituent, the nature of the protecting groups and the glycosylation method, in order to minimize the number of protection/deprotection steps and not defeat the whole purpose of the protecting group-free glycoligation strategy. As

part of this streamlining effort, only one set of glycosylation conditions was to be used with the same anomeric substituent, the thiosulfoxide for the glycosyl donor and the thioglycoside precursor for the glycosyl acceptor. The protecting groups would thus be chosen accordingly in view of performing the deprotection reaction in a one-pot manner. Furthermore, as is generally the case in glucosamine derivatives, the β-stereoselectivity of the glycosylation reaction would easily be accommodated using the participating group at the C2 position; when this would not be possible - in case of the azide chemistry - then additives such as solvents would be used to control the stereoselective outcome of the glycosylation reaction. Finally, the intention was to explore different protecting groups at the nitrogen in the glucosamine series to further test the functional group compatibility of this key ligation reaction.

Overall, the stereoselective synthesis of oligo-β-(1→6)-glucosamine mimetics required the glucosamine building blocks to bear a temporary protecting group at O-6 that can be removed under mild conditions, permanent orthogonal protecting groups stable under glycosylation conditions at O-3 and O-4, and ideally, a participating protecting group at the amine to control the formation of trans β-(1→6) linkages (Figure 3).



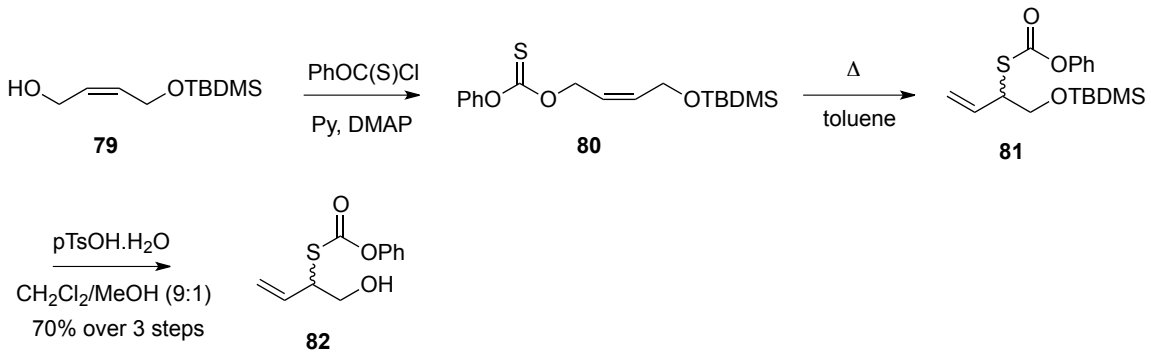
X = anomeric leaving group
R_1 = participating protecting group
R_2 = R_3 = permanent protecting group
R_4 = temporary protecting group

Figure 3: Strategy for the synthesis of β-(1→6) linkages

2.2.2 Synthesis of the Disaccharide Mimetics

2.2.2.1 Synthesis of the Allylic Thiocarbonate Acceptor

The preparation of the acceptor **82**, developed previously in the Crich group[131], is presented in Scheme 25.



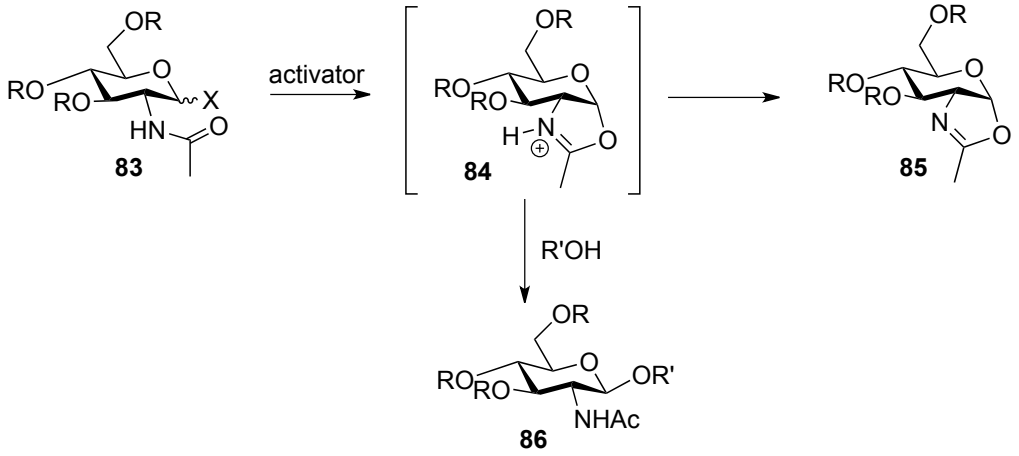
Scheme 25: Preparation of the the allylic thiocarbonate acceptor 82

Thus, the essential allylic thiocarbonate moiety **82** was synthesized in a straightforward manner starting with the conversion of the monosilylated *cis*-but-2-ene-1,4-diol **79** to its corresponding phenyloxythiocarbonate compound **80** by reaction with phenyl chlorothionocarbonate in presence of catalytic DMAP in pyridine. Upon heating in refluxing toluene compound **80** underwent a [3,3]-sigmatropic rearrangement to give the TBDMS-protected acceptor **81**. Desilylation of crude compound **81** with *p*-toluenesulfonic acid monohydrate (*p*TsOH.H_2O) gave the desired acceptor **82** in a 70% yield over 3 steps.

2.2.2.2 Preparation of the Unprotected Monosaccharide Disulfide Donor

The synthesis of β-(1→6)-oligo-glucosamine mimetics was first envisioned in their biologically relevant form[29,30] starting from *N*-acetyl-D-glucosamine. The preparation of oligosaccharides containing 2-acetamido-2-deoxy-D-glucose

(GlcNAc) is an important task in synthetic carbohydrate chemistry[132-137]. Common glycosylation reactions in this series fail to give the desired coupling product as they proceed with neighboring-group participation leading to the formation of a stable oxazolinone, compound **85** as the main product (Scheme 26)[138].

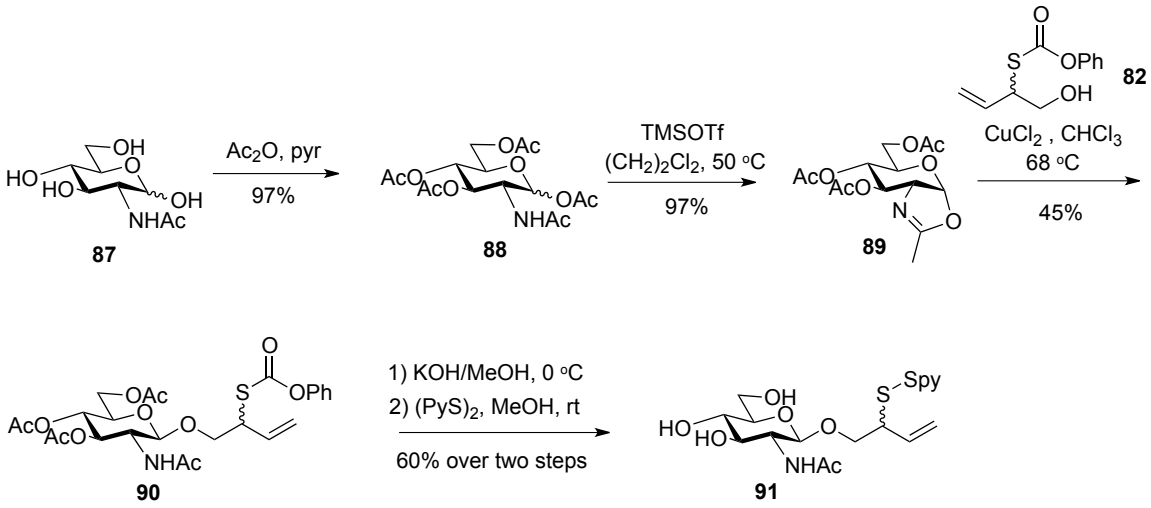


Scheme 26: Oxazolinone formation mechanism

As a result, the efficiency of glycosidic coupling reactions involving *N*-acetyl-glucosamine donors is significantly lower than that of other glycosides, because of the poor reactivity of the oxazolinium intermediate **84**. Significant effort has been directed towards the development of efficient glycosylation methods using the oxazolinone as the glycosyl donor, for the formation of the required β-glycosides[139,140]. However, the low reactivity of **84** requires relatively harsh conditions for it to be activated, for instance, *p*-toluenesulfonic acid in refluxing toluene[132,140], which causes decomposition of both the glycosyl donor and the forming β-glycoside. In regard to these results, mild activation conditions were investigated instead and Wittmann[138] and Lennartz[138] reported that the treatment

of the oxazolinone in refluxing chloroform, in the presence of either anhydrous cupric bromide ($CuBr_2$) or chloride ($CuCl_2$) enabled the formation of the desired β-glycosides of *N*-acetyl glucosamines in moderate to good yields. Then, Jensen[141] and co-workers showed that rare Earth metal triflates such as scandium triflate ($Sc(OTf)_3$) were also good Lewis acid catalysts for the formation of the oxazolinone from *N*-acetyl galacto- and glucosamines.

Following this methodology, the synthesis of the monosaccharide disulfide donor **91** was carried as outlined in Scheme 27.



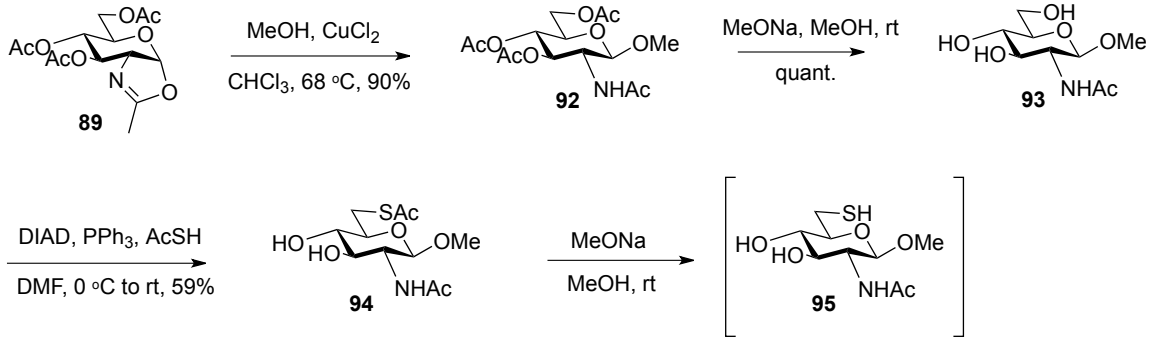
Scheme 27: Synthesis of the unprotected disulfide monosaccharide 91

The synthesis started from the commercially available *N*-acetyl-D-glucosamine, which was first peracetylated in the usual manner to give compound **88**. Oxazolinone **89** was obtained in an almost quantitative yield, by reaction with peracetylated *N*-acetyl-glucosamine **88** and trifluoromethanesulfonic acid (TMSOTf)[139] in 1,2-dichloroethane at 50 ºC. Although not a high-yielding reaction, the coupling of **89** with the acceptor **82** in the presence of an excess of

$CuCl_2$ turned out to be an efficient way to allow the direct formation of the desired 1,2-trans β-glycoside **90**. The anomeric configuration was confirmed by a ^1H NMR experiment centered on the value of the vicinal coupling constant ^3J between the H1 and H2 protons. This coupling constant, ^3J, is correlated to the dihedral angle H1-C1-C2-H2 (ω) through the Karplus plot. Theoretically, an axial-axial vicinal coupling constant for an antiperiplanar H1-C1-C2-H1 conformation (ω = 180º) observed in 1,2-*trans* glycosides is usually between 7 Hz and 10 Hz. On the other hand, in the case of 1,2-*cis* glycosides the axial-equatorial vicinal coupling constant, which corresponds to a dihedral angle ω of 60º is between 1 to 4 Hz. The $^3J_{1,2}$ value for compound **90** was found to be 9.3 Hz, which is in agreement with the theoretical values given from the Karplus plot. The subsequent steps, concomitant saponification of the thiocarbonate functionality and the acetate groups as well as the sulfenyl transfer reaction proceeded as expected. Compound **90** was hydrolyzed using a 1M solution of potassium hydroxide (KOH) in dry methanol at 0 ºC[131], which was followed by sulfenyl transfer upon treatment with 2,2'-dipyridyl disulfide, giving rise to the targeted unprotected sulfenyl donor **91** as a 1:1 mixture of diastereomers. This mixture was deliberately not separated since the chirality at the allylic carbon is lost during the rearrangement step.

2.2.2.3 Preparation of the Based-Thiol Monosaccharide Moiety

The second part of this [1+1] coupling reaction consisted in the preparation of the 6-deoxy-6-thiol monosaccharide unit. The synthesis of **95** was set following a straightforward process as shown in Scheme 28.



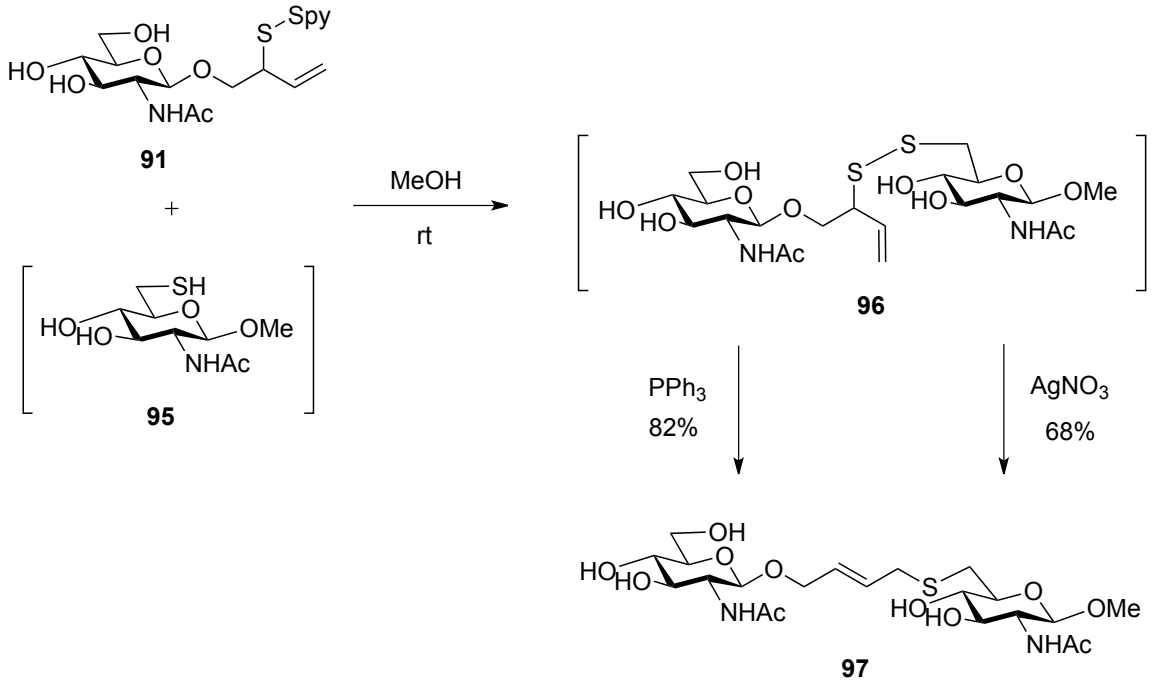
Scheme 28: Synthesis of the based thiol monosaccharide

The methyl β-glycoside **92** was obtained under the same standard glycosylation conditions as previously described[138] in this series but in a significantly higher yield than that of the coupling of acceptor **82**, underlining the relatively low reactivity of **82** towards the oxazoline glycosyl donor. The β-stereoselectivity of the coupling reaction was confirmed by ^{1}H NMR ($^3J_{1,2}$ = 8.0 Hz). Deacetylation of **92** using Zemplén conditions gave methyl *N*-acetyl-β-D glucosaminide **93**. Introduction of the thioacetate functionality at the C6 position was readily achieved in a one-step fashion, by a chemo- and regioselective Mitsunobu[142] reaction. The primary alcohol was thus selectively converted to its 6-thioacetate derivative without the need of protecting groups at the remaining free secondary alcohols. Care was required for the handling of the free primary thiol **95**, which was prone to oxidation to its disulfide counterpart. Therefore, the hydrolysis step was carried out under oxygen-free conditions, which necessitated the preparation

of a fresh solution of sodium methoxide (NaOMe) in degassed methanol. Unprotected 6-thio-glycoside **95** was then ready to be subjected to the ligation reaction.

2.2.3 The Ligation Reaction: Coupling of the Unprotected Monosaccharide Moieties

With the two monosaccharide building blocks in hand, attention was then focused on the key step of this synthesis, which consisted of the conjugation of the monosaccharide thiol **95** with the anomeric disulfide monosaccharide donor **91**.



Scheme 29: Ligation of disaccharyl sulfenyl donor 91 and thiol 95

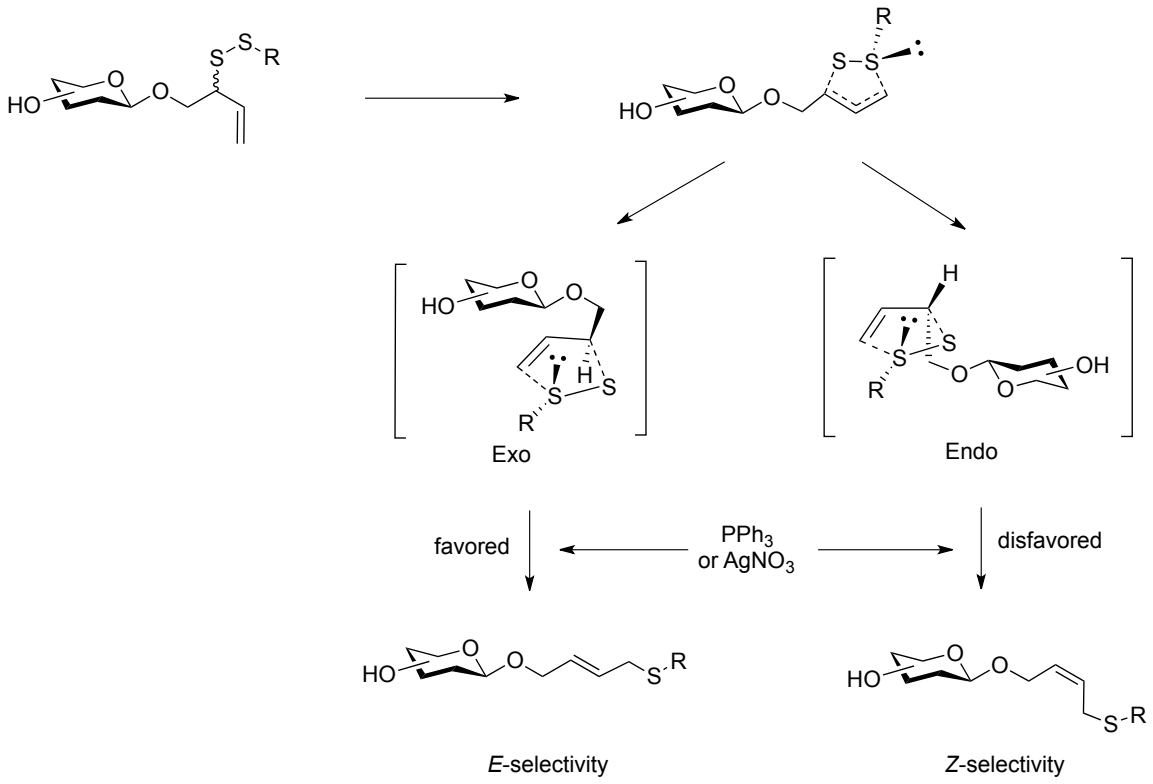
As discussed in section 1.8, the standard protocol for this transformation was developed in polar media and at room temperature[115,116,131]. According to the

conditions set forth, the first step of this transformation – the sulfenyl transfer – was carried out in regular methanol and proceeded smoothly as anticipated. The sulfenyl transfer reaction could easily be followed by naked eye as the side-product, the pyridyl-thiol, is characterized by a persistent yellow color. However, the advancement of the reaction was followed by TLC and electrospray mass spectrometry to ensure the complete consumption of the based-thiol monosaccharide **95**. At this point, the disulfide disaccharide intermediate **96** was ready to undergo the final step of this two-step process, which consisted of a [2,3]-sigmatropic rearrangement followed by phosphine-mediated desulfurization leading to the incorporation of an allylic thioether bond between the sugar moieties.

Initially developed in the presence of a phosphine reagent[116], the desulfurization step was first promoted by triphenylphosphine as the thiophilic reagent. Previous studies undertaken in the Crich laboratory showed that the use of a more nucleophilic phosphine, for instance a trialkylphosphine, was accompanied by the formation of undesired coupling products, due to competitive reaction between the phosphine and the pre-formed disulfide intermediate[115,116]. Given these observations, the choice of the phosphine reagent was then limited to the triarylphosphine series rather than the alkylphosphines, despite their low solubility in polar solvents. Thus, because of the poor solubility of triarylphosphines in polar solvents, another alternative, the use of silver nitrate salts,[143] has also been investigated and developed in the Crich laboratory as a replacement for triphenylphosphine reagents. Studies indicated that the silver

nitrate salts were more reactive towards the desulfurative rearrangement of allylic disulfides than their triphenylphosphine counterparts, allowing the transformation of unreactive substrates while fulfilling the same reaction criteria; the reaction proceeds in a few hours at room temperature, in polar solvents and with high *E*-selectivity.

The coupling reactions proceeded in good yield, independently of the thiophilic reagent used. The installation of the 2-butenyl linker took place with complete *trans*-selectivity ($^3J_{trans}$ = 16.8 Hz) giving rise to the formation of the *E*-isomer exclusively in both cases (PPh_3 and $AgNO_3$ conditions), as was expected with respect to related [2,3]-sigmatropic rearrangements, such as the Mislow-Evans rearrangement[112] as was discussed in section 1.9 or the [2,3]-Wittig rearrangement[144]. A proposed mechanism for this transformation is shown in scheme 30.



Scheme 30: [2,3]-Sigmatropic rearrangement mechanism

By analogy with similar rearrangements, the mechanism of this transformation was expected to proceed *via* an envelope-like transition state, where two different patterns could be drawn, with regard to the relative orientation of the homoallylic methylene group, either endo or exo to the five-membered ring; the exo-mode being the more favorable as it displays less unfavorable interactions.

2.2.4 Synthesis of the Tetrasaccharide Mimetics

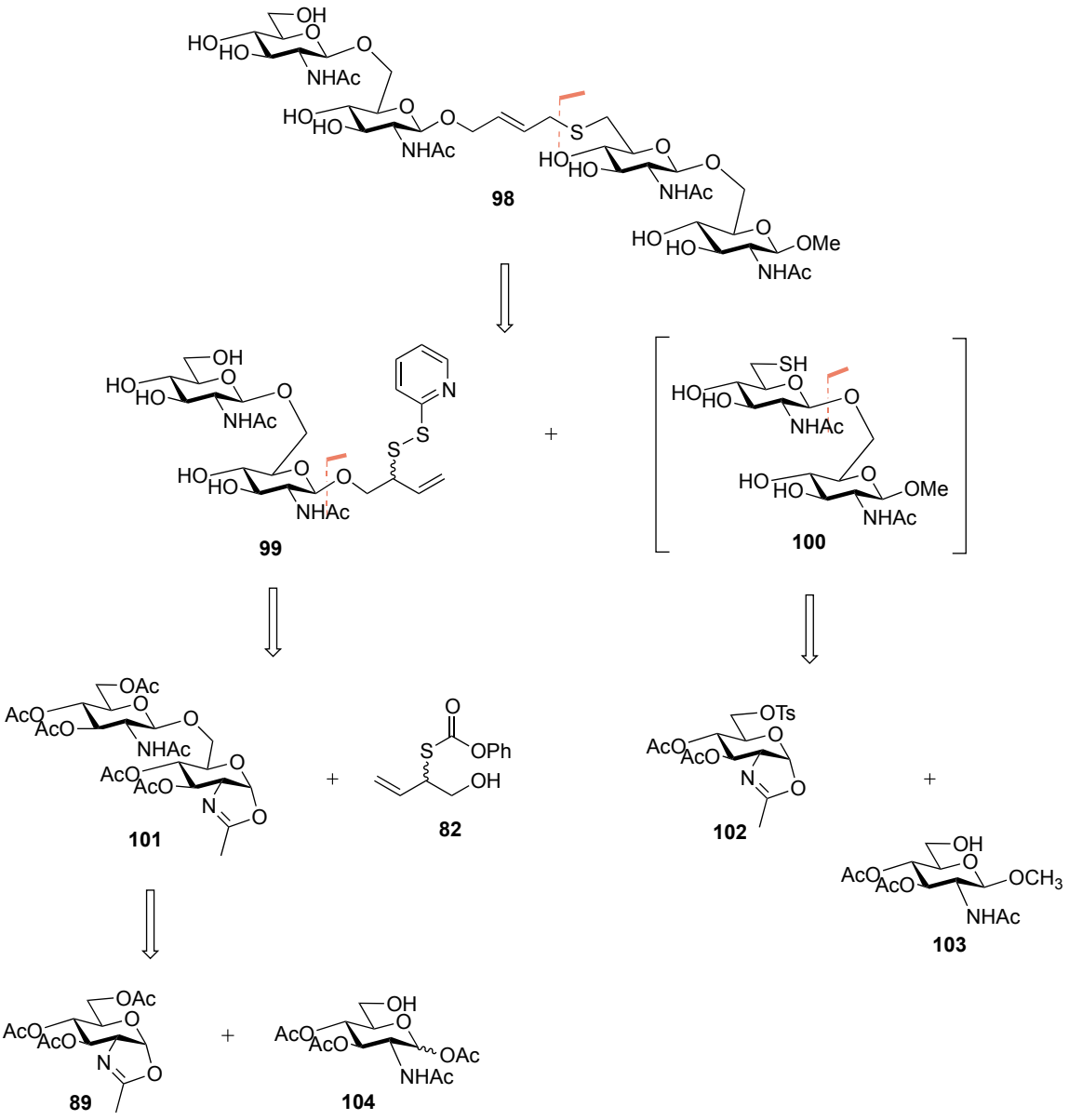
Seeking to apply the scope of this facile [2,3]-sigmatropic rearrangement of allylic disulfides to the synthesis of oligosaccharide mimetics, the preparation

of two tetrasaccharide mimetics was carried out following the same building block approach strategy used for the synthesis of the monosaccharide mimetic **97**.

2.2.4.1 The First Approach: The NHAc Series

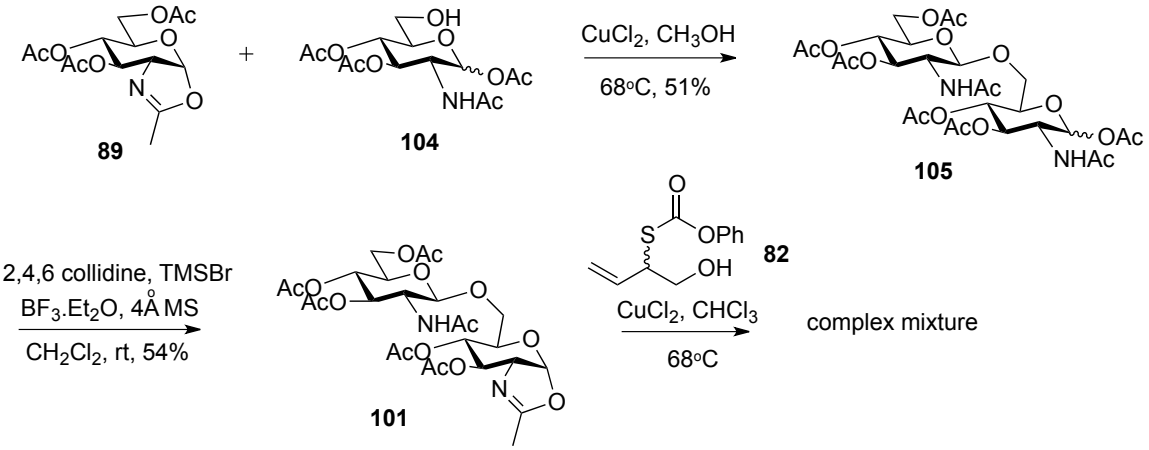
2.2.4.1.1 Preparation of the Unprotected Disulfide Disaccharide Building Blocks

Following the initial approach, the synthesis of the disulfide disaccharide building block started with the *N*-acetyl glucosamine series. The synthesis of the target disaccharide building blocks was envisioned as schematized in the retrosynthetic scheme below.



Scheme 31: Retrosynthetic analysis (NHAc series)

Given the satisfactory results obtained from the coupling reactions using the oxazolinone **89** as the glycosyl donor, the construction of the disaccharide moieties was undertaken according to that same synthetic route (Scheme 32).



Scheme 32: Attempted construction of building block 99

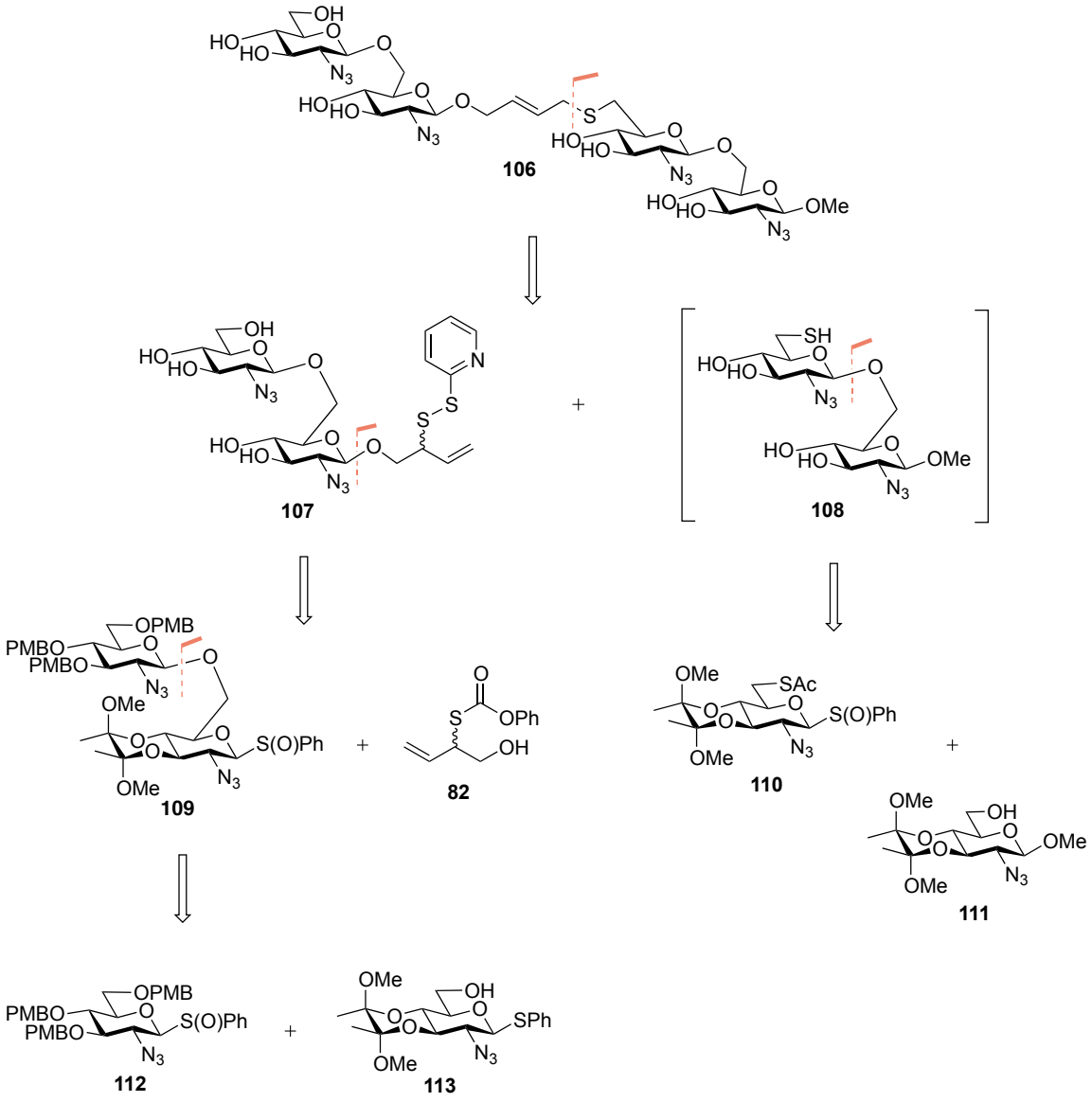
Disaccharide **105** was obtained under standard Cu (II) conditions[138] and in a good yield, with respect to the reported yields found in the literature for coupling reactions made in the NHAc series. The oxazolinone disaccharide **101** was prepared from **105**, in 54% yield, via in-situ formation of the corresponding anomeric bromide using TMSBr, BF_3Et_2O and 2,4,6-collidine under anhydrous conditions. Unfortunately, the coupling of the oxazolinone disaccharide donor **101** with acceptor **82** gave results far below expectations and yielded an inseparable, complex mixture of products along with the desired coupling product, which was observed by electrospray mass spectrometry. These results were in line with what was observed earlier and confirmed the low reactivity of the allylic thiocarbonate acceptor towards oxazolinone donors. A further reason for the low efficiency of these coupling reactions may be the use of multiple electron-withdrawing protecting groups on the glycosyl donor which significantly

lowers its reactivity – a manifestation of the “disarmed” effect of the *O*-acetyl groups, a phenomenon that was described by Fraser-Reid[145], and which is also referred as to the “armed/disarmed” principle. This notion will be presented in part II of this dissertation. Given these considerations, the use of acetate as a protecting group at the nitrogen and as a C2-stereodirecting, participating group, was considered no to be suitable for the synthesis of the tetrasaccharide mimetic. The strategy was therefore redirected towards the azide chemistry and the avoidance of disarming protecting groups.

2.2.4.2 The Second Approach: The Azido Series

2.2.4.2.1 Strategies for the Synthesis of the Tetrasaccharide Mimetic

The synthesis of the tetrasaccharide mimetic was next attempted in the 2-azido-2-deoxyglucose series as envisaged in the retrosynthetic scheme shown below.

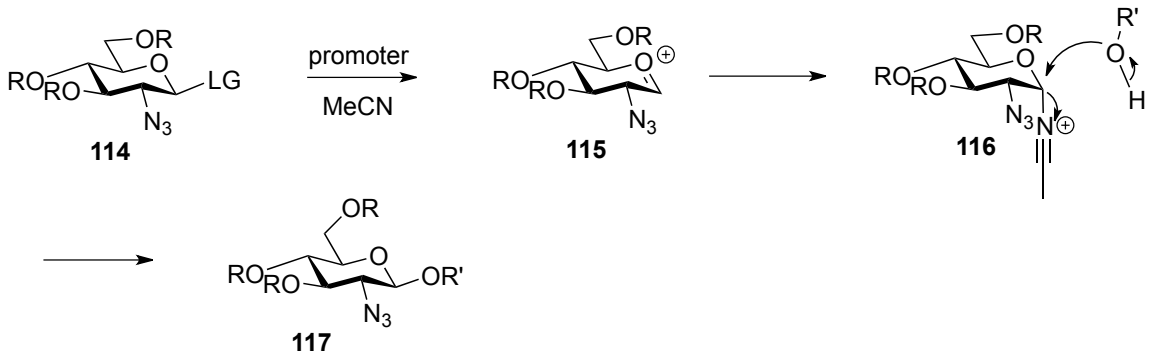


Scheme 33: General retrosynthetic scheme (N_3 series)

Different protecting groups at the nitrogen[133] of glucosamine derivatives have been investigated to prevent the formation of the oxazolinone while keeping neighboring group assistance to ensure the formation of 1,2-trans glycosides, including the phthaloyl (Phth)[146,147], or carbamates such as the

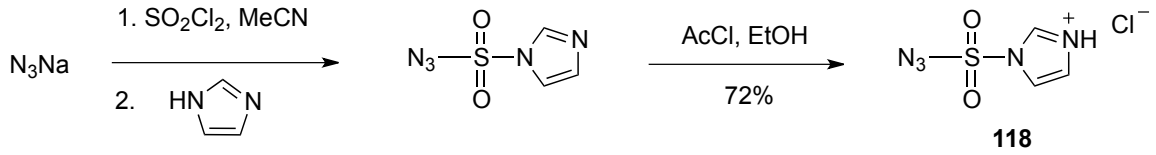
trichloroethoxycarbonyl (Troc)[148-150]. The 2-azido group[42,151-153], which is distinct in that it is not capable of neighboring group participation, has also been used for this purpose, especially when α-glycosides were required. The absence of β-directing neighboring group participation needed for the synthesis of β-glycosides can be overcome through use of the nitrile effect[42,154,155].

The influence of solvents on anomeric stereocontrol is a well known phenomenon[156]. Ether and nitrile solvents such as acetonitrile can exert a stereodirecting effect on the outcome of the glycosylation reaction, also referred as to the ether effect[151,157] and the nitrile effect respectively. In the nitrile effect, after activation and departure of the leaving group (LG), the forming oxocarbenium ion intermediate is trapped, by acetonitrile via the formation of a covalent α-acetonitrilium ion **116**, leaving the β-face open for attack by the incoming glycosyl acceptor, which displaces the latter in a S_N2 fashion to give the β-glycoside **117** (Scheme 34).



Scheme 34: The nitrile effect

The installation of the azido group at the C2 position was envisaged under Stick's[158] conditions, using imidazole-1-sulfonyl azide hydrochloride **118** as the diazotransfer reagent, whose synthesis is reported in Scheme 35.



118

Scheme 35: Preparation of the imidazole-1-sulfonyl azide hydrochloride

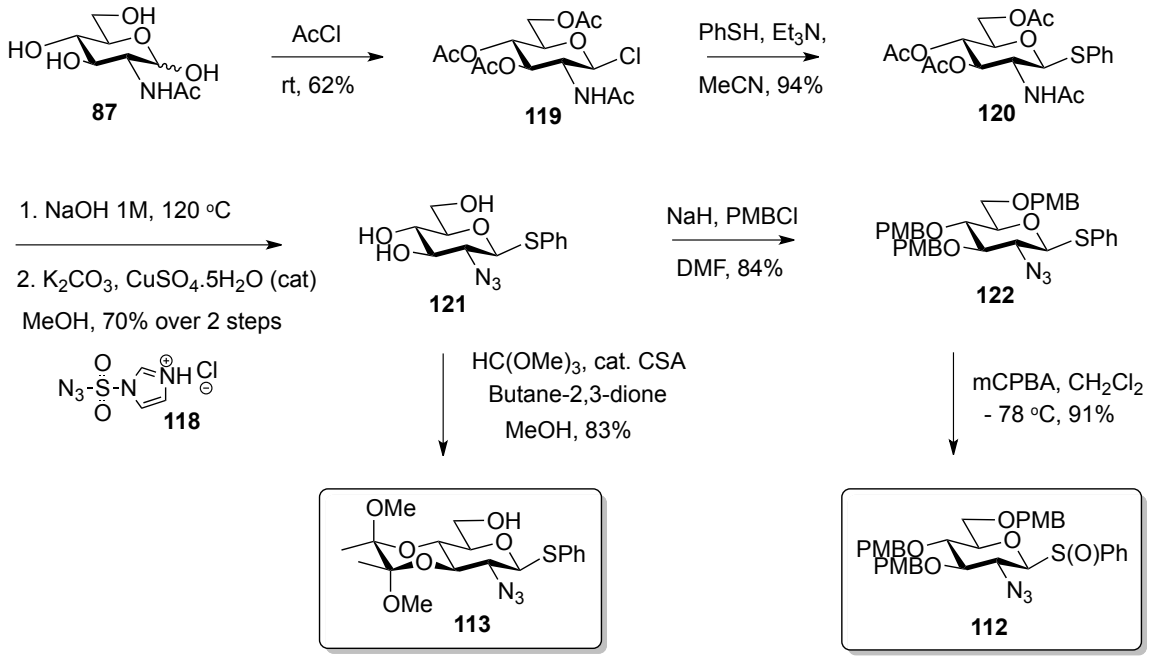
In order to optimize the reactivity of the glycosyl donor and considering the strong electron-withdrawing character of the 2-azido group, armed protecting groups such as ethers were employed, to mask the hydroxyl functionalities. Following this logic, the *p*-methoxybenzyl ether (PMB) was selected on the basis of its anticipated orthogonality with the 2-azido group and the acceptor **82** – unlike the more commonly used benzyl ether group. The regioselective functionalization at the 6-position would be ensured by using the Ley's cyclohexane diacetal (CDA)[159,160] protecting group since it is highly efficient for the protection of the *trans*-diequatorial-1,2-diol functionality in carbohydrate chemistry. Moreover, both the PMB and CDA protecting groups are acid labile, suggesting a one-pot deprotection step. Only one set of glycosylation conditions was used, whose choice was conditioned by the presence of the acid-sensitive PMB groups, which are cleaved under mild acidic conditions (e.g 5 to 10% TFA), and the allylic disulfide functionality. Based on these considerations, Kahne's[161-

[163] sulfoxide glycosylation method was selected. This method uses a glycosyl sulfoxide as the donor and trifluoromethanesulfonic anhydride as the promoter; leading to the formation of a covalent glycoside triflate as the intermediate species, as identified in pioneering work done by Crich and coworkers[164,165].

The synthesis of the tetrasaccharide mimetic is presented in the next two sections.

2.2.4.2.2 Preparation of the Unprotected Disaccharide Disulfide 107

The synthesis of the disulfide disaccharide moiety started with the preparation of both the glycosyls donor **38** and acceptor **39** as outlined in scheme 36.

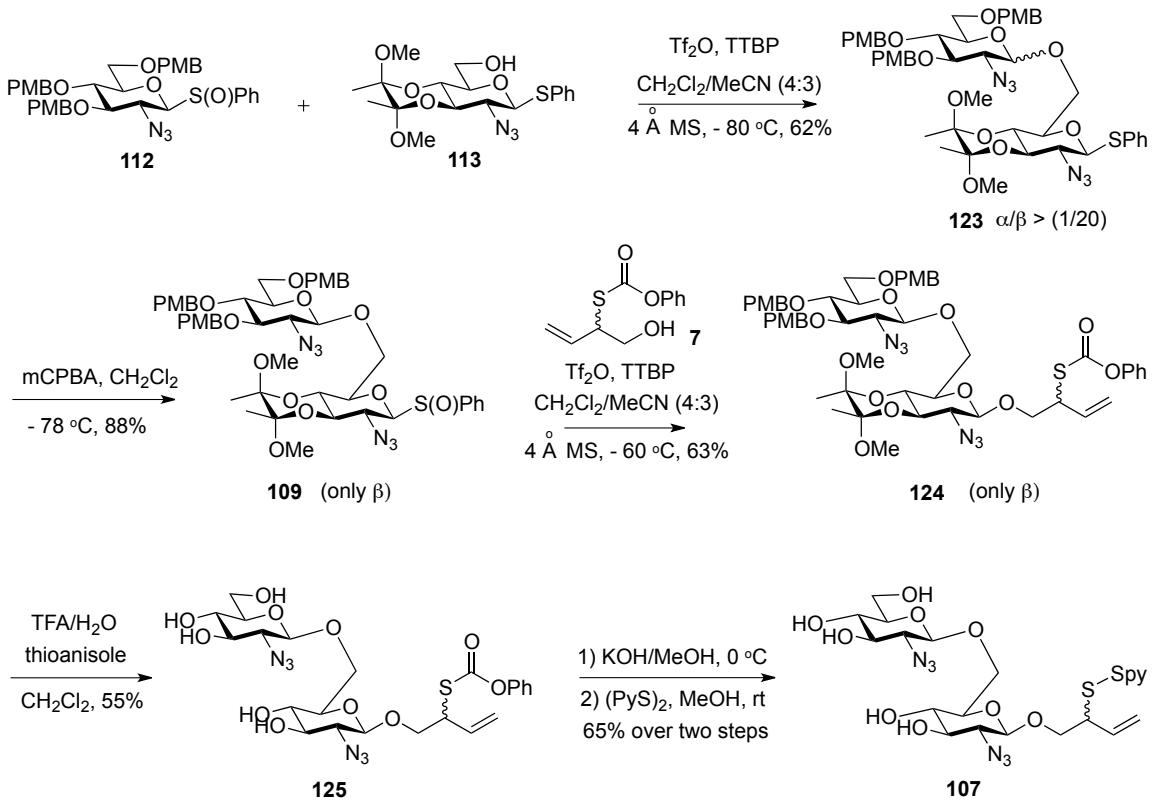


Scheme 36: Preparation of glycosyl donor 112 and acceptor 113

A common path was used for the synthesis of compounds **112** and **113**, beginning with commercially available *N*-acetyl-D-glucosamine. The synthesis started with installation of the chloride at the anomeric position, followed by peracetylation upon treatment with acetyl chloride, giving rise to a mixture of α/β chloro peracetyl *N*-acetylglucosamine. The subsequent synthesis was conducted only with the β-chloro compound **119** because of the low reactivity of the α anomer. Compound **119** was converted to its corresponding thioglycoside **120** by reaction with thiophenol[166] in 92% yield ($^3J_{1,2}$ = 10.4 Hz). Thioglycoside **120** was fully deprotected in the presence of 1 M NaOH[166] prior to installation of the azido group at the 2-position by reaction with imidazole-1-sulfonyl azide hydrochloride[158] **118** to give the 2-azido β-thioglycoside **121** in 70% yield over the two steps. Then, from compound **121**, a one step reaction using trimethyl orthoformate and butane-2,3-dione in presence of a catalytic amount of CSA afforded glycosyl acceptor **113**[159] in 83% yield. Installation of the PMB groups at the 3-, 4-, and 6-positions was carried out under standard conditions[167] to give compound **122** in 84% yield, which was finally oxidized in presence of *m*-CPBA[168] to give the β-glycosyl sulfoxide donor **112** as an equal mixture of diastereomers and in 91% yield.

With the glycosyl donor and acceptor in hand, the synthesis was carried out through the formation of the unprotected disulfide disaccharide moiety as

depicted in Scheme 37 proceeding first with the coupling of compounds **112** and **113** using Kahne's glycosylation conditions[161-163].



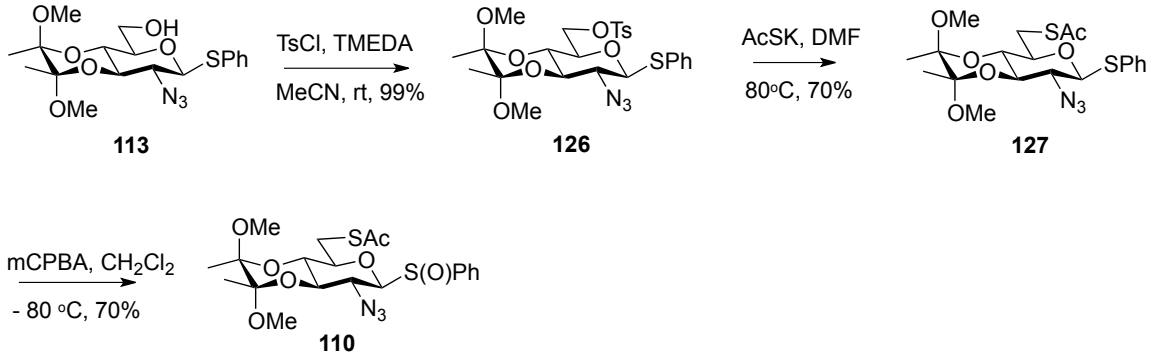
Scheme 37: Synthesis of the unprotected disaccharide disulfide precursor 107

The glycosyl sulfoxide donor **112** was activated with Tf_2O in presence of the glycosyl acceptor **113**, in a 4:3 mixture of CH_2Cl_2:MeCN. An excess of a non-nucleophilic base, TTBP*[169], was used in order that the PMB groups would withstand the glycosylation conditions. The use of Kahne's sulfoxide methodology allowed the activation of the thiosulfoxide donor **112** in presence of the thioglycoside **113** in the reaction medium, as described for related

compounds by the van Boom group[162,170]. The glycosylation reaction was conducted at low temperature (- 80 ºC) because of the high reactivity of the sulfoxide donor **112**, which was easily prone to react at higher temperatures, in an intramolecular fashion via neighboring group participation of the ether group at O-6 to form a 1,6-anhydro by-product[171]. The stereoselectivity of the glycosylation reaction was controlled by the nitrile effect[42,154,155]. Disaccharide **123** was thus obtained with high diastereoselectivity in favor of the β-anomer (α/β > 1/20) and in 62% yield. The β-selectivity of the reaction was confirmed by ^{1}H NMR experiments ($^3J_{1,2}$ = 7.6 Hz). The resulting disaccharide was then oxidized to its sulfoxide counterpart using *m*-CPBA[168], to further allow the introduction of the acceptor **82** at the anomeric position. The coupling reaction between **109** and **82** proceeded with complete β-stereoselectivity ($^3J_{1,2}$ = 8.8 Hz) and afforded the disaccharide disulfide precursor **124** in 63% yield. Hydrolysis of **124** took place upon treatment with aqueous trifluoroacetic acid (TFA)[172] in presence of thioanisole, and afforded the fully deprotected disaccharide **125**. Finally, saponification of **125** was followed by treatment with 2,2'-dipyridyl disulfide[131] to give the target compound **107** as a 1:1 mixture of diastereomers and in 65% yield over the two steps.

2.2.4.2.3 Preparation of the Unprotected Based-Thiol Disaccharide Building Block 108

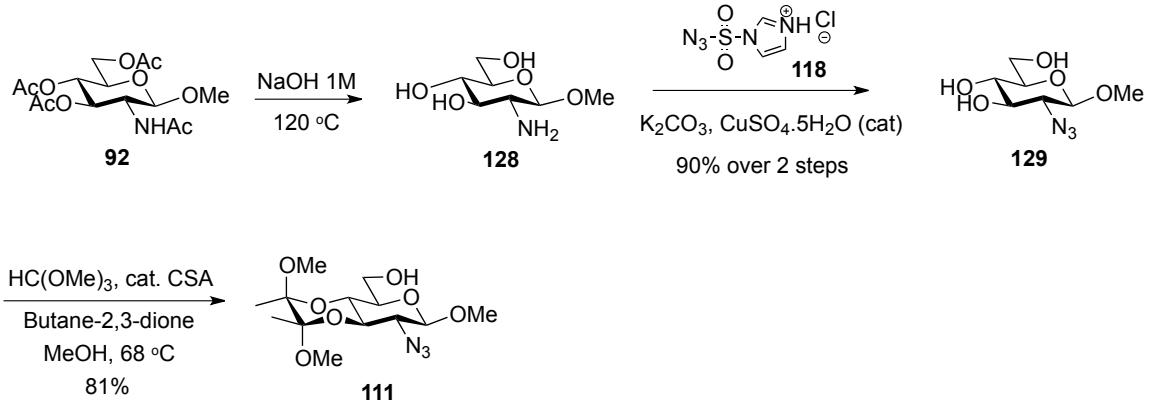
The synthesis of **108** was carried out in a straightforward manner from intermediates **110** and **111**. The synthesis of the thiosulfoxide donor **110** was conducted as schematized below (Scheme 38).



Scheme 38: Synthesis of the thiosulfoxide donor 110

Functionalization at the 6-position proceeded first with introduction of the tosyl group[173], giving rise to compound **126** in a quantitative yield. This was followed by displacement of the tosyl group by potassium thioacetate[173], which gave the desired 6-thioacetate precursor **127** in 67% yield. Finally, compound **127** was treated with *m*-CPBA under the usual conditions to give the glycosyl sulfoxide donor **110** in 70% yield and as a single diastereomer.

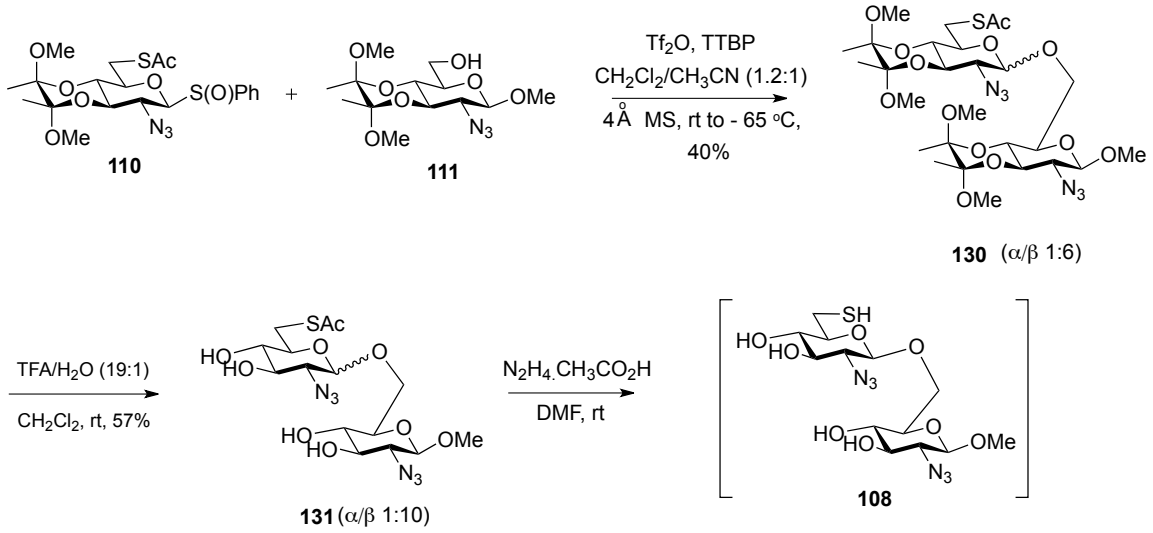
The glycosyl acceptor **111** was synthesized on the same basis as glycosyl acceptor **113** as shown in Scheme 39.



Scheme 39: Synthesis of the glycosyl acceptor 111

After complete hydrolysis of the acetate groups, the azido functionality was installed at the 2-position[158] to give compound **129** in 90% overall yield. Finally, protection of the 3- and 4- hydroxyl groups with the CDA protecting group[159] afforded the target glycosyl acceptor **111** in 81% yield.

Elaboration of the disaccharide based-thiol was then completed as presented in Scheme 40.

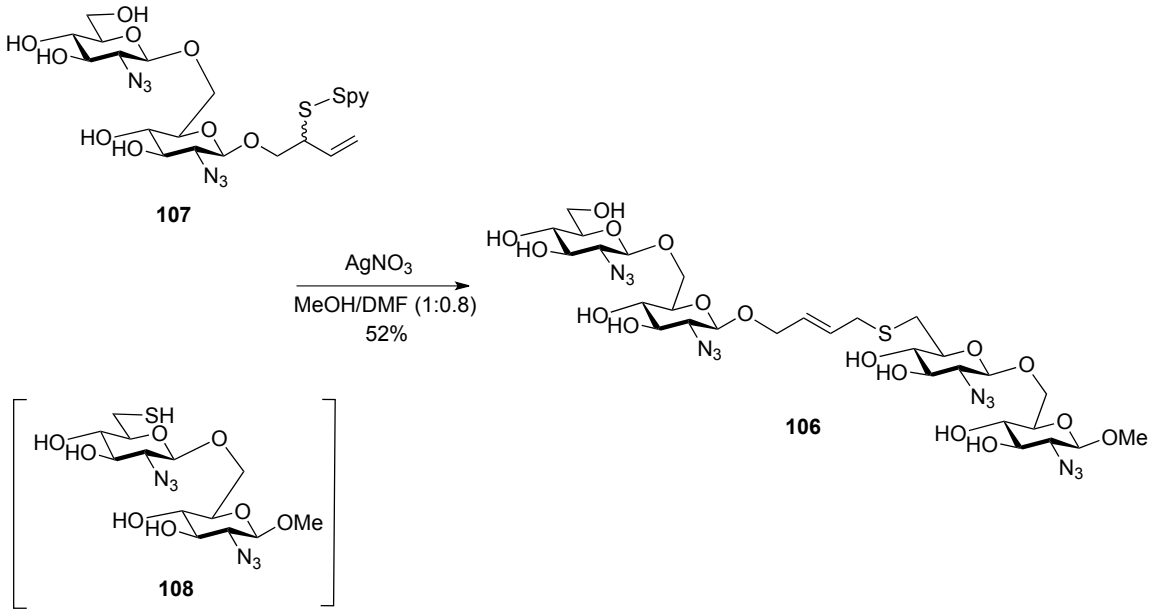


Scheme 40: Synthesis of the deprotected based-thiol disaccharide 108

The glycosyl donor **110** and acceptor **111** were coupled under Kahne's glycosylation conditions[161-163], in a 3:1 mixture of CH_2Cl_2:MeCN and yielded disaccharide **130** as a 1:6 α/β mixture of anomers in a moderate yield. The mixture was subjected to aqueous TFA in dichloromethane to give the deprotected disaccharide **131** as a 1:10 mixture of α/β anomers, from which the β-anomer ($^3J_{1,2}$ = 7.8 Hz) was purified by column chromatography. Hydrolysis of the 6-thioacetate to give the 6-primary thiol completed the synthesis of the disaccharide based-thiol building block **108**. The reaction was carried out under neutral conditions under an oxygen-free atmosphere in dimethylformamide, by reaction with hydrazine acetate. Because of sensitivity to aerial oxidation, the resulting deprotected disaccharide **108** was not isolated and was used in crude form in the final step of the synthesis.

2.2.4.2.4 The Ligation reaction: Conjugation of Unprotected Disaccharide Moieties 107 and 108

With the two disaccharide building blocks in hand, the final step of the synthesis of the tetrasaccharide mimetic **106** were carried out by coupling both unprotected disaccharide building blocks **107** and **108** as shown in Scheme 41.



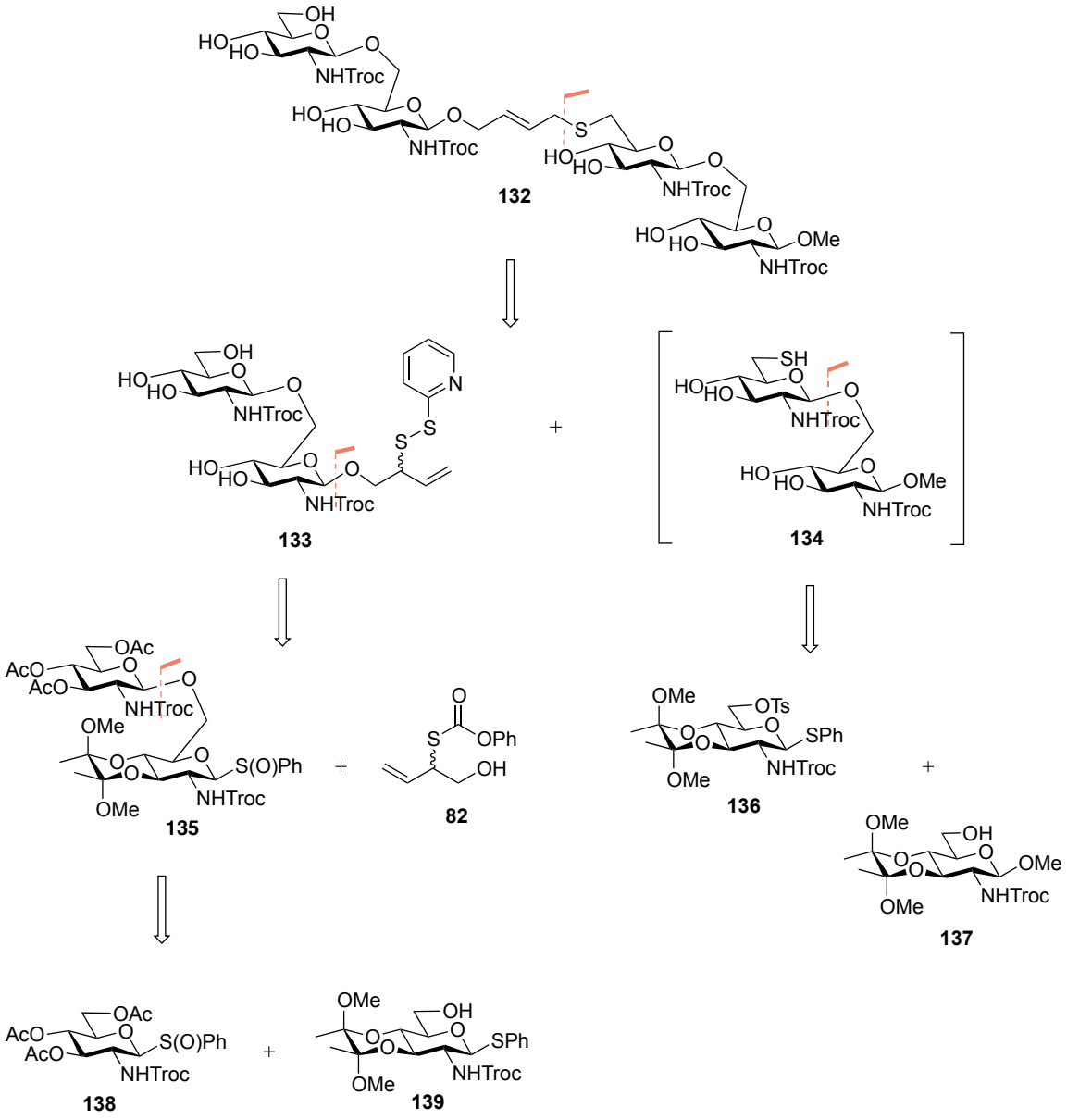
Scheme 41: Ligation of disaccharyl sulfenyl donor 107 and thiol 108

The transformation took place smoothly as expected, under the standard conditions previously described[116,131] and gave the target tetrasaccharide mimetic **106** in moderate yield. The desulfurization step was carried out with silver nitrate[143] to ensure retention of the azide functionality at the 2-position, and proceeded with complete *E*-selectivity giving rise to compound **106** as the only isomer detected, in 52% yield.

2.2.4.3 The Third Approach: The NHTroc Series

The last example targeted to test the applicability of this methodology centered on the use of the *N*-Troc-protected glucosamine series. Both disaccharide moieties were synthesized according to a similar strategy as the one employed for the elaboration of the preceeding glycomimetics, as presented

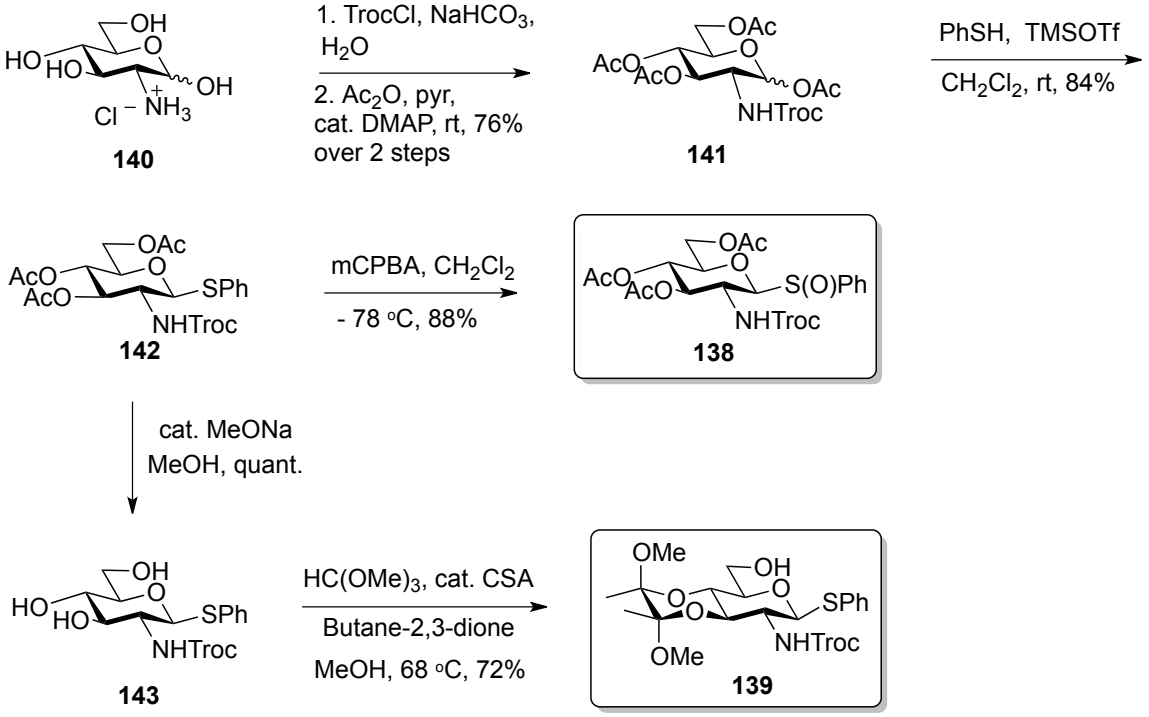
in the next two sections. An overall retrosynthetic scheme is presented below (Scheme 42).



Scheme 42: General retrosynthetic scheme (*N*-Troc series)

2.2.4.3.1 Preparation of the Unprotected Disulfide Disaccharide Building Block 133

The synthesis started with the construction of the disulfide disaccharide unit **133**, for which the synthesis of the corresponding glycosyl donor **138** and acceptor **139** is outlined in the scheme below.

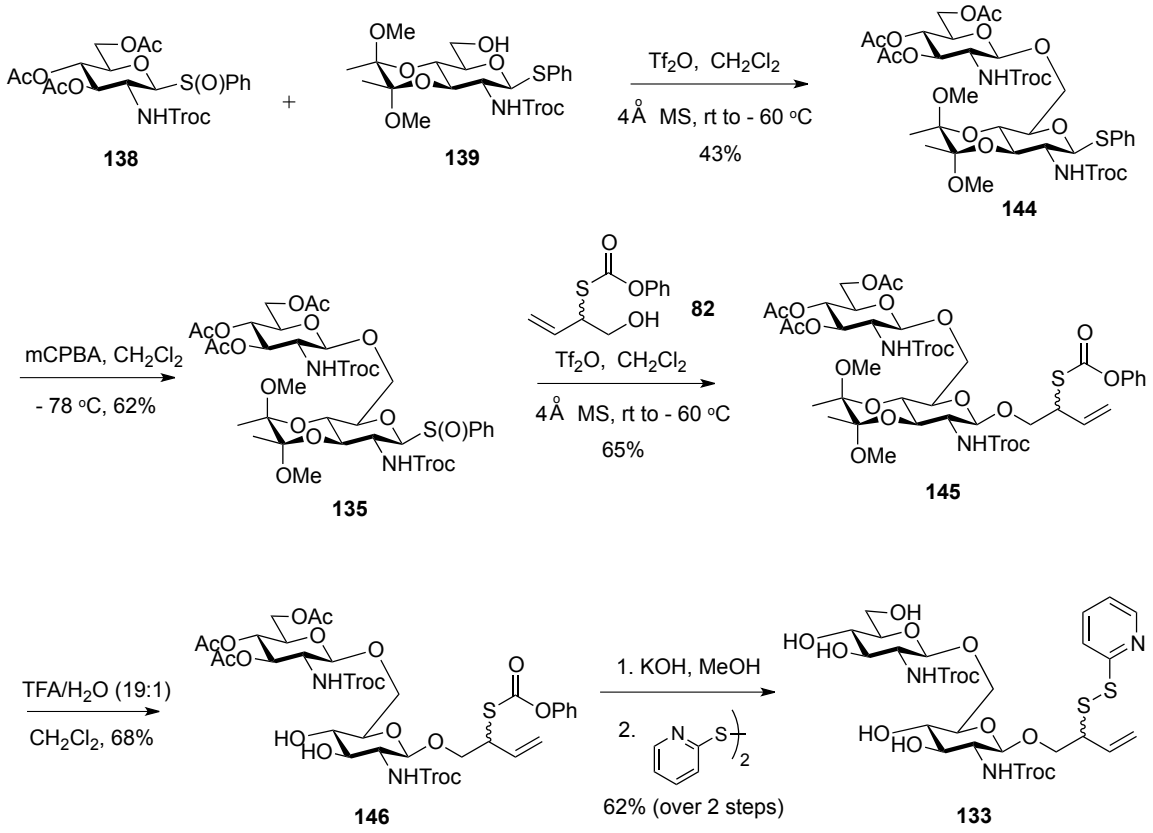


Scheme 43: Synthesis of glycosyl donor 138 and acceptor 139

The synthesis of compounds **138** and **139** was quite straightforward and started from commercially available D-glucosamine hydrochloride **140**. Installation of the carbamate functionality at the 2-position followed by peracetylation under the usual conditions afforded compound **141**[174,175], in 76% over two steps and in an α/β mixture. Functionalization of the anomeric position by introduction of thiophenol[175] gave the thioglycoside **142**, whose β-selectivity was ensured by neighboring group participation from the Troc group ($^3J_{1,2}$ = 9.6 Hz). This reaction was followed by *m*-CPBA oxidation to give the thiosulfoxide donor **138** as a

single diastereomer, and in 88% yield. Deacetylation of compound **142** under Zemplén conditions followed by Ley's[176] CDA protection of the 4- and 6-positions gave the targeted thioglycosyl acceptor **139** in 72% yield.

The synthesis of the first disaccharide building block **133** was undertaken as follows (Scheme 44).



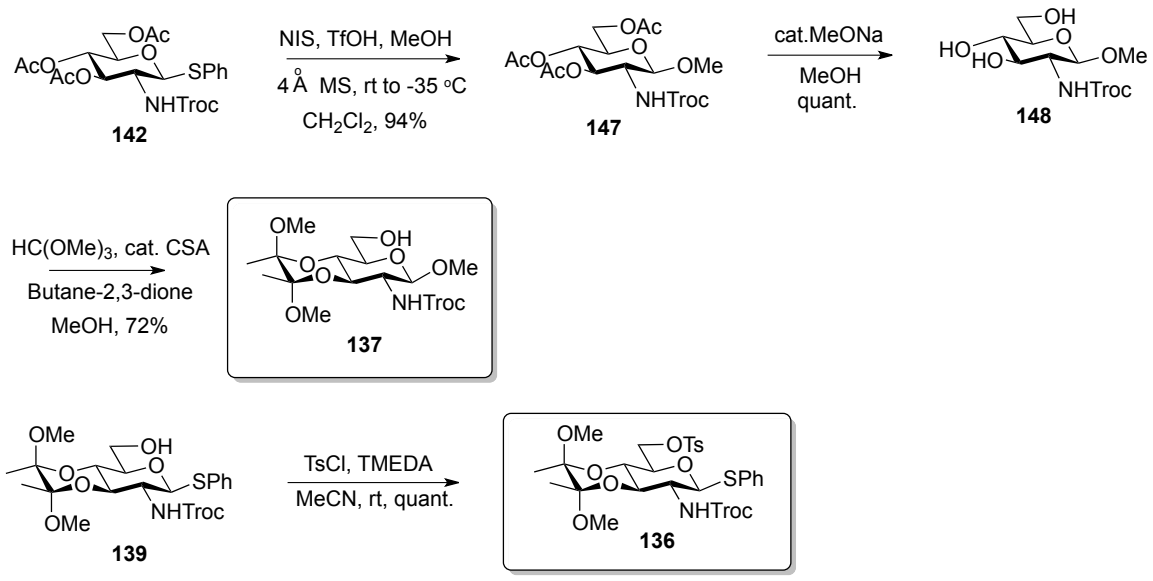
Scheme 44: Synthesis of the unprotected disulfide disaccharide moiety 133

Kahne's sulfoxide glycosylation conditions were applied for the synthesis of the disaccharide **144**, which was obtained in a modest 43% yield, but with complete β-stereoselectivity ($^3J_{1,2}$ = 7.6 Hz). A sufficient amount of this intermediate could be prepared to confidently carry out the remainder of the synthesis without the need for optimizing the reaction conditions. The synthesis

was then advanced with the introduction of the essential allylic acceptor **82** at the anomeric position, which took place after the thioglycoside **144** was oxidized to its thiosulfoxide counterpart **135**. The disaccharide disulfide precursor **145** was obtained with total β-stereoselectivity ($^3J_{1,2}$ = 9.6 Hz) and in 65% yield. Hydrolysis of the CDA protecting group under aqueous TFA conditions afforded compound **146** in 68% yield. Finally, the synthesis of the unprotected disulfide disaccharide **133** was achieved by the standard deacetylation of intermediate **146** upon treatment with 1 M KOH in MeOH, followed with installation of the disulfide functionality by reaction with 2,2'-dipyridyl disulfide, to give the target compound **133** as a 1:1 mixture of diastereomers.

2.2.4.3.2 Preparation of the Unprotected Based-Thiol Disaccharide Building Bloc 134

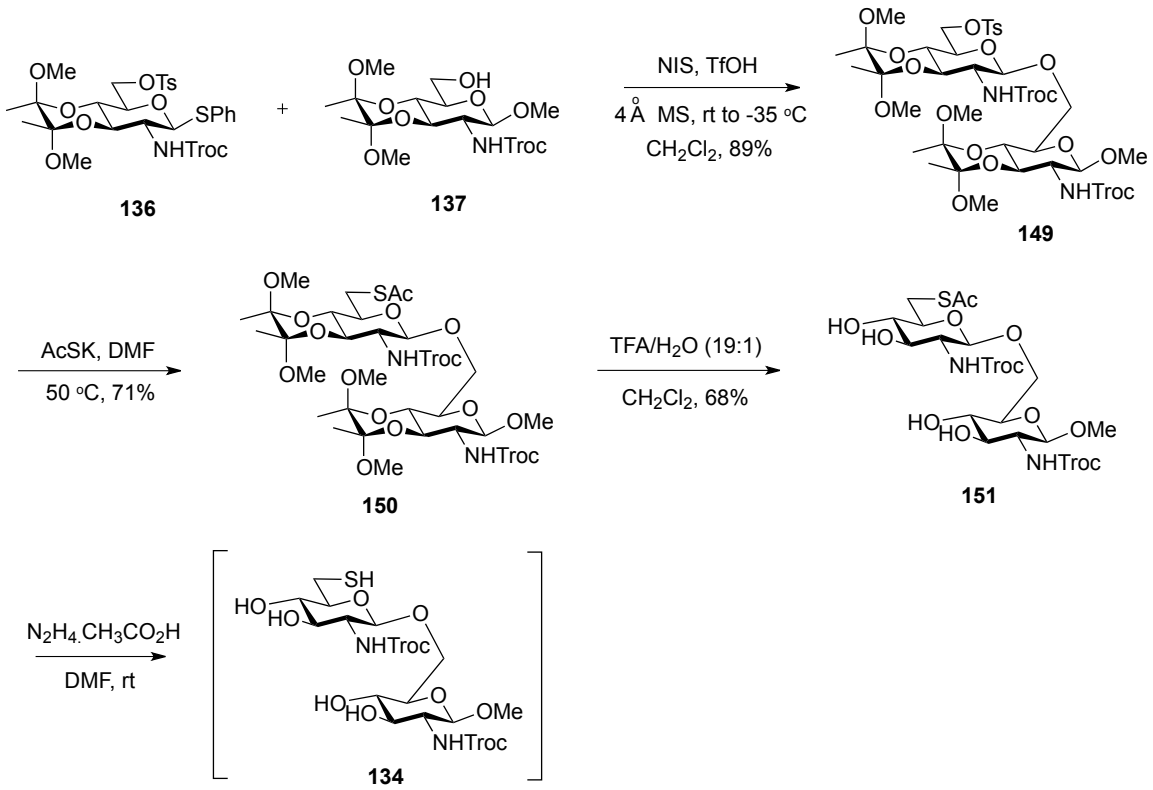
The last step toward the elaboration of the tetrasaccharide mimetic in the *N*-Troc series consisted of the synthesis of the based-thiol disaccharide moiety, which was prepared from the glycosyls donor **136** and acceptor **137** as schematized in Scheme 45.



Scheme 45: Synthesis of glycosyl donor 136 and acceptor 137

Compound **142** was used as the starting material for the synthesis of the glycosyl acceptor **137**, which was obtained in three steps starting with introduction of the methoxy group at the anomeric position. The coupling of thioglycoside **142** with methanol under *N*-iodosuccinimide (NIS)/trifluoromethanesulfonic acid (Tf_2O) conditions[177] gave the corresponding methyl glycoside **147** in excellent yield and stereoselectivity ($^3J_{1,2}$ = 9.2 Hz). Hydrolysis of **147** under Zemplén conditions was followed by installation of the CDA protecting group[159] at the 3- and 4-positions to give the glycosyl acceptor **137** in 72% yield. The glycosyl donor **136** was synthesized in a one step process starting from intermediate **139**, which was reacted with *p*-toluenesulfonyl chloride (TsCl)[173] in presence of a base, tetramethylethylenediamine (TMEDA) and obtained in quantitative yield.

The preparation of the based-thiol disaccharide was then completed as set out in Scheme 46.



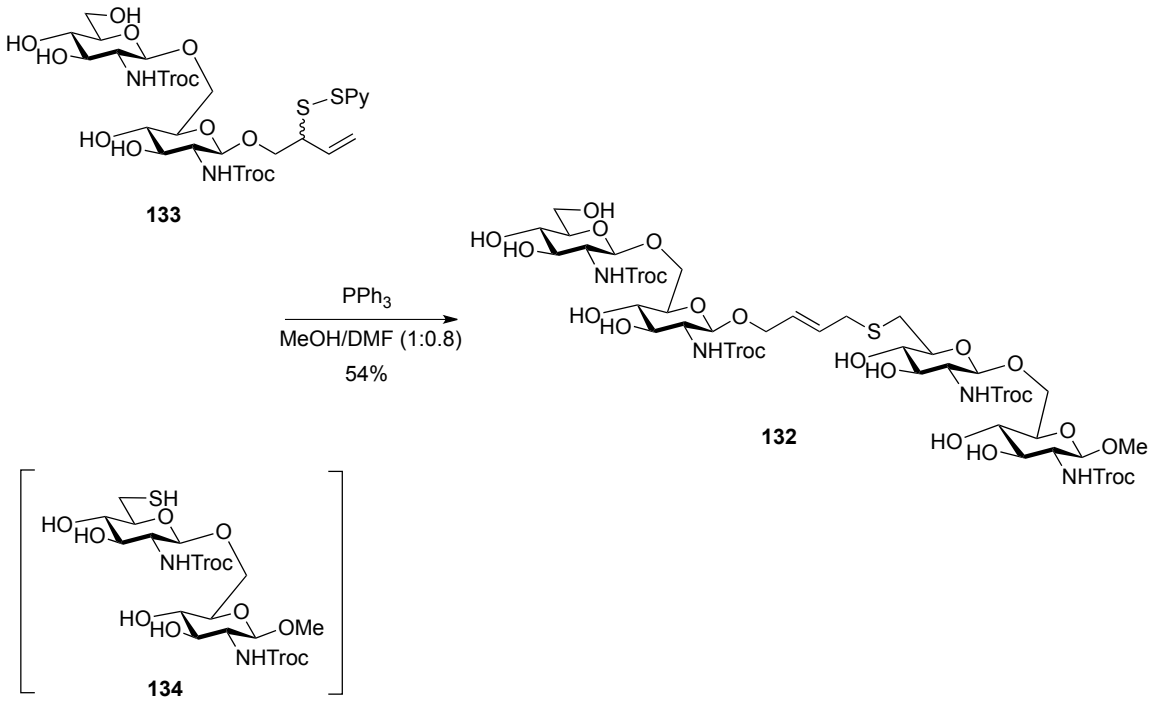
Scheme 46: Synthesis of the based-thiol disaccharide 134

The coupling efficiency of the glycosylation reactions in the *N*-Troc series was significantly higher under NIS/TfOH conditions[177] than with BSP/Tf_2O/TTBP conditions[178], under which the formation of an orthoester by-product was observed. Disaccharide **149** was therefore synthesized under NIS/TfOH conditions, which was obtained in very good yield (89%) and complete stereoselectivity. Subsequently, the thioacetate functionality was introduced at the 6-position by displacement of the *p*-toluenesulfonyl group by potassium thioacetate[173] to give compound **150** in 71%. Hydrolysis of the CDA protecting groups was carried out under aqueous acidic conditions and gave the fully deprotected 6-thioacetate-disaccharide precursor **151** in 68%. Careful

precautions were used for the hydrolysis of **151**, which was achieved with hydrazine acetate at room temperature. The resulting disaccharide was directly engaged in the final step of the synthesis without further purification.

2.2.4.3.3 The Ligation Reaction: Conjugation of Unprotected Disaccharide Moieties 133 and 134

Finally, the key step of this synthesis, the ligation reaction, completed the construction of the tetrasaccharide mimetic in the *N*-Troc series. The two disaccharide building blocks were assembled under the standard conditions and the transformation took place uneventfully, giving rise to the last tetrasaccharide mimetic **132** in 54% yield. The desulfurative rearrangement was promoted under triphenylphosphine conditions for purification reasons.



Scheme 47: Ligation of disaccharyl sulfenyl donor 133 and thiol 134

2.3 Conclusion

This chapter presented a novel approach for the preparation of oligosaccharide mimetics by the means of a recently developed [2,3]-sigmatropic rearrangement of allylic disulfides. Two pre-assembled sugar units were attached together via a small, thioether linkage, whose installation proceeded with complete chemoselectivity. The features of this facile transformation were exploited to construct these glycomimetics without protecting groups. The use of the azide and the trichloroethoxycarbonyl groups demonstrated the compatibility of this transformation with diverse functionalities. This method could then been used as an alternative for the construction of large, linear oligosaccharide mimetics from pre-assembled small sugar units.

PART II: STEREOELECTRONIC INFLUENCE OF C-O BONDS ON *C*- AND *O*-GLYCOSYLATION

CHAPTER 3

INTRODUCTION

3.1 The Glycosyl Oxocarbenium Ion: a Transient Intermediate

As briefly introduced in section 1.4, the glycosylation reaction is a complex phenomenon that involves numerous components and the mechanism that lies behind it has not yet been fully understood. Unless anchimeric assistance by a NPG at C2 of the sugar occurs, the mechanism of the glycosylation reaction is not clear-cut. Two extreme schemes can be readily drawn going from a direct bimolecular S_N2 displacement of the anomeric substituent, which corresponds to an associative mechanism, to an unimolecular S_N1 reaction via the formation of a glycosyl oxocarbenium ion, in which case a dissociative pattern is involved. Yet, it has been commonly accepted that a cationic intermediate, the putative oxocarbenium ion, was, at some point of the reaction, involved in the mechanistic scheme of the glycosylation reaction. Although conventionally drawn out in almost all the mechanistic patterns in carbohydrate chemistry involving the forming or the breaking of bonds at the anomeric carbon, in reality, evidence of the actual existence of the oxocarbenium ion has still to be proven experimentally[179,180]. To address this issue, indirect methods most commonly computational or NMR spectroscopic studies, have served as tools to gain better inside into the general features of this supposedly key intermediate.

If oxocarbenium ion is an intermediate in glycosylation processes, the abundance of carbohydrate molecules in higher organisms implies that many biological processes proceed via the formation of oxocarbenium ion intermediates. Biological mechanisms that consider to include oxocarbenium ion intermediates are encountered for instance, in the biosynthesis of cyclic ADP-ribose (cADP), an important intermediate for intracellular calcium signaling and, of more interest for carbohydrate chemists, glycosidases, enzymes involved in the breakdown of glycosidic bonds. As a result, understanding the chemical and physical properties of the oxocarbenium ion goes to the heart of glycochemistry and glycobiology. The hydrolysis of glycosidic bonds, which is in fact the inverse reaction of the glycosidic bond formation, has been subjected to a tremendous amount of work, in both mechanistic enzymology, whose mechanisms first were proposed by Koshland[181] in 1953 and then revisited over the years[182], and in carbohydrate chemistry. This is especially true for the acid-catalyzed hydrolysis of glycopyranosides[183] whose mechanism will be discussed in Chapter 5. Mechanistically, it has been generally accepted by both communities, chemists and enzymologists, that the breaking of the glycosidic bond involves the formation of a species exhibiting a high degree of oxocarbenium ion character. Indeed, the strategy adopted by enzymologists in the concept of glycosidase inhibitors, seeks to mimic the transition state of the hydrolysis of the glycosidic bond, which is believed to go through an exploded transition state, in other words, to mimic the structure of the oxocarbenium ion, by miming its positive charge and/or geometry[184] (Figure 4).

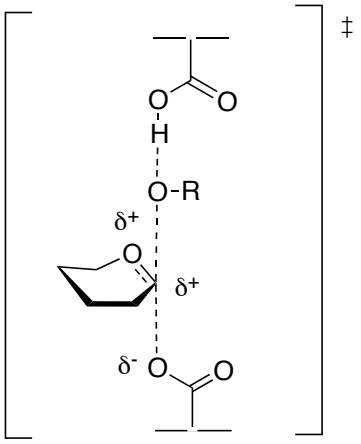
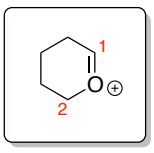
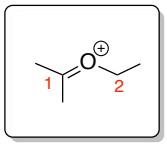


Figure 4: Proposed transition state during the glycosidic bond cleavage

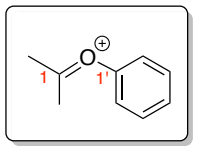
Failing to observe the glycosyl oxocarbenium ion experimentally, structurally related, but more stable species than the oxocarbenium ion have been studied as probes. Falling into this category, examples such as simple alkoxycarbenium ions, prepared first by Meerweein then observed and described experimentally by NMR spectroscopy in superacids by different research groups, such as the Olah group, have rendered plausible the idea that comparable intermediates could be envisaged in the mechanistic pattern of the glycosylation reaction. Some NMR spectroscopy characteristics of several of these intermediates are outlined in Figure 5.



^{13}C NMR 150 MHz,
CH_2Cl_2/CD_2Cl_2 (10:1), - 80 °C
δ 227.8 (C_1), 82.5 (C_2), 35.4, 19.5, 12.1.



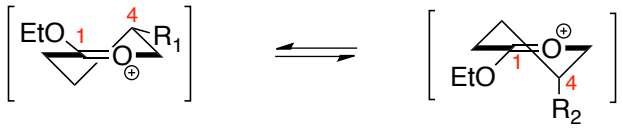
^{13}C NMR, 25 MHz, SO_2ClF, - 40 °C
δ 245.1 (C_1), 68.8 (C_2), 32.2, 27.0



^{13}C NMR, 25 MHz, SO_2ClF, - 78 °C
δ 248.3 (C_1), 154.2 ($C_{1'}$), 131.9, 131.1
118.0, 32.2, 29.1

Figure 5: ^{13}C NMR features of some alkoxycarbenium ions

In line with this, Woerpel[185] provided complementary information by investigating the characteristics of polysubstituted cyclic dioxocarbenium ions, for which he determined that the orientation of alkoxy substituents on the half-chair conformation are governed by electronic interactions with the electron deficient cyclic oxocarbenium ion, thus forcing the alkoxy substituents to occupy pseudo-axial positions, unlike their alkyl counterparts, which prefer to sit at the equatorial positions of the half-chair conformation (Scheme 48)[186,187].



R_1 = alkyl R_2 = alkoxy

Scheme 48: Preferred orientation of alkoxy and alkyl substituents on a cyclic dioxocarbenium ion

Clearly, the geometry of the oxocarbenium ion is a crucial piece of information that is needed in order to understand the stereoselective outcome of glycosylation reactions. Computational studies remain a powerful, indirect method to provide theoretical explanations for experimental observations. Considerable studies by density functional theory (DFT) calculations have been undertaken by the Whitfield[188-190] laboratory to predict the different conformational preferences adopted by the glycosyl oxocarbenium ion. A key feature inherent to their geometry is an appreciable sp^2 hybridization character at the anomeric carbon C1, imposing near perfect planarity on the C5-O5-C1-C2 torsional angle (ω = 0°). To this angle corresponds a series of plausible equilibrating conformers for the glycopyranosyl cation ring[191] of different

energies, which are presented in a 3D spherical representation along with the chair, boat and skew boat conformers that link them (Figure 6).

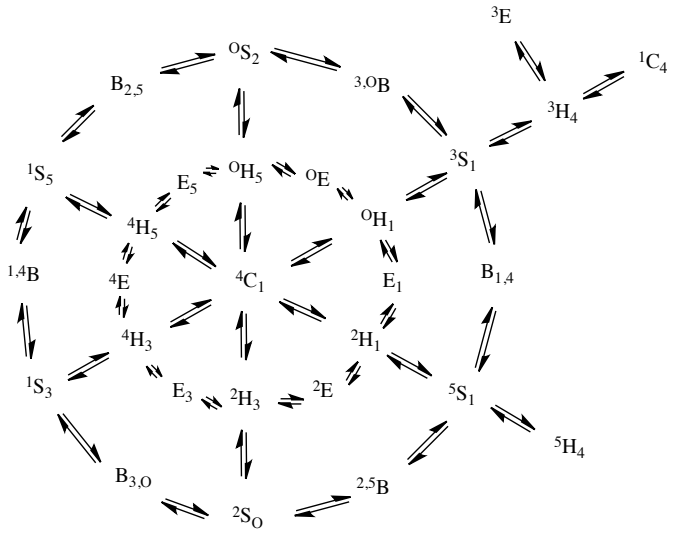


Figure 6: Conformational representations of glycopyranosyl ring

The 12 boats (*B*) and skew boats (*S*) are located at the outer circle, 12 of the envelopes (*E*) and the half-chairs (*H*) are on the inner circle, whose central position is occupied by the $^{4}C_1$ chair conformation. Further, Whitfield[188] demonstrated that more than one favorable conformation of minimum energy existed for the glycopyranosyl oxocabenium ion besides the classical $^{4}H_3$ half-chair conformation[188], notably in the glucose and the mannose series that he studied extensively. The ^{4}E envelope conformation was identified as the lowest energy conformation for the simple tetrahydropyranyl oxocarbenium ion[190]. Details of these conformations will be presented in the next chapter.

Yet, oxocarbenium ions can have an existence only if a stabilizing anion or solvent are proximate, such as the triflate anion as described by Crich[165], resulting in a contact ion pair (CIP) or a solvent separated ion pair (SSIP). The

question of whether or not an entity of this type could have a real existence in the typical organic medium used in glycosylation reactions, mostly dichloromethane, was raised rightly a few years ago by Sinnott[192], who pointed out that if aqueous solutions cannot sustain a good charge separation of such polarized species, then a fortiori solvents like dichloromethane (ε = 8.93 at 25 °C), with a dielectric constant far less than water (ε = 78.30 at 25 °C) cannot do so. From this reasoning another question arises as to the actual lifetime of the oxocarbenium ion? Jencks[180] and coworkers estimated the lifetime of the glycosyl oxocarbenium ion to be around ~ 10^{-12} s at room temperature and in an aqueous solution devoid of nucleophiles – the half-life of bond vibration being ~10^{-13} s. This estimated lifetime in aqueous solution is very different from the lifetime evaluated by Yoshida[193-196], of simple alkoxycarbenium ions, which he found to be on the scale of minutes in dichloromethane, at – 80 °C and the absence of a strong nucleophile.

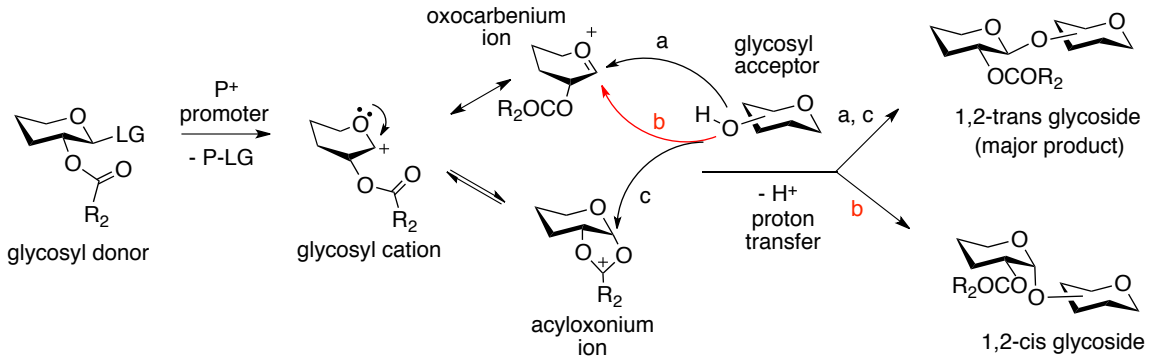
On this basis, any firm conclusions will be hard to draw and subjective because of the indirect nature of all of these experiments. However, many consistent data such as the evidence of glycosylation reactions exhibiting unimolecular kinetics[197,198] lean towards the acceptation of the postulate of the transient existence of a glycosyl oxocarbenium intermediates.

3.2 General Chemical Glycosylation Mechanism

Mechanistically, the glycosylation reaction corresponds to an acetal formation, which in itself involves one of the most empirical concepts of organic

chemistry, C-O bond formation and yet, one of the most puzzling mechanisms. The focus of this section will be to give a general overview of the mechanism of the glycosylation reaction by bringing its key intermediates into perspective, with a particular emphasis on one class of glycosylation reaction, the 4,6-*O*-benzylidene-directed glycopyranosylation reaction.

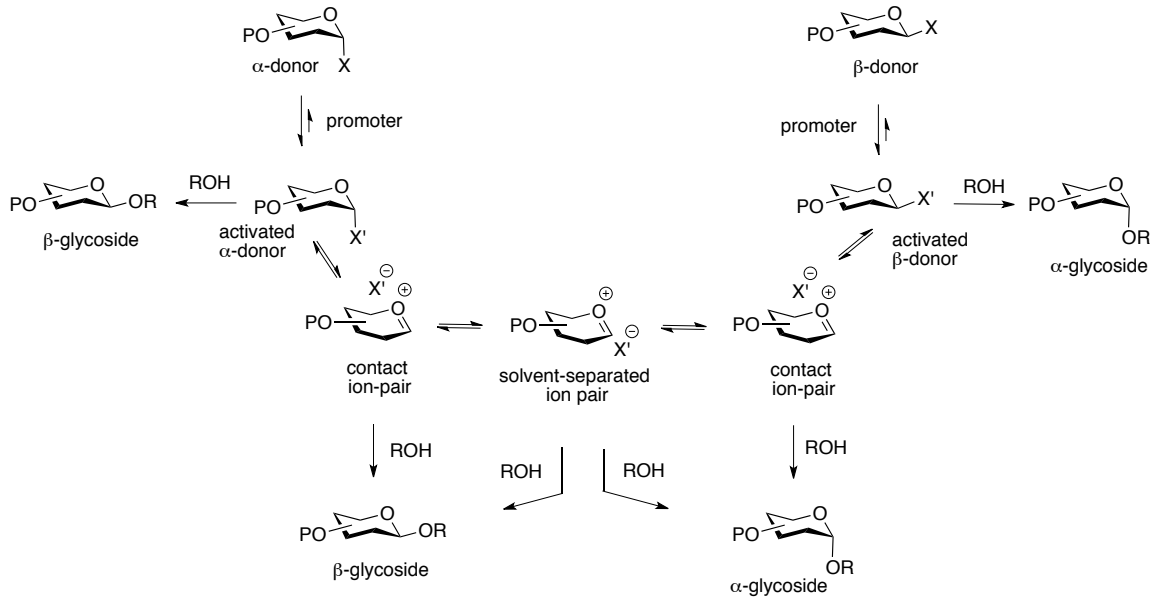
The nature of the protecting group at the C2 position of the glycosyl donor can influence the mechanistic scheme of the glycosylation reaction and thereby, its outcome. When a participating group is present at C2 – most commonly *O*- or *N*-acyl groups – the departure of the activated leaving group can be assisted by this later, leading to the formation of an acyloxonium ion, which temporarily blocks one face of the sugar, giving rise to the 1,2-trans glycosides as the major product (Scheme 49)[57].



Scheme 49: Mechanism of the glycosylation reaction in presence of a NPG

On the other hand, in absence of a NPG at C2, a different mechanistic pattern takes place. The overall picture of the mechanism of the glycosylation reaction has been known for a long time and falls somewhere between a pure S_N2 nucleophilic substitution pathway and a S_N1 mechanism, which clearly leaves

one with a broad tray of possible mechanistic schemes. Details have been added onto the picture first advanced by Rhind-Tutt and Vernon[197], followed by the work of Lucas and Schuerch[199], and finally revisited in the seminal contribution of Lemieux[39] et al. According to this picture the glycosyl donor exists in a series of equilibria of more or less loose ions pairs that stretch from its activation until its transformation into the desired glycoside, with the position of the equilibrium as well as the population of each intermediate species being functions of the conditions set. The general scheme of these equilibria depicted by Lemieux is presented in Scheme 50.



Scheme 50: Lemieux ion-pair glycosylation mechanism

A typical S_N2 reaction involves both, a good nucleophile and nucleofuge and the rate of the reaction is of course subjected to variations depending on these two variables, as well as the nature of the carbon skeleton. The fairly poor nucleophilicity of glycosyl acceptors and the unfavorable S_N2 substitution attack

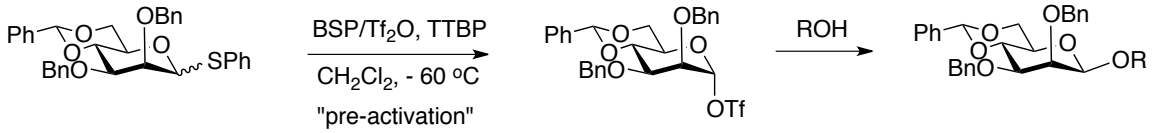
at α-oxygen-substituted carbon are all factors that disfavor a S_N2 mechanism. It is therefore not surprising that most glycosylation reactions are considered to proceed via a dissociative mechanism, and the difficulty to achieve complete anomeric stereocontrol in absence of a NPG follows from these mechanistic assumptions. Glycosyl halides, introduced first by Koenigs and Knorr[38] as glycosyl donors, have been one of the class of substrates for which a pure S_N2 pattern has been observed[197].

Although, many glycosylation reactions proceed via a dissociative mechanism, insight into the details of S_N1-like glycosylation mechanism is still limited,[200] therefore examples of such reactions will not be presented here. Instead, attention will be paid towards the mechanistic scheme of a glycosylation mechanism more relevant to the work presented here, the 4,6-*O*-benzylidene directed glycosylation reaction.

3.2.1 4,6-*O*-Benzylidene-Directed Glycosylation Reaction

Groundbreaking studies undertaken in the Crich[201,202] laboratory to unravel the mechanism of the glycosylation reaction, more specifically the ones involving 4,6-*O*-benzylidene protected donors, started with the solution of the challenging problem of the formation of β-mannosidic linkages. In 1996, Crich[201] discovered that the 4,6-*O*-benzylidene protecting group was a determining factor in controlling the β-selectivity of the mannopyranoside reaction. Long dreaded by carbohydrate chemists, a facile access to β-mannosides has been paved from Crich's seminal papers on sulfoxide glycosylation method[162,203] – initially

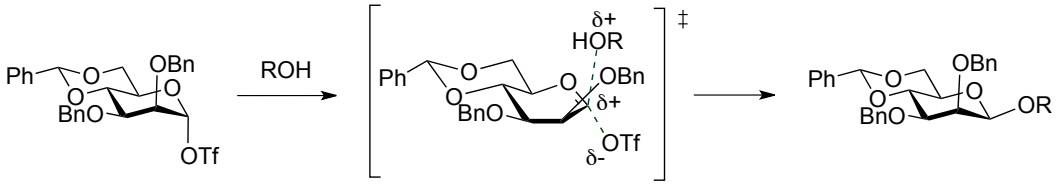
introduced by the Kahne group[161] – wherein he identified by low-temperature NMR experiments in CD_2Cl_2, that α-covalent glycosyl triflates were the key intermediate species in glycosylation reactions involving trifluoromethanesulfonic anhydride (Tf_2O) as the promoter[165]. When 4,6-O-benzylidene-α-D-mannopyranosyl sulfoxide donors react with Tf_2O, in the presence of ether-type non-participating protecting groups at O2 and O3, the coupling reaction results in the formation of β-D-mannosides[204]. On the basis of the established reaction protocol, the β-mannosylation reaction typically involves a two-step process. The sulfoxide donor is first pre-activated with Tf_2O at low temperature to promote the formation of the covalently bound α-mannosyl triflate, which is followed by addition of the acceptor to give the β-mannoside product, with typically high yield and high selectivity. The scope of this reaction was later on expanded to α- and β-D-mannopyranosyl thioglycoside[205] donors, which were also found to be excellent substrates for the induction of α-mannosyl triflates by the means of the electrophilic BSP/Tf_2O combination[178] (Scheme 51).



Scheme 51: Synthesis of β-D-mannopyranosides

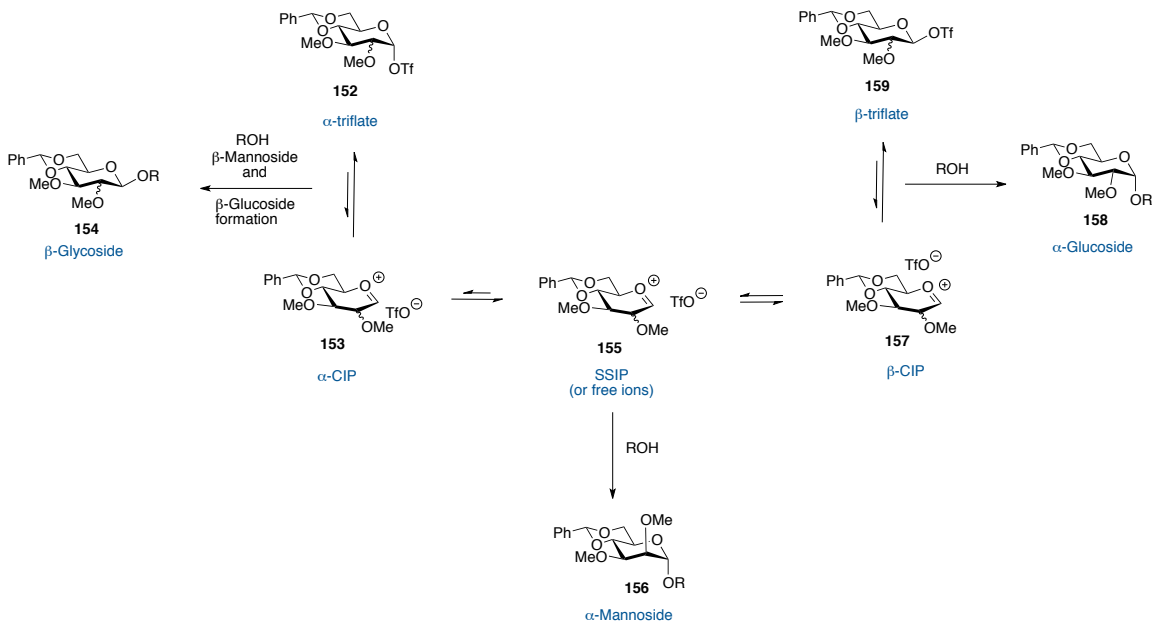
The first set of studies undertaken towards the elucidation of the 4,6-*O*-benzylidene-directed β-mannosylation mechanism using primary ^2H kinetic isotopic effects[206] (KIE) (500 MHz, ^1H) led Crich to the conclusion that the

mechanism of the β-mannosylation reaction was most likely governed by an unimolecular nucleophilic substitution, until very recently, complementary studies on primary ^{13}C kinetic isotopic effects[207] (higher magnetic field, 200 MHz for ^{13}C) supported by DFT calculations showed that the β-mannosylation mechanism as well as the α- and β-glucosylation reactions were associative in nature (S_N2 like) going via the intermediacy of an exploded transition state where the incoming alcohol displaces the triflate group from the opposite face (Scheme 52)[207].



Scheme 52: Exploded transition state

In the case of the formation of α-glucosides **158**, a covalently bound β-triflate **159** should be considered to corroborate the associative nature of its mechanism. On the other hand, a dissociative mechanism (S_N1 like) was found to account for the formation of α-mannosides **156** necessitating the formation of a SSIP **155** with close similarities of a glycosyl oxocarbenium ion. The formation of the α-anomer is favored from the oxocarbenium ion as would dictate the anomeric effect. An overall picture is presented in Scheme 53[207].



Scheme 53: Mechanism of α- and β- gluco and mannopyranosides formation with 4,6-*O*-benzylidene protected donors as determined by KIE measurements

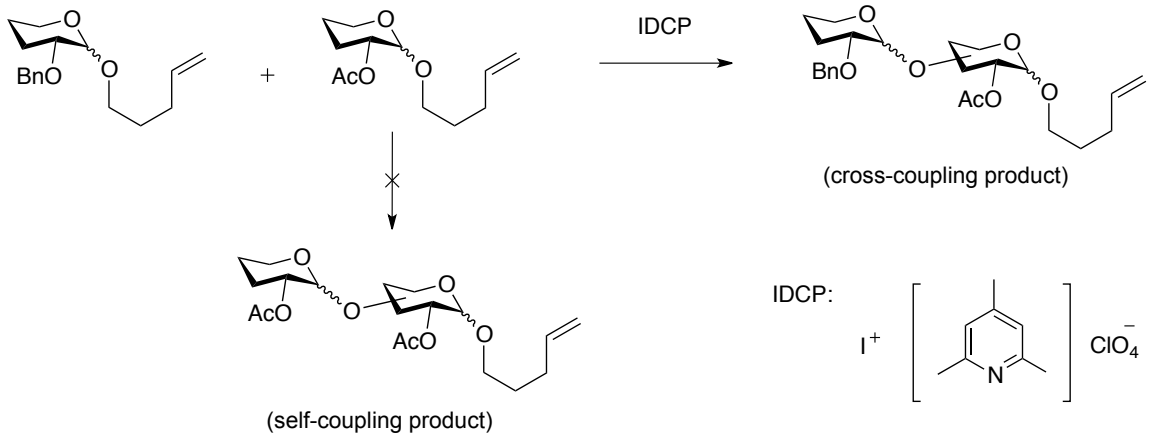
This mechanistic scheme was confirmed again for α- and β-mannosylation by cation clock experiments[198] ran in the Crich laboratory. Further discussion on the stringent conditions imposed on reactivity by the 4,6-*O*-benzylidene group will be presented in the next two chapters.

3.3. The "Armed/Disarmed" Concept

As shown in part one of this manuscript carbohydrate chemistry entails, in the vast majority of the cases, the extensive use of protecting groups. Initially intended to ensure the regioselectivity of the glycosidic bond formation, protecting groups are now seen to play an important role in the reactivity of

glycosyl donors as well as in the stereochemical outcome of the glycosylation reaction. The ability to tune the reactivity of glycosyl donors and acceptors through the modification of protecting groups, is a direct application of the seminal “armed-disarmed” concept introduced by Fraser-Reid[145] and is a major focus for the improvement of oligosaccharide synthesis. The past two decades have witnessed an increase in the understanding of the effect of protecting groups on anomeric reactivity, providing the basis for the development of efficient methods and strategies for the synthesis of oligosaccharides such as, the one pot synthesis,[50,176] and the automated solid phase synthesis[52] discussed previously in Chapter 1.

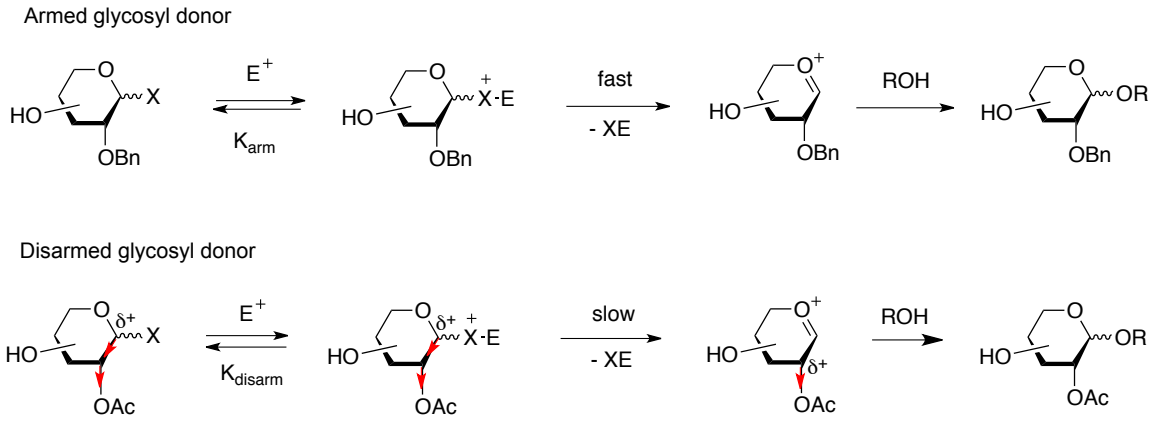
First noted by Paulsen[151] in 1982, Fraser-Reid[145,208] observed a few years later that the nature of the substituent at O2 had a considerable influence on the rate of hydrolysis of glycosyl donors. This was followed by his early observation that 2-*O*-akylated pentenyl glycosides reacted faster than their 2-*O*-acylated counterparts, in presence of a halonium ion source, for instance, iodonium dicollidine perchlorate (IDCP) when no evidence of self-condensation of the pentenyl glycoside acceptor was detected[145]. In other words, benzylated pentenyl glycosyl donors react faster than their acetylated counterparts (Scheme 54)[208].



Scheme 54: "Armed-disarmed" principle

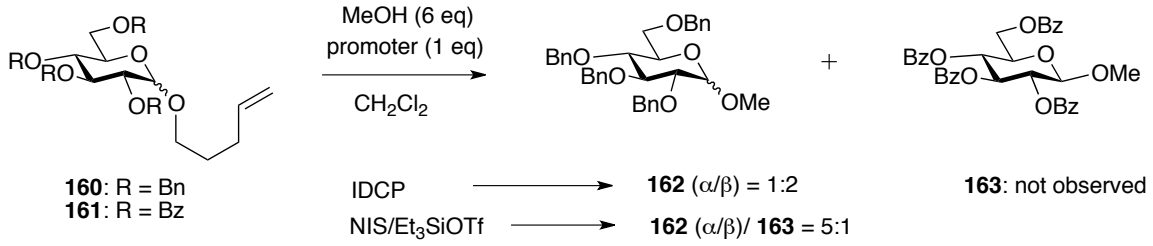
This difference in reactivity was ascribed to a difference in the electron-withdrawing character of the protecting group, from which Fraser-Reid[145] stipulated that, an armed glycosyl donor was defined as one bearing electron donating groups, such as ether groups, most often, benzyl groups. On the other hand, a disarmed glycosyl donor was defined as a system bearing electron-withdrawing groups such as ester groups, most commonly benzoyl or acetate groups. A similar observation was noted for cyclic acetal protecting groups such as 1,3-dioxanes or 1,3-dioxalanes, which, as Fraser-Reid[209] also reported, affected anomeric reactivity, although the origin of this disarming effect is rather different in nature than the one encountered in acyclic protecting groups, as discussed further in the next section. A mechanistic rationale was advanced to explain this disparity in reactivity based on electronic factors according to which the partial or full forming positive charge at the endocyclic oxygen/anomeric carbon in the course of the glycosylation reaction, is either stabilized or

destabilized by, respectively, the electron-donating or electron-withdrawing nature of the protecting group at C2 (Scheme 55)[208].



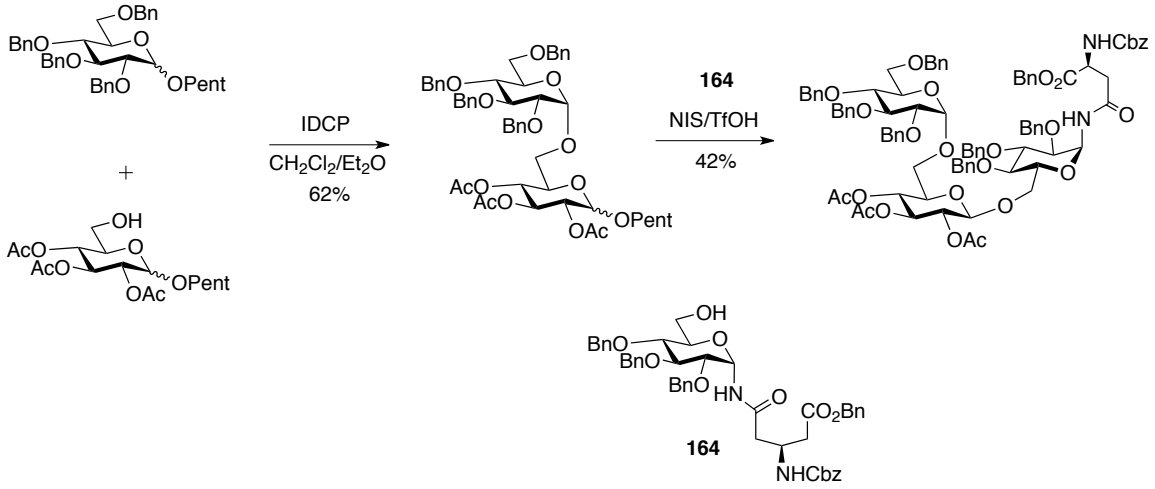
Scheme 55: Rationale for the "armed/disarmed" effect in glycosyl donors

With this in mind, Fraser-Reid demonstrated that benzylated donors could be activated selectively in presence of an equimolar amount of the benzoylated donor when competing with one equivalent of the promoter ICDP and in presence of an excess of methanol, to give the corresponding benzylated methyl glycoside. However, modifying the reaction conditions by changing the nature of the promoter for example, the *N*-iodosuccinimide (NIS)/triethylsilyltriflate (Et_3SiOTf)[210,211] combination, led to the activation of the disarmed donor **161** and gave a 5:1 mixture of both methyl glycosides (Scheme 56).



Scheme 56: Competition reaction between an armed and a disarmed glycosyl pentenyl donors

From these observations, Fraser-Reid was able to exploit his armed/disarmed concept and use it as the basis for the elaboration of a one-pot synthesis of a trisaccharide[145,212] based on a chemoselective synthesis strategy (Scheme 57).

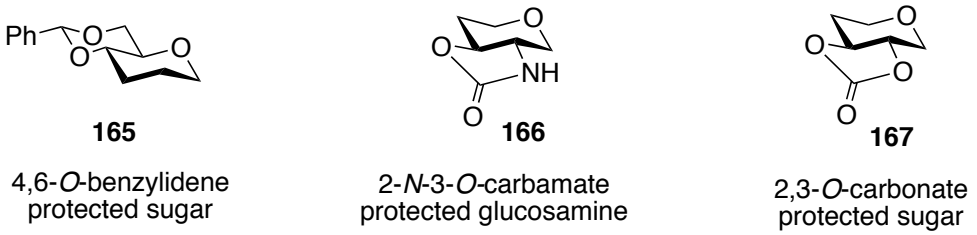


Scheme 57: Fraser-Reid's one-pot trisaccharide synthesis

3.4 Cyclic Acetal Protecting Groups

Cyclic acetals such as the 4,6-*O*-benzylidene **165** or either cyclic carbamates **165** or carbonates **167** as shown in Figure 7, are commonly employed in oligosaccharide synthesis strategy as temporary protecting groups, for their chemoselectivity as well as their directing effect in glycosylation reactions. However, the origin of the disarming effect that they exert on glycosyl reactivity is unclear, which impedes any type of mechanistic rationale and makes predictions on the glycosylation stereochemistry hard to make. Extensive

computational studies has been done by Whitfield[188,190] and al. to understand the somehow unusual behavior of these protecting groups, by predicting the different theoretical conformational geometries adopted by the pyranose ring in the course of the glycosylation reaction, in different sugar series.



165 4,6-*O*-benzylidene protected sugar

166 2-*N*-3-*O*-carbamate protected glucosamine

167 2,3-*O*-carbonate protected sugar

Figure 7: Examples of cyclic acetal protecting groups

Fraser-Reid[209], who was the first to notice the rather slow rate of hydrolysis of trans-fused acetal protecting groups over acyclic protecting groups, eg, the 4,6-O-benzylidene protected glucose vs. its tetra-benzylated counterpart, proposed a “torsional disarmament” explanation for this phenomenon, explaining that trans-fused protecting groups inhibit the flattening of the ring that is imposed by the planar geometry about the C2-C1-O5-C5 bond angle of the glycosyl oxocarbenium intermediate. This argument was quick implemented by Ley[159,160] and co-workers in their pioneering work on the protection of *trans* vicinal diols with 1,2-diacetals such as the cyclohexane-1,2-diacetal (CDA) encountered in Chapter 2 or the butane-2,3-diacetal (BDA), protecting groups that have found widespread application in carbohydrate chemistry. Ley also suggested that 1,2-diacetals induce torsional strain because of the rigidity that the bicyclic system imparts on the pyranose ring. The slower reactivity of glycosyl donors bearing cyclic protecting groups compared to that of classical glycosyl donors has

similarly been exploited towards chemoselective glycosylation as another example of the “armed/disarmed” principle.

Another cyclic acetal protecting group of particular interest is the 4,6-*O*-benzylidene acetal. The discovery of its β-directing effect in mannopyranosylation reactions and of its determining factor for the highly stereoselective installation of the β-mannosidic linkage, has led several groups to further study the singular properties of this protecting group, either experimentally[53] or computationally[188,213]. The exact role of the 4,6-*O*-benzylidene acetal, as well as its reactivity profile is not well understood and several explanations have been advanced to explain its behavior, among which is Crich’s[164] suggestion that the benzylidene group “serves to shift an entire series of CIP/SSIP equilibria toward the covalent glycosyl triflates”. An important contribution in the understanding of the origin of the disarming effect of the benzylidene group was made by Bols[53] and co-workers who attributed this phenomenon to the locking of the C6-O6 bond in its most disarming conformation, the trans-gauche (*tg*) conformation, in which C6-O6 is antiperiplanar to C5-O5 when the electron-withdrawing character of the C6-O6 bond is maximized, leading to the destabilization of the electron deficient oxocarbenium intermediate. This aspect will be extensively discussed later in Chapter 5 of this thesis.

3.5 Problems to be Addressed in this Part

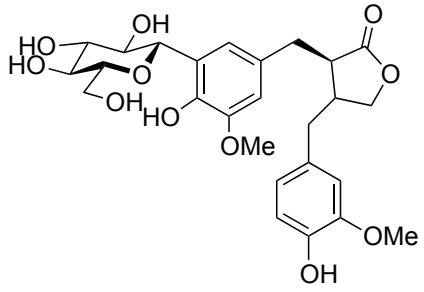
The next two chapters of this thesis are dedicated to the study of the effect of C-O bonds on the anomeric reactivity, by first looking at the influence of the C3-O3 bond on the stereochemical outcome of *C*-glycoside formation in 4,6-*O*-benzylidene protected donors in the D-mannose as well as in the D-glucose series. Later on in Chapter 5, the focus will be directed towards the understanding of the effect of the 4,6-*O*-benzylidene group on galactose reactivity by probing the disarming influence of the trans-gauche conformation of the C5-C6 bonds.

CHAPTER 4

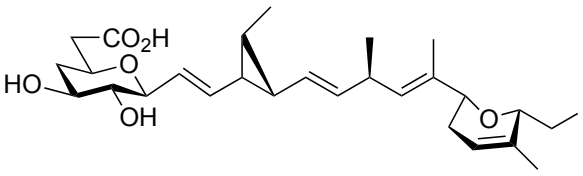
EFFECT OF THE C3-O3 BOND IN *C*-GLYCOSYLATION REACTIONS WITH 4,6-*O*-BENZYLIDENE PROTECTED 3-DEOXY GLUCO- AND MANNOPYRANOSIDE DONORS

4.1 Introduction

C-Glycosides are natural mimics of *O*-glycosides; they occur when the exocyclic oxygen of the glycosidic bond is replaced by a carbon atom. Comparatively to their *O*-counterparts, *C*-glycosides are rarely found in Nature and are not biosynthesized by higher organisms. A number of naturally occurring *C*-glycosides have been isolated from their natural resources and examples are presented in Figure 8[214,215].



Trachelospermum asiaticum



Ambruticin

Figure 8: Examples of naturally occurring *C*-glycosides

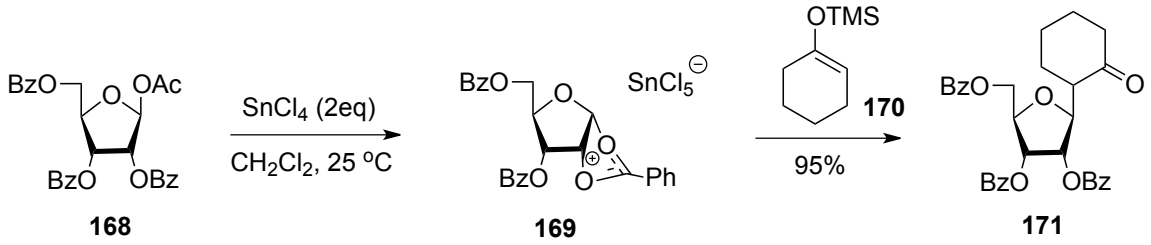
Because of the ease of alkoxy substituents to act as good leaving groups when they are protonated, *O*-glycosides are very labile to acidic and enzymatic hydrolyses. Such a mechanism is not applicable in the case of a C-C bond and as a result *C*-glycosides exhibit a greater stability to metabolic degradation. Other distinctive physical properties that derive from the *C*-glycosidic linkage are, for

instance, the inability to form a hydrogen bond and the absence of an anomeric effect. Owing to their attractive chemical and physical properties, a growing interest in the chemistry of *C*-glycosides has thus emerged from the scientific community whose consequent efforts have been directed toward their use as scaffolds for the development of potential glycosidase inhibitors.

The study described in this chapter was undertaken with a view to determining the factors that govern the stereoselectivity in the formation of *C*-glycosides, with a particular emphasis on the influence of the C3-O3 bond on the outcome of the glycosylation reaction. The synthesis of *C*-glycosides according to a standard protocol from 3-OBn- as well as 3-deoxy-4,6-*O*-benzylidene-protected donors will be described in both the glucose and the mannose series. The coupling reactions described make use of one set of glycosylation conditions, the standard BSP or/DPSO/Tf_2O activation cocktail.

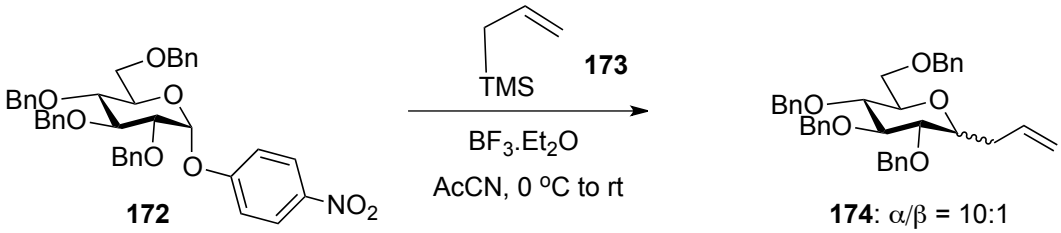
4.1.2 *C*-Glycoside Formation

Various approaches have been reported in the literature for the preparation of *C*-glycosides[214,215]. The most commonly used method – parallel with the preparation of *O*-glycosides – consists of the direct addition of the carbon-based nucleophile on the electrophilic glycosyl oxocarbenium ion. The first reaction of this type was reported by Hanessian[216] et al., in the early 1970's and concerned the synthesis of *C*-nucleosides. The Lewis-acid mediated attack of silyl enol ether **170** on protected glucofuranoside **168** afforded the corresponding β-*C*-nucleoside **171** in 95% yield (Scheme 58).



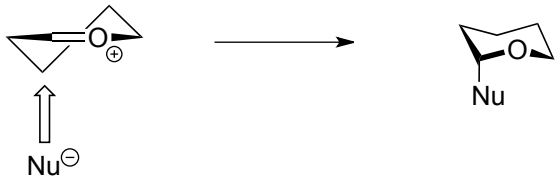
Scheme 58: Synthesis of a *C*-nucleoside

About a decade later, Kishi[217] *et al*., extended this approach to the pyranoside series, by reacting a silicon-based nucleophile, allyltrimethysilane **173** with the 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside derivative **172** in the presence of a Lewis acid, boron trifluoride etherate (BF_3Et_2O). The reaction resulted in the formation of the corresponding α-*C*-allyl-glucoside **174**, with high diastereoselectivity (α/β = 10:1) (Scheme 59).



Scheme 59: Synthesis of a *C*-allyl-glycopyranoside

The high α-selectivity observed in the product was interpreted by Kishi[217] *et al.*, in terms of pseudo-axial attack of the nucleophile on the half-chair conformation of the oxocarbenium ion as schematized below (Scheme 60).



Scheme 60: Pseudo-axial attack of the nucleophile on an oxocarbenium ion

Kishi's observations were supported by Woerpel's[218-221] extensive studies towards the determination of the factors involved in controlling the selectivity of *C*-glycoside formation. Toward this end, he investigated the different conformational preferences of five- and six-membered ring, mono- or polysubstituted oxocarbenium ions toward carbon-based nucleophiles along with the interactions that are responsible for them. Several conclusions were drawn from these studies. A recurrent observation pointed out the importance of stereolectronic factors in directing the axial attack of the nucleophile on the preferred conformation of the oxocarbenium ion, leading to the formation of the product in its most stable $^4C_1$ chair conformation[221]. These observations will be further discussed in the results and discussion section of this chapter.

4.1.3 The Glucose/Mannose Paradox

When phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside *S*-oxide was reacted with Tf_2O in the Crich laboratory, unexpected results were obtained. The α-coupling product was obtained indicating that the 4,6-*O*-benzylidene protecting group is α-directing in the glucose series, rather than β-directing as in the mannose series[222,223]. Logically, Crich reasoned that this

difference in stereoselectivity observed between the two series might involve the change in the orientation of the substituent at C2. Following this hypothesis, a series of experiments were conducted in the 2-deoxy and in the 3-deoxy series as well as in the 2-deoxy-fluoro and the 3-deoxy-fluoro glucose and mannose series **12-15**, to probe the influence of the C2-O2 and C3-O3 bonds (Figure 9)[224,225].

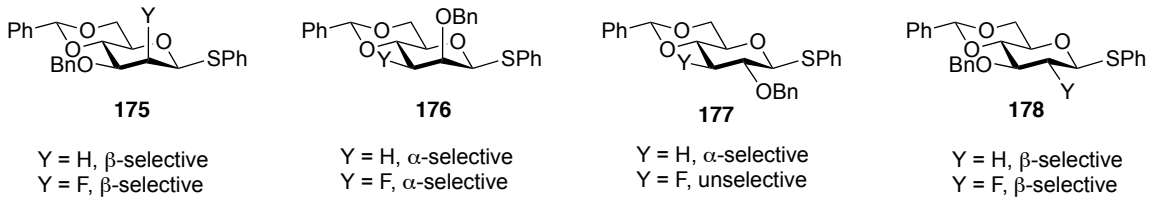
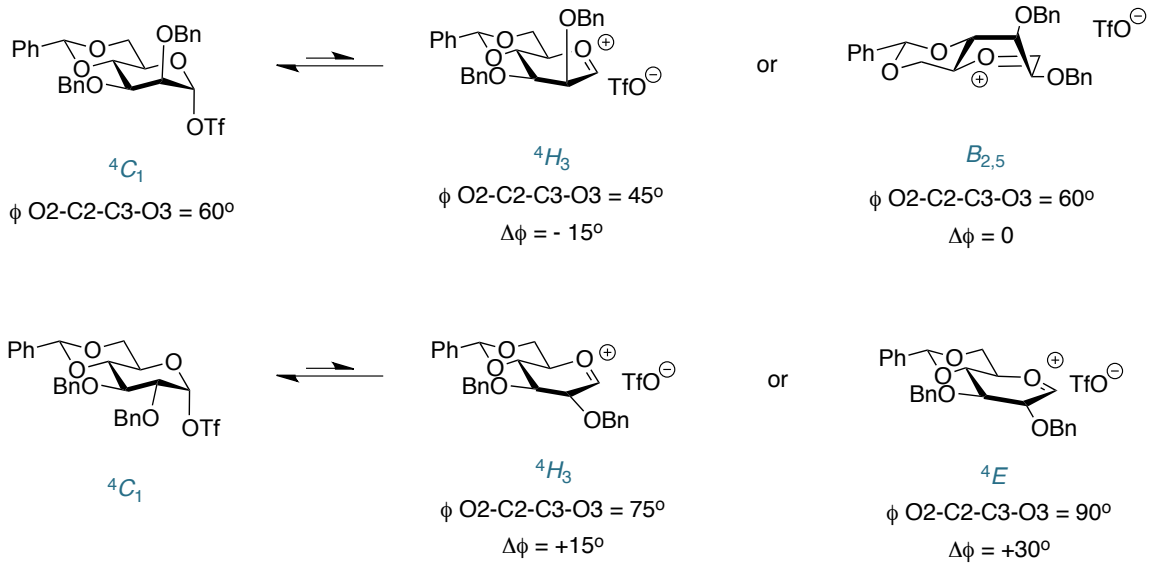


Figure 9: Deoxy and deoxy-F gluco- and mannopyranosyl donors

These modifications resulted in a loss of α- and β-selectivity in the glucose and the mannose series respectively, confirming the importance of the C2-O2 and C3-O3 bonds in controlling the selectivity in *O*-glycosylation reactions with 4,6-*O*-benzylidene-protected donors.

The presence of the 4,6-*O*-benzylidene protecting group clearly restricts the pyranose moiety ring flip, imposing very similar conformations on the glucosyl and mannosyl oxocarbenium ions. Whitfield, Nukada, and co-workers computed that the glycosyl oxocarbenium ion in 4,6-*O*-benzylidene-protected donors, adopts a $B_{2,5}$ boat conformation in the mannose series and a ^{4}E envelope in the glucose series, besides the common $^{4}H_{3}$ chair conformation[190,213]. Thus, different factors must be responsible for this reversal of selectivity. Ultimately, Crich[225] and coworkers identified the C2-O2-C3-O3 torsional angle as a key factor in directing

the stereoselective outcome in the glycosylation reaction. In the case of the mannose series, the conversion from a $^4C_1$ ground state conformation in the covalent α-mannosyl triflate to a $^4H_3$ half-chair conformation results in a compression of the C2-O2-C3-O3 dihedral angle, which is thermodynamically unfavorable since it increases steric strain between the O2 and O3 substituents. On the other hand, the value of the C2-O2-C3-O3 torsional angle remains unchanged when the oxocarbenium ion adopts a $B_{2,5}$ boat conformation. An opposite trend is observed in the glucose series. As the covalent triflate fragments into either of the oxocarbenium ion geometries, i.e, the $^4H_3$ half-chair or the ^4E envelope conformations, the O2-C2-C3-O3 torsional angle relaxes from 60° to either 75° or 90° respectively, reducing therefore the energy requirement for the oxocarbenium ion formation (Scheme 61).



Scheme 61: Evolution of the O2-C2-C3-O3 torsional angle in the mannose and glucose series on oxocarbenium ion formation

Consequently, the formation of the oxocarbenium ion in 4,6-*O*-benzylidene-protected donors is more disfavored in the mannose than in the glucose series. On this basis, it was suggested that the oxocarbenium ion is more readily populated in the glucose than in the mannose series, resulting in a shift in the key equilibria (Scheme 53) further toward ion pairs than is the case in the mannose series, which more strongly favors the covalent glycosyl triflate.

More recently, studies undertaken in the Crich laboratory[207] led him to propose an alternative mechanism for the formation of 4,6-*O*-benzylidene-protected α-glucosides. Primary ^{13}C KIE studies demonstrated that the formation of α-glucosides proceeds via a β-glucoside triflate intermediate, and follows a Curtin-Hammett kinetic scheme[207]. Finally, although the mechanism of the glycosylation reaction in 4,6-*O*-benzylidene-protected donors has been clarified in the glucose and the mannose series, the origin of the reversal of selectivity observed between glucose and mannose remains unknown.

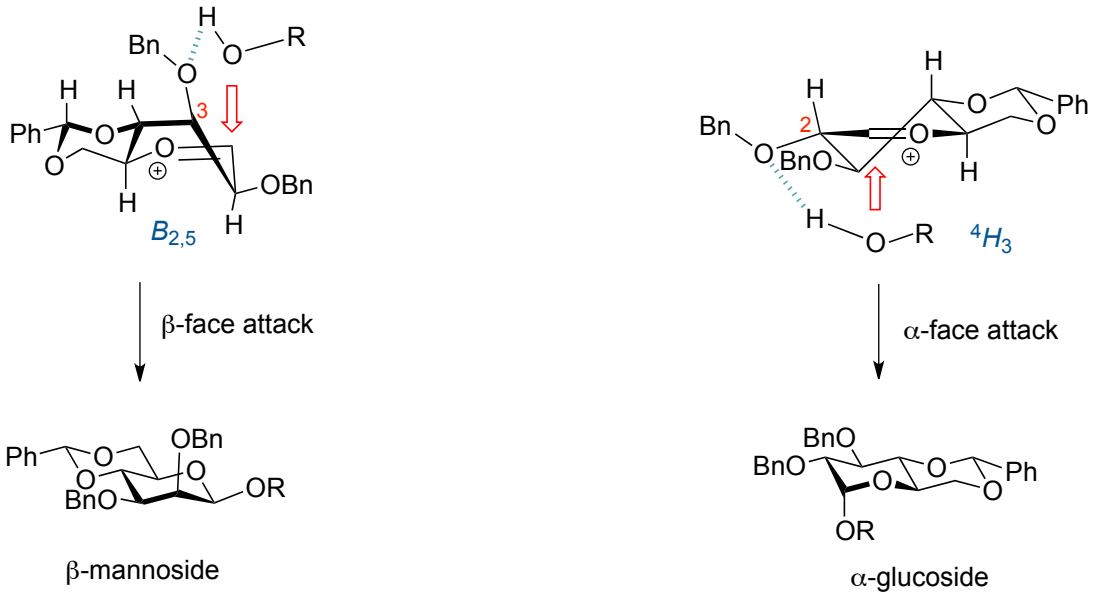
4.2 Results and Discussion

4.2.1 Preliminary Studies

Crich[226] and Sharma showed that the formation of *C*-glycosides in 4,6-*O*-benzylidene-protected glycosyl donor systems followed the same selectivity pattern as that of *O*-glycosides, namely α-*C*-glycosides are formed in the glucose series and β-*C*-glycosides in the mannose series, implying that carbon-based nucleophiles behave in a similar fashion as alcohols. This same trend of selectivity between *O*- and *C*-glycoside formation was also observed when the

screening of protecting groups at the O3 position of the glycosyl donor was investigated. The change to a 3-*O*-carboxylate protecting group from a 3-*O*-benzyl ether group resulted in a reversal of selectivity in *C*[227]- and O[228]-glycoside formation in the mannose series. Consequently, Crich hypothesized that the formation of *C*- and *O*-glycosides likely follows a common mechanistic pathway.

Computational calculations carried out by Whitfield and later by Pratt suggested, on the other hand, that the stereocontrolled formation of *O*-glycosides in the 4,6-*O*-benzylidene-directed β-mannopyranosylation reactions might result from a hydrogen bond between O3 of the glycosyl donor and the hydrogen of the incoming alcohol acceptor, directing the attack of the acceptor on the β-face of the glycosyl triflate intermediate. In the case of glucose, a hydrogen bond was observed computationally between O2 of the glycosyl donor and the alcohol acceptor, promoting therefore the formation of the α-glucose product (Scheme 62).



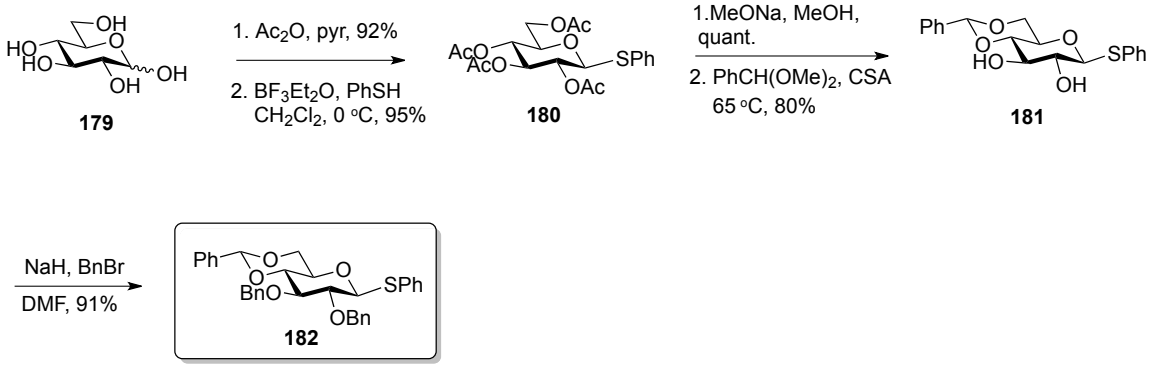
Scheme 62: Rationalization of the hydrogen bonding hypothesis in the mannose and the glucose series

Such a hypothesis is moot in the case of the formation of *C*-glycosides. The studies reported in this chapter were undertaken aiming to probe the influence of the C3-O3 bond on the stereoselectivty of *C*-glycoside formation with a view to shedding further light on the mechanisms of *O*- and *C*-glycoside formation.

4.2.2 Syntheses of the 4,6-O-Benzylidene Protected Glycosyl Donors

4.2.2.1 In the Glucose Series

The 4,6-*O*-benzylydene protected glucopyranosyl donor **182** was prepared by known methods[222], starting from commercially available D-glucose **179** as outlined in Scheme 63.



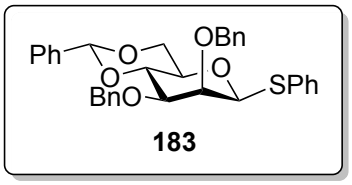
Scheme 63: Preparation of the glucosyl donor 182

Peracetylation of D-glucose **179** under standard conditions was followed by introduction of thiophenol at the anomeric carbon and gave compound **180** in 95% yield. Deacetylation of **180** using Zemplén conditions and installation of the

benzylidene acetal gave compound **181** in 80% yield. Finally, the hydroxyl groups at O2 and O3 were masked as benzyl ethers giving rise to the target donor **182** in 91% yield.

4.2.2.2 In the Mannose Series

The 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-protected β-D-mannopyranosyl donor[229] **183** was not synthesized since it was available in the laboratory. Its synthesis will therefore not be presented here.



183

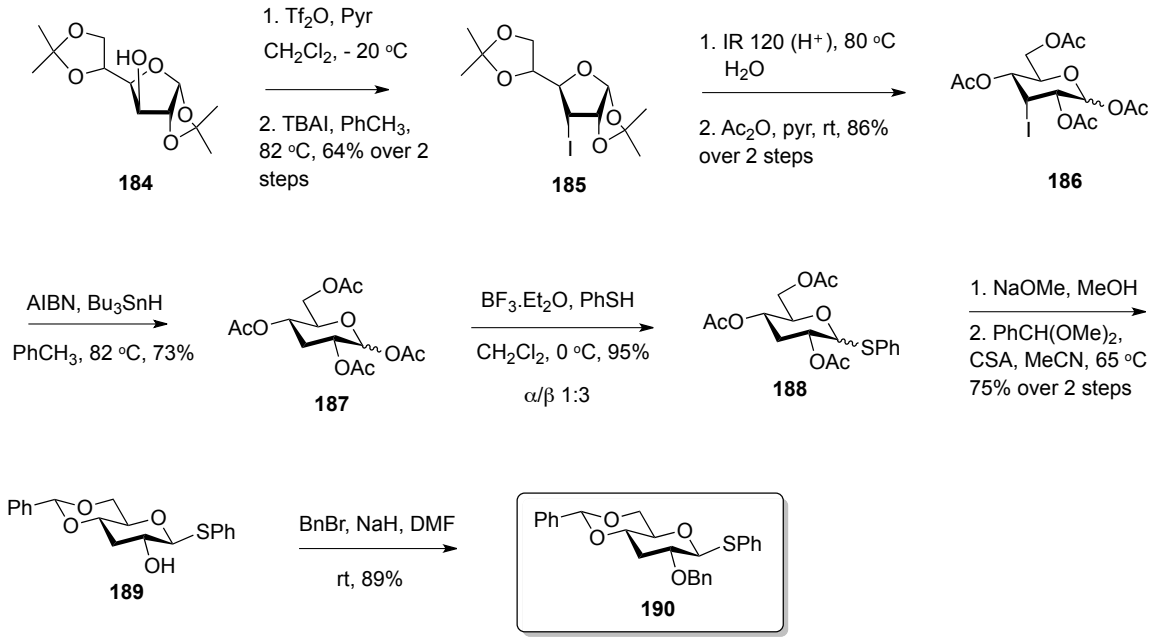
Figure 10: 2,3-di-*O*-benzyl-4,6-*O*-benzylidene protected mannosyl donor 183

4.2.3 Syntheses of the 2-O-Benzyl-4,6-O-Benzylidene Protected 3-Deoxy Glycosyl Donors

The 3-deoxy glycosyl donor analogs **190** and **192** were prepared according to known procedures[224], from a common synthetic pathway. Their syntheses are outlined in the next two sections.

4.2.3.1 In the Glucose Series

The synthesis of glycosyl donor **190** was carried out as depicted in Scheme 64.



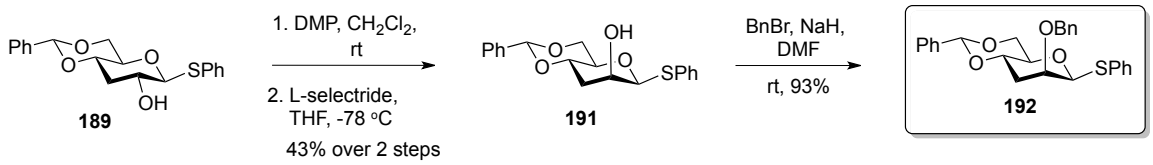
Scheme 64: Synthesis of the 3-deoxy glucosyl donor 190

Di-acetone-D-glucose **184** was converted to the iodo derivative **185** in a two-step sequence starting first with esterification in presence of Tf_2O and pyridine in dichloromethane then, displacement by iodine, which gave **185** in 64% yield over the two steps. Hydrolysis of the acetonide groups under acidic conditions was followed by peracetylation affording **186** in its pyranose form predominantly and in 82% yield over the two steps. Then treatment of **186** in presence of tributyltin hydride ($HSnBu_3$) and azobisiosobutyronitrile in hot toluene led to radical diodination, giving rise to the 3-deoxy glycoside **187** in 73% yield. Subsequent to this point, a series of standard steps were carried out starting with introduction of thiophenol at the anomeric position followed with deacetylation under Zemplén conditions then 4,6-*O*-benzylidene protection, which gave the target donor in a 1:3 α/β mixture, of which only the β anomer **189** was carried on further in the

synthesis. Finally, benzyl protection of O2 under the usual conditions gave the target 3-deoxy thioglycoside donor **190**.

4.2.3.2 In the Mannose Series

The synthesis of the last donor **192** was achieved in three steps starting from the common 3-deoxy intermediate **189** (Scheme 65)

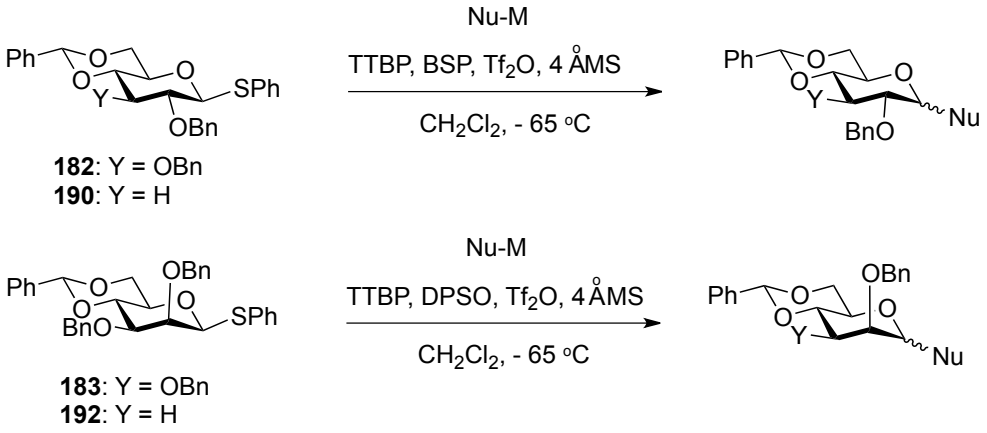


Scheme 65: Synthesis of the 3-deoxy mannosyl donor 192

Dess-Martin periodinane oxidation of **189** was followed by reduction of the resulting ketone with L-selectride and gave a α-D-glucose/β-D-mannose mixture from which compound **191** was isolated in 43% yield over the two steps. Finally benzyl protection of O-2 gave the final target compound, the 3-deoxy mannosyl donor **192** in 83% yield.

4.2.4 Coupling Reactions: Formation of the *C*-Glycosides

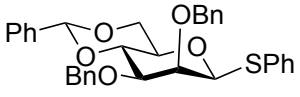
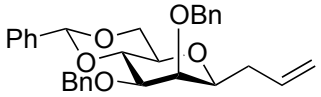
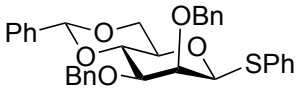
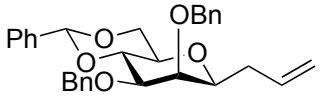
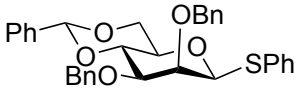
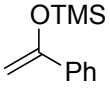
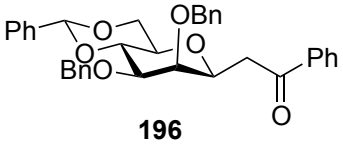
With all the glycosyl donors in hand, attention was given to the coupling reactions. A single set of glycosylation conditions was used for all the sugar series, i.e, the standard BSP or DPSO/TTBP/Tf_2O activation method with pre-activation of the glycosyl donor at – 65 °C in CH_2Cl_2 followed by addition of an excess of the nucleophile (Nu-M), allyltrimethysilane, allyltributylstannane or α-trimethylsiloxystyrene. A general scheme is presented below.



Scheme 66: *C*-glycoside formation protocol

4.2.4.1 In the 3-*O*-Benzylated Series

In order to verify the previous published work from the Crich laboratory the coupling reactions in the normal mannose and glucose series were conducted. The results of these studies are presented below (Table 2)[230].

Entry	Donor	Nucleophile	Product	Yield
1	 **183**	 **173**	 **193**	57%
2	 **183**	 **194**	 **193**	60%
3	 **183**	 **195**	 **196**	76%

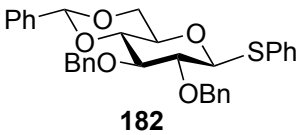
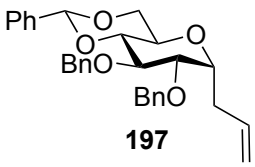
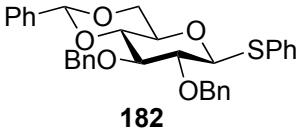
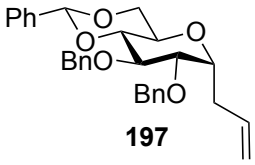
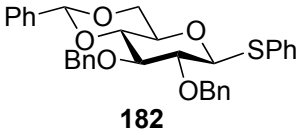
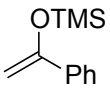
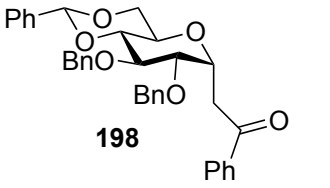
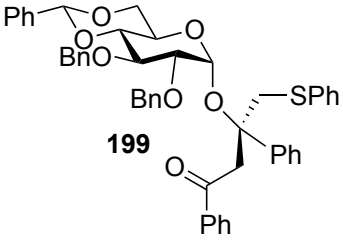
4	 **182**	 **173**	 **197**	56%
5	 **182**	 **194**	 **197**	58%
6	 **182**	 **195**	 **198** +  **199**	40% 40%

Table 2: *C*-glycoside formation in the mannose and glucose series

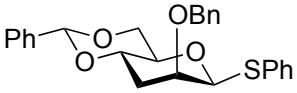
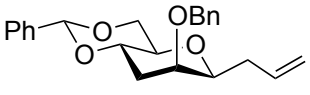
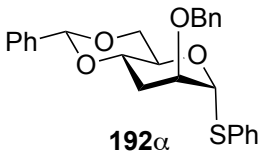
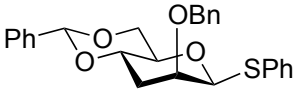
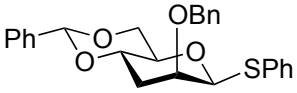
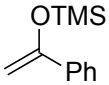
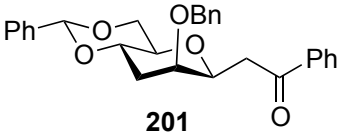
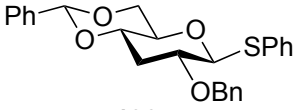
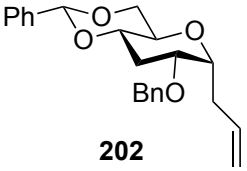
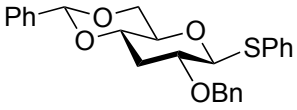
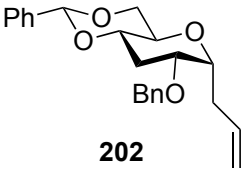
The results obtained from this first set of coupling reactions confirm Crich's[226] earlier observations that the formation of *C*-glycosides is β-selective in the mannose series and α-selective in the glucose series. The stereochemical assignments at the anomeric carbon were confirmed by nuclear Overhauser effect 1D NMR experiments, which displayed the diagnostic correlations indicated in Figure 11.

Figure 11: Determination of the anomeric stereochemistry of the *C*-glycosides by NOE

The *C*-glycosides **193**, **196**, **197** and **198** were obtained with complete stereoselectivity in both, the mannose and the glucose series and in moderate to good yields. A significant amount of double adduct **199** was formed from the reaction of glycosyl donor **182** with α-trimethylsiloxystyrene **195** highlighting here the ambident character of this nucleophile, with possible attack from both ends, either via the vinylic carbon or the oxygen atom. The *O*-glycoside **199** was formed with high α-selectivity and isolated as a single anomer. Adduct **198** and the double adduct **199** were obtained in an equimolar ratio and 80% overall yield. The formation of the *O*-glycoside derivative did not occur in the case of the mannose series and reaction of mannosyl donor **183** with nucleophile **195** took place uneventfully, with formation of a single product, compound **196** in 76% yield.

4.2.4.2 In the 3-Deoxy Series

A similar series of experiments were conducted in the 3-deoxy glucose and mannose series from which comparable results were obtained as summarized in Table 3[230].

Entry	Donor	Nucleophile	Product	Yield
1	 **192**	 **173**	 **200** +  **192α**	35% 17%
2	 **192**	 **194**	 **200**	58%
3	 **192**	 **195**	 **201**	75%
4	 **190**	 **173**	 **202**	60%
5	 **190**	 **194**	 **202**	63%

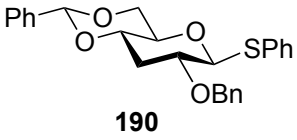
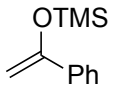
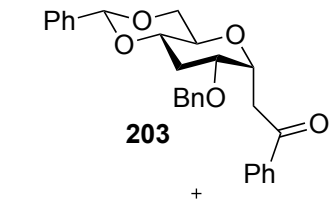
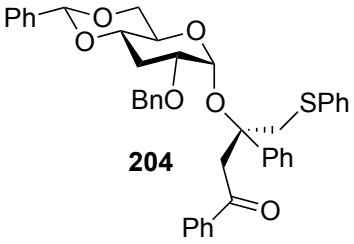
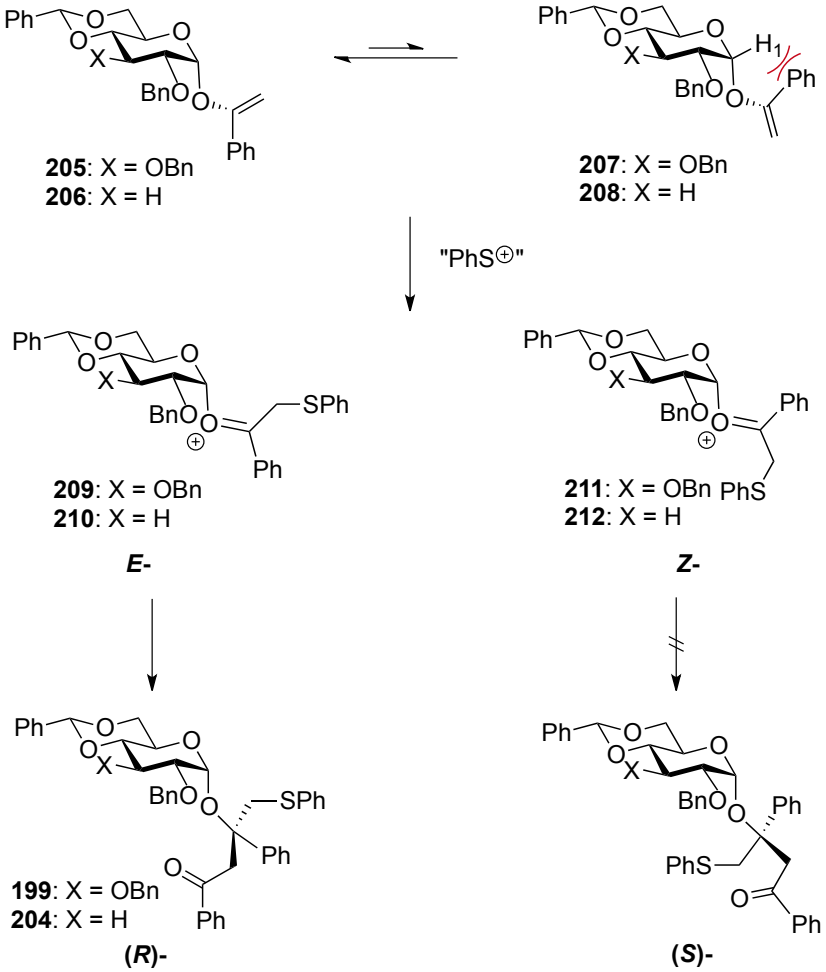
6	 **190**	 **195**	 **203** +  **204**	34% 37%

Table 3: *C*-glycoside formation in the 3-deoxy mannose and glucose series

The *C*-glycosides were formed again with complete stereoselectivity in the mannose as well as in the glucose series, with moderate to good yields. An interesting by-product **192α** arose from the reaction of 3-deoxy-mannosyl donor **192** with the least nucleophilic acceptor, allyltrimethylsilane **173**, along with the expectedcoupling product **200**. The β-mannosyl donor **192** isomerized to its α anomer in the course on the glycosylation reaction, corroborating the greater reactivity of the 3-deoxy-mannose donor **192** compared to its normal series **183**. Formation of a double adduct **204** was also observed in the 3-deoxy glucose series, from the reaction of 3-deoxy-glycosyl donor **190** with α-trimethylsiloxystyrene **195**. Compounds **203** and **204** were formed with complete α-selectivity and only a single isomer was isolated in each of the cases.

The double adducts **203** and **204** were both formed as single diastereomers at the newly formed remote stereogenic center and, although the

stereochemistry of this center has not been rigorously proven, it is predicted to be (*R*)-on the basis of the mechanistic rationale presented in Scheme 67. The formation of double adducts **203** and **204** is consistent with previous results obtained in the Crich laboratory wherein reaction of donors **182** or **183** with pinacolone trimethylsilyl enol gave similar double adducts, also predominantly in the glucose series[226].



Scheme 67: Stereoselective formation of adducts 199 and 204

Assuming the adoption of the oxo-anomeric effect preferred conformation about the glycosidic bond in the initial adduct, the proposed mechanism considersthe

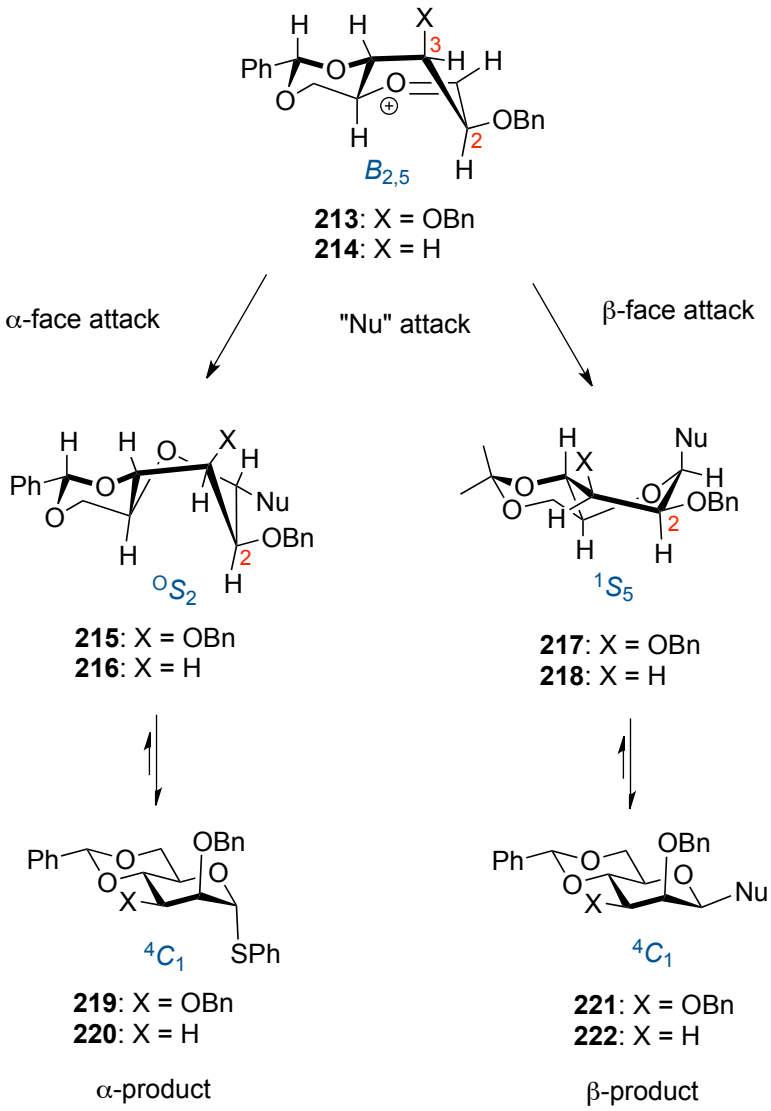
two possible rotamers **205**/**207** and **206**/**208** in each of the glucose series (3-OBn and 3-deoxy) about the vinyl-O bond of which the former is preferred for steric reasons. Trapping of the vinyl glycoside with phenyl sulfenyl triflate – a side-product arising from the activation of the thioglycoside donor with Tf_2O and BSP – from the more exposed face gives riseto two oxocarbenium ions with opposite geometry, *E*- or *Z*-, of which the *E*-isomer is expected to predominate based on the greater population of the vinyl glycoside rotamer **205**/**206**. Assuming the continued operation of the exo-anomeric effect, reaction of the *E*-oxocarbenium ions **209**/**210** on its more exposed face with a second equivalent of silyl enol ether leads to the preferential formation of the observed products **199** and **204** (Scheme 67). This analysis closely resembles those adopted in the literature to explain the face selectivity of Dields-Alder reaction of glycosyl dienes[231-233]. An interesting feature of the formation of the double adducts **199** and **204** concerns the reactivity of the oxocarbenium ions **209** and **210**, which necessarily suffer attack by external nucleophiles more quickly than they undergo fragmentation to a ketone (phenylthioacetophenone) and a glycosyl oxocarbenium ion. Similar *O*-glycosyl oxocarbenium ions to **209**-**212** studied in the Crich laboratory also showed a preference for nucleophilic addition over decomposition to their corresponding glycosyl oxocarbenium ion and a carbonyl derivative – in that case formaldehyde[234].

4.2.4.3 Mechanistic Rationale for the Stereoselectivity of *C*-Glycoside Formation

It is clear from comparison of Tables 2 and 3 that the C3-O3 bond in 4,6-*O*-benzylidene-protected glycosyl donors is not the control element in the stereoselective formation of *C*-glycosides, unlike for the formation of *O*-glycosides. The stereoselective outcome in the formation of *C*-glycosides may be interpreted by considering the preferred conformational geometry of the oxocarbenium ion, as well as the steric interactions that arise in the course of the attack of the nucleophile.

4.2.4.3.1 In the Mannose Series

The stereoselective formation of the *C*-glycoside adducts is explained as depicted in Scheme 68, by using the oxocarbenium ion model.



Scheme 68: Proposed mechanistic rationale for *C*-mannoside formation

The spherical representation of the different pyranoside ring conformations (Figure 6) shows that the $B_{2,5}$ conformation is intermediate between two other conformers, the $^{O}S_2$ **215/216** and the $^{1}S_5$ **217/218** skew boat conformers, to which it distorts by attack on the α-face and the β-face respectively. Assuming the oxocarbenium ion model, the β-selectivity observed in the mannose series can be explained by the pseudo-axial attack of the incoming nucleophile on the

β-face of the $B_{2,5}$ conformation of the mannopyranosyl ion, positioning thereby the nucleophile in a pseudo-axial orientation in the resulting $^1S_5$ skew boat conformation **217/218**. The unfavorable 1,3-diaxial-type interaction between the incoming nucleophile and the C3-X bond in the course of the reaction is reduced as the reaction proceeds and the pyranose ring distorts to the $^1S_5$ skew boat – this interaction does not therefore play a major stereodeterming role in this process. Rather the key interaction appears to be an unfavorable steric clash between the incoming nucleophile and the C2-H2 bond on the α-face of the oxocarbenium ion, which retards attack on the α-face. This interaction is best visualized with the aid of a Newman projection (Figure 12).

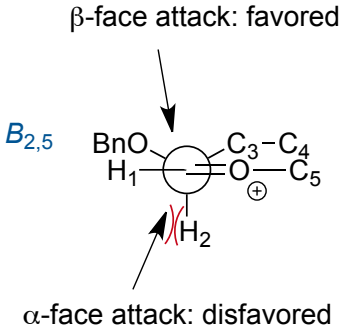
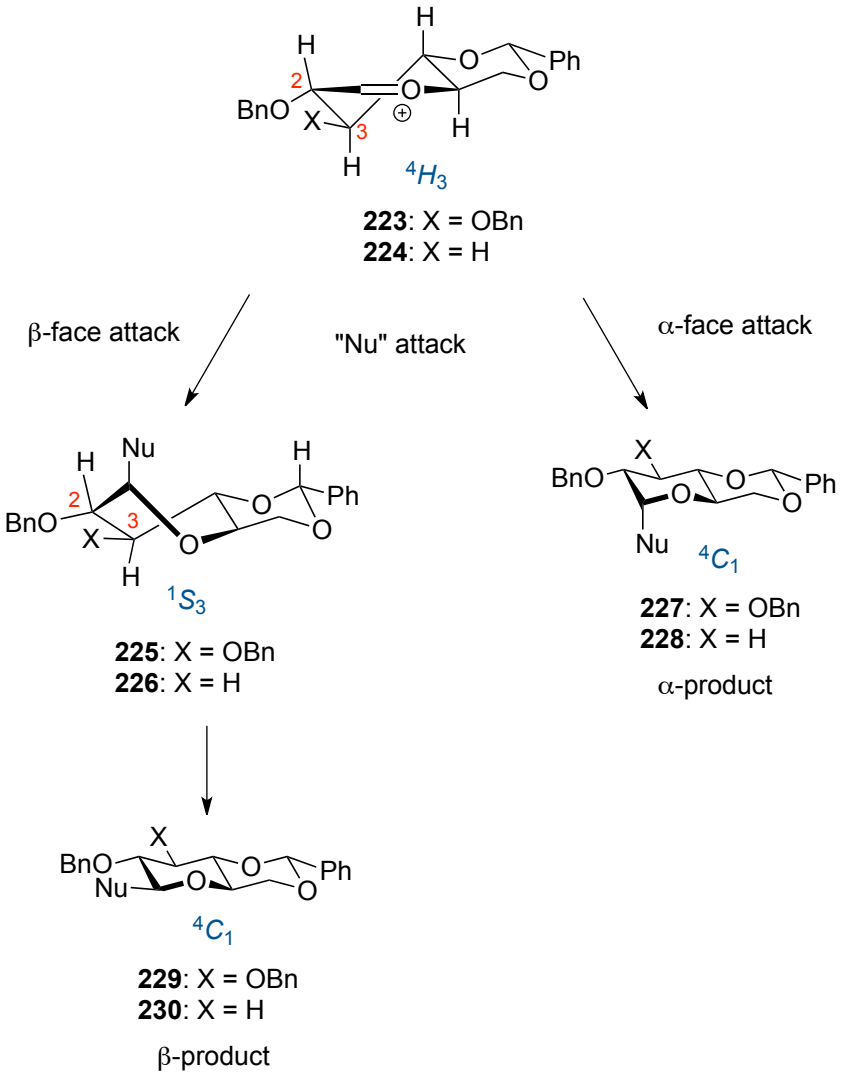


Figure 12: Newman projections about the C1-C2 bond showing the attack of the nucleophile on the 4,6-*O*-benzylidene-protected mannosyl oxocarbenium ion

Finally, the C2-H2 bond of the glycosyl donor appears to be a determining factor in controlling the stereoselective formation of β-*C*-mannosides.

4.2.4.3.2 In the Glucose Series

A comparable model was also proposed for the 4,6-*O*-benzylidene-protected glucose series as presented in Scheme 69.



Scheme 69: Proposed mechanistic rationale for *C*-glucoside formation

Pseudo-axial attack of the nucleophile on the α-face (the bottom face) of the preferred $^4H_3$ half-chair conformation of the 4,6-*O*-benzylidene-protected glucosyl oxocarbenium ion **223** or **224**, leads to the direct formation of the α-glycoside, in its most stable $^4C_1$ chair conformation. Nucleophilic attack on the β-face of the

oxocarbenium ion gives rise to a higher energy $^{1}S_{3}$ skew boat conformer **225** or **226**, in which an unfavorable torsional interaction is again observed between the C2-H2 bond and the incoming nucleophile. A Newman representation of the unfavorable C2-H2 torsional interaction in the case of glucose is presented in Figure 13.

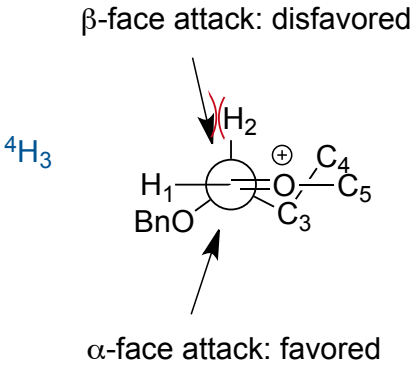


Figure 13: Newman projections about C1-C2 showing the attack of the nucleophile on the 4,6-O-benzylidene-protected glucopyranosyl ion

The results obtained in the glucose series follow the same conclusions than the ones made in the mannose series. The C2-H2 bond seems to be a crucial element in directing the attack of the nucleophile toward one face of the oxocarbenium ion.

4.2.5 Comparison with *O*-Glycoside Formation

The reaction of alcohol acceptors with 4,6-*O*-benzylidene-protected 3-deoxy mannoside donors is slightly α-selective in the formation of *O*-mannosides, whereas the formation of *C*-glycosides takes place with complete β-stereoselectivity. Moreover, unlike for *O*-glycosides, the stereoselectivity in the

formation of *C*-glycosides is not altered on going to the 3-deoxy series. Assuming that *C*-glycosides are formed via the intermediacy of a glycosyl oxocarbenium ion, just as it was proven for the formation of α-*O*-mannosides, then different factors might have to be invoked to account for the loss of selectivity in *O*-glycoside formation.

The loss of α-selectivity observed in the formation of *O*-glycosides cannot be explained in terms of hydrogen bonding since computational studies indicates a hydrogen bond between O2 of the donor and the incoming alcohol acceptor and O2 is retained in the 3-deoxy series. Rather, a change in mechanism for the formation of *O*-glycosides in the 3-deoxy series to that of the normal glucose series (3-OBn) is proposed. As discussed previously, KIE studies suggest that the formation of the α-*O*-glucosides proceeds via an associative S_N2 mechanism with a concerted displacement of a transient β-glucosyl triflate[207]. For the 3-deoxy glycosides, gluco- and manno-, a dissociative oxocarbenium ion-based mechanism is more likely owing to the absence of the electron-withdrawing C3-O3 bond[164,235]. As an sp^3 oxygen-centered nucleophile (0.55<*A*-value<0.75)[236] is considerably smaller than a sp^2 vinylic carbon-centered nucleophile (1.49<A-value<1.68)[236], the type of interactions proposed in Figures 5 and 6 to explain the face selectivity of *C*-glycoside formation are much reduced for *O*-glycoside formation resulting in the loss of selectivity in the case of the *O*-glycosides. The difference in steric bulk of alcohols and allyl-metal-based nucleophiles and the corresponding reduction in the importance of the nucleophile/C2-H2 interaction are best appreciated with the Newman projection of Figure 14.

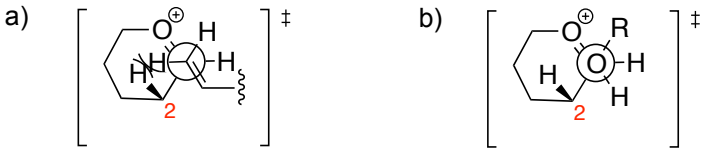


Figure 14: Newman representations of the transition states for antiperiplanar attack by a) π-type *C*-nucleophiles and b) alcohols on the disfavored face of the glycosyl oxocarbenium ions

The difference in the bulkiness of an alcohol nucleophile and a vinyl nucleophile adequately accounts for the loss of α-selectivity observed in the formation of *O*-glucosides as compared to *C*-glucosides for attack on a common oxocarbenium ion.

4.3 Conclusion

The *C*-glycosides were formed with complete α- and β-stereoselectivity in the glucose and the mannose series respectively, regardless of the substituent (H or OBn) at C3, demonstrating the lack of influence of the C3-O3 bond in *C*-glycosides formation, as opposed to the O3 substituent selectivity-dependence that Crich observed in the formation of *O*-glycosides.

CHAPTER 5

TOWARD THE UNDERSTANDING OF THE α-DIRECTING EFFECT OF THE 4,6-*O*-BENZYLIDENE GROUP IN THE GALACTOSE SERIES

5.1 Introduction

Literature data indicate that the reaction of 4,6-*O*-benzylidene-protected galactopyranosyl donors carrying ether-type non-participating protecting groups at O2 and O3 are predominantly α-directing in their coupling with non-hindered alcohol acceptors[237-239]. In presence of a participating group at the C2 position of the glycosyl donor, the glycosylation reaction takes place, as commonly expected, with β-selectivity[240,241]. However, several instances showed, in similar 4,6-*O*-benzylidene-protected galactopyranosyl systems, that neighboring group participation failed to proceed with complete β-selectivity, leading in some cases to the formation of the α-coupling product as the major product[242,243], if not as the only product[54]. The latter situation was observed when the 4,6-*O*-di-*tert*-butylsilylene protecting group, developed in the Kiso laboratory, was used in place of the 4,6-benzylidene acetal. Thus, Kiso[54,55,244] found such a silylene-protected system to be highly α-selective independently of the nature of the substituent used at C2 of the glycosyl donor. Two different explanations have been invoked to account for the observed α-directing effect of the 4,6-*O*-benzylidene or the DTBS protecting group in the galactose series, an electronic and a steric hypothesis. The former hypothesis is built around the supposed stabilization of the 4,6-*O*-acetal-protected oxocarbenium ion by the benzylidene

acetal[242], whereas the proponents of the steric hypothesis claim that the apparent α-selectivity is a result of the shielding of the β-face of the oxocarbenium ion by the acetal[54].

The fact that 4,6-*O*-acetals exert a disarming effect in glycosides reactivity is a well-accepted phenomenon[209,245]. Their effect on reactivity in the galactose series is, on the other hand, far less known and an acceptable explanation for it has still to be proposed. In this context, a study of the reactivity of 4,6-*O*-acetals in the D-galactose series was undertaken with the emphasis on probing the disarming influence of the trans gauche conformation of C5-C6 bonds with the aim of gaining better insights into the observed α-directing effect of 4,6-*O*-acetal-protected donors in galactopyranosylation reaction. The results of this study are presented in this chapter.

5.1.1 Preliminaries Studies

5.1.1.1 The Electronic Hypothesis

5.1.1.1.1 The Electronic Effect of the Hydroxylic Substituent

The effects of the substituents on reactivity have been studied extensively by Bols[246-248] and co-workers in their seminal work on the acidity of polyhyddroxylated piperidinium[246] compounds, as a study model for oxocarbenium ions. Bols found that stereoisomers having axial hydroxyl substituents were consistently less acidic (higher pKa values) than their equatorially oriented counterparts, regardless of their position on the piperidinium ring (Figure 15)[246].

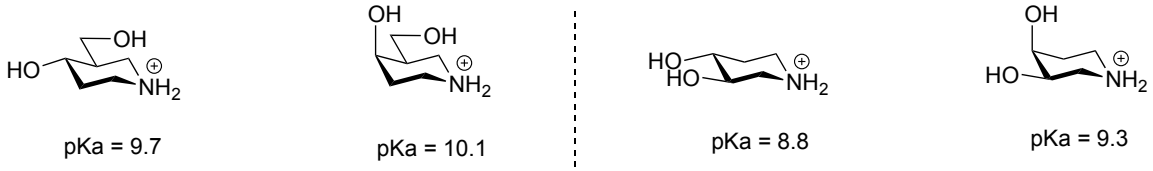


Figure 15: Relative acidity of stereoisomeric piperidinium ions

This observation was rationalized in terms of the electron-withdrawing character of the hydroxyl substituent, which Bols[247,249] postulated to be lower for an axial than for an equatorial substituent. Later on, Bols applied this postulate to carbohydrate derivatives, to explain the disparities in the rate of hydrolysis of methyl-D-glycopyranosides (Figure 16)[248].

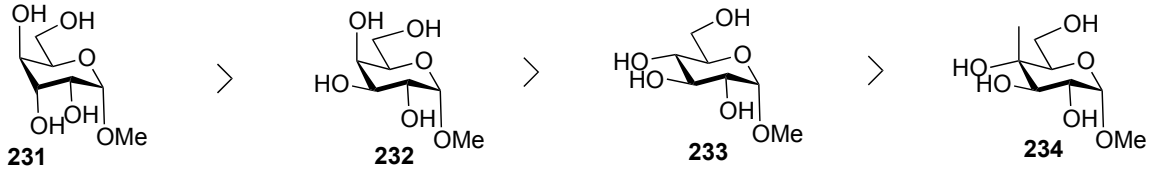


Figure 16: Relative rate of hydrolysis of methyl α-D-glycopyranosides

The fact that the rate of hydrolysis of stereoisomeric glycosides is function of the number of axial hydroxyl substituents – the greater the number of axial hydroxyl substituents, the faster the rate – had been observed by Armstrong and Glover[250] back in 1908. However, it was only in 1955, that the first explanation to this phenomenon was proposed by Edwards[251], who termed it “the relief of the steric strain” to refer to the unfavorable 1,3-diaxial interactions present in the ground state of the glycoside being released as the pyranose ring distorts to the oxocarbenium geometry. This steric hypothesis was later displaced by an electronic explanation advanced by Withers[252] known as “the field effect”. As

shown in Figure 16, the rate of hydrolysis of guloside **231** is faster than the rate of hydrolysis of galactoside **232**, which is in turn faster than the rate of hydrolysis of glucoside **233**. The exact cause of this effect in carbohydrates has not been clearly understood, but it was postulated that a charge-dipole interaction[249] between the axial hydroxyl substituent and the cationic oxocarbenium ion is most likely responsible for the relative difference in the rate of hydrolysis observed between sugar series[186,248,253] (Figure 17)[249].

Figure 17: Charge-dipole hypothesis

As shown in Figure 17, when the dipole formed by the hydroxyl substituent at C4 is oriented away from the electron-deficient center (as is the case in the glucose series) it results in destabilization, whereas a perpendicular orientation (observed in galactose derivatives) leads to a greater stabilization.

5.1.1.1.2 The Through-Space Hypothesis

The systematic enhancement of reactivity observed in the hydrolysis of methyl-α-D-galactopyranosides as compared to their glucose counterparts has been rationalized in an elegant manner by Deslongchamps[186], who demonstrated that the rate of acetolysis of methyl α-D-glycopyranoside was dependent on the

electron-donating ability of the C4 substituent, which is large in the galactose series, but much less appreciable in the glucose series (Figure 18)[186].

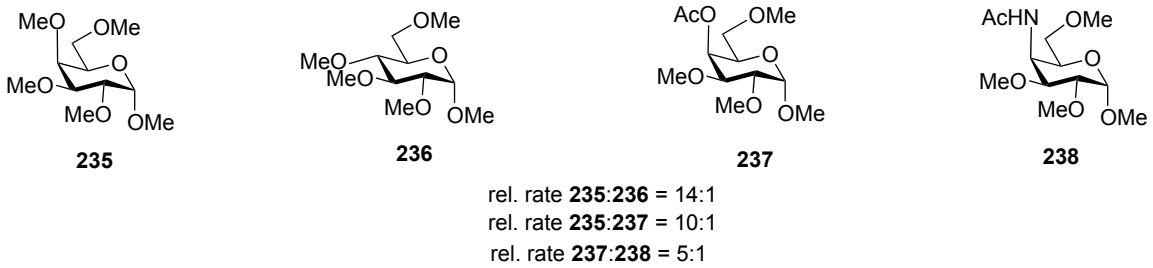
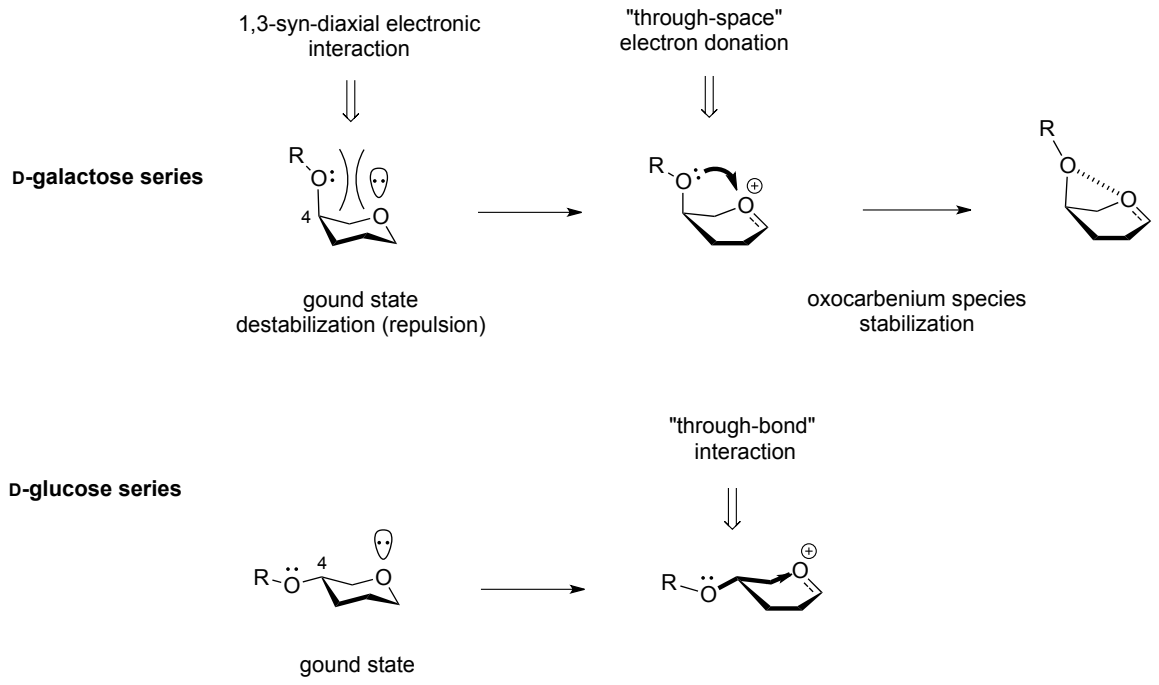


Figure 18: Relative acetolysis rate of methyl α-D-glycopyranosides

To account for the large kinetic effect observed in the galactose series, Deslongchamps argued against the possibility of a through bond interaction stabilization (inductive effect) as observed in the glucose, but instead pointed to a stronger effect such as a through space donation from the axially oriented substituent at C4 and the incipient oxocarbenium ion. This interaction, which destabilizes the ground state conformation of galactopyranoside derivatives due to electrostatic repulsion, becomes stabilizing as the oxocarbenium ion forms[186] (Scheme 70).



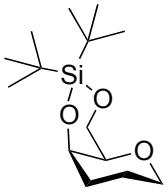
Scheme 70: "Through-space" interaction between the substituent at C4 and the developing oxocarbenium ion

Such an interaction is geometrically not possible in the glucose series because of the equatorial orientation of the hydroxyl substituents on the pyranose ring. Deslonchamps supported his "through-space" interaction hypothesis with *ab-initio* calculations.

5.1.1.2 The Steric Hypothesis

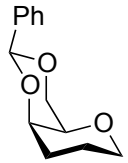
Another rational, the steric hypothesis, has been proposed by Kiso[54] et al., after the discovery, in the Kiso laboratory, of the 4,6-*O*-DTBS acetal as a determining element in the formation of α-(1,2-cis)-galactopyranosides[54,55]. In terms of conformation, the DTBS group is comparable to the benzylidene acetal. Both of these protecting groups lock the O4 and O6 of the donor in a six-

membered ring system, except that the di-*tert*-butylsilyl group **239** is more hindered than the phenyl ring **240** (Figure 19).



239

4,6-*O*-DTBP-protected glycopyranoside

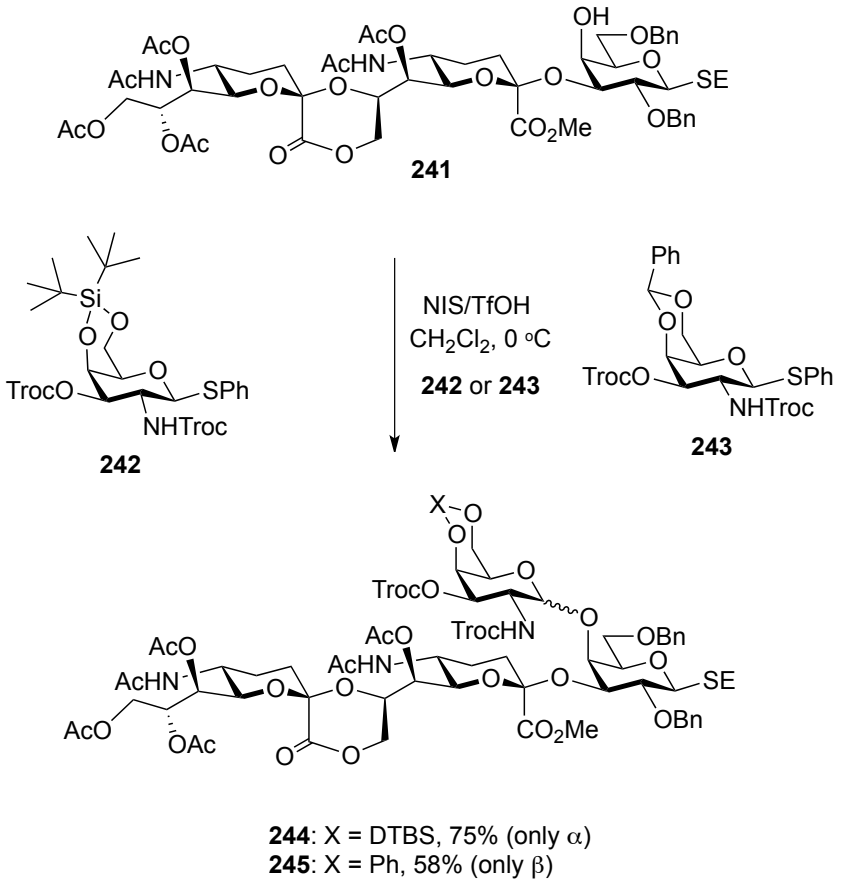


240

4,6-*O*-benzylidene-protected glycopyranoside

Figure 19: Di-t*ert*-butylsilyl and benzylidene acetals

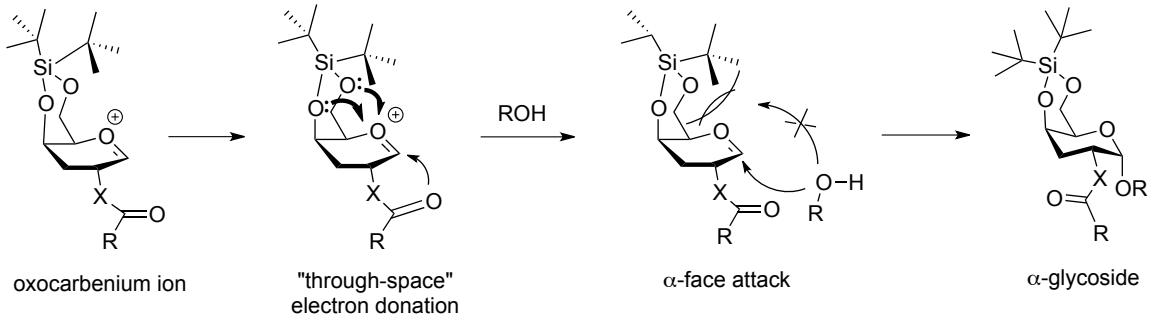
However, a drastic change of selectivity was observed in the coupling of 4,6-*O*-di-*tert*-butysilyl- **242** and 4,6-*O*-benzylidene-protected galactosyl **243** donors with acceptor **241**, under the NIS/TfOH glycosylation conditions. The α-coupling product was obtained stereoselectively when using donor **242**, despite the presence of the *N*-participating group at C2. The 4,6-*O*-benzylidene-protected galactosyl donor **243** gave the β-galactopyranoside **245** exclusively (Scheme 71)[54].



Scheme 71: Examples of galactopyranosylation reaction with 4,6-O-protected DTBS and benzylidene

The considerable steric bulk of the DTBS group was used by Kiso[54] to explain the observed α-directing effect in galactosylation reactions using 4,6-*O*-di-*tert*-butysilyl-protected donors. While building his hypothesis on Deslongchamps' through-space interaction theory[186], Kiso advanced that *ab-initio* calculations showed that the interatomic distance between the *t*Bu groups and the anomeric center was shortened in the course of the glycosylation reaction. The through space interaction observed between the axially oriented substituent at C4 with the electron-deficient oxocarbenium ion in the galactose series resulted in a

decrease in the interatomic distance between those two. X-Ray crystallographic analysis showed that the introduction of a di-tert-butylsilylene group resulted in the flattening of the C4-C5-C6 bond because of the sofa-like conformation adopted by the pyranose ring. As a result, the β-face of the galactoside is shielded by the ^{t}Bu group, which leaves the α-face as the only possible face of attack by the acceptor (Scheme 72)[54].



Scheme 72: The steric hypothesis

A similar steric explanation was also advanced earlier by Jacquinet[254] who postulated that the phenyl ring of the benzylidene group shielded the top face of the sugar in galactose series thereby favoring the α-glycoside over the β-glycoside.

5.1.1.3 The Disarming Effect of the 4,6-*O*-Benzylidene Group in the Glucose series

In D-aldohexopyranoses, the conformation of the hydroxymethyl substituent is an equilibrium of three staggered conformations: the gauche-gauche conformation (*gg*), the trans-gauche conformation (*tg*) (the least

abundant rotamer observed in hexopyranosides) and the gauche-trans conformation (*gt*), which correspond to three minima on the plot of the potential energy surface of rotation about the C5-C6 bond[255]. In this formalism, the first letter describes the dihedral relationship between O6 and O5 and the second letter refers to the relationship between O6 and C4 (Figure 20). Factors such as the 1,3 *syn*-diaxial interaction, the gauche-gauche effect, hydrogen bonding and the solvent effect, have been shown to influence the C5-C6 rotameric population[256].

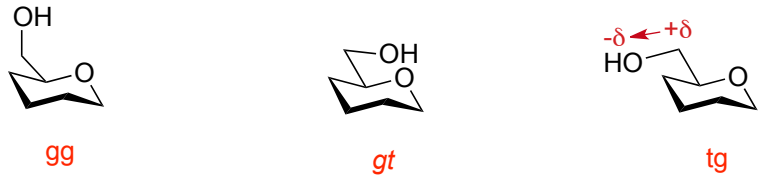
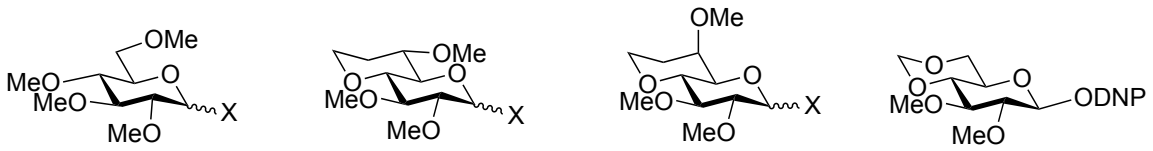


Figure 20: Staggered conformers of the exocyclic C5-C6 bond in D-aldohexopyranoses

Based on the charge-dipole hypothesis, the *tg* conformer is expected to be the least reactive because of the antiperiplanar orientation of the C6-O6 bond with respect to the C5-O5 bond, leading to the destabilization of the forming oxocarbenium ion.

A few years ago, Bols[53] and co-workers investigated the origin of the disarming effect of 4,6-*O*-benzylidene derivatives in the D-glucose series, by evaluating the contribution of the electronic effects coming from the locking of the C5-C6 bond in the deactivating trans-*gauche* conformation (*tg*), with respect to the torsional disarmament. Thus, Bols conducted a series of kinetics studies in

which he altered the conformation about the exocyclic C5-C6 bond in a range of glycopyranoside systems, in order to determine which factors were responsible for the disarming effect of the 4,6-O-benzylidene group in the glucose series (Figure 21)[53].



X = α-OMe or β-ODNP

Figure 21: Conformationally constraint glucopyranoside probes

These models were all designed to incorporate the same type of *trans*-decalin skeleton as in the 4,6-*O*-benzylidene-protected glucopyranosides and so, to have the same torsional constraints while allowing systematic variation of the orientation of the C6-O6 bond. The conclusions drawn by Bols[53] highlighted first of all, a significant destabilization arising from the locking of the C5-C6 bond in the *tg* conformation, resulting in a maximization of the electron-withdrawing ability of the C6-O6 bond and therefore, an overall destabilization of the glycosyl oxocarbenium ion. Finally, the torsional strain was also shown to equally contribute to the observed disarming effect encountered in 4,6-*O*-benzylidene protected glucopyranoside systems.

5.1.2 Reactivity of the Benzylidene Acetal in the Galactose Series: A Logical Reactivity Pattern

Given on all these considerations, electronic and kinetic, one might expect that a different reactivity pattern would be expected in 4,6-*O*-benzylidene-protected galactoside derivatives as compared to the perbenzyl analogues. Unlike their glucose counterparts, 4,6-*O*-benzylidene-protected galactosides are locked in a *cis*-fused system, where the C5-C6 bond is held in the favorable *gg* conformation. Thus, based on the “through-space” space interaction observed by Deslongchamps[186] characteristic of galactoside derivatives, it was hypothesized that a similar interaction could also emanate from the optimal orientation of the C6-O6 bond in 4,6-*O*-protected acetal galactosides. Following up on this logic, the 4,6-*O*-benzylidene protecting group should have an arming effect on galactosyl reactivity, by anticipation of the larger through-space interaction arising from the favorable positioning of both, the C4-O4 and the C6-O6 bonds, held perpendicular to the C5-O5 bond and thereby maximizing the through-space stabilization onto the oxocarbenium ion (Figure 22).

Figure 22: Oxocarbenium stabilization in 4,6-*O*-acetal-protected systems

5.2 Results and Discussion

Adapting Bols’[53] model study to the galactose series, similar conformationally locked probes were synthesized and carried through acidic

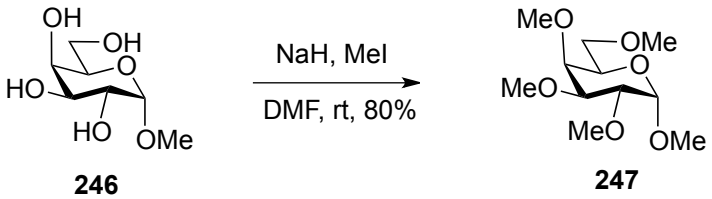
hydrolysis measurements in the case of the methyl α-D-galactopyranoside derivatives and spontaneous hydrolysis as for the dinitrophenyl galactopyranoside probes. The results of this investigation are detailed in the following sections starting first with the chemical synthesis of probes **247**, **254R**, **254S**, **255**, **256R**, **256S** and **263**.

5.2.1 Synthesis of α-Methyl and β-Dinotrophenyl Galactoside Substrates

5.2.1.1 Preparation of the Methyl Galactoside Substrates

5.2.1.1.1 Synthesis of Methyl 2,3,4,6 –Tetra-*O*-Methyl –α-D-Galactopyranoside 247

A one-step synthesis staring from commercially available methyl α-D-galactoside **246** afforded the monocyclic reference substrate **247**. Thus, permethylation of **246** by reaction with sodium hydride and methyl iodide gave the monocyclic probe **247** in 80% yield.

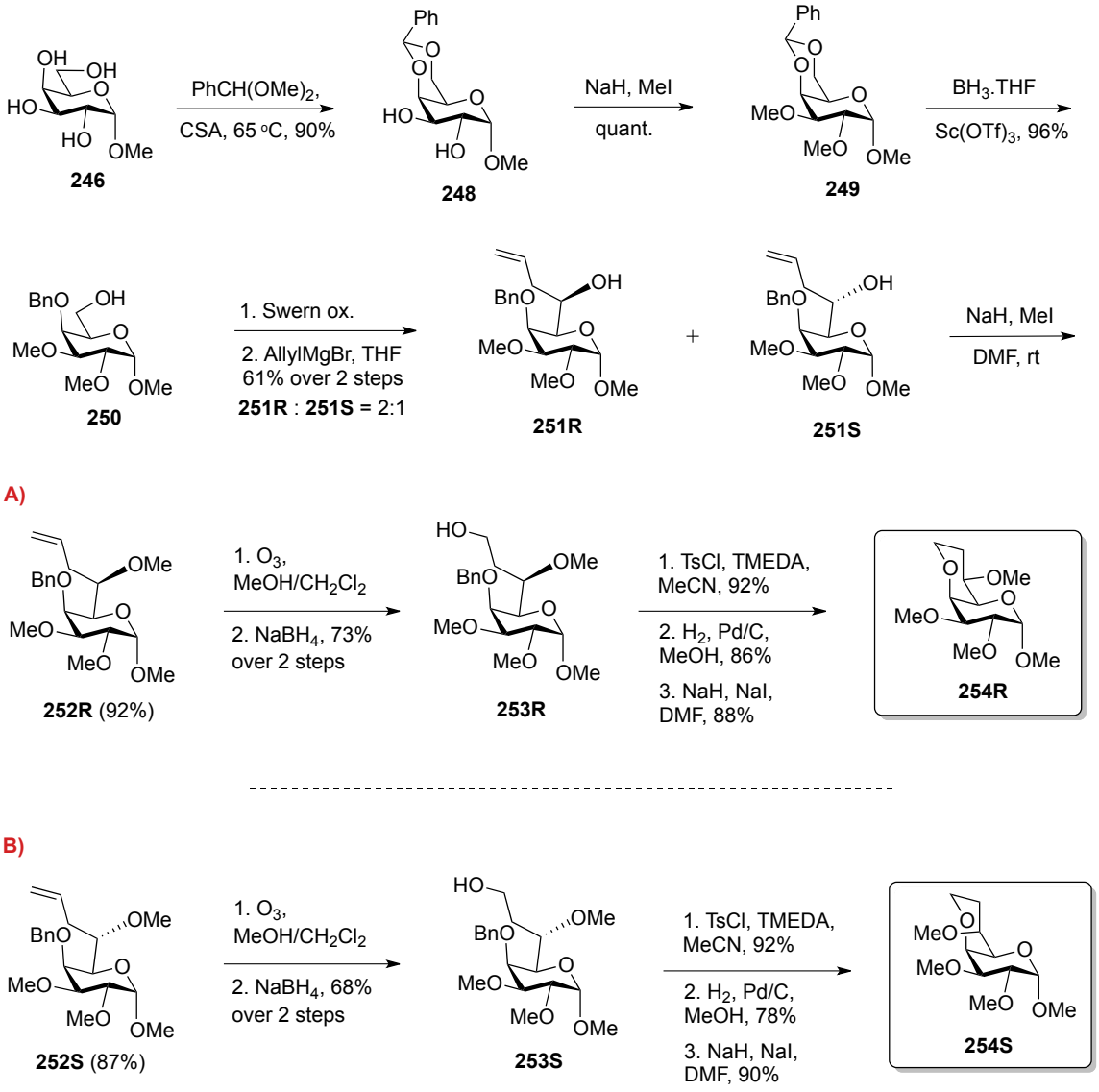


246 **247**

Scheme 73: Synthesis of monocyclic methyl galactopyranoside probe 247

5.2.1.1.2 Synthesis of (6R) and (6S)-Methyl 4,8-Anhydro-7-Deoxy-2,3,6-tri-*O*-Methyl-Glycero-D-Galacto-Octopyranosides 254R and 254S

Bicyclic diastereomers **254R** and **254S** were synthesized as set out in Scheme 74.



Scheme 74: Synthesis of methyl α-D-galatopyranosides 254R and 254S

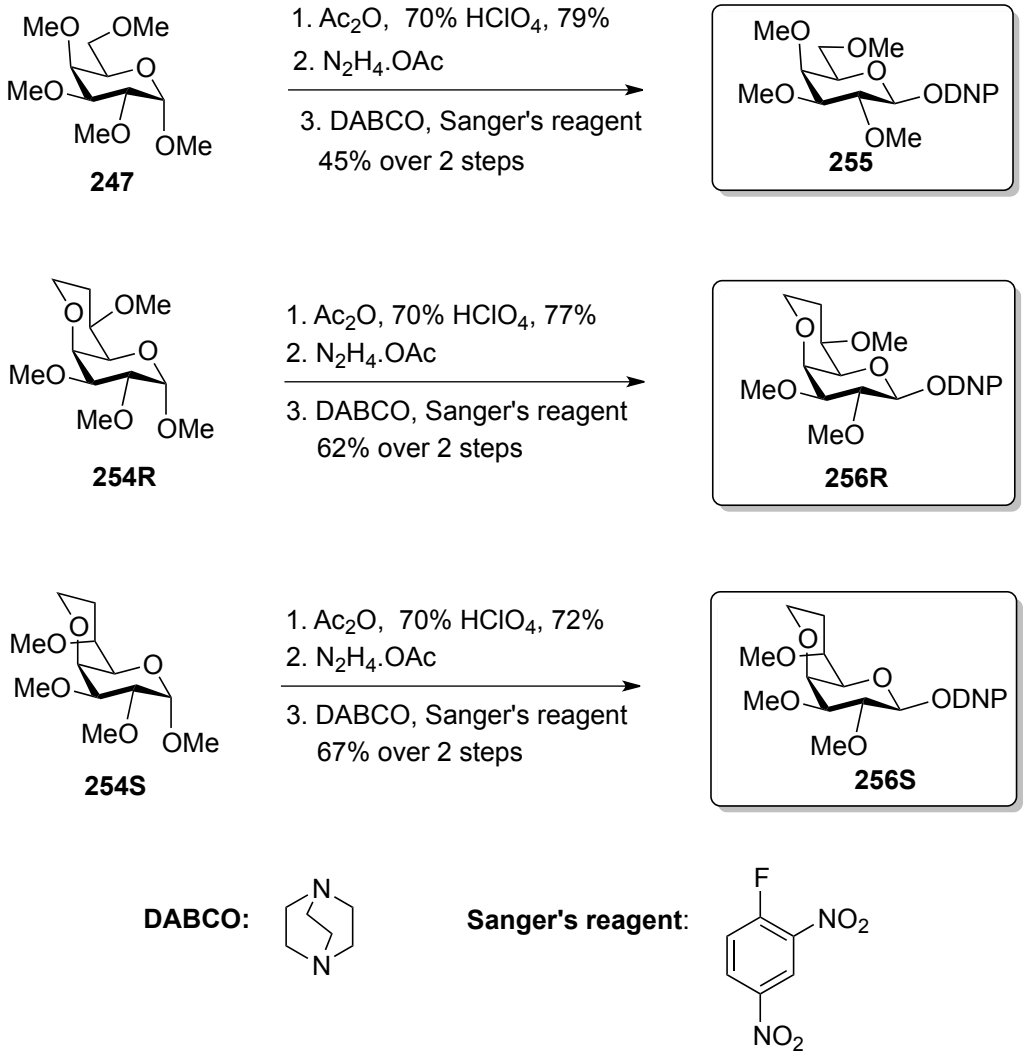
The synthesis started from commercially available methyl α-D-galactoside **246** with installation of the benzylidene protecting group at the O4 and O6 positions in the usual manner, followed by methylation of the resulting O2 and O3 positions to give dimethyl ether derivative **249**. Regioselective reductive ring opening of the 4,6-*O*-benzylidene acetal was carried out in presence of borane-tetrahydrofuran

complex and scandium triflate[257] giving rise to the corresponding 4-*O*-benzyl ether compound **250** in 96% yield. Swern oxidation of the primary alcohol **250** afforded the corresponding aldehyde, which after addition of allyl magnesium bromide in anhydrous THF gave a 2:1 diastereomeric mixture of separable adducts **251R** and **251S**, in 61% overall yield over the two steps. The stereochemistry of compounds **251R** and **251S** was assigned after the formation of the bicyclic derivatives **254R** and **254S**. Subsequent to this point, the syntheses of compounds **251R** and **251S** were carried out independently to give the respective final bicyclic compound **254R** and **254S** as shown in Scheme 74, pathways A and B. Secondary alcohol **251R** was methylated and gave the corresponding methyl ether adduct **252R**. Oxidative cleavage of terminal alkene **252R** by ozonolysis was followed by in-situ reduction of the corresponding aldehyde, affording **253R** in 73% overall yield. Tosyl protection of the resulting primary alcohol was followed by hydrogenolysis of the benzyl ether functionality. Finally, in-situ displacement of the tosyl group by iodine occurred prior to the ring closure by S_N2 displacement of the iodide by the alcoholate, giving rise to the corresponding target bicyclic compound **254R**. The same procedure was followed for the diastereomeric compound **254S**. The stereochemistry at C6 was confirmed by 1D NOE correlation between protons $H6_{ax}$ and $H4_{eq}$ in the case of diastereomer **254R**. This correlation is absent in compound **254S**, for which a NOE correlation between protons $H6_{eq}$ and $H8_{eq}$ was observed.

5.2.1.2 Preparation of 2,4-Dinitrophenyl Galactoside Substrates

5.2.1.2.1 Synthesis of 2,4-Dinitrophenyl 2,3,4,6-Tetra-O-Methyl-β-D-Galactopyranoside and 4,8-Anhydro-7-Deoxy-2,3,6,tri-O-Methyl Glycero-D-Galacto-Octopyranosides 255, 256R and 256S

The preparation of the 2,4-dinitrophenyl probes **255**, **256R** and **256S** was carried out in a straightforward manner as outlined in Scheme 75.

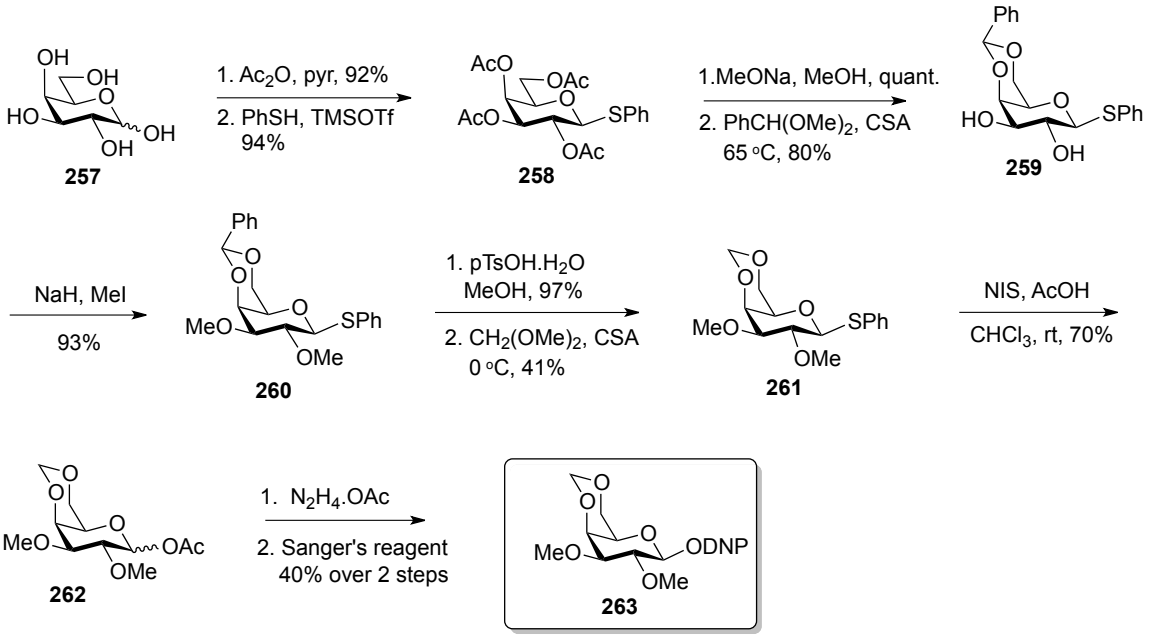


Scheme 75: Synthesis of 2,4-dinitrophenyl probes 255, 256R and 256S

Probes **255**, **256R** and **256S** were synthesized according to the same synthetic scheme starting from their corresponding methyl α-D-galactoside derivates. The synthesis involved first the acetolysis of the methyl glycosides using 70% perchloric acid in presence of acetic anhydride. This was followed by hydrolysis of the corresponding anomeric acetate derivative on reaction with hydrazine acetate. Finally, the introduction of the 2,4-dinitrophenyl group was performed by reaction of the resulting hemiacetal with 1-fluoro-2,4-dinitrobenzene, in presence of a nucleophilic base, DABCO. The β-configuration of each of the probes was confirmed by NMR data ($^3J_{1,2}$ = 7.2-7.5 Hz).

5.2.1.2.2 Synthesis of 2,4-Dinitrophenyl 2,3-di-O-Methyl-4,6-Methylidene-β-D-Galactopyranoside 263

The last compound of the series was synthesized following standard manipulations as depicted in Scheme 76.



Scheme 76: Synthesis of 2,4-DNP-4,6-*O*-methylene galactopyranoside 263

D-galactose was peracetylated in the usual manner prior the functionalization of the anomeric position by introduction of thiophenol. β-Thioglycoside ($^3J_{1,2}$ = Hz) **258** was deacetylated under Zemplén conditions after which acid catalyzed treatment with benzaldehyde dimethyl acetal gave the corresponding 4,6-*O*-benzylidene protected donor **259** in 80% yield. Methyl ether protection of the remaining alcohols afforded galactoside **260**. Subsequent acidic hydrolysis of the benzylidene group was followed by the installation of the methylene acetal at the O4 and O6 positions upon treatment with formaldehyde dimethyl acetal in the presence of a catalytic amount of CSA, provided compound **261** in 41% yield. Conversion of the anomeric thioglycoside to the corresponding acetoxy derivative was carried out under the NIS/AcOH glycosylation conditions within an hour, affording compound **262** in 70% yield. Finally hydrazine acetate-mediated deacetylation of **262** was followed by the introduction of the 2,4-dinitrophenyl moiety at the anomeric position, giving rise to the target bicyclic methylene acetal probe **263** in 40% overall yield.

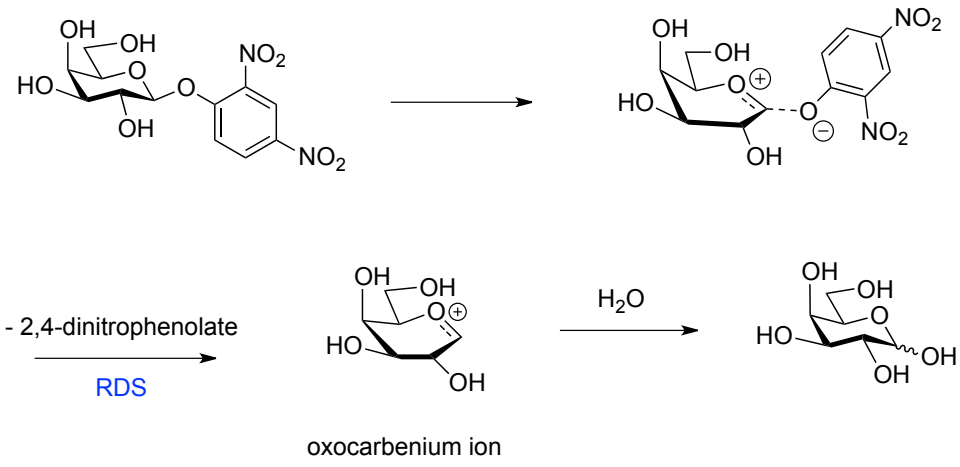
5.2.2 Kinetic Studies

5.2.2.1 Spontaneous Hydrolysis of 2,4-Dinitrophenyl Galactopyranosides

5.2.2.1.1 General Mechanism

Cocker and Sinnott[258] demonstrated in their early work that the spontaneous hydrolysis of 2,4-dinitrophenyl β-D-galactopyranosides obeys a first-

order rate reaction and is pH independent at 25 °C between pH 1.6 and 8.4, above which a specific base-catalyzed reaction rapidly takes place. Thus, the rate of liberation of 2,4-dinitrophenolate is uncatalyzed within this pH range and will therefore not be affected by protonation equilibria. Accordingly, the departure of the 2,4-dinitrophenolate can only be assisted by the lone pair of the endocyclic oxygen – provided that the reaction is conducted in non-nucleophilic media – giving rise to the transient glycosyl oxocarbenium ion in the rate determining step. Finally, the glycosyl oxocarbenium ion is trapped by water to give an α/β mixture of D-galactose as shown in Scheme 77.



Scheme 77: Mechanism of the spontaneous hydrolysis of 2,4-DNP-galactopyranosides between pH 1.6 and 8.4

5.2.2.1.2 Kinetic Measurements

The kinetic parameters were obtained by measuring spectrophotometrically in dilute solutions, the rate of formation of 2,4-dinitrophenolate at λ = 400 nm. The solvolyses of probes **255**, **256R**, **256S** and

263 were easy to follow experimentally since the 2,4-dinitrophenyl glycoside derivatives and the 2,4-dinitrophenolate anion, the two chromophores present in solution, absorbe light at different wavelengths, around λ = 280-290 nm and λ = 400 nm respectively, therefore giving rise to distinct UV spectra. Each measurement was recorded under the same conditions.

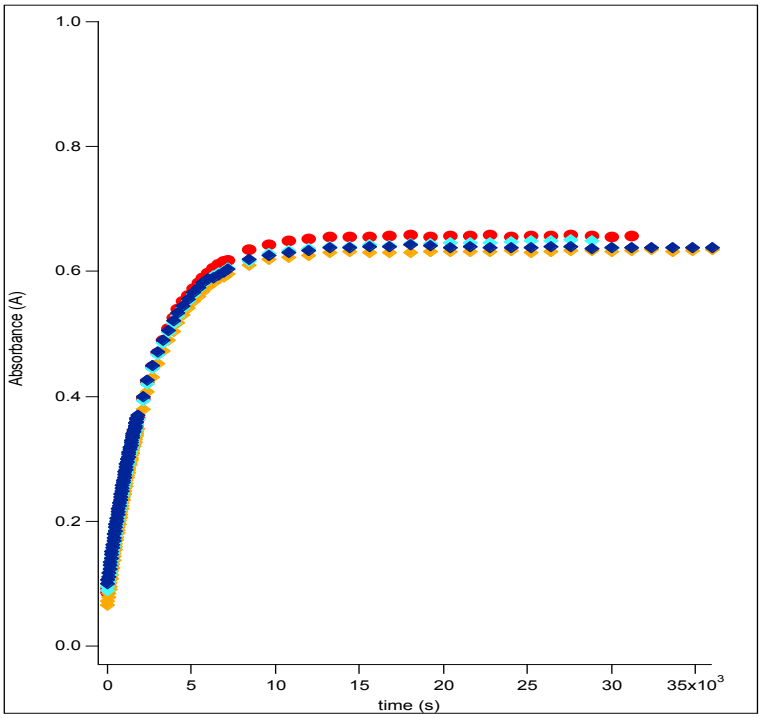
5.2.2.1.2.1 Protocol for the Spontaneous Hydrolysis of 2,4-Dinitrophenyl Galactopyranosides

The rate of spontaneous hydrolysis of the 2,4-dinitrophenyl β-D-galactosides were measured in a phosphate buffered saline solution (pH = 6.5, *c* = 25 mM, C_{KCl} = 0.4 M KCl) to which was added dioxane to ensure full solubility of the substrates. The absorbance was recorded at 400 nm over different periods of time. In order to obtain reliable data, the measurements were not stopped until the reaction had reached at least five times the half-life of the compound. Then, each reaction was repeated three to four times for consistency. Finally, the rate constants were measured at five different temperatures (42 °C, 50 °C, 60 °C, 68 °C and 75 °C) and at a single concentration (C = 0.5 mM) for each compound. The kinetic data obtained in this manner are presented in the following sections.

5.2.2.1.2.2 First Order Rate Constants Determination

The graphs of absorbance as a function of time A = f(*t*), were plotted for each compound at T = 42 °C, 50 °C, 60 °C, 68 °C and 75 °C and the rate constants *k* were calculated for each temperature from the slopes. An example of

one of the plots obtained for a given temperature is shown in Graph 1, and the remainder are presented in the appendix.



Graph 1: Formation of 2,4-dinitrophenolate as a function of time at λ = 400 nm and T = 68 °C

A summary of the averaged *k* values obtained for each compound for this set of temperatures is presented in Table 4.

	49	**57** (*gg*)	**50R** (*gt*)	**50S** (*tg*)
T = 315 K	$1.85 \times 10^{-5} \pm 4.65 \times 10^{-8}$ s^{-1}	$8.06 \times 10^{-6} \pm 2.54 \times 10^{-8}$ s^{-1}	$4.61 \times 10^{-6} \pm 1.13 \times 10^{-8}$ s^{-1}	$3.55 \times 10^{-6} \pm 8.50 \times 10^{-9}$ s^{-1}
T = 323 K	$4.90 \times 10^{-5} \pm 1.19 \times 10^{-7}$ s^{-1}	$2.23 \times 10^{-5} \pm 7.02 \times 10^{-8}$ s^{-1}	$1.32 \times 10^{-5} \pm 5.30 \times 10^{-8}$ s^{-1}	$1.04 \times 10^{-5} \pm 3.00 \times 10^{-8}$ s^{-1}
T = 333 K	$1.57 \times 10^{-4} \pm 2.27 \times 10^{-7}$ s^{-1}	$7.20 \times 10^{-5} \pm 3.88 \times 10^{-7}$ s^{-1}	$4.85 \times 10^{-5} \pm 1.16 \times 10^{-7}$ s^{-1}	$3.90 \times 10^{-5} \pm 1.23 \times 10^{-7}$ s^{-1}
T = 341 K	$3.82 \times 10^{-4} \pm 5.76 \times 10^{-7}$ s^{-1}	$1.85 \times 10^{-4} \pm 7.27 \times 10^{-7}$ s^{-1}	$1.22 \times 10^{-4} \pm 3.69 \times 10^{-7}$ s^{-1}	$9.84 \times 10^{-5} \pm 4.49 \times 10^{-7}$ s^{-1}
T = 348 K	$7.64 \times 10^{-4} \pm 9.96 \times 10^{-7}$ s^{-1}	$3.83 \times 10^{-4} \pm 1.55 \times 10^{-6}$ s^{-1}	$2.60 \times 10^{-4} \pm 8.08 \times 10^{-7}$ s^{-1}	$2.12 \times 10^{-4} \pm 7.88 \times 10^{-7}$ s^{-1}

Table 4: Averaged rate constants calculated for compounds 255, 263, 256R and 256S at different temperatures

5.2.2.1.2.3 The Arrhenius Equation

The Arrhenius equation correlates the rate constant k to the temperature, in the form

$$k = Ae^{-Ea/RT} \quad \text{(Eq 1)}$$

where A is the frequency, or pre-exponential factor, *Ea*, the activation energy, R, the gas constant and T, the temperature.

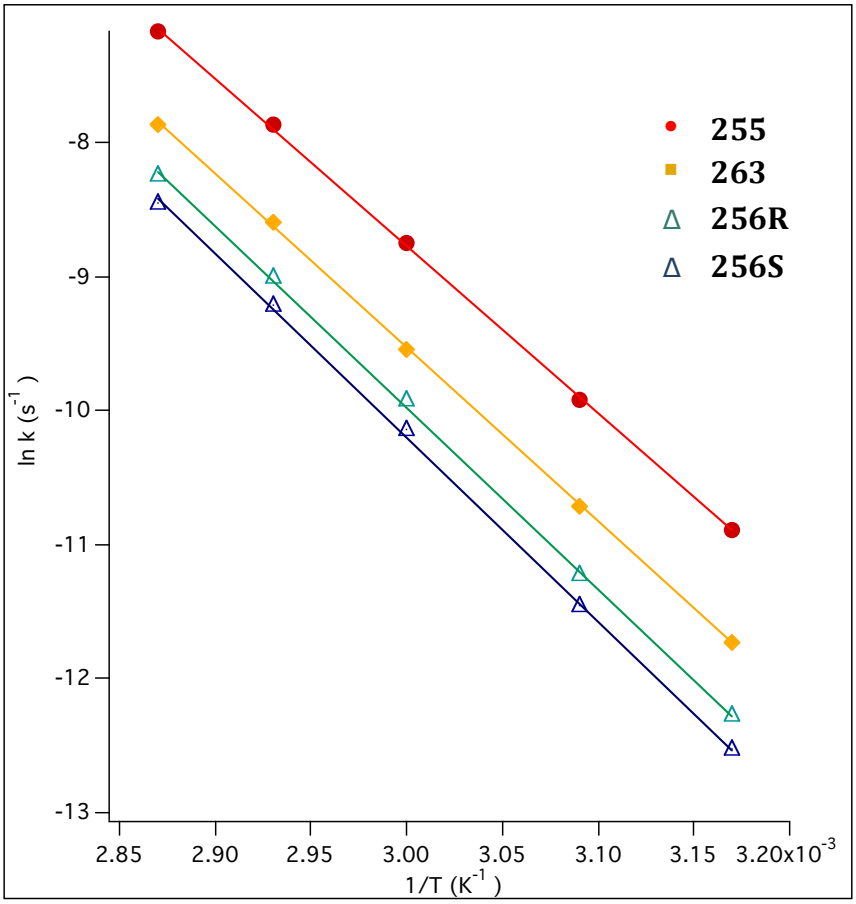
The plot of ln *k* versus the inverse temperature (1/*T*) provides the activation energy value from the slope of the curve and the pre-exponential factor from the y intercept.

The entropy of activation $\Delta S^{\ddagger}$ was calculated from equation 2[259] as follows

$$\frac{\Delta S^{\ddagger}}{19.15} = \log k - 10.753 - \log T + \frac{Ea}{19.15T} \quad \text{(Eq. 2)}$$

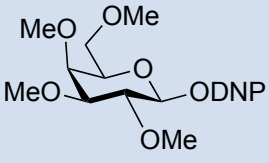
where *k* represents the rate constant at a given temperature *T*.

The Arrhenius plot was then constructed for each compound on the basis of the averaged *k* values (Table 4) obtained at these five different temperatures.



Graph 2: The Arrhenius plot of 2,4-DNP galactoside probes

The kinetic parameters for each compound are summarized in Table below.

Compound	Structure	$\Delta S^{\ddagger}$ ($J.mol^{-1}K^{-1}$)	A × s	E_a (kJ/mol)	k × s (T = 37 °C)	Relative hydrolysis rate
255		- 13.07	1.01 × 10^{-3}	104	1.01 × 10^{-5}	1

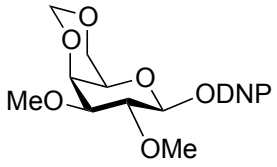
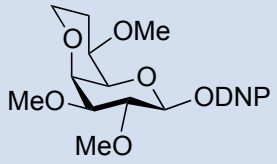
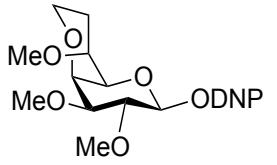
263		- 8.87	5.00 × 10^{-4}	108	4.33 × 10^{-6}	0.43
256R		- 8.48	3.35 × 10^{-4}	113	2.50 × 10^{-6}	0.23
256S		+ 4.54	2.75 × 10^{-4}	114	1.85 × 10^{-6}	0.17

Table 5: Experimental kinetic parameters for the sponotaneous hydrolysis of 2,4-DNP galactosides 255, **263**, **256R** and **256S**

Comparisons of the relative rates of hydrolysis of monocyclic compound **255** with bicyclic compounds **263**, **256R** and **256S** as probes for the *gg*, *tg* and *gt* conformers show that cis-fused systems also suffer from a torsional disarming effect regardless of the orientation of the C6-O6 bond. In other words, the presence of a cis-fused ring slows down the distortion of the pyranose ring to the geometry imposed by the oxocarbenium ion, resulting in a slower release of 2,4-dinitrophenolate. The electronic influence of the C6-O6 bond parallels that predicted by the charge-dipole hypothesis, namely that the *gg* conformer, compound **263**, is the most reactive one and the *tg* conformer, compound **256S**, the least reactive and hence the most disarmed, as shown from the relative rate of hydrolysis of compound **256S** being about six times slower than that of monocyclic probe **255**. A clear arming effect arises from the additional axially

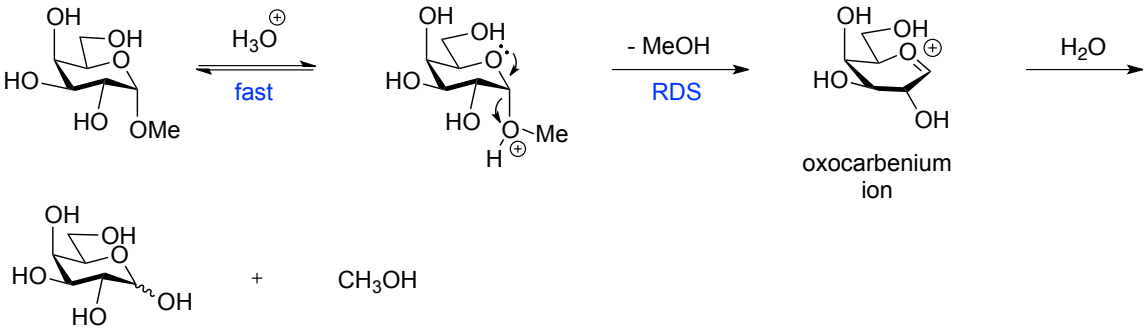
oriented C6-O6 bond as anticipated; the *gg* conformer **263** is more reactive than either the *gt* or *tg* conformer. However, the overall stabilizing interaction of the two axial C4-O4 and C6-O6 bonds is not sufficient to compensate the disarming effect coming from the locking of the rings (k_{49} = 2 x k_{57}). Thus, Table 5 points to the torsional disarming effect as the preponderant factor affecting the reactivity of conformationally restrained galactopyranosides. This disarming effect is revealed in the form of the increased activation energy *Ea* needed for the reaction to overcome the formation of high energy intermediates in the transition state, on going to the formation of the products (ΔE_a = 10 kJ/mol between monocyclic probe **255** and the *tg* conformer **256S**).

5.2.2.2 Acid Catalyzed Hydrolysis of Methyl Glycosides

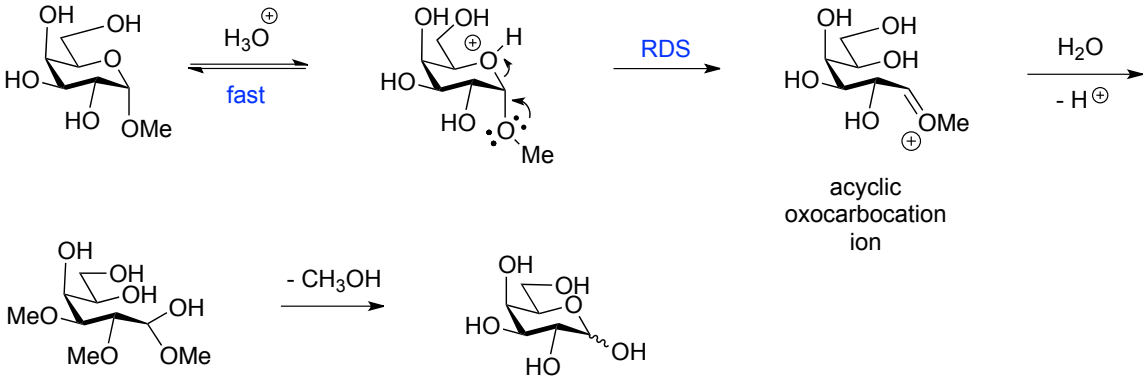
5.2.2.2.1 General Mechanism

The acid catalyzed hydrolysis of alkyl or aryl glycopyranosides has been thoroughly studied and many related papers can be found in the literature[183]. The assumed, or most commonly well-accepted mechanism is one that is believed to proceed by exocyclic protonation of the glycosidic oxygen atom followed by unimolecular heterolysis of the glycosyl-oxygen bond, leading to a glycopyranosyl oxocarbenium ion and the aglycone. The rate-determining step occurs at the breaking of the glycosidic bond, in other words, on the formation of the oxocarbenium ion. The protonation of the exocyclic oxygen is the fast step of the reaction (Scheme 78, pathway A).

a) Exocyclic protonation



b) Endocyclic protonation



Scheme 78: Acid catalyzed hydrolysis of methyl α-D-glycopyranosides via a) exocyclic and b) endocyclic protonation

Evidence such as, the oxygen isotopic effect determined in ^{18}O-enriched water or the existence of a linear free energy relationship between the acid-catalyzed hydrolysis of alkyl glycoppyranosides and spontaneous processes giving rise to the same cyclic oxocarbenium intermediate, has been used to support this mechanism. Methyl α-D-glycopyranosides were shown to predominantly hydrolyze by this mechanistic route. An alternative pathway, protonation at the endocyclic oxygen, has also been considered as a plausible mechanism in the

hydrolysis of pyranosyl acetals and proofs of it taking place in polar solvents and even water have been documented. In this later hypothesis, a higher energy intermediate is formed due to the opening of the pyranose ring, leading to the formation of an acyclic oxocarbenium ion (Scheme 78, pathway B)

5.2.2.2.2 Kinetic Measurements

The acidic hydrolysis experiments were conducted by following the change in the optical rotation value over the course of time polarimetrically. Each compound was measured according to the same protocol.

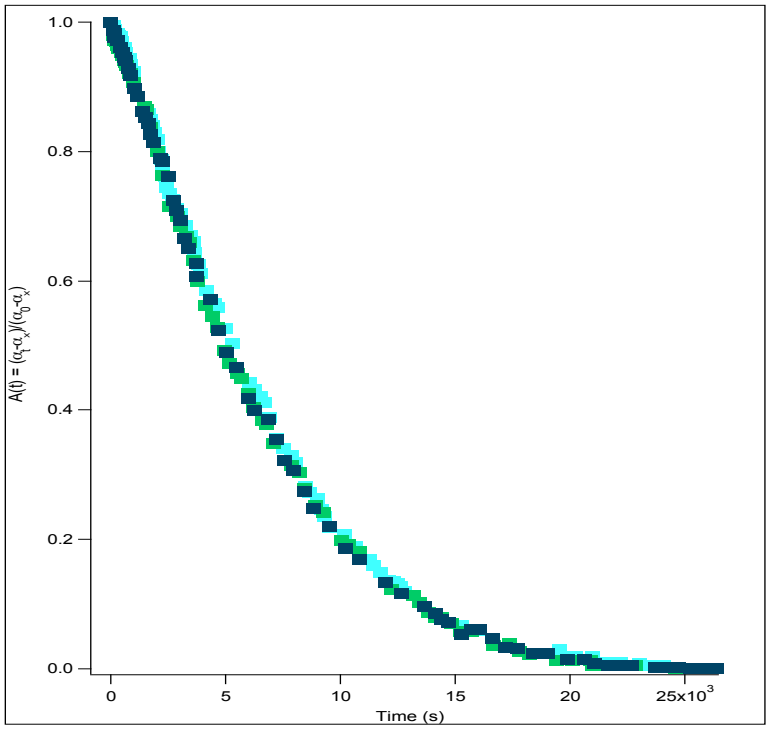
5.2.2.2.2.1 Protocol for the Acid Catalyzed Hydrolysis

The acidic hydrolysis of the methyl α-D-galactosides **247**, **254R** and **254S** was conducted at the same concentration C = 33 mM and in aqueous perchloric acid (*c* = 2.0 M). The optical rotation values were recorded until no further change was observed. The measurements were stopped once no more starting material was detectable by mass spectrometry (MS ES^+). The experiment was repeated three times for each compound, to ensure the consistency of the data obtained.

5.2.2.2.2.2 First Order Rate Constant Determination

The recorded optical rotation values were analyzed with the aid of an equation of the type $A(t) = (\alpha(t) - \alpha(inf))/ (\alpha(0) - \alpha(inf))$ where α(inf) represents the optical rotation value at the end time, then fitted as an exponential curve in

the form of $y(t) = y_o + a \times \exp^{(-bt)}$ with the *b* value representing the first-order rate constant *k* of the reaction. Examples of the curves obtained from these experiments are showed in Graph 3 and the full set of plots is given in the appendix.



Graph 3: Acid catalyzed hydrolysis of methyl α-D-galactopyranosides

After extraction of the rate constant *k*, an average of these values was calculated within experimental errors. The results of these experiments are summarized in Table 6.

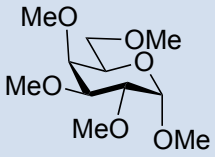
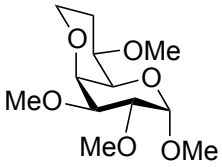
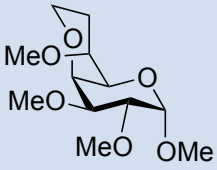
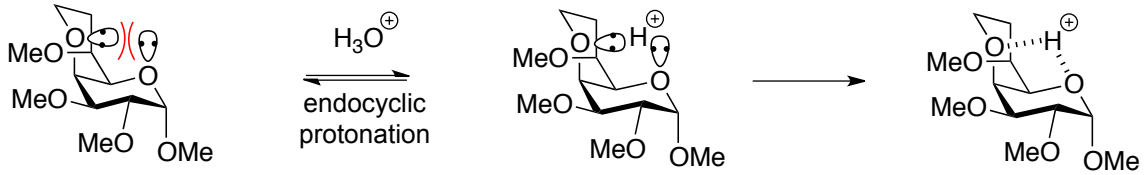
Compound	Structure	$k \times 10^5\ s^{-1}$ (T = 82 °C)	Relative hydrolysis rate
247		13.5 ± 0.28	1
254R		10.5 ± 0.23	0.78
254S		10.7 ± 0.22	0.79

Table 6: Rate constants for the acid catalyzed hydrolysis of methyl α-D-galactosides 247, 254R and 254S

Analogous with the results observed in the spontaneous hydrolysis of the 2,4-dinitrophenyl substrates, the presence of a fused system retards the formation of the oxocarbenium ion and the rate of acidic hydrolysis is faster in the case of monocyclic probe **247** than bicyclic probes **254R** or **254S**. Surprisingly, it seems that the orientation of the C6-O6 bond has no apparent effect on the reactivity of the oxocarbenium ion since the acidic hydrolysis of **254R** and **254S** occurs at same rates within experimental errors ($k_{gt} \approx k_{tg}$), whereas the charge-dipole

theory would have predicted a slower rate for the hydrolysis of the *tg* conformer as it was observed by Bols[53] in the acid hydrolysis of methyl α-D-glucopyranoside derivatives. From comparison of Tables 2 and 3, it is obvious that the trend observed for the relative spontaneous hydrolysis of constraint 2,4-dinitrophenyl galactopyranosides does not hold anymore in the case of the acidic hydrolysis of similar methyl α-galactopyranoside probes. Clearly, there is no free energy relationship relating the spontaneous hydrolysis of 2,4-DNP galactosides to the acid catalyzed hydrolysis of α-methyl counterparts. These results suggest that a different mechanism is most likely involved in the acidic hydrolysis of conformationally locked methyl α-galatopyranoside systems that does not include the intermediacy of a cyclic oxocarbenium ion, pointing therefore toward an endocyclic protonation mechanism. Yet, since a difference in the relative rate of hydrolysis between **247** and **254R**/**254S** is noted, an exocyclic protonation pathway cannot be excluded, but is no longer favored. The hypothesis of an endocyclic protonation confirms what was observed during the spontaneous hydrolysis of compounds **255**, **263**, **256R** and **256S**, namely that the formation of the oxocarbenium ion is a high energy process - due to the disarming effect coming from the bridging of O4 and O6. This effect is overridden in the acid-catalyzed hydrolysis reaction by a switch to the endocyclic protonation pathway. A counter-argument to this hypothesis arises from the fact that such a mechanism has not been observed in similar reactions in the glucose series and because an endocyclic protonation is not stereoelectronically favored for methyl α-D-glycopyranosides[260]. Going back to Deslongchamps'[186] hypothesis, the

ground state of galactopyranosides is characterized by a 1,3-syn diaxial electronic interaction (electrostactic repulsion) between the axial substituent at C4 and the axial lone pair of the endocyclic oxygen. This unfavorable interaction should be relatively stronger in conformationally restrained molecules such as compounds **254R** or **254S**, since the freedom of rotation about the C4-O4 bond is lost, leading to a closer positioning between O4 and O5. Consequently, the protonation step in the acid catalyzed hydrolysis of bicyclic galactopyranoside systems is most likely assisted by the lone pairs of both oxygen atoms O4 and O5 via hydrogen bonding, directing thereby the site of protonation at the endocyclic oxygen while relieving the LP/LP interaction observed in the ground state of galactopyranoside systems (Scheme 79).



Scheme 79: Endocyclic protonation hypothesis

5.3 Conclusion

The results obtained from this set of kinetic studies confirmed what Fraser-Reid observed about twenty years ago, namely that 4,6-*O*-acetals exert a disarming effect on glycosides reactivity. In the case of the galactose series, the origin of this disarming effect appears to be mostly torsional, affecting directly the glycosyl oxocarbenium ion by retarding its formation. However, this disarming

effect is tempered by the favorable electronic interactions arising from the through-space donation of the two axially oriented C4-O4 and C6-O6 bonds into the developing oxocarbenium ion. From these results, it seems that the α-directing effect observed in 4,6-*O*-acetal-protected galactopyranosyl donor might most likely be due to thermodynamic rather than kinetic controls.

CHAPTER 6

OVERALL CONCLUSION

The applicability of a novel ligation method between a disulfide and a thiol functional to the preparation of oligosaccharide mimetics was demonstrated in the first part of this thesis through the chemical synthesis of linear β-(1→6)-*N*-acetyl glucosamine mimetics. Large oligosaccharide mimetics can be generated from small, pre-assembled sugar building blocks, by linking them together with a small thioether linkage via the desulfurative rearrangement of allylic disulfides. This facile transformation takes place at room temperature under mild conditions and is favored in polar media, allowing the manipulation of polar molecules without the need of protecting groups. This methodology is suitable for the modification of thiols and cysteine residues and is highly compatible with a wide range of functional groups, which supposes potentials application across carbohydrate chemistry field.

Different mechanistic aspects of the glycosylation reaction were brought into light by investigating the stereoelectronic influence of the proximal C-O bonds in 4,6-*O*-benzylidene-protected glycoside systems. In contrast with the formation of *O*-glycosides, *C*-glycosides are formed stereoselectively in the glucose and the mannose series, independently of the nature of the substituent at C3 in other words, the C3-O3 bond was found to have no discernible effect on the outcome of *C*-glycosylation reaction, whereas it had been previously shown to have a major effect on the outcome of *O*-glycosylation. A different mechanistic scheme was proposed to account for this change in selectivity based on the

changing face of selectivity of an oxocarbenium ion intermediate according to the nature of the nucleophile.

4,6-*O*-Acetal-protected galactopyranosides were shown to suffer from a torsional disarming effect despite the *cis*-fused conformation of the rings. However, this effect is lesser in the galactose series than in the glucose series because of the favorable electronic interactions arising from the two axially oriented C4-O4 and C6-O6 bonds.

CHAPTER 7

EXPERIMENTAL SECTION

General

The reactions were all conducted under inert atmosphere of either argon or nitrogen. All solvents were dried and distilled by standard procedures. All the reagents were purchased from commercial sources and used as received, unless otherwise stated. The products were purified by silica gel (60 Å, 230 × 450 mesh) column chromatography. The optical rotation values were recorded on an Autopol III automatic polarimeter in $CHCl_3$ unless otherwise stated. NMR experiments were recorded on either a Mercury 400 MHz or a Varian 500 MHz instruments for ^{1}H and ^{13}C spectra. Melting points were measured on a Barnstead electrotermal (9100) instrument and are uncorrected. Electrospray mass spectra were recorded on a Waters Micromass LCT premier XE mass spectrophotometer in conjuction with the Waters Acquity UPLC. The absorbance was measured on a Varian Cary-Bio 50 UV/Visible spectrophotometer using a stoppered quartz cuvette.

Only data for new compounds are provided here.

General Protocols:

A. General Procedure for Saponification of Phenoxycarbonylthioxybutenyl Groups and Installation of the Pyridyl Disulfide Moiety. To a solution of the glycosyl thiocarbonate (0.5 mmol) in MeOH (2.5 mL) was added, dropwise at 0 ºC a freshly prepared solution of 1M KOH (2.3 mmol, 1.5 eq per group to be

saponified). The resulting mixture was stirred for 0.5 h then neutralized by careful addition of Amberlyst-15 resin and then filtered. The filtrate was added dropwise to a solution of 2,2'-dipyridyl disulfide (0.7 mmol) in MeOH at 0 ºC. The resulting mixture was allowed to warm to room temperature and stirred for 4 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give the desired products.

B. General Procedure for the Preparation of Cyclic Bisacetals. Camphorsulfonic acid (0.34 mmol) was added to a stirred solution of the glycoside (3.4 mmol) in methanol (32 mL) at room temperature. Then, trimethyl orthoformate (18.5 mmol) and butane-2,3-dione (4.0 mmol) were added and the mixture was heated at reflux for 14-16 h. The mixture was then basified to pH = 8 by addition of triethylamine and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography to give the desired bisacetals.

C. General Procedure for the Preparation and Isolation of Tosylates. *p*-Toluenesulfonyl chloride (4.86 mmol) and tetramethylethylenediamine (4.86 mmol) were added sequentially to a stirred solution of the glycoside (0.24 mmol) in acetonitrile (25 mL) at room temperature. The mixture was stirred for 2-5 h then, poured into ice and extracted twice with dichloromethane. The combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography.

D. General Procedure for the Introduction of the 6-Acetylthio Group from

the Corresponding Tosylates. To a solution of tosylate (2.12 mmol) in DMF (28 mL) was added potassium thioacetate (4.24 mmol). The reaction mixture was heated to 80 ºC (50 ºC in case of the disaccharide) for 18-36 h then concentrated in vacuo. The residue was taken up in dichloromethane and washed with water. The aqueous phase was extracted twice with dichloromethane. The combined organic layers were dried, filtered and concentrated and the 6-acetylthio derivatives were isolated by silica gel column chromatography.

E. General Procedure for the Oxidation of Thioglycosides to Glycosyl Sulfoxides. To a stirred solution of thioglycoside (1.06 mmol) in dichloromethane (30 mL) was added dropwise at -80 ºC a freshly prepared solution of *m*-chloroperoxybenzoic acid (1.04 mmol) in dichloromethane (3.8 mL). The resulting mixture was stirred at -80 ºC for 0.5-1.5 h then quenched by addition of saturated aqueous $NaHCO_3$. The resulting mixture was allowed to warm to room temperature and the aqueous phase was extracted twice with dichloromethane. The combined organic layers were dried, filtered, concentrated and purified by silica gel column chromatography to yield the desired glycosyl sulfoxides.

F. General Procedure for Glycosylation under NIS/TfOH conditions. The glycosyl donor (0.56 mmol) and glycosyl acceptor (0.73 mmol) were stirred in dichloromethane (4 mL) at room temperature in presence of activated 4Å powdered molecular sieves for 0.5 h before the reaction mixture was cooled to –35 ºC. Then, *N-iodosuccinimide* (1.12 mmol) and trifluoromethanesulfonic acid (0.34 mmol) were added sequentially and the resulting mixture was stirred for 2 h. The reaction was quenched by addition of 20% $Na_2S_2O_3$ and allowed to warm

to room temperature and the aqueous phase was extracted twice with dichloromethane. The combined organic layers were dried, filtered, concentrated and purified by silica gel column chromatography to yield the desired product.

G. General Procedure for Deprotection of 2-(Phenyloxycarbonylthioxy)-3-butenyl Disaccharides with Trifluoroacetic Acid. To a stirred solution of the disaccharide (0.14 mmol) and thioanisole (1.35 mmol) in dichloromethane (8 mL) was added an aqueous solution of trifluoroacetic acid, TFA/H_2O (19:1) (4mL), at room temperature. The resulting mixture was stirred for 0.5 to 1 h at room temperature, taken up in toluene and then evaporated. The deprotected disaccharide was isolated by silica gel column chromatography.

H. General Procedure for the Triphenylphosphine-Promoted Rearrangement of Allylic Disulfides. A solution of acetylthio sugar (0.20 mmol) in methanol (1.7 mL) was sparged with nitrogen before a freshly prepared solution of 1M sodium methoxide in degassed methanol (0.2 mL) was added. The resulting mixture was stirred for 0.5 h, quickly neutralized by addition of dry Amberlyst IR 120 resin, filtered and then directly added to a stirred solution of the allylic sulfenyl donor (0.24 mmol) in methanol (2 mL) at room temperature. The resulting mixture was stirred at room temperature until TLC showed complete consumption of the thiol (14 h). Then, triphenylphosphine (0.24 mmol) was added at room temperature and the resulting mixture was stirred for an additional 16 h. The mixture was evaporated in vacuo and subjected to chromatographic purification eluting with dichloromethane/methanol (15:1).

I. General Procedure for the Formation of *C*-glycosides under the Standard Glycosylation Method using the BSP or DPSO/TTBP/Tf_2O Systems

To a stirred solution of donor (1 equiv), BSP or DPSO (1.2 equiv), TTBP (1.5 equiv) and 4 Å molecular sieves in dichloromethane (0.05 M) was added at -65 ºC Tf_2O(1.2 equiv). The resulting mixture was stirred for 0.75 h before a solution of the acceptor (5 equiv) in dichloromethane (0.20 M) was slowly added. The resulting mixture was stirred at – 65 ºC for 3 to 12 h. The reaction was quenched at - 65 ºC by adding a saturated solution of $NaHCO_3$. The temperature was allowed to warm to room temperature naturally. The mixture was taken up in dichloromethane and the molecular sieves was filtered through celite before phase separation. The organic phase was washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography eluting with hexanes/ethyl acetate 15:1 unless otherwise stated afforded the desired *C*-coupling products.

2-(Phenyloxycarbonylthioxy)-3-butenyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside 90.

To a stirred solution of the oxazolinone (2.5 g, 7.6 mmol) and 2-(Phenoxycarbonylthioxy)-3-butenol (425 mg, 1.9 mmol) in chloroform was added, at room temperature, copper chloride (1.5 g, 11.4 mmol). The resulting mixture was heated at reflux for 14 h. The reaction mixture was allowed to warm to room temperature before saturated aqueous $NaHCO_3$ was added. The resulting mixture was filtered through celite and washed twice with saturated aqueous

$NaHCO_3$. The combined organic layers were dried, filtered and concentrated. The glycoside was isolated by silica gel column chromatography hexane/dichloromethane/ethyl acetate (1:1:2) as a white foam in an approximately 1:1 mixture of diastereomers (473 mg, 43%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, *J* = 8.0 Hz, 2 × 2H), 7.22 (t, *J* = 7.6 Hz, 2 × 1H), 7.12 (d, *J* = 6.4 Hz, 2 × 2H), 5.74-5.98 (m, 2 × 2H) 5.18-5.40 (m, 2 × 3H), 5.04 (t, *J* = 9.6 Hz, 2 × 1H), 4.74 (t, J = 8.0 Hz, 2 × 1H), 4.02-4.28 (m, 2 × 4H), 3.86 (q, J = 8.8, J = 17.8 Hz, 2 × 1H), 3.82-3.66 (m, 2 × 2H), 2.04 (s, 2 × 3H), 2.00 (s, 2 × 6H), 1.92 (s, 2 × 3H),^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 171.0, 170.6, 169.6, 151.2, 134.0, 133.8, 129.8, 126.5, 121.5, 119.1, 119.0, 101.4,100.7, 72.4, 72.1, 71.6, 70.4, 68.8, 62.2, 54.8, 54.6, 48.9, 48.2, 23.6, 23.5, 20,9, 20.8, ESIHRMS calcd for $C_{25}H_{31}NO_{11}SNa$ $[M + Na]^+$ 576.1516, found 576.1516.

2-(2-Pyridyldisulfanyl)-3-enyl-2-acetamido-2-deoxy-β-D-glucopyranoside 91. Compound **91** was obtained from **90** according to procedure **A** in 60% yield over two steps. Compound **91** was eluting from silica gel chromatography with dichloromethane/methanol (25:1) and isolated as a white foam in a 1:1 mixture of diastereomers: ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 2 × 1H), 7.94-7.78 (m, 2 × 2H), 7.21 (t, *J* = 5.6 Hz, 2 × 1H), 5.87-5.67 (m, 2× 1H), 5.19 (dd, *J* = 4.8, *J* = 16.8 Hz, 2 × 1H), 5.11 (d, *J* = 10.4 Hz, 2 × 1H), 4.47-4.39 (m, 2 × 1H), 4.16-4.50 (m, 2 × 1H), 3.86 (dd, *J* = 5.6, *J* = 9.6, Hz, 2 × 1H), 3.82-3.75 (m, 2 × 1H), 3.74-3.63 (m, 2 × 4H), 3.50-3.42 (m, 2 × 1H), 3.36-3.23 (m, 2 × 4H), 1.98 (s, 2 × 3H), ^{13}C NMR (100 MHz, CD_3OD) δ 172.5, 160.5, 148.9, 148.8, 138.1, 138.0, 134.2, 133,8, 121.1, 121,0, 120.2, 121.1, 118.4, 118.3, 116.9, 102.1, 101.7, 76.9, 76.7,

74.8, 74.7, 74.6, 71.4, 70.9, 69.9, 69.8, 61.6, 61.5, 56.1, 56.0, 54.4, 54.1, 22.1, 2.0, ESIHRMS calcd for $C_{17}H_{24}N_2O_6S_2Na$ $[M + Na]^+$ 439.0974, found 439.0978.

Methyl 2-acetamido-6-*S*-acetyl-2-deoxy-6-deoxy-β-D-glucopyranoside 94. Diizopropyl azodicarboxylate (0.25 mL, 1.22 mmol) was added dropwise at 0 ºC to a stirred solution of triphenylphosphine (326 mg, 1.24 mmol) in dimethylformamide (2 mL). The mixture was stirred at 0 ºC for 1 h and gave a light yellow precipitate. A solution of deprotected compound **93** (240 mg, 1.02 mmol) and thiolacetic acid (0.09 mL, 1.22 mmol) in dimethylformamide (1.7 mL) was added dropwise at 0 ºC and the resulting mixture was stirred for 20 h at room temperature, resulting in a clear yellow solution. The mixture was concentrated in vaccuo and the residue was purified by silica gel chromatography (eluting with dichloromethane/methanol 15:1) to give the desired acetylthio compound **94** as a white solid (176 mg, 59%) mp 108 ºC, $[\alpha]^{RT}_D$ + 36.8 (*c* MeOH), ^{1}H NMR (300 MHz, CD_3OD) δ 4.26 (d, *J* = 8.7 Hz, 1H), 3.66-3.55 (m, 2H), 3.48-3.38 (m, 4H), 3.38-3.26 (m, 4H), 3.20 (t, *J* = 9 Hz, 1H), 2.80 (dd, *J* = 8.1, *J* = 8.7 Hz, 1H), 2.32 (s, 3H), 1.94 (s, 3H), ^{13}C NMR (75 MHz, CD_3OD) δ 195.8, 172.6, 102.2, 75.0, 74.6, 73.9, 56.0, 55.7, 30.9, 29.2, 21.8, ESIHRMS calcd for $C_{11}H_{19}NO_6S$ Na $[M + Na]^+$ 316.0831, found 316.0849.

Methyl 6-[4-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)-2E-butenyl]thio-2- acetamido-2-deoxy-β-D-glucopyranoside 97.

Compound **97** was prepared according to general procedures **H** and similarly was subjected to the silver nitrate rearrangement (cf. compound **106**) and isolated as a white foam eluting from silica gel in dichloromethane/methanol

(20:1) in 82% (Ph_3P) and 68% yields ($AgNO_3$): $[\alpha]^{RT}{}_D$ + 41.0 (*c* 0.5, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 5.80 = 5.60 (m, 2H), 4.40 (d, *J* = 8.0 Hz, 1H), 4.32 (d, *J* = 8.8 Hz, 1H), 4.27 (d, *J* = 8.8 Hz, 1H), 4.09 (dd, *J* = 5.2, *J* = 12.8 Hz, 1H), 3.88 (d, *J* = 12.0 Hz, 1H), 3.72-3.61 (m, 4H), 3.48-3.20 (m, 12H), 2.94 (d, *J* = 13.6 Hz, 1H), 2.62 (dd, *J* = 8.0 Hz, *J* = 14.4 Hz, 1H), 1.98 (s, 3H), 1.97 (s, 3H), ^{13}C NMR (100 MHz, CD_3OD) δ 172.6, 129.6, 128.8, 102.4, 102.3, 100.6, 77.0, 76.8, 74.9, 74.8, 73.6, 70.9, 68.7, 61.6, 56.1, 56.0, 55.9, 34.0, 32.1, 21.9, 21.8, ESIHRMS calcd for $C_{21}H_{36}N_2O_{11}SNa$ $[M + Na]^+$ 547.1938, found 547.1942.

Phenyl 2-azido-2-deoxy-3,4,6-tri-*O*-(*p*-methoxybenzyl)-1-thio-β-D-glucopyranoside 122.

To a stirred solution of thioglycoside **121** (800 mg, 2.7 mmol) in dimethylformamide (6.4 mL) was added, portion-wise, at 0 ºC sodium hydride (542 mg, 16.1 mmol) The resulting mixture was stirred for 0.5 h at 0 ºC before p-methoxybenzylchloride (2.2 mL, 16.1 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 2 h then quenched by addition of methanol. The mixture was concentrated and purified by silica gel column chromatography 0.5% Et_3N hexane/ethyl acetate (4:1) gave compound **122** (1.6 g, 92%) as a light yellow solid: mp, $[\alpha]^{RT}{}_D$ – 45.8 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.2, *J* = 8.0 Hz, 2H), 7.32-7.24 (m, 7H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.92-6.82 (m, 2H), 4.78 (s, 2H), 4.72 (d, *J* = 10.4 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.52-4.46 (m, 2H), 4.40 (d, *J* = 9.6 Hz, 1H), 3.80 (s, 9H), 3.76-3.66 (m, 2H), 3.58-3.42 (m, 3H), 3.32 (t, *J* = 9.6 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 159.6, 159.4, 133.8, 131.5, 130.5, 130.3,

130.1, 130.0, 129.8, 129.6, 129.2, 128.5, 114.2, 114.1, 114.0, 86.1, 85.0, 79.6, 76.9, 75.7, 74.9, 73.3, 65.6, 65.3, 55.5, ESIHRMS calcd for $C_{36}H_{39}N_3O_7S$ [M + Na]$^+$ 680.2406, found 680.2404.

Phenyl 2-azido-2-deoxy-3,4,6-tri-*O*-(*p*-methoxybenzyl)-1-thio-β-D-glucopyranoside-*S*-Oxide 112.

Compound **112** was obtained in a diastereomeric mixture and 92% yield according to general procedure E. Purification by silica gel chromatography in 0.5% Et_3N hexane/ethyl acetate (4:1) afforded **112** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.63 (m, 2H), 7.51 (d, *J* = 4.8 Hz, 2H), 7.45 (dd, *J* = 2.4, *J* = 3.2 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 3H), 7.25 (t, *J* = 8.0 Hz, 3H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.92-6.81 (m, 4H), 4.83 (d, *J* = 1.6 Hz, 1H), 4.89-4.65 (m, 3H), 4.48 (dd, *J* = 7.2, *J* = 8.0 Hz, 3H), 4.31 (d, *J* = 11.6 Hz, 1H), 4.17 (dd, *J* = 9.6, *J* = 12.0 Hz, 1H), 3.86-3.3.77 (m, 13H), 3.74-3.67 (m, 2H), 3.66-3.57 (m, 1H), 3.56-3.45 (m, 4H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 159.6, 140.3, 139.4, 131.6, 131.5, 130.1, 130.0, 129.9, 129.7, 129.6, 129.3, 129.2, 125.6, 124.9, 114.2, 114.1, 114.0, 113.9, 94.5, 91.8, 84.8, 84.7, 80.9, 80.4, 75.8, 75.7, 74.9, 73.5, 73.4, 68.4, 68.3, 61.0, 60.2, 55.5, ESIHRMS calcd for $C_{36}H_{39}N_3O_8SNa$ [M + Na]$^+$ 696.2356, found 696.2359.

Phenyl 2-Azido-2-deoxy-3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-1-thio-β-D-glucopyranoside 113.

Title compound **113** was obtained from compound **121** in 83% yield according to general procedure **B**. Compound **113** was isolated as a white solid and eluted from silica gel chromatography with hexane/ethyl acetate (2:1): mp 110 ºC; $[\alpha]^{RT}$

$_D$ + 47.3 (*c* 1.0, $CDCl_3$) ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 2.4, *J* = 5.6 Hz, 2H), 7.37-7.30 (m, 3H), 4.40 (d, *J* = 9.6 Hz, 1H), 3.92-3.83 (m, 1H), 3.77-3.68 (m, 2H), 3.63 (t, *J* = 9.6 Hz, 1H), 3.54-3.49 (m, 1H), 3.39 (t, *J* = 9.6 Hz, 1H), 3.33 (s, 3H), 3.28 (d, *J* = 5.6 Hz, 1H), 3.23 (s, 3H), 194 (dd, *J* = 5.6 Hz, *J* = 7.2 Hz, 1H), 1.33 (s, 3H), 1.27 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 129.4, 128.9, 100.4, 99.9, 86.3, 78.3, 73.2, 65.8, 61.7, 61.5, 48.3, 48.3, 17.8, 17.7, ESIHRMS calcd for $C_{18}H_{25}N_3O_6SNa$ $[M + Na]^+$ 434.1362, found 434.1354.

Phenyl 2-Azido-2-deoxy-3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-1-thio-2'-azido-2'-deoxy-3',4',6'-tri-*O*-(*p*-methoxybenzyl)]-β-D-gentiobioside 123.

Glycosyl sulfoxide **112** (1.2 g, 1.78 mmol) was premixed with glycosyl acceptor **113** (880 mg, 2.14 mmol), 2,4,6-tri-*tert*-butylpyrimidine (TTBP*) (886 mg, 3.57 mmol) and activated 4Å powdered molecular sieves in dichloromethane/acetonitrile (4:3) (3.6 mL) and the resulting mixture was stirred at room temperature for 0.5 h then cooled at -80 ºC before trifluoromethanesulfonic anhydride (0.33 mL, 1.96 mmol) was added dropwise. The reaction mixture was stirred at - 80 ºC for 1.5 h, quenched by addition of aqueous saturated $NaHCO_3$ and then allowed to warm to room temperature. The aqueous phase was extracted twice with dichloromethane. The organic layers were combined, dried, filtered and concentrated in vaccuo. Purification by silica gel column chromatography in 0.5% Et_3N hexane/ethyl acetate (4:1 to 2.5:1) gave the resulting disaccharide (1.05 g, 62%) as a white foam: ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.53 (m, 2H), 7.36-7.27 (m, 5H), 7.27-7.22 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.83 (dd, *J* = 5.6, *J* = 8.8 Hz, 3H), 4.83-

4.69 (m, 3H), 4.58-4.37 (m, 3H), 4.14 (d, *J* = 10.8 Hz, 1H), 3.90-3.46 (m, 16H), 3.44-3.19 (m, 11H), 1.32 (s, 3H), 1.27 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 159.5, 134.1, 133.8, 130.4, 130.0, 129.8, 129.3, 128.6, 114.1, 114.0, 102.4, 100.4, 100.0, 86.4, 83.1, 78.2, 75.9, 75.8, 75.5, 75.2, 74.9, 74.7, 73.4, 72.2, 71.2, 68.4, 68.1, 66.6, 66.3, 65.6, 61.7, 60.2, 55.5, 55.4, 48.3, 17.8, 17.7, ESIHRMS calcd for $C_{48}H_{58}N_6O_{13}Na$ $[M + Na]^+$ 981.3680, found 981.3682.

Phenyl 2-Azido-2-deoxy-3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-1-thio-[2'-azido-2'-deoxy-3',4',6'-tri-*O*-(*p*-methoxybenzyl)]-β-D-gentiobioside-*S*-Oxide 109.

Title compound **109** was isolated as a white foam in 88% yield and in an approximately 1:1 mixture of diastereomers. Compound 53 was prepared from compound 52 according to general procedure **E** and eluted from silica gel in 0.5% Et_3N hexane/ethyl acetate (3:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.60 (m, 2 × 2H), 7.55-7.45 (m, 2 × 3H), 7.33-7.20 (m, 2 × 4H), 7.12-7.02 (m, 2 × 2H), 6.91-6.79 (m, 2 × 6H), 4.80-4.66 (m, 2 × 3H), 4.54 (dd, *J* = 9.6, *J* = 10.8 Hz, 1 × 1H), 4.48-4.38 (m, 2 × 2H), 4.21 (dd, *J* = 5.6, *J* = 9.6 Hz, 1 × 1H), 4.02-3.84 (m, 2 × 3H), 3.83-3.73 (m, 2 × 10H), 3.73-3.44 (m, 2 × 6H), 3.43-3.14 (m, 2 × 9H), 1.34 (s, 2 × 3H), 1.26 (s, 2 × 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 139.1, 131.7, 131.4, 130.3, 130.0, 129.9, 129.8, 129.7, 129.6, 129.4, 129.3, 125.4, 124.7, 114.2, 114.1, 114.0, 102.9, 102.1, 100.5, 100.1, 95.2, 91.7, 91.4, 82.7, 79.8, 78.8, 77.5, 75.4, 75.3, 75.0, 74.9, 74.8, 73.5, 73.4, 73.1, 68.5, 68.2, 67.7, 66.4, 66.1, 65.8, 57.7, 55.5, 55.4, 48.4, 48.3, 17.8, 17.7; ESIHRMS calcd for $C_{48}H_{58}N_6O_{14}SNa$ $[M + Na]^+$ 997.3629, found 997.3614

2-(Phenyloxycarbonylthioxy)-3-butenyl-2-azido-2-deoxy-3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-[2'-azido-2'deoxy-3',4',6'-tri-*O*-(*p*-methoxybenzyl)]-β-D-gentiobioside 124.

Disaccharide glycosyl sulfoxide **109** (560 mg, 0.57 mmol) was premixed with 2-(Phenoxycarbonylthioxy)-3-butenol **82** (266 mg, 1.20 mmol), 2,4,6-tri-*tert*-butylpyrimidine (TTBP*) (314 mg, 1.26 mmol) and activated 4Å powdered molecular sieves in dichloromethane/acetonitrile (4:3) (2 mL) and the resulting mixture was stirred at room temperature for 0.5 h then cooled at -60 ºC before trifluoromethanesulfonic anhydride (0.15 mL, 0.86 mmol) was added dropwise. The reaction mixture was stirred at -60 ºC for 8 h. The reaction mixture was then cooled to -80 ºC, quenched by addition of aqueous saturated $NaHCO_3$ and then allowed to warm to room temperature. The aqueous phase was extracted twice with dichloromethane. The organic layers were combined, dried, filtered and concentrated in vaccuo. Purification by silica gel column chromatography 0.5% Et_3N hexane/ethyl acetate (6:1 to 3:1) gave the coupling product (390 mg, 63%) as a white foam, in an approximately 1:1 mixture of diastereomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.11 (m, 2 ×10H), 7.17-7.10 (m, 2 ×2H), 7.45 (d, *J* = 7.2 Hz, 2 × 2H), 6.90-6.79 (m, 2 ×3H), 6.03-5.92 (m, 2 ×1H) 5.43 (d, *J* = 16.8 Hz, 2 × 1H), 5.25 (d, *J* = 9.6 Hz, 2 × 1H), 4.80-4.67 (m, 2 ×4H), 4.55 (dd, *J* = 7.2, *J* = 11.6 Hz, 2 × 1H), 4.47-4.35 (m, 2 ×3H), 4.29-4.17 (m, 2 ×3H), 3.92-3.81 (m, 2 ×1H), 3.79 (s, 2 × 6H), 3.78 (s, 2 × 3H), 3.73-4.49 (m, 2 ×7H), 3.49-3.19 (m, 2 ×10H), 1.33 (s, 2 × 3H), 1.27 (s, 2 × 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.2, 169.0, 159.6, 159.5, 159.4, 156.6, 151.4, 134.2, 134.1, 130.3, 130.2, 130.0,

130.0, 129.9, 129.8, 129.7, 126.4, 126.3, 124.7, 121.7, 121.6, 121.5, 120.3, 118.9, 115.7, 114.2, 114.1, 114.0, 103.0, 102.9, 102.8, 102.7, 100.2, 100.0, 83.2, 83.0, 75.4, 75.2, 74.9, 74.6, 73.4, 73.3, 71.4, 71.2, 70.8, 70.1, 70.0, 68.4, 67.1, 66.5, 63.2, 55.5, 55.4, 48.7, 48.3, 45.9, 18.0, 17.9, 17.8, 17.7; ESIHRMS calcd for $C_{53}H_{64}N_6O_{16}SNa$ 1095.3997, found 1095.4004.

2-(Phenyloxycarbonylthioxy)but-3-enyl 2,2'-diazido-2,2'-dideoxy-β-D-gentiobioside 125.

The title compound **125** was obtained from compound **124** according to general procedure **G** as a white foam eluted from silica gel with dichloromethane/methanol (20:1) in approximately a 1:1 mixture of diastereomers and 67% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.3 Hz, 2 × 2H), 7.26 (t, *J* = 7.2 Hz, 2 × 1H), 7.15 (d, *J* = 9.2 Hz, 2 × 2H), 6.06-5.95 (m, 2 × 1H), 5.41 (d, *J* = 15.2 Hz, 2 × 1H), 5.23 (d, *J* = 10.8 Hz, 2 × 1H), 4.48 (dd, *J* = 7.3, *J* = 8.8 Hz, 2 × 1H), 4.41 (d, *J* = 8.0 Hz, 2 × 1H), 4.28-4.18 (m, 2 × 3H), 3.93-3.60 (m, 2 × 7H), 3.47 (dd, *J* = 6.4, *J* = 8.0 Hz, 2 × 1H), 3.34-3.06 (m, 2 × 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 134.9, 129.5, 126.2, 121.3, 117.7, 117.6, 102.7, 102.3, 102.1, 101.9, 94.7, 76.8, 76.2, 75.1, 75.0, 70.7, 70.6, 70.3, 69.0, 67.1, 61.3, 48.6, ESIHRMS calcd for $C_{23}H_{30}N_6O_{11}SNa$ $[M + Na]^+$ 621.1591, found 621.1593.

2-(Pyridyldithio)but-3-enyl-2,2'-diazido-2,2'-dideoxy-β-D-gentiobioside 107.

The title compound **107** was obtained according to general procedure **A** as a white foam eluting from silica gel in dichloromethane/methanol (20:1) in approximately a 1:1 mixture of diastereomers and in 65% yield over two steps:

^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (d, *J* = 4.0 Hz, 2 × 1H), 8.75 (dd, *J* = 4.0, *J* = 8.4 Hz, 2 × 1H), 7.83-7.77 (m, 2 × 1H), 7.21 (dd, *J* = 4.8, *J* = 7.2 Hz, 2 × 1H), 5.90-5.78 (m, 2 × 1H), 5.30-5.21 (m, 2 × 1H), 5.15 (d, *J* = 10.8 Hz, 2 × 1H), 4.96-4.85 (m, 2 × 1H), 4.47-4.32 (m, 2 × 2H), 4.24-3.98 (m, 2 × 3H), 3.91-3.64 (m, 2 × 7H), 4.48-3.05 (m, 2 × 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 148.9, 137.9, 133.9, 121.1, 120.3, 120.2, 118.4, 102.7, 101.8, 76.8, 76.2, 75.1, 74.9, 70.6, 70.4, 69.8, 69.0, 67.0, 61.4, 53.8; ESIHRMS calcd for $C_{21}H_{29}N_7O_9S_2Na$ $[M + Na]^+$ 610.1366, found 1379.

Phenyl 2-Azido-2-deoxy-3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-1-thio-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside 126.

The title compound **126** was obtained according to general procedure **C** as a white solid in a quantitatif yield, by elution from silica gel with hexane/ethyl acetate (3:1): mp 134 ºC; $[\alpha]^{RT}_D$ + 12.3 (*c* 1.0, $CDCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.34-7.25 (m, 4H), 4.29 (t, *J* = 10.4 Hz, 2H), 4.21 (dd, *J* = 4.0, *J* = 10.8 Hz, 1H), 3.67-3.53 (m, 3H), 3.31 (d, *J* = 9.6 Hz, 1H), 3.28 (s, 3H), 3.23 (d, *J* = 7.6 Hz, 1H), 3.20 (s, 3H), 2.67 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 134.4, 133.0, 130.3, 130.1, 129.3, 129.0, 128.2, 100.5, 100.1, 86.1, 77.6, 75.4, 73.0, 67.3, 65.3, 61.1, 48.6, 48.4, 21.9, 17.8, 17.7, ESIHRMS calcd for $C_{25}H_{31}N_3O_8S_2Na$ $[M + Na]^+$ 588.1450, found 588.1440.

Phenyl 2-Azido-2-deoxy-6-acetylthio-3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-1-thio-β-D-glucopyranoside 127.

The title compound **127** was prepared according to general procedure **D** and isolated as a light yellow foam eluted from silica gel with hexane/ethyl acetate (6:1) in 78% yield: $[\alpha]^{RT}{}_{D}$ + 132.1 (*c* 1.0, $CDCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 6.4, *J* = 7.2 Hz, 2H), 7.35-7.30 (m, 3H), 4.35 (d, *J* = 9.6 Hz, 1H), 3.67 (t, *J* = 9.6 Hz, 1H), 3.62-3.55 (m 1H), 3.51-3.43 (m, 2H), 3.30 (s, 3H), 3.22 9s, 3H), 3.07 (q, J = 7.2, J= 14 Hz, 1H), 2.35 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 134.5, 133.2, 130.7, 129.2, 129.1, 128.9, 100.4, 100.13, 86.2, 76.7, 73.0, 68.6, 61.5, 48.4, 48.3, 30.7, 30.1, 17.8, 17.7, ESIHRMS calcd for $C_{20}H_{27}N_3O_6Na$ $[M + Na]^+$492.1239, found 492.1245.

Phenyl 6-Acetylthio-2-azido-2-deoxy-3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-1-thio-β-D-glucopyranoside-*S*-Oxide 110.

Compound **110** was prepared according to general procedure **E** and isolated as a white solid eluted from silica gel in hexane/ethyl acetate (4:1) in 70% yield: mp 125 ºC; $[\alpha]^{RT}{}_{D}$ – 12.3 (*c* 1.0, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.58 (m, 2H), 7.55-7.51 (m, 3H), 4.01 (dd, *J* = 9.6, *J* = 10.8 Hz, 1H), 3.83 (t, *J* = 9.6 Hz, 1H), 3.72 (d, *J* = 9.6 Hz, 1H), 3.54 (d, *J* = 9.6 Hz), 3.43-3.31 (m, 5H), 3.20 (s, 3H), 2.83 (dd, *J* = 8.0, *J* = 14.0 Hz, 1H), 2.19 (s, 3H), 1.27 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 139.1, 131.5, 129.2, 125.6, 100.5, 100.2, 91.9, 77.8, 73.3, 68.8, 57.6, 48.4, 48.3, 30.6, 29.8, 17.8, 17.7, ESIHRMS calcd for $C_{20}H_{27}N_3O_7S_2Na$ $[M + Na]^+$ 508.1188, found 508.1183.

Methyl 2-Azido-2-deoxy-3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-β-D-glucopyranoside 111.

Compound **111** was obtained as a white foam according to general procedure **B** and isolated from silica gel with hexane/ethyl acetate (2:1) in 81% yield: $[\alpha]^{RT}_{D}$ = + 70.3 (*c* 1.0, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.2 (d, *J* = 8 Hz, 1H), 3.88-3.80 (m, 1H), 3.76-3.66 (m, 2H), 3.60 (dd, *J* = 9.6, *J* = 10.8 Hz, 1H), 3.53 (s, 3H), 3.48-3.42 (m, 1H), 3.39 (dd, *J* = 7.2, *J* = 8.4 Hz, 1H), 3.28 (s, 3H), 3.23 (s, 3H), 2.50 (dd, *J* = 5.6, *J* = 8.0 Hz, 1H), 1.31 (s, 3H), 1.26 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.6, 100.3, 99.9, 76.9, 74.2, 71.0, 66.0, 62.9, 61.2, 57.6, 48.3, 17.8, 17.7, ESIHRMS calcd for $C_{13}H_{23}N_3O_7Na$ $[M + Na]^+$ 365.1434, found 365.1432.

Methyl 2,2'-Diazido-2,2'-dideoxy-6'- acetylthio-β-D-gentiobioside 131.

Glycosyl sulfoxide **110** (340mg, 0.70 mmol) was premixed with 2,4,6-tri-*tert*-butylpyrimidine (TTBP*) (244 mg, 0.98 mmol) and activated 4Å powdered molecular sieves in dichloromethane/acetonitrile (3:1) (2.6 mL) and the resulting mixture was stirred at room temperature for 0.5 h then cooled at -65 ºC before trifluoromethanesulfonic anhydride (0.14 mL, 0.84 mmol) was added dropwise. The glycoside sulfoxide was preactivated for 10 min before a solution of the glycosyl acceptor **111** (466 mg, 1.4 mmol) in dichloromethane (0.8 mL) was added. The resulting mixture was stirred for 8 h at -65 ºC quenched by addition of aqueous saturated $NaHCO_3$ and then allowed to warm to room temperature. The aqueous phase was extracted twice with dichloromethane. The organic layers were combined, dried, filtered and concentrated in vaccuo. The crude protected disaccharide was taken to the acid hydrolysis step without further purification to give compound **131** as a white foam eluted from silica gel with dichloromethane/methanol (20:1) in 64% yield: $[\alpha]^{RT}_{D}$ + 18.5 (*c* 1.0, MeOH) NMR

(400 MHz, $CDCl_3$) δ 4.42 (d, *J* = 7.8 Hz, 1H), 4.24 (d, *J* = 7.8 Hz, 1H), 4.16 (dd, *J* = 1.8, *J* = 11.4 Hz, 1H), 3.70 (dd, *J* = 6.9 Hz, *J* = 11.7 Hz, 1H), 3.60-3.51 (m, 1H), 3.46 (dd, *J* = 7.2, *J* = 8.1 Hz, 1H), 3.35 (s, 1H), 3.32-3.24 (m 8H), 3.23-3.08 (m, 4H), 2.98 (dd, *J* = 8.1, *J* = 14.1 Hz, 1H), 2.33 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 102.9, 102.6, 75.9, 75.2, 75.0, 74.7, 73.4, 70.6, 69.1, 67.0, 48.7, 47.0, 30.6, 29.2, ESIHRMS calcd for $C_{15}H_{24}N_6O_9SNa$ $[M + Na]^+$ 487.1223, found 487.1232.

Methyl 6-[4-*O*-(2,2'-Azido-2,2'-dideoxy-β-D-gentiobiosyloxy)but-2*E*-enyl]-thio-2,2'-azido-2,2'- 6-thio-α-D-gentiobioside 106.

Thiol precursor **108** (40 mg, 0.09 mmol) was dissolved in dimethylformamide (0.8 mL) at room temperature and hydrazine acetate (12 mg, 0.13 mmol) was added. The resulting mixture was stirred for 0.75 h and directly transferred to a stirred solution of sulfenyl donor **107** (56 mg, 0.1 mmol) in methanol (1mL). The resulting mixture was stirred until TLC showed complete consumption of the free thiol compound (18 h). Silver nitrate (26 mg, 0.20 mmol) was then added and the resulting mixture was stirred at room temperature, under light exclusion, for an additional 36 h. The resulting mixture was filtered through a patch of celite and silica and concentrated. Purification by silica gel chromatography dichloromethane/methanol (15:1) afforded the desired compound as a white foam in 52% yield: $[\alpha]^{RT}_{D}$ + 65.8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 5.84-5.67 (m, 2H), 4.62 (s, 2H), 5.52-4.36 (m, 5H), 4.23 (dd, *J* = 9.5, *J* = 12.0 Hz, 5H), 3.87 (d, *J* = 12.0 Hz, 2H), 3.83-3.62 (m, 5H), 3.56 (s, 3H), 3.54-3.43 (m, 5H), 3.42-3.05 (m, 15H), 2.95 (d, *J* = 15.0 Hz, 1H), 2.63 (q, *J* = 7.0 Hz, 1H); ^{13}C NMR

(100 MHz, CD_3OD) δ 130.4, 128.6, 102.9, 102.6, 100.6, 77.2, 76.8, 76.1, 75.9, 75.2, 75.1, 74.8, 72.9, 70.6, 70.5, 70.3, 69.1, 69.0, 68.9, 67.0, 66.9, 61.3, 56.2, 33.9, 31.4; ESIHRMS calcd for $C_{29}H_{46}Cl_3N_{12}O_{17}SNa$ $[M + Na]^+$ 889.2722, found 889.2736.

Phenyl 3,4,6-Tri-*O*-acetyl- 2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranoside 142.

To a stirred solution of compound **141** (10 g, 19.2 mmol) in dichloromethane (100 mL) was added respectively at room temperature, trimethylsilyl trifluoromethanesulfonate (TMSOTf) (4.2 mL, 23 mmol) and benzenethiol (2.4 mL, 23 mmol). The resulting mixture was stirred for 4 h then, neutralized by addition of triethylamine and concentrated. Purification by silica gel column chromatography (hexane/ethyl acetate 3:1) afforded compound **142** (9.2 g, 84%) as a light yellow solid: mp 87 ºC; $[\alpha]^{RT}{}_D$ + 18.5 (*c* 1.0, CHCl3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 3.2, *J* = 4.0 Hz, 2H), 7.29 (dd, *J* = 2.0, *J* = 3.2 Hz, 3H), 4.95 (d, *J* = 9.6 Hz, 1H), 5.27 (t, *J* = 9.6 Hz, 1H), 5.01 (t, *J* = 9.6 Hz, 1H), 4.85 (d, *J* = 10.8 Hz, 1H), 4.74 (ddd, *J* = 12.0, *J* = 16 Hz, 2H), 4.24-4.412 (m, 2H), 3.76-3.66 (m, 2H), 2.06 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.7, 154.2, 133.1, 132.3, 129.2, 128.5, 119.2, 86.8, 77.6, 75.9, 74.7, 73.4, 68.8, 62.6, 55.2, 21.0, 20.9, 20.8; ESIHRMS calcd for $C_{21}H_{24}Cl_3NO_9SNa$ $[M + Na]^+$ 594.0135, found 594.0112.

Phenyl 3,4,6-*O*-Acetyl-2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranoside-*S*-Oxide 138.

The title compound **138** was prepared according to general procedure **E**, eluting from silica gel chromatography with hexane/ethyl acetate (2:1) and isolated as a white foam in 88% yield: mp 134 ºC; $[\alpha]^{RT}_{D}$ + 31.0 (*c* 1.0, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 2.5, *J* = 3.2 Hz, 2H), 7.52 (dd, *J* = 2.4, *J* = 3.2 Hz, 3H), 5.68 (d, *J* = 8.8 Hz, 1H), 5.44 (t, *J* = 9.6 Hz, 1H), 4.92 (t, *J* = 9.6 Hz, 1H), 4.80 (d, *J* = 10.4 Hz, 1H), 4.62 (d, *J* = 12.4 Hz, 1H), 4.44 (d, *J* = 12 Hz, 1H), 4.16 (m, 2H), 3.86 (dd, *J* = 9.6, *J* = 10.8 Hz, 1H), 3.78 (m, 1H), 2.00 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 169.6, 153.9, 138.8, 131.6, 129.1, 125.9, 95.3, 93.3, 76.4, 74.6, 72.6, 68.1, 61.7, 51.7, 20.9, 20.8, ESIHRMS calcd for $C_{21}H_{24}Cl_3NO_{10}SNa$ $[M + Na]^+$ 610.0084, found 610.0067.

Phenyl 2-deoxy-3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-1-thio-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranoside 139.

To a stirred solution of thioglycoside **142** (1g, 1.65 mmol) in MeOH (8.8 mL) was added a catalytic amount of 25% sodium hydroxide in MeOH (0.18 mmol) at room temperature. The resulting mixture was stirred for 1 h, neutralized by addition of Amberlyst IR 120 resin, filtered and concentrated to give phenyl 2-(2,2,2-trichloroethoxycarbonylamino)-1-thio-β-D-glucopyranoside **143**, which was subjected to general protocol **B** directly, giving the title compound as a white foam, eluted from silica gel with hexane/ethyl acetate (1.5:1) in 72% yield: mp; $[\alpha]^{RT}_{D}$ + 54.5 (*c* 1.0, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 2.4, *J* = 4.0 Hz, 2H), 7.31 (dd, *J* = 2.4, *J* = 4.4 Hz, 3H), 5.10 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 2H) 4.10 (dd, *J* = 7.2, *J* = 9.6 Hz, 1H), 3.93-3.85 (m, 1H), 3.77-3.70 (m, 1H), 3.66 (t, *J* = 9.6 Hz, 1H), 3.62-3.56 (m, 1H), 3.41 (brs, 1H), 3.10 (dd, *J* = 4.4, *J* = 5.6

Hz, 1H), 3.24 (s, 3H), 3.21 (s, 3H), 1.91 (dd, *J* = 5.6, *J* = 7.6 Hz, 2H), 1.27 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 133.0, 132.0, 129.4, 129.3, 128.4, 100.3, 99.8, 86.1, 78.1, 77.4, 74.7, 70.1, 67.0, 61.7, 54.7, 48.2, 48.1, 17.8, 17.8, ESIHRMS calcd for $C_{21}H_{28}Cl_3NO_8SNa$ $[M + Na]^+$ 582.0449, found 582.0494.

Phenyl 3',4',6'-Tri-*O*-acetyl-2,2'-dideoxy-3,4-*O*-(2,3-dimethoxybutan-2,3-diyl)- 1-thio-2,2'-bis(2,2,2-trichloroethoxycarbonylamino)-β-D-gentiobioside 144.

Glycosyl sulfoxide **138** (310 mg, 0.53 mmol) was stirred in dichloromethane (1.6 mL) and in presence of activated 4Å powdered molecular sieves at room temperature for 0.5 h. The resulting mixture was cooled at at -65 ºC before trifluoromethanesulfonic anhydride (0.10 mL, 0.58 mmol) was added dropwise. The glycoside sulfoxide was preactivated for 10 min before a solution of the glycosyl acceptor **139** (350 mg, 0.62 mmol) in dichloromethane (0.4 mL) was added. The resulting mixture was stirred for 7 h at -65 ºC quenched by addition of aqueous saturated $NaHCO_3$ and then allowed to warm to room temperature. The aqueous phase was extracted twice with dichloromethane. The organic layers were combined, dried, filtered and concentrated in vaccuo. Purification by silica gel column chromatography hexane/ethyl acetate (5:1 to 2:1) gave the resulting disaccharide as a white foam (230 mg, 43%): $[\alpha]^{RT}_{D}$ + 44.2 (*c* 1.0, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.43-7.33 (m, 3H), 5.36-5.06 (m, 2H), 5.00 (d, *J* = 7.6 Hz, 2H), 4.81-4.69 (m, 3H), 4.64 (dd, *J* = 8.8, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 8.0 Hz, 1H), 4.28-4.21 (m, 2H), 4.15-4.02 (m, 3H), 3.75-3.52 (m, 4H), 3.39 (t, *J* = 9.6 Hz, 2H), 3.20 (s, 3H), 3.17 (s, 3H), 2.07 (s, 3H), 2.03 (s,

3H), 2.01 (s, 3H), 1.26, (s, 3H), 1.24 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 169.3, 168.4, 153.1, 152.5, 132.2, 128.5, 127.7, 100.2, 99.0, 98.7, 94.5, 84.9, 78.1, 75.7, 73.5, 71.2, 70.5, 67.7, 67.3, 66.6, 66.3, 60.9, 54.9, 53.4, 47.0, 46.9, 19.7, 19.6, 16.6, 16.5, ESIHRMS calcd for $C_{36}H_{46}Cl_6N_2O_{17}SNa$ 1043.0549, found 1043.0546.

Phenyl 3',4',6'Tri-*O*-acetyl-2,2'-dideoxy-3,4-*O*-(2,3-dimethoxybutan-2,3-diyl)-1-thio-2,2'-bis(2,2,2-trichloroethoxycarbonyl-amino)-β-D-gentiobioside-*S*-Oxide 135.

The title compound **135** was obtained as a white foam by general procedure **E** from **144** and eluted from silica gel in hexane/ethyl acetate (2:1) in 88% yield: mp 134 ºC; $[\alpha]^{RT}_{D}$ + 31.0 (*c* 1.0, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 2.5, *J* = 3.2 Hz, 2H), 7.52 (dd, *J* = 2.4, *J* = 3.2 Hz, 3H), 5.68 (d, *J* = 8.8 Hz, 1H), 5.44 (t, *J* = 9.6 Hz, 1H), 4.92 (t, *J* = 9.6 Hz, 1H), 4.80 (d, *J* = 10.4 Hz, 1H), 4.62 (d, *J* = 12.4 Hz, 1H), 4.44 (d, *J* = 12 Hz, 1H), 4.16 (m, 2H), 3.86 (dd, *J* = 9.6, *J* = 10.8 Hz, 1H), 3.78 (m, 1H), 2.00 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 169.6, 153.9, 138.8, 131.6, 129.1, 125.9, 95.3, 93.3, 76.4, 74.6, 72.6, 68.1, 61.7, 51.7, 20.9, 20.8, ESIHRMS calcd for $C_{21}H_{24}Cl_3NO_{10}SNa$ $[M + Na]^+$ 610.0084, found 610.0067.

2-(Phenyloxycarbonylthioxy)but-3-enyl 3',4',6'-Tri-O-acetyl-2,2'-dideoxy-3,4-O-(2,3-dimethoxybutan-2,3-diyl)-2,2-bis-(2',2',2'-trichloroethoxycarbonyl-amino) β-D-gentiobioside 145.

Disaccharide glycosyl sulfoxide donor **135** (280 mg, 0.27 mmol) was mixed with acceptor **82** (120 mg, 0.54 mmol) and activated 4Å powdered molecular sieves in

dichloromethane (1.2 mL) and the resulting mixture was stirred at room temperature for 0.5 h then cooled at -60 ºC before trifluoromethanesulfonic anhydride (0.07 mL, 0.40 mmol) was added dropwise. The reaction mixture was stirred at -60 ºC for 12 h. The reaction mixture was then cooled to -75 ºC, quenched by addition of aqueous saturated $NaHCO_3$ and then allowed to warm to room temperature. The aqueous phase was extracted twice with dichloromethane. The organic layers were combined, dried, filtered and concentrated in vaccuo. Purification by silica gel column chromatography hexane/ethyl acetate (4:1 to 2:1) gave the coupling product as a white foam, in an approximately 1:1 mixture of diastereomers (202 mg, 40% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.2 Hz, 2 × 2H), 7.25-7.13 (m, 2 × 3H), 6.1-5.85 (m, 2 × 1H), 5.40 (d, *J* = 16.8 Hz, 2 × 1H), 5.35-5.20 (m, 2 × 3H), 5.05 (dd, *J* = 8.8, *J* = 9.6 Hz, 2 × 2H), 4.85-4.65 (m, 2 × 6H), 3.90-3.80 (m, 2 × 1H), 3.75-3.50 (m, 2 × 5H), 3.45 (dd, *J* = 8.0, *J* = 10.0 Hz, 2 × 1H), 3.25 (s, 2 × 3H), 2.08 (s, 2 × 3H), 1.98 (s, 2 × 6H), 1.28 (s, 2 × 3H), 1.24 (s, 2 × 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.6, 169.7, 154.2, 151.3, 134.1, 133.8, 129.7, 126.4, 121.6, 121.5, 119.2, 119.1, 101.1, 100.1, 99.9, 95.7, 76.9, 74.7, 72.2, 71.9, 71.6, 70.2, 68.8, 68.6, 68.3, 67.7, 62.2, 62.1, 56.5. 55.7, 55.4, 49.0, 48.6, 48.2, 48.1, 29.9, 21.0, 20.8, 17.9, 17.8, ESIHRMS calcd for $C_{41}H_{52}Cl_6N_2O_{20}SNa$ $[M + Na]^+$ 1157.0885, found 1157.0890.

2-(Phenyloxycarbonylthioxy)but-3-enyl 3',4',6'-Tri-*O*-acetyl-2,2'-dideoxy-2,2'-bis(2,2,2-trichloroethoxycarbony-lamino)-β-D-gentiobioside 146.

Hydrolysis of the bis(acetal) group was carried out according to general procedure **G**. The title compound **146** was isolated as a white foam from silica gel eluted with hexane/ethyl acetate 1:1 to 1:3 as an approximately 1:1 mixture of diastereomers in 68% yield NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.2, *J* = 8.4 Hz, 2 × 2H), 7.28-7.21 (m, 2 × 1H), 7.16 (dd, *J* = 8.4 Hz, 2 × 2H), 6.00-6.57 (m, 2 × 1H), 5.55-5.45 (d, *J* = 16.8 Hz, 2 × 1H), 5.40 (d, *J* = 16.8 Hz, 2 × 1H), 5.25 (d, *J* = 10.4 Hz, 2 × 1H), 5.25-5.20 (m, 2 × 1H), 5.05 (t, *J* = 9.6 Hz, 2 × 1H), 4.80-4.65 (m, 2 × 4H), 4.55 (bs, 2 × 1H), 4.30-4.05 (m, 2 × 5H), 3.90-3.60 (m, 2 × 6H), 3.60-3.30 (m, 2 × 4H), 2.10 (s, 2 × 3H), 2.03 (s, 2 × 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 171.0, 169.7, 155.3, 154.6, 151.3, 134.1, 133.8, 129.8, 126.5, 121.6, 121.5, 119.4, 119.3, 101.5, 95.5, 77.0, 75.1, 75.0, 74.8, 74.7, 74.3, 72.2, 71.5, 69.3, 68.7, 62.1, 58.3, 58.1, 56.4, 48.8, 48.4, 29.9, 21.1, 20.8, ESIHRMS calcd for $C_{35}H_{42}Cl_6N_2O_{18}SNa$ $[M + Na]^+$ 1043.0182, found 1043.0209.

2-(2-Pyridyldithio)but-3-enyl 2,2'-dideoxy-2,2'-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-gentiobioside 133.

Installation of the disulfide moiety on **146** was undergone under general procedure **A**. The title compound **133** was isolated as a white foam eluting from silica gel in dichloromethane/methanol (20:1) as an approximately 1:1 mixture of diastereomers in 62% yield over two steps: ^1H NMR (400 MHz, CD_3OD) δ 8.36 (d, *J* = 4.8 Hz, 2 × 1H), 7.91 (dd, *J* = 7.2, *J* = 8.4 Hz, 2 × 1H), 7.87-7.79 (m, 2 × 1H), 7.20 dd, *J* = 4.8, *J* = 7.2 Hz, 2 × 1H), 5.90-5.74 (m, 2 × 1H), 5.15 (dd, *J* = 9.6, *J* = 16.8 Hz, 2 × 2H), 4.85-4.64 (m, 2 × 10H), 4.53-4.33 (m, 2 × 2H), 4.21-4.00 (m, 2 × 2H), 3.88 (d, *J* = 12.0 Hz, 2 × 1H), 3.82-3.59 (m, 2 × 4H), 3.50-3.21

(m, 2 × 9H), ^{13}C NMR (100 MHz, CD_3OD) δ 155.8, 149.1, 148.8, 138.1, 134.1, 133.8, 122.2, 121.0, 120.3, 118.6, 118.3, 102.1, 101.8, 101.7, 76.8, 75.8, 74.6, 74.5, 74.4, 71.1, 70.9, 70.0, 69.8, 69.0, 61.6, 58.0, 57.8, 54.4, 54.3, 29.6, ESIHRMS calcd for $C_{27}H_{35}Cl_6N_3O_{13}S_2Na$ $[M + Na]^+$ 905.9637, found 905.9640.

Methyl 3,4,6-Tri-*O*-acetyl-2-(2,2,2-trichloroethoxycarbonyl-amino)-2-deoxy-β-D-glucopyranoside 147.

The title compound **147** was prepared according general procedure **F** and isolated in 94% yield as a white solid eluted from silica gel with hexane/ethyl acetate (2:1): mp 115 ºC; $[\alpha]^{RT}{}_D$ + 12.5 (*c* 1.0, $CDCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (dd, *J* = 9.2, *J* = 10.4 Hz, 1H), 5.20 (bs, 1H), 5.07 (dd, *J* = 8.8, *J* = 10.0 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 4.65 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 7.6 Hz, 1H), 4.28 (dd, *J* = 4, *J* = 4.8 Hz, 1H), 4.15 (d, *J* = 10.0 Hz, 1H), 3.72 (d, J = 7.2 Hz, 1H), 3.64 (ddd, *J*= 8.8, *J* = 17,6 Hz, 1H), 3.52 (s, 3H), 2.03 (s, 6H), 2.09 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.7, 154.3, 119.2, 102.0, 74.7, 72.0, 68.9, 62.2, 57.4, 56.4, 55.1, 21.0, 20.8, ESIHRMS calcd for $C_{16}H_{22}Cl_3NO_{10}Na$ $[M + Na]^+$ 516.0207, found 516.0211.

Methyl 3,4-*O*-(2,3-dimethoxy-butane-2,3-diyl)-2-(2,2,2-trichloroethoxycarbonyl-amino)-2-deoxy-β-D-glucopyranoside 137.

Compound **147** (600 mg, 1.66 mmol) was dissolved in MeOH (8.3 mL) at room temperature and a catalytic amount of 25% NaOMe in MeOH (0.16 mmol) was added. The resulting mixture was stirred for 1h before the pH of the solution was adjusted to 7 by addition of Amberlyst IR 120 resin. The resulting mixture was filtered and concentrated and dried under vacuo to give compound **148**, which

was treated according to general procedure **B** and eluted from silica gel with hexane/ethyl acetate (1:1) in 72% yield as a white solid: mp 105 ºC; $[\alpha]^{RT}_{D}$ + 123.0 (*c* 1.0, $CDCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 4.72 (dd, *J* = 12.4, *J* = 18 Hz, 3H), 4.10 (dd, *J* = 7.2, *J* = 9.2 Hz, 1H), 3.92-3.84 (m, 1H), 3.80-3.74 (m,1H), 3.69 (t, *J* = 10.0 Hz, 1H), 3.58-3.53 (m, 1H), 3.50 (s, 3H), 3.40-3.28 (m, 1H), 3.25 (s, 3H), 3.21 (s, 3H), 2.01 (dd, *J* = 4.8, *J* = 8.0 Hz, 1H), 1.28 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.2, 119.1, 102.2, 100.2, 99.8, 74.6, 74.1, 68.3, 67.2, 61.4, 57.2, 56.0, 48.2, 48.1, 17.9, 17.8, ESIHRMS calcd for $C_{16}H_{26}Cl_3NO_9Na$ $[M + Na]^+$ 504.0571, found 504.0572.

Phenyl 2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-1-thio-6-*O*-p-toluenesulfonyl-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranoside 136.

The title compound **136** was prepared following general procedure **C**, eluted from silica gel with hexane/ethyl acetate (3:1) and isolated in a quantitatif yield as a white solid: mp 144 ºC; $[\alpha]^{RT}_{D}$ + 84.2 (*c* 1.0, $CDCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.34-7.20 (m, 5H), 5.03 (dd, *J* = 6.4, *J* = 10.0 Hz, 2H), 4.73 (s, 2H), 4.30 (d, *J* = 10.8 Hz, 1H), 4.23 (dd, *J* = 4.0 Hz, *J* = 10.8 Hz, 1H), 4.07 (dd, *J* = 10.0, *J* = 11.2 Hz, 1H), 3.67 (dd, *J* = 2.4, *J* = 3.2 Hz, 1H), 3.59 (t, *J* = 9.6 Hz, 1H), 3.31-3.23 (m, 1H), 3.29 (s, 3H), 3.18 (s, 3H), 2.40 (s, 3H), 1.25 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 133.3, 130.1, 129.2, 128.5, 128.2, 100.4, 100.0, 85.6, 77.6, 75.4, 74.6, 69.7, 67.7, 66.5, 54.3, 48.5, 48.2, 21.9, 17.9, 17.7, ESIHRMS calcd for $C_{28}H_{34}Cl_3NO_{10}Na$ $[M + Na]^+$736.0587, found 736.0594.

Methyl 2,2'-dideoxy-3,4;3',4'-di-*O*-(2,3-dimethoxy-butan-2,3-diyl)-2,2'-bis(2,2,2-trichloroethoxycarbonyl-amino)-6-*O*-*p*-toluenesulfonyl-β-D-gentiobioside 149.

The title compound **149** was prepared according to general procedure **F** and isolated as a white foam eluted from silica gel with hexane/ethyl acetate (5:1 to 3:1) in 89% yield: mp, $[\alpha]^{23}{}_{D}$ = + 72.7 (*c* 1.0, $CDCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.10 (bs, 2H), 4.88 (bs, 1H), 4.80-4.62 (m, 5H), 4.31 (d, *J* = 10.8 Hz, 1H), 4.16 (dd, *J* = 5.6, *J* = 10.8 Hz, 1H), 4.12-3.97 (m, 3H), 3.68 (dd, *J* = 6.4, *J* = 8.8 Hz, 3H), 3.59-3.45 (m, 5H), 3.40-3.12 (m, 14H), 2.45 (s, 3H), 1.28 (s, 6H), 1.25 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 154.1, 145.2, 132.9, 130.1, 128.4, 128.2, 101.9, 101.6, 100.2, 99.8, 95.8, 95.7, 74.8, 74.5, 73.8, 73.6, 72.3, 71.7, 69.7, 69.2, 68.5, 67.7, 67.0, 57.3, 57.2, 56.5, 55.7, 55.6, 48.5, 48.4, 48.2, 48.1, 29.9, 21.9, 18.9, 17.8, ESIHRMS calcd for $C_{38}H_{54}Cl_6N_2O_{19}SNa$ $[M + Na]^+$1107.1070, found 1107.1086.

Methyl 6'-Acetylthio-2,2'-dideoxy-3,4;3',4'-di-*O*-(2,3-dimethoxy-butane-2,3-diyl)-2,2'-bis(2,2,2-trichloroethoxycarbonyl-amino)]-β-D-gentiobioside 150.

The title compound **150** was obtained following general procedure **D** as a light yellow foam by elution from silica gel chromatography with hexane/ethyl acetate (6:1) in 71% yield: $[\alpha]^{RT}{}_{D}$ + 82.3 (*c* 1.0, $CDCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16-5.0 (m, 1H), 4.92-4.83 (m, 1H), 4.78-4.63 (m, 5H), 4.12-3.99 (m, 3H), 3.74-3.65 (m, 2H), 3.64-3.56 (m, 1H), 3.53-3.42 (m, 6H), 3.33 (dd, *J* = 5.2, *J* = 7.2 Hz, 3H), 3.23 (s, 3H), 3.21 (s, 3H), 3.20 (s, 3H), 3.18 (s, 3H), 3.04 (q, *J* = 10.0 Hz, *J* = 18.8 Hz, 1H), 2.33 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$)

δ 195.1, 154.6 154.0, 129.2, 128.8, 101.8, 101.6, 100.1, 100.0, 99.8, 95.8, 77.6, 75.9, 74.8, 74.6, 74.2, 74.1, 72.7, 72.5, 70.1, 68.4, 67.8, 57.6, 57.3, 55.9, 48.5, 48.3, 48.1, 30.7, 30.2, 19.0, 17.9, 17.8, ESIHRMS calcd for $C_{33}H_{50}Cl_6N_2O_{17}SNa$ $[M + Na]^+$1011.0859, found 1011.0869.

Methyl 2,2'-dideoxy-2,2'-bis(2,2,2-trichloroethoxycarbonyl-amino)-6'-acetylthio-β-D-gentiobioside 151.

The title compound **151** was prepared from **150** following general procedure **G** and eluted from silica gel with dichloromethane/methanol (20:1) as a white foam in 68% yield: $[\alpha]^{RT}_D$ – 6.0 (*c* 1.0, $CHCl_3$) NMR (400 MHz, $CDCl_3$) δ 4.84-4.69 (m, 6H), 4.60 (s, 1H), 4.45 (d, *J* = 7.6 Hz, 1H), 4.29 (d, *J* = 8.8 Hz, 1H), 4.11 (d, *J* = 10.4 Hz, 1H), 3.72-3.56 (m, 2H), 3.45-3.29 (m, 7H), 3.21 (dd, *J* = 8.8, *J* = 9.4 Hz, 3H), 2.90 (dd, *J* = 7.2, *J* = 13.6 Hz, 1H), 2.34 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 155.9, 102.4, 102.1, 91.5, 75.6, 75.0, 74.6, 74.4, 74.2, 74.1, 74.0, 72.1, 71.4, 69.5, 48.5, 47.4, 30.8, 29.3, 25.6, 19.8, ESIHRMS calcd for $C_{21}H_{30}Cl_6N_2O_{13}SNa$ $[M + Na]^+$ 782.9497, found 782.9501.

Methyl 6-*S*-[4-*O*-(2,2'-dideoxy-2,2'-(2,2,2-trichloroethoxycarbonylamino)-β-D-gentiobiosyloxy)but-2*E*-enyl]-2,2'-dideoxy-(2,2,2-trichloroethoxycarbonyl-amino-6-thio-α-D-gentiobioside 132.

Methyl 2,2'-dideoxy-2,2'-bis(2,2,2-trichloroethoxycarbonyl-amino)-6'-S-acetyl-β-D-gentiobioside **151** (30 mg, 0.04 mmol) was dissolved in dimethylformamide (0.5 mL) at room temperature and hydrazine acetate (12 mg, 0.13 mmol) was added. The resulting mixture was stirred for 1.25 h and directly transferred to a stirred solution of disaccharide sulfenyl donor **133** (42 mg, 0.05 mmol) in methanol (0.8

mL). The resulting mixture was stirred until TLC showed complete consumption of the free thiol compound (20 h). Triphenyl phosphine (13 mg, 0.05 mmol) was then added and the resulting mixture was stirred at room temperature for an additional 40 h. The resulting mixture was filtered through a patch of celite and silica and concentrated. Purification by silica gel chromatography dichloromethane/methanol (15:1) afforded the desired compound **132** as a white foam eluting from silica gel in dichloromethane/methanol (15:1) and in 54% yield: $[\alpha]^{RT}{}_{D}$ + 72.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 5,85-5.58 (m, 2H), 4.92 (d, *J* = 4.1 Hz, 3H), 4.93-4.86 (m, 12H), 4.85 (d, *J* = 4.0 Hz, 2H), 4.80 (d, *J* = 12.1 Hz, 2H), 4.73 (dd, *J* = 9.7, *J* = 12.2, 3Hz), 4.62 (dd, *J* = 8.9, *J* = 11.3, 2Hz), 4.54-4.37 (m, 2H), 4.36-4.24 (m, 2H), 4.19 (d, *J* = 4.0 Hz, 2H), 4.13-4.01 (m, 1H), 3.89 (d, *J* = 11.3, 1H), 3.77-3.59 (m, 4H), 3.53-3.18 (m, 18H), 2.96 (d, *J* = 13.0 Hz, 1H), 2.63 (dd, *J*= 5.7, *J* = 8.1 Hz, 1H), ^{13}C NMR (100 MHz, CD_3OD) δ 153.8, 153.6, 130.4,128.7, 102.8, 102.5, 100.7, 78.2, 77.7, 76.2, 75.9, 75.8, 75.3, 75.2, 74.9, 72.5, 72.3, 70.7, 70.6, 70.4, 69.2, 69.0, 68.6, 67.5, 67.3, 61.5, 56.3, 33.9, 32.2.

2,3-*O*-Di-benzyl-4,6-*O*-benzylidene -1-allyl-1-deoxy-β-D-mannopyranose 193. Compound **193** was prepared by the general glycosylation procedure **I** and obtained in 57 to 60% yield as a white solid: mp = 80.9 – 90.5 °C, $[\alpha]^{RT}{}_{D}$ - 26.0 (*c* = 1.0 M, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 1.5, 7.5 Hz, 2H), 7.42 – 7.29 (m, 13H), 5.72 – 5.63 (m, 2H), 5.10 -5.02 (m, 3H), 4.93 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 12.5 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.30 – 4.24 (m, 2H), 3.86 (t, *J* = 10.0 Hz, 1) 3.81 (d, *J* = 2.0 Hz, 1H), 3.74 (dd, *J* = 2.5, 9.5 Hz, 1H),

3.46 (t, *J* = 7.0 Hz, 1H), 3.39 (dt, *J* = 5.0, 10.0 Hz, 1H), 2.47 (dt, *J* = 6.5, 14.0 Hz, 1H), 2.26 (dt, *J* = 7.0, 14.0 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.4, 137.7, 134.3, 128.8, 128.5, 128.4, 128.3, 128.2, 127.7, 127.6, 127.5, 126.0, 117.5, 101.3, 80.7, 79.6, 79.5, 76.3, 75.0, 73.1, 72.0, 68.7, 35.5, 29.7, ESIHRMS calcd for $C_{30}H_{32}O_5Na$ $[M + Na]^+$ 495.2147, found 495.2142.

2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-deoxy-1-(2-oxo-2-phenylethyl)-β-D-mannopyranose 196.

Compound **196** was prepared by the general glycosylation procedure **I** and obtained in 76% yield as a colorless oil: $[\alpha]^{RT}_D$ – 10.4 (*c* = 0.75 M, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.0 Hz, 2H), 7.59 – 7.51 (m, 3H), 7.46 - 7.34 (m, 8H), 7.32 – 7.25 (m, 4H), 7.17 – 7.09 (m, 3H), 5.65 (s, 1H), 5.02 (d, *J* = 11.5 Hz, 1H), 4.96 (d, *J* = 12.5 Hz, 1H), 4.81 (d, *J* = 12.5 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.26 (ddt, *J* = 1.5, 6.5, 9.5, 2H), 4.15 (t, *J* = 6.0 Hz, 1H), 4.05 (d, *J* = 1.5 Hz, 1H), 3.88 (dd, *J* = 3.0, 9.5 Hz, 1H), 3.83 (t, *J* = 10.0 Hz, 1H), 3.48 (dt, *J* = 5.0, 10.0 Hz, 1H), 3.24 (dd, *J* = 5.5, 17.5 Hz, 1H), 3.13 (dd, *J* =7.5, 17.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 138.5, 138.0, 137.7, 136.5, 133.3, 120.9, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 126.1, 101.4, 80.4, 79.4, 75.9, 75.6, 75.0, 73.3, 71.8, 68.6, 39.6, ESIHRMS calcd for $C_{35}H_{34}O_6Na$ $[M + Na]^+$ 573.2252, found 573.2255.

2,3-*O*-Di-benzyl-4,6-*O*-benzylidene -1-allyl-1-deoxy-α-D-glucopyranose 197.

Compound **197** was prepared by the general glycosylation procedure **I** and obtained in 56 to 58% yield as a white solid: mp = 90.8 – 91.2 °C, $d[\alpha]^{RT}_D$– 0.9 (*c* = 0.75 M, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 1.5, 8.0 Hz, 2H),

7.41 – 7.27 (m, 13H), 5.81 – 5.73 (m, 1H), 5.13 (dd, *J* = 1.5, 17.0 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.92 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.26 – 4.21 (m, 1H), 4.08 (dd, *J* = 5.5, 8.0 Hz, 1H), 3.90 – 3.86 (m, 1H), 3.76 (dd, *J* = 5.5, 8.5 Hz, 1H), 3.70 – 3.64 (m, 3H), 2.54 (t, *J* = 7.5 Hz, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.1, 137.4, 134.3, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 126.0, 117.2, 101.1, 82.7, 79.4, 78.7, 74.9, 74.8, 73.6, 69.4, 63.4, 30.7, ESIHRMS calcd for $C_{30}H_{32}O_5Na$ $[M + Na]^+$ 495.2147, found 495.2138

2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-(2-oxo-2-phenylethyl)-α-D-glucopyranose 198 and [(1R)-2-Oxo-1,2-diphenyl-1-(phenylthiomethyl)ethyl] 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 199.

Compounds **198** and **199** were obtained by the general glycosylation procedure **I**. Purification by column chromatography eluting with hexanes/ethyl acetate 4:1 gave a 1:1 mixture of *C*- and *O*-glucosides in 80% yield.

198: isolated as a colorless oil, $[\alpha]^{RT}_D$ + 17.6 (*c* = 0.75 M, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$)δ 7.90 (d, *J* = 7.5 Hz, 2H), 7.56 (dd, *J* = 7.0, 8.0 Hz, 1H), 7.51 – 7.43 (m, 4H), 7.40 – 7.35 (m, 5H), 7.34 – 7.26 (m, 8H), 5.57 (s, 1H), 4.96 – 4.93 (m, 2H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 17.6 Hz, 1H), 4.21 (dd, *J* = 3.0, 9.5 Hz, 1H), 3.91 – 3.83 (m, 2H), 3.72 – 3.64 (m, 3H), 3.50 – 3.46 (m, 1H), 3.29 (dd, *J* = 7.5, 16 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 138.5, 137.7, 137.3, 137.0, 133.2, 128.9, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 126.0, 101.2, 82.4, 78.8, 78.7, 74.8, 73.8,

72.0, 69.3, 64.7, 36.0, ESIHRMS calcd for $C_{35}H_{34}O_6Na$ [M + Na]$^+$ 573.2253, found 573.2251.

199: isolated as a colorless oil, $[\alpha]^{RT}_D$ + 28.0 (*c* = 0.25 M, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$)δ 7.87 (d, *J* = 7.0 Hz, 2H), 7.57 – 7.15 (m, 27H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.46 (s, 1H), 5.08 (d, *J* = 3.5 Hz, 1H), 4.84 (d, *J* = 11.5, 1H), 4.74 (d, *J* = 11.0 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.18 – 4.11 (m, 2H), 4.01 (d, *J* = 8.0 Hz, 1H), 3.98 (d, *J* = 12.0 Hz, 1H), 3.88 – 3.82 (m, 2H), 3.70 (d, *J* = 14.0 Hz, 1H), 3.50 – 3.43 (m, 2H), 3.67 (dd, J = 3.5, 9.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.8, 141.3, 138.9, 138.2, 137.6, 137.5, 137.1, 133.0, 129.5, 128.9, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.2, 126.1, 126.0, 101.2, 93.9, 82.7, 82.5, 79.6, 78.4, 75.2, 73.8, 68.9, 63.2, 45.9, 43.1, 29.7, ESIHRMS calcd for $C_{49}H_{46}O_7SNa$ [M + Na]$^+$ 801.2862, found 801.2852.

2-*O*-Benzyl-4,6-*O*-benzylidene-1-allyl-1,3-dideoxy- β-D-mannopyranose 200. Compound **200** was prepared from **192** by the general glycosylation procedure **I** and obtained in 52 to 59% yield as a colorless oil: $[\alpha]^{RT}_D$ + 1.7 (*c* = 0.75 M, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 2.0, 8.0 Hz, 2H), 7.40 - 7.28 (m, 8H), 5.76 – 5.67 (m, 1H), 5.57 (s, 1H), 5.05 (ddd, *J* = 1.5, 10.0, 17.0 Hz, 2H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.27 (dd, *J* = 5.0, 10.5 Hz, 1H), 3.98 (m, 1H), 3.81 (t, *J* = 10.5 Hz, 1H), 3.65 (d, *J* = 1.0 Hz, 1H), 3.53 (dt, *J* = 1.5, 7.0 Hz, 1H), 3.44 (dt, *J* = 5.0, 10.0 Hz, 1H), 2.54 – 2.45 (m, 2H), 2.35 (dt, *J* = 7.5, 14.5 Hz, 1H), 1.67 (dt, *J* = 3.0, 13.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 137.6, 134.4, 129.0, 128.4, 128.3, 128.1, 127.8, 126.1,117.3, 101.9, 80.1,

74.5, 74.1, 73.8, 71.2, 69.2, 35.5, 32.0, 29.7, ESIHRMS calcd for $C_{23}H_{26}O_4Na$ [M + Na]$^+$ 389.1731, found 389.1733.

_S_-Phenyl 2-_O_-Benzyl-4,6-_O_-benzylidene-3-deoxy-α-D-thio-mannopyranoside 192-α.

192-α: isolated as a colorless oil, [α]$^{RT}_D$ – 34.1 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, J = 1.5, 8.0 Hz, 2H), 7.38 (dd, J = 1.5, 8.0 Hz, 2H), 7.32 - 7.20 (m, 11 H), 5.53 (s, 1H), 5.49 (s, 1H), 4.54 (dd, J = 12.0, J = 17.5 Hz, 2H), 4.26 (dt, J = 5.0, J = 10.0 Hz, 1H), 4.13 (dd, J = 5.0, J = 10.0 Hz, 1H), 4.07 – 4.02 (m, 1H), 3.93 (brs, 1H), 3.77 (t, J = 10.5 Hz, 1H), 2.82 – 2.38 (m, 1H), 1.96 (dt, J = 2.0, J = 13.0 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 137.2, 134.1, 131.5, 129.1, 128.5, 128.3, 128.0, 127.7, 127.5, 126.2, 102.3, 86.2, 76.5, 74.3, 71.2, 69.0, 69.1, 30.7, ESIHRMS calcd for $C_{26}H_{26}O_4SNa$ [M + Na]$^+$ 457.1450, found 457.1433.

2-_O_-Benzyl-4,6-_O_-benzylidene-1,3-dideoxy-1-(2-oxo-2-phenylethyl)- β-D-mannopyranose 201.

Compound **201** was prepared from compound **192** by the general glycosylation procedure **I** and obtained in 75% yield in a mixture α/β > 1:20. The β anomer was isolated as a colorless oil: [α]$^{RT}_D$ - 21.7 (*c* = 0.75 M, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* 1.5, 8.5 Hz, 2H), 7.58 (t, *J* = 7.0 Hz, 1H), 7.50 (dd, *J* = 2.0, 8.0 Hz, 2H), 7.39 – 7.34 (m, 4H), 7.26 – 7.24 (m, 1H), 7.22 – 7.18 (m, 3H), 5.59 (s, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.26 (dd, *J* = 3.0, 4.5 Hz, 2H), 3.98 (ddd, *J* = 4.5, 9.5, 13.5 Hz, 1H), 3.85 (t, *J* = 3.0 Hz, 1H), 3.78 (t, *J* = 10.5 Hz, 1H), 3.53 (ddd, *J* =5.0, 9.0, 10.5 Hz, 1H), 3.30 (d, *J* = 7.0 Hz,

2H), 2.53 (dt, *J* = 3.5, 14.0 Hz, 1H), 1.84 – 1.78 (m, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 137.6, 136.8, 133.3, 129.0, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 126.1, 102,0, 76.2, 74.4, 74.0, 73.7, 71.2, 69.1, 39.6, 31.8, 29.7, ESIHRMS calcd for $C_{28}H_{28}O_5Na$ $[M + Na]^+$ 467.1834, found 467.1830.

2-*O*-Benzyl-4,6-*O*-benzylidene-1-allyl-1,3-dideoxy-α-D-glucopyranose 202.

Compound **202** was prepared from compound **190** by the general glycosylation procedure and obtained in 60 to 63% yield as a white solid: mp = 101.2 – 101.8 °C, $[\alpha]^{RT}_D$ + 30.2 (*c* = 0.75 M, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 2.0, 8.0 Hz, 2H), 7.40 – 7.30 (m, 8H), 5.89 -5.81 (m, 1H), 5.52 (s, 1H), 5.17 (dd, *J* = 9.0, 10.0 Hz, 2H), 4.58 (q, *J* = 12.0 Hz, 2H), 4.22 (dd, *J* = 4.3, 9.9 Hz, 1H), 4.12 (ddd, *J* = 3.8, 5.5, 7.3 Hz, 1H), 3.85 (ddd, *J* = 4.7, 5.5, 11.6 Hz, 1H), 3.63 (dd, *J* = 9.5, 10.5 Hz, 1H), 3.58 – 3.49 (m, 2H), 2.71 – 2.64 (m, 1H), 2.47 – 2.43 (m, 1H), 2.37 (dt, *J* = 4.3, 11.7 Hz, 1H), 1.85 (q, *J* = 1.6 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$)δ 138.0, 137.4, 134.5, 129.1, 128.5, 128.4, 127.8, 127.5, 126.1, 117.2, 101.7, 74.6, 74.0, 71.0, 69.7, 64.9, 30.8, 29.7, 28.9; ESIHRMS calcd for $C_{23}H_{26}O_4Na$ $[M + Na]^+$ 389.1729, found 389.1725.

2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-1-(2-oxo-2-phenylethyl)-α-D-glucopyranose 203 and [(1R)-2-Oxo-1,2-diphenyl-1-(phenylthiomethyl)ethyl] 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside 204.

Compounds **203** and **204** were obtained by the general glycosylation procedure I from compound **190**. Purification by column chromatography eluting with hexanes/ethyl acetate 4:1 gave a 1.8:2 mixture of *C*- and *O*-glucosides in 71% yield.

203: isolated as a white solid, mp = 90.8 – 91.2 °C $[\alpha]^{RT}_{D}$ + 32.4 (*c* = 0.5 M, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.48 – 7.45 (m, 4), 7.39 – 7.27 (m, 8H), 5.50 (s, 1H), 4.98 – 4.94 (m, 1H), 4.55 (s, 2H), 4.17 (, 1H), 3.89 (dt, *J* = 5.0, *J* = 12.5 Hz, 1H), 3.63 – 3.50 (m, 3H), 4.70 (d, *J* = 4.5 Hz, 1H), 3.37 (dd, *J* = 8.0, 16.5, 1H), 2.41 (dt, *J* = 4.0, 12.0, 1H), 1.85 (q, *J* = 12.0, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 137.7, 137.3, 137.2, 133.1, 129.1, 128.6, 128.5, 128.4, 128.2, 127.8, 127.6, 126.1, 101.7, 73.3, 71.6, 71.2, 69.7, 66.2, 34.5, 31.4, 29.7, ESIHRMS calcd for $C_{28}H_{28}O_5Na$ $[M + Na]^+$ 467.1834, found 467,1831.

204: isolated as a colorless oil; $[\alpha]^{RT}_{D}$ + 57.6 (*c* = 0.5 M, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)δ 7.86 (d, *J* = 7.5 Hz, 2H), 7.58 – 7.53 (m, 3H), 7.48 (dd, *J* = 2.0, 8.0 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.39 – 7.18 (m, 15H), 7.09 (t, *J* = 7.5 Hz, 1H), 5.39 (s, 1H), 5.05 (d, *J* = 3.5 Hz, 1H), 4.04 (s, 2H), 4.17 (d, *J* = 18.5 Hz, 1H), 4.07 – 4.00 (m, 3H), 3.76 (dd, *J* = 5.0, 15.0 Hz, 1H), 3.72 (d, *J* = 13.5 Hz, 1H), 3.43 – 3.34 (m, 3H), 2.19 – 2.16 (m, 1H), 1.97 (q, *J* = 12.0 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.8, 141.7, 138.0, 137.5, 137.4, 137.0, 133.0, 129.6, 129.1, 128.8, 128.6, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.4, 127.2, 126.3, 125.9, 101.8, 92.5, 82.2, 76.9, 74.6, 71.0, 69.1, 64.8, 46.1, 43.1, 29.8, ESIHRMS calcd for $C_{42}H_{40}O_6SNa$ $[M + Na]^+$ 695.2443, found 695.2449.

Methyl 4-*O*-Benzyl-2,3-di-*O*-methyl-α-D-galactopyranoside 250.

To a vigorously stirred solution of compound **249** (4g, 12.9 mmol) in dichloromethane (116 mL) was added at room temperature BH_3.THF (64 mL, 64.5 mmol). The resulting mixture was stirred for 0.75 h then scandium triflate

$Sc(OTf)_3$ (950 mg, 1.9 mmol) was added portion-wise. The mixture was stirred for 5 h then quenched by sequential additions of methanol and triethylamine and concentrated in vaccuo. The resulting residue was purified by silica gel chromatography (eluting with hexanes/ethyl acetate 1:2) to give the desired primary alcohol **250** as a colorless oil (3.87 g, 96%): $[\alpha]^{RT}_D$ + 108.8 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.30 (m, 5H), 4.94 (d, *J* = 12.0 Hz, 1H), 4.91 (d, *J* = 4.0 Hz, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 3.91 (d, *J* = 2.8 Hz, 1H), 3.78-3.70 (m, 3H), 3.58 (dd, *J* = 2.4, *J* = 3.2 Hz, 1H), 3.55 - 3.49 (m, 7H), 3.40 (s, 3H), 1.80 (dd, *J* = 3.2, 7.2 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.8, 128.7, 128.3, 98.2, 81.1, 78.2, 74.7, 73.8, 70.5, 62.6, 59.1, 58.8, 55.6, ESIHRMS calcd for $C_{16}H_{24}O_6Na$ $[M + Na]^+$ 335.1471, found 335.1461.

(6-R) Methyl 6-*C*-Allyl-4-*O*-benzyl-2,3-di-*O*-methyl-α-D-galactopyranoside 251R and (6-S) Methyl 6-*C*-Allyl-4-*O*-benzyl-2,3-di-*O*-methyl-α-D-galactopyranoside 251S.

To a stirred solution of oxalyl chloride (6.0 mL, 69.1 mmol) in dichloromethane (220 mL) was added at – 78 ºC dimethyl sulfoxide (9.9 mL, 0.13 mol). The resulting mixture was stirred for 0.75 h before a solution of **250** (5.4 g, 17.2 mmol) in dichloromethane (104 mL) was added. The resulting mixture was stirred for 2.5 h then triethylamine (100 mL, 0.34 mol) was added and the mixture stirred for an additional hour at – 78 ºC before it was allowed to warm up to 0 ºC and then stirred for 1h. The temperature was allowed to warm to room temperature and the mixture was stirred for one more hour. The resulting mixture was washed once with a 1 M solution of HCl. The aqueous phase was extracted twice with

dichloromethane. The combined organic layers were dried, filtered and concentrated in vaccuo. The crude aldehyde (5.3 g, 17.3 mmol) was dissolved in tetrahydrofuran (76 mL). The resulting mixture was cooled to – 30 ºC then allylmagnesium bromide 1 M solution in diethyl ether (68 mL) was slowly added. The resulting mixture was stirred for 5 h then poured into a 1 M solution of HCl. The aqueous phase was extracted twice with dichloromethane. The combined organic layers were dried, filtered and concentrated. Purification by silica gel chromatography (eluting with hexanes/ethyl acetate 2:3) gave the desired compounds **251R** (2.8 g) and **251S** (1.5 g) in a 2:1 ratio as a colorless oil and a white solid respectively.

251R: $[\alpha]^{RT}_{D}$ + 190 (*c* =1.5 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 6.4 Hz, 2H), 7.37 - 7.26 (m, 3H), 5.87 - 5.76 (m, 1H), 5.12 (dd, *J* = 7.2, 10.8 Hz, 2H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.89 (d, *J* = 4.0 Hz, 1H), 4.68 (d, *J* = 12.4 Hz, 1H), 4.16 (d, *J* = 2.4 Hz, 1H), 3.82 - 3.75 (m, 2H), 3.60 - 3.47 (m, 8H), 3.43 - 3.39 (m, 4H), 2.58 - 2.53 (m, 1H), 2.12 - 2.04 (m, 1H), 1.54 (d, *J* = 4.8 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 134.7, 128.7, 128.5, 128.2, 118.7, 98.3, 81.1, 78.1, 74.7, 72.7, 72.4, 68.4, 59.1, 58.6, 55.6, 38.6, ESIHRMS calcd for $C_{19}H_{28}O_6Na$ $[M + Na]^+$ 375.1784, found 375.1782.

251S: mp 83 – 85 °C, $[\alpha]^{RT}_{D}$ + 39.4 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.25 (m, 5H), 5.85 - 5.74 (m, 1H), 5.08 - 5.02 (m, 3H), 4.96 (dd, *J* = 2.4, 3.2 Hz, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 3.97 (s, 1H), 3.89 (dd, *J* = 4.2, 10.4 Hz, 1H), 3.80 - 3.76 (m, 1H), 3.61 - 3.48 (m, 9H), 3.44 - 3.40 (m, 3H), 3.23 (s, 1H), 2.17 (t, *J* = 6.4 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 134.7, 128.8,

128.6, 128.2, 117.6, 98.3, 81.4, 78.1, 75.8, 74.7, 71.5, 71.2, 59.1, 59.0, 55.7, 37.5, ESIHRMS calcd for $C_{19}H_{28}O_6Na$ $[M + Na]^+$ 375.1784, found 375.1778.

(6-R) Methyl 6-*C*-Allyl-4-*O*-benzyl-2,3,6-tri-*O*-methyl-α-D-galactopyranoside 252R and (6-S) Methyl 6-*C*-Allyl-4-*O*-benzyl-2,3,6-tri-*O*-methyl-α-D-galactopyranoside 252S.

To a stirred solution of compound **251** (3 g, 8.5 mmol) in dimethylformamide (21 mL) was added portion-wise at 0 ºC NaH (430 mg, 12.8 mmol). The resulting mixture was stirred for 0.5 h at 0 ºC before iodomethane (2.1 mL, 34.1 mmol) was added dropwise. The temperature was allowed to warm up to room temperature then stirred for 5 h and quenched by addition of methanol. The mixture was concentrated and purified by silica gel column chromatography (eluting with hexanes/ethyl acetate 1:2) to give compounds **252R** (2.9 g, 92%) as a colorless oil and **252S** (2.7 g, 87%) as a white solid.

252R: $[\alpha]^{RT}_{D}$ + 124.4 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 6.4 Hz, 1H), 5.94 - 5.82 (m, 1H), 5.12 (dd, *J* = 10.4, 17.2 Hz, 2H), 5.00 (d, *J* = 11.6 Hz, 1H), 4.87 (d, *J* = 4.0 Hz, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.15 (s, 1H), 3.76 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.59 - 3.54 (m, 3H), 3.54 - 3.46 (m, 6H), 3.41 (s, 3H), 3.28 (s, 3H), 2.66 - 2.59 (m, 1H), 2.39 - 2.29 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 134.0, 128.5, 128.2, 127.7, 117.8, 98.5, 81.2, 77.9, 77.2, 74.8, 73.4, 70.7, 59.0, 58.3, 57.0, 55.9, 33.4, ESIHRMS calcd for $C_{20}H_{30}O_6Na$ $[M + Na]^+$ 389.1940, found 389.1949.

252S: mp 86 – 88 °C, $[\alpha]^{RT}_{D}$ + 157.2 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.32 (m, 4H), 7.30 - 7.26 (m, 1H), 5.84 - 5.74 (m, 1H), 5.06 - 5.00

(m, 2H), 4.94 (dd, *J* = 3.2, 8.8 Hz, 2H), 4.60 (d, *J* = 11.2 Hz, 1H), 3.89 (d, *J* = 2.4 Hz, 1H), 3.78 (dd, *J* = 3.2, 9.2 Hz, 1H), 3.59 - 3.50 (m, 8H), 3.49 - 3.44 (m, 4H), 3.42 (s, 3H), 2.19 - 2.12 (m 1H), 1.94 - 1.87 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 134.5, 128.6, 128.4, 128.0, 117.3, 97.6, 81.9, 80.2, 78.3, 74.4, 74.1, 74.0, 60.1, 59.0, 58.9, 55.2, 35.2, ESIHRMS calcd for $C_{20}H_{30}O_6Na$ $[M + Na]^+$ 389.1940, found 389.1942.

Methyl 4-*O*-Benzyl-7-deoxy-2,3-di-*O*-methyl-α-D-glycero-D-galacto-octopyranoside 253R and 254S.

Ozone was purged at – 70 ºC to a stirred solution of compound **252** (2 g, 5.5 mmol) in a 7:1 mixture dichloromethane/methanol (260 mL) until the color of the solution became persistent blue. O_2 was purged for a few minutes then $NaBH_4$ (900 mg, 24 mmol) was added under Argon and the resulting mixture allowed to warm up to room temperature. The mixture was stirred for 10 h then concentrated in vacuuo. The residue was taken up in ethyl acetate and washed once with HCl 1 M. The aqueous phase was extracted twice with dichloromethane. The combined organic layers were dried, filtered and concentrated. Purification by silica gel chromatography (eluting with hexanes/ethyl acetate 1:2) gave the desired compounds **253R** (1.47 g, 73% over two steps) and **253S** (1.35 g, 68% over two steps) as a white solid and a colorless oil respectively.

253R: mp 82 – 84 °C, $[\alpha]^{RT}_{D}$ + 100.1 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.35 - 7.30 (m, 2H), 7.27 - 7.23 (m, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 4.87 (d, *J* = 3.2 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.14 (s,

1H), 3.85 - 3.69 (m, 3H), 3.68 - 3.55 (m, 3H), 3.54 - 3.44 (m, 6H), 3.41 (s, 3H), 3.29 (s, 3H), 2.35 (brs, 1H), 2.10 - 2.03 (m, 1H), 1.86 - 1.77 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 128.7, 128.5, 128.1, 127.7, 98.5, 81.3, 78.0, 77.6, 74.7, 73.5, 71.2, 60.1, 59.1, 58.5, 57.6, 56.1, 32.1, ESIHRMS calcd for $C_{19}H_{30}O_7Na$ $[M + Na]^+$ 393.1889, found 393.1899.

253S: $[\alpha]^{RT}_D$ + 68.4 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.25 (m, 5H), 4.98 (d, *J* = 12.4 Hz, 1H), 4.91 (d, *J* = 3.2 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 3.83 (brs, 1H), 3.76 (dd, *J* = 3.2, 10.0 Hz, 1H), 3.64 - 3.39 (m, 15H), 3.40 (s, 3H), 1.43 - 1.33 (m, 1H), 1.32 - 1.21 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 130.1, 128.7, 128.6, 128.1, 97.7, 81.7, 80.7, 78.3, 74.8, 74.3, 73.8, 60.8, 60.7, 59.0, 58.9, 55.3, 33.0, ESIHRMS calcd for $C_{19}H_{30}O_7Na$ $[M + Na]^+$ 393.1889, found 393.1883.

Methyl 4-*O*-Benzyl-7-deoxy-2,3-di-*O*-methyl-8-*O*-*p*-toluenesulfonyl-α-D-glycero-D-galacto-octopyranoside 253-1-R.

To a stirred solution of compound **253R** (1.4 g, 3.8 mmol) in acetonitrile (38 mL) was added at room temperature tosyl chloride (1.45 g, 7.6 mmol) and tetramethylethylenediamine (1.20 mL, 7.6 mmol) respectively. The resulting mixture was stirred for 2.5 h then, poured into ice and extracted twice with dichloromethane. The combined organic layers were dried, filtered and concentrated in vaccuo. The residue was purified by silica gel chromatography hexanes/ethyl acetate (1:1) and gave **253-1-R** (1.82 g, 92%) as a colorless oil: $[\alpha]^{RT}_D$ + 65.9 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.38 - 7.26 (m, 6H), 4.99 (d, *J* = 11.6 Hz, 1H), 4.78 (d. *J* = 4.0 Hz, 1H),

4.53 (d, *J* = 10.8 Hz, 1H), 4.20 - 4.13 (m, 1H), 4.12 - 4.04 (m, 2H), 3.71 (dd, *J* = 3.2, 9.6 Hz, 1H), 3.55 - 3.50 (m, 8H), 3.44 (d, *J* = 8.8 Hz, 1H), 3.28 (s, 3H), 3.18 (s, 3H), 2.42 (s, 3H), 2.18 - 2.09 (m, 1H), 1.95 - 1.86 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 138.9, 133.3, 130.0, 128.6, 128.2, 127.8, 98.4, 81.3, 77.9, 75.2, 74.6, 73.5, 71.4, 67.3, 59.1, 58.5, 57.6, 55.8, 29.7, 21.7, ESIHRMS calcd for $C_{26}H_{36}O_9SNa$ $[M + Na]^+$ 547.1978, found 547.1973.

Methyl 4-*O*-Benzyl-7-deoxy-2,3-di-*O*-methyl-8-*O*-*p*-toluenesulfonyl-β-L-glycero-D-galacto-octopyranoside 253-1-S.

Compound **253-1-S** was obtained under the same conditions as compound **253-1-R**, as a white solid (92%): mp 87-89 °C, $[\alpha]^{RT}{}_D$ + 59.9 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.38 - 7.25 (m, 6H), 4.98 (d, *J* = 11.2 Hz, 1H), 4.88 (d, *J* = 4.0 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.09 - 4.03 (m, 2H), 3.84 (d, *J* = 1.6 Hz, 1H), 3.75 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.55 - 3.45 (m, 9H), 3.37 (s, 3H), 3.34 (s, 3H), 2.41 (s, 3H), 1.71 - 1.63 (m, 1H), 1.51 - 1.42 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 138.4, 133.2, 130.1, 128.8, 128.7, 128.2, 128.1, 97.7, 81.7, 78.2, 77.6, 74.5, 74.5, 73.8, 67.0, 60.7, 59.1, 58.9, 55.2, 30.5, 21.9, ESIHRMS calcd for $C_{26}H_{36}O_9SNa$ $[M + Na]^+$ 547.1978, found 547.1982.

Methyl 7-deoxy-2,3-di-*O*-methyl-8-*O*-p-toluenesulfonyl-α-D-glycero-D-galacto-octopyranoside 253-2-R.

To a solution of tosylate **253-1-R** (1.6 g, 3.5 mmol) in a 10:1 mixture methanol/ethyl acetate (26 mL) was added palladium on charcoal (10%, 650 mg). The hydrogenolysis was performed using a hydrogenation apparatus under

40 psi H_2 and the reaction was run for 4 h. The resulting mixture was filtered through celite and concentrated in vaccuo. Purification by silica gel chromatography hexanes/ethyl acetate (1:2) afforded compounds **253-2-R** (1.15 mg, 86%) as a colorless oil: $[\alpha]^{RT}_{D}$ + 81.0 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.24 - 4.12 (m, 3H), 3.62 - 3.52 (m, 2H), 3.51 - 3.41 (m, 8H), 3.39 (s, 3H), 3.33 (s, 3H), 2.41 (s, 4H), 2.21 - 2.12 (m, 1H), 1.81 - 1.73 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 133.2, 130.0, 128.2, 98.1, 79.5, 77.4, 75.8, 70.8, 67.3, 65.7, 59.6, 59.2, 58.0, 55.7, 31.5, 21.9, ESIHRMS calcd for $C_{19}H_{30}O_9SNa$ $[M + Na]^+$ 457.1508, found 457.1497.

Methyl 7-deoxy-2,3-di-*O*-methyl-8-*O*-p-toluenesulfonyl-β-L-glycero-D-galacto-octopyranoside 253-2-S.

Compound **253-2-S** was obtained under the same conditions as compound **253-2-R**, as a white solid (78%): mp 85 – 87 °C, $[\alpha]^{RT}_{D}$ + 68.7 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 - 7.78 (m, 2H), 7.33 (d, *J* = 6.4 Hz, 2H), 4.87 (d, *J* = 3.2 Hz, 1H), 4.22 - 4.14 (m, 2H), 3.61 - 3.52 (m, 3H), 3.50 - 3.43 (m, 7H), 3.42 - 2.35 (m, 7H), 2.58 (brs, 1H), 2.43 (s, 3H), 2.12 - 2.02 (m, 1H), 1.85 - 1.76 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 133.2, 130.1, 128.1, 97.8, 79.4, 77.8, 77.6, 72.3, 67.1, 67.0, 60.0, 59.2, 58.0, 55.5, 30.5, 21.9, ESIHRMS calcd for $C_{19}H_{30}O_9SNa$ $[M + Na]^+$ 457.1508, found 457.1515.

Methyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-α-D-glycero-D-galacto-octopyranoside 254R.

To a stirred solution of alcohol **253-2-R** (1.1 g, 2.5 mmol) in dimethylformamide (25 mL) at room temperature were added NaH (102 mg, 3.0 mmol) and NaI (304 mg, 2.0 mmol) respectively. The resulting mixture was stirred for 1 h, quenched by addition of methanol and concentrated in vacuo. Purification by silica gel chromatography hexanes/ethyl acetate (1:1) afforded compound **254R** (582 mg, 88%) as a white solid: mp 58 – 60 °C, $[\alpha]^{RT}_{D}$ + 198.0 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (d, *J* = 3.0 Hz, 1H), 4.14 (dd, *J* = 4.5, 12.0 Hz, 1H), 4.05 (d, *J* = 3.0 Hz, 1H), 3.71 - 3.67 (m, 2H), 3.55 (dd, *J* = 3.5, *J* = 10.5 Hz, 1H), 3.52 (s, 1H), 3.50 (s, 3H), 3.48 (s, 3H), 3.44 - 3.38 (m, 4H), 3.35 (dt, *J* = 3.8, 11.7 Hz, 1H), 1.98 (dq, *J* = 4.7, 12.5 Hz, 1H), 1.75 (dd, *J* = 4.5, 12.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.8, 78.7, 78.0, 74.2, 66.4, 64.3, 59.7, 58.4, 56.0, 55.8, 29.9, 26.8, ESIHRMS calcd for $C_{12}H_{22}O_6Na$ $[M + Na]^+$ 285.1314, found 282.1313.

Methyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-β-L-glycero-D-galacto-octopyranoside 254S.

Compound **254S** was obtained under the same conditions as compound **254R**, as a colorless oil (90%): $[\alpha]^{RT}_{D}$ + 225.4 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (d, 4.0 Hz, 1H), 3.98 (d, *J* = 3.0 Hz, 1H), 3.82 (dd, *J* = 5.5, 11.5 Hz, 1H), 3.70 - 3.63 (m, 2H), 3.59 (d, *J* = 3.0 Hz, 1H), 3.50 - 3.49 (m, 4H), 3.45 (s, 4H), 3.40 (s, 3H), 3.38 (s, 3H), 1.98 (m, 1H), 1.63 (d, *J* = 11.2 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.7, 78.5, 77.8, 74.4, 70.0, 64.9, 62.6, 59.6, 57.8, 56.9, 55.6, 25.3, ESIHRMS calcd for $C_{12}H_{22}O_6Na$ $[M + Na]^+$ 285.1314, found 282.1320.

2,4-Dinitrophenyl 2,3,4,6-Tetra-*O*-methyl-α-D-galactopyranoside 255.

To a stirred solution of **247** (2.5 g, 10.0 mmol) in acetic anhydride (29 mL) was added at room temperature aqueous $HClO_4$ (70%, 80 µL). The resulting mixture was stirred for 0.25 h then quenched by addition of a solution of saturated $NaHCO_3$ (140 mL). After 2.5 h stirring at room temperature, the mixture was neutralized with solid $NaHCO_3$. The aqueous solution was extracted three times with dichloromethane. The combined organic layers were dried, filtered and concentrated in vaccuo. The residue was purified by silica gel chromatography hexanes/ethyl acetate (1:1) and gave a mixture of the corresponding anomeric acetate compound (2.20 g, 79%) in a 5:1 α/β mixture as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (major anomer, α) δ 6.32 (d, *J* = 4.0 Hz, 1H), 3.90 (dd, *J* = 6.0, *J* = 7.6 Hz, 1H), 3.73 - 3.60 (m, 2H), 3.53 - 3.51 (m, 8H), 3.42 (s, 3H), 3.34 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 90.2, 80.0, 77.0, 75.5, 71.6, 70.8, 61.5, 59.4, 59.2, 58.2, 21.3, ESIHRMS calcd for $C_{12}H_{22}O_7Na$ $[M + Na]^+$ 301.1263, found 301.1261.

To a solution of the anomeric acetate mixture (2.1 g, 7.55 mmol) in methanol (37 mL) was added hydrazine acetate (835 mg, 9 mmol) at room temperature. The resulting mixture was stirred for 1 h and concentrated. The crude residue was taken up in dimethylformamide (42 mL) then DABCO (2.9 g, 25 mmol) and DNFB (1.1 mL, 8.81 mmol) were respectively added. The resulting mixture was stirred for 6 h and concentrated in vaccuo. The residue was taken up in dichloromethane the organic phase was washed with water, dried over Na_2SO_4 and concentrated. The residue was recrystallized in ether/hexane to give **15** (45% over 2 steps) as a light yellow foam: $[\alpha]^{RT}_{D}$ – 16.4 (*c* = 1.0 M, $CHCl_3$), ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.38 (dd, *J* = 2.8, 9.2 Hz, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 5.04 (d, *J* = 7.2 Hz, 1H), 3.74 - 3.66 (m, 3H), 3.62 - 3.53 (m, 8H), 3.37 (s, 3H), 3.27 (dd, *J* = 2.4, 9.6 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 141.4, 128.9, 121.8, 117.5, 101.4, 83.8, 79.9, 74.8, 74.7, 71.0, 61.7, 61.6, 59.6, 58.9, ESIHRMS calcd for $C_{16}H_{22}N_2O_{10}Na$ $[M + Na]^+$ 425.1172 found, 425.1175.

2,4-Dinitrophenyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-α-D-glycero-D-galacto-octopyranoside 256R.

To a stirred solution of **254R** (640 mg, 2.4 mmol) in acetic anhydride (7.4 mL) was added at room temperature aqueous $HClO_4$ (70%, 20 µL). The resulting mixture was stirred for 0.25 h then quenched by addition of saturated $NaHCO_3$ (40 mL). After 2.5 h stirring at room temperature, the mixture was neutralized with solid $NaHCO_3$. The aqueous solution was extracted three times with dichloromethane. The combined organic layers were dried, filtered and concentrated in vaccuo and purified by silica gel column chromatography hexanes/ethyl acetate (1:1). To a stirred solution of the resulting compound (400 mg, 1.38 mmol) in methanol (7.0 mL) was added a freshly prepared solution of 1M NaOH in methanol (0.14 mmol). After complete consumption of the starting material, the reaction mixture was neutralized by addition of Amberlyst resin IR 120 and concentrated in vaccuo. The resulting crude compound was dissolved in dimethylformamide (8.0 mL) then was added at room temperature DABCO (472 mg, 4.80 mmol) and dinitrofluorobenzene (DNFB) (0.20 mL, 1.64 mmol) respectively. The resulting mixture was stirred for 5 h and concentrated. The residue was taken up in ethyl acetate and washed twice with water. The aqueous

solution was extracted twice times with ethyl acetate. The combined organic layers were dried, filtered and concentrated in vaccuo. The residue was purified by silica gel chromatography hexanes/ethyl acetate (1:1 to 1:2) and gave compound **256R** as a light yellow foam (352 mg, 62% over two steps): $[\alpha]^{RT}{}_{D}$ -16.2 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$ δ 8.72 (d, *J* = 3.2 Hz, 1H), 8.39 (dd, *J* = 2.4, 10.0 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 5.03 (d, *J* = 7.2 Hz, 1H), 4.16 (dd, *J* = 4.0, 11.6 Hz, 1H), 3.82 (s, 1H), 3.77 - 3.72 (m, 2H), 3.63 (s, 3H), 3.54 (s, 3H), 3.46 - 3.41 (m, 5H), 3.27 (dd, *J* = 3.2, 9.6 Hz, 1H), 2.03 - 1.91 (m, 1H), 1.82 - 1.74 (m, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 141.4, 139.7, 129.1, 121.8, 117.8, 102.1, 81.9, 79.7, 77.2, 72.9, 70.2, 66.5, 61.6, 58.6, 56.1, 26.4, ESIHRMS calcd for $C_{17}H_{22}N_2O_{10}Na$ $[M + Na]^+$ 437.1272, found 4378.

2,4-Dinitrophenyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-β-L-glycero-D-galacto-octopyranoside 256S.

Compound **256S** was obtained under the same conditions as compound **256R**, as a light yellow solid (67% over 2 steps): mp 58 – 60 °C, $[\alpha]^{RT}{}_{D}$ + 23.4 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, *J* = 3.0 Hz, 1H), 8.43 - 8.41 (m, 1H), 7.36 (dd, *J* = 3.5, 9.0 Hz, 1H), 5.09 (d, *J* = 7.5 Hz, 1H), 4.06 (s, 1H), 3.88 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.78 - 3.71 (m, 2H), 3.64 (s, 3H), 3.57 - 3.53 (m, 5H), 3.43 (s, 3H), 3.27 - 3.24 (m, 1H), 2.04 - 1.96 (m, 1H), 1.67 (d, *J* = 14.5, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 141.3, 139.7, 128.6, 121.7, 117.3, 101.6, 81.5, 79.2, 73.7, 70.1, 68.5, 62.5, 61.4, 57.9, 56.8, 24.6, ESIHRMS calcd for $C_{17}H_{22}N_2O_{10}Na$ $[M + Na]^+$ 437.1272, found 4369

Phenyl 4,6-*O*-Benzylidene-2,3 -di-*O*-methyl-1-thio-β-D-galactopyranoside 260.

To a solution of phenyl 4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (5.0 g, 13.9 mmol) in dimethyformamide (32 mL) was added at 0 ºC NaH (1.8 g, 55.5 mol). The resulting mixture was stirred for 0.5 h then iodomethane (3.5 mL, 55.5 mol) was added dropwise and the temperature allowed to warm up to room temperature. The resulting mixture was stirred for 2 h then quenched by addition of methanol and concentrated in vaccuo. The residue was taken up in dichloromethane and the organic phase washed twice with water, dried over Na_2SO_4 and concentrated. Purification by silica gel chromatography hexanes/ethyl acetate (5:2) afforded compound **260** (5.0 g, 93%) as a white solid: mp 122-124 °C, $[\alpha]^{RT}_{D}$ + 15.2 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 - 7.69 (m, 2H), 7.49 - 7.46 (m, 2H), 7.38 - 7.35 (m, 3H), 7.26 - 7.23 (m, 3H), 5.52 (d, *J* = 4.8 Hz, 1H), 4.50 (dd, *J* = 4.0, 9.6 Hz, 1H), 4.40 - 4.30 (m, 2H), 3.55 - 3.44 (m, 8H), 3.32 (dd, *J* = 4.0, 9.6 Hz, 1H), 2.95 - 2.87 (m,1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 133.2, 129.6, 129.0, 128.4, 127.7, 126.9, 101.7, 86.6, 83.7, 77.6, 73.3, 70.1, 69.7, 61.2, 58.0, ESIHRMS calcd for $C_{21}H_{24}O_5SNa$ $[M + Na]^+$ 411.1142 found, 411.1145.

Phenyl 2,3-Di-*O*-methyl-4,6-methylidene-1-thio-β-D-galactopyranoside 261.

To a stirred solution of compound **260** (5 g, 12.9 mmol) in methanol (126 mL) was added at room temperature *p*-toluenesulfonic acid (245 mg, 1.29 mmol). The resulting mixture was stirred for 9 h, neutralized by addition of triethylamine and concentrated in vaccuo. Purification by silica gel chromatography hexanes/ethyl

acetate 1:2 afforded phenyl 2,3-di-*O*-methyl-1-thio-β-D-galactopyranoside (3.7 g, 97%) as a colorless oil: $[\alpha]^{RT}_{D}$ - 7.3 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 6.4 Hz, 2H), 7.29 - 7.19 (m, 3H), 4.52 (d, *J* = 9.6 Hz, 1H), 4.09 (s, 1H), 3.93 - 3.87 (m, 1H), 3.81 - 3.75 (m, 1H), 3.54 (s, 3H), 3.49 - 3.43 (m, 4H), 3.34 (dd, *J* = 8.8, 9.6 Hz, 1H), 3.20 (dd, *J* = 8.8, 3.2 Hz, 1H), 2.94 - 2.84 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 131.8, 129.6, 127.6, 87.5, 84.8, 78.7, 78.2, 66.6, 62.7, 61.4, 57.9, ESIHRMS calcd for $C_{14}H_{20}O_5SNa$ $[M + Na]^+$ 323.0929 found, 323.0917.

To a stirred solution of phenyl 2,3-di-*O*-methyl-1-thio-β-D-galactopyranoside (2.8 g, 9.33 mmol), in acetonitrile (47 mL), was added camphore sulfonic acid (220 mg, 0.93 mmol) and formaldehyde dimethyl acetal (2.0 mL, 22.4 mmol) respectively. The resulting mixture was heated at 40 ºC for 48 h, neutralized by addition of triethylamine and concentrated in vaccuo. Purification by silica gel chromatography hexanes/ethyl acetate 1:2 afforded compound **22** (1.20 g, 41%) as a white solid: mp 118 – 120 °C, $[\alpha]^{RT}_{D}$ – 2.0 (*c* = 1.0 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 6.4 Hz, 2H), 7.28 - 7.18 (m, 3H), 5.14 (d, *J* = 5.6 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.48 (d, *J* = 9.6 Hz, 1H), 4.12 (d, *J* = 12.0 Hz, 1H), 3.52 (s, 3H), 3.48 (s, 3H), 3.44 (dd, *J* = 12.4, 9.6 Hz, 1H), 3.33 (s, 1H), 3.20 (d, *J* = 8.8 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 132.5, 129.1, 127.7, 93.7, 87.5, 83.4, 77.8, 72.8, 70.6, 69.0, 61.3, 58.3, ESIHRMS calcd for $C_{15}H_{20}O_5Na$ $[M + Na]^+$ 335.0929 found, 335.0917

2,4-Dinitrophenyl 2,3-Di-*O*-methyl-4,6-methylidene-β- D-galactopyranoside 263.

To a stirred solution of compound **261** (320 mg, 1.02 mmol) in chloroform (6.4 mL) was added at room temperature NIS (278 mg, 1.18 mmol) and dry glacial acetic acid (0.12 mL, 2.05 mmol) respectively. The resulting mixture was stirred for 2 h and quenched by addition of a 10% aqueous solution of $Na_2S_2O_3$. The aqueous solution was extracted twice with dichloromethane. The combined organic layers were dried, filtered and concentrated in vaccuo. The residue was purified by silica gel chromatography hexanes/ethyl acetate (1:1) and gave 2,3-di-*O*-methyl-4,6-methylidene-1-thio-α-D-galactopyranoside acetate (142 mg, 52%) 2,3-di-*O*-methyl-4,6-methylidene-1-thio-β-D-galactopyranoside acetate (28 mg, 18%).

2,3-Di-*O*-Methyl-4,6-methylidene-1-thio-α-D-galactopyranoside Acetate (major anomer): white solid, mp 165 – 168 °C, $[\alpha]^{RT}_{D}$ + 151.3 (*c* = 0.15 M, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (d, *J* = 3.0 Hz, 1H), 5.20 (d, *J* = 6.5 Hz, 1H), 4.75 (d, *J* = 6.5 Hz, 1H), 4.17 – 4.11 (m, 2H), 3.86 – 3.80 (m, 2H), 3.86 – 3.80 (m, 2H), 3.73 (s, 1H), 3.59 (dd, *J* = 3.0, *J* = 10.0 Hz, 1H), 3.55 (s, 3H), 3.49 (s, 3H), 2.14 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 93.5, 90.4, 77.3, 76.3, 72.7, 68.6, 65.4, 59.2, 58.1, 21.1, ESIHRMS calcd for $C_{11}H_{18}O_7Na$ $[M + Na]^+$ 285.0950, found 285.0948.

2,3-Di-*O*-Methyl-4,6-methylidene-1-thio-β-D-galactopyranoside Acetate (minor anomer): colorless oil, $[\alpha]^{RT}_{D}$ + 91.2 (*c* = 0.50 M, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (d, *J* = 8.8 Hz, 1H), 5.19 (d, *J* = 6.4 Hz, 1H), 4.73 (d, *J* = 5.6 Hz, 1H), 4.15 (d, *J* = 13.2 Hz, 1H), 4.06 (d, *J* = 3.6 Hz, 1H), 3.78 (d, *J* = 15.0 Hz, 1H), 3.61 – 3.48 (m, 8H), 3.27 (dd, *J* = 3.2, *J* = 9.6 Hz, 1H), 2.16 (s, 3H), ^{13}C

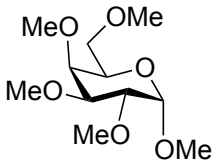
NMR (100 MHz, $CDCl_3$) δ 169.8, 94.2, 93.8, 81.6, 78.6, 72.5, 68.6, 68.0, 61.2, 58.5, 21.4, ESIHRMS calcd for $C_{11}H_{18}O_7Na$ $[M + Na]^+$ 285.0950, found 285.0955.

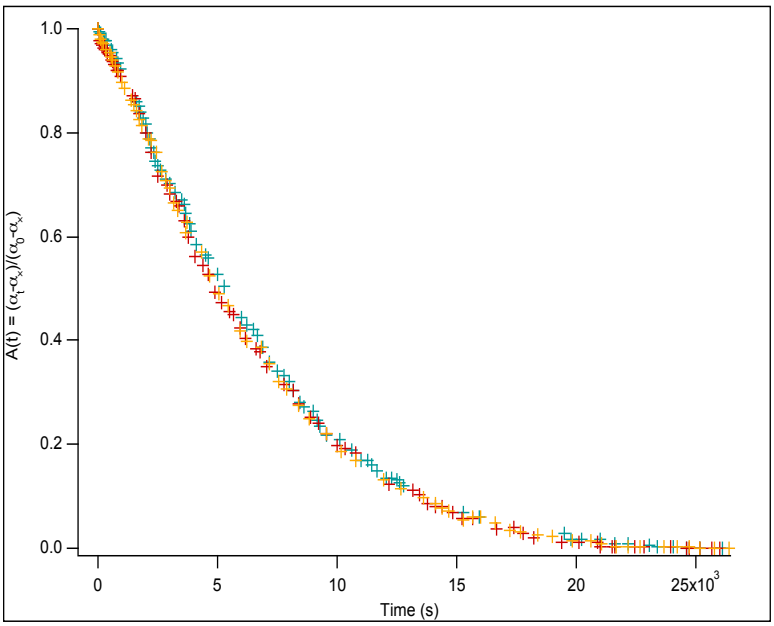
To a stirred solution of 2,3-di-*O*-methyl-4,6-methylidene-1-thio- D-galactopyranoside acetate (290 mg, 1.11 mmol) in methanol (5.5 mL) was added a freshly prepared solution of 1 M NaOH in methanol (0.11 mmol). After complete consumption of the starting material, the reaction mixture was neutralized by addition of Amberlyst resin IR 120 and concentrated in vaccuo. The resulting crude compound was dissolved in dimethylformamide (6.4 mL) then was added at room temperature DABCO (380 mg, 3.86 mmol) and dinitrofluorobenzene (0.17 mL, 1.32 mmol) respectively. The resulting mixture was stirred for 5 h and concentrated. The residue was taken up in ethyl acetate and washed twice with water. The aqueous solution was extracted twice times with ethyl acetate. The combined organic layers were dried, filtered and concentrated in vaccuo. The residue was purified by silica gel chromatography hexanes/ethyl acetate (1:1 to 1:2) and gave compound **263** as a light yellow foam (171 mg, 40% over 2 steps): $[\alpha]^{RT}_{D}$ – 2.1 (*c* = 0.75 M, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.5 Hz, 1H), 8.40 (dd, *J* = 2.5, 9.0 Hz, 1H), 7.37 (d, *J* = 9.5 Hz, 1), 5.22 (d, *J* = 6.5 Hz, 1H), 5.15 (d, *J* = 7.5 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.19 (d, *J* = 12.5 Hz, 1H), 4.16 (d, *J* = 3.5 Hz, 1H), 3.90 (dd, *J* = 1.5, 13.0 Hz, 1H), 3.84 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.68 (s, 3H), 3.63 (s, 1H), 3.59 (s, 3H), 3.55 (dd, *J* = 3.0, 9.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 141.3, 139.6, 128.6, 121.8, 117.1, 101.0, 93.6, 80.9, 78.8, 72.0, 68.3, 68.0, 61.4, 58.6, ESIHRMS calcd for $C_{15}H_{18}N_2O_{10}Na$ $[M + Na]^+$ 409.0859 found, 409.0862.

APPENDIX

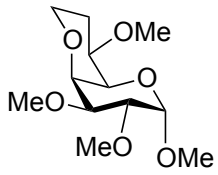
Plots for the acid catalyzed hydrolysis of methyl α-D-galactopyranosides **247**, **254R** and **254S** (T 82 ºC, [HClO4] = 2.0 M).

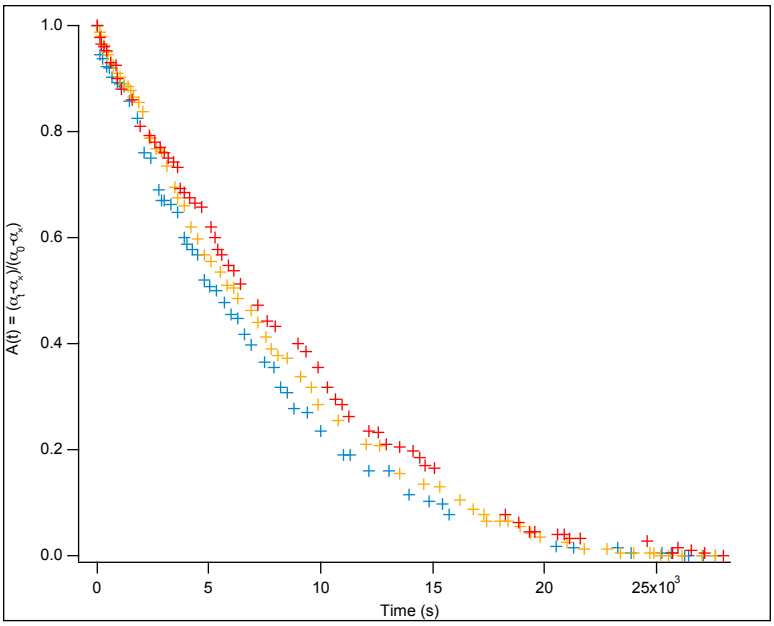
Methyl 2,3,4,6-tetra-*O*-methyl-α-D-galatopyranoside 247.



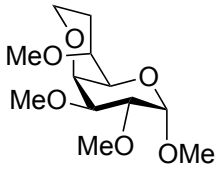


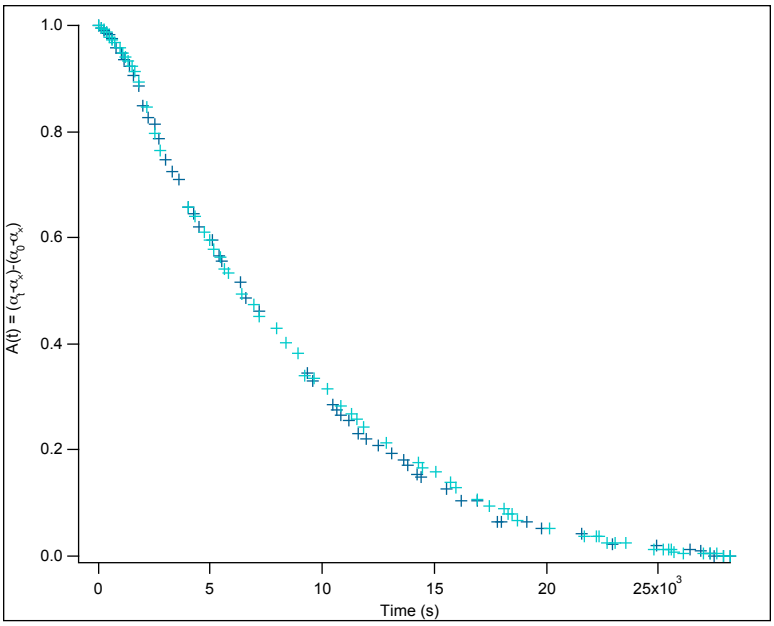
Methyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-α-D-glycero-D-galacto-octopyranoside 254R.





Methyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-β-L-glycero-D-galacto-octopyranoside 254S.

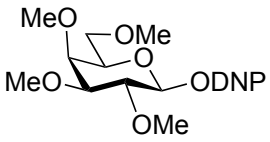


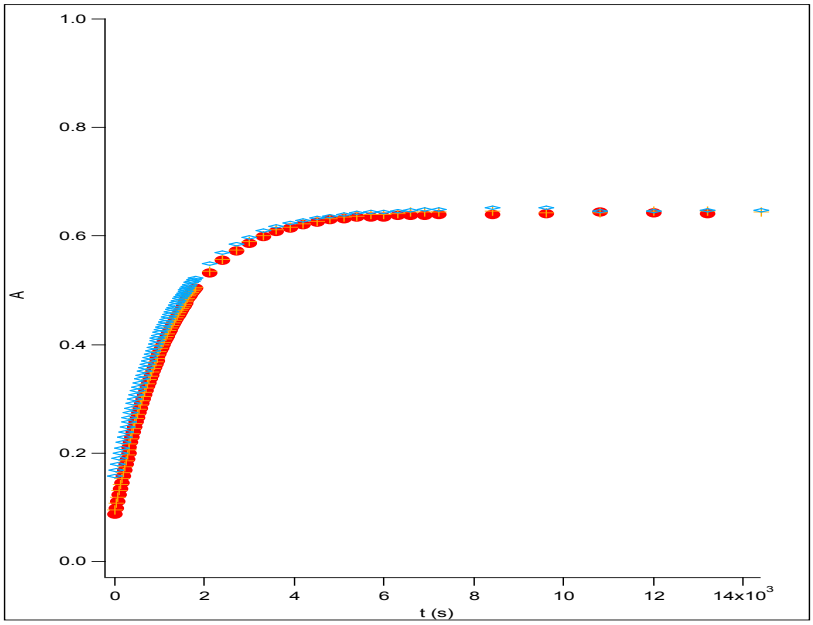


Plots for the spontaneous hydrolysis of 2,4-DNP galactopyranosides **255**, **256R**, **256S** and **263** (phosphate buffered saline solution: pH = 6.5, C = 25 mM, [KCl] = 0.4 M).

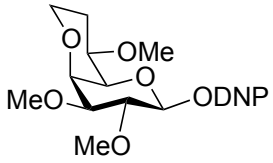
Only one plot (T = 75 ºC) is represented for each of these four compounds since all the plots are similar at any temperature.

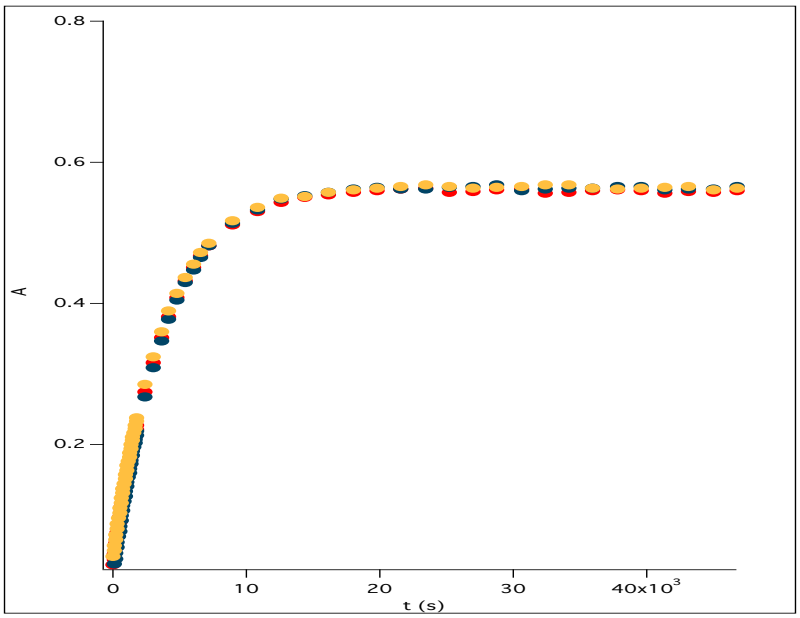
2,4-Dinitrophenyl 2,3,4,6-Tetra-*O*-methyl-α-D-galactopyranoside 255.



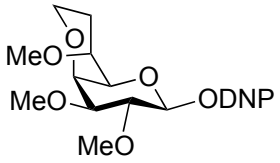


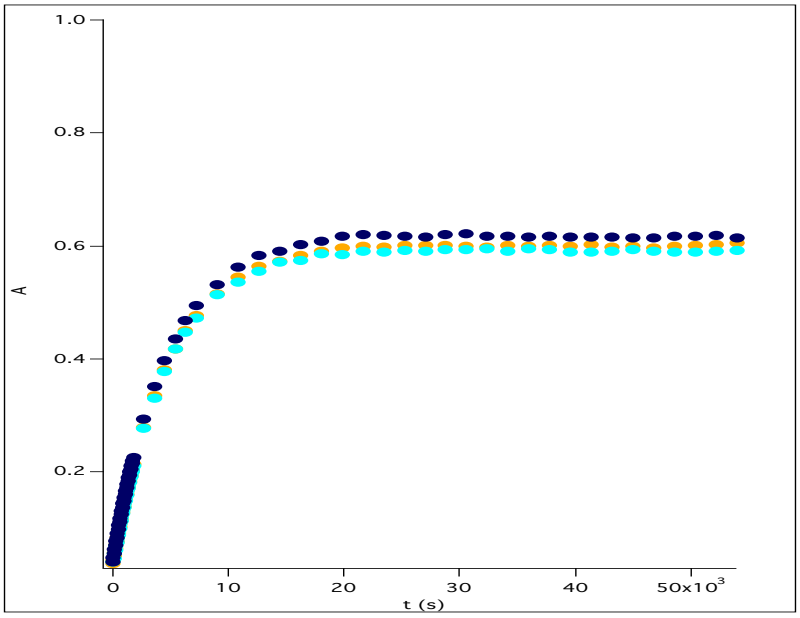
2,4-Dinitrophenyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-α-D-glycero-D-galacto-octopyranoside 256R.





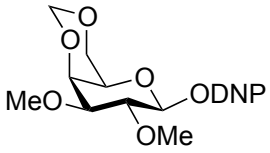
2,4-Dinitrophenyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-β-L-glycero-D-galacto-octopyranoside 256S.

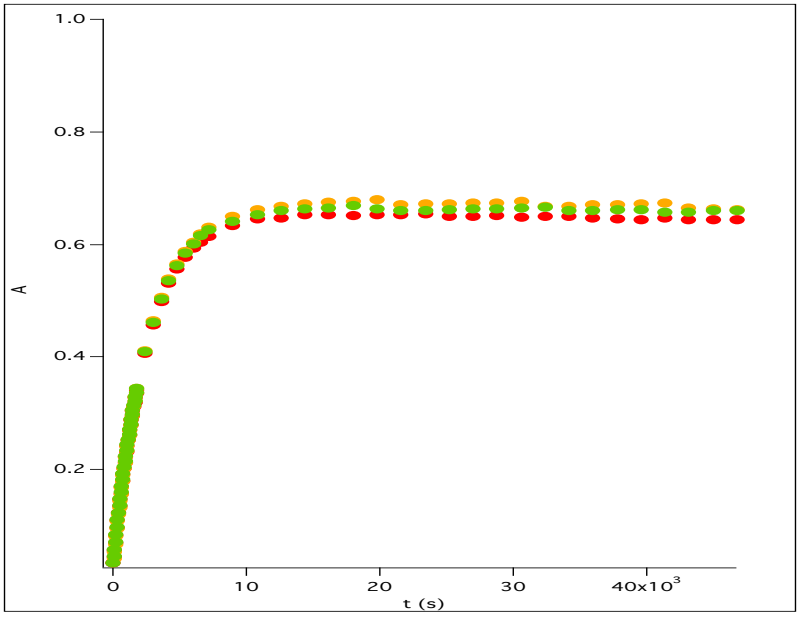




2,4-Dinitrophenyl 2,3-Di-*O*-methyl-4,6-methylidene-β-D-galactopyranoside

263.





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ABSTRACT

SYNTHESIS OF OLIGOSACCHARIDE MIMETICS BY THE DESULFURATIVE REARRANGEMENT OF ALLYLIC DISULFIDES AND STEREOELECTRONIC INFLUENCE OF C-O BONDS ON *C*- AND *O*-GLYCOSYLATION

by

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May 2013

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Major: Chemistry

Degree: Doctor of Philosophy

This dissertation focuses on two different problems. The first part of this manuscript presents the application of a novel methodology to access the synthesis of oligosaccharide mimetics while the second part focuses on the study of the stereoelectronic effects of proximal C-O bonds in *C*- and *O*-glycosylation reactions.

The first chapter provides a brief overview of the important roles that oligosaccharides and glycoconjugates play in biological processes and sets out the major advances that have been made in the past few decades in the synthesis of such complex structures while bringing out the ongoing challenges and the limitations that impede the development of general methods with broad applicability.

In chapter two, the emphasis is placed on a new thioligation reaction developed in the Crich laboratory as a means for the chemical synthesis of linear mimetics of an important bacterial motif, the β-(1→6)-*N*-acetyl glucosamine

polymer. Small, protecting group-free, pre-assembled sugar units are linked together into larger oligosaccharide chains by the desulfurative rearrangement of allylic disulfides.

The first part of chapter three presents the general mechanistic aspects of *O*-glycosylation reactions, before detailing them further in the context of glycosylation reactions using 4,6-*O*-benzylidene-protected donors. The second part covers underlying principles of protecting group reactivity and their affects on glycosylation reaction.

Chapter four looks into the stereoelectronic influence of the C3-O3 bond in 4,6-*O*-benzylidene protected gluco- and mannopyranoside donors. The stereoselective formation of *C*-glycosides in the 3-deoxy mannose and glucose series is compared to that in the more usual 3-OBn series. The results of this study provided complementary insights into the determining elements controlling the stereoselective formation of *C*-glycosides.

In chapter five, the influence of the 4,6-*O*-benzylidene group on reactivity is investigated in the galactose series by probing the disarming influence of the *tg* conformation of the C5-C6 bonds. Kinetic studies on 4,6-*O*-alkylidene galactoside derivatives and their carba-analogs revealed that, similarly to the glucose series, 4,6-*O*-acetals also exert a disarming effect on galactopyranosides reactivity.

This manuscript ends with an overall conclusion presented in chapter six. All compounds characterizations and data plots are presented in chapter seven, in the experimental section.

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Publications
1. "Probing the Influence of 4,6-*O*-Acetal on the Reactivity of Galactopyranosyl Donors: Verification of the Disarming Influence of the Trans-Gauche Conformation of C5-C6 Bonds" **Moume-Pymbock, M**.; Crich, D. (Manuscript in preparation)

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