NOVEL GLYCOSYLATION METHODOLOGY AND THE SYNTHESIS OF HETEROANALOGUES OF DISACCHARIDES

by

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Abstract

The use of phenyl selenoglycosides as glycosyl donors and acceptors in glycosylation reactions is described. The versatility of these novel compounds is illustrated by the selective activation of "armed" and "disarmed" phenyl selenoglycoside donors over "armed" ethyl thioglycoside acceptors with silver trifluoromethanesulfonate in the presence of potassium or silver carbonate to give disaccharides in excellent yields. The selective activation of glycosyl bromide donors over phenyl selenoglycoside acceptors is realized by silver trifluoromethanesulfonate promotion in the presence of collidine. Such selectivity is also demonstrated by the preferential activation of glycosyl trichloroacetimidate donors in the presence of selenoglycoside acceptors with triethylsilyl trifluoromethanesulfonate. The central role of selenoglycosides is illustrated by the synthesis of a trisaccharide that profits from the sequential, selective activation of a glycosyl bromide donor over a selenoglycoside acceptor and the resulting selenoglycoside disaccharide over a thioglycoside acceptor. The liberation of the anomeric hydroxyl group from a phenyl selenoglycoside is also described.

Radical cation-initiated glycosylation reactions of phenyl selenoglycosides are described. Glycosylations of selenoglycosides effected by the single-electron-transfer (SET) reagent tris(4-bromophenyl)aminium hexachloroantimonate (BAHA) are examined with primary and secondary hydroxyl acceptors. Reactions in the presence of the SET quenching reagent 1,2,4,5-tetramethoxybenzene, to assess whether BAHA-mediated glycosylation reactions indeed involve single-electron-transfer or whether they are acid

catalyzed, indicate the dominance of the SET process. The oxidation potentials of various selenoglycosides are determined by cyclic voltammetry.

Heteroanalogues of methyl and allyl kojibiosides, methyl maltoside and methyl isomaltosides are synthesized for evaluation as glycosidase inhibitors. The glycosyl trichloroacetimidate of 2,3,4,6-tetra-O-acetyl-5-thioglucopyranose is used as a new donor to glycosylate selectively protected glucopyranosyl acceptors with 2-OH and 6-OH positions free, under triethylsilyl trifluoromethanesulfonate promotion, to afford the 1,2-linked and the 1,6-linked disaccharides as 3:1 and 1.5:1 α:β mixtures, respectively. Methyl α-D-glucopyranoside acceptors containing 4-OH and 4-SeH functions are glycosylated with the same donor under triethylsilyl triflate catalysis, to give exclusively the α-5'-thiodisaccharide, and a 4:1 α/β mixture of the 4-seleno-5'-thiodisaccharides, respectively. The disaccharides are deprotected to give heteroanalogues for evaluation as glycosidase inhibitors.

This thesis is dedicated to my family,

for giving me the inspiration and the boundless encouragement

that I needed to get this far.

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LIST OF ABBREVIATIONS

Ac	Acetyl
All	Allyl
AgOTf	Silver trifluoromethanesulfonate
BAHA	Tris(4-bromophenyl)aminium hexachloroantimonate
$BF_3.OEt_2$	Boron trifluoride etherate
Bz	Benzoyl
Bzl	Benzyl
COSY	Correlated spectroscopy
DMF	*N, N*-dimethylformamide
ELAM	Endothelial leukocyte adhesion molecule
Glc	Glucose
GlcNAc	*N*-acetylglucosamine
Gal	Galactose
gp	Glycoprotein
HIV	Human immunodeficiency virus
IDCP	Iodonium di-sym-collidine perchlorate
Man	Mannose
MSB	Methylsulfenyl bromide
MT	Methyl trifluoromethanesulfonate
NBS	*N*-bromosuccinimide
NeuAc	*N*-acetylneuraminic acid
NIS	*N*-iodosuccinimide
NMR	Nuclear magnetic resonance
$NOBF_4$	Nitrosyl tetrafluoroborate

NOESY	Nuclear Overhauser enhancement spectroscopy
NPG	n-Pentenyl glycoside
PhSeOTf	Phenyl selenenyl trifluoromethanesulfonate
Phth	Phthalimido
RCI	Radical cation-initiated
SCE	Standard calomel electrode
SET	Single electron transfer
TESOTf	Triethylsilyl trifluoromethanesulfonate
TfOH	Trifluoromethanesulfonic acid
TLC	Thin layer chromatography
TMB	1,2,4,5-tetramethoxybenzene
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
triflate (OTf)	Trifluoromethanesulfonate

CHAPTER I

INTRODUCTION

1.1. CELL-SURFACE CARBOHYDRATES

The realization that carbohydrates play a role in diverse and crucial biological recognition processes has created much interest in the field of carbohydrate chemistry. Carbohydrates have long been recognized for their structural and protective functions and are widely accepted as being a source of energy. A more powerful role of carbohydrates, in the form of conjugates such as glycoproteins and glycolipids, as mediators in various types of cellular interactions has emerged.[1] Carbohydrate-protein interactions play a vital role in, for example, hormonal regulation, fertilization, and immunological protection (antigen-antibody recognition). Their role in host-pathogen interaction is demonstrated in their function as receptors for viruses, bacteria, and toxins.[1,2] Carbohydrate structures are known to be antigenic determinants of the human blood group system.[3] Oligosaccharide epitopes expressed on cell surfaces of leukocytes act as ligands for ELAM-1, which is a selectin responsible for adhesion and migration of leukocytes to endothelial cells during inflammatory responses.[4]

The following section illustrates the biological significance of carbohydrates by way of selected examples and demonstrates the applicability of synthetic oligosaccharides.

1.2. BIOLOGICAL SIGNIFICANCE OF CARBOHYDRATES

1.2.1. Cell-cell interaction: Role of Carbohydrates in Cell Adhesion:

Endothelial leukocyte adhesion molecule-1 (ELAM-1) is a member of the selectin group of proteins expressed on the surface of endothelial cells of blood vessel walls. It is induced in the presence of an inflammatory agent and is responsible for the recruitment and migration of leukocytes to sites of inflammation and tissue injury.[4] The recognition of ELAM-1 and the leukocytes is mediated by the carbohydrate epitopes expressed on the surface of the leukocytes. The carbohydrate ligand is a tetrasaccharide known as sialyl Lewis^x, the structure of which is shown in Figure 1.1.

Although the recruitment of leukocytes is essential for the initiation of tissue repair, an abnormal recruitment of leukocytes in diseases such as rheumatoid arthritis, causes chronic inflammation. Since sialyl Lewis^x has been shown to be the ligand recognized by ELAM-1, sialyl Lewis^x and its analogues are being examined as potential therapeutics to inhibit selectin-mediated inflammation, thus providing a new class of anti-inflammatory drugs. The administration of such antiadhesive drugs leads to an exhaustion of the selectin binding sites rendering them unavailable for leukocyte binding (Figure 1.2). Various research groups are currently engaged in the chemical and/or enzymatic synthesis of sialyl Lewis^x and its analogues. These aspects will be discussed in greater detail in forthcoming sections.

1.2.2. Blood Group Antigens

The ABO system is one of the human blood group systems. The specificity of this system depends on the oligosaccharide structures of glycoproteins and glycolipids expressed on the surface of erythrocytes or on

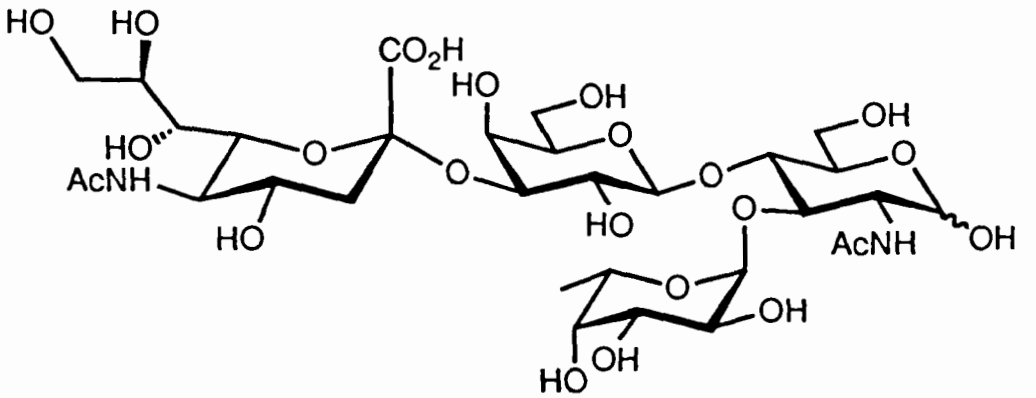
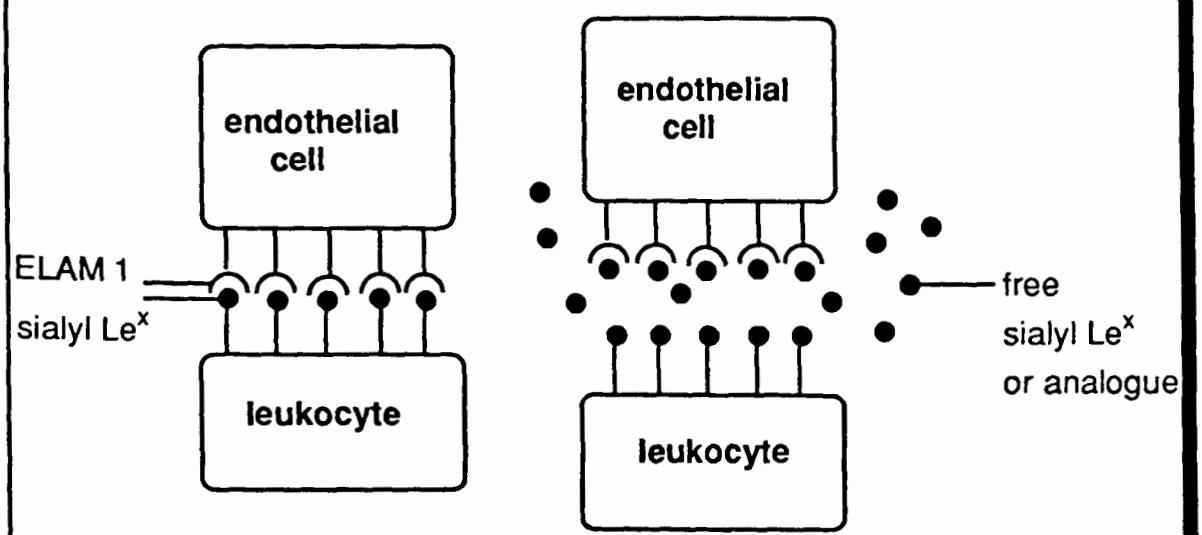


Figure 1.1. Sialyl Lewis X



a) adhesion of a leukocyte to an endothelial cell mediated by the interaction of sialyl Le^x and ELAM-1

b) adhesion is prevented by the addition of free sialyl Le^x or its analogue

Figure 1.2. Mechanism of action of antiadhesive drugs

soluble glycoproteins.[3] Individuals with type O blood group possess a characteristic trisaccharide referred to as the H antigen, the structure of which is shown in Figure 1.3. The antigen associated with blood group A is a tetrasaccharide with an additional *N*-acetyl-D-galactosamine residue at the terminal position of the H antigen. Type B specificity is associated with a terminal D-galactose residue. The sera of individuals not possessing one of the above antigens contain antibodies directed against that particular antigen.

The blood group antigens were first synthesized by Lemieux and co-workers,[5] a fact that had a great impact on medical science. As shown in Figure 1.4, through a series of chemical transformations, the synthetic haptens were attached to a solid support to construct immunoadsorbents.[6] These immunoadsorbents were applied to overcome blood group incompatibilities during blood transfusions and organ transplants.[7] Thus, to facilitate a transfusion from a type-A donor to a type-B recipient, the recipient's plasma was passed through immunoadsorbents containing the A antigen. This allowed the selective removal of anti-A-antibodies present in the recipient's serum and reduced the risk of haemolysis.

1.2.3. Host-pathogen Recognition: Infection by HIV:

Acquired immunodeficiency syndrome (AIDS) causes the destruction of a type of white blood cells known as the T4 lymphocyte cells, thereby interfering with the body's immune defenses and leaving it more susceptible to infections. AIDS is caused by the human immunodeficiency virus (HIV). The viral infection is initiated by the association of the glycoprotein gp120 on the viral envelope with the CD4 receptors expressed on the surface of the T4 cells (Figure 1.5). Thus, interference of this primary interaction could provide a potential anti-viral therapy.[8]

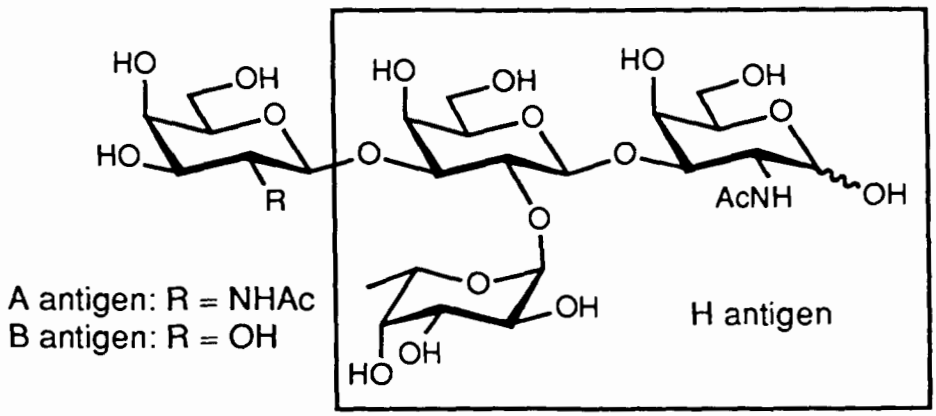


Figure 1.3. Blood group antigens of the ABO system

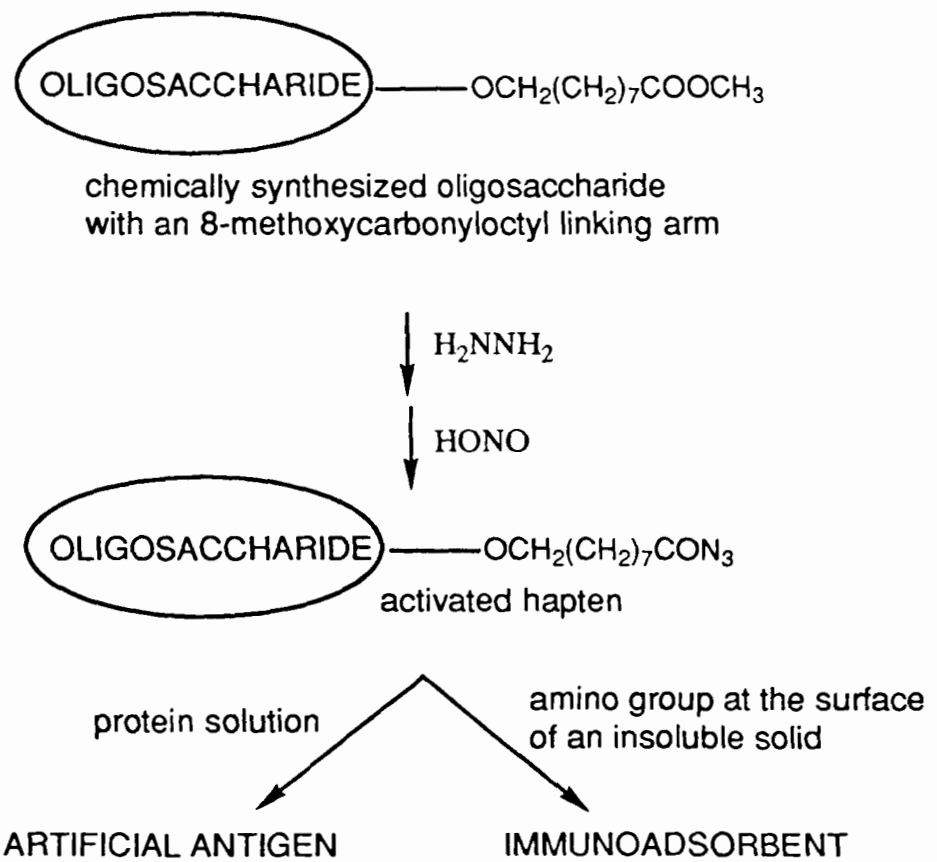


Figure 1.4. Preparation of artificial antigens and immunoadsorbents

Viral glycoprotein gp120 is heavily *N*-glycosylated.[9] The viral infectivity is strongly dependent on the nature of the oligosaccharides of gp120. Their biosynthesis occurs via a precursor Glc_3-Man_9-$GlcNAc_2$, and requires the trimming enzymes glucosidase I, which is involved in the cleavage of the terminal α-1,2-linked glucose residue from the precursor, and glucosidase II, which removes the subsequent two α-1,3-linked glucose residues (Figure 1.6).[10] Sugar analogues such as 1-deoxynojirimycin, *N*-butylnojirimycin and castanospermine are known to be effective inhibitors of glucosidase I (Figure 1.7). These compounds have been used to block the natural biosynthetic pathway of oligosaccharide processing. Altering the carbohydrate structure of gp120 results in a lower affinity of gp120 and CD4, thereby interfering with viral infectivity.[11] The search for other glycosidase inhibitors for therapeutic purposes is currently an active area of research.

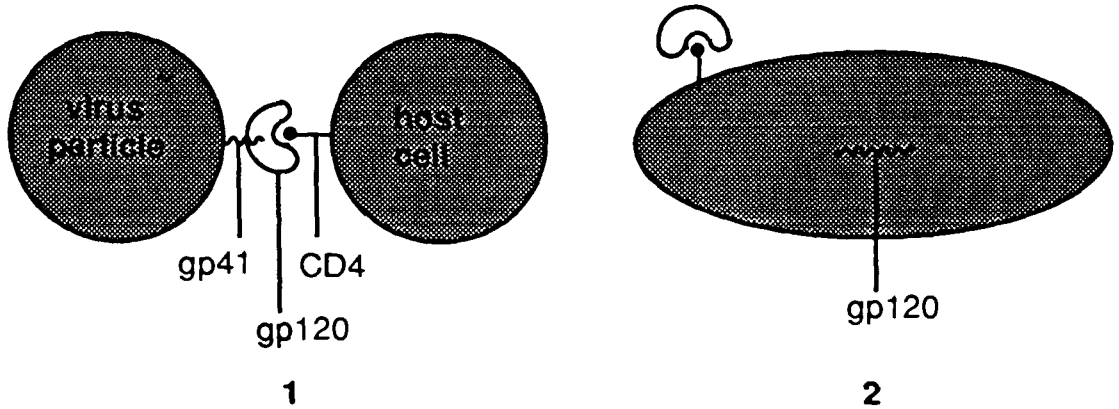


Figure 1.5. 1. Binding of viral glycoprotein gp120 with cell surface molecule CD4.
2. Fusion of viral membrane and cell membrane

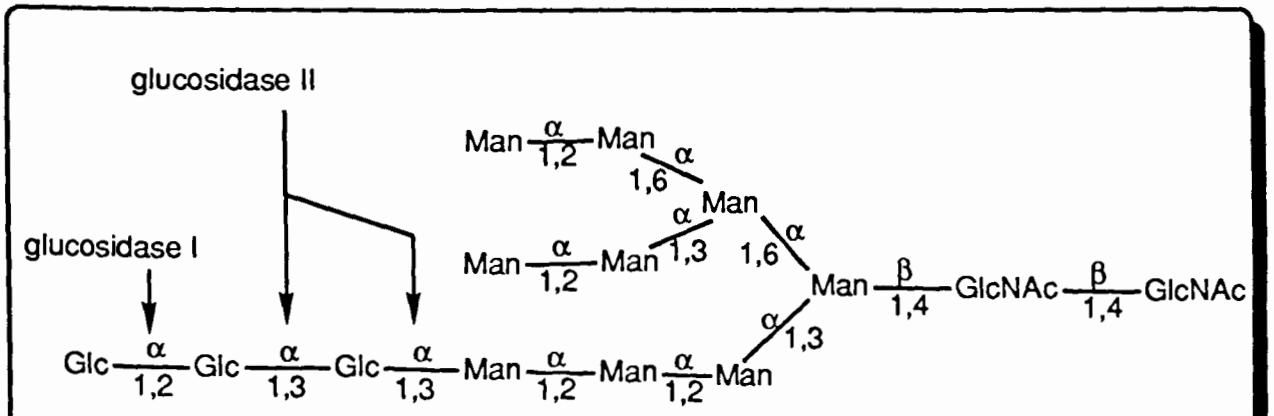
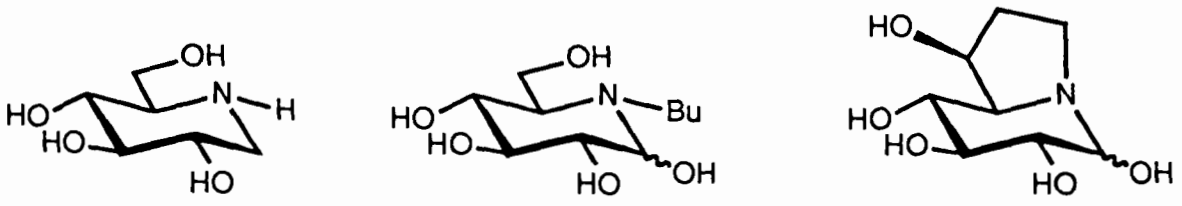


Figure 1.6. Precursor of *N*-linked glycoproteins



1-deoxynojirimycin N-butylnojirimycin castanospermine

Figure 1.7. Glucosidase inhibitors

1.3. Need for Oligosaccharide Synthesis

A better understanding of the role of carbohydrates in these and other recognition processes requires access to the biologically relevant oligosaccharide portions of glycoproteins and glycolipids. Purification of these materials from natural sources is not always trivial and the desired degree of purity is difficult to attain. Moreover, the quantity of materials isolated may not be sufficient to perform the desired studies. Chemical synthesis offers an alternative route to these compounds. In addition to fulfilling the need for structurally well-defined molecules, chemical synthesis also provides structural analogues of the natural compounds. This allows a more thorough investigation of their structure, conformation and biological activity.

1.4. Applications of Synthetic Oligosaccharides

Numerous synthetic oligosaccharides are currently being applied for diagnostic and therapeutic purposes. For example, oligosaccharides corresponding to the antigenic determinants of *Salmonella* bacteria have been used to detect the elevated levels of antibodies in sera of patients infected with the bacterium.[12] Glycoconjugates of biologically active oligosaccharides have been used to raise and characterize monoclonal antibodies that have been applied for diagnostic purposes.[13] Carbohydrate-based protective vaccines comprised of artificial antigens, prepared by linking oligosaccharide haptens to immunogenic carriers, are being applied, for example, in protection against meningococcal infections.[14] The ability of certain oligosaccharides to inhibit the action of glycoprocessing enzymes has been applied towards the treatment of diseases such as diabetes and the prevention of host-pathogen recognition.[15]

Conformational modeling of oligosaccharides by theoretical calculations and nuclear magnetic resonance spectroscopy[16] provides a better understanding of the biological role of carbohydrates and is being applied towards rational drug design.[17] X-ray crystal structures of carbohydrate-protein complexes, where the protein may be an enzyme,[18] lectin[19] or an antibody,[20] allow carbohydrate-protein interactions to be investigated at the molecular level and provide information regarding, for example, the mechanism of enzyme action.

1.5. Oligosaccharide Synthesis

1.5.1. General Aspects

The recognition function of carbohydrates is a consequence of the diverse assortment of structures generated from a few simple sugars due to the variety of linkage positions, the possibility of α- and β- configurations at the anomeric center, and the possibility of branching. These are the very reasons that make oligosaccharide synthesis so challenging.

The synthesis of oligosaccharides requires the regioselective and stereoselective linking of two polyfunctional sugar components. One of the components is functionalized with a suitable leaving group at the anomeric position; this component is referred to as the glycosyl donor. The general strategy for the synthesis is based on the nucleophilic displacement of the leaving group by the alcohol or glycosyl acceptor with the assistance of a suitable promoter. The achievement of the desired regioselectivity usually requires the selective protection of all the hydroxyl groups of the glycosyl acceptor except the one that is involved in the formation of the glycosidic bond. The blocking strategy should be such that the two reacting species may be

easily manipulated. It should enable selective deprotection without adversely affecting the previously existing glycosidic bonds or the other blocking groups in subsequent steps leading to higher oligosaccharides. The glycosylation must occur in a stereoselective manner, the stereochemistry of the glycosidic link being influenced by the nature of the blocking groups present on both the glycosyl donor and acceptor, which exert steric as well as electronic influences. The following section describes the salient features of oligosaccharide synthesis. These have been reviewed in the literature[21].

1.5.2. Methods of Stereoselective Oligosaccharide Synthesis

Depending on the configuration of the anomeric, center two types of glycosides are possible (Figure 1.8) .

a) 1,2-*trans*-type : This type is encountered in oligosaccharides having a β-D-linkage in the *gluco*- and *galacto*- series and an α-D-linkage in the *manno*- series.

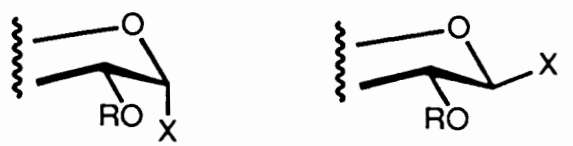
b) 1,2-*cis*-type : α-D-linked oligosaccharides of the *gluco*- and *galacto*- series and a β-D-linkage in the *manno*- series lead to 1,2-*cis*- type glycosides.

To achieve the desired stereoselectivity the following synthetic approaches are available.

1. 1,2-*trans*- glycosylations: The neighbouring group-assisted glycosylations resulting in the formation of 1,2-*trans*-glycosides.

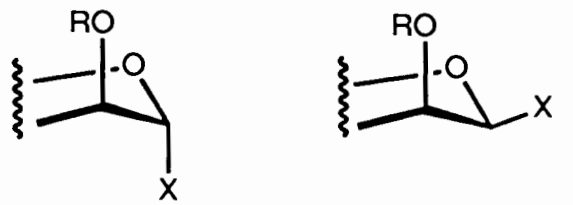
2. 1,2-*cis*-β-D-glycosylations: The heterogeneous catalytic procedure and the internal delivery method for the synthesis of 1,2-*cis*-glycosides of the *manno*- series.

3. 1,2-*cis*-α-D-glycosylations: The *in situ* anomerization procedure and the internal delivery method utilized to procure 1,2-*cis-gluco*- and *galactosides.*



1,2-*cis*- type
α-D-glucoside

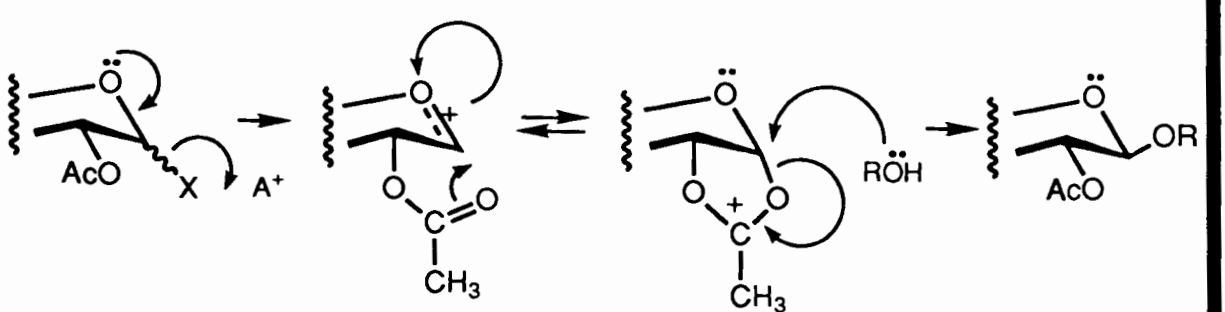
1,2-*trans*- type
β-D-glucoside



1,2-*trans*- type
α-D-mannoside

1,2-*cis*- type
β-D-mannoside

Figure 1.8. 1,2-*cis*- and 1,2-*trans*- glycopyranosides



α- or β- glycosyl donor

oxocarbenium ion

acetoxonium ion

1,2-*trans*-glycoside

Figure 1.9. Neighbouring group participation in a glycosylation reaction

1.5.2a. 1,2-*trans*- Glycosylations: The presence of a neighbouring group-active substituent at the 2-position of the glycosyl acceptor plays an important role in the stereoselective preparation of 1,2-*trans*-glycosides. When an acetyl or benzoyl group is attached to the carbon atom next to the carbon atom undergoing nucleophilic substitution, it participates in the reaction by forming an acetoxonium ion following the promoter-assisted expulsion of the leaving group. Owing to the steric influences exerted by this five membered ring, the nucleophilic attack occurs preferentially from the *trans*- side. Since the reaction likely proceeds with the initial formation of an oxocarbenium ion, stereospecific synthesis of 1,2-*trans*-glycosides is achieved regardless of the initial configuration of the glycosyl donor. This is illustrated in Figure 1.9.

1.5.2b. 1,2-*cis*-β-D-Glycosylations: One of the challenges facing synthetic oligosaccharide chemists has been the synthesis of β-D-mannopyranosides. This linkage is found in all asparagine-linked glycoproteins, making it an important target for synthesis. Due to the 1,2-*cis*- nature of these glycosides, these compounds are not accessible *via* neighbouring group participation. Moreover, both steric and stereoelectronic factors disfavour the formation of the β- isomer.

These difficulties have been addressed by a number of groups. The heterogeneous catalytic procedure was introduced by Paulsen and Lochhoff.[22] In this procedure a mannosyl bromide is taken as a starting material and the glycosylation is performed in the presence of an insoluble catalyst such as silver silicate[22] or silver zeolite.[23] The silver halide formed during the reaction is precipitated and thus prevented from assisting anomerization (Figure 1.10). This method, however, necessitates the use of reactive coupling partners, and the reactions are not always stereoselective. This complicates separation and

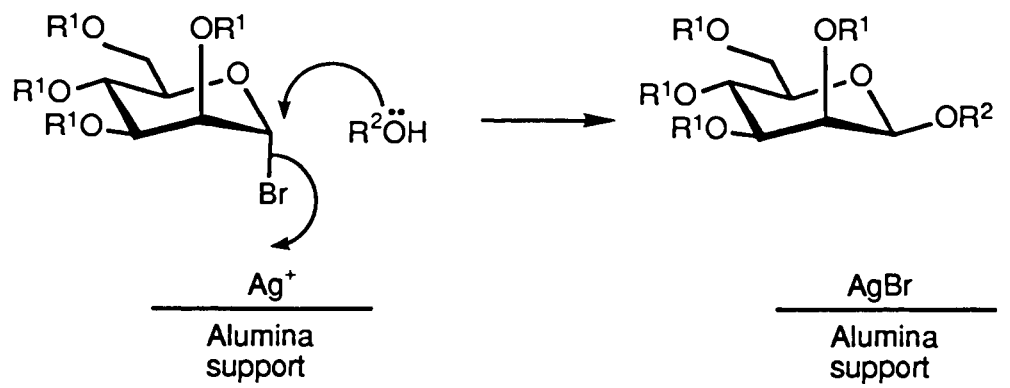


Figure 1.10. Preparation of β-D-mannopyranosides by heterogeneous catalysis

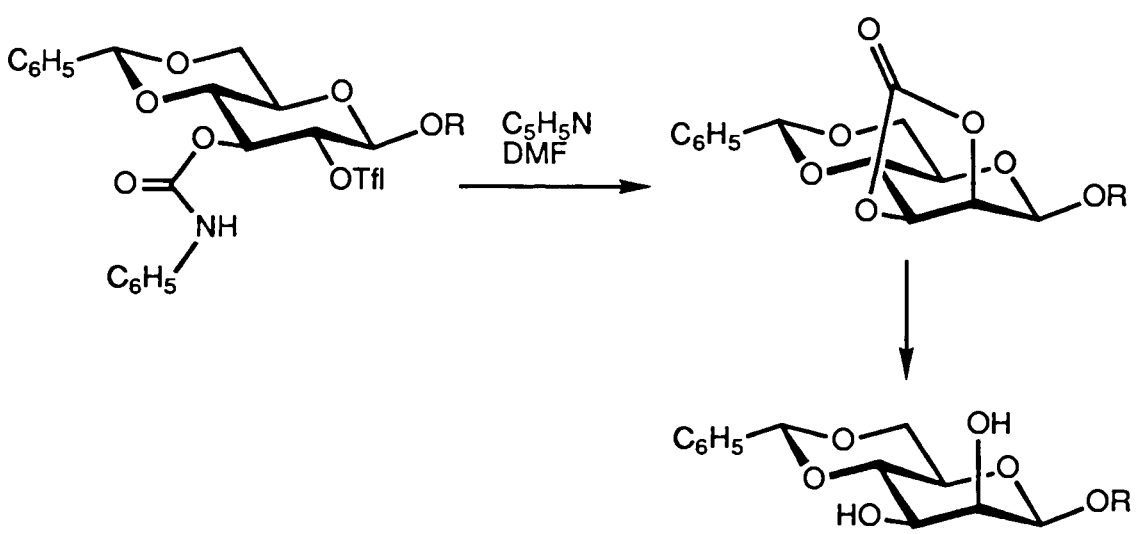


Figure 1.11. Preparation of β-D-mannopyranosides from β-D-glucopyranosides

isolation of the desired β anomer. In view of the fact that mannose is the C-2 epimer of glucose, another approach to β-D-mannopyranosides has been that of inversion at the C-2 position of β-D-glucopyranosides. This is effected by either intramolecular[24] or intermolecular[25] inversion. The intramolecular inversion is illustrated in Figure 1.11. A β-glycoside is prepared by conventional methods. A triflate group is positioned at C-2 and is displaced by a phenylurethane group at C-3. This inverts the configuration at C-2, leading to a β-mannoside. Another method involves the synthesis of a β-D-glucoside, oxidation of the 2-OH group to the ulose, and stereoselective reduction to give the β-D-mannoside.[26]

The recently reported intramolecular aglycon delivery method, by two separate groups, offers an attractive alternative for the synthesis of β-D-mannopyranosides. The approach of Barresi and Hindsgaul[27] is shown in Figure 1.12. The aglyconic alcohol is coupled to a vinyl ether substituent at C-2 of the glycosyl donor. Activation of the ethylthio functionality at the anomeric position with NIS and 4-methyl-2,6-di-*t*-butylpyridine (4-Me-DTBP) is accompanied by intramolecular rearrangement, delivering the alcohol on the β-face of the glycosyl donor stereoselectively. A similar approach was simultaneously reported by Stork and Kim[28] who employed a silicon connector (Figure 1.13).

1.5.2c. 1,2-*cis*-α-D-Glycosylations: To synthesize an α-D-linked *gluco-* or *galactoside*, the presence of a non-neighbouring group-active substituent at the C-2 position of the donor is essential. Nucleophilic displacement of the leaving group in the β-D halides with inversion of configuration at the anomeric center, thus yields α-D-glycosides. However, the β-halides are quite reactive and anomerize to the more stable α- anomer. This accounts for the loss in stereoselectivity associated with the above method.

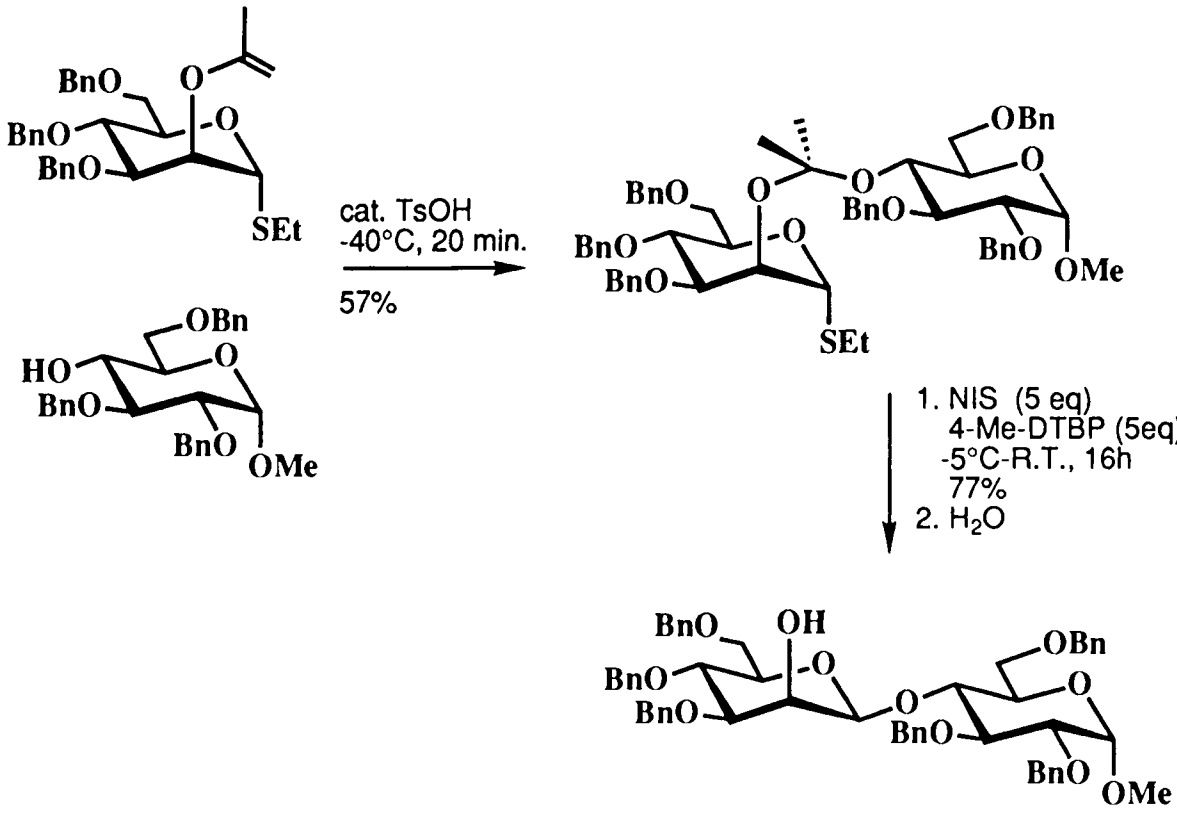


Figure 1.12. Synthesis of β-D-mannosides *via* internal delivery

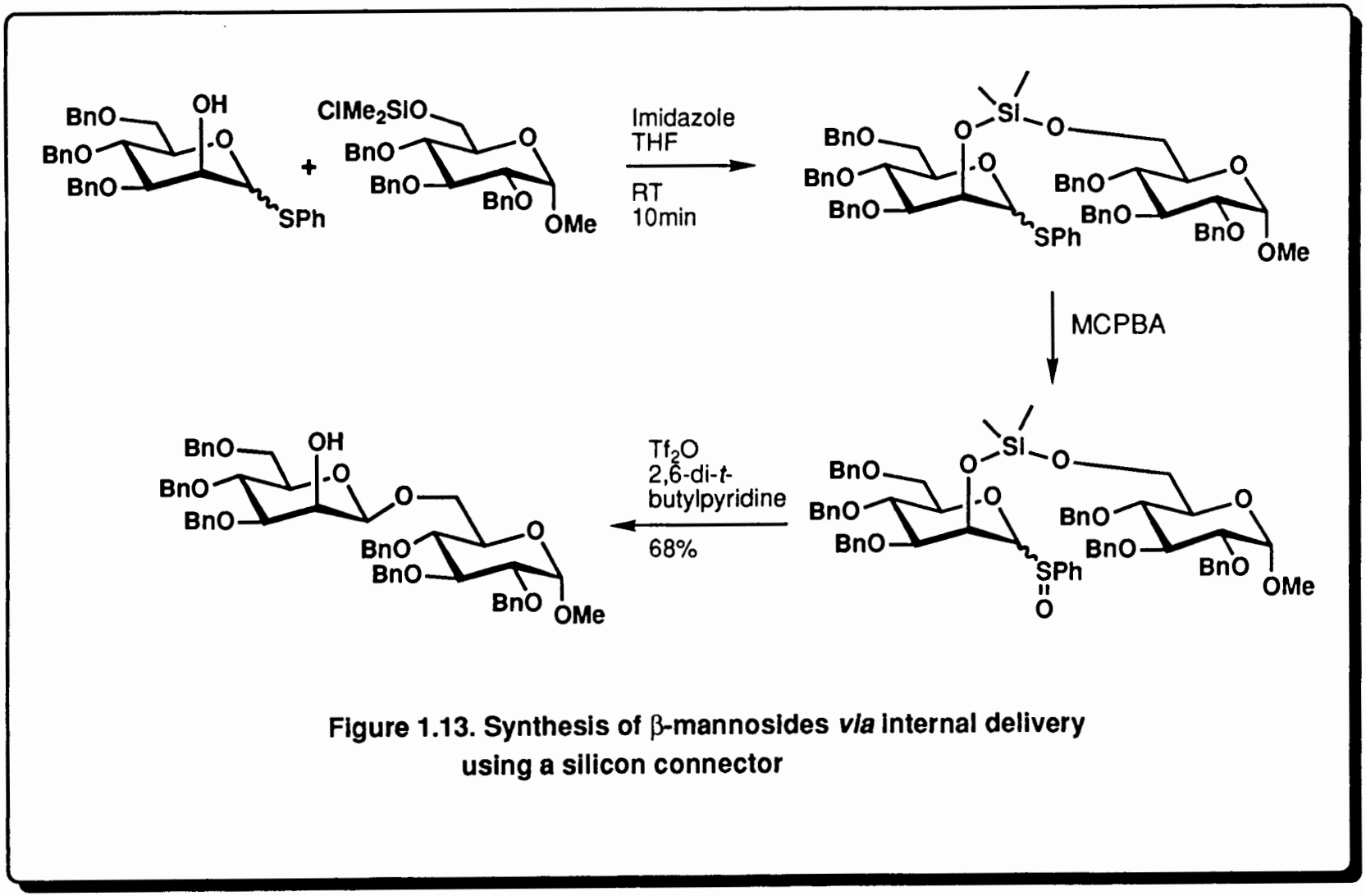


Figure 1.13. Synthesis of β-mannosides *via* internal delivery using a silicon connector

The *in situ* anomerization procedure was introduced by Lemieux *et al.*[29] for the synthesis of 1,2-*cis*-glycosides. This procedure utilizes the more stable α-glycosyl halide donors for the synthesis of α-glycosides. The α-anomer is anomerized to the β- anomer with tetraethylammonium bromide. The β- anomer is kinetically more labile and reacts preferentially with the glycosyl acceptor with inversion at C-1 to afford an α-glycoside. The equilibrium is restored by further anomerization of the α- bromide to the β- bromide (Figure 1.14).

Intramolecular glycosylations, as discussed in the previous section, offer the advantage of being able to control the stereochemical outcome of the reaction. This method has also been extended by Bols[30] towards the stereocontrolled synthesis of α-glucosides and α-galactosides. In this approach the silyl group was tethered to the glycosyl donor rather than the glycosyl acceptor (Figure 1.15).

1.5.3 Activation of the Anomeric Center

The functionalization of the anomeric center has been performed in a variety of ways. The more prominent methodologies are briefly reviewed in the following section.

1.5.3a. Halides:- The classical method of oligosaccharide synthesis is by the Koenigs-Knorr reaction[31] which involves the activation of a glycosyl halide donor by silver salts in the presence of an proton acceptor. This procedure has been modified by replacing silver salts by mercury-containing compounds, these conditions being referred to as the Helferich conditions.[32] The proton acceptors generally used are 2,4,6-collidine and 1,1,3,3-tetramethylurea. The reactivity of the commonly used promoters is of the order AgOTf > AgOTf / Ag_2CO_3 > $AgClO_4$ / Ag_2CO_3 > $HgBr_2$ > $Hg(CN)_2$ / $HgBr_2$ > $Hg(CN)_2$ > Et_4NBr. The reactivity of the halide donor declines as the halide substituent changes from iodine to fluorine.

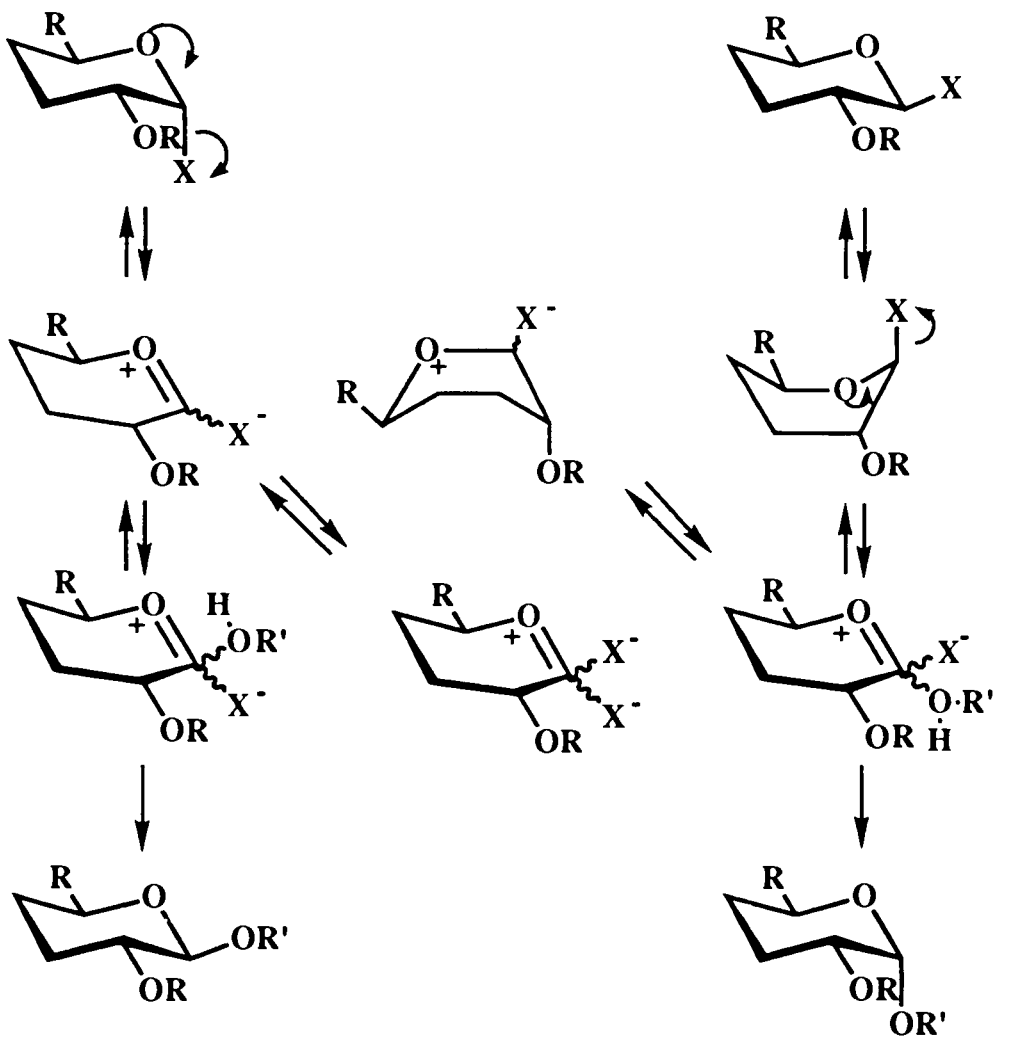


Figure 1.14. Synthesis of 1,2-*cis*-glycosides *via* the *in situ* anomerization procedure

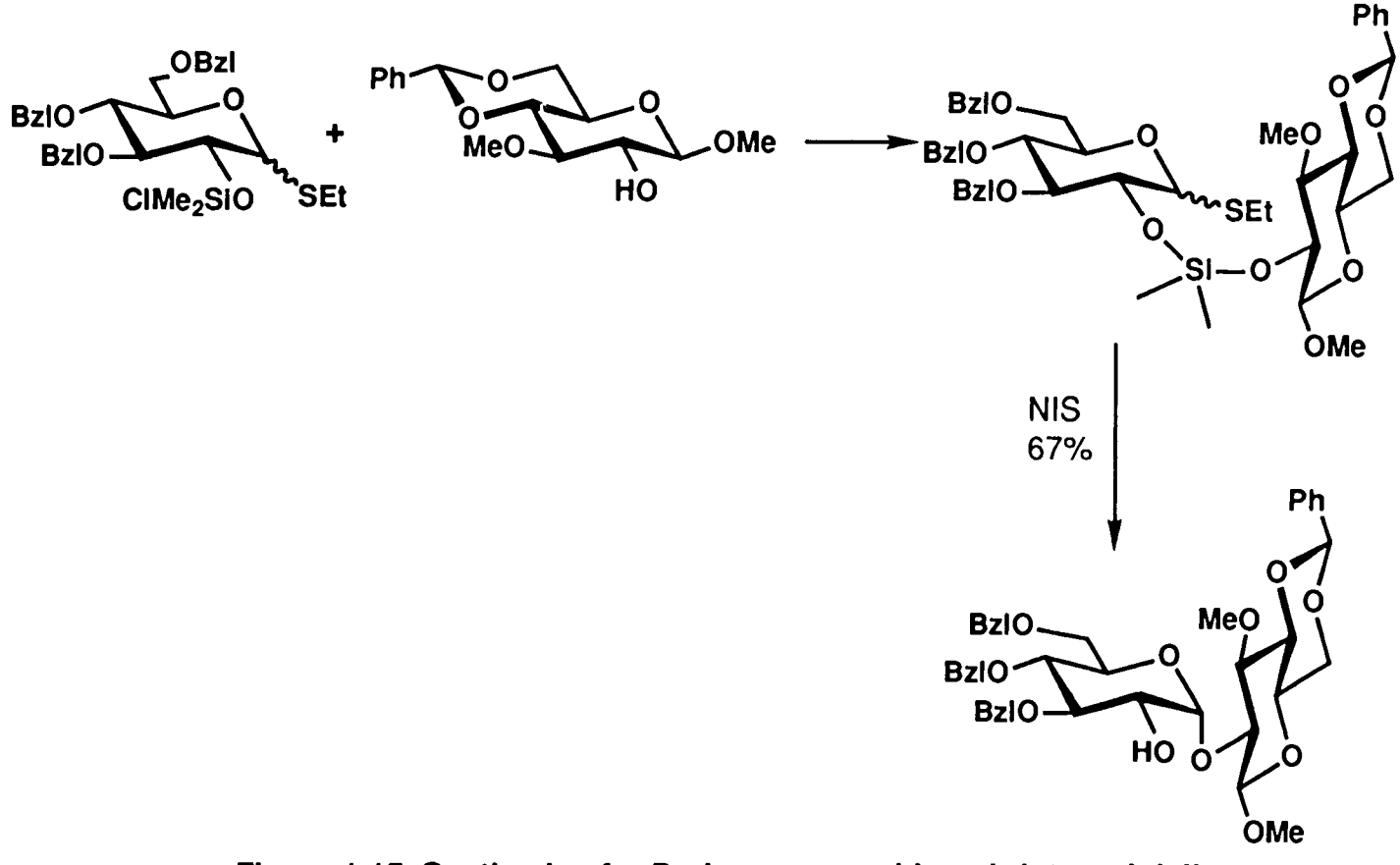


Figure 1.15. Synthesis of α-D-glucopyranosides *via* internal delivery using a silicon connector

Thus, iodides are too unstable but bromides, chlorides[21] and fluorides[33] are suitable for glycosylation reactions.

The use of glycosyl halide donors presents some inconveniences. Their thermal instability and high susceptibility to hydrolysis causes their ready breakdown to the hemiacetal. The comparatively more stable glycosyl fluorides were introduced as glycosyl donors under $SnCl_2$-$AgClO_4$ promotion by Mukaiyama *et al.* in 1981.[33a] This method of glycosylation has been exploited subsequently by others using a variety of promoters such as trimethylsilyl trifluoromethanesulfonate (TMSOTf),[33b] and boron trifluoride etherate ($BF_3.OEt_2$).[33c]

1.5.3b. Orthoesters:- The use of orthoesters for efficient oligosaccharide synthesis was described by Kochetkov and co-workers.[34]

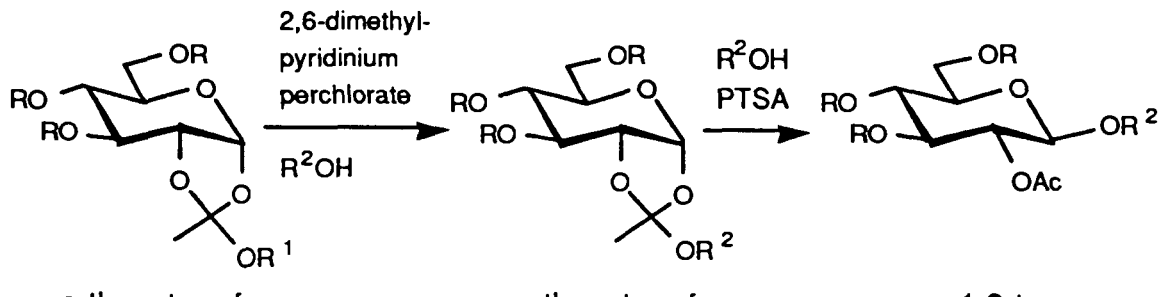


Figure 1.16. The use of orthoesters in oligosaccharide synthesis

The first step in this two-stage process requires the reaction of a simple orthoester with the glycosyl acceptor in the presence of a catalytic amount of 2,6-dimethylpyridinium perchlorate. These re-esterification conditions afford the desired orthoester which is then rearranged on treatment with the glycosyl

acceptor and a catalyst such as *p*-toluenesulfonic acid, to give the 1,2-trans glycoside (Figure 1.16).

A similar approach for the synthesis of 1,2-trans 2-amino-2-deoxyglycosides was followed by Piskorz *et al.* with oxazoline derivatives.[35]

1.5.3c. Trichloroacetimidates:- Glycosyl acetimidates were suggested as glycosyl donors by Pougny and Sinay.[36] However, syntheses with these donors proved to be cumbersome, because the relative inertness of the substrates required reactive coupling partners. This idea was modified by Schmidt and Michel[37a] who introduced and established the use of trichloroacetimidate glycosyl donors in oligosaccharide synthesis.

Glycosyl trichloroacetimidates are conveniently prepared by the reaction of a hemiacetal with trichloroacetonitrile in the presence of a base, the α, β-strereoselectivity being controlled by the choice of the base used.[37d] A weak base like potassium carbonate affords the kinetically favoured β-trichloroacetimidate and a stronger base like sodium hydride affords the thermodynamically favoured α-product (Figure 1.17).

The activation of trichloroacetimidates is achieved with a catalytic amount of acid such as boron trifluoride etherate ($BF_3.OEt_2$),[37] trimethylsilyl trifluoromethanesulfonate (TMSOTf)[37] or triethylsilyl trifluoromethanesulfonate (TESOTf)[38] The stereoselectivity of the glycosylation can be influenced further by the choice of acid.[37] A neighbouring group-active substituent at the C-2 position of the glycosyl donor favours 1,2-*trans* glycoside formation, as would be expected. In the absence of such a group, the use of $BF_3.OEt_2$ as a catalyst favours inversion at the anomeric center and produces glycosides with configurations opposite to those of the starting trichloroacetimidates. TMSOTf, a

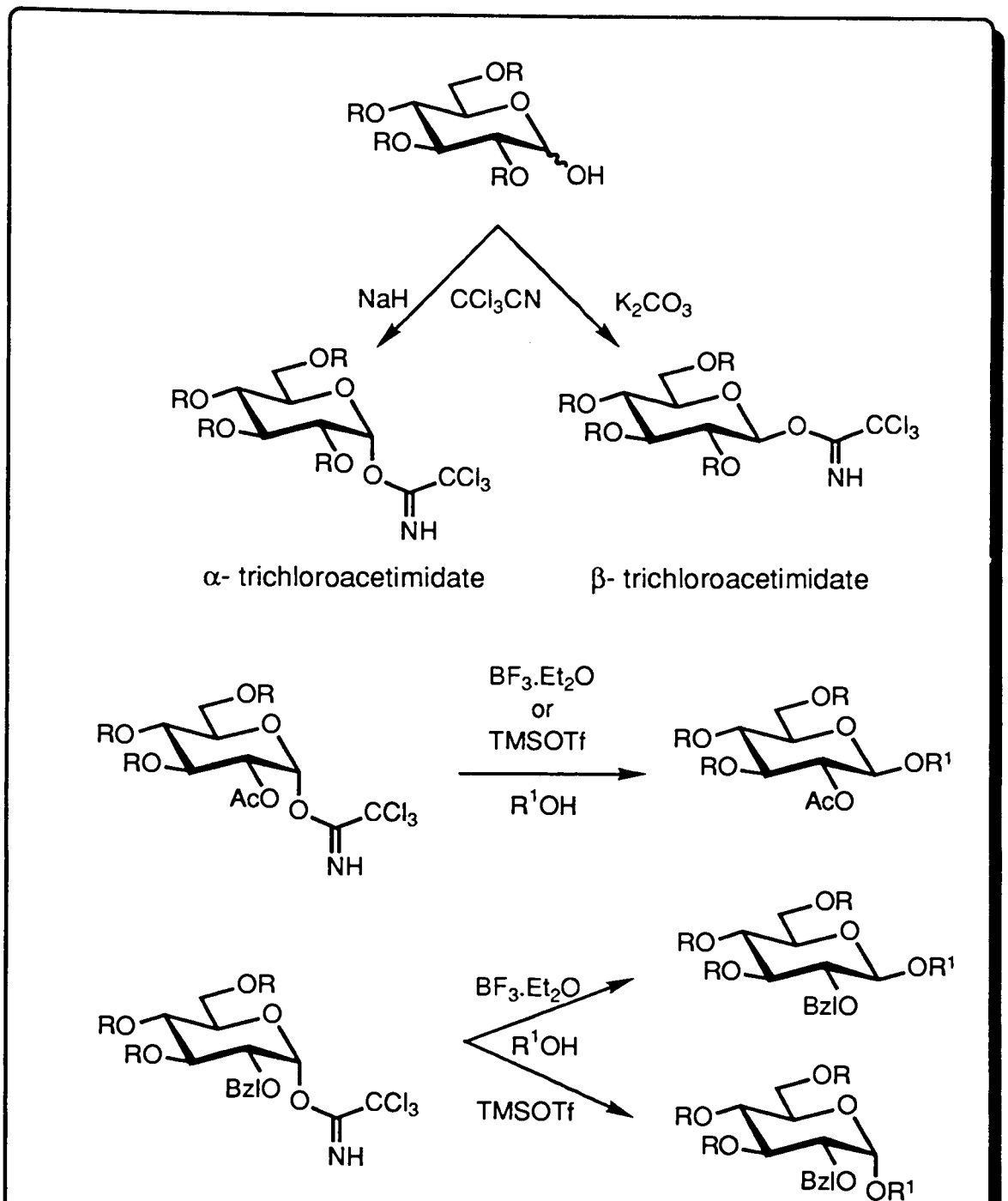


Figure 1.17. Preparation and glycosylation of glycosyl trichloroacetimidates.

stronger catalyst, favours α-glycoside formation regardless of the initial configuration of the glycosyl trichloroacetimidate.

1.5.3d. n-Pentenyl glycosides:- The use of n-pentenyl glycosides (NPGs) as glycosyl donors in oligosaccharide synthesis was pioneered by Fraser-Reid and co-workers.[39] *N*-bromosuccinimide and iodonium dicollidine perchlorate were the original promoters and the reaction was proposed to proceed through a series of transformations, as illustrated in Figure 1.18.

Subsequently, Mootoo *et al.*[40] launched the concept of armed and disarmed glycosyl donors. This can be explained as follows. The reactivities of NPGs can be modified by the manipulation of the protecting groups. These workers attributed the difference in reactivities to the group at C-2 in particular. Thus, an activating ether functionality at C-2, for example, a benzyl ether, increases the reactivity of the NPG. The compound is thereby referred to as an armed glycoside. On the other hand, an ester protecting group, such as an acetate or a benzoate, produces the opposite effect. The glycoside is now referred to as a disarmed glycoside. The result of glycosylating a disarmed NPG with an armed NPG is shown in Figure 1.19. Exclusive formation of the cross-coupled product is observed and the self-coupled product is not detected. This procedure was further refined by the use of more active promoters such as N-iodosuccinimide/ trifluoromethanesulfonic acid or N-iodosuccinimide/ triethylsilyl triflate as a source of halonium ion, which enabled the activation of disarmed NPGs in addition to armed NPGs.[41]

This 'armed and disarmed' strategy, which was initially developed for n-pentenyl glycosides, was also applied to other glycosl donors such as thioglycosides and glycals, as will be discussed in forthcoming sections.[42]

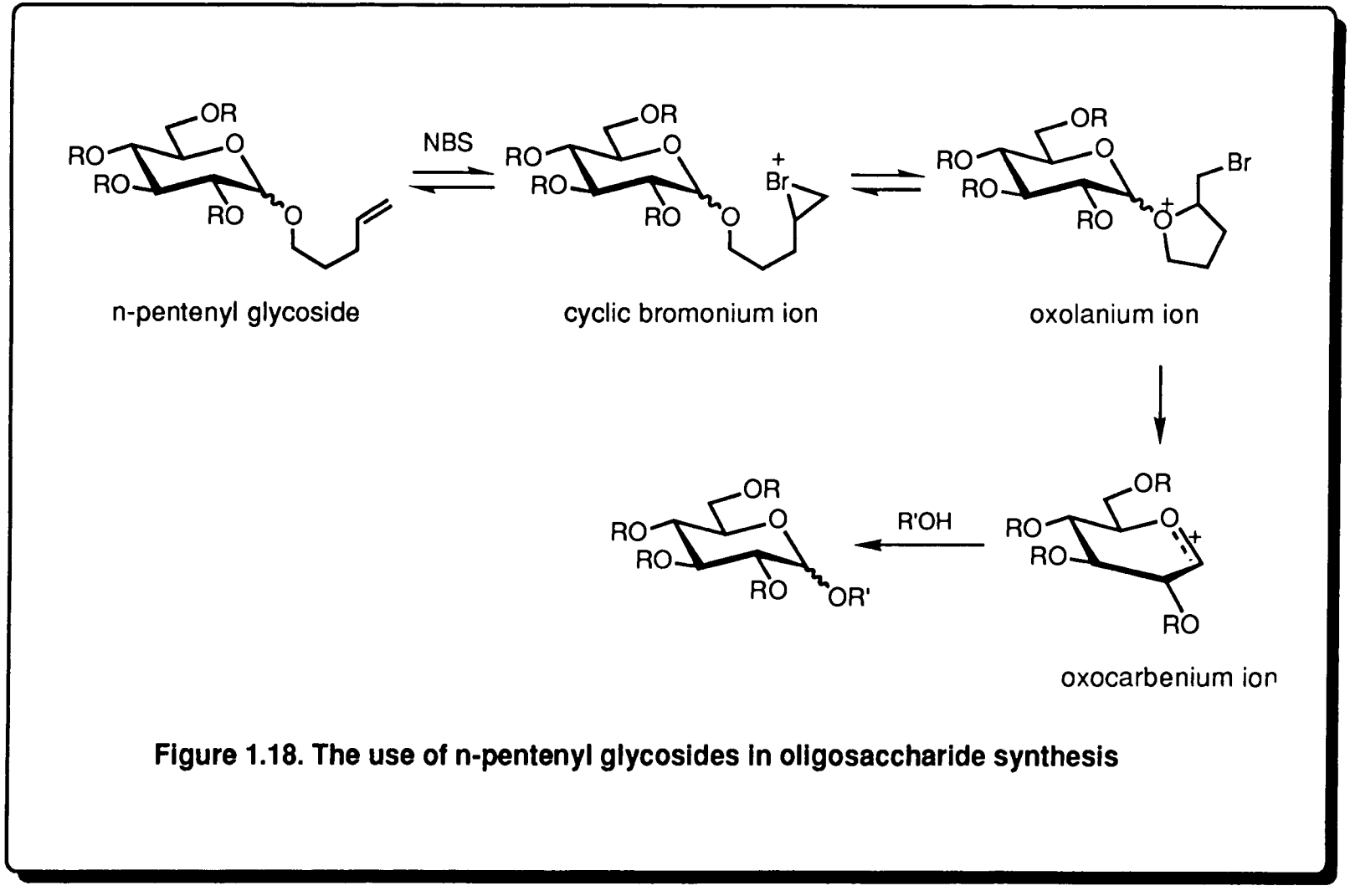


Figure 1.18. The use of n-pentenyl glycosides in oligosaccharide synthesis

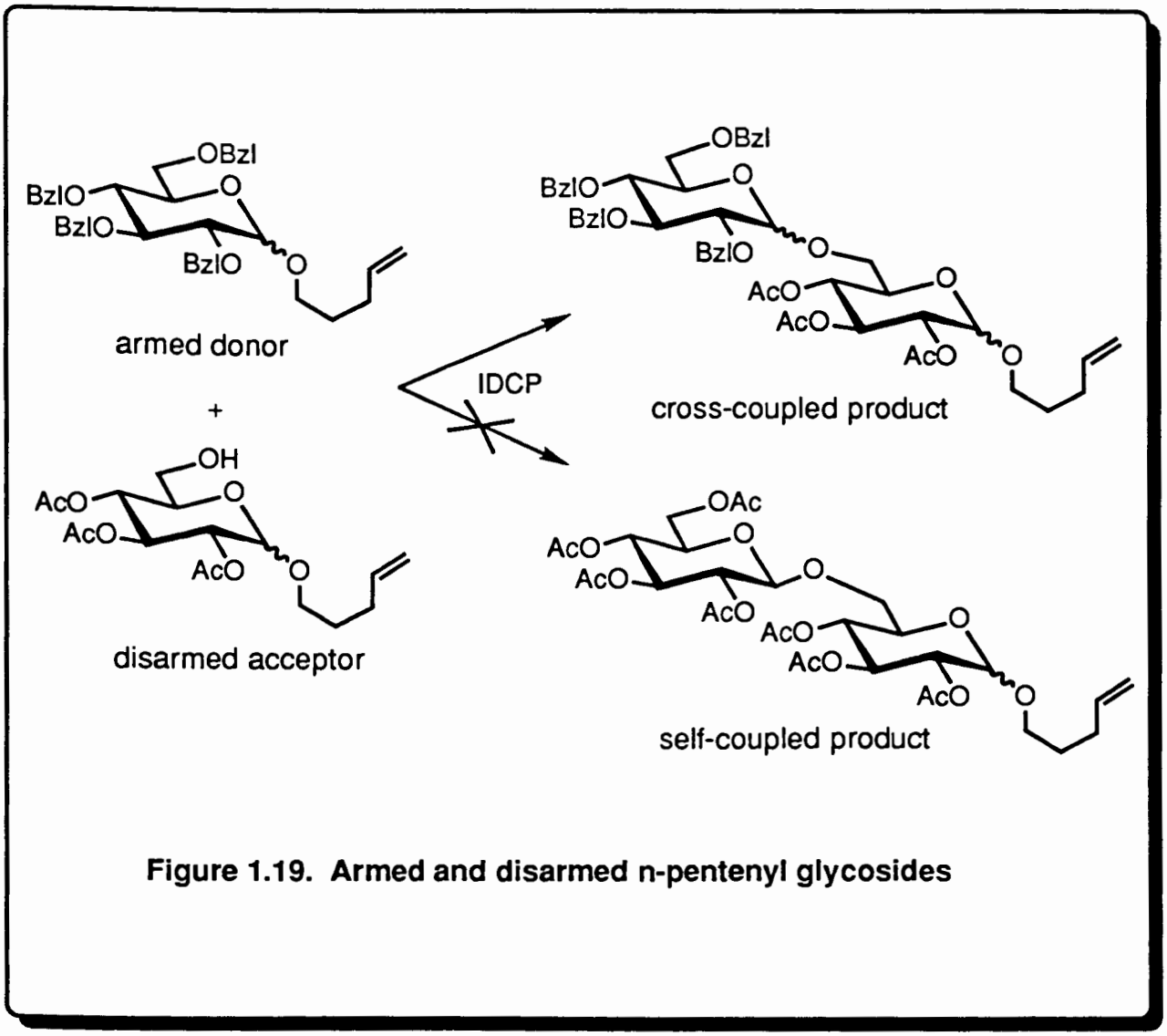


Figure 1.19. Armed and disarmed n-pentenyl glycosides

1.5.3e. Glycals:- 1,2 unsaturated sugar derivatives are known as glycals. The glycosylation of a glycal involves the addition of a halonium ion and an acceptor across the double bond (Figure 1.20). Halogenation and haloetherification of glycals was initially investigated by Lemieux and co-workers.[43] Lemieux and Morgan established halonium di-sym-collidine complexes as a source of bromonium and iodonium ions. *N*-iodosuccinimide-promoted glycosylations of glycals were reported by Thiem *et al.*[44] The oxidative coupling of glycals for the synthesis of more complex systems was further exploited by Danishefsky's research group. They employed Fraser-Reid's preferential activation technique to couple an armed glycal with a disarmed glycal acceptor using iodonium dicollidine perchlorate as the promoter.[45] This method offers convenient access to α-2-deoxy glycosides. Griffith and Danishefsky[46] have applied this methodology towards the synthesis of β-2-deoxy-2-amino glycosides and presented the sulfonamidoglycosylation of glycals. This two-step procedure requires the initial halosulfonamidation of the glucal followed by a rearrangement of the $NHSO_2Ph$ group from C-1 to C-2 and concomitant glycosylation with a glycosyl acceptor. In another approach, glycals were converted to 1,2 anhydro derivatives. Subsequent opening of the epoxides effected an inversion in configuration at the anomeric center, affording the β-glycosides[47] (Figure 1.20).

1.5.3f. Thioglycosides:- The stability of thioglycosides towards various protection and deprotection procedures has made them versatile glycosyl donors in oligosaccharide synthesis. Their activation is based on the use of electrophilic promoters, which react with sulfur to generate a sulfonium ion that is subsequently displaced by a glycosyl acceptor (Figure 1.21).

A number of thiophilic activators have been investigated in the last few years. These include methyl triflate (MT),[48] dimethyl(methylthio)sulfonium triflate

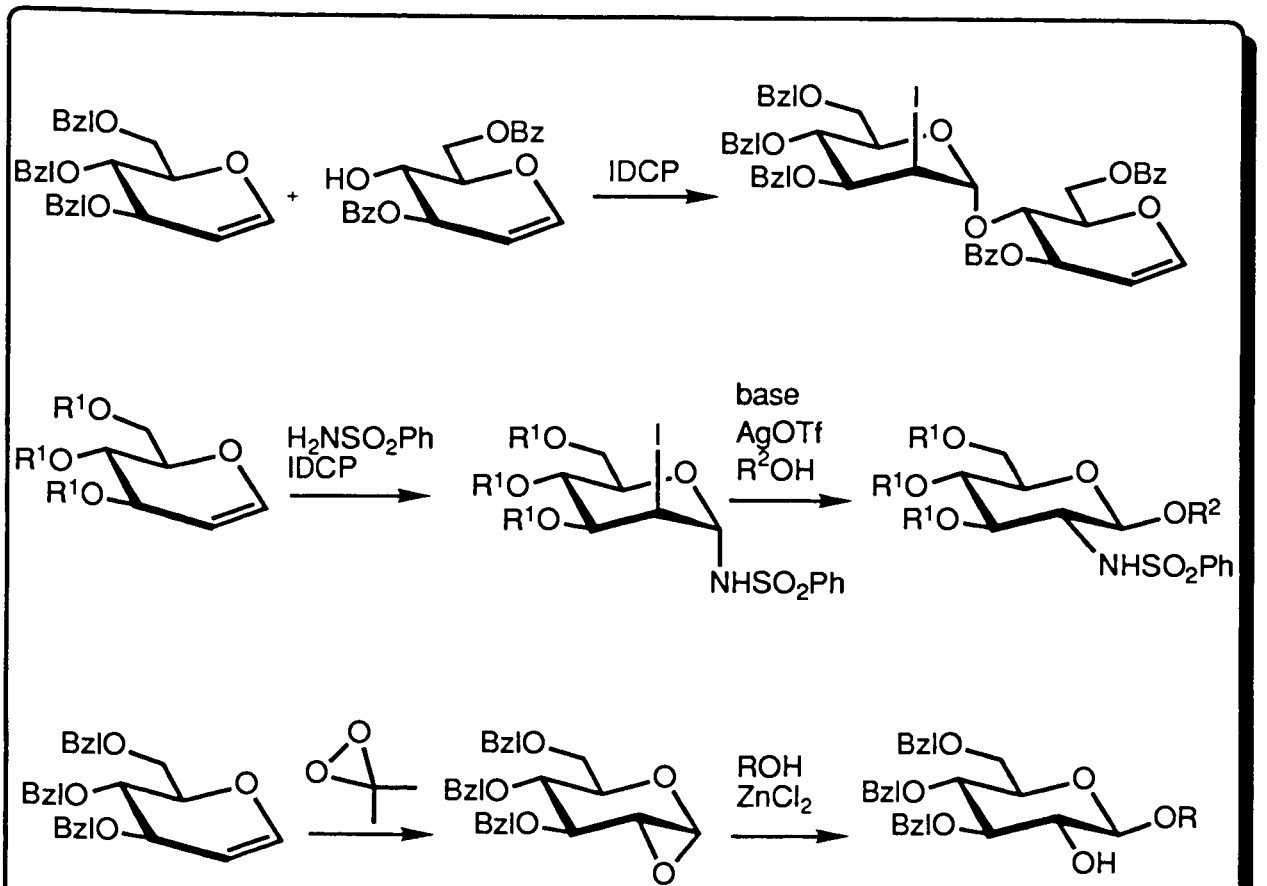


Figure 1 20. The use of glycals in oligosaccharide synthesis

(DMTST),[49] *N*-bromosuccinimide (NBS),[50] nitrosyl tetrafluoroborate ($NOBF_4$),[51] phenylselenenyl triflate (PhSeOTf).[52] However, due to their toxicity, potential carcinogenicity (MT, DMTST), irreproducible yields ($NOBF_4$) and stereoselectivities (PhSeOTf), alternative promoters were required.

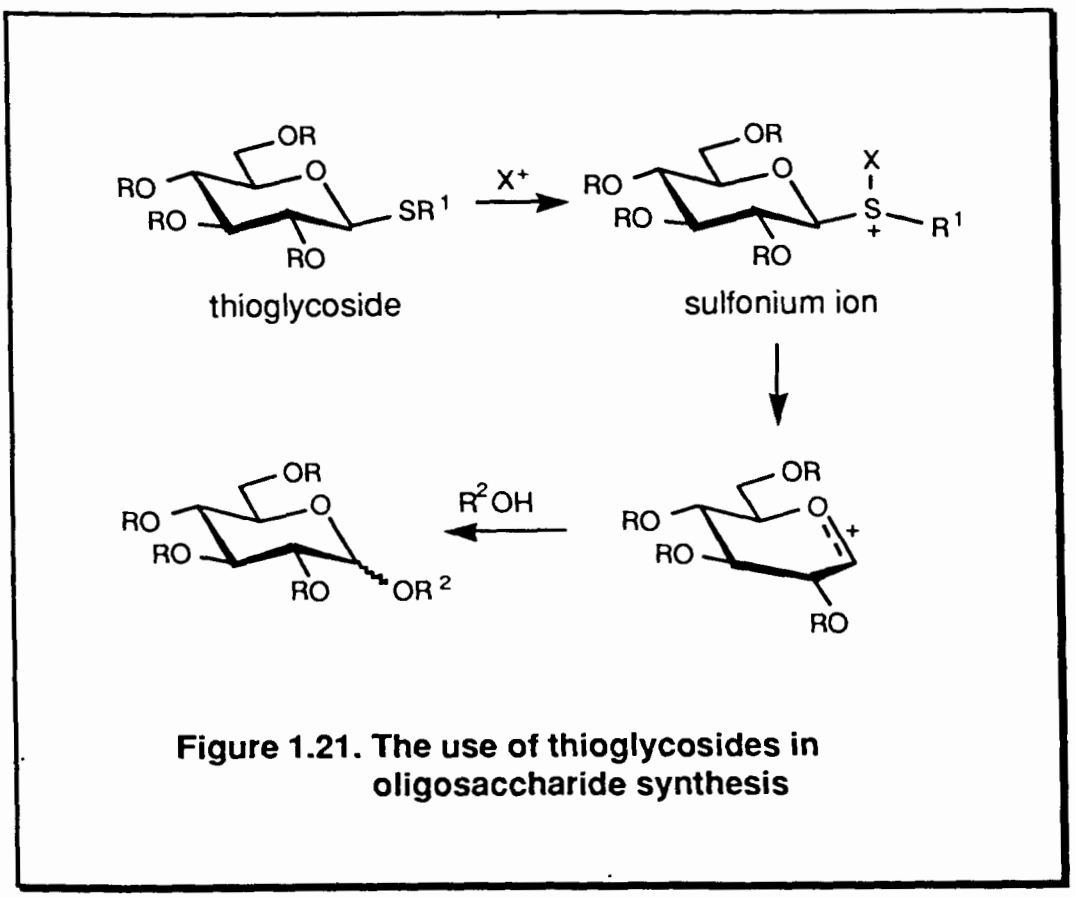


Figure 1.21. The use of thioglycosides in oligosaccharide synthesis

Veeneman and van Boom[53] described iodonium dicollidine perchlorate as a thiophilic promoter and incorporated Fraser-Reid's armed *vs* disarmed protocol. Thus, the armed benzylated thioglycoside was preferentially activated over the disarmed acetylated thioglycoside (Figure 1.22). In an analogous fashion to the case with the NPGs, a more reactive promoter like *N*-iodosuccinimide/ triflic acid was effective in promoting the disarmed as well as the armed thioglycoside[54] (Figure 1.22).

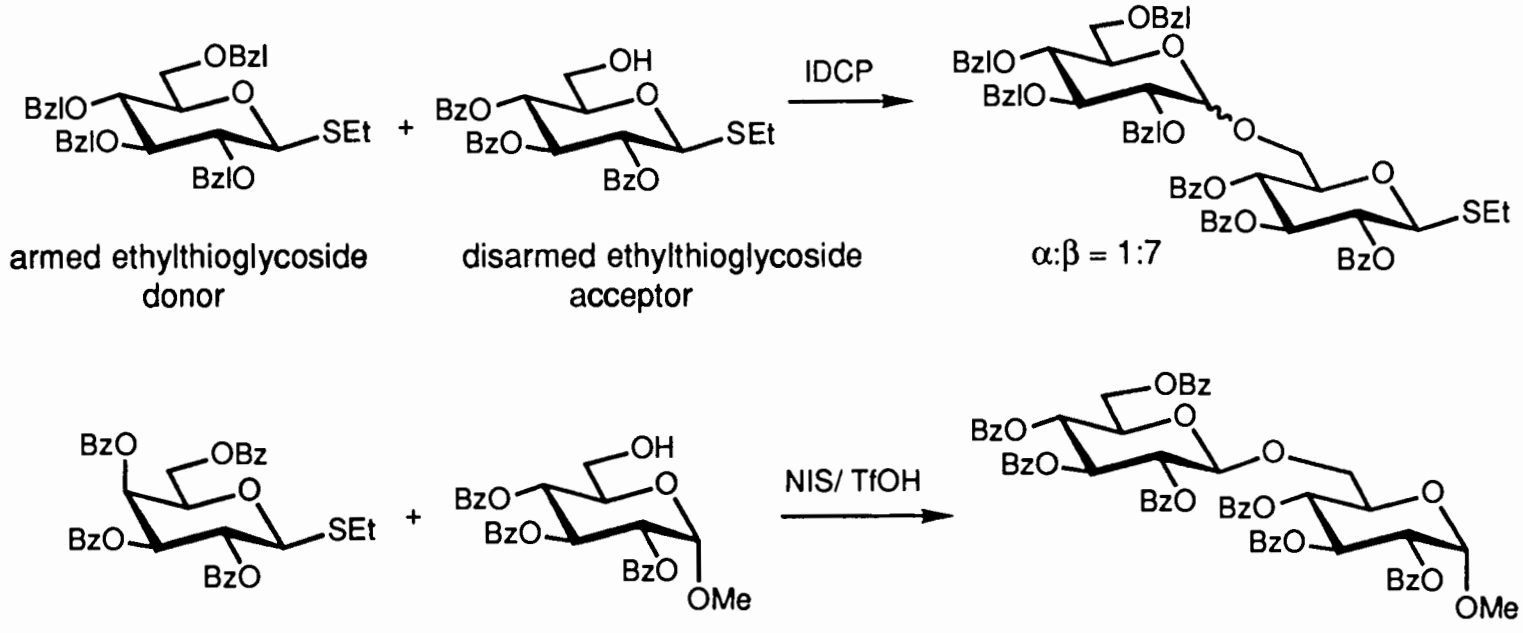


Figure 1.22. Armed and disarmed thioglycosides

1.5.3g. Solid-Phase Oligosaccharide Synthesis

The concept of solid-phase oligosaccharide synthesis is an attractive alternative to synthesis in solution. It provides a simple method of synthesis that eliminates tedious purification and protecting group manipulation. Solid-phase synthesis can be accomplished, in principle, by either of the following approaches (Figure 1.23).

1. Extension of the oligosaccharide at its reducing end:- The glycosyl acceptor at the nonreducing terminal can be linked to the solid support and chain extension can be effected by its reaction with a solution-based glycosyl donor.
2. Extension of the oligosaccharide at its nonreducing end:- The glycosyl donor at the reducing end can be attached to the solid support and chain extension can be effected by its reaction with a solution-based acceptor.

The former strategy has been attempted by a number of research groups.[55] It has been applied by Douglas et al. in the polymer-supported solution synthesis of oligosaccharides.[56] Glycosyl acceptors were bound to the polymer [$HOCH_2CH_2(OCH_2CH_2)_n$ OCH_3, n=80-160] (PEG), and were glycosylated with glycosyl bromide and glycosyl trichloroacetimidate donors. Di- and trisaccharides were produced in good yields after repeated rounds of glycosylation. The attractiveness of this method is the ease of isolation of the final product by its precipitation from the solution. Verduyn et al. have applied the above approach towards the synthesis of heptaglucoside in 18% yield based on the initial PEG bound monosaccharide.[57] However, the glycosylations are slow and they lack the stereoselectivity that established solution methodologies can provide. Moreover, functional group manipulations are required on the oligosaccharide attached to the solid support and this creates difficulties.

More recently Danishefsky and coworkers[58] have employed the latter strategy and applied it to glycal donors and acceptors for the solid-phase

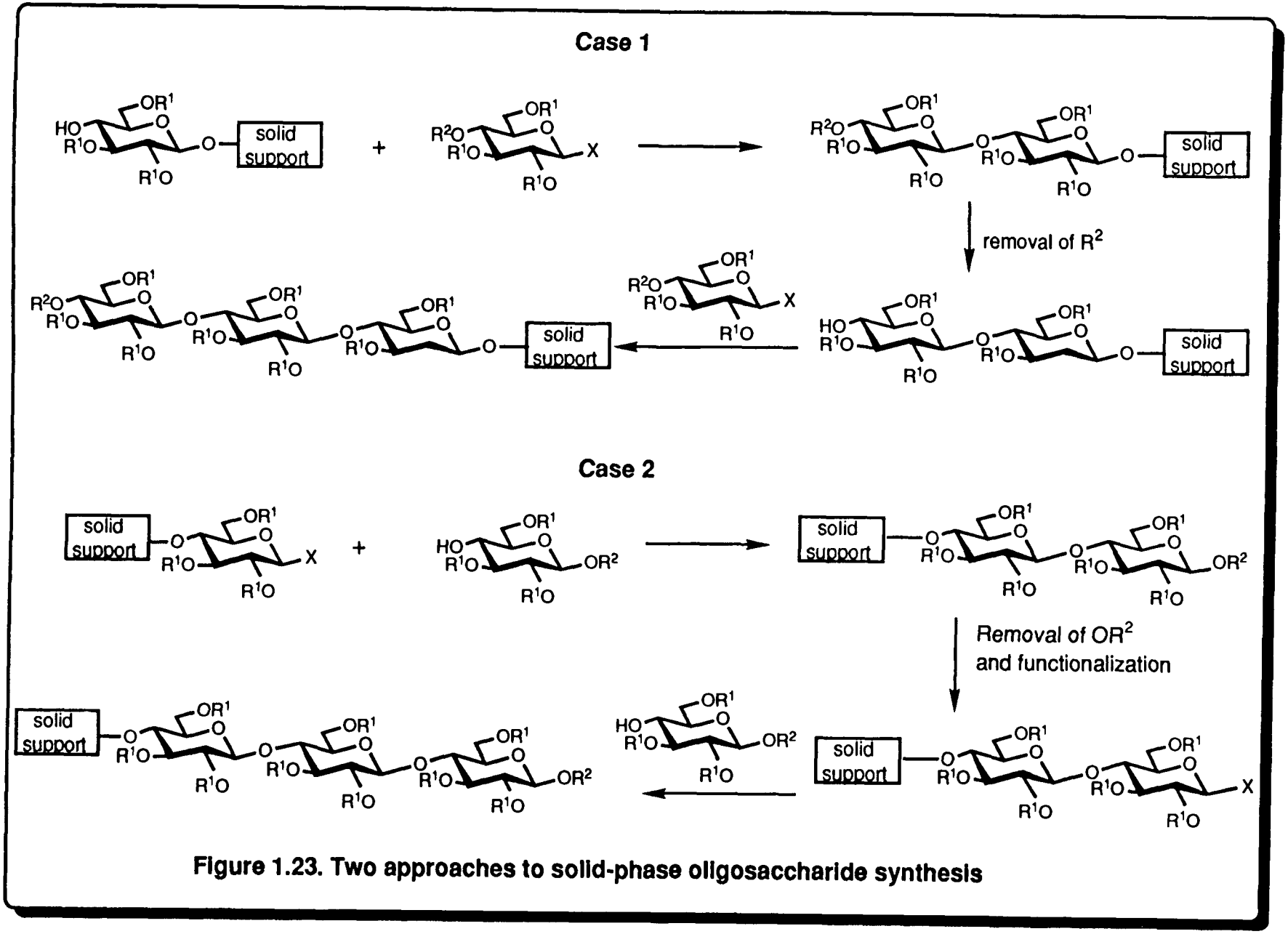


Figure 1.23. Two approaches to solid-phase oligosaccharide synthesis

synthesis of oligosaccharides (Figure 1.24). In this approach a latent glycal donor was tethered to a solid support. The donor was activated by epoxidation and subsequently used to glycosylate a suitably protected glycal acceptor in a stereoselective fashion. The reaction was repeated in a similar manner resulting in chain elongation. Although this strategy is still at its initial stage of development, and the yields are far lower than desired, this method may provide a stepping stone to automated oligosaccharide synthesis.

1.6. Enzymatic Oligosaccharide Synthesis

Enzymatic oligosaccharide synthesis has become a popular complement to chemical synthesis. The enzymatic approach offers the advantage of avoiding protection and deprotection of the reacting partners due to the highly regioselective and stereoselective nature of the reactions.

The two classes of enzymes used for effecting the synthesis of oligosaccharides are glycosidases and transferases. Glycosidases[59] are a group of enzymes that bring about the degradation of polysaccharides. Their reversed hydrolytic activity has been utilized for the condensation of sugars to produce higher-order oligosaccharides. The general principles are illustrated in Figure 1.25. Glycosidases are more accessible and are less expensive than glycosyl transferases. However, owing to the difficulty in isolation of the products, and the low regiospecificity observed in these reactions, glycosidases are of limited applicability.

Glycosyl transferases[59] are a group of enzymes which catalyze the transfer of a monosaccharide moiety of a sugar nucleotide to a suitable acceptor, resulting in the formation of a glycosidic linkage. This reaction may be represented as shown in Figure 1.26. The seven major nucleotides found in

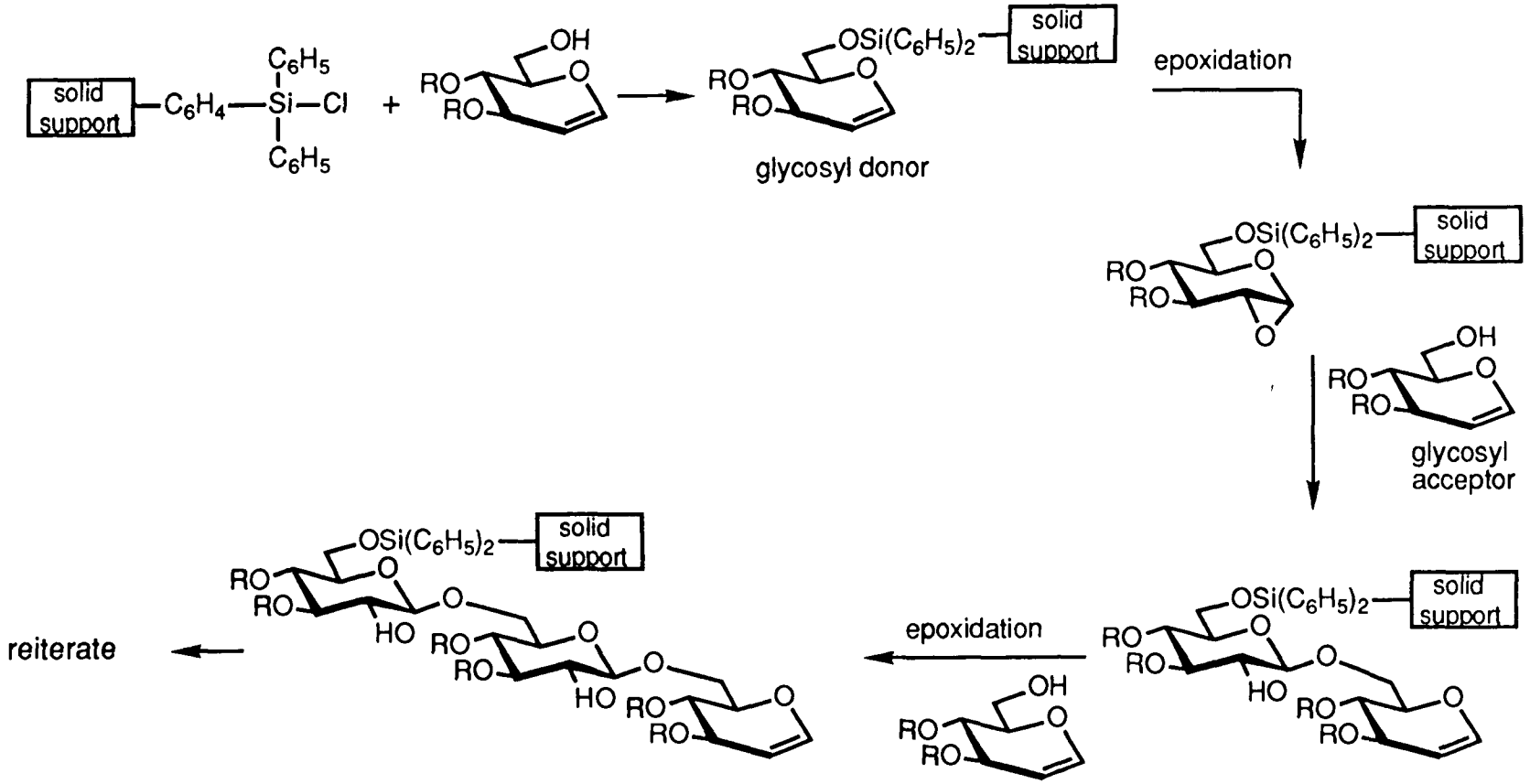


Figure 1.24. Solid-phase oligosaccharide synthesis with glycals

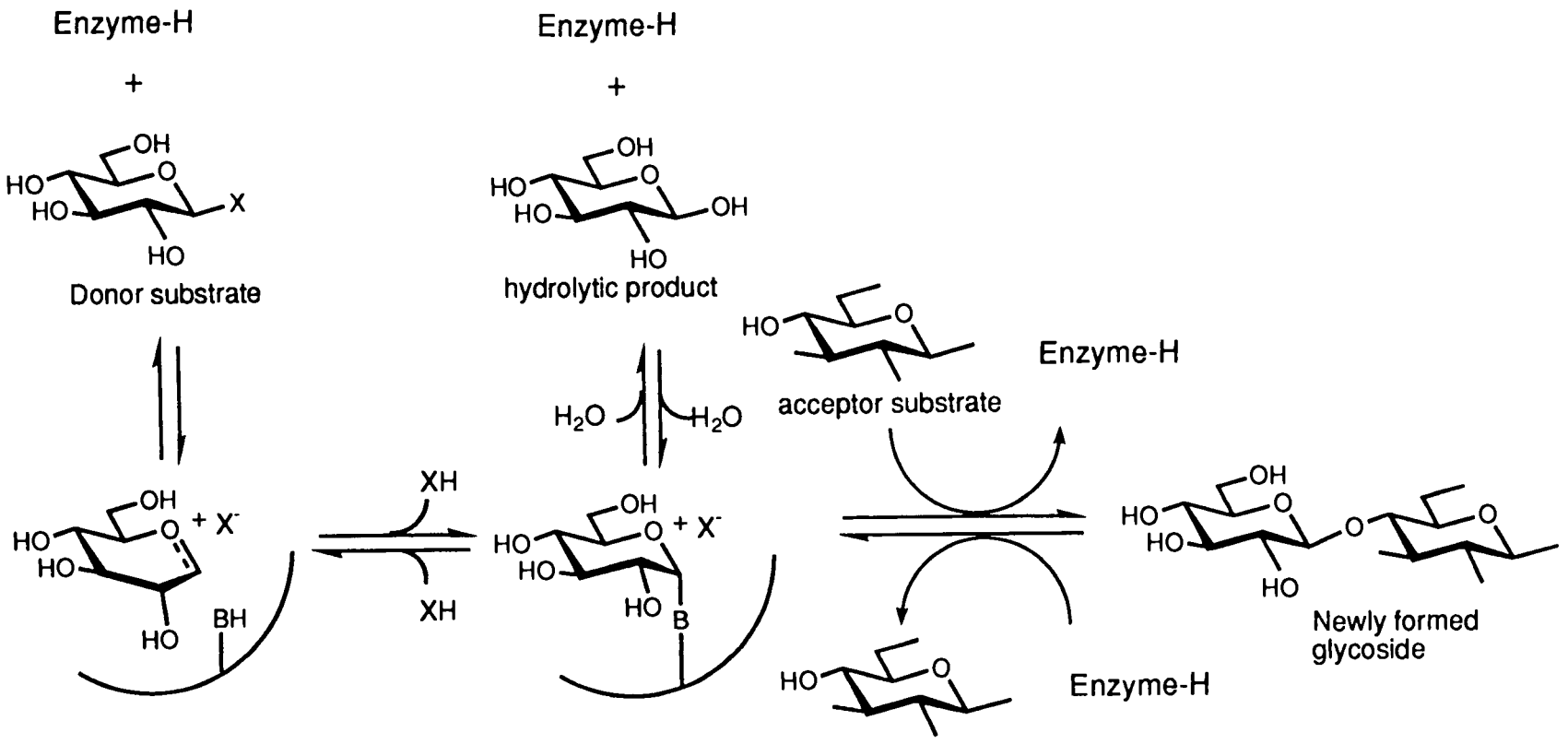


Figure 1.25. Glycosidases in oligosaccharide synthesis

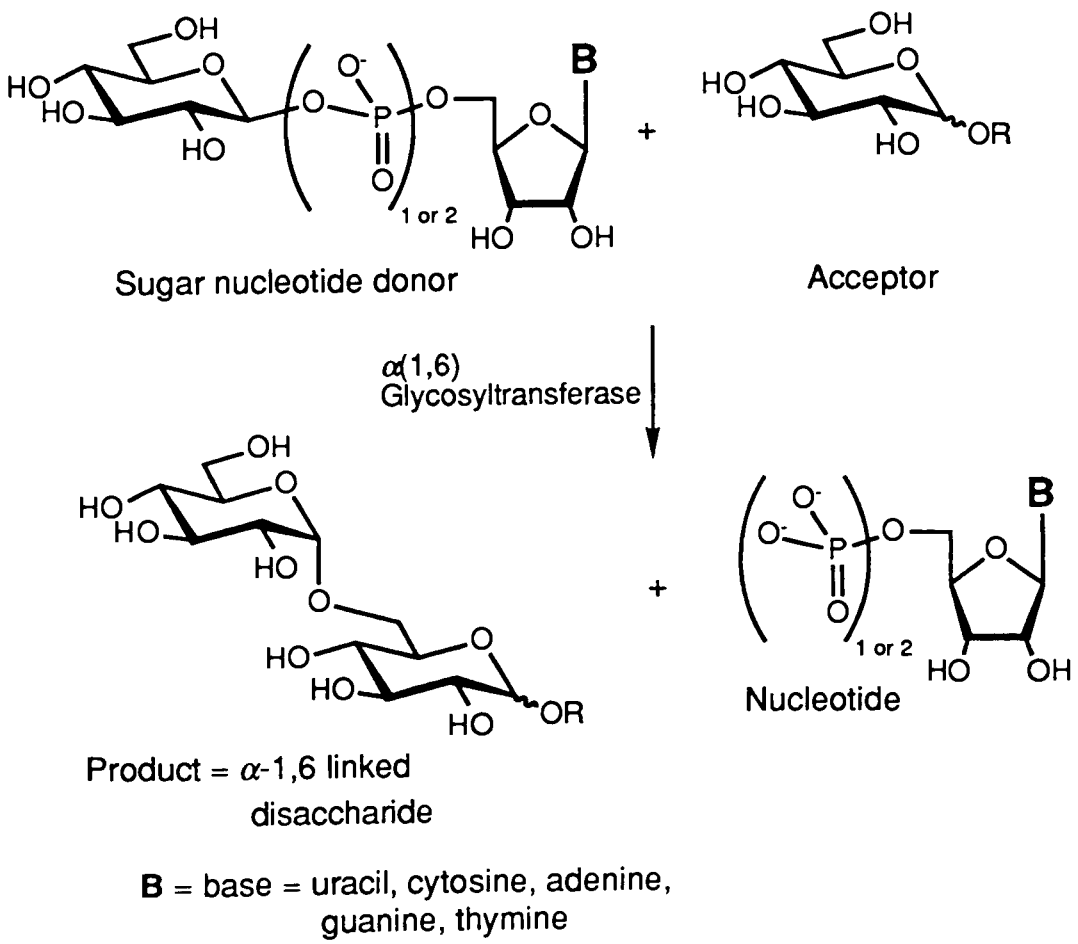


Figure 1.26. Glycosyltransferases in oligosaccharide synthesis

mammalian systems are UDP-Glc, UDP-Gal, UDP-GlcNAc, UDP-GalNAc, GDP-Man, GDP-Fuc and CMP-NeuAc. All these are diphosphates except for the activated form of *N*-acetylneuraminic acid (NeuAc) which is a monophosphate nucleotide.

The use of glycosyl transferases, however, is limited by the availability of the required enzyme in sufficient quantities. The sugar nucleotides are expensive and require prior synthesis. Moreover, the accumulation of stoichiometric amounts of the nucleotides during the course of the reaction exerts an inhibitory influence on the enzyme. Another principle drawback is that the majority of these enzymes require cofactors such as ATP or NAD(P)H which are very expensive and add to the cost of the synthesis. Also, due to the high degree of specificity exhibited by these enzymes, unnatural sugar analogues are not always accessible *via* this approach (see later, however).

These difficulties have been addressed by various research groups. Enzymes have been immobilized on a solid support to allow their recovery and reuse.[60] The sugar nucleotides can now be generated *in situ*[61] through a series of enzymatic reactions, requiring only catalytic amounts of the nucleotides and nucleoside phosphates. This circumvents the generation of stoichiometric amounts of the nucleotide, thereby suppressing enzyme inhibition.[62] Strategies have been developed for the enzymatic regeneration of cofactors during the reaction. Thus, ATP is regenerated from ADP or AMP in situ.[63] The synthesis of sialyl-*N*-acetyllactosamine presented by Ichikawa *et al.*[63] demonstrates the application of these ideas (Figure 1.27). The disaccharide Gal-β–(1,4)-GlcNAc was glycosylated with NeuAc with α–(2-6)-sialyltransferase. The activated form of NeuAc, which is CMP-NeuAc, was regenerated *in situ*. The enzymatic cycle was completed by three other enzymes, regenerating five other cofactors. The

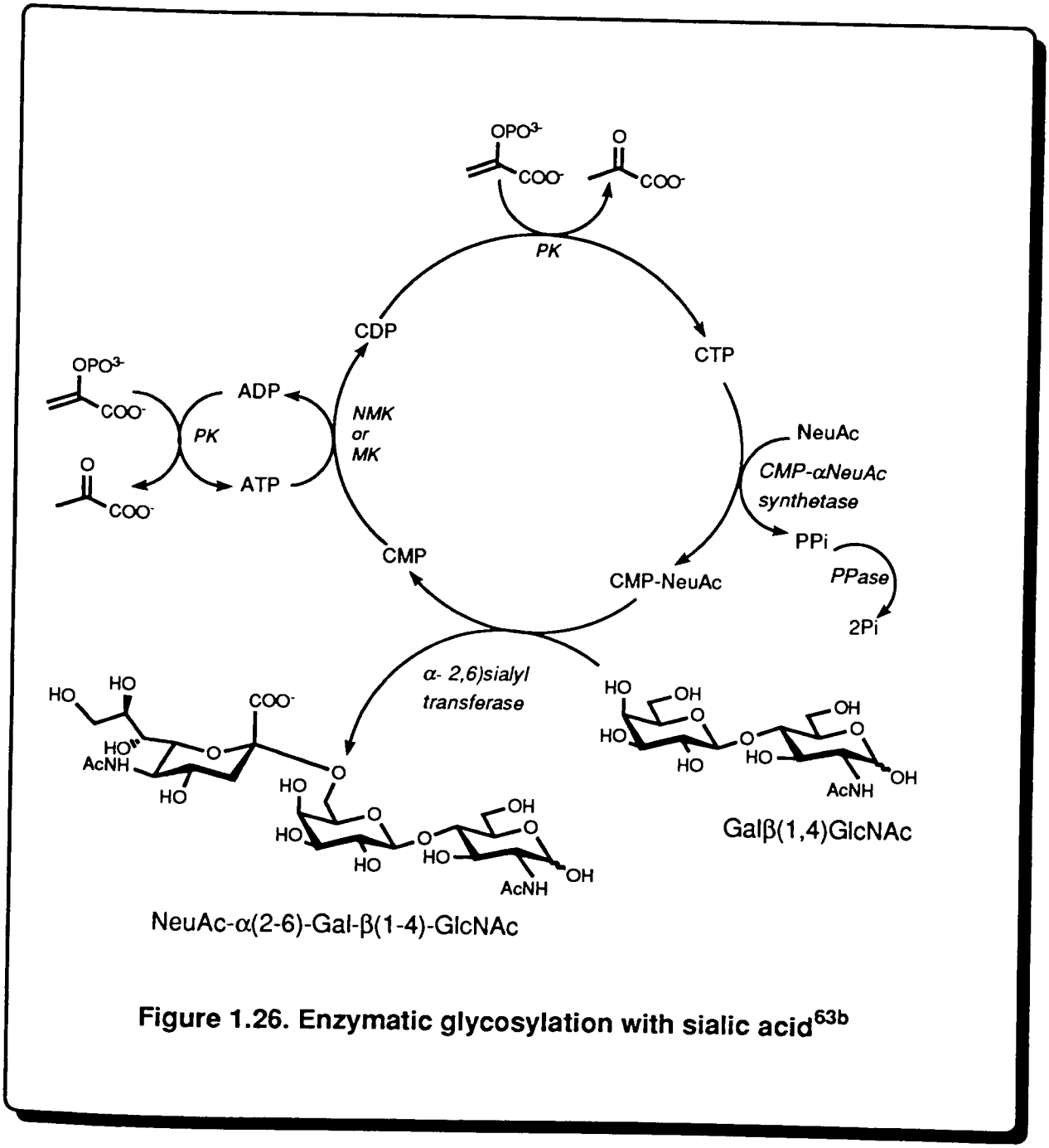


Figure 1.26. Enzymatic glycosylation with sialic acid[63b]

regeneration of nicotinamide cofactors is more complicated due to their instability in solution. A number of regeneration systems have been developed where NAD(P)H is enzymatically obtained from NAD.[62] With regard to the synthesis of sugar analogues, glycosyltransferases have been used to effect the transfer of unnatural substrates. The enzyme α–(1-4)- fucosyl transferase, that effects the transfer of a fucose residue from the fucose nucleotide GDP-fucose has also been employed for fucose analogs such as 3-deoxyfucose and arabinose; structural analogs of the Lewis-a trisaccharide have thus been synthesized.[64] Similarly, the transferase β–(1-4)-GalT has effected glycosylation with an unnatural donor, UDP-5S-Gal, as illustrated in Figure 1.28.[65] In an alternative approach, natural monosaccharide substrates have been transferred to unnatural acceptors such as 1-deoxynojirimycin and 5-thioglucose (Figure 1.29).[66] However, the receptivity of the enzyme towards its modified substrate is less than 10% that of the natural one and yields are often low.

Although the enzymatic approach has been effective in furnishing a large variety of oligosaccharides, this approach is often limited to small scale reactions, affording milligram quantities of product, just sufficient for characterization. Cloning techniques are now being applied to obtain enzymes in desired quantities and to modify the specificity of enzymes so that they can accomodate a wider range of substrates.[63]

Although these procedures are currently confined to a few specialized groups, these innovative technologies have great potential for oligosaccharide synthesis on a commercial scale.

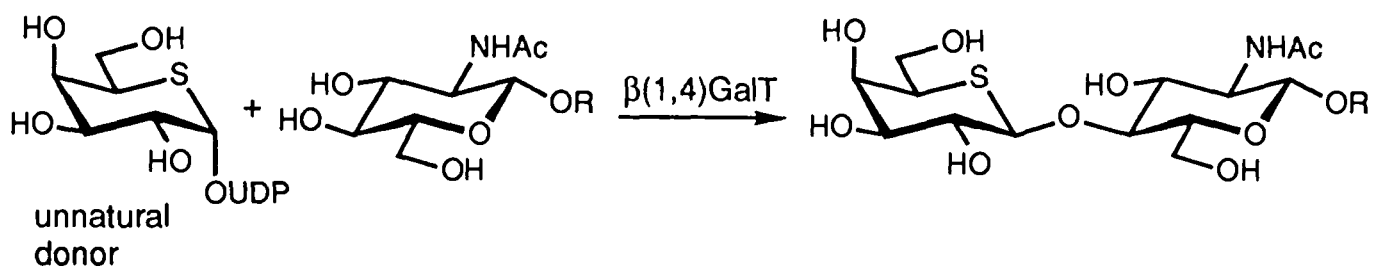


Figure 1.28. Enzymatic transfer of an unnatural donor

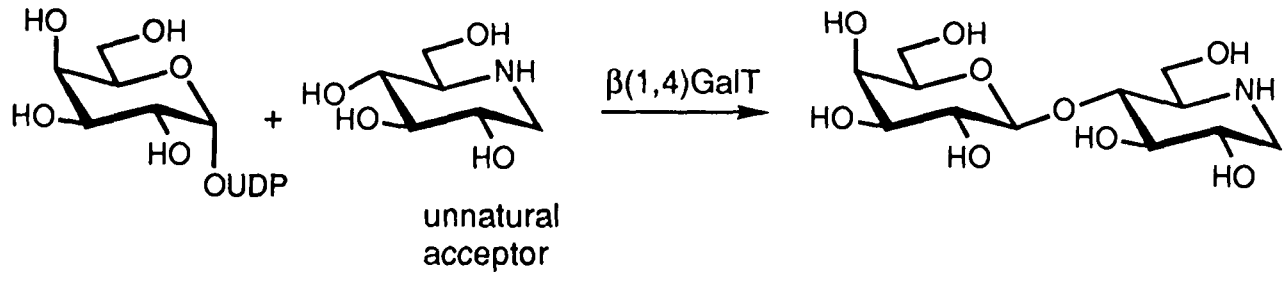


Figure 1.29. Enzymatic transfer to an unnatural acceptor

1.7. Glycosylation with Sialic Acid

The synthesis of oligosaccharides containing sialic acid[67] (sialosides) is particularly challenging for the following reasons. The presence of a carboxylic group at the anomeric position of sialic acid disfavours its glycosylation due to both steric as well as stereoelectronic factors. The deoxy carbon adjacent to the anomeric center offers no opportunity for stereochemical control and the glycosylations are often not stereoselective. Moreover, complications arise due to competitive elimination, leading to the 2,3-dehydro derivative as an undesirable side product.

In spite of these impediments, there are a number of reports of successful chemical syntheses of complex sialosides. Thioglycosides of *N*-acetyl neuraminic acid (NeuAc) have been used as glycosyl donors for glycosylation of a variety of acceptors with promoters such as DMTST,[68] NIS/TfOH,[69] MSB/AgOTf,[70] Stereocontrolling auxiliary groups such as phenylthio-[71] or phenylseleno-[72] groups at the C-3 position of NeuAc have been employed to direct alcohol attack to the α face. Glycosylations are generally conducted in acetonitrile to favor α-glycosylation. A very elegant strategy involves the use of 'lightly protected' acceptors.[67,70] An acceptor with more than one unprotected hydroxyl group is termed 'lightly protected.' This approach utilizes the differential reactivity of the hydroxyl groups to achieve the desired linkage, which at the same time, minimizes steric effects of nearby, bulky protecting groups which may impede glycosylation.

Some examples of α-sialyl oligosaccharide synthesis are presented. Lonn and Stervall[70] reported the glycosylation of a lightly protected lactose derivative with a sialosyl xanthate in the presence of AgOTf/MSB in an exceptionally high yield of 82% (Figure 1.30). Kameyama *et al.*[73] described the first synthesis of

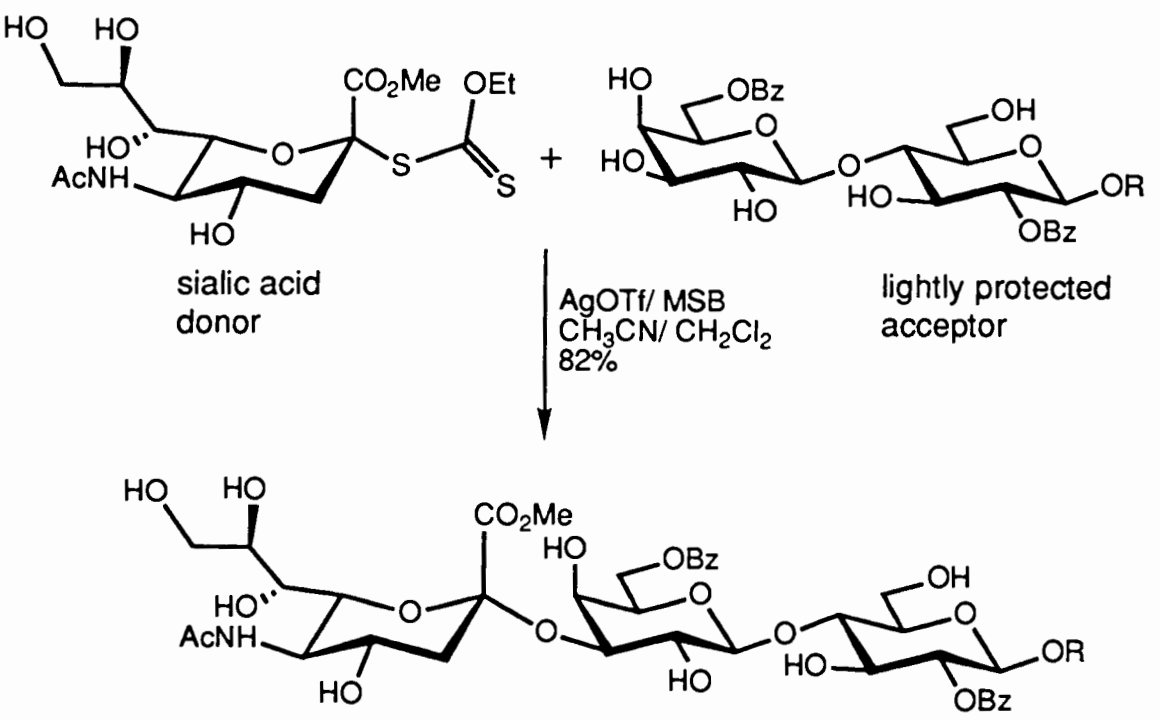


Figure 1.30. Chemical glycosylation of sialic acid with a 'lightly protected' acceptor

sialyl Lewis^x, a hexasaccharide which is a ligand recognized by ELAM-1 as well as a tumor-associated antigen. Very impressive syntheses of more complex disialogangliosides,[74] multiply sialylated oligosaccharides,[75] and dimeric sialyl Lewis^x [76] have also been reported.

To alleviate the problems associated with the chemical glycosylation of NeuAc, a number of research groups have adopted a combined chemical and enzymatic approach to α-sialosides. In this approach, oligosaccharide precursors are synthesized by conventional chemical methods, deprotected and subsequently sialylated enzymatically. For example, Sabesan and Paulson have followed this strategy for the synthesis of a series of α-sialyl oligosaccharides on a 10-20 mmol scale.[77]

The completely enzymatic synthesis of sialyl-*N*-acetyllactosamine was described by Ichikawa *et al.* with *in situ* regeneration of the sugar nucleotide CMP-sialic acid,63 as previously discussed in Section 1.4, Figure 1.25.

In spite of these enviable syntheses, there remains a demand for more flexible and more generalized glycosylation methods which yield oligosaccharides with greater stereoselectivity and in higher yields.

1.8. THESIS OVERVIEW

The second chapter of this thesis describes the development of novel glycosylation methodology with the use of phenyl selenoglycosides as glycosyl donors and acceptors in oligosaccharide synthesis. The versatility of these compounds is demonstrated firstly, by their selective activation over ethyl thioglycosides with silver trifluoromethanesulfonate in the presence of potassium or silver carbonate, and secondly, by their inertness under conditions of activation of glycosyl halides by silver trifluoromethanesulfonate promotion in the

presence of collidine and glycosyl trichloroacetimidate donors with triethylsilyl trifluoromethanesulfonate, which permits their use as glycosyl acceptors.

The third chapter of this thesis describes radical-cation-initiated glycosylation reactions of phenyl selenoglycosides. Glycosylations of selenoglycosides effected by the single-electron-transfer (SET) reagent tris(4-bromophenyl)aminium hexachloroantimonate (BAHA) are examined with primary and secondary hydroxyl acceptors. Reactions in the presence of the SET quenching reagent 1,2,4,5-tetramethoxybenzene, to assess whether BAHA-mediated glycosylation reactions, indeed involve single-electron-transfer or whether they are acid catalyzed are described. The oxidation potentials of various selenoglycosides are determined by cyclic voltammetry.

The fourth chapter describes the synthesis of heteroanalogues of methyl and allyl kojibiosides, methyl maltoside and methyl isomaltosides for evaluation as glycosidase inhibitors. The glycosyl trichloroacetimidate of 2,3,4,6-tetra-O-acetyl-5-thioglucopyranose is used as a new donor to glycosylate selectively protected glucopyranosyl acceptors with 2-OH and 6-OH positions free, under triethylsilyl trifluoromethanesulfonate promotion, to afford the 1,2-linked and the 1,6-linked disaccharides as 3:1 and 1.5:1 α:β mixtures, respectively. Methyl α-D-glucopyranoside acceptors containing 4-OH and 4-SeH functions are glycosylated with the same donor under triethylsilyl triflate catalysis, to give exclusively the α-5'-thiodisaccharide, and a 4:1 α/β mixture of the 4-seleno-5'-thiodisaccharides, respectively. The disaccharides are deprotected to give heteroanalogues for evaluation as glycosidase inhibitors.

CHAPTER II

NOVEL GLYCOSYLATION METHODOLOGY. THE USE OF PHENYL SELENOGLYCOSIDES AS GLYCOSYL DONORS AND ACCEPTORS IN OLIGOSACCHARIDE SYNTHESIS

2.1. INTRODUCTION

In the last decade there has been a strong impetus for the development of new and improved methods of oligosaccharide synthesis. The wide ranging reactivities and stereoselectivities of the numerous glycosyl donors and acceptors restrict the development of more generalized synthetic methods. The synthesis of every oligosaccharide target presents itself as a unique challenge. Therefore, the development of general chemical methods of synthesis that require fewer synthetic manipulations, result in higher yields and increased stereoselectivity, and enable selective activation are desired.

One of the recent contributions to this end includes the strategy of "armed" and "disarmed" glycosyl donors. This method is based on the differential reactivities conferred upon reacting partners by the nature of the protecting groups (Section 1.3.3d). However, this innovative approach suffers from two major disadvantages. Firstly, the "armed" glycosyl donors require the presence of a benzyl substituent at the C-2 position, which is a non-neighbouring group active substituent. This compromises the stereoselectivity of the glycosylation reaction. Complex α,β- mixtures of oligosaccharides are produced that are often difficult to separate. Secondly, the synthesis of a target oligosaccharide is

usually dictated by the choice of protecting groups that may require selective removal in subsequent steps. Hence, it may not always be viable to position an activating benzyl substituent at the C-2 position.

An alternative strategy derives from the availability of two reacting units, the glycosyl X, and the glycosyl Y unit, in such a way that one of these units can be selectively activated over the other. This strategy relies on the ability to functionalize the anomeric centers of the glycosyl X and glycosyl Y units with different leaving groups, where one remains latent when the other one is activated.

This type of selectivity in glycosyl activation was initially described by Silwanis et al.[78] The authors demonstrated the control of reactivities of phenyl thioglycosides by the choice of the para substituent. The selective activation of a methyl thio- or phenyl thioglycoside over a comparatively inert (*p*-nitrophenyl)-thioglycoside was shown. More recently, Roy et al.[79] described a study of the effects of activating and deactivating substituents on the reactivities of para-substituted (phenylthio)-α-sialosides in glycosylation reactions (Figure 2.1). Thus, electron donating substituents on the (phenylthio-)α-sialosides afforded "active" glycosyl donors that were glycosylated under *N*-iodosuccinimide/ triflic acid (NIS/ TfOH) and dimethyl(methylthio)sulfonium triflate (DMTST) promotion. An electron withdrawing group such as the nitro group afforded "latent" thioglycosides which were inert. They had the potential of being activated towards electrophilic promotion following the conversion of the nitro group into an NH-acetyl function. Subsequently, Sliedregt et al.[80] combined the approach of "active" and "latent" thioglycosides with the concept of "armed" and "disarmed" glycosyl donors, providing greater flexibility in glycosylation reactions.

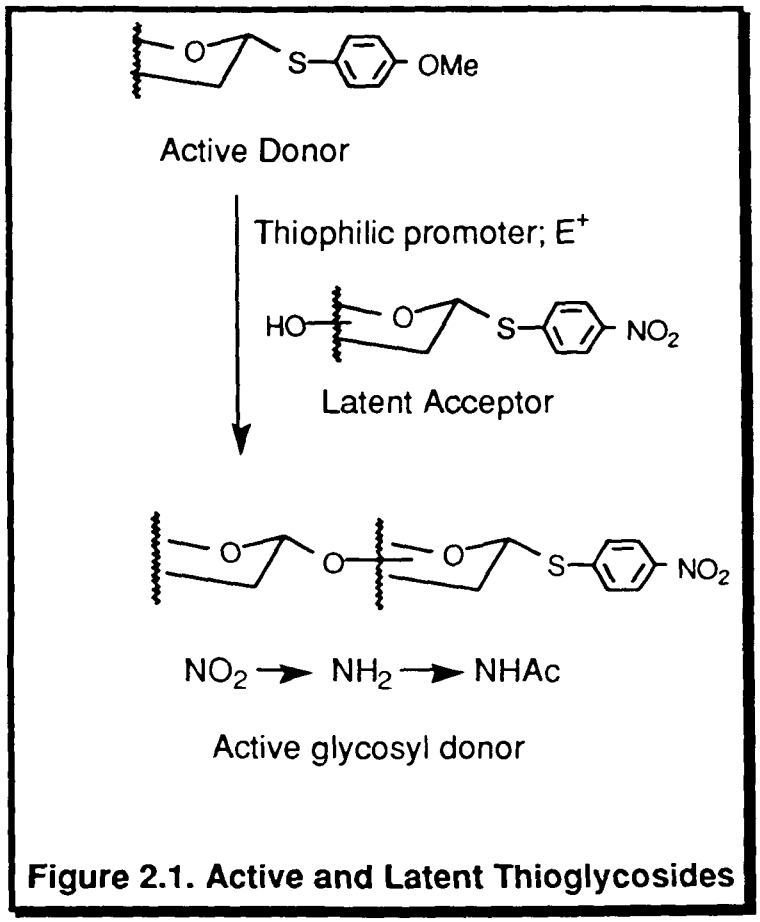


Figure 2.1. Active and Latent Thioglycosides

We decided to explore the potential of phenyl selenoglycosides in glycosylation reactions. These compounds had not been exploited as glycosyl donors. We embarked on establishing a viable method of glycosylating selenoglycosides with the desire of exploring selective activation strategies.

2.2. RESULTS AND DISCUSSION

2.2.1. Synthesis of Phenyl Selenoglycosides

The synthesis of aryl and alkyl selenoglycosides has been reported in the literature.[81] Some of the various methods that have been developed for their synthesis are summarized in Figure 2.2. The method of Wagner and Nuhn[82]

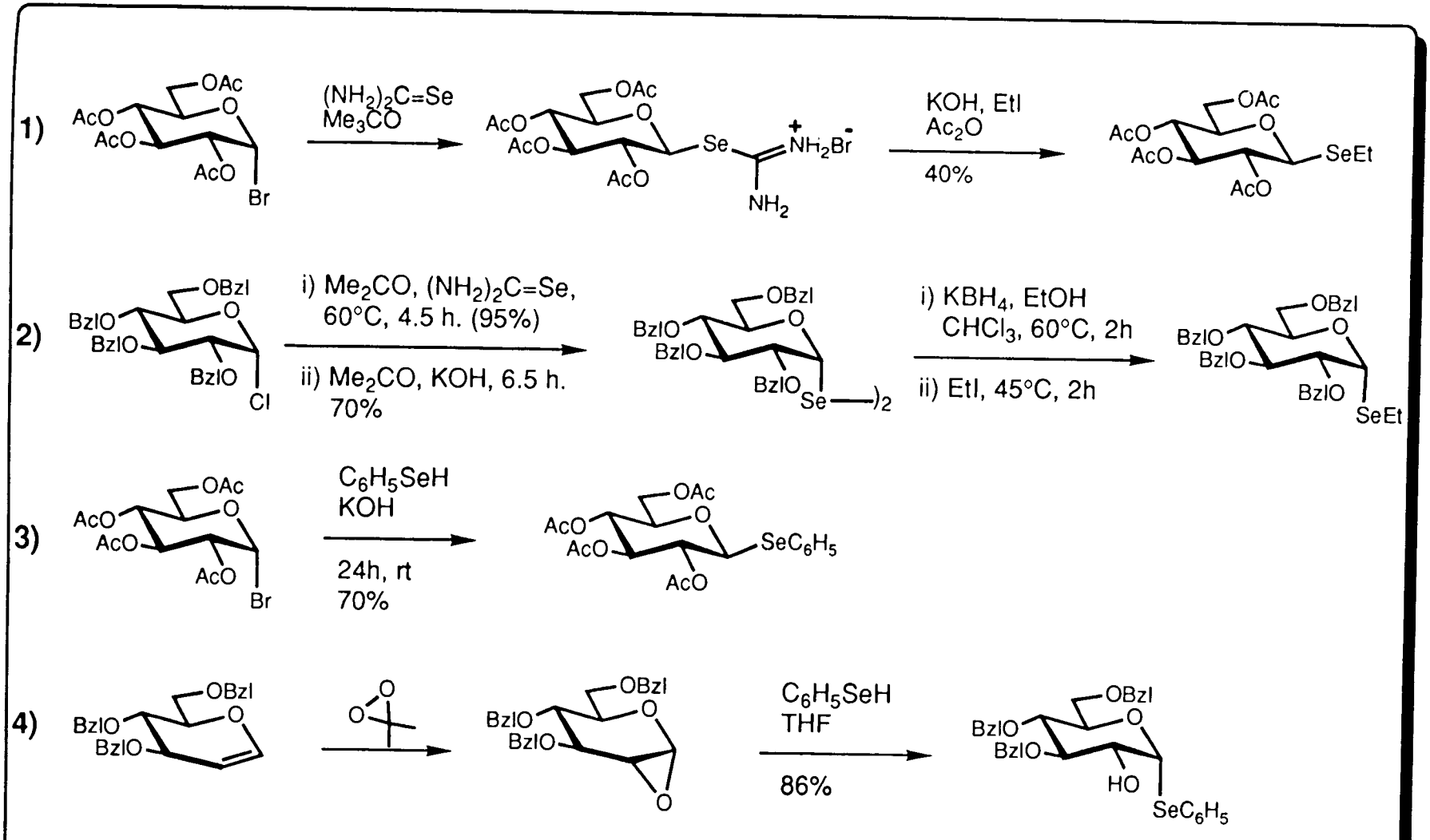


Figure 2.2. Methods of synthesis of selenoglycosides in the literature.

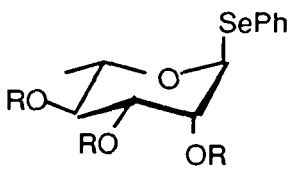
(Figure 2.2, equation 1) involved the reaction of α-acetobromoglucose with seleno-urea followed by the trapping of the α-seleno-uronium salt with ethyl iodide to generate the β-ethyl selenoglycoside. Benhaddou et al.[83] prepared β-selenoglycosides by the reaction of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl chloride with potassium phenyl selenolate (Figure 2.2, equation 2). Other methods involve the displacement of a halide at the anomeric position with an aryl or alkyl selenolate[84] (Figure 2.2, equation 3) and the stereoselective opening of a 1,2-epoxide with phenylselenol (Figure 2.2, equation 4).[85]

These and other preparations[86] were cumbersome and involved multistep syntheses. Some required the prior synthesis of unstable glycosyl halides. We envisaged an easier route to phenyl selenoglycosides in a manner analogous to the method of Ferrier and Furneaux[87] for the synthesis of thioglycosides.

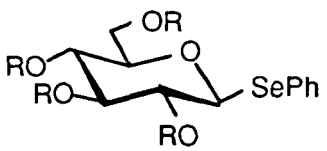
A panel of phenyl selenoglycosides **1-10**, shown in Figure 2.3, was synthesized.[88]

Peracetylated α-L-rhamnopyranoside **11** was reacted with phenylselenol in the presence of boron trifluoride etherate ($BF_3.OEt_2$) to afford an α:β mixture of the corresponding phenyl seleno L-rhamnopyranosides **1** and **2** in 84% yield (Figure 2.4, equation 1). The phenylselenol was freshly prepared by the hypophosphorus acid reduction of diphenyldiselenide.[89] A similar reaction of peracetylated β-D-glucopyranoside **12** afforded predominantly the corresponding phenyl seleno-β-D-glucopyranoside **3** and a minor amount of the α anomer **4** (Figure 2.4, equation 2) in a combined yield of 91%. The phenyl selenoglycoside of the glucosamine derivative was obtained in a similar fashion. The treatment of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido-β-D- glucopyranoside **13**[90] with phenylselenol and $BF_3.OEt_2$ afforded exclusively the β-phenyl selenoglycoside **5**

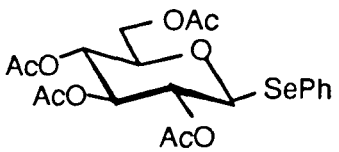
in 93% yield. Hence, this method appears to be an improved and a more general and efficient approach to the synthesis of selenoglycosides.



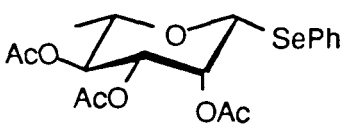
1. R = Ac
6. R = H
9. R = Bzl



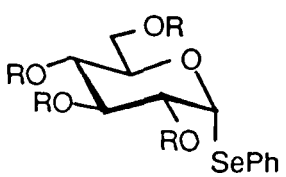
3. R = Ac
7. R = H
10. R = Bzl



5



2



4. R = Ac
8. R = H

Figure 2.3. Phenyl selenoglycoside donors

Deacetylation of compounds **1** and **3** under Zemplen's conditions (sodium methoxide in methanol) afforded the deprotected compounds **6** and **7** quantitatively. Subsequent benzylation with sodium hydride and benzyl bromide afforded the perbenzylated derivatives **9** and **10** in yields of 87% and 85%, respectively (Figure 2.5).

All these compounds are crystalline (except **6**) and odourless. They are stable compounds, enabling their ready purification, storage and easy manipulation (as opposed to conventional glycosyl donors such as glycosyl halides and glycosyl trichloroacetimidates).

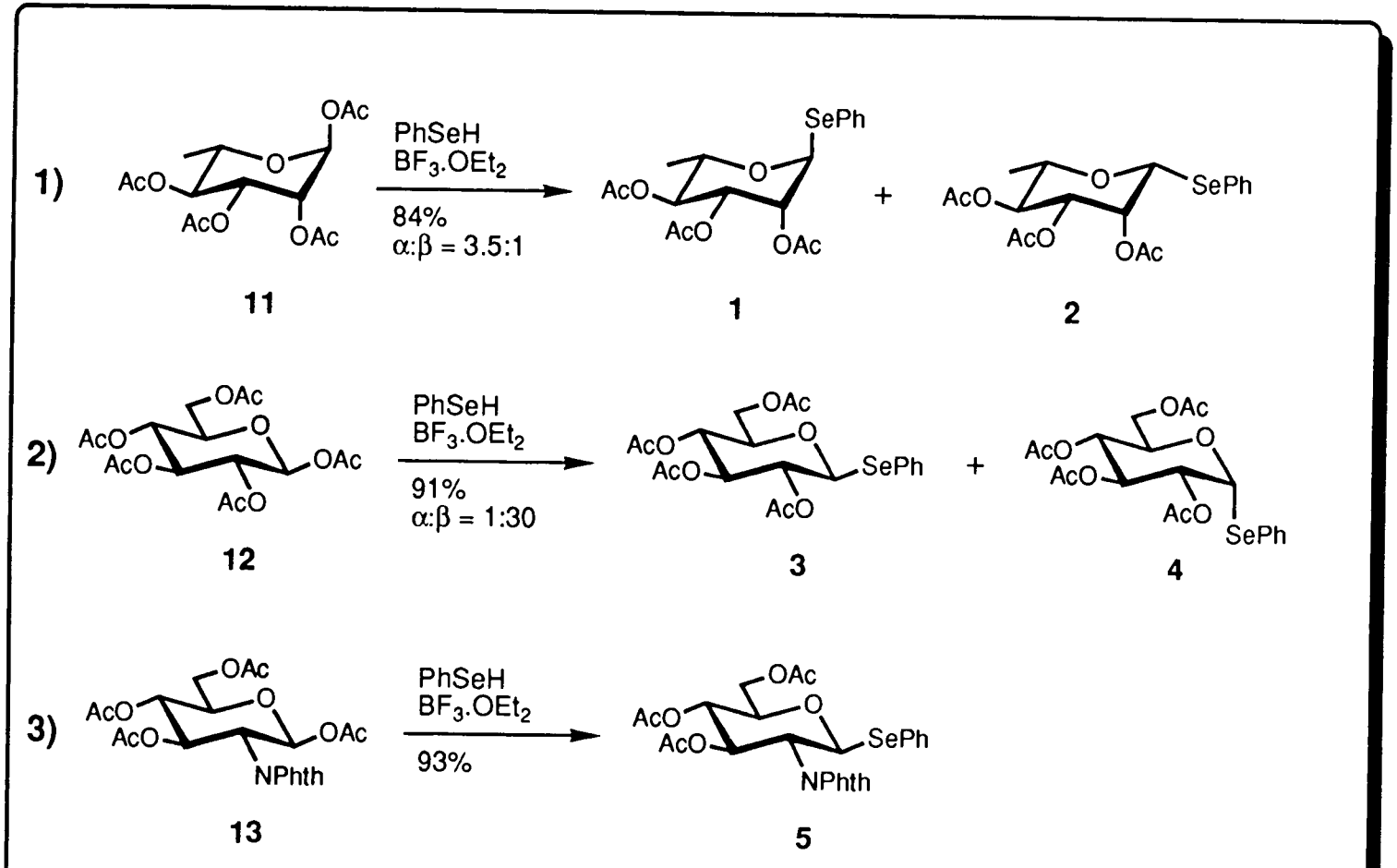


Figure 2.4. Preparation of phenyl selenoglycosides of L-rhamnose, D-glucose and D-glucosamine.

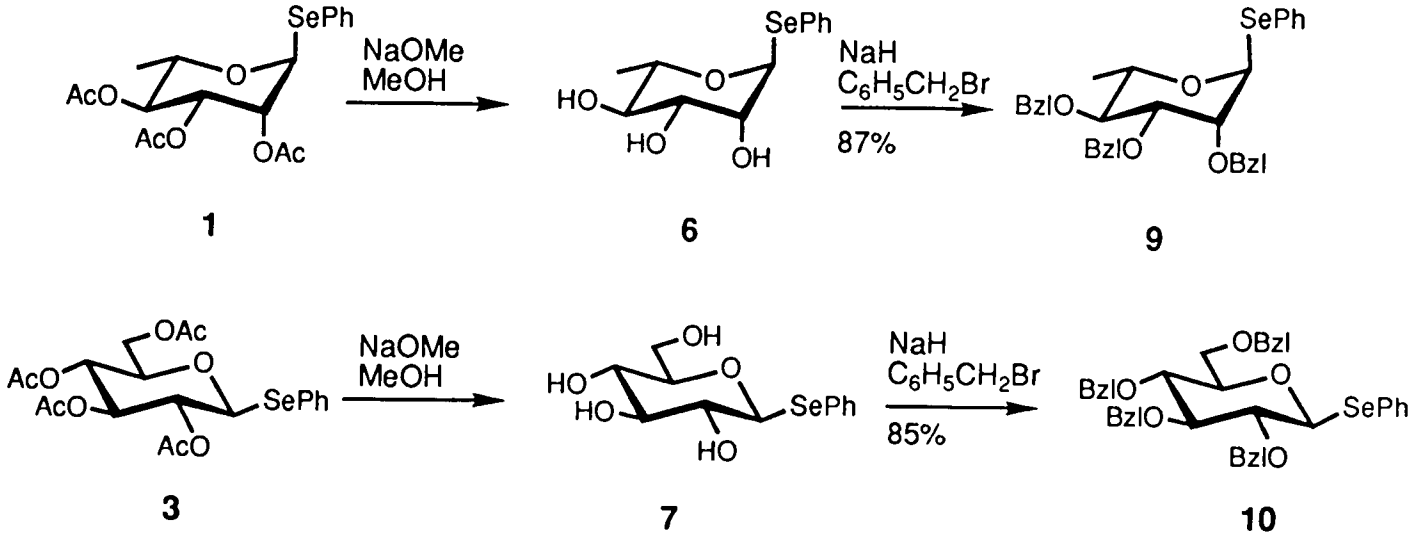
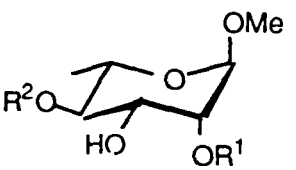


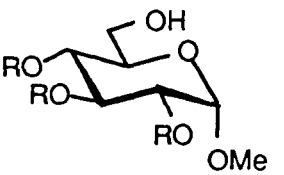
Figure 2.5. Preparation of perbenzylated phenyl selenoglycosides of α-L-rhamnose and β-D-glucose.

2.2.2. Glycosylations of Methyl Glycoside Acceptors with Phenyl Selenoglycosides

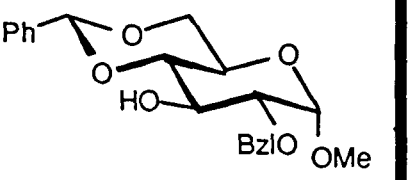
In order to determine the efficiency of the glycosylations with selenoglycosides, methyl glycoside acceptors were initially examined. Both primary and secondary alcohol acceptors were synthesized (Figure 2.6, **14-18**). The syntheses of compounds **14, 15, 16** and **17** have been reported previously in the literature.



	R^1	R^2
14.	Ac	Ac
18.	Bz	Bzl



15. R = Bz
16. R = Bzl



17

Figure 2.6. Methyl glycoside acceptors

2.2.2a. Synthesis of methyl glycoside acceptors

The methyl glycoside acceptor **14**[91] was prepared by the method of Kamiya et al.[92] (Figure 2.7). The reaction of the methyl glycoside **19** with trimethyl orthoacetate in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded the 2,3-orthoacetate **20**. Subsequent acetylation of the 4-OH group with acetic anhydride/ pyridine afforded compound **21**, which, without further purification, was treated with 80% aqueous acetic acid to effect the regioselective opening of the orthoacetate and to provide the block **14** in an overall yield of 60%.

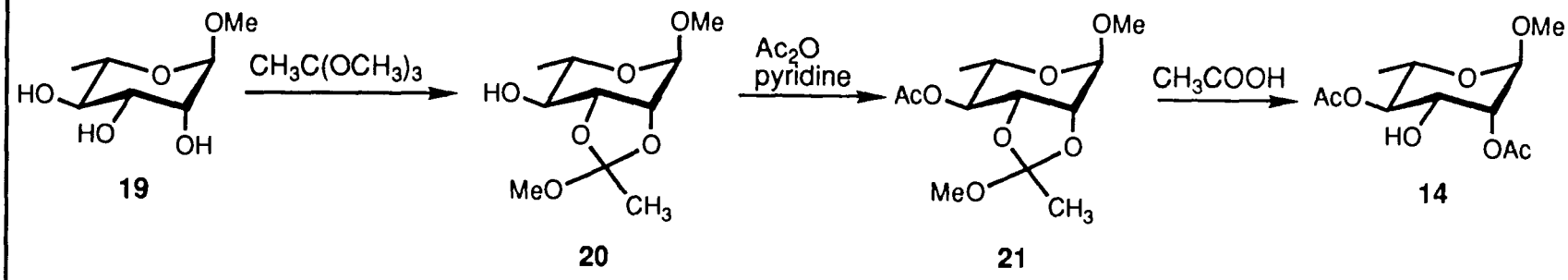


Figure 2.7. Synthesis of methyl 2,4-di-O-acetyl-α-L-rhamnopyranoside

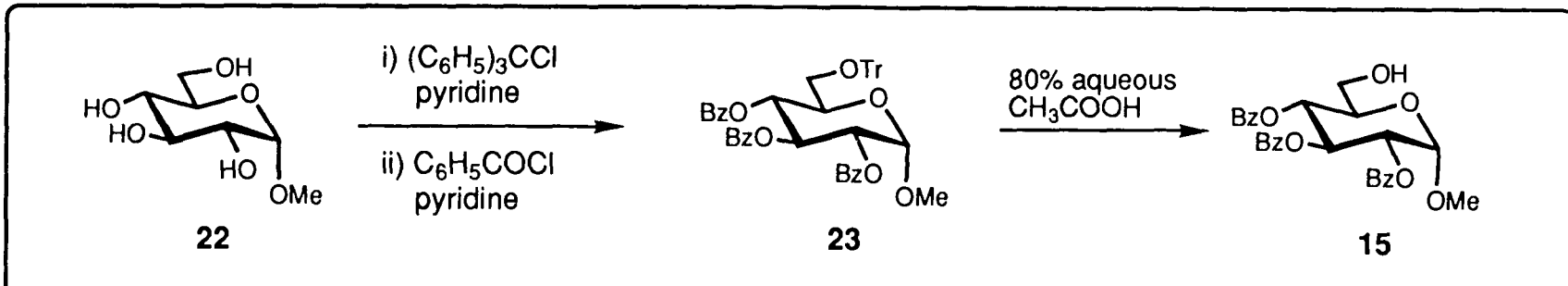


Figure 2.8. Synthesis of methyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside

Methyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside **15** was prepared by conventional methods[93] (Figure 2.8). Selective tritylation of the 6-OH position of the methyl glycoside **22** was effected by the treatment with trityl chloride and pyridine. Subsequent benzoylation with benzoyl chloride/ pyridine afforded compound **23**. Detritylation was achieved with 80% aqueous acetic acid, to provide **15**.

The glycosyl acceptor **16** was obtained from the methyl glycoside **22** by the following three step sequence (Figure 2.9). The hydroxyl groups at the 4 and the 6 positions of **22** were protected by means of a benzylidene acetal, introduced by reaction with α,α-dimethoxytoluene in the presence of a catalytic amount of *p*-toluenesulfonic acid in acetonitrile. The block **22** was employed for the synthesis of acceptors **16** and **17**. The diol **24** was converted to its 2,3-di-O-benzyl derivative **25** with sodium hydride and benzyl bromide. The benzylidene acetal was cleaved stereoselectively by the method of Bhattacharjee and Gorin[94] affording exclusively the 6-hydroxy compound **16**. Following the procedure of Garegg et al.,[95] the diol **24** was selectively benzylated at the 2-position under phase-transfer conditions.[96]

The acceptor **18** was obtained by a modification of the procedure utilized to procure the acceptor **14** (Figure 2.10). The methyl glycoside **19** was reacted with trimethyl orthobenzoate and a catalytic amount of *p*-toluenesulfonic acid in order to selectively protect positions 2 and 3 with an orthoester functionality. Benzylation of the 4-OH followed by the rearrangement of the orthoester afforded acceptor **18**.

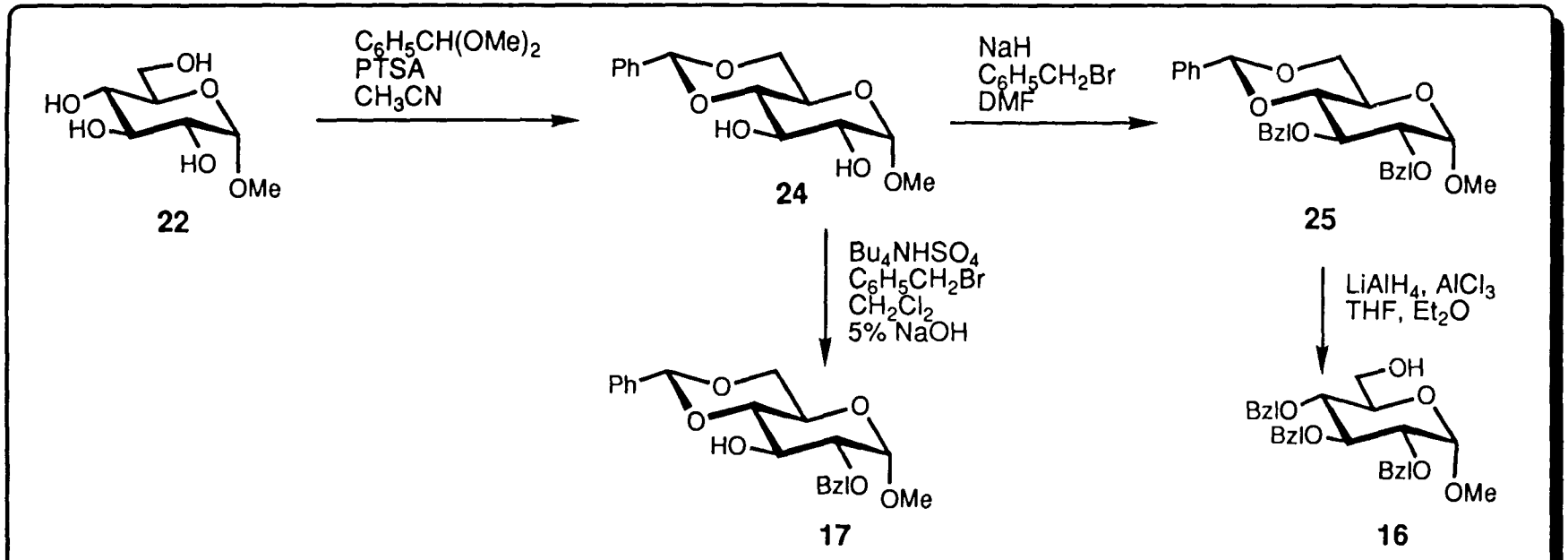


Figure 2.9. Synthesis of Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside and Methyl 2-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside

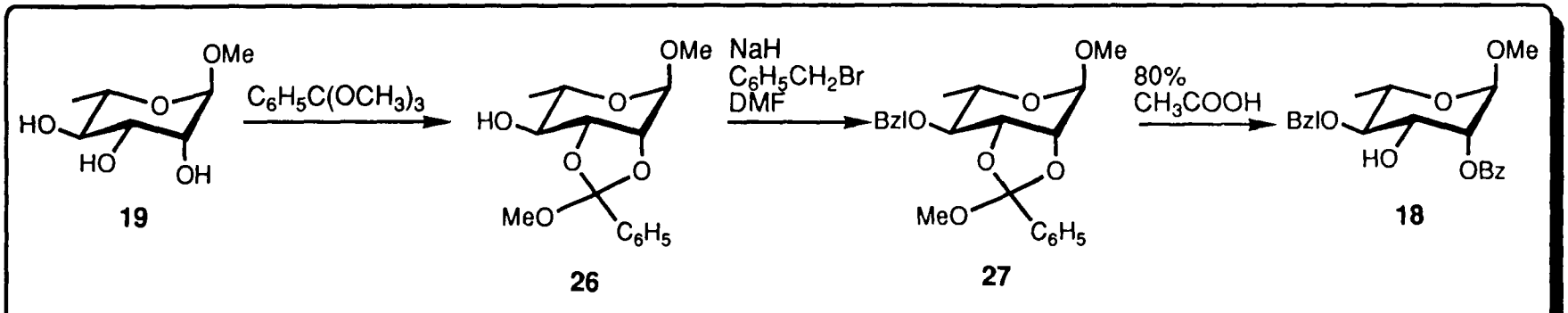


Figure 2.10. Synthesis of Methyl 2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside

2.2.2b. Glycosylation of Methyl Glycosides

Initial activation of the phenyl selenoglycosides was attempted with conventional promoters. The selenoglycosides were observed to be amenable to activation by thiophilic promoters such as methyl triflate,[48] phenylselenenyl triflate,[52] a mixture of cupric bromide-tetrabutyl ammonium bromide-silver triflate,[97] nitrosyl tetrafluoroborate[51] and mercuric chloride.[98]

The glycosylation of glycosyl acceptor **14** with selenoglycoside **1** in the presence of phenylselenenyl triflate required 2.5 h for completion and proceeded in a moderate yield of 51%, providing a 4:1 mixture of the α and β disaccharides **28** and **29** (Table 2.1, entry 1). The glycosylation of the above substrate was not efficient in the presence of methyl triflate at room temperature (Table 2.1, entry 2). On heating to 50°C for 20 h, a 4:1 mixture of the α,β disaccharides **28** and **29** was isolated in a 74% yield (Table 2.1, entry 3). The glycosylation was also performed with a mixture of cupric bromide-tetrabutyl ammonium bromide-silver triflate as promoter. In this case, the stereoselective formation of the α-disaccharide **28** occurred in a modest yield (60%) (Table 2.1, entry 4). At this point it was decided to attempt the glycosylation of a more reactive acceptor containing a primary hydroxyl group rather than a secondary one. Mercuric chloride-mediated glycosylation of the more reactive acceptor **15** with selenoglycoside **1** provided the corresponding disaccharide **30** in a poor yield (25%) (Table 2.1, entry 5). The glycosylation of compound **15** with **1** proved to be more successful under nitrosyl tetrafluoroborate activation and the disaccharide **30** was obtained in 77% yield (Table 2.1, entry 6). These methods were inadequate for synthesis on a preparative scale and a more efficient method was required.

Table 2.1. The use of conventional promoters for selenoglycoside activation.

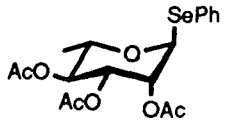
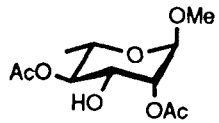
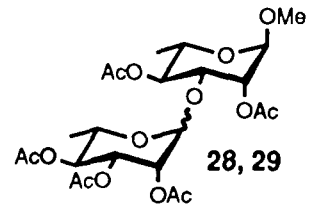
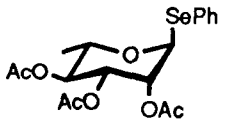
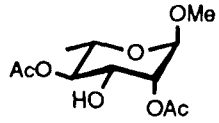
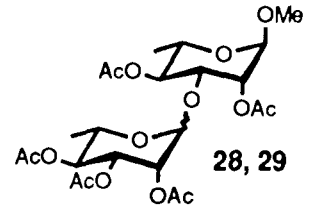
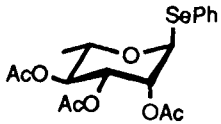
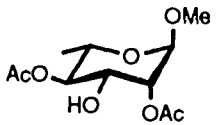
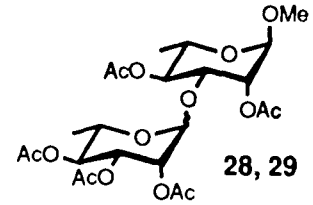
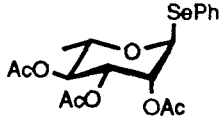
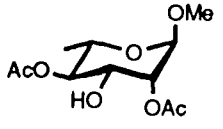
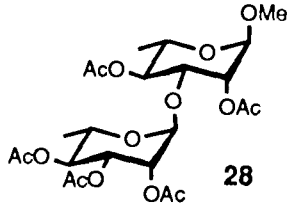
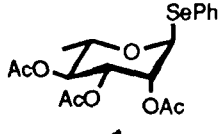
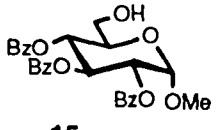
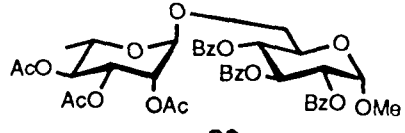
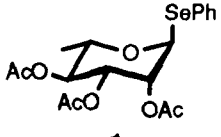
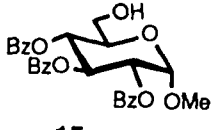
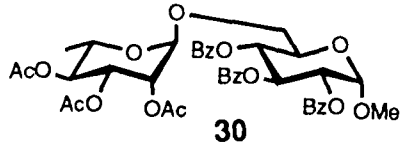
Entry	Donor	Acceptor	Promoter	Time (h)/ Temperature	Product	Yield (%)
1	 **1**	 **14**	PhSeOTf	20° C, 2.5 h	 **28, 29**	51% α:β = 4:1
2	 **1**	 **14**	MeOTf	20° C, 48 h	 **28, 29**	30-40% α:β = 4:1
3	 **1**	 **14**	MeOTf	55° C, 20 h	 **28, 29**	74% α:β = 4:1

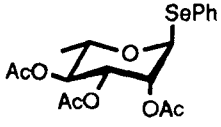
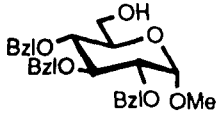
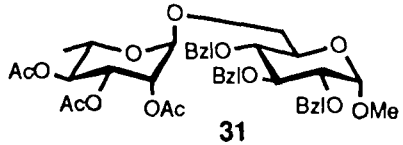
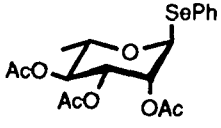
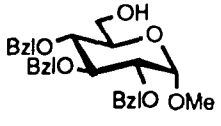
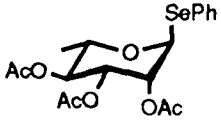
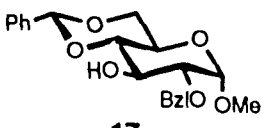
Table 2.1. The use of conventional promoters for selenoglycoside activation.

Entry	Donor	Acceptor	Promoter	Time (h)/ Temperature	Product	Yield (%)
4	 **1**	 **14**	$CuBr_2$ $(Bu_4N)^+Br^-$ AgOTf	20° C, 15-20 min	 **28**	60%
5	 **1**	 **15**	$HgCl_2$	20° C, 48 h	 **30**	20 %
6	 **1**	 **15**	$NOBF_4$	20° C, 30 min	 **30**	77%

To this end, experimentation with other activators was continued. Glycosylation of methyl glycoside acceptor **16** with selenoglycoside donor **1** was attempted with silver triflate as promoter. The glycosylation did not proceed smoothly and the disaccharide **31** was isolated in a low 25% yield (Table 2.2, entry 1). The poor yield was the result of accumulation of triflic acid in the reaction and the reaction was repeated in the presence of a conventional proton acceptor, 1,1,3,3-tetramethylurea (TMU). Unexpectedly, the reaction was suppressed and the selenoglycoside remained inactive under these reaction conditions (Table 2.2, entry 2 and 3). Although disappointing at that time, this observation proved to be essential for the development of selective activation strategies discussed in forthcoming sections. It was then decided to attempt the glycosylation of the aforementioned substrates with silver triflate as promoter, but in the presence of an inorganic base such as potassium carbonate. Under these reaction conditions disaccharide **31** was obtained in 85% yield (Table 2.2, entry 4). A similar glycosylation of acceptor **16** with selenoglycoside **5** afforded stereoselectively the 1,2-trans-linked product **32** in a yield of 84% (Table 2.2, entry 5). Hence, these reaction conditions appeared to be the most favourable conditions for the glycosylations with selenoglycosides thus far examined. The reactions proceeded in short reaction times under very mild conditions and proved to be stereoselective and high yielding.

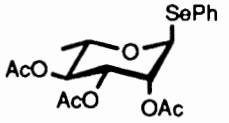
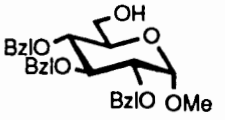
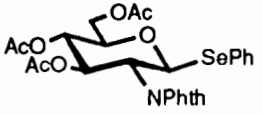
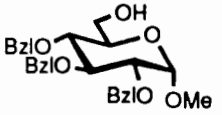
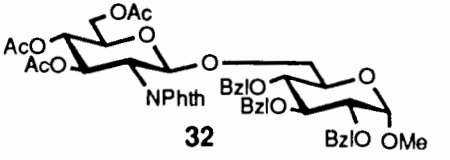
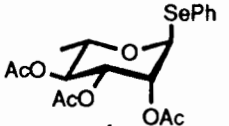
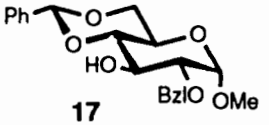
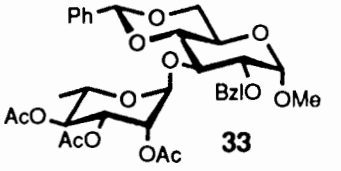
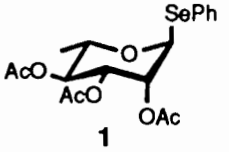
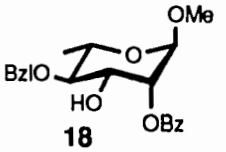
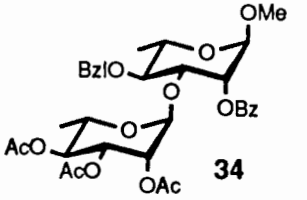
The viability of silver triflate-mediated activation of selenoglycosides in the presence of potassium carbonate was examined further with a glycosyl acceptor containing secondary hydroxyl groups and other protecting groups. The glycosylation of methyl glycosides **17** and **18** with selenoglycoside donor **1** afforded the disaccharides **33** and **34** stereoselectively in moderate yields of 70% and 60%, respectively (Table 2.2, entries 6,7).

Table 2.2. Glycosylation of methyl glycoside acceptors with selenoglycoside donors under AgOTf promotion[a]

Entry	Donor	Acceptor	Base	Molar Ratio[a]	Time (h)	Product	Yield (%)
1	 **1**	 **16**	none	1 : 1 : 2	12	 **31**	25
2	 **1**	 **16**	TMU	1 : 1.2 : 2 : 3.5	24	No Reaction	
3	 **1**	 **17**	TMU	1 : 1.2 : 2 : 3.5	24	No Reaction	

[a]donor : acceptor : AgOTf : base

Table 2.2. Glycosylation of methyl glycoside acceptors with selenoglycoside donors under AgOTf promotion[a]

Entry	Donor	Acceptor	Base	Molar Ratio[b]	Time (h)	Product	Yield (%)
4	 **1**	 **16**	K_2CO_3	1 : 1.5 : 3.5	1	 **31**	85
5	 **5**	 **16**	K_2CO_3	1 : 1.2 : 6	1	 **32**	84
6	 **1**	 **17**	K_2CO_3	1 : 1.2 : 3.5	1	 **33**	70
7	 **1**	 **18**	K_2CO_3	1 : 1.2 : 2	5	 **34**	62

[a]Reactions in the presence of 5 equivalents of K_2CO_3 with respect to AgOTf. [b]donor : acceptor : AgOTf

2.2.3. Selective Activation of Selenoglycosides Over Thioglycosides

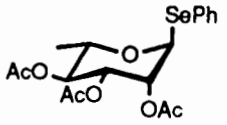
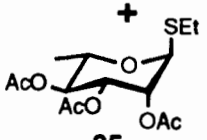
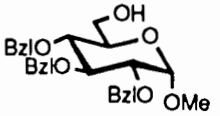
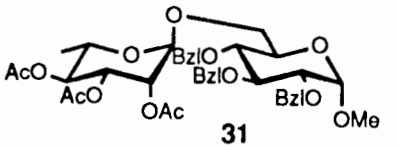
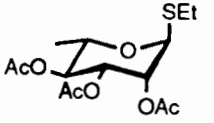
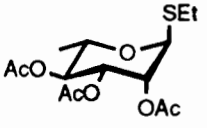
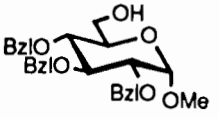
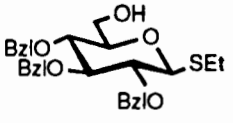
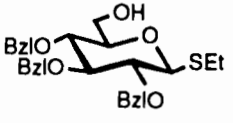
One of the original purposes of establishing selenoglycosides as glycosyl donors was to be able to determine conditions to selectively activate phenyl selenoglycosides over thioglycosides. To this end, experiments were performed to ascertain whether thioglycosides would remain inactive under the conditions established for selenoglycoside activation. The thioglycoside **35** was synthesized according to literature procedures[99] and the following two control experiments were performed. A mixture of phenyl selenoglycoside **1** and the corresponding ethyl thioglycoside **35** was allowed to compete for the glycosyl acceptor **16** under silver triflate promotion in the presence of K_2CO_3. Remarkably, the ethyl thioglycoside **35** remained inactive and was recovered from the reaction mixture in 91% yield. On the other hand, the phenyl selenoglycoside reacted completely to form the disaccharide **31** in a yield of 82% (Table 2.3, entry 1). In another experiment, the thioglycoside **35** was reacted with the acceptor **16**, under the aforementioned conditions. A ^1H nmr spectrum of the crude reaction mixture indicated that no reaction had occurred (Table 2.3, entry 2).

2.2.3a Synthesis of Thioglycoside Acceptors

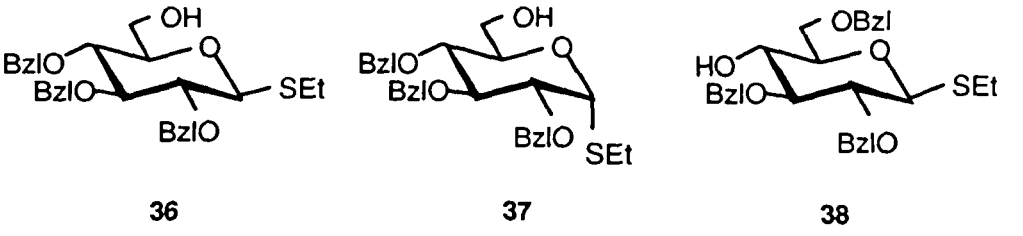
Encouraged by this observed selectivity, a panel of thioglycoside acceptors **36**, **37**, **38** was synthesized (Figure 2.11).

Recalling the results of van Boom *et al.*[53] regarding the greater reactivity of perbenzylated (armed) thioglycosides and the possibility of their selective activation over the acetylated and the benzoylated counterparts (disarmed glycosides), it was decided to synthesize our substrates as the benzylated compounds in order to evaluate the scope of our selective activation strategy. The synthesis of these compounds is discussed in the following section.

Table 2.3. Control experiments performed

Entry	Donor	Acceptor	Molar ratio[a,b]	Time (h)	Product	Yield %
1	 **1** +  **35**	 **16**	1 : 1 : 2 : 4	1.5	 **31** +  **35**	86 91
2	 **35**	 **16**	1 : 1 : 2	24	No reaction	
3	 **36**	 **36**	1 : 4.5	24	No cross-coupling	

[a]Reactions in the presence of 5 equivalents of K_2CO_3 with respect to AgOTf. [b]donor : acceptor : AgOTf



36 37 38

Figure 2.11. Ethyl thioglycoside acceptors

The thioglycoside block **36** was prepared from peracetylated β-D-glucopyranose **9** in 5 steps (Figure 2.12). The thioglycoside **39** was synthesized by the reaction of its peracetylated precursor **9** with ethanethiol in the presence of $BF_3.OEt_2$.[100] Deacetylation under Zemplen's conditions was followed by the selective protection of the 4-OH and 6-OH with a benzylidene group to give the crystalline compound **41.**[101] Benzylation of the diol **41** with NaH/benzyl bromide afforded **42**. This block functioned as the precursor for the three target substrates **36**, **37** and **38**. The regioselectivity of the reductive opening of benzylidene acetals can be controlled depending on the choice of reagents employed[102] (Figure 2.13). The cleavage of the benzylidene acetal with $NaCNBH_3/HCl$[103] affords the 4-OH compound. The use of $LiAlH_4$/ $AlCl_3$[94] provides the alternative 6-OH compound. This has been attributed to the steric effects exerted by the substituent at the C-3 position. In the case of $NaCNBH_3/HCl$, the electrophile is a proton and the O-4 position is protonated, to provide eventually the 4-OH compound. With $LiAlH_4$/ $AlCl_3$, the electrophile $AlCl_3$ is bulkier as compared to the proton and prefers to attack the more

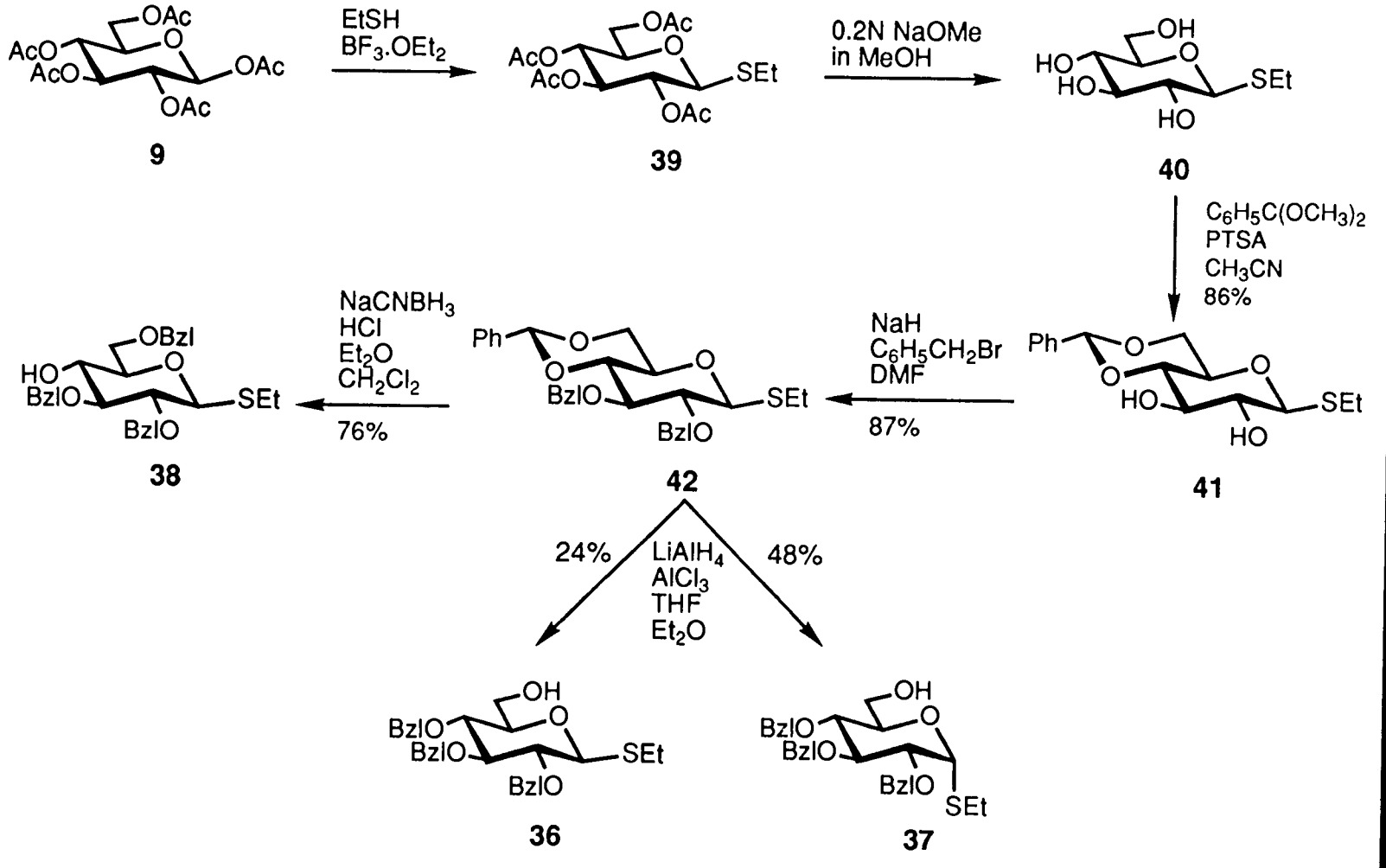


Figure 2.12. Synthesis of ethyl thioglycoside acceptors.

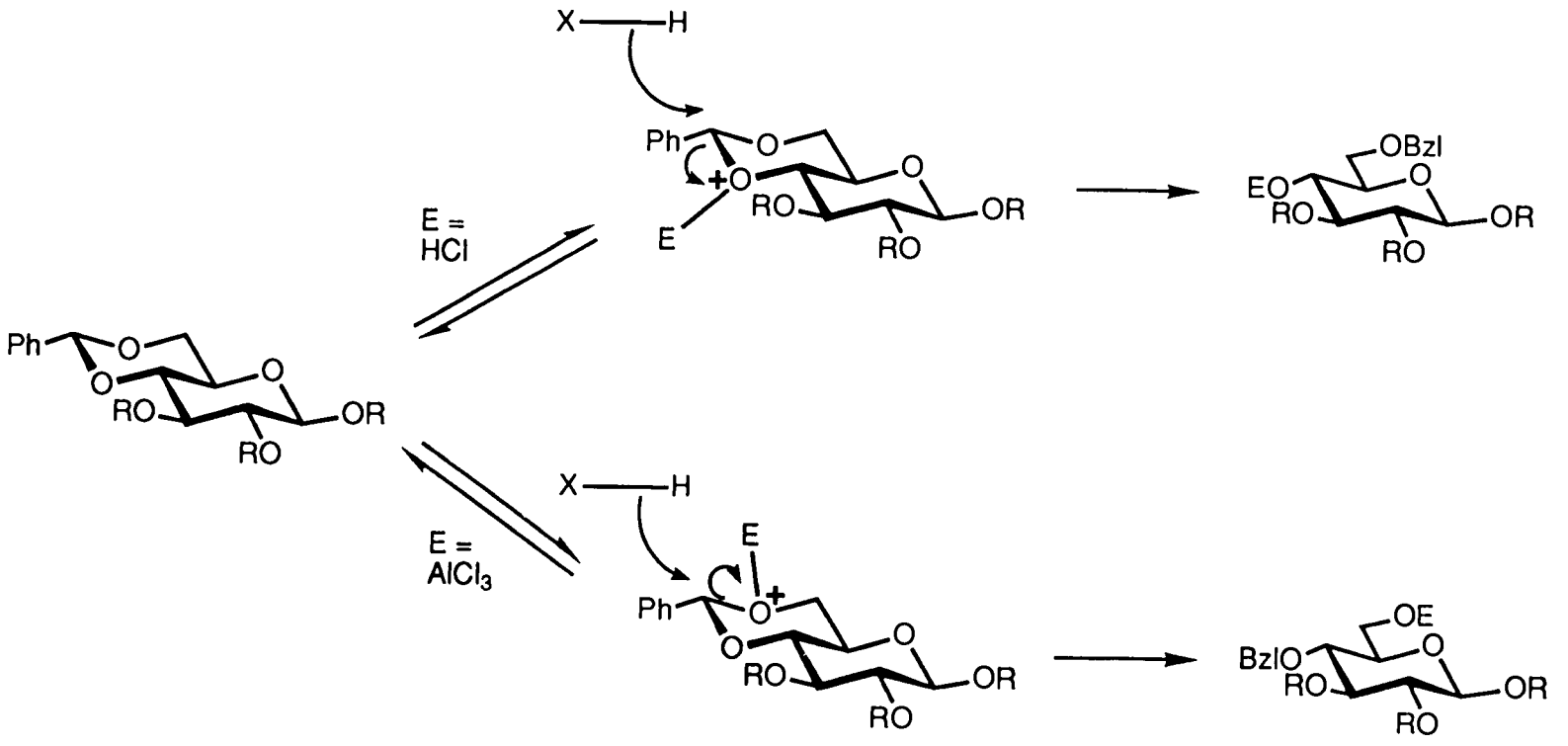


Figure 2.13. Regioselective reductive cleavage of benzylidene acetals.

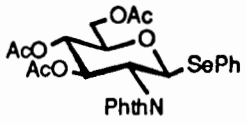
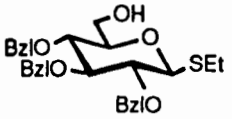
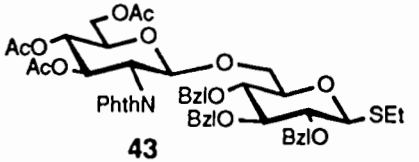
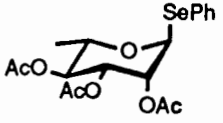
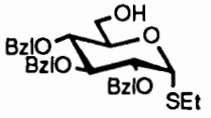
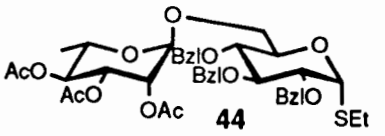
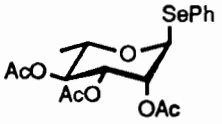
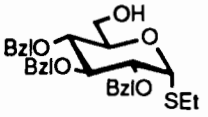
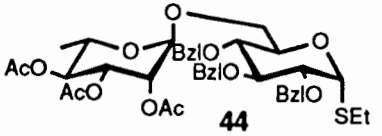
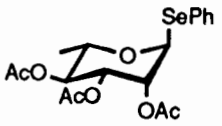
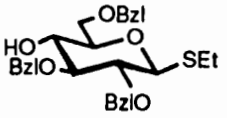
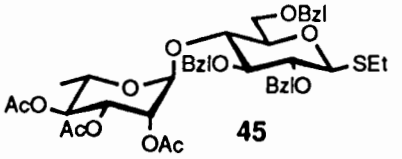
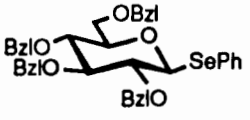
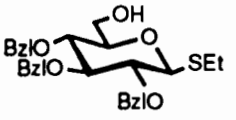
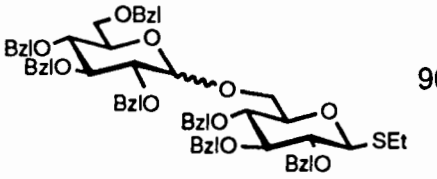
exposed O-6 position and leads, in turn, to the 6-OH compound. Hence, the reaction of **36** with $NaCNBH_3$/HCl provided the 4-hydroxy compound **38**. On the other hand, the use of $LiAlH_4$/ $AlCl_3$ afforded the 6-hydroxy compound **36**. Fortuitously, under these strongly acidic conditions the β-thioglycoside **36** partially anomerized to the α anomer **37**, thus providing another thioglycoside acceptor.[100] In another control experiment, the thioglycoside **36** was treated with AgOTf/ K_2CO_3. No cross-coupling was observed in this reaction (Table 2.3, entry 3).

2.2.3b. Glycosylation of Thioglycoside Acceptors

A series of glycosylations was performed. The "armed" thioglycoside acceptor **36** was glycosylated with the phenyl selenoglycoside donor **5** under AgOTf promotion in the presence of K_2CO_3, affording stereoselectively the β-disaccharide **43** in 84% yield (Table 2.4, entry 1). Similarly, the reaction of the thioglycosides **37** and **38** with selenoglycoside donor **1** produced the corresponding disaccharides **44** and **45** in yields of 80% and 78%, respectively (Table 2.4, entries 2 and 4). Glycosylations were also performed with Ag_2CO_3 as the base instead of K_2CO_3 (Table 2.4 , entry 3). The results of these reactions were analogous to those observed for K_2CO_3. To establish the scope of this novel selective activation method, the reaction of the more reactive perbenzylated selenoglycoside, an "armed" sugar, with an "armed" thioglycoside was considered next. This glycosylation proceeded in an excellent 90% yield and afforded a mixture of the α and β disaccharides **46** and **47** in a ratio of 2.5:1 (Table 2.4, entry 5).

Thus, the preferential activation of both armed and disarmed phenyl selenoglycosides over armed ethyl thioglycosides is demonstrated and it augers

Table 2.4. Glycosylation of thioglycoside acceptors with selenoglycoside donors[a]

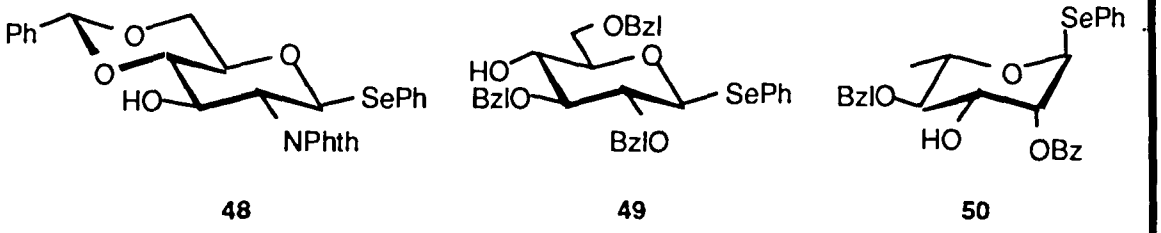
Entry	Donor	Acceptor	Base	Molar ratio[b]	Time (h)	Product	Yield %
1	 **5**	 **36**	Ag_2CO_3	2 : 1 : 6	1	 **43**	84
2	 **1**	 **37**	K_2CO_3	1 : 1 : 3	1.5	 **44**	80
3	 **1**	 **37**	Ag_2CO_3	1 : 1 : 3	1	 **44**	80
4	 **1**	 **38**	Ag_2CO_3	2 : 1 : 6	1	 **45**	78
5	 **10**	 **39**	K_2CO_3	1.2 : 1 : 6	1.5	 **46,47** α:β = 2.5:1	90

[a]Reactions in the presence of 5 equivalents of K_2CO_3 or 3 equivalents of Ag_2CO_3 with respect to AgOTf.
[b]donor : acceptor : AgOTf

well for the intrinsic higher reactivity of phenyl selenoglycosides over ethyl thioglycosides.

2.2.4. Selective Activation of Glycosyl Halides Over Selenoglycosides

As noted earlier, it was observed that the phenyl selenoglycosides were rendered unreactive in the presence of conventional proton acceptors such as 1,1,3,3-tetramethylurea and collidine. Since these are the conditions under which conventional glycosyl halide donors are activated,[21b] it followed that there was a potential of selectively activating glycosyl halide donors over selenoglycosides. To investigate these possibilities, the selenoglycoside acceptors **48**, **49**, and **50** were synthesized (Figure 2.14).



48 **49** **50**

Figure 2.14. Phenyl selenoglycoside acceptors

2.2.4a. Synthesis of Phenyl Selenoglycoside Acceptors

It was envisaged that the deacetylation of selenoglycoside **5** followed by the selective protection of the 4-OH and 6-OH positions with a benzylidene acetal functionality would afford the selenoglycoside acceptor **48** (Figure 2.15). Deacetylation of **5** was attempted with a freshly prepared solution of sodium

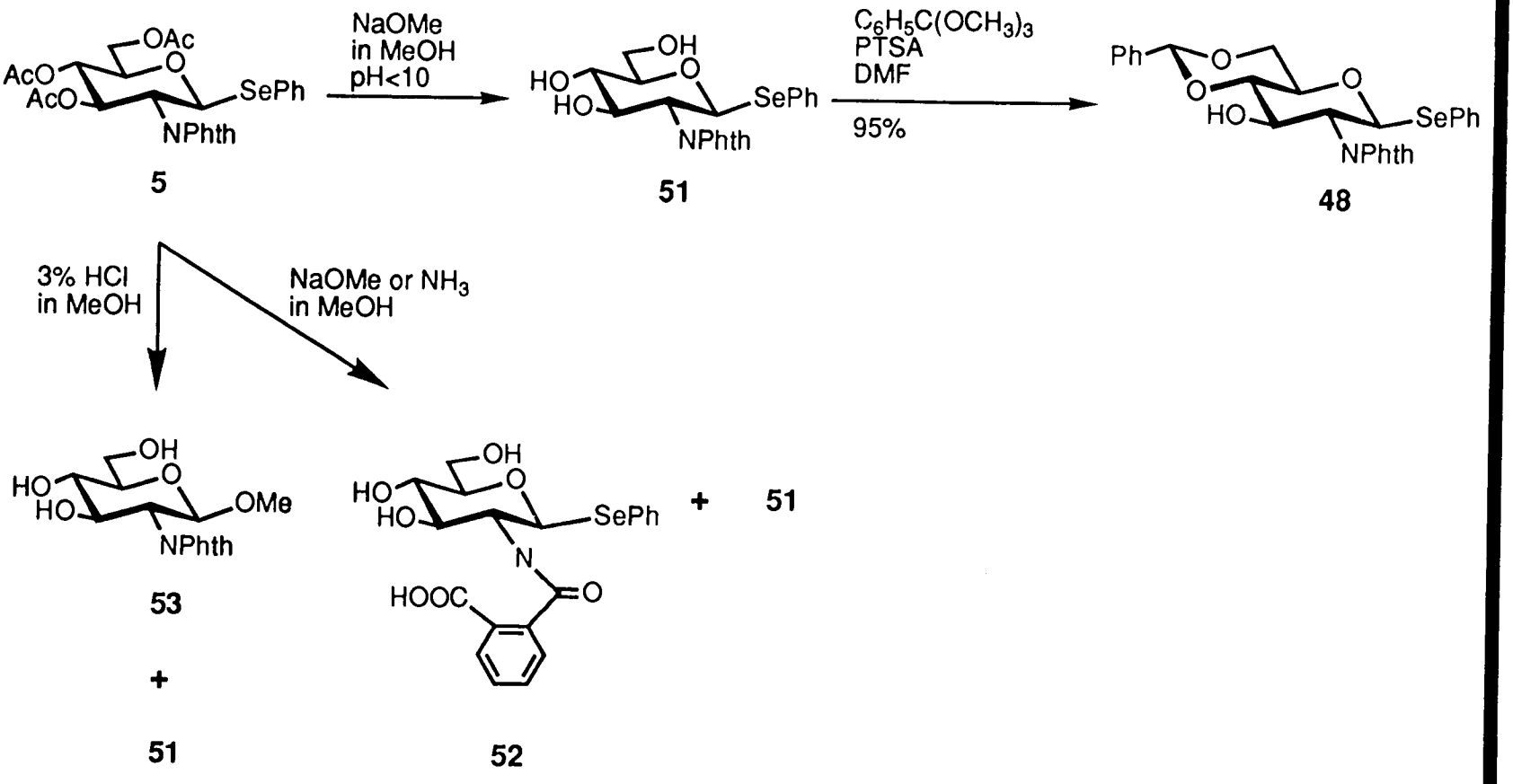


Figure 2.15. Synthesis of selenoglycoside acceptor: phenyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside

methoxide in methanol. Unexpectedly, two products were formed, as observed by TLC. Deacetylation by ammonolysis afforded the same result. The two products of the reaction were isolated. On analysis of the ^{1}H NMR spectra of the two compounds, the less polar component of the two was found to be the desired compound **51**. The more polar component was compound **52** in which the phthalimido group had opened up. This was confirmed by refluxing compound **52** in acetic anhydride and pyridine, which effected cyclization and yielded the compound **5**.

The deacetylation of **5** was then attempted under acidic conditions. Selenoglycoside **5** was treated with a 3% solution of HCl in methanol. Two products were again observed by TLC. Isolation and purification of these compounds revealed that the more polar component corresponded to the desired deacetylated product **51**. However, the less polar component was the corresponding methyl glycoside **53**.

A more efficient deacetylation procedure was required. It was observed that deacetylation with NaOMe/ MeOH was effective, provided that the pH of the reaction was not allowed to rise above 10. The reaction was monitored closely by TLC and was quenched as soon as it appeared to be complete. The opening of the phthalimido group was thus avoided. Subsequent reaction of **51** with α,α-dimethoxytoluene and a catalytic amount of *p*-toluenesulfonic acid enabled the selective protection of the 4-OH and the 6-OH groups, affording the block **48** in 91% yield.

The synthesis of phenyl 2,3,6-tri-O-benzyl-1-seleno-α-D-glucopyranoside was designed in an analogous manner to that of the thioglycoside acceptor **38** (Figure 2.16). The deacetylation of the peracetylated phenyl selenoglycoside of glucose **3** was performed by ammonolysis. The corresponding deblocked sugar

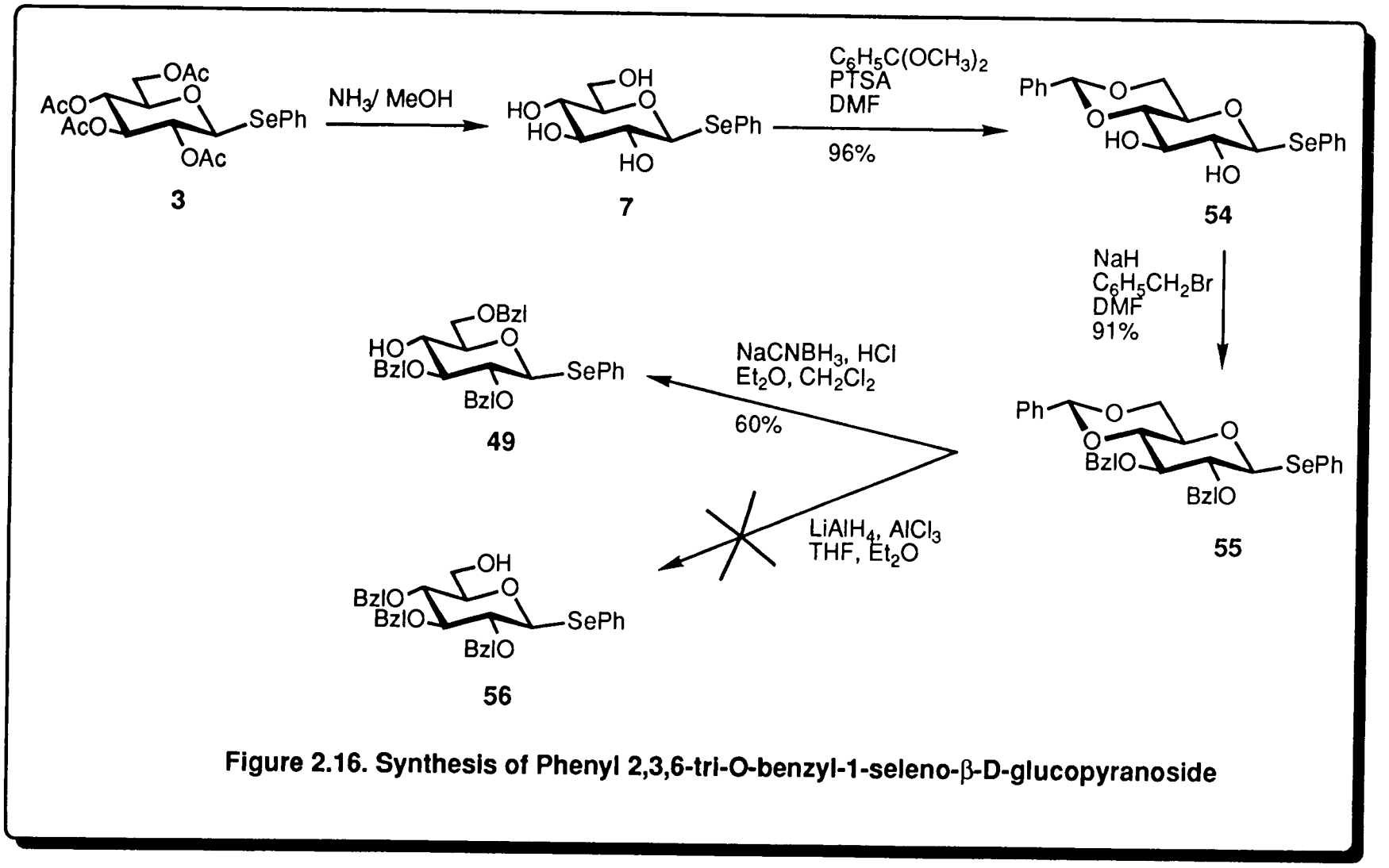


Figure 2.16. Synthesis of Phenyl 2,3,6-tri-O-benzyl-1-seleno-β-D-glucopyranoside

7 was treated with α,α-dimethoxytoluene in the presence of a catalytic amount of *p*-toluenesulfonic acid to provide **54** in 96% yield. Benzylation of the diol **54** afforded compound **55**. The final step of the synthesis was the reductive cleavage of the benzylidene acetal of compound **55**, which was attempted by the method of Garegg et al.[103] However, this procedure did not proceed as desired. The reaction of **55** with $NaCNBH_3$/ HCl was initially performed at room temperature. A very polar compound was detected by TLC. It was conjectured that due to the instability of the selenoglycoside under strongly acidic conditions, hydrolysis of the selenoglycoside to the hemiacetal was occurring. After attempting the reaction under a variety of conditions the optimum conditions found were to conduct the reaction at 0°C and to quench the reaction as soon as the hydrolytic product appeared, regardless of whether the starting compound had been completely consumed or not. Thus, compound **49** was obtained in a 60% yield. The regioselective reductive cleavage of the benzylidene acetal was also performed with $LiAlH_4$/ $AlCl_3$ by the method of Bhattacharjee and Gorin[94a] in an attempt to procure the 6-hydroxy compound **56.** This proved to be unsuccessful, yielding only hydrolysis products, and was not pursued any further.

The synthesis of the selenoglycoside acceptor **50** was planned as shown in Figure 2.17.[104] Phenyl selenoglycoside **1** was deacetylated by ammonolysis conditions, affording deprotected compound **6** quantitatively. The hydroxyl groups at positions 2 and 3 were selectively protected with an isopropylidene functionality, introduced by the reaction of **6** with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid. Benzylation of compound **57** yielded **58**. The hydrolysis of the isopropylidene acetal was effected by refluxing in HCl/ MeOH. The diol **59** was reacted with trimethylorthobenzoate and *p*-

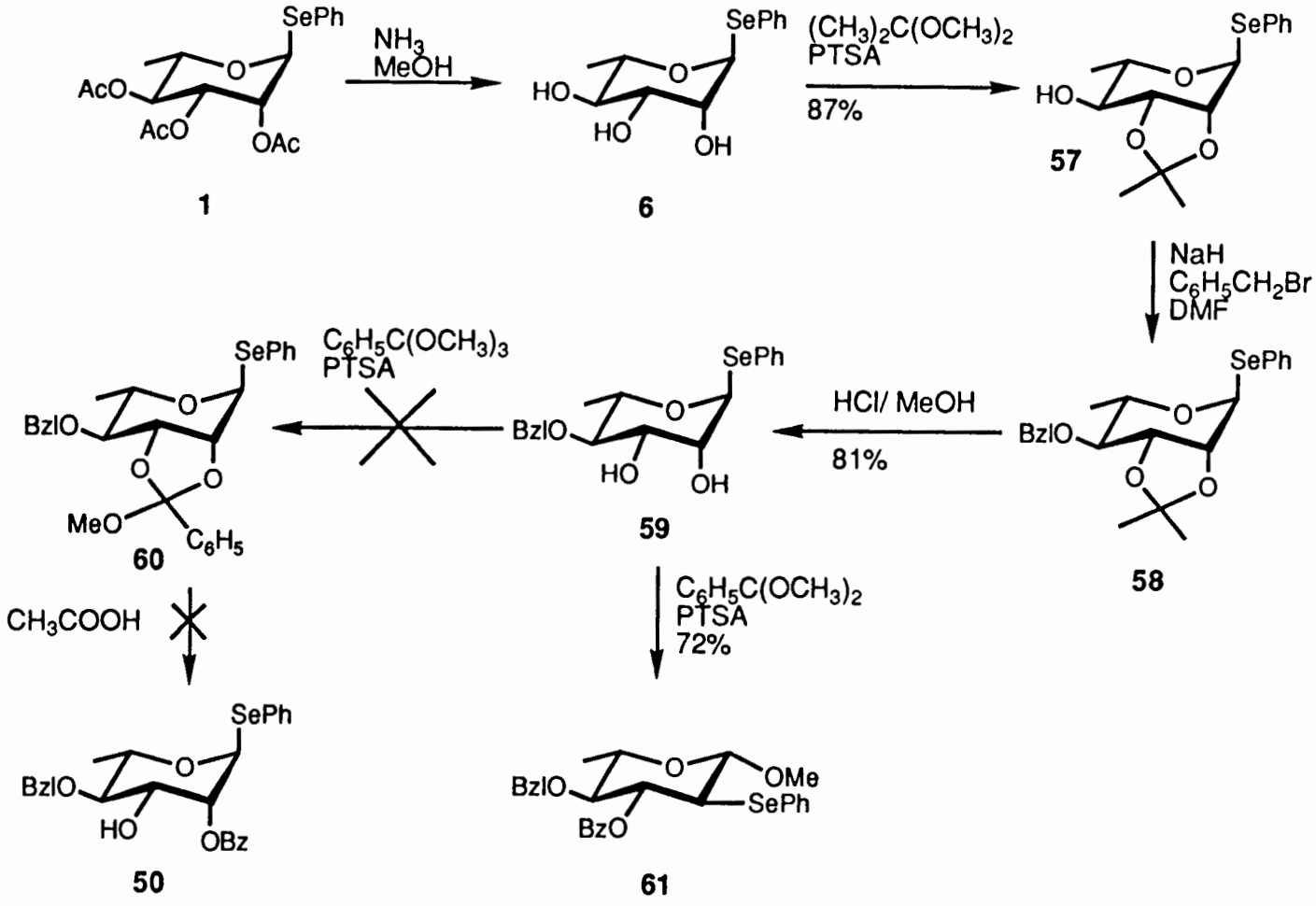
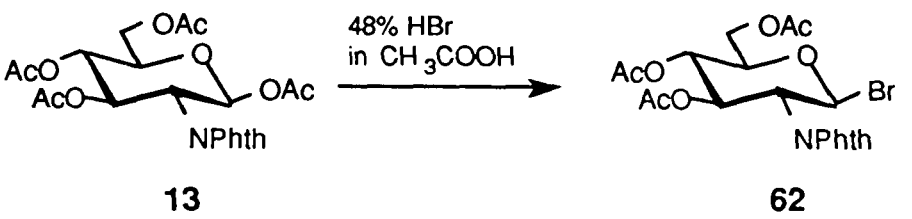


Figure 2.17. Synthesis of Methyl 3-O-benzoyl-4-O-benzyl-2,6-dideoxy-2-phenylseleno-β-L-glucopyranoside

toluenesulfonic acid. Without further purification, the mixture was treated with 80% acetic acid. Surprisingly, the desired compound was not formed. On examination of the NMR spectra, the product appeared to be the rearranged compound **61**. Auzanneau and Bundle[99] have observed an analogous 1,2-migration with a similar reaction performed with ethyl thioglycosides in acetonitrile. In the case of thioglycosides, the intramolecular rearrangement has been overcome by the use of *N,N*-dimethylformamide as a solvent for the reaction instead of acetonitrile. This modification was not successful with the selenoglycosides and the synthesis of this block was not pursued any further.

2.2.4b. Glycosylations of selenoglycoside acceptors with a glycosyl halide donor

The glycosyl donor 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide **62** was synthesized according to the method of Lemieux et al.[90] as shown in Figure 2.18. The reaction of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside **13** with 48% HBr in acetic acid afforded the bromide **62.**



13 **62**

Figure 2.18. Synthesis of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido β-D-glucopyranosyl bromide

AgOTf-mediated glycosylations of the selenoglycoside donors **48** and **49** with the bromide **62** were performed in the presence of collidine (Figure 2.19). The corresponding disaccharides **63** and **64** were isolated in modest yields of 60%.

Control Experiment It was suspected that the preferential coordination of silver triflate to the organic base rendered it unavailable for coordination to and activation of the selenium atom. This assumption was corroborated by the following experiment. Siver triflate-mediated glycosylation of the methyl glycoside acceptor **16** with selenoglycoside **1** was performed in the presence of a hindered organic base, 2,6-di-*tert*-butyl-4-methylpyridine. As expected, the selenoglycoside was activated under these conditions to afford a 7:1 mixture of the orthoester **65** and the disaccharide **31** (Figure 2.20). These results are in accord with the results of Banoub and Bundle[105] who showed that the use of strong organic bases in glycosylation reactions favours the formation of the orthoester as opposed to the disaccharide. This is attributed to the reduced ability of the weak conjugate acid to effect the rearrangement of the orthoester to the disaccharide.

2.2.5. Selective Activation of a Glycosyl Trichloroacetimidate over Phenyl Selenoglycosides

The use of glycosyl trichloroacetimidate glycosyl donors in oligosaccharide synthesis is well established.[37b] It was envisaged that their selective activation over selenoglycosides would prove to be very useful in oligosaccharide synthesis. Activation of glycosyl trichloroacetimidates is achieved in the presence of a catalytic amount of an acid such as boron trifluoride etherate ($BF_3.OEt_2$), trimethylsilyl trifluoromethanesulfonate (TMSOTf)

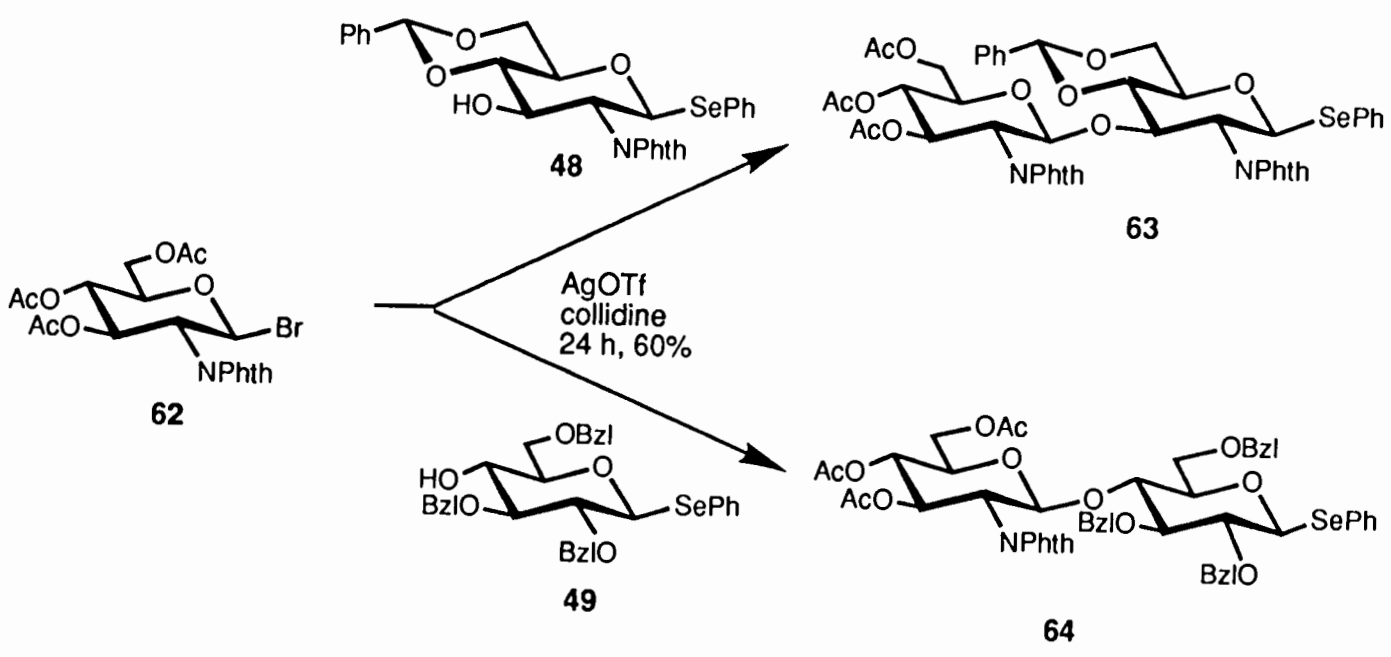


Figure 2.19. Selective activation of a glycosyl bromide over selenoglycosides

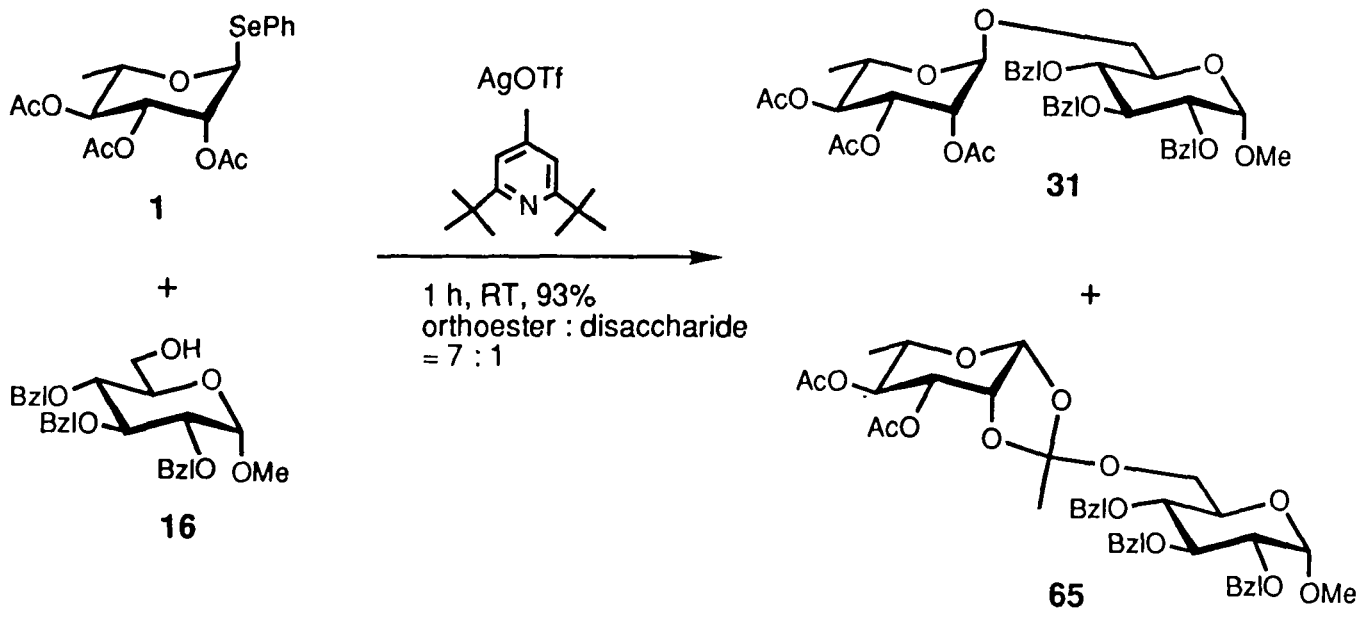
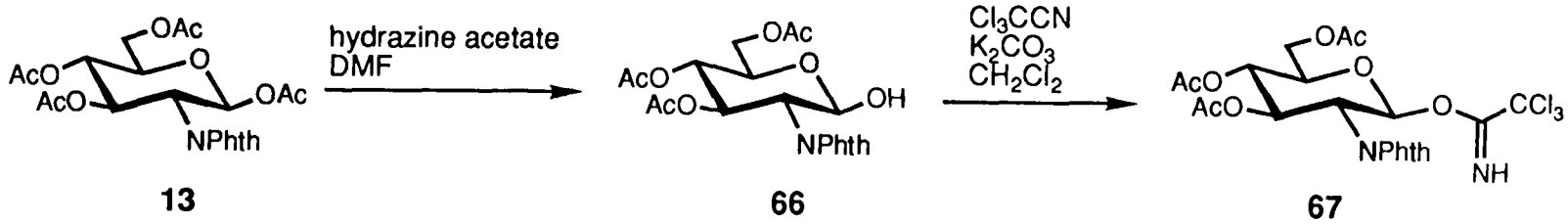


Figure 2.20. Control experiment with hindered base

or triethylsilyl trifluoromethanesulfonate (TESOTf). The question was whether selenoglycosides were amenable to the acidic conditions.

The stability of phenyl selenoglycosides towards 0.7 equivalent of TESOTf was examined. The selenoglycoside **48** was found to be stable to these conditions at -78°C but it started decomposing when the temperature was raised above 0°C. Fortunately, glycosylation reactions with trichloroacetimidates are generally conducted at low temperatures at which the selenoglycosides are stable.

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate **67** was synthesized according to a reported procedure[106] (Figure 2.21). The selective deacetylation of the anomeric acetate of compound **13** was effected with hydrazine acetate. Treatment of the hemiacetal **66** with trichloroacetonitrile and potassium carbonate afforded the trichloroacetimidate **67.** The selective glycosylation of selenoglycoside acceptors **48** and **49**, as represented in Figure 2.22, proceeded in excellent yields to give the disaccharides **63** and **64**, respectively, as their selenoglycosides.



13 66 67

Figure 2.21. Synthesis of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido β-D-glucopyranosyl trichloroacetimidate

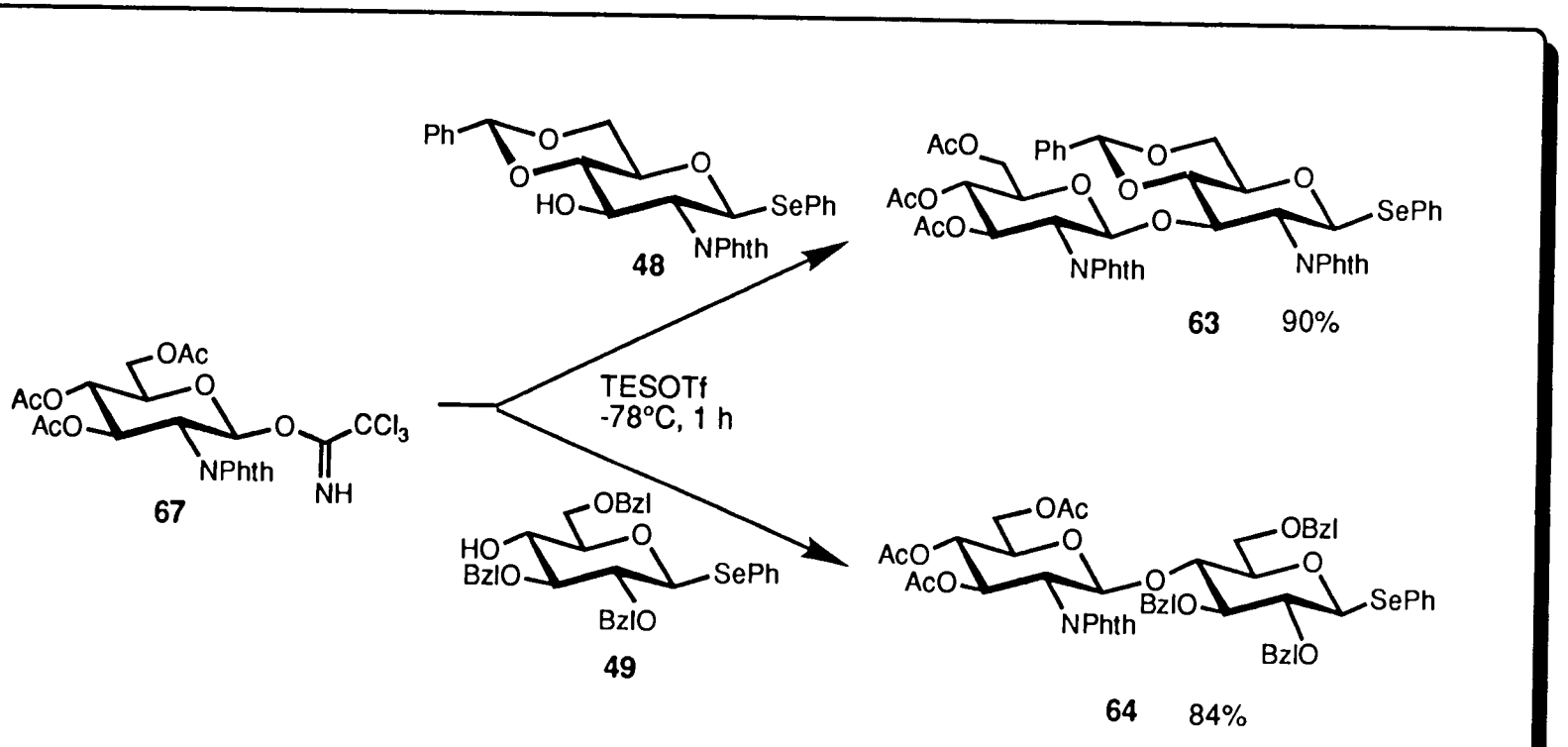


Figure 2.22. Selective activation of a glycosyl trichloroacetimidate over selenoglycosides

2.2.6 The Impact of Selective Activation

Convergent block synthesis of oligosaccharides is more desirable and more efficient than the linear, stepwise approach as it minimizes the protecting group manipulation of complex oligosaccharide fragments. A limitation of this approach is the necessity to functionalize the anomeric center of the oligosaccharide block. Such manipulations at this stage of the synthesis often result in the loss of precious material. The selective activation strategies thus far described are essential in overcoming these types of difficulties. The ability to achieve selectivity in activation can provide blocks that can function both as glycosyl acceptors or glycosyl donors depending on the choice of the reaction conditions (Figure 2.23).

This type of versatility is accomplished with selenoglycosides and is illustrated by the synthesis of the trisaccharide **67** (Figure 2.24). The selective activation of the glycosyl trichloroacetimidates over selenoglycosides enables the glycosylation of selenoglycoside acceptor **48** with the donor **67**. The resulting disaccharide is obtained as a selenoglycoside. This requires no further manipulations for functionalization of the anomeric center and is directlyglycosylated, under mild and efficient conditions, to afford the trisaccharide **68**. This trisaccharide is obtained as a thioglycoside and is amenable to activation by thiophilic promoters without requiring any further manipulations prior to glycosylation.

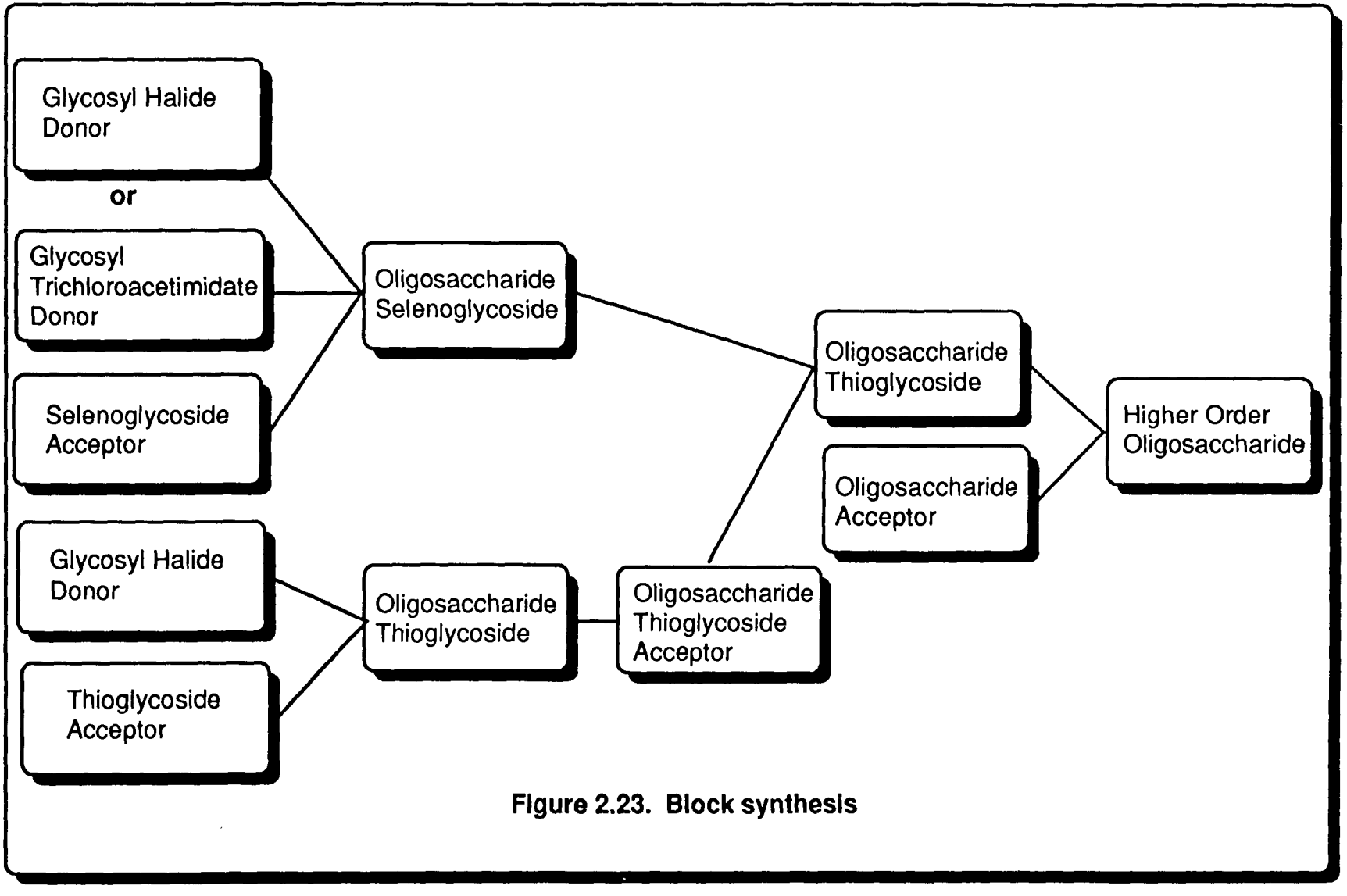


Figure 2.23. Block synthesis

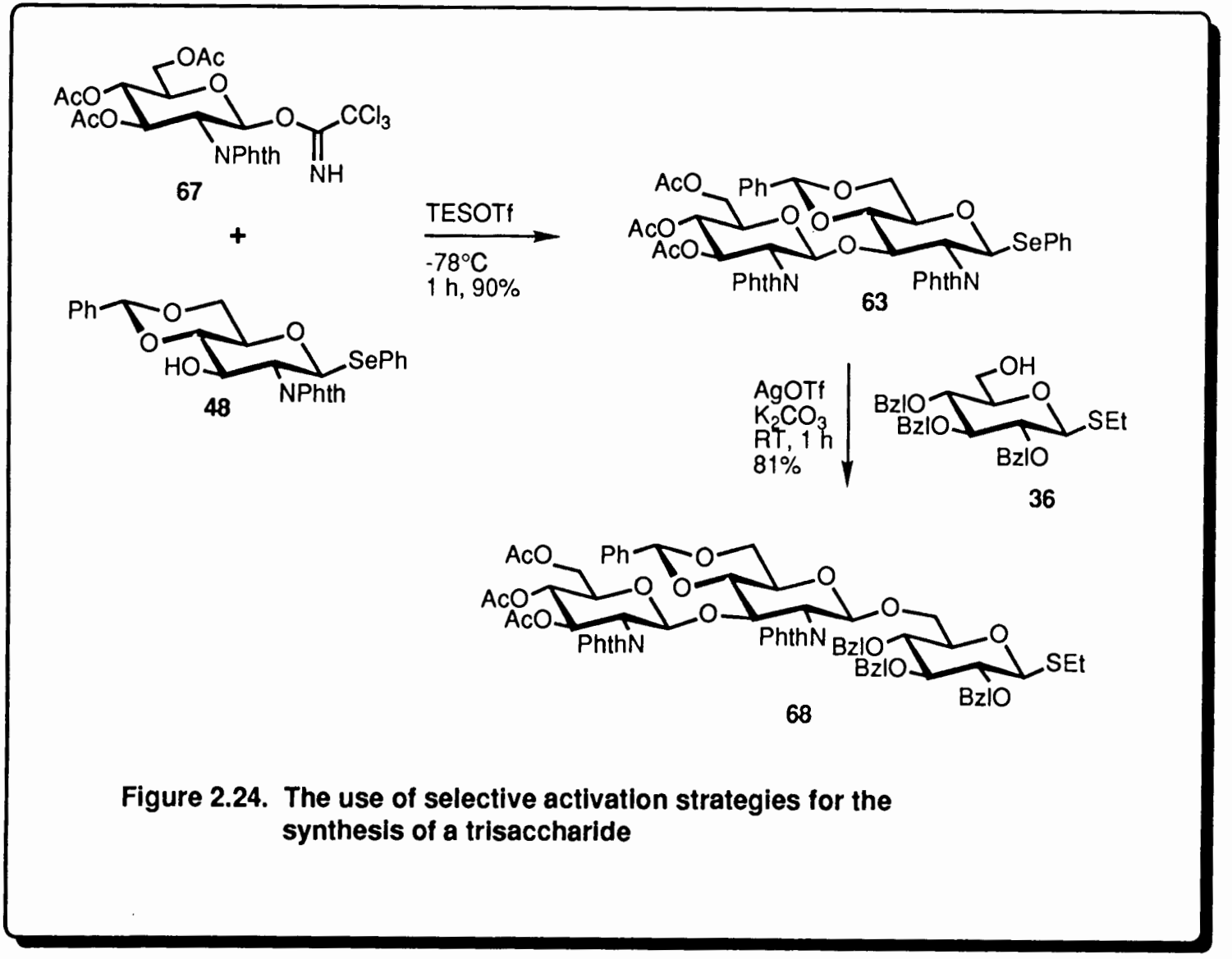
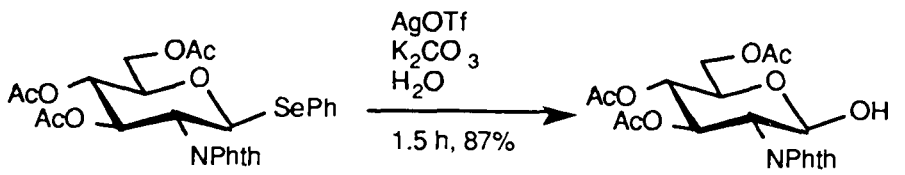


Figure 2.24. The use of selective activation strategies for the synthesis of a trisaccharide

2.2.7. Synthesis of Hemiacetals from Selenoglycosides

Hemiacetals are important intermediates for the synthesis of glycosyl donors such as trichloroacetimidates and other sugar derivatives. The efficient liberation of the anomeric center is desirable. To this end, we investigated the hydrolysis of the selenoglycoside **5** with silver triflate followed by a quench with water. The hemiacetal **66** was obtained in 87% yield (Figure 2.25).



5 **66**

Figure 2.25. Synthesis of a hemiacetal from a selenoglycoside

2.3 OTHER WORK ON SELENOGLYCOSIDE ACTIVATION

Since our earlier disclosure on the applicability of selenoglycosides in oligosaccharide synthesis, Zuurmond et al.[107] have investigated selenoglycoside activation with different promoters. The authors have obtained promising results with the iodonium ion-mediated glycosylations of selenoglycosides and a variety of acceptors in the presence of iodonium di-sym-collidine perchlorate (IDCP) (Figure 2.26, equation 1) or *N*-iodosuccinimide/ triflic acid (Figure 2.26, equation 2). The authors reaffirmed the possibility of

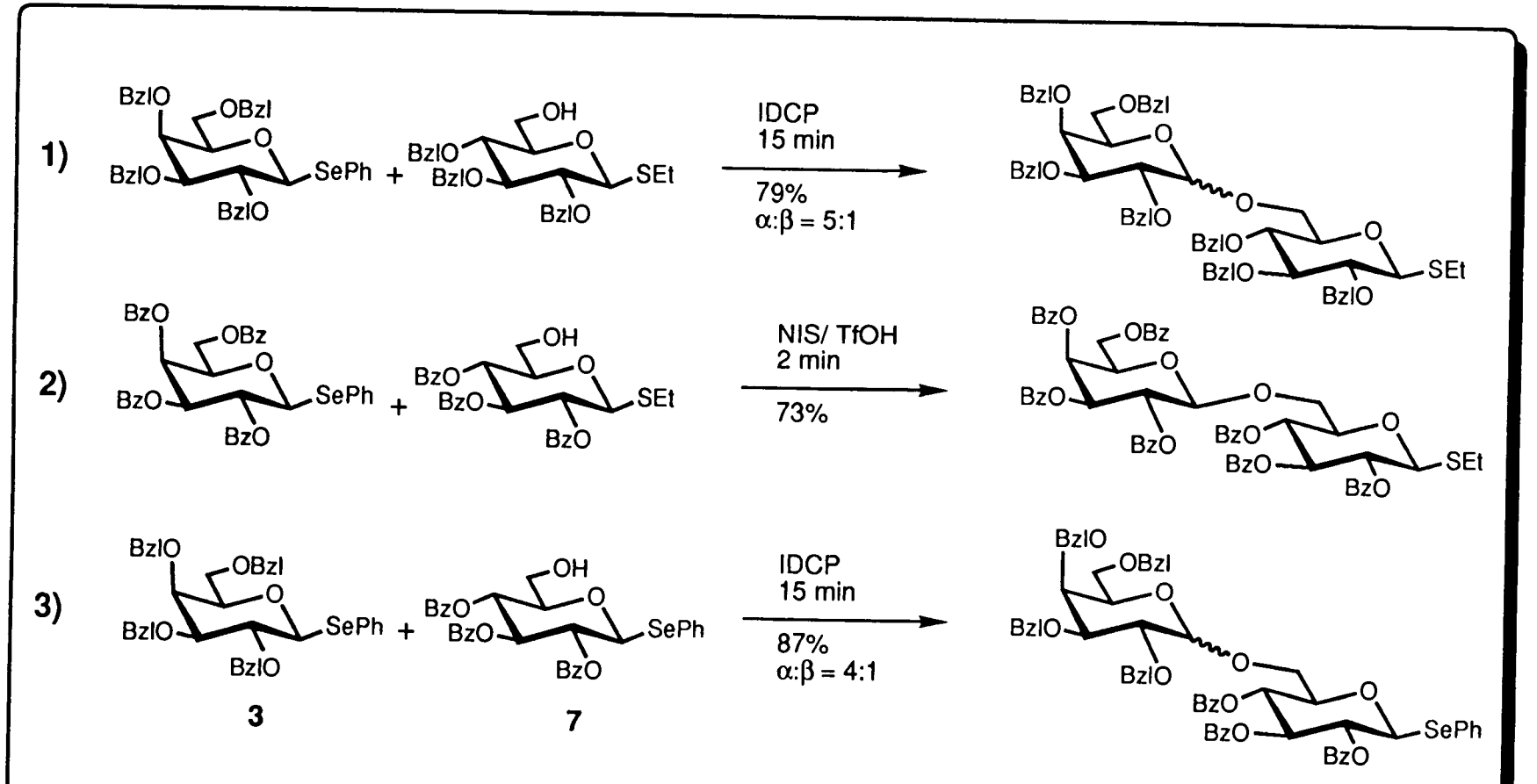


Figure 2.26. Other work on selenoglycoside activation

preferential activation of "armed" and "disarmed" phenyl selenoglycosides over ethyl thioglycosides under IDCP activation. They also extended the "armed" and "disarmed" concept to selenoglycosides by achieving the glycosylation of an armed selenoglycoside donor with a disarmed selenoglycoside acceptor (Figure 2.26, equation 3).

2.4. CONCLUSIONS

An efficient method of synthesis of phenyl selenoglycosides by the reaction of the acetylated derivatives with phenylselenol in the presence of one molar equivalent of $BF_3.OEt_2$, has been developed. These selenoglycosides have been used effectively as both donors and acceptors in various selective activation strategies.

The versatility of these novel compounds was illustrated by the selective activation of "armed" and "disarmed" phenyl selenoglycoside donors over "armed" ethyl thioglycosides acceptors with silver trifluoromethanesulfonate in the presence of potassium or silver carbonate to give disaccharides in excellent yields. The selective activation of glycosyl bromide donors over phenyl selenoglycoside acceptors was realized by silver trifluoromethanesulfonate promotion in the presence of collidine. Such selectivity was also demonstrated by the preferential activation of glycosyl trichloroacetimidate donors in the presence of selenoglycoside acceptors with triethylsilyl trifluoromethanesulfonate. The central role of selenoglycosides is illustrated by the synthesis of a trisaccharide that profits from the sequential, selective activation of a glycosyl bromide donor over a selenoglycoside acceptor and the

resulting selenoglycoside disaccharide over a thioglycoside acceptor. The liberation of the anomeric hydroxyl group from a phenyl selenoglycoside was also effected under silver triflate promotion.

The preferential activation and deactivation of selenoglycosides relative to the other glycosyl-X moieties indicates that they can play a pivotal role in the synthesis of an oligosaccharide, and suggest that they will certainly become part of the arsenal of the synthetic oligosaccharide chemist.

CHAPTER III
RADICAL CATION-INITIATED GLYCOSYLATIONS

3.1. Introduction

In contrast to conventional Lewis acid-mediated glycosylations that are two-electron processes, radical cation-initiated glycosylations involve single-electron-transfer. Radical-cation initiated (RCI) glycosylations can be represented as shown in Figure 3.1. These require the initial generation of a radical cation by the transfer of a single electron from the aglyconic chalcogen to a suitable single-electron-acceptor. Subsequent cleavage of the C_1-X bond results in the formation of the oxocarbocation which undergoes nucleophilic attack by an alcohol to generate a new glycosidic linkage. The single electron transfer from the glycosyl donor can be effected either electrochemically,[108-110] photochemically[111] or chemically.[112]

The electrochemical glycosylation method was introduced by Noyori and Kurimoto[108] for achieving glycosylations with aryl O-glycosides. This novel concept was extended by Balavoine et al.[109] and Amatore et al.,[110] independently, to phenyl S-glycosides (Figure 3.2). Since the oxidation potentials of the phenyl S-glycosides are lower than the those of the corresponding phenyl O-glycosides, the electrochemical glycosylation of the former class of compounds offered the advantage of conducting glycosylations at a lower oxidation potential, providing compatibility with a wider variety of protecting groups.

Chemically-induced radical cation-initiated glycosylations of thioglycosides were reported by Marra et al.[112a] (Figure 3.3) The authors employed tris(4-bromophenyl)aminium hexachloroantimonate (BAHA) as the single electron

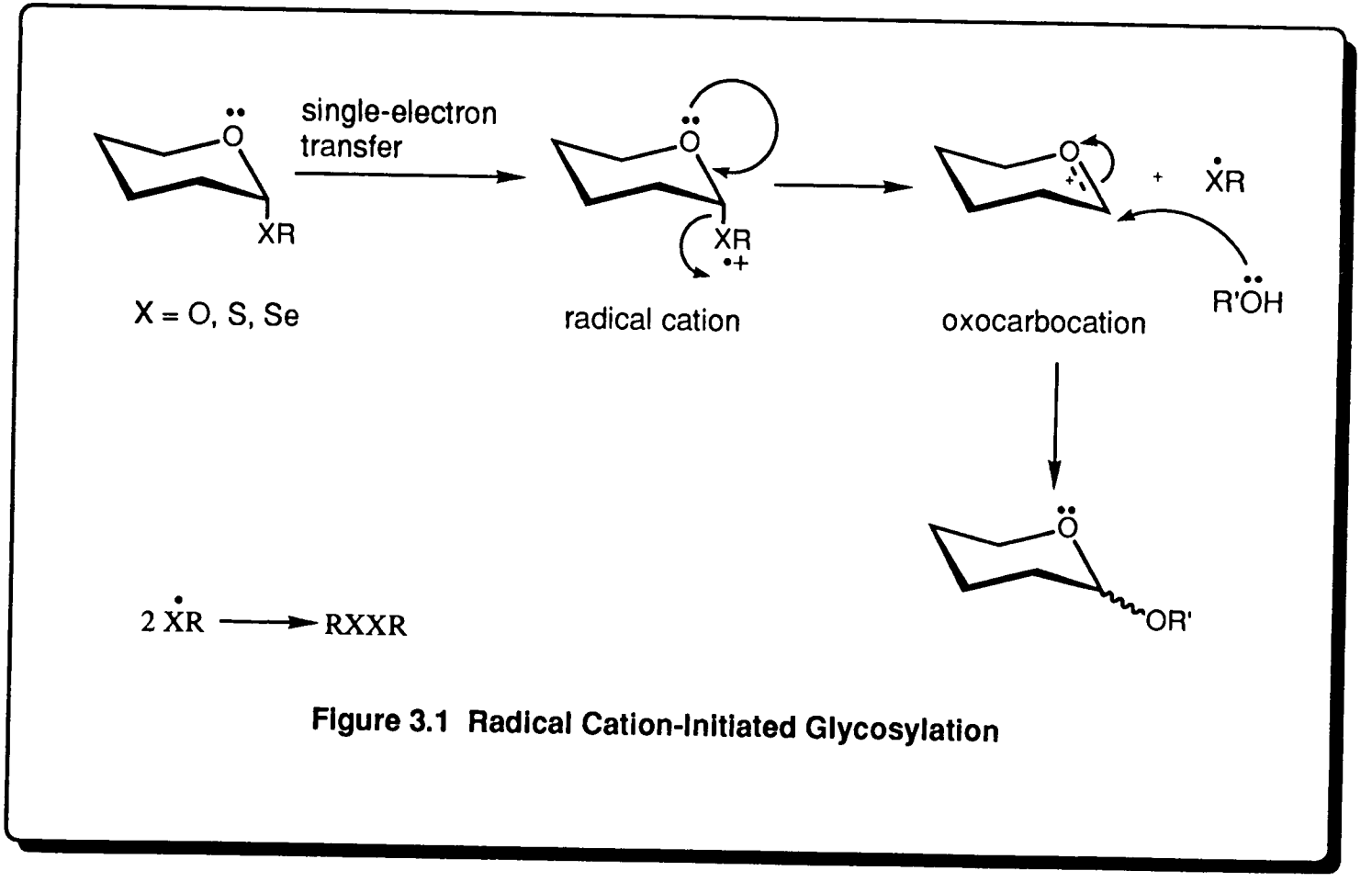


Figure 3.1 Radical Cation-Initiated Glycosylation

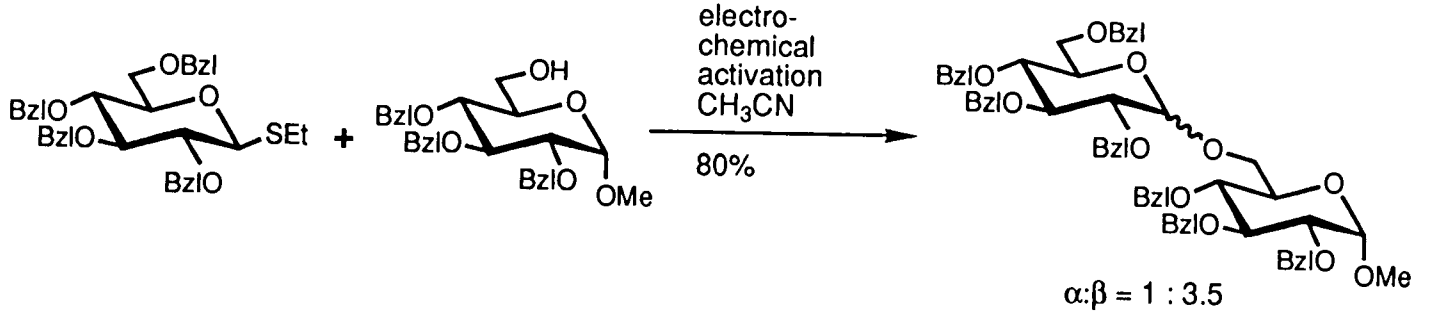


Figure 3.2. Electrochemically-induced RCI glycosylation.[110b]

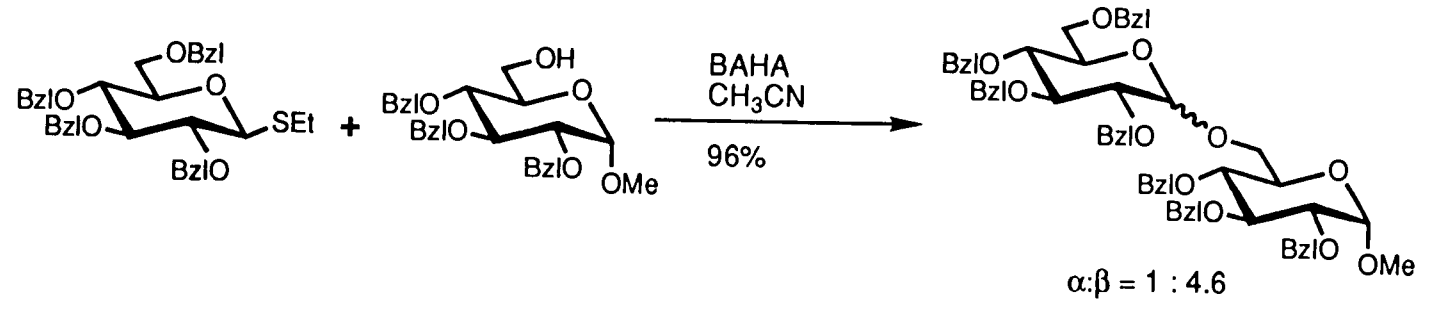


Figure 3.3. Chemically-induced RCI glycosylation[112]

transfer reagent, to effect glycosylations with ethyl thioglycosides. At the time of this communication we were pursuing similar experiments and using BAHA to effect RCI glycosylations of selenoglycosides.[113]

3.2. Results and Discussion

3.2.1. Determination of Oxidation Potentials of Phenyl Selenoglycosides

In order to perform RCI glycosylations, a single electron transfer reagent was required, the choice of which depended on the ease of oxidation of the selenoglycosides. Hence, the oxidation potentials of various selenoglycosides were determined by cyclic voltammetry.

A cyclic voltammetry experiment involves the application of a voltage to the working electrode within a predetermined range, in either a positive or negative direction.[114] The direction of the scan is reversed and the potential is returned to its initial value. The potential of the working electrode is controlled in reference to a standard saturated calomel electrode (SCE) or a silver/ silver chloride electrode (Ag/ AgCl). The cyclic voltammogram thus obtained is a plot of the current at the working electrode versus the applied voltage.

Cyclic voltammetry was performed on 1.0 mmolar solutions of the substrates in dry acetonitrile. Tetraethylammonium perchlorate (0.1 M) was used as the supporting electrolyte. The cyclic voltammograms were measured at a platinum electrode with reference to a standard saturated calomel electrode. The instrument was calibrated with ferrocene as the standard. The voltage was scanned from 0-2 V in the anodic direction at which point the direction of the scan was reversed. The forward scan showed one anodic wave having a peak potential corresponding to the oxidation potential of the substrate. The reverse scan did not show any cathodic peaks. This is typical of an 'EC type mechanism'

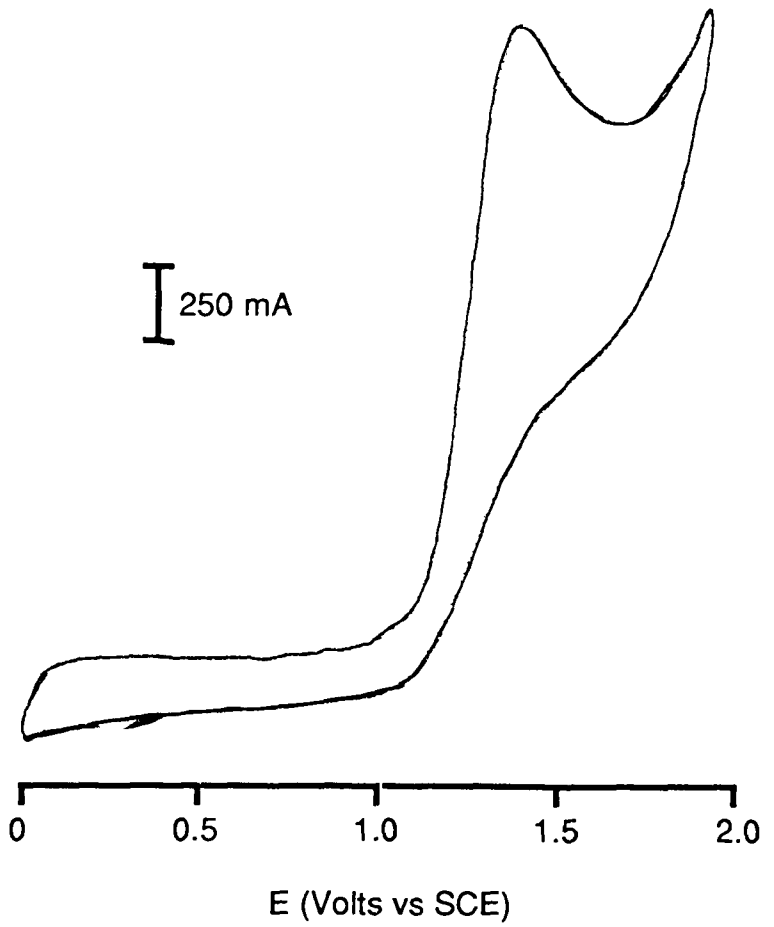


Figure 3.4. **Cyclic voltammogram of Phenyl 2,3,4-tri-O-acetyl-1-deoxy-1-seleno-α-L-rhamnopyranoside (1) (0.1 mmol) at a scan rate 200 mV/s in CH_3CN. Working electrode: Pt. Reference electrode: SCE. Supporting electrolyte: 0.1 M tetraethylammonium perchlorate.**

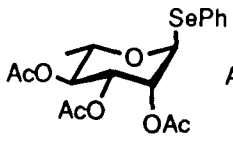
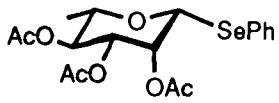
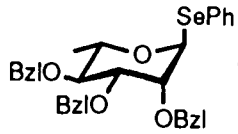
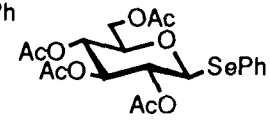
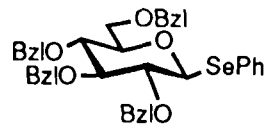
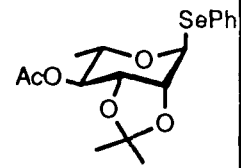
in which the initial electrochemical reaction is followed by a chemical reaction. This observation is consistent with the disproportionation of the radical-cation to the oxocarbocation. The oxidation potentials of the selenoglycosides investigated are shown in Table 3.1. They fall in the range of 1.35-1.5 V. These values are lower than the oxidation potentials of S-glycosides and O-glycosides.[114] This is reflective of the ionization potentials of oxygen, sulfur, and selenium that decrease in the same order.[115]

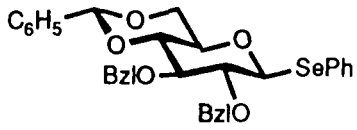
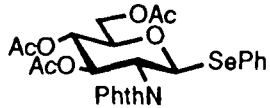
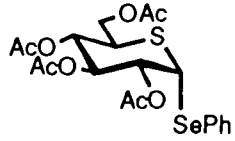
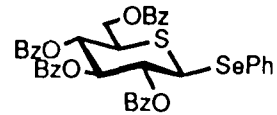
3.2.2. Radical Cation-Initiated Glycosylations

The SET reagent employed for RCI glycosylations of selenoglycosides was tris(4-bromophenyl)aminium hexachloroantimonate (BAHA). The reduction potential of BAHA is reported as 1.05V *vs* SCE.[116] Since the oxidation potentials of the selenoglycosides are higher than that of the aminium salt, it was initially expected that the oxidation of selenoglycosides by BAHA would be thermodynamically unfavourable. However, Kamata et al.[117] have reported the radical-cation-mediated desulfurization of thiiranes with BAHA as SET reagent (Figure 3.5). The oxidation potentials of their substrates were in the range of 1.44-1.84V in acetonitrile *vs* SCE. Thereafter, Marra et al.[112] claimed to effect RCI glycosylations of thioglycosides with BAHA, in spite of the higher oxidation potentials of the thioglycosides (Figure 3.3). The following investigation was thus launched.

RCI glycosylations of primary and secondary hydroxyl acceptors with armed and disarmed selenoglycosides were investigated with BAHA as the SET reagent. The glycosylation of methyl glycoside **16** with selenoglycoside **1** yielded the disaccharide **31** in 76% yield (Table 3.2, entry 1). Glycosylation of the above acceptor with a more reactive armed selenoglycoside donor **10** proceeded in

Table 3.1. Oxidation Potentials[a] of Selenoglycosides

Seleno-glycoside						
Oxidation potential (V)	**1.35**	**1.41**	**1.42**	**1.50**	**1.33**	**1.35**

Seleno-glycoside					
Oxidation potential (V)	**1.39**	**1.41**	**1.52**	**1.47**	**1.48**

[a] Oxidation potentials measured *vs* a standard saturated calomel electrode in dry acetonitrile with 0.1M tetraethylammonium perchlorate as supporting electrolyte at a scan rate of 200 mV/sec.

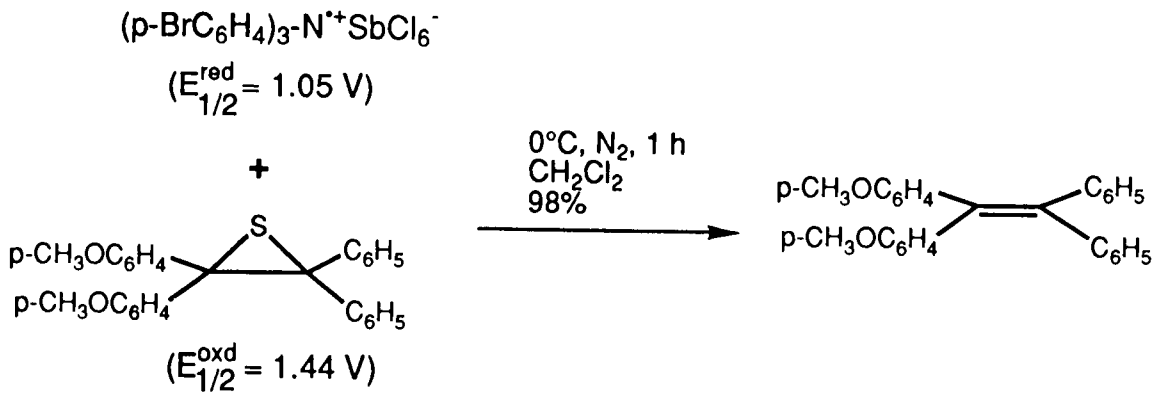
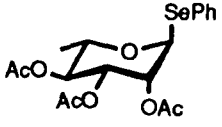
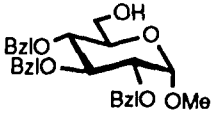
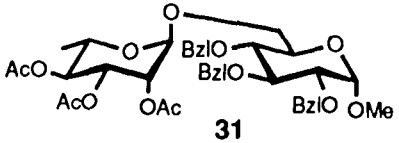
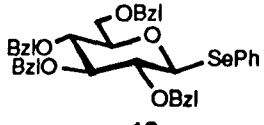
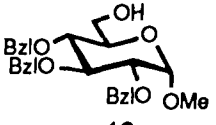
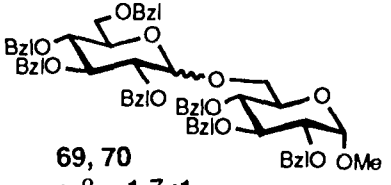


Figure 3.5. Desulfurization of thiiranes by BAHA-mediated single electron transfer.[117]

Table 3.2. BAHA-mediated glycosylations of a primary hydroxyl acceptor with selenoglycoside donors

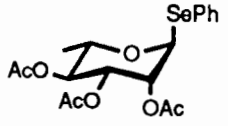
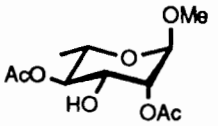
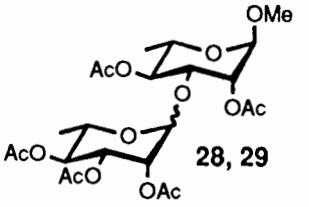
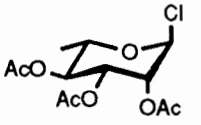
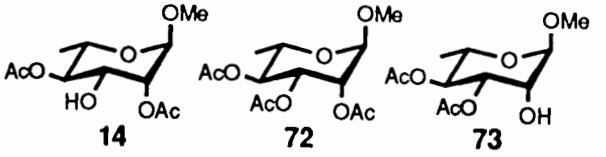
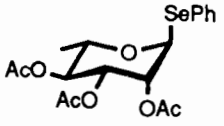
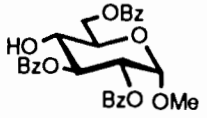
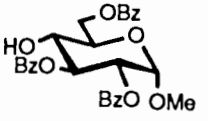
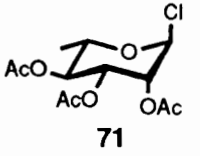
Entry	Donor	Acceptor	Molar Ratio[a]	Time (h)	Product	Yield (%)
1	 **1**	 **16**	2 : 1 : 3	2	 **31**	76
2	 **10**	 **16**	1 : 0.8 : 1.5	3	 **69, 70** α:β = 1.7 :1	94

[a]donor : acceptor : BAHA

94%, to yield an α:β mixture of disaccharides **69** and **70** in a 1:1 ratio (Table 3.2, entry 2). These glycosylations were effected at ambient temperature.

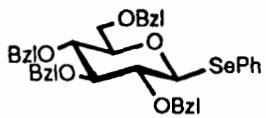
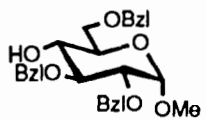
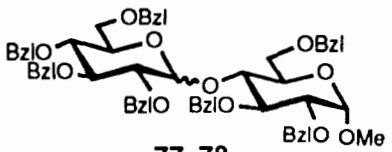
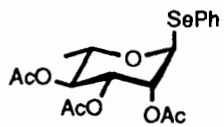
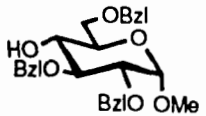
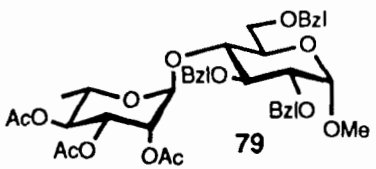
Initial attempts to extend this methodology to secondary alcohol acceptors proved to be unsuccessful. Glycosylation of methyl glycoside **14** with selenoglycoside **1** afforded a mixture of products. In addition to the 52% disaccharides, 36% of the 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl chloride **71** was formed by the reaction of the donor **1** with chloride ions in solution (Table 3.3, entry 1). Along with the recovered acceptor **14**, trans-esterification products **72** and **73** were also obtained. A similar glycosylation of the unreactive acceptor **74** did not provide any of the desired disaccharide **75**. Although the selenoglycoside activation had been effected, as suggested by the isolation of the chloride **71**, 90% of the glycosyl acceptor **74** was recovered from the reaction mixture (Table 3.3, entry 2). Modulation of the reactivity of the acceptor was required. Hence, the benzylated acceptor **76** was synthesized. The synthesis of compounds **74** and **76** is discussed in Section 4.4.3. Glycosylation of the methyl glycoside acceptor **76** with the selenoglycoside **10** afforded an α/β mixture of the disaccharides **77** and **78** in a yield of 50% (Table 3.4, entry 1). The reaction did not reach completion and the unreacted acceptor was recovered. The yield of the reaction based on the recovered acceptor was 90%. Based upon these results it was deduced that glycosylations of secondary acceptors were not that efficient and perhaps required additional amounts of the promoter to achieve completion. In the following glycosylation of the same acceptor with the selenoglycoside **1**, the concentration of the promoter BAHA was increased from 1.5 molar equivalents to 3 molar equivalents with respect to the selenoglycoside. As observed in earlier experiments, this glycosyl donor had a tendency to form the corresponding chloride under the reaction conditions. Therefore, a two fold excess of the donor **1** was used to ensure that rhamnopyranosyl chloride

Table 3.3. Unsuccessful BAHA-mediated glycosylations of secondary hydroxyl acceptors with selenoglycoside donors

Entry	Donor	Acceptor	Molar Ratio[a]	Time (h)	Product	Yield (%)
1	 **1**	 **14**	1 : 1 : 1	1	 **28, 29**	52% α:β = 6:1
					 **71**	36%
					 **14** **72** **73**	45%
2	 **1**	 **74**	1 : 0.8 : 1.5	1	 **74**	90%
					 **71**	60%

[a]donor : acceptor : BAHA

Table 3.4. Successful BAHA-mediated glycosylations of secondary hydroxyl acceptors with selenoglycoside donors[a]

Entry	Donor	Acceptor	Molar Ratio[a]	Time (h)	Product	Yield (%)
1	 **10**	 **76**	1 : 0.8 : 1.5	2	 **77, 78**	90%[b]
2	 **1**	 **76**	2 : 1 : 6	2	 **79**	91%[b]

[a]donor : acceptor : BAHA. [b]yield based on acceptor recovered

formation did not reduce the yield of the reaction. The disaccharide **79** was obtained in 73% yield (Table 3.4, entry 2) and 20% of the acceptor remained unreacted; the yield of the reaction based on the acceptor recovered was 91%.

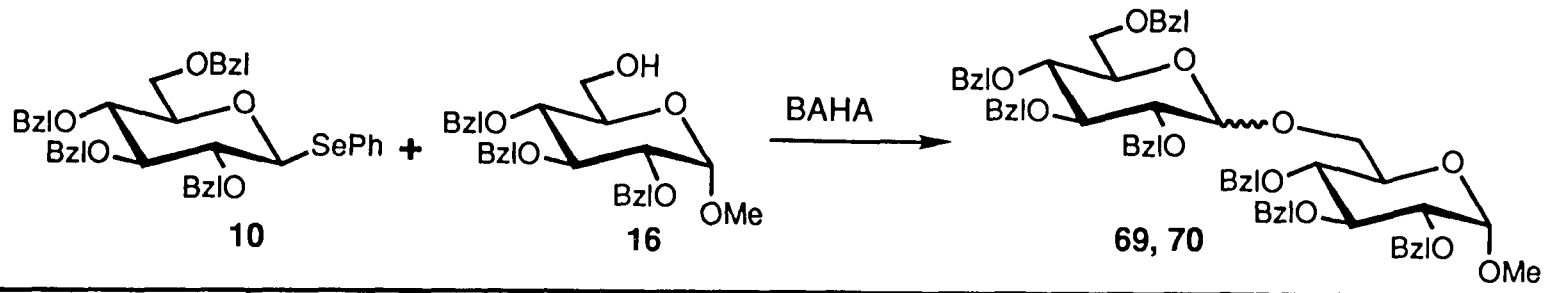
3.2.3. RCI Glycosylations or Acid Catalysis?

We realized that the aminium salt BAHA had the potential of effecting glycosylations via two possible mechanisms. The first mechanism, as discussed thus far, involved the intermediacy of radical-cations generated via single electron transfer from the selenoglycoside to the aminium radical cation. Owing to the strongly acidic nature of the reaction medium, a second possibility of acid catalysis was also considered. To distinguish between these possibilities the following approach was adopted.

An effective method of exploring electron-transfer-reactions is by the use of SET quenching reagents. 1,2,4,5-Tetramethoxybenzene (TMB) has been used as an effective SET quenching reagent for the evaluation of BAHA-mediated SET reactions.[117,118] Since the oxidation potential of TMB (0.81 V)[119] is lower than the oxidation potentials of the selenoglycosides, it should be capable of interfering with the BAHA-mediated glycosylations if SET was the dominant mechanism. In the case of acid catalysis the use of TMB as a quencher should produce little or no change in the outcome of the reaction.

The BAHA-mediated glycosylations of the methyl glycoside acceptor **16** and selenoglycoside **10** were performed in dichloromethane and in acetonitrile as the solvents, in the absence and the presence of the quencher TMB (Table 3.5). The reactions in a given solvent were performed simultaneously under identical conditions and concentrations of reactants. The reactions were closely monitored by TLC. A TLC comparison of the reactions with and without quencher in acetonitrile revealed that after 1 h the glycosyl acceptor **16** had completely

Table 3.5. Quenching experiments with phenyl 2,3,4,6-tetra-O-benzyl-1-seleno-β-D-glucopyranoside



	CH_2Cl_2		CH_3CN	
	Time	Result	Time	Result
WITHOUT QUENCHER[a]	3 h	disaccharides **69, 70** 94%, α:β = 1.8 : 1	1 h	disaccharides **69, 70** 89%, α:β = 1.7 : 1
WITH QUENCHER[b,c]	3 h	acceptor **16** recovered (96%)	1 h	disaccharides **69, 70** 78%, α:β = 1 : 7

[a]donor : acceptor : BAHA = 1: 0.8 : 1.5. [b]Quencher = 1,2,4,5-tetramethoxybenzene
[c]donor : acceptor : BAHA : quencher = 1: 0.8 : 1.5 : 6

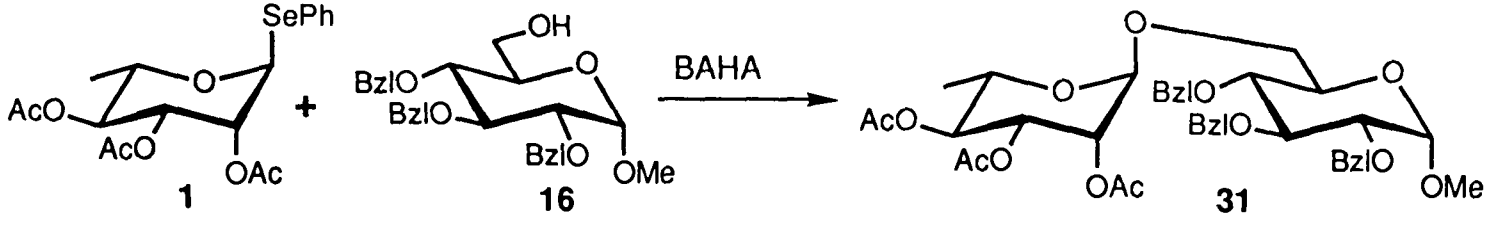
reacted in the latter case but was still detectable in the former reaction. The yield of the disaccharides isolated in the reaction with quencher (78%) was lower than the reaction in the absence of the quencher (89%). The reaction in the presence of TMB conducted in dichloromethane was completely quenched and the reactants were recovered almost quantitatively.

The results of a similar investigation performed for the glycosylation of the acceptor **16** with the selenoglycoside **1** are shown in Table 3.6. As in the above case, the reaction was completely quenched in the presence of the quencher TMB when dichloromethane was the solvent of the reaction, and the reactants were recovered quantitatively. In acetonitrile, 60% disaccharide **31** was obtained in the absence of the quencher. No unreacted acceptor was present at the completion of the reaction. A TLC comparison of this reaction after 1 h with an analogous reaction in the presence of TMB indicated that the reaction had been suppressed in the presence of the quencher. A substantial amount of the unreacted acceptor was detected by TLC in addition to the expected disaccharide. The unreacted acceptor was recovered from the reaction in a yield of 25%.

We also decided to probe the nature of the BAHA-mediated glycosylations with the ethyl thioglycoside **80** (Table 3.7). The glycosylation in dichloromethane afforded an α/β mixture of the disaccharides **69** and **70**. This result contrasts with that of Marra et al.[111] who reported that no reaction occurs in dichloromethane. An analogous reaction in the presence of the quencher was completely quenched. In acetonitrile, the quencher was effective in suppressing the reaction; the disaccharides were isolated in a low 28% yield and the unreacted acceptor was reisolated in a yield of 63%.

Upon analysis of these results we initially speculated that the BAHA-mediated glycosylations were occurring by a combination of single electron

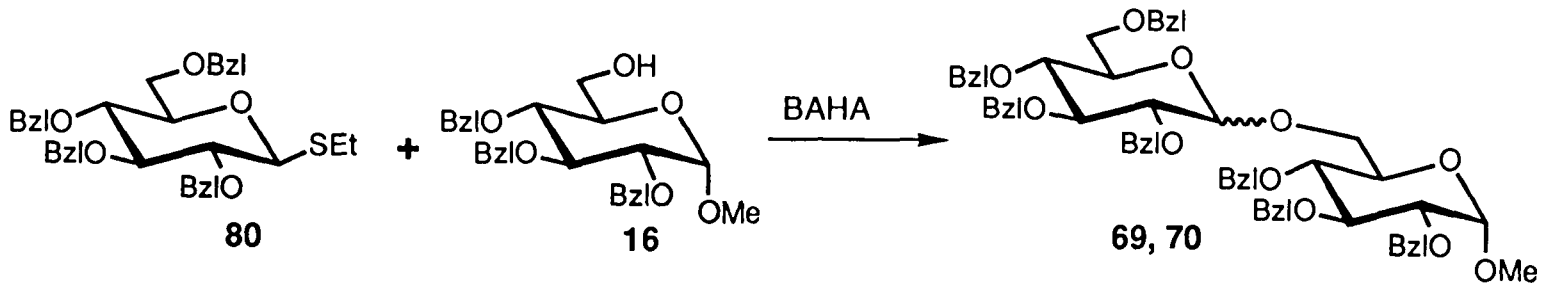
Table 3.6. Quenching experiments with phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside



	CH_2Cl_2		CH_3CN	
	Time	Result	Time	Result
WITHOUT QUENCHER[a]	2 h	disaccharide **31** 76%	1 h	disaccharide **31** 60%
WITH QUENCHER[a]	2 h	acceptor **16** recovered (96%) donor **1** recovered (95%)	1 h	disaccharide **31** (51%) acceptor **16** recovered (25%)

[a]donor : acceptor : BAHA = 1: 0.8 : 1.5. [b]Quencher = 1,2,4,5-tetramethoxybenzene.
[c]donor : acceptor : BAHA : quencher = 1: 0.8 : 1.5 : 6

Table 3.7. Quenching experiments with ethyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside



	CH_2Cl_2		CH_3CN	
	Time	Result	Time	Result
WITHOUT QUENCHER[a]	2 h	disaccharides **69, 70** 88%, α:β = 1.5 : 1	0.5 h	disaccharides **69, 70** 81%, α:β = 1 : 1
WITH QUENCHER[b,c]	2 h	acceptor **16** recovered (94%) donor **1** recovered (96%)	0.5 h	disaccharides **69, 70** 28%, α:β = 1 : 4.5 acceptor **16** recovered (63%)

[a]donor : acceptor : BAHA = 1: 0.8 : 1.5. [b]Quencher = 1,2,4,5-tetramethoxybenzene.
[c]donor : acceptor : BAHA : quencher = 1: 0.8 : 1.5 : 6

transfer and acid catalysis. In dichloromethane, SET was the dominant pathway since the reactions were completely quenched in the presence of the quencher TMB in all three cases investigated. In acetonitrile, however, the reactions continued to proceed in spite of the presence of TMB. We speculated that in spite of having quenched the SET reaction, an alternative acid catalyzed pathway was available to the reactants. The acid catalyzed reaction was less efficient than the RCI reaction; therefore, an incomplete reaction was observed. However, this reasoning did not explain why a similar result was not observed in dichloromethane, since Lewis acid catalyzed glycosylations are generally conducted in the latter solvent.

We suggest, therefore, the following explanation for our observations. Since the oxidation potential of BAHA is lower than that of the selenoglycosides, the direct oxidation of the selenoglycosides by BAHA is thermodynamically unfavourable. We postulate that the oxidation is preceded by the formation of a complex between the selenium atom of the selenoglycoside and the aminium radical-cation. This adduct has a modified oxidation potential and is amenable to oxidation. Similar adducts have been proposed by Gilbert and Marriott[120] for the reaction of $NH_3^{\bullet+}$ with various sulfides and sulfoxides.

The polarity of acetonitrile should facilitate the initial ion-pair dissociation of BAHA and enable the complexation of the selenium and the aminium radical-cation. This would lead to an incomplete quenching of the glycosylations by TMB in acetonitrile. Hence, SET is the dominant mechanism of the reaction in both dichloromethane and acetonitrile and the acid catalyzed pathway is of lesser importance. This conclusion is further supported by the result of a glycosylation reaction in the presence of anisole as the SET quenching reagent. The oxidation potential of anisole is +1.76 V.[118] Since this value is higher than that of the substrates, the quencher should have no appreciable effect on the SET

glycosylations. The methyl glycoside acceptor **16** and the selenoglycoside **1** were reacted in the presence of anisole with BAHA as the promoter. As predicted, the reaction was not quenched and the disaccharide **31** was isolated in 79% yield.

The question of the stereochemical outcome of the reactions remains to be addressed. The glycosylations with the selenorhamnoside **1** proceed in a 1,2-trans fashion, as expected due to the anchimeric assistance offered by the acetate substituent at the C-2 position of the glycosyl donor. The glycosylation with the perbenzylated selenoglucoside **10** in dichloromethane favours the formation of the thermodynamically more stable α-disaccharide **69**. The stereoselectivity of the reactions in acetonitrile are noteworthy. Glycosylations in acetonitrile are reported to occur via the intermediacy of a glycosyl-acetonitrilium ion. Several workers have proposed that the acetonitrilium ion forms at the α-face (Figure 3.6).[121]

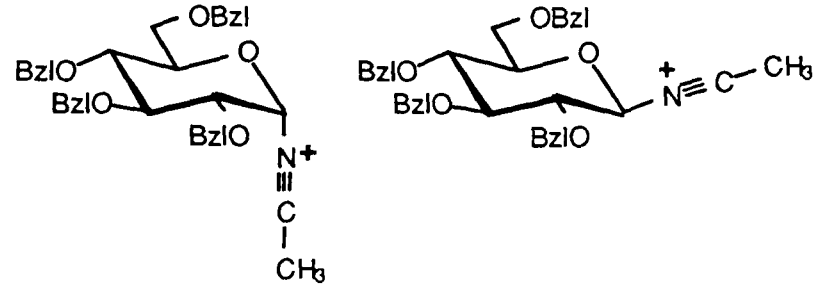


Figure 3.6. α and β nitrilium ions

This intermediate then undergoes an inversion in the presence of a glycosyl acceptor. Thus, acetonitrile has been the solvent of choice to promote β-

glycosylations with substrates possessing a non-participating substituent at the C-2 position. However, other workers have proposed an equatorial acetonitrilium ion (Figure 3.6),[122] the stability of which was attributed to the reverse anomeric effect. Subsequent inversion by the acceptor was postulated to account for the preferential formation of the α-disaccharide in these cases.

In our glycosylations with selenoglycoside **10**, the results in dichloromethane and acetonitrile are comparable and the α-disaccharide **69** is only slightly favoured. These results are inconsistent, therefore with either of the above proposals. We suggest that the reaction is under thermodynamic control.

In contrast to the lack of stereoselectivity of this glycosylation in acetonitrile in the absence of the quencher TMB, reactions in the presence of TMB afforded predominantly the β-disaccharide **70**. We speculate that this is due to the formation of an encounter complex of the TMB and the oxocarbocation. This type of complex was initially proposed by Carlson et al.[123] for interactions of benzene with oxygen heterocycles Thus, the electron cloud of the aromatic ring interacts with the positive end of the dipole of the ring and shields its α-face. (Figure 3.7). Nucleophilic attack occurs, therefore, at the β-face.

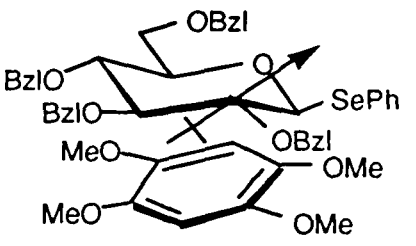


Figure 3.7. Encounter complex

3.3. Conclusion

Phenyl selenoglycosides are amenable to radical-cation-initiated glycosylations effected by the single electron transfer reagent tris(4-bromophenyl)aminium hexachloroantimonate (BAHA). The glycosylations of reactive primary alcohol acceptors are promising, although the glycosylations of unreactive acceptors are less efficient. Acceptors of moderate reactivity require a greater concentration of the promoter to achieve a high yield of product.

The oxidation potentials of various selenoglycosides have been determined. The oxidation potentials of BAHA (1.05 V) and the selenoglycosides (1.35-1.5 V) indicate that the direct oxidation of selenoglycosides via single electron transfer by BAHA is not probable. We suggest a prior complexation of the selenoglycoside and BAHA that produces a complex of modified oxidation potential, followed by single electron transfer.

Results based on quenching experiments support the existence of the SET mechanism in dichloromethane and acetonitrile and suggest that the acid catalyzed pathway is of lesser importance.

CHAPTER IV

SYNTHESIS OF HETEROANALOGUES OF DISACCHARIDES CONTAINING SULFUR AND SELENIUM FOR EVALUATION AS GLUCOSIDASE INHIBITORS

4.1. INTRODUCTION

The application of glycosidase inhibitors in biochemical studies as well as in medicinal chemistry has placed considerable emphasis on their synthesis. Glycosidase inhibitors have been used as probes for the determination of the topography of the active sites of enzymes and to provide a better understanding of the mechanism of enzyme action.[124] Therapeutically, they have a potential as anti viral agents, for example in HIV treatment,[8] as antibacterial[125] and anticancer agents,[126] and in the treatment of metabolic disorders such as diabetes.[15] The following sections provide a little more insight regarding the need for efficient inhibitors of glycosidases.

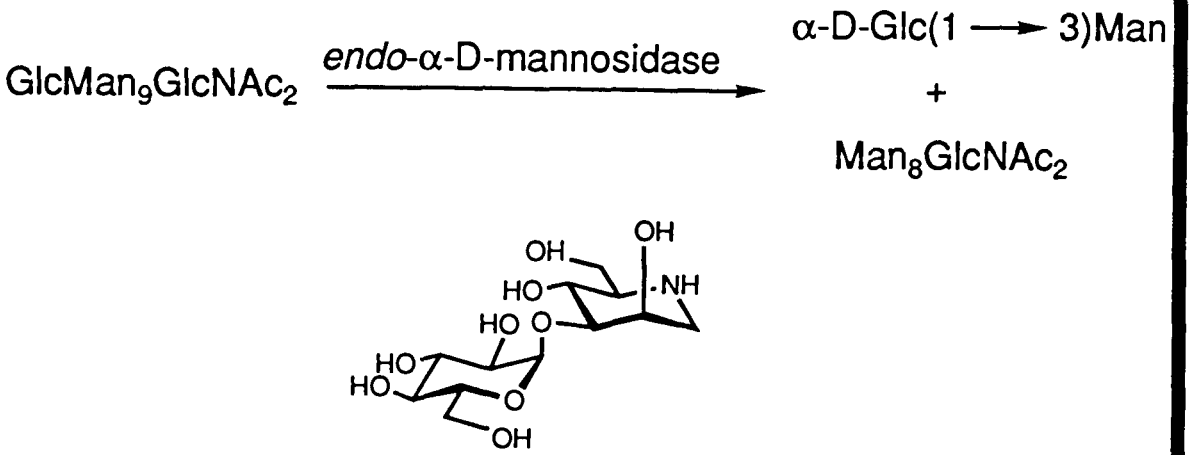
4.1.1. Applications of Gycosidase Inhibitors

4.1.1a. Glycosidase Inhibitors as Structure-Function Probes

Glycosidase inhibitors have been used to provide a better understanding of the mechanism of enzyme hydrolysis. Chemical modifications of the natural substrates have been performed to afford analogues that possess good affinity towards the enzyme and yet remain chemically inert towards hydrolysis. These inhibitors were then used to probe structure-function relationships.

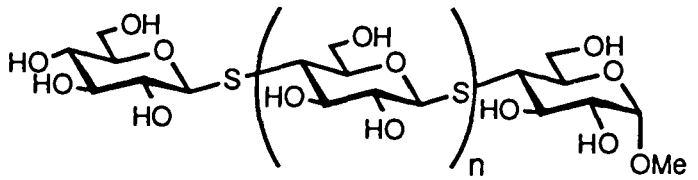
For example, in a recent study, Spohr et al.[124a] have applied these principles to investigate the nature of the binding site of the enzyme endo-α-D-mannosidase. This enzyme is responsible for the hydrolysis of the oligosaccharide $GlcMan_9GlcNAc_2$ to release the disaccharide α-D-Glc(1-3)-D-Man. A potent inhibitor of the enzyme is the mannojirimycin derivative shown in Figure 4.1. Spohr et al.[124a] have synthesized the analogues of this inhibitor by the chemical replacement of the hydroxyl substituents on the glucose and mannose residues with hydrogen, fluorine and methyl groups. They have also replaced the glucose unit with other monosaccharide residues and studied the potencies of these inhibitors. From their results on substrate specificities they were able to assess the relative importance of each hydroxyl group in the formation of hydrogen bonds in the enzyme-inhibitor complex.

Another study was presented by Schou et al.[124d] that involved cellulases. Cellulases are a group of enzymes that bring about the hydrolysis of cellulose to glucose and cellobiose. Mechanistic evaluation of these enzymes is thwarted due to the insolubility of cellulose. Smaller portions of the natural substrate, for example, di- and trisaccharides as well as unnatural substrate analogues are in use for the mapping of the active site of the enzyme. For this purpose Schou et al.[124d] have synthesized various 4-thiocellooligosaccharides as inhibitors of cellulases (Figure 4.2). The inhibition constants of these enzymes were found to be in the micromolar range; the inhibition increased with the increase in the chain length of the inhibitor.



Inhibitor of *endo*-α-D-mannosidase:
1-deoxy-3-O-(α-D-glucopyranosyl)-mannojirimycin

Figure 4.1. Mannojirimycin disaccharide as an inhibitor of *endo*-α-D-mannosidase[124a]



n = 1,2,3

Figure 4.2. 4-Thiocellooligosaccharides as inhibitors of cellulases[124d]

4.1.1b. Glycoprocessing Inhibitors

An important class of inhibitors is one that inhibits the processing of *N*-linked oligosaccharides. As mentioned in Section 1.2.3, all *N*-linked oligosaccharides are derived from a common precursor $Glc_3Man_9GlcNAc_2$, linked to the lipid dolichol, that is transferred to an asparagine residue of a protein by a transferase enzyme.[127] Subsequent elaboration of the oligosaccharide is mediated by several enzymes. The trimming enzyme Glucosidase I effects the removal of the distal α-1,2-linked glucose residue (Figure 4.3). Glucosidase II is specific for the α-1,3-glucose linkages and removes the two innermost glucose units. Subsequent removal of four α-1,2-linked mannose residues by Mannosidase I is followed by the successive addition of a GlcNAc residue and cleavage of two mannose residues linked in an α-1,3- and α-1,6- manner by the enzyme Mannosidase II. At this stage, various transferases bring about the addition of other sugars such as 2-acetamido-2-deoxy-D-glucose, D-glucose, D-galactose, D-mannose, sialic acid, and L-fucose, to afford complex-type or high-mannose-type glycans.

The reason for targeting these enzymes is to produce aberrant glycans that lead to modified glycoproteins. The effects of such a modification of the oligosaccharide on the properties of the glycoprotein can then be investigated and provide an insight into the role of oligosaccharides in glycoprotein function.

A variety of inhibitors of these trimming enzymes is now established.[128] 1-Deoxynojirimycin, *N*-alkylated-1-deoxynojirimycin, and castanospermine are some of the effective Glucosidase I inhibitors with K_i values in the micromolar range. 1-Deoxymannojirimycin and swainsonine are known to inhibit the Mannosidases I and II, respectively.[15]

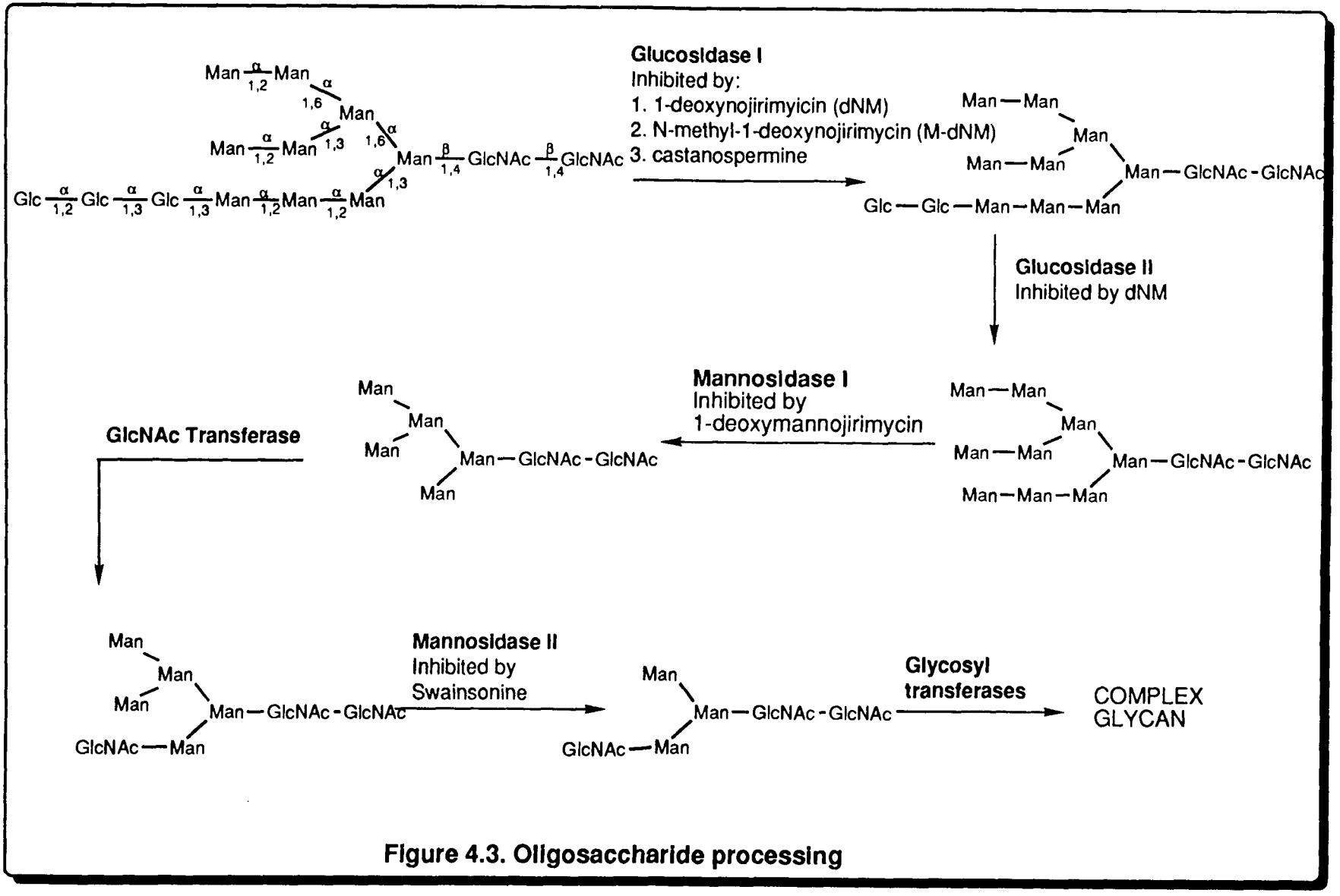


Figure 4.3. Oligosaccharide processing

4.1.1c. Pharmaceutical Applications of Glucosidase Inhibitors

The role of oligosaccharides in HIV infection was described in Section 1.2.3. The viral infection is initiated by the association of the glycoprotein gp120 on the viral envelope with the CD4 receptors expressed on the surface of the T4 cells. Inhibitors of glycoprotein processing enzymes have been shown to possess anti-HIV activity[129] and are candidates as anti-HIV therapeutic agents (Figure 1.7).

Diabetes mellitus is caused by an increase in the level of glucose in the blood. Glucosidase inhibitors such as acarbose have been used to retard the digestion of carbohydrates by the enzyme α-amylase. Blood sugar levels are thus reduced by this interference in carbohydrate metabolism.

4.1.1d. Glycosidase Inhibitors in Affinity Chromatography

Another use of glycosidase inhibitors is in the isolation and purification of enzymes by affinity chromatography.[130] Substrate analogues are covalently bound to a polymer support and when crude enzyme extracts are passed through the column, the affinity of the enzyme for the ligand causes it to bind selectively. For example, *p* aminophenyl-β-D-thiogalactopyranoside is a competitive inhibitor of β-Galactosidase and has been applied in the construction of affinity supports for enzyme purification.

4.1.2. Design of Enzyme Inhibitors

One of the mechanisms of enzyme hydrolysis can be represented as shown in Figure 4.4. The active site of the enzyme contains a carboxyl group that is capable of protonating the glycosidic oxygen atom (A).The intermediacy of a flattened oxocarbocation in a half chair conformation that is stabilized by

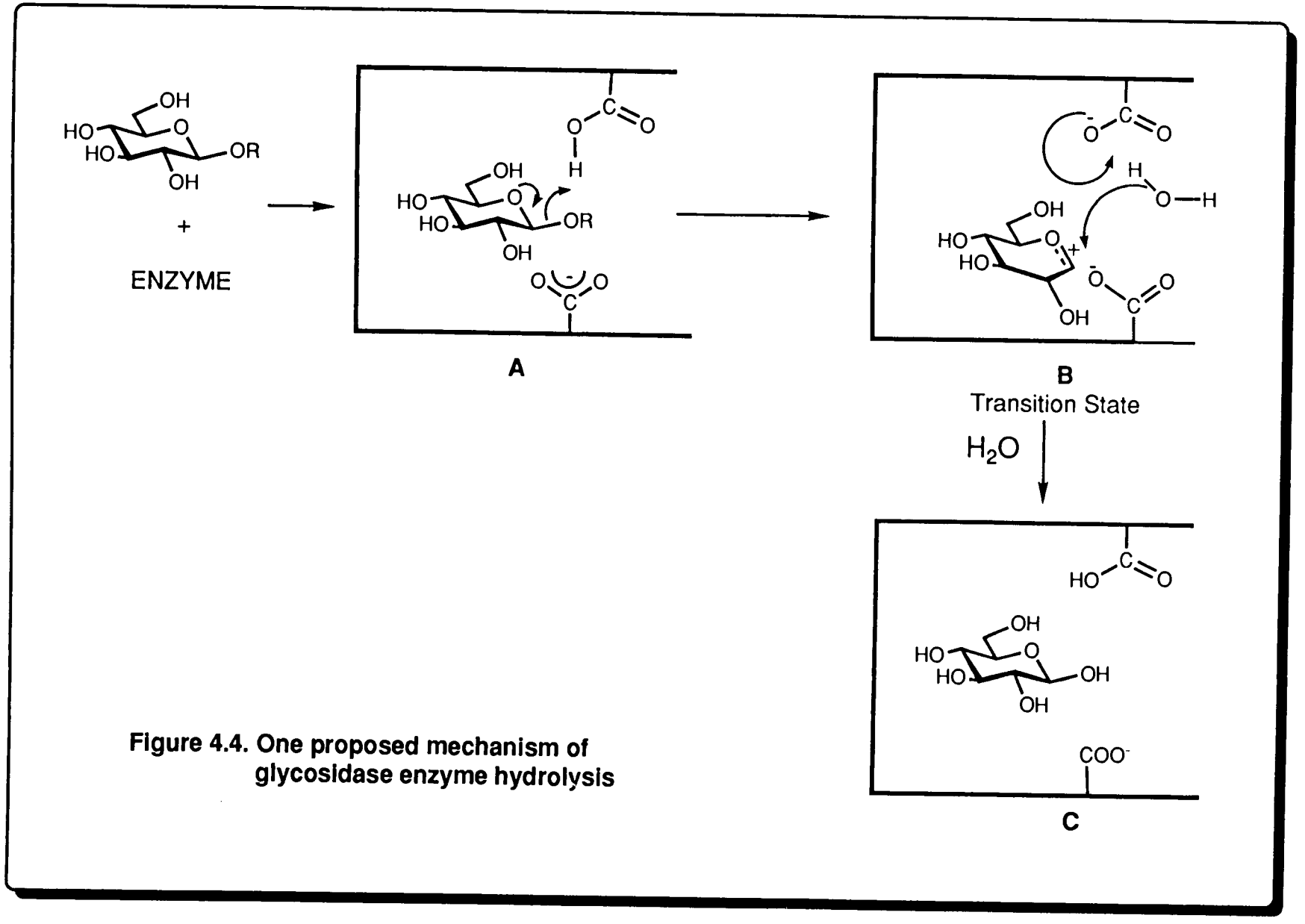


Figure 4.4. One proposed mechanism of glycosidase enzyme hydrolysis

another suitably disposed carboxyl group in the enzyme active site (B) has been proposed. The final step involves the reaction of the oxocarbocation with water.

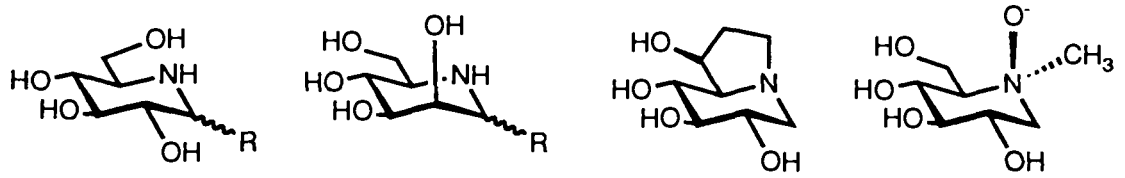
The two structural types of enzyme inhibitors that have been targeted are substrate analogues and transition state analogues. Substrate analogues are designed to structurally resemble the natural substrate and yet remain unsusceptible to enzymatic hydrolysis. Transition state analogues are designed to mimic the charge and/or the flattened half-chair conformation of the oxocarbocation.

4.1.3. Nitrogen-Based Glycosidase Inhibitors

Nojirimycin and mannojirimycin derivatives (Figure 4.5, **a-d**), in addition to resembling the substrate, have the ability to form an ionic bond with the carboxylate group in the enzyme active site and are potent glucosidase inhibitors.[128c] The active form of these substances is the cationic form and so their inhibition potencies are likely to be related to their basic character. Compounds with half-chair like conformations, such as the lactone **(g)** and the lactam **(h)**, are good transition state analogues[128a,b] (Figure 4.6). Amidine derivatives **(k,l,m)** (Figure 4.7) fulfill both steric as well as electronic requirements and are some of the strongest inhibitors known.[128b, 131]

4.1.4. Sulfur-Based Glycosidase Inhibitors

Much of the activity on the synthesis of inhibitors has centered on compounds containing nitrogen in the sugar ring. However, extension to derivatives containing sulfur is comparatively limited even though they have been known to be inhibitors for quite some time. Their resistance to enzyme



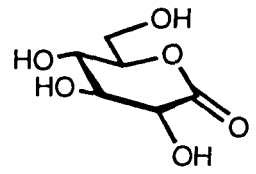
a. R = H
b. R = OH

c. R = H
d. R = OH

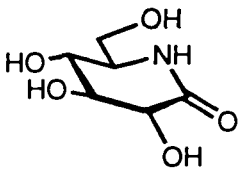
e

f

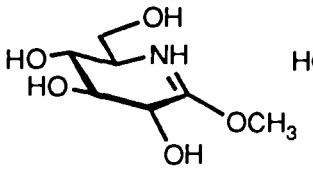
Figure 4.5. Charge-based glucosidase inhibitors



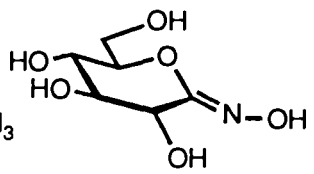
g



h

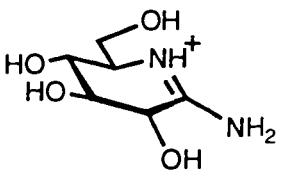


i

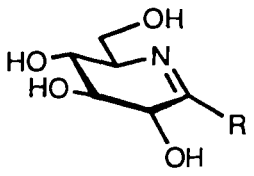


j

Figure 4.6. Conformation-based glucosidase inhibitors



k



l. R = NH_2,
m. R = NHOH

Figure 4.7. Conformation- and charge-based glucosidase inhibitors

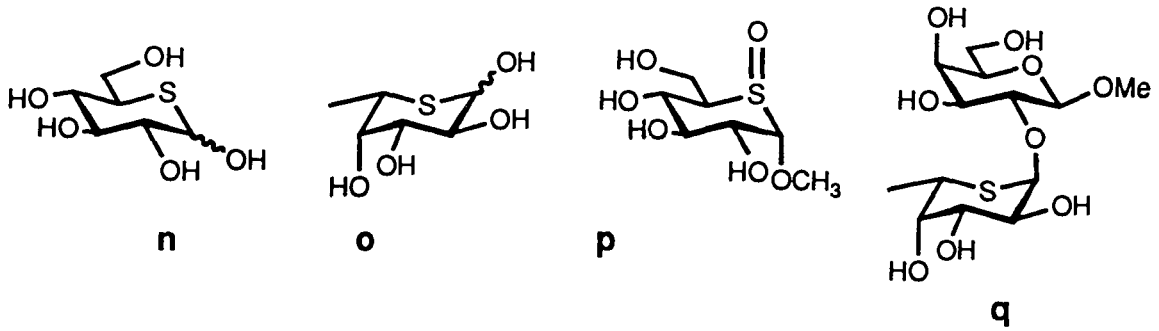


Figure 4.8. Endocyclic sulfur-based glucosidase inhibitors

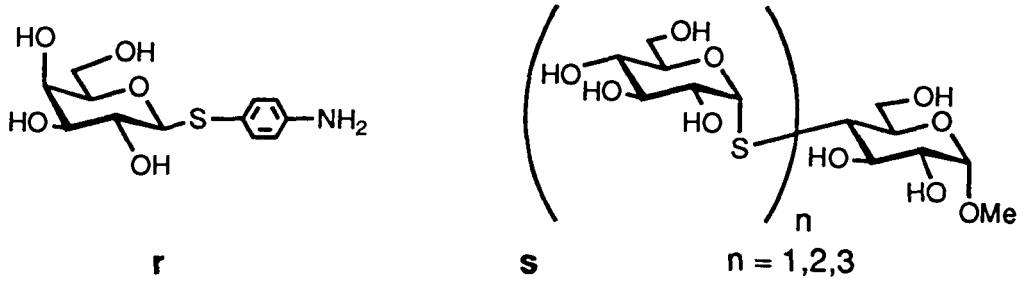


Figure 4.9. Exocyclic sulfur-based glucosidase inhibitors

hydrolysis makes them promising targets for evaluation of their biological activity.[128a, 130, 132, 133]

Some of the biologically active thio-sugars with sulfur in the ring are shown in Figure 4.8. 5-Thio-α-D-glucopyranose **(n)**[128b] and 5-thio-α-L-fucopyranose **(o)**[134] have been shown to be reasonably strong inhibitors of α-glucosidases and α-fucosidases, respectively, with K_i values in the millimolar range. Compound **(p)** is an order of a magnitude less potent.[128b] Recently, the fucose derivative **(q)** has been reported to have excellent inhibitory activity against the enzyme α-L-fucosidase (30μm).[135] Another type of sulfur-based inhibitors is oligosaccharides with sulfur in the interglycosidic linkage (Figure 4.9, 4.2).

4.2. RESEARCH OBJECTIVES

Our group embarked on a project to synthesize heteroanalogues of sugars for evaluation as glucosidase inhibitors. Some of the proposed compounds are shown in Figure 4.10.

As inhibitors of Glucosidase I and II, we propose the synthesis of O, S, Se and N heteroanalogues related to the disaccharide α-Glc-(1-2)-α-Glc where the heteroatom replaces the endocyclic as well as the interglycosidic oxygen atom. With precedence that higher-order oligosaccharides provided greater inhibition,[124b] heteroanalogues of the trisaccharide α-Glc-(1-2)-α-Glc-(1-3)-α-Glc were also proposed. Sulfonium ion analogues related to castanospermine were envisaged with the assumption that due to the permanent positive charge, an effective transition state analogue will be obtained. Examples of similar trends

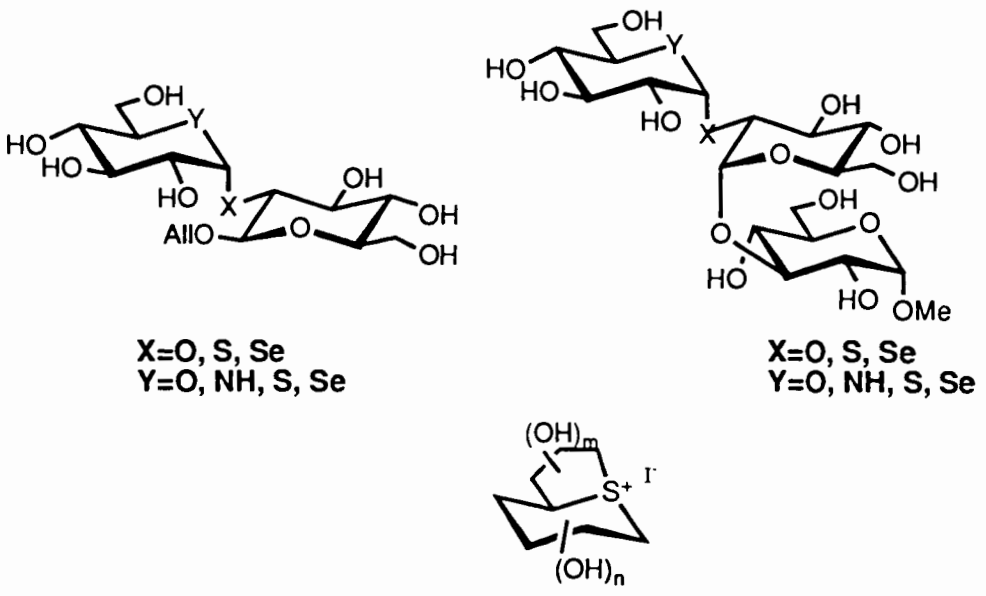


Figure 4.10. Glucosidase inhibitors under investigation

are available in the literature where di-N-alkylated nojirimycin derivatives are more potent inhibitors than the non-alkylated counterparts.[136]

My contribution to this project was the synthesis of the monosaccharide **81** and the disaccharides **82-86** (Figure 4.11) for evaluation as glucosidase inhibitors.

4.3. EXISTING HIGHER-ORDER SULFUR- AND SELENIUM-BASED HETEROANALOGUES

4.3.1. Exocyclic Sulfur and Selenium

Disaccharides with sulfur in the glycosidic linkage have been previously synthesized by a variety of methods including S_N2-type reactions involving the action of a thiolate anion on a glycosyl halide,[137] the displacement of a leaving group by a 1-thioglycopyranose[138] and more recently, by the condensation of benzylated 1,6-anhydroglucopyranose with a suitably protected 4-thioglucopyranoside to give predominantly an α-linked disaccharide.[139] These methods have been used to procure thiogentiobiose **(t)**,[138] 4-thiocellooligosaccharides (Figure 4.2), 4-thiomaltooligosaccharides **(s)**[133] and more recently, β-*n*-propyl 2-thiokojibioside **(u)**,[140] and 2-thiokojibiose **(u)**,[141] and 2-thiosophorose**(v)** (Figure 4.12).[141]

The first seleno-sugar, selenoisotrehalose **(w)**,[142] was reported as early as 1917. However, no general synthesis of oligosaccharides containing selenium is available and selenoglycoside analogues of a reducing disaccharide are hitherto unknown. Moreover, there are no reports to date of disaccharides of 5-thioglucose with sulfur or selenium in the interglycosidic linkage. The synthesis

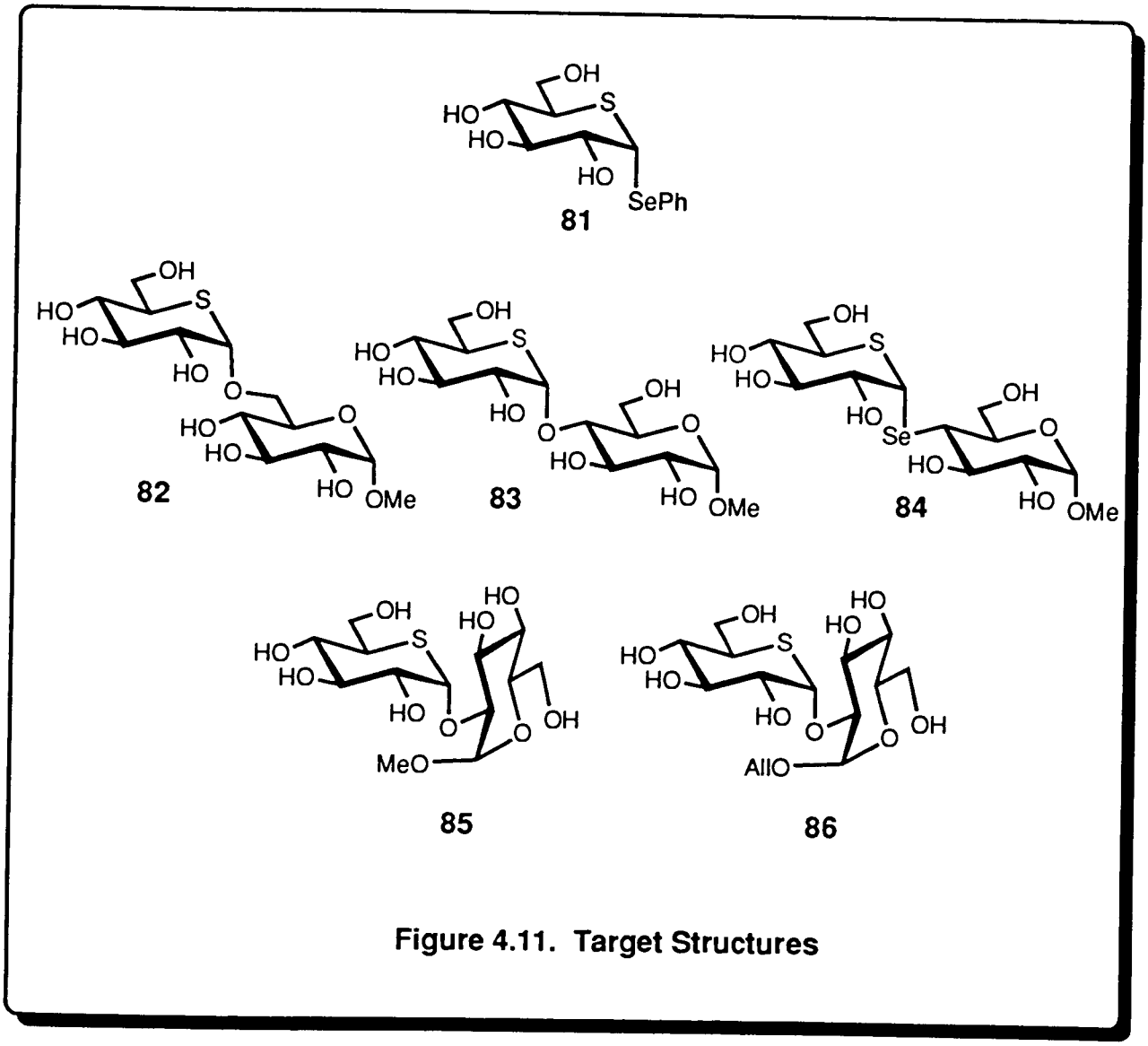


Figure 4.11. Target Structures

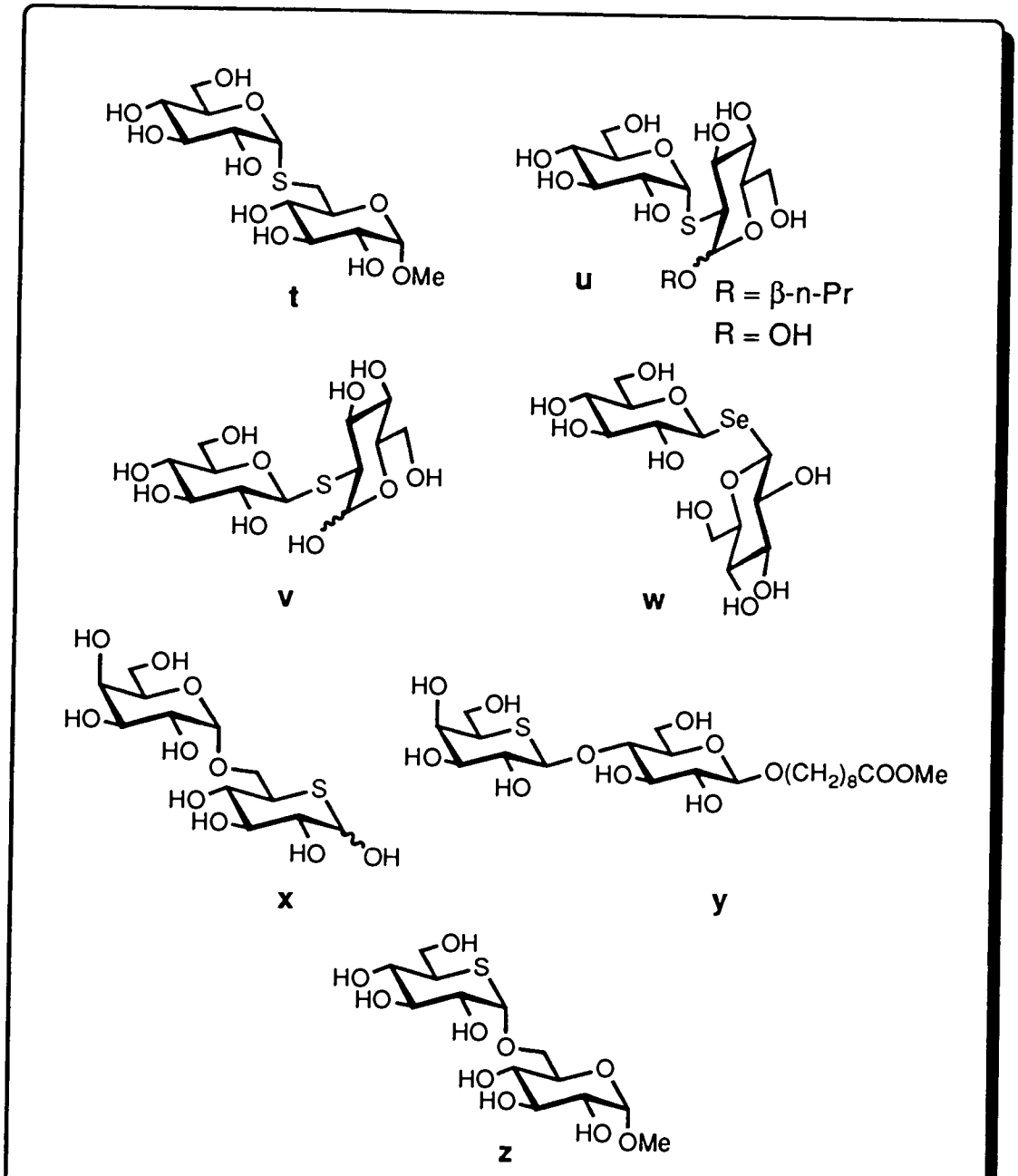


Figure 4.12. Existing higher order sulfur and selenium heteroanalogues of disaccharides

of heteroanalogues with sulfur in the ring of the nonreducing sugar and either oxygen or selenium in the interglycosidic linkage is described in forthcoming sections.

4.3.2. Endocyclic Sulfur and Selenium

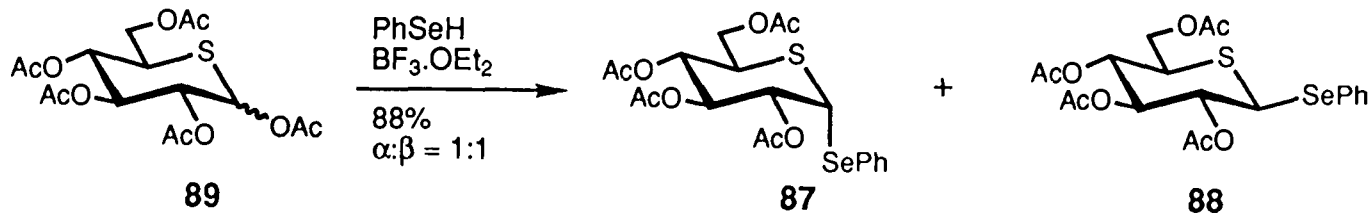
At the commencement of this project there were no prior reports of disaccharides or trisaccharides containing an endocyclic sulfur atom. The first report was presented by Wong et al.[143] who obtained the disaccharide **(x)** by an enzymatic method (Figure 4.12). Thereafter, Yuasa et al.[132] synthesized the first disaccharide with sulfur in the ring of the non-reducing sugar **(y)** by an enzymatic approach. An indirect approach to the thioisomaltoside **(z)** via an acyclic precursor was adopted by Hashimoto et al.[144] A simpler, yet effective method of synthesis, remained elusive, however.

We decided to use conventional glycosylation methodology to achieve the first chemical glycosylation of 5-thioglucose to give disaccharides containing sulfur in the ring of the non-reducing sugar residue.

4.4. RESULTS AND DISCUSSION

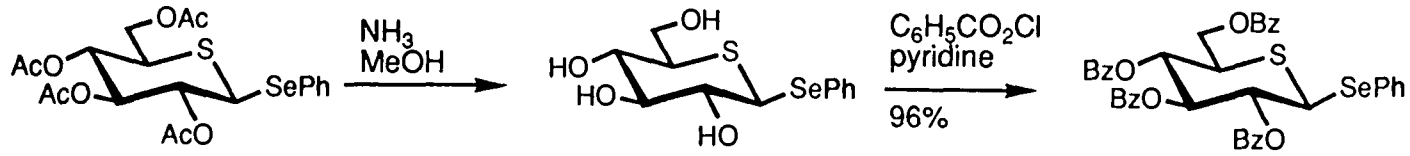
4.4.1. Glycosylation with Selenoglycosides of Thioglucose.

Our initial efforts focused on the use of phenyl selenoglycosides of 2,3,4,5-tetra-O-acetyl-5-thioglucopyranose. The synthesis of the phenyl selenoglycosides **87** and **88** was attempted in a similar manner to that described for the phenyl selenoglycosides of glucose. A solution of the peracetylated 5-thio-α,β-D-glucopyranoside **89**[145] and phenyl selenol was treated with boron trifluoride etherate at 0°C. This reaction resulted in excessive decomposition, as



89 87 88

Figure 4.13. Preparation of the phenyl selenoglycosides of 5-thioglucose



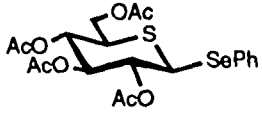
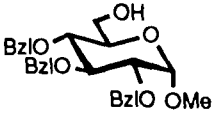
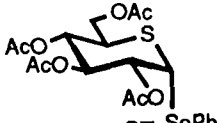
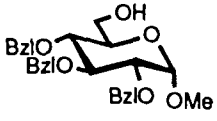
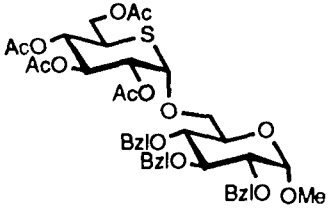
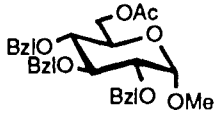
88 95 96

Figure 4.14. Preparation of the perbenzoylated phenyl selenoglycoside of 5-thioglucose.

suggested by the baseline material observed by TLC. Reactions performed with tin tetrachloride produced similar results. The optimum conditions for this synthesis were found to be the addition of boron trifluoride etherate to the reaction mixture at -78° C followed by a gradual increase of the temperature. Under these conditions the reaction required 36 h for completion and afforded a 1:1 α/β mixture of the selenoglycosides **87** and **88** (Figure 4.13).

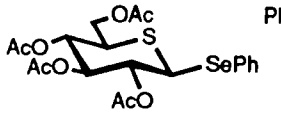
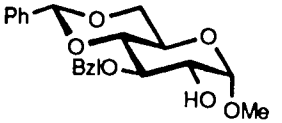
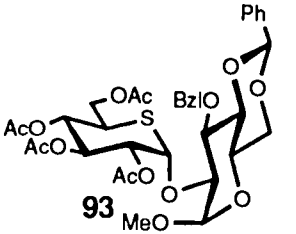
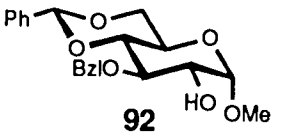
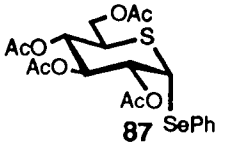
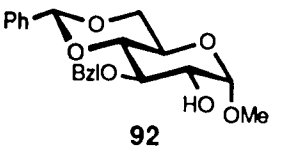
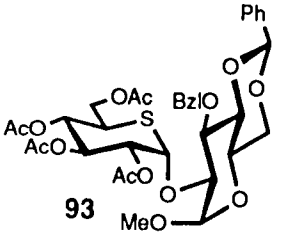
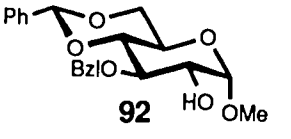
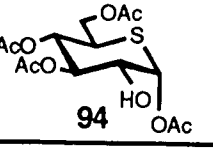
Glycosylations with phenyl selenoglycoside **88** were attempted with silver triflate as the promoter. Glycosylation of the methyl glycoside acceptor **16** with **88** in the presence of up to 10 molar equivalents of silver triflate at varying concentrations proved to be ineffective (Table 4.1, entry 1). The use of nitrosyl tetrafluoroborate ($NOBF_4$) as the promoter for the reaction of the selenoglycoside **88** was examined next. $NOBF_4$ is an established promoter for thioglycosides (Section 1.5.3f) and in order to avoid complications due to the endocyclic sulfur, one molar equivalent of $NOBF_4$ was employed at -78° C. The reaction was allowed to proceed for 2 h at -78° C and for another 2 h at ambient temperature at which point the reaction appeared to be complete, as determined by TLC. The α-disaccharide **90** was isolated in 35% yield and no β disaccharide was detected (Table 4.1, entry 2). The extraordinary α-stereoselectivity of this glycosylation reaction, in spite of a participating acetate substituent at the C-2 position of the glycosyl donor, was an unexpected, yet encouraging result. As more glycosylations with 5-thioglucopyranosyl donors were conducted, the preferential formation of the α-product emerged as the common feature. The low yield of this reaction was due to transesterification and 50% of the acetylated acceptor **91** was isolated. This type of acetyl group migration from a glycosyl donor to the free hydroxyl group of a reactive acceptor is frequently observed in the presence of a Lewis acid.[147]

Table 4.1. Glycosylations with selenoglycosides of 5-thioglucose

Entry	Donor	Acceptor	Promoter	Molar Ratio[a]	Reaction Conditions	Product	Yield (%)
1	 **88**	 **16**	AgOTf	1 : 1 : 10	RT, 4 h	No Reaction	
2	 **87**	 **16**	$NOBF_4$	1 : 1 : 1	-78°C for 2 h RT for 2 h	 **90**	35%
						 **91**	50%

[a]donor : acceptor : promoter.

Table 4.1. Glycosylation with selenoglycosides of 5-thioglucose

Entry	Donor	Acceptor	Promoter	Molar Ratio[a]	Reaction Conditions	Product	Yield (%)
3	 **88**	 **92**	$NOBF_4$	1 : 1 : 1	-30°C to 0°C in 2.5 h	 **93**	35%[b]
						 **92**	24%
4	 **87**	 **92**	$NOBF_4$	1 : 1 : 1	-30°C to 0°C in 2.5 h	 **93**	22%[c]
						 **92**	45%
						 **94**	33%

[a]donor : acceptor : promoter. [b]44% yield with respect to acceptor recovered. [c]47% yield with respect to acceptor recovered.

Encouraged by the observed α-stereoselectivity of $NOBF_4$-promoted glycosylations with the selenoglycoside of thioglucose, and with the target kojibiose derivative **85** in mind, a suitably blocked acceptor with a free hydroxyl group at the C-2 position was synthesized. By the method of Garegg et al.[95] the diol **24** was selectively benzylated at the C-3 position under phase-transfer conditions to afford the block **92**. Also obtained was the 2-benzylated compound **17**.

$NOBF_4$-mediated glycosylations of acceptor **92** with selenoglycoside **88** was attempted. As in the case of the acceptor **16**, the α-selectivity of the glycosylation was preserved (Table 4.1, entry 3). Unfortunately, the α-disaccharide **93** was isolated in a low 35% yield (44% based on unreacted acceptor recovered). In a similar glycosylation with the α-selenoglycoside **87**, the α-disaccharide **93** was the only disaccharide isolated in a yield of 22% (43% based on unreacted acceptor recovered) (Table 4.1, entry 4). In addition to the recovered acceptor (50%), the more polar product identified as the compound **94**, formed by the migration of the acetate group, was also isolated. This product had been detected in prior reactions but had not been isolated as it was thought to be the hemiacetal. Reaction 4 was repeated at a lower temperature of -78° C to circumvent this rearrangement and to promote coupling. However, this was of no avail.

To overcome the impediments associated with the peracetylated selenoglycosides, we contemplated the synthesis of the perbenzoylated counterpart **96** (Figure 4.14). The deacetylation of **89** with ammonia/ methanol followed by benzoylation in the presence of benzoyl chloride and pyridine afforded **96** in 96% yield. Preliminary glycosylations with this donor were poor

yielding due to excessive elimination and a substantial amount of the corresponding glucal was obtained.

4.4.2. Synthesis of 5'-S-Isomaltoside from the Glycosyl Trichloroacetimidate of 5-Thioglucose

Since the reactions of the selenoglycosides did not appear too promising at this point, our attention turned to the use of the trichloroacetimidate of 2,3,4,6-tetra-O-acetyl-5-thioglucopyranose as the glycosyl donor.

Retrosynthetic analysis of the disaccharides **82-86** indicated that the formation of an α-glycosidic bond may be effected with a β-trichloroacetimidate **98** (Figure 4.15). This assumption was based on the results of Schmidt et al[37]. who reported that the glycosylations of glycosyl trichloroacetimidate donors with non-participating substituents at C-2 occur with inversion of configuration at the anomeric centre (Section 1.5.3c). However, our trichloroacetimidate had an acetate substituent at the C-2 position and whether or not it offered anchimeric assistance remained to be examined.

The selective 1-O-deacetylation of the peracetylated sugar was effected by the method of Excoffier et al.[148] with hydrazine acetate. The mixture of hemiacetals **99** thus formed consisted predominantly of the α-anomer due to a strong anomeric effect associated with 5-thioglucose. This mixture was treated with trichloroacetonitrile and potassium carbonate in anticipation of the formation of the β-trichloroacetimidate as reported by Schmidt et al.[37] for the analogous reaction with D-glucose. (Section 1.5.3c). In contrast to Schmidt's results, compounds **99** reacted to afford predominantly the α-isomer **100** (84%) and a minor amount (3%) of the β-isomer **98**. We suggest that this is the direct result of the α-preference of the hemiacetal **99**.

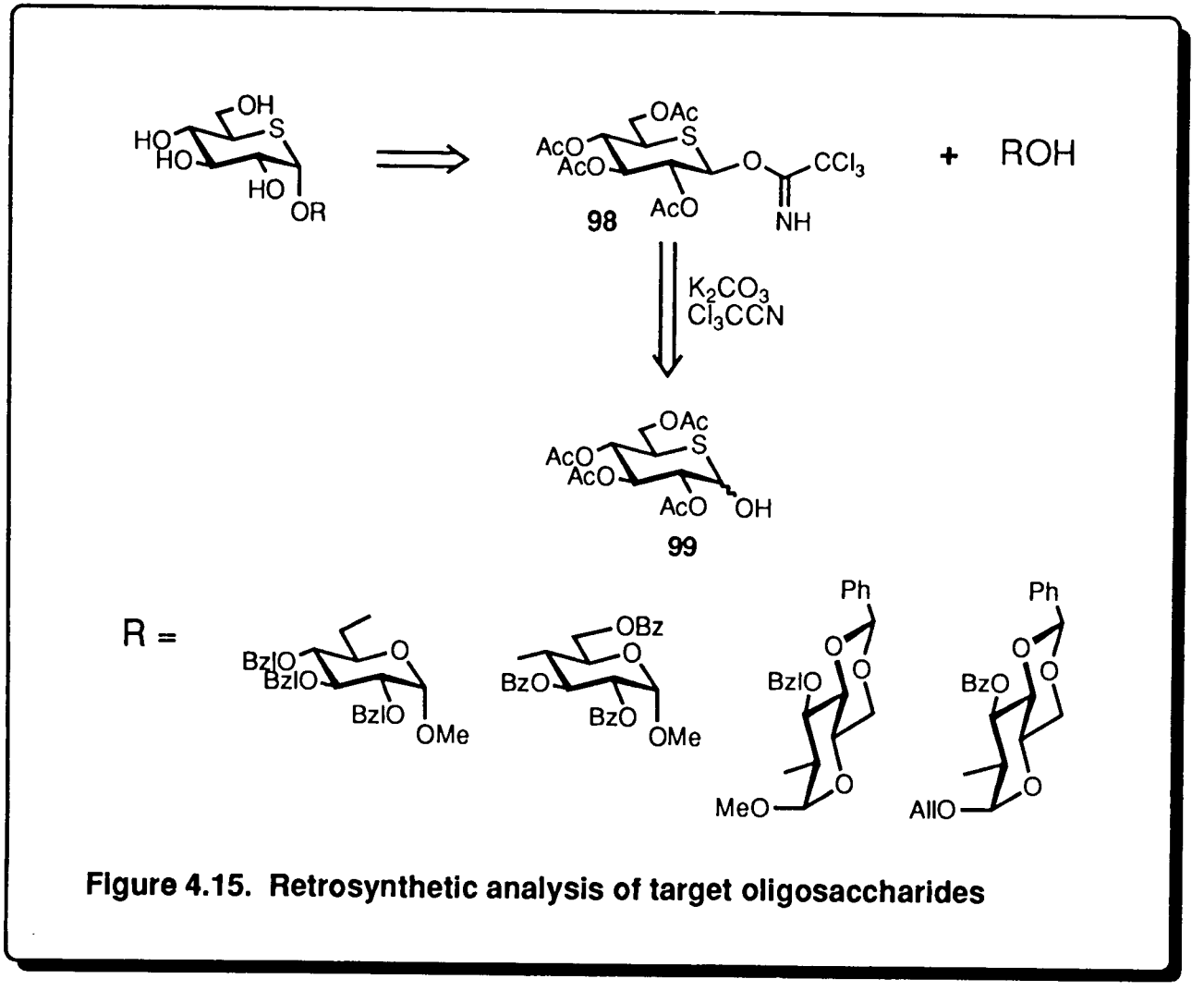


Figure 4.15. Retrosynthetic analysis of target oligosaccharides

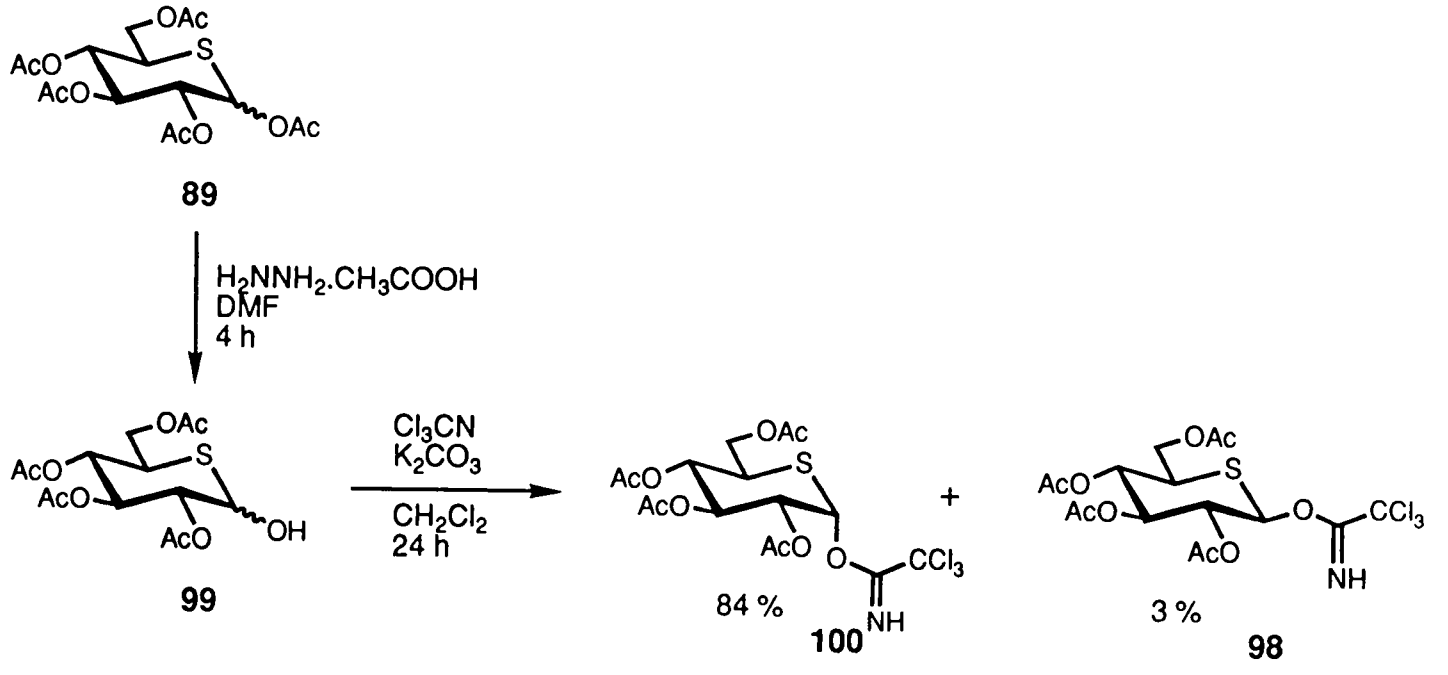


Figure 4.16. Synthesis of 2,3,4,6-tetra-O-acetyl-5-thioglucopyranosyl trichloroacetimidate

Triethylsilyl triflate was employed as the promoter for the glycosylation of the 6-hydroxy acceptor **16** with the glycosyl trichloroacetimidate **100**. An improvement in the reaction yield was observed (80%) as compared to the $NOBF_4$-mediated glycosylatons with selenoglycosides of thioglucose. Although the α-selectivity was not conserved, an α-preference was maintained and the α- and β- disaccharides **90, 101** were obtained in a 1.5:1 ratio. (Figure 4.17).

Debenzylation of the disaccharide **90** with H_2 in the presence of Pd/C proved to be unsuccessful due to the poisoning of the catalyst by the sulfur in the sugar. A one step deacetylation and debenzylation was effected with sodium in liquid ammonia (Figure 4.18). Initial endeavors afforded two compounds corresponding to the completely deprotected compound **82** and the partially deprotected compound **102**. In subsequent reactions the addition of sodium to a mixture of **90** in THF and liquid ammonia was continued untill complete deprotection was observed by TLC. Chromatographic purification of **82** proved to be ineffective and the compound was purified as its peracetylated derivative **103** and then deacetylated under Zemplen's conditions. Compound **82** was obtained in an overall yield of 60% with respect to the blocked disaccharide **90**.

4.4.3. Synthesis of 5'-S-Maltoside from the Glycosyl Trichloroacetimidate of 5-Thioglucose

The synthesis of methyl maltoside **83** required a suitably blocked sugar with a free hydroxyl group at the C-4 position. Since earlier results showed that the removal of benzyl substituents on thioglucose derivatives was problematic, alternative blocking groups were desired that facilitated deprotection in a convenient manner. Additionally, a block obtained with minimum protecting group manipulations would be ideal. These requirements were met by the

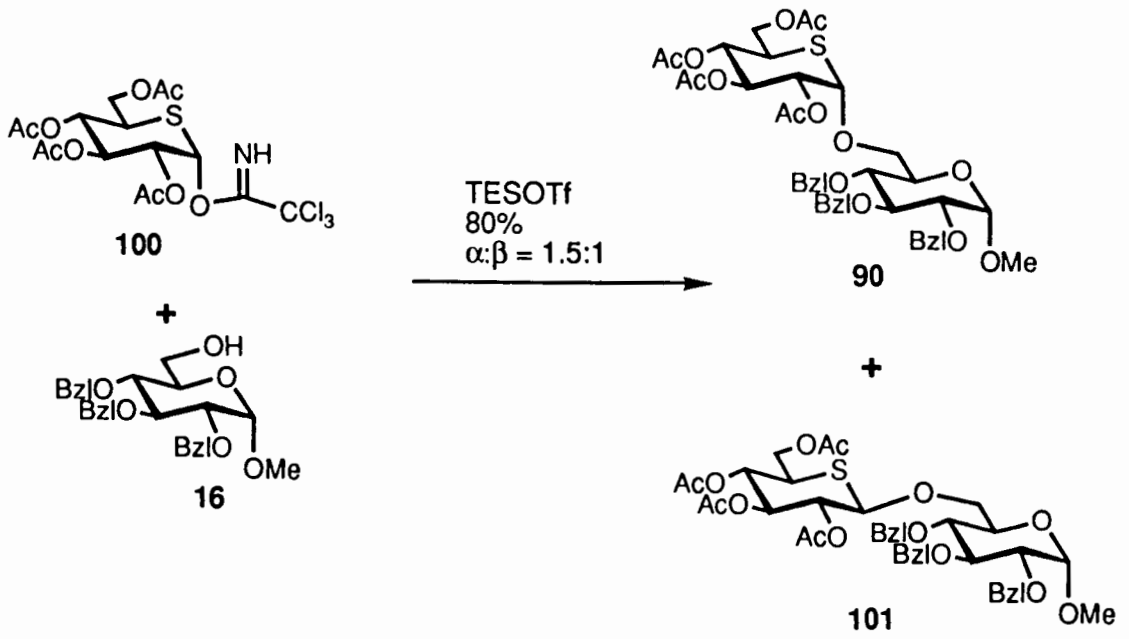


Figure 4.17. Synthesis of Methyl 2,3,4-tetra-O-benzyl-6-O-(2,3,4,6-tetra-O-acetyl--5'-thio-α-D-glucopyranosyl)-α/β-D-glucopyranoside

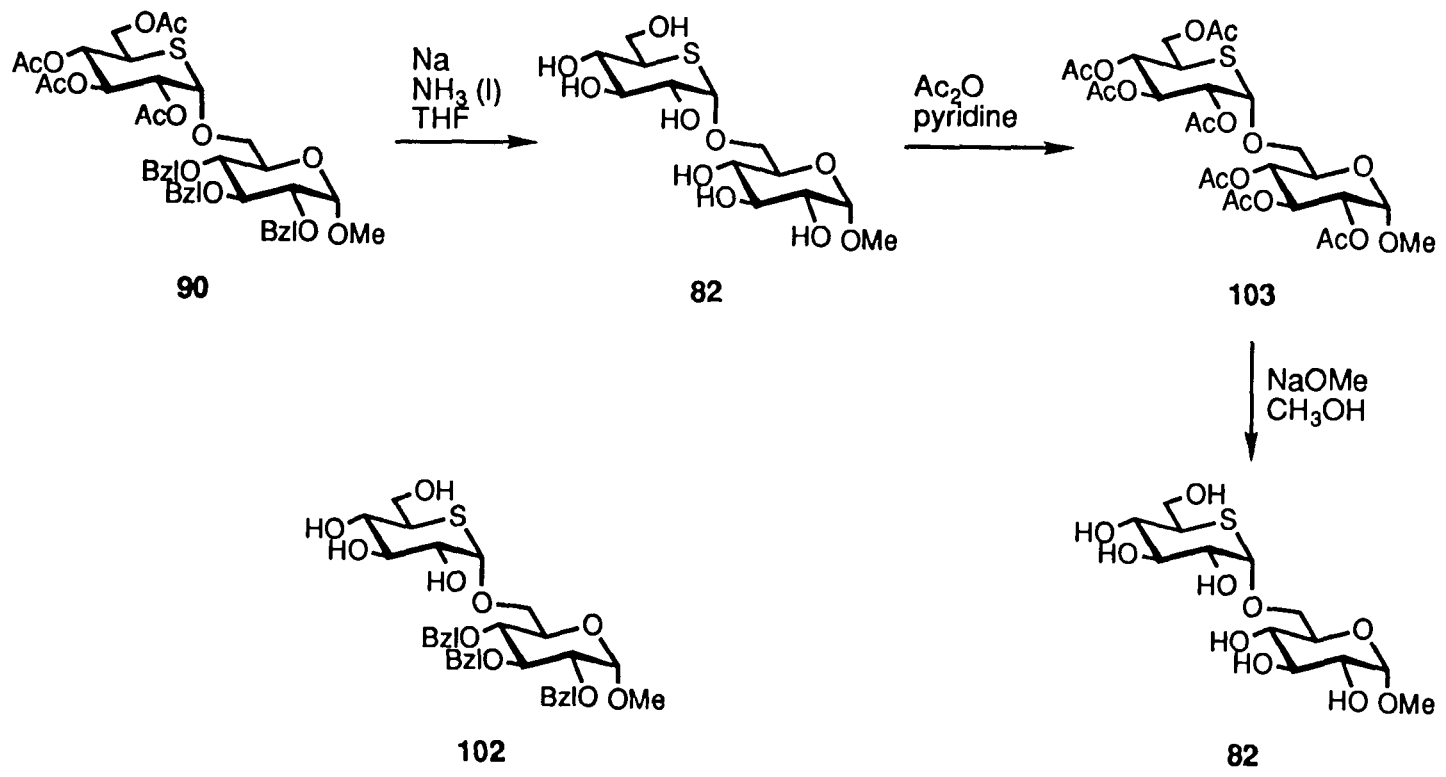
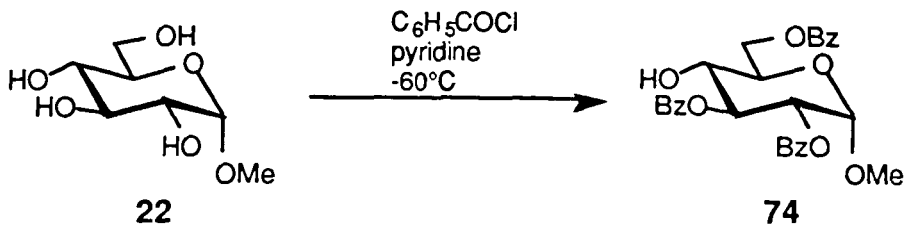


Figure 4.18. Deprotection of Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside

glycosyl acceptor **74**. The selective benzoylation of methyl α-D-glucopyranoside with benzoyl chloride at 60° C afforded the desired block **74** in one step.[149] This regioselectivity is a manifestation of the reduced reactivity of the 4-OH of glucose as compared to the other hydroxyl groups.



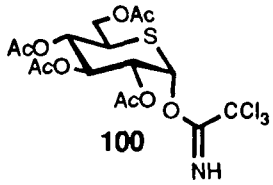
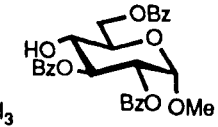
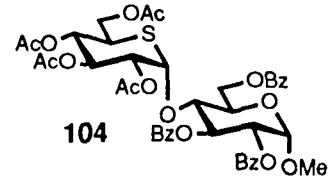
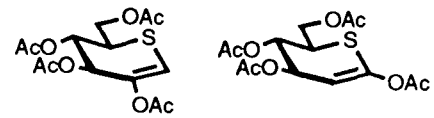
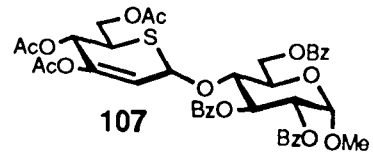
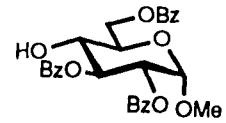
22 **74**

Figure 4.19. Synthesis of Methyl 2,3,6-tri-O-benzoyl-α-D-glucopyranoside

The glycosylation of the acceptor **74** with the trichloroacetimidate **100** was attempted under varying conditions of promoter concentration, reactant concentration and temperature. Some of the results are shown in Table 4.2 and are briefly discussed below.

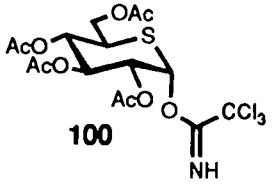
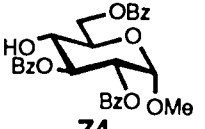
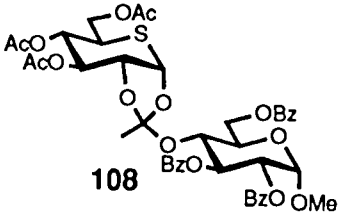
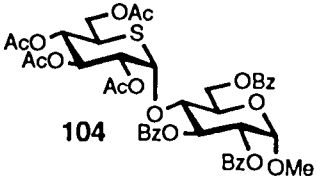
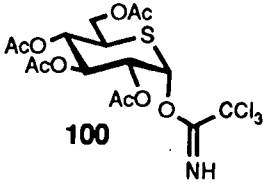
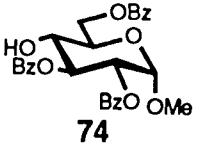
Initial glycosylations were attempted with 0.1 equivalent of TESOTf as the promoter. The promoter was added to a mixture of the reactants at -78° C. Different reactions were quenched at different temperatures and their outcomes were examined. When the temperature of the reaction mixture was allowed to rise to room temperature a complex mixture of products was formed (Table 4.2, entry 1). Most significantly, the desired (1-4) linked disaccharide **104** was obtained in exclusively an α– configuration and the corresponding β–disaccharide was not detected. In addition, a mixture of the glucals **105** and **106** was obtained in 30% yield. The side product **107** and unreacted acceptor **74**

Table 4.2. Synthesis of Methyl 2,3,6-tri-O-benzoyl-4-O-(2,3,4,6-tetra-O-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside and the corresponding orthoester.

Entry	Donor	Acceptor	Ratio[a]	Reaction Conditions	Product	Yield (%)
1	 **100**	 **74**	1 : 1 : 0.1	-78°C for 1 h RT for 45 min	 **104**	50%
					 **105:** glucal 1 **106:** glucal 2 **105:106** = 3:1	30%
					 **107**	
					 **74**	

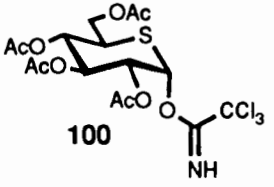
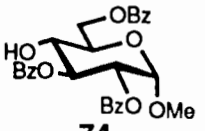
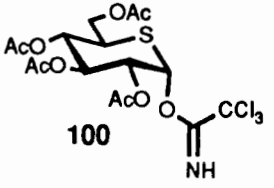
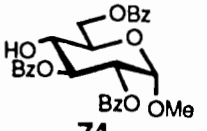
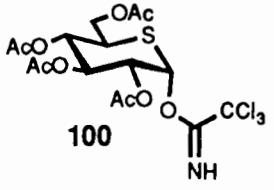
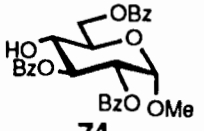
[a]donor : acceptor : promoter.

Table 4.2. Synthesis of Methyl 2,3,6-tri-O-benzoyl-4-O-(2,3,4,6-tetra-O-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside and the corresponding orthoester.

Entry	Donor	Acceptor	Molar Ratio[a]	Reaction Conditions	Product	Yield (%)
2	 **100**	 **74**	1 : 0.7 : 0.1	-78°C for 6 h	 **108**  **104** **(108:104 = 6:1)** donor: **19** acceptor: **74**	43% 7%
3	 **100**	 **74**	1 : 1 : 0.1	-78°C for 1 h -50°C for 1.5 h	orthoester: **108** α-disaccharide: **104** **(108:104** = 15:1)	83% 5%

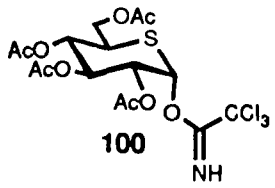
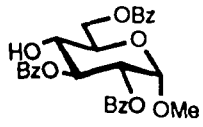
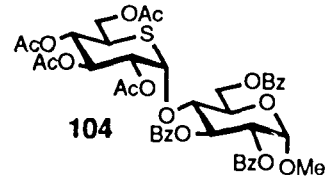
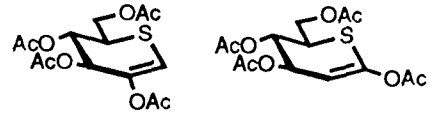
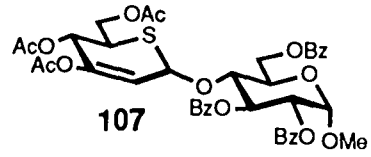
[a]donor : acceptor : promoter.

Table 4.2. Synthesis of Methyl 2,3,6-tri-O-benzoyl-4-O-(2,3,4,6-tetra-O-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside and the corresponding orthoester.

Entry	Donor	Acceptor	Molar Ratio[a]	Reaction Conditions	Product	Yield (%)
4	 **100**	 **74**	1 : 1 : 0.2	-78°C for 1 h RT for 1 h	α-disaccharide: **104** glucal 1: **105** glucal 2: **106** (**105:106** = 9:1) **107** acceptor: **74**	40% 40%
5	 **100**	 **74**	1 : 1 : 0.2	-78°C for 1 h -50°C for 1 h	α-disaccharide: **104** orthoester: **108** (**108:104** = 9:1)	8% 80%
6	 **100**	 **74**	2 : 1 : 0.2	-78°C for 1 h RT for 1 h	α-disaccharide: **104** glucal 1: **105** glucal 2: **106** (**105:106** = 1:2) **107** acceptor: **74**	45%

[a]donor : acceptor : promoter.

Table 4.2. Synthesis of Methyl 2,3,6-tri-O-benzoyl-4-O-(2,3,4,6-tetra-O-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside.

Entry	Donor	Acceptor	Ratio[a]	Reaction Conditions	Product	Yield (%)
7	 **100**	 **74**	1 : 1 : 0.1	-78°C for 1 h RT for 1 h	 **104**	85%
					 **105:** glucal 1 **106:** glucal 2 (**105:106** = 2.5:1)	6%
					 **107**	4%

[a]donor : acceptor : promoter.

were also isolated. In another reaction, the temperature was maintained below -70° C (Table 4.2, entry 2). In this case, the side products **105**, **106** and **107** were avoided. However, a mixture of the orthoester **108** and the α– disaccharide **104** was obtained in a 6:1 ratio, in addition to unreacted donor and acceptor. When the reaction was quenched at -50° C a 15:1 mixture of the orthoester and disaccharide was isolated in a combined yield of 88%. Minor amounts of glycal and acceptor were detectable by TLC (Table 4.2, entry 3). These were the best experimental conditions for the formation of the orthoester. However, improved reaction conditions for the synthesis of the disaccharide remained to be obtained.

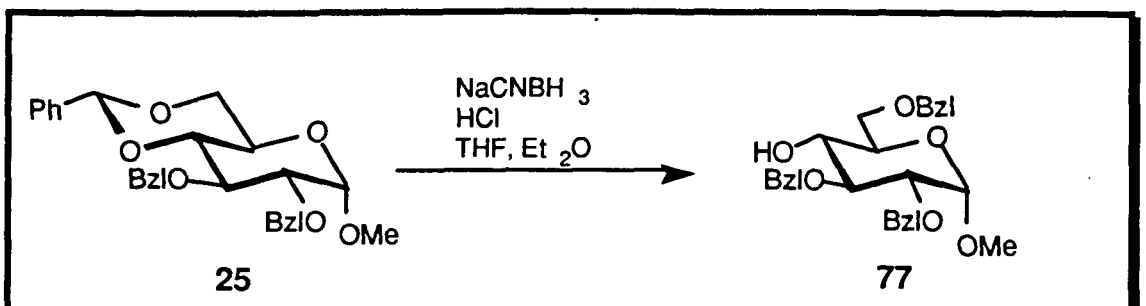
An increased concentration of the promoter (0.2 equivalents with the respect to the donor) did not prove to be advantageous and substantial amounts of the elimination side products were obtained, in addition to a low yield of the disaccharide (40%) (Table 4.2, entry 4). The use of two equivalents of the glycosyl donor **100** with respect to the acceptor was contemplated. However, the yield of the disaccharide remained below 50% and unreacted acceptor was again recovered. When an analogous experiment that employed 0.2 equivalents of TESOTf was quenched at -50° C, a 9:1 mixture of the orthoester **108** and α-disaccharide **104** was obtained in a combined 88% yield (Table 4.2, entry 5). It is noteworthy that all these experiments were stereoselective for the formation of the α-disaccharide and no β– anomer was detected.

Until this point we were of the opinion that inefficient reactions were a consequence of the low reactivity of the glycosyl donor **100**. However, we hypothesized that a complexation of the acceptor with the trichloroacetamide produced in the reaction may be impeding complete reaction of the acceptor. Therefore, in the following experiment, a two fold excess of the acceptor was

employed (Table 4.2, entry 6). The yield of the disaccharide escalated to 85%, with minor amounts of glucals **105** and **106**, compound **107** and unreacted acceptor being isolated.

Thus, on analysis of these results the following conclusions may be made. The glycosylations with the trichloroacetimidate **100** and an unreactive acceptor such as **74** occur stereoselectively in favour of the α-product. The temperature at which this reaction is quenched is of great significance in controlling its outcome, the orthoester **108** being isolated at lower temperatures. Higher temperatures lead to the formation of side products **105, 106** and **107** due to elimination as does the use of a higher concentration (0.2 equivalent) of the promoter. The optimum condition for this glycosylation is realized with the use of an excess of the acceptor rather than the donor. A comparison of experiments 3 and 5 illustrates the effect of an increased acid concentration on the ratio of orthoester to α-disacccharide, where a greater acid concentration decreases the proportion of the disaccharide from 15:1 to 9:1.

In order to ascertain the effect of an increase in the reactivity of the reacting partners on the stereochemical outcome of the reaction, we examined the glycosylation of a more reactive benzylated acceptor **77**.



25 77

Figure 4.20. Synthesis of Methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside

This acceptor was synthesized by the regioselective reduction of the benzylidene acetal of compound **20** by the method of Garegg et al.[103] (Figure 20). In this case, a loss in stereoselectivity was observed, as expected with the more reactive acceptor, and a 1:1 mixture of the α and β disaccharide **109** and **110** was obtained (Figure 21).

Deprotection of the disaccharide **104** under Zemplen conditions afforded the target disaccharide **83**.

4.4.4. Synthesis of 5'-Thio-4-selenomaltoside from the Glycosyl Trichloroacetimidate of 5-Thioglucose

The strategy for the synthesis of 4-seleno-5'-thiomaltopyranoside was similar to that of the 4-0-5'-thiomaltopyranoside. It necessitated the synthesis of the selectively protected 4-selenoglucopyranoside acceptor **111**. The synthesis of this compound was performed by Blair Johnston and is shown in Figure 4.22 . The displacement of the 4-O-trifluoromethanesulfonate of methyl 2,3,6-tri-0-benzoyl-α-D-galactopyranoside **112** by potassium selenocyanate[150] afforded the selenocyanate **113**. This was reduced with sodium borohydride[151] to provide the selenol **111**. Attempted column purification and/or crystallization resulted in the oxidation of the selenol to the diselenide **115**. Although the selenol showed appreciable air stability, slow oxidation to the corresponding diselenide occurred over a period of days. The diselenide was crystallized and fully characterized. Thus the crude selenol was used for subsequent glycosylations immediately after preparation. The acceptor **111** was glycosylated with the glycosyl donor **100** in the presence of 0.1 equivalent of TESOTf as the promoter. At -78° C no coupling of the above reactants was observed. (Table 4.3, entry 1). At room temperature a 4.5:1, α/β mixture of the

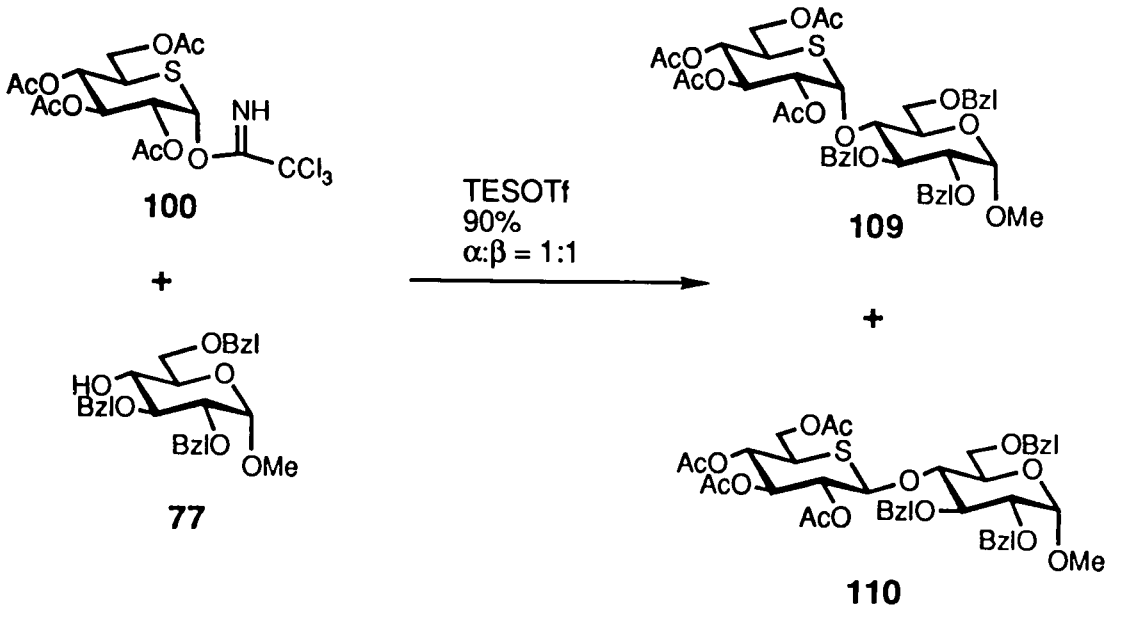


Figure 4.21. Synthesis of Methyl 2,3,6-tri-O-benzyl-4-O-(2,3,4,6-tetra-O-acetyl--5'-thio-α-D-glucopyranosyl)-α/β-D-glucopyranosides.

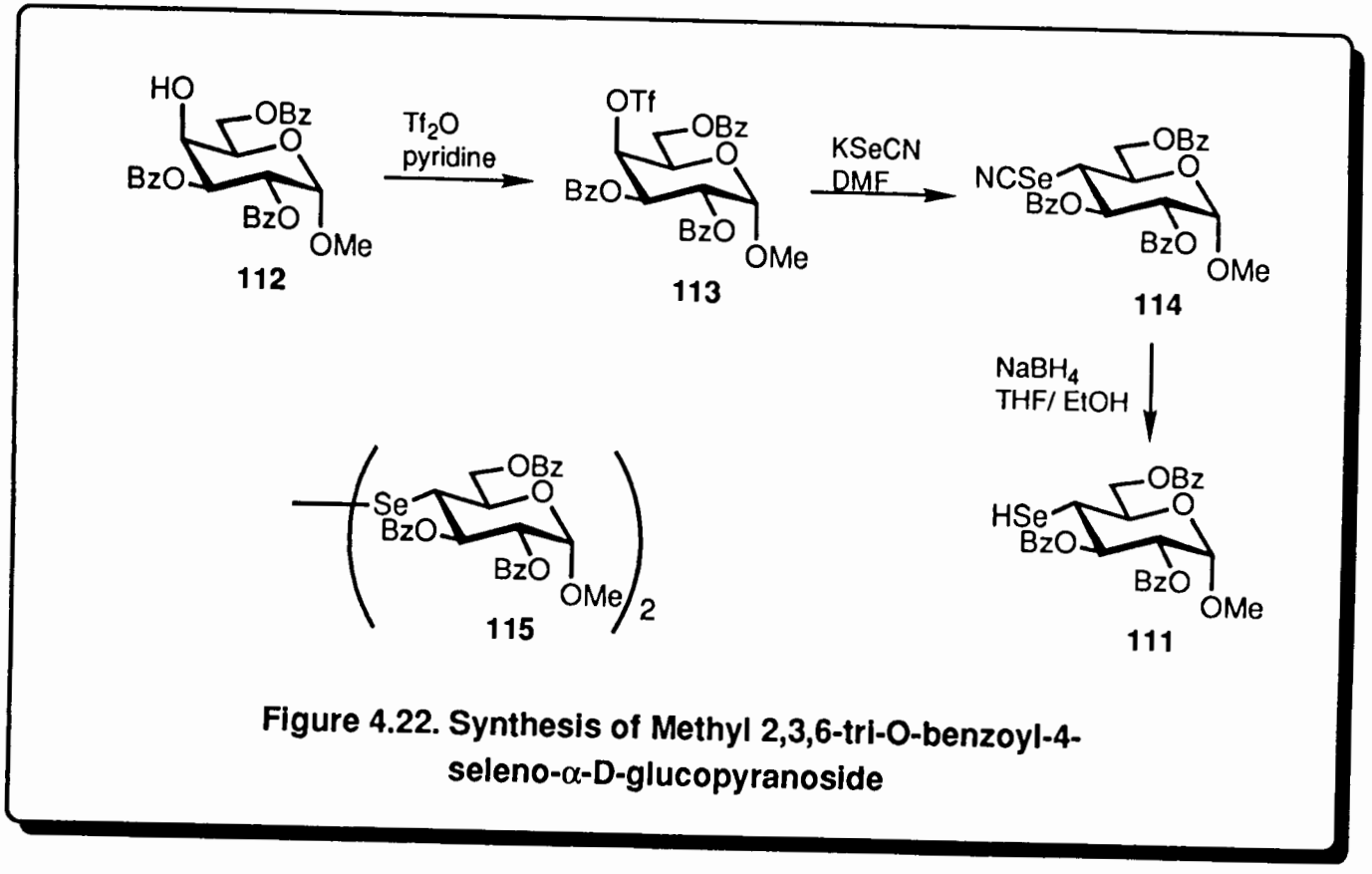
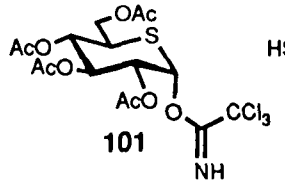
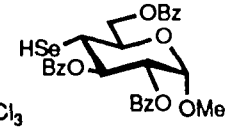
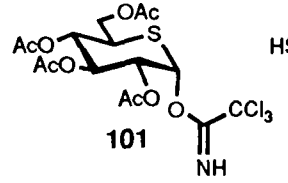
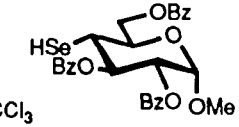
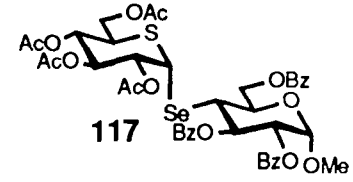
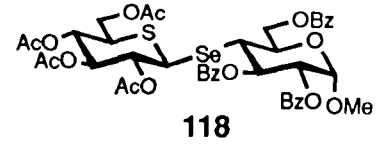
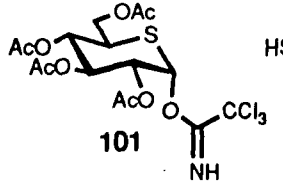
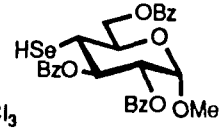


Figure 4.22. Synthesis of Methyl 2,3,6-tri-O-benzoyl-4-seleno-α-D-glucopyranoside

Table 4.3. Synthesis of Methyl 2,3,6-tri-O-benzoyl-4-deoxy-4-seleno-(2,3,4,6-tetra-O-acetyl-5'-thio-α/β-D-glucopyranosyl)-α-D-glucopyranoside.

Entry	Donor	Acceptor	Ratio[a]	Reaction Conditions	Product	Yield (%)
1	 **101**	 **115**	1 : 1 : 0.1	-78°C for 4 h	No Reaction	
2	 **101**	 **115**	1 : 1 : 0.2	-78°C for 15 min RT for 1 h	 **117**	46%
					 **118**	11%
3	 **101**	 **115**	1 : 1 : 0.1	-78°C for 15 min RT for 1 h	α-disaccharide: **117**	33%
					β-disaccharide: **118**	7%

[a]donor : acceptor : promoter.

disaccharides **116** and **117** was obtained (Table 4.3, entry 2). When the effect of an increased promoter concentration was examined, the stereoselectivity of the reaction remained unchanged but the yield of the reaction improved to 40%. (Table 2, entry 2). The deprotection of the disaccharide **116** was accomplished with sodium methoxide in methanol to afford the target compound **84** in 75% yield.

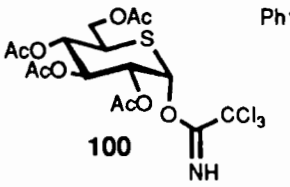
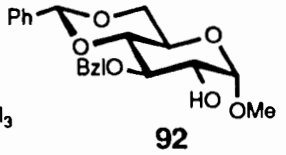
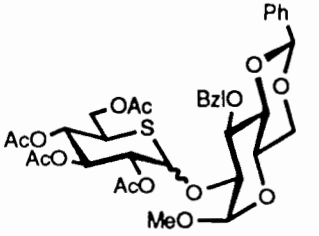
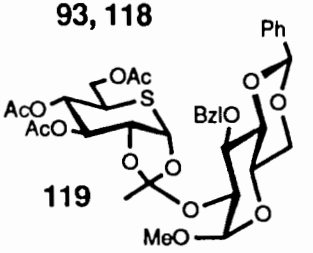
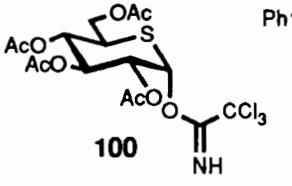
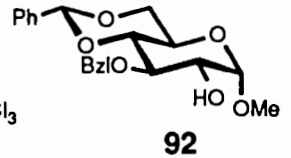
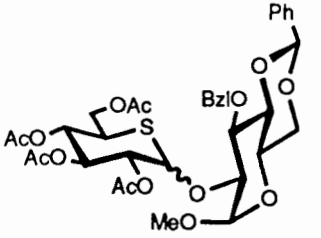
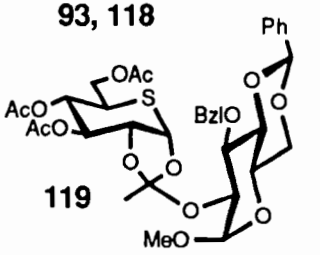
4.4.5. Synthesis of 5'-S-Kojibiosides from the Glycosyl Trichloroacetimidate of 5-Thioglucose

Earlier attempts on the synthesis of disaccharide **93** from selenoglycosides of thioglucose, although stereoselective, proved to be unsuccessful in terms of yields. An alternative synthesis using the triichloroacetimidate donor **100** was investigated.

Glycosylation of the acceptor **92** with the glycosyl trichloroacetimidate **100** at -78°C and with the sequential addition of two aliquots of 0.1 equivalent of triethylsilyl triflate afforded the α- and β- disaccharides **93** and **118** in a 3.5:1 ratio (Table 4.4, entry 1). A minor amount of the orthoester **119** was also isolated. In another experiment with 2 aliquots of 0.7 equivalent of TESOTf, a proportion of the orthoester **119** was formed (40%) (Table 4.4, entry 2) and the α to β ratio of the disaccharides also obtained was 10:1 (40%).

The separation of the mixture of α and β disaccharides proved to be difficult by chromatography and required chemical manipulation. The mixture was treated with 80% aqueous acetic acid to effect the hydrolysis of the benzylidene acetal. The mixture of diols **120** was then acetylated to give **121** and **122** which were separated at this stage by column chromatography (Figure 4.23). The α-anomer **122** was deacetylated with ammonia in methanol.

Table 4.4. Synthesis of Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-acetyl-5'-thio-α/β-D-glucopyranosyl)-α-D-glucopyranoside and the corresponding orthoester.

Entry	Donor	Acceptor	Molar Ratio[a]	Reaction Conditions	Product	Yield (%)
1	 **100**	 **92**	1 : 1.3 : 0.1 +0.1	-78°C for 4 h	 **93, 118**	90% α:β= 3.5:1
					 **119**	3%
2	 **100**	 **92**	1 : 0.8 : 0.07 +0.07	-78°C for 2 h	 **93, 118**	40% α:β= 10:1
					 **119**	40%

[a]donor : acceptor : promoter.

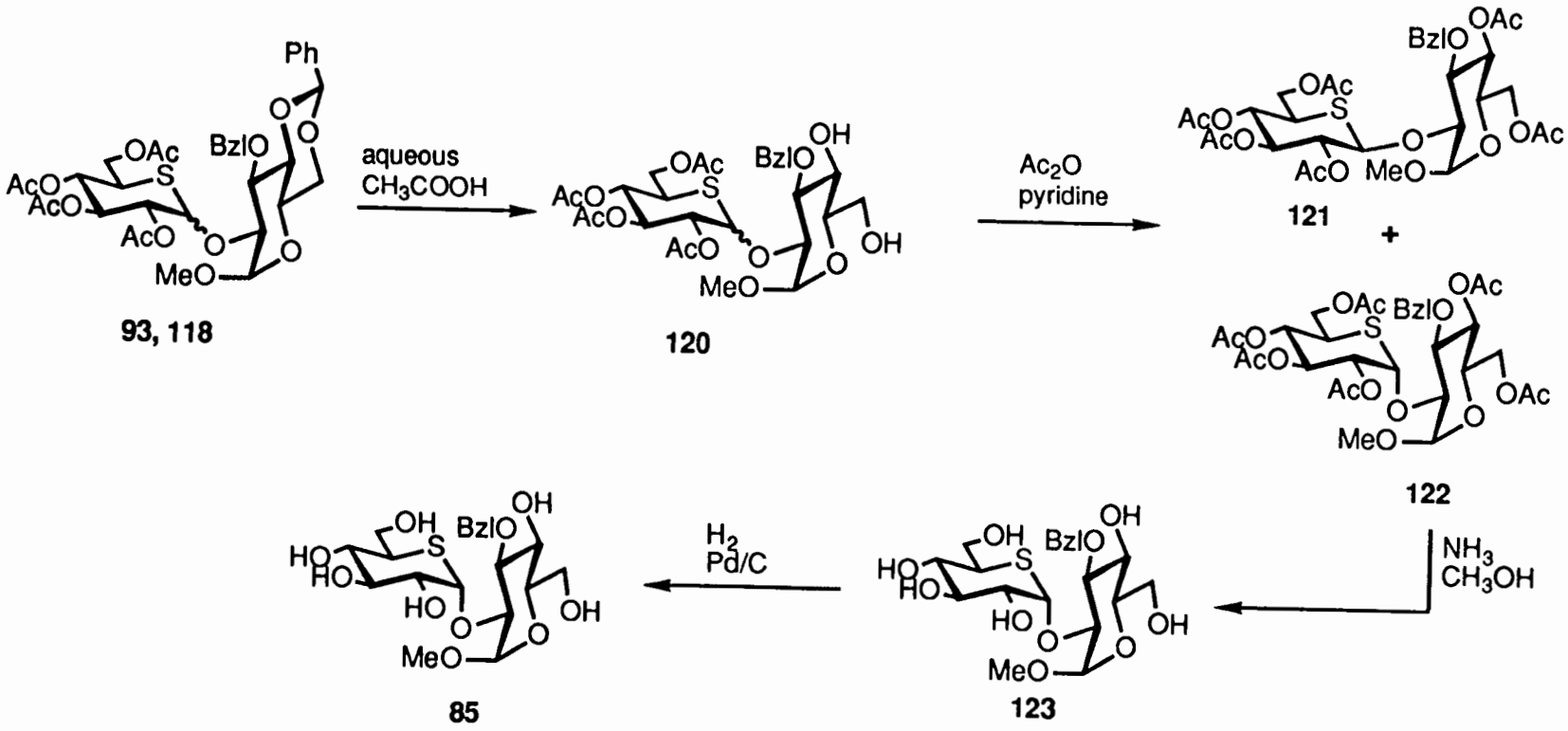


Figure 4.23. Deprotection of Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside.

Subsequent debenzylation with H_2 in the presence of Pd/C required 72 h and a large excess of Pd/C. The disaccharide **85** was thus obtained in a yield of 60%.

At this point, in order to procure more disaccharide for biological studies, the synthesis of more glycosyl acceptor was necessary. It was decided to synthesize the acceptor **124** instead of **92**. This block possessed a benzoyl substituent at C-3 rather than a benzyl group, whose removal would be more easily achieved. Moreover, the acceptor was synthesized as its allyl glycoside that had the potential of being removed to provide the hemiacetal and be functionalized as the trichloroacetimidate of the disaccharide. This block would be useful for further elaboration to the trisaccharide.

The acceptor **124** was synthesized by conventional methods (Figure 4.24). A Fischer allylation of glucose afforded an α,β-mixture of allyl glycosides **126** that was selectively protected at the 4 and 6 positions with a benzylidene acetal. The α and β isomers were separated at this stage and the α-isomer was benzoylated to give compound **129**. The selective removal of the benzoyl substituent at C-2 was effected with hydrazine hydrate and the method of Ishido et al.[152] These authors report similar selective debenzoylation of analogous methyl glycosides.

The acceptor **124** was glycosylated with the trichloroacetimidate **100** in the presence of 0.1 equivalent of TESOTf to afford an anomeric mixture of the disaccharides **130** and **131** in a ratio of 9:1 (Table 4.5, entry 1). The improved α selectivity of this reaction may be due to the lower reactivity of acceptor **124** as compared to **92** due to the replacement of the activating benzyl substituent with a benzoate group. At lower temperatures, the orthoester **132** was obtained (Table 4.5, entry 2). The α and β disaccharides were again inseparable by chromatography. However, the pure α– isomer was fractionally crystallized from

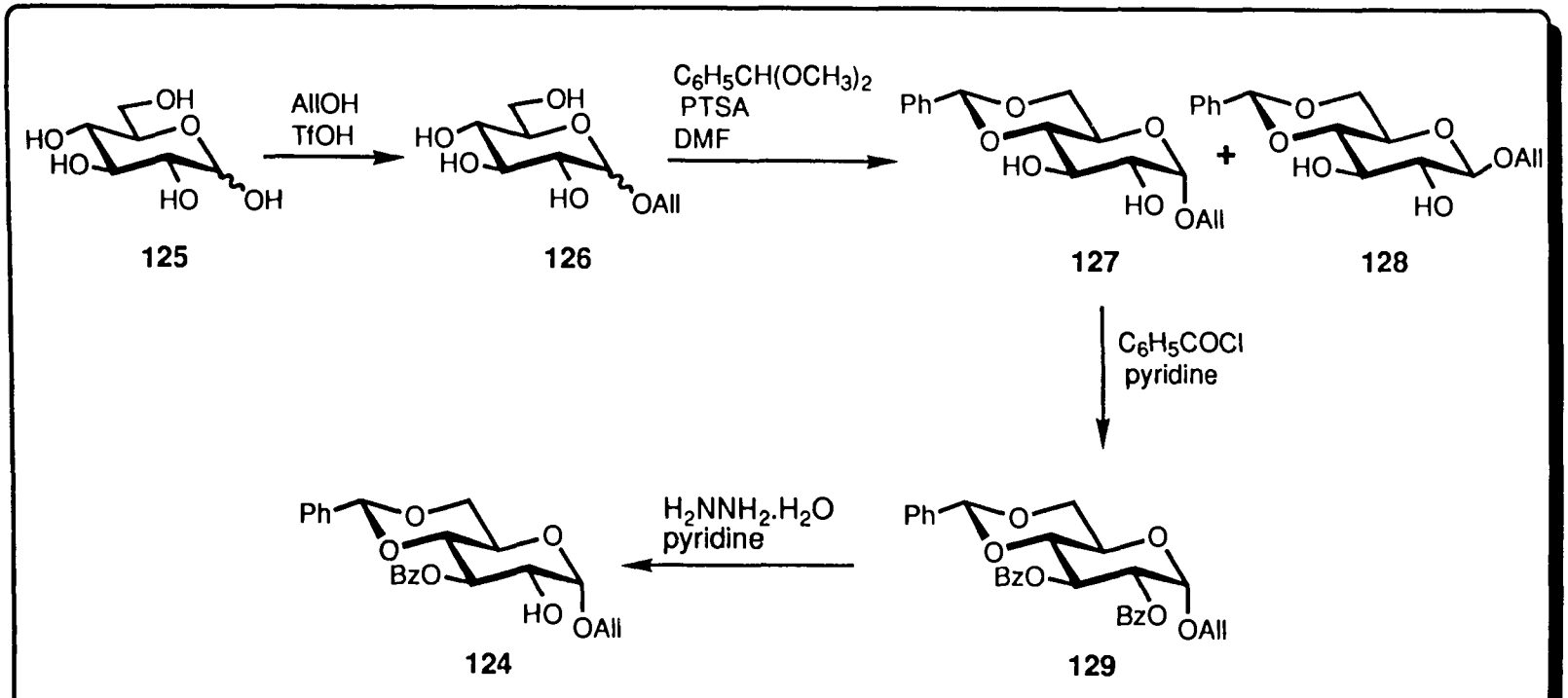
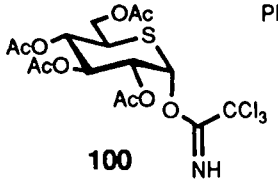
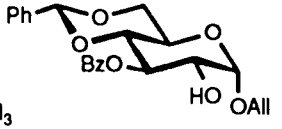
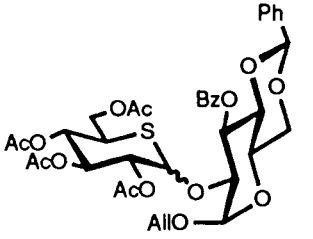
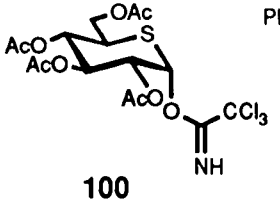
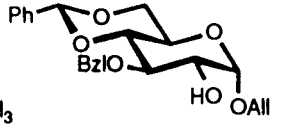
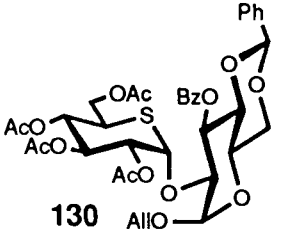
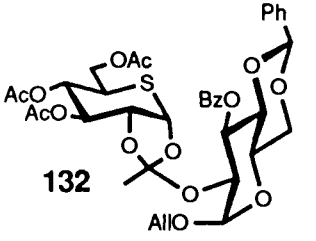
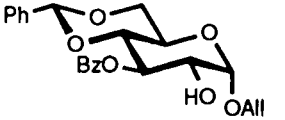
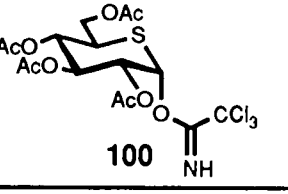


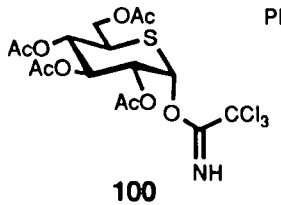
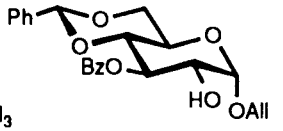
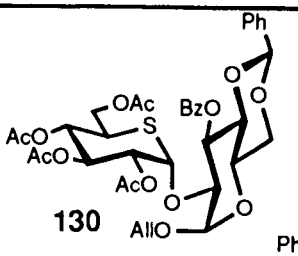
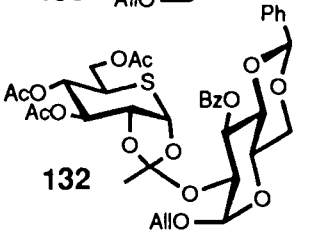
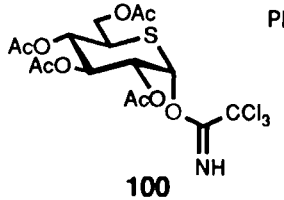
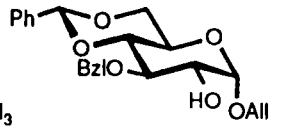
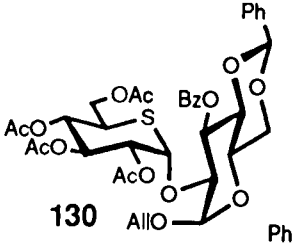
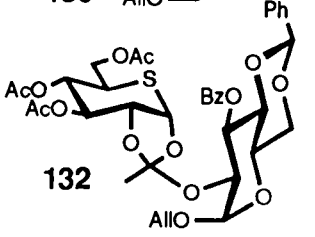
Figure 4.24. Synthesis of Allyl 4,6-O-benzylidene-3-O-benzoyl-α-D-glucopyranoside

Table 4.5. Synthesis of Allyl 3-O-benzoyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-acetyl-5'-thio-α/β-D-glucopyranosyl)-α-D-glucopyranoside and the corresponding orthoester.

Entry	Donor	Acceptor	Molar Ratio[a]	Reaction Conditions	Product	Yield (%)
1	 **100**	 **124**	1 : 2 : 0.1	-78°C for 1 h RT for 1 h	 **130, 131** α:β = 9:1	80%
2	 **100**	 **124**	1 : 2 : 0.1	-78°C for 2 h	 **130**	9%
					 **132**	9%
					 **124**  **100**	

[a]donor : acceptor : promoter.

Table 4.5. Synthesis of Allyl 3-O-benzoyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-acetyl-5'-thio-α/β-D-glucopyranosyl)-α-D-glucopyranoside and the corresponding orthoester.

Entry	Donor	Acceptor	Molar Ratio[a]	Reaction Conditions	Product	Yield (%)
3	 **100**	 **124**	1 : 2 : 0.1 +0.1	-78°C for 3 h	 **130**	16%
					 **132**	54%
					(130:132 = 1:3.5)	
4	 **100**	 **124**	1 : 2 : 0.07 +0.07	-78°C for 3 h	 **130**	19%
					 **132**	56%
					(130:132 = 1:3)	

[a]donor : acceptor : promoter.

the mixture. Entries 3 and 4 of Table 4.5 show the results of two reactions performed at different promoter concentrations, other reaction conditions being kept constant. Similar yields and orthoester to disaccharide ratios suggest that the product dependence of the reactions is a function of temperature rather than acid concentrations.

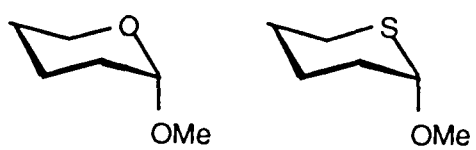
The disaccharide **130** was deprotected by the initial hydrolysis of the benzylidene acetal with 80%CH_3COOH followed by deesterification under Zemplen conditions to afford the target disaccharide **86**.

4.5. PREFERENTIAL FORMATION OF α-DISACCHARIDES

The exceptional behaviour of 5-thiohexopyranosyl donors to afford preferentially the α-product despite the presence of a participating acetate at the 2- position of the glycosyl donor has been described in the preceding sections. Our observations are in accord with those of Hashimoto and Isumi[135] who have reported a similar preference with 5-thio-L-fucopyranosyl donors.
Joseph and Rollin[153] have suggested that this is due a low degree of participation of the C-2 acetate. This does not seem to be a likely explanation since we have isolated a number of orthoesters of considerable stability.

In our opinion, the stereoselectivity may be accounted for by the thermodynamic stability of the axially oriented aglycon. The anomeric effect in 5-thioglucose is known to be stronger than in glucose. Whereas D-glucose exists as the α-anomer to the extent of 36% in aqueous solution,[154] the former compound exists as the α-anomer in 80%.[155] This likely results from favourable orbital interactions as well as a lesser steric effect in the former case. Evidence to suggest this has been published by Pinto and Leung[156] who have studied the

anomeric effect of X-C-Y systems. The experimentally observed ΔG values for 2-methoxyoxacyclohexane and 2-methoxythiacyclohexane indicate a greater α-preference for the thiacyclohexane derivative. This has been accounted for in terms of a dominance of the orbital interaction component (Figure 4.25). The lesser steric effect in the thia analogues is reflected in the A values of 2-methyl-1-oxacyclohexane (2.86 kcal mol^{-1})[157] and -thiacyclohexane (1.40 kcal mol^{-1}).[158] Our results are also in agreement with those of Jagannadhan et al.[159] who report a greater thermodynamic stability of the α-S-carbocation *vs* the α-O-carbocation.[159]



$\Delta G°_{experimental}$	-0.46	-1.53
$\Delta G°_{orbital}$	-0.42	-1.23
$\Delta G°_{steric}$	-0.77	-0.35
$\Delta G°_{electrostatic}$	-0.81	-0.63

Figure 4.25. Comparison of the component analysis of the anomeric effect in (O-C-O) vs (S-C-O) systems[156]

4.6. ORTHOESTERS: FORMATION AND REARRANGEMENT

The formation of the orthoesters **108**, **119**, **132** was confirmed by the use of ^{1}H and ^{13}C NMR spectra. The singlet corresponding to the protons of the C-methyl was observed at a higher field than the signals attributed to the other

acetoxy methyl groups.[160] This is usually an indication of orthoester formation. Moreover, as is usually the case in orthoesters the ^{13}C chemical shift of the C-methyl was separated and downfield as compared to the signals of the acetoxy methyls. This was further confirmed in the ^{13}C-^{1}H chemical-shift correlated spectrum where a correlation was observed between the peak attributed to the protons and the carbon of the C-methyl group. A ^{13}C signal in the region of 120 ppm (due to the orthoester carbon) is also an indication of orthoester formation. Such a peak was observed in the ^{13}C spectra of compounds **108** (122.4 ppm), **119**(121.9 ppm), **132**(121.9 ppm) and it did not correlate with any peak in the 1H spectra.

We speculated that the α-disaccharides might arise from the rearrangement of the orthoesters. To verify this postulate the orthoesters **119** and **132** that were isolated at temperatures below -50°C were reintroduced into the same initial reaction conditions but the reaction mixtures were warmed to room temperature. The orthoester **109** rearranged to afford only the α-disaccharide **104** in a 40% yield. Also isolated were the acceptor **74**, and the glucals **105** and **106**. The orthoester **132** gave predominantly a mixture of the α- and β-disaccharides **130, 131** in a ratio of 7:1. Thus, the results of the rearrangement of these orthoesters is reflective of results obtained in reactions that were conducted without their isolation. We suggest that the preferential α–disaccharide formation is preceded by orthoester formation.

Orthoesters generally rearrange to afford the 1,2-trans product (Section 1.5.3b). These orthoesters are in the *exo*-configuration. We thought that our orthoesters may possess an *endo*-configuration thereby rearranging to the unexpected α-disaccharide. This possibility was examined by NOESY experiments. The NOESY contacts of the C-methyl group were observed with

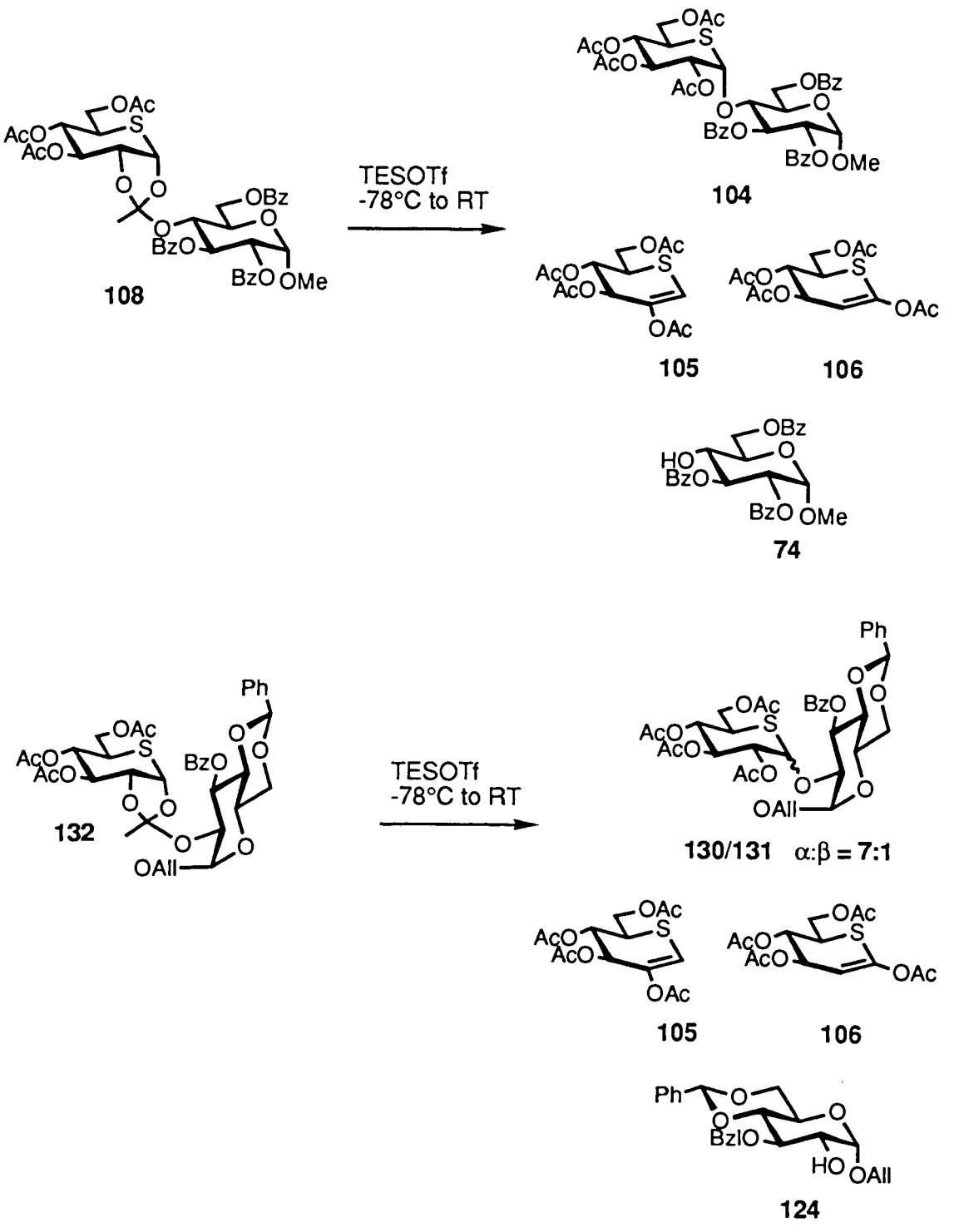


Figure 4.26. Orthoester rearrangement

the H-3 of the nonreducing sugar residue (Figure 4.27). This disagreed with our assumption and implied an *exo*-configuration of the orthoester.

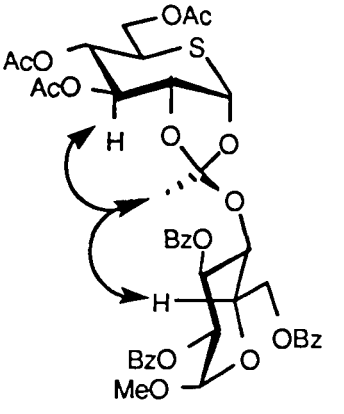


Figure 4.27. Important noesy contacts

The formation of an α-product from an orthoester rearrangement is not entirely unprecedented. Studies performed by Garegg et al.[161] showed that the stereochemical outcome is dependent on a variety of factors. Alcohols with lower electron densities and lesser steric accessibilities led to a greater proportion of the α-product. The nature of the counterion also exerted some control over the outcome of the reaction.

4.7 CONCLUSIONS

Novel sulfur and selenium heteroanalogues of methyl isomaltoside, methyl maltoside, and methyl- and allyl kojibioside have been synthesized for evaluation as glycosidase inhibitors. The glycosylation of various acceptors with selenoglycosides of 5-thioglucose proceeded in a stereoselective fashion to furnish the α-disaccharides in spite of the presence of a participating acetate substituent at the 2 position of the glycosyl donor. The yields of these reactions were, however, low due to transesterification.

The glycosyl trichloroacetimidate of 2,3,4,6-tetra-O-acetyl-5-thioglucopyranose was a more efficient glycosyl donor and was used to glycosylate selectively protected glucopyranosyl acceptors with 2-OH and 6-OH positions free, under triethylsilyl trifluoromethanesulfonate promotion, to afford the 1,2-linked and the 1,6-linked disaccharides as 9:1 and 1.5:1 α:β mixtures, respectively. Methyl α-D-glucopyranoside acceptors containing 4-OH and 4-SeH functions were glycosylated with the same donor under triethylsilyl triflate catalysis, to give exclusively the α-5'-thiodisaccharide, and a 4:1 α/β mixture of the 4-seleno-5'-thiodisaccharides, respectively. The selectivity of the glycosylations was dependent on the reactivity of the glycosyl acceptor, the least reactive acceptor affording exclusively the α-product. The corresponding orthoesters were isolated and rearranged to afford preferentially the α-disaccharides. This suggests that disaccharide formation is preceded by orthoester formation. The disaccharides were deprotected to give heteroanalogues for evaluation as glycosidase inhibitors.

CHAPTER V

EXPERIMENTAL

5.1. GENERAL EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting-point apparatus and are uncorrected. Optical rotations were measured with a Rudolph Research Autopol II automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer at 400.13 and 100.6 MHz, for proton and carbon, respectively, unless otherwise stated. The spectra were recorded in deuterochloroform or deuterium oxide. Chemical shifts are given in ppm downfield from TMS for those spectra measured in deuterochloroform, and downfield from 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for those spectra measured in deuterium oxide. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. All new compounds were characterized by either microanalysis or electrospray mass spectrometry. The microanalyses were performed by Mr. Mickey Yang at Simon Fraser University. The electrospray mass spectrometry was performed by Dr. Joseph Banoub at the Department of Fisheries and Oceans, Newfoundland.

All new compounds were fully characterized by the use of routine ^{1}H, ^{13}C, ^{1}H-homonuclear and ^{1}H-^{13}C inverse-detected NMR spectra. The ^{1}H-homonuclear chemical-shift correlated (COSY) spectra[162] were acquired using a pulse sequence d1-90°-d0-45°-FID with quadrature detection in both dimensions. The initial data sets of 1024 x 512 data points were zero-filled once in the F_1 direction to give a final data set of 1024 x 1024 real data points. For

the inverse detection experiments a four-pulse sequence was used for the $^{1}H\{^{13}C\}$-^{13}C correlation.[163] The data sets of 2048 x 512 data points were zero-filled once in the F_1-direction, to give a final data set of 1024 x 1024 real data points.

Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with Merck silica gel 60F-254 as the adsorbent. The developed plates were air-dried, exposed to UV light and/or sprayed with 5% sulfuric acid in ethanol, and heated at 150°C. All compounds were purified by medium-pressure column chromatography on Kieselgel 60 (230-400 mesh) according to a published procedure.

Solvents were distilled before use and were dried, as necessary, by literature procedures. Solvents were evaporated under reduced pressure and below 40°C.

Reactions performed under nitrogen were also carried out in deoxygenated solvents. Transfers under nitrogen were effected by means of standard Schlenk-tube techniques.

5.2. EXPERIMENTAL SECTION FOR CHAPTER II

Phenyl 2,3,4-Tri-O-acetyl-1-seleno-α,β-L-rhamnopyranoside (1,2). A mixture of diphenyl diselenide (1.2 g, 3.8 mmol) and 50% hypophosphorous acid (12 mL) was refluxed under nitrogen with vigorous stirring until the mixture was colourless (5 h). The reaction mixture was cooled and anhydrous dichloromethane (6 mL) was added. The solution of phenylselenol in CH_2Cl_2 was transferred under nitrogen into a round bottom flask containing water (7 mL) by means of a syringe. The reaction mixture was rinsed with additional portions of CH_2Cl_2 (2x3 mL) which were transferred as above. After shaking the organic layer with water, it was syringed into a round bottom flask containing magnesium sulfate, under N_2. The water layer was rinsed with CH_2Cl_2 (3 mL) and the CH_2Cl_2 layer transferred as above. The dried phenylselenol solution was then added to 1,2,3,4-tetra-O-acetyl-α-D-rhamnopyranoside **(11)** (1.2 g, 3.6 mmol) with a syringe. The magnesium sulfate was washed with CH_2Cl_2 (3x5 mL) and the washings were transferred to the reaction mixture. The reaction mixture was cooled to 0°C and BF_3OEt_2 (0.42 mL, 3.4 mmol) was added. After 22 h the reaction mixture was neutralized with Et_3N and washed with water (2x15 mL). The organic layer was dried over magnesium sulfate and concentrated to give a syrup which was chromatographed with hexane-ethyl acetate (3:1) as eluant. [R_f α-isomer **1** = 0.35, β-isomer **2** = 0.27]. The products were obtained as powders and were crystallized from ethanol, (α : 1.02 g, 66%, β : 0.28 g, 18%). mp α-isomer **(1)** 117°C, $[\alpha]_D^{25}$ -141° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$) δ 17.3 (C-6), 20.6, 20.8, 20.9 ($3COCH_3$), 67.6 (C-5), 69.7 (C-3), 71.0 (C-4), 72.0 (C-2), 82.7 [$^1J(^{13}C,^1H)$ 171 Hz, (C-1)], 128.1-134.2 (Ar), 169.8 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 1.25 (3H, d, $J_{5,6}$ = 6.2 Hz, H-6), 2.00, 2.08, 2.12 (9H, 3s, $3COCH_3$),

4.24 (1H, m, H-5), 5.14 (1H, t, $J_{3,4+4,5}$ = 19.8 Hz, H-4), 5.27 (1H, dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.6 Hz, H-3), 5.56 (1H, dd, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 5.65 (1H, d, $J_{1,2}$ = 1.3 Hz, H-1), 7.1-7.7 (5H, m, Ar); Anal. Calcd for $C_{18}H_{22}O_7Se$: C, 50.36; H, 5.17, Found: C, 50.50; H, 5.20. mp β-isomer **(2)** 101°C, $[\alpha]_D^{23}$ 31° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 17.7 (C-6), 20.5, 20.6, (3CO*C*H_3), 70.3 (C-4), 71.7 (C-2, C-3), 76.0 (C-5), 80.8 [$^1J(^{13}C,^1H)$ 156 Hz, (C-1)], 128.2-134.3 (Ar), 169.7, 170.1 (3*C*OCH$_3$); ^1H NMR ($CDCl_3$): δ 1.28 (3H, d, $J_{5,6}$ = 6.2 Hz, H-6), 1.96, 2.03, 2.18 (3s, 9H, 3COC*H*$_3$), 3.50 (1H, m, H-5), 4.98 (1H, dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ =10.2 Hz, H-3), 5.09 (1H, d, $J_{1,2}$ = 1.0 Hz, H-1), 5.10 (1H, t, $J_{3,4+4,5}$ = 19.6 Hz, H-4), 5.65 (1H, dd, $J_{1,2}$ = 1.0 Hz, $J_{2,3}$ = 3.5 Hz, H-2), 7.1-7.3 (5H, m, Ar); Anal. Calcd for $C_{18}H_{22}O_7Se$: C, 50.36; H, 5.17. Found: C, 50.21; H, 5.22.

Phenyl 2,3,4,6-Tetra-O-acetyl-1-seleno β, α-D-glucopyranoside (3,4). A mixture of diphenyl diselenide (4.0 g, 12.8 mmol) and 50% hypophosphorous acid (40 mL) was refluxed under nitrogen with vigorous stirring until the mixture was colourless (6 h). The reaction mixture was cooled and anhydrous dichloromethane (20 mL) was added. The solution of phenylselenol in CH_2Cl_2 was transferred under N_2 into a round bottom flask containing water by means of a syringe. The reaction mixture was rinsed with additional portions of CH_2Cl_2 (2x10 mL) which were transferred as above. After shaking the organic layer with water, it was syringed into a round bottom flask containing magnesium sulfate, under N_2. The water layer was rinsed with CH_2Cl_2 (10 mL) and the CH_2Cl_2 layer transferred as above. The dried phenylselenol solution was then added to 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranoside **(12)** (5.01 g, 12.8 mmol) with a syringe. The magnesium sulfate was washed with CH_2Cl_2 (3x10 mL) and the

washings were transferred to the reaction mixture. The reaction mixture was cooled to 0°C and BF_3OEt_2 (1.6 mL, 13.0 mmol) was added slowly. After 17 h the reaction mixture was neutralized with Et_3N and washed with water (2x25 mL). The organic layer was dried over magnesium sulfate and concentrated to give a syrup which was chromatographed with hexane-ethyl acetate (2:1) as eluant. [R_f α-isomer **4** = 0.38, β-isomer **3** = 0.31]. The products were obtained as powders and compound **3** was crystallized from ethanol. (α : 0.21 g, 3%, β : 5.54 g, 89%). **(3)** mp= 98.0 °C, $[\alpha]_D^{21}$ = -25.0° (*c* 1.0 in CH_2Cl_2); lit.[84] mp = 99°C, $[\alpha]_D^{20}$ -26.6°; ^{13}C NMR ($CDCl_3$): δ 20.5, 20.7 (4COCH$_3$), 62.1 (C-6), 68.3 (C-4), 70.9 (C-2), 73.9 (C-3), 76.9 (C-5), 80.9 [$^1J(^{13}C,^1H)$ 159 Hz, (C-1)], 128.2-135.2 (Ar), 169.1, 169.2, 170.0, 170.4 (4*C*OCH$_3$); ^1H NMR ($CDCl_3$): δ 1.98, 2.01, 2.07, (12H, 4s, 4COC*H*$_3$), 3.69 (1H, ddd, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 2.7 Hz, $J_{5,6b}$ = 4.5 Hz, H-5), 4.18 (2H, m, H-6a, H-6b), 4.88 (1H, d, $J_{1,2}$ = 10.2 Hz, $^2J_{H,Se}$ = 15.8 Hz, H-1), 5.0 (1H, t, $J_{1,2+2,3}$ = 19.0 Hz, H-2), 5.03 (1H, t, $J_{3,4+4,5}$ = 19.5 Hz, H-4), 5.19 (1H, t, $J_{2,3+3,4}$ = 18.5 Hz , H-3), 7.2-7.5 (5H, m, Ar); Anal. Calcd for $C_{20}H_{24}O_9Se$: C, 49.29; H, 4.96. Found: C, 49.44; H, 4.87. **(4)** $[\alpha]_D^{22}$ = 240° (*c* 0.1 in CH_2Cl_2); lit.[86] $[\alpha]_D^{20}$ 198°; ^{13}C NMR ($CDCl_3$): δ 20.5, 20.7 (4COCH$_3$), 61.8 (C-6), 68.3 (C-4), 69.8 (C-5), 71.1 (C-3), 71.2 (C-2), 82.8 [$^1J(^{13}C,^1H)$ 173 Hz, (C-1)], 127.4-135.2 (Ar), 169.5, 169.6, 169.9, 170.4 (4*C*OCH$_3$); ^1H NMR ($CDCl_3$): δ 2.00, 2.02, 2.04, 2.08 (12H, 4s, 4COC*H*$_3$), 3.96 (1H, dd, $J_{5,6a}$ = 2.1 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.26 (1H, dd, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6b), 4.50 (1H, ddd, $J_{4,5}$ = 10.1 Hz, $J_{5,6a}$ = 2.1 Hz, $J_{5,6b}$ = 5.0 Hz, H-5), 5.04 (1H, dd, $J_{1,2}$ = 5.6 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 5.08 (1H, t, $J_{3,4+4,5}$ = 19.5 Hz, H-4), 5.38 (1H, t, $J_{2,3+3,4}$ = 19.5 Hz, H-3), 6.15 (1H, d, $J_{1,2}$ = 5.8 Hz, H-1), 7.1-7.6 (5H, m, Ar); Anal. Calcd for $C_{20}H_{24}O_9Se$: C, 49.29; H, 4.96. Found: C, 49.07; H, 4.90.

Phenyl 3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside (5). A mixture of diphenyl diselenide (1.3 g, 4.2 mmol) and 50% hypophosphorous acid (10 mL) was refluxed under N_2 with vigorous stirring until the mixture was colourless (3 h). The reaction mixture was cooled and anhydrous dichloromethane (8 mL) was added. The solution of phenylselenol was transferred under N_2 into a round bottom flask containing water by means of a syringe. The reaction mixture was rinsed with additional portions of CH_2Cl_2 (2x4 mL) which were transferred as above. After washing the organic layer with water, it was syringed into a round bottom flask containing magnesium sulfate. The water layer was rinsed with CH_2Cl_2 (5 mL) and the washings were transferred as above. The dried phenylselenol solution was then added to 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside **(13)**[90] (2.0 g, 4.2 mmol) with a syringe. The magnesium sulfate was washed with CH_2Cl_2 (2x5 mL) and the washings were transferred to the reaction mixture. The reaction mixture was cooled to 0°C and BF_3OEt_2 (0.51 mL, 4.2 mmol) was added slowly. After 22 h the reaction mixture was neutralized with Et_3N and washed with water (2x15 mL). The organic layer was dried over magnesium sulfate and concentrated to give a syrup that was chromatographed with hexane-ethyl acetate (2.5:2) as eluant; R_f = 0.4. The product was obtained as a foam and was crystallized from hexane-ethyl acetate (5:1), (2.25 g, 93%); mp = 136.5 °C, $[\alpha]_D^{25}$ 35.0° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.3, 20.5, 20.7 ($3COCH_3$), 54.7 (C-2), 62.1 (C-6), 68.7 (C-4), 71.4 (C-3), 76.9 (C-5), 78.4 (C-1), 123.6-135.4 (Ar), 169.4, 170.0, 170.5 ($3COCH_3$); ^1H NMR ($CDCl_3$): δ 1.82, 2.02, 2.09 (3s, 9H, $3COCH_3$), 3.88 (1H, ddd, H-5, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 2.3 Hz, $J_{5,6b}$ = 4.8 Hz, H-5), 4.21 (1H, dd, $J_{5.6a}$ = 2.3 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6a), 4.27 (1H, dd, $J_{5,6b}$ = 4.8 Hz, $J_{6b,6a}$ = 11.8 Hz, H-6b), 4.38 (1H, t, $J_{1,2+2,3}$ = 20.8

Hz, H-2), 5.12 (1H, dd, $J_{3,4}$ = 9.1 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 5.77 (1H, t, $J_{2,3+3,4}$ = 19.3 Hz, H-3), 5.89 (1H, d, $J_{1,2}$ = 10. 5 Hz, $J_{H,Se}$ = 12.0 Hz, H-1), 7.2-7.9 (9H, m, Ar); Anal. Calcd for $C_{26}H_{25}O_9NSe$: C, 54.36; H, 4.39; N, 2.44. Found: C, 54.49; H, 4.44; N, 2.37.

Phenyl 2,3,4,-Tri-O-benzyl-1-seleno-β-D-glucopyranoside (9). Freshly prepared sodium methoxide solution in methanol (0.2 N, 40 mL) was added to phenyl 2,3,4,-tri-O-acetyl-1-seleno-β-D-glucopyranoside **(1)** (5.1 g, 11.9 mmol). The reaction mixture was stirred overnight, neutralized with Amberlyst 15 ion-exchange resin, filtered, and concentrated to afford the deacetylated selenoglycoside. Phenyl 1-seleno-β-D-glucopyranoside **(6)** was dissolved in dry, freshly distilled *N,N*-dimethylformamide (60 mL) and the solution was added slowly to a stirred suspension of sodium hydride (3.0 g, 75.0 mmol) in DMF (40 mL) at 0°C. The reaction mixture was stirred for 30 min following which benzyl bromide (8.6 mL, 72.3 mmol) was added dropwise. The reaction mixture was stirred overnight under N_2. On completion of the reaction, as indicated by TLC, excess sodium hydride was decomposed by the addition of methanol. The reaction mixture was poured into water (100 mL) and the desired compound was extracted into ethyl acetate (3x50 mL) and washed with water (2x50 mL). The organic extracts were dried over magnesium sulfate and concentrated. The resulting syrup was purified by column chromatography with hexane-ethyl acetate (8:1) as eluant, R_f = 0.32. The desired product was obtained as a solid (6.8 g, 86%). $[\alpha]_D^{20}$ -100° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 17.8 (C-6), (C-5), 71.95, 72.0, 75.5 ($CH_2C_6H_5$), 77.2 (C-2), 80.3 (C-3, C-4), 84.1 [$^1J(^{13}C,^1H)$ 167 Hz, (C-1)], 127.6-138.5 (Ar). ^1H NMR ($CDCl_3$): δ 1.39 (3H, d, $J_{5,6}$ = 6.0 Hz, H-6), 3.71 (1H, t, $J_{3,4+4,5}$ = 18.6 Hz, H-4), 3.85 (1H, dd, $J_{2,3}$ =

3.0 Hz, $J_{3,4}$ = 8.9 Hz, H-3), 4.04 (1H, m, H-5), 4.06 (1H, dd, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 4.60 (2H, AB pattern, CH_2C$_6$H$_5$), 4.63 (1H, d, J = 12.4 Hz, CHHC$_6$H$_5$), 4.68 (1H, d, J = 10.8 Hz, CHHC$_6$H$_5$), 4.71 (1H, d, J = 12.4 Hz, CHHC$_6$H$_5$), (1H, d, J = 10.8 Hz, CHHC$_6$H$_5$), 5.79 (1H, d, $J_{1,2}$ = 1.6 Hz, H-1), 7.20-7.60 (20H, m, Ar); Anal. Calcd for $C_{33}H_{34}O_4Se$: C, 69.10; H, 5.98. Found: C, 69.35; H, 5.98.

Phenyl 2,3,4,6-Tetra-O-benzyl-1-seleno-β-D-glucopyranoside (10). Freshly prepared sodium methoxide solution in methanol (0.2 N, 35 mL) was added to phenyl 2,3,4,6-tetra-O-acetyl-1-seleno-β-D-glucopyranoside **(3)** (4.14 g, 8.5 mmol). The reaction mixture was stirred overnight, neutralized with Amberlyst 15 ion-exchange resin, filtered, and concentrated to afford the deacetylated selenoglycoside. Phenyl 1-seleno-β-D-glucopyranoside **(7)** (1.82 g, 7.1 mmol) was dissolved in dry, freshly distilled *N,N*-dimethylformamide (25 mL) and the solution was added slowly to a stirred suspension of sodium hydride (2.13 g, 53.2 mmol) in DMF (15 mL) at 0°C. The flask was rinsed with additional portions of DMF(3x5 mL) and the contents added to the reaction mixture. The reaction mixture was stirred for 30 min following which benzyl bromide (5.8 mL, 48.8 mmol) was added dropwise. The reaction mixture was stirred overnight under N_2. On completion of the reaction, as indicated by TLC, excess sodium hydride was decomposed by the addition of methanol. The reaction mixture was poured into water (100 mL) and the desired compound was extracted into ethyl acetate (3x60 mL), washed with water (30 mL) and sodium chloride (30 mL). The organic extracts were dried over magnesium sulfate and concentrated. The resulting syrup was purified by column chromatography with hexane-ethyl acetate (9:1) as eluant, R_f = 0.30. The desired product was obtained as a solid

(4.1 g, 85%), which was crystallized from ethanol to yield fluffy white crystals. mp 79.0°C, $[\alpha]_D^{26}$ 11° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 69.0 (C-6), 73.4. 75.0, 75.2, 75.7 ($4CH_2C_6H_5$), 77.8 (C-3), 80.2 (C-5), 81.4 (C-2), 83.0 (C-1), 86.8 (C-4), 127.5-138.4 (Ar), ^1H NMR ($CDCl_3$): δ 3.49 (1H, m, H-5), 3.53 (1H, t, $J_{1,2+2,3}$ = 17.0 Hz, H-2). 3.68 (2H, m, H-3, H-4), 3.75 (1H, dd, $J_{5,6a}$ = 4.3 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6a), 3.80 (1H, dd, $J_{5,6b}$ = 2.0 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6b), 4.54 (1H, d, *J* = 12.0 Hz, $CHHC_6H_5$), 4.60 (1H, d, *J* = 10.8 Hz, $CHHC_6H_5$), 4.62 (1H, d, *J* = 12.0 Hz, $CHHC_6H_5$), 4.73 (1H, d, *J* = 10.2 Hz, $CHHC_6H_5$), 4.86 (1H, d, $J_{1,2}$ = 9.5 Hz, H-1), 4.82-4.92 (4H, m, $2CHHC_6H_5$), 7.1-7.8 (25H, m, Ar); Anal. Calcd for $C_{40}H_{40}O_5Se$: C, 70.68; H, 5.93, Found: C, 70.94; H, 5.79.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (24).[165] Methyl α-D-glucopyranoside **(22)** (10 g, 51.5 mmol) was dissolved in dry freshly distilled acetonitrile (250 mL). α, α-Dimethoxytoluene (20 mL, 126.8 mmol) and *p*-toluenesulfonic acid (o.1 g, 0.5 mmol) were added. The reaction mixture was stirred under nitrogen for 48 h and neutralized with Et_3N. Evaporation of the solvent afforded a white solid that was dissolved in CH_2Cl_2, washed successively with water and sodium hydrogen carbonate. The organic extracts were dried over magnesium sulfate and concentrated. The residue was washed with hot hexane and crystallized from hexane-ethyl acetate to afford the *title compound* **(24)** (12 g, 85%); mp 168°C, $[\alpha]_D^{20}$ 112° (*c* 1.0 in $CHCl_3$); lit[165] mp 166-167°C, $[\alpha]_D^{20}$ 110° (*c* 1.0 in $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 55.4 ($OCH3$), 60.3 (C-5), 69.0 (C-6), 71.4, 72.7 (C-2, C-3) 81.0 (C-4), 100.0 [$^1J(^{13}C,^1H)$ 170 Hz, (C-1)], 102.0 ($OCHC_6H_5$), 126.0-137.0 (Ar). ^1H NMR ($CDCl_3$): δ 3.39 (3H, s, OCH_3), 3.43 (1H, t, $J_{5,6a+6a,6b}$ = 18.5 Hz, H-6a), 3.56, 3.63 (2H, bm, H-2, H-3), 3.76 (1H, m, H-5), 3.90 (1H, t, $J_{3,4+4,5}$ = 18.5 Hz, H-), 4.25 (1H, dd, $J_{5,6b}$ =

4.2 Hz, $J_{6a,6b}$ = 9.5 Hz, H-6b), 4.70 (1H, d, $J_{1,2}$ = 3.9 Hz, H-1), (1H, s, OC*H*C_6H_5), 7.20-7.60 (5H, m, Ar).

Methyl 2,3-Di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (25).[166] Methyl 4,6-O-benzylidene-α-D-glucopyranoside **(24)** (10.0 g, 35.4 mmol) was dissolved in dry, freshly distilled *N,N*-dimethylformamide (70 mL) and the solution was slowly added to a stirred suspension of sodium hydride (5.7 g, 142.5 mmol) in DMF (20 mL) at 0°C. Benzyl bromide (17.0 mL, 142.9 mmol) was then added dropwise. The reaction mixture was stirred overnight under nitrogen. On completion of the reaction, as indicated by TLC, excess NaH was decomposed by the addition of MeOH. The reaction was poured into water and the desired compound was extracted into ethyl acetate, dried over magnesium sulfate, and concentrated. The resulting residue was purified by column chromatography with hexane-ethyl acetate (5:1) as eluant, R_f = 0.4. The syrup was crystallized from hexane-ethyl acetate to yield fluffy white crystals of the *title compound* (12.5 g, 83%). mp = 91°C, $[\alpha]_D^{20}$ -32° (*c* 1 in $CHCl_3$); lit.[166] mp = 85-86°C, $[\alpha]_D^{20}$ -32° (*c* 1 in $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 55.2 (O*C*H3), 62.3 (C-5), 69.0 (C-6), 73.7, 75.2 (2*C*$H_2C_6H_5$) 78.8, 79.2 (C-2,3), 82.1 (C-4), 99.2 (C-1), 100.2 (*C*$H_2C_6H_5$), 126.0-139.0 (Ar). ^1H NMR ($CDCl_3$): δ 3.41 (3H, s, OC*H*$_3$), 3.58 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.9 Hz, H-2), 3.62 (1H, t, $J_{2,3+3,4}$ = 18.7 Hz, H-3), 3.72 (1H, t, $J_{5,6a+6a,6b}$ = 20.5 Hz, H-6a), 3.85 (1H, m, H-5), 4.07 (1H, t, $J_{3,4+4,5}$ = 18.5 Hz, H-4), 4.28 (1H, dd, $J_{5,6b}$ = 4.8 Hz, $J_{6a,\ 6b}$ = 10.0 Hz, H-6b), 4.68-4.95 (4H, 4d, 2C*H*$_2C_6H_5$), 4.61 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 5.57 (1H, s, OC*H*C_6H_5), 7.2-7.6 (15H, m, Ar).

Methyl 2,3,4-Tri-O-benzyl-α-D-glucopyranoside (16)[95] $LiAlH_4$ (0.5 g, 12.1 mmol) was added in three parts to a solution of methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside **(25)** (1.1 g, 2.4 mmol) in Et_2O (10 mL) and CH_2Cl_2 (10 mL). The mixture was gradually heated to reflux. A solution of $AlCl_3$ (1.1 g, 8.3 mmol) in Et_2O (10 mL) was slowly added to the above mixture over a period of 30 min. The reaction was refluxed for three hours at which point TLC indicated the completion of the reaction. The reaction mixture was cooled. EtOAc (8 mL) was added dropwise followed by water (20 mL). The mixture was diluted with Et_2O (20 mL), the organic extracts were washed with water (3x10 mL), dried over $MgSO_4$, and concentrated. The resulting residue was purified by column chromatography with hexane-ethyl acetate (1.5:1) as eluant. [R_f = 0.4]. The product was obtained as a powder (0.9 g, 82%). $[\alpha]_D^{20}$ 20.0° (*c* 1.0 in CH_3Cl); lit[95]: $[\alpha]_D^{20}$ 20.0° (*c* 1.0 in CH_3Cl); ^{13}C NMR ($CDCl_3$): δ 55.2 (OCH_3), 61.9 (C-6), 70.7 (C-5), 73.4, 75.0, 75.7 ($3CH_2C_6H_5$) 77.4 (C-4), 80.0 (C-2), 81.9 (C-3), 98.2 (C-1) 127.6-138.7 (Ar). ^1H NMR ($CDCl_3$): δ 1.6 (1H, bd, O*H*), 3.36 (3H, t, OCH_3), 3.50 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.52 (1H, t, $J_{3,4+4,5}$ = 18.5 Hz, H-4), 3.65 (1H, m, H-5), 3.68-3.80 (2H, bm, H-6a, H-6b), 4.01 (1H, t, $J_{2,3+3,4}$ = 18.4 Hz, H-3), 4.57 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.64 (1H, d, *J* = 10.9 Hz, $CHHC_6H_5$), 4.67 (1H, d, *J* = 12.0 Hz, $CHHC_6H_5$), 4.80 (1H, d, *J* = 12.0 Hz, $CHHC_6H_5$), 4.84 (1H, d, *J* = 10.8 Hz, $CHHC_6H_5$), 4.89 (1H, d, *J* = 10.9 Hz, $CHHC_6H_5$), 4.96 (1H, d, *J* = 10.8 Hz, $CHHC_6H_5$), 7.20-7.50 (15H, m, Ar).

Methyl 2-O-Benzoyl-4-O-benzyl-α-L-rhamnopyranoside (18). Methyl α-L-rhamnopyranoside **(19)** (2.5 g, 14 mmol) was dissolved in acetonitrile (25 mL) and trimethyl orthobenzoate (3.5 mL, 18 mmol), and *p*-toluenesulfonic acid (5

mg, 0.3 mmol) were added. The reaction mixture was partially concentrated on the rotary evaporator and stirred at 50°C for 2h. The reaction mixture was left overnight at ambient temperature. Triethylamine (2 drops) was added and the reaction mixture was concentrated. Without further purification, the above residue was dissolved in THF (16 mL) and the solution was added dropwise to a stirred suspension of sodium hydride (0.9 g, 22.5 mmol) in THF (6 mL) at 0°C. Benzyl bromide (2.7 mL, 23 mmol) was then added dropwise. The reaction mixture was stirred overnight under nitrogen. On completion of the reaction, as indicated by TLC, excess sodium hydride was decomposed by the addition of methanol. The reaction was poured into H_2O (75 mL) and the desired compound was extracted into ethyl acetate (2 x 30 mL), dried over $MgSO_4$ and concentrated to yield a dark yellow syrup. 80% Aqueous acetic acid (10 mL) was added to the above residue and stirred for 10 min. The acetic acid was removed by co-distillation with EtOH. The residue was purified by column chromatography with hexane-ethyl acetate (4:1) as eluant, [R_f = 0.36]. The product was obtained as a syrup (3.8 g, 73%). $[\alpha]_D^{19}$ 21.0° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 18.0 (C-6), 54.8 (OCH_3), 67.2 (C-5), 70.4 (C-3), 73.2 (C-2), 74.9 ($CH_2C_6H_5$) 81.6 (C-4), 98.4 [$^1J(^{13}C,^1H)$ 170 Hz, (C-1)], 127.7-138.1 (Ar), 166.1 (*C*OCH3). ^1H NMR ($CDCl_3$): δ (3H, d, $J_{5,6}$ = 6.2 Hz, H-6), 2.2 (1H, bd, *J* = 4.9, O*H*), 3.38 (3H, s, OCH_3), 3.47 (1H, t, $J_{3,4+4,5}$ = 18.6 Hz, H-4), 3.80 (1H, m, H-5), 4.21 (1H, m, H-3), 4.75 (1H, d, $J_{1,2}$ = 1.4 Hz, H-1), 4.752 (1H, d, *J* = 11.0 Hz, $CHHC_6H_5$), 4.86 (1H, d, *J* = 11.0 Hz, $CHHC_6H_5$), 5.34 (1H, dd, $J_{1,2}$ = 1.4 Hz, $J_{2,3}$ = 3.1 Hz, H-2), 7.25-8.1 (10H, m, Ar).

Activation of selenoglycoside (1) with methyl triflate: A mixture of phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside **(1)** (87 mg, 0.2 mmol) and

methyl 2,4-di-O-acetyl-α-L-rhamnopyranoside **(14)** (54 mg, 0.2 mmol) and 4Å molecular sieves was stirred in anhydrous CH_2Cl_2 (5 mL) under N_2 for 1 h. Methyl triflate (50 ml, 0.4 mmol) was added and the reaction mixture was warmed to 55° C and stirred for 20 h. The reaction mixture was cooled to room temperature and Et_3N was added. The mixture was fitered through celite and washed with water (2 x 20 mL). The organic layer was dried over magnesium sulfate and concentrated. The resulting colourless oil was purified by column chromatography with hexane-ethyl acetate (2:1) as eluant: Rf = 0.32; A mixture of α and β disaccharides, **(28)**[92] and **(29)**[92], was isolated (61.5 mg, 57%); α:β = 4:1. Yield based on recovered selenoglycoside **(1)**=74%.

Activation of selenoglycoside (1) with phenylselenenyl triflate: Phenylselenenyl chloride (41.2 mg, 0.2 mmol) was added to a mixture of CH_2Cl_2 (2ml) and freshly activated powdered 4Å molecules sieves (0.5g). The mixture was cooled in an ice bath and AgOTf (55.6 mg, 0.2 mmol) was added. After 5 minutes phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside **(1)** (89 mg, 0.2 mmol) was added followed by methyl 2,4-di-O-acetyl-α-L-rhamnopyranoside **(14)** (56 mg, 0.2 mmol) and the reaction was warmed to ambient temperature while stirring under N_2 for 2.5h. Et_3N was added and reaction was stirred for 10 min. The mixture was filtered through celite and washed with water (10 ml). The organic layer was dred over magnesium sulfate and concentrated. The resulting colourless oil was purified by column chromatography with hexane-ethyl acetate (2:1) as eluant: Rf = 0.32; A mixture of α and β disaccharides, **28**[92] and **29**,[92] was isolated (55 mg, 51%) α:β=4:1.

Activation of selenoglycoside (1) with $CuBr_2$-$(Bu)_4NBr$-AgOTf: A mixture of $CuBr_2$ (0.1 g, 0.4 mmol), (Bu)4NBr (17 mg, 0.05 mmol), and AgOTf (0.12 g, 0.5 mmol), and dry 4Å molecular sieves was weighed into a dry Schlenk tube. A mixture of phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside **1** (0.12 g, 0.3 mmol) and methyl 2,4-di-O-acetyl-α-L-rhamnopyranoside **14** (0.06 g, 0.2 mmol) in CH_3NO_2 (8 mL) was added to the above mixture by means of a cannula, under N_2. The flask was rinsed with additional portions of CH_3NO_2 (2 x 1 mL). After 1 h the reaction mixture was filtered through celite, and washed successively with a saturated solution of sodium hydrogen carbonate (10 mL), and sodium chloride solution (10 mL). The organic layer was dried over magnesium sulfate and concentrated. The nitromethane was removed by co-distillation with ethanol. The residue was purified by column chromatography with hexane-ethyl acetate (2:1) as eluant, Rf = 0.32. The desired disaccharide **(28)**[92] was obtained as a solid (58 mg, 50%).

Activation of selenoglycoside (1) with $HgCl_2$: A mixture of the phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside **(1)** (0.11 g 0.25 mmol), methyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside **(15)** (0.1 g 0.2 mmol) and 4Å molecular sieves was dried under vacuum overnight. Anhydrous dichloromethane (7 mL) was added and the reaction mixture was stirred under N_2 for 1 h. $HgCl_2$ (136 mg, 0.5 mmol) was added and the reaction was stirred under N_2 for 48 h. The reaction mixture was filtered through celite and concentrated. The resulting residue was purifed by column chromatography with hexane-ethyl acetate (1.75:1) as eluant, R_f=0.30. The *title compound* **(30)** was isolated as a foam (44 mg, 28%). The unreacted acceptor **(15)** was also isolated (40 mg). The yield of the *title compound* **(30)** with respect to acceptor recovered was 38 %.

Activation of selenoglycoside (1) with $NOBF_4$: A mixture of the phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside **(1)** (0.11 g, 0.25 mmol), methyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside **(15)** (0.1 g, 0.2 mmol) and 4Å molecular sieves was dried under vacuum overnight. Anhydrous dichloromethane (3 mL) was added and the reaction mixture was stirred under N_2 for 1 h. $NOBF_4$ (30 mg, 0.26 mmol) was added. On completion of the reaction (30 min), as indicated by TLC, the reaction mixture was poured into a saturated solution of sodium hydrogen carbonate, extracted into dichloromethane and washed with $NaHCO_3$. The organic extracts were dried over magnesium sulfate, concentrated, and the resulting residue was purifed by column chromatography with hexane-ethyl acetate (1.5:1) as eluant, [R_f = 0.36]. The *title compound* **(30)** was isolated as a foam (120 mg, 77%); $[\alpha]_D^{22}$ 6.9° (*c* 1 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 17.3 (C-6'), 20.6, 20.7, 20.8 ($3COCH_3$), 55.7 (OCH_3), 66.6, 66.7 (C-5', 6), 69.0 (C-5), 69.5, 69.7 (C-2, 2'), 69.8 (C-4), 70.5 (C-3), 71.1 (C-4'), 72.1 (C-3'), 71.1 (C-4'), 72.1 (C-3'), 96.9 [$^1J(^{13}C,^1H)$ 177 Hz, (C-1)], 98.2 [$^1J(^{13}C,^1H)$ 172 Hz, (C-1')]. ^1H NMR ($CDCl_3$): δ 1.13 (3H, d, $J_{5',6'}$ = 6.2 Hz, H-6'), 1.97, 2.03, 2.13 (9H, 3s, $3COCH_3$), 3.50 (3H, s, OCH_3), 3.70 (1H, dd, $J_{5,6a}$ = 7.0 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6a), 3.78-3.9 (2H, m, H-5', 6b), 4.27 (1H, m, H-5), 4.86 (1H, d, $J_{1',2'}$ = 1.3 Hz, H-1'), 5.04 (1H, dd, $J_{3',4'+4',5'}$ = 19.6 Hz, H-4'), 5.20-5.34 (4H, m, H-1, 2, 2', 3'), 5.45 (1H, t, $J_{3,4+4,5}$ = 19.8 Hz, H-4), 6.15 (1H, t, $J_{2,3+3,4}$ = 19.1 Hz, H-3), 7.20-8.20 (15H, m, Ar); Anal. Calcd for $C_{40}H_{42}O_{16}$: C, 61.69; H, 5.44; Found: C, 61.44, 5; H, 5.63.

Typical glycosylation procedure for activation of selenoglycosides with AgOTf/ K_2CO_3. A mixture of the selenoglycoside donor (0.25 mmol), the glycosyl acceptor (0.21 mmol) and 4Å molecular sieves was dried under

vacuum overnight. Anhydrous dichloromethane (8 mL) was added and the reaction mixture was stirred under N_2 for 1 h. Dry potassium carbonate was added followed by silver triflate. On completion of the reaction, as indicated by TLC, the reaction mixture was filtered through celite and washed with water (2x10 mL). The organic layer was dried over magnesium sulfate, concentrated, and the resulting residue was purifed by column chromatography.

Methyl 2,3,4-Tri-O-benzyl-6-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-D-glucopyranoside (31). The product was purified by column chromatography with hexane-ethyl acetate (2.5:1) as eluant, R_f = 0.37. $[\alpha]_D^{22}$ 13.0° (*c* 0.7 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 17.3 (C-6'), 20.7, 20.75, 20.8 ($3COCH_3$), 55.2 (OCH_3), 66.4 (C-5'), 66.9 (C-6), 69.1 (C-5), 69.9 (C-3'), 70.1 (C-2'), 71.2 (C-4'), 73.4, 75.0, 75.7 ($3CH_2C_6H_5$), 77.9 (C-4), 80.2 (C-2), 82.1 (C-3), 97.8, 97.9 (C-1, C-1'), 127.6-138.8 (Ar), 169.85, 169.94 ($3COCH_3$); ^1H NMR ($CDCl_3$): δ 1.17 (3H, d, $J_{5',6'}$ = 6.0 Hz, H-6'), 1.98, 2.05, 2.13 (9H, 3s, $3COCH_3$), 3.39 (3H, s, OCH_3), 3.41 (1H, dd, $J_{3,4+4,5}$ = 17.2 Hz, H-4), 3.50 (1H, dd, $J_{5,6a}$ = 5.9 Hz, $J_{6a,6b}$ = 10.9 Hz, H-6a), 3.54 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.78 (1H, ddd, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 5.9 Hz, $J_{5,6b}$ = 1.5 Hz, H-5), 3.84 (1H, dd, $J_{5,6b}$ = 1.5 Hz, $J_{6a,6b}$ = 10.9 Hz, H-6b), 3.85 (1H, m, H-5'), 3.99 (1H, t, $J_{2,3+3,4}$ = 18.5 Hz, H-3),4.54 (1H, d, *J* = 11.2 Hz, $CHHC_6H_5$), 4.58 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.66 (1H, d, $J_{1',2'}$ = 1.7 Hz, H-1'), 4.67 (1H, d, *J* = 11.9 Hz, $CHHC_6H_5$), 4.79 (1H, d, *J* = 11.9 Hz, $CHHC_6H_5$), 4.81 (1H, d, *J* = 10.8 Hz, $CHHC_6H_5$), 4.90 (1H, d, *J* = 11.2 Hz, $CHHC_6H_5$), 4.96 (1H, d, *J* = 10.8 Hz, $CHHC_6H_5$), 5.04 (1H, t, $J_{3',4'+4',5'}$ = 19.8 Hz, H-4'), 5.21 (1H, dd, $J_{1',2'}$ = 1.7 Hz, $J_{2',3'}$ = 3.6 Hz, H-2'), 5.27 (1H, dd, $J_{2',3'}$ = 9.8 Hz, $J_{3',4'}$ = 9.8 Hz, H-3'), 7.20-7.40 (15H, Ar); Anal. Calcd for $C_{40}H_{48}O_{13}$: C, 65.21; H, 6.57; Found: C, 65.11; H, 6.69.

Methyl 2,3,4-Tri-O-benzyl-(2,3,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-β-D-glucopyranoside (32). The product was purified by column chromatography with hexane-ethyl acetate (1.5:1) as eluant, R_f=0.30. $[\alpha]_D^{21}$ 42.5° (*c* 1.0 in CH_2Cl_2); 13C NMR ($CDCl_3$): δ 20.4, 20.6, 20.7 (3CO*C*H3), 54.5 (C-2'), 54.9 (O*C*H_3), 62.1 (C-6'), 68.7 (C-6), 69.0, 69.2 (C-4, C-5), 70.7 (C-3'), 71.9 (C-5'), 73.3, 74.7, 75.6 (3*C*$H_2C_6H_5$), 77.6 (C-4), 79.7 (C-2), 81.8 (C-3), 97.9 [$^1J(^{13}C,^1H)$ 169 Hz, (C-1)], 98.3 [$^1J(^{13}C,^1H)$ 169 Hz, (C-1')], 123.4-138.7 (Ar), 169.4, 170.1, 170.6 (3*C*OCH$_3$). ^{1}H NMR ($CDCl_3$): δ 1.85, 2.02, 2.08 (9H, 3s, 3COC*H*$_3$), 3.16 (3H, s, OC*H*$_3$), 3.23 (1H, t, $J_{3,4+4,5}$ = 18.4 Hz, H-4), 3.38 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 3.61-3.69 (2H, m, H-5, H-6a), 3.84 (1H, t, $J_{2,3+3,4}$ = 18.2 Hz, H-3), 3.86 (1H, m, H-5'), 4.06-4.13 (2H, m, H-6b, C*H*HC_6H_5), 4.16 (1H, dd, $J_{5',6a'}$ = 2.3 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6a'), 4.32 (1H, dd, $J_{5',6b'}$ = 4.5 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6b'), 4.36 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.39 (1H, dd, $J_{1',2'+2',3'}$ = 18.6 Hz, H-2'), 4.41 (1H, d, *J* = 10.5 Hz, C*H*HC_6H_5), 4.56 (1H, d, *J* = 12.0 Hz, C*H*HC_6H_5), 4.64 (1H, d, *J* = 10.8 Hz, C*H*HC_6H_5), 4.71 (1H, d, *J* = 12.0 Hz, CH*H*C_6H_5), 4.85 (1H, d, *J* = 10.8 Hz, CH*H*C_6H_5), 5.17 (1H, t, $J_{3',4'+4',5'}$ = 19.0 Hz, H-4'), 5.43 (1H, d, $J_{1',2'}$ = 8.5 Hz, H-1'), 5.79 (1H, dd, $J_{2',3'+3',4'}$ = 19.6 Hz, H-3'), 7.0-7.9 (19H, m, Ar); Anal. Calcd for $C_{48}H_{51}O_{15}N$: C, 65.37; H, 5.83; N, 1.59. Found: C, 65.41; H, 5.95; N, 1.62.

Methyl 2-O-Benzyl-4,6-O-benzylidene-3-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-D-glucopyranoside (33). The product was purified by column chromatography with hexane-ethyl acetate (2.25:1) as eluant, R_f=0.30. $[\alpha]_D^{21}$ -19.0° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 16.6 (C-6'), 20.7, 20.75, 20.8 (3CO*C*H$_3$), 55.3 (O*C*H$_3$), 62.5 (C-5), 65.9 (C-5'), 69.0 (C-6), 69.4 (C-3'), 69.7 (C-

2'), 71.2 (C-4'), 73.4 ($CH_2C_6H_5$), 74.2 (C-3), 79.7 (C-4), 80.4 (C-2), 97.9 [$^1J(^{13}C,^1H)$ 174 Hz, (C-1')], 98.6 [$^1J(^{13}C,^1H)$ 172 Hz, (C-1)], 101.7 ($OCHC_6H_5$), 126.3-137.6 (Ar), 169.8, 170.0, 170.2 (3 $COCH_3$). ^1H NMR ($CDCl_3$): δ 0.77 (1H, d, J = 6.2 Hz, H-6'), 1.95, 1.98, 2.10 (9H, 3s, $3COCH_3$), 3.36 (3H, s, OCH_3), 3.52 (1H, t, $J_{3,4+4,5}$ = 18.5 Hz, H-4), 3.54 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.3 Hz, H-2), 3.70 (1H, t, $J_{5,6a+6a,6b}$ = 20.0 Hz, H-6a), 3.81 (1H, dt, $J_{5,6b}$ = 4.7 Hz, $J_{4,5+5,6a}$ = 18.5 Hz, H-5), 4.14 (1H, t, $J_{2,3+3,4}$ = 19.0 Hz, H-3), 4.17 (1H, m, H-5'), 4.25 (1H, dd, $J_{5,6b}$ = 4.7 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6b), 4.53 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.57 (1H, d, J = 12.0 Hz, $CHHC_6H_5$), 4.74 (1H, d, J = 12.0 Hz, $CHHC_6H_5$), 4.95 (1H, t, $J_{3',4'+4',5'}$ = 20.0 Hz, H-4'), 5.13 (1H, d, $J_{1',2'}$ = 1.5 Hz, H-1'), 5.29 (1H, dd, $J_{2',3'}$ = 3.5 Hz, $J_{3',4'}$ = 9.3 Hz, H-3'), 5.35 (1H, dd, $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 3.5 Hz, H-2'), 5.52 (1H, s, $OCHC_6H_5$), 7.20-7.50 (10H, m, Ar); Anal. Calcd for $C_{33}H_{40}O_{13}$: C, 61.48; H, 6.25; Found: C, 61.31; H, 6.22.

Methyl 2-O-Benzoyl-4-O-benzyl-3-O-(2,3,4-tri-O-acetyl-α-rhamnopyranosyl)-α-L-rhamnopyranoside (34). The product was purified by column chromatography with hexane-ethyl acetate (2.5:1) as eluant, R_f=0.32. $[\alpha]_D^{21}$ -19.5° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 17.1, 18.1 (C-6, C-6'), 20.6, 20.7 ($3OCOCH_3$), 54.9 (OCH_3), 67.2, 67.6 (C-5, C-5'), 69.0 (C-3'), 69.8 (C-2'), 70.7 (C-4'), 72.7 (C-2), 75.6 ($CH_2C_6H_5$), 78.3 (C-3), 80.2 (C-4), 98.0 [$^1J(^{13}C,^1H)$ 175 Hz, (C-1)], 99.5 [$^1J(^{13}C,^1H)$ 172 Hz, (C-1')], 127.7-137.9 (Ar), 166.0, 169.7 ($COCH_3$). ^1H NMR ($CDCl_3$): δ 1.06 (3H, d, $J_{5',6'}$ = 6.0 Hz, H-6'), 1.36 (3H, d, $J_{5,6}$ = 6.0 Hz, H-6), 1.91, 1.94, 2.08 (9H, 3s, $3OCOCH_3$), 3.37 (3H, s, OCH_3), 3.61 (1H, t, $J_{3,4+4,5}$ = 19.2 Hz, H-4), 3.78 (1H, m, H-5'), 3.86 (1H, m, H-5), 4.21 (1H, dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 4.71 (1H, d, J = 10.9 Hz, $CHHC_6H_5$),

4.77 (1H, d, $J_{1,2}$ = 1.8 Hz, H-1), 4.89 (1H, d, J = 10.9 Hz, CH*H*C_6H_5), 4.98 (1H, t, $J_{3',4'+4',5'}$ = 19.8 Hz, H-4'), 5.03 (1H, d, $J_{1',2'}$ = 1.7 Hz, H-1'), 5.20 (1H, dd, $J_{2',3'}$ = 3.5 Hz, $J_{3',4'}$ = 10.0 Hz, H-3'), 5.30-5.34 (2H, m, H-2, H-2'), 7.25-8.15 (10H, m, Ar); Anal. Calcd for $C_{33}H_{40}O_{13}$: C, 61.48; H, 6.25; Found: C, 61.65; H, 6.22.

Selenoglycoside, thioglycoside competition experiment (Table I, entry 5) A mixture of phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside **(1)** (0.15 g, 0.35 mmol), ethyl 2,3,4-tri-O-acetyl-1-thio-α-L-rhamnopyranoside **(35)** (0.12 g, 0.35 mmol), methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside **(16)** (0.35 g, 0.75 mmol) and 4Å molecular sieves was dried under vacuum overnight. Anhydrous dichloromethane (10 mL) was added and the reaction mixture was stirred under N_2 for 1 h. Dry potassium carbonate (0.8 g, 5.8 mmol) was added followed by silver triflate (0.35 g, 1.37 mmol). After 24 h. the reaction mixture was filtered through celite and washed with water (2x10 mL). The organic layer was dried over magnesium sulfate and concentrated. The resulting syrup was purified by column chromatography with toluene-ethyl acetate (5:1) as eluant; R_f of recovered thioglycoside **(35)** = 0.4; disaccharide **(31)** = 0.28. The disaccharide **(31)** was obtained as a syrup (0.21 g, 86%), and the unreacted thioglycoside **(35)** was recovered as a powder (0.11 g, 91%).

Ethyl 4,6-O-benzylidene-1-thio-β-D-glucopyranoside (41)[101] A freshly prepared solution of sodium methoxide in methanol (0.2 N, 60 mL) was added to ethyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside **(39)** (3 g, 7.6 mmol). The reaction mixture was stirred overnight, neutralized with Amberlyst 15 ion-exchange resin, filtered, and concentrated to afford the deacetylated

thioglycoside **(40)**, quantitatively. Ethyl 1-thio-β-D-glucopyranoside **(40)** was dissolved in dry, freshly distilled acetonitrile (50 mL) and α, α-dimethoxytoluene (4 mL, 26.7 mmol) and *p*-toluenesulfonic acid (20 mg, 0.1 mmol) were added. The reaction mixture was stirred overnight under nitrogen and neutralized with Et_3N. The acetonitrile was removed in vacuo and the residue was dissolved in CH_2Cl_2, washed successively with sodium hydrogen carbonate and water. The organic extracts were dried over magnesium sulfate and concentrated. The residue was washed with hot hexane and crystallized from hexane-ethyl acetate to afford the *title compound* **(41)** (3.6g, 86%); mp 168°C, $[\alpha]_D^{20}$ 112° (*c* 1.0 in CH_3Cl); lit[101] mp 166-167°C, $[\alpha]_D^{20}$ 110° (*c* 1.0 in CH_3Cl); ^1H NMR ($CDCl_3$): δ 1.33 (3H, t, SCH_2CH_3), 2.67 (1H, bd. O*H*), 2,76 (2H, m, SCH_2CH_3), 2.89 (1H, bs, O*H*), 3.45-3.55 (2H, m, H-2, H-5), 3.57 (1H, t, $J_{3,4+4,5}$ = 18.4 Hz, H-4), 3.76 (1H, t, $J_{5,6a+6a,6b}$ = 20.3 Hz, H-6a), 3.83 (1H, dt, $J_{2,3+3,4}$ = 17.3 Hz, H-3), 4.35 (1H, dd, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 10.4 Hz, H-6b), 4.46 (1H, d, $J_{1,2}$ = 9.8 Hz, H-1), 5.54 (1H, s, $OCHC_6H_5$), 7.30-7.50 (20H, m, Ar)

Ethyl 2,3-Di-O-benzyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside (42)[101] Ethyl 4,6-O-benzylidene-1-thio-β-D-glucopyranoside **(41)** (2.5 g, 7.8 mmol) was dissolved in dry, freshly distilled *N,N*-dimethylformamide (20 mL) and the solution was slowly added to a stirred suspension of sodium hydride (1.4 g, 35.0 mmol) in DMF (5 mL) at 0°C. Benzyl bromide (4.5 mL, 37.8 mmol) was then added dropwise. The reaction mixture was stirred overnight under nitrogen. On completion of the reaction, as indicated by TLC, excess NaH was decomposed by the addition of MeOH. The reaction mixture was poured into water and was extracted into ethyl acetate, dried over magnesium sulfate, and concentrated. The resulting residue was purified by column chromatography with hexane-ethyl

acetate (6.5:1) as eluant, R_f=0.35. The syrup was crystallized from EtOH (95%) to yield fluffy white crystals of the *title compound* (3.3 g, 87%). mp 130°C, $[\alpha]_D^{20}$ -45° (*c* 1 in CH_3Cl); lit.[101] mp 118°C, $[\alpha]_D$ -43° (*c* 1 in CH_3Cl); ^1H NMR ($CDCl_3$): δ 1.32 (3H, t, SCH_2CH_3), 2,76 (2H, m, SCH_2CH_3), 3.46, 3.71, 3.78, 3.81 (5H, H-2, 3, 4, 5, 6a), 4,36 (1H, dd, $J_{5,6b}$ = 4.9 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6b), 4.56 (1H, d, $J_{1,2}$ = 9.8 Hz, H-1), 4.77-4.97 (4H, $2CH_2C_6H_5$), 5.51 (1H, s, $OCHC_6H_5$), 7.2-7.5 (15H, m, Ar).

Ethyl 2,3,6-Tri-O-benzyl-1-thio-β-D-glucopyranoside (38)[101] Hydrogen chloride in diethyl ether was added to ethyl 2,3-di-O-benzyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside **(42)** (1.0 g, 2.0 mmol) and $NaCNBH_3$ (1.7 g, 27.1 mmol) in THF (30 mL) containing 4A° molecular sieves until the reaction mixture stopped bubbling. The reaction was then stirred under N_2 at 0°C. After 1.5 h the starting material had almost completely reacted, as determined by TLC. The reaction mixture was poured into ice cold water and extracted into CH_2Cl_2. The combined organic extracts were washed with sodium hydrogen carbonate, dried over magnesium sulfate and concentrated. Column chromatography of the resulting syrup with hexane-ethyl acetate (2.5:1) as eluant (R_f=0.36) afforded the desired compound as a solid (0.76 g, 76 %); mp 64°C, $[\alpha]_D^{20}$ -34.0° (*c* 1.0 in CH_3Cl); lit:[101] mp 66°C, $[\alpha]_D$ -38.0° (*c* 1.0 in CH_3Cl); ^1H NMR ($CDCl_3$): δ 1.32 (3H, t, SCH_2CH_3), 2.75 (2H, m, SCH_2CH_3), 3.41 (1H, t, $J_{1,2+2,3}$ = 18.4 Hz, H-2), 3.46 (1H, q, H-5), 3.51 (1H, t, $J_{2,3+3,4}$ = 17.5 Hz, H-3), 3.63 (1H, t, $J_{3,4+4,5}$ = 18.3 Hz, H-4), 3.71 (1H, dd, $J_{5,6a}$ = 5.1 Hz, $J_{6a,6b}$ = 10.4 Hz, H-6a), 3.75 (1H, dd, $J_{5,6b}$ = 4.5 Hz, $J_{6a,6b}$ = 10.4 Hz, H-6b), 4.48 (1H, d, $J_{1,2}$ = 9.7 Hz, H-1), 4.57 (2H, AB pattern), 4.74 (1H, d, *J* = 10.2 Hz, $CHHC_6H_5$), 4.78 (1H, d, *J* = 11.4 Hz, $CHHC_6H_5$), 4.92 (1H, d, *J* = 10.2 Hz, $CHHC_6H_5$), 4.93 (1H, d, *J*

= 11.4 Hz, CH*H*C_6H_5), 7.20-7.50 (15H, m, Ar);

Ethyl 2,3,4-Tri-O-benzyl-1-thio-β/α-D-glucopyranoside (36,[167][37][168]**)** $LiAlH_4$ (1.2 g, 31.6 mmol) was added in three parts to a solution of 2,3-di-O-benzyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside **(42)** (3.3 g, 6.7 mmol) in Et_2O (35 mL) and CH_2Cl_2 (35 mL). The mixture was gradually heated to reflux. A solution of $AlCl_3$ (3.5 g, 26.2 mmol) in Et_2O (35 mL) was slowly added to the above mixture over a period of 30 min. The reaction was refluxed for three hours at which point TLC indicated the completion of the reaction. The reaction mixture was cooled. EtOAc (20 mL) was added dropwise followed by water (50 mL). The mixture was diluted with Et_2O (60 mL), the organic extracts were washed with water (3x20 mL), dried over $MgSO_4$, and concentrated. The resulting residue was purified by column chromatography with hexane-ethyl acetate (3:1) as eluant. [R_f β-isomer **36** = 0.33, α-isomer **37** = 0.27]. The products were obtained as powders (β : 0.8 g, 24%, α : 1.6 g, 48%). mp β-isomer **(36)** 113°C, $[\alpha]_D^{20}$ 0° (*c* 1.0 in CH_3Cl); lit:[167] mp 78°C, $[\alpha]_D$ -1° (*c* 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.33 (3H, t, SCH_2CH_3), 2.76 (2H, m, SCH_2CH_3), 3.37 (1H, ddd, $J_{4,5}$ = 9.8 Hz, $J_{5,6a}$ = 4.7 Hz, $J_{5,6b}$ = 2.7 Hz, H-5), 3.41 (1H, dd, $J_{1,2+2,3}$ = 18.5 Hz, H-2), 3.58 (1H, t, $J_{3,4+4,5}$ = 19.9 Hz, H-4), 3.70 (1H, dd, $J_{5,6a}$ = 4.7 Hz, $J_{6a,6b}$ = 11.9 Hz, H-6a), 3.71 (1H, t, $J_{2,3+3,4}$ = 17.5 Hz, H-3), 3.87 (1H, dd, $J_{5,6b}$ = 2.7 Hz, $J_{6a,6b}$ = 11.9 Hz, H-6b), 4.50 (1H, d, $J_{1,2}$ = 9.9 Hz, H-1), 4.65 (1H, d, *J* = 10.8 Hz, C*H*HC_6H_5), 4.75 (1H, d, *J* = 10.1 Hz, C*H*HC_6H_5), 4.86 (1H, d, *J* = 10.8 Hz, CH*H*C_6H_5), 4.87 (1H, d, *J* = 11.0 Hz, C*H*HC_6H_5), 4.91 (1H, d, *J* = 10.1 Hz, CH*H*C_6H_5), 4.93 (1H, d, *J* = 11.0 Hz, CH*H*C_6H_5), 7.20-7.50 (15H, m, Ar). Anal. Calcd for $C_{29}H_{34}O_{15}S$: C, 70.42; H, 6.93. Found: C, 70.42; H, 6.91. α-isomer **(37)**: mp 64°C, $[\alpha]_D^{20}$ 110° (*c* 1.0 in CH_3Cl); lit:[168] mp 61-63.5°C, $[\alpha]_D$ 111° (*c*

1.0 in CH_3Cl); ^{13}C NMR ($CDCl_3$): δ 14.7 (SCH_2CH_3), 23.7 (SCH_2CH_3), 61.9 (C-6), 71.1 (C-5), 72.4, 75.0, 75.6 ($3CH_2C_6H_5$) 77.3 (C-4), 79.7 (C-2), 82.4 (C-3), 83.0 (C-1) 127.6-138.7 (Ar). ^1H NMR ($CDCl_3$): δ 1.28 (3H, t, SCH_2CH_3), 2.54 (2H, m, SCH_2CH_3), 3.54 (1H, t, $J_{3,4+4,5}$ = 18.6 Hz, H-4), 3.70-3.82 (3H, m, H-6a, H-6b, H-2), 3.89 (1H, t, $J_{2,3+3,4}$ = 18.5 Hz, H-3), 4.08 (1H, dt, $J_{4,5+5,6a+5,6b}$ = 16.5 Hz, H-5), 4.65 (1H, d, J = 11.0 Hz, $CHHC_6H_5$), 4.67 (1H, d, J = 11.5 Hz, $CHHC_6H_5$), 4.74 (1H, d, J = 11.5 Hz, $CHHC_6H_5$), 4.79 (1H, d, J = 10.9 Hz, $CHHC_6H_5$), 4.89 (1H, d, J = 11.0 Hz, $CHHC_6H_5$), 4.97 (1H, d, J = 10.9 Hz, $CHHC_6H_5$), 5.35 (1H, d, $J_{1,2}$ = 5.4 Hz, H-1), 7.20-7.50 (15H, m, Ar). Anal. Calcd for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93. Found: C, 70.41; H, 6.92.

Ethyl 2,3,4-Tri-O-benzyl-6-O-(2,3,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (43). The product was purified by column chromatography with hexane-ethyl acetate (1.5:1) as eluant, R_f=0.31. $[\alpha]_D^{21}$ 14.0° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 15.9 (SCH_2CH_3), 20.5, 20.8 ($COCH_3$), 24.8 (SCH_2CH_3), 54.6 (C-2'), 62.1 (C-6'), 68.6 (C-6), 69.0 (C-4'), 70.9 (C-3'), 71.9 (C-5'), 74.8, 75.4, 75.6 ($3CH_2C_6H_5$), 78.0 (C-2 or 4), 78.4 (C-5), 81.7 (C-2 or 4), 84.6 [$^1J(^{13}C,^1H)$ 154 Hz, (C-1)], 86.4 (C-3), 97.9 [$^1J(^{13}C,^1H)$ 166 Hz, (C-1')], 123.0-139.0 (Ar), 169.3, 170.2, 170.5 ($3COCH_3$). ^1H NMR ($CDCl_3$): δ 1.17 (3H, t, SCH_2CH_3), 1.85, 2.03, 2.06 (9H, 3s, $3COCH_3$), 2.54 (2H, m, SCH_2CH_3), 3.30 (2H, m, H-2, H-4), 3.40 (1H, m, H-5), 3.58 (1H, t, $J_{2,3+3,4}$ = 17.5 Hz, H-3), 3.62 (1H, dd, $J_{5,6b}$ = 6.1 Hz, $J_{6a,6b}$ = 10.6 Hz, H-6b), 3.84 (1H, ddd, $J_{4',5'}$ = 10.1 Hz, $J_{5',6a'}$ = 2.3 Hz, $J_{5',6b'}$ = 4.5 Hz, H-5'), 4.06 (1H, dd, $J_{5,6a}$ = 1.4 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6a), 4.16 (1H, dd, $J_{5',6a'}$ = 2.3 Hz, $J_{6a',6b'}$ = 12.1 Hz, H-6a'), 4.31 (1H, dd, $J_{5',6b'}$ = 4.5 Hz, $J_{6a',6b'}$ = 12.1 Hz, H-6b'), 4.35 (1H, t, $J_{1',2'+2',3'}$ = 21.7 Hz, H-2'), 4.36 (1H, d, J = 10.9 Hz,

C*H*HC$_6$H$_5$), 4.37 (1H, d, $J_{1,2}$ = 9.7 Hz, H-1), 4.62 (1H, d, J = 10.9 Hz, CH*H*C$_6$H$_5$), 4.67 (1H, d, J = 10.2 Hz, C*H*HC$_6$H$_5$), 4.74 (1H, d, J = 11.0 Hz, C*H*HC$_6$H$_5$), 4.76 (2H, d, 2CH*H*C$_6$H$_5$), 5.18 (1H, t, $J_{3',4'+4',5'}$ = 19.2 Hz, H-4'), 5.44 (1H, d, $J_{1',2'}$ = 8.5 Hz, H-1'), 5.76 (1H, dd, $J_{2',3'+3',4'}$ = 19.7 Hz, H-3'), 7.11-7.76 (19H, m, Ar); Anal. Calcd for $C_{49}H_{53}O_{15}NS$: C, 64.53; H, 5.86; N, 1.54. Found: C, 64.40; H, 5.92; N, 1.47.

Ethyl 2,3,4-Tri-O-benzyl-6-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-1-thio-α-D-glucopyranoside (44). The product was purified by column chromatography with toluene-ethyl acetate (8:1) as eluant, R_f=0.34. $[\alpha]_D^{21}$ 44.0° (*c* 0.5 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 14.6 (SCH_2CH_3), 17.3 (C-6'), 20.6, 20.75, 20.8 ($3COCH_3$), 23.5, (SCH_2CH_3), 66.3 (C-5'), 66.8 (C-6), 69.0 (C-3'), 69.7 (C-2'), 70.3 (C-5), 71.1 (C-4'), 72.3, 75.0, 75.7 ($3CH_2C_6H_5$), 77.8 (C-4), 79.7 (C-2), 82.5 (C-1, C-3), 97.7 [$^1J(^{13}C,^1H)$ 172 Hz, (C-1')], 127.6-138.6 (Ar), 169.7, 169.91, 169.94 ($3COCH_3$).^{1}H NMR ($CDCl_3$): δ 1.18 (3H, d, $J_{5',6'}$ = 6.2 Hz, H-6'), 1.31 (3H, t, SCH_2CH_3), 1.98, 2.05, 2.14 (9H, 3s, $3COCH_3$), 2.58 (2H, m, SCH_2CH_3), 3.40 (1H, dd, $J_{3,4+4,5}$ = 18.8 Hz, H-4), 3.52 (1H, dd, $J_{5,6a}$ = 6.4 Hz, $J_{6a,6b}$ = 10.7 Hz, H-6a), 3.83 (1H, dd, $J_{1,2}$ = 5.4 Hz, $J_{2,3}$ = 9.2 Hz, H-2), 3.83-3.94 (3H, m, H-3, H-6b, H-5'), 4.25 (1H, ddd, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 6.4 Hz, $J_{5,6b}$ = 1.5 Hz, H-5), 4.56 (1H, d, J = 11.2 Hz, C*H*HC$_6$H$_5$), 4.65 (1H, d, $J_{1',2'}$ = 1.7 Hz, H-1'), 4.66 (1H, d, J = 11.5 Hz, C*H*HC$_6$H$_5$), 4.75 (1H, d, J = 11.5 Hz, CH*H*C$_6$H$_5$), 4.77 (1H, d, J = 10.8 Hz, C*H*HC$_6$H$_5$), 4.91 (1H, d, J = 11.2 Hz, CH*H*C$_6$H$_5$), 4.97 (1H, d, J = 10.8 Hz, CH*H*C$_6$H$_5$), 5.05 (1H, t, $J_{3',4'+4',5'}$ = 19.8 Hz, H-4'), 5.22 (1H, dd, $J_{1',2'}$ = 1.7 Hz, $J_{2',3'}$ = 3.5 Hz, H-2'), 5.26 (1H, dd, $J_{2',3'}$ = 3.5 Hz, $J_{3',4'}$ = 10.0 Hz, H-3'), 5.39 (1H, d, $J_{1,2}$ = 5.4 Hz, H-1), 7.10-7.50 (15H, m, Ar); Anal. Calcd for $C_{41}H_{50}O_{12}S$: C, 64.21; H, 6.57; Found: C, 64.40;

H, 6.80.

Ethyl 2,3,6-Tri-O-benzyl-4-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-1-thio-β-D-glucopyranoside (45). The product was purified by column chromatography with hexane-ethyl acetate (2.5:1) as eluant, R_f=0.39. $[\alpha]_D^{21}$ 1.0° (*c* 0.9 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 15.1 (SCH_2CH_3), 16.9 (C-6'), 20.6 ($COCH_3$), 24.7 (SCH_2CH_3), 66.7 (C-5'), 68.6 (C-6), 69.1 (C-3'), 70.1 (C-2'), 70.9 (C-4'), 73.0 ($CH_2C_6H_5$), 74.7 (C-4), 75.3 ($CH_2C_6H_5$), 75.6 ($CH_2C_6H_5$), 79.0 (C-5), 82.0 (C-2), 84.5 (C-3), 85.0 (C-1), 97.1 (C-1'). ^1H NMR ($CDCl_3$): δ 1.32 (3H, t, SCH_2CH_3), 1.94, 1.99, 2.07 (9H, 3s, $3COCH_3$), 2.75 (2H, m, SCH_2CH_3), 3.41 (1H, m, H-5), 3.51 (1H, t, $J_{1,2+2,3}$ = 18.3 Hz, H-2), 3.59 (1H, t, $J_{2,3+3,4}$ = 17.8 Hz, H-3), 3.69-3.78 (2H, m, H-6a, H-6b), 3.94 (1H, t, $J_{3,4+4,5}$ = 18.6 Hz, H-4), 4.03 (1H, m, H-5'), 4.46 (1H, d, $J_{1,2}$ = 9.4 Hz, H-1), 4.55 (2H, AB pattern, $CH_2C_6H_5$), 4.70 (1H, d, *J* = 10.0 Hz, $CHHC_6H_5$), 4.77 (1H, d, *J* = 11.3 Hz, $CHHC_6H_5$), 4.93 (1H, d, *J* = 10.0 Hz, $CHHC_6H_5$), 4.96 (1H, t, $J_{3',4'+4',5'}$ = 19.9 Hz, H-4'), 5.01 (1H, d, $J_{1',2'}$ = 1.7 Hz, H-1'), 5.08 (1H, d, *J* = 11.3 Hz, $CHHC_6H_5$), 5.16 (1H, dd, $J_{1',2'}$ = 1.7 Hz, $J_{2',3'}$ = 3.5 Hz, H-2'), 5.23 (1H, dd, $J_{2',3'}$ = 3.5 Hz, $J_{3',4'}$ = 10.0 Hz, H-3'), 7.20-7.40 (15H, m, Ar); Anal. Calcd for $C_{41}H_{50}O_{12}S$: C, 64.21; H, 6.57; Found: C, 64.16; H, 6.54.

Ethyl 2,3,4-Tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α,β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (46,47). The product was purified by column chromatography with hexane-ethyl acetate (4:1) as eluant, R_f=0.4, to give a 2.5:1 α/β mixture. ^{13}C NMR ($CDCl_3$), α-isomer **46**: δ 15.1 (SCH_2CH_3), 25.0 (SCH_2CH_3), 65.8 (C-6), 72.3, 73.4, 74.9, 75.0, 75.4 ($5CH_2C_6H_5$), 75.5 ($2CH_2C_6H_5$), 79.0 (C-5), 81.7 (C-3'), 81.9 (C-2), 85.0 (C-1),

97.1 (C-1'), 68.9, 70.2, 77.7, 77.8, 80.2, 86.6 (C-3, C-4, C-2', C-4', C-5', C-6'), 127.5-138.7 (Ar). ^{1}H NMR ($CDCl_3$), α-isomer **46**: δ 1.26 (3H, t, SCH_2CH_3), 2.69 (2H, m, SCH_2CH_3), 3.19 (1H, dd, $J_{1,2+2,3}$ = 18.2 Hz, H-2), 3.48 (1H, m, H-5), 3.59 (1H, dd, $J_{1',2'}$ = 3.3 Hz, $J_{2',3'}$ = 9.7 Hz, H-2'), 3.60-3.74 (5H, m, H-3, H-4', H-6a', H-4, H-6b'), 3.86 (1H, m, H-5'), 3.98 (1H, t, $J_{2',3'+3',4'}$ = 18.6 Hz, H-3'), 4.42-4.50 (3H, m, H-1, $2CHHC_6H_5$), 4.57 (1H, d, J = 10.2 Hz, $CHHC_6H_5$), 4.63 (1H, d, J = 12.0 Hz, $CHHC_6H_5$), 4.67 (1H, d, J = 11.0 Hz, $CHHC_6H_5$), 4.71-4.92 (8H, m, $3CHHC_6H_5$, $5CHHC_6H_5$), 4.98 (1H, d, J = 10.8 Hz, $CHHC_6H_5$), 5.07 (1H, d, $J_{1',2'}$ = 2.3 Hz, H-1'), 7.1-7.5 (35H, m, Ar); Anal. Calcd for $C_{63}H_{68}O_{10}S$: C, 74.38; H, 6.74; Found (α : β mixture) : C, 74.18; H, 6.98.

Phenyl 4,6-O-Benzylidene-2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside (48). A freshly prepared solution of sodium methoxide in methanol (0.3 N, 3.5 mL) was added to a solution of phenyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside **(5)** (6.0 g, 10.4 mmol) in dry methanol (50 mL). The reaction mixture was stirred for 2 h at pH 11. Upon completion, the reaction was adjusted to a pH of 5 with Amberlyst 15 ion-exchange resin. The reaction mixture was filtered, concentrated, and dried under vacuum. The residue was dissolved in dry *N,N*-dimethylformamide (45 mL) and α,α-dimethoxytoluene (4.1 mL, 27.4 mmol) and *p*-toluenesulfonic acid were added. The reaction mixture was heated at approximately 60°C for 4 h, cooled to room temperature, diluted with CH_2Cl_2, and washed twice with aqueous sodium hydrogen carbonate. The organic extracts were dried over magnesium sulfate and concentrated to give a syrup that was purified by column chromatography with hexane-ethyl acetate (1.6:1) as eluant; R_f=0.4. The *title compound* was obtained as a foam (5.3 g, 95%); $[\alpha]_D^{23}$ 27.0° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR

($CDCl_3$): δ 56.8 (C-2), 68.5 (C-6), 69.7 (C-3), 71.4 (C-5), 80.1 [$^1J(^{13}C,^1H)$ 163 Hz, (C-1)], 81.9 (C-4), 101.9 ($OCHC_6H_5$), 123.0-138.0 (Ar). ^1H NMR ($CDCl_3$): δ 3.57 (1H, t, $J_{3,4+4,5}$ = 18.3 Hz, H-4), 3.67 (1H, dt, $J_{4,5+5,6a}$ = 19.5 Hz, $J_{5,6b}$ = 4.7 Hz, H-5), 3.79 (1H, t, $J_{5,6a+6a,6b}$ = 20.1 Hz, H-6a), 4.38 (1H, t, $J_{1,2+2,3}$ = 20.5 Hz, H-2), 4.40 (1H, dd, $J_{5,6b}$ = 4.7 Hz, $J_{6a,6b}$ = 10.2 Hz, H-6b), 4.61 (1H, dd, $J_{2,3+3,4}$ = 19.0 Hz, H-3), 5.55 (1H, s, $OCHC_6H_5$), 5.85 (1H, d, $J_{1,2}$ = 10.5 Hz, $^2J_{H\text{-}Se}$ = 13.3 Hz, H-1), 7.0-8.0 (14H, m, Ar); Anal. Calcd for $C_{27}H_{23}O_6NSe$: C, 60.68; H, 4.32; N, 2.61. Found: C, 60.45; H, 4.21; N, 2.72.

Phenyl 2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside (52) and the open phthalimido compound (52). Freshly prepared sodium methoxide solution in methanol (0.2 N, 13 mL) was added to phenyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside **(5)**. (1.6 g, 2.8 mmol). The reaction mixture was stirred overnight, neutralized with Amberlyst 15 ion-exchange resin, filtered, and concentrated. Two products were formed, as indicated by TLC. The less polar component **(51)** was purified by column chromatography with hexane-ethyl acetate-methanol (4:4:1) as eluant; R_f = 0.4; (0.65 g, 48%); ^1H NMR ($CDCl_3$): δ 3.50 (1H, m, H-5), 3.62 (1H, t, $J_{3,4+4,5}$ = 18.0 Hz, H-4), 3.82 (1H, dd, $J_{5.6a}$ = 3.8 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 3.90 (1H, dd, $J_{5,6b}$ = 3.2 Hz, $J_{6b,6a}$ = 12.0 Hz, H-6b), 4.23 (1H, $_AJ$ = 20.6 Hz, H-2/3), 4.32 (1H, $_AJ$ = 28.8 Hz, H-3/2), 5.79 (1H, d, $J_{1,2}$ = 10. 1 Hz, H-1), 7.1-7.9 (9H, m, Ar). The more polar component **(52)** was purified by column chromatography with ethyl acetate-methanol-water (6:3:1) as eluant; R_f = 0.5; (0.34 g, 25%). ^1H NMR (D_2O): δ 3.45-3.55 (2H, m, H-5, H-2), 3.67-3.77 (2H, m, H-6a, H-3/4), 3.85-3.99 (2H, m, H-6b, H-4/3), 5.17 (1H, d, $J_{1,2}$ = 10.5 Hz, H-1), 7.20-7.80 (9H, m, Ar). Compound **(52)** was dissolved in pyridine and acetic anhydride, and the

reaction mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature, poured into cold water, and extracted with CH_2Cl_2. The organic layer was washed successively with HCl (2N) and aqueous sodium hydrogen carbonate. The organic extracts were dried over magnesium sulfate and concentrated to give a syrup. The ^1H NMR of the product indicated that it was compound **(5)**.

Phenyl 4,6-O-Benzylidene-1-seleno-β-D-glucopyranoside (54). Phenyl 2,3,4,6-tetra-O-acetyl-1-seleno-β-D-glucopyranoside **(4)** (2.0 g, 4.1 mmol) was dissolved in methanol (25 mL) and ammonia was bubbled through the solution periodically, until deacetylation was complete. The solvent was evaporated, the dry deacetylated sugar was dissolved in freshly distilled *N,N*-dimethylformamide (8 mL) and α,α-dimethoxytoluene (1.2 mL, 8.0 mmol) and *p*-toluenesulfonic acid (0.15 g, 0.79 mmol) were added. The reaction mixture was heated under N_2 for 2 h. The reaction mixture was cooled, extracted into dichloromethane, and washed successively with sodium hydrogen carbonate (15 mL) and water (15 mL). The organic extracts were dried over sodium sulfate and concentrated. The dried residue was dissolved in ethyl acetate and excess hexane was added, resulting in the precipitation of the desired compound. The precipitate was filtered and dried and the above procedure was repeated to yield the *title compound* as a white solid (1.67 g, 96%), $[\alpha]_D^{21}$ -43.3° (*c* 0.67 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 68.6 (C-6), 71.7 (C-4 or 5), 73.3 (C-2), 74.5 (C-3), 80.3 (C-5 or 4), 85.0 (C-1), 101.9 ($OCHC_6H_5$), 126.3-136.9 (Ar). ^1H NMR ($CDCl_3$): δ 3.40-3.54 (3H, m, H-2, H-5, H-4), 3.76 (1H, t, $J_{5,6a+6a,6b}$ = 20.0 Hz, H-6a), 3.82 (1H, t, $J_{2,3+3,4}$ = 17.0 Hz, H-3), 4.38 (1H, dd, $J_{5,6b}$ = 4.3 Hz, $J_{6a,6b}$ = 10.4 Hz, H-6b), 4.83 (1H, d, $J_{1,2}$ = 9.9 Hz, $^2J_{H,Se}$ = 20.6 Hz, H-1), 5.50 (1H, s, $OCHC_6H_5$),

7.2-7.7 (10H, m, Ar); Anal. Calcd for $C_{19}H_{20}O_5Se$: C, 56.03; H, 4.95. Found: C, 56.00; H, 5.03.

Phenyl 2,3-Di-O-benzyl-4,6-O-benzylidene-1-seleno-β-D-glucopyranoside (55). Phenyl 4,6-O-benzylidene-1-seleno-β-D-glucopyranoside **(54)** was dissolved in dry, freshly distilled *N,N*-dimethylformamide (15 mL) and the solution was added slowly to a stirred suspension of sodium hydride (0.43 g, 10.9 mmol) in DMF (5 mL) at 0°C. Benzyl bromide (1.3 mL, 11.3 mmol) was then added dropwise. The reaction mixture was stirred overnight under nitrogen. On completion of the reaction, as indicated by TLC, excess sodium hydride was decomposed by the addition of methanol. The reaction was poured into water and the desired compound was extracted into ethyl acetate (3x15 mL), dried over magnesium sulfate and concentrated. The resulting syrup was dried thoroughly under vacuum and the remaining solid was crystallized from hexane-ethyl acetate (10:1) to afford the *title compound* as fluffy white crystals (1.2 g). The mother liquor was purified by column chromatography with hexane-ethyl acetate (10:1) as eluant, R_f=0.35. The desired product was obtained as a solid (0.24 g), overall yield (1.44 g, 91%); mp 135.5°C, $[\alpha]_D^{26}$ -43.5° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 68.7 (C-6), 71.4 (C-5), 75.3, 75.7 ($2CH_2C_6H_5$) 81.1 (C-2), 81.6 (C-4), 83.2 (C-3), 83.7 [$^1J(^{13}C,^1H)$ 157 Hz, (C-1)], 101.2 ($OCHC_6H_5$), 126.0-138.3 (Ar). ^1H NMR ($CDCl_3$): δ 3.46 (1H, dt, $J_{4,5+5,6a}$ = 19.2 Hz, $J_{5,6b}$ = 4.8 Hz, H-5), 3.53 (1H, dd, $J_{1,2+2,3}$ = 18.0 Hz, H-2), 3.68 (1H, t, $J_{3,4+4,5}$ = 18.8 Hz, H-4), 3.79 (1H, t, $J_{5,6a+6a,6b}$ = 20.0 Hz, H-6a), 3.82 (1H, t, $J_{2,3+3,4}$ = 18.0 Hz, H-3), 4.40 (1H, dd, $J_{5,6b}$ = 4.9 Hz, $J_{6a,6b}$ = 11.2 Hz, H-6b), 4.77 (1H, d, *J* = 11.0 Hz, $CHHC_6H_5$), 4.82 (2H, AB pattern, $CH_2C_6H_5$), 4.93 (1H, d, $J_{1,2}$ = 9.2 Hz, H-1), 4.93 (1H, d, *J* = 11.0 Hz, $CHHC_6H_5$), 5.50 (1H,

OC*H*C_6H_5), 7.20-7.70 (20H, m, Ar); Anal. Calcd for $C_{33}H_{32}O_5Se$: C, 67.46; H, 5.49. Found: C, 67.52; H, 5.54.

Phenyl 2,3,6-Tri-O-benzyl-1-seleno-β-D-glucopyranoside (49) Hydrogen chloride in diethyl ether was added to phenyl 2,3-di-O-benzyl-4,6-O-benzylidene-1-seleno-β-D-glucopyranoside **(55)** (1.2 g, 2.0 mmol) and $NaCNBH_3$ (0.88 g, 14.0 mmol) in THF (40 mL) containing 4A° molecular sieves at 0°C until the reaction mixture was acidic. The reaction was then stirred under N_2 at 0°C. After 1.5 h the starting material had almost completely reacted, as determined by TLC. The reaction mixture was poured into ice cold water and extracted into CH_2Cl_2. The combined organic extracts were washed with sodium hydrogen carbonate, dried over magnesium sulfate and concentrated. Column chromatography of the resulting syrup with hexane-ethyl acetate (4:1) as eluant (R_f=0.30) afforded the desired compound as a solid (1.1 g, 92%); $[\alpha]_D^{21}$ -43.0° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 70.4 (C-6), 71.7 (C-4), 73.7, 75.1, 75.4 (3*C*$H_2C_6H_5$) 79.2 (C-5), 81.1 (C-2), 83.2 [$^1J(^{13}C,^1H)$ 157 Hz, (C-1)], 86.3 (C-3) 127.7-138.5 (Ar).^1H NMR ($CDCl_3$): δ 3.47 (1H, m, H-5), 3.50 (1H, dd, $J_{1,2+2,3}$ = 18.2 Hz, H-2), 3.53 (1H, t, $J_{2,3+3,4}$ = 17.0 Hz, H-3), 3.66 (1H, t, $J_{3,4+4,5}$ = 19.0 Hz, H-4), 3.77 (2H, d, H-6a, H-6b), 4.55 (1H, d, *J* = 12.0 Hz, C*H*HC_6H_5), 4.60 (1H, d, *J* = 12.0 Hz, CH*H*C_6H_5), 4.73 (1H, d, *J* = 10.4 Hz, C*H*HC_6H_5), 4.79 (1H, d, *J* = 11.4 Hz, C*H*HC_6H_5), 4.87 (1H, d, *J* = 10.4 Hz, CH*H*C_6H_5) 4.88 (1H, d, $J_{1,2}$ = 8.5 Hz, H-1), 4.92 (1H, d, *J* = 11.4 Hz, CH*H*C_6H_5), 7.10-7.60 (20H, m, Ar); Anal. Calcd for $C_{33}H_{34}O_5Se$: C, 67.23; H, 5.81 Found: C, 67.46; H, 6.07.

Phenyl 2,3-O-isopropylidene-1-seleno-α-L-rhamnopyranoside (57). Ammonia was periodically bubbled through a solution of phenyl 2,3,4-tri-O-

acetyl-1-seleno-α-L-rhamnopyranoside **(1)** (2.1 g, 4.9 mmol) in anhydrous methanol (3 mL), while stirring under N_2 for 2 h. The solvent was evaporated and the residue was dried in vacuo. Dimethoxypropane (8 mL, 65.1 mmol) and *p*-toluenesulfonic acid (150 mg, 0.8 mmol) were added to the above residue. The reaction was stirred under N_2 for 4 h and neutralized with Et_3N. The solution was concentrated to afford a syrup that was purified by column chromatography with hexane-ethyl acetate (3:1) as eluant, R_f=0.36. The product was crystallized from hexane-ethyl acetate to afford white crystals of the *title compound* (1.5 g, 87%). mp = 87°C, $[\alpha]_D^{20}$ -247° (*c* 1 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 17.0 (C-6), 26.5 (*C*H3), 28.2 (*C*H3), 68.8 (C-5), 75.3 (C-4), 77.4 (C-2), 78.4 (C-4), 80.9 [$^1J(^{13}C,^1H)$ 170 Hz, (C-1)], 109.9 (O*C*O). 127.9-134.3 (Ar). ^1H NMR ($CDCl_3$): δ 1.24 (3H, d, $J_{5,6}$ = 6.1 Hz, H-6), 1.35, 1.52 (2H, s, CH_3), 2.25 (1H, bd, O*H*), 3.49 (1H, bt, $J_{3,4+4,5}$ = 18.3 Hz, H-4), 3.99 (1H, m, H-5), 4.11 (1H, dd, $J_{2,3}$ = 5.4 Hz, $J_{3,4}$ = 7.6 Hz, H-3), 4.45 (1H, d, $J_{2,3}$ = 5.4 Hz, H-2), 6.01 (1H, s, H-1), 7.20-7.65 (5H, m, Ar); Anal. Calcd for $C_{15}H_{20}O_4Se$: C, 52.48; H, 5.87. Found: C, 52.41; H, 5.20.

Phenyl 4-O-benzyl-1-seleno-α-L-rhamnopyranoside (58). Phenyl 2,3-O-isopropylidene-1-seleno-α-L-rhamnopyranoside **(57)** (0.5 g, 1.5 mmol) was dissolved in dry, freshly distilled *N,N*-dimethylformamide (2.5 mL) and the solution was slowly added to a stirred suspension of sodium hydride (0.12 g, 3.0 mmol) in DMF (4.5 mL) at 0°C. Benzyl bromide (0.35 mL, 3.0 mmol) was then added dropwise. The reaction mixture was stirred overnight under nitrogen. On completion of the reaction, as indicated by TLC, excess NaH was decomposed by the addition of MeOH. The reaction mixture was poured into water and the desired compound was extracted with ethyl acetate, dried over magnesium

sulfate, and concentrated. The resulting residue was dissolved in ethanol (8 mL) containing 0.1M HCl (4 mL) and refluxed for 2.5 h. On complete hydrolysis of the acetal the reaction mixture was neutralized with solid potassium hydrogen carbonate, filtered and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate and concentrated. The residue was purified by column chromatography with hexane-ethyl acetate (2:1) as eluant, R_f=0.3. The product was crystallized from EtOH (100%) to yield fluffy white crystals of the *title compound* (0.46 g, 81%). mp = 118.5°C, $[\alpha]_D^{20}$ -265° (*c* 0.75 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 17.7 (C-6), 70.4 (C-5), 72.0 (C-3), 73.1 (C-2), 4.76 ($CH_2C_6H_5$), 81.6 (C-4), 85.3 [$^1J(^{13}C,^1H)$ 168 Hz, (C-1)], 127.6-133.7 (Ar). ^1H NMR ($CDCl_3$): δ 1.38 (3H, d, $J_{5,6}$ = 6.2 Hz, H-6), 2.12 (bs, 2O*H*), 3.43 (1H, t, $J_{3,4+4,5}$ =18.6 Hz, H-4), 4.11 (1H, dd, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 9.1 Hz, H-3), 4.10 (1H, m, H-5), 4.27 (1H, dd, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 3.4 Hz, H-2), 4.76 (2H, AB pattern, $CH_2C_6H_5$), 5.74 (1H, d, $J_{1,2}$ = 1.3 Hz, H-1), 7.26-7.58 (10H, m, Ar); Anal. Calcd for $C_{19}H_{22}O_4Se$: C, 58.02; H, 5.64. Found: C, 58.18; H, 5.52.

Methyl 3-O-Benzoyl-4-O-benzyl-6-deoxy-2-phenylseleno-β-L-glucopyranoside (61) To a solution of phenyl 4-O-benzyl-1-seleno-α-L-rhamnopyranoside **(59)** (0.28 g, 0.71 mmol) in *N,N*-dimethylformamide (1 mL) were added trimethyl orthobenzoate (0.3 mL, 1.8 mmol), and *p*-toluenesulfonicacid (5.0 mg, 0.03 mmol). The reaction was stirred under N_2 overnight. On complete reaction of the diol, the reaction mixture was neutralized with Et_3N and concentrated. The mixture was washed with water and extracted into dichloromethane. The organic extracts were dried over magnesium sulfate and concentrated. The residue was purified by column chromatography with hexane-ethyl acetate (5:1) as eluant, R_f=0.33. The product was crystallized from

EtOH (100%) to yield white crystals of the *title compound* (0.26g, 72%). mp = 120.5°C, $[\alpha]_D^{20}$ -48.5° (*c* 1 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 17.9 (C-6), 48.2 (C-2), 56.9 (OCH_3), 71.0 (C-5), 74.9 (C-3), 75.1 ($CH_2C_6H_5$), 83.2 (C-4), 102.9 [$^1J(^{13}C,^1H)$ 161 Hz, (C-1)], 127.8-137.3 (Ar), 165.7 (COC_6H_5). ^1H NMR ($CDCl_3$): δ 1.32 (3H, d, $J_{5,6}$ = 6.0 Hz, H-6), 3.14 (1H, dd, $J_{1,2}$ = 9.0 Hz, $J_{2,3}$ = 11.3 Hz, H-2), 3.32 (1H, t, $J_{3,4+4,5}$ = 17.8 Hz, H-4), 3.38 (1H, m, H-5), 3.51 (3H, s, OCH_3), 4.11 (1H, d, $J_{1,2}$ = 9.0 Hz, H-1), 4.63 (2H, AB pattern, $CH_2C_6H_5$), 5.45 (1H, dd, $J_{2,3}$ = 11.3 Hz, $J_{3,4}$ = 8.5 Hz, H-3), (15, m, Ar); Anal. Calcd for $C_{27}H_{28}O_5Se$: C, 63.40; H, 5.52. Found: C, 63.44; H, 5.50.

Phenyl 4,6-O-Benzylidene-2-deoxy-2-phthalimido-3-O-(3,4,6-tri-O-acetyl-2 deoxy-2-phthalimido-β-D-glucopyranosyl)-1-seleno-β-D-glucopyranoside (63).

1. Preparation from the bromide (62). A mixture of silver trifluoromethanesulfonate (0.28 g, 1.1 mmol), collidine (0.15 mL, 1.0 mmol) and dry 4A° molecular sieves in anhydrous dichloromethane (2 mL) was stirred under N_2 for 1.5 h. The mixture was cooled to 0°C and a solution of phenyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside **(48)** (0.15 g, 0.26 mmol) in CH_2Cl_2 (1.5 mL) was added by means of a cannula, under N_2. The flask was rinsed with additional portions of CH_2Cl_2 (3x0.5 mL). The reaction mixture was stirred for 1 h and checked by TLC to confirm that no reaction had yet occurred. The reaction mixture was cooled to -78°C and a solution of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide **(62)**[90] (0.41 g, 0.8 mmol) in CH_2Cl_2 (2 mL), cooled to -78°C was added dropwise. The flask was rinsed with additional portions of CH_2Cl_2 (3x0.5 mL) and the dropping funnel was also rinsed with CH_2Cl_2 (2x1.5 mL). After 24 h the reaction mixture

was filtered through celite, concentrated, and washed successively with hydrochloric acid (1N) and aqueous sodium hydrogen carbonate. The organic extracts were dried over magnesium sulfate and concentrated to give a foam that was chromatographed with hexane-ethyl acetate (1:1.5) as eluant; R_f = 0.29. The *title compound* **(63)** was obtained as a white foam (0.15 g, 60%). It was crystallized from hexane-ethyl acetate.

2. Preparation from the trichloroacetimidate (67). A mixture of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate **(67)**[106] (0.20 g, 0.3 mmol), phenyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside **(48)** and 4A° molecular sieves in anhydrous dichloromethane (4 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78°C and triethylsilyl triflate (0.005 mL, 0.024 mmol) was added. A TLC after 20 min indicated that the reaction was almost complete. After 1.5 h the reaction mixture was neutralized with triethylamine, filtered through celite, and concentrated. The resulting syrup was chromatographed with hexane-ethyl acetate (1:1.5) as eluant; R_f=0.29. The *title compound* **(63)** was isolated as a foam (0.27 g, 90%). It was crystallized from hexane-ethyl acetate; mp 272°C, $[\alpha]_D^{22}$ 56.0° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.2, 20.5, 20.7 (3*C*OCH3), 55.0(C-2'), 55.6 (C-2), 61.4 (C-6'), 68.5 (C-4'), 68.6 (C-6), 70.9 (C-3'), 71.6, 71.7 (C-5, C-5'), 76.2 (C-3), 80.3 (C-1), 80.7 (C-4), 97.4 (C-1'), 101.7 (O*C*HC_6H_5), 123.3-137.1 (Ar), 169.2, 170.0, 170.6 (3*C*OCH3). ^1H NMR ($CDCl_3$): δ 1.68, 1.89, 2.01 (9H, 3s, 3COCH_3), 3.35 (1H, m, H-5'), 3.65 (1H, dt, $J_{5,6}$ = 4.7 Hz, $J_{4,5+5,6}$ = 19.3 Hz, H-5), 3.74-3.84 (3H, m, H-4, H-6a, H-6a'), 3.93 (1H, dd, $J_{5',6b'}$ = 3.5 Hz, $J_{6a',6b'}$ = 12.2 Hz, H-6b'), 4.13 (1H, dd, $J_{1',2'+2',3'}$ = 19.0 Hz, H-2'), 4.34 (1H, dd, $J_{5,6b}$ = 4.7 Hz, $J_{6a,6b}$ = 10.6 Hz, H-6b), 4.36 (1H, $J_{1,2+2,3}$ = 20.3 Hz, H-2), 4.75 (1H, dd, $J_{2,3+3,4}$ = 18.5 Hz, H-3),

5.04 (1H, dd, $J_{3',4'+4',5'}$ = 19.3 Hz, H-4'), 5.45 (1H, dd, $J_{2',3'+3',4'}$ = 19.7 Hz, H-3'), 5.50 (1H, $J_{1',2'}$ = 8.5 Hz, H-1'), 5.57 (1H, s, OC*H*C_6H_5), 5.59 (1H, d, $J_{1,2}$ = 11.0 Hz, H-1), 7.0 - 7.9 (18H, m, Ar); Anal. Calcd for $C_{47}H_{42}O_{15}N_2Se$: C, 59.19; H, 4.44; N, 2.94. Found: C, 59.18; H, 4.61; N, 2.81.

Phenyl 2,3,6-Tri-O-benzyl-4-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-1-seleno-β-D-glucopyranoside. (64).

1. Preparation from the bromide (62). A mixture of silver trifluoromethanesulfonate (0.25 g, 1.0 mmol), collidine (0.14 mL, 1.0 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (2 mL) was stirred under N_2 for 1.5 h. The mixture was cooled to 0°C and a solution of phenyl 2,3,6-tri-O-benzyl-1-seleno-β-D-glucopyranoside **(49)** (0.15 g, 0.25 mmol) in CH_2Cl_2 (1.5ml) was added by means of a cannula, under N_2. The flask was rinsed with additional portions of CH_2Cl_2 (3x0.5 mL). The reaction mixture was stirred for 1h and checked by TLC to confirm that no reaction had yet occurred. The reaction mixture was cooled to -78°C and a solution of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide **(62)**[90] (0.39 g, 0.8 mmol) in CH_2Cl_2 (1.5 mL), cooled to -78°C was added dropwise. The flask was rinsed with additional portions of CH_2Cl_2 (3x0.5 mL) and the dropping funnel was also rinsed with CH_2Cl_2 (2x1 mL). The reaction mixture was stirred for 36 h, filtered through celite, and washed successively with hydrochloric acid (1N, 2x7 mL) and aqueous sodium hydrogen carbonate. The organic extracts were dried over magnesium sulfate and concentrated to give a syrup that was chromatographed with toluene-ethyl acetate (5:1) as eluant; R_f= 0.32. The *title compound* **(64)** was obtained as a white foam (0.15g, 60%).

2. Preparation from trichloroacetimidate (67). A mixture of 3,4,6-tri-O-acetyl-

2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate **(67)**[106] (0.13 g, 0.2 mmol), phenyl 2,3,6-tri-O-benzyl-1-seleno-β-D-glucopyranoside **(49)** and 4A° molecular sieves in anhydrous CH_2Cl_2 (3 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78°C and triethylsilyl triflate (0.003 mL, 0.013 mmol) was added. A TLC after 15 min indicated that the reaction was almost complete. After 1.5 h the reaction mixture was neutralized with triethylamine, filtered through celite and concentrated. The resulting syrup was chromatographed with hexane-ethyl acetate (2:1) as eluant; R_f=0.32. The *title compound* **(64)** was isolated as a foam (0.14 g, 84%). $[\alpha]_D^{22}$ -23° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.3, 20.6 (*C*OCH3), 55.4 (C-2'), 61.5 (C-6'), 68.2 (C-6), 68.8 (C-4'), 70.8 (C-3'), 71.8 (C-5'), 72.8, 74.8, 75.2 (3*C*$H_2C_6H_5$), 75.2 (C-4), 79.5 (C-5), 81.1 (C-2), 82.9 (C-1), 84.9 (C-3), 97.3 (C-1'), 123.6-139.0 (Ar), 169.4, 170.0, 170.6 (3*C*OCH_3). ^1H NMR ($CDCl_3$): δ 1.82, 1.95, 1.98 (9H, 3s, 3COC*H*$_3$), 3.23 (1H, ddd, $J_{4,5}$ = 9.8 Hz, $J_{5,6a}$ = 3.7 Hz, $J_{5,6b}$ = 1.0 Hz, H-5), 3.38-3.49 (3H, m, H-6a, H-5', H-2), 3.54 (1H, dd, $J_{5,6b}$ = 1.0 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6b), 3.59 (1H, t, $J_{3,4+4,5}$ = 17.5 Hz, H-3), 3.78 (1H, dd, $J_{5',6a'}$ = 2.1 Hz, $J_{6a',6b'}$ = 12.4 Hz, H-6a'), 4.08 (2H, m, H-4, H-6b'), 4.26 (1H, dd, $J_{1',2'+2',3'}$ = 19.0 Hz, H-2'), 4.40 (2H, AB pattern, C*H*$_2C_6H_5$), 4.61 (1H, d, *J* = 10.0 Hz, C*H*HC_6H_5), 4.71 (1H, d, $J_{1,2}$ = 9.7 Hz, H-1), 4.72 (1H, d, *J* = 10.0 Hz, CH*H*C_6H_5), 4.80 (1H, d, *J* = 11.5 Hz, C*H*HC_6H_5), 5.05 (1H, d, *J* = 11.5 Hz, CH*H*C_6H_5), 5.11 (1H, t, $J_{3',4'+4',5'}$ = 19.2 Hz, H-4'), 5.61 (1H, d, $J_{1',2'}$ = 8.5 Hz, H-1'), 5.73 (1H, dd, $J_{2',3'+3',4'}$ = 19.7 Hz, H-3'), 7.1-7.9 (24H, m, Ar); Anal. Calcd for $C_{53}H_{53}O_{14}NSe$: C, 63.17; H, 5.31; N, 1.39. Found: C, 63.28; H, 5.32; N, 1.19.

3,4-Di-*O*-acetyl-1,2-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranos-6-yl)-β-L-rhamnopyranose orthoacetate (65) A mixture of the selenoglycoside **(1)** (0.13 g 0.3 mmol), glycosyl acceptor **(16)** (0.12 g 0.3 mmol) 2,6-di-*tert*-butyl-4-methylpyridine (0.18 g, 0.9 mmol) and 4Å molecular sieves was dried under vacuum overnight. Anhydrous dichloromethane (8 mL) was added and the reaction mixture was stirred under N_2 for 1 h. Silver triflate (0.23 g, 0.9 mmol) was added. On completion of the reaction in 1.5 h, as indicated by TLC, the reaction mixture was filtered through celite and washed with water (2x10 mL). The organic layer was dried over magnesium sulfate, concentrated, and the resulting residue was purifed by column chromatography with hexane-ethyl acetate (1.6:1) as eluant, R_f=0.35. A mixture of the orthoester **(65)** and the disaccharide **(31)** was isolated in a combined yield of 93% (0.17 g, **65:31**=7:1, 81% of **65**, 12% of **31**). ^{13}C NMR ($CDCl_3$): δ 17.4 (C-6), 20.7 ($2COCH_3$), 25.4 (CCH_3), 55.1 (OCH_3), 60.8 (C-6'), 69.1 (C-5), 69.4 (C-5'), 70.7, 70.3 (C-3, C-4), 75.7, 74.8, 73.3 ($3CH_2C_6H_5$), 76.7 (C-2), 77.6 (C-4'), 79.9 (C-2'), 82.0 (C-3'), 97.2 (C-1), 98.1 (C-1'), 124.4 (OCO), 127.5-138.8 (Ar), 169.6, 170.3 ($2COCH_3$); ^1H NMR ($CDCl_3$): δ 1.26 (3H, d, $J_{5',6'}$ = 6.0 Hz, H-6), 1.75 (3H, s, CCH_3), 2.02, 2.06 (6H, 2s, $2COCH_3$), 3.37 (3H, s, OCH_3), 3.37 (1H, s, OCH_3), 3.47 (1H, m, H-5), 3.50-3.58 (2H, m, H-2', 4'), 3.65 (1H, dd, $J_{5',6a'}$ = 1.7 Hz, $J_{6a',6b'}$ = 9.9 Hz, H-6a'), 3.72 (1H, m, H-5'),), 3.78 (1H, dd, $J_{5',6b'}$ = 3.8 Hz, $J_{6a',6b'}$ = 9.9 Hz, H-6b'), 3.97 (1H, t, $J_{1,2+2,3}$ = 18.4 Hz, H-3'), 3.54 (1H, t, $J_{1,2+2,3}$ = 5.0 Hz, H-2), 4.61 (1H, d, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.29 (1H, d, $J_{1,2}$ = 2.3 Hz, H-1), 7.20-7.40 (15H, Ar); Anal. Calcd for $C_{40}H_{48}O_{13}$: C, 65.21; H, 6.57; Found: C, 65.42; H, 6.69.

Ethyl 2,3,4-Tri-O-benzyl-6-O-(4,6-O-benzylidene-2-deoxy-2-phthalimido-3-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (68). A mixture of phenyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-3-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-1-seleno-β-D-glucopyranoside **(63)** (0.13 g, 0.13 mmol), ethyl 2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranoside **(36)** (0.05 g, 0.10 mmol) and 4A° molecular sieves was dried under vacuum overnight. Anhydrous dichloromethane (8 mL) was added and the reaction mixture was stirred under N_2 for 1 h. Dry potassium carbonate (0.55 g, 3.9 mmol) was added followed by silver triflate (0.2 g, 0.78 mmol). On completion of the reaction (1.5 h), as indicated by TLC, the reaction mixture was filtered through celite and washed with water (2x10 mL). The organic layer was dried over magnesium sulfate, concentrated, and the resulting residue was purifed by column chromatography with hexane-ethyl acetate (1:1.2) as eluant, R_f=0.34. The *title compound* **(68)** was isolated as a foam (0.10 g, 81%). $[\alpha]_D^{22}$ 8.0° (*c* 0.6 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 15.1 ($SCH_2\mathit{C}H_3$), 20.2, 20.5, 20.7 ($3CO\mathit{C}H_3$), 24.4 ($S\mathit{C}H_2CH_3$), 59.9 (C-2"), 55.3 (C-2'), 61.4 (C-6"), 66.3 (C-5'), 68.0 (C-6), 68.5 (C-4"), 68.8 (C-6'), 71.0 (C-3"), 71.6 (C-5"), 74.7, 75.2, 75.3, 75.5 ($3\mathit{C}H_2C_6H_5$, C-3'), 77.8 (C-4), 78.3 (C-2), 80.8 (C-4'), 81.5 (C-5), 84.4 (C-1), 86.4 (C-3), 97.3 (C-1"), 98.4 (C-1'), 101.7 ($O\mathit{C}HC_6H_5$), 123.3-138.5 (Ar), 169.2, 170.0, 170.6 ($3\mathit{C}OCH_3$). ^1H NMR ($CDCl_3$): δ 1.18 (3H, t, $SCH_2C\mathit{H}_3$), 1.17, 1.90, 2.03 (9H, 3s, $3COC\mathit{H}_3$), 2.49 (2H, m, $SC\mathit{H}_2CH_3$), 3.15-3.28 (2H, m, H-4, H-2, H-5), 3.29 (1H, m, H-5"), 3.47 (1H, dd, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6a), 3.50 (1H, t, $J_{2,3+3,4}$ = 17.0 Hz, H-3), 3.57 (1H, dt, $J_{4',5'+5',6a'}$ = 19.2 Hz, $J_{5',6b'}$ = 4.6 Hz, H-5'), 3.75-3.86 (3H, m, H-4', H-6a", H-6a'), 3.90 (1H, dd, $J_{5,6b}$ = 1.2 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6b), 3.96 (1H, dd, $J_{5",6b"}$ = 3.2 Hz, $J_{6a",6b"}$ = 12.0 Hz,

H-6b"), 4.15 (1H, dd, $J_{1",2"+2",3"}$ = 19.0 Hz, H-2"), 4.21 (1H, d, J = 11.0 Hz, C*H*HC$_6$H$_5$), 4.24 (1H, dd, $J_{1',2'+2',3'}$ = 18.7 Hz, H-2'), 4.27 (1H, d, $J_{1,2}$ = 9.7 Hz, H-1), 4.30 (1H, dd, $J_{5',6b'}$ = 4.5 Hz, $J_{6a',6b'}$ = 10.0 Hz, H-6b'), 4.50 (1H, d, J = 10.5 Hz, C*H*HC$_6$H$_5$), 4.64 (1H, d, J = 10.0 Hz, C*H*HC$_6$H$_5$), 4.69 (1H, d, J = 11.0 Hz, CH*H*C$_6$H$_5$), 4.77 (1H, dd, $J_{2',3'+3',4'}$ = 19.5 Hz, H-3'), 4.81 (2H, 2d, 2CH*H*C$_6$H$_5$), 5.05 (1H, d, $J_{1',2'}$ = 8.5 Hz, H-1'), 5.06 (1H, t, $J_{3",4"+4",5"}$ = 18.0 Hz, H-4"), 5.47 (1H, t, $J_{2",3"+3",4"}$ = 19.6 Hz, H-3"), 5.51 (1H, d, $J_{1",2"}$ = 8.2 Hz, H-1"), 5.59 (1H, s, OC*H*C$_6$H$_5$), 7.0-7.5 (28H, m, Ar); Anal. Calcd for $C_{70}H_{70}O_{20}N_2S$: C, 65.12; H, 5.46; N, 2.17. Found: C, 65.16; H, 5.56; N, 2.04.

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (66).[169] Phenyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside **(5)** (0.07 g. 0.1 mmol) was dissolved in dichloromethane (5 mL) and the reaction mixture was stirred under nitrogen for 15 min. Silver triflate (0.19 g, 0.7 mmol) was then added followed by water (0.005 mL, 0.3 mmol). After 1.5 h the reaction mixture was quenched with excess K_2CO_3 and filtered through celite. The filtrate was evaporated and the resulting residue was chromatographed with hexane-ethyl acetate (1:1.6) as eluant, *Rf*=0.4. The *title compound* was isolated as a powder (0.46 g, 87 %); the physical and ^{1}H NMR spectroscopic data matched those reported in the literature[169]. ^{1}H NMR ($CDCl_3$): δ 1.88, 2.03, 2.13 (3s, 9H, 3COC*H*$_3$), 3.94 (1H, ddd, $J_{4,5}$ = 10.1 Hz, $J_{5,6a}$ = 2.2 Hz, $J_{5,6b}$ = 4.6 Hz, H-5), 4.19 (1H, dd, $J_{5.6a}$ = 2.2 Hz, $J_{6a,6b}$ = 10.3 Hz, H-6a), 4.24-4.33 (2H, m, H-6b, H-2), 5.18 (1H, dd, $J_{3,4+4,5}$ = 19.1 Hz, H-4), 5.63 (1H, d, $J_{1,2}$ = 8.4 Hz, H-1), 5.86 (1H, t, $J_{2,3+3,4}$ = 19.7 Hz, H-3), 7.7-8.0 (9H, m, Ar);^{13}C NMR ($CDCl_3$): δ 20.4, 20.6, 20.7 (3CO*C*H$_3$), 56.2 (C-2), 62.1 (C-6), 69.1 (C-4), 70.6 (C-3), 72.2 (C-5), 92.7 (C-1), 123.7-134.3 (Ar), 167.8, 169.5, 170.0, 170.7 (5*C*O).

5.3. EXPERIMENTAL SECTION FOR CHAPTER III

Typical Experimental Procedure for BAHA-mediated glycosylations with phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside (1) in dichloromethane or acetonitrile. A mixture of phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside **(1)** (87 mg, 0.2 mmol) and acceptor and 4Å molecular sieves were stirred in anhydrous solvent (4 mL) under N_2 for 1 h. BAHA was added and the reaction mixture was stirred until completion. The reaction mixture was cooled to 0°C and neutralized with Et_3N. The mixture was filtered through celite with dichloromethane. The filtrate was concentrated and purified by column chromatography with hexane-ethyl acetate as eluant.

Typical Experimental Procedure for BAHA-mediated glycosylations with Phenyl 2,3,4,6-Tetra-O-benzyl-1-seleno-β-D-glucopyranoside (10) and Ethyl 2,3,4,6-Tetra-O-benzyl-1-thio-β-D-glucopyranoside (80) in dichloromethane or acetonitrile. A mixture of phenyl 2,3,4,6-tetra-O-benzyl-1-seleno-β-D-glucopyranoside **(10)** or ethyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside **(80)** (0.1 mmol) and acceptor (0.08 mmol) and 4Å molecular sieves were stirred in anhydrous solvent (2 mL) under N_2 for 1 h. BAHA (0.15 mmol) was added and the reaction mixture was stirred until completion. The reaction mixture was cooled to 0°C and neutralized with Et_3N The mixture was filtered through celite with dichloromethane. The filtrate was concentrated and purified by column chromatography with hexane-ethyl acetate as eluant.

Methyl 2,3,4-Tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)-β-D-glucopyranoside (69, 70).[170] The product was purified

by column chromatography with hexane-ethyl acetate (3:1) as eluant, [R_f = 0.4] to give an α/β mixture. The pure β-isomer was fractionally crystallized from the mixture. ^{13}C NMR ($CDCl_3$), α-isomer **69**: δ 97.2 (C-1'), 97.8 (C-1), ^1H NMR ($CDCl_3$), δ 3.35 (3H, s, OCH_3), 3.44 (1H, dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 3.5-3.9 (9H, H-4, 5, 6a, 6b, 2', 4', 5', 6a', 6b"), 3.95 (1H, t, $J_{2',3'+3',4'}$ = 19.0 Hz, H-3'), 3.98 (1H, t, $J_{2,3+3,4}$ = 18.6 Hz, H-3), 4.54 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.97 (1H, d, $J_{1',2'}$ = 3.0 Hz, H-1'), 4.37-4.95 (14 H, C$H_2C_6H_5$), 7.0-7.5 (35H, m, Ar). β-isomer **70**: mp 133°C, $[\alpha]_D^{20}$ 18.0° (*c* 1.0 in $CHCl_3$); lit[170a] mp 130-131.5°C, $[\alpha]_D^{20}$ 17.1° (*c* 1.0 in $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 55.4 (O*C*H3), 98.1 [$^1J(^{13}C,^1H)$ 169 Hz, (C-1)], 103.9 [$^1J(^{13}C,^1H)$ 159 Hz, (C-1)], ^1H NMR ($CDCl_3$,: δ 3.34 (3H, s, OCH_3), 3.45 (1H, m, H-5), 3.48-3.78 (8H, H-2, 4, 6a, 2', 3', 4', 6a' 6b'), 3.85 (1H, m, H-5), 4.01 (1H, t, $J_{2,3+3,4}$ = 18.3 Hz, H-3), 4.21 (1H, dd, $J_{5,6b}$ = 1.5 Hz, $J_{6a,6b}$ = 10.6 Hz, H-6b), 4.37 (1H, d, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.50-5.04 (14 H, 7C$H_2C_6H_5$), 4.62 (1H, d, $J_{1,2}$ = 3.1 Hz, H-1), 7.0-7.5 (35H, m, Ar).

2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyl chloride (71).[171] ^1H NMR ($CDCl_3$): δ 1.26 (3H, d, $J_{5,6}$ = 6.3 Hz, H-6), 2.02, 2.06, 2.16 (9H, 3s, 3COCH_3), 4.16 (1H, m, H-5), 5.13 (1H, t, $J_{3,4+4,5}$ = 20.0 Hz, H-4), 5.38 (1H, dd, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 3.3 Hz, H-2), 5.55 (1H, dd, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 10.2 Hz, H-3), 5.93 (1H, d, $J_{1,2}$ = 1.8 Hz, H-1).

Methyl 2,3,4-Tri-O-acetyl-α-L-rhamnopyranoside (72).[171] ^1H NMR ($CDCl_3$): δ 1.21 (3H, d, $J_{5,6}$ = 6.2 Hz, H-6), 1.96, 2.02, 2.13 (9H, 3s, 3COCH_3), 3.36 (3H, s, OCH_3), 3.85 (1H, m, H-5), 4.61 (1H, d, $J_{1,2}$ = 1.6 Hz, H-1), 5.05 (1H, t, $J_{3,4+4,5}$ = 19.8 Hz, H-4), 5.21 (1H, dd, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 3.4 Hz, H-2), 5.26

(1H, dd, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 10.9 Hz, H-3).

Methyl 3,4-Di-O-acetyl-α-L-rhamnopyranoside (73).[172] ^{1}H NMR ($CDCl_3$): δ 1.18 (3H, d, $J_{5,6}$ = 6.2 Hz, H-6), 2.02, 2.08 (9H, 3s, 3COCH_3), 3.37 (3H, s, OCH_3), 3.82 (1H, m, H-5), 4.66 (1H, d, $J_{1,2}$ = 1.5 Hz, H-1), 4.01 (1H, dd, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 4.83 (1H, t, $J_{3,4+4,5}$ = 19.8 Hz, H-4), 5.15 (1H, dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 10.3 Hz, H-3).

Methyl 2,3,6-Tri-O-benzoyl-α-D-glucopyranoside (74).[173] Methyl-α-D-glucopyranoside **(22)** (1.5 g, 7.7 mmol) was treated with pyridine (40 mL) and the reaction mixture was cooled to -60°C. Benzoyl chloride (5 mL, 43 mmol) was added dropwise. The reaction mixture was warmed up slightly when it stopped stirring and was subsequently recooled. After 3 h the starting material had completely reacted, as determined by TLC. The reaction mixture was quenched with excess methanol and warmed up to room temperature. The reaction mixture was washed successively with H_2O, HCl (2N), and $NaHCO_3$. The organic extracts were dried over magnesium sulfate and concentrated. The resulting syrup was purified by column chromatography with toluene-ethyl acetate (8:1) as eluant [R_f = 0.32] to afford the *title compound* **(74)** as a foam (2.5 g, 64%); $[\alpha]_D^{21}$ 146.0° (*c* 1.0 in CH_2Cl_2), lit[173]: $[\alpha]_D^{20}$ 144.0° (*c* 1.0 in CH_3Cl); ^{1}H NMR ($CDCl_3$): δ 3.36 (1H, d, $J_{4,OH}$ = 4.8 Hz, O*H*), 3.45 (3H, s, OCH_3), 3.87 (1H, dt, $J_{3,4+4,5}$ = 19.0 Hz, $J_{4,OH}$ = 4.8 Hz, H-4), 5.14 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 5.27 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 5.78 (1H, dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 7.20-8.20 (15H, m, Ar).

Methyl 2,3,6-Tri-O-benzyl-α-D-glucopyranoside (76).[174] Hydrogen chloride in

diethyl ether was added to methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside **(25)** (1.2 g, 2.6 mmol) and $NaCNBH_3$ (0.11 g, 1.8 mmol) in THF (30 mL) containing 4Å molecular sieves until the reaction mixture was acidic. The reaction mixture was stirred under N_2 for 15 min. The reaction mixture was poured into ice cold water and extracted into CH_2Cl_2. The combined organic extracts were washed with sodium hydrogen carbonate, dried over magnesium sulfate and concentrated. Column chromatography of the resulting syrup with hexane-ethyl acetate (2.3:1) as eluant [R_f = 0.34] afforded the desired compound as a syrup (0.9 g, 75%); $[\alpha]_D^{21}$ 11.0° (*c* 1.0 in CH_2Cl_2), lit[174]: $[\alpha]_D^{20}$ 11.0° (*c* 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.39 (3H, s, OCH_3), 3.50 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.66 (1H, t, $J_{3,4+4,5}$ = 18.1 Hz, H-4), 3.65-3.74 (3H, H-5, 6a, 6b), 3.79 (1H, t, $J_{2,3+3,4}$ = 18.4 Hz, H-3), 4.56 (2H, AB pattern, $CH_2C_6H_5$), 4.63 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.66 (1H, d, *J* = 12.0 Hz, $CHHC_6H_5$), 4.74 (1H, d, *J* = 11.5 Hz, $CHHC_6H_5$), 4.77 (1H, d, *J* = 12.0 Hz, $CHHC_6H_5$), 5.0 (1H, d, *J* = 11.5 Hz, $CHHC_6H_5$), 7.10-7.50 (15H, m, Ar).

Methyl 2,3,6-Tri-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-α,β-D-glucopyranosyl)-α-D-glucopyranoside (77, 78).[175] The product was purified by column chromatography with hexane-ethyl acetate (4.5:1) as eluant, [R_f of **77** and **78** = 0.4, R_f of recovered **76** = 0.2], to give a 1:1 α/β mixture of disaccharides (43 mg, 50%), and **76** (18 mg, 43%). ^{13}C NMR ($CDCl_3$), α-isomer **77**: δ 96.4 (C-1'), 105.1 (C-1). ^{13}C NMR ($CDCl_3$), β-isomer **78**: δ 102.2 (C-1'), 105.1 (C-1).

Methyl 2,3,6-Tri-O-benzyl-4-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-D-glucopyranoside (79). The product was purified by column chromatography

with hexane-ethyl acetate (2:1) as eluant, [R_f of disaccharide **79** = 0.25, R_f of acceptor **76** = 0.33], to give the disaccharide **79** as a syrup (53 mg, 73%), and **76** (10 mg, 20%). The yield based on unreacted **76** is 91%. $[\alpha]_D^{22}$ 32° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 17.0 (C-6'), 20.6, 20.7 ($3COCH_3$), 55.2 (OCH_3), 66.7 (C-5'), 68.6 (C-5), 69.1 (C-6), 69.9 (C-3'), 70.2 (C-2'), 71.1 (C-4), 73.2 ($2CH_2C_6H_5$), 75.1 (C-3), 75.3 ($CH_2C_6H_5$), 79.8 (C-3), 80.5 (C-2), 97.2 (C-1'), 97.9 (C-1), 127.2-137.9 (Ar); ^1H NMR ($CDCl_3$): δ 1.17 (3H, d, $J_{5',6'}$ = 6.0 Hz, H-6'), 1.98, 1.99, 2.06 (9H, 3s, $3COCH_3$), 3.36 (3H, s, OCH_3), 3.58 (1H, dd, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.2 Hz, H-2), 3.65 (1H, dd, $J_{5,6a}$ = 2.8 Hz, $J_{6a,6b}$ = 9.2 Hz, H-6a), 3.70-3.77 (2H, m, H-4, H-6), 3.82-3.94 (2H, m, H-3, H-5), 4.04 (1H, m, H-5'), 4.51 (2H, AB pattern, $CH_2C_6H_5$), 4.58 (1H, d, $J_{1,2}$ = 3.8 Hz, H-1), 4.60 (1H, d, *J* = 12.0 Hz, $CHHC_6H_5$), 4.69-4.76 (2H, $CHHC_6H_5$), 4.95 (1H, d, $J_{1',2'}$ = 1.8 Hz, H-1'), 4.98 (1H, t, $J_{3',4'+4',5'}$ = 20.0 Hz, H-4'), 5.11 (1H, d, *J* = 11.0 Hz, $CHHC_6H_5$), 5.15 (1H, dd, $J_{1',2'}$ = 1.8 Hz, $J_{2',3'}$ = 3.3 Hz, H-2'), 5.25 (1H, dd, $J_{2',3'}$ = 3.3 Hz, $J_{3',4'}$ = 10.1 Hz, H-3'), 7.30-7.50 (15H, Ar); Anal. Calcd for $C_{40}H_{48}O_{13}$: C, 65.21; H, 6.57; Found: C, 65.11; H, 6.69.

Typical Experimental Procedure for BAHA-mediated glycosylations with Phenyl 2,3,4-Tri-O-acetyl-1-seleno-α-L-rhamnopyranoside (1) in dichloromethane or acetonitrile in the presence of the quencher. A mixture of phenyl 2,3,4-tri-O-acetyl-1-seleno-α-L-rhamnopyranoside **(1)** (87 mg, 0.2 mmol), methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside **(16)** (46 mg, 0.1 mmol), 1,2,4,5-tetramethoxybenzene (240 mg, 1.2 mmol) and 4Å molecular sieves were stirred in anhydrous solvent (4 mL) under N_2 for 1 h. BAHA (245 mg, 0.3 mmol) was added and the reaction mixture was stirred under N_2 for as long as the corresponding experiment in the absence of the quencher. The reaction mixture

was cooled to 0°C and neutralized with Et_3N. The mixture was filtered through celite with dichloromethane. The filtrate was concentrated and purified by column chromatography with hexane-ethyl acetate as eluant.

Typical Experimental Procedure for BAHA-mediated glycosylations with Phenyl 2,3,4,6-Tetra-O-benzyl-1-seleno-β-D-glucopyranoside (10) and Ethyl 2,3,4,6-Tetra-O-benzyl-1-thio-β-D-glucopyranoside (80) in dichloromethane or acetonitrile in the presence of the quencher. A mixture of phenyl 2,3,4,6-tetra-O-benzyl-1-seleno-β-D-glucopyranoside **(10)** or ethyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside **(80)** (0.1 mmol) and methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside **(16)** (40 mg, 0.08 mmol), 1,2,4,5-tetramethoxybenzene (115 mg, 0.6 mmol) and 4Å molecular sieves were stirred in anhydrous solvent (2 mL) under N_2 for 1 h. BAHA (115 mg, 0.15 mmol) was added and the reaction mixture was stirred under N_2 for as long as the corresponding experiment in the absence of the quencher. The reaction mixture was cooled to 0°C and neutralized with Et_3N. The mixture was filtered through celite with dichloromethane. The filtrate was concentrated and purified by column chromatography with hexane-ethyl acetate as eluant.

5.4. EXPERIMENTAL SECTION FOR CHAPTER IV

Phenyl 2,3,4,6-Tetra-O-acetyl-1-seleno-5-thio-α, β-D-glucopyranoside (87,88). A mixture of diphenyl diselenide (1.9 g, 6.1 mmol) and 50% hypophosphorous acid (19 mL) was refluxed under nitrogen with vigorous stirring until the mixture was colourless (4 h). The reaction mixture was cooled and anhydrous dichloromethane (10 mL) was added. The solution of

phenylselenol in CH_2Cl_2 was transferred under N_2 into a round bottom flask containing water by means of a syringe. The reaction mixture was rinsed with additional portions of CH_2Cl_2 (2x5 mL) which were transferred as above. After shaking the organic layer with water, it was syringed into a round bottom flask containing magnesium sulfate, under N_2. The water layer was rinsed with CH_2Cl_2 (10 mL) and the CH_2Cl_2 layer transferred as above. The dried phenylselenol solution was then added to a mixture of 1,2,3,4,6-penta-O-acetyl-5-thio-α,β-D-glucopyranoside **(89)** (1.7 g, 4.2 mmol) with a syringe. The magnesium sulfate was washed with CH_2Cl_2 (2x5 mL) and the washings were transferred to the reaction mixture. The reaction mixture was cooled to -78°C, $BF_3.OEt_2$ (0.55 mL, 4.5 mmol) was added slowly and the reaction mixture was allowed to warm to room temperature. After 36 h the reaction mixture was neutralized with Et_3N and washed with water (2x15 mL) and saturated aqueous sodium hydrogen carbonate. The organic layer was dried over magnesium sulfate and concentrated to give a syrup which was chromatographed with hexane-ethyl acetate (2:1) as eluant. [R_f α-isomer **87** = 0.3, β-isomer **88** = 0.28]. The products were obtained as powders and crystallized from ethanol (1.8 g, 85%). (α : 0.93 g, 43%; β : 0.87 g, 42%). α-isomer **(87)** mp = 117° C, $[\alpha]_D^{21}$ = 288° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.5 ($4COCH_3$), 41.2 (C-5), 45.8 (C-6), 61.2 (C-1), 71.9 (C-2), 72.3 (C-4), 75.3 (C-3), 128.0-135.8 (Ar), 169.5, 169.8, 170.4 ($4COCH_3$); ^1H NMR ($CDCl_3$): δ 1.80, 2.00, 2.01, 2.05 (12H, 4s, $4COCH_3$), 3.70 (1H, m, H-5), 4.06 (1H, dd, $J_{5,6a}$ = 3.1 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.34 (1H, dd, $J_{5,6b}$ = 5.7 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 4.85 (1H, d, $J_{1,2}$ = 4.6 Hz, H-1), 5.18 (1H, dd, $J_{1,2}$ = 4.6 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 5.18 (1H, dd, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 10.8 Hz, H-4), 5.53 (1H, t, $J_{2,3+3,4}$ = 19.5 Hz , H-3), 7.2-7.5 (5H, m, Ar); Anal. Calcd for $C_{20}H_{24}O_9SSe$: C, 47.72; H, 4.81. Found: C,

47.60; H, 4.89. β-isomer **(88)** $[\alpha]_D^{22}$ = 10° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.4, 20.5, 20.6 (4COCH$_3$), 42.4 (C-5), 45.9 (C-1), 61.2 (C-6), 71.8 (C-4), 74.2 (C-2), 74.6 (C-3), 126.4-135.7 (Ar), 169.2, 169.3, 169.6, 170.4 (4*C*OCH$_3$); ^1H NMR ($CDCl_3$): δ 1.98, 2.00, 2.04, 2.06 (12H, 4s, 4COC*H*$_3$), 3.20 (1H, ddd, $J_{4,5}$ = 10.8 Hz, $J_{5,6a}$ = 3.4 Hz, $J_{5,6b}$ = 5.2 Hz, H-5), 4.01 (1H, d, $J_{1,2}$ = 10.8 Hz, $J_{1,Se}$ = 13.6 Hz, H-1), 4.06 (1H, dd, $J_{5,6a}$ = 3.4 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.18 (1H, dd, $J_{5,6b}$ = 5.2 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 5.01 (1H, t, $J_{2,3+3,4}$ = 19.1 Hz, H-3), 5.16 (1H, dd, $J_{1,2}$ = 10.8 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 5.22 (1H, dd, $J_{3,4}$ = 9.6 Hz, $J_{4,5}$ = 10.8 Hz, H-4), 7.1-7.6 (5H, m, Ar); Anal. Calcd for $C_{20}H_{24}O_9SSe$: C, 47.72; H, 4.81. Found: C, 47.62; H, 4.77.

Phenyl 1-Seleno-5-thio-α-D-glucopyranoside (81). A freshly prepared solution of sodium methoxide in methanol (0.2N, 1.5 mL) was added to **87** (60 mg, 1.19 mmol) and the mixture was stirred under nitrogen for 3 h. The solution was acidified to a pH of 3 with Rexyn (H^+) resin, and filtered. The filtrate was neutralized with Amberlite basic ion exchange resin, filtered and concentrated. The residue was purified by column chromatography (silica gel) with hexane-dichloromethane-methanol (3:1:1) as eluant, [R_f = 0.4]. The *title compound* was obtained as a powder (34 mg, 85%) and was crystallized from ethanol. ^{13}C NMR (acetone d_6): δ 46.3 (C-5), 51.8 (C-1), 61.5 (C-6), 74.6 (C-4), 75.7 (C-2), 76.1 (C-3). ^1H NMR (D_2O): 3.27 (1H, dt, $J_{4',5'}$ = 10.3 Hz, $J_{5',6a'}$ = 3.1 Hz, $J_{5',6b'}$ = 5.6 Hz, H-5), 3.54 (1H, t, $J_{2,3+3,4}$ = 18.1 Hz, H-3), 3.61 (1H, t, $J_{3,4+4,5}$ = 19.2 Hz, H-4), 3.83 (1H, dd, $J_{5,6a}$ = 3.1 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 3.90 (1H, dd, $J_{5,6b}$ = 5.6 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 3.78 (1H, dd, $J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 9.3 Hz, H-2), 4.7 (1H, d, $J_{1,2}$ = 4.5 Hz, H-1). 7.3-7.7 (5H, Ar). ES-MS Calcd. for $C_{12}H_{16}O_4SSe$: $M^{+\bullet}$ 335; Found: 358 $(M+Na)^{+\bullet}$.

Methyl 2,3,4-Tri-O-benzyl-6-O-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (90).

1. Preparation from selenoglycoside (88). A mixture of phenyl 2,3,4,6-tetra-O-acetyl-1-seleno-5-thio-β-D-glucopyranoside **(88).** (0.05 g, 0.1 mmol), methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside **(16)** (0.05 g, 0.1 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (1 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and nitrosyl tetrafluoroborate (0.01 g, 0.1 mmol) was added. After 2 h at -78° C the reaction mixture was warmed to room temperature. A TLC indicated that the reaction was almost complete. The mixture was filtered through celite, concentrated and chromatographed with hexane-ethyl acetate (1.75:1) as eluant [R_f = 0.26]. The *title compound* was isolated as a syrup (0.1 g, 46%). Also isolated was methyl 2,3,4-tri-O-benzyl-6-O-acetyl-α-D-glucopyranoside **(92)** (23 mg, 45%). α-disaccharide **90**: $[\alpha]_D^{20}$ 150.9° (*c* 0.53 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.5, 20.53, 20.7 ($4COCH_3$), 38.3 (C-5'), 55.2 (OCH_3), 61.3 (C-6'), 66.5 (C-6), 70.4 (C-5), 70.8 (C-3'), 72.3 (C-4'), 73.1 ($CH_2C_6H_5$), 74.9 (C-2'), 75.0, 75.7 ($2CH_2C_6H_5$), 77.9 (C-4), 79.9, 80.0 (C-1', C-2, C-5'), 82.0 (C-3), 97.8 (C-1), 121.5-138.8 (Ar), 169.4, 169.6, 169.9, 170.5 ($4COCH_3$). ^1H NMR ($CDCl_3$): δ 1.93, 1.99, 2.01, 2.03 (12H, 4s, $4COCH_3$), 3.35-3.41 (1H, m, H-5), 3.38 (3H, s, OCH_3), 3.41 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.52 (1H, t, $J_{3,4+4,5}$ = 18.8 Hz, H-4), 3.72 (1H, dd, $J_{5,6a}$ = 1.2 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6a), 3.76 (1H, ddd, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 1.2 Hz, $J_{5,6b}$ = 4.5 Hz, H-5), 3.86 (1H, dd, $J_{5,6b}$ = 4.5 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6b), 3.98 (1H, t, $J_{2,3+3,4}$ = 18.7 Hz, H-3), 3.99 (1H, dd, $J_{5',6a'}$ = 3.0 Hz, $J_{6a',6b'}$ = 12.1 Hz, H-6a'), 4.32 (1H, dd, $J_{5',6b'}$ = 4.5 Hz, $J_{6a',6b'}$ = 12.1 Hz, H-6b'), 4.57 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.65 (1H, d, J = 11.0 Hz, $CHHC_6H_5$), 4.68 (1H, d, J = 12.0 Hz, $CHHC_6H_5$), 4.76 (1H, d, *J* = 12.0 Hz,

CH*H*C_6H_5), 4.82 (1H, d, J = 11.0 Hz, C*H*HC_6H_5), 4.91 (1H, d, J = 11.0 Hz, CH*H*C_6H_5), 4.98 (1H, d, J = 11.0 Hz, CH*H*C_6H_5), 5.0 (1H, d, $J_{1',2'}$ = 3.0 Hz, H-1'), 5.11 (1H, dd, $J_{1',2'}$ = 3.0 Hz, $J_{2',3'}$ = 10.1 Hz, H-2'), 5.27 (1H, dd, $J_{3',4'+4',5'}$ = 20.5 Hz, H-4'), 5.49 (1H, t, $J_{2',3'+3',4'}$ = 19.6 Hz, H-3'), 7.25-7.40 (15H, m, Ar); Anal. Calcd for $C_{42}H_{50}O_{14}S$: C, 62.2; H, 6.22. Found: C, 62.31; H, 6.31. **92**: ^{1}H NMR ($CDCl_3$): δ 2.02 (3H, s, COC*H*$_3$), 3.37 (3H, s, OC*H*$_3$), 3.48 (1H, t, $J_{2,3+3,4}$ = 19.0 Hz, H-3), 3.53 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.7 Hz, H-2), 3.81 (1H, m, H-5), 4.01 (1H, t, $J_{3,4+4,5}$ = 18.1 Hz, H-4), 4.20-4.30 (2H, H-6a, H-6b), 4.59 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.56, 4.66, 4.80, 4.83, 4.87, 5.06 (6H, 6d, 3C*H*$_2$$C_6H_5$), 7.2-7.5 (15H, Ar).

2. Preparation from the trichloroacetimidate (100). A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)** (0.18 g, 0.35 mmol), methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside **(16)** (0.13 g, 0.27 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (2 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.01 mL, 0.04 mmol) was added. The reaction mixture was stirred at -78° C for 2.5 h. An aliquot of the reaction mixture was taken and quenched with triethylamine. A TLC of this aliquot indicated that the reaction was almost complete. The reaction mixture was further treated with TESOTf (0.005 mL, 0.2 mmol) and the reaction mixture was warmed to room temperature. The reaction was quenched with triethylamine, filtered through celite, and concentrated to give a black syrup that was chromatographed with hexane- ethyl acetate (1.75:1) as eluant [R_f α-disaccharide **90** = 0.26; β-disaccharide **101** = 0.20]. (α-isomer **90**: 0.1 g, 46%, β-isomer **101**: 0.07 g, 34%).

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (93).

1. Preparation from selenoglycoside (87). A mixture of phenyl 2,3,4,6-tetra-O-acetyl-1-seleno-5-thio-α-D-glucopyranoside **(87).** (56 mg, 0.1 mmol), methyl-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside **(92)** (43 mg g, 0.1 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (1 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -30° C and nitrosyl tetrafluoroborate (14 mg g, 0.1 mmol) was added. The reaction was allowed to warm to 0° C in 2.5 h. A TLC indicated that the selenoglycoside **(87)** had completely reacted although acceptor **(92)** was still present. The mixture was filtered through celite, concentrated and chromatographed with hexane-ethyl acetate (1.25:1) as eluant [R_f = 0.34]. The *title compound* **(93)** was isolated as a syrup (18 mg, 22%). Also recovered was unreacted acceptor **(92)** (23 mg, 45%) and 1,3,4,6-tetra-O-acetyl-5-thio-α-D-glucopyranoside **(94)** (14 mg, 33%). α-disaccharide **93**: ^{13}C NMR ($CDCl_3$): δ 20.5, ($4COCH_3$), 37.9 (C-5'), 55.1 (OCH_3), 60.6 (C-6'), 62.3 (C-5), 69.0 (C-6), 71.0 (C-3'), 71.7 (C-4'), 75.0 (C-2), 75.4, 75.5 (C-2', $CH_2C_6H_5$), 76.3 (C-1'), 76.7 (C-3), 82.5 (C-4), 96.7 (C-1), 101.4 ($OCHC_6H_5$), 126.0-138.3 (Ar), 169.4, 170.3 ($4COCH_3$). ^1H NMR ($CDCl_3$): δ 1.99, 2.01, 2.02, 2.09 (12H, 4s, $4COCH_3$), 3.38 (3H, s, OCH_3), 3.44 (1H, m, H-5'), 3.60 (1H, dd, $J_{5',6a'}$ = 2.3 Hz, $J_{6a',6b'}$ = 12.3 Hz, H-6a'), 3.71 (1H, t, $J_{3,4+4,5}$ = 18.4 Hz, H-4), 3.76 (1H, t, $J_{5,6a + 6a,6b}$ = 20.5 Hz, H-6a), 3.84 (1H, dt, $J_{5,6b}$ = 4.3 Hz, $J_{4,5 + 5,6a}$ = 19.5 Hz, H-5), 3.96 (1H, dd, $J_{5',6b'}$ = 3.7 Hz, $J_{6a',6b'}$ = 12.3 Hz, H-6b'), 4.01 (1H, dd, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 10.1 Hz, H-2), 4.05 (1H, t, $J_{2,3+3,4}$ = 18.2 Hz, H-3), 4.29 (1H, dd, $J_{5,6b}$ = 4.3 Hz, $J_{6a,6b}$ = 9.5 Hz, H-6b), 4.72 (1H, d, J = 11.8 Hz, $CHHC_6H_5$), 4.77 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1), 4.97 (1H, d, J = 11.8 Hz, $CHHC_6H_5$), 5.01 (1H, dd, $J_{1',2'}$ = 2.9 Hz, $J_{2',3'}$ = 10.0

Hz, H-2'), 5.05 (1H, d, $J_{1',2'}$ = 2.8 Hz, H-1'), 5.24 (1H, dd, $J_{3',4'+4',5'}$ = 20.5 Hz, H-4'), 5.54 (1H, dd, $J_{2',3'+3',4'}$ = 19.6 Hz, H-3'), 5.6 (OC*H*C_6H_5), 7.2-7.5 (10H, m, Ar). Anal. Calcd for $C_{35}H_{42}O_{14}S$: C, 58.49; H, 5.89. Found: C, 58.21; H, 5.90. **94**: ^{1}H NMR ($CDCl_3$): δ 2.05, 2.06, 2.09, 2.2 (12H, 4s, 4COC*H*$_3$), 3.48 (1H, m, H-5), 4.03 (1H, dd, $J_{5,6a}$ = 3.0 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.06 (1H, dd, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 9.4 Hz, H-2), 4.36 (1H, dd, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 5.22 (1H, t, $J_{2,3+3,4}$ = 19.3 Hz , H-3), 5.31 (1H, dd, $J_{3,4+4,5}$ = 20.2 Hz, H-4), 5.98 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1).

2. Preparation from the trichloroacetimidate (100). A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)** (0.23 g, 0.4 mmol), methyl-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside **(92)** (0.19 g, 0.5 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (4 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.01 mL, 0.04 mmol) was added. The reaction mixture was stirred at -78° C for 2.5 h. An aliquot of the reaction mixture was taken and quenched with triethylamine. A TLC of this aliquot was performed and the presence of starting materials in addition to product was observed. The reaction mixture was further treated with TESOTf (0.01 mL, 0.40 mmol) and after 4 h the reaction mixture was quenched with triethylamine. The reaction mixture was then warmed to room temperature, filtered through celite, and concentrated to give a foam that was chromatographed with toluene- ethyl acetate (3.5:1) as eluant [R_f disaccharide **93** = 0.28; orthoester **119** =0.35]. A mixture of the α and β disaccharides was obtained (0.29 g, 90%, α-isomer **93**: 0.22 g, 68%, β-isomer **118** 0.07 g, 23%). Also isolated was the orthoester **119** (0.01 g, 3%). **118** ^{1}H NMR ($CDCl_3$): δ 4.82 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 5.03 (1H, d, $J_{1,2}$ = 9.1 Hz, H-1), 5.06 (1H, dd, $J_{1,2+2,3}$ = 16.3 Hz, H-2'), 5.30 (1H, dd, $J_{3,4+4,5}$ = 19.5 Hz, H-

4'), 5.40 (1H, t, $J_{2,3+3,4}$ = 17.0 Hz , H-3'), 5.55 (1H, s, OC*H*C_6H_5).

Methyl 2-O-(5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (85). Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (**93**).(47 mg, 0.7 mmol) was treated with 80% aqueous acetic acid (4 mL) and heated at 50° C for 4 h. The acetic acid was removed in vacuo, and the residue was dissolved in methanol (4 mL) and treated with ammonia until deacetylation was complete, as determined by TLC. The solution was concentrated and the residue was dissolved in ethanol (3 mL). Ethyl acetate (2 mL), acetic acid (7 mL) and Pd/C were added and the reaction mixture was stirred under an atmosphere of hydrogen at 52 psi overnight. A TLC indicated that no reaction had occurred. Excess Pd/C was added, the reaction mixture was stirred for another 48 h, and filtered through celite. The residue was purified by column chromatography with ethyl acetate-methanol-water as eluant [R_f = 0.3] to afford the *title compound* (24 mg, 60%). ^{13}C NMR (D_2O): δ 45.7 (C-5'), 57.8 (O*C*H_3), 62.9 (C-6'), 63.5 (C-6), 72.5 (C-4), 74.1 (C-3/3'), 74.4 (C-4'), 76.3 (C-5), 76.7 (C- 3/3'), 77.9, 78.1 (C-2, C-2'), 82.7 (C-1'), 98.9 (C-1), ^1H NMR (D_2O): δ 3.20 (1H, ddd, $J_{4',5'}$ = 10.5 Hz, $J_{5',6a'}$ = 3.1 Hz, $J_{5',6b'}$ = 5.4 Hz, H-5'), 3.40 (3H, s, OCH_3), 3.43 (1H, t, $J_{3,4+3,4}$ = 19.0 Hz, H-4), 3.58-3.66 (2H, m, H-4', H-5), 3.66-3.77 (4H, m, H-6b, H-6a, H-3, H-3'), 3.77-3.80 (3H, H-6a', H-2', H-2), 3.90 (1H, t, $J_{5',6b'}$ = 5.4, $J_{6a',6b'}$ = 11.8 Hz, H-6b'), 4.86 (1H, d, $J_{1,2}$ = 3.0 Hz, H-1'), 4.98 (1H, d, $J_{1',2'}$ = 3.2 Hz, H-1). For the deprotection of an α/β mixture of the disaccharides **93** and **118**, after removal of the benzylidene acetal with aqueous acetic acid, the residue was dried over magnesium sulfate, concentrated and treated with acetic anhydride and pyridine. After 24 h the solution was concentrated by cold distillation and purified by column

chromatography with hexane-ethyl acetate 2:1 as eluant [R_f α-isomer **122** = 0.3, β-isomer **121**= 0.28]. **122** ^{1}H NMR ($CDCl_3$): δ 1.97, 1.99, 2.0, 2.02 (12H, 4s, 4COCH_3), 2.1 (6H, s, 2COCH_3), 3.27 (1H, ddd, $J_{4',5'}$ = 11.0 Hz, $J_{5',6a'}$ = 2.6 Hz, $J_{5',6b'}$ = 3.8 Hz, H-5'), 3.38 (3H, s, OCH_3), 3.64 (1H, dd, $J_{5',6a'}$ = 2.6 Hz, $J_{6a',6b'}$ = 12.2 Hz, H-6a'), 3.87 (1H, ddd, $J_{4,5}$ = 10.2 Hz, $J_{5,6a}$ = 2.3 Hz, $J_{5,6b}$ = 4.8 Hz, H-5), 3.95 (1H, t, $J_{2,3+3,4}$ = 19.0 Hz, H-3), 3.96 (1H, dd, $J_{5',6b'}$ = 3.8 Hz, $J_{6a',6b'}$ = 12.2 Hz, H-6b'), 4.03-4.08 (2H, m, H-2, H-6a), 4.24 (1H, dd, $J_{5,6b}$ = 4.8 Hz, $J_{6a,6b}$ = 11.2 Hz, H-6b), 4.71 (1H, d, J = 11.2 Hz, CHHC$_6$H$_5$), 4.79 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1), 4.80 (1H, d, J = 11.2 Hz, CHHC$_6$H$_5$), 5.01 (1H, dd, $J_{1',2'}$ = 3.0 Hz, $J_{2',3'}$ = 10.0 Hz, H-2'), 5.07 (1H, d, $J_{1',2'}$ = 3.0 Hz, H-1'), 5.11 (1H, dd, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 10.2 Hz, H-4), 5.23 (1H, dd, $J_{3',4'}$ = 9.6 Hz, $J_{4',5'}$ = 11.0 Hz, H-4'), 5.54 (1H, t, $J_{2',3'+3',4'}$ = 19.5 Hz, H-3'), 7.2-7.4 (5H, m, Ar). Compound **122** was deprotected as above to afford **85**.

Phenyl 2,3,4,6-Tetra-O-benzoyl-1-seleno-5-thio-β-D-glucopyranoside (96). Phenyl 2,3,4,6-tetra-O-acetyl-seleno-5-thio-β-D-glucopyranoside **(89)** (0.35 g, 0.7 mmol) was dissolved in methanol (5 mL) and ammonia gas was bubbled through the solution periodically, until deacetylation was complete. The solvent was evaporated and the dry deacetylated sugar was dissolved in pyridine (5 mL). The solution was cooled to 0°C and benzoyl chloride (0.8 mL, 6.9 mmol) was added dropwise. The reaction mixture was warmed to room temperature. After 3 h the excess benzoyl chloride was quenched with methanol and the pyridine was evaporated. The remaining residue was dissolved in dichloromethane, and washed successively with hydrochloric acid (2N) and sodium hydrogen carbonate. The organic extracts were dried over magnesium sulfate and concentrated to give a foam that was

chromatographed with hexane-ethyl acetate (3:1) as eluant [R_f = 0.4]. The *title compound* was obtained as a white solid and was crystallized from ethanol (100%). (0.52 g, 96%). mp = 143° C, $[\alpha]_D^{21}$ = 52° (*c* 0.5 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 42.5 (C-1), 46.2 (C-5), 61.8 (C-6), 72.6 (C-2, C-3), 74.5 (C-4). ^1H NMR ($CDCl_3$): δ 3.68 (1H, m, H-5), 4.34 (1H, d, $J_{1,2}$ = 10.3 Hz, H-1), 4.41 (1H, dd, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.56 (1H, dd, $J_{5,6b}$ = 4.0 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 5.66 (1H, t, $J_{2,3+3,4}$ = 19.0 Hz , H-3), 5.72 (1H, t, $J_{1,2+2,3}$ = 19.4 Hz , H-2), 5.84 (1H, t, $J_{3,4+4,5}$ = 19.8 Hz , H-4), 7.2-8.1 (20 H, m, Ar); Anal. Calcd for $C_{40}H_{32}O_8SSe$: C, 63.91; H, 4.29. Found: C, 63.80; H, 4.10.

O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate (100). A mixture of α and β peracetylated 5-thioglucose **(89)** (1.21 g, 3.0 mmol) was dissolved in *N,N*-dimethylformamide (30 mL). Hydrazine acetate was added (0.4 g, 3.9 mmol) and the reaction mixture was stirred under nitrogen for 3 h. A TLC was performed to confirm the exhaustion of starting material. Ethyl acetate (50 mL) was added and the reaction mixture was diluted with dichloromethane (50 mL) and washed with aqueous sodium chloride (5%, 2x30 mL). The organic extracts were dried over magnesium sulfate, filtered and concentrated. The syrup was purified by column chromatography with hexane-ethyl acetate (1:1.2) as eluant, R_f = 0.34. A mixture of 2,3,4,6-tetra-O-acetyl-5-thio-α/β–D-glucopyranosides **(99)** was obtained as a foam (1.0 g, 91%). Compouds **(99)** (2.0 g, 5.5 mmol) was dissolved in dichloromethane (24 mL). Trichloroacetonitrile (5.5 mL, 55 mmol) and potassium carbonate (7.5 g, 54.2 mmol) were added and the reaction was stirred under nitrogen for 24 h. On completion of the reaction, the mixture was diluted with ether, filtered through

celite and concentrated. The resulting brown foam was chromatographed with hexane-ethyl acetate (2:1) as eluant [R_f α-isomer = 0.35; β-isomer = 0.25].The *title compound* was obtained as a foam (α-isomer **100**: 2.2 g, 81%, β-isomer **98**: 0.09 g, 3%). **100** $[\alpha]_D^{20}$+217° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.4, (4CO*C*H_3), 40.1 (C-5), 60.8 (C-6), 70.6 (C-3), 71.7 (C-4), 73.5 (C-2), 75.8 (C-1), 90.7 (*C*Cl_3), 160.7 (*C*=N), 169.4, 169.6, 170.3 (4*C*OCH$_3$). ^1H NMR ($CDCl_3$): δ 1.99, 2.02, 2.05, 2.07 (12H, 4s, 4COC*H*$_3$), 3.63 (1H, ddd, $J_{4,5}$ = 10.9 Hz, $J_{5,6a}$ = 3 Hz, $J_{5,6b}$ = 4.8 Hz, H-5), 4.07 (1H, dd, $J_{5,6a}$ = 3.0 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 4.39 (1H, dd, $J_{5,6b}$ = 4.8 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6b), 5.30 (1H, dd, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 5.37 (1H, dd, $J_{3,4}$ = 10.0 Hz, $J_{4,5}$ = 10.8 Hz, H-4), 5.56 (1H, t, $J_{2,3+3,4}$ = 19.7 Hz, H-3), 6.34 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1), 8.68 (1H, s, N*H*CCl$_3$). Anal. Calcd. for $C_{16}H_{20}O_9NCl_3S$: C, 37.76; H, 3.96; N, 2.75. Found: C, 37.80; H, 4.01; N, 2.55. β-isomer **98** ^{13}C NMR ($CDCl_3$): δ 41.0 (C-5), 62.2 (C-6), 70.8 (C-4), 72.4 (C-4, C-2), 76.2 (C-1). ^1H NMR ($CDCl_3$): δ 2.02, 2.04, 2.05, 2.08 (12H, 4s, 4COC*H*$_3$), 3.37 (1H, m, H-5), 4.21 (1H, dd, $J_{5,6a}$ = 4.3 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6a), 4.33 (1H, dd, $J_{5,6b}$ = 5.4 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6b), 5.15 (1H, t, $J_{2,3+3,4}$ = 16.3 Hz, H-3), 5.37 (1H, t, $J_{3,4+4,5}$ = 18.4 Hz, H-4), 5.51 (1H, t, $J_{1,2+2,3}$ = 15.0 Hz, H-2), 6.07 (1H, d, $J_{1,2}$ = 7.6 Hz, H-1), 8.71 (1H, s, N*H*CCl$_3$). Anal. Calcd. for $C_{16}H_{20}O_9NCl_3S$: C, 37.76; H, 3.96; N, 2.75. Found: C, 38.08; H, 4.12; N, 2.51.

Methyl 2,3,4-Tri-O-benzyl-6-O-(2,3,4,6-tetra-*O*-acetyl-5'-thio-β-D glucopyranosyl)-α-D-glucopyranoside (101). This compound was obtained in the reaction of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)** and methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside **(16)** along with the α- isomer **(90)** (page 204). $[\alpha]_D^{20}$+27.8° (*c* 1.08 in CH_2Cl_2);

^{13}C NMR ($CDCl_3$): δ 20.4, 20.5, 20.6 ($4COCH_3$), 41.0 (C-5'), 55.2 (OCH_3), 62.4 (C-6'), 69.2 (C-6), 69.9 (C-5), 71.4 (C-4'), 73.1 (C-3'), 73.3 ($CH_2C_6H_5$), 74.7 (C-2'), 74.9, 75.6 ($2CH_2C_6H_5$), 77.7 (C-4), 80.2 (C-2), 81.9 (C-3, C-1'), 97.9 (C-1), 127.5-138.8 (Ar), 169.1, 169.2, 169.7, 170.4 ($4COCH_3$). ^1H NMR ($CDCl_3$): δ 1.96, 1.99, 2.02, 2.06 (12H, 4s, $4COCH_3$), 3.10 (1H, m, H-5'), 3.37 (3H, s, OCH_3), 3.41 (1H, t, $J_{3,4+4,5}$ = 19.0 Hz, H-4), 3.50 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 3.63 (1H, dd, $J_{5,6a}$ = 4.9 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6a), 3.73 (1H, m, H-5), 3.94-3.99 (2H, m, H-3, H-6b), 4.13 (1H, dd, $J_{5',6a'}$ = 4.0 Hz, $J_{6a',6b'}$ = 11.8 Hz, H-6a'), 4.27 (1H, dd, $J_{5',6b'}$ = 5.5 Hz, $J_{6a',6b'}$ = 11.8 Hz, H-6b'), 4.55 (1H, d, J = 11.6 Hz, $CHHC_6H_5$), 4.58 (1H, d, $J_{1',2'}$ = 8.5 Hz, H-1'), 4.59 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.66 (1H, d, J = 12.0 Hz, $CHHC_6H_5$), 4.78 (1H, d, J = 12.0 Hz, $CHHC_6H_5$), 4.79 (1H, d, J = 11.0 Hz, $CHHC_6H_5$), 4.87 (1H, d, J = 11.0 Hz, $CHHC_6H_5$), 4.97 (1H, d, J = 11.6 Hz, $CHHC_6H_5$), 5.04 (1H, t, $J_{2',3'+3',4'}$ = 18.3 Hz, H-3'), 5.30 (1H, t, $J_{3',4'+4',5'}$ = 19.4 Hz, H-4'), 5.31 (1H, t, $J_{1',2'+2',3'}$ = 16.0 Hz, H-2'), 7.20-7.50 (15H, m, Ar); Anal. Calcd for $C_{42}H_{50}O_{14}S$: C, 62.2; H, 6.22. Found: C, 62.08; H, 6.19.

Methyl 2,3,4-Tri-O-acetyl-6-O-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (103). Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (**90**) (0.21 g, 0.26 mmol) was dissolved in THF (5 mL) and cooled to -78 C. Ammonia was condensed into the flask (10 mL) and sodium was added untill the reaction was complete, as determined by TLC (approx. 150 mg). At this time a persistent blue colour was observed. The reaction was quenched with methanol and the reaction was allowed to warm to room temperature. The ammonia was evaporated with a slow stream of air and the reaction mixture was neutralized

with Amberlyst H^+ ion exchange resin. The residue obtained after concentration was treated with acetic anhydride (4 mL) and pyridine (4 mL) and stirred for 24 h. The solution was washed successively with water, HCl (2N), sodium hydrogen carbonate and dried over magnesium sulfate. The residue was chromatographed with hexane-ethyl acetate (1:2) as eluant [R_f = 0.34]. The *title compound* **103** was obtained as a syrup (0.11 g, 67 %). ^{13}C NMR ($CDCl_3$): δ 20.5, 20.6, (7COCH$_3$), 38.5 (C-5'), 55.4 (OCH$_3$), 61.2 (C-6'), 67.1 (C-6), 67.9 (C-5), 69.4 (C-4), 70.3 (C-2), 70.8, 70.9 (C-3, C-3'), 72.2 (C-4'), 74.7 (C-2'), 79.9 (C-1'), 96.6 (C-1), 169.5, 170.0, 170.1, 170.5 (7COCH$_3$). ^1H NMR ($CDCl_3$): δ 1.99, 2.00, 2.01, 2.04, 2.06, 2.07, 2.08 (21H, 7s, 7COCH$_3$), 3.42 (3H, s, OCH$_3$), 3.44-3.52 (2H, m, H-5', H-6a), 3.88 (1H, dd, $J_{5,6b}$ = 5.9 Hz, $J_{6a,6b}$ = 10.9 Hz, H-6b), 3.97 (1H, m, H-5), 4.03 (1H, dd, $J_{5',6a'}$ = 2.7 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6a'), 4.35 (1H, dd, $J_{5',6b'}$ = 4.8 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6b'), 4.81-4.88 (2H, m, H-1', H-2), 4.91 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 5.03 (1H, t, $J_{3,4+4,5}$ = 19.6 Hz, H-4), 5.14 (1H, t, $J_{1',2'}$ = 2.6, $J_{2',3'}$ = 10.0 Hz, H-2'), 5.28 (1H, t, $J_{3',4'+4',5'}$ = 20.4 Hz, H-4'), 5.5 (2H, H-3, H-3'). Anal. Calcd for $C_{22}H_{38}O_{17}S$: C, 48.65; H, 5.75. Found: C, 48.52; H, 5.76.

Methyl 6-O-(5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (82). A freshly prepared solution of sodium methoxide in methanol (0.2N, 5 mL) was added to methyl 2,3,4-tri-O-acetyl-6-O-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside **(103)** (0.50 g, 0.08 mmol) and the mixture was stirred under nitrogen for 6 h. The solution was acidified to a pH of 3 with Rexyn (H^+) resin, filtered. and concentrated. The residue was purified by column chromatography with ethyl acetate-methanol-water (6:3:1) as eluant, [R_f = 0.34]. Further purification by Sephadex LH20 filtration yielded the *title compound* **(82)**

(24 mg, 82%). $[\alpha]_D^{20}$ +319.0° (*c* 1 in CH_3OH); ^{13}C NMR (D_2O; 150.23 MHz): δ 45.7 (C-5'), 57.8 (OCH_3), 62.7 (C-6'), 68.9 (C-6), 72.1 (C-4), 72.6 (C-5), 73.8 (C-2), 76.3, 76.6 (C-3', C-3, C-4'), 78.0 (C-2'), 84.5 (C-1'), 102.1 (C-1). ^1H NMR (D_2O; 600.14 MHz): δ 3.20 (1H, dt, $J_{4',5'}$ = 10.0 Hz, $J_{5',6a'}$ = 3.2 Hz, $J_{5',6b'}$ = 5.6 Hz, H-5'), 3.37 (3H, s, OCH_3), 3.44 (1H, t, $J_{3,4+4,5}$ = 19.4 Hz, H-4), 3.51 (1H, dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 3.54-3.68 (4H, m, H-4', H-3, H-3', H-6a), 3.76-3.80 (2H, m, H-5, H-2'), 3.81 (1H, dd, $J_{5',6a'}$ = 3.2 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6a'), 3.87 (1H, dd, $J_{5',6b'}$ = 5.6 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6b'), 4.10 (1H, dd, $J_{5,6b}$ = 4.4 Hz, $J_{6a,6b}$ = 11.1 Hz, H-6b), 4.72 (1H, d, $J_{1',2'}$ = 2.9 Hz, H-1'), 4.76 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1). ES-MS Calcd. for $C_{13}H_{24}O_{10}S$: $M^{+\bullet}$ 372; Found: 395 $(M+Na)^{+\bullet}$.

Methyl 2,3,6-Tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (104). A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)** (0.15 g, 0.3 mmol), methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside **(74)** (0.3 g, 0.6 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (3 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.007 mL, 0.03 mmol) was added. The reaction mixture was stirred at -78° C for 1 h. An aliquot of the reaction mixture was taken and quenched with triethylamine. A TLC of this aliquot was performed and the presence of starting materials in addition to product was observed. The reaction mixture was then warmed to room temperature and stirred for 1 h. A TLC at this point indicated that the reaction was complete. The reaction mixture was again cooled to -78° C and neutralized with collidine. The reaction mixture was then filtered, and washed successively with hydrochloric acid (5%), and aqueous sodium

hydrogen carbonate. The organic extracts were dried over magnesium sufate and concentrated to give a foam that was chromatographed with hexane-ethyl acetate (1.5:1) as eluant, [R_f = 0.32]. The *title compound* **(104)** was obtained as a white foam (0.21 g, 87%). $[\alpha]_D^{20}$ +218.7° (*c* 12.3 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.4, 20.5 ($4COCH_3$), 37.5 (C-5'), 55.6 (OCH_3), 60.7 (C-6'), 63.2 (C-6), 67.9 (C-5), 70.3 (C-3'), 71.7 (C-4'), 72.4 (C-4, C-2), 73.1 (C-3, C-2',), 80.1 (C-1'), 96.9 (C-1), 128.4-133.5 (Ar), 165.4, 165.9, 166.3 ($3COC_6H_5$) 169.3, 169.5, 169.7 ($4COCH_3$). ^1H NMR ($CDCl_3$): δ 1.95, 1.99 (12H, 2s, $4COCH_3$), 3.36 (1H, dt, $J_{4',5'}$ = 10.7 Hz, $J_{5',6a'}$ = 2.6 Hz, $J_{5',6b'}$ = 4.1 Hz, H-5'), 3.47 (3H, s, OCH_3), 3.79 (1H, dd, $J_{5',6a'}$ = 2.6 Hz, $J_{6a',6b'}$ = 12.2 Hz, H-6a'), 4.23-4.33 (2H, m, H-5, H-6b'), 4.40 (1H, t, $J_{3,4+4,5}$ = 18.6 Hz, H-4), 4.60-4.68 (2H, m, H-6a, H-6b), 5.03 (1H, dd, $J_{1',2'}$ = 3.3 Hz, $J_{2',3'}$ = 10.4 Hz, H-2'), 5.12 (1H, dd, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 5.14 (1H, d, $J_{1,2}$ = 3.4 Hz, H-1), 5.15 (1H, d, $J_{1',2'}$ = 3.3 Hz, H-1'), 5.21 (1H, dd, $J_{3',4'}$ = 9.7 Hz, $J_{4',5'}$ = 10.7 Hz, H-4'), 5.39 (1H, t, $J_{2',3'+3',4'}$ = 20.1 Hz, H-3'), 6.15 (1H, dd, $J_{2,3}$ = 9.8 Hz, $J_{3,4}$ = 9.1 Hz, H-3), 7.3-8.2 (15H, Ar). Anal. Calcd. for $C_{42}H_{44}O_{17}S$: C, 59.15; H, 5.20. Found: C, 59.40; H, 5.25.

Methyl 4-O-(5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (83). A freshly prepared solution of sodium methoxide in methanol (0.2N, 2 mL) was added to disaccharide **104** (0.75 mg, 0.09 mmol) and the mixture was stirred under nitrogen for 3 h. The solution was acidified to a pH of 3 with Rexyn (H+) resin, and filtered. The filtrate was neutralized with Amberlite basic ion exchange resin, filtered and concentrated. The residue was purified by column chromatography with hexane-dichloromethane-methanol (1.2:1:1) as eluant, [R_f = 0.32]. The *title compound* **83** was obtained as a syrup (25 mg, 74%). $[\alpha]_D^{20}$ +102° (*c* 0.5 in CH_3OH), ^{13}C NMR (D_2O): δ 46.5 (C-5'), 57.8 (OCH_3), 62.6, 62.8

(C-6, 6'), 74.0 (C-2), 72.8, 76.0, 76.5, 76.7, 78.1, 78.2 (C-2', 3', 4', 3, 4, 5), 85.5 [$^1J(^{13}C,^1H)$ 163 Hz, (C-1')], 101.8 [$^1J(^{13}C,^1H)$ 167 Hz, (C-1)],. ^1H NMR (D_2O): δ 2.98 (1H, ddd, $J_{4',5'}$ = 10.0 Hz, $J_{5',6a'}$ = 3.5 Hz, $J_{5',6b'}$ = 5.1 Hz, H-5'), 3.35 (3H, s, OCH_3), 3.53 (1H, dd, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 3.55-3.88 (9H, m, H-2', 3', 4', 6a', 6b', 4, 5, 6a, 6b), 3.89 (1H, t, $J_{2,3}$ = 9.8, $J_{3,4}$ = 8.3 Hz, H-3), 4.77 (1H, d, $J_{1,2}$ = 3.8 Hz, H-1), 5.30 (1H, d, $J_{1',2'}$ = 3.3 Hz, H-1'). ES-MS Calcd. for $C_{13}H_{24}O_{10}S$: $M^{+\bullet}$ 372; Found: 395 $(M+Na)^{+\bullet}$.

Methyl 2,3,6-Tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (104), glucals (105, 106) and (107). A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)** (0.25 g, 0.5 mmol), methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside **(74)** (0.13 g, 0.25 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (5 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.011 mL, 0.05 mmol) was added. The reaction mixture was stirred at -78° C for 1 h. An aliquot of the reaction mixture was taken and quenched with triethylamine. A TLC of this aliquot was performed and the presence of starting materials in addition to a product was observed. The reaction mixture was then warmed to room temperature and stirred for 1 h. A TLC at this point indicated that the trichloroacetimidate donor **100** had been consumed. The reaction mixture was again cooled to -78° C and neutralized with triethylamine. The reaction mixture was then filtered through celite and concentrated to give a foam that was chromatographed with hexane-ethyl acetate (1.5:1) as eluant. The disaccharide **104** was isolated as a white foam (0.09 g, 45%). In addition, a mixture of glycals **105** and **106** and compound **107** were isolated (0.11 g). Compounds **105** and

106 were separated from **108** by column chromatography with hexane-ethyl acetate (2:1) as eluant, [R_f **105** and **106** = 0.32; **107** = 0.30]. **105:** ^{13}C NMR ($CDCl_3$): δ 20.66, 20.7, 20.73 ($4COCH_3$), 40.0 (C-5), 62.4 (C-6), 67.0 (C-3), 68.9 (C-4), 113.5 (C-2), 136.2 (C-1), 169.8, 170.4 ($4COCH_3$). ^1H NMR ($CDCl_3$): δ 2.05, 2.08, 2.10, 2.12 (12H, 4s, $4COCH_3$), 3.36 (1H,bq, $J_{4,5+5,6a+5,6b}$ = 20.0 Hz, H-5), 4.31 (1H, dd, $J_{5,6a}$ = 7.4 Hz, $J_{6a,6b}$ = 11.7 Hz, H-6a), 4.38 (1H, dd, $J_{5,6b}$ = 7.2 Hz, $J_{6a,6b}$ = 11.7 Hz, H-6b), 5.41 (1H, dd, $J_{3,4}$ = 4.2 Hz, $J_{4,5}$ = 5.5 Hz, H-4), 5.50 (1H, d, $J_{3,4}$ = 4.2 Hz, H-3), 6.10 (1H, s, H-1); **106:** ^{13}C NMR ($CDCl_3$): δ 20.6-20.7 ($4COCH_3$), 37.2 (C-5), 61.6 (C-6), 66.3 (C-3), 69.7 (C-4), 114.8 (C-2), 136.0 (C-1), 168.0-170.0 ($4COCH_3$). ^1H NMR ($CDCl_3$): δ 2.01-2.12 (12H, 4s, $4COCH_3$), 3.76 (1H, ddd, $J_{4,5}$ = 11.0 Hz, $J_{5,6a}$ = 6.5 Hz, $J_{5,6b}$ = 3.5 Hz, H-5), 4.30-4.38 (2H, m, H-6a, H-6b), 5.34 (1H, dd, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 11.5 Hz, H-4), 5.69 (1H, d, $J_{3,4}$ = 3.5 Hz, H-3), 6.14 (1H, s, H-2). Anal. Calcd. for a mixture of **105** and **106** $C_{14}H_{18}O_8S$: C, 48.55; H, 5.24. Found: C, 48.72; H, 5.44. **107:** mp 196° C. ^{13}C NMR ($CDCl_3$): δ 20.5, 20.7, 20.8 ($3COCH_3$), 37.0 (C-5'), 55.5 (OCH_3), 61.2 (C-6'), 63.2 (C-6), 68.3 (C-5), 68.9 (C-4'), 72.4 (C-2), 73.1 (C-3), 73.4 (C-4), 77.3 (C-1'), 96.8 (C-1), 120.8 (C-2'), 128.4-133.5 (Ar), 144.5 (C-3') 165.5, 165.9, 166.4 ($3COC_6H_5$) 168.6, 170.0, 170.4 ($3COCH_3$). ^1H NMR ($CDCl_3$): δ 1.99, 2.04, 2.06 (9H, 3s, $3COCH_3$), 3.41 (1H, ddd, $J_{4',5'}$ = 10.5 Hz, $J_{5',6a'}$ = 3.1 Hz, $J_{5',6b'}$ = 4.2 Hz, H-5'), 3.44 (3H, s, OCH_3), 4.14 (1H, dd, $J_{5',6a'}$ = 3.1 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6a'), 4.17-4.24 (2H, m, H-5, H-4), 4.38 (1H, dd, $J_{5',6b'}$ = 4.2 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6b'), 4.61-4.70 (2H, m, H-6a, H-6b), 5.12 (1H, dd, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 5.14 (1H, s, H-1'), 5.16 (1H, d, $J_{1,2}$ = 3.4 Hz, H-1), 5.52 (1H, dd, $J_{2',4'}$ = 2.0 Hz, H-2'), 5.56 (1H, ddd, $J_{1',4'}$ = 0.9 Hz, $J_{2',4'}$ = 2.0 Hz, $J_{4',5'}$ = 10.5 Hz, H-4'), 6.13 (1H, dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 8.4 Hz, H-3), 7.2-8.2 (15H, Ar). Anal. Calcd. for $C_{40}H_{40}O_{15}S$: C, 60.60; H, 5.09, Found: C, 60.29; H, 5.02.

3,4,6-Tri-*O*-acetyl-1,2-(methyl 2,3,6-tri-*O*-benzoyl-α–D-glucopyranos-4-yl)-α–D-5'-thioglucopyranose orthoacetate (108). A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)** (0.10 g, 0.20 mmol), methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside **(74)** (0.09 g, 0.17 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (2 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.005 mL, 0.02 mmol) was added. The reaction mixture was stirred at -78° C for 1 h, warmed to -50°C and stirred for another 1.5 h. An aliquot of the reaction mixture was taken and quenched with collidine at -78°C. A TLC of this aliquot indicated that the reaction was complete. The reaction mixture was again cooled to -78° C and neutralized with collidine. The mixture was filtered and washed successively with hydrochloric acid (5%) and aqueous sodium hydrogen carbonate. The organic extracts were dried over magnesium sufate and concentrated to give a foam that was chromatographed with hexane-ethyl acetate (1.5:1) as eluant, [R_f = 0.32]. A mixture of the orthoester **(108)** and the disaccharide **(104)** was isolated in a combined yield of 88% (0.12 g, **108:104**=15:1, 83% of **108**, 5% of **104**). **108:** ^{13}C NMR ($CDCl_3$): δ 20.4, 20.5 ($3COCH_3$), 24.4 ($CCH3$), 39.7 (C-5), 55.4 (OCH_3), 61.2 (C-6), 63.1 (C-6'), 68.6 (C-5'), 70.1 (C-4), 70.7 (C-4'), 71.5 (C-3'), 71.8 (C-2'), 72.7 (C-3), 77.4 (C-1), 79.1 (C-2), 96.8 (C-1'), 122.4 (CCH_3), 128.3-133.3 (Ar), 165.5, 166.0, 166.3 ($3COC_6H_5$) 169.3, 169.4, 170.3 ($4COCH_3$). ^{1}H NMR ($CDCl_3$): δ 1.62 (3H, s, CCH_3), 1.75, 1.93, 2.02 (9H, 3s, $3COCH_3$), 3.23 (1H, ddd, $J_{4',5'}$ = 10.2 Hz, $J_{5',6a'}$ = 3.2 Hz, $J_{5',6b'}$ = 5.7 Hz, H-5'), 3.41 (3H, s, OCH_3), 3.93 (1H, dd, $J_{5',6a'}$ = 3.2 Hz, $J_{6a',6b'}$ = 12.1 Hz, H-6a'), 4.08-4.20 (3H, m, 6', 4, 5), 4.32 (1H, dd, $J_{1',2'}$ = 5.5 Hz, $J_{2',3'}$ = 7.5 Hz, H-2'), 4.53 (1H, dd, $J_{5,6}$ = 3.9 Hz, $J_{6a,6b}$ = 12.1

Hz, H-6a), 4.63 (1H, dd, $J_{5,6b}$ = 2.0 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6b), 4.88 (1H, dd, $J_{2',3'}$ = 7.5 Hz, $J_{3',4'}$ = 9.2 Hz, H-3'), 4.97 (1H, t, $J_{3',4'+4',5'}$ = 19.7 Hz, H-4'), 5.12 (1H, d, $J_{1,2}$ = 3.9 Hz, H-1), 5.21 (1H, dd, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 5.36 (1H, d, $J_{1',2'}$ = 5.4 Hz, H-1'), 5.93 (1H, dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 8.2 Hz, H-3), 7.3-8.2(15H, Ar). Anal. Calcd. for $C_{42}H_{44}O_{17}S$: C, 59.15; H, 5.20. Found: C, 59.28; H, 5.17.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α/β-D-glucopyranosyl)-α-D-glucopyranoside (109,110). A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)** (0.08 g, 0.15 mmol), methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **(77)** (0.14 g, 0.30 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (1.5 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.0034 mL, 0.015 mmol) was added. The reaction mixture was stirred at -78° C for 1 h, then warmed to room temperature and stirred for 1 h. A TLC at this point indicated that the reaction was complete. The reaction mixture was again cooled to -78° C and neutralized with collidine. The reaction mixture was then filtered, and washed successively with hydrochloric acid (5%) and sodium hydrogen carbonate. The organic extracts were dried over magnesium sulfate and concentrated to give a foam that was chromatographed with hexane-ethyl acetate (1.3:1) as eluant, [R_f α-isomer **109** = 0.36; β-isomer **110** = 0.32].The *title compounds* **109** and **110** were obtained as syrups (α: 51 mg, 43%, β: 54 mg, 45%). α-Isomer **109:** $[\alpha]_D^{20}$+131.5° (*c* 0.73 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.5 ($4COCH_3$), 38.7 (C-5'), 55.3 (OCH_3), 61.0 (C-6'), 69.2 (C-5), 69.4 (C-6), 70.7 (C-3'), 72.1 (C-4'), 72.4 (C-4), 73.2 ($CH_2C_6H_5$), 73.5 ($CH_2C_6H_5$), 74.0 (C-2'), 74.5 ($CH_2C_6H_5$), 79.2 (C-1'), 80.9 (C-2), 81.8 (C-3), 97.5 (C-1), 127.3-138

(Ar), 169.3, 169.7, 170.4 (4*C*OCH$_3$). ^{1}H NMR ($CDCl_3$): δ (1.97, 1.99, 2.01, 2.02,12H, 4s, 4COC*H*$_3$), 3.24 (1H, dt, $J_{4',5'}$ = 10.8 Hz, $J_{5',6a'+5',6b'}$ = 6.8 Hz, H-5'), 3.40 (3H, s, OC*H*$_3$), 3.59 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.1 Hz, H-2), 3.62 (1H, dd, $J_{5',6a'}$ = 2.8 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6a'), 3.68 (1H, dd, $J_{5,6a}$ = 1.5 Hz, $J_{6a,6b}$ = 11.0 Hz, H-6a), 3.78 (1H, dd, $J_{5,6b}$ = 4.2 Hz, $J_{6a,6b}$ = 11.0 Hz, H-6b), 3.88 (1H, ddd, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 1.5 Hz, $J_{5,6b}$ = 4.2 Hz, H-5), 4.0 (1H, t, $J_{2,3+3,4}$ = 17.8 Hz, H-3), 4.05-4.15 (2H, m, H-4, H-6b'), 4.51 (1H, d, *J* = 10.5 Hz, C*H*HC$_6$H$_5$), 4.54-5.42 (4H, m, 3C*H*HC$_6$H$_5$, H-1), 4.70 (1H, d, *J* = 11.8 Hz, CH*H*C$_6$H$_5$), 5.01 (1H, d, *J* = 10.5 Hz, CH*H*C$_6$H$_5$), 5.22 (1H, t, $J_{3',4'+4',5'}$ = 20.3 Hz, H-4'), 5.25 (1H, dd, $J_{1',2'}$ = 3.0 Hz, $J_{2',3'}$ = 10.2 Hz, H-2'), 5.38 (1H, t, $J_{2',3'+3',4'}$ = 19.8 Hz, H-3'), 5.61 (1H, d, $J_{1',2'}$ = 3.0 Hz, H-1'), 7.1-7.4 (15H, m, Ar). Anal. Calcd for $C_{42}H_{50}O_{14}S$: C, 62.20; H, 6.22. Found: C, 62.29; H, 6.39. β-Isomer **110:** $[\alpha]_D^{20}$+33° (*c* 0.84 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.7 (4COC*H*$_3$), 40.6 (C-5'), 55.5 (OC*H*$_3$), 61.4 (C-6'), 68.1 (C-6), 70.1 (C-5), 71.9 (C-4'), 73.6, 73.9 (C-3', 2C*H*$_2$C$_6$H$_5$), 75.2 (2'), 76.2 (C*H*$_2$C$_6$H$_5$), 76.9 (C-4), 79.86, 79.9 (C-2. C-3), 81.3 (C-1'), 98.5 (C-1), 127.5-138.6 (Ar), 169.0, 169.3, 169.8, 170.5 (4*C*OCH$_3$). ^{1}H NMR ($CDCl_3$): δ (1.96, 1.97, 1.99, 2.05, 12H, 4s, 4COC*H*$_3$), 2.46 (1H, m, H-5'), 3.35 (3H, s, OC*H*$_3$), 3.49 (1H, dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.7 Hz, H-2), 3.57 (1H, m, H-5), 3.66 (1H, dd, $J_{5,6a}$ = 1.0 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6a), 3.73 (1H, t, $J_{2,3+3,4}$ = 18.7 Hz, H-3), 3.81 (1H, dd, $J_{5,6b}$ = 2.8 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6b), 3.84-3.92 (2H, m, H-6a', H-4), 4.19 (1H, dd, $J_{5',6b'}$ = 4.0 Hz, $J_{6a',6b'}$ = 11.8 Hz, H-6b'), 4.43 (1H, d, *J* = 12.0 Hz, C*H*HC$_6$H$_5$), 4.52 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1),4.51 (1H, d, *J* = 12.2 Hz, C*H*HC$_6$H$_5$), 4.65 (1H, d, $J_{1',2'}$ = 9.3 Hz, H-1'), 4.74-4.87 (5H, m, C*H*HC$_6$H$_5$, $_3$CH*H*C$_6$H$_5$, H-3'), 5.19 (1H, t, $J_{3',4'+4',5'}$ = 20.3 Hz, H-4'), 5.29 (1H, t, $J_{1',2'+2',3'}$ = 19.0 Hz, H-2'), 7.1-7.5 (15H, m, Ar). Anal. Calcd for $C_{42}H_{50}O_{14}S$: C, 62.20; H, 6.22. Found: C, 62.22; H, 6.27.

Methyl 2,3,6-Tri-O-benzoyl-4-selenocyanato-α-D-glucopyranoside (114) Methyl 2,3,6-tri-O-benzoyl-α-D-glucopyranoside **(113)** (5.18 g, 10.0 mmol) was dissolved in a mixture of dichloromethane (50 mL) and pyridine (2.0 mL, 25 mmol) and cooled to -30°C. Triflic anhydride (2.5 mL, 15 mmol) was added dropwise over 10 min. The mixture was warmed to room temperature over 0.5 h and then recooled in an ice bath. Cold, saturated, aqueous sodium hydrogen carbonate (30 mL) was added and the mixture was stirred for 10 min. The organic phase was separated and the aqueous phase was extracted with dichloromethane (30 mL). The combined organic extracts were washed with cold, 5% aqueous HCl (30 mL) and sodium hydrogen carbonate (30 mL), and dried over magnesium sulfate. Removal of the solvent afforded the methyl 2,3,6-tri-O-benzoyl-4-trifluoromethanesulfonyl-α-D-glucopyranoside **(113)** (6.47 g) as a light yellow foam. The crude triflate was dissolved in *N,N*-dimethylformamide (55 mL) and treated with potassium selenocyanate (1.75 g, 12.1 mmol) at 50°C and stirred for 3 h. The mixture was cooled, poured into ice water (850 mL) and stirred until a solid was formed. This was collected by filtration and washed with water. The crystals were dissolved in CH_2Cl_2 and dried over magnesium sulfate. Solvent removal afforded the *title compound* **(114)** as a pale yellow solid. Recrystallization from chloroform/hexane gave the pure product (4.77 g, 80%); mp 198-199°C (slight decomposition above 195°C); $[\alpha]_D^{27}$ 65.0° (*c* 2.0 in $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 45.8 (C-4), 56.0 (OCH_3), 64.0 (C-6), 69.4 (C-5), 69.6 (C-3), 72.9 (C-2), 97.4 (C-1), 98.1 (*C*N). ^1H NMR ($CDCl_3$): δ 3.48 (3H, s, OCH_3), 3.59 (1H, t, $J_{3,4+4,5}$ = Hz, H-4), 3.47 (1H, ddd, $J_{4,5}$ = 5.5 Hz, $J_{5,6a}$ = 2.0 Hz, $J_{5,6b}$ = 1.3 Hz, H-5), 4.83 (1H, dd, $J_{5,6a}$ = 1.3 Hz, $J_{6a,6b}$ = 6.5 Hz, H-6a), 4.88 (1H, dd, $J_{5,6b}$ = 2.0 Hz, $J_{6a,6b}$ = 6.5 Hz, H-6b), 5.23 (1H, d, $J_{1,2}$ = 1.8 Hz, H-1), 5.27 (1H, dd, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 6.8 Hz, H-2), 6.11 (1H, dd, $J_{2,3}$

= 6.8 Hz, $J_{3,4}$ = 5.5 Hz, H-3), 7.33-8.13 (15H, m, Ar); Anal. Calcd for $C_{29}H_{25}NO_8Se$: C, 58.59; H, 4.24; N, 2.36. Found: C, 58.67; H, 4.22; N, 2.23.

Methyl 2,3,6-Tri-O-benzoyl-4-seleno-α-D-glucopyranoside (111) Methyl 2,3,6-tri-O-benzoyl-4-selenocyanato-α-D-glucopyranoside **(114)** (0.6 g, 1.0 mmol) was dissolved in THF:EtOH, 5:1 (24 mL) and cooled in an ice bath while sodium borohydride (0.18 g, 4.8 mmol) was added in small portions over 15 min. The reaction mixture was warmed to room temperature and stirred for 40 min. After recooling in an ice bath, Et_2O (100 mL) was added and excess $NaBH_4$ was hydrolyzed by the cautious addition of 5% aqueous HCl solution (10 mL). The mixture was stirred for 5 min. The ether phase was separated and washed with H_2O (2x10 mL) and saturated aqueous NaCl solution (10 mL). The organic phase was dried over magnesium sulfate and concentrated to yield the *title compound* **(111)** (0.57g) as a colourless foam which solidified on cooling. ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.2 (C-4), 55.6 (OCH_3), 65.0 (C-6), 71.8 (C-5), 72.7 (C-3), 73.2 (C-2), 97.5 (C-1). ^1H NMR (400 MHz, $CDCl_3$) δ -0.07 (1H, d, $^1J_{Se,H}$ = 45.5 Hz, $^3J_{SeH,4}$ = 7.9 Hz, Se*H*), 3.62 (1H, dt, $J_{3,4+4,5}$ = 22.0 Hz, $^3J_{SeH,4}$ = 7.9 Hz, H-4), 3.94 (3H, s, OCH_3), 4.24 (1H, ddd, $J_{4,5}$ = 11.0 Hz, $J_{5,6a}$ = 4.4 Hz, $J_{5,6b}$ = 2.7 Hz, H-5), 4.80 (1H, dd, $J_{5,6a}$ = 4.4 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.83 (1H, dd, $J_{5,6b}$ = 2.7 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 5.18 (1H, dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 5.22 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 5.89 (1H, dd, $J_{2,3}$ = 9.8 Hz, $J_{3,4}$ = 11.0 Hz, $^3J_{H,Se}$ = 5.0 Hz, H-3), 7.30-8.15 (15H, m, Ar). **(115)** The air oxidation of methyl 2,3,6-tri-O-benzoyl-4-seleno-α-D-glucopyranoside **(115)** afforded the corresponding diselenide that was recrystallized from ethanol. mp 118-120°C; $[\alpha]_D^{24}$ 59.2° (*c* 1.2 in $CHCl_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.8 (C-4), 55.6 (OCH_3), 65.0 (C-6), 70.0 (C-5), 70.8 (C-3), 73.2 (C-2), 97.3 (C-1). ^1H

NMR (400 MHz, $CDCl_3$) δ 3.34 (3H, s, OCH_3), 3.48 (1H, t, $J_{3,4+4,5}$ = 22.2 Hz, H-4), 4.28 (1H, ddd, $J_{4,5}$ = 11.8 Hz, $J_{5,6a}$ = 1.9 Hz, $J_{5,6b}$ = 6.1 Hz, H-5), 4.67 (1H, dd, $J_{5,6a}$ = 1.9 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6a), (1H, dd, $J_{5,6b}$ = 6.1 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6b),5.13 (1H, d, $J_{1,2}$ = 3.4 Hz, H-1), 5.18 (1H, dd, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 5.96 (1H, t, $J_{2,3+3,4}$ = 20.5 Hz, H-3), 7.15-8.15 (15H, m, Ar); Anal. Calcd for $C_{56}H_{56}O_{16}Se_2$: C, 59.16; H, 4.43. Found: C, 59.12; H, 4.38.

Methyl 2,3,6-Tri-*O*-benzoyl-4-seleno-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α/β-D-glucopyranosyl)-α-D-glucopyranoside (116,117) A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)** (0.05 g, 0.1 mmol), methyl 2,3,6-tri-*O*-benzoyl-4-seleno-α-D-glucopyranoside **(111)** (0.1 g, 0.18 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (1 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.002 mL, 0.01 mmol) was added. The reaction mixture was stirred at -78° C for 1 h. An aliquot of the reaction mixture was taken and quenched with Et_3N at -78°C. A TLC performed at this point indicated that no reaction had occurred. The reaction mixture was then warmed to room temperature and stirred for another 1.5 h. A TLC at this point indicated that the reaction was complete. The reaction mixture was again cooled to -78° C and neutralized with collidine. The reaction mixture was then filtered, and washed successively with hydrochloric acid (5%) and aqueous sodium hydrogen carbonate. The organic extracts were dried over magnesium sulfate and concentrated to give a foam that was chromatographed with hexane-ethyl acetate (1.3:1) as eluant, [R_f α-isomer **116** = 0.33; β-isomer **117** = 0.23].The *title compounds* **116** and **117** were obtained as foams and were crystallized from

ethanol (α:40 mg, 45%, β:10 mg, 11%). α-isomer **116**: mp 184°C, $[\alpha]_D^{20}$ +292° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 19.9, 20.3, 20.4, 20.5 (4COCH$_3$), 41.4 (C-5'), 42.8 (C-4), 44.9 [$^1J(^{13}C,^1H)$ 156 Hz, (C-1)], 55.6 (OCH$_3$), 60.8 (C-6'), 65.0 (C-6), 68.7 (C-5), 71.6 (C-3'), 71.7 (C-4), 72.1 (C-3), 73.4 (C-2), 73.9 (C-2'), 97.3 [$^1J(^{13}C,^1H)$ 173 Hz, (C-1)], 128.3-133.4 (Ar), 165.2, 165.8, 166.2 (3COC$_6$H$_5$) 168.9, 169.3, 169.35, 170.4 (4COCH$_3$). ^1H NMR ($CDCl_3$): δ 1.59, 1.91, 2.0, 2.04 (12H, 4s, 4COCH$_3$), 3.36 (1H, t, $J_{3,4+4,5}$ = 22.6 Hz, H-4), 3.44 (3H, s, OCH$_3$), 3.61 (1H, ddd, $J_{4',5'}$ = 10.5 Hz, $J_{5',6a'}$ = 4.6 Hz, $J_{5',6b'}$ = 2.9 Hz, H-5'), 4.03 (1H, dd, $J_{5',6a'}$ = 2.9 Hz, $J_{6a',6b'}$ = 12.3 Hz, H-6a'), 4.28 (1H, ddd, $J_{4,5}$ = 9.4 Hz, $J_{5,6a}$ = 2.2 Hz, $J_{5,6b}$ = 6.3 Hz, H-5), 4.43 (1H, dd, $J_{5',6b'}$ = 4.6 Hz, $J_{6a',6b'}$ = 12.3 Hz, H-6b'), 4.68 (1H, dd, $J_{5,6a}$ = 6.3 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6a), 4.75 (1H, d, $J_{1',2'}$ = 5.6 Hz, H-1'), 4.90 (1H, dd, $J_{5,6b}$ = 2.2 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6b), 5.01 (1H, dd, $J_{1',2'}$ = 5.6 Hz, $J_{2',3'}$ = 10.0 Hz, H-2'), 5.12 (1H, t, $J_{2',3'+3',4'}$ = 19.3 Hz, H-3'), 5.14 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 5.21 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 5.22 (1H, dd, $J_{3',4'}$ = 9.1 Hz, $J_{4',5'}$ = 10.5 Hz, H-4'), 6.20 (1H, dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 10.8 Hz, H-3), 7.2-8.2 (15H, Ar). Anal. Calcd for $C_{42}H_{44}O_{16}SSe$: C, 55.08; H, 4.84. Found: C, 54.94; H, 4.86. β-isomer **117**: mp 175°C. ^{13}C NMR ($CDCl_3$): δ 19.9, 20.3, 20.4, 20.5 (4COCH$_3$), 39.3 (C-1'), 43.0 (C-4), 45.9 (C-5'), 55.6 (OCH$_3$), 60.8 (C-6'), 64.8 (C-6), 69.0 (C-3), 70.6 (C-5), 71.5 (C-4'), 73.3 (C-2), 73.8 (C-2'), 74.5 (C-3'), 97.4 (C-1), 128.2-133.3 (Ar), 165.2, 165.8, 166.2 (3COC$_6$H$_5$) 168.9, 169.3, 169.35, 170.4 (4COCH$_3$). ^1H NMR ($CDCl_3$): δ 1.86, 1.92, 1.96, 2.02 (12H, 4s, 4COCH$_3$), 2.71 (1H, ddd, $J_{4',5'}$ = 10.5 Hz, $J_{5',6a'}$ = 3.0 Hz, $J_{5',6b'}$ = 4.5 Hz, H-5'), 3.44 (3H, s, OCH$_3$), 3.55 (1H, t, $J_{3,4+4,5}$ = 22.7 Hz, H-4), 3.77 (1H, dd, $J_{5',6a'}$ = 3.0 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6a'), 4.08 (1H, dd, $J_{5',6b'}$ = 4.5 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6b'), 4.11 (1H, d, $J_{1',2'}$ = 10.8 Hz, H-1'), 4.40 (1H, ddd, $J_{4,5}$ = 11.5 Hz, $J_{5,6a}$ = 3.3 Hz, $J_{5,6b}$ = 1.9 Hz,

H-5), 4.75-4.83 (2H, m, H-3', H-6'), 4.86 (1H, dd, $J_{5,6b}$ = 1.9 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6b), 4.97 (1H, dd, $J_{1',2'}$ = 10.8, $J_{2',3'}$ = 9.5 Hz, H-2'), 5.13 (1H, dd, $J_{3',4'}$ = 9.5 Hz, $J_{4',5'}$ = 10.5 Hz, H-4'), 5.20 (1H, d, $J_{1,2}$ = 3.4 Hz, H-1), 5.25 (1H, dd, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 9.9 Hz, H-2), 5.92 (1H, dd, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 11.2 Hz, H-3), 7.3-8.2 (15H, Ar). Anal. Calcd for $C_{42}H_{44}O_{16}SSe$: C, 55.08; H, 4.84. Found: C, 54.84; H, 4.79.

Methyl 4-seleno-(-5'-thio-α–D-glucopyranosyl)-α-D-glucopyranoside (84). A freshly prepared solution of sodium methoxide in methanol (0.2N, 2.5 mL) was added to disaccharide **(116)** (95 mg, 0.1 mmol) and the mixture was stirred under nitrogen for 3 h. The solution was acidified to a pH of 3 with Rexyn (H^+) resin, and filtered. The filtrate was neutralized with Amberlite basic ion exchange resin, filtered and concentrated. The residue was purified by column chromatography with hexane-dichloromethane-methanol (1.2:1:1) as eluant, [R_f = 0.32]. The *title compound* **(84)** was obtained as a foam (35 mg, 81%). $[\alpha]_D^{20}$ +510.7° (*c* 0.75 in CH_3OH);^{13}C NMR (D_2O): δ 47.6 (C-1'), 48.7 (C-4), 49.9 (C-5'), 57.9 (OCH_3), 62.8 (C-6), 65.3 (C-6'), 74.1 (C-5), 75.3 (C-2), 75.6 (C-3), 76.3 (C-4'), 78.0 (C-2'), 78.4 (C-3'), 102.3 (C-1). ^1H NMR (D_2O): δ 3.02 (1H, t, $J_{3,4+4,5}$ = 22.0 Hz, H-4), 3.20 (1H, dt, $J_{4',5'}$ = 10.4 Hz, $J_{5',6a'+5',6b'}$ = 9.2 Hz, H-5'), 3.44 (3H, s, OCH_3), 3.47 (1H, t, $J_{2',3'+3',4'}$ = 18.4 Hz, H-3'), 3.53 (1H, dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.58 (1H, dd, $J_{3',4'}$ = 9.1 Hz, $J_{4',5'}$ = 10.4 Hz, H-4'), 3.84-3.96 (5H, m, H-5, 6a', 6b', 2, 6a), 3.93 (1H, t, $J_{2,3+3,4}$ = 19.0 Hz, H-3), 4.04 (1H, dd, $J_{5,6b}$ = 1.9 Hz, $J_{6a,6b}$ = 11.9 Hz, H-6b), 4.68 (1H, d, $J_{1',2'}$ = 4.3 Hz, H-1'), 4.84 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1). ES-MS Calcd. for $C_{13}H_{24}O_9SSe$: $M^{+\bullet}$436; Found: 459 $(M+Na)^{+\bullet}$.

3,4,6-Tri-*O*-acetyl-1,2-(methyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranos-2-yl)-α-D-5'-thio-α-D-glucopyranose orthoacetate (119). A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)** (0.15 g, 0.3 mmol), methyl-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside **(92)** (0.1 g, 0.24 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (3 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.005 mL, 0.02 mmol) was added. The reaction mixture was stirred at -78° C for 1 h. An aliquot of the reaction mixture was taken and quenched with triethylamine. A TLC of this aliquot indicated the presence of starting materials and product. The reaction mixture was treated further with TESOTf (0.005 mL, 0.02 mmol). After another 1 h the reaction mixture was quenched with triethylamine. The reaction mixture was then warmed to room temperature, filtered through celite, concentrated, and chromatographed with toluene-ethyl acetate (3.5:1) as eluant [R_f orthoester **119** = 0.30; disaccharide **93** = 0.28]. The *title compound* **(119)** was obtained as a powder (0.07 g, 40%) Also isolated were the α/β-disaccharides **93** and **118** (0.07 g, 40%, α:β = 10:1). Orthoester **119** :^{13}C NMR ($CDCl_3$): δ 20.6 ($3COCH_3$), 22.9 ($CCH3$), 37.9 (C-5'), 55.2 (OCH_3), 61.3 (C-6), 62.2 (C-2'), 70.3 (C-6'), 73.3, 74.3 (C-3, C-4), 74.8 (C-5'), 75.5 ($CH_2C_5H_5$), 76.7 (C-2), 82.2 (C-4'), 99.8 (C-1'), 101.3 ($OCOC_6H_5$), 121.9 (CCH_3), 126.0-138.5 (Ar), 169.4 ($3COC_6H_5$). ^{1}H NMR ($CDCl_3$): δ 1.52 (3H, s, CCH_3), 2.03 (3H, s, $COCH_3$), 2.07 (6H, s, $2COCH_3$), 3.40 (3H, s, OCH_3), 3.49 (1H, m, H-5'), 3.64 (1H, t, $J_{3,4+4,5}$ = 18.3 Hz, H-4), 3.74 (1H, t, $J_{5,6a+6a,6b}$ = 20.1 Hz, H-6a), 3.77-3.83 (2H, m, H-2, H-5), 3.90 (1H, t, $J_{2,3+3,4}$ = 18.5 Hz, H-3), 4.10 (1H, dd, $J_{5',6a'}$ = 3.1 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6a'), 4.25-4.36 (3H, m, H-6b, H-2', H-6b'), 4.71 (1H, d, J = 11.0 Hz, $CHHC_6H_5$), 4.80 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.85 (1H, d, J = 11.0 Hz,

CH*H*C_6H_5), 5.03-5.13 (2H, m, H-4', H-3'), 5.35 (1H, d, $J_{1',2'}$ = 5.5 Hz, H-1'), 5.56 (OC*H*C_6H_5), 7.2-7.5 (10H, m, Ar). Anal. Calcd for $C_{35}H_{42}O_{14}S$: C, 58.49; H, 5.89. Found: C, 58.23; H, 5.88.

Allyl 3-O-Benzoyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (130). A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)**. (0.3 g, 0.6 mmol), allyl 3-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside **(124)** (0.49 g, 1.2 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (6 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.014 mL, 0.06 mmol) was added. The reaction mixture was stirred at -78° C for 1 h. An aliquot of the reaction mixture was quenched with triethylamine. A TLC of this aliquot indicated the presence of starting materials and product was observed. The reaction mixture was allowed to reach room temperature and stirred for another 1 h. It was then cooled to -70° C, quenched with collidine and warmed to room temperature. The mixture was washed successively with hydrochloric acid (2N), and sodium hydrogen carbonate, dried over magnesium sulfate and concentrated. The residue was chromatographed with hexane-ethyl acetate (1.3:1) as eluant [R_f = 0.32]. A mixture of the α and β disaccharides (9:1) was obtained (360 mg, 80%, α-isomer **130**: 324 mg, 72%, β-isomer **131**: 36 mg, 8%). α-disaccharide **130**: mp 185° C $[\alpha]_D^{20}$ 206° (*c* 1.0 in CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.3, 20.5, 20.51, 20.8 (4CO*C*H_3), 38.2 (C-5'), 60.5 (C-6'), 68.8 (O*C*H_2CHCH_2) 68.9 (C-6), 70.7 (C-3), 71.45 (C-3'), 71.51 (C-4'), 75.0 (C-2'), 75.6 (C-2), 77.5 (C-1'), 79.5 (C-4), 95.1 (C-1), 101.6 (O*C*HC_6H_5), 118.4 (OC_{H_2}*C*HCH_2), 126.1-130.1 (Ar), 169.0, 169.3, 170.4 (4*C*OCH$_3$). ^1H NMR ($CDCl_3$): δ 1.77, 1.94, 1.99, 2.06 (12H, 4s, 4COC*H*$_3$), 3.05

(1H, m, H-5'), 3.56 (1H, dd, $J_{5',6a'}$ = 3.5 Hz, $J_{6a',6b'}$ = 12.8 Hz, H-6a'), 3.75-3.85 (3H, m, H-6b', H-6a, H-4), 3.98-4.05 (1H, $OCHHCHCH_2$), 4.14 (1H, dd, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 4.22-4.26 (1H, $OCHHCHCH_2$), 4.32 (1H, dd, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6b), 4.96 (1H, d, $J_{1',2'}$ = 3.0 Hz, H-1'), 4.99 (1H, dd, $J_{1',2'}$ = 3.0 Hz, $J_{2',3'}$ = 9.6 Hz, H-2'), 5.01 (1H, d, $J_{1,2}$ = 3.0 Hz, H-1), 5.1 (1H, dd, $J_{3',4'+4',5'}$ = 21.2 Hz, H-4'), 5.22-5.29 (1H, OCH_2CHCH_2), 5.28 (1H, dd, $J_{2',3'+3',4'}$ = 20.5 Hz, H-3'), 5.36-5.41 (1H, OCH_2CHCH_2), 5.53 ($OCHC_6H_5$), 5.91 (1H, t, $J_{2,3+3,4}$ = 20.2 Hz, H-3), 5.88-5.98 (1H, OCH_2CHCH_2), 7.2-8.2 (10H, m, Ar). Anal. Calcd for $C_{37}H_{42}O_{16}S$: C, 57.36; H, 5.46. Found: C, 57.11; H, 5.57.

Allyl 2-O-(5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (86). Allyl 3-O-benzyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-*O*-acetyl-5'-thio-α-D-glucopyranosyl)-α-D-glucopyranoside (**130**).(125 mg, 0.16 mmol) was treated with 80% aqueous acetic acid (4 mL) and heated at 50° C for 4 h. The acetic acid was removed in vacuo, the residue was dried over magnesium sulfate and concentrated. A freshly prepared solution of sodium methoxide in methanol (0.2N, 2.0 mL) was added and the mixture was stirred under nitrogen for 3 h. The solution was acidified to a pH of 3 with Rexyn (H^+) resin, and filtered. The *title compound* (**86**) was crystallized from the reaction mixture with hexane-dichloromethane-methanol (45 mg, 75%). $[\alpha]_D^{20}$ +260° (*c* 1 in CH_3OH); ^{13}C NMR (D_2O): δ 50.5 (C-5'), 67.8 (C-6'), 68.5 (C-6), 76.3 (OCH_2CHCH_2), 77.4 (C-4), 81.1 (C-4'), 68.2, 79.1, 79.6, 81.6, 82.7, 82.9 (C-2, 3, 4, 2', 3', OCH_2CHCH_2), 87.5 (C-1'), 101.8 (C-1), 127.1 (OCH_2CHCH_2); ^1H NMR (D_2O): δ 3.17 (1H, ddd, $J_{4',5'}$ = 10.5 Hz, $J_{5',6a'}$ = 3.3 Hz, $J_{5',6b'}$ = 5.2 Hz, H-5'), 3.43 (1H, t, $J_{3,4+4,5}$ = 19.0 Hz, H-4), 3.59 (1H, t, $J_{3',4'+4',5'}$ = 19.5 Hz, H-4'), 3.63-3.86 (8H, m, H-2, 3,

5, 2', 3', 6a', 6a, 6b, OCH_2CHCH_2), 3.88 (1H, t, $J_{5',6b'}$ = 5.2, $J_{6a',6b'}$ = 12.0 Hz, H-6b'), 4.05 (1H, t, $J_{5,6a}$ = 6.9, $J_{6a,6b}$ = 12.0 Hz, OCH_2CHCH_2), 4.21 (1H, t, $J_{5,6b}$ = 5.8, $J_{6a,6b}$ = 12.4 Hz, OCH_2CHCH_2), 4.85 (1H, d, $J_{1',2'}$ = 3.0 Hz, H-1'), 5.14 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1) 5.22-5.38 (2H, m, OCH_2CHCH_2), 5.94 (1H, m, OCH_2CHCH_2). Anal. Calcd for $C_{15}H_{26}O_{10}S$: C, 45.22; H, 6.53. Found: C, 45.04; H, 6.85.

3,4,6-Tri-*O*-acetyl-1,2-(allyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranos-2-yl)-α-D-5'-thio-α-D-glucopyranose orthoacetate (132). A mixture of O-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl) trichloroacetimidate **(100)**. (0.15 g, 0.3 mmol), allyl-3-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside **(124)** (0.24 g, 0.6 mmol) and dry 4Å molecular sieves in anhydrous dichloromethane (3 mL) was stirred under nitrogen for 1 h. The reaction mixture was cooled to -78° C and triethylsilyl triflate (0.007 mL, 0.03 mmol) was added. The reaction mixture was stirred at -78° C for 1 h. An aliquot of the reaction mixture was taken and quenched with triethylamine. A TLC of this aliquot indicated the presence of unconsumed starting materials. The reaction mixture was again treated with TESOTf (0.007 mL, 0.03 mmol). TLC after another 2 h indicated completion of the reaction. The reaction mixture was quenched with triethylamine, warmed to room temperature, filtered through celite and concentrated. The residue was chromatographed with hexane-ethyl acetate (1.5:1) as eluant [R_f orthoester **132** = 0.32; disaccharide **130** = 0.28]. The *title compound* **132** was obtained as a powder (0.124 g, 54%) Also isolated was the α-disaccharide **130** (36 mg, 16%). Orthoester **132** : ^{13}C NMR ($CDCl_3$): δ 20.6, 20.7, 20.8 ($3COCH_3$), 22.5 ($CCH3$), 39.9 (C-5'), 61.4 (C-6'), 62.5 (C-5), 68.7 (OCH_2CHCH_2), 69.0 (C-6), 70.3 (C-4'), 70.5 (C-3), 73.0 (C-

2), 73.2 (C-3'), 78.7 (C-2'), 79.8 (C-4), 97.1 (C-1), 101.6 ($OCHC_6H_5$), 118.6 (OCH_2CHCH_2), 121.9 (CCH_3), 126.2-137.0 (Ar), 165.3 (COC_6H_5), 169.5, 169.6, 170.5 ($3COCH_3$). ^1H NMR ($CDCl_3$): δ 1.64 (3H, s, CCH_3), 2.0 (3H, s, $COCH_3$), 2.06 (6H, s, $2COCH_3$), 3.43 (1H, m, H-5'), 3.72-3.80 (2H, m, H-4, H-6a), 3.95-4.04 (3H, m, H-2, H-5, $OCHHCHCH_2$), 4.06 (1H, dd, $J_{5',6a'}$ = 3.2 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6a'), 4.22-4.32 (4H, m, H-6b', H-2', H-6b, $OCHHCHCH_2$), 4.98-5.06 (2H, m, H-3', H-4'), 5.08 (1H, d, $J_{1,2}$ = 3.8 Hz, H-1), 5.24-5.42 (1H, m, OCH_2CHCH_2), 5.34 (1H, d, $J_{1',2'}$ = 5.5 Hz, H-1'), 5.49 ($OCHC_6H_5$), 5.74 (1H, t, $J_{2,3+3,4}$ = 19.4 Hz, H-3), 5.94 (1H, m, OCH_2CHCH_2), 7.2-8.2 (10 H, m, Ar). Anal. Calcd for $C_{37}H_{42}O_{16}S$: C, 57.36; H, 5.46. Found: C, 57.21; H, 5.74.

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