Sulfonium salt activation in oligosaccharide synthesis

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Chapter 1

General Introduction

1.0 Introduction

Oligosaccharides and glycoconjugates play important roles in a wide variety of processes in nature. The elucidation of the mechanisms of these processes at a molecular level can be facilitated by the availability of the involved sugar constructs. However, isolation of these molecules from natural sources can be complicated since the total amount of material present in biological samples is often limited and must be separated from chemically and structurally similar yet different compounds. Therefore, the acquisition of oligosaccharides and glycoconjugates in a pure form and in sufficient amounts relies predominantly on advances in synthetic organic chemistry. Present state of the art oligosaccharide and glycoconjugate synthesis indicates that the diversity and complexity in the molecular architecture of this class of biomolecules offers various appealing synthetic challenges.

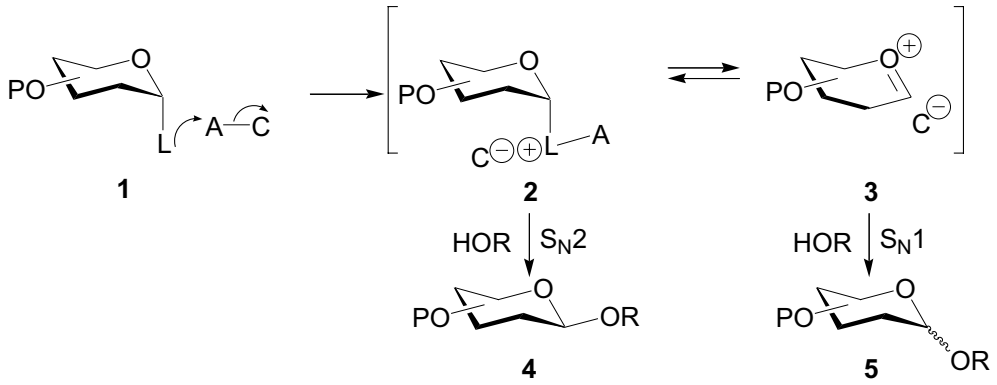
In this chapter, a concise introduction to some basic principles of oligosaccharide synthesis is presented, followed by an overview of cyclic diol protecting groups and the influence these groups may exert on the outcome of glycosylation reactions. In the final section, the objective and content of this thesis are outlined.

1.1 Chemical Oligosaccharide Synthesis: A Focus on Protecting Groups

1.1.1 Mechanism of Chemical Glycosylation

The development of synthetic procedures for the stereoselective introduction of glycosidic linkages is a pivotal goal in carbohydrate chemistry. Since Koenigs and Knorr described the first stereoselective glycosylation reaction,[1] numerous accounts of the synthesis of glycosidic linkages have been reported.[2] The efficient chemical construction of a glycosidic bond by organic synthesis entails the regio- and stereoselective condensation of two polyfunctional reaction partners ideally affording a single product. A typical glycosylation reaction‡ (Scheme 1) starts with the activation of the anomeric substituent (leaving group, L) of a glycosyl donor by an appropriate promoter/activator (A-C). The bond between the anomeric carbon atom and L is partly or even completely broken, affording an electrophilic glycosyl species which undergoes S_N2- or S_N1-type nucleophilic attack by the hydroxy group of an acceptor (ROH) to form the glycosidic bond.[3]

Scheme 1: General mechanism of glycosylation.



The outcome of a glycosylation reaction in terms of yield and stereochemistry is difficult to predict because of its dependence on correlating factors such as the potency of the anomeric leaving group, the activator/promoter system, the reaction solvent, the temperature, and the identity of both the donor and acceptor. Apart from these factors the protecting groups of both reaction partners play a crucial role.

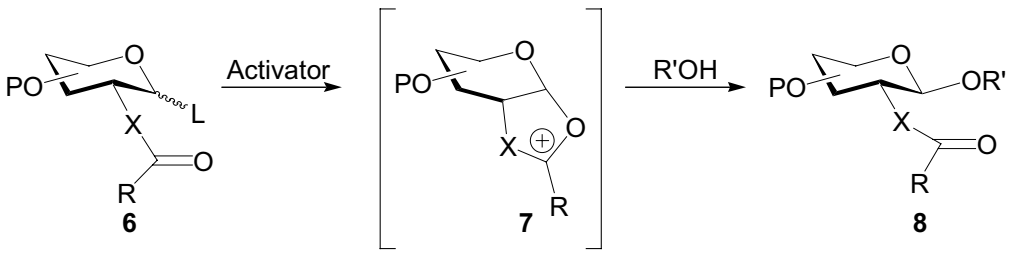
‡In carbohydrate chemistry, an acceptor molecule is said to be glycosylated with a carbohydrate-based donor whereas a saccharide donor is said to be glycosidated when condensed with an acceptor.

1.1.2 Influence of Protecting Groups in Oligosaccharide Synthesis

1.1.2.1 Introduction

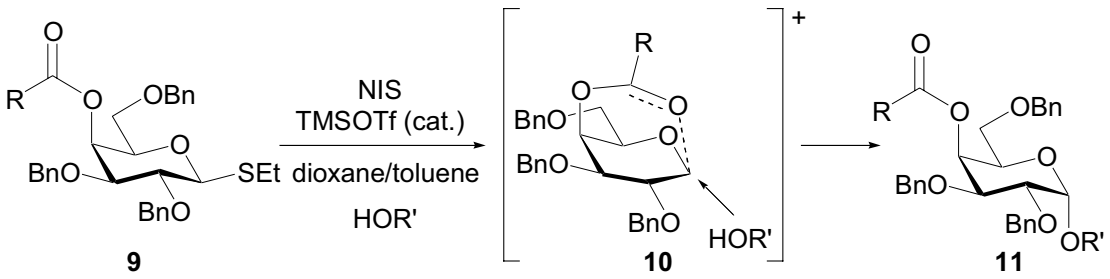
Originally devised to ensure regioselectivity, protecting groups[4] on the reaction partners also exhibit a major influence on the efficiency and stereoselectivity of glycosylation events. This is best illustrated by the stereoselective introduction of 1,2-*trans* glycosides by neighbouring group participation (NGP) of 2-acyl protecting groups (Scheme 2).

Scheme 2: Neighbouring group assisted glycosylation.



After activation of glycosyl donor **6**, the intermediate anomeric electrophile is intramolecularly trapped by a C-2 carbonyl function to give cyclic acyloxonium ion **7**. This ion can only undergo an S_N2-type attack, leading to *trans* glycoside **8**.[5] Apart from 2-*O* and 2-*N* acyl groups, remote acyl groups occasionally direct the stereochemistry of a glycosylation reaction. For example, the α-selectivity observed in the coupling of 4-*O*-acyl galactopyranoside donors can be partially attributed to the influence of the acyl moiety (Scheme 3).[6]

Scheme 3: Remote neighbouring group participation.

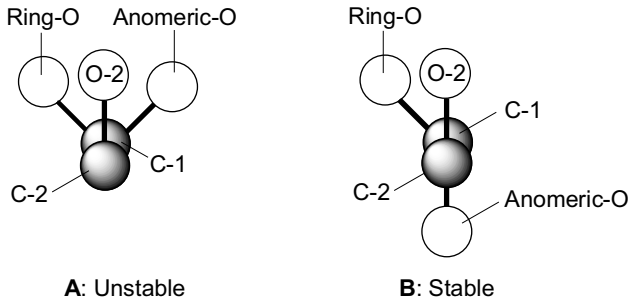


Upon activation of thiodonor **9** with *N*-iodosuccinimide (NIS)/trimethylsilyl trifluoromethanesulfonate (TMSOTf), the developing positive charge at the anomeric

center is stabilized by the axially oriented acyl function,[6b] thereby shielding the β-face from glycosidation and providing stereoselective access to the axial anomer **11**.

An effective tool such as the 2-*O*-acyl group for the stereoselective formation of 1,2-*trans* bonds is lacking for the introduction of 1,2-*cis* linkages. Evidently, the synthesis of 1,2-*cis*-bonds demands the use of a glycosyl donor equipped with a non-participating C-2 function (*e.g.* benzyloxy or azide). Activation of a properly protected donor with an equatorial C-2 substituent as in glucose results in a glycosyl species which may undergo attack by the acceptor alcohol from both the axial and equatorial side. Attack from the axial side is said to be promoted by the anomeric effect, which can be qualified as the thermodynamic preference of an electronegative substituent on the anomeric carbon atom to adopt an axial orientation. The phenomenon has been rationalised as deriving from $n_O \rightarrow \sigma^*_{CO}$ hyperconjugative delocalisation, resulting in a lower energy for the axially substituted product as compared to an equatorial one.[7-9] Despite the favourable influence of the anomeric effect on the formation of 1,2-*cis* linkages in the *gluco*-series (equatorial C-2 substituent), the degree of selectivity as obtained for the introduction of *trans*-glycosides is seldom attained. The construction of *cis*-linkages with donors bearing an axial C-2 substituent, as in β-D-mannosides and β-L-rhamnosides, is even more daunting for the following reasons. First, equatorial attack of the acceptor molecule suffers from unfavourable steric interactions with the axial C-2 substituent. Second, *cis*-product formation does not benefit from stabilisation by the anomeric effect. Third, there is an additional α-favouring interaction, the so-called Δ2 effect (Figure 1).[10,11]

Figure 1: The Δ2 Effect: in **A**, the three oxygen atoms are in close proximity resulting in conformational instability. **B** lacks this stereo-electronic repulsion and is therefore more stable.



A: Unstable **B**: Stable

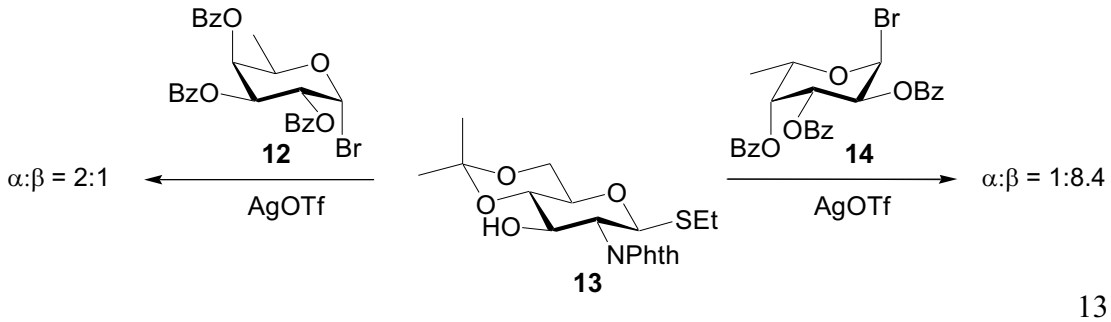
The challenge to construct 1,2-*cis* bonds in the *manno*-series (axial C-2 substituent) has resulted in the development of several methodologies, including insoluble silver salt promoted S_N2 displacements of α-mannosyl bromides and rhamnosides[12] and glycosidation of 2-*O*-sulfonyl mannosyl[13-15] and rhamnosyl

sulfonates.[16] More indirect methods are based on manipulation at C-2 (direct *gluco* → *manno* inversion[17-19] or oxidation → reduction[20-23]) or tethering of the aglycon to the glycosyl donor prior to the actual coupling.[24-30]

Protecting groups, applied to mask the functional groups in donor glycosides influence not only the stereochemistry but also the reactivity of both the donor and acceptor in a glycosylation reaction. Protecting groups exert an important effect on the reactivity of the anomeric leaving group in a donor. The observation that an *n*-pentenyl glycoside bearing a C-2 benzyloxy substituent was hydrolysed much faster than its C-2 acyloxy counterpart led Fraser-Reid and coworkers to state that '*the pentenyl group could be "armed" or "disarmed" by the type of protecting group placed on the C-2 oxygen*'.[31] As a variety of glycosyl donors complies with the 'armed-disarmed' phenomenon, it has become a basic rule in carbohydrate chemistry that a glycosyl donor bearing a relatively strong electron withdrawing C-2 functionality such as an acyloxy group is less reactive than its C-2 alkyloxy or silyloxy counterpart. This is further solidified by the Ley and Wong laboratories and their work on the computational determination of the relative reactivity values (RRV's) of thioglycosides in which the deactivating ability of a set of C-2 substituents on the reactivity of an otherwise unaltered thiogalactoside was quantified as $-N_3$ > -O(ClAc) > -NPhth > -OBz > -OBn.[32] The 'armed-disarmed' concept is often elegantly exploited in chemoselective glycosylation strategies.[33]

Although the influence of protecting groups on the reactivity of glycosyl acceptors in terms of electronic effects has been studied to a lesser extent,[34,35] it is commonly accepted that benzylated acceptors are more reactive than the corresponding acylated acceptors.[36] As the bulk of both the glycosyl donor and acceptor is represented by protecting groups added to the original saccharide core, steric hindrance due to the sheer size of the protecting groups around the donor and acceptor reaction sites is an important factor in terms of yield and stereoselectivity. In this respect, it is of interest that Spijker and Van Boeckel established the occurrence of double stereodifferentiation in the transition state of glycosylation reactions.[37] Condensation of D-fucosyl bromide **12** with D-glucosamine derivative **13** predominantly afforded the unexpected α-linked product, thereby overruling intramolecular anchimeric assistance of the 2-*O*-benzoate (Scheme 4).

Scheme 4: Double stereodifferentiation.

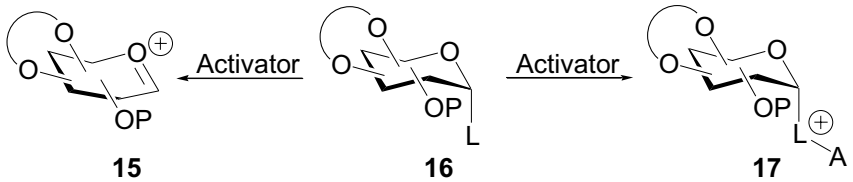


In contrast, coupling of the mirror image L-fucosyl bromide donor **14** with the same acceptor afforded predominantly the β-product. These opposing outcomes in stereoselectivity can be explained by a steric hindrance in the transition state that leads to mismatched (**12**+**13**) and matched (**14**+**13**) donor/acceptor pairs.

1.1.2.2 Cyclic Protecting Groups in Oligosaccharide Synthesis

Besides ethers (benzyl, allyl), esters (acetyl, benzoyl) and silyl ethers (TBDMS, TBDPS) to mask hydroxyl groups, diol protecting groups have found widespread application in oligosaccharide synhesis. The arsenal of diol protecting groups includes the cyclic carbonate, various acetals such as the benzylidene, anisylidene and isopropylidene acetal, Ley's diacetals and the more recently developed cyclic silyl ethers and oxazolidinones. Apart from their advantageous properties for regiospecific protection, they are also recognised for their ability to induce stereoselectivity in glycosylation reactions. The tendency of glycosyl donors equipped with such groups to influence the formation of either the axially or equatorially oriented glycosidic bond can be rationalised by Fraser-Reid's observation that cyclic acetals affect the reactivity of glycosyl donors by exercising a torsional effect on the formation of the planar oxacarbenium ion.[38,39]

Scheme 5: Torsional effects in donor activation.



15 **16** **17**

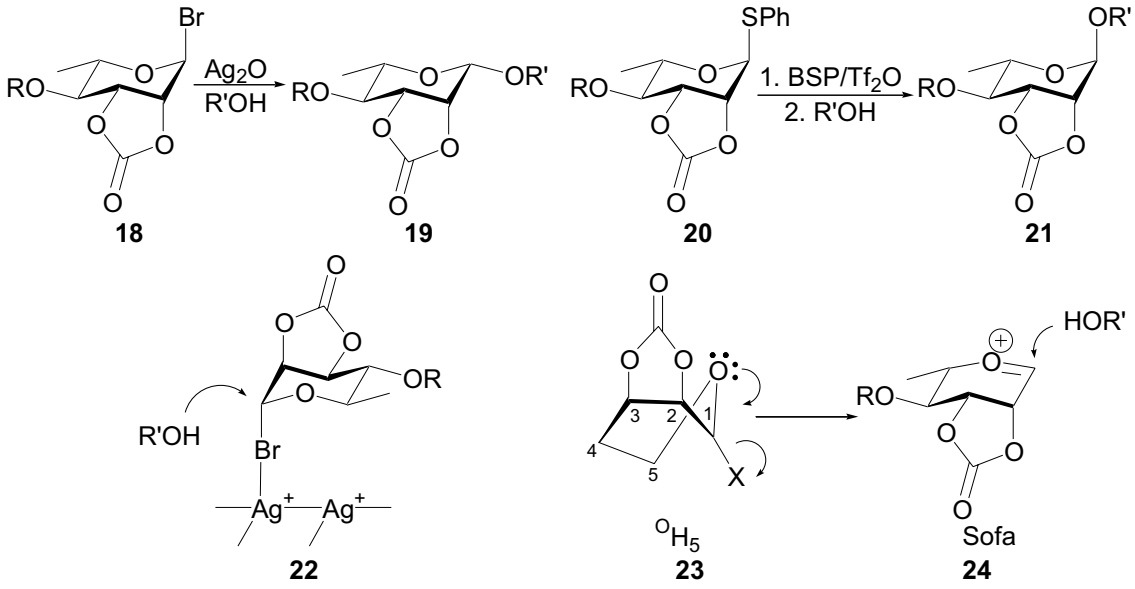
Depending on the locus of the ring-protected diol in the pyranose ring, this effect can either facilitate or oppose rehybridisation of the anomeric carbon atom upon activation of **16** thereby encouraging either formation of the α-selective oxacarbenium ion‡ (**15**, Scheme 5) which leads to the thermodynamically preferred axially substituted product, or to formation of a reactive species (**17**) which can undergo S_N2-type reactions. In the following sections, the influence of diol protecting groups on the reactivity of glycosyl donors and the stereoselectivity of glycosylation reactions will be discussed and some illustrative examples given.

‡Due to the anomeric effect, glycosidation of cation **15** will afford mainly the α-oriented (axial) substituent in this case, hence the terminology α-selective oxacarbenium ion.

1.1.2.2.1 Cyclic Carbonates and Oxazolidinones

Gorin and Perlin applied 2,3-*O*-carbonates in the synthesis of β-mannosides from α-mannosyl bromides with the aid of heterogeneous catalysis.[40] In a similar approach, Kochetkov and coworkers showed that 2,3-*O*-carbonyl protected α-L-rhamnosyl bromides can be β-selectively glycosidated with various acceptors (*e.g.* **18→19**).[41] In contrast, Crich *et al.* found that the 1-benzenesulfinyl piperidine (BSP)/trifluoromethanesulfonic anhydride (Tf_2O) mediated glycosidation of similarly protected phenyl α-D-thiomannopyranosides[42] and α-L-thiorhamnopyranosides[43] at low temperature gave stereoselective entry to axially coupled disaccharides (*e.g.* **20→21**). The contrasting stereochemical outcome in the couplings of 2,3-*O*-carbonyl rhamnosyl bromides and thiorhamnosides can be explained as follows (Scheme 6).

Scheme 6: Selectivity of rhamnosyl bromide and thiorhamnoside glycosylations.

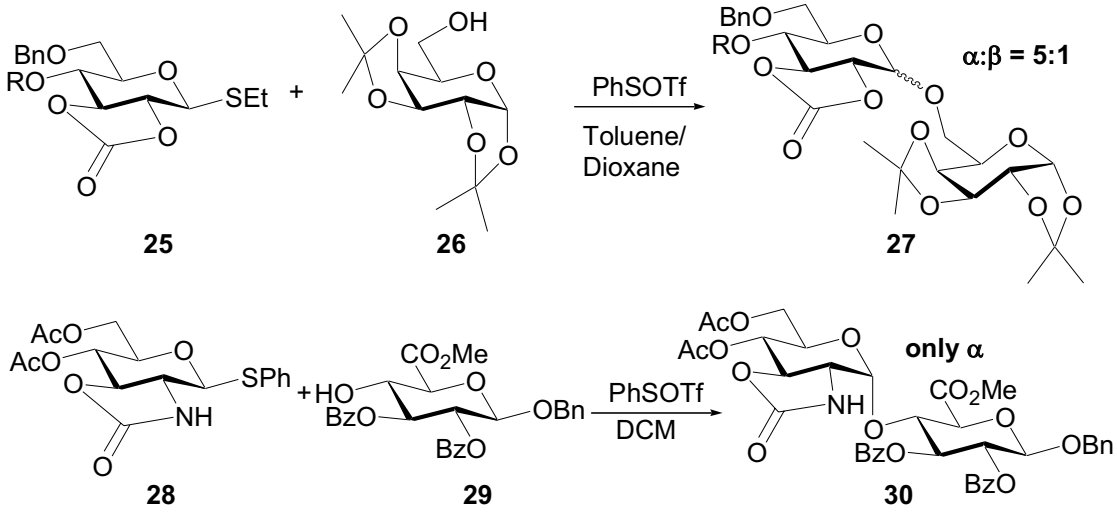


Complexation of the anomeric bromide in **18** with the insoluble silver salt, as proposed by Van Boeckel and coworkers,[44] afforded the activated complex **22** in which the α-face is shielded resulting in an S_N2-type attack by the nucleophile from the β-side. The α-selectivity observed with thioglycosides **20** can be explained by taking into account that the 2,3-*O*-carbonyl group locks the pyranose ring in a $^{O}H_5$ half chair conformation **23**,[45] which is thought to facilitate the formation of the α-selective oxacarbenium ion **24** upon activation.

The 2,3-carbonate was also employed in *gluco*-type donors. For instance, the phenylsulfenyltrifluoromethanesulfonate (PhSOTf) mediated coupling of ethyl 2,3-*O*-carbonyl-1-thio-β-D-glucopyranoside **25** with diacetonegalactose **26** in a mixture of

toluene and dioxane, as described by Boons *et al.* preferentially afforded α-dimer **27** (Scheme 7).[46]

Scheme 7: α-Selective condensations of 2,3-*O*-carbonyl thioglucoside **25** (R = tetra-*O*-benzoyl-β-D-galactosyl) and 2,3-oxazolidinone thioglucoside **28**.



The Kerns group reported that 2,3-oxazolidinone equipped thioglucoside **28** was α-selectively condensed with a number of acceptors using PhSOTf as the activator at low temperature in DCM.[47]

The effect of 3,4-*O*-carbonyl protection in thiorhamnoside donors in the stereoselective synthesis of equatorially linked rhamnosides was also investigated and found to be moderately β-directing.[48]

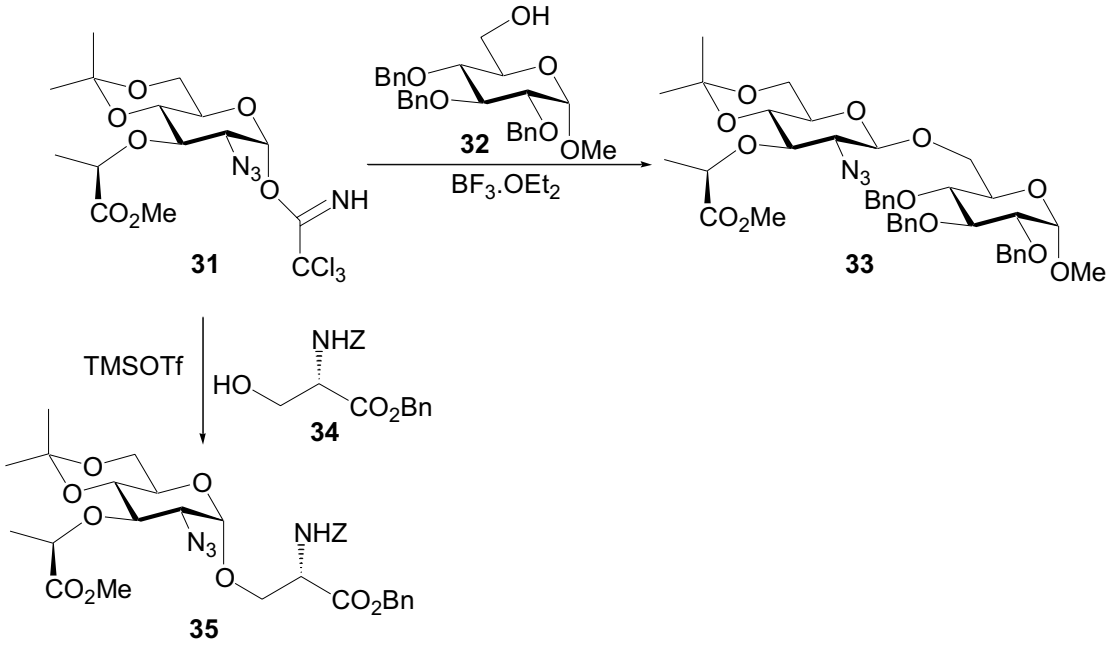
1.1.2.2.2 Cyclic acetals

The isopropylidene acetal, formally a ketal, and its derivatives such as the cyclohexylidene and -pentylidene acetal, can be effectively used in the regioselective protection of 1,2-*cis* diol systems. Rhamno- and mannopyranosides equipped with a 2,3-cyclic acetal essentially exhibit the same behaviour as their cyclic carbonate counterparts: heterogeneous catalysis of anomeric bromides affords β-selectivity[49-52] while homogeneous reactions preferentially guide the glycosidation towards the axially linked product.[43,53,54]

Apart from the protection of vicinal diols, cyclic acetals are applied to mask the 4,6-diol function of pyranoses. An interesting report by Schmidt and Kinzy described that 4,6-*O*-isopropylidene protected 2-azido-2-deoxy glucopyranosyl trichloroacetimidates can be α- or β-selectively glycosylated by reactive glycosyl acceptors depending on the reactivity of the promoter (Scheme 8).[55] Glycosidation of

trichoroacetimidate **31** with primary alcohol **32** under the agency of $BF_3{\cdot}OEt_2$ afforded β-anomer **33** selectively. On the other hand, condensation of **31** with **34** catalysed by TMSOTf afforded α-product **35** exclusively.

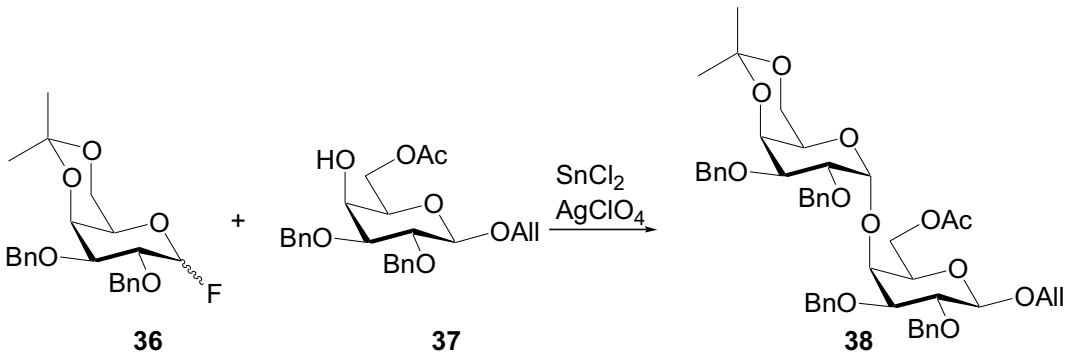
Scheme 8: Stereoselective glycosylations based on the potency of the promoter.



An explanation for these observations may be that complexation of $BF_3{\cdot}OEt_2$ with the anomeric leaving group leads to an activated complex which does not collapse to an oxacarbenium ion-like species due to the torsionally disarming isopropylidene acetal,[35] thereby enabling S_N2-type nucleophilic substitution. Activation of the α-trichloroacetimidate with the more potent TMSOTf affords the α-selective cation.

Ogawa and Nakahara applied a 4,6-*O*-isopropylidene acetal in the α-selective coupling of galactosyl fluorides with several 4-OH galactosyl acceptors.[56] For instance, fluoride donor **36** was condensed with galactosyl acceptor **37** to give the α-linked disaccharide **38** (Scheme 9).

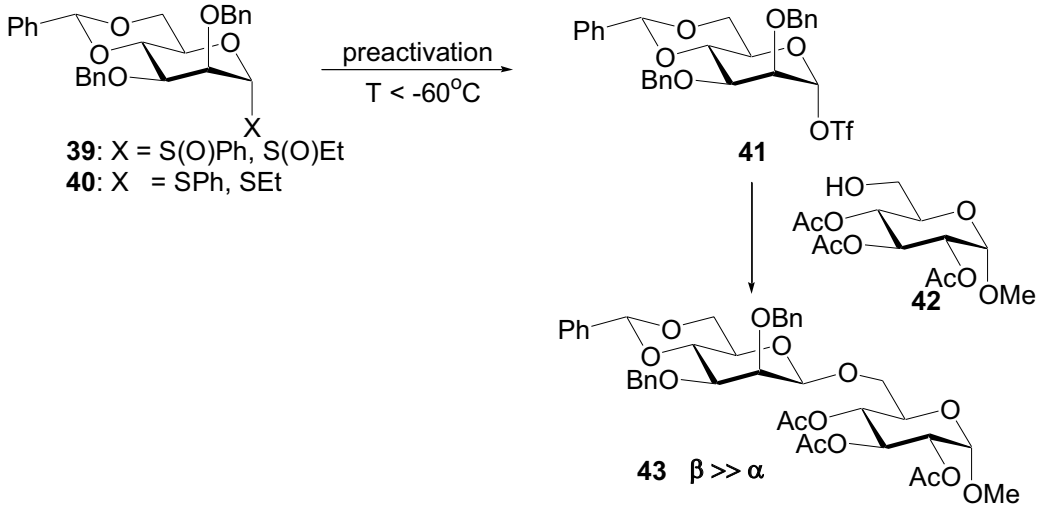
Scheme 9: Stereoselective α-galactosidation.



Later, the Ogawa group studied the effect of 4,6-*O*-cyclic protection in the intramolecular aglycon delivery based β-glycosidation of 2-*O*-*p*-methoxybenzyl mannopyranosides.[29,30] In terms of yield and selectivity, it was established that the 4,6-*O*-cyclohexylidene gave the best results as compared with the 4,6-*O*-isopropylidene and 4,6-*O*-benzylidene.[57]

The Crich laboratory, following initial research on sulfoxides by the Kahne group,[58] developed a highly β-selective mannosylation protocol using 4,6-*O*-benzylidene protected mannopyranosyl sulfoxides **39**.[59,60] The reaction involves a two step one-pot activation-coupling sequence in which first the sulfoxide is treated with Tf_2O at -60°C in dichloromethane in the presence of the acid scavenger 4-methyl-2,6-di-*tert*-butylpyridine (DTBMP), followed by the addition of an acceptor. Mechanistic scrutiny of the reaction path by low temperature NMR analysis strongly suggests the presence of α-anomeric triflate **41** which is stabilised by the torsionally disarming benzylidene function (Scheme 10). The axial triflate is thought to undergo S_N2-type displacement upon addition of for instance acceptor **42**, leading to the formation of β-mannoside **43**.[61]

Scheme 10: Crich's β-selective mannosylation approach.

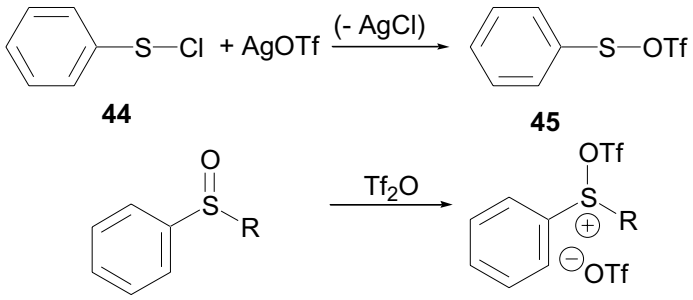


On the basis of α-deuterium kinetic isotope effects in 4,6-*O*-benzylidene directed β-mannosylation, Crich and Chandrasekera concluded that displacement of the anomeric triflate by the carbohydrate acceptor proceeds with the development of substantial oxacarbenium ion character.[62] The importance of the 4,6-*O*-benzylidene group for β-selective mannosylation was confirmed by Sun and Crich, who demonstrated that 4,6-*O*-benzylidene protected thiomannosides **40** could be preferentially glycosidated equatorially employing *in situ* generated PhSOTf (**45**,

Scheme 11) as an activator using the preactivation-coupling sequence (Scheme 10).[63,64]

Contrary, application of the sulfoxide-Tf_2O and thioglycoside-PhSOTf methodology to 4,6-*O*-benzylidene protected glucosides gave disaccharides with high α-selectivity.[65] This result possibly stems from *in situ* anomerisation of α-triflates to their more reactive β counterparts. These β-triflates react quicker in an S_N2-type displacement upon addition of the acceptor, affording the axial linkage. The PhSOTf-thiomannoside protocol was further improved from an experimental point of view by employing the crystalline and shelf-stable *S*-(4-methoxyphenyl) benzenethiosulfinate **46** (MPBT) in combination with Tf_2O as activator system instead of PhSOTf.[66] Shortly afterwards, the highly potent 1-benzenesulfinyl piperidine **47** (BSP)/Tf_2O activation system was introduced for the β-selective synthesis of mannoside linkages.[67]

Scheme 11

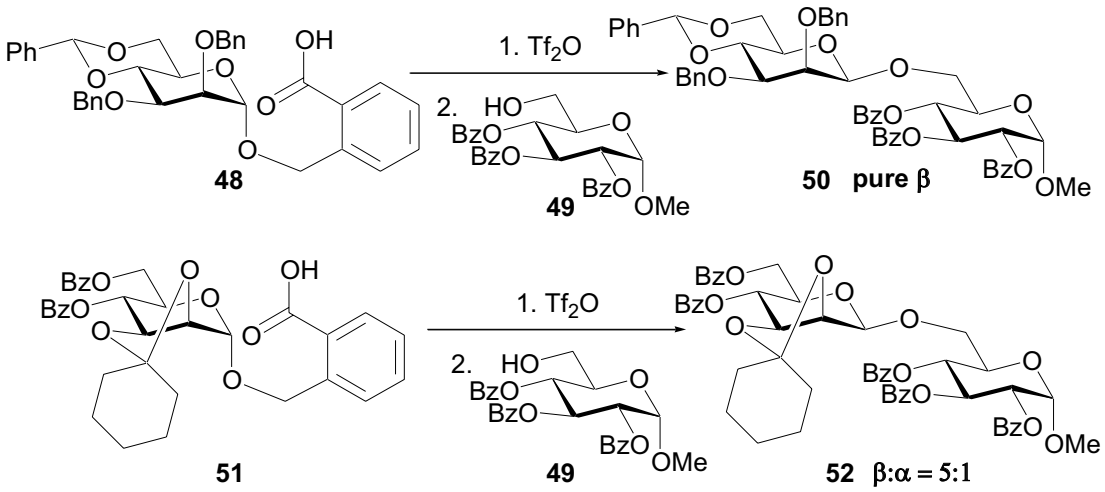


46: R = -*S*-*p*-OMePh (MPBT)
47: R = 1-piperidino (BSP)

In a comparative study, Weingart and Schmidt established that 4,6-*O*-benzylidene protected α-mannopyranosyl trichloroacetimidates can be glycosidated under inverse conditions[68] at low temperature to give β-mannosides with similar efficiency, as observed in the sulfoxide method. They reasoned that since only a catalytic amount of the promoter TMSOTf is used, an anomeric triflate is not feasible. A twist-boat which preferentially undergoes attack from the β-face was proposed as the reactive intermediate.[69]

Kim *et al.* applied 4,6-*O*-benzylidene protection in their β-selective mannosylation protocol using 2-(hydroxycarbonyl)benzyl (HCB) mannosides. This approach, like the work of Crich, entails low temperature Tf_2O mediated preactivation of the donor in the presence of DTBMP followed by acceptor addition (Scheme 12).[70] For instance, preactivation of mannoside **48** followed by addition of acceptor **49** afforded the β-mannoside **50** as the sole isomer. However, in some cases, performing the glycosidation without preactivation also led to preferential β-product formation and β-selectivity was also observed when a 2,3-*O*-cyclohexylidene group was present in the donor, albeit less pronounced (Scheme 12, **51→52**).

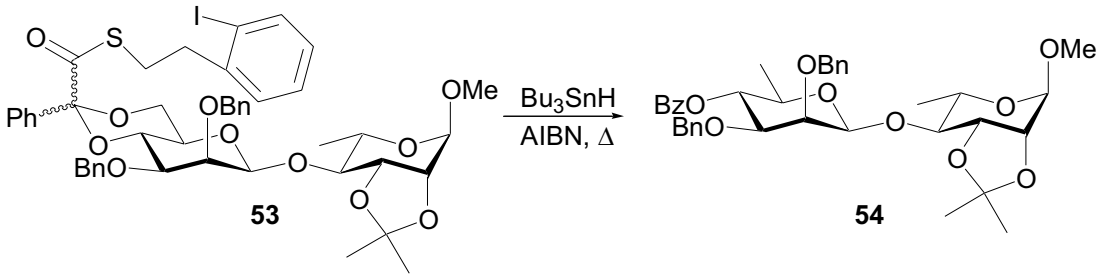
Scheme 12: Kim's HCB glycosyl donors.



Nagai *et al.* have reported that the triflate deficient montmorillonite K-10 clay assisted glycosidation of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl diethyl phosphite with various acceptors gave access to β-mannosides in high yields and selectivities.[71]

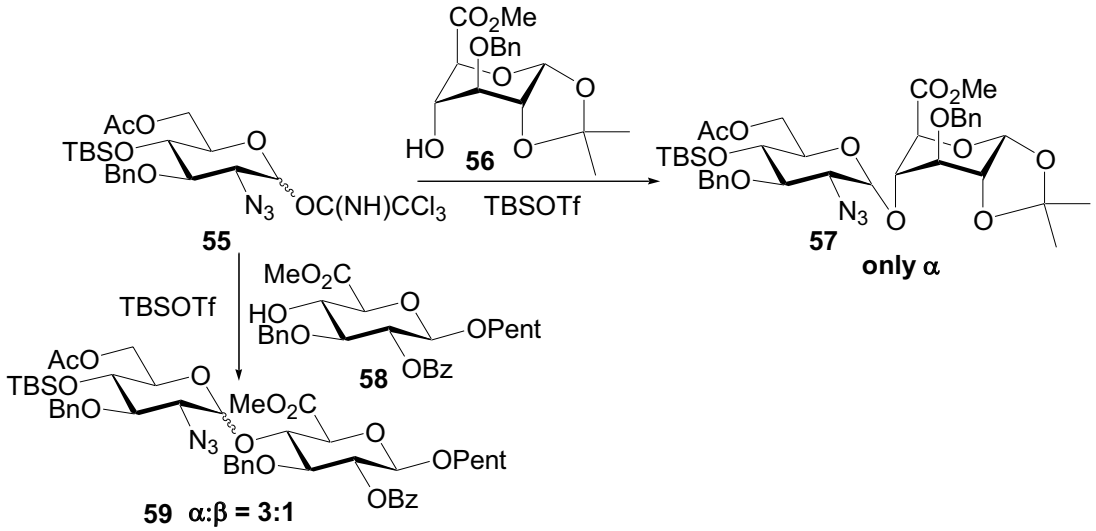
The Crich β-mannosylation approach has also found application in β-D-rhamnoside synthesis. First, thiomannoside **53** carrying a 4,6-*O*-benzylidene that is functionalised with a thiol ester at the benzylic position is coupled β-selectively. Ensuing radical fragmentation of the ketal affords the 6-deoxy mannoside, *i.e.* the D-rhamnoside (Scheme 13).[72,73]

Scheme 13: Radical fragmentation towards β-D-rhamnoside **54**.



An interesting example in which cyclic protection is used on the acceptor glycoside to induce stereoselectivity in a glycosylation reaction is described by Seeberger and coworkers. Locking the conformation of glucuronic acid acceptor **56** in the $^1C_4$ form and glycosylation with glycosyl donor **55** gave only the desired 1,2-*cis*-linked disaccharide **57** (Scheme 14). Glycosidation of **55** with unlocked acceptor **58** gave a mixture of anomers.[74]

Scheme 14: Conformational locking of the acceptor moiety.

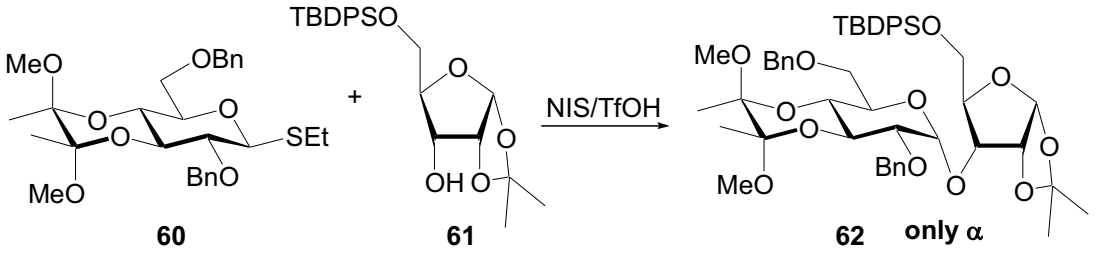


1.1.2.2.3 1,2-diacetals

The pioneering work of the Ley laboratory with respect to the application of 1,2-diacetals such as the dispiroketal (dispoke), the cyclohexane-1,2-diacetal (CDA) and the butane-2,3-diacetal (BDA) in carbohydrate synthesis has found widespread application.[75,76] In general, 1,2-diacetals are employed to mask diequatorial diol systems.

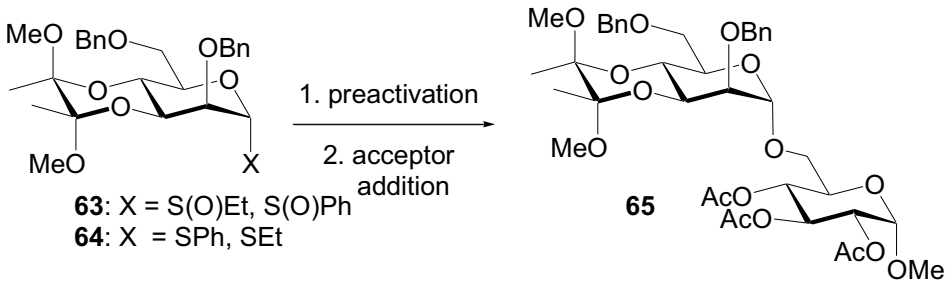
Van Boom and coworkers exploited the BDA group in the synthesis of a clustered disaccharide polyphosphate analogue of Adenophostin A (Scheme 15).

Scheme 15: α-selective glycosidation of a BDA 3,4-protected thioglucoside.



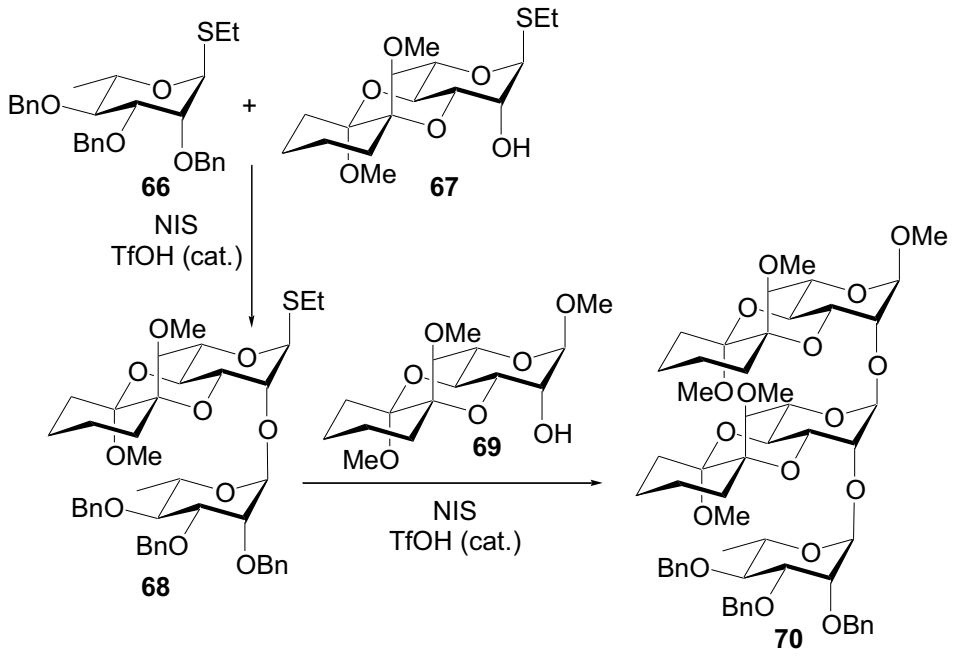
In the NIS/triflic acid (TfOH) promoted coupling of **60** and **61**, only formation of α-anomer **62** was observed.[77] α-Selectivity was also noted by Crich *et al.* in the glycosidation of BDA 3,4-protected mannopyranosyl sulfoxides and thiomannosides in the absence of participating protecting groups (Scheme 16).[42]

Scheme 16: α-selective glycosidation of BDA 3,4-protected mannosides.



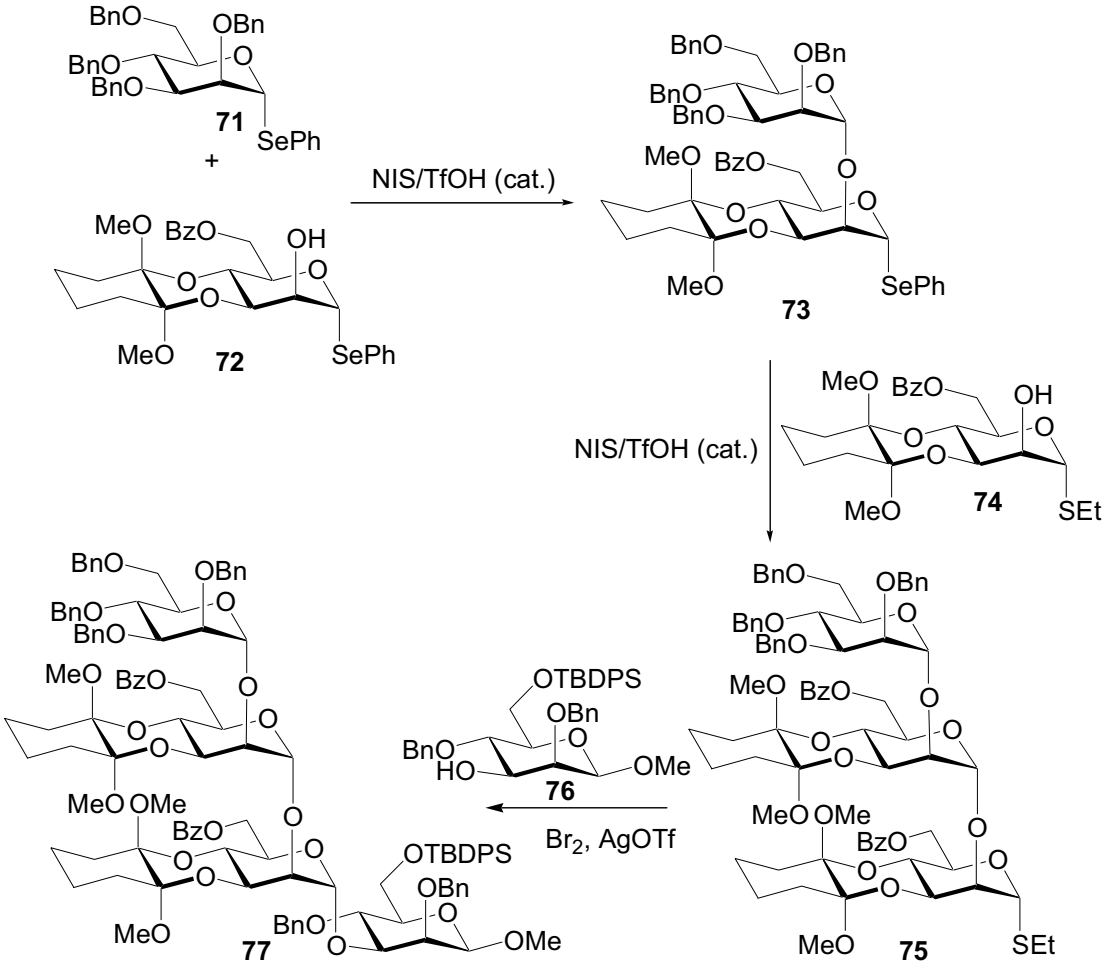
The perception that the rigidity of 1,2-diacetals induces torsional strain[38,39,78] has prompted the development of reactivity tuning in chemoselective glycosidation reactions. Ley and Priepke applied this concept in a one-pot synthesis of a trisaccharide unit found in the common Group B *Streptococci* polysaccharide antigen (Scheme 17).[79]

Scheme 17: Chemoselective glycosidation based on the torsionally disarming CDA-group.



This chemoselective glycosylation strategy could be further extended by employing phenylseleno donors and slower reacting ethyl thioglycosides, thereby distinguishing up to four levels of reactivity (Scheme 18).[80]

Scheme 18: Chemoselective glycosylation based on reactivity tuning of seleno- and thioglycosides.

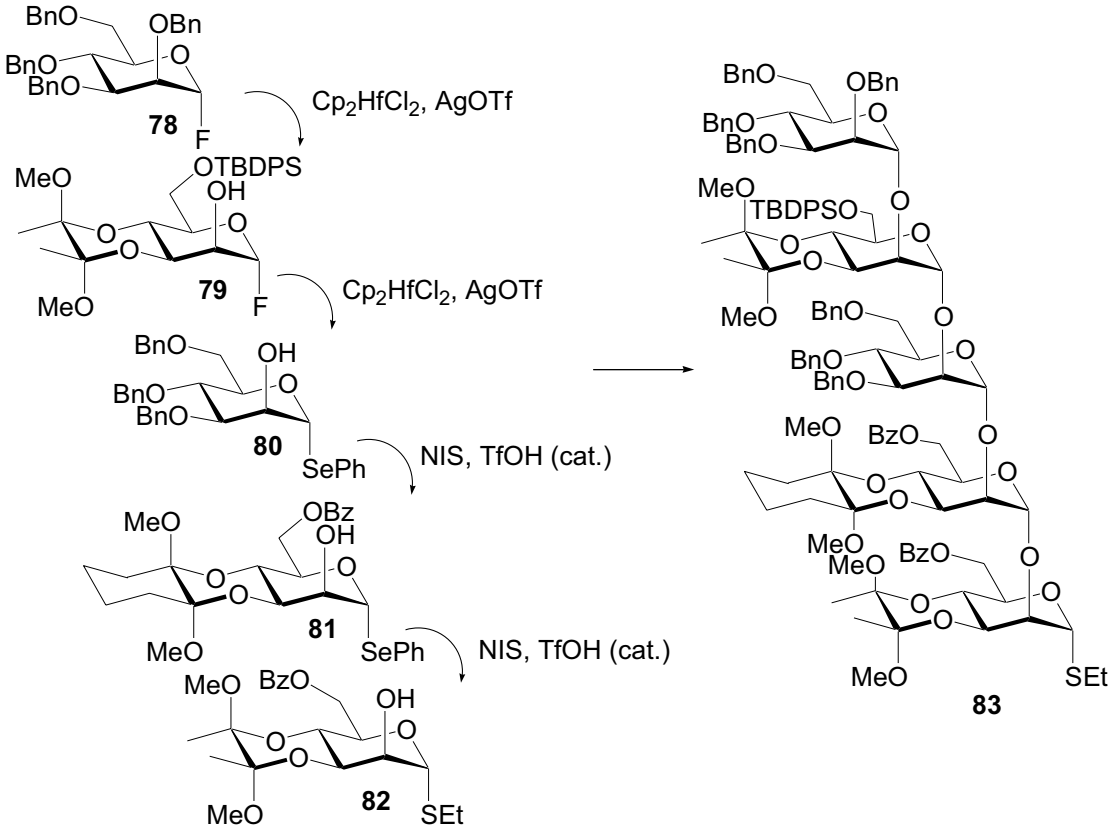


Armed selenodonor **71** is selectively activated in the presence of the torsionally disarmed selenoglycoside **72**, which serves as the acceptor, affording **73**. Ensuing chemoselective condensation of selenoglycoside **73** with thioglycoside **74** gave trisaccharide **75**, which was converted to the α-bromide and coupled with acceptor **76** to afford tetrasaccharide **77**.

A next development entailed the combination of the above described chemoselective glycosylation approach with the concept of orthogonal[81] glycosylation. This approach was shown to enable one-pot syntheses of linear[82] as well as branched pentameric oligosaccharides[83] employing up to three different anomeric leaving groups. For example, armed mannosyl fluoride **78** was chemoselectively condensed with disarmed fluoride **79** (Scheme 19). The resulting

dimer was orthogonally glycosidated with armed selenide **80** followed by chemoselective condensation of the formed trimer with disarmed selenide **81**. Ensuing coupling of thioglycoside acceptor **82** gave pentasaccharide **83**.

Scheme 19: Orthogonal-chemoselective sequential one-pot glycosylation.



The above examples demonstrate the potential of cyclic protection in stereoselective oligosaccharide synthesis. In view of the preference for either the axial or the equatorial product which can be achieved by varying the position of the diol protection, further exploration in this field seems a worthwhile goal. Especially combinations of cyclic protection and chemoselective and/or orthogonal glycosylation strategies present attractive research targets.

1.3 Thesis Outline

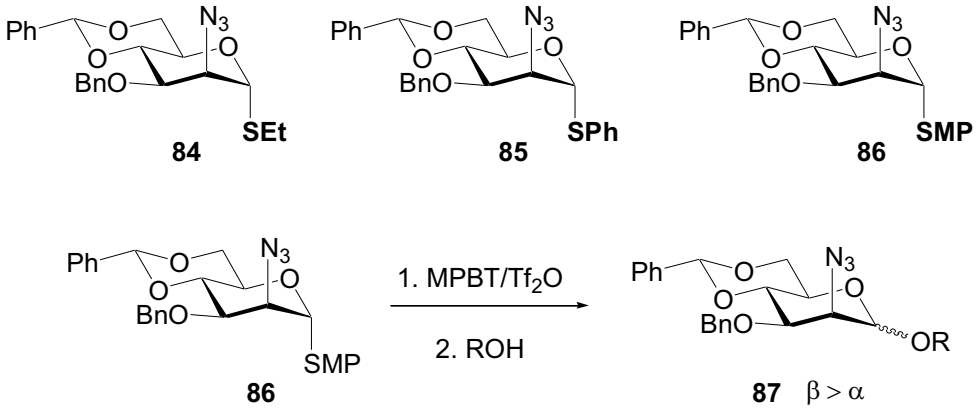
Although in the last decades considerable progress has been made in the assembly of complex oligosaccharides, the statement of Paulsen in 1982 that '*there are no universal reaction conditions for oligosaccharide syntheses*' is not overruled.[2a] The meticulous fundamental and methodical research on which this

progress is based, will have to be continued to access the vast array of structurally diverse oligosaccharide constructs.

The research described in this thesis is aimed at the use of 1-thio and 1-hydroxyl donors in combination with sulfonium triflate activation reagents in the stereoselective construction of glycosidic bonds and the application of these methodologies in the synthesis of biologically active oligosaccharide constructs.

The initial finding by Crich and Smith that conformationally restricted 4,6-*O*-benzylidene protected thiomannosides can be efficiently and β-selectively glycosidated by the two-step low temperature 4-(methoxyphenyl)benzenethiosulfinate (MPBT)/trifluoromethanesulfonic anhydride (Tf_2O) protocol[66] encouraged the exploration of this activation system in the glycosidation of the analogously protected 2-azido-2-deoxy thiomannosides **84**-**86** (Scheme 20). The development of a stereoselective synthesis of 2-azido-2-deoxy-β-D-mannosides would give access to biologically relevant β-ManNHAc containing oligosaccharides.

Scheme 20: 2-Azido-2-deoxy thiomannosides.

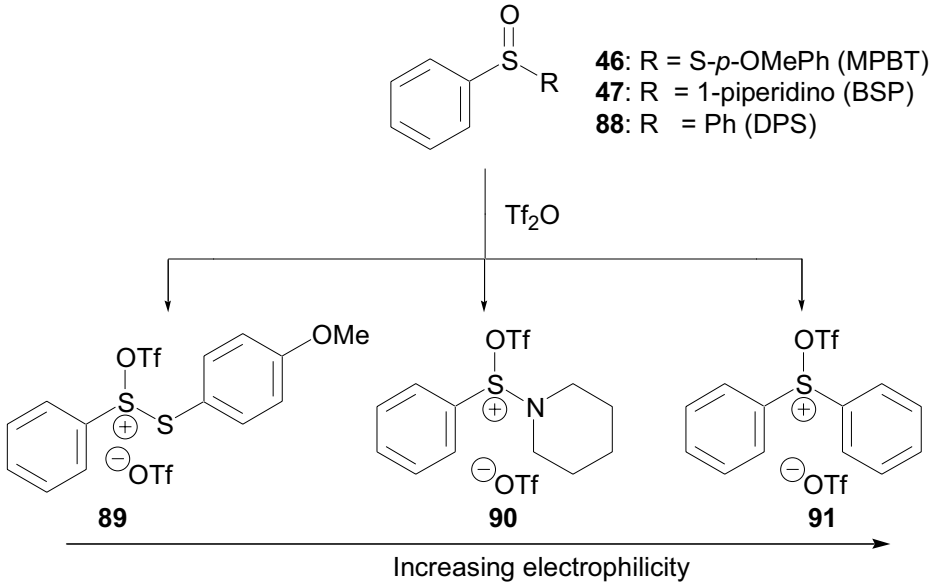


As described in **Chapter 2**, application of the MPBT/Tf_2O protocol in the activation of the highly disarmed donors **84** and **85** did not lead to a productive condensation with glycosyl acceptors. By counterbalancing the disarming nature of the 2-azido functionality by installation of the more nucleophilic *p*-methoxyphenylthio (SMP) residue on donor **86** and by preactivating at a higher temperature (-60→-35ºC), application of the MPBT/Tf_2O protocol with several acceptors gave access to 2-azido-2-deoxy-β-D-mannosides in high yield and good selectivity (*e.g.* **86→87**).[84]

The advent of the more potent 1-(benzenesulfinyl)piperidine (BSP)/Tf_2O activation system[67] (**47**) was an incentive to explore its potency in the glycosidation of thiomannosazides **85** and **86**. In **Chapter 3**, it is shown that glycosidation of 1-thiophenyl donor **85** by the BSP protocol did not lead to reproducible results but that

subjection of the more reactive **86** to these conditions afforded coupled products uneventfully.[85,86] It was reasoned that sulfonium triflate species **90** generated in the BSP protocol suffers from stabilisation by the nitrogen lone pair and that sulfonium triflate **91** generated by treatment of diphenylsulfoxide (DPS) **88** with Tf_2O would be more powerful (Scheme 21).

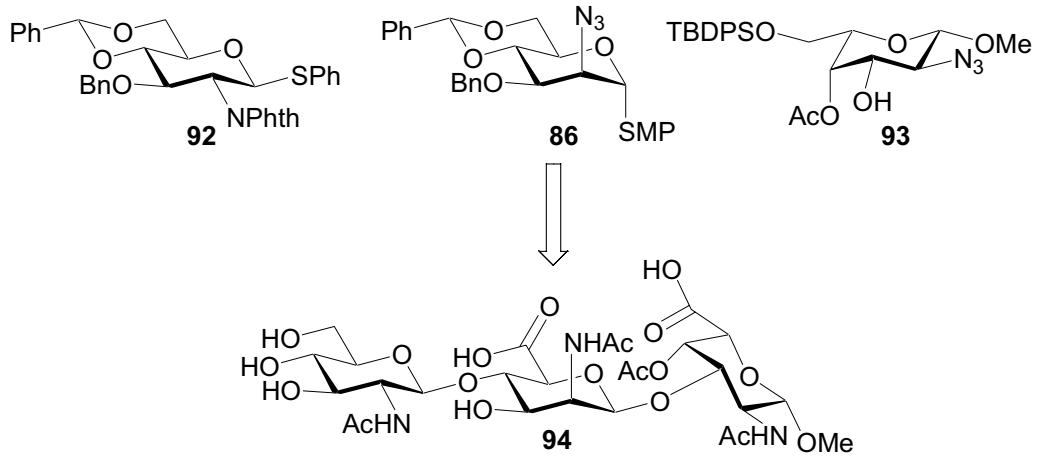
Scheme 21: Sulfonium Triflate Activators.



Indeed, subjection of thiophenyl donor **85** to this reagent combination afforded coupled products in good yields. The β-selectivity in these glycosylations is strongly dependent on the steric accessibility of the acceptor alcohol function. The reactivity difference in the BSP and DPS activation systems was exploited in a chemoselective glycosylation strategy.[85,87]

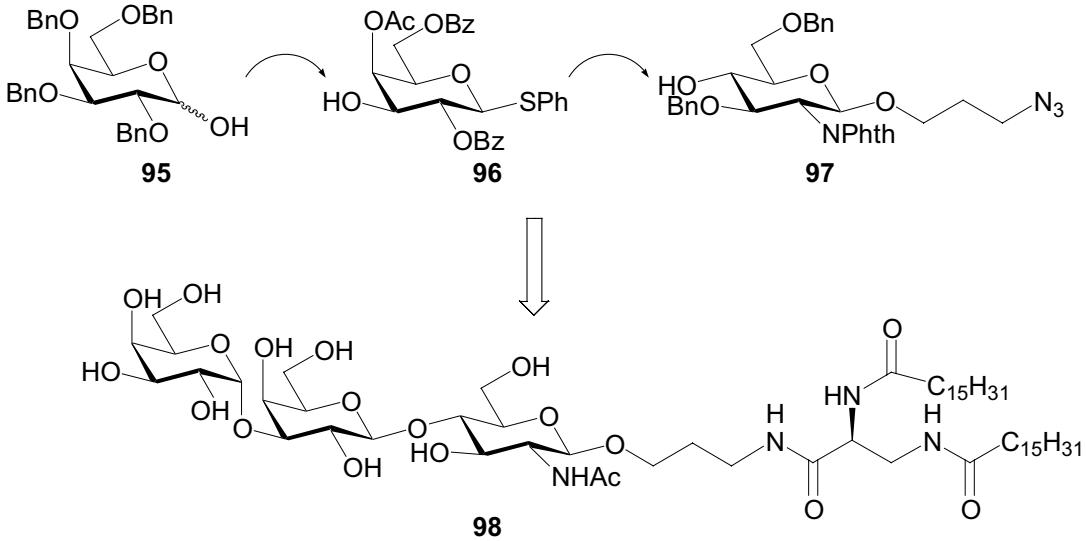
In **Chapter 4**, the first synthesis of the repeating unit of the acidic polysaccharide of the bacteriolytic complex of lysoamidase is presented (Scheme 22). Lysoamidase is effective in combating external infectious diseases caused by Gram-positive bacteria. Its activity is based on the presence of several hydrolytic activities in the complex, including glycyl-glycine endopeptidase, *N*-acetylmuramyl-L-alanine amidase and an endoacetylglycosidase which cleaves *N*-acetylglucosaminyl-*N*-acetylmuramic acid linkages.[88-90] The methodology described in chapters 2 and 3 was applied in the β-selective condensation of **86** with L-galactosamine building block **93**, which was prepared in 12 steps from L-galactono-1,4-lactone. Ensuing introduction of the glucosamine unit **92** followed by a deprotection-oxidation-deprotection sequence afforded the desired trisaccharide **94**.[91]

Scheme 22: Assembly of the lysoamidase trimeric repeat.



The α-Gal epitope [Gal-(α1,3)-Gal-(β1,4)-GlcNAc] is a major obstacle in the field of xenotransplantation of tissues or organs from pigs to monkeys (or humans) due to hyperacute rejection.[92,93] At the same time, the strong immunological response to α-Gal may be beneficial in vaccinology or immune therapy. To investigate the latter, neoglycoconjugate **98** comprising the linear B type 2 trisaccharide (α-Gal epitope) connected to a membrane binding entity was synthesised (Scheme 23).

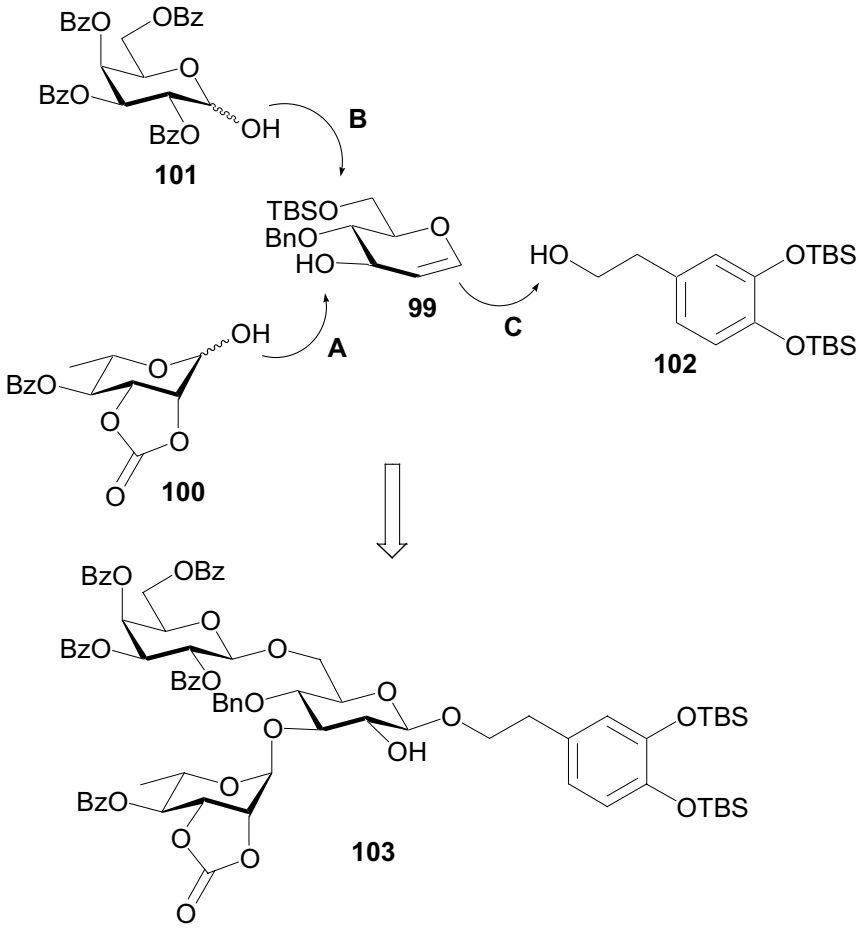
Scheme 23: Construction of neoglycoconjugate **98**.



Chapter 5 describes the synthesis of the trisaccharide part of the conjugate by a one-pot orthogonal coupling sequence using DPS/Tf_2O as the sole activation system.[94] Deprotection of the trisaccharide was followed by functionalisation of the spacer-amine with a di-amino scaffold which was decorated with palmitoates to afford the membrane binding entity.[95]

Phenylethanoid glycosides (PhGs) are widely distributed in the plant kingdom and display a variety of biological functions.[96] PhGs are characterised by a (2-phenyl)-ethyl-β-D-glucopyranoside which is functionalised with an aromatic acid (*e.g.* cinnamic acid, caffeic acid). Furthermore, monosaccharides may decorate the glucose core. In **Chapter 6**, an approach towards the generic synthesis of phenylethanoid glycoside tetramers is presented. The construction of these structures combines the concepts of orthogonality and induced stereoselectivity by cyclic protection.

Scheme 24: Synthetic approach to the PhG jionoside backbone.



For instance, 2,3-*O*-carbonyl protected 1-hydroxyl rhamnose **100** was condensed with glucal acceptor **99** using DPS/Tf_2O, affording the α-anomer as the sole isomer (**A**, Scheme 24). Desilylation and condensation of the resulting primary alcohol with 1-

hydroxyl galactose **101** (**B**) followed by oxidative coupling of the glucal with phenylethanol **102** (**C**) afforded jionoside precursor **103**.
In the final chapter of this thesis, a summary is outlined as are some future prospects.

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